ESTRO School

Epidemiology of Cancer in Early Life

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Objectives

- To debate health priority for cancer services in early life
- To consider the impact of age growth and development upon risk of cancers in early life.
- To explore the impact of normal processes of adolescence upon an individual's capacity to participate in treatments and trials.
- To propose strategies for enhancing outcome within clinical trials for TYA population


EDWARD DE BONO'S
THINKING HATS
BIG PICTURE
keeping group focused, & deciding change
observation & overview
logical sequence
thinking about thinking
focus
control panel
process control overview
just the facts.
FACT -or- BELIEF
checked
unchecked
computer like
facts & figures
neutral & objective
make map a terrain of facts
let's use this hat now
always true
usually true
generally true
by & large
more often than not
about half the time
often
sometimes true
occasionally true
been known to happen
never true
cannot be true
intuitive emotional
i feel...
gut reaction
intuition: based on experience
emotion decisions in the end
"putting on" red hat allows emotions at specific points v. constant
formality
no need to justify emo's.
positive optimistic
more logical and backed up than "a good feeling"
exploration & constructive
speculative speculation
looking forward
benefit
Why it will work
provocative very likely good chance no better known possible remote or long shot
what if we...?
alternatives
change
new
fresh
growth
creative generative
new ways of looking @ things
escape from old ideas
movement -vs- judgement
po.
provocations
suspension
stepping stone
who wants?
both logical
Why it won't work.
always logical, not emotional
negative critical
reasons for judgement given
challenging facts & figures
easier to be destructive than constructive
not problem solving, just pointing out the problem
look back to experience
graphic facilitation by Brandy Agerbeck Loosetooth.com
using hats to focus on 1 hat
take on that role
switch hats
use all hat to assess problem fully
simplify thinking

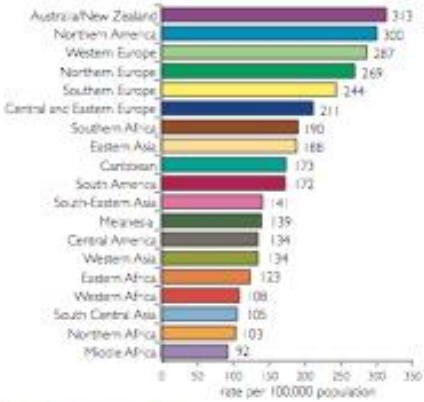
CANCER RESEARCH UK

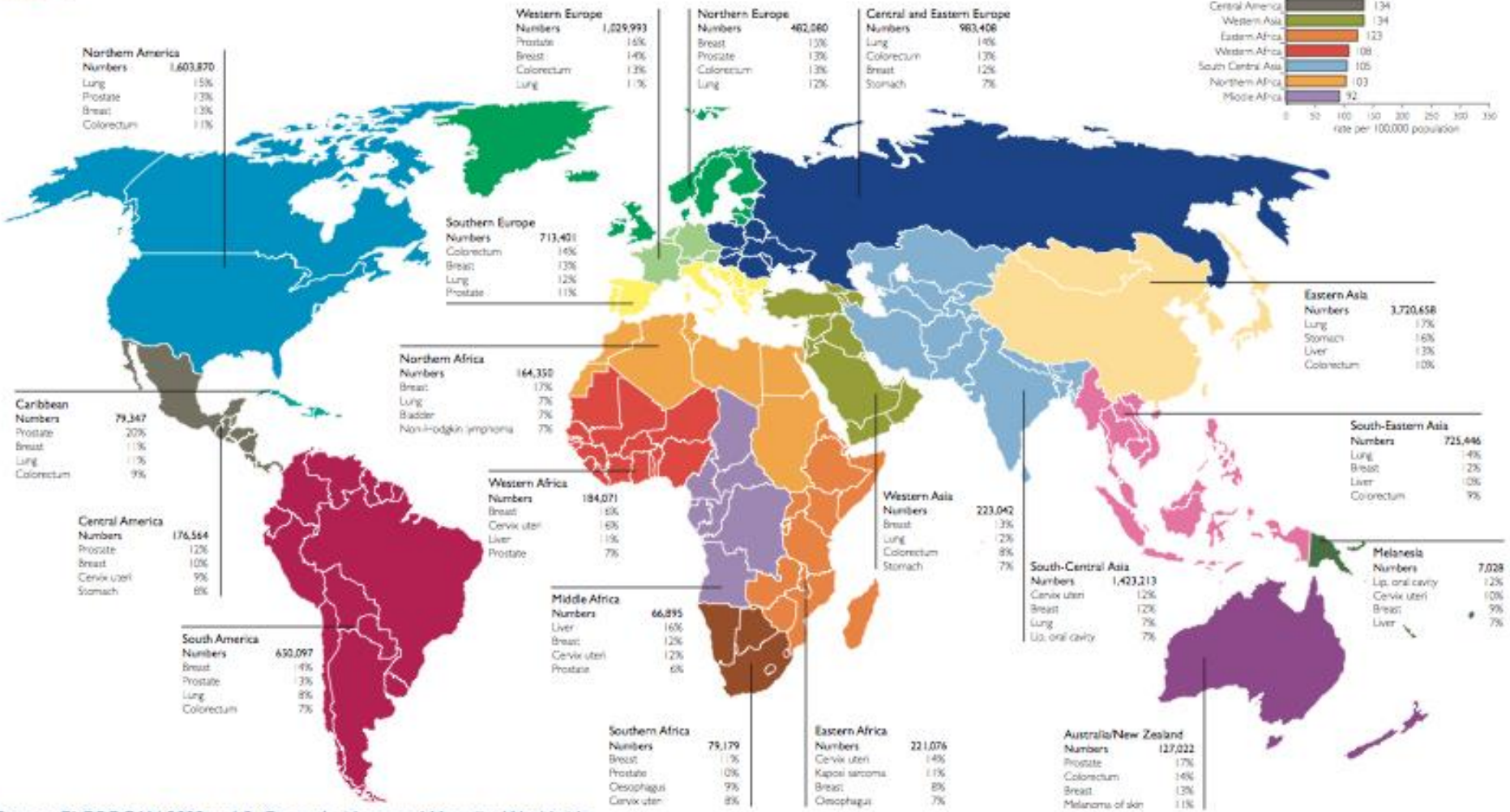
International Agency for Research on Cancer

World Health Organization

Cancer Incidence Worldwide

Breakdown of the estimated 12.7 million new cases, World-age standardised incidence rates and the most commonly diagnosed cancers by the different regions of the world, 2008.

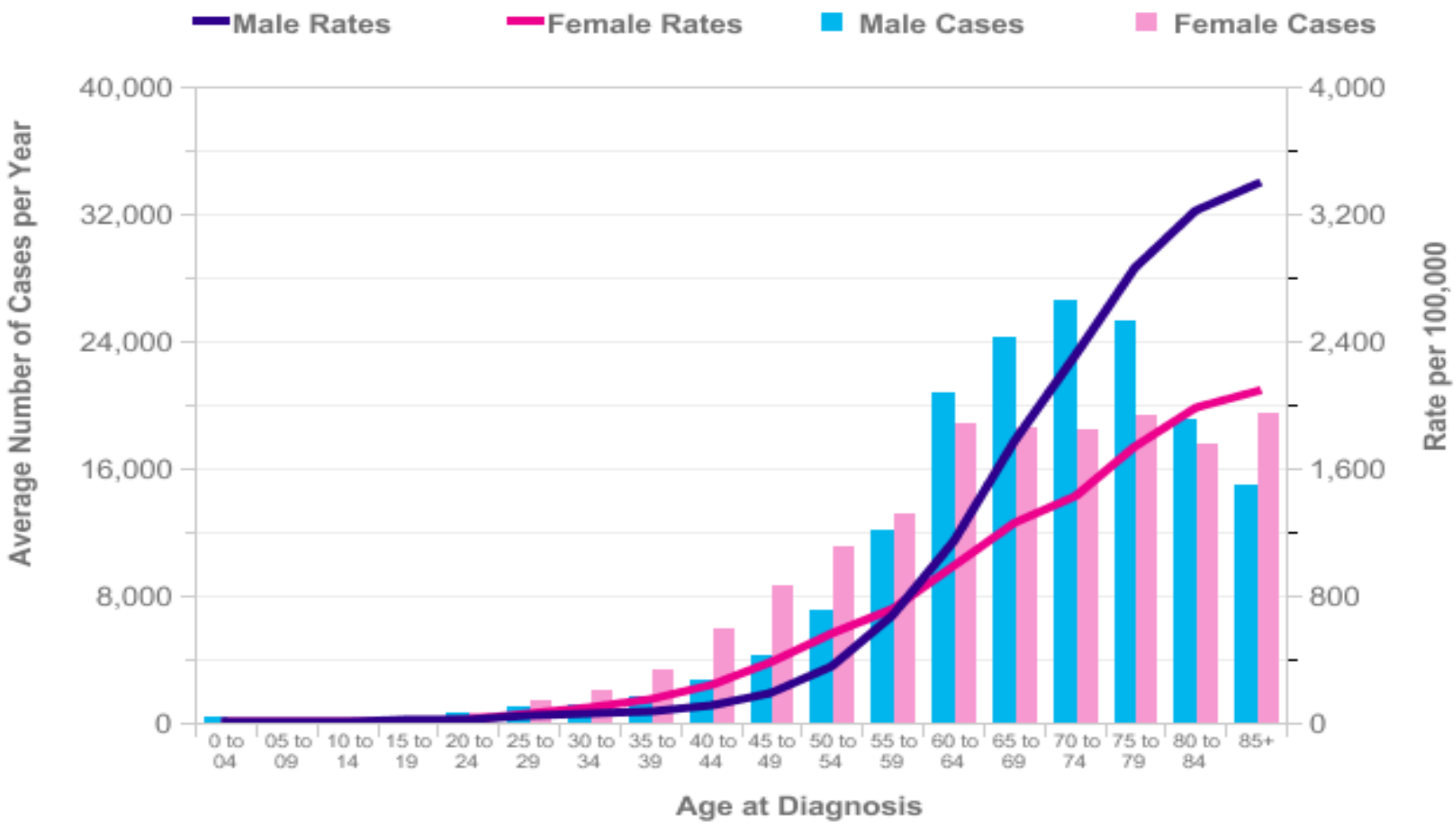




Source: GLOBOCAN 2008, v. 1.2, Cancer Incidence and Mortality Worldwide. IARC, 2010 (http://globocan.iarc.fr)
Map updated February 2011

http://info.cancerresearchuk.org/cancerstats/

All Cancers Excluding Non-Melanoma Skin Cancer (C00-97 Excl. C44): 2008-2010
Average Number of New Cases Per Year and Age-Specific Incidence Rates per 100,000 Population, UK



Go to **www.menti.com** and use the code **88 93 45**

Strategies to improve outcomes for TYA age group in clinical trials?

Debate:

Specialist cancer services for children and young people are a vital health priority

Arguments for
Arguments against

2 minutes

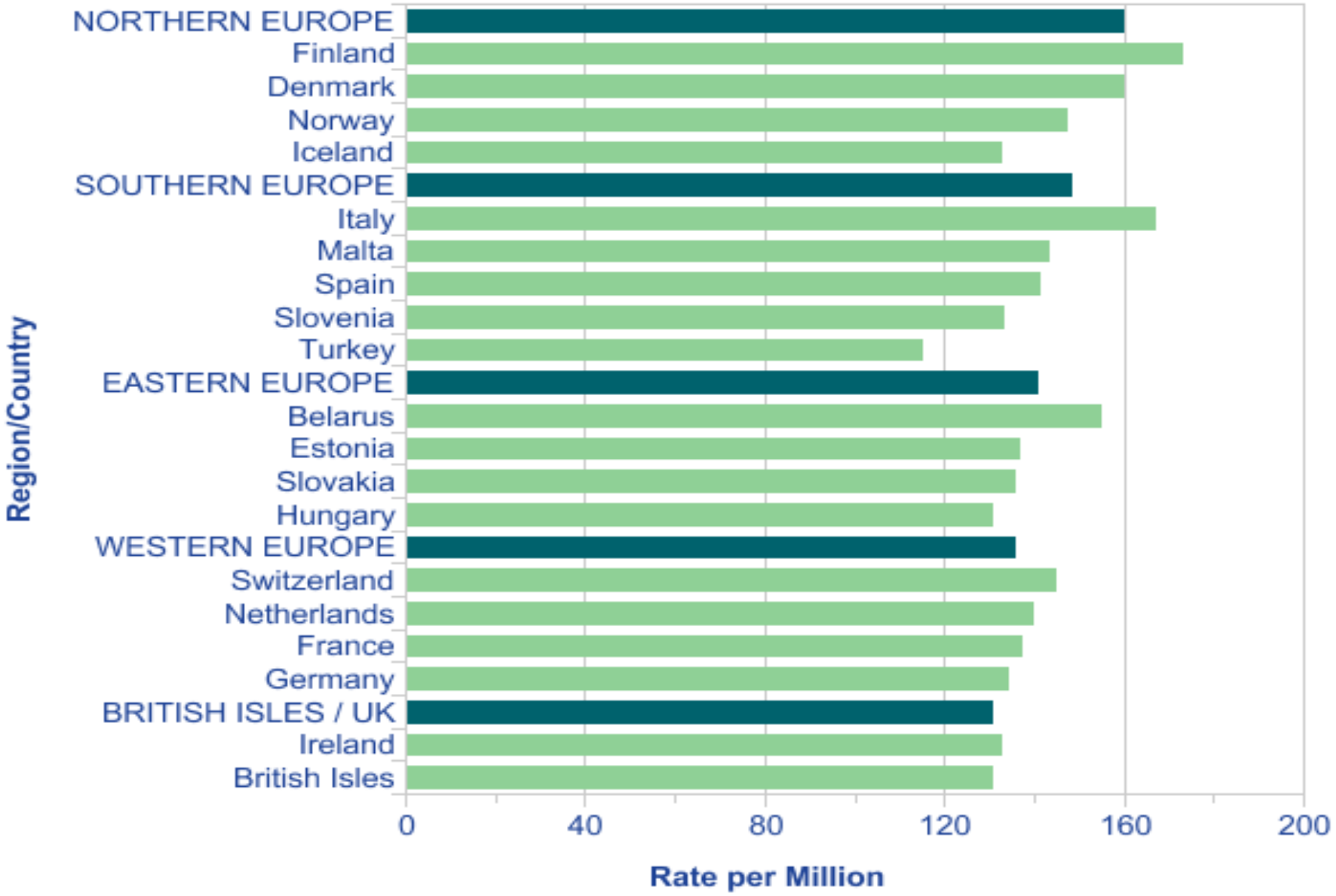
Go to **www.menti.com** and use the code **88 93 45**

Strategies to improve outcomes for TYA age group in clinical trials?

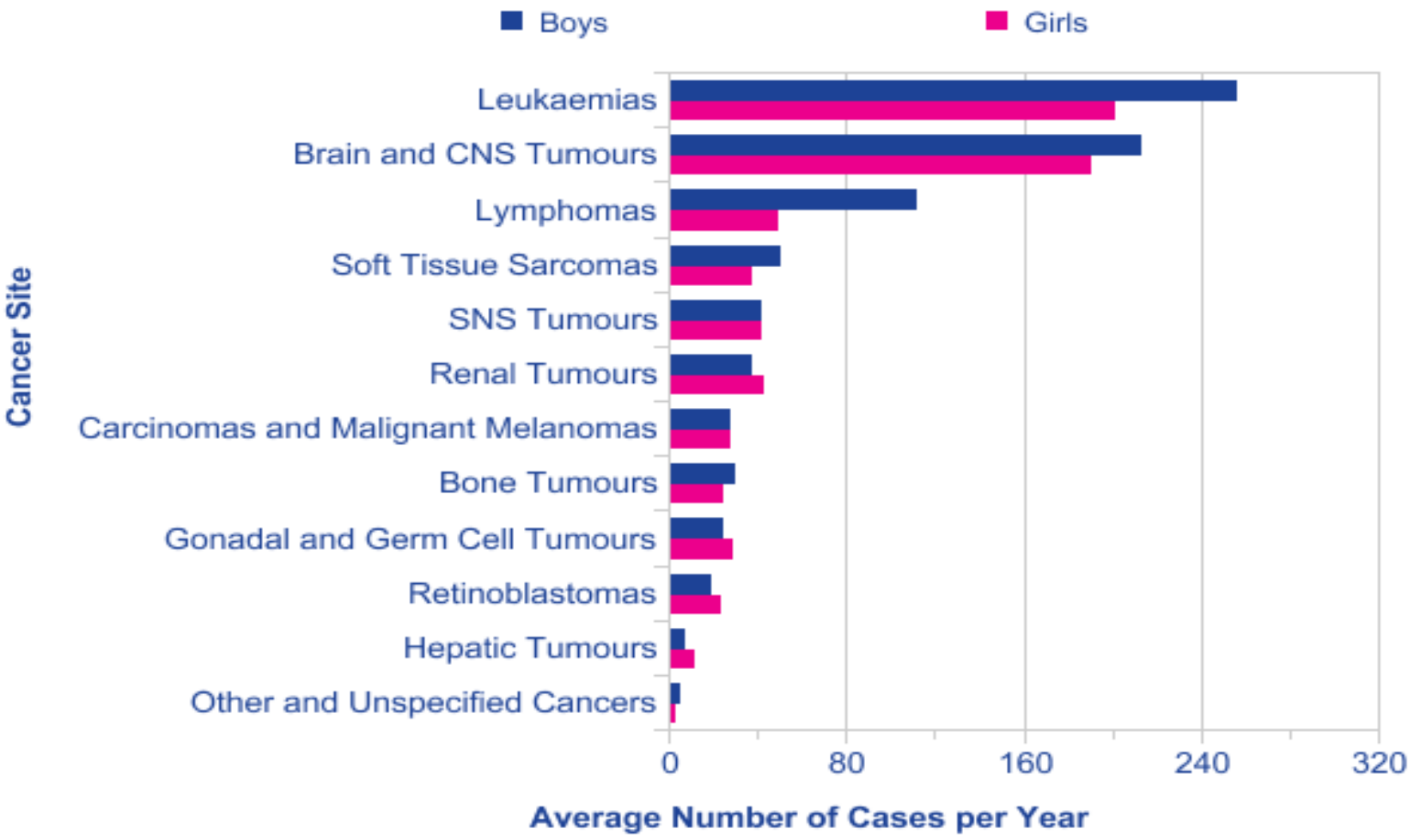
Objectives

- To consider the impact of age growth and development upon risk of cancers in early life.

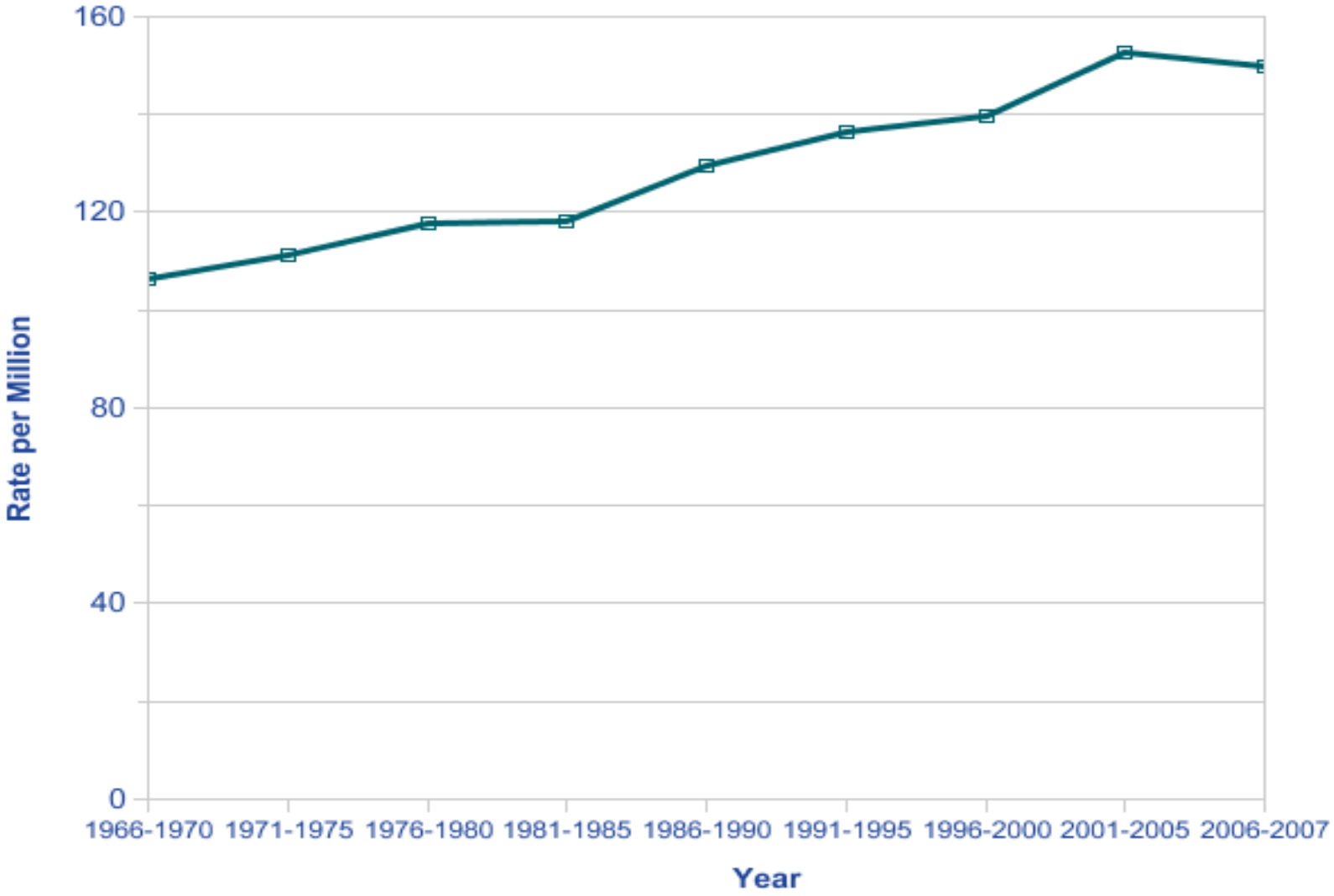
All Childhood Cancers: 1988-1997World Age-Standardised Incidence Rates per Million Population, Children (0-14), Europe



All Childhood Cancers: 2006-2007Average Number of New Cases Diagnosed per Year, Children (0-14), Great Britain



All Childhood Cancers*: 1966-1970 to 2006-2007 World Age-Standardised Incidence Rates per Million Population, Children Aged 0-14, Great Britain



Cumulative cancer risk:

It has been estimated that around one child in every 500 will develop some form of cancer by 14 years of age in Great Britain

1 in 200 by age 22 years

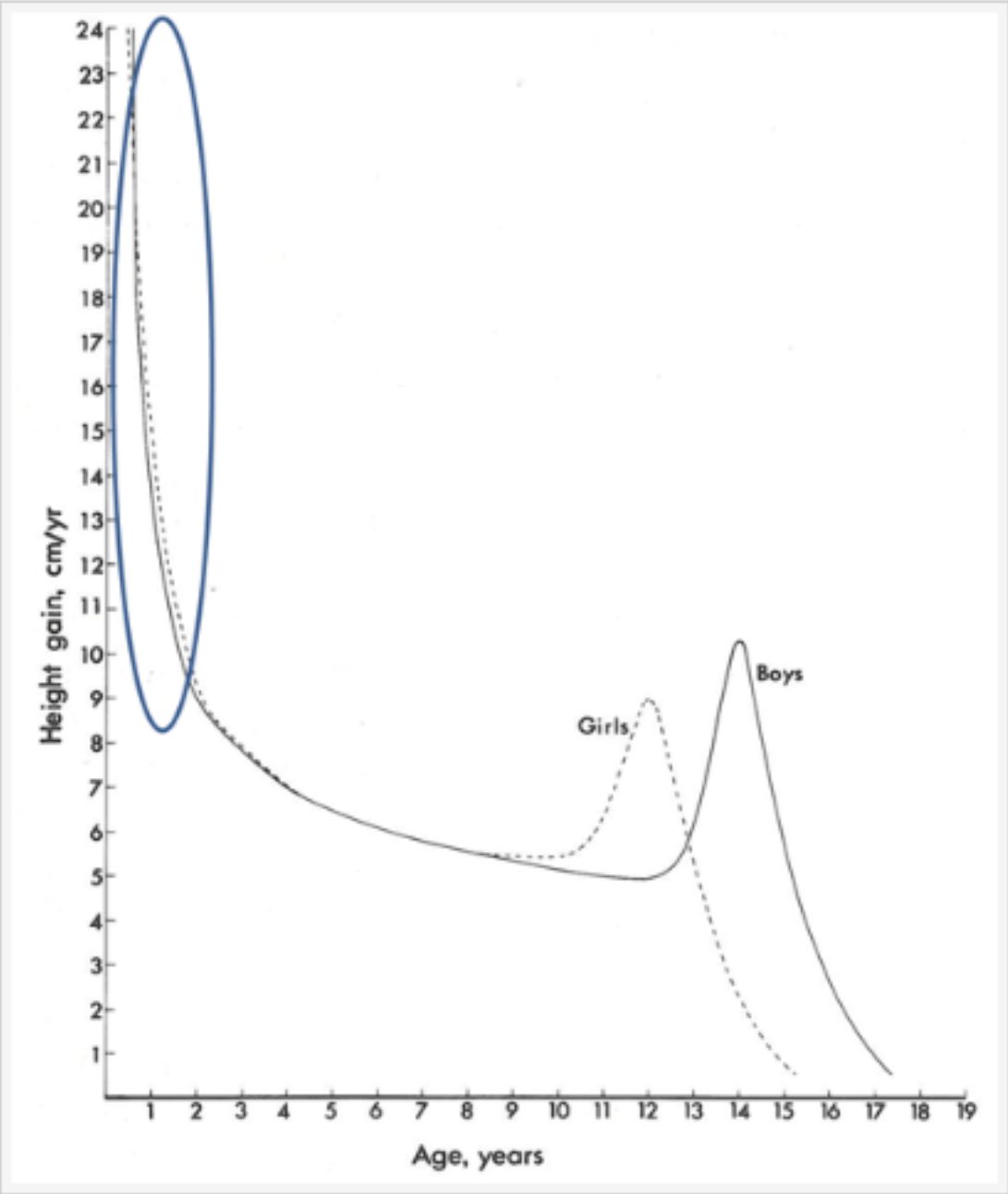
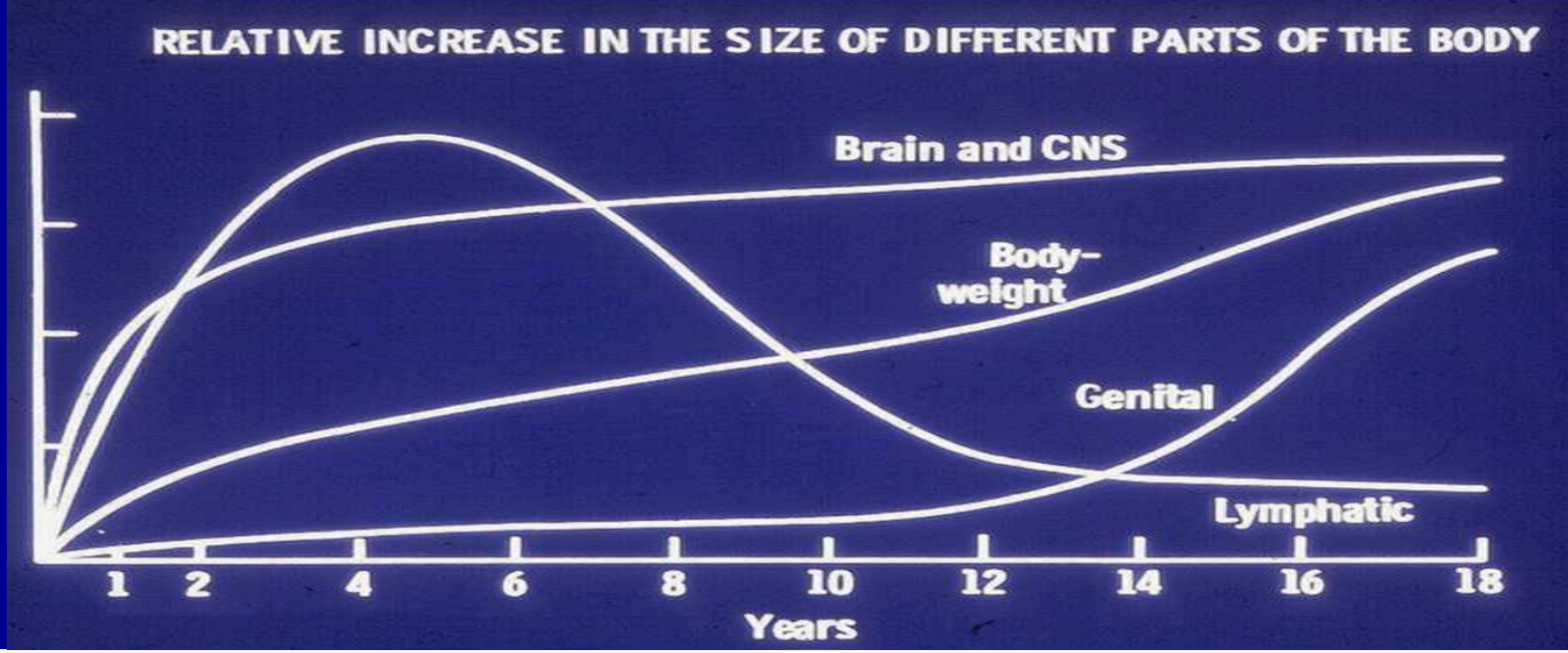
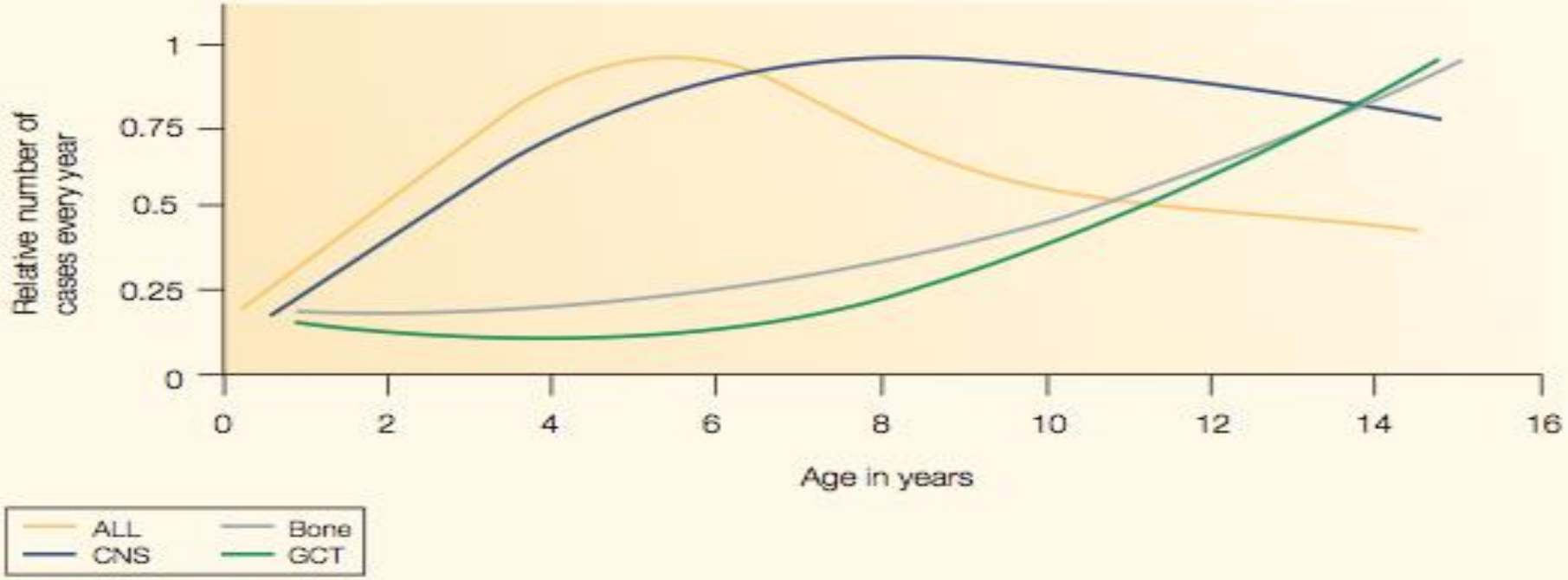


Figure: Growth velocity curve (UK)

Source: Tanner et al (1966)[2]

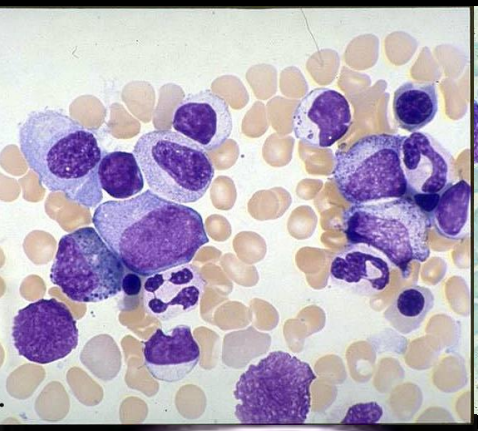

RELATIVE INCREASE IN THE SIZE OF DIFFERENT PARTS OF THE BODY
Brain and CNS
Body-weight
Genital
Lymphatic
1
2
4
6
8
10
12
14
16
18
Years

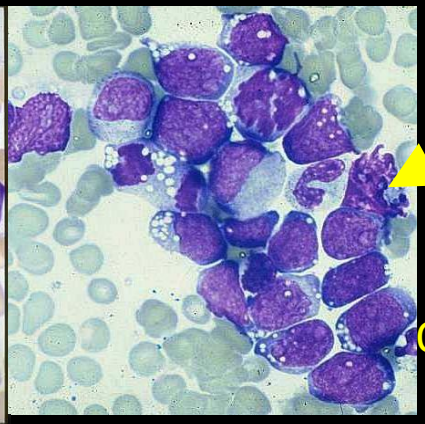

Relative number of cases every year
1
0.75
0.5
0.25
0
0
2
4
6
8
10
12
14
16
Age in years
ALL
CNS
Bone
GCT

Childhood malignancies: Cytology / Imaging

Normal

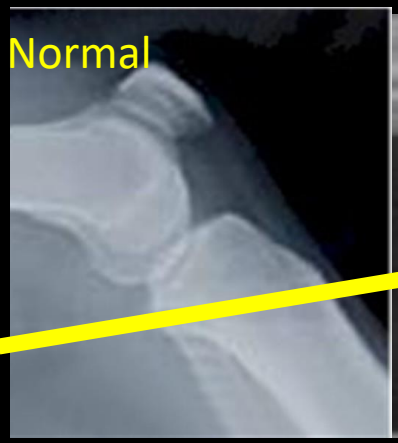
Abnormal



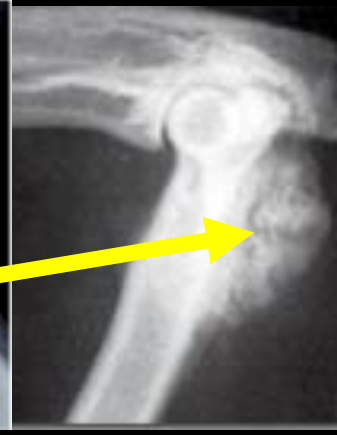


Leukaemia

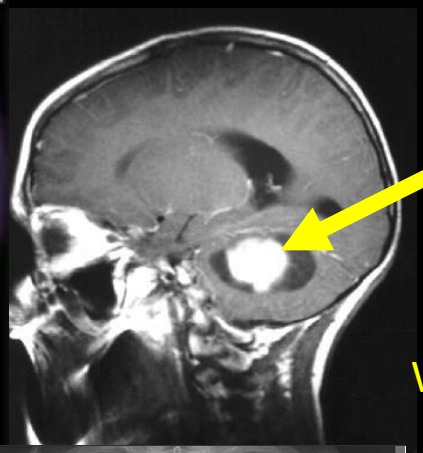
Normal



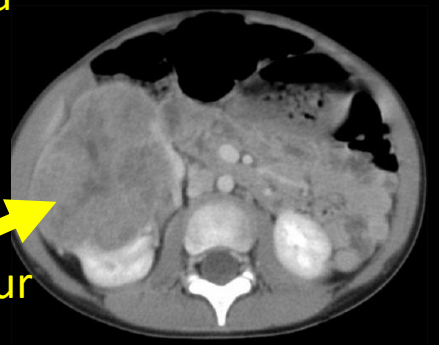
Osteosarcoma

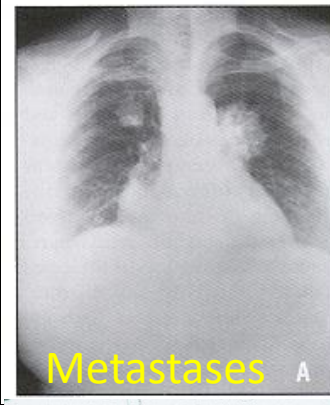


Cerebellar astrocytoma

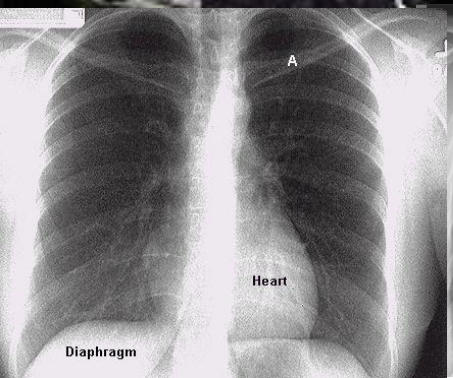


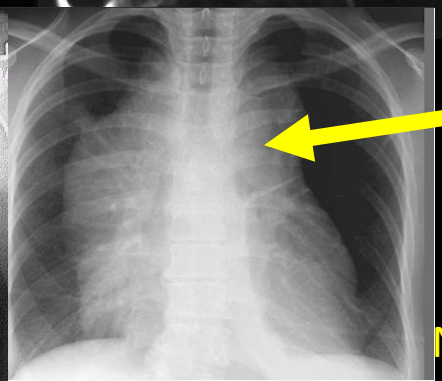
Wilms Tumour



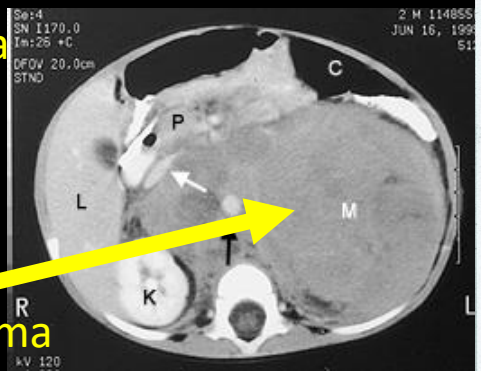


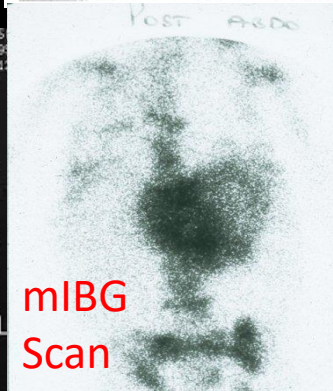
Lymphoma





Neuroblastoma





Evidence for a Developmental Hypothesis for Childhood Cancer

Scotting Perilongo & Walker
Nature Reviews Cancer (2005) 5; 481-488

- **Fidelity of Embryonic / Fetal / Immature**

Cell ⟶ **Tissue**
microenvironment ⟵

- **Teratocarcinomas**

Mimic many tissues. If transplanted back into growing embryos revert to normal cell behaviour
(Martin 1981, Andrews 2002)

A Developmental Hypothesis for Childhood Cancer

Scotting Perilongo & Walker Nature Reviews Cancer (2005) 5; 481-488

Children's Tumours

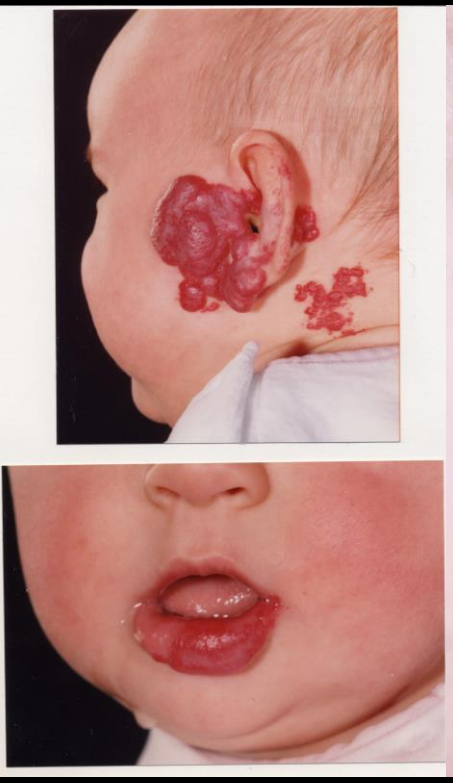
- **Differ in their frequency and tissues of origin,**
- **numbers and types of genetic mutations,**
- **sensitivity to chemotherapy**
- **arise within growing and developing organs, at a time when the tissue microenvironment promotes rapid growth development. The majority are sporadic. Although the more you look, the more predisposing mutations you find**

Normal developing tissues

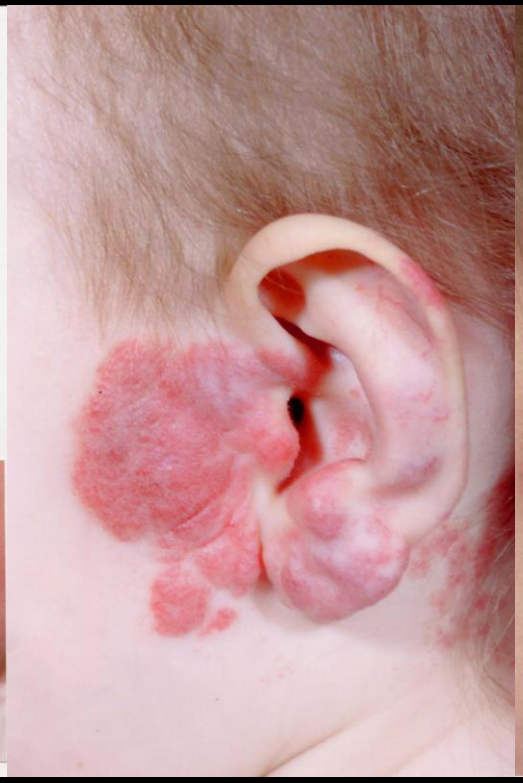
- **have biological characteristics that sustain growth and development: ie. sustained cell division, migration and resistance to cell death**
- **Tissue growth rates decelerate after birth through to end of adolescence.**

Clinical phenomena where tumour growth arrests or involutes

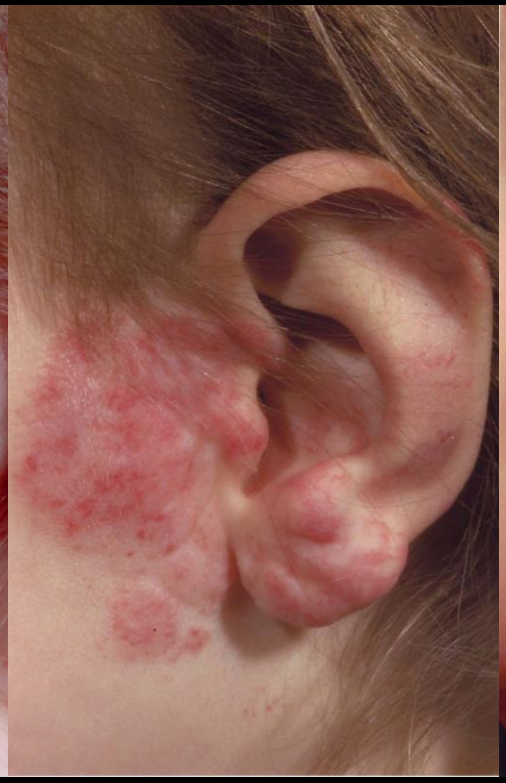
- **Congenital Haemangioma ***
- Congenital Cardiac Rhabdomyoma of Tuberous Sclerosis by 1-2 years
- Arrest of TAM in Downs by 6/12 - 1 year
- Neuroblastoma 4s involution by 6/12 – 1 yr
- Infantile fibrosarcoma, by 1 yr
- Arrested progression of infantile multi-system Langerhans Cell Histiocytosis by 3-5 yrs
- Arrested development / progression retinoblastoma by 5-6 yrs
- Arrested tumour growth pilocytic astrocytoma *



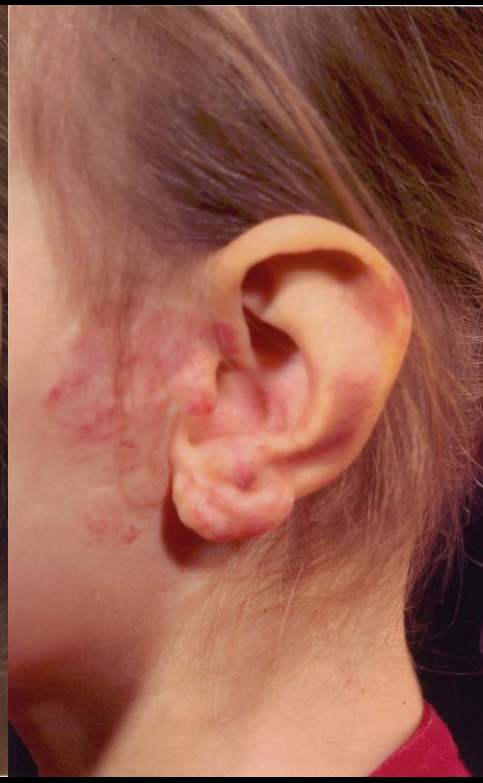
4 m



16m

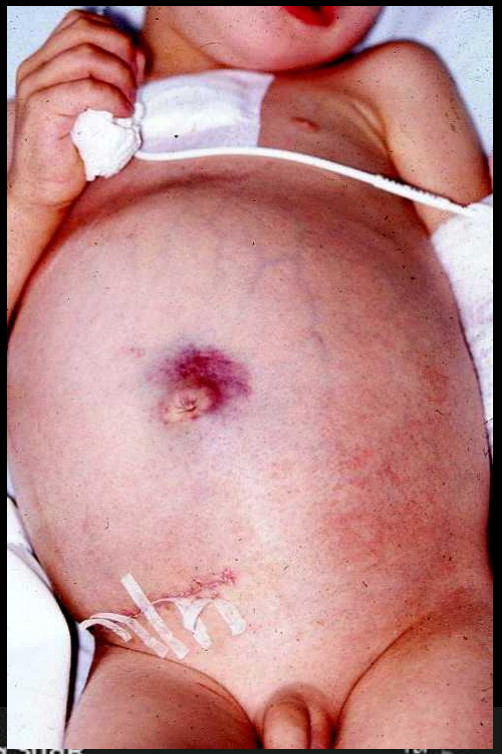


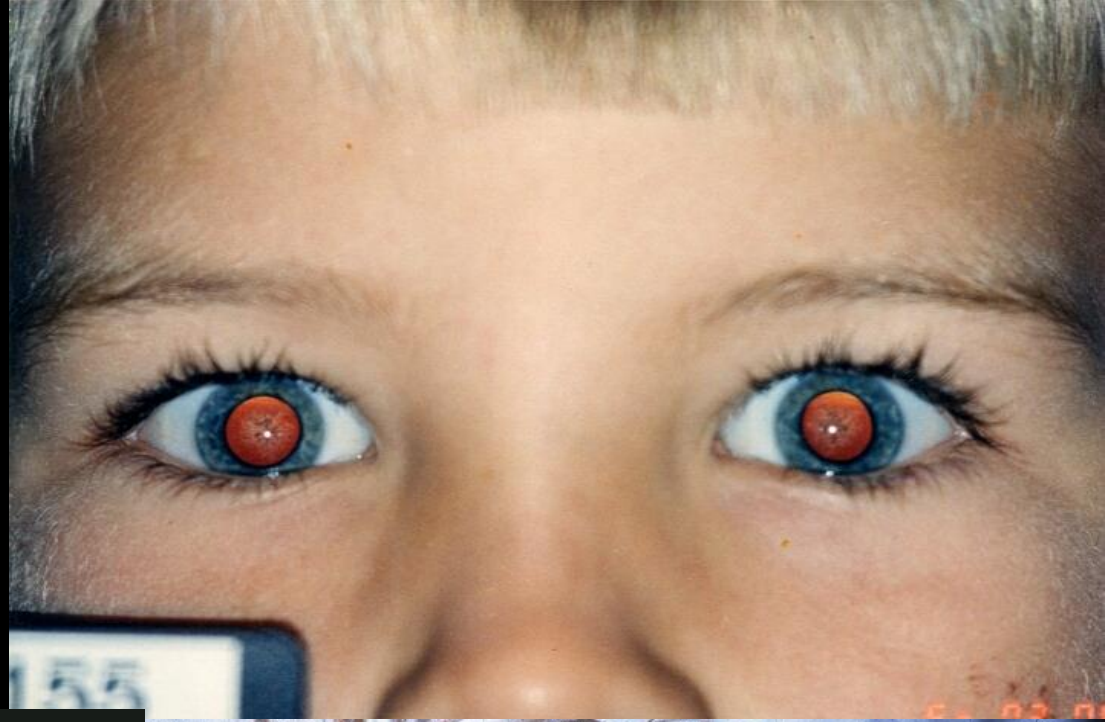
28m

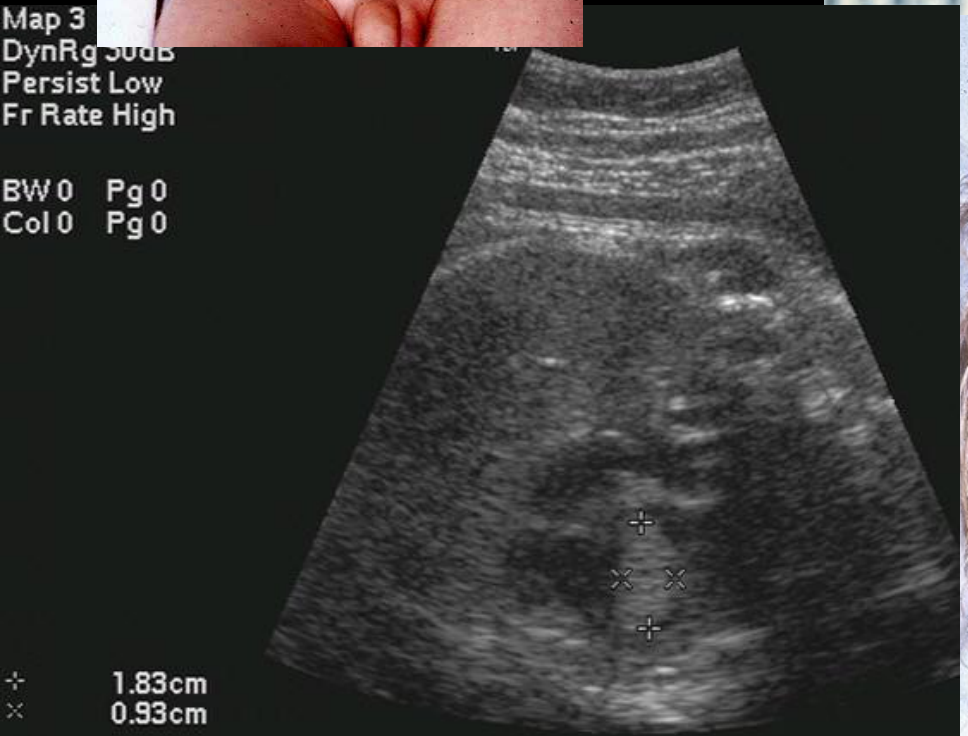


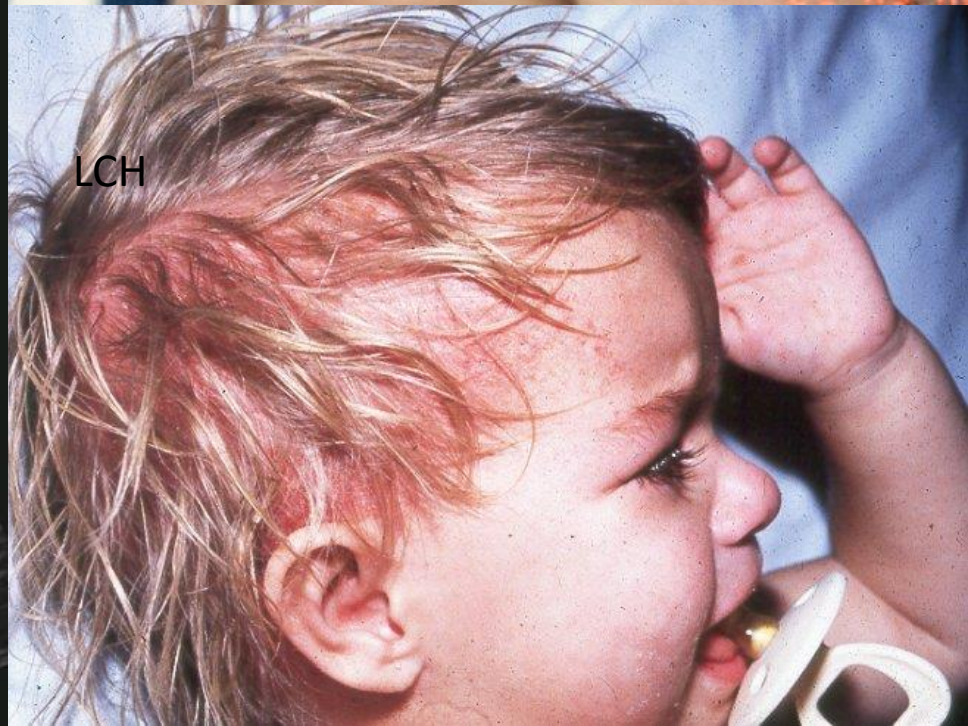
42m

Capillary Haemangioma

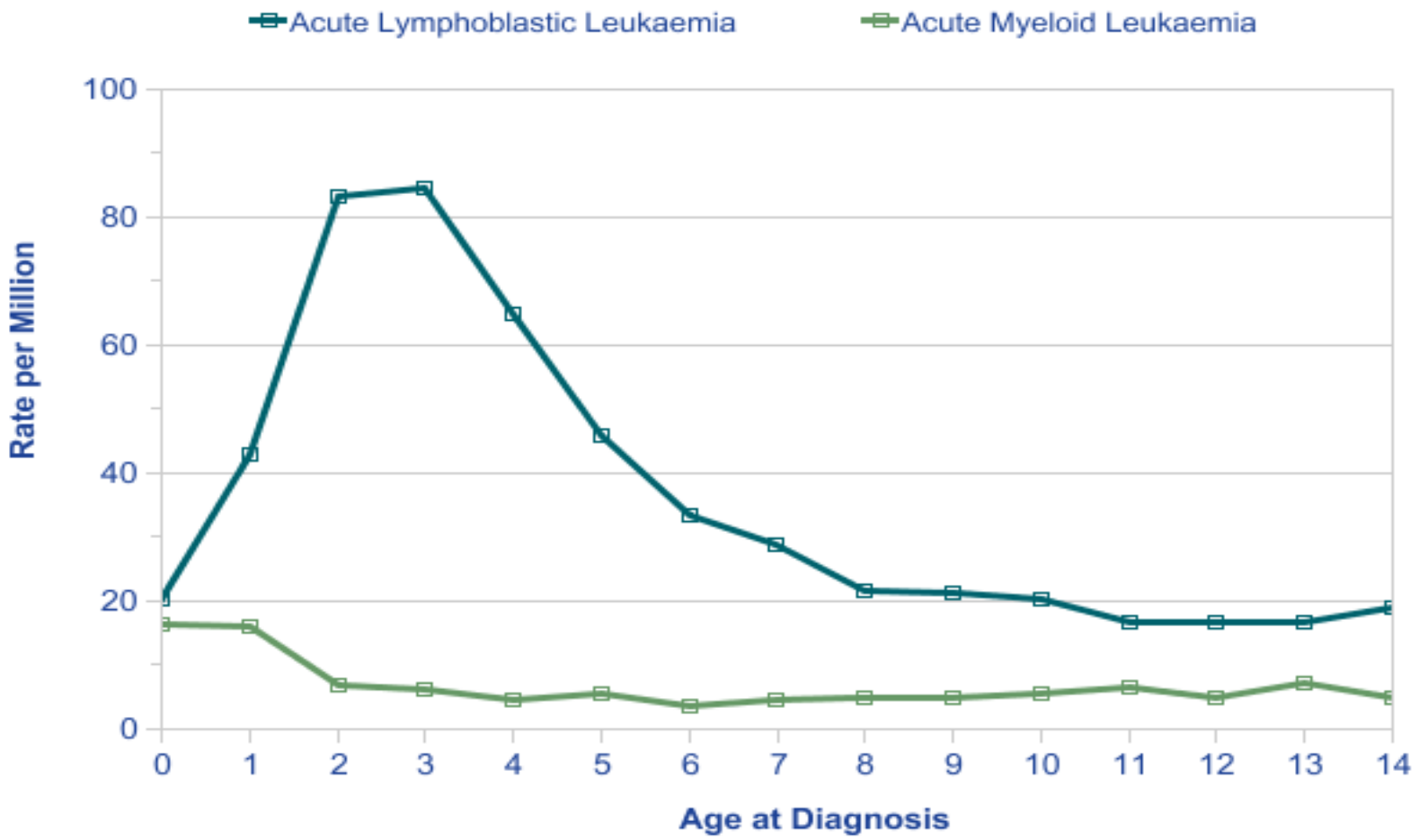





Map 3
DynRg 50dB
Persist Low
Fr Rate High
BW 0 Pg 0
Col 0 Pg 0
1.83cm
0.93cm


LCH

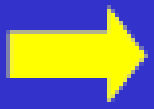
Leukaemias: 1996-2005
Incidence Rates per Million Population, Children (0-14), Great Britain



FREQUENCY AND RISK OF ACUTE LYMPHOBLASTIC LEUKAEMIA?

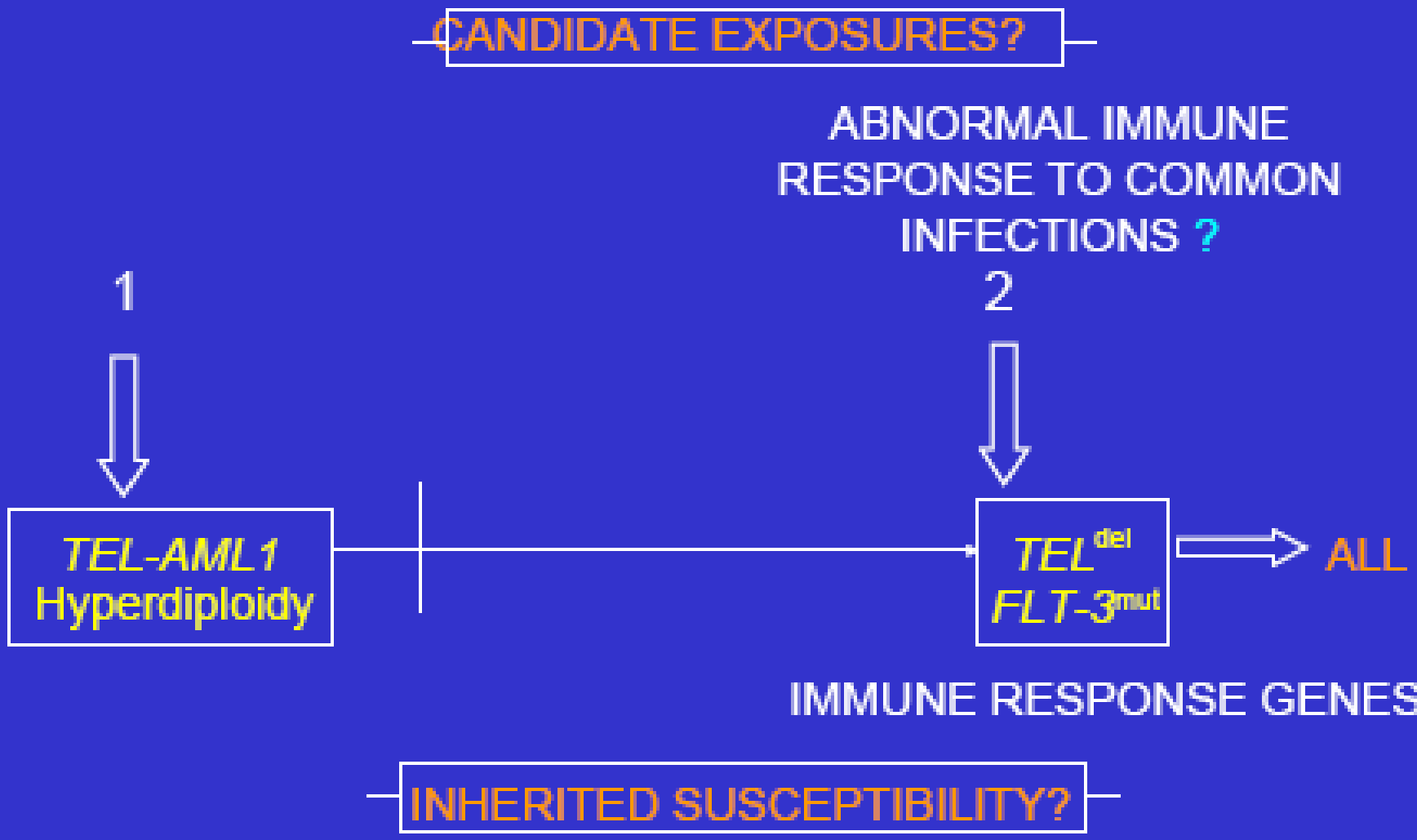
Risk of ALL	~ 1	in	2,000
Risk of ALL with *TEL-AML1*	~ 1	in	10,000
Risk of *TEL-AML1*$^{+}$ cord blood	~ 1	in	100

LEUKAEMIA IS INITIATED, PRE-NATALLY AT ~100 x THE DISEASE RATE



POST-NATAL SECONDARY EVENTS ARE THE BOTTLENECK FOR LEUKAEMIA AETIOLOGY

A CAUSAL MECHANISM FOR CHILDHOOD LEUKAEMIA



Why do so many children get ALL

A higher risk of ALL in children living in more affluent areas, compared with the most deprived, has persisted in Great Britain over many decades, including in the latest analysis, with data on all children diagnosed in England & Wales up to 2005

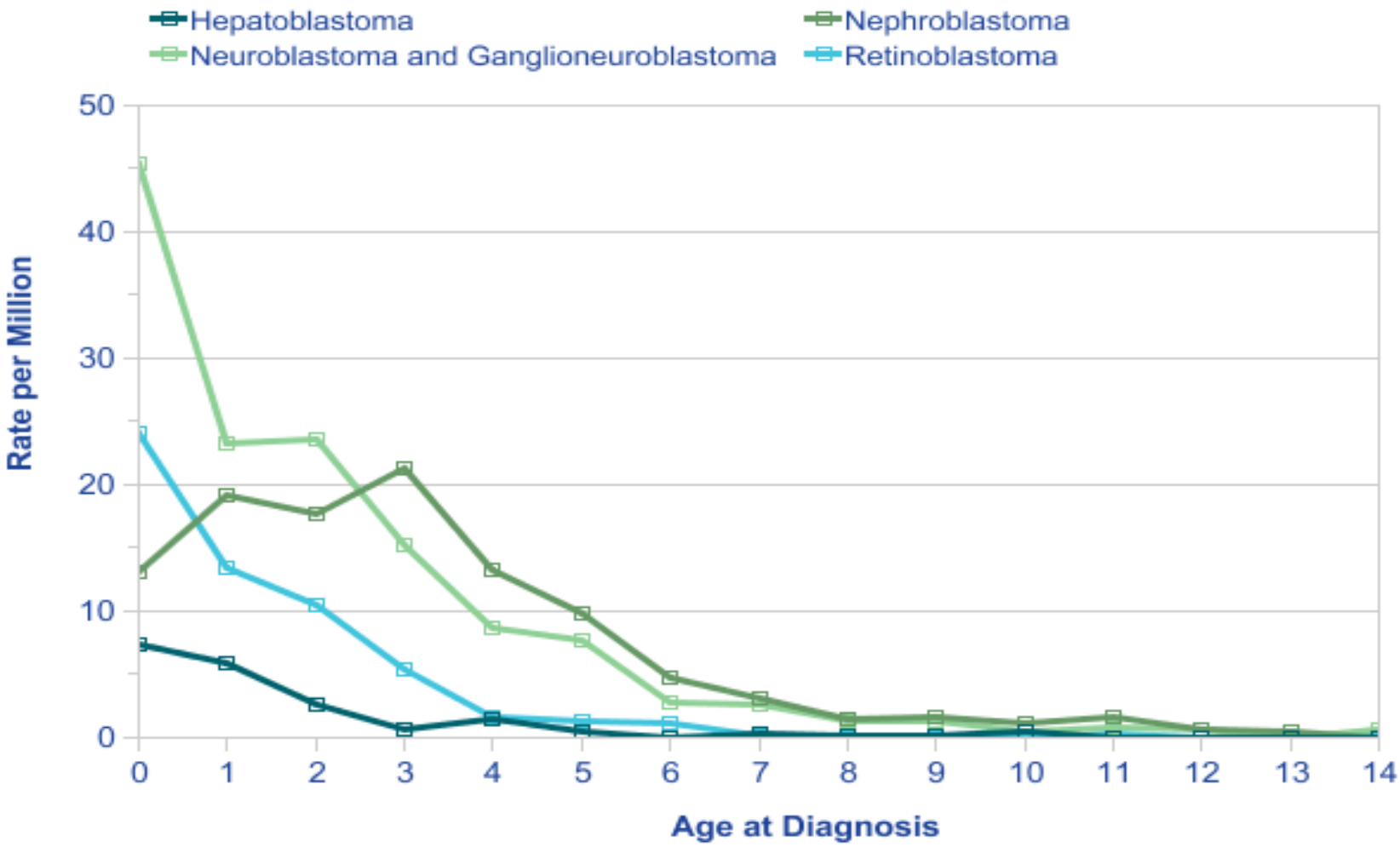
Hypotheses for aetiology of ALL

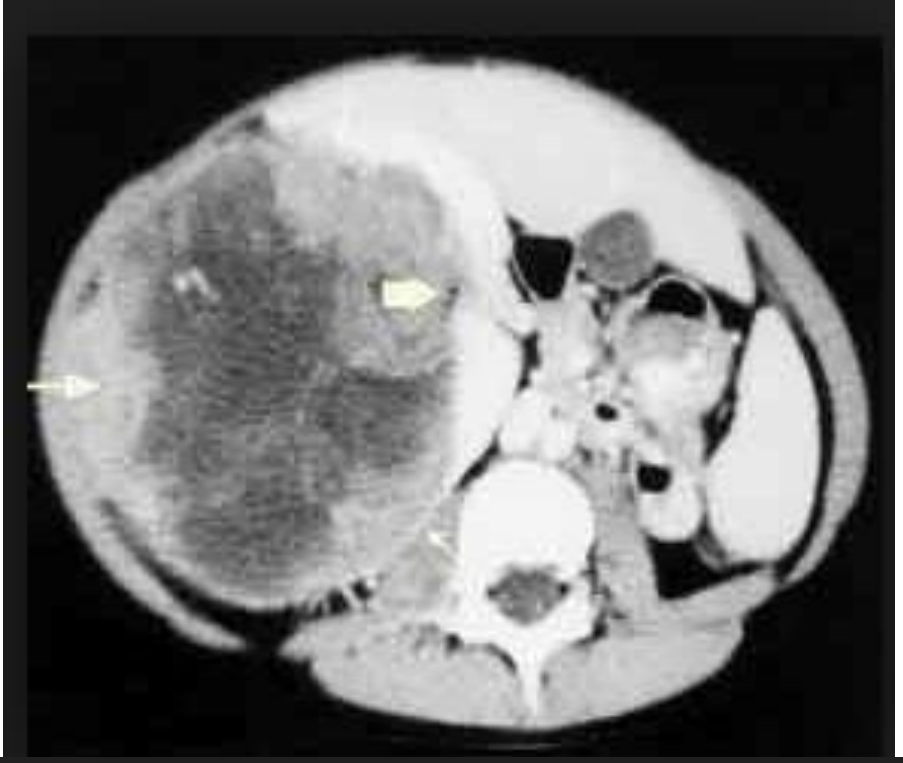
- **The ‘delayed infection’ hypothesis**

  some childhood leukaemia are the result of a rare response to an unidentified infection following geographic or social isolation early in life);27
- **The ‘population mixing’ hypothesis**

  leukaemia results from an unfamiliar or uncommon infection which the child is exposed to through new contact with people from different geographical areas

Embryonal Tumours: 1996-2005
Incidence Rates per Million Population, Children (0-14), Great Britain





Now account for < 30% of Wilms Tumour

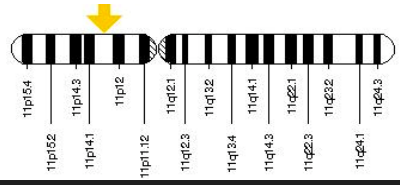
WT1

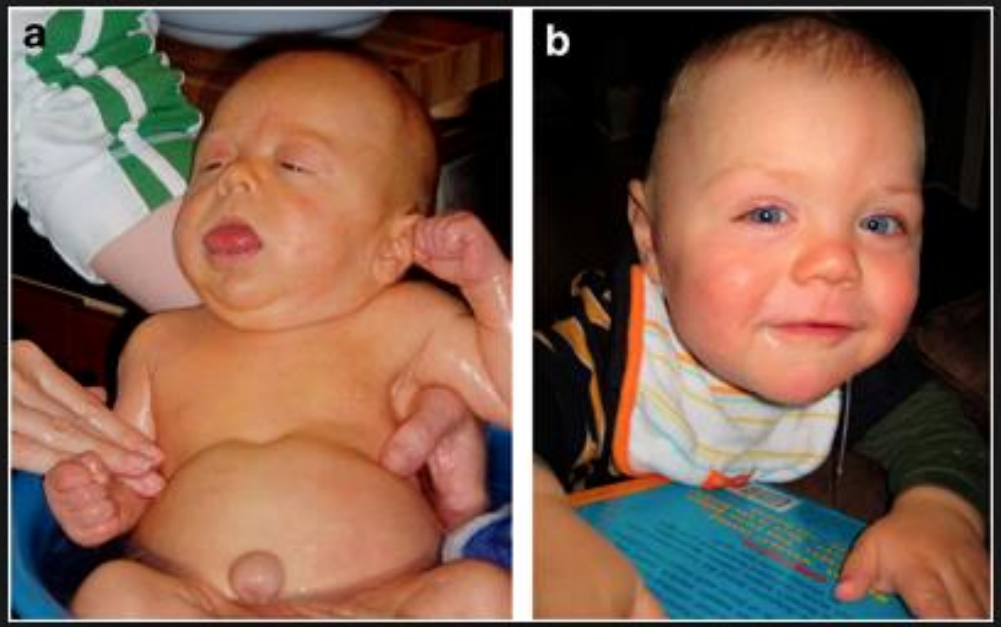
Frasier Syndrome

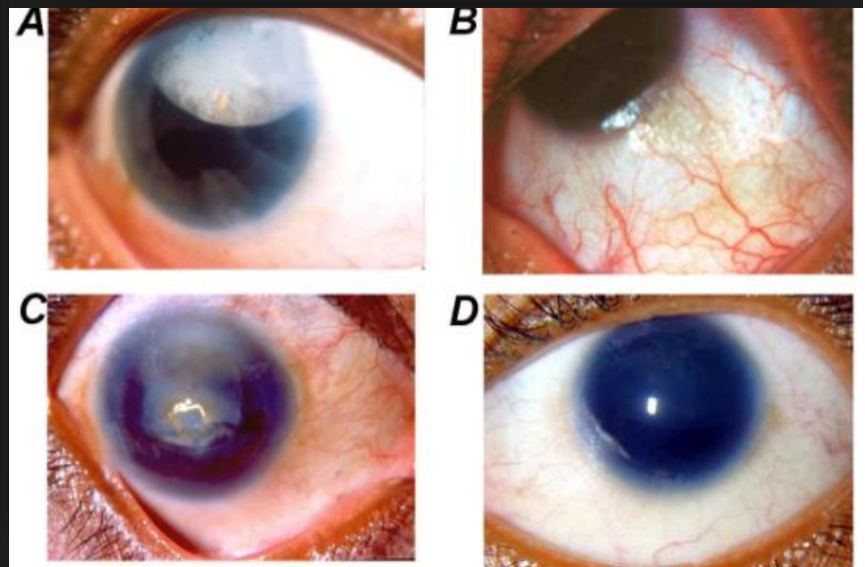
Denys Drash

WAGR

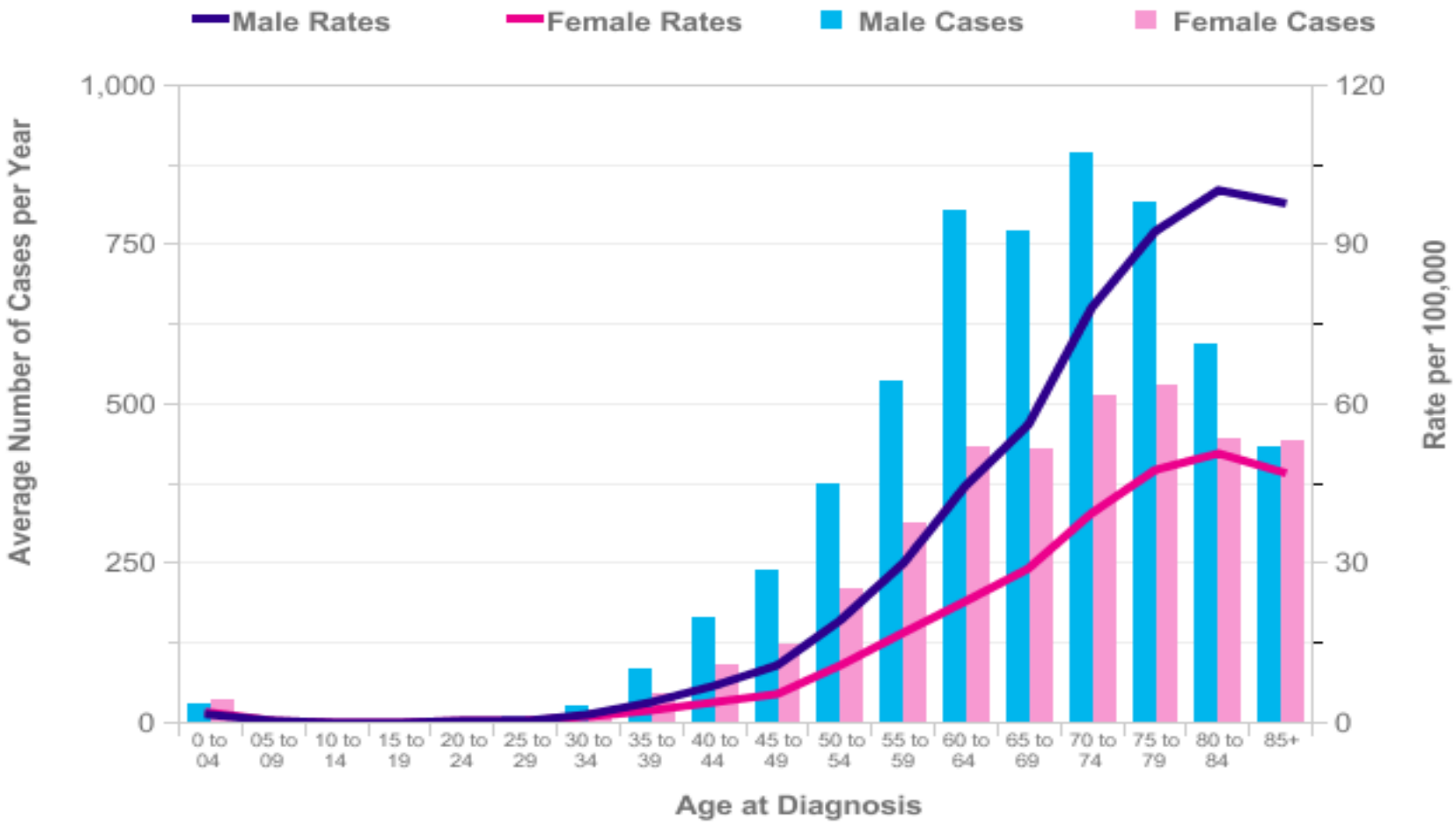
p53

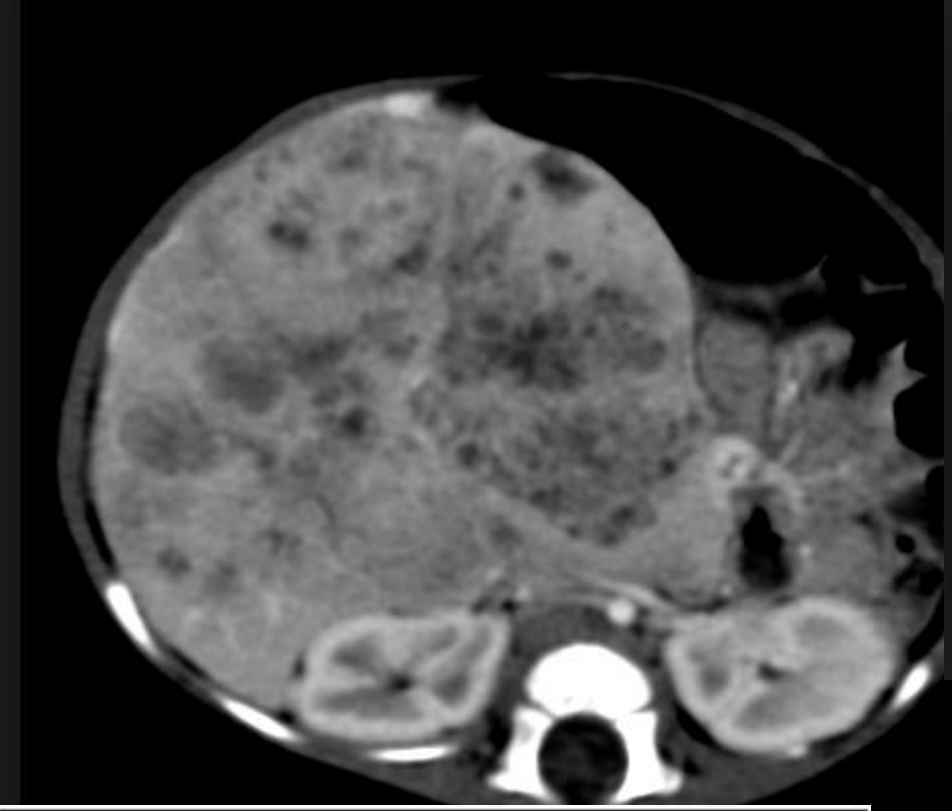


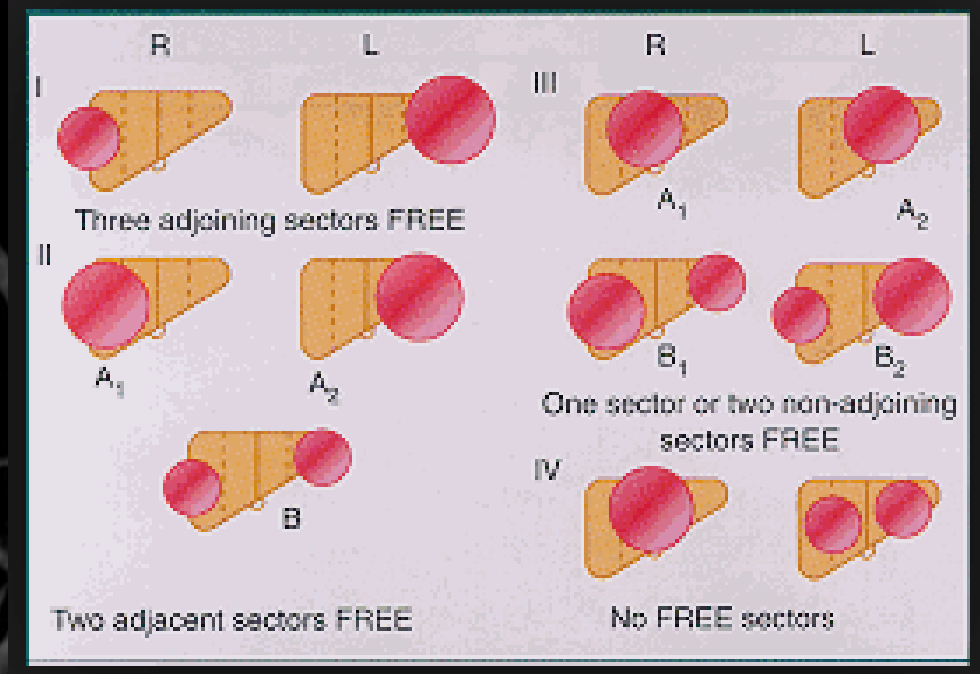


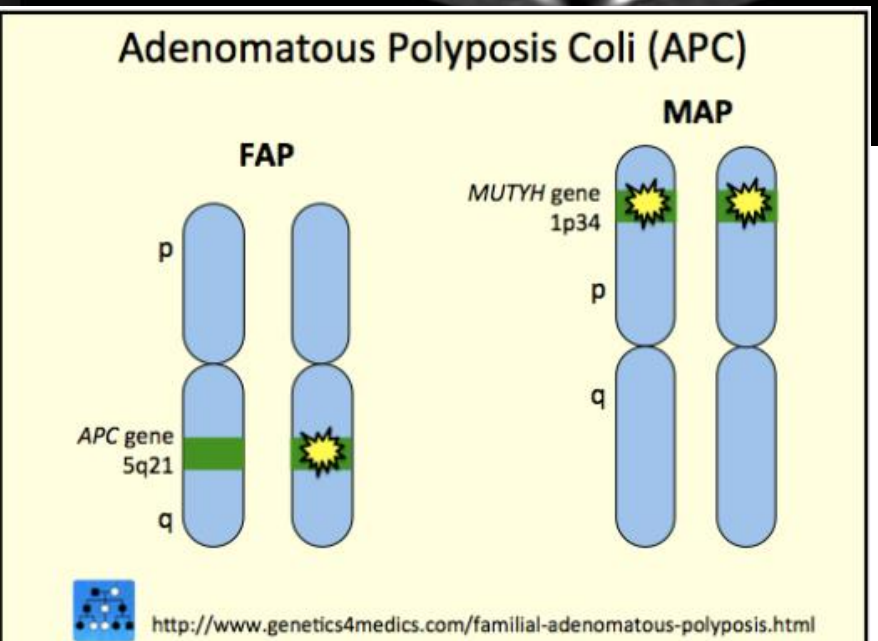


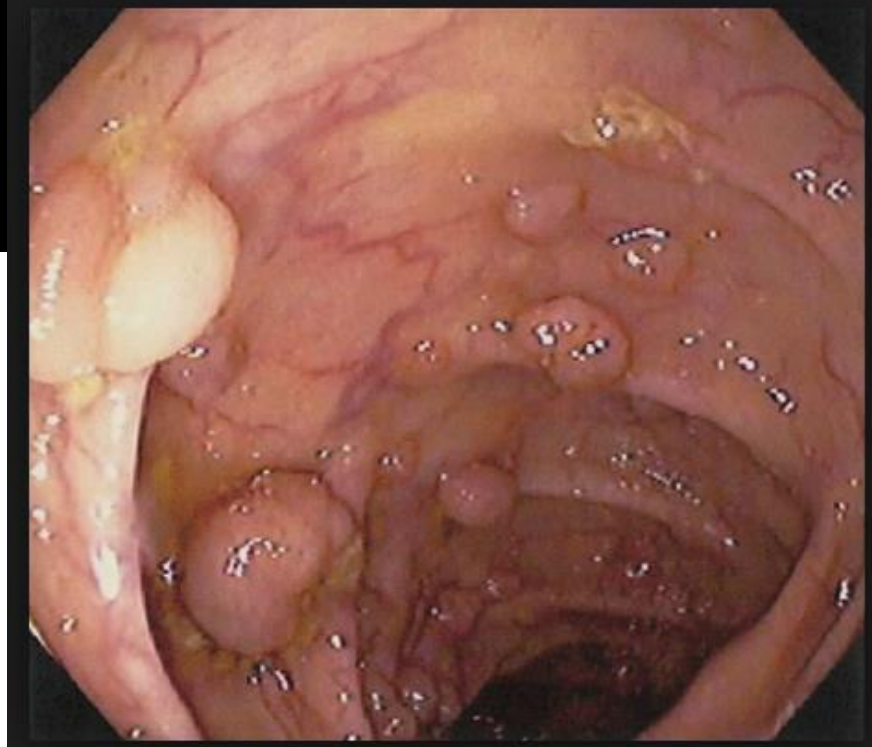
Kidney Cancer (C64-C66,C68): 2008-2010 Average Number of New Cases Per Year and Age-Specific Incidence Rates per 100,000 Population, UK



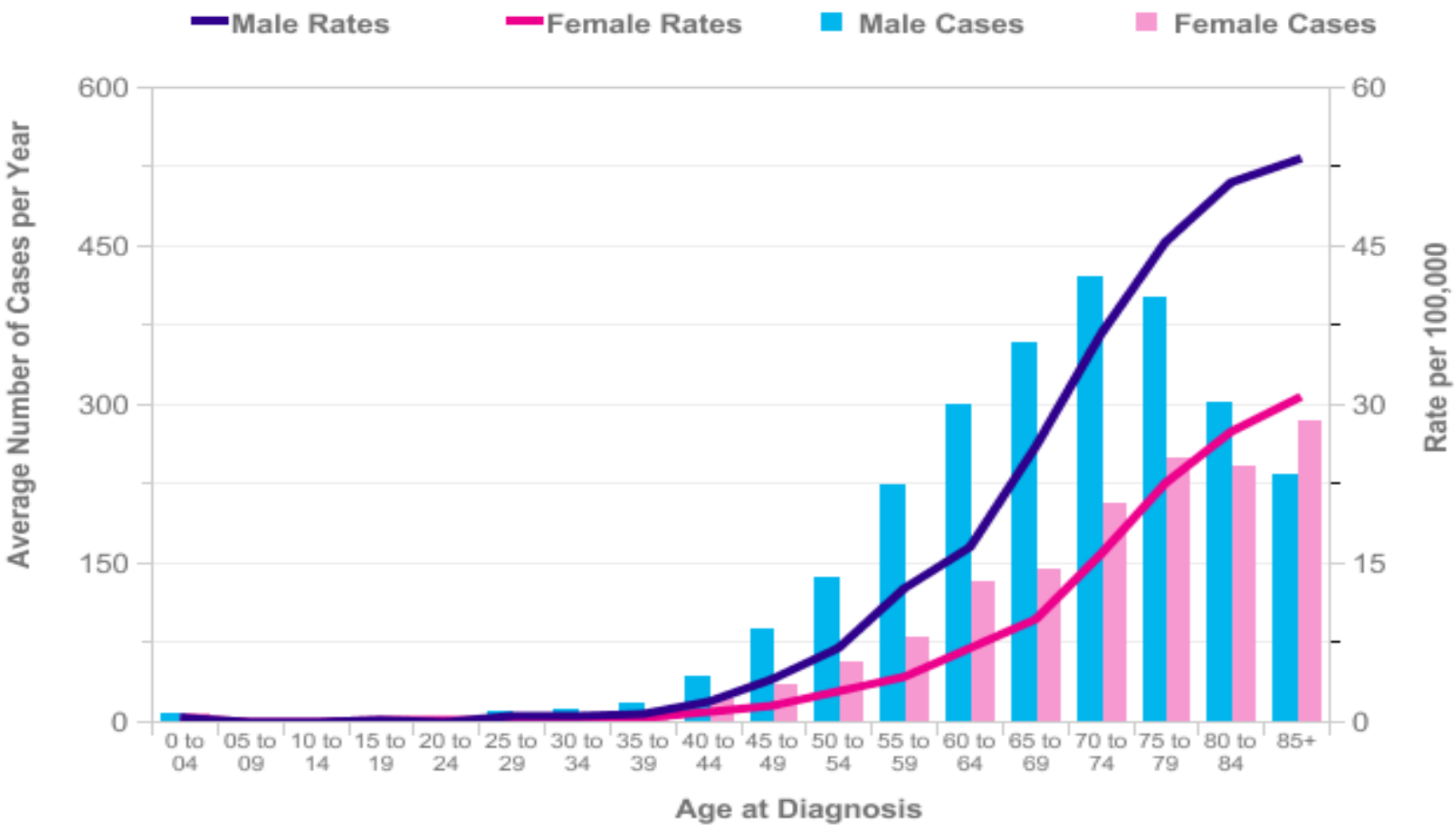


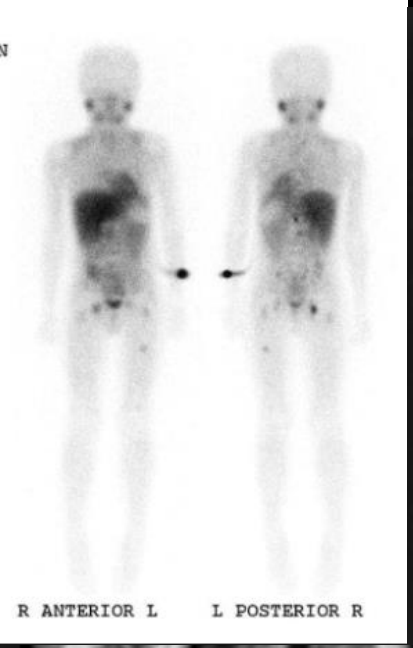

R
L
I
Three adjoining sectors FREE
II
A1
A2
B
Two adjacent sectors FREE
R
L
III
A1
A2
B1
B2
One sector or two non-adjoining sectors FREE
IV
No FREE sectors

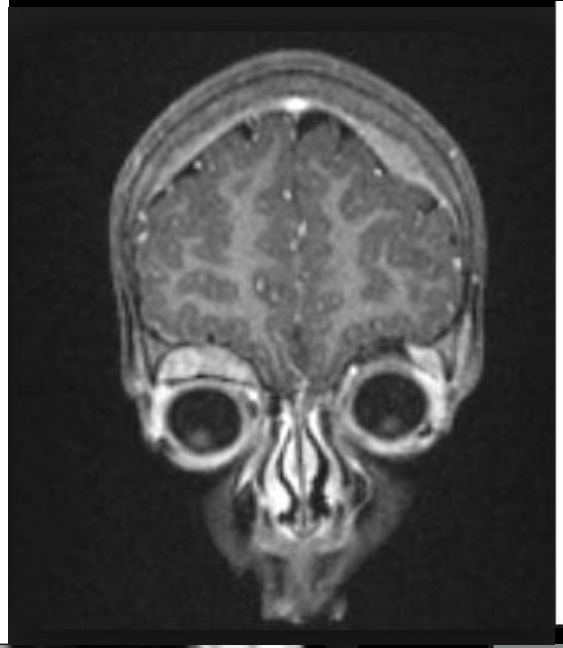

Adenomatous Polyposis Coli (APC)
FAP
p
APC gene
5q21
q
MAP
MUTYH gene
1p34
p
q
http://www.genetics4medics.com/familial-adenomatous-polyposis.html

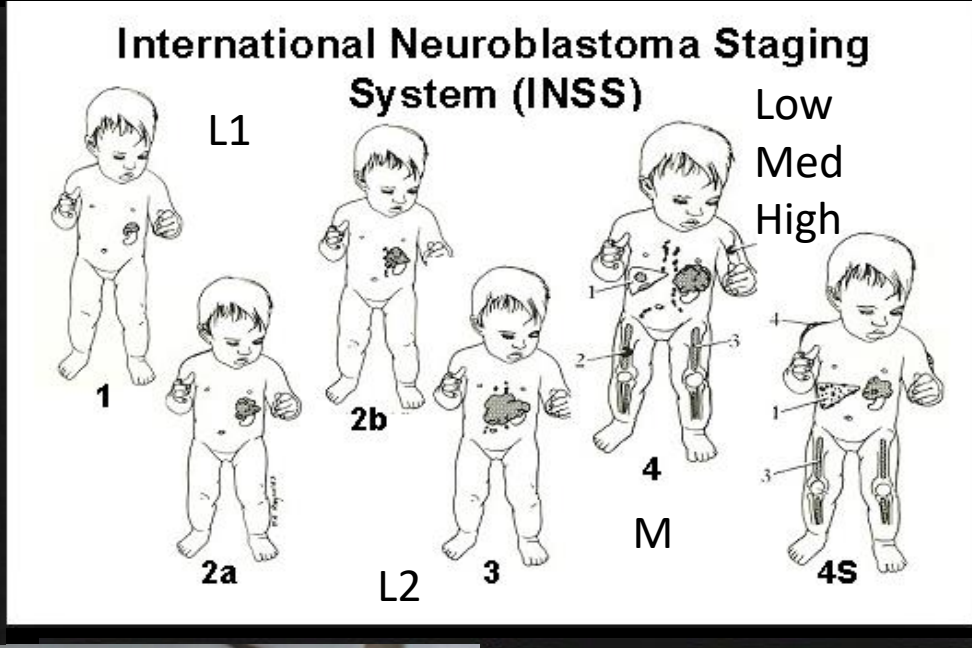


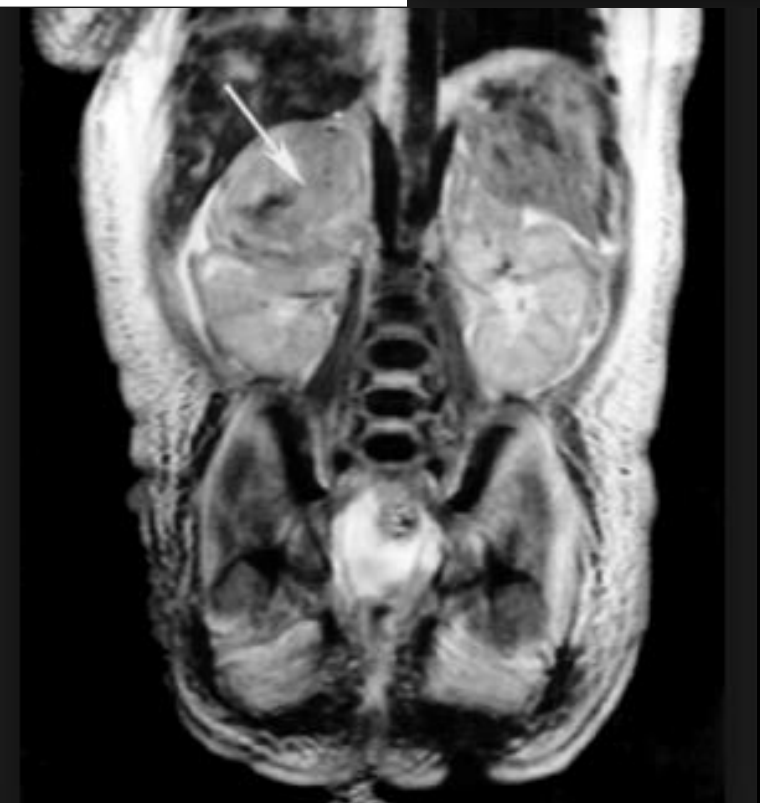
Liver Cancer (C22): 2008-2010
Average Number of New Cases Per Year and Age-Specific Incidence Rates per 100,000 Population, UK

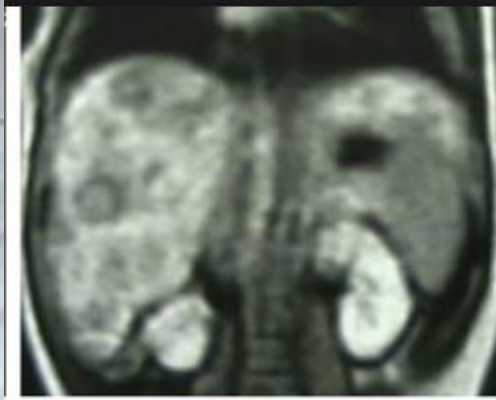


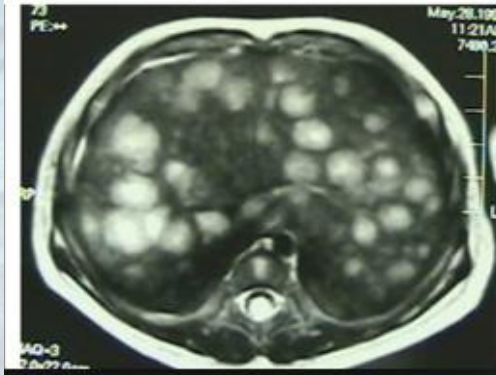

R ANTERIOR L
L POSTERIOR R

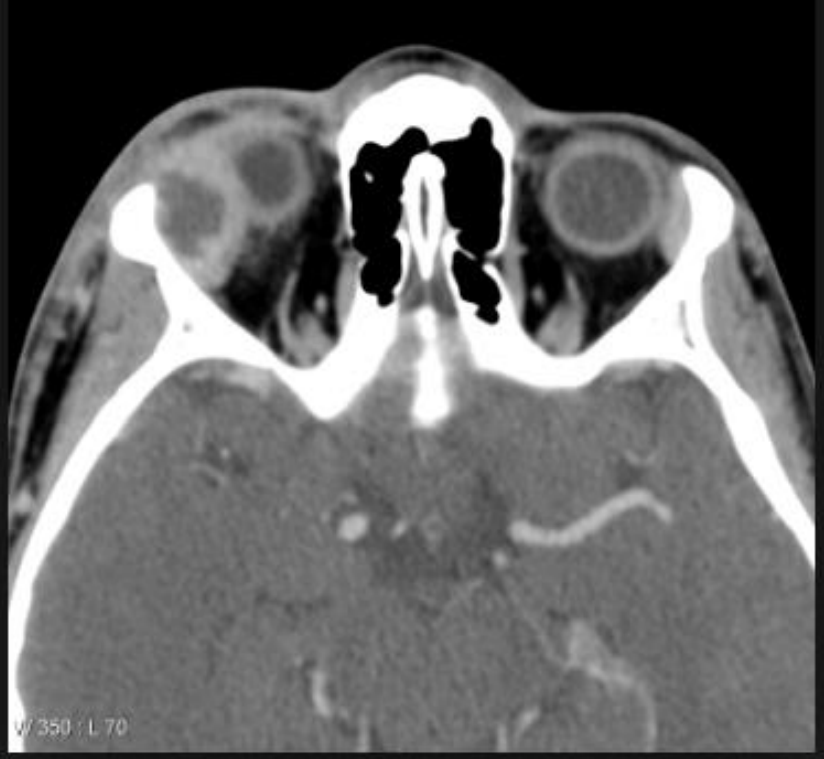


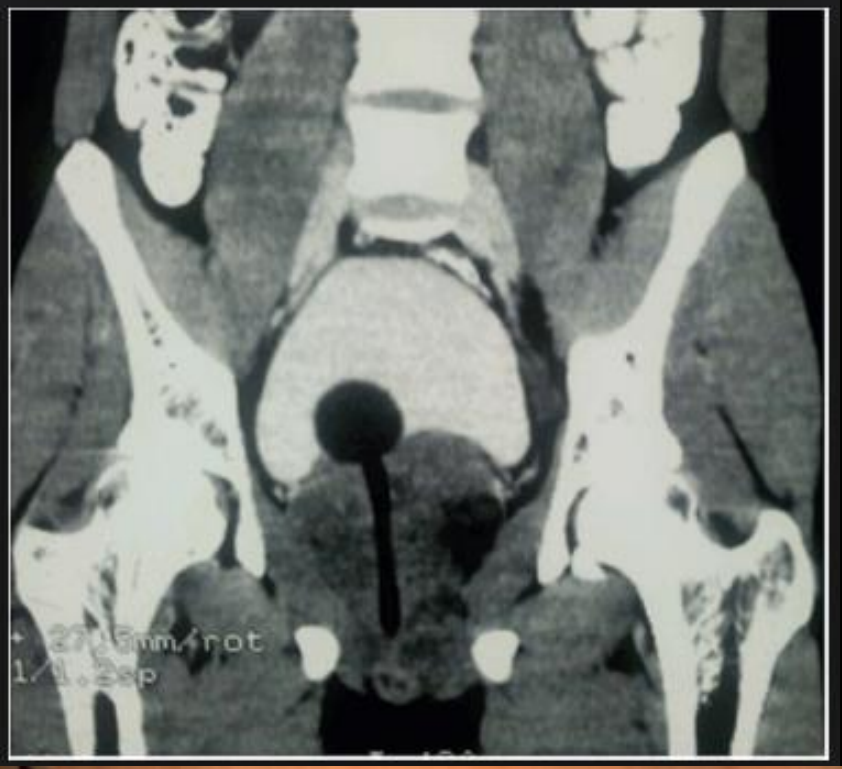

International Neuroblastoma Staging System (INSS)
L1
1
2a
2b
3
4
4S
L2
M
Low
Med
High

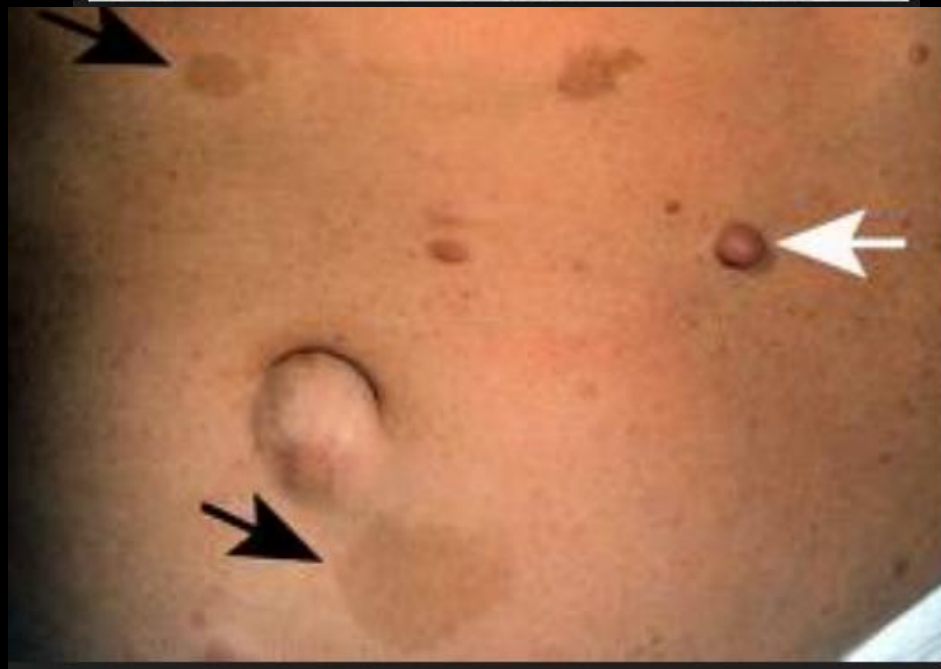




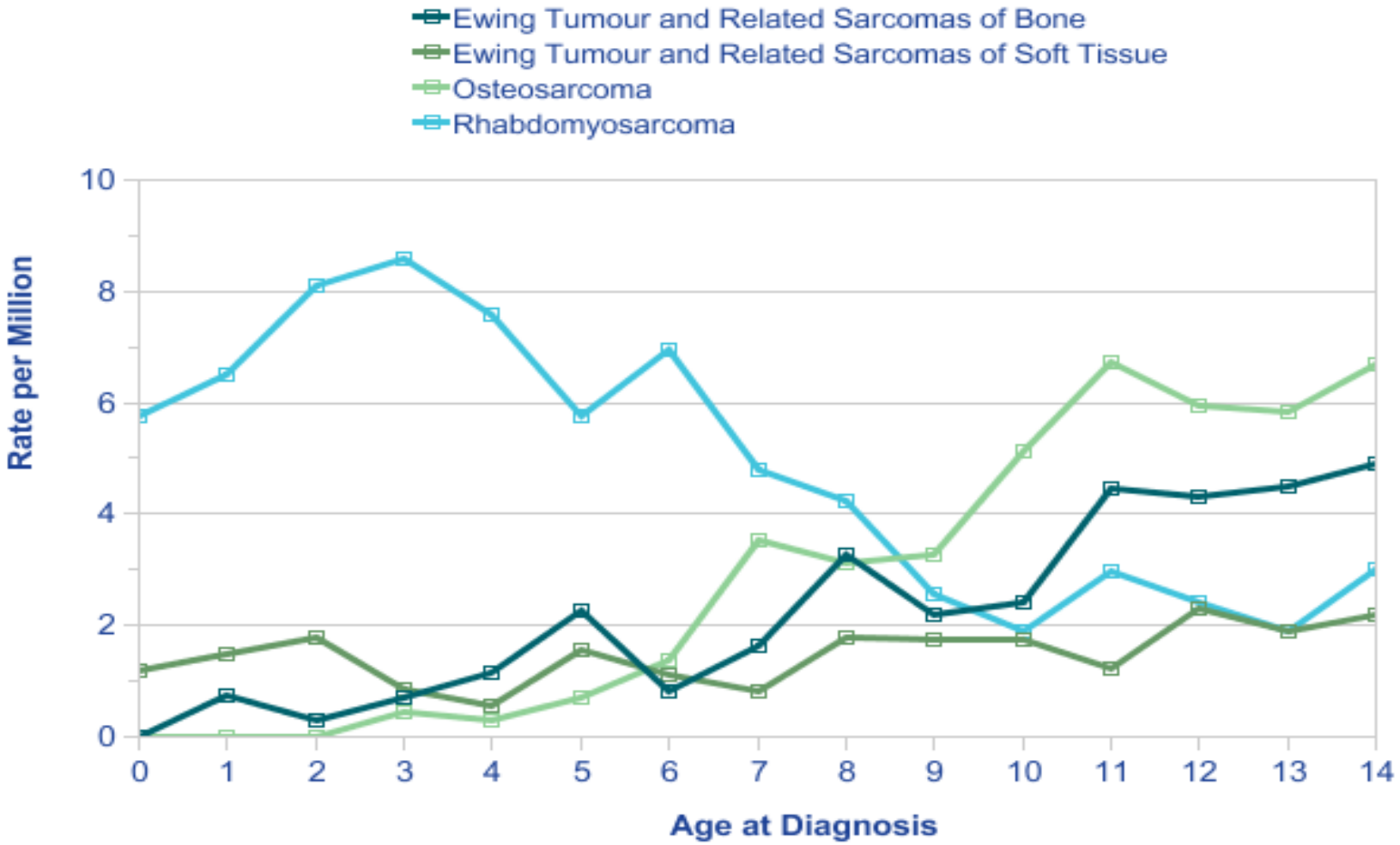



W 350 / L 70

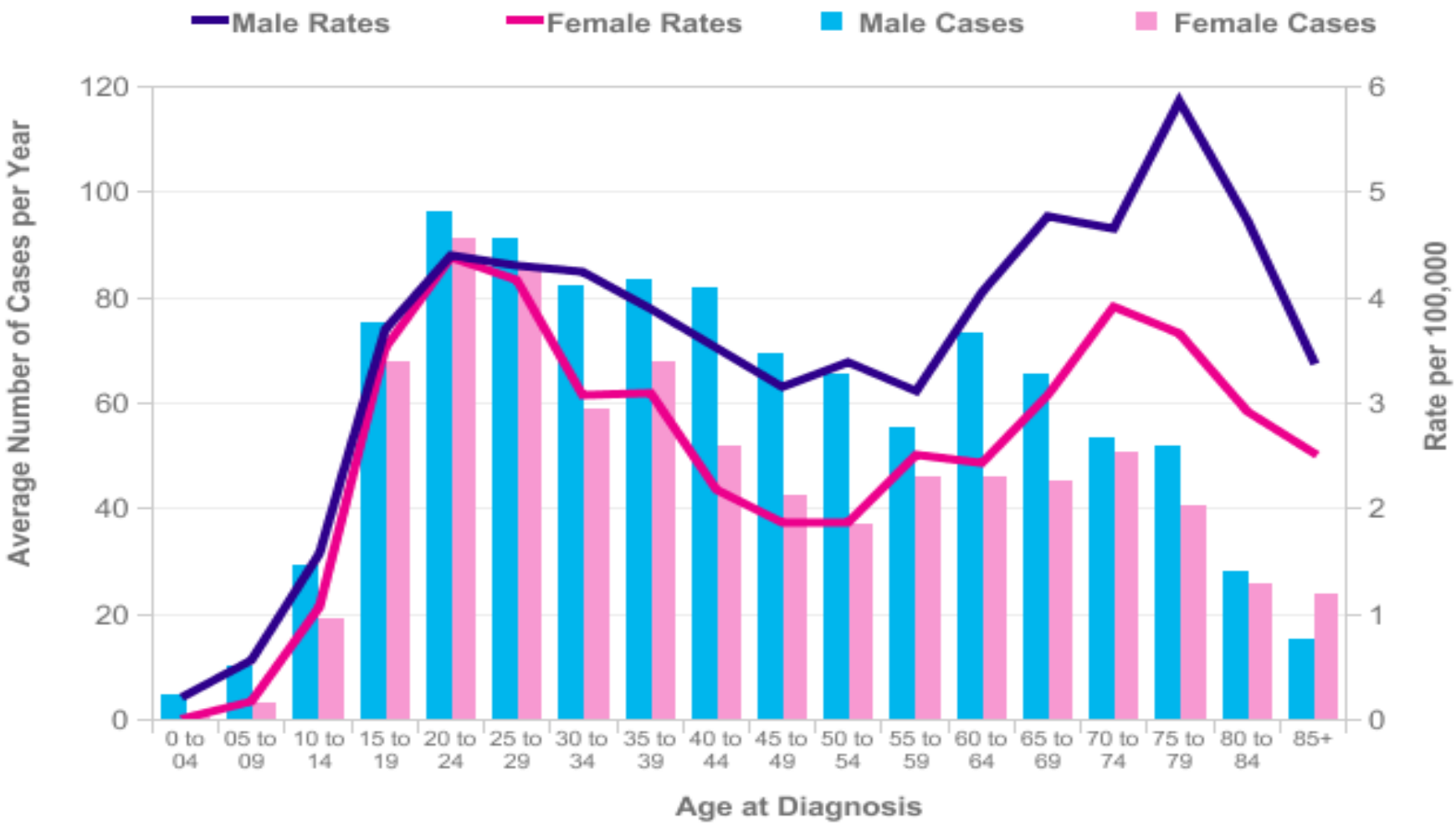




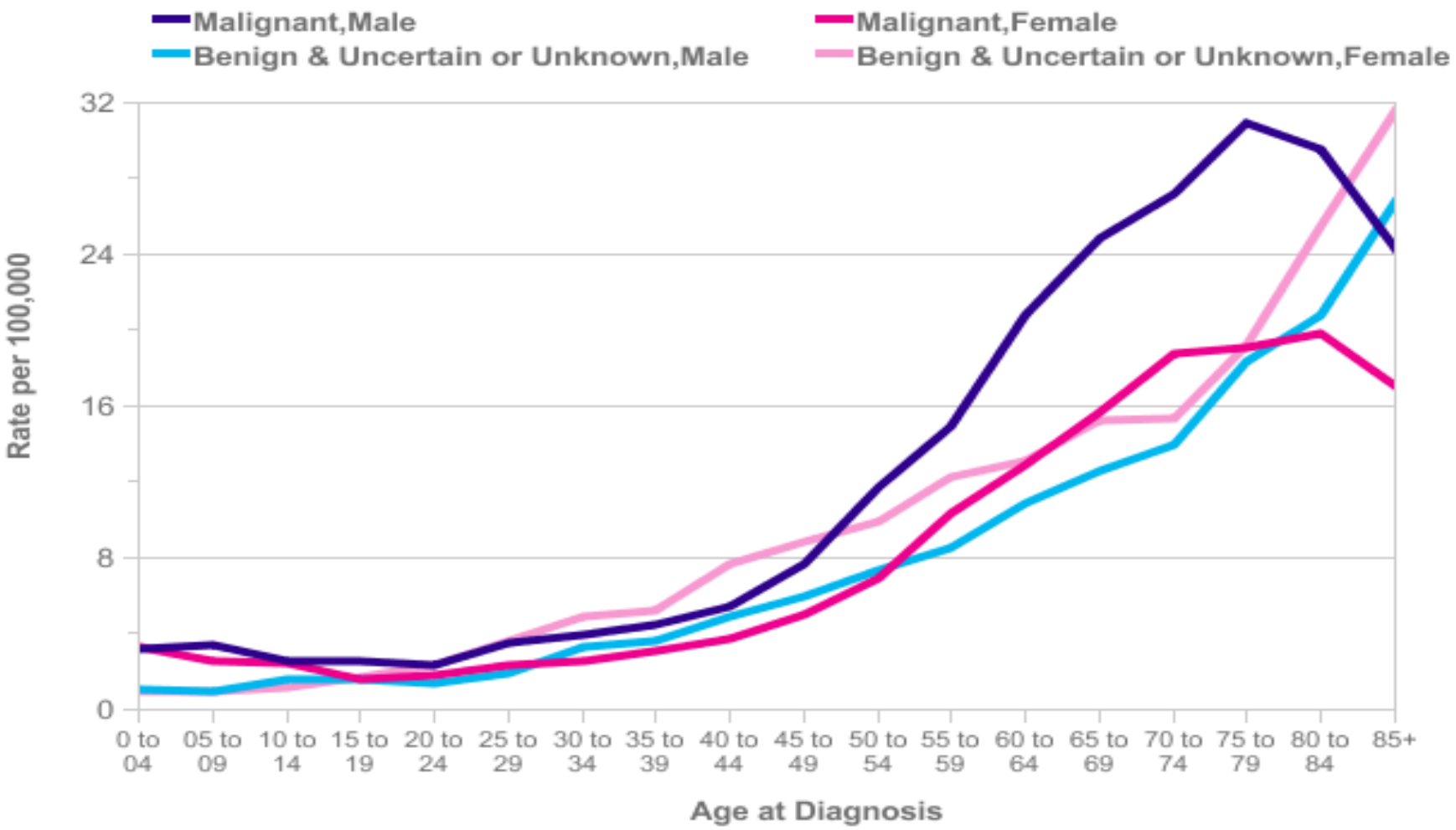
Bone and Soft Tissue Sarcomas: 1996-2005
Incidence Rates per Million Population, Children (0-14), Great Britain



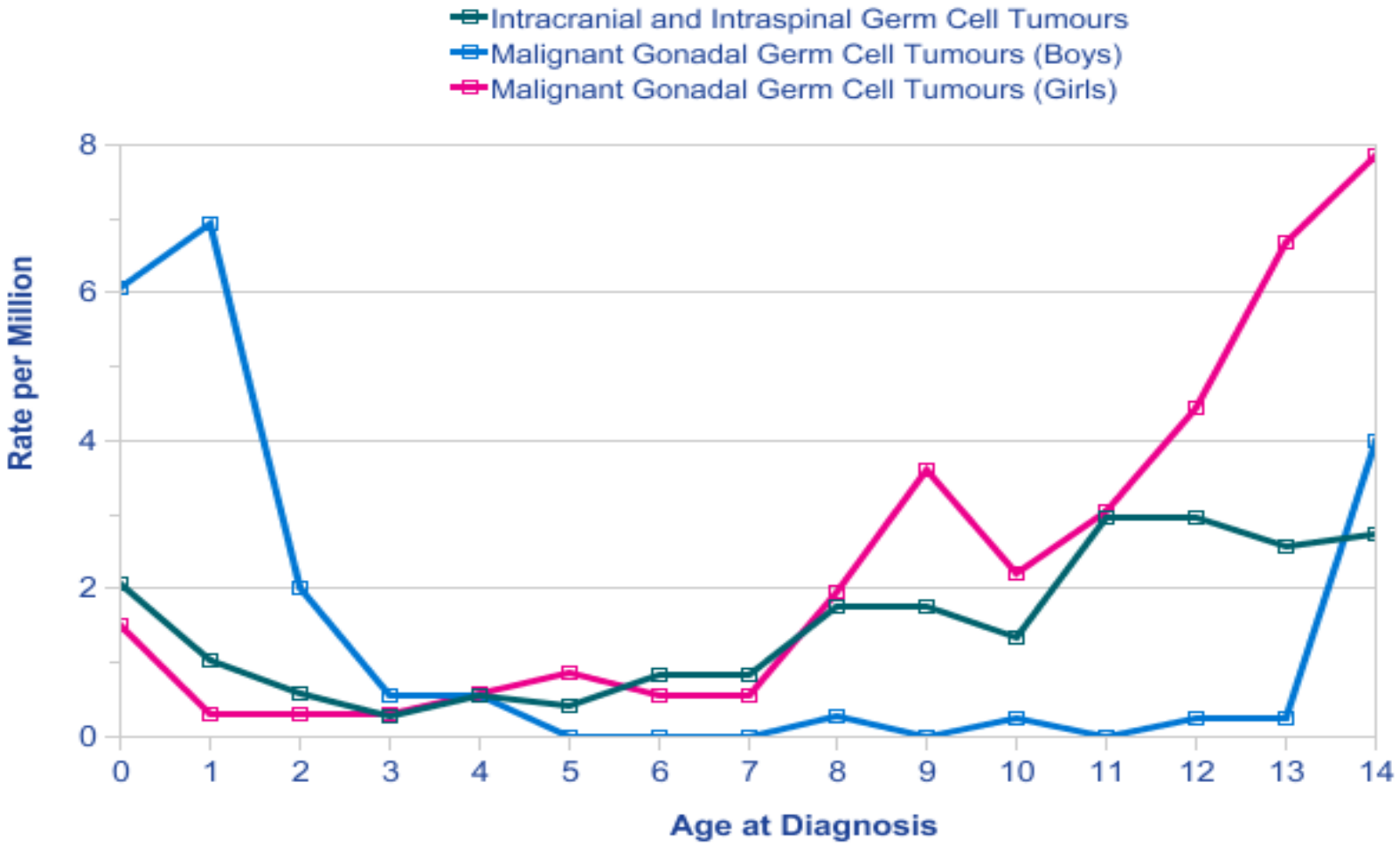
Hodgkin Lymphoma (C81): 2008-2010
Average Number of New Cases Per Year and Age-Specific Incidence Rates per 100,000 Population, UK



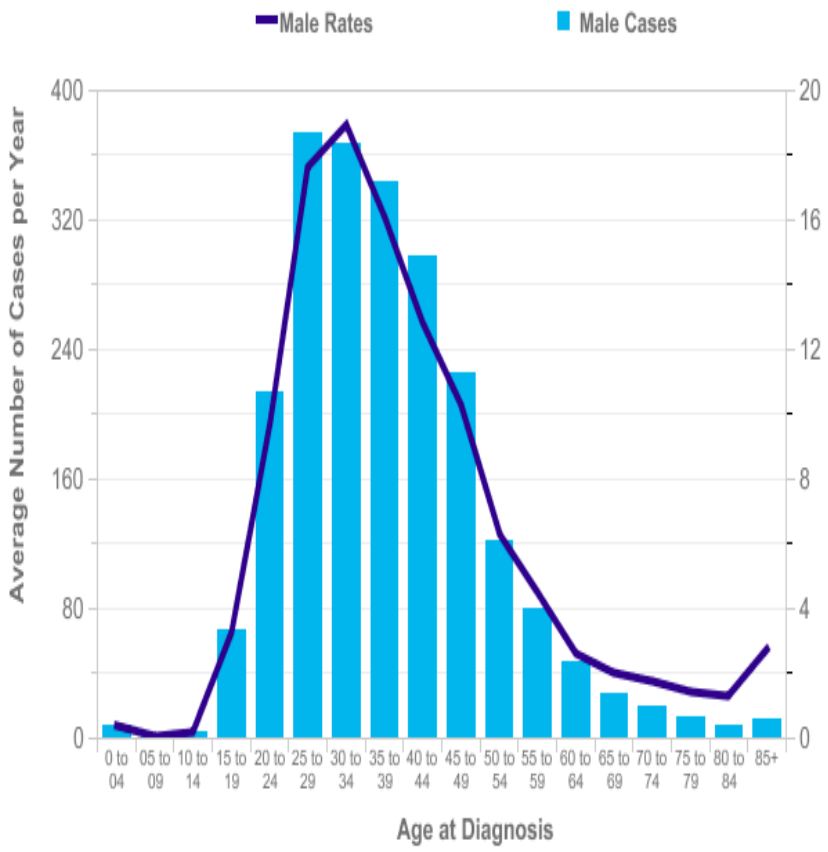
Brain CNS and other intracranial tumours Age-Specific Incidence Rates per 100,000 Population, UK

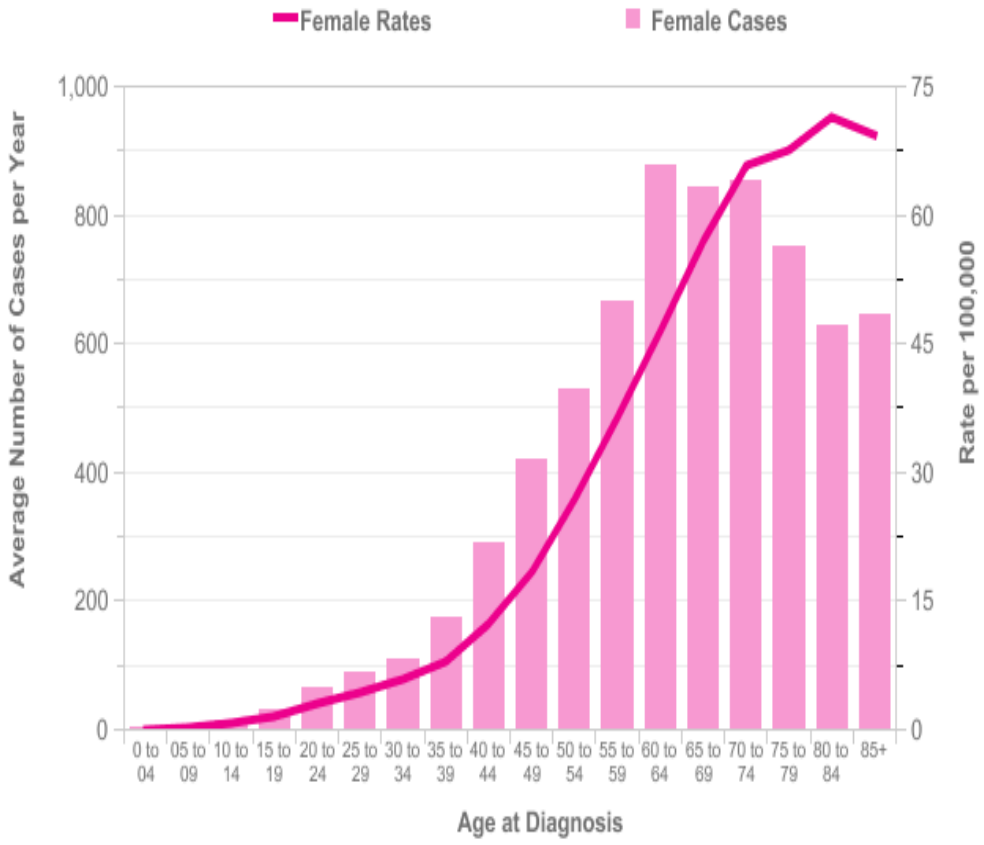


Gonadal and Germ Cell Tumours: 1996-2005 Incidence Rates per Million Population, Children (0-14), Great Britain



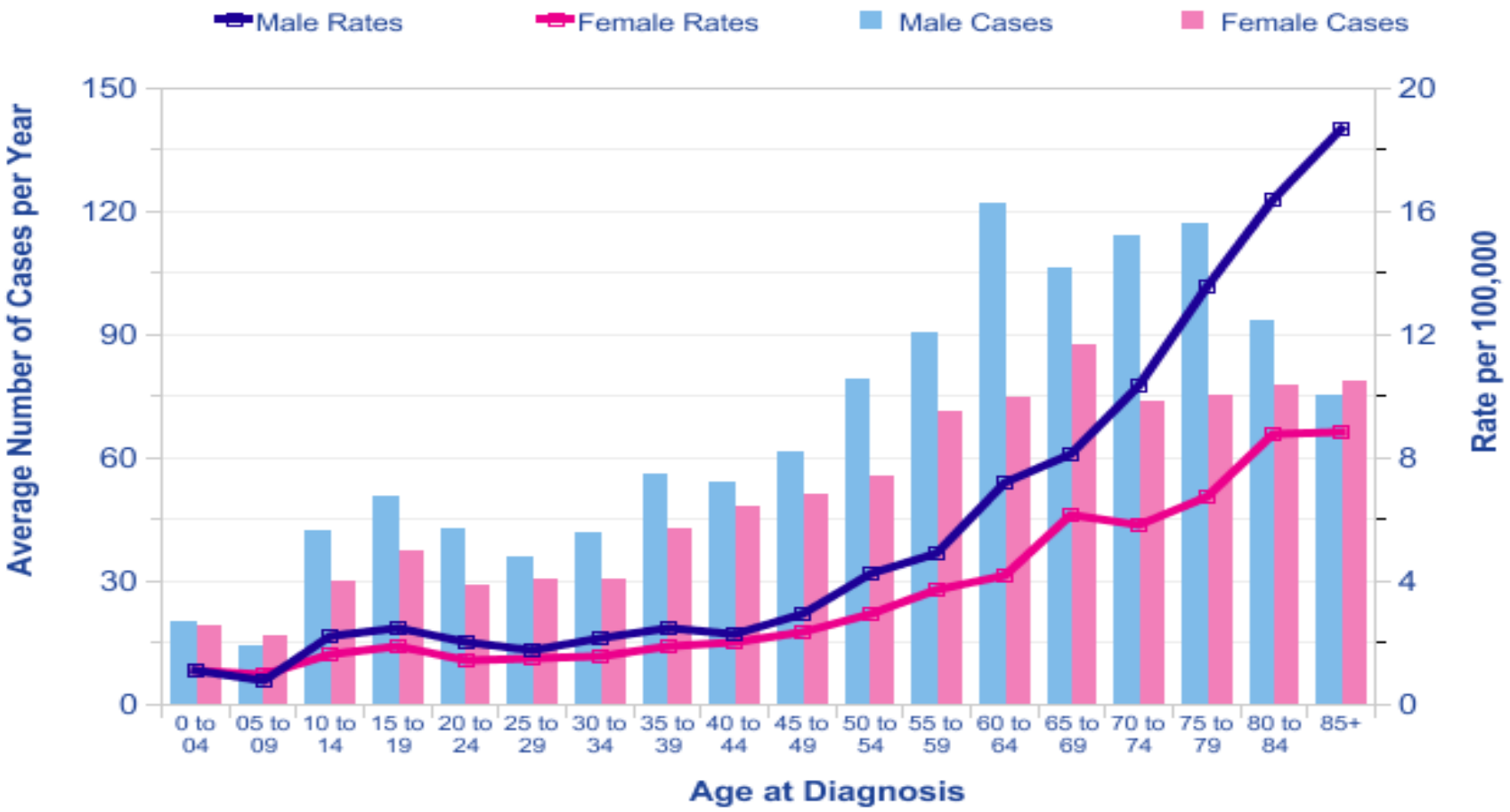
Testicular and Ovarian



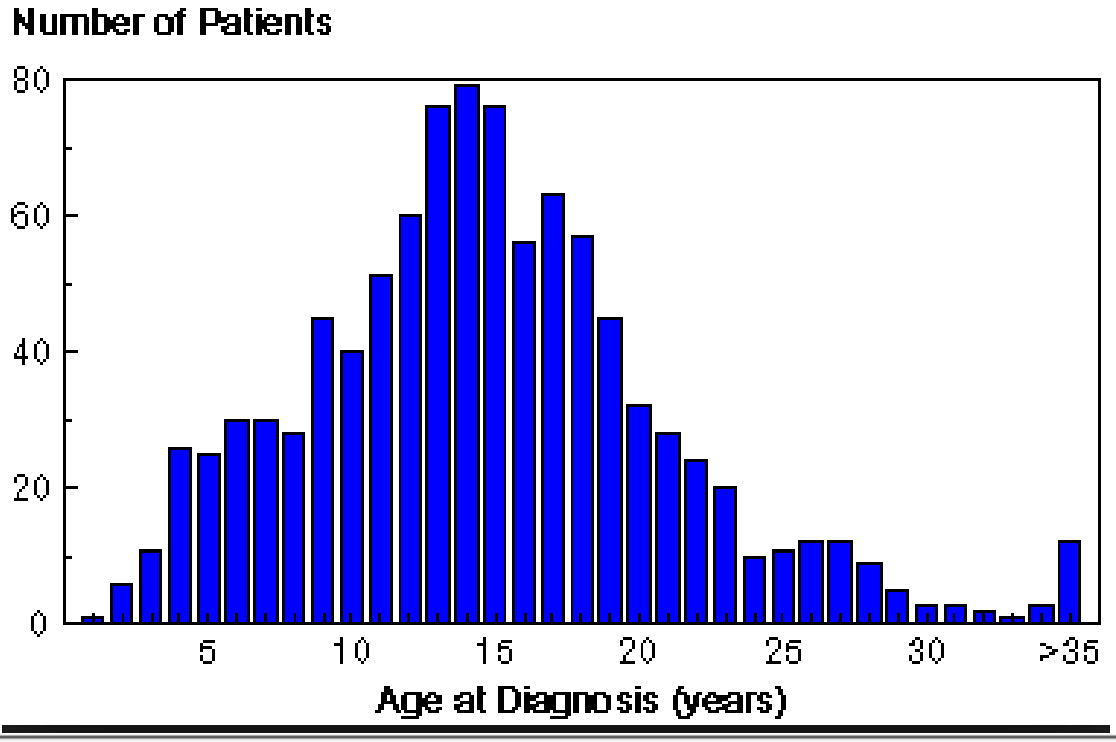


Bone and Connective Tissue (C40-C41,C47,C49): 2006-2008

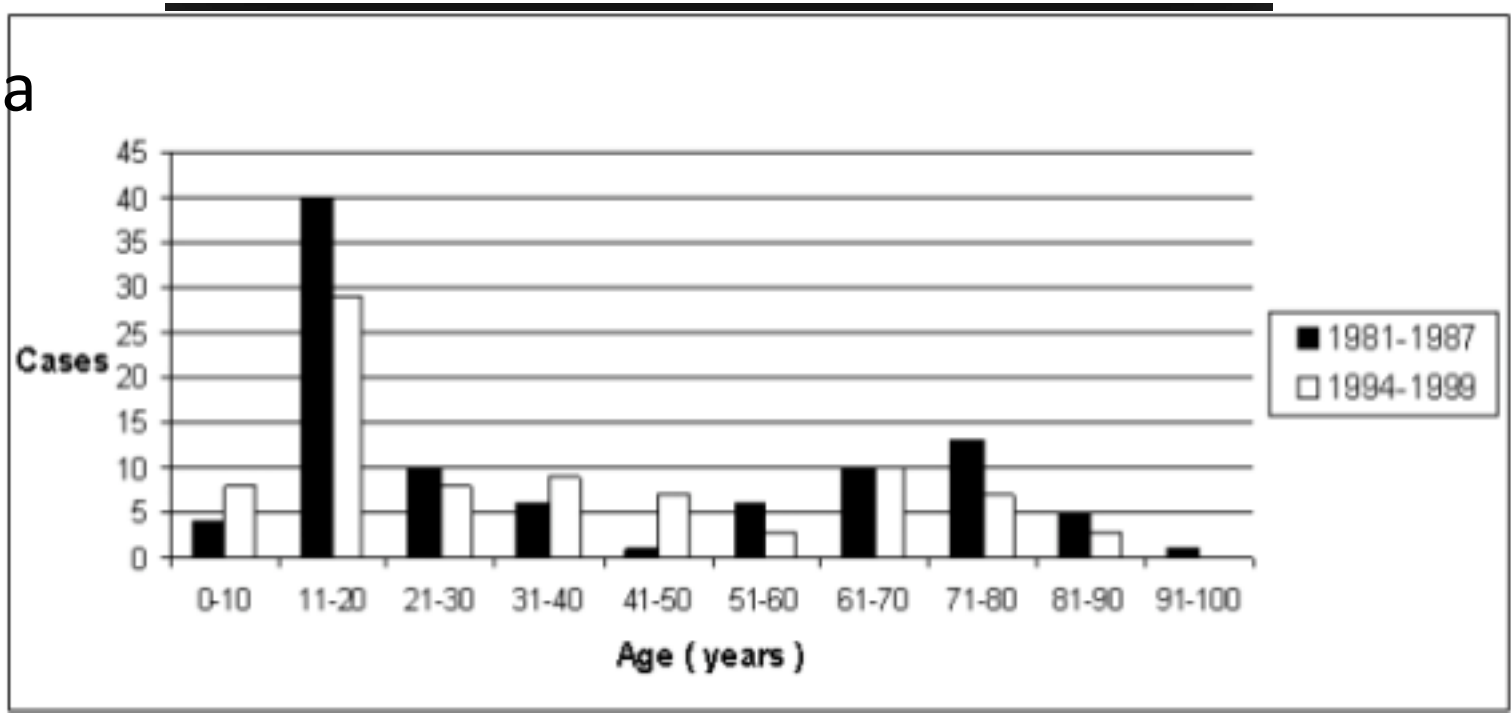
Average Number of New Cases Per Year and Age-Specific Incidence Rates per 100,000 Population, UK



Ewings



Osteosarcoma



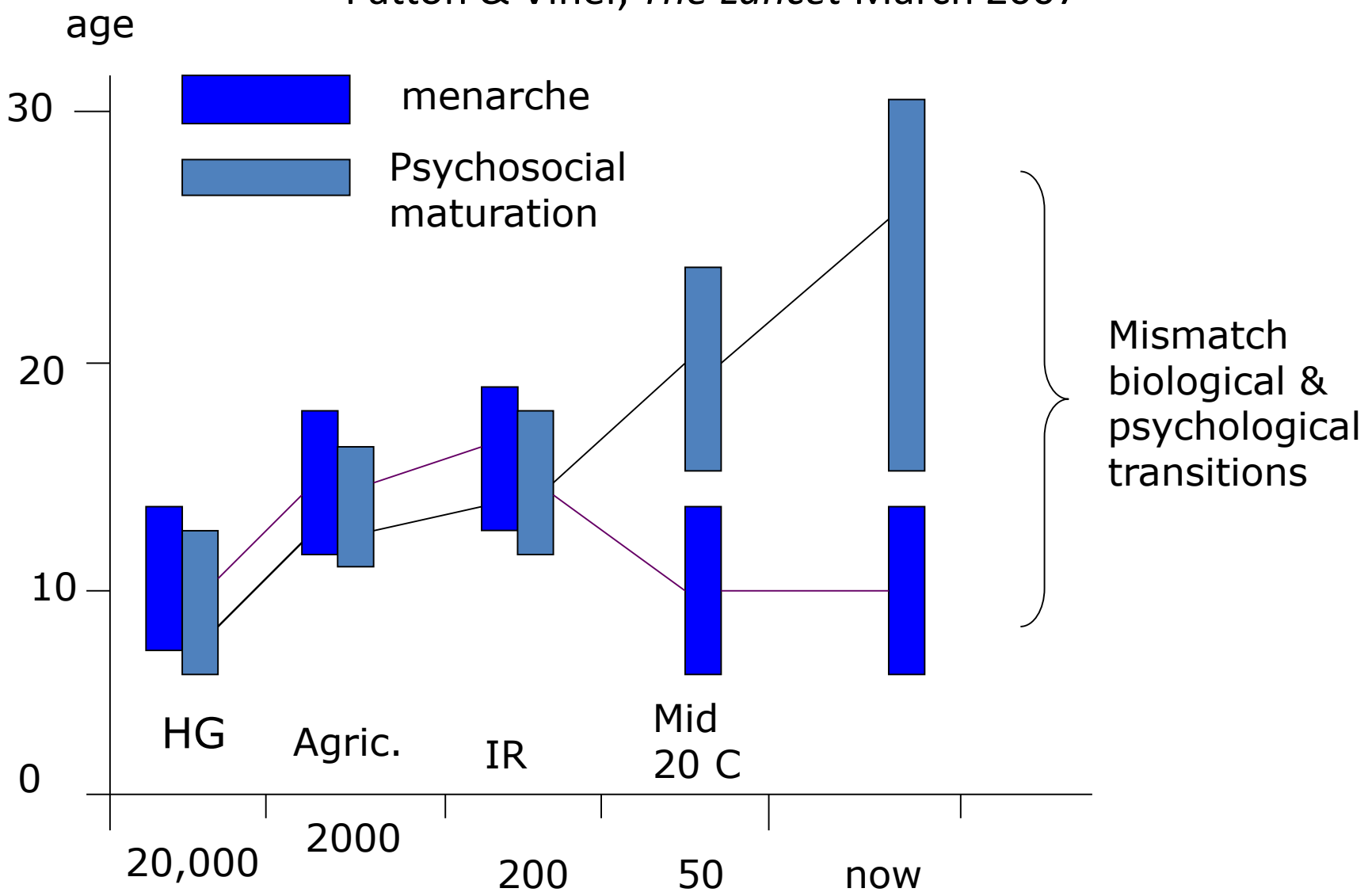
Suggest overarching hypothesis for cause of cancer in early life

Objectives

- To explore the impact of normal processes of adolescence upon an individual's capacity to participate in treatments and trials.

Changing relation b/t puberty & psychosocial transitions into adulthood

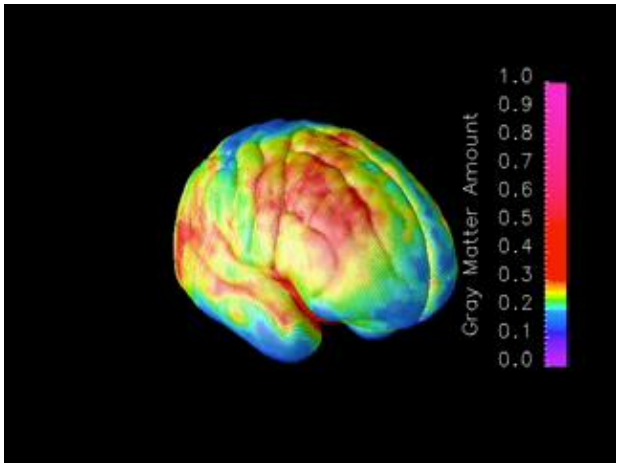
Patton & Viner, *The Lancet* March 2007

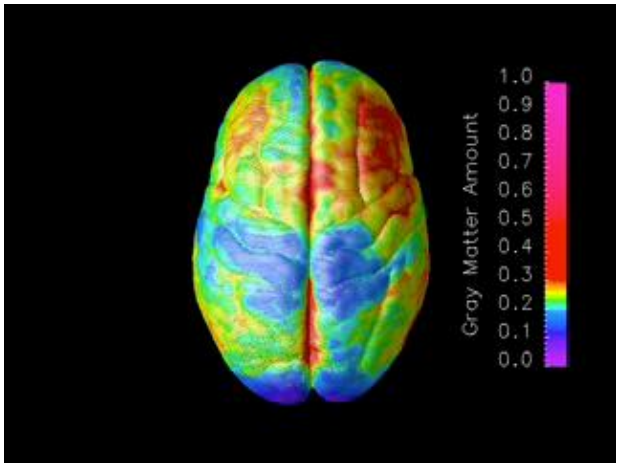


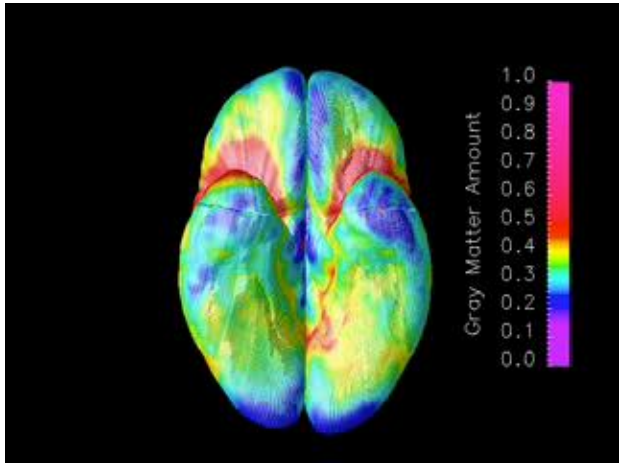
Dynamic mapping of human cortical development during childhood through early adulthood

Nitin Gogtay*†, Jay N. Giedd*, Leslie Lusk*, Kiralee M. Hayashi‡, Deanna Greenstein*, A. Catherine Vaituzis*, Tom F. Nugent III*, David H. Herman*, Liv S. Clasen*, Arthur W. Toga‡, Judith L. Rapoport*, and Paul M. Thompson‡

8174–8179 | PNAS | May 25, 2004 | vol. 101 | no. 21







Gray matter density changes 5yrs to 20yrs

Developmental stage

Am I normal?

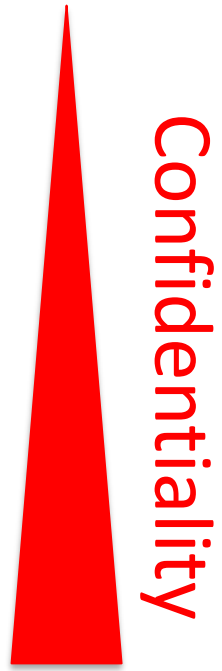
Early	(10-14)	biological focus

Who am I?

Middle	(15-17)	peer focus

Where am I going?

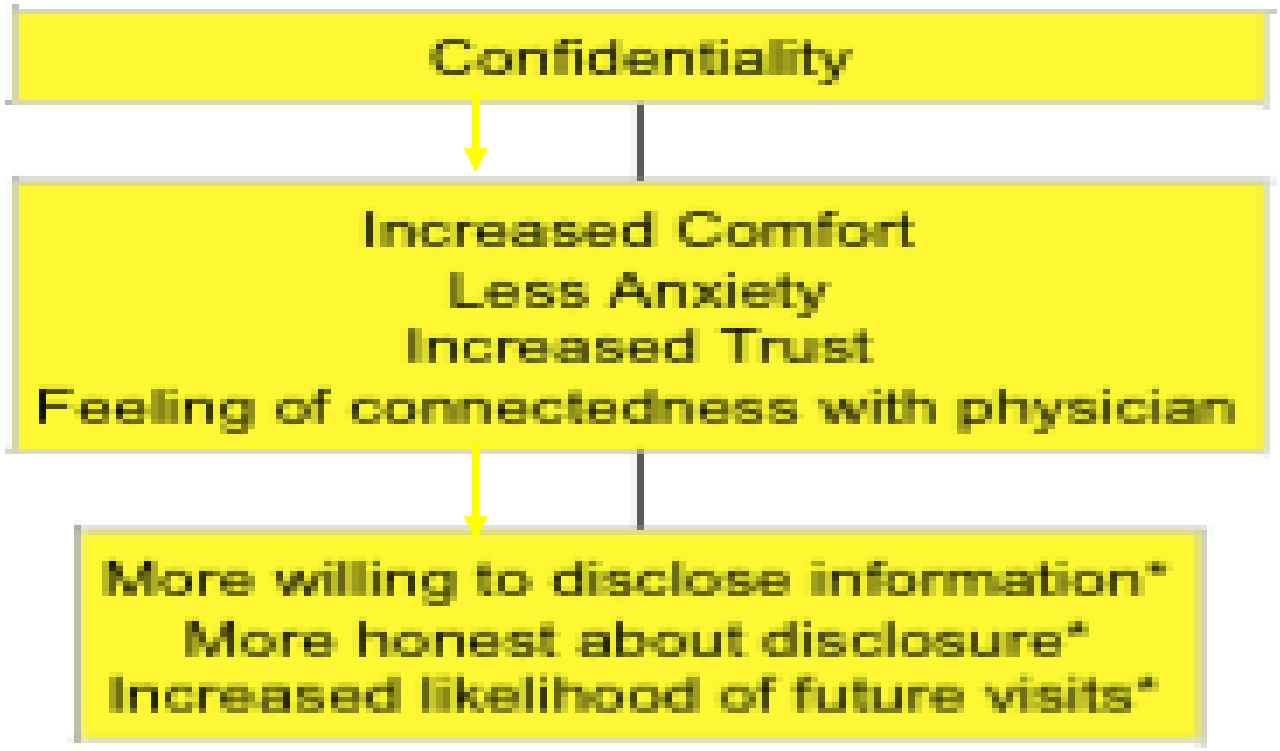
Late	(18+)	educational/vocational intimate relationships



Communication style implications

At the start of the consultation...

Explain terms & exceptions because...

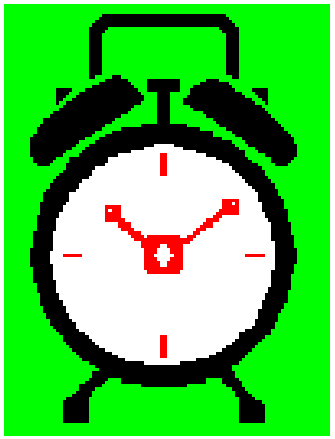


Ford *et al*. JAMA, 1997

P<0.001

A time of immense change

3 Clocks



Physical

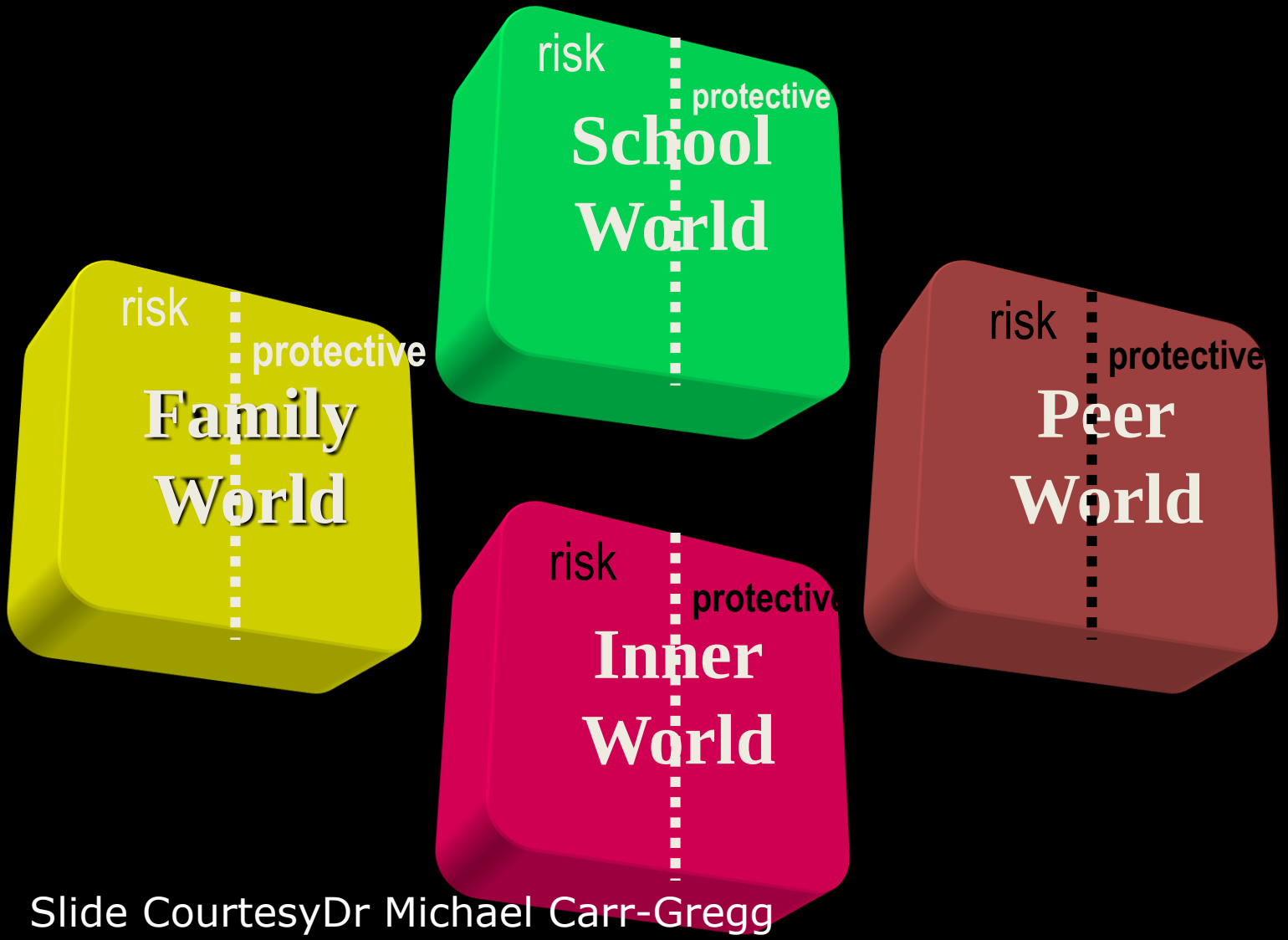
Intellectual

Emotional

Development in each can be at different rates and do not necessarily sync with chronological age

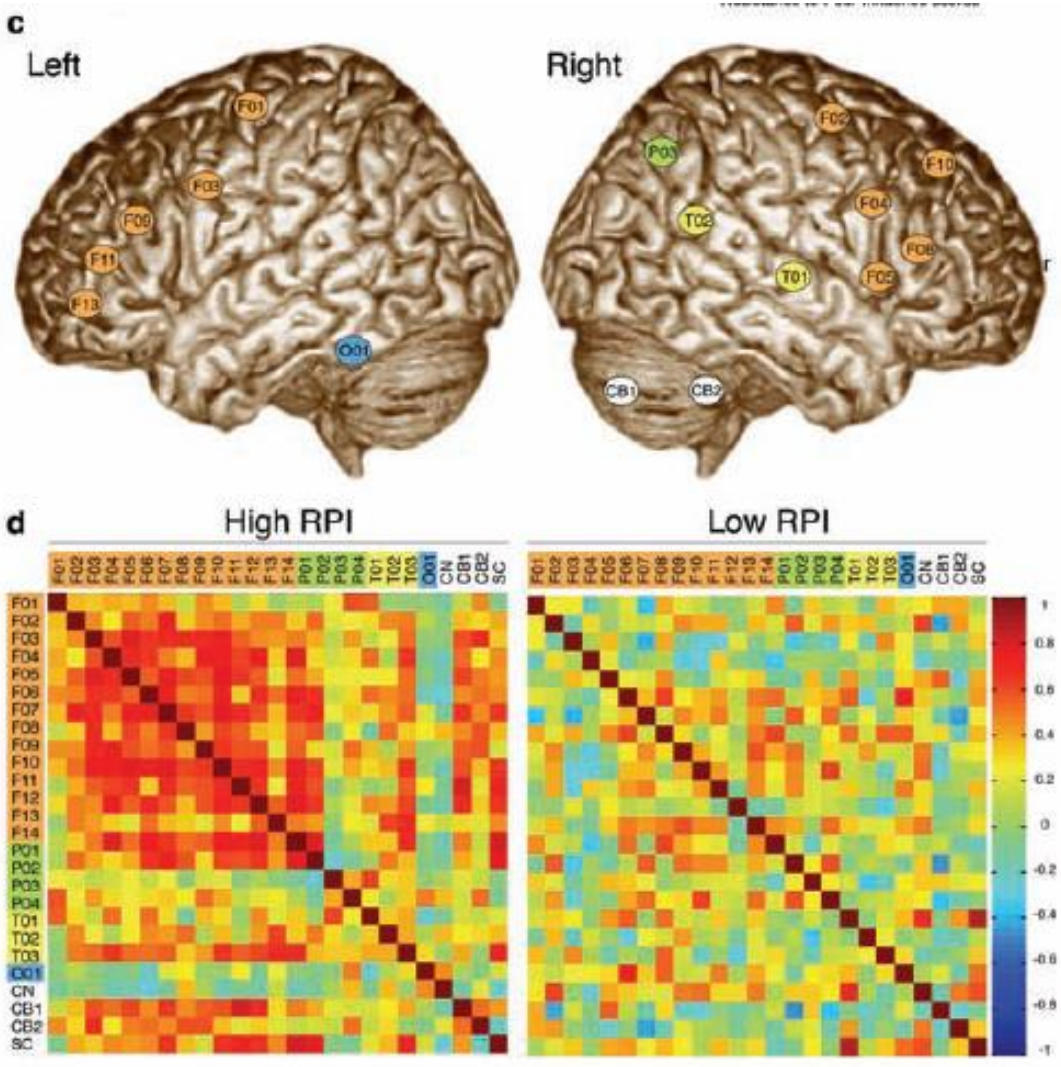
Slide courtesy of Dr Michael Carr-Gregg

Risk and protective factors



Slide CourtesyDr Michael Carr-Gregg

Interregional correlations of fMRI measurements of Latent Variable Interval between paired brain regions in subjects identified by testing to have high or low ResistanceTo Peer Influence (RPI) and exposed to films of aggressive hand waving.



Grosbras, M.H., Osswald, K., Jansen, M., Toro, R., McIntosh, A.R., Steinberg, L., Poulsen, C., Leonard, G. and Paus, T. 2007. Neural Mechanisms of Resistance to Peer Influence in Early Adolescence. *Journal of*

Challenges that Face 15-30 Year-Olds

HEEADSSS

- **H**ome and Relationships
- **E**ducation and Employment
- **E**ating
- **A**ctivities and Hobbies

  AT THIS STAGE REASSURE ABOUT CONFIDENTIALITY
- **D**rugs, Alcohol and Tobacco
- **S**ex and Relationships
- **S**elf harm and Depression
- **S**afety and Abuse

ASSURE CONFIDENTIALITY

The teenager is your patient!

"Anything we talk about today is confidential. That means I cannot tell others, including your parents, about it without your permission. The only exceptions would be if I thought you, or someone else, was at risk of serious harm. In that case I would need to tell someone else."

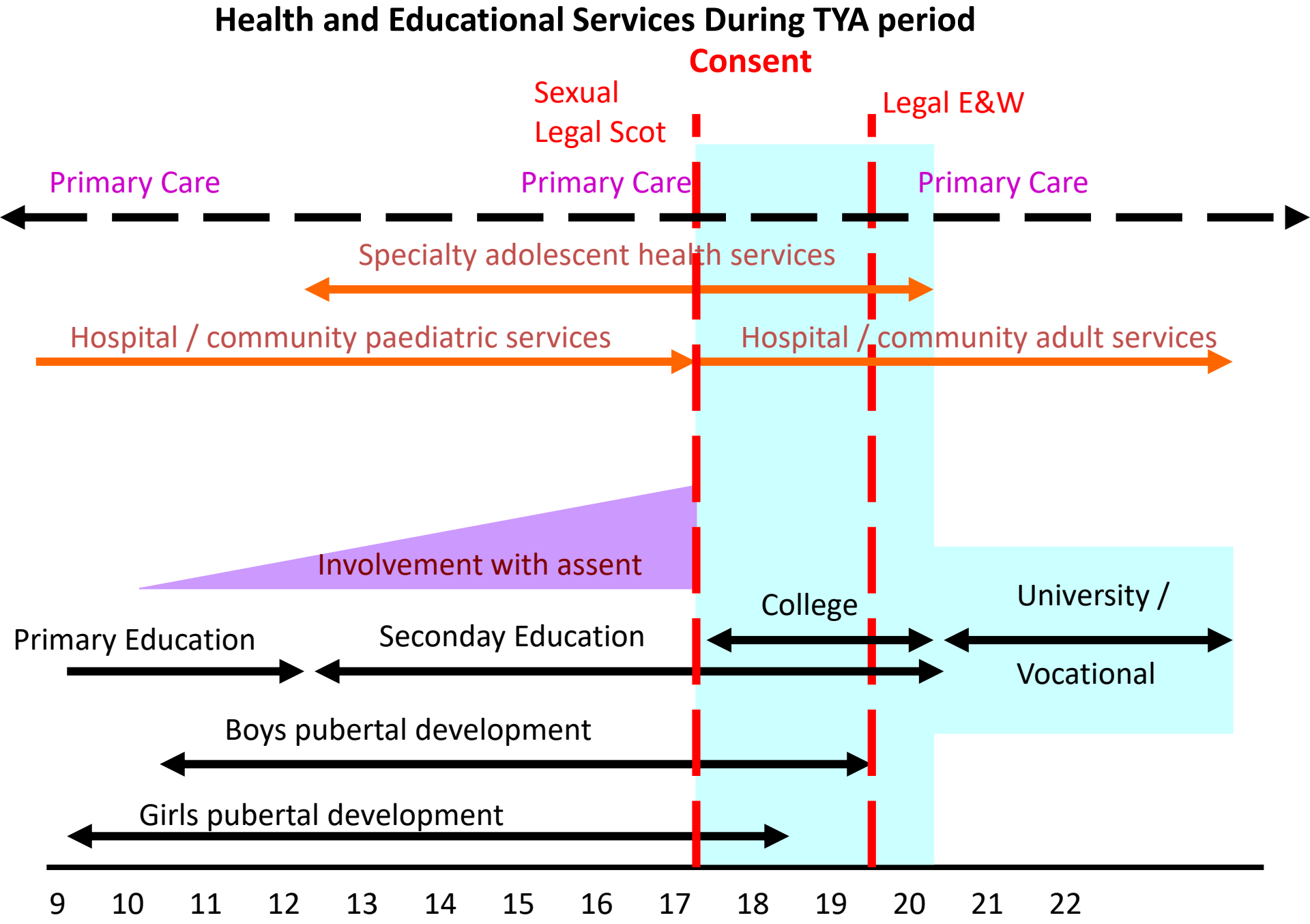
But don't ignore the parents!

The HEEADSSS assessment

- **HOME:** How is it at home at the moment? Do you have your own space? Who do you get on best with? Could you talk to them if you were worried about anything?
- **EDUCATION:** How's school going? What are you best at? Do you know what you want to do when you leave? Do you have a good group of friends?
- **EATING:** Has your weight changed recently? Are you worried about it? Have you ever dieted? How much exercise do you get?
- **ACTIVITIES AND HOBBIES:** Do you have a good social life? What do you do to relax?
- **DRUGS, ALCOHOL, TOBACCO:** Lots of teenagers try smoking/alcohol, have you? Have you been offered drugs? Is it hard for you to say no in this situation?
- **SEX AND RELATIONSHIPS:** Young people can start to develop intimate relationships, have you handled that part of your relationship yet? What do you know about contraception? Have you ever felt pressured?
- **SELF HARM AND DEPRESSION:** How is life in general? How are you sleeping? Do you ever think about hurting yourself? Do you ever feel so down that life isn't worth living?
- **SAFETY AND ABUSE:** have you ever been seriously injured? Have you ever been in a fight? Is anyone harming you, or making you do things you don't want to?

TYA Cancer Statistics

- 173,000 cases of cancer diagnosed TYA worldwide in 2008
- > 3-fold variation in world incidence rates between regions
- In European Union, ~14,700 cases of TYA cancer in 2008.
- Age-specific incidence rate for all cancers in 15-19 year-olds in 19 European countries increased from 147 per million (1970s) to 165 (1980s) and 193 (1990s)
- Ranked increases: carcinomas (3.9%), soft tissue sarcomas (2.6%), lymphomas (2.4%), GCTs (1.7%) and CNS tumours (1.4%).
- US age-specific incidence rate was 220 per million (15-19yrs) and 371 (20–24 years)
- US incidence rates have increased significantly in both age-groups since 1975: Except STS and Carcinoma (15-19)


Health and Educational Services During TYA period
Consent
Sexual
Legal Scot
Legal E&W
Primary Care
Primary Care
Primary Care
Specialty adolescent health services
Hospital / community paediatric services
Hospital / community adult services
Involvement with assent
College
University /
Vocational
Primary Education
Seconday Education
Boys pubertal development
Girls pubertal development
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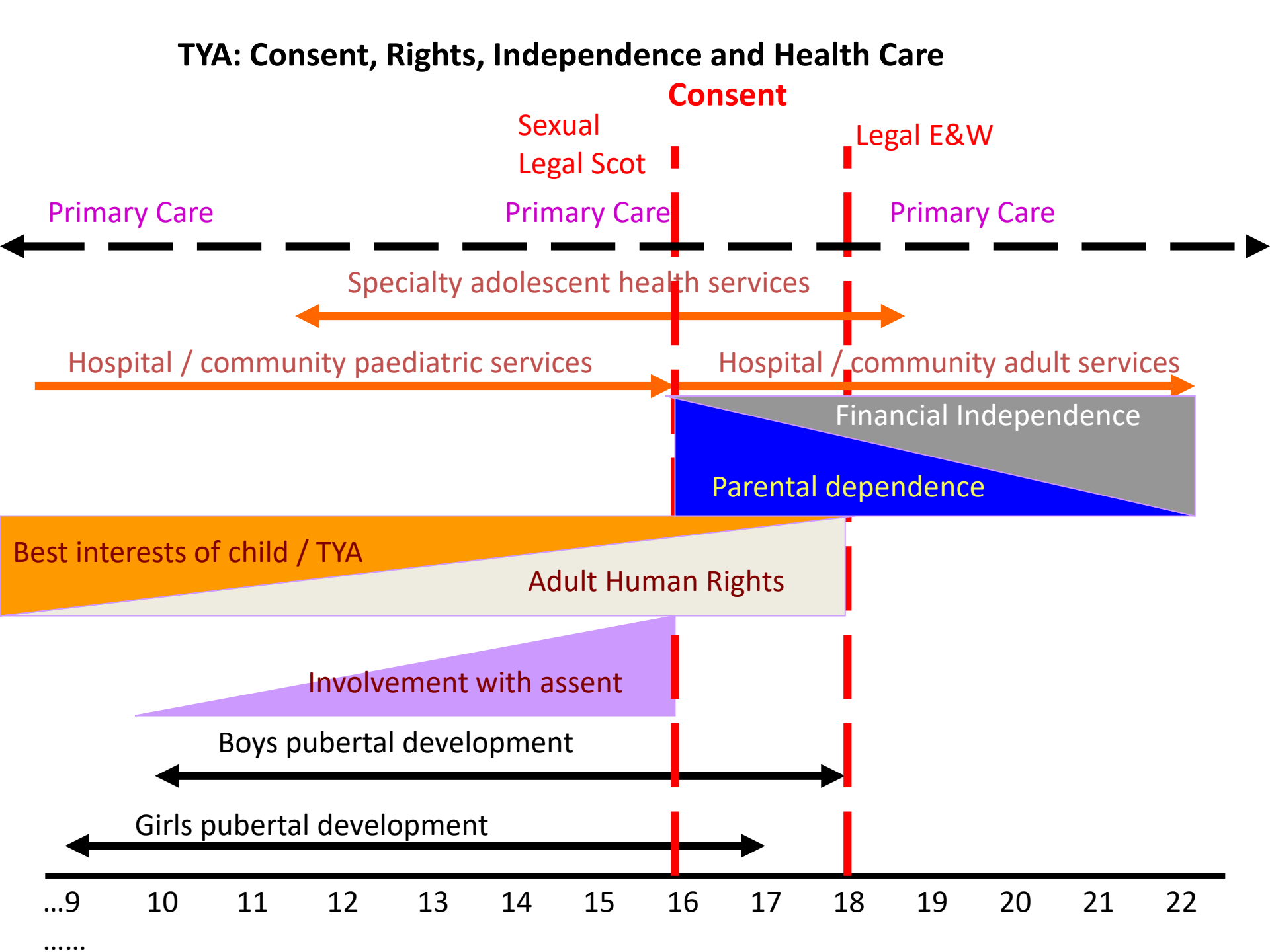

TYA: Consent, Rights, Independence and Health Care
Consent
Sexual
Legal Scot
Legal E&W
Primary Care
Primary Care
Primary Care
Specialty adolescent health services
Hospital / community paediatric services
Hospital / community adult services
Financial Independence
Parental dependence
Best interests of child / TYA
Adult Human Rights
Involvement with assent
Boys pubertal development
Girls pubertal development
…9
10
11
12
13
14
15
16
17
18
19
20
21
22
……

Units index

- **Birmingham:** Queen Elizabeth Hospital Young Persons Unit
- **Birmingham:** Birmingham Children's Hospital
- **Birmingham:** Royal Orthopaedic Hospital
- **Bristol:** Bristol Royal Hospital for Children
- **Cambridge:** Addenbrooke's Hospital
- **Cardiff:** University Hospital of Wales
- **Edinburgh :** Royal Hospital for Sick Children
- **Edinburgh:** Western General Hospital
- **Glasgow:** Beatson West of Scotland Cancer Centre
- **Glasgow:** Royal Hospital for Sick Children (Yorkhill)
- **Hull:** Castle Hill Hospital
- **Leeds:** Leeds General Infirmary
- **Leeds:** St James's University Hospital Young Adult Unit
- **Leicester:** Leicester Royal Infirmary
- **Liverpool:** Alder Hey Children's Hospital
- **London:** University College Hospital London
- **London:** University College Hospital London Cancer Centre
- **Manchester:** The Christie Hospital NHS Trust
- **Manchester:** Manchester Royal Children's Hospital
- **Newcastle:** The Great North Children's Hospital
- **Newcastle:** The Freeman Hospital
- **Nottingham:** Nottingham City
- **Sheffield:** Weston Park Hospital
- **Sheffield:** Royal Hallamshire Hospital
- **Southampton:** Southampton General Hospital
- **Surrey:** The Royal Marsden Hospital
- **The Wirral:** Clatterbridge Centre for Oncology

TEENAGE CANCER TRUST

A CHARITY DEVOTED TO IMPROVING THE LIVES OF TEENAGERS AND YOUNG ADULTS WITH CANCER

Units in development

We are working towards building more units. Below is a list of units that are under development.

- Manchester Royal Infirmary
- Queens Medical Centre, Nottingham
- Bristol University Hospitals - Young Person's Unit
- Edinburgh, Royal Hospital for Sick Children (replacement)
- Edinburgh, Western General
- Glasgow, Royal Hospital for Sick Children (replacement)
- Southampton General Hospital
- Our Lady's Children's Hospital, Crumlin, Dublin
- Alder Hey Hospital (reprovision)

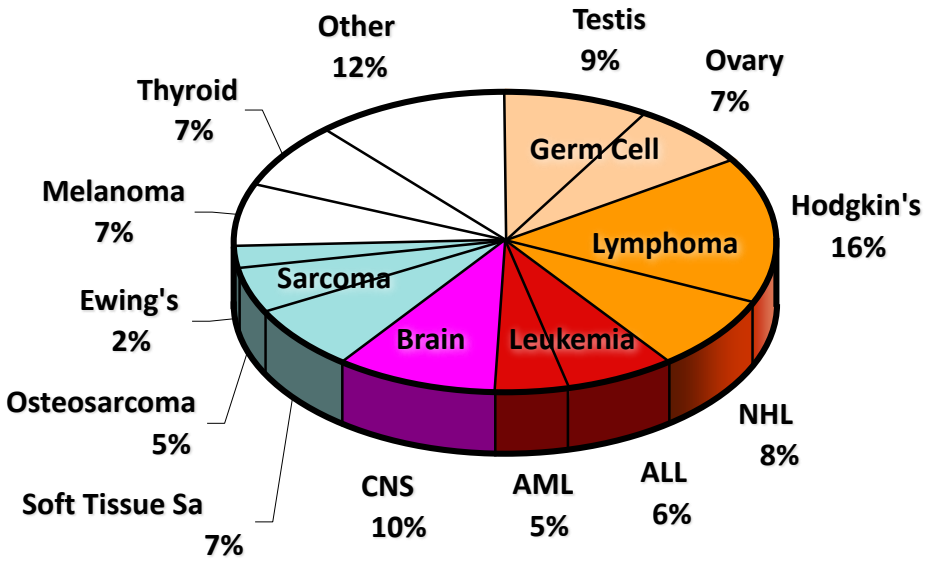
Objectives

- To propose strategies for enhancing outcome within clinical trials for TYA population

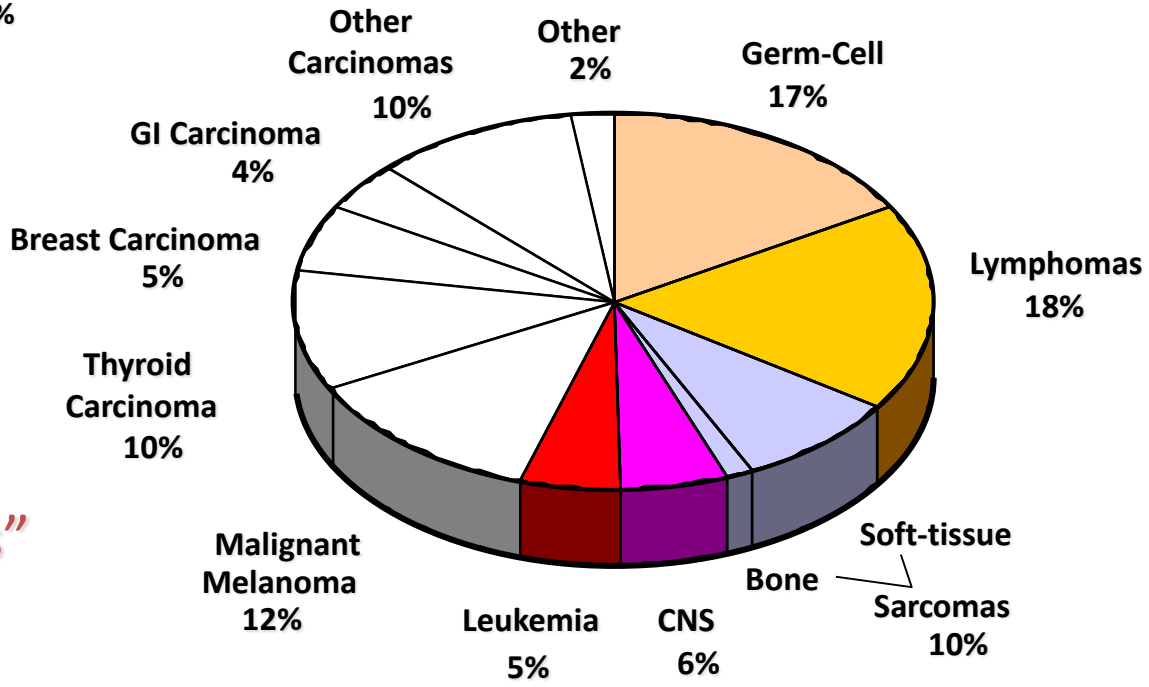
Cancers in Older Adolescents and Young Adults

SEER, 1975-1998

Age 15-19 Years



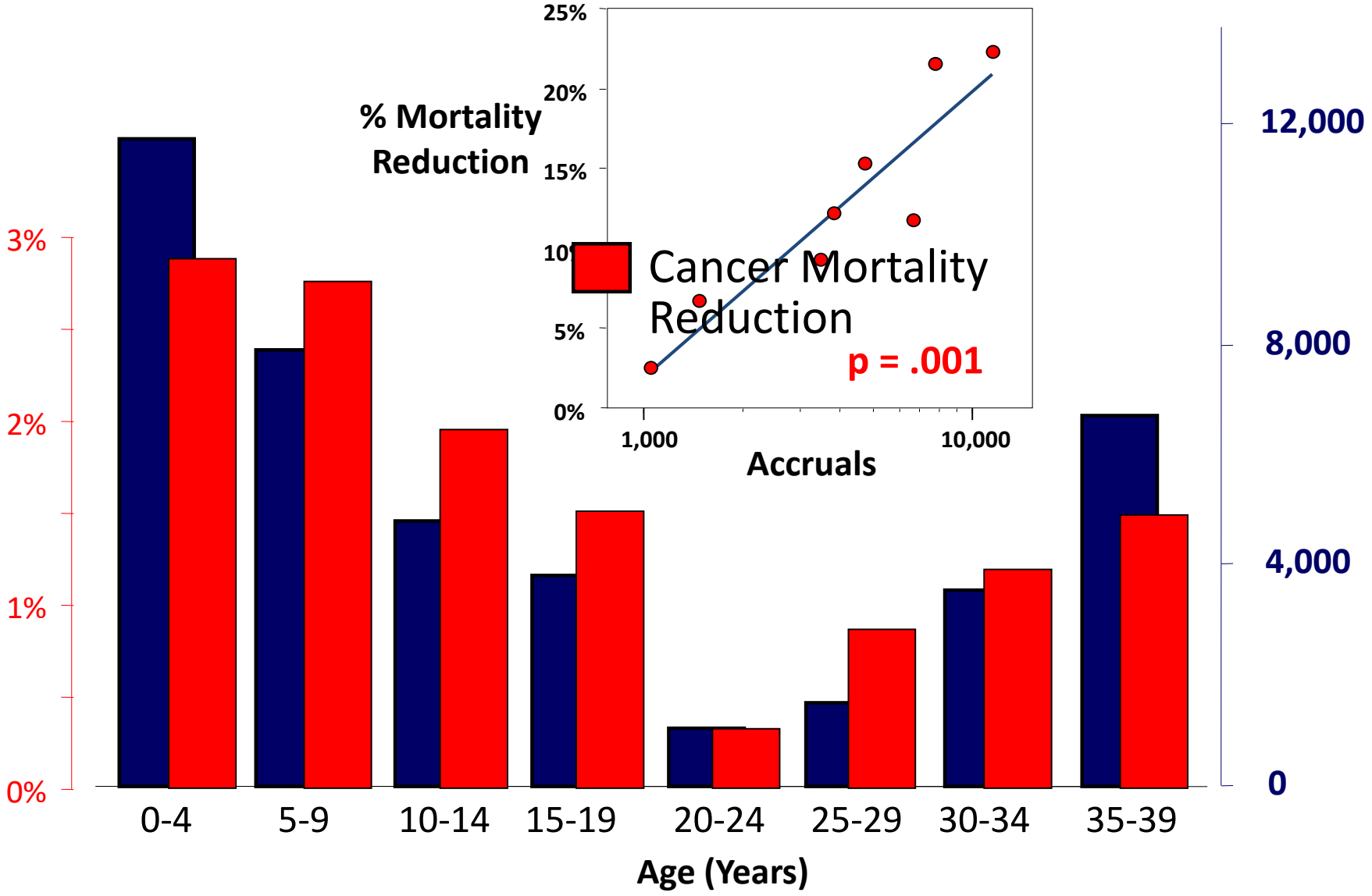
Age 20-29 Years



The segments in color represent "paediatric malignancies"

National Treatment Trial Accruals, 1990-1998

National Cancer Mortality Reduction, 1990-1998

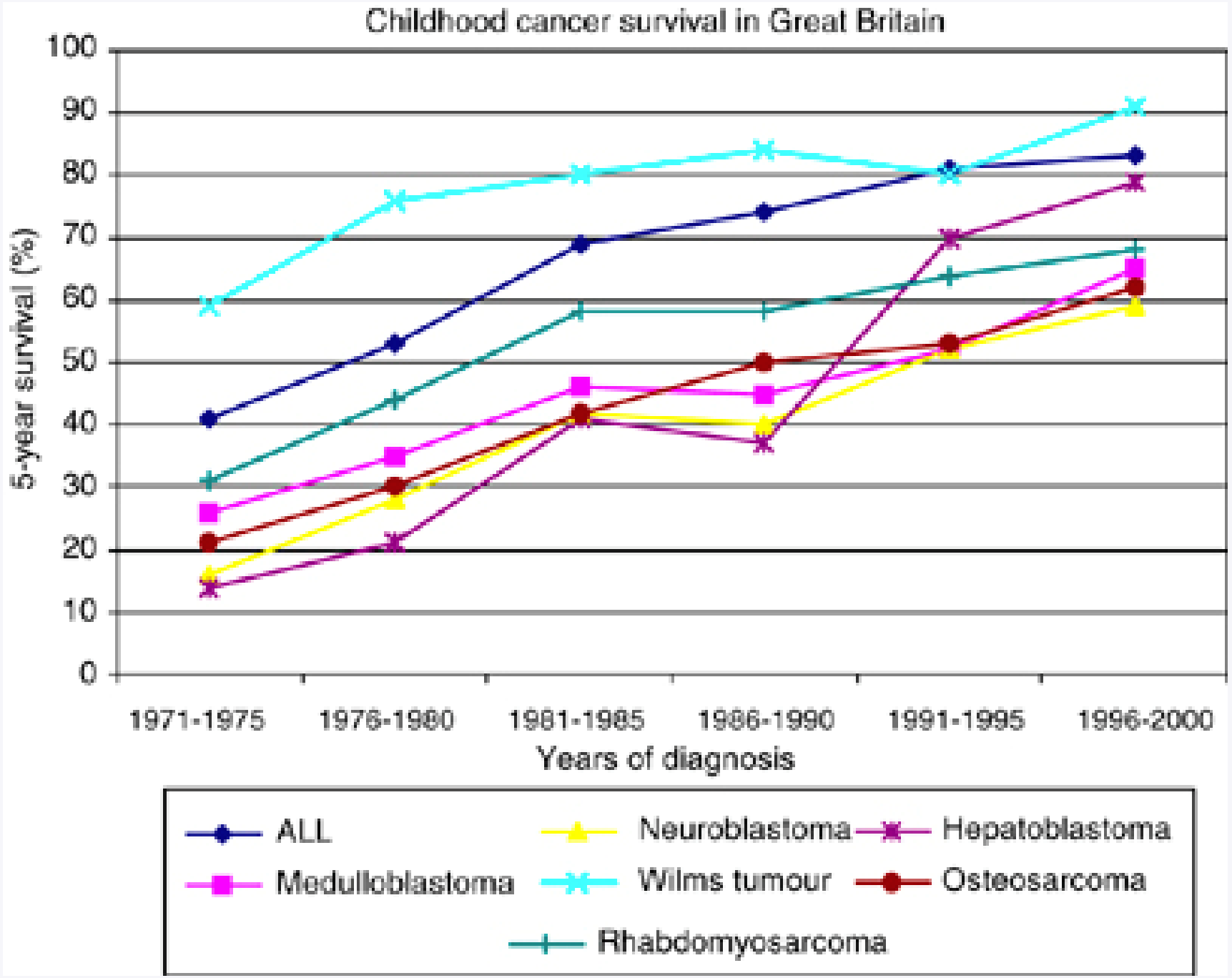


Buzz Group

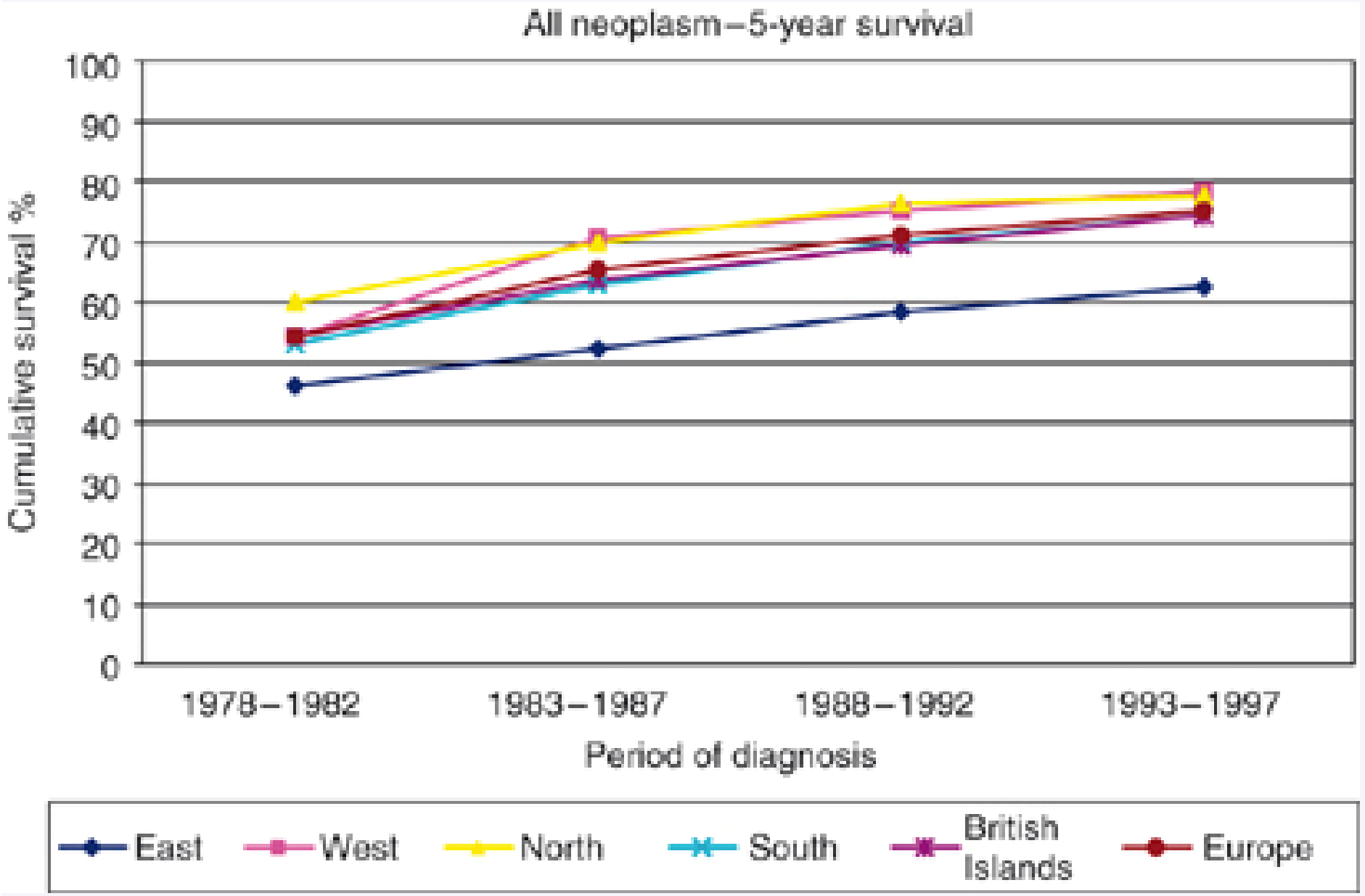
If survival rates are poorer for this TYA age group: what strategies within clinical trials could be adopted to enhance outcomes?

Go to **www.menti.com** and use the code **88 93 45**

Strategies to improve outcomes for TYA age group in clinical trials?


Childhood cancer survival in Great Britain
100
90
80
70
60
50
40
30
20
10
0
5-year survival (%)
1971-1975
1976-1980
1981-1985
1986-1990
1991-1995
1996-2000
Years of diagnosis
ALL
Neuroblastoma
Hepatoblastoma
Medulloblastoma
Wilms tumour
Osteosarcoma
Rhabdomyosarcoma

European Survival Statistics Childhood Cancer

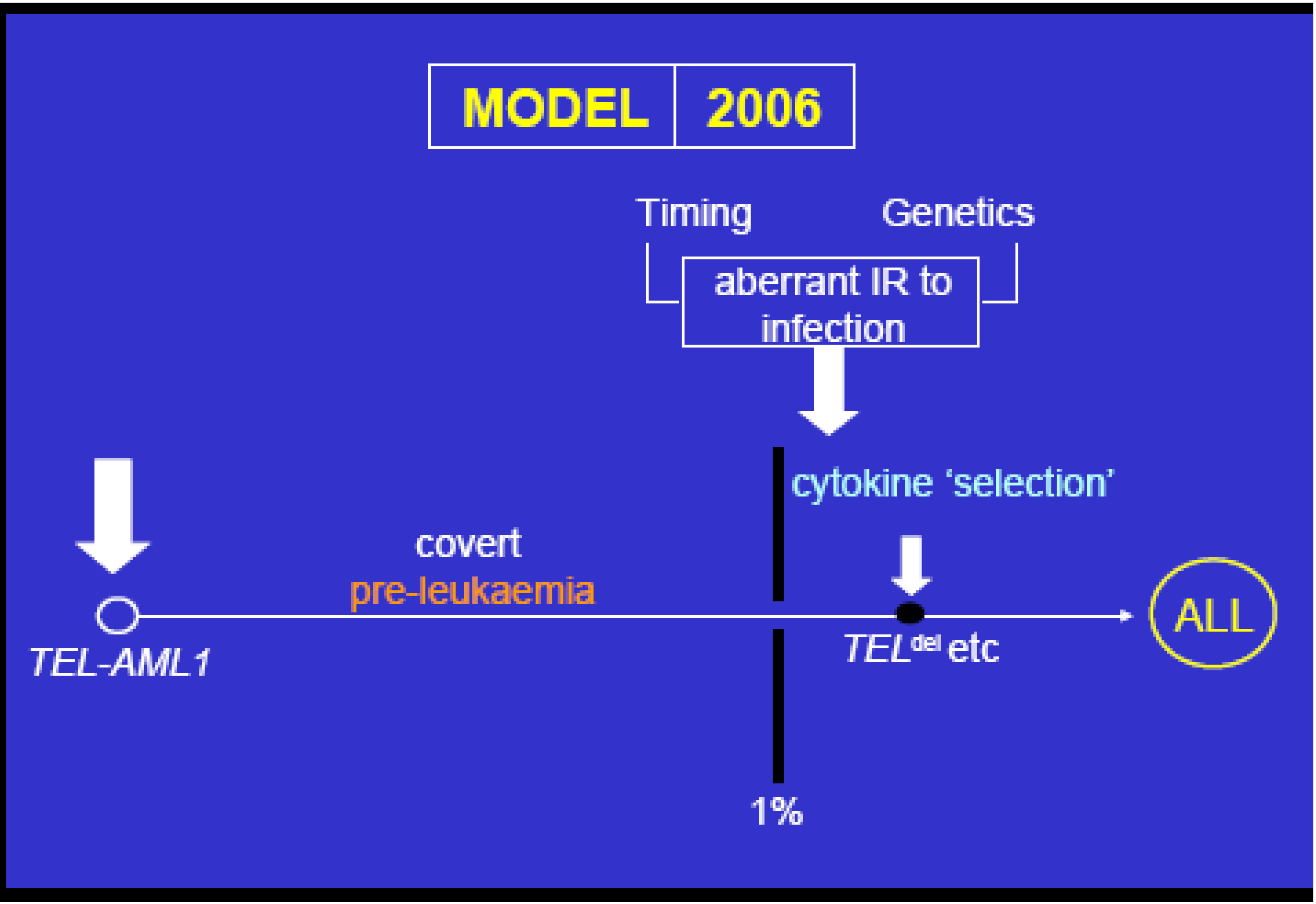


Survivorship: UK statistics 2005-2012

- At the end of 2005, it was estimated that around 26,000 people in Great Britain were long-term childhood cancer survivors, who had survived five years or longer after diagnosis with childhood cancer.
- It is estimated that by the end of 2012 there will be at least 33,000 people in the UK who are alive having previously been diagnosed with a childhood cancer and who survived their cancer for at least five years.

Our Objectives?

- To debate health priority for cancer services in early life
- To consider the impact of age growth and development upon risk of cancers in early life.
- To explore the impact of normal processes of adolescence upon an individual's capacity to participate in treatments and trials.
- To propose strategies for enhancing outcome within clinical trials for TYA population

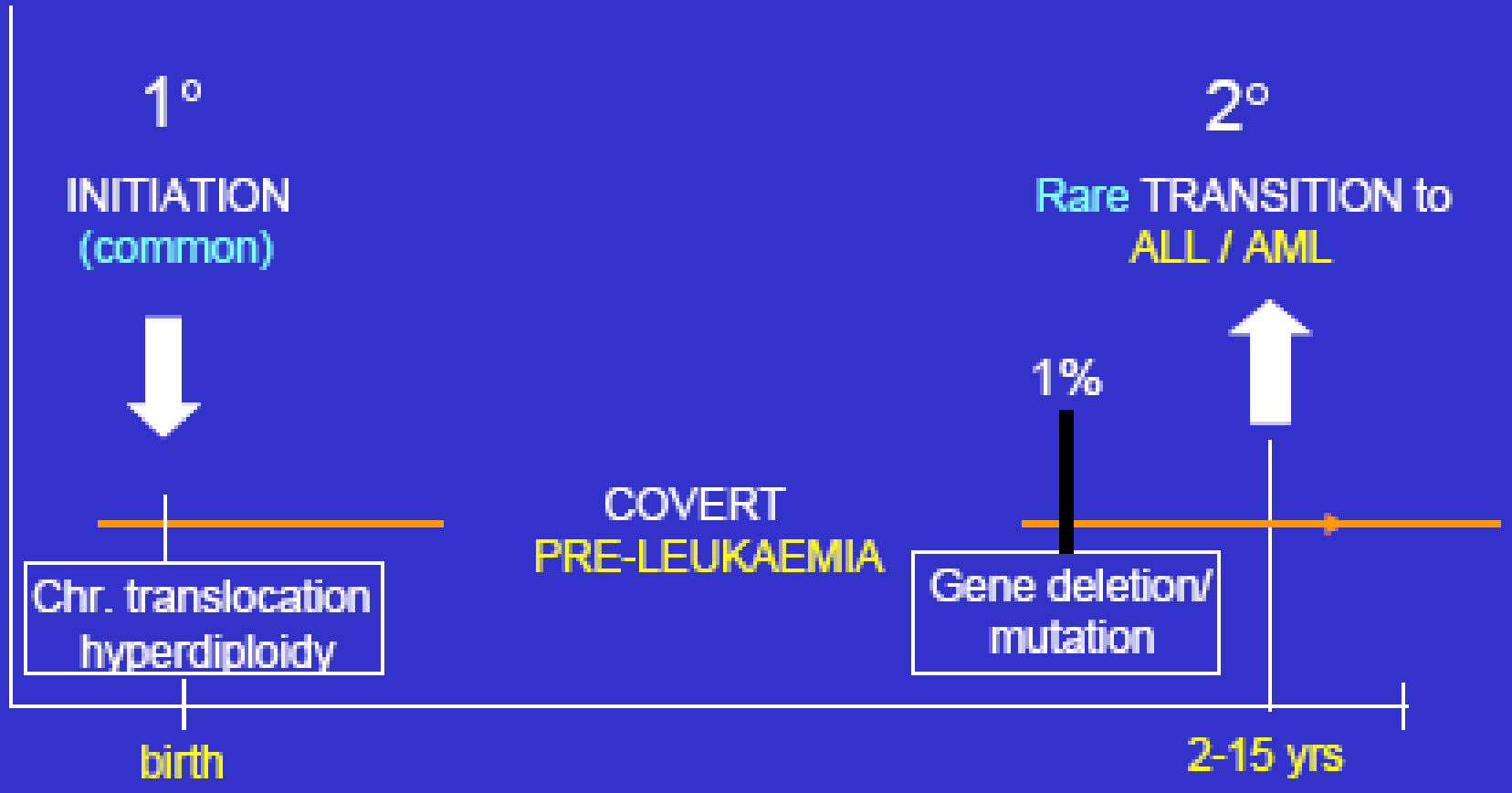

MODEL 2006
Timing
Genetics
aberrant IR to infection
cytokine 'selection'
covert
pre-leukaemia
TEL-AML1
TEL del etc
ALL
1%

EPIDEMIOLOGICAL EVIDENCE SUPPORTING THE 'DELAYED INFECTION' HYPOTHESIS

- Increased common infections in *infancy* are *protective*
- Increased social contacts in *infancy* are *protective*
  - parity
  - attendance at playgroups

  (- proxies for infection)

NATURAL HISTORY OF PAEDIATRIC ACUTE LEUKAEMIAS



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WWW.ESTRO.ORG/SCHOOL

Imaging in Medulloblastoma and Ependymoma

Tim Jaspan
University Hospital
Nottingham

ESTRO School

MEDULLOBLASTOMA

Medulloblastoma - demographics

- Commonest pediatric malignant brain tumor
- 15-20% of all pediatric brain tumors
- 80% <15 years old, 20% <2 years old
- 40% of pediatric posterior fossa tumors
- Slightly more common in boys
- Mean age at diagnosis – 7yrs; peaks at 1-5 yrs and 6-9yrs

Medulloblastomas

1-5 yr:

- Often arise from inferior medullary velum of the vermis
- Usually presents as a midline tumor
- Spherical pattern of growth, projecting into enlarged 4V
- Hydrocephalus at diagnosis in 95% of case

6-9 yr + older:

- Sometimes mimics cerebellopontine angle tumor
- More often in cerebellar hemispheres

Molecular classification

- New molecular subgroups identified
- SHH, WNT, Group 3, Group 4
- Subgroups show different clinical/biological behaviour
- Potential for improved risk stratification/tailored treatment

Subgroup features

- **WNT:** occur mainly along the CP/CPA axis
  - good prognosis
- **SHH:**>50% cerebellar hemispheric
  - intermediate prognosis
- **GP 3:** primarily midline/juxtaventricular, enhancement +/++
  - poor prognosis, early dissemination
- **Gp 4:** midline/4th ventricle based, enhancement 0/+
  - dissemination common

Imaging

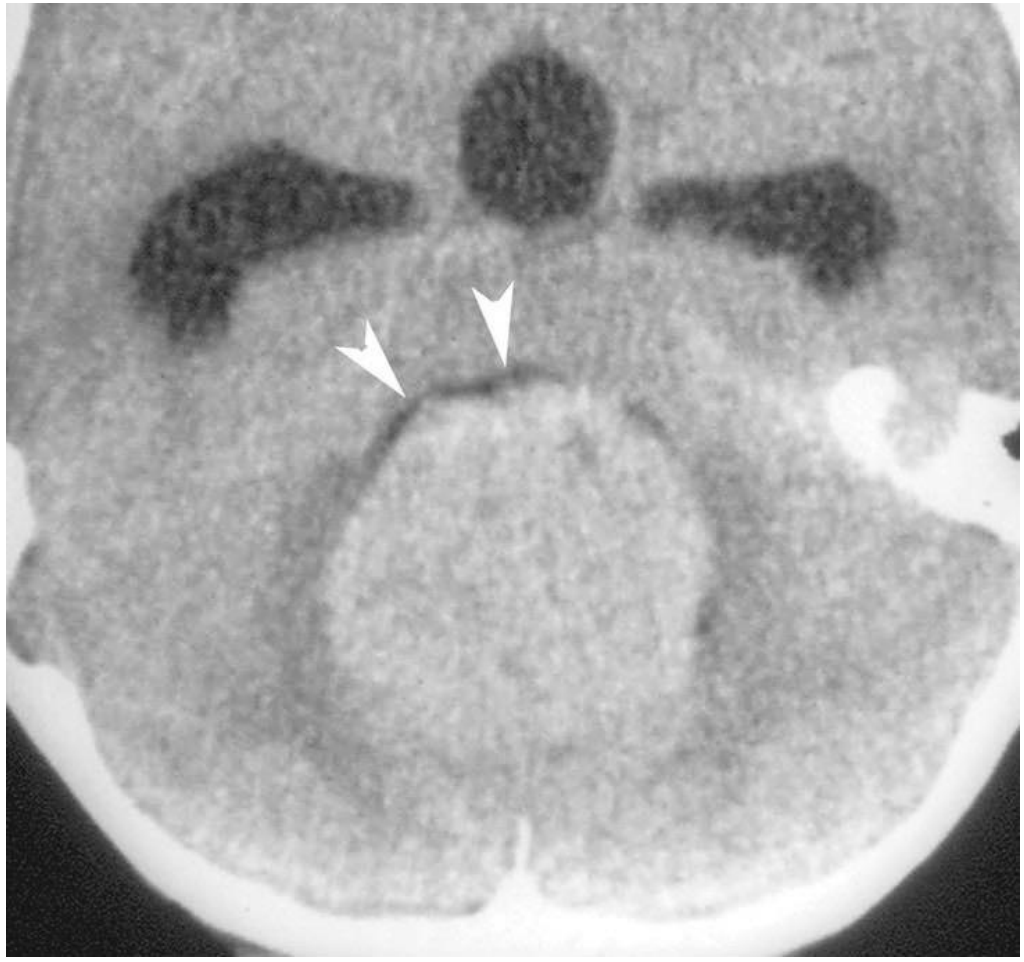
Diagnostic modalities:

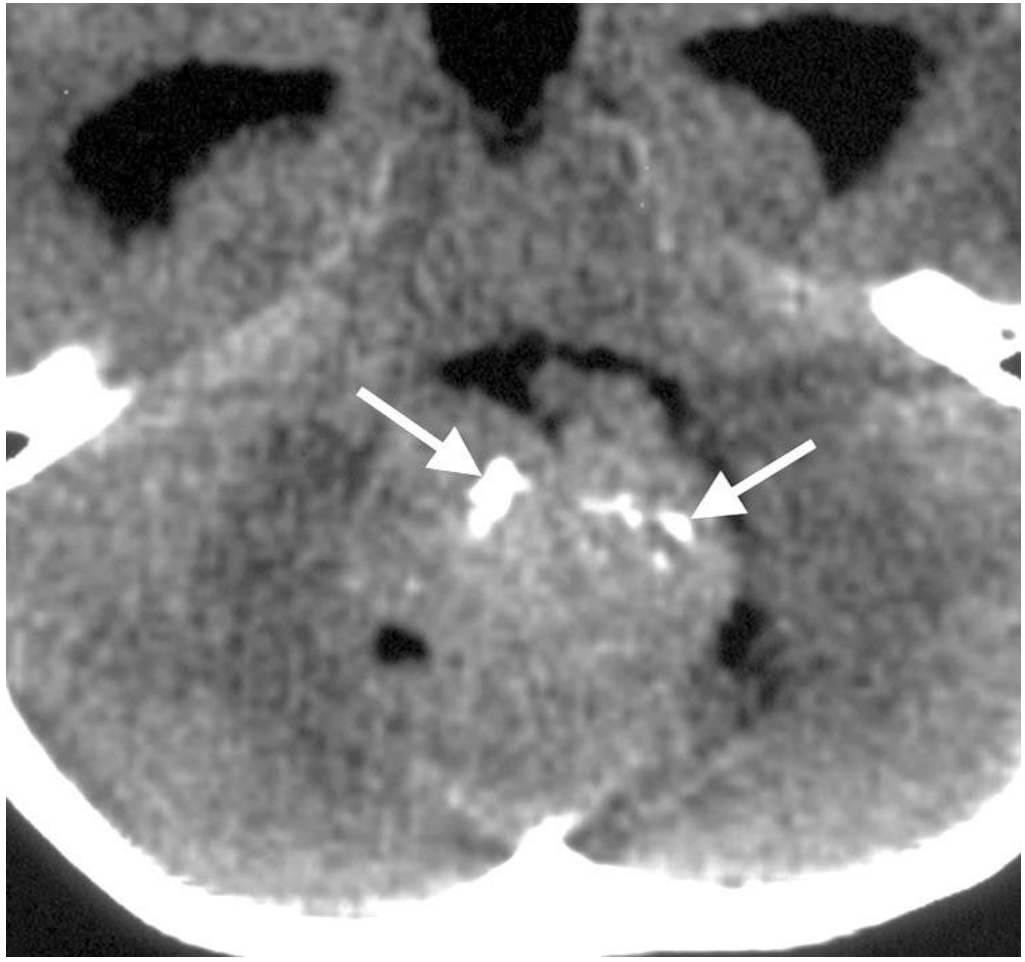
- CT - Restricted to initial diagnosis
- MRI - Neuraxial MRI is the standard of care

Medulloblastoma - CT

- Often first diagnostic imaging
- Mildly hyperdense (unusual for post. fossa tumors); reflects high cellular density/nuclear-to-cytoplasmic ratio
- Calcifications in approx 20%
- Cysts in 50-60%
- Surrounding oedema often seen
- Enhancement variable/prominent

CT

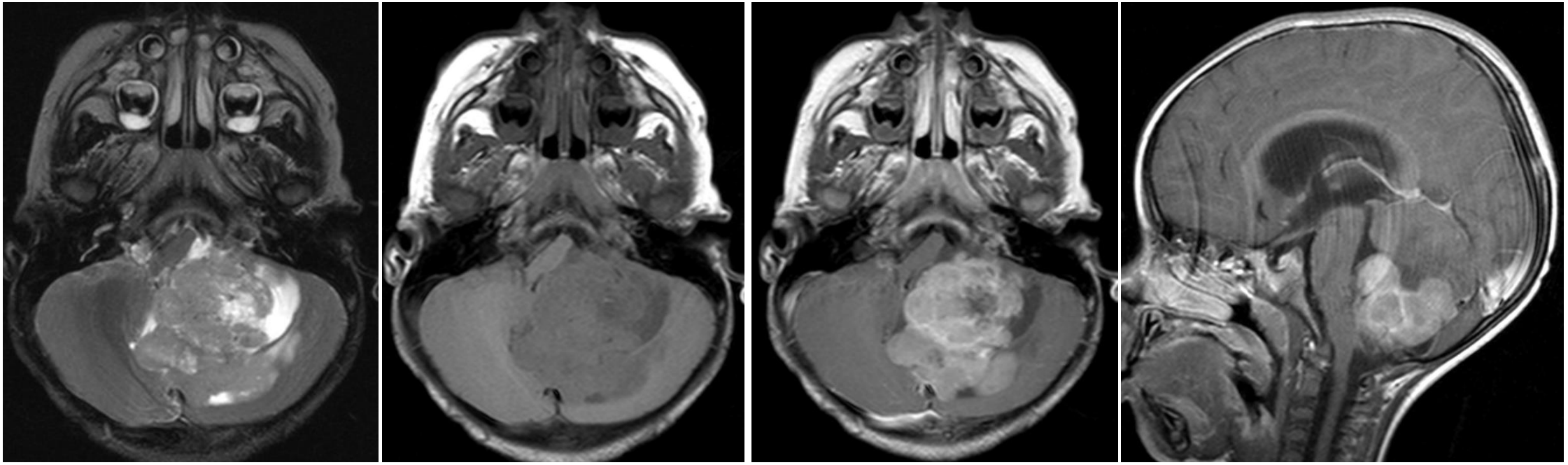




Medulloblastoma - MRI

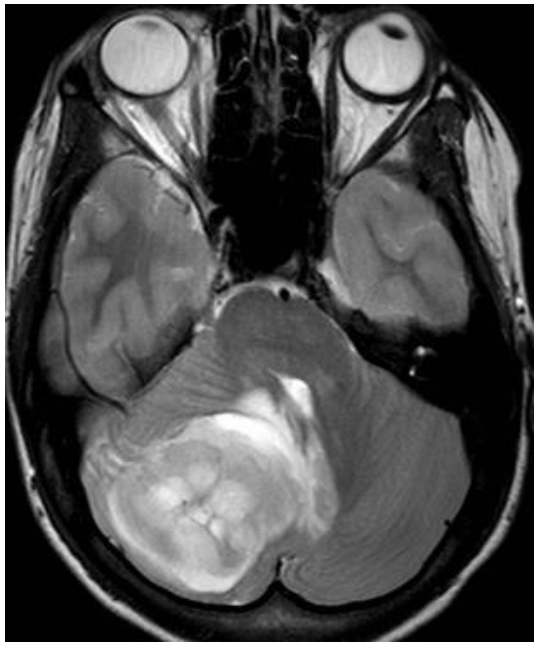
- Iso to mildly T1 hypointense/mixed T2 SI
- Grows circumferentially to fill/obliterate 4V
- Doesn't usually extend out through foramen of Luschka
- More aggressive lesions invade brainstem and/or adjacent cerebellar parenchyma
- Haemorrhage, necrosis or cystic change in 20-50%
- Generally strong or heterogeneous enhancement
- DWI: typically restricted diffusion (dark on ADC maps)
- MRS: elevated Choline and Taurine, low NAA

MB - WNT



T2 T1 T1 post Gd T1 post Gd

MB - SHH



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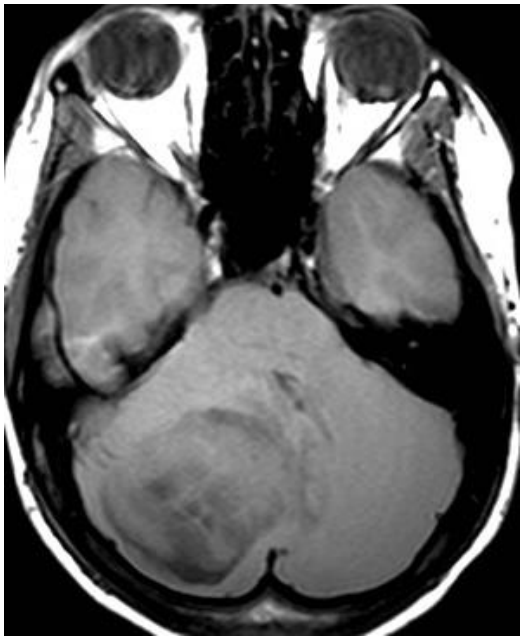

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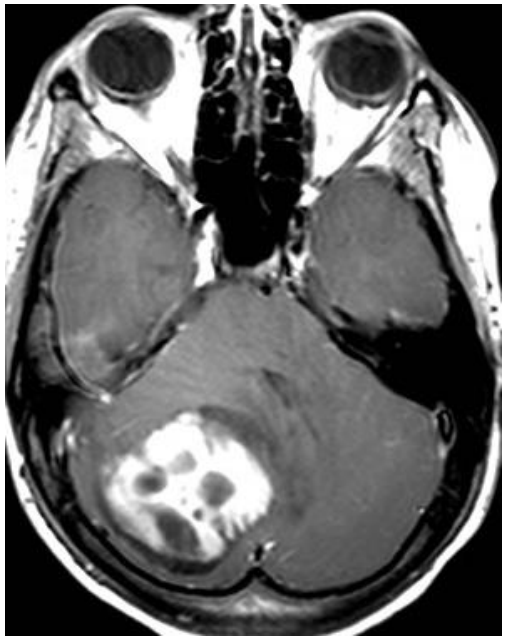
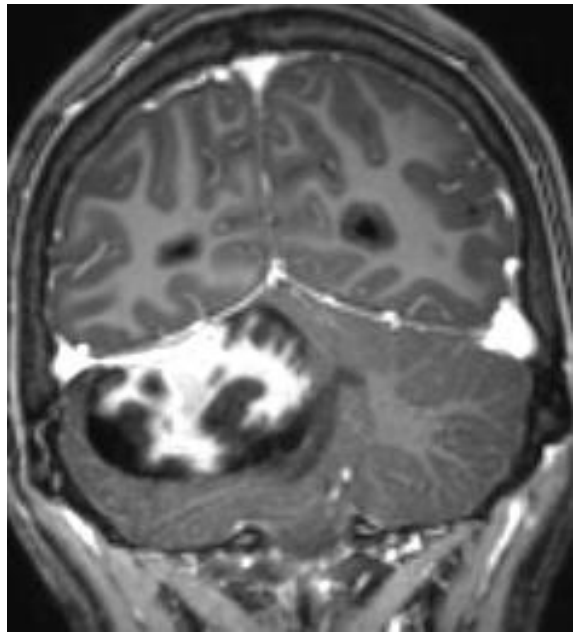


T1 post Gd



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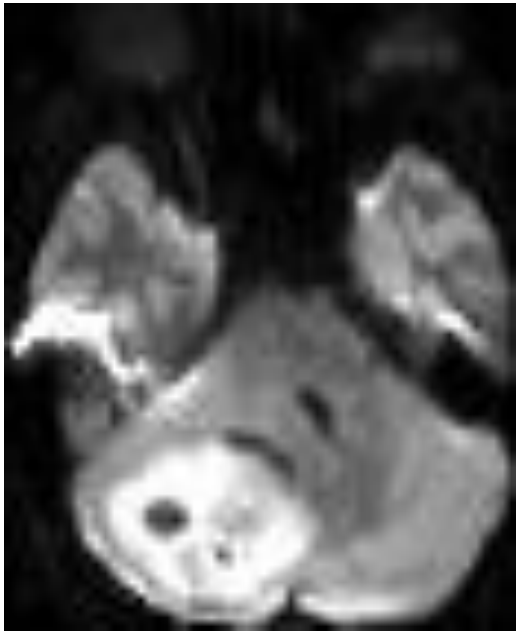
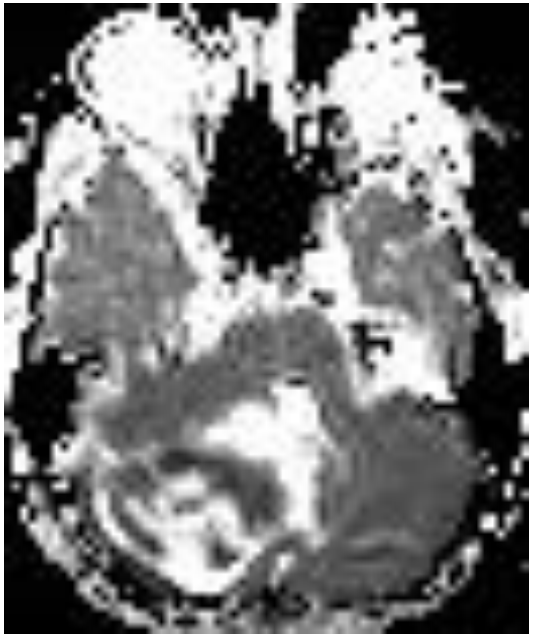


DWI



ADC

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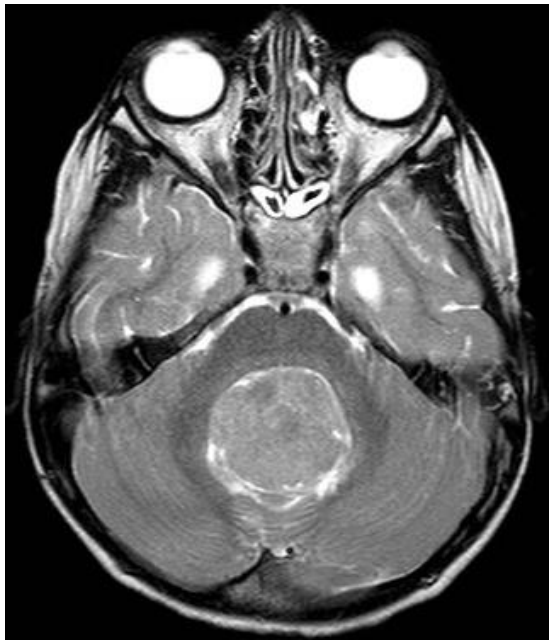
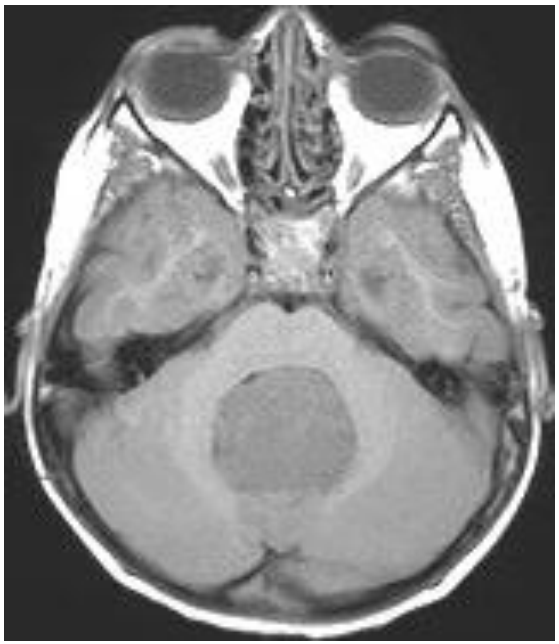
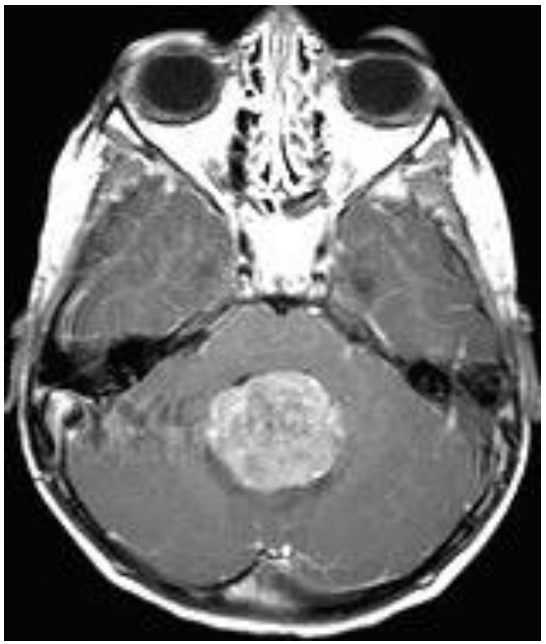
MB - Gp 3



T2



T1



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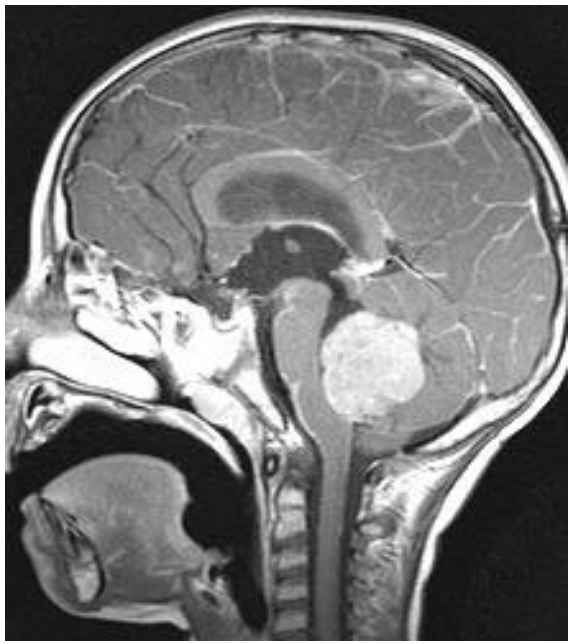

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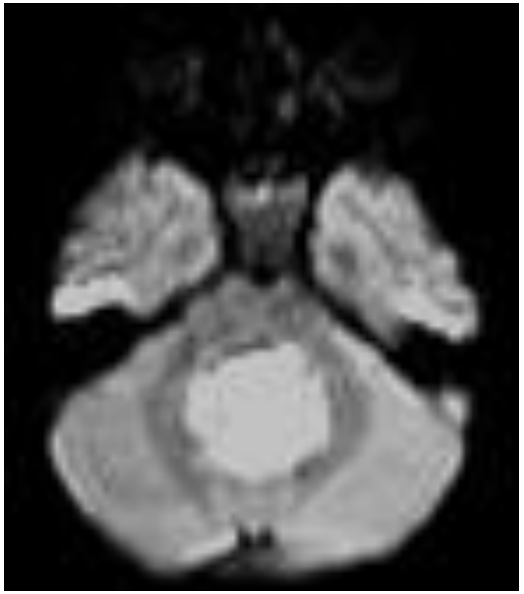
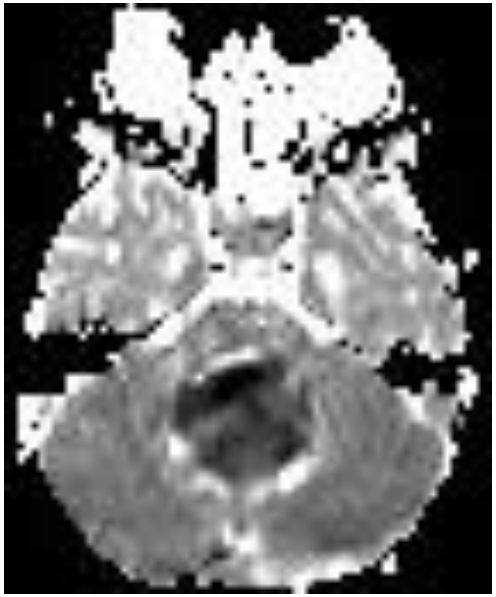


DWI



ADC

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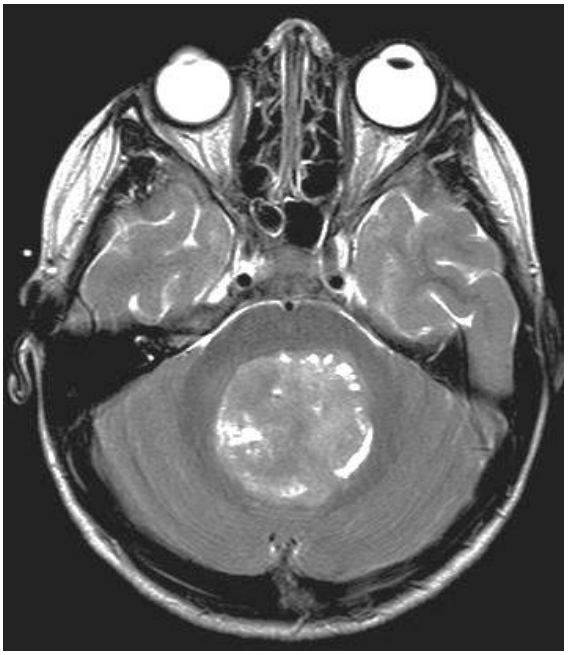
MB - Gp 4



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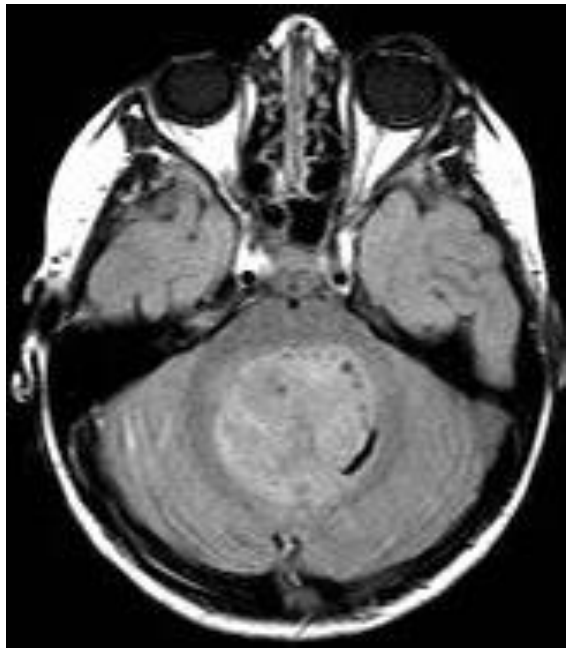
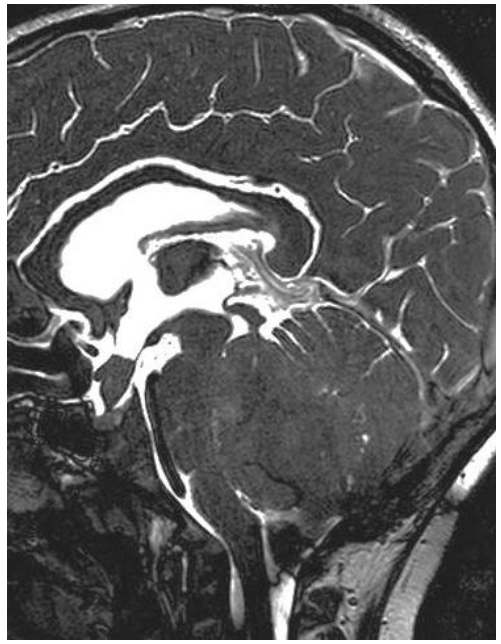
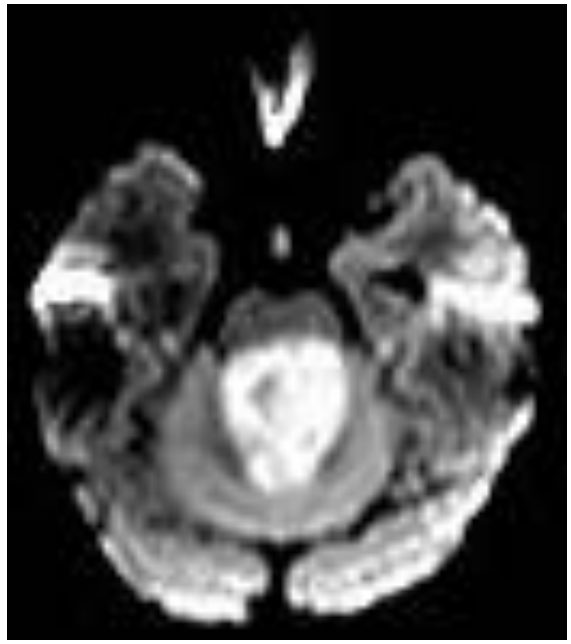


FLAIR



CISS



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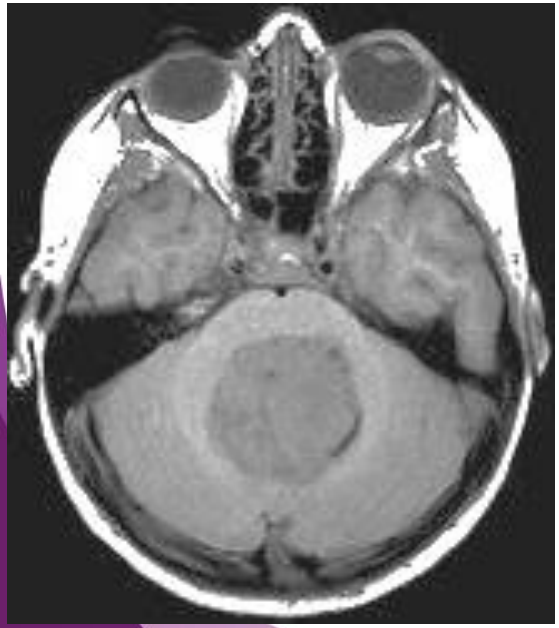
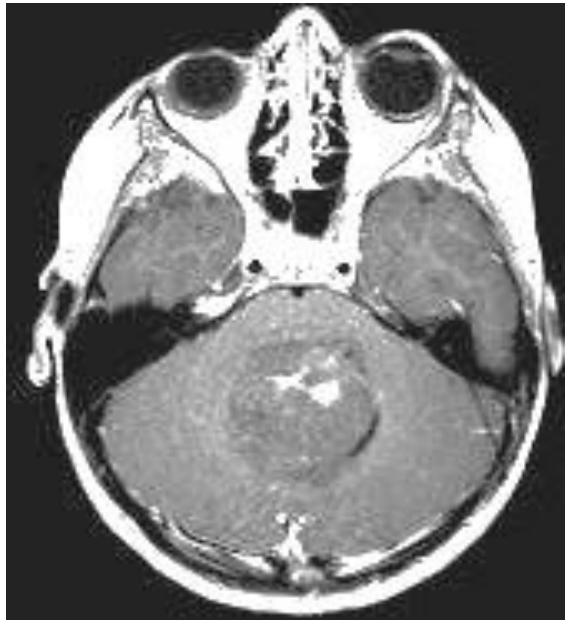


T1



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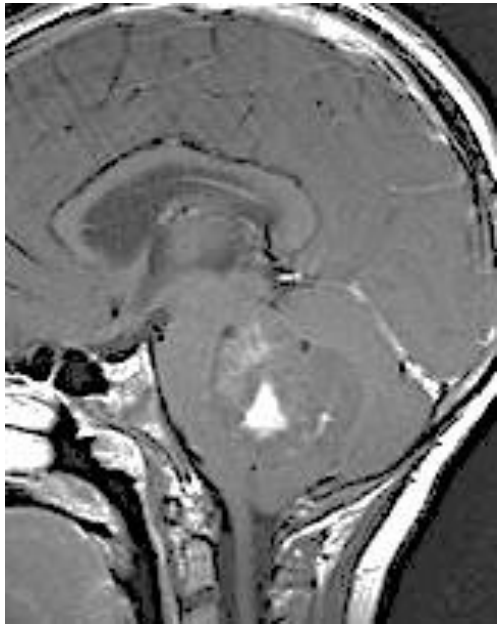
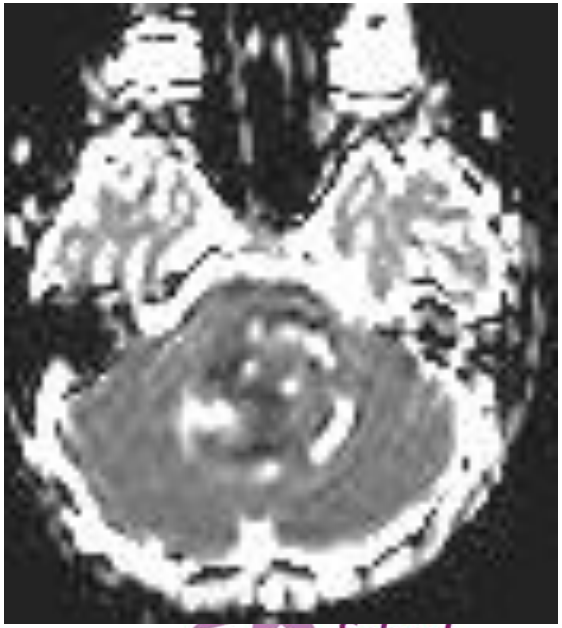
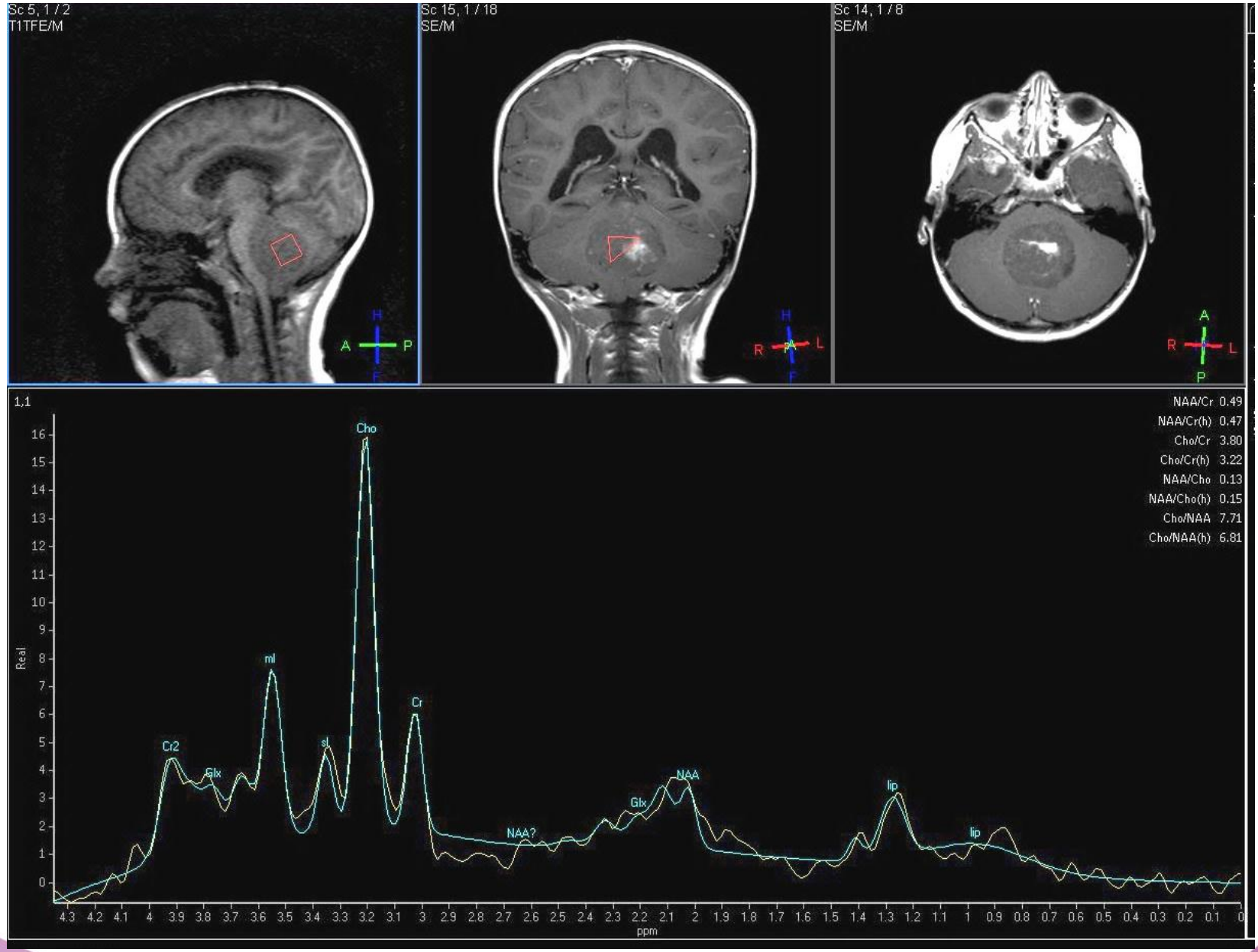


T1 post Gd

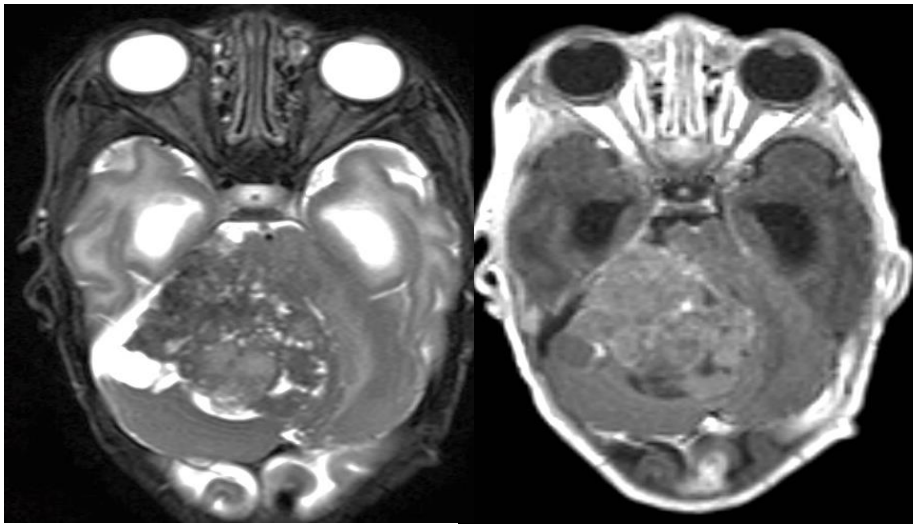


ADC

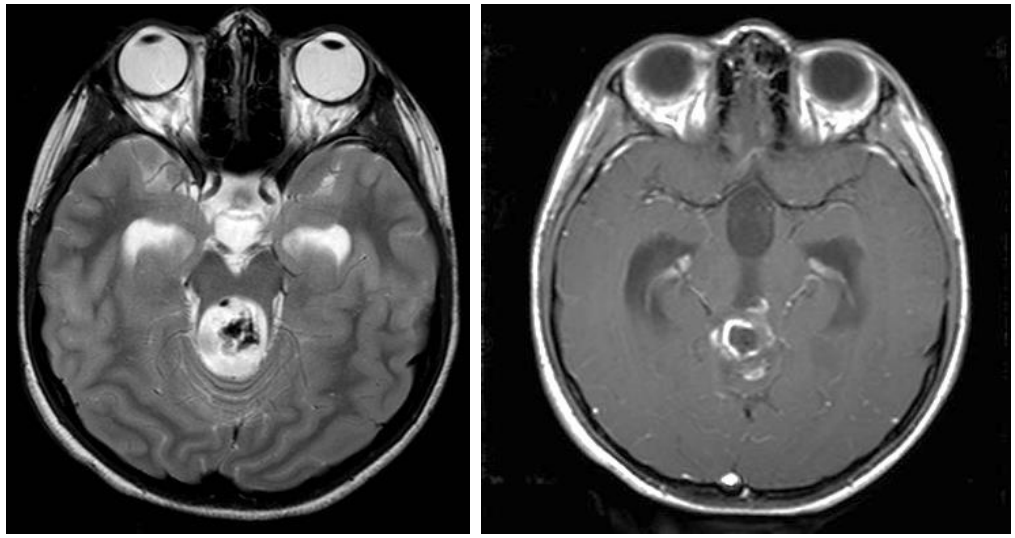
MR Spectroscopy – short echo



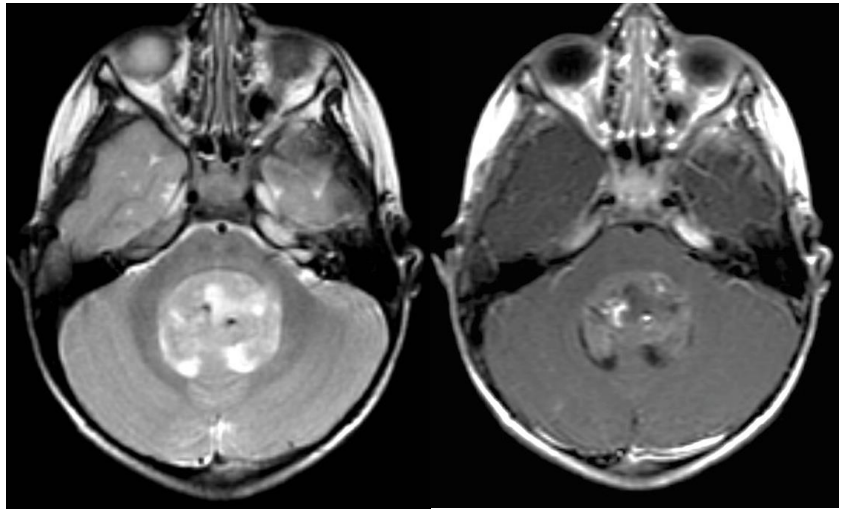
Differential diagnosis



ATRT



Ependymoma

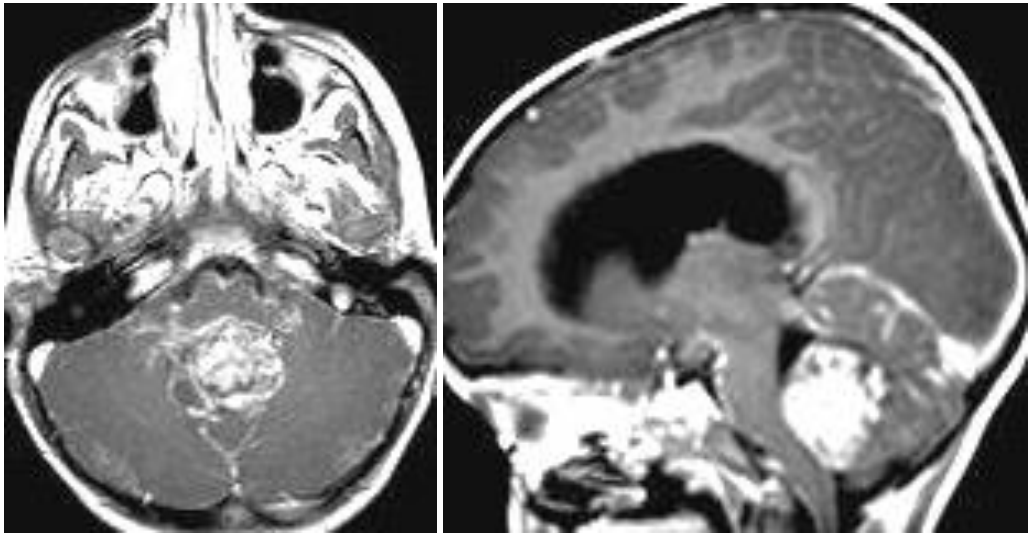


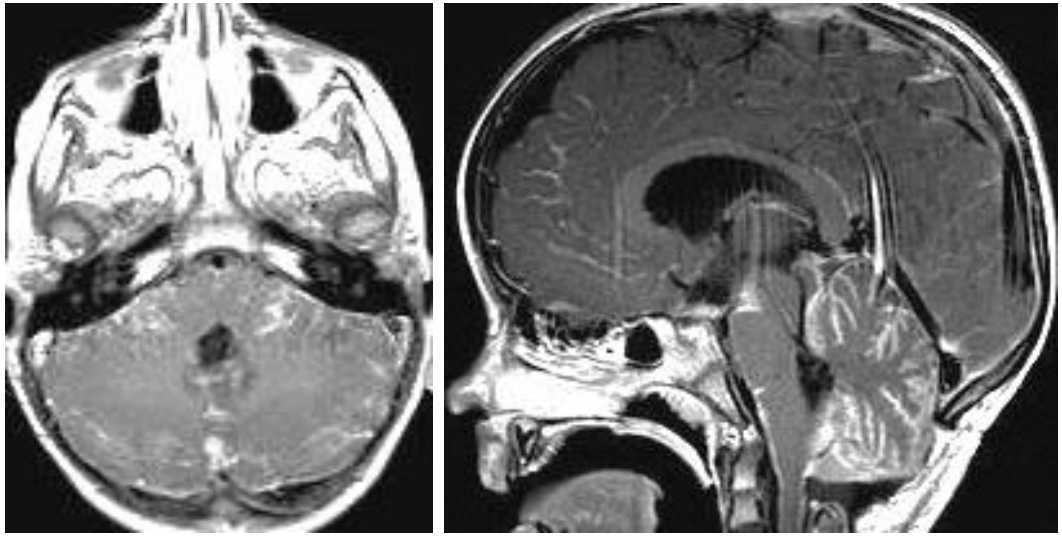
JPA

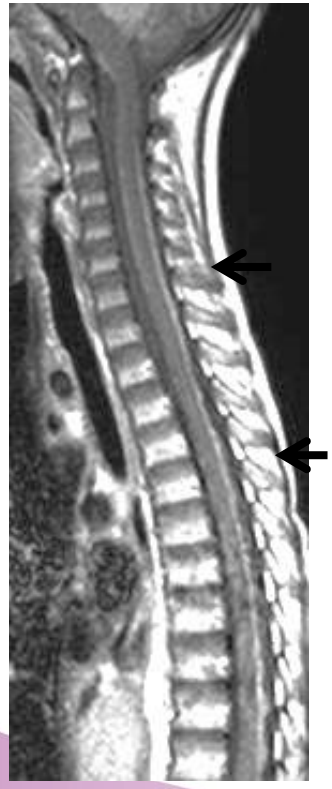
Distant spread

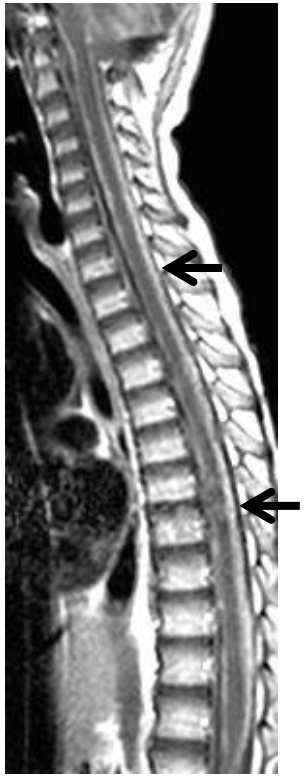
- Must image **entire** neuraxis
- Must image **before** surgery
- Spinal imaging < 3 weeks from surgery inaccurate (false positives) – can lead to delay in definitive surgery
- Metastatic spread in approx 20% at diagnosis
- Local CSF dissemination appears more linear
- Distant spread often more nodular, but also linear
- 5% extra CNS spread

Metastatic spread at diagnosis









Sept ‘12
Pre op

Oct ‘13
Post i/t
etopiside

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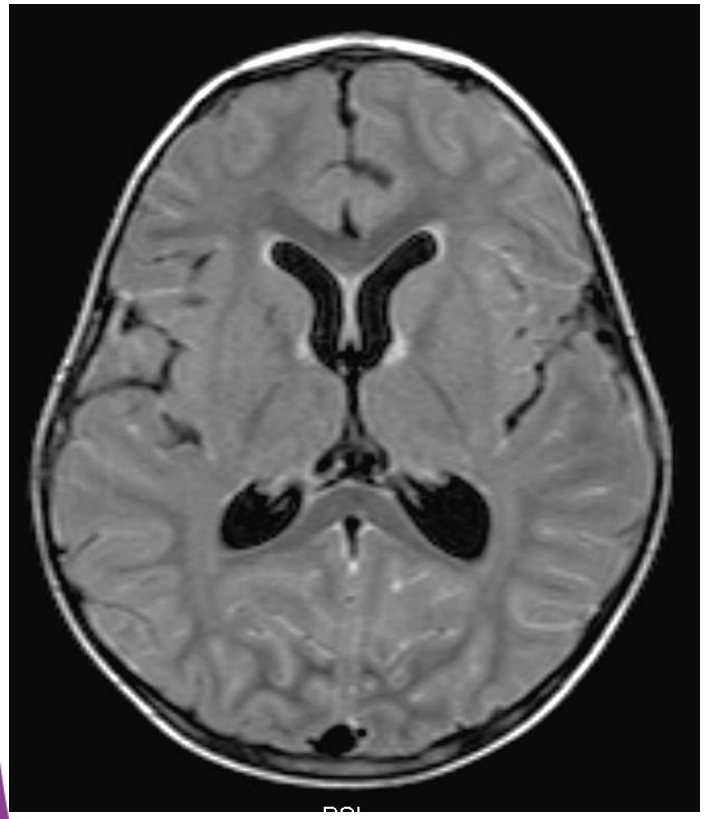
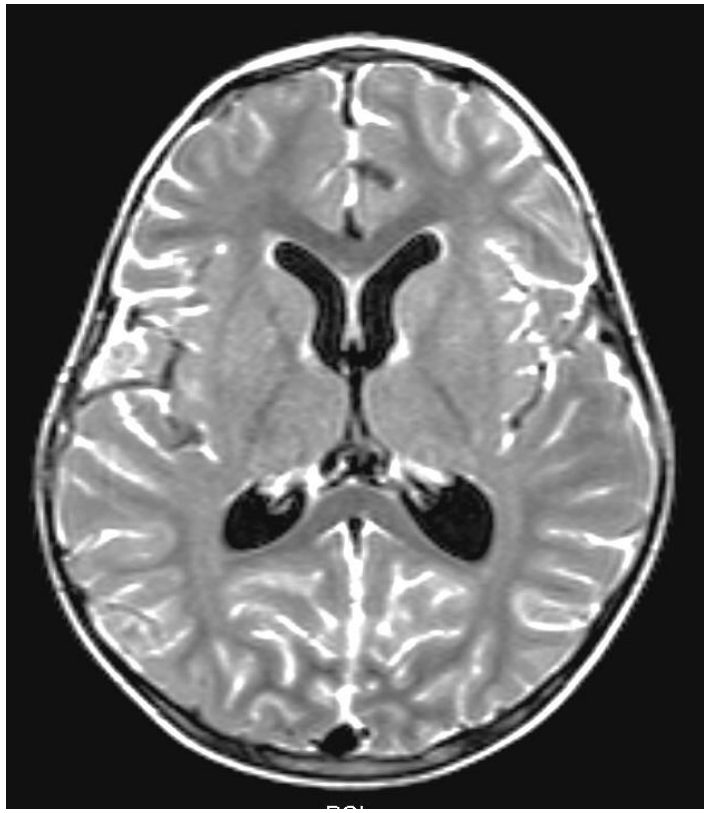
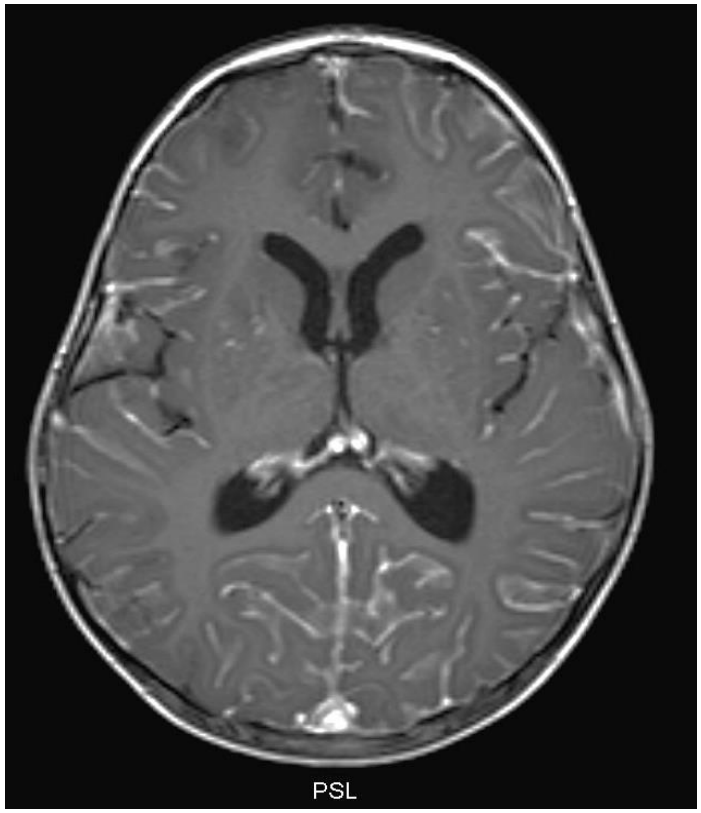
Leptomeningeal spread



Pre Gd FLAIR



Post Gd FLAIR



Post Gd T1

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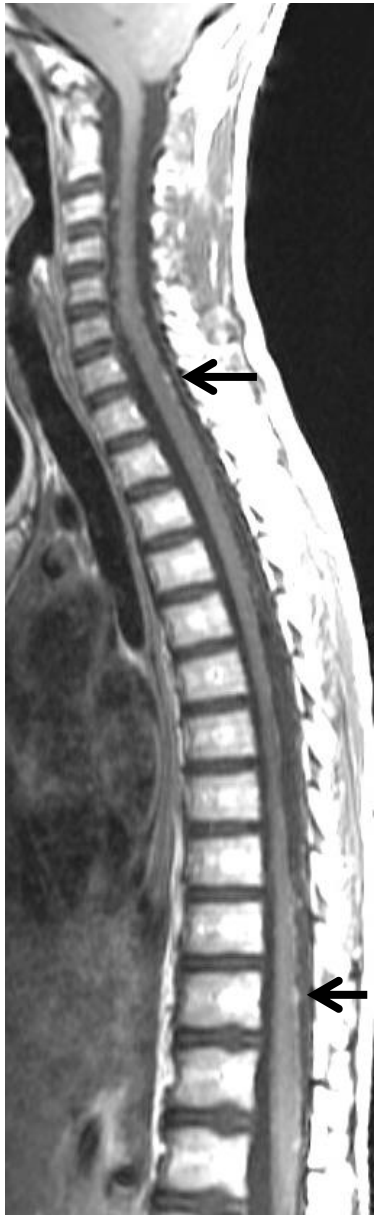
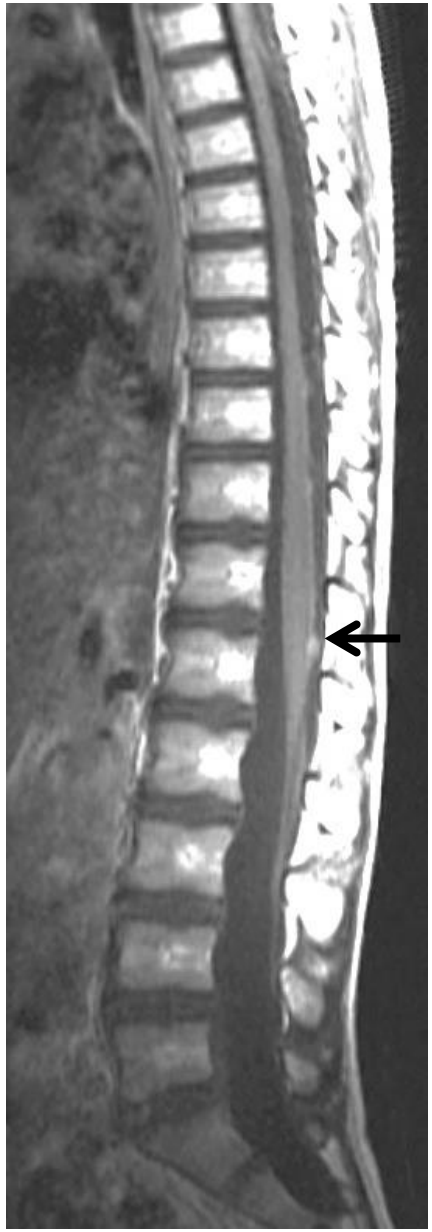
Nodular spinal disease





Risk stratification

Prognosis closely related to:

- Age at diagnosis
- Extent of disease at diagnosis (presence of metastases)
- Extent of residual disease after surgical resection
- Histological type
- Genomic and metabolic aspects increasingly important

Risk stratification

- **Average risk:**
  Children >3yrs
  No metastatic disease after total or near total resection
- **High risk:**
  Children <3yrs (from predictions of outcome studies)
  Children with overt metastatic disease (CSF or imaging +ve)
  Residual tumor >1.5cm^2

Staging – tumor size (T)

- T1 <3cm in diameter
- T2 ≥ 3cm in diameter
- T3a >3cm in diameter with extension
- T3b >3cm in diameter with unequivocal extension into brainstem
- T4 >3cm in diameter with extension beyond cerebral aqueduct and/or down into cervical canal

Staging – metastatic disease (M)

- **M0** No evidence of subarachnoid or hematogenous spread
- **M1** Tumor cells found in CSF
- **M2** Intracranial tumor beyond primary site
- **M3** Gross nodular seeding in spinal subarachnoid space
- **M4** Metastases outside the cerebrospinal axis (esp bone)

Staging – surgical residual tumor

- **R0:** no residual tumor
- **R1:** residual tumor ≤ 1.5cm²
- **R2:** Residual tumor > 1.5cm²
- **R3:** Residual tumor infiltrating brainstem
- **R4:** Residual tumor extending out of the posterior fossa

Risk stratification - outcome

- Non-disseminated MB patients have high likelihood of long-term survival – 80% 5-year survival
- Intensified therapy increases survival in disseminated disease BUT with major quality of life issues

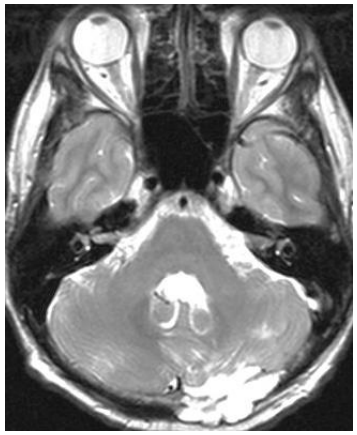
Radiology follow up screening

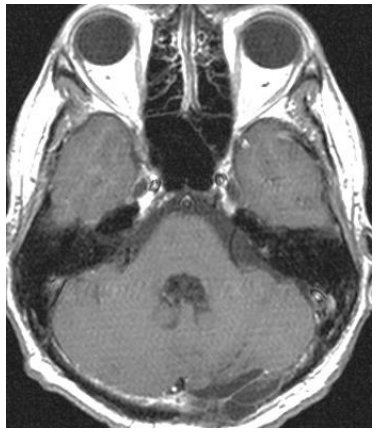
- Imaging interval dictated by trial regimes – typically 3-6 month intervals for first 5 yrs following initial therapy (for recurrence or new CSF spread)
- Imaging of brain and whole spine
- Role of long term imaging uncertain/debatable

Tumour recurrence

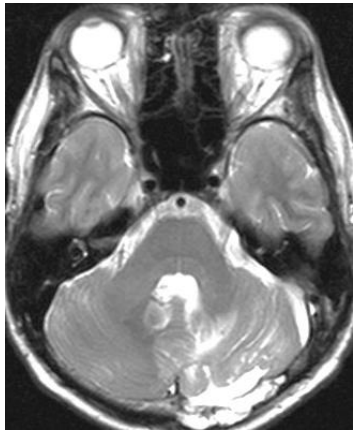
- Recurrence generally reflects appearance of original tumour
- Some recurrences don’t enhance or may only be detected by DWI
- Look for ‘hidden’ sites – anterior cranial fossa, sacral cul-de-sac

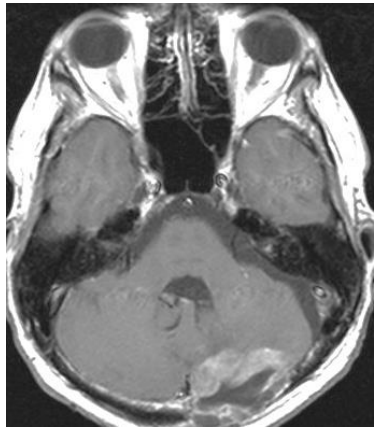
Late recurrence - nodular



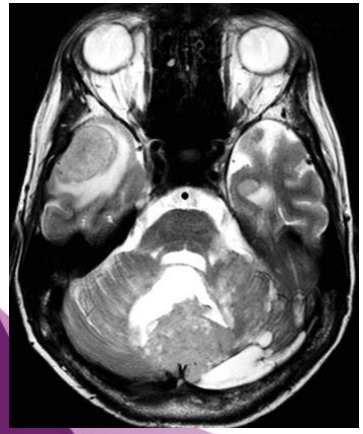


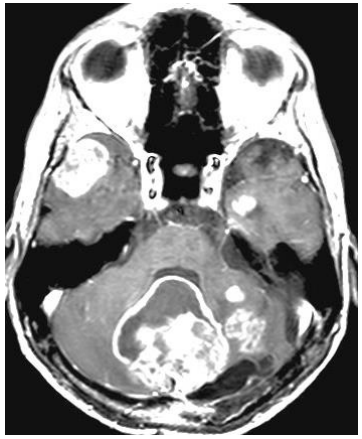
April 2006 – 6 years post surgery





July 2013 – 13 years post surgery





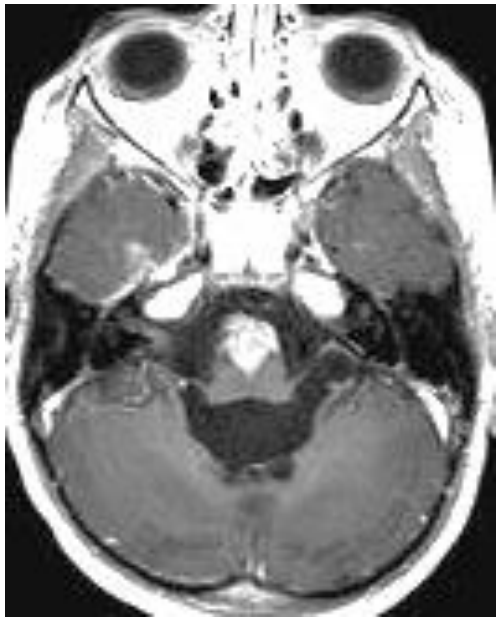
August 2015 – 15 years post surgery

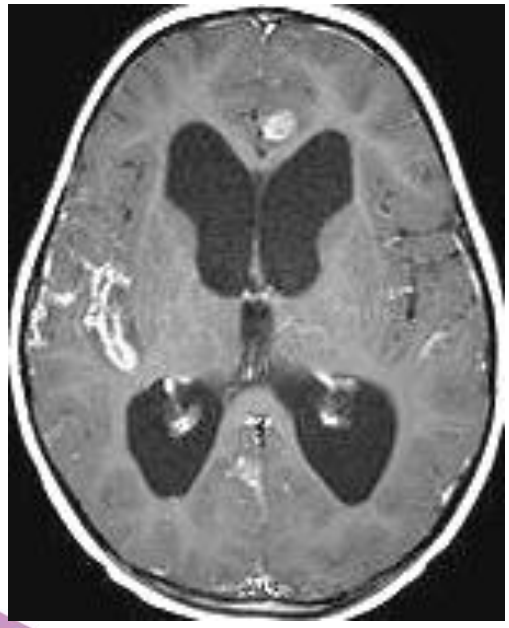
T2

T1 post Gd

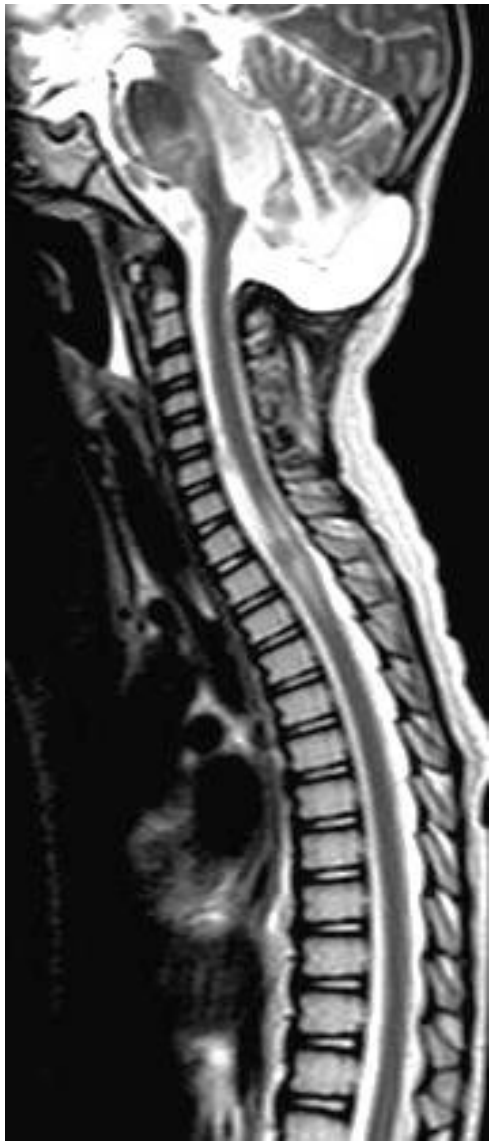
ESTRO School

Recurrence – nodular and linear

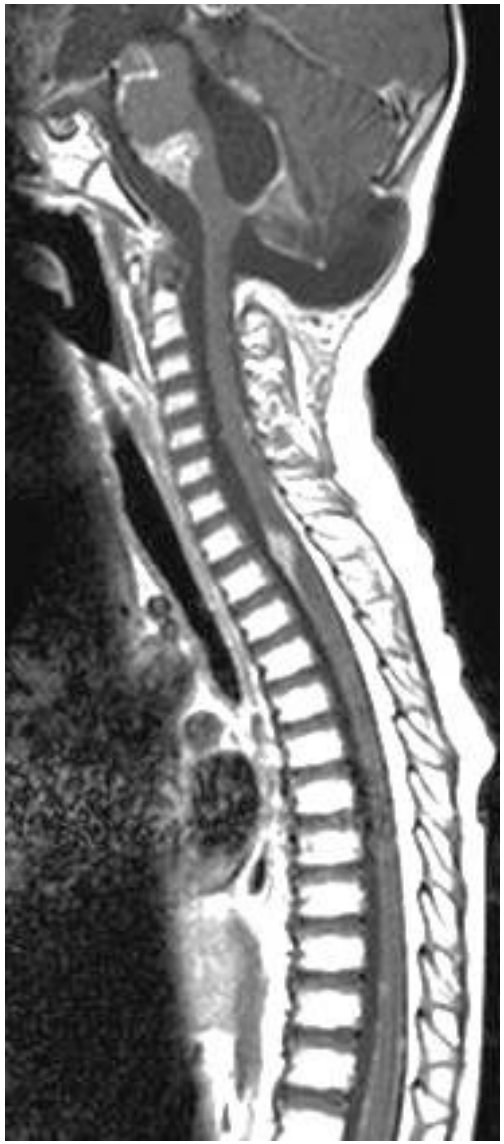




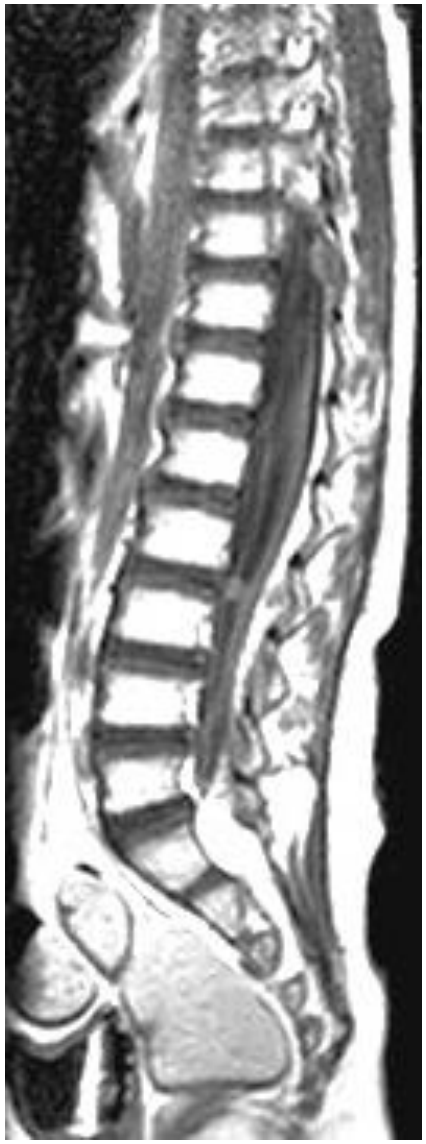
T1 post Gd



T2



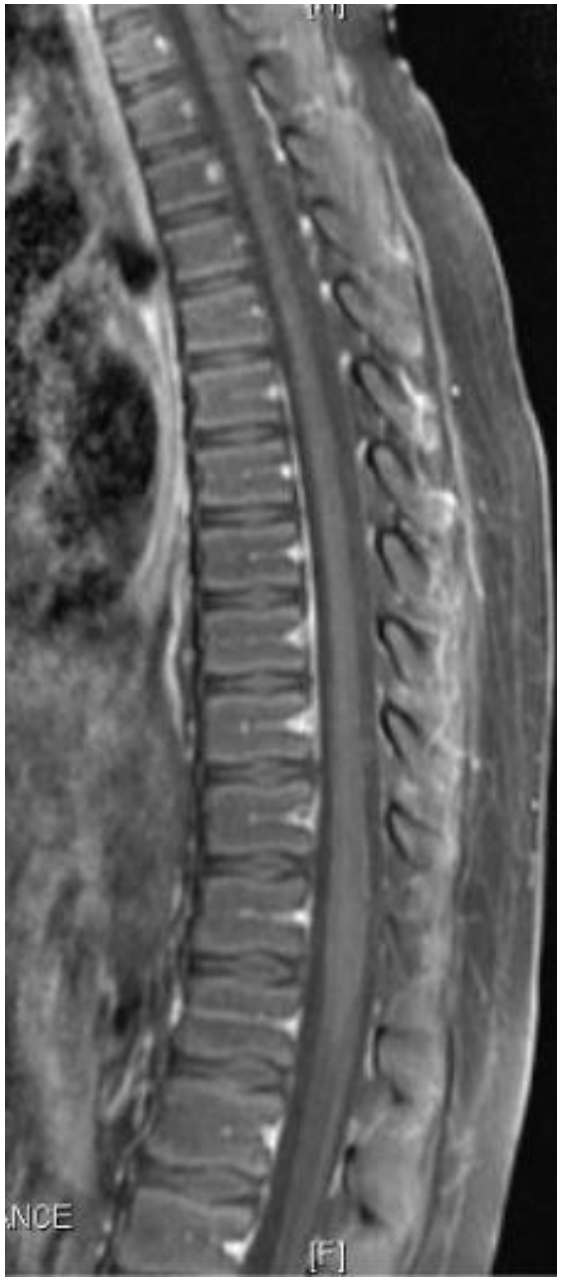
T1 post Gd



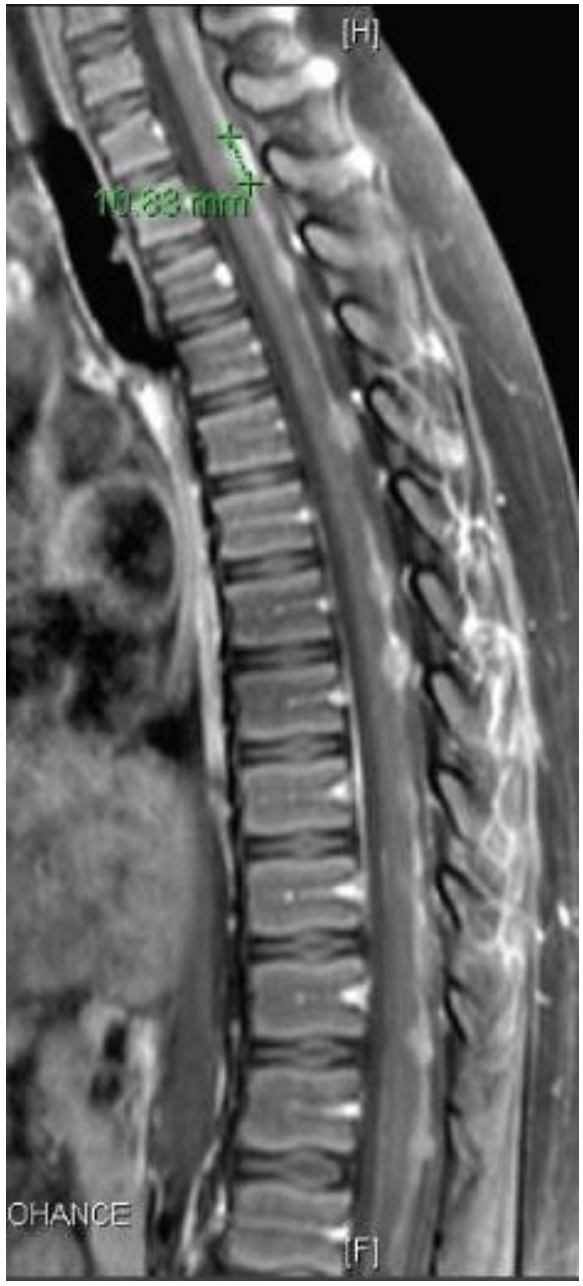
T1 post gd

ESTRO School

Recurrence after craniospinal RT



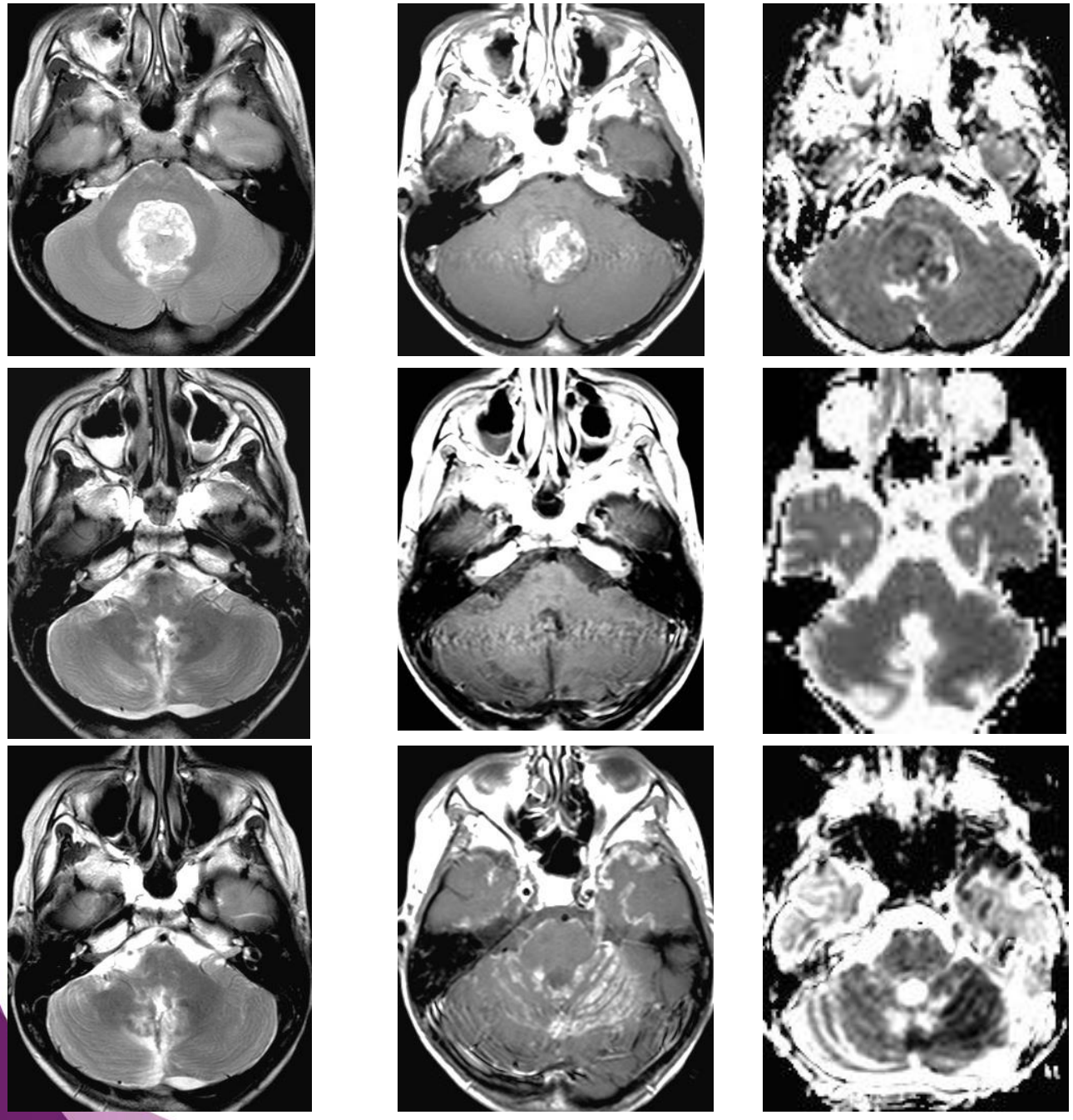
Pre RT



Post RT

ESTRO School

Late recurrence on DWI - linear



Presentation

10 mths post RT

15 mths post RT

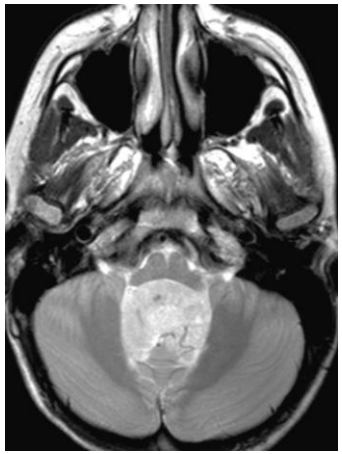
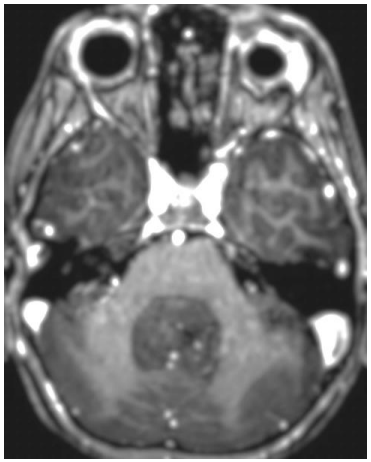
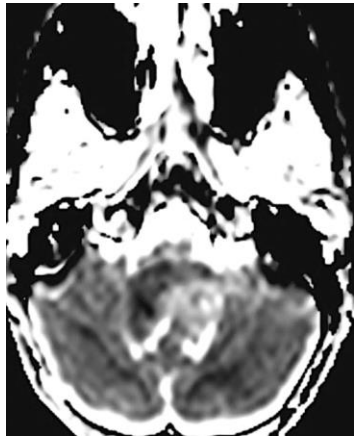
T2

T1 post Gd

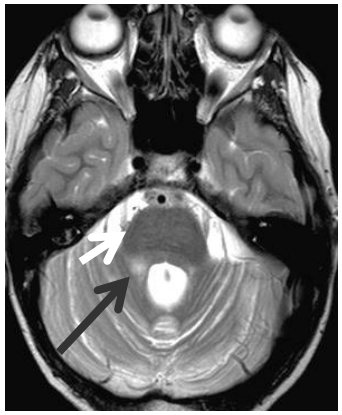
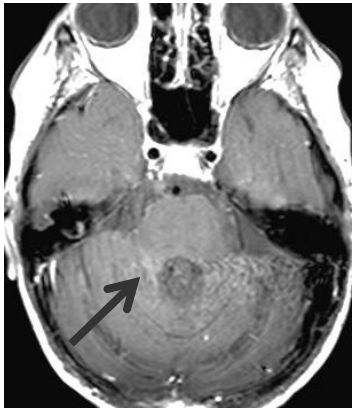
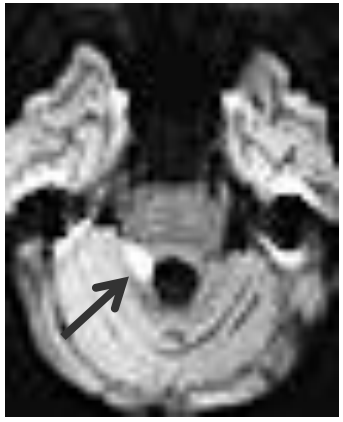
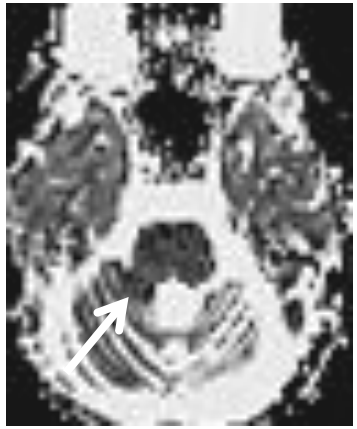
ADC

ESTRO School

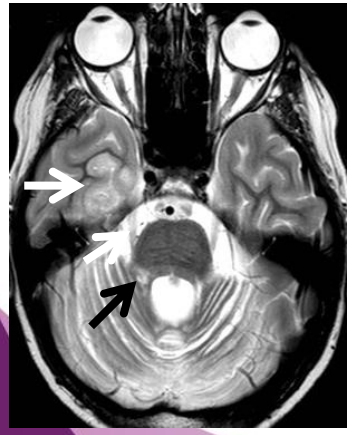
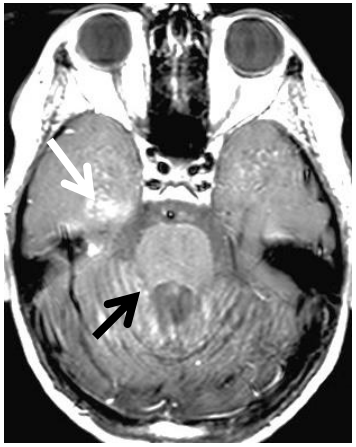
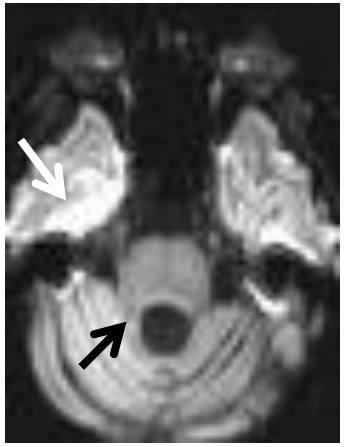
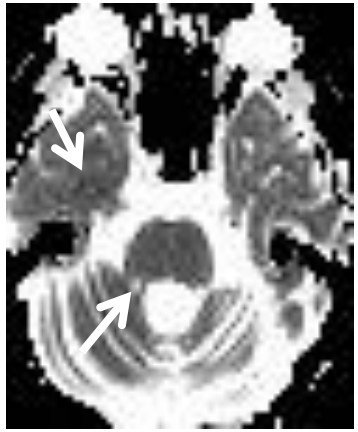
Late recurrence on DWI - nodular

Presentation

2 yrs later-
pre SRT

1 yr post SRT

T2 T1 post Gd DWI ADC

ESTRO School

Late effects

- Brain: Intellectual deficit
- Ocular lens: Cataract
- Retina: Radiation retinopathy
- Optic nerve: Neuritis
- Inner ear: Sensorineural hearing loss
- Hypothalamic-pituitary axis: Endocrinopathies
- Spinal cord: Chronic progressive myelitis

Late effects - radiology

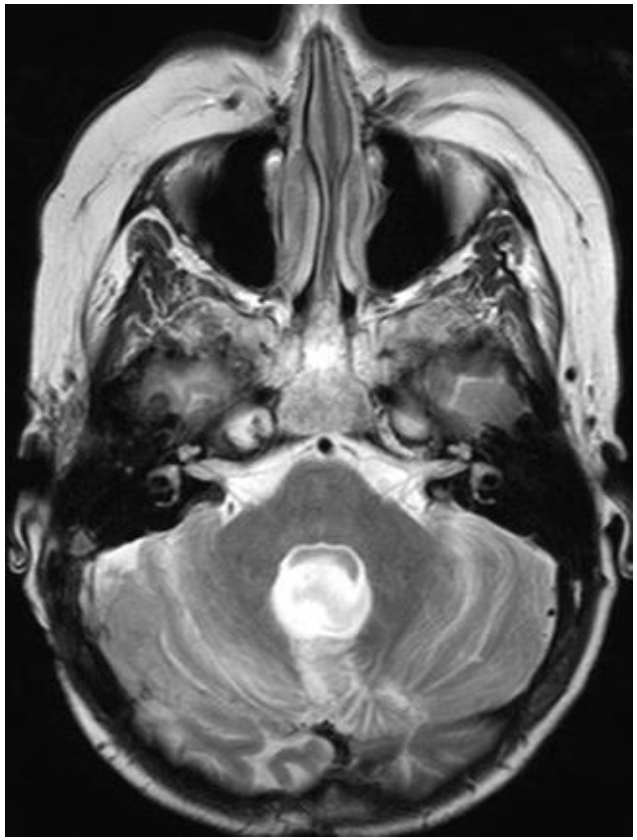
- White matter damage
- Radionecrosis
- Tumors – meningioma
- Cavernomas
- Posterior fossa syndrome

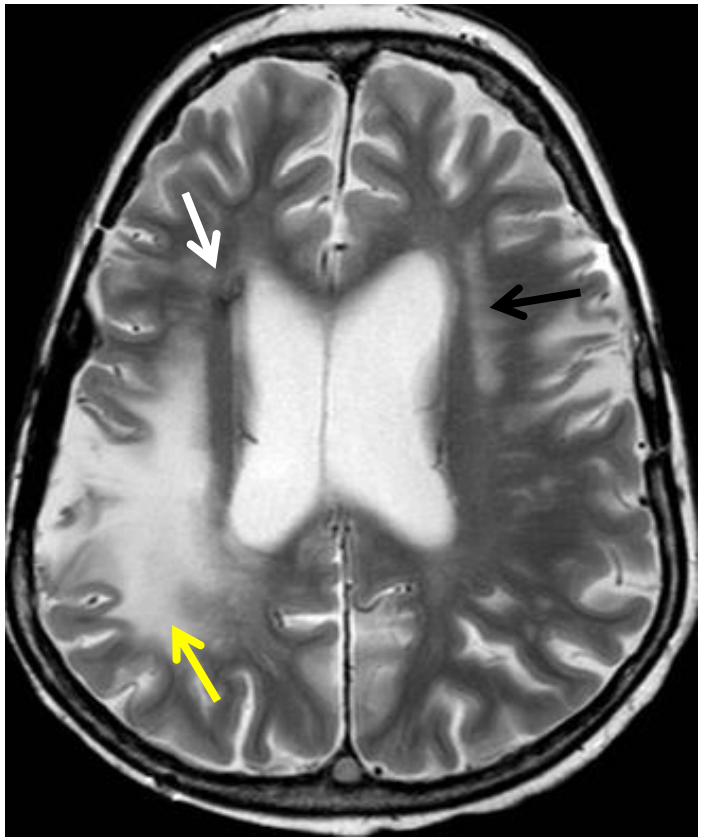
White matter injury

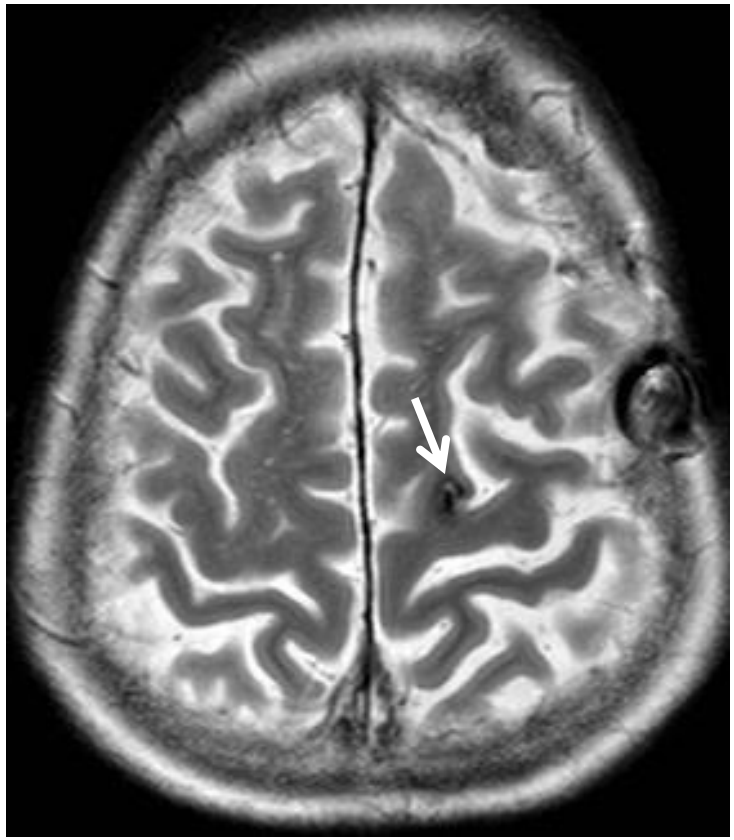
- **Post surgical damage**

- **Leucoencephalopathy:**
  i. Punctate/small T2 or FLAIR hyperintensities in frontoparietal white matter
  ii. Confluent T2/FLAIR hyperintensities in frontoparietal WM
  iii. White matter cysts

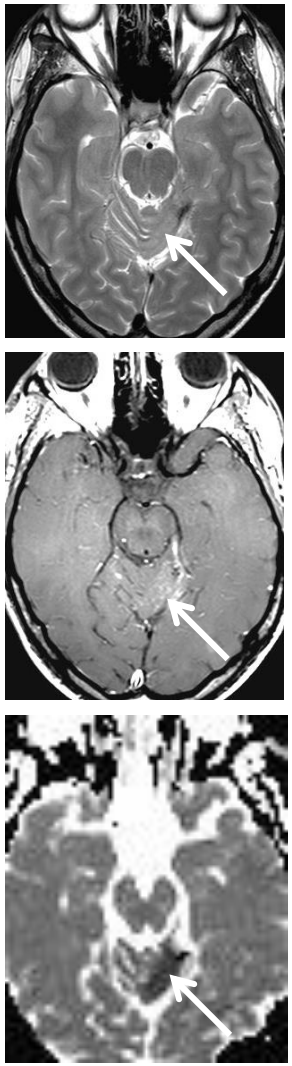
Leucoencephalopathy, post surgical encephalomalacia, cavernomas



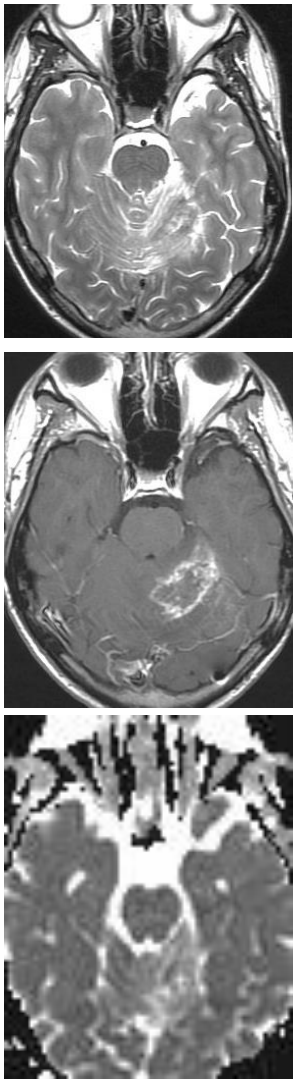




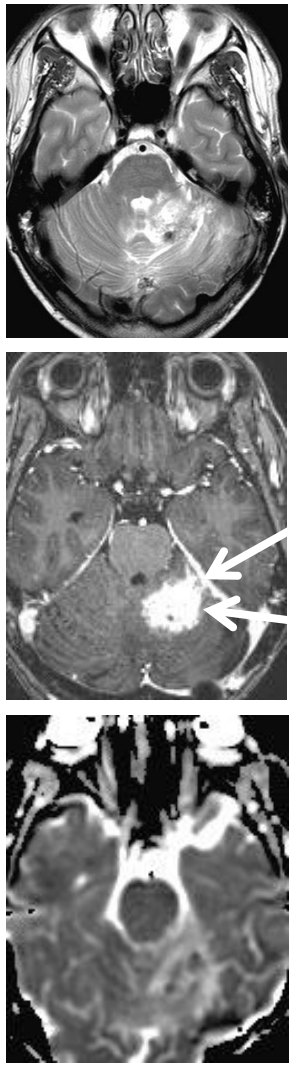
Radionecrosis

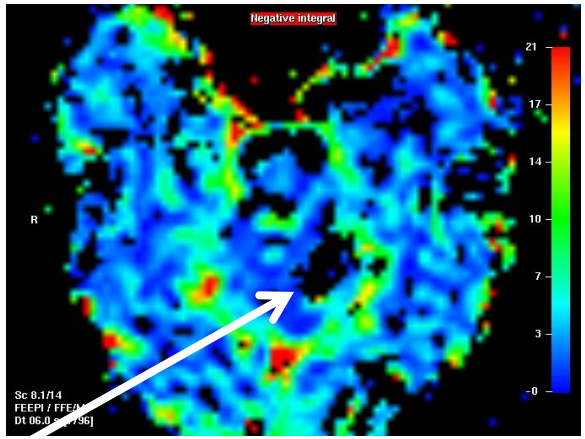


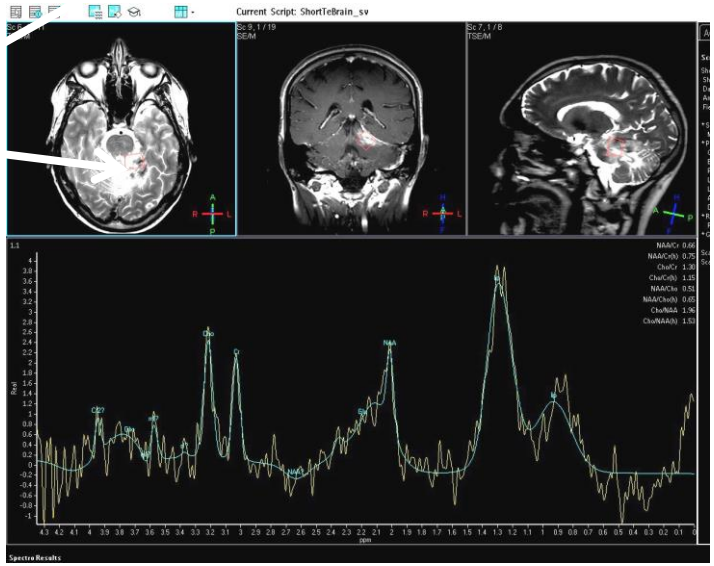
12.2014 - at recurrence



06.2015 - 5 mths post protons

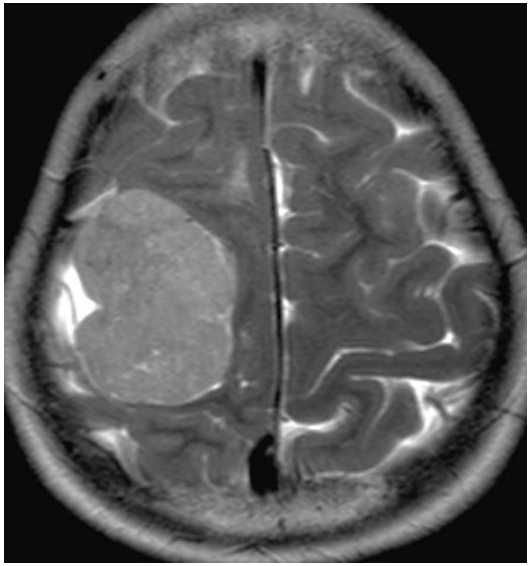




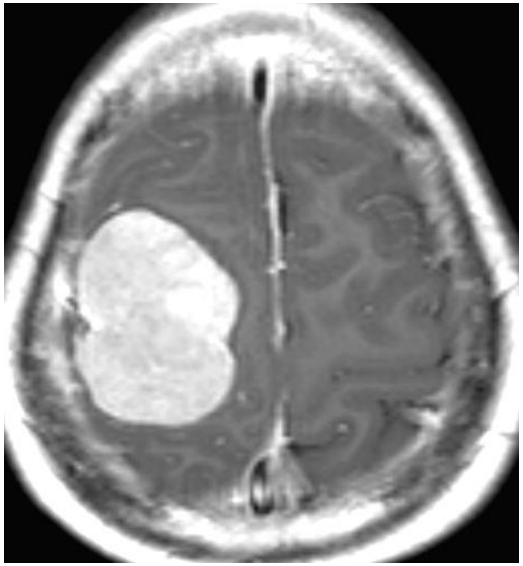


11.2015 - 10 mths post protons

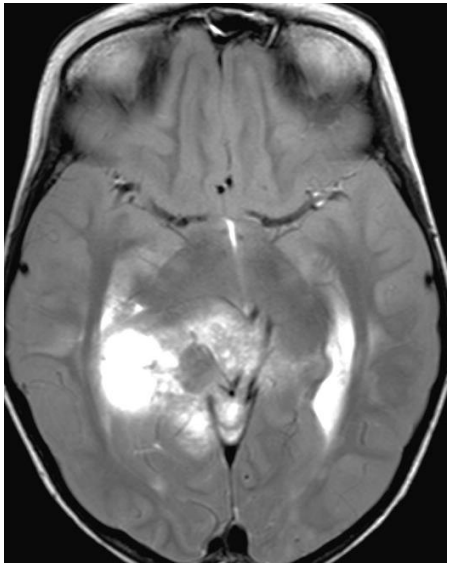
Late effects - meningioma



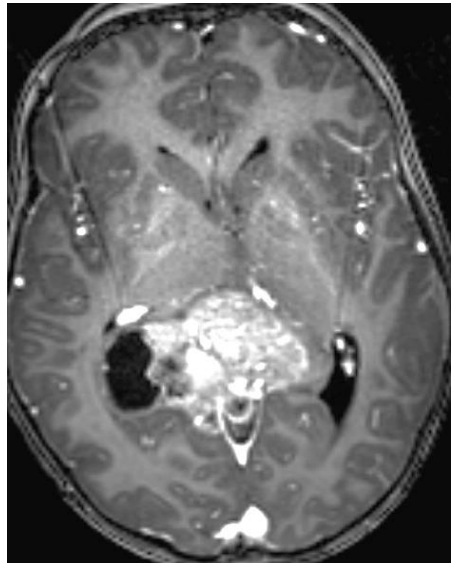
T2



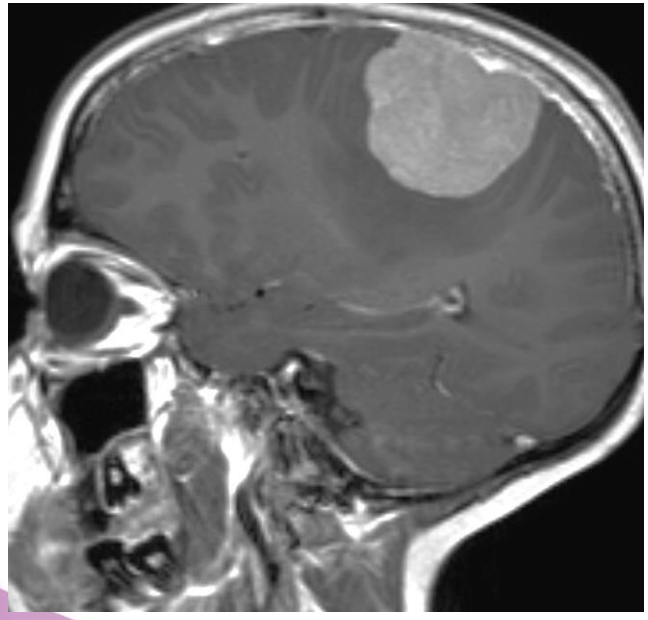
T1 post Gd



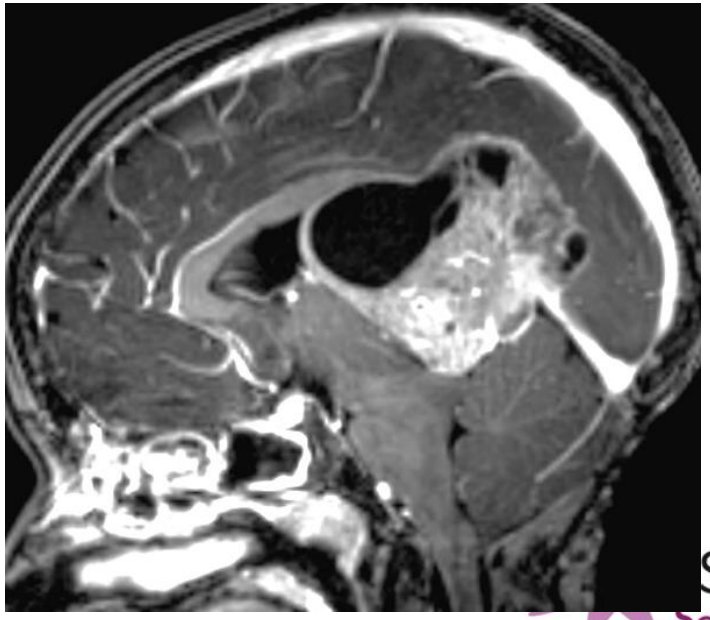
T2



T1 post Gd



T1 post Gd

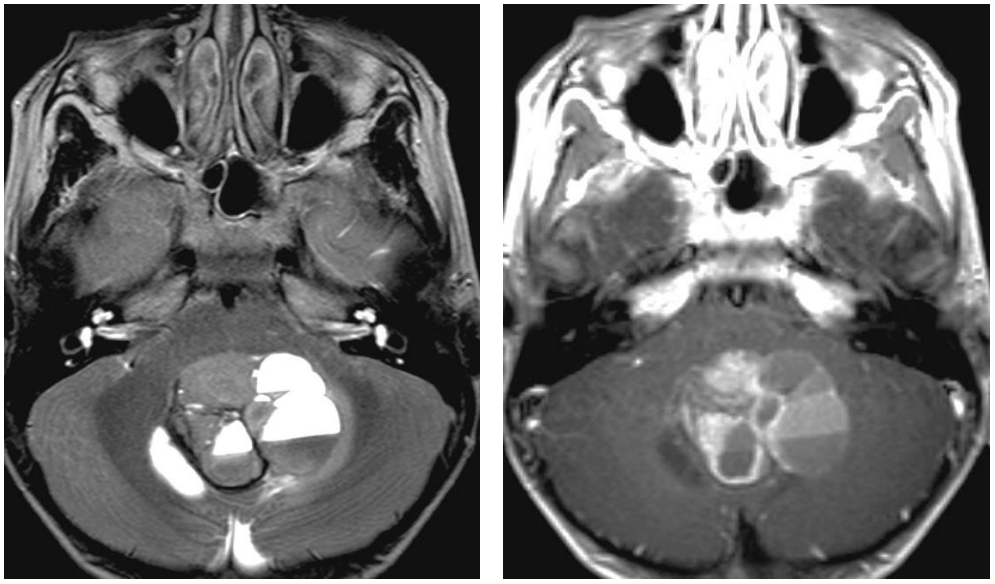


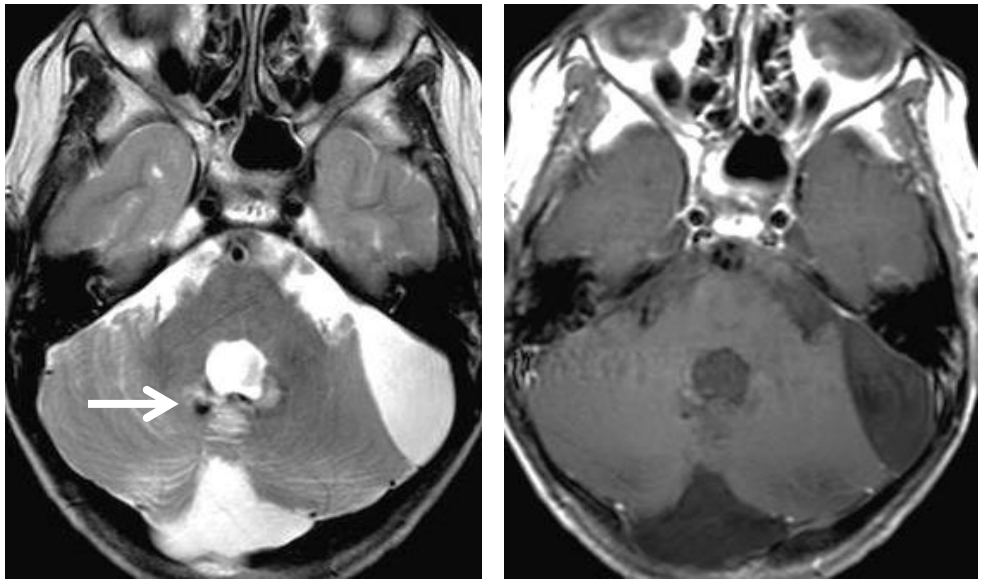
T1 post Gd

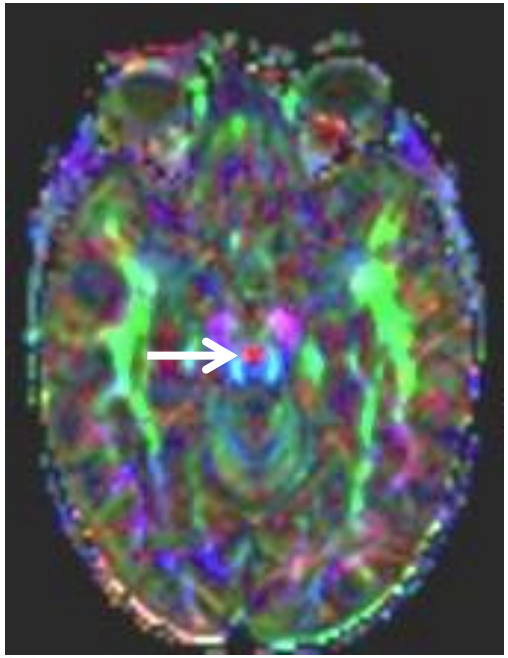
Posterior Fossa Syndrome

- Occurs in approx. 15-25% of midline medulloblastomas
- Onset usually within 12-24 hrs of surgery
- Slowly improves, but significant long term morbidity
- Results from surgical damage to the efferent cerebellar pathways
- Correlated with hypertrophic olivary degeneration (inferior olivary nuclei)
- ? Damage to dentate nuclei/superior cerebellar peduncles
- May see decreased CBF in frontal lobes

PFS imaging







Presentation

1 year later

ESTRO School

EPENDYMOMA

Ependymoma - background

- Most common in childhood
- Second most common childhood brain tumor (10%)
- Occurs anywhere in neuraxis
- 60% post. fossa, 30% supratentorial, 10% spinal
- Account for 15% of post. fossa tumors
- Most frequently diagnosed between 2 and 5 years
- Slightly more common in boys

Ependymoma - background

- Arise from neuroepithelial lining of ventricles or central canal of spinal cord
- Recent studies suggest radial glial stem cells as origin
- Most post. fossa ependymomas arise in 4V
- Most of supratentorial ependymomas are intraparenchymal, also from 3V or lateral ventricles

Ependymoma - background

- Infratentorial tumors grow exophytically from the ventricular surface of medulla:
  Floor of 4V (60%): extending through Magendie onto dorsal surface of cord
  Lateral aspect of 4V (30%): extending through Luschka into CP angle and over anterolateral aspect of pons, medulla
  Roof of 4V (10%)
- Similar presentation to MB but usually longer duration of symptoms (6-12 months v 4 months for MB's)

Ependymoma - Pathology

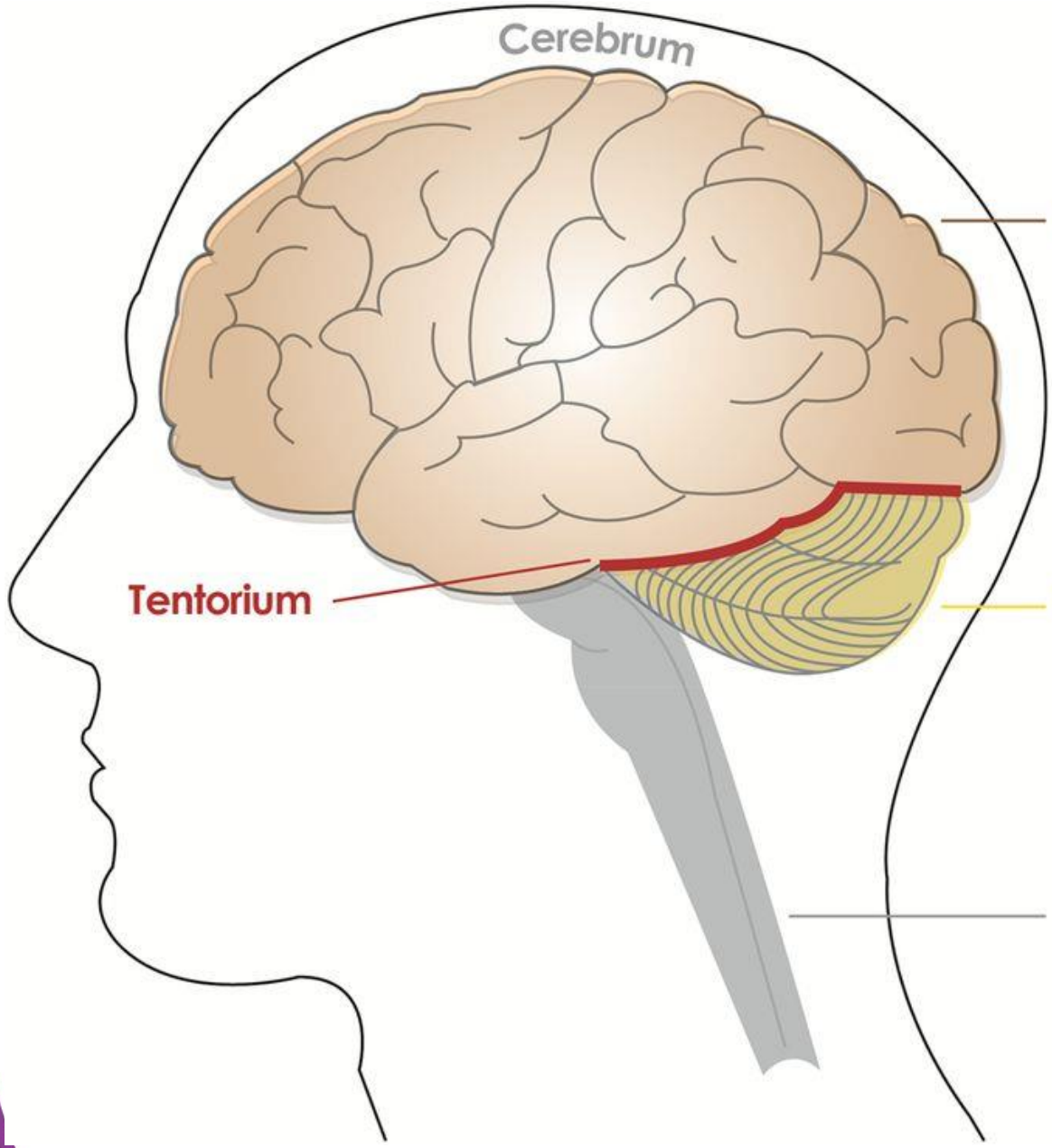
- Gd I – subependymoma and myxopapillary ependymoma
- Gd II – Ependymoma
- Gd III – Anaplastic ependymoma. Presence of hypercellular areas, necrosis, microvascular proliferation, high mitotic indices confer worse PFS

Anaplastic histology + infratentorial location carries increased mortality risk in younger children

Supratentorial location associated with higher mortality in older patients

Ependymoma - Genetics

- 2 demographic, genetic and clinical subgroups in posterior fossa ependymomas
- Group A (PFA) and group B (PFB)
- PFA - mainly in infants, lateral post. fossa localization: poor prognosis
- PFB - mainly in older children/adults: better prognosis



Supratentorial Ependymoma

C11orf95-RELA+, about 70% supratentorial ependymoma.
More common in children than adult

C11orf95-RELA- and YAP1 fusion+,
More common in younger children

Infratentorial Ependymoma

PFA:CIMP+; younger age; poor prognosis

PFB:CIMP-; older age; better prognosis

Spinal Cord Ependymoma

More common in adults than in children
Frequent *NF2* mutation; better prognosis

ESTRO School

Ependymoma - surgery

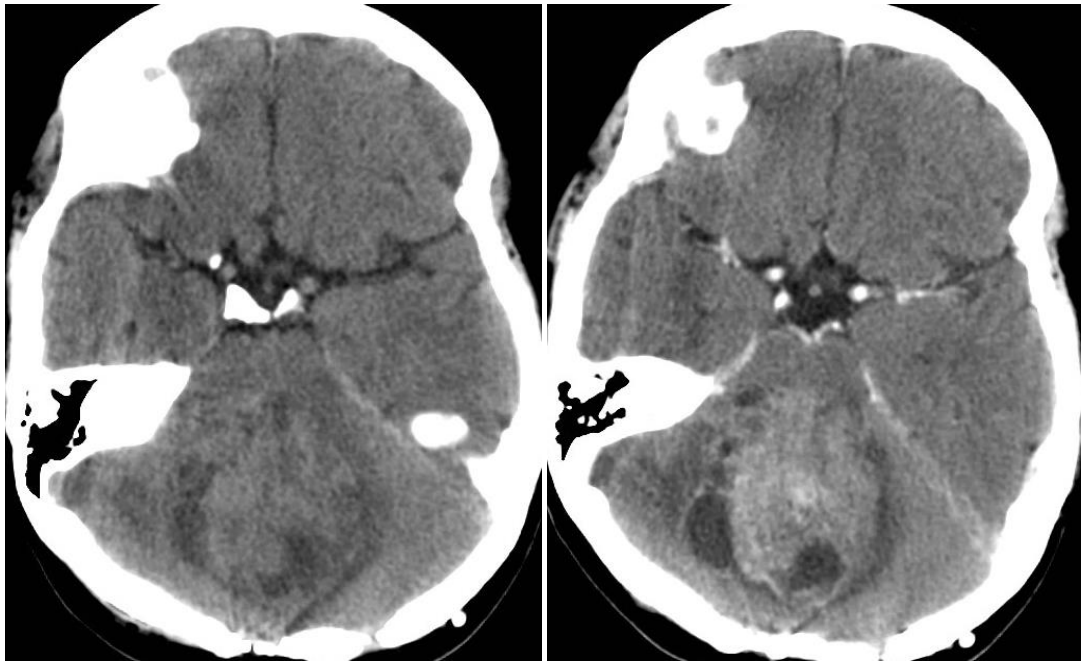
- GTR of tumors arising from floor or lateral aspect of 4V difficult as tumor applied to surface of brainstem and cranial nerves
- Extent of resection most important prognostic factor
- Intra-operative MRI optimal – enables ‘on table’ further resection
- Post op imaging (24-48 hrs) to assess degree of resection
- Second look surgery should be considered for residuum
- Consensus MDT useful for further follow-up/surgery

Imaging

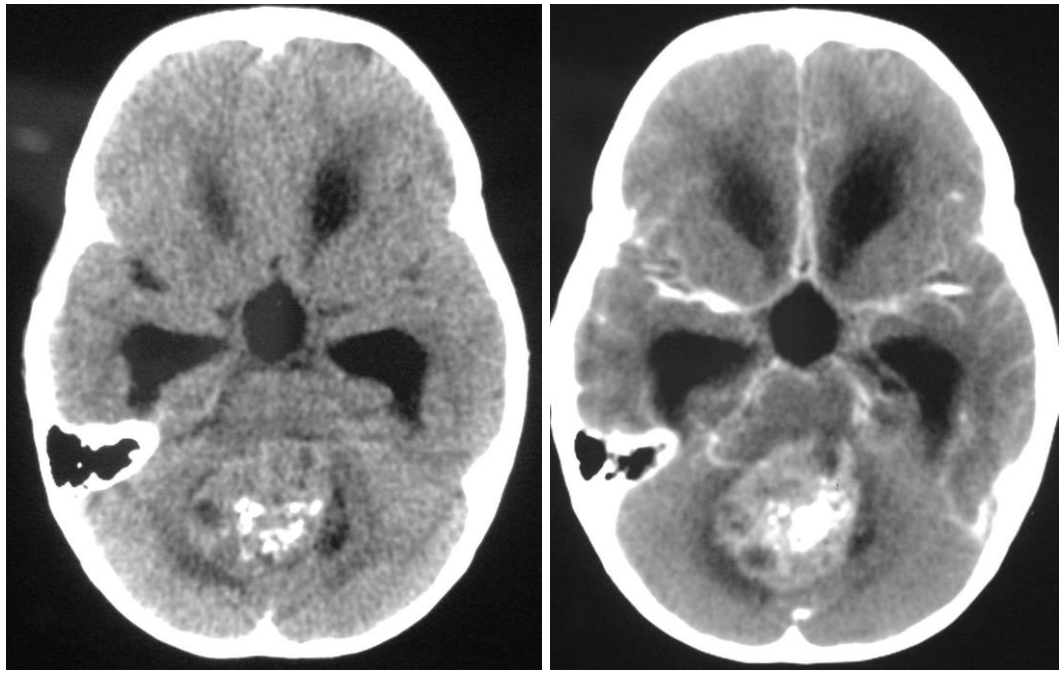
Ependymoma - CT

- Typically iso to mildly hyperdense, often heterogeneous
- Approx 50% calcification (diffuse, coarse or nodular)
- Cysts 20%, haemorrhage 10%
- Soft, pliable tumor (“like toothpaste”)
- Extends out through 4V outlets
- Enhancement is variable and irregular

CT – Infratentorial Ependymoma



Pre contrast Post contrast



Pre contrast Post contrast

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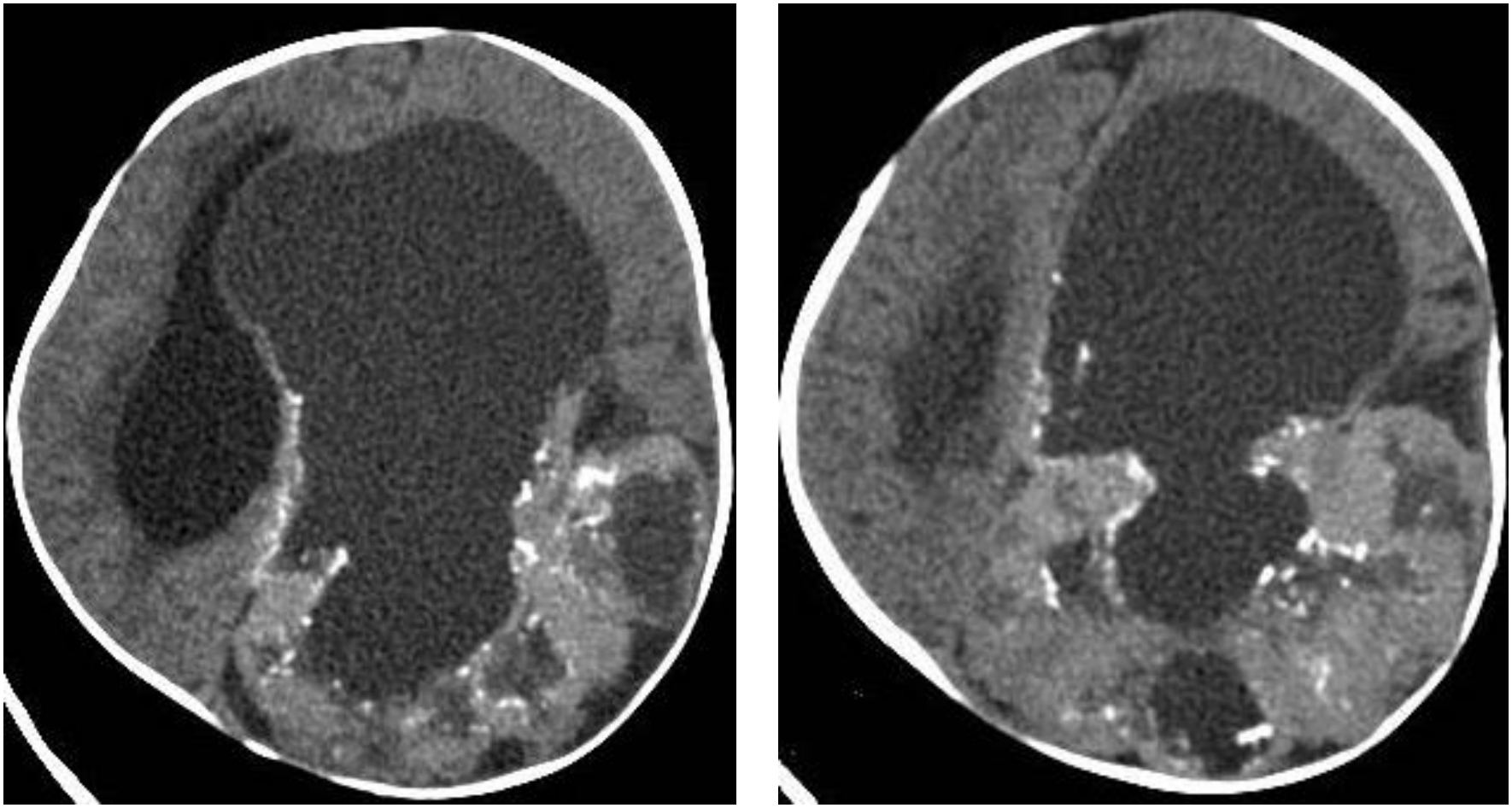
CT – supratentorial ependymoma



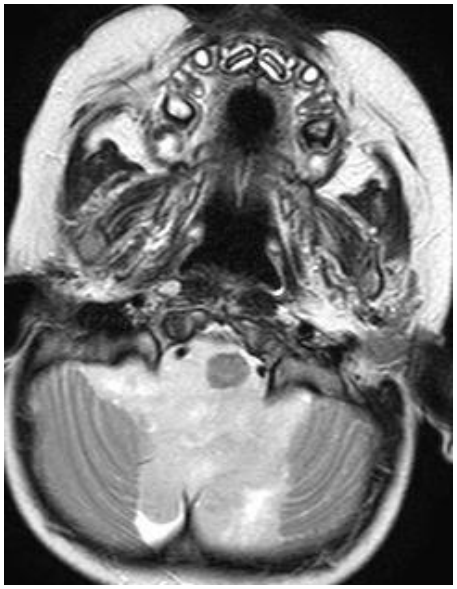
Ependymoma - MRI

- Heterogeneous tumor
- Solid components iso- to hyperintense on T2/FLAIR
- T2 hyperintense cysts frequently seen
- Hypointense areas reflect calcification and/or hemorrhage
- Usually iso- to hypointense on T1
- Enhancement is variable
- Post. fossa tumors grow to fill 4V; may invade brainstem

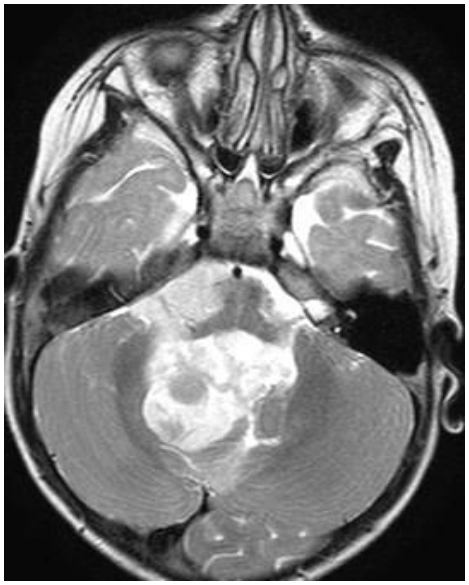
Ependymoma - MRI

- 30-50% extend into the cervical spinal canal
- Encasement of vessels/nerves better seen than on CT
- Usually increased diffusion on DWI/patchy restricted diffusion on ADC
- MRS: non-specific tumor spectra (notably high Choline)

MRI: posterior fossa - lateral



T2



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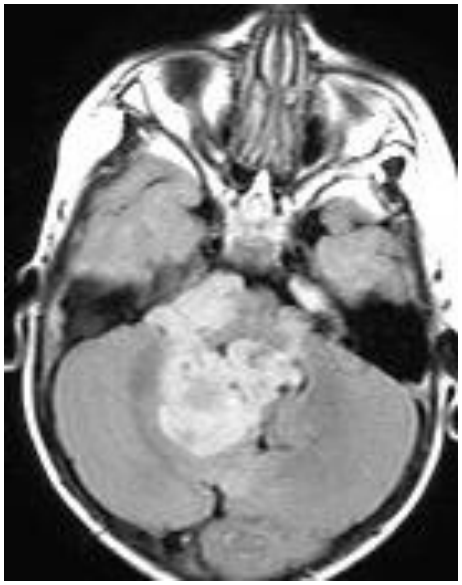
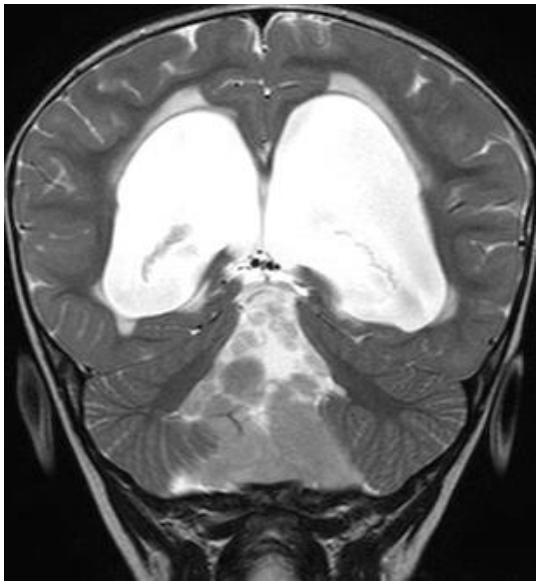


FLAIR



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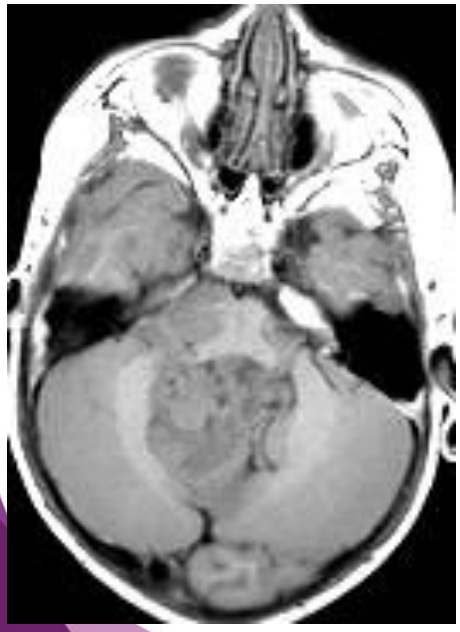
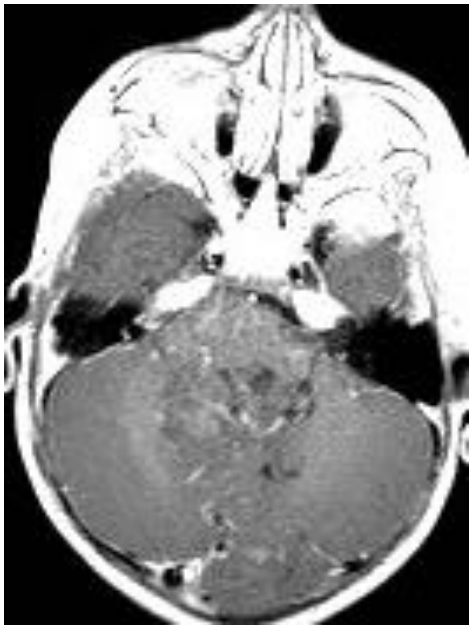
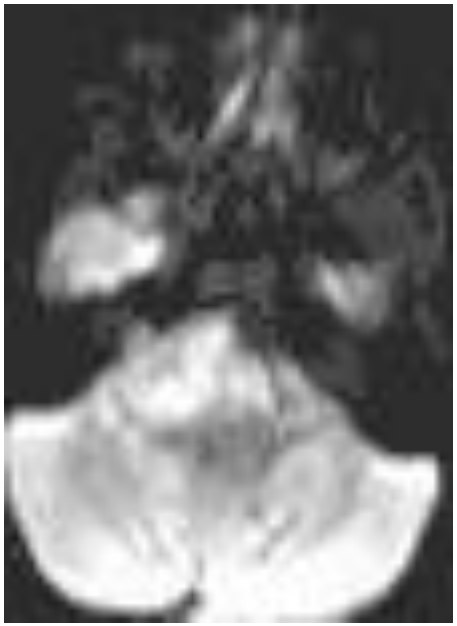


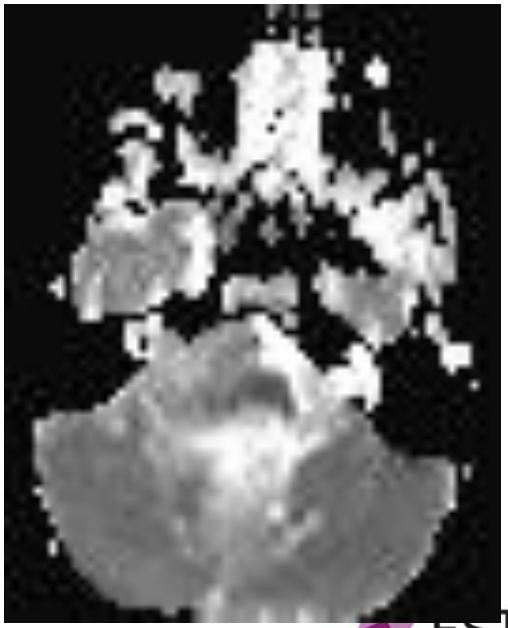
T1



T1 post Gd



DWI



ADC

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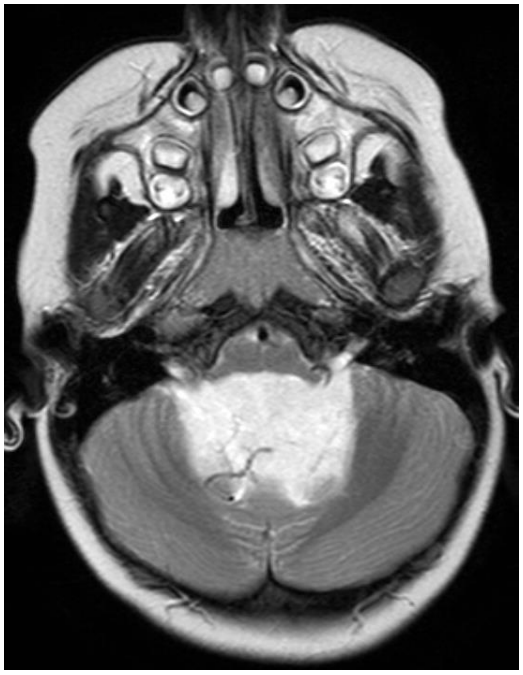
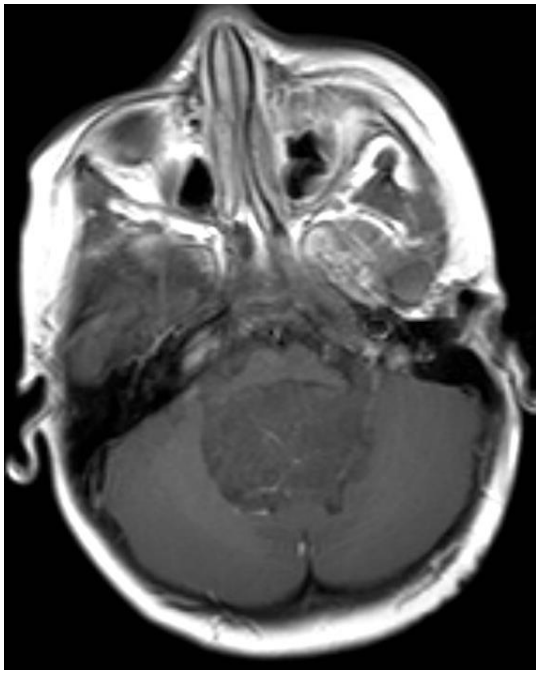
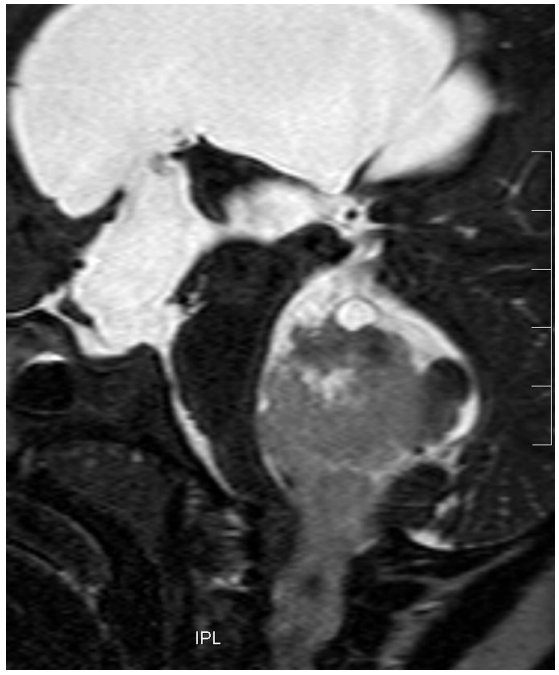
MRI: posterior fossa - midline



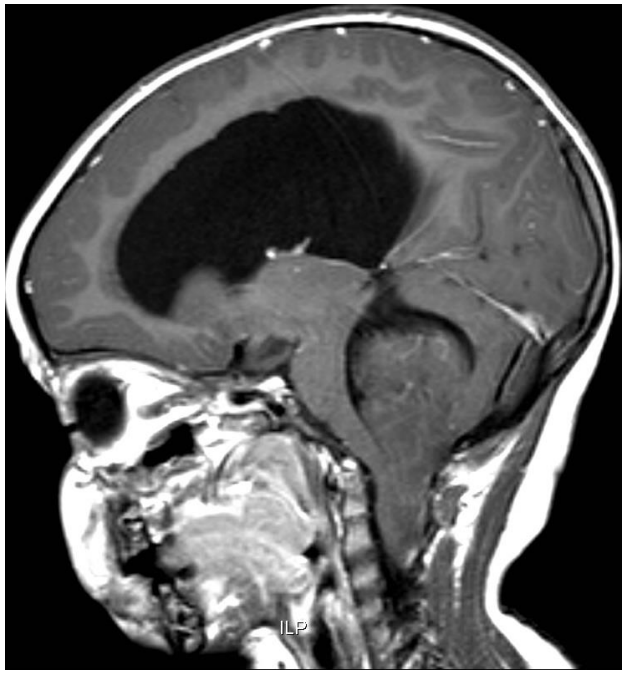
Ax T2



T1 post Gd

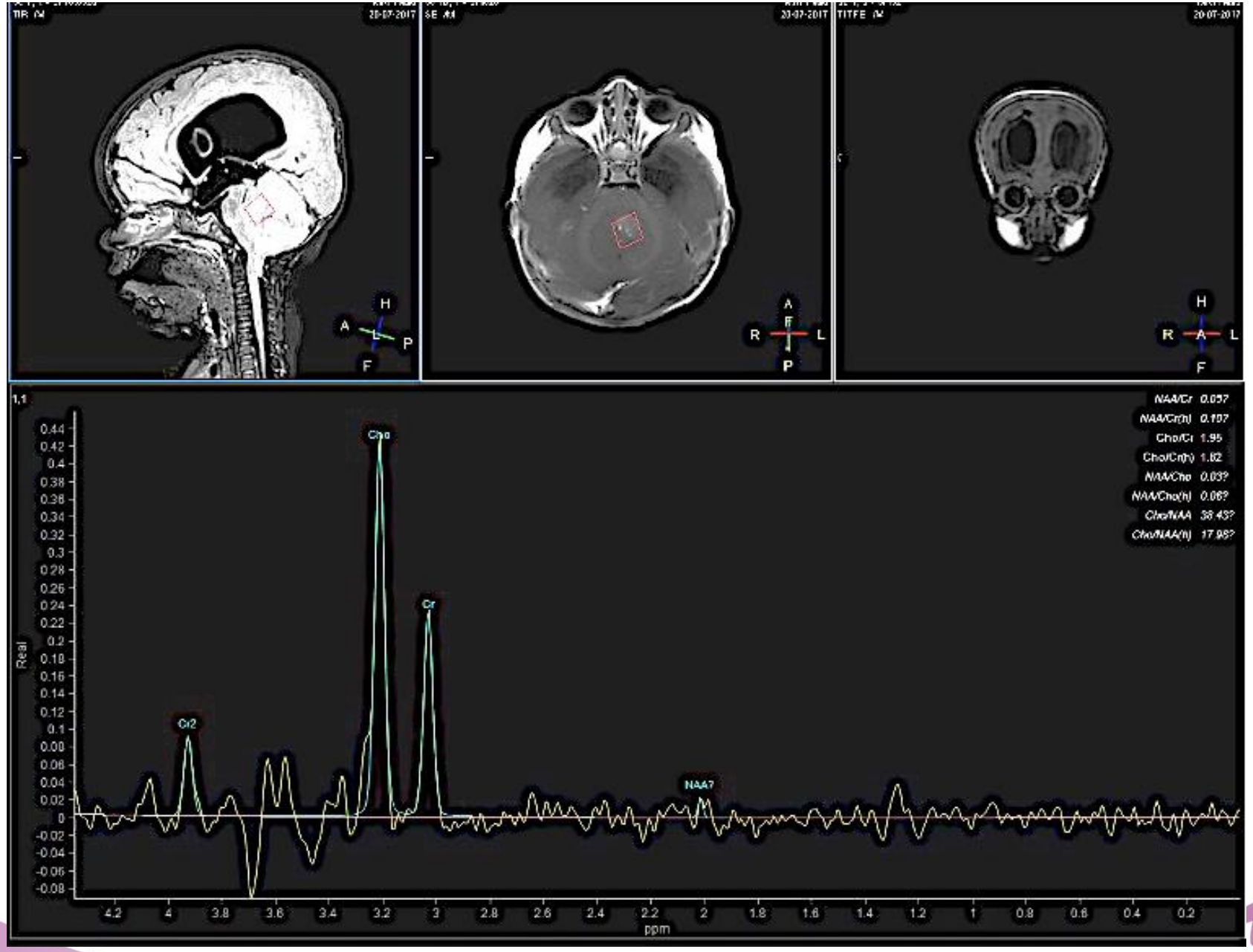


CISS

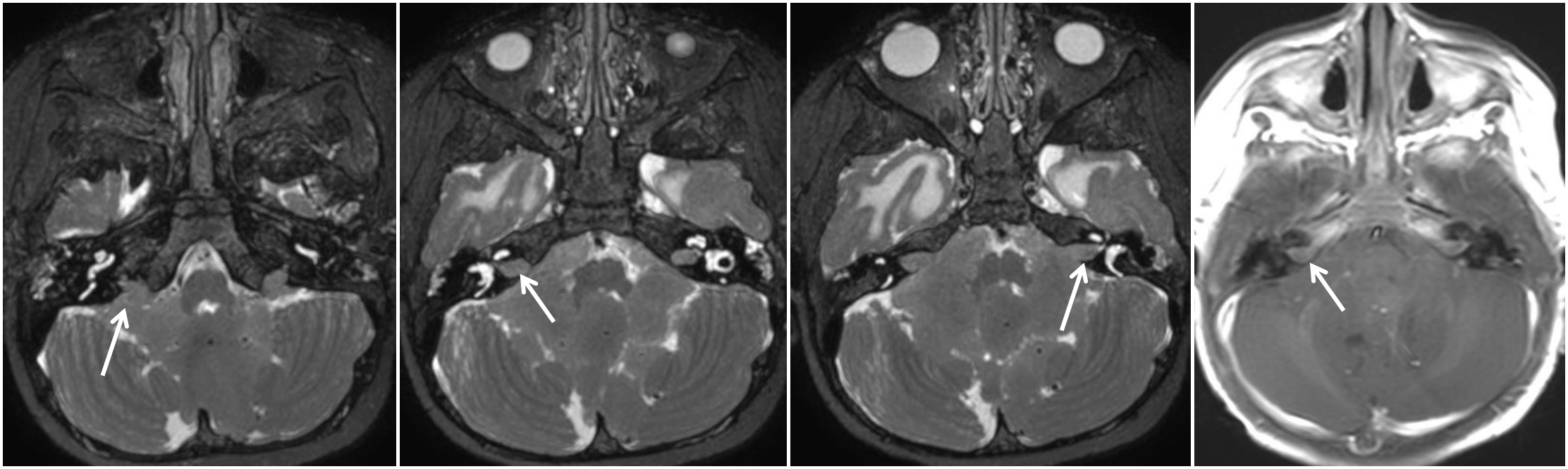


T1 post Gd

Ependymoma – MRS short echo



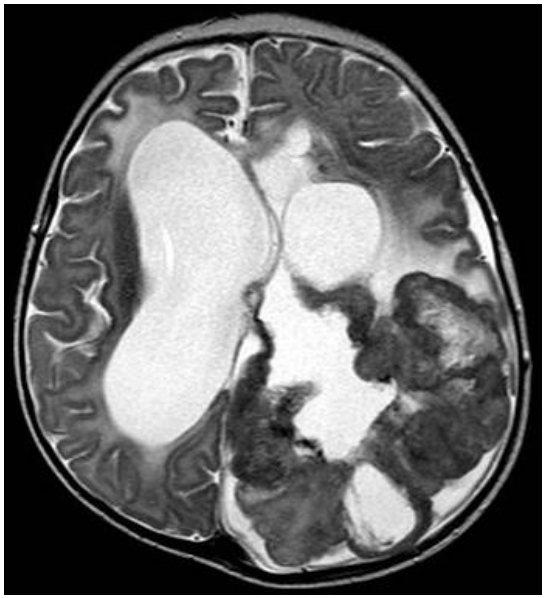
High resolution (CISS) imaging



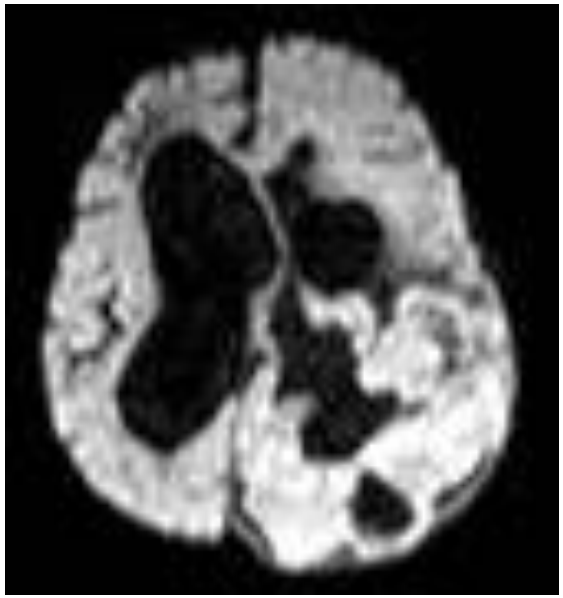
Axial CISS

Ax T1 post Gd

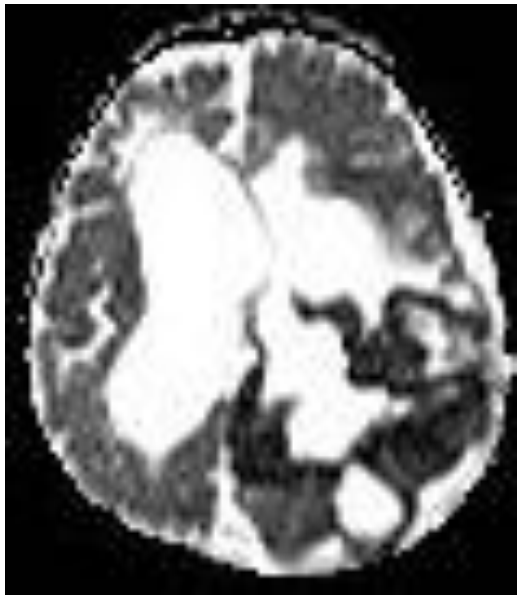
MRI – supratentorial ependymoma



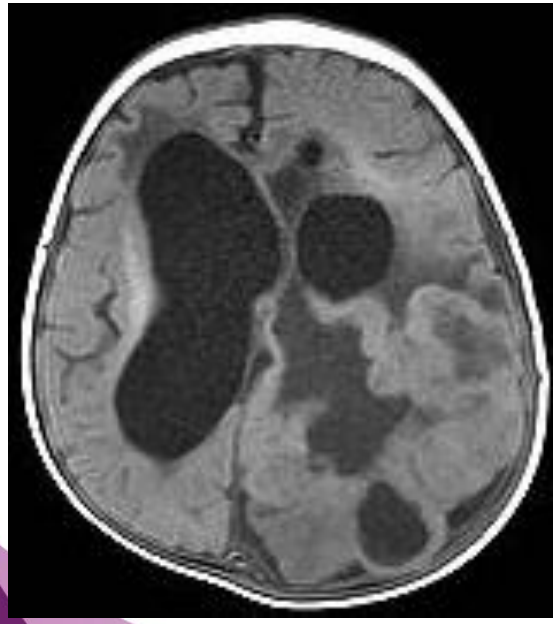
T2



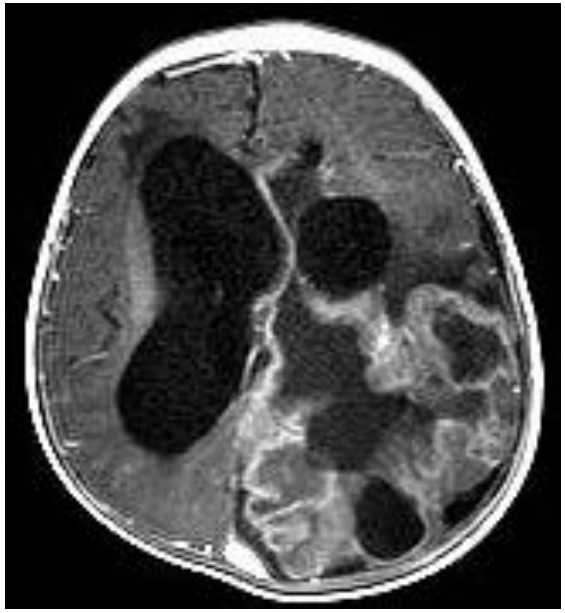
DWI



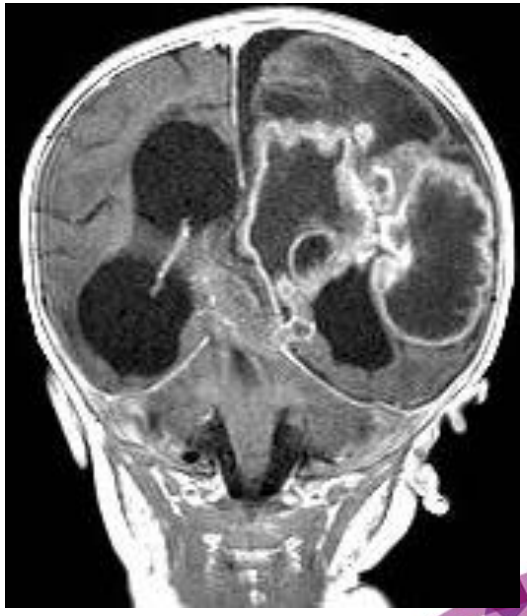
ADC



T1



T1 post Gd



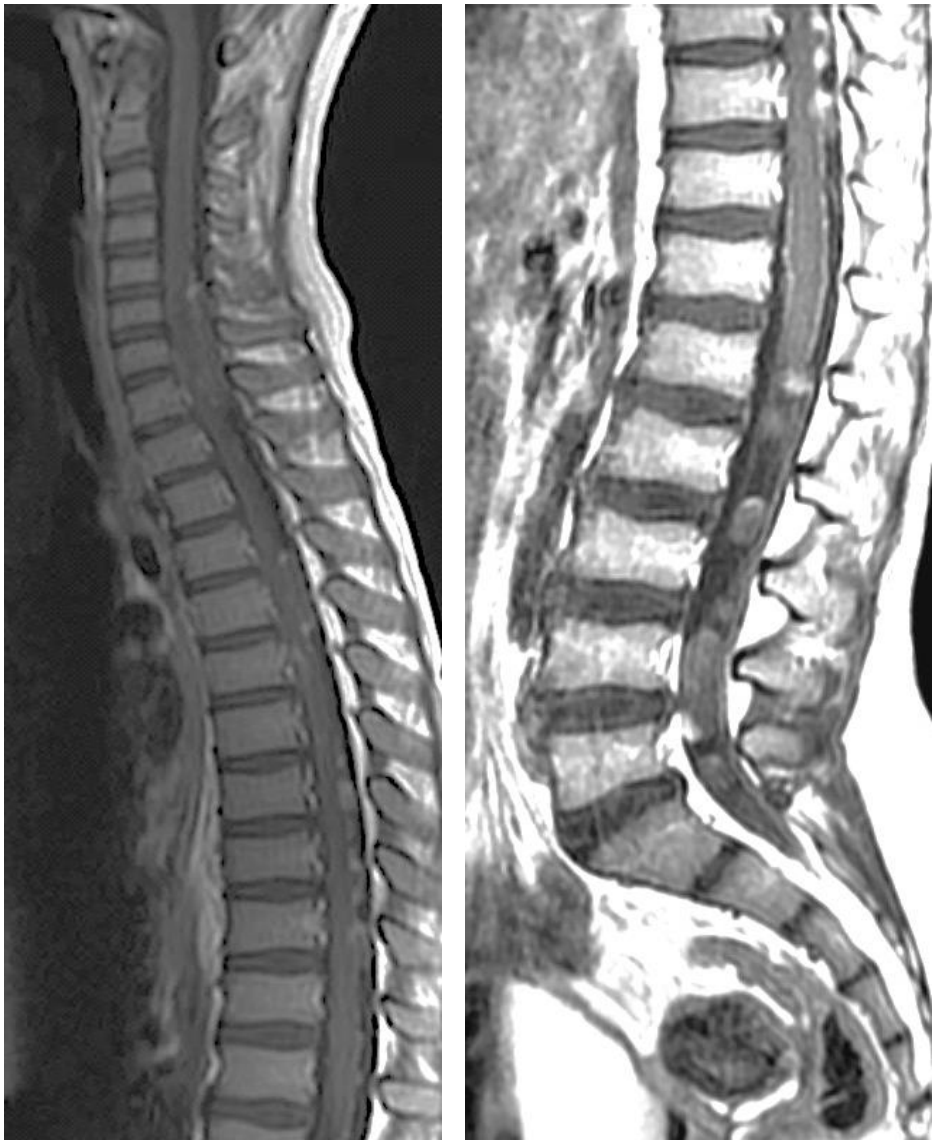
T1 post Gd

ESTRO School

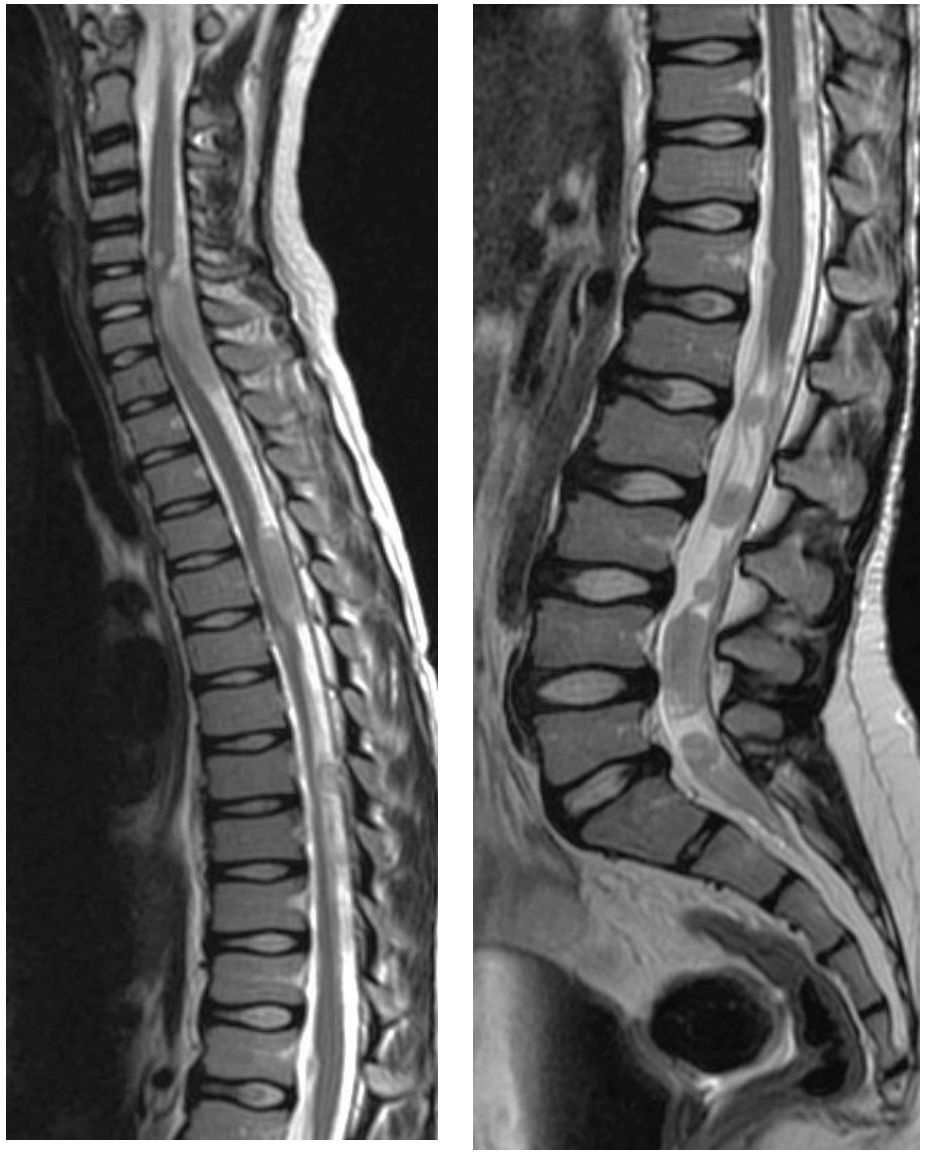
Distant spread

- Approx 15% risk of spinal spread from post. fossa tumors
- Spread occurs throughout the CSF pathways
- Most often nodular
- Very uncommon at presentation
- Infratentorial tumors have higher risk of seeding than supratentorial tumors
- More common with anaplastic ependymoma
- Incidence of leptomeningeal spread varies with:
  Tumor grade (low grade 5%, high grade 10-15%)
  Tumor location (5% supratentorial, 10-15% infratentorial)

Spinal metastases



T1 post Gd



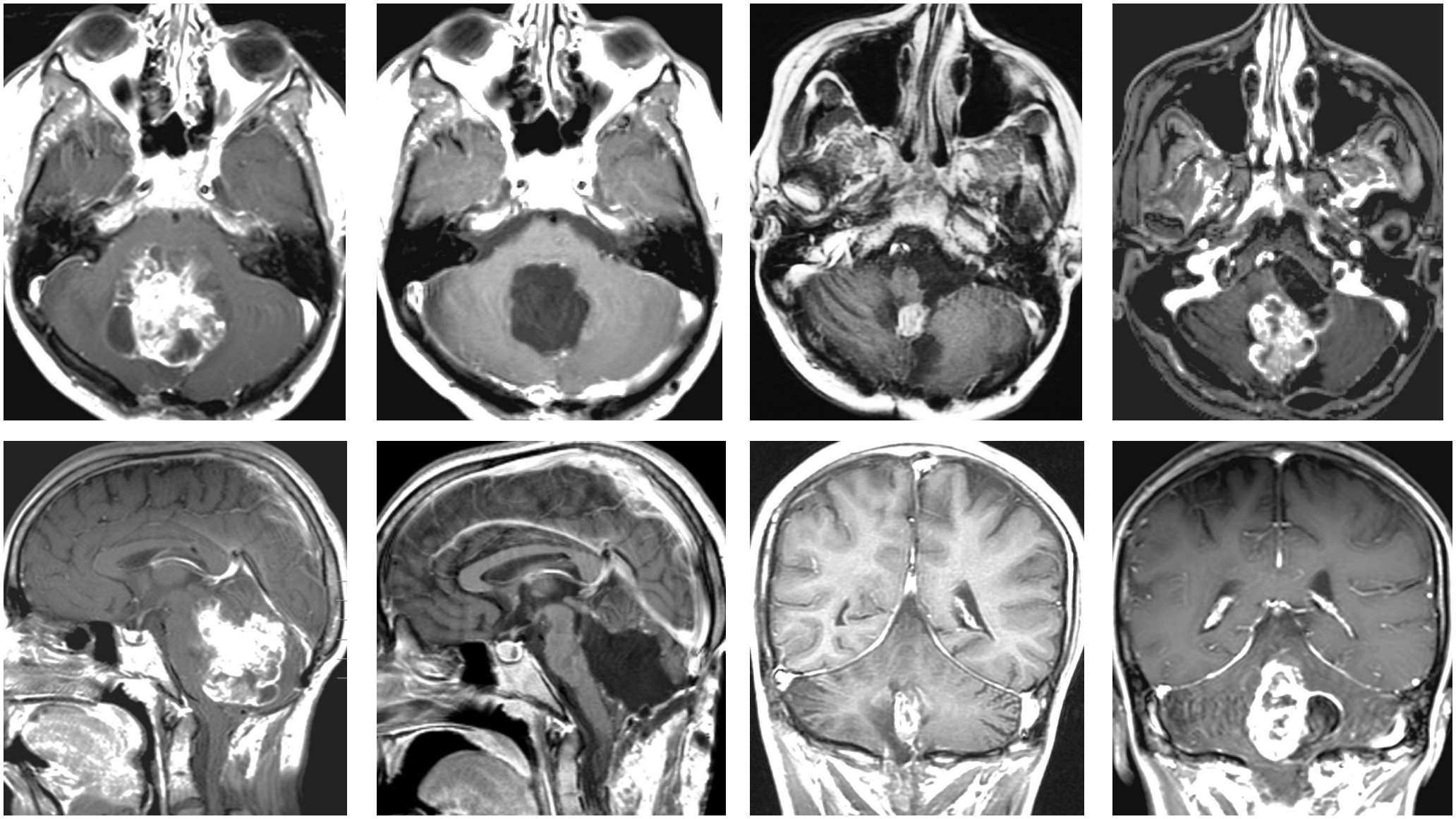
T2

ESTRO School

Tumour recurrence

- 5 yr survival: 50-64%
- Recurrences typically local
- Median time to recurrence 13-25 months
- Distant recurrence in approx 20%
- Very late recurrences (up to 20 years) not uncommon

Recurrence – Grade 2



Presentation – Aug ‘09

1 day post op

Recurrence – Mar ‘13

Post DXT + chemo – June ‘13

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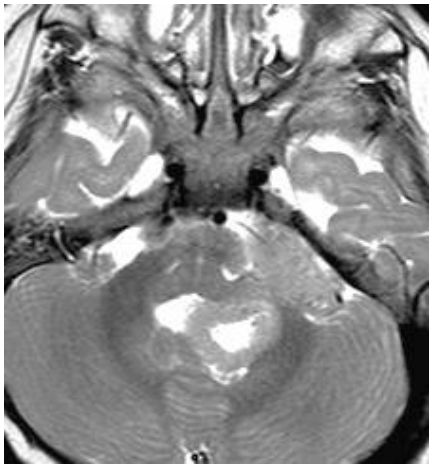
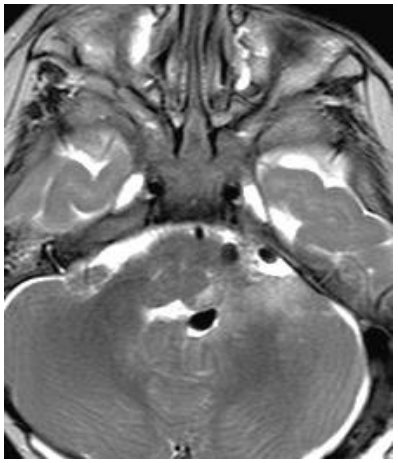
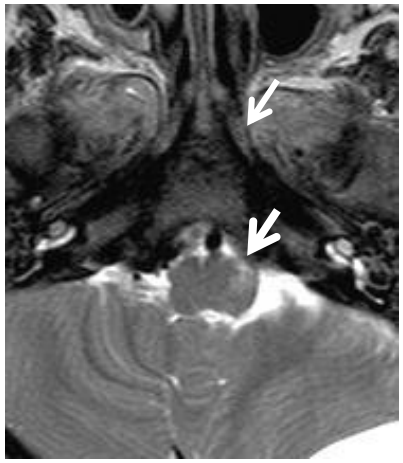
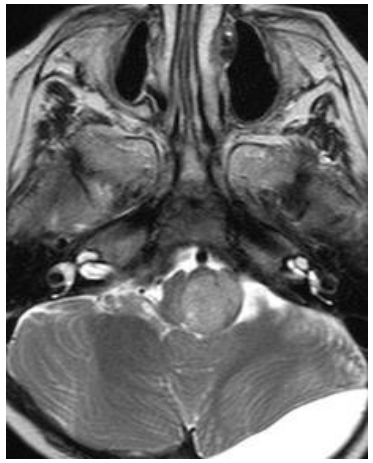
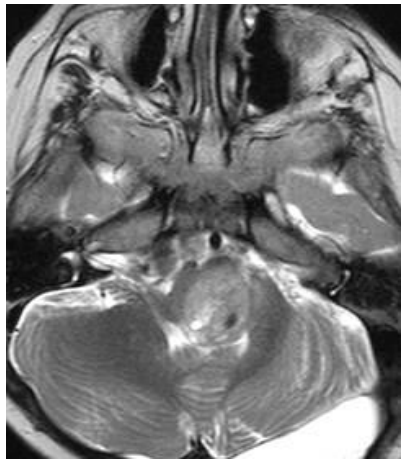
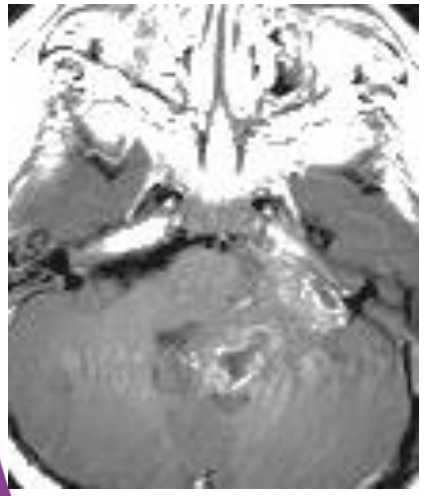
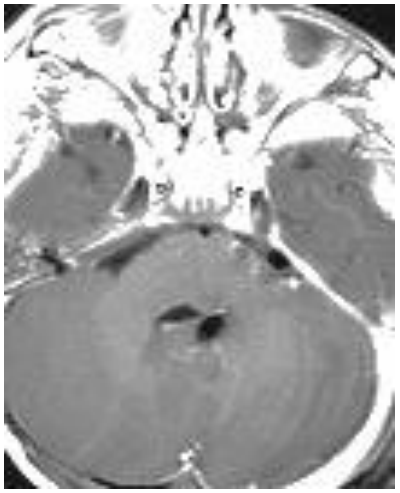
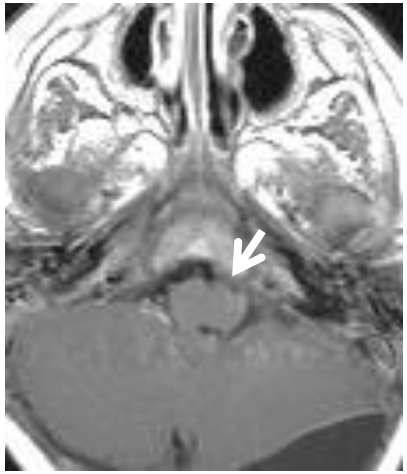
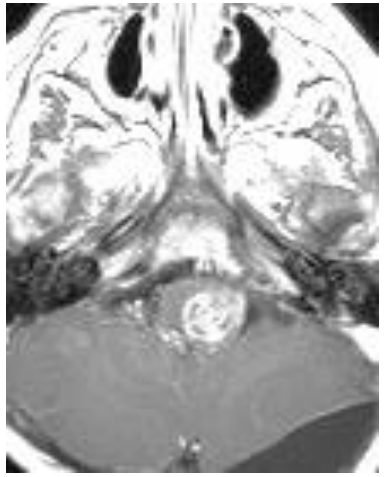
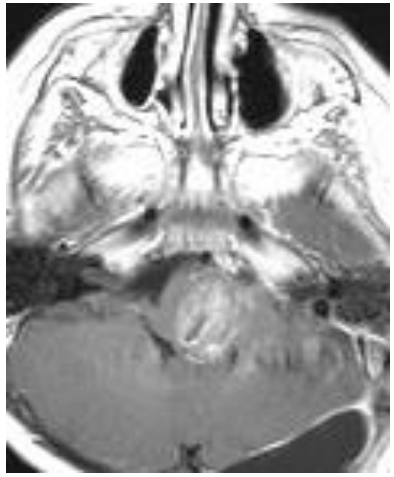
Recurrence – Grade 3

Jan ‘14

Jan ‘14 – 1 day post op

Jan ’15

April ‘15

May ‘15 - 1 month post re-resection

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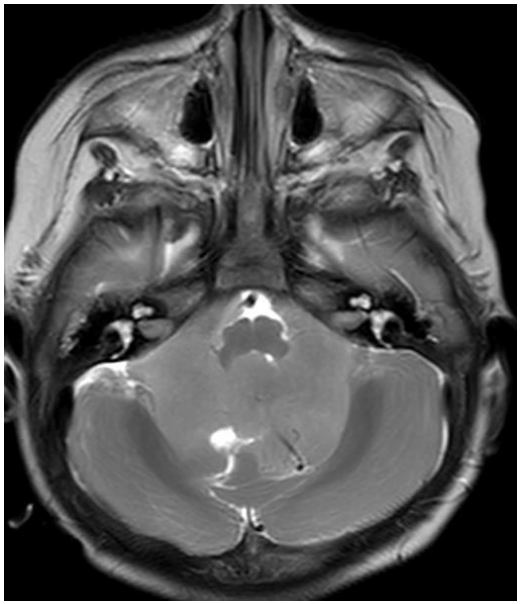
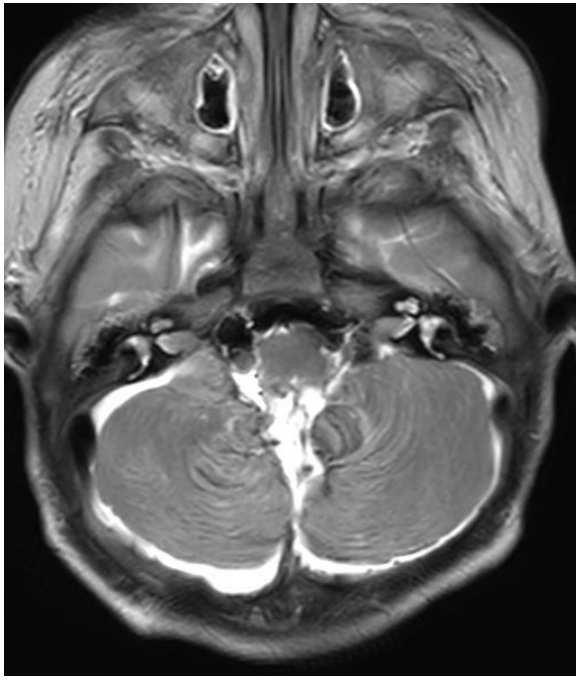
June 17

Sept 17

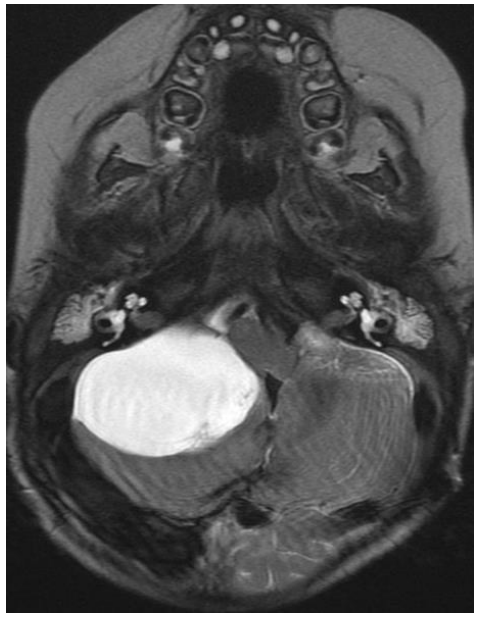
Cystic recurrence



T2



Day 2 post op



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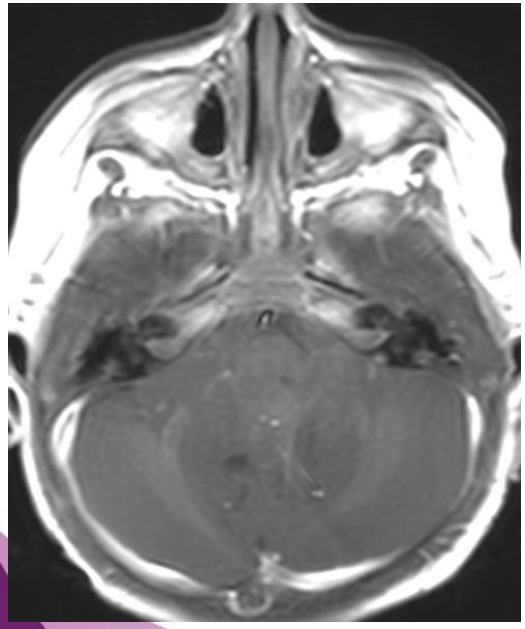
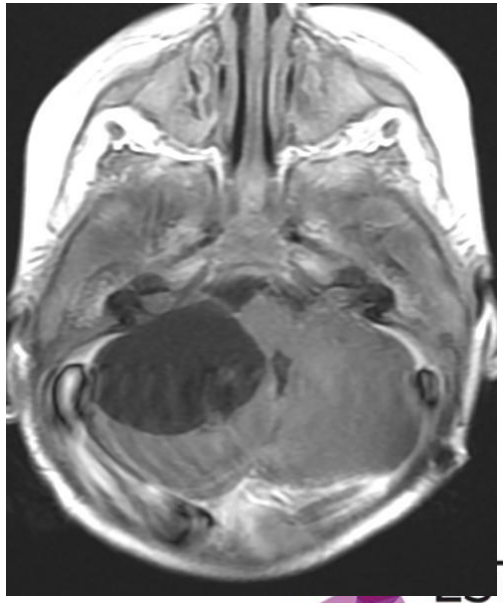


T1 post Gd



T1 post Gd

Outcome

- 50% relapse
- 25% live > 5yrs after relapse
- Age impacts on treatment and outcomes
- Surgery +/- chemo (commoner in early life) carries worse prognosis
- Surgery +/- RT +/- Chemo (commoner in older children) carries better prognosis

Radiology screening

- Imaging interval dictated by trial regimes
- Use of high resolution T2 imaging facilitates detection of residual tumour and early recurrences
- Determines viability of further surgery
- After end of treatment, every 3 years – late recurrences, radiation induced meningiomas

Summary

- Tumor localization and spread reflects cell origin
- Increasing importance of molecular/genetic evaluation
- Staging and evaluation of extent of surgery very important in disease stratification/prognosis
- Tumor spread may be subtle – diffusion changes only, hidden sites (e.g. anterior skull base, spinal cul-de-sac)
- MDT assessment offers optimal management
- Neuraxial imaging must be the norm
- Late imaging important to look for late recurrences and late effects/secondary tumors

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KLINIK UND POLIKLINIK FÜR STRAHLENTHERAPIE
UNIVERSITÄTSKLINIKUM LEIPZIG

Part I :

General aspects

Clinical features, histology, surgery, staging, prognostic factors, outcome

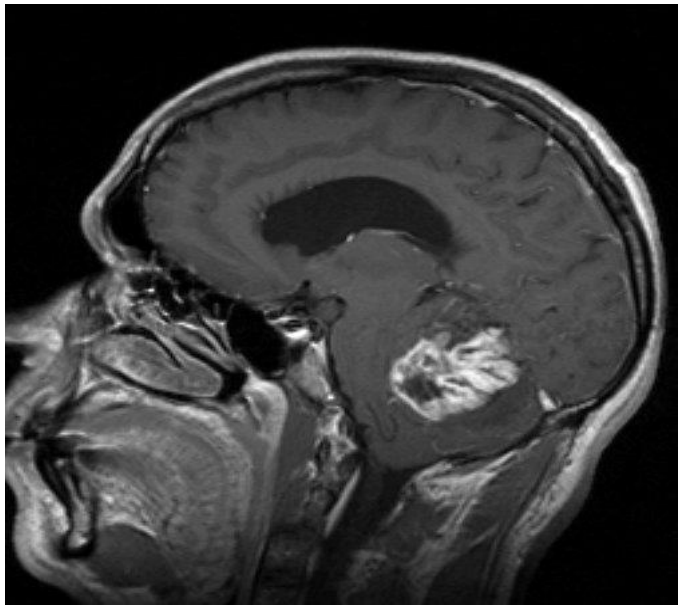
R. Kortmann / B. Timmermann

Ependymoma

Distribution

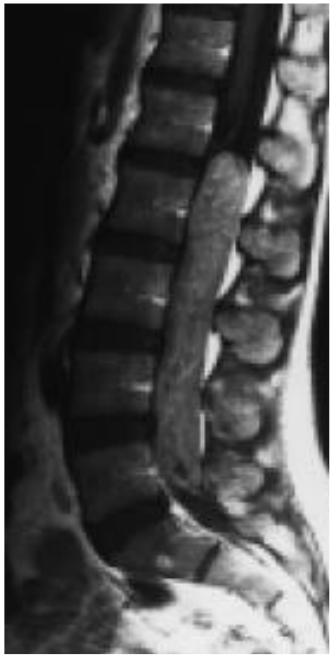
Intracranial (60%)
Supratentorial : 30%
Infratentorial : 70%

4-16 years (ca)
Supratent : 35%
Infratent : 50%



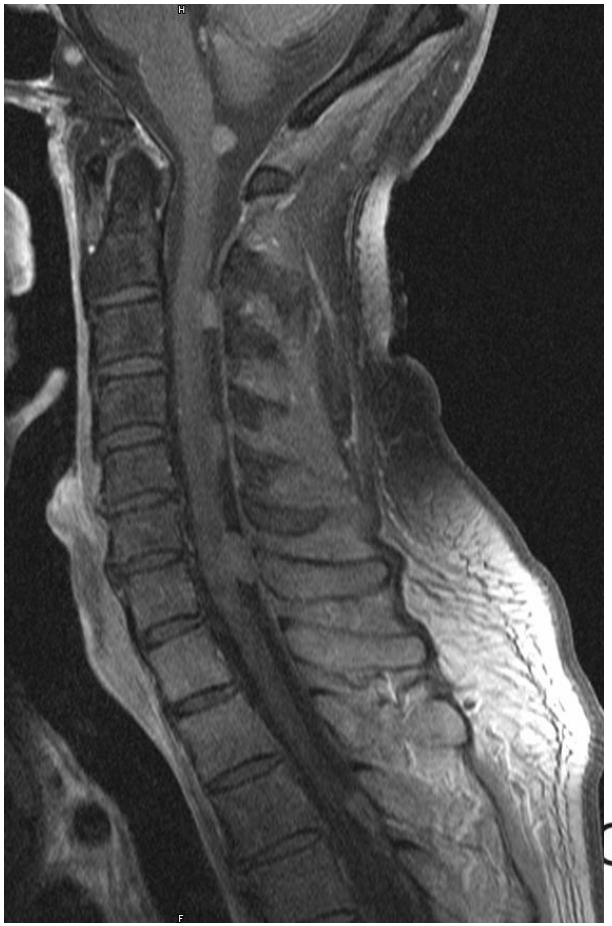
Spinal (30%)
Intramedullary (thoracal) (10%)
Extramedullary (lumbar) (20%)

4-16 years (ca)
Intramed : 10%
Conus 5%



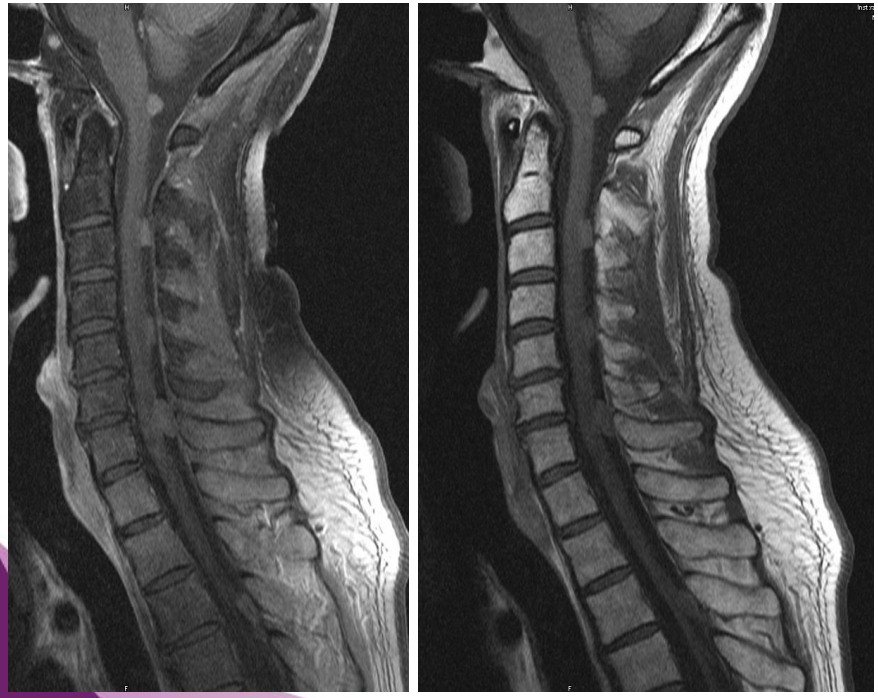
Schiffer et al., 1991

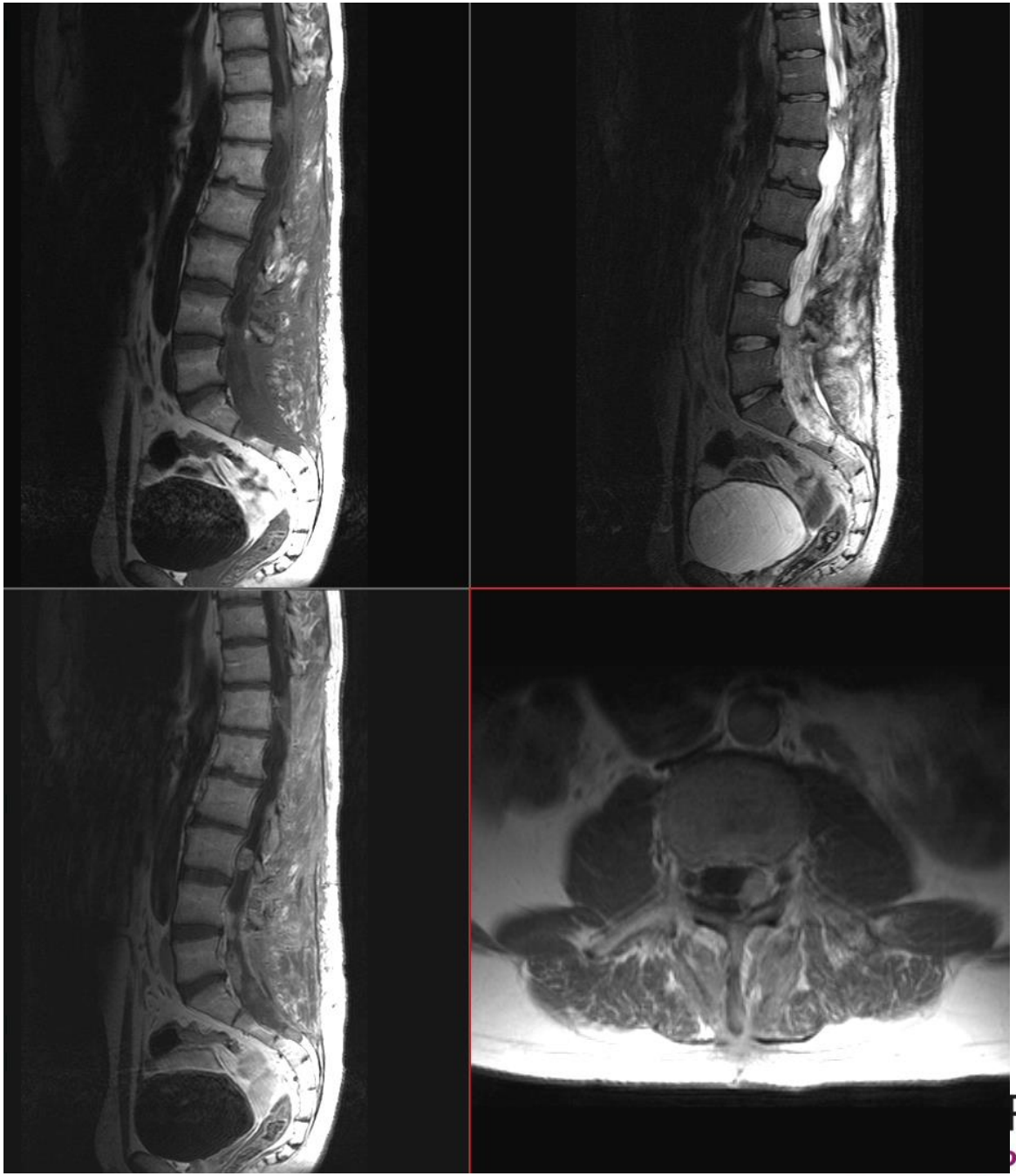
Metastases
Extramedullary
< 5 – 10%



Ependymoma

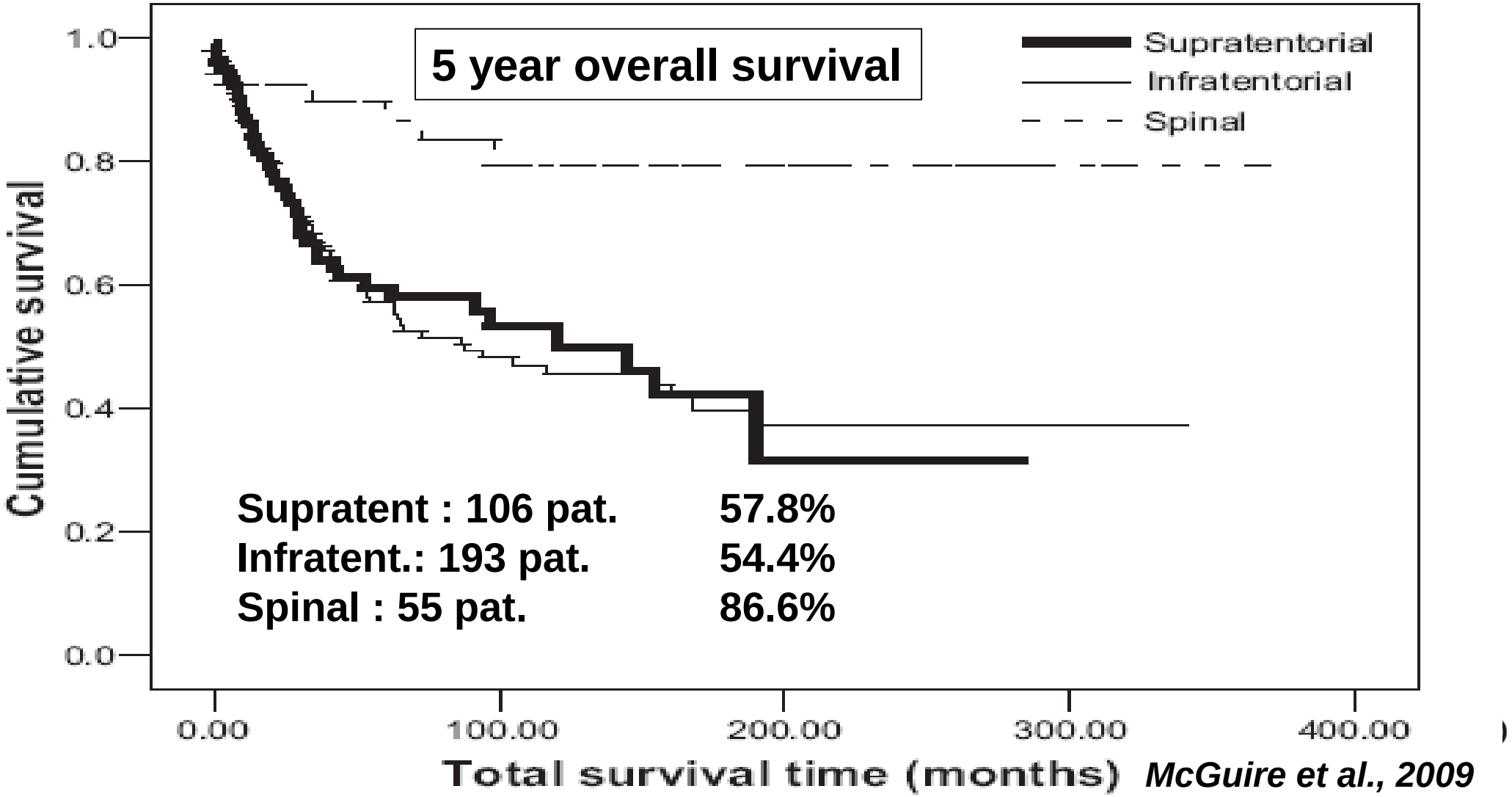
Ependymoma
Spinal metastases





Ependymoma

Intracranial and spinal ependymoma
SEER Analysis / n=354 patients (children only)

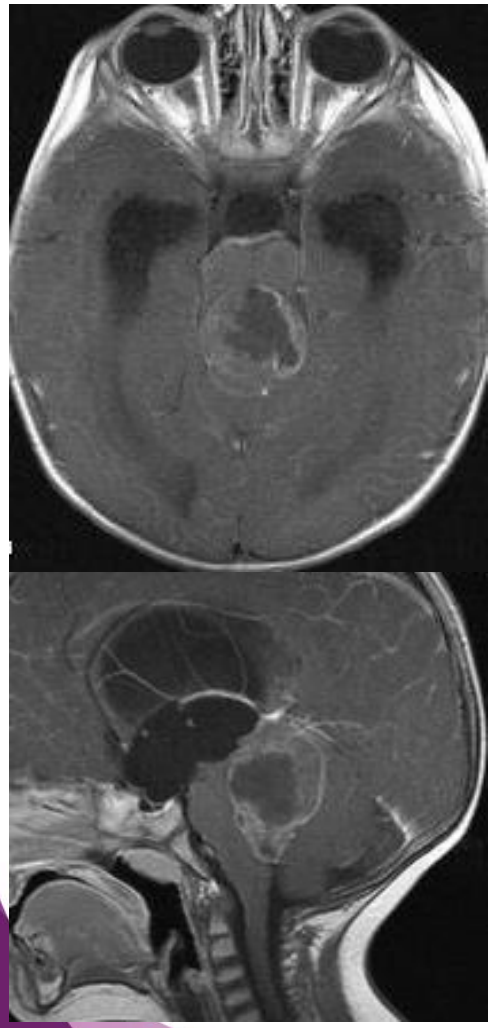


McGuire et al., 2009

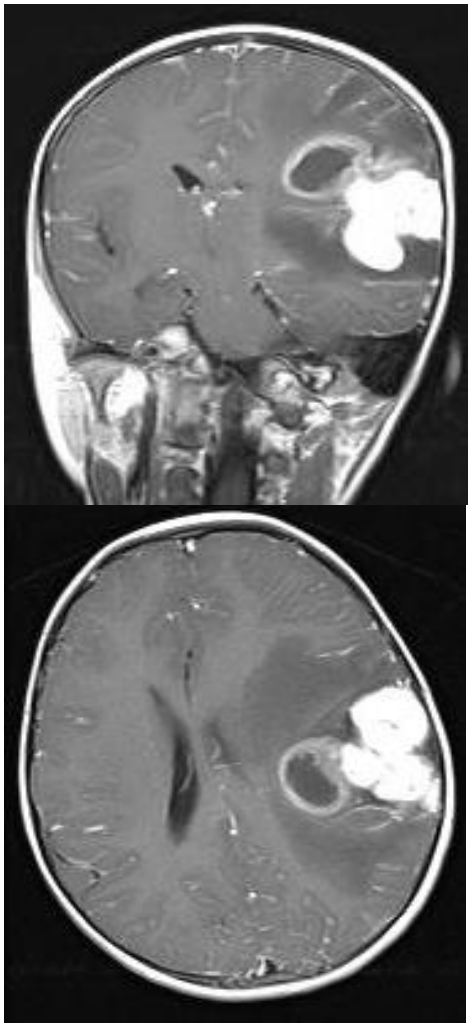
Ependymoma

Localisation of tumour

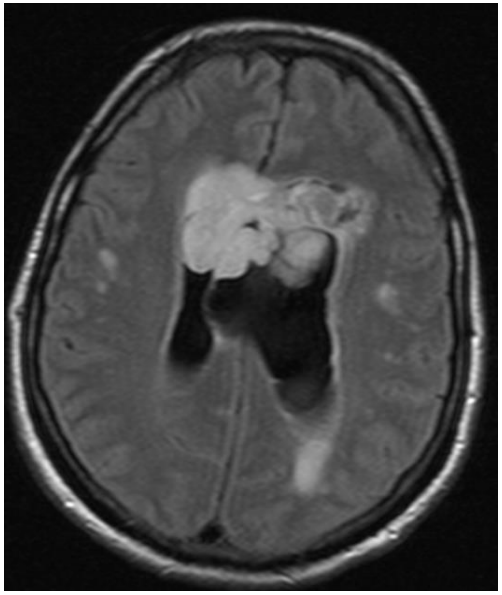
Infratentorial

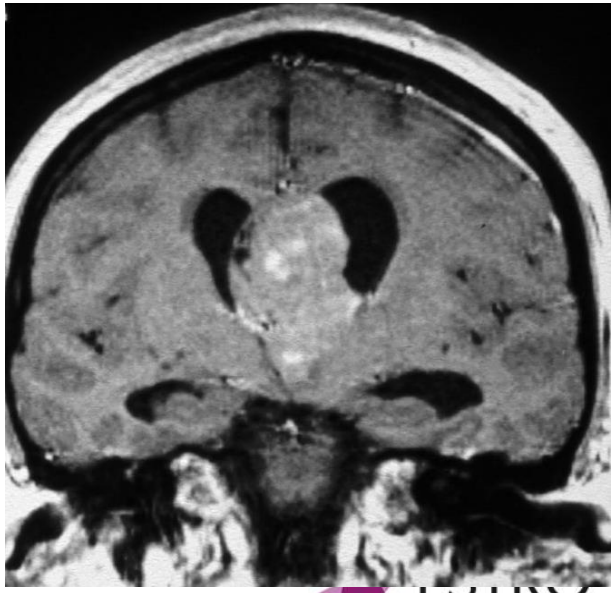


Supratentorial



Supratentorial (interventricular often in adults)





Ependymoma

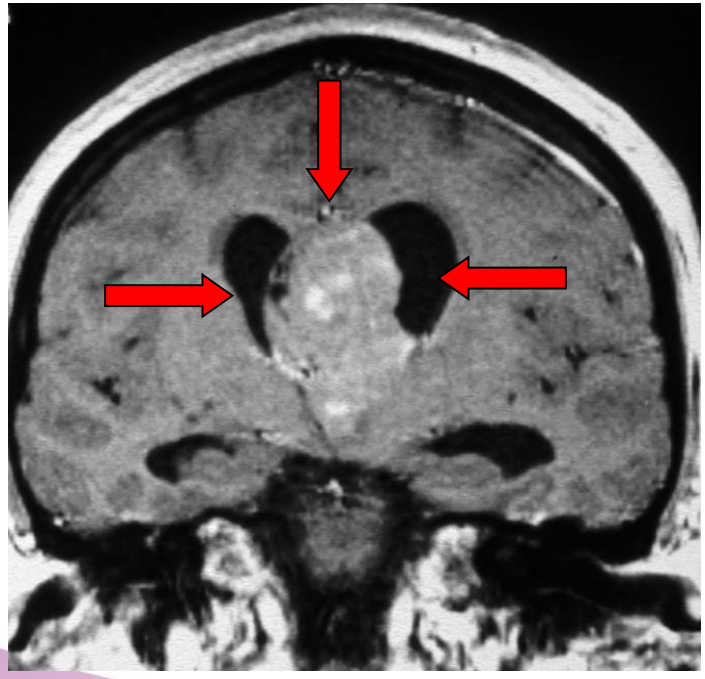
Therapeutic strategy

Surgery → **extent of resection**

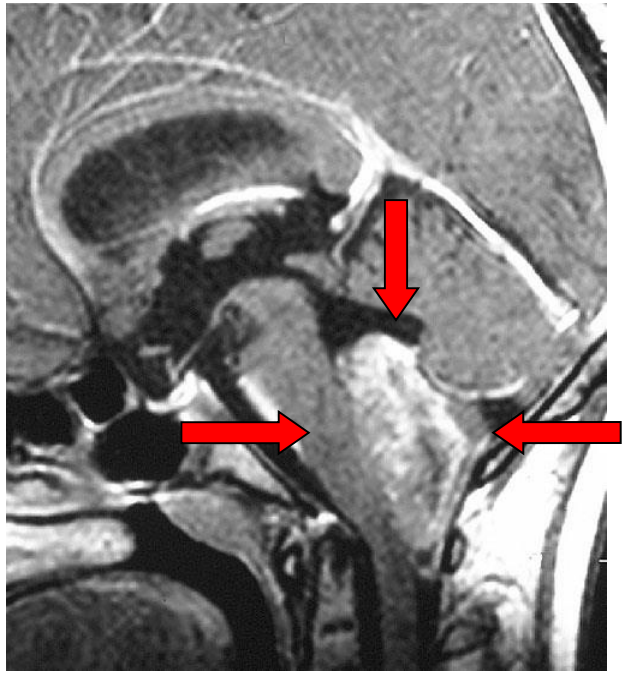
Postoperative RT → **local RT / entire PF /CSA**

Chemotherapy → **protocol**

Supratentorial



Infratentorial



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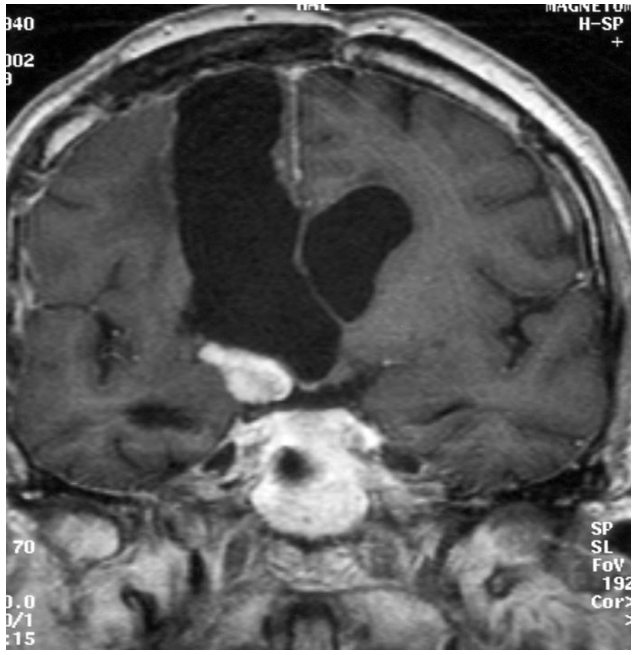
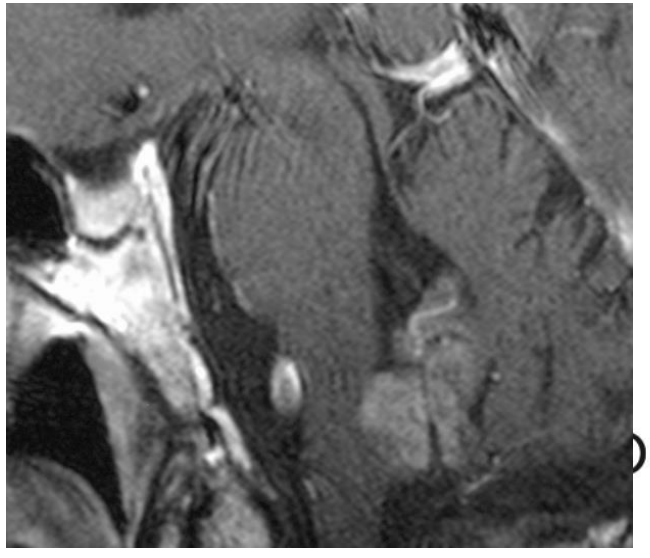
Intracranial ependymoma

Postoperativ radiotherapy

Criteria for therapeutic decision

- **Localisation**
  - supra- / infratentorial
- **WHO Grade**
  - WHO Gr. II
  - WHO Gr. III (anapl.)
- **Extent of resection**
  - complete / incomplete
- **Metastases**
  - no / yes
- **Age**
  - < 3-5 years
  - > 3-5 years





Intracranial ependymoma

Clinical features

Staging

Intracranial ependymoma

Age and sex distribution

Author (series)	Sex	Age
McGuire et al., 2009 (SEER) (55 spinal tumours included / 8.7%)	Male : 370 (58.3%) Female : 265 (41.7%)	0-4 years : 329 (51.8%) 4-18 years : 306 (48.2%)
Merchant et al., 2009 (St. Jude)	Male : 95 (62.1%) Female 58 (37.9%)	< 3 years : 78 (51%) >/= 3 years : 75 (49.0%)

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Intracranial ependymoma

Clinical features

Depending on location

1. Posterior fossa tumours :

- raised intracranial pressure
- visual disturbances
- ataxia and hemiparesis
- dizziness
- neck pain
- cranial nerve palsies.

2. Supratentorial tumours

- headache, seizures
- focal neurologic deficits depending on region involved

Intracranial ependymoma

Staging

Staging before radiotherapy (before surgery)

- Pre- / postoperative MR (brain)
- MR of spinal canal
  (before surgery and before lumbar puncture)

Prognostic factors

Intracranial ependymoma

Prognostic factors

Tumour site (infratentorial / supratentorial) progression – free survival at 5 years

Author	Pat.	Tumour site Survival	p-value
Schild et al., 1998	45	Infratent. 68% Supratent. 62%	n. s.
Timmermann et al. 2000*	29 26	Infratent. 53.1% Supratent. 72.4%	n. s.
Merchant 2008 et al.**	122 31	Infratent. 65.8% Supratent. 82.9%	0.16 / n. s.
Jaing et al.,2004	28 15	Infratent. 42.5% Supratent. 50.9%	n. s.
Mansur et al.,2005	48 12	Infratent. 65.2% Supratent. 31.3%	n. s.

**** 3 year event-free survival, ** 7 year event-free survival***

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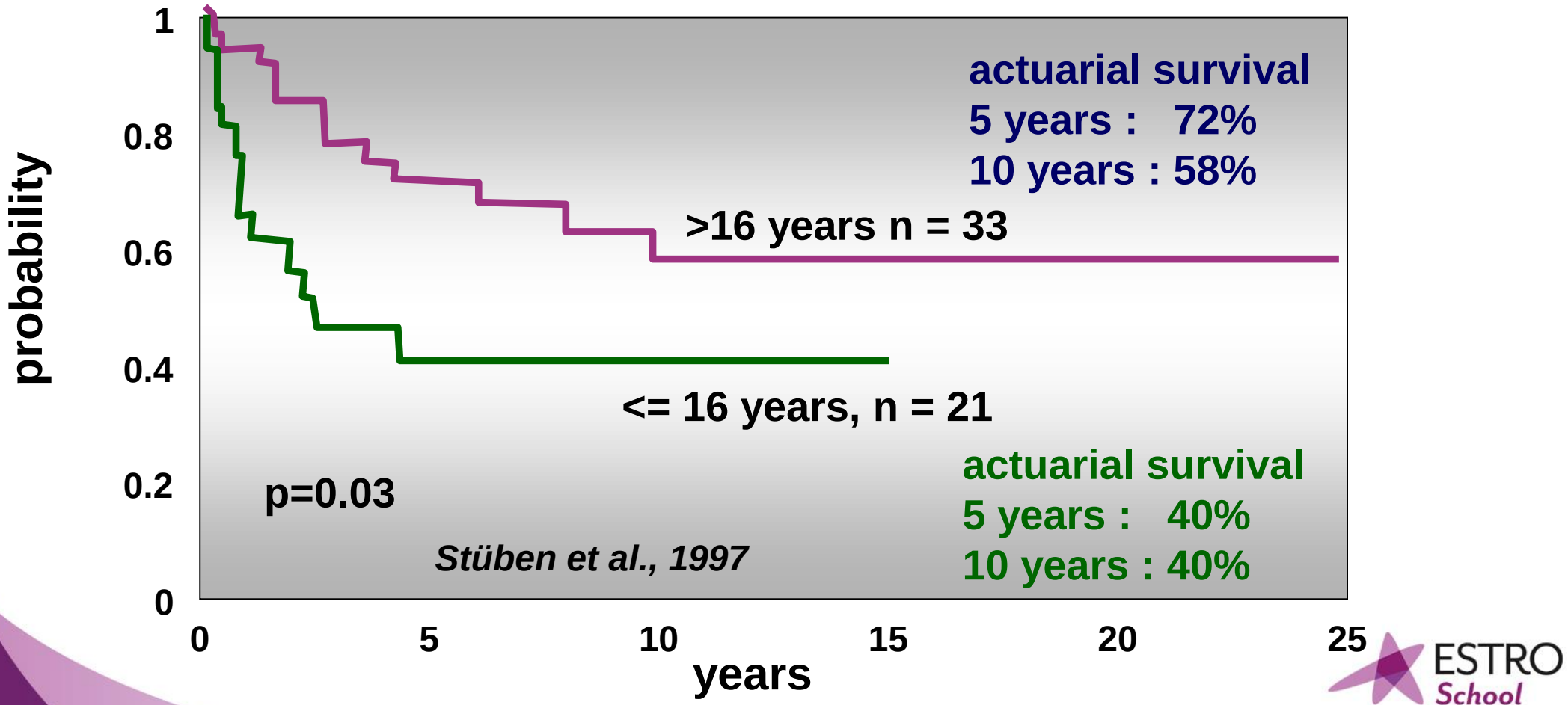
Intracranial ependymoma

Prognostic factors / age
cut – off : 16 years

supratentorial : 17 pat. , infratentorial : 22 pat. , spinal : 15 pat.



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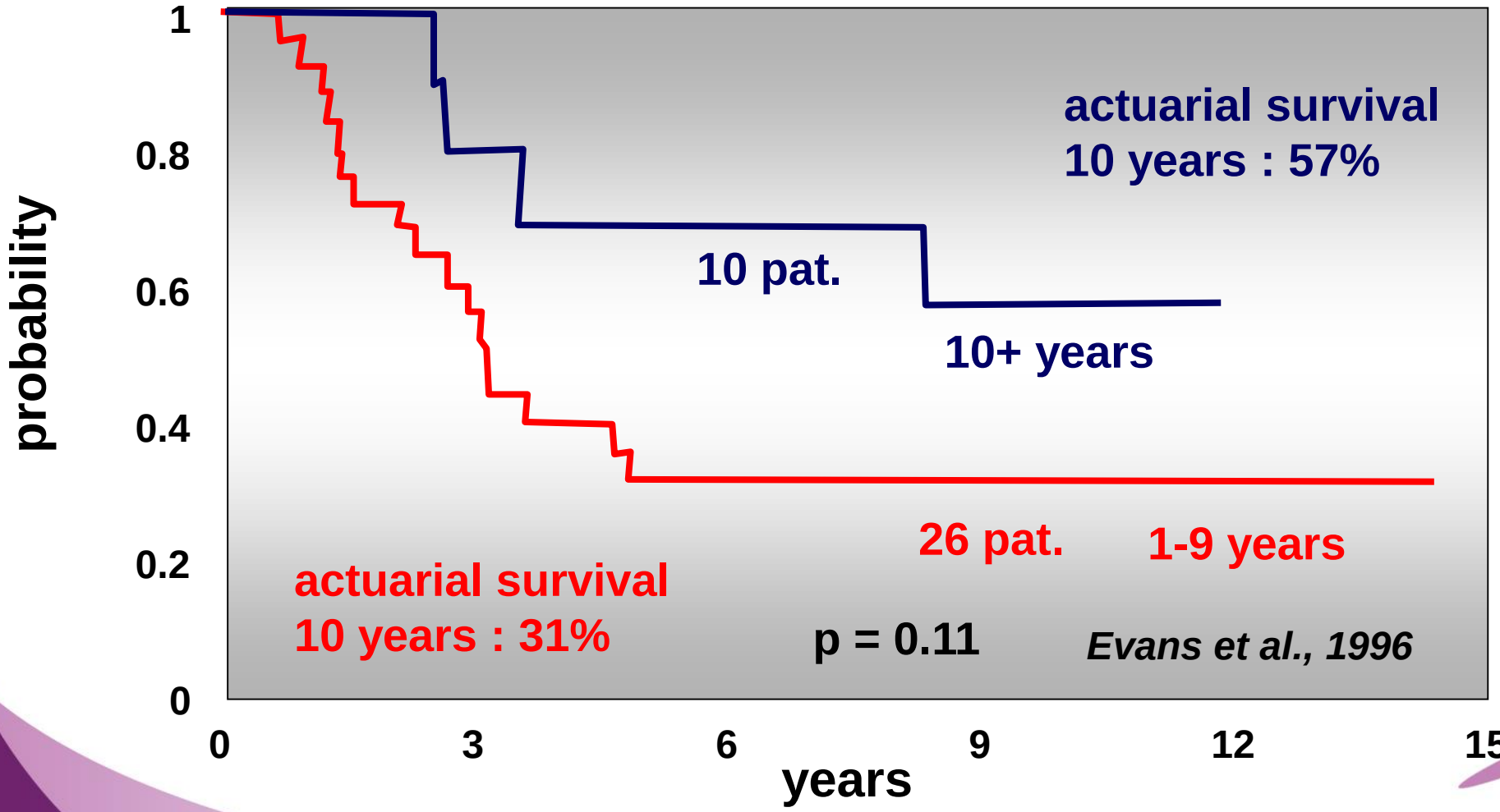
Intracranial ependymoma

Prognostic factors / age
cut : off : 10 years

CCSG random. study / survival by age



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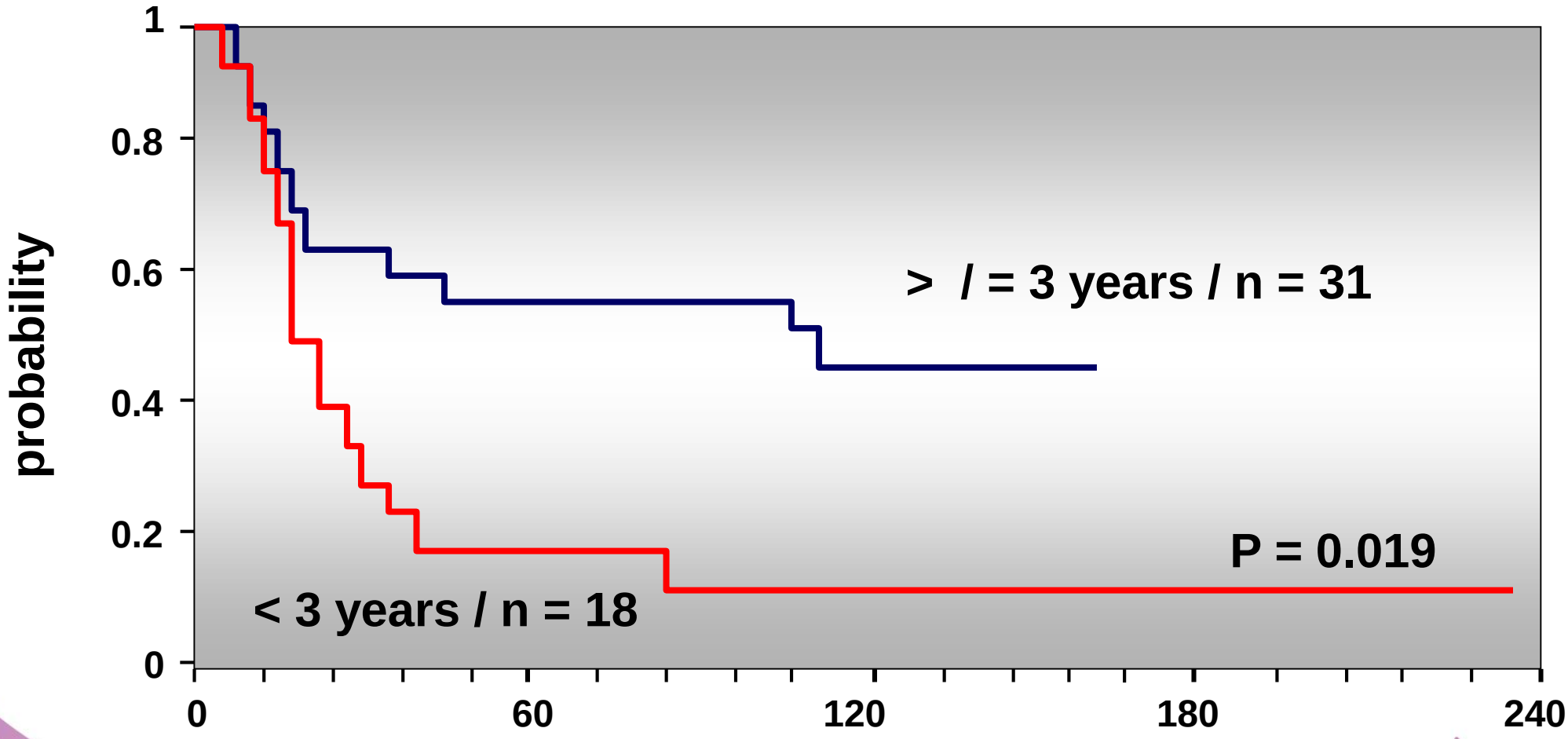
Intracranial ependymoma

Prognostic factors / age

cut – off : 3 years

Progression-free survival / by age



Shu et al., 2007

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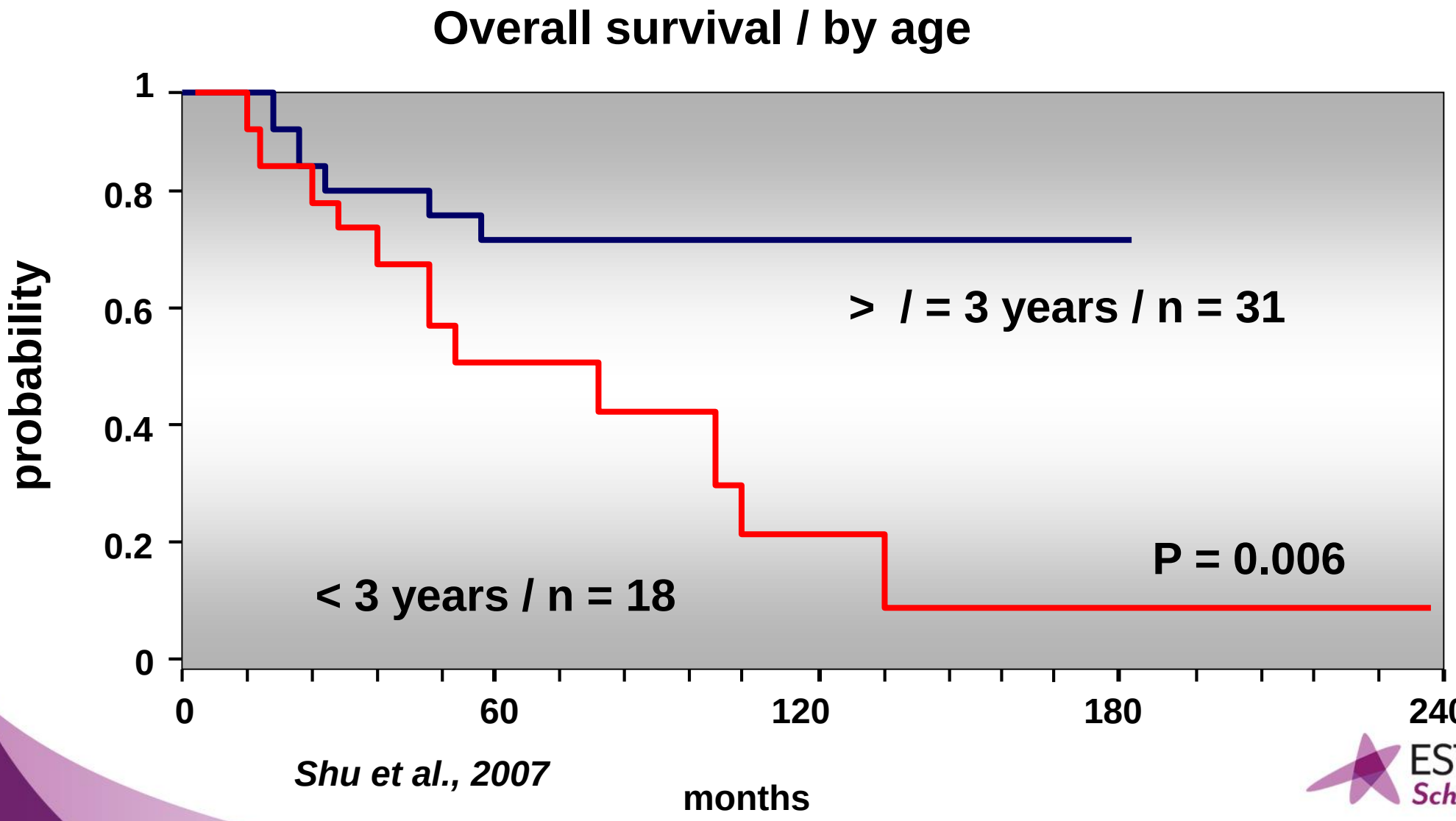
Intracranial ependymoma

Prognostic factors / age
cut – off : 3 years



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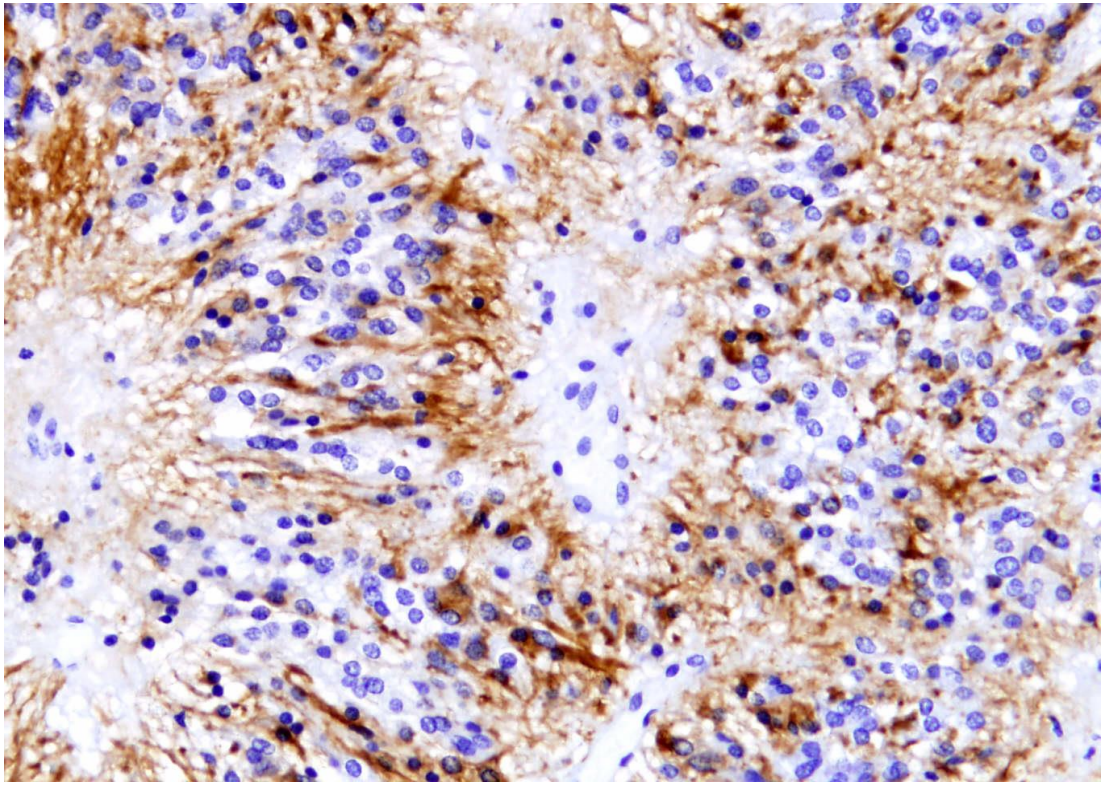
Intracranial ependymoma

Prognostic factors

Histology



Controversial results

- **Classification**
- **Institutional policies**

Need for standards

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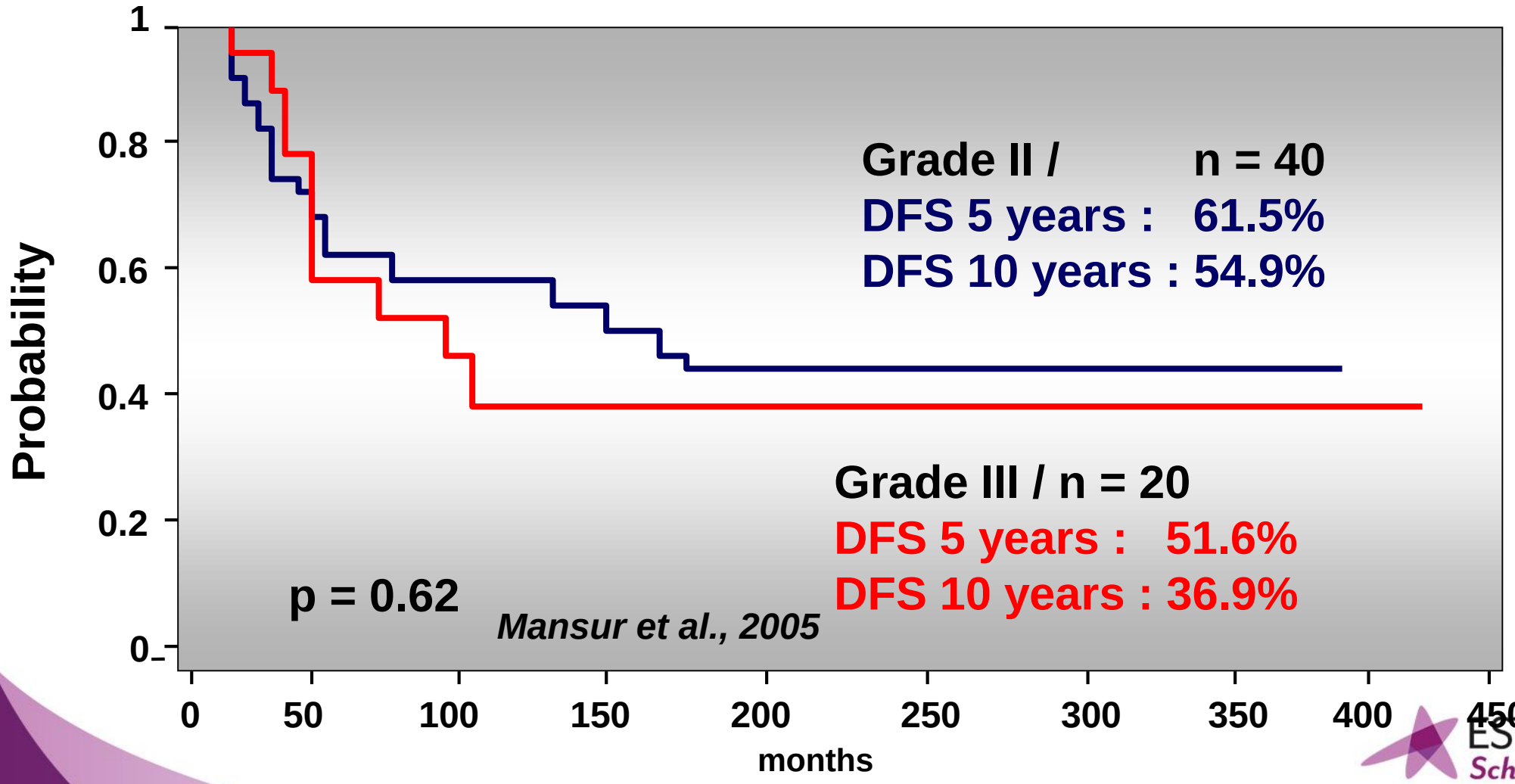
Intracranial ependymoma

Prognostic factors / grading
disease-free survival



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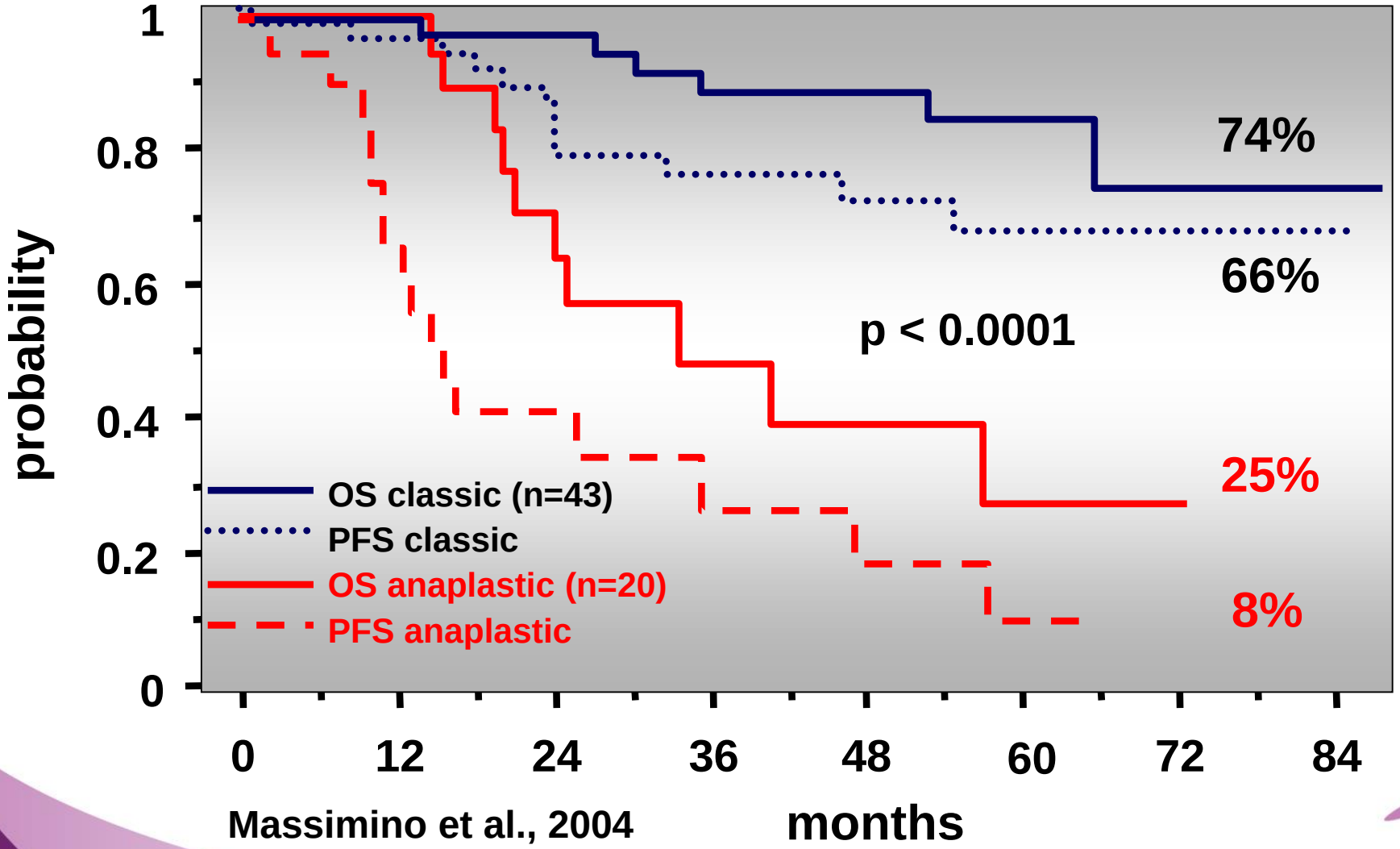
Intracranial ependymoma

Prognostic factors

AEIOP OS/PFS according to histological grading



Massimino et al., 2004

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Intracranial ependymoma

Prognostic factors

Histology / discrepancies in diagnosis

	SFOP 73 Babies 27 months (5-62)	UKCCSG 73 Babies 19 months (4-38)
Classic WHO grade II	17%	**74%**
Anaplastic WHO grade III	**83%**	13%
Awaiting review	-	12%

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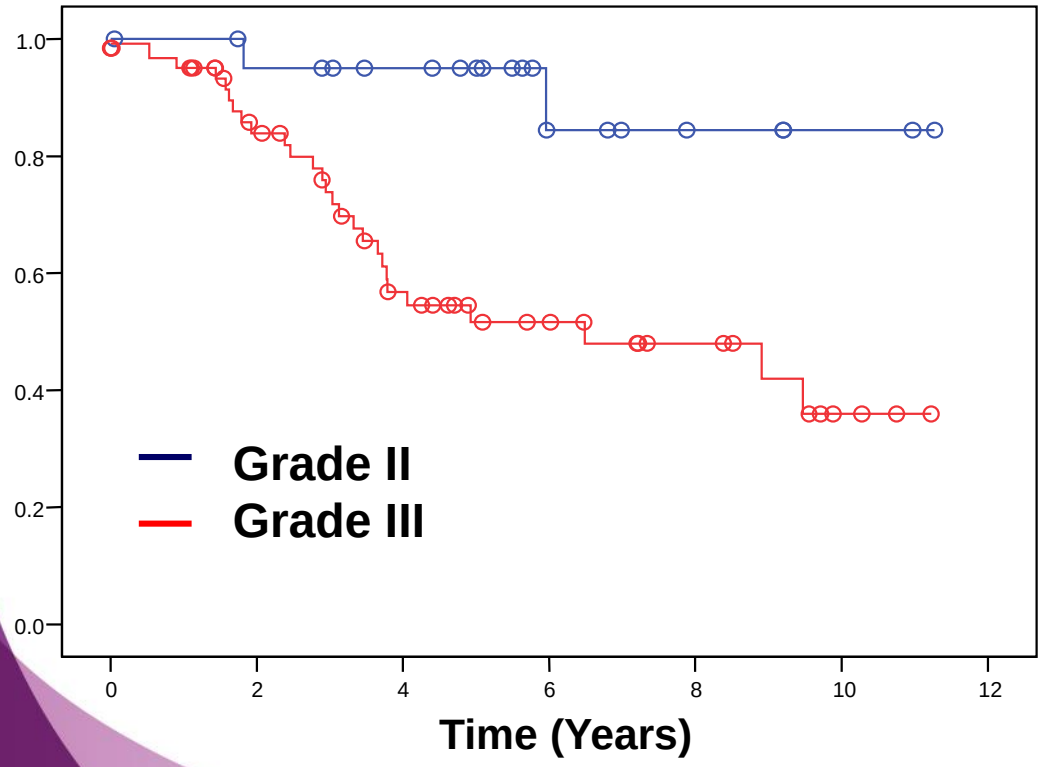
Intracranial ependymoma

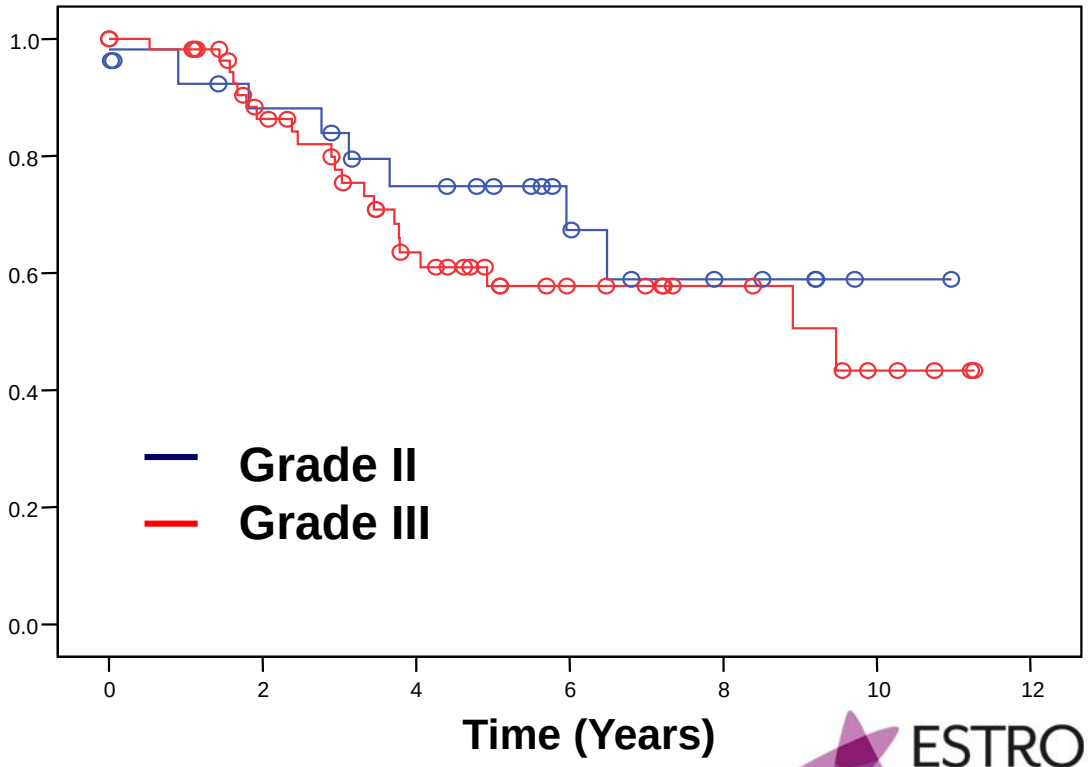
Histological assesmant of grading / discrepancies between pathologists / european panel

Overall survival with respect to investigator

Pathologist A



Pathologist B



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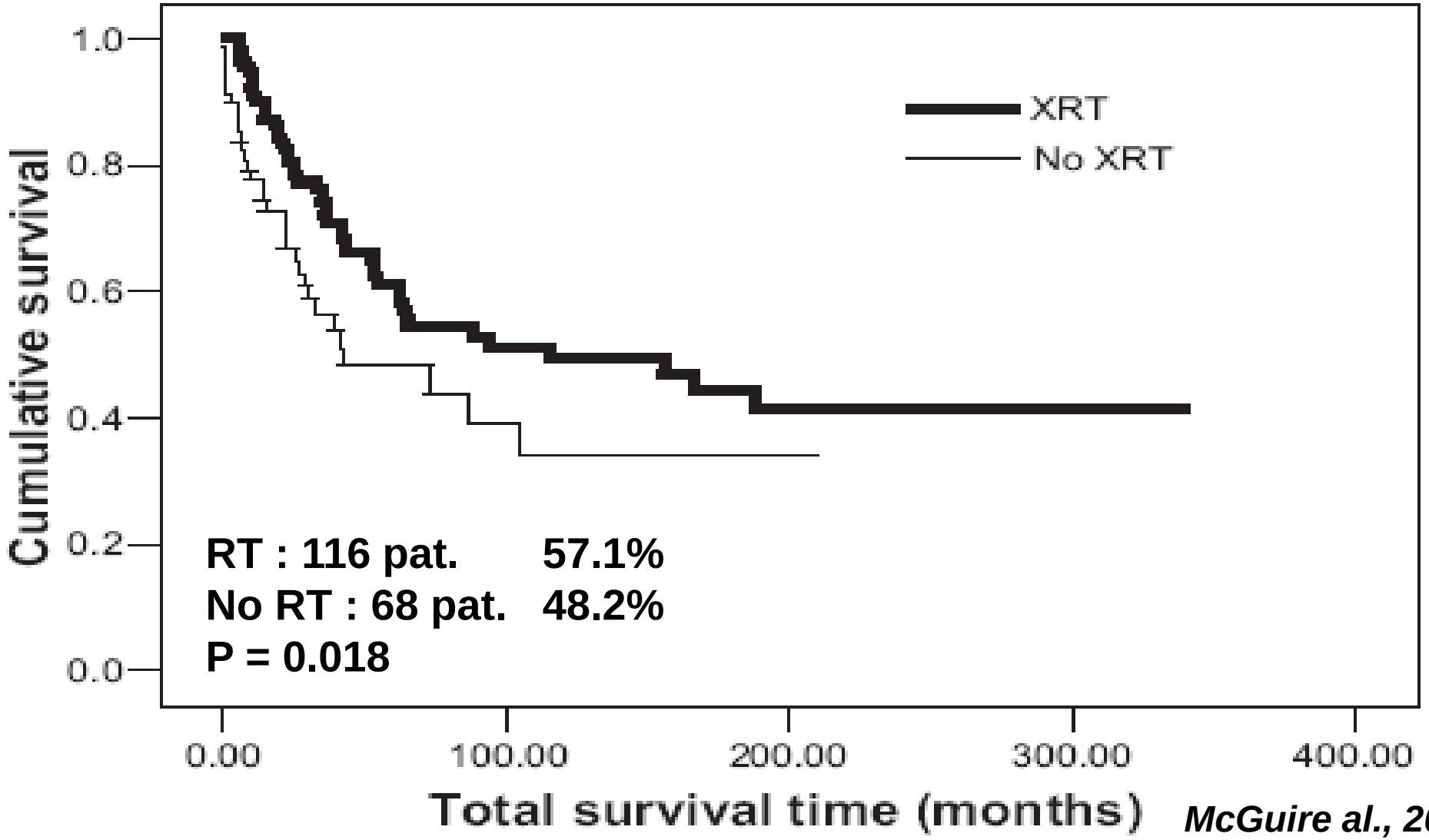
Intracranial ependymoma

Impact of postop. RT on outcome
Overall survival / infratentorial tumours / SEER data bank

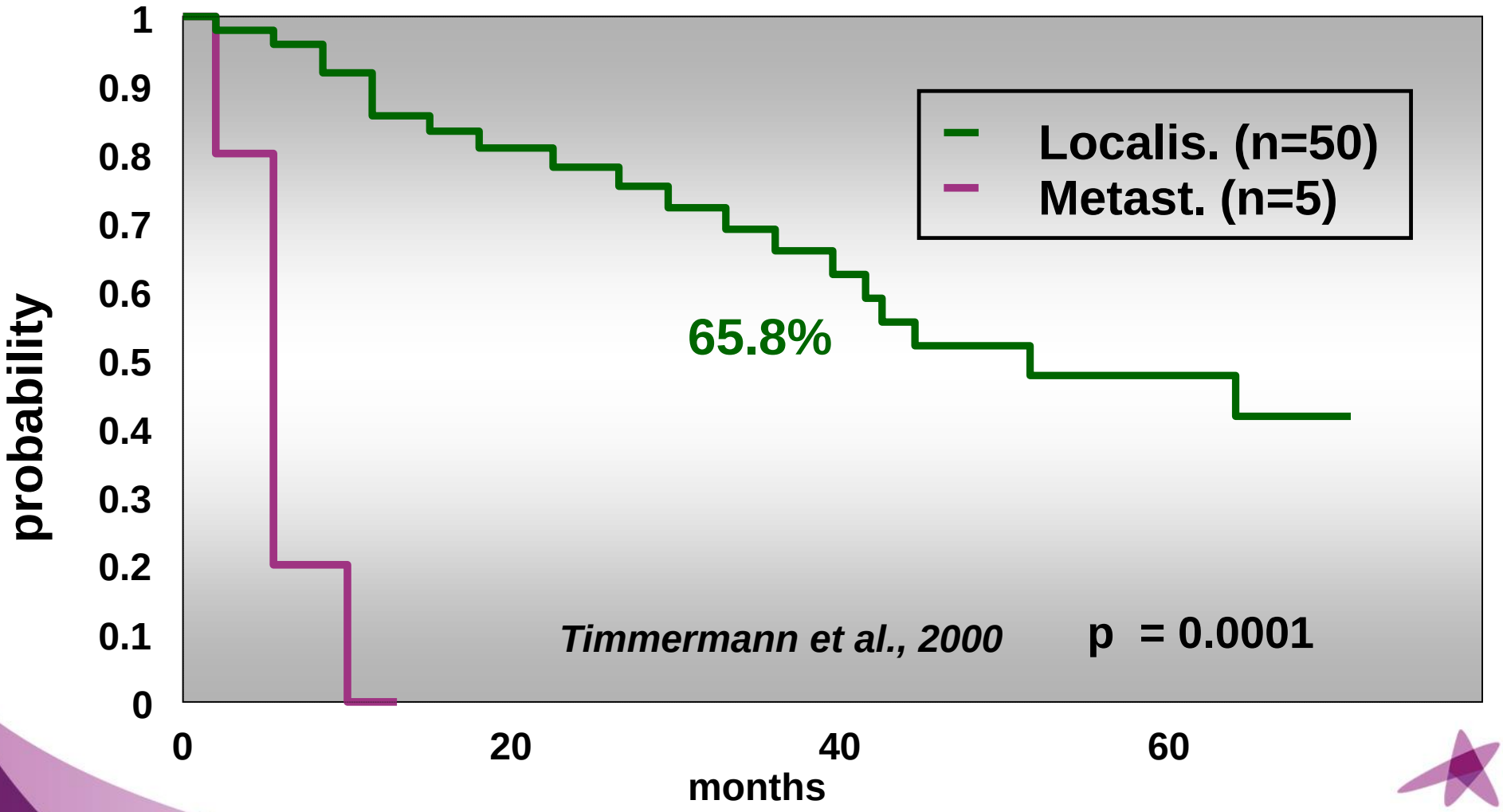


McGuire al., 2009

Intracranial ependymoma

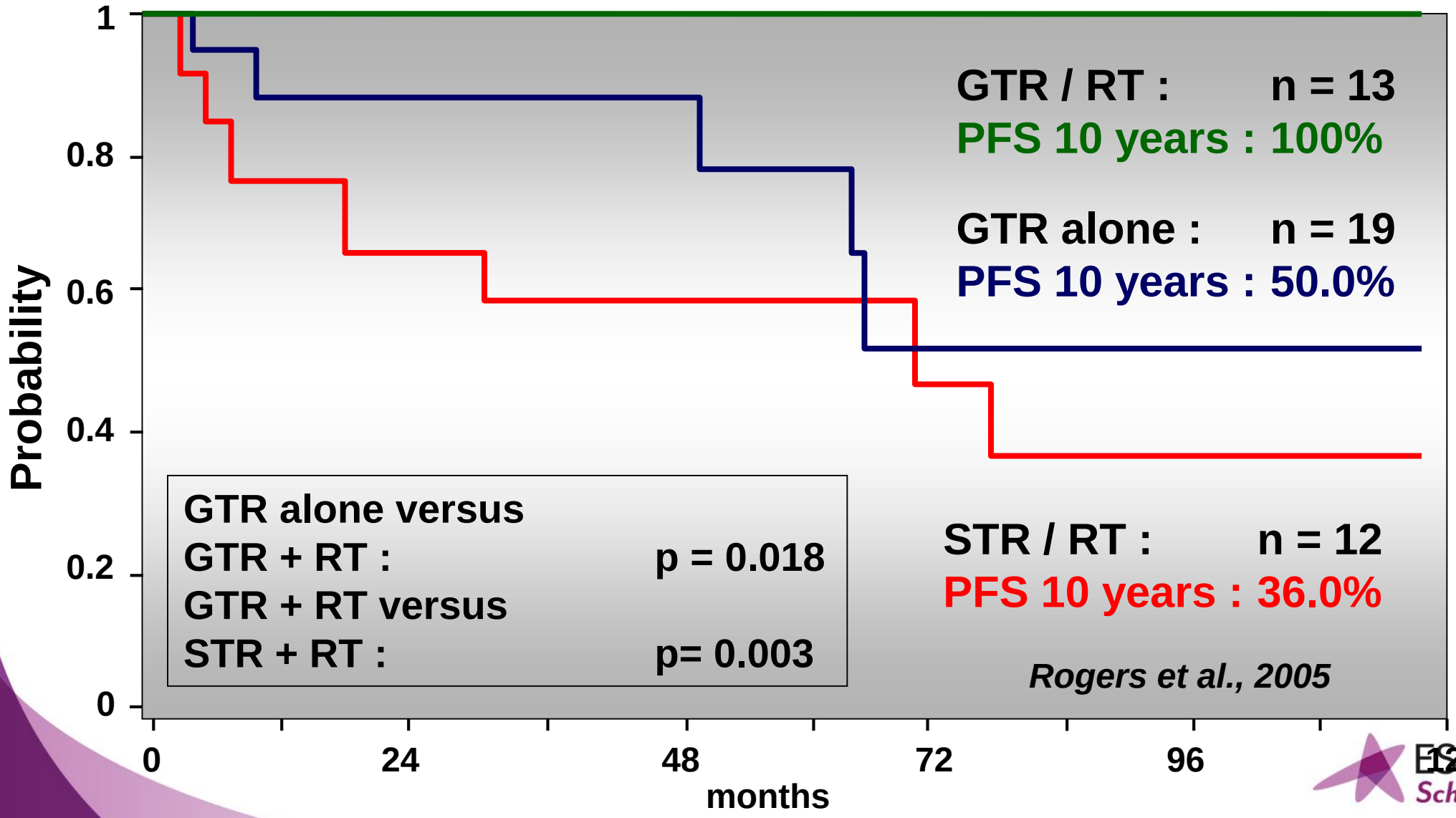
Anapl. ependymoma / HIT 88/89/91

Relapse-free survival / extent of disease



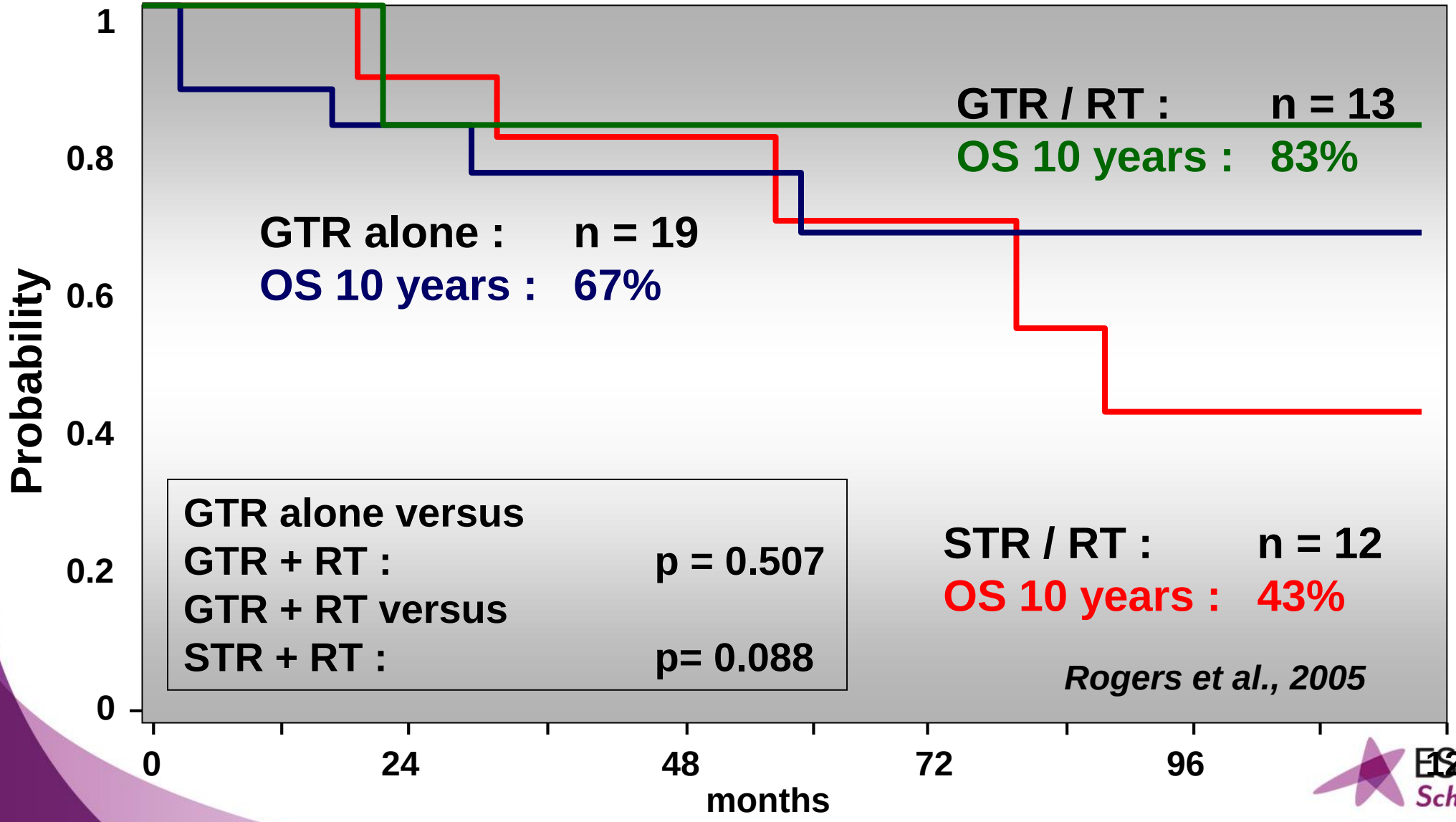
Intracranial ependymoma

Impact of postop. RT on outcome (54 Gy)
Actuarial local control rates



Intracranial ependymoma

Impact of postop. RT on outcome (54 Gy)
overall survival



Intracranial ependymoma

Postoperative radiotherapy / 5 year survival

Author	Pat.	Surg. only	Surg. + RT
Mork	12 16	17% -	**-** **40%**
Ferrante	7 10	18% -	**-** **68%**
Perilongo*	16 74	20.4% -	**-** **38.2%**
Rousseau*	15 65	0% -	**-** **45%**
Jaing	**31** **12**	**48.6%** **-**	**-** **57.9%**

*** Event – free survival**

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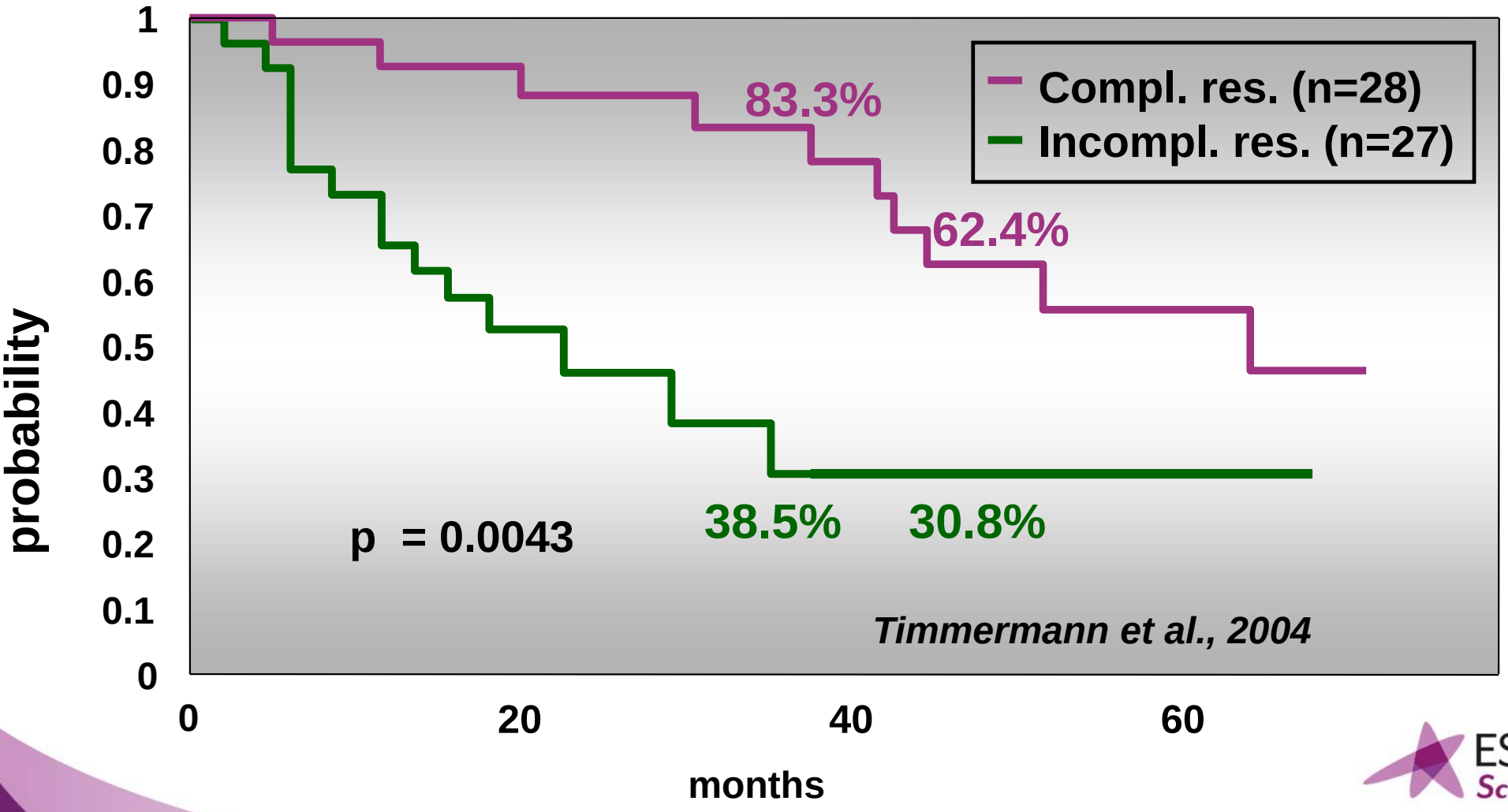
Intracranial ependymoma

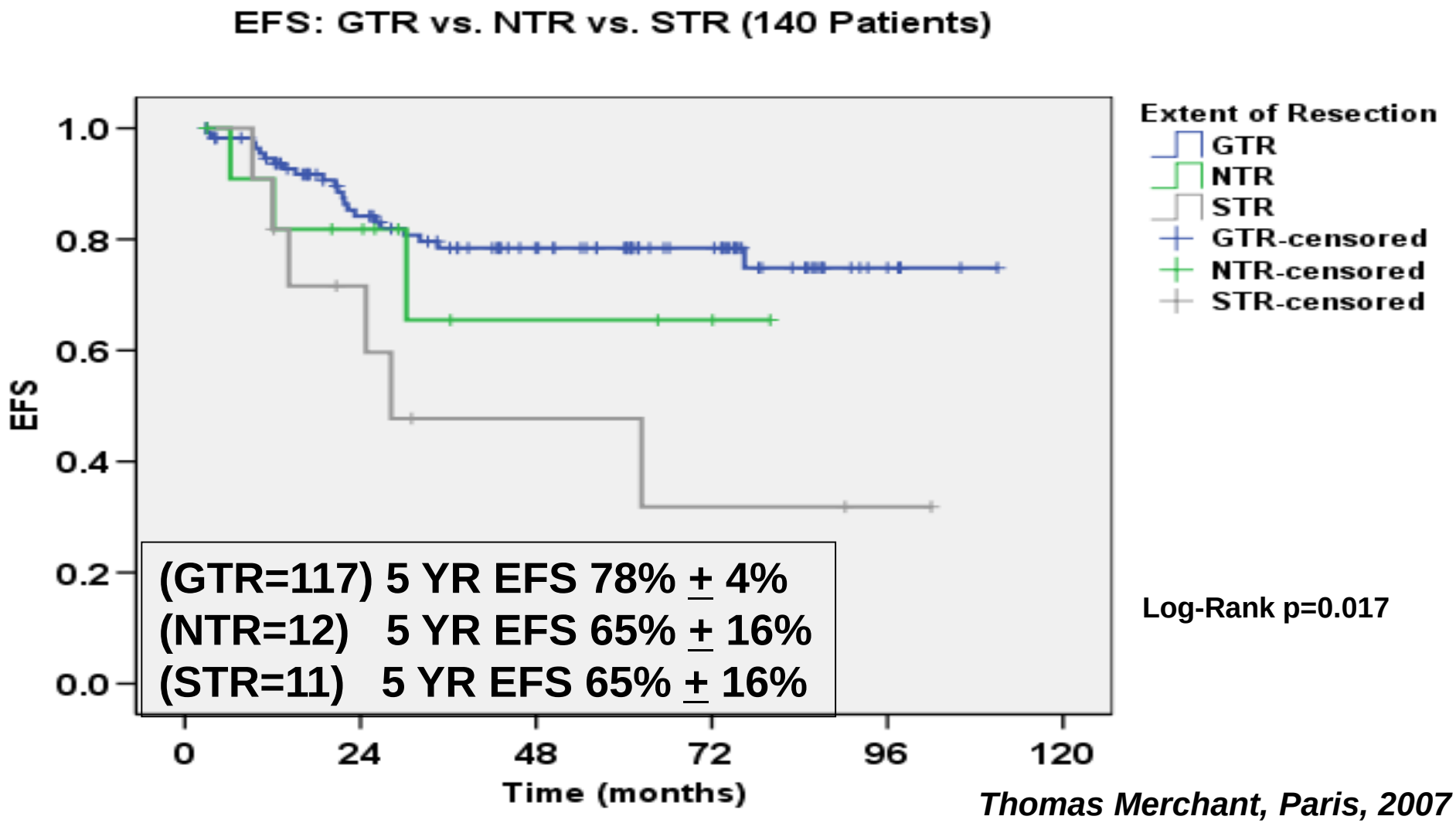
Anapl. ependymoma / HIT 88/89/91

Relapse – free survival / residual tumour



Intracranial ependymoma

Extent of resection / St. Jude series / event-free survival

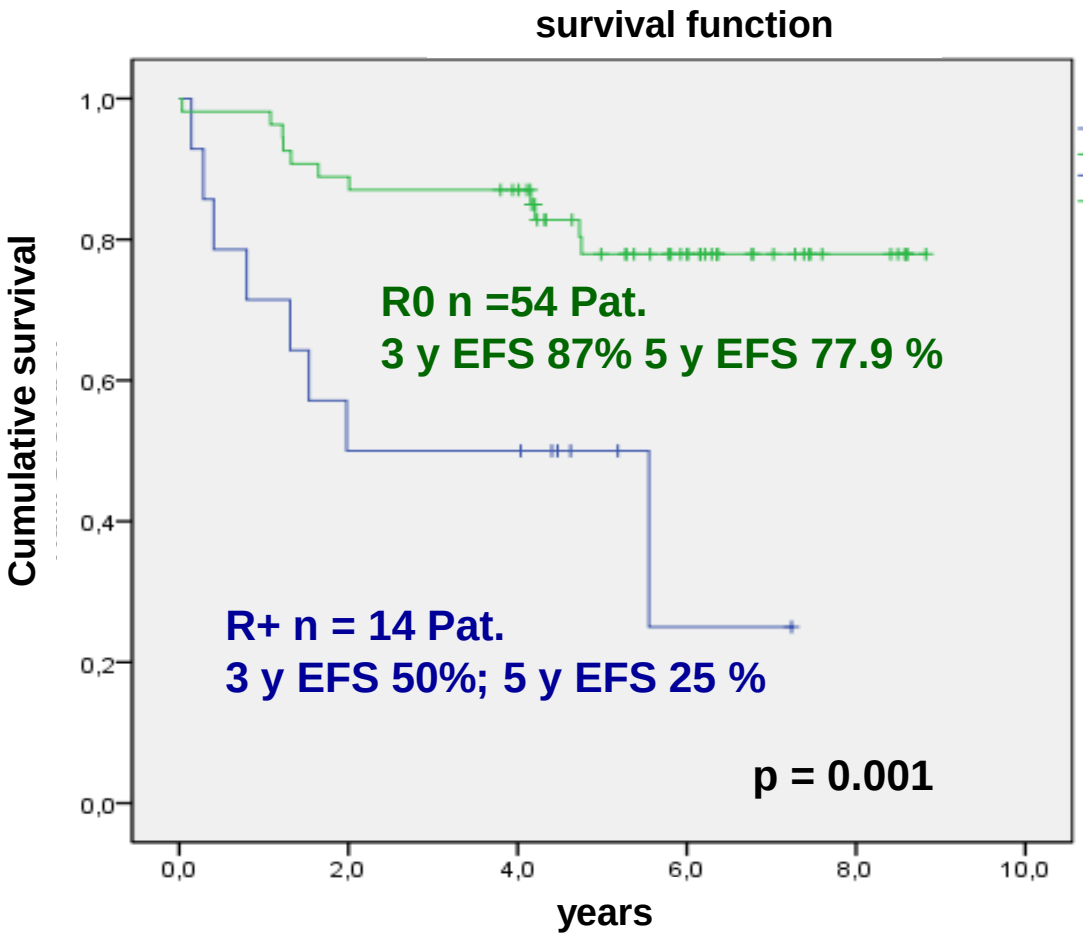


Thomas Merchant, Paris, 2007

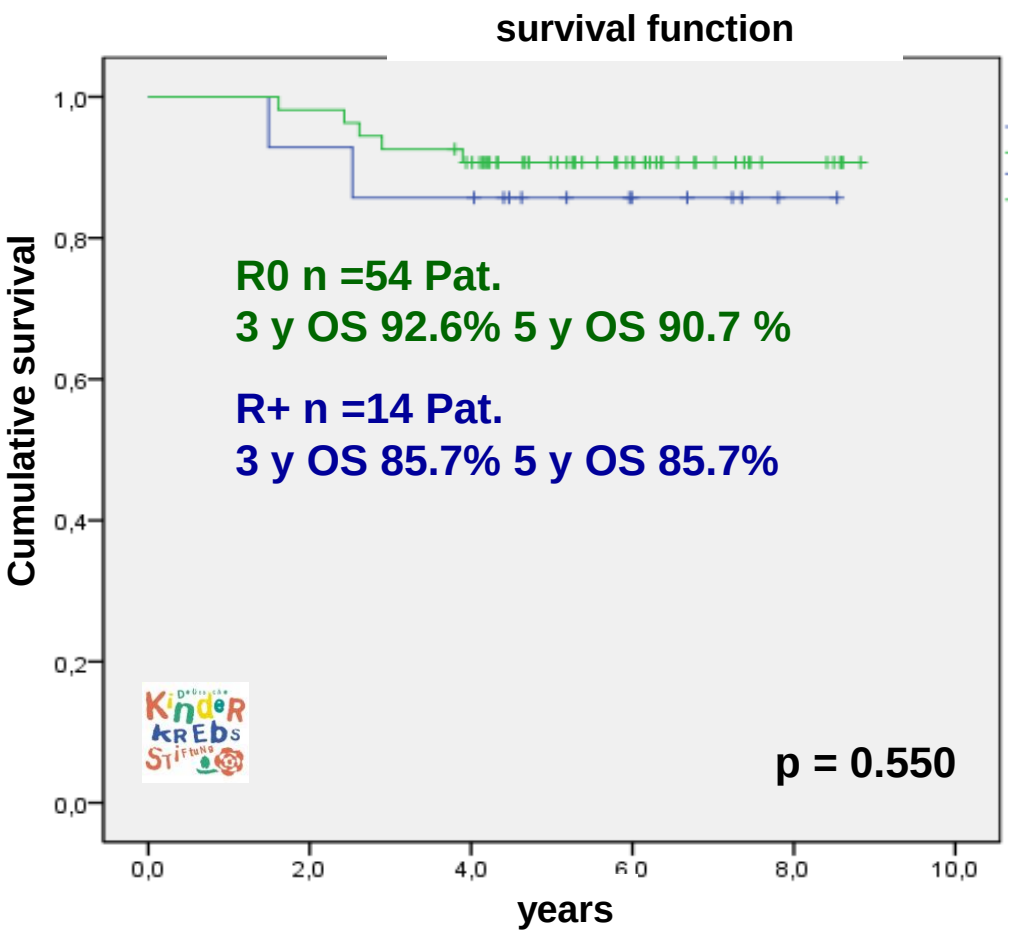
Intracranial ependymoma

HIT 2000 hfx / Extent of res. / EFS / OS / Gr II/III - R0 vs. R+

EFS



OS



Kortmann et al., ISPNO 2010

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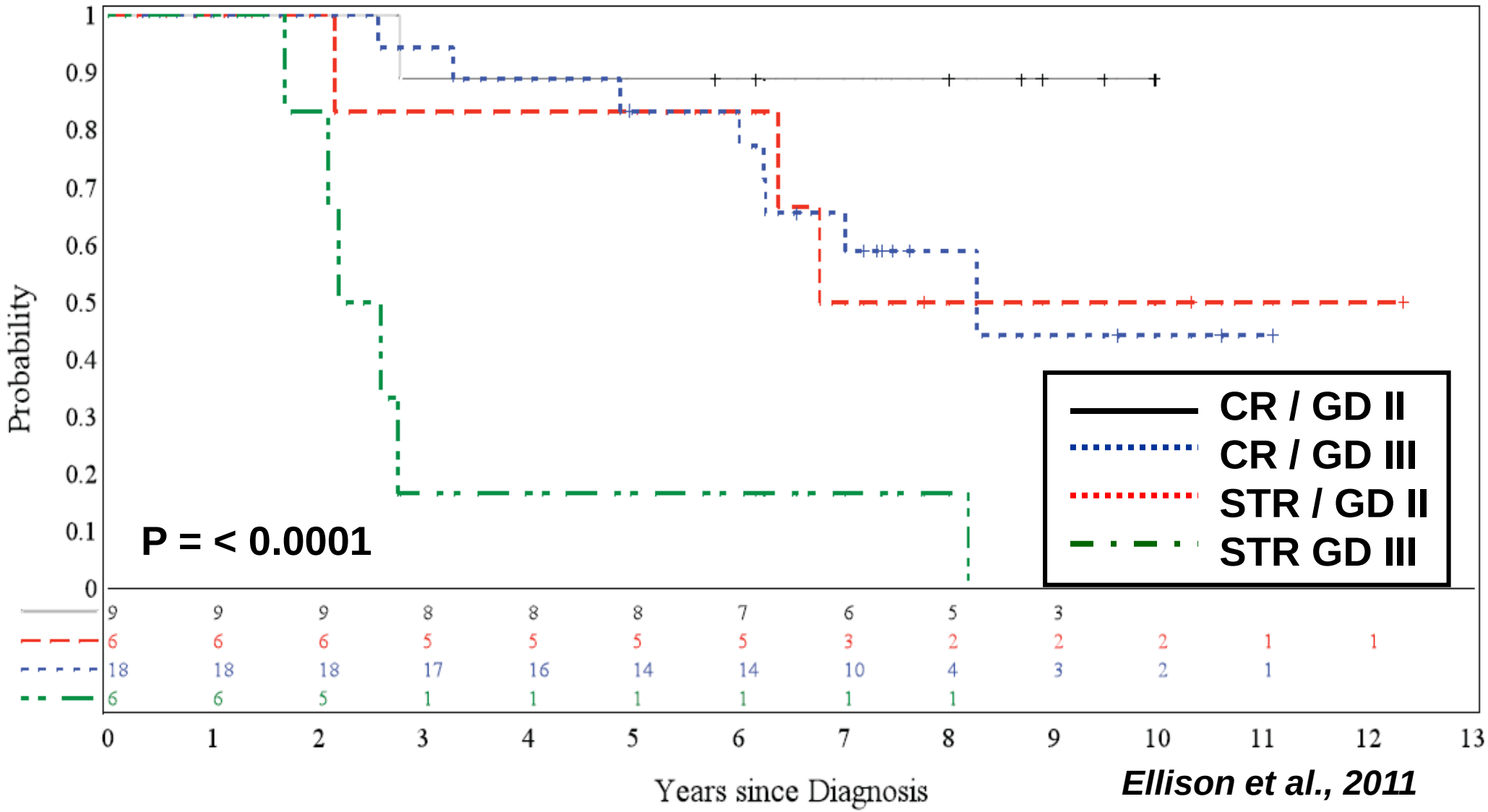
Intracranial ependymoma

Prognostic factors extent of resection and Grading

AEIOP series (Massimino et al., 2004) / overall survival



Ellison et al., 2011

Intracranial ependymoma

Adverse prognostic factors
3 yr event-free survival / european data

Subtotal Resection

- **53% vs. 83%** ***p=0.029***

Anaplastic Tumor Grade

- **50% vs. 94%** ***p<0.0001***

Pre-irradiation Chemotherapy

- **54% vs. 86%** ***p=0.0017***

Multivariate Analysis

- **Extent of Resection** ***p=0.018***
- **Tumor Grade** ***p=0.0003***
- **Pre-irradiation Chemoth.** ***p=0.0106***

Intracranial ependymoma

Molecular genetic profiles and prognostic implications
Location posterior fossa

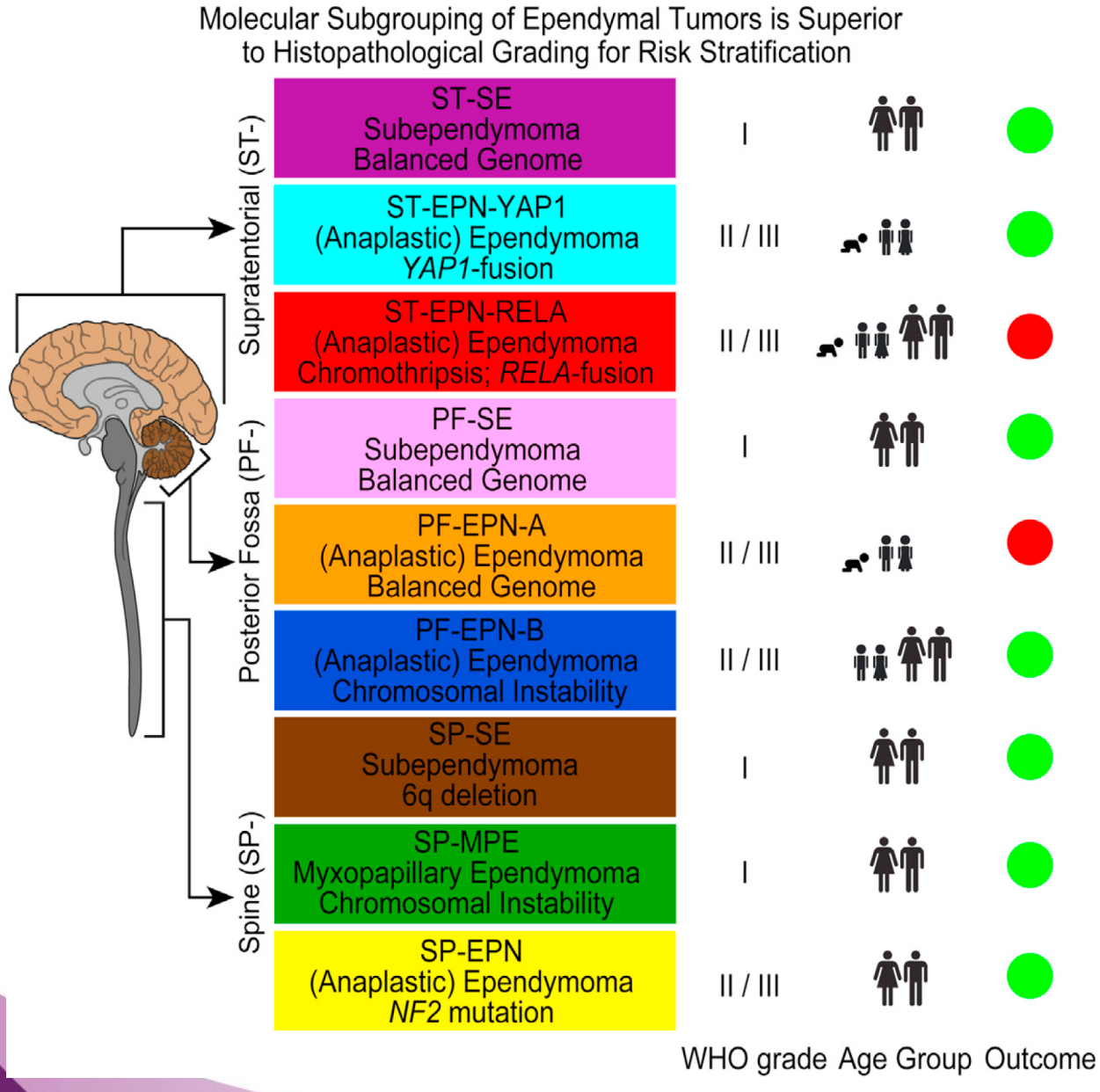
Table 2. Multivariable Cox Proportional Hazards Regression Model of Progression-Free and Overall Survival

Variable	Hazard Ratio	95% CI	*P*
Progression-free survival (n = 777)			
Age	0.99	0.98 to 1.00	.13
Male	1.25	1.02 to 1.54	.03
Incomplete resection	1.84	1.49 to 2.28	< .001
Adjuvant first-line radiation	0.63	0.49 to 0.79	< .001
Chemotherapy	1.04	0.81 to 1.34	.76
EPN_PFA subgroup	2.14	1.31 to 3.49	.002
Overall survival (n = 778)			
Age	0.98	0.96 to 1.00	.12
Male	1.41	1.97 to 1.85	.01
Incomplete resection	2.13	1.60 to 2.82	< .001
Adjuvant first-line radiation	0.52	0.38 to 0.72	< .001
Chemotherapy	0.90	0.65 to 1.26	.54
EPN_PFA subgroup	4.30	1.88 to 9.87	< .001

Ramaswamy et al., 2016

Intracranial ependymoma

Molecular classification of ependymal tumors across all CNS compartments, histopathological grades, and age groups



Pajtler et al., 2015

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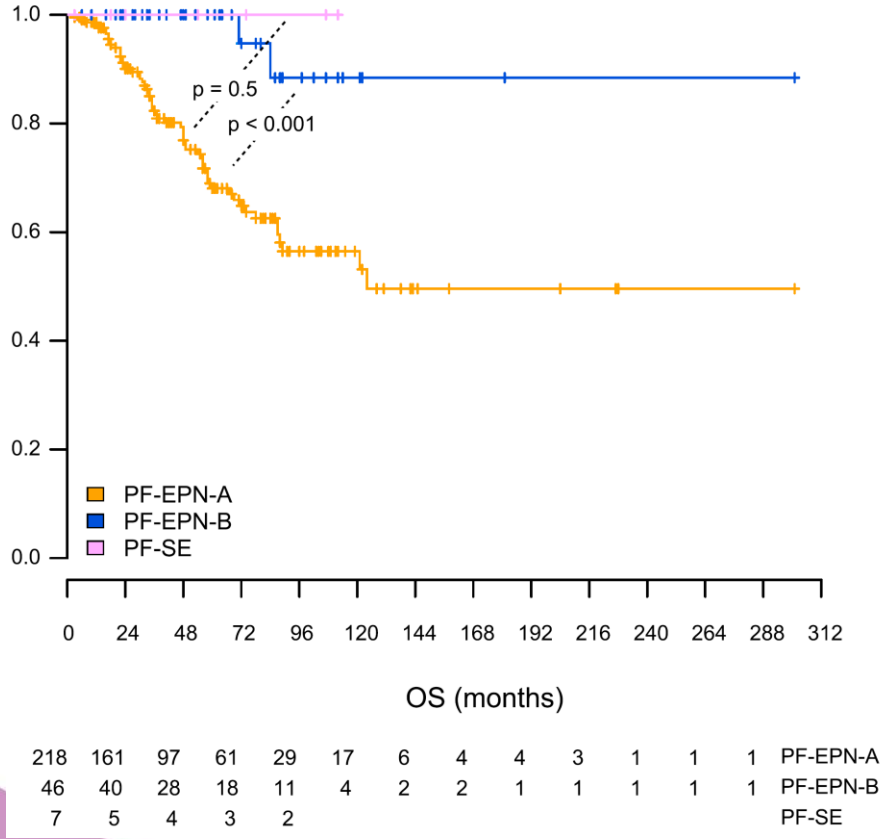
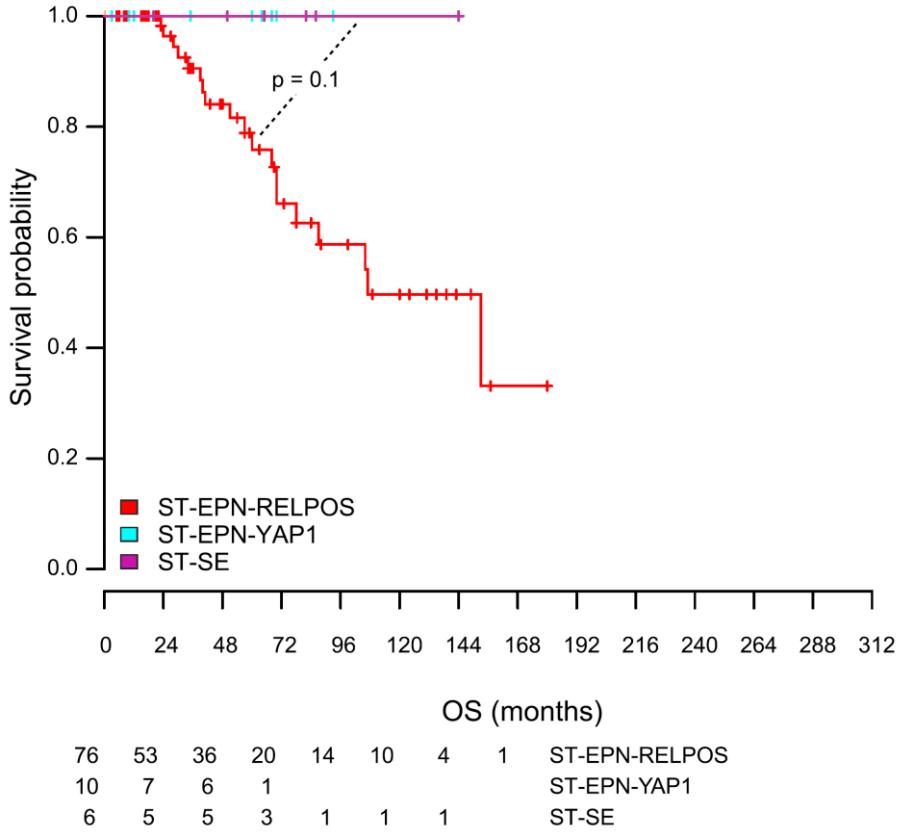
Intracranial ependymoma

Molecular classification of ependymal tumors across all CNS compartments, histopathological grades, and age groups

	Posterior fossa		supratentorial	
	EPN-PFA	EPN-PFB	EPN-YAP	EPN-RELA
5-year PFS	33%	73%	66%	29%
5-year OS	68%	100%	100%	75%
Nb of pat.	240	51	13	88

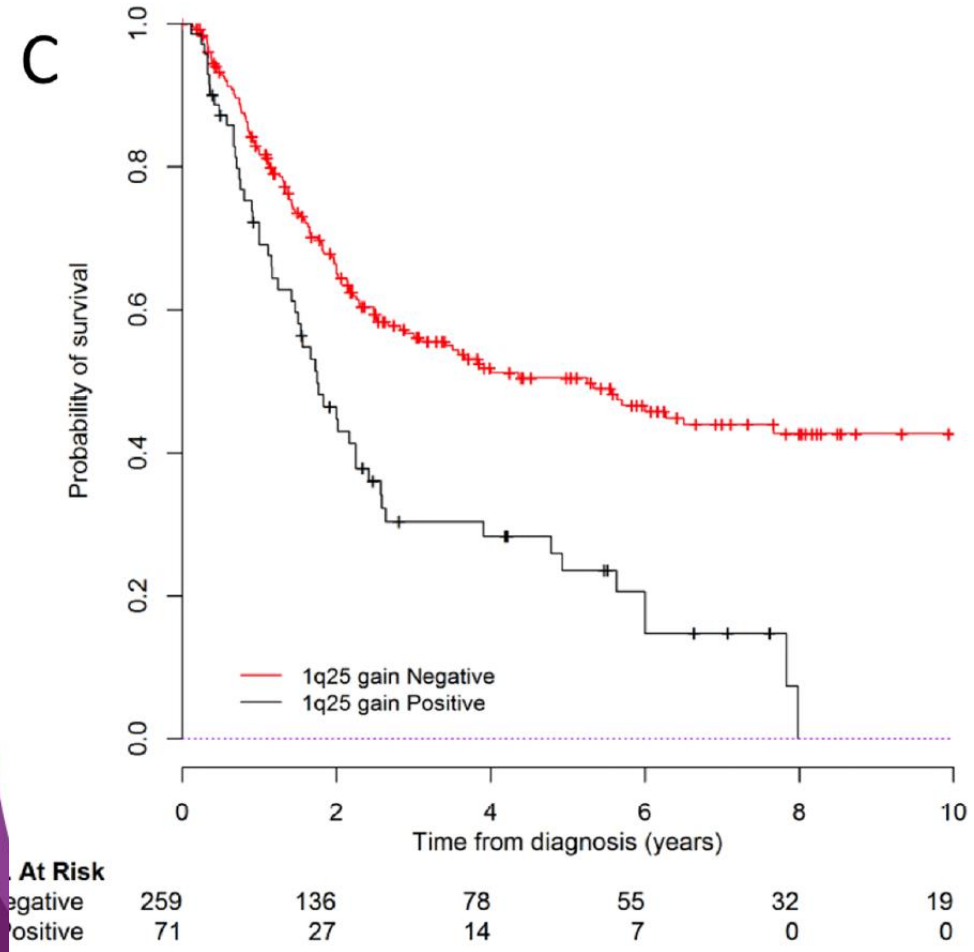
Pajtler et al., 2015

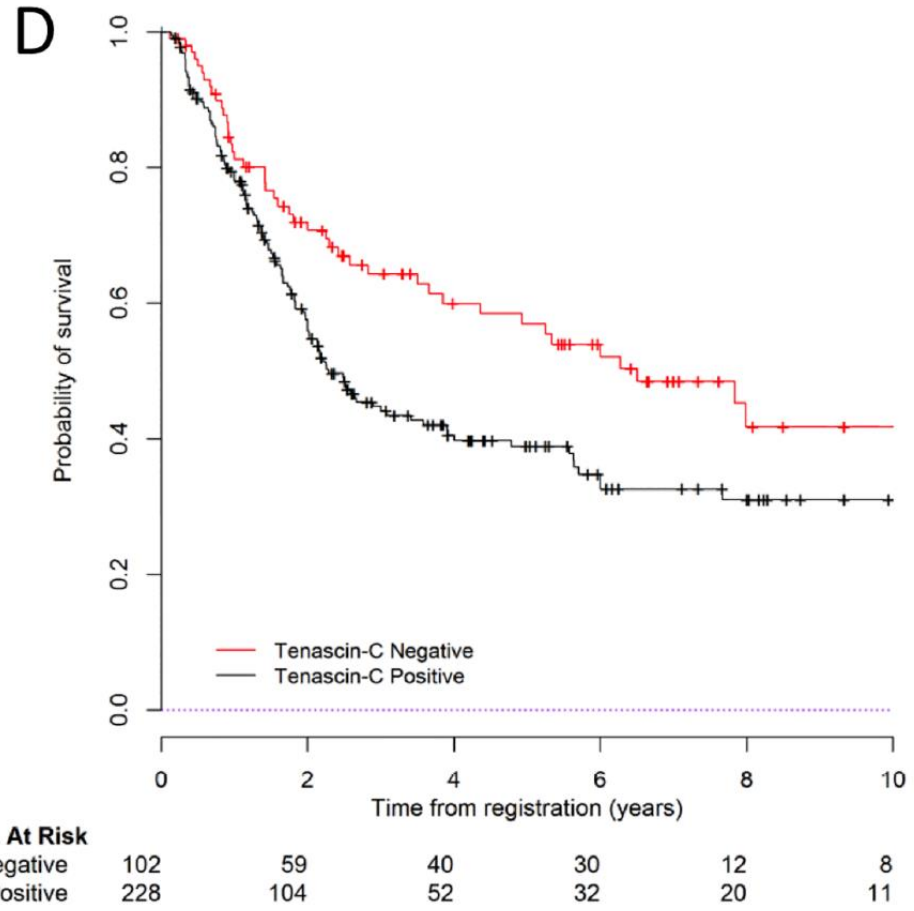




Intracranial ependymoma

Molecular genetic profiles and prognostic implications
PF location / 1q25 gain / Tenascin C /OS





Andreiuolo et al., SIOP Ependymoma Working Group, 2017

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Intracranial ependymoma

Molecular genetic profiles and prognostic implications
PF location / 1q25 gain / Tenascin C /OS

Table 2. Multivariable model for overall survival in patients with posterior fossa ependymomas (N = 325). The multivariable Cox regression model is stratified by cohort and radiotherapy‡.

Prognostic factors		Hazard Ratio	95% confidence interval	p-value
Age at diagnosis	<36months	1		0.1662
	≥ 36 months	0.685	[0.402; 1.170]	
Grade	II	1		0.0283
	III	1.710	[1.059; 2.761]	
Extent of resection	Incomplete	1		0.0043
	Complete	0.525	[0.338; 0.817]	
Tenascin-C	Negative	1		0.0184
	Positive	1.941	[1.118; 3.367]	
1q25 gain	Negative	1		0.0001
	Positive	2.491	[1.561; 3.976]	

Andreiuolo et al., SIOP Ependymoma Working Group, 2017

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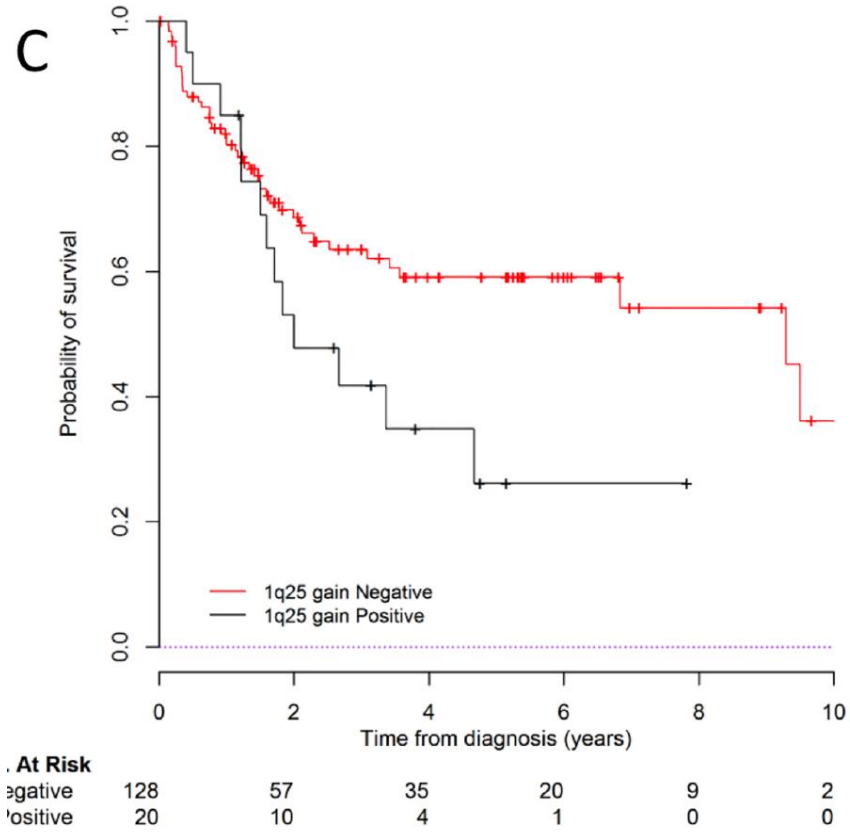
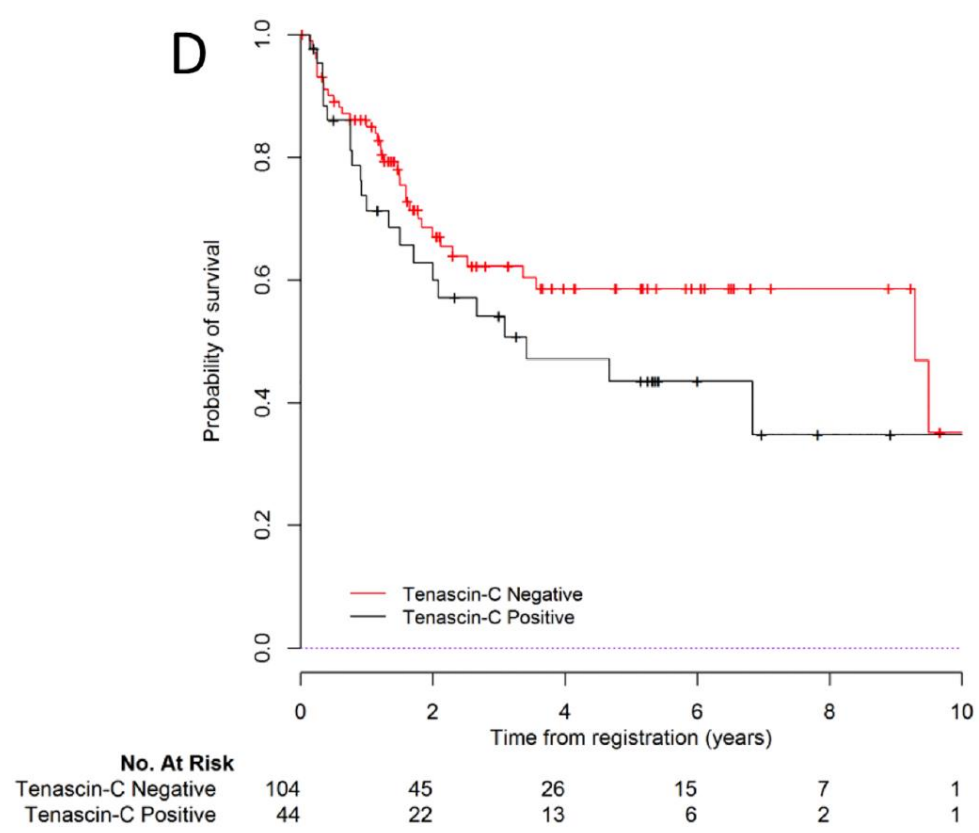
Intracranial ependymoma

Molecular genetic profiles and prognostic implications
Supratentorial location / 1q25 gain / Tenascin C /OS





Andreiuolo et al., SIOP Ependymoma Working Group, 2017

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Intracranial ependymoma

Molecular genetic profiles and prognostic implications
Supratentorial location / 1q25 gain / Tenascin C /OS

Table 3. Multivariable model for overall survival in patients with supratentorial ependymomas (N = 145). The multivariable Cox regression model is stratified by cohort and radiotherapy.

Prognostic factors		Hazard Ratio	95% confidence interval	p-value
Age at diagnosis	<36months	1		0.1617
	≥ 36 months	2.881	[0.655; 12.680]	
Grade	II	1		0.0613
	III	4.787	[0.928; 24.676]	
Extent of resection	Incomplete	1		0.1871
	Complete	0.565	[0.242; 1.319]	
Tenascin-C	Negative	1		0.1149
	Positive	0.474	[0.188; 1.199]	
1q25 gain	Negative	1		0.0067
	Positive	3.261	[1.389; 7.658]	

In supratentorial tumours ca 75% RELA fusion

Andreiuolo et al., SIOP Ependymoma Working Group, 2017

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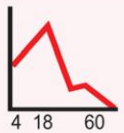
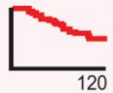
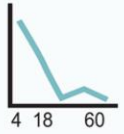
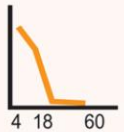
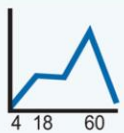
Intracranial ependymoma

Molecular genetic profiles and prognostic implications

General Consensus Statements

1. Outside of clinical trials, treatment decisions should not be based on grading (II vs III)
2. ST and PF ependymomas are different diseases although the impact on therapy is still evolving
3. Central radiological and histological review should be a principal component of future clinical trials
4. Molecular subgrouping should be part of all clinical trials henceforth
5. Submission of fresh-frozen tumor samples as well as of blood samples will be mandatory in future clinical trials

Subgroup Consensus Statements

Molecular subgroup	Tumor Location	Genetics	Age Distribution (yrs)	Gender Distribution	Survival (OS;months)	Subgroup-specific consensus
ST-EPN-RELA		Aberrant 11q  Chromothripsis	 4 18 60		 120	There is not enough evidence to recommend distinct treatment approaches. Outcome should be further validated in prospective and retrospective studies.
ST-EPN-YAP1		Aberrant 11q 	 4 18 60		 120	It should be rapidly determined whether the YAP1 subgroup is associated with favorable clinical outcome.
PF-EPN-A		 Balanced	 4 18 60		 120	Outside of clinical trials, in patients > 12 months of age, maximal safe resection and focal radiotherapy is the standard of care.
PF-EPN-B		 Chromosomal Instability	 4 18 60		 120	An observation only clinical trial will be implemented to determine the opportunity of de-escalating therapy.

Pajtler et al., 2017

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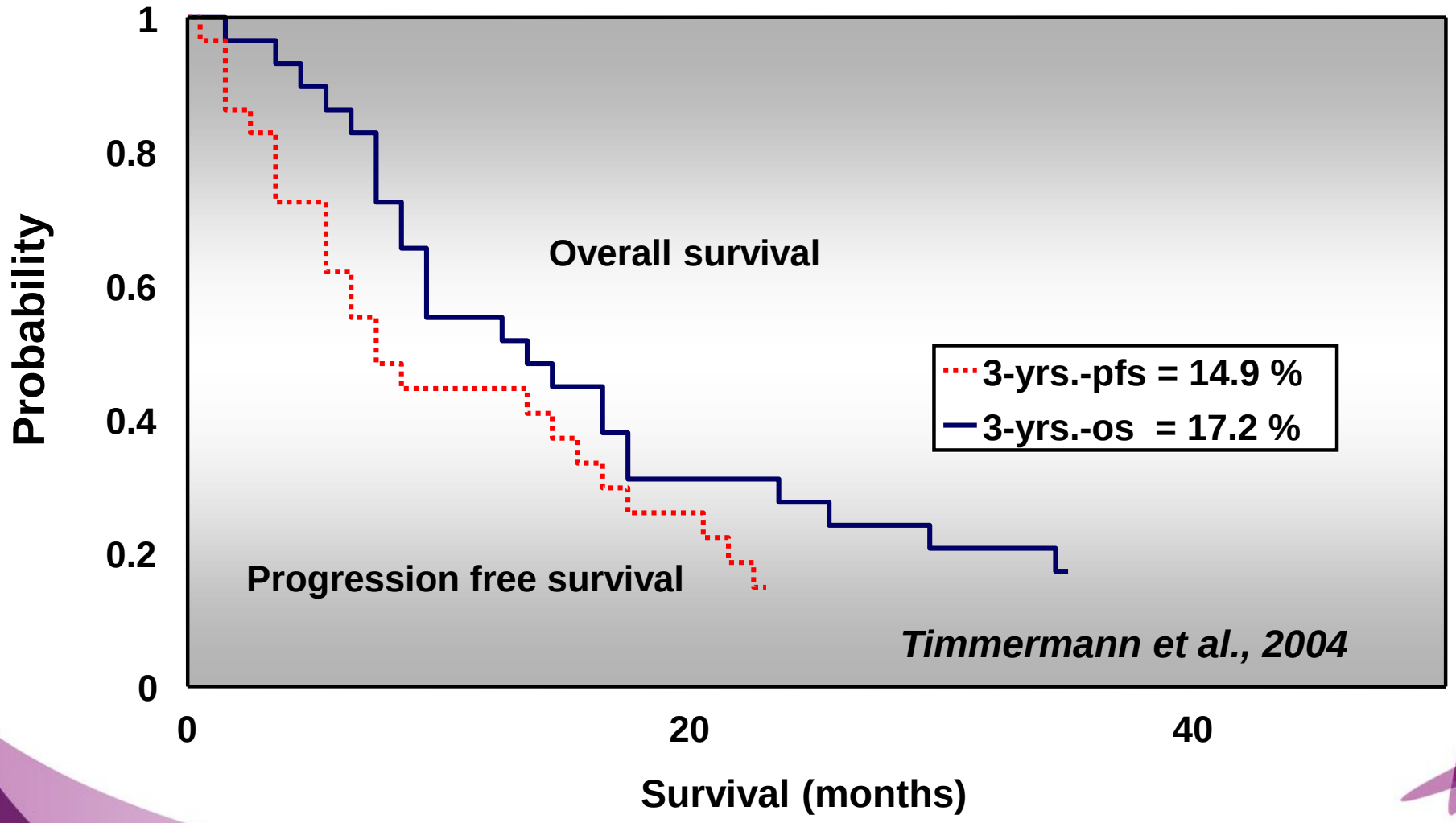
Management in the infant

Intracranial ependymoma

Anapl. ependymoma / HIT SKK

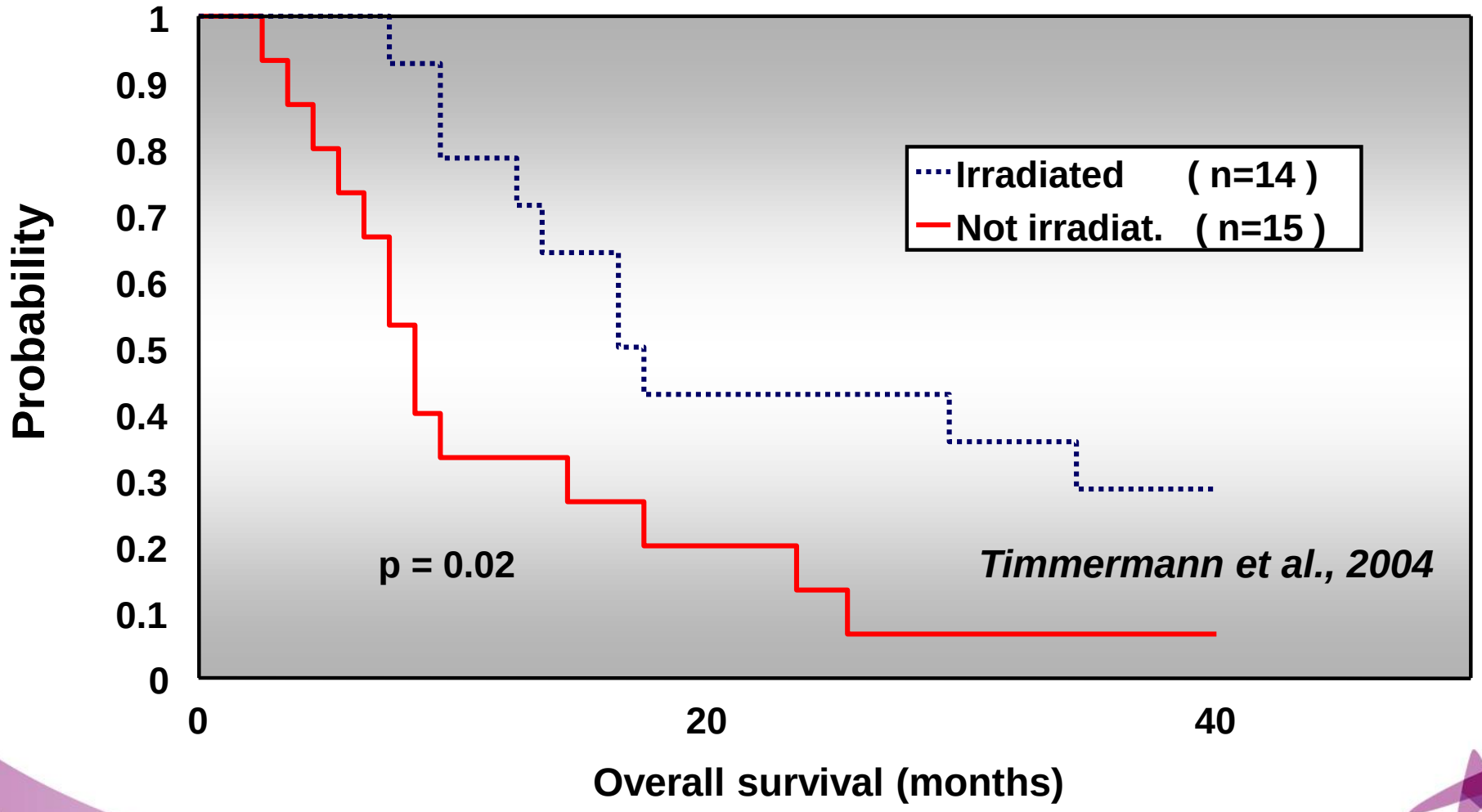
Role of RT in infants (< 3 years) / PFS - OS



Intracranial ependymoma

Anapl. ependymoma / HIT SKK

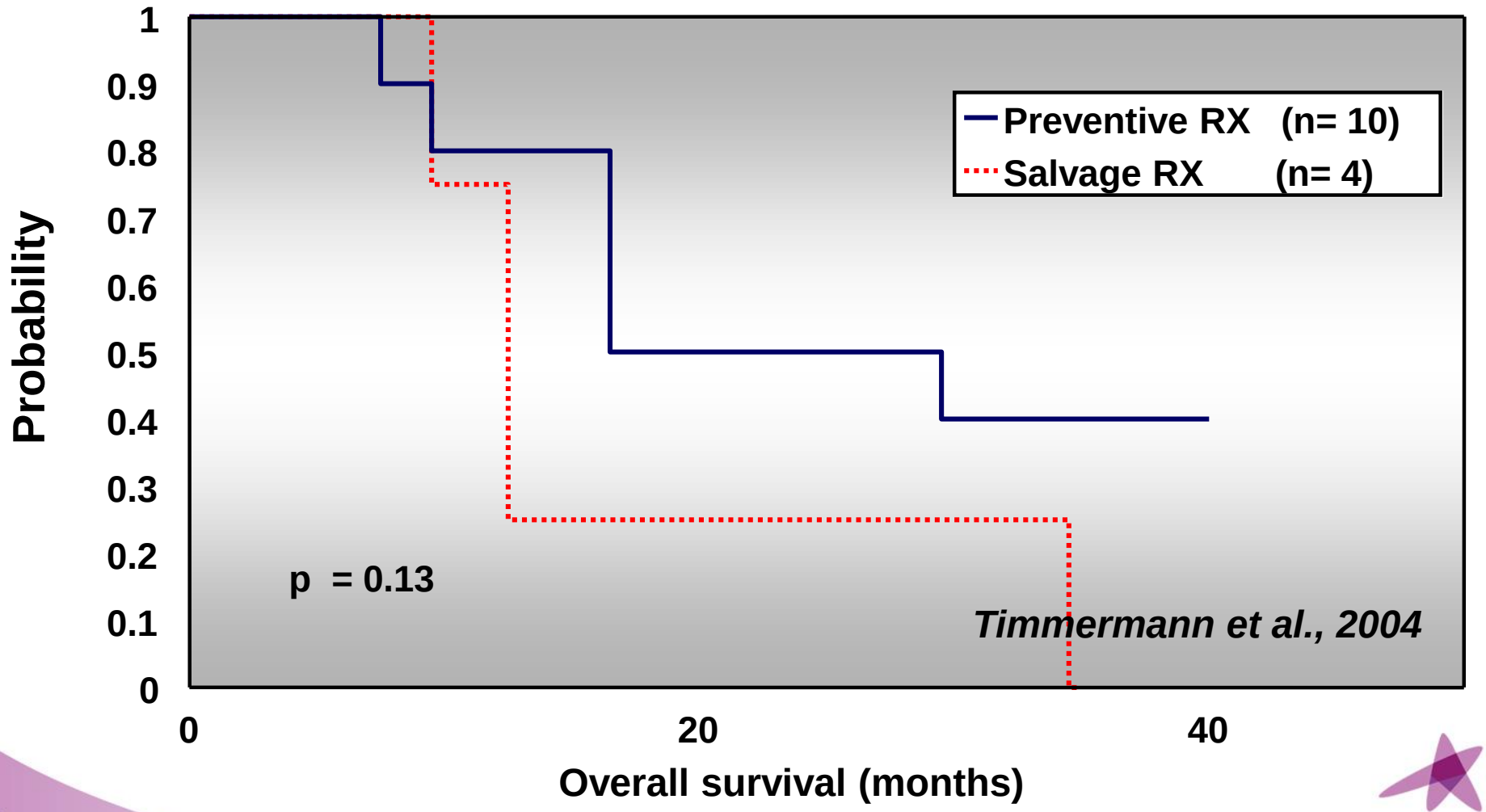
Role of RT in infants (< 3 years) / RT yes - no



Intracranial ependymoma

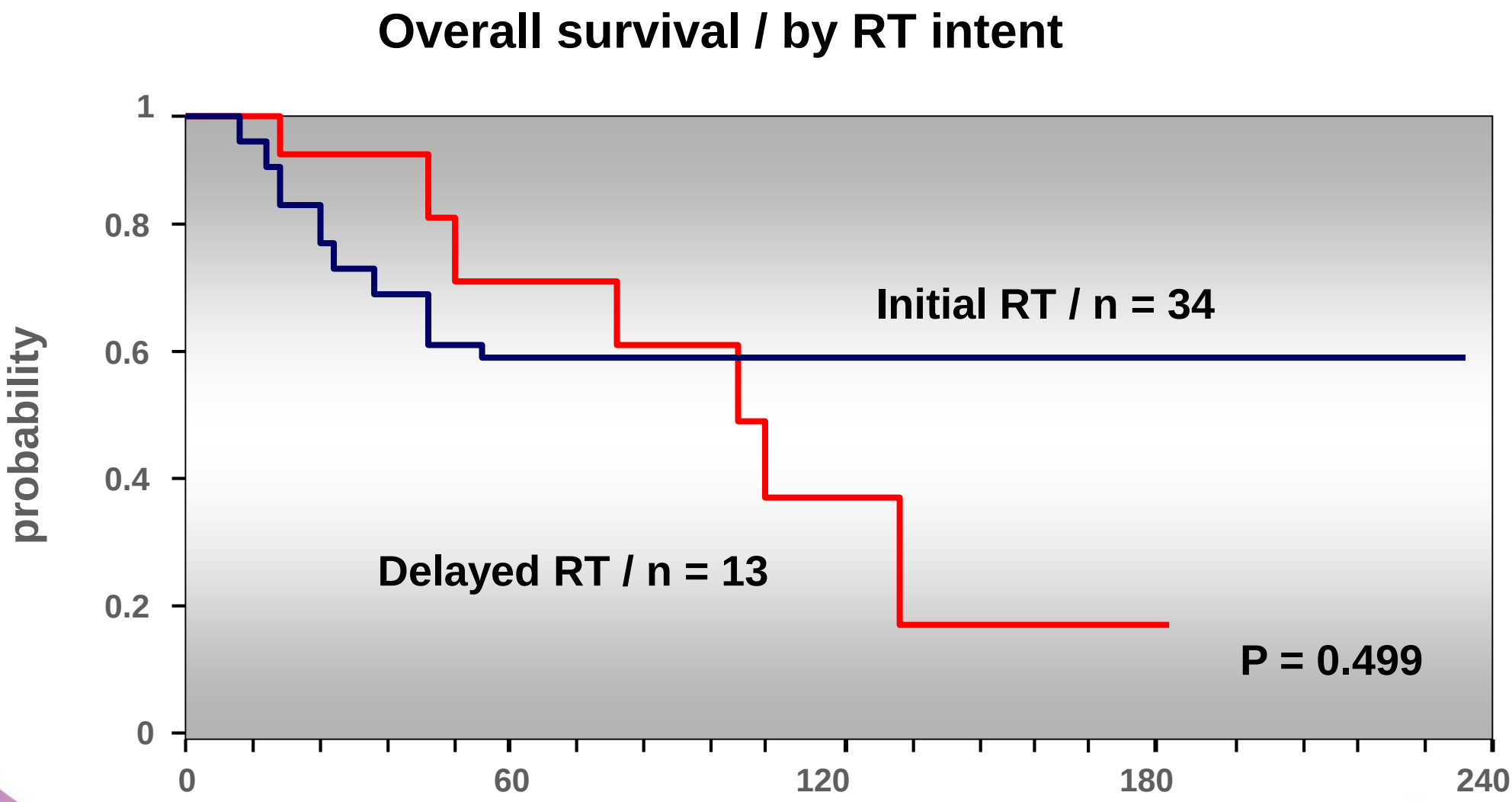
Anapl. ependymoma / HIT SKK

Role of RT in infants (< 3 years) / up front RT yes - no



Intracranial ependymoma

Impact of timing of RT on survival



Shu et al., 2007

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Intracranial ependymoma

Anapl. ependymoma / HIT SKK

Parameter of radiotherapy	No. of patients	3-Year OS rate (%)	95% CI	*P*-value
Given	21	66.7	46.5-86.8	
Not given	13	38.5	12.0-64.9	0.21
Preventive	12	66.7	40.0-93.3	
Salvage	9	66.7	35.9-97.5	0.62
CSI+boost	11	54.5	25.1-83.9	
Local fields	10	80.0	55.2-100	0.69

Timmermann et al., 2004

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Intracranial ependymoma

Ependymoma ° II/° III

HIT 2000 / age : 4 – 21 years / M0

Surgery → **RT tumour site only 68 Gy, 2 x 1.Gy / day (boost 72 Gy in persistent residual disease) weekly VCR in Gr. III** → **In grade III Chx HIT SKK 2000* 5x alternating CP/VCR CARBO/VP16 *no i.th. MTX**

M 1 – 3 : RT CSA : 40 Gy hfx (2 x 1 Gy / day), boost tumour site 68 Gy, 72 Gy in persistent Tu., 50 Gy to spinal deposits + Chx. HIT SKK

HIT 2000 / age : < 4 years / M0

Surgery → **Regardless of grade Chx HIT SKK 2000*** → **RT tumour site only 54 Gy, 5 x 1.8 Gy / week (stereotactic boost in pers.disease)**

M 1 – 3 : RT CSA : 24 Gy, boost to tumour 54 gy + deposits 44.8Gy

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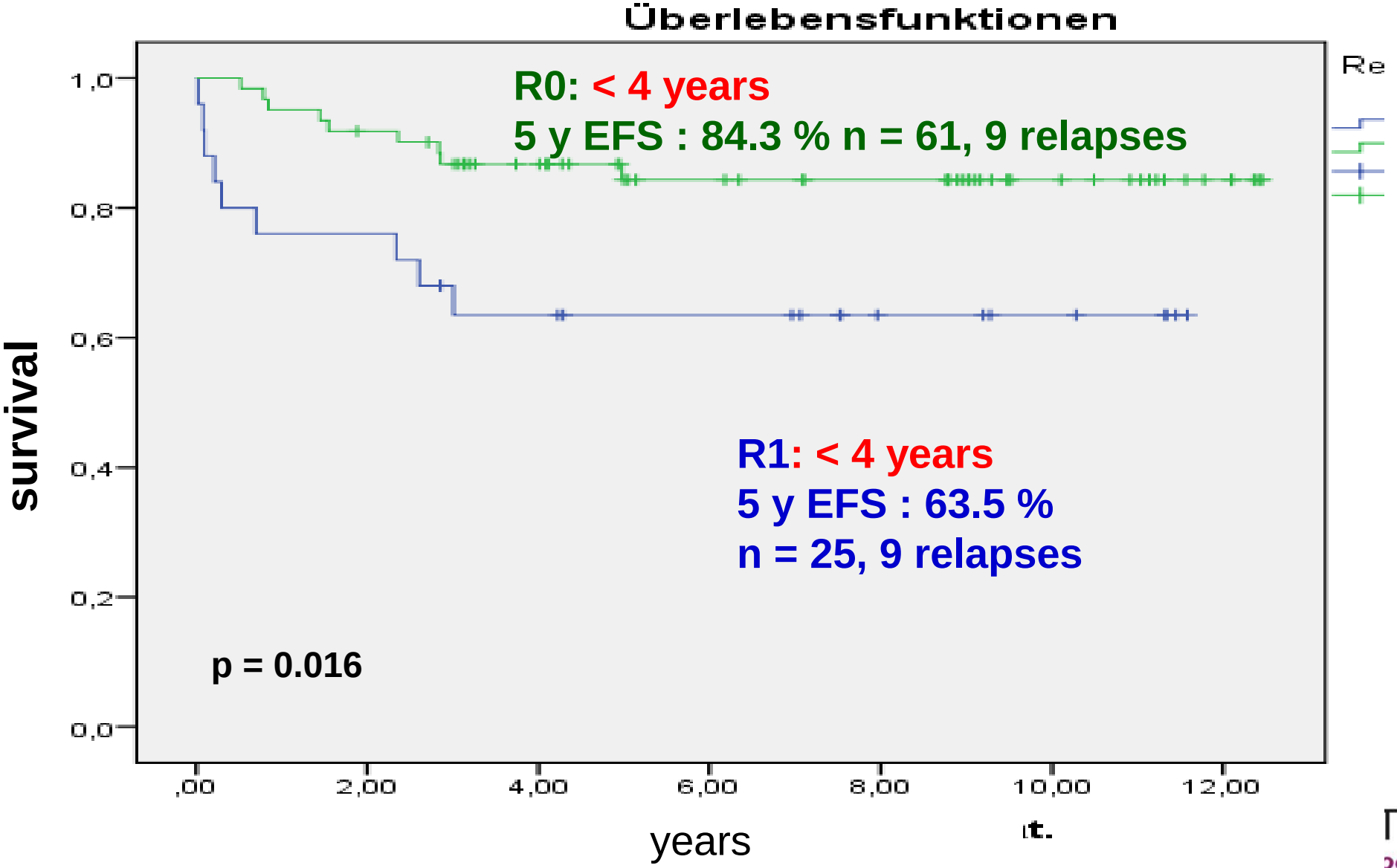
Intracranial ependymoma

EFS - Ependymoma ° II+° III <4 years / R 0 versus R +



Intracranial ependymoma

Ependymoma – international data / „infants“

Author, year	Pat.	RT	Survival
Grill et al., 2001	73	Chx only / RT at PD	4 y PFS : 26%/ 4 y. OS : 59% (23% without RT)
Grundy et al., 2007	89	Chx. only RT at PD	M0 EFS OS 3 y 47.6 79.3% 5 y 41.8% 63.4%
Fouladi et al., 2009	21	Planned RT < 18 mon : 48Gy 18-30 mon. :51 Gy > 30 mon. : 54 Gy	5 y PFS : 33% 5 y. OS : 62%
Massimino et al.,	41	Chx. only / RT at PD	5 y PFS : 26%/ 5 y. OS : 37%
Merchant et al., 2009	78	RT only	5 y EFS : 68.6%/ OS : 80.4%
Grundy et al., 2010	11	Chx. only / RT at PD	1 y PFS : 1/11/ 1 y. OS : 9.1%
Timmermann et al., 2004 HIT 88-89/91	34	RT : 21 No RT : 13	3 year PFS : 23.3% 3 year OS RT : 66.7%/ no RT : 38.5%
HIT 2000	51	R0 : 61 R+ : 25	5 year PFS R0 : 84.3 / R+ : 63.5%

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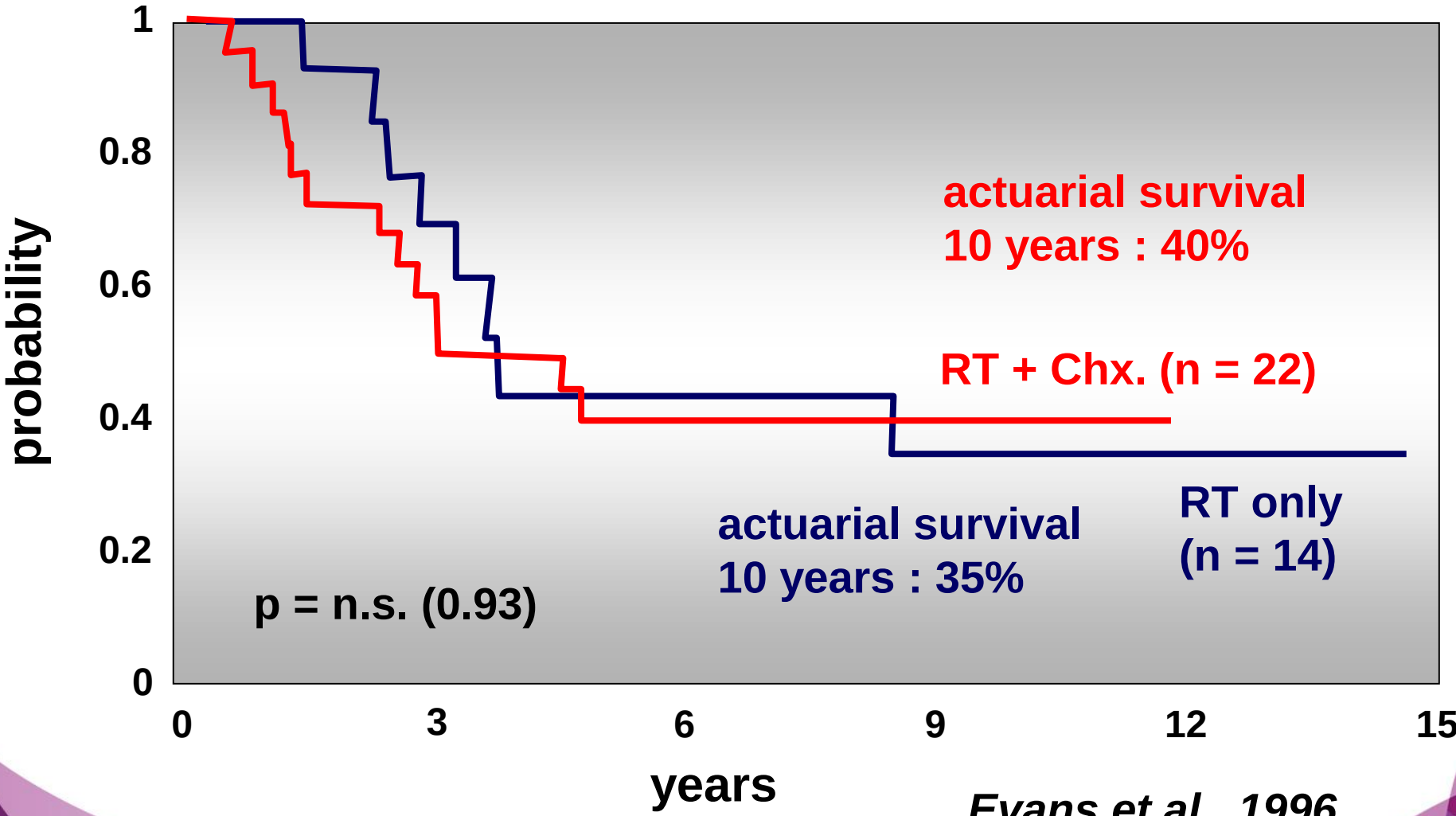
Role of chemotherapy

Intracranial ependymoma

CCSG random. study / survival by arm (+/- chx.



Evans et al., 1996

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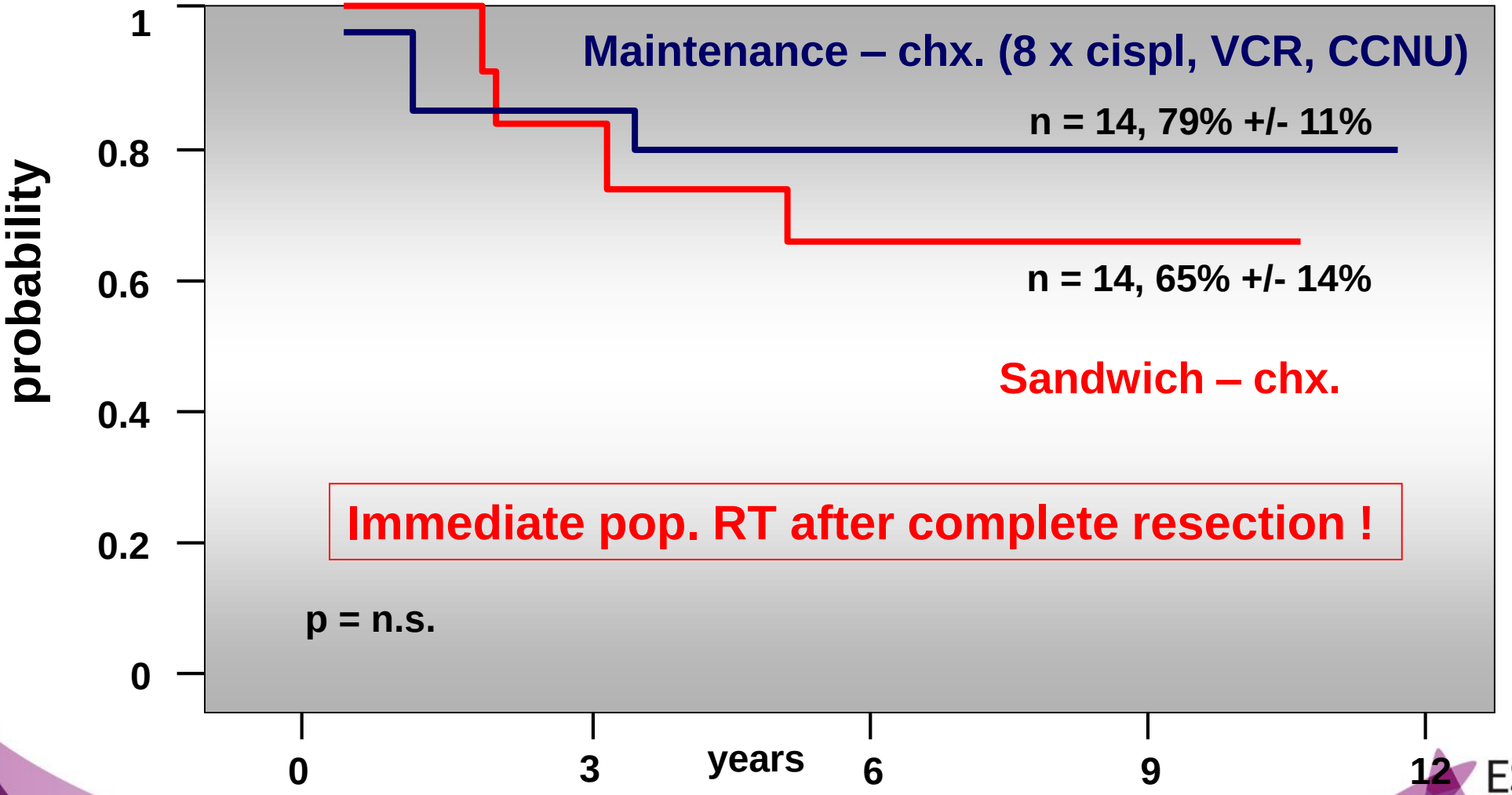
Intracranial ependymoma

HIT 91 random. study / Sandwich vs. maintenance

Event-free survival / R0 / n = 26



HIT – study group, 2007, unpublished

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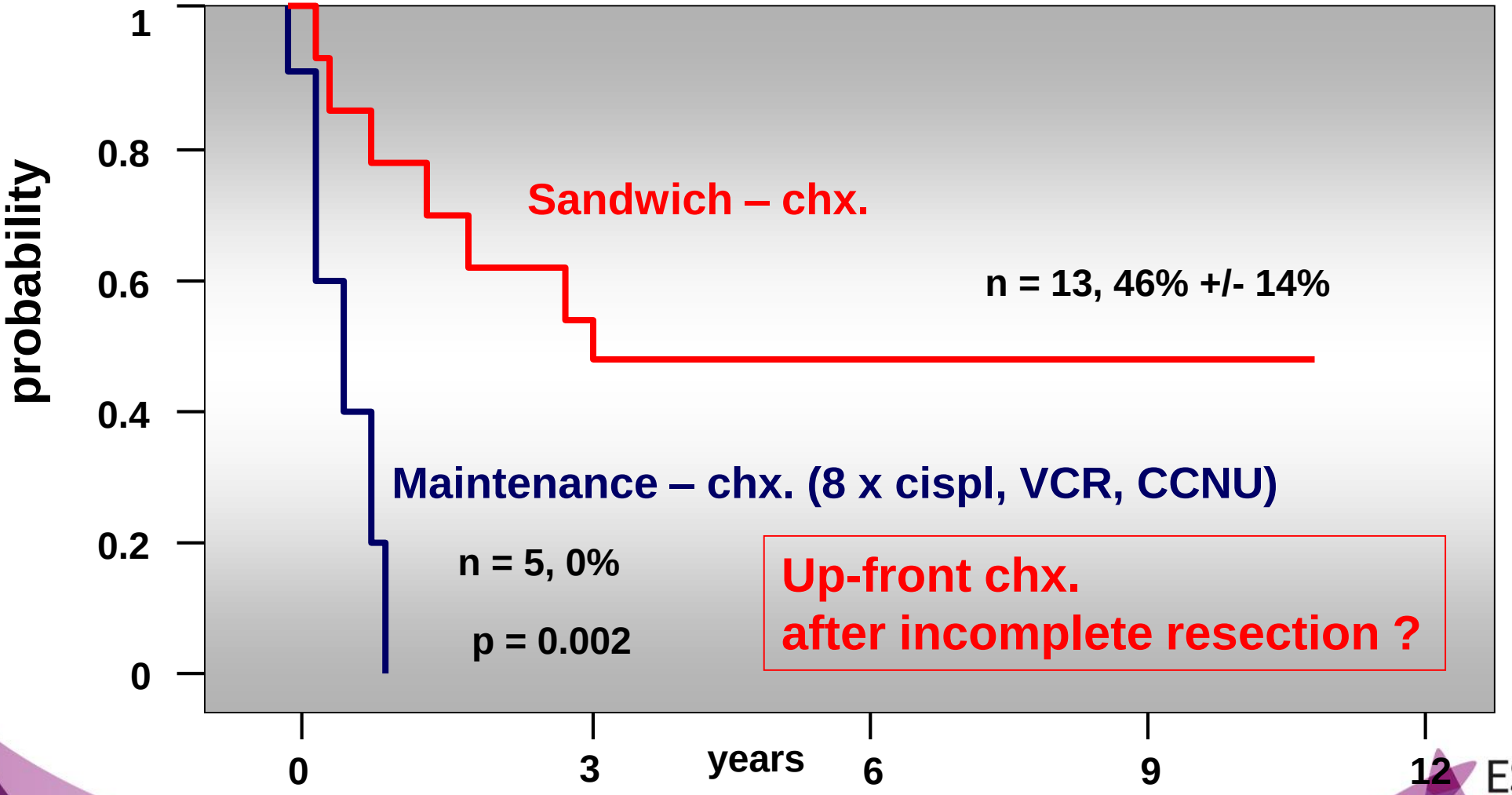
Intracranial ependymoma

HIT 91 random. study / Sandwich vs. maintenance

Event-free survival / R1 / n = 18



HIT – study group, 2007, unpublished

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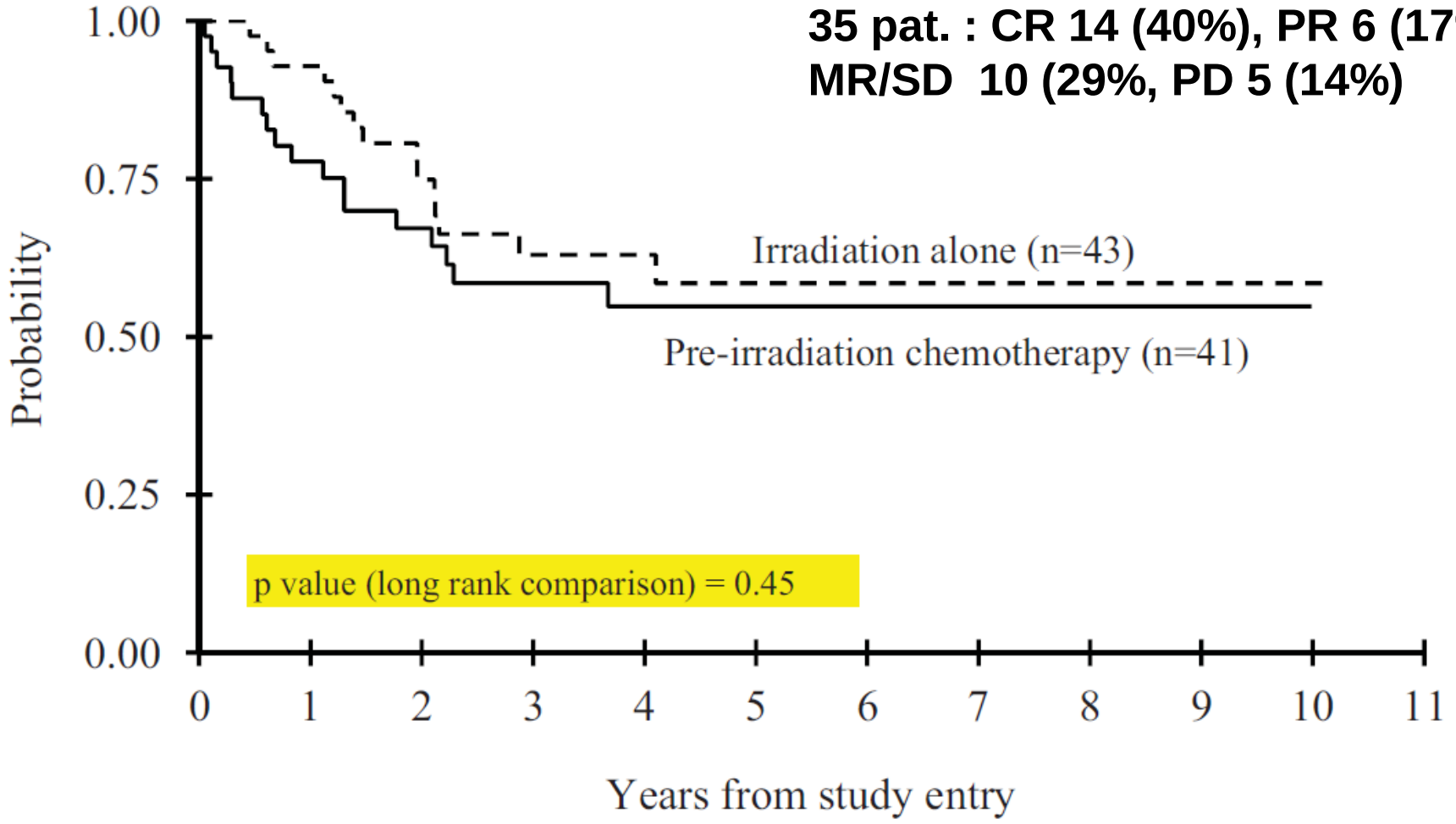
Intracranial ependymoma

CCG 9942 phase II pre-Irradiation chx in incompletely resected ependymoma (=/> 3 years) n= 41, n=43 RT alone after compl. Resection
Chx : VCR, Cisplat, VP 16, Cycloph. (RT local 54-59.4Gy

Response to chx. :
35 pat. : CR 14 (40%), PR 6 (17%)
MR/SD 10 (29%, PD 5 (14%)



Garvin et al., 2012

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Intracranial ependymoma

Summary

Prognostic factors

- extent of resection,
- age,
- grading (consensus !) future role ?
- molecular genetic markers / stratification

Dose – response relationship

- > 54 Gy
- role of hfx unclear (studies)
- duration of overall treatment time

RT of tumour site (CSA in M+ disease)

- 3 – D conformal technique
- radiosurgery (hypofractionated ?)

RT in children < 3-5 years

- immediate RT (?)

Role of Chx. unclear (studies)

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Thank you very much for your attention

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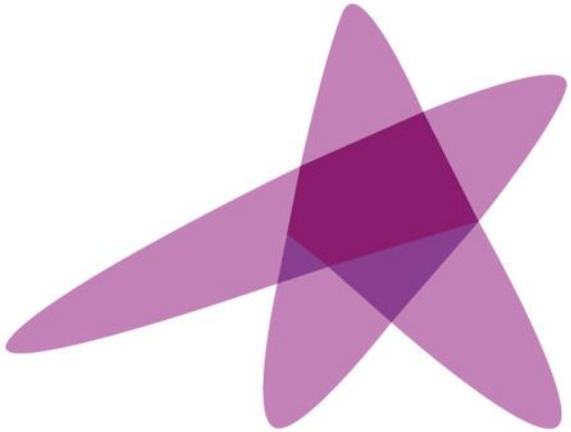

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Part II :

RT;
treatment techniques, target volumes & dose prescriptions

B. Timmermann
Essen, Germany

Topics

- Target volumes
- Doses
- Timing
- Techniques

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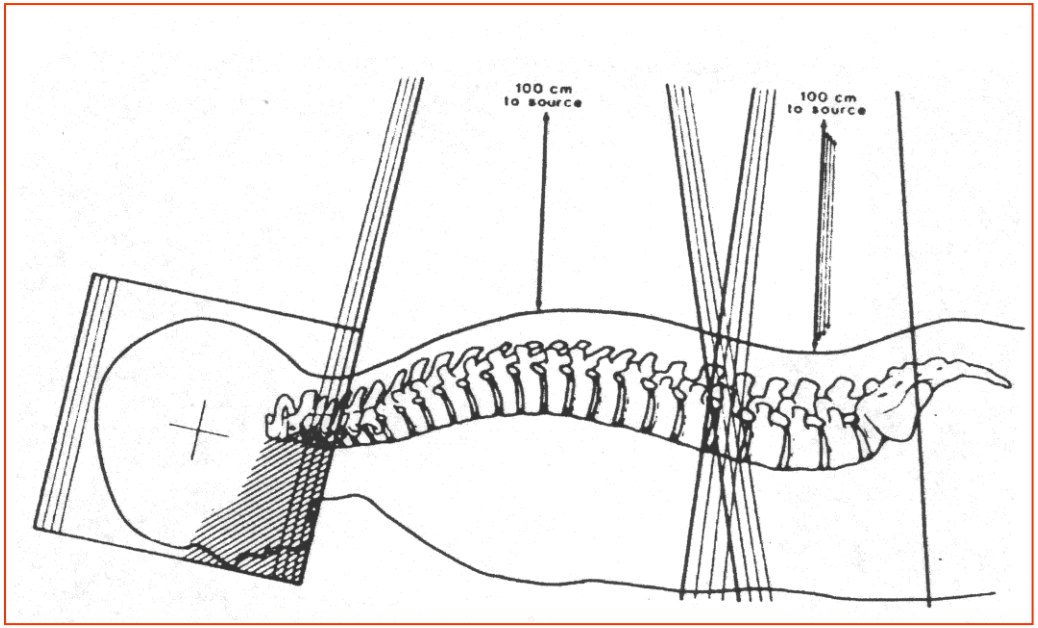
Introduction of the 3 cornerstones in oncology: CNS tumours

Period	Modality	Survival
- 1930	OP	0-10%
1930 - 60	OP + RT	40-50%
1960 - 90	OP + RT + CTX	60%

Target Volumes for Brain Tumours

- Craniospinal Irradiation
- (RT CNS TU pub. Harvey Cushing 1930)



" Over this period
we have adopted,
with encouraging results,
the principle of irradiation
of the entire brain and cord
as one undivided volume."

Farr und Paterson, 1953

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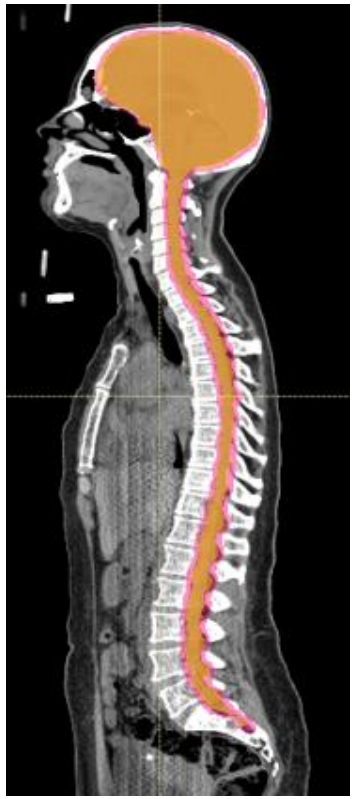
Target volumes over time, CNS



- **HIT-Studies, 20th century**

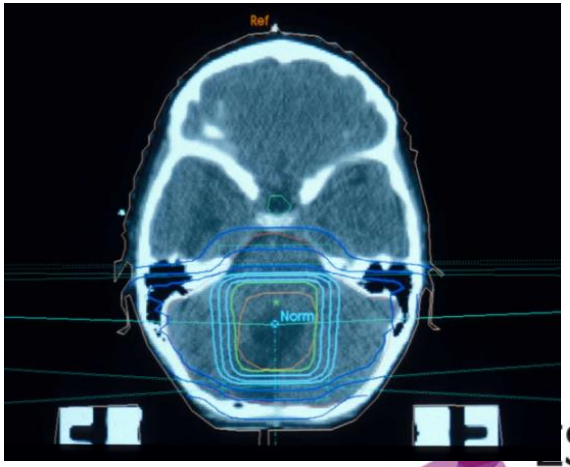
CSI: MB, Ependymoma, st PNET

Tumor: Glioma

- **HIT-Studies, 21st century**

CNS: st PNET, MB

Tumor: Glioma, Ependymoma, MB



Target volumes

Which general target volume approaches do you know for brain tumours?

Craniospinal RT

Whole brain RT

Ventricular RT

Posterior fossa RT

Local/Tumour bed RT

Which are standard today in the RT approach for ependymomas?

- Craniospinal RT
- Tumour bed RT
- (Boost for residue)

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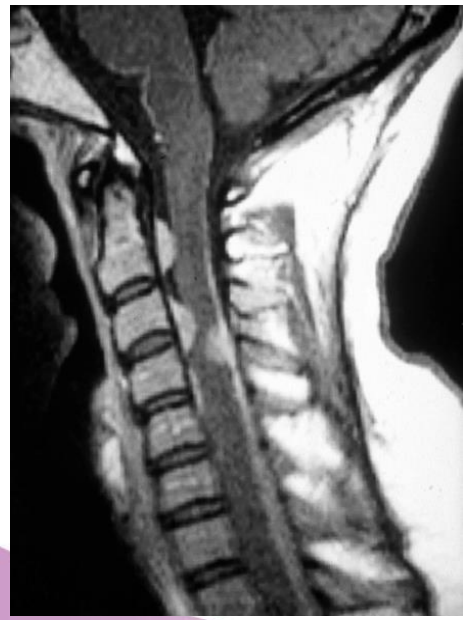
Indication for tumour bed RT in ependymomas?

- Localized disease (M0)

Low risk for spinal seeding!

Risk for spinal seeding at (first) relapse

Total	20/291	7%
WHO II	6/132	5%
WHO III	7/83	8%
RT CSA	9/96	9%
No RT CSA	4/119	3%



Vanuytsel et al, 1992

RT of CSF space can be omitted ?

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Primarily local relapses!

Pattern of relapse

Author	Pat.	Survival after 5 years	Local relapses
Goldwein et al. 1990	51	46%	29/30
Grabenbauer et al.,1991	31	54%	8/13
Timmermann et al.,2000	55	76% (3 years)	20/25
Guyotat et al., 2002	34	62%	16/17
Massimino et al., 2004	63	75%	15/23
Merchant et al 2008	153	81 % (7 Jahre)	21/36

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No impact of CSI on relapse rate!

Outcome according to RT volume

Author	Outcome after	
	Local RT	Craniospinal RT
Goldwein et al 1990	31% 5-year PFS	27% 5-year PFS
Vanuytsel et al 1992	38% 5-year PFS	46% 5-year PFS
Rousseau et al 1994	40% 5-year EFS	49% 5-year EFS
Stuben et al 1997	58% 5-year PFS	45% 5-year PFS
Mc Laughlin et al 1998	1/17 Leptomeningeal relapses	0/15 Leptomeningeal relapses
Oya et al 2002	3/37 Leptomeningeal relapses	1/10 Leptomeningeal relapses

Pattern of relapse: **local relapses predominantly!**
Merchant et al., 2002: 5/6 relapses occurred locally

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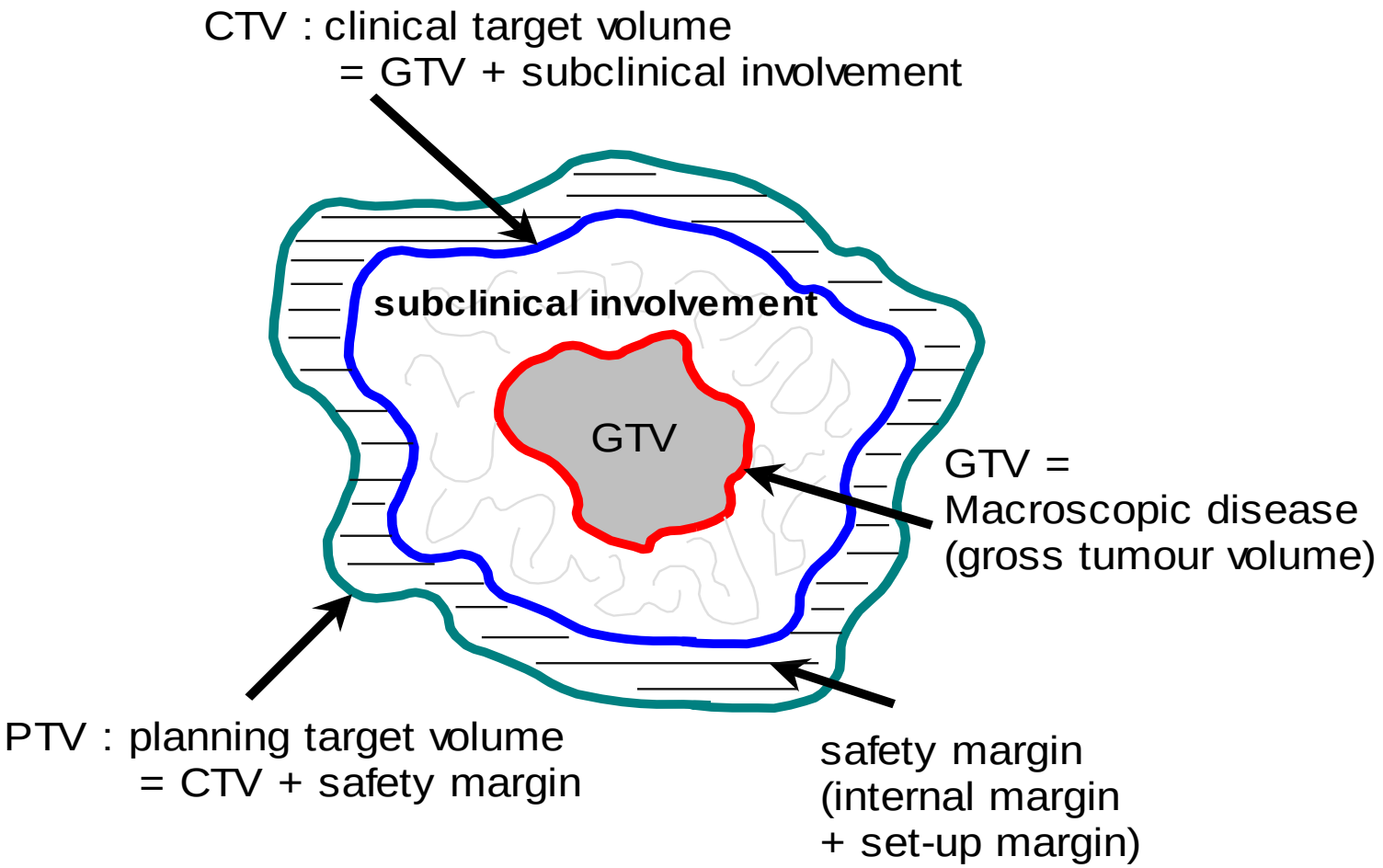
Target Volume according to ICRU 50/62 Report



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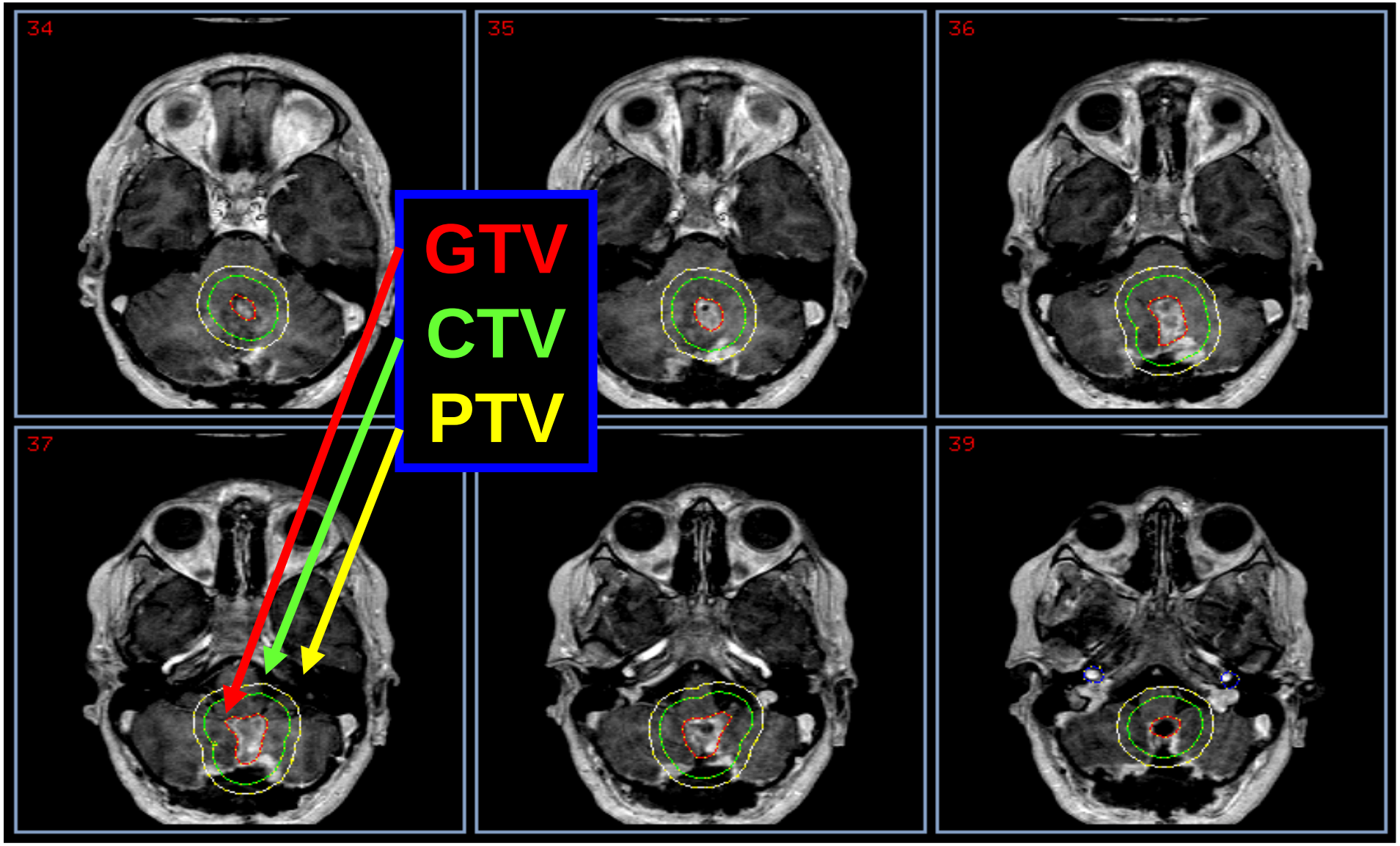
Intracranial ependymoma

Treatment technique / 3 D conformal RT



Merchant et al., 2004

Target definition and margins

In ependymomas:

- CTV = GTV/Tumour bed plus 5-10 mm (***modified acoording to…?***)
- PTV = CTV + ~ 3-5 mm

- *Nowadays in studies with image guidance rather 5 mm CTV margin*

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Target definition and margins

SIOP Ependymoma II
FINAL Protocol
Version 1.2_November 14th, 2013

MRI obtained immediately before radiotherapy should be used for treatment planning.
To properly delineate target volumes for this study, complete information defining the extent of disease before and after surgery is needed.
Pre- and post-operative MRI, in particular pre- and post-gadolinium contrast T1, T2, and FLAIR sequences, should be reviewed. Sequences that best define post-operative tumour bed and residual disease at each time point should be utilized to define the GTV and registered to planning CT.

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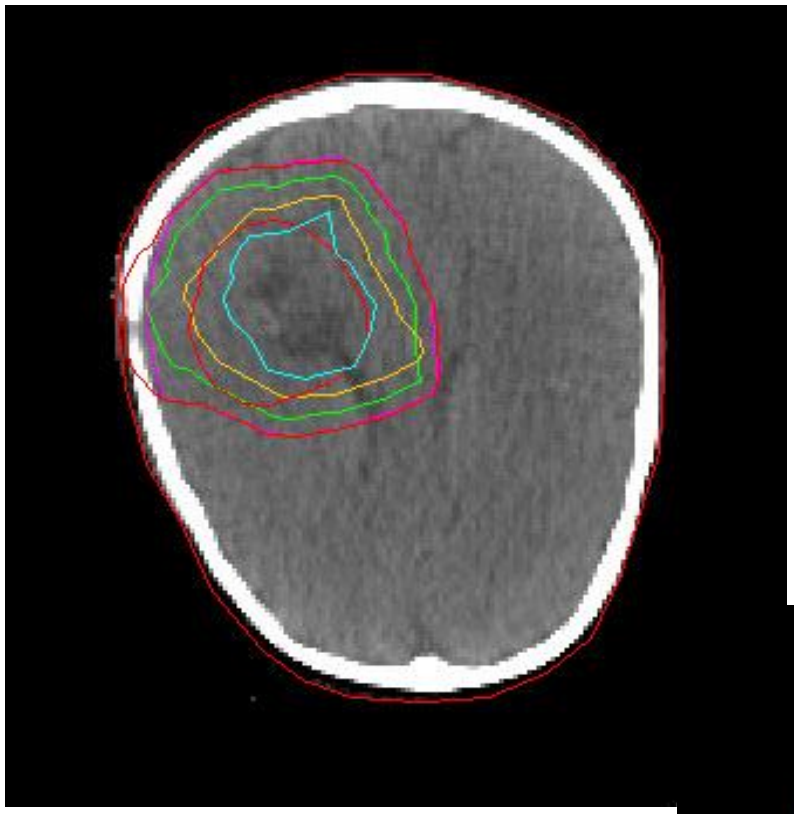
How to delineate tumour bed volume?

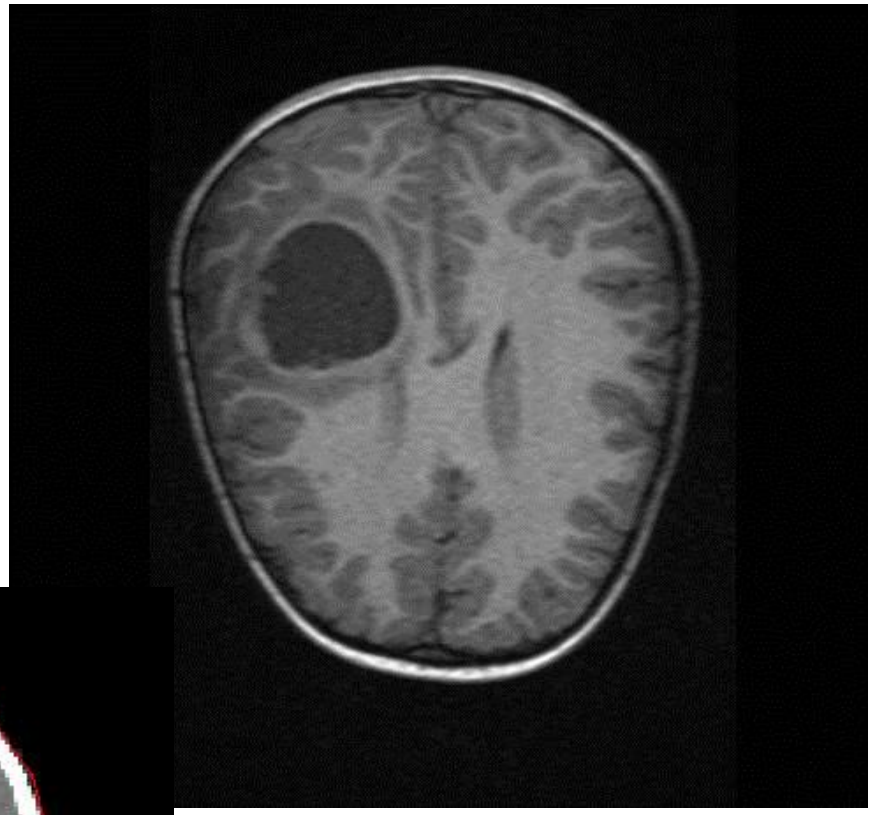
Take into account:

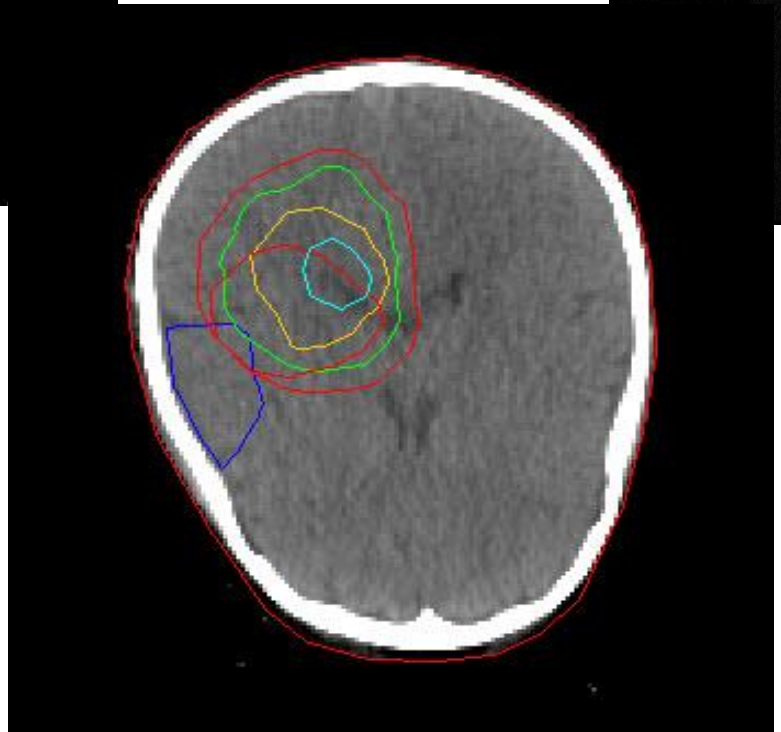
- Preop. extension
- postoperative shift
- Anatomical borders (bones, dura)

Anatomical „shifts & borders“



See
shift after
Surgery!





Red: initial TU
Blue: TU bed
Green: CTV
Pink: PTV (1)

(Yellow: PTV (2)
based on Tu bed)

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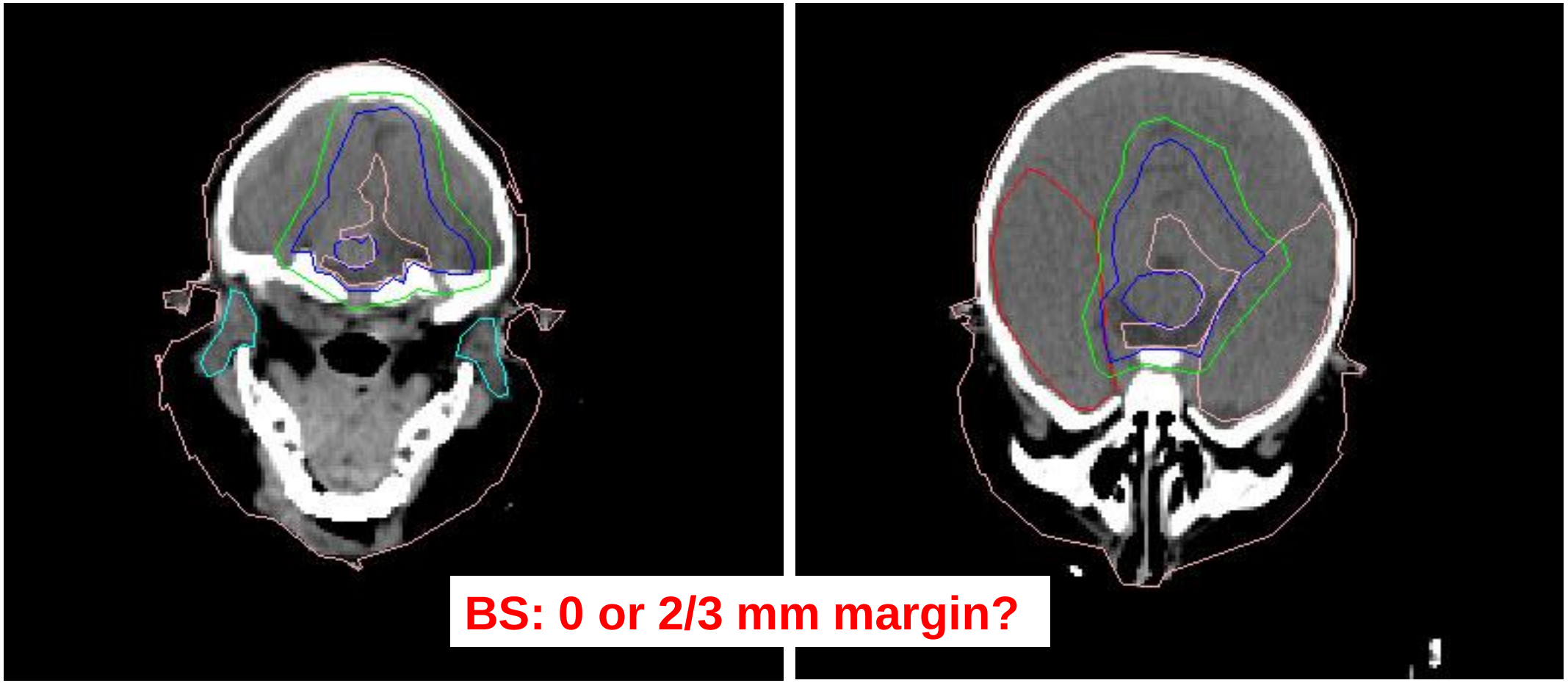
Anatomical „shifts & borders“

See volume adaptation – bone, brainstem and temporal lobes



BS: 0 or 2/3 mm margin?

Rosè: Tu bed
Blue: CTV green: PTV

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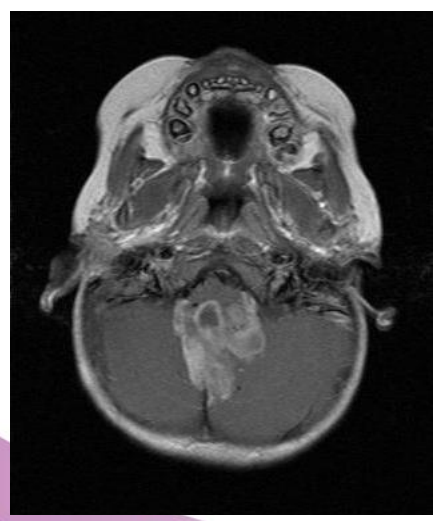
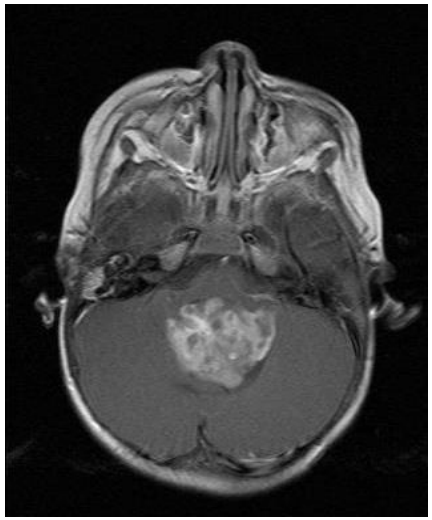
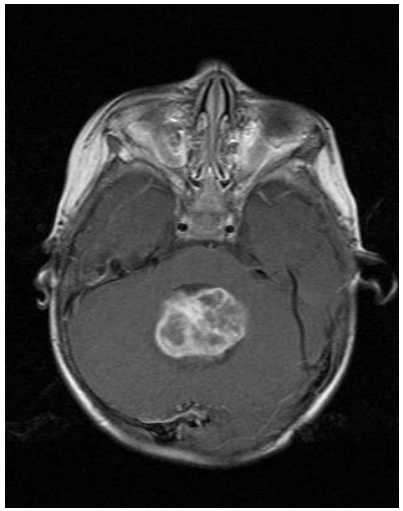
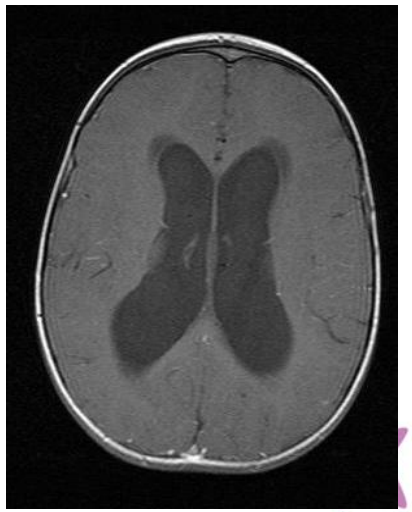
- ✓ DOB: 05.08.2005;
- ✓ October 2006: Diagnosis of infratentorial anaplastic ependymoma (WHO grade III), M0;
- ✓ His past medical history was unremarkable with the exception of bilateral internal and external chronic otitis

CASE

HISTORY OF THE PRESENT ILLNESS:

- ✓ Repetitive Vomiting;
- ✓ 10/2006: Hydrocephalus occlusus -> external ventricular drainage;
- ✓ Preoperative MRI: fourth ventricular mass with predominant solid enhancement on postgadolinium T1-weighted images.

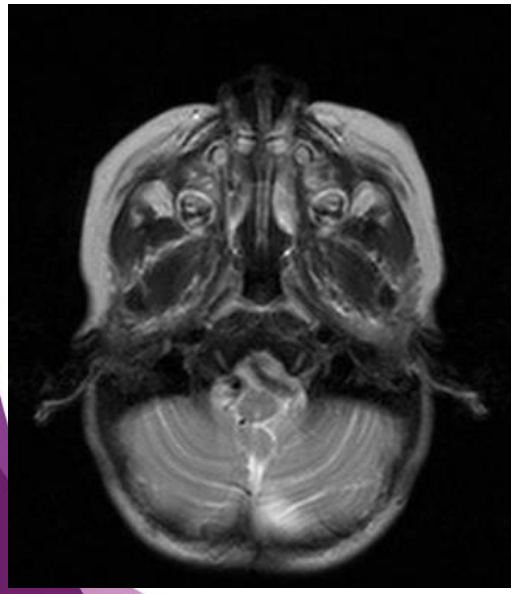
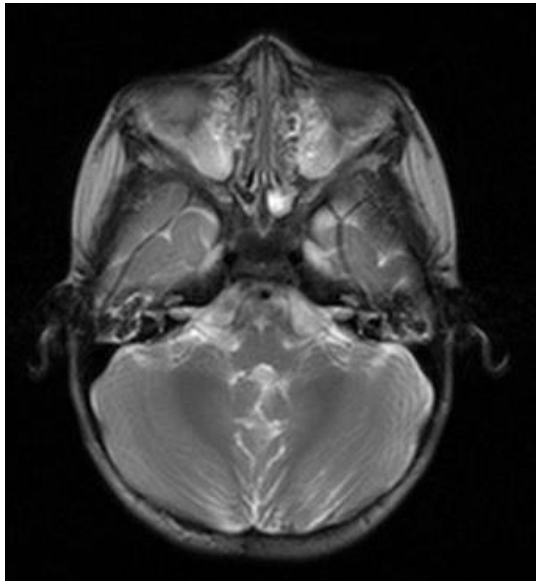
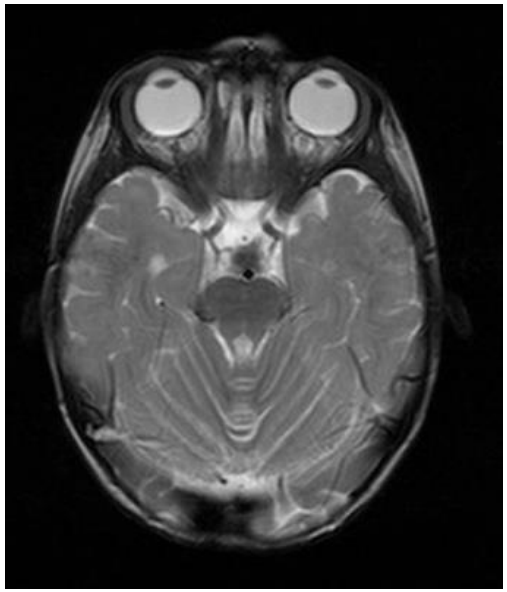
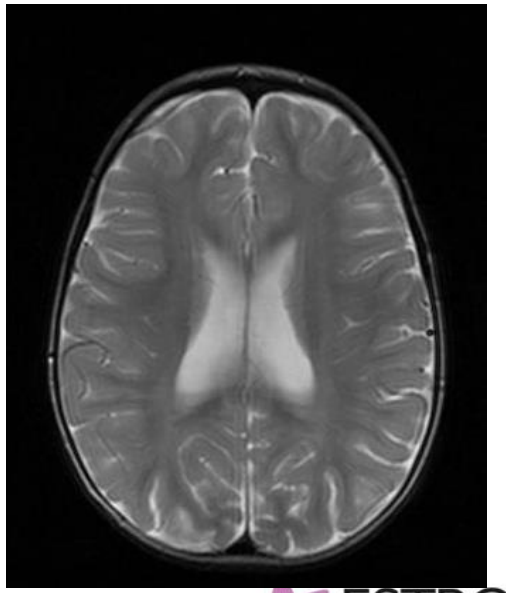
✓02.11.06: Questionable complete tumor resection

According to surgeon's opinion there was some residual tumor but the postoperative MRI was told not displaying any macroscopic residual.

✓ 13.11.06: Port-a-cath-Implantation;

✓ 25.11.06: Start Chemotherapy according to HIT 2000 BiS4;

✓ 05.11.07: Radiation therapy planned.

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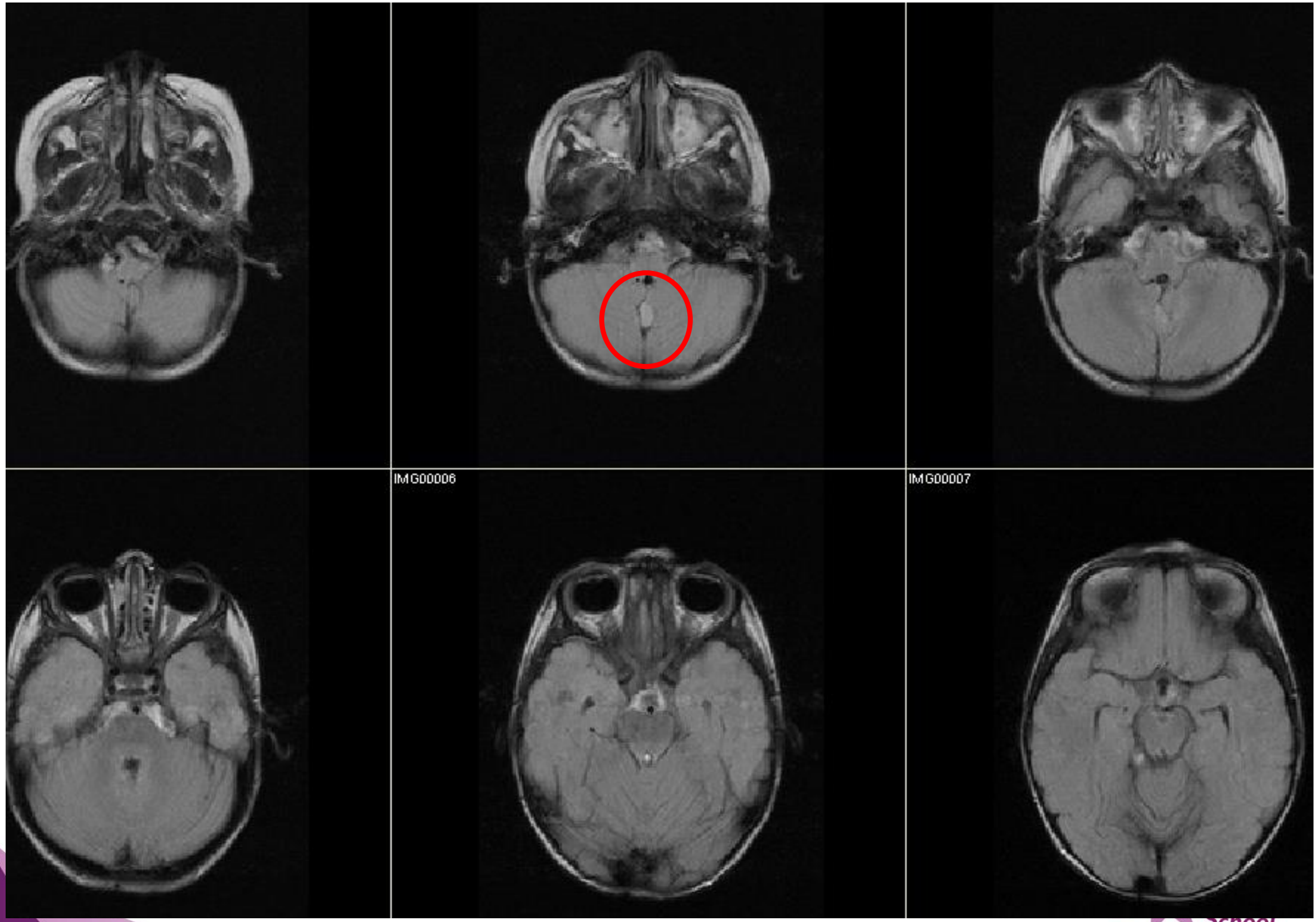
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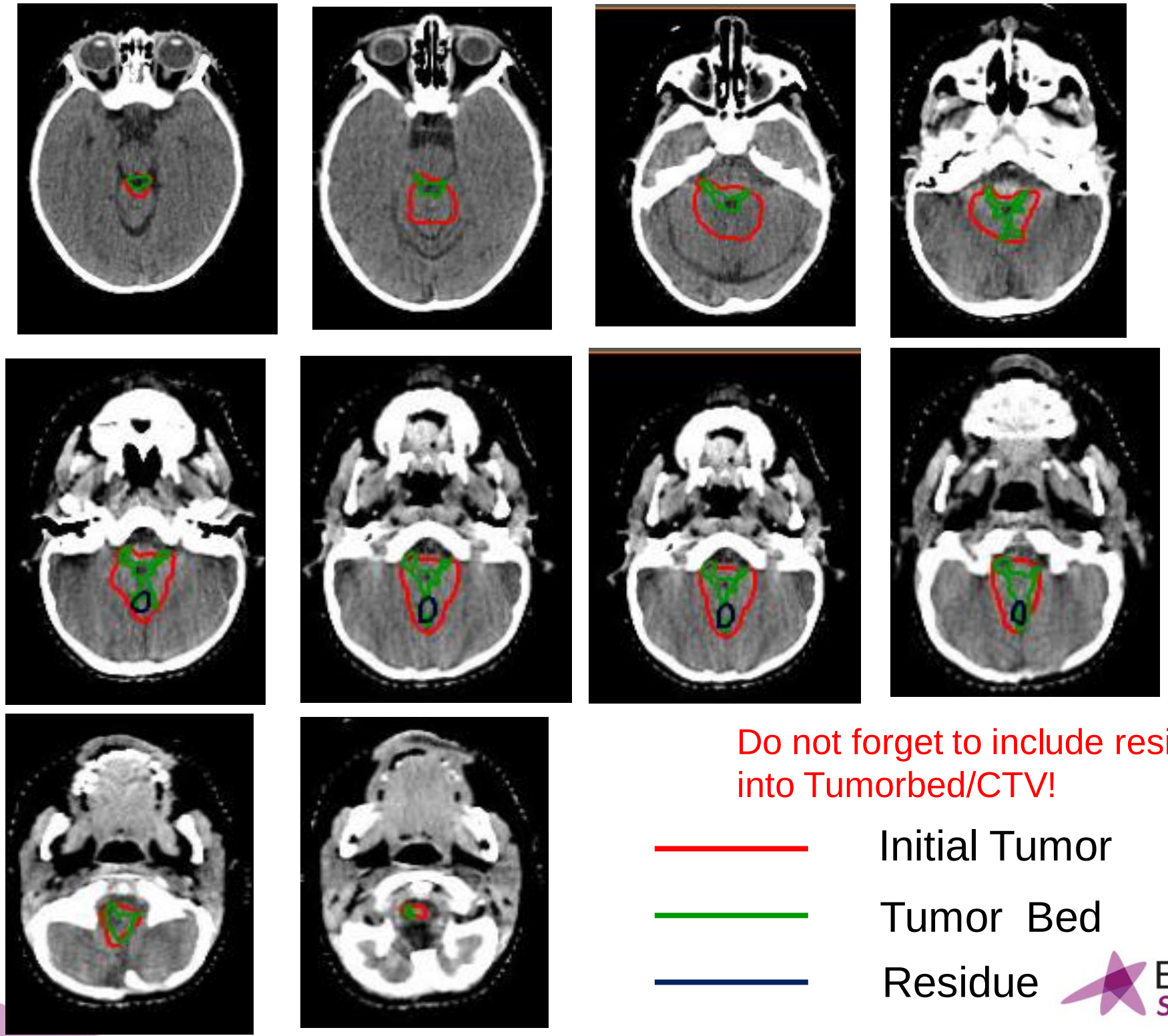
IMG00007



Do not forget to include residue into Tumorbed/CTV!

Initial Tumor

Tumor Bed

Residue

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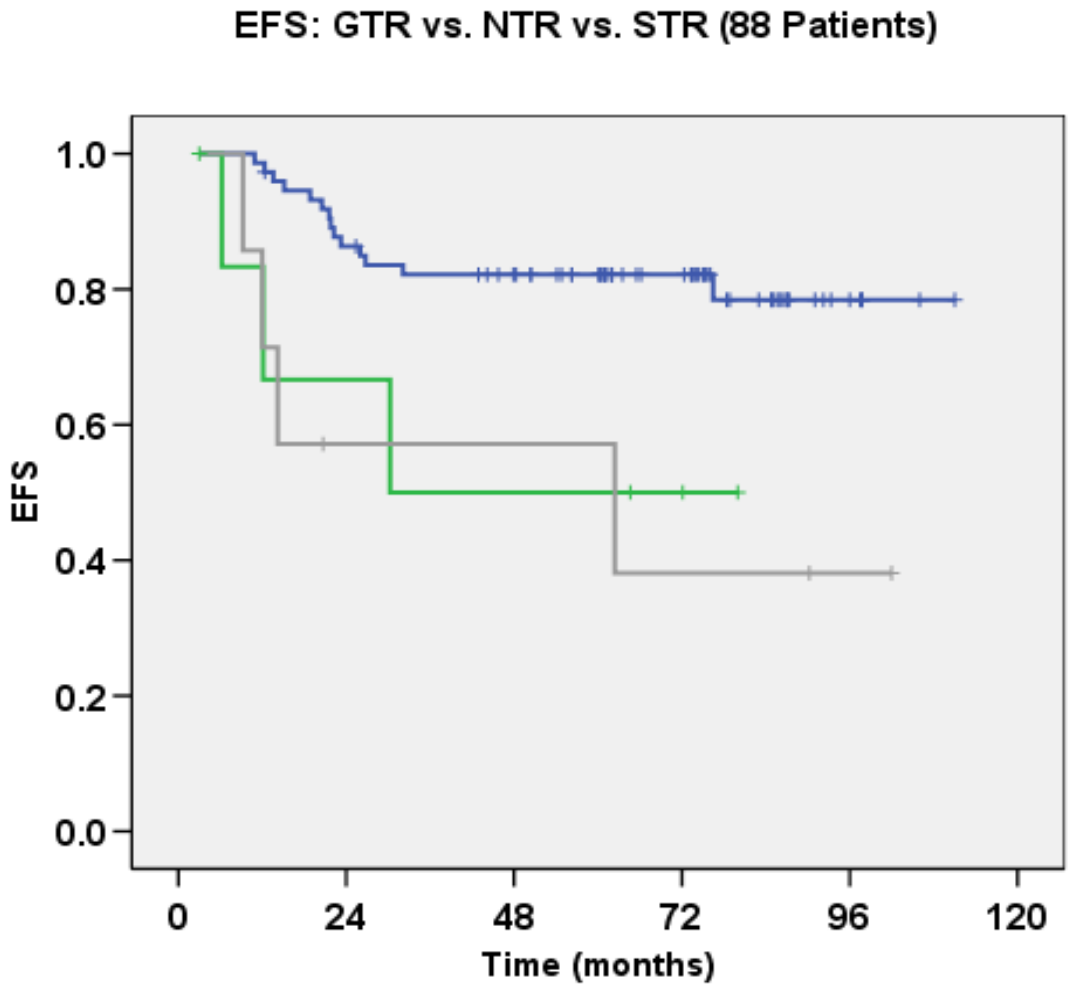
Indication for tumour boost in ependymomas?

- In residual disease after chemo/RT – (R+ diesease)

Impact Surgery

(GTR=64) 5 YR EFS 82% ± 5%
(NTR=7) 5 YR EFS 50% ± 20%
(STR=7) 5 YR EFS 57% ± 19%



R+ disease has negative impact!

T. Merchant, **ACNS0121**
EPENDYMOMA

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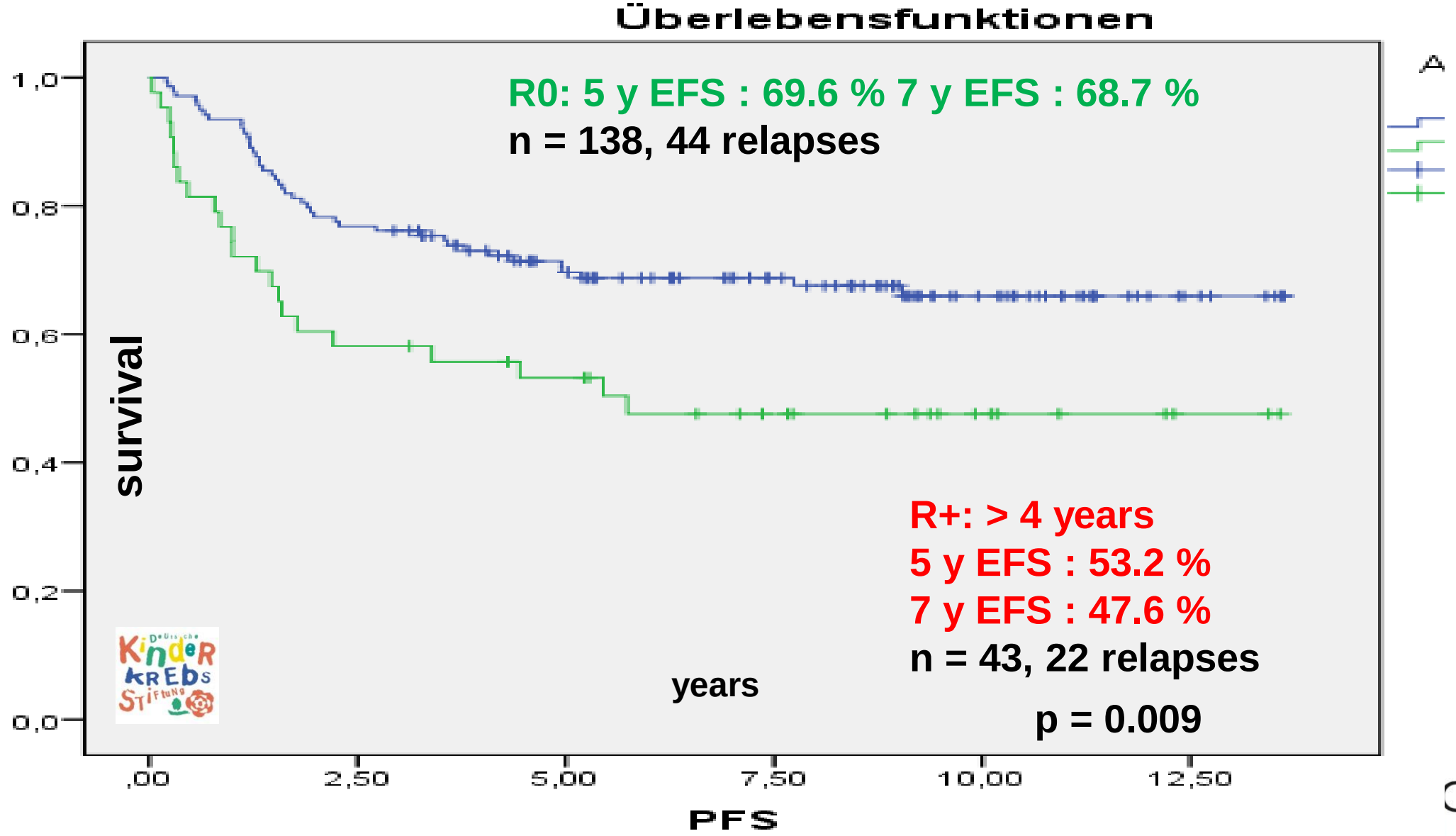
R+ disease has negative impact on EFS!

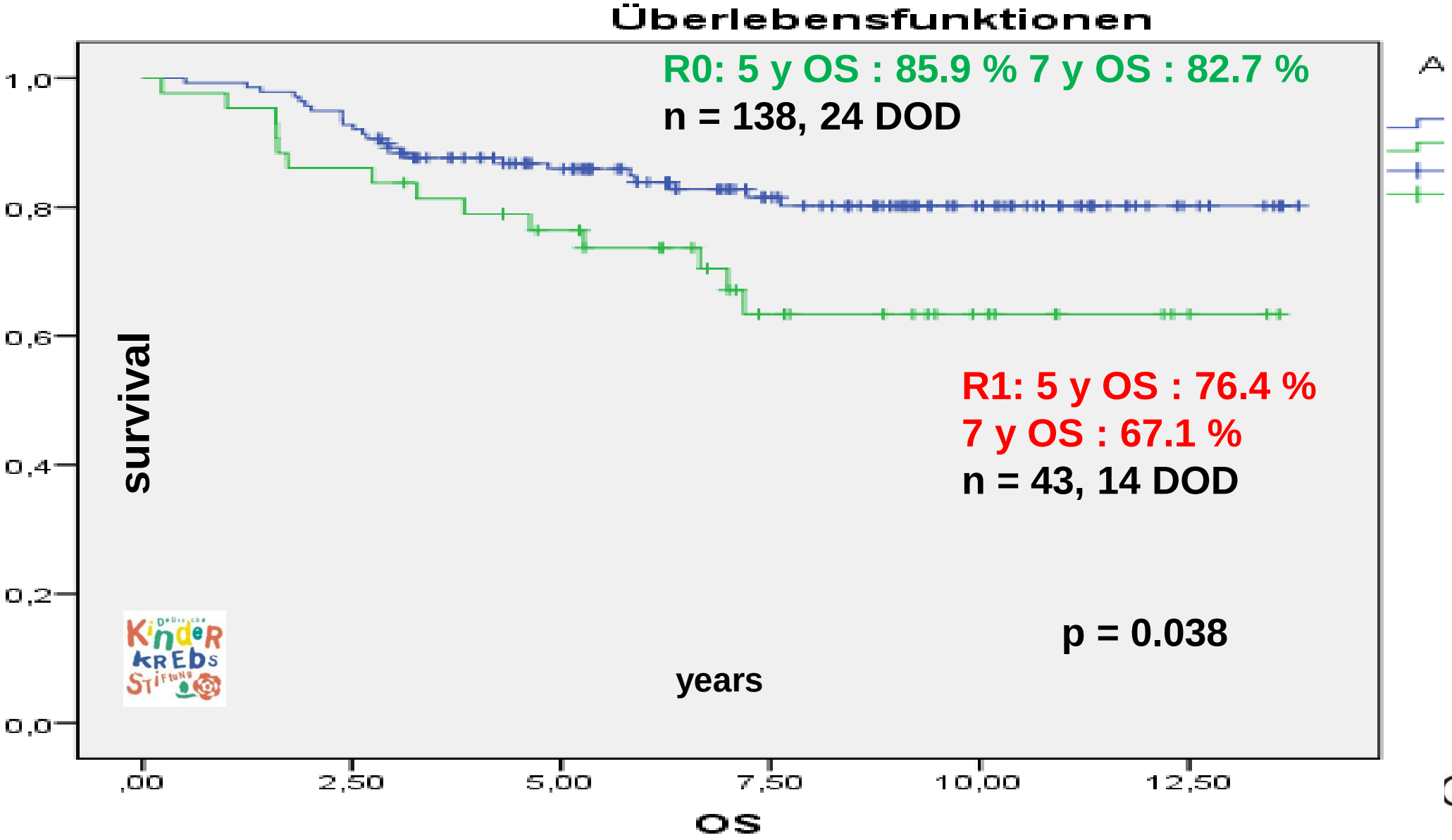
HIT 2000: EFS - EP ° II+° III

>4 years / R 0 versus R +



R+ disease has negative impact on OS!

HIT-2000: OS - EP ° II+° III
>4 years / R 0 versus R +



R+ disease has negative impact on OS!

- Massimo, 2016:
  AEIOP study

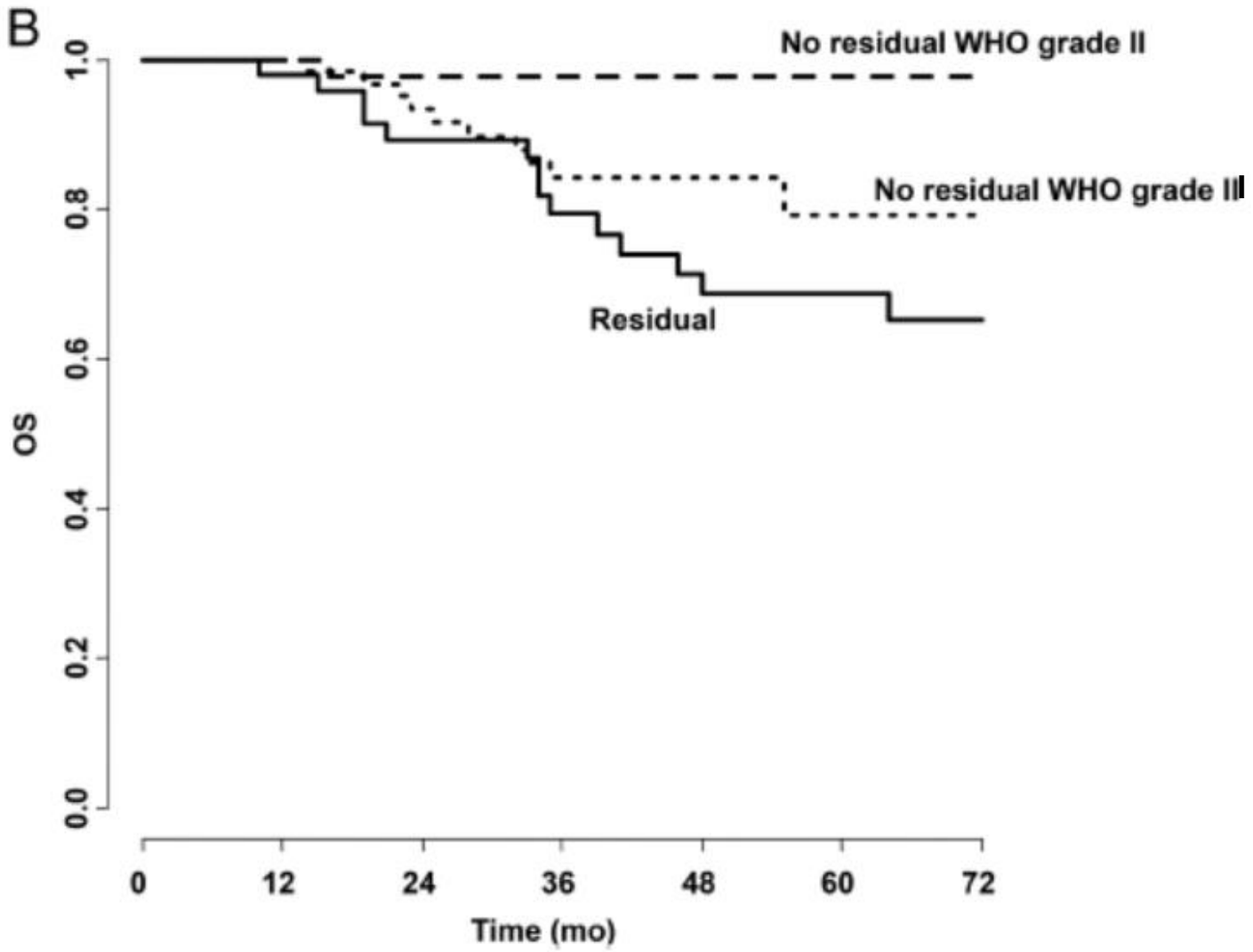


Fig. 3. (A) Kaplan-Meier PFS and (B) OS curves by outcome of first surgery.

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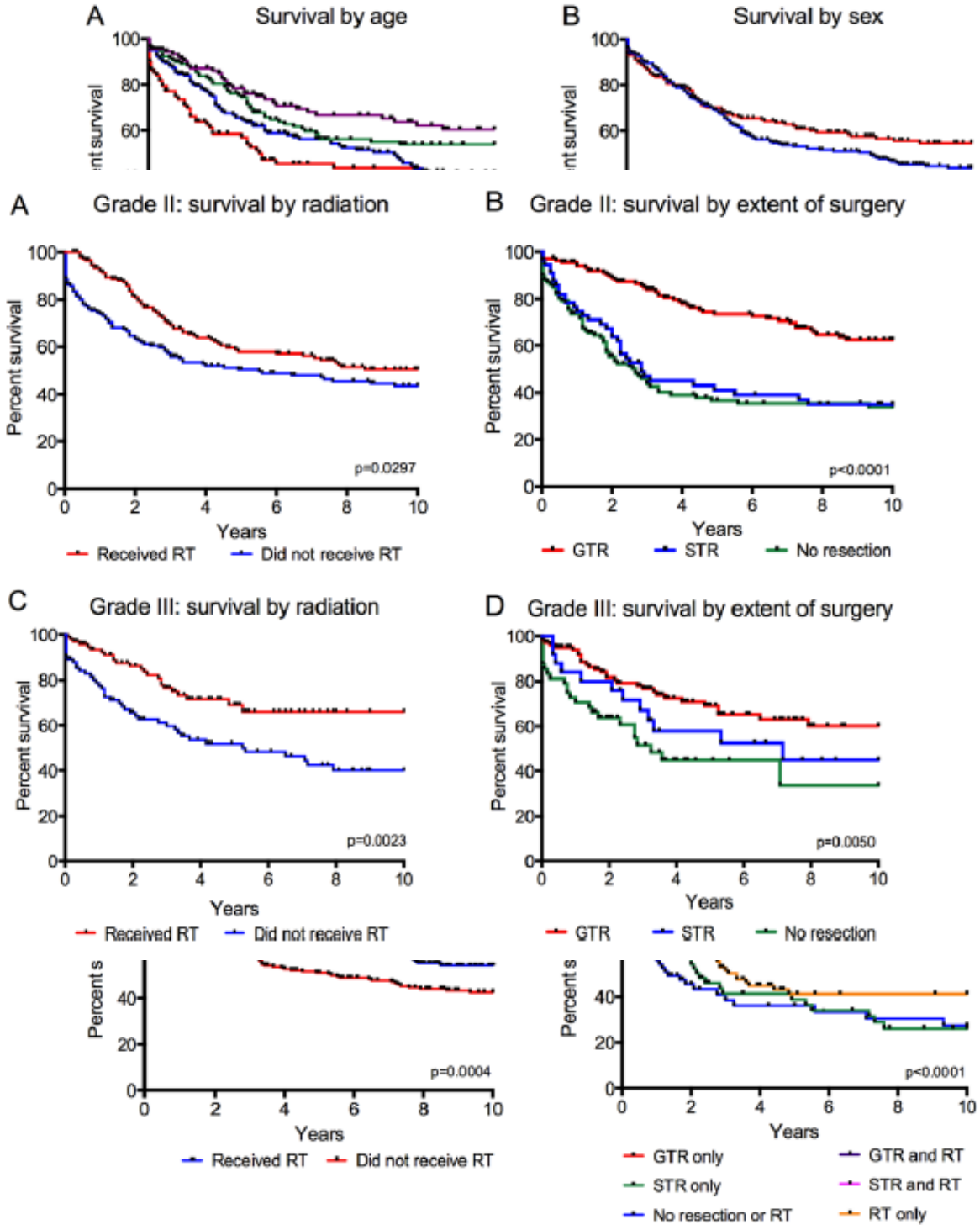
WILEY Pediatric Blood & Cancer
SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY
aspho The American Society of Pediatric Hematology/Oncology

and extent of resection for
ren: A population-based study

Mack[2] | J.H. Suh[3] | S.T. Chao[3] |



Positive predictive factors:

- Higher age > 1 yr
- RT
- GTR
- Regardless of grading

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Boost

- In residual disease to be considered
- CTV = persisting residue (***at time of boost planning***)
- PTV = CTV + 3-5 mm margin if feasible for OARs

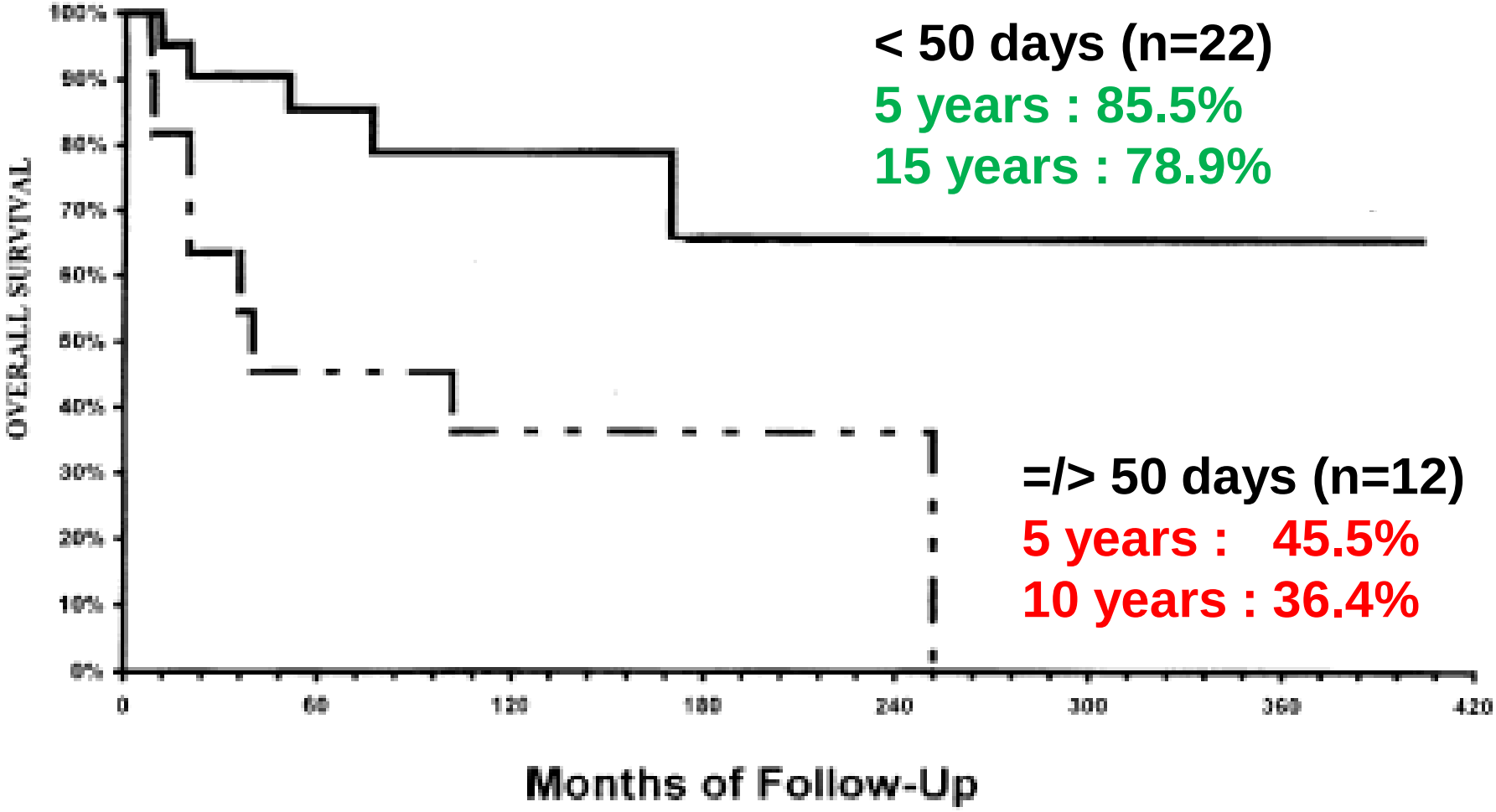
Overall treatment time

Does it matter?

Shorter treatment time superior – EFS!

Duration of treatment / disease-free survival

Paulino et al., 2000



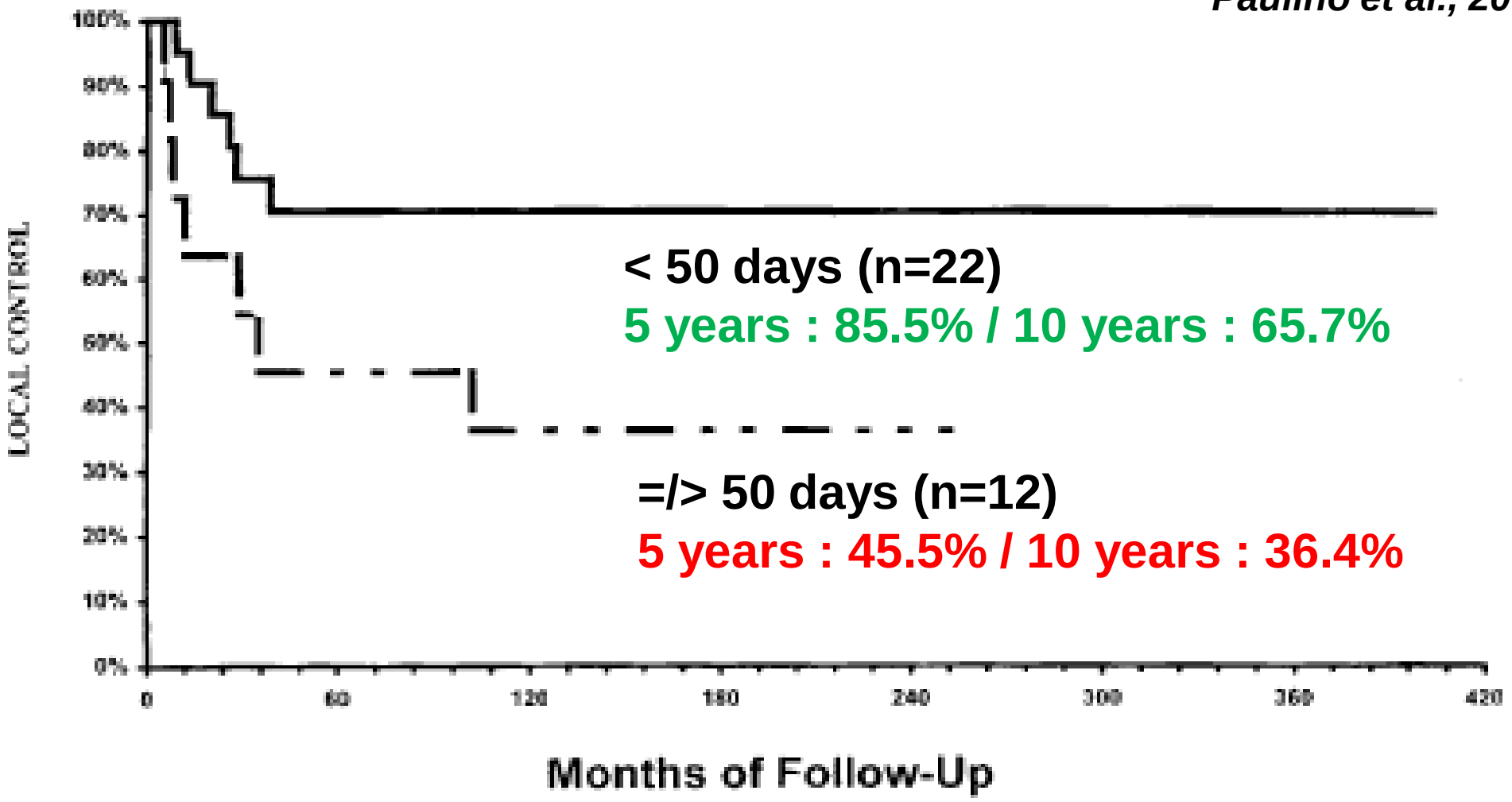
< 50 days (n=22)
5 years : 85.5%
15 years : 78.9%

=/> 50 days (n=12)
5 years : 45.5%
10 years : 36.4%

Shorter treatment time superior - OS!

Duration of treatment / overall survival

Paulino et al., 2000



Indication for craniospinal RT in ependymomas?

- In M1, M2/3 disease

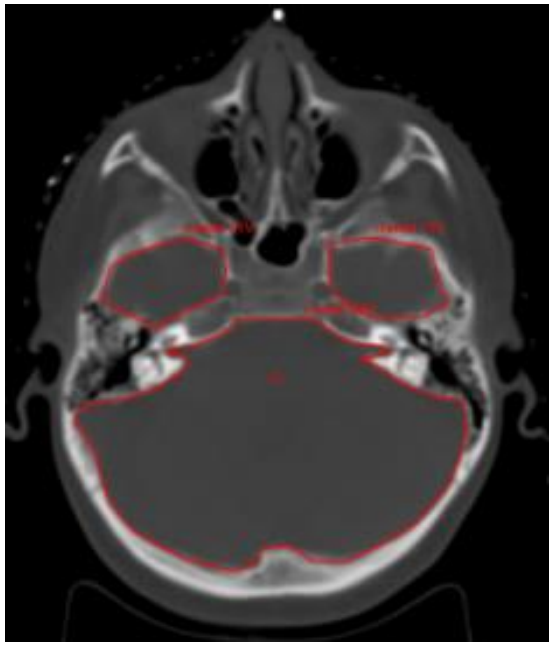
Craniospinal RT

Target volume:

- Intracranial volume/spinal canal (=CTV) plus PTV margin (3-5-10 mm)
- Vertebral bodies (if growing child) to be included to ~20 Gy!

SIOPe Brain Tumour Group

Consensus atlas on CTV delineation for craniospinal radiotherapy



Whole brain - CTV

- Bony windows
- Outline inner table of skull
- Ensure to include
  - Cribriform plate
  - Middle cranial fossa
  - Pituitary fossa

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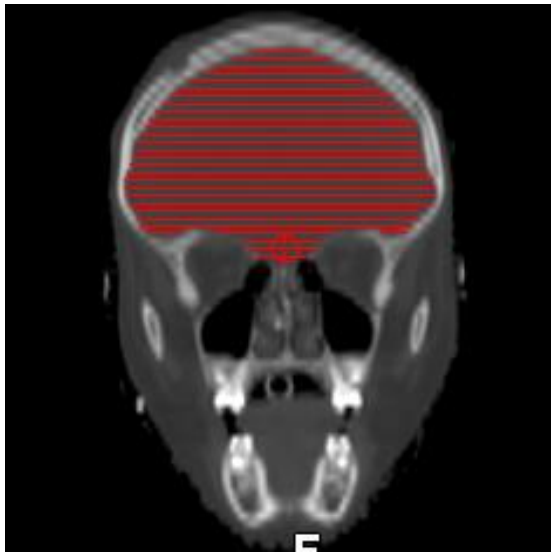
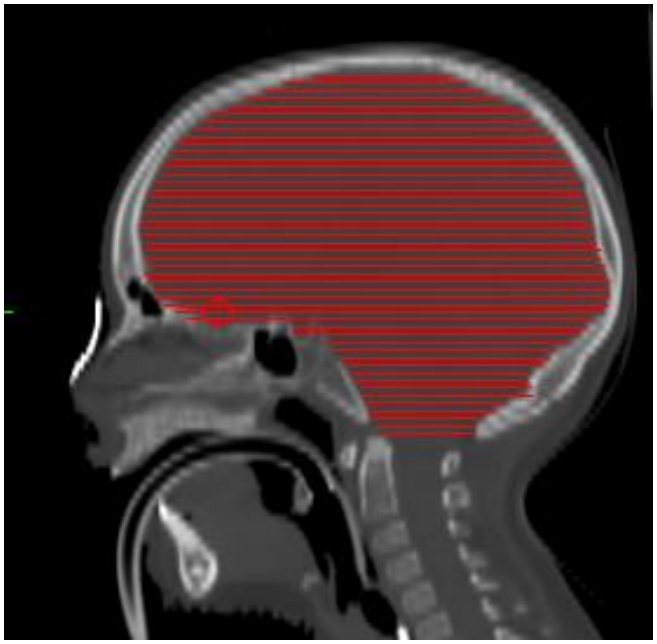
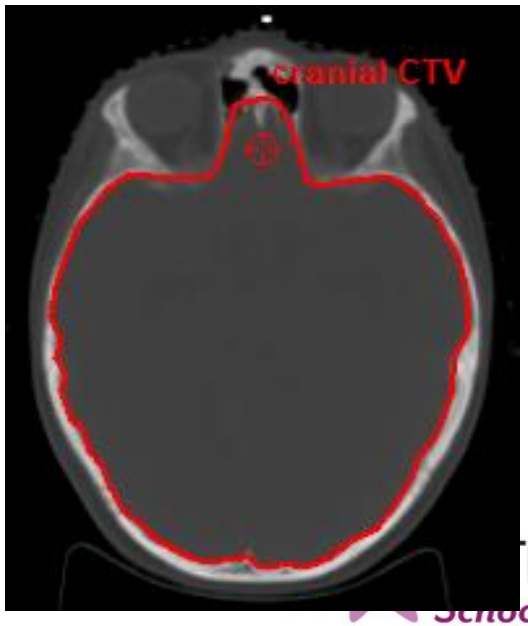
Cranial CTV – cribriform plate

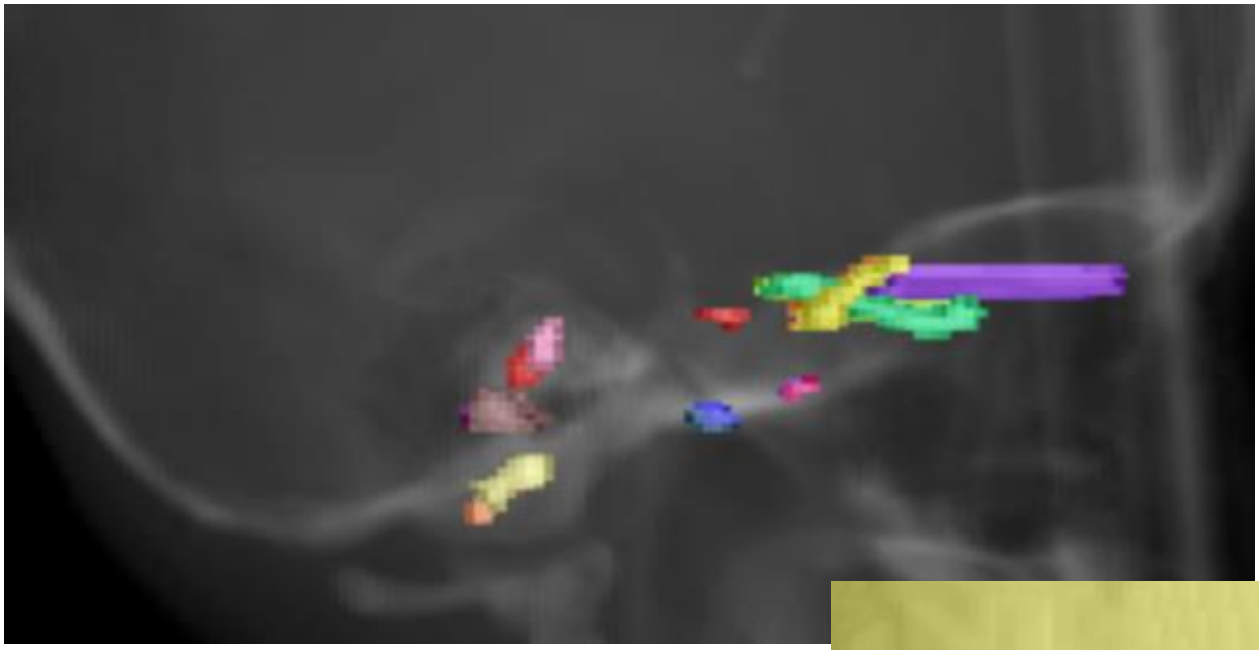


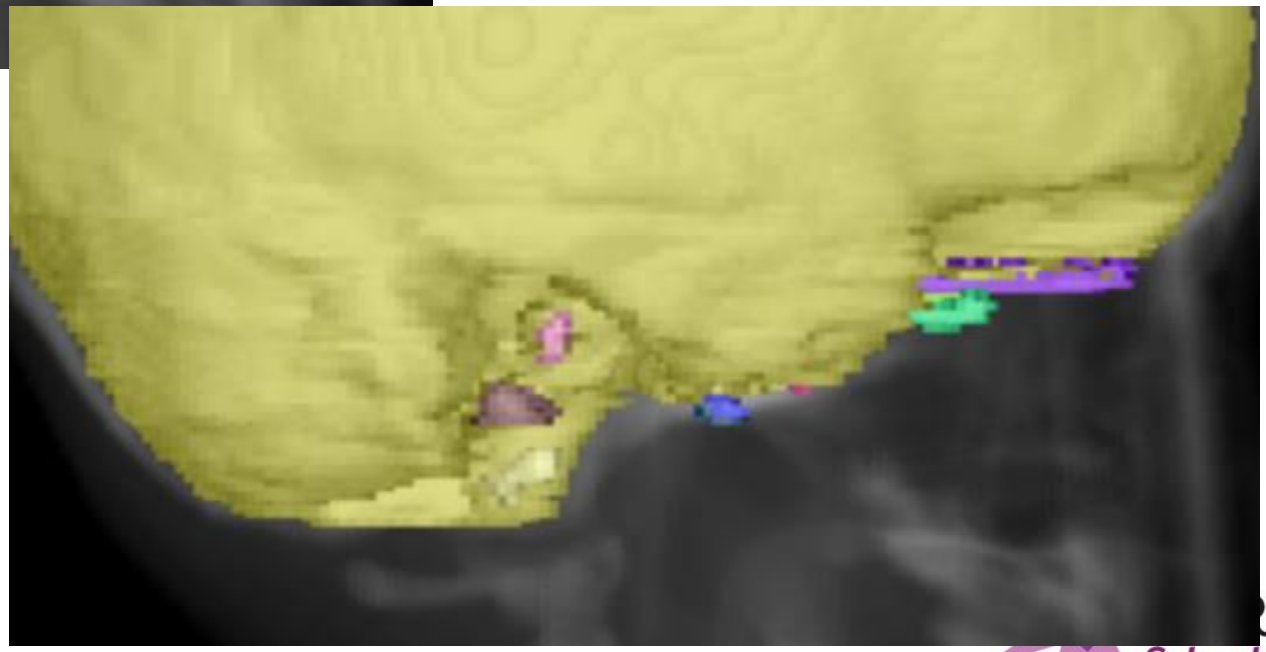




SIOP-BTG

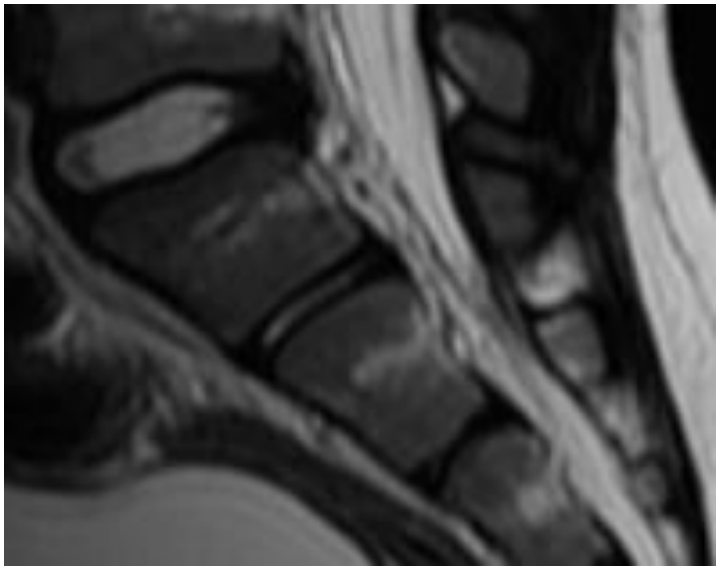
Cranial nerve foramen to be covered?





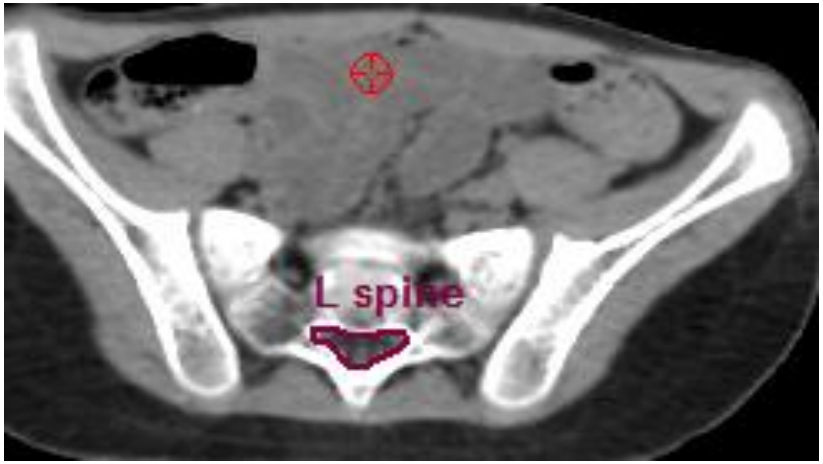
SIOP-BTG

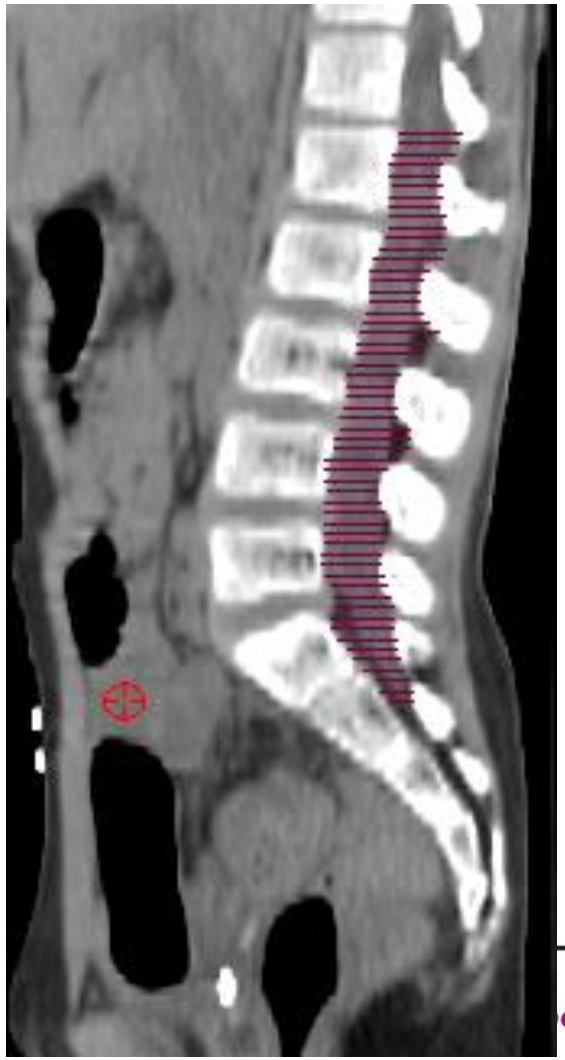
Inferior limit of spinal CTV - illustration



- Inferior limit is at the the lower limit of the thecal sac on a pre-operative spinal MRI
- Seek expert

neuro-radiological advice





SIOP-BTG

Doses

Standard doses – still true?

- TU/PF ~54 Gy
- CSI ~36 Gy

Doses:

Higher doses superior!

- dose response relationship!

Author	Pat.	Survival	
		< 45 Gy	>45 Gy
Salazar	28	10%	56%
Philips	25	0%	87%
Marks	25	33%	70%
Kim	32	20%	46%
Garret	50	14%	50%
Goldwein	51	18%	51%

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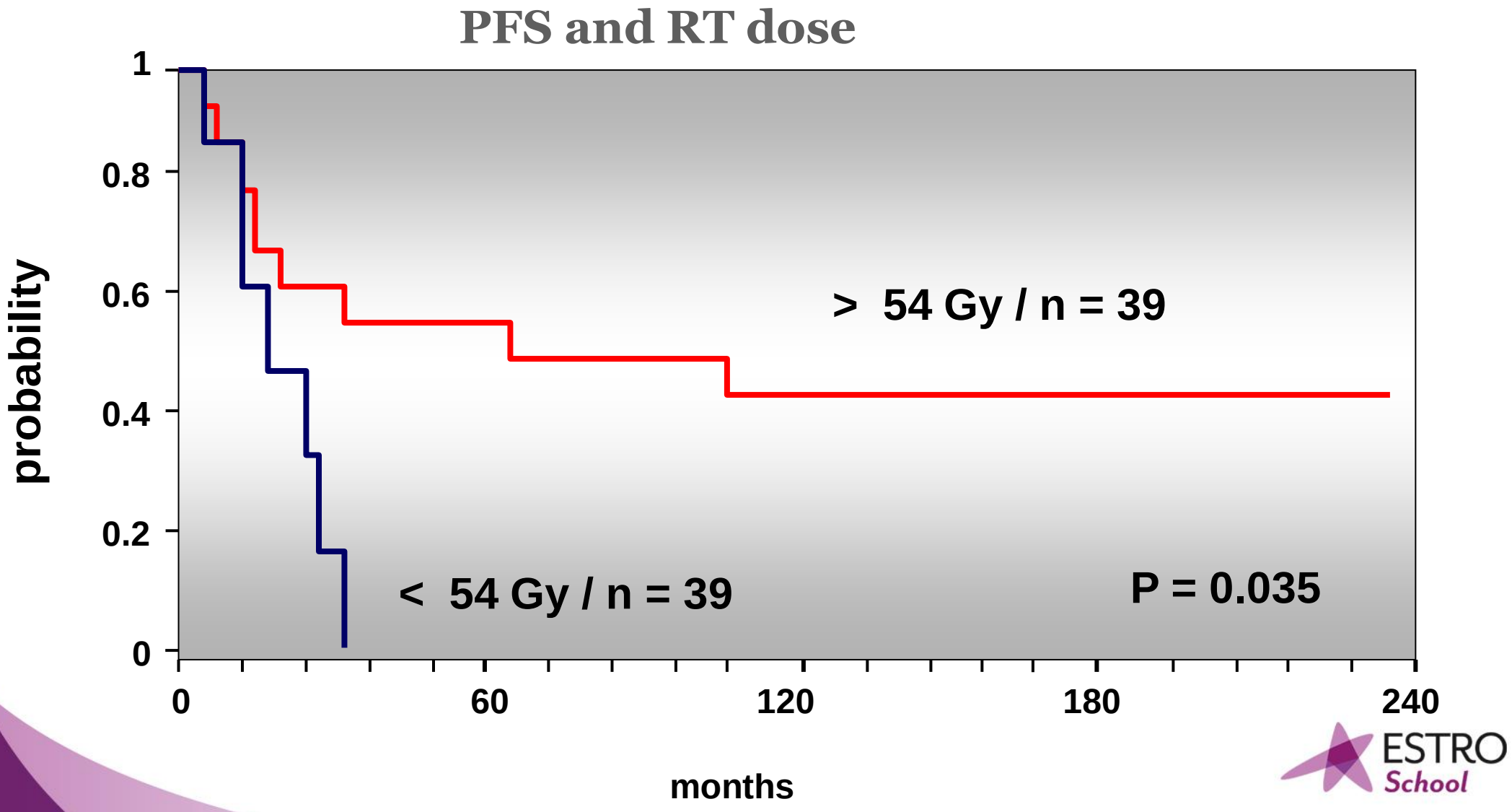
Higher doses – superior PFS!

Dose – response relationship

Shu et al., 2007



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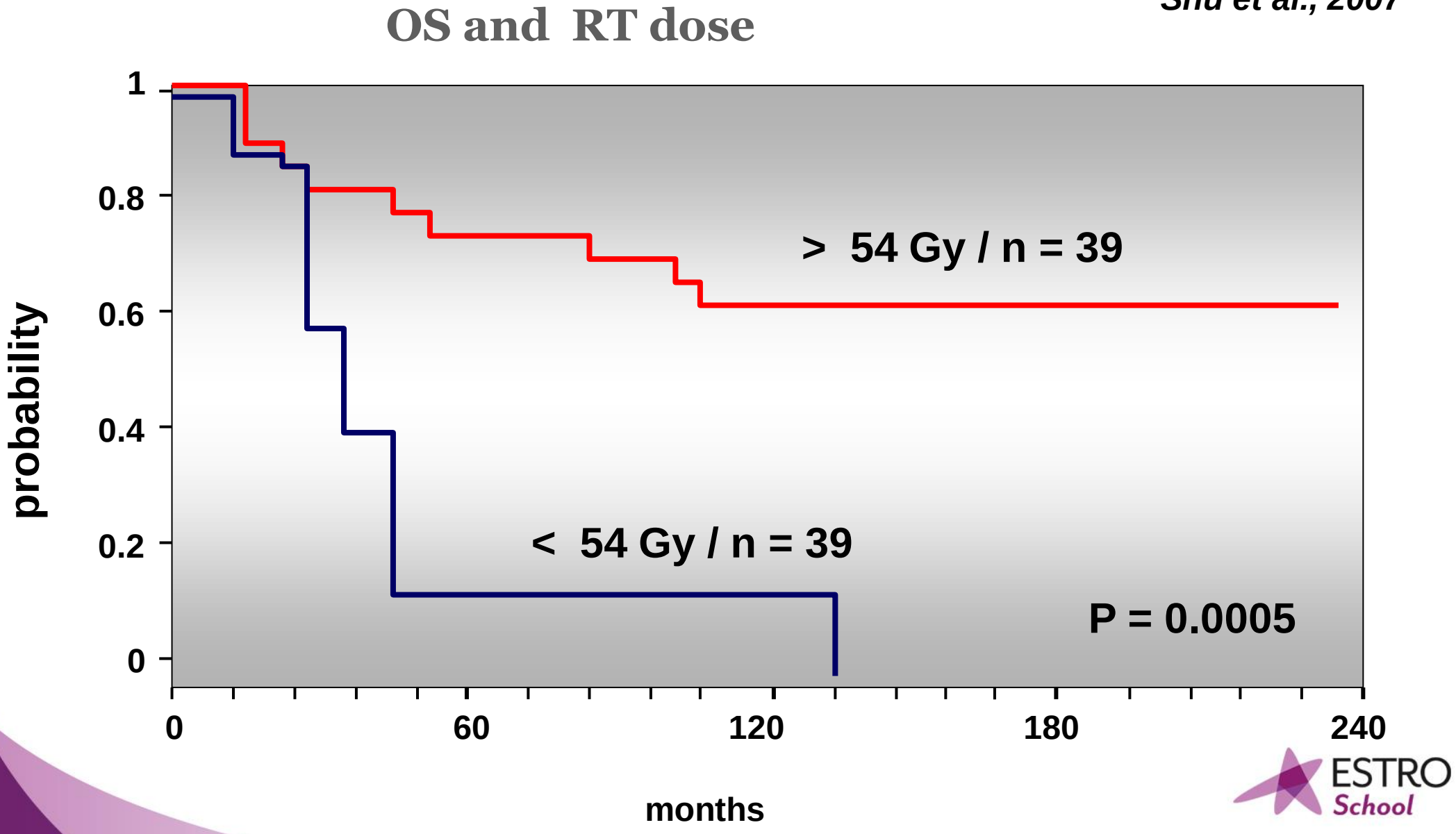
Higher doses superior - OS!

Dose – response relationship

Shu et al., 2007

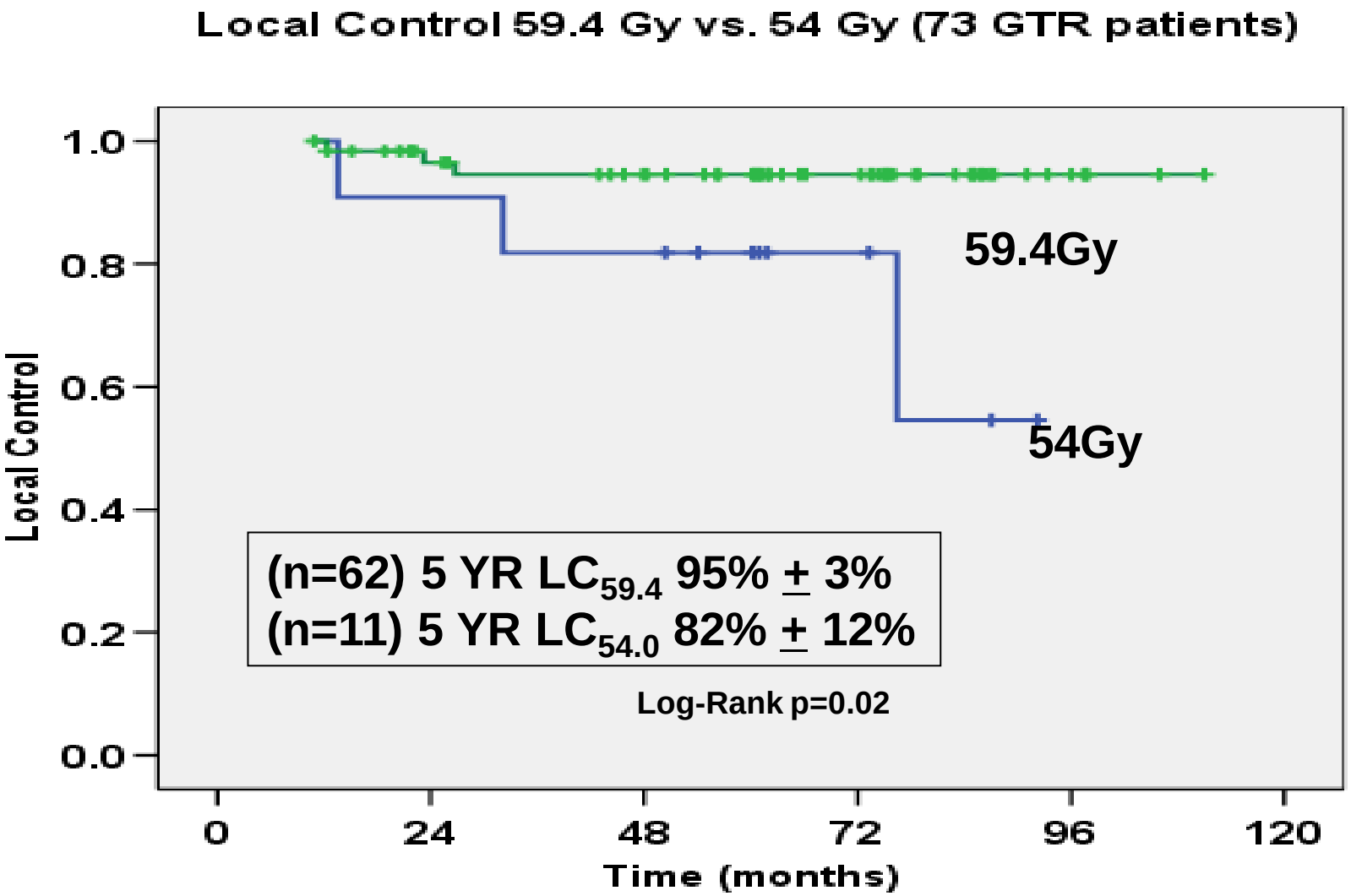


Higher doses superior - LC!

Dose – response relationship

GTR, different grading

Thomas Merchant, Paris, 2003



- Pattern of failure Analysis
- n = 206 pts
- med. FU 53.8 mo

- Higher RT dose superior
- CTX?
- local failures predominant

Radiotherapy and Oncology 122 (2017) 362–367

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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Table 1
Characteristics of patients.

	Cohort (n = 202)	No event (n = 112)	With event (n = 90)
Age at diagnosis			
Median (range)	4.5 (1.0:22.0)	5.0 (1.0:22.0)	4 (1.0:22.0)
Sex			
Male	113 (55.9%)	59 (52.7%)	54 (60.0%)
Female	89 (44.1%)	53 (7.3%)	36 (40.0%)
RT-Dose (n = 202)			
Median (range)	57.6 (48.6:66.0)	59.4 (50.4:66.0)	55.0 (48.6:64.8)
Duration of RT (days)			
Median (range)	46.0 (26.0:77.0)	46.0 (33.0:77.0)	45.0 (26.0:65.0)
RT-T			
2D/CRT-3D	116 (57.7%)	55 (49.5%)	61 (67.8%)
IMRT	68 (33.8%)	45 (40.5%)	23 (25.6%)
PBRT	15 (7.5%)	9 (8.1%)	6 (6.7%)
Mix proton/ photon	2 (1.0%)	2 (1.8%)	0 (0.0%)
Missing	1	1	0
Chemotherapy			
No	131 (64.9%)	79 (70.5%)	52 (57.8%)
Yes	71 (35.1%)	33 (39.5%)	38 (42.2%)
Pre-RT	60 (84.5%)	28 (84.8%)	32 (84.2%)
Post-RT	4 (5.6%)	3 (9.1%)	1 (2.6%)
Pre & post-RT	7 (9.9%)	2 (6.1%)	5 (13.2%)

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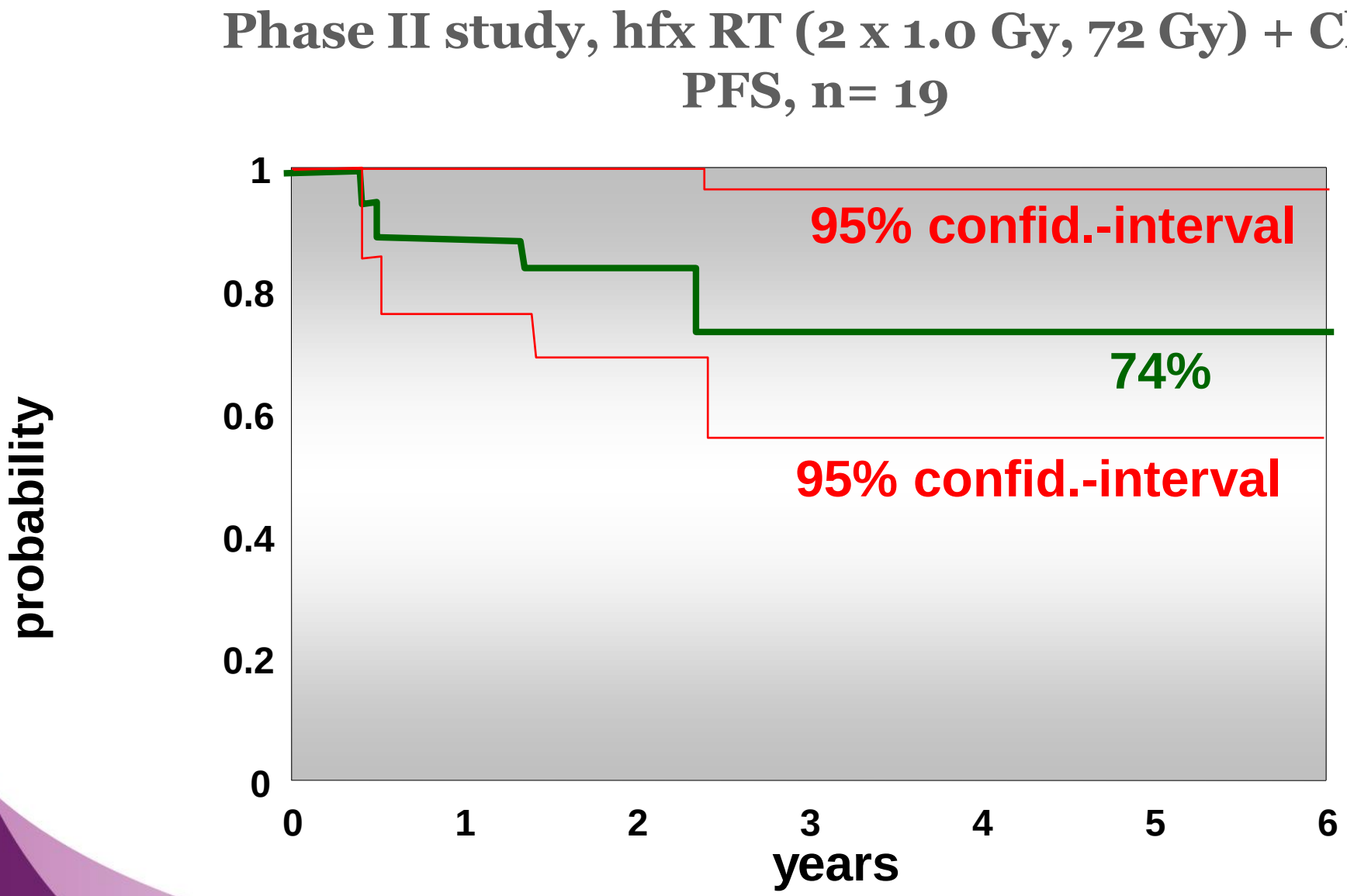
High dose/HFX – high PFS!

Dose – response relationship

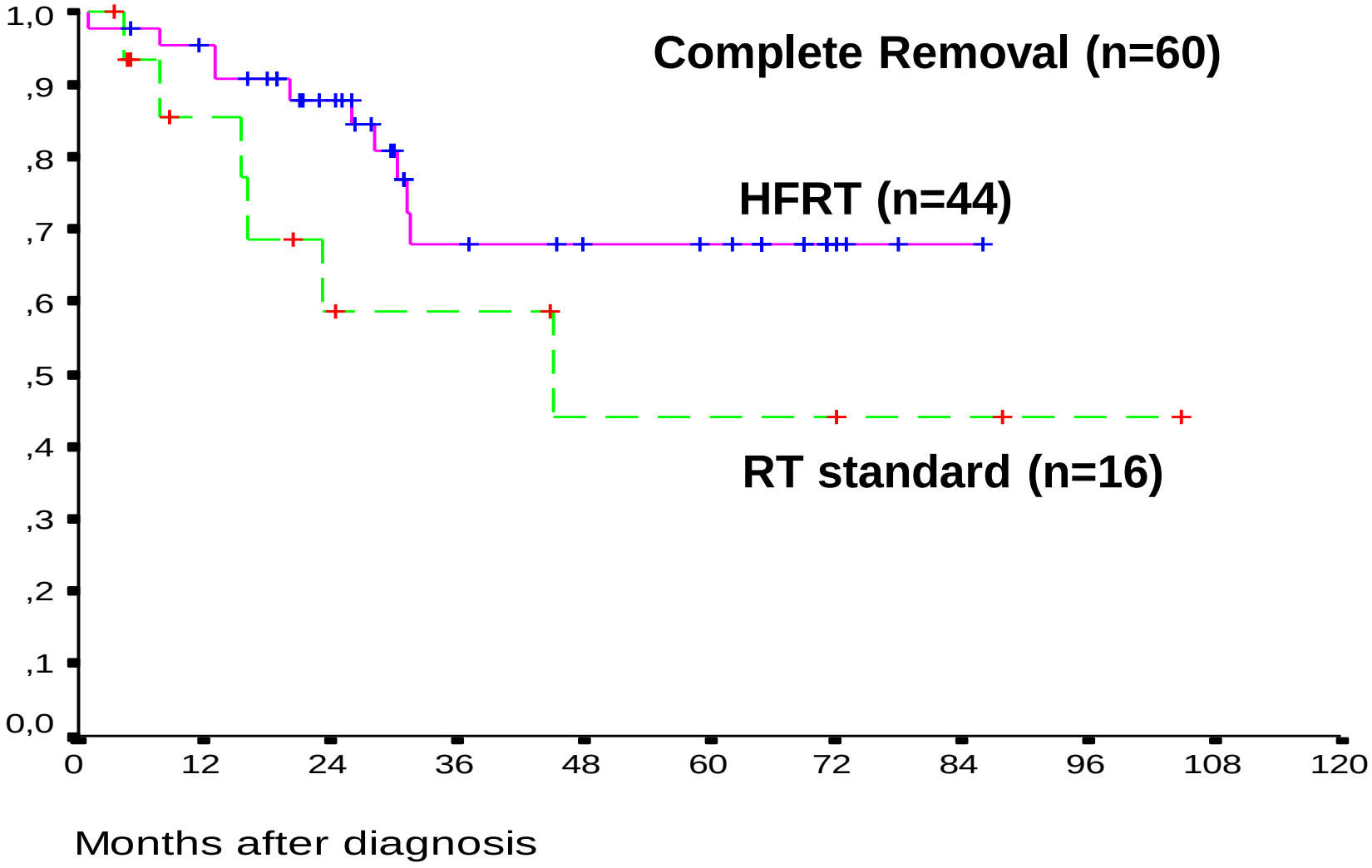
Needle et al., 1997



HFX- DFS!

Dose – response relationship

European experiences, pooled data



Ependymoma / outcome according to R0/+ and dose escalation

Group	Pat.	PFS	OS
Milan 2004	63 (hfx . 46 children)	5 years R0 : 65% R+ : 35%	5 years 82% 61%
SFOP 2009	24 (hfx 60/66Gy)	5 years </= 60 Gy : 52.6% 66Gy : 80%	5 years 73.7% 80%
St. Jude 2009	153	7 years R0 : 77.3% R+ : 34.2%	7 years R0 : 88.0% R+ : 52.4%
HIT 2000 (interim analysis)	181	7 years R0 : 68.7% R+ : 47.6 %	7 years R0 : 82.7% R+ : 67.1%

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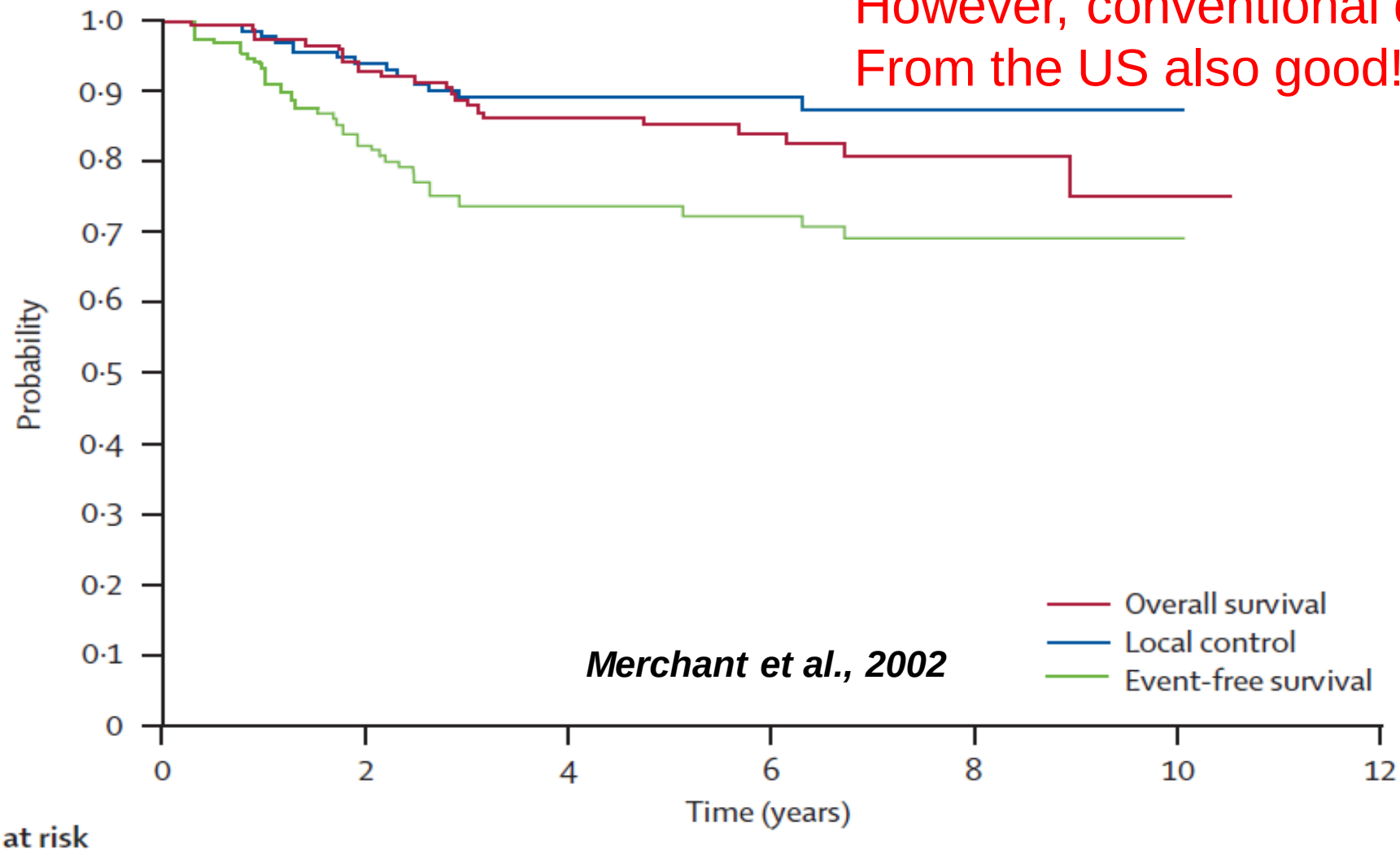
3 D RT tumour site only / 59,4 Gy (5 x 1.8 Gy)

However, conventional data
From the US also good!



Number at risk						
Overall survival	153	141	101	79	47	13
Local control	153	134	85	66	38	7
Event-free survival	153	134	85	66	38	7

Present dose „standard“

- Tumour 54-59.4 Gy
- CSI 36 Gy

- Residue ? Gy… Boost i.e. 2 x 4 Gy or 10 x 2

studies on boost needed!

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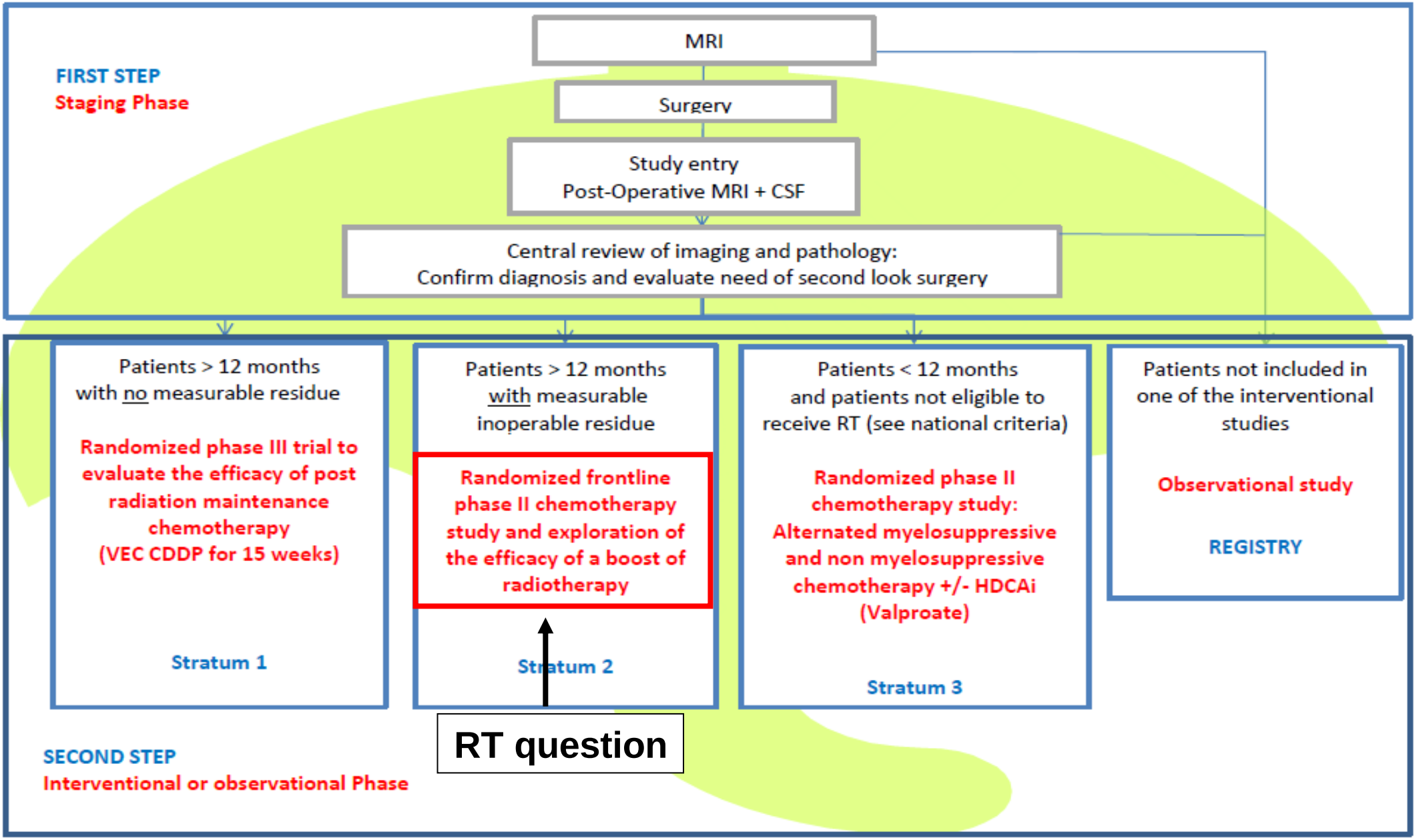
SIOP Ependymoma II study



SIOP Ependymoma II - PTV1 target volume

Target volume definition

Clinical Target Volume (**CTV**): the **CTV includes the GTV** with an added margin to treat subclinical microscopic disease **and is anatomically confined** (i.e. the CTV is limited to the confines of the bony calvarium, falx and tentorium or extend up to but not beyond neuroanatomic structures surely not invaded by tumor).

The **CTV margin will be 0.5 cm** for all patients.

Planning Target Volume (**PTV**): the PTV is a geometric expansion of the CTV to take in to account for uncertainties in immobilisation, daily patient positioning and image registration.

The **PTV margin will be 0.3 cm - 0.5** cm in all directions.

The size of the required margins will depend on the quality of the immobilization device chosen and the departmental reproducibility records for the patient position and chosen device.

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SIOP Ependymoma II - dose prescription

Total dose: the **total dose to the PTV is 59.4 Gy**.
NB: children younger than 18 months (and older than 12 months) at irradiation **without post-surgical residual disease or children with risk factors**, namely multiple surgeries (more than 2) or poor neurological status **will receive 54 Gy.**
Residual TU-boost 2 x 4.0 Gy
Fractionation:
all patients will receive a daily fraction of **1.8 Gy, 5 x / week**.

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SIOP Ependymoma II – PTV2 boost target volume

Target Volumes

Gross Tumour Volume (**GTV**): the GTV includes **all the measurable pathological tissue with or without contrast enhancement after surgery/ies** as documented by MRI at the end of conformal treatment to tumour bed.

Clinical target Volume (**CTV**): **CTV=GTV** i.e. no additional margin to be applied to GTV for CTV. This is to restrict the boost volume as far as possible, in view of the likely adjacency of the brainstem for most patients, the hypofractionated schedule and the resulting cumulative biological effective dose.

Planning Target Volume (**PTV**): the PTV is a geometric expansion of the GTV/CTV to take in to account for uncertainty in immobilisation, daily patient positioning and image registration. The **PTV margin is 0.2-0.3 cm** in all directions according to local policies.

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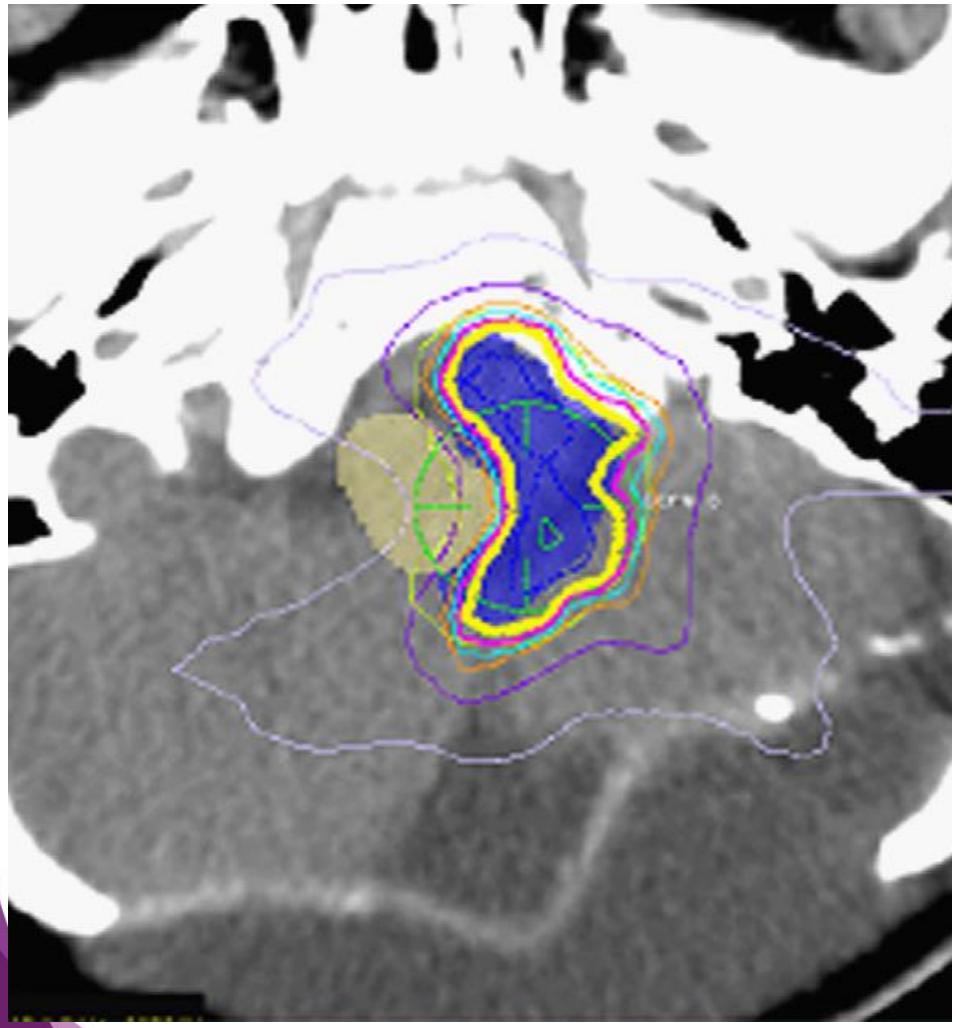
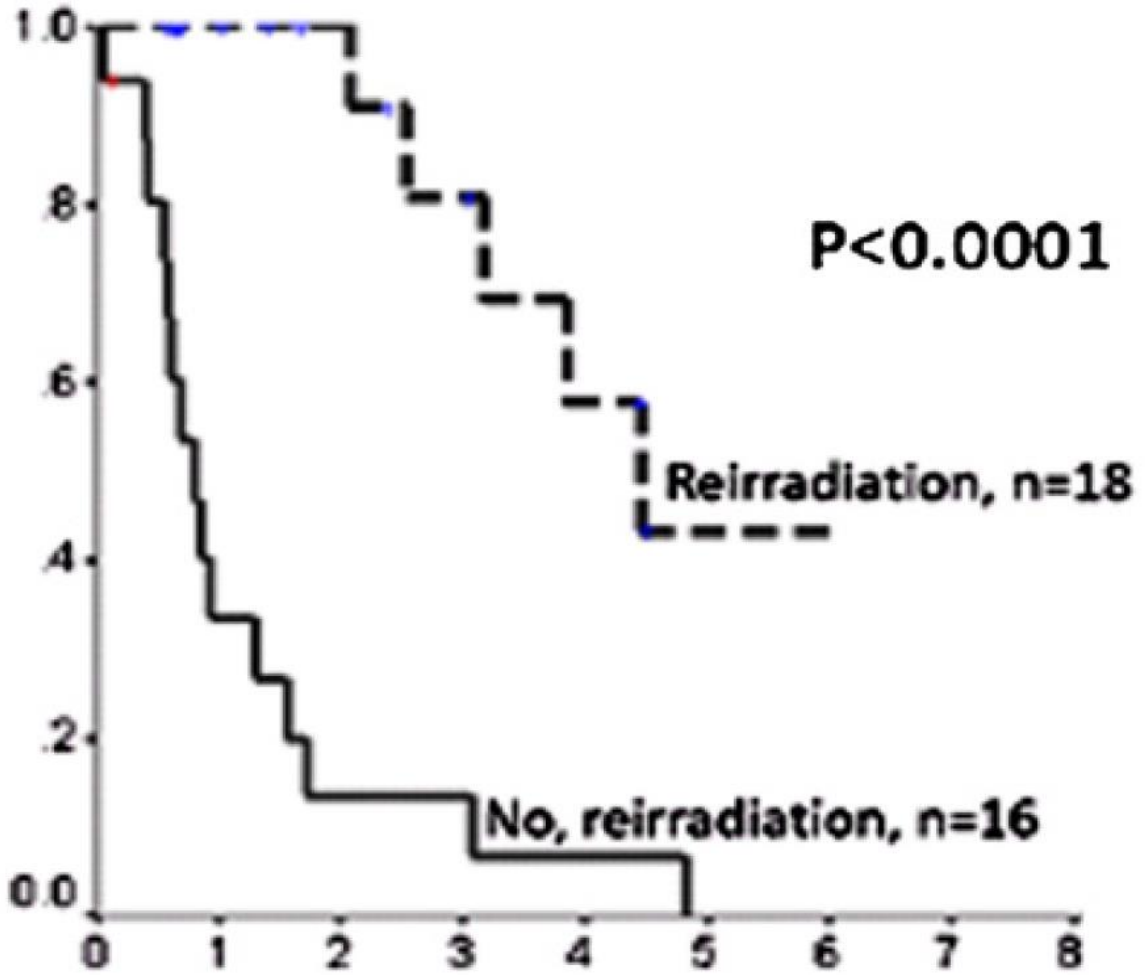
Recurrences

Data

Bouffet et al., 2011





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Clinical Investigation: Pediatric Cancer

Survival Benefit for Pediatric Patients With Recurrent Ependymoma Treated With Reirradiation

Eric Bouffet, M.D.,* Cynthia E. Hawkins, M.D., Ph.D.,† Walid Ballourah, M.D.,* Michael D. Taylor, M.D., Ph.D.,‡ Ute K. Bartels, M.D.,* Nicholas Schoenhoff,§ Elena Tsangaris,* Annie Huang, M.D., Ph.D.,* Abhaya Kulkarni, M.D., Ph.D.,‡ Donald J. Mabbot, Ph.D.,§ Normand Laperriere, M.D.,¶ and Uri Tabori, M.D.*

**Department of Hematology/Oncology, †Department of Pathology, ‡Division of Neurosurgery, and §Department of Psychology, The Hospital for Sick Children, and University of Toronto, Toronto, Ontario, Canada; and ¶Department of Radiation Oncology, Princess Margaret Hospital, Toronto, Ontario, Canada*

Received Aug 26, 2011, and in revised form Sep 26, 2011. Accepted for publication Oct 17, 2011

- n = 47 recurrences (1. RT 54-59.4 Gy)
- 29 x OP+CTX vs. 18 x reRT (50.4 – 59.4 Gy +/- CSA) +/-OP
- No higher grade acute toxicity
- **7 vs 81% OS after 3 yrs. - / + reRT**
- Late adverse events: endocrine dysfunction, neurocognitive issues

The second chance

Study	N	Tech/ Dose	Survival
Stafford '00	12	SRS/18	Median survival 3.4 yr/3-yr LC 68%
Merchant	38	variable	5-year OS 100% (CSI), 67% (FRT) 20% (SRS)
Kano '09	36	SRS/15	Median survival 19 mon/ 5-yr PFS 46%
Stauder '12	26	SRS/18	Median survival 5.5 yr/3-PFS 66%
Bouffet '12	18	FRT/>54	3-year PFS 56%
Hoffman '14	12	FSRT/24	Median EFS 3.4 years/ 2-year OS 71%
Eaton '15	15	Proton	Median PFS 19 months/3-year PFS 28%
Lobon '16	32	36 Gy	Median PFS 1.2 yr /OS 3.5 yr

A RETROSPECTIVE STUDY OF SURGERY AND REIRRADIATION FOR RECURRENT EPENDYMOMA

THOMAS E. MERCHANT, D.O., PH.D., FREDERICK A. BOOP, M.D., LARRY E. KUN, M.D., AND ROBERT A. SANFORD, M.D.

Department of Radiological Sciences, Division of Radiation Oncology, St. Jude Children's Research Hospital, Memphis, TN

N = 38 recurrent Ependymomas
(21 local, 13 met, 4 comb.)
First RT local (med. 59.4 Gy)
Re RT as focale SRT(6), CRT (13)
or **CSA (19)**
Med. cum Dose: 111.6 Gy
3/13 focal RT -> Mets
Late tox.: Radionecrosis,
Myelopathy, motor weakness

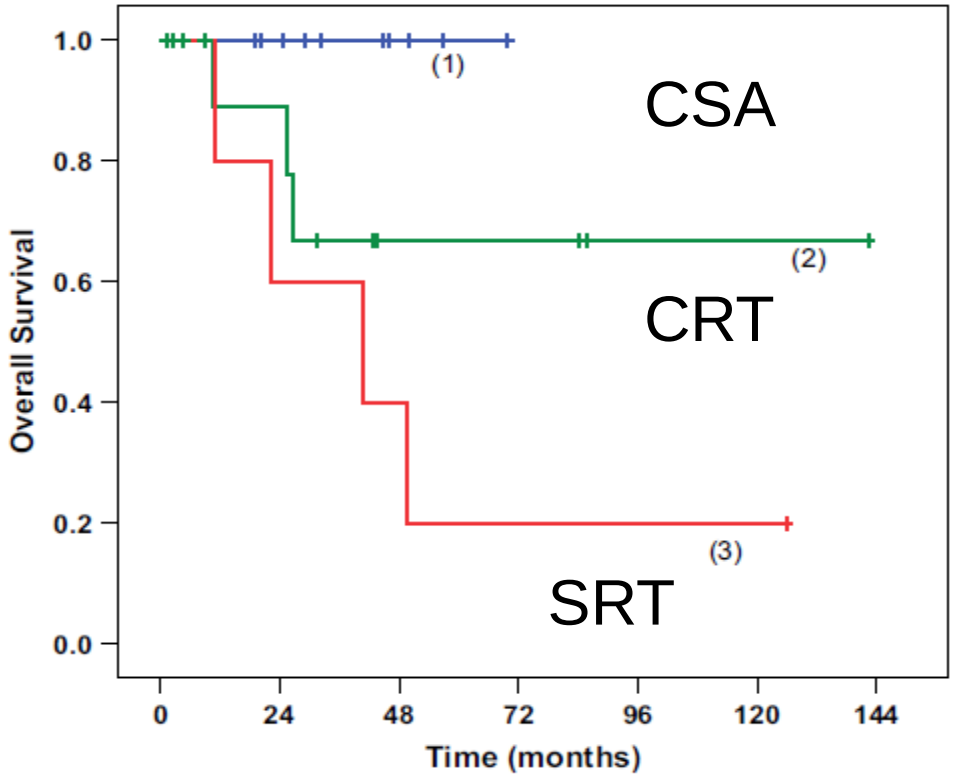

Fig. 5. Overall survival dated from the start of reirradiation according to treatment method and initial tumor pattern failure (blue (1) = 12 patients with initial metastatic failure treated with craniospinal reirradiation; green (2) = 13 patients with local failure retreated with focal fractionated irradiation; red (3) = 5 patients with local failure treated with radiosurgery).

Neuro-Oncology 18:iii159–iii164, 2016.
doi:10.1093/neuonc/now082.23

NEURO-ONCOLOGY

Abstracts

RO-23. RECURRENT EPENDYMOMA A CHALLENGING THERAPY: RE-IRRADIATION PROLONGS SURVIVAL IN FAILURE OF RADICAL RESECTION

Stephan Tippelt[1], Ruth Mikasch[1], Monika Warmuth-Metz[5], Torsten Pietsch[7], Robert Kwiechien[3], Andreas Faldum[3], Stefan Rutkowski[2], Katja Von Hoff[2], Martin Mynarek[2], Udo Bode[4], Nele Siegler[1], Gudrun Fleischhack[1], and Rolf-Dieter Kortmann[6]; [1]University Hospital Essen, Pediatric Hematology and Oncology, Essen, Germany; [2]University Hospital Hamburg, Pediatric Hematology and Oncology, Hamburg, Germany; [3]University Münster, Institute of Biostatistics and Clinical Research, Münster, Germany; [4]University of Bonn, Childrens Hospital, Pediatric Hematology and Oncology, Bonn, Germany; [5]University of Wuerzburg, Neuroradiology, Würzburg, Germany; [6]University of Leipzig, Department of Radiotherapy and Radioonkology, Leipzig, Germany; [7]University of Bonn, Medical Center, Institute of Neuropathology, Bonn, Germany

INTRODUCTION: In pediatric patients with ependymoma the 10-year overall survival (OS) rate is 64% with poor 5-year OS rates of only 42-55% in infancy. Beside maximal radical resection local radiotherapy is standard of care; chemotherapy is controversially discussed. In recurrence treatment options are rare. Re-resection with maximal radical intense is indicated in local relapses. In unresectable or metastatic disease longterm prognosis is fatal. Merchant et al. and others showed prolonged OS rates after re-irradiation even in metastatic disease. PATIENTS AND METHODS: From 55 patients of the German HIT2000 and HIT-REZ study cohort with recurrent ependymomas who received re-irradiation data as age; stage of disease; time and extent of surgery; time, dose and volume of radiotherapy; time and kind of chemotherapy at primary diagnosis and relapse; date and disease state at last follow up and causes of death were analyzed. OS time was estimated based on Kaplan–Meier-analysis and compared to a cohort of 40 patients without re-irradiation. RESULTS: The 55 patients (74% male) with a median age at primary diagnosis/first recurrence of 5.4/8.4 years showed metastatic disease at recurrence in 47% and a median time to first progression of 22 months. Median OS after first relapse was 31 (CI 21-41) months with 5-year-OS rate of 33%. In comparison to the cohort without re-irradiation significant better 5-year-OS rate was observed in patients with residual tumor at time of re-irradiation (40 vs. 8%). CONCLUSION: Re-irradiation can lead to prolonged survival if radical surgery is impossible and is highly recommended in these cases.

- Data from the German HIT Rez study:
- 47% of relapses after re-RT were disseminations!

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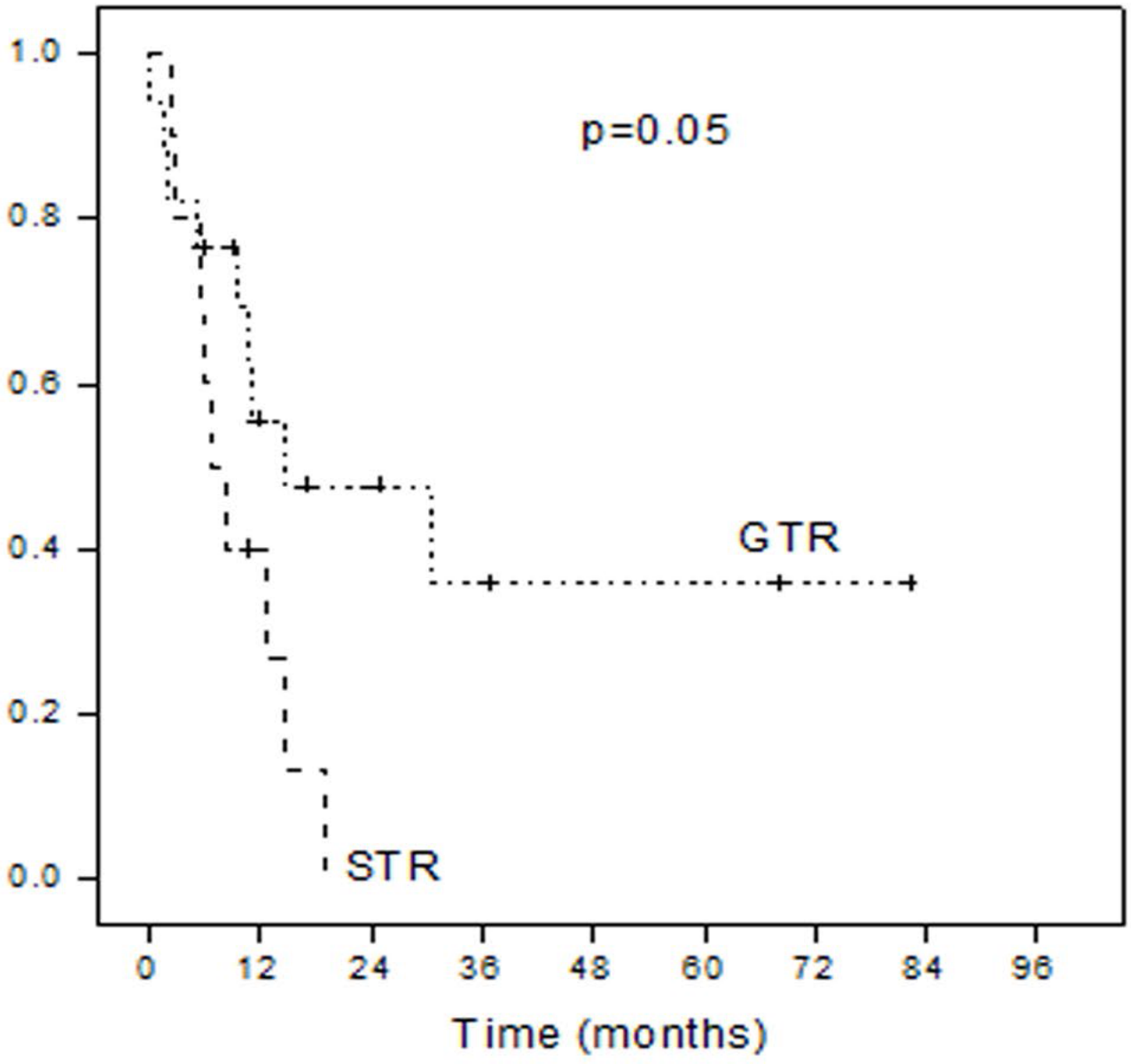
Resection in recurrent Ependymomas



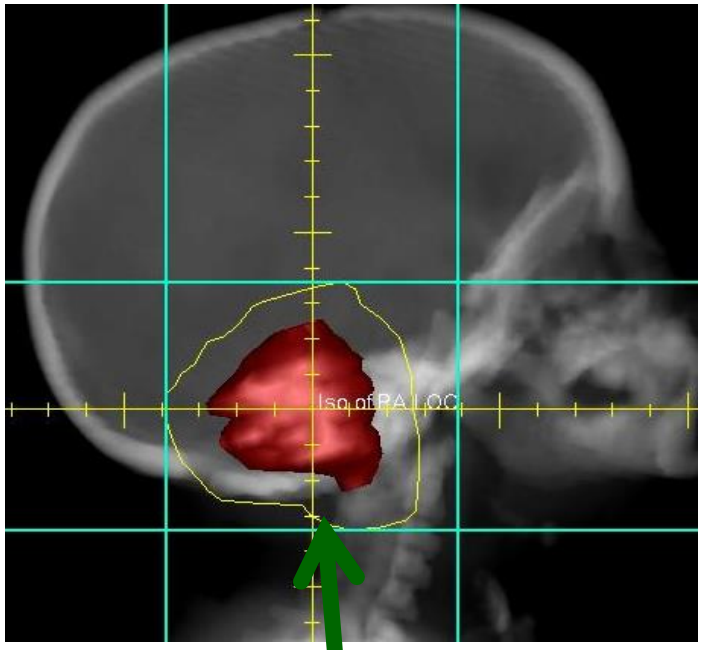
32 Re-RT
- n=15 local rec, n=17 mets
- 14-59.4 Gy in local RT, 30-54Gy in CSI-RT
- Med. PFS after re-RT 1.2 yrs
- Med. OS after re-RT 3.5 yrs
- 5 radionecrosis

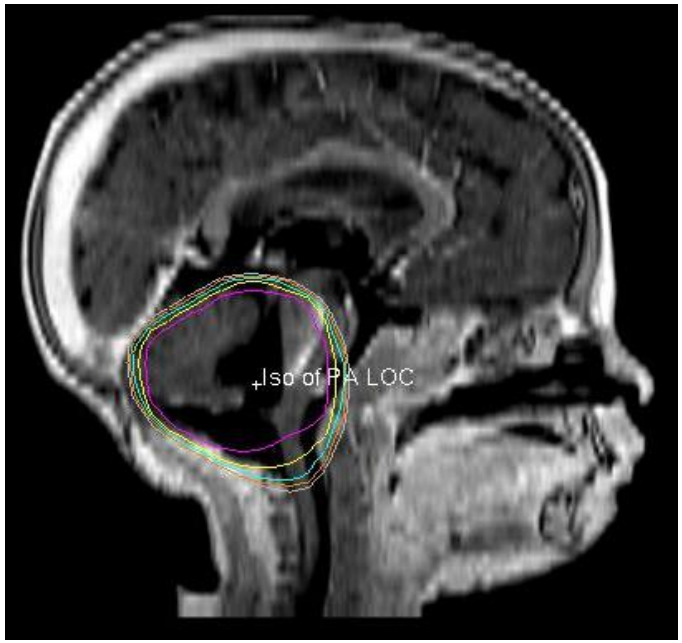
Lobón et al., 2016

General lessons learned

- RT interval as short as 3-6 months seems to be enough (Mayer et al, 2008)
- Cumulative doses of about 100-110 Gy seem to be feasible (Mayer et al, 2008)
- Feasibility depend on RT volume (Mayer et al, 2008)
- Optimal fractionation scheme unclear with regard to necrosis (conventional vs. Hypofractionation vs. SRT) (Sminia et al, 2012)
-

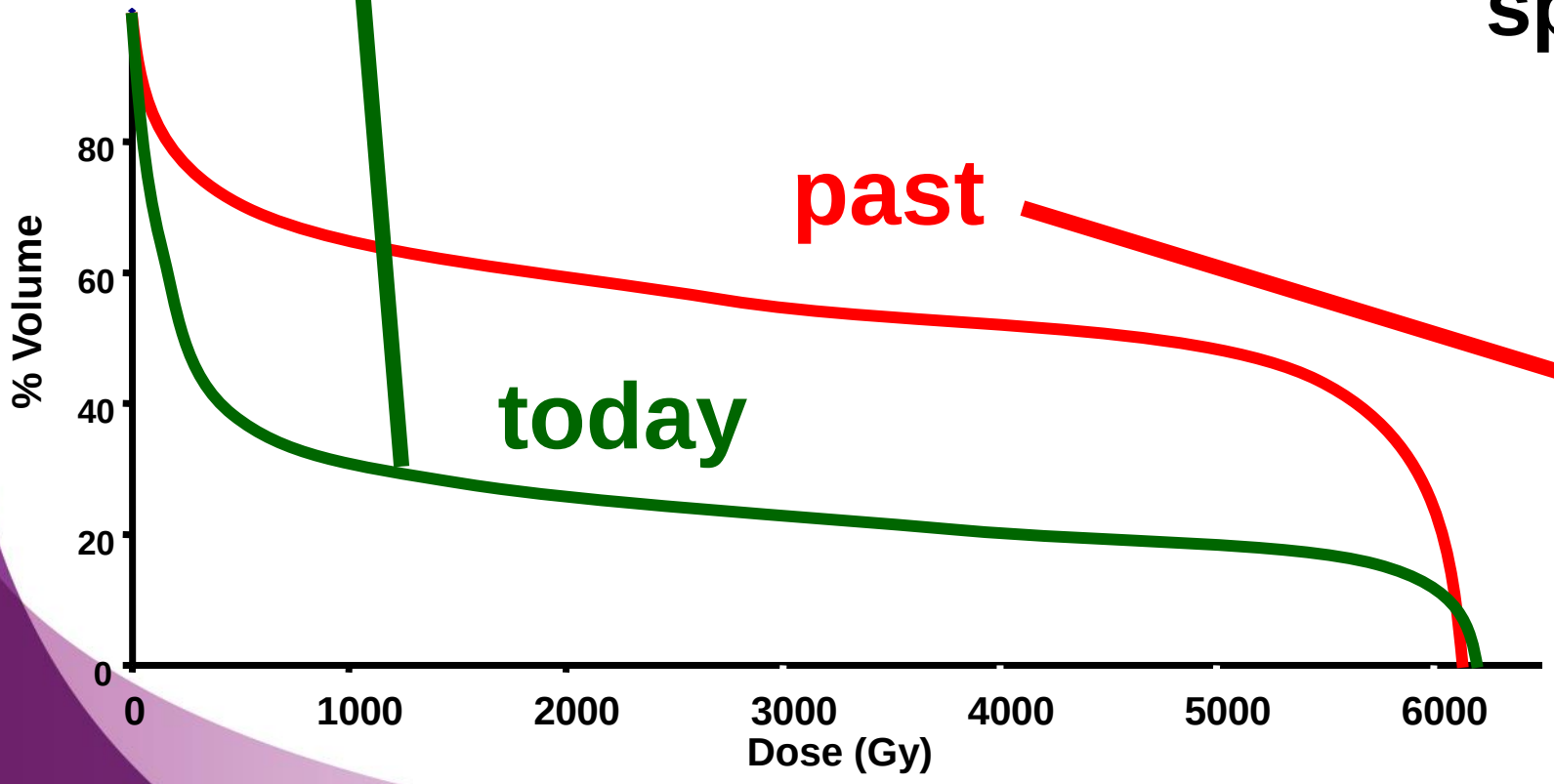
Techniques

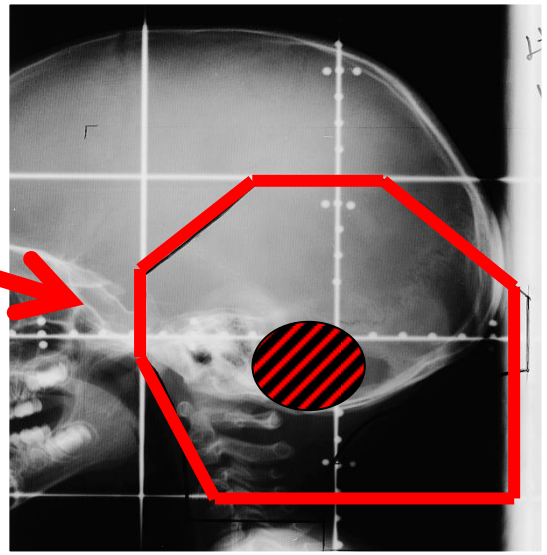




Dose reduction By modern techniques:

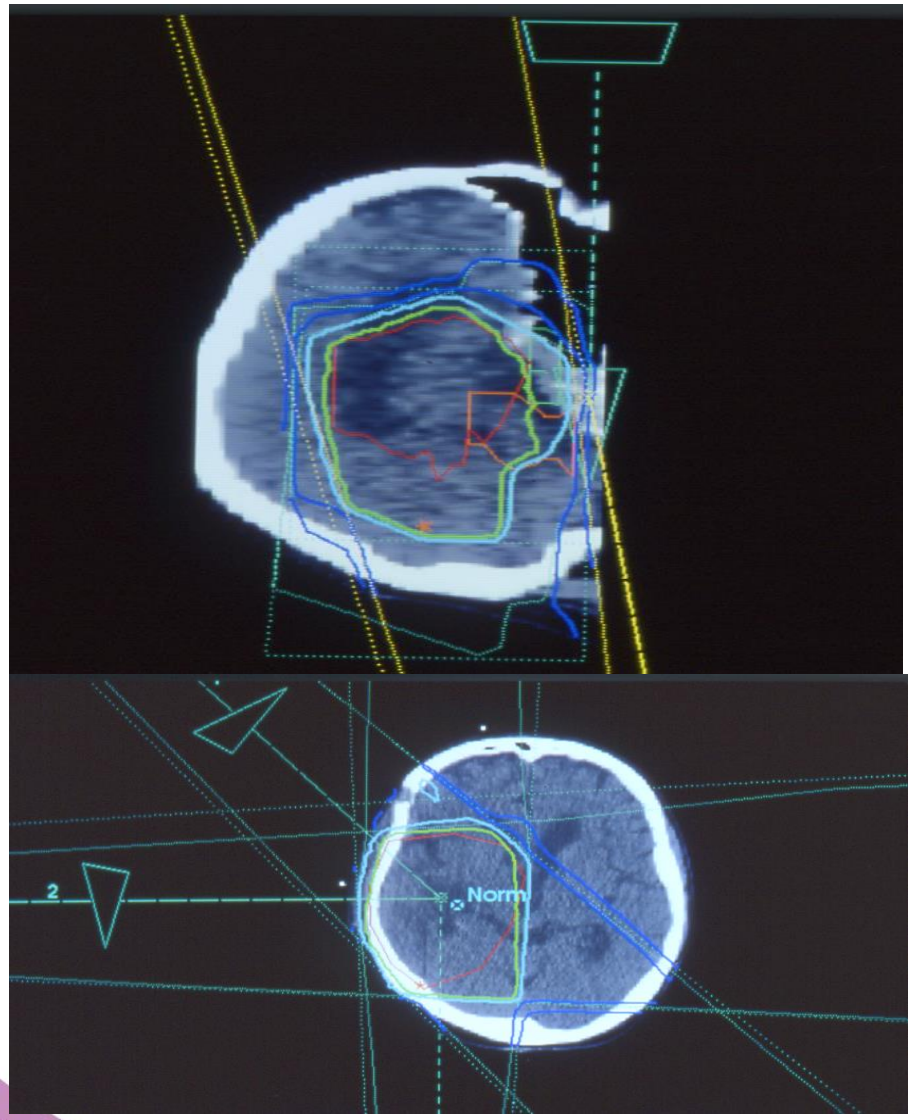
Temporal lobe sparing

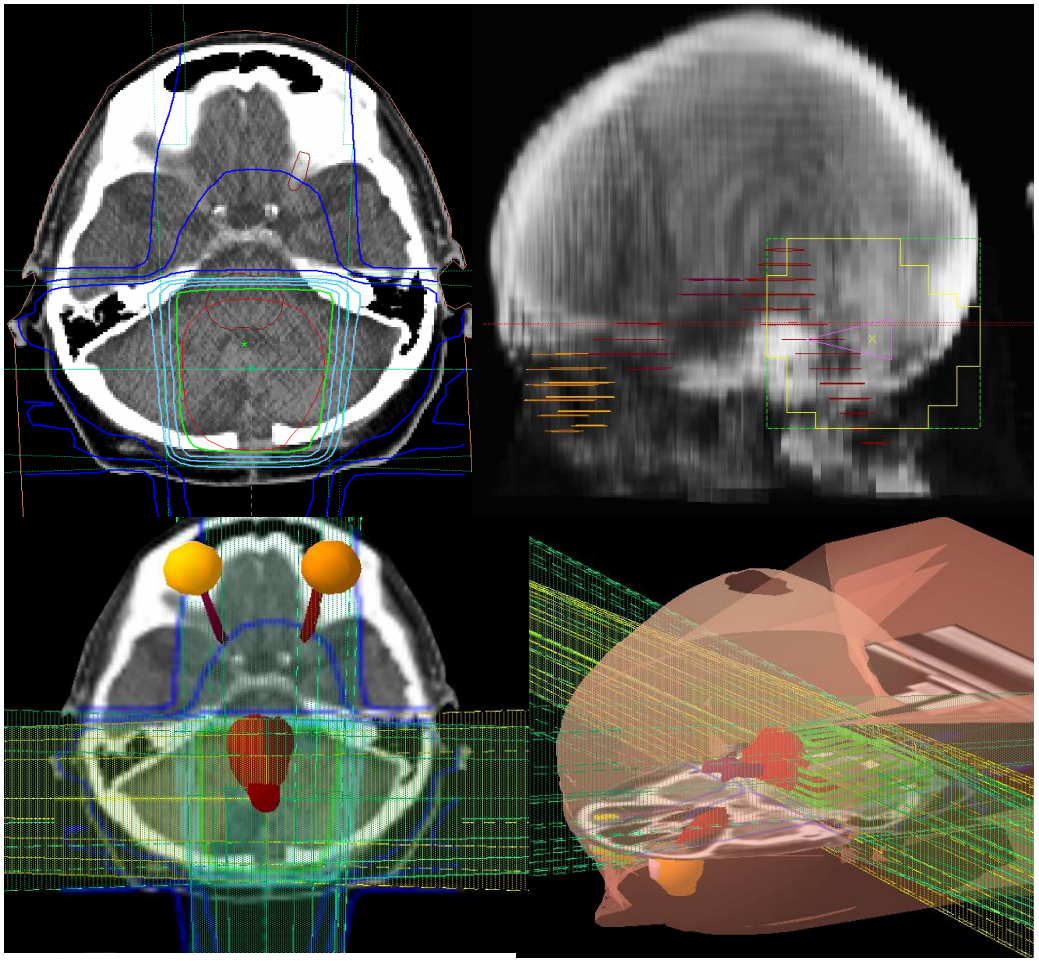




Merchant, 2004

3-D conformal local XRT





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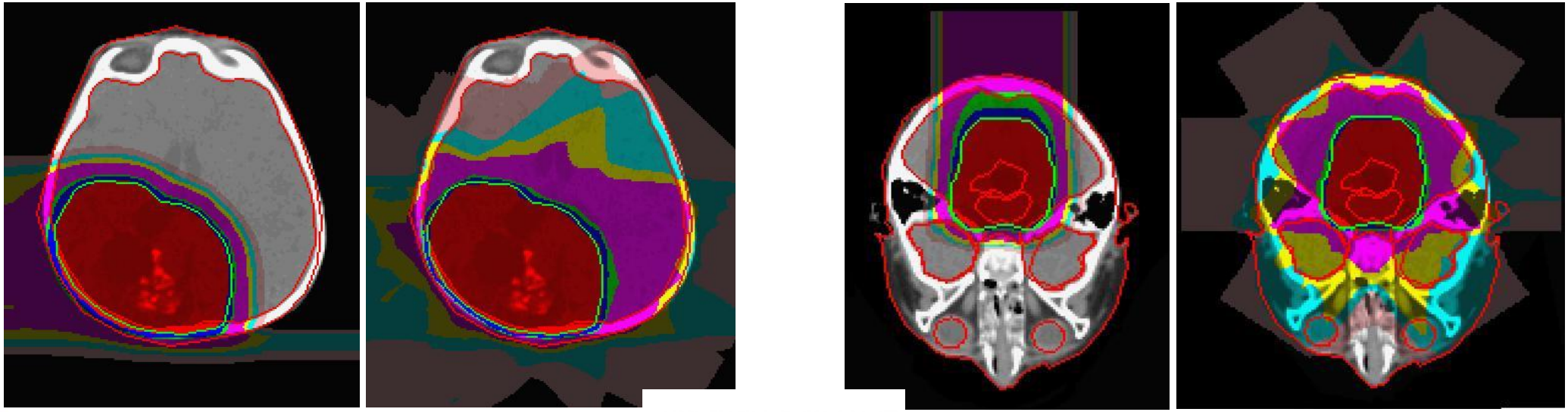
Local Proton Beam Therapy

- Supratentorial case PT vs. XRT
- Infratentorial case PT vs. XRT



PAUL SCHERRER INSTITUT

PSI

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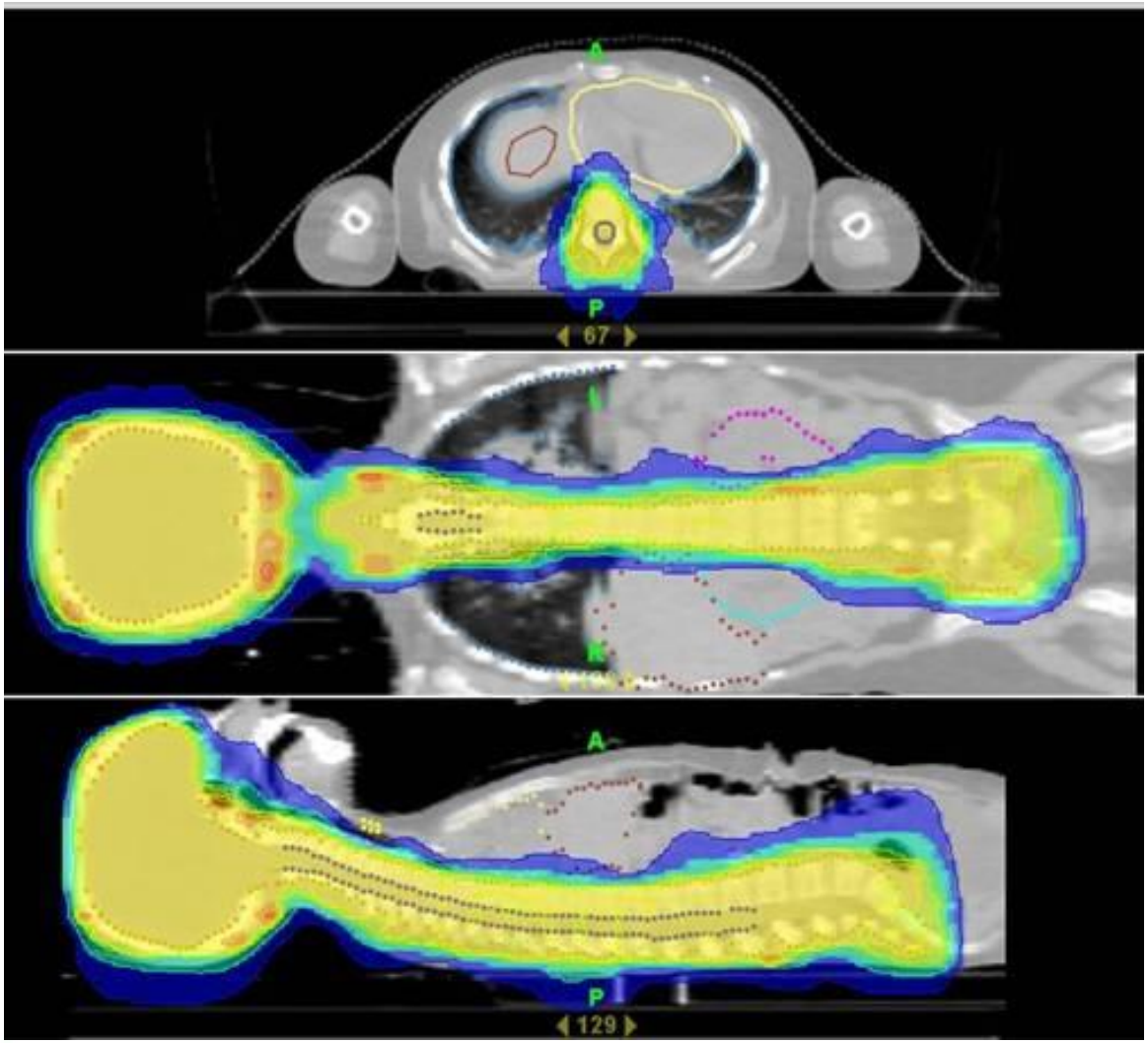
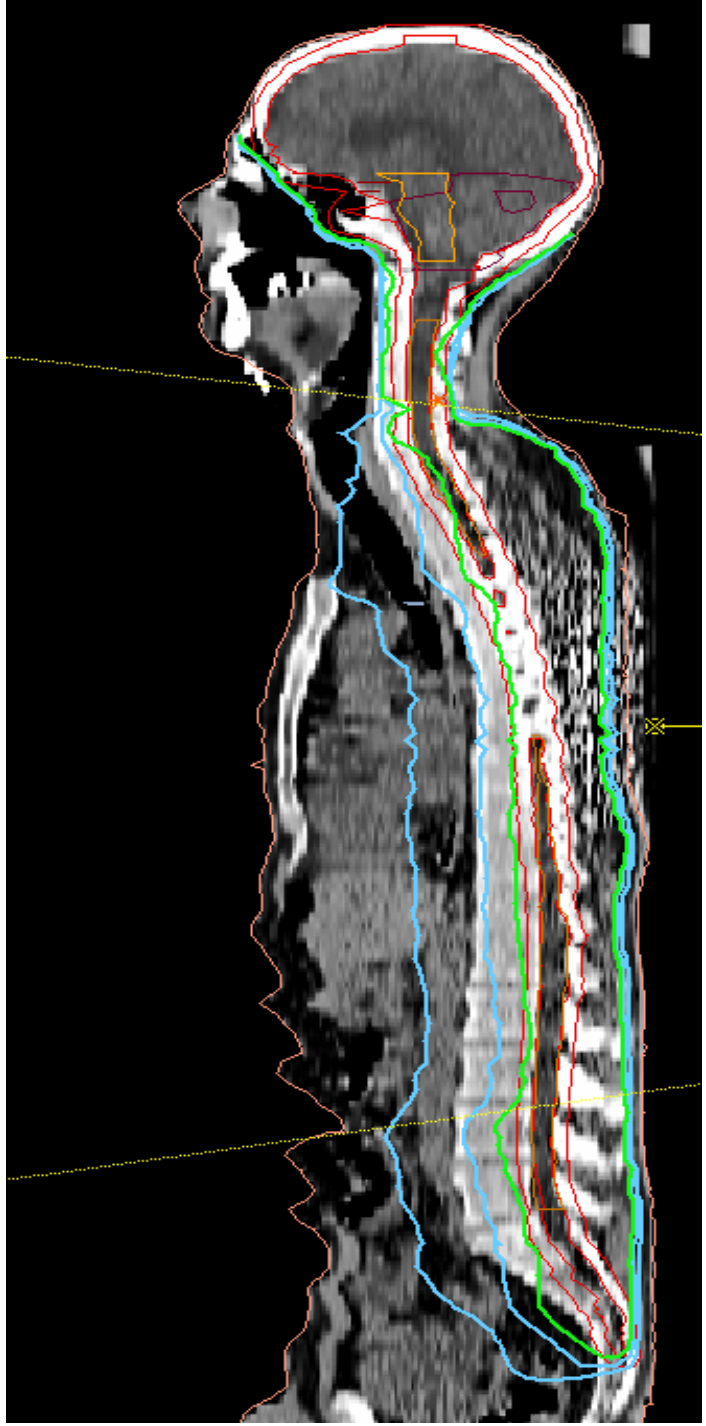
Modern CSI, XRT





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CSI with Protons: optimized ventral dose distribution

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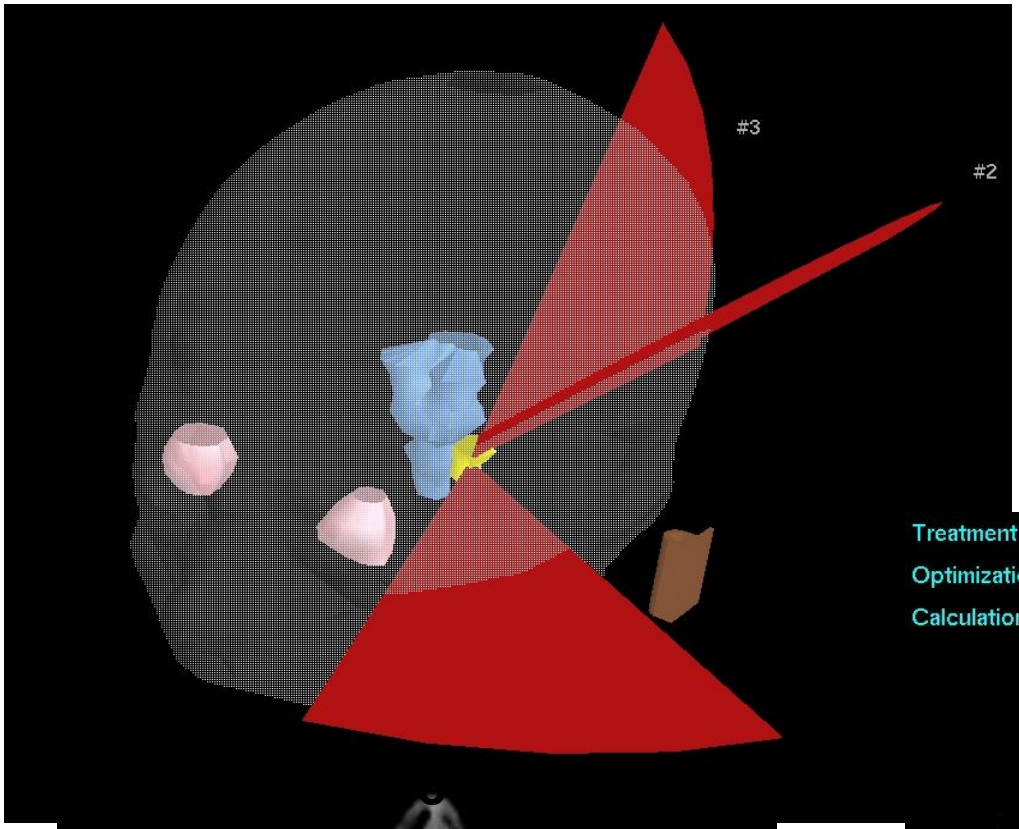
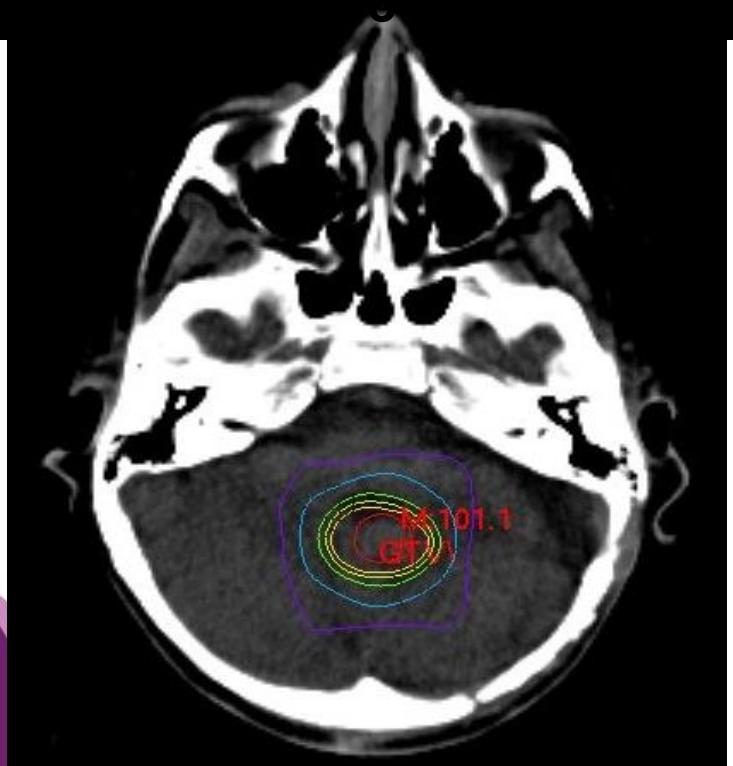
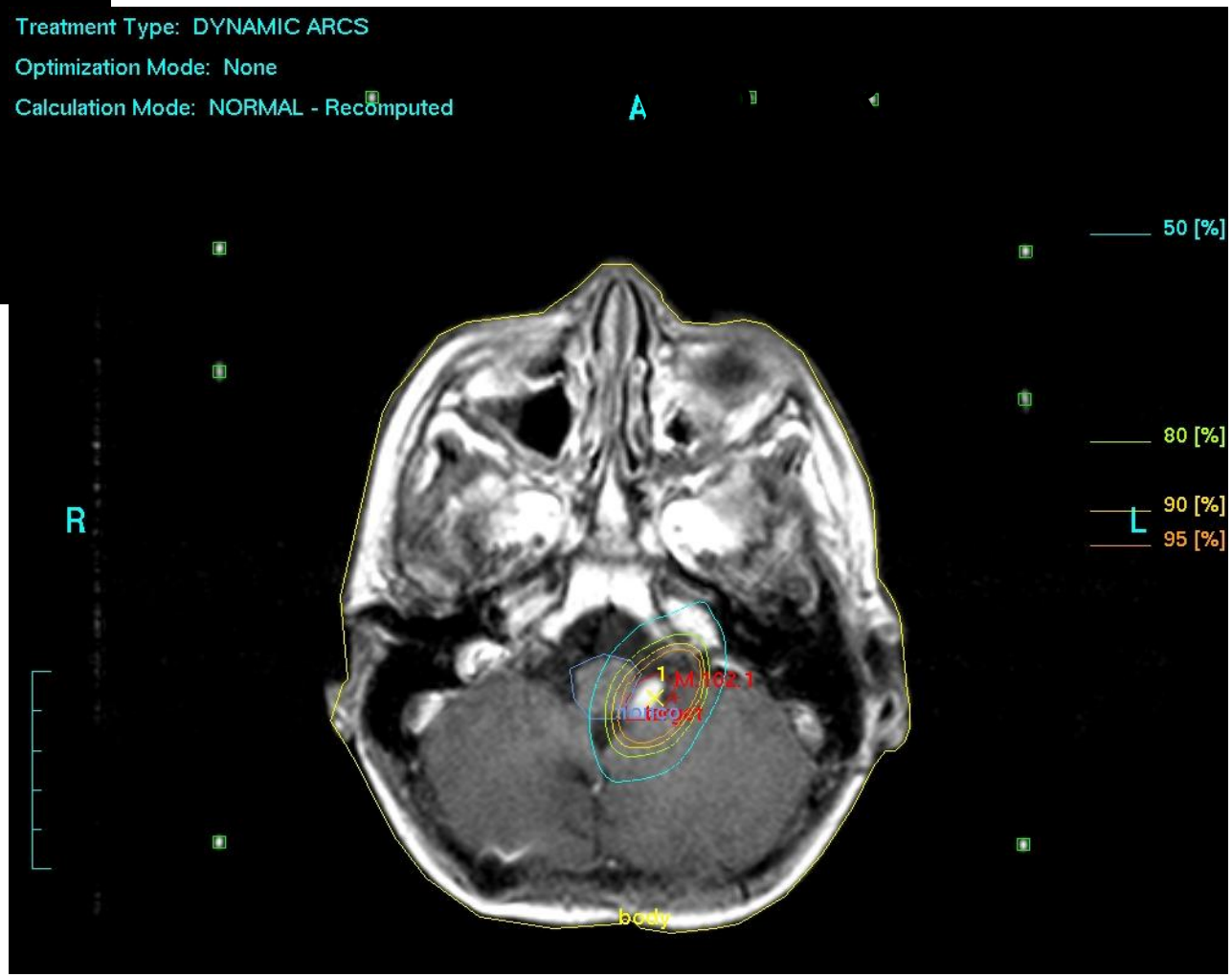
SRT in Ependymoma for the boost to he residue

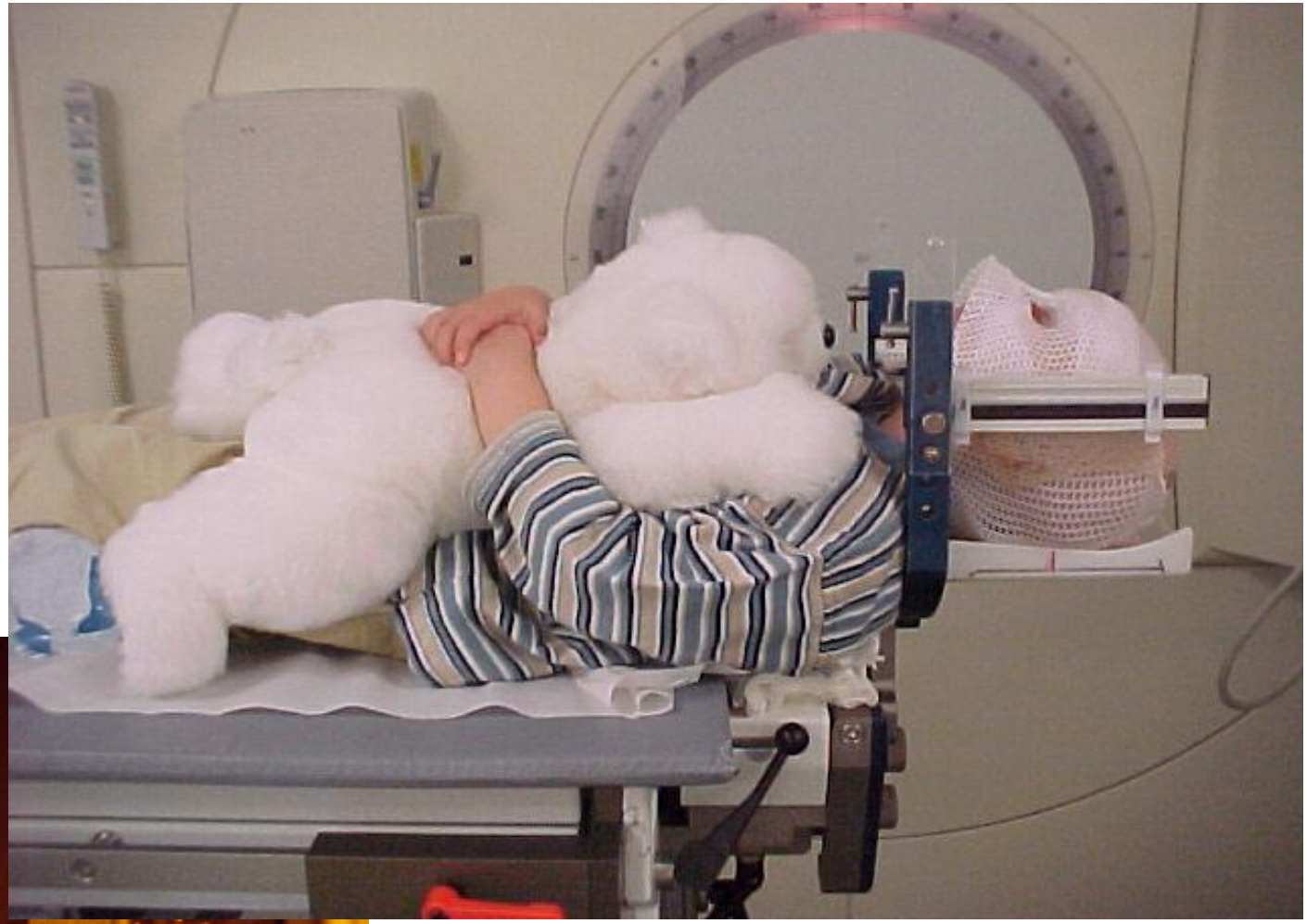
Source: Lorenza Gandola
Italy, AEIOP 03

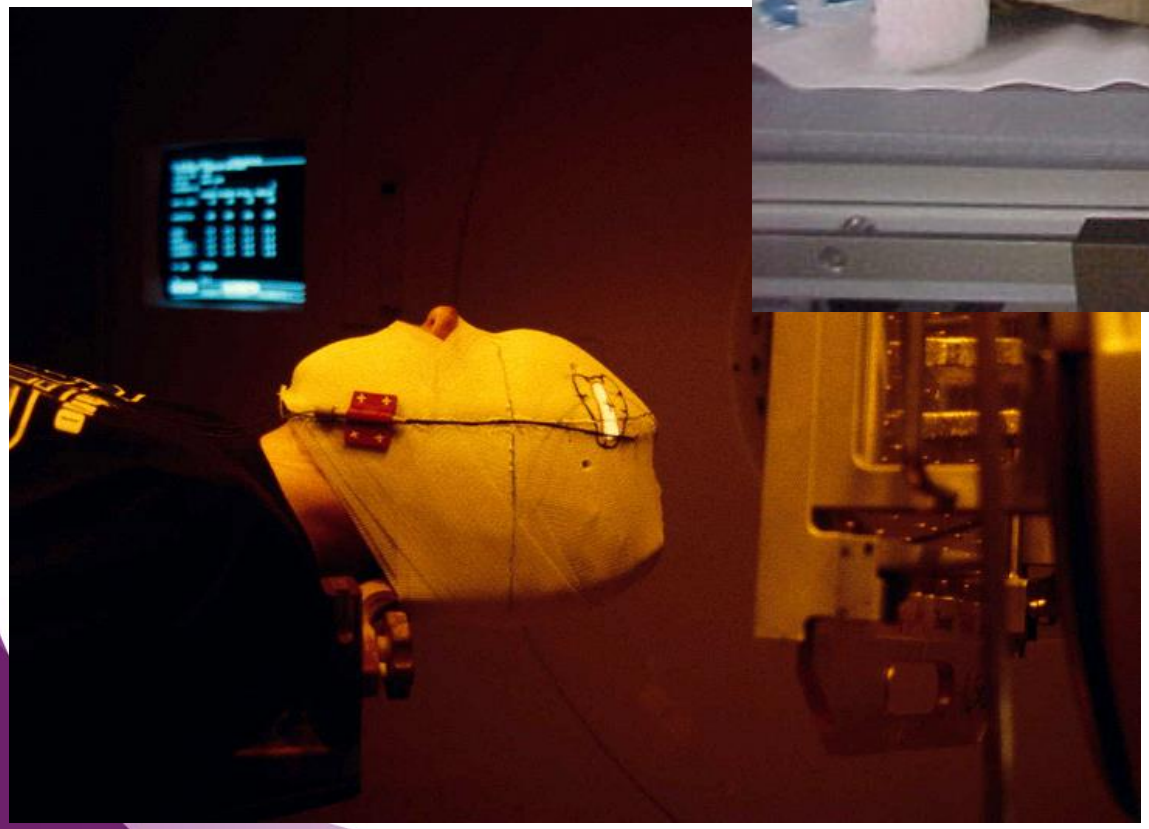






Positioning Children for Stereotactical RT





Thanks to
K. Dieckmann
and
R.-D. Kortmann

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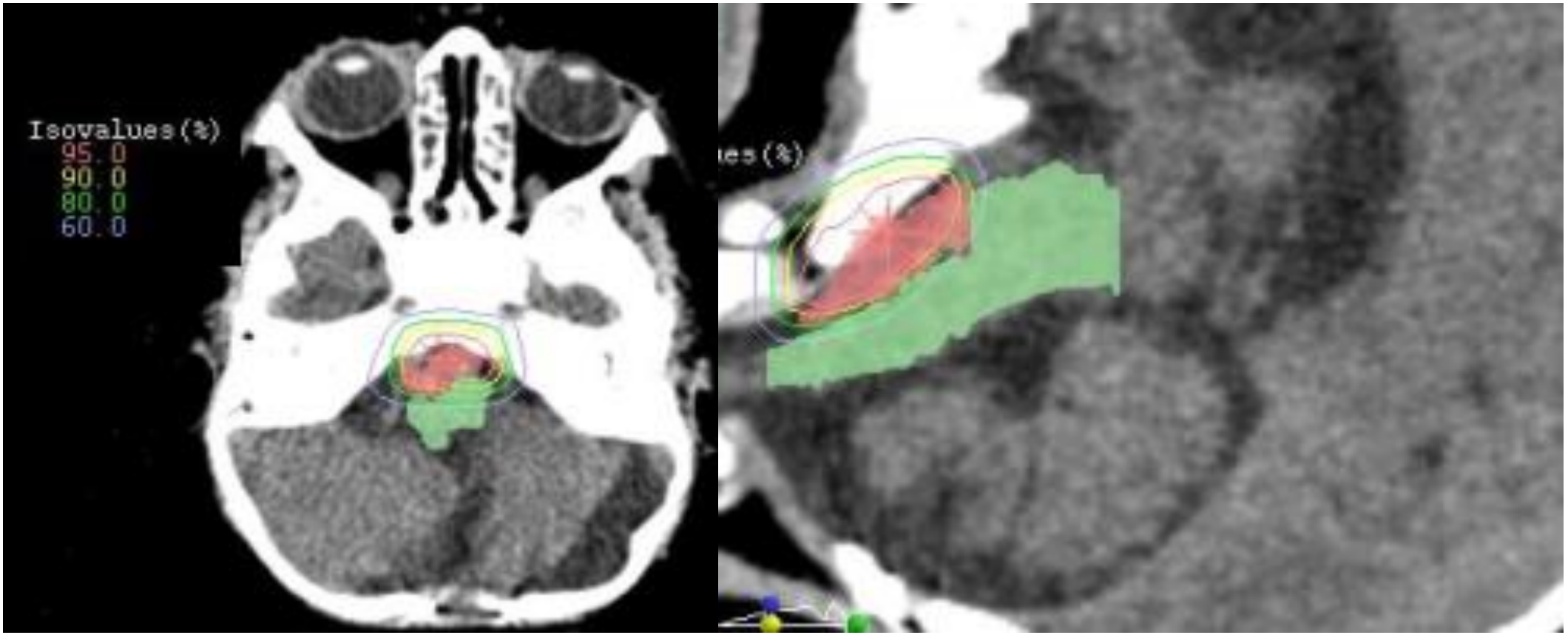
Stereotactic Boost with protons 2x4Gy



- Within HIT 2000 Boost (2 x 4 Gy)
- Local center refused to perform boost
- Internal decision: keep BS below 70% of boost dose
- GTV only treated

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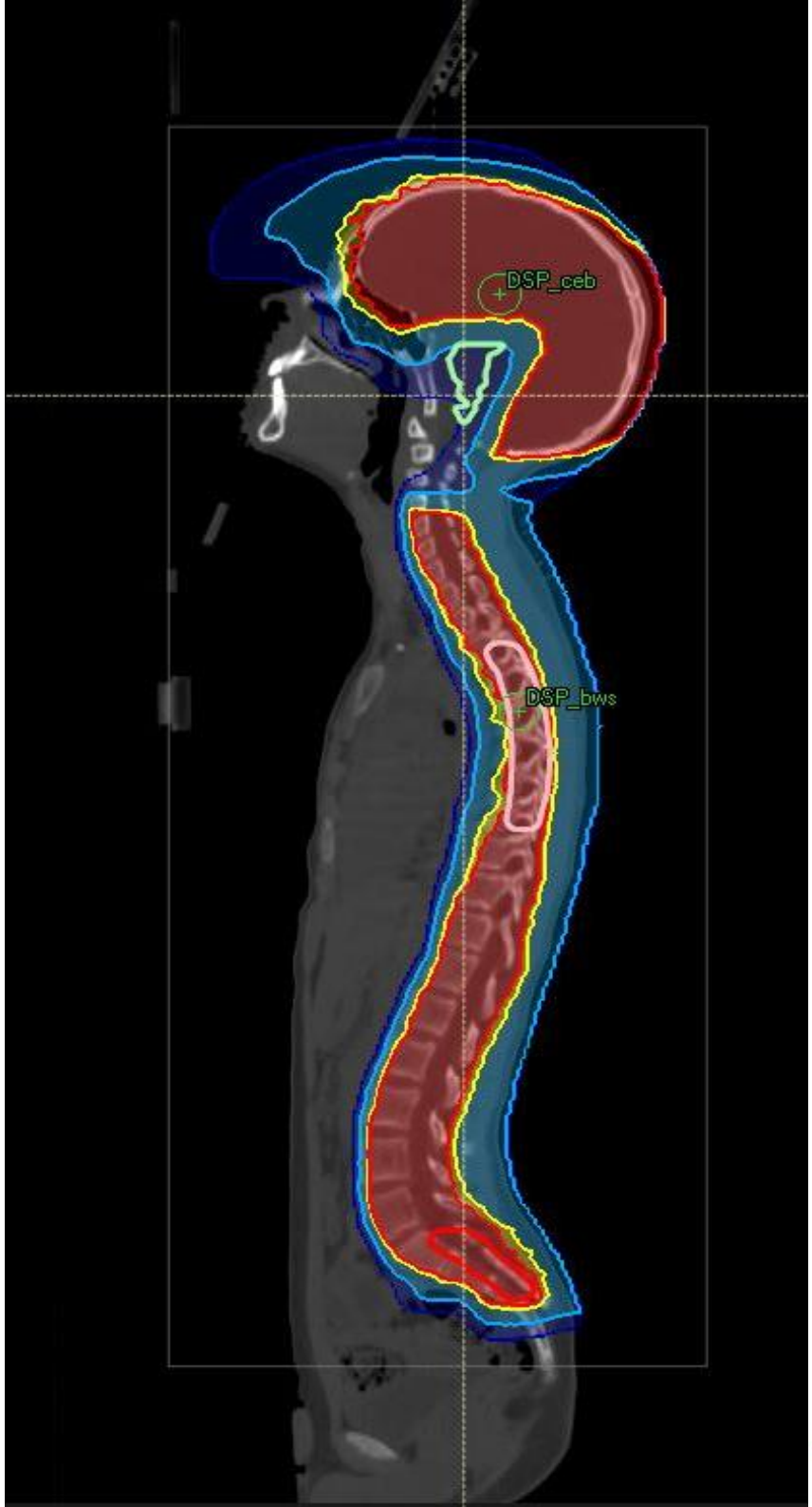
CSI at 2nd recurrence with spinal mets – protons

- dicom data transfer
- matching dose plans
- image guidance
- highly conformal RT (PBT)
- IMPT: sparing of BS in area having received 2 local RT series close to BS before



Conclusion

- RT important; GTR important
- RT dose-response relationship proven
- Pattern of 1st relapse mainly local
- M0: Local RT to 54-59.4 Gy standard today (age?)
- CSI reserved for M+ disease
- Role of Boost for residual disease (i.e. 2 x 4 Gy)?
- In recurrences again surgery plus RT (maybe even CSI as risk for dissemination seems to be quite high)
- Modern techniques beneficial for volume reduction and improved feasibility

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Recommendation for Literature

VOLUME 35 · NUMBER 21 · JULY 20, 2017

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Current Clinical Challenges in Childhood Ependymoma: A Focused Review

Thomas E. Merchant

ESTRO School

THANK YOU AND - A WONDERFUL X-MAS TIME!

Christmas greetings from Essen, Germany

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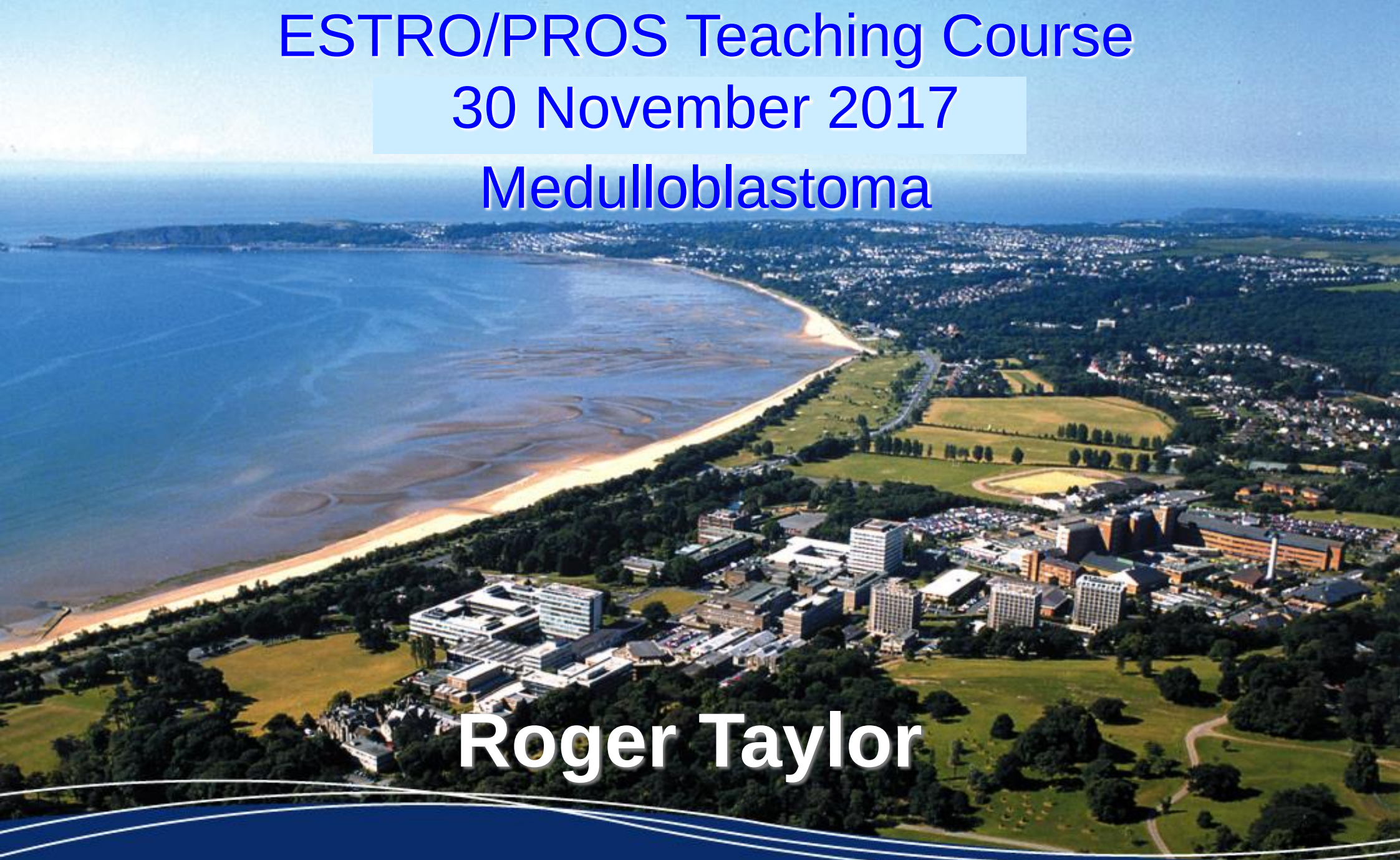
WWW.ESTRO.ORG/SCHOOL

ESTRO/PROS Teaching Course

30 November 2017

Medulloblastoma



Roger Taylor

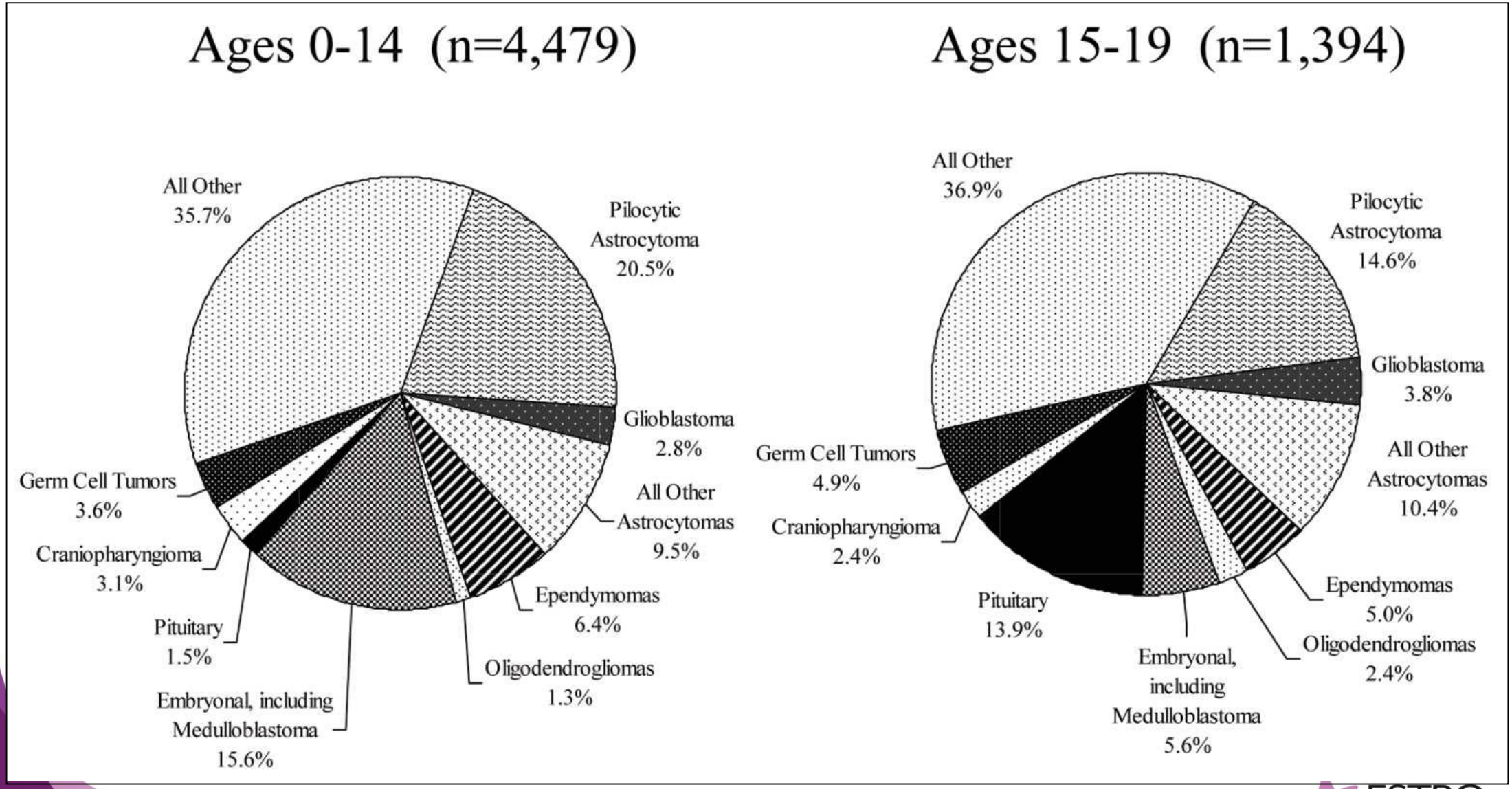
SWANSEA UNIVERSITY
PRIFYSGOL ABERTAWE

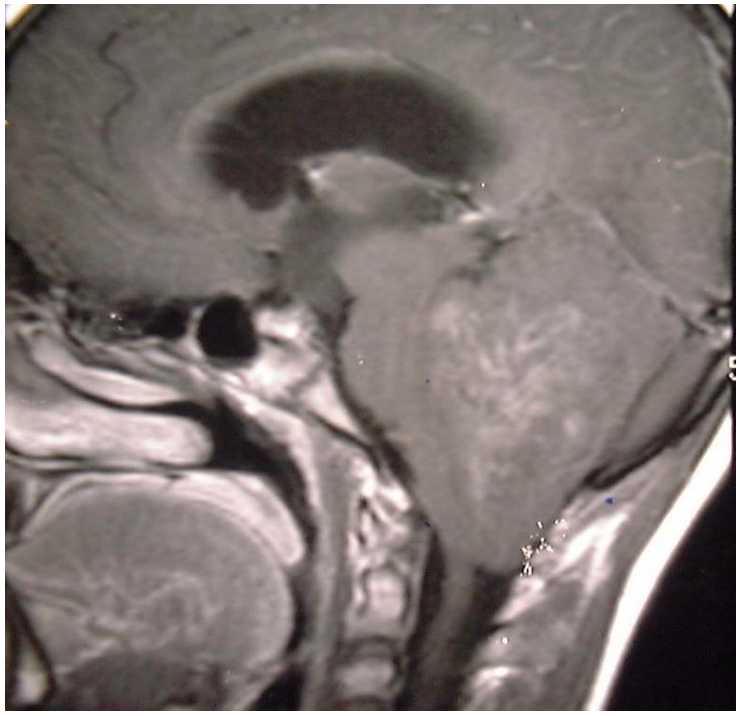
SOUTH WEST WALES CANCER CENTRE

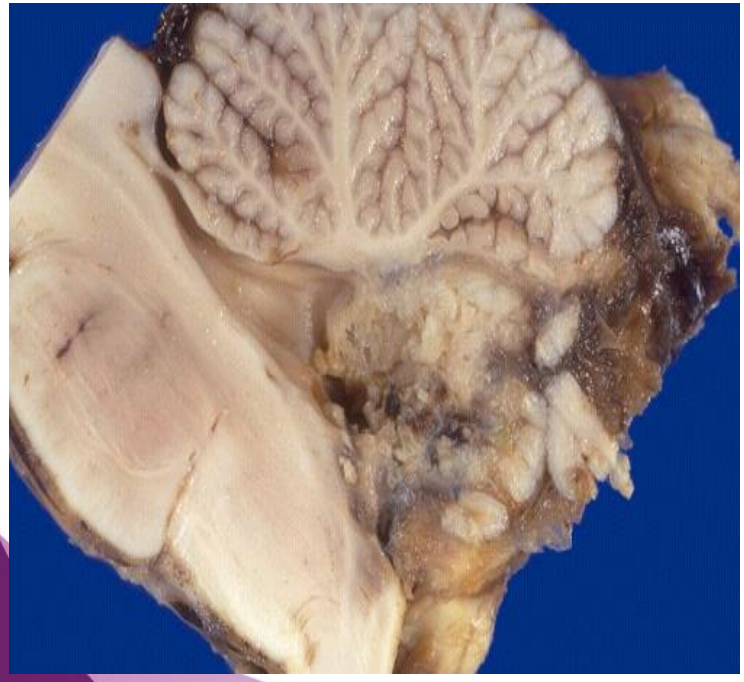
Paediatric Brain Tumour Epidemiology

- Incidence 2.6-5.4 per 100,000 children aged <19
- Approximately 29% of childhood cancer
- Survival rate around 65% overall

Distribution of Childhood Primary Brain Tumours CBTRUS 2000-2004







Medulloblastoma

- 20% of paediatric brain tumours
- Propensity for leptomeningeal spread
- Craniospinal Radiotherapy (CSRT) essential
- ~ 30% have evidence of leptomeningeal spread at diagnosis
- Radiosensitive ('radio-curable') and chemosensitive
- Long-term toxicity of treatments problematic, particularly for infants

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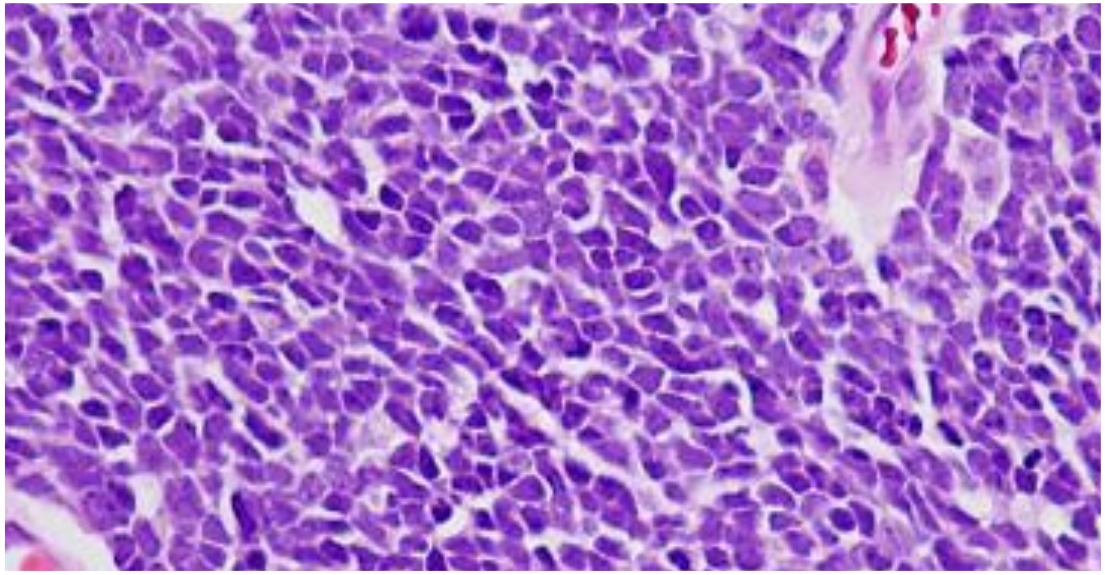
Medulloblastoma - Histology

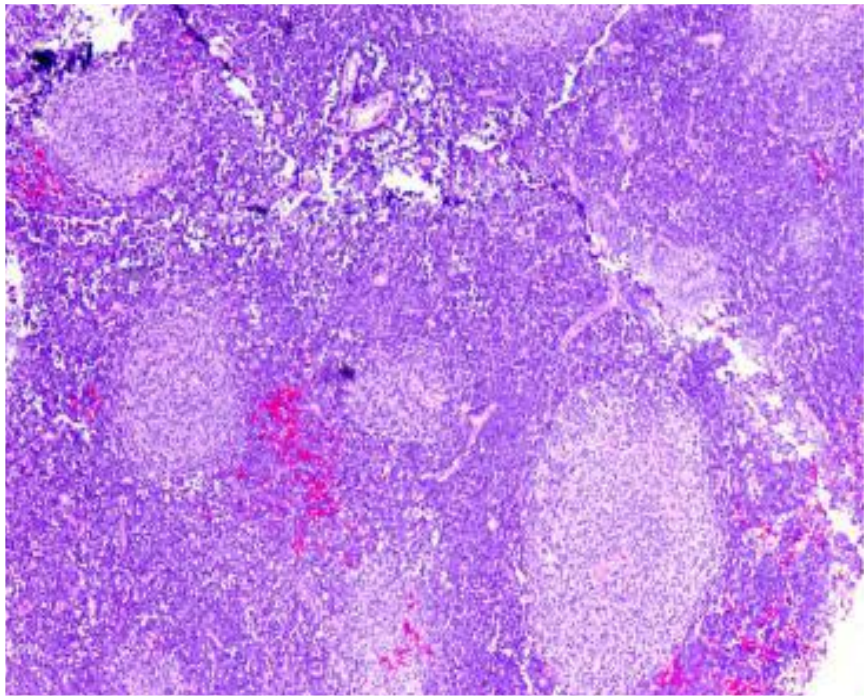
Medulloblastomas are malignant and invasive tumours classified as WHO grade IV

They are highly cellular neoplasms that are composed of cells with small to medium sized, hyperchromatic nuclei and little apparent cytoplasm.

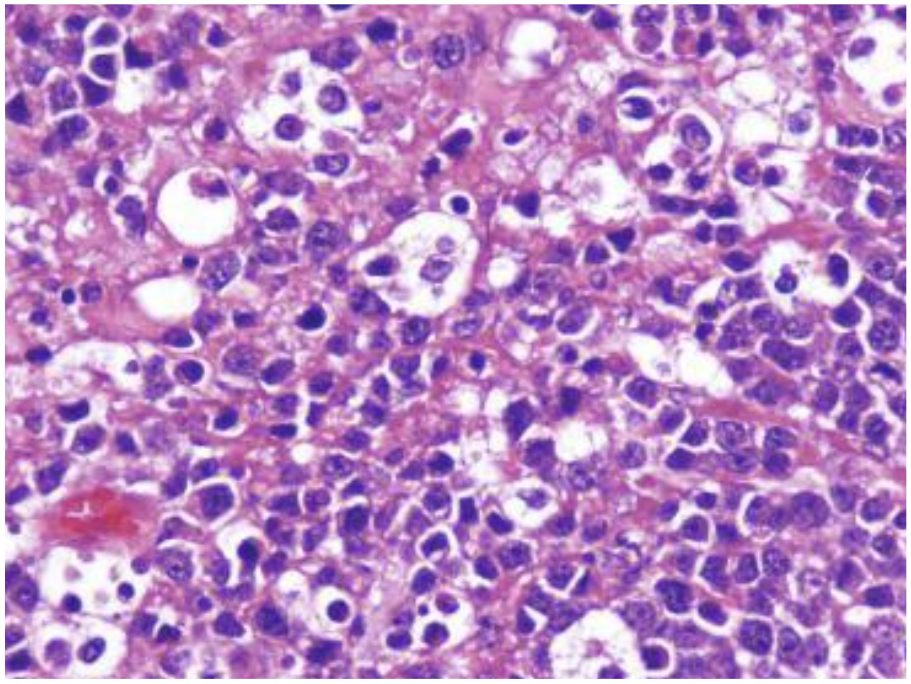


Classic medulloblastoma showing a diffuse pattern of tumor growth with poor cellular differentiation, nuclear molding, and minimal indistinct cytoplasm

Medulloblastoma
Histological Varieties



Nodular/desmoplastic



Large cell

Medulloblastoma histology
WHO 2016

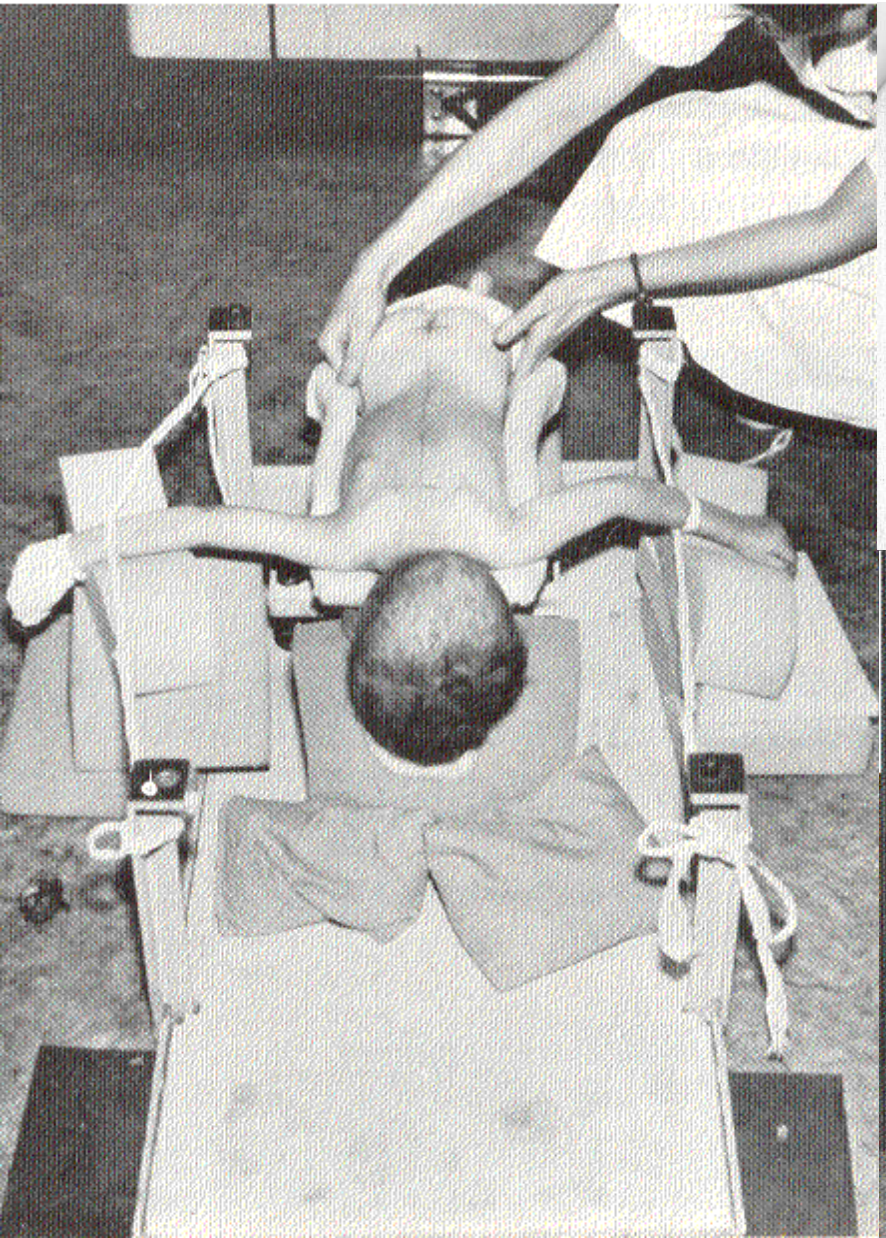
- There are long-established histological variants of medulloblastoma that have clinical utility (e.g., desmoplastic/nodular, medulloblastoma with extensive nodularity, large cell, and anaplastic)

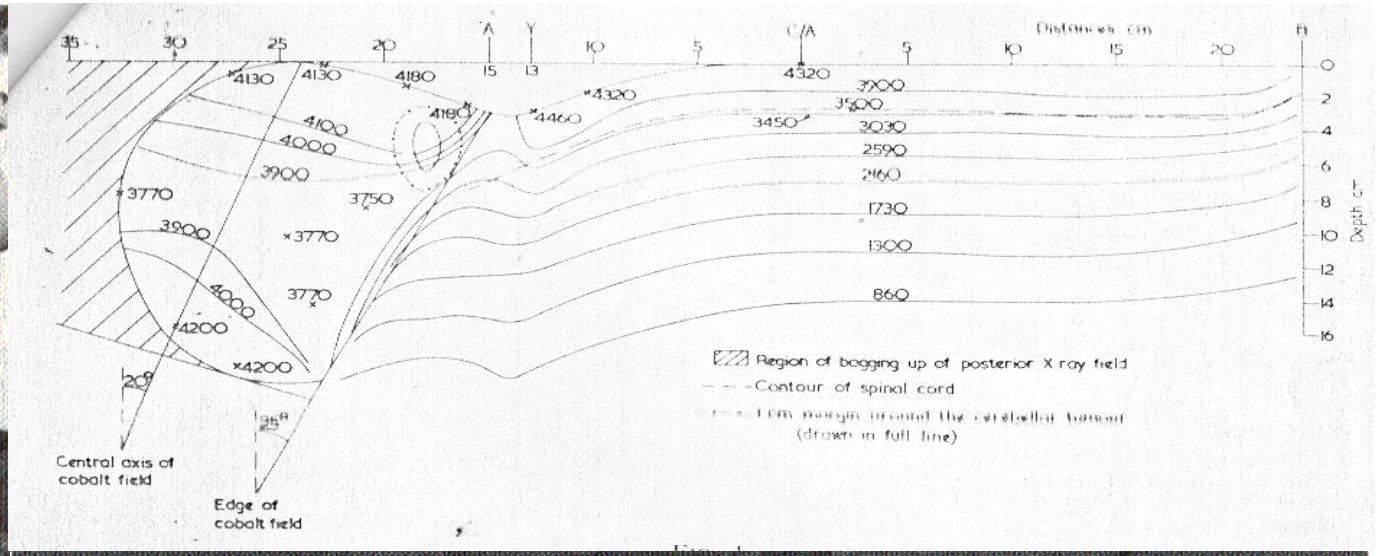
- It is now widely accepted that there are four molecular genetic groups of medulloblastoma: WNT-activated, SHH-activated, and the numerically designated “group 3” and “group 4”

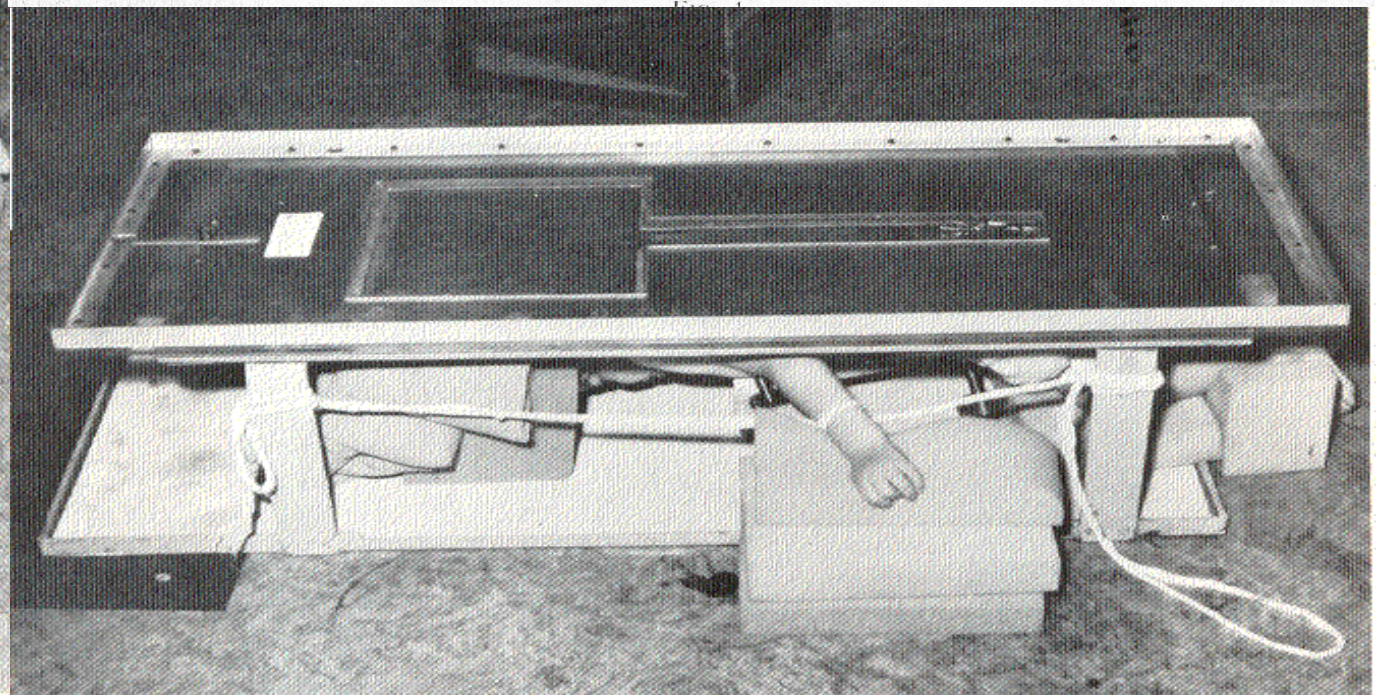
Craniospinal Radiotherapy History

- 1936 - Radiotherapy first used to treat medulloblastoma (Cutler et al)
- 1950s - Recognised by Paterson (1953) that there was a risk of CSF dissemination and that CSRT was necessary - orthovoltage CSRT
  - 1970s - megavoltage (^{60}Co) CSRT established
  - van Dyk et al 1977 (IJROBP 2: 993-1005)

Craniospinal Radiotherapy
London Hospital Technique
Bottrill et al, 1965, BJR 38 122-130







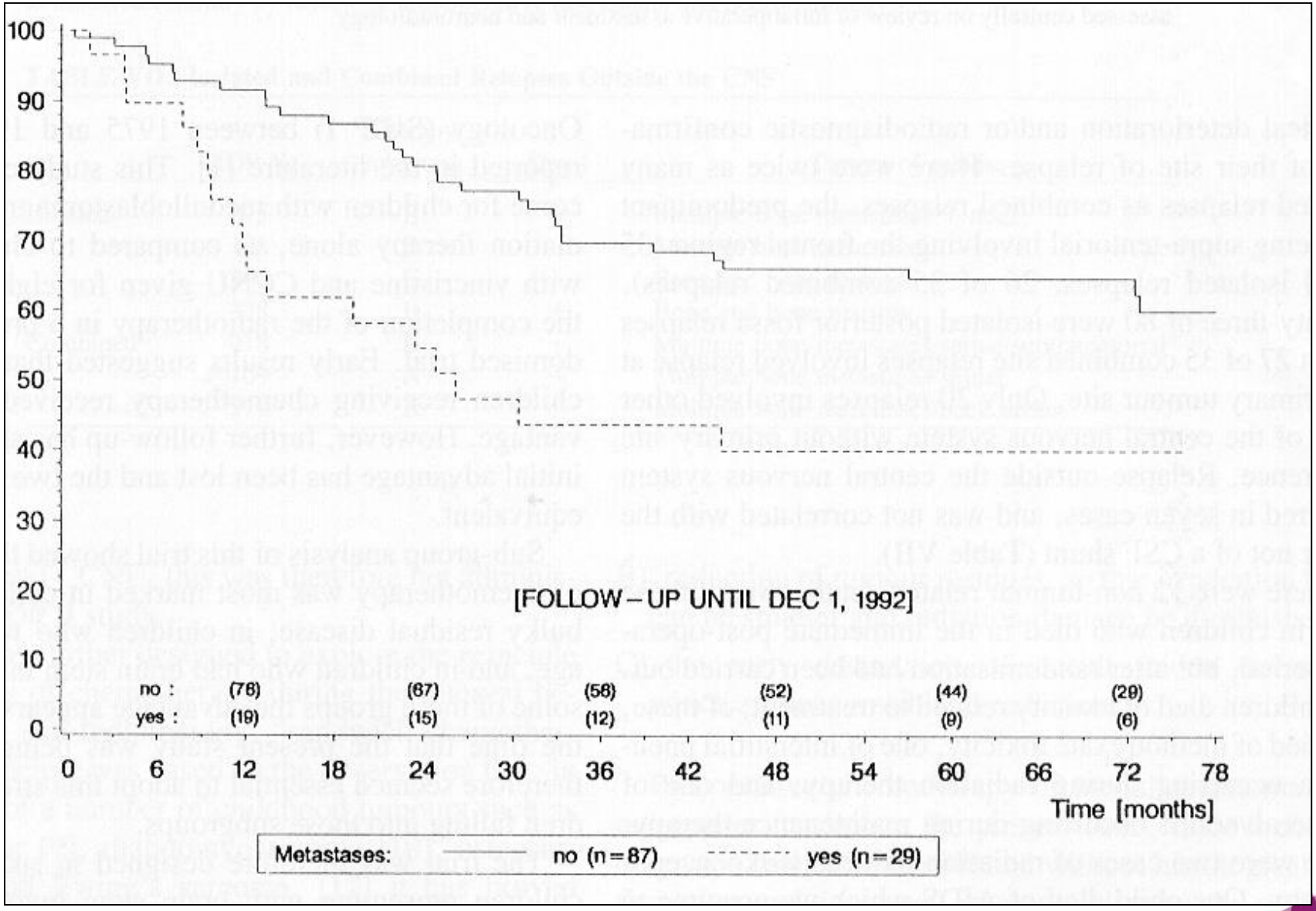
SIOP 1

- 1975-1979
- 286 patients with medulloblastoma, 45 patients with ependymoma
- Randomisation between RT alone and RT followed by VCR/CCNU for 1 year
- Overall survival 53% at 5 years, 45% at 10 years
- At close of trial survival advantage for chemotherapy (p=0.005), which was later lost owing to late relapses
  - Tait DM et al, Eur J Cancer 1990; 26: 464-469

SIOP 2

- 1984-1989
- 446 patients registered, 364 randomised
- Randomised study of pre-RT chemotherapy:
  - Procarbazine, VCR, MTX
- High-risk cases based on SIOP 1 parameters routinely given post-RT VCR/CCNU chemo
- No benefit for pre-RT chemotherapy
- Radiotherapy dose randomisation (35 Gy vs 25 Gy) for low-risk cases
  - Bailey CC et al, Med Pediatr Oncol 1995; 25: 166-178

SIOP II - Event-free Survival for High Risk Patients With or Without Metastases at Diagnosis



Medulloblastoma - Randomised Studies of Craniospinal RT Dose

- SIOP II (1984-1989)
- 25 Gy - 55.3% 5 year EFS
- 35 Gy - 67.6% 5 year EFS
- p = 0.07

- POG/CCG (1986 - 1990)
- 23.4 Gy - 52% 8 year EFS
- 36.0 Gy - 67% 8 year EFS
- p = 0.141

PNET-3

Results of a Randomized Study of Preradiation Chemotherapy Versus Radiotherapy Alone for Nonmetastatic Medulloblastoma: The International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 Study

By Roger E. Taylor, Clifford C. Bailey, Kath Robinson, Claire L. Weston, David Ellison, James Ironside, Helen Lucraft, Richard Gilbertson, Diana M. Tait, David A. Walker, Barry L. Pizer, John Imeson, and Linda S. Lashford

- 1992 - 2000
- 169 medulloblastoma patients randomised
- Supratentorial PNET – later excluded, but analysed separately

Journal of Clinical Oncology, Vol 21, No 8 (April 15), 2003: 1581-1591

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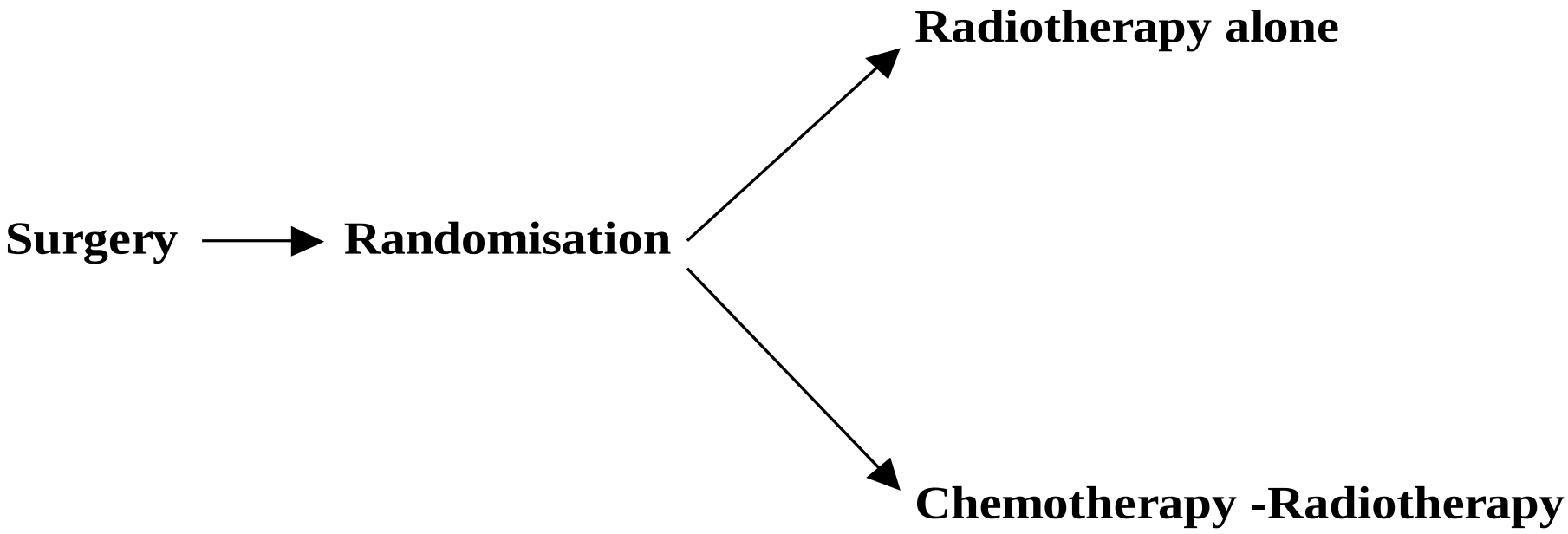
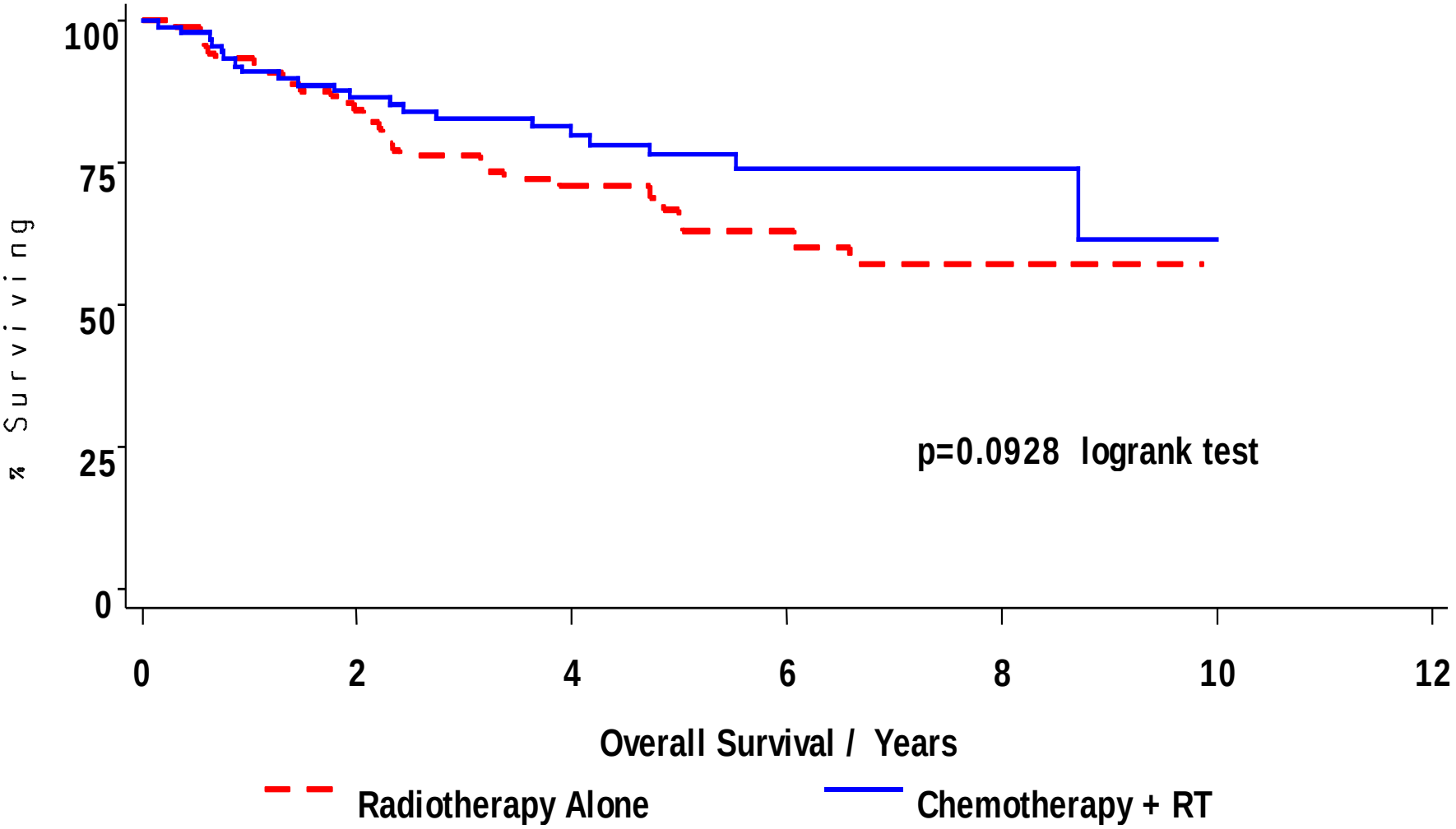
SIOP/UKCCSG PNET-3
TRIAL SCHEMA
1992 - 2000



Carboplatin, Cyclophosphamide, Etoposide, Vincristine

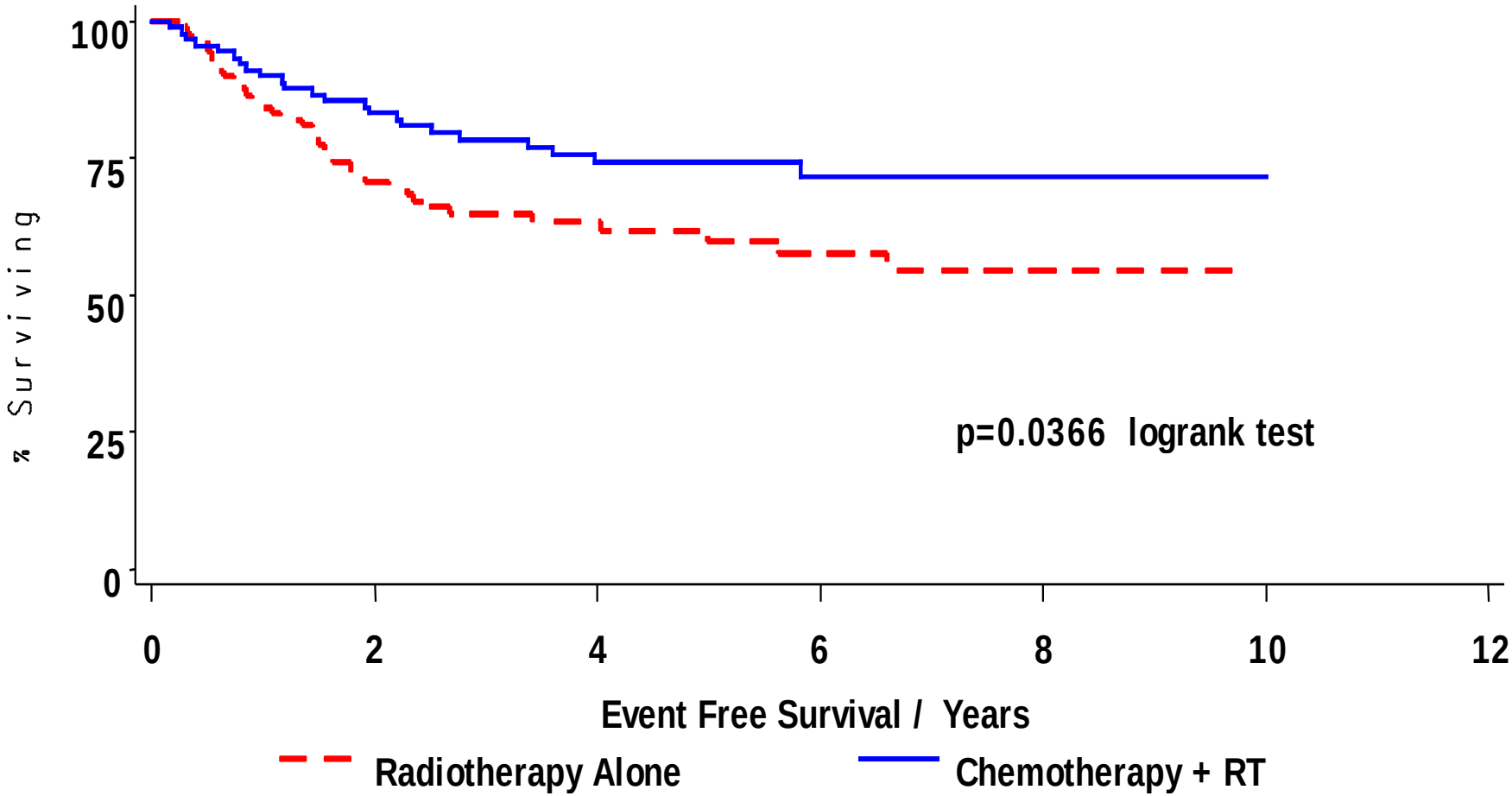
SIOP/UKCCSG PNET-3

Overall Survival According to Treatment Allocated



SIOP/UKCCSG PNET-3

Event-Free Survival According to Treatment Allocated



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SIOP/UKCCSG PNET-3 Multivariate Analysis for Event-Free Survival

Variable	Parameter Estimate	Standard Error	Chi - Squared	p	Hazard Ratio
Time To Complete RT	0.728	0.283	6.63	0.0100	2.07
Treatment Allocated	0.633	0.282	5.03	0.0248	1.88

Treatment with chemotherapy and completing radiotherapy within 50 days had a significant impact on EFS in multivariate analysis

Reduced Health Status Following Pre-RT Chemotherapy and Craniospinal Irradiation

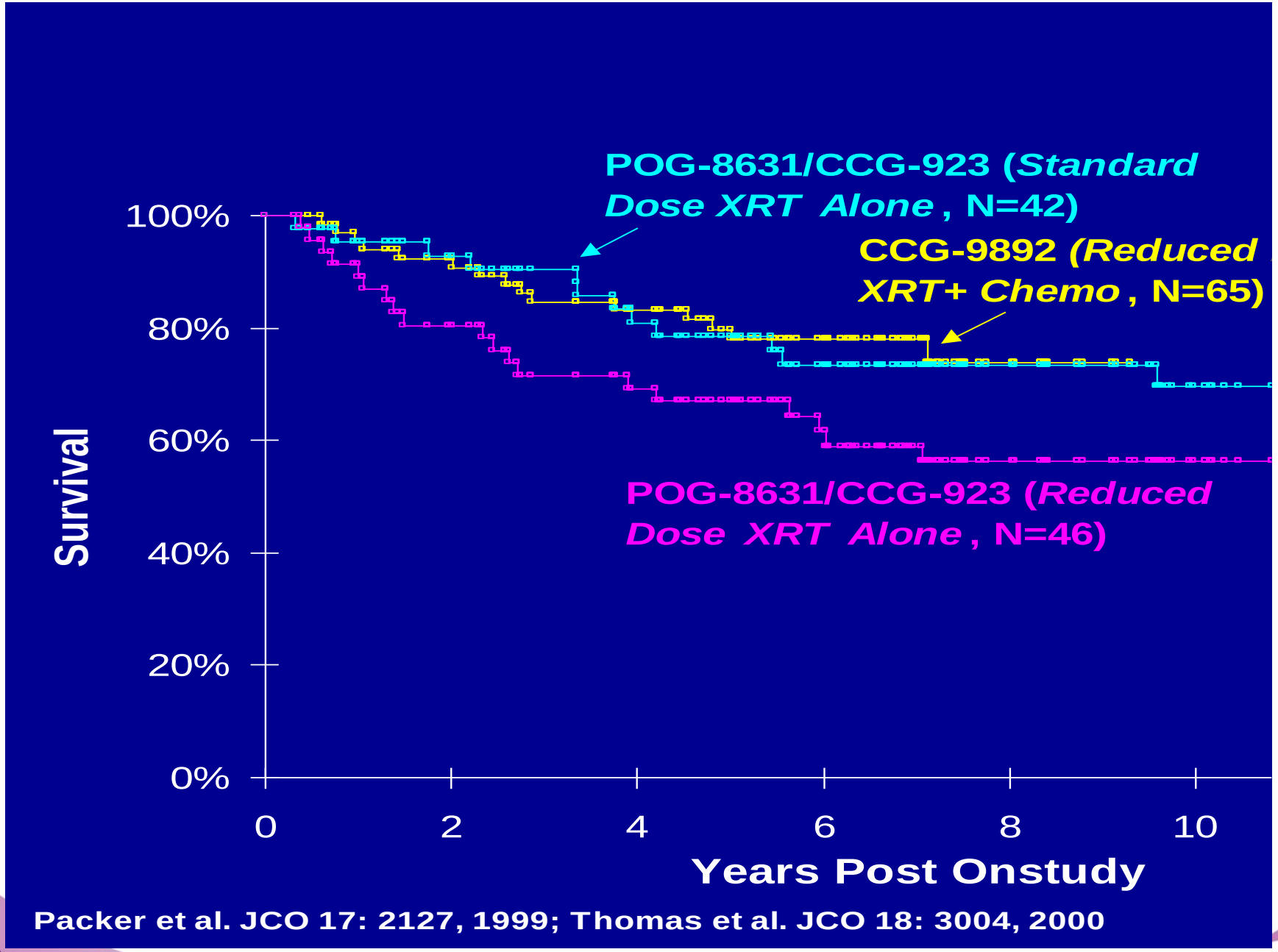
- PNET-3 Study (1992-2000) – Randomised Study of Pre-RT chemotherapy vs RT alone
- 73% of 147 eligible patients aged 6.6 to 24.3 years were assessed at a mean of 7.2 years after diagnosis
- Health status was significantly poorer in the group treated in the CSI plus CT arm of the trial
- Also trends to poorer outcomes for behaviour and quality of life scores
- The CSI plus CT group were also significantly more restricted physically and needed more therapeutic and educational support

- Bull KS, Spoudeas HA, Yadegarfar G, Kennedy CR
- J Clin Oncol 2007; 25: 4239-4245

HIT 91, Patients aged 6-18
Kortmann et al, 2000, IJROBP 46, 269-279

- 1991 - 1997
- 158 patients enrolled, 137 randomised
- Sandwich chemotherapy (ifosfamide, etoposide, MTX, cisplatin, cytarabine) vs post-RT CVP
- Overall 3 year RFS 70%
- M0: 72%, M1: 65%, M2/3: 30%
- M0-1 – Pre-RT chemotherapy: 65%
- Immediate RT: 78% (p = <0.03)

Reduced Dose Radiotherapy Is Feasible in Standard-Risk Medulloblastomas If Combined with Adjuvant Chemotherapy



Packer et al. JCO 17: 2127, 1999; Thomas et al. JCO 18: 3004, 2000

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Infant (age < 3) Medulloblastoma

- Late effects problematic
- Higher risk of M+ disease
- Historically poor prognosis
- Relatively lower proportion have received a complete resection compared with older children
- Generally RT avoidance strategies have resulted in adverse disease control outcomes
- GPOH study of chemotherapy alone successful in infants with desmoplastic histology – includes intraventricular methotrexate
- Intensive chemotherapy – long-term outcomes not clear
- Balance between tumour control and toxicity still unclear
- Ongoing clinical trials

Medulloblastoma Staging

- LP with cytospin > 14 days after surgery
- Craniospinal MR imaging
  - Preferably pre-operatively, but if post-operative should be 24-72 hours after surgery
- Post-operative cranial MR to assess amount of post surgical residue

Medulloblastoma
Chang Staging

- M0 - No evidence of metastases
- M1 - No metastases on scan, but unequivocal tumour cells seen in CSF from LP >14 days after surgery
- M2 - Metastases in supratentorial meninges
- M3 - Metastases in spinal meninges
  - [M4 – metastases beyond CNS]

MB Risk Groups (early 2000s)

- **Standard (Average) Risk:**
- Chang Stage M0, complete resection or <1.5 cm^2 residual tumour on post-operative MR 24-72 hours after surgery

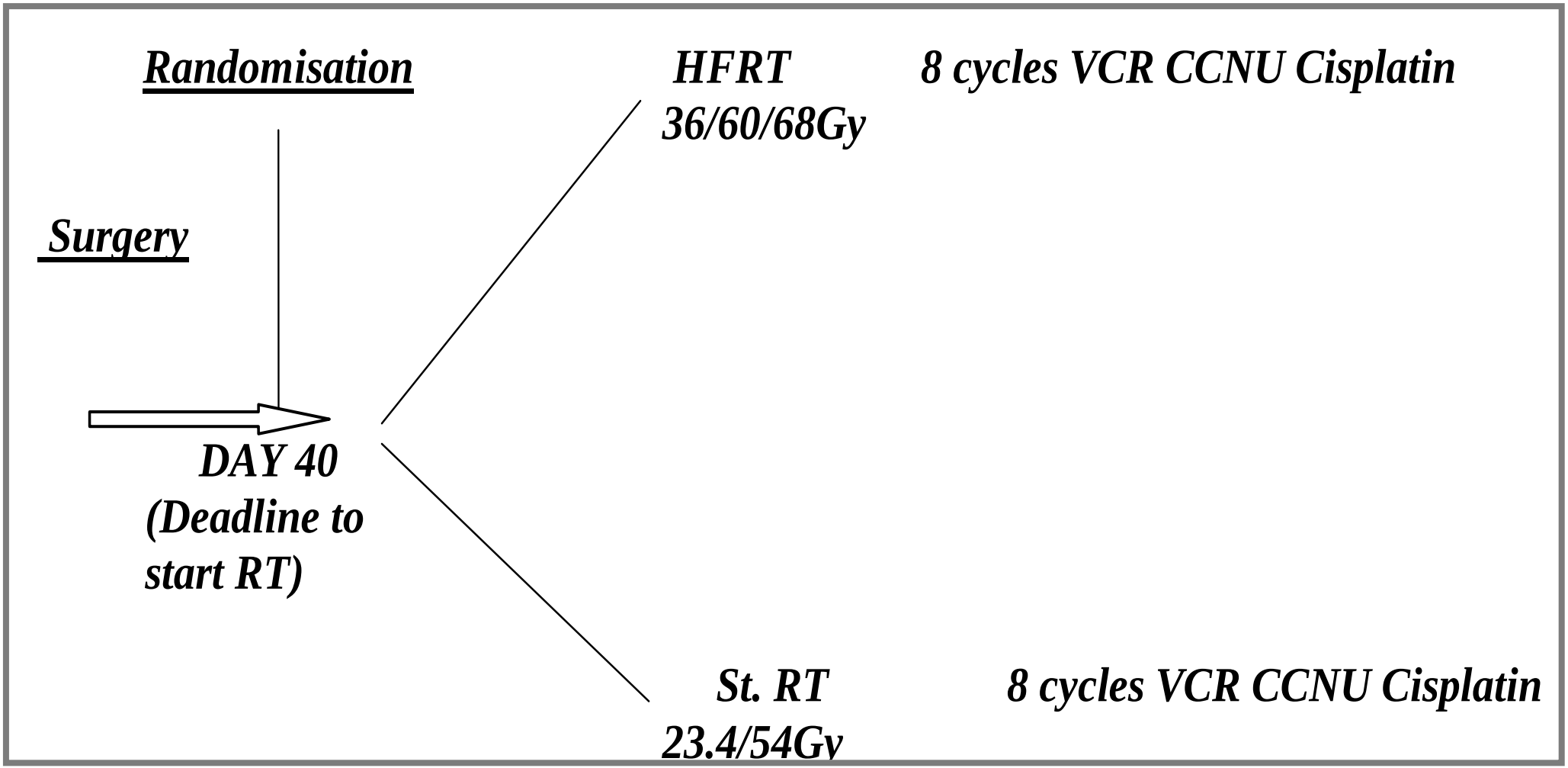
- **High risk:**
- M1-3 and/or >1.5 cm^2 residual tumour on post-operative MR 24-72 hours after surgery
- Supratentorial PNET

- *Large Cell Anaplastic Histology*

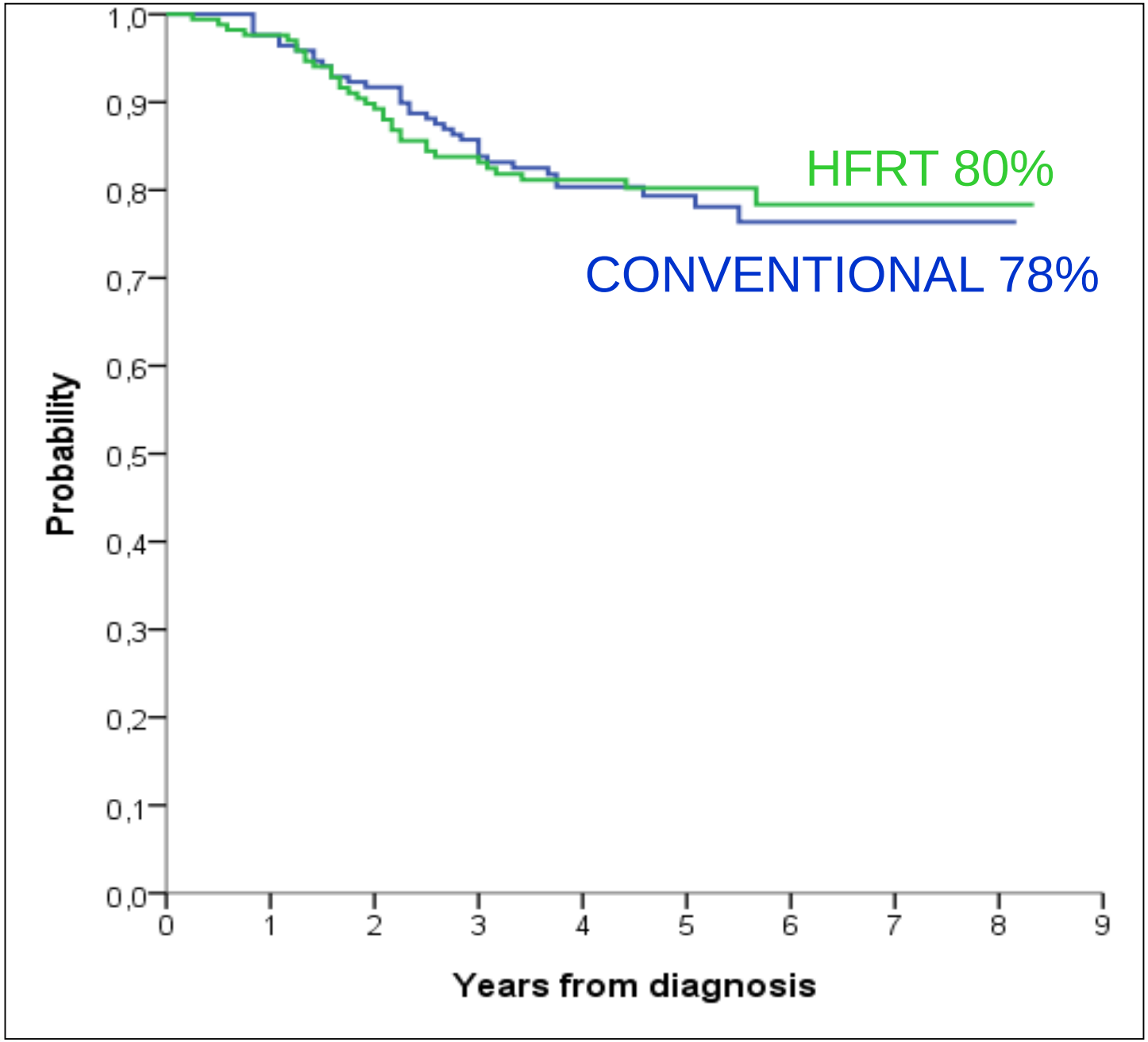
HIT/SIOP Study for Non-Metastatic (M0) Medulloblastoma (PNET-4)

- 2000 - 2006
- Can HFRT improve therapeutic ratio for RT?:
- Can event-free survival be improved without an increase in neuropsychological long-term effects?
- Standardised assessment of long-term effects - Health Utilities Index (HUI), endocrine assessment
- Prospective evaluation of biological markers

HIT/SIOP PNET-4
M0 Medulloblastoma



PNET-4 Event-Free Survival



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PNET-4 Analysis

- Patients with postoperative residual tumour >1.5cm² had a significantly inferior prognosis compared to patients without residual tumour
- EFS at 5 years 64% vs 82±2%, p<0.01
- Patients with RT starting < 49 days after surgery had a 5 year EFS of 81% compared with 67% for patients who commenced RT >= 49 days after surgery, p=0.04

Quality of Survival and Growth in Children and Young Adults in the PNET4 European Controlled Trial of Hyperfractionated Versus Conventional Radiation Therapy for Standard-Risk Medulloblastoma

Colin Kennedy, MBBS, MD,* Kim Bull, PhD,* Mathilde Chevignard, MD,†,‡ David Culliford, MSc,* Helmuth G. Dörr, MD,§ François Doz, MD,‖ Rolf-Dieter Kortmann, MD,¶ Birgitta Lannering, MD,# Maura Massimino, MD,** Aurora Navajas Gutiérrez, MD,†† Stefan Rutkowski, MD,‡‡ Helen A. Spoudeas, MD,§§ and Gabriele Calaminus, MD,‖‖, on behalf of the, PNET4 study group of the Brain Tumour Group of The European branch of the International Society of Paediatric Oncology (SIOP-E)

Int J Radiat Oncol Biol Phys 2014; 88: 292e300

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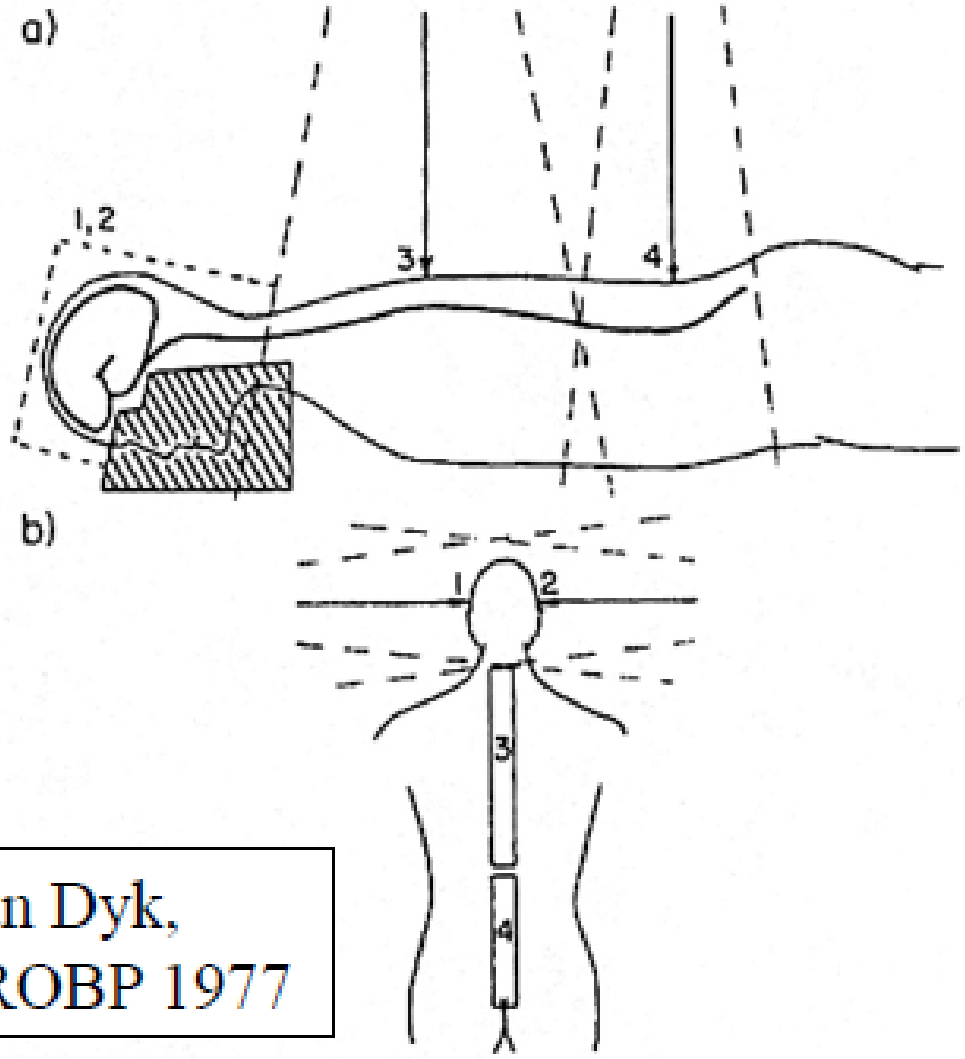
Kennedy et al

- Standardised questionnaires on executive function, health status, behaviour, health-related quality of life, and medical, educational, employment, and social information
- Data were provided by 151 of 244 eligible survivors (62%) at a median age at assessment of 15.2 years and median interval from diagnosis of 5.8 years

Kennedy et al, 2014

- Hyperfractionated Radiotherapy (HFRT) was associated with better executive function and worse growth but without accompanying change in health status, behaviour, or quality of life

Standard CSRT Technique



Van Dyk, IJROBP 1977

- Patient prone in a head rest with neck extended
- Junction of non-coplanar fields over the cervical spine
- Extended SSD or second posterior field to cover whole length of spine/second junction over the spinal cord

Target Volumes

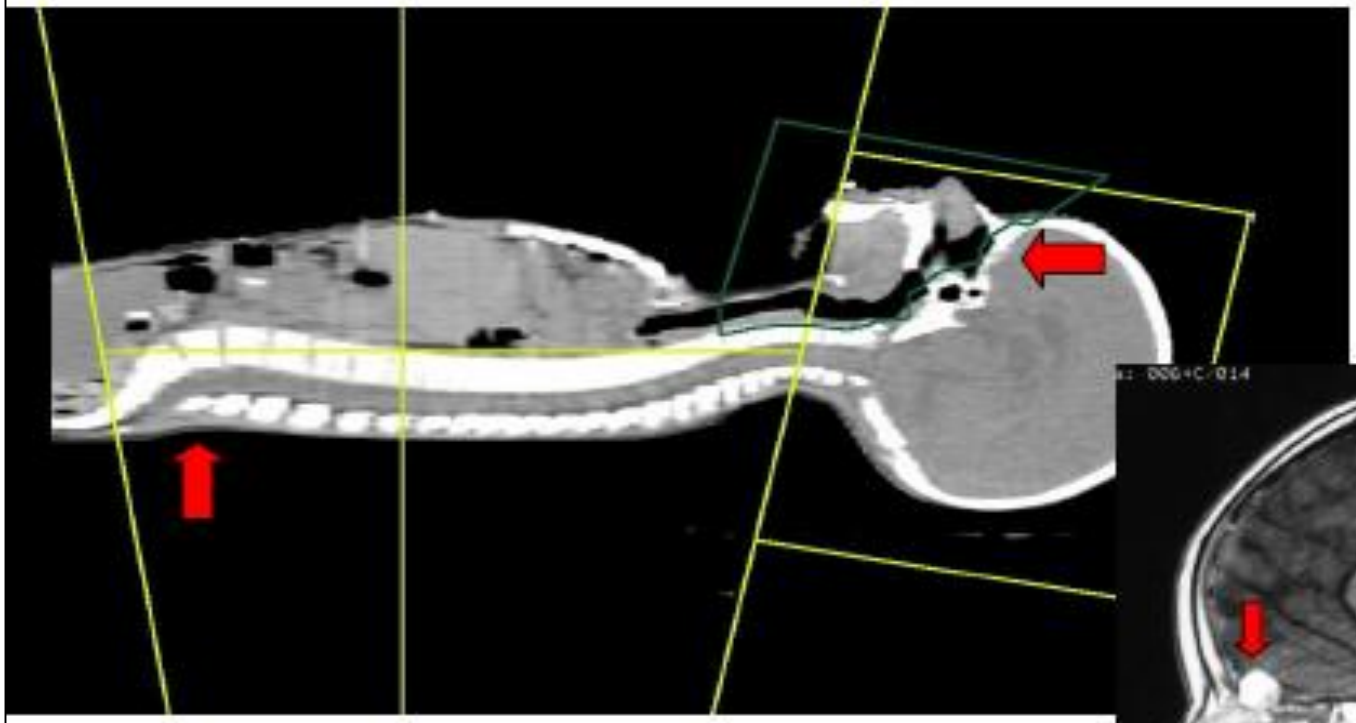
- Craniospinal Axis
- Posterior Fossa
- Tumour Bed

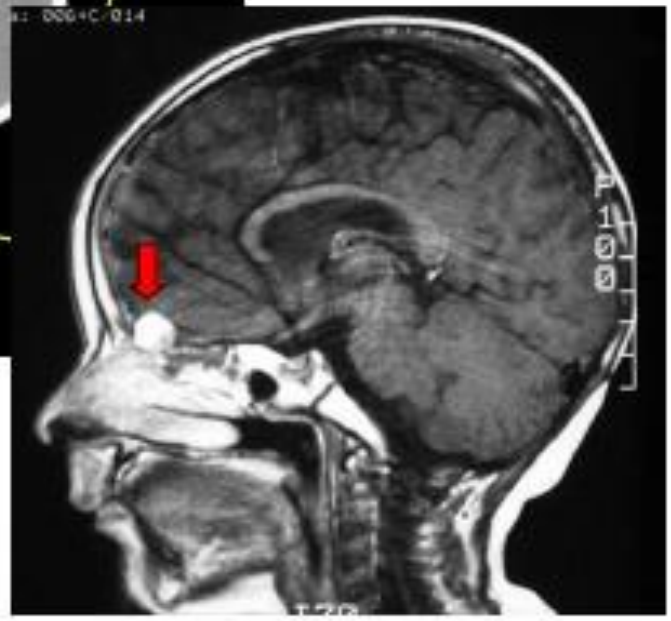
Target Volume (CTV)
Cranial Fields

- Meninges surrounding whole brain and ventricular system
- Particular attention to cribriform fossa, temporal fossa, base of skull
- Irradiate the full width of vertebrae for children

Target Volume for CSRT

- Problem areas:
  - frontal region/ cribriform plate
  - caudal extent of thecal sac

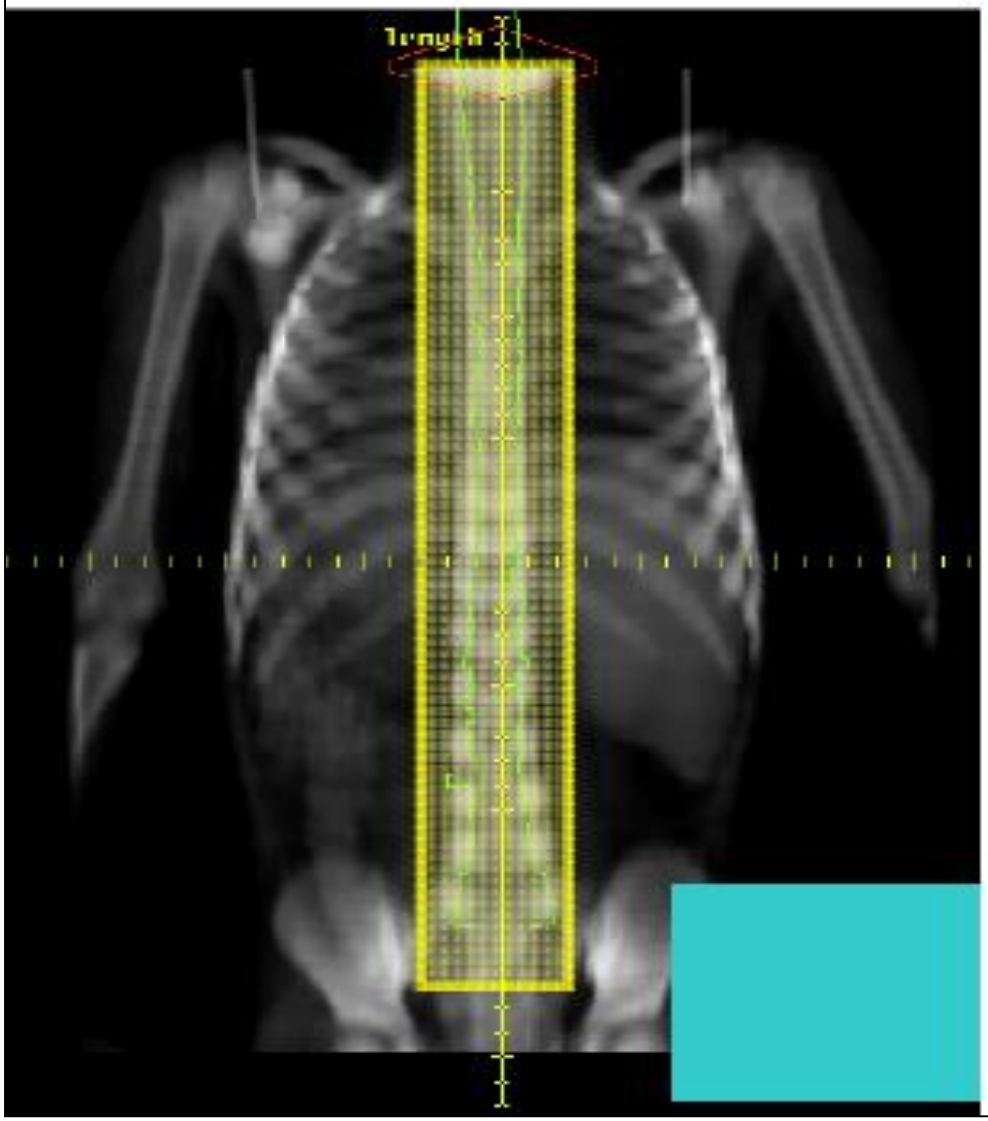




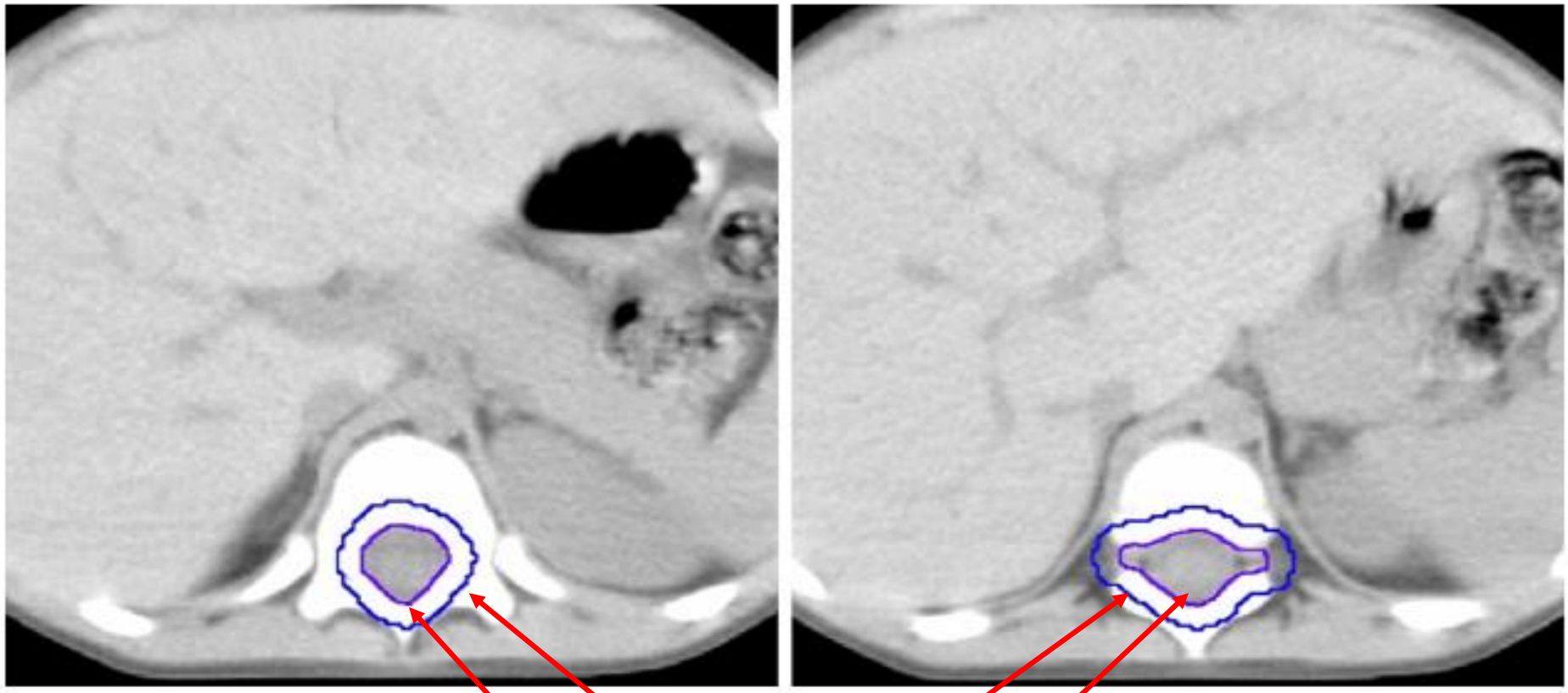
Target Volume (CTV)
Spinal Fields

- Meninges extending to the lower border of the thecal sac as determined by MR scanning

- Extensions of nerve roots as far as intervertebral foramena



- ACNS0331:
  - "...laterally on both sides to cover the recesses of the entire vertebral bodies, with at least 1cm margin on either side"
  - Lower limit "...2 cm below the termination of the subdural space"..."at least to the inferior border of the 2nd sacral segment (S2/3 interspace)"



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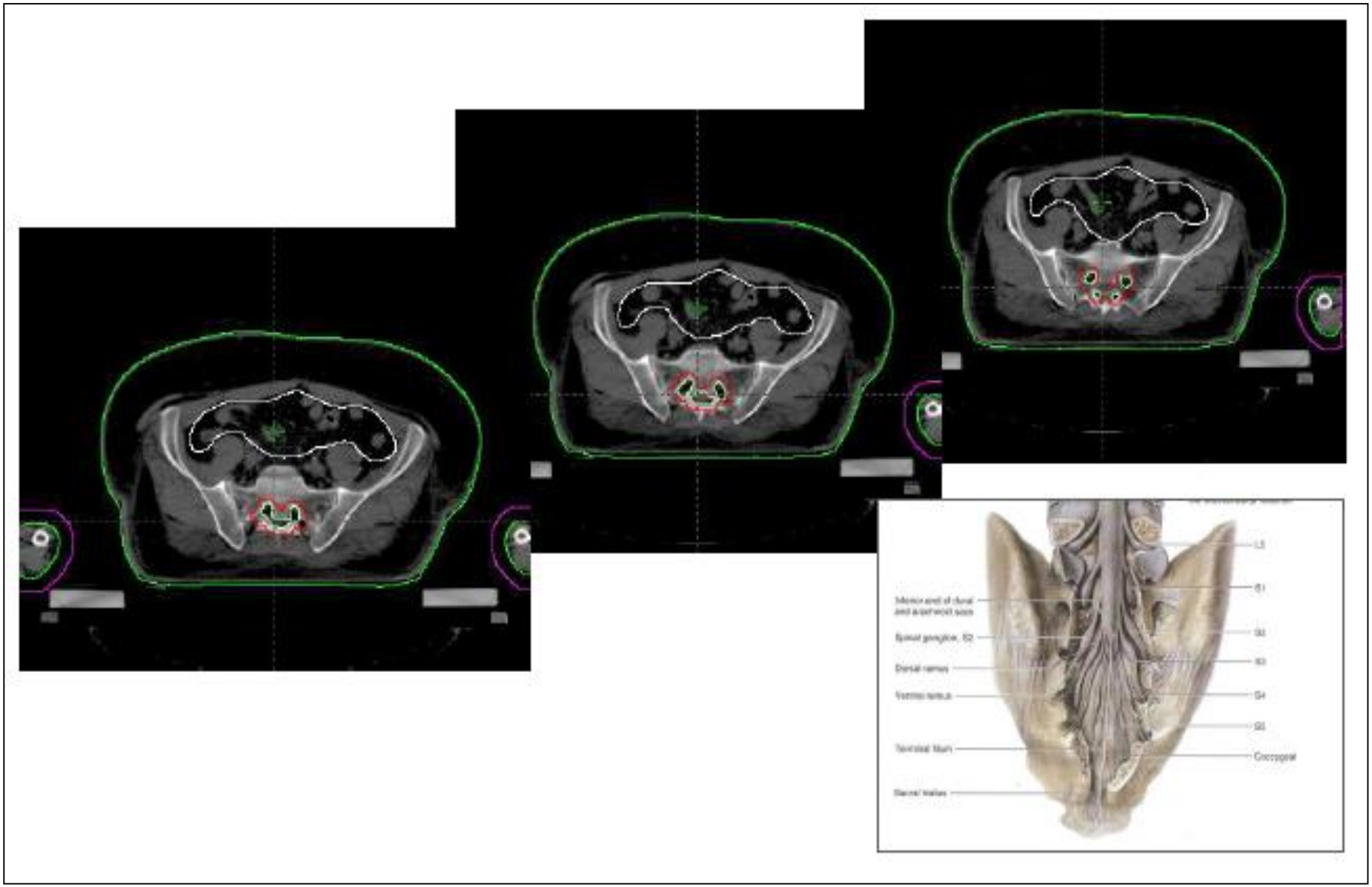
Target Volume for CSRT
Sacral Roots



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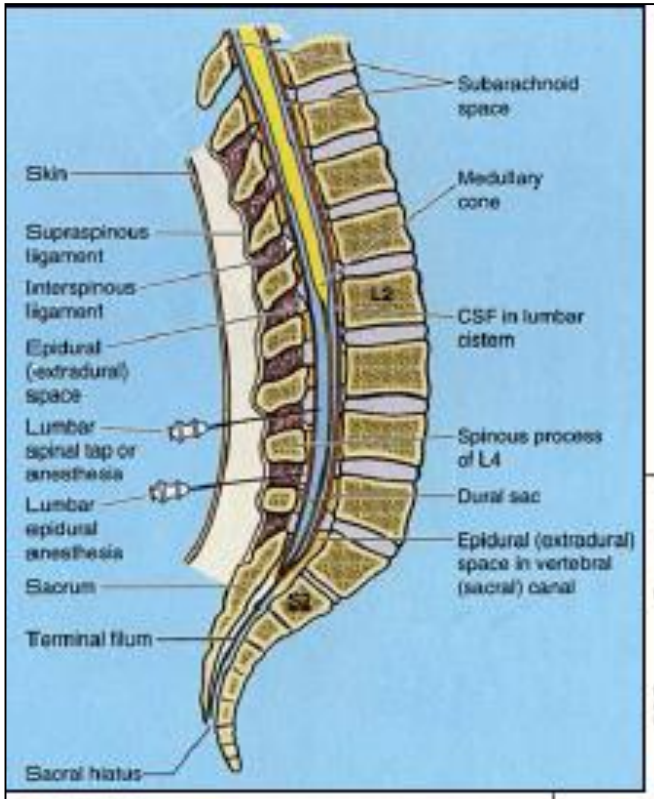
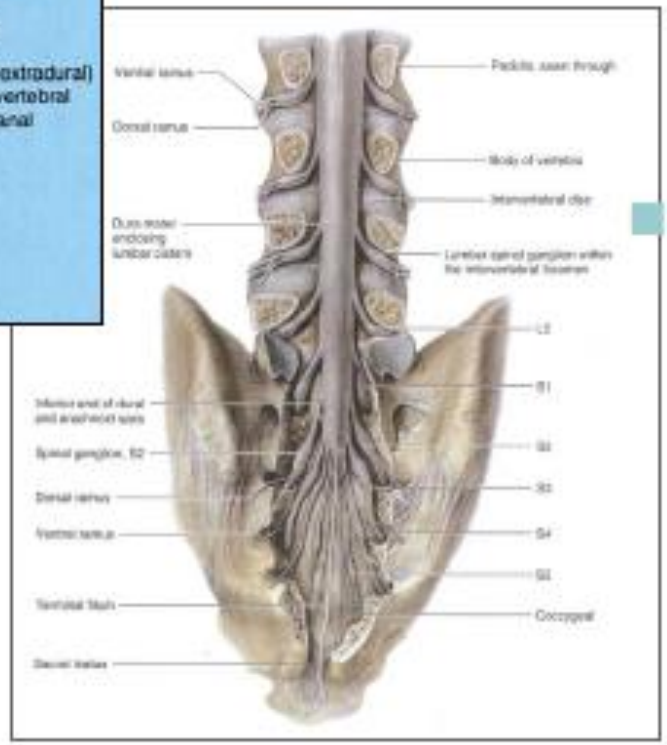
CSRT – Thecal Sac





- Dural sac "generally" ends at S1/2
- But:
  - ~50% by bottom S1
  - >90% by bottom S2
  - <10% above L5/S1
- MRI is **essential** for accurate determination of the caudal extent of the thecal sac

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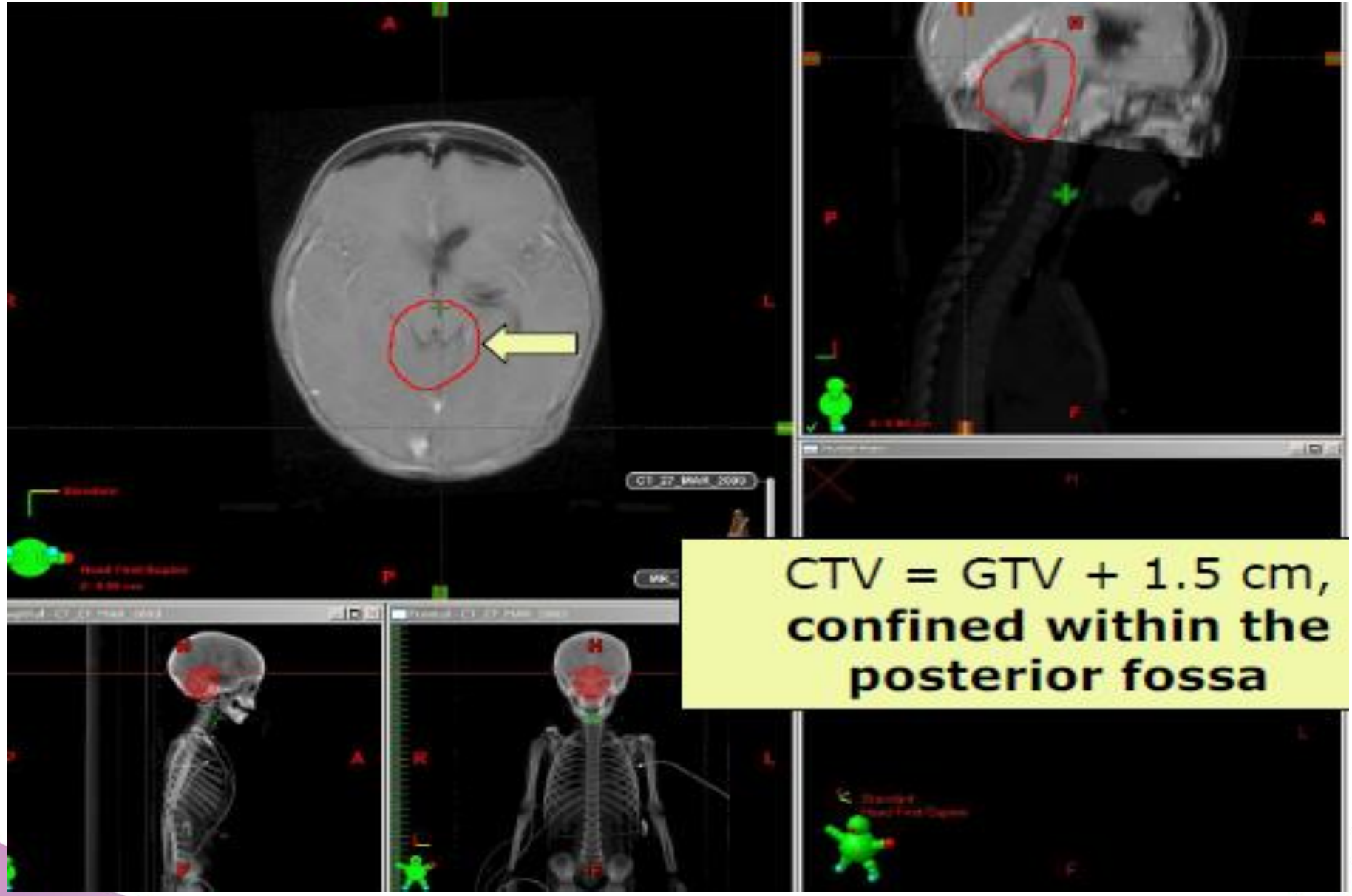
Target Volume (CTV)
Whole Posterior Fossa

- Meninges surrounding the cerebellum as far as tentorium
- Spinal cord meninges 2 cm beyond lower limit of tumour
- Include post-operative meningocoel

Target Volume for Tumour Bed RT

- GTV:
- Any residual tumour on imaging
- Post-surgical cavity including tumour/brain interface prior to resection
- Allow for post-surgical changes to anatomy
- CTV margin – varies according to trial - 1.0 cm for future SIOP trials
- PTV according to institutional policy

Medulloblastoma
Tumour Bed Boost



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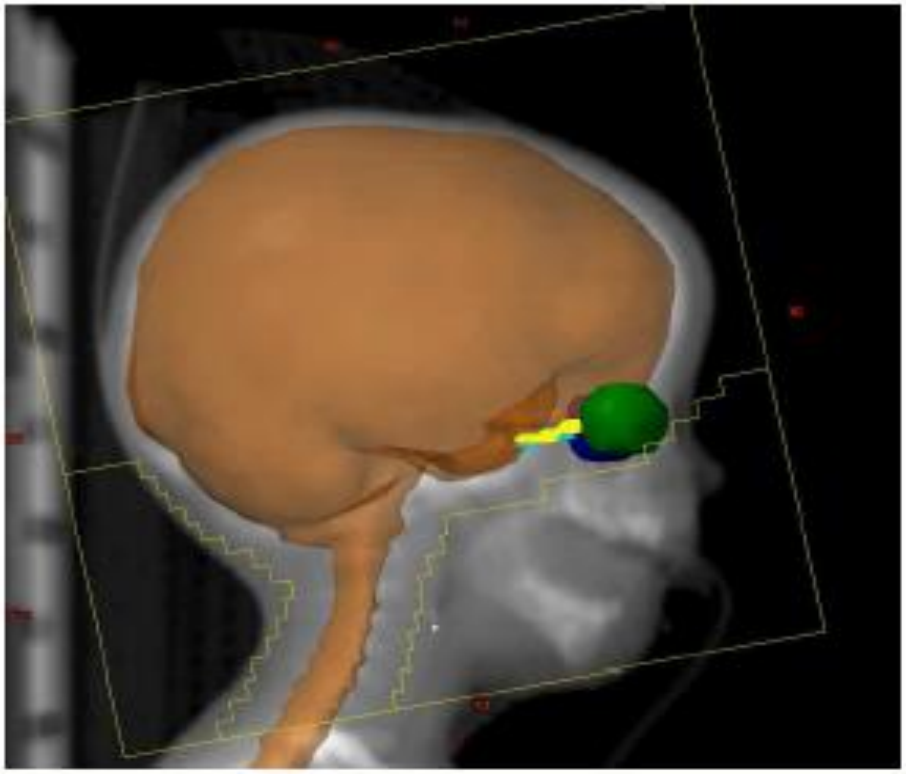
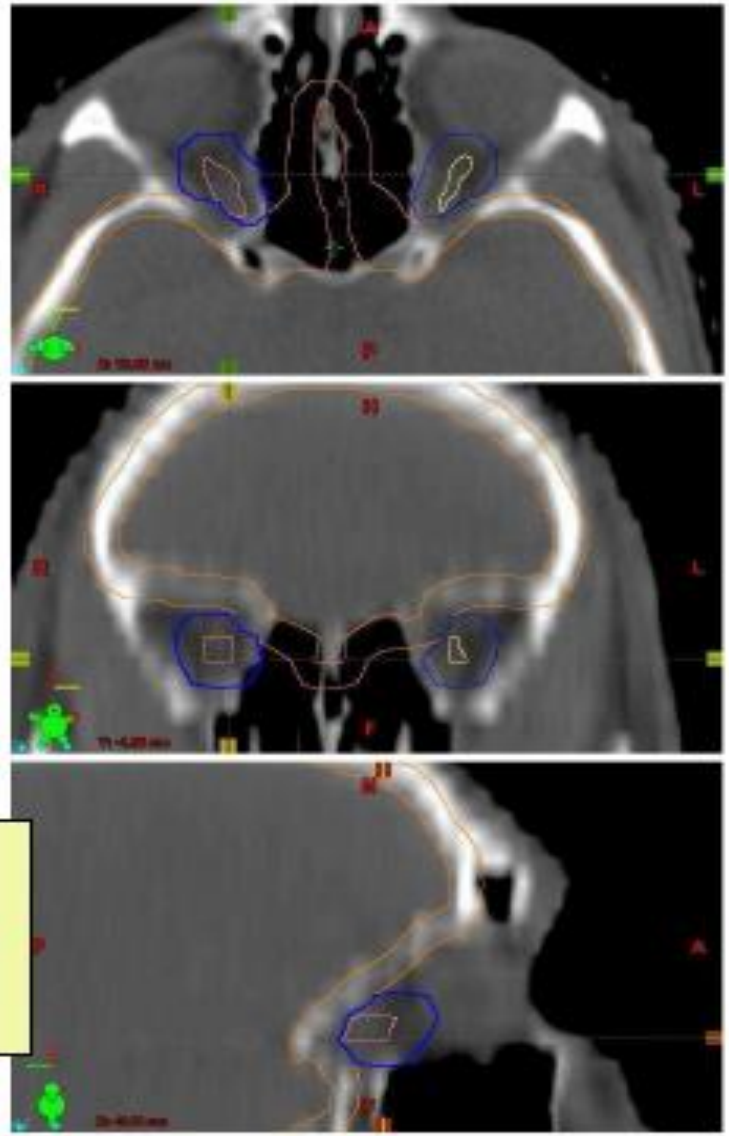
Target Volume for CSRT
Optic Nerves?





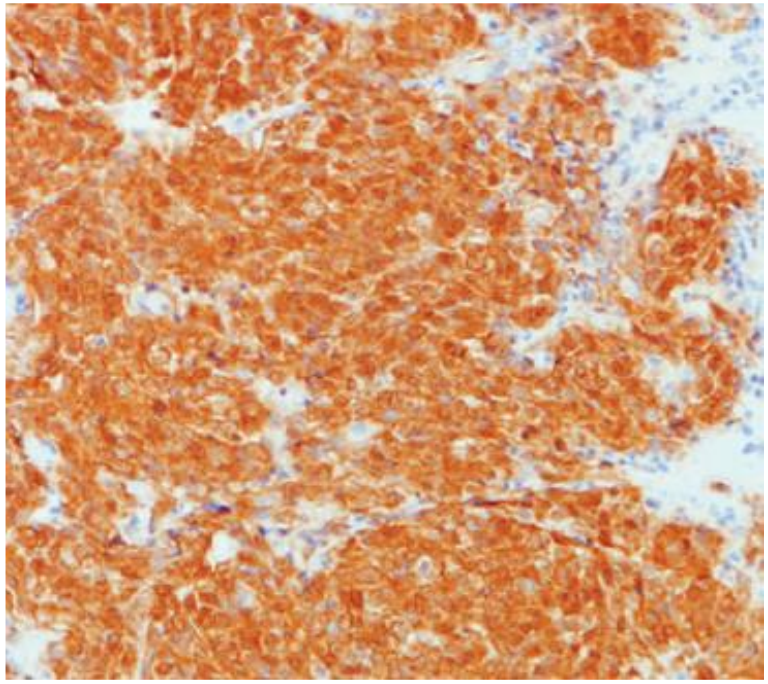
Dose to optic nerve PTV (V95%):
- 3D CRT 99% (range 95%–100%)
- Tomotherapy 81% (range 49.9%–96%)

Definition of Disease-Risk Stratification Groups in Childhood Medulloblastoma Using Combined Clinical, Pathologic, and Molecular Variables

David W. Ellison, Mehmet Kocak, James Dalton, Hisham Megahed, Meryl E. Lusher, Sarra L. Ryan, Wei Zhao, Sarah Leigh Nicholson, Roger E. Taylor, Simon Bailey, and Steven C. Clifford

- β-Catenin nuclear and cytoplasmic immunoreactivity in MB with Wnt pathway activation

- Indication of good prognosis



Biological characterisation of tumours leading to subgroups based on clinical and biological parameters from PNET-3

Acta Neuropathol
DOI 10.1007/s00401-011-0800-8

ORIGINAL PAPER

Medulloblastoma: clinicopathological correlates of SHH, WNT, and non-SHH/WNT molecular subgroups

David W. Ellison · James Dalton · Mehmet Kocak · Sarah Leigh Nicholson · Charles Fraga · Geoff Neale · Anna M. Kenney · Dan J. Brat · Arie Perry · William H. Yong · Roger E. Taylor · Simon Bailey · Steven C. Clifford · Richard J. Gilbertson

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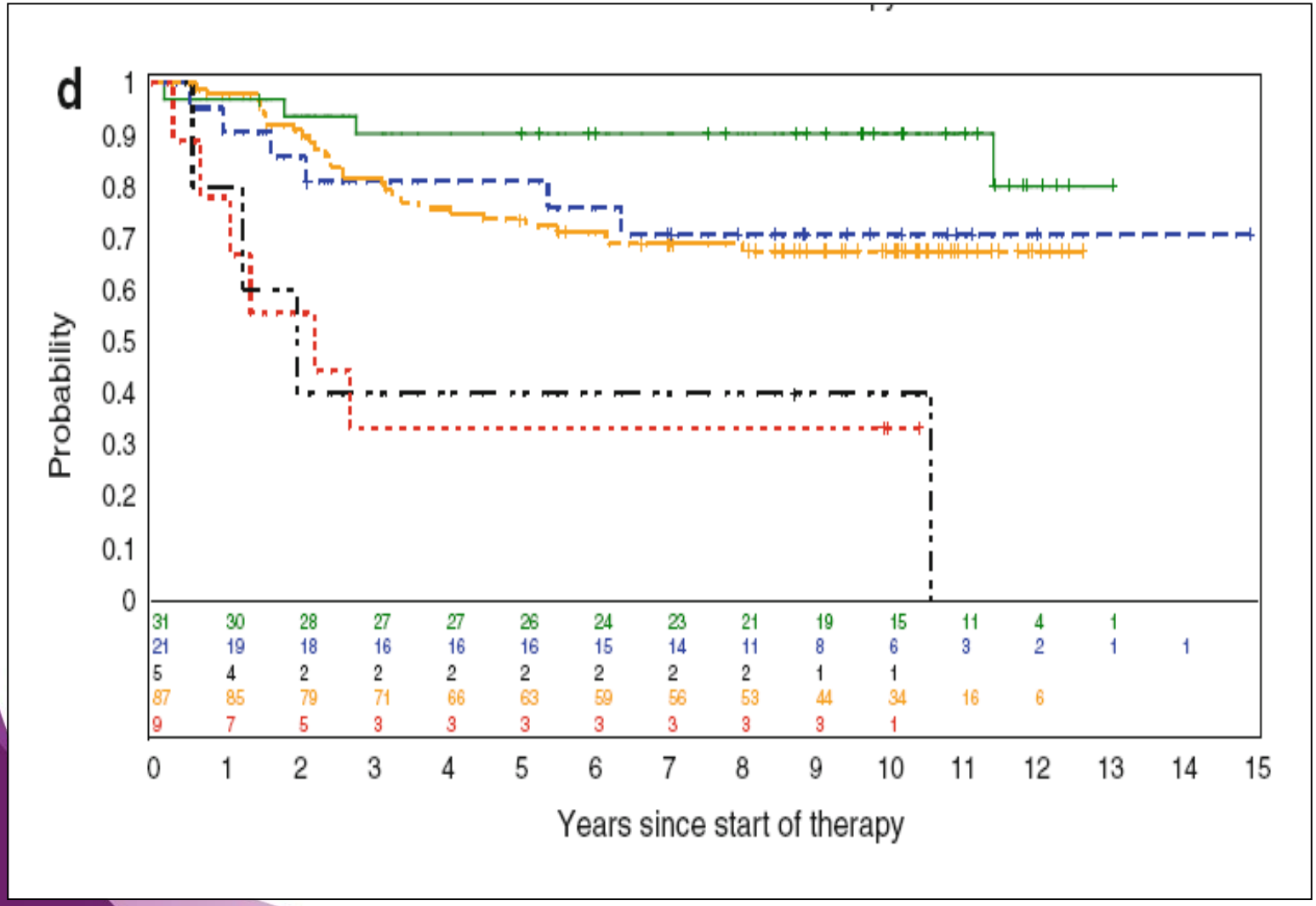
Prognosis Based on Combined Clinical, Pathological and Biological Parameters from PNET-3 Study

SR=M0, non-LCA, MYC-, HR=M+ or LCA or MYC+



Wnt
SHH St risk
non-SHH/Wnt SR
SHH HR
Non SHH/Wnt HR

Ellison et al
Acta neuropathol
2011

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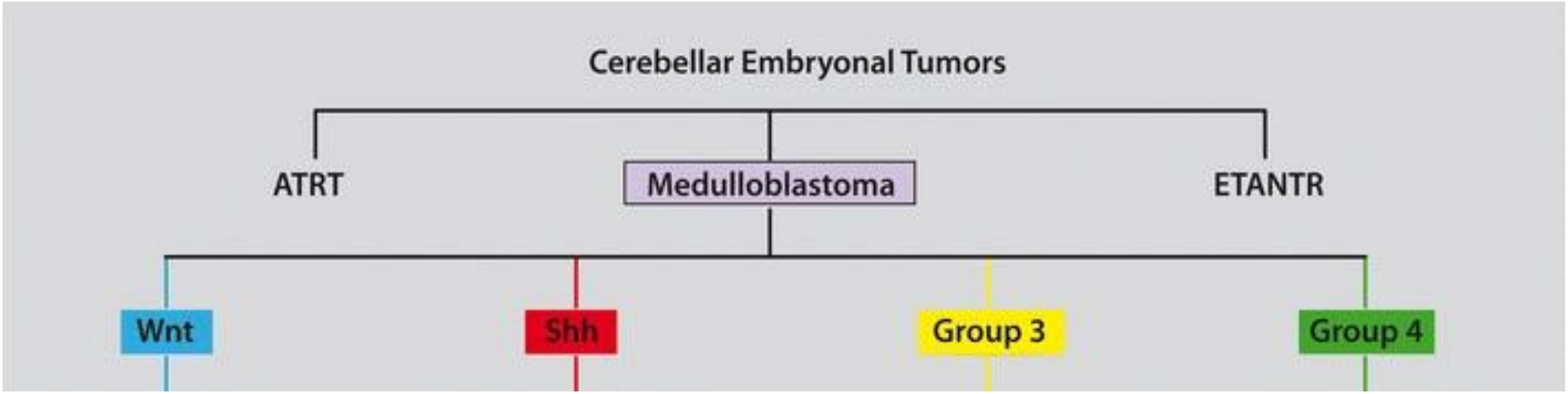
New Concept for Embryonal Tumours



ETANTR
Embryonal Tumor with Abundant Neuropil and True Rosettes

Medulloblastoma Histopathology WHO 2016

- (i) Medulloblastoma, WNT-activated
- (ii) Medulloblastoma, SHH-activated, TP53-mutant
- (iii) Medulloblastoma, SHH-activated, TP53-wildtype
- (iv) Medulloblastoma, non-WNT/non-SHH, Group 3
- (v) Medulloblastoma, non-WNT/non-SHH, Group 4

WNT Medulloblastoma

- Very good prognosis
- Long-term survival > 90%
- Majority have classical histology
- Beta-catenin nucleo-positivity, *CTNNB1* gene mutations, and monosomy 6
- Rarely the WNT subgroup may include large cell/anaplastic cases. Can occur at all ages, but is infrequent in infants
- M:F ratio approximately 1:1

SHH Medulloblastoma

- Include *TP53*-mutant and *TP53*-wildtype subgroups
- Named after the sonic hedgehog signalling pathway, considered to drive tumour initiation in the majority of cases
- Frequency bimodal, and is frequent in both infants aged less than 3 years and adults
- M:F ratio approximately 1:1.
- Prognosis similar to Group 4 and intermediate between WNT and Group 3

SHH Medulloblastoma

- Majority of nodular/desmoplastic MBs are included within the SHH subgroup. However around 50% of SHH subgroup MB have other histological subtypes, including classical, large cell/anaplastic, and MBEN varieties.

- Individuals with germline mutations of the SHH receptor PTCH have Gorlin's syndrome

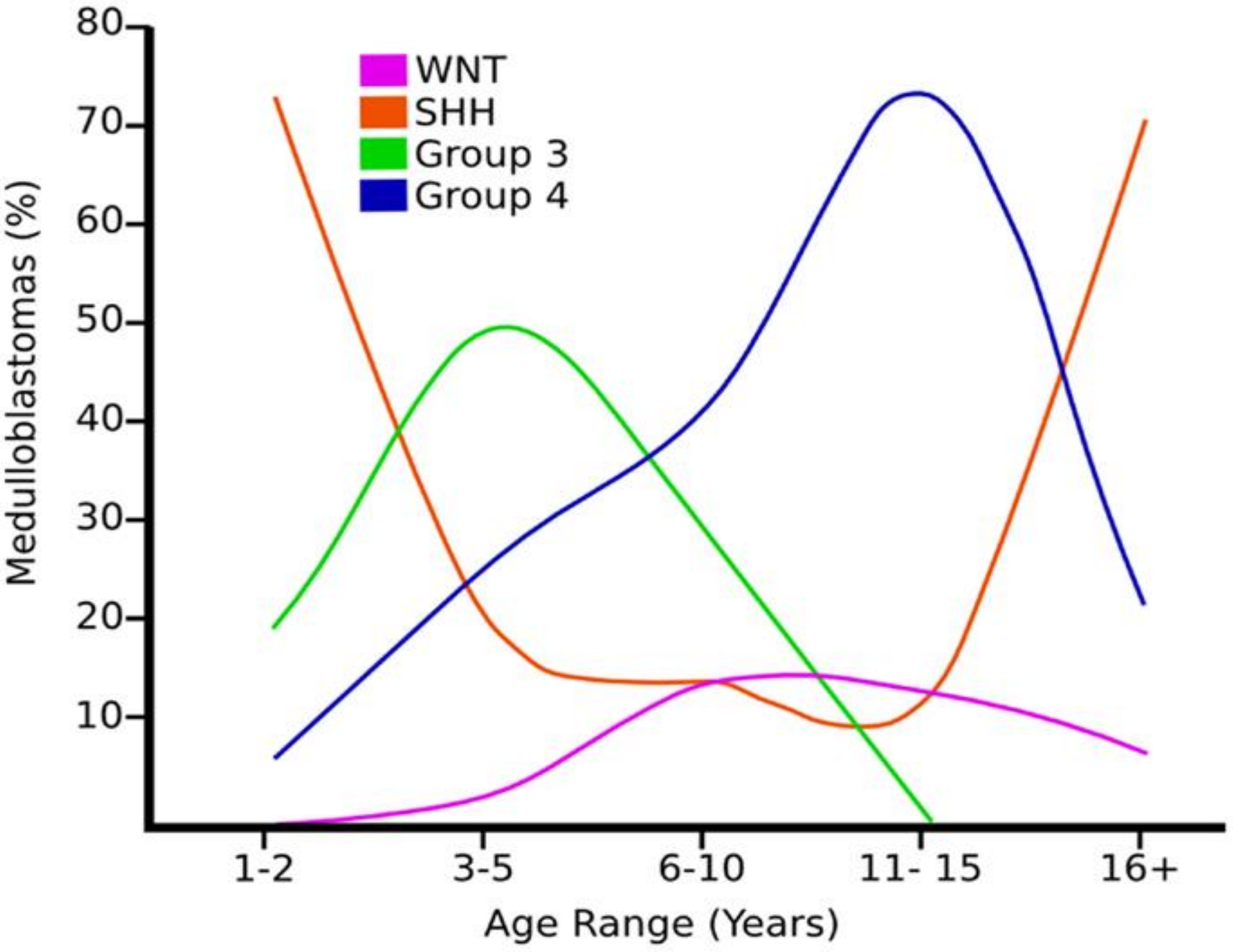
Group 3 Medulloblastoma

- Subgroup of MB with the worst prognosis
- Majority classical histology and include the majority of large-cell/anaplastic tumours
- M > F, and arise in infants and older children, but only rarely in adults
- Frequently present with metastases.
- Characterized by high-level amplification of the *MYC* proto-oncogene, and almost all cases exhibit aberrant *MYC* expression
- Group 3 MB genome exhibits high levels of genomic instability and often harbours gains of chromosomes 1q, 7, and 17q, and deletions of 10q, 11, 16q, and 17p.

Group 4 Medulloblastoma

- Intermediate to good prognosis similar to patients with SHH tumours
- Include classical and large cell/anaplastic histologies
- Approx 30–40% of MB cases
- M:F ratio 3:1
- Molecular pathogenesis not currently clear

Genetic profile	Histology	Prognosis
Medulloblastoma, WNT-activated	Classic	Low-risk tumour; classic morphology found in almost all WNT-activated tumours
	Large cell / anaplastic (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-mutant	Classic	Uncommon high-risk tumour
	Large cell / anaplastic	High-risk tumour; prevalent in children aged 7–17 years
	Desmoplastic / nodular (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-wildtype	Classic	Standard-risk tumour
	Large cell / anaplastic	Tumour of uncertain clinicopathological significance
	Desmoplastic / nodular	Low-risk tumour in infants; prevalent in infants and adults
	Extensive nodularity	Low-risk tumour of infancy
Medulloblastoma, non-WNT/non-SHH, group 3	Classic	Standard-risk tumour
	Large cell / anaplastic	High-risk tumour
Medulloblastoma, non-WNT/non-SHH, group 4	Classic	Standard-risk tumour; classic morphology found in almost all group 4 tumours
	Large cell / anaplastic (rare)	Tumour of uncertain clinicopathological significance


WNT
SHH
Group 3
Group 4
Medulloblastomas (%)
80
70
60
50
40
30
20
10
1-2
3-5
6-10
11- 15
16+
Age Range (Years)

Medulloblastoma European Consensus 2015

- All tumours subtyped by 450 K array or validated method - preferably 2 techniques as part of initial clinical workup
- Neurosurgeons should aim for maximal safe removal: NTR (to be defined) is acceptable and prognostically equivalent to GTR for staging
- QOL short, medium and long term is a high priority and should be evaluated in all patients
- Reduced CSI RTX for STR/NTR + M0; re evaluate 1.5 cm^2 residual as high risk criterion
- All wnt properly subtyped < 16 years old have excellent prognosis and should be treated with reduced radiation/chemotherapy
- SHH + TP53 mutation = very poor prognosis: new treatment options needed especially if germline TP53 mutation
- Every SHH patient/family should be offered genetic counselling
- All SHH tumours should be sequenced for somatic and germline mutations of TP53, PTCH, SUFU as part of the diagnostic process
- Recurrent tumours should be rebiopsied before using targeted therapy or 2 years beyond initial diagnosis or diagnosis is in doubt
- Central review of MRI scans, pathology and radiotherapy planning in real time for considered for clinical trial or registry
- All patients should be treated on a molecularly informed clinical trial.
- Snap frozen tissue, paraffin embedded, blood and CSF should be collected on all patients

SIOP PNET 5

Stratification of therapy based on pathological subtypes and biological markers in addition to clinical parameters

SIOP-PNET5-MB
New protocol: v12.0_29-Jun-2017

New protocol approved by German ethics committee - September 2017

New trial title:

AN INTERNATIONAL PROSPECTIVE TRIAL ON MEDULLOBLASTOMA (MB) IN CHILDREN OLDER THAN 3 TO 5 YEARS WITH WNT BIOLOGICAL PROFILE (PNET 5 MB – LR and PNET 5 MB – WNT-HR), AVERAGE-RISK BIOLOGICAL PROFILE (PNET 5 MB - SR), OR TP53 MUTATION, AND REGISTRY FOR MB OCURRING IN THE CONTEXT OF GENETIC PREDISPOSITION

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Mandatory PNET5-MB diagnostic testing:

Current (*introduced in 2014 amendment):

Pathology review
H&E
IHC panel: GFAP, synaptophysin, NFP, EMA, INI-1, vimentin, Ki-67 and reticulin special stain

WNT subgroup assignment
IHC: β-catenin
CTNNB1 mutation
Chromosome 6 status – iFISH or SNP array

MYC and *MYCN* amplification
iFISH or SNP array

Testing in accredited labs - Mandatory

Core research evaluations (all patients)
RNA-seq (Newcastle)
850K array (Newcastle/Heidelberg)
Panel-seq (Heidelberg)

Forthcoming amendment (Autumn 2017):

Pathology review to WHO (2016) criteria:
Add GAB1, YAP1, filamin A, Lin28 to 2014 panel

Subgroup assignment: WNT, SHH, G3, G4
Consensus from 2 independent methods, from…
1. IHC (above)
2. 850K/EPIC DNA methylation array
3. Methylation signature assay (e.g. Sequenom)

WNT subgroup assignment
CTNNB1 mutation plus subgroup assignment (above)

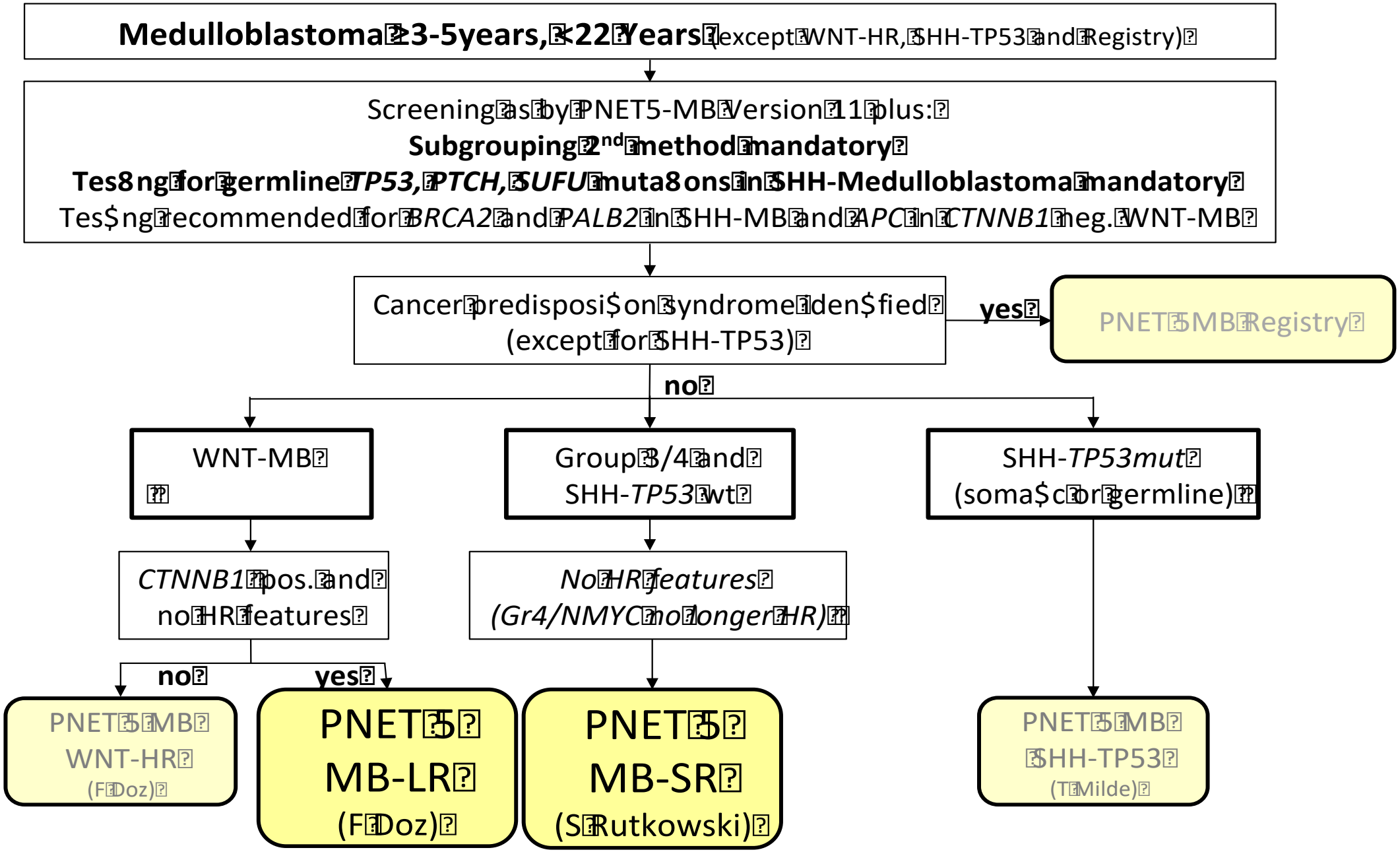
MYC and *MYCN* amplification
As 2014

Somatic mutation analysis of *PTCH, SUFU, TP53* (SHH patients)
Perform by Sanger or Panel; Validate by Sanger

Germline mutation testing – all relevant syndromes
Perform if tumour *PTCH, SUFU* or *TP53* mutation-positive
*Optional testing for *APC* (*CTNNB1* –ve WNT), Fanconi (*BRCA2/PALB2*).
Rapid genetics referral for germline patients

PNET5 – Stratification

Nr. 8

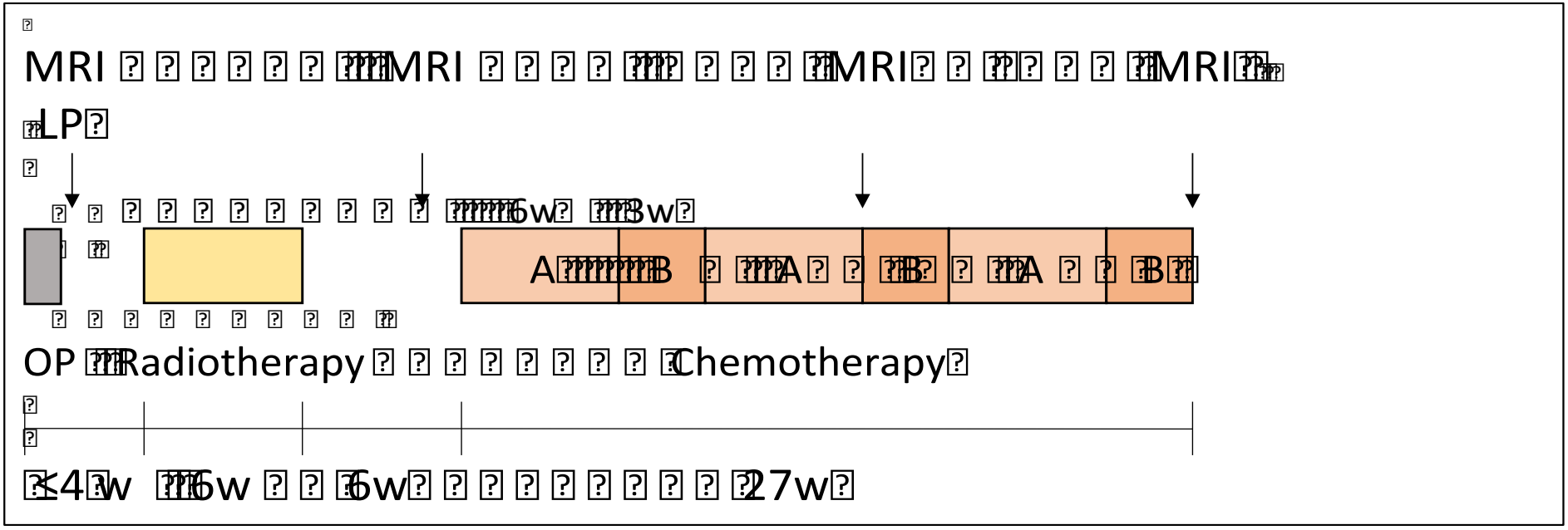


PNET5 – LR

Key inclusion criteria:

- WNT posi$ve MB (CMB, DMB)
- **With *CTNNB1* somatic mutation**
- Age <16 years
- M0
- R<1,5cm²

RT – CSRT 18 Gy



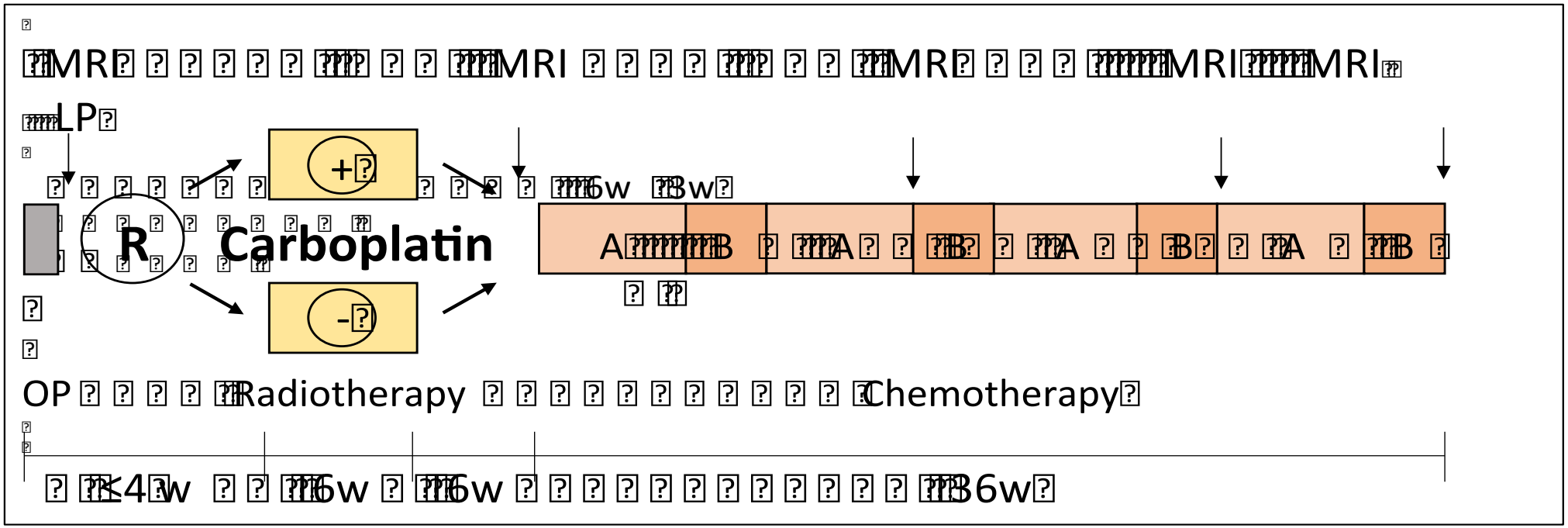
Status 08/2017: 26 of required 60 patients recruited (43%)

PNET5 – SR

Key inclusion criteria:

- Group 3/4 (non-WNT/non-SHH) or SHH-TP53 wildtype
- CMB ≥ 1 DMB
- CMYC/NMYC neg. or **group 4 NMYC pos./CMYC neg.**
- M0
- R<1,5cm²

CSRT – 23.4 Gy



Status 08/2017: 79 of required 300 patients recruited (26%)

PNET5 – SHH-TP53

Key inclusion criteria:

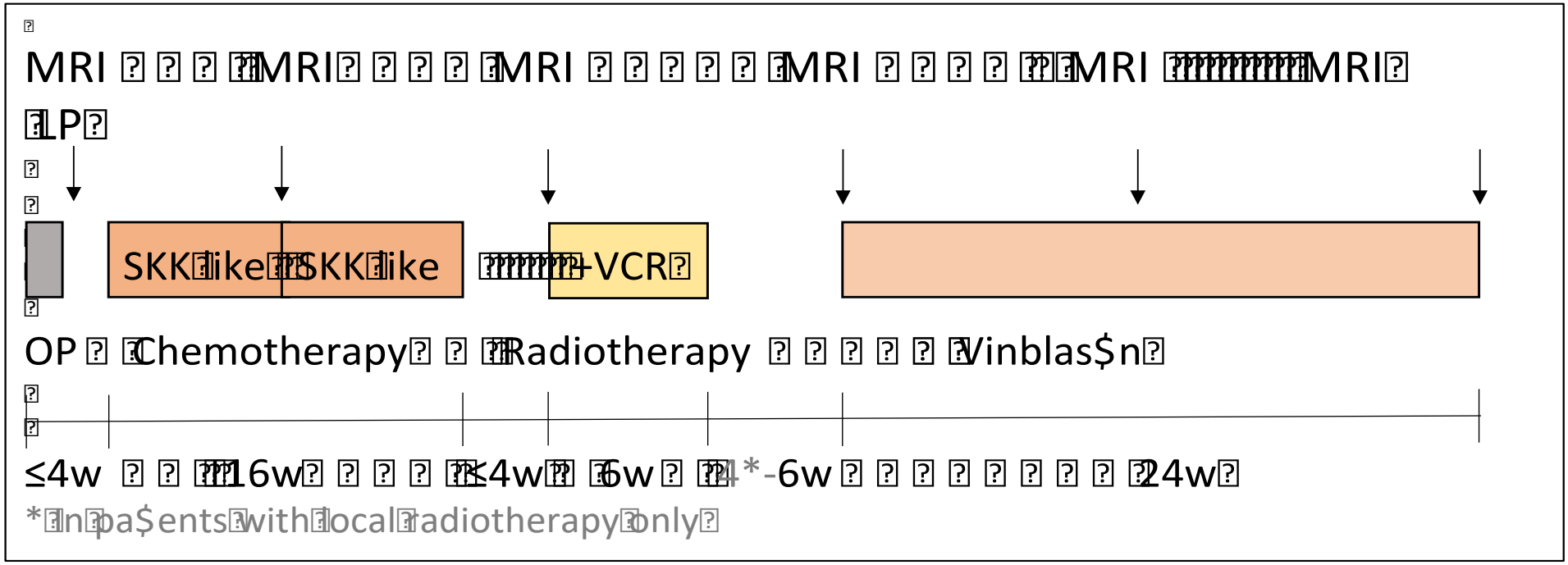
- SHH MB with *TP53* mutation
- *TP53* germline evaluation mandatory
- All histology subtypes
- M0 and M+
- >3-5 years with no upper age limit

"SKK-like" chemotherapy (with i.ventr. MTX):

w1: Doxorubicin (or Carboplatin)/VCR
w3, w5: HD-MTX/VCR
w7: Carboplatin/VCR

Radiotherapy (with weekly VCR 1,5mg/m²):

Germline *TP53mut* M0: **Focal RT**
Safety margin 3 3.4 Gy, tumor 5 4.0 Gy, ??
Germline *TP53mut* M+: CSI 2 3.4 Gy, tumor 5 4.0 Gy
Somatic *TP53mut*: CSI 3 6.0 Gy, tumor 5 4.0 Gy



Key inclusion criteria:

- WNT positive with HR-features:
  - age ≥ 16 years and/or
  - M+ and/or
  - R+
- CMB, DMB or LCAMB
- MYC/MYCN negative or positive
- WNT without *CTNNB1* mutation (if not germline APC-mutation, rare)

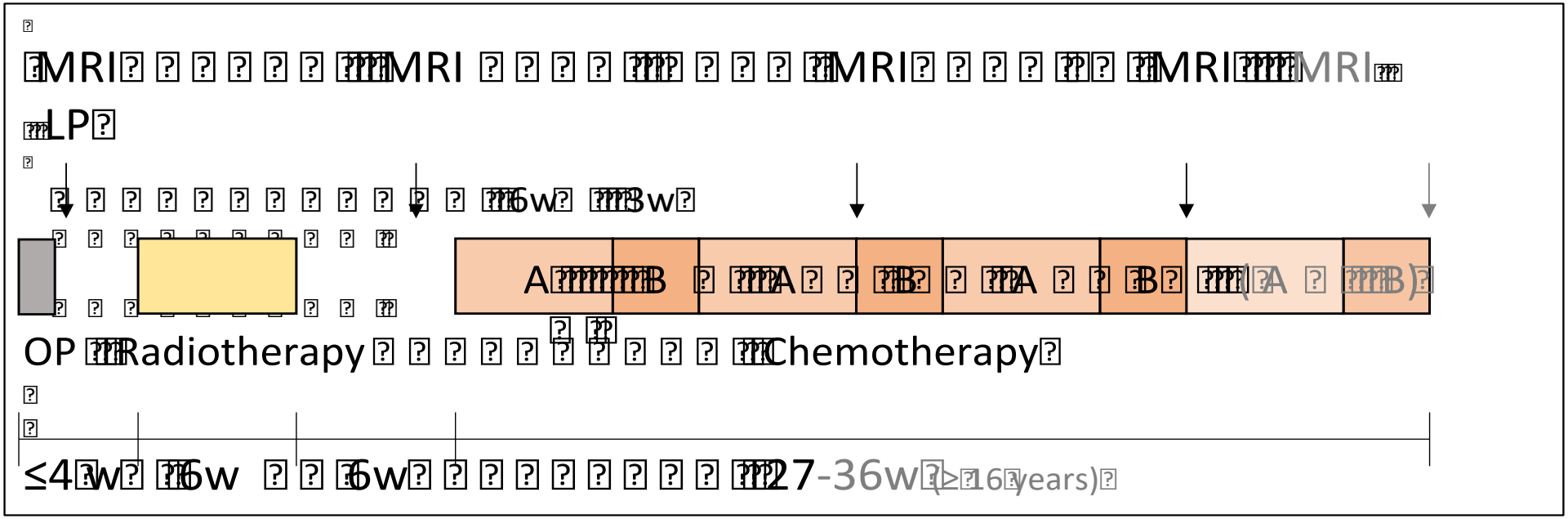
Radiotherapy:

<u>< 16 years and ≥ 16 years without metastasis:</u>

CSI **23.4 Gy,** primary tumor 54.0 Gy

<u>≥ 16 years and metastasis:</u>

CSI **36.0 Gy,** primary tumor 54.0 Gy



PNET5 – Late effects evaluation

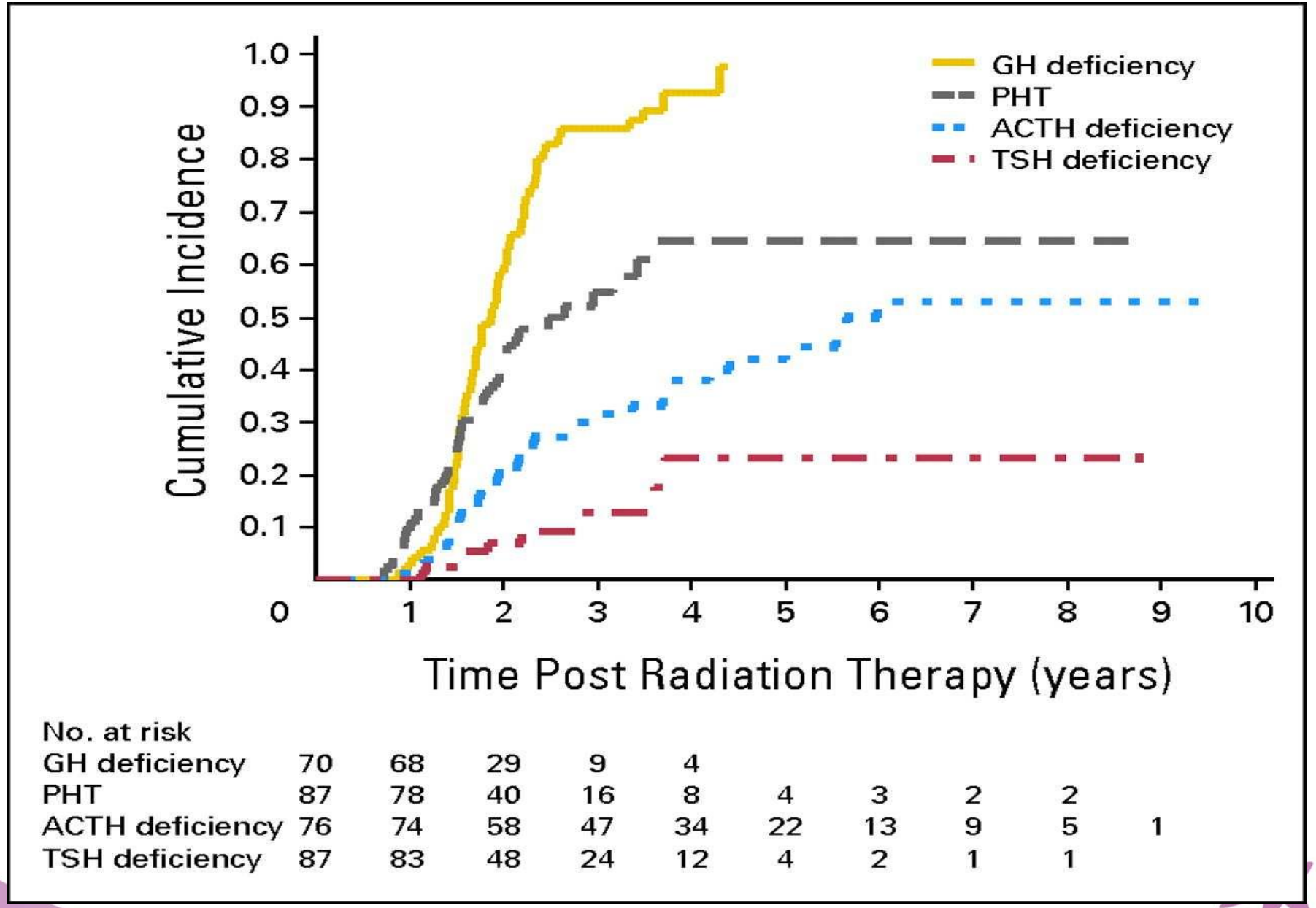
Late effects evaluation 2 and 5 years after initial surgery:

- Auxiology
- Neurology
- **Pure tone audiometry**
- Endocrinology
- **Leucencephalopathy** (only 2 years post-OP, assessment by review institution)
- **Brief ataxia rating scale**
- **QoS assessment**
- **Neuropsychology**

Radiotherapy Late Effects

Organ/Tissue	Dose Threshold	Late Toxicity
Central Nervous System	~ 18 Gy	Neuropsychological damage, reduced IQ, learning and behaviour difficulties
Pituitary	~ 18 Gy for impaired GH secretion, higher threshold (~ 40 Gy) for other hormones	Multiple hormone deficiencies, particularly growth hormone (GH), also adreno-cortico trophic hormone (ACTH) and thyroid stimulating hormone (TSH)
Thyroid	20 Gy	Reduced thyroid hormone secretion
Gonads	1-2 Gy (testes), 6-10 Gy (ovaries)	Infertility if irradiation of the testes or ovaries cannot be avoided
Bone	Threshold ~ 10 Gy fractionated RT Worst in young children treated with > 20 Gy	Impaired bone growth, and associated impairment of soft tissue development. This is particularly severe in the facial, head and neck regions
Kidney	12-15 Gy	Hypertension, reduced renal function
Dentition	~ 4-10 Gy	Dental caries, impaired dental development and mal-development of jaw
Eye	~ 10 Gy (Cataract), ~ 25 Gy Dry eye	Cataract, dry eye
Second (radiation induced) malignancy	Low threshold for adenocarcinomas, e.g. breast, thyroid. High threshold for sarcomas	e.g. breast and thyroid cancers after RT for Hodgkin's Disease, Sarcomas after RT for many cancers, including brain tumours

Medulloblastoma – Post-Treatment Endocrine Deficiencies



No. at risk										
GH deficiency	70	68	29	9	4					
PHT	87	78	40	16	8	4	3	2	2	
ACTH deficiency	76	74	58	47	34	22	13	9	5	1
TSH deficiency	87	83	48	24	12	4	2	1	1	

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Vertebral growth

- Age, gender and risk group/CSI dose each have a significant effect on vertebral growth
- Effect of risk group/CSI dose greatest for growth of lumbar vertebrae
  - Posterior elements > anterior
- Supports the notion of a "threshold" at ~25 Gy…

Hartley… Merchant, IJROBP 2008

Medulloblastoma
Differences between adults and children

- Location: in children tends to arise in the vermis, whereas in adults the cerebellar hemisperes are primarily involved
- Histopathological subtype: in children the majority of histological subtypes consist of the classical variant. In adults, the desmoplastic variant is frequently found
- Lesser frequency of metastatic disease: in children generally 30%. In adult series the incidence is 8-13%

Medulloblastoma
Differences between adults and children

- Incidence of late relapses: in children late relapses uncommon. In adult series, similar plateaus normally not observed
- Type of metastatic spread: in children majority of relapses are disseminated and in the CNS. In adults there is a higher tendency for isolated relapses, the relative contribution of extracranial metastases is higher, although still uncommon

Questions?

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MEDULLOBLASTOMA

Part II: Target Volumes, Dose Prescription, Treatment Techniques, Ongoing Studies

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MD Anderson Cancer Center

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Goals and Objectives

At the end of the presentation, the participant should be able

- To discuss appropriate radiotherapy target volumes and doses for children with medulloblastoma
- To discuss appropriate timing for radiotherapy as well as the influence of radiotherapy treatment protraction
- To discuss techniques currently available for craniospinal and tumor bed irradiation
- To discuss ongoing studies dealing with medulloblastoma

History of Radiotherapy

- 1949 Lampe and MacIntyre report results of craniospinal RT with 28% survival
- 1953 Paterson and Farr report 5-year survival of 41% with more fractionated craniospinal technique

Radiotherapy Volume

	SURVIVAL ACCORDING TO RT VOLUME		
	Posterior Fossa only	Posterior fossa + spine	Craniospinal
University of Lund	5%	25%	53%
University of Toronto	0%		53%
Strong Memorial Hospital	No RT: 0% Whole brain RT: 20%		50%

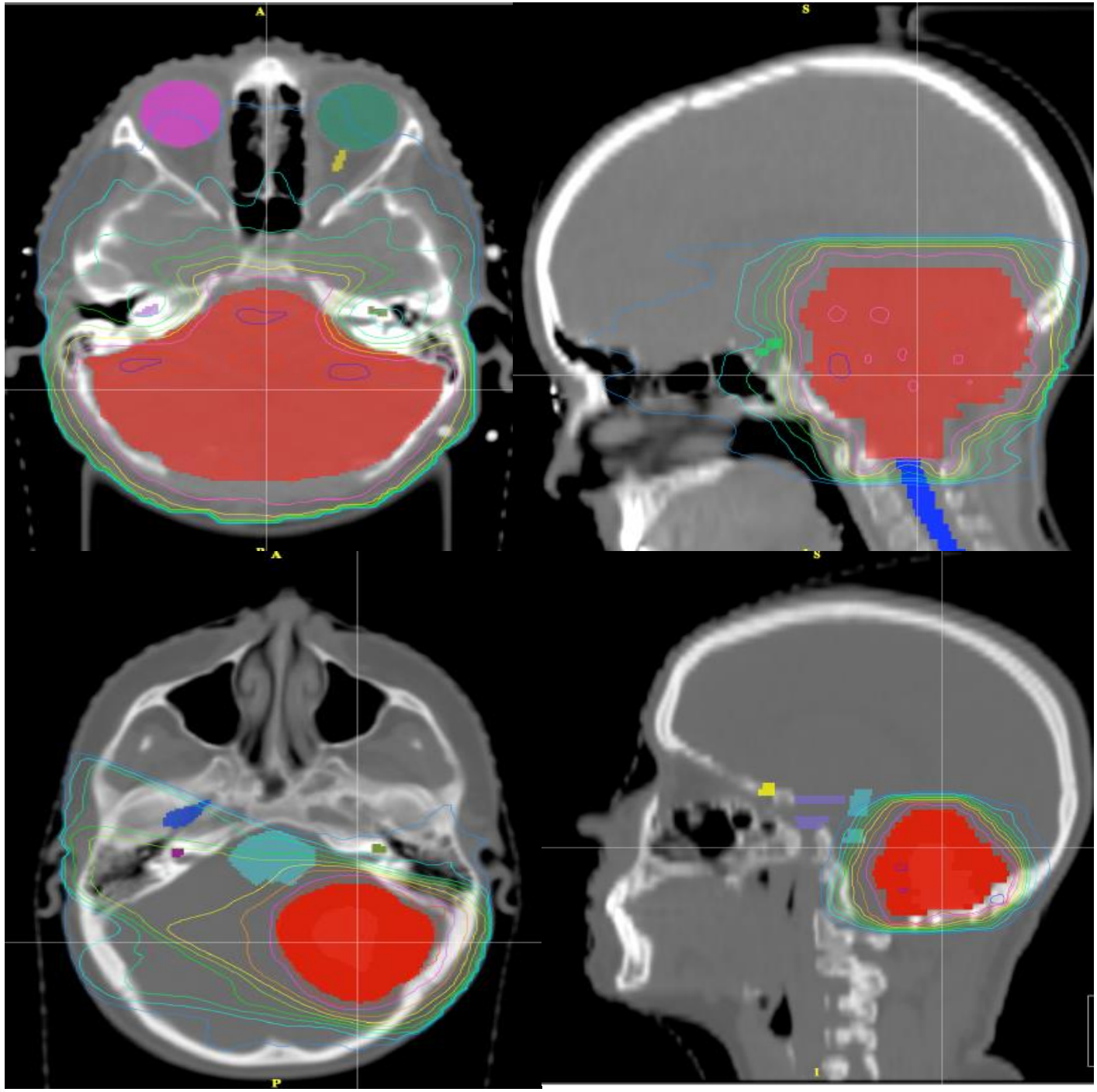
Radiotherapy Volume

- French M4 Protocol delivered 2 course of "8 in 1" chemotherapy followed by 2 courses of high-dose methotrexate after surgery
- RT was given only to the posterior fossa and spine
- Of 16 children, only 3 (18%) were disease-free and alive at mean follow-up of 6 years
- Most common site of relapse was supratentorial (9/13 cases)

Bouffet E et al. Int J Radiat Oncol Biol Phys 1992; 24:79-85

RT Boost Volume

- The entire posterior fossa has been the standard volume which needs to receive the boost
- In era of conformal RT and better imaging, tumor bed boost might suffice



POSTERIOR FOSSA BOOST

TUMOR BED BOOST

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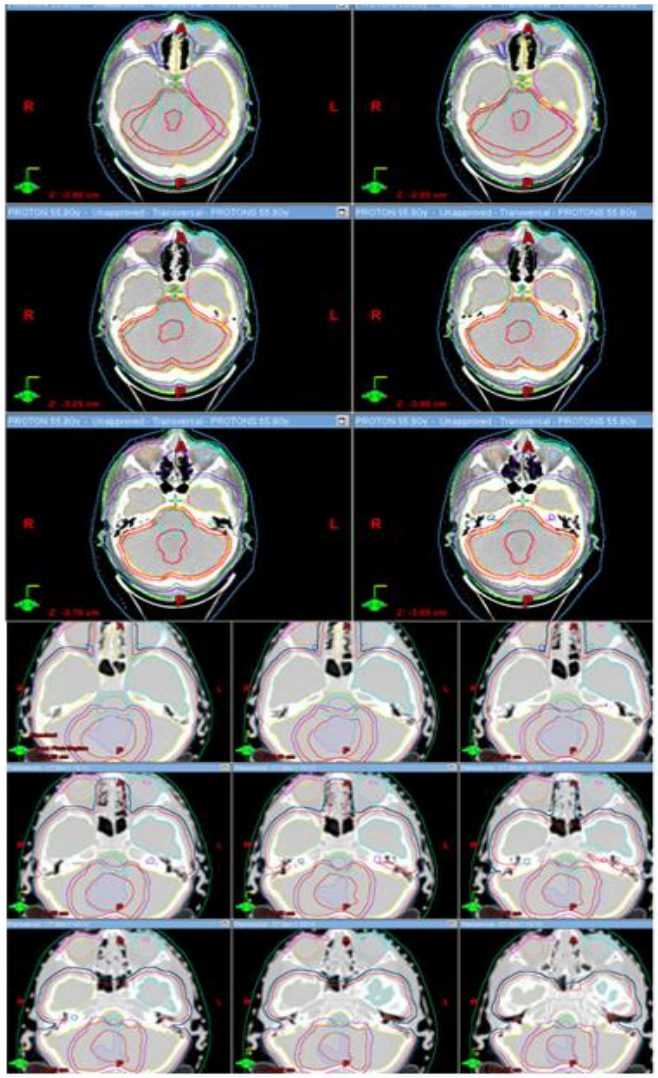

POSTERIOR FOSSA BOOST
Clinical target volume (CTV) is the entire posterior fossa
Planning target volume is 3 to 5 mm expansion on the CTV

TUMOR BED BOOST
Clinical target volume (CTV) is
The tumor bed and any residual tumor with a 0.5 to 1.5 cm margin
Planning target volume (PTV)
Is a 3 to 5 mm expansion on CTV

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RT Boost Volume (Tumor Bed Boost)

Author/ Institution	N	Median follow-up (months)	No. failing in non-tumor bed posterior fossa
Wolden et al. MSKCC	**32**	**56**	**1/32 (3%)* *isolated**
Douglas et al. U Washington	**33**	**37**	**1/33 (3%)**
Merchant et al. Multi-institutional	**73**	**32.4**	**3/73 (4%)* *2 isolated**
Paulino AC et al. Methodist/TCH	**50**	**68**	**1/50 (2%)***
Carrie C et al MSFOP	**108**	**46 (MSFOP2007) 152 (MSFOP98)**	**1/108 (0.9%)**

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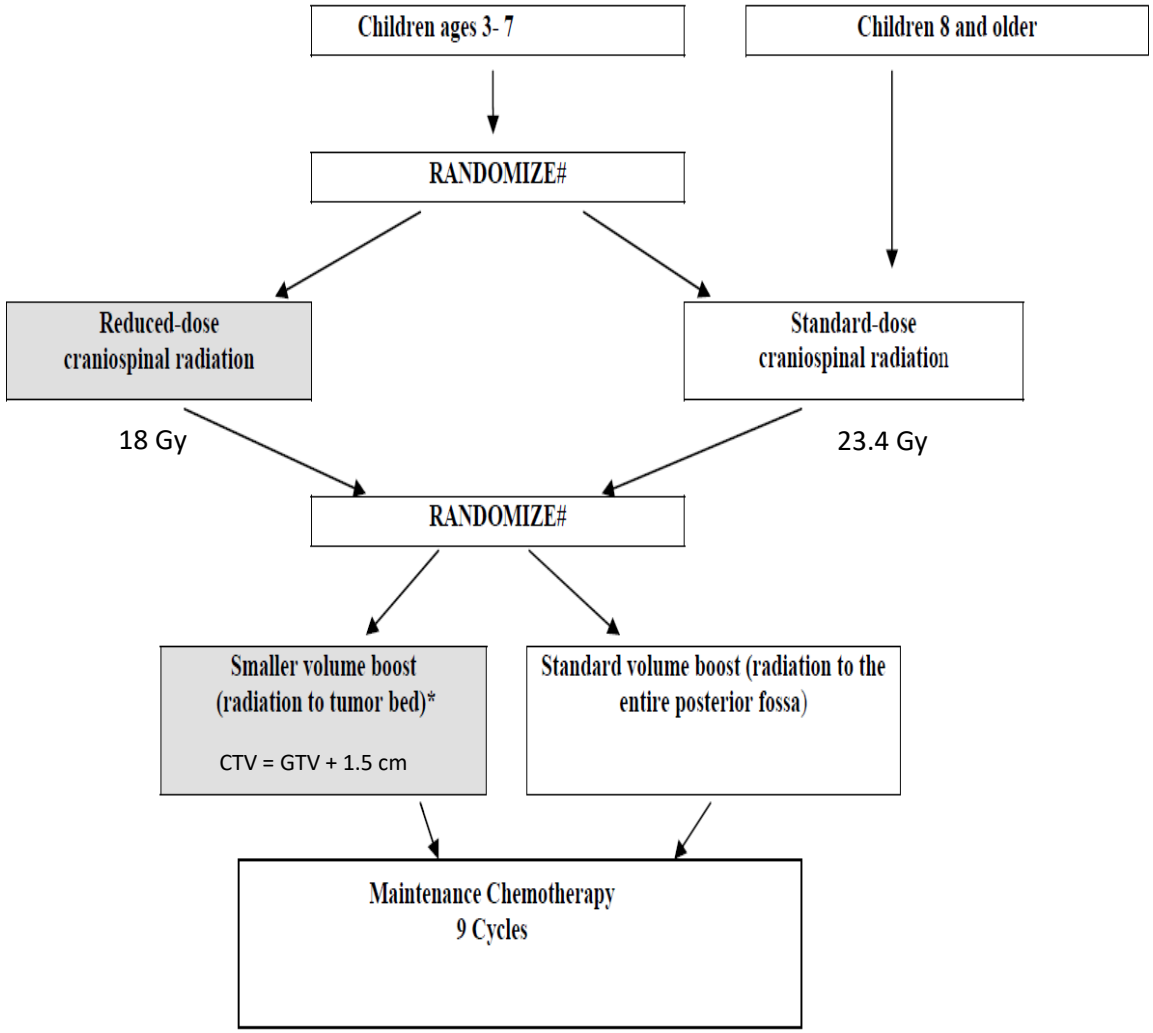
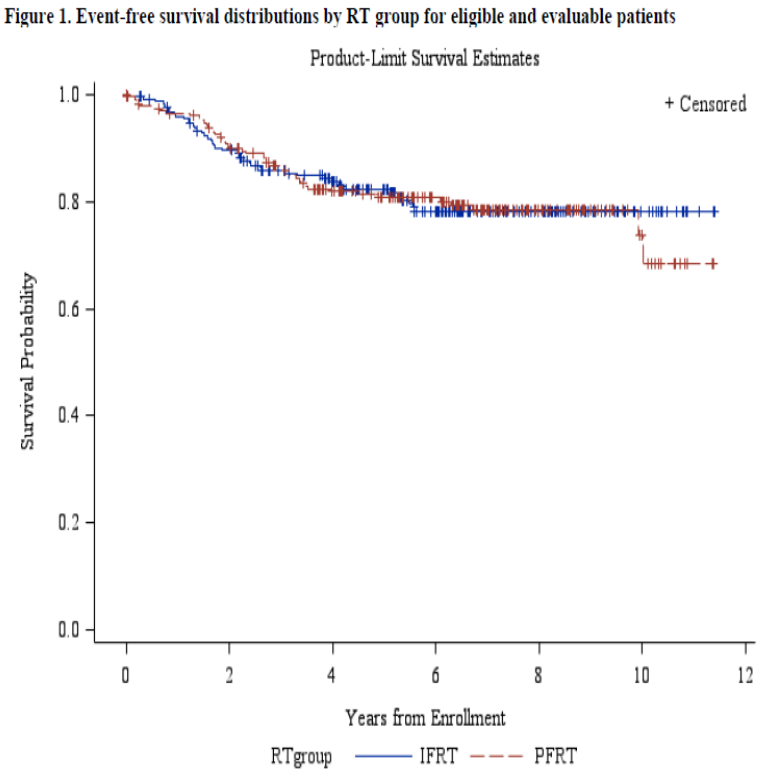
Children's Oncology Group ACNS0031





Cochlear-Sparing Radiotherapy in Medulloblastoma

	Median follow-up (months)	Mean dose to cochlea	Mean cisplatin Dose	Pediatric Oncology Group Ototoxicity Grade (number of patients)				
				Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Conventional RT N=11	51	54.2 Gy (53.2-55.8)	220mg/ m^2	2	2	0	6	1
IMRT N=15	18	36.7 Gy (23.4-50.8)	290mg/ m^2	6	4	3	1	1
IMRT N=88*	41	35.3 (standard risk), 43 Gy (high risk)	300 mg/ m^2	29	32	11	13	3
Protons N=35*	12	30 CGE	303 mg/ m^2	19	14		2	

64%

13%

18%

5%

* Number of ears

Huang E et al. IJROBP 2002; 52:599-605, Paulino AC et al. IJROBP 2010; 78:1445-50, Moeller BJ et al. Radiat Oncol 2011; 6:58

Posterior Fossa RT Dose

- Princess Margaret Hospital (Berry)
  5 yr OS 73% $\geq$ 52Gy, 51% < 51 Gy
- Mayo Clinic (Garton)
  10-yr RFS 72% $\geq$ 50 Gy, 24% < 50 Gy
- Mallinckrodt (Silverman)
  5 yr OS 85% $\geq$ 50 Gy, 36% < 50 Gy
- Joint Center for Radiation Therapy (Tarbell)
  5-yr Local control 82% $\geq$ 53 Gy, 50% < 53 Gy

Craniospinal RT Dose

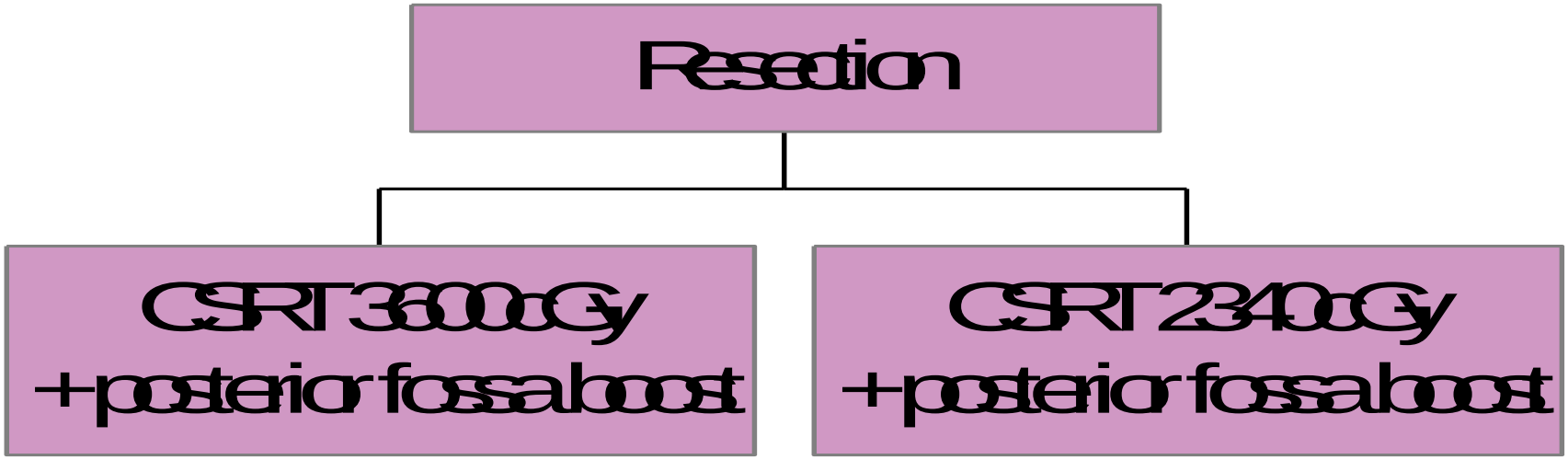
- Single institution studies from UCSF and Northwestern University delivering lower dose CSRT (24-30 Gy) with chemotherapy in M0 patients
- Current standard in North America is to use 2340 cGy CSRT followed by boost in addition to chemotherapy for standard risk patients

Risk Category

- Standard or Average Risk
  M0 and tumor residual < 1.5 cm^2
- High Risk
  M+ or tumor residual $\geq$ 1.5 cm^2

CCG923/POG8631

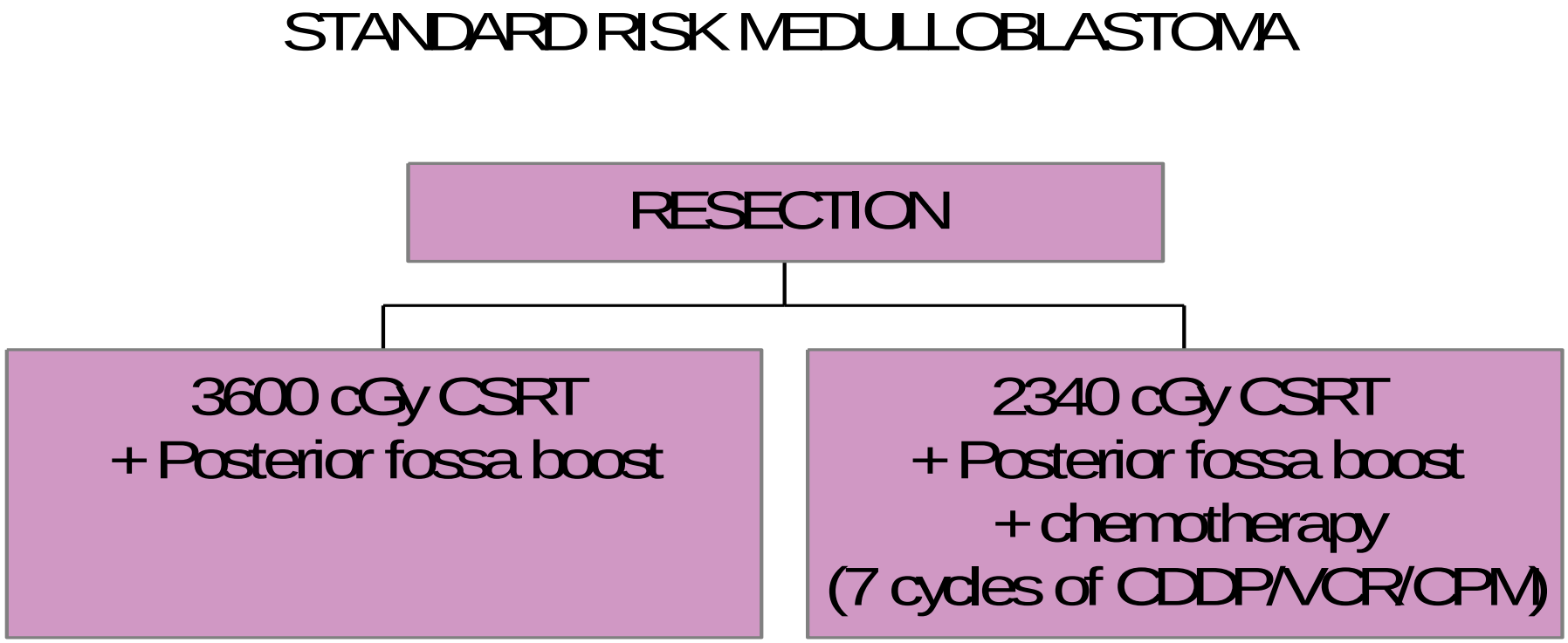
STANDARD RISK MEDULLOBLASTOMA



CCG923/POG8631

- Interim analysis showed increased number of isolated neuraxis failures
- Study closed early
- 8-year EFS rates were 67% (36 Gy) and 52% (23.4 Gy), p = 0.14
- Only 91 of 126 patients were eligible for review because of incomplete staging or more extensive disease

CCG9014/POG9331



CCG9014/POG9331

- Study was not completed due to poor accrual of patients
- Single arm prospective study (CCG9892) using 2340 cGy CSRT + chemotherapy reported 86% and 79% 3- and 5-year PFS

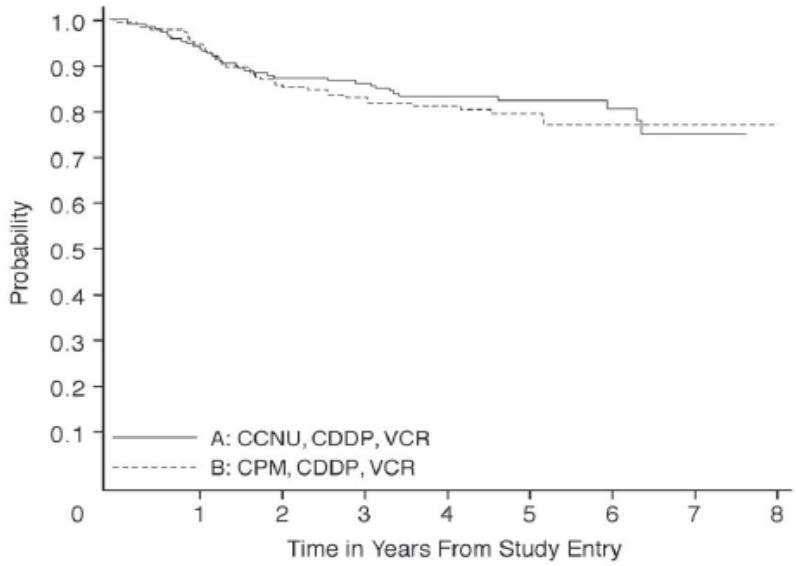
A9961: Standard-Risk Medulloblastoma

2340 cGy CSI + posterior fossa boost
to total dose of 5580 cGy

Compared two different chemotherapy Regimen: CCNU, CDDP, VCR vs. CDDP, VCR, CPM

Regimen	Drug	Dosage
A		
Day 0	CCNU	75 mg/m^2 by mouth
Day 1	CDDP	75 mg/m^2 intravenously
Day 1, 7, 14	VCR	1.5 mg/m^2; max 2 mg intravenous bolus, maximum of eight doses
B		
Day 0	CDDP	75 mg/m^2 intravenously
Day 1, 7, 14	VCR	1.5 mg/m^2; max 2 mg, intravenous bolus
Day 21, 22	Cyclo	1,000 mg/m^2 intravenously over 60 min daily

Abbreviations: CCNU, lomustine; CDDP, cisplatin; VCR, vincristine; max, maximum; Cyclo, cyclophosphamide; min, minute.



5-year EFS is 81%
No EFS or overall survival difference
Infection more common with CPM
Electrolyte abnormality more common with CCNU

Packer RJ et al. J Clin Oncol 2006; 24:4202-8

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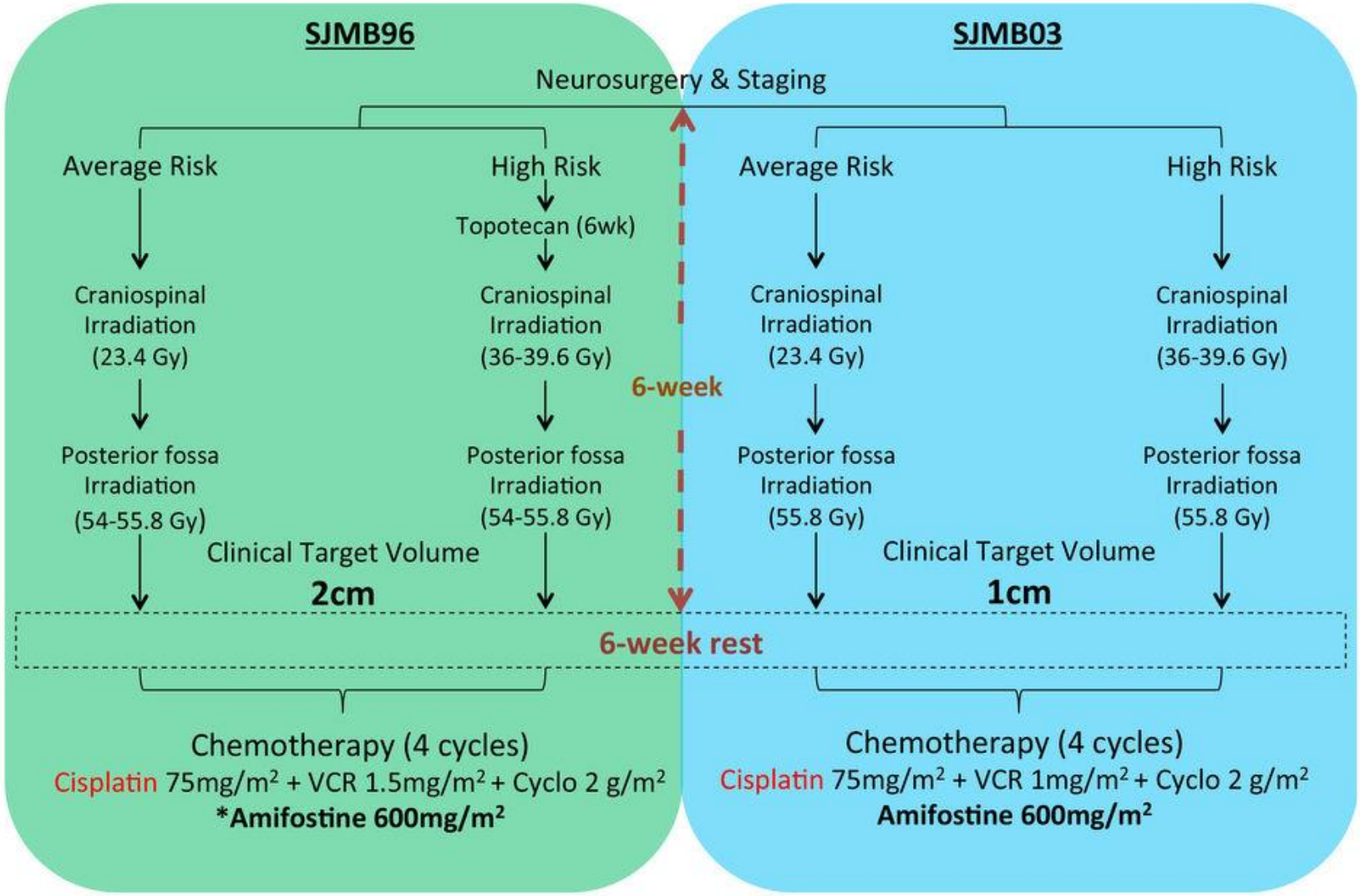
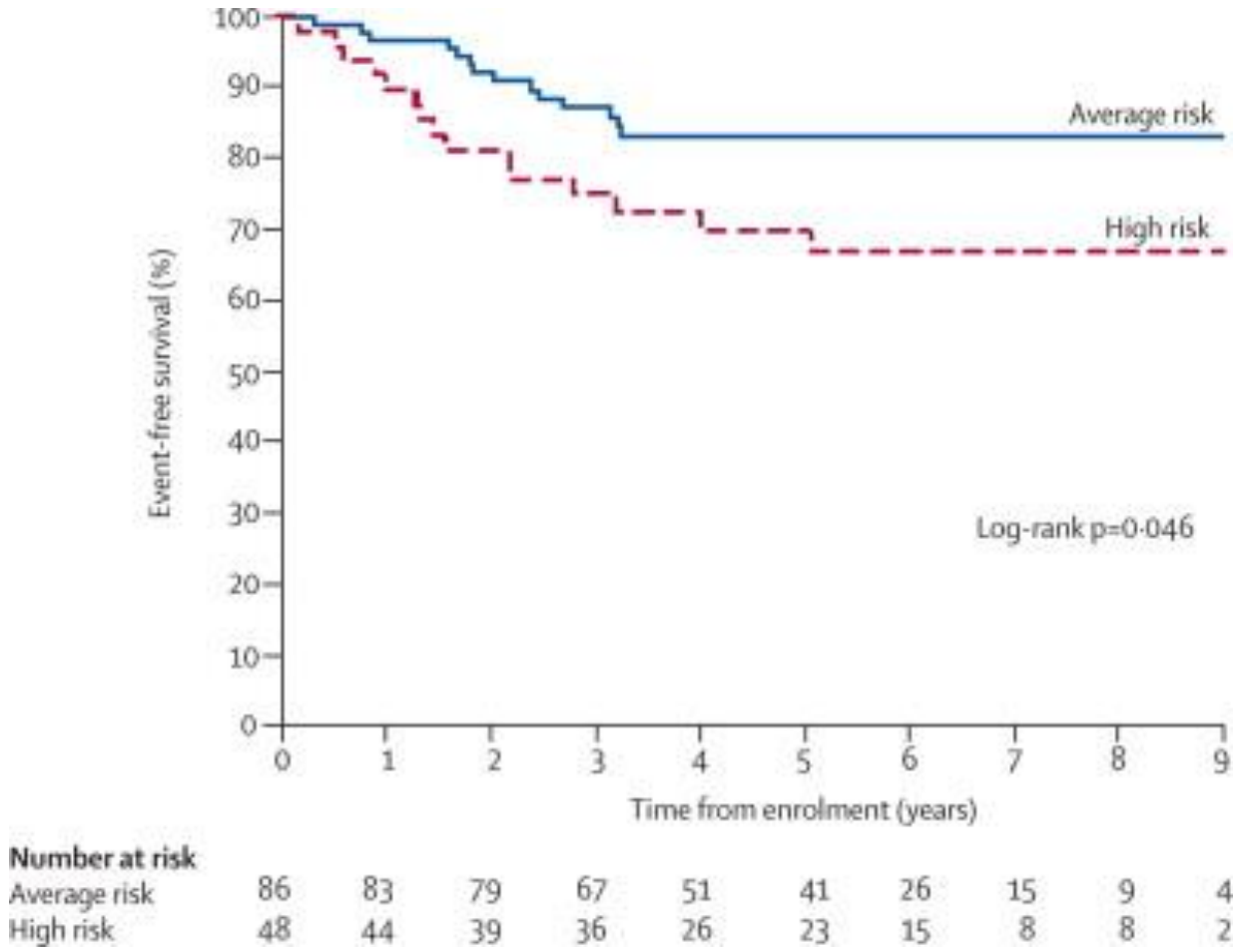
SJMB96 and SJMB03



SJMB96



5-yr OS and EFS

AR: 85% and 83%
HR: 70% and 70%

Gajjar A et. al. Lancet Oncol 2006; 7:813-20

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Neurocognitive Effects

	N	Older Average Risk		Older High Risk		Younger Average Risk		Younger High Risk	
		Intercept	Slope Points/yr	Intercept	Slope Points/yr	Intercept	Slope Points/Yr	Intercept	Slope Points/Yr
IQ	104	97.08	-0.42	97.00	-1.56	93.73	-2.41	94.05	-3.71
Reading	91	97.24	-2.05	99.26	-1.05	100.25	-4.81	95.94	-3.90
Spelling	90	95.65	-2.62	94.30	1.02	90.68	-2.60	97.14	-5.31
Math	93	94.12	-1.84	92.91	0.37	87.80	-0.77	96.00	-3.73

Mulhern RK et al. J Clin Oncol 2005; 23:5511-9

Craniospinal RT Dose (1800 cGy)

- Children's Hospital of Philadelphia
- A prospective study used 1800 cGy CSRT and 5580 cGy to the posterior fossa with 8 cycles of VCR, CCNU and CDDP in 10 children 18-60 mos
- 4-year survival was 69%
- No marked change in IQ scores among survivors

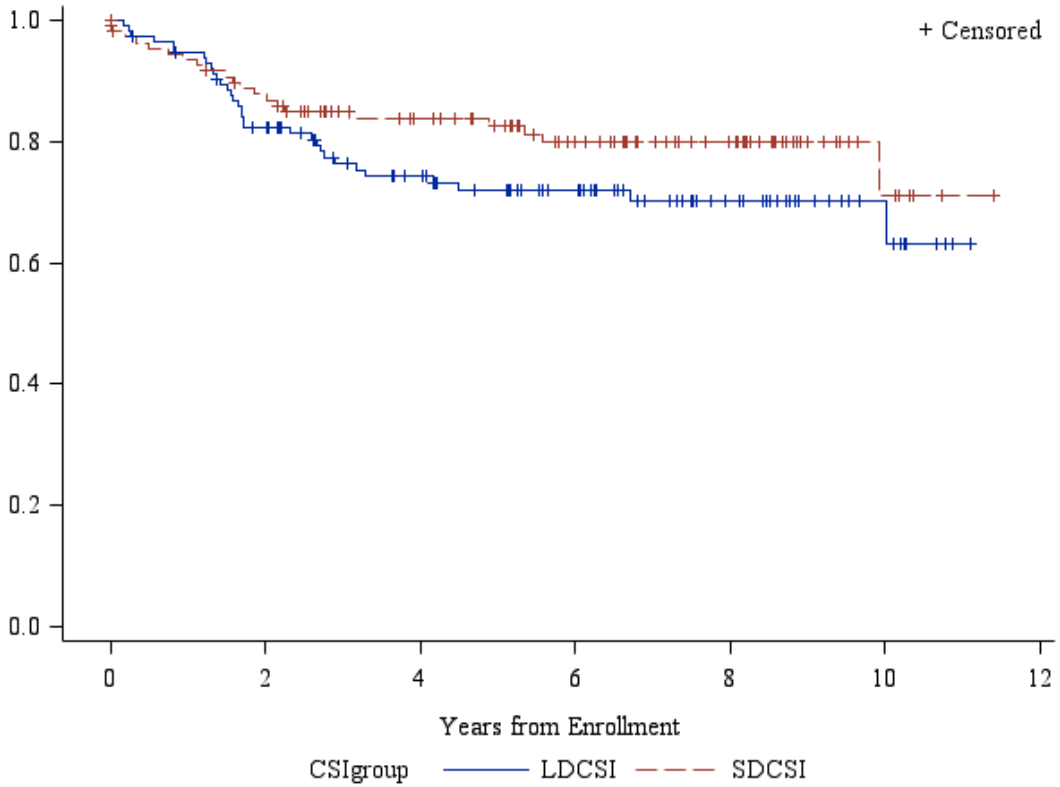
Goldwein JW et al. Int J Radiat Oncol Biol Phys 1996; 34:899-904

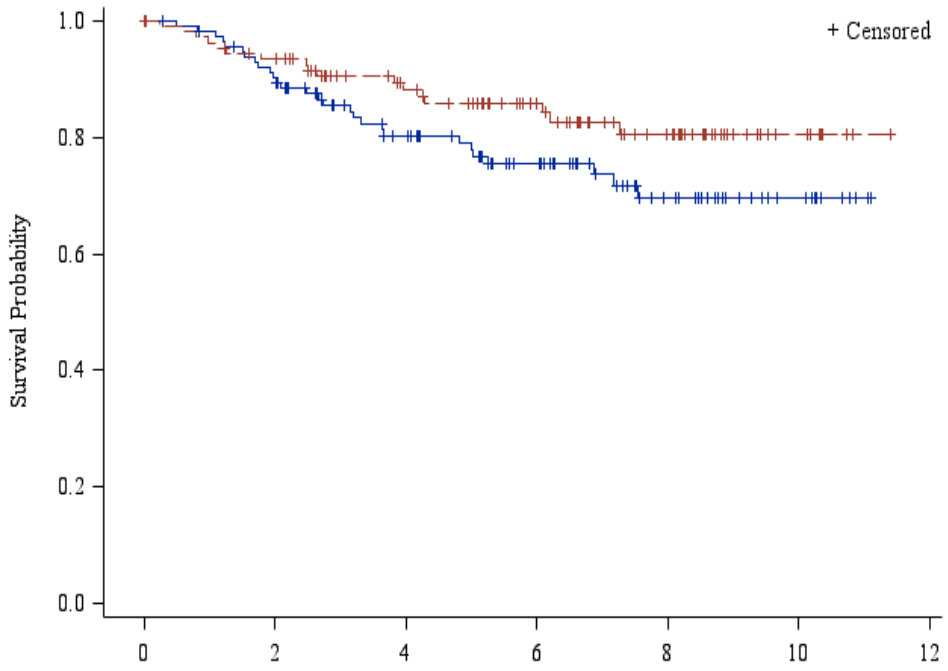
Craniospinal RT Dose (1800 cGy)

- Indiana University
- 7 children (age 20-64 mos) treated with 4 mos of chemotherapy followed by 1800 cGy CSRT + 54 Gy PF boost
- 3 patients relapsed (all outside PF)
- 2 of 3 were salvaged
- 4/6 survivors have endocrine deficits
- All 6 required special assistance in school

Jakacki RI et al. Int J Radiat Oncol Biol Phys 2004; 60:531-6

ACNS0031 Protocol: 18 Gy vs. 23.4 Gy CSI





Overall survival at 5 years was 78.1 ± 4.4% for patients ages 3–7 who received low-dose irradiation therapy to the CSI vs 85.9 ± 3.8% for the standard CSI dose. Event-free survival at 5 years was 72.1 ± 4.8% for the LD-CSI group, compared to 82.6 ± 4.2% for SD-CSI.

Michalski JM et al. ASTRO 2016 Meeting, Philadelphia

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Chemotherapy

- Four randomized trials addressing the issue of chemotherapy
- Currently, chemotherapy is used in conjunction with low-dose CSRT in standard-risk medulloblastoma
- Chemotherapy is also used in conjunction with standard-dose CSRT in high-risk medulloblastoma

SIOP-1

- 286 pts randomized to 30-45 Gy CSRT, 50-55 Gy PFRT +/- VCR + CCNU x 1 year
- No difference in survival
- Benefit in patients receiving chemotherapy in those with subtotal resection, brainstem involvement and T3 or T4 disease

Tait DM et al. Eur J Cancer 1990; 26:464-9

CCG/RTOG

- 233 pts randomized to 35-40 Gy CSRT, 50-55 Gy PFRT +/- VCR, CCNU, prednisone x 1 year
- No difference in survival
- Benefit in those receiving chemotherapy with T3, T4 or M+ disease

Evans AE et al. J Neurosurg 1990; 72:572-82

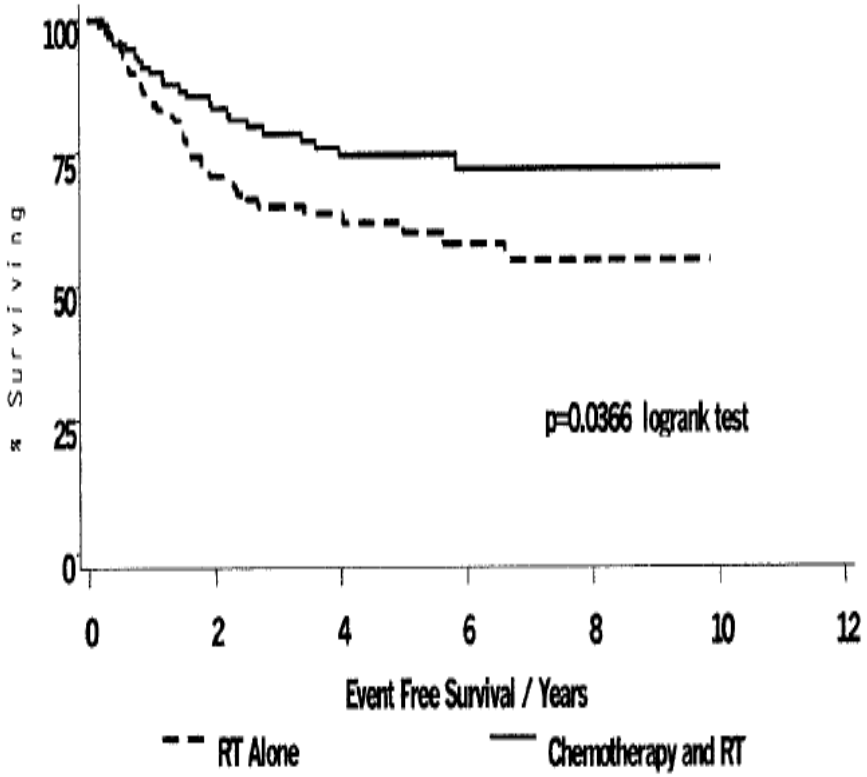
POG

- 78 pts randomized to 35 Gy CSRT + 54 Gy PFRT +/- MOPP
- Borderline difference in 5-year survival, favoring chemotherapy, 74% vs. 56%, (p = 0.06)
- Pts $\geq$ 5 yrs old, females and non-whites had the most benefit

Krischer JP et al. J Neurosurg 1991; 74:905-9

SIOP/UKCCSG (PNET-3)

- 217 pts with M0 or M1 disease randomized to 35 Gy CSRT, 55 Gy PFRT +/- pre-RT VCR, VP-16, Carboplatin and CPM
- Improvement in 5-year event-free survival with chemotherapy (74.2% vs. 59.8%, p = 0.036)



Taylor RE et al. J Clin Oncol 2001

Radiotherapy Treatment Duration

Author (Institution)	Outcome
Del Charco (Florida)	5-year RFS: 76% for $\leq$ 45 days and 43% for > 45 days, Posterior Fossa Control: 89% vs. 68%
Paulino (Iowa)	5-year PFS: 67% for < 50 days and 42% for $\geq$ 50 days, Posterior Fossa Control: 70% vs. 46%
Chan (MGH)	5-year Posterior Fossa Control: 81% for < 48 days and $\geq$ 48 days
Taylor (UKCCSG)	3-year EFS: 78.5% for < 50 days and 53.7% for $\geq$ 50 days

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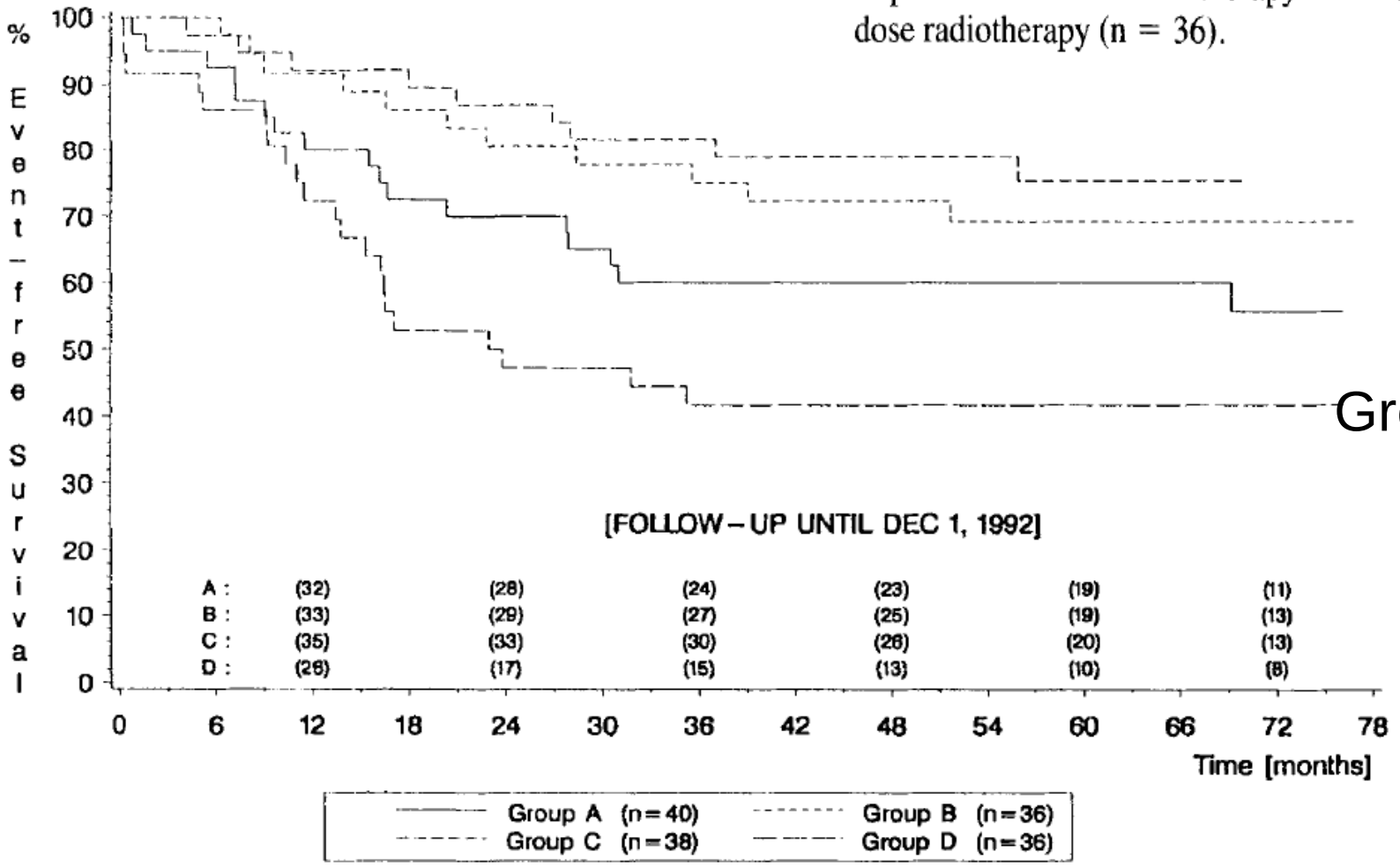
SIOP II Study

Group A—Received standard radiotherapy alone (n = 40).

Group B—Reduced radiotherapy alone (n = 36).

Group C—Sandwich chemotherapy followed by standard radiotherapy (n = 38).

Group D—Sandwich chemotherapy followed by reduced dose radiotherapy (n = 36).



Group D

Bailey CC et al. Med Pediatr Oncol 1995;25:166-78

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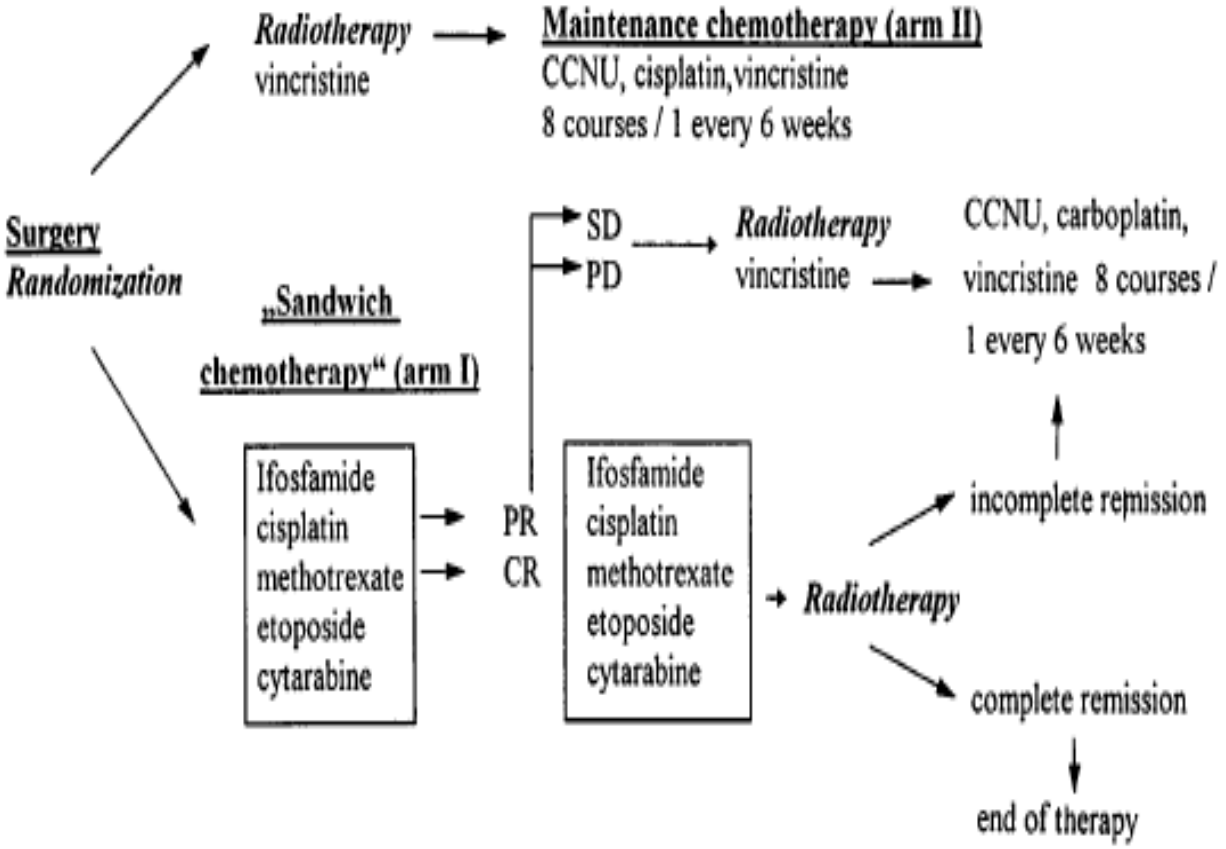
HIT'91


Radiotherapy
vincristine
Maintenance chemotherapy (arm II)
CCNU, cisplatin, vincristine
8 courses / 1 every 6 weeks
Surgery
Randomization
„Sandwich chemotherapy" (arm I)
SD
PD
Radiotherapy
vincristine
CCNU, carboplatin,
vincristine 8 courses /
1 every 6 weeks
Ifosfamide
cisplatin
methotrexate
etoposide
cytarabine
PR
CR
Ifosfamide
cisplatin
methotrexate
etoposide
cytarabine
Radiotherapy
incomplete remission
complete remission
end of therapy

HIT'91 Trial

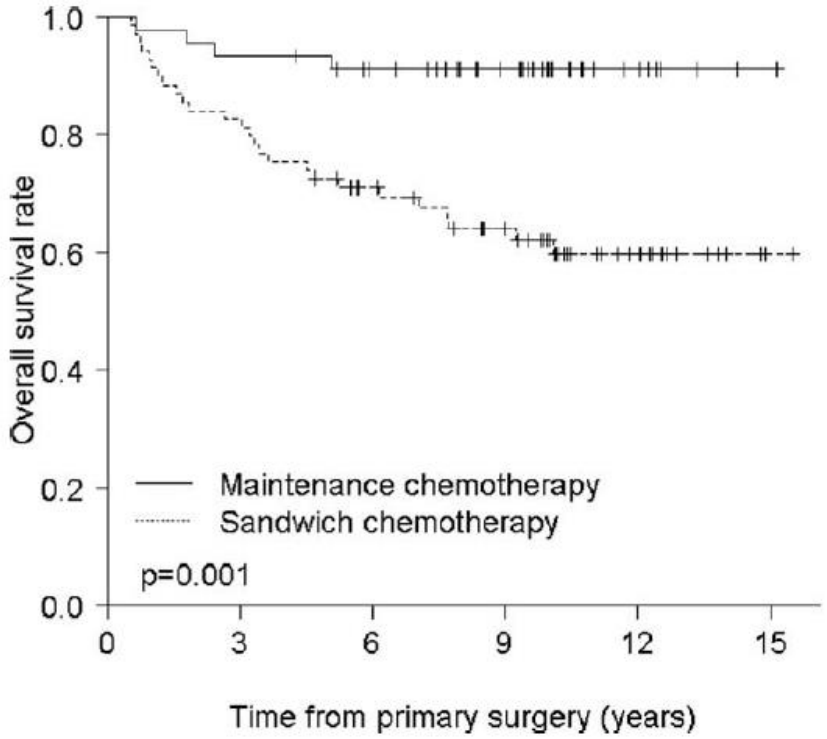


Fig. 3 – Overall survival of patients with complete staging and M0 disease according to therapy (as treated).

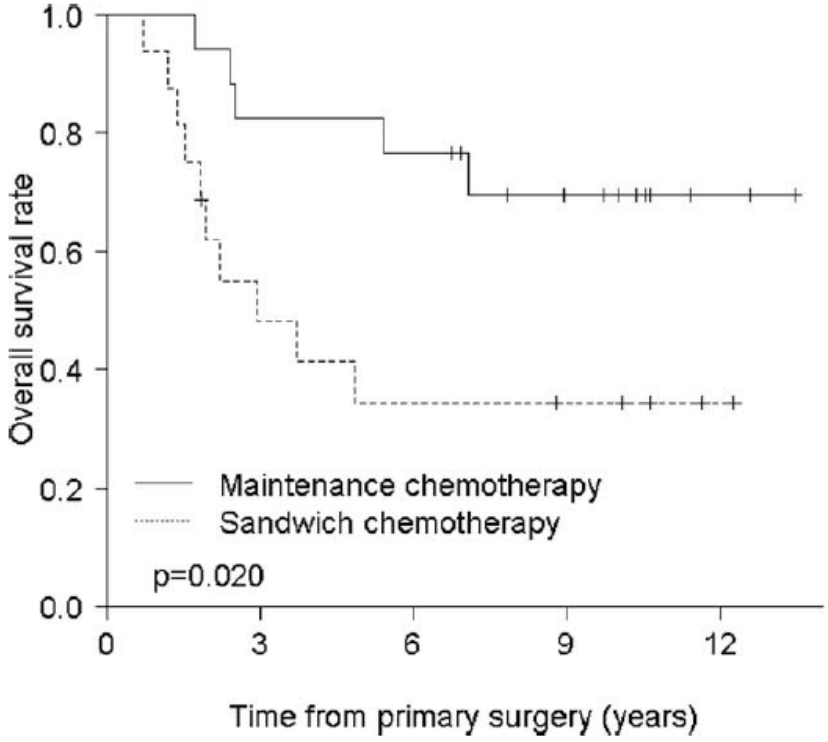


Fig. 4 – Overall survival of patients with complete staging and M1 disease according to therapy (as treated).

von Hoff K et al. Eur J Cancer 2009; 45:1209-17

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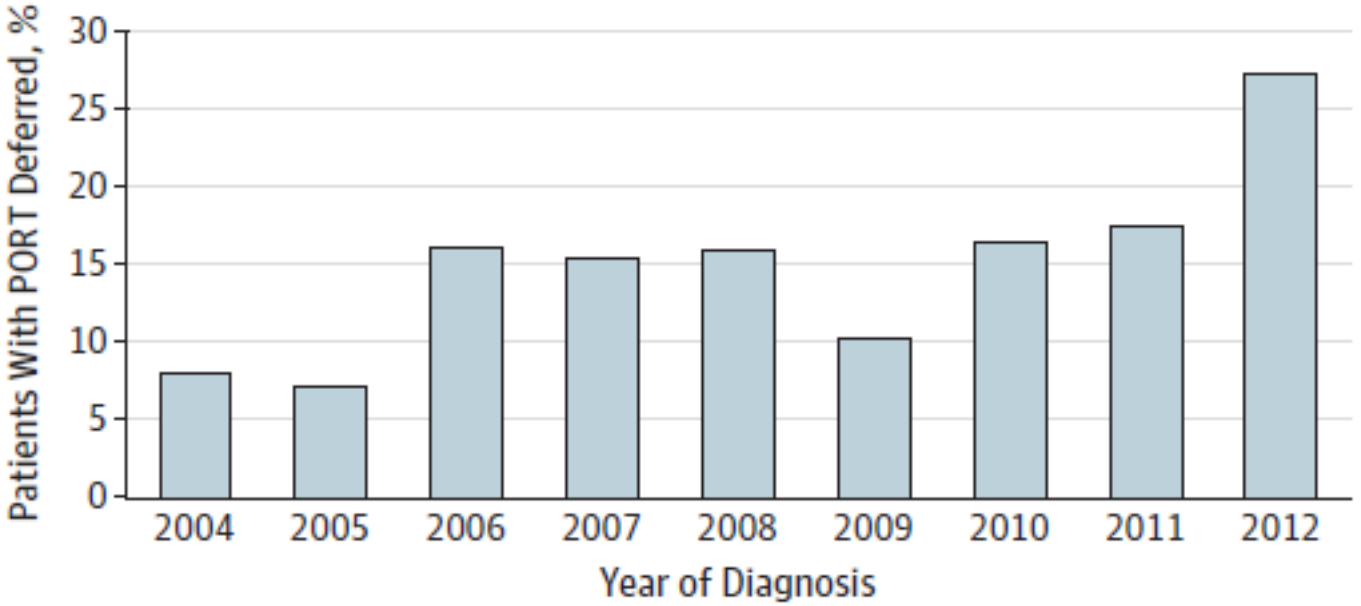
Radiotherapy Deferral/Delay > 90 days

Figure 1. Percentage Distribution by Year of Diagnosis of 816 Patients Age 3 to 8 Years With Postoperative Radiotherapy (PORT) Deferred



Kann BH et al. JAMA Oncol 2016; published online Aug 4, 2016

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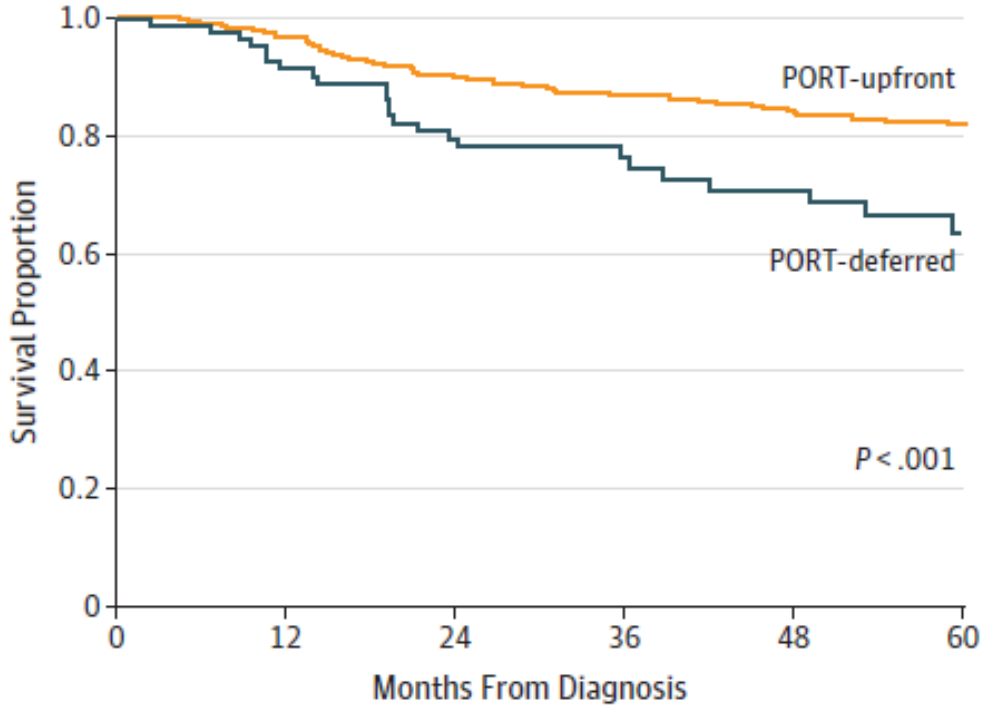
Radiotherapy Deferral/Delay > 90 days

Figure 2. Plot of Overall Survival for All 474 Patients Included in Survival Analysis



No. at risk						
PORT-deferred	83	73	55	43	33	21
PORT-upfront	391	367	321	264	204	155

PORT indicates postoperative radiotherapy.

Kann BH et al. JAMA Oncol 2016; published online Aug 4, 2016

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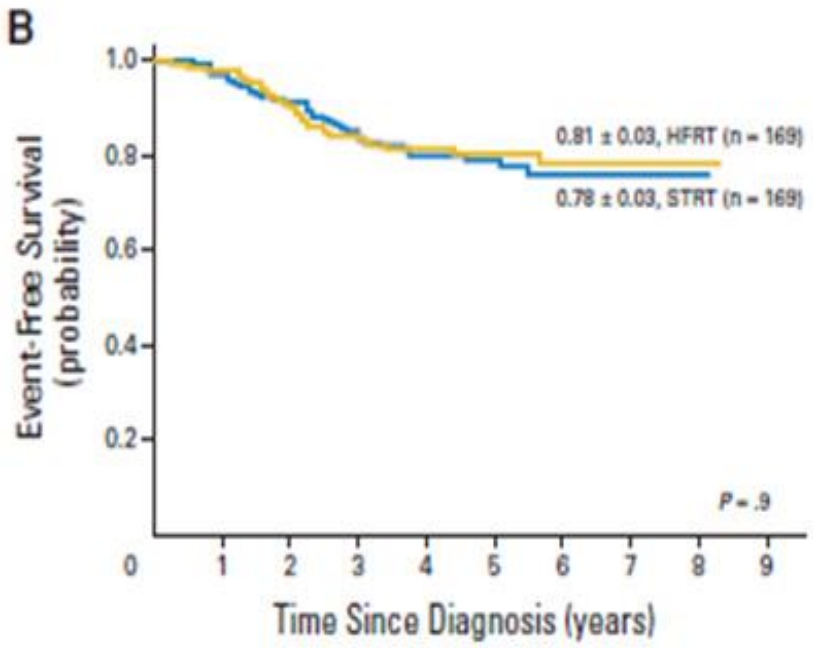
Hyperfractionated Radiotherapy (HIT-SIOP PNET 4)

340 children (age 4 to 21 years) with standard-risk medulloblastoma randomized to hyperfractionated RT (36 Gy CSI, 60 Gy whole posterior fossa, 68 Gy tumor bed at 1 Gy BID) and conventional RT (23.4 Gy, 54 Gy whole posterior fossa at 1.8 Gy daily)

8 cycles of cisplatin, lomustine and vincristine



Severe hearing loss was not different
In the two groups

Lannering B et al. J Clin Oncol 2012; 30:3187-93

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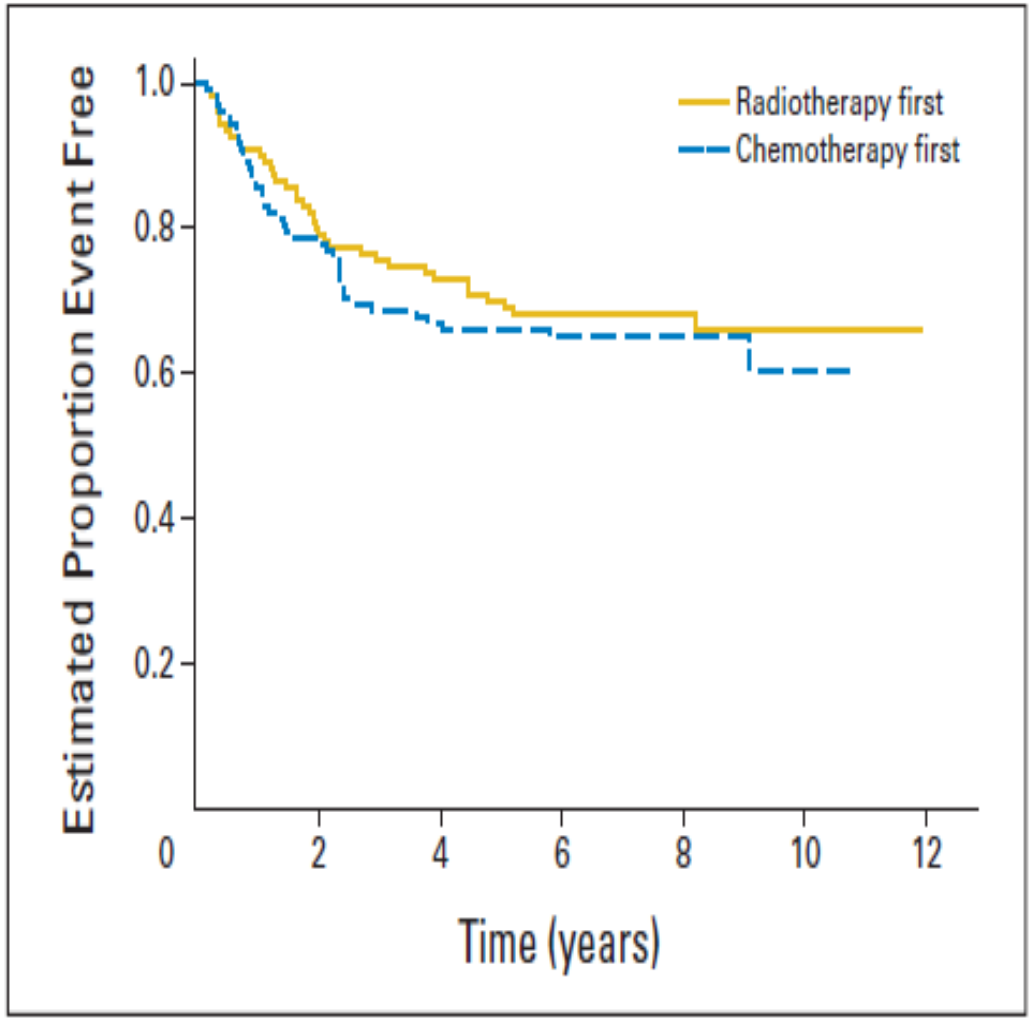
Standard-Risk Medulloblastoma

Study	Treatment	Chemotherapy	5-year EFS	5-year OS
SJMB96 (Gajjar)	23.4 Gy CSI, 36 Gy PF, 55.8 Gy/31 fx TB	Yes	83%	85%
Packer (CCG A9961)	23.4 Gy CSI, 55.8 Gy PF	Yes	81%	86%
Lannering (HIT SIOP PNET 4)	23.4 Gy CSI, PF 55.8 Gy	Yes	77%	87%

POG9031: High-Risk Medulloblastoma

- 112 patients randomized to each arm
- 35.2 Gy-40 Gy CSI
- 3 cycles of CDDP and VP-16 prior to XRT or XRT followed by the same chemotherapy. Both received consolidative vincristine and cyclophosphamide
- Five-year EFS:66% (Chemo first arm) and 70% (XRT first arm), p=0.54



Tarbell NJ et al. J Clin Oncol 2013; 31:2936-41

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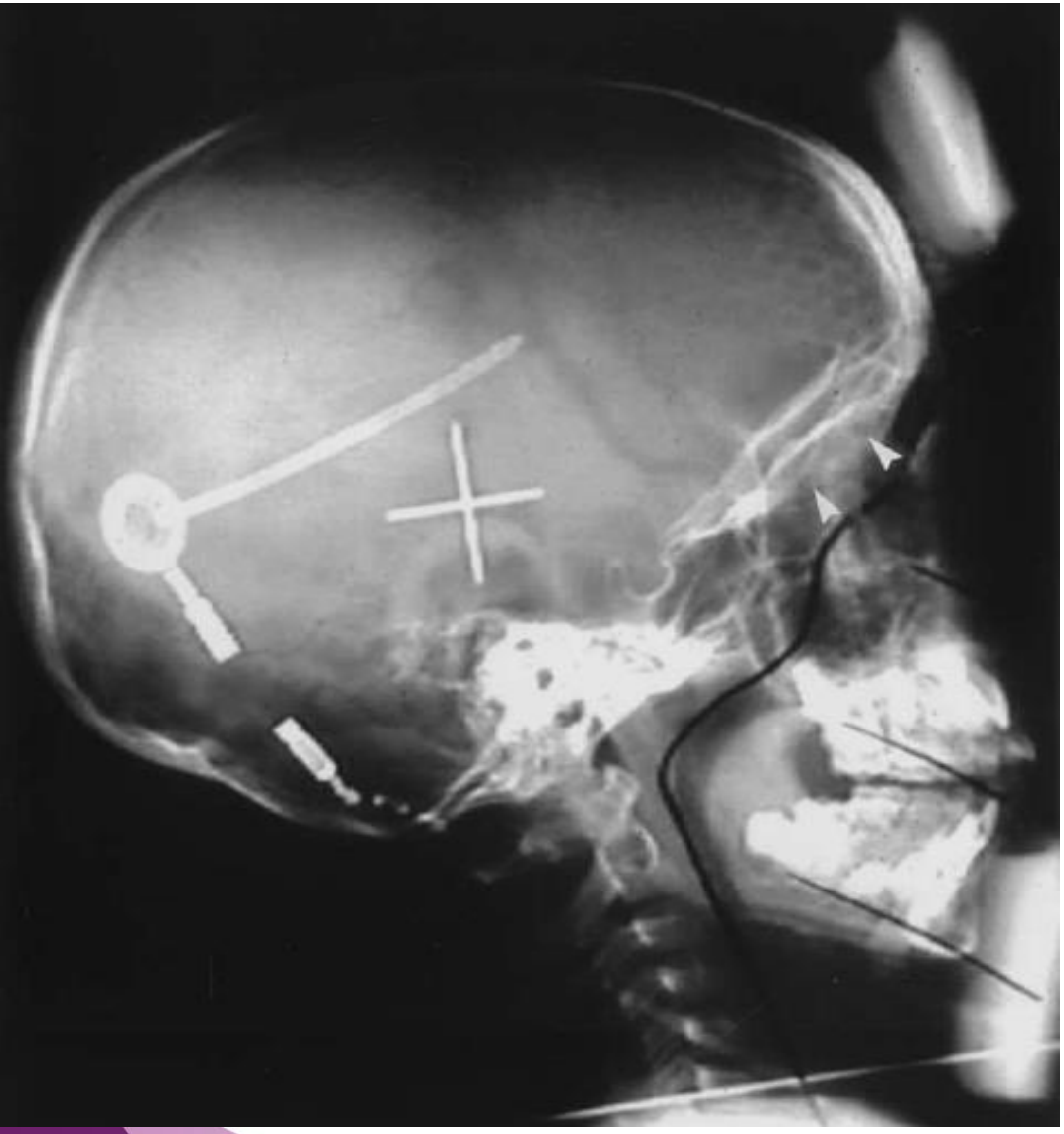
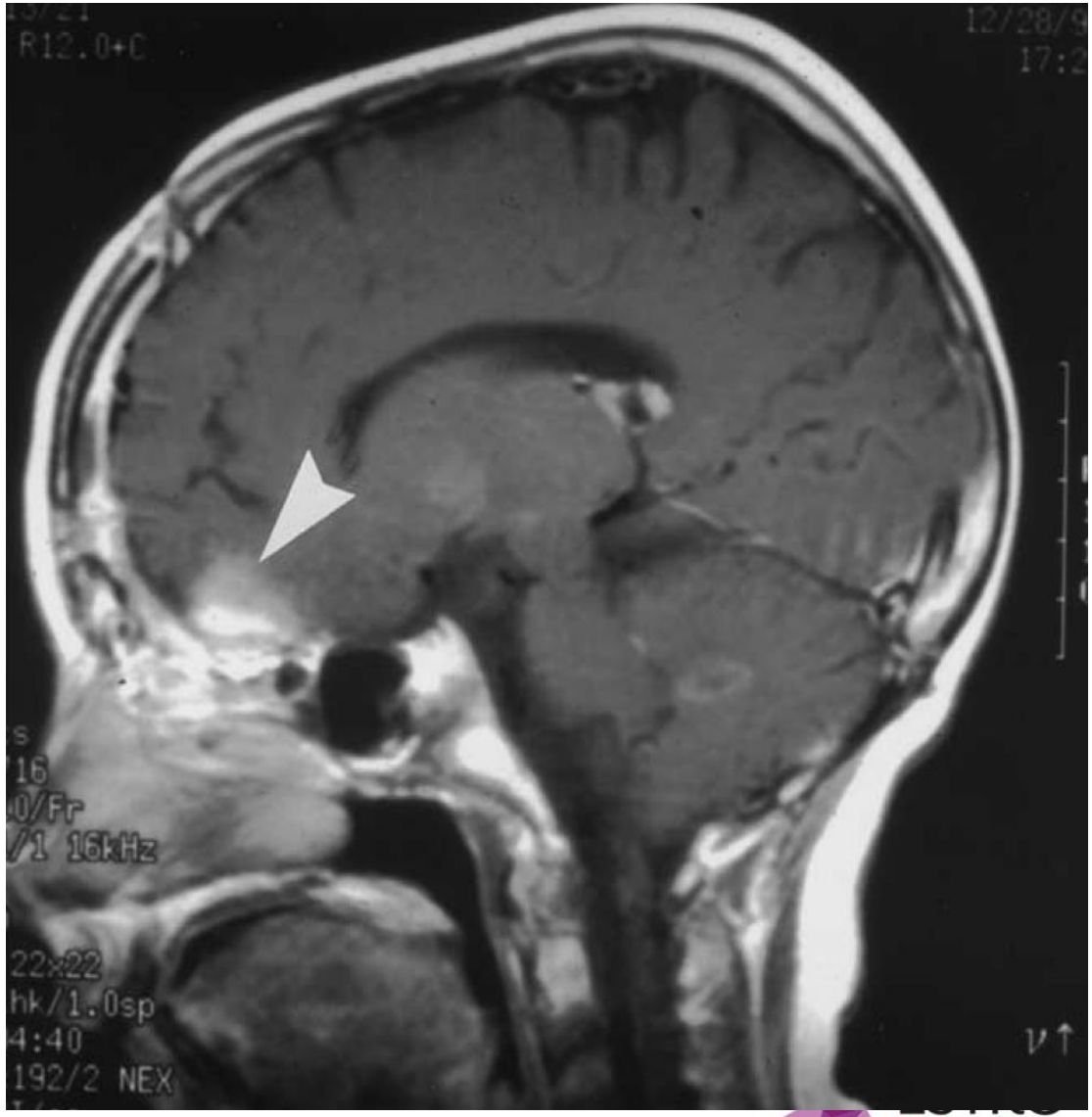
Cribriform Plate and Subfrontal Recurrence





Thecal Sac Termination

- Traditional teaching is to place lower border of spinal field at bottom of S2
- Several studies have shown that termination of thecal varies according to patient anatomy with most being at S2 but can be from S1 to S4
- Need to look at MRI of spine to determine termination of thecal sac

Thecal Sac Termination

Radiologic (MRI)

Vertebral level	Frequency
S1	4 (17%)
Upper S2	3 (13%)
Mid S2	2 (8%)
Lower S2	7 (29%)
Upper S3	5 (21%)
Mid S3	1 (4%)
Lower S3	1 (4%)
S4	1 (4%)

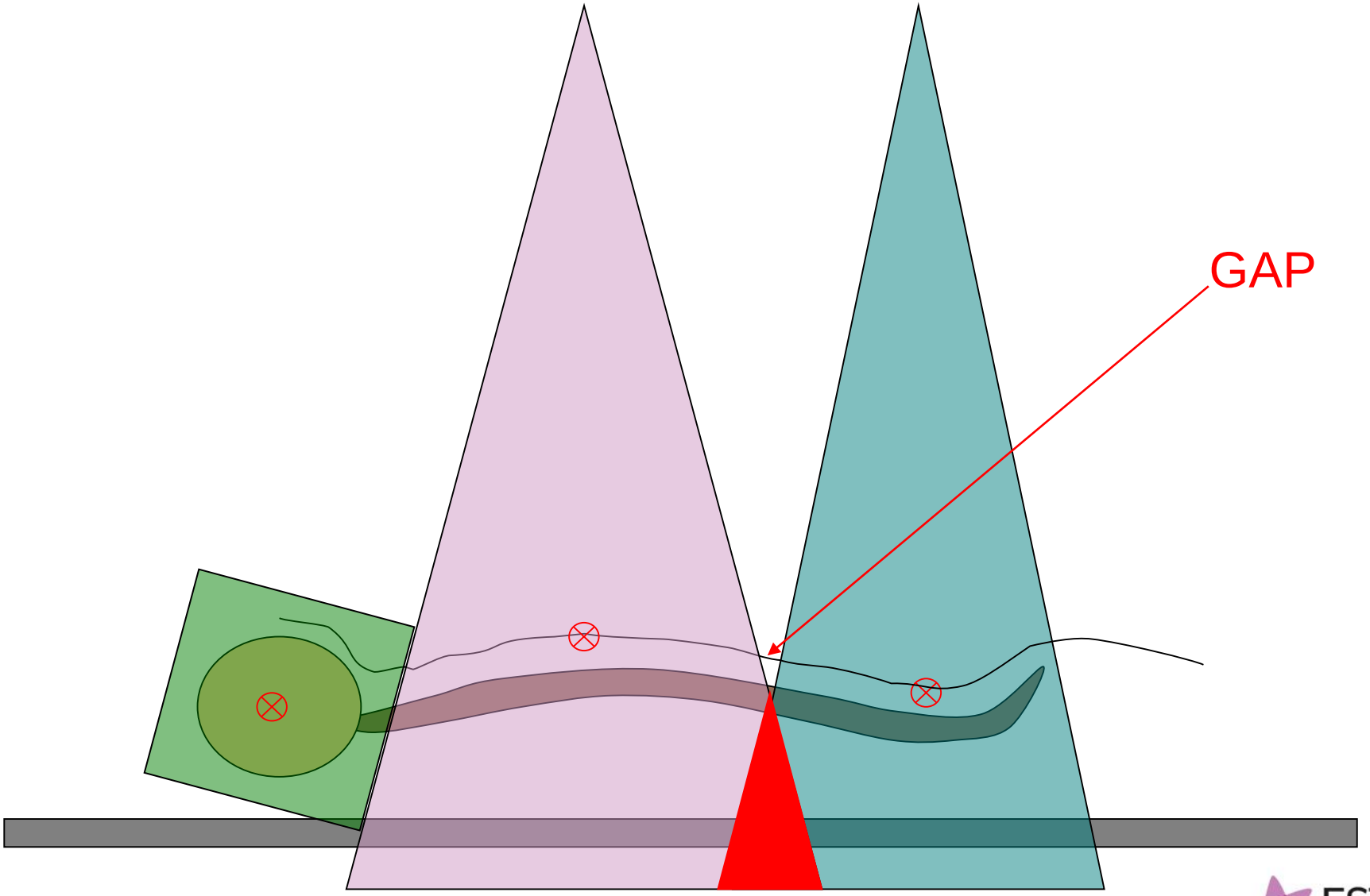
Dunbar SF et al. Int J Radiat Oncol Biol Phys 1993; 26:669-73

Cadaveric Study

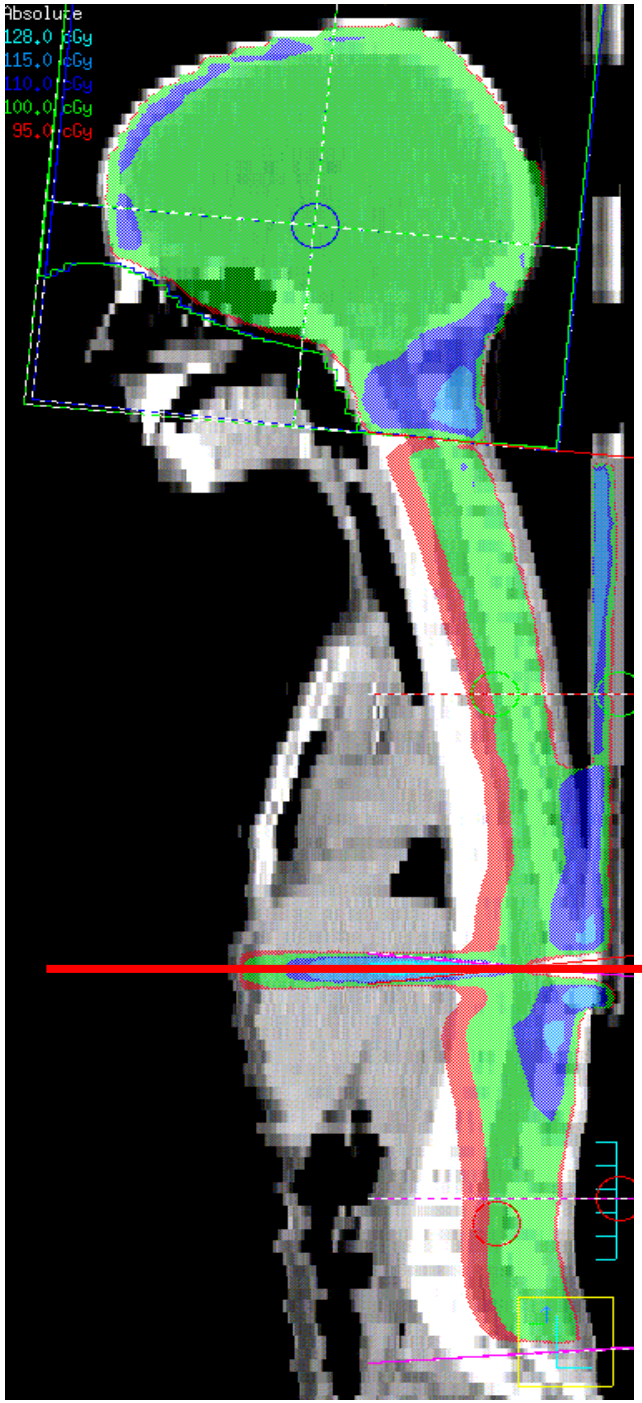
Vertebral level	Frequency
Mid S1	2 (7%)
Lower S1	1 (4%)
S1-S2	7 (26%)
Upper S2	1 (4%)
Mid S2	5 (19%)
Lower S2	2 (7%)
S2-S3	6 (22%)
Upper S3	1 (4%)
Mid S3	1 (4%)
S3-S4	1 (4%)

Hansasuta A et al. Pediatr Neurosurg 1999; 30:176-9

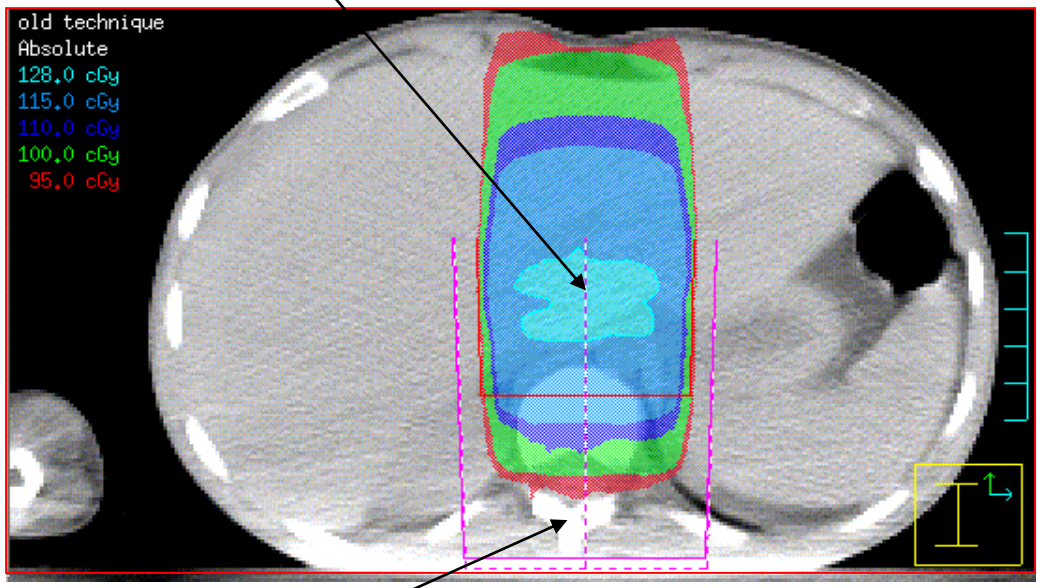
Prone Technique (traditional)



Gap and Overlap



overlap



gap

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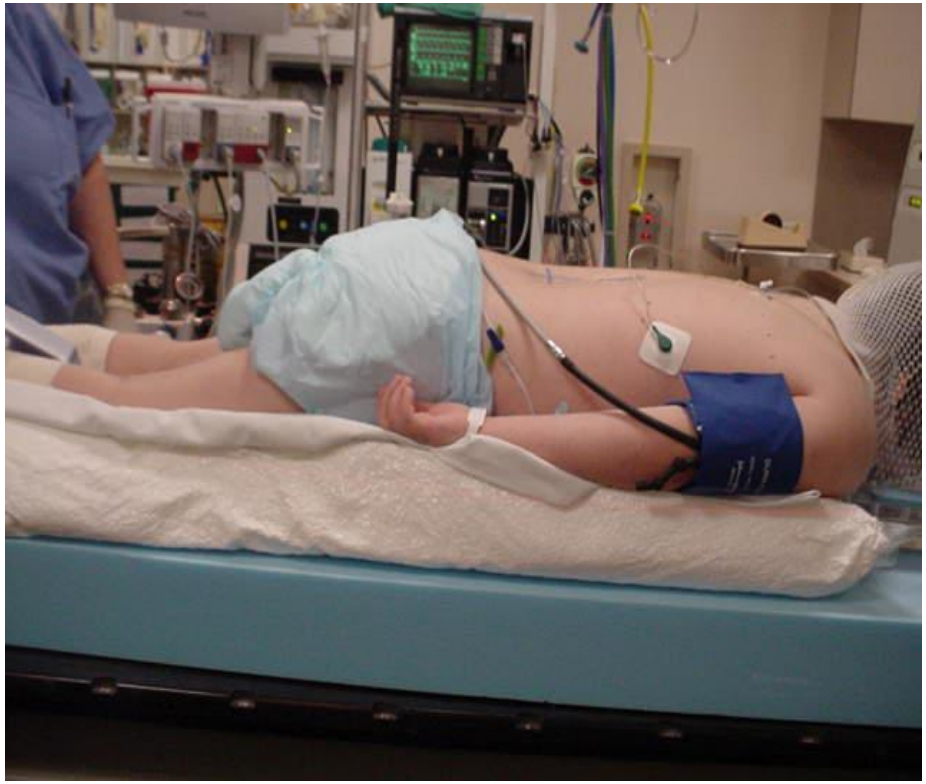
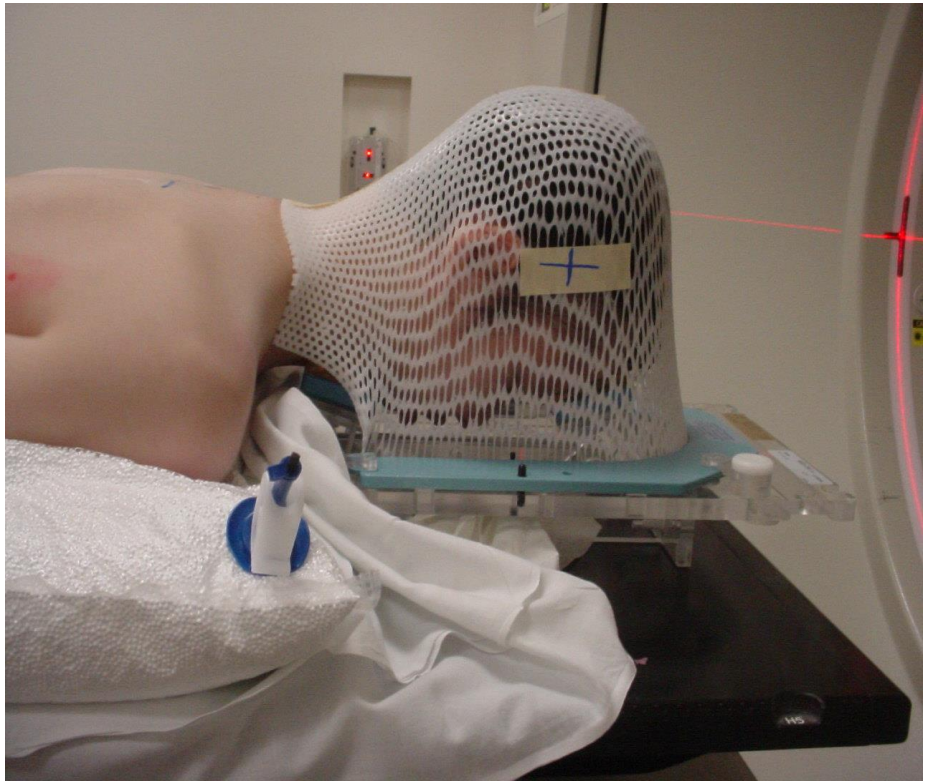
Some tips for craniospinal irradiation

- Need to make sure junctions are not overdosed or underdosed (junction change every 5 fractions or intrafraction junctions)
- Keep cranial-spinal junction low to lower dose to oral cavity and thyroid gland
- Put spine to spine junction below the distal end of spinal cord

Why Prone?





The entrance of all treatment fields can be directly visualized on the patient.

Prior to digital couch positioning there was no way to accurately shift the patient otherwise.

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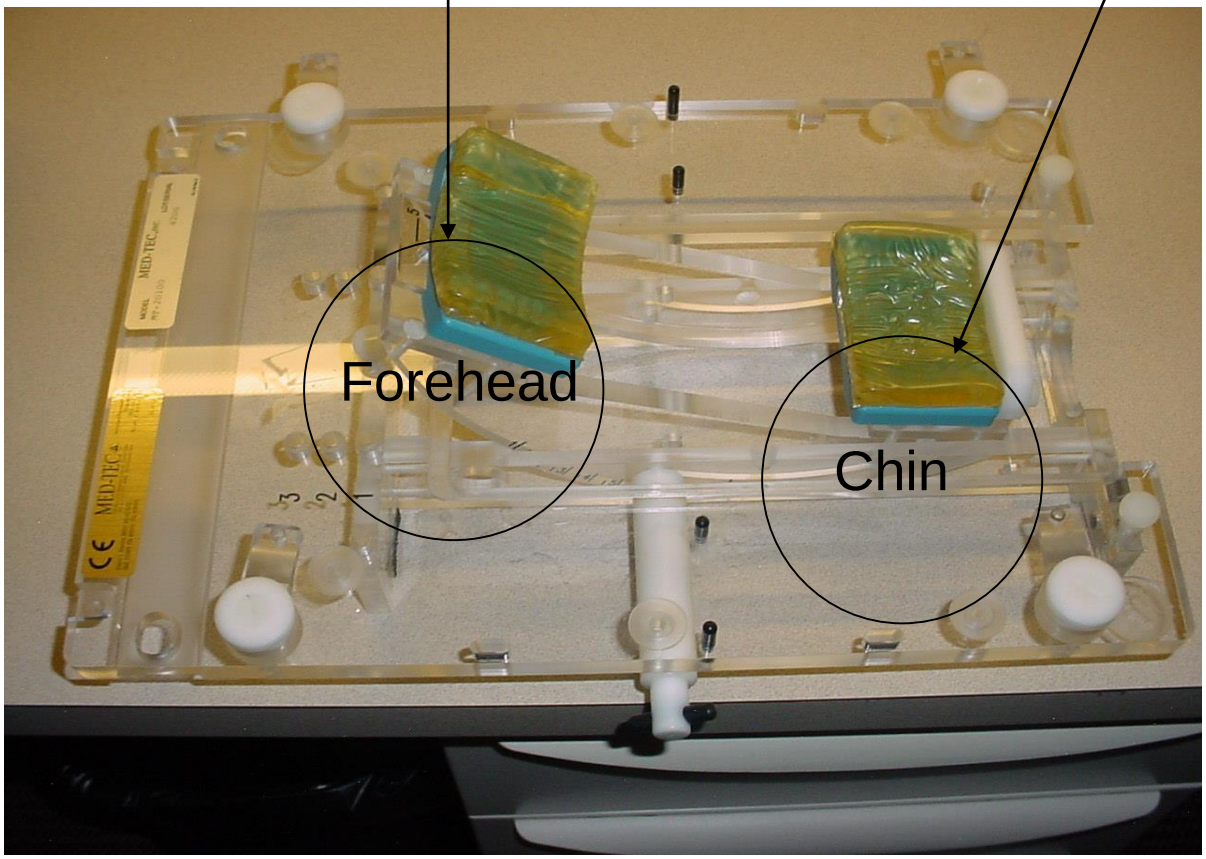
Prone Face Holder

Forehead holder cushioned but does not secure head in same place.

Chin holder is padded and has a solid plastic stop at the bottom.



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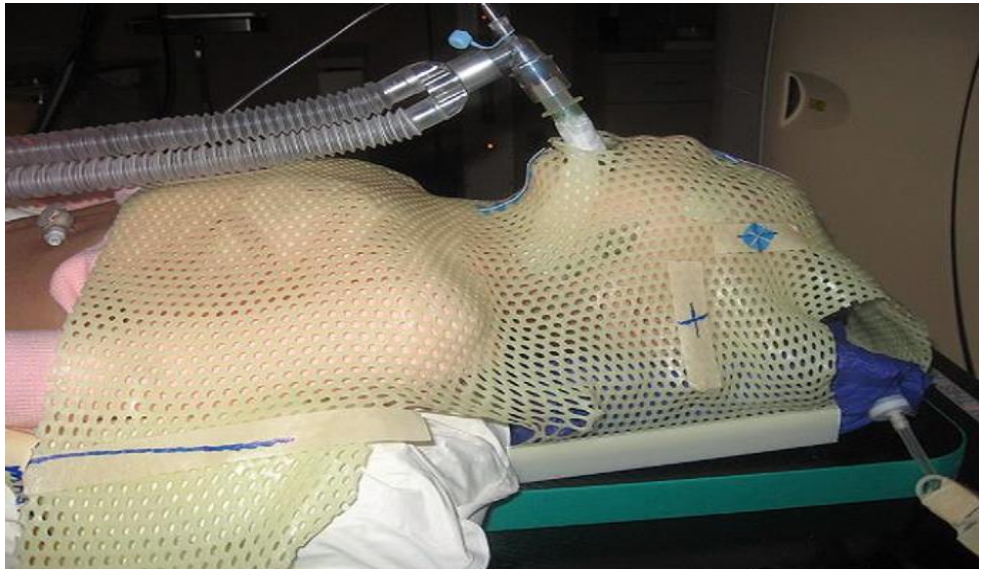
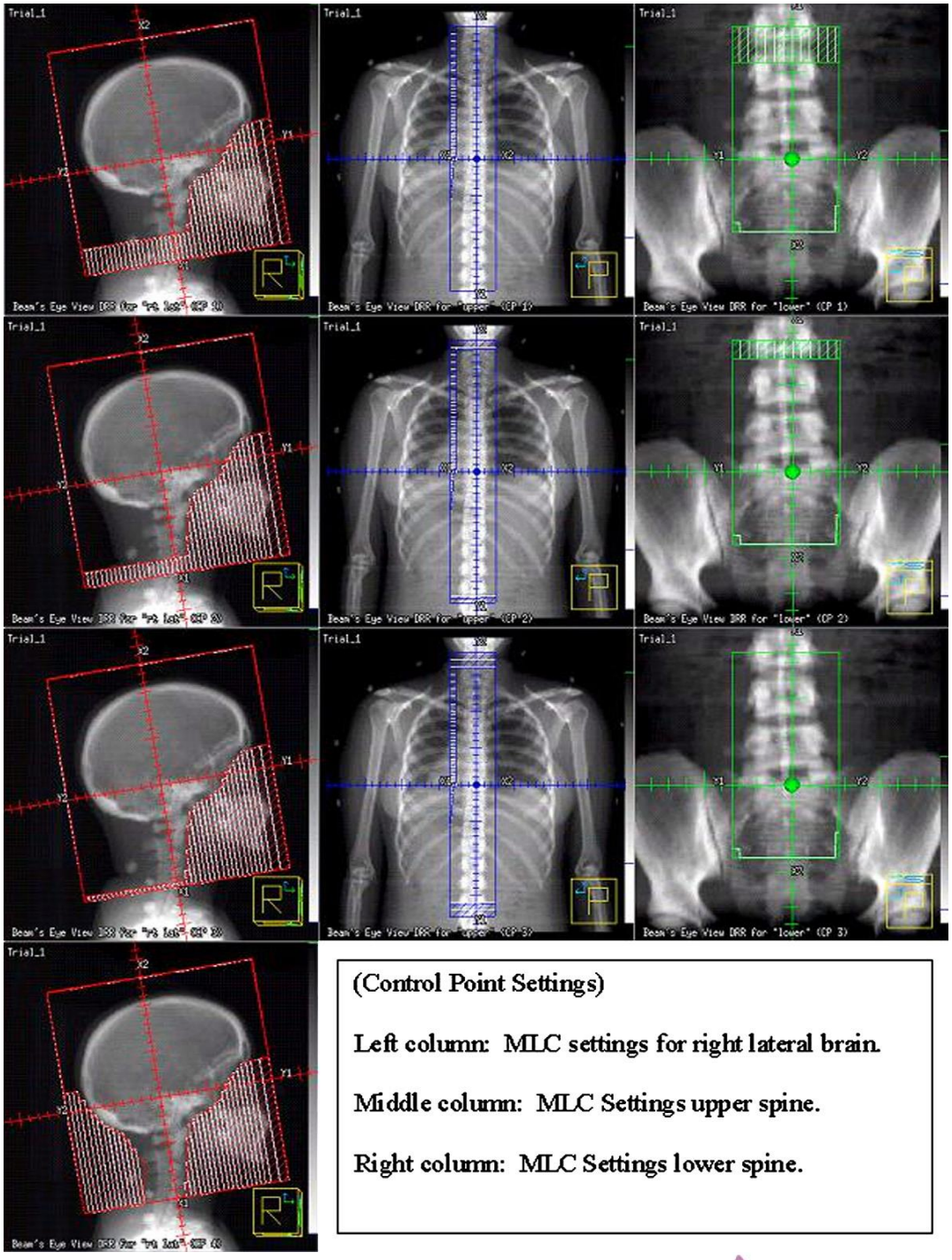
Why supine?

Less Discomfort
Less Movement and More Reproducible
Better Anesthesia Access

Initial experience of 23 pts with 21 month follow-up at The Methodist Hospital revealed no junction recurrences and no myelopathy



South M et al. Int J Radiat Oncol Biol Phys 2008; 71:477-83



(Control Point Settings)

Left column: MLC settings for right lateral brain.

Middle column: MLC Settings upper spine.

Right column: MLC Settings lower spine.

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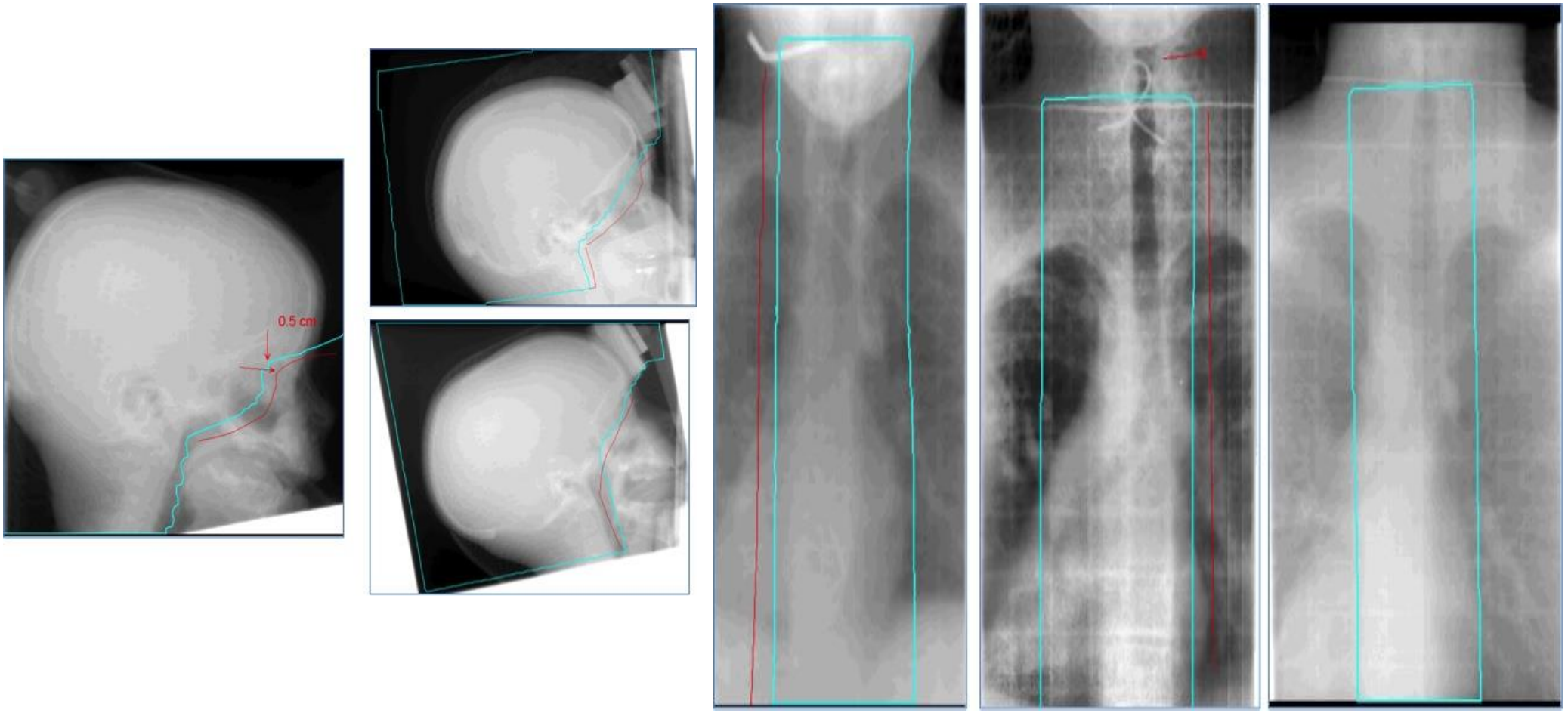
Prone vs. Supine Craniospinal Irradiation



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Prone vs. Supine CSI

Table 1 Port film rejection rates according to craniospinal position

Radiation therapy field	Prone	Supine	*P* value
Cranium	27/78 (35%)	6/73 (8%)	< .0001
Upper spine	16/75 (21%)	23/71 (32%)	.14
Lower spine	8/60 (13%)	8/42 (16%)	.41
Upper + lower spine	24/135 (18%)	31/113 (27%)	.09

Verma J et al. Pract Radiat Oncol 2015; 5:93-8

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Prone vs. Supine CSI

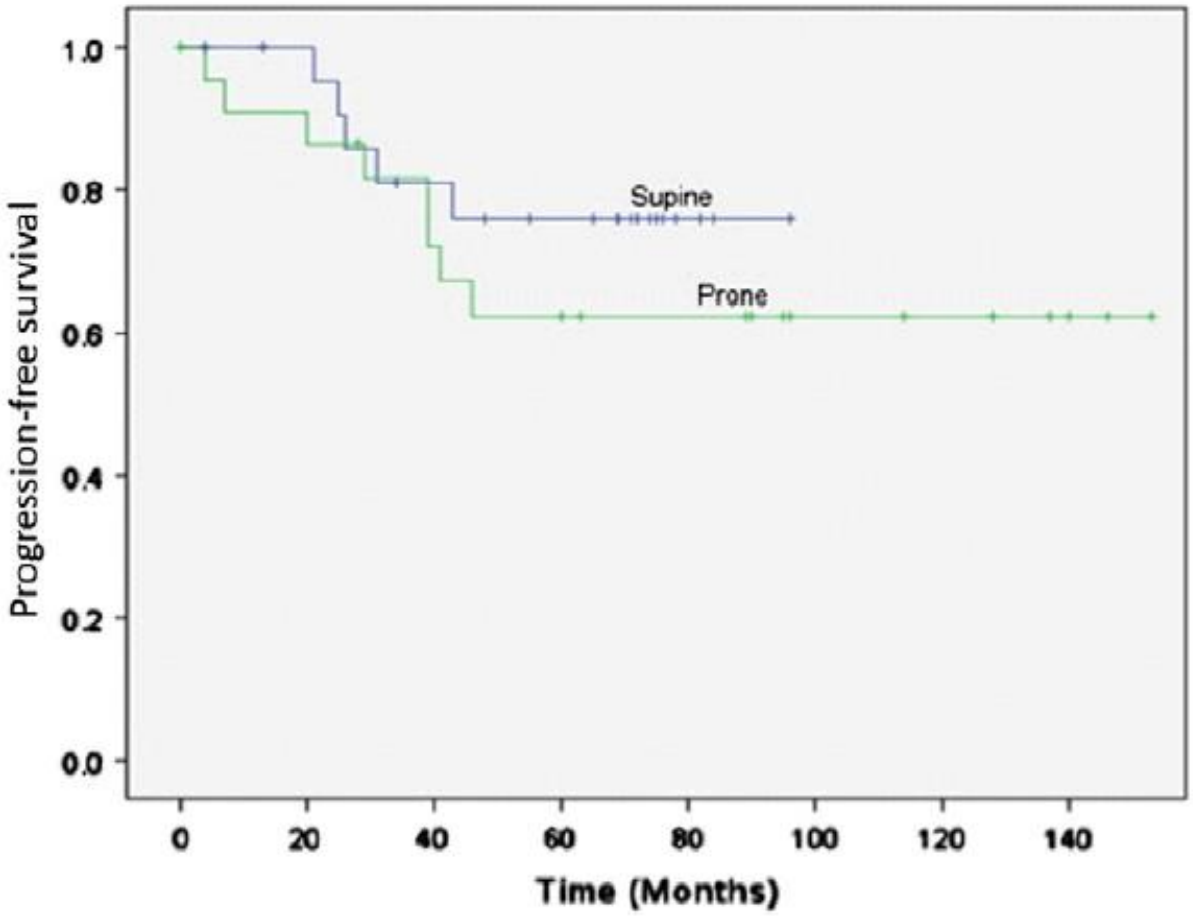

Figure 2 Progression-free survival of patients with medulloblastoma treated with supine and prone craniospinal irradiation, $P = .37$.

Verma J et al. Pract Radiat Oncol 2015; 5:93-8

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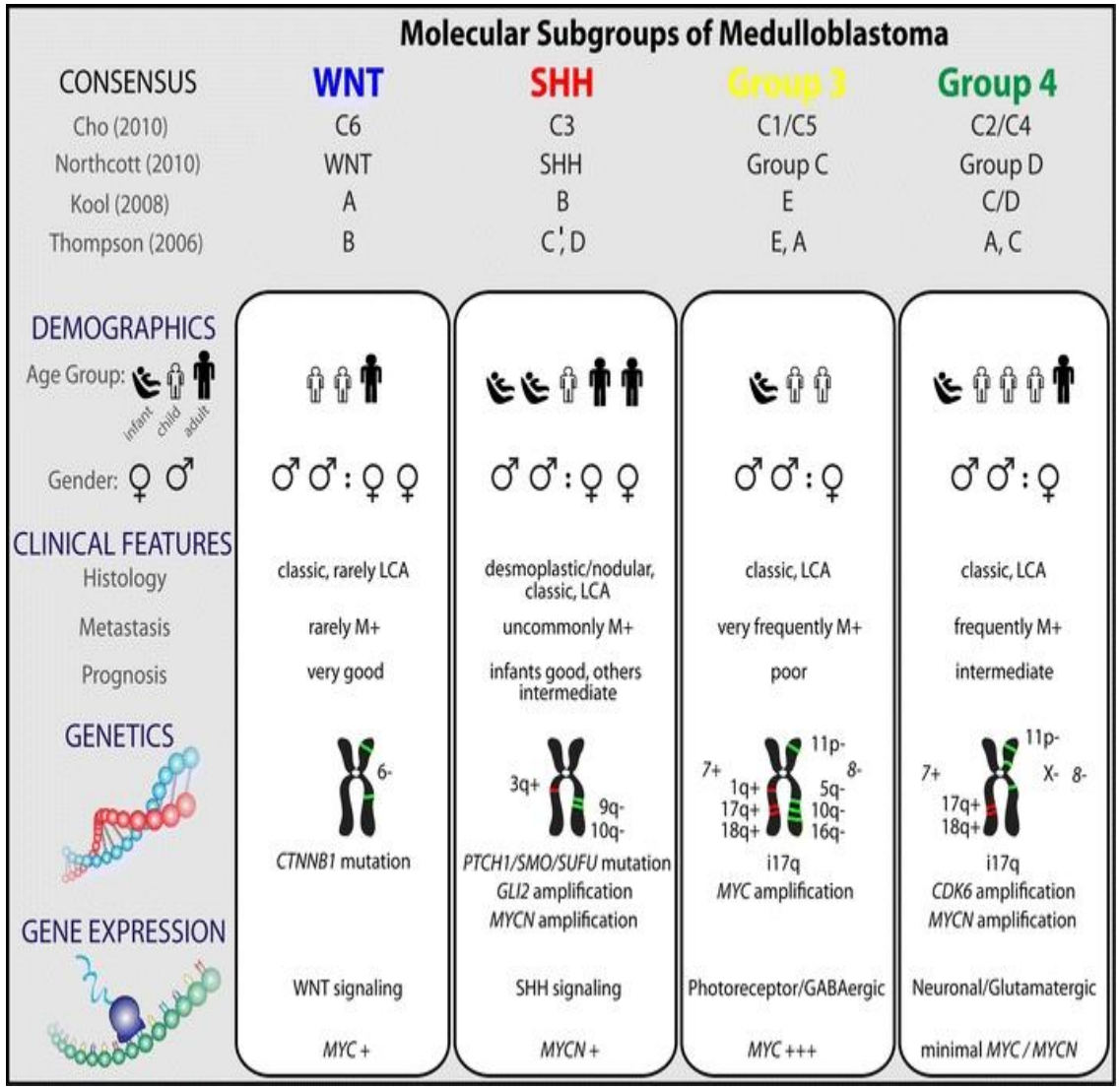
Molecular Subtypes of Medulloblastoma



Taylor MD et al. Acta Neuropathol 2012; 123:465-72

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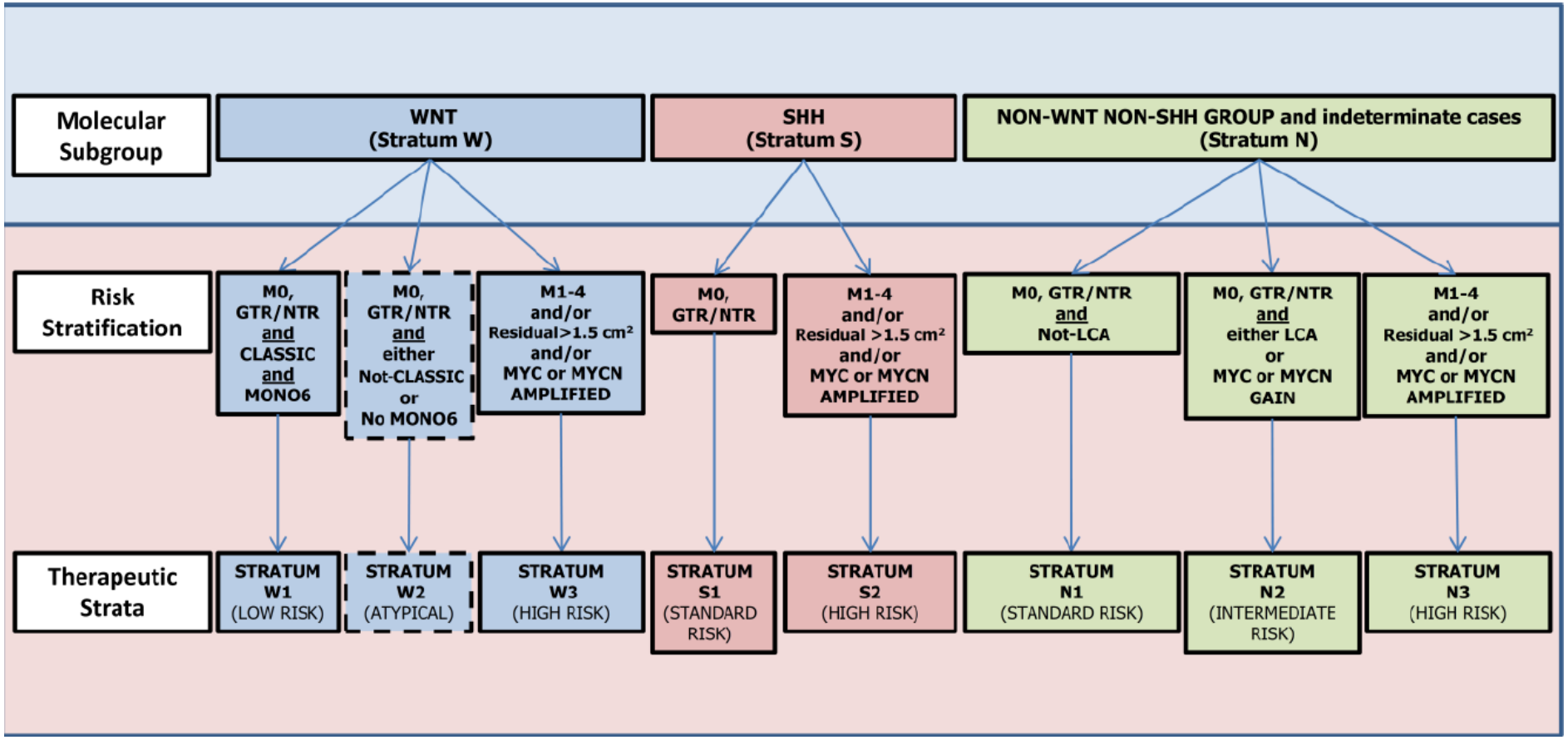
SJMB12 Protocol

A CLINICAL AND MOLECULAR RISK-DIRECTED THERAPY FOR NEWLY DIAGNOSED MEDULLOBLASTOMA (SJMB12)

Study design:



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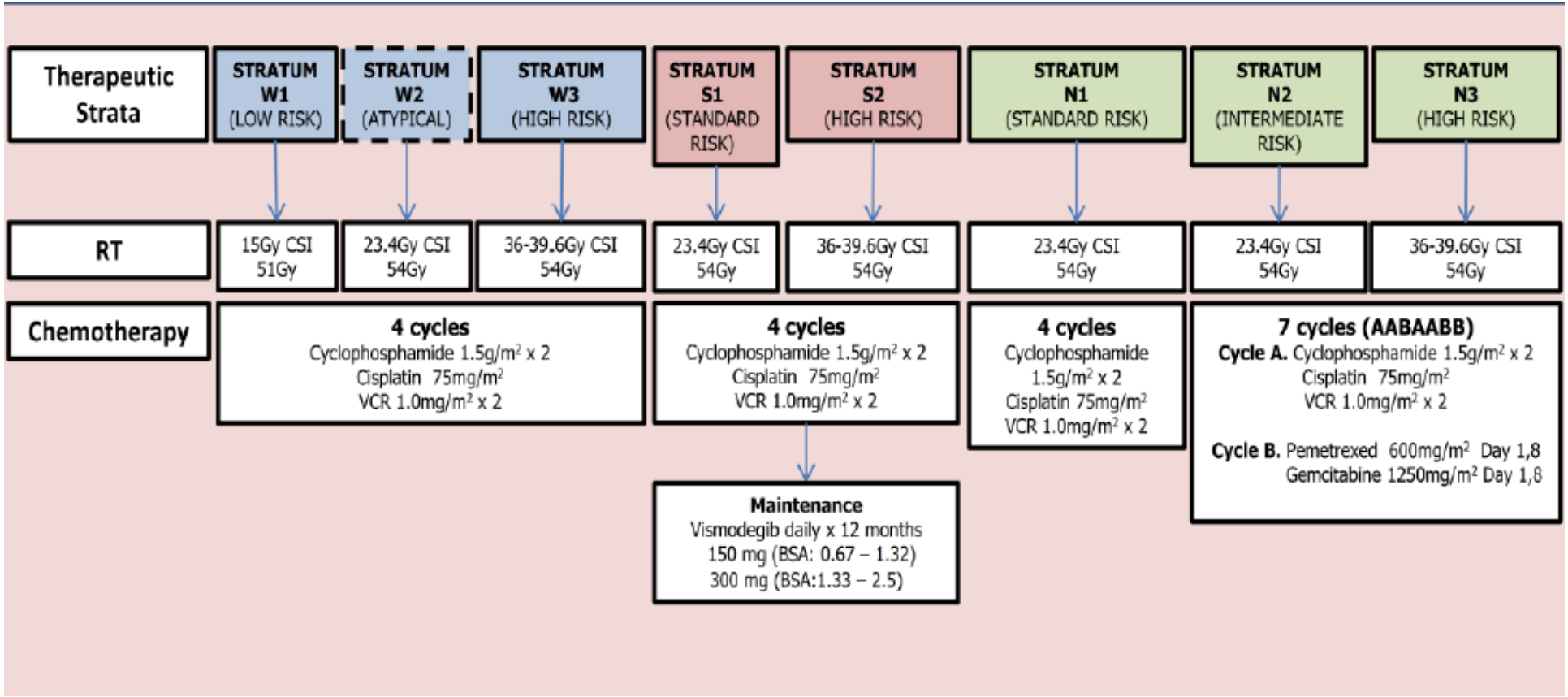
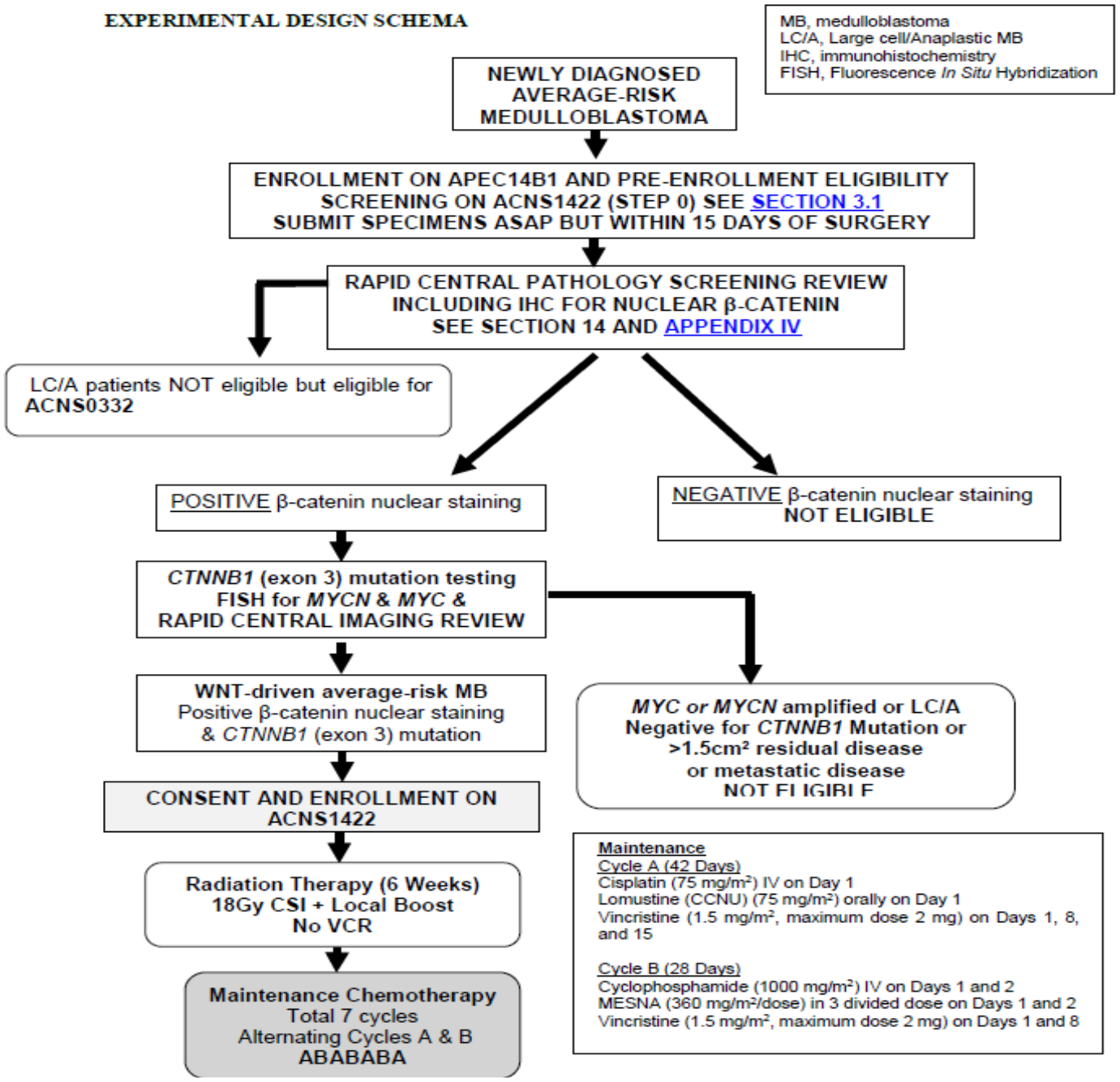
SJMB12 Protocol



Children's Oncology Group ACNS1422



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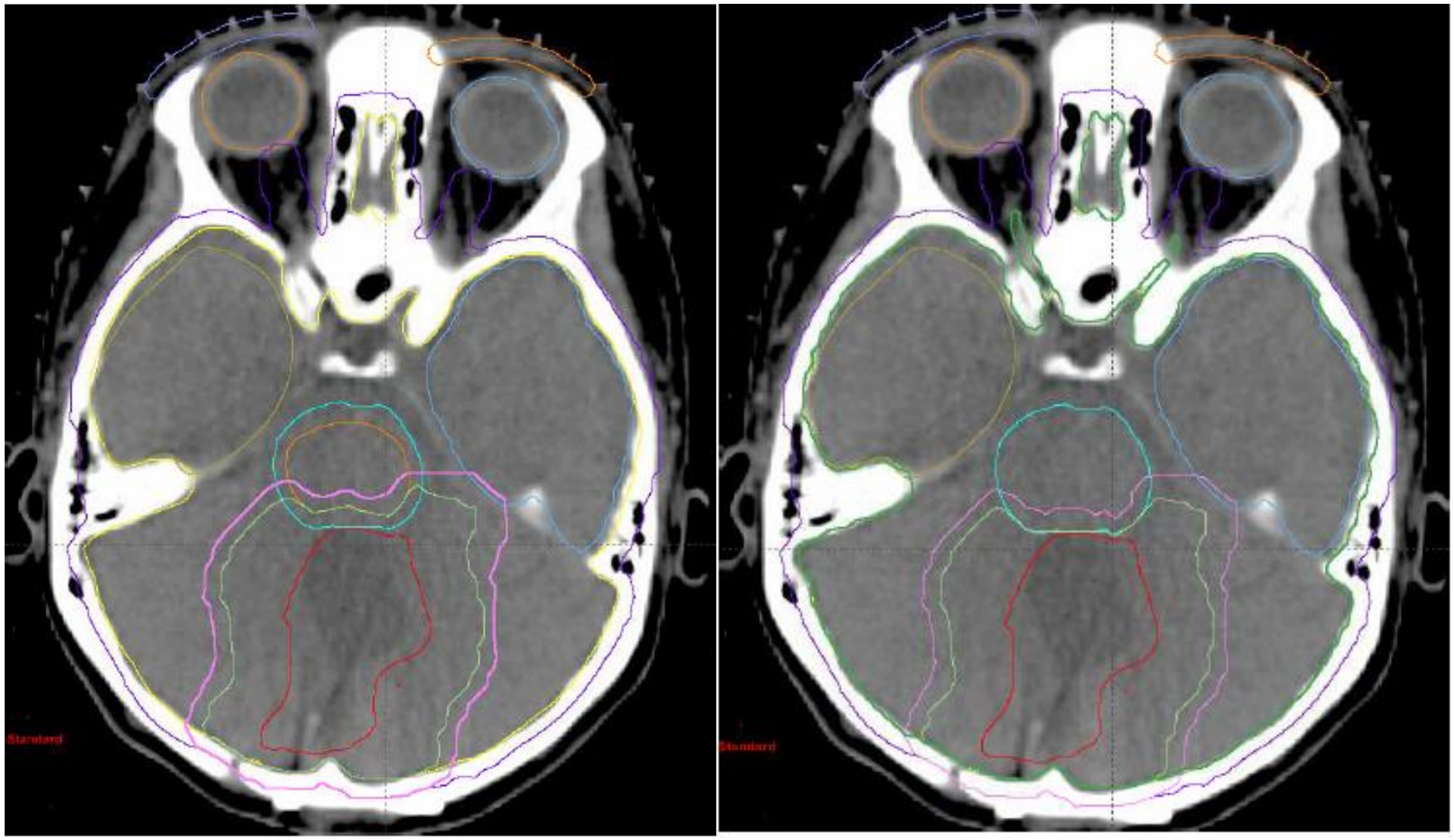
Children’s Oncology Group ACNS1422



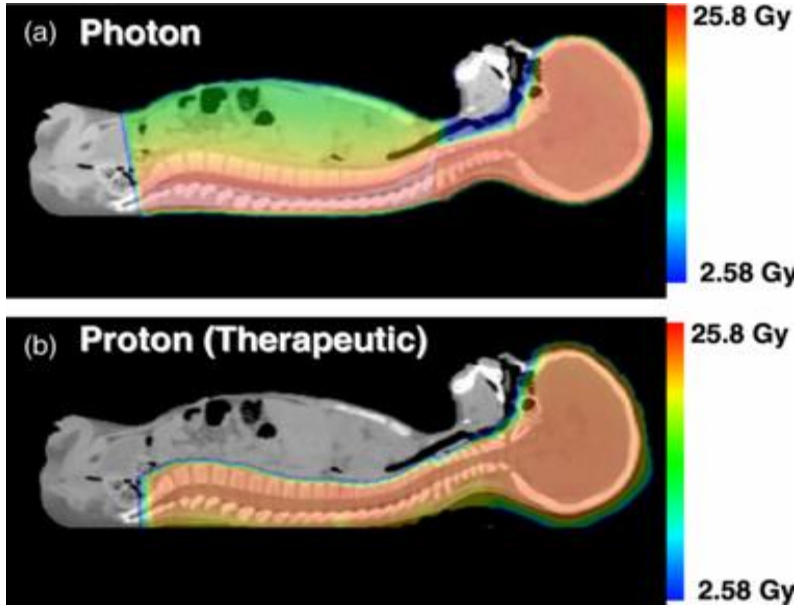
Protons for Childhood Medulloblastoma

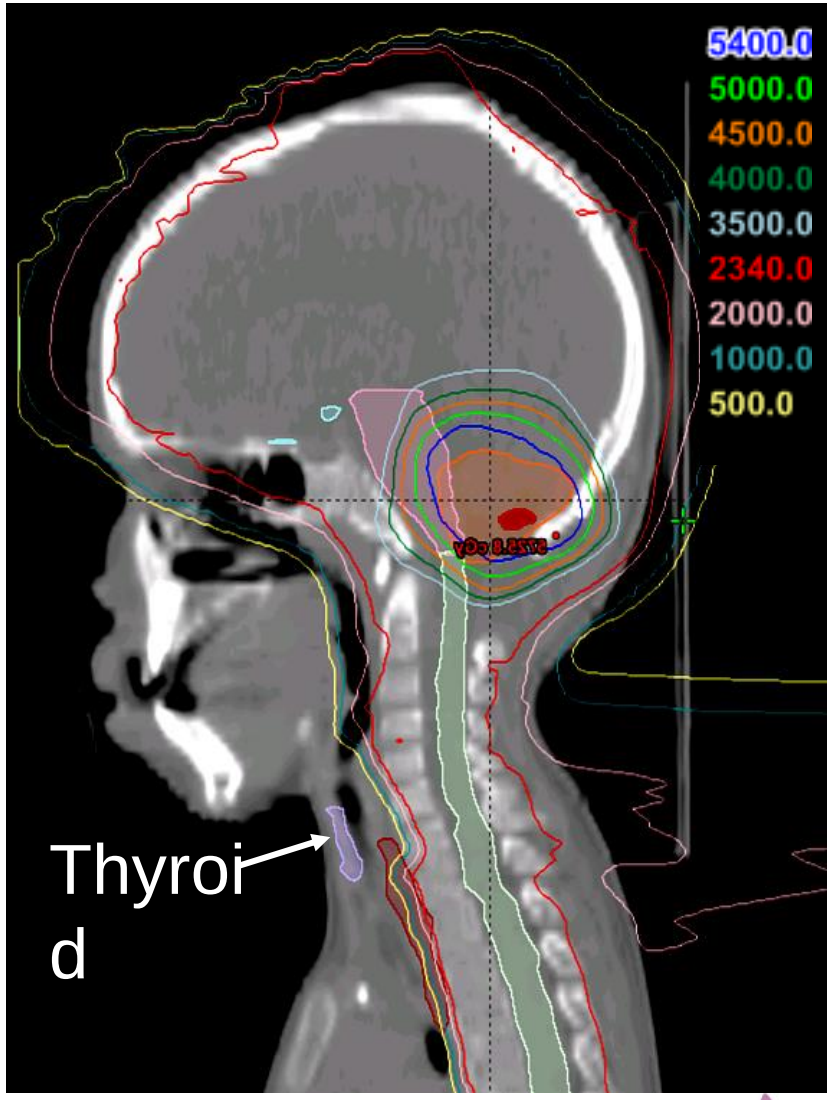
- 109 children treated at MGH from 2002-2011
- Median follow-up: 38.8 months
- 16 relapses (14.7%) noted
- Relapses were supratentorial in 8, spinal in 11 and tumor bed (posterior fossa) in 5
- One isolated spinal failure at junction of 2 fields

Sethi RV et al. Int J Radiat Oncol Biol Phys 2014; 88:655-63

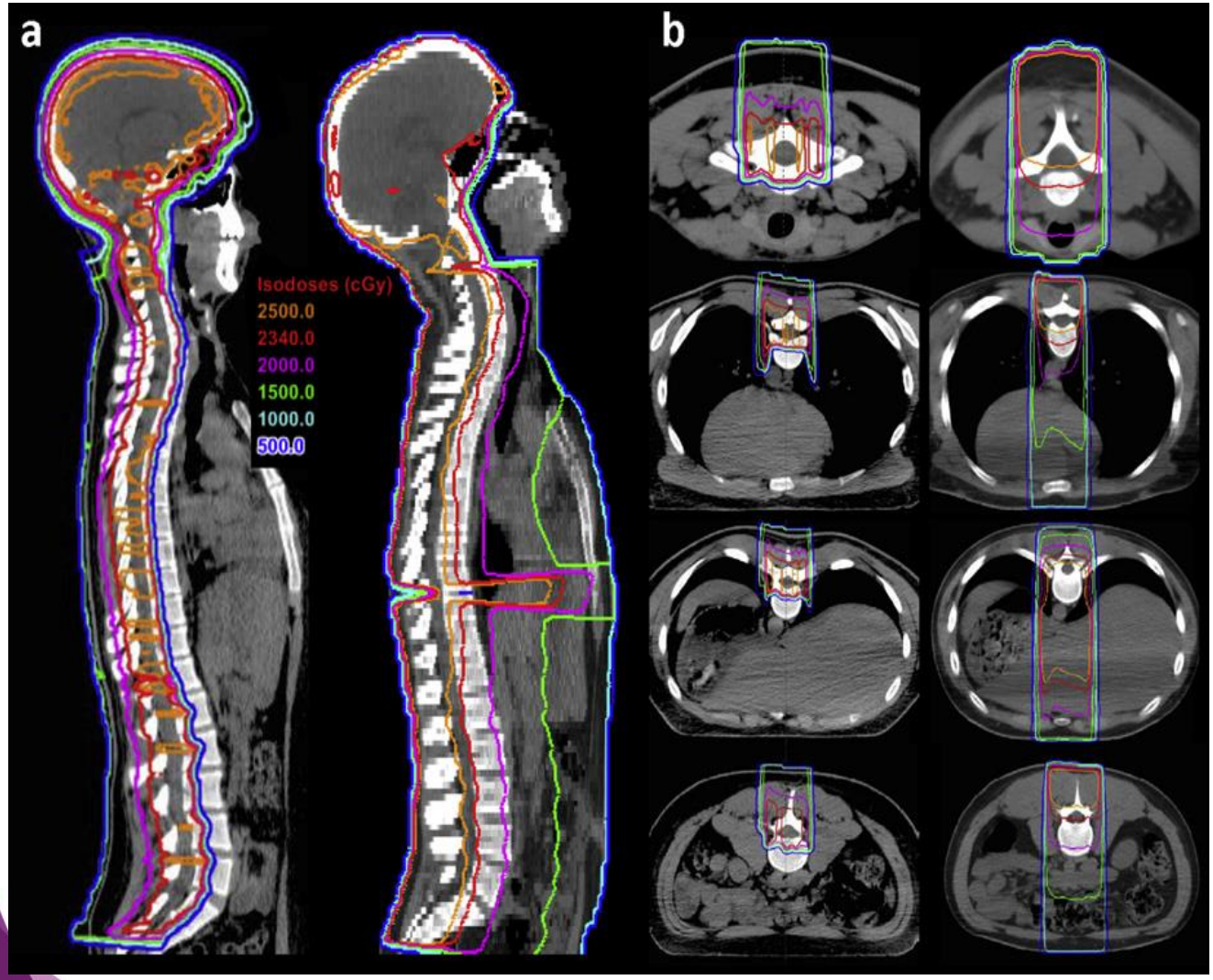
Proton CSI for Medulloblastoma

Organ	Mean Dose (Gy)	Maximum Dose (Gy)
Thyroid	0	4
Testis	0	0
Pituitary	24	24
Hypothalamus	25	30
Esophagus	9	25





Proton Craniospinal Irradiation



	Proton	Photon
Weight loss > 5% p=0.004	16%	64%
Grade 2 nausea/ vomiting p=0.004	26%	71%
Esophagitis (medical management) p<0.001	5%	57%
Anemia p=0.04	17%	48%

Less Acute Toxicity

Brown AP et al. Int J Radiat Oncol Biol Phys 2013; 86:277-84

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Medulloblastoma
Hypothyroidism

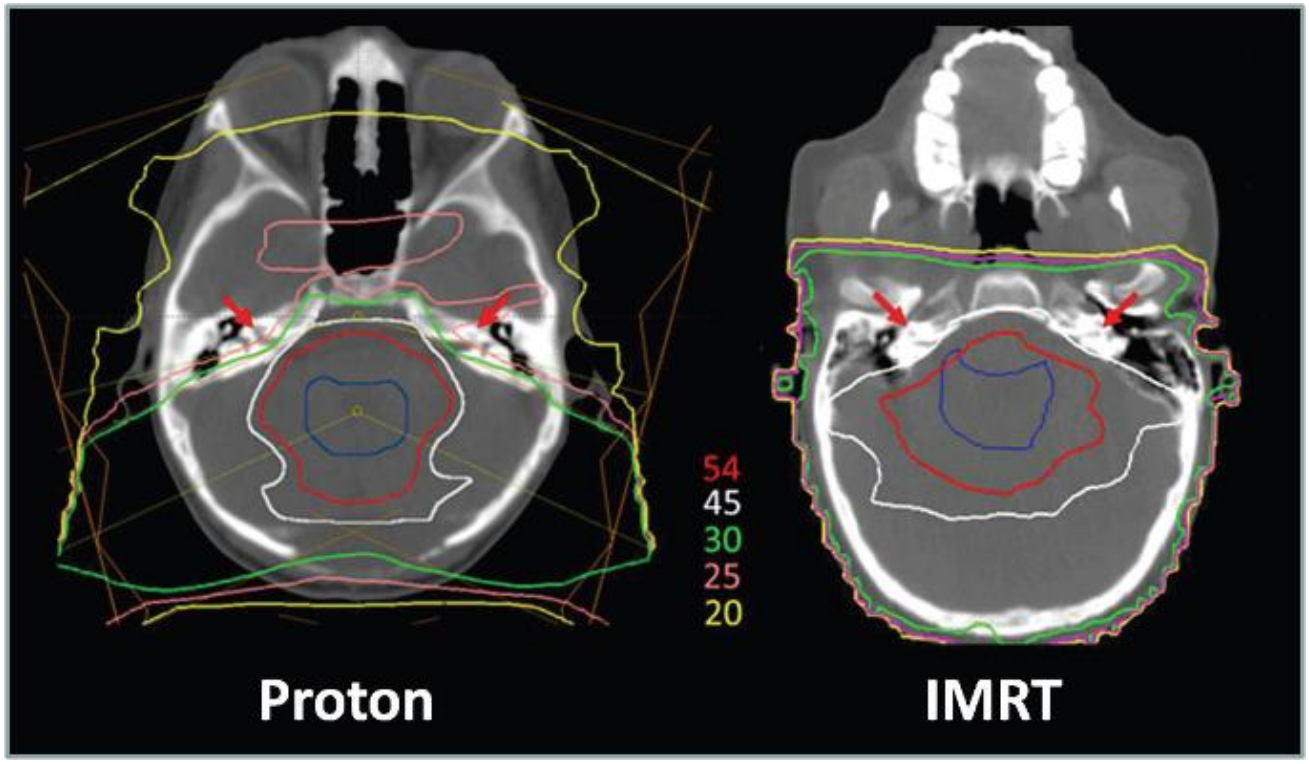
	Proportion with Hypothyroidism
Protons (MGH)	9/40 (22.5%)
Photons (Emory)	24/37 (64.9%)

P < 0.001

Eaton BR et al. Neuro Oncol 2016; 18:881-7

Medulloblastoma

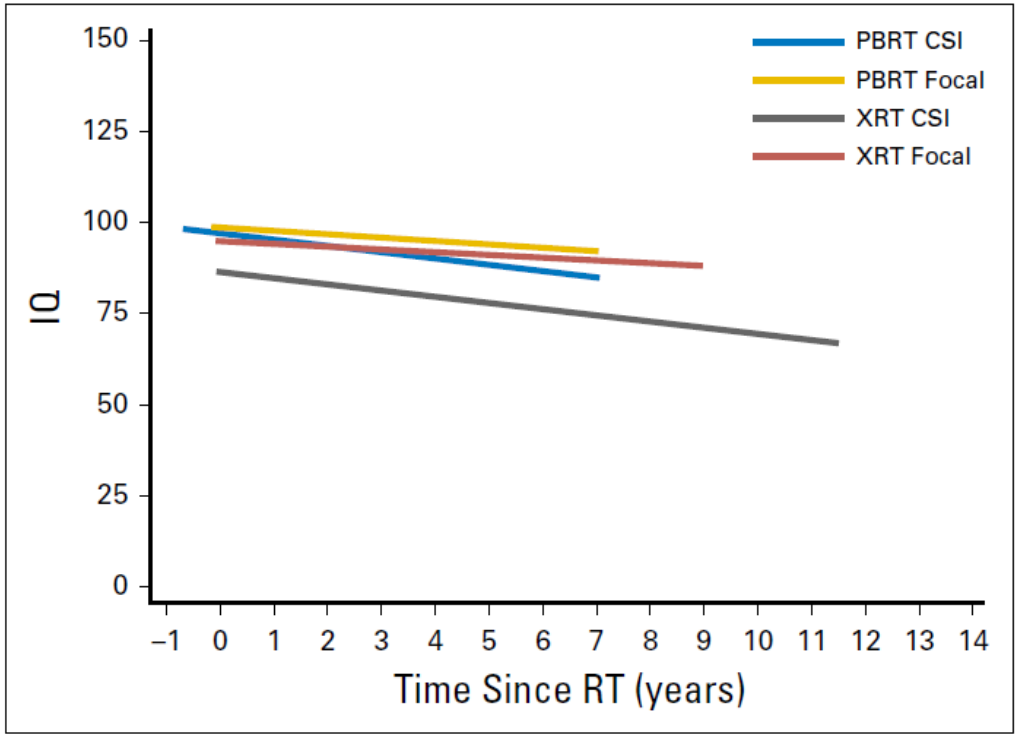
Ototoxicity



Moeller BJ et al. Radiat Oncol 2011; 6:58

Pediatric Brain Tumors and IQ

MD Anderson Proton Center/TCH Experience



Protons: -0.7 IQ points/year (p = 0.13)
Photons: -1.1 IQ points/year (p = 0.004)

Kahalley LS et al. J Clin Oncol 2016; 34:1043-9

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Standard-Risk Medulloblastoma Survival Outcomes

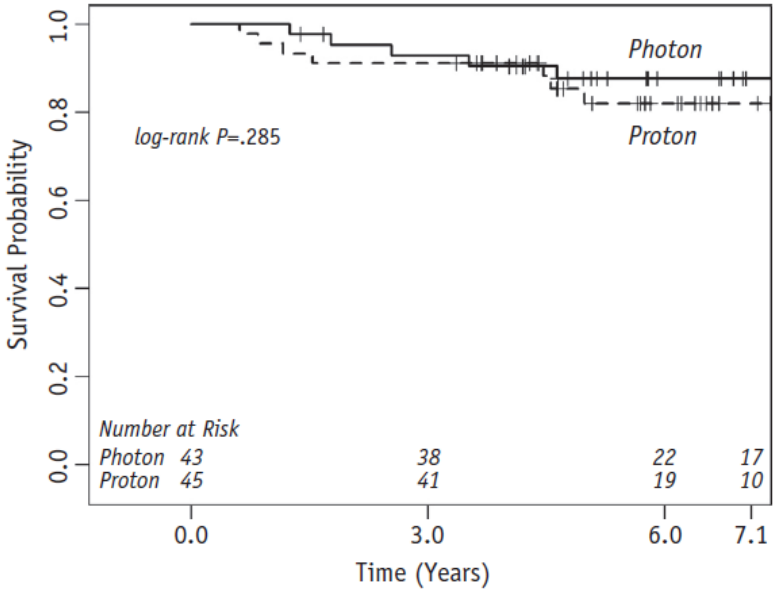

Fig. 1. Kaplan-Meier curves of overall survival for medulloblastoma patients treated with photon and proton radiation therapy.

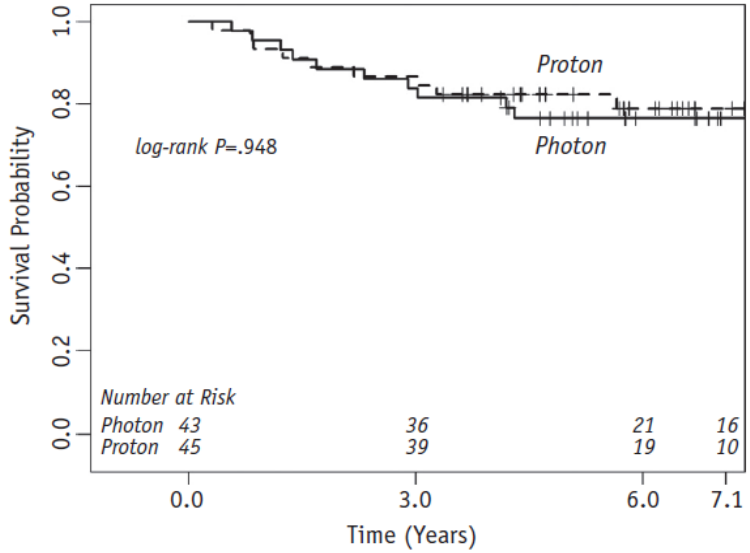

Fig. 2. Kaplan-Meier curves of relapse-free survival for medulloblastoma patients treated with photon and proton radiation therapy.

Eaton BR et al. Int J Radiat Oncol Biol Phys 2016; 94:133-8

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Standard-Risk Medulloblastoma

Patterns of Failure

Table 3 Patterns of failure between proton- and photon-treated cohorts

Characteristic	Proton therapy (n=45)	Photon therapy (n=43)	*P* value*
Total no. of relapses (%)	10 (22.2)	10 (23.3)	.908
Patterns of failure			1.000
Diffuse or leptomeningeal disease (%)	5 (50)	5 (50)	
Isolated focal spine (%)	2 (20)	3 (30)	
Isolated posterior fossa (%)	1 (10)	2 (20)	
Isolated brain, other (%)	1 (10)	0	
Posterior fossa plus focal spine (%)	1 (10)	0	

* *P* value is calculated by χ^2 test or Fisher exact test, where appropriate.

Eaton BR et al. Int J Radiat Oncol Biol Phys 2016; 94:133-8

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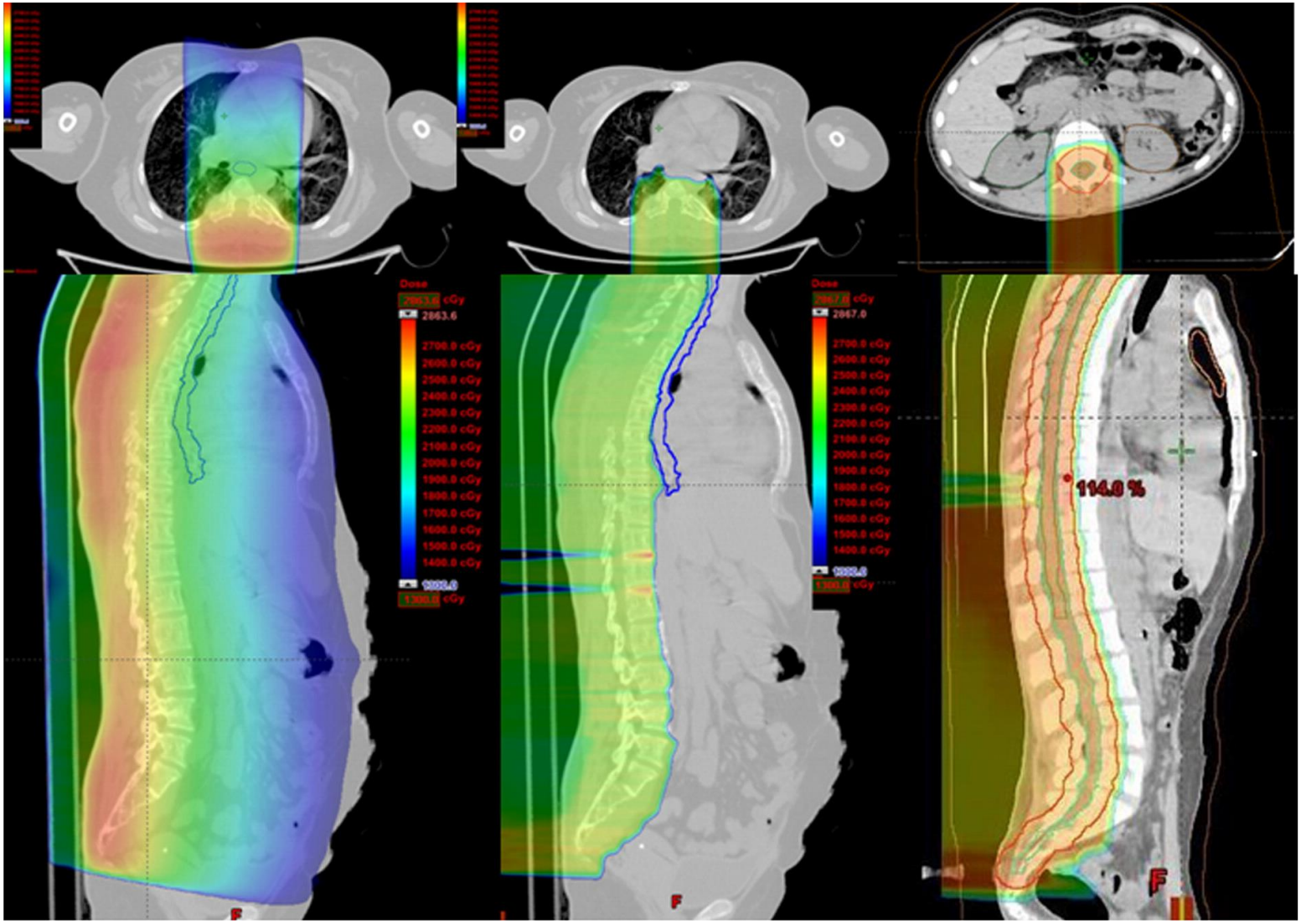
Should the Entire Vertebral Body Be Treated?



McMullen K et al. Pract Radiat Oncol 2013; 3:337-43

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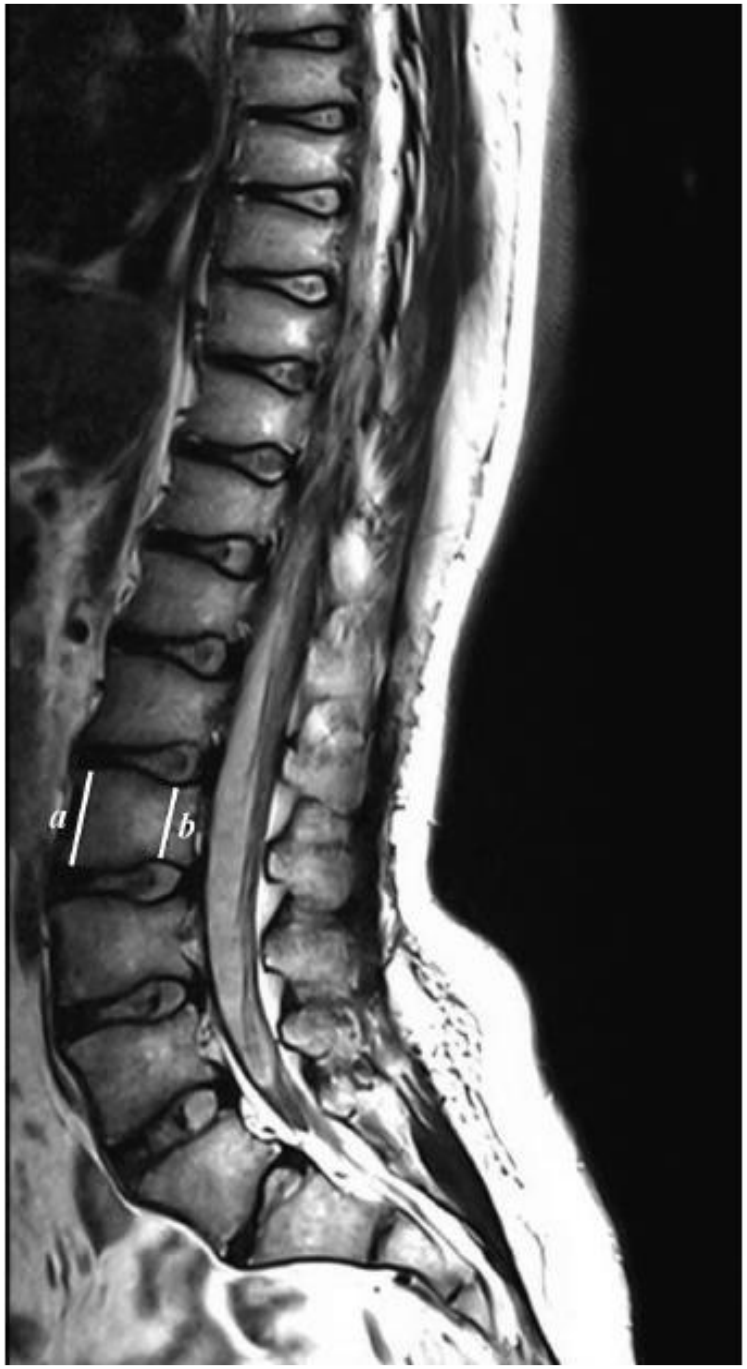
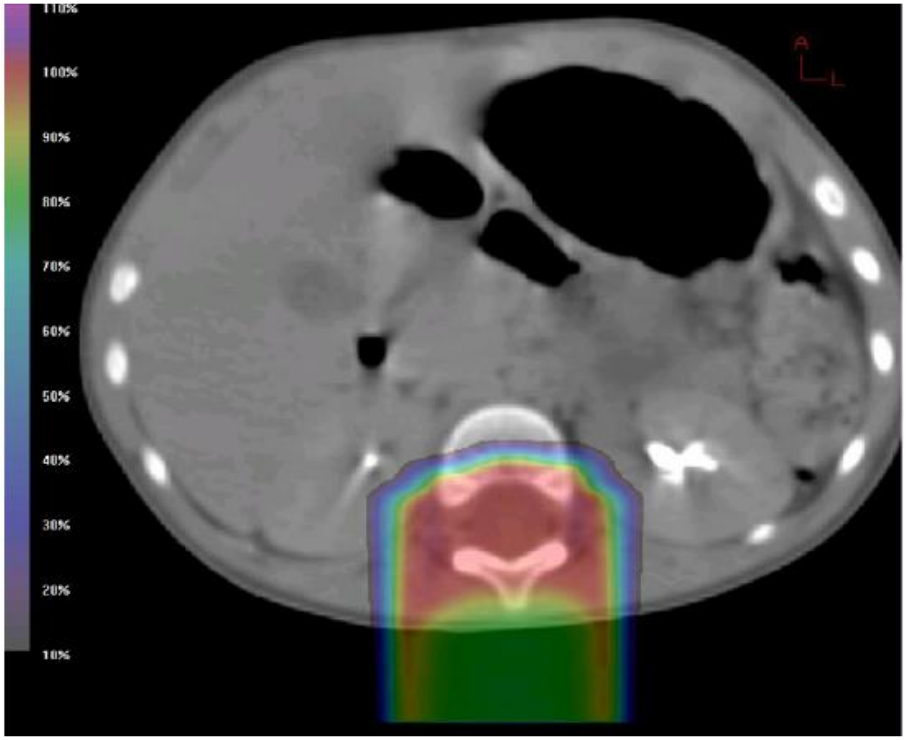


Vertebral Body Sparing Proton Therapy



MacEwan I et al. Adv Radiat Oncol 2017; 2:220-7

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Vertebral Body Sparing Proton Therapy

Table 2 Radiographic follow-up and scoliosis

Variable	Patient A	Patient B	Patient C	Patient D	Patient E	Median
Clinical follow-up (y)	15.8	14.8	13.6	11.8	8.7	13.6
Radiographic follow-up (y)	7.1	14.1	13.1	12.3	3.7	12.3
Scoliosis	Yes	Yes	No	No	No	–
Maximum Cobb angle (degrees)	36.2°	19.3°	3.9°	9.7°	9.7°	–

MacEwan I et al. Adv Radiat Oncol 2017; 2:220-7

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Conclusions

- Various radiotherapy treatment parameters have been implicated in the treatment outcome of children with medulloblastoma
- These radiotherapy parameters include radiotherapy volume, dose, duration and timing
- Current studies are looking at treatment modifications (escalation and de-escalation of therapy) according to molecular subtype

Thank you for your attention!

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Normal CNS anatomy – Organs at risk

Tim Jaspan

Nottingham University Hospital

ESTRO 2017

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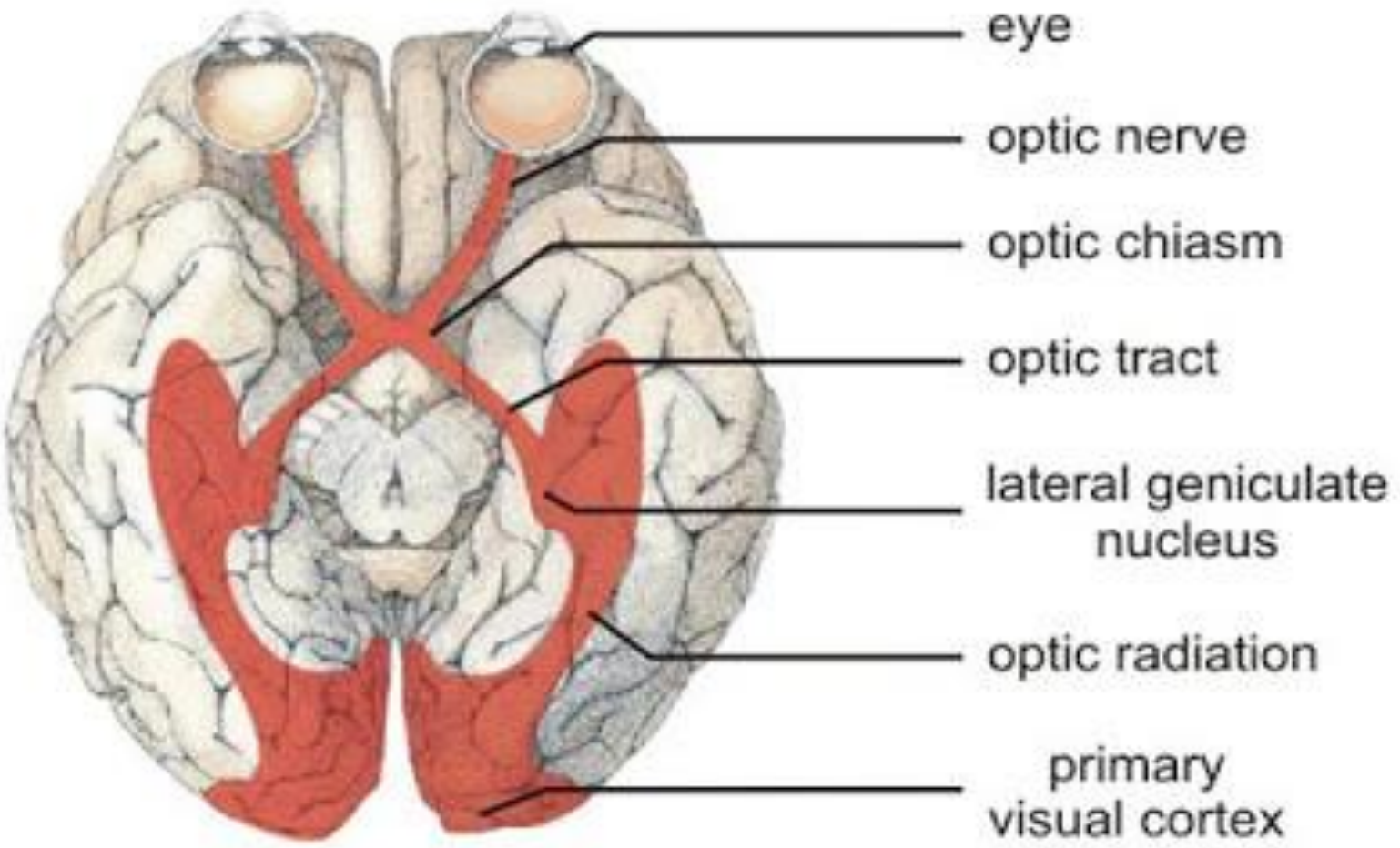
Organs at risk

- Scalp
- Lenses
- Retinae
- Lacrimal glands
- Optic nerves, chiasm and tracts
- Pituitary/hypothalamus
- Cochlea
- Hippocampi
- Brainstem
- Cervical spinal cord
- Parotid

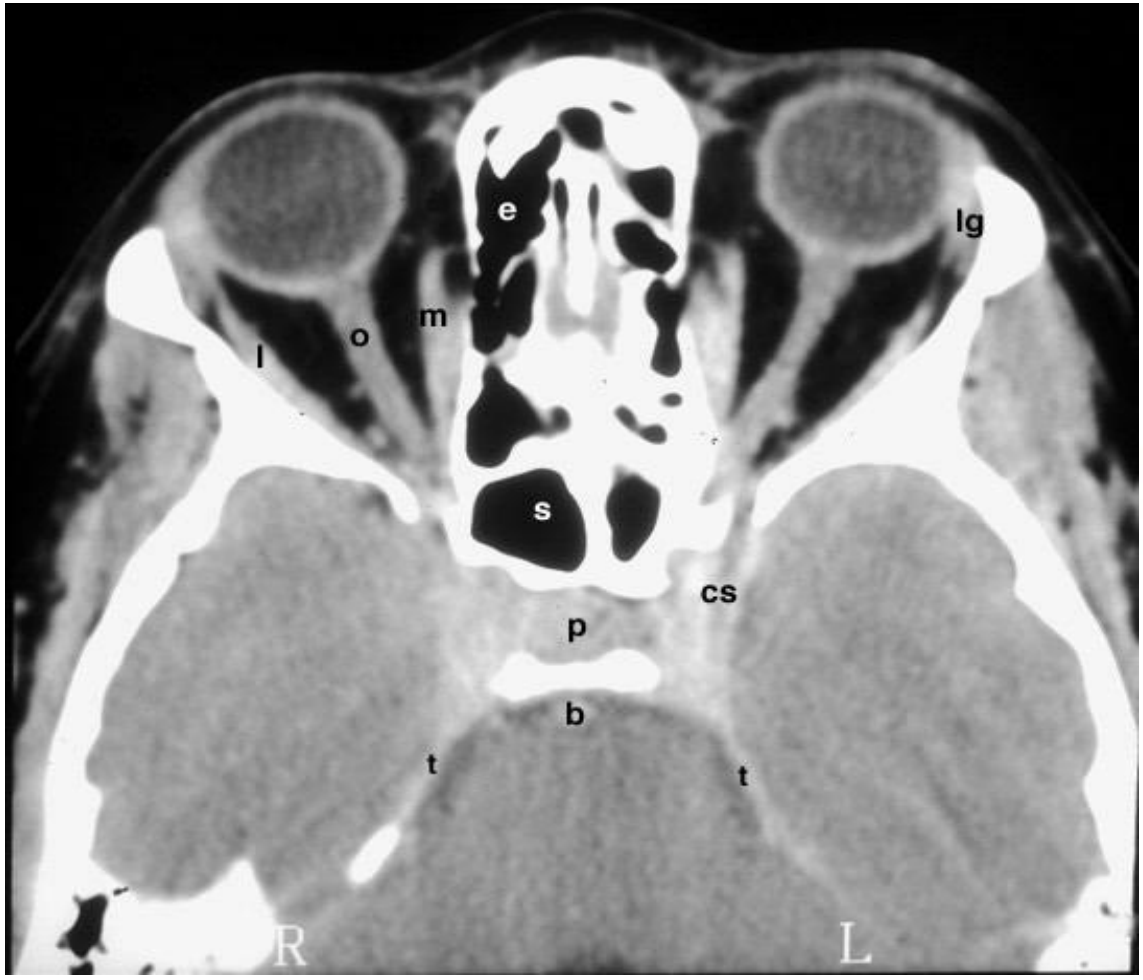
Visual pathway

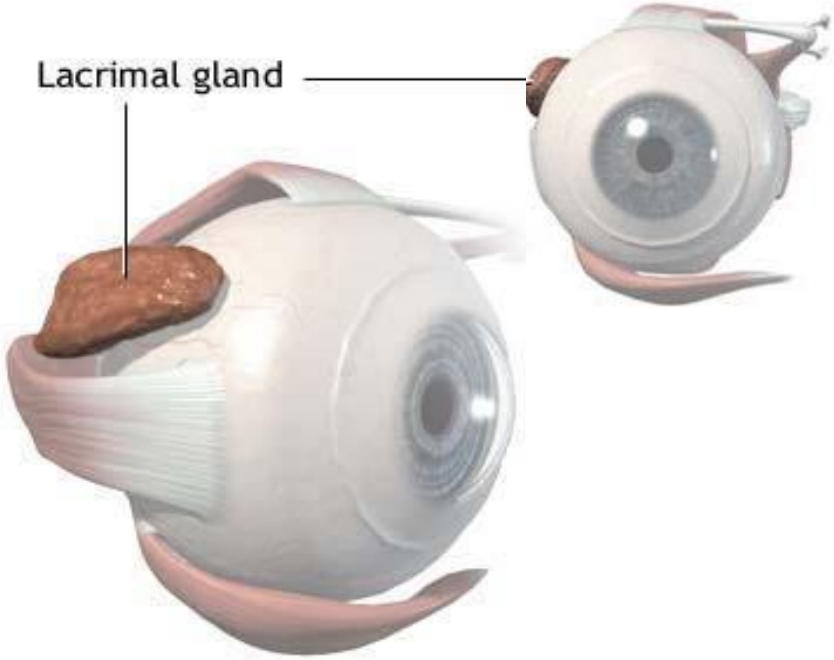


Intra-orbital structures

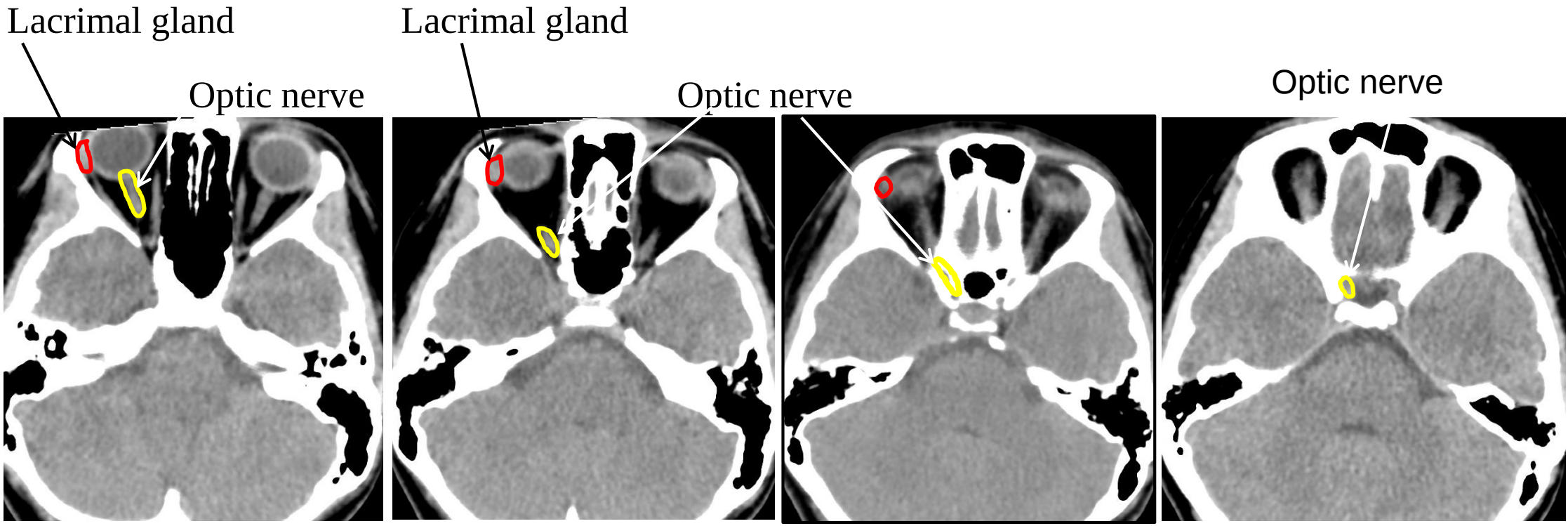
- Lens
- Retina
- Optic nerves
- Lacrimal glands

Optic nerves + lacrimal gland - CT

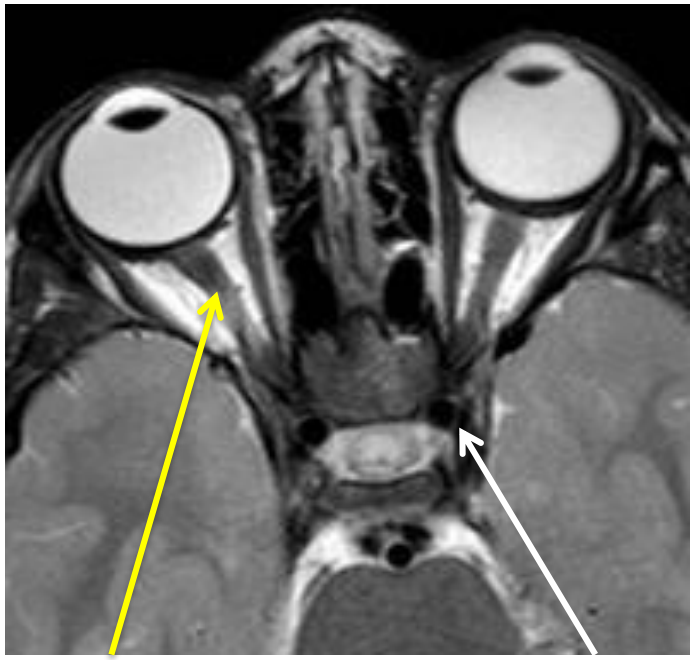




Optic nerves – CT axial

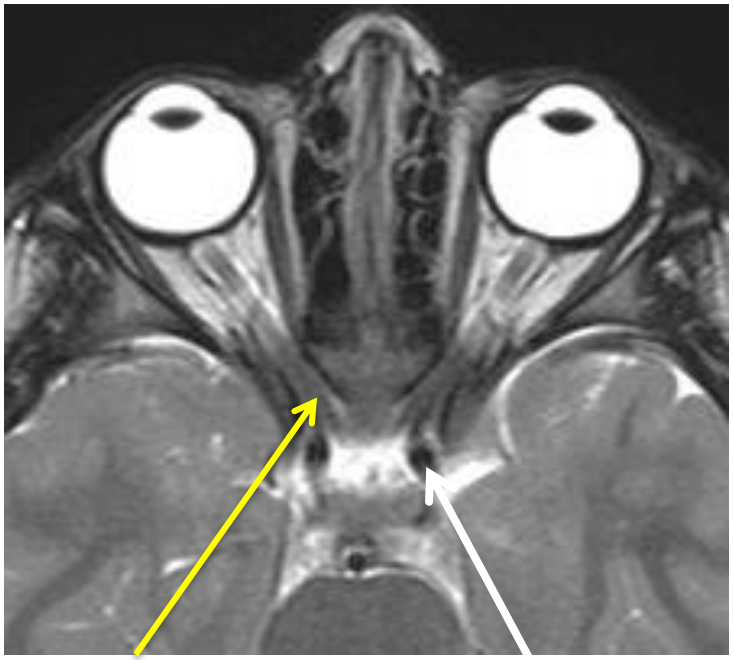


Optic nerves – MRI axial



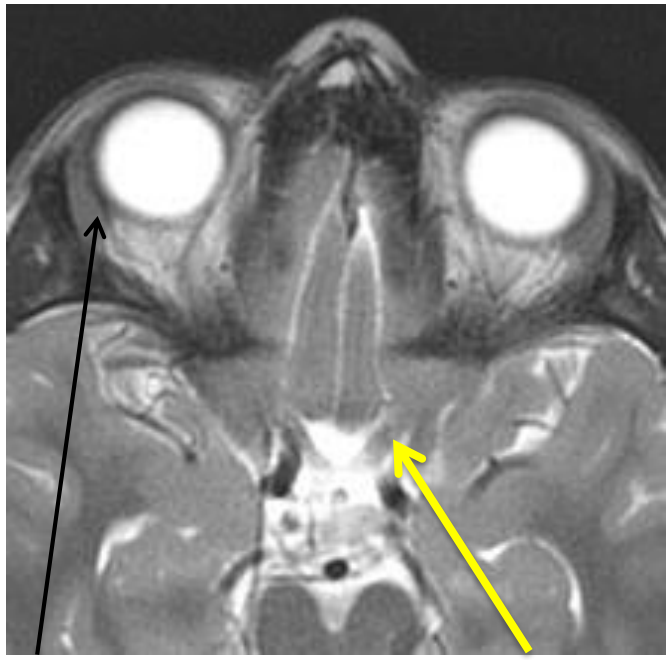
Intraorbital segment

ICA



Intra-canalicular segment

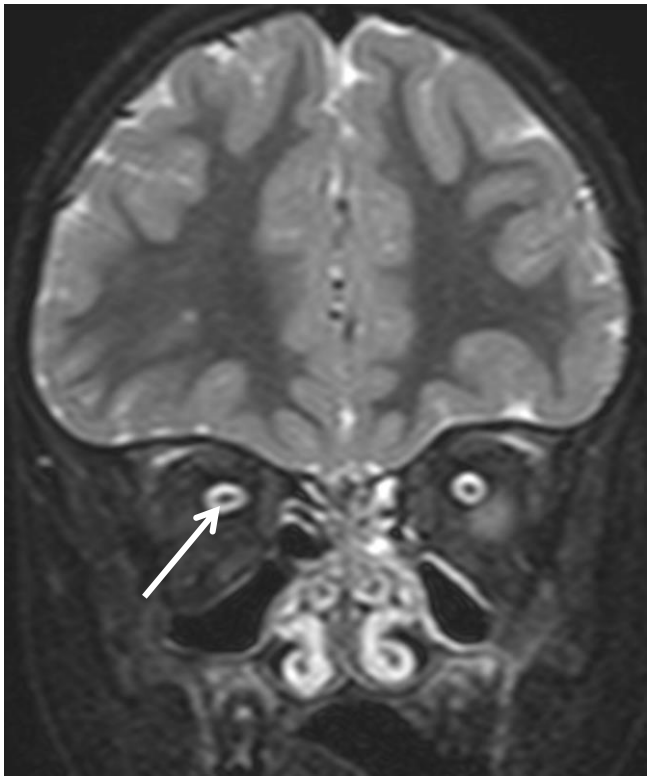
ICA



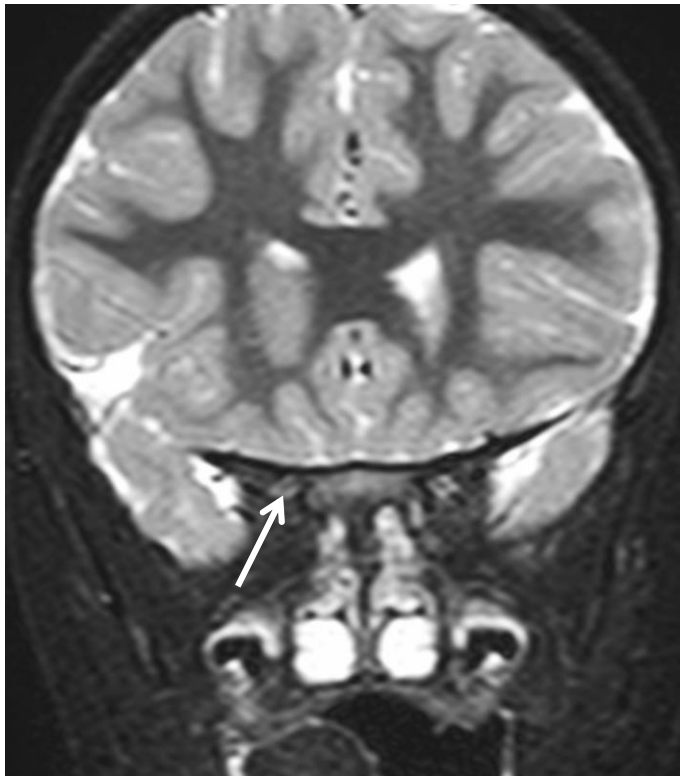
Lacrimal gland

Cisternal segment

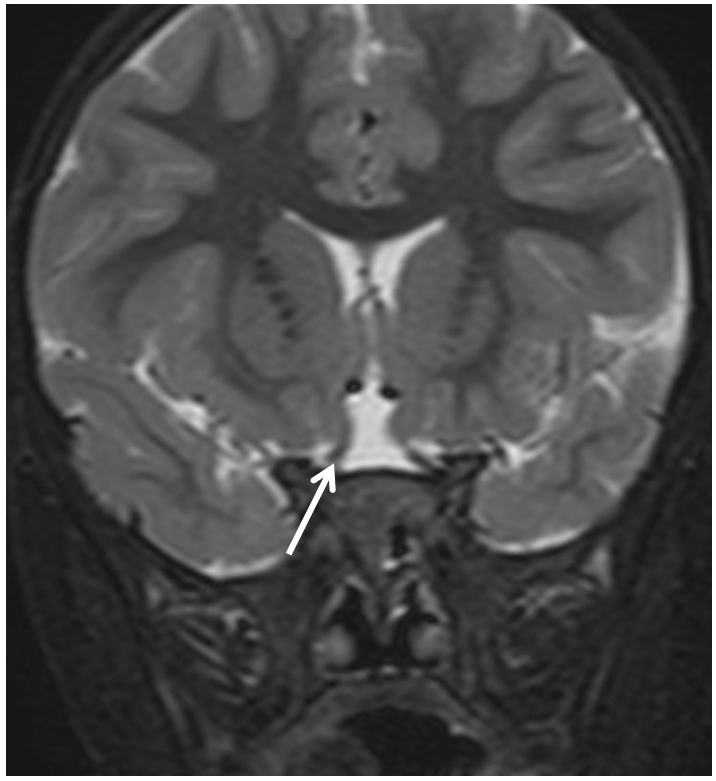
Optic nerves - Coronal



Intraorbital ON



Intra-canalicular ON

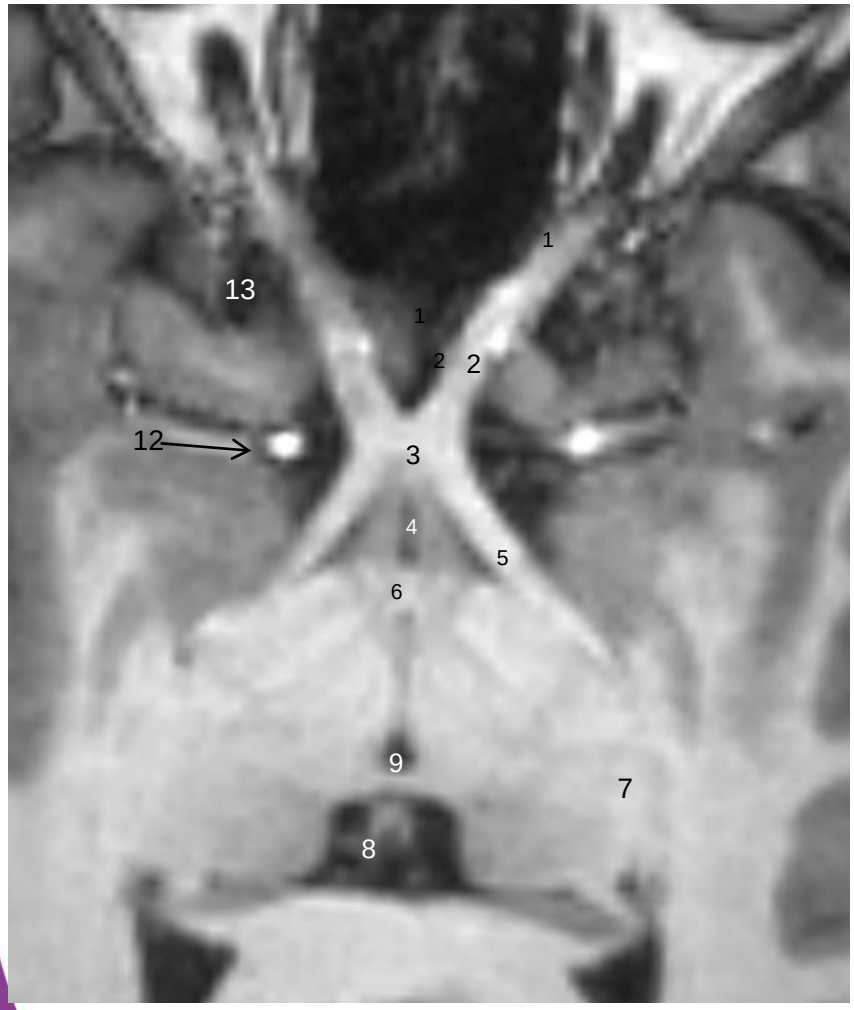


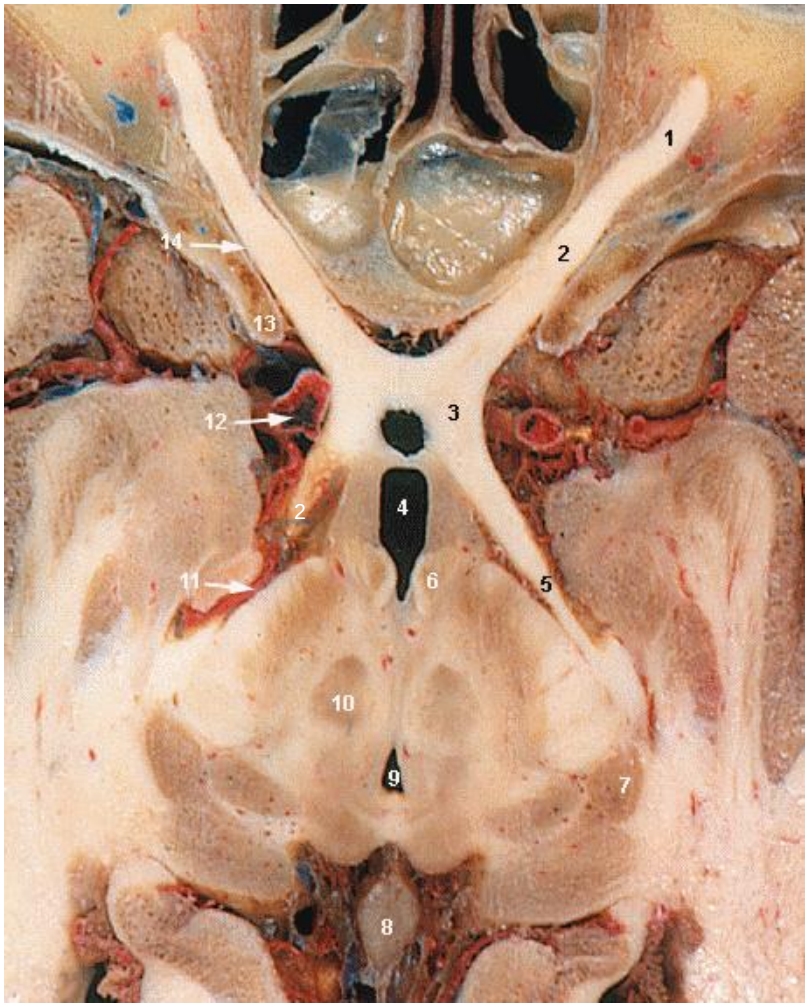
Cisternal ON

Optic chiasm

- Probably most crucial organ at risk
- Lies below hypothalamus, third ventricle and its optic recess
- Anterior cerebral arteries lie ventrally, and ICA's laterally
- Approx 14mm transverse width, 8mm AP, 2-5mm height
- Slopes slightly upwards and backwards
- Must contour on multiple slices – gaps in contour will lead to missing essential volume for computing dose-volume histogram
- Check contour on sagittal or coronal images

Chiasm





1 = intraorbital segment
2 = canalicular segment
3 = optic chiasm
4 = 3V
5 = optic tract
6 = mammillary body
7 = lateral geniculate body
8 = Pineal gland
9 = aqueduct
10 = Red nucleus
11 = ant choroidal artery
12 = ICA
13 = ant clinoid process
14 = optic canal

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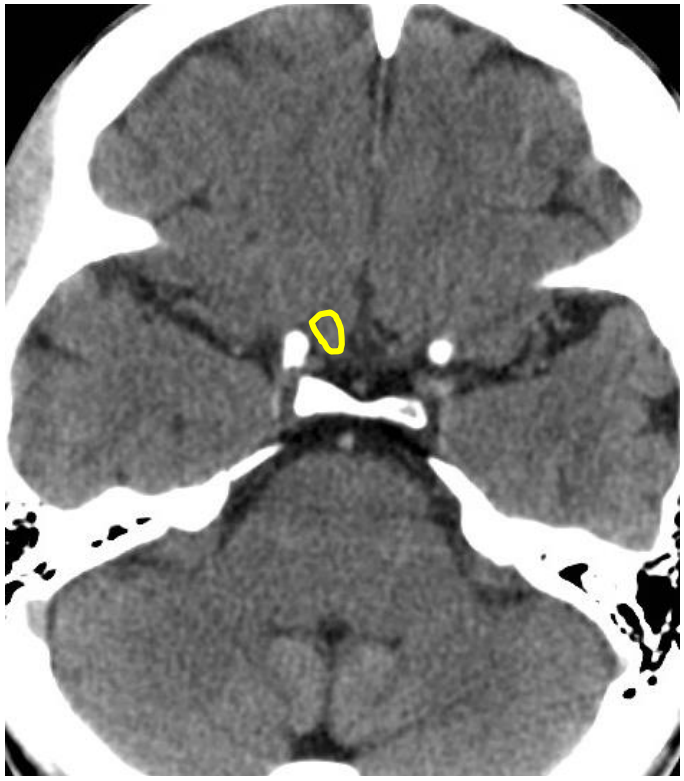
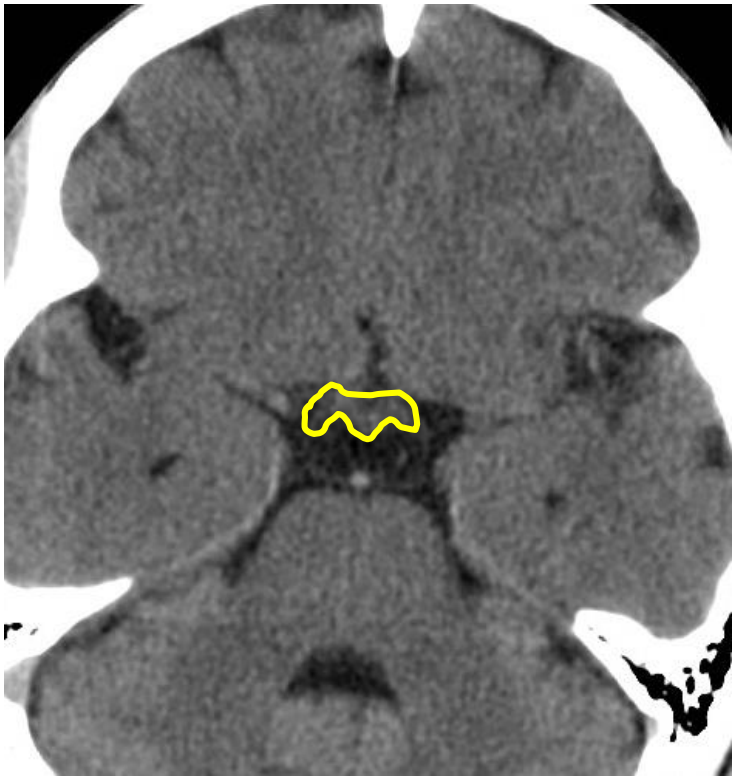
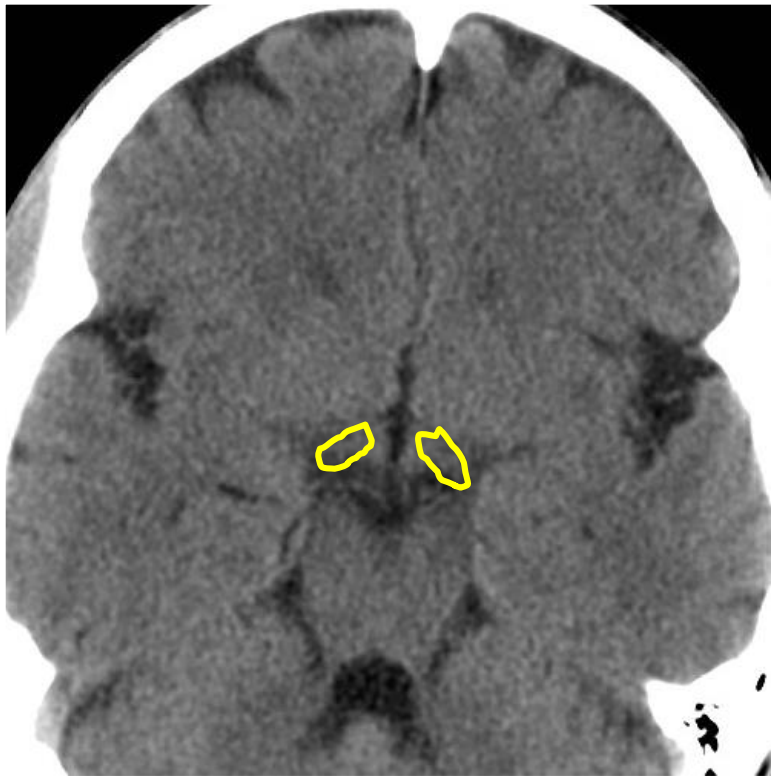
Chiasm and tracts – Axial CT



Cisternal segment of ON



Chiasm



Optic tracts

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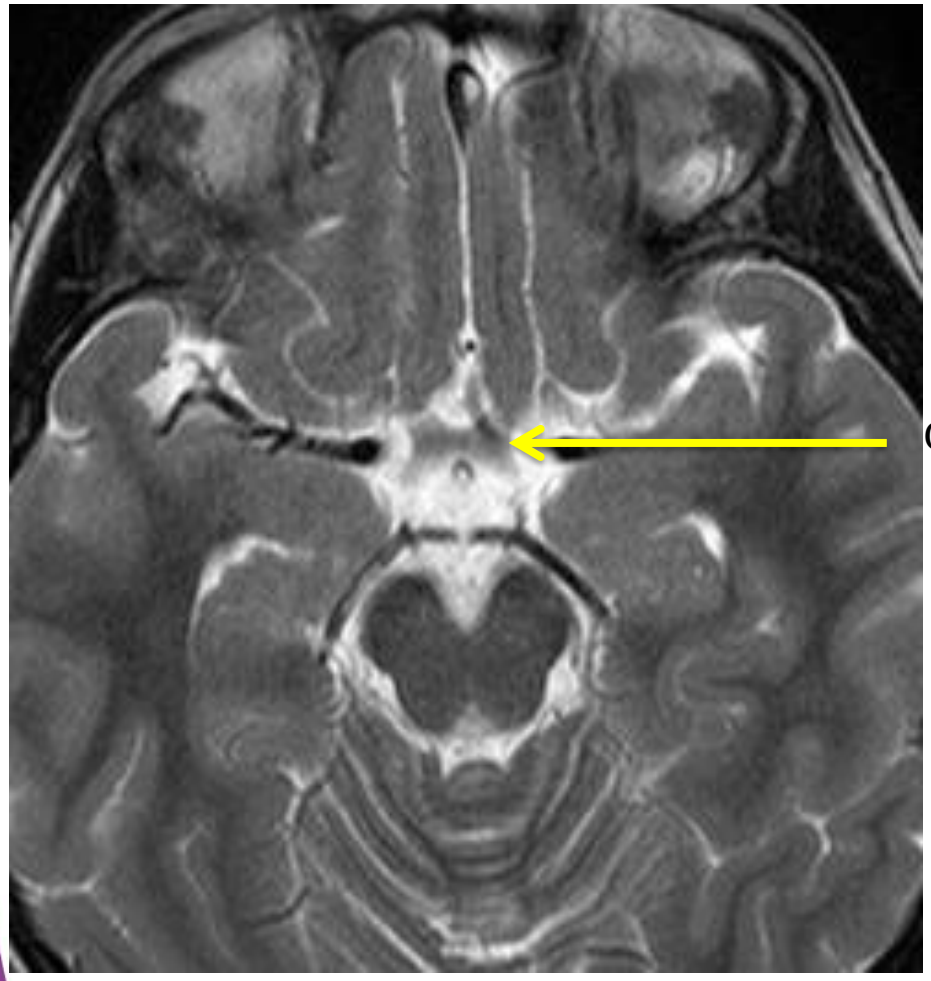
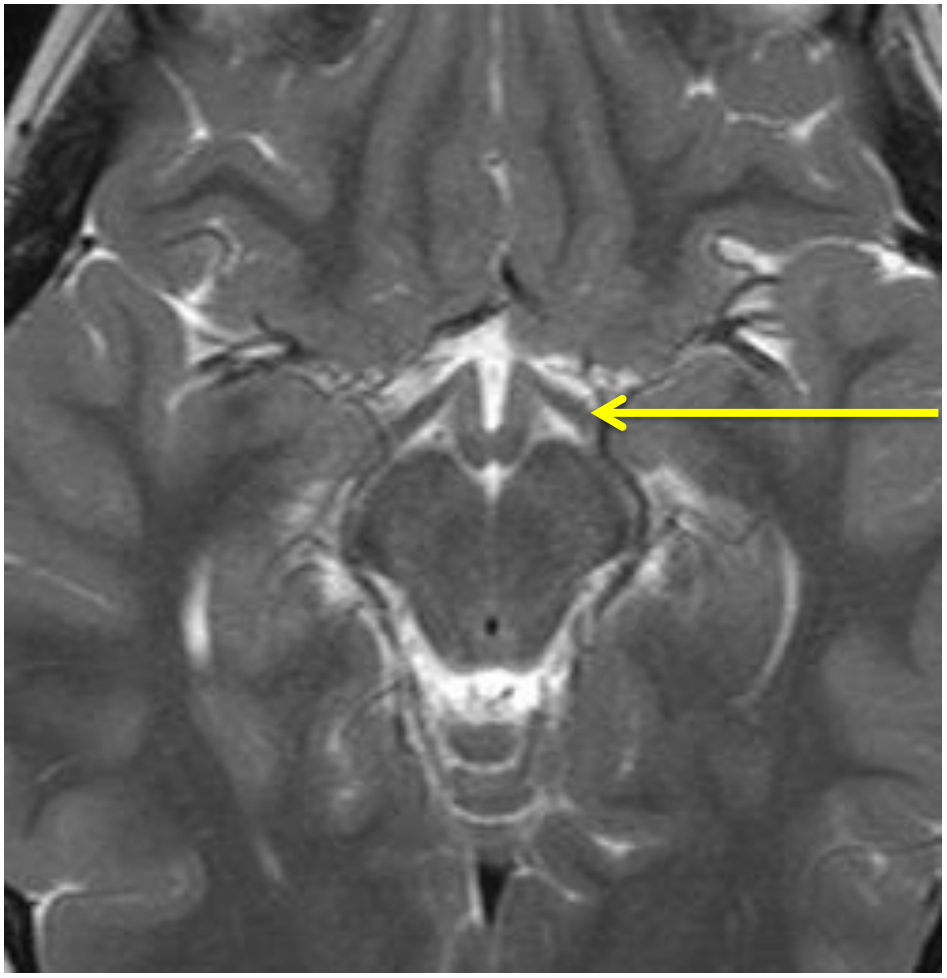
Chiasm and optic tracts – Axial MRI





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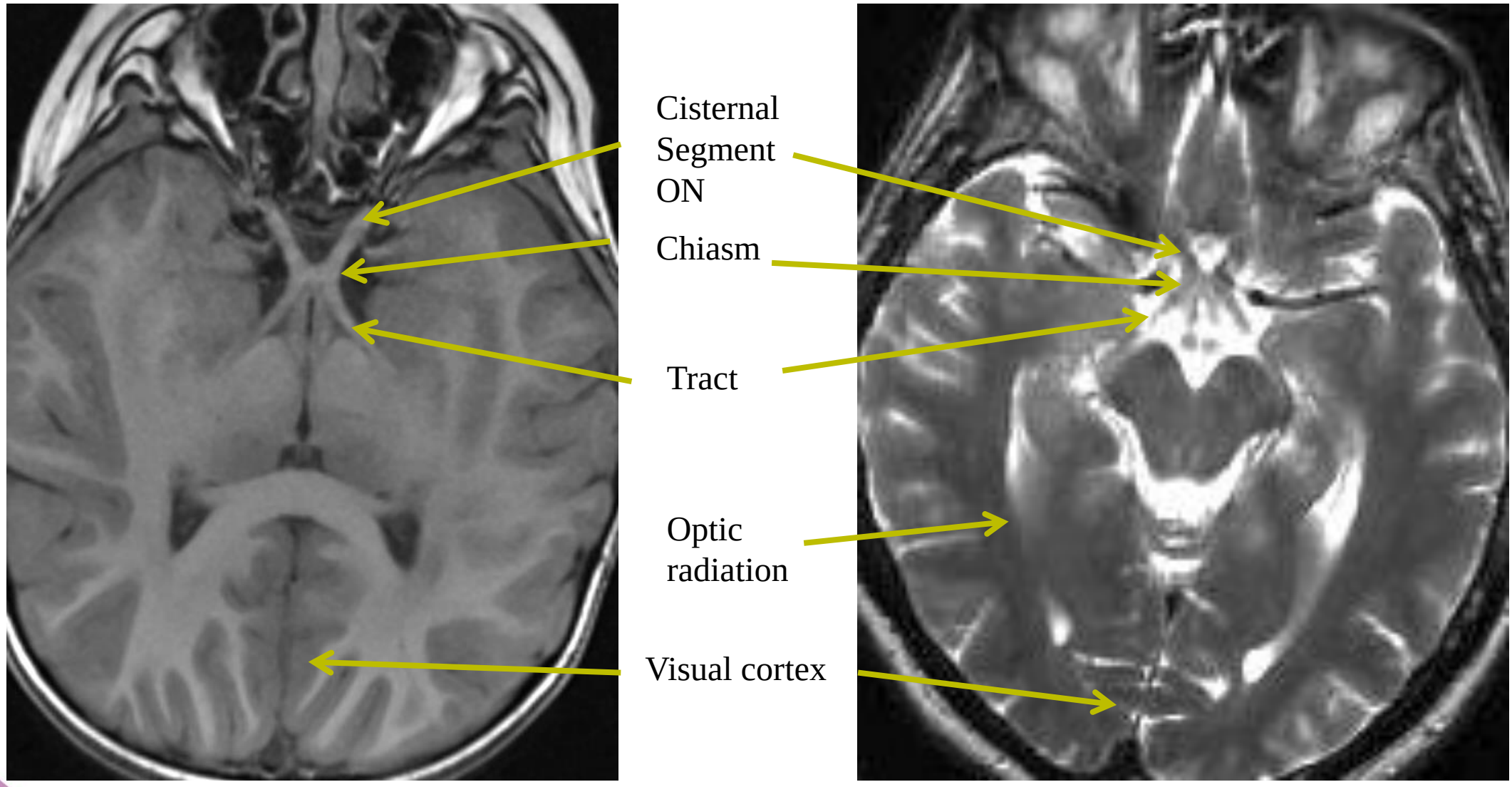
Chiasm + optic tracts – Axial MRI



T1

T2

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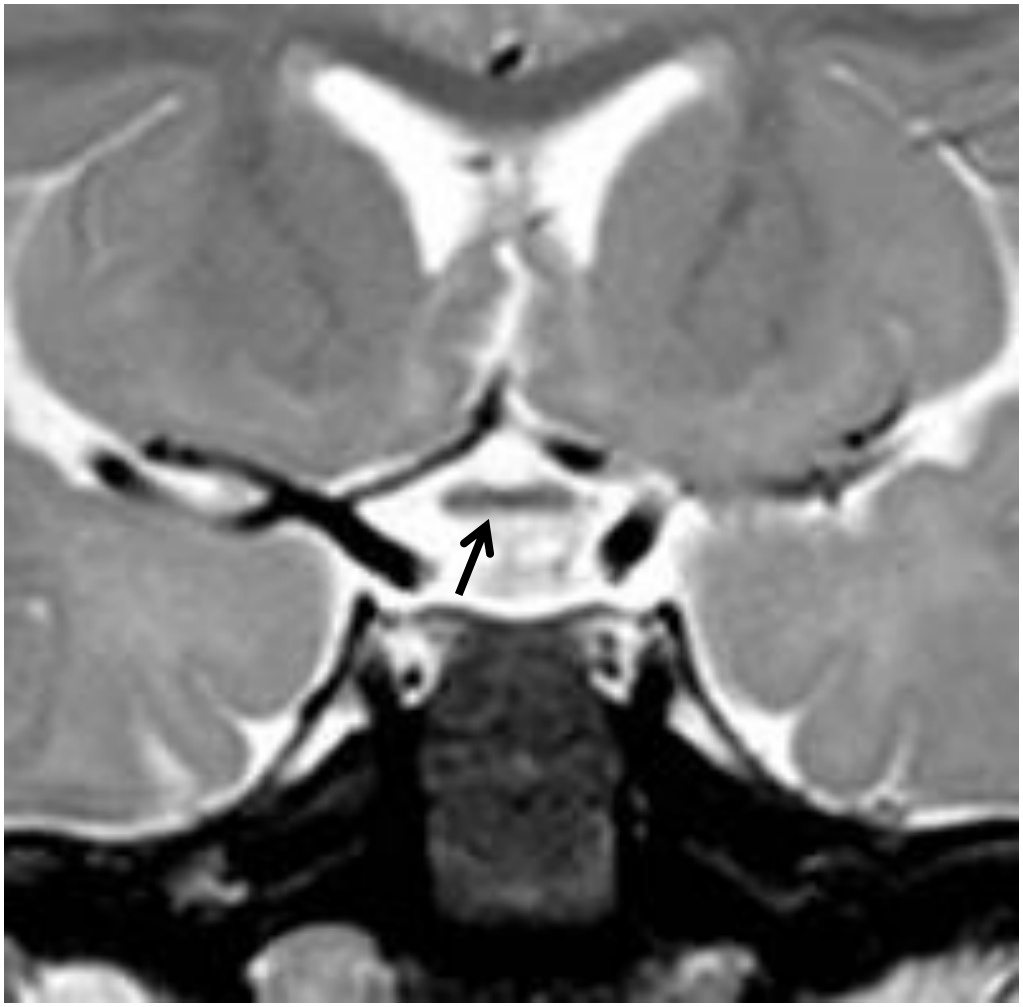
Chiasm – Coronal and sagittal MRI



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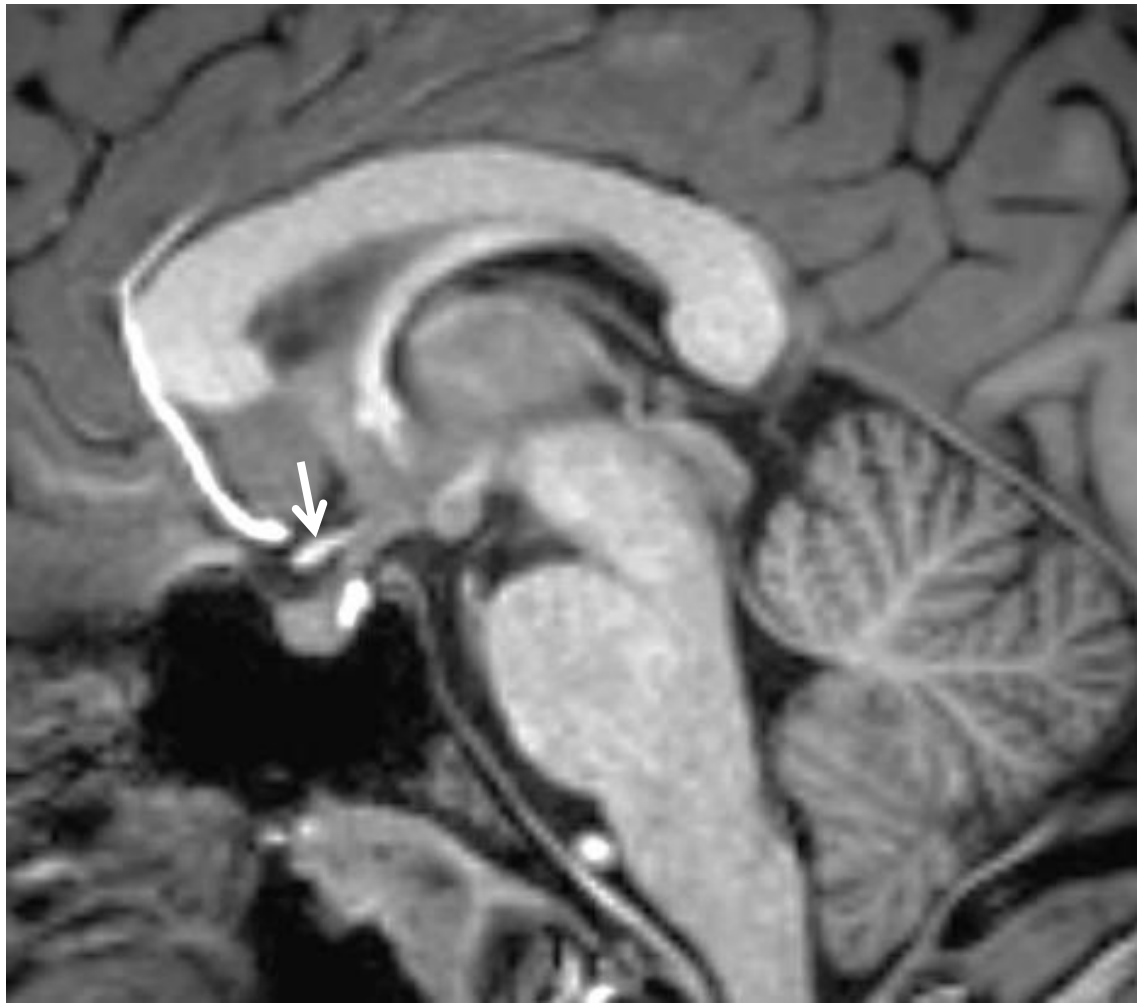
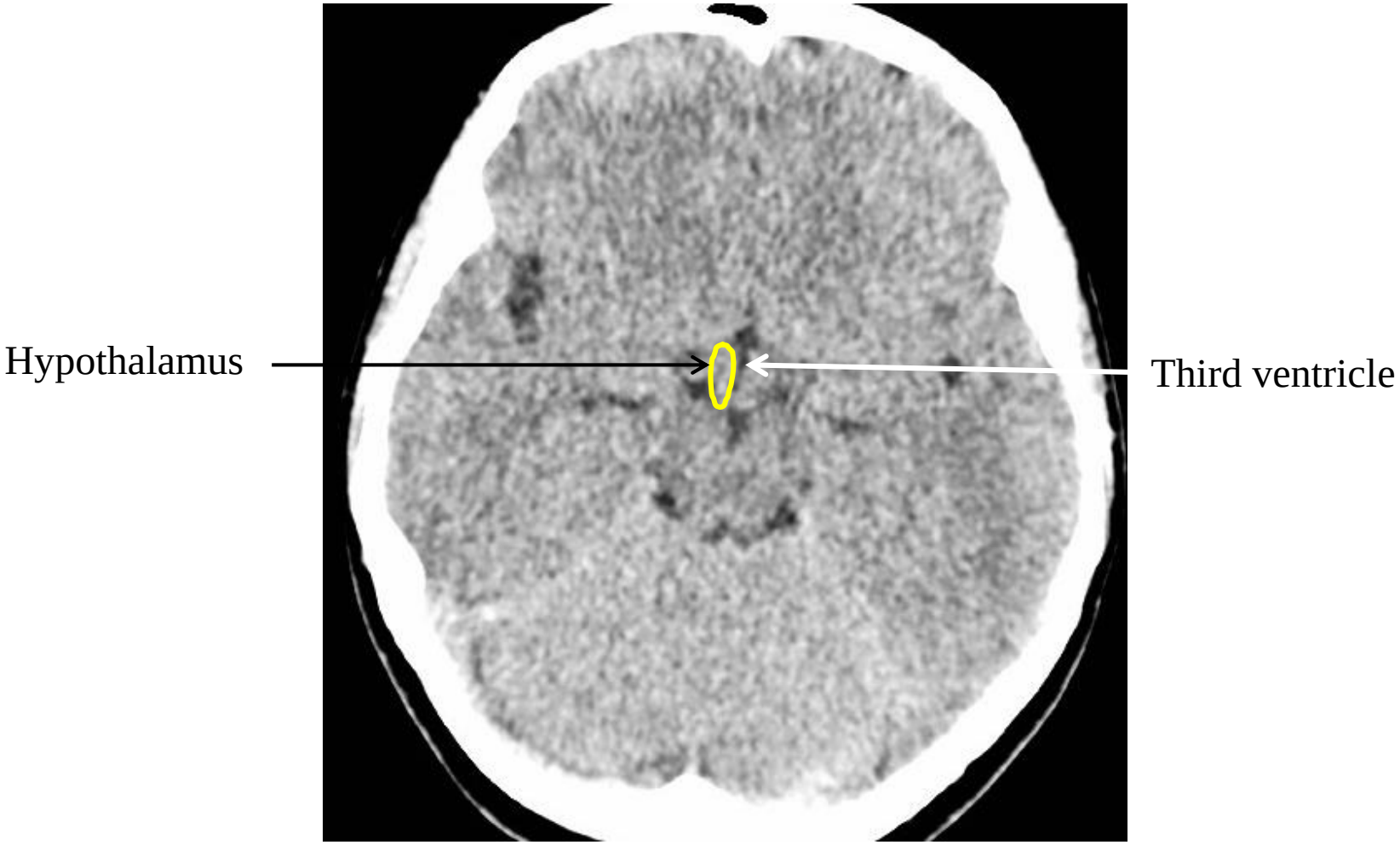


T1

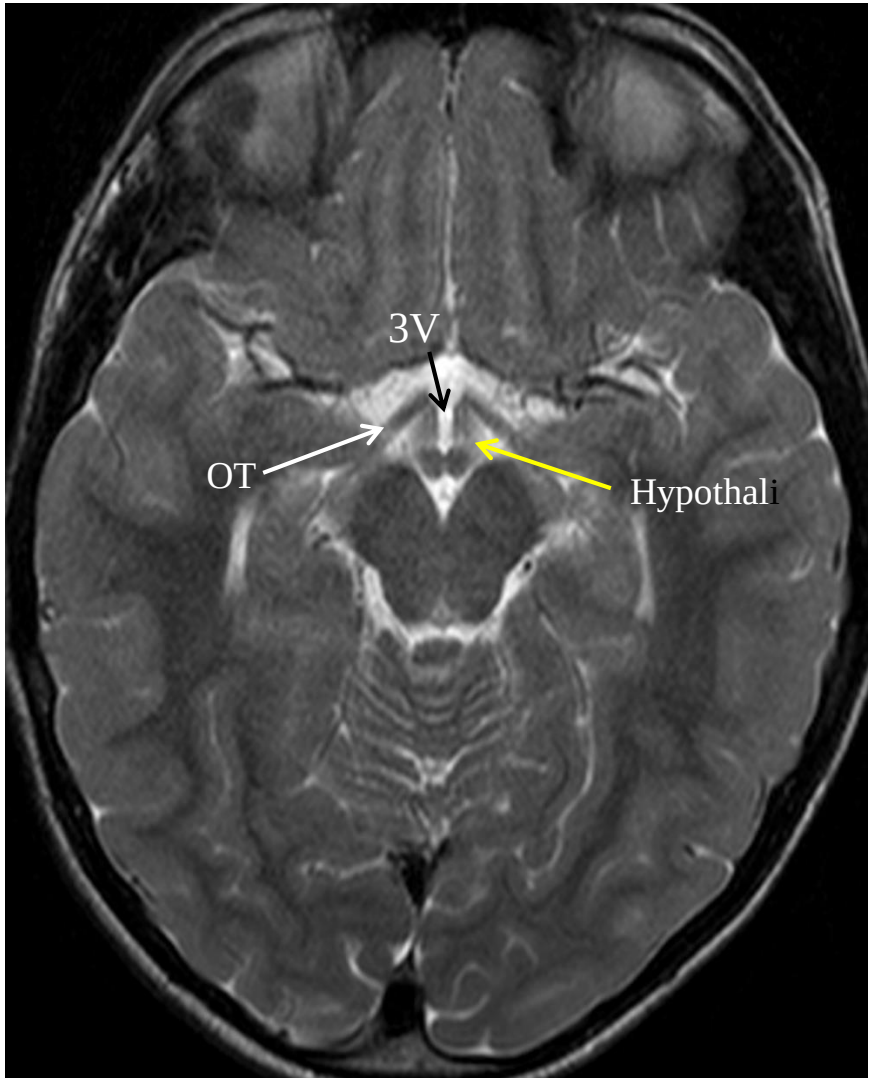
Hypothalamic-Pituitary axis

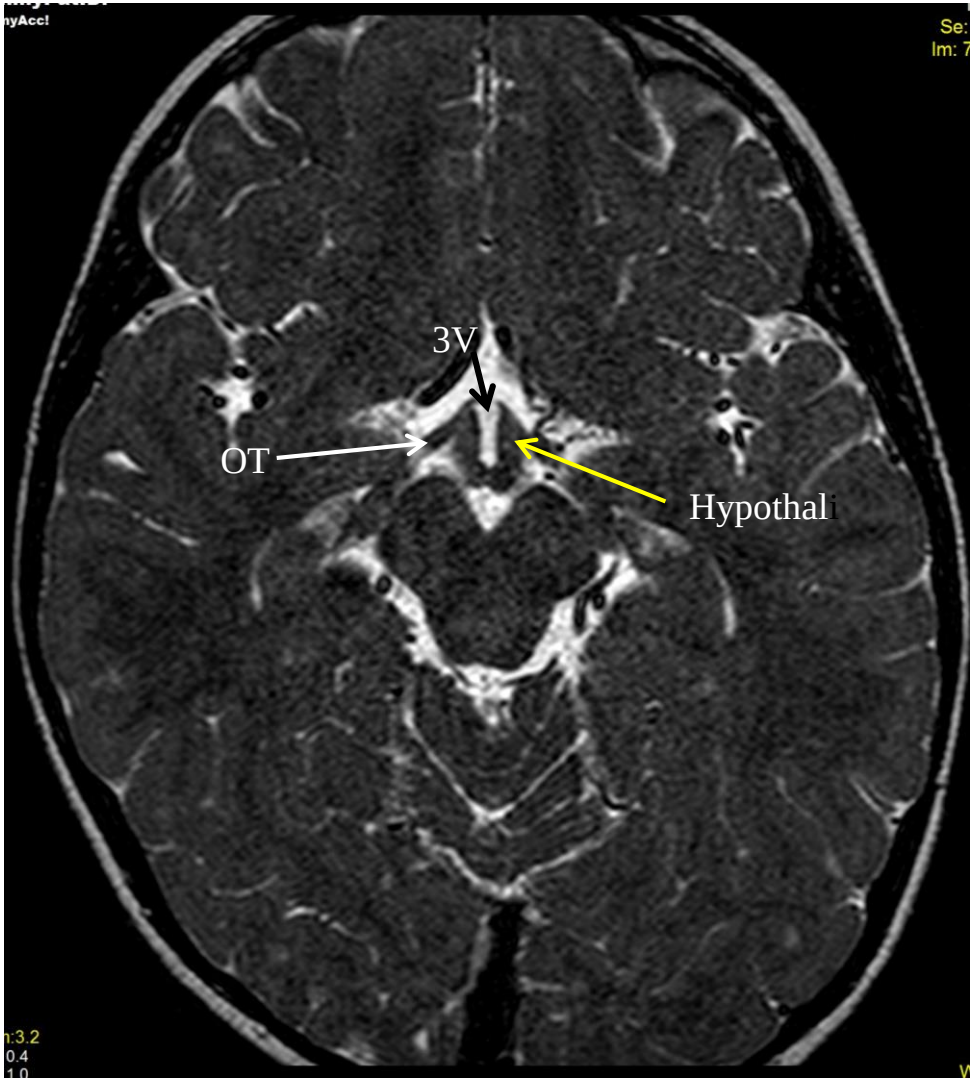
- Hypothalamus
- Infundibulum
- Pituitary gland

Hypothalamus – Axial CT



Hypothalamus – axial MRI





Hypothalamus (Hypo) and optic tract (OT)

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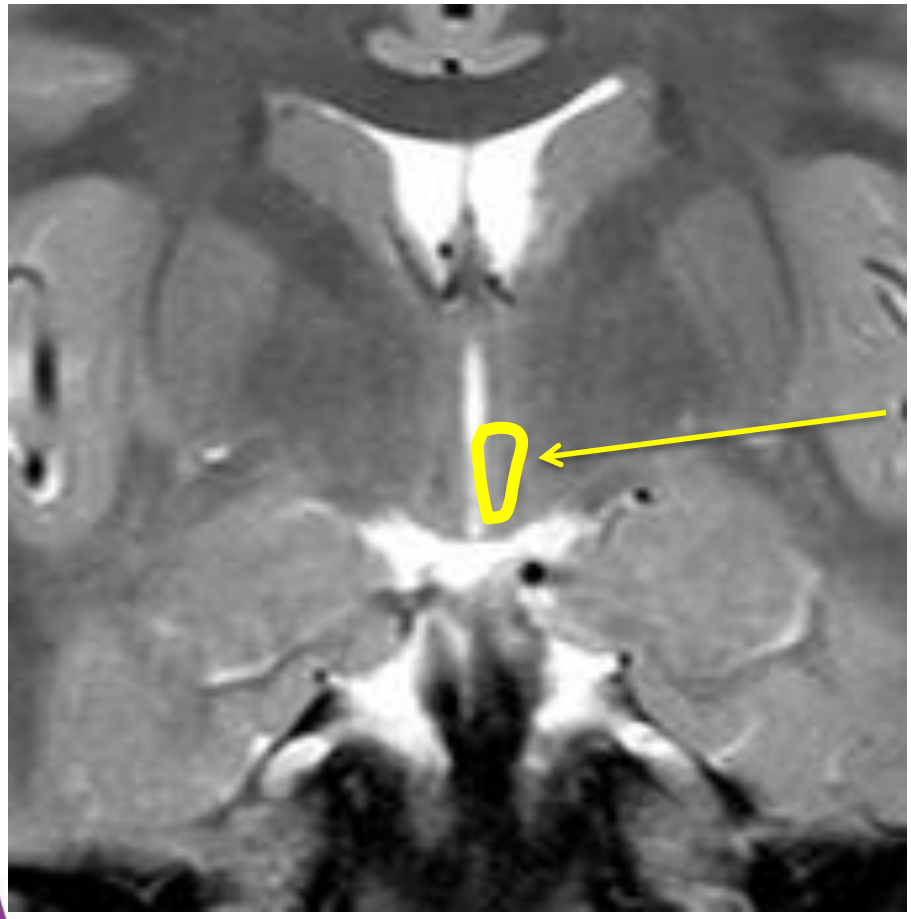
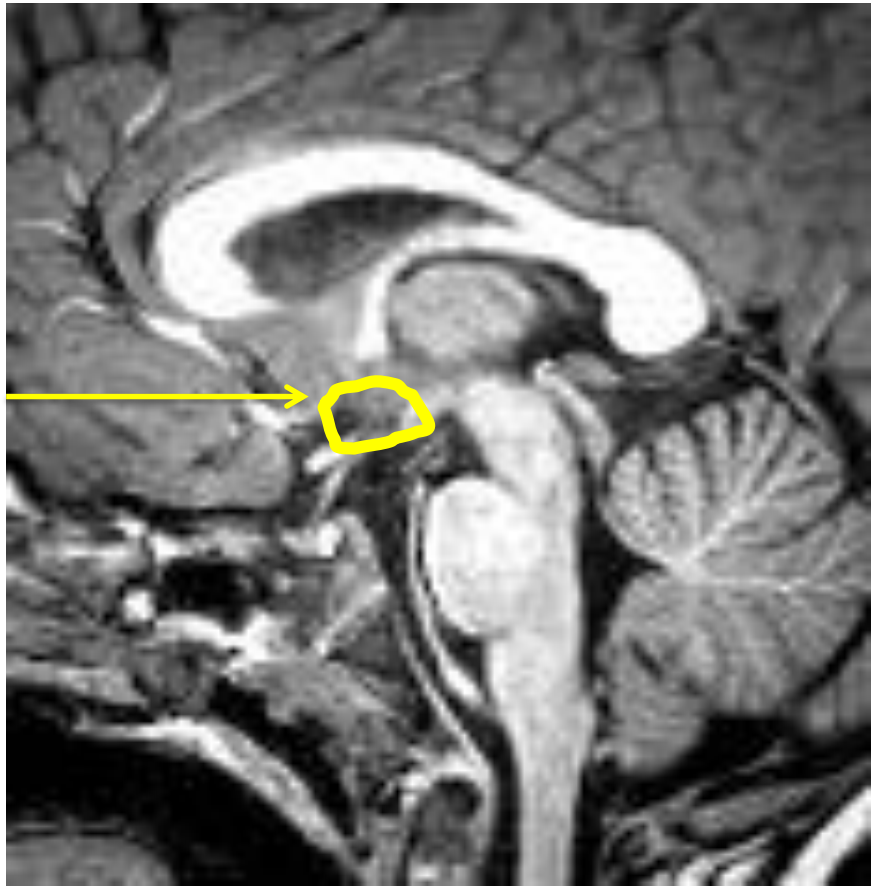
Hypothalamus – coronal and sagittal



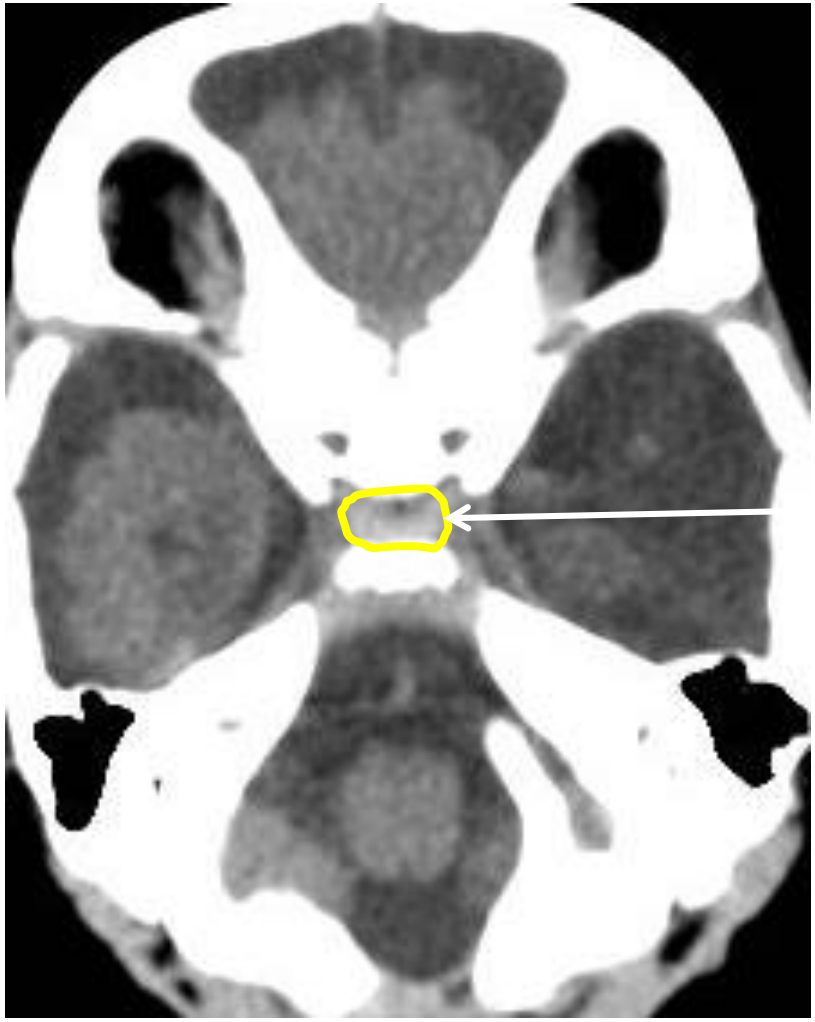
Hypothalamus

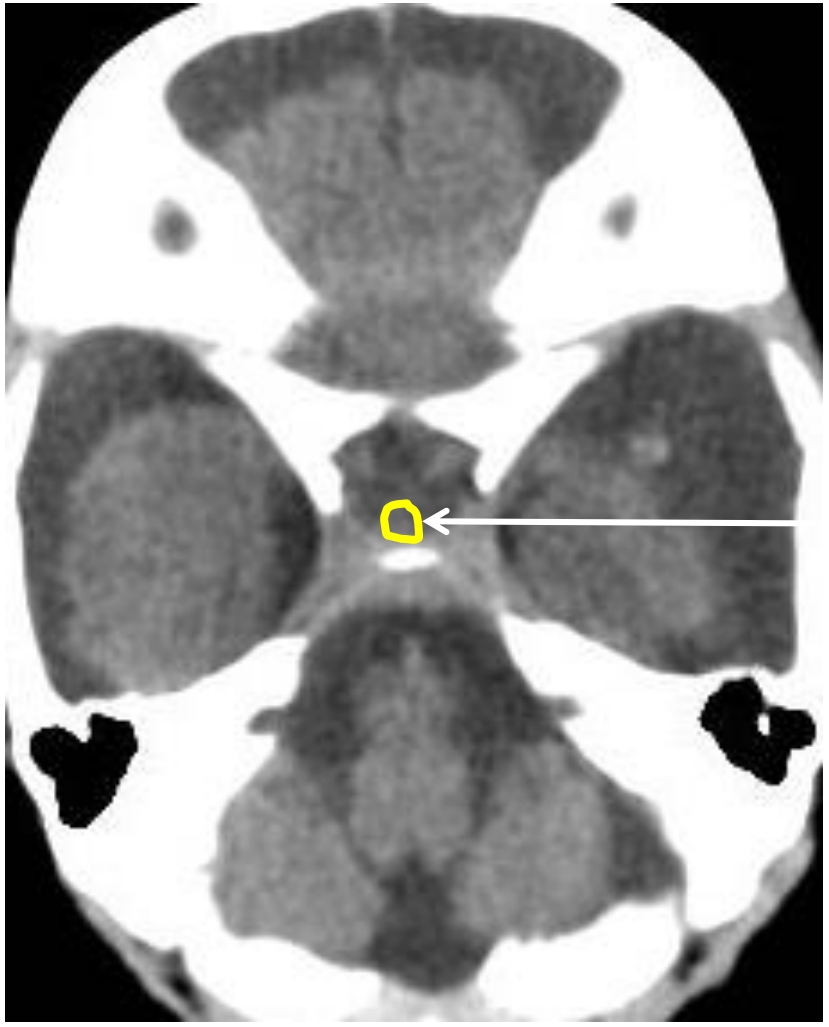


Pituitary gland

- Craniocaudal dimensions vary with age and sex
- Ranges from 6mm in infants to 12mm for pubertal girls and pregnant women
- Pituitary stalk is normally about 2mm thick

Pituitary gland axial CT





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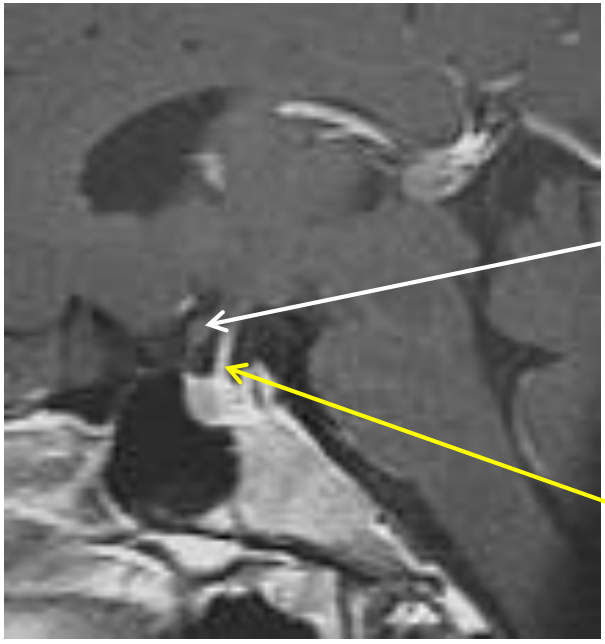
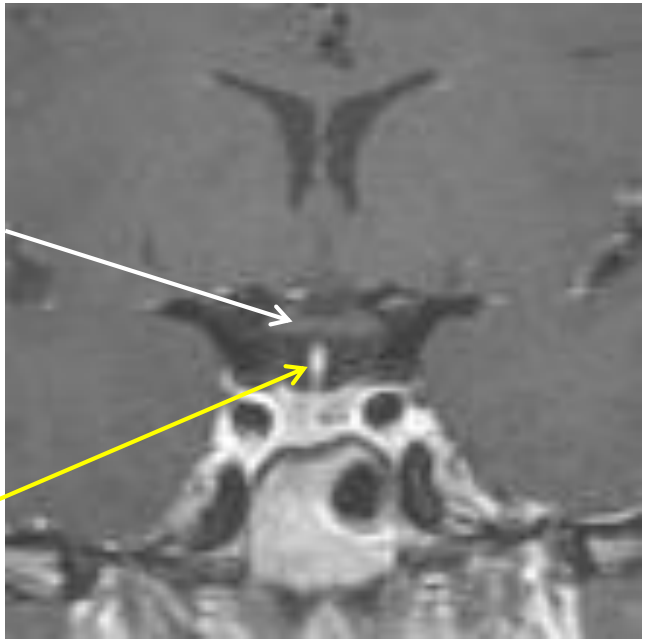
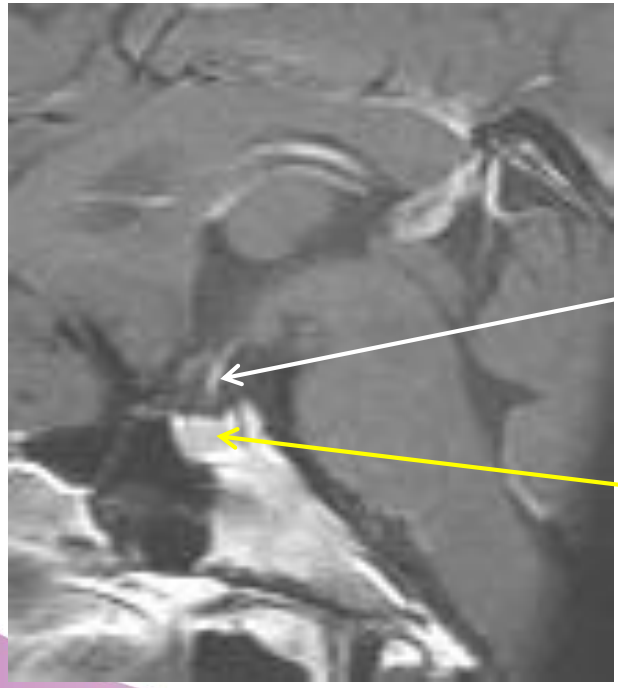
Pituitary gland – Sagittal + coronal MRI



Chiasm

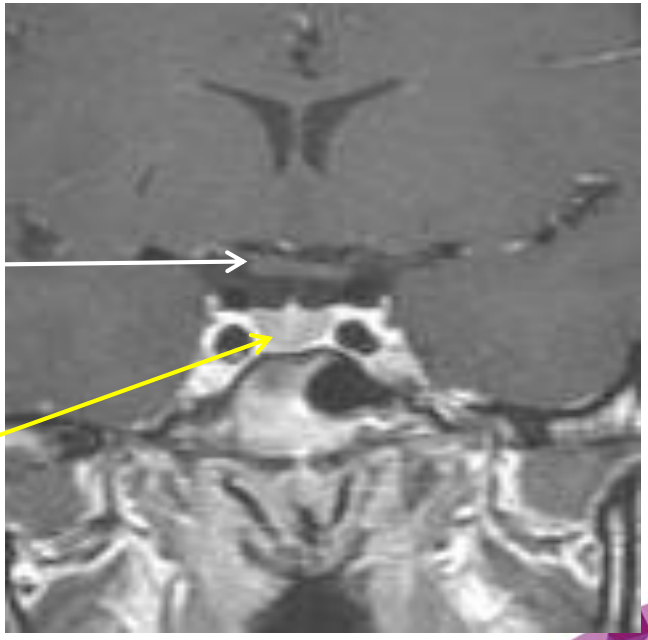
Infundibulum





Chiasm

Pituitary gland



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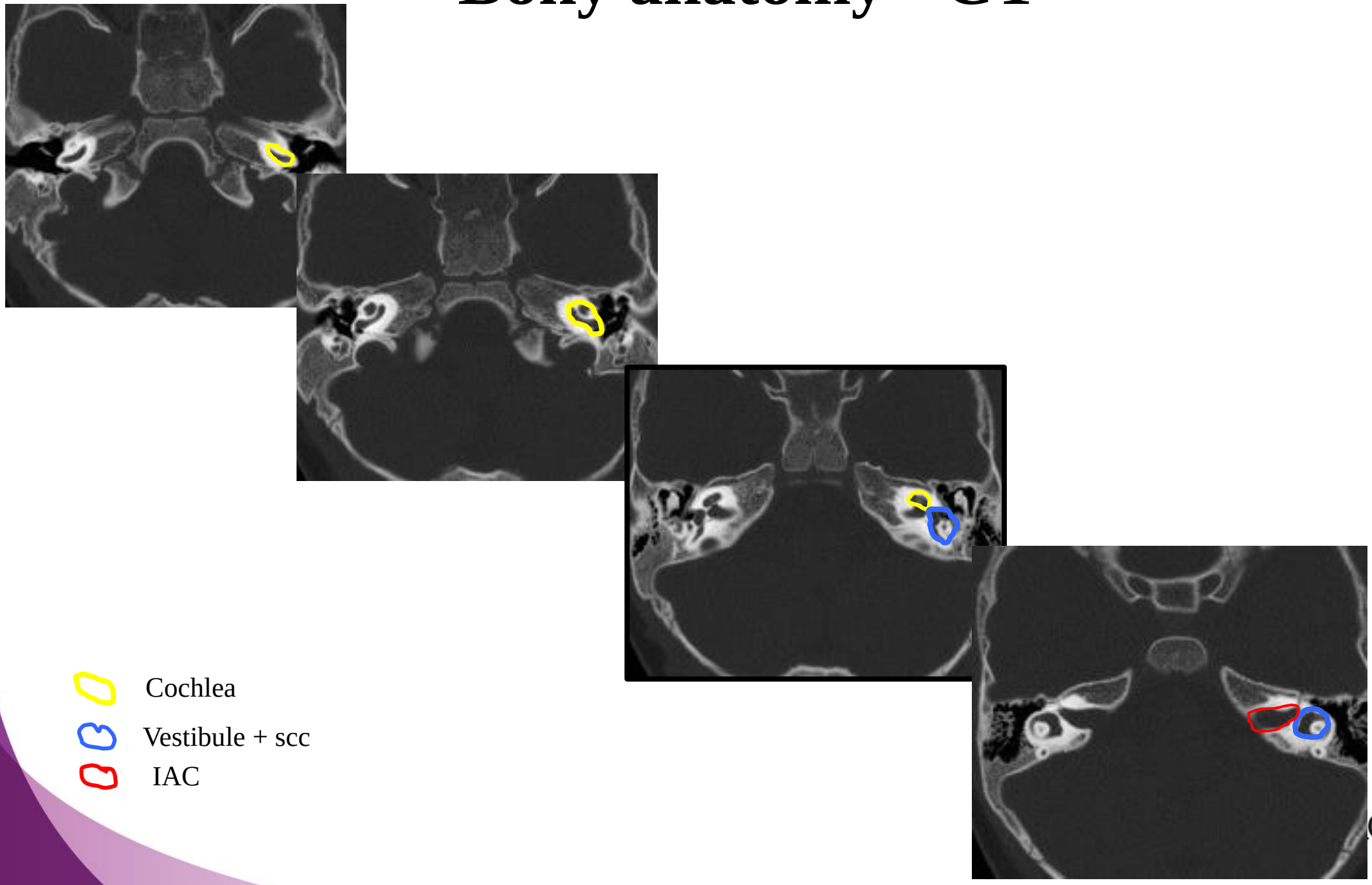
Hearing mechanism

- Vestibulocochlear nerves
- Cochleas

Bony anatomy - CT

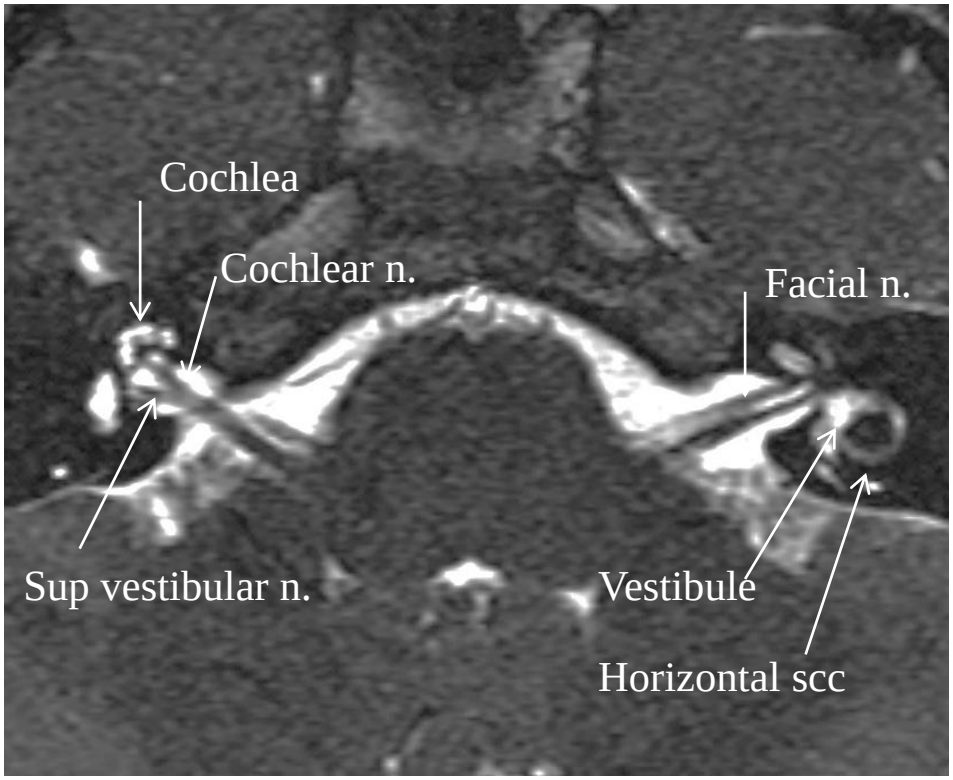


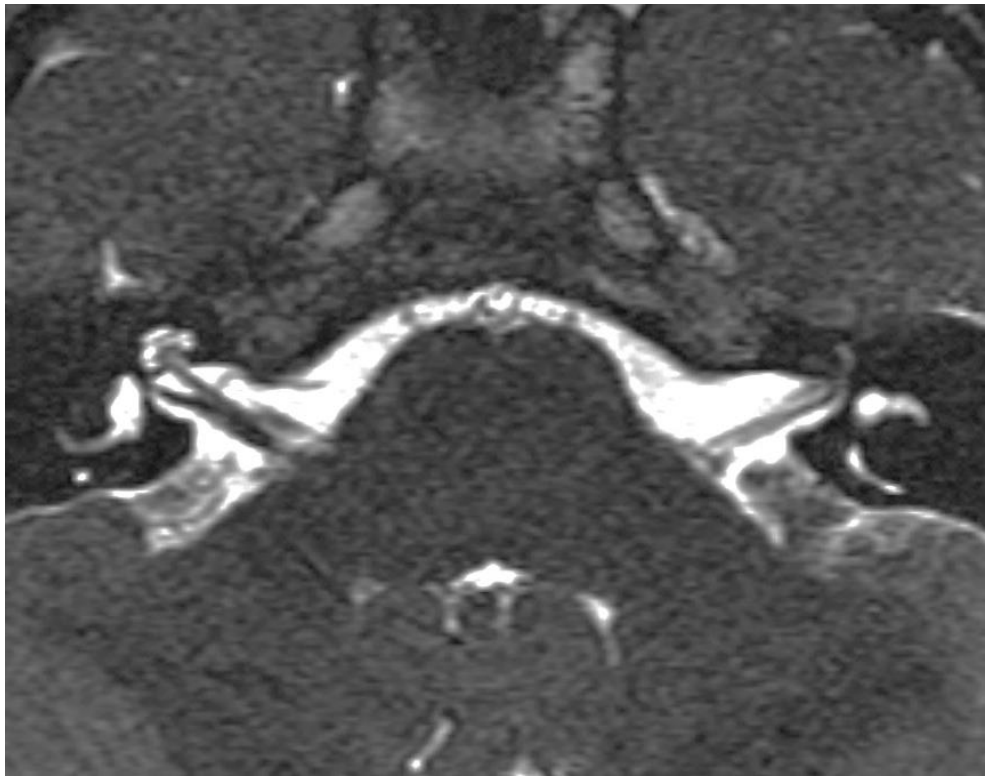
Cochlea

Vestibule + scc

IAC

Labyrinthine anatomy - MRI





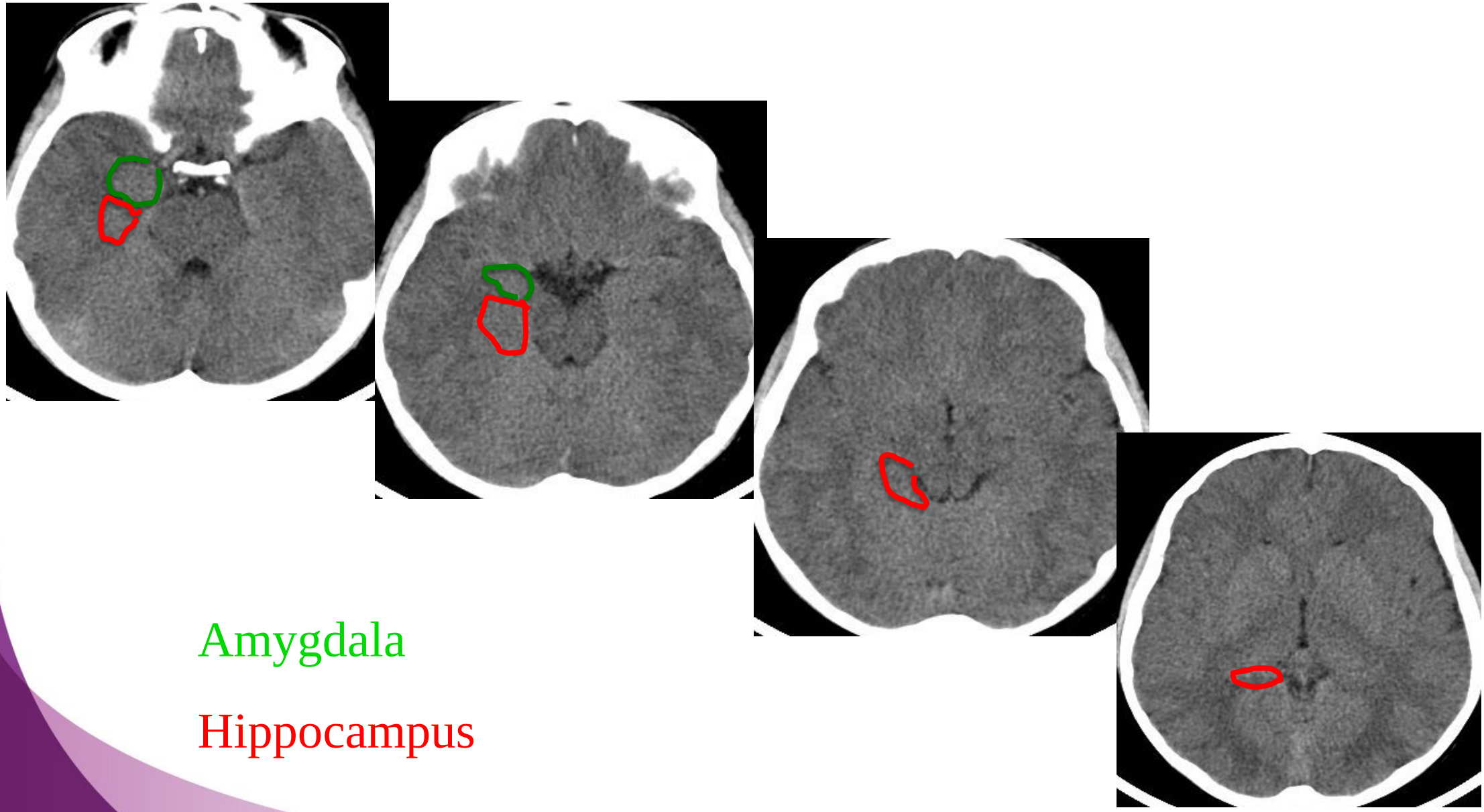
Hippocampus

- Composed of the dentate gyrus and cornu ammonis regions
- Part of limbic system
- Limbic system function: cooperation in learning, consolidation and retrieval of information; essential for formation of new memories
- Bilateral and unilateral radiation injury of the hippocampus alters learning and memory formation
- Mean doses of >45G to left temporal lobe associated with significant declines in longitudinal IQ

Hippocampal landmarks

- Lies medial to temporal horn of lateral ventricle throughout
- Quadrigeminal and ambient cisterns at its medial borders
- Need to use thin slices for contouring (1-2mm)
- Easy to identify on sagittal images – check to confirm correct contours drawn on axial images

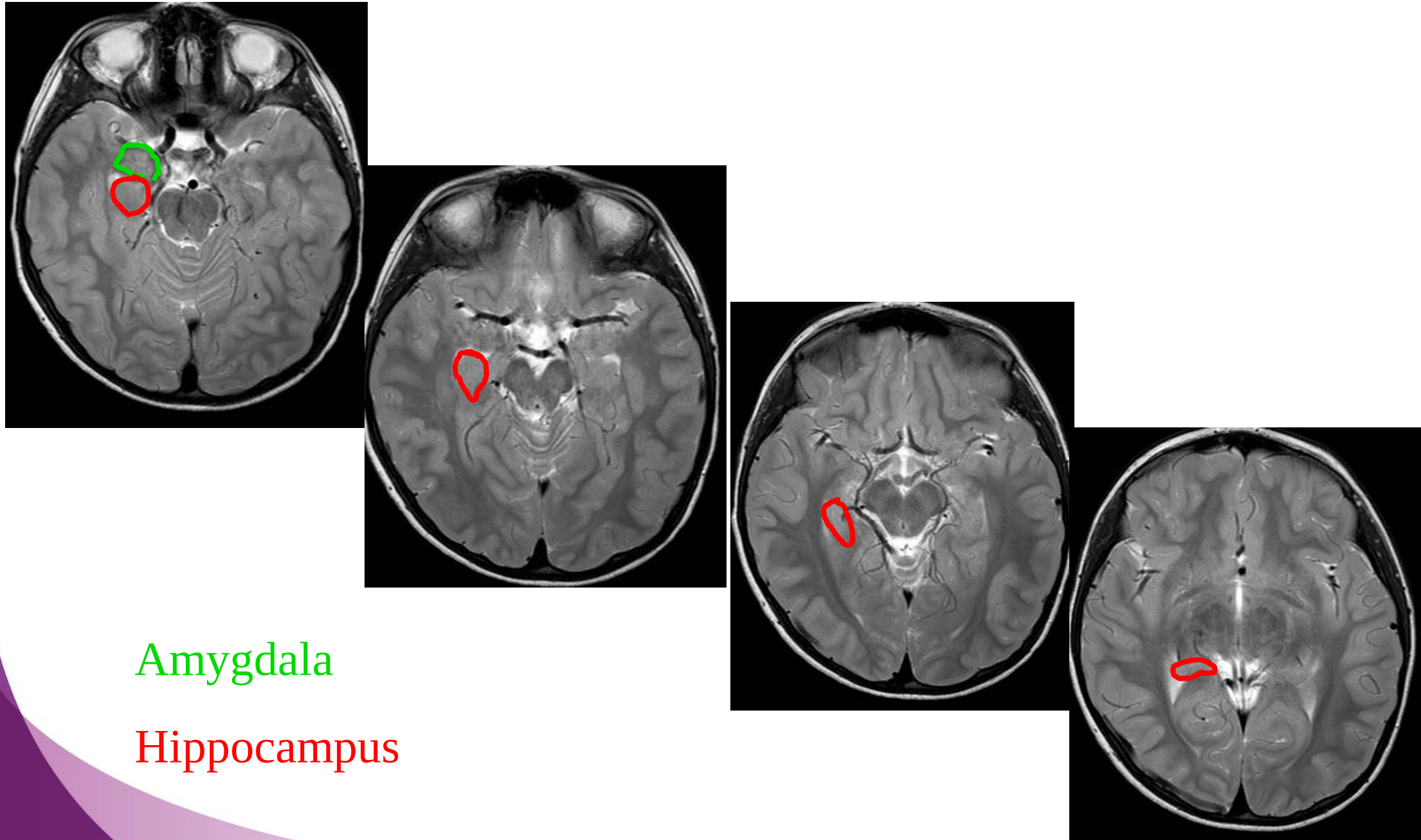
Hippocampus - CT



Amygdala

Hippocampus

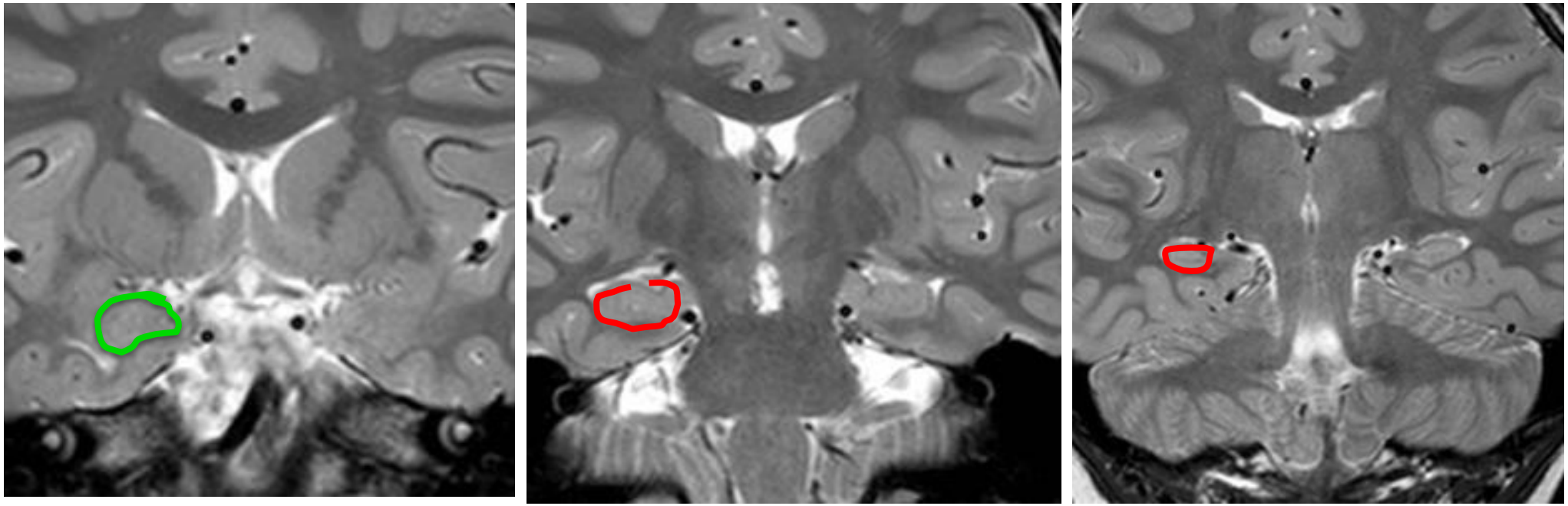
Hippocampus - MRI



Amygdala

Hippocampus

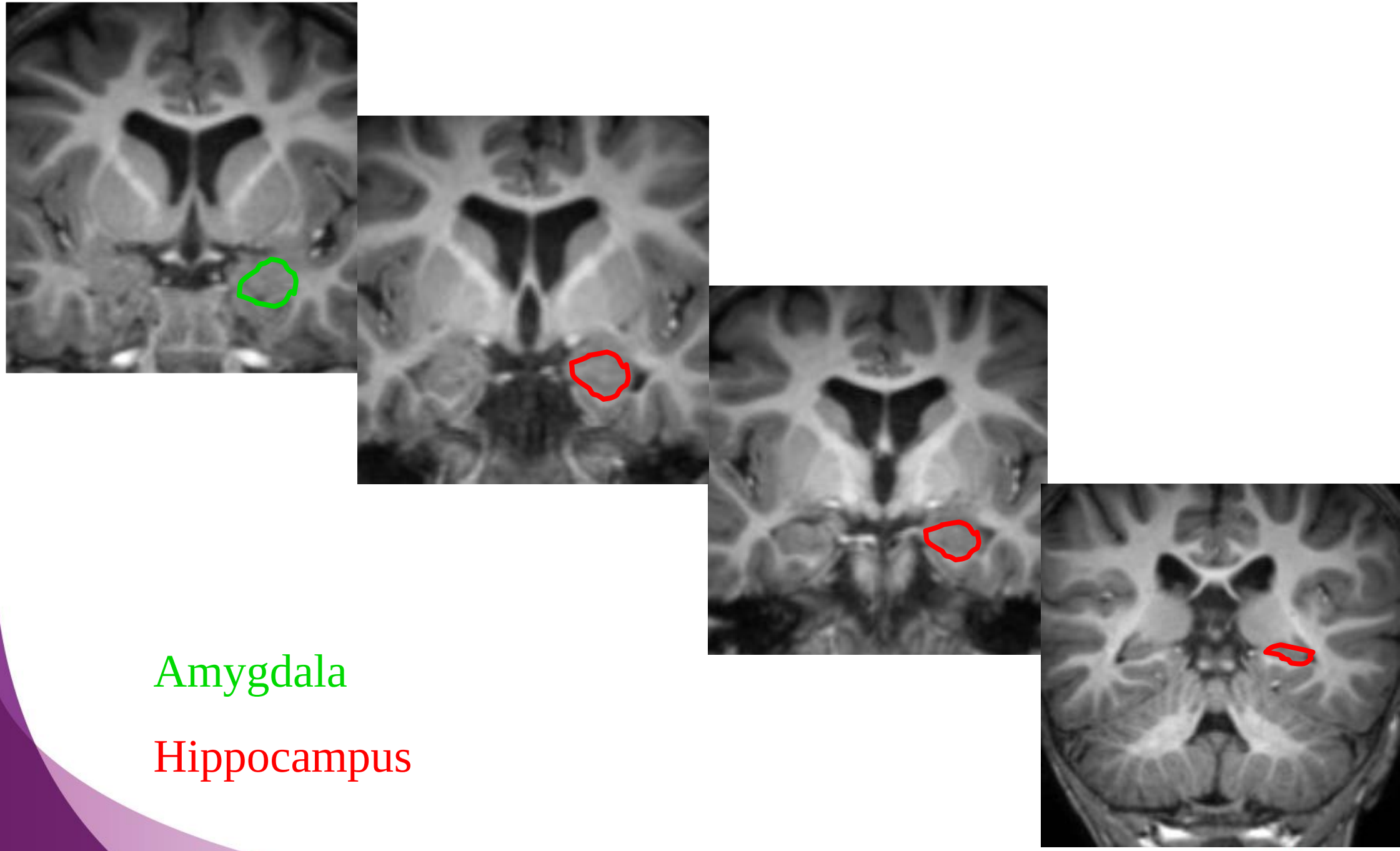
Mesial temporal lobe – T2



Amygdala

Hippocampus

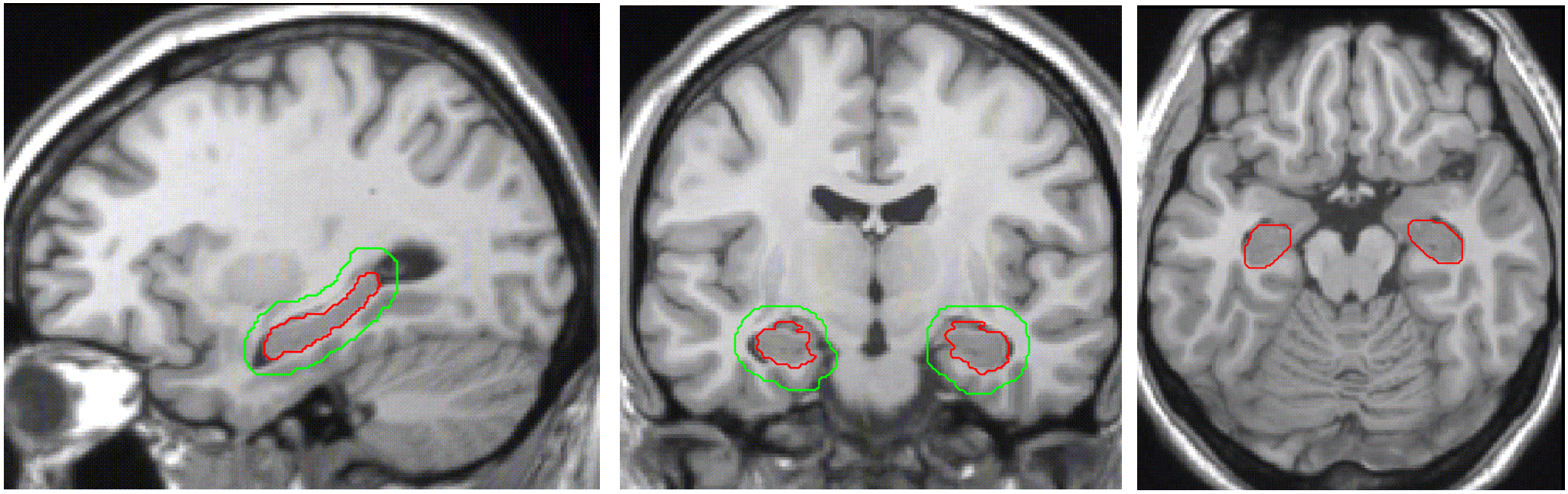
Mesial temporal lobe – T1



Amygdala

Hippocampus

Hippocampal contouring

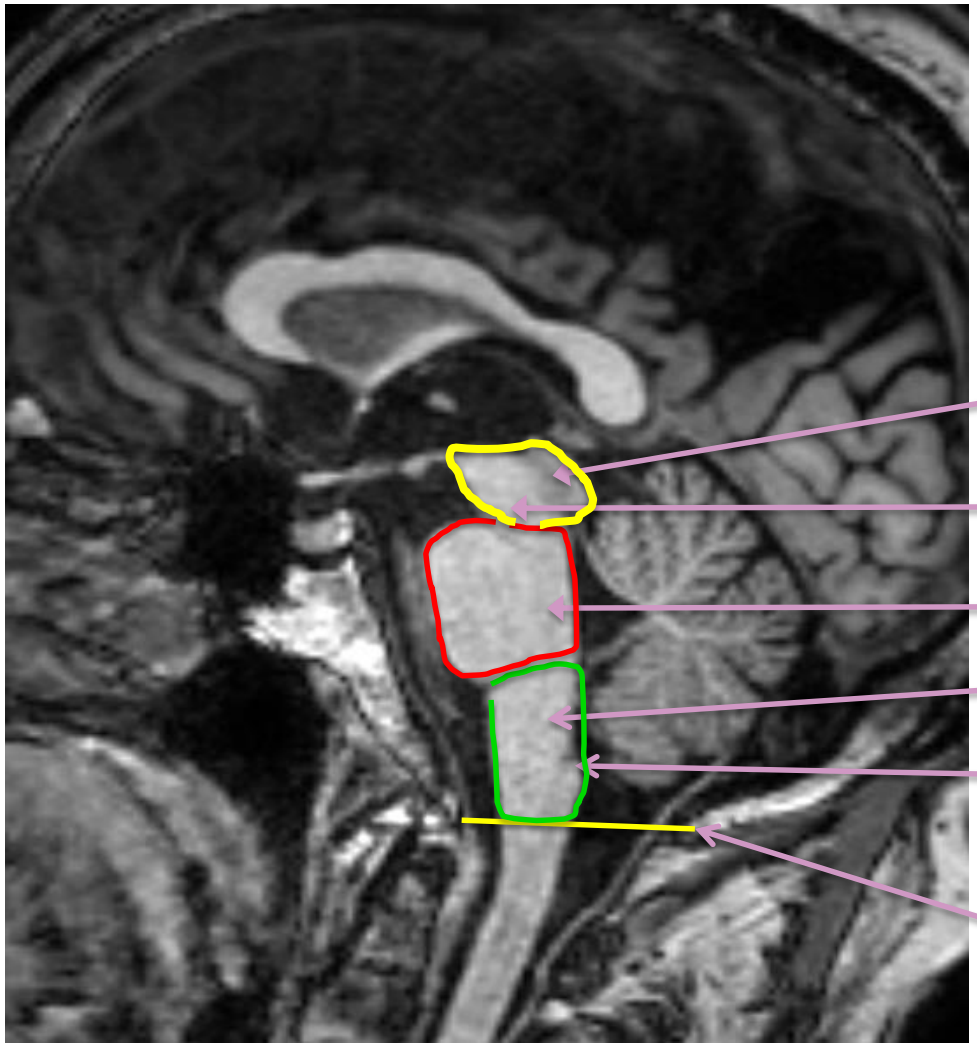


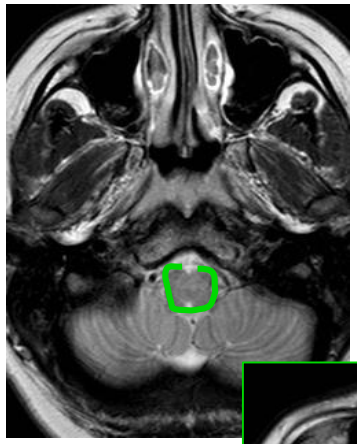
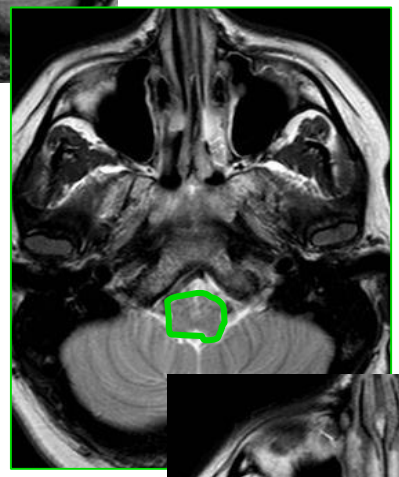
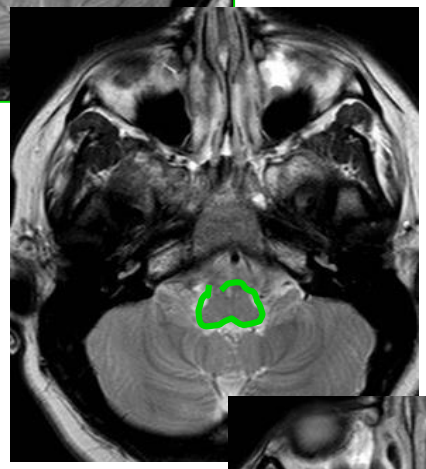
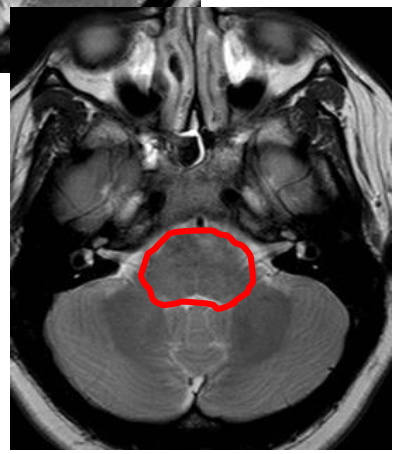
Brainstem

- Midbrain
- Pons
- Medulla

- The brainstem should be contoured from the superior border of the foramen magnum to the upper part of the mesencephalon (midbrain)
- Cross reference to sagittal plane images when contouring

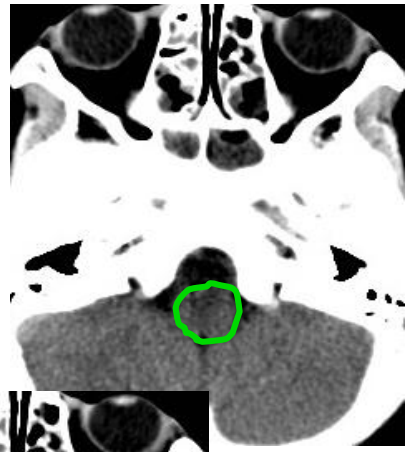
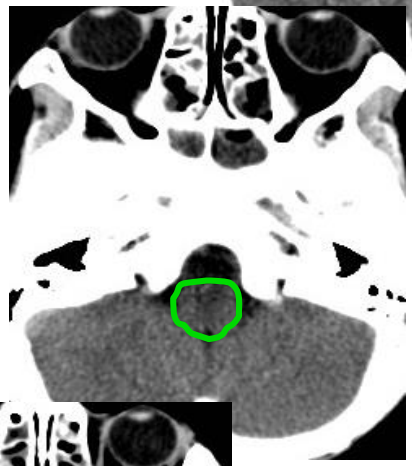
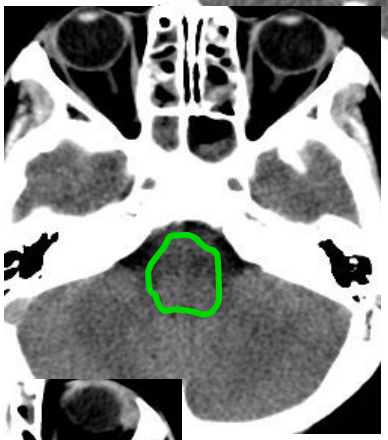
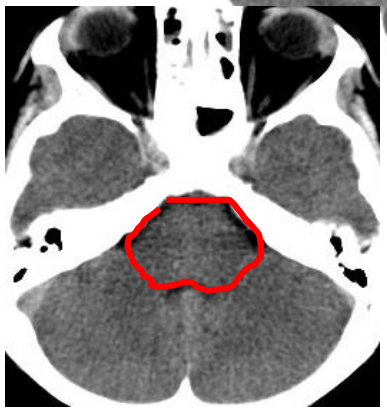
Brainstem


Midbrain tectum
Midbrain (mesencephalon)
Pons
Medulla
Obex
Foramen magnum

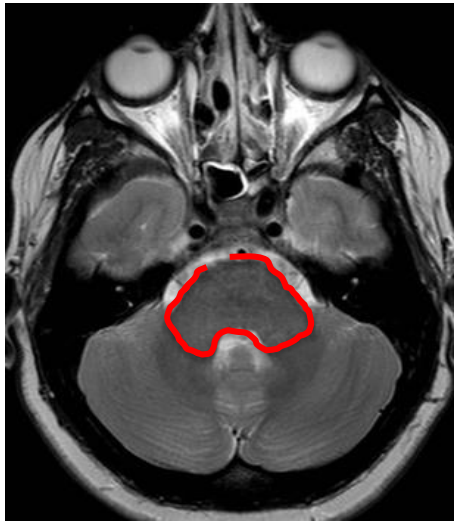





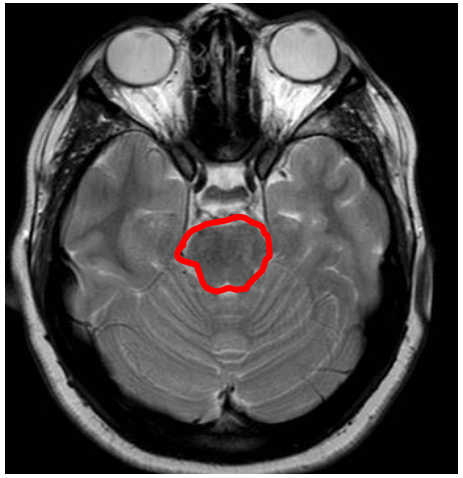
Medulla

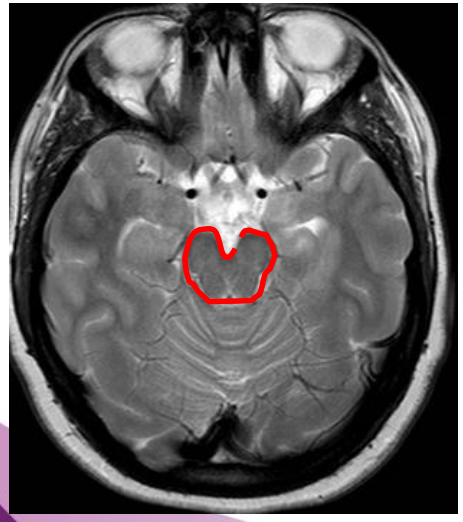
Pons

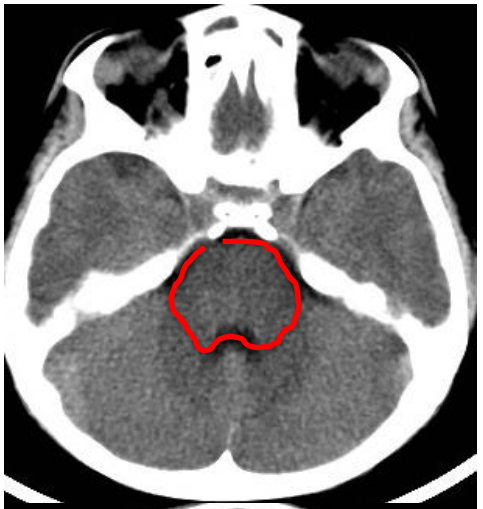
ESTRO School

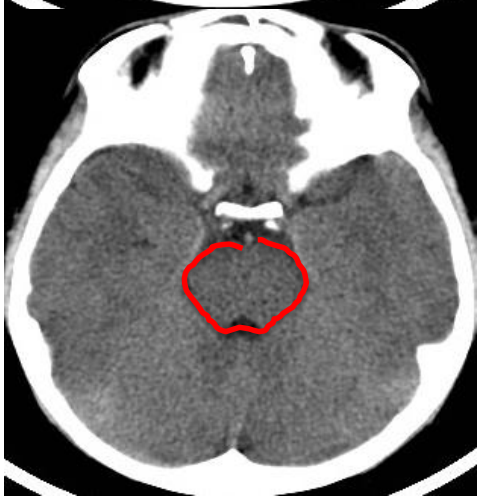


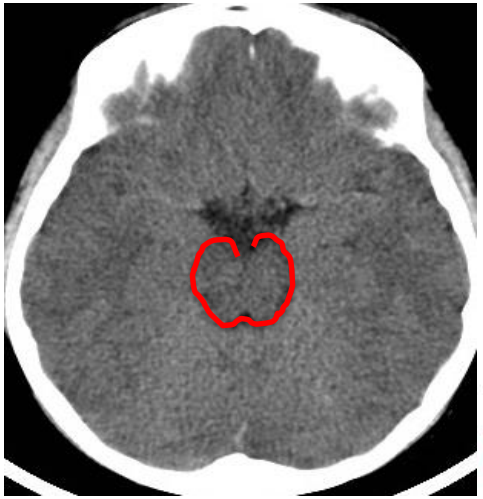




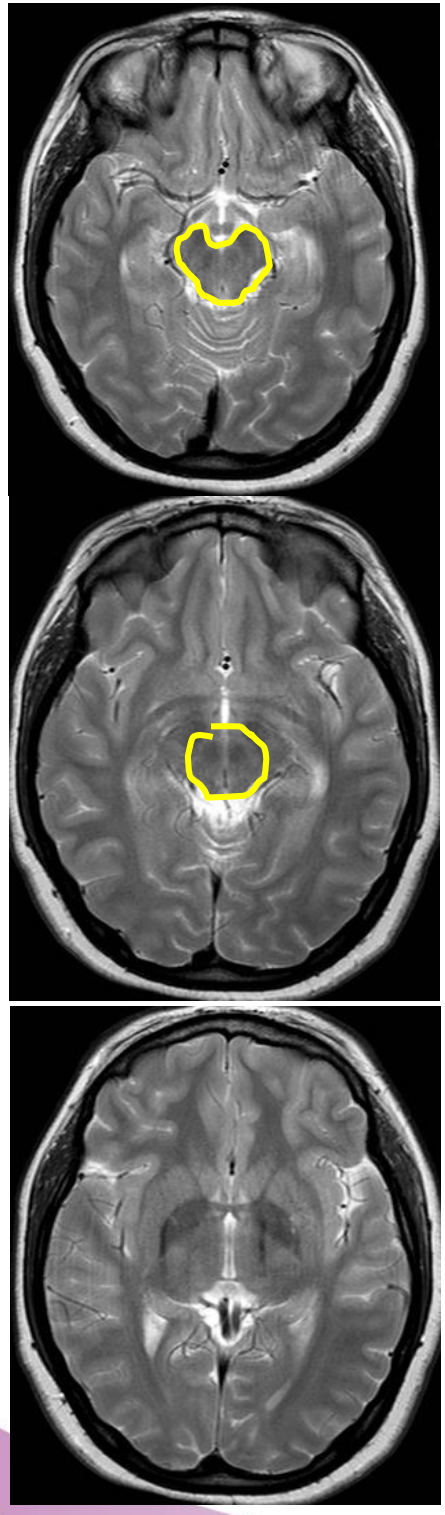
Pons



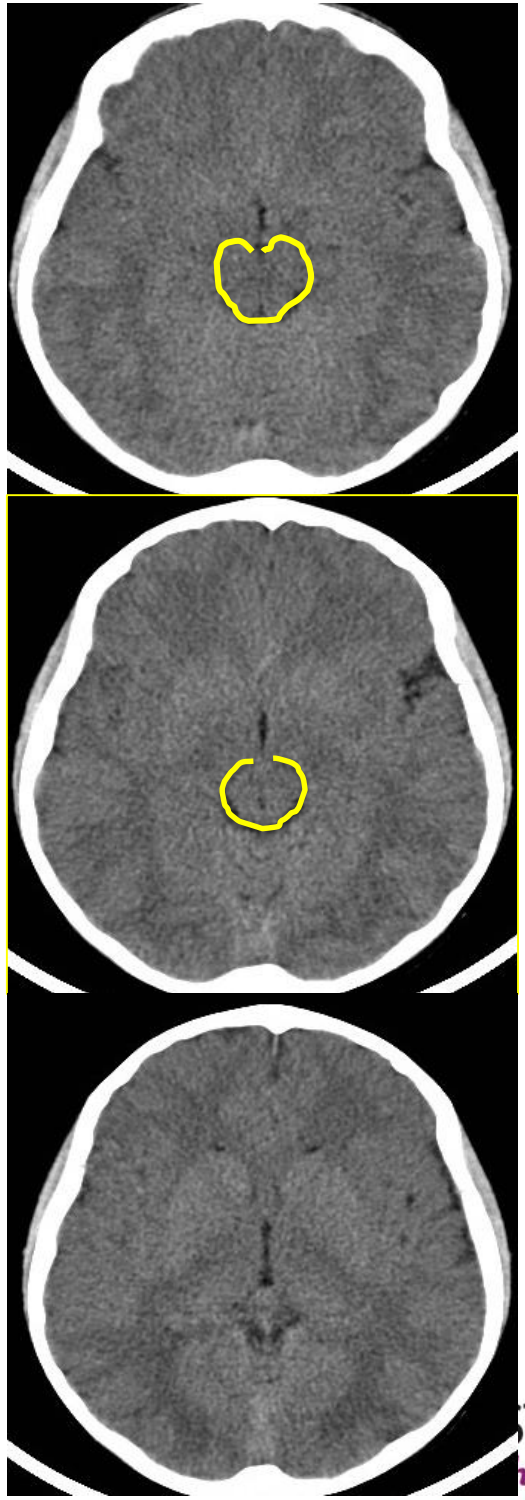




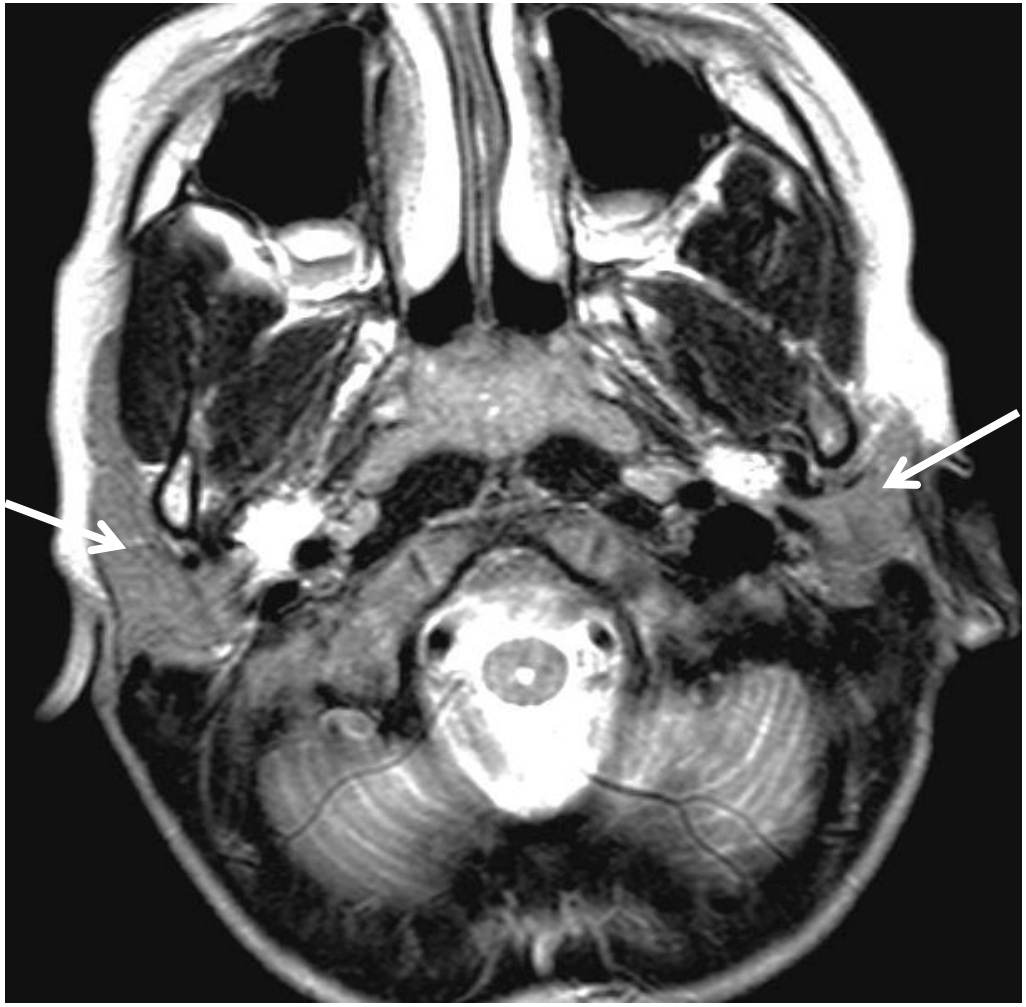
ESTRO School

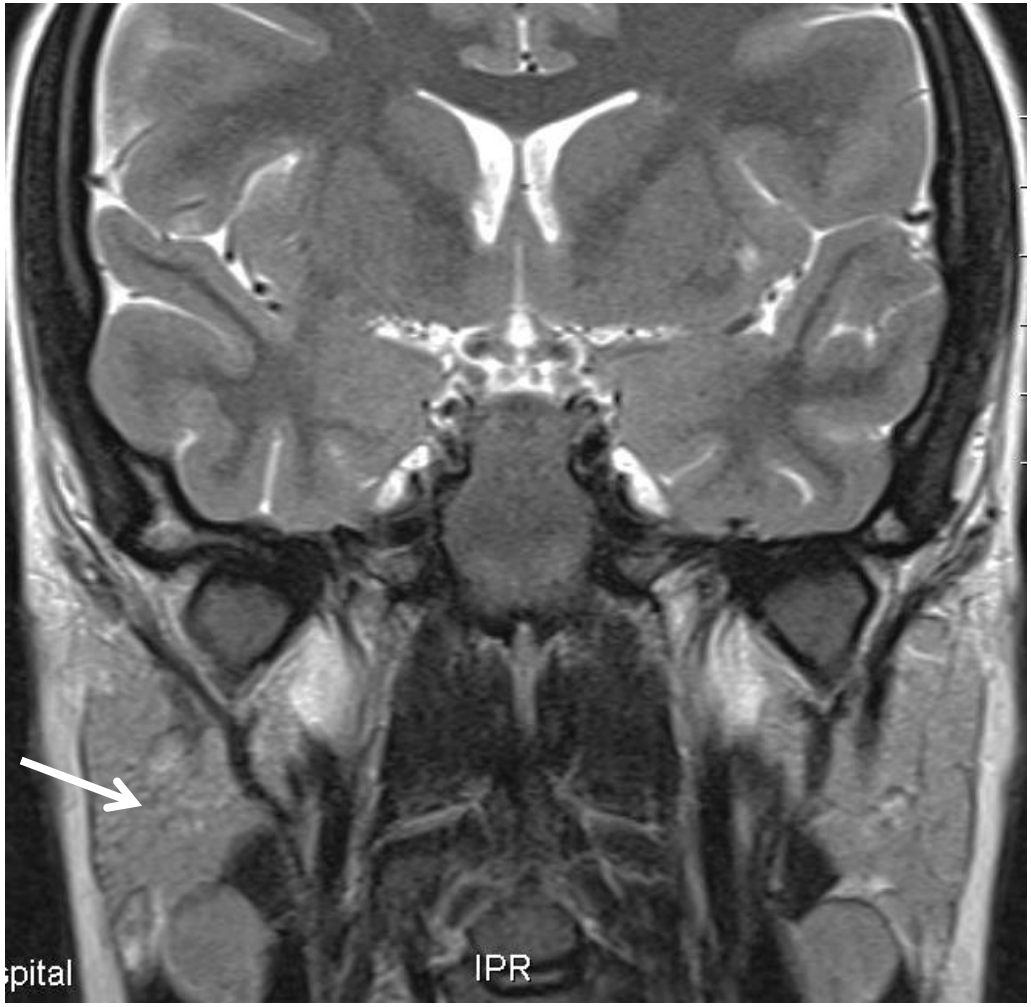


Midbrain



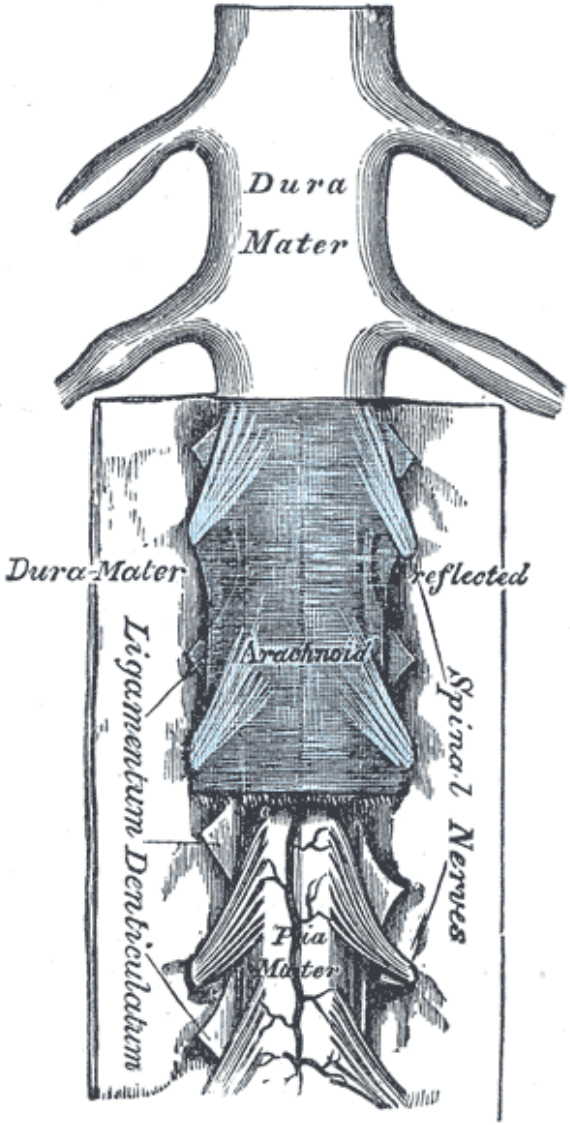
Parotid glands

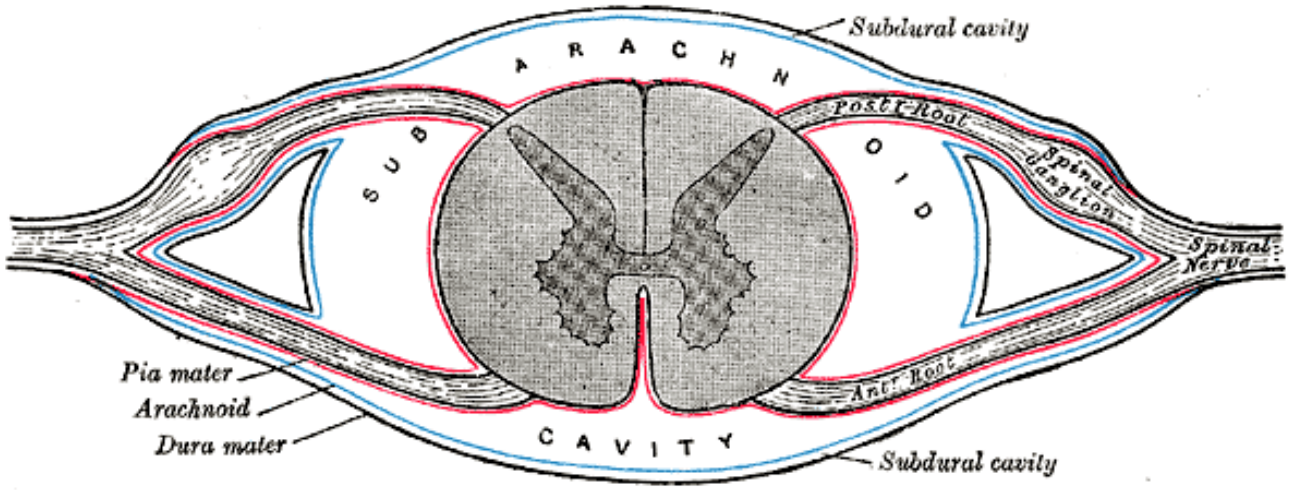




Spine anatomy

Spinal compartments





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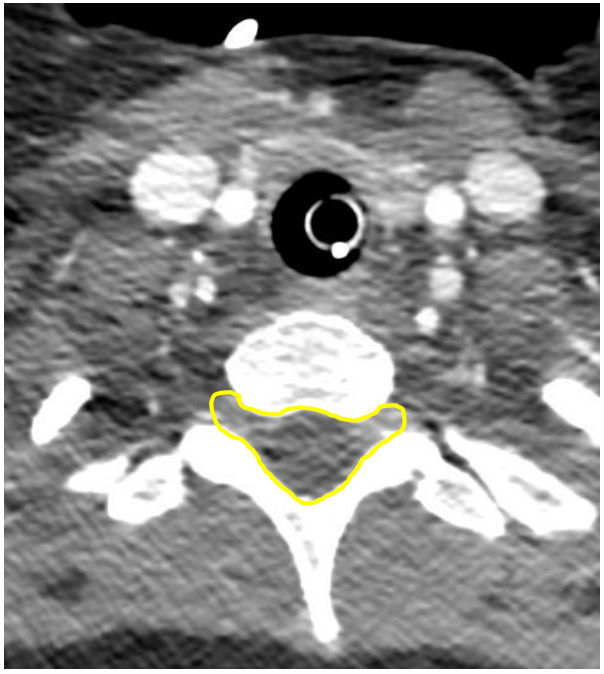
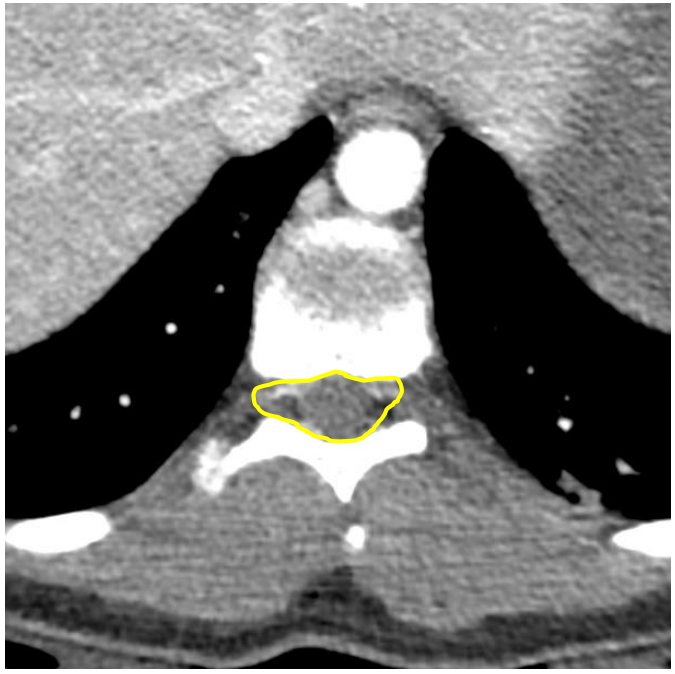
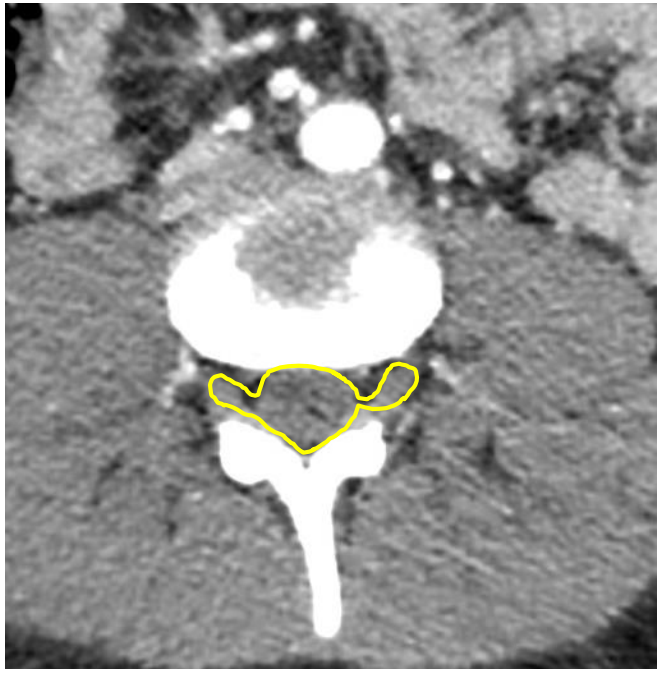
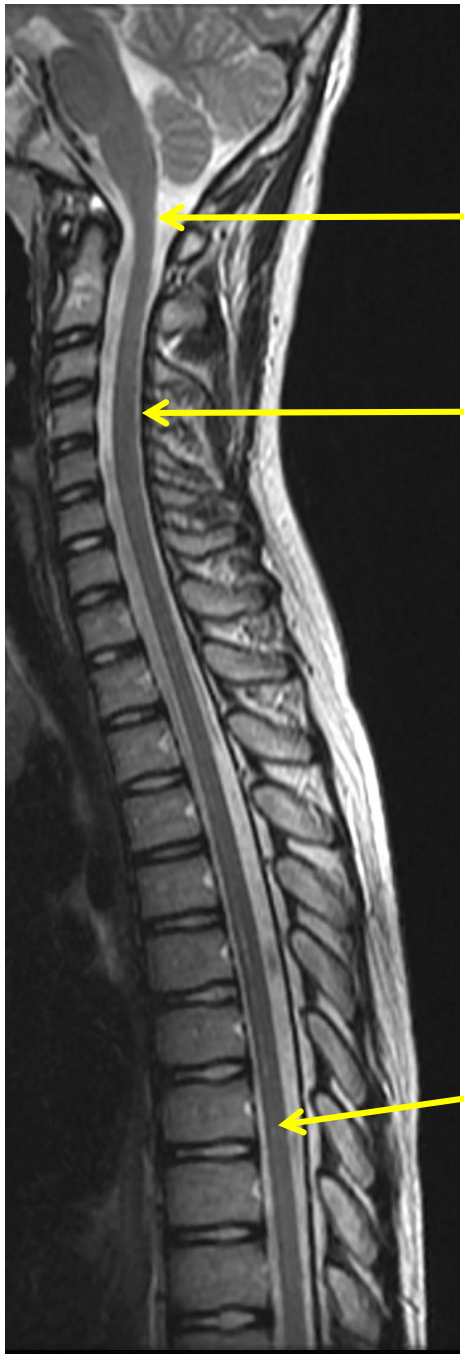
Spine anatomy – axial CT







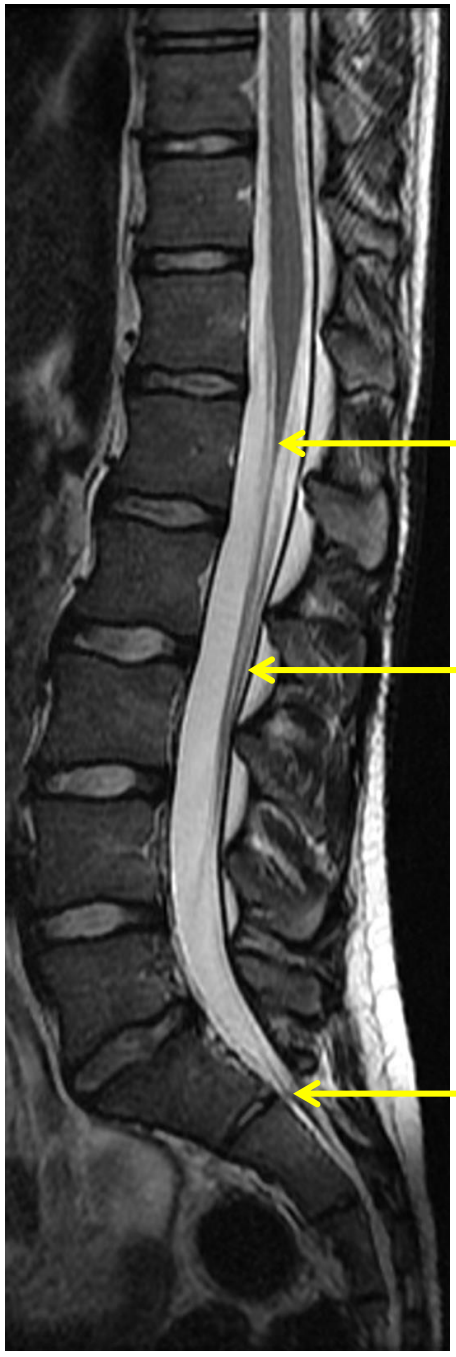
Sagittal MRI



Craniocervical junction

Cervical cord

Thoracic cord



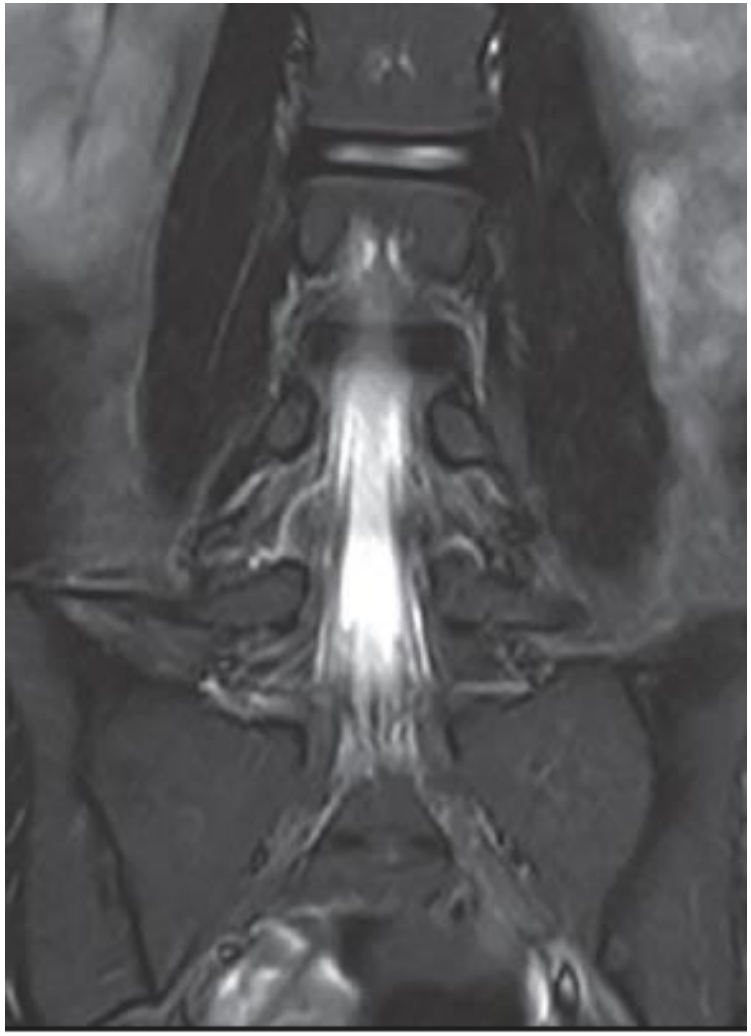
Conus

Cauda equina

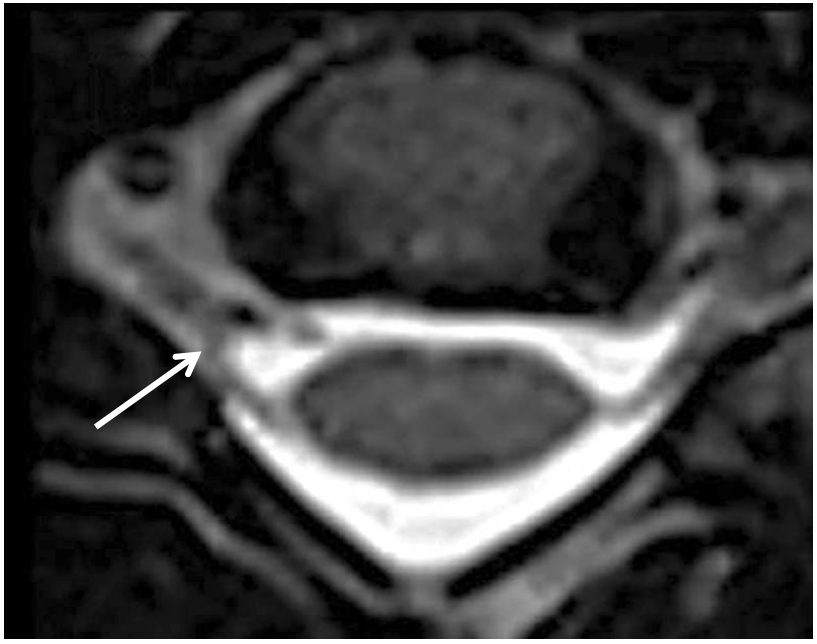
Thecal sac termination

ESTRO School

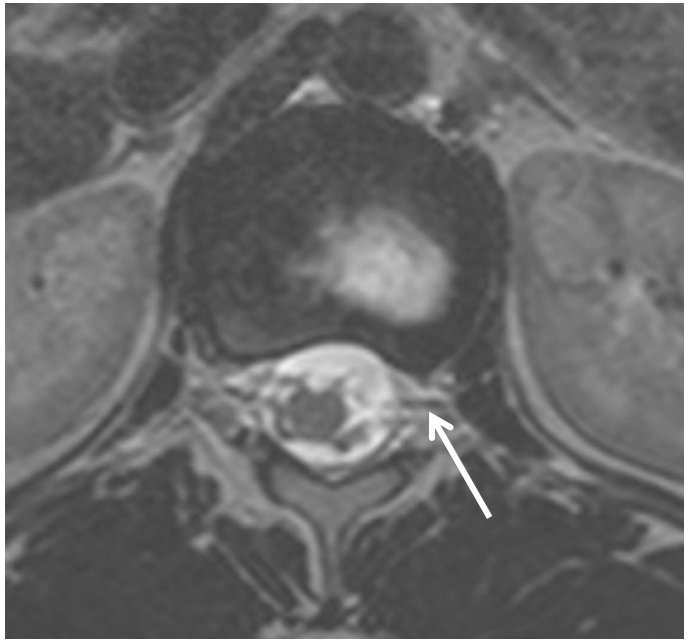
Coronal MRI



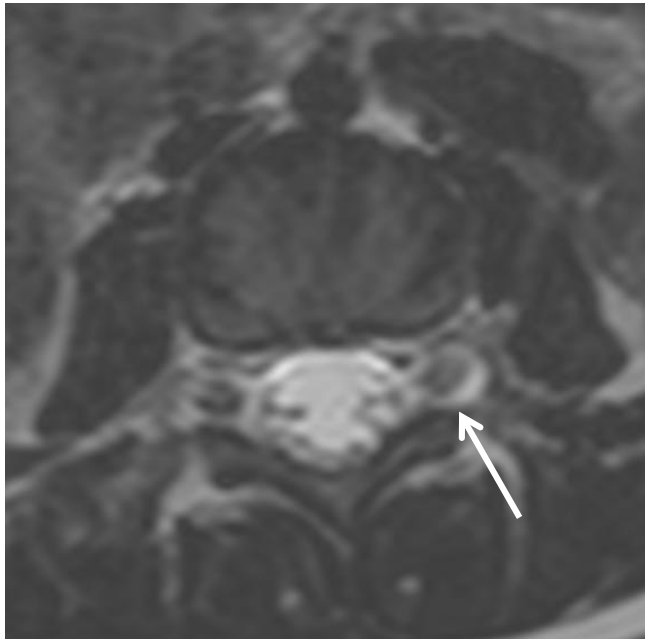
Axial MRI



Cervical



Thoracic



Lumbar

Summary

- MRI provides superior localisation and visualization of anatomical structures
- Fusion with CT necessary for optimal planning
- T2 provides good tissue contrast
- T1volume imaging optimal for fusion

WYS IATI

Daniel Kahneman coined the acronym WYS IATI which is an abbreviation for

"What you see is all there is".

It is one of the human biases that he explores when he describes how human decision-making is not entirely based on rational thought.

A Paediatric Oncologist's view on "Precision Medicine" for cancers in early life?

David Walker

On behalf of the Children's Brain Tumour Research Centre

University of Nottingham

My objectives are to:

- To consider mechanisms of brain injury and their impact on patient quality of life as a basis for designing strategies to reduce brain injury.

- To consider new drug developments and the associated challenges of delivering precision medicine to clinical practice.

- To add the priority of delivery systems designed to optmize delivery of drugs to CNS tumours as a priority for future clinical practice.

PRECISION MEDICINE DEBATE

NEURO VS ONCOLOGY

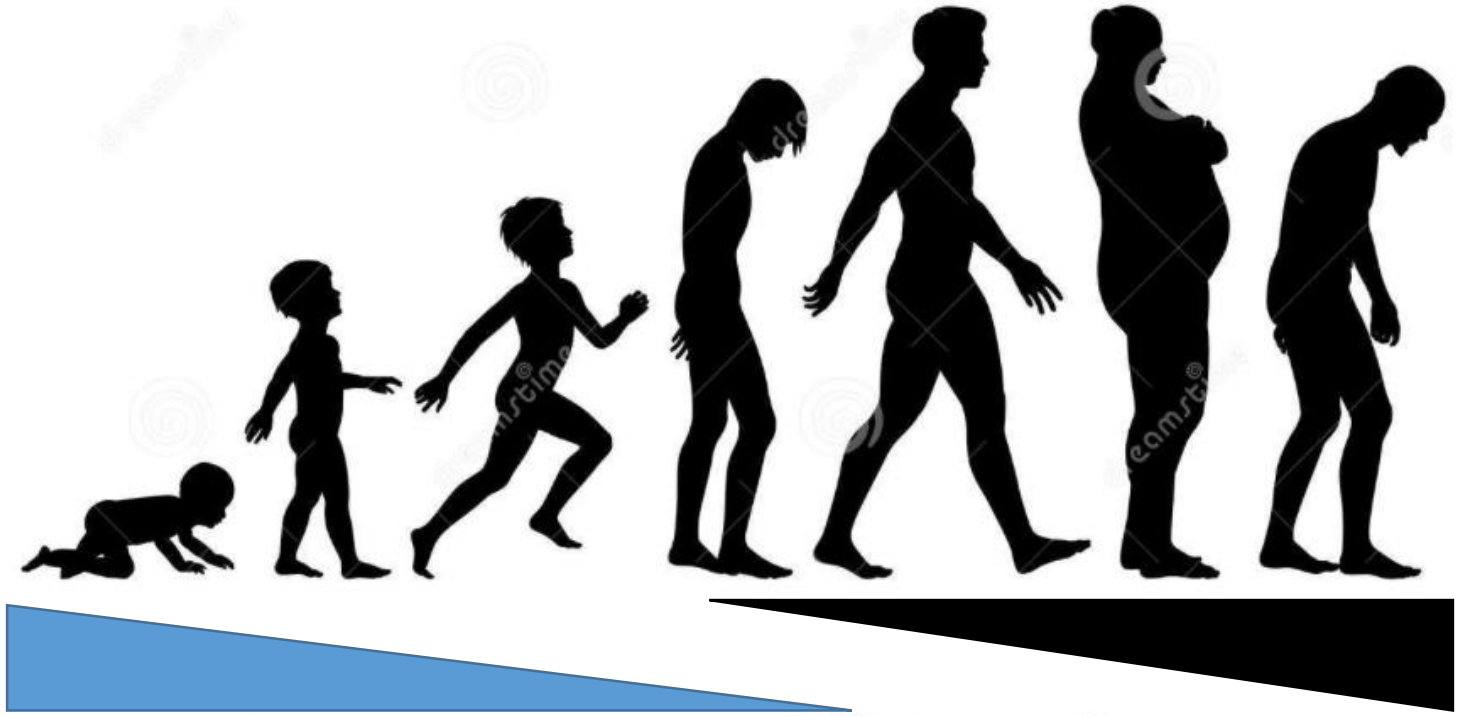
Avoiding the Harm

Neurological Symptoms
Neurological Signs
Raised intra-Cranial Pressure
Hydrocephalus
Epilepsy diagnosis and treatment
Blindness
Neuro-fibromatosis type 1
Neurofibromatosis type 2
Tuberous Sclerosis
Diencephalic syndrome
Rehabilitation
Cognitive Neuro-Psychology

Improving the Survival

Histology and Bio Diagnosis
Staging of Tumour
Cytotoxic Chemotherapy
Bio-targeted therapy
CNS targeted therapy
Involved Field Radiotherapy
Extended field Radiotherapy
Cancer Registration
Clinical Trials
Survival Curves
Late Effects / Quality of Life
Transition

Growth
Development



Ageing
Degeneration

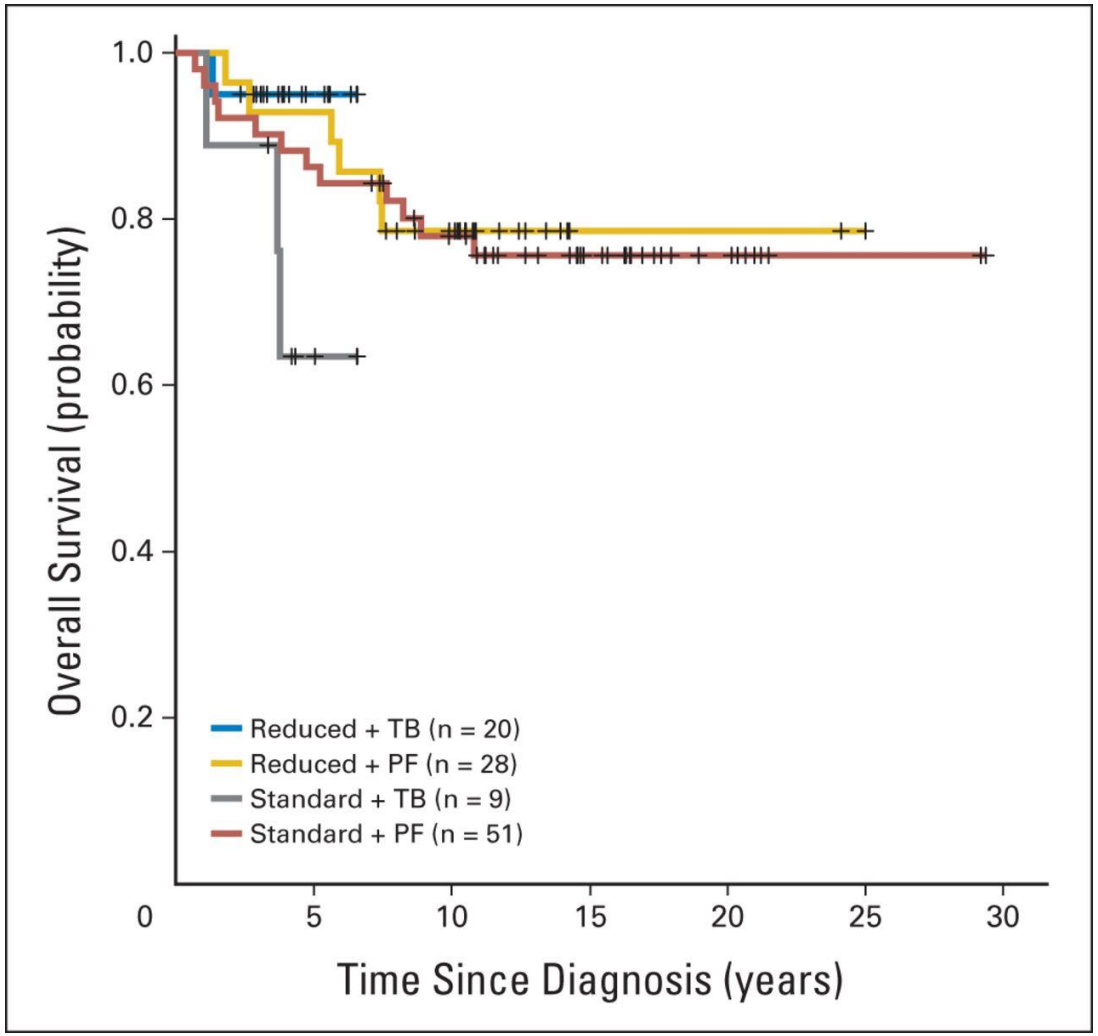
Impact of Craniospinal Dose, Boost Volume, and Neurologic Complications on Intellectual Outcome in Patients With Medulloblastoma

Iska Moxon-Emre, Eric Bouffet, Michael D. Taylor, Normand Laperriere, Nadia Scantlebury, Nicole Law, Brenda J. Spiegler, David Malkin, Laura Janzen and Donald Mabbott

JCO **June 10, 2014** vol. 32 no. 17 **1760-1768**

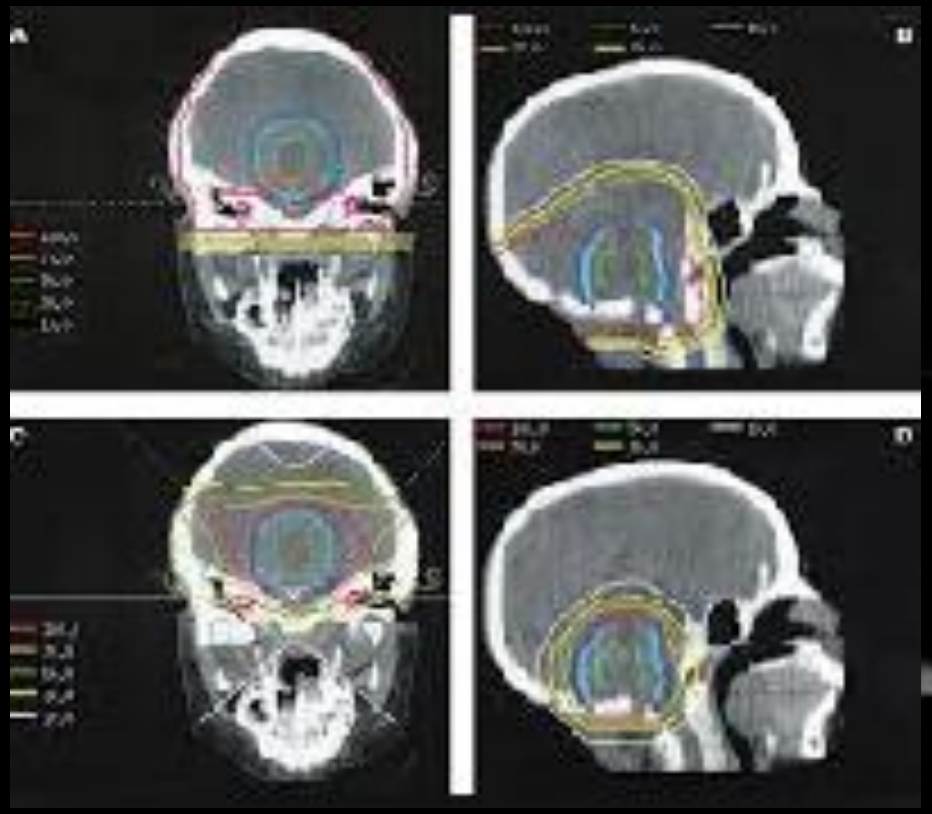
First Study of which I am aware where neurological and neurosurgical complications have been factored into model of cognitive consequences of treatment for medulloblastoma

Kaplan-Meier plot showing overall survival probability for patients with medulloblastoma separated by treatment group.

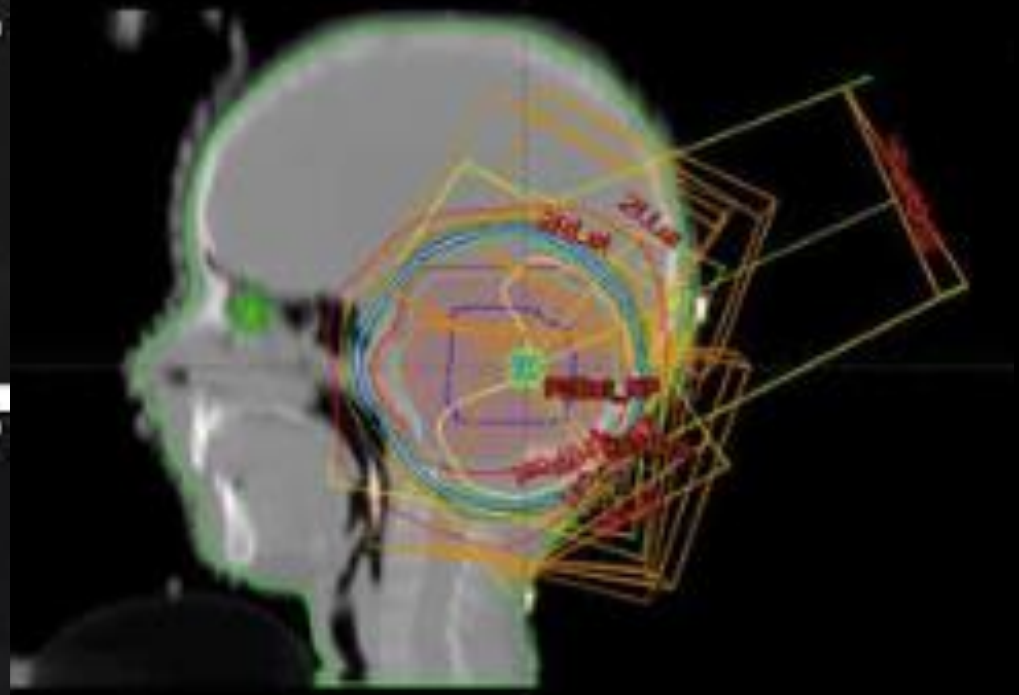


Iska Moxon-Emre et al. JCO 2014;32:1760-1768

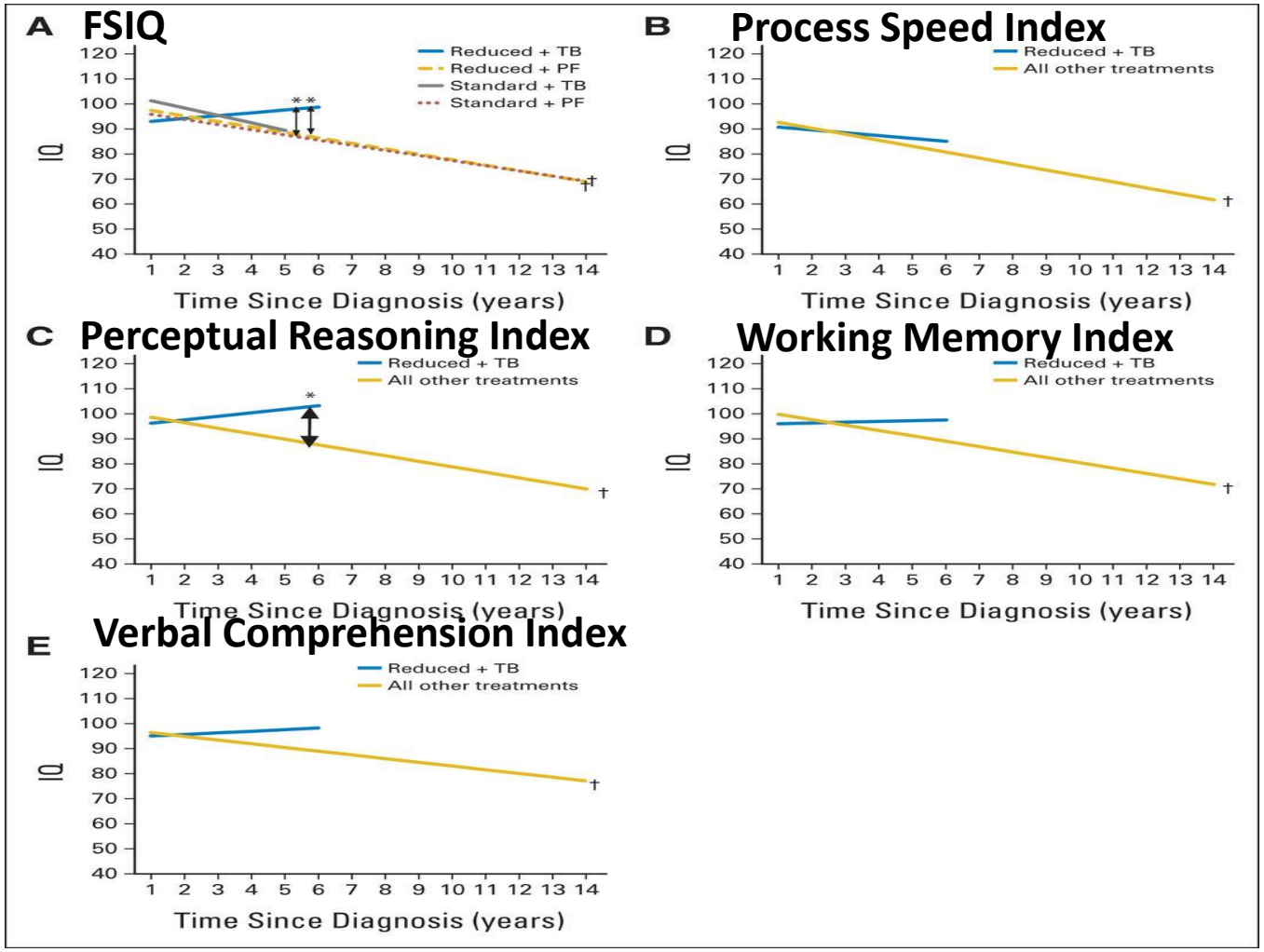
TUMOUR BED RADIATION FIELD



POSTERIOR FOSSA RADIATION FIELD



Estimated declines in (A) Full Scale Intelligence Quotient (IQ) score over time for patients in each of four treatment groups (reduced-dose craniospinal irradiation [CSR] + tumor bed [TB] boost, n = 19; reduced-dose CSR + posterior fossa [PF] boost, n = 27;...



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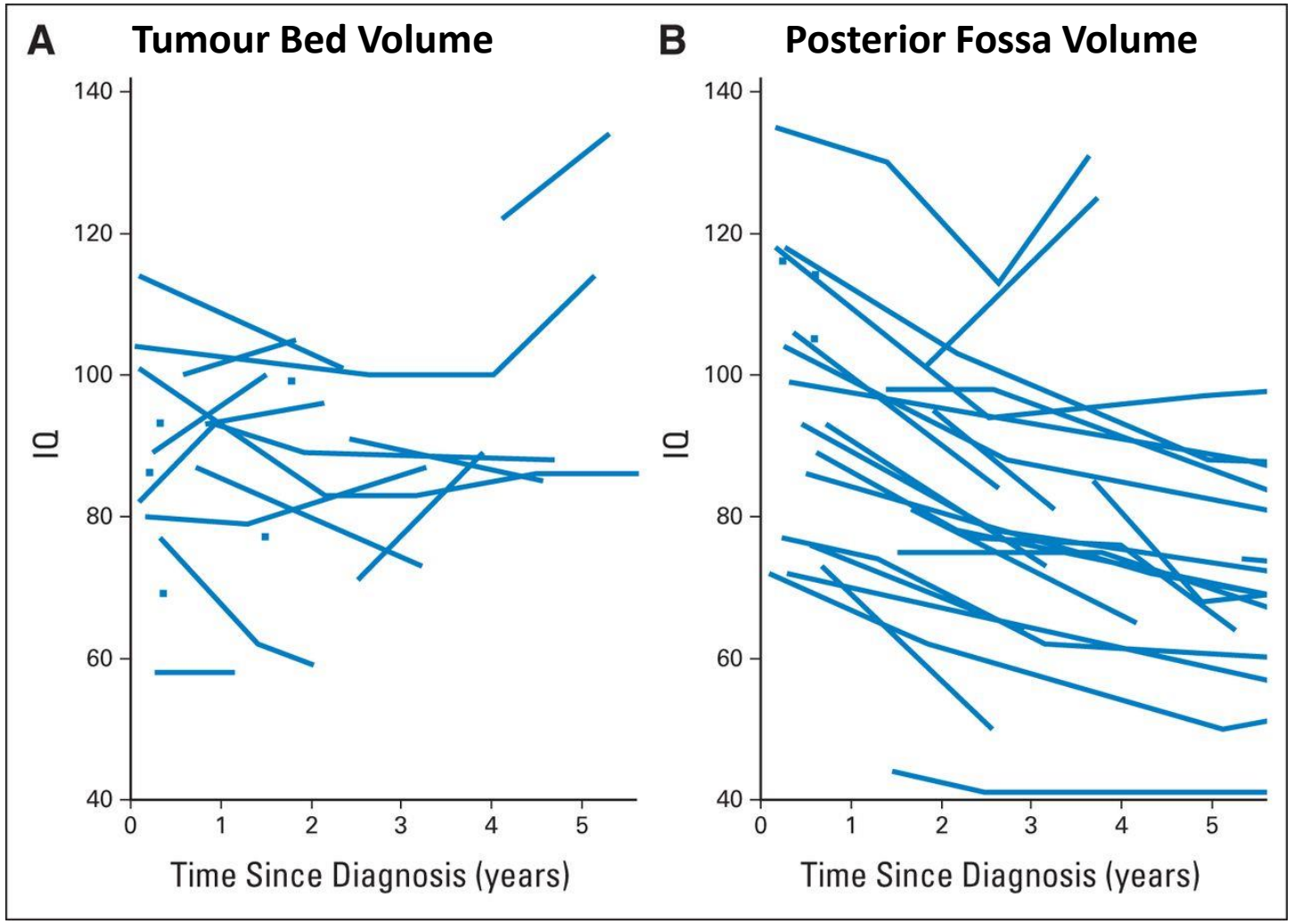
Observed Full Scale Intelligence Quotient (IQ) scores in comparable timeframe for patients treated with (A) reduced-dose craniospinal irradiation (CSR) plus tumor bed boost (n = 19) and (B) reduced-dose CSR plus posterior fossa boost (n = 28).



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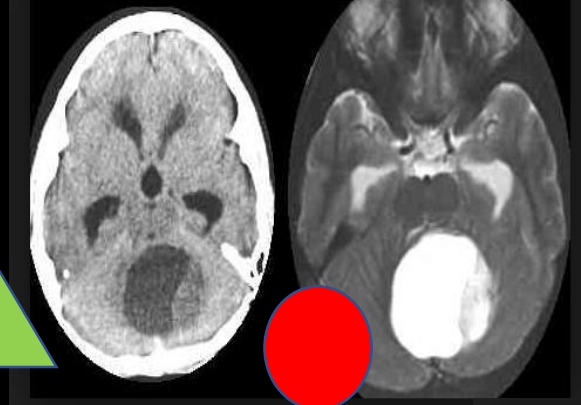
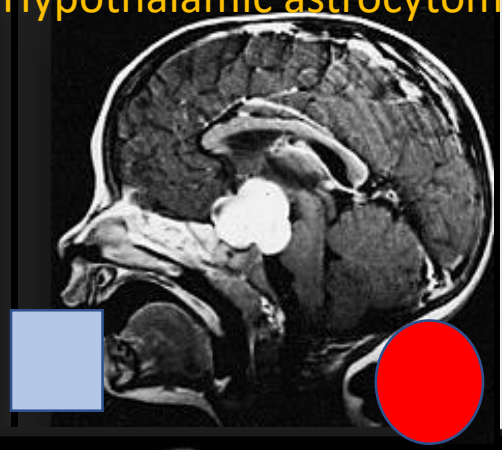
Index	Total Patients			
	No.	Mean	SE	Comparison *P*
FSIQ				
Hydrocephalus*				.001
Yes	47	80.63	2.36	
No	57	87.55	2.00	
Mutism				< .001
Yes	23	77.67	3.11	
No	81	86.68	1.74	
PSI				
Hydrocephalus*				.16
Yes	43	77.46	1.96	
No	55	82.28	1.53	
Mutism				.003
Yes	23	74.55	2.36	
No	75	82.58	1.41	
PRI				
Hydrocephalus*				< .001
Yes	50	82.18	2.51	
No	58	90.22	2.15	
Mutism				< .001
Yes	24	80.26	3.44	
No	84	88.50	1.94	
WMI				
Hydrocephalus*				.03
Yes	45	82.60	2.27	
No	54	90.59	1.85	
Mutism				.002
Yes	24	83.31	2.92	
No	75	88.96	1.71	
VCI				
Hydrocephalus*				.009
Yes	50	84.41	2.03	
No	57	90.62	1.75	
Mutism				.02
Yes	24	83.10	2.69	
No	83	89.18	1.52	

FSIQ, Full Scale IQ;
PRI, Perceptual Reasoning;
PSI, Processing Speed;
VCI, Verbal Comprehension;
WMI, Working Memory.

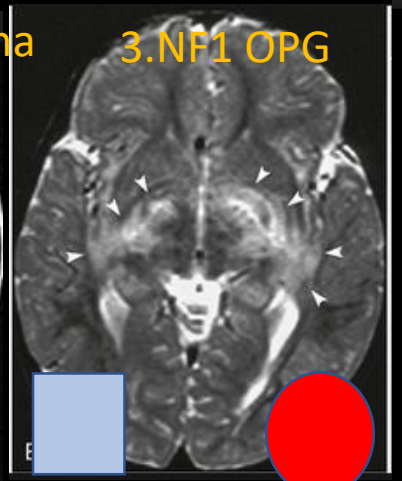
1.Cerebellar astrocytoma



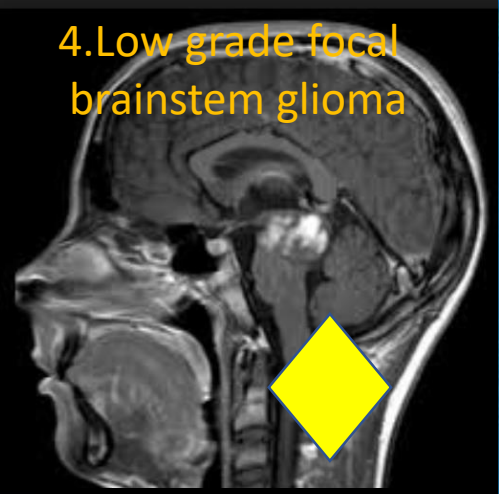
2.Hypothalamic astrocytoma



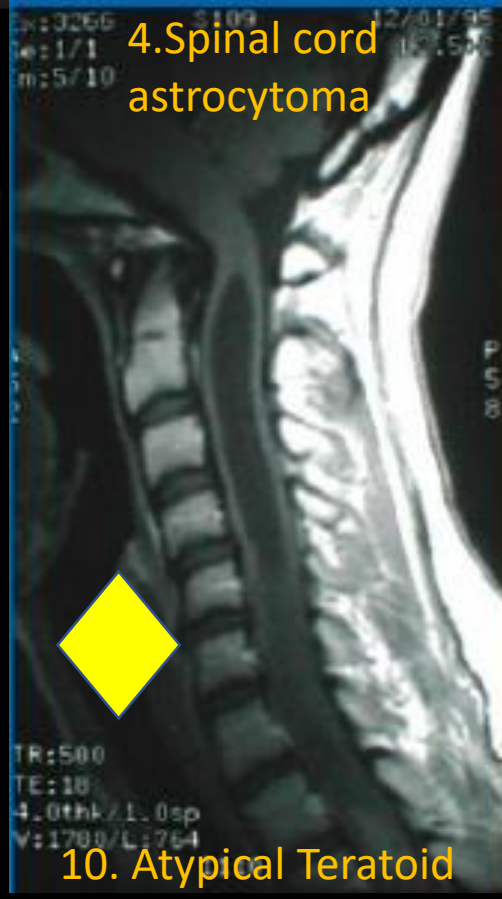
3.NF1 OPG



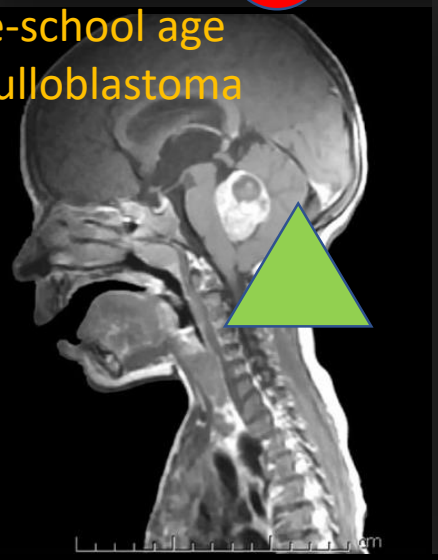
4.Low grade focal brainstem glioma



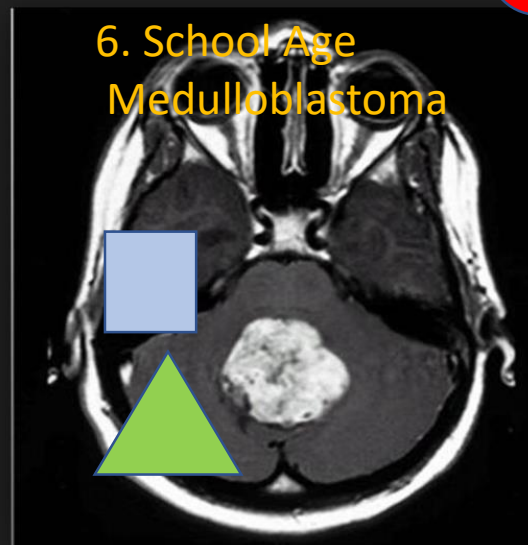
4.Spinal cord astrocytoma



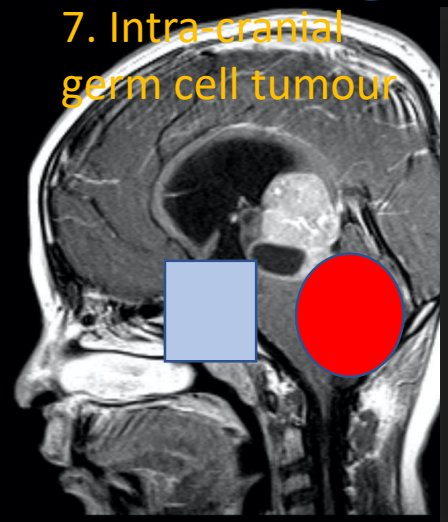
5.Pre-school age medulloblastoma



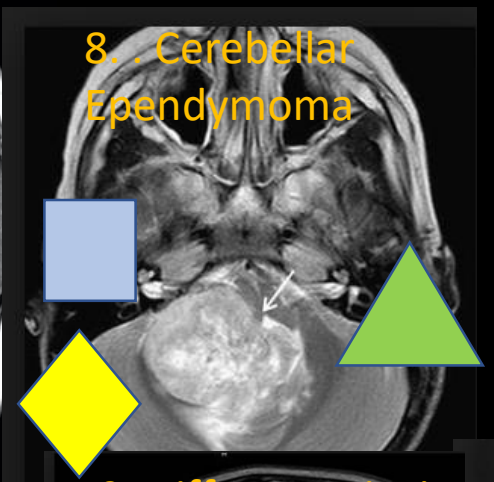
6. School Age Medulloblastoma



7. Intra-cranial germ cell tumour

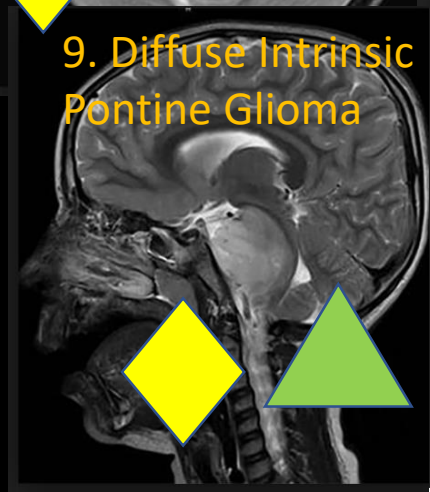


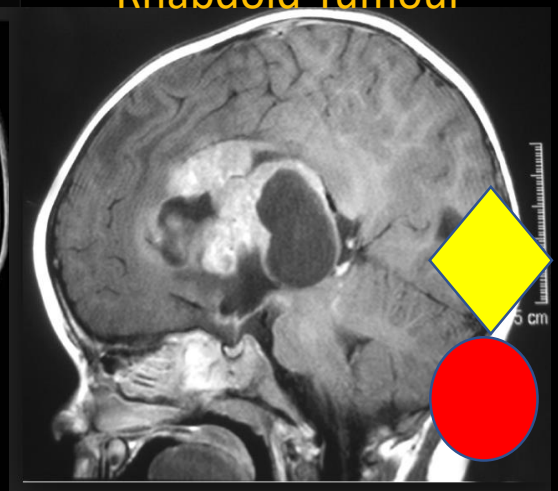
8. . Cerebellar Ependymoma



10. Atypical Teratoid Rhabdoid Tumour

9. Diffuse Intrinsic Pontine Glioma





Cerebellar / Cognitive

Focal injury

Blindness

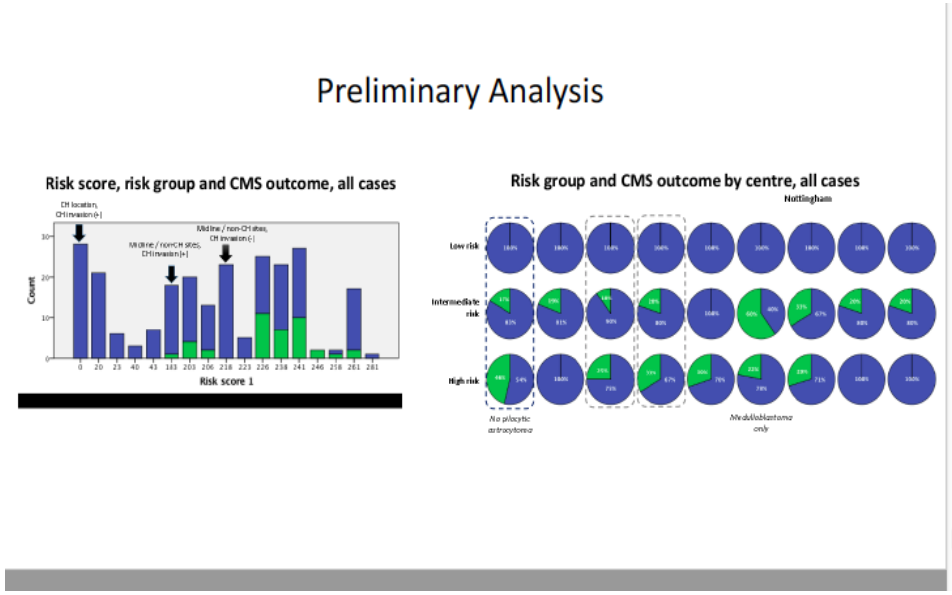
Endocrinopathy

10 Typical cases of child brain tumour

Strategies to Reduce Brain Injury from Brain Tumour in Early Life

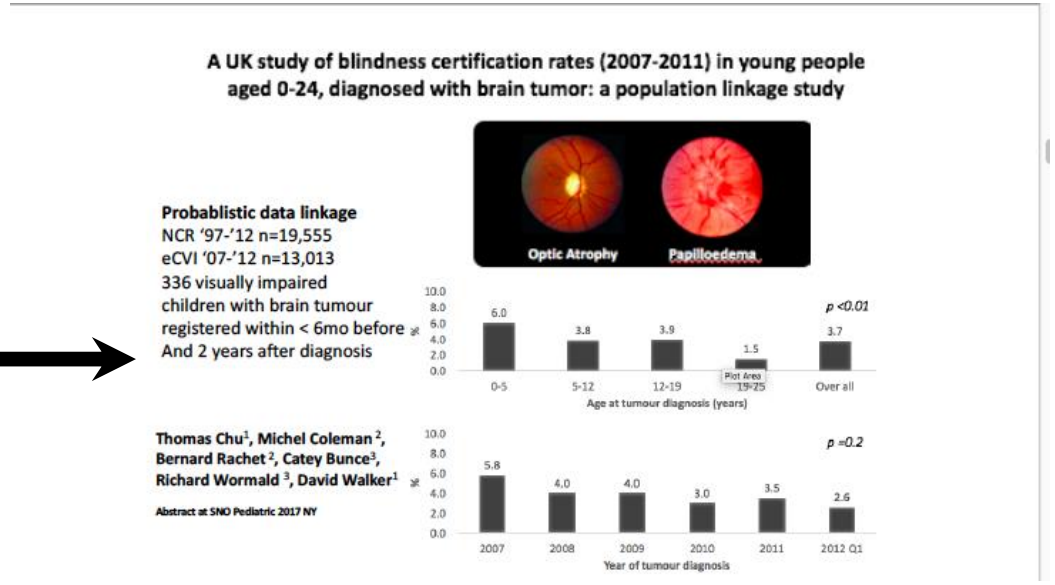
Accelerate Diagnosis – Surveillance - Screening

Redefining and representing key symptoms



Reduce Risk of Surgical Injury - CMS

Identify Vision Loss as a new brain tumour-related population outcome measure



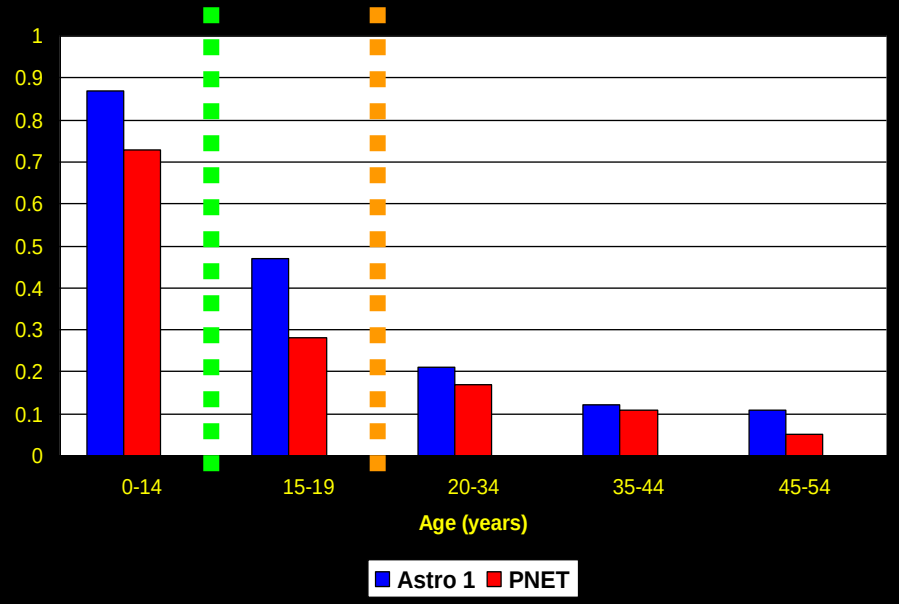
My objectives are to:

- To consider mechanisms of brain injury and their impact on patient quality of life as a basis for designing strategies to reduce brain injury.

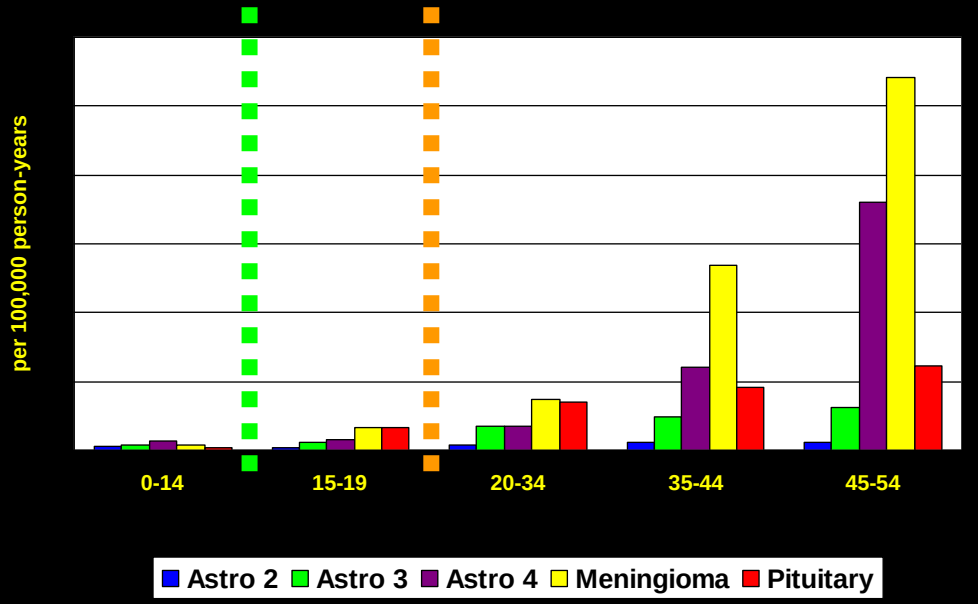
- To consider new drug developments and the associated challenges of delivering precision medicine to clinical practice.

- To add the priority of delivery systems designed to optmize delivery of drugs to CNS tumours as a priority for future clinical practice.

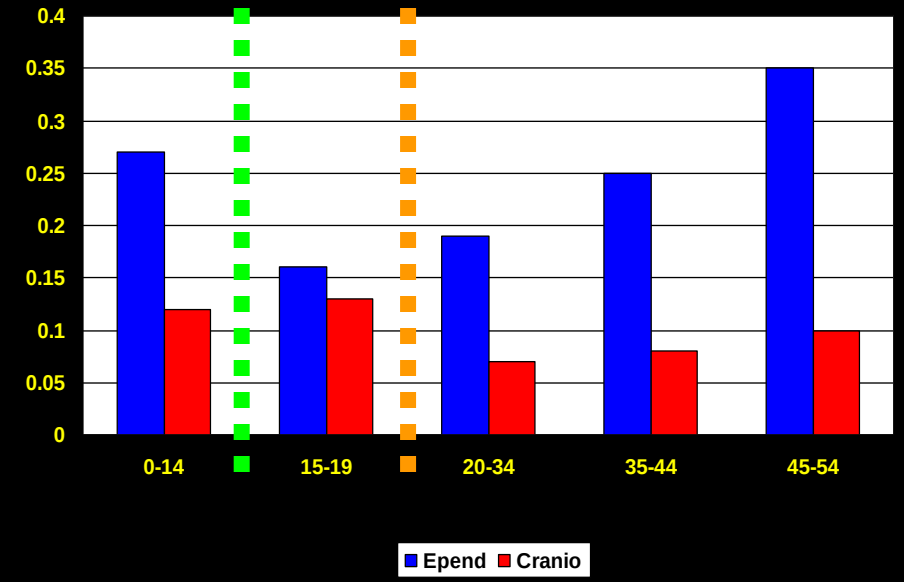
Falling Incidence: Astrocytoma Grade I and PNET, CBTRUS, 1997-2001



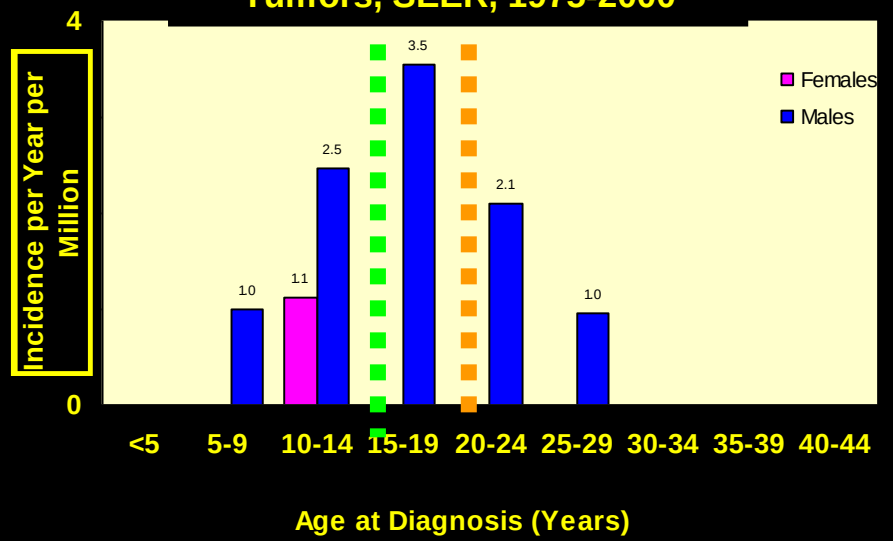
Rising Incidence: Astrocytoma Gr II, III, IV, Meningioma, Pituitary Tumors, CBTRUS, 1997-2001

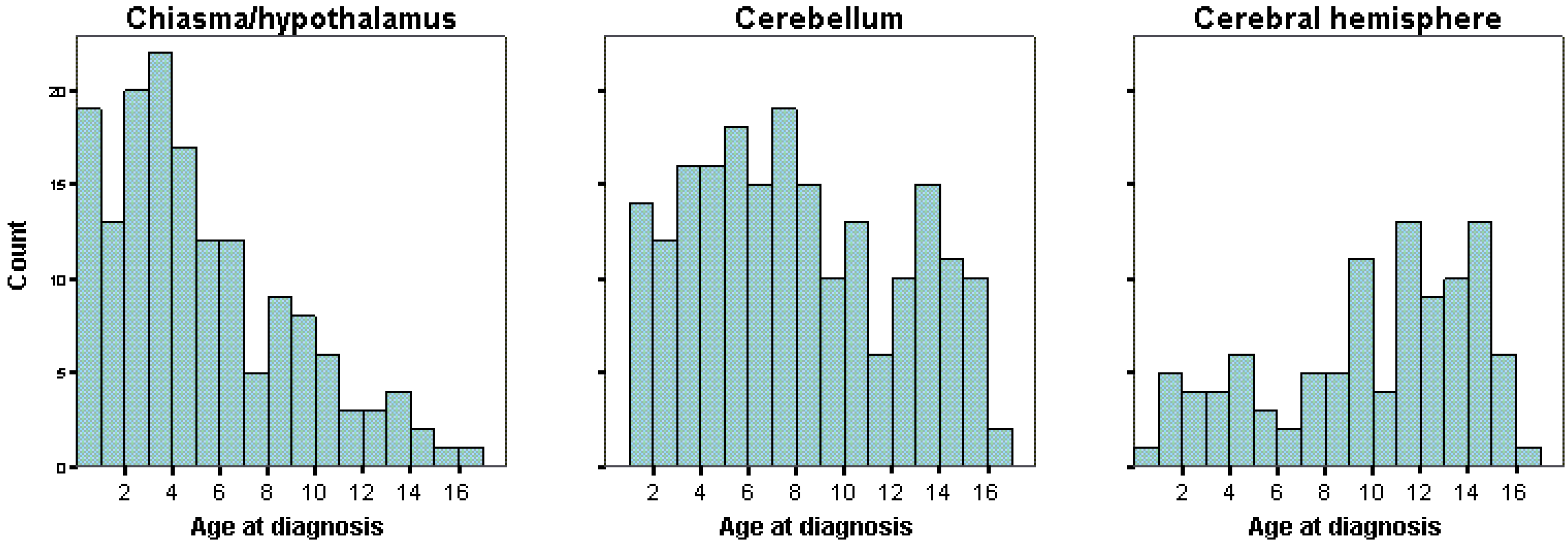


Varying Incidence Ependymoma and Craniopharyngioma, CBTRUS, 1997-2001



Peak Incidence of CNS Germ Cell Tumors, SEER, 1975-2000




Chiasma/hypothalamus
Count
0
5
10
15
20
2
4
6
8
10
12
14
16
Age at diagnosis
Cerebellum
2
4
6
8
10
12
14
16
Age at diagnosis
Cerebral hemisphere
2
4
6
8
10
12
14
16
Age at diagnosis

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PMC full text: Cell Mol Life Sci. 2012 Jun; 69(11): 1799–1811.
Published online 2011 Dec 13. doi: 10.1007/s00018-011-0898-9
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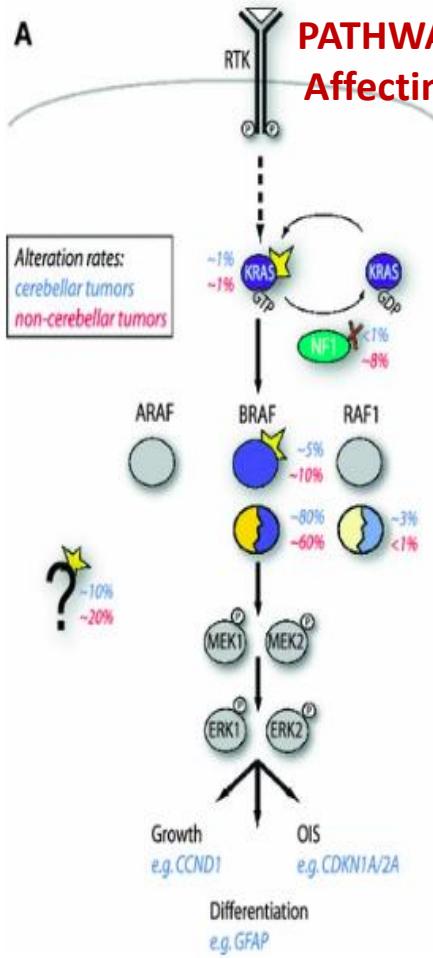
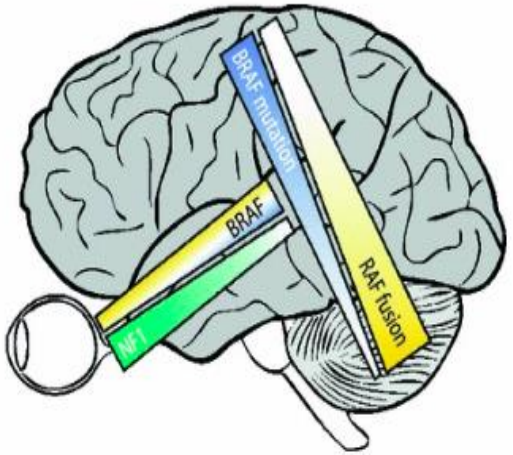
Oncogene Induced Senescence

Fig. 2



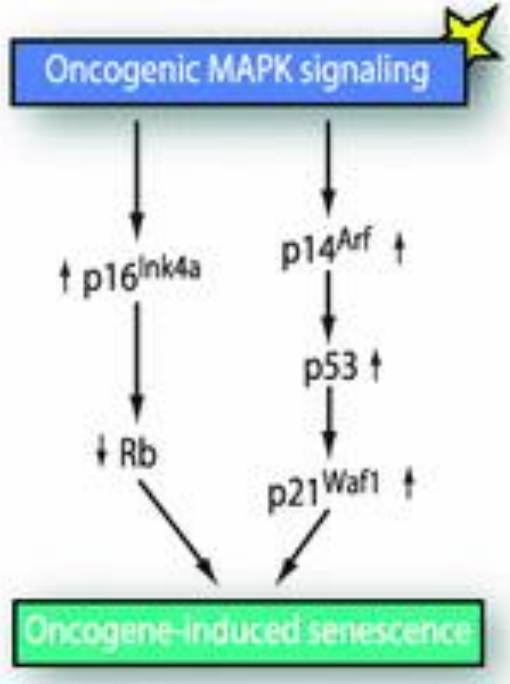
REPRESENTATION OF MAPK PATHWAY WITH ABERRATIONS Affecting 50-100% of Pilocytic Astrocytomas



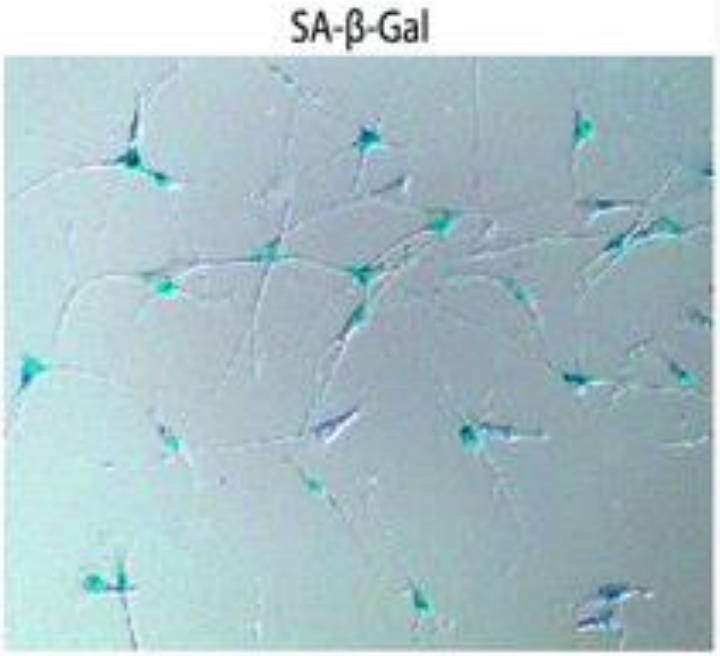
MAPK PATHWAY ALTERATIONS ARE UNEVENLY DISTRIBUTED ACROSS BRAIN REGIONS

Excessive MAPK activation induces Irreversible cell cycle arrest by $p16^{Ink4a}$/Rb or the $p14^{Arf}$/p53 pathway.

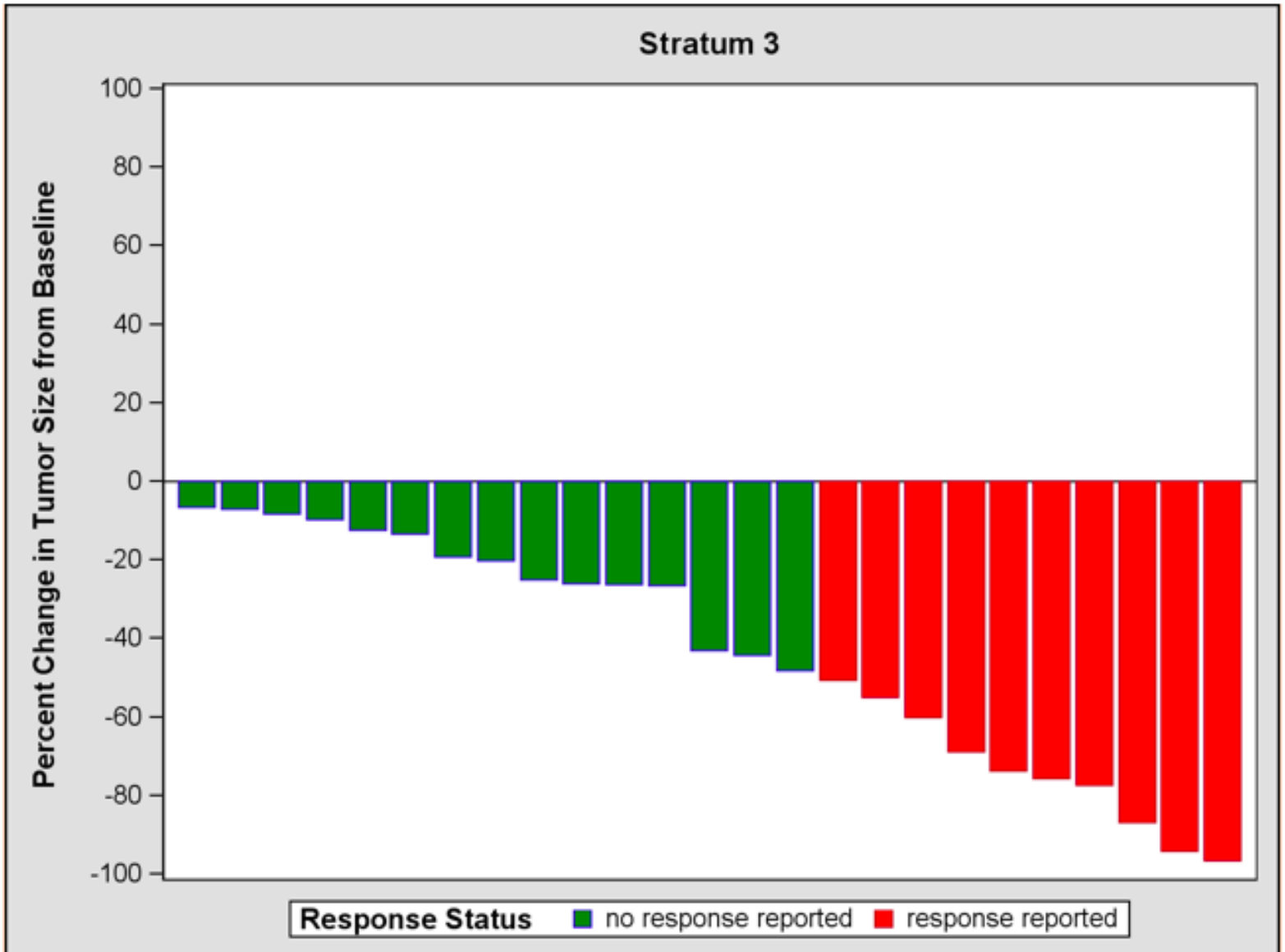
Primary cultured pilocytic astrocytoma cells display clear *SA-β-Gal* activity indicative cell cycle arrest



OIS markers:
e.g. SAHF, SA-β-Gal, $p21^{Waf1}$, $p16^{Ink4a}$



Phase II trial of selumetinib in patients with recurrent/progressive LGG.



25 patients with NF-1 enrolled on stratum 3, there were 10 PR, 14 SD and 1 PD while the patients were on treatment.

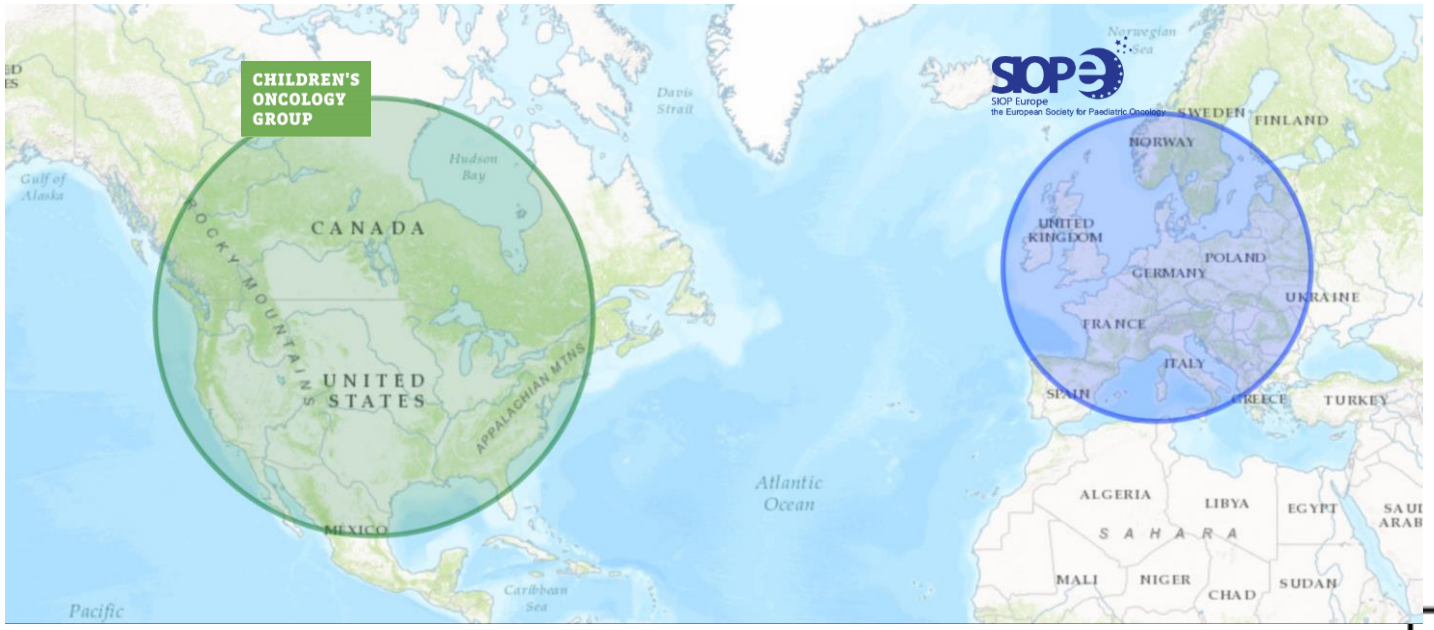
No visual assessments

The 2 year PFS for stratum 3 was 96±4%.

(Personal communication Fangusaro and Onar-Thomas, 2017).

NF1 LGG SIOP COG Proposed phase 3 RCT Astra Zeneca

Schema



NF-1

Randomization

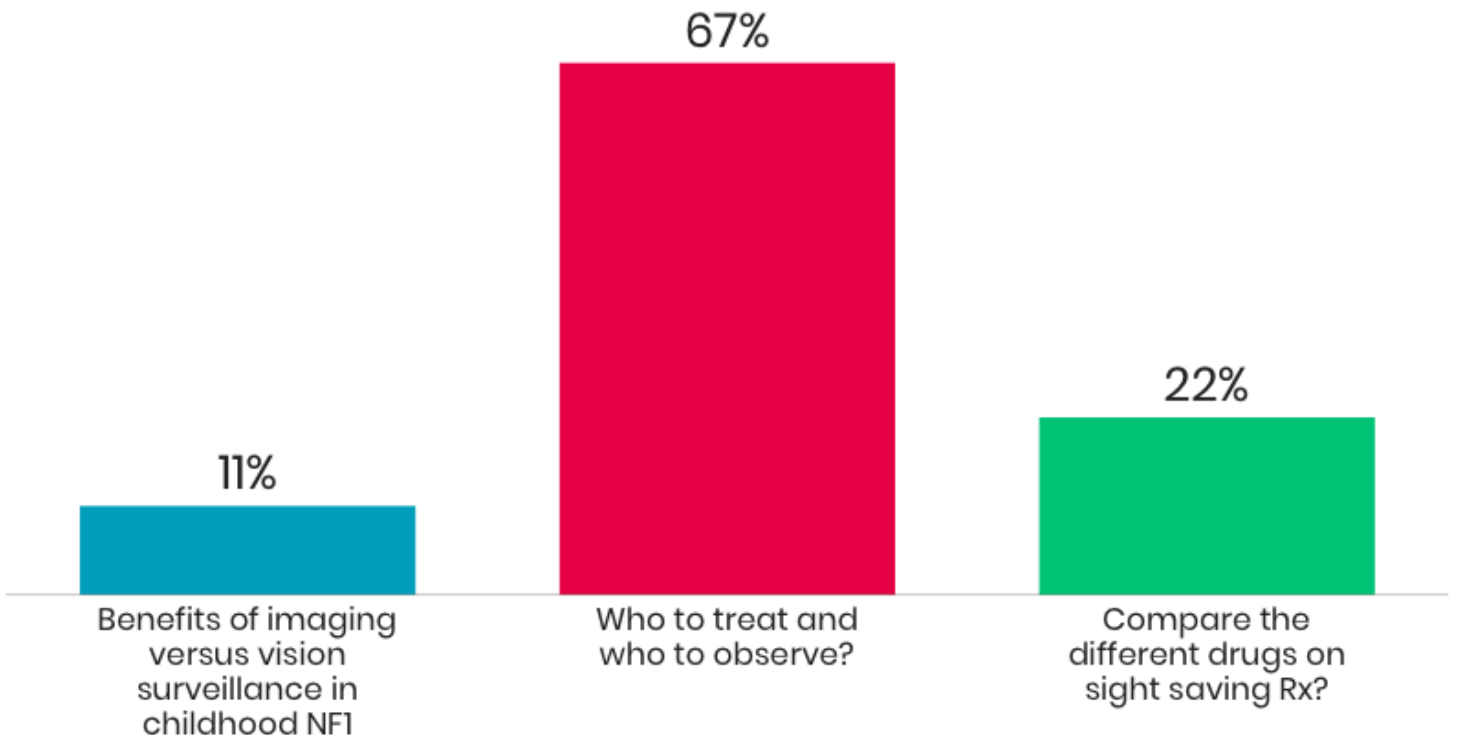
CV (approximately 1 year)

Selumetinib (approximately 2 years)

Go to **www.menti.com** and use the code **66 37 40**

Which research question is most important?

Mentimeter

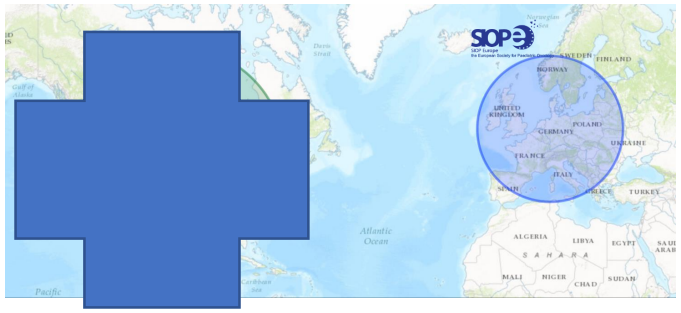


18

NF1-associated OPG: Treatment strategies and Trial Design

Visual risk assessment score

WHO TO TREAT / OBSERVE	LOW	MODERATE	SIGNIFICANT
Treatments / Strategies	OBSERVE	R → Vinblastine R → Vincristine-Carboplatin ? → MEK inhibitor	



Other drugs

Primary Outcome PFS and Vision

Medulloblastoma Genetic Subtypes Age and Outcomes

FISH and CHIPS: the recipe for improved prognostication and outcomes for children with medulloblastoma.

Cancer Genet. 2011 Nov;204(11):577-88. doi: 10.1016/j.cancergen.2011.11.001.

Ramaswamy V, Northcott PA, Taylor MD.

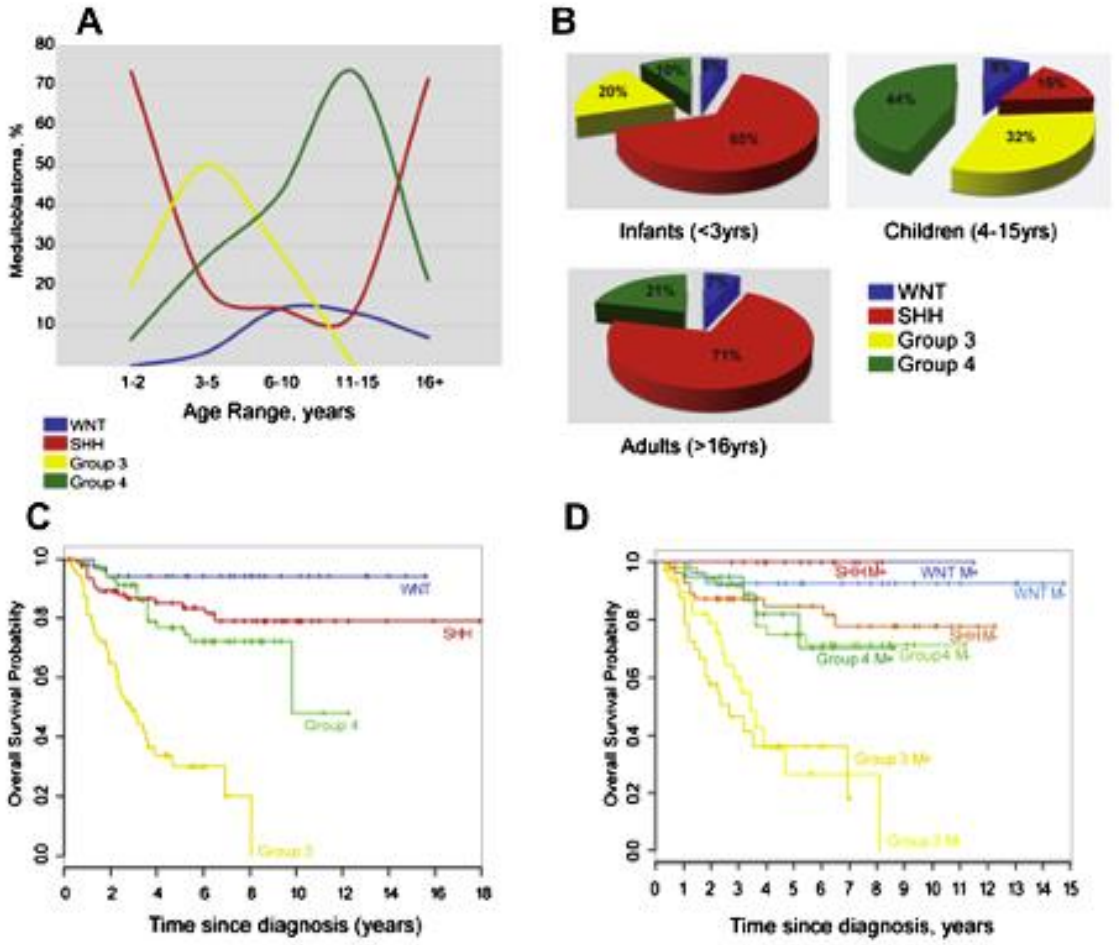
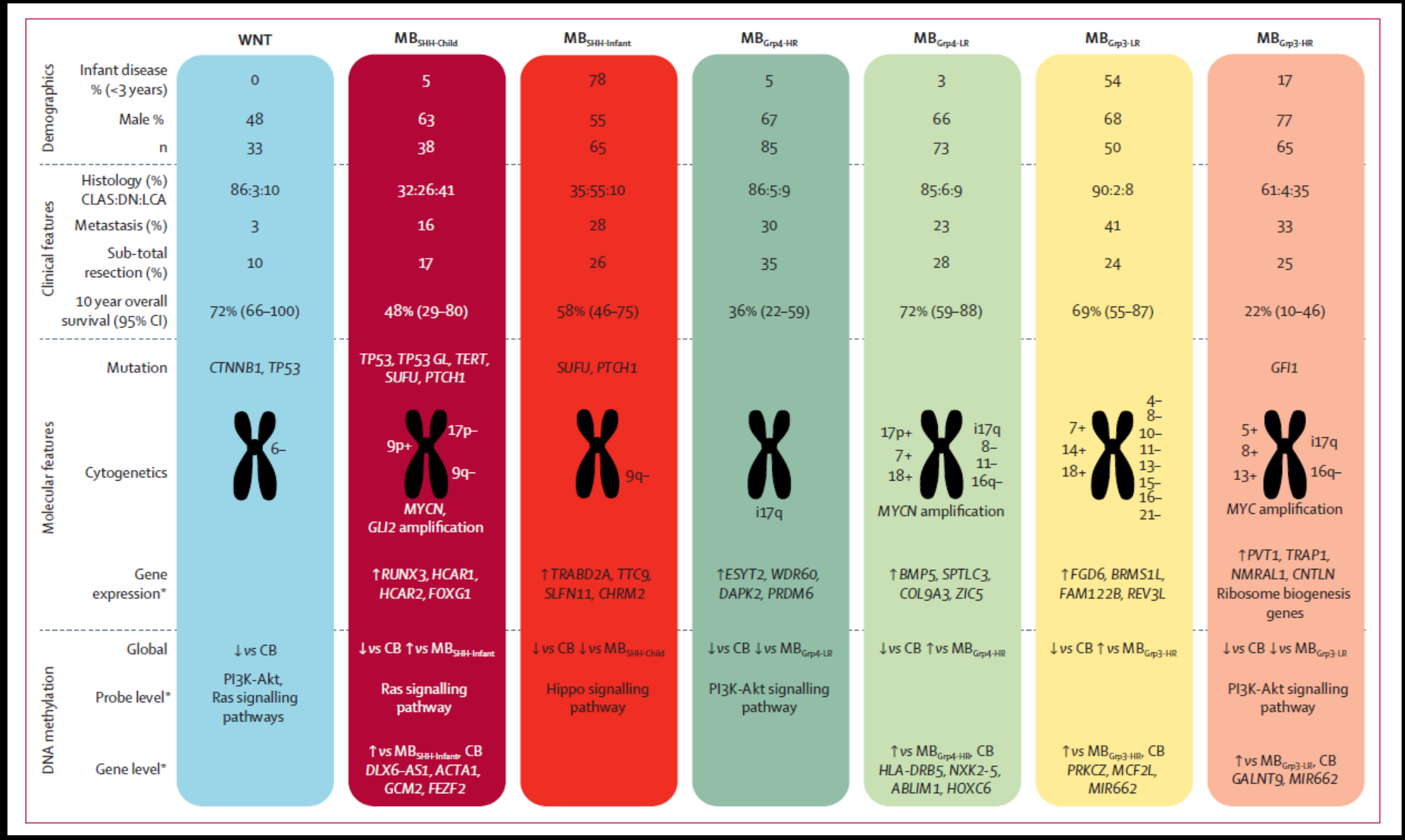
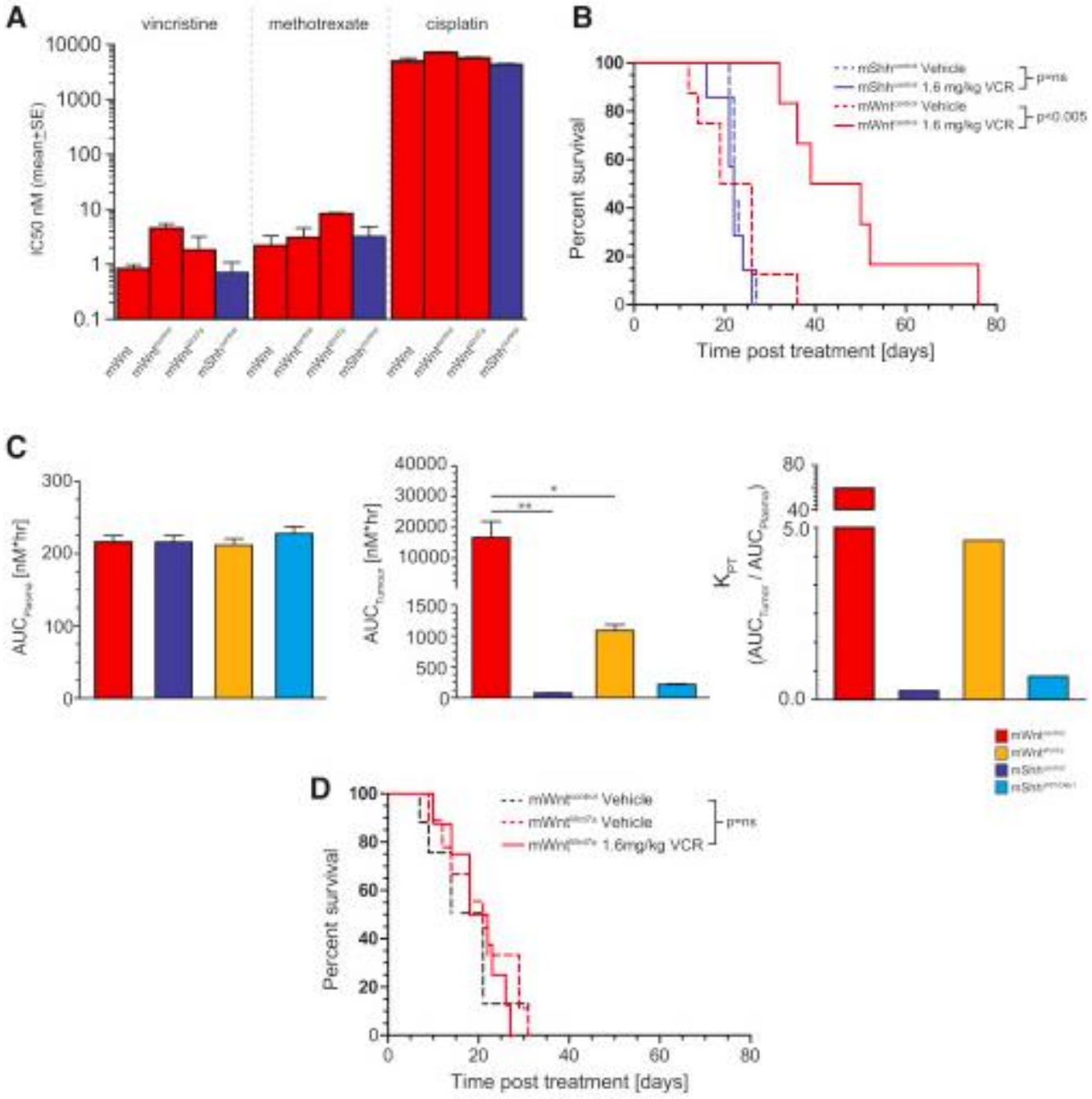


Figure 1 The age distribution and outcome in medulloblastoma. (A) Age at diagnosis by medulloblastoma subgroup. y-axis label: Medulloblastomas, %; x-axis label: Age range, years. (B) Pie type chart of the frequency of subtypes in the infant (<3 y), childhood (3–16 y) and adult (>16 y) groups. (C) Kaplan–Meier analysis showing overall survival (OS) of combined tissue microarray cohorts from both DKFZ/Heidelberg and Johns Hopkins University (n = 287) separated by subgroup. (D) Kaplan–Meier analysis from Figure 1C showing subgroups separated by metastatic status. (Adapted/Reprinted with permission. © 2011 American Society of Clinical Oncology. All rights reserved. Northcott PA et al, J Clin Oncol; 29(11), 2011:1408–1414, (23).)



Novel molecular subgroups for clinical classification and outcome prediction in childhood medulloblastoma a cohort study Edward C Schwalbe et al. Lancet Oncology , Volume 18, No. 7, p958–971, July 2017



BBB function dictates medulloblastoma exposure and response to vincristine in vivo

Medulloblastoma genotype dictates blood brain barrier phenotype

Timothy N. Phoenix,[1] et al

Cancer Cell

Volume 29, Issue 4, 11 April 2016, Pages 508–522

High Grade Glioma: Genetic, Epigenetic, Proteomic, Age, Anatomical and Outcomes

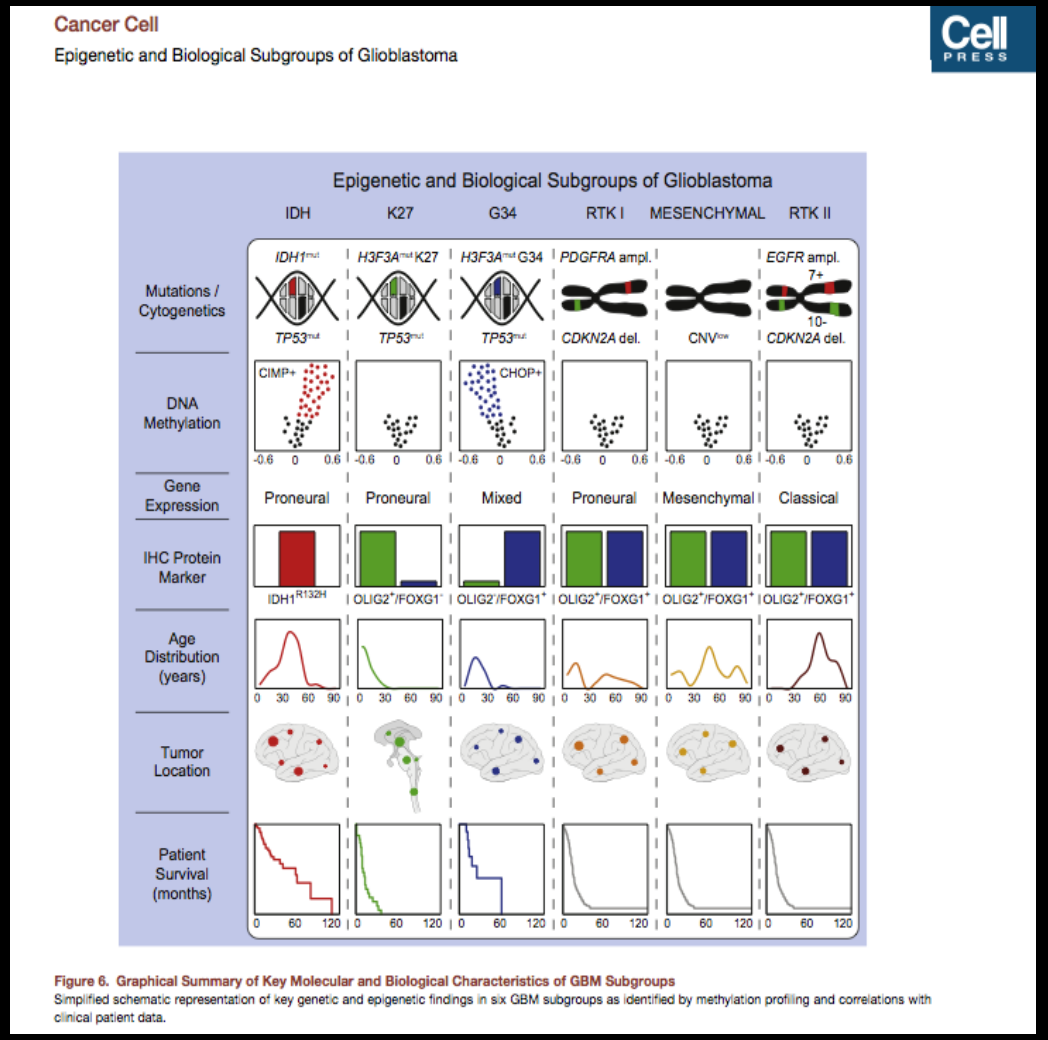
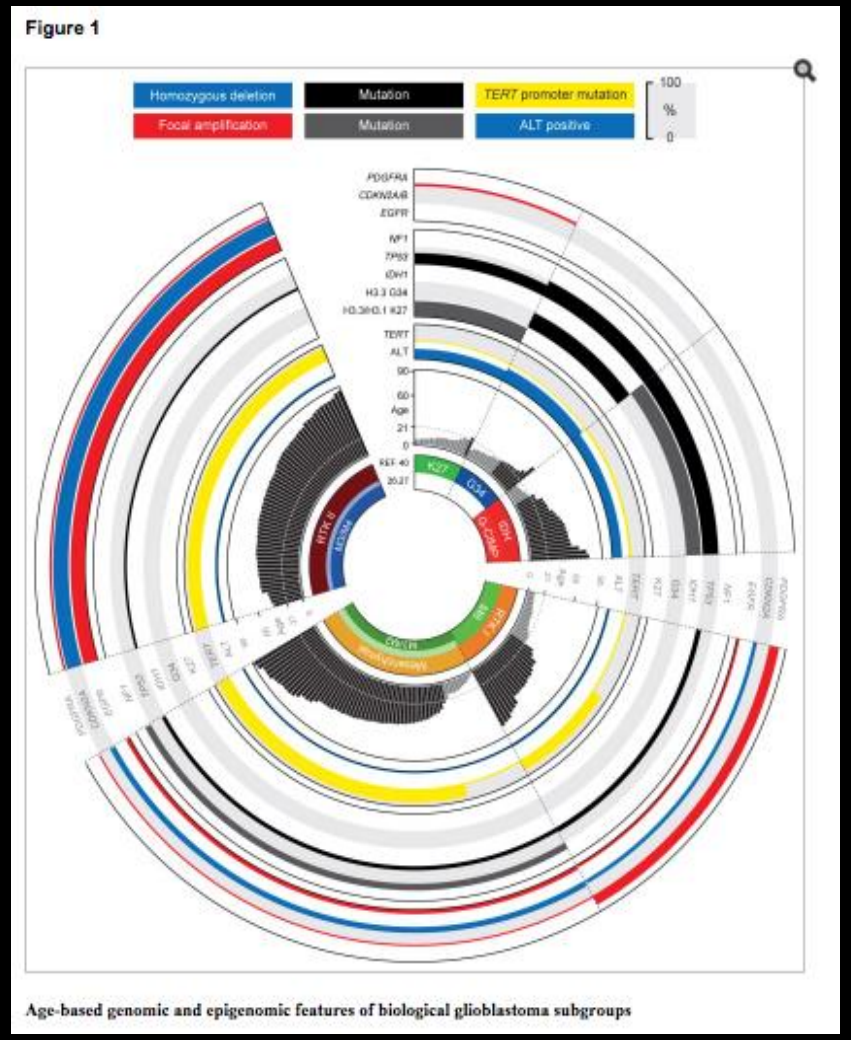


Figure 6. Graphical Summary of Key Molecular and Biological Characteristics of GBM Subgroups
Simplified schematic representation of key genetic and epigenetic findings in six GBM subgroups as identified by methylation profiling and correlations with clinical patient data.

Sturm Witt Pfister et al Cancer Cell 22, 425–437, October 16, 2012



Age-based genomic and epigenomic features of biological glioblastoma subgroups

Sturm D, Pfister SM et al. Nat Rev Cancer. 2014 Feb;14(2):92-107.

PRECISION MEDICINE DEBATE

NEURO VS ONCOLOGY

Avoiding the Harm

Neurological Symptoms
Neurological Signs
Raised intra-Cranial Pressure
Hydrocephalus
Epilepsy diagnosis and treatment
Blindness
Neuro-fibromatosis type 1
Neurofibromatosis type 2
Tuberous Sclerosis
Diencephalic syndrome
Rehabilitation
Cognitive Neuro-Psychology

Improving the Survival

Histology and Bio Diagnosis
Staging of Tumour
Cytotoxic Chemotherapy
Bio-targeted therapy
CNS targeted therapy
Involved Field Radiotherapy
Extended field Radiotherapy
Cancer Registration
Clinical Trials
Survival Curves
Late Effects / Quality of Life
Transition

My objectives are to:

- To consider mechanisms of brain injury and their impact on patient quality of life as a basis for designing strategies to reduce brain injury.

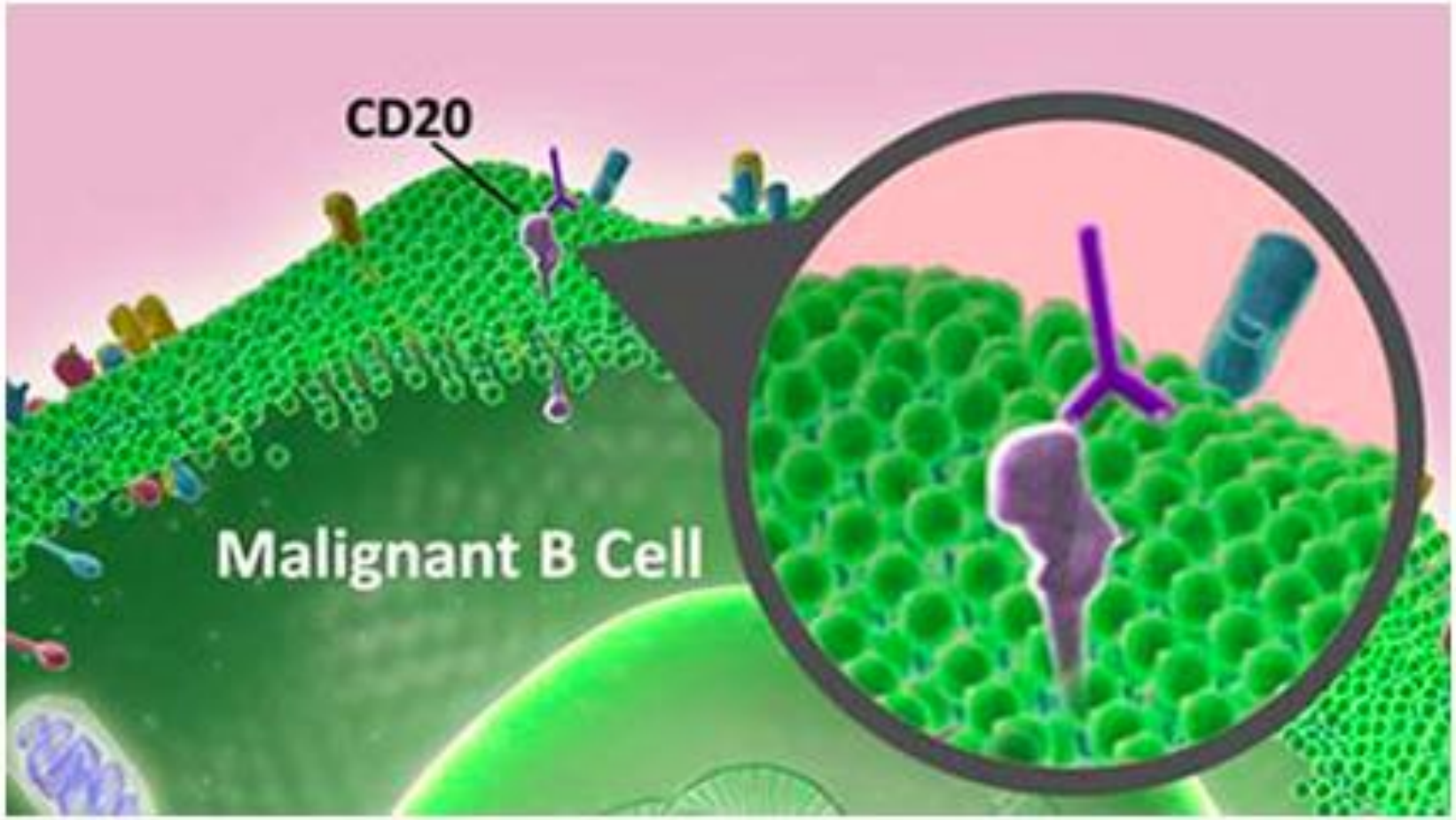
- To consider new drug developments and the associated challenges of delivering precision medicine to clinical practice.

- To add the priority of delivery systems designed to optmize delivery of drugs to CNS tumours as a priority for future clinical practice.

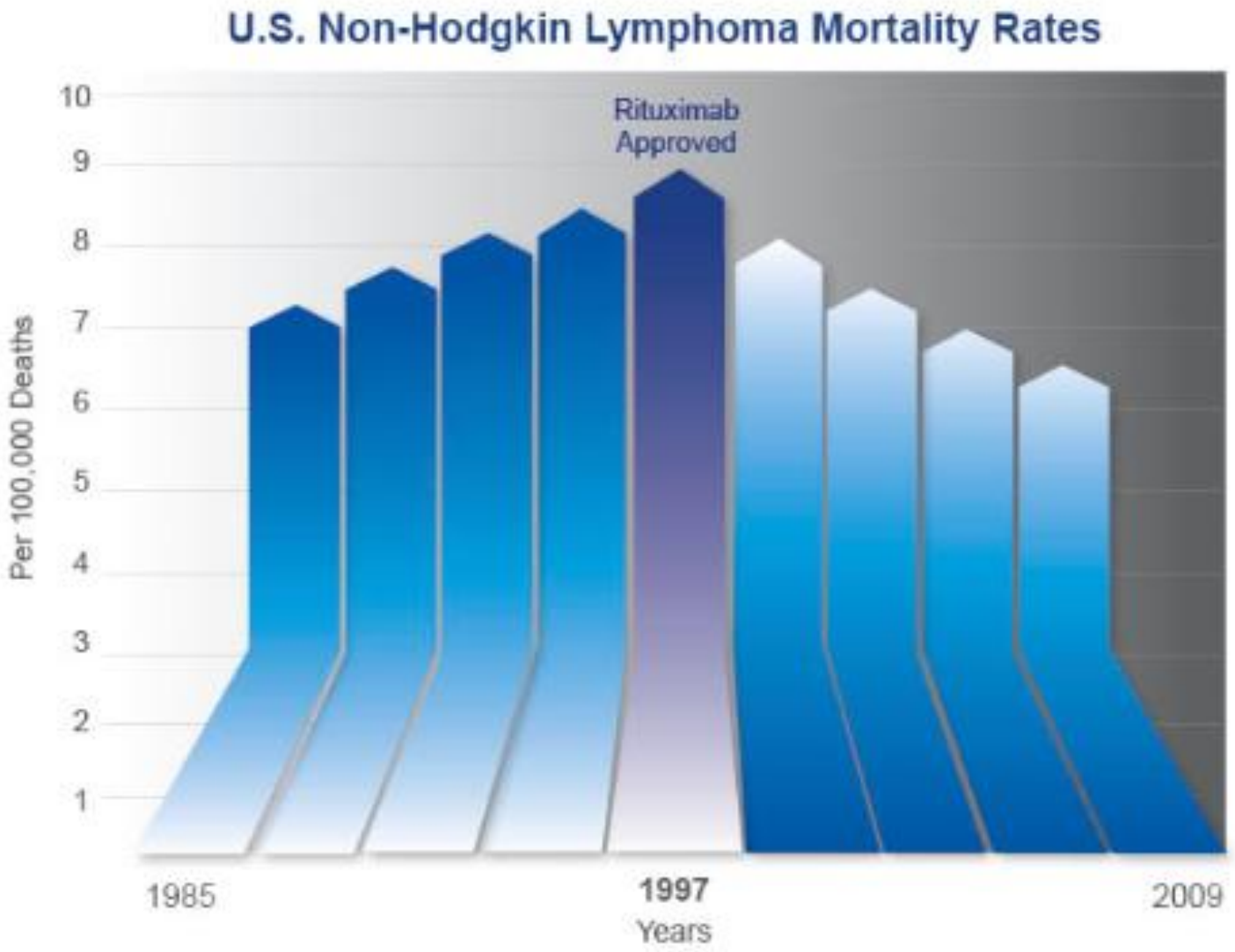
The Current Challenge of Precision Medicine a lot of potential targets in a lot of diseases

The Project Plan

Previous Successes



Rituximab binds to a surface protein, called CD20, located on mature B cells. Once bound, the antibody activates the body's immune system, which then attacks the cancer cells.



13 year delay to include children in trials of Rituximab
Inter-B-NHL 2010
Closed early in 2015 due to significant beneficial effect

The Neuroblastoma Special Interest Group (SIG) of the Children's Cancer and Leukaemia Group (CCLG) – the UK professional organisation representing clinicians involved in treating children with cancer – notes the final determination of NICE in relation to Dinutuximab (anti-GD2 monoclonal antibody), published on 15 July 2016, and its decision not to recommend Dinutuximab (Unituxin, United Therapeutics) for the treatment of high-risk neuroblastoma.

NICE Committee Concludes……

- ‘the dinutuximab regimen appears to confer a small event-free survival advantage and overall survival advantage compared with isotretinoin…’
- ‘2.81 life years (approximately 33.7 months) were gained for the dinutuximab regimen compared with isotretinoin alone’
- i.e. patients could expect to live for nearly 3 years longer if treated with anti-GD2-based immunotherapy rather than retinoic acid maintenance alone.
- ‘dinutuximab does not represent a cost-effective use of NHS resources…’

NICE Committee Concludes……

- NICE applies special criteria for treatment of patients with short life expectancy, the median life expectancy of patients with high-risk neuroblastoma of 4 years is greater than the stated threshold of 24 months and therefore these special criteria could not be applied (paragraph 4.21)

!

Does this reflect the views of parents or children's specialist

Does this comply with our duty within the Children Acts?

Can this cost judgement be applied to children where they are diagnosed at age less than 2 years and therefore the 2 year limit represents a doubling of their life span

Time 1

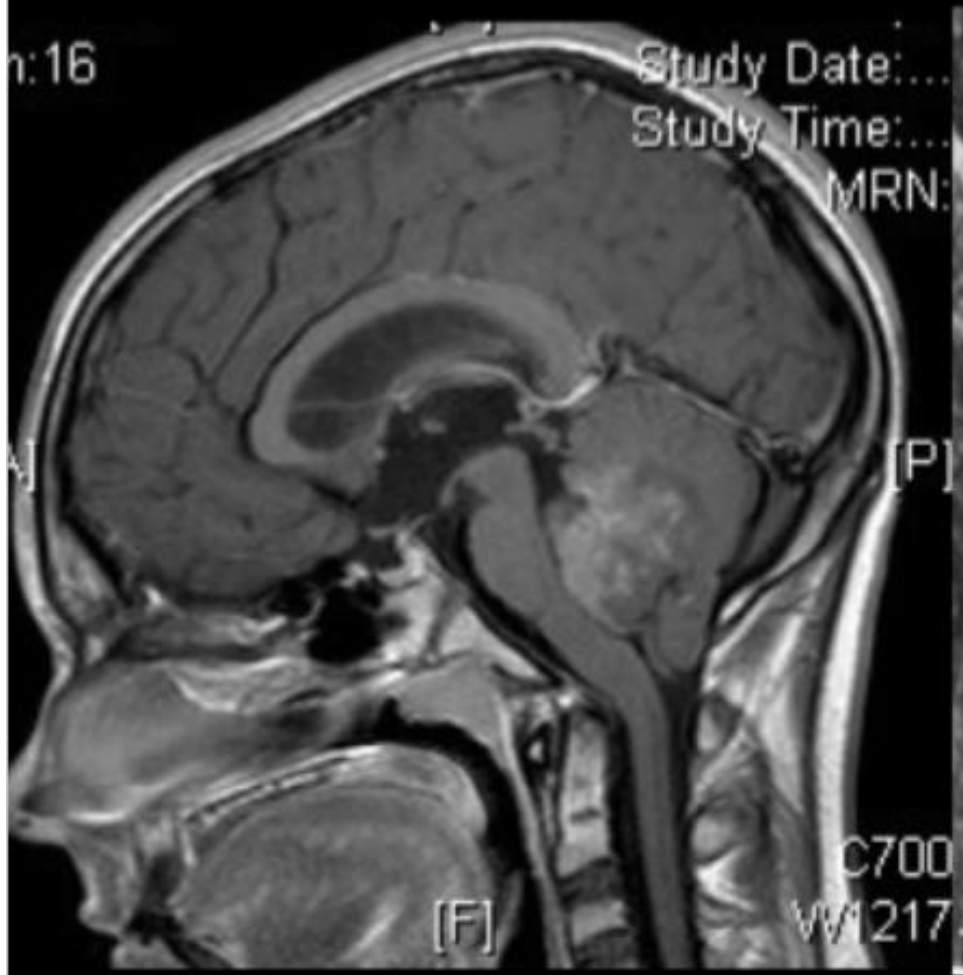
Use up to 3 words to describe your understanding of Precision Medicine in Paediatric Oncology

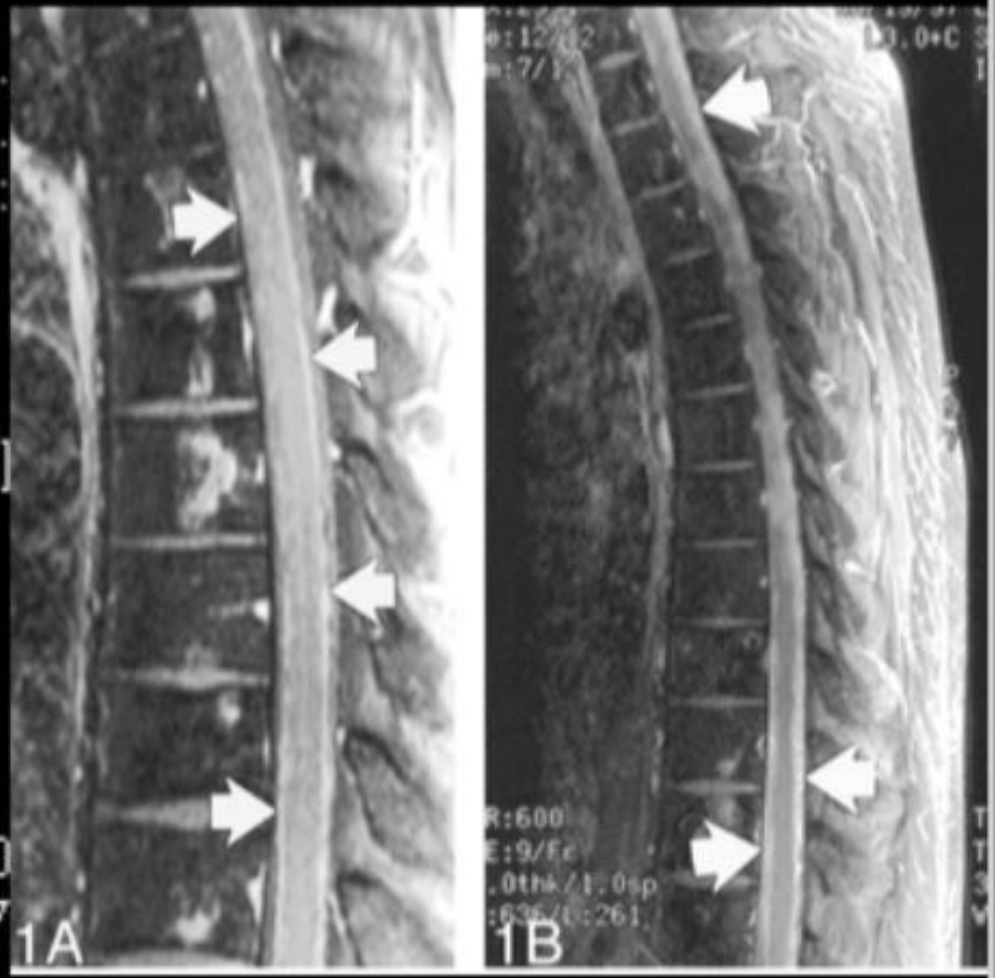
This question is not active | Activate question

Votes: 73


HE AIMS AND FIRES WITH BARELY A CONSCIOUS THOUGHT...
ZAP
ZACK
ZRAP
ZARP
...TRUSTING TO A UNIQUE, INBORN TALENT FOR SPACIAL GEOMETRY-- HONED BY MONTHS OF PRACTICE IN THE DANGER ROOM-- THAT MAKES HIM AWARE OF THE POSITION OF EVERY CAR IN THE ROOM...
ZOOP
ZORP
ZRAM
...AND TELLS HIM EXACTLY WHAT FIRING ANGLE WILL ENABLE HIM TO DESTROY THEM ALL WITH A SINGLE OPTIC BLAST.

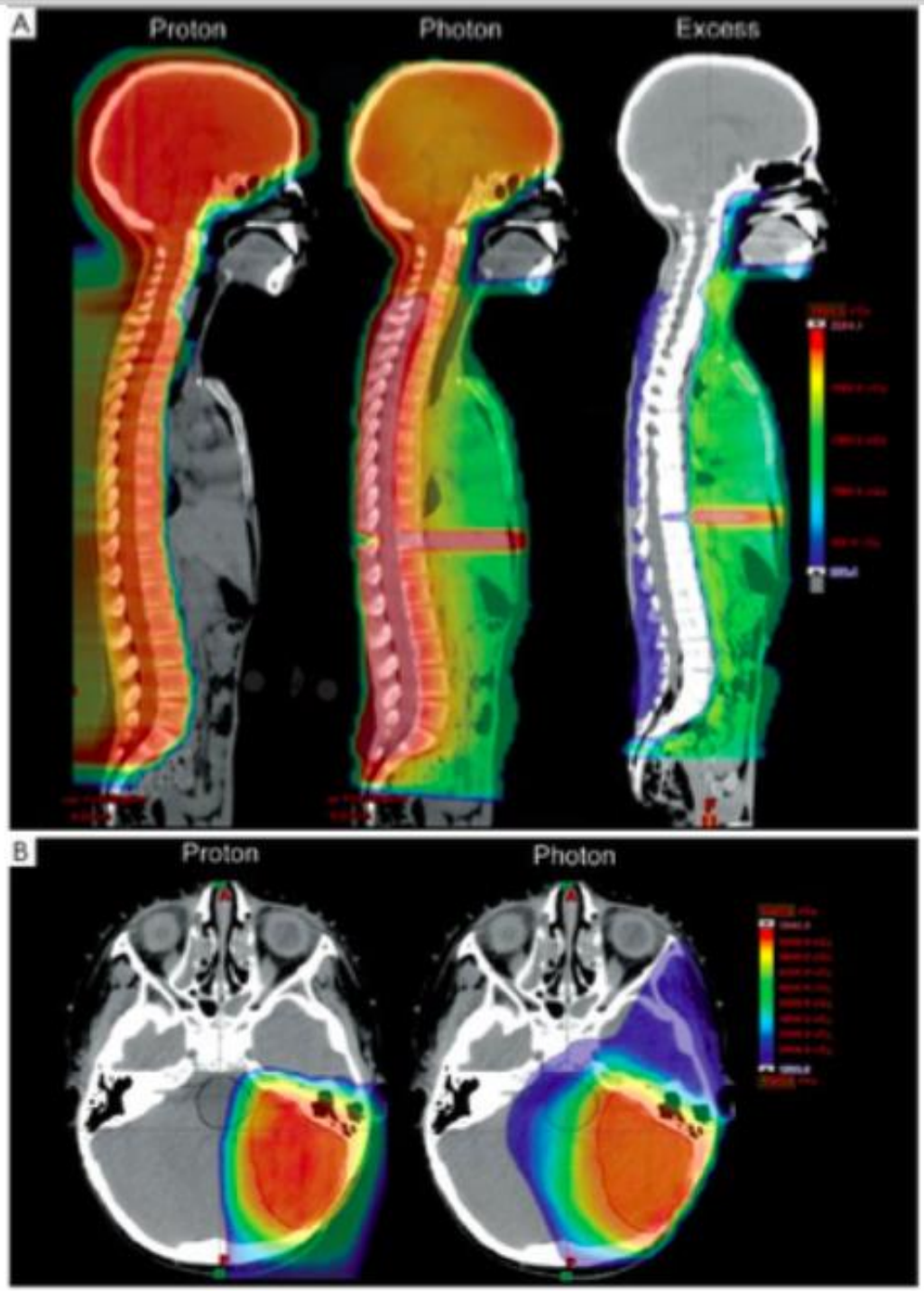
Cerebellar Medulloblastoma with Spinal Metastases



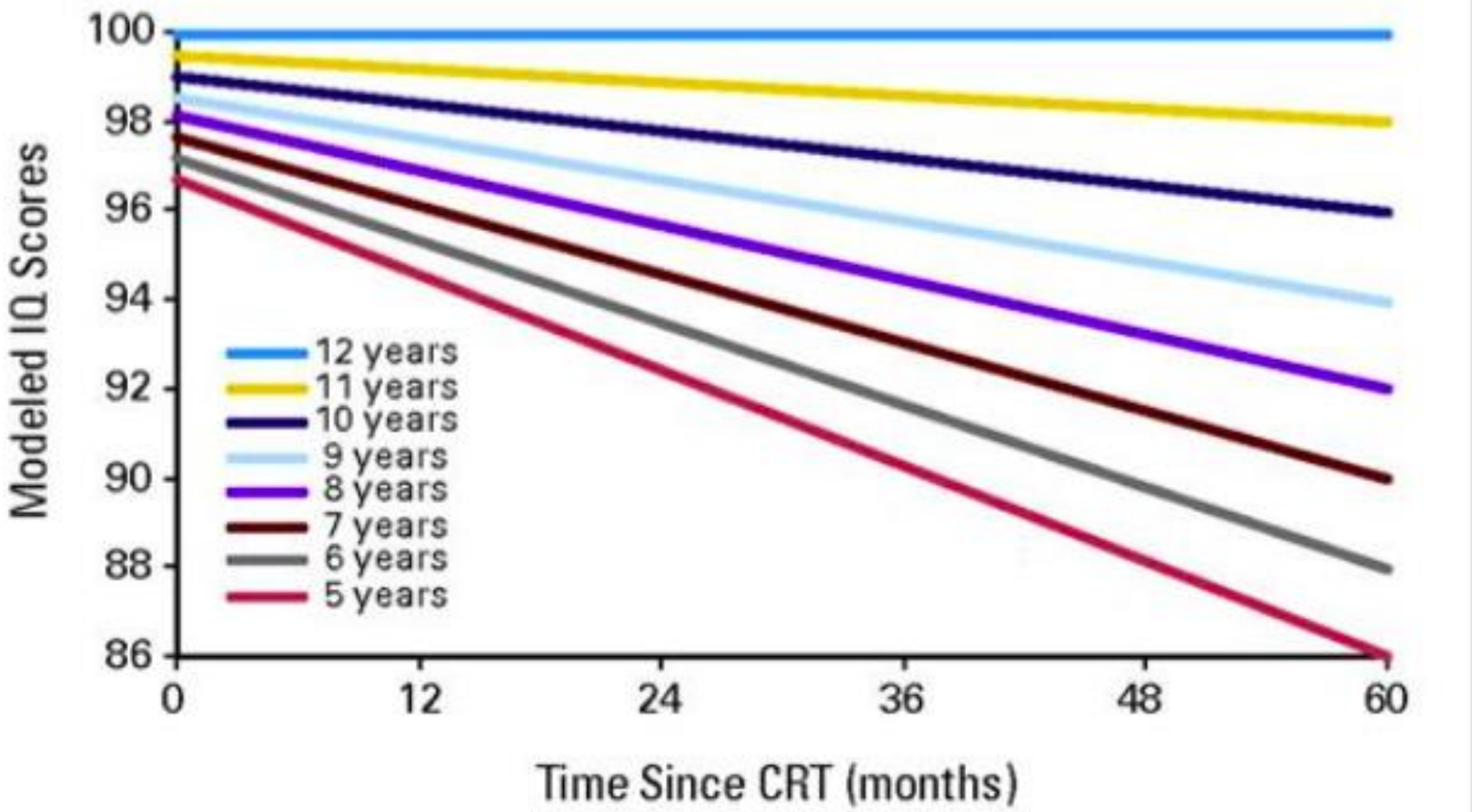


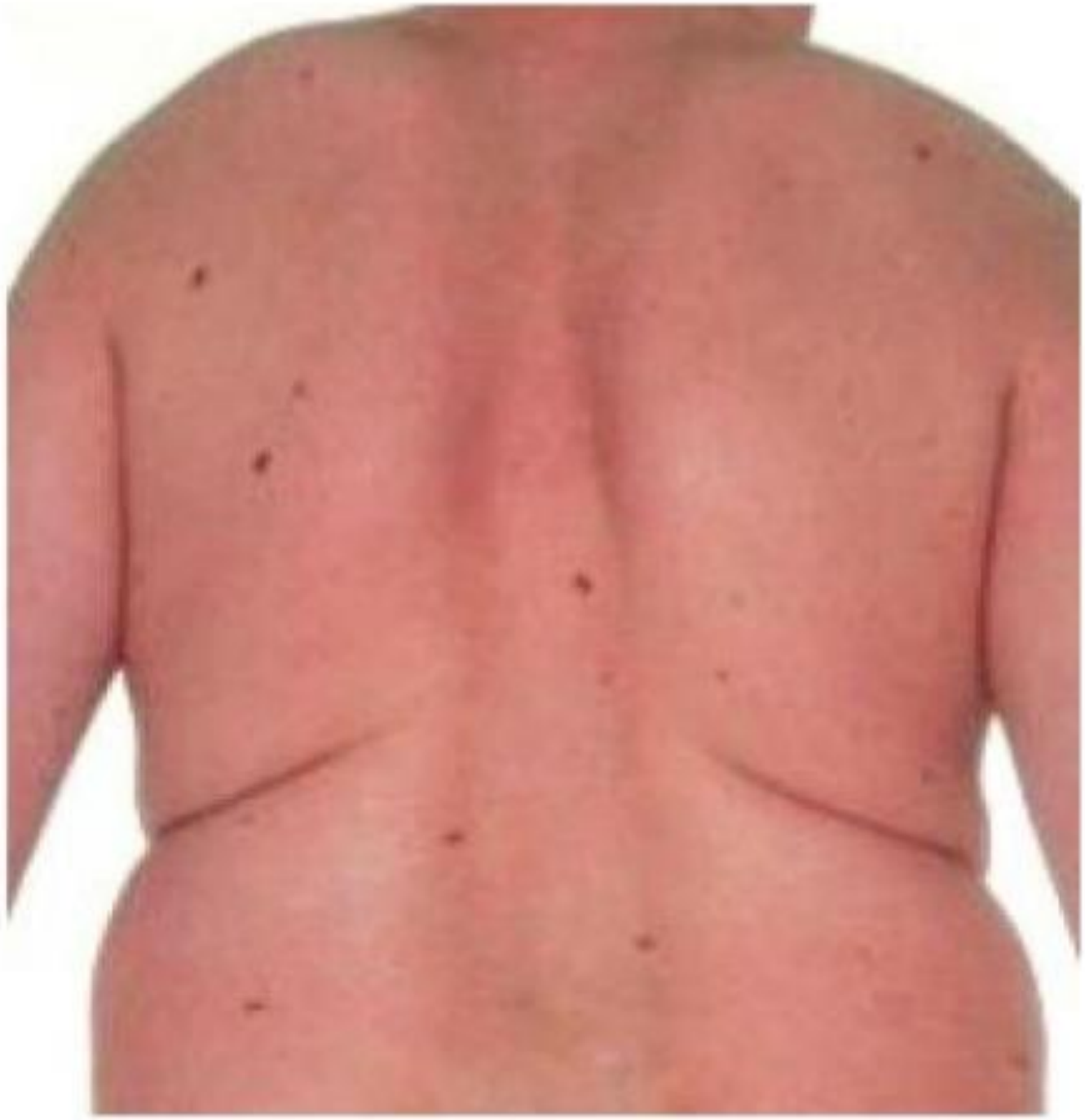
Survival Rates: No metastases ~ 80% 5-10yr + Chemo & Cranio Spinal RT 24Gy

Metastases ~ 60% 5-10 yr + Chemo & Cranio Spinal RT ≥36 Gy


A
Proton
Photon
Excess
B
Proton
Photon

IQ modelling after cranial irradiation during childhood



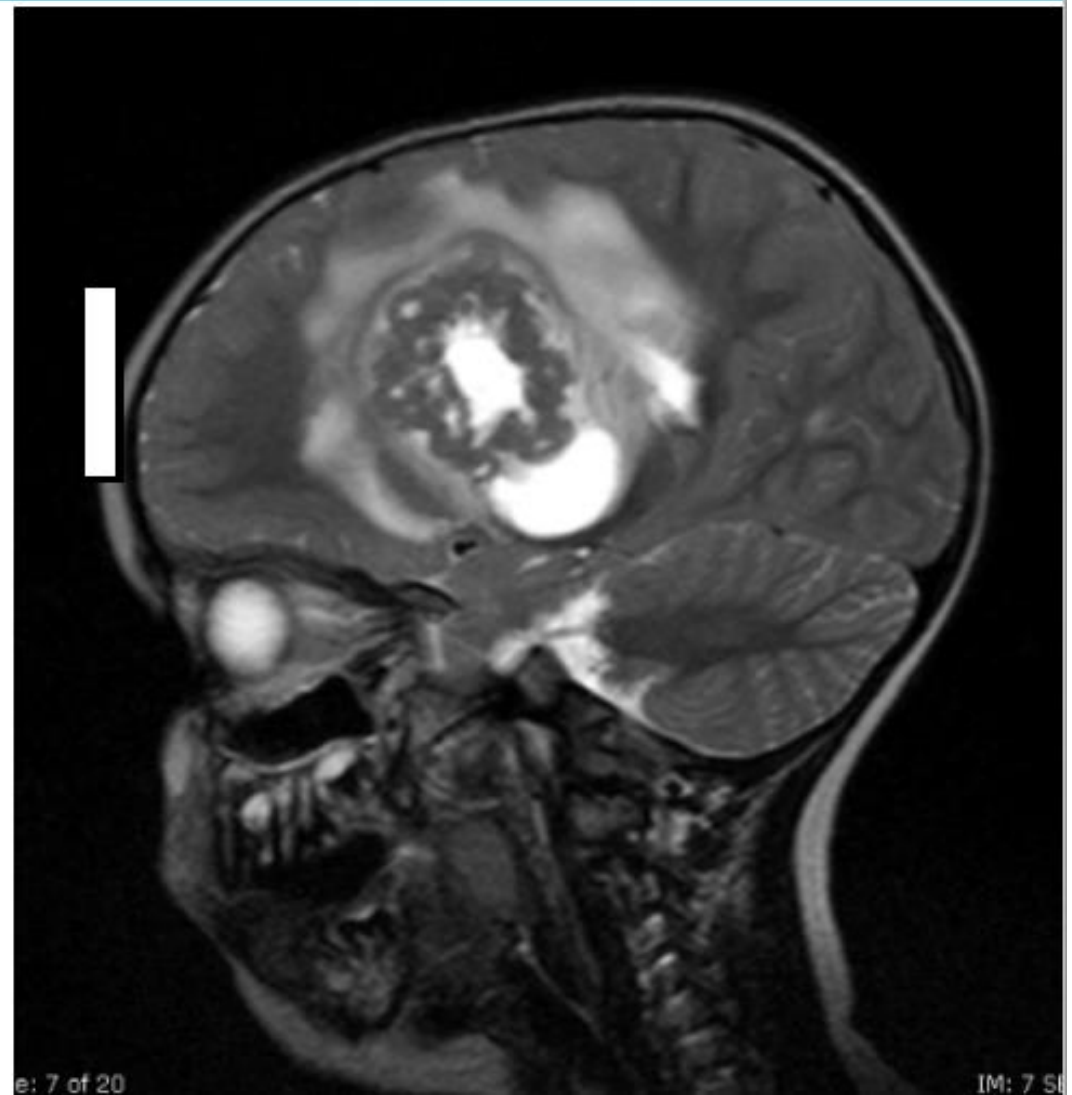


Children's Brain Tumour Drug Delivery Consortium
Accelerating Progress in Drug Delivery

children with cancer uk
fighting the UK's biggest child killer

ATRT

Partially sensitive to intensified systemic chemotherapy
IT therapy in use
New targets may emerge
Local drug delivery to primary tumour site - not explored



Children's Brain Tumour Drug Delivery Consortium
Accelerating Progress in Drug Delivery

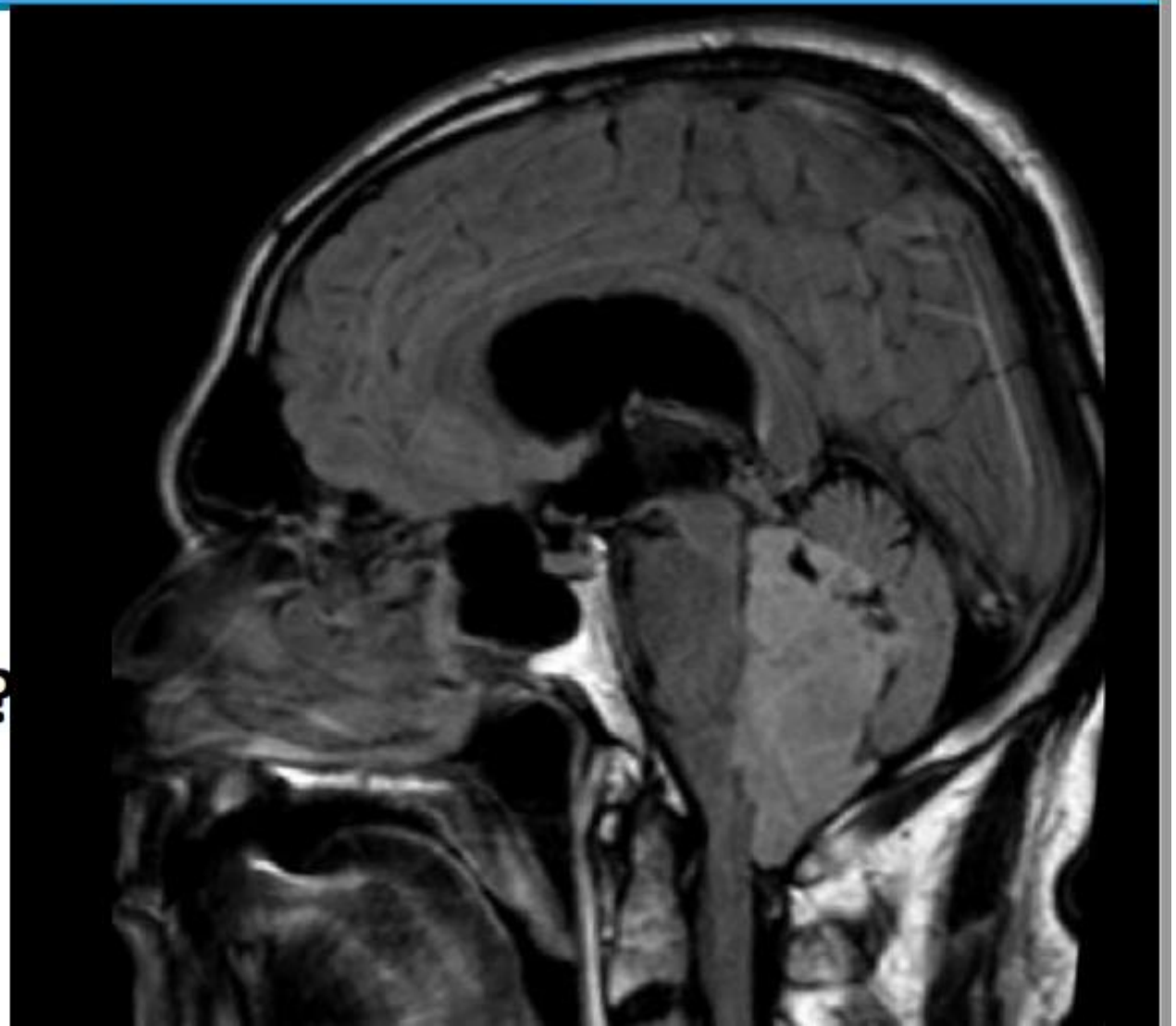
children with cancer uk
fighting the UK's biggest child killer

Ependymoma

Resistant to Chemotherapy

Give systemically

Are they sensitive?

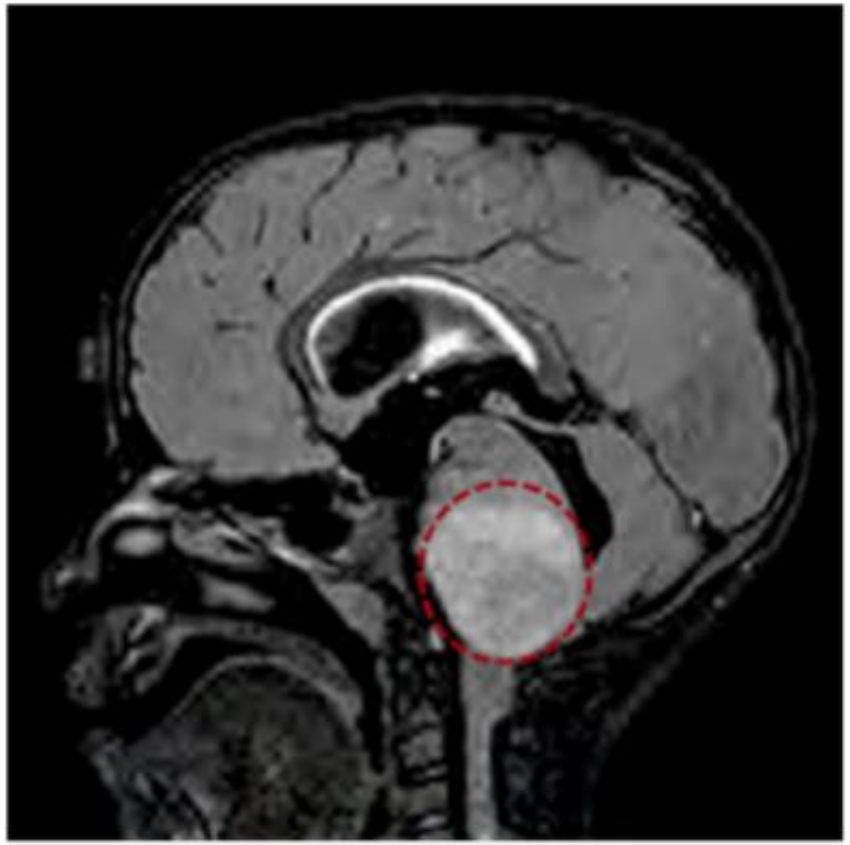


Children's Brain Tumour Drug Delivery Consortium
Accelerating Progress in Drug Delivery

children with cancer uk
fighting the UK's biggest child killer

DIPG

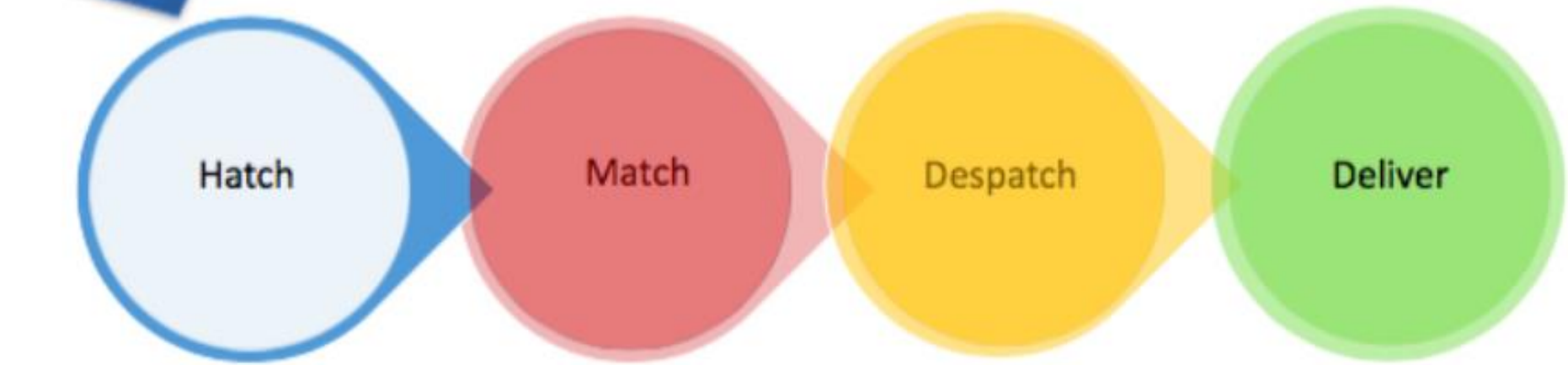
Resistant to
Chemotherapy
Give systemically
New targets emerging
Drug delivery may reverse
Sensitivity
Test new targeted drugs
with delivery system



Diffuse intrinsic pontine glioma (DIPG) is inoperable because of the tumor's vital location on the brainstem.

HATCH, MATCH, DESPATCH and DELIVER

A drug delivery programme to optimise medical therapy for brain tumours : A PROPOSAL FOR A COLLABORATIVE NETWORK



Tumour Biology

Targets
Pathways
Bioinformatics

Drugs

Chemotherapeutics
Biological agents
Existing or new

Tumour Biology

Drug/ biomodifier

Delivery system/route
Intra-*CSF*
Interstitial
Enhanced systemic
Sustained release
Enhanced local

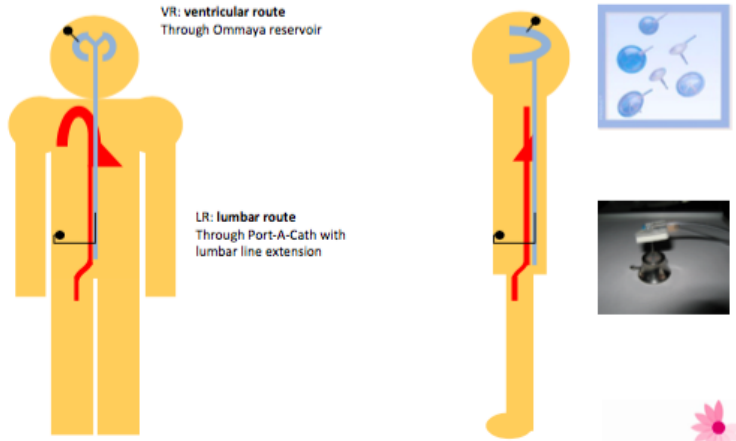
Delivery system testing
Does it get into the brain?
Does it get into the cell?
Does it damage the tumour?
Does it damage the brain?

Enhanced Experimental Models
3D C—culture
Organotypic
Blood brain barrier
Rotary Cell Culture System
In vivo orthotopic resection model

Clinical trials
Licensing
Commercialisation
Clinical practice

Children's Brain Tumour Research Centre

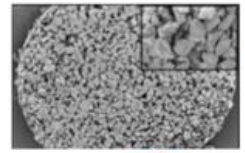
Intra-CSF administration



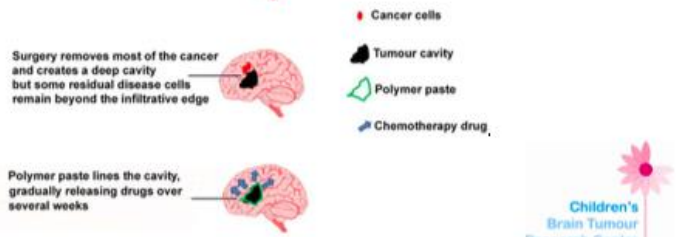
Children's Brain Tumour Research Centre

Drug Delivery

Cutting edge research aiming to deliver chemotherapy drugs to the brain using innovative biomaterials



Polymer Microparticles



Children's Brain Tumour Research Centre

Version 7

Intrepid Clinical Trial

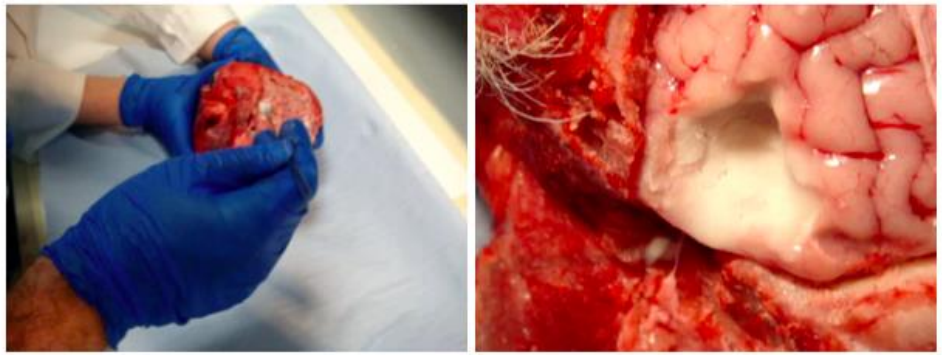
- A new human trial in infusional intrathecal therapy
- Investigating the dose and duration of infusion.
- Intrathecal delivery is an attractive option for children with Leptomeningeal metastases (which are difficult to treat, and have poor survival outcomes).
- Researchers at Nottingham are undertaking the initial trial of feasibility, safety and tolerability before the study opens at other sites.

@CRCTU CANCER RESEARCH UK UNIVERSITY OF BIRMINGHAM

Children's Brain Tumour Research Centre

Version 7

PLGA/PEG matrix application *ex vivo*



Children's Brain Tumour Drug Delivery Consortium
Accelerating Progress in Drug Delivery

children with cancer uk
fighting the UK's biggest child killer

Website:
www.cbtddc.org

April 2017:
413 followers on Twitter;
50 individuals registered on website.

Twitter: @CBTDDC

My objectives are to:

- To consider mechanisms of brain injury and their impact on patient quality of life as a basis for designing strategies to reduce brain injury.

- To consider new drug developments and the associated challenges of delivering precision medicine to clinical practice.

- To add the priority of delivery systems designed to optmize delivery of drugs to CNS tumours as a priority for future clinical practice.

Clinical application of biomarkers

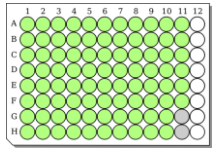
Deliver certified assays and tests

FISH, IHC, sequencing, SNP, 450K, MassArray, NGS

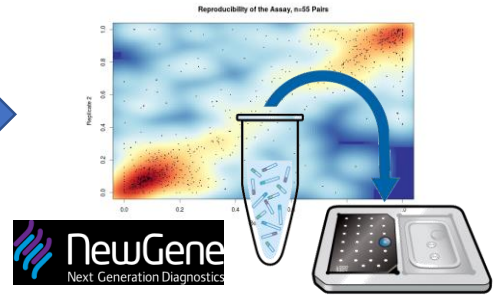
validated biomarkers

CANCER RESEARCH UK Programme

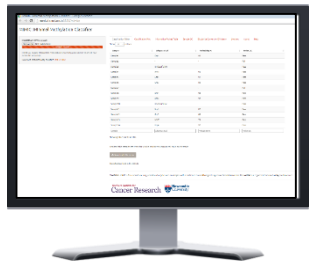
develop and validate real-time assay



certified assay



open source classifier



Centralised real-time diagnostics (21 days)

Partners

NCRI National Cancer Research Institute

SIOPE SIOP Europe

CCLG

newcastle node molecular pathology

NHS

NewGene Next Generation Diagnostics

CANCER RESEARCH UK

Future

Q4 2017: All UK patients

SIOP-PNET5-MB, SIOP-YC-MB and SIOP-HR-MB (Trials)

Non-trials

Real-time WGS – 100K Genomes project

Newcastle University

SIOP-PNET5-MB: Research study progress

- **Core panel sequencing methods**
- Define panels over Summer (post DFKZ meta-analysis)

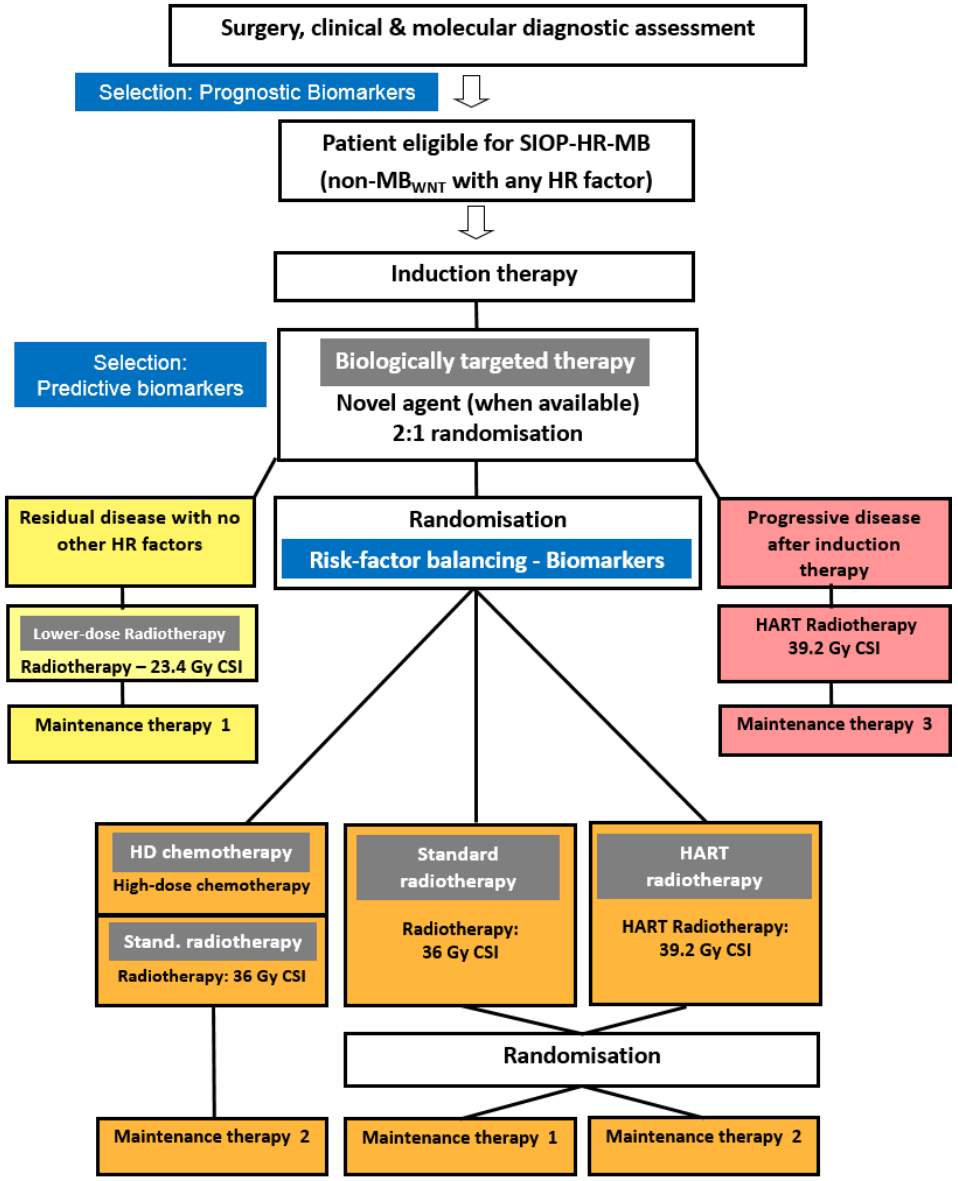
- **WGS**
- On hold – need is dependent upon question. Reserve samples until resolved

- **Links to QoS and pharmacogenomics studies**
- Not essential at outset – develop as trial progresses
- Proposals in development: PNET4

- **Other studies:**
- Define as trial progresses / preliminary data becomes available (e.g. blood, CSF)

- **Funding**
- CRUK funding in place: core studies and international reference centre

SIOP-HR-MB: Biology components



- **Upfront patient selection:**
- Prognostic biomarkers

- **Upfront patient selection:**
- Predictive biomarkers / targeted therapies*

- **Balance risk-factors across randomisation arms**

- **Flexibility**

- Amendments as further risk-factors are validated

- Targeted therapies as targets/biomarkers are validated

- **Comprehensive biological studies**

- As per SIOP-PNET5-MB infrastructure/plans

- Studies across cohorts

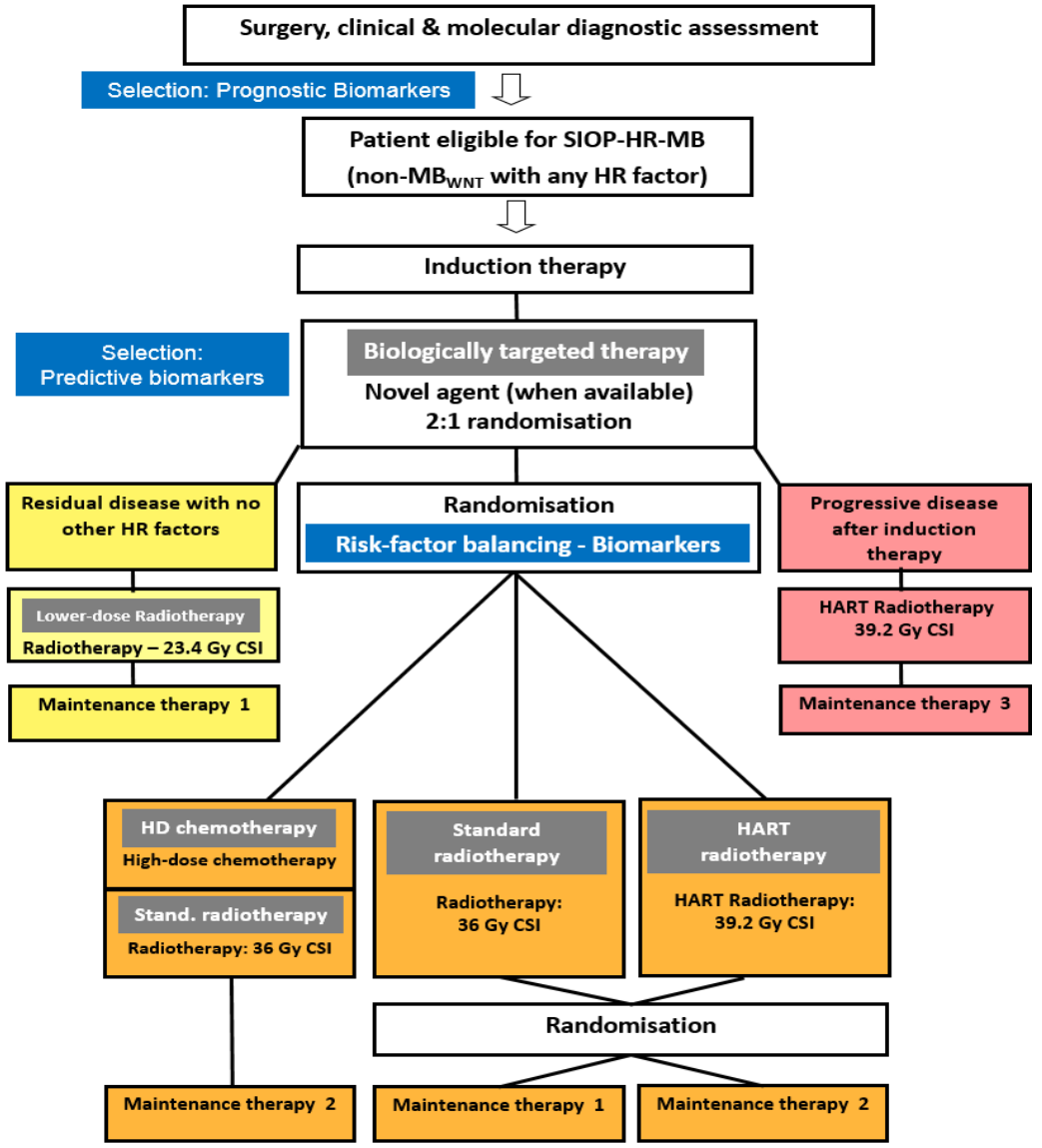
- **Funding application submitted**
- **Q4 2017 outcome (UK/Sponsor)**
- **2018 SIOPE partners**

Non-infants (PNET5-MB and HR-MB): Next biology steps

- **Next biomarkers / refine risk-stratification:**
- New subgroups
- Level of evidence?
- When?

- **New strategies for VHR patients**

- **Identify targeted therapeutics:**
- Link to pre-clinical / early-phase initiatives
- HR-MB window



My objectives have been to:

- Develop approaches to measuring brain injury and the quality of life consequences and investigate ways to reduce it
- Translate research into clinical practice through health services research and international clinical trials
- Optimize delivery of drugs to CNS tumours as a priority for future clinical practice

I will ask the audience to represent the public in suggesting how research funding should be spent to accelerate progress for the children affected by brain tumour and their families in the next decade.”

QoL in adult survivors of childhood brain tumours

A population study & *A Conceptual Model*

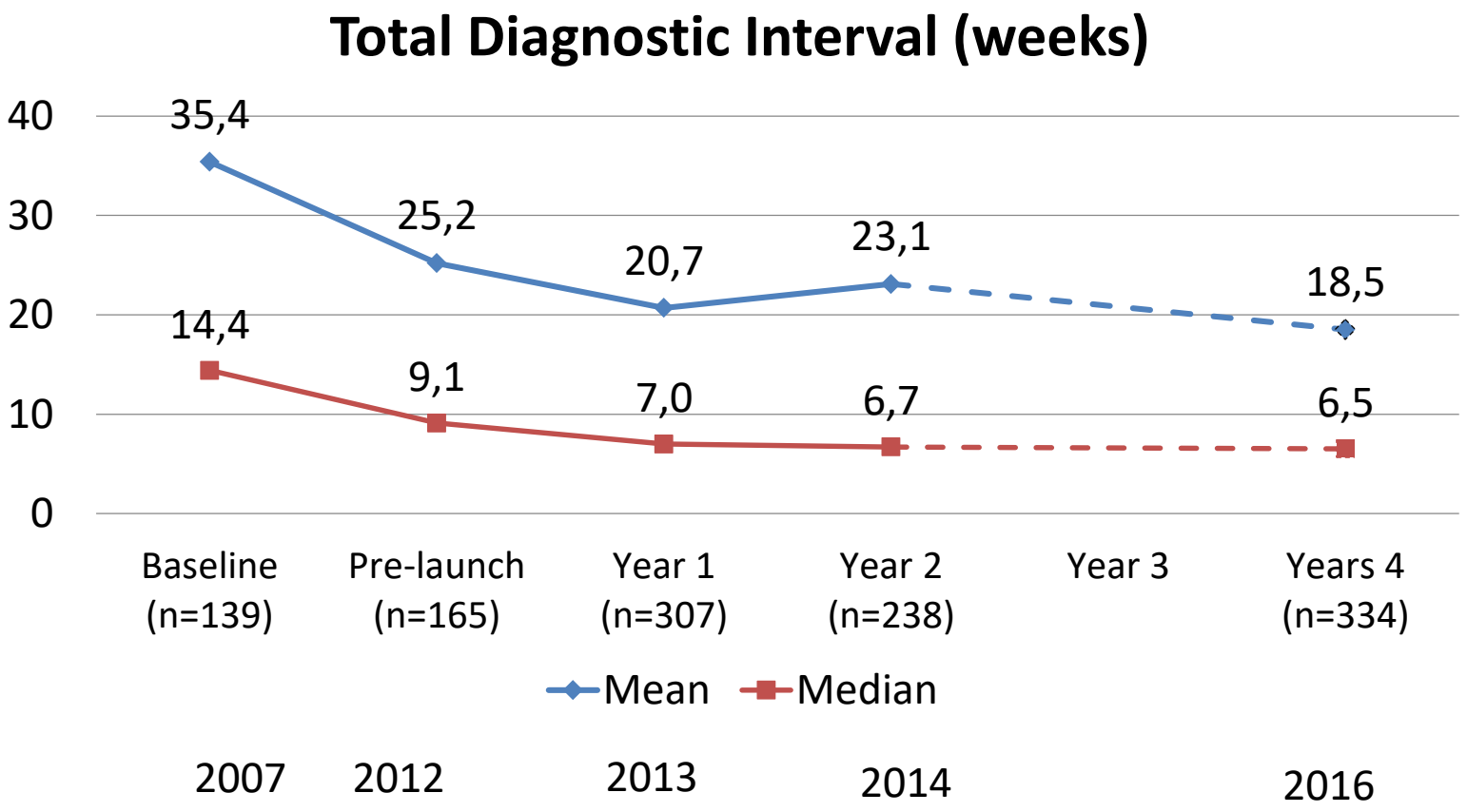
HRQL deficits in adult survivors. EJC(2009) 2552–2561. Boman et al Case Control Study

- Persistent deficits: cognition, sensory functions, mobility, self-care & overall health
- Worse for IGCT, oligos / other glioma, medulloblastoma.
- Mild to moderate disability ~ 60%
- Education and Independence::
  - need for remedial training ,
  - lower educational status
  - greater reliance on governmental subsidies in adulthood
  - support as parents

Multifactorial late effects model: EJPN (2015) 1e21; Tallen et al: Systematic Literature Review

- Tumour-related
- “Surgical neurotoxicity”
- Radiotherapy
- Neurocognitive and behavioural impairments
- Endocrine deficits
- Neuropathies
- Neurovascular injury
- Sensory deficits
- Consequences of chemotherapy
- Encephalopathy and neurocognitive decline
- Premature Ageing
- Second Tumours

Total Diagnostic Interval



HEAD SMART | EARLY DIAGNOSIS OF BRAIN TUMOURS

Online activity

Facebook

- Page Likes: 36, 229
- Post Reach (Average over period): 7,221

Twitter

- Page Likes: 4,253
- Impressions per day (Average over period): 1,079

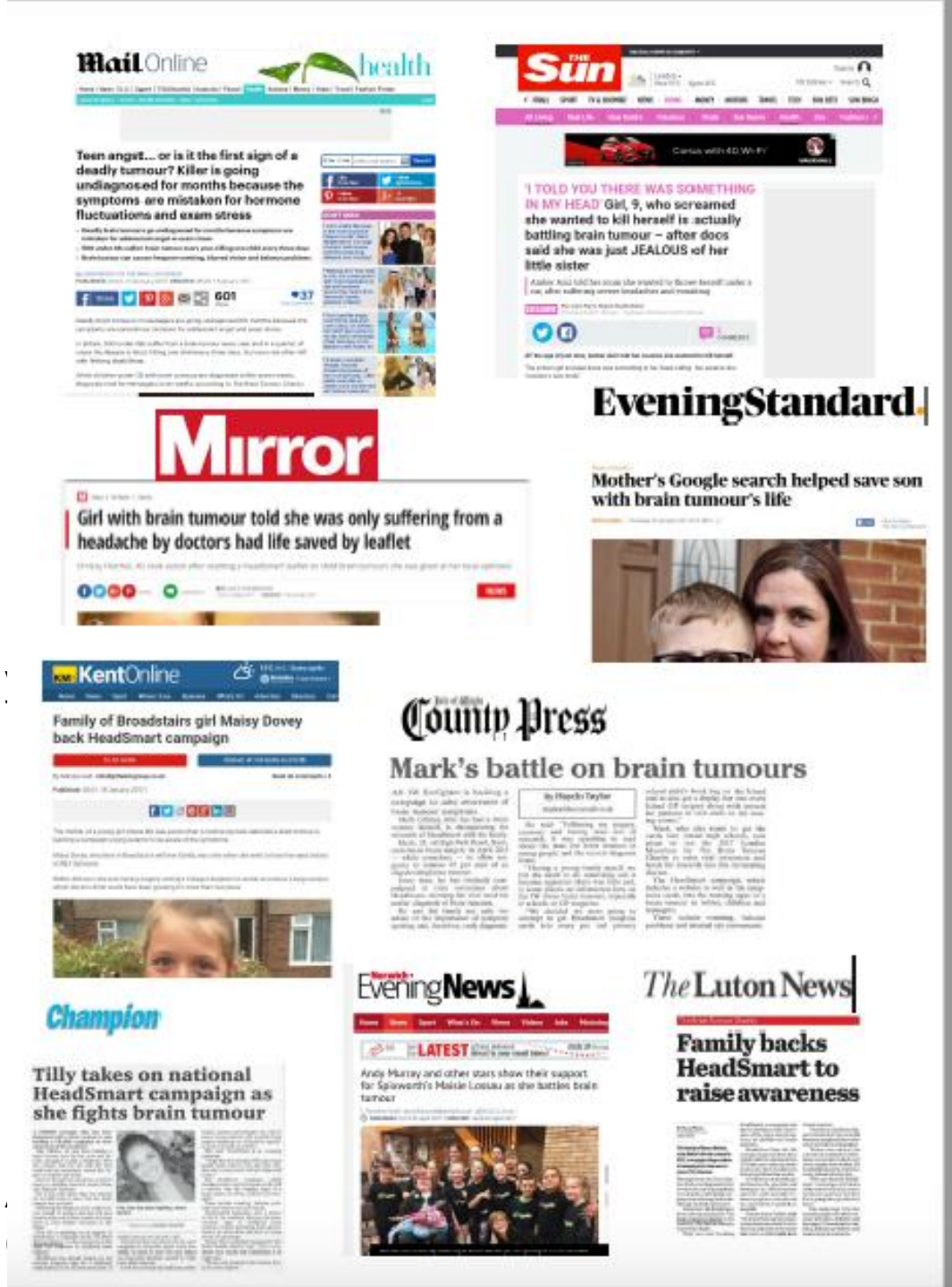
Website

- Sessions: 51,014 (Same period 2016: 55,952 – note that no exclusions such as Head Office IP address were in place)
- Page Views: 112,351 (Same period 2016: 89,811)
- Pages/Session: 2.20 (Same period 2016: 1.61)
- Average Session Duration: 1 minute, 12 seconds (Same period 2016: 53 seconds)
- Bounce Rate: 66% (Same period 2016: 78%)

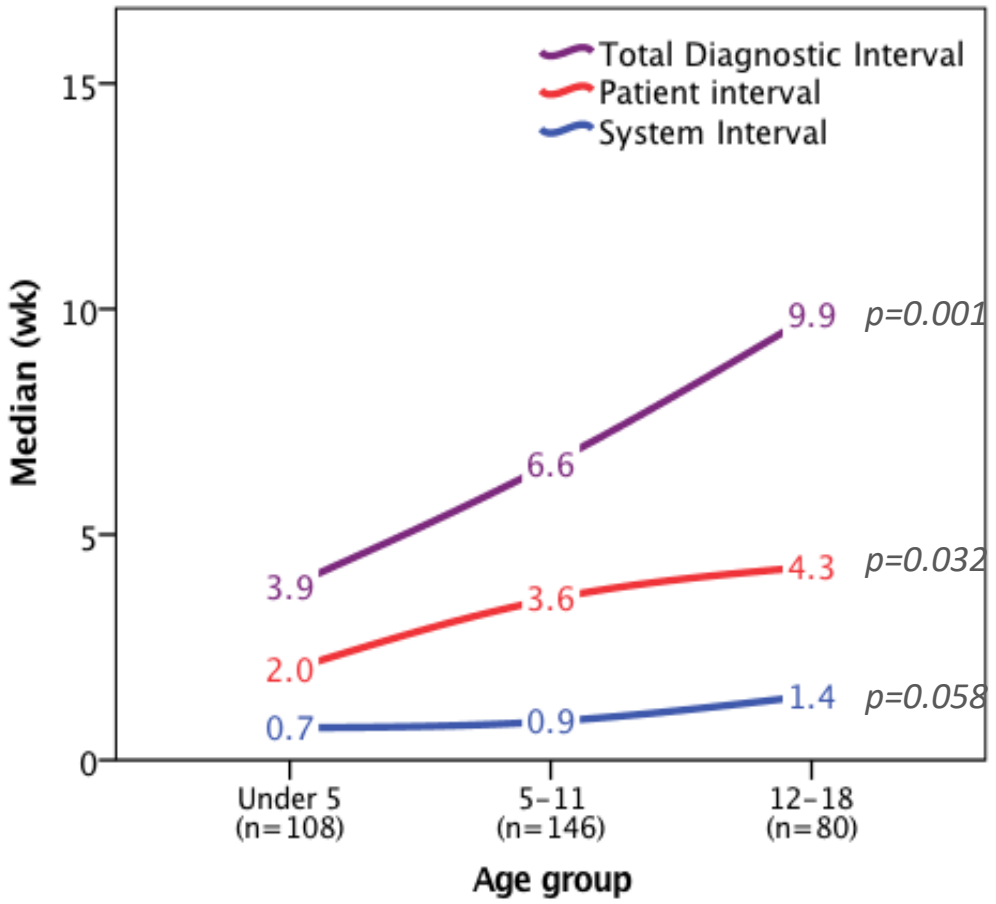
Media and PR

AVE: £582,437.60
Reach: 16,393,799
Collage on next page

HEADSMART
be brain tumour aware



HeadSmart Year 4
Key measures by age group

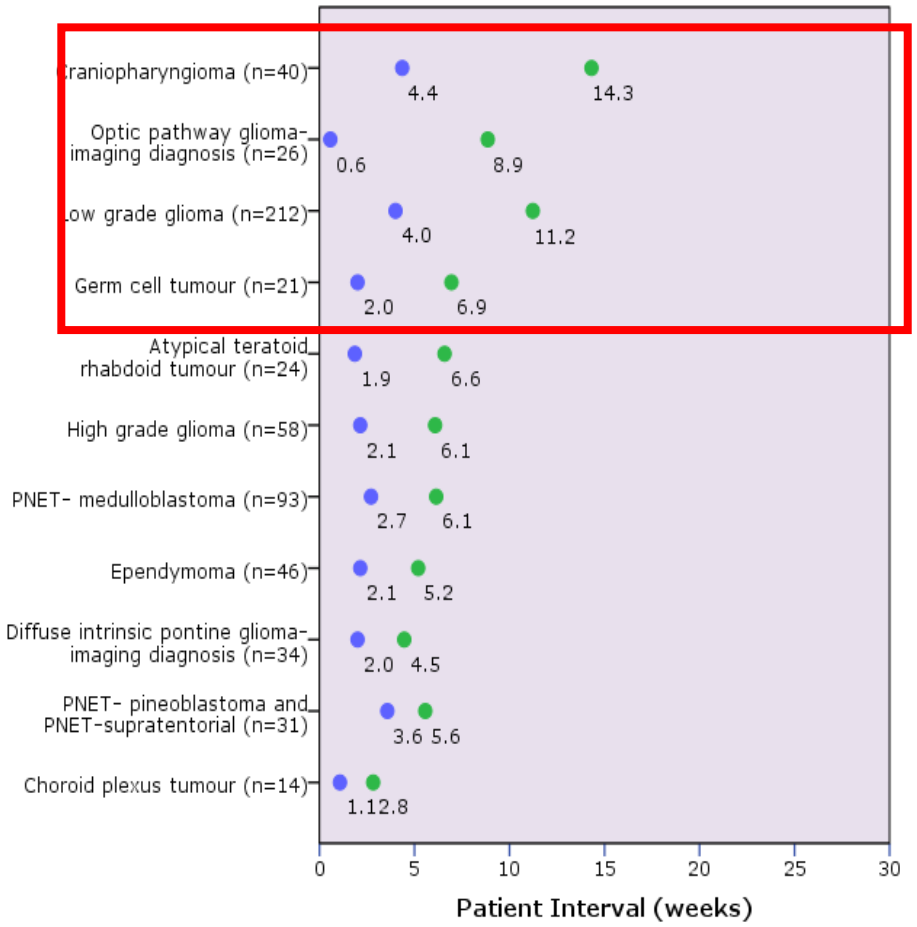


Only cases with complete information (of all three dates) were included

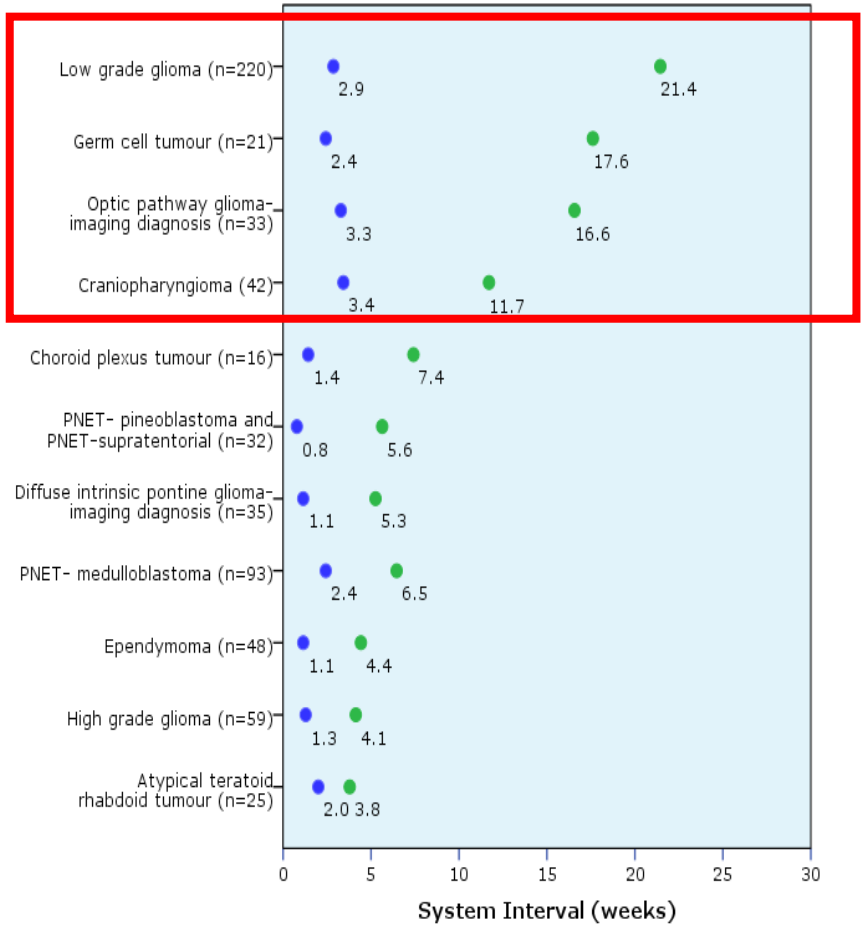
Diagnostic Intervals for <18 yrs brain tumour referrals UK 2011-2013 HeadSmart Dataset

Ranked by differences between Mean (blue) – Median (green) (skew)

Patient Intervals



System Interval



A UK study of blindness certification rates (2007-2011) in young people aged 0-24, diagnosed with brain tumor: a population linkage study

Thomas Chu[1], **Michel Coleman**[2], **Bernard Rachet**[2], **Catey Bunce**[3], **Richard Wormald**[3], **David Walker**[1]

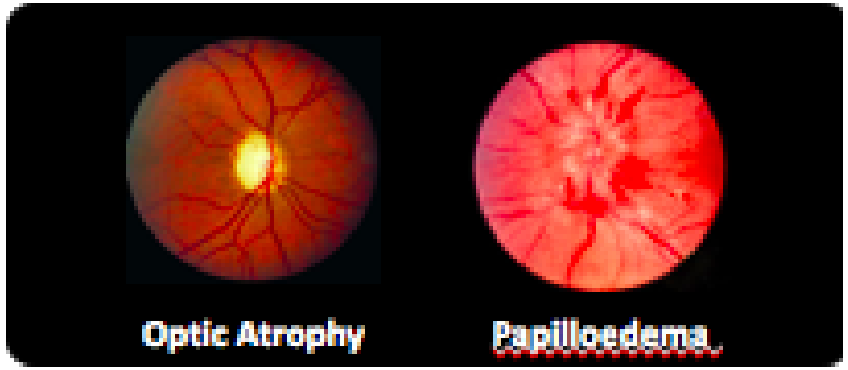
Abstract at SNO Pediatric 2017 NY

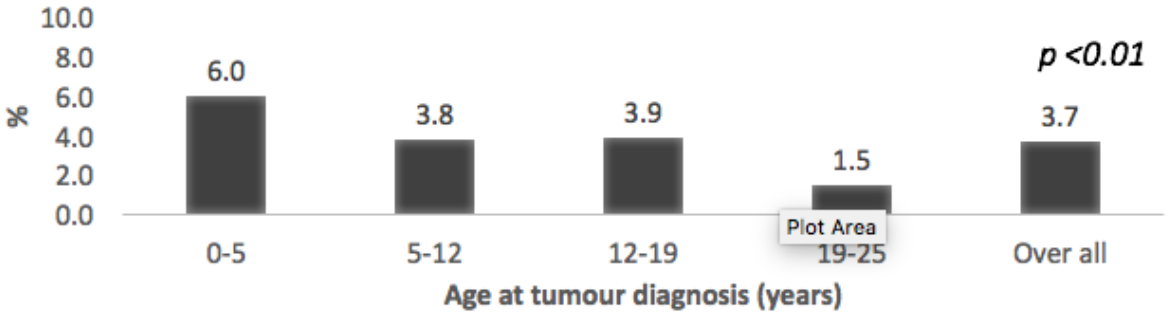
Probablistic data linkage

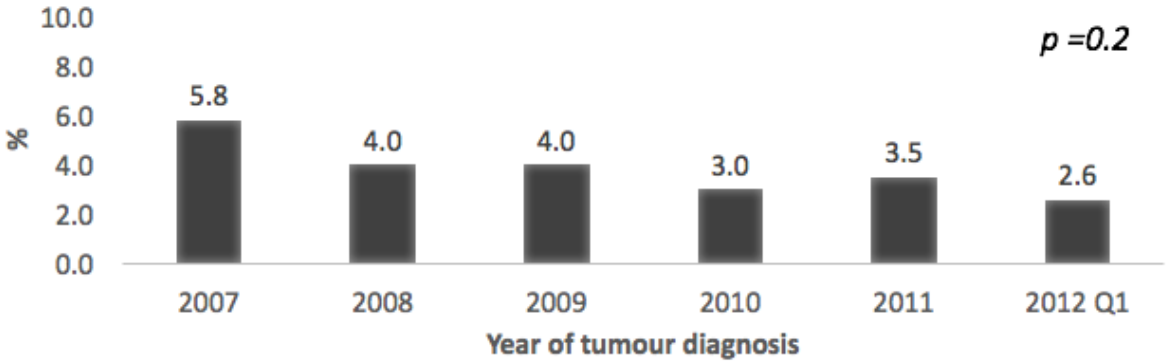
NCR '97-'12 n=19,555

eCVI '07-'12 n=13,013

336 visually impaired children with brain tumour registered within < 6mo before And 2 years after diagnosis

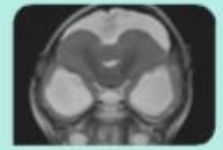




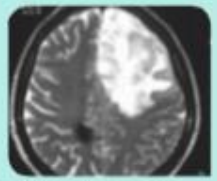


HEAD SMART | EARLY DIAGNOSIS OF BRAIN TUMOURS

PRESENTING SYMPTOMS OF BRAIN TUMOURS BY SUB-SPECIALTY



A young child with hydrocephalus caused by a brain tumour will have an increasing head circumference and developmental delay or regression.



Supratentorial tumours can cause change in personality, mood or disinhibition. They can also cause symptoms of anorexia. A brain tumour needs to be considered as part of the differential diagnosis.

Psychiatry

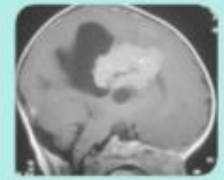
- Anorexia
- Behavioural change
- Depression
- Psychosis

Community

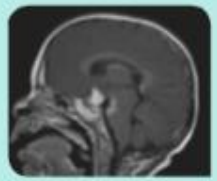
- Developmental delay
- Developmental regression
- Increasing head circumference

Neurology

- Seizures
- Motor weakness
- CN palsies
- Ataxia/cerebellar
- Focul neurological deficits



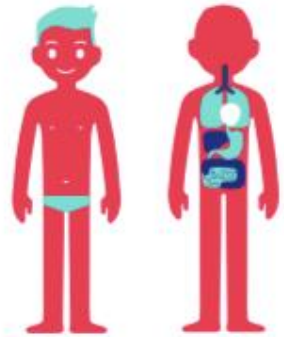
A supratentorial cortical tumour will present with focal neurological signs such as weakness.



Central tumours such as optic pathway glioma are slow growing and will present with progressive visual symptoms that may present to an ophthalmologist.

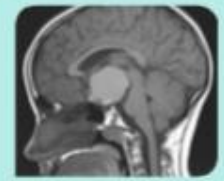
Ophthalmology

- Papilloedema
- Decreased visual acuity
- Nystagmus/parinauds
- Diplopia
- Squint
- Visual field defect
- Blindness
- Ptosis
- Proptosis
- Ocular palsies
- Ophthalmoplegia

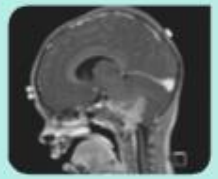


Endocrinology

- Growth problem
- Hypo-pit/pituitary dysfunction
- Diabetes insipidus
- Precocious or delayed puberty
- Menstrual irregularities
- Galactorrhoea
- Gynaecomastia
- Cushing's
- Obesity/weight gain



Central tumours such as a craniopharyngioma are slow growing and will present with abnormal growth or precocious or delayed puberty. These children may also have visual symptoms.



Head tilt or torticollis can be caused by a posterior fossa tumour. These symptoms may present to ENT specialists as head tilt and torticollis have other common ENT causes.

Ear, nose and throat

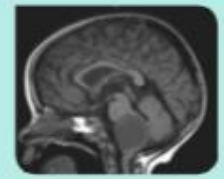
- Dizziness
- Vertigo
- Torticollis
- Head tilt
- Hearing loss
- Tinnitus

Gastroenterology

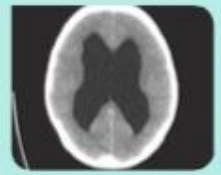
- Nausea and vomiting
- Abdominal pain
- Reflux
- Failure to thrive
- Dysphagia

Respiratory

- Recurrent chest infections
- Apnoeas



Recurrent respiratory infections can occur secondary to aspiration caused by a bulbar palsy. This MRI shows a brainstem tumour which causes cranial nerve palsies.



A child with hydrocephalus caused by a brain tumour will have persistent vomiting. In infants where the sutures are not yet fused there will be no other signs of hydrocephalus aside from macrocephaly.

HeadSmart is funded and promoted by The Brain Tumour Charity and run in partnership with the Children's Brain Tumour Research Centre (CBTRC) and the Royal College of Paediatrics and Child Health (RCPCH). The Brain Tumour Charity Registered Charity No. 1100034 (England and Wales) SC044081 (Scotland). CBTRC Charitable Status Inland Revenue No. XS0256. RCPCH Registered Charity No. 1057944 (England and Wales) SC039899 (Scotland).

headsmart.org.uk


National Lottery
Awards 2017
National Lottery
Awards 2017

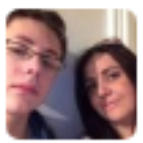
Claire Lloyd
@LloydysBabydoll

Follow

@HeadSmartUK you from the bottom of our hearts. That info saved his life ! Still a long road but we'll get there #LifeSavers 2/2

RETWEETS	LIKES
5	11

11:54 am - 22 Sep 2016



Claire Lloyd
@LloydysBabydoll

Follow

@HeadSmartUK Tues noon saw yr website, by lunchtime my son's tumour had been found & he'd had surgery to relieve the hydrocephalus.Thank 1/2

2 7

Where next with accelerating diagnosis
A precision medicine challenge

- Non invasive diagnostics
- Imaging characterisation
- Liquid Biopsy / Case selection for Imaging
- Population screening / early detection

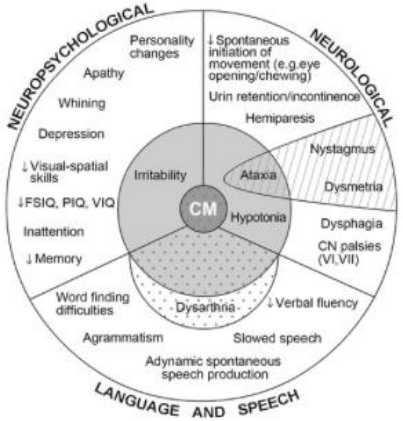
Cerebellar Mutism Syndrome

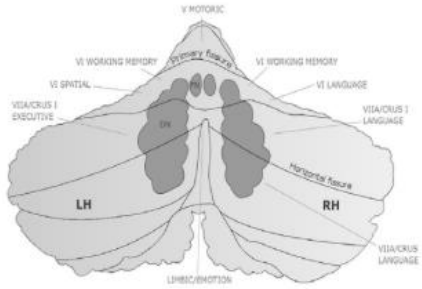
A brain tumour took away the daughter we knew. I've never stopped fighting to get her back

share

Posterior Fossa Society

CMS RESEARCH PUBLICATIONS MEMBERS EVENTS LINKS





2014
MSc and BMedSci student projects

2015
Posterior Fossa Society meeting

2016
International CMS Symposium at ISPNO

ISPNO LIVERPOOL

2016
4* accelorator award

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

2016
JTF funding : salary

JAMES TUDOR FOUNDATION

2017
CwC Workshop Grant

children with cancer UK
fighting the UK's biggest child killer

2017
TBTC Workshop Grant

The BRAIN TUMOUR CHARITY

2017
The Nottingham CMS Workshop

An international strategy to develop a web based paediatric pre-operative stratification tool for children at risk of cerebellar mutism

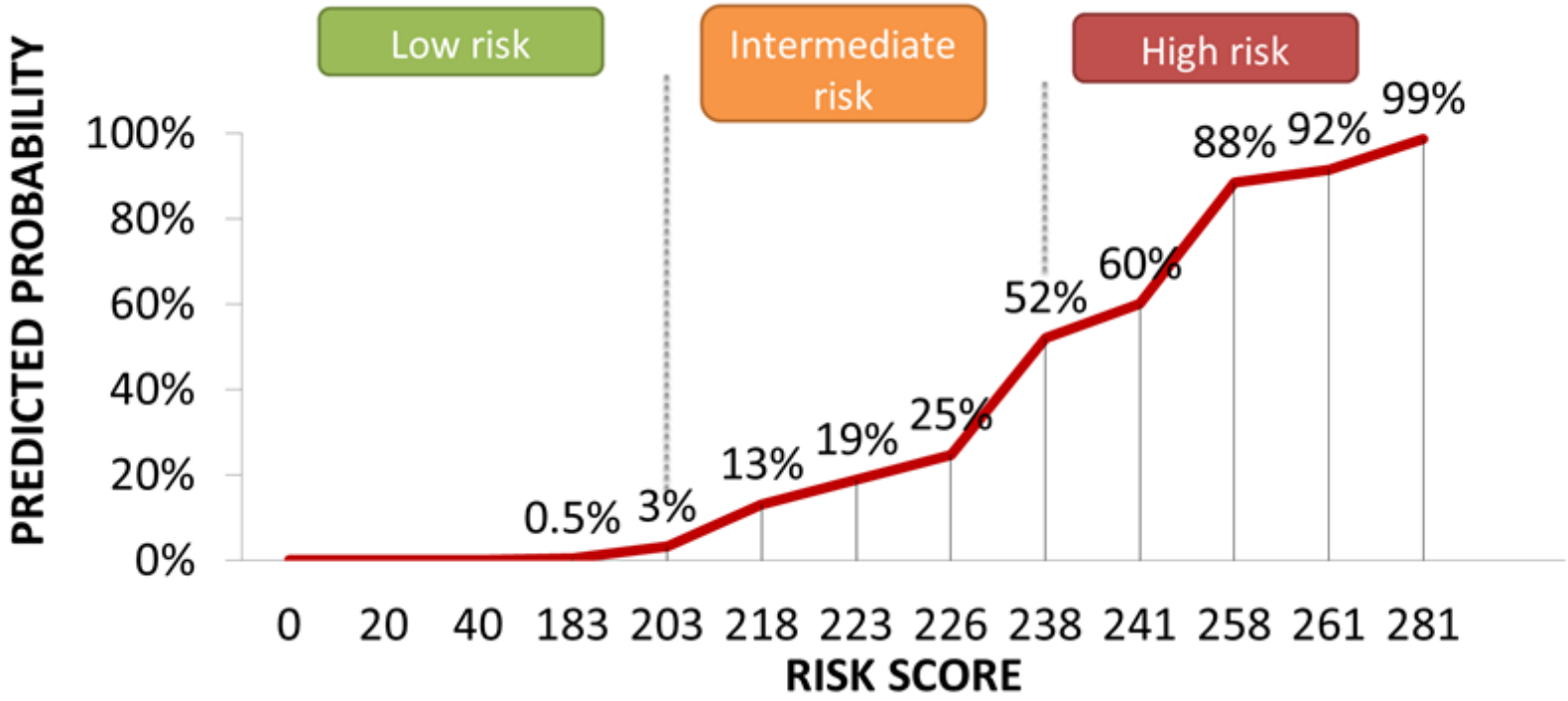
David Walker and Jo-Fen Liu

Donald MacArthur, Connnor Mallucci, Shivram Avula, Rob Dineen, R.Kumar, Richard Grundy, Barry Pizer

On behalf of the International CMS Collaboration

Nottingham CMS Workshop 2017

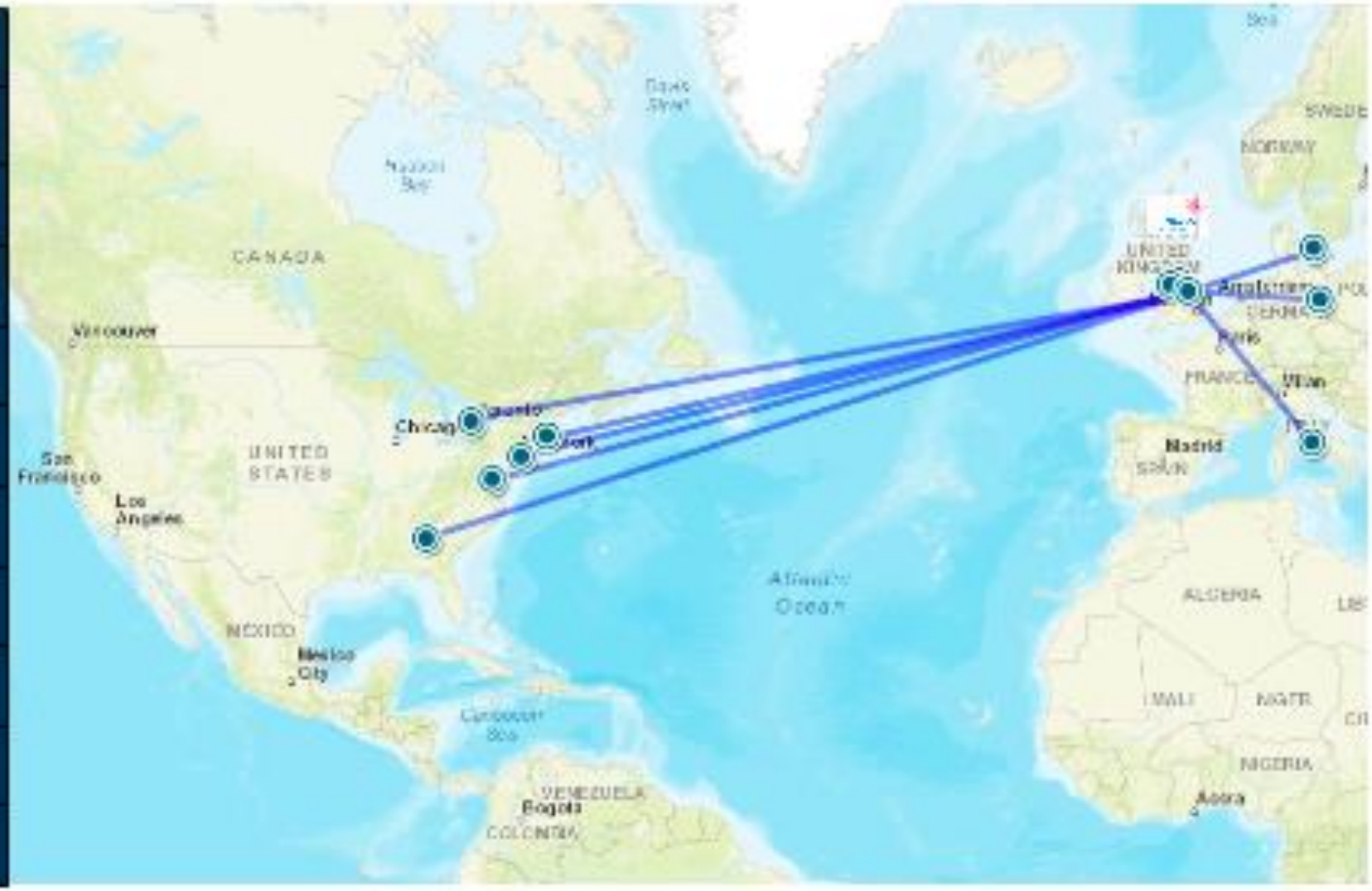
Preliminary predictive risk model based on 89 patients from two centres Nottingham and Liverpool



Our preliminary model has an accuracy of 88.8% (79/89).
The Nottingham CMS workshop dataset will be used to further refine/validate the risk scoring system

The Nottingham CMS Workshop 9-10 May 2017

- Atlanta
- Berlin
- Boston
- Copenhagen
- Liverpool
- Manchester
- New York
- Nottingham
- Rome
- Toronto
- Washington



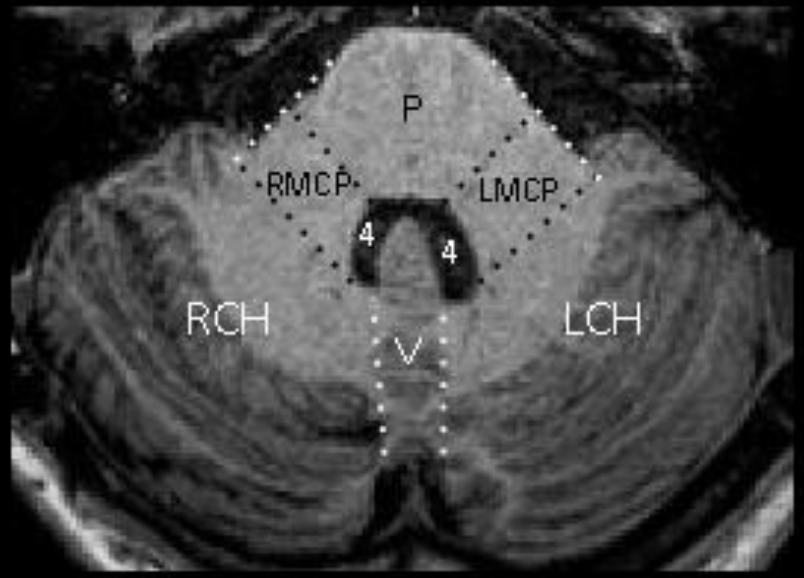
children with cancer UK

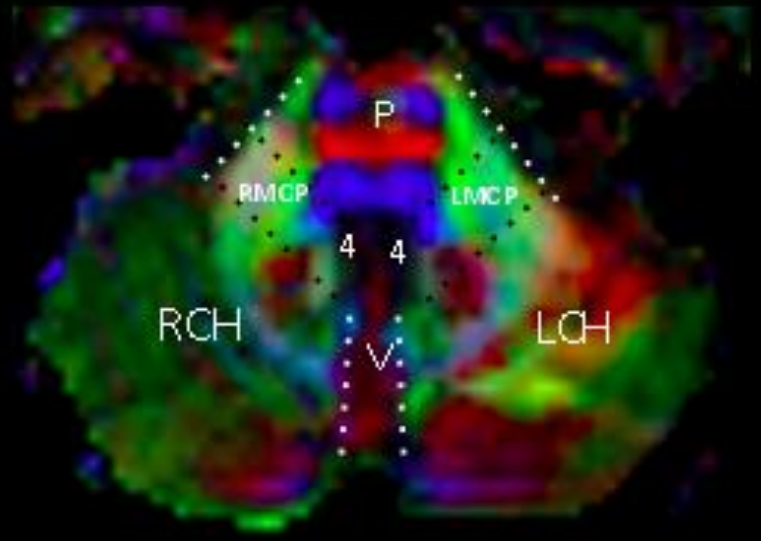
JAMES TUDOR FOUNDATION

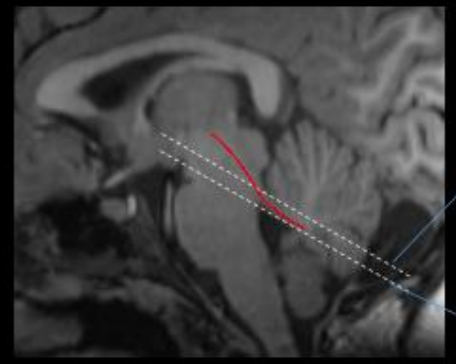
The BRAIN TUMOUR CHARITY

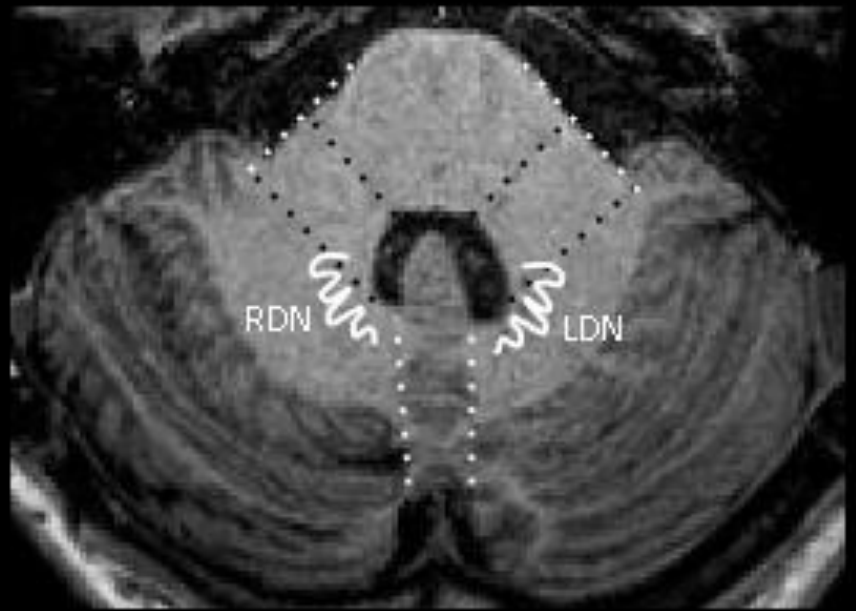
The University of Nottingham

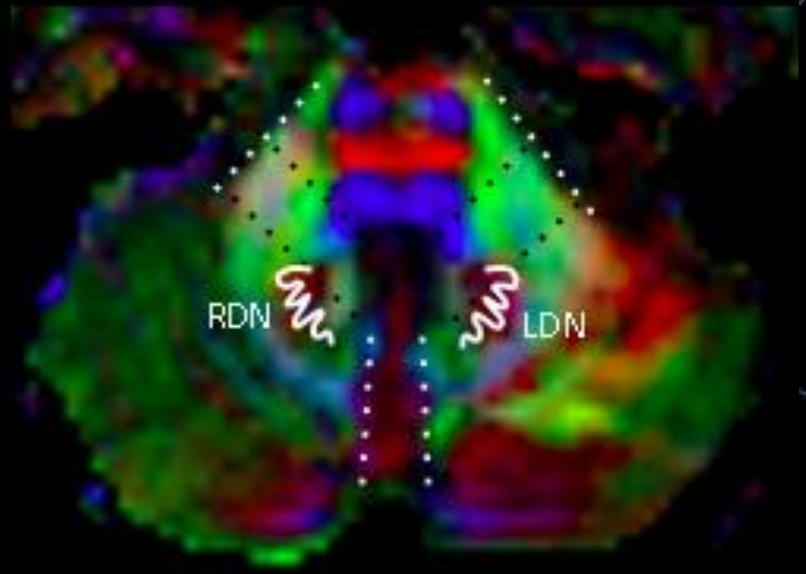
- Superior cerebellar peduncles

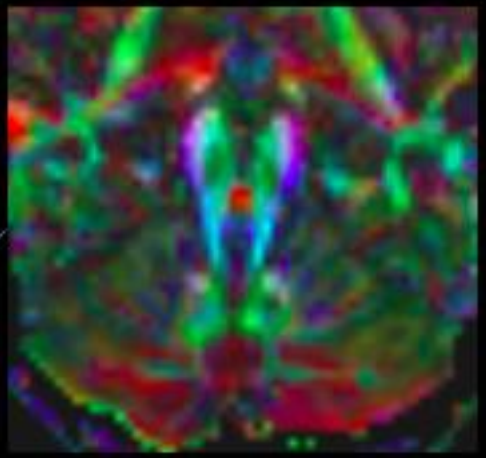


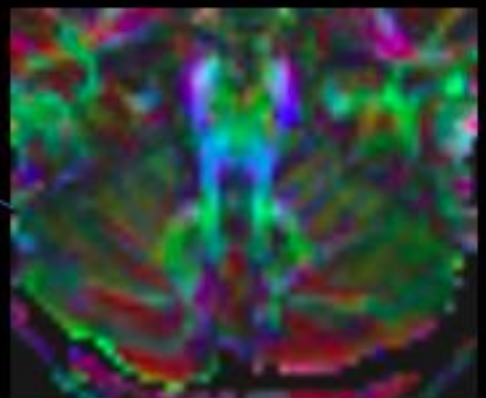












Global
Top 100
University

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Imaging data analysis




Children's Brain Tumour Research Centre

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Key themes from surgical statements review:

- Caution with use of ultrasonic aspirator/settings
- Avoidance of retraction/ disturbance to cerebellar peduncles
- Great care around floor of fourth ventricle
- Increasing acceptance of leaving a residuum in medulloblastoma cases
- Preoperative anticipation of mutism risk

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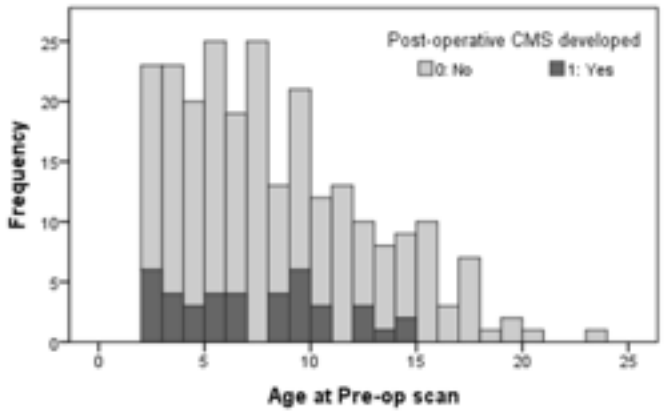
Age at pre-operative scan (n=247)



	n	Age (years) Mean± SD	*p-value*
CMS (-)	207	8.43± 4.56	0.117
CMS (+)	40	7.22 ±3.73	

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CMS outcome

- Patients who developed post-operative CMS are more likely to be medulloblastoma cases
- Other symptoms
  - cerebellar motor syndrome (32/40; 80%),
  - emotional lability (27/40; 68%)
  - brainstem dysfunction (26/40; 65%)
  - hypotonia (23/40; 58%)
  - oropharyngeal dysfunction/dysphagia (20/40; 50%)
  - cerebellar cognitive affective syndrome (18/40; 45%).

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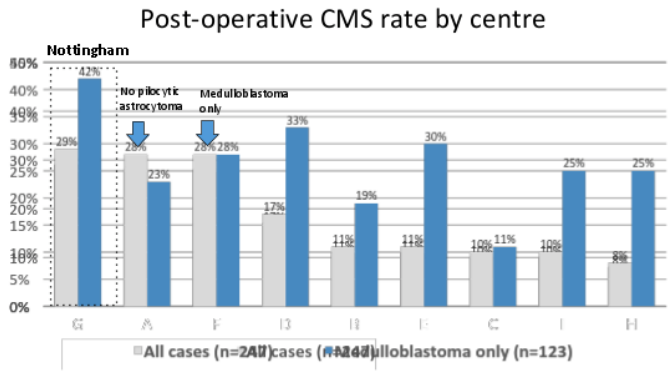
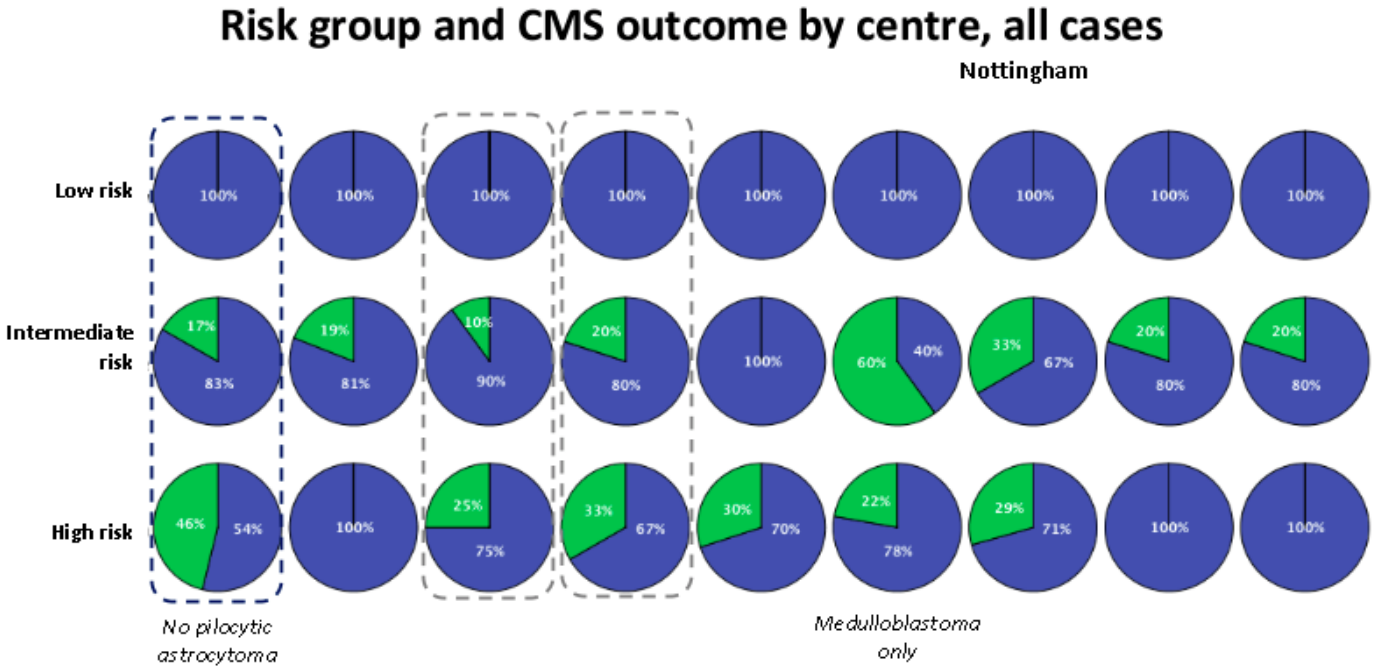
Preliminary Analysis





Next steps

1. Identify potential risk factors of post-operative cerebellar mutism and revise the model;
2. Develop an e-learning training module targeted on doctors in training;
3. Assess whether potential users find these functionalities useful and acceptable using quantitative and qualitative methods.
4. Follow up meetings

Objectives

- To highlight the clinical challenge of brain injury for children with brain tumour and their families

- To identify population strategies that are in early use
  - to reduce these risks of brain injury through accelerating diagnosis of brain tumours,
  - to assess risk of post operative brain injury

- To consider priorities for future research to help the children and their families

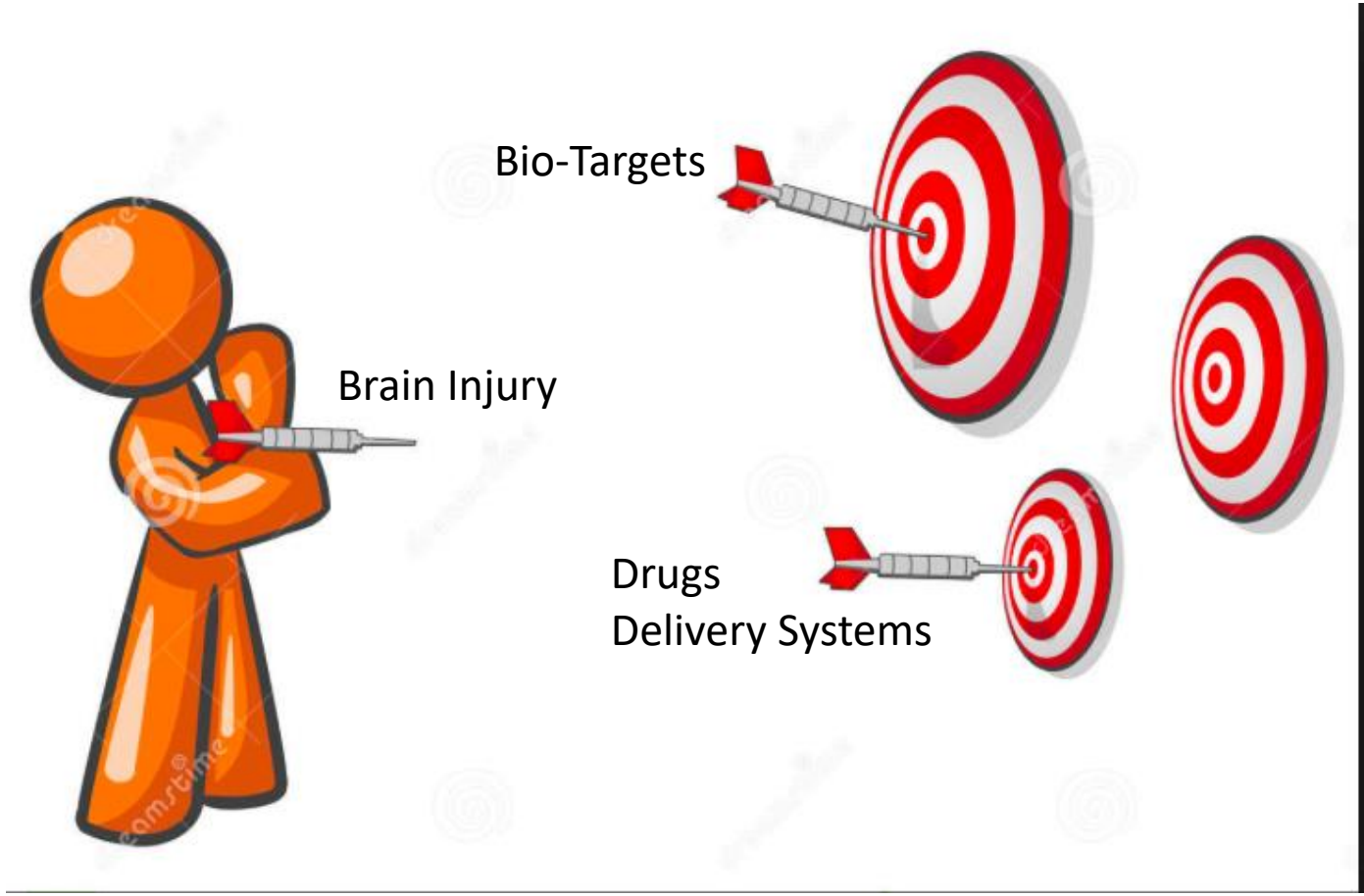
Research Impact Methods
Driving Change in Clinical Disciplines

Biology
Pathology
Pharmacology
Physiology
Biochemistry
Physics
Chemistry
Genetics

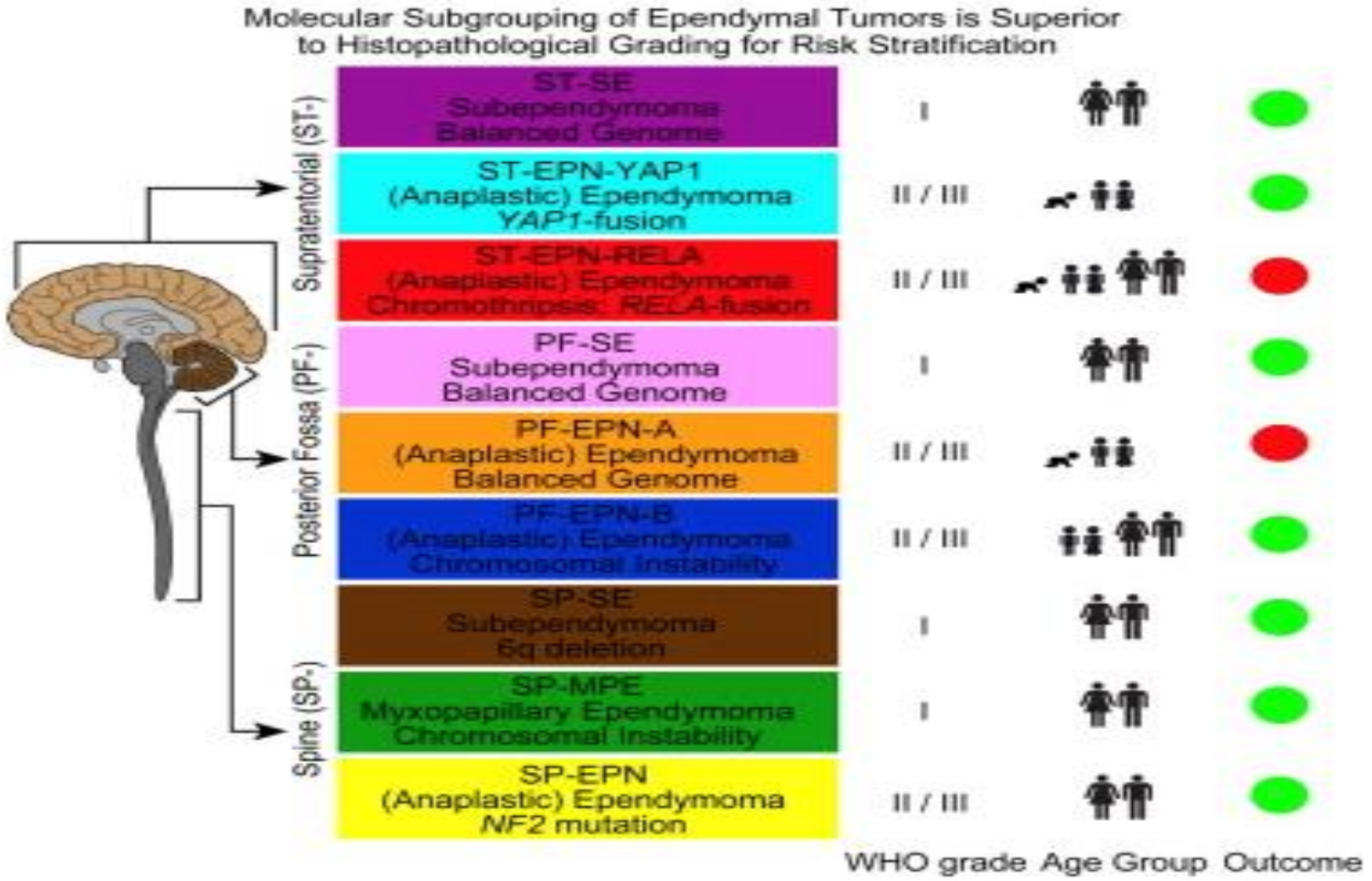
Population registries
Cohort Studies
Data Linkage
Clinical Trials
Quality Improvement
Awareness Methods
Surveys
Focus Groups
Qualitative methods
Public Engagement

Precision Medicine
for Children and Young People's Brain Tumours

- Is here to stay
- Can be applied to all stages of cancer journey from before diagnosis to survivorship
- Requires leaders to generate priority for children and young people specifically
- Young people and their advocates have a big part to play



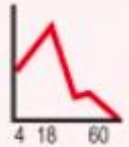
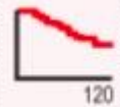
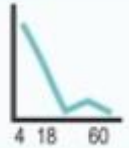
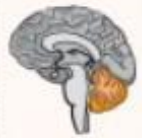
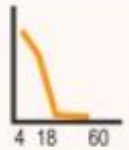
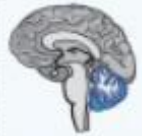
Molecular Classification of Ependymal Tumors across all CNS Compartments, Histopathological Grades, and Age Groups



General Consensus Statements

1. Outside of clinical trials, treatment decisions should not be based on grading (II vs III)
2. ST and PF ependymomas are different diseases although the impact on therapy is still evolving
3. Central radiological and histological review should be a principal component of future clinical trials
4. Molecular subgrouping should be part of all clinical trials henceforth
5. Submission of fresh-frozen tumor samples as well as of blood samples will be mandatory in future clinical trials

Subgroup Consensus Statements

Molecular subgroup	Tumor Location	Genetics	Age Distribution (yrs)	Gender Distribution	Survival (OS;months)	Subgroup-specific consensus
ST-EPN-RELA		 Aberrant 11q Chromothripsis	 4 18 60	 ♂ > ♀	 120	There is not enough evidence to recommend distinct treatment approaches. Outcome should be further validated in prospective and retrospective studies.
ST-EPN-YAP1		 Aberrant 11q	 4 18 60	 ♂ < ♀	 120	It should be rapidly determined whether the YAP1 subgroup is associated with favorable clinical outcome.
PF-EPN-A		 Balanced	 4 18 60	 ♂ > ♀	 120	Outside of clinical trials, in patients > 12 months of age, maximal safe resection and focal radiotherapy is the standard of care.
PF-EPN-B		 Chromosomal Instability	 4 18 60	 ♂ < ♀	 120	An observation only clinical trial will be implemented to determine the opportunity of de-escalating therapy.

Cerebellar Mutism Amy

- 9 yrs old presenting with double vision, headaches,, vomiting and neck stiffness
- Bilateral papilloedema, upgaze limitation, left hand incoordinaiton, no ataxia, normal gait
- CT scan midline cerebellar tumour, 4 cms, mild hydrocephalus.
- Dexamethaosne 48 hours, operation to relieve hydrocephalus and remove tumour. Histo: Medulloblastoma
- Post operatively 24 hours speech incomprehensible, left eye deviated down
- 48 hours Admitted to ICU with aspiration pneumonia
- 72 hours developed triplegia of both arms and left leg, not responding to commands
- At 3weeks: Swallowing and comprehension started to improve
- At 7 weeks Underwent radiotherapy 35 / 54 Gy starting to swallow safely
- At 4 months able to walk, talk in short sentences, had good comprehension and eat solid foods.
- Plans were made for return to education thereafter

The family experience

- It was a land of inference and insinuation. . . On the one hand we had nurses who treated our daughter as if she could see, hear and understand everything; on the other we had those who clearly felt she had been reduced to the level of an infant. If communications were hampered by a lack of time, ignorance and politeness, then they were stalled even more by the constant presence of my daughter, who for all but the first two days of the four months we were in hospital was unable to communicate. No one could guess what she might or might not want to hear...
- What we needed at this time was access to independent written material about the complications that can follow brain injury. We felt we were trying to piece together a picture when we only had a few pieces of the jigsaw. . .
- . . . Further enlightenment came when a doctor gave us a book on neurosurgery, with a section marked for us to read. . . the marked section wasabout cerebellar mutism, the syndrome affecting Amy. All the worrying symptoms – the total inability to communicate, the obsessive, repetitive tics, the almost autistic withdrawal from the world – were described.We were not in unchartered waters after all. At last we had a map.
- . . . When she was first able to communicate, which she did with the aid of a speaking machine, it became apparent that she had taken in quite a lot. She had acquired a medical vocabulary and could even spell most of the words

Table 1
WISC-III^{UK} Index scores

	WISC-III^{UK} index scores *12 months post resection*		WISC-III^{UK} index scores *2 years 4 months post resection*	
	Score	Percentile	Score	Percentile
Verbal Comprehension	125	95	111	77
Perceptual Organization	98	45	90	25
Freedom from Distractibility	115	84	124	95
Processing Speed	74	4	75	5

Table 2
Table 1: WISC-III^{UK} subtest scores

	Subtest scores WISC-III^{UK} *12 months post resection*	Subtest scores WISC-III^{UK} *2 years 4 months post resection*
Vocabulary	18	15
Similarities	16	12
Arithmetic	14	15
Digit Span	11	14
Information	11	16
Comprehension	12	5
Picture Completion	13	10
Digit Symbol Coding	5	5
Block Design	10	10
Object Assembly	11	10
Picture Arrangement	5	5
Symbol Search	6	6
Mazes	5	10

Amy’s memory

- I only remember the odd thing from when I had mutism syndrome. I don’t remember it ever feeling frustrating though. It was just something that was happening. I remember my parents used to give me choices by holding things up for me and trying to choose the one I looked at. Sometimes these choices were probably wrong but a lot of the time I don’t think I registered this, or if I did I didn’t care, not like I’d given up because I don’t think I felt that much emotionally. I do remember my brother and sister coming in and doing ‘funny shows’ for me in the playroom though, and I used to laugh at those.
- I remember going on a computer program at the hospital school and, while I was aware that someone was guiding my hand, I felt like I was doing some of the work. When I was watching a dog show outside, I remember clapping afterwards (though this must have been my mum moving my hands for me). In a music therapy session I remember using an ‘ocean drum’.
- It’s interesting that I remember it was me doing things when actually it was just people moving my hands. I do remember the names of the people that helped me, better than my mum does though, and can picture their faces.
- “At home, I think my emotions came back, or became more defined. And not long after that, I started speaking again. When I went back to school I was quite annoyed with how much people asked me if I was okay or if I needed help when I was just getting on with what I was doing. That must have been because of my slow reactions. They have got better since but sometimes that still happens. I’ve just had to learn to accept it and I’m not that good at asking for help when I need it anyway so I often do need it”

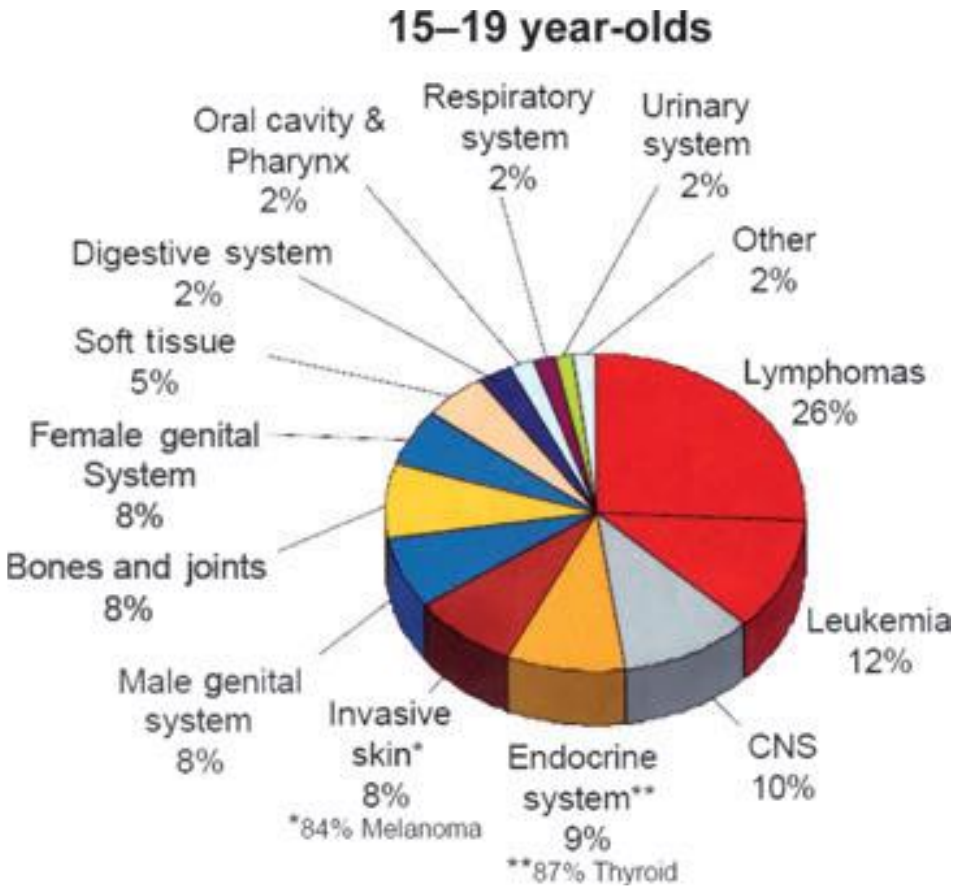
ESTRO School

Hodgkin`s Disease, Role of RT
(Treatment techniques, target volumes, dose prescriptions)

Karin Dieckmann
Medical University Vienna , Austria

Epidemiology

- While HL represents only approximately **4–5%** of all cancers in children **< 15 y.**
- **16%** in the adolescent, making HL the most **common malignancy** within this age group (15–19 years old)



Bleyer, W.A., O'Leary, M., Barr, R. & Ries, L.A.G. (eds) (2006) National Cancer Institute, NIH Pub. No. 06-5767 Bethesda, MD

Histology

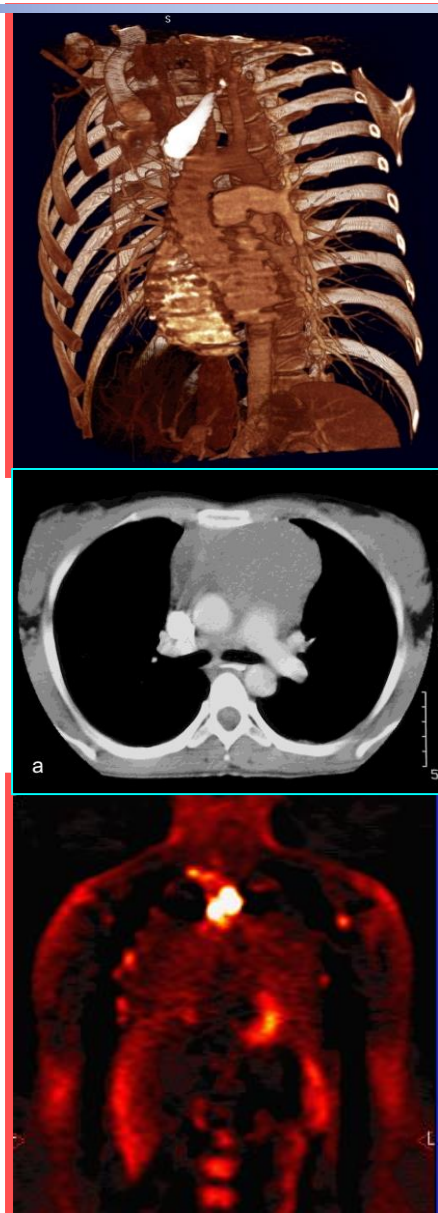
- The WHO classification system separates Hodgkin lymphoma into two broad categories:
  - **‘‘Classical,’’** comprising **lymphocyte depleted, nodular sclerosis, mixed cellularity, and classical lymphocyte rich**
  - **‘‘Lymphocyte predominant’’** Hodgkin lymphoma (previously known as paragranuloma,)
- *90% of Hodgkin Lymphoma are of the* ***‘‘Classical’’ type***

Obligatory Staging analysis at time of diagnosis I:

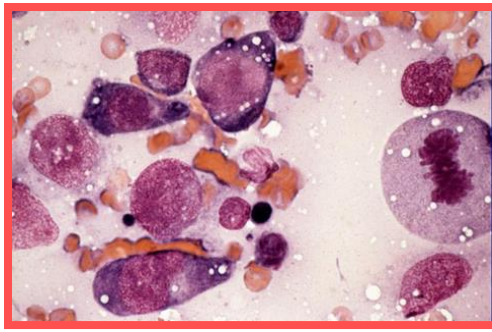
- **Clinical examination** with detailed documentation of all palpable lymph nodes and their location
- **Laboratory examination**: complete blood count, erythrocyte sedimentation, GPT, GOT, LDH, creatinin, albumin, IGA, IGM, IGG, Virology
- **Biopsy / Operation** of an enlarged peripheral LN

Staging analysis at time of diagnosis II

- Chest x-ray (facultatory)
- Chest CT with lung and soft tissue window
- MRI or CT of the neck, abdomen, and pelvis
- Ultrasound
- FDG-PET or FDG-PET-CT or FDG-PET-MRI

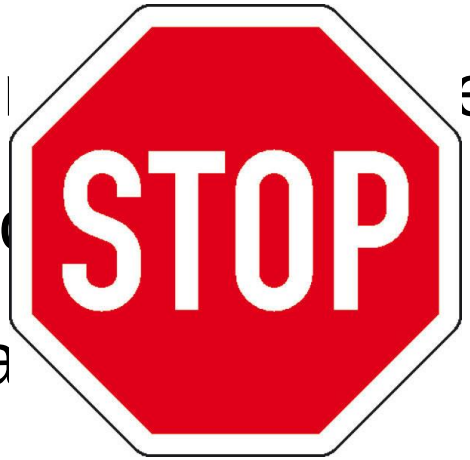


Staging analysis at time of diagnosis III



- ECG and EEG (factultatory)

- 1-2 bone marrow aspiration and biopsies
- Bone scan i e involvement
- In case of b : bone scintigraphy
- Selective La

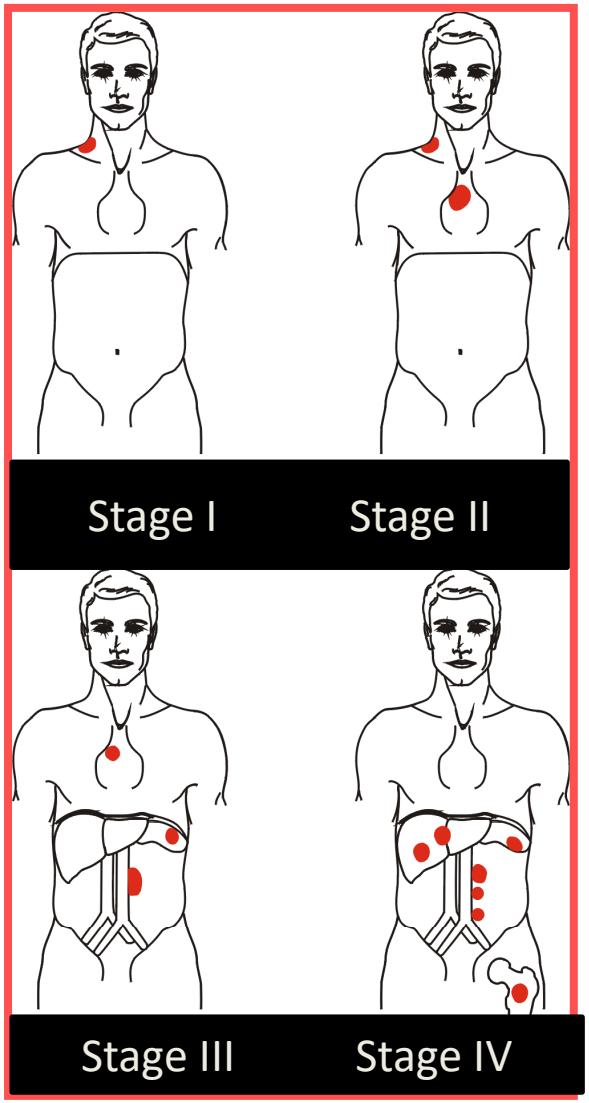


In case of positive PET

Ann Arbor Staging System
Cotswold Modification

- Stage I : a single lymph node region
- Stage II : ≥ 2 lymph node region,
  same side of diaphragm
- Stage III : lymph node region,
  2 sides of diaphragm
- Stage IV : diffuse, disseminated

- B signs : 1/3 of the children
  - Fever > 38°C
  - Recurrent night sweats
  - Weight loss >10% (6 m.)



Low /intermediate/high risk groupe

- **Low risk** :

  Stage I and IIA

  without risk factors

- **Intermediate risk :**

  Stage I and IIA with risk factors and Stage IIB and IIIA

  (ESR ≥ 30mm/h; Bulk ≥ 200 ml; E-lesions)

- **High risk :**

  Stage IIBE, IIIAE, IIIB, IV

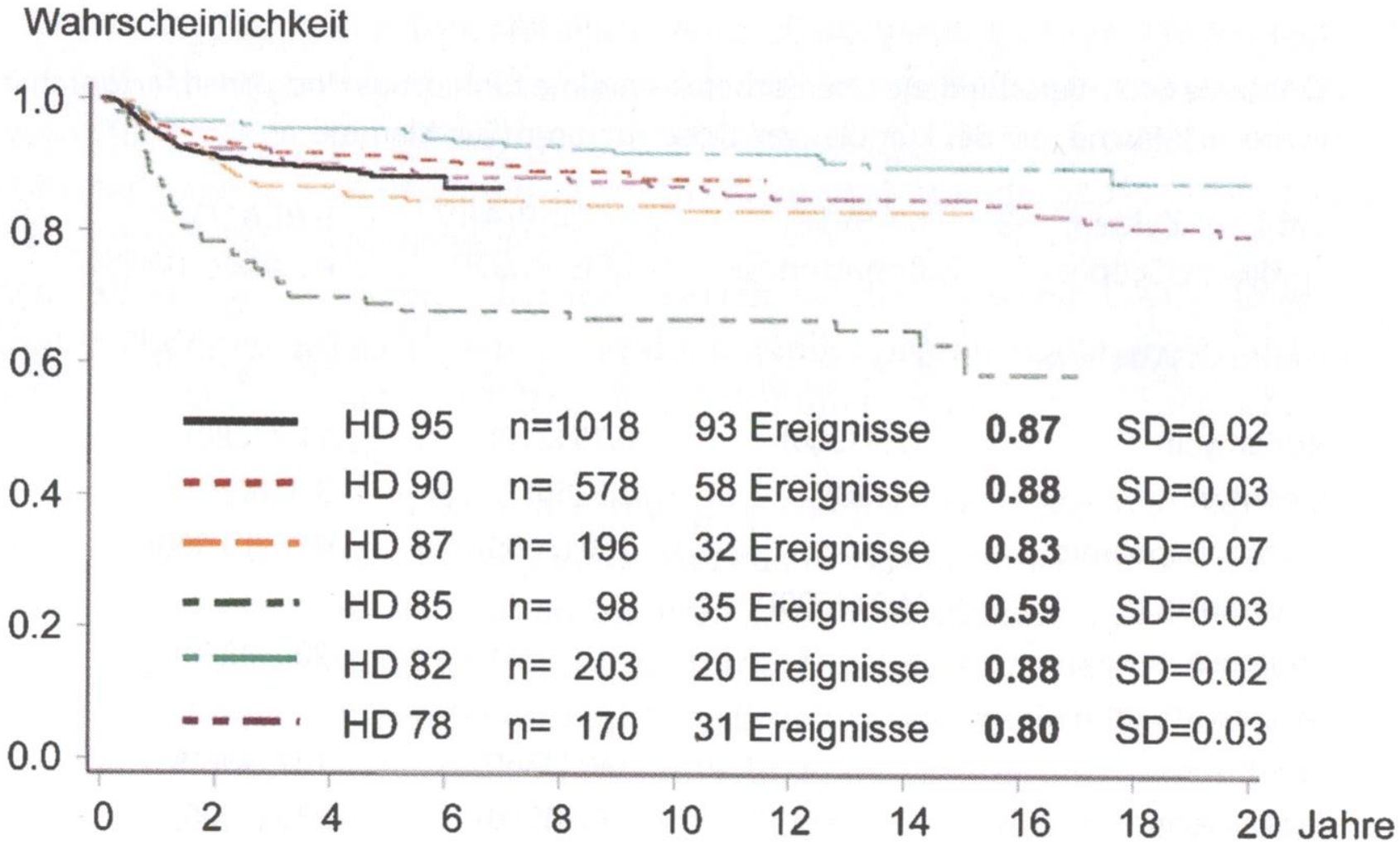
REVIEW
Children's Oncology Group's 2013 Blueprint for Research: Hodgkin Lymphoma

Kara M. Kelly, MD,[1]* David Hodgson, MD,[2] Burton Appel, MD,[3] Lu Chen, PhD,[4] Peter D. Cole, MD,[5] Terzah Horton, MD, PhD,[6] and Frank G. Keller, MD[7] on behalf of the COG Hodgkin Lymphoma Committee

Study group	Study	Risk group	# Enrolled	Outcome
COG	C5942 [5]	All	826	10 years EFS 83.5 ± 1.3% 10 years OS 92.5 ± 1%.
	C59704 [6]	High	98	5 years EFS 94 ± 2.4% 5 years OS 97 ± 1.9%
	P9426 [13]	Low	255	8 years EFS 86.3 ± 1.4% 8 year OS 96.5 ± 3.5%
	P9425 [7]	Intermediate/High	216	5 years EFS 84 ± 3% 5 years OS 95 ± 2%
	AHOD0431 [8]	Low	278	4 years EFS 79.8 ± 2.6% 4 years OS 99.4 ± 0.6%
	AHOD0031 [9]	Intermediate	1,712	4 years EFS 85.0 ± 0.9% 4 years OS 97.8 ± 0.4%
German/Euronet	GPOH-2002 [10]	All	573	5 years EFS 89 ± 1.4% 5 years OS 97.4 ± 0.7%
St. Jude/Stanford/Dana Farber	HOD99 [1]	Low Intermediate and high	88 141	2 years EFS 90.8 ± 6.1% 3 years EFS 79 ± 4% 5 years OS 97 ± 2%

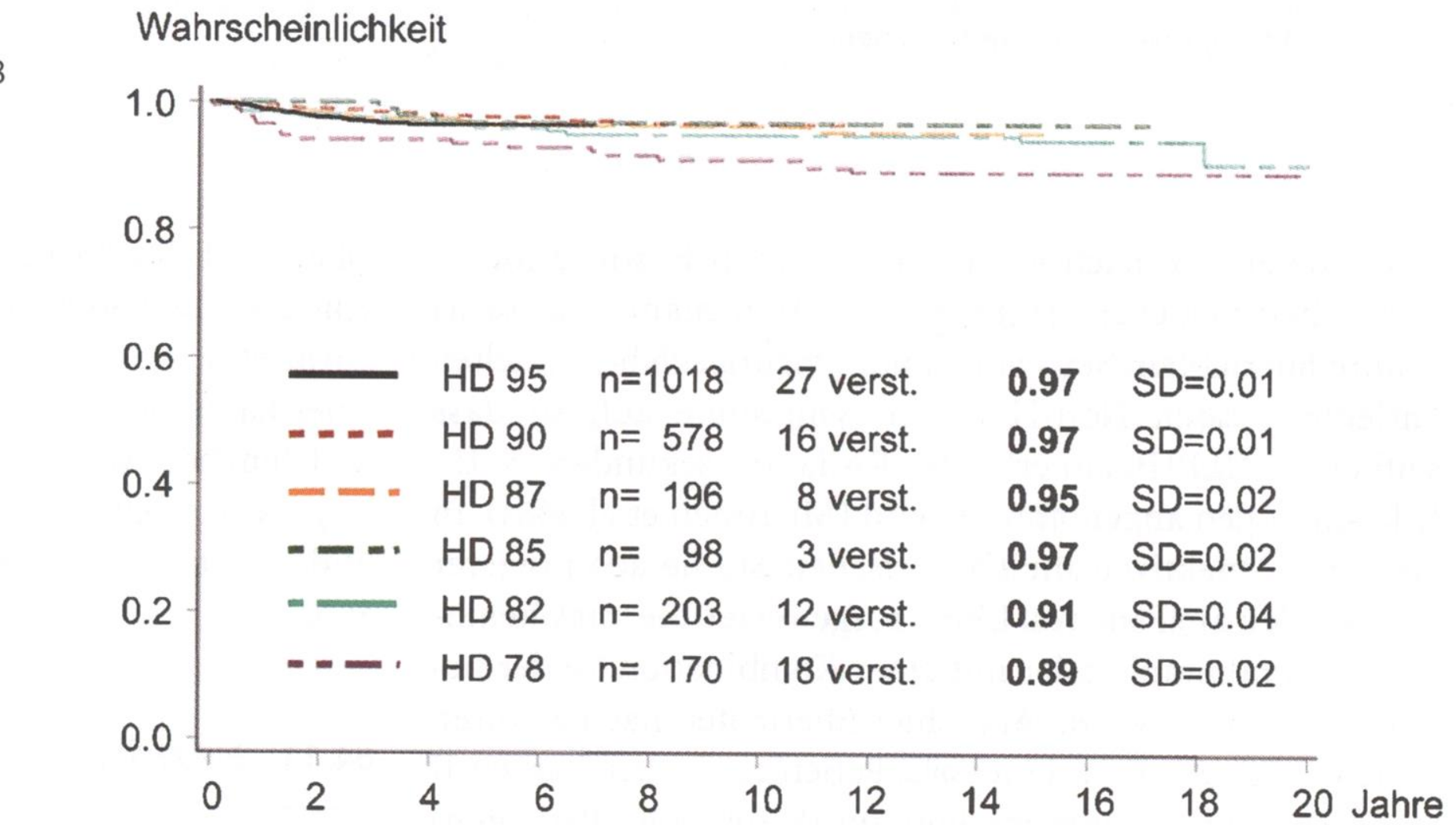
- 5-10 year OS in all in studies for children with Hodgkin`s disease is 92-99% .

Event Free Disease der GPOH-HD-Studies 1978-1995



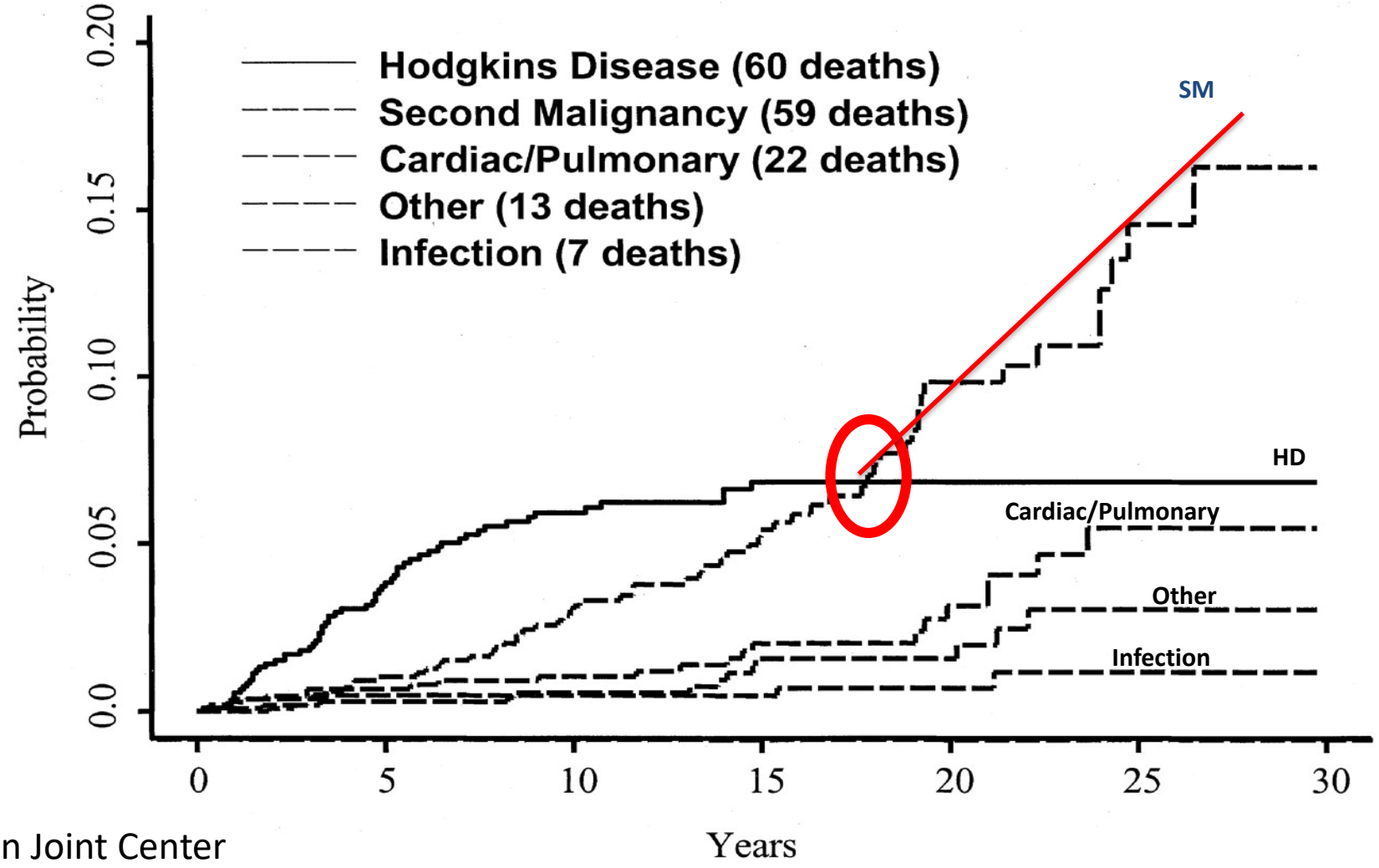
Dörffel et al.2003

Overall Survival of the GPOH-HD-Studies 1978-1995 after combined Chemo/Radiotherapy



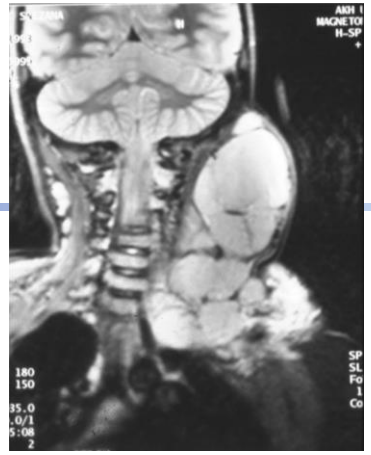
Dörffel et al.2003

Reasons for changing treatment concepts in Hodgkin`s Disease



Boston Joint Center

Lymphnode involvement in Hodgkin`s disease:



- **Supradiaphgramatic lymphadenopathy** (cervical +++) :
  80% of HD cases ; usually non inflammatory, painless,
  ferm, sometimes tender

  Mauch, Cancer 1993;71:2062

- **Mediastinal involvement** (leading to symptoms : dyspnea, cough, …) :
  > 50% of HD cases (up to 75% of HD)
  - 1/3 if < 10 y.
  - > 2/3 if adolescents
  - Rarely isolated (< 5%)

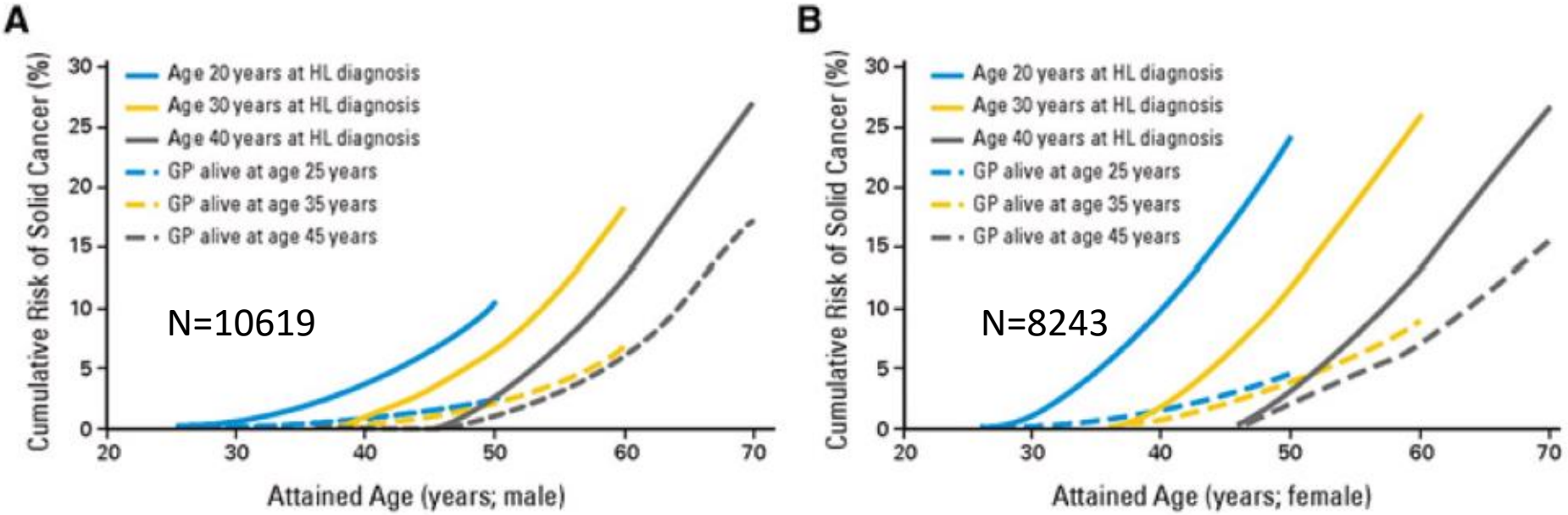
  Crnkovich, JCO 1987:5(7)1041

- **isolated infradiaphragmatic** involvement : < 5%

Late Effects in the Era of Modern Therapy for Hodgkin Lymphoma

David C. Hodgson[1]

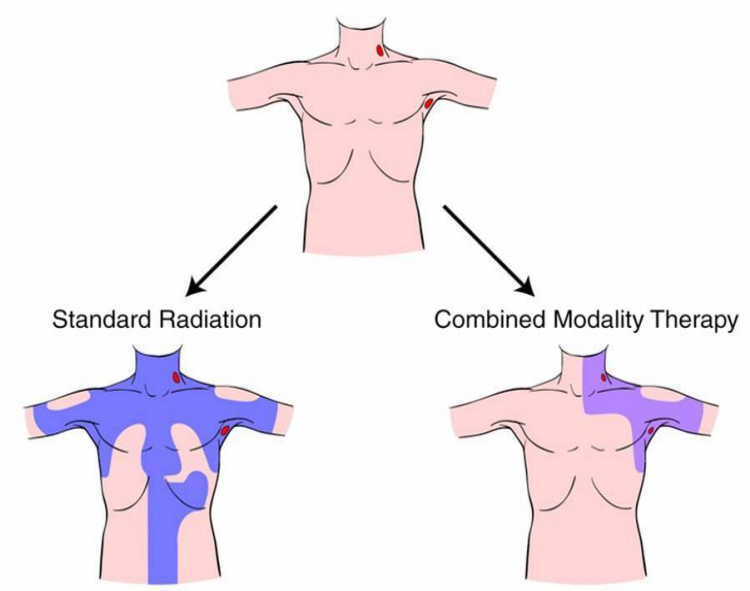
Cumulative risk of solid cancer among HD survivors compared with the general population



Based on volume, dose, age increase of secondary cancer, heart disease, endocrine dysfunction.

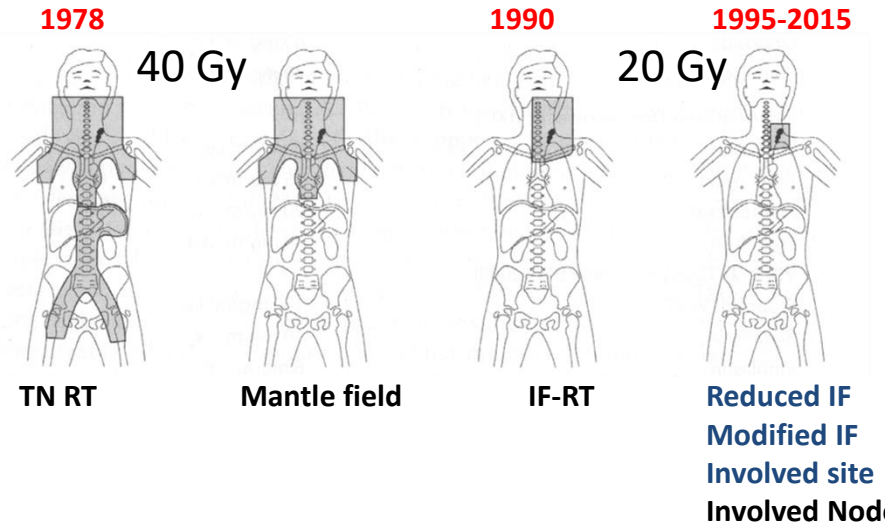
Hematology 2011

Philosophy of Paediatric Hodgkin`s Treatment



- Risk adapted treatment strategy since the 80ies

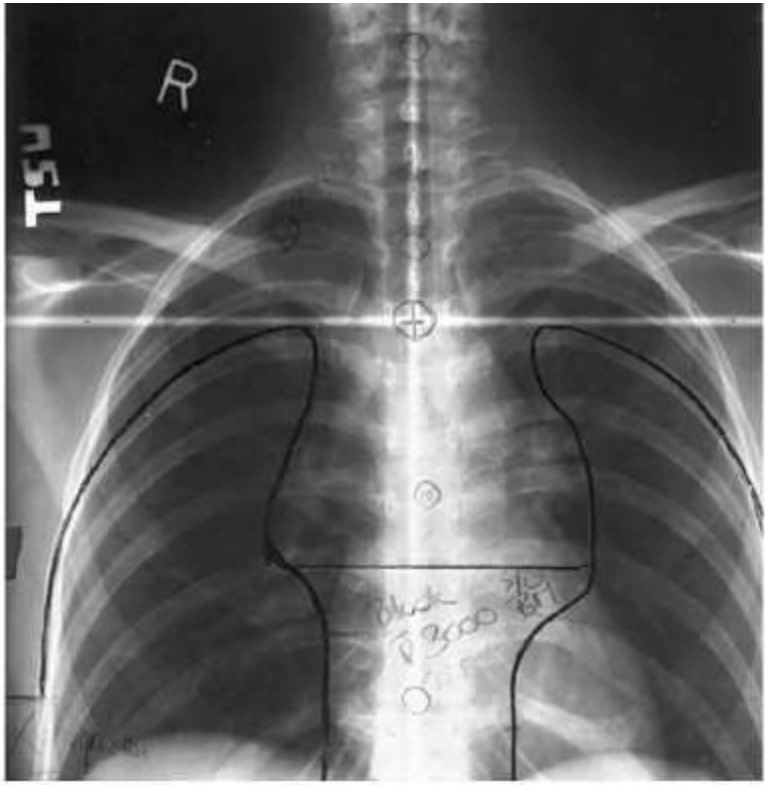
- Adaptation of the chemotherapy



- RT-field size adaption
- Dose reduction
- Avoidance of RT

Subtotal Nodal Irradiation – The Mantle Field

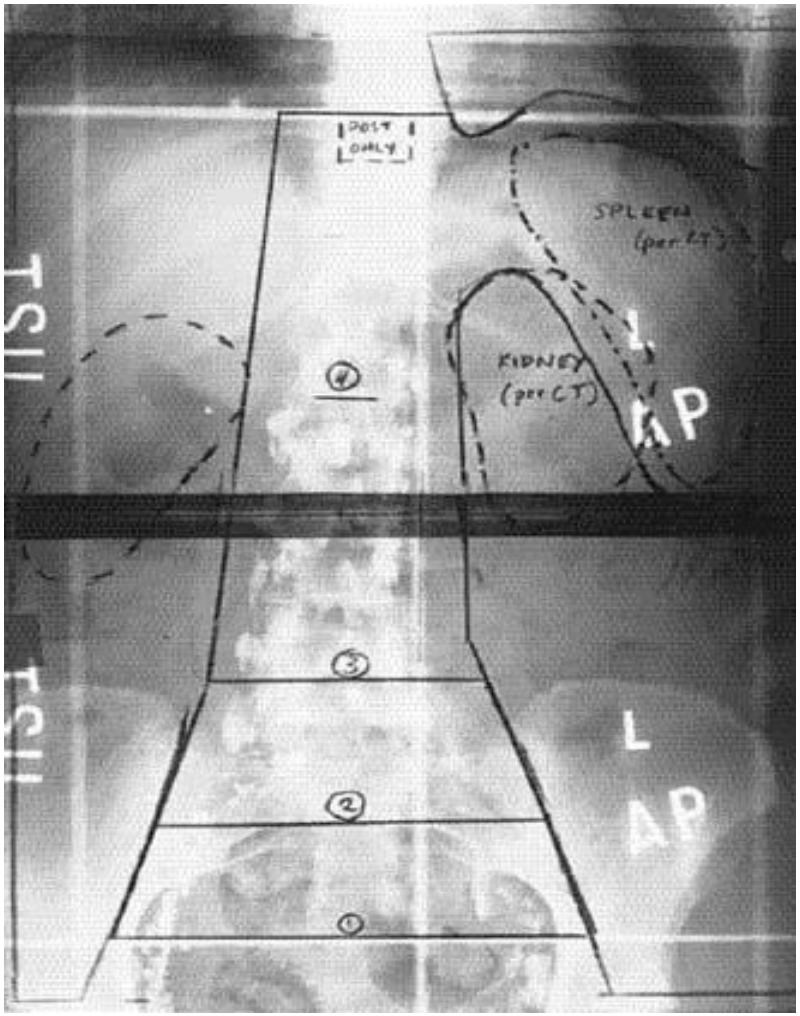
- The classic mantle includes all of the major lymph node regions above the diaphragm.
- Individually contoured lung blocks are designed to conform to the patient's anatomy and tumor distribution.



Source: *Principles & Practice of Radiation Oncology* (4th Edition)

Subtotal Nodal Irradiation

- The classic subdiaphragmatic irradiation field for HD is the inverted-Y, which includes the retroperitoneal and pelvic lymph nodes and spleen

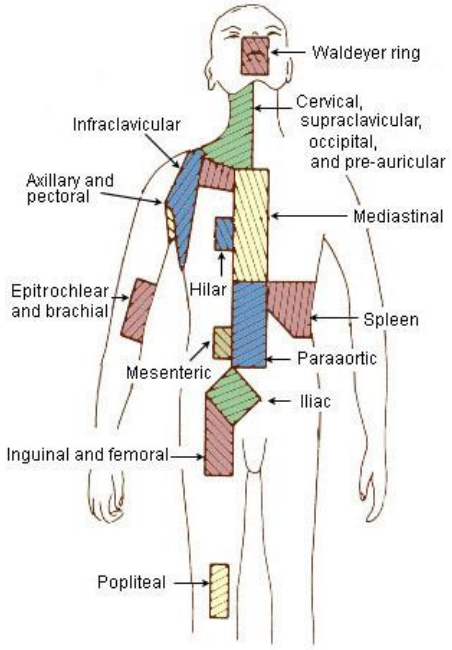


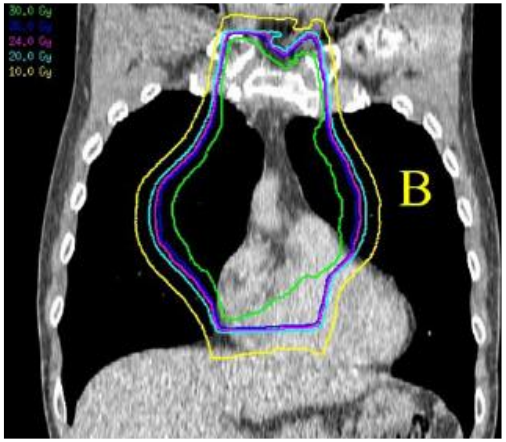
Source: *Principles & Practice of Radiation Oncology* (4th Edition)

Classical Involved Field

- **PTV** : ***prechemotherapy*** Tu Extension
  involved lymph node regions
  - Based on 2D Lymphnode description

- NO **GTV**
- NO **CTV**





Involved Node

- First proposed by **Girinsky T. 2006**
  - Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: concepts and guidelines;

    Girinsky T. et at.; Radiother Oncol. 2006 Jun;79(3):270-7)
- Radiation of primary involved lymph node **after chemotherapy**
  - Currently Adult Hodgkin Trials (EORTC/GELA-H10; GHSG HD-17)

Involved Node concept EORTC

Initially involved cervical and axillary lymph nodes ***in PR***:

- **GTV**: lymph node remnant(s) alone
- **CTV**: the initial volume of the LN before CT
- **CTV-PTV margin**: 1cm isotopic margin

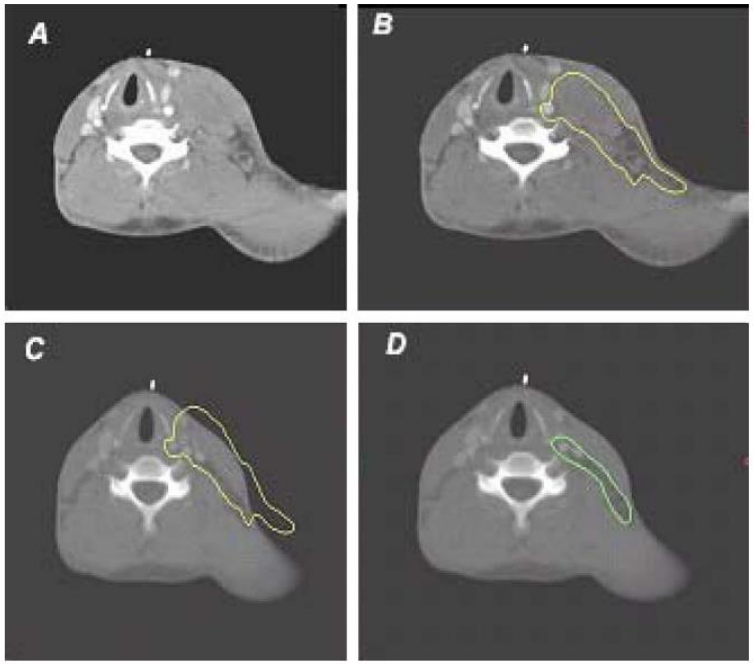


Fig. 1. Clinical target contouring (CTV) of a cervical tumor mass in complete remission (CR) after chemotherapy. (A) Prechemotherapy axial CT scan. (B) Contouring of the initial tumor volume (yellow color). (C) Initial tumor volume superimposed on the postchemotherapy axial CT (yellow color). (D) Adequate CTV contouring taking into account the initial tumor volume on the postchemotherapy axial CT (green color).

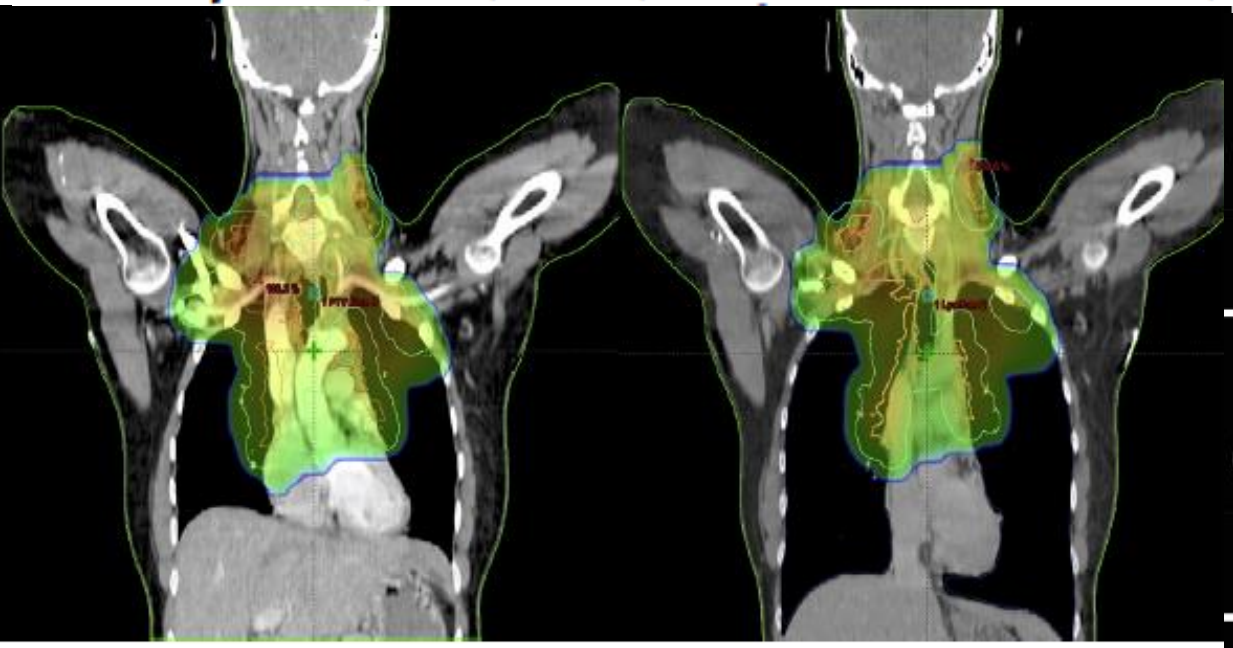
Involved node concept EORTC

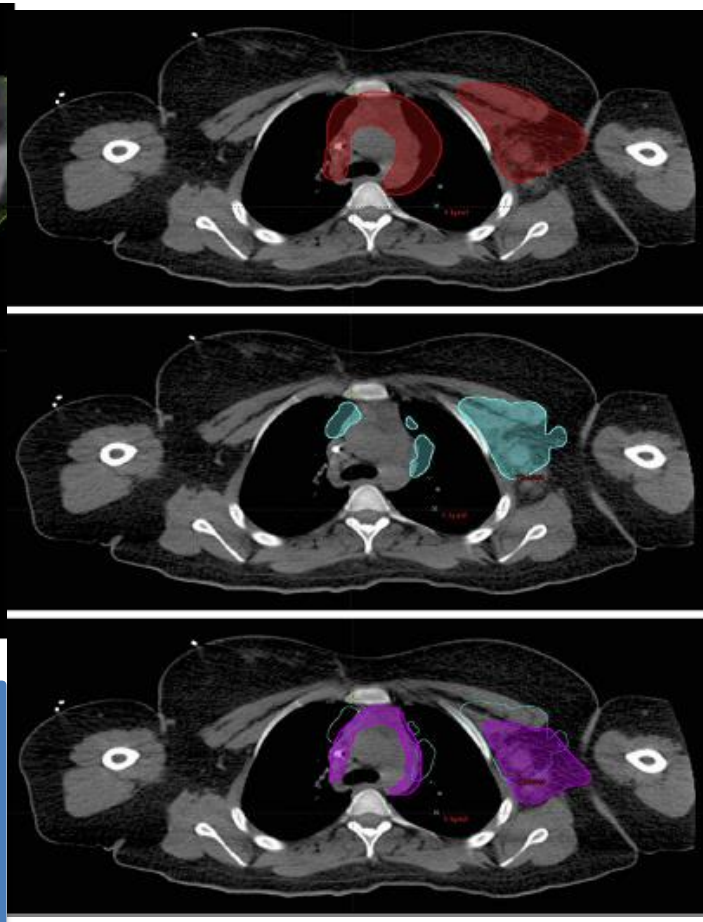
Initially involved mediastinal area ***in PR***:

- **GTV**: lymph node remnant(s) or remaining mass alone
- **CTV**: encompassing ***volume of the mediastinal mass before*** chemotherapy ***according to post chemotherapy topography***
  - length of lymph nodes ***before*** CHT
  - Width of lymph nodes ***after*** CHT
  - displaced normal structure not included
  - not exceed lateral mediastinal borders
  - vessels not included (whenever possible)
- **CTV-PTV margin**: 1cm isotopic margin

Modern Radiation Therapy for Hodgkin Lymphoma: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group (ILROG)

Lena Specht, MD, PhD,* Joachim Yahalom, MD, on behalf of ILROG

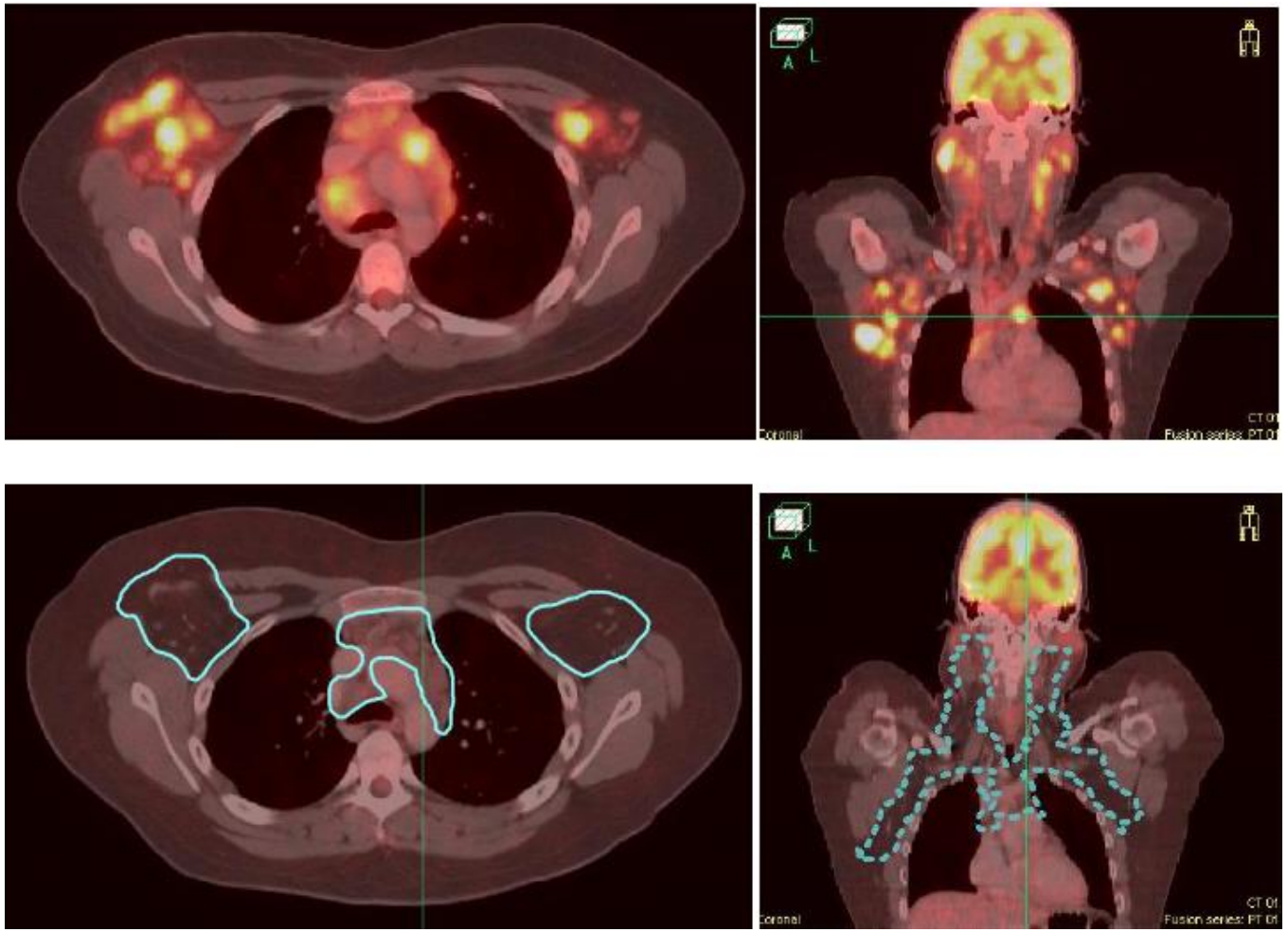




Involved Site Radiotherapy represents a significant reduction in the volume included in the previous used IFRT

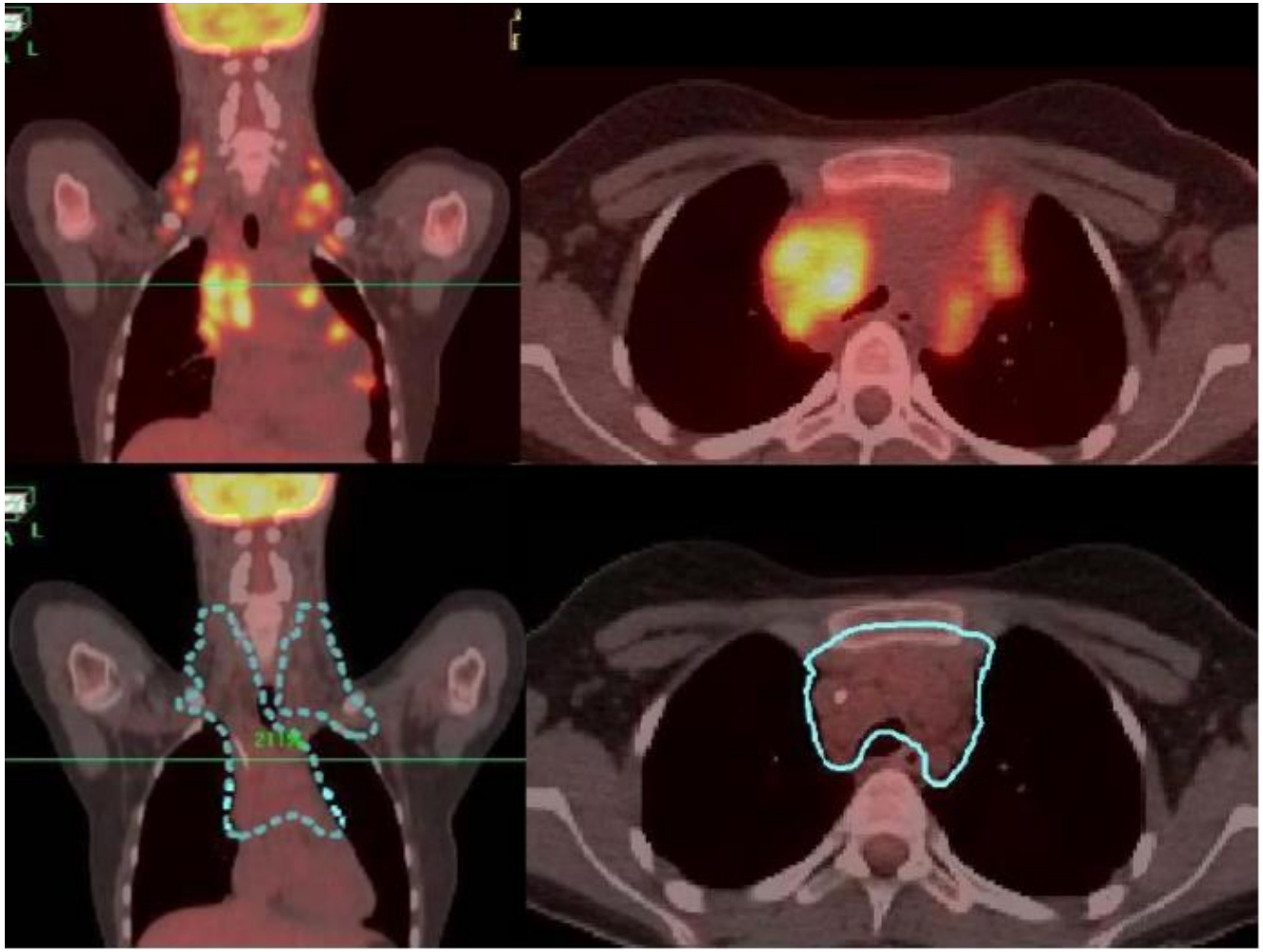
Int J Radiation Oncol Biol Phys, Vol. 89, No. 4, pp. 854–862, 2014

Involved side Irradiation



CTV: Primary tumor extension in CC 1-2 cm dir. adapted to the post chemotherapy anatomy plus 5 mm in lateral dir.

Involved side Irradiation



FULL-TEXT ARTICLE

Pract Radiat Oncol. 2015 Mar-Apr;5(2):85-92. doi: 10.1016/j.prro.2014.05.003. Epub 2014 Jul 9.

Implementation of contemporary radiation therapy planning concepts for pediatric Hodgkin lymphoma: Guidelines from the International Lymphoma Radiation Oncology Group.

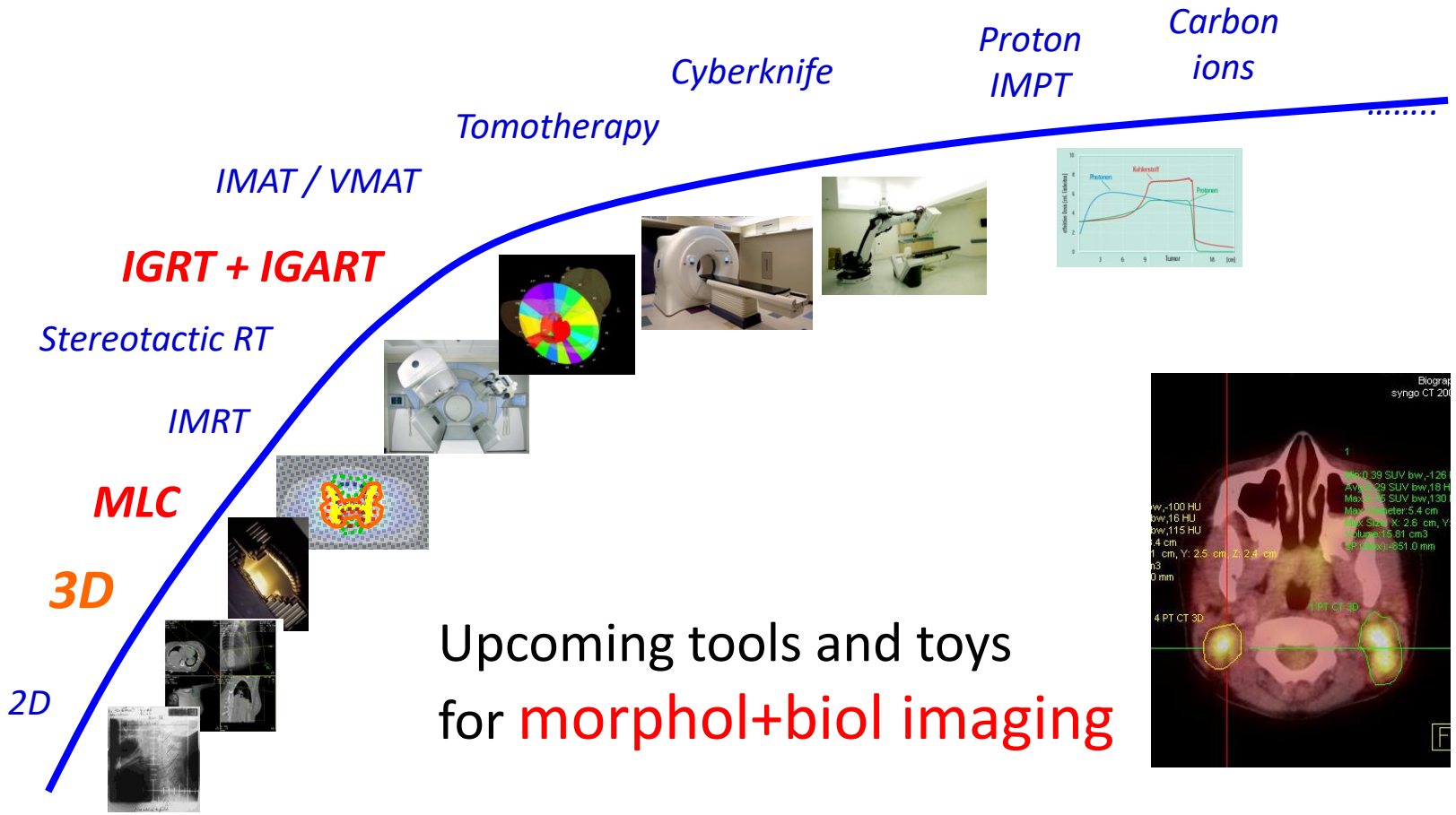
Hodgson DC[1], Dieckmann K[2], Terezakis S[3], Constine L[4]; International Lymphoma Radiation Oncology Group.

Author information

Abstract

The optimal management of children with **Hodgkin lymphoma** (HL) should limit the risk of treatment-related toxicity without compromising **disease** control. Consequently, increasing effort is being directed to retaining the demonstrated efficacy of **radiation therapy** (RT) in maximizing the cure of HL while reducing the **radiation** exposure of normal tissues. Historically, **guidelines** for RT volume definition used in **pediatric** HL trials have referenced 2-dimensional imaging and bony landmarks to define classical involved field RT. With recognition of the efficacy of chemotherapy, the data on the adverse late effects of **radiation**, and the evolution of advanced imaging techniques that reveal the location of both tumor and normal tissues, it is necessary that **radiation** techniques for children and adolescents be refined. The **concepts** described by the **International** Commission on **Radiation** Units provide a common approach for field definition using 3-dimensional computed tomographic--based RT **planning** and volumetric image guidance. Here we describe the application of these **concepts** in the **planning** of RT for **pediatric** HL. This will be increasingly important as current and upcoming **pediatric** HL trials will employ these **concepts** to deliver RT.

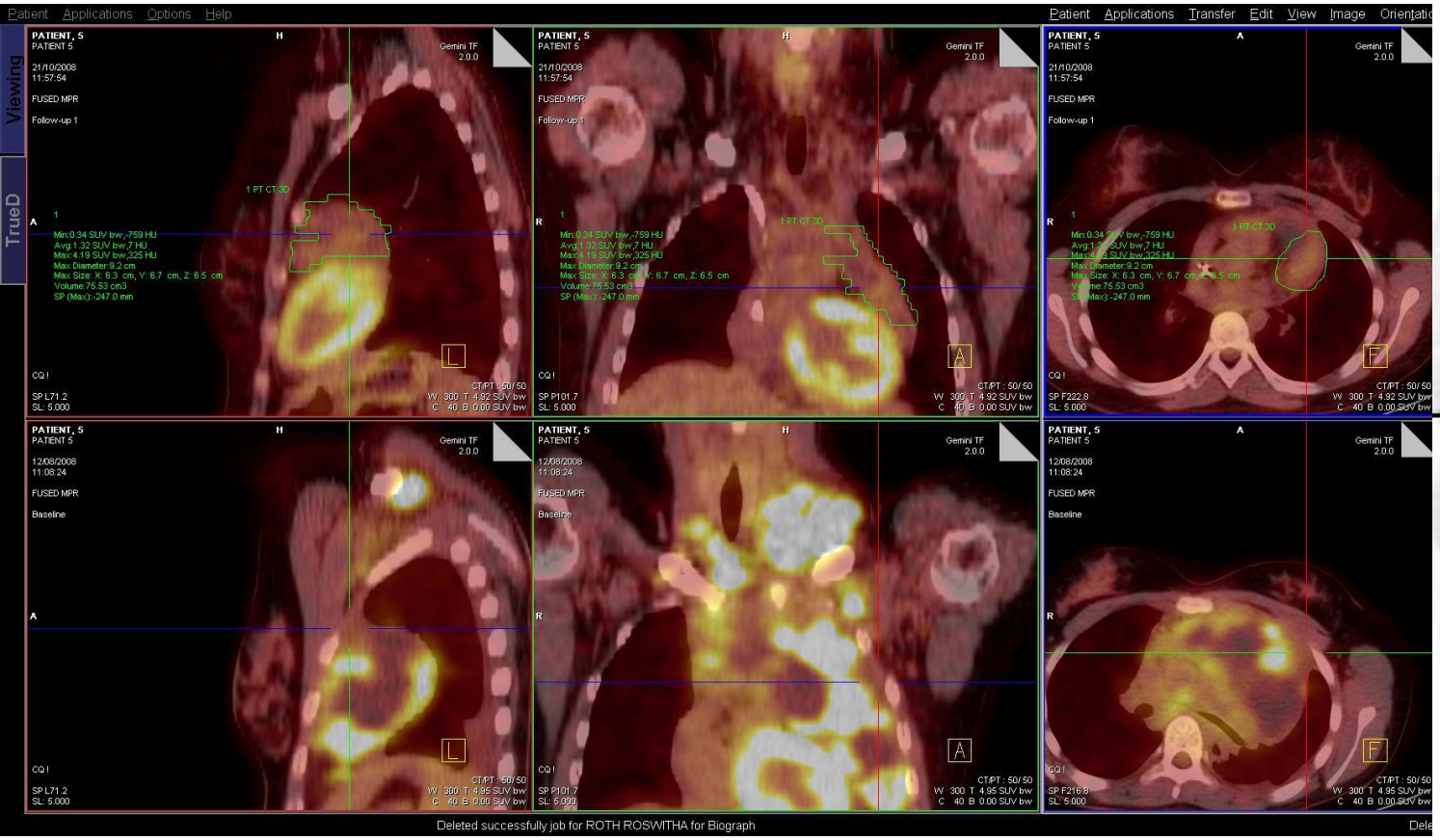
PROGRESS in Radiation Oncology

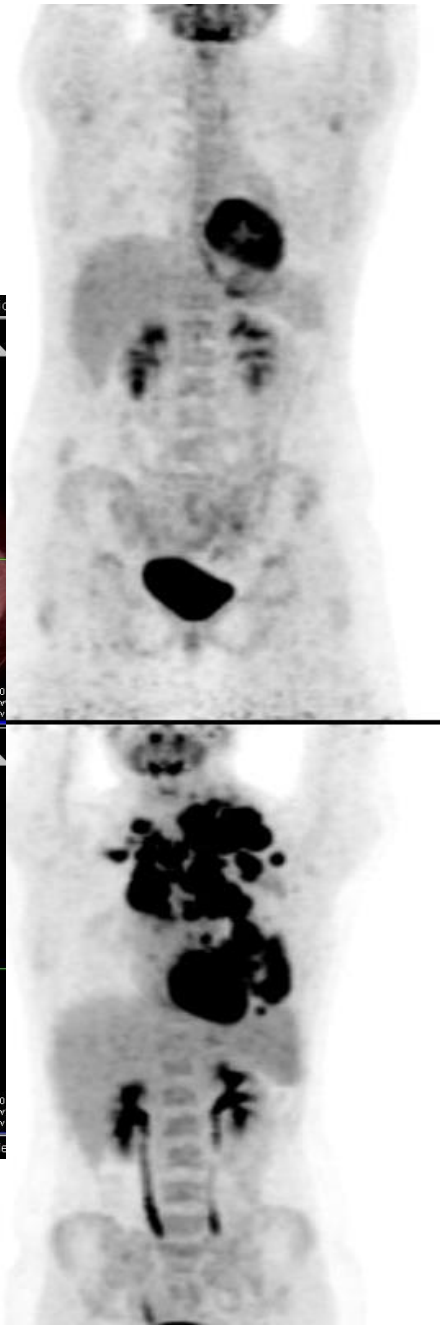


Upcoming tools and toys
for morphol+biol imaging

Advances in **imaging**, **treatment planning**, **treatment delivery**, have made it possible **to better define** and further **decrease RT volumes** in may situation

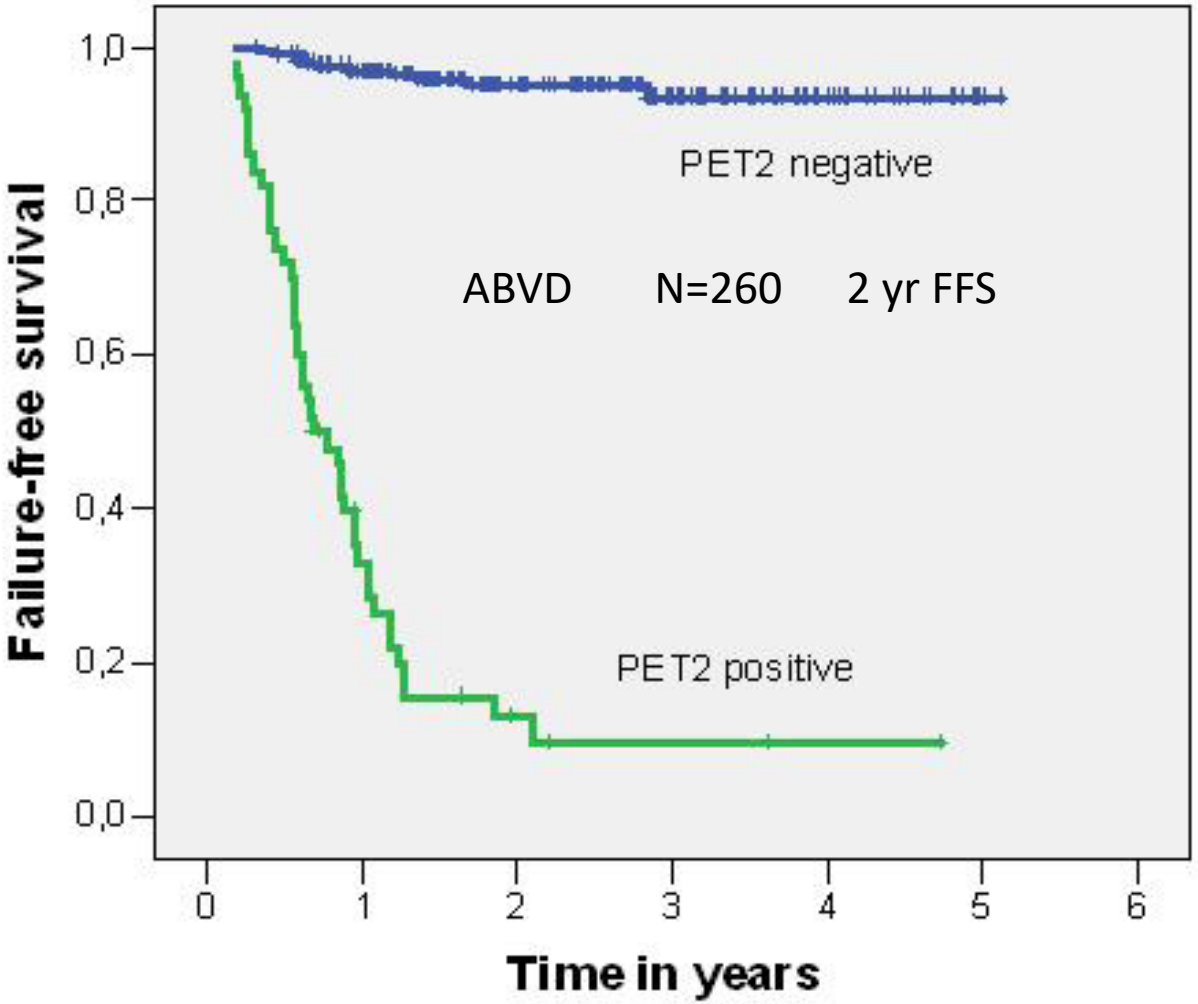
PET-CT after 2 cycles of chemotherapy





PET –CT at time of diagnosis

Early Response Assessment after 2 Cycles ChT



Gallamini A, Hutchings M et al.: JCO 2007

Partridge	2000
Naumann	2004
Hutchings	2005
Gallamini	2010
Girinsky	2007
Itti	2013
Le Roux	2011

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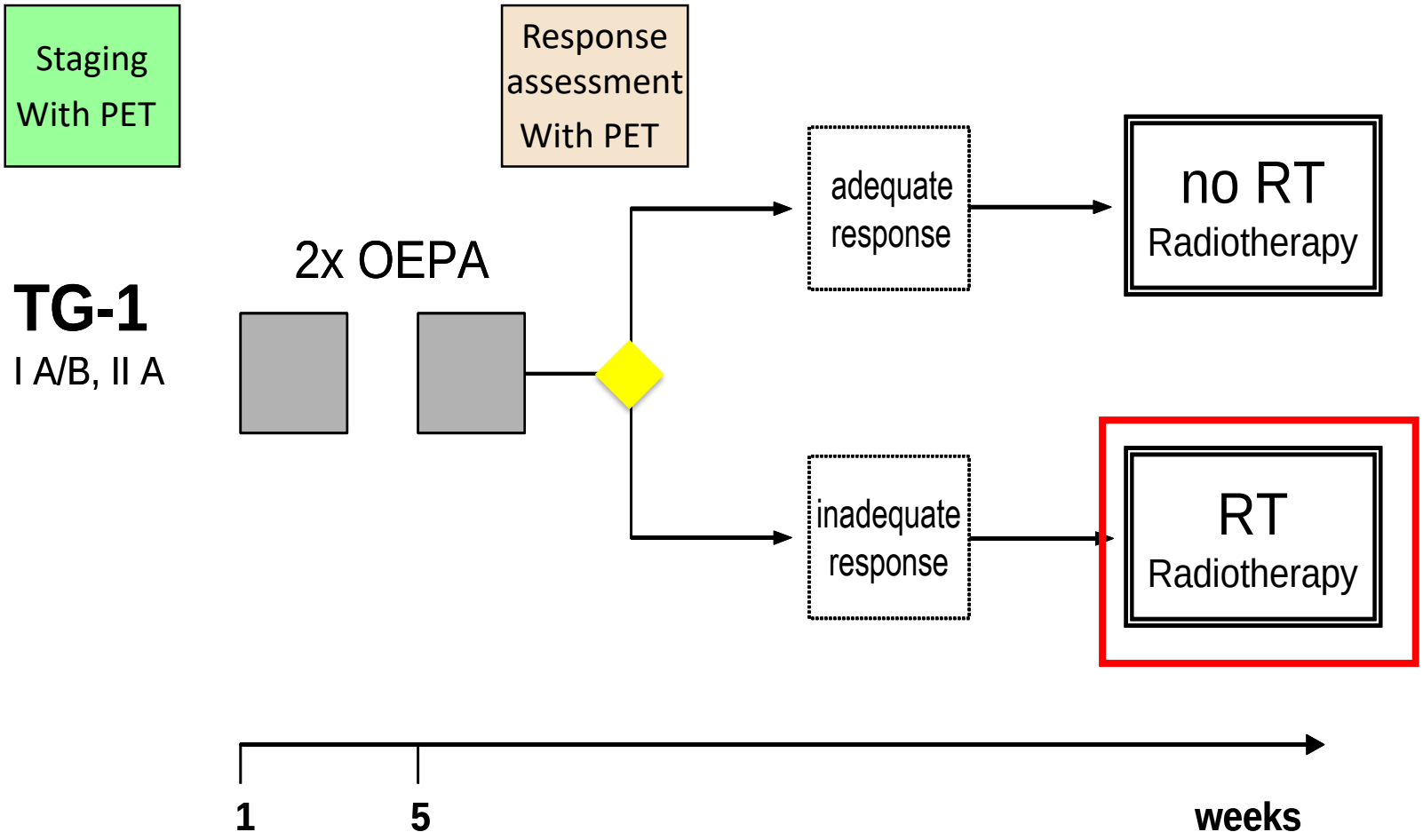
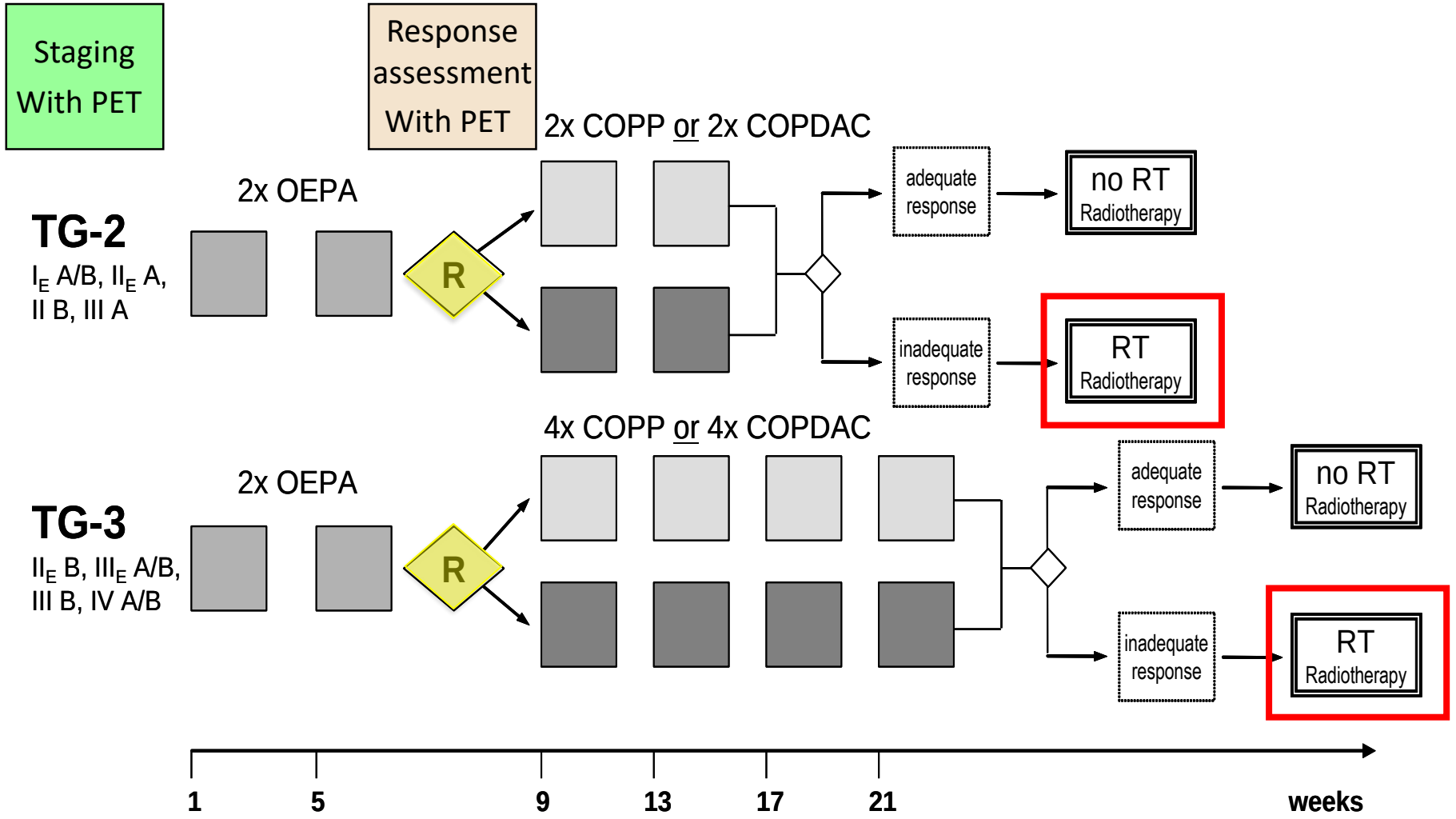
EuroNet-PHL-C1Study design to avoid RT

Radiotherapy TG – 1; low risk group



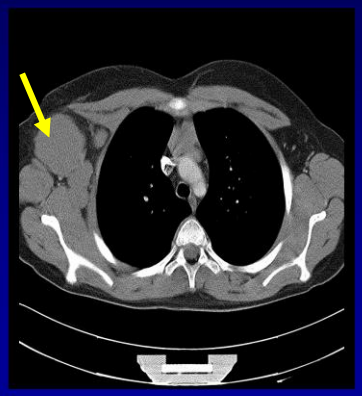
EuroNet-PHL-C1 study design

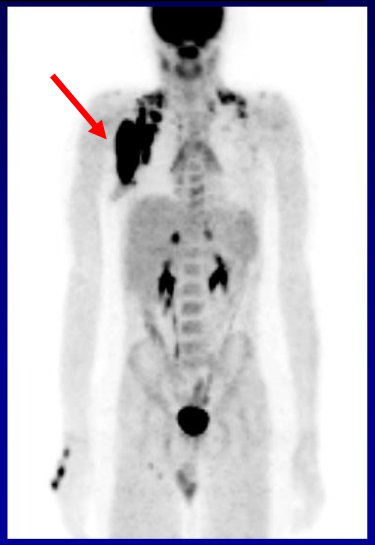
Radiotherapy TG – 2 / 3; intermediate and high risk



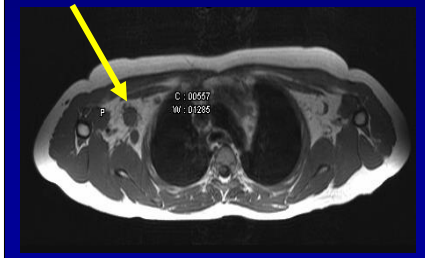
FDG-PET vs CT/MRI for response

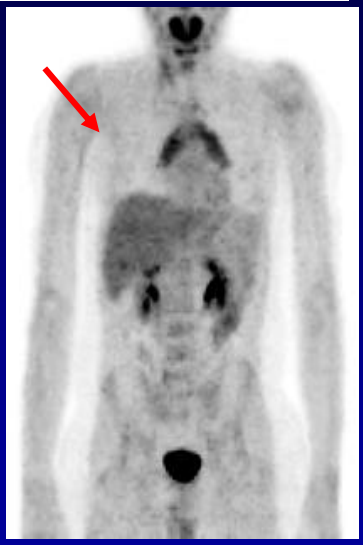
Patient with HL at presentation





Patient with HL after chemotherapy





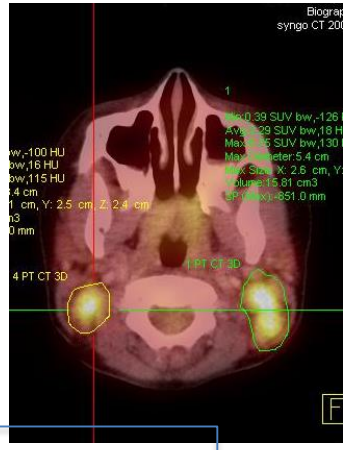
Introduction of PET-CT into Hodgkin`s staging

TG-1: 677
noRT: 418 (61.7%)
RT: 259 (38.3%)

TG-2 447
noRT: 216 (48.3%)
RT: 231 (51.7%)

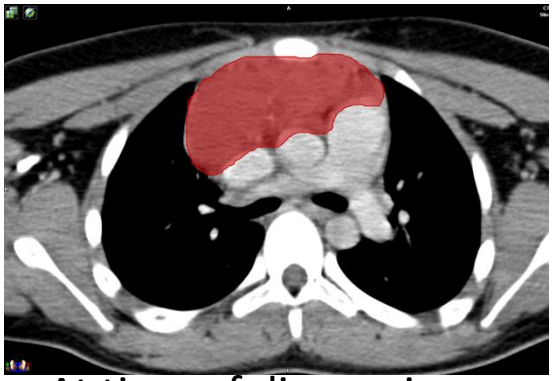
TG-3: 854
noRT: 281 (32.9%)
RT: 573 (67.1%)

- Multi Slice CTs
- morphol+biol imaging

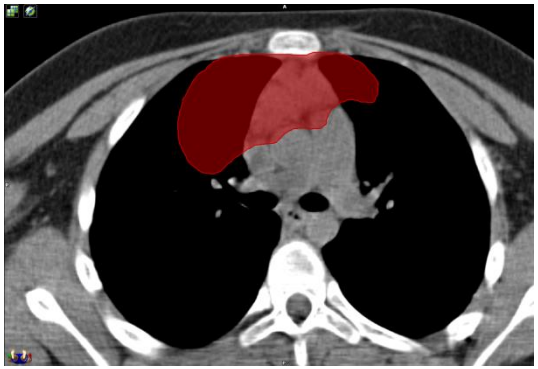


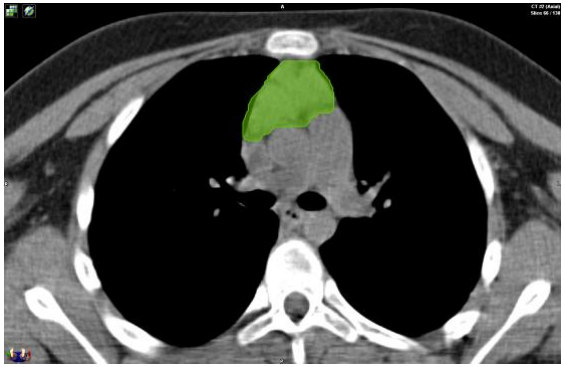
Radiotherapy could be avoided in about 50% of the patients

Target delineation adaptation to the post ChT tumor extension taking into account the primary extension

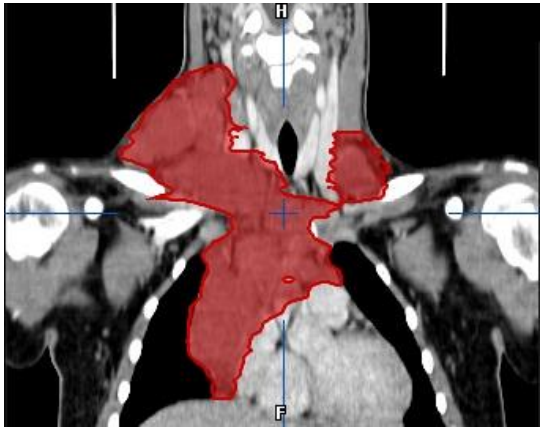


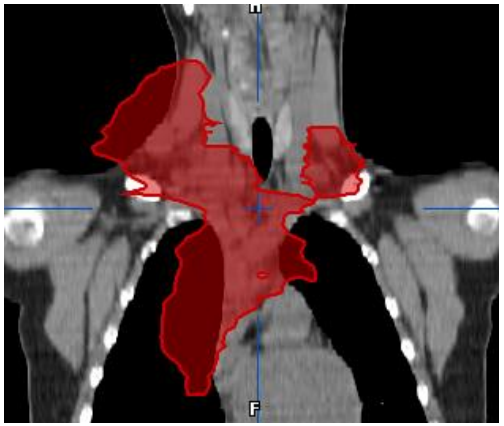
At time of diagnosis

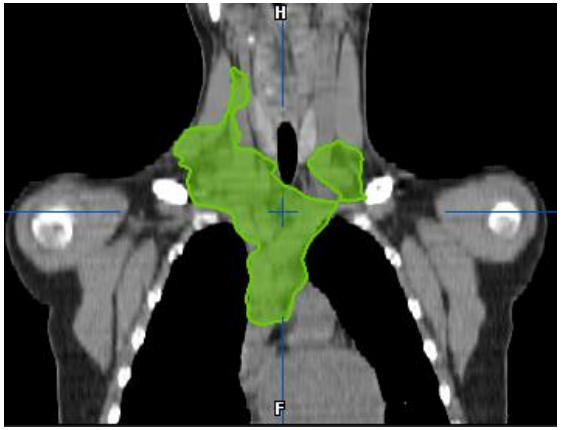




post chemoadaptation to the mediastinal structures

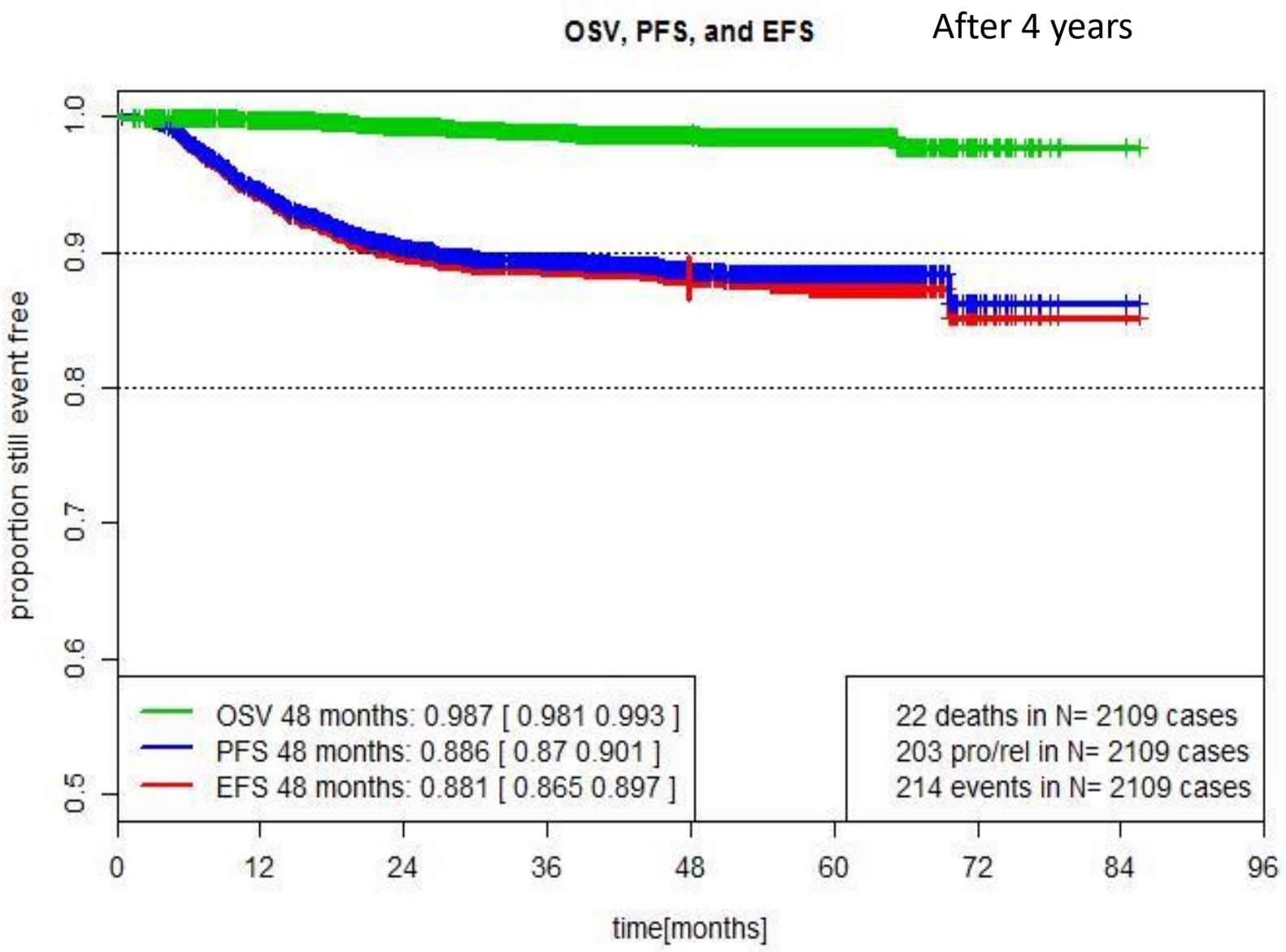






Reduction of Dose and Volume at the organs at risk

Overall Survival and Event free Survival



After 4 years

OSF 99%

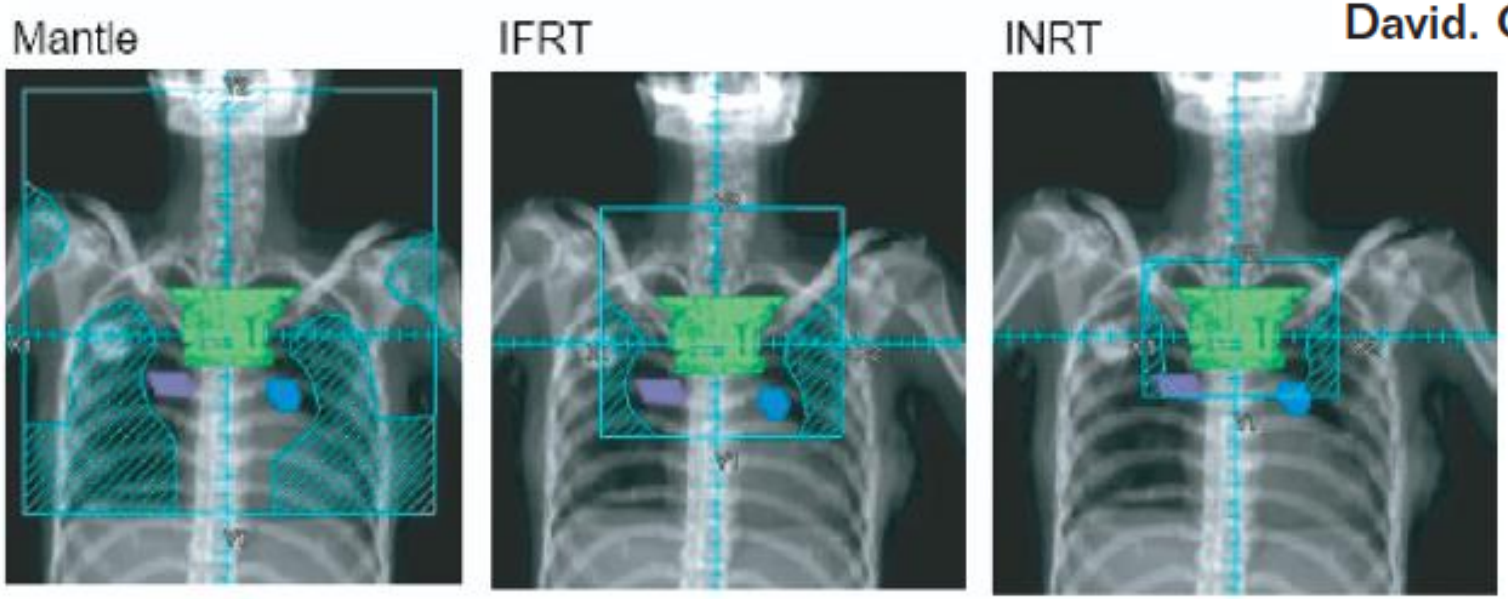
PFS 89%

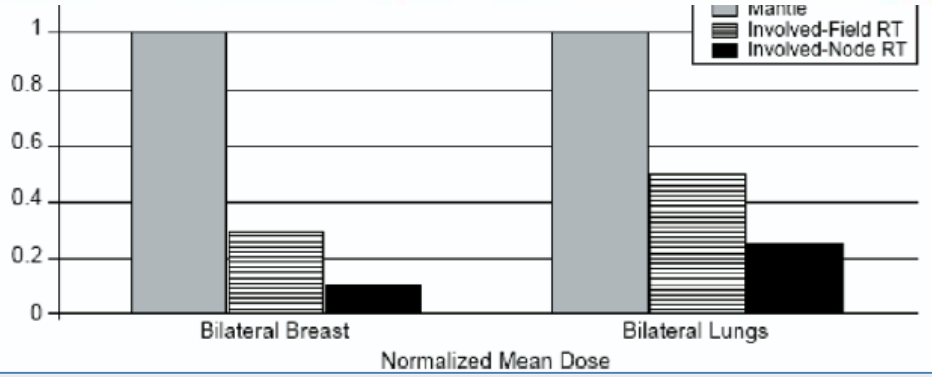
EFS 88%

by courtesy Dr. Dirk Hasenclever

Pediatric Hodgkin Lymphoma: Maximizing Efficacy and Minimizing Toxicity

David. C. Hodgson





More than 50% Volume Reduction at breast and lung changing from extended field to involved field to involved node RT

Semin Radiat Oncol 17:230-242 © 2007

A Comparative Evaluation of Normal Tissue Doses for Patients Receiving Radiation Therapy for Hodgkin Lymphoma on the Childhood Cancer Survivor Study and Recent Children's Oncology Group Trials

Rachel Zhou, MRT(T), HBSc,* Angela Ng, MEd, MRT(T),*
Louis S. Constine, MD,† Marilyn Stovall, PhD,‡
Gregory T. Armstrong, MD, MSCE,§ Joseph P. Neglia, MD, MPH,‖
Debra L. Friedman, MD,¶ Kara Kelly, MD,#
Thomas J. FitzGerald, MD,**,†† and David C. Hodgson, MD, MPH‡‡

Change in dose and volume :

1970-1986; 50HL/761 HL;

CCSS 40Gy (20.0-57.9Gy) more extended field/appa

2002-2009; 68 HL pts; AHOD 0031 15-25 Gy involved field/involved site

2009-2012; 123 HL pts; COG AHOD 15-25Gy Involved field/involved site

Int J Radiation Oncol Biol Phys, Vol. 95, No. 2, pp. 707–711, 2016

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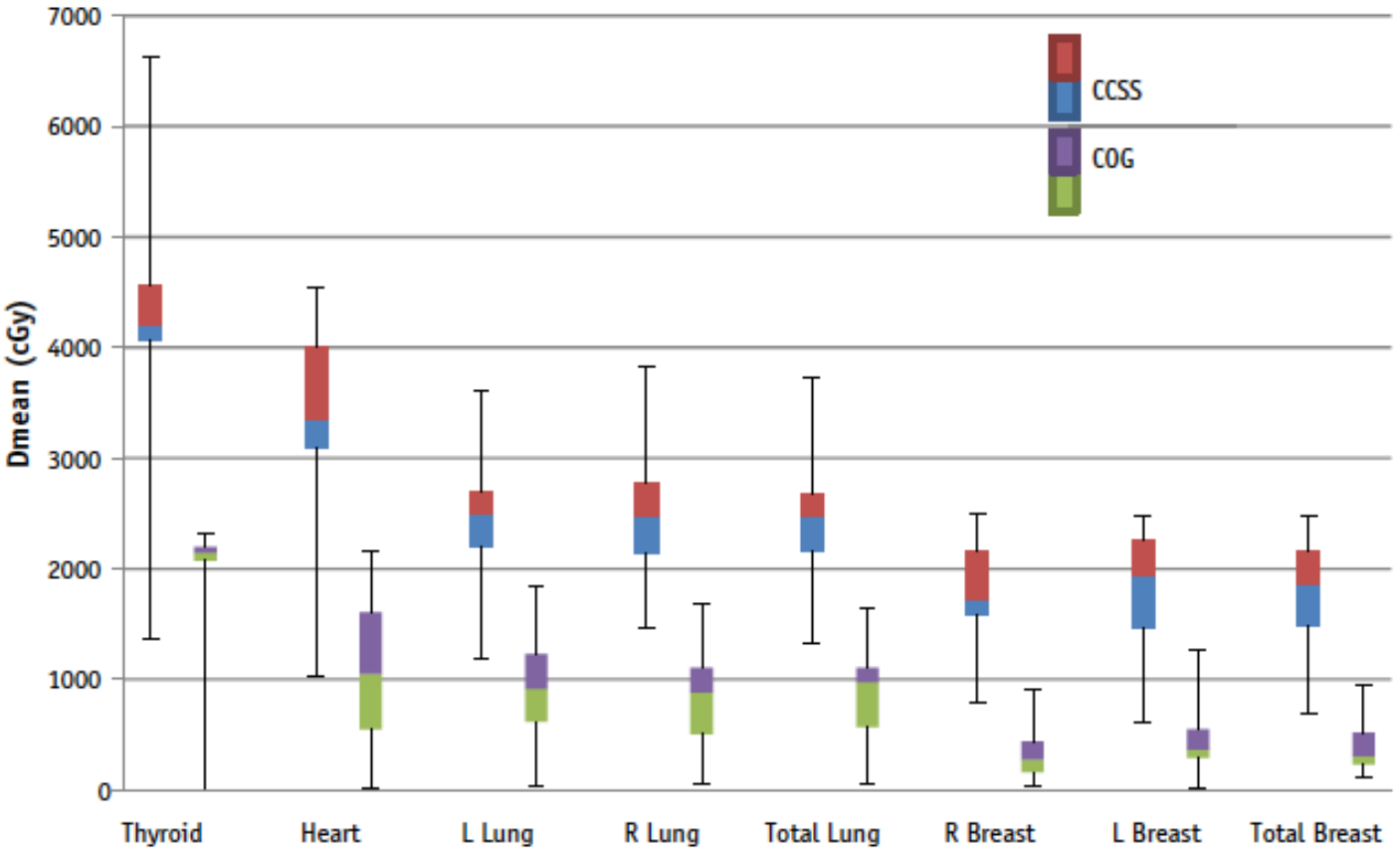
Early stages of Hodgkin´s Disease



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Early stages of Hodgkin´s Disease

	COG relative Dose reduct.	COG absolute Dose reduct.	V5 Volume CCSS	V5 Volume COG	Mean dose reduction at OAR Influence Volume vs dose
breast	83.5%	15.5Gy	61%	17%	40% smaller volumes
heart	68.6%	22.9 Gy	99%	61%	24% smaller volumes
lung	61.0%	15.0 Gy			12% smaller volumes
thyroid	49.0%	20.7 Gy			Dose reduction

The influence of a lower prescription dose versus a smaller treatment varies and depend on the tissue and disease stage

- Breast profits most from smaller **irradiated volume**

Int J Radiation Oncol Biol Phys, Vol. 95, No. 2, pp. 707–711, 2016

A Comparative Evaluation of Normal Tissue Doses for Patients Receiving Radiation Therapy for Hodgkin Lymphoma on the Childhood Cancer Survivor Study and Recent Children's Oncology Group Trials

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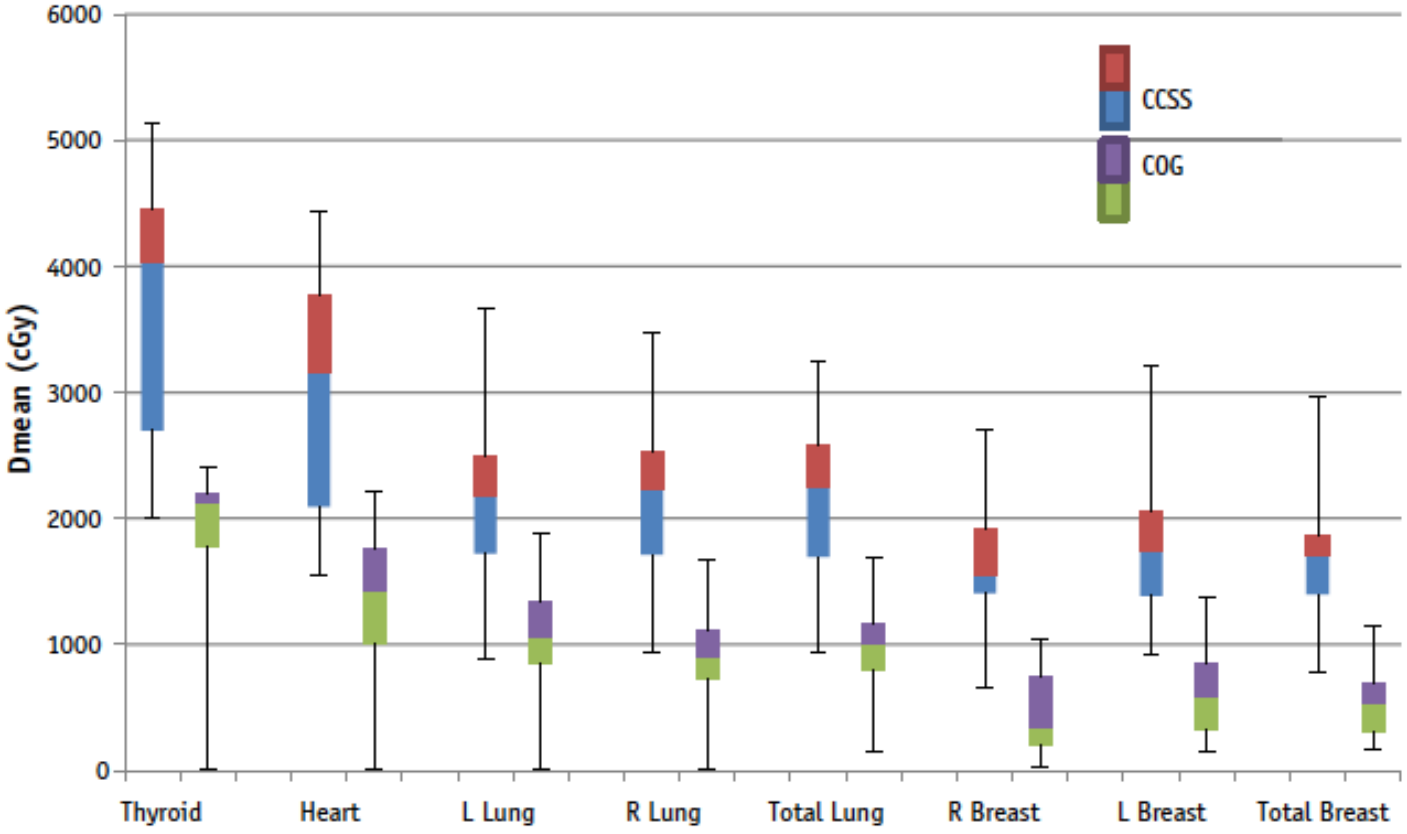
Debra L. Friedman, MD,¶ Kara Kelly, MD,#
Thomas J. FitzGerald, MD,**,†† and David C. Hodgson, MD, MPH‡‡

Advanced Stages of Hodgkin`s disease



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Advanced Stages of Hodgkin`s disease

	COG relative Dose reduct.	COG absolute Dose reduct.	V5 Volume CCSS	V5 COG	Mean dose reduction at OAR Influence Volume vs dose
breast	70.0%	11.6 Gy	59%	28%	27% smaller volume
heart	55.1%	17.4 Gy	99%	75%	9% smaller volume
lung	51.0%	11.1 Gy			2% smaller volume
thyroid	47.2%	19.0 Gy			Dose reduction

Advanced stage do not profit as much as early stages from Volume reduction Extended field vs Involved -side

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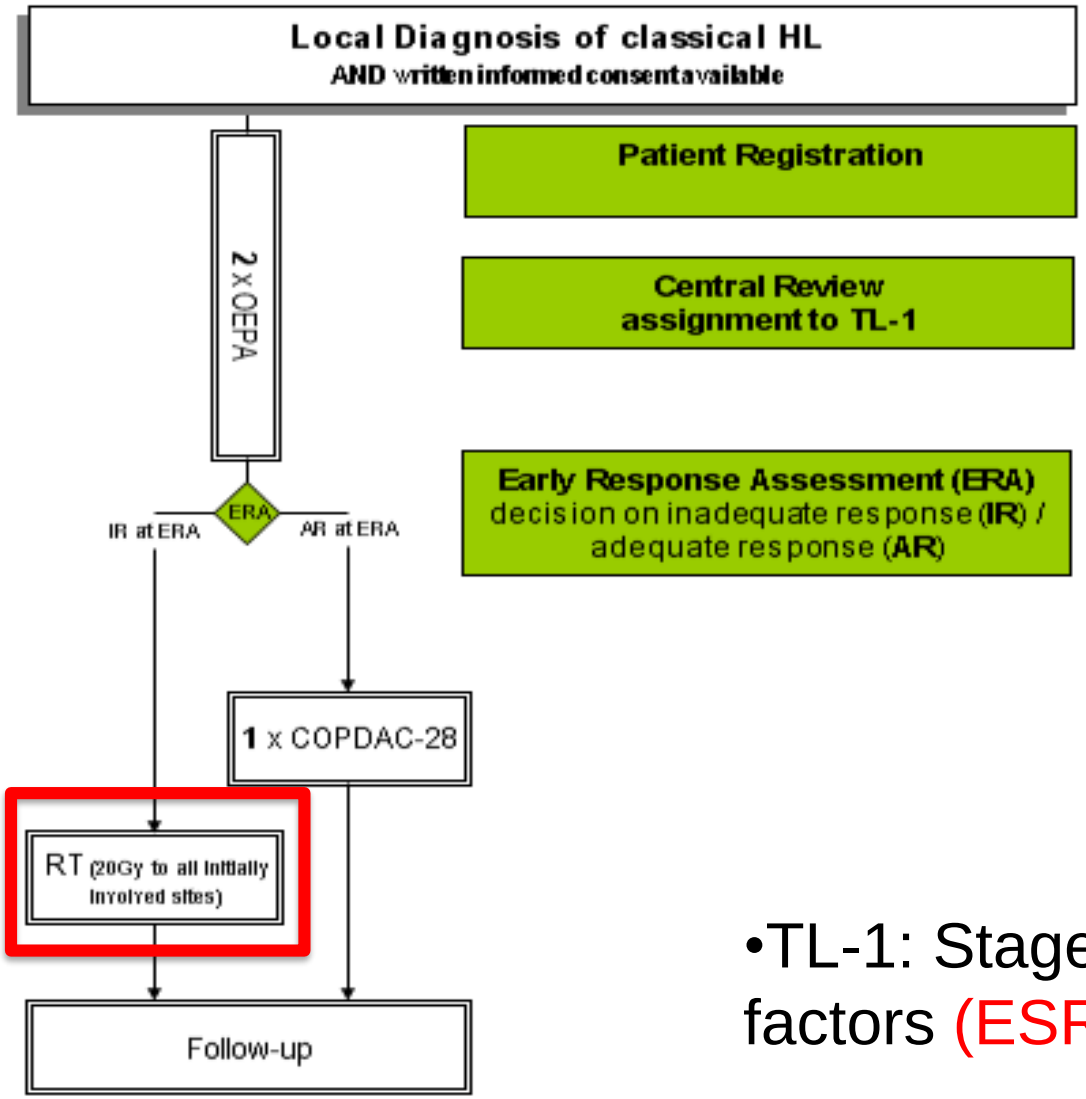
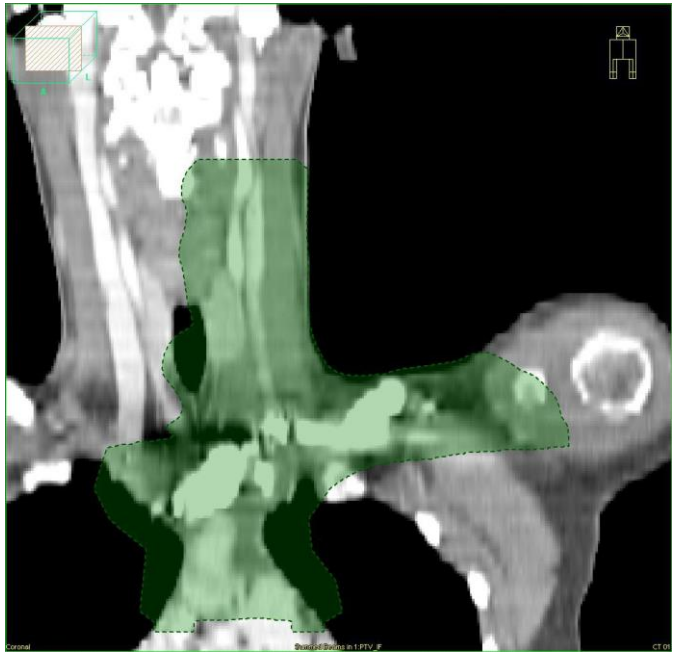
EuroNetPHL-C2 Study low risk

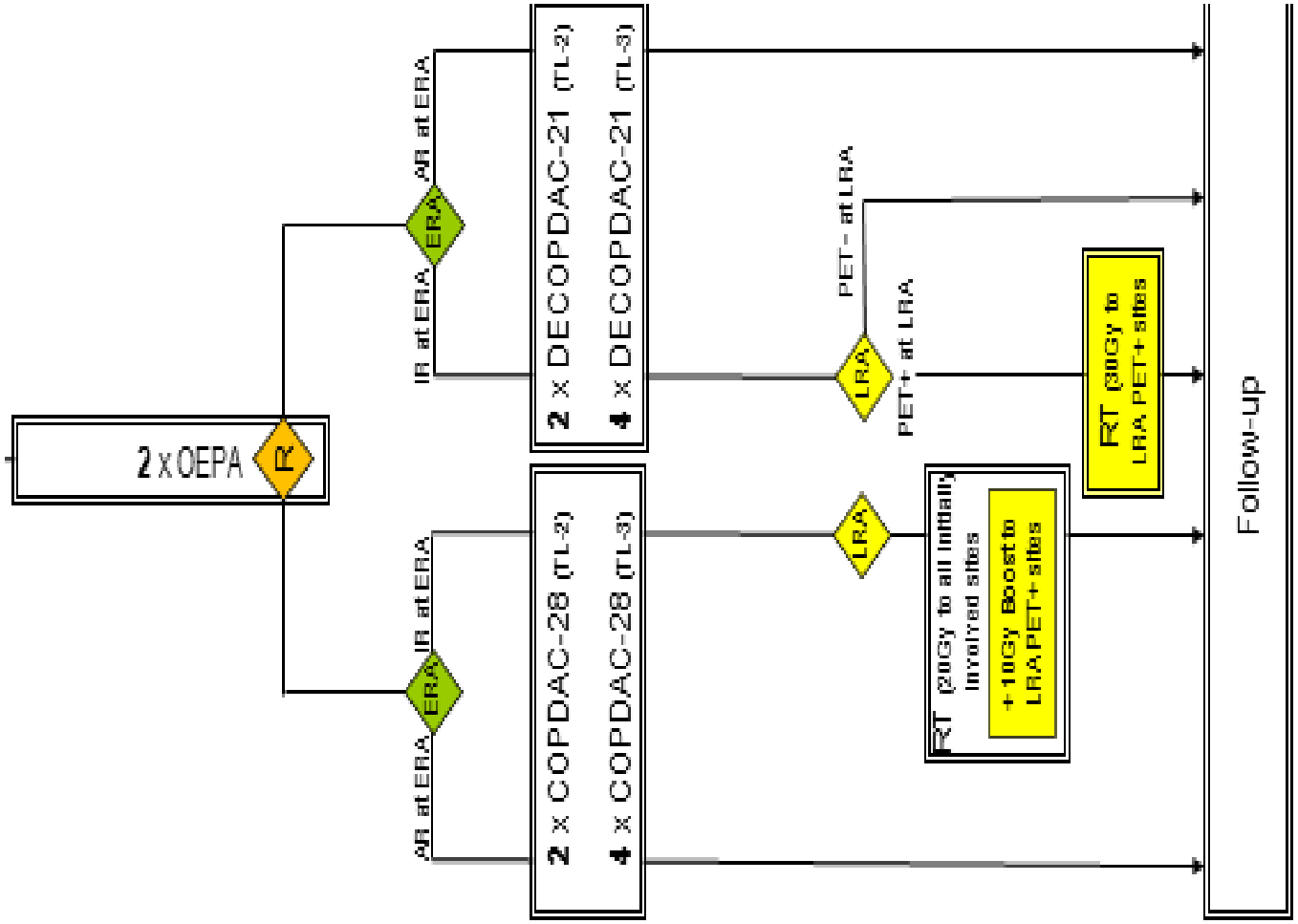




•TL-1: Stage I and IIA without risk factors (ESR, E-lesions, bulk)

Reduction of RT indications; =20% of the patients will get RT

EuroNet-PHL C2 intermediate and high risk



DEACOPDAC 21

PET(+) LRA:

PET(+)Involved LN

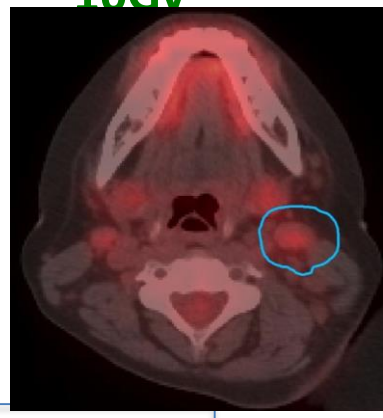
Dose 30Gy

Standard Arm:

Involved site 20 Gy

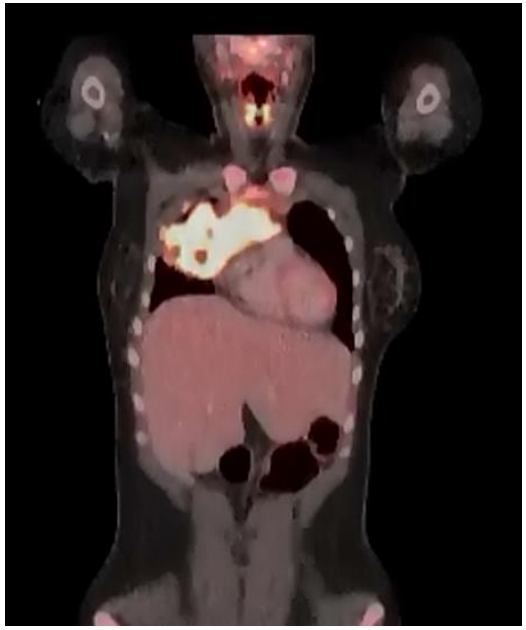
PET(+) LN in LRA:

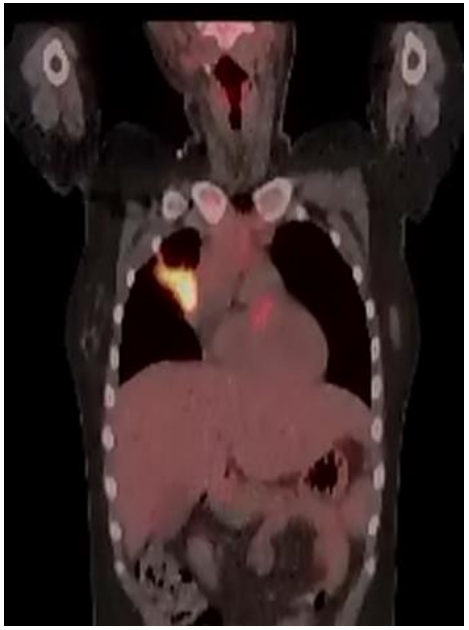
Involved LN boost 10Gy

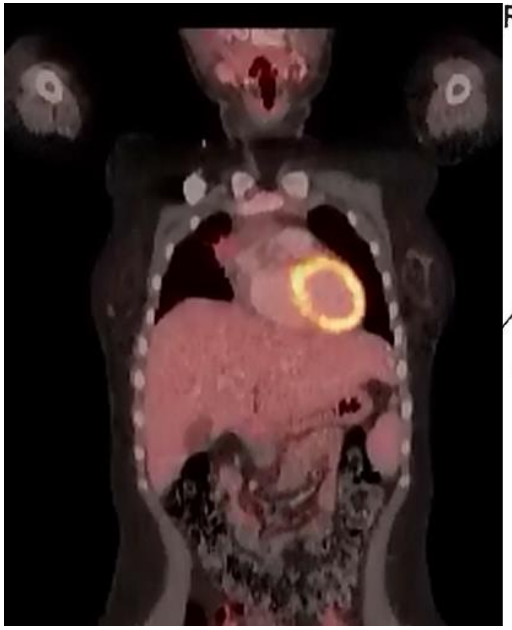


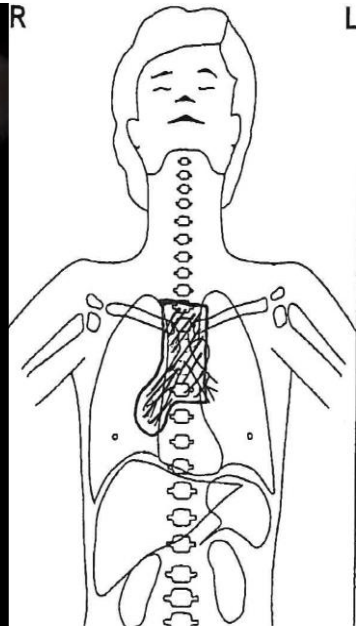
- RT Volume Reduction in 50% of the irradiated patients

Treatment proposal according to the EuroNet PHL C2 Study
TL2: Stage I and IIB with risk factors







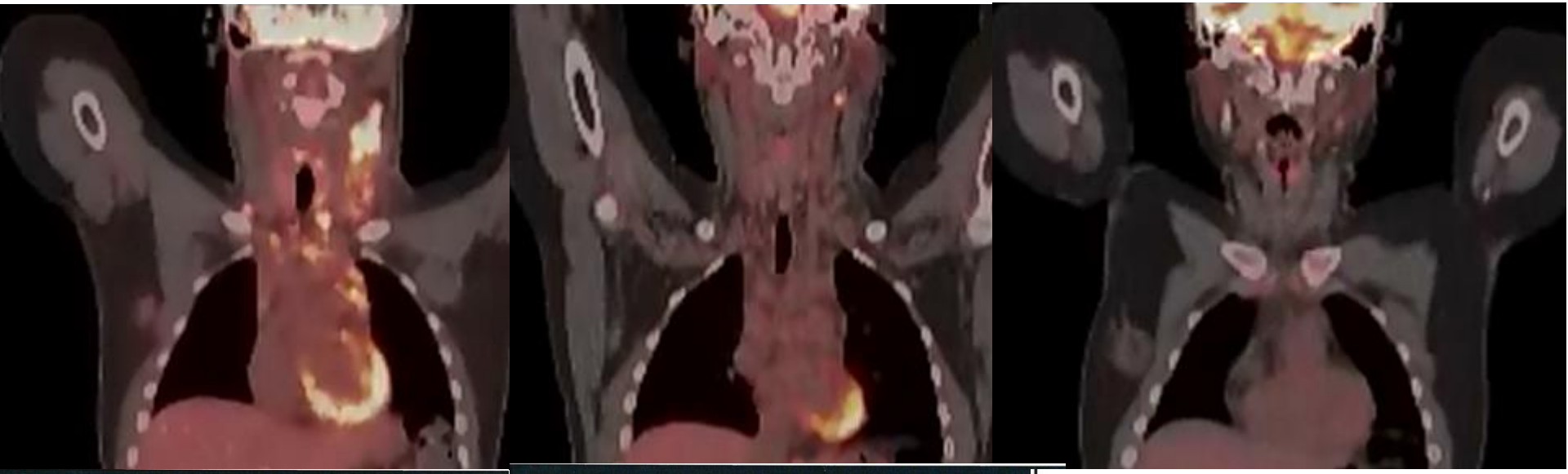


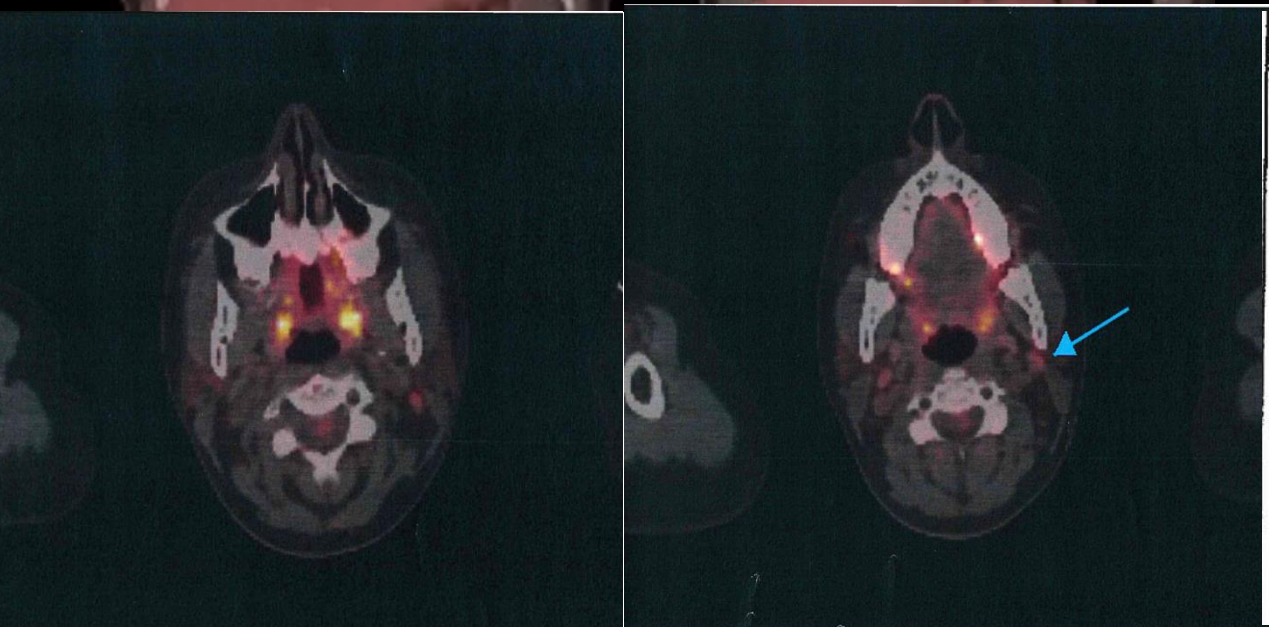
At time of diagnosis ERA LRA

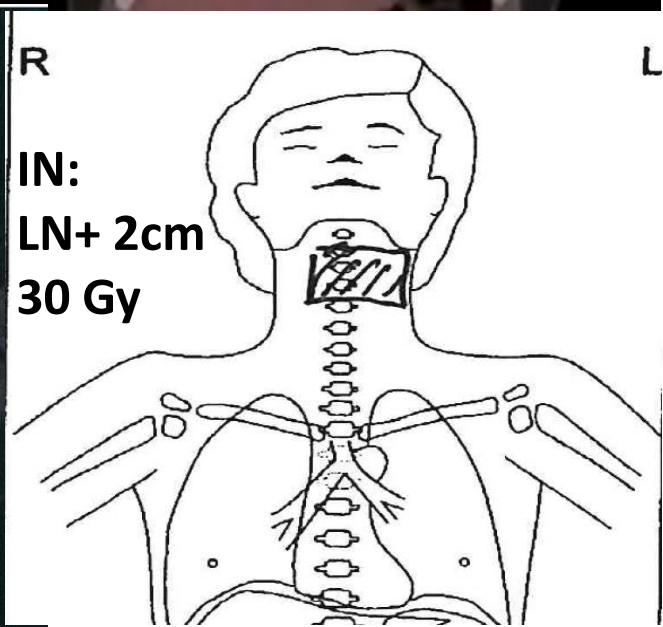
2x OEPA
2x COPDAC-28
ERA PET positive → primary Tumor extension without boost

Treatment proposal according to the EuroNet PHL C2 Study

TL2: Stage IIA with risk factors; 2 OEPA plus DEACOPDAC 21;





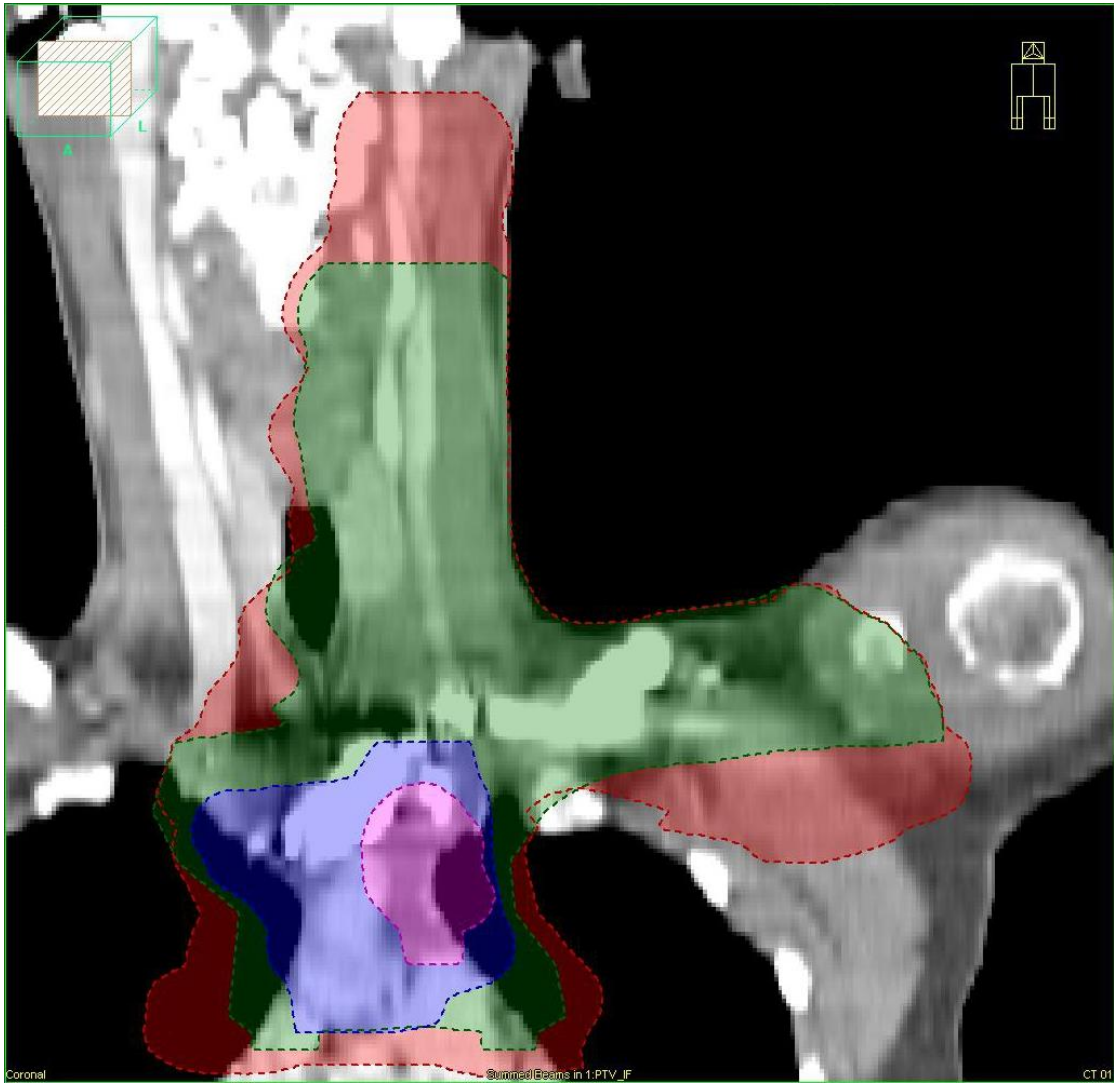


Change of RT Volumes according to Chemotherapy response

Involved field RT

Involved site RT

LRA PET positive LN



Patterns of Failure After Involved Field Radiation Therapy for Pediatric and Young Adult Hodgkin Lymphoma

Minh-Phuong Huynh-Le, Stephanie A. Terezakis, MD[1]

Background. Involved field radiation therapy (IFRT) is integral in curative therapy for Hodgkin lymphoma (HL), although primarily used in patients with intermediate/high-risk HL. We present failure patterns and clinical outcomes in a cohort of pediatric and young adult patients with HL treated with IFRT at the Johns Hopkins Hospital. ***Procedure.*** Patients ≤40 years old with intermediate/high-risk HL who received chemotherapy and IFRT from 1997 to 2012 were included in this retrospective analysis. Patients were evaluated for failure patterns, overall survival (OS), and event-free survival (EFS) using Kaplan–Meier curves, descriptive statistics, and Cox proportional hazard regressions. ***Results.*** We reviewed 74 patients (45 pediatric and 29 young adult) with a median follow-up of 4.4 years. The mean age at diagnosis was 21.4 years. Patients received a median of 29.75 Gy of IFRT (range 15–39.6 Gy). The majority of pediatric patients received ABVE-PC chemotherapy (n = 25) and <30 Gy of radiation (n = 33) while most young adults received ABVD chemotherapy (n = 24) and ≥30 Gy (n = 25). Estimated 5-year OS and EFS were 96% and 81%, respectively. Thirteen patients had recurrence; eight were pediatric. Distant relapse alone comprised 83% of failures in patients receiving ≥30 Gy. Of the seven patients who received <30 Gy and had recurrence, six had local failure as a component of their recurrence. Caucasian race ($P = 0.02$) and nodular sclerosing histology ($P = 0.01$) predicted for increased EFS. Late effects were minimal and all deaths (n = 4) were from HL. ***Conclusions.*** In this series, pediatric and young adult patients were treated with differing chemoradiation and had distinct recurrence patterns. Pediatr Blood Cancer 2014;61:1210–1214.

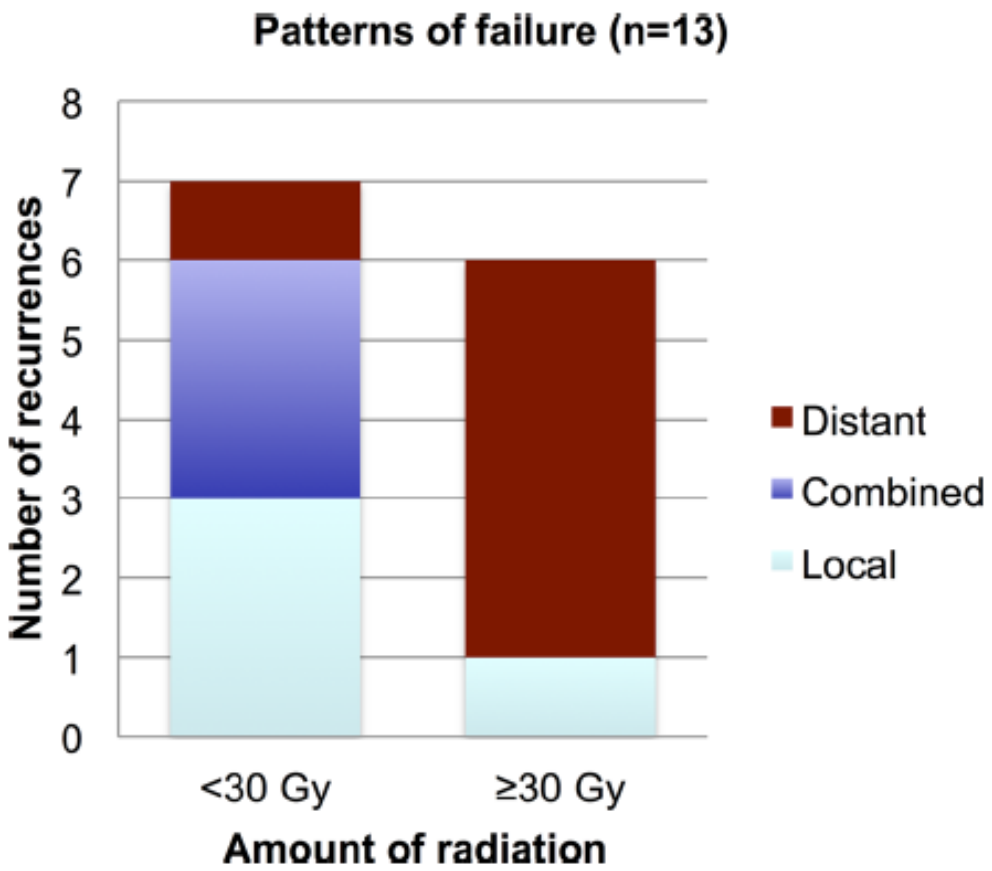
TABLE I. Demographic and Clinical Characteristics

	All patients (n = 74)	Pediatric (n = 45)	Young adult (n = 29)
Age at diagnosis (y)			
Mean	21.4	15.2	31.2
Range	4.1–39.9	4.1–20.6	22.6–39.9
Male (n, %)	43 (58%)	30 (67%)	13 (45%)
Clinical staging (n, %)			
II	46 (62%)	22 (49%)	24 (83%)
III	12 (16%)	10 (22%)	2 (7%)
IV	16 (22%)	13 (29%)	3 (10%)
"B" symptoms (n, %)	32 (43%)	20 (44%)	12 (41%)
Bulky disease (n, %)	20 (27%)	12 (27%)	8 (28%)
Chemotherapy (n, %)			
ABVD	28 (38%)	4 (9%)	24 (83%)
ABVE-PC	25 (34%)	25 (56%)	0 (0%)
Other	21 (28%)	16 (35%)	5 (17%)
Radiation therapy (n, %)			
Conventional	68 (92%)	41 (91%)	27 (93%)
3D-conformal	1 (1%)	0 (0%)	1 (3%)
Intensity modulated	1 (1%)	1 (2%)	0 (0%)
Unspecified	4 (6%)	3 (7%)	1 (3%)
Radiation doses (n, %)			
<30 Gy	37 (50%)	33 (73%)	4 (14%)
≥30 Gy	37 (50%)	12 (27%)	25 (86%)

Pediatr Blood Cancer 2014;61:1210–1214

Patterns of Failure After Involved Field Radiation Therapy for Pediatric and Young Adult Hodgkin Lymphoma

Stephanie A. Terezakis, MD[1];
Minh-Phuong Huynh-Le,



13/74 pts relapsed:

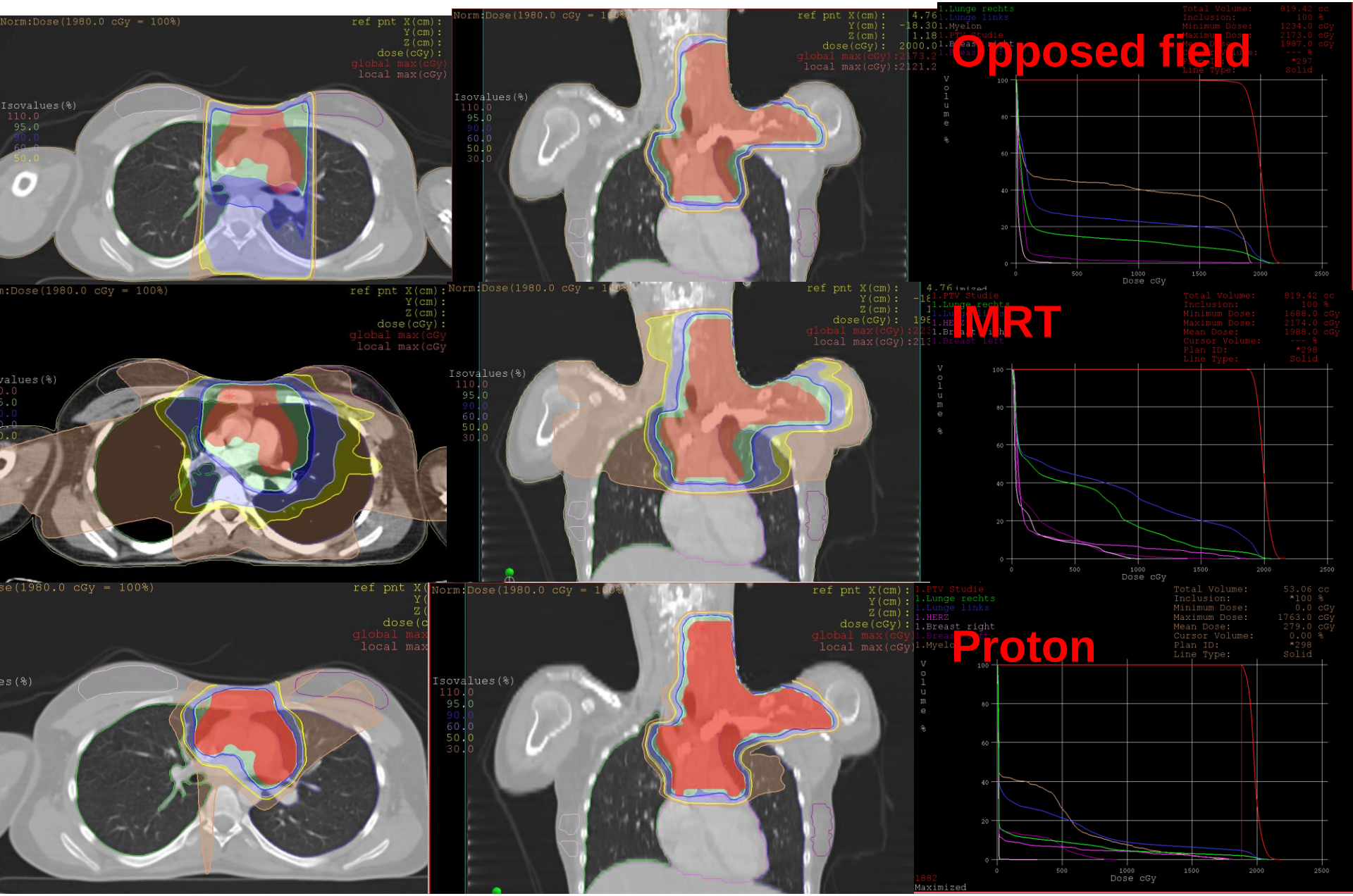
4 local
3 combined
6 distant

Patients with higher RT dose had less local relapses but they got less CT.

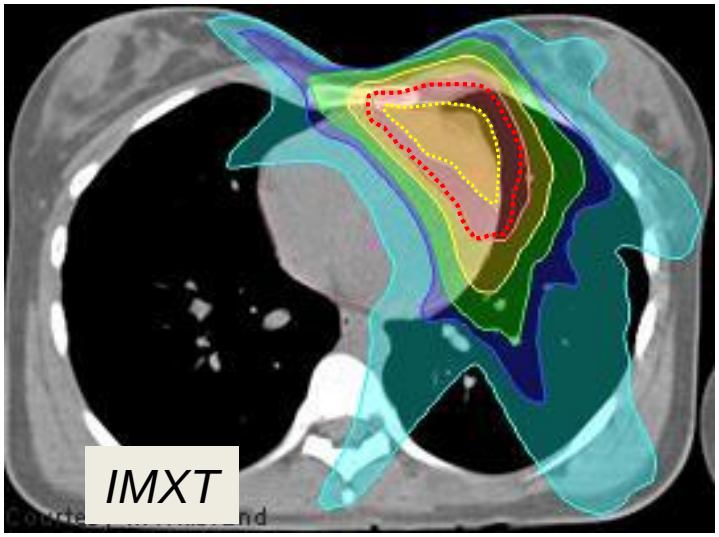
Balance between Chemo and Radiotherapy.

Pediatr Blood Cancer 2014;61:1210–1214

Research in Techniques and Energies



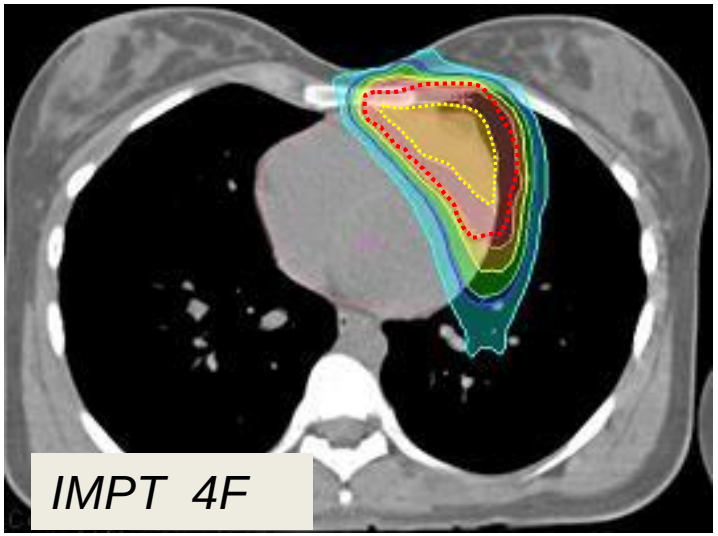
Planning studies for mediastinal Hodgkin Involvement

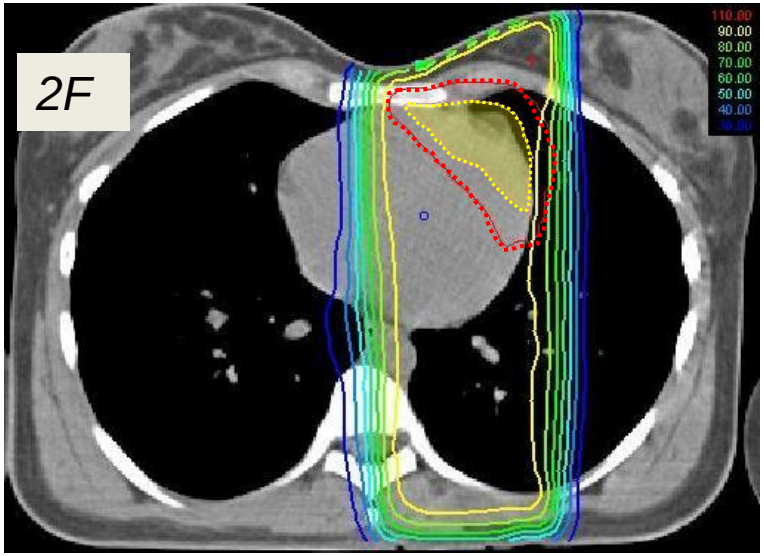


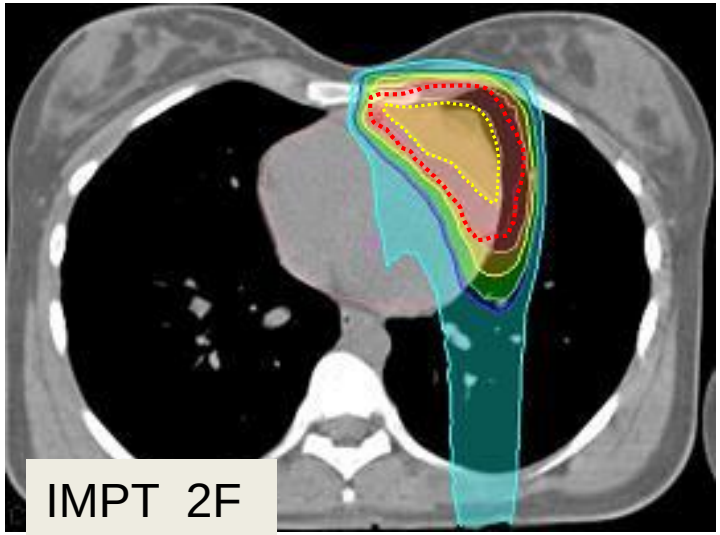
110%
95%
80%
70%
60%
50%
30%

CTV

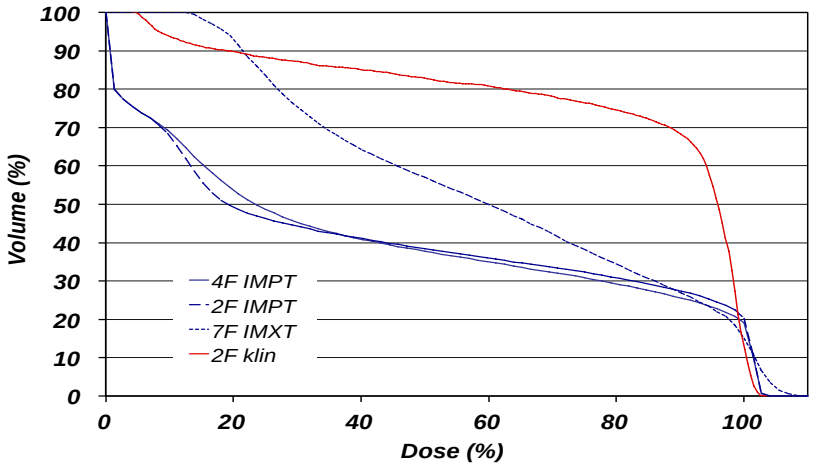
PTV



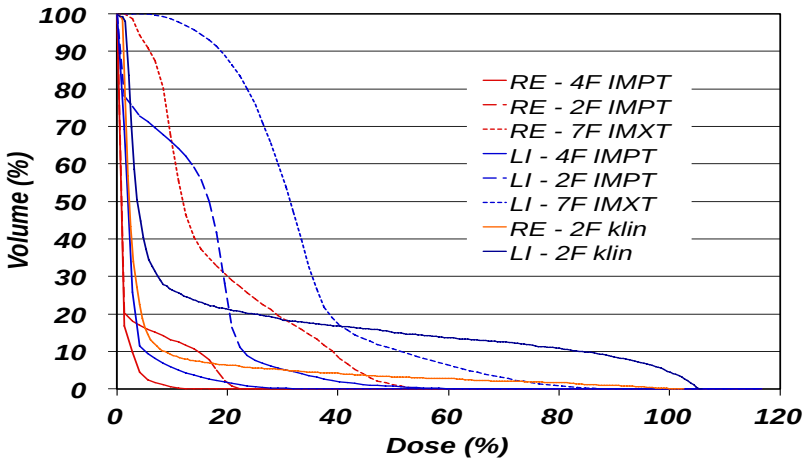




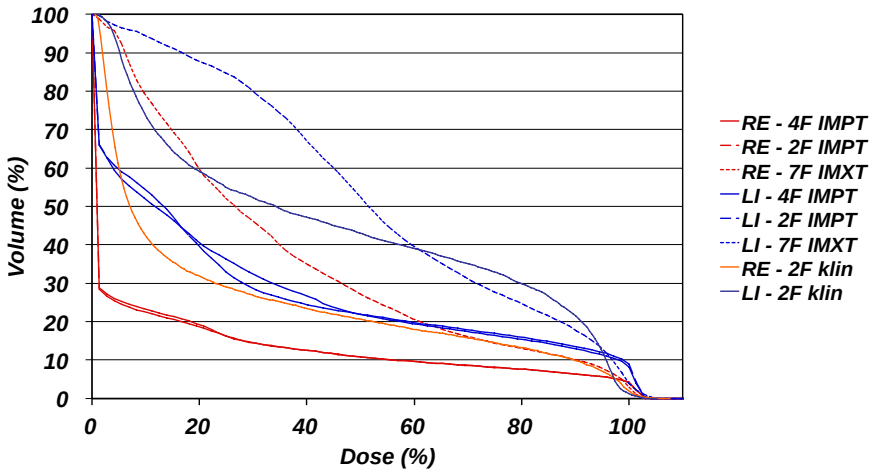
DVH parameter - Heart



DVH parameter – OAR breast

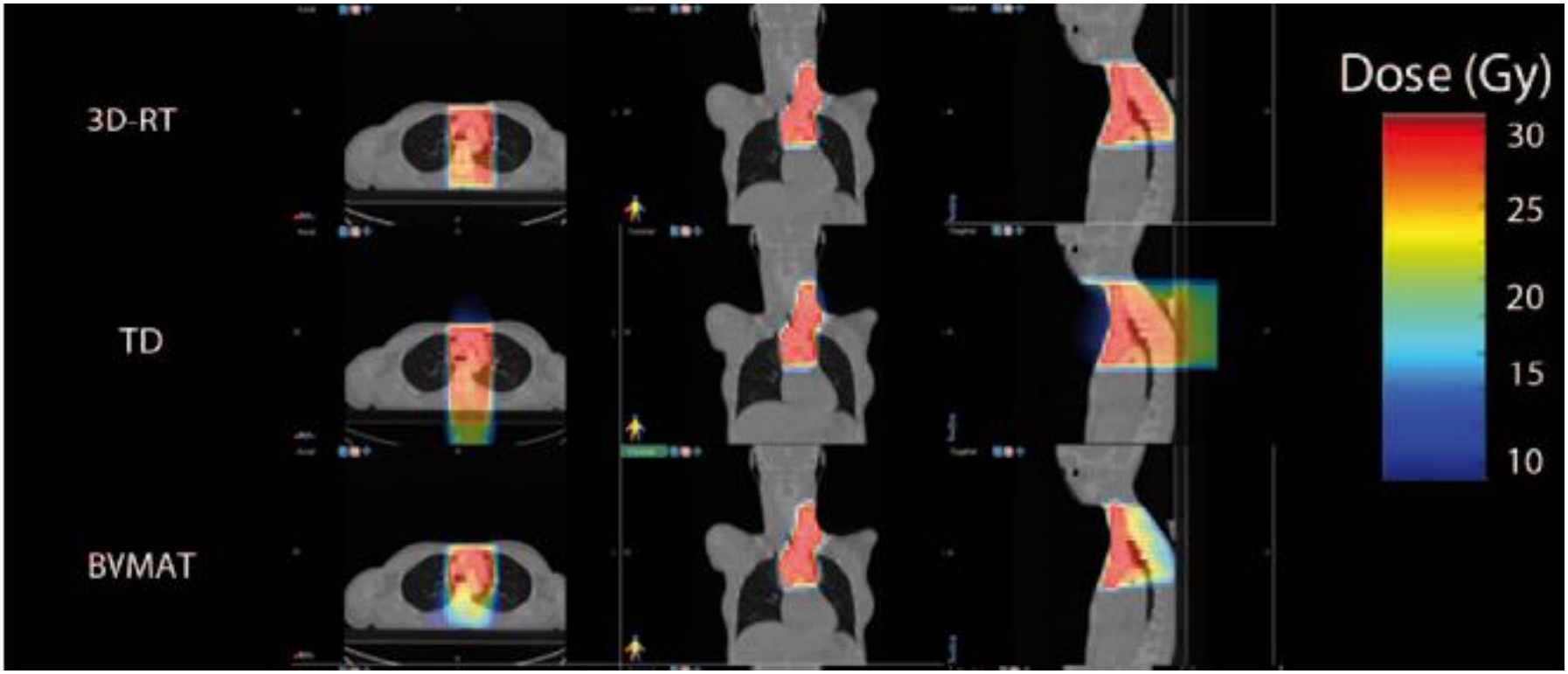


DVH parameter - lung



Novel radiotherapy techniques for involved-field and involved-node treatment of mediastinal Hodgkin lymphoma

Frank Lohr[1] · Dietmar Georg[2,3]



- All advanced photon techniques result in similar potential benefits and disadvantages

Novel radiotherapy techniques for involved-field and involved-node treatment of mediastinal Hodgkin lymphoma

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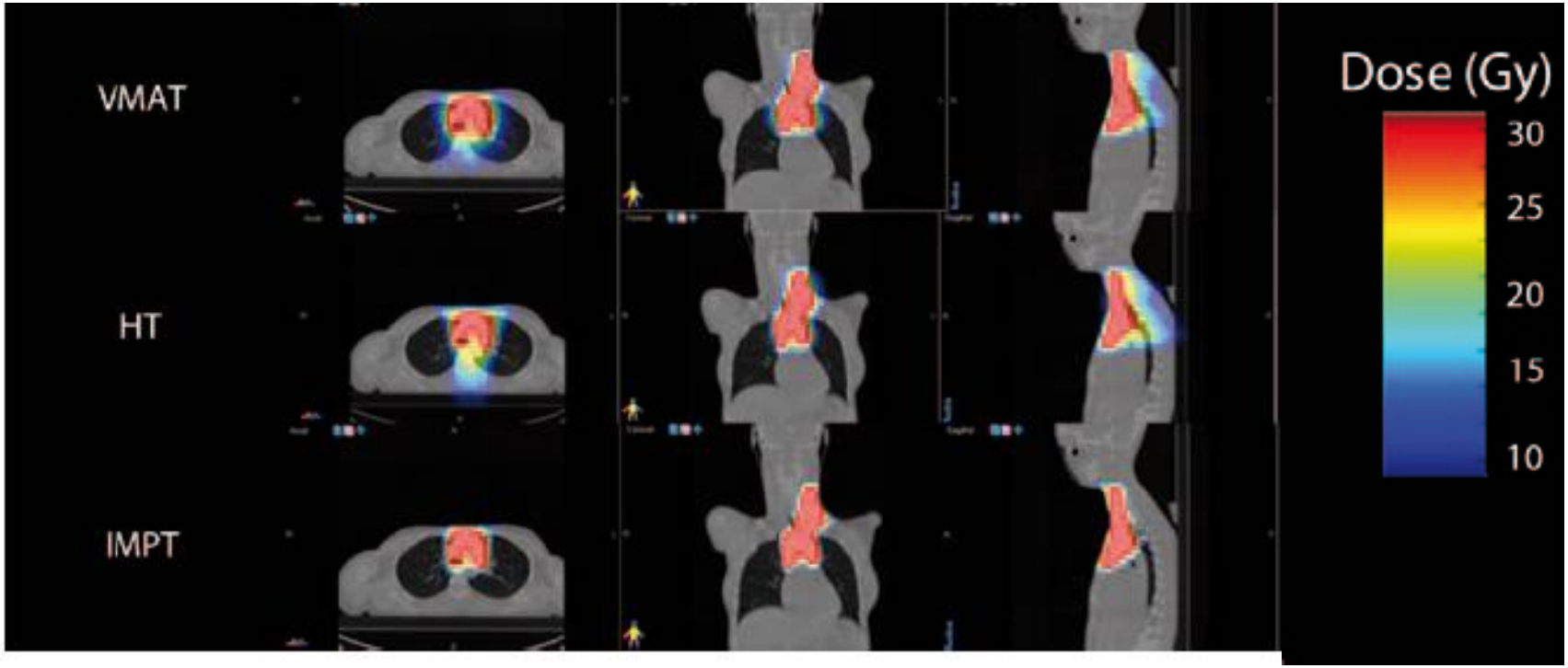


- Proton provide both high dose conformality and reduced integral dose
- Reduction of the treated volume most effectively reduces OAR dose

Can protons play a Role in Hodgkin`s disease?

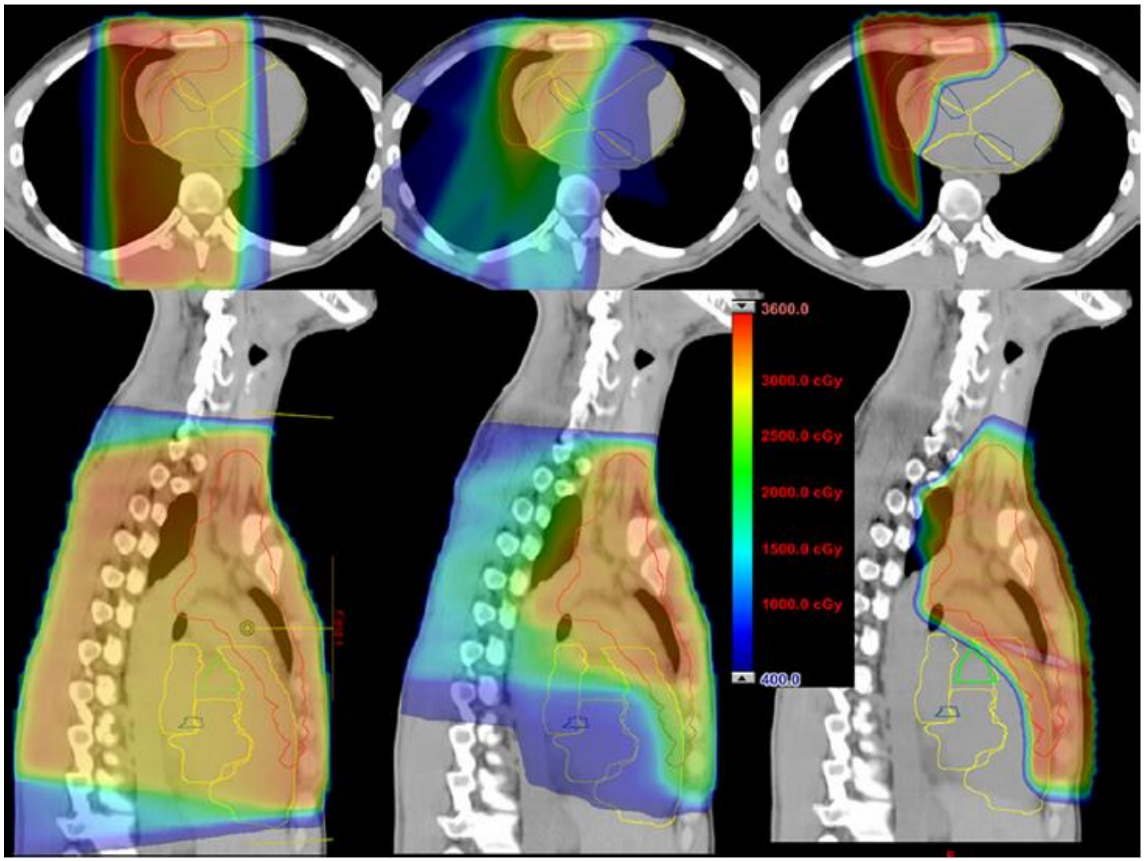
- Young patients
- Very good local tumor control
- Long term survivors

Reduction of long term-side effects

Reducing size of irradiated volume

Effective Dose Reduction to Cardiac Structures Using Protons Compared With 3DCRT and IMRT in Mediastinal Hodgkin Lymphoma

Bradford S. Hoppe,



N=13

RT dose:

21 Gy + 4.5Gy boost

30 Gy + 5.4Gy boost

30 Gy + 9 Gy plus LRA PET+

Technique:

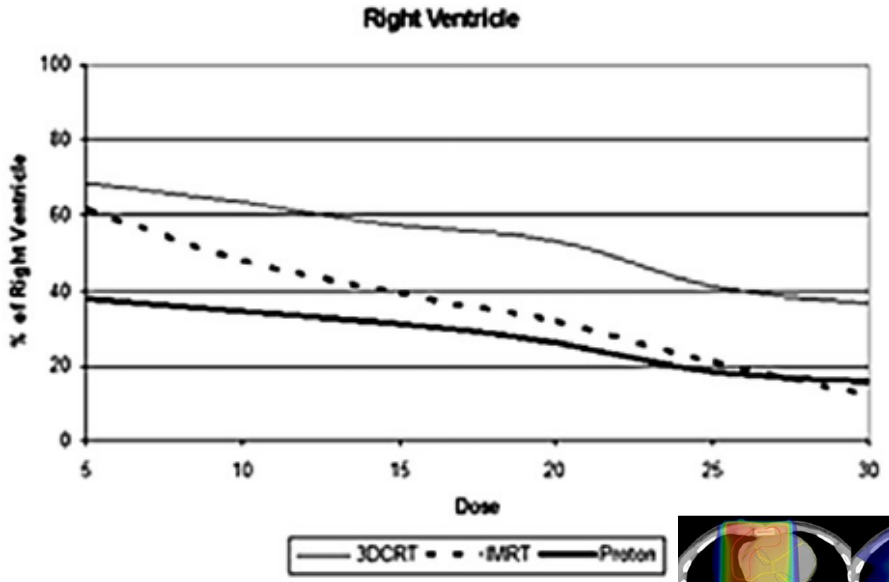
3DCRT

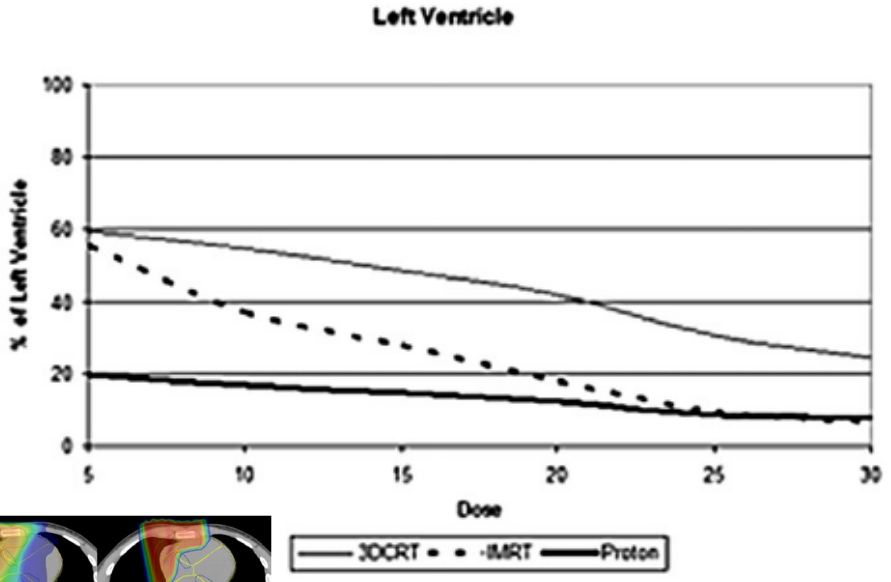
IMRT

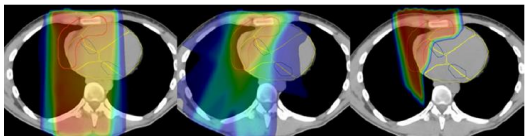
3D conformal PT

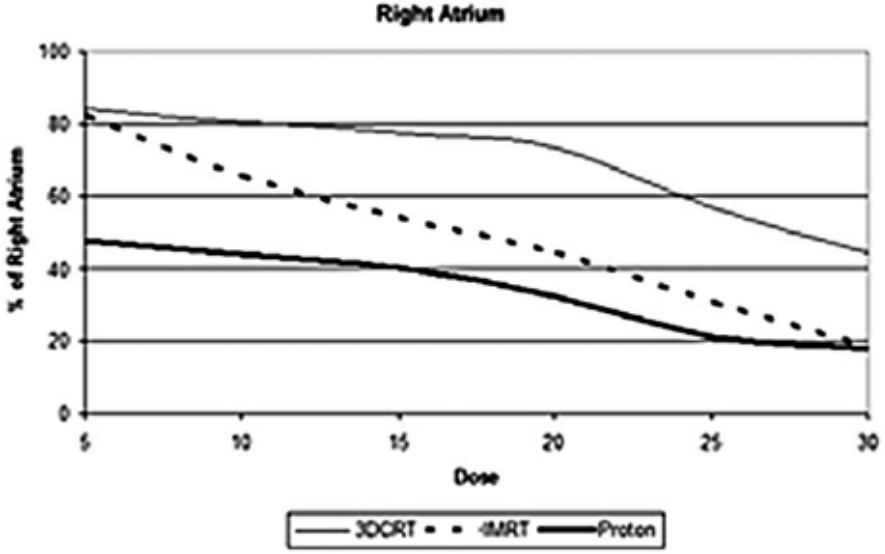
Int J Radiation Oncol Biol Phys, Vol. 84, No. 2, pp. 449–455, 2012

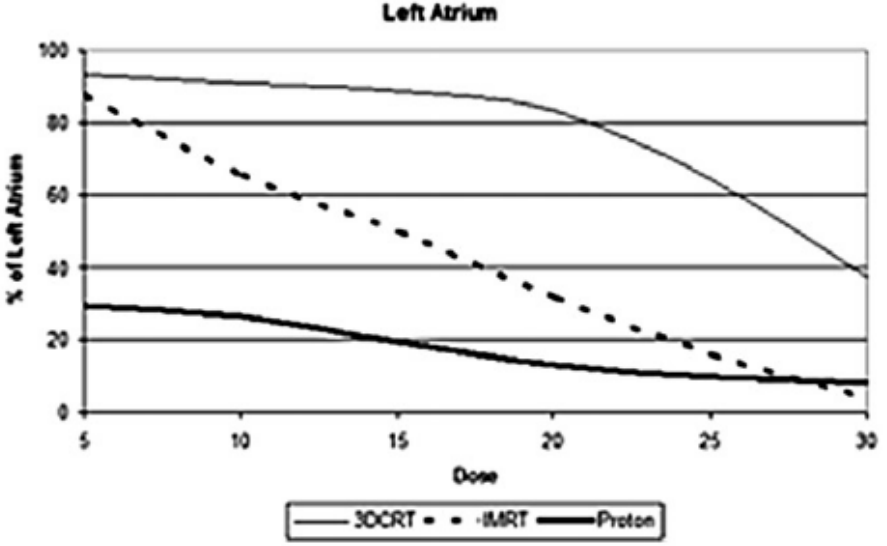
Effective Dose Reduction to Cardiac Structures Using Protons Compared With 3DCRT and IMRT in Mediastinal





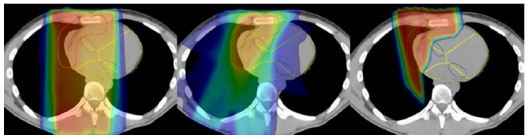




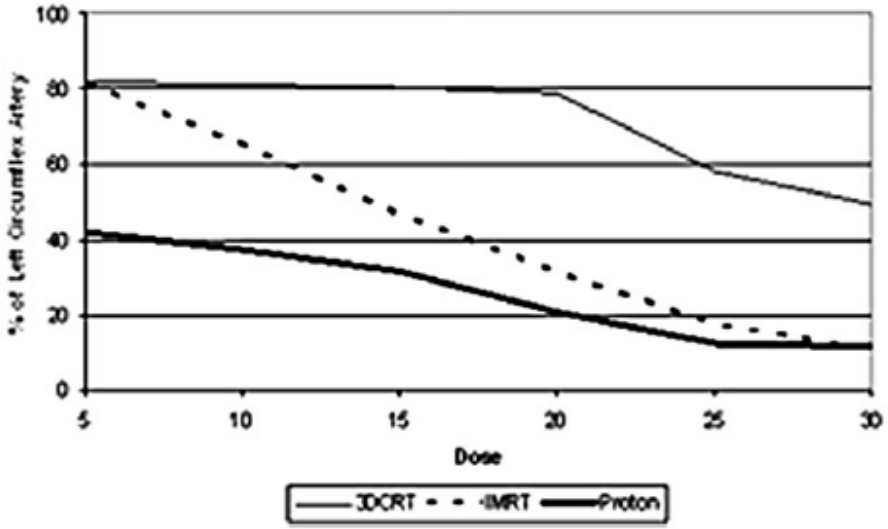


Effective Dose Reduction to Cardiac Structures Using Protons Compared With 3DCRT and IMRT in Mediastinal Hodgkin Lymphoma

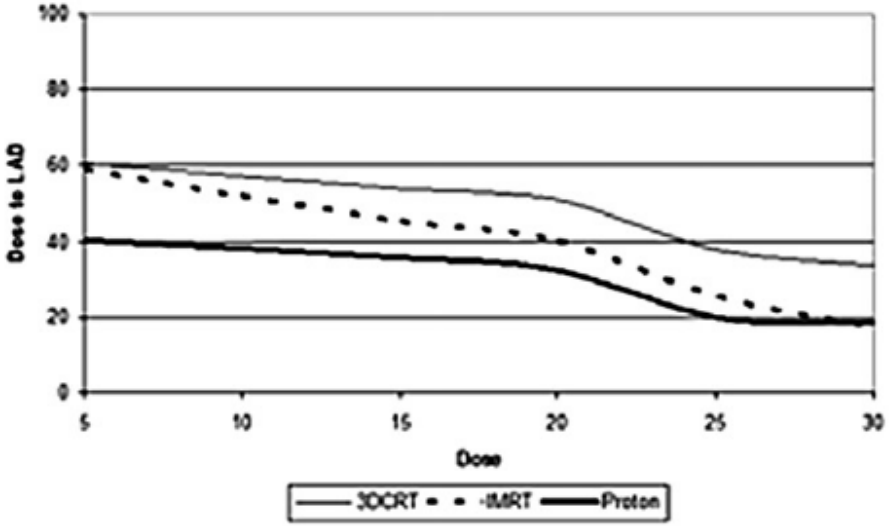
Bradford S. Hoppe,



Left Circumflex Artery



Left Anterior Descending Artery

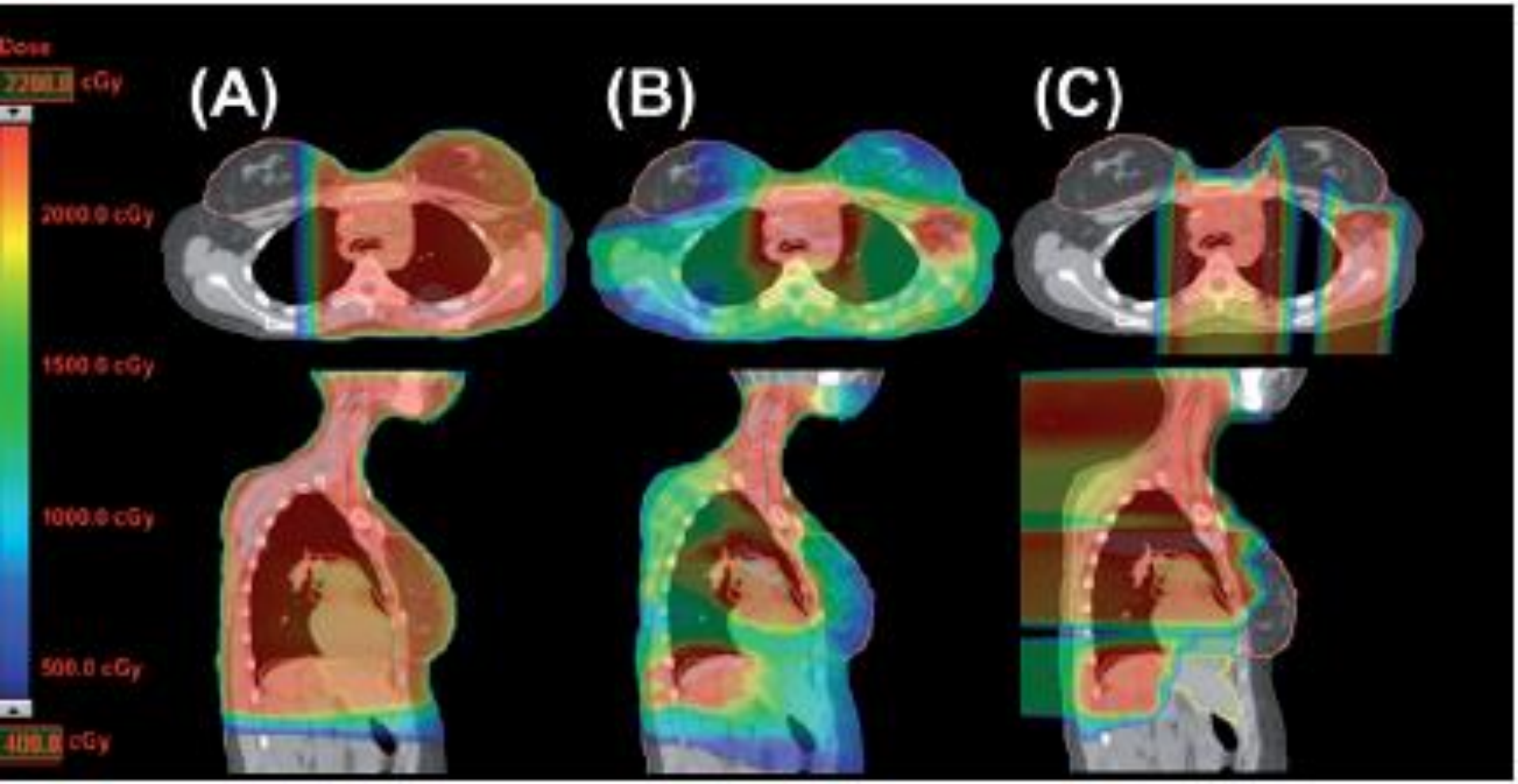


Cardiac subunit	3DCRT Median dose	IMRT Median dose	PT Median dose
Heart	21Gy (15-25Gy)	12 Gy (10-19 Gy)	8Gy (RBE)(6-13 Gy)
Mitral valve	28 Gy (20-30Gy)	9 Gy (5-17Gy)	0Gy (RBE) (0-0Gy)
Left circumflex A	30 Gy (21-30Gy)	16 Gy (9-20 Gy)	5Gy (RBE) (0-16 Gy)
Right circumfelx A	29 Gy (21-31 Gy)	22 Gy (11-30 Gy)	20Gy (RBE) (10-24 Gy)

Int J Radiation Oncol Biol Phy

Proton therapy in a pediatric patient with stage III Hodgkin lymphoma

ADAM HOLTZMAN[1]



3D CRT IMRT PT

Acta Oncologica, 52:3, 592-594,

Proton therapy in a pediatric patient with stage III Hodgkin lymphoma ADAM HOLTZMAN[1]

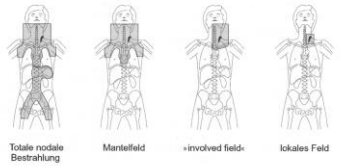
	3DCRT	IMRT	PT*	3DCRT-PT		IMRT-PT		3DCRT-IMRT	
	Mean dose	Mean dose	Mean dose	RR	AR (Gy)	RR	AR (Gy)	RR	AR (Gy)
Body (J)**	185	201	101	45%	84	50%	100	−8%	−16
Breasts (Gy)	8.2	7.5	1.8	78%	6.4	76%	5.7	9%	0.7
Heart (Gy)	16.7	16	12.3	26%	4.4	23%	3.7	4%	0.7
Lungs (Gy)	12.6	14.1	9.4	25%	3.2	33%	4.7	−12%	−1.5
Stomach (Gy)	21.7	19.9	12.2	44%	9.5	39%	7.7	8%	1.8
Bowel (Gy)	11.2	10.2	4.7	58%	6.5	54%	5.5	9%	1
Esophagus (Gy)	18	17.9	16.2	10%	1.8	9%	1.7	1%	0.1
Liver (Gy)	3.8	6.2	0.3	92%	3.5	95%	5.9	−63%	−2.4

- Reduction of the Mean Dose at all OAR with Proton therapy
- Proton provide both high dose conformality and reduced integral dose

But

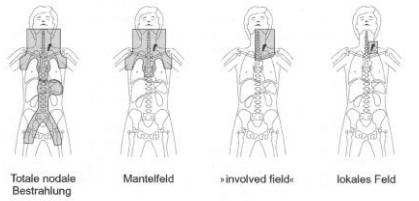
- Plan reflects the situation of a short moment.
- There are still movements of the organs.
- To bring the beam at the right moment to the tumor.
- Proton therapy might be indicated in special situations in HL.

Conclusion



- CT alone or combined CT-RT are at the moment the most promising treatment options in Hodgkin`s disease.
- Children and Young adults become long-term survivors and have an increased risk of delayed adverse health outcomes.
- Radiotherapy can provide long term side effects in case of **high dose ??** at the OAR.
- Increase of chemotherapy does not resolve the problem of long term side effects. New therapy approaches are needed.

Conclusion



- Radiotherapy is still a very important treatment option in selected Hodgkin`s patients.

Further steps to go:

- Based on adequate imaging, continue to reduce the Target volume as the most efficient way to reduce dose at the OAR.
- Use the best advanced Photon technique (3D conformal RT, Tomo, IMRT, VMAT) for individual case, to reduce dose at OAR.
  - Proton therapy may provide high dose conformity and reduced integral dose.

Studies are needed to evaluate the advantage of protons in Extended Hodgkin`s Disease in the mediastinum.

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Rhabdomyosarcoma: General Aspects

Arnold C. Paulino, MD, FACR, FASTRO
Professor of Radiation Oncology
MD Anderson Cancer Center

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

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Goals and Objectives

At the end of the presentation, the participant should be able to

1. Determine the influence of site of origin and histologic subtype including fusion status on outcome of rhabdomyosarcoma
2. Discuss the work-up for children with rhabdomyosarcoma
3. Gain an understanding of the stage, group and risk group in rhabdomyosarcoma

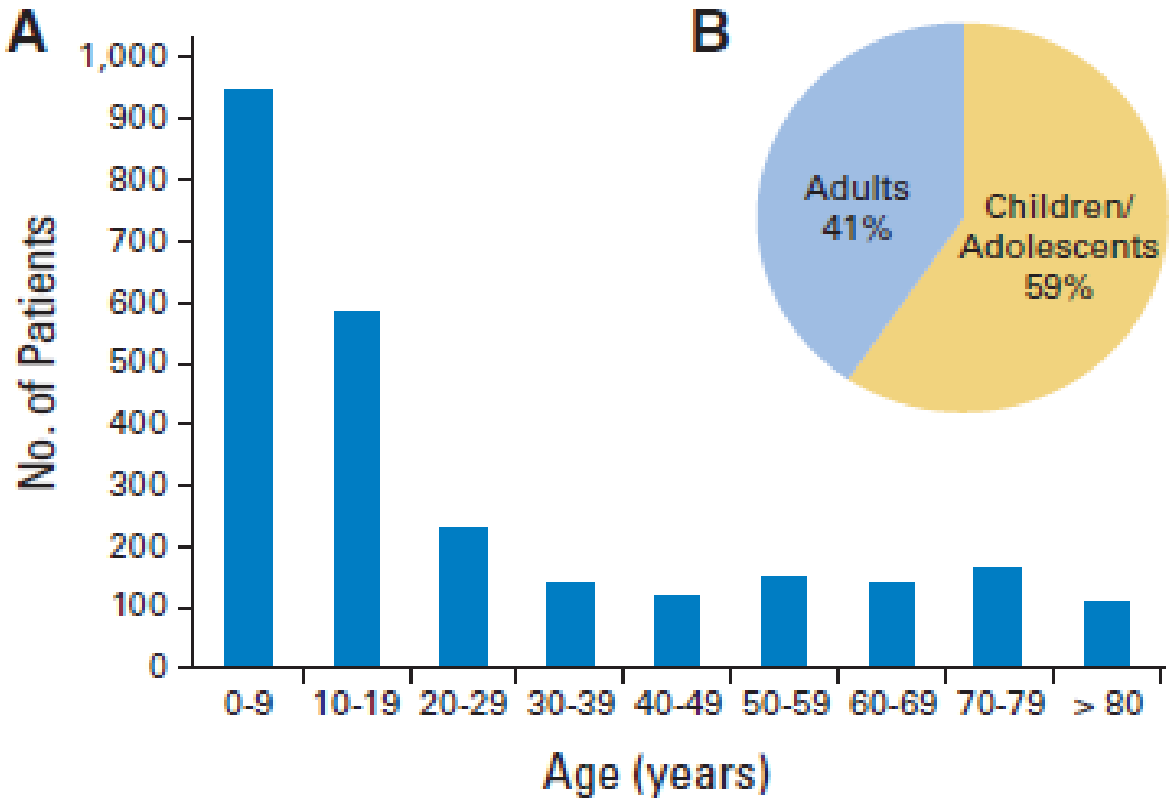
Rhabdomyosarcoma

- Accounts for about 3-4% of malignant disease in children < 15 years
- Most common soft tissue sarcoma in children
- Annual incidence of RMS is 4.4 per million in white children and 1.3 per million in black children
- A small proportion associated with genetic conditions (Li-Fraumeni syndrome, NF-1, Beckwith-Wiedemann syndrome)

Rhabdomyosarcoma

- Slight male predominance (1.4:1)
- 70% occur before the age of 10 years with the peak incidence between 2 to 5 years
- Very heterogeneous group of patients secondary to age, histologic subtype, location and presentation

Age Distribution of Rhabdomyosarcoma (SEER 1973-2005)



Sultan I et al. J Clin Oncol 2009; 27:3391-7

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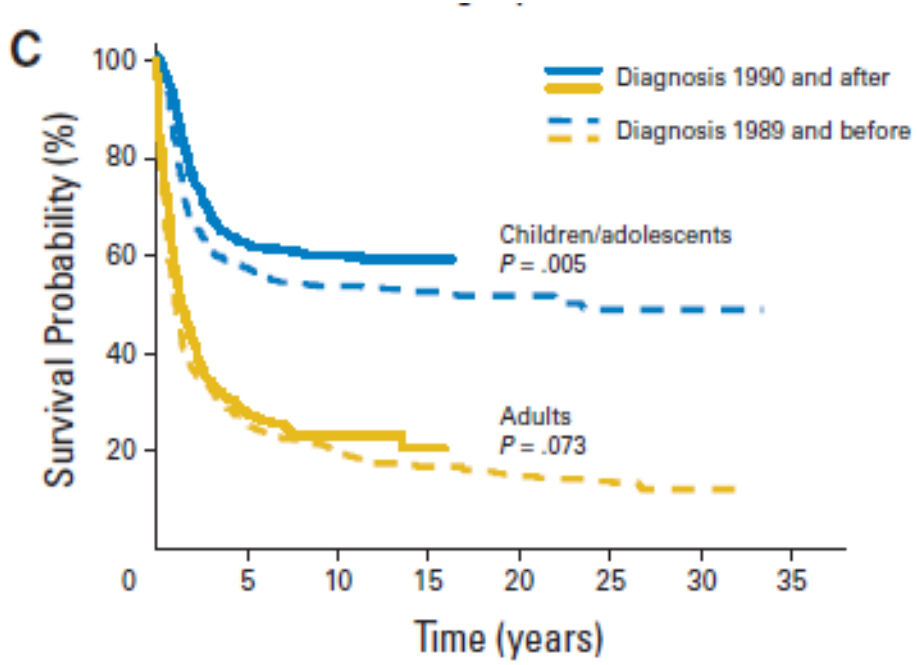
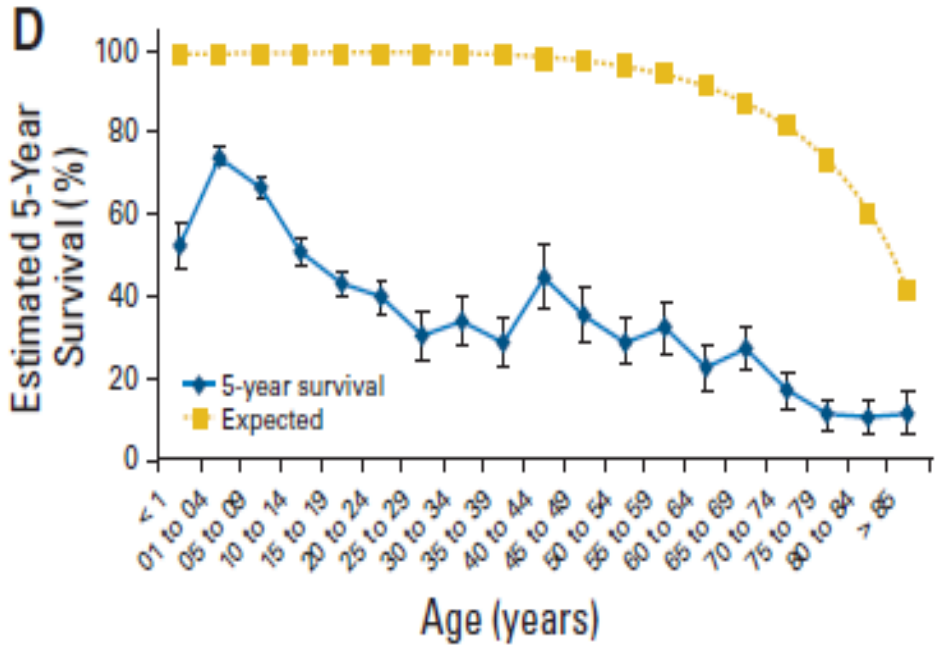
Survival According to Age in Rhabdomyosarcoma (SEER 1973-2005)





Sultan I et al. J Clin Oncol 2009; 27:3391-7

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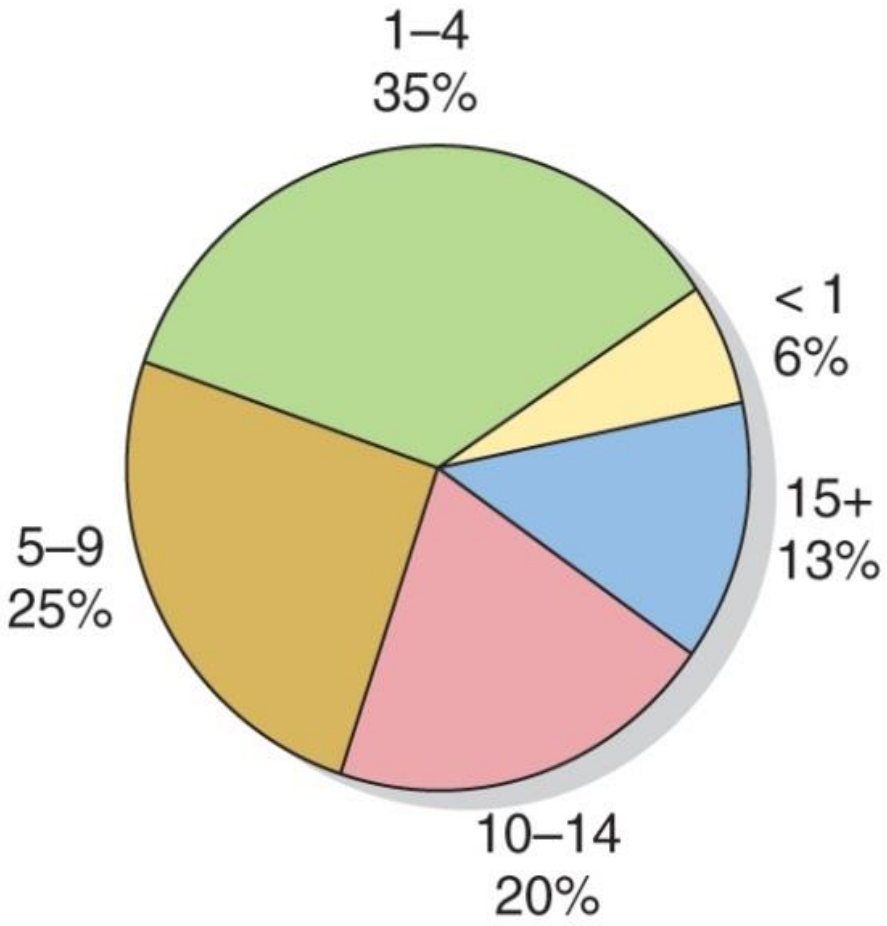
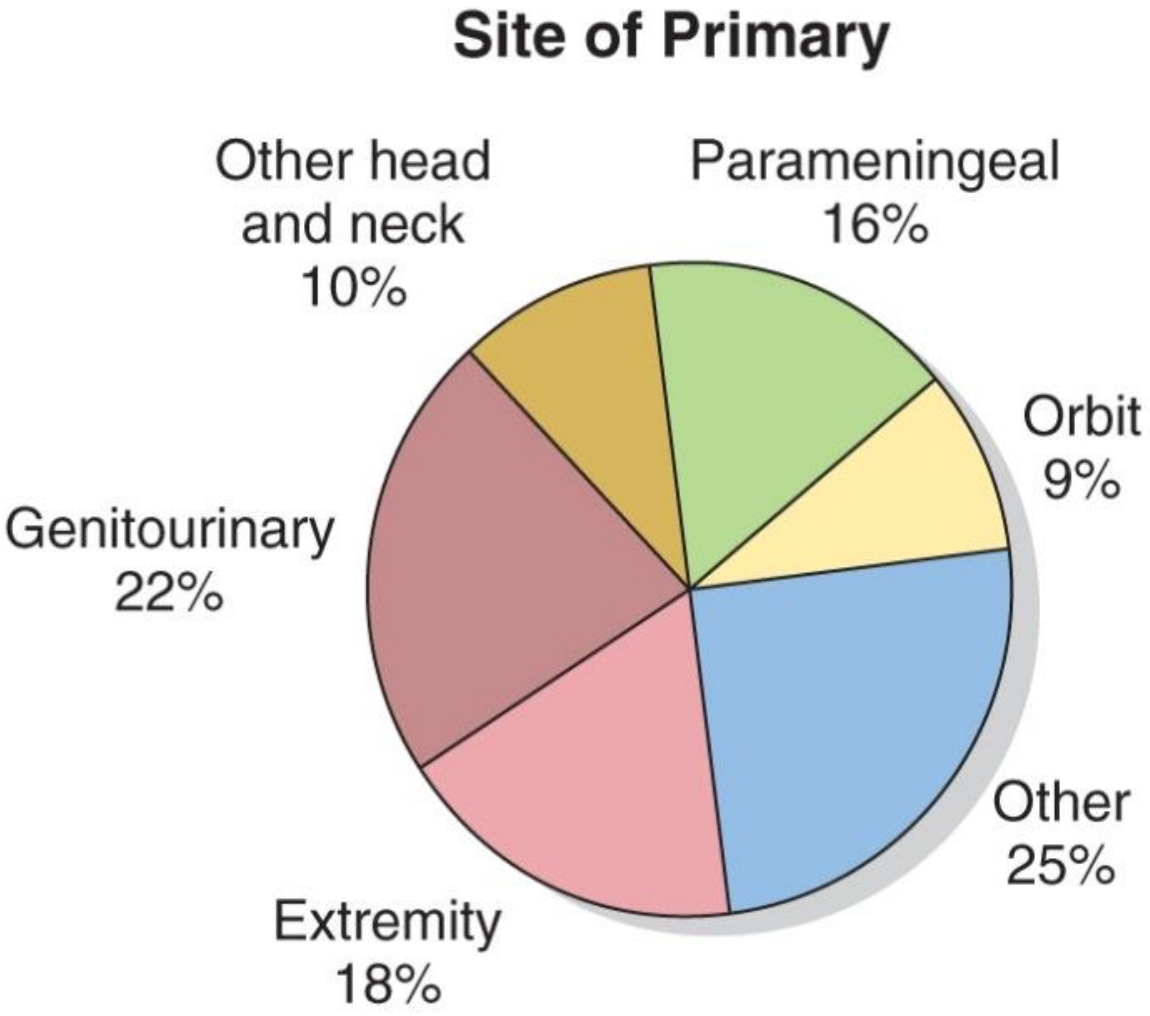
Age at Presentation

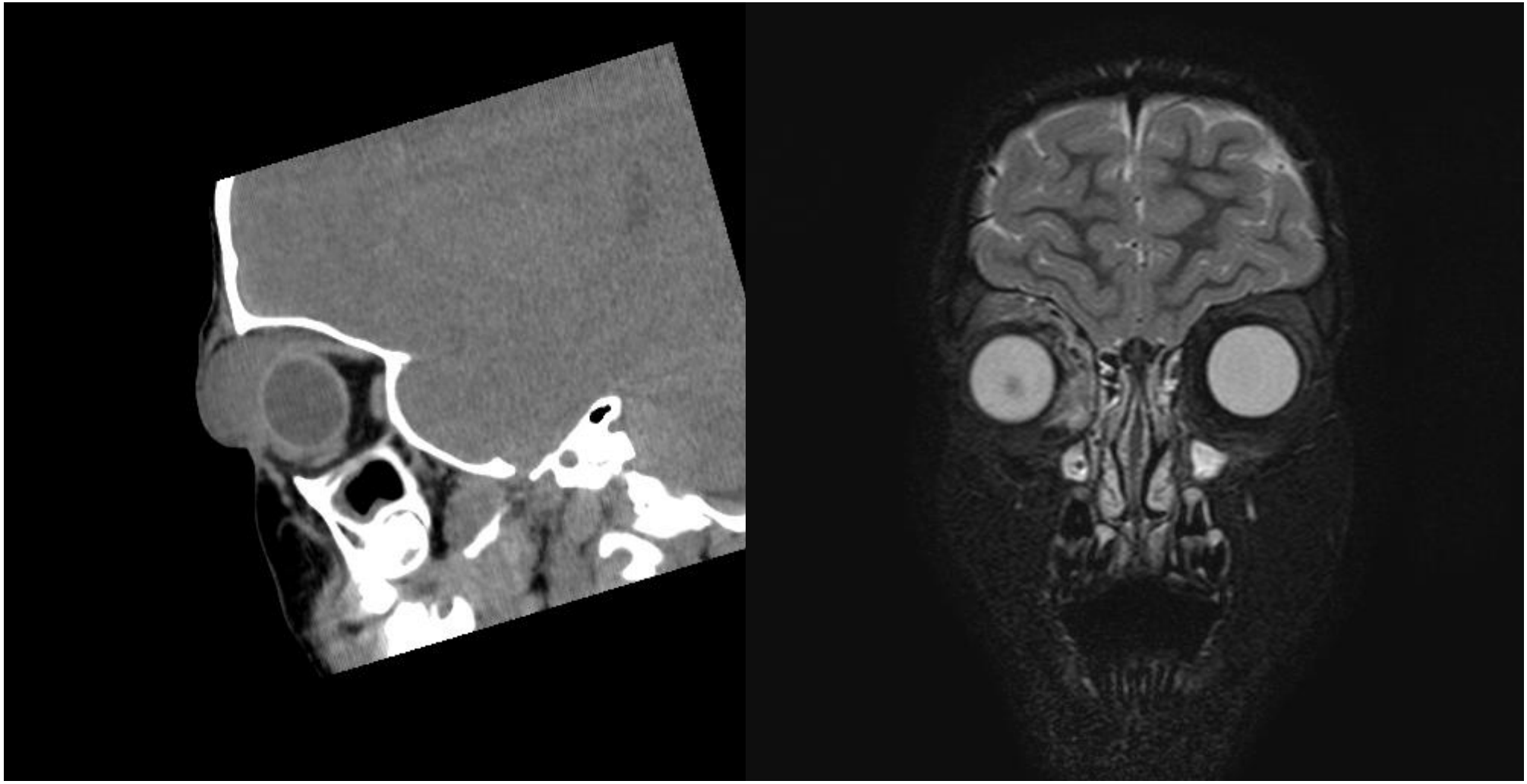


McDonald SM et al. In Halperin EC et al. Pediatric Radiation Oncology 2011

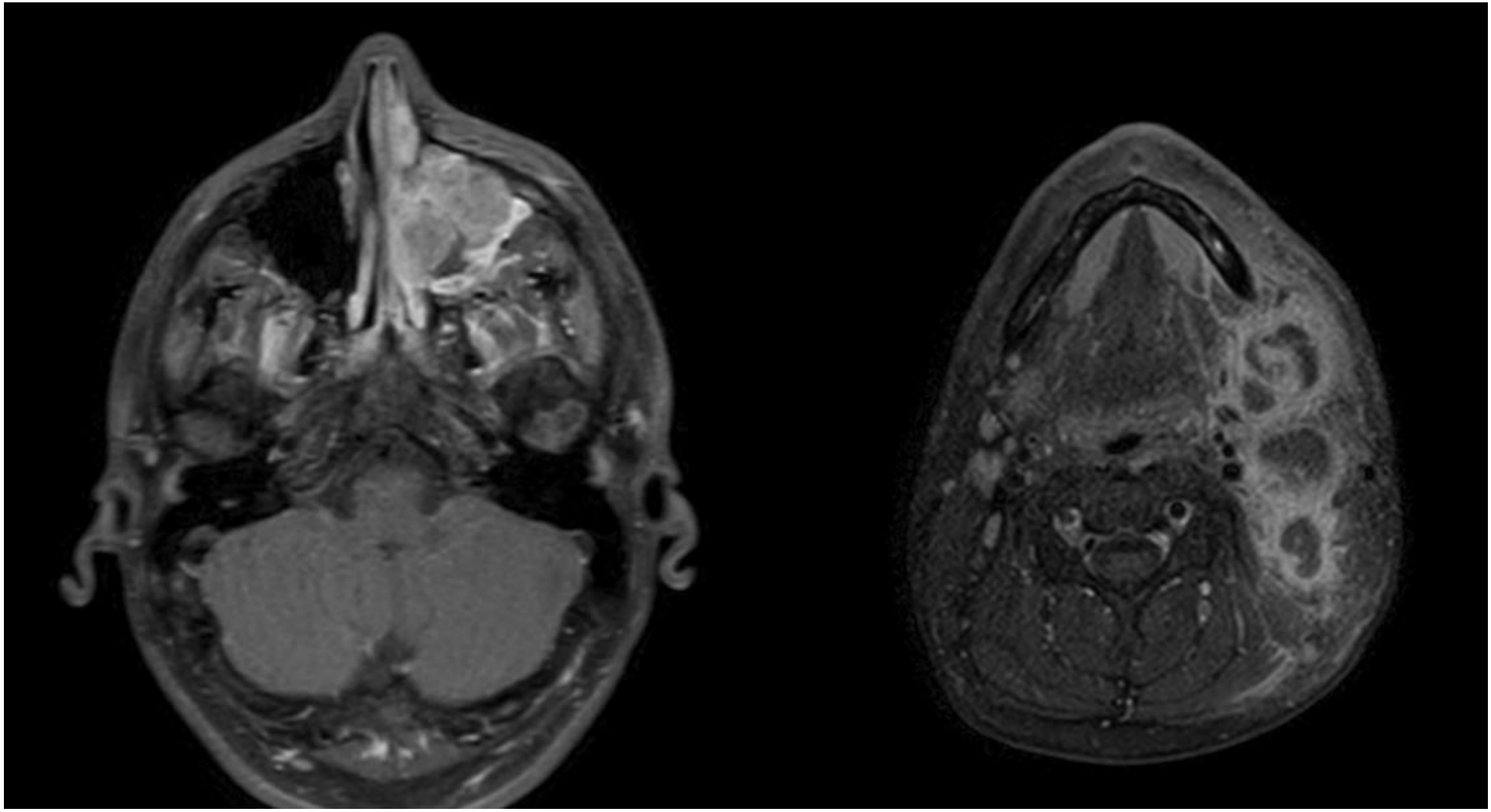


McDonald SM et al. In Halperin EC et al. Pediatric Radiation Oncology 2011

Orbit



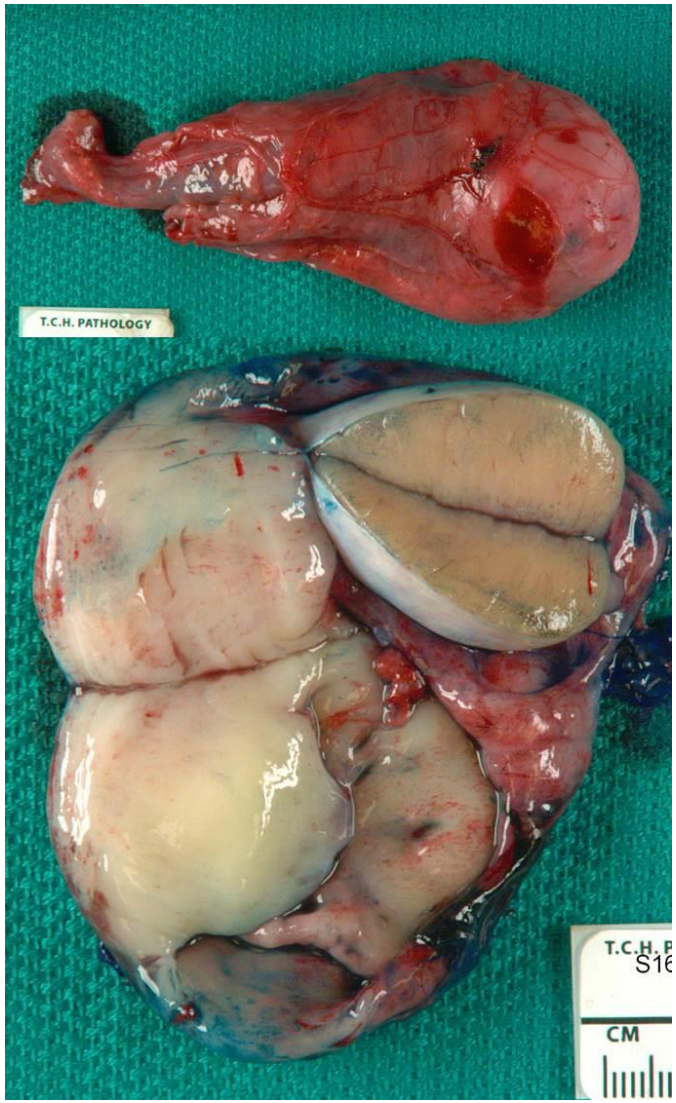
Parameningeal Site: Maxillary Sinus



Parameningeal Sites

- Middle Ear
- Nasal Cavity
- Paranasal Sinuses (Maxillary, Ethmoid, Sphenoid)
- Nasopharynx
- Infratemporal Fossa
- Pterygopalatine Fossa
- Parapharyngeal area

Genitourinary: Paratesticular



Courtesy of Dr. John Hicks, Texas Children's Hospital

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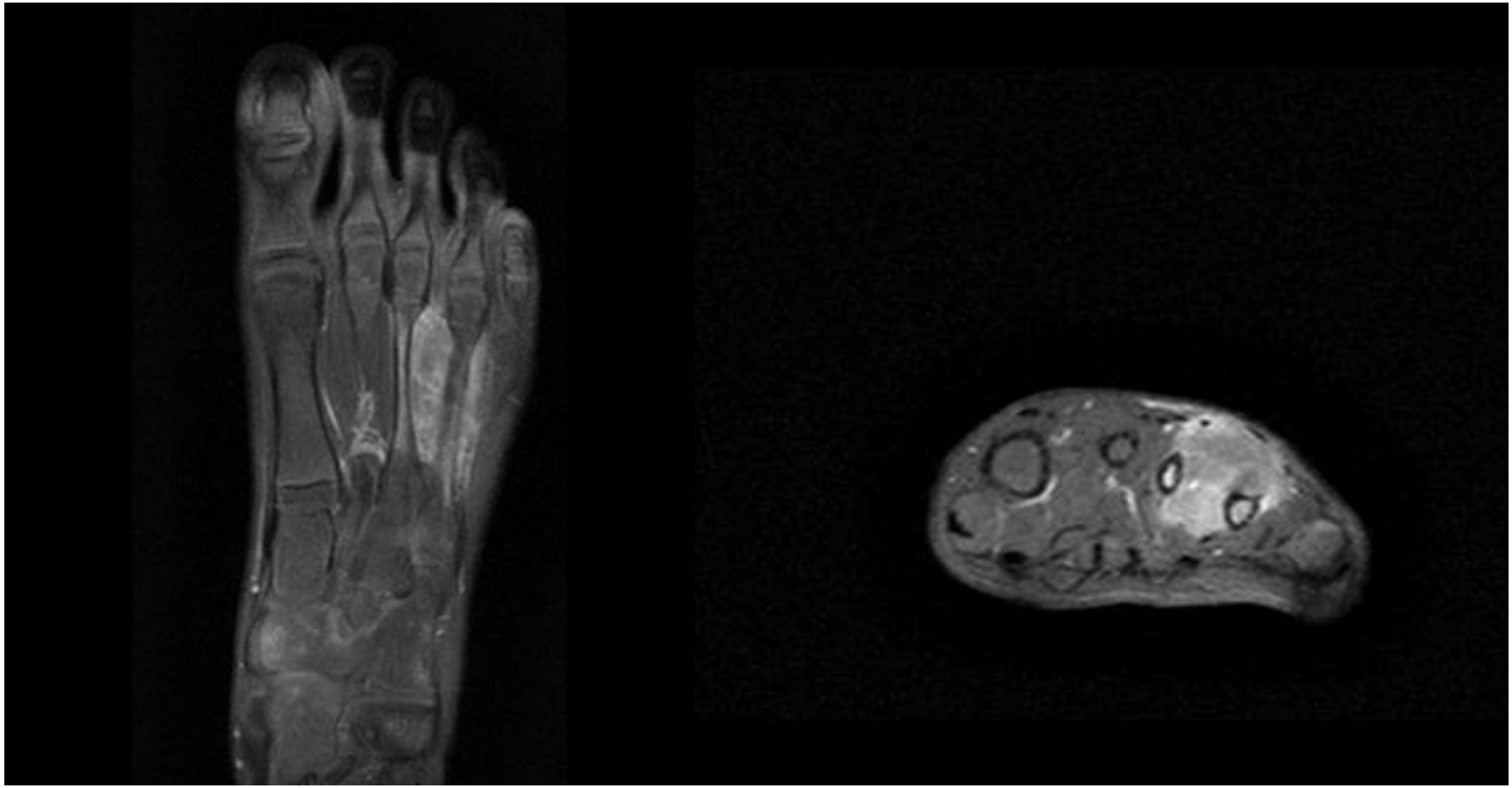
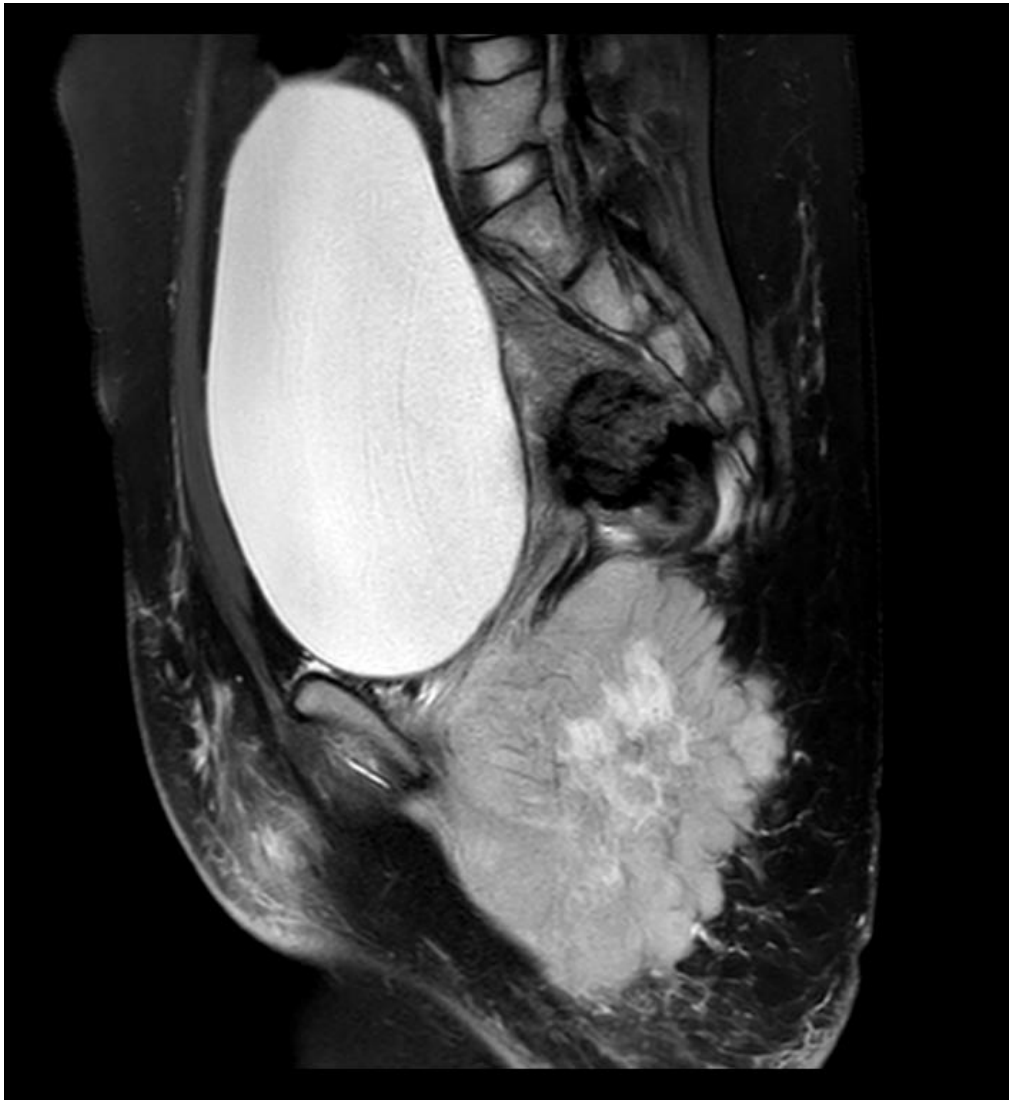
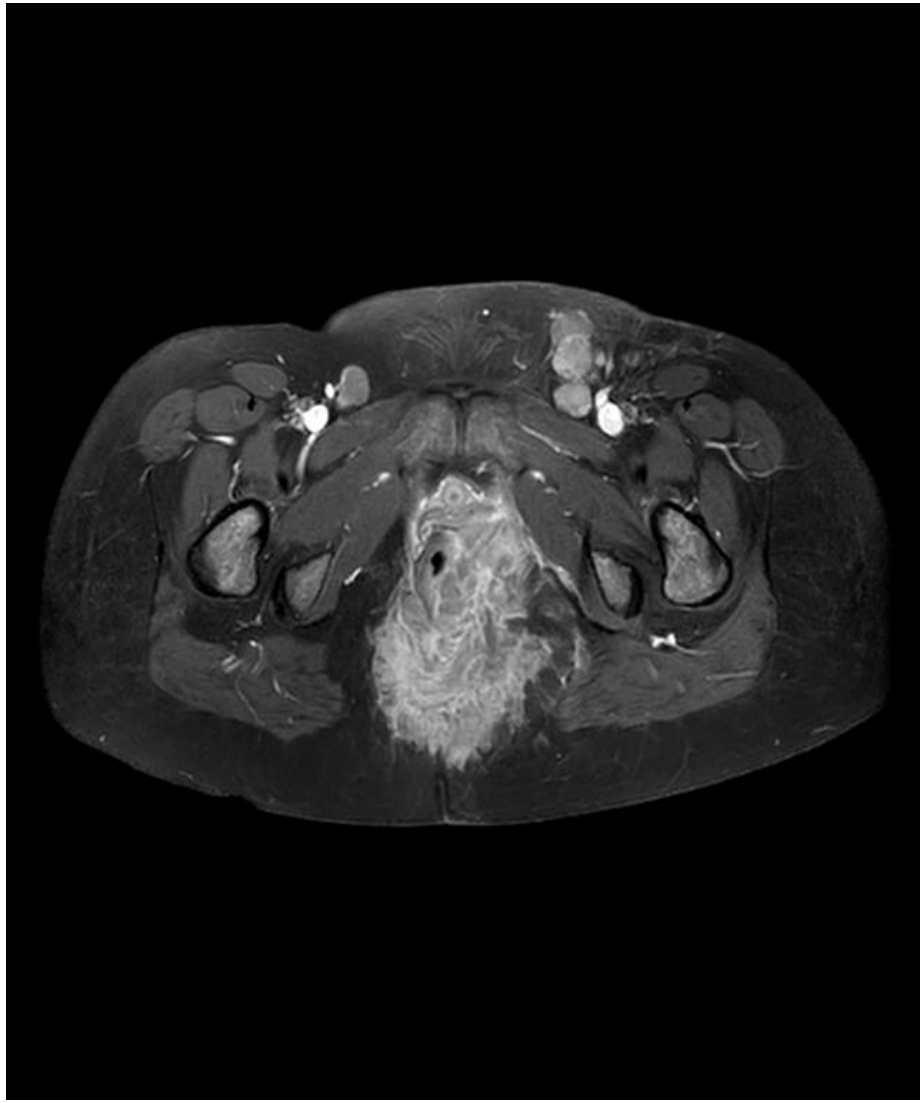
Extremity



Perirectal

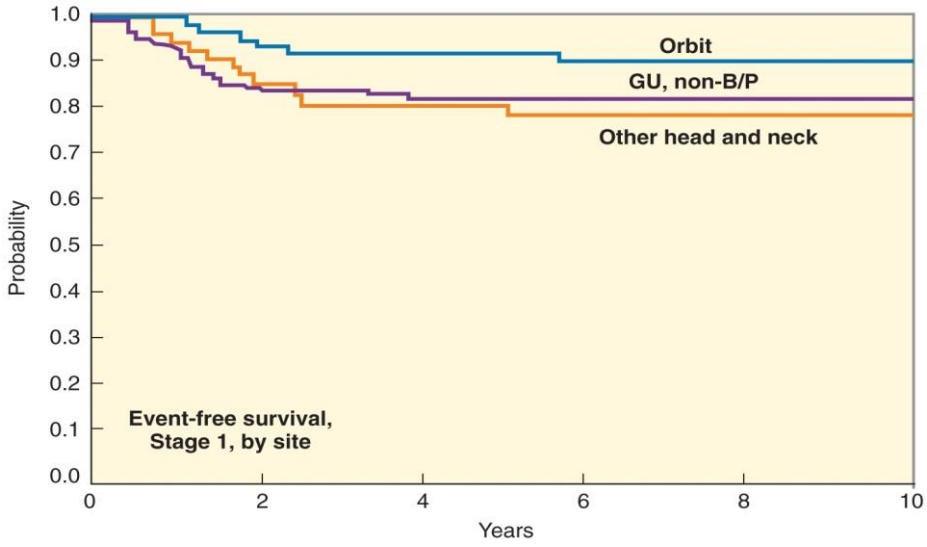


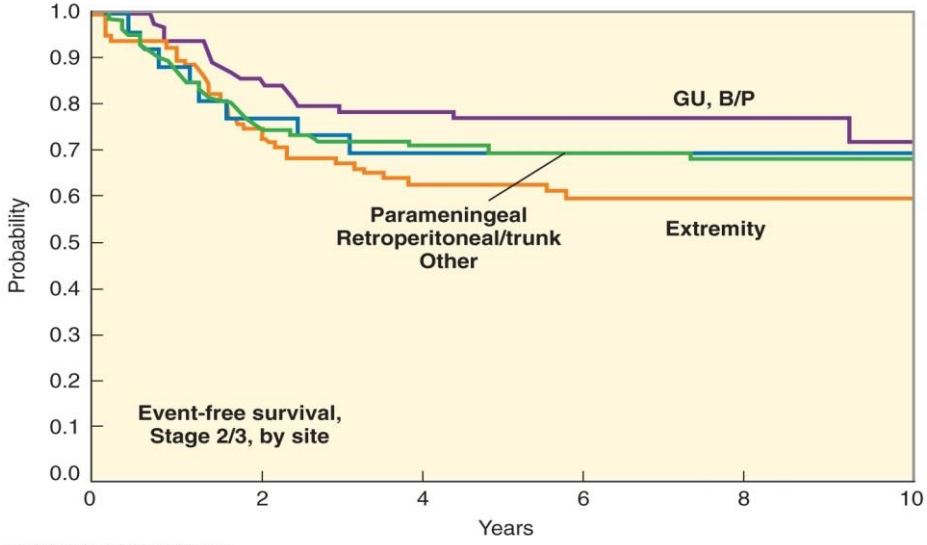


Tumor Location

Favorable Sites

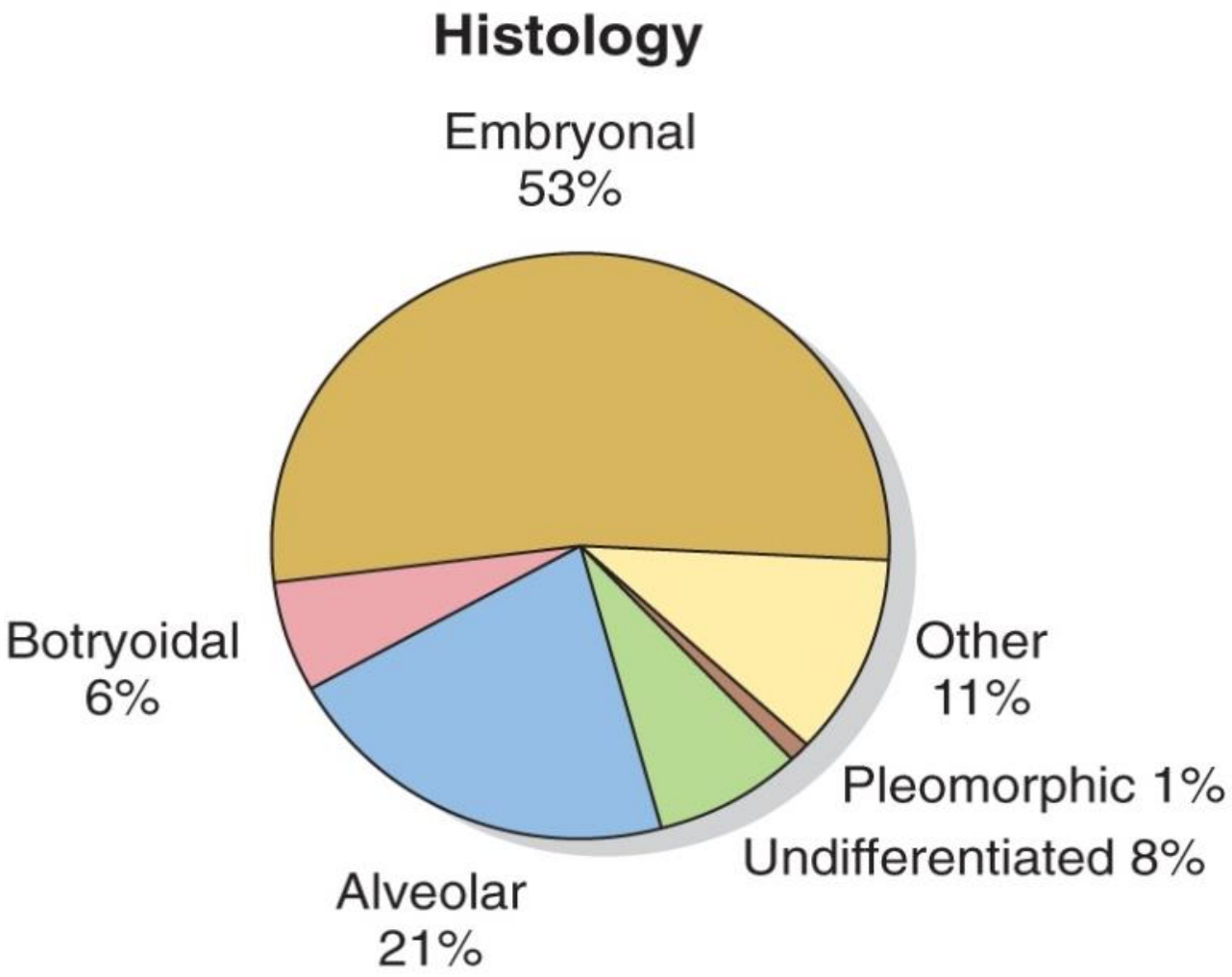
1. Orbit
2. Non-bladder/ non-prostate genitourinary sites
3. Non-parameningeal head and neck sites





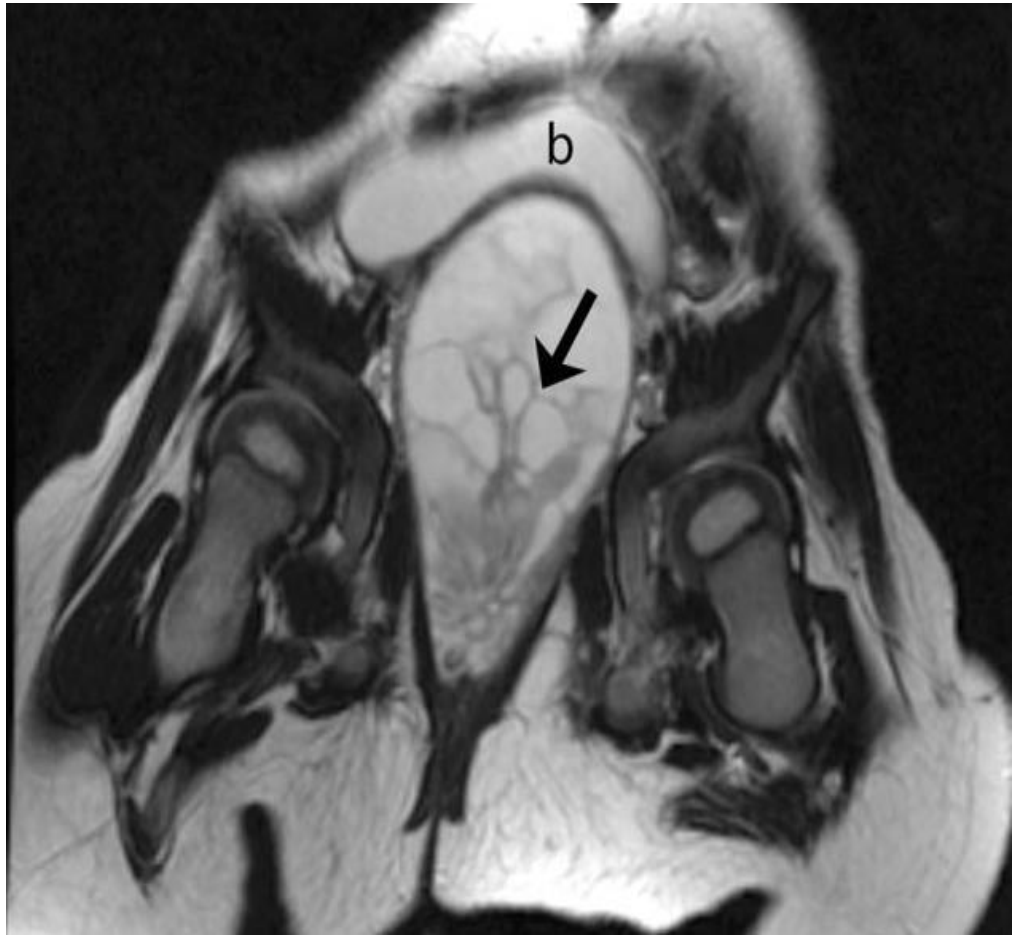
Tumor Pathology

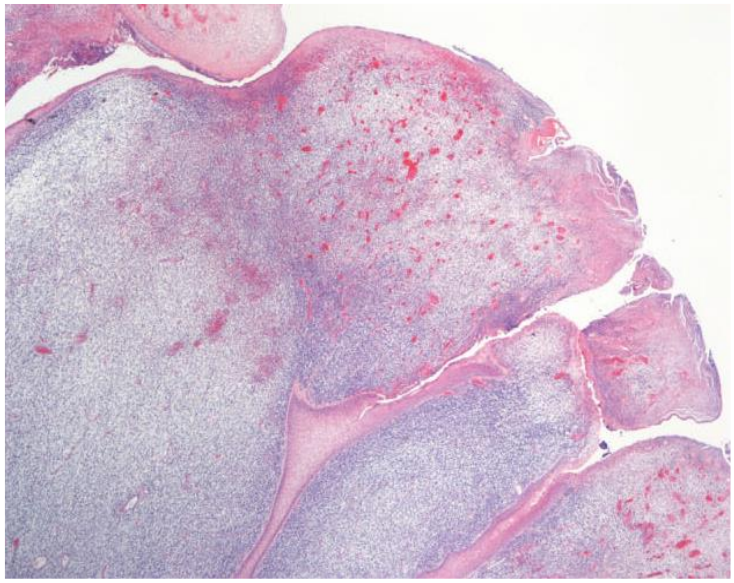
- Embryonal – most common, head and neck and genitourinary sites
- Sarcoma botryoides (cluster of grapes) – subtype of embryonal, better prognosis, tend to occur in cavities (head and neck, bile duct, vagina, bladder)
- Spindle cell – subtype of embryonal, better prognosis, paratesticular and head and neck sites
- Alveolar – worse prognosis, extremity and perineal sites, nodal metastasis worse
- Pleomorphic – rare in children, described in adult population
- Undifferentiated sarcoma – unfavorable histology, used to be included in Intergroup Rhabdomyosarcoma Studies now in COG NRSTS protocols

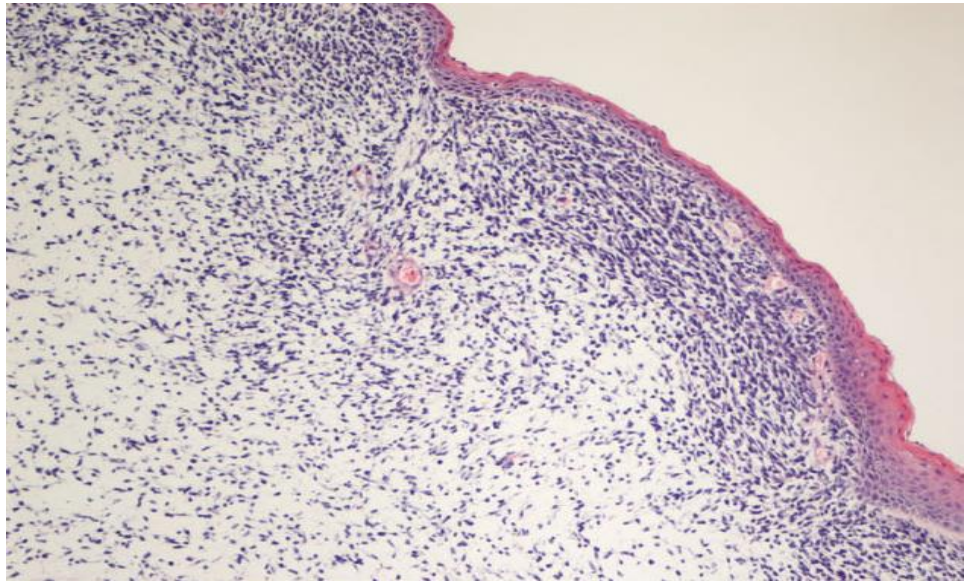


McDonald SM et al. In Halperin EC et al. Pediatric Radiation Oncology 2011

Sarcoma Botryoides







Kobi M et al. J Magn Reson Imaging 2009; 29:708-12

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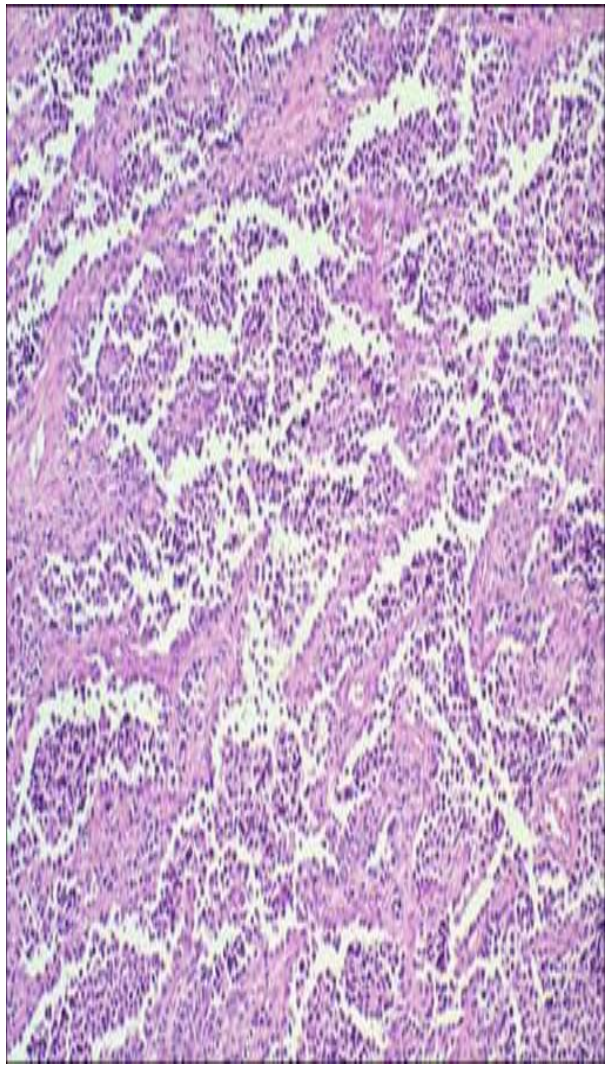
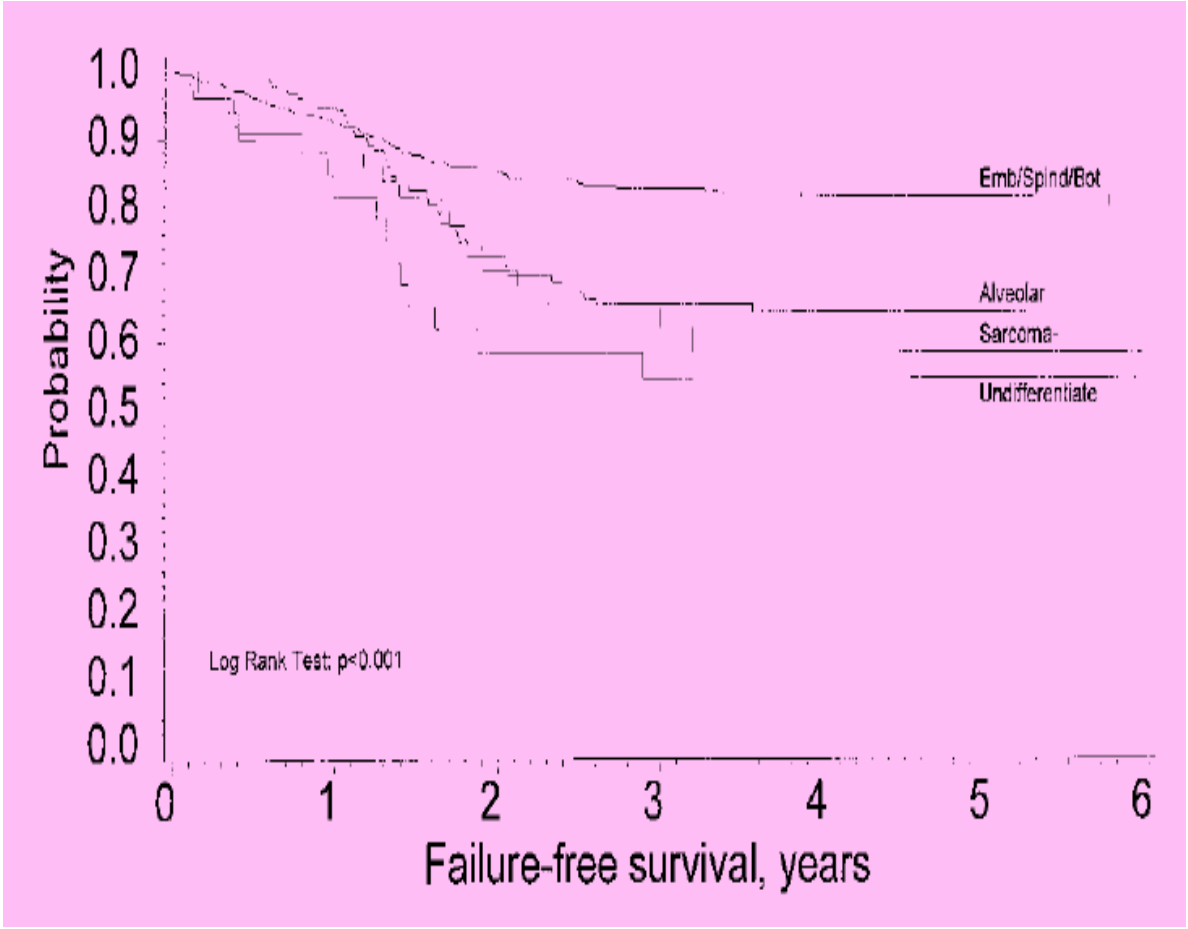
Tumor Pathology Subtype





Crist WM et al. J Clin Oncol 2001; 19:3091-102

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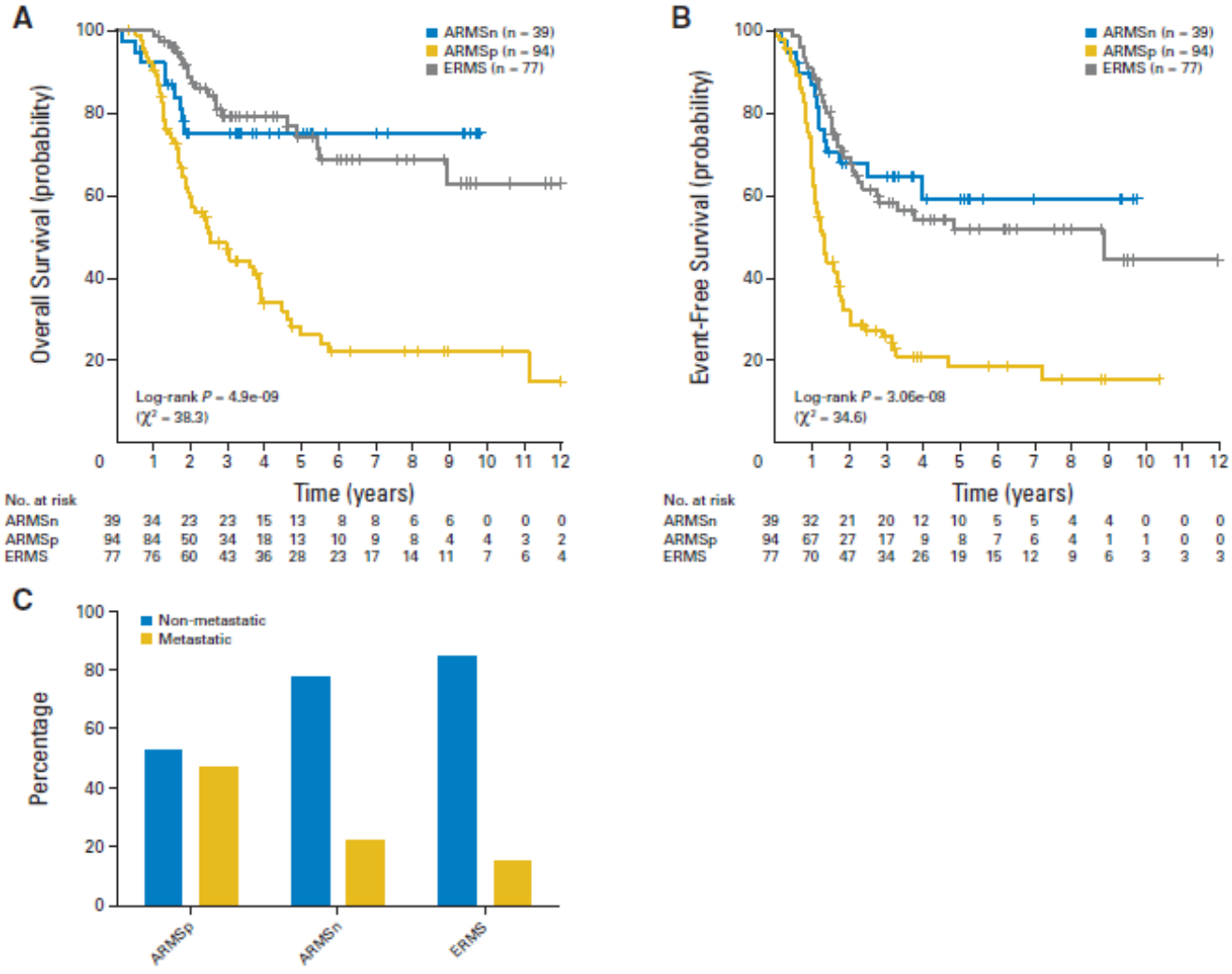
Alveolar Rhabdomyosarcoma

- Alveolar RMS is associated with characteristic balanced chromosomal translocations t (2; 13) (q35;q14) and t (1;13)(p36;p14) which form a fusion gene between the 5' end of either *PAX3* or *PAX7* and the 3' end of *FOXO1*
- These alterations are seen in 70 to 80% of ARMS and associated with poor prognosis

Influence of Translocation in Alveolar RMS



Williamson D et al. J Clin Oncol 2010; 28:2151-8

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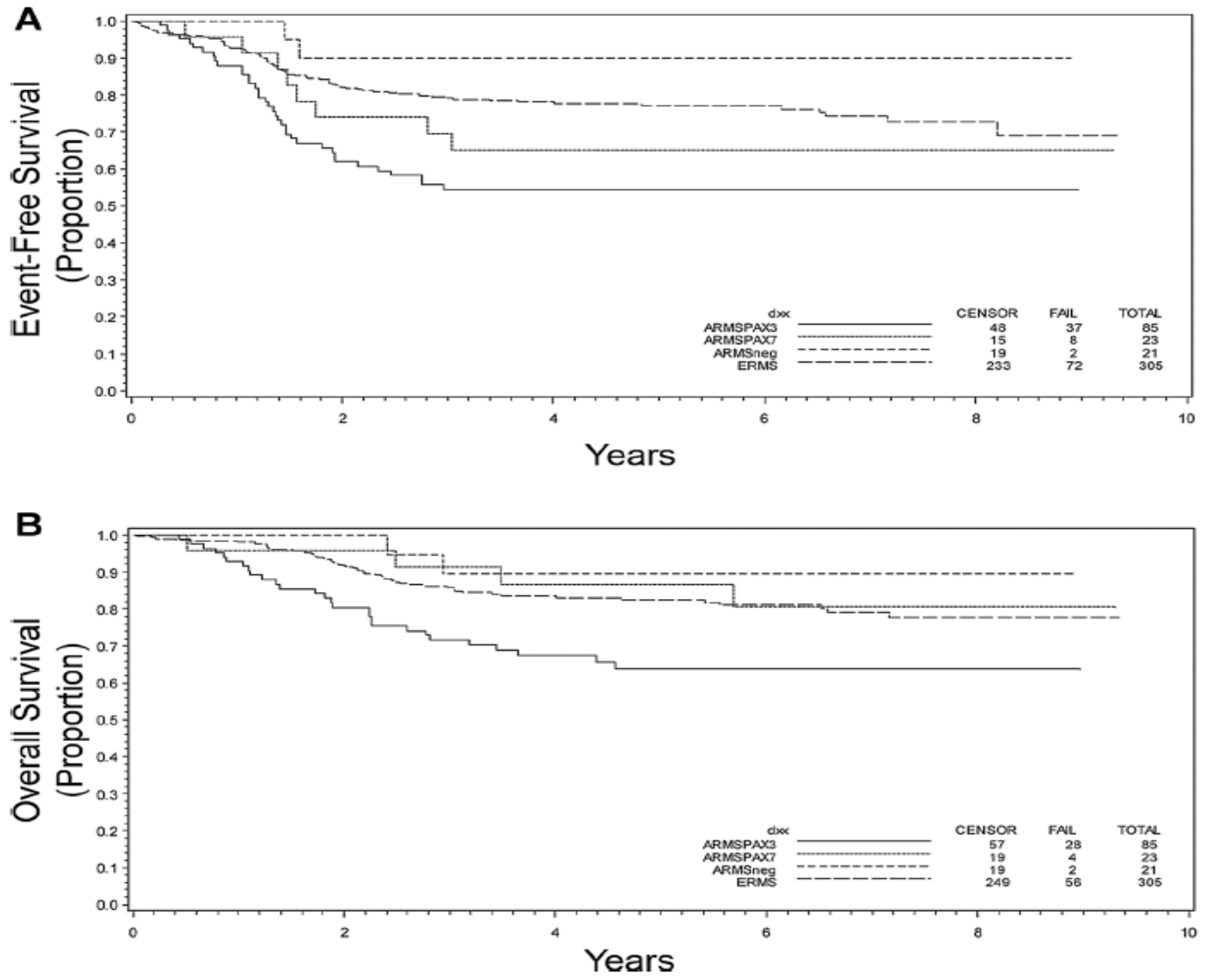
Molecular Classification: D9803 Intermediate-Risk RMS



Skapek SX et al. Pediatr Blood Cancer 2013; 60:1411-7

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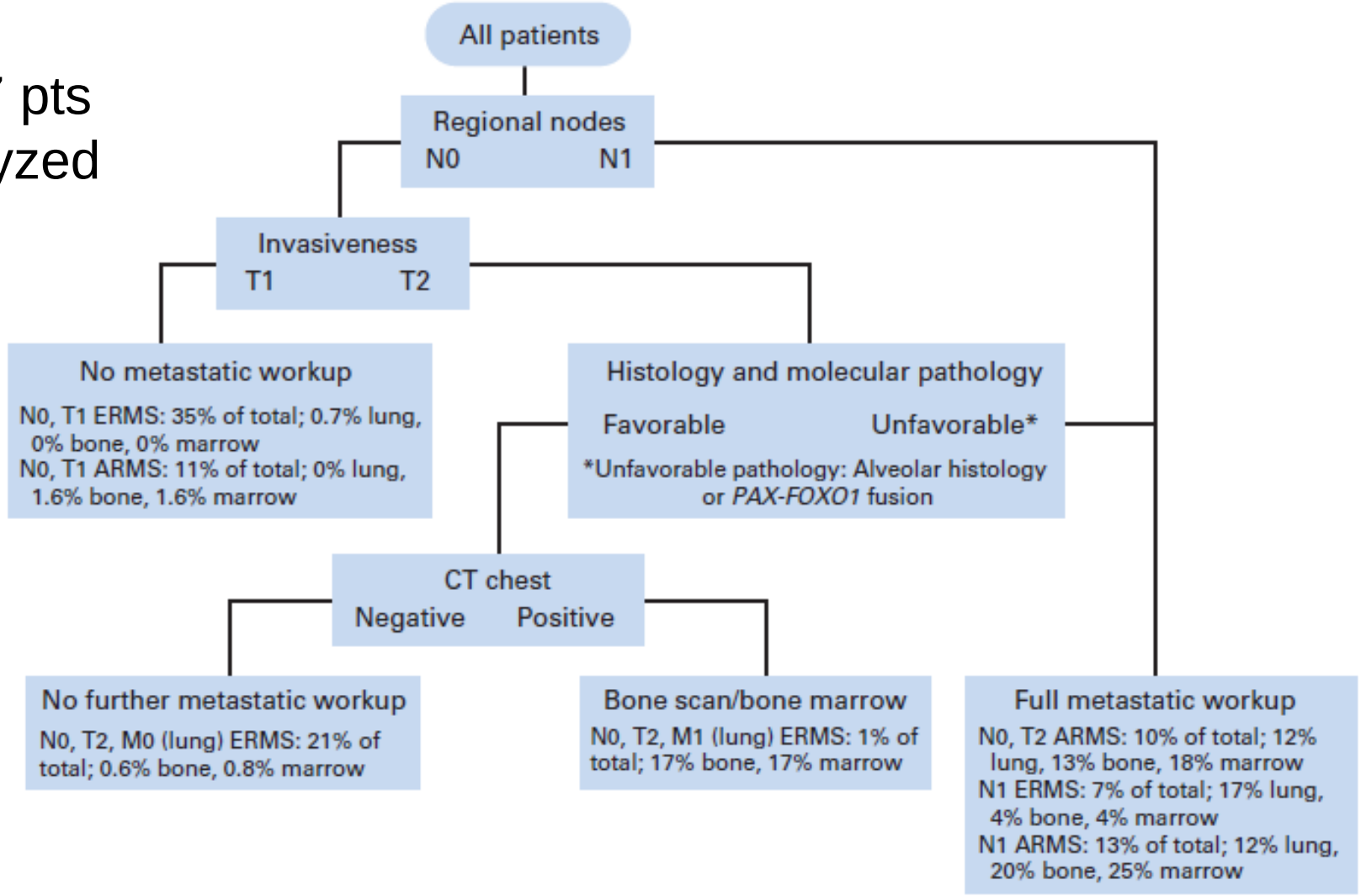
Work–up for Rhabdomyosarcoma

- Chest X-ray
- CT scan of chest
- MRI base of skull and brain (parameningeal)
- CT scan of abdomen and pelvis (genitourinary and extremity sites)
- Regional lymph node evaluation
- Bone scan (selected cases)
- Bone marrow biopsy and aspirate (selected cases)

NCI PDQ Summary 2017

Staging Evaluation (COG Soft Tissue Sarcoma Group)

1687 pts analyzed



Weiss AR et al. J Clin Oncol 2013; 31:3226-3232

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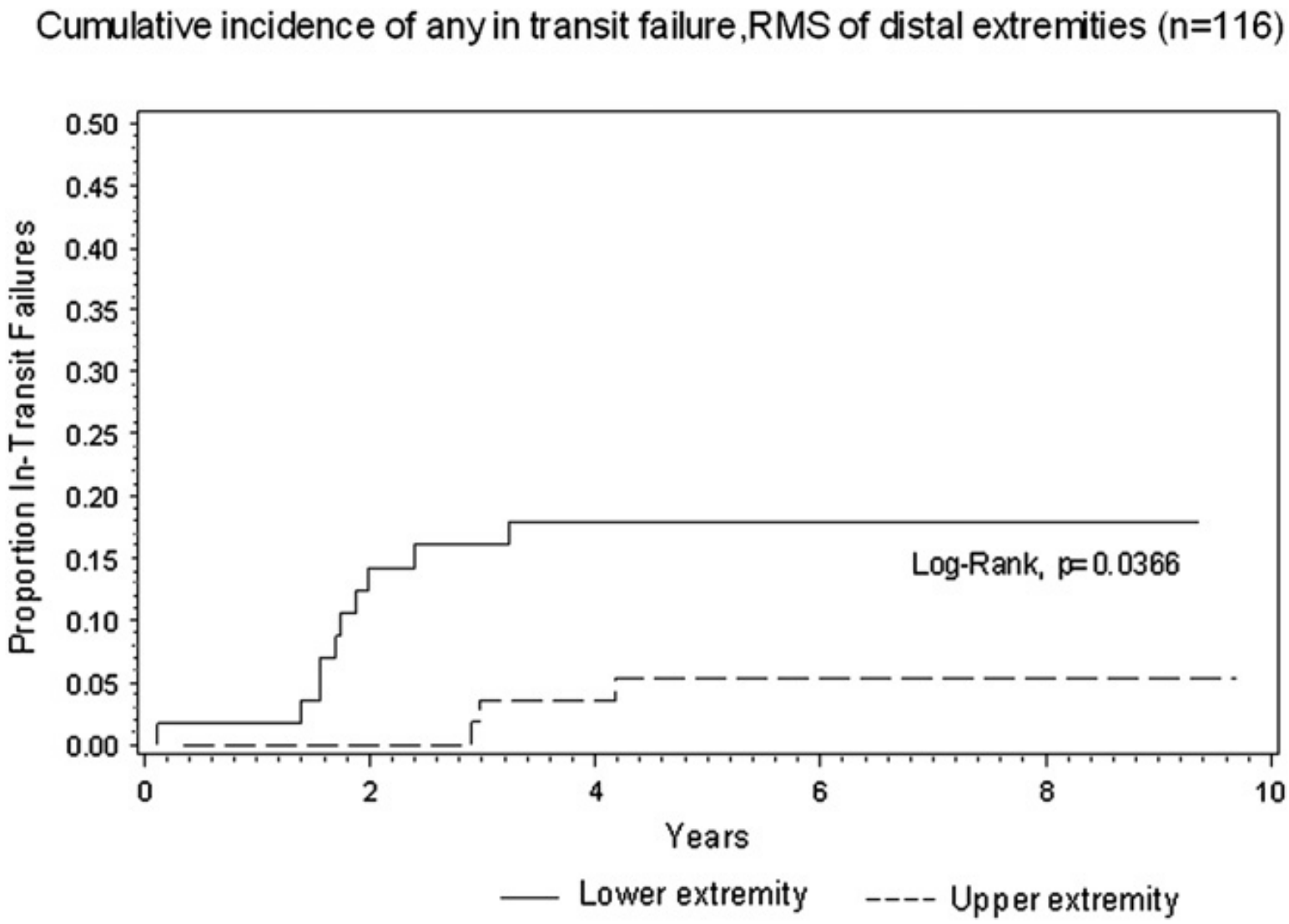
Lymph node Metastases

Site	Number of Patients	Lymph Node Metastases
Extremity	181	22 (12%)
Paratesticular	107	28 (26%)
Bladder	29	6 (21%)
Prostate	12	5 (42%)
Female genital organs	17	1 (6%)
Orbit	39	0 (0%)
Other head & neck	96	8 (8%)
Trunk	65	2 (3%)

Lawrence W Jr. et al. Cancer 1987; 60:910-5

In-Transit Lymph Node Spread in Extremity



La TH et al. Int J Radiat Oncol Biol Phys 2011; 80:1151-7

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Retroperitoneal Lymph Node Dissection in Paratesticular Rhabdomyosarcoma (SEER)

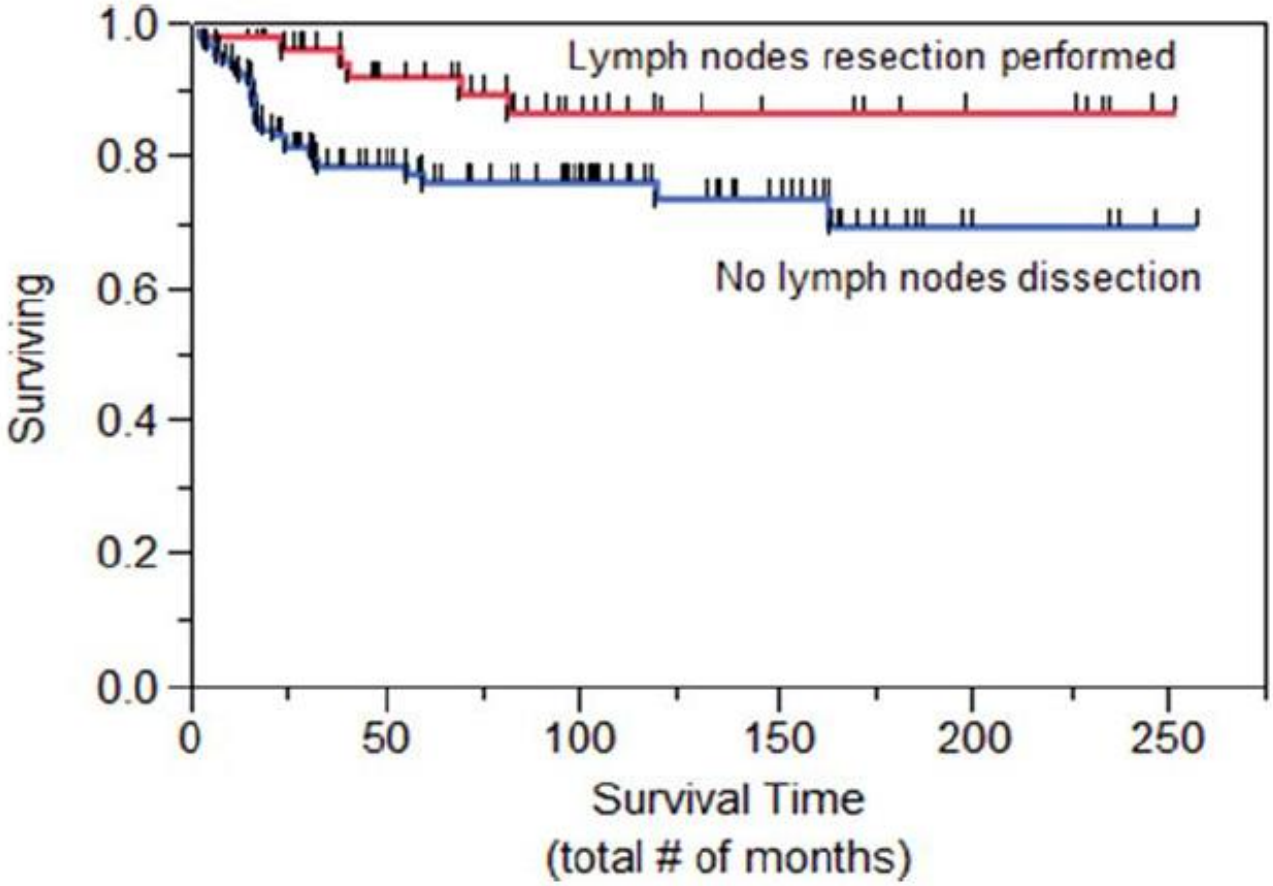

Figure 2. Overall survival of patients with paratesticular rhabdomyosarcoma treated with and without lymph node dissection is shown ($P = .028$).

Dang ND et al. Cancer 2013; 119:3228-3233

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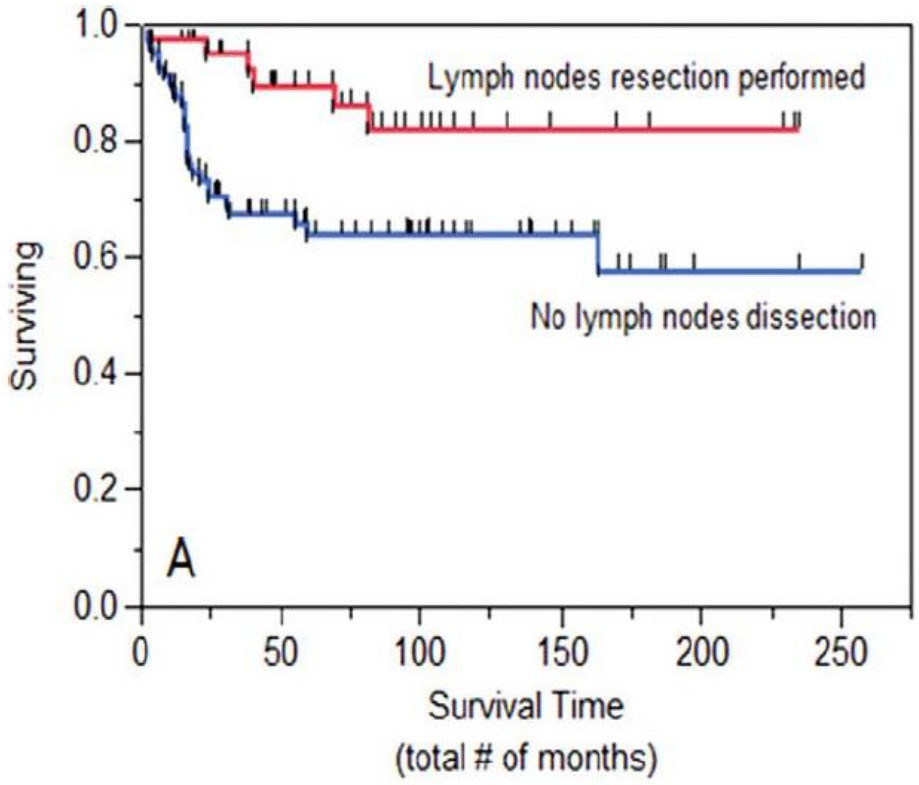
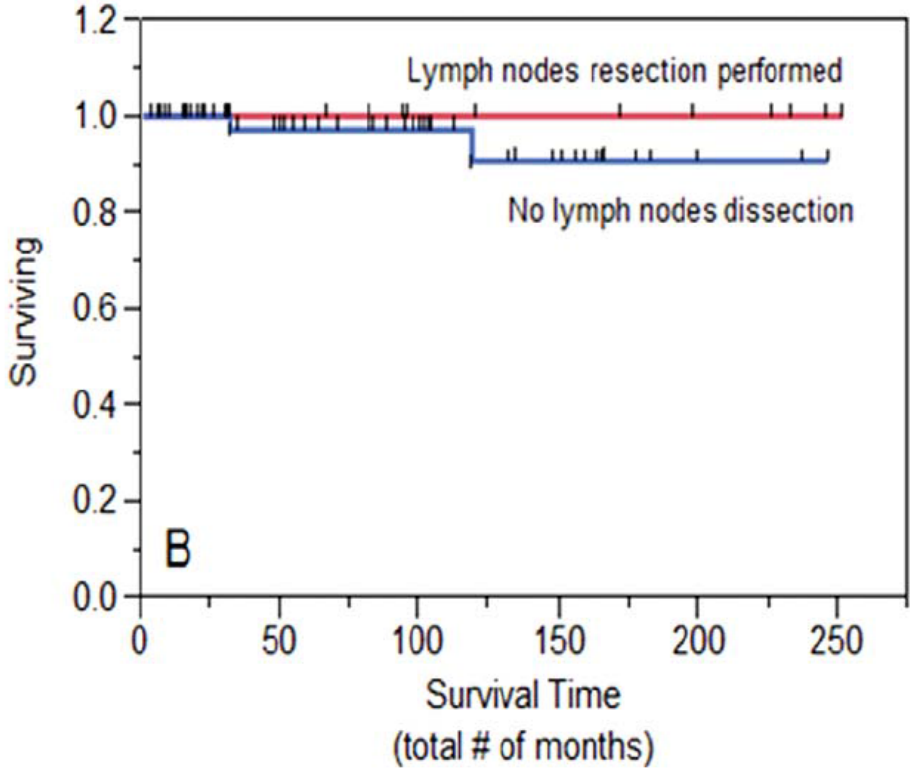
Retroperitoneal Lymph Node Dissection in Paratesticular Rhabdomyosarcoma (SEER)

Age ≥ 10 years (p = 0.009)



Age < 10 years (p = 0.37)



Dang ND et al. Cancer 2013;
119:3228-3233

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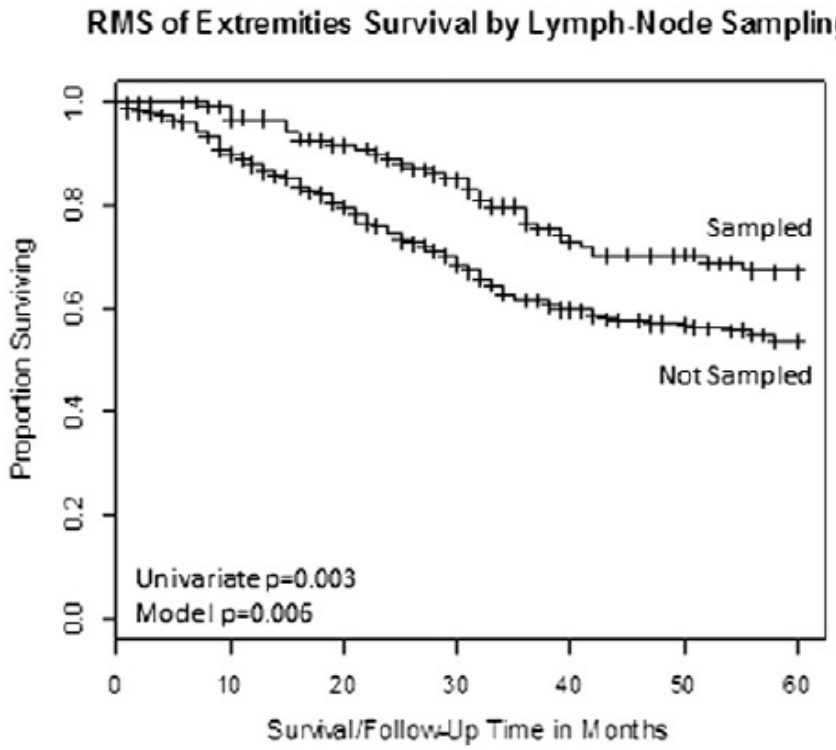
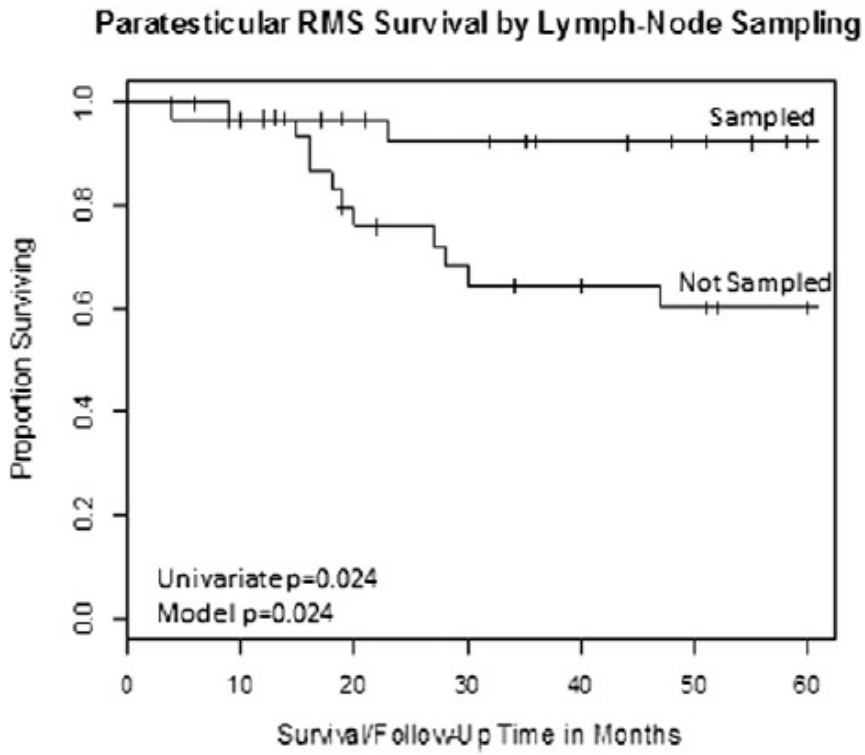
Lymph Node Sampling





Lobeck I et al. J Pediatr Surg 2017; 52:614-17

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Lymph Node Evaluation

- Imaging of regional nodes (head and neck – cervical and supraclavicular nodes, lower extremity – inguinal/femoral nodes, upper extremity – axillary nodes)
- Sentinel node biopsy and sampling for extremity tumors
- Ipsilateral retroperitoneal dissection for imaging positive paraaortic nodes or > 10 year old male with paratesticular rhabdomyosarcoma

Alveolar Head & Neck RMS and Nodal Failure: MD Anderson Experience

- 14 patients with alveolar head and neck RMS. Six of 14 had nodal disease at presentation
- 6/8 (75%) regional nodal relapses occurred in patients with no evidence of nodal disease (N0) at presentation.
- The other two nodal failures were in N+ neck. One had marginal failure and the other occurred in the neck when the entire region was not treated just the involved nodal area
- Currently doing prophylactic nodal irradiation and including all stations at risk

Ludmir EB et al. ASTRO 2017

PET-CT and Nodal Assessment

TABLE II. Comparison of PET–CT and Conventional Imaging (CI) Assessment of Lymph Nodes Measuring ≥1.0 cm in Greatest Diameter

	PET–CT assessment			
Conventional imaging	Benign (n)	Malignant (n)	Indeterminate (n)	CI total (n)
Assessment				
Benign	3	0	0	3
Malignant	1	15	0	16
Indeterminate	17	0	1	18
PET–CT total (n)	21	15	1	37

Federico SM et al. Pediatr Blood Cancer 2013; 60:1128-34

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PET-CT on Rhabdomyosarcoma

Table 2 Summary of patient-level diagnostic data: detection of nodal and distant metastatic involvement

Study	Image	N	Sensitivity		Specificity	
			PET	Conventional imaging	PET	Conventional imaging
Nodal involvement						
Federico *et al*[18]	PET-CT	30	0.8	–	1	–
Ricard *et al*[26]	PET-CT	13	1	0.75	0.89	1
Tateishi *et al*[19]	PET-CT	35	1	0.86	0.95	0.9
Volker *et al*[20]	PET	4*	1	0.67	1	1
Distant metastatic involvement						
Federico *et al*[18]	PET-CT	30	1	0.17	0.92	1
Ricard *et al*[26]	PET-CT	13	1	0.83	1	0.86
Tateishi *et al*[19]	PET-CT	35	0.95	0.55	0.8	0.43

*Total N=46; 12 RMS; data available on 4 with extremity primary tumour.
PET, positron emission tomography; RMS, rhabdomyosarcoma.

PET-CT may increase initial staging accuracy, specifically in the detection of nodal and distant metastatic spread.
Limited data on outcome according to PET-CT response

Norman G et al. BMJ Open 2015; 5:e006030

PET-CT and Locoregional Control Before Chemo, Before RT and After RT

Table 2 Summary of 3-y local relapse-free survival (LRFS) estimates based on PET or coregistered CT studies performed at 3 time points of interest

	Baseline imaging			Preradiation imaging			Postradiation imaging		
LRFS	SUV ≤7 (95% CI)	SUV >7 (95% CI)	*P*	PET− (95% CI)	PET+ (95% CI)	*P*	PET− (95% CI)	PET+ (95% CI)	*P*
Based on PET results	96% (89%-100%)	79% (62%-96%)	.08	97% (90%-100%)	81% (69%-93%)	.06	94% (88%-100%)	75% (56%-93%)	.02
	≤5 cm (95% CI)	>5 cm (95%CI)	*P*	≤2.4 cm (95% CI)	>2.4 cm (95% CI)	*P*	0 cm (immeasurable residual or no mass) (95% CI)	>0 cm (measurable residual mass) (95% CI)	*P*
Based on tumor size by CT	93% (84%-100%)	81% (64%-98%)	.13	94% (86%-100%)	80% (65%-95%)	.10	92% (83%-100%)	69% (46%-92%)	.01

Abbreviations: 95% CI = 95% confidence interval; CT = computed tomography; PET = positron emission tomography; PET− = PET negative; PET+ = PET positive.

Dharmarajan KV et al. Int J Radiat Oncol Biol Phys 2012; 84:996-1002

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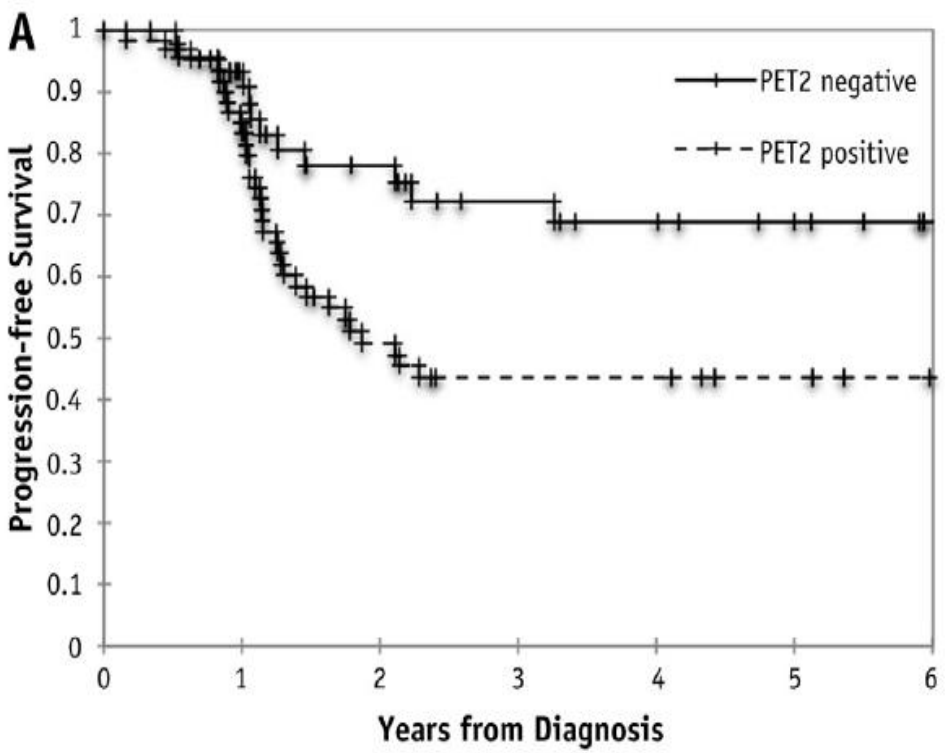
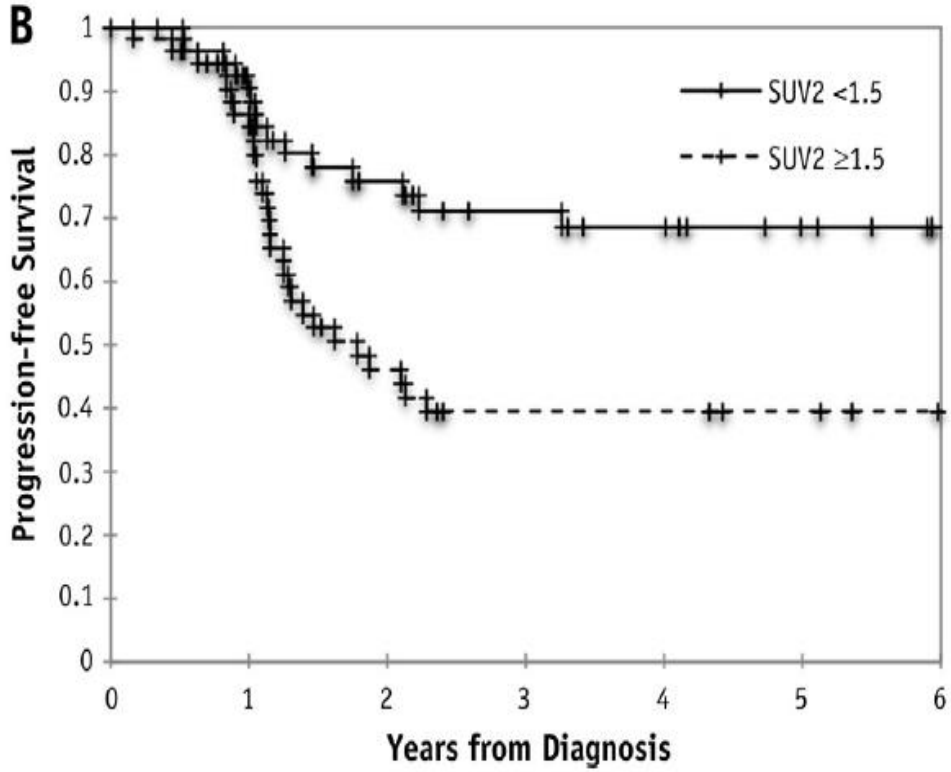
Post Induction-Chemo PET



p = 0.01



p = 0.005

Casey DL et al. Int J Radiat Oncol Biol Phys 2014; 90: 1136-42

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Staging Process

- Assign a Stage – determined by primary site, tumor size (widest dimension), and presence or absence of lymph node and/or distant metastasis

- Assign a Group – determined by the status of initial surgical resection or biopsy, with pathologic assessment of margin and lymph node involvement, before initiation of therapy

- Assign a Risk Group – determined by stage, group and histology

Rhabdomyosarcoma Stage

Stage	Sites	Tumor Invasiveness	Tumor Size	Lymph Node Status	Metastasis
1	Orbit Other H&N Non-bladder, non-prostate GU Biliary Tract	T1/T2	A or B	Any N	M0
2	Bladder or prostate Extremity Parameningeal Other	T1/T2	A	N0 or Nx	M0
3	Same a Stage 2	T1/T2	A B	N1 Any N	M0
4	All	T1/T2	A or B	Any N	M1

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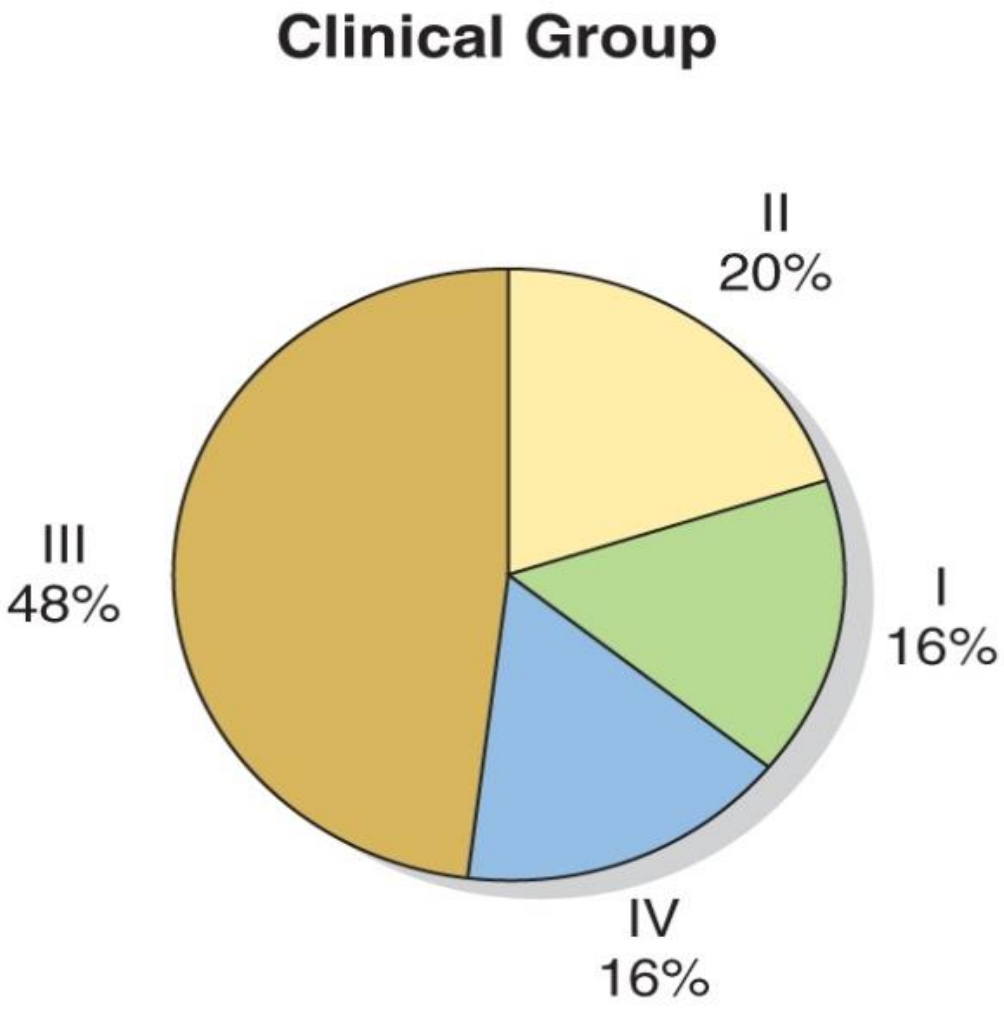
Rhabdomyosarcoma Grouping System

Group I	Localized disease, completely resected
	a. Confined to muscle or organ of origin
	b. Infiltration outside the muscle or organ of origin
Group II	Gross total resection with
	a. Microscopic residual disease
	b. Regional lymphatic spread, resected
	c. Both
Group III	Incomplete resection with gross residual disease
	a. After biopsy only
	b. After major resection (more than 50%)
Group IV	Distant metastatic disease present at onset



McDonald SM et al. In Halperin EC et al. Pediatric Radiation Oncology 2011

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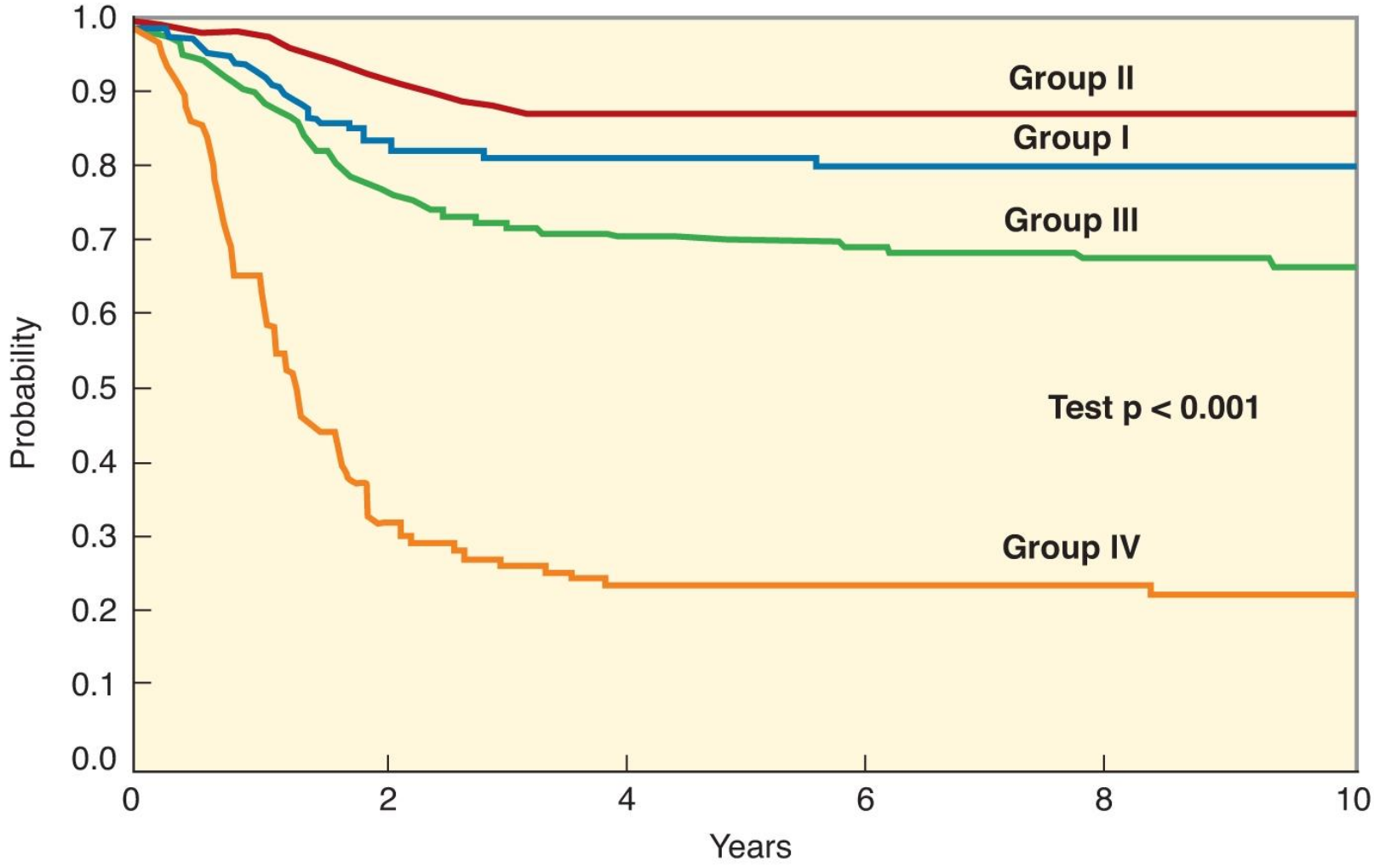
Outcome According to Group



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Stage, Group and Risk Stratification

B. RMS Staging and Risk Stratification

Stage

Group
- I Gross resection, negative margins
- II Gross resection, microscopic positive margins, with or without regional nodal spread
- III Biopsy only or gross residual disease
- IV Distant metastases present (including malignant pleural/peritoneal effusion, tumor implants, CSF involvement)

Stage
- 1 Favorable site
- 2 Unfavorable site, < 5 cm (OR any size bladder/ prostate), no evidence of nodal disease
- 3 Unfavorable site, > 5 cm (OR evidence of nodal involvement)
- 4 Metastatic disease

Site

Favorable
- Orbit
- Head and neck (not parameningeal)
- Genitourinary (not bladder/prostate)
- Biliary tract/liver

Unfavorable
- Parameningeal
- Extremity
- Bladder/prostate
- Not otherwise specified

Risk Stratification

Low (FN only)	Group I, Stage 1, 2 Group II, Stage 1, 2 Group III, Stage 1 orbit
Intermediate (any)	Group I/II/III FP-RMS any stage Group I/II, Stage 3 FN-RMS Group III any stage FN-RMS (except for orbit) Group IV, Stage 4 FN-RMS age <10 yo
High (any)	Group IV, Stage 4 FN-RMS age > 10 yo Group IV, Stage 4 FP-RMS

FN: Fusion negative
FP: Fusion positive

Borinstein SC et al. Pediatr Blood Cancer 2017; e26809

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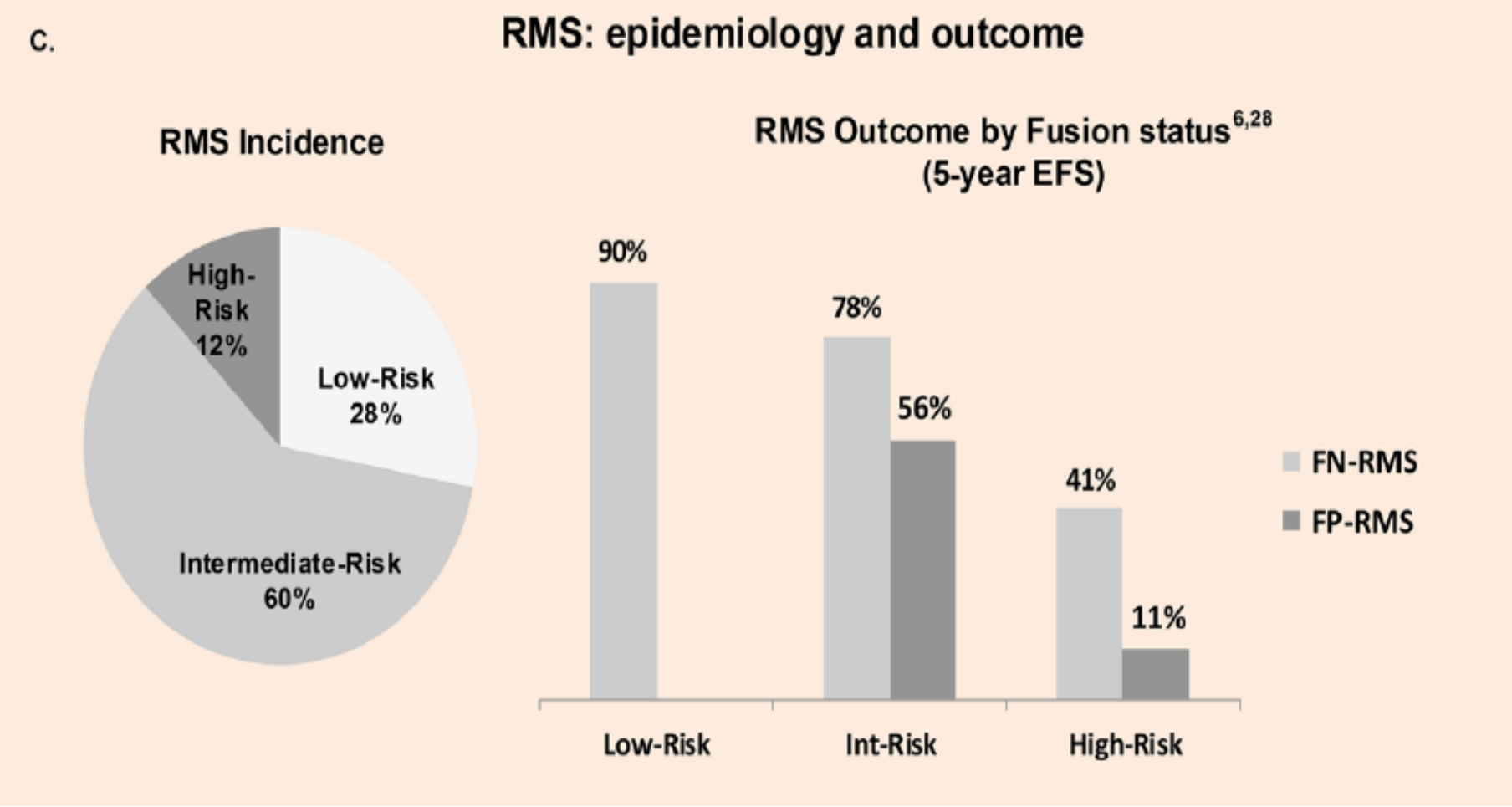
Stage, Group and Risk Stratification



Borinstein SC et al. Pediatr Blood Cancer 2017; e26809

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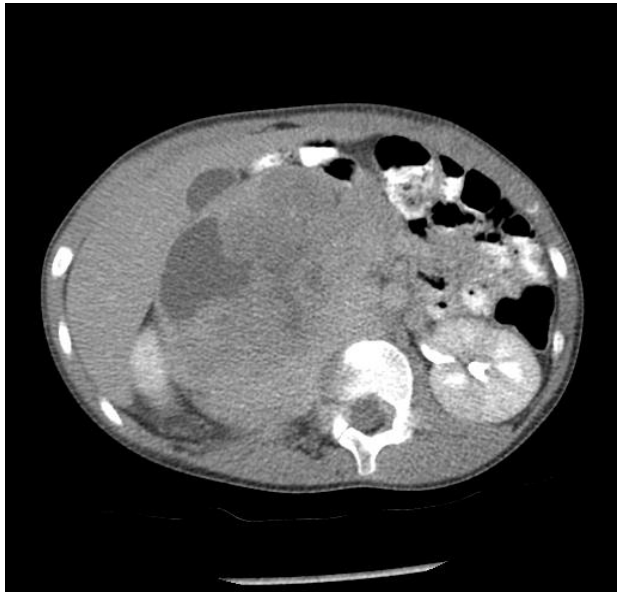
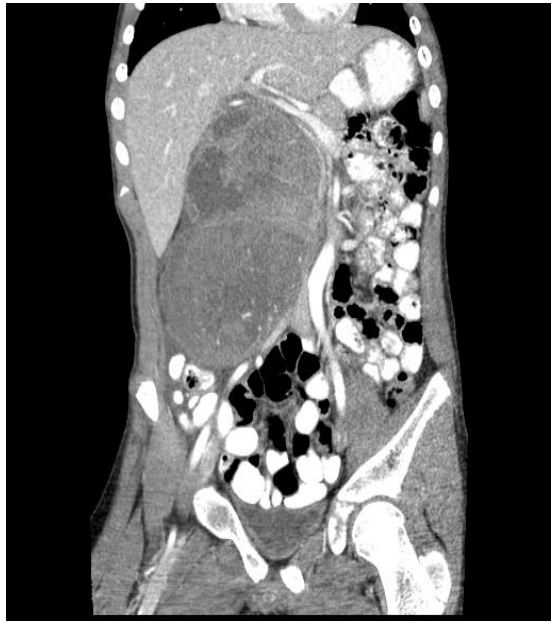
EXAMPLES OF STAGE, GROUP AND RISK GROUP

Case 1: Retroperitoneal Mass

- 12 year old female patient with biopsy proven embryonal RMS arising from the retroperitoneum
- Work up negative for lymph node and distant metastasis





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Case 1: Retroperitoneal Mass

- STAGE
  - unfavorable site
  - invasive
  - > 5 cm
  - No
  - Mo

  Stage 3

- GROUP
  - biopsy only
  - No
  - Mo

  Group III

INTERMEDIATE RISK GROUP

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Case 2: Paratesticular Mass

- 13 year old boy with left testicular enlargement
- Ultrasound reveals a left scrotal mass
- Patient underwent left inguinal orchiectomy which revealed a 4 cm embryonal rhabdomyosarcoma with negative margins of resection
- CT scan of the abdomen did not reveal any nodal metastasis
- Ipsilateral nodal dissection revealed 2 of 7 left paraaortic nodes had rhabdomyosarcoma
- No distant metastasis on work-up

Case 2: Paratesticular Mass

- STAGE
  - favorable site
  - invasive
  - < 5 cm
  - N1
  - M0

  Stage 1

- GROUP
  - complete removal
  - negative margins
  - LN +, removed

  Group II

LOW RISK GROUP

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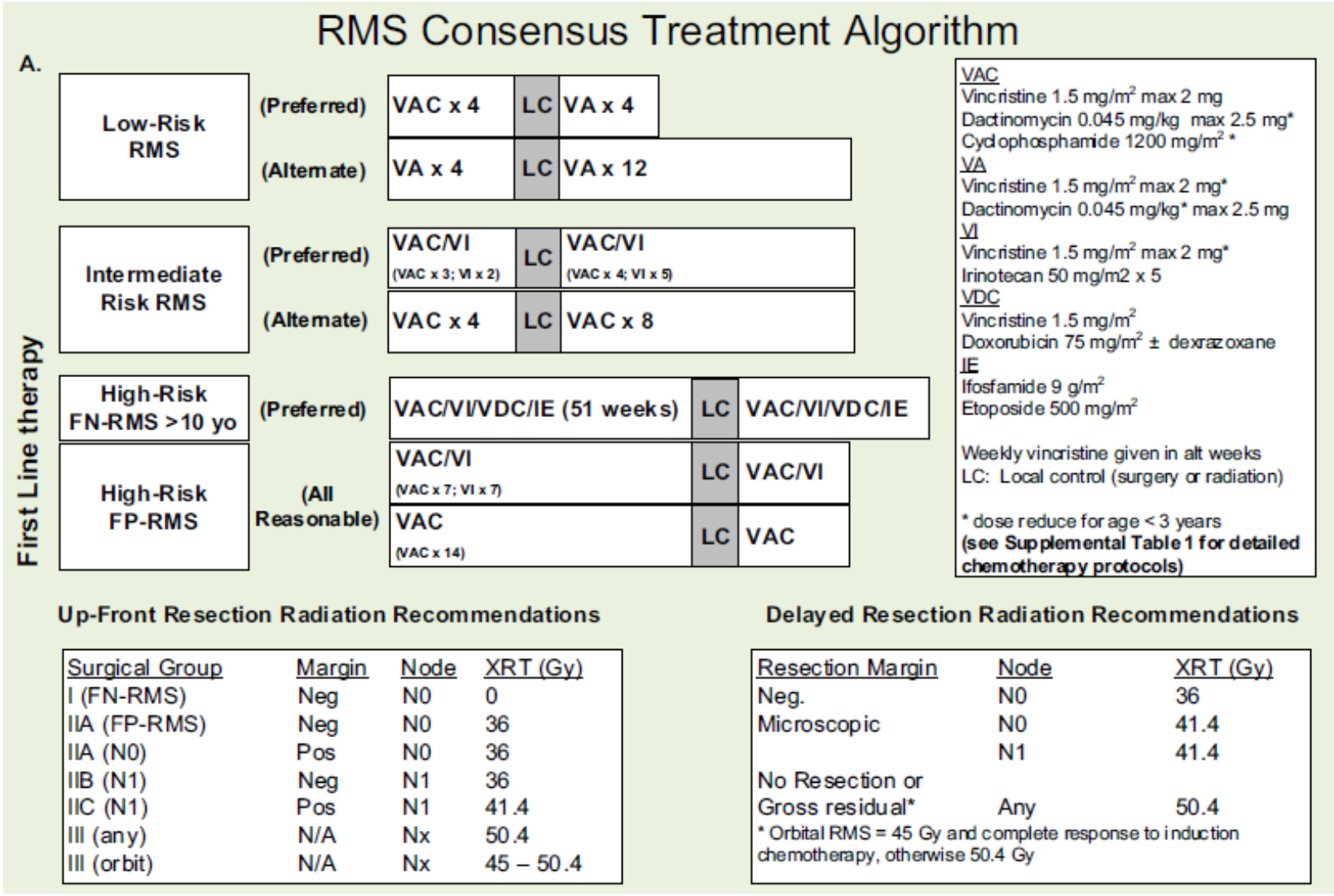
Treatment Algorithm



Up-Front Resection Radiation Recommendations

Surgical Group	Margin	Node	XRT (Gy)
I (FN-RMS)	Neg	N0	0
IIA (FP-RMS)	Neg	N0	36
IIA (N0)	Pos	N0	36
IIB (N1)	Neg	N1	36
IIC (N1)	Pos	N1	41.4
III (any)	N/A	Nx	50.4
III (orbit)	N/A	Nx	45 – 50.4

Delayed Resection Radiation Recommendations

Resection Margin	Node	XRT (Gy)
Neg.	N0	36
Microscopic	N0	41.4
	N1	41.4
No Resection or Gross residual*	Any	50.4

* Orbital RMS = 45 Gy and complete response to induction chemotherapy, otherwise 50.4 Gy

Borinstein SC et al. Pediatr Blood Cancer 2017; e26809

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Rhabdomyosarcoma: Role of Radiotherapy

Arnold C. Paulino, MD, FACR, FASTRO
Professor of Radiation Oncology
MD Anderson Cancer Center

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

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Goals and Objectives

At the end of the presentation, the participant should be able to

1. Discuss general principles of treatment for children with rhabdomyosarcoma
2. Discuss acceptable radiotherapy doses and volumes used in rhabdomyosarcoma
3. Discuss outcomes according to different parameters such as radiotherapy dose, volume, fractionation and timing

Rhabdomyosarcoma

Rhabdomyosarcoma requires two types of treatment

A. Systemic – Chemotherapy

B. Local – Surgery, Radiotherapy or Both

This often gives the best results

Local Control

Surgery

- About 35% of cases at initial diagnosis resectable (15% Group I and 20% Group II)
- Mutilating for some sites (orbit, parameningeal)

Radiotherapy

- Rhabdomyosarcoma, unlike other soft tissue sarcomas, is radiosensitive
- Could be used for hard to resect sites and metastatic sites

Decision Making for Local Control: Surgery vs. Radiotherapy

- Age of the Child
- Resectability
- Functional/ Cosmetic Outcome
- Presence of Regional Node Metastasis
- Presence of Distant Metastasis

Intergroup Rhabdomyosarcoma and Children's Oncology Group Studies

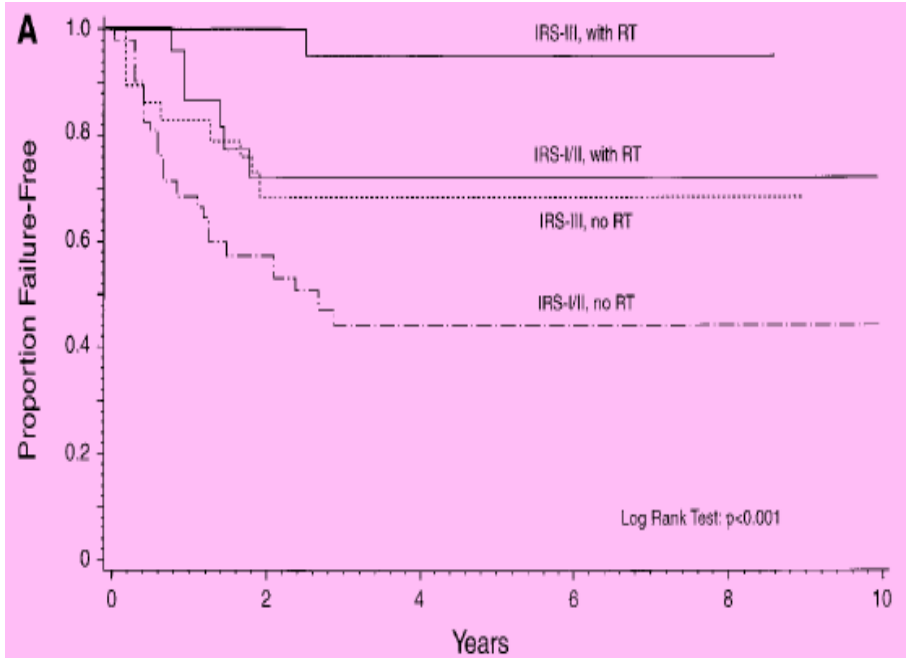
Study	Years
Intergroup Rhabdomyosarcoma Study I (IRS-I)	1972 to 1978
Intergroup Rhabdomyosarcoma Study II (IRS-II)	1978 to 1984
Intergroup Rhabdomyosarcoma Study III (IRS-III)	1984 to 1991
Intergroup Rhabdomyosarcoma Study IV (IRS-IV)	1991 to 1997
IRS V - D9803 (Intermediate Risk)	1999 to 2005
IRS V - D9602 (Low Risk)	1997 to 2004
IRS V - D9802 (High Risk)	1999 to 2004
Children's Oncology Group ARST0331 (Low Risk)	2004 to 2008
Children's Oncology Group ARST0431 (High Risk)	2006 to 2008
Children's Oncology Group ARST0531 (Intermediate Risk)	2006 to 2014
Children's Oncology Group ARST1431 (Intermediate Risk)	Open

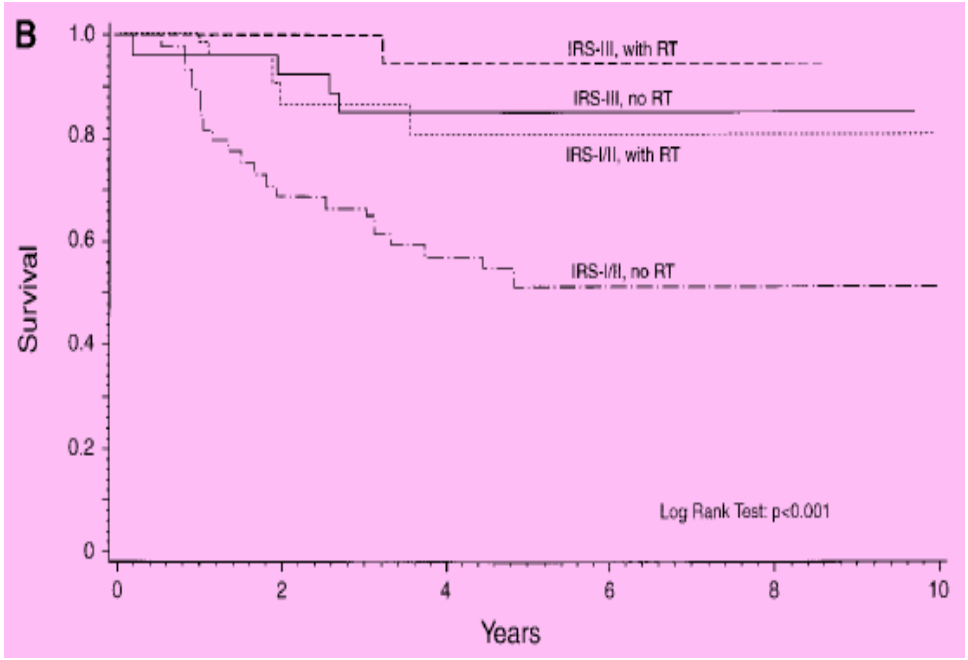
Who needs radiation?

- Group I, alveolar/Fusion positive RMS
- Group II
- Group III
- Group IV

Unfavorable histology and Radiotherapy (IRS I to III)

Unfavorable histology = alveolar RMS and undifferentiated sarcoma





Wolden SL et al. J Clin Oncol 1999; 17:3468-75

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Radiotherapy Dose

Radiotherapy Dose Recommendations in IRS-IV and IRS-V

Group	Radiotherapy Dose (Gy) IRS-IV	Radiotherapy Dose (Gy) IRS-V
I (embryonal)	0	0
I (alveolar)	41.4	36
IIA (+ margins)	41.4	36
IIB (+ nodes, resected)	41.4	41.4
III (orbit)	50.4 or 59.4	45
III (non-orbit)	50.4 or 59.4	50.4
IV	50.4	50.4

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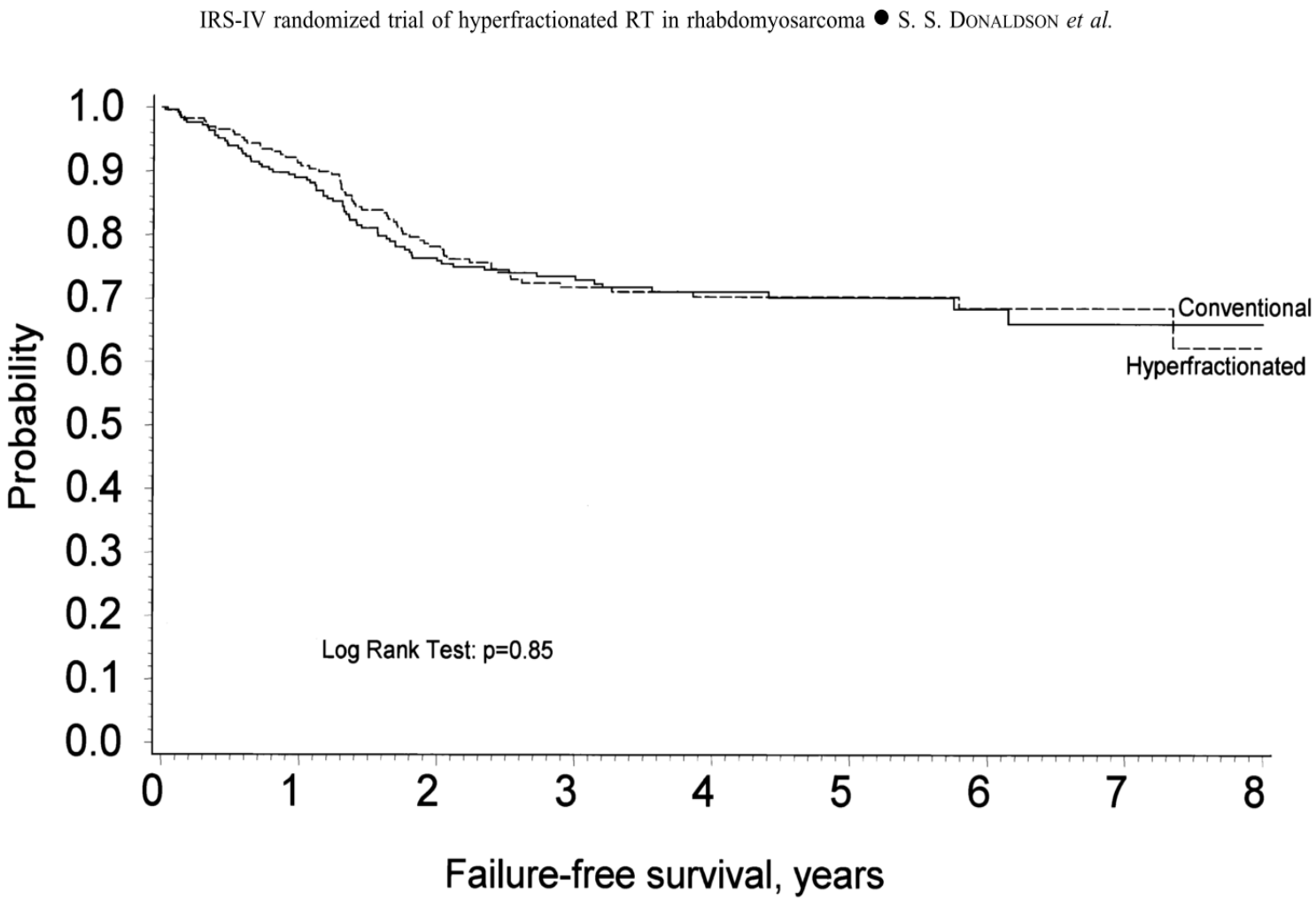
EpSSG RMS Radiotherapy

IRS Group	**embryonal RMS**	**alveolar RMS**
I	no RT	41.4 Gy; 23 F
IIa, b and c	41.4 Gy; 23 F	41.4 Gy; 23 F
III followed by:		
- secondary complete resection	36 Gy; 20 F *(partial response)* 41.4 Gy; 23 *F (minor partial response, SD)* *Subgroup C: option A (no RT) or B (36 Gy)*	41.4 Gy; 23 F
- second look surgery but incomplete secondary resection	50.4 Gy; 28 F	50.4 Gy; 28 F
- clinical complete remission, no second look surgery	41.4 Gy; 23 F	50.4 Gy; 28 F
- partial remission, minor PR, SD, progressive disease, no second surgery	50.4 Gy; 28 F (+ Boost of 5.4 Gy; 3 F) orbit and PR (>2/3) 45 Gy; 25 F	50.4 Gy; 28 F (+ Boost of 5.4 Gy; 3 F)

from Henry Mandeville (ASTRO 2017)

Dose Escalation for Group III RMS (IRS-IV)



Donaldson SS et al. Int J Radiat Oncol Biol Phys 2001; 51:718-28

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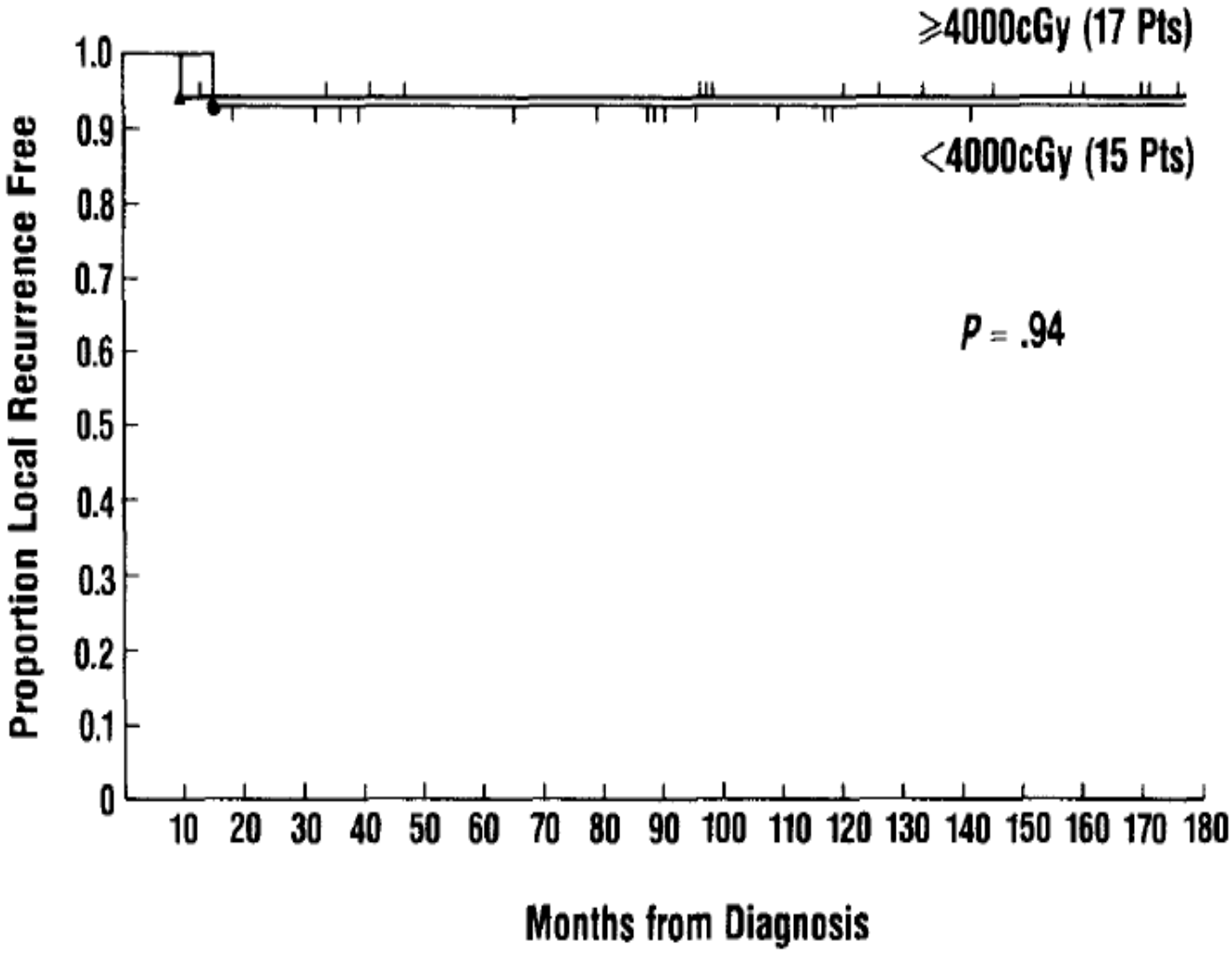
Randomized Trial IRS-IV

- No difference in local failure between conventional and hyperfractionated arms
- Acute toxicity (mucositis 66% vs. 46% p = 0.03) for parameningeal sites (nausea and vomiting 13% vs. 5% p = 0.02) (skin reactions 16% vs. 7% p = 0.03) and non-parameningeal head and neck sites were increased in hyperfractionated arm
- Incidence of local failure (13%) = distant failure (13%)
- Standard of care for Group III RMS is conventional radiotherapy with chemotherapy

Dose Reduction in Group II Rhabdomyosarcoma

Group IIA (n=19),
< 40 Gy (n = 8)

Group IIC (n=13),
< 40 Gy (n = 7)



Mandell L et al. J Clin Oncol 1990; 8:1536-42

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Dose Reduction in Low-Risk Rhabdomyosarcoma

- Children's Oncology Group D9602 Study
- Eligibility:
    1. nonmetastatic rhabdomyosarcoma in a favorable site (orbit, non-parameningeal head and neck, nonprostate/nonbladder genitourinary, biliary tract)
    2. nonmetastatic rhabdomyosarcoma in an unfavorable site with gross total resection of all tumor at diagnosis (Group I or II)
    3. initially alveolar subtype included (1997) but later excluded (1999)

Breneman J et al. Int J Radiat Oncol Biol Phys 2012; 83:720-6

Group IIA RMS (+ Margin)

	N	Chemotherapy	Radiotherapy	Local Failure
Favorable Site	62	VA	36 Gy	15%
Unfavorable Site	16	VAC	36 Gy	0%

Breneman J et al. Int J Radiat Oncol Biol Phys 2012; 83:720-6

Group IIA RMS (+ Margin) Favorable Sites

	N	Chemotherapy	Radiotherapy	Local Failure
D9602	62	VA	36 Gy	15%
IRS-III	52	VA	41.4 Gy	11%
IRS-IV	43	VAC/VAI/VIE	41.4 Gy	2%

Breneman J et al. Int J Radiat Oncol Biol Phys 2012; 83:720-6

Group IIA RMS (+ Margin) Unfavorable Sites

	N	Chemotherapy	Radiotherapy	Local Failure
D9602	16	VAC	36 Gy	0%
IRS-III	38	VA	41.4 Gy	14%
IRS-IV	28	VAC/VAI/VAE	41.4 Gy	7%

Breneman J et al. Int J Radiat Oncol Biol Phys 2012; 83:720-6

Group III Orbital RMS

	N	Chemotherapy	Radiotherapy	Local Failure
D9602	77	VA	45 Gy	14%
IRS-III	71	VA	41.4-50.4Gy	16%
IRS-IV	50	VAC/VIE/VAE	50.4-59.4 Gy	4%

In the COG study (ARST0331), 45 Gy was used for Group III orbital RMS with the addition of cyclophosphamide to the chemotherapy regimen.

Breneman J et al. Int J Radiat Oncol Biol Phys 2012; 83:720-6

Group III Orbital RMS

Protocol	Dose (Gy)	Chemotherapy	Timing of RT (week)	5-year local failure rate (%)	5-year failure-free survival (%)
IRS-III (n = 71)	41.4 – 50.4	VA	2 or 6	16	79
IRS-IV (n = 49)	50.4-59.4	VAC(26.4g/m^2)/ VAI/VIE	9	2	94
D9602	45	VA	13	14	86
ARST0331	45	VAC(4.8g/m^2)	13	13	87
CR (n = 15)				0	100
PR/SD (n =38)				16	84

Ermoian RP et al. Pediatr Blood Cancer 2017; 64:e26540

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Clinical Target Volume

IRS-IV

- Blocked Edge (50.4 Gy) = GTV + 2 cm

IRS-V

- CTV1 (36 Gy) = GTV + 1.5 cm
- CTV2 (14.4 Gy) = GTV + 0.5 cm

ARST0331
ARST0431
ARST0531

- CTV1 (36 Gy) = GTV1 + 1 cm
- CTV2 (14.4 Gy) = GTV2 + 1 cm

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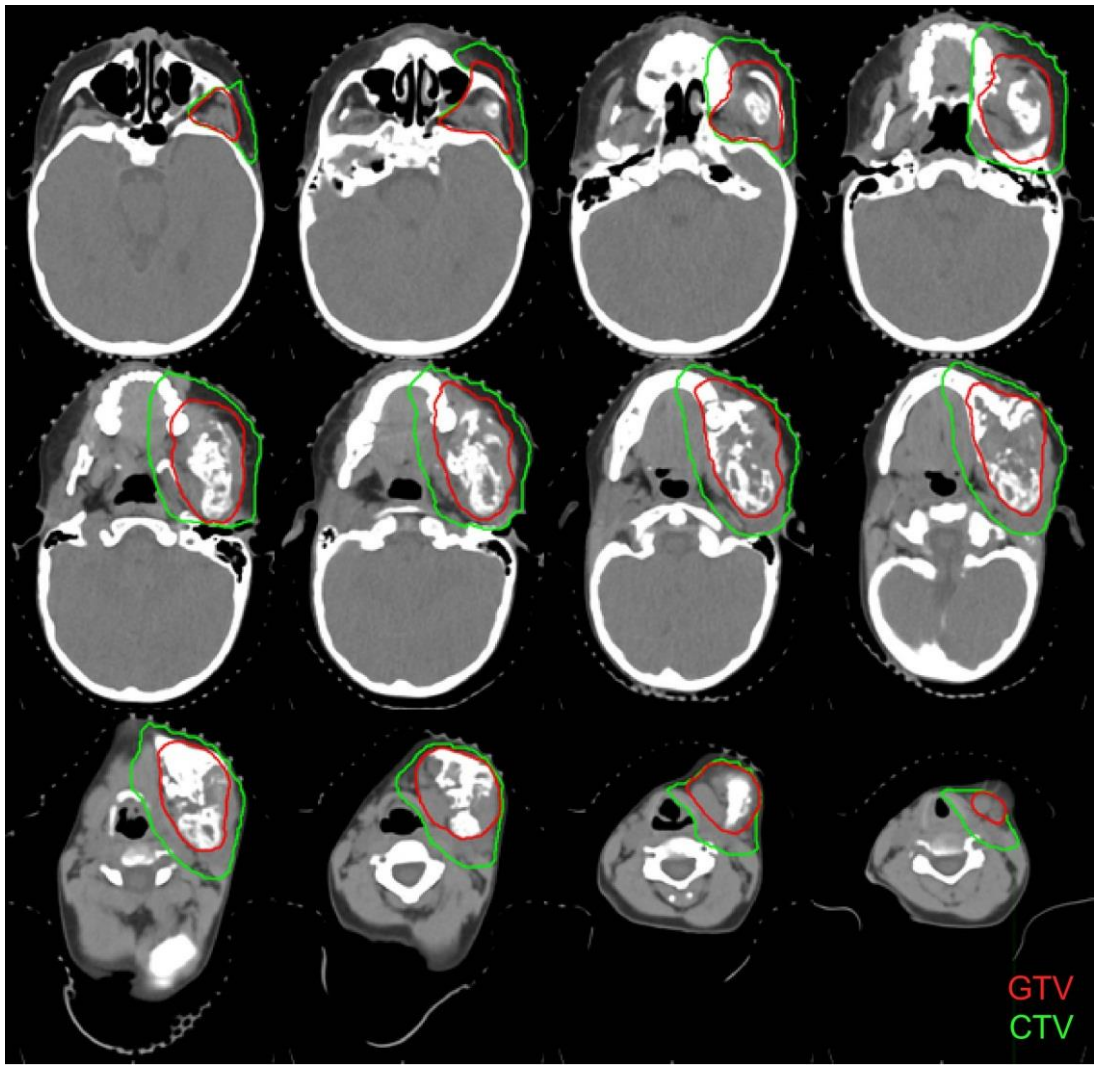
Clinical Target Volume



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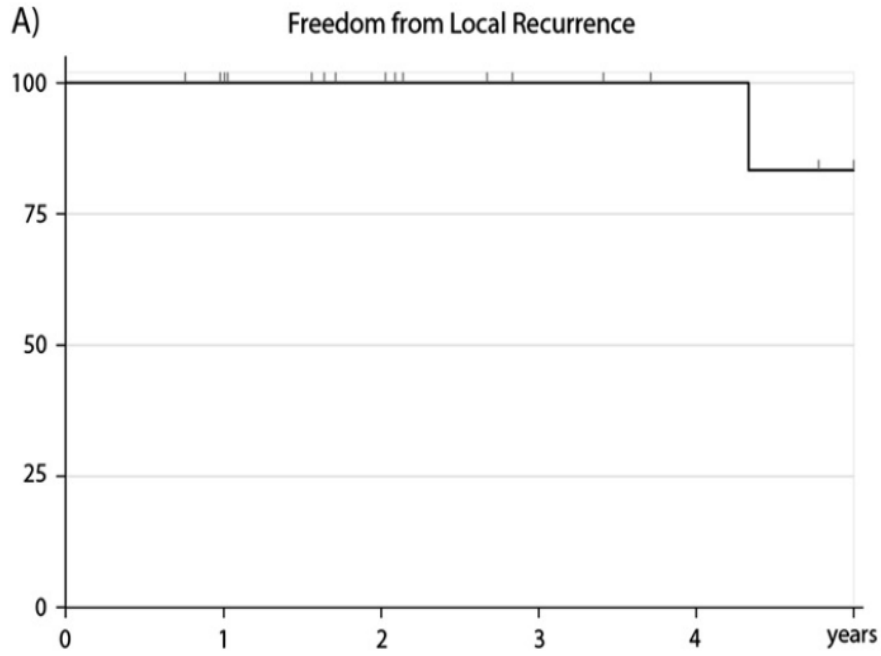
Use of Cone Down Boost

- 14 patients with head and neck RMS treated with cone down boost
- Pre-chemo volume treated to 30 – 45.6 Gy
- Post-chemo volume boosted 50.4 to 55.2 Gy
- 100% local control at 3 years



McDonald MW et al. Int J Radiat Oncol Phys 2008; 72:884-91

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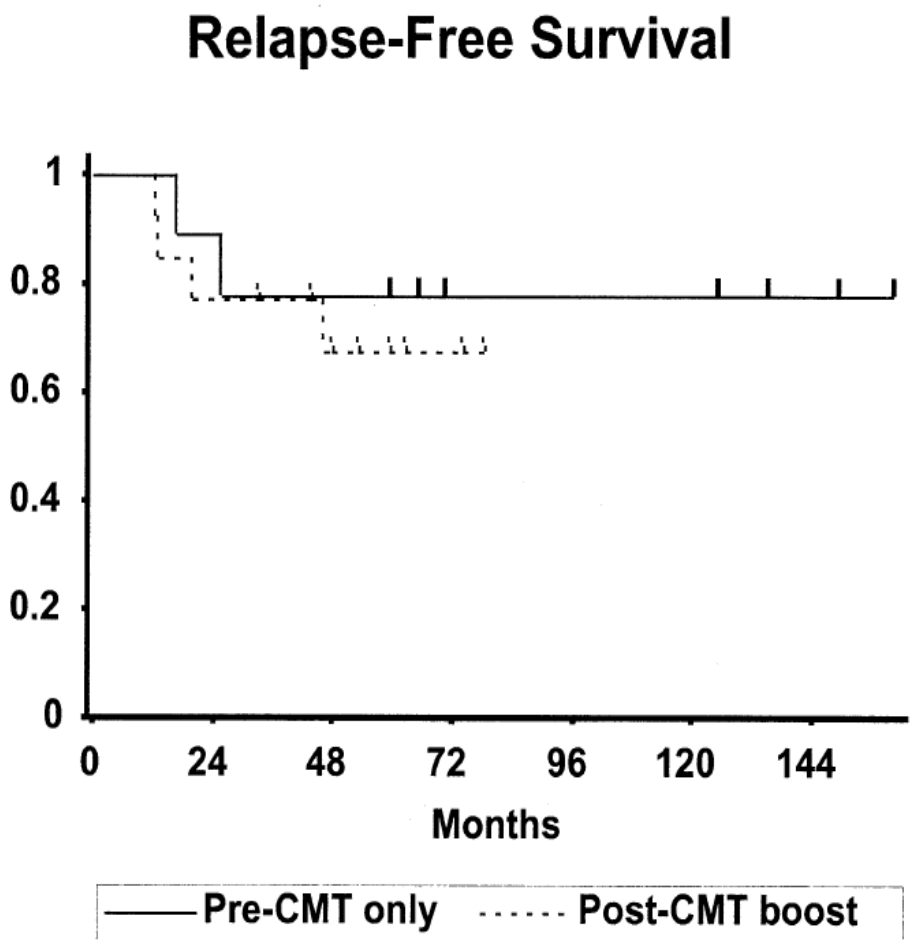
Use of Cone Down Boost

- 30 patients with parameningeal RMS
- Prior to 1992, pre-chemo volume treated to 45 – 59.4 Gy
- After 1992, pre-chemo volume treated to 30.6 – 40 Gy followed by cone down boost to 41.4 – 55.2 Gy
- No difference in local control between two time methods



Chen C et al. Int J Radiat Oncol Biol Phys 2003; 55:1294-99

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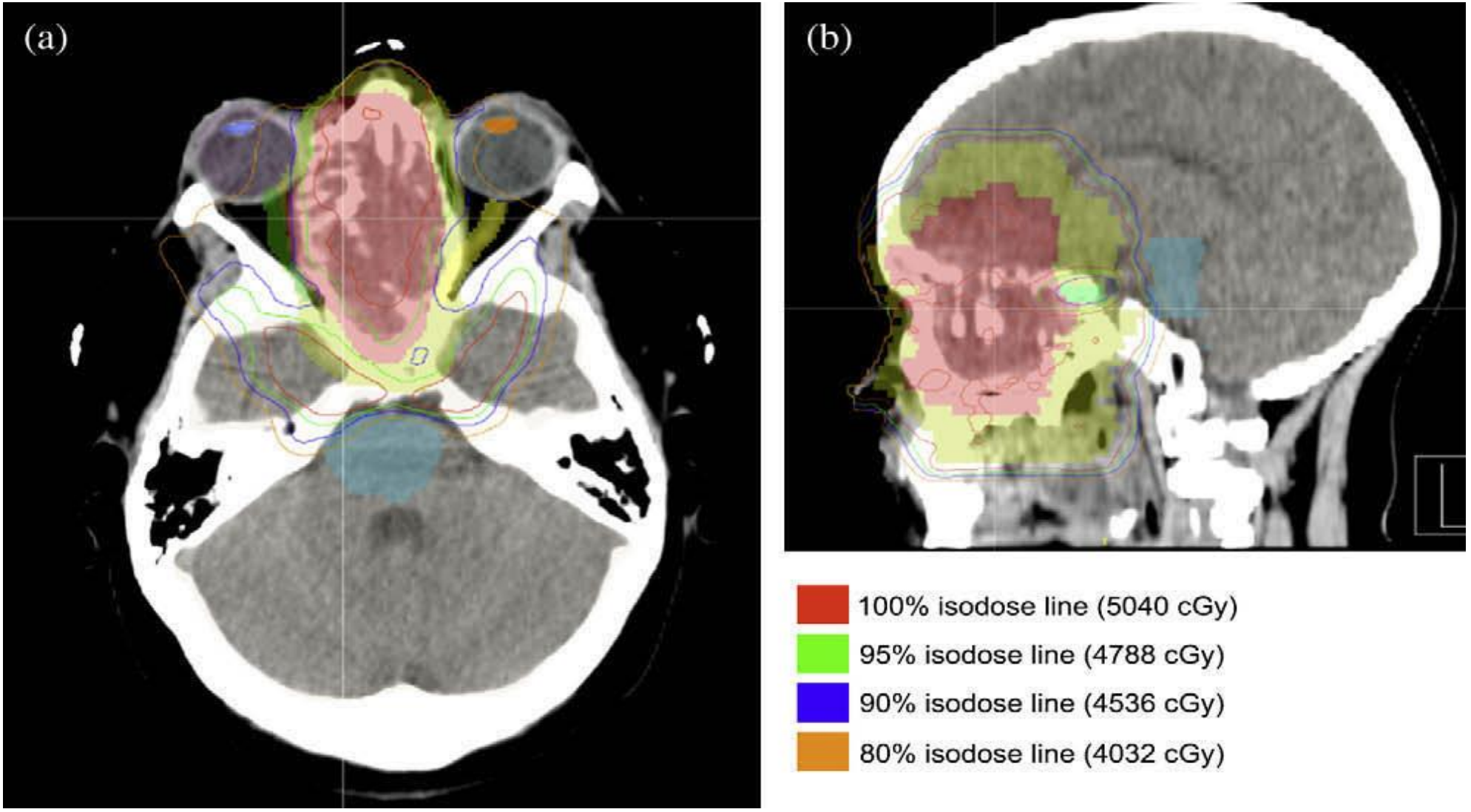
Intensity Modulated Radiation Therapy



Curtis AE et al. Int J Radiat Oncol
Biol Phys 73:173-7

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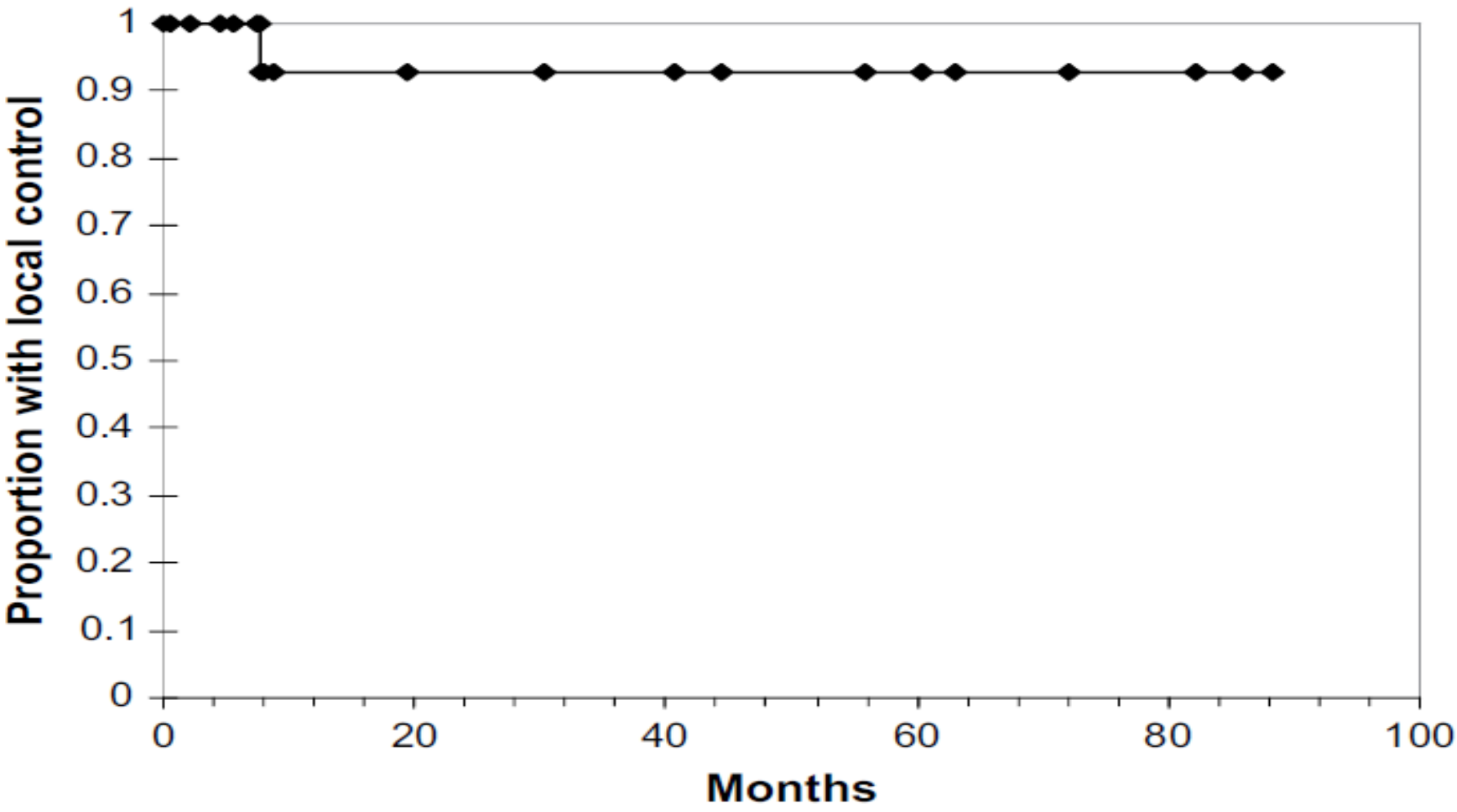
Intensity Modulated Radiation Therapy



Curtis AE et al. Int J Radiat Oncol Biol Phys 73:173-7

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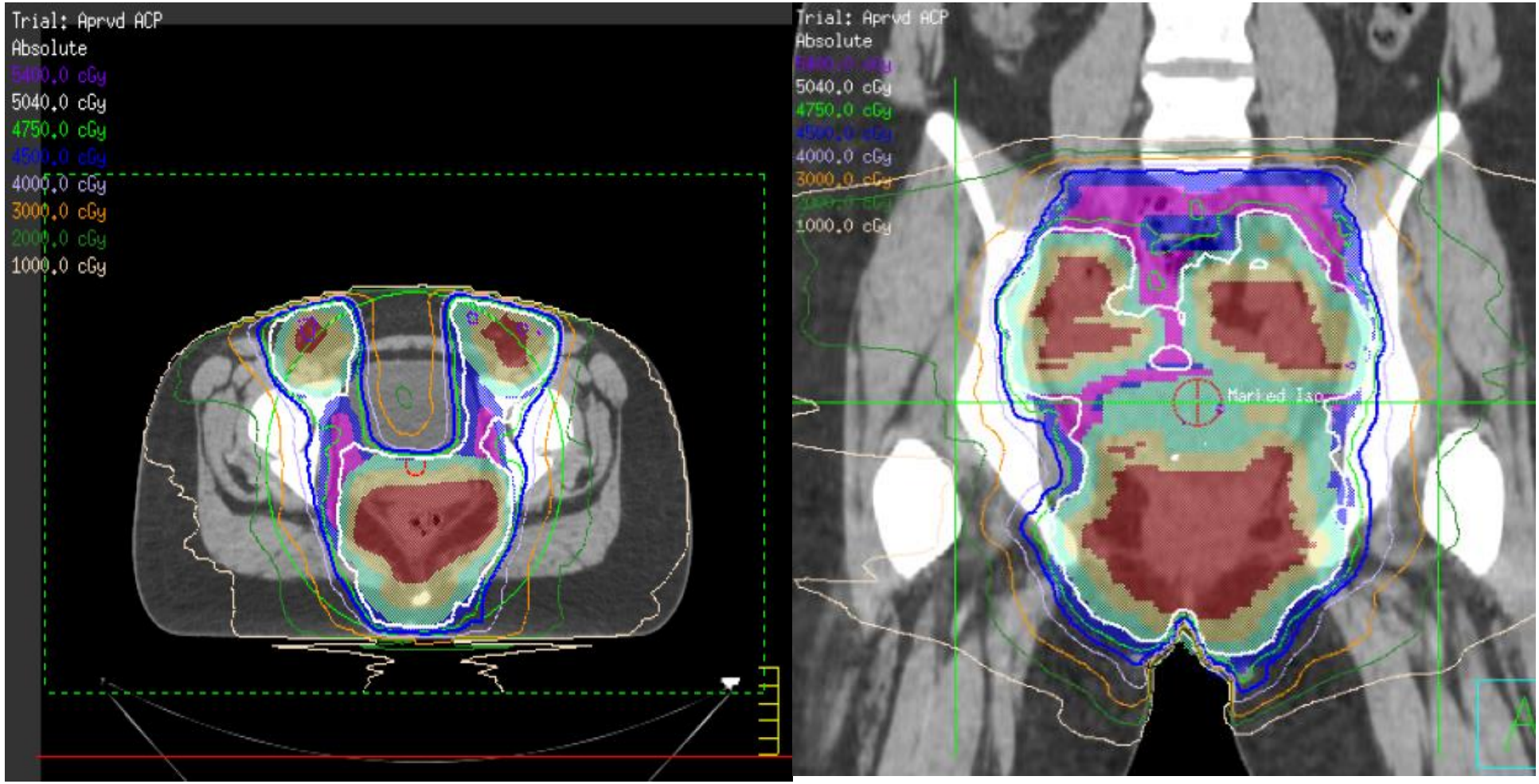
Embryonal rhabdomyosarcoma of perirectal area with bilateral inguinal metastases



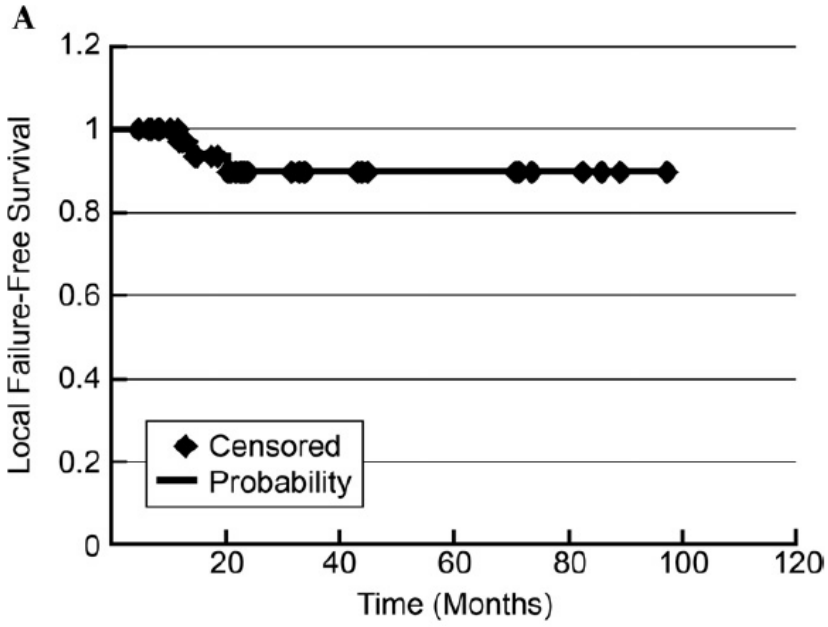
IMRT with Dose-Painting in Rhabdomyosarcoma

Table 4 Dose-volume histogram statistics for critical structures

Organ	DP-IMRT	Sequential IMRT	Difference	Decrease* (%)
Mean dose (cGy)				
Bladder	2739	3278	539	16
Bowel	1067	1281	214	17
Rectum	2977	3570	593	17
Body	605	730	125	17
Bone V_{20} (cm^3)				
Vertebral	69	90	21	23
Right femur	0	5	5	100
Pelvis	37	54	17	31
All	105	147	42	29

Abbreviations: DP = dose painting; IMRT = intensity modulated radiation therapy; V_{20} = volume receiving ≥20 Gy.

* Data are decrease in mean dose with DP-IMRT and percentage of sequential IMRT bone volume spared by DP-IMRT.



N = 41

Yang JC et al. Int J Radiat Oncol Biol Phys 2012; 84:e371-8

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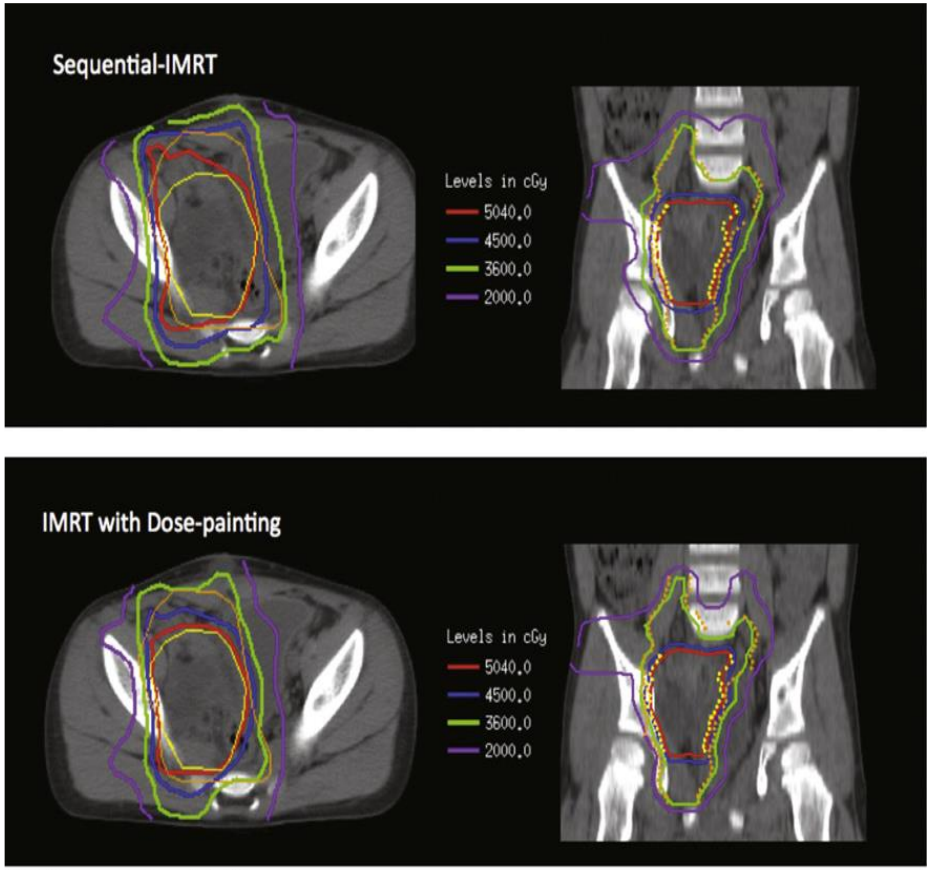
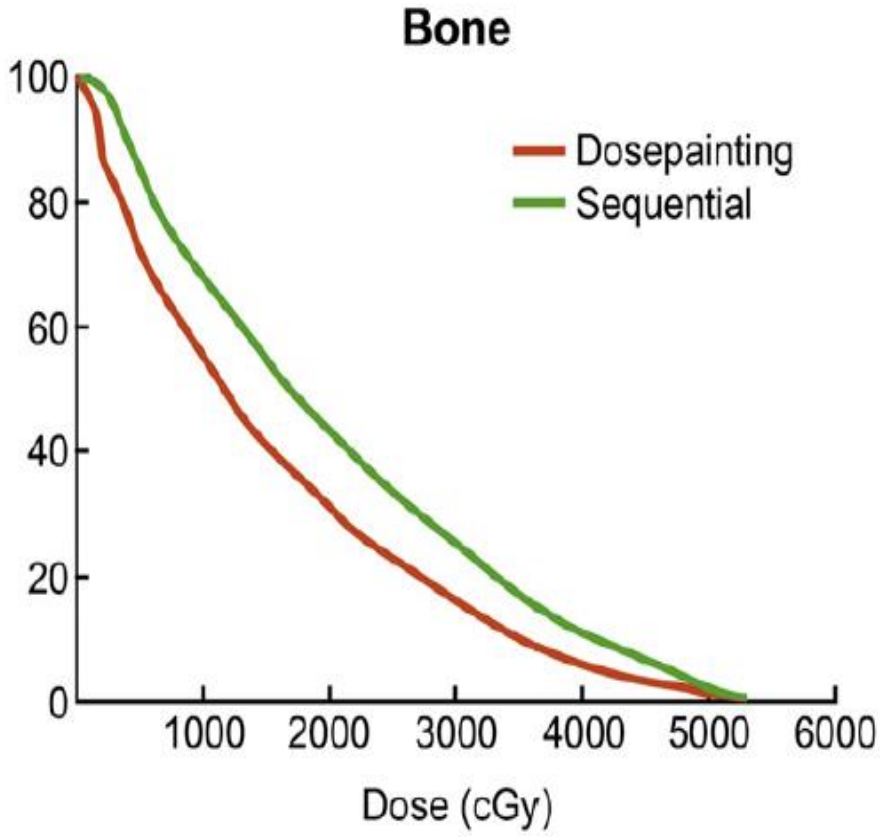
IMRT with Dose-Painting in Rhabdomyosarcoma



*PTV_{5040}=yellow, PTV_{3600}=orange



Yang JC et al. Int J Radiat Oncol Biol Phys 2012; 84:e371-8

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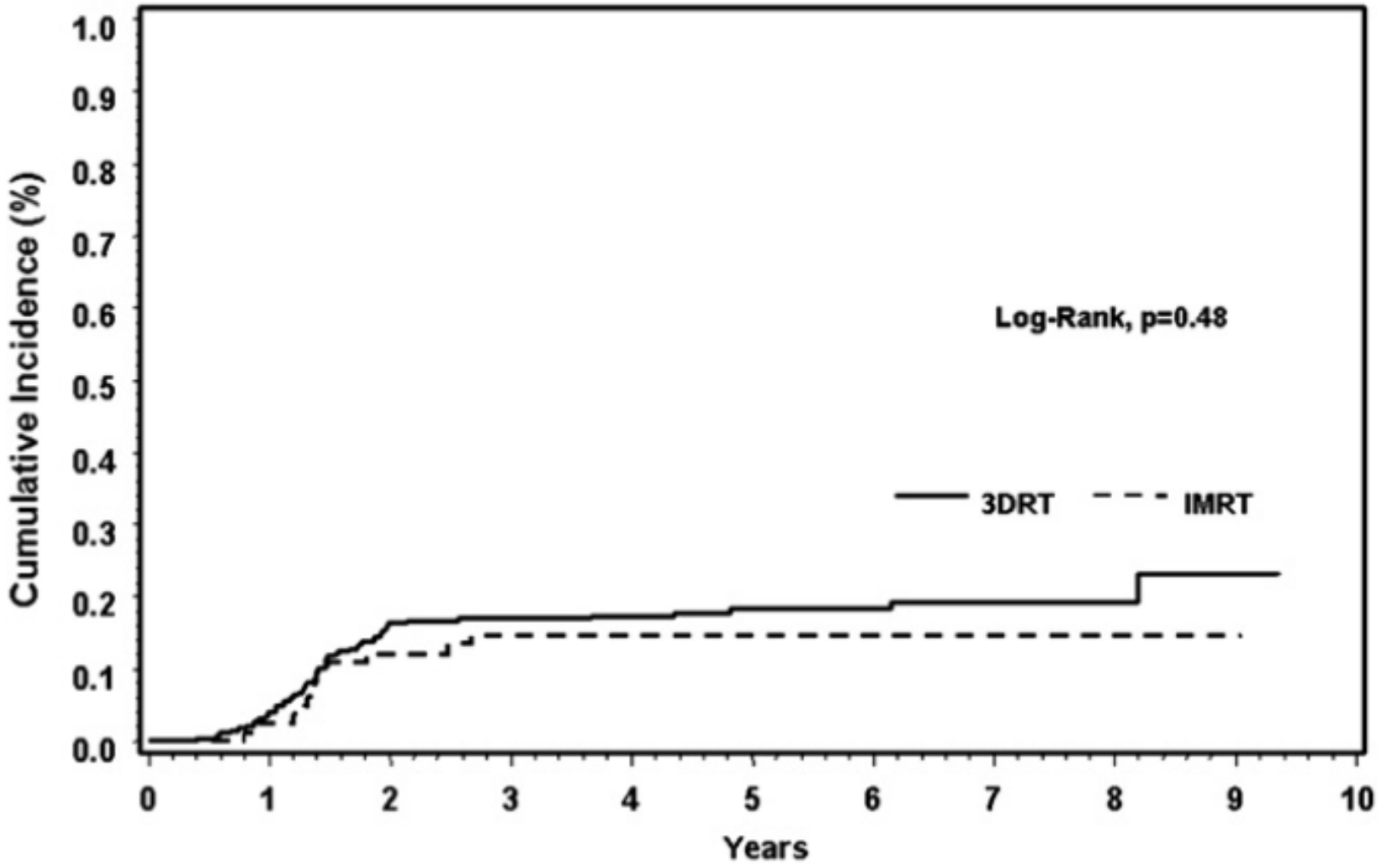
IMRT for Rhabdomyosarcoma

First Author/ Institution	N	Tumor Location	CTV Margin	Local Control Rate
Curtis The Methodist Hospital/ Baylor	19	Parameningeal (36%) Orbit (32%) Other Head & Neck (32%)	1.5 cm	92.9% (4-year)
McDonald Emory Clinic	20	Parameningeal (70%) Orbit (10%) Other Head & Neck (20%)	1-2 cm (36 Gy) 0.5-1 cm (boost) PTV	100% (3-year)
Wolden Memorial Sloan-Kettering Cancer Center	28	Parameningeal (75%) Orbit (11%) Other Head & Neck (14%)	1.5 cm	95% (3-year)
Lin Children's Oncology Group	87	Parameningeal (63%) Orbit and Other Head & Neck (9%) GU Bladder/Prostate (18%) Other (10%)	2 cm PTV	85% (5-year)

3-D vs. IMRT in RMS (COG D9803)



Lin C et al. Int J Radiat Oncol Biol Phys 2012; 82:1764-70

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3-D vs. IMRT in RMS (COG D9803)

	IMRT	3-D CRT
Median follow-up	4.2 years	5.7 years
5-year local failure rate	15%	18%

Advantages of IMRT
1. PTV receiving 95% of prescribed dose greater for IMRT
2. Lower mean dose to brainstem with IMRT
3. Both treatment have similar target dose heterogeneity

Lin C et al. Int J Radiat Oncol Biol Phys 2012; 82:1764-70

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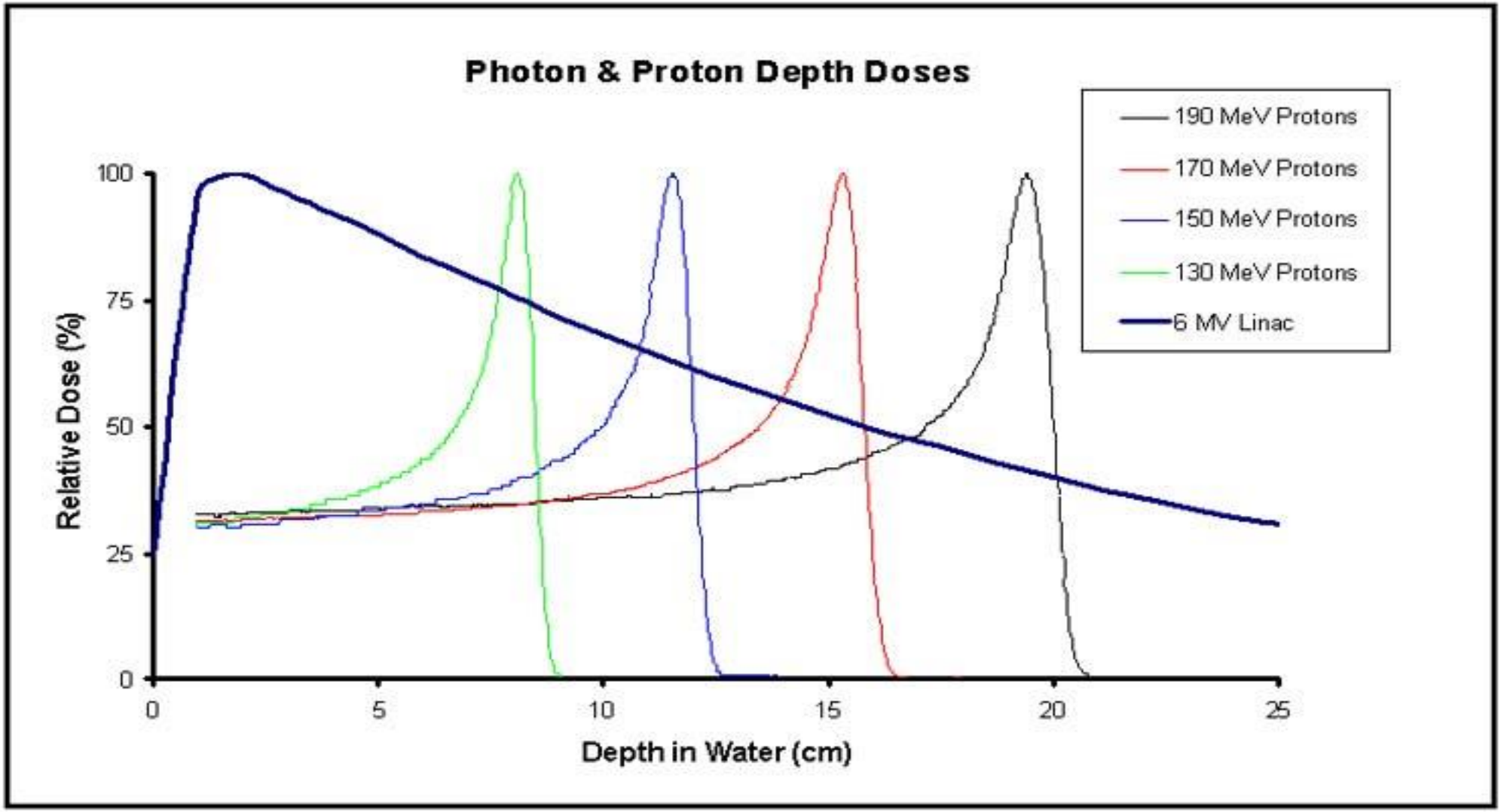
Proton Therapy



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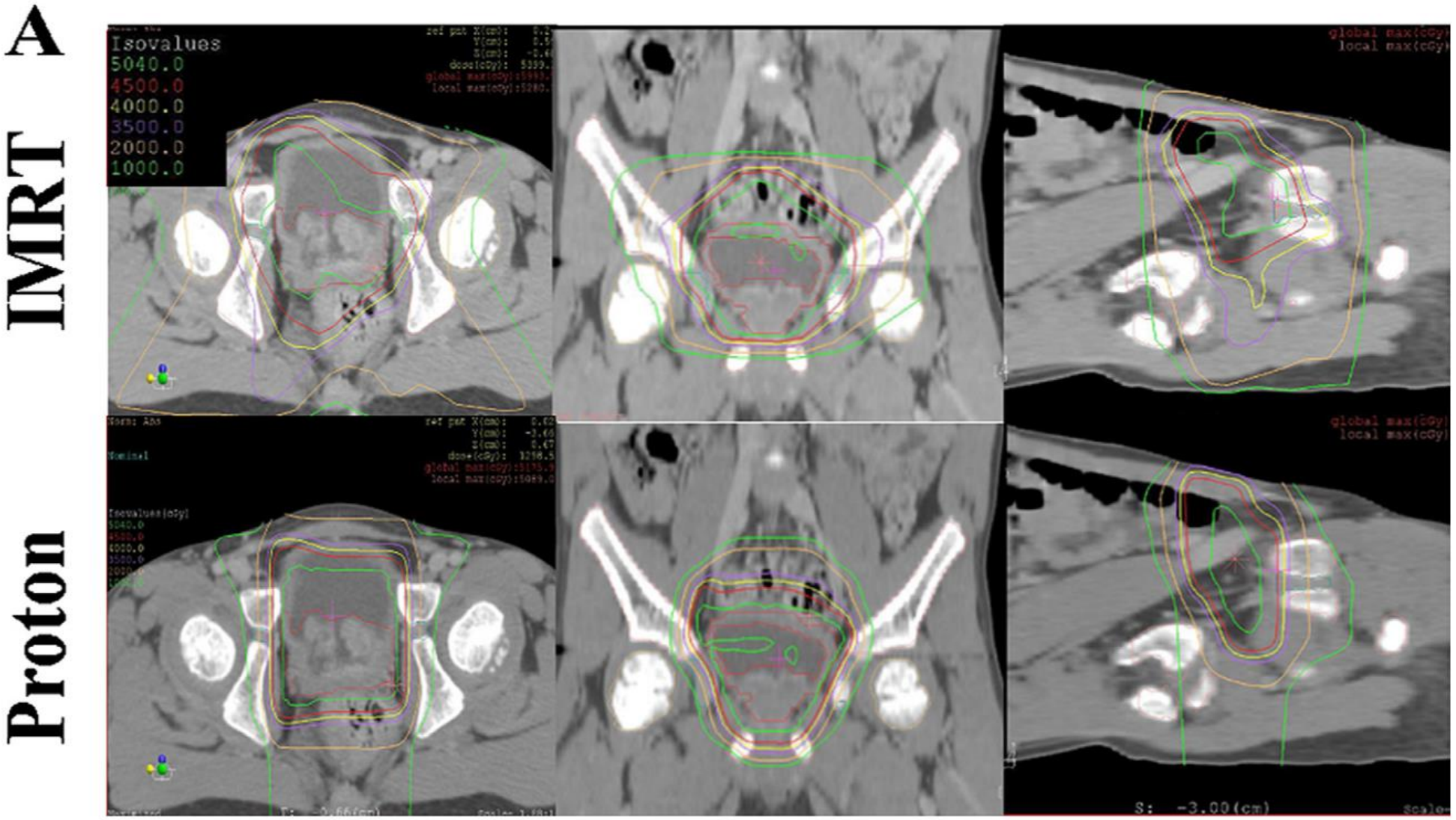
Protons and Genitourinary Rhabdomyosarcoma



Cotter S et al. Int J Radiat Oncol Biol Phys 2011; 81:1367-73

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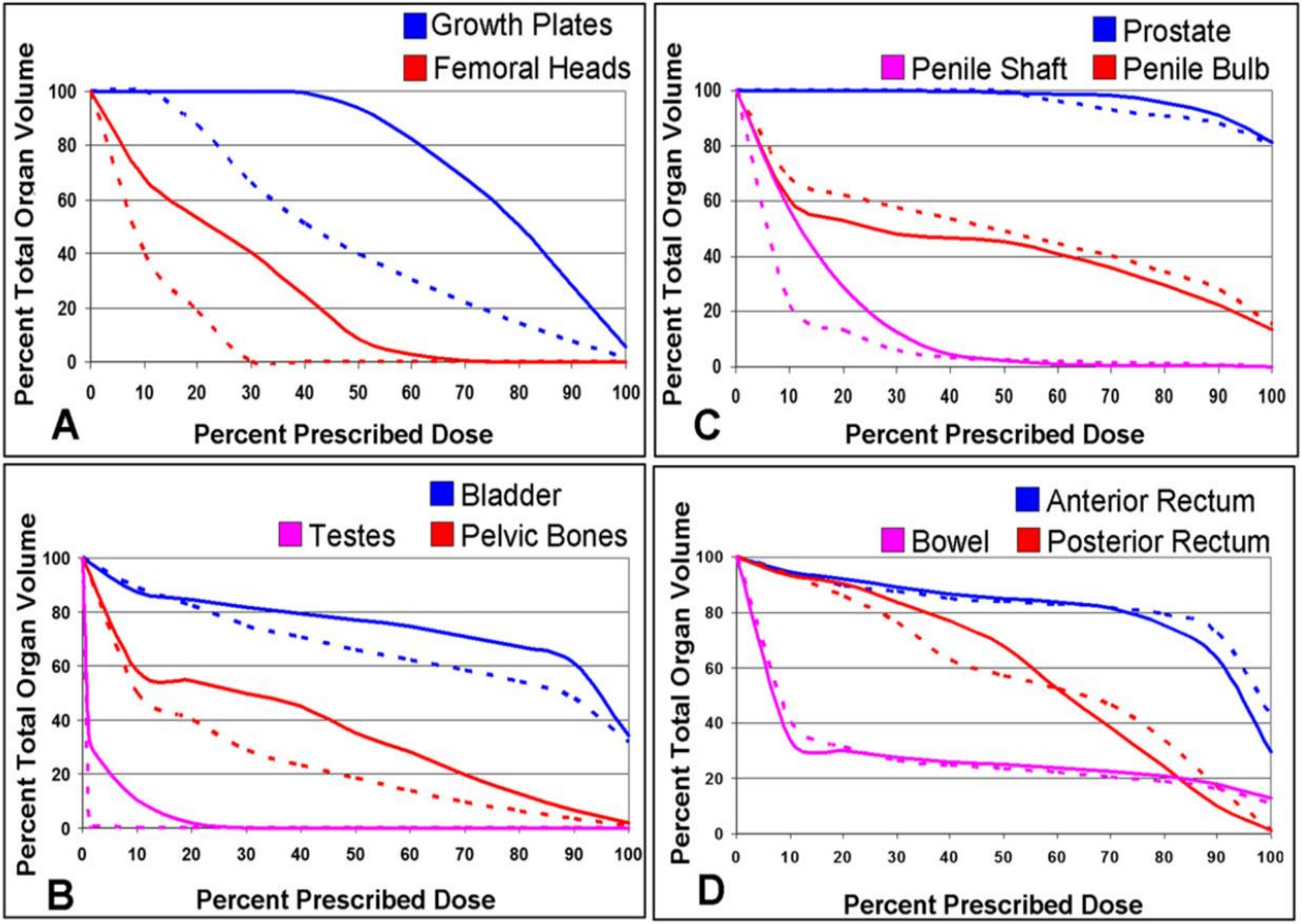

Cotter S et al. Int J Radiat Oncol Biol Phys 2011; 81:1367-73

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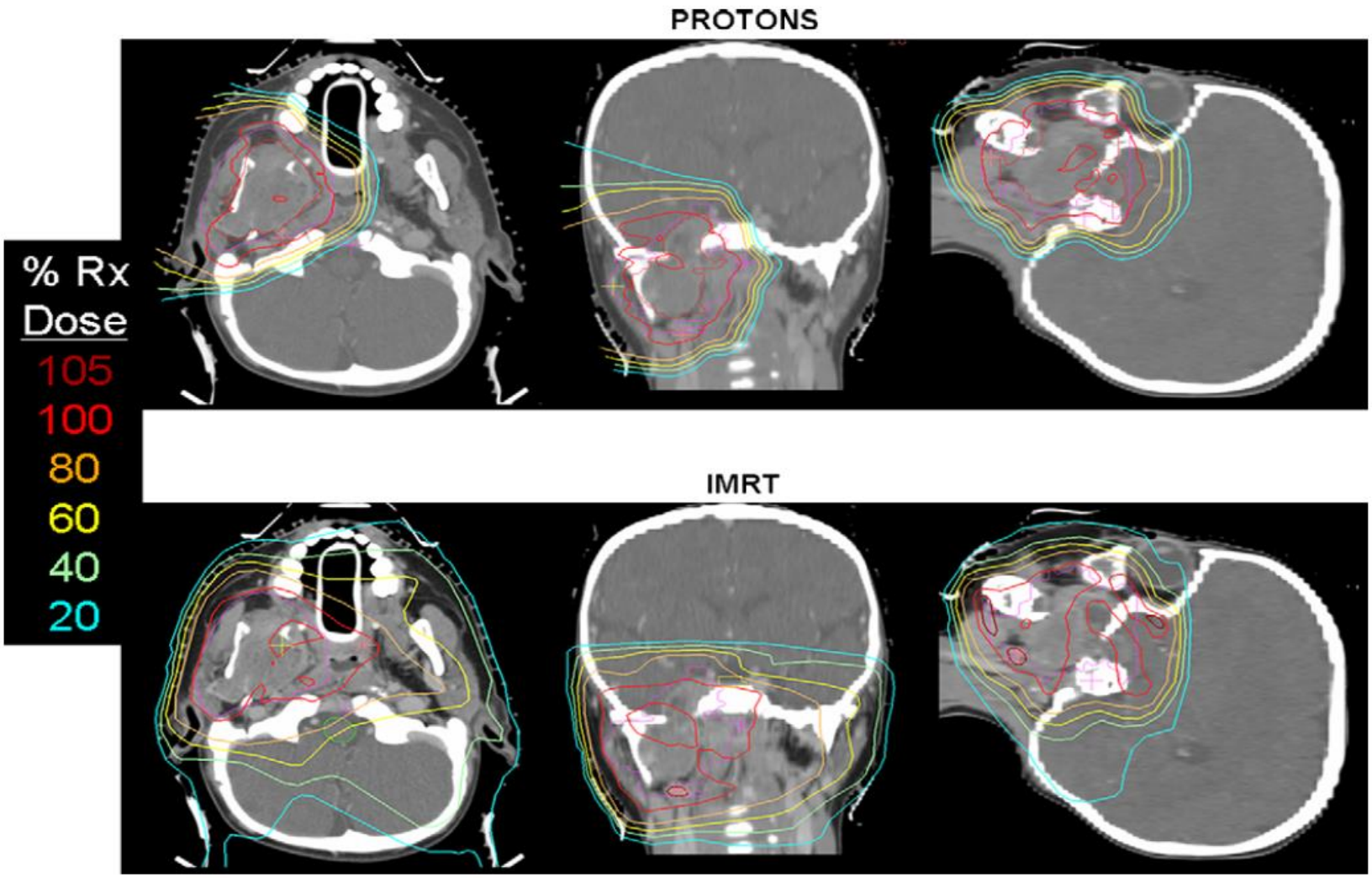
Protons and Parameningeal Rhabdomyosarcoma



Childs SK et al. Int J Radiat Oncol Biol Phys 2012; 82:635-42

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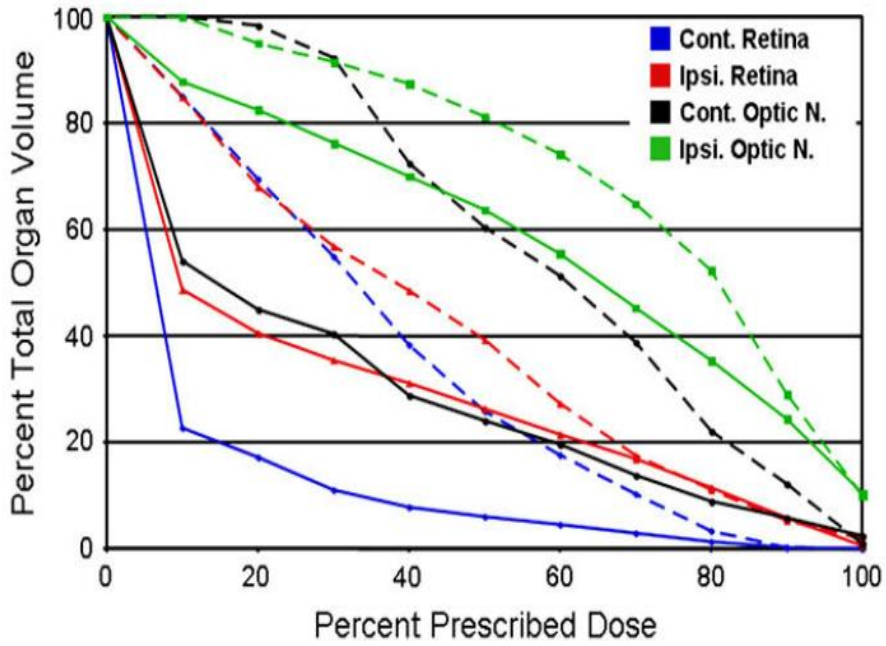

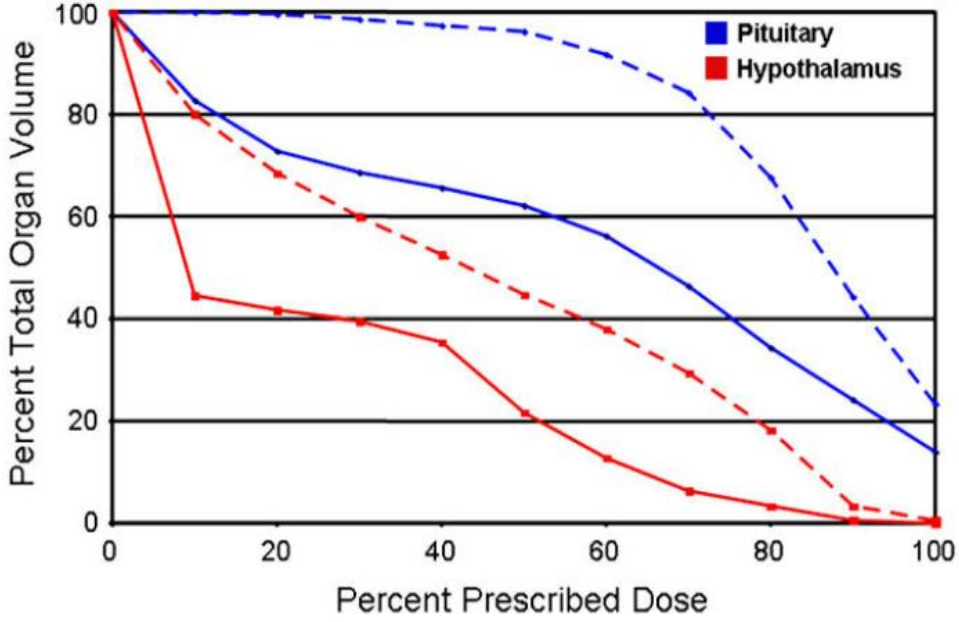

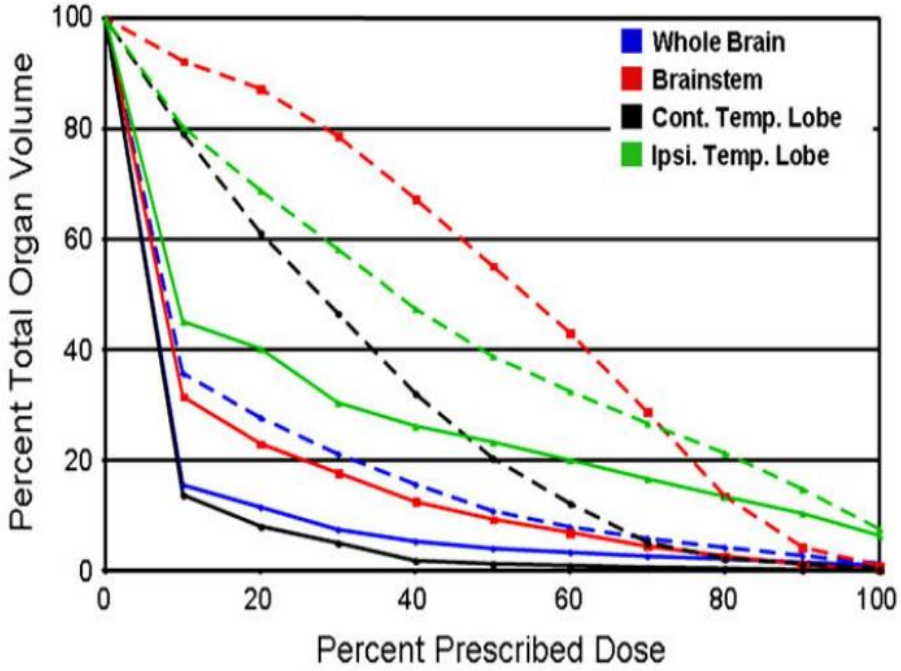

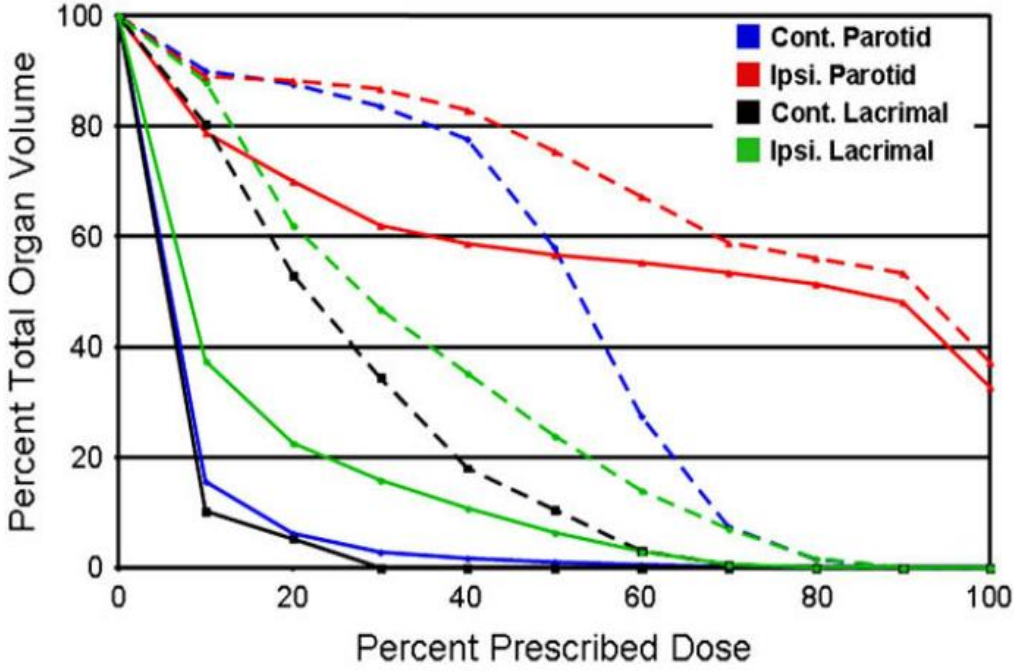

Childs SK et al. Int J Radiat Oncol Biol Phys 2012; 82:635-42

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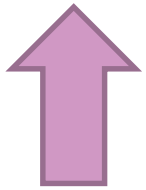
Protons for Parameningeal Rhabdomyosarcoma

Table 2. Incidence of recorded toxicities in patients with parameningeal rhabdomyosarcoma: Comparison of proton data with previously published studies

	Protons: MGH (n = 10) Median f/u: 5 y		IRS II-III* (n = 213) Median f/u: 7 y		IMRT: MSKCC† (n = 21) Median f/u: 2 y		University of Iowa‡ (n = 17) Median f/u: 20 y	
Toxicity	n	%	n	%	n	%	n	%
Decreased growth velocity	3/10	30	92/190	48	NR		9/15	60
Growth hormone replacement	2/10	20	36/190	19	1/21	5	6/15	40
Other endocrinopathies	1/10	10	17/213	8	NR		1/15	7
Facial hypoplasia	7/10	70	74/76	97	1/21	5	11/15	73
Visual complications	0		45/213	21	2/21	10	9/11	82
Auditory complications	0		36/213	17	NR		6/8	75
Dentition	3/10	30	NR		NR		7/7	100
Chronic nasal and sinus congestion	2/10	20	35/71	49	4/21	19	NR	
Secondary malignancies	0		4/213	2	2/21	10	1/17	6

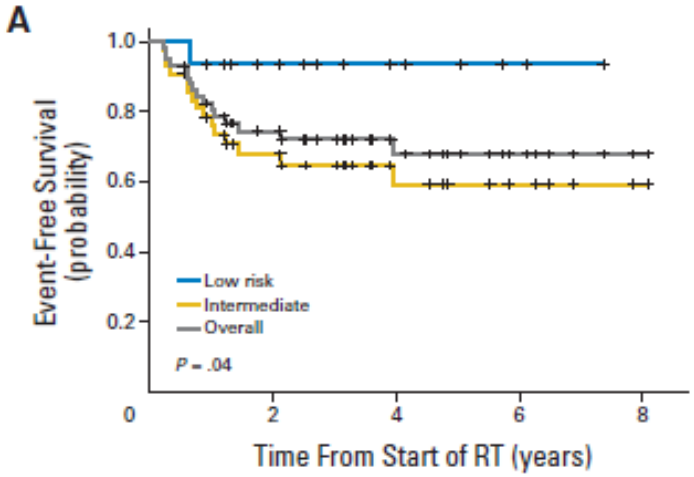


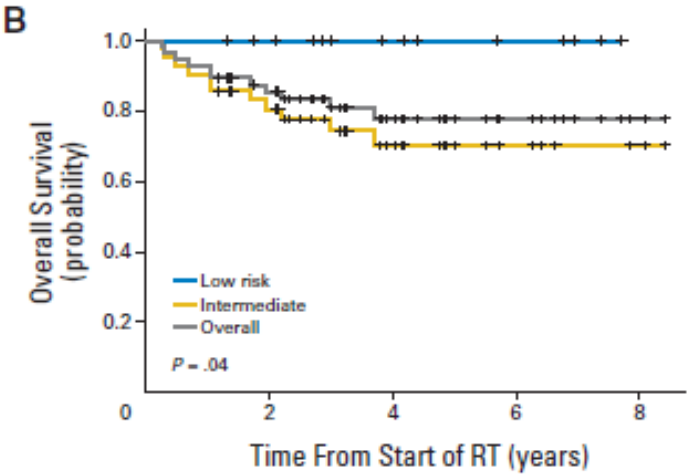
2-D Radiotherapy

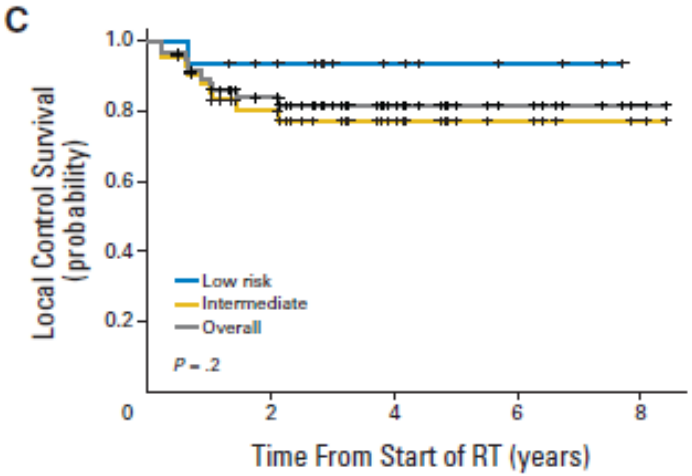
Childs SK et al. Int J Radiat Oncol Biol Phys 2012; 82:635-42

ESTRO School

Phase II Trial of Proton Therapy







Five-year OS, EFS and LC rates similar to comparable trials that used photons

Ladra MM et al. J Clin Oncol 2014; 32:3762-70

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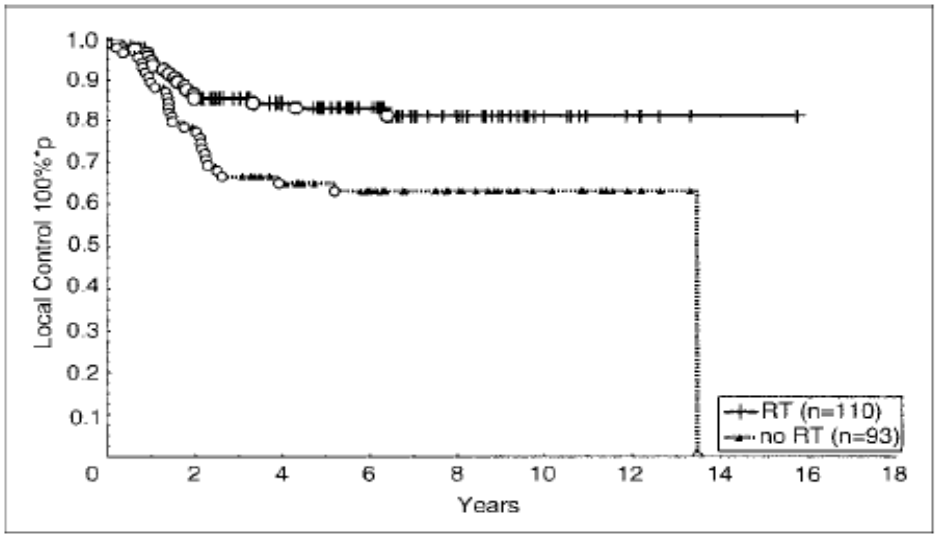
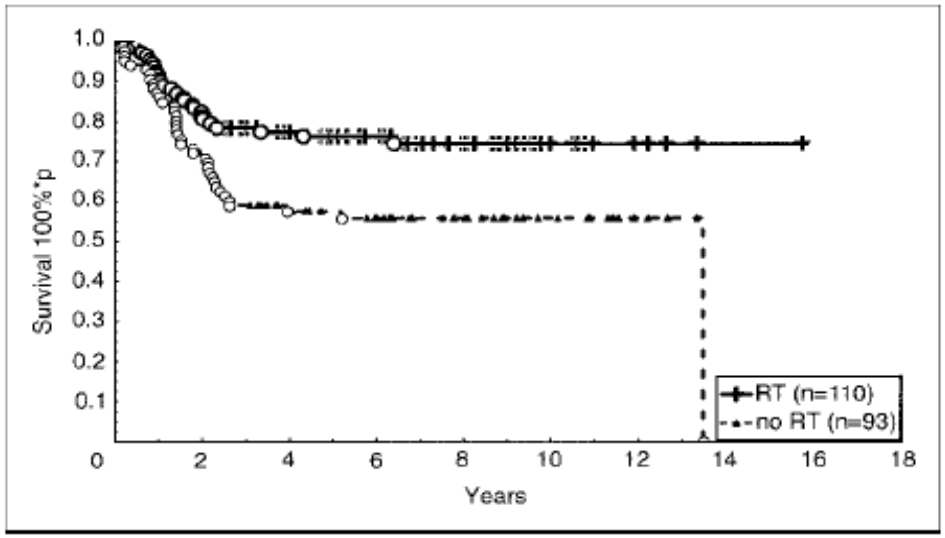
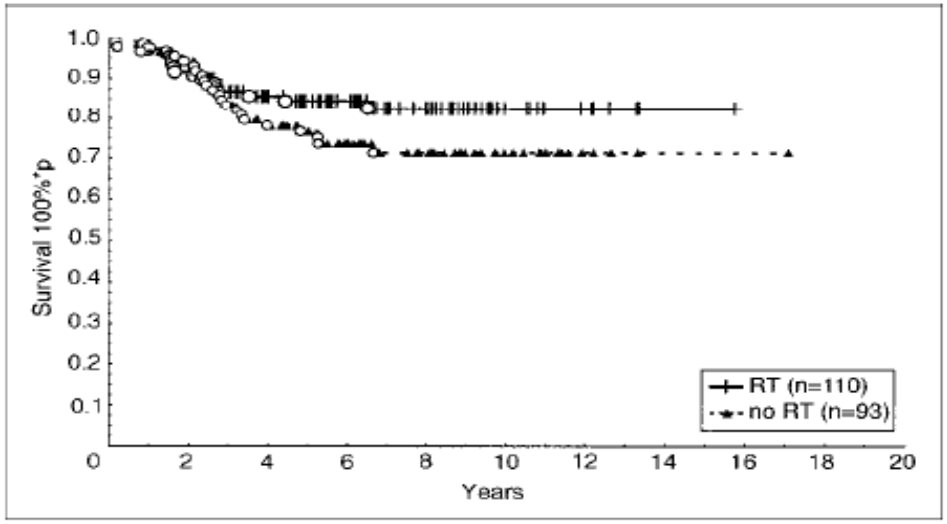
Postoperative Radiotherapy (Group II)







172/203 (85%) had Group IIA Disease (microscopic margin at resection)

Schuck A et al. J Clin Oncol 2004; 22:143-9

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Group II RMS (Omission of Radiotherapy)

	%		*p*
	RT	No RT	
Favorable histology (n = 114)			
LC	87	69	< 0.03
EFS	80	68	ns
OS	91	87	ns
Unfavorable histology (n = 89)			
LC	80	51	< 0.06
EFS	74	35	< 0.003
OS	80	56	< 0.015
Favorable site (n = 79)			
LC	84	63	< 0.045
EFS	84	63	< 0.041
OS	97	87	ns
Unfavorable site (n = 124)			
LC	83	67	< 0.09
EFS	73	54	< 0.05
OS	79	68	ns

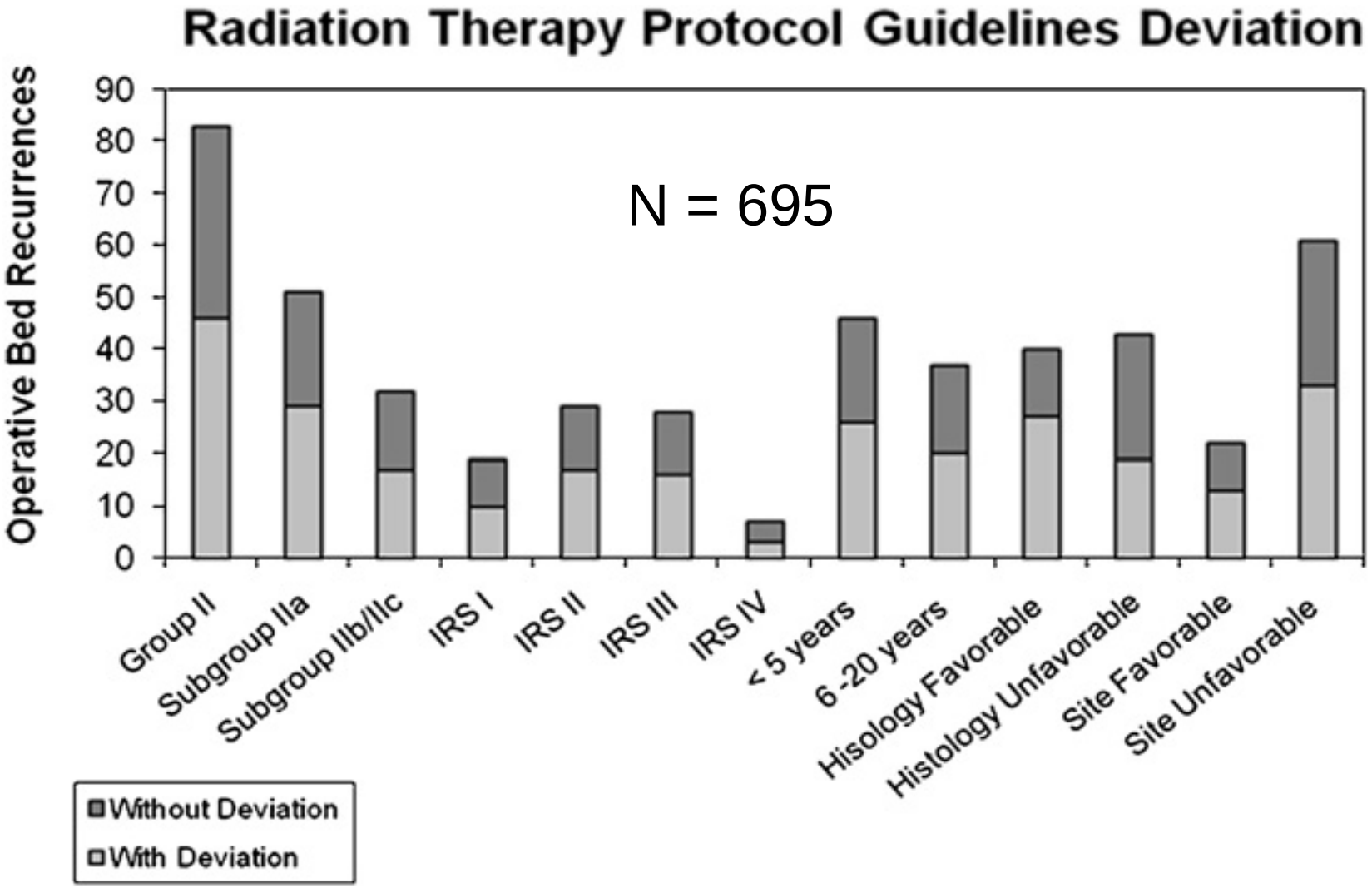
Schuck A et al. J Clin Oncol 2004; 22:143-9

Group II RMS (Omission of Radiotherapy)

	%		*p*
	RT	No RT	
Initial tumor size < 5cm (n = 127)			
LC	86	63	< 0.003
EFS	80	58	< 0.009
OS	91	84	ns
Tumor size > 5 cm (n = 70)			
LC	80	69	ns
EFS	70	56	ns
OS	72	65	ns
Favorable histology and tumor size < 5cm (n = 82)			
LC	88	64	< 0.01
EFS	83	64	< 0.045
OS	94	87	ns

Schuck A et al. J Clin Oncol 2004; 22:143-9

Non-Compliance with RT Guidelines (Group II RMS)



Million L et al. Int J Radiat Oncol Biol Phys 2011; 80:333-8

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Non-Compliance with RT Guidelines (Group II RMS)

83 of 695 pts (11.9%) with Group II tumors recurred in operative bed; 46 (55%) did not receive the intended RT including 19 who did not receive RT

	Tumor Bed Recurrence	Proportion with RT Non-compliance
Group IIA	51/506 (10.1%)	29/51 (57%)
Group IIB and IIC	32/189 (16.9%)	17/32 (53%)

Million L et al. Int J Radiat Oncol Biol Phys 2011; 80:333-8

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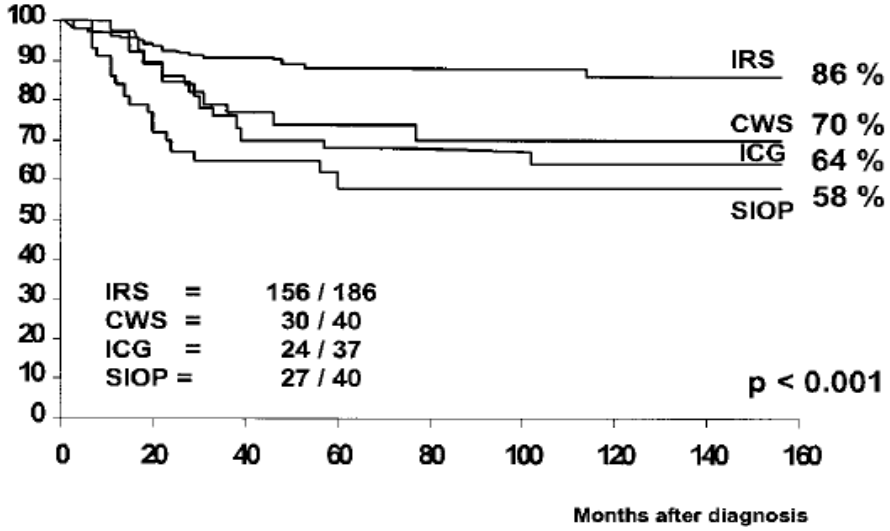
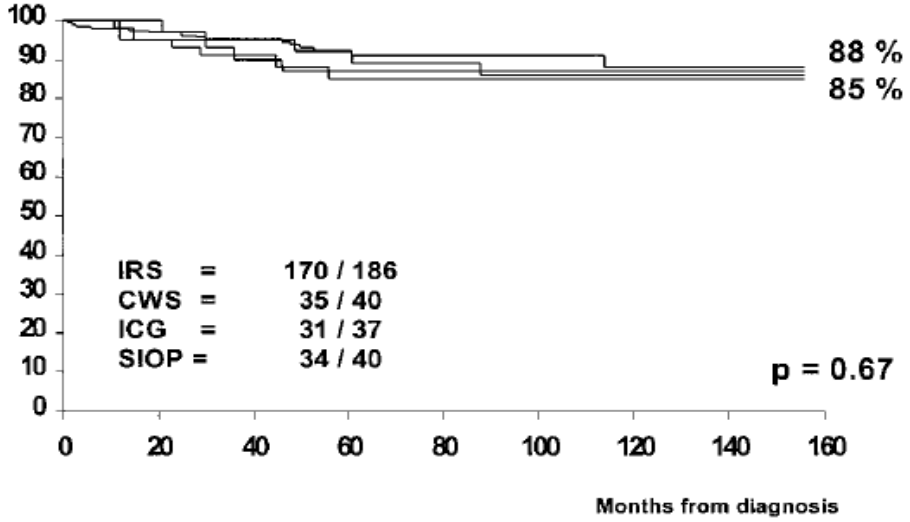
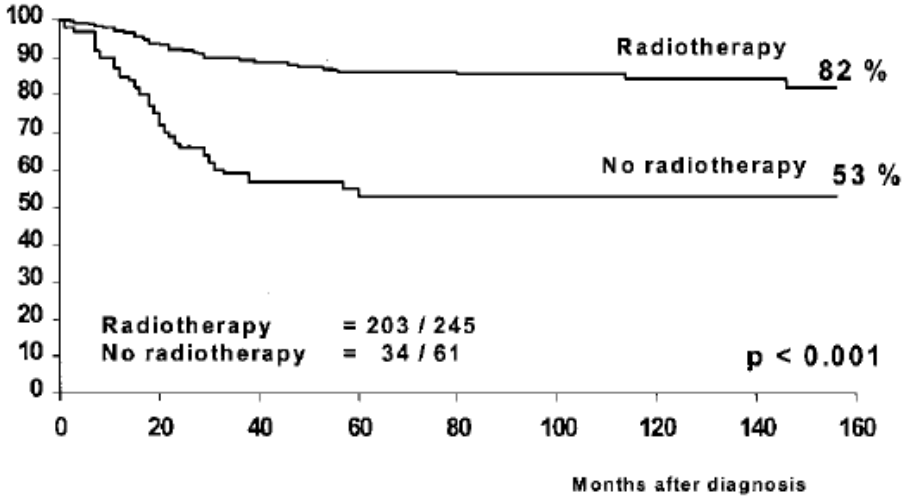
Orbital RMS: International Workshop







Type of Sequelae	European Patients (pooled data) No. of Survivors Affected	%	IRSG Patients* % Survivors Affected (n = 94)
Globe removed	9/83	11	14
Cataract	36/71	51	82
Reduced vision in affected eye	37/68	54	70
Dry eye	20/72	28	23
Painful eye	10/72	14	14
Keratitis	10/72	14	18
Corneal ulcer	4/72	6	4
Retinal damage	8/72	11	3
Ptosis	26/72	36	28
Orbital hypoplasia	27/72	29	59
Maxillary hypoplasia	7/72	10	11

*IRSG data based on data from patients treated in the IRS III study.[9]

Oberlin O et al. J Clin Oncol 2001; 19:197-204

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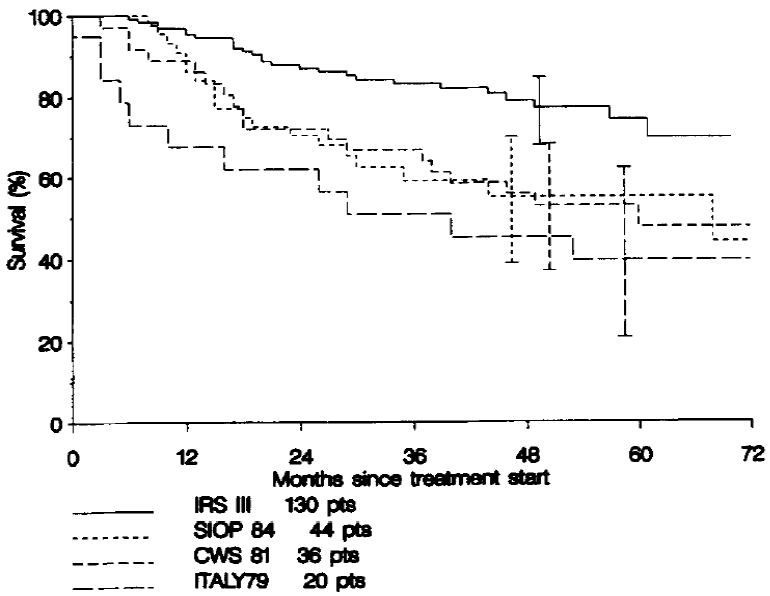
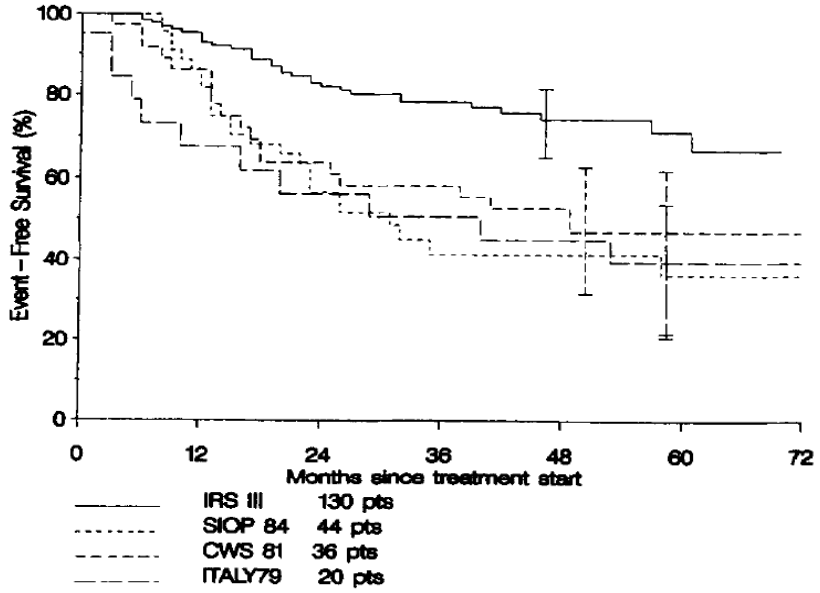
Parameningeal RMS (International Work-Up)

	IRS-III	SIOP 84	CWS 81	ICS 79
No. achieving complete response	117	39	27	11
No. failure	17 (14%)	20 (51%)	10 (37%)	3 (27%)
Local relapse as a component of failure	11 (65%)	19 (95%)	9 (90%)	3/3 (100%)
No XRT	0	13	0	0





Beck V et al. Int J Radiat Oncol Biol Phys 1996; 36:533-40

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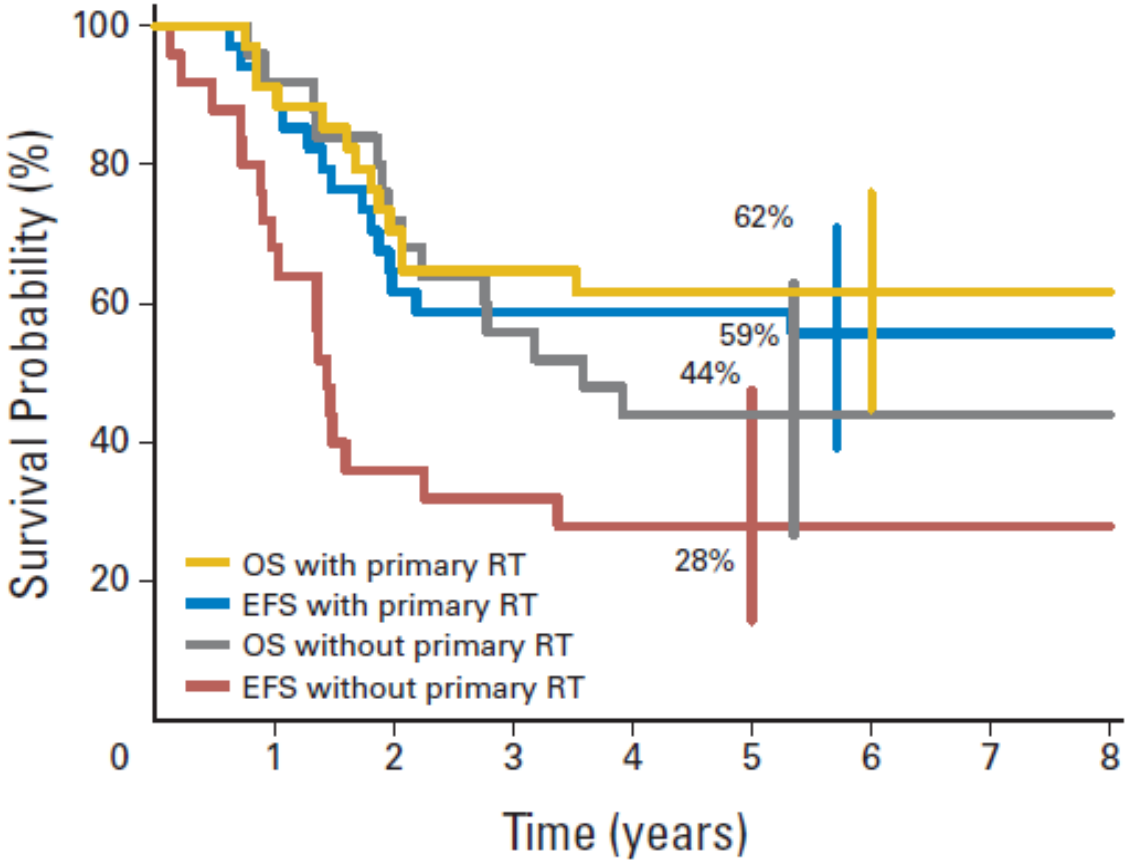
Parameningeal RMS (Omission of RT)



No. of patients at risk									
OS w/ prim. RT	25	17	9	8	7	6	6	5	5
EFS w/ prim. RT	34	31	21	20	19	19	16	15	13
OS w/o prim. RT	25	23	18	14	11	10	9	7	7
EFS w/o prim. RT	34	31	24	22	20	20	18	17	15

Defachelles AS et al. J Clin Oncol 2009; 27:1310-5

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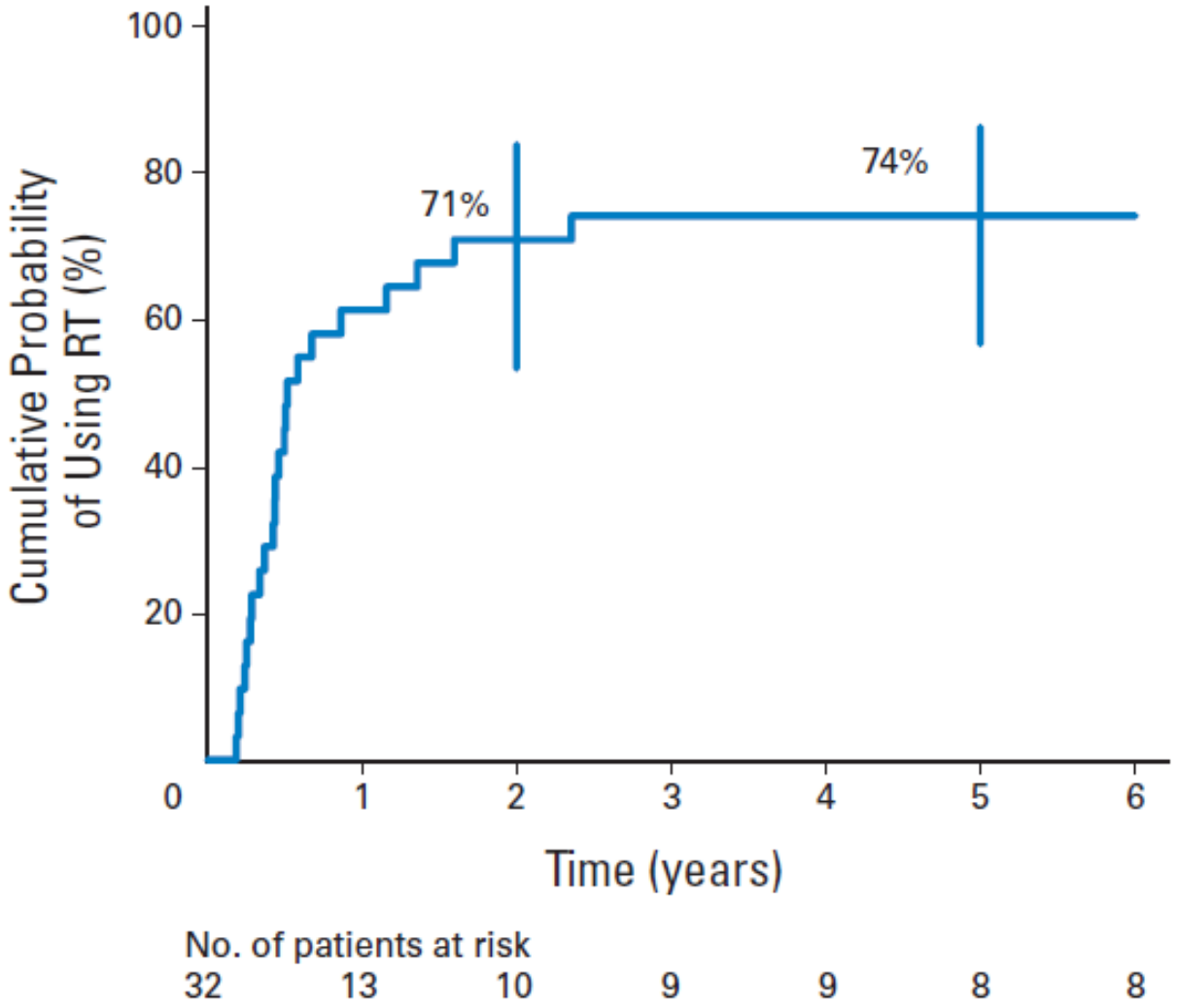
Parameningeal RMS (Omission of RT)



Defachelles AS et al. J Clin Oncol 2009; 27:1310-5

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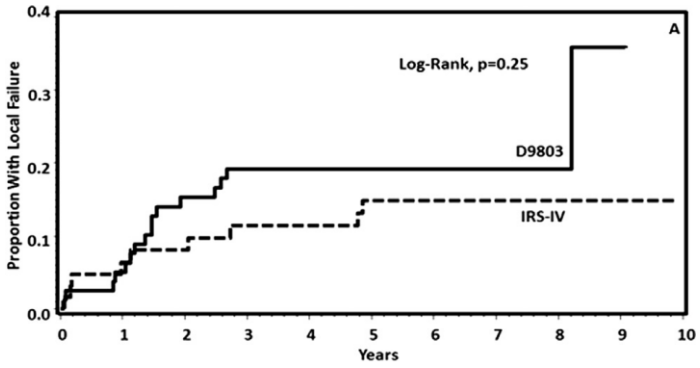
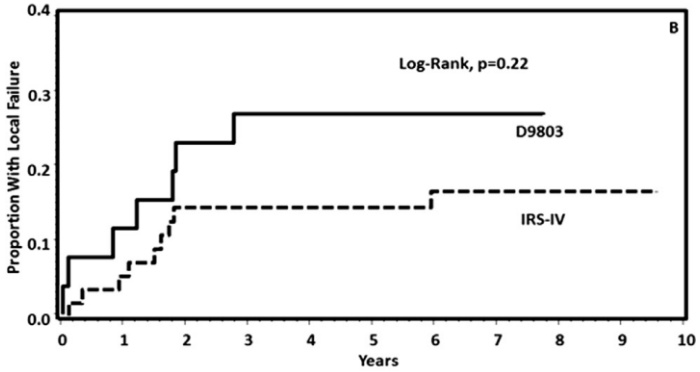
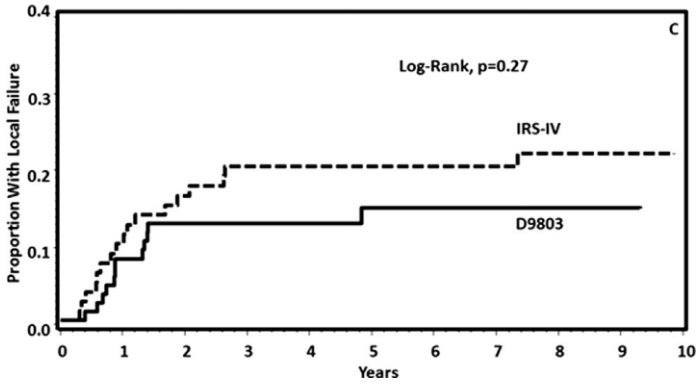
Timing of Radiotherapy



No high –risk features



Cranial nerve palsy or bone erosion



Intracranial extension

Spalding AC et al. Int J Radiat Oncol Biol Phys 2013; 87:512-6

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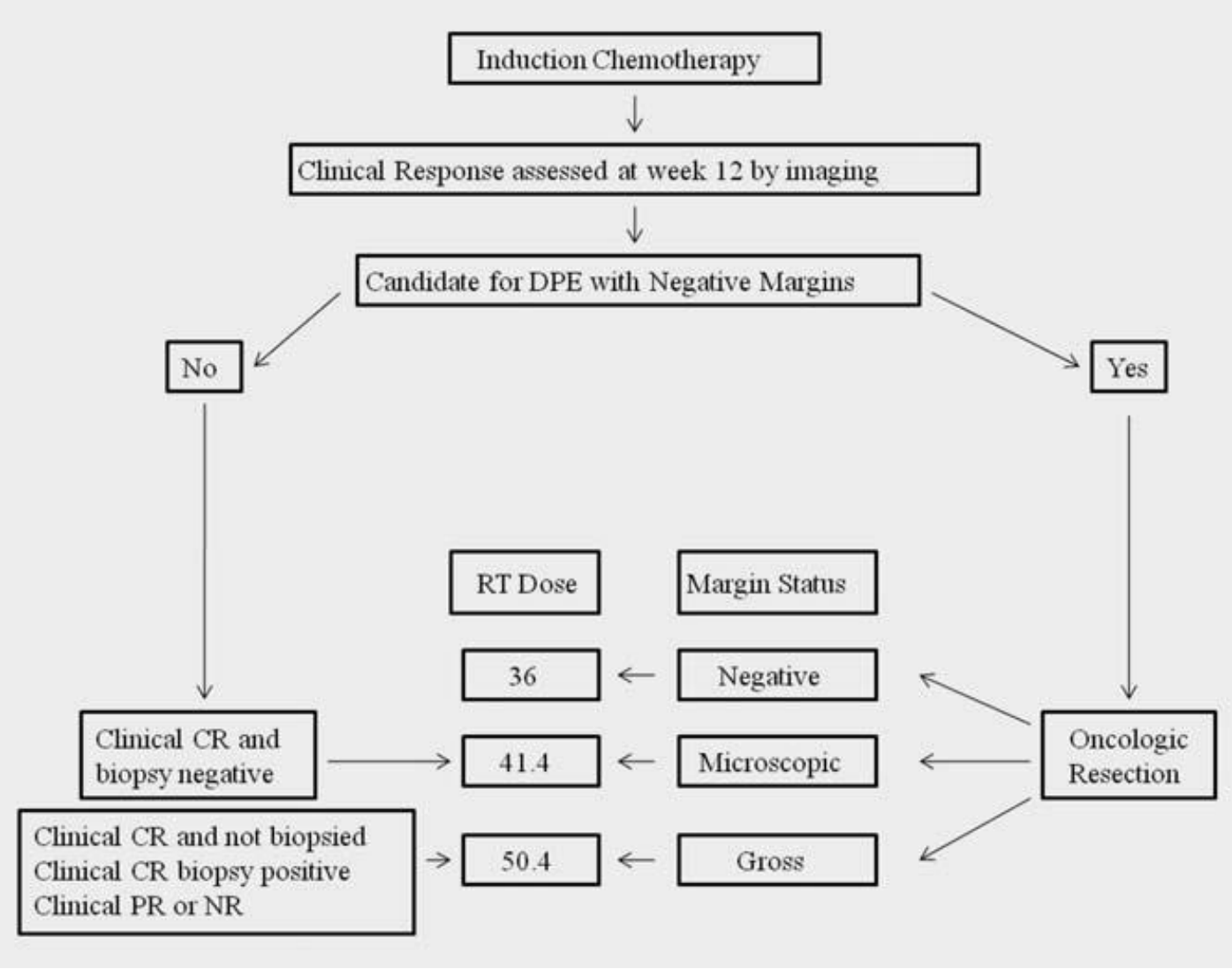
Delayed Primary Excision and RT Dose Modification



Rodeberg DA et al. Int J Cancer 2015; 137:204-11

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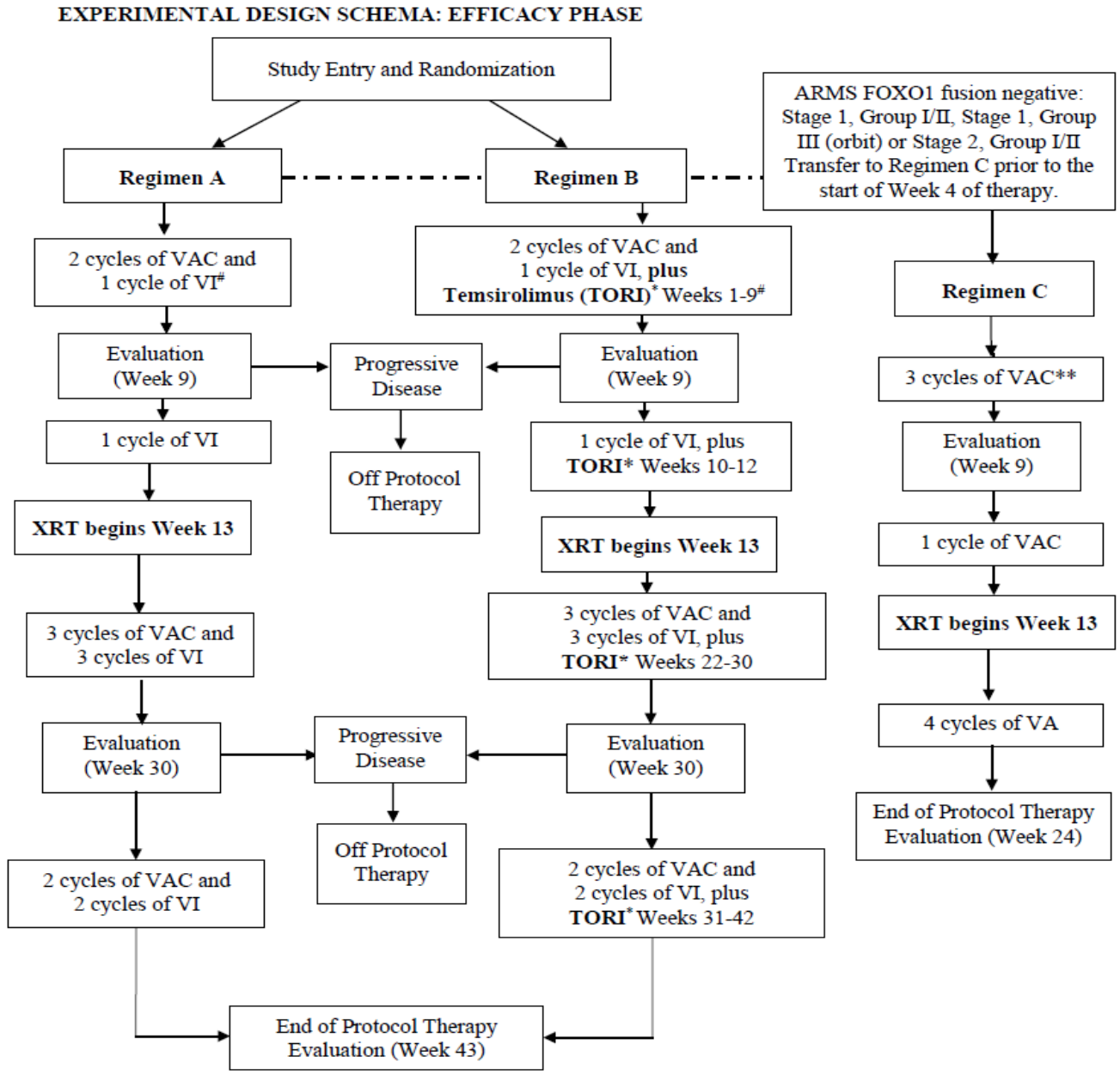
Delayed Primary Excision and RT Dose Modification

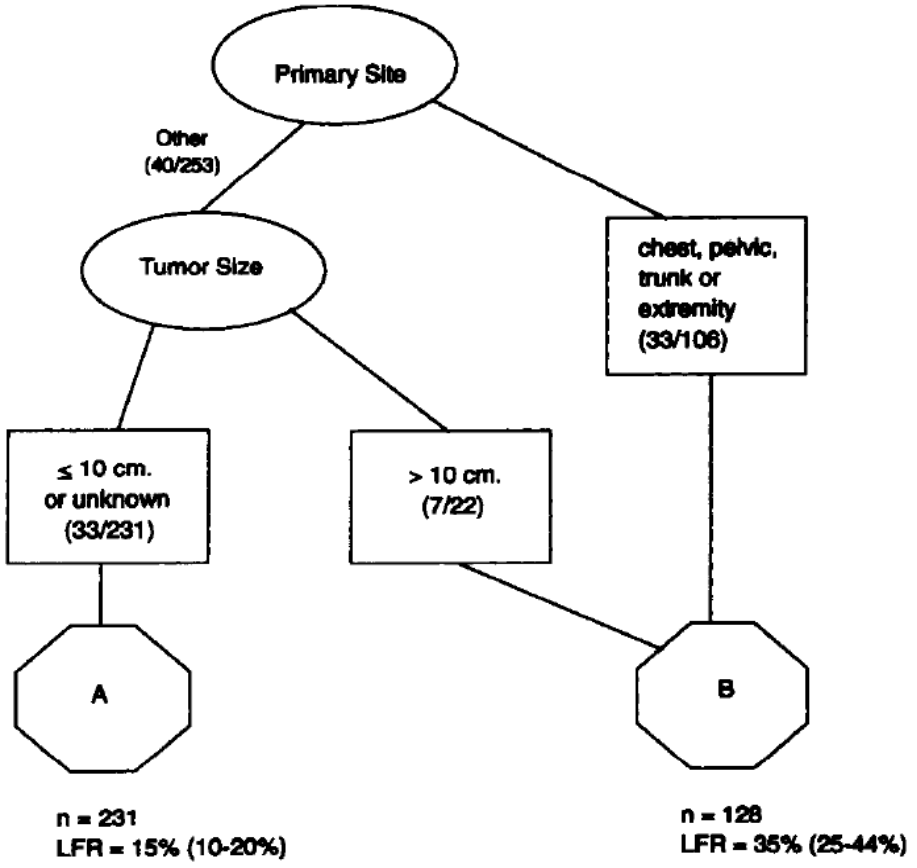
- 161 patients with Group III tumors (bladder dome, extremity, trunk) enrolled on COG D9803 were evaluated
- Seventy-three (45%) underwent DPE with removal of all gross disease in 61 (84%)
- 43/73 had negative margins and received 36 Gy
- 19/73 had microscopic positive margins and received 41.4 Gy
- The local 5-year local failure rate were 0% for bladder dome, 7% for extremity and 20% for trunk, similar to IRS-IV which did not encourage DPE

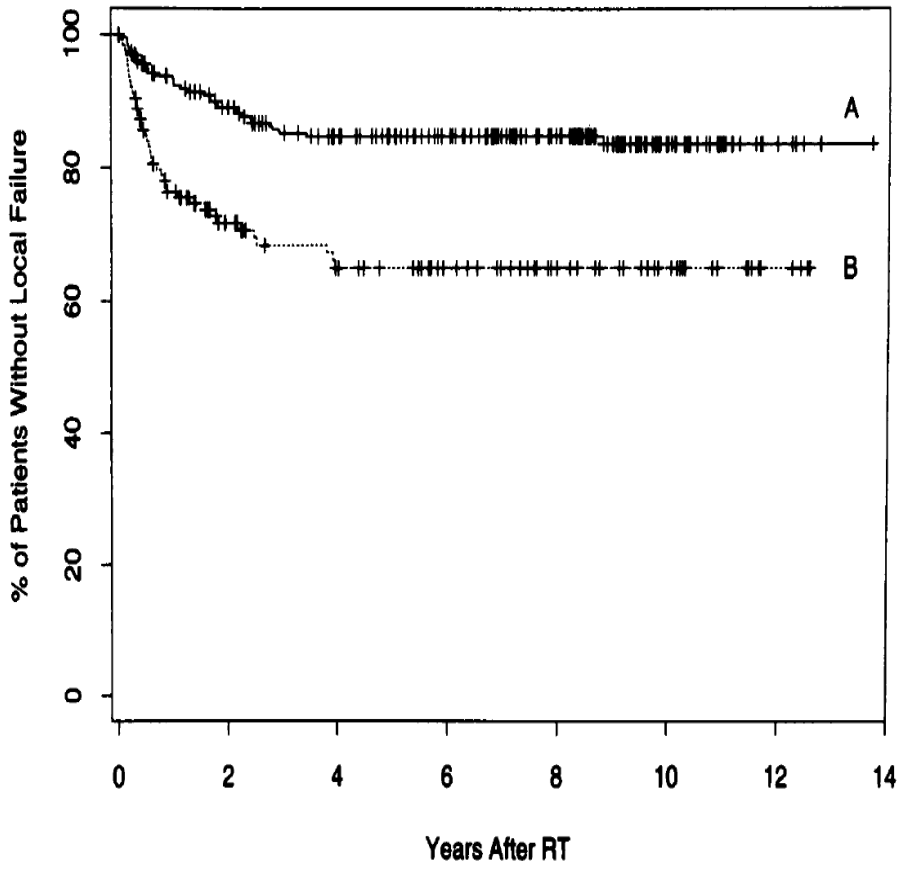
Rodeberg DA et al. Int J Cancer 2015; 137:204-11

Children's Oncology Group ARST1431



Local Failure in Group III (IRS-II)





Wharam MD et al. Int J Radiat Oncol Biol Phys 1997; 38:797-804

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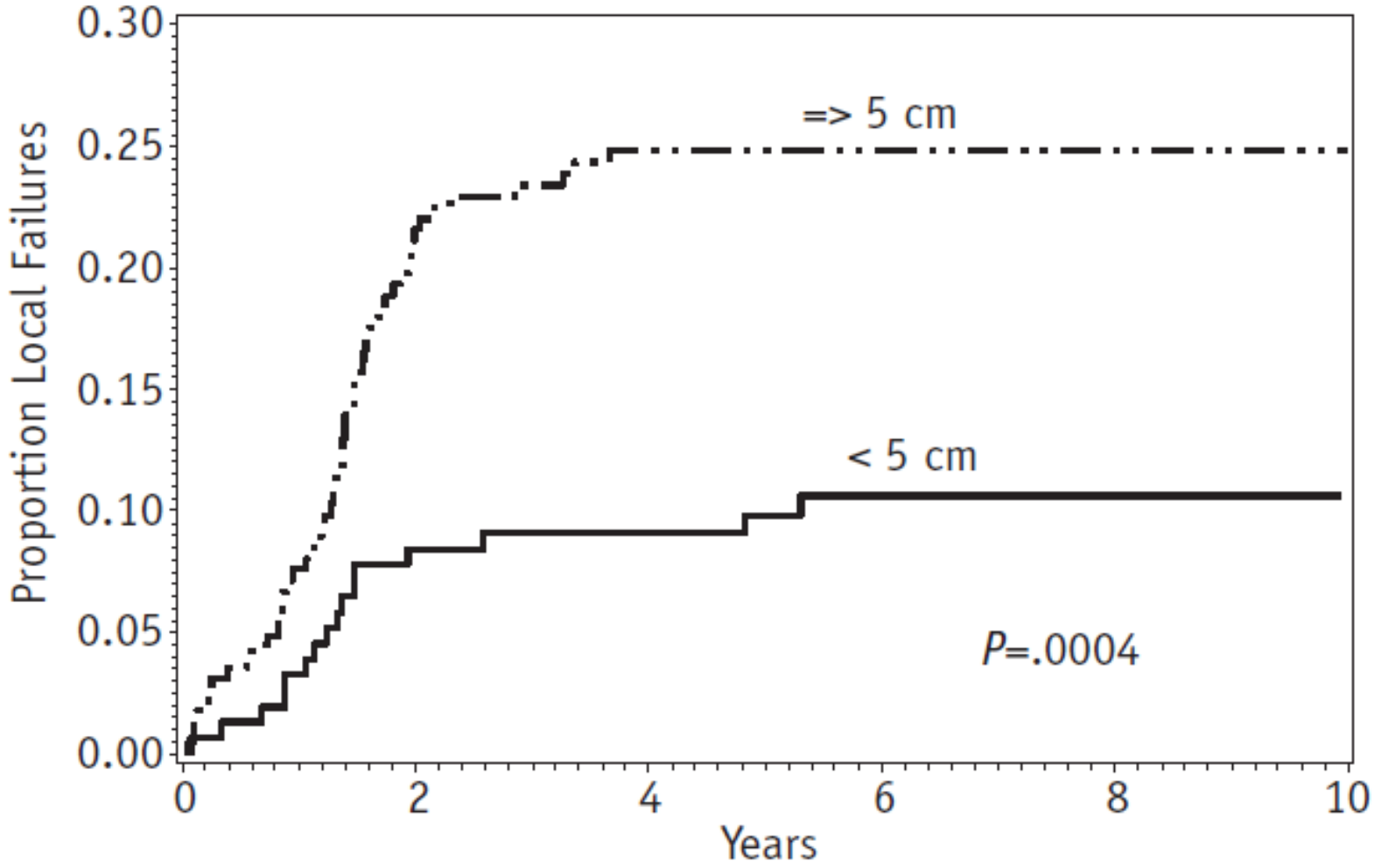
Local Control According to Tumor Size: D9803 Intermediate-Risk Study



Wolden SL et al. Int J Radiat Oncol Biol Phys 2015; 93:1071-6

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COG ARST1431

- Dose escalation to 59.4 Gy for tumors > 5 cm at initial diagnosis
- Cone down after 36 Gy is allowable for residual disease
- In the case of complete response (CR) by imaging (MRI/CT and PET-CT or negative biopsy), 36 Gy is allowed
- In delayed primary excision, dose de-escalation is allowed: 36 Gy for negative margins and 41.4 Gy for positive margins

Radiotherapy Dose: COG ARST1431

Group	No CR at week 9**	CR at week 9	DPE, negative margin	DPE, positive margin	DPE, gross residual
I, FOXO1+	36 Gy	36 Gy	N/A	N/A	N/A
II	36 Gy	36 Gy	N/A	N/A	N/A
III, ≤ 5cm*	50.4 Gy	36 Gy	36 Gy	41.4 Gy	50.4 Gy
III, > 5cm*	59.4 Gy	36 Gy	36 Gy	41.4 Gy	59.4 Gy

*Tumor size at initial diagnosis
**CR defined as radiologic CR by CT/MRI and PET or biopsy

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Patients Likely to Benefit from Local Therapy to Metastatic Sites

- Location of Metastasis
- Number of Metastasis
- Histology is considered favorable
- Age of patient

Metastatic Rhabdomyosarcoma

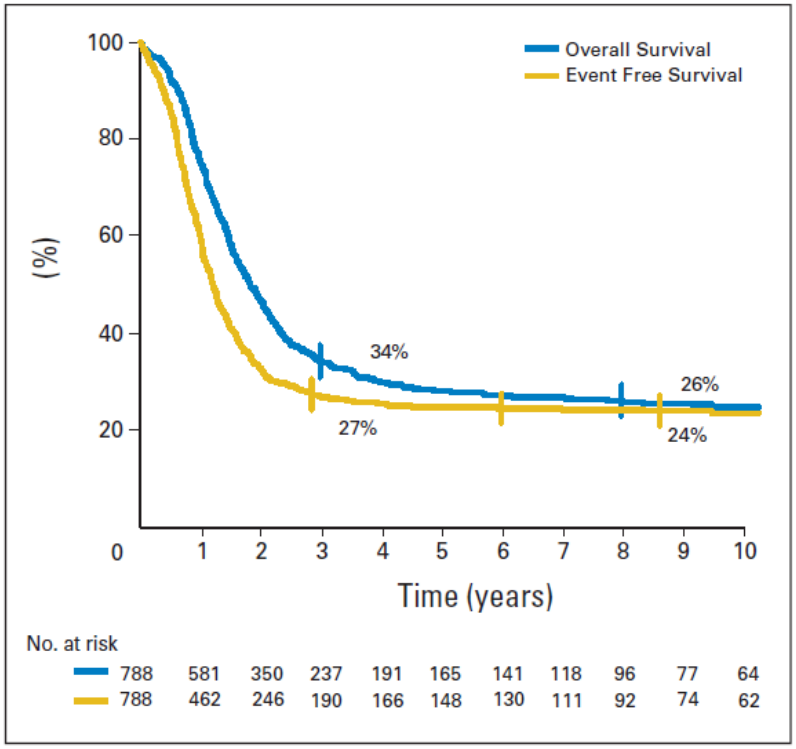

Fig 1. Overall survival and event-free survival of all 788 patients.

Table 2. Cox Regression Model for Prognostic Factors on EFS: Multivariate Analysis Adjusted on Continent (United States and Europe; n = 769)

Prognostic Factor	Relative Risk	95% CI	Log-Rank Test (*P*)
Age, years			
Favorable 1-9	1		
Unfavorable ≤ 1 or ≥ 10	1.6	1.4 to 1.9	< .0001
Site			
Favorable			
Orbit	1		
Non-PM			
PM			
Bladder/prostate			
Paratesticular/vagina			
Unfavorable	1.4	1.2 to 1.7	.0003
Limbs			
Other			
Bone or bone marrow involvement			
No	1		
Yes	1.4	1.1 to 1.6	.002
No. of metastatic sites			
≤ 2	1		
≥ 3	1.4	1.1 to 1.7	.003

Abbreviations: EFS, event-free survival, PM, parameningeal.

Oberlin O et al. J Clin Oncol 28:2384-9, 2008

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Metastatic Rhabdomyosarcoma

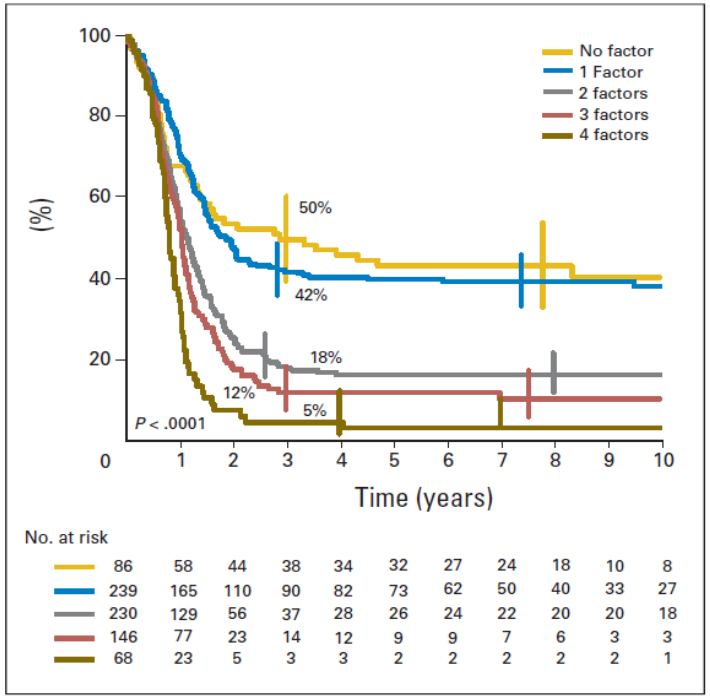

Fig 2. Event-free survival of patients according to number of unfavorable prognostic factors. The relative risks of event are respectively 1, 1.02, 1.9, 2.3, and 3.5.

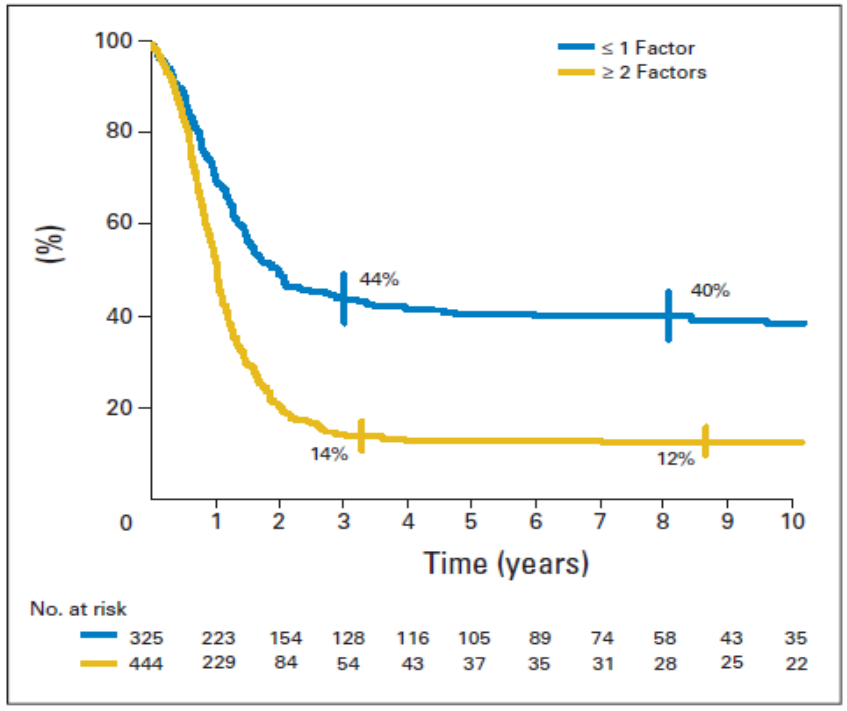

Fig 3. Event-free survival of patients according to risk score.

Oberlin O et al. J Clin Oncol 28:2384-9, 2008

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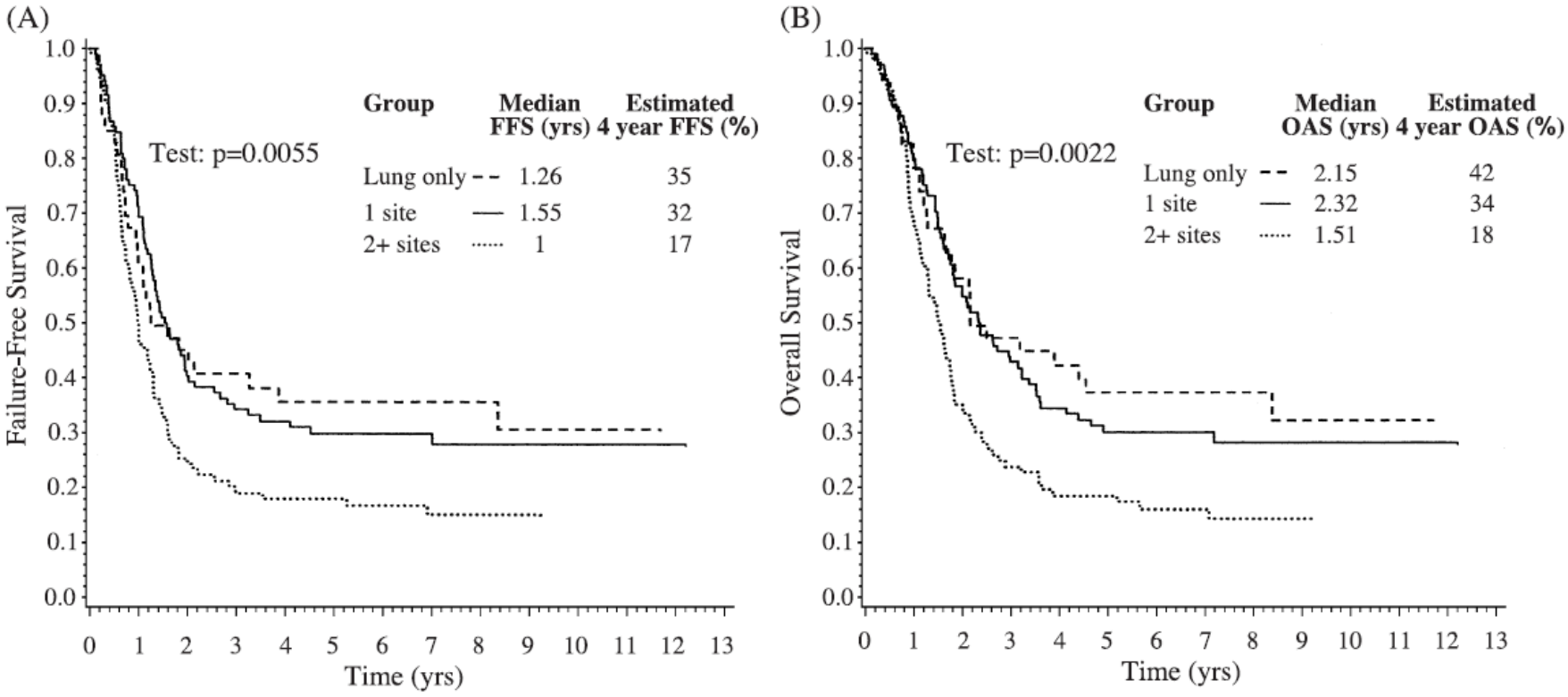
Metastatic Rhabdomyosarcoma (IRS-IV)



Rodeberg D et al. J Pediatr Surg 2005; 40:256-62

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Local Control with Fractionated Radiotherapy to Extrapulmonary Metastatic Sites

Author/Institution/ Year	Tumor	Number of Sites	Median Dose to Metastatic Site	Local Control
Liu University of Colorado 2011	Rhabdomyosarcoma and Ewing Sarcoma	(?/13 patients)	50.4 Gy	92% (5 yr)
Casey MSKCC 2015	Rhabdomyosarcoma and Ewing Sarcoma	49	42.4 Gy (BED) for RMS 50.7 Gy (BED) for ES	91% (3 yr)
Skamene Mc Gill University 2015	Rhabdomyosarcoma	10	36 to 50.4 Gy	100% (6 to 88 months follow-up)

Rhabdomyosarcoma (IRS-IV)

Table 2 Response to prior chemotherapy and disease recurrence patterns for patients who received pulmonary radiotherapy

	XRT [n (%)]		*P*
	Yes (n = 30)	No (n = 16)	
Recurrence			
Yes	11 (37)	11 (69)	
No	19 (63)	5 (31)	.06
Relapse site			
Lung	6 (20)	7 (44)	
Other	5 (17)	4 (25)	
None	19 (63)	5 (31)	.12
PR			
Yes	25 (83)	9 (56)	
No	5 (17)	7 (44)	.08
CR			
Yes	17 (57)	3 (19)	
No	13 (43)	13 (81)	.03

Rodeberg D et al. J Pediatr Surg 2005; 40:256-62

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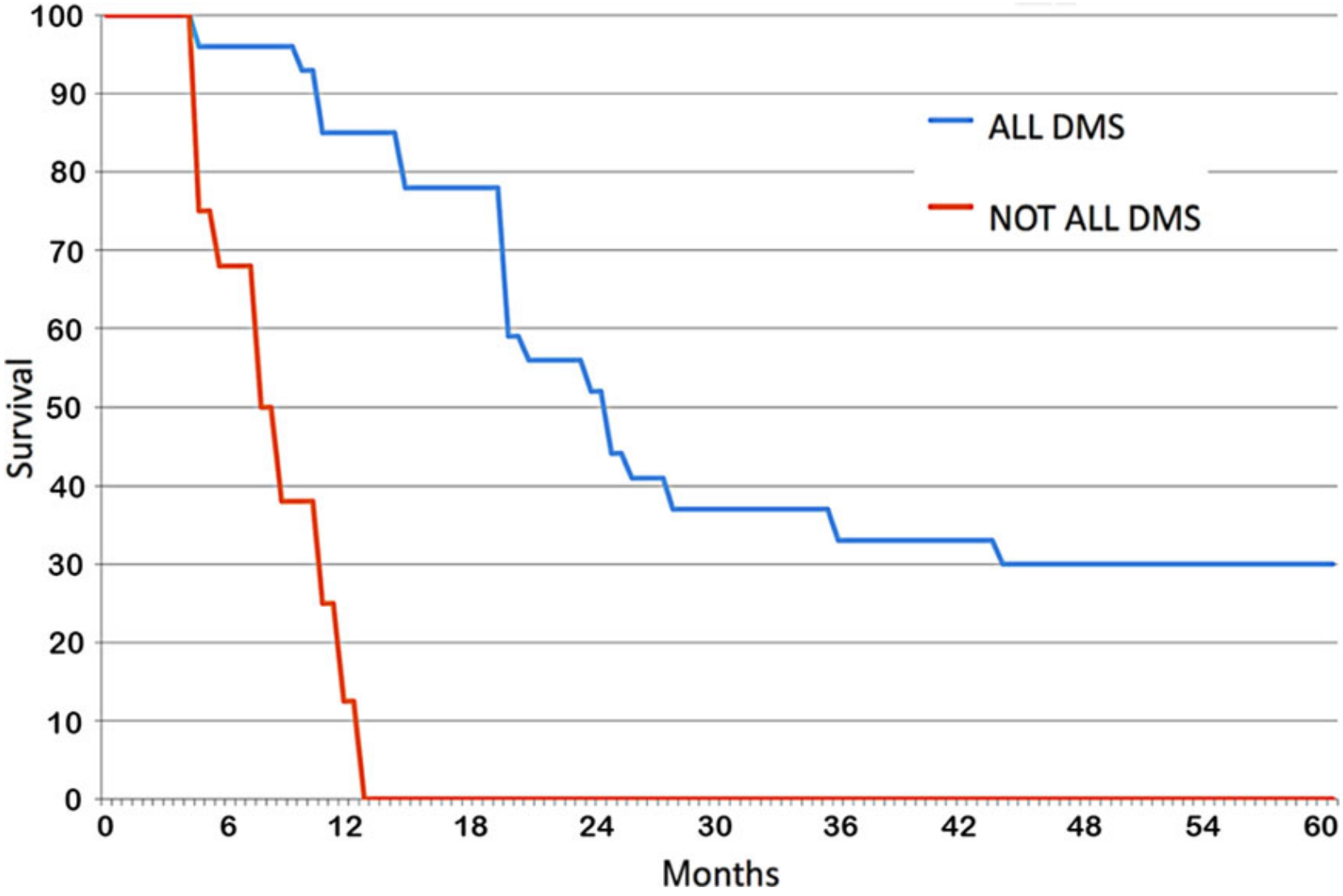
Radiotherapy to Metastatic Sites (BCM Experience)



Mohan AC et al. Pediatr Blood Cancer 2017 Oct 19 (ahead of print)

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COG ARST1431 (Intermediate Risk RMS)

17.7.5 Standard (non-SBRT) radiation dose guidelines for individual metastatic lesions requiring irradiation (all non-bone sites, all non-lung sites and bone sites >5cm).

	Dose (Gy)
Sites of initial metastases in CR	40 in 20 fractions
Lesions which are SD or PR	50 in 25 fractions

17.7.6 SBRT Dose Guidelines for lesions that are SD or PR at completion of chemotherapy

	Dose/fraction (Gy)	**Dose (Gy)**
PTV2 =GTV2	7.0	35
PTV1= CTV2 + 2mm	6.0	30
After 15Gy whole lung		
PTV2 = GTV2	6.0	30
PTV1 = CTV2+2mm	5.0	25

17.7.7 SBRT Dose Guidelines for lesions that are CR at completion of chemotherapy

PTV2 =GTV2	6.0	30
PTV1= CTV2 + 2mm	5.0	25
After 15Gy whole lung		
PTV2 = GTV2	5.0	30
PTV1 = CTV2+2mm	4.0	20

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COG ARST1431: Dose Constraints with SBRT

(Based on AAPM TG101 Report)

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥ Grade 3)
Optic Pathway	<0.2 cc	18 Gy (3.6 Gy/fx)	22.5 Gy (4.5 Gy/fx)	neuritis
Cochlea		24.7 Gy (4.95 Gy/fx)	hearing loss	
Brainstem	<1 cc	23.4 Gy (4.68 Gy/fx)	31 Gy (6.2 Gy/fx)	cranial neuropathy
Spinal Cord	<0.25 cc <1.2 cc	20.2 Gy (4.05 Gy/fx) 12.1 Gy (2.43 Gy/fx)	27 Gy (5.4 Gy/fx)	myelitis
Thecal Sac	<2.5 cc <5 cc	20.2 Gy (4.05 Gy/fx) 15 Gy (3 Gy/fx)	30 Gy (6 Gy/fx)	myelitis
Cauda Equina	<5 cc	27 Gy (5.4 Gy/fx)	28.8 Gy (5.76 Gy/fx)	neuritis
Sacral Plexus	<3 cc	27 Gy (5.4 Gy/fx)	28.8 Gy (5.76 Gy/fx)	neuropathy
Rib	<1 cc	31.5 Gy (6.3 Gy/fx)	38.7 Gy (7.74 Gy/fx)	Pain or fracture
Esophagus*	<5 cc	24.7 Gy (4.95 Gy/fx)	31.5 Gy (6.3 Gy/fx)	stenosis/fistula
Ipsilateral Brachial Plexus	<3 cc	27 Gy (5.4 Gy/fx)	28.8 Gy (5.76 Gy/fx)	neuropathy
Heart/Pericardium	<15 cc	28.8 Gy (5.76 Gy/fx)	34.2 Gy (6.84 Gy/fx)	pericarditis
Great vessels	<10 cc	42.3 Gy (8.46 Gy/fx)	47.7 Gy (9.54 Gy/fx)	aneurysm
Trachea and Ipsilateral Bronchus*	<4 cc	16.2 Gy (3.24 Gy/fx)	34.2 Gy (6.84 Gy/fx)	stenosis/fistula
Skin	<10 cc	27 Gy (5.4 Gy/fx)	28.8 Gy (5.76 Gy/fx)	ulceration
Stomach	<10 cc	25.2 Gy (5.04 Gy/fx)	28.8 Gy (5.76 Gy/fx)	ulceration/fistula
Duodenum*	<5 cc	16.2 Gy (3.24 Gy/fx)	28.8 Gy (5.76 Gy/fx)	ulceration
Jejunum/Ileum*	<5 cc	17.5 Gy (3.51 Gy/fx)	31.5 Gy (6.3 Gy/fx)	enteritis/obstruction
Colon*	<20cc	22.5 Gy (4.5 Gy/fx)	34.2 Gy (6.84 Gy/fx)	colitis/fistula
Rectum*	<20cc	22.5 Gy (4.5 Gy/fx)	34.2 Gy (6.84 Gy/fx)	proctitis/fistula
Bladder wall	<15 cc	16.4 Gy (3.28 Gy/fx)	34.2 Gy (6.84 Gy/fx)	cystitis/fistula
Penile Bulb	<3 cc	27 Gy (5.4 Gy/fx)	45 Gy (9 Gy/fx)	impotence
Femoral Heads (Right & Left)	<10 cc	27 Gy (5.4 Gy/fx)		necrosis
Renal hilum/vascular trunk	<2/3 volume	20.7 Gy (4.14 Gy/fx)		malignant hypertension
Parallel Tissue	**Volume**	**Critical Volume Dose**		**Endpoint (≥ Grade 3)**
Lung (Right & Left)	1500 cc	11.2 Gy (2.25 Gy/fx)		Basic Lung Function
Lung (Right & Left)	1000 cc	12.1 Gy (2.4 Gy/fx)		Pneumonitis
Liver	700 cc	18.9 Gy (3.78 Gy/fx)		Basic Liver Function
Renal cortex (Right & Left)	200 cc	15.7 Gy (3.15 Gy/fx)		Basic renal function

Previous Whole Lung Irradiation

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥ Grade 3)
Spinal Cord	<0.25 cc <1.2 cc	18.2 Gy (3.64 Gy/fx) 10.9 Gy (2.18 Gy/fx)	20.2 Gy (4.05 Gy/fx)	myelitis
Thecal Sac	<2.5 cc <5 cc	18.2 Gy (3.64 Gy/fx) 13.5 Gy (2.7 Gy/fx)	25 Gy (5 Gy/fx)	myelitis
Rib	<1 cc	26.5 Gy (5.3 Gy/fx)	33.7 Gy (6.74 Gy/fx)	Pain or fracture
Esophagus*	<5 cc	19.7 Gy (3.94 Gy/fx)	26.5 Gy (5.3 Gy/fx)	stenosis/fistula
Ipsilateral Brachial Plexus	<3 cc	22 Gy (4.4 Gy/fx)	23.8 Gy (4.76 Gy/fx)	neuropathy
Heart/Pericardium	<15 cc	23.8 Gy (4.76 Gy/fx)	29.2 Gy (5.84 Gy/fx)	pericarditis
Great vessels	<10 cc	37.3 Gy (7.46 Gy/fx)	42.7 Gy (8.54 Gy/fx)	aneurysm
Trachea and Ipsilateral Bronchus*	<4 cc	11.2 Gy (2.24 Gy/fx)	29.2 Gy (5.84 Gy/fx)	stenosis/fistula
Skin	<10 cc	22 Gy (4.4 Gy/fx)	23.8 Gy (4.76 Gy/fx)	ulceration
Stomach	<10 cc	20.2 Gy (4.04 Gy/fx)	23.8 Gy (4.76 Gy/fx)	ulceration/fistula
Duodenum*	<5 cc	11.2 Gy (2.24 Gy/fx)	23.8 Gy (4.76 Gy/fx)	ulceration
Jejunum/Ileum*	<5 cc	12.5 Gy (2.51 Gy/fx)	26.5 Gy (5.3 Gy/fx)	enteritis/obstruction
Colon*	<20cc	17.5 Gy (3.5 Gy/fx)	29.2 Gy (5.84 Gy/fx)	colitis/fistula
Parallel Tissue	Volume	**Critical Volume Dose**		**Endpoint (≥ Grade 3)**
Lung (Right & Left)	500 cc	11.2 Gy (2.25 Gy/fx)		Basic Lung Function
Lung (Right & Left)	300 cc	12.1 Gy (2.4 Gy/fx)		Pneumonitis
Lung (Right & Left)+	35%	20 Gy		Pneumonitis
Liver	200 cc	18.9 Gy (3.78 Gy/fx)		Basic Liver Function
Liver+	50%	30 Gy		Basic Liver Function

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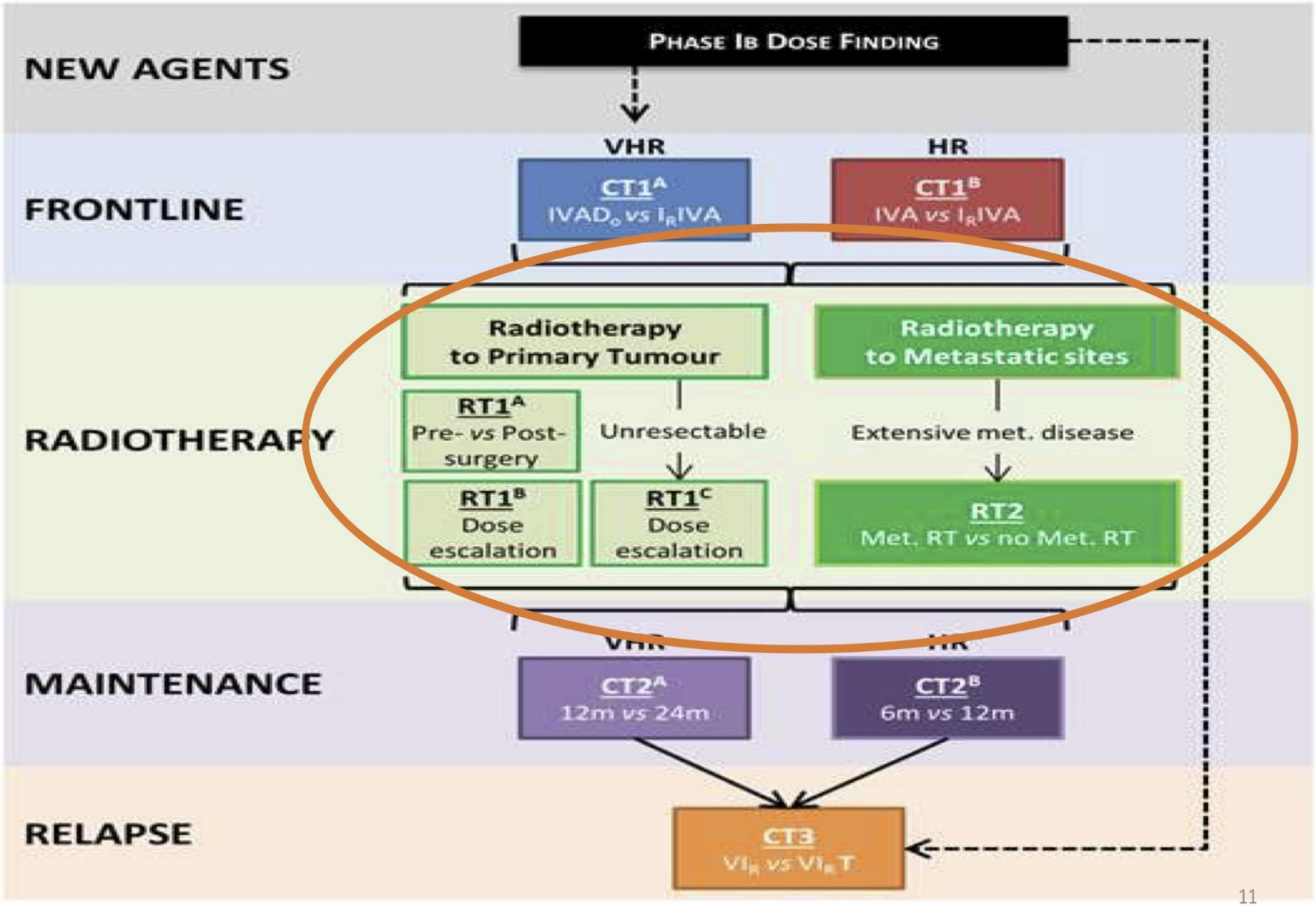
A multiarm-multistage study for children and adults with localised and metastatic Frontline and Relapsed RhabdoMyoSarcoma

The FaR-RMS Study

Henry Mandeville, ASTRO 2017



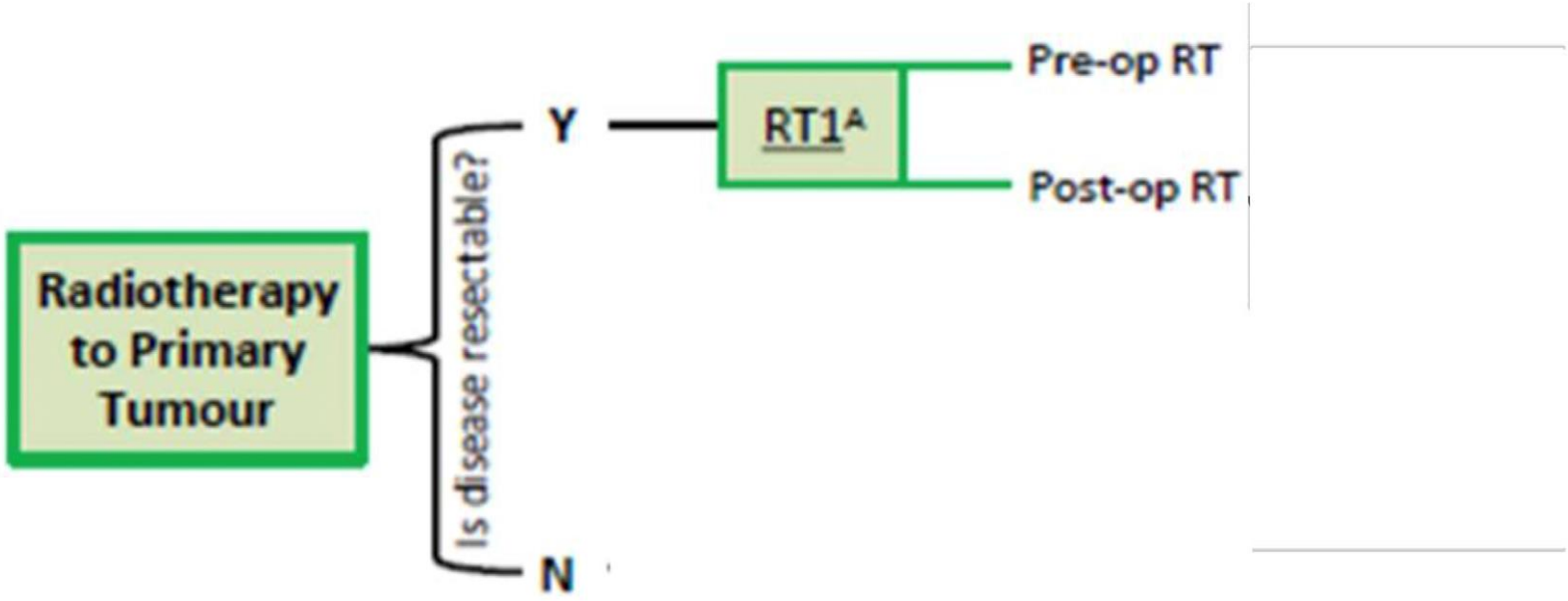
Henry Mandeville, ASTRO 2017

Aims of the FaR-RMS trial:
Local Control

- To improve local control though optimising radiotherapy
  - Protons/ IMPT, Photons/ IMRT, SRS/ SABR, Brachytherapy
- 3 radiotherapy questions will be addressed:
  i. Benefit of giving RT preoperatively (RT1a)
  ii. Benefit dose escalation of RT in patients with higher local failure risk (RT1b & c)
  iii. Benefit of RT to all metastatic sites (RT2)
- Patients may be eligible for entry into more than 1 RT randomisation

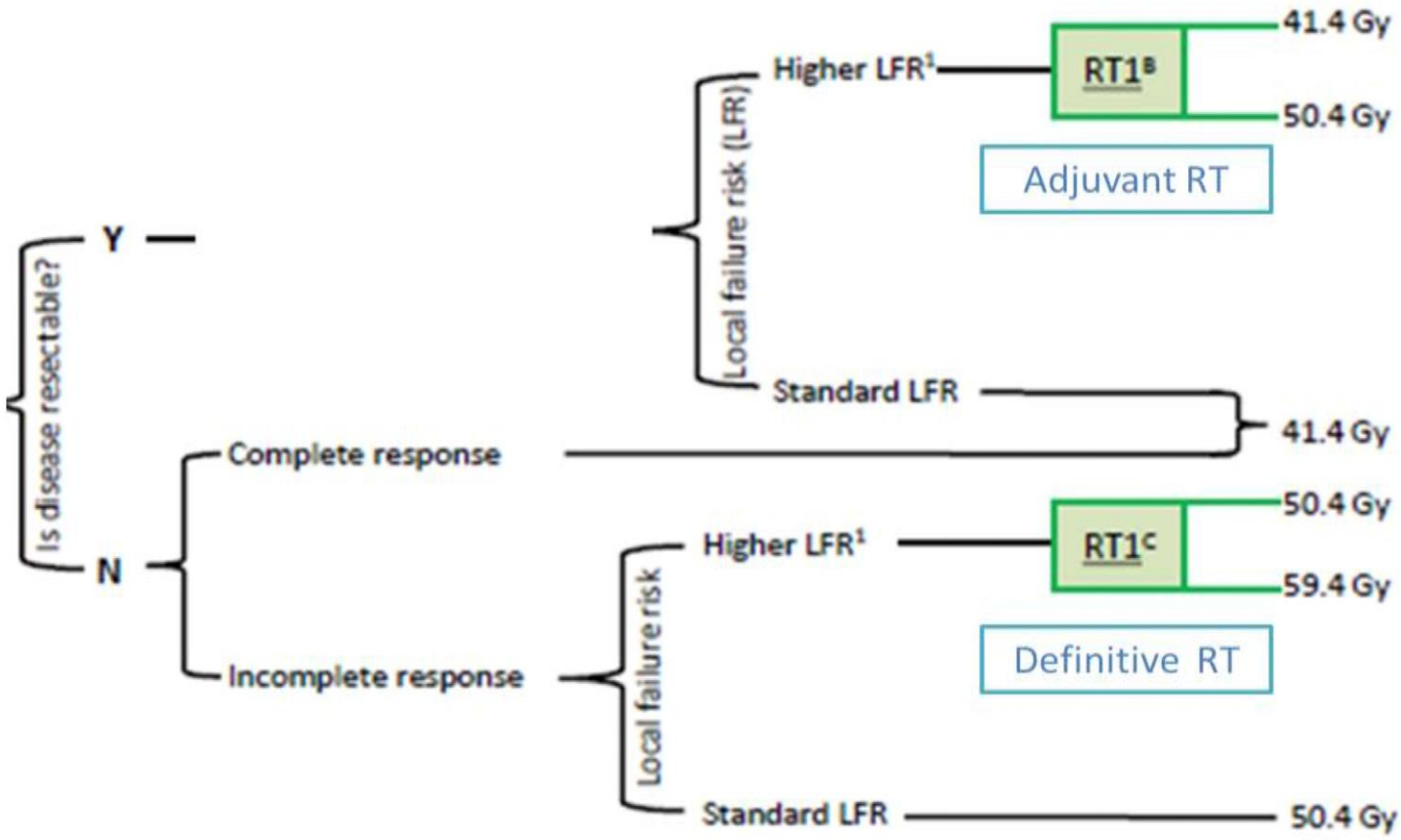
RT1a: Pre-operative vs Post-operative Radiotherapy

- **Phase III Study** (n= 350)
- **Inclusion criteria:**
  - Primary tumour resectable (predicted **R0/ R1** resection) after 3 cycles of induction chemotherapy
  - Adjuvant radiotherapy required (local decision) , in addition to surgical resection



RT1b & c: Dose escalation of RT to improve local control

Higher LFR: >5cm, unfavourable site, ≥10y or metastatic disease



Henry Mandeville, ASTRO 2017

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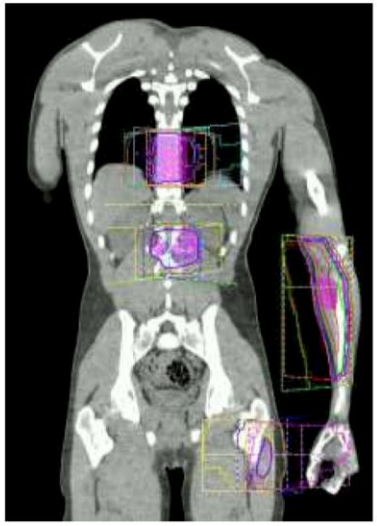
RT2: Evaluating the benefit of radiotherapy to metastatic sites

Extensive metastases ≥4 mets, pulmonary mets not in CR

- Metastatic radiotherapy to all metastatic sites that can be feasibly treated
  - Dose & schedule dependent on sites & extent of disease
- Met RT will commence week 22-25 (concurrently with locoregional RT)
- N=210; Assumed baseline 3y EFS 40%
- Randomised Phase II design; Bayesian methods



Limited metastatic disease

≤3 metastases or Pulmonary metastases in CR

- No randomised question
- Radical treatment of all metastatic sites
- Treatment options include stereotactic ablative body radiotherapy (SABR/ SBRT)
- Whole lung RT for lung mets in CR

Study endpoints

- Primary endpoints: LFFS *(Primary RT)* & EFS *(Met RT)*
- Late complications: ≤5 years
- Acute toxicity: ≤30 days post RT
- Wound complications: ≤120 days of surgery
- Quality of life for Preop RT & Met RT questions
  - PedsQL across all age groups

Conclusions

- Radiotherapy is an important component of treatment in childhood rhabdomyosarcoma
- There is emerging literature that the use of a postchemotherapy volume for the boost field does not compromise local control
- Intensity-modulated radiation therapy for rhabdomyosarcoma has resulted in excellent local control rates
- Preliminary data indicate that proton therapy does not seem to compromise local control

Conclusions

- Omission of radiotherapy in Group II and Group III rhabdomyosarcoma results in higher local failure and in some sites can impact on survival
- Current trials in North America and Europe are looking at dose escalation up to 59.4 Gy for children with high risk for local failure
- It is unclear whether radiotherapy to metastatic sites improve overall outcome of patients

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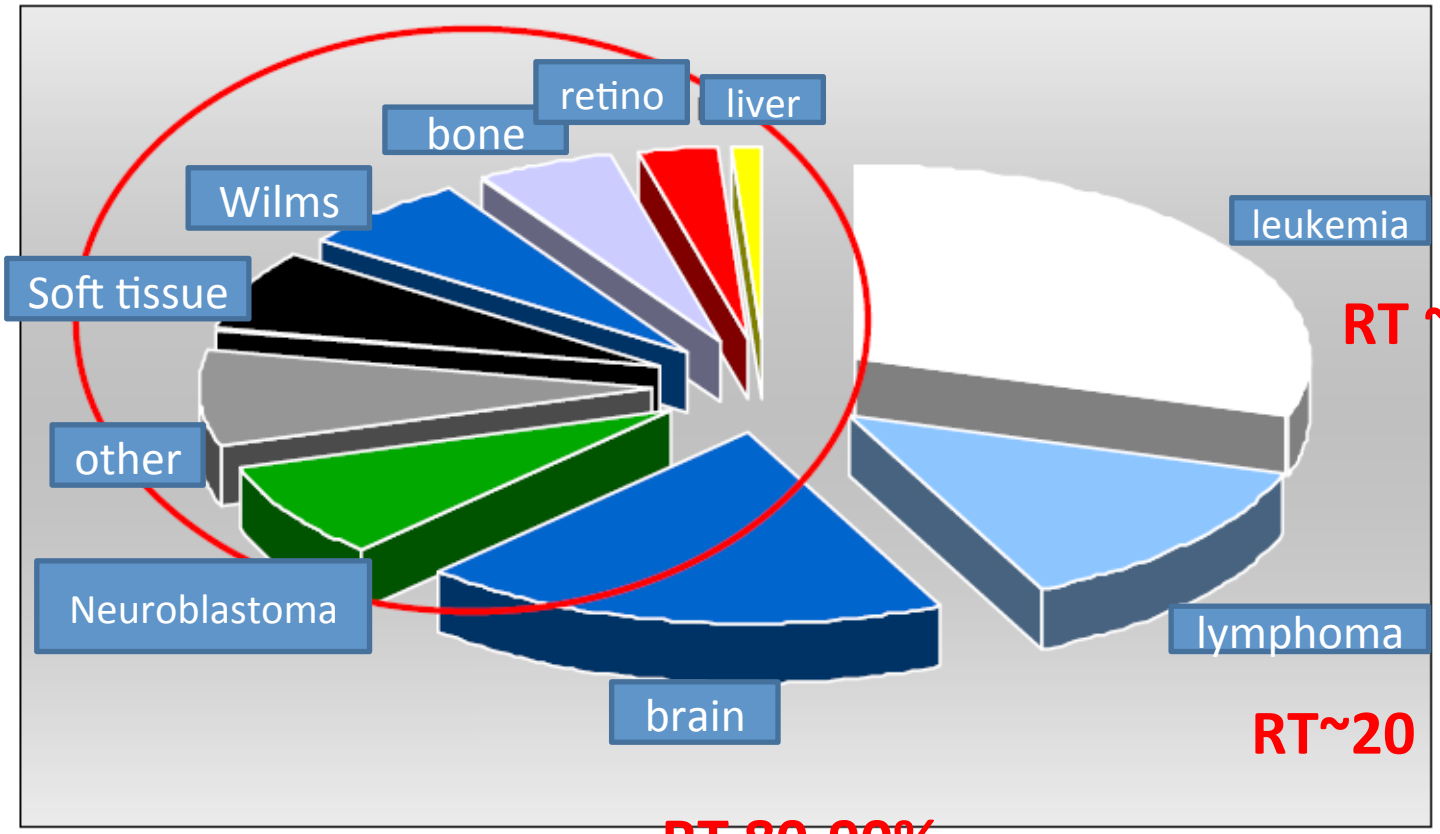
Late effects non-CNS Tumors

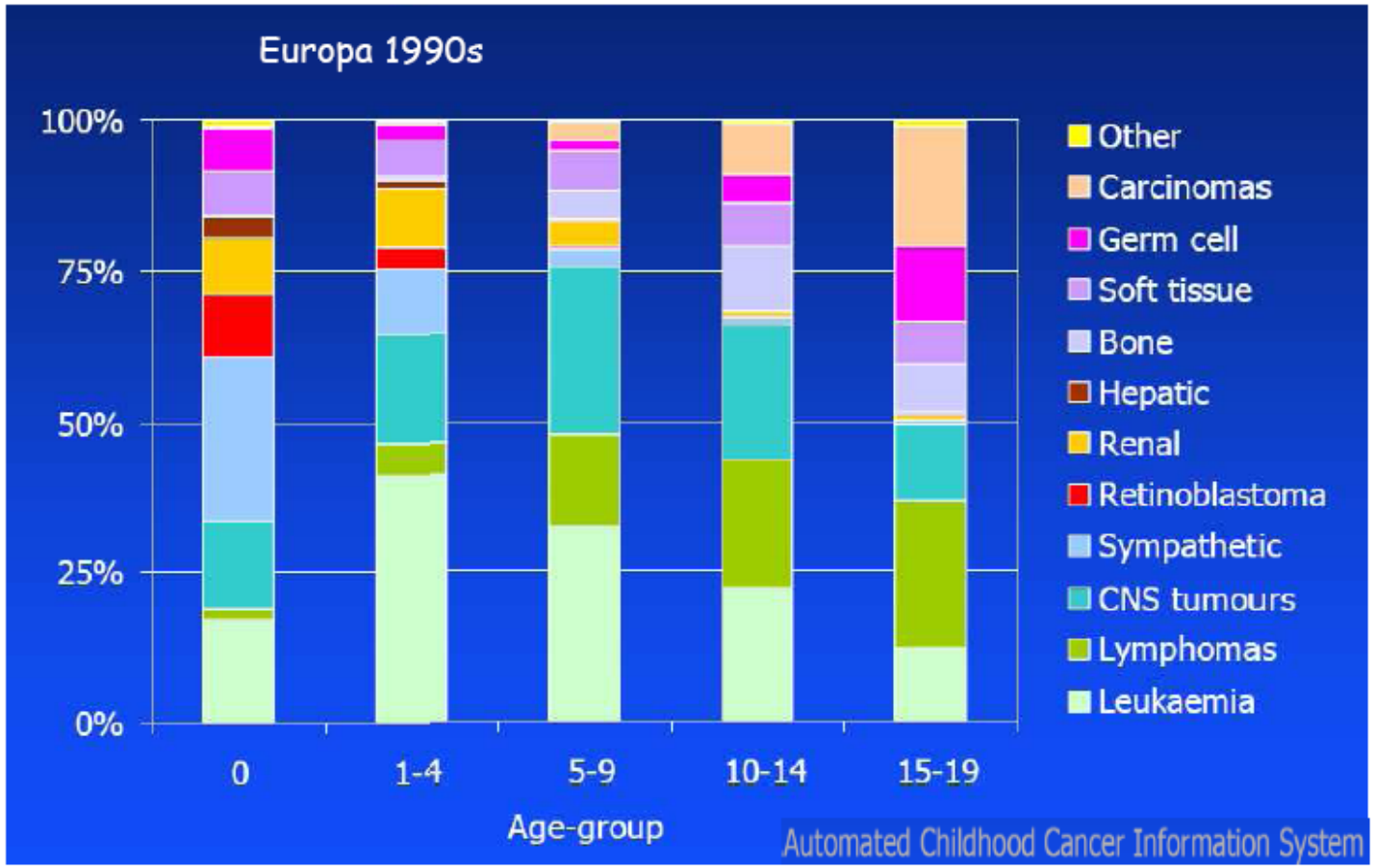
Karin Dieckmann
Medical University Vienna , Austria

Tumors in paediatric oncology
- Epidemiology -



15 / 100.000 Children per year

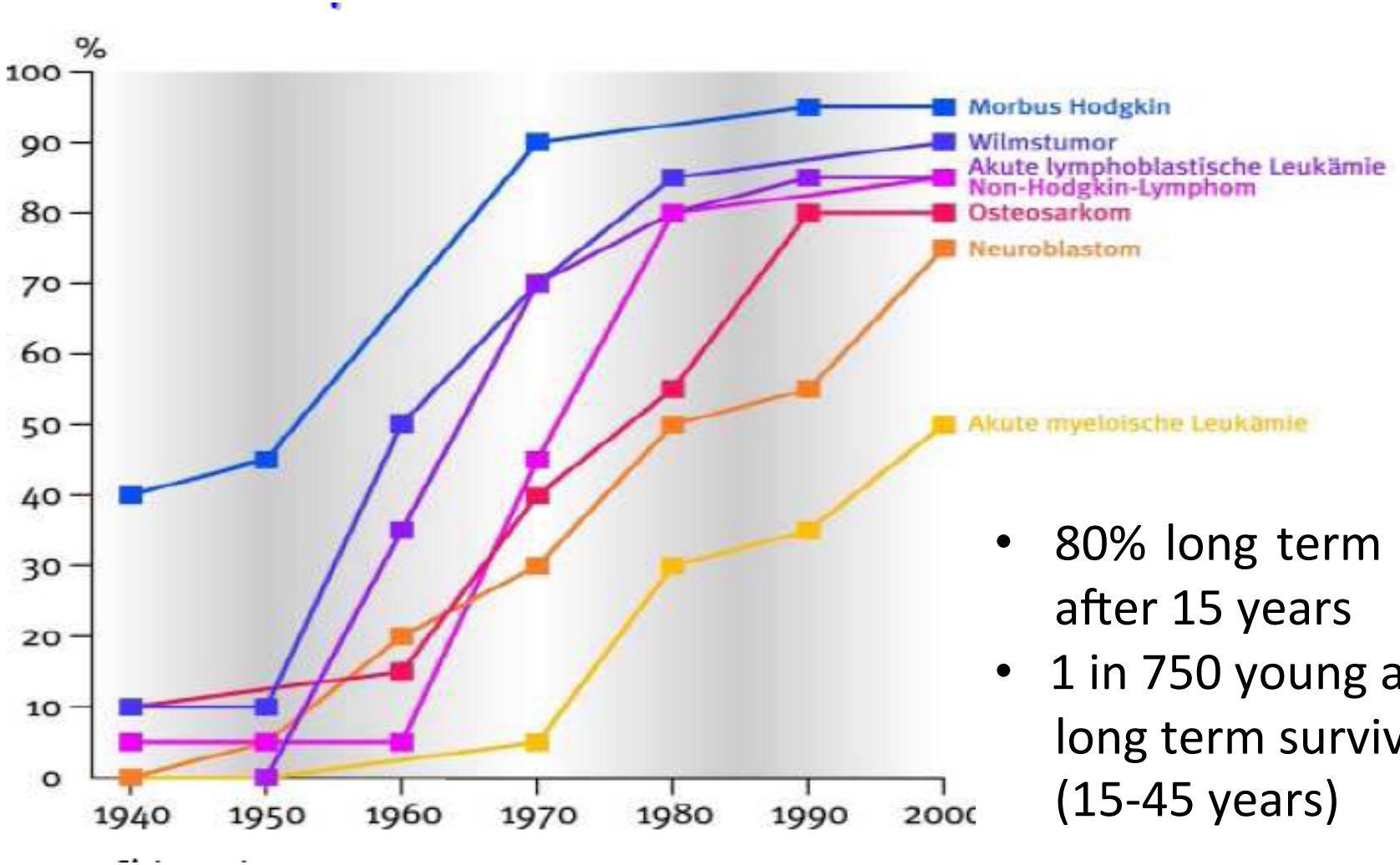
Age Specific Cancer- Incidence



The Lancet, 2004, Volume 364, Issue 9451, Pages 2074-2076

50% of the children get a combined treatment with Chemo- and Radiotherapy

5-Year Relative Survival Rates for Children < 15 years of Age

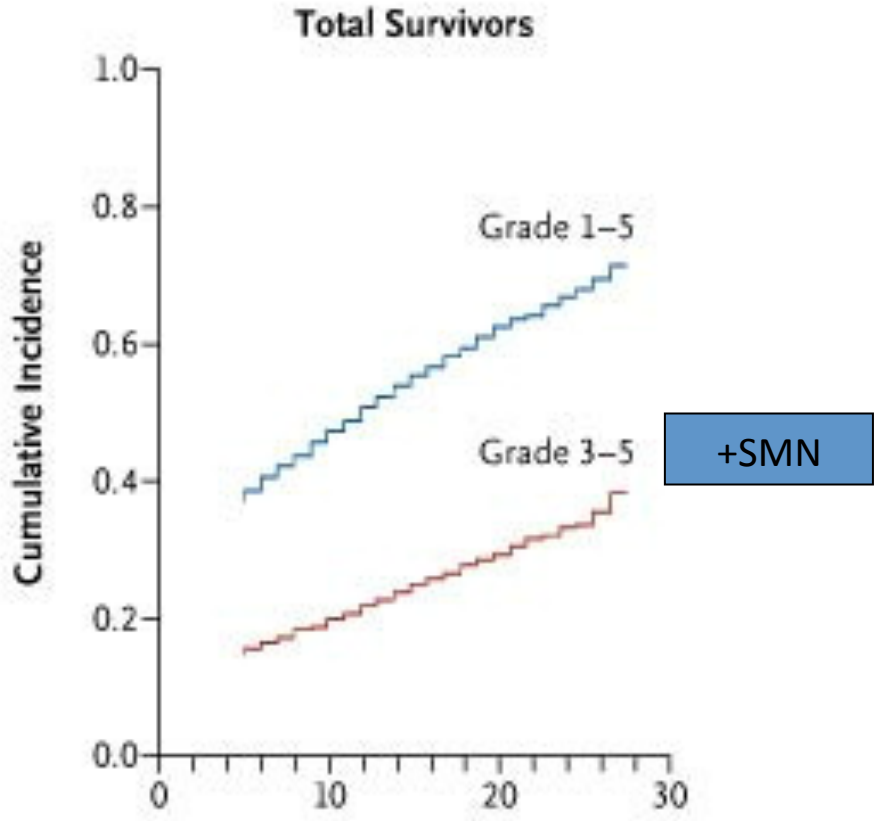


- 80% long term survivor after 15 years
- 1 in 750 young adults is long term survivor (15-45 years)

Chronic Health Conditions in Adult Survivors of Childhood Cancer

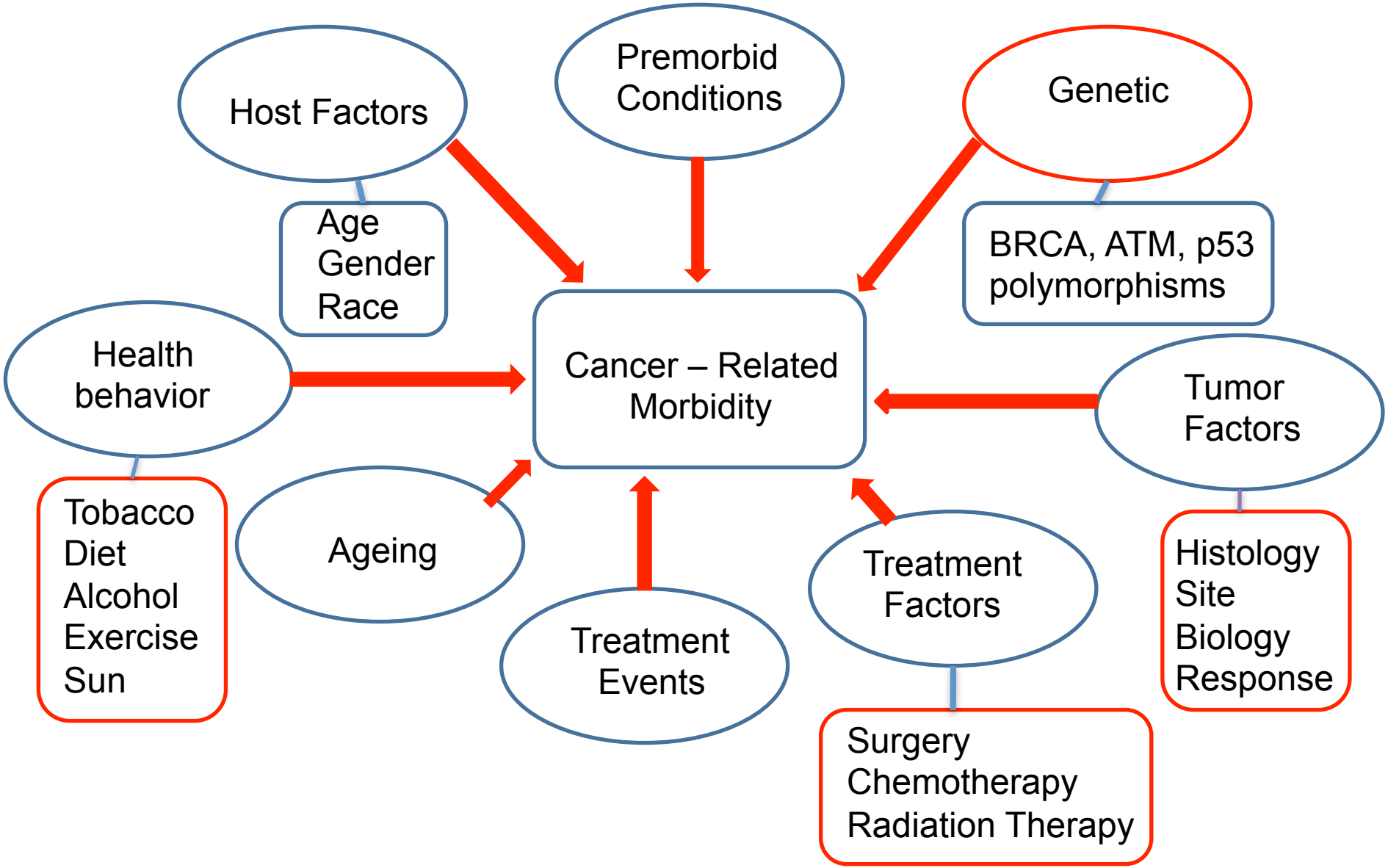
N=10.397 survivors / 3.034 sibblings

- **≈75%** of the long term survivors develop at least one chronic health condition
- **≈40%** have a serious health problem
- **≈33% have multiple conditions** life threatening conditions
- **The incidence of health conditions increases over time and does not appear to plateau**



Oeffinger, N Engl J Med 2006

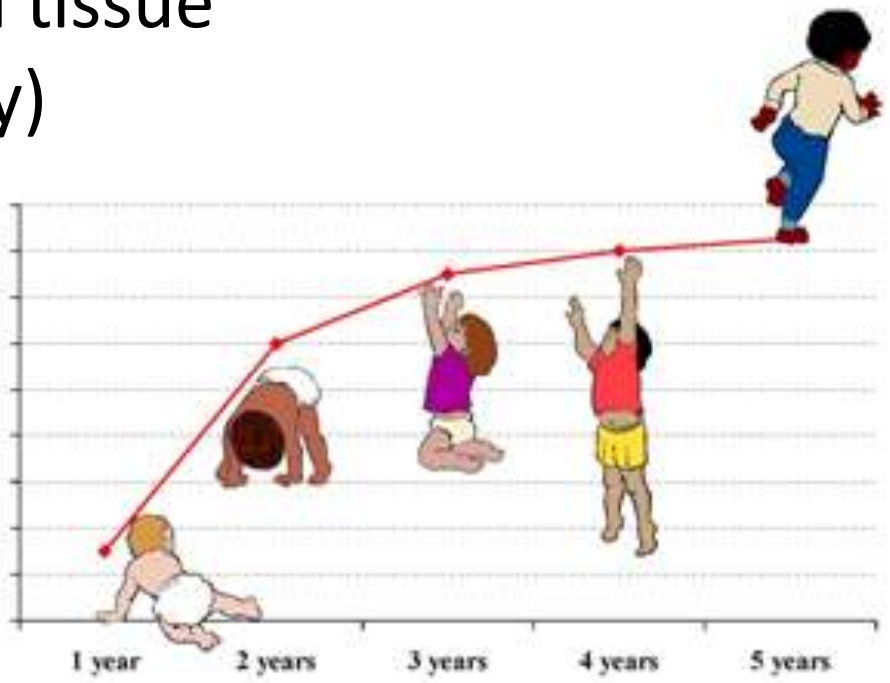
Multifactorial Factors influence tumor control and longterm side effects



Factors affecting Radiation Injury

- age at time of treatment
- total dose given
- dose homogeneity
- dose per fraction
- volume of the irradiated tissue
- type of radiation (energy)

- surgery/chemotherapy in addition



Long term side effects after Thoracic Irradiation

Heart

- Coronary artery disease
- Valvular disease
- Pericardial disease
- Arrhythmias

Lung

- Fibrosis
- Restrictive-obstructive lung disease
- Interstitial pneumonitis
- Sec. cancer

Thyroid

- Hypothyreosis
- Hyperthyroidism
- Sec. Cancer

Skeletal

- Abnormal chest wall development
- Sec. cancer

Breast

- Hypoplasia
- Sec. cancer

Dickerman Pediatrics 2007; 119;554-568

Long term side effects after abdominal Irradiation

Gastrointestinal tract

- Gastrointestinal fibrosis
- Obstruction
- Sec. Cancer

Spleen

- Asplenie

Kidney

- Nephropathy
- Cancer
- Hypertonus

Bladder

- Fibrosis
- Cystitis
- Dysfunctioning voiding
- Sec.Cancer

Gonads

- Ovarian failure
- Testicular failure
- Sec.Cancer

Dickerman Pediatrics 2007; 119;554-568

Long term side effects after Irradiation

Muscle/soft tissue

- Atrophy
- Cancer (sarcoma)

Skeletal

- Osteopenia
- Osteoporosis
- Growth retardation

Skin

- Melanocytic Nevi
- Malignant Melanoma
- Non melanotic skin cancer

Dickerman Pediatrics 2007; 119;554-568

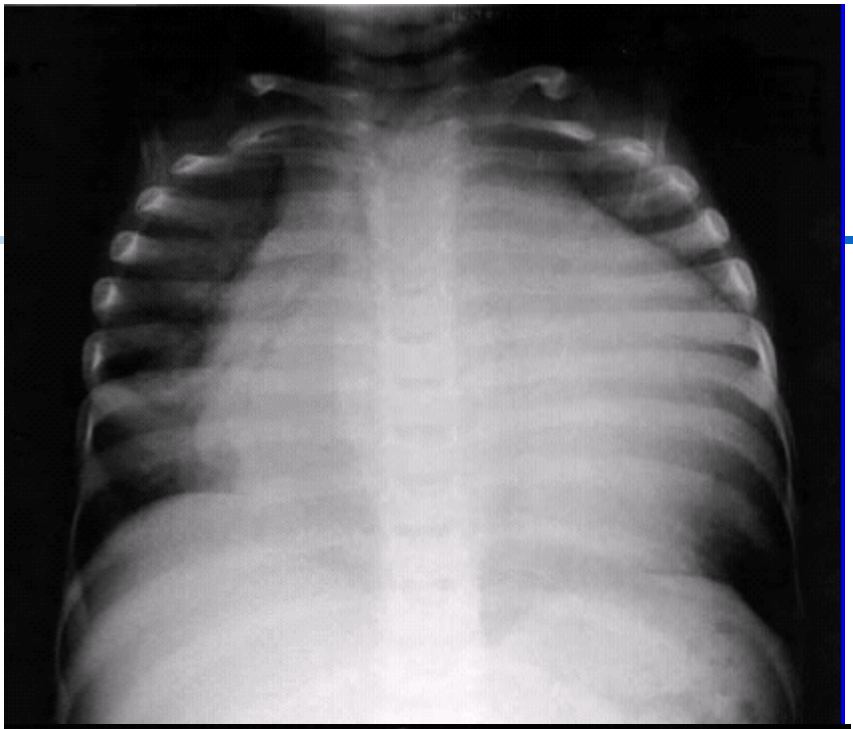
Relative Risk of Chronic Health Conditioning among cancer survivors

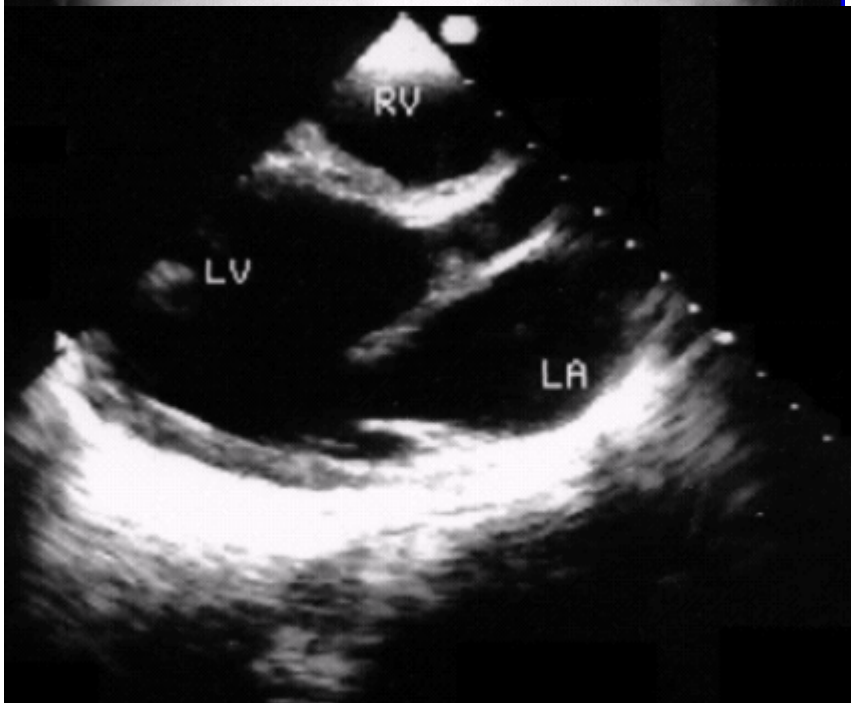
Kevin C. Oeffinger, M.D.,

Cancer Diagnosis or Treatment Exposure	Grade 1–4	Grade 3 or 4	≥2 Conditions
	Relative Risk (95% Confidence Interval)		
Siblings	1.0	1.0	1.0
Chemotherapy			
Any chemotherapy	3.2 (2.9–3.4)	8.1 (6.8–9.6)	4.5 (4.0–5.0)
Alkylating agent	3.8 (3.5–4.2)	9.9 (8.3–11.8)	5.6 (5.0–6.4)
Anthracycline	4.3 (3.9–4.7)	11.0 (9.2–13.1	5.8 (5.0–6.6)
Radiation therapy			
Any irradiation	3.4 (3.1–3.6)	7.9 (6.6–9.4)	5.2 (4.6–5.9)
Brain irradiation	3.1 (2.8–3.3)	7.0 (5.8–8.5)	4.8 (4.2–5.5)
Chest irradiation	4.7 (4.3–5.2)	10.6 (8.8–12.7)	8.2 (7.1–9.4)
Abdominal irradiation	3.7 (3.3–4.0)	8.8 (7.3–10.6)	5.8 (5.1–6.7)
Pelvic irradiation	4.2 (3.8–4.7)	10.5 (8.6–12.7)	6.8 (5.9–7.9)
Specific combinations			
Chest radiation plus bleomycin	7.8 (6.2–9.8)	13.6 (9.8–18.7)	13.3 (10.1–17.6)
Chest radiation plus anthracycline	6.0 (5.2–6.9)	13.0 (10.4–16.3)	9.7 (8.1–11.8)
Chest radiation plus abdominal or pelvic irradiation	4.7 (4.2–5.2)	10.9 (8.9–13.2	8.5 (7.3–9.9)
Anthracycline plus an alkylating agent	4.3 (3.9–4.8)	10.9 (9.0–13.1)	6.0 (5.2–6.9)
Abdominal or pelvic irradiation plus an alkylating agent	4.0 (3.6–4.4)	10.0 (8.2–12.1)	6.2 (5.4–7.2)

Outline

- Heart
- Skeletal impairment /Soft tissue
- Breast
- Secondary Cancer





Cardiac Disease

- **Chemotherapy**

Anthracyclin-Cardiomyopathy

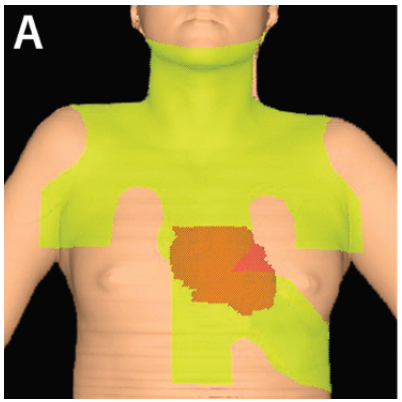
- **Mediastinal Irradiation**

Valvular defects

Coronary artery diseases

Myocardial diseases

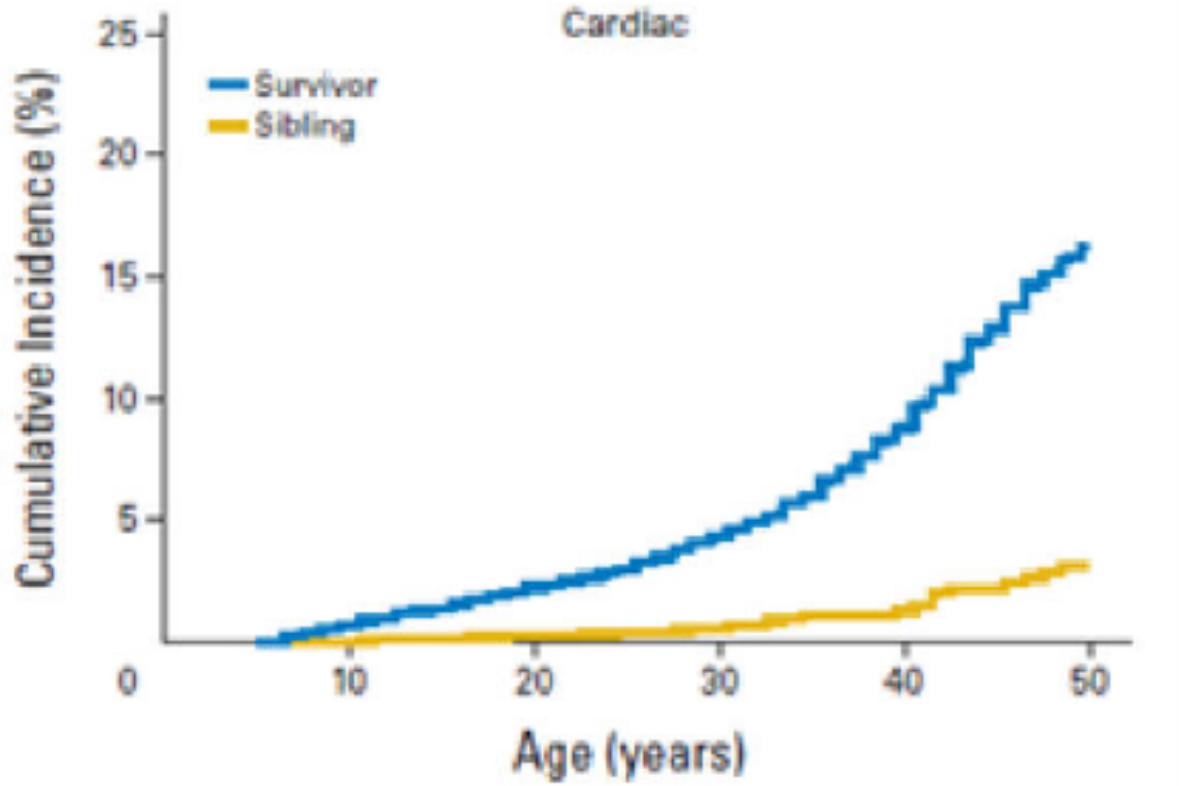
Pericardial disease



Late Cardiotoxicity in Aging Adult Survivors of Childhood Cancer

Gregory T. Armstrong, MD, MSCE[a] and Jordan D. Ross, BS[b]

[a]St. Jude Children's Research Hospital



Cumulative incidence of grade 3 to 5 conditions within 40 years after treatment up to 15 %

Prog Pediatr Cardiol. 2014 September 1; 36(1-2): 19–26.

Late Cardiotoxicity in Aging Adult Survivors of Childhood Cancer

Gregory T. Armstrong, MD, MSCE[a] and Jordan D. Ross, BS[b]

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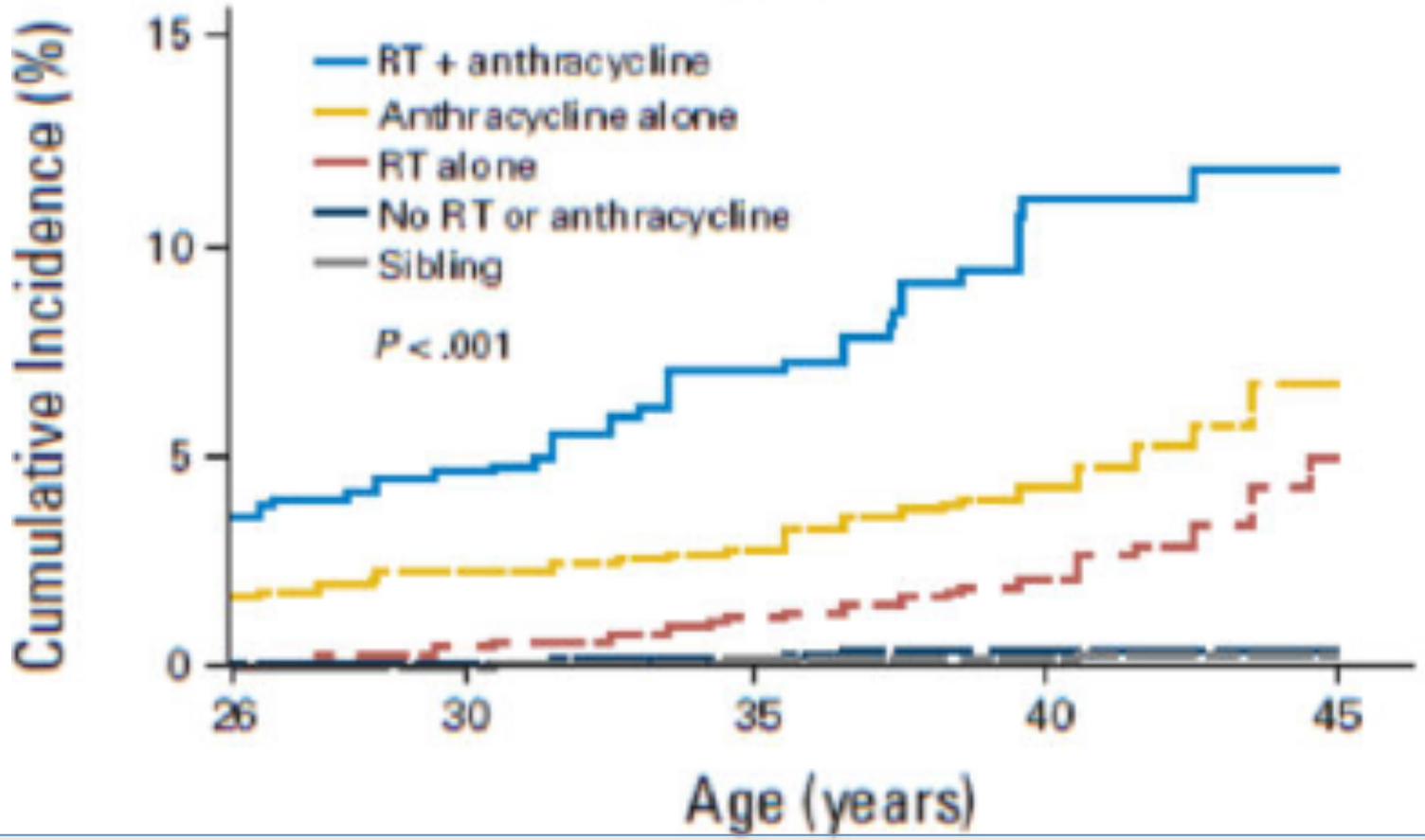


Congestive Heart failure by therapeutic exposure compared with sibilings

Prog Pediatr Cardiol. 2014 September 1; 36(1-2): 19–26.

Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort

Daniel A Mulrooney

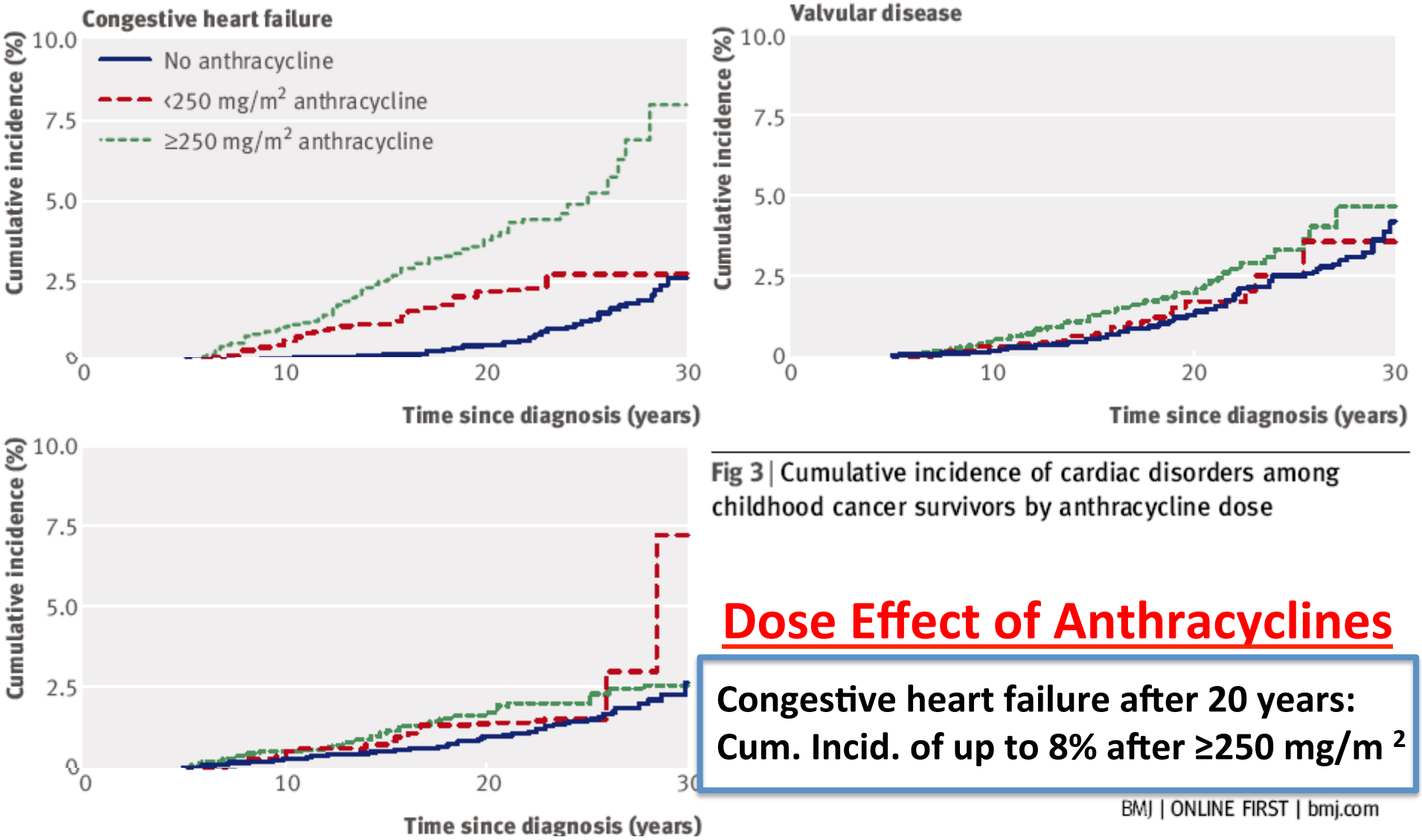


Fig 3 | Cumulative incidence of cardiac disorders among childhood cancer survivors by anthracycline dose

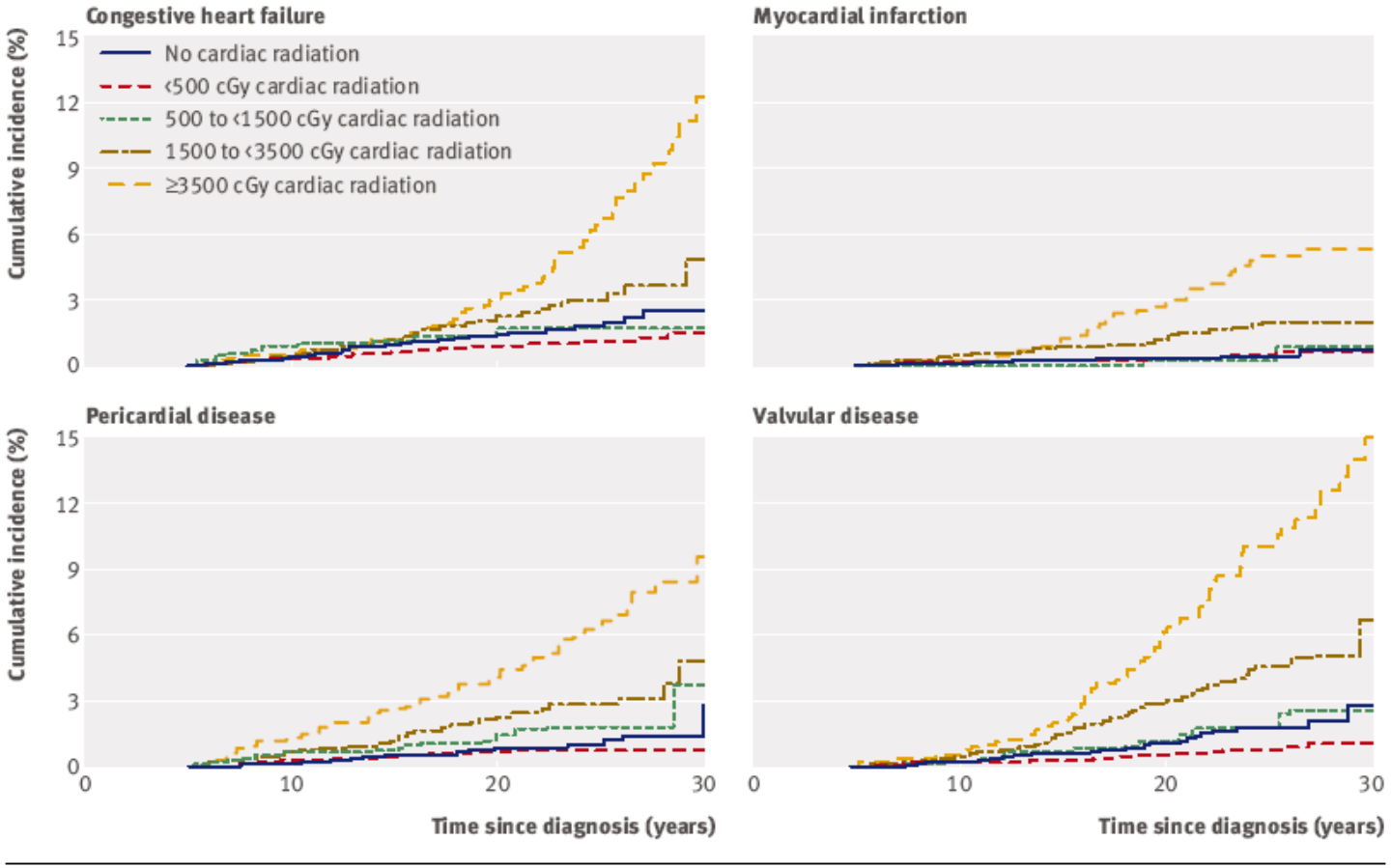
Dose Effect of Anthracyclines

Congestive heart failure after 20 years: Cum. Incid. of up to 8% after ≥250 mg/m ^{2}

Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort

Daniel A Mulrooney

Effect of Radiotherapy Dose



Effect of ≥ 35 Gy on Muscle, Pericard and Valve
10-20 years after Mediastinal Irradiation

BMJ | ONLINE FIRST | bmj.com

Late Valvular and Other Cardiac Diseases After Different Doses of Mediastinal Radiotherapy for Hodgkin Disease in Children and Adolescents: Report From the Longitudinal GPOH Follow-Up Project of the German–Austrian DAL-HD Studies

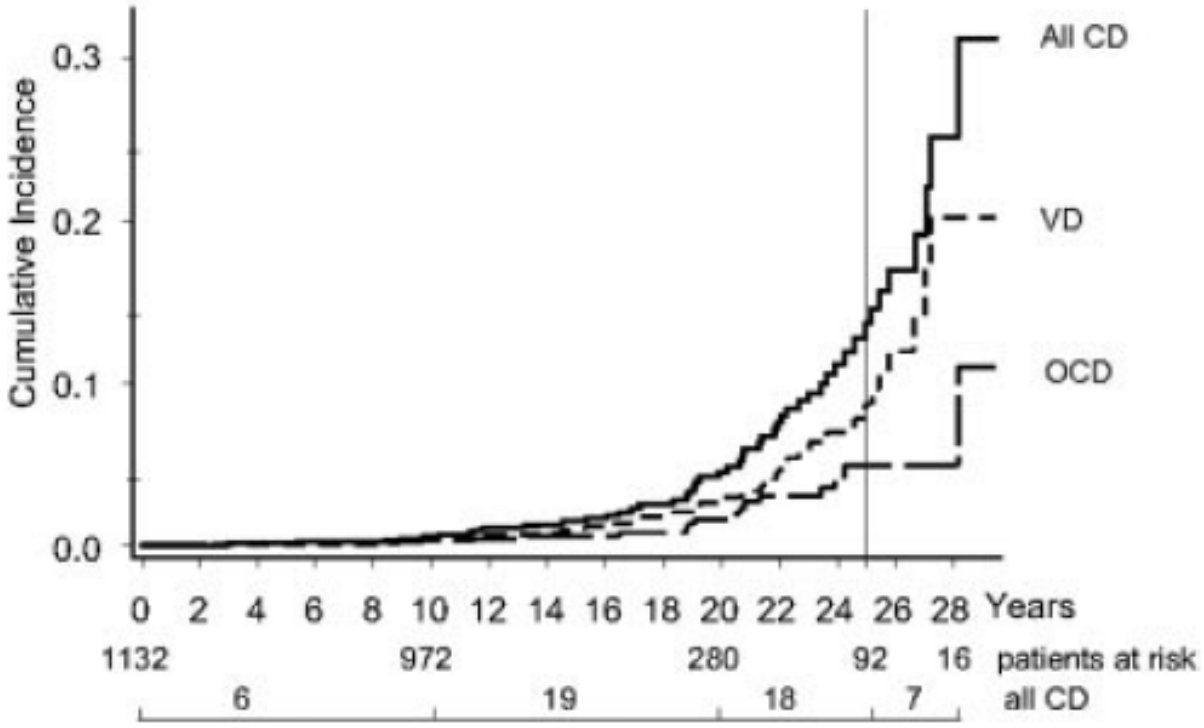
Günther Schellong, MD,[1]

HD-78, HD 82, HD-85, HD-87, HD-90
N= 1.132

Stage	**Stage I**	**20%**
	Stage II	**44%**
	Stage III	**24%**
	Stage IV	**12%**
Age at treatment time	**12.8 (range 2.5-17.9)**	
Median follow up	**15.1 (range 3.1- 29.4)**	
Age at last information	**27.9 (range 8.7- 44.0)**	

Pediatr Blood Cancer 2010;55:1145–1152

Late Valvular and Other Cardiac Diseases After Different Doses of Mediastinal Radiotherapy for Hodgkin Disease in Children and Adolescents: Report From the Longitudinal GPOH Follow-Up Project of the German–Austrian DAL-HD Studies



Günther Schellong,

Cumulative incidence of CD was 14% at 25ys; 31% at 28ys.
VD was 9% at 25ys; 20% at 28ys.
OCD was 5% at 25ys; 11% at 28ys.

Pediatr Blood Cancer 2010;55:1145–1152

Late Valvular and Other Cardiac Diseases After Different Doses of Mediastinal Radiotherapy for Hodgkin Disease in Children and Adolescents: Report From the Longitudinal GPOH Follow-Up Project of the German–Austrian DAL-HD Studies

Günther Schellong,

TABLE II. Number of Cardiac Diseases (CD) by Mediastinal Radiation (MedRD) Group

	MedRD-36	MedRD-30	MedRD-25	MedRD-20	MedRD-0	All
Patients/Group	248	133	282	171	298	1,132
Valvular defects	25	3	5	0	0	33
Coronary artery diseases incl. 8 infarctions	10	2	1	1	0	14
Myocardial diseases	10	0	3	0	1	14
Conduction disorders	7	2	1	0	0	10
Pericardial diseases	7	0	1	0	0	8
Patients with CD[a]	32	7	9	1	1	50

[a]The sums of diagnoses exceed the number of patients because 20 patients had more than one diagnosis (maximum 4 diagnoses).

Valvular defects >> Coronary artery diseases > Cardiomyopathy

After 25 years CD was 21% in the MedRD-36 group,
10% in the MedRD-group,6%,5%, and 3% in the lower group

Pediatr Blood Cancer 2010;55:1145–1152

Late Valvular and Other Cardiac Diseases After Different Doses of Mediastinal Radiotherapy for Hodgkin Disease in Children and Adolescents: Report From the Longitudinal GPOH Follow-Up Project of the German–Austrian DAL-HD Studies

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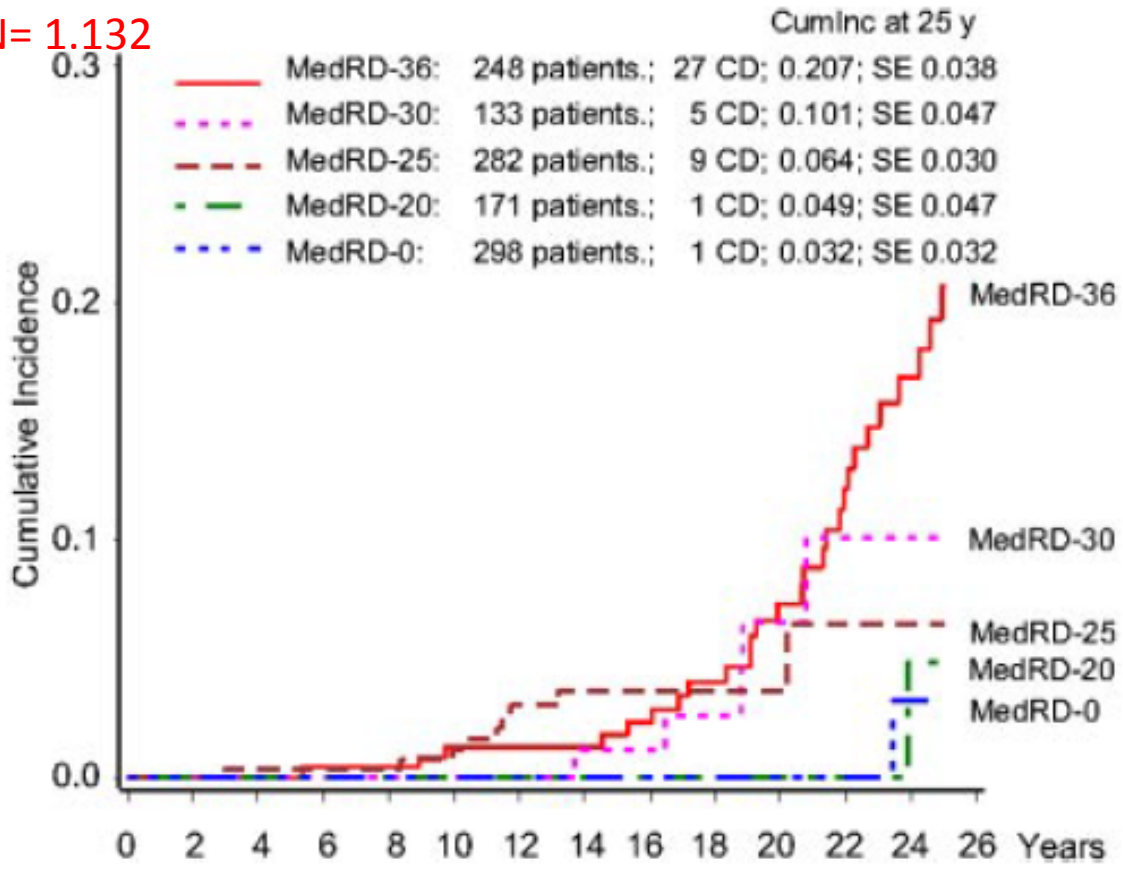

Cardiac Disease

Median interval between HD Treatment and diagnosis of CD was 19.5 years (range 3.0-28.2)

Median age of the patients at diagnosis of CD was 32.2 (15-41 Years)

Pediatr Blood Cancer 2010;55:1145–1152

Late Valvular and Other Cardiac Diseases After Different Doses of Mediastinal Radiotherapy for Hodgkin Disease in Children and Adolescents: Report From the Longitudinal GPOH Follow-Up Project of the German–Austrian DAL-HD Studies

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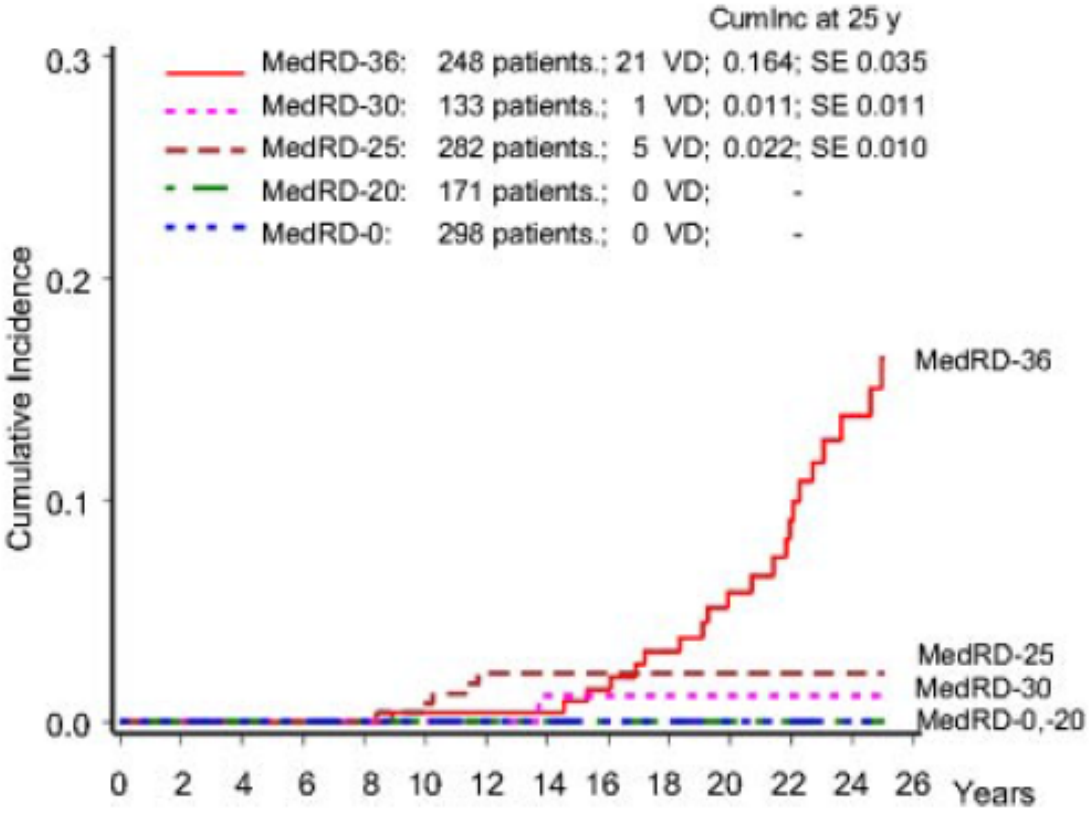


Valvular Disease

MedRD was the only risk factor with significant impact on CD-free survival (P=0.0025)

Pediatr Blood Cancer 2010;55:1145–1152

Late Valvular and Other Cardiac Diseases After Different Doses of Mediastinal Radiotherapy for Hodgkin Disease in Children and Adolescents: Report From the Longitudinal GPOH Follow-Up Project of the German–Austrian DAL-HD Studies

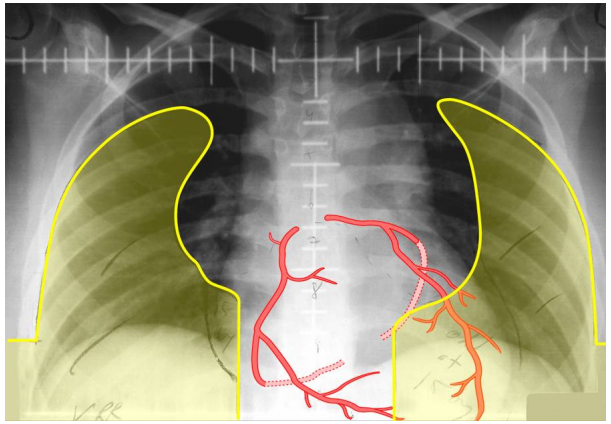
Günther Schellong, MD,[1]

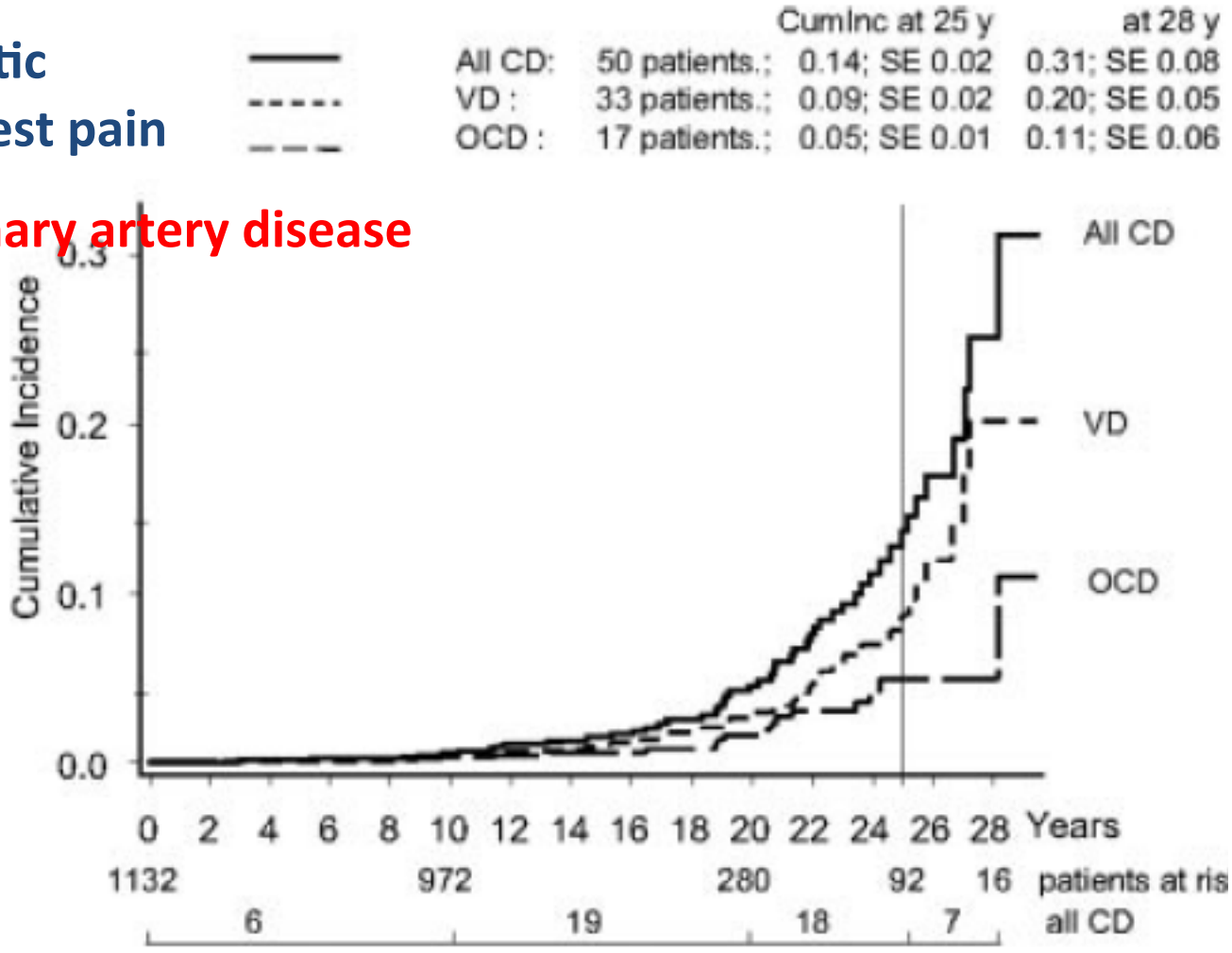
Cardiac Diseases: N=50

22/50 pts.: Asymptomatic

28/50pts. : Dyspnea; Chest pain

4/50pts.: Death of coronary artery disease





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Patients with CD[a]	32	7	9	1	1	50

Frequency of affected valves

Aortic	24
Mitral	14
Pulmonary	3
Tricuspidal	6

Valvular defects (n=33):

1	21
2	10
3	2

16/33 of the valvular defects were mild

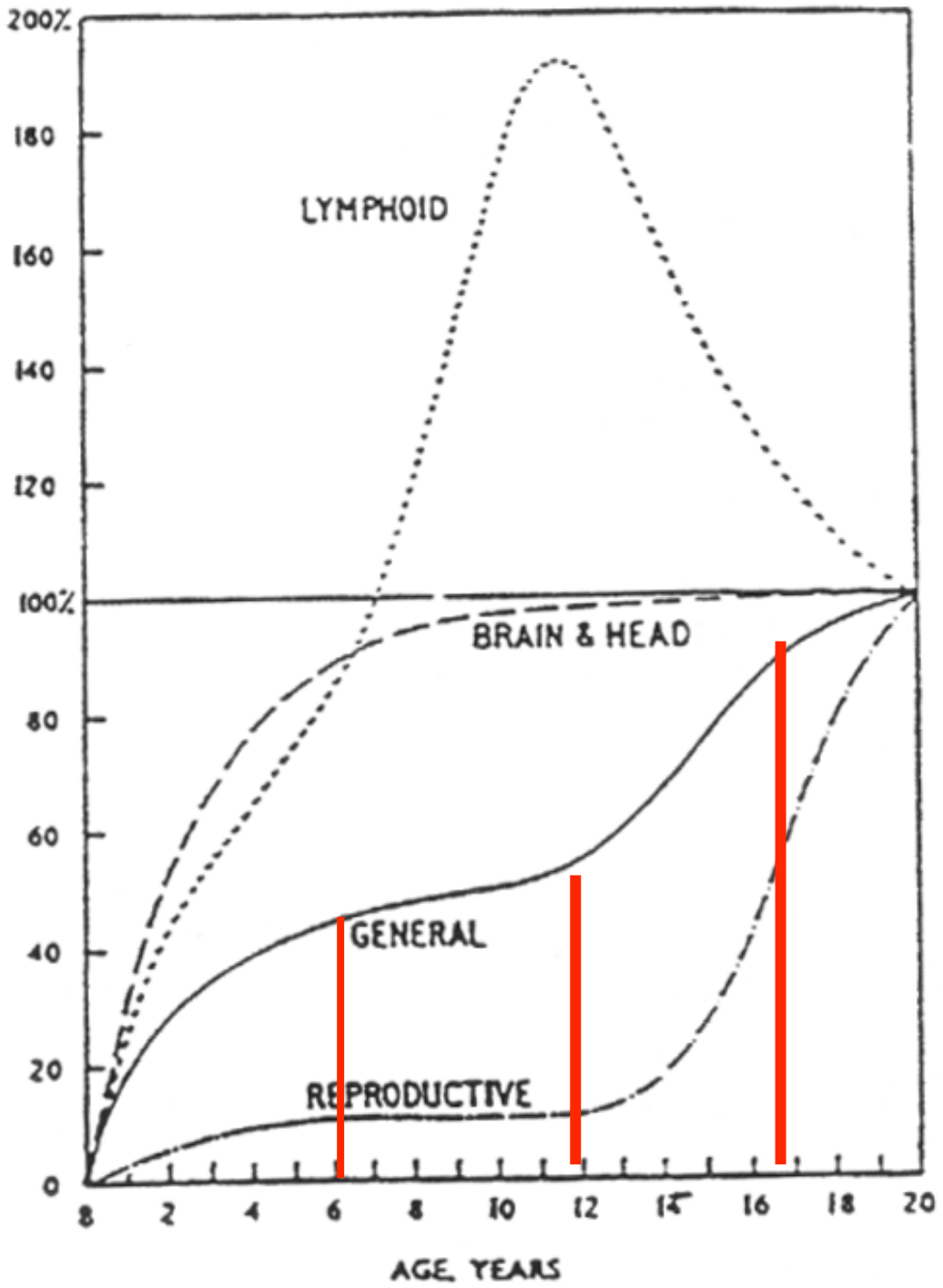
17/ 33 of the valvular defects were moderate or severe

Pediatr Blood Cancer 2010;55:1145–1152

Factors Increasing the Risk of Cardiac Sequelae

Patient factors

- **CT:** anthracycline
- **RT-field** (whole mediastinum)
- **Age** < 18 years
- **follow up time**: >10 years
- Baseline cardiac disease
- left ventricular dysfunction
- associated hypertension
- **Smoking**
- **engaging in extreme/competitive athletics**



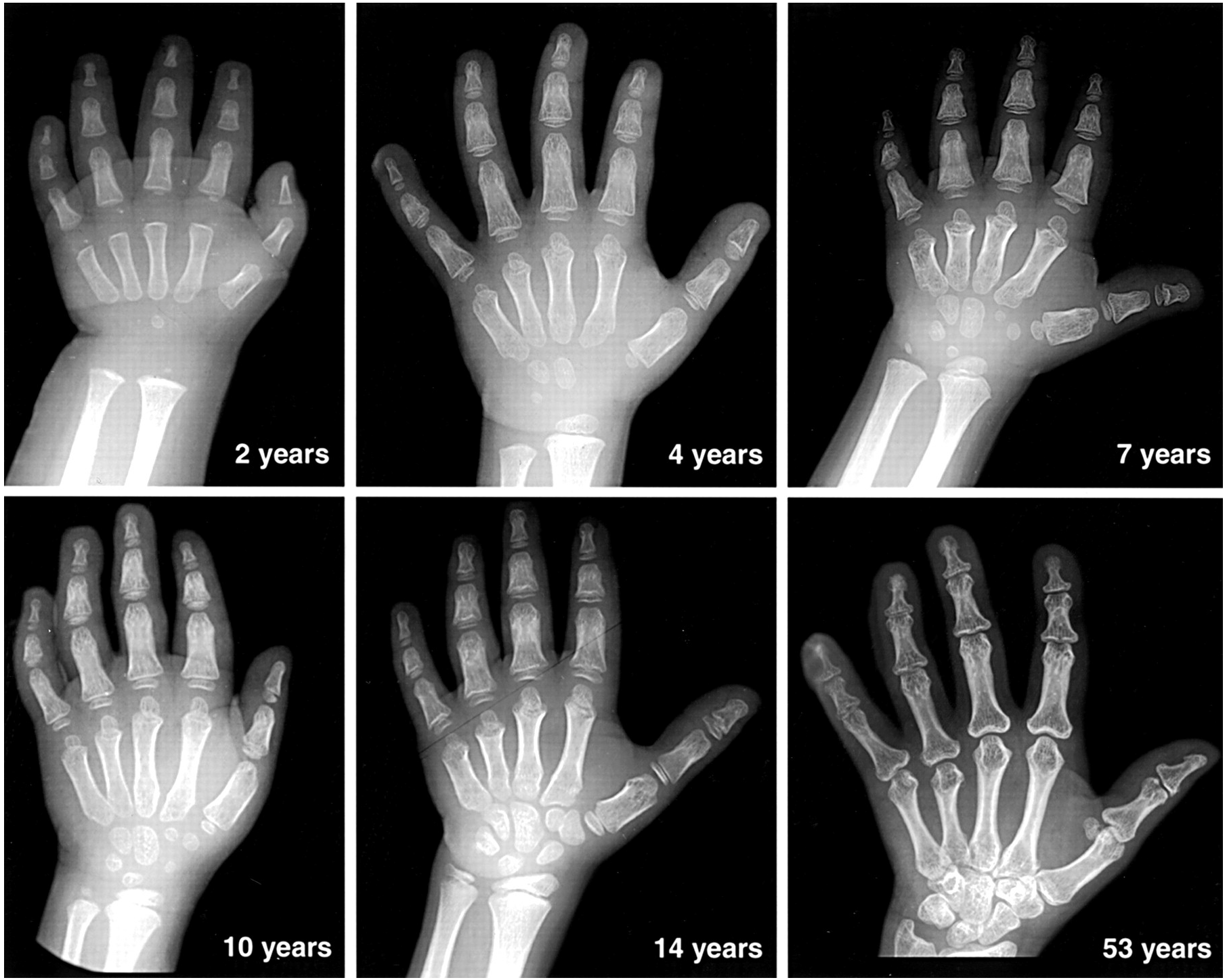
Development Curves

Stage of development of different tissues according to age
0-20 Years

Important time intervals

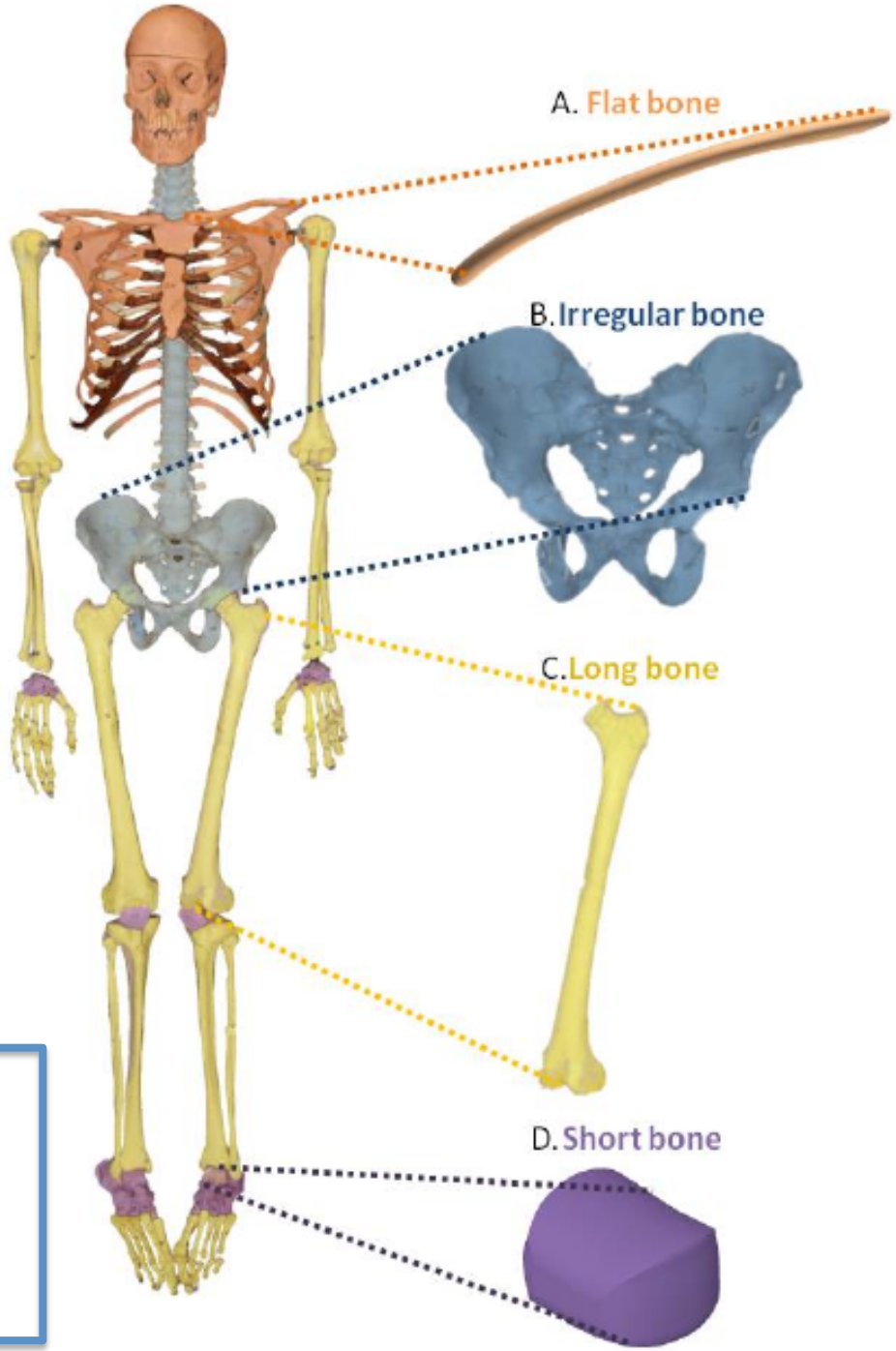
- 0-6 years
- Prepubertal/pubertal growing phase (pubertal status)

modifiziert nach Rubin 1982


2 years
4 years
7 years
10 years
14 years
53 years

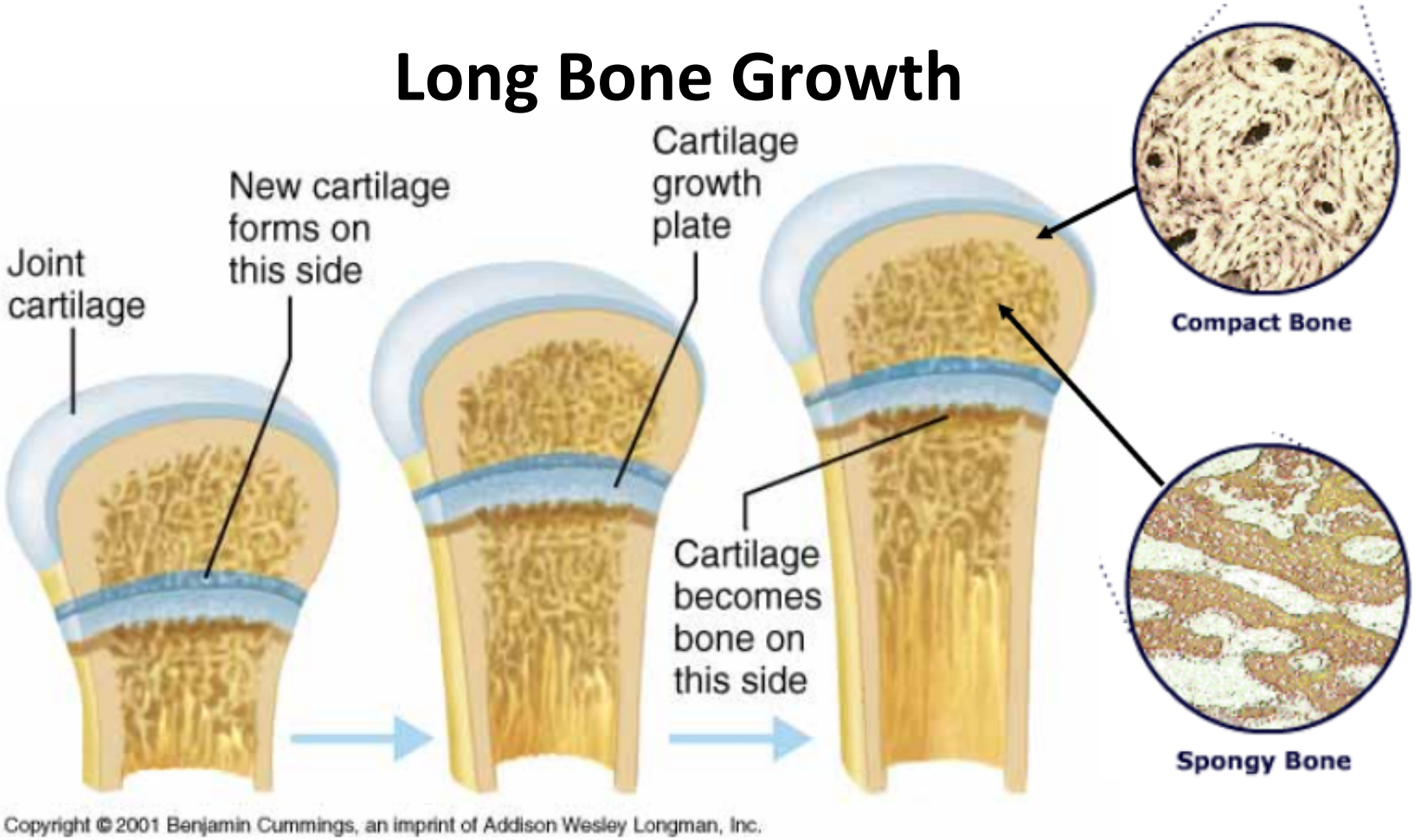
Bone Types

- Long bones
- Short bones
- Flat bones
- Irregular bones



Radiation induced
Bone Growth Inhibition
occurs in different parts of the bones

Long Bone Growth



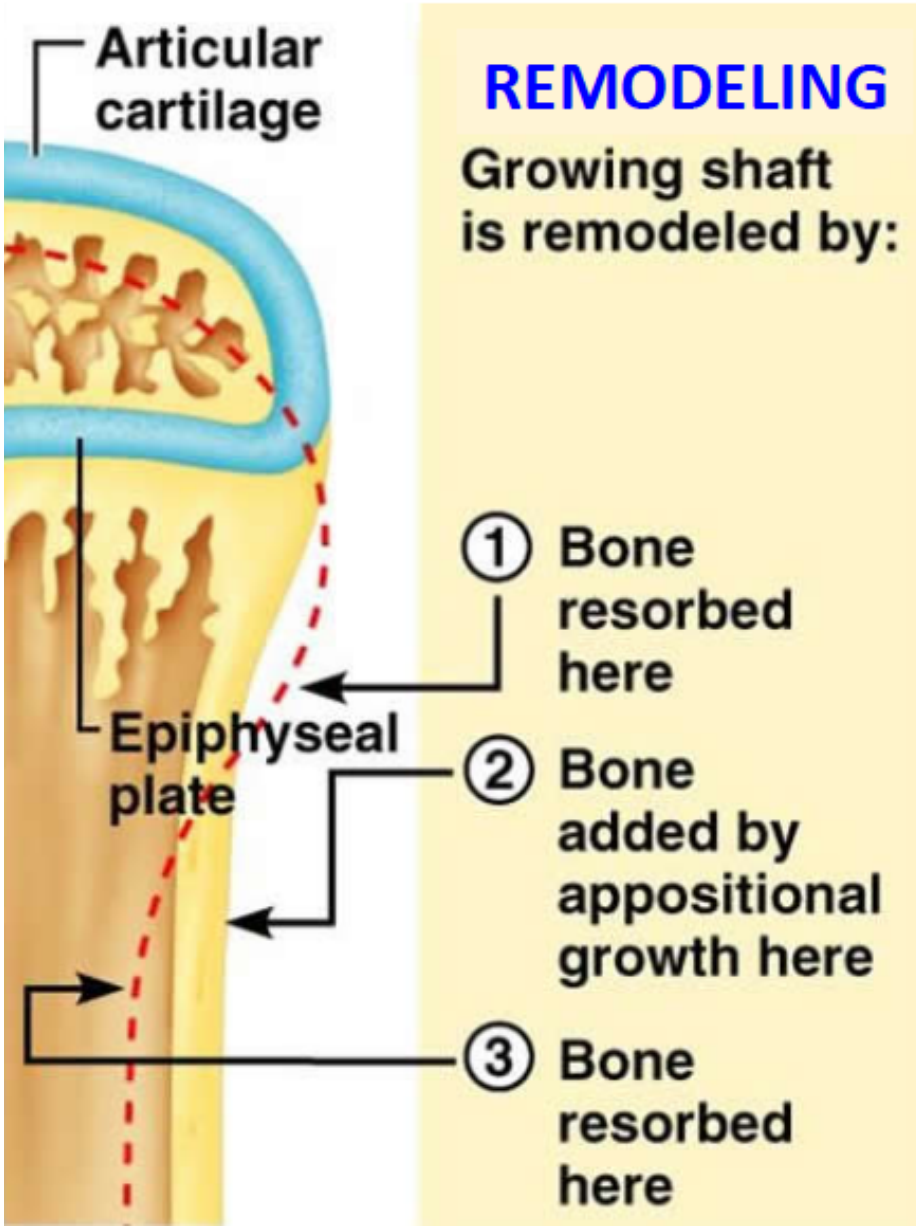
Lengthening of the bone occurs at epiphyseal-diaphyseal junction

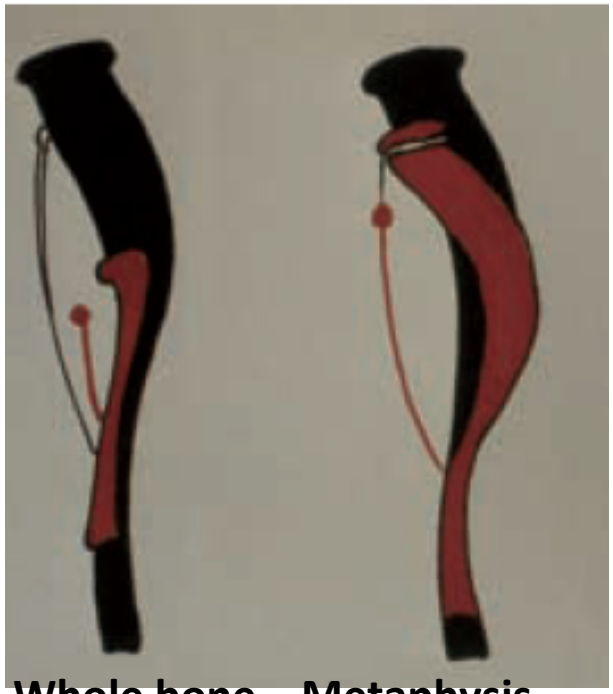
- cartilage cells proliferate by mitosis in this area

Diaphyseal cartilage cells hypertrophy

- matrix becomes calcified & broken into spicules by vascular tissue from marrow cavity
- Bone deposited on spicules

Long Bone Growth





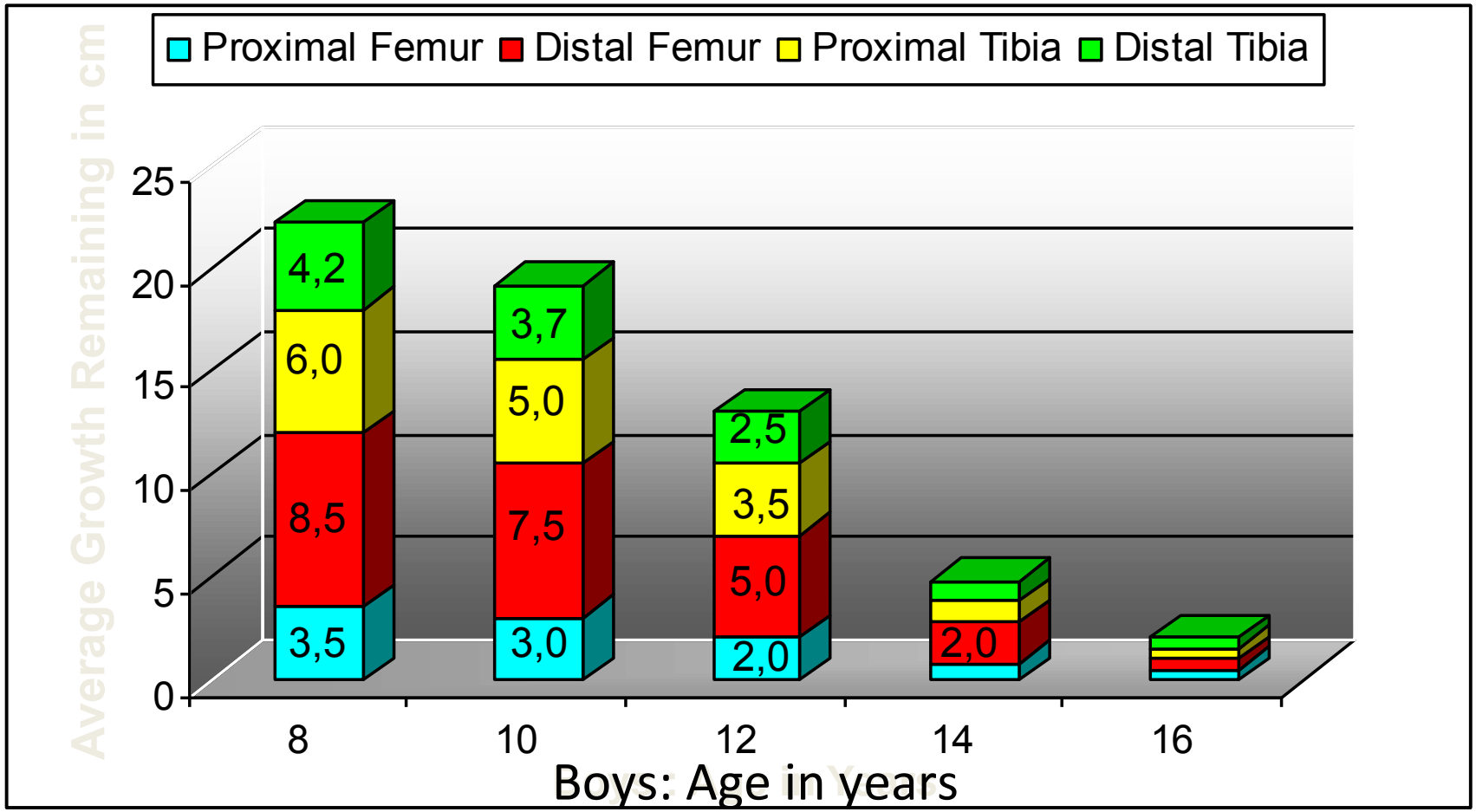
Whole bone Metaphysis

Diaphysis Epiphysis

Rubin 1959

Average Growth Remaining in cm ; lower extremity

Boys



Survivors of childhood cancer ; Assesssment and Management
Mosby 1998

The Effects of Radiation Therapy on Bone Growth[1]

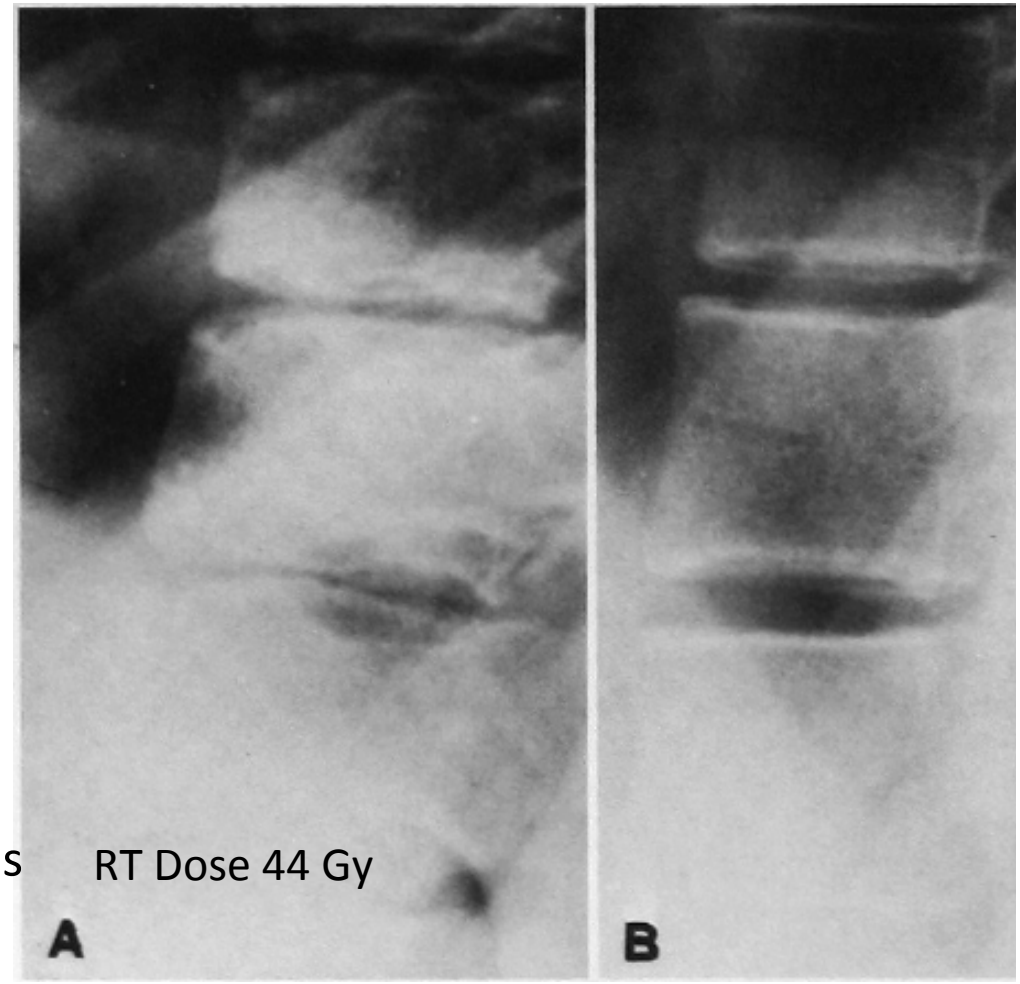
John C. Probert, M.A.B.M., F.F.R., D.M.R.T.,[2] and
Bruce R. Parker, M.D.

1975

N= 29 Children > 35 Gy
N= 15 Children < 25 Gy
15,000 normal Children

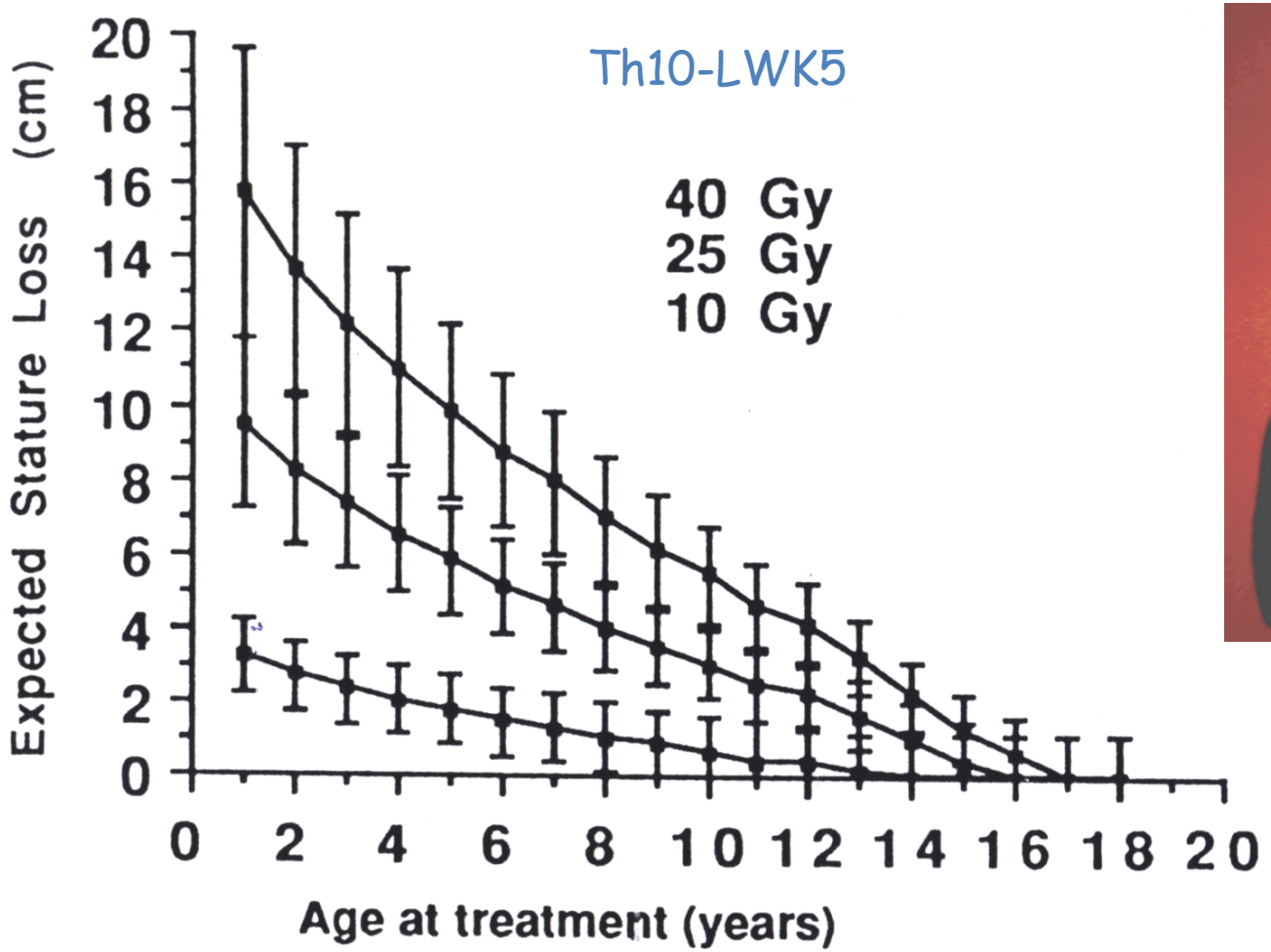
- Retardation in children < 6 years during puberty

- Vertebral bodies decreased in height
- Disk spaces are narrowed
- Irregularities of the cortical end-plates
- Asymmetric ossification

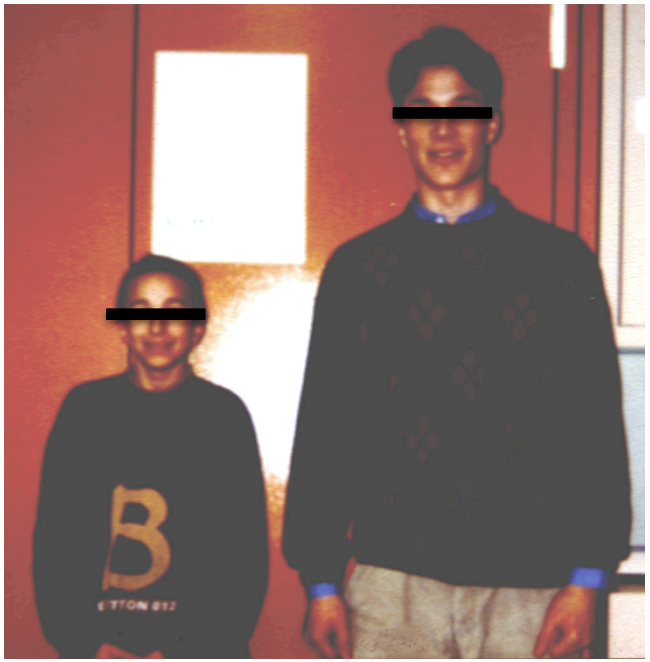


RT Dose 44 Gy

Stature Loss Following Skeletal Irradiation for Childhood Cancer



RT+hormonal dysfunction



Medulloblastoma
Age < 2 years
CSI 25 Gy / 1.8Gy ED
Local Boost 25,4 Gy

Silber et al. J Clin Oncol 8: 1990

Late bone and soft tissue sequelae of childhood radiotherapy

Dörr W, Kallfels S, Herrmann T

Diagnosis	Number of patients	Percentage of patients
Hodgkin + non-Hodgkin lymphoma	68	46.5
Nephroblastoma	31	21.2
Bone and soft tissue sarcoma	24	16.4
Neuroblastoma	12	8.2
Others	11	7.5

N= 146

Treatment time 1970-1997

Mean planning dose 35.8 Gy (10.0-71.8Gy); 1.7Gy(range 1.0-4.0Gy)

OAR doses ($EQD2_{3Gy}$)

Median Age 8,8 years (range 0.2-17 years)

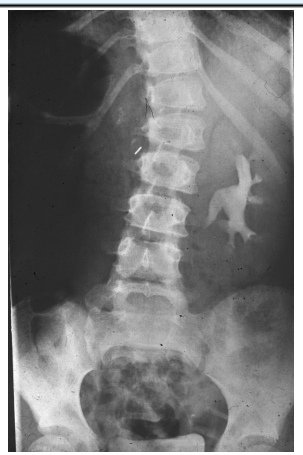
Median time since treatment 9.2 years (range 0.9-17.7 years)

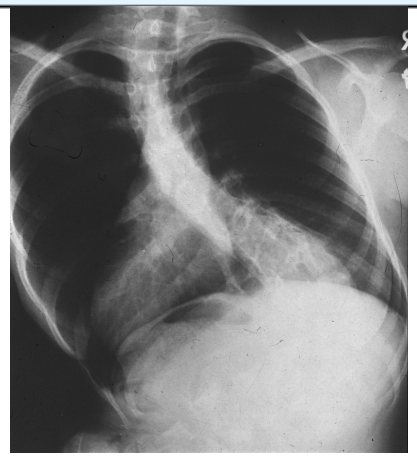
Strahlenther Onkol 2013 · 189:529–534

Late bone and soft tissue sequelae of childhood radiotherapy

Dörr W, Kallfels S, Herrmann T

Sequela	Grade 1: minor		Grade 2: substantial	
	Number of patients	Percentage of patients	Number of patients	Percentage of patients
Scoliosis	27	18.5	15	10.3
Kyphosis	10	6.8	2	1.4
Osseous hypoplasia	20	13.7	9	6.2
Asymmetry	30	20.5	10	6.8
Soft tissue defects	11	7.5	8	5.5
Any	44	30.1	31	21.2





Strahlenther Onkol 2013 · 189:529–534

Late bone and soft tissue sequelae of childhood radiotherapy

Dörr W, Kallfels S, Herrmann T

N= 146

Treatment time 1970-1997

Median Age 8,8 years

(range 0.9-17.7 years)

Median time since treatment

9.2 years

Pathological findings 75/146

- Minor 44 (59%)
- Substancial 31 (41%)

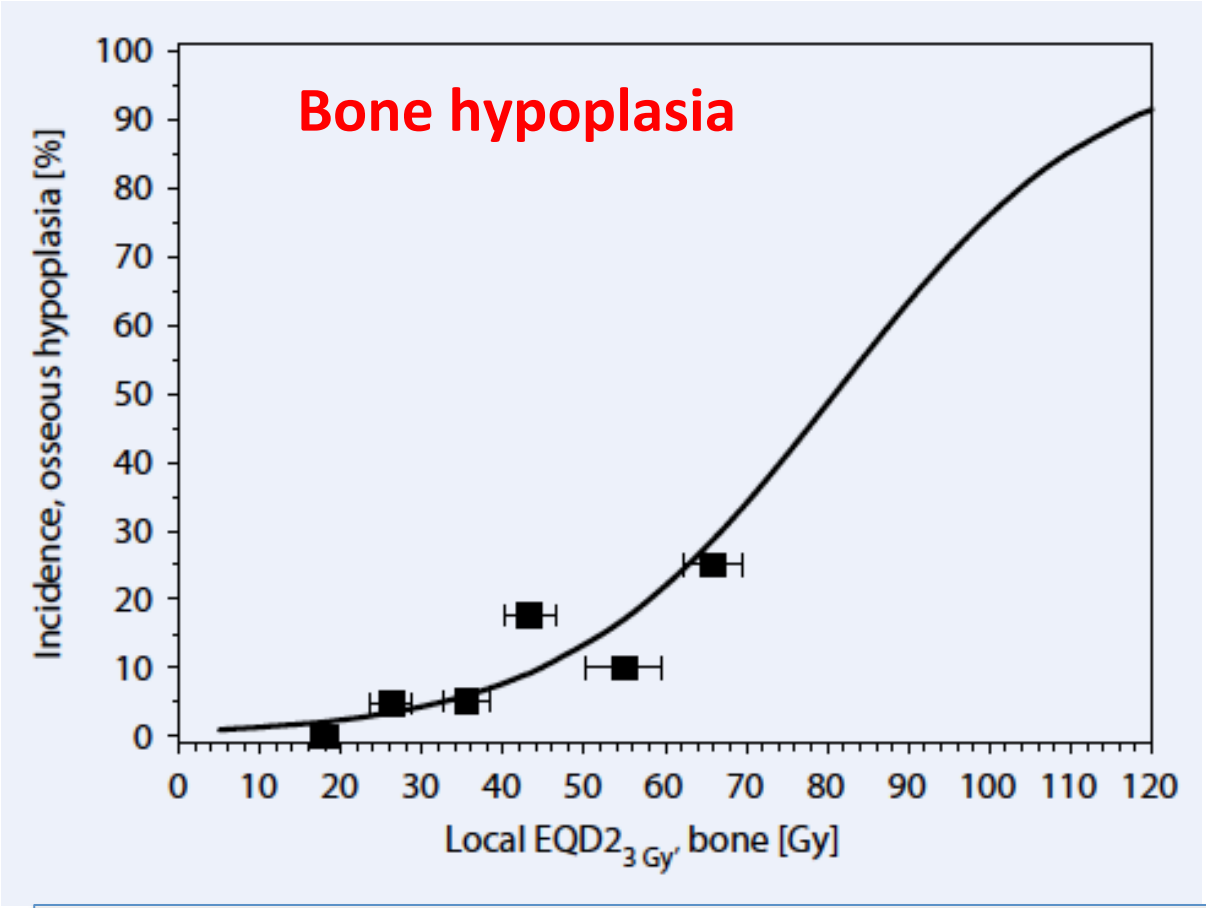
Strahlenther Onkol 2013 · 189:529–534

Substanial growth defects in bone and soft tissue are frequent in

- **children < 6 years , dose < 35 Gy**
- **children > 6 years , dose > 35 Gy**

Late bone and soft tissue sequelae of childhood radiotherapy

Dörr W, Kallfels S, Herrmann T

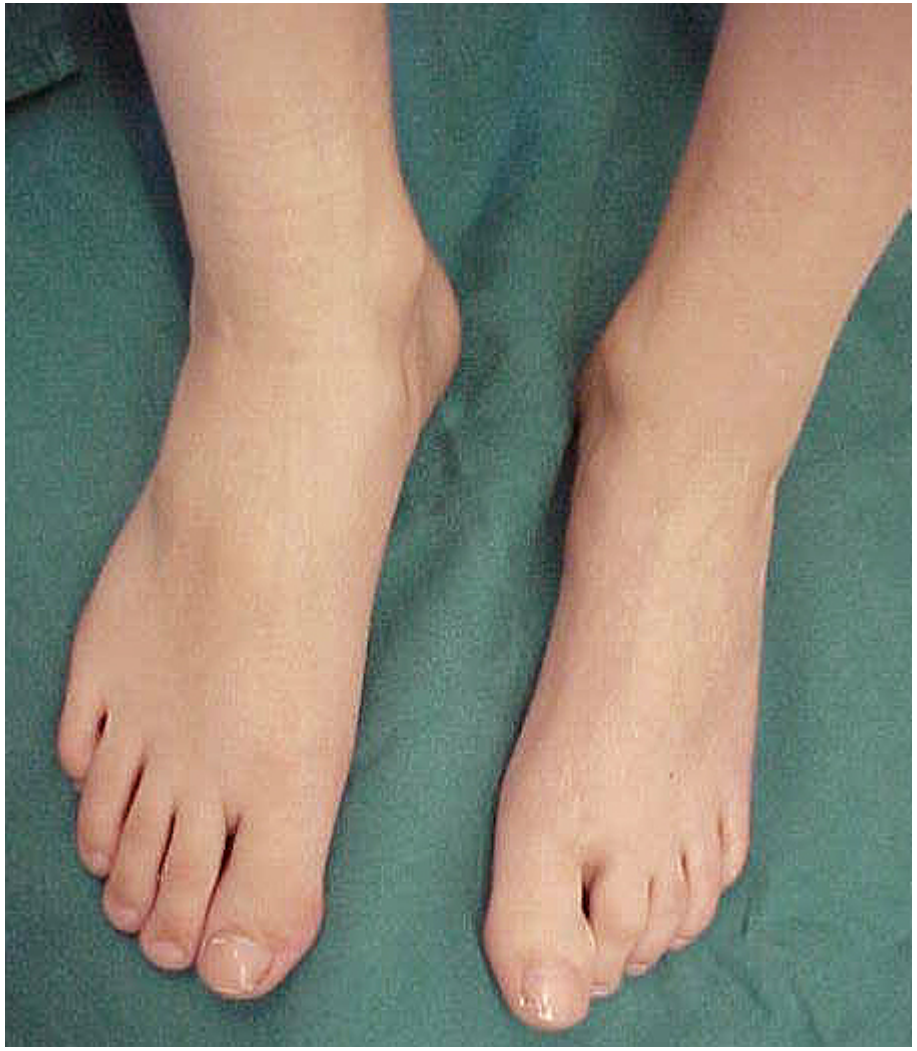


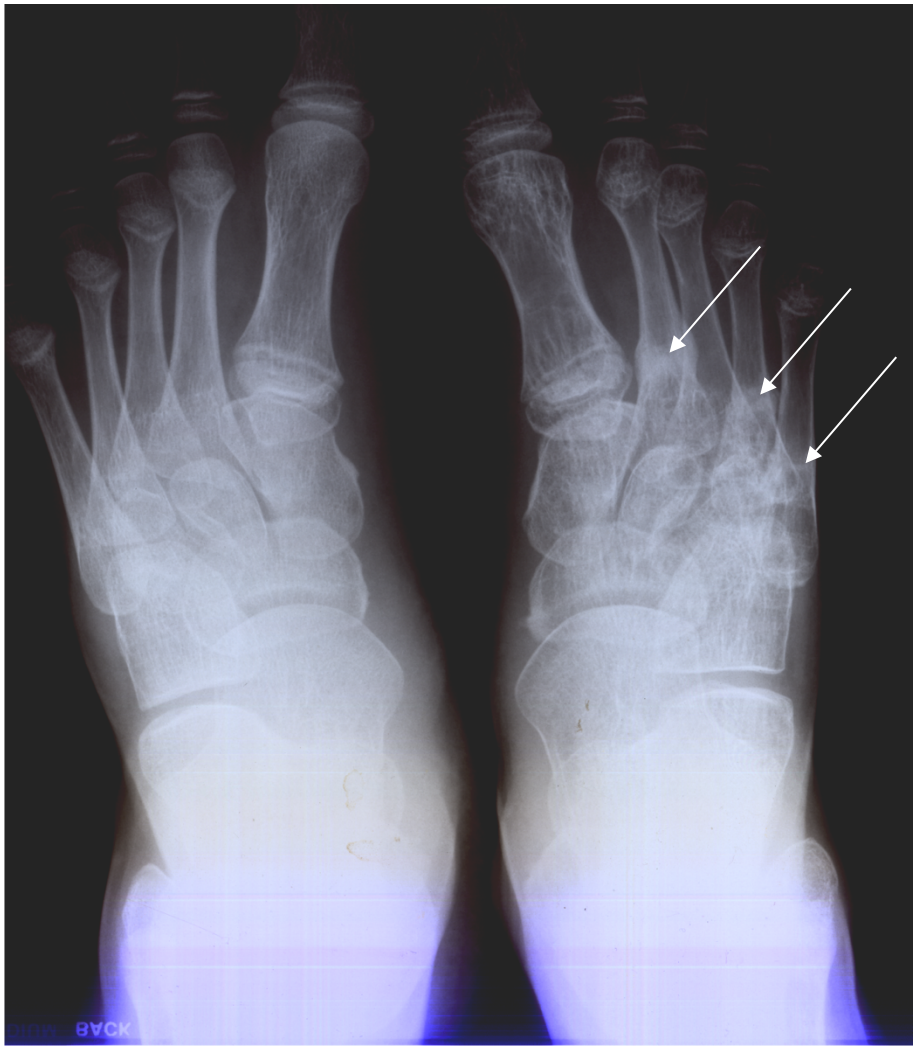
Important factors:

Treatment dose
Treatment age

50%- incidence dose for bone hypoplasia is in the range of **20Gy in very young children**.

Strahlenther Onkol 2013 · 189:529–534





Ewing Sarcoma left foot RT dose 45 Gy

2004: 4 J. post RT

Stress fracture

Rarefication of the bony structure

LATE EFFECTS OF RADIOTHERAPY FOR PEDIATRIC EXTREMITY SARCOMAS

ARNOLD C. PAULINO, M.D.*†

PATIENT`s data:

10 Boys; 5 Girls

Median age 13 years (range 3.5-20 years)

Median follow up 20 years (range 6-36 years)

8 Ewing Sarcoma

4 Synovial Sarcoma

2 alveolar Sarcoma

1 Fibrosarcoma

Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 1, pp. 265–274, 2004

LATE EFFECTS OF RADIOTHERAPY FOR PEDIATRIC EXTREMITY SARCOMAS

ARNOLD C. PAULINO, M.D.*†

10 lower extremity
5 upper extremity

Dose:
9 Pts. Median dose 55,8Gy (range 45-66 Gy)
6 Pts. Median dose 63 Gy (range 41,4-66,4Gy)

Scoring according LENT SOMA scale for growing bone, soft tissue, and muscle

	Grade 1	Grade 2	Grade 3	Grade 4
Growing bone	Mild curvature or length discrepancy <2 cm	Moderate curvature or discrepancy 2–5 cm	Severe curvature or discrepancy >5 cm	Epiphysiodesis, severe functional deformity
Edema	Present/asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction
Atrophy	≤10%	>10–20%	>20–50%	>50%
Mobility and extremity function	Present/asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction

Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 1, pp. 265–274, 2004

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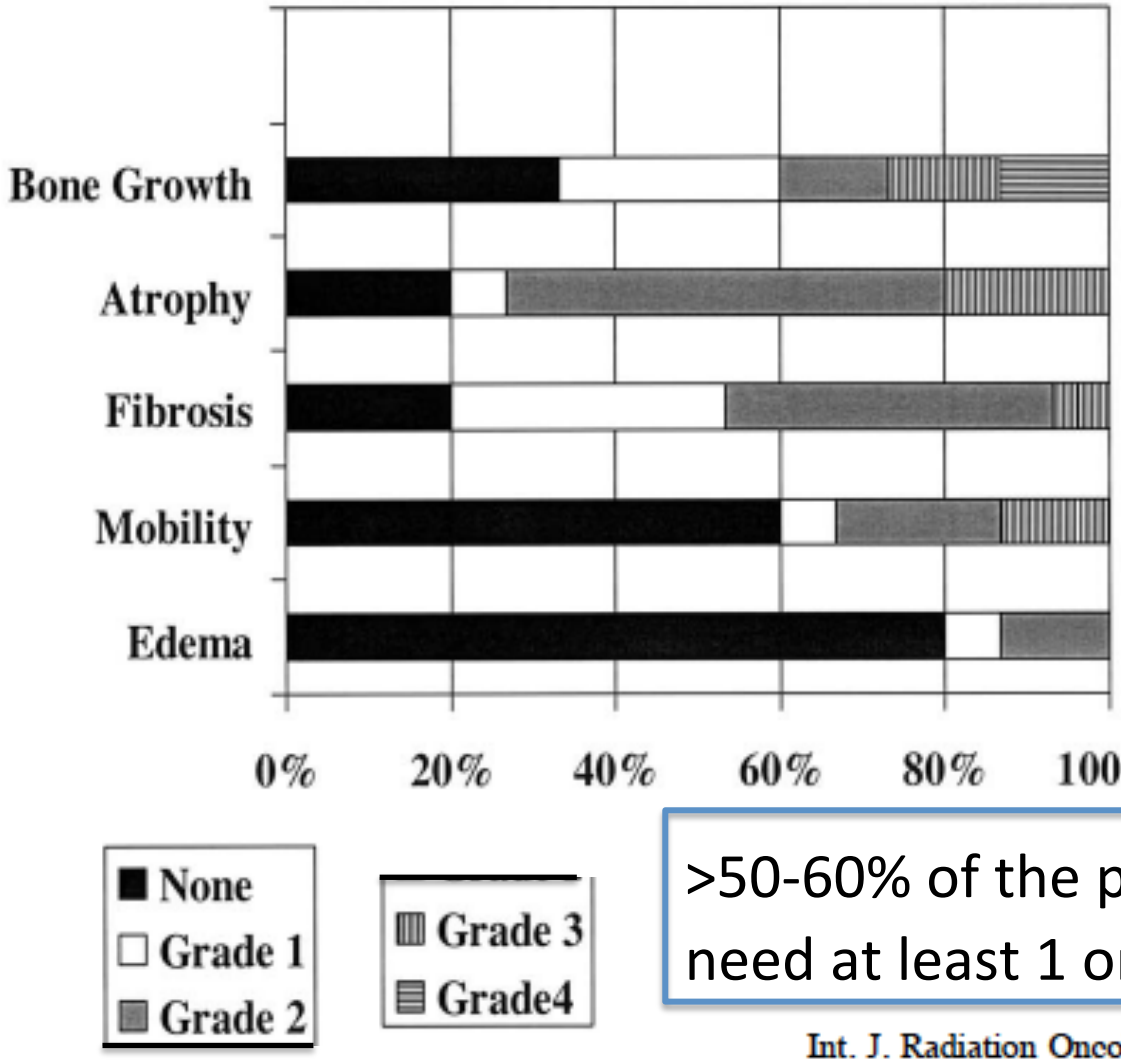


- 6 pts grade 1-2

bone growth abnormalities

- Age < 15 years
- Median limb discrepancy

2.5 cm (range1-7cm)

- Age ≤ 10 years 4.2cm

Age > 10 years 1.5 cm

>50-60% of the pts with lower extremity RT need at least 1 orthopedic op after treatment

Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 1, pp. 265–274, 2004

LATE EFFECTS OF RADIOTHERAPY FOR PEDIATRIC EXTREMITY SARCOMAS

ARNOLD C. PAULINO, M.D.*†

Timeline of late effects

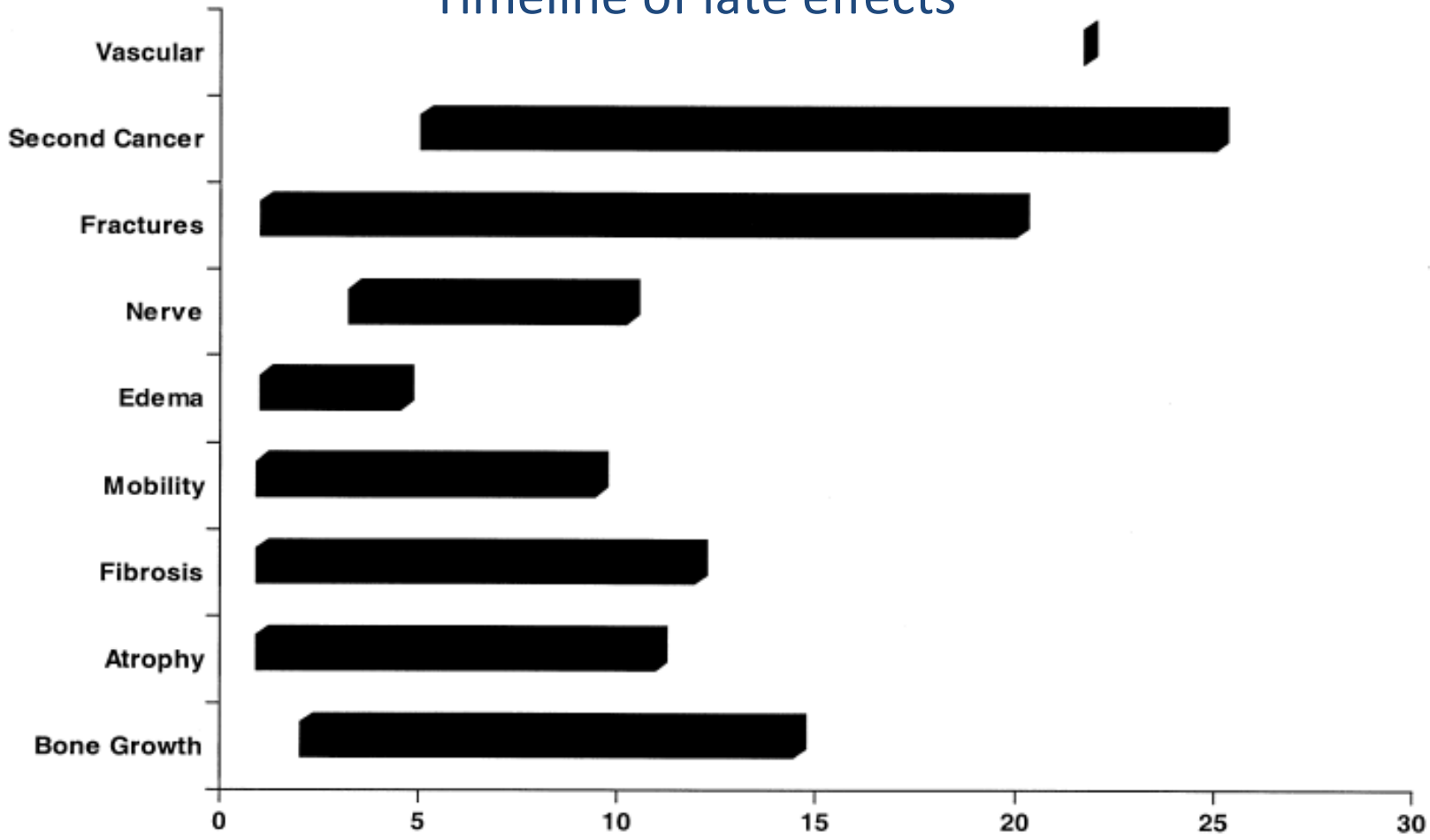
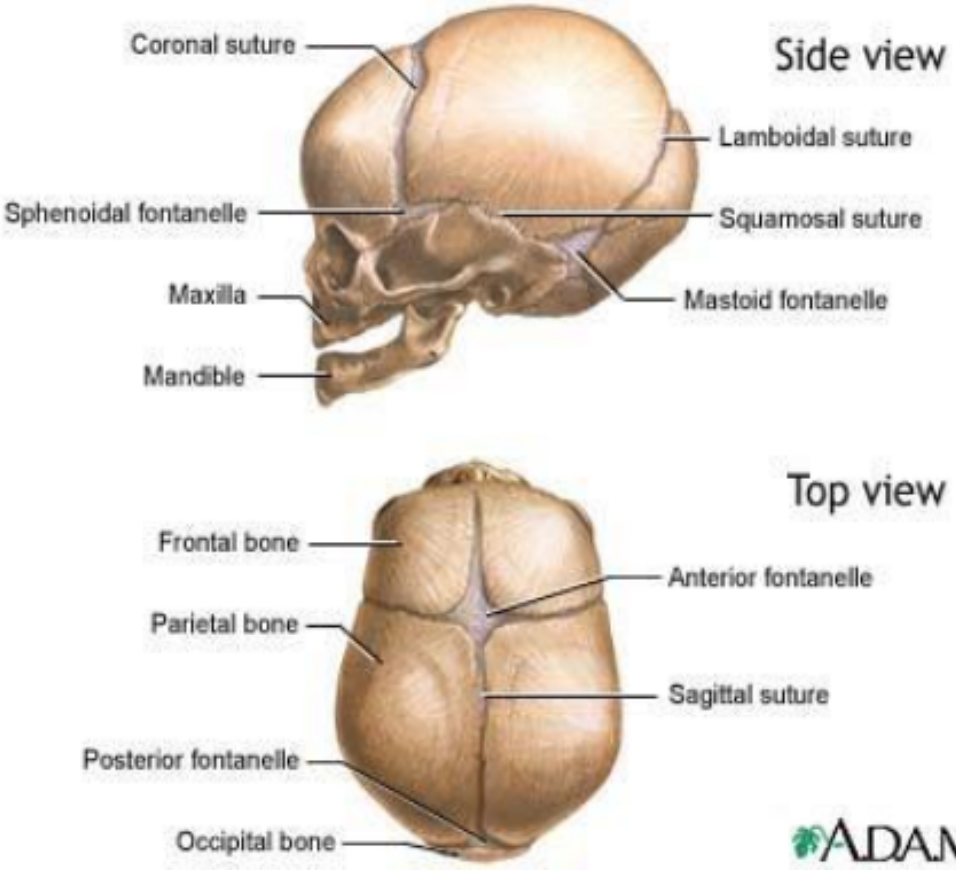


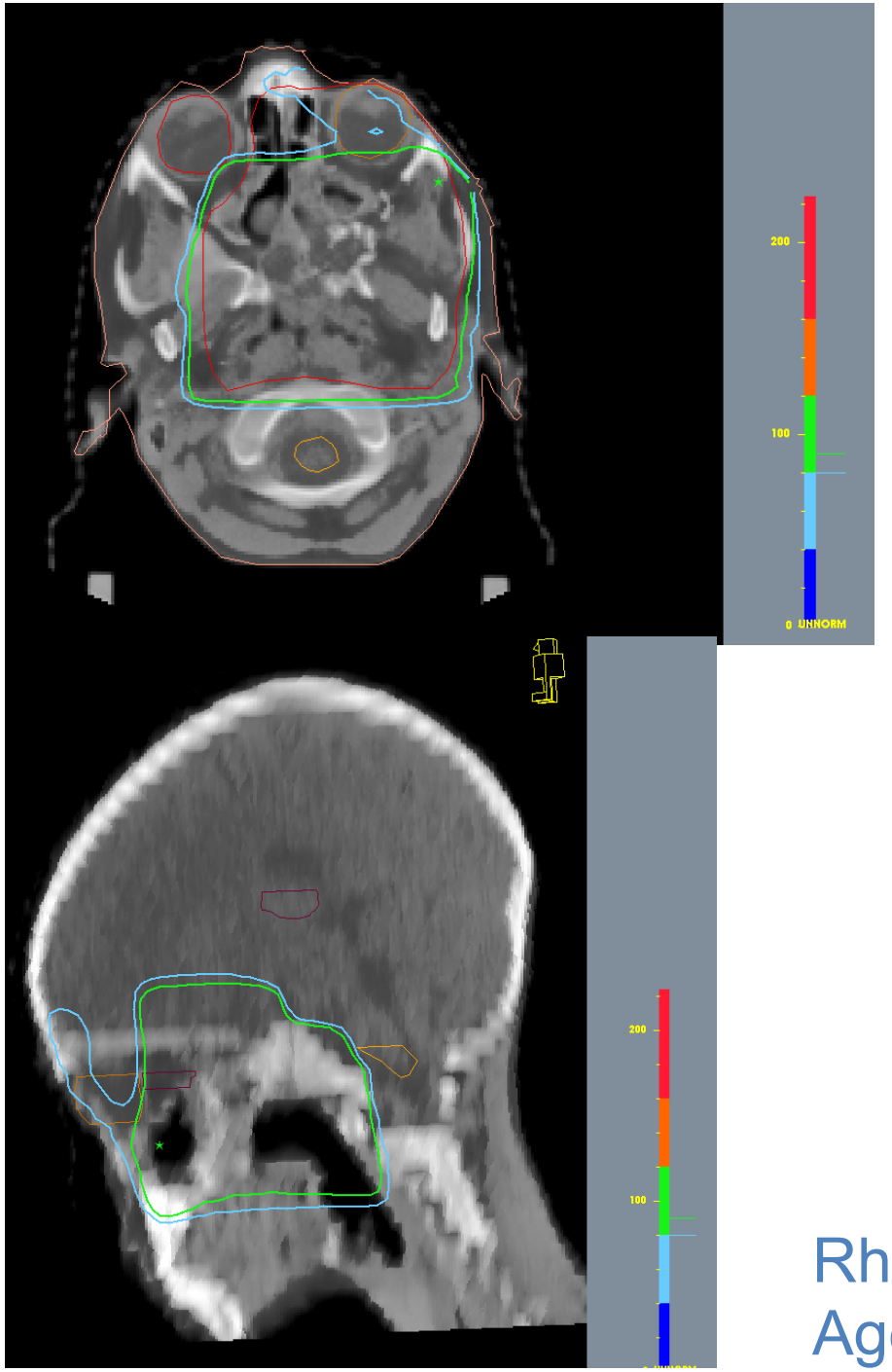
Fig. 2. Timeline of late effects after radiotherapy for pediatric extremity sarcomas.

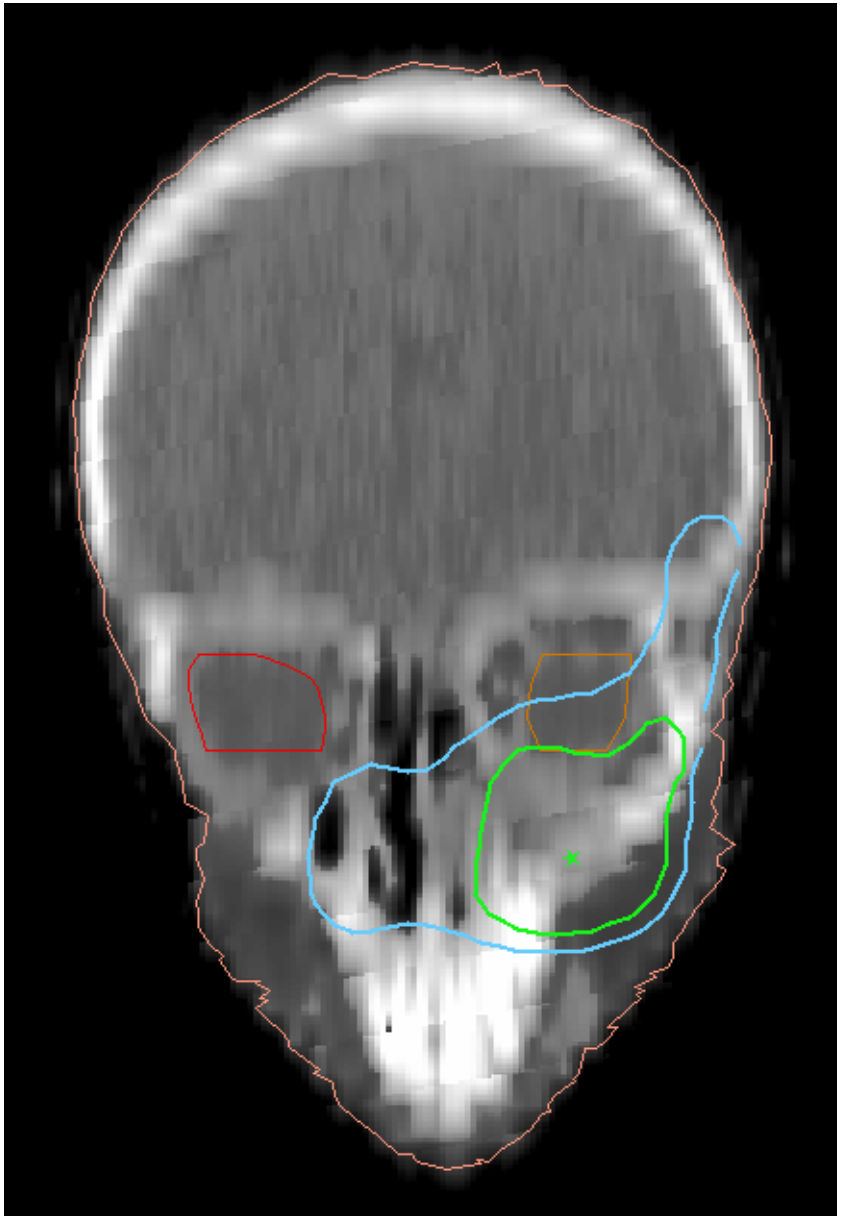
Int. J. Radiation Oncology Biol. Phys., Vol. 60, No. 1, pp. 265–274, 2004

Scull and Face Growth



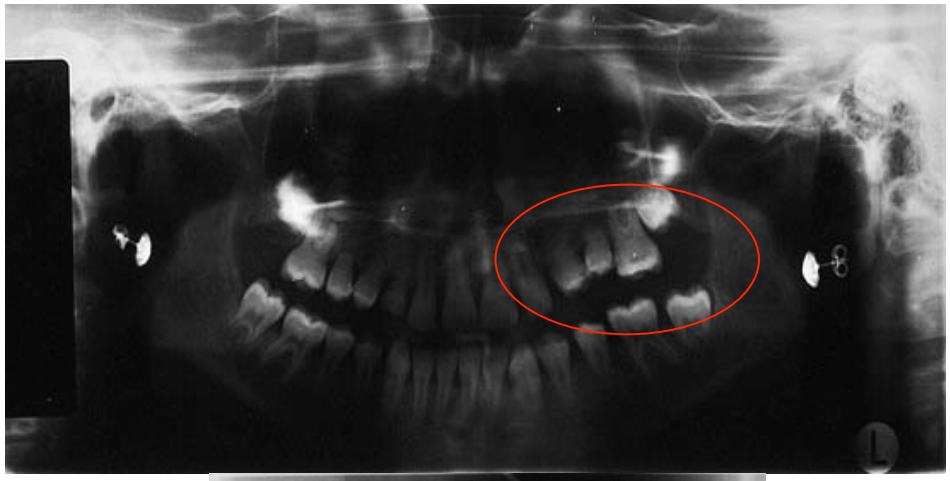
- Cranium:
  - Sutures allow growth during infancy & childhood
  - Fastest growth in first two years
  - Increases until 15-16 yo
- Face is small due to small jaw and absent sinuses
  - Face and jaw grow due to teeth eruptions

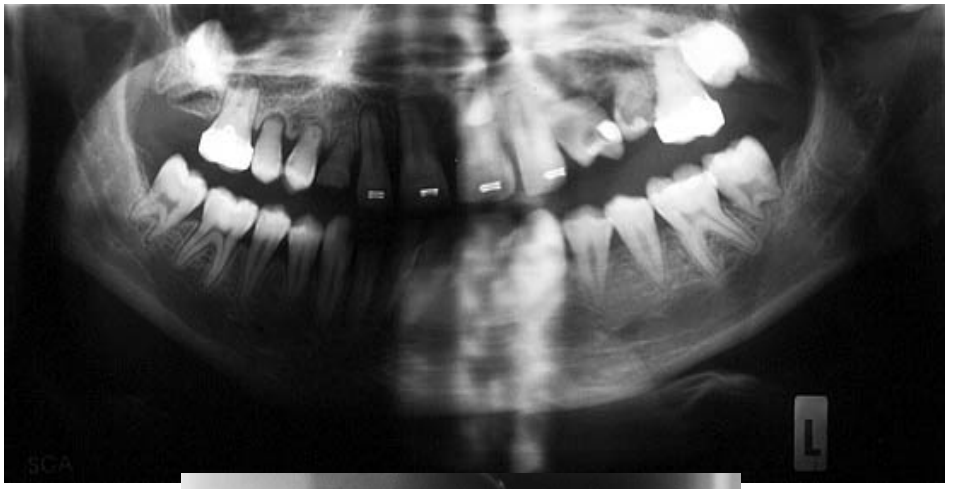


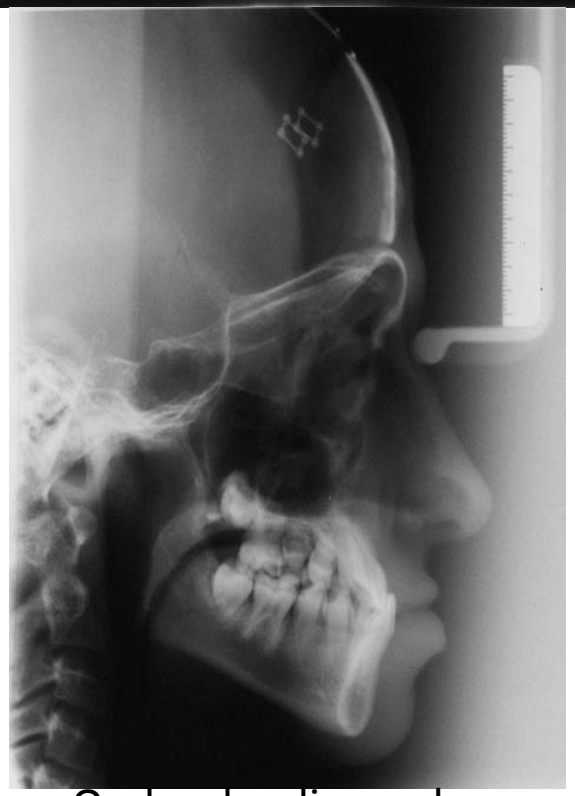


Rhabdomyosarcoma 45 Gy
Age at RT treatment 6years (1990)

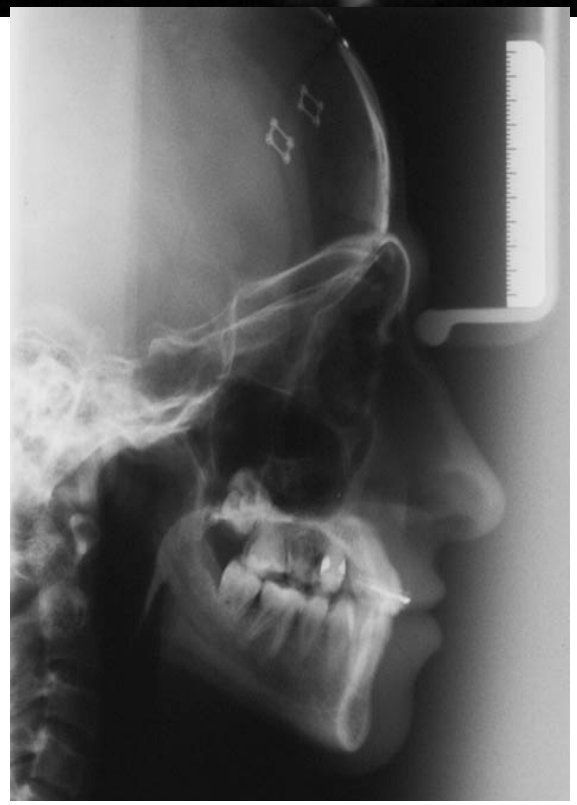
Dentation Status

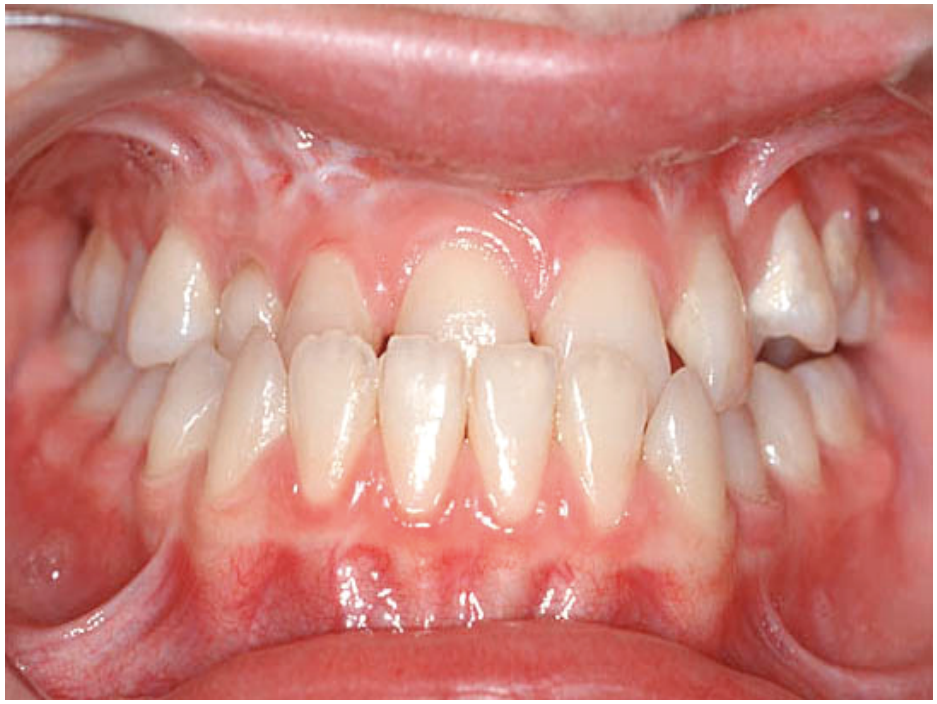


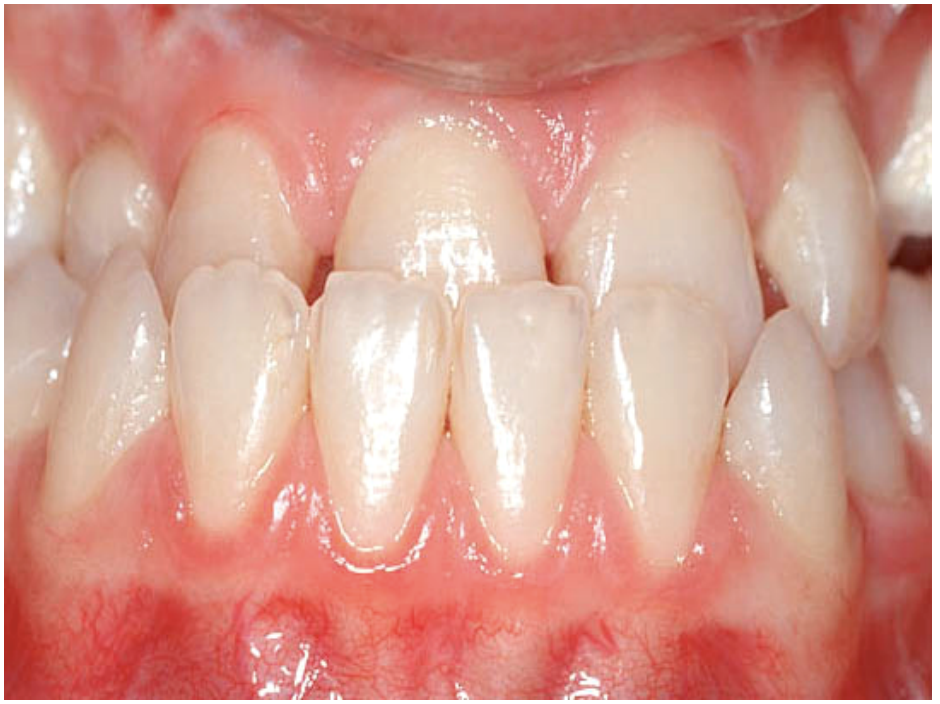


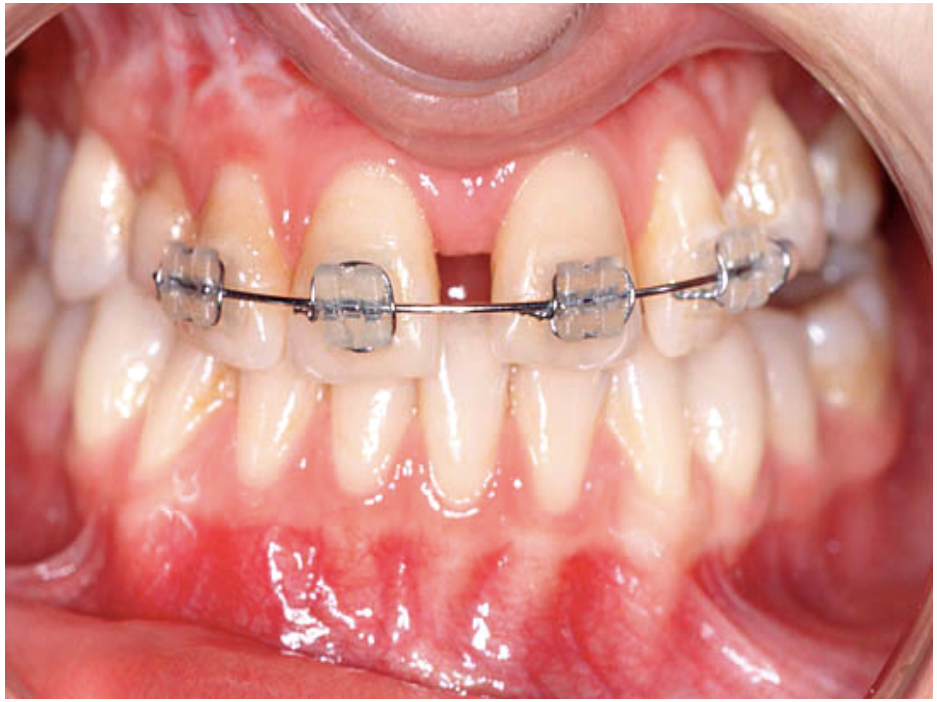


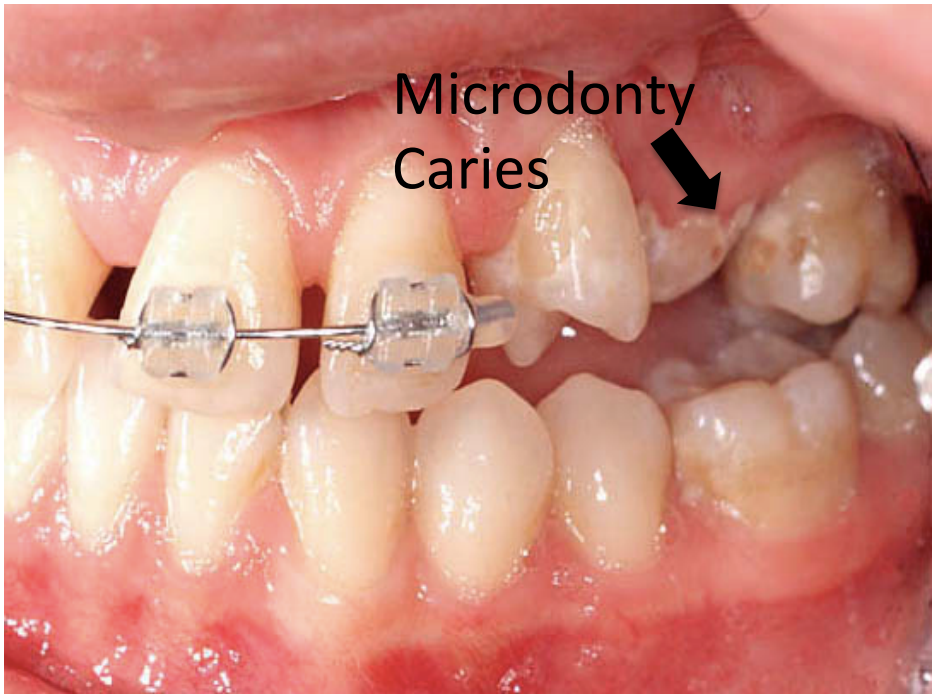
Occlusal radiograph







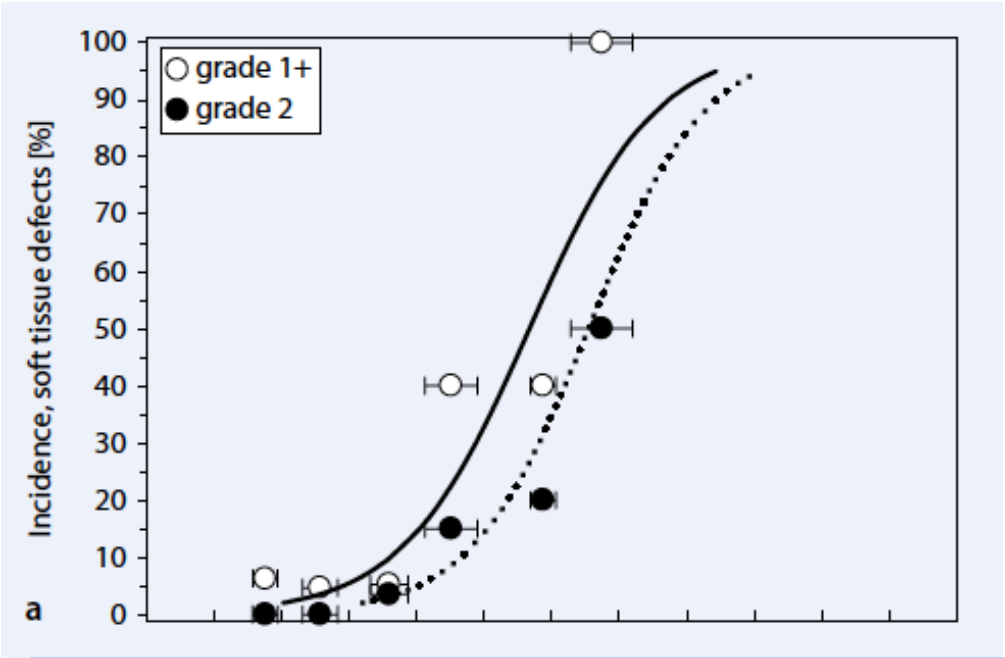


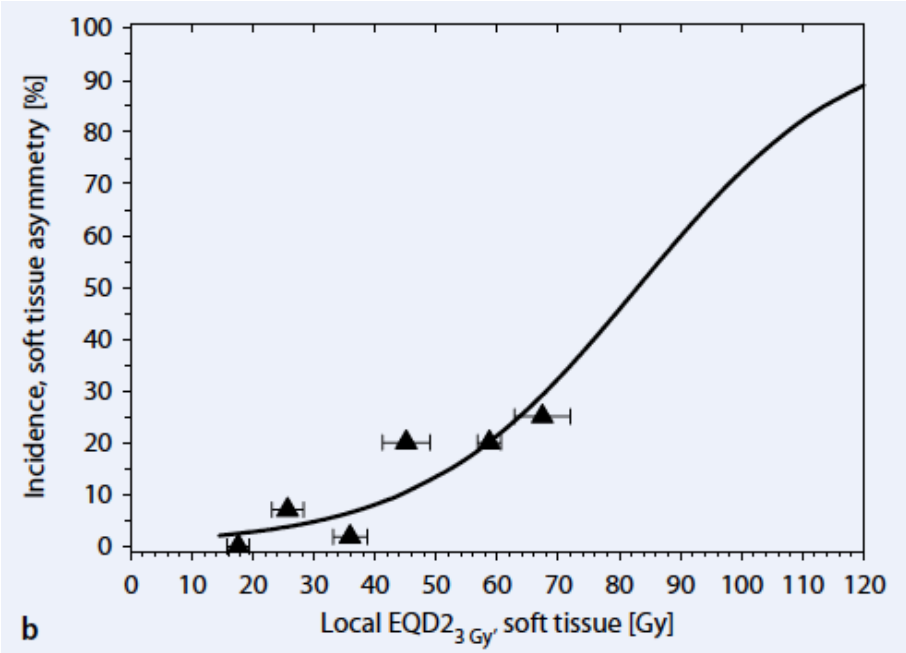

Microdonty
Caries

Late bone and soft tissue sequelae of childhood radiotherapy

Dörr W, Kallfels S, Herrmann T

Dose effects for soft tissue



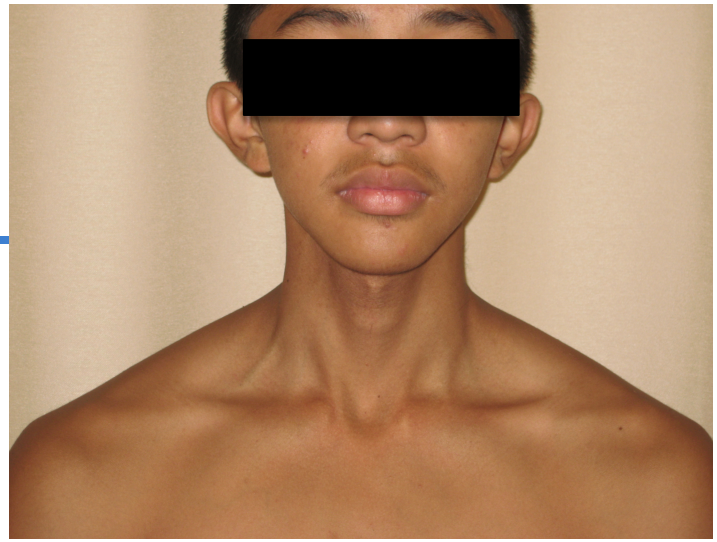


Soft tissue defects may be expected in doses >35- 40 Gy

5% after a dose <30Gy

Strahlenther Onkol 2013 · 189:529–534

Soft tissue and Muscle Hypoplasia

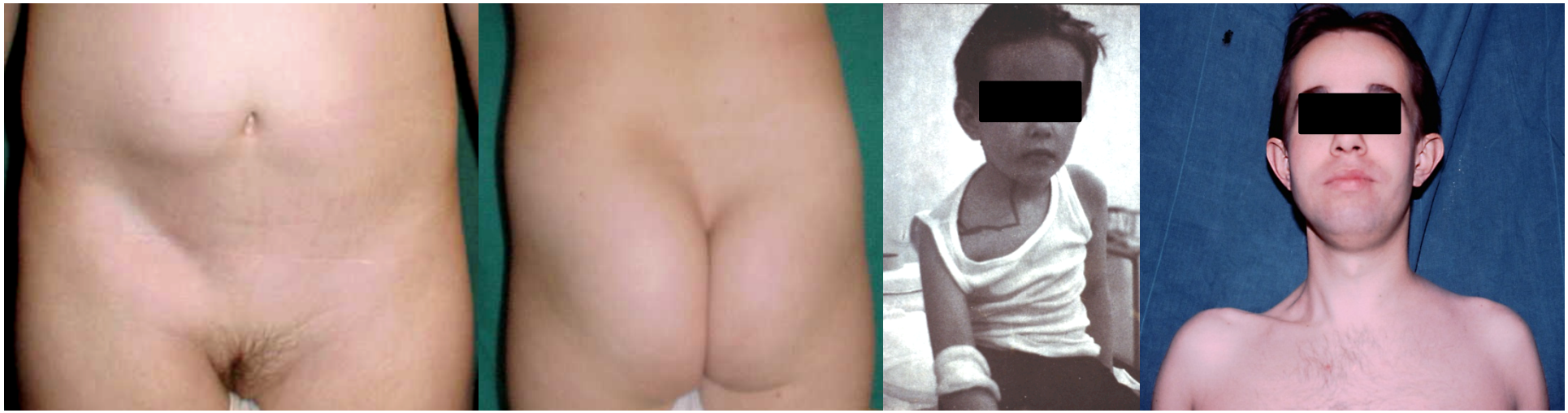


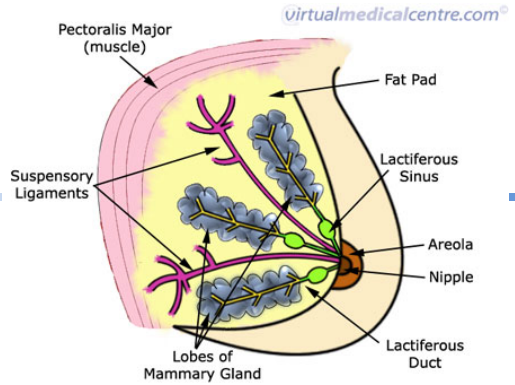
Radiotherapy

>20 Gy -35Gy (growing child)

<20 Gy (very little children)

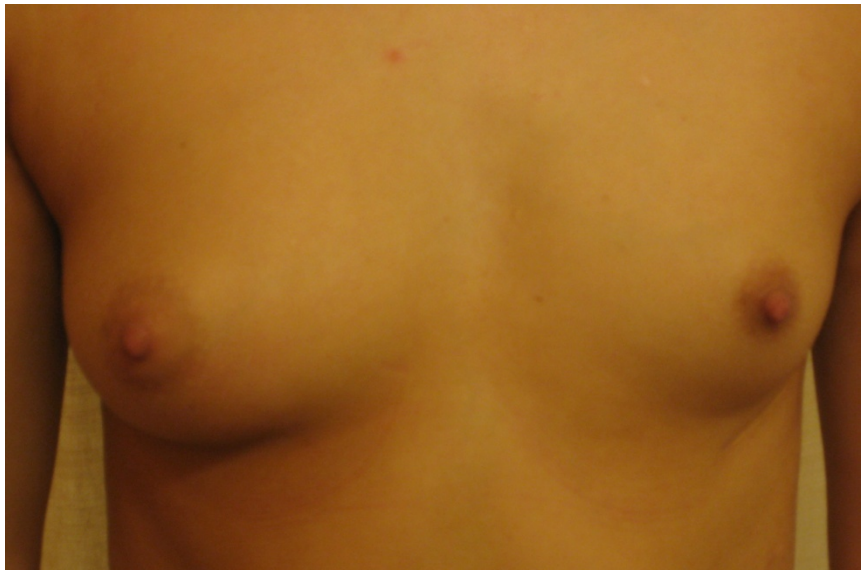
Muscle atrophy
Soft tissue atrophy

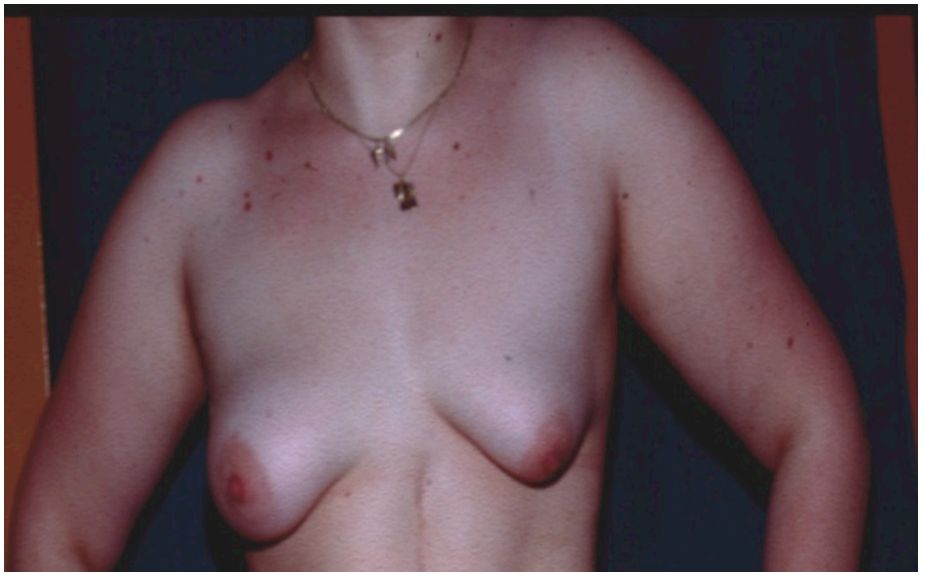




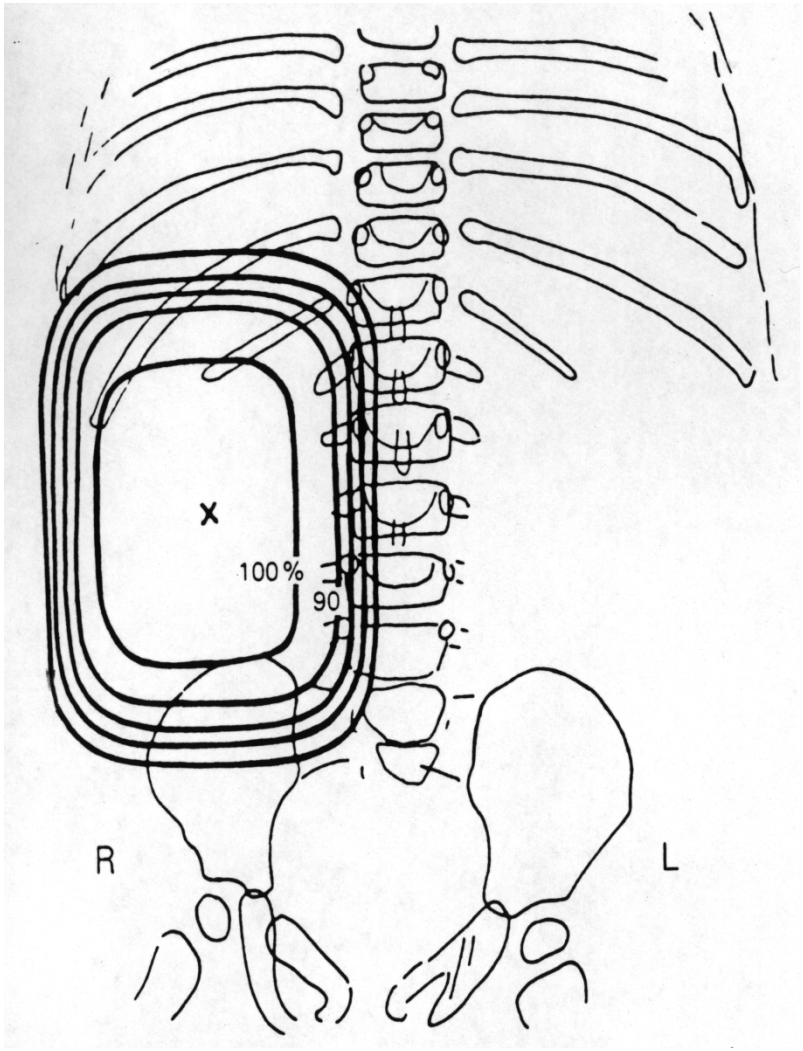
Dose and side effects in breast in very young children

- Doses < 10 Gy — reduction of the breast development (Hypoplasia)
- Doses > 20 Gy — ablate development altogether
- Low doses — failure to lactate



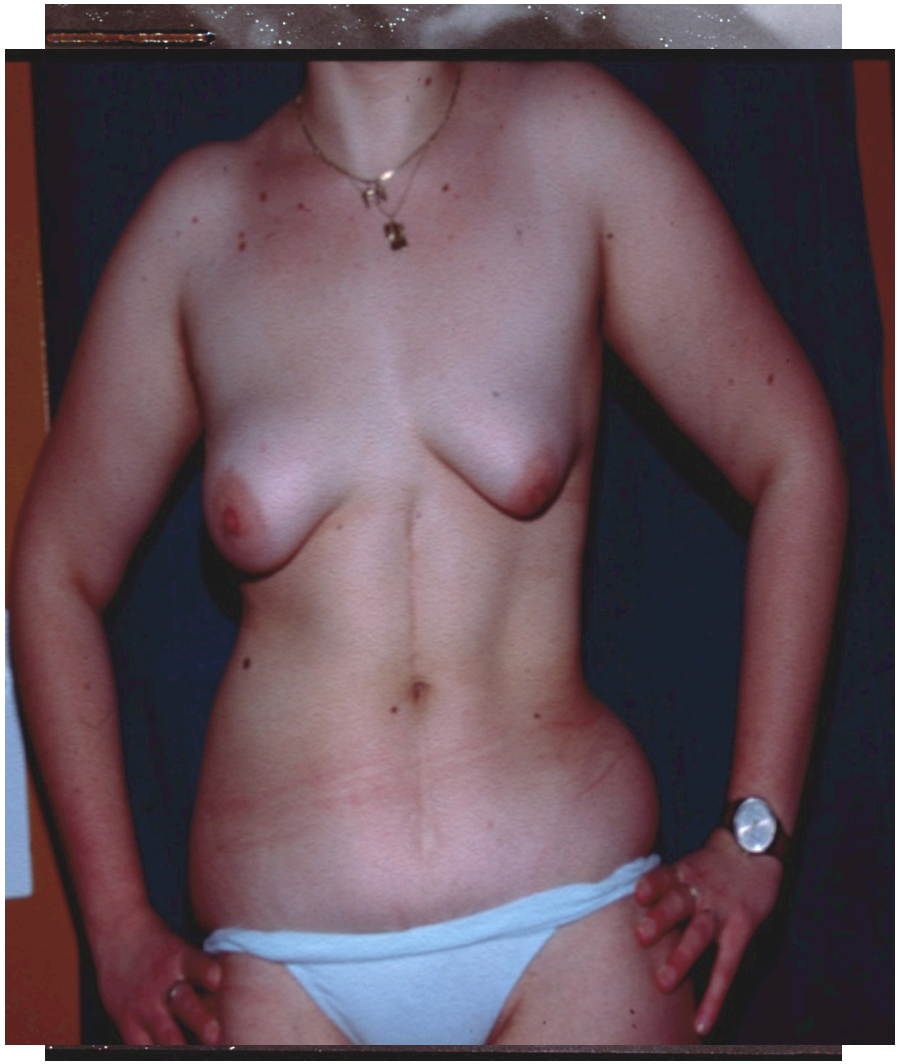


Soft tissue disturbance after RT



Isodose distribution Co-60 - Therapy

Willich et al.1990 Strahlenther. Onkol 166



St.p. Nephrectomy 2 / 82
CT: Wilmstumorstudy 1981
RT : 22,5 Gy 3 - 4 / 82

Late Cardiotoxicity in Aging Adult Survivors of Childhood Cancer

Gregory T. Armstrong, MD, MSCE[a] and Jordan D. Ross, BS[b]

[a]St. Jude Children's Research Hospital

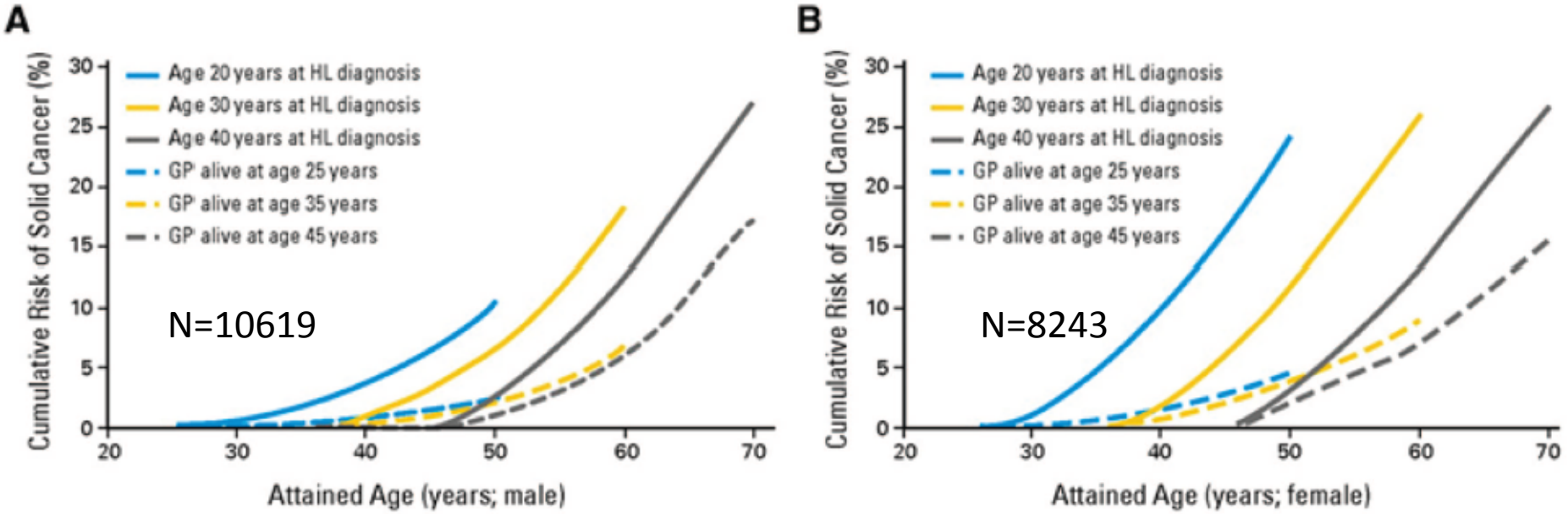
Second Malignancies

Prog Pediatr Cardiol. 2014 September 1; 36(1-2): 19–26.

Late Effects in the Era of Modern Therapy for Hodgkin Lymphoma

David C. Hodgson[1]

Cumulative risk of solid cancer among **HD survivors** compared with the general population

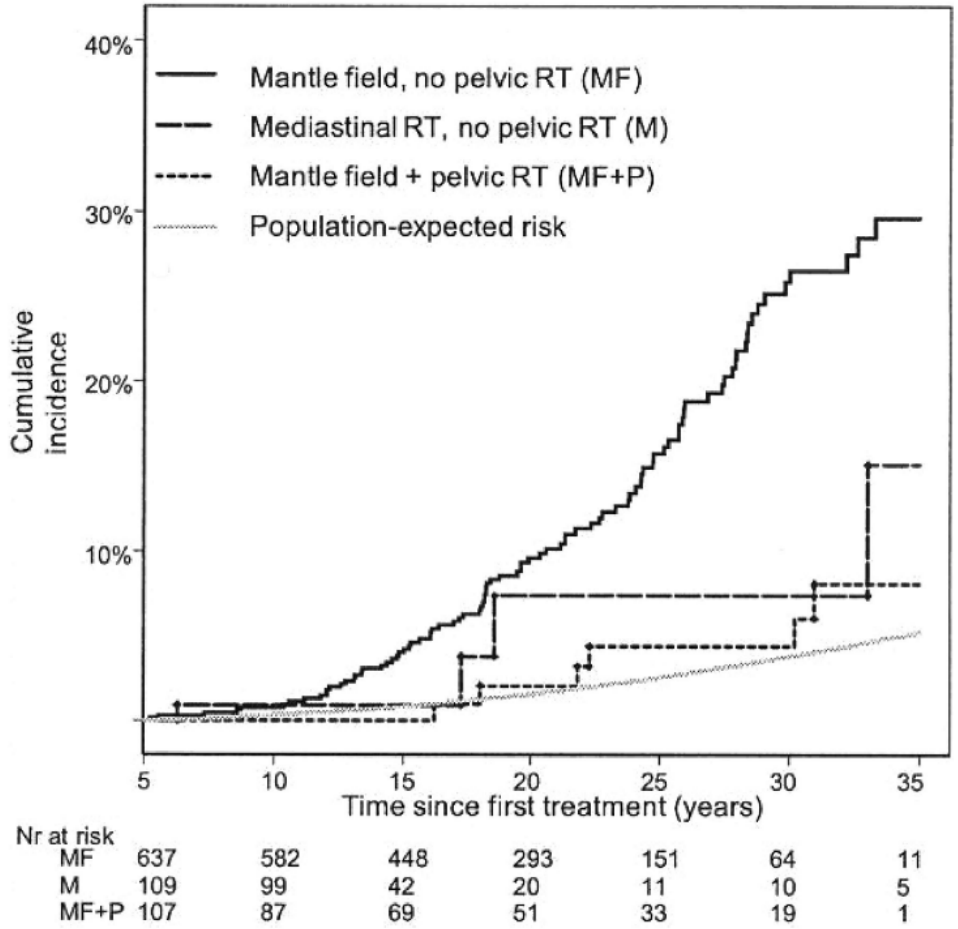


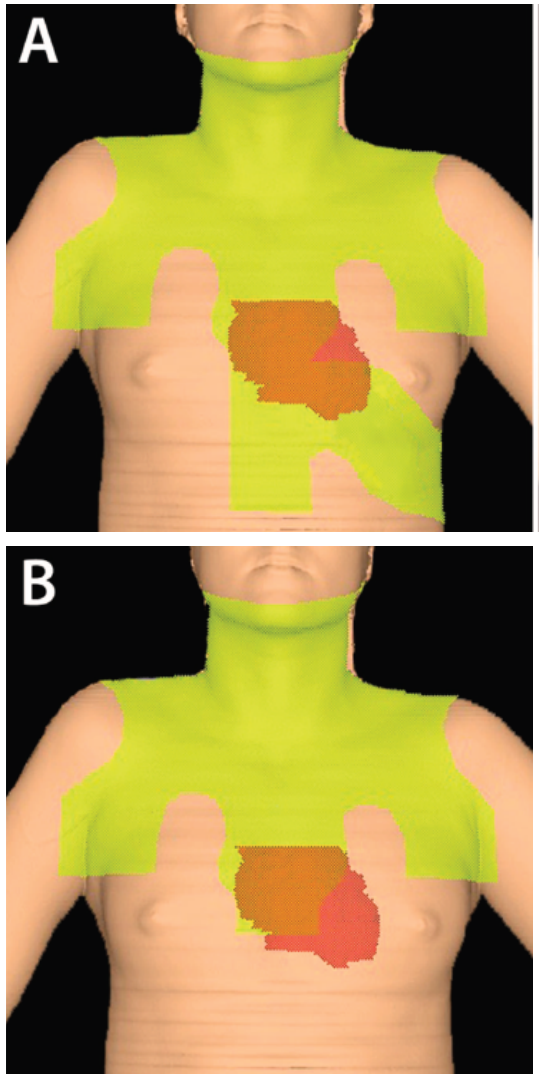
Based on volume, dose, age and sex increase of **secondary cancer**, heart disease,endocrine dysfunction.

Hematology 2011

Late Effects in the Era of Modern Therapy for Hodgkin Lymphoma

David C. Hodgson[1]





Mantle RT 35-45 Gy is associated with
a **2-20 fold increased relative risk of breast cancer**

Hematology 2011

Breast Cancer After Chest Radiation Therapy for Childhood Cancer

Chaya S. Moskowitz,

1230 female childhood survivors of the Childhood Cancer Survivor Study

Characteristic	All Participants (N = 1,230) No.	%	Breast Cancer (n = 203) No.	%	No Breast Cancer (n = 1,027) No.	%
Primary childhood cancer						
Hodgkin lymphoma	678	55.1	167	82.3	511	49.7
Wilms tumor	143	11.6	7	3.4	136	13.2
Non-Hodgkin lymphoma	99	8.1	9	4.4	90	8.8
Neuroblastoma	90	7.3	1	0.5	89	8.7
Leukemia	81	6.6	4	2.0	77	7.5
Bone tumor	75	6.1	12	5.9	63	6.1
Soft tissue sarcoma	55	4.5	3	1.5	52	5.1
CNS tumor	9	0.7	0	0.0	9	0.9
Age at diagnosis of primary cancer, years						
Median	13.0		15.0		12.0	
Range	0-20		3-20		0-20	

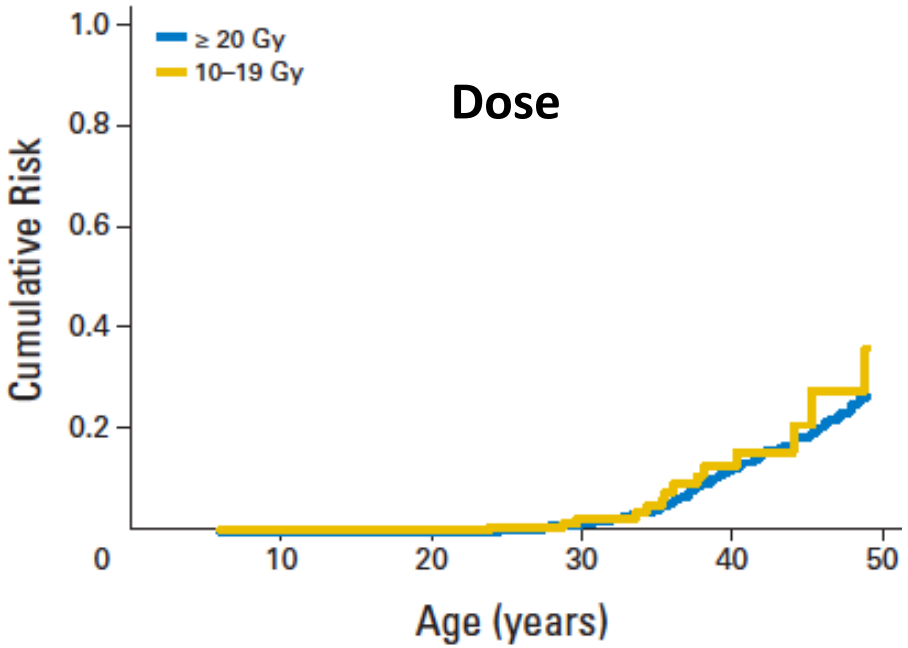
203/1230= 16% developed a breast cancer.

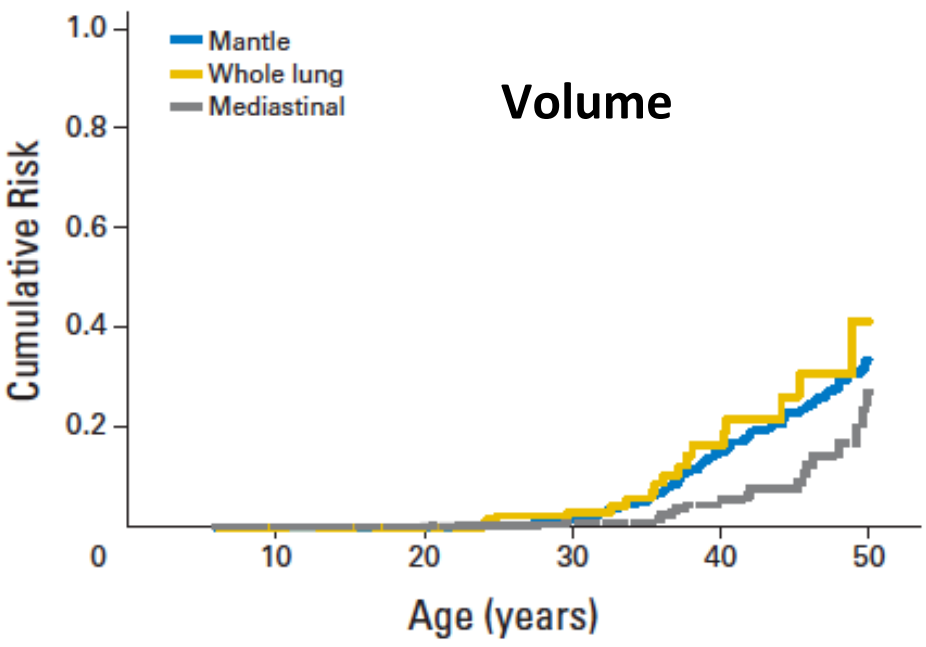
Median age at RT-treatment of the primary tumor 15 (0-20) years .

J Clin Oncol 32:2217-2223.

Breast Cancer After Chest Radiation Therapy for Childhood Cancer

Chaya S. Moskowitz,



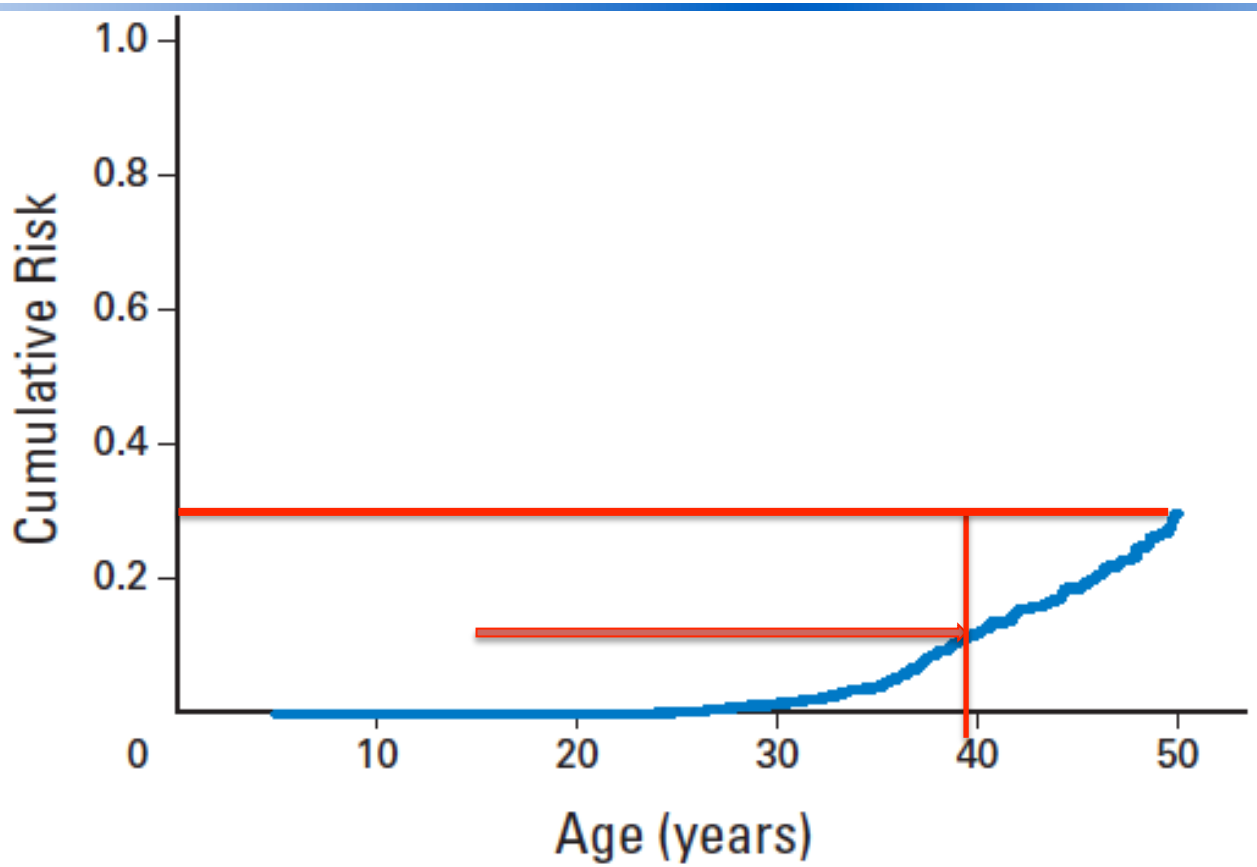


Elevated Risk of Breast Ca :

- No difference in dose: low and higher dose RT
- Field size of primary treatment fields

Breast Cancer After Chest Radiation Therapy for Childhood Cancer

Chaya S. Moskowitz,

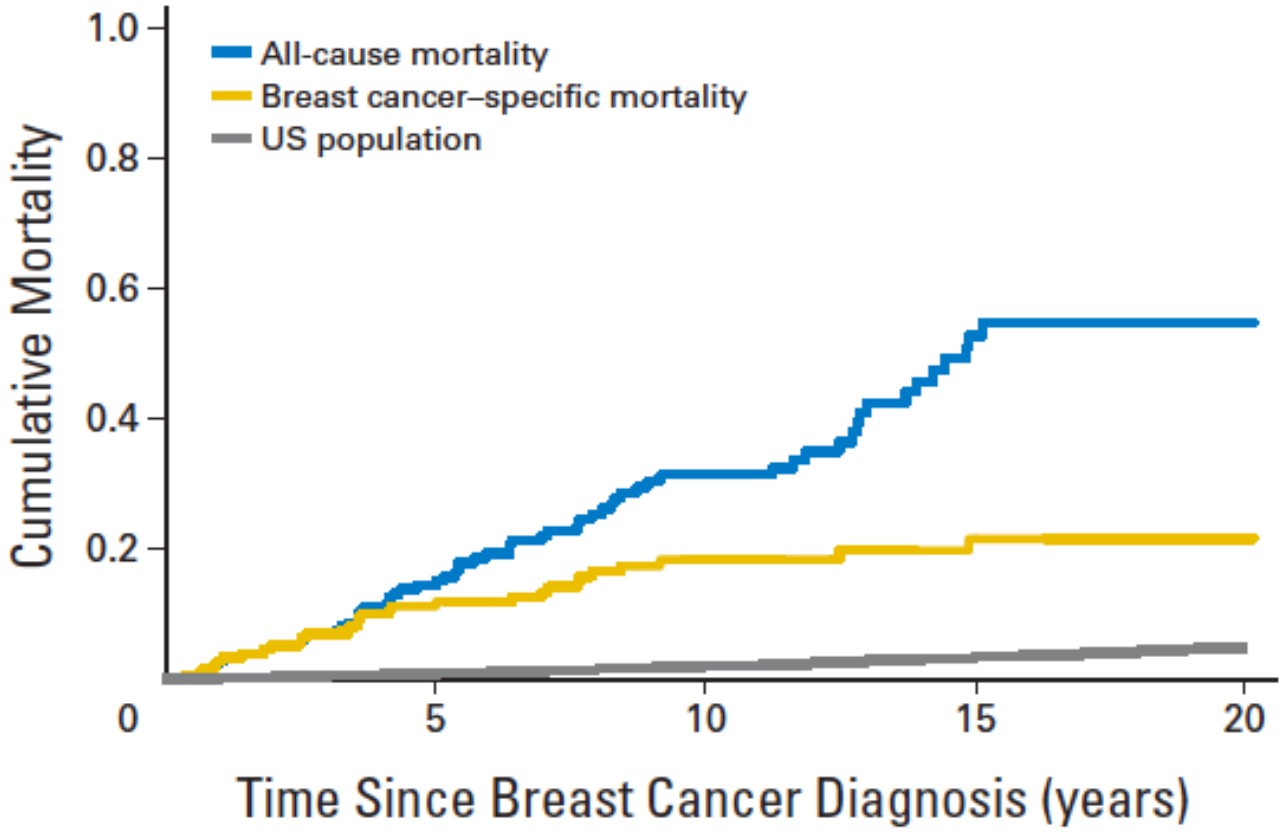


- Median time to breast cancer was 23 years (range 7 to 41 y)
- Median age was 39 years
- 30% Cumulative risk of breast cancer at the age of 50 years

J Clin Oncol 32:2217-2223.

Breast Cancer After Chest Radiation Therapy for Childhood Cancer

Chaya S. Moskowitz,



- Breast cancer after childhood cancer is associated with substancial mortality.
- sBC more aggressiv?

J Clin Oncol 32:2217-2223.

Breast Cancer in Young Women After Treatment for Hodgkin's Disease During Childhood or Adolescence

Schellong et al

	n	median	range
female	590		
Age at diagnosis of HD (years)		13.8	2.9-17.9
Radiation dose to the chest region (Gy)		30	0-50
Alive at last follow- up	534		
Age (years)		31.1	6.7-47.0
Follow- up (years)		17.8	0.1-33.7

- all patients got a 3-4year interval questionaire

Deutsches Ärzteblatt International | Dtsch Arztebl Int 2014; 111(1–2): 3–9

Breast Cancer in Young Women After Treatment for Hodgkin's Disease During Childhood or Adolescence

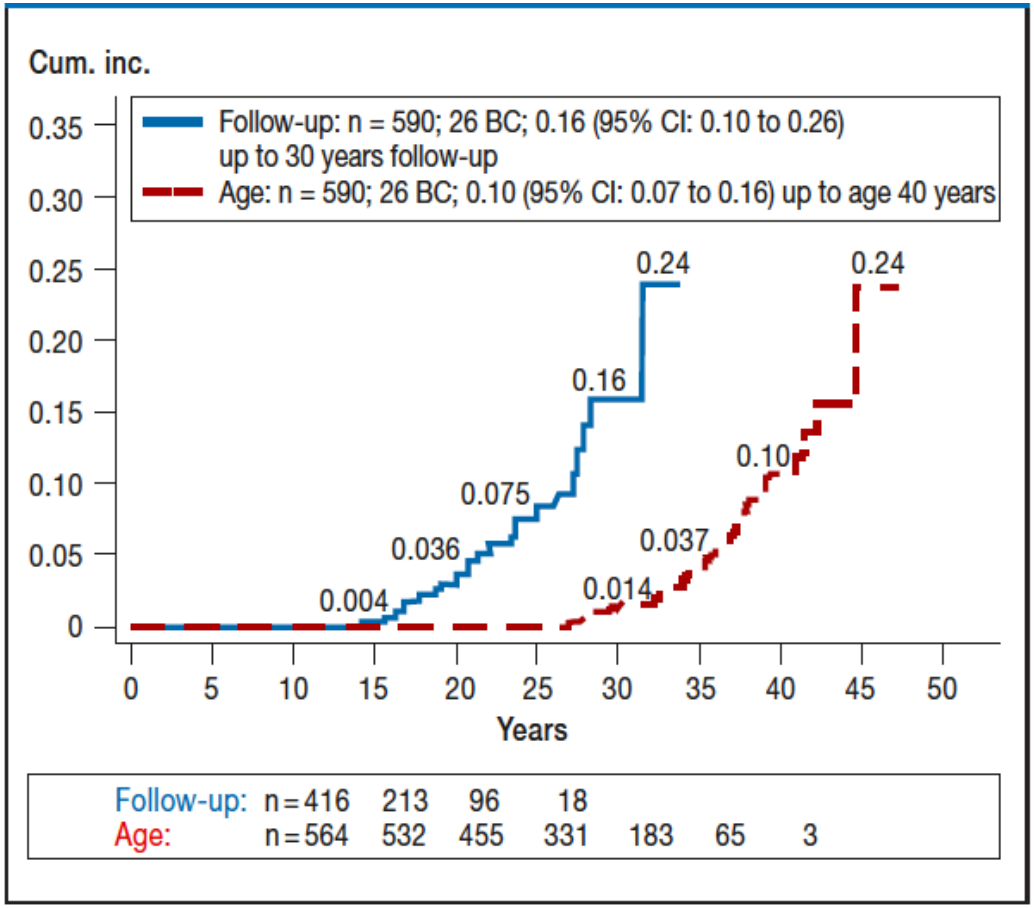
Schellong et al

26/590 women with breast cancer	n	Median	Range
Age at HD (years)		13.3	9.9–16.2
HD recurrence	7		
Radiation dose for HD (Gy) (infraclavicular region/mediastinum/axilla)		35	20–41 (1 pat. 0)
incl. radiotherapy for recurrence		35.5	20–45 (1 pat. 0)
Interval between HD and BC (years)		20.7	14.3–31.3
Age at diagnosis of breast cancer (years)		35.3	26.8–44.6
Hormone receptor status ER/PR+	24		
Grading G2	16		
Ductal histology	20		
Advanced stage	13		
Bilateral (synchronous or metachronous)	6		
BC recurrence	8		
Death due to BC	3		

Deutsches Ärzteblatt International | Dtsch Arztebl Int 2014; 111(1–2): 3–9

Breast Cancer in Young Women After Treatment for Hodgkin's Disease During Childhood or Adolescence

Schellong et al



Cumulative incidence

30 years follow up:

16% (95%CI: 10% to 26%)

Age of 40 years:

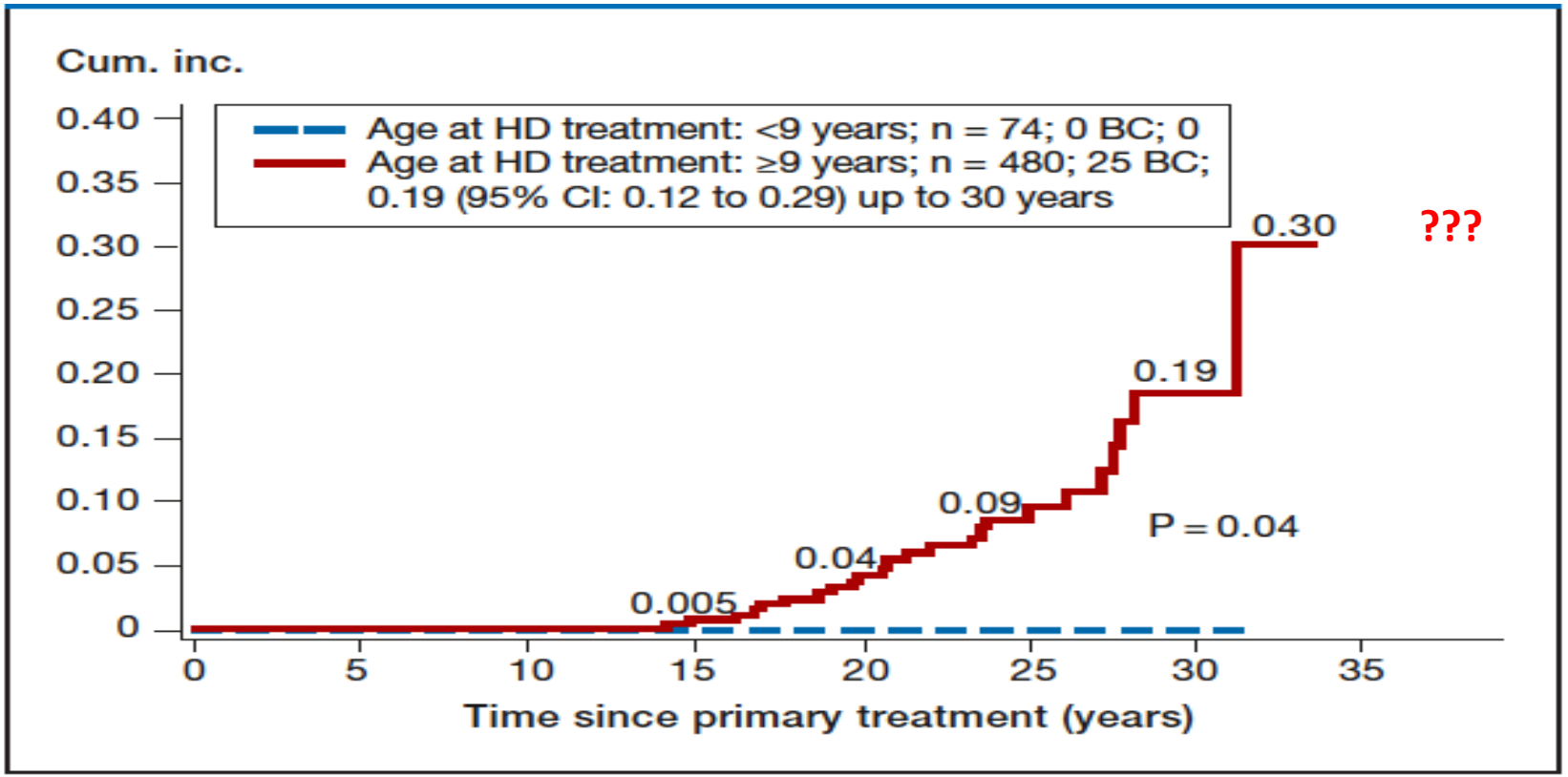
10% (95% CI: 7%to 16%)

The median SIR for sBC calculated for 25 to 45 year old women 24(range 18-49).**sBC Risk is 24 times higher than in the age-machted general population.**

Deutsches Ärzteblatt International | Dtsch Arztebl Int 2014; 111(1–2): 3–9

Breast Cancer in Young Women After Treatment for Hodgkin's Disease During Childhood or Adolescence

Schellong et al



No sBC have been observed in the group of patients younger 9 years at time of HD treatment.

Deutsches Ärzteblatt International | Dtsch Arztebl Int 2014; 111(1–2): 3–9

Secondary Malignancies Following Treatment for Hodgkin's Lymphoma in Childhood and Adolescence

Cumulative incidence of SMN after treatment for Hodgkin's lymphoma in childhood and adolescence

First author (reference number)	Age at HL diagnosis (years)	Patient recruitment period	Pts. in study (no.)	Median follow-up (years)	Pts. with SMN (no.)	Cumulative incidence at: 20 years	25 years	30 years	SIR	95% CI
Sankila (14)	<21	1943–87	1641		62*	6.9%		18%	7.7	5.9–9.9
Wolden (15)	<21	1960–95	694	12.3	56*	m 9.7%			m 10.6	6.6–16.0
						f 16.8%			f 15.4	10.6–21.5
Green (16)	<20	1960–89	182	17.1	28	12.7%		26.3%	m 9.4	4.1–18.5
									f 10.2	5.6–17.1
Metayer (17)	<21	1935–94	5925	10.5	195*	6.5%	11.7%		7.7	6.6–8.8
Bhatia (18)	<16	1955–86	1380	17	212*	10.6%		26.3%	18.5	15.6–21.7
Constine (19)	<19	1960–90	930	16.8	102*		19.0%		14.2	11.6–17.3
O'Brien (20)	"children"	1970–90	110	20.6	18*	17.0%		29.4%	22.9	14.2–35
DAL/GPOH	<18	1978–2002	2548	14.3	138*	7.0%	11.2%	18.7%	9.1	4.8–10.8

Deutsches Ärzteblatt International | Dtsch Arztebl Int 2015; 112: 320–7

Updated Relevance of Mammographic Screening Modalities in Women Previously Treated with Chest Irradiation for Hodgkin Disease[1]

Catherine Colin, MD, PhD

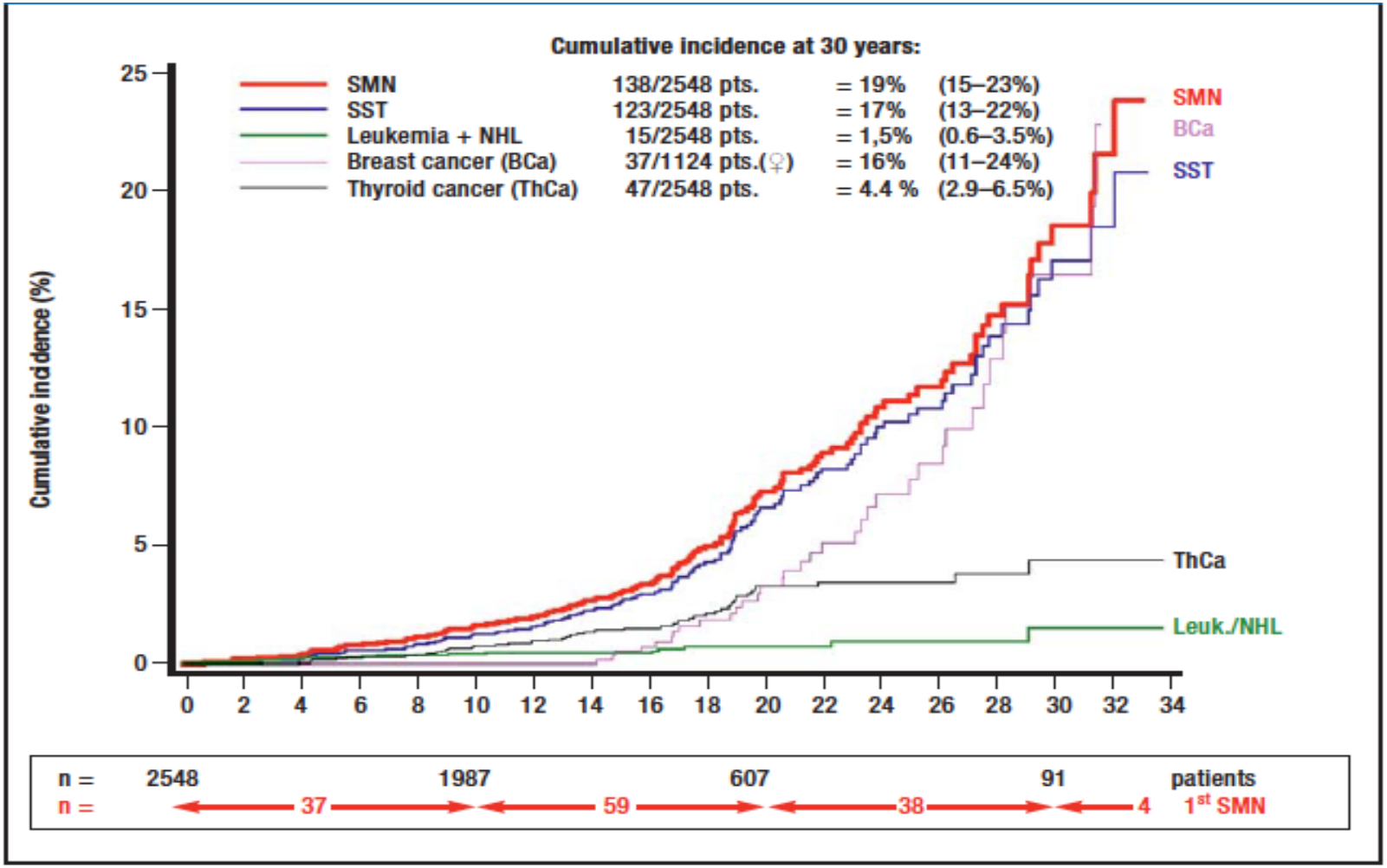
Screening Program after Radiotherapy

Recommendations for Breast Imaging Screening from National or International Organizations

Organization and Year	Cumulative Radiation Dose (Gy)	Annual Screening Protocol
Children's Oncology Group, 2004 (3)	≥20	Mammography at ≥25 years or 8 years after RT
Children's Oncology Group, 2008 (4)	≥20	Mammography and MR imaging at ≥25 years or 8 years after RT
American Cancer Society, 2007 (5)	10–30 (RT)	Mammography ≥30 years, MR imaging ≥30 years
UK National Breast Cancer Screening Program, 2009 (6)	<17 (RT)	MR imaging at 25–29 years, mammography and/or MR imaging at 30–50 years, three yearly mammographic examinations at >50 years in the NHSBSP
EUSOMA Group, 2010 (7)	NA	MR imaging ≥8 years after RT
Children's Oncology Group, 2010 (8)	≥20	Mammography and MR imaging at ≥25 years or 8 years after RT

Note.—EUSOMA = European Society of Breast Cancer Specialists, NA = not available, NHSBSP = National Health Service Breast Screening Program, RT = radiation therapy.

Secondary Malignancies Following Treatment for Hodgkin's Lymphoma in Childhood and Adolescence



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Strategies for late Effect Risk Reduction; Treatment Concepts have to be developed across the age spectrum

Initial Therapeutics:

- Modification of CT and RT to limit doses and/or substitute for agents with reduced risk for long term effects

Survivorship:

- Develop secondary prevention strategies for survivors at risk for long term complications

Radiotherapy in children has to be performed under optimal conditions of modern imaging, modern techniques, and experienced staff.

Conclusion

- Side effects after Radiotherapy **cannot be completely avoided,**but perhapse reduced.
- Side effects after Radiotherapy are age, sex, volume and dose dependent, they can be increased by life-style and nutrition.
- Damage of the organ system **may not become** clinically **evident for many years**.
- To reduce chronic morbidity and premature mortality **long-term follow-up programs and guidelines** have to be implemented.

ESTRO School

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Ewing's sarcoma:
clinical features, histology, surgery, staging, prognostic factors, outcome

Umberto Ricardi

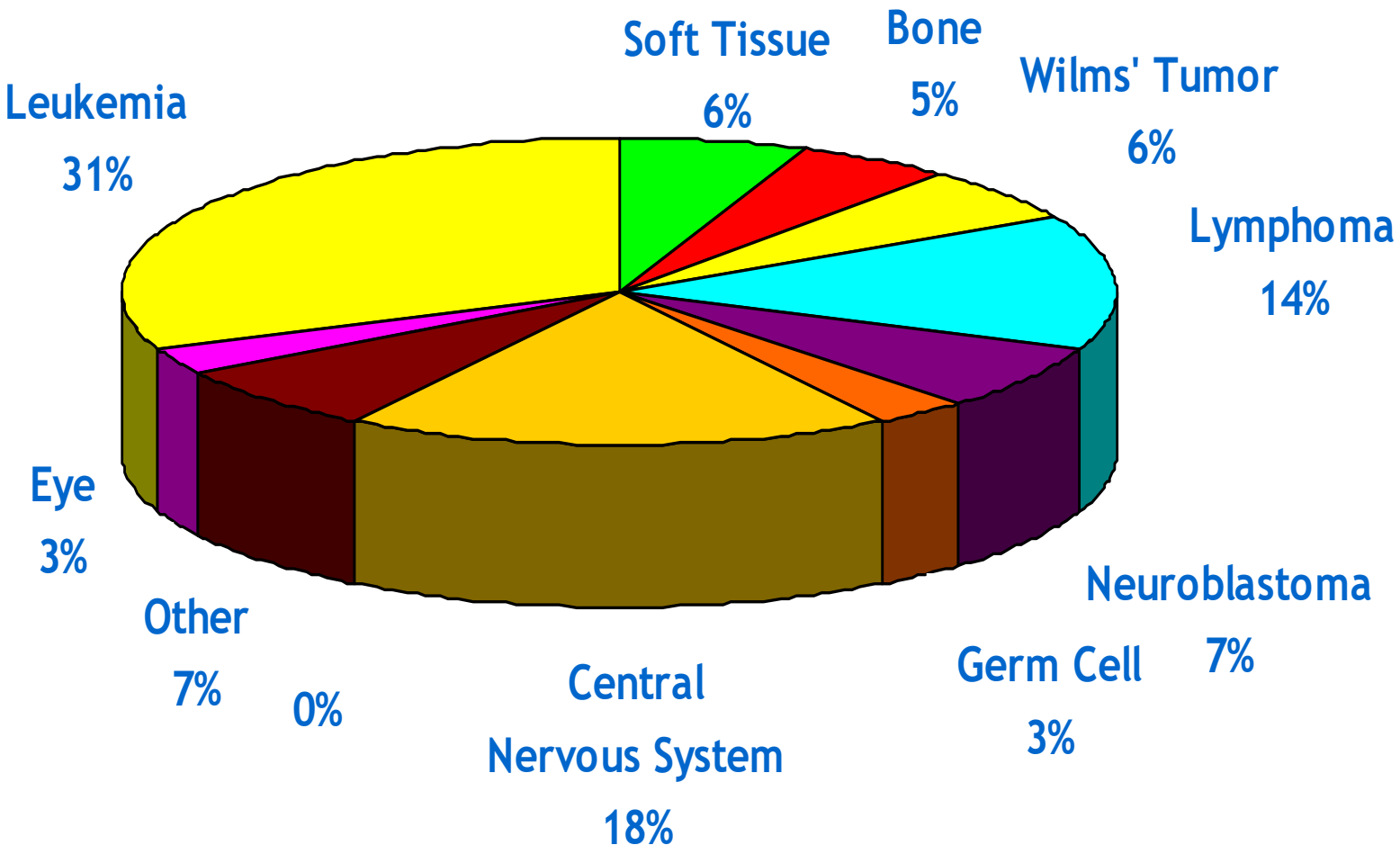
DEPARTMENT OF
ONCOLOGY
UNIVERSITY OF TURIN

ESTRO School

PRESENTATION OUTLINE (Part I)

- Introduction
- Epidemiology
- Clinical Presentation
- Radiology
- Pathology
- Staging and Prognostic features

Distribution of Common Pediatric Malignancies



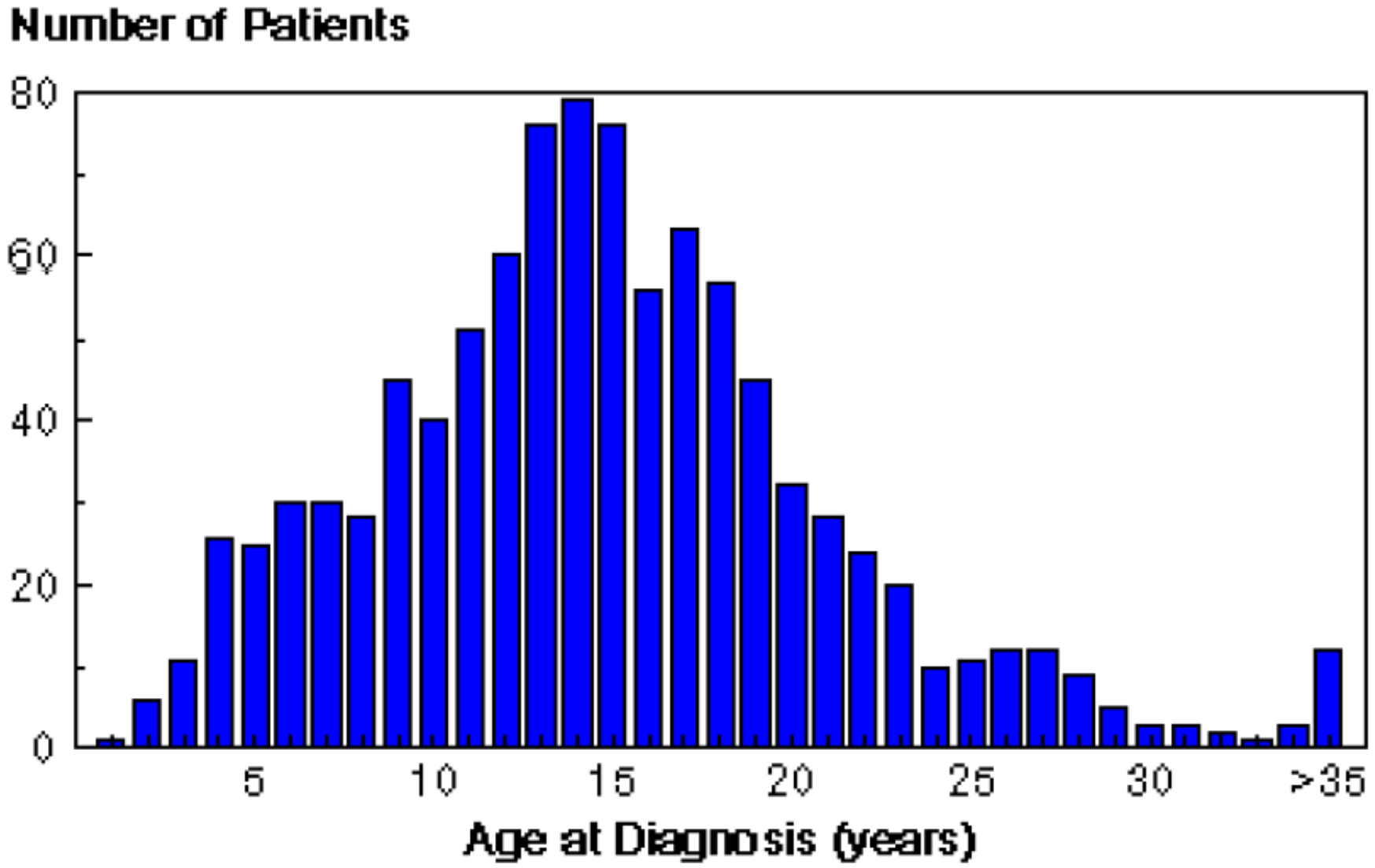
Ewing's sarcoma is the second most frequent primary malignant bone tumor, after osteosarcoma

ESTRO School

Epidemiology

- ES is nonetheless an infrequent cancer, with approximately 250-300 new cases diagnosed in patients < 20 yrs of age per year in North America
- Incidence is low before age of 5 yrs: 0.6 per million, but progressively rises towards puberty (peak rate of 5 per million)
- The most common age of diagnosis is the 2nd decade of life (65%)
- Males > Females (1.3 : 1)

Distribution by Age



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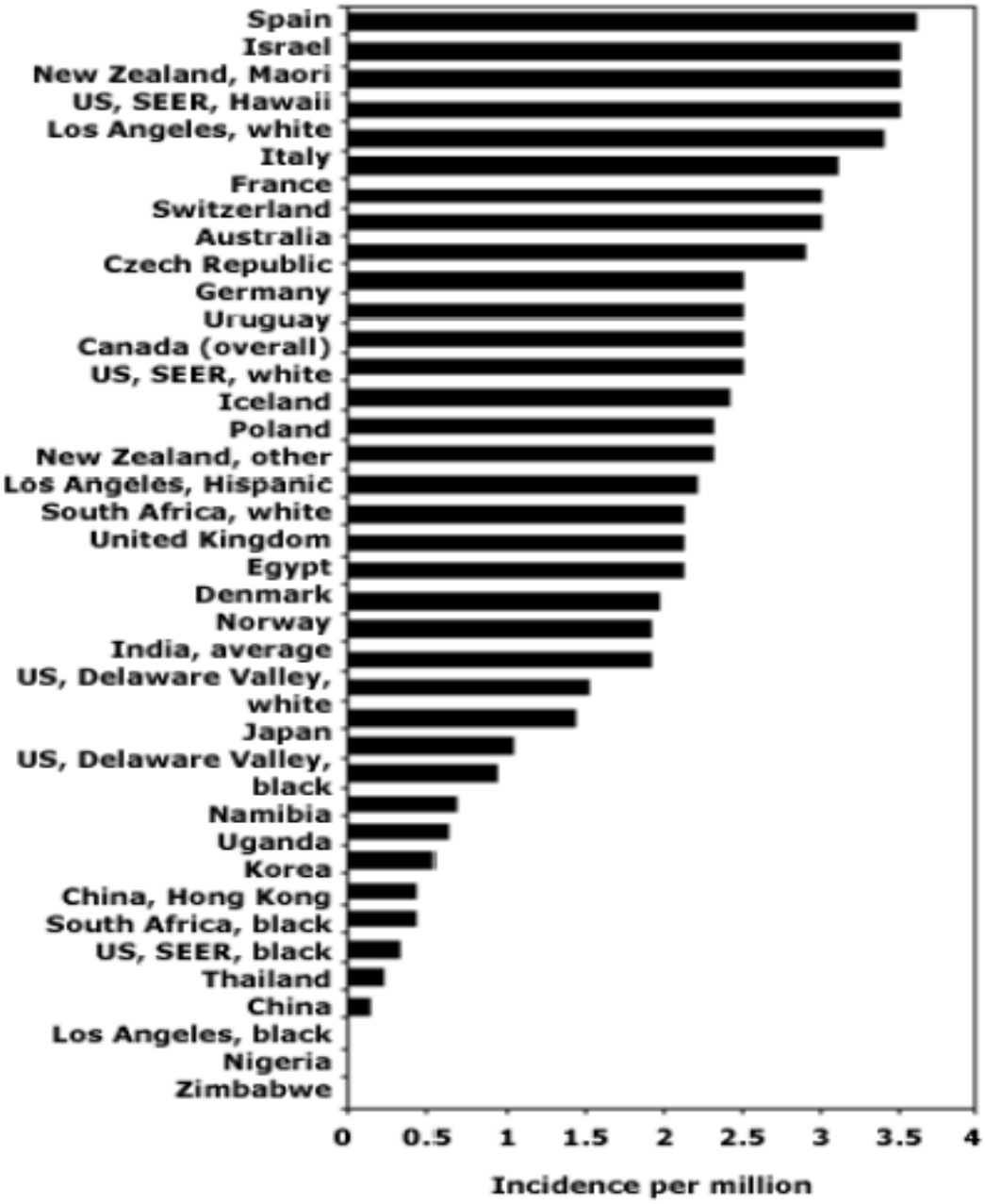
Distribution by Etnicity



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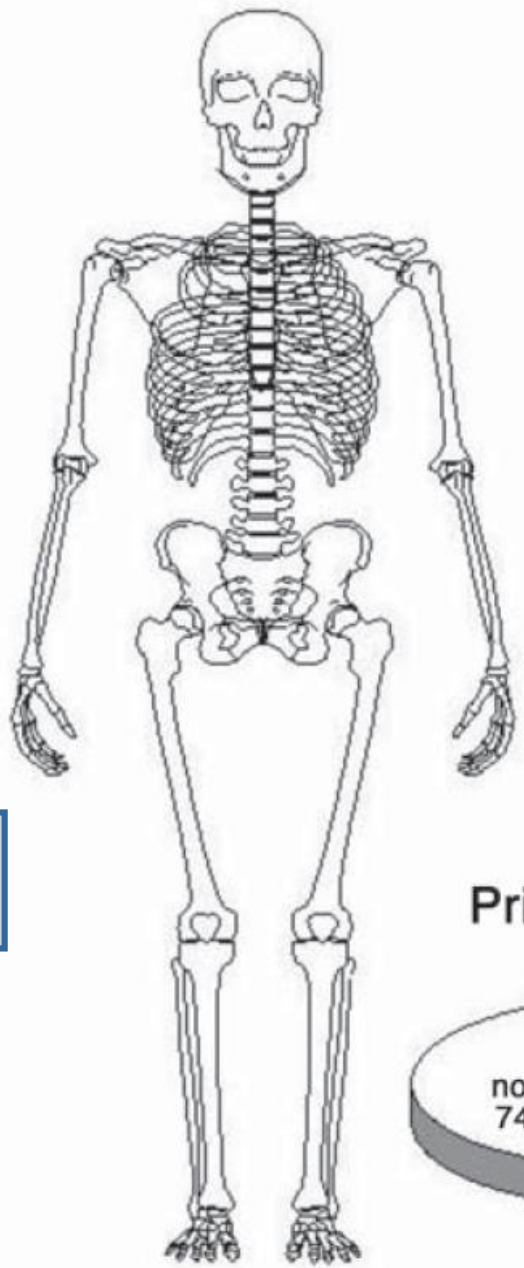
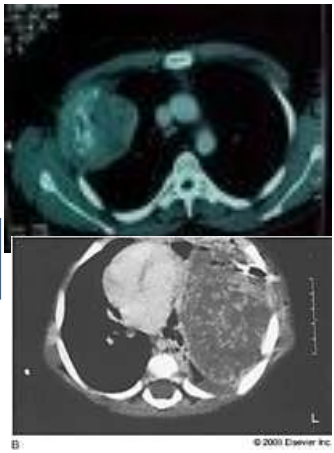
Distribution by Site

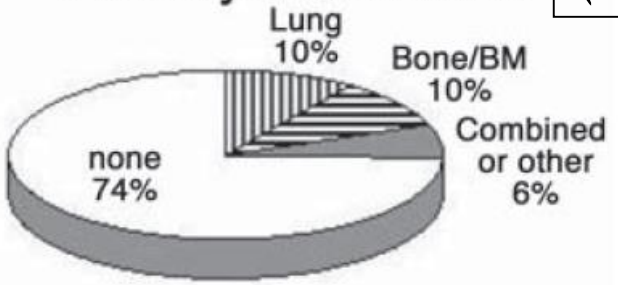
Humerus	6.0%
Ulna	1.0%
Radius	1.0%
Hand	1.0%
Femur	20.0%
Fibula	8.0%
Tibia	10.0%
Foot	3.0%



Skull	2%
Chest wall:	16%
Clavicle	1.5%
Skapula	4.0%
Ribs	10.0%
Sternum	0.5%
Spine	6.0%
Pelvis	26.0%



Primary metastases (≈25%)



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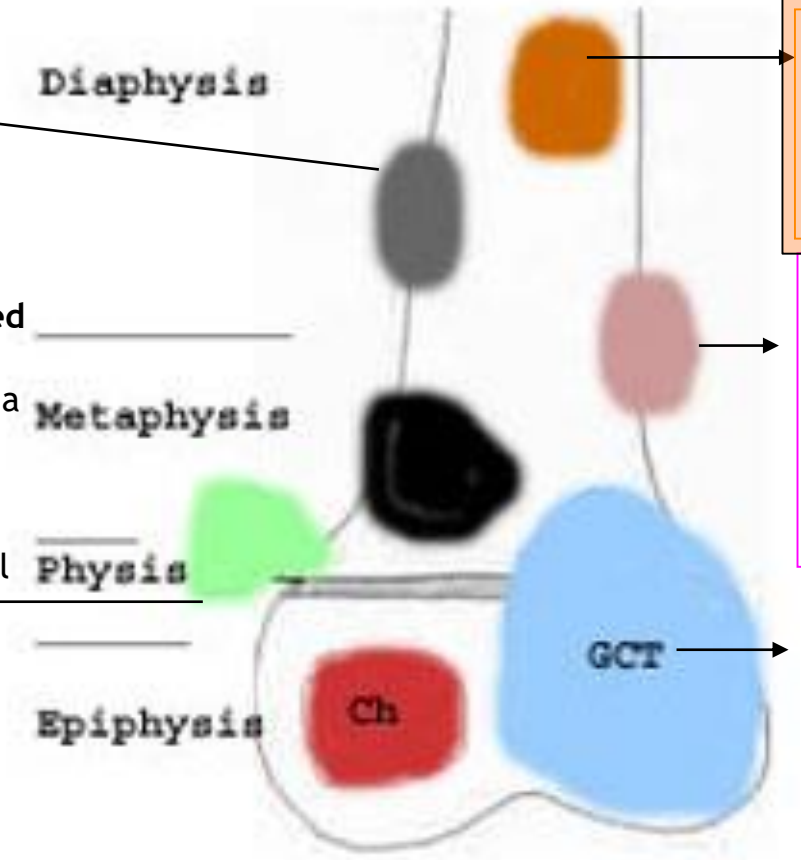
SITE OF LONG BONE INVOLVEMENT

Diaphyseal lesions centered in the cortex:
Adamantinoma, osteoid osteoma

Metaphyseal intramedullary lesions:
Osteosarcoma is usually centered in the metaphysis.
Chondrosarcoma and fibrosarcoma often present as metaphyseal lesions. Osteoblastoma, enchondroma, fibrous dysplasia, simple bone cyst, and aneurysmal bone cyst are common in this location.

Metaphyseal exostosis:
Osteochondroma

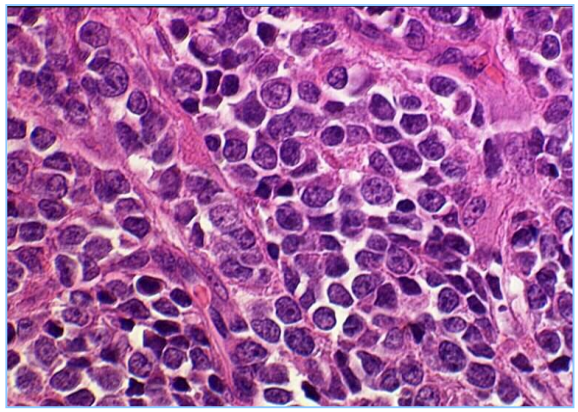


Diaphyseal intramedullary lesions:
Favored location for Ewing's sarcoma, lymphoma, myeloma.
Common for fibrous dysplasia and enchondroma

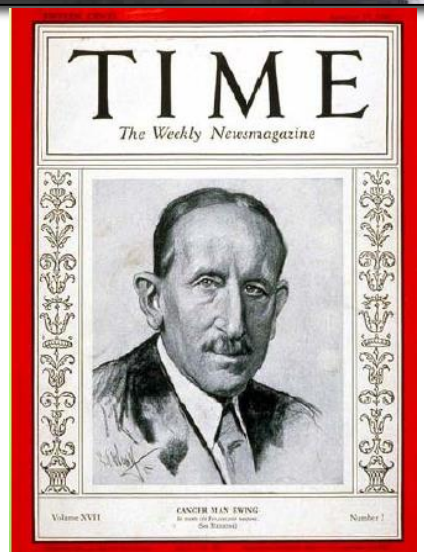
Metaphyseal lesions centered in the cortex:
Classic location for a non-ossifying fibroma (NOF). Also, a common site for osteoid osteoma.

Epiphyseal lesions:
Chondroblastoma (Ch) and Giant Cell Tumor (GCT) are almost invariably centered in the epiphysis.
Chondroblastoma is a rare tumor seen in children and adolescents with open growth plates. GCT is the most common tumor of epiphyses in skeletally mature individuals with closed growth plates. GCT often shows metaphyseal extension.

Diffuse endothelioma of bone
Proc New York Pathology Society, 1921



First Professor of Pathology
at Cornell University



James Stephen Ewing: …. as a tumor of the shaft of long bones that, in contrast to osteosarcoma, is sensitive to radiation

Endothelial origin
(an idea that prevailed until the mid-1980s)

Neural origin

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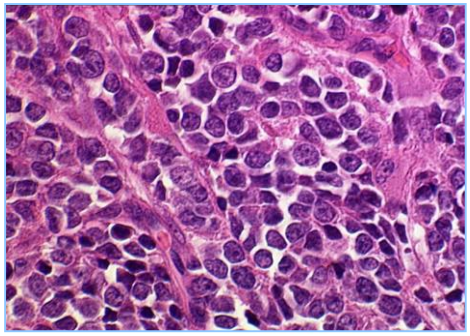
Ewing's sarcoma family of tumours

- *Although Ewing's sarcoma most commonly is an undifferentiated tumor of bone, it may arise also from soft tissues* ***(extraosseous Ewing's sarcoma - EES)***

- *A more differentiated form of this entity, known as* ***peripheral primitive neuroectodermal tumor (pPNET)****, occurs as a primary tumor of bone or soft tissues*

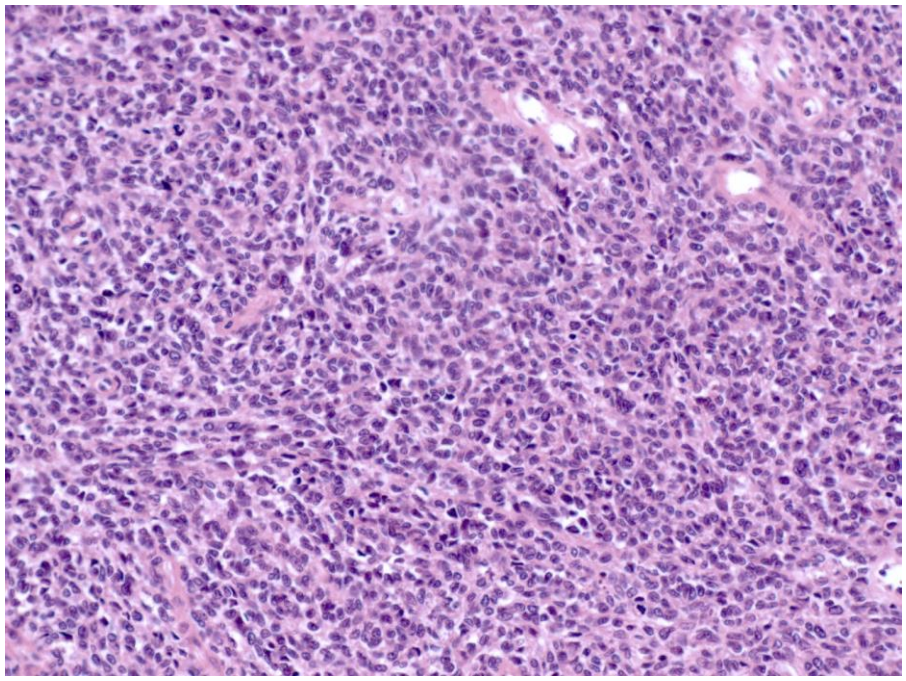
- ***Ewing's sarcoma family of tumors (ESFT): a spectrum of a single neoplastic entity***

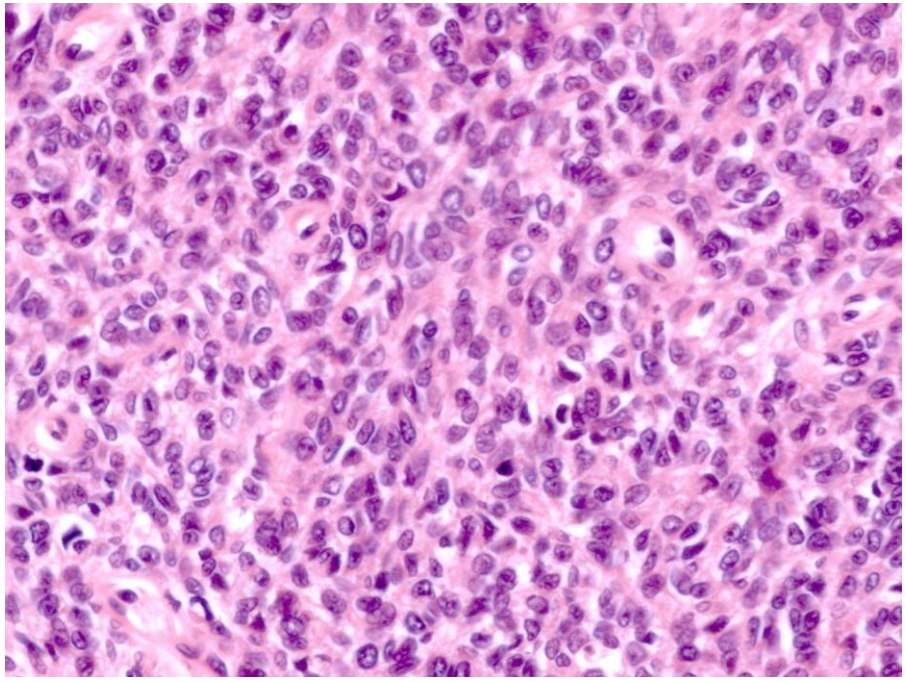


Pathology

ES is one of the pediatric Small Round Blue Cell Tumors (SRBCT)

Histologic appearance: monotonous population of **small round cells** with high nuclear to cytoplasmic ratios arrayed in sheets





Origin from epithelial and neuronal elements

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Spectrum of Ewing's sarcoma family

EWING'S SARCOMA

ATYPICAL EWING'S SARCOMA

- **PNET (Primitive Neuroectodermal Tumor)**
- **PN (Peripheral Neuroepithelioma)**
- **ASKIN TUMOR (Malignant tumor of the thoraco-pulmonary region)**

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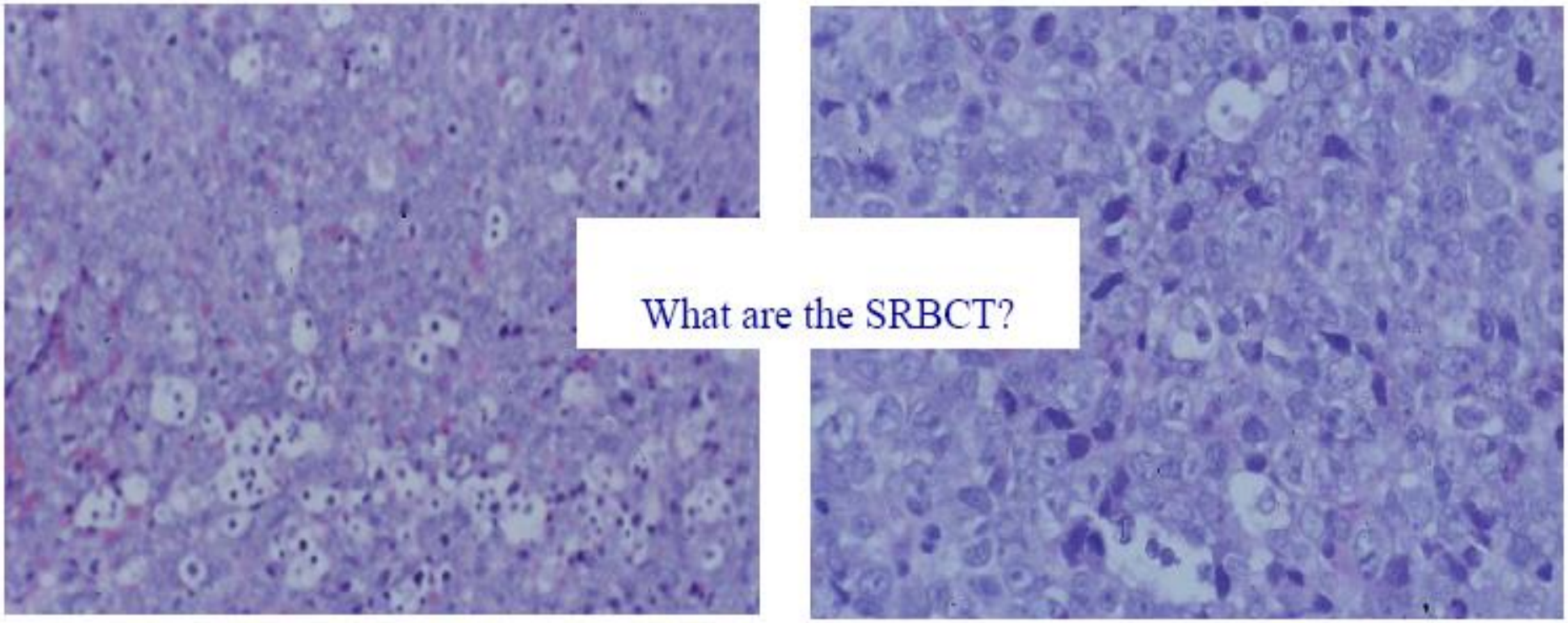
Histologic features of ES overlap to varying degrees with the other SRBCT of childhood

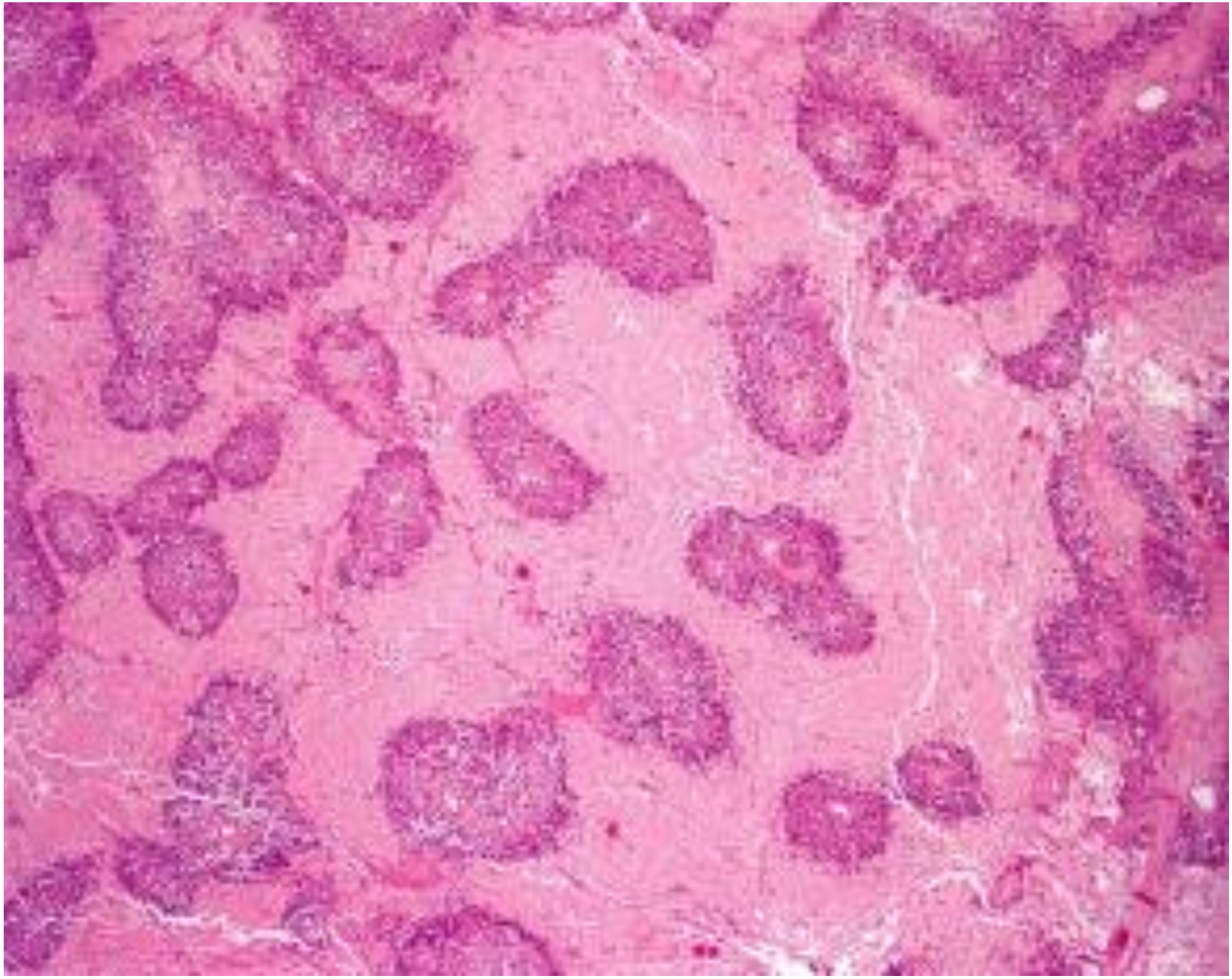


Small Round Blue Cell Tumor (SRBCT)
NB/Lymphoma/RMS/ES/PNET

Association between growth pattern and types of SRBCT

GROWTH PATTERN	TYPE OF SRBCT
DIFFUSE	NHL; ES/PNET; MCHS; MCC
FILIGREE	ES/PNET
NESTING	NB; DSRCT; MCC
STAGHORN	SS; MCHS
ALVEOLAR	ARMS
SPINDLE/FASCICULAR	SS; MCHS; ERMS

NHL: Non-Hodgkin's lymphoma, ES,PNET: Ewing's sarcoma/Primitive neuroectodermal tumor, MCHS: Mesenchymal chondrosarcoma; MCC: Merkel cell carcinoma; NB: Neuroblastoma; DSRCT: Desmoplastic small round cell tumor, SS: Synovial sarcoma; ARMS: Alveolar rhabdomyosarcoma; ERMS: Embryonal rhabdomyosarcoma



Filigree growth pattern with necrosis: typical for ES/PNET

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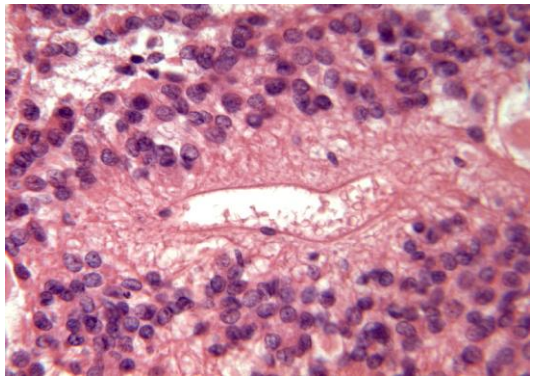
ASSOCIATION BETWEEN SOME HISTOLOGIC FINDINGS WITH TYPES OF MAIN SRBCT

HISTOLOGIC FINDINGS	TYPE OF SRBCT
ILL-DEFINED ROSETTES	ES/PNET
EXTENSIVE NECROSIS	NB; ES/PNET
WELL-DEVELOPED ROSETTES	NB
FIBRILLAR BACKGROUND OF NEUROPIL	NB
GANGLION CELLS	NB
CALCIFICATION	SS; NB; MCHS
PSEUDO-OSTEOID COLLAGEN	SS
CELL NESTS, TUBULES, GLANDS	SS; DSRCT
DESMOPLASTIC STROMA	DSRCT
MULTINUCLEATED TUMOR GIANT CELLS	ARMS
MYXOID STROMA	ERMS
WELL-DIFFERENTIATED CARTILAGE	SCOGS; MCHS
POORLY-DIFFERENTIATED CARTILAGE	SCOGS; MCHS
PAGETOID SPREAD (SKIN OR MUCOSA)	MCC



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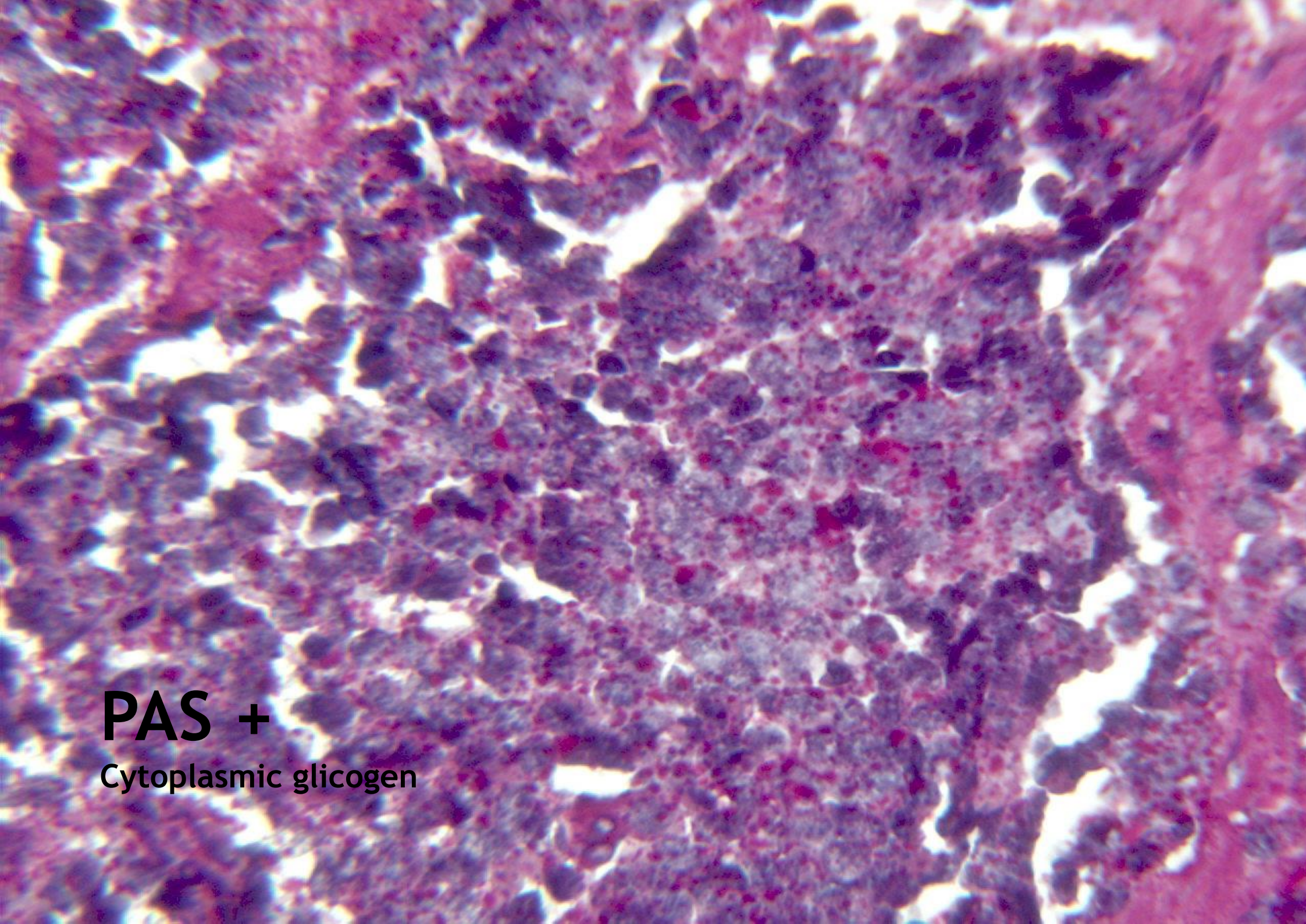
Immunohistochemical findings

- usually PAS +
- usually MIC2 (CD99) +
- immunoreactivity for vimentin
- immunoreactivity for cytokeratins (>20%)
- +/- neuronal markers (neural differentiation staining such as NSE, S-100 protein, Leu-7)


PAS +
Cytoplasmic glicogen

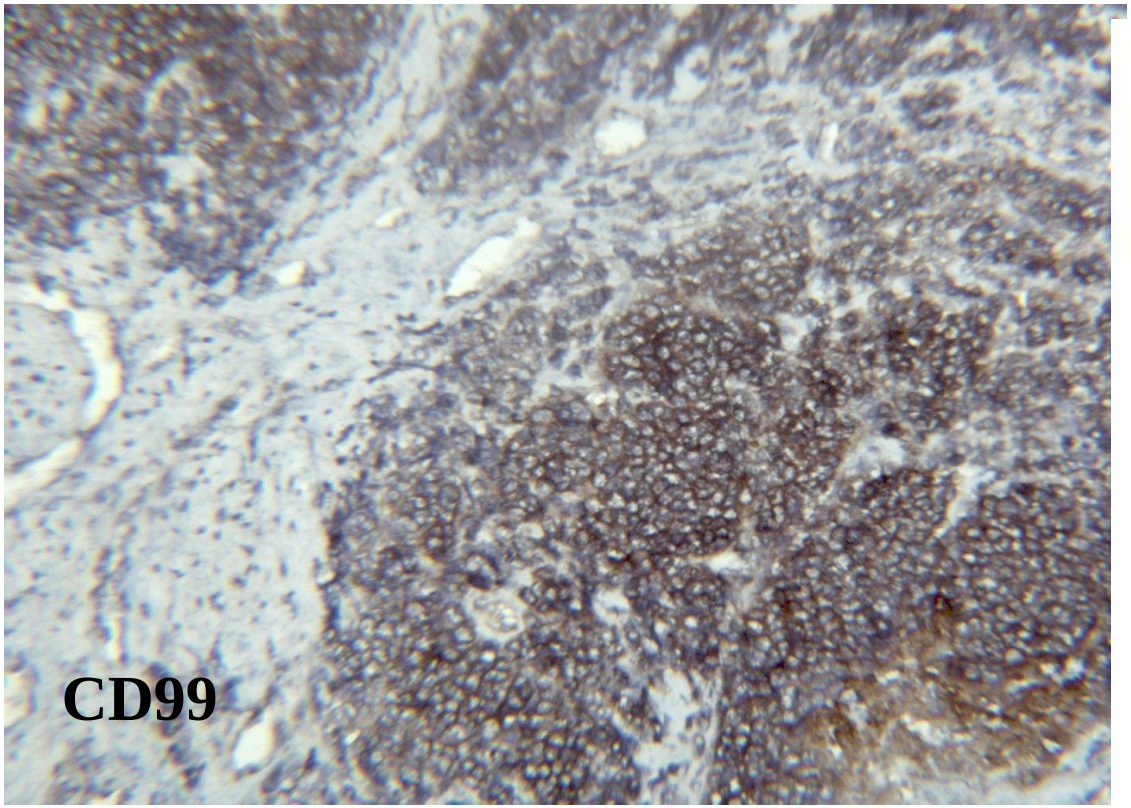


TABLE 32–11 FREQUENCY OF CD99 IMMUNOREACTIVITY IN ES/PNET FAMILY AND OTHER SMALL ROUND CELL TUMORS

Diagnosis	Positive (%)
ES/PNET	95
T-lymphoblastic lymphoma	92
Poorly differentiated synovial sarcoma	50
Small cell osteosarcoma	23
Rhabdomyosarcoma	21
Desmoplastic small round cell tumor	16
Small-cell carcinoma	9
Merkel cell carcinoma	9
Neuroblastoma	0

Data are from Scotlandi et al.[319] and Stevenson et al.[335]

- **CD99 is a 32 kDa cell-surface glycoprotein**
- **CD99 function is unknown**
- **CD99 is highly expressed on EWS cells (strong diffuse membrane staining in a “chain-mail pattern”)**

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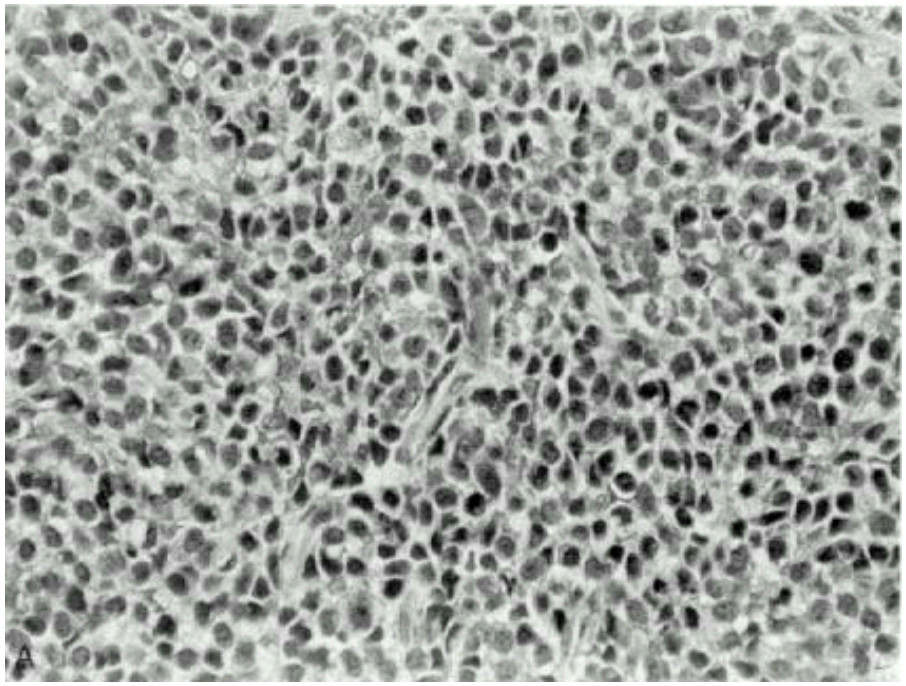

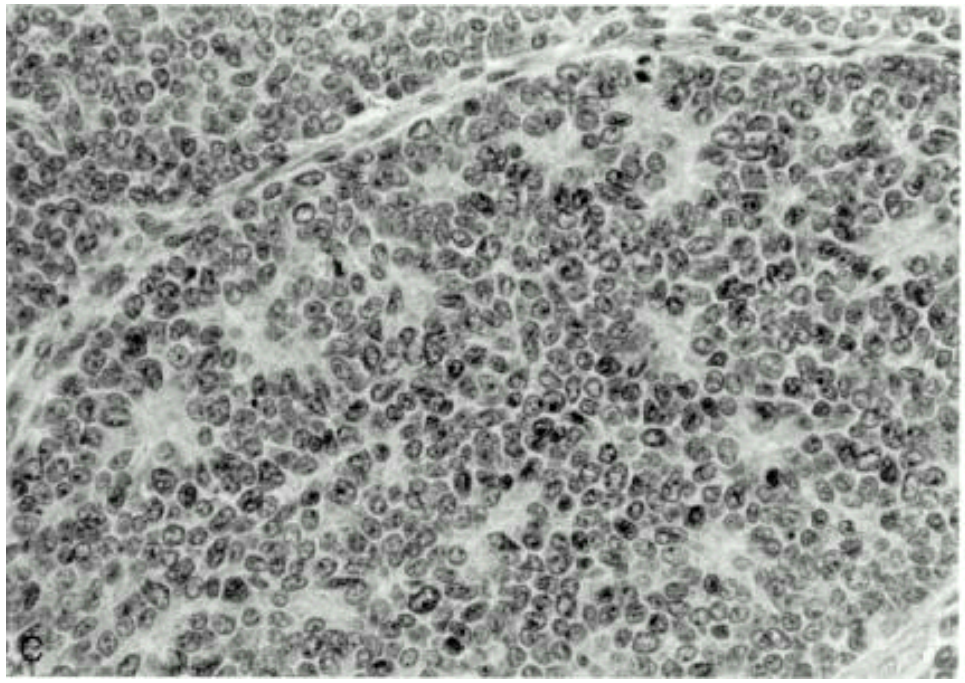

Ewing's Sarcoma

Primitive Neuroectodermal Tumor (PNET)/Peripheral Neuroepithelioma (PN)

t(11;22)(q24,q12)

t(11;22)(q24,q12)

pathognomonic

- Unifying diagnostic criterion for Ewing's family of tumors

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Reciprocal translocation between chromosomes 11 and 22 results in the formation of the fusion gene

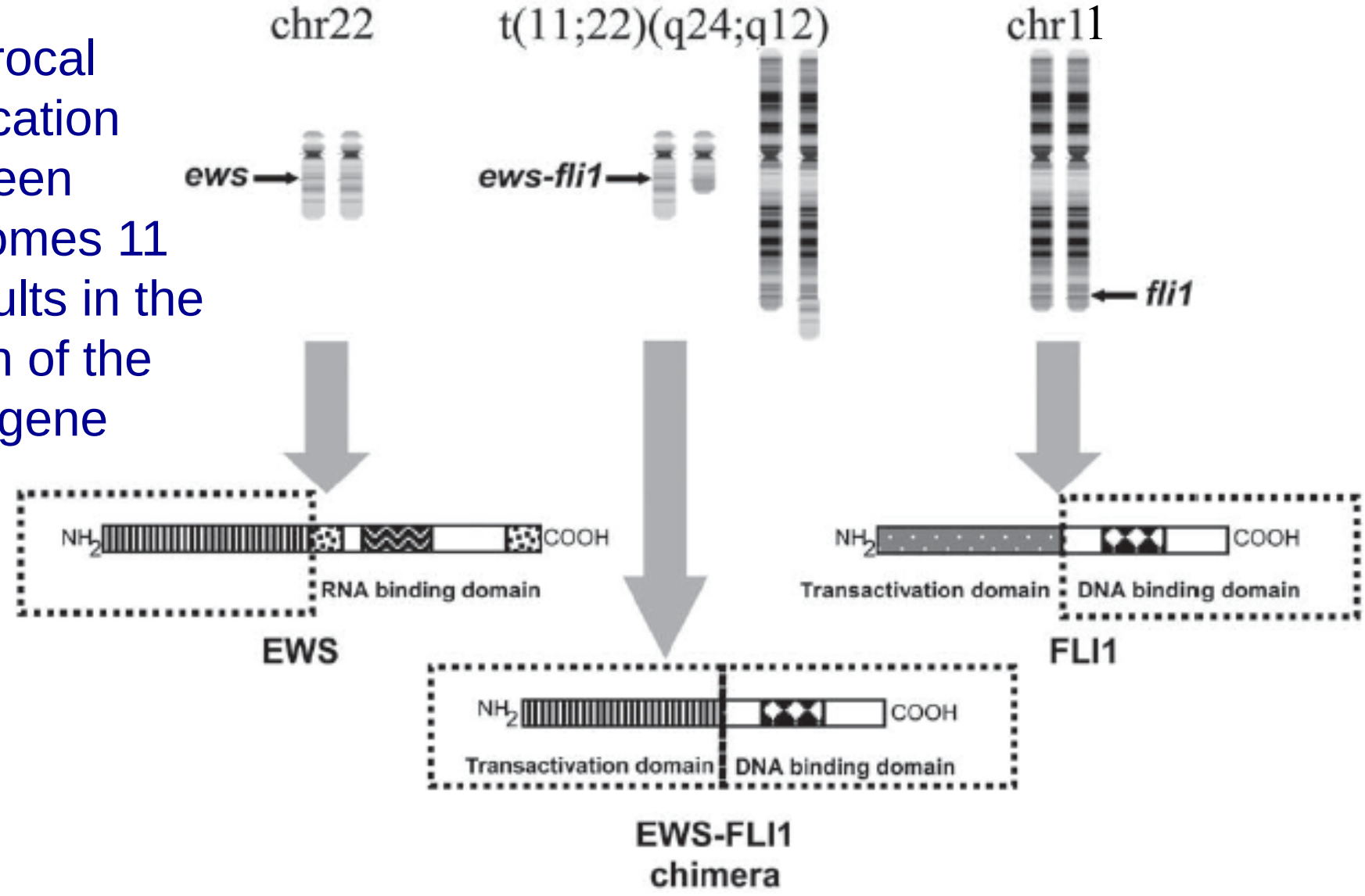

Figure 4. The reciprocal translocation between chromosomes 11 and 22 results in the formation of an *ews-fli1* fusion gene on the abnormal chromosome 22 that codes for a chimeric transcription factor with the N-terminal transcriptional regulatory domain deriving from *ews* and the *ets*-specific DNA-binding domain derived from *fli1*.

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Molecular Diagnosis

Tumor	Translocation	Fusion Gene
Ewing/PNET	t(11;22)(q24;q12)	*EWS/FLI1*
	t(21;22)(q22;q12)	*EWS/ERG*
Alveolar Rhabdomyosarcoma	t(2;13)(q35;q14)	*PAX3/FKHR*
	t(1;13)(p36;q14)	*PAX7/FKHR*
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*EWS/WT1*
Synovial Sarcoma	t(X;18)(p11.2;q11.2)	*SYT/SSX1+2*
Congenital Fibrosarcoma	t(12;15)(p13;q25)	*ETV6/NTRK3*
Clear Cell Sarcoma	t(12;22)(q13;q12)	*EWS/ATF1*

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Clinical Presentation

- Loco-regional pain (90%) (often mistaken for “bone growth” or injuries from sport or everyday activities)
- Swelling (70%) and/or palpable mass of the affected site
- Fever (20%)
- Pathological fracture
- Weight loss, malaise

- Labs: no blood, serum, or urine test specific for ES

Biopsy

- The most adequate sampling is achieved by **open biopsy**
- Biopsy is usually **incisional**, rather than excisional, and **usually from the soft tissue extension** of the primary bone mass
- Biopsy incision is **usually longitudinal**, so as to not violate tissue flap planes and neurovascular structures (to facilitate surgery, when needed)

Diagnostic Work-Up

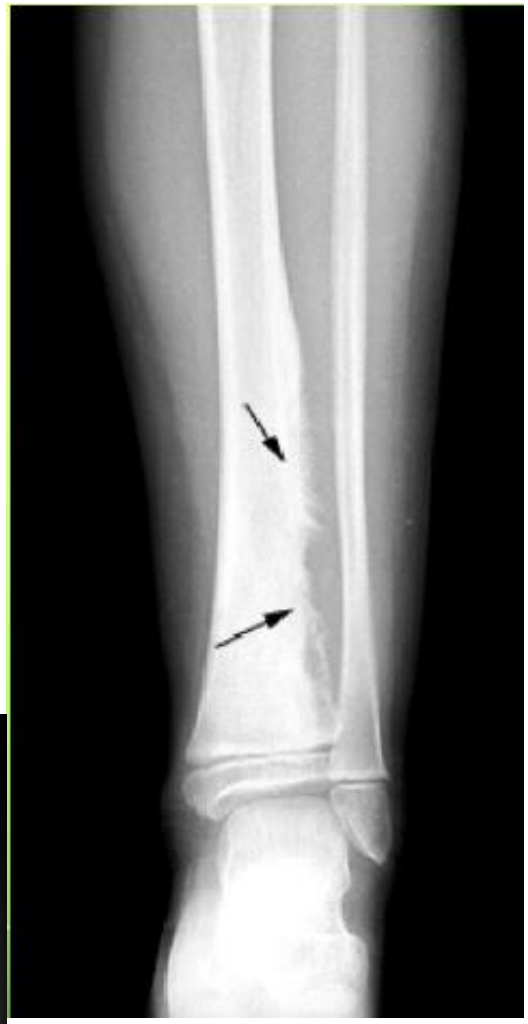
Plain films

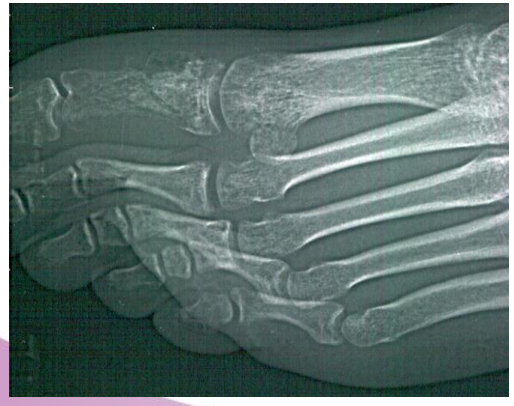
• Diaphyseal location: poorly marginated destructive lesion; the erosion of the cortex and spread to soft tissues are accompanied by a multilaminated periosteal reaction (Onion peel)

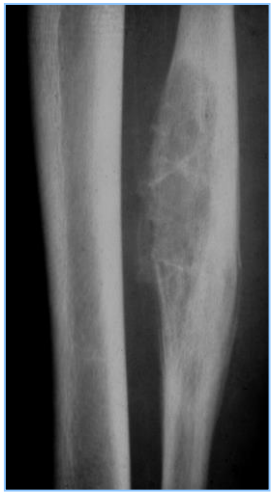
• Detachment of the periosteum (Codman triangle)

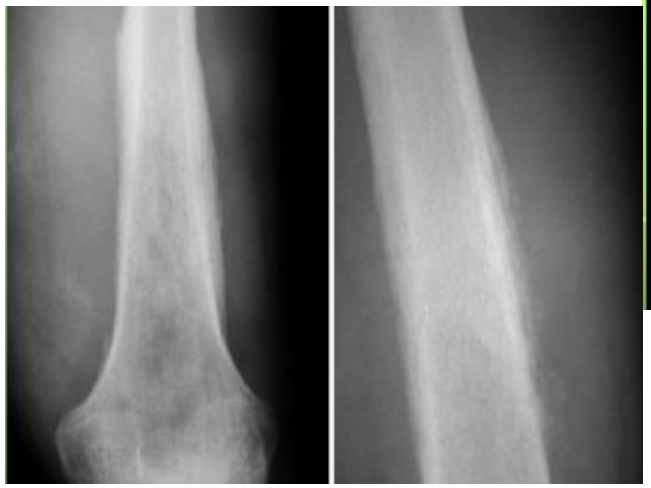
• Spiculae of calcification in soft tissues

• 10~15% pathologic fractures









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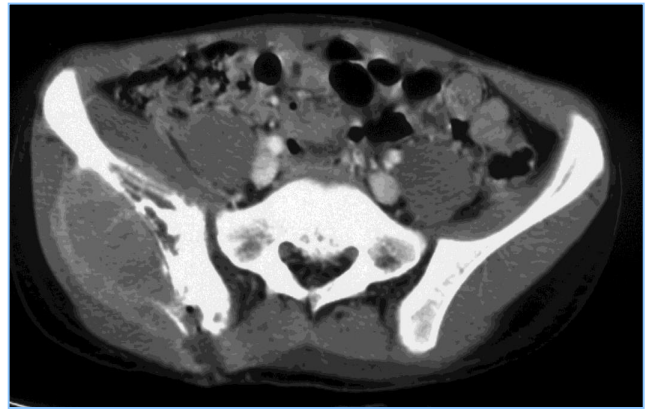
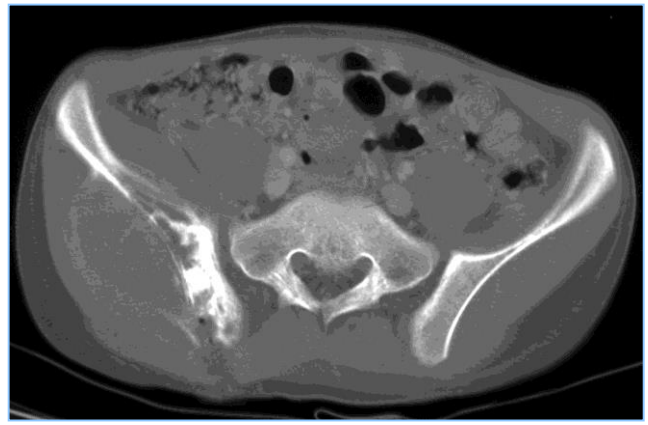
CT Scan

- A sclerotic appearance may be present, especially in flat bones

- Sclerosis is secondary to bony reaction, not tumor bone formation as is seen in osteosarcoma



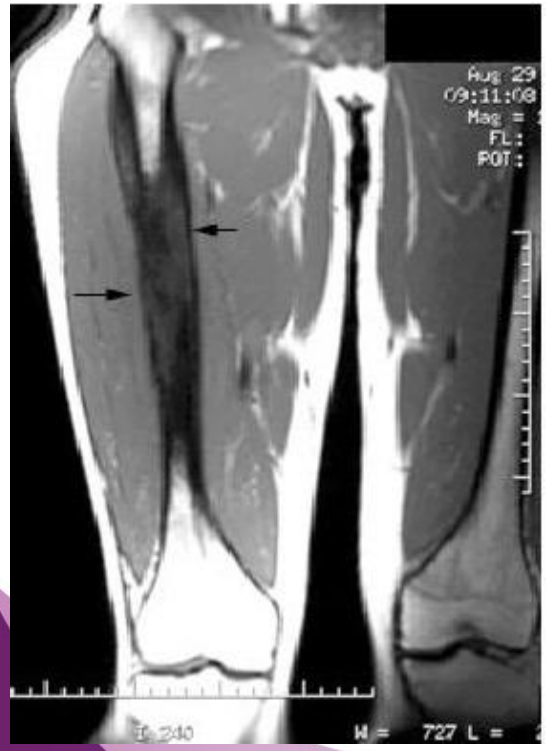


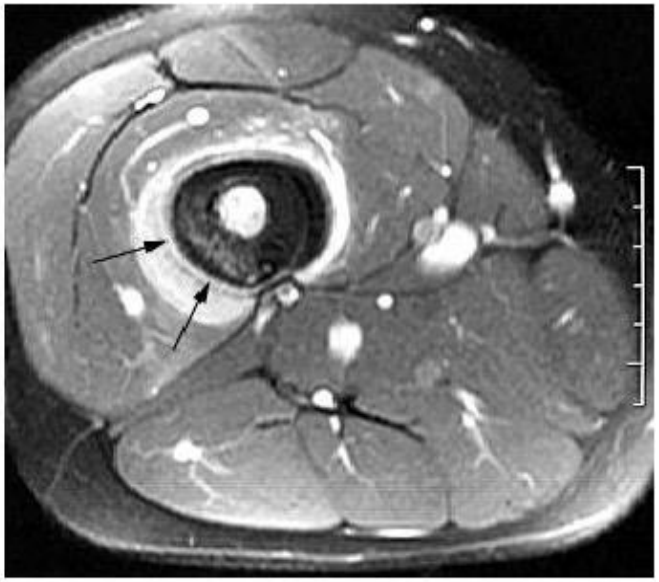
Diagnostic Work-Up

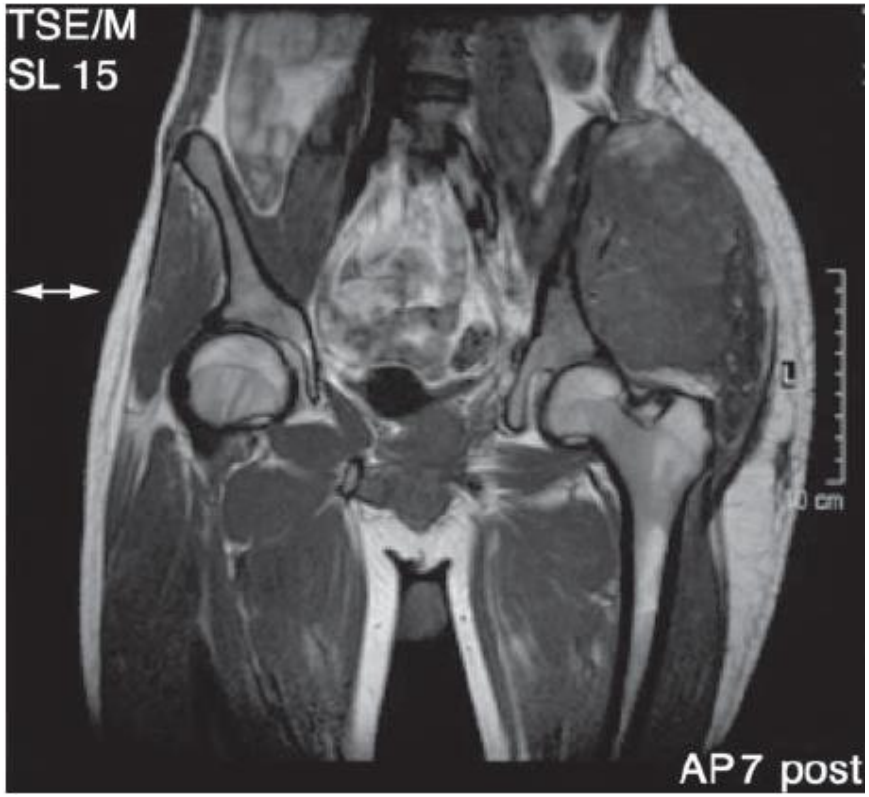
MRI

Precise definition of the local extent of disease:

- Intramedullary extension
- Relation of the lesion to adjacent blood vessels and nerves







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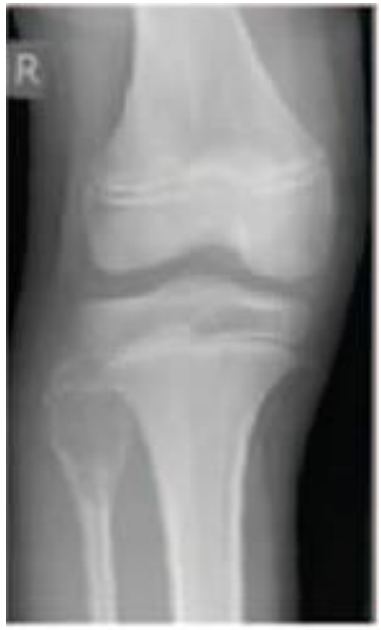
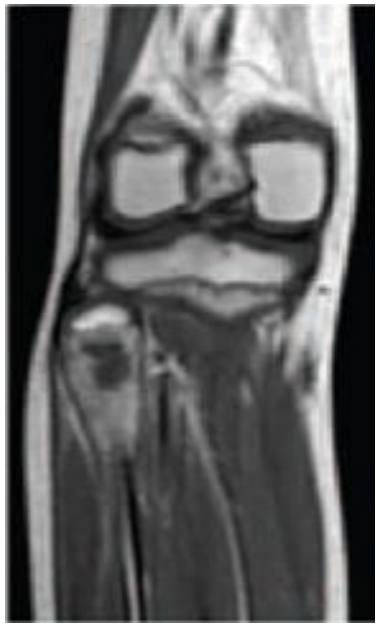
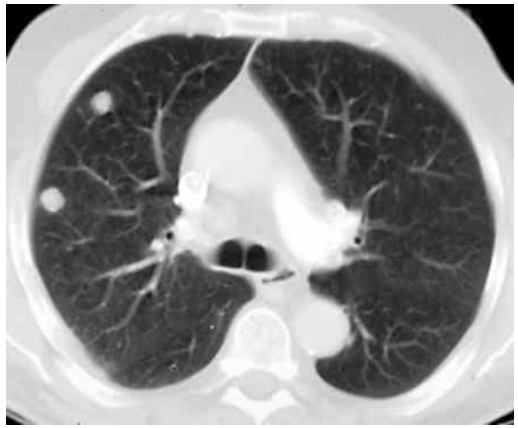
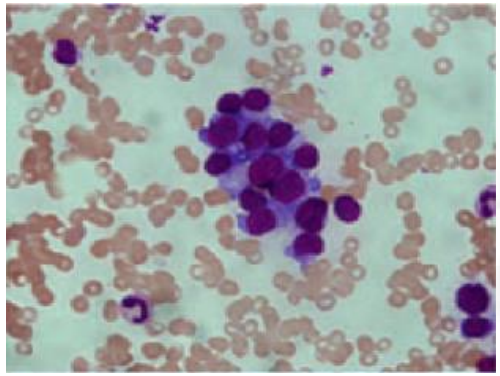
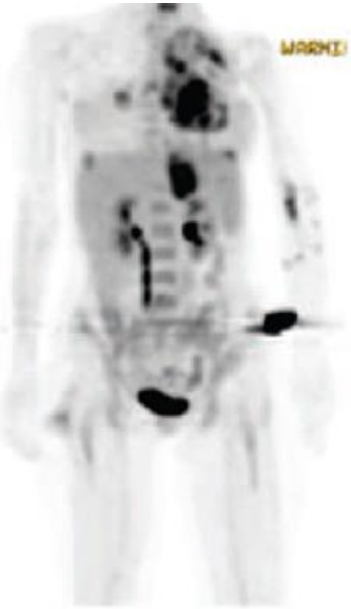
Staging and Prognostic factors

Ewing's Staging Workup

Investigation	Primary tumor	Metastases
X-ray: 2 planes, whole bone and adjacent joints	++	At suspicious sites
MRI and/or CT	++	At suspicious sites
Biopsy: histology and molecular biology	++	At suspicious sites
Bone marrow aspiration and biopsy		++
Thoracic CT		++
Whole-body 99m-technetium bone scan	++	++
FDG-PET	±	±

Note. ++ = mandatory; ± = indicated if available.

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Bone Cancer, Version 2.2017

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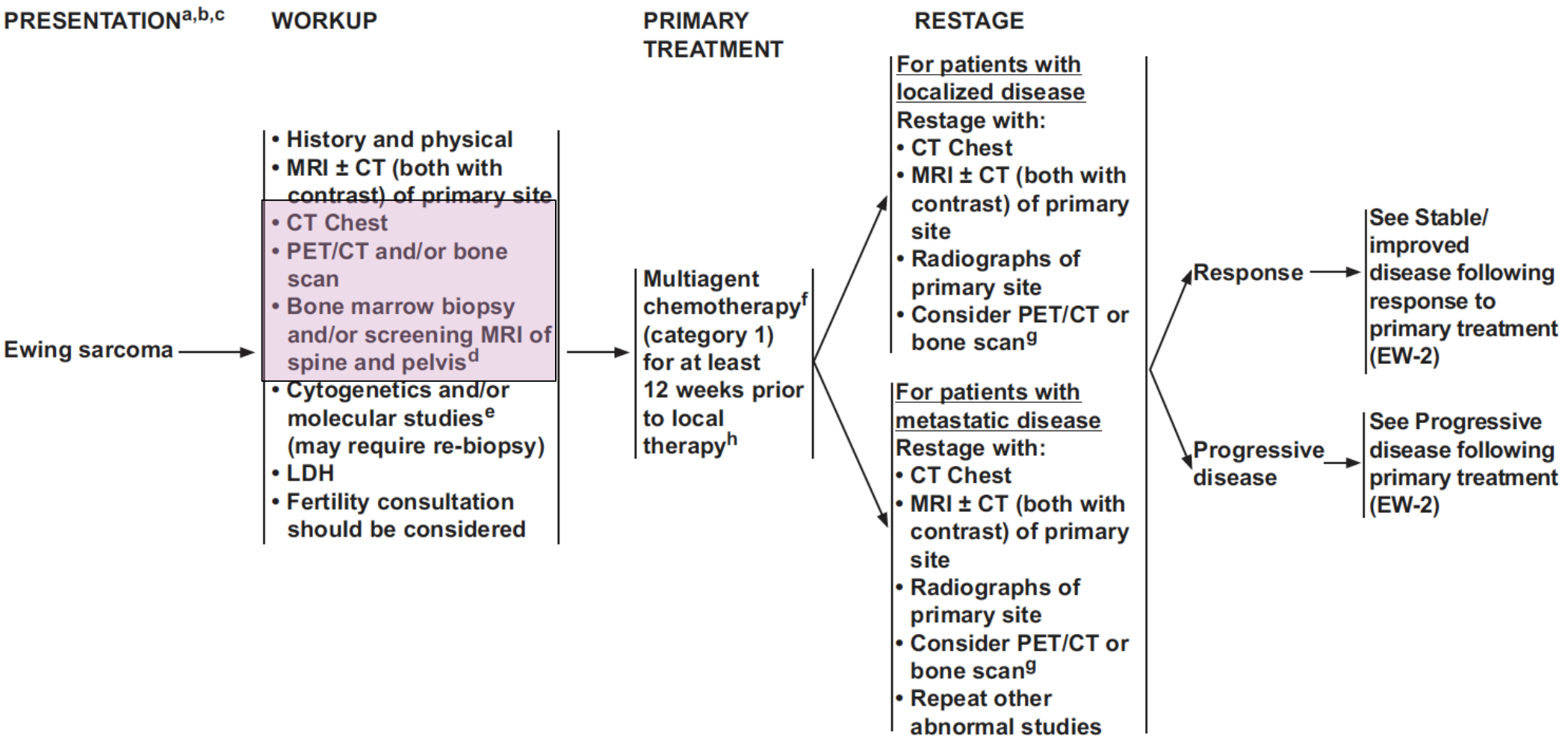

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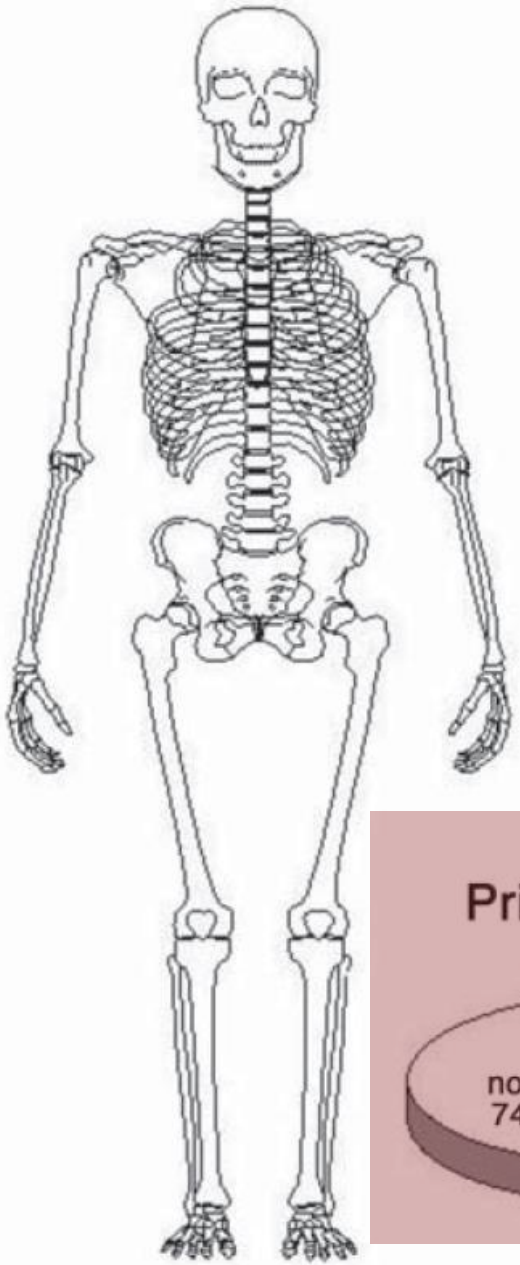
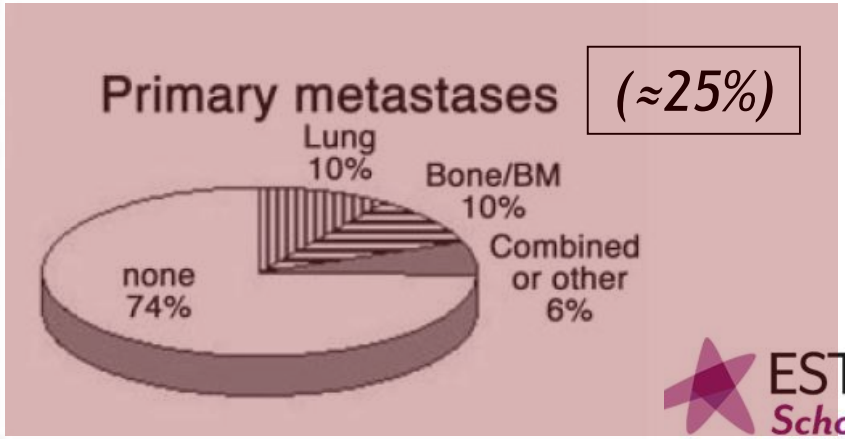
Localized vs Metastatic disease

Humerus	6.0%
Ulna	1.0%
Radius	1.0%
Hand	1.0%
Femur	20.0%
Fibula	8.0%
Tibia	10.0%
Foot	3.0%



Skull	2%
Chest wall:	16%
Clavicle	1.5%
Skapula	4.0%
Ribs	10.0%
Sternum	0.5%
Spine	6.0%
Pelvis	26.0%



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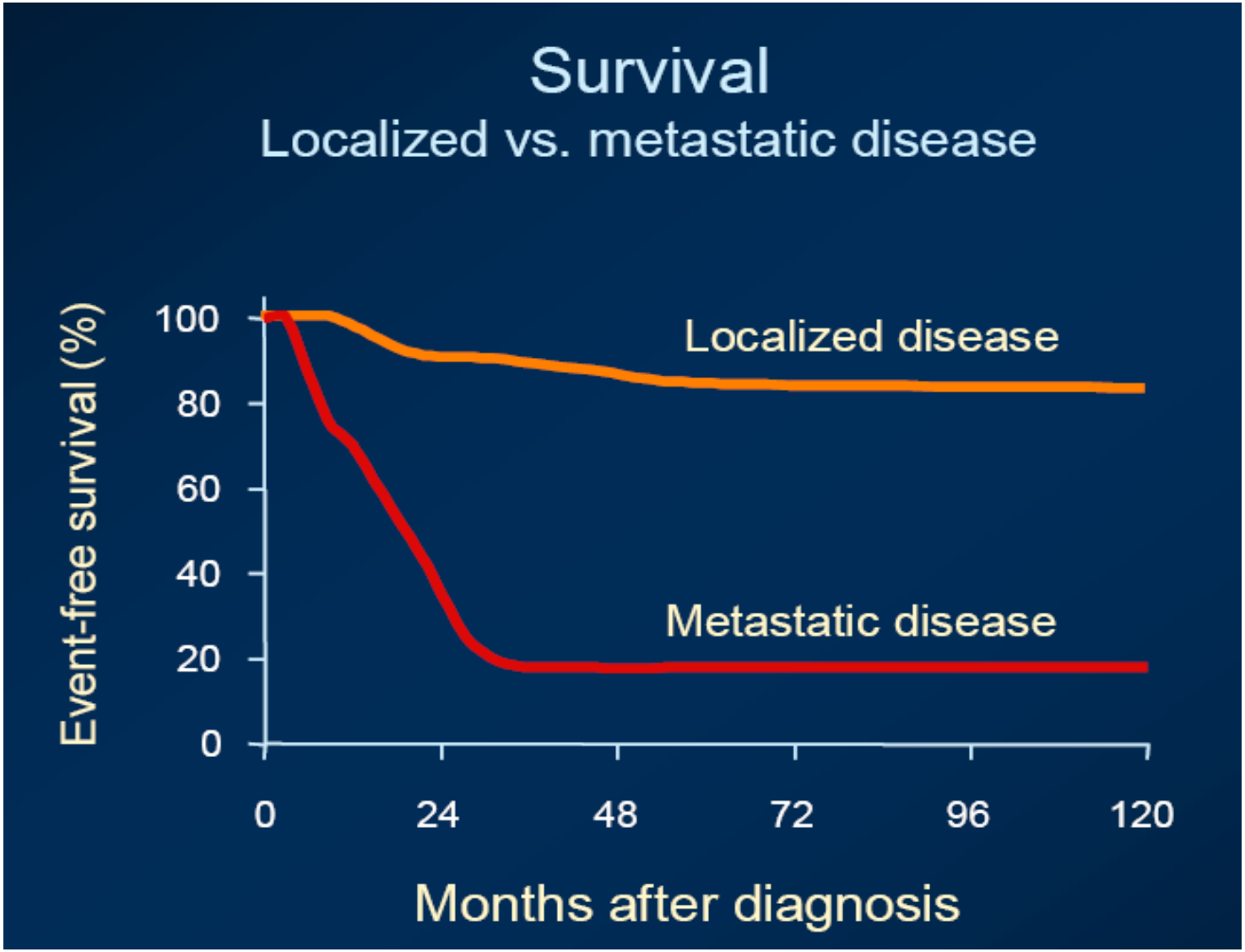
Localized vs Metastatic disease



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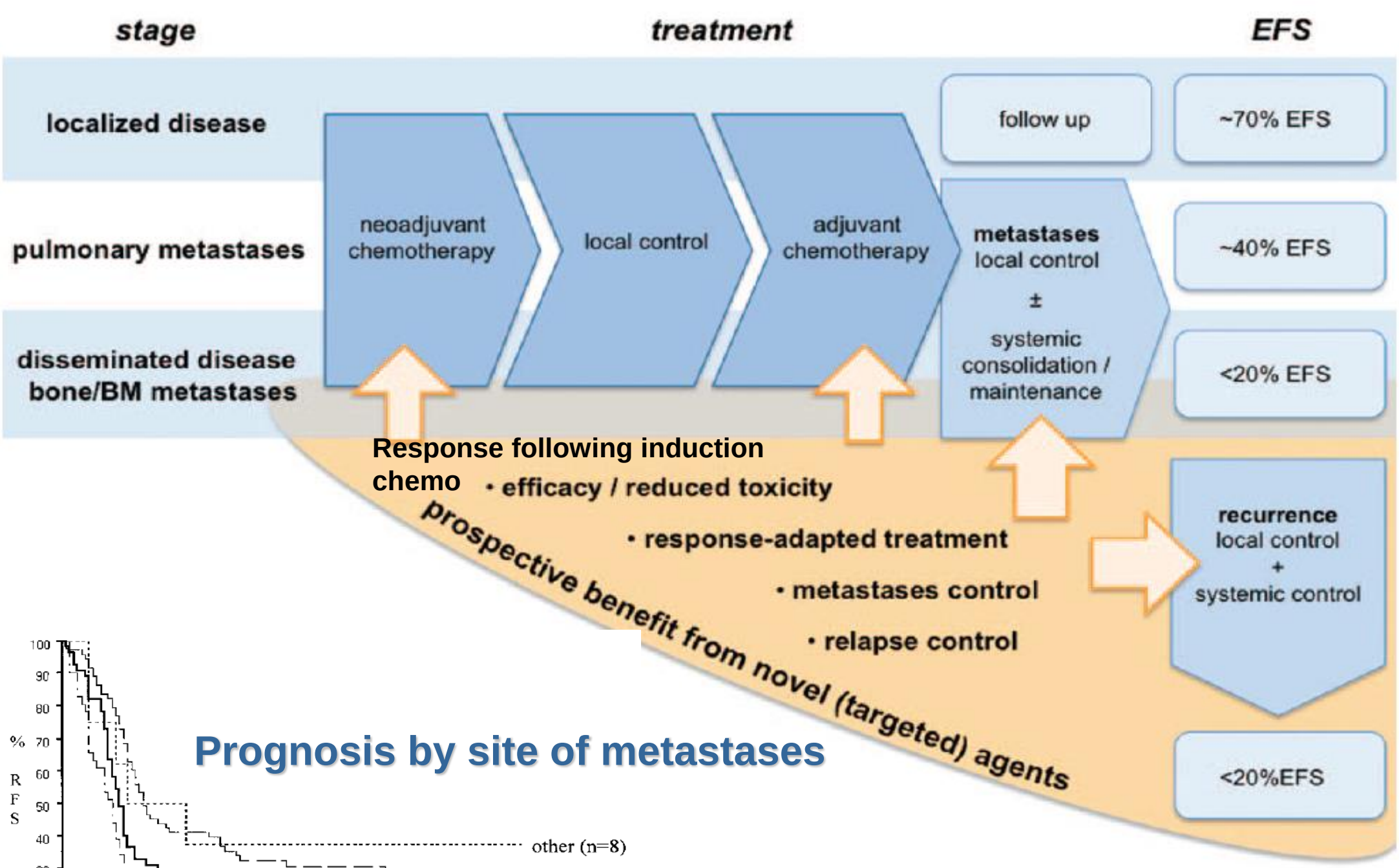

Prognosis by site of metastases

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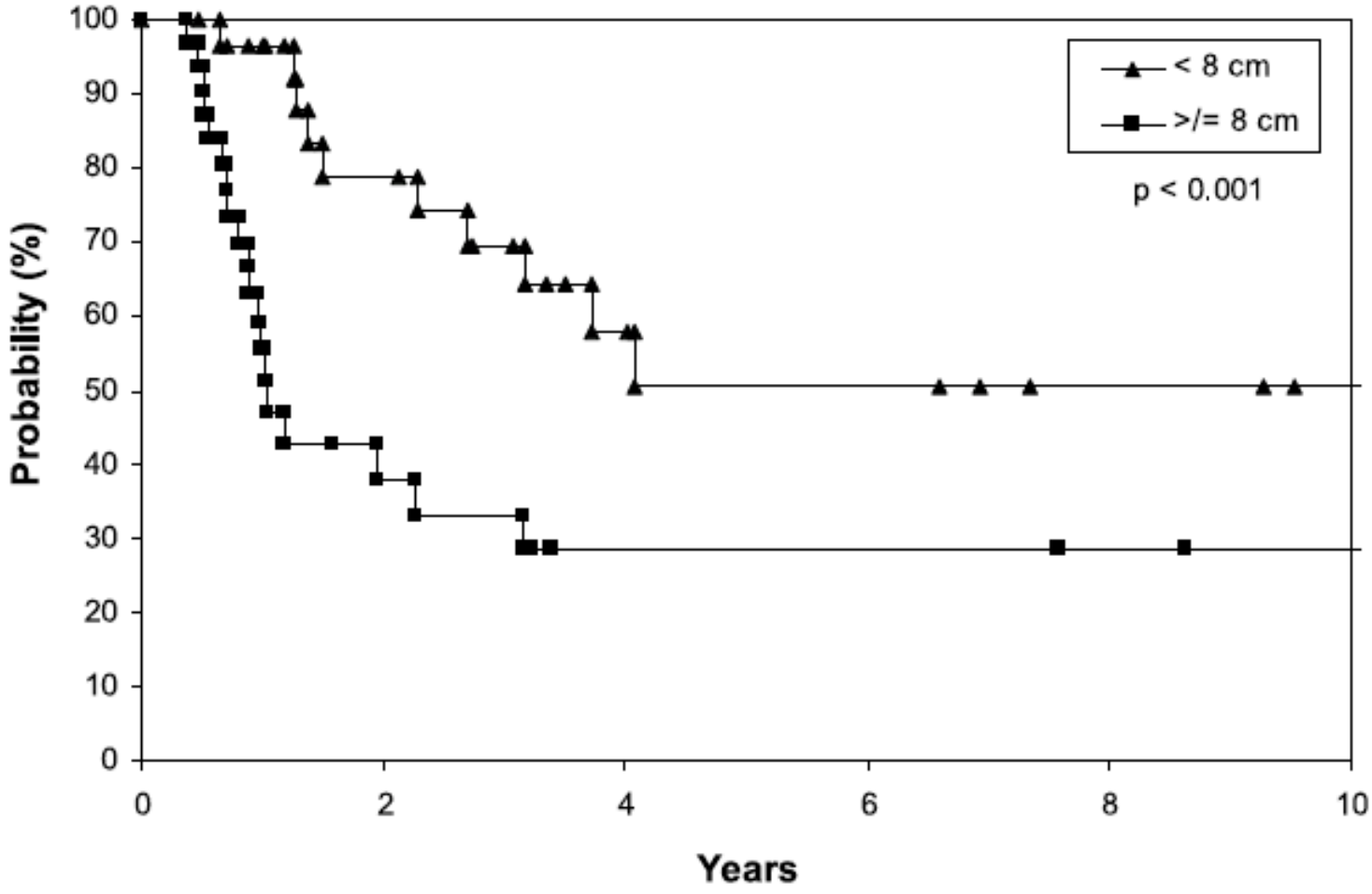
Prognosis by Tumor size (Tumor volume)



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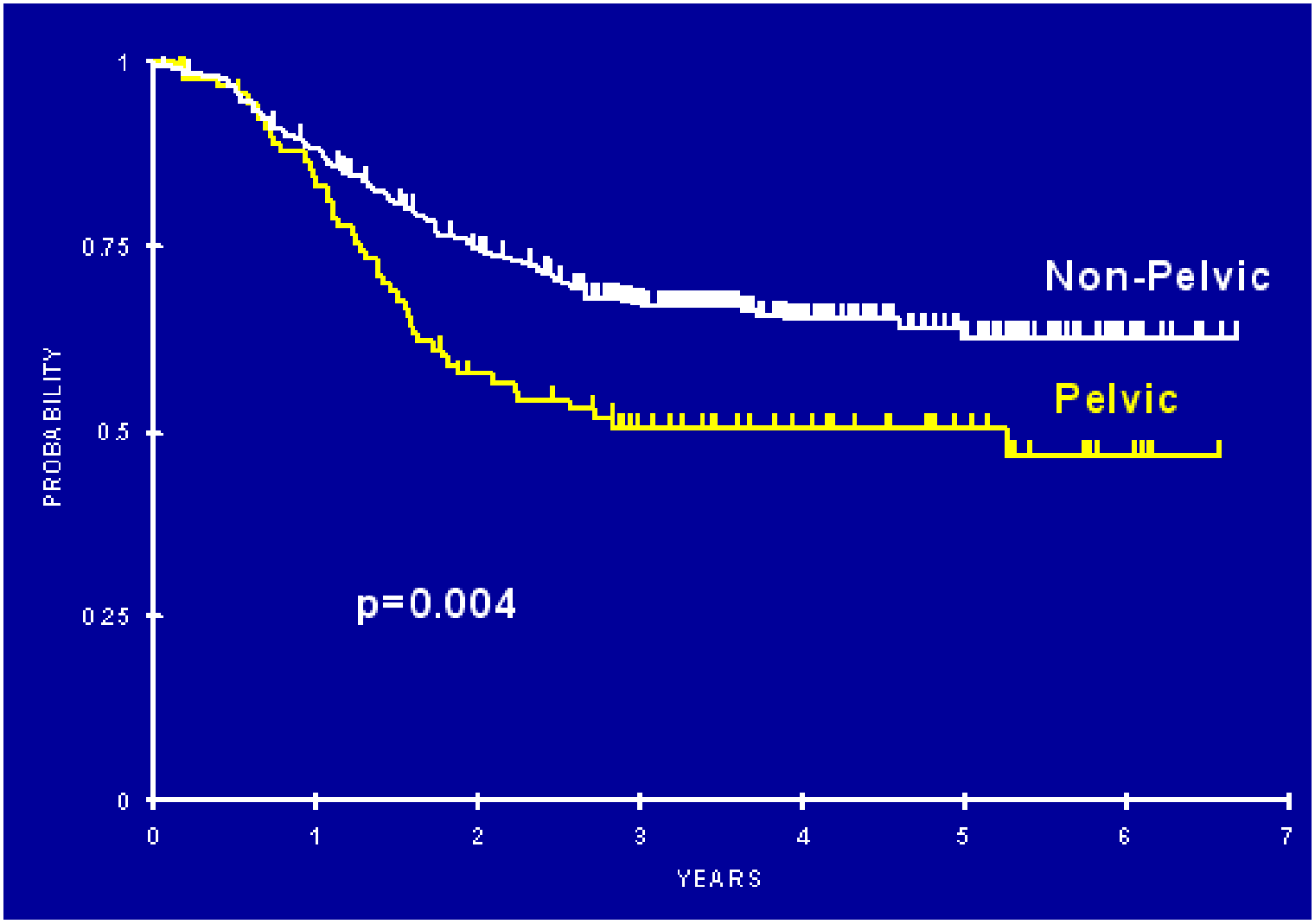
Prognosis by Tumor site

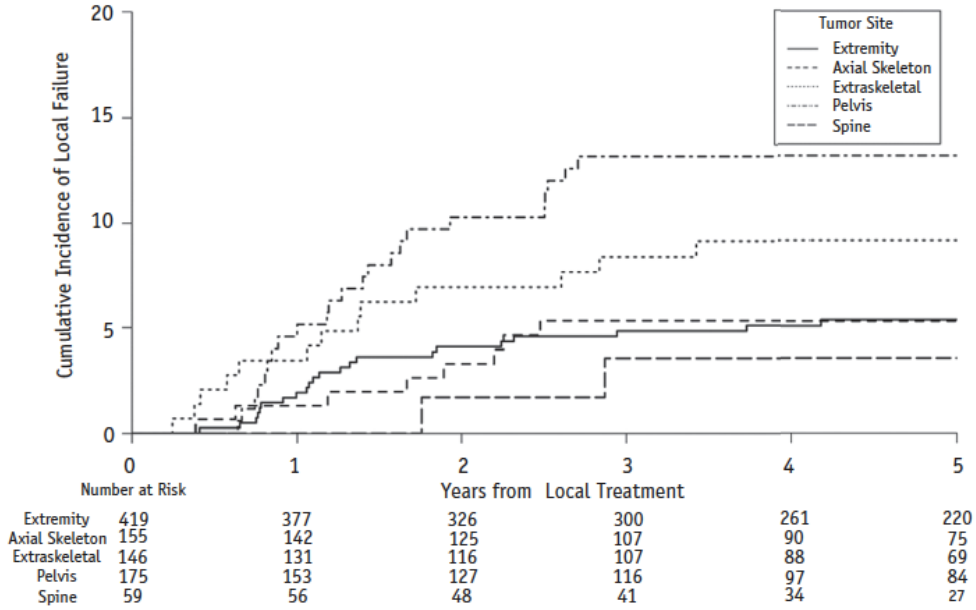


Identification of Patients With Localized Ewing Sarcoma at Higher Risk for Local Failure: A Report From the Children's Oncology Group

Safia K. Ahmed

Int J Radiation Oncol Biol Phys, Vol. 99, No. 5, pp. 1286–1294, 2017

b



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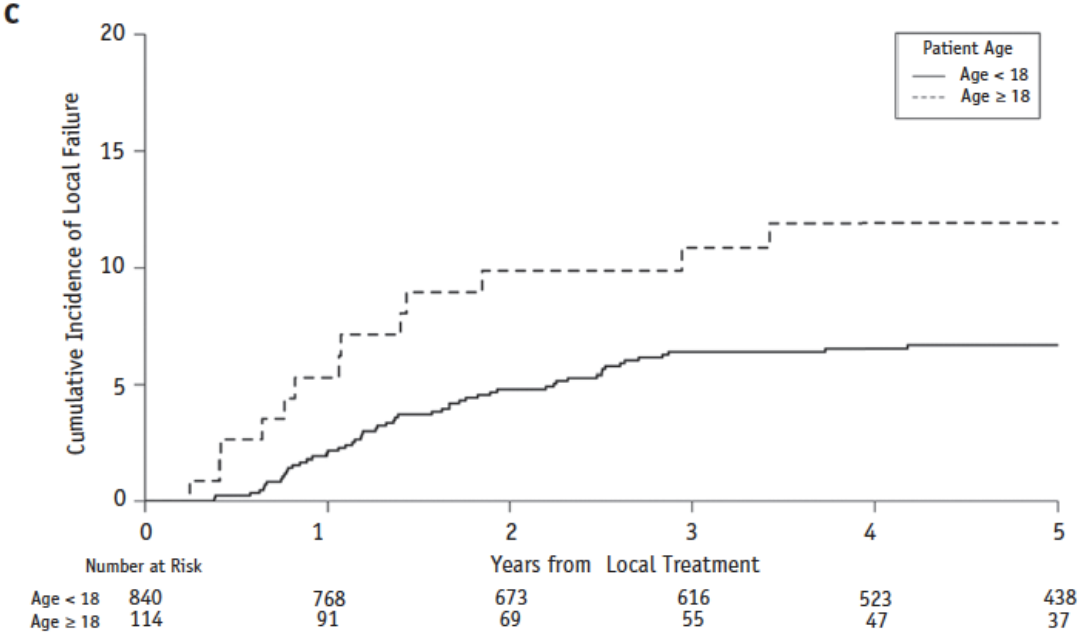

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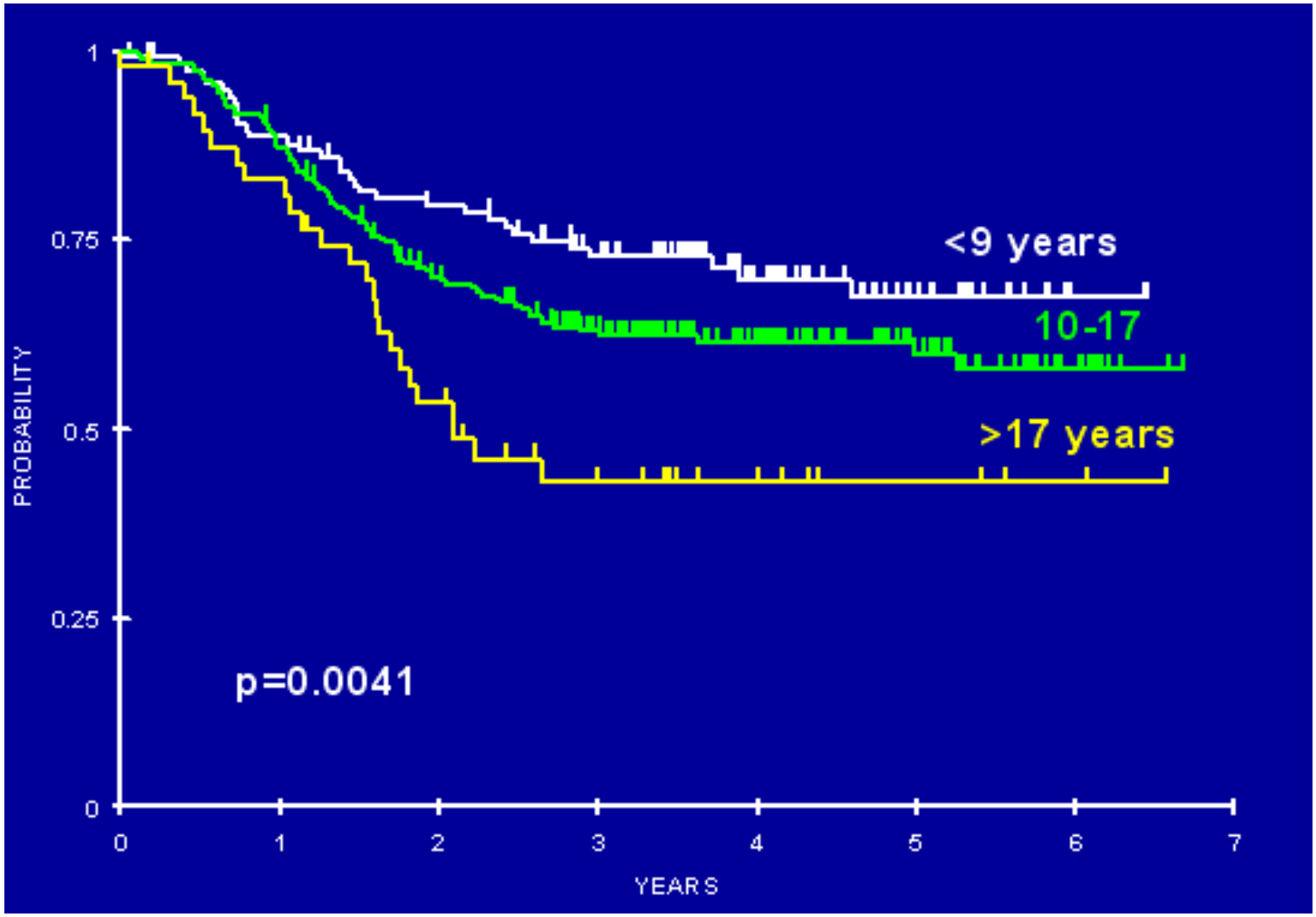
Prognosis by Age



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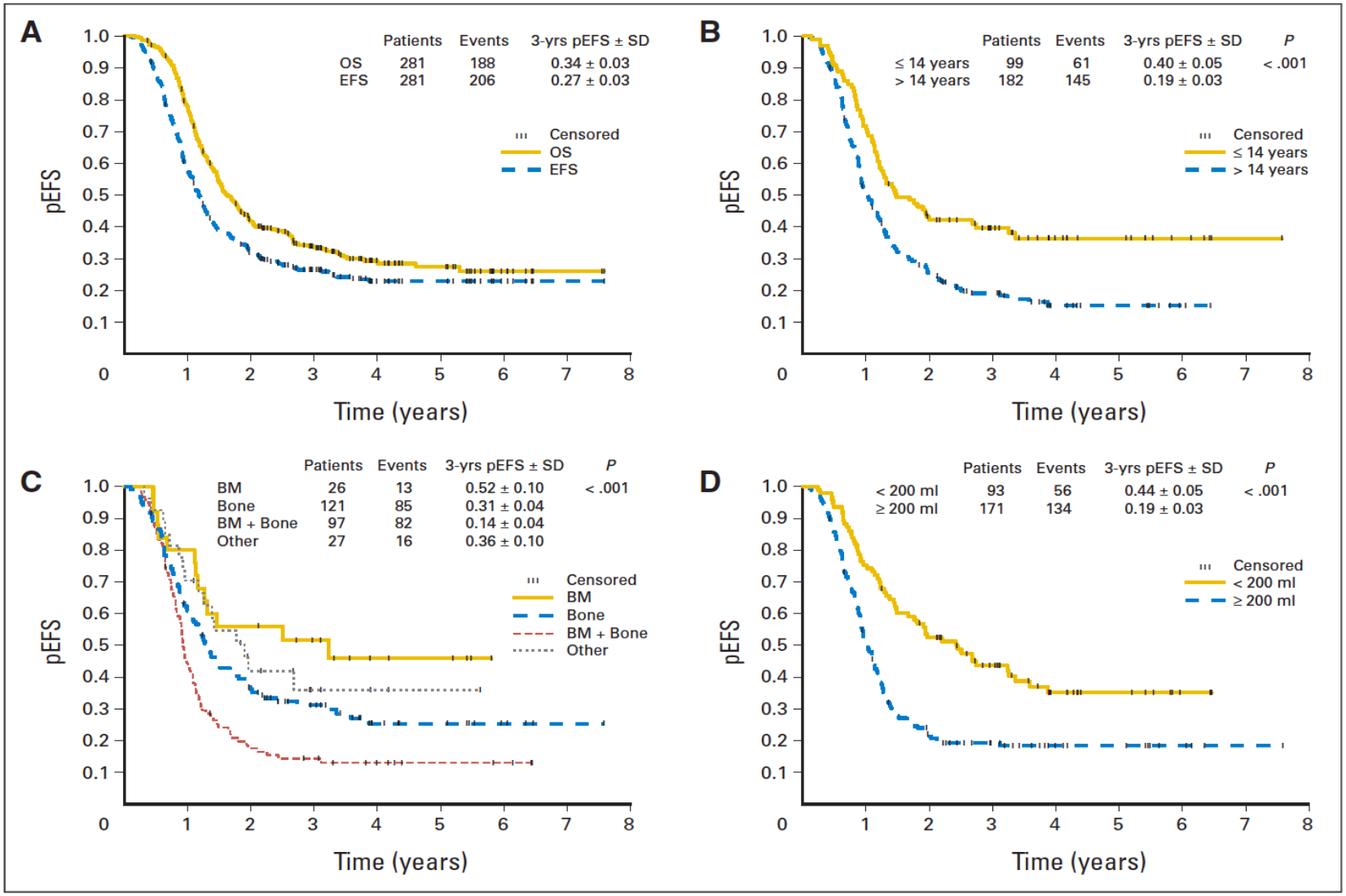
Primary Disseminated Multifocal Ewing Sarcoma: Results of the Euro-EWING 99 Trial

Ruth Ladenstein, Ulrike Pötschger, Marie Cécile Le Deley, Jeremy Whelan, Michael Paulussen, Odile Oberlin, Henk van den Berg, Uta Dirksen, Lars Hjorth, Jean Michon, Ian Lewis, Alan Craft, and Heribert Jürgens



J Clin Oncol 28:3284-3291. © 2010

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Original Article

Clinical Outcome of Children and Adults With Localized Ewing Sarcoma

Impact of Chemotherapy Dose and Timing of Local Therapy

Abha A. Gupta, MD[1]; Alberto Pappo, MD[2]; Natasha Saunders, MD[1]; Sevan Hopyan, MD[3]; Peter Ferguson, MD[4]; Jay Wunder, MD[3]; Brian O'Sullivan, MD[5]; Charles Catton, MD[5]; Mark Greenberg, MBBS[1]; and Martin Blackstein, MD[6]

-29 pediatric patients and 24 adult patients, treated between 1990 and 2005

-No difference in type of local therapy offered (surgery or radiotherapy, vs both)

Cancer July 1, 2010

Characteristic	Pediatric Patients No. (%) Median [Range]	Adult Patients No. (%) Median [Range]	P
Median age, y	13.4 [0.29–16.2]	26.1 [16.7-66.5]	
Site of primary tumor			
Lower extremity	13 (45)	9 (37.5)	
Upper extremity	1 (3.4)	1 (4.2)	
Axial			
Spine	5 (17.2)	3 (12.5)	
Rib	2 (6.9)	2 (8.3)	
Pelvis	2 (6.9)	6 (25)	
Other	4 (13.8)	1 (4.2)	
Soft tissue	2 (6.9)	2 (8.3)	
Local therapy			
Radiation	10 (35)	7 (29)	
Surgery	16 (55)	11 (46)	
Surgery+radiation	3 (10)	6 (25)	
Chemotherapy			
Median no. of cycles	16 [10-17]	10 [6-10]	
Total dose of doxorubicin, mg/m^2	370 [111-490]	375 [295-375]	.14
Dose intensity of doxorubicin, mg/m^2/wk	9.77 [5.3-12.1]	12.0 [10.75-15.2]	.0001
Total dose of ifosfamide, g/m^2	69.3 [14.3-72.2]	44.8 [8.8-45.1]	.0001
Dose intensity of Ifosfamide, mg/m^2/wk	27.2 [6.58-39.0]	26.7 [5.41-46.8]	NS
Total dose of cyclophosphamide, g/m^2	10.5 [2.7-17.3]	6 [4.7-6]	.0001
Dose intensity of cyclophosphamide, mg/m^2/wk	3.79 [1.97-11.24]	4.0 [3.5 – 5.75]	NS
Mo to local treatment	3.38 [0.85-14.9]	7.63 [3.68-20.9]	.0003

Table 2. Event-Free and Overall Survival of Pediatric and Adult Patients

		3-Year EFS	P^a	3-Year OS	P^a
Localized	Adult	43±13		59±12	
	Pediatric	70±9	.10	81±7.7	.02
Localized nonpelvic	Adult	48±17		67±13	
	Pediatric	75±8.7	.18	88±6.5	.04

EFS indicates event-free survival; OS, overall survival.
[a] Comparing pediatric versus adult patients.

Adults with localized EWS have an inferior outcome compared with pediatric patients

Table 3. Univariate Analysis of Prognostic Features for EFS in Pediatric and Adult Patients

Feature	HR	95% CI	P
Pelvic	3.95	1.45-10.8	.007
Mo to local treatment	1.13	1.04–1.23	.003
Total dose of cyclophosphamide	0.77	0.61-0.97	.03
Total dose of ifosfamide	0.98	0.95-1.0	.077
Dose intensity of doxorubicin	1.30	0.978-1.73	.071

EFS indicates event-free survival; HR, hazard ratio; 95% CI, 95% confidence interval.

Table 4. Multivariate Analysis of Prognostic Features for EFS in Pediatric and Adult Patients

Parameter	HR	95% CI	P
Pelvic primary tumor	4.26	1.28-14.1	.018
Mo to local treatment	1.19	1.1-1.31	.002

EFS indicates event-free survival; HR, hazard ratio; 95% CI, 95% confidence interval.

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A Comparison of Pediatric vs. Adult Patients with the Ewing Sarcoma Family of Tumors

Vivek Verma[1] *University of Nebraska Medical Center, Omaha,*

1983-2013 database

N=1870 (960 pediatric < 18 years, 894 adults > 18years)
SEER: 68% versus 57% locoregional
26% versus 33% distant

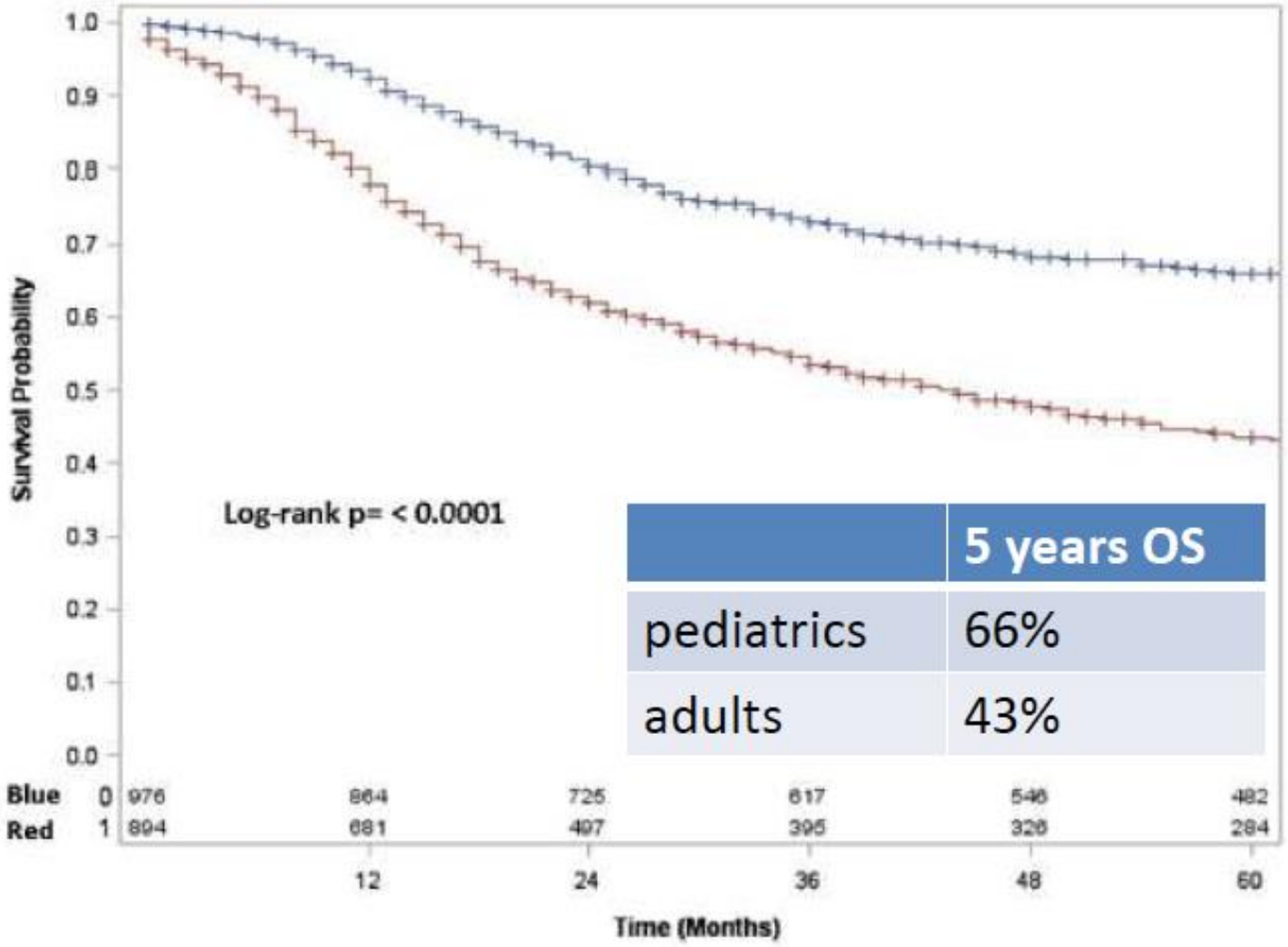
Results: median survival 103 months (95% CI 78-145)
5 y OS: 55%
10 y OS: 49%

median CSS 143 months (95% CI 99-258)
5 y CSS: 57%
10 y CSS: 51%

frontiers in Oncology 08 May 2017

A Comparison of Pediatric vs. Adult Patients with the Ewing Sarcoma Family of Tumors

Vivek Verma[1]; *University of Nebraska Medical Center, Omaha,*



N=1870

Pediatric (0) < 18 y

Adult (1) >18 y

	5 years OS
pediatrics	66%
adults	43%

in Oncology : 08 May 2017

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Clinical outcome of children and adults with Ewing Sarcoma

- Adults affected with ES have worse outcome compared to pediatric patients:
  - ✓ Lower doses of alkylating agents
  - ✓ Timing of local therapy
  - ✓ Increased prevalence of pelvic ES in adult patients

Clinical outcome of children and adults with Ewing Sarcoma

- Children:
  - ✓ Clinical trial-based protocols
- Adults:
  - ✓ Treatment is often institution-specific

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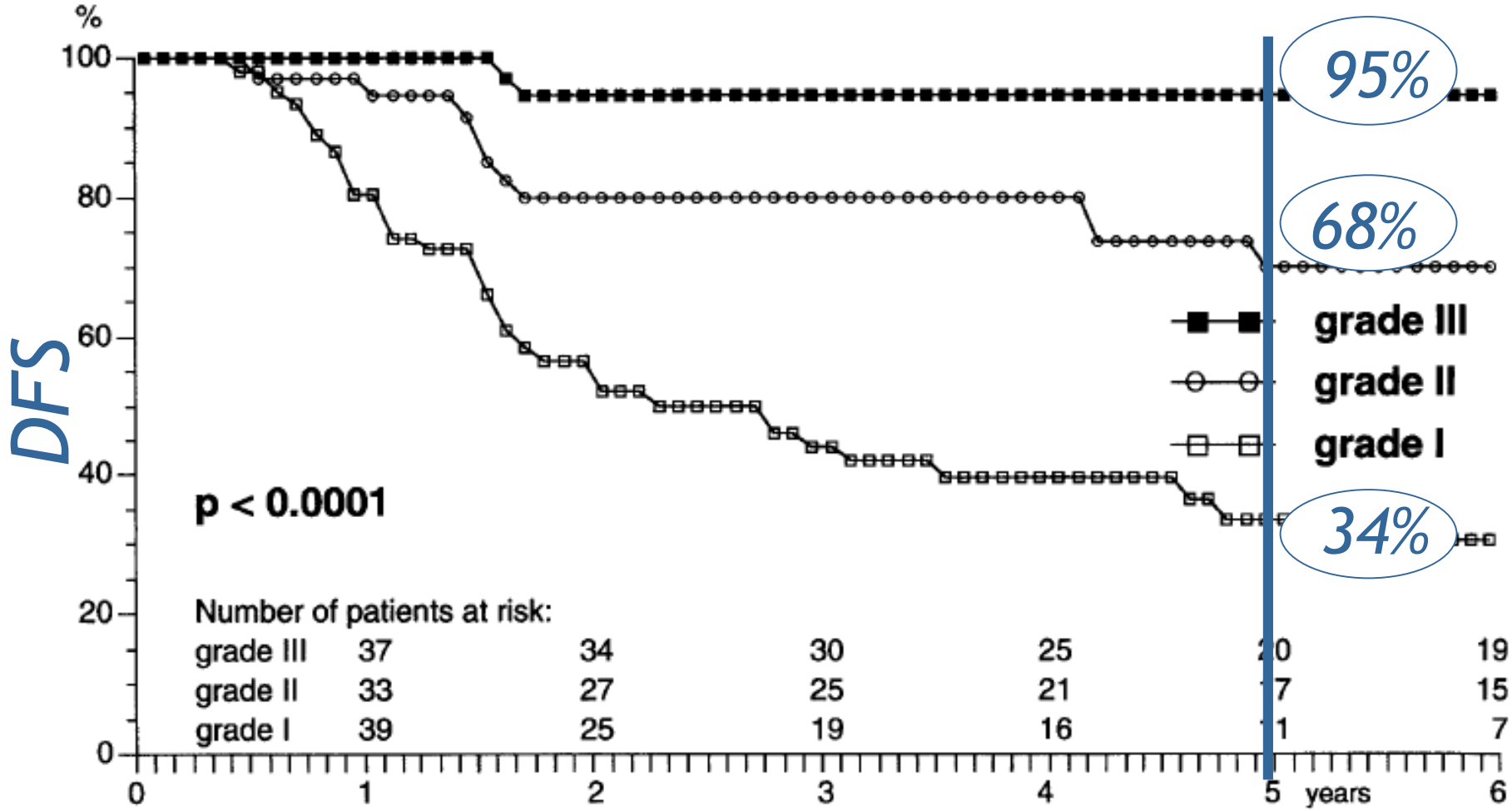
Chemotherapy-Induced Tumor Necrosis as a Prognostic Factor in Localized Ewing's Sarcoma of the Extremities

By P. Picci, B.T. Rougraff, G. Bacci, J.R. Neff, L. Sangiorgi, A. Cazzola, N. Baldini, S. Ferrari, M. Mercuri, P. Ruggieri, P. Caldora, M.S. Benassi, N. Fabbri, C. Monti, and M. Campanacci

JCO 1997



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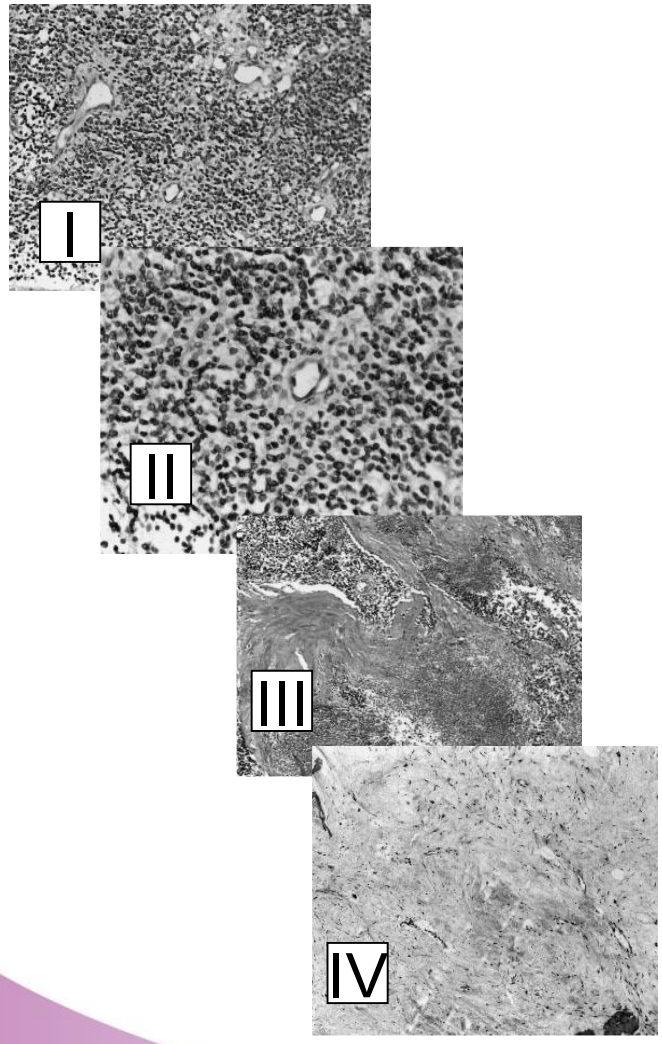
The Histological Response to Chemotherapy as a Predictor of the Oncological Outcome of Operative Treatment of Ewing Sarcoma*

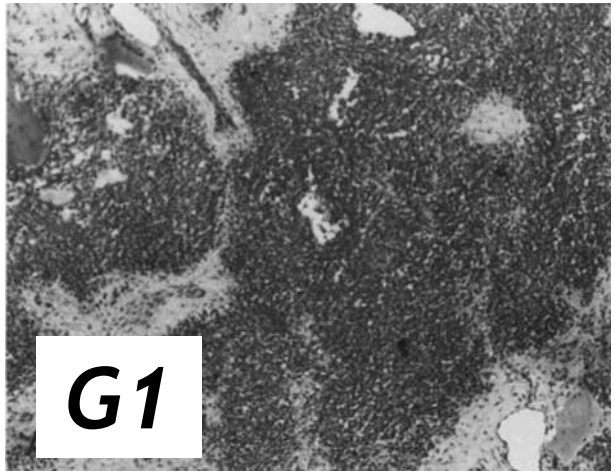
BY JAY S. WUNDER, M.D.†, GABE PAULIAN, B.SC.‡, ANDREW G. HUVOS, M.D.‡, GLENN HELLER, PH.D.‡, PAUL A. MEYERS, M.D.‡, AND JOHN H. HEALEY, M.D.‡, NEW YORK, N.Y.

JBJS 1998

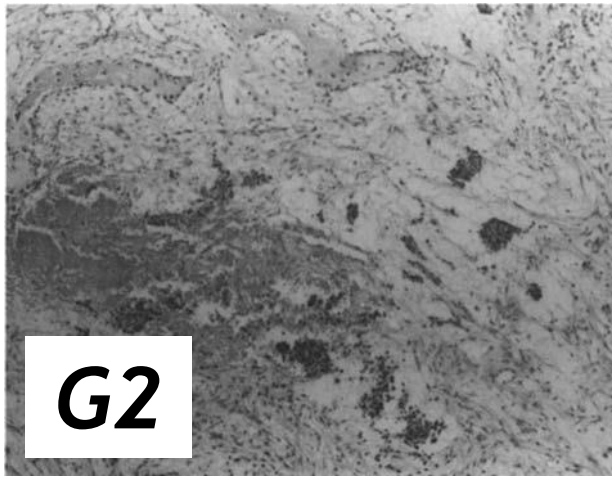


Grade	Percentage Necrosis	Histologic Appearance
I	0-49	Little or no necrosis
II	50-89	Areas of acellular tumor osteoid and/or fibrotic material attributable to the effect of chemotherapy, with other areas of viable tumor
III	90-99	Predominant areas of acellular tumor osteoid and/or fibrotic material attributable to the effect of chemotherapy, with only scattered foci of viable tumor cells
IV	100	No pathologic evidence of viable tumor within the specimen

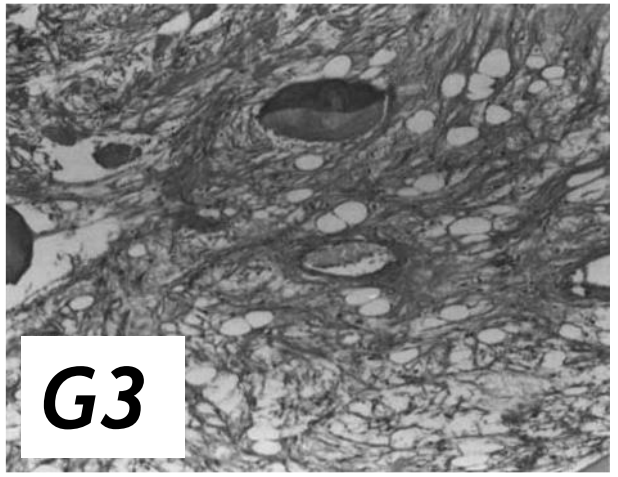
Chemotherapy-induced Tumor Necrosis grade (Picci score):



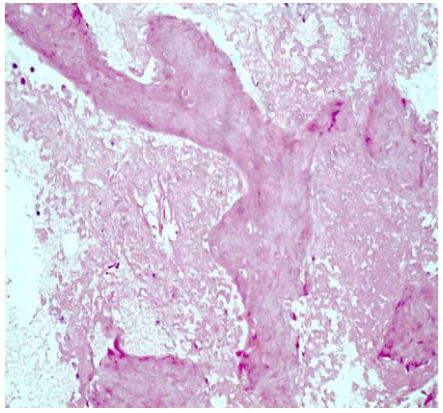
Macroscopic foci of viable tumor cells (>10 x field)



Isolated microscopic foci of viable tumor cells (<10 x field)



No viable tumor



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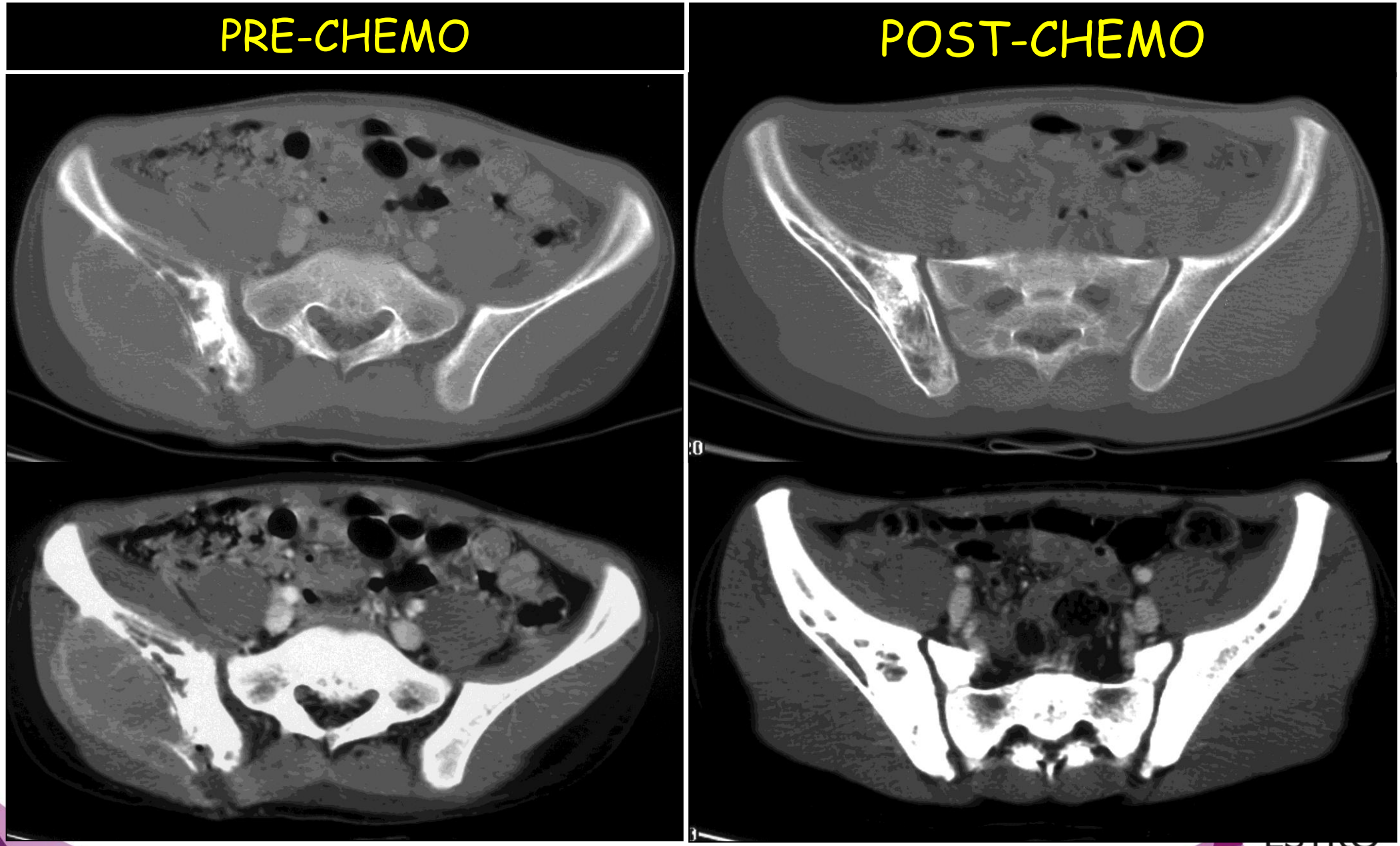
Non-pathologic evaluation of response to chemotherapy

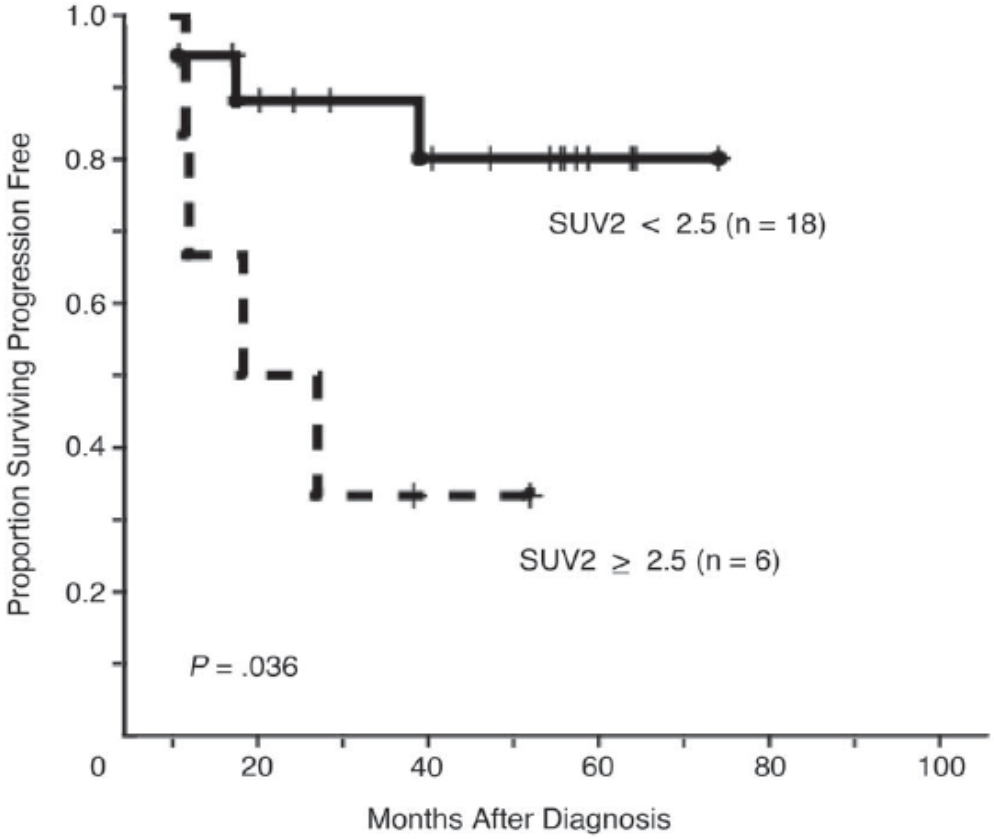


[^{18}F]Fluorodeoxyglucose Positron Emission Tomography Predicts Outcome for Ewing Sarcoma Family of Tumors

Table 2. SUV1, SUV2, SUV2:1, and Percent Necrosis by Tumor Histology

Clinical Feature		No. of Patients
Prechemotherapy		34
SUV1		
Mean	7.9	
Range	2.3-32.8	
Postchemotherapy		36
SUV2		
Mean	2.1	
Range	0-4.3	
Reduction in SUV		34
SUV2:1		
Mean	0.37	
Range	0.00-1.00	
Histologic evaluation		34
Favorable (≤ 10% viable tumor)		25
Unfavorable (> 10% viable tumor)		9

Abbreviations: SUV1, maximum standard uptake value prior to chemotherapy; SUV2, maximum standard uptake value after chemotherapy; SUV2:1, ratio of SUV2 to SUV1.



SUV2 is predictive of PFS

FDG PET imaging correlates with histologic response to neoadjuvant CT

D. S. Hawkins et Al, J Clin Oncol 23:8828-8834. 2005

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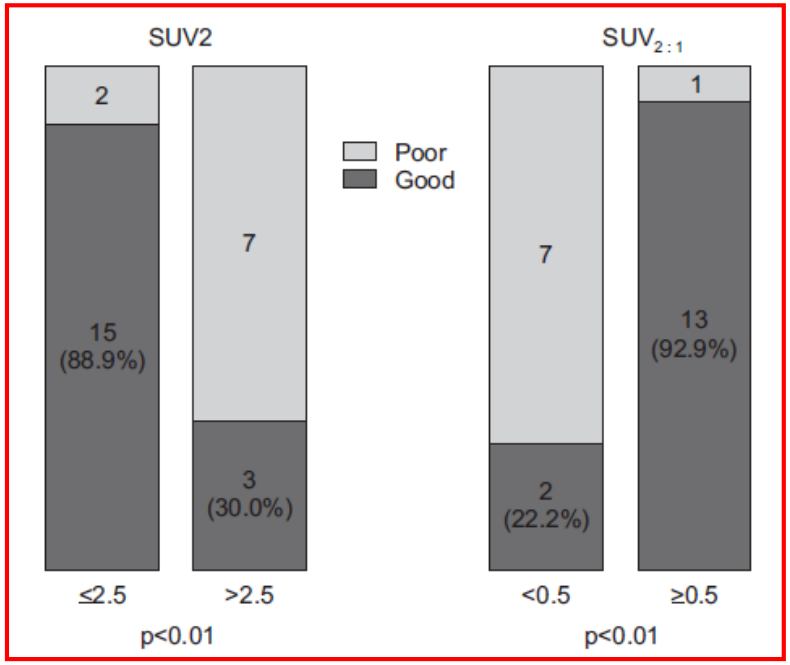
Cancer Res Treat. 2011;43(3):170-175

Assessment of Chemotherapy Response Using FDG-PET in Pediatric Bone Tumors: A Single Institution Experience

Dong Hwan Kim, MD
Seung Yeon Kim, MD
Hyeon Jeong Lee, MD
Bong Sup Song, MD
Dong Ho Kim, MD
Joong Bum Cho, MD
Jung Sub Lim, MD
Jun Ah Lee, MD

	Histologic response	FDG-PET findings					
		SUV1	p-value	SUV2	p-value	$SUV_{2:1}$	p-value
Overall	Good	7.91±6.41 (n=15)	0.95	2.04±1.01 (n=18)	0.04	0.69±0.20 (n=15)	<0.01
	Poor	8.10±7.50 (n=8)		6.36±5.13 (n=9)		0.13±0.48 (n=8)	
OS	Good	11.58±9.72 (n=5)	0.48	2.53±1.06 (n=8)	0.06	0.69±0.14 (n=5)	0.03
	Poor	8.10±7.50 (n=8)		6.36±5.13 (n=9)		0.13±0.48 (n=8)	
ESFT	Good	6.07±3.28 (n=10)	–	1.66±0.82 (n=10)	–	0.69±0.23 (n=10)	–
	Poor	–		–		–	

Values are presented as the mean±standard deviation. FDG-PET, [F-18]-fluorodeoxy-D-glucose-positron emission tomography; SUV, standard uptake value; $SUV_{2:1}$, decreased SUV ratio, i.e., (SUV1-SUV2)/SUV1; OS, osteosarcoma; ESFT, Ewing sarcoma family of tumors.



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Treatment

Cure from Ewing's sarcoma can only be achieved with both chemotherapy and local control

Survival

- Patients with localized disease:

  5-year EFS: 60-70%

- Patients with metastatic disease:

  5-year EFS: 20%

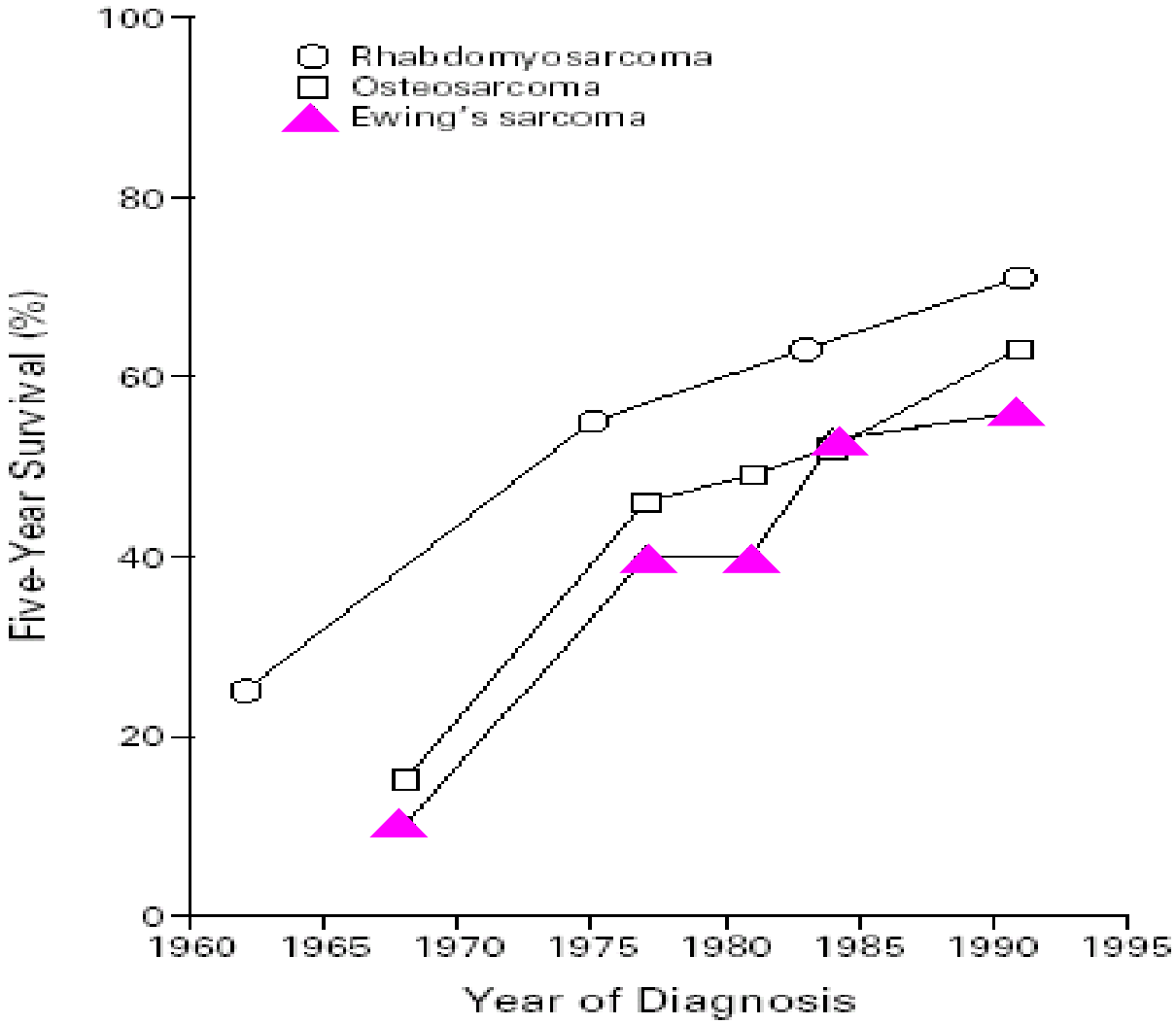
Treatment Principles

- Treatment paradigm
  - Upfront Chemo (CTX) → Local Therapy → Consolidation Chemo (CTX)

Treatment

- ✓ Before the era of chemotherapy, fewer than 10% of patients with ES survived, despite the well known radiosensitivity of this tumor
- ✓ Patients commonly died of metastases within 2 years, indicating the need for systemic treatment

Five Year Survival Rates Among Children with Sarcomas: Improvement Over Time



From: Arndt C and Crist W. N Engl J Med 341:342-352, 1999

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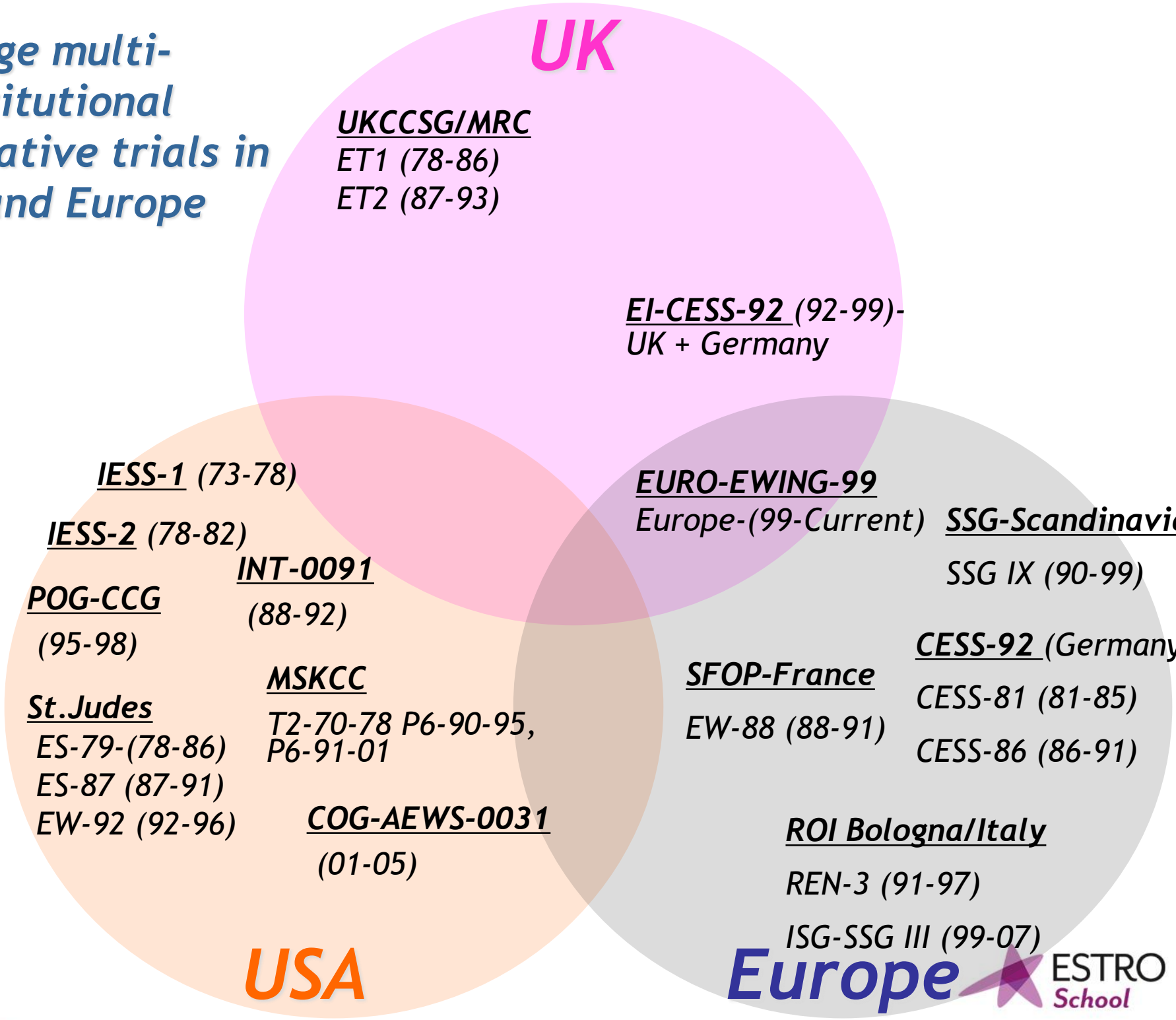
Large multi-institutional collaborative trials in USA and Europe



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Clinical studies in localized Ewing's sarcoma

St. Jude studies	Tumor size as prognostic factor (< or > 8 cm) (ES-79), with less prognostic relevance when more intensive treatment is used (EW-92)
UKCCSG/MRC studies	Tumor site as the most important prognostic factor (extremity vs axial vs pelvis) (ET-1)
	Importance of high dose alkylating agents (ET-2)
CESS studies	Tumor volume (< or > 100 ml) and histological response (CESS-81) as prognostic factors
	Tumor volume (< or > 200 ml) and histologic response as prognostic factors (CESS-86); intensive treatment with Ifo for high risk pts
EICESS studies	Type of local therapy, stage, histologic response

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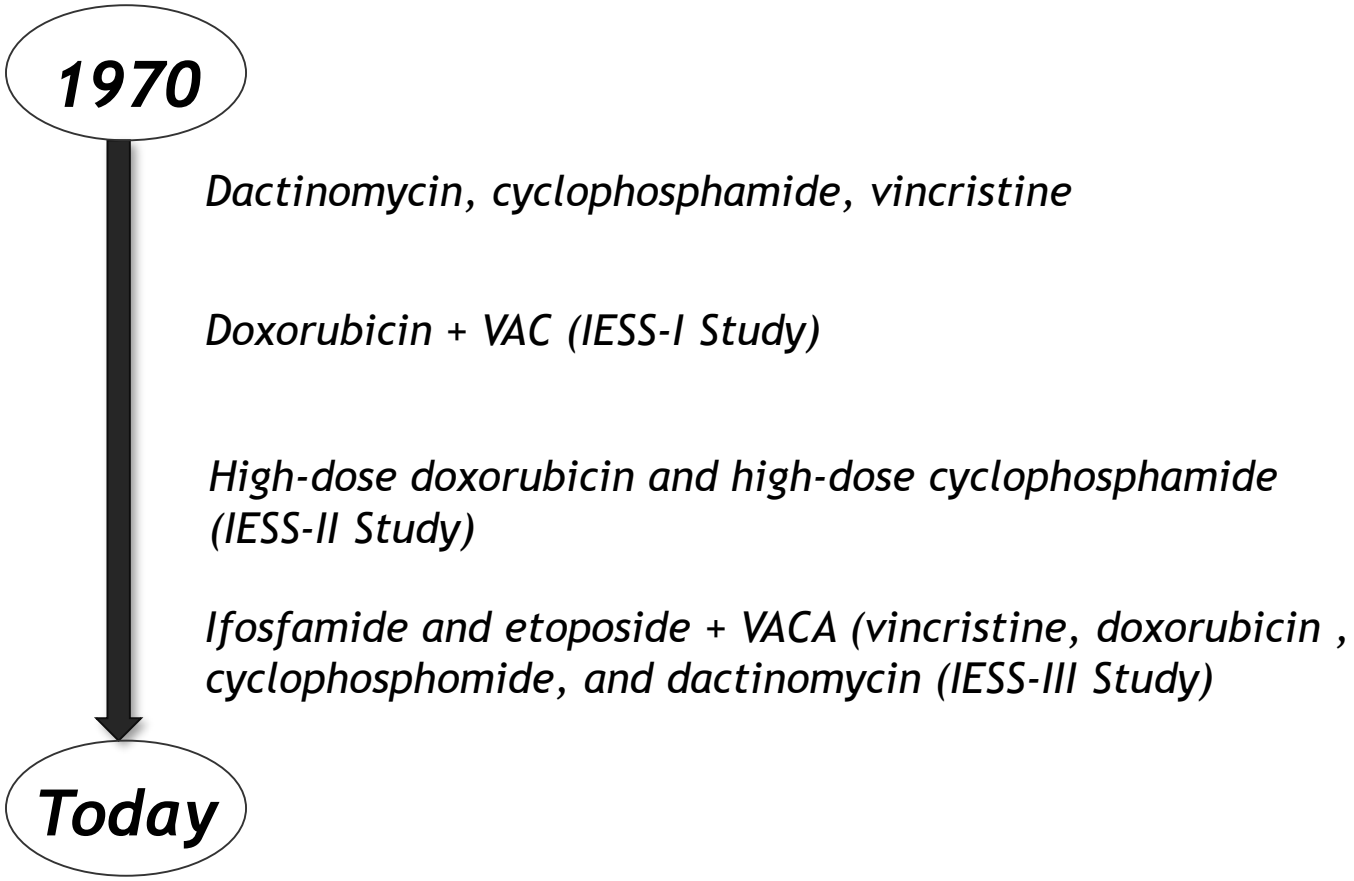
Timeline of major changes in CT



The standard of care today is a 5-6 drugs regimen of vincristine, doxorubicin, cyclophosphamide, actinomycin-D, ifosfamide, and etoposide

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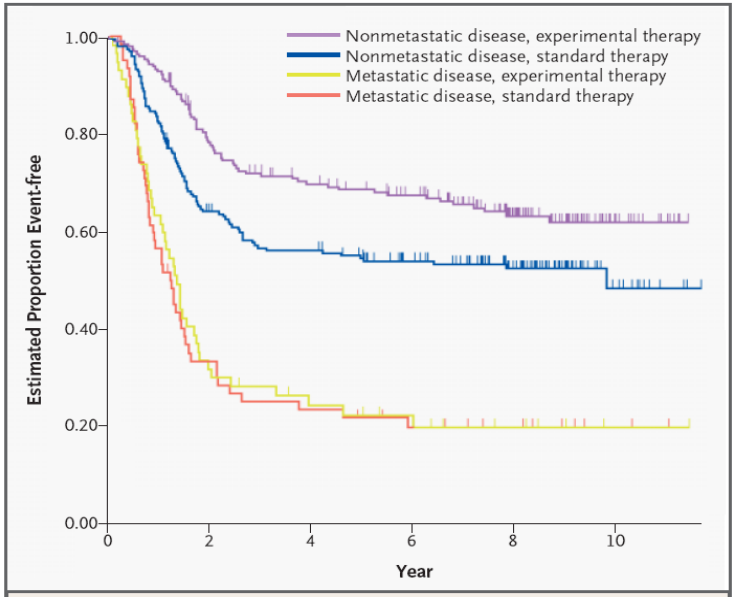
The NEW ENGLAND JOURNAL of MEDICINE

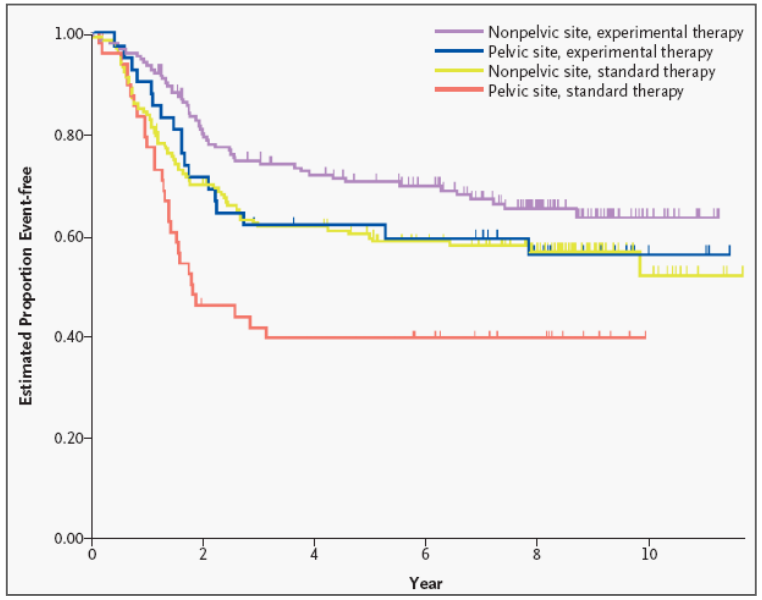
Addition of Ifosfamide and Etoposide to Standard Chemotherapy for Ewing's Sarcoma and Primitive Neuroectodermal Tumor of Bone

METHODS

Patients 30 years old or younger with Ewing's sarcoma, primitive neuroectodermal tumor of bone, or primitive sarcoma of bone were eligible. The patients were randomly assigned to receive 49 weeks of standard chemotherapy with doxorubicin, vincristine, cyclophosphamide, and dactinomycin or experimental therapy with these four drugs alternating with courses of ifosfamide and etoposide.

Grier H.E., 2003





The addition of Ifosfamide and etoposide to standard regimen significantly improves the outcome for non metastatic ES and pelvic site

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VOLUME 26 · NUMBER 27 · SEPTEMBER 20 2008

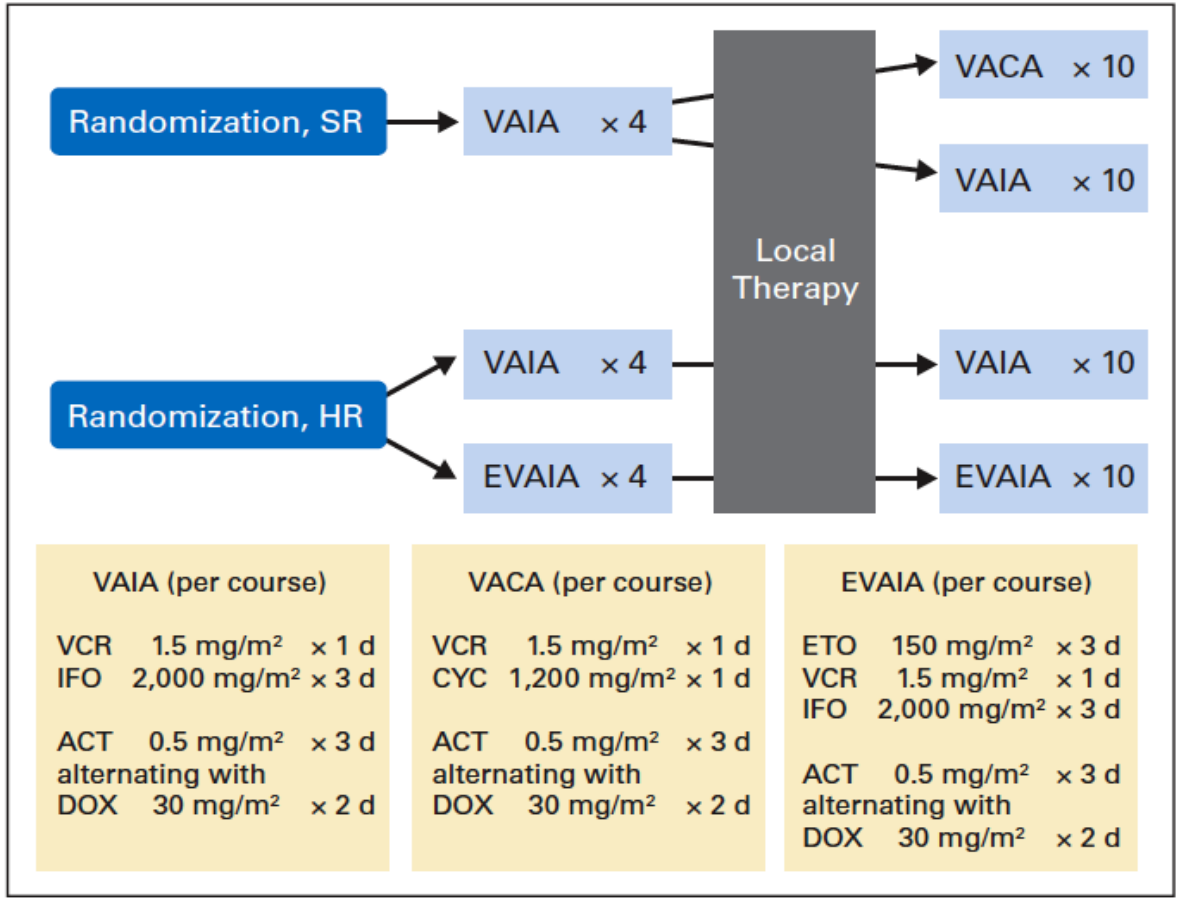
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Results of the EICESS-92 Study: Two Randomized Trials of Ewing's Sarcoma Treatment—Cyclophosphamide Compared With Ifosfamide in Standard-Risk Patients and Assessment of Benefit of Etoposide Added to Standard Treatment in High-Risk Patients

The **European Intergroup Cooperative Ewing's Sarcoma Study** investigated whether cyclophosphamide has a similar efficacy as ifosfamide in standard-risk (SR) patients and whether the addition of etoposide improves survival in high-risk (HR) patients.

-155 SR patients and 492 HR patients were enrolled
- median follow-up 8.5 years



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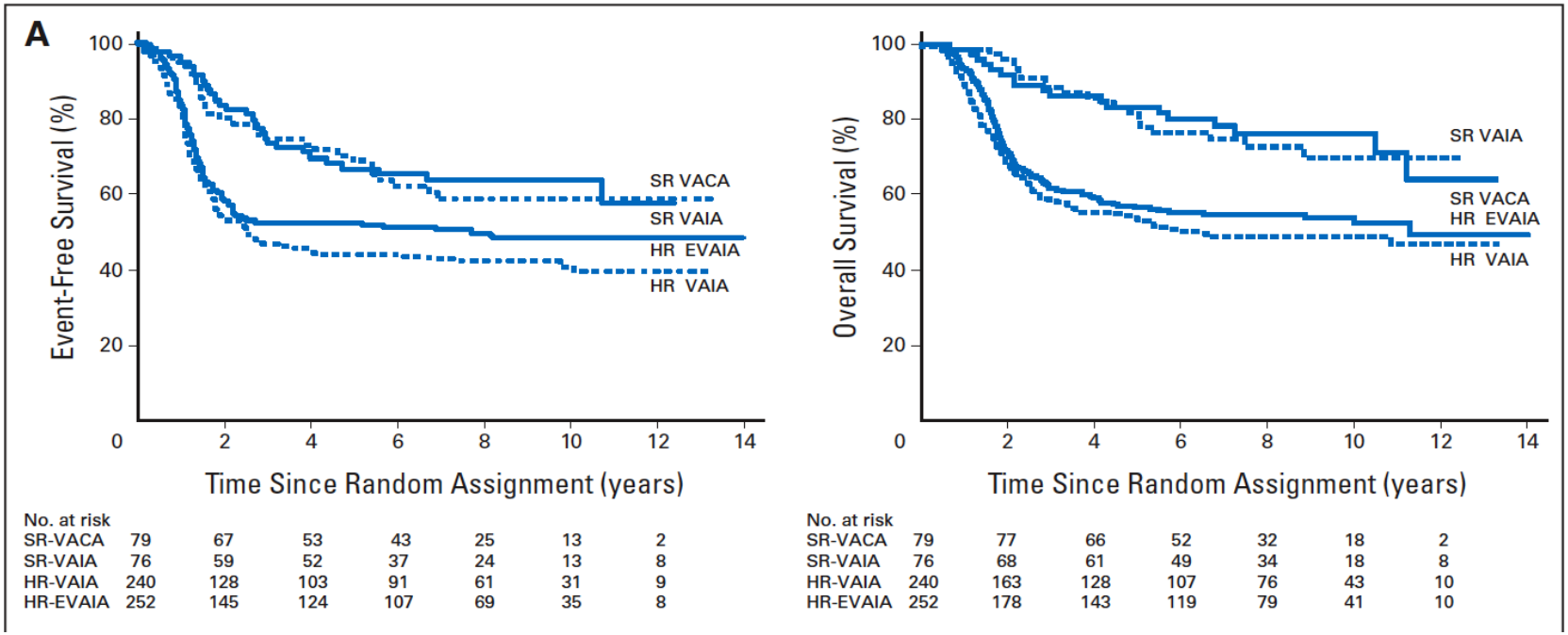

	SR-VACA arm	SR-VAIA arm
3y EFS	73%	74%
3y OS	90%	86%

	HR-EVAIA arm	HR-VAIA arm
3y EFS	52%	47%
3y OS	62%	59%

*In the **SR group**, the hazard ratios (VACA vs VAIA) for EFS and OS were 0.91 (95% CI, 0.55 to 1.53) and 1.08 (95% CI, 0.58 to 2.03), respectively. There was a higher incidence of hematologic toxicities in the VACA arm.*

*In the **HR group**, the EFS and OS hazard ratios (EVAIA v VAIA) indicated a 17% reduction in the risk of an event (95% CI, 35% to 5%; P .12) and 15% reduction in dying (95% CI, 34% to 10%), respectively.*

Cyclophosphamide seemed to have a similar effect on EFS and OS as ifosfamide in SR patients but was associated with increased toxicity.
In HR patients, the addition of **etoposide** seemed to be beneficial

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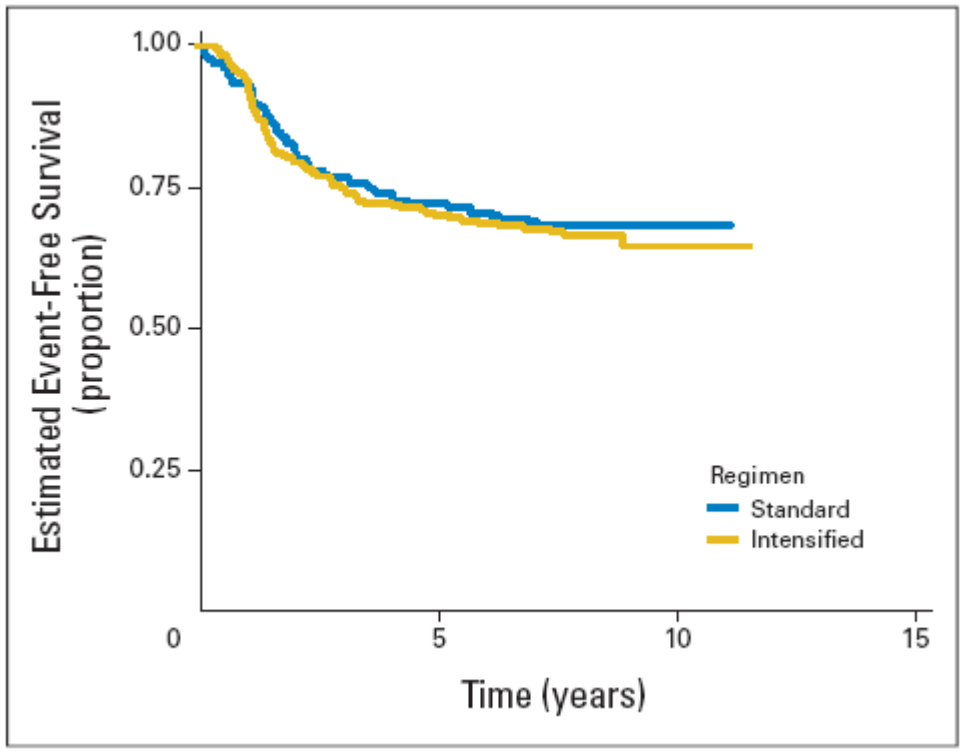
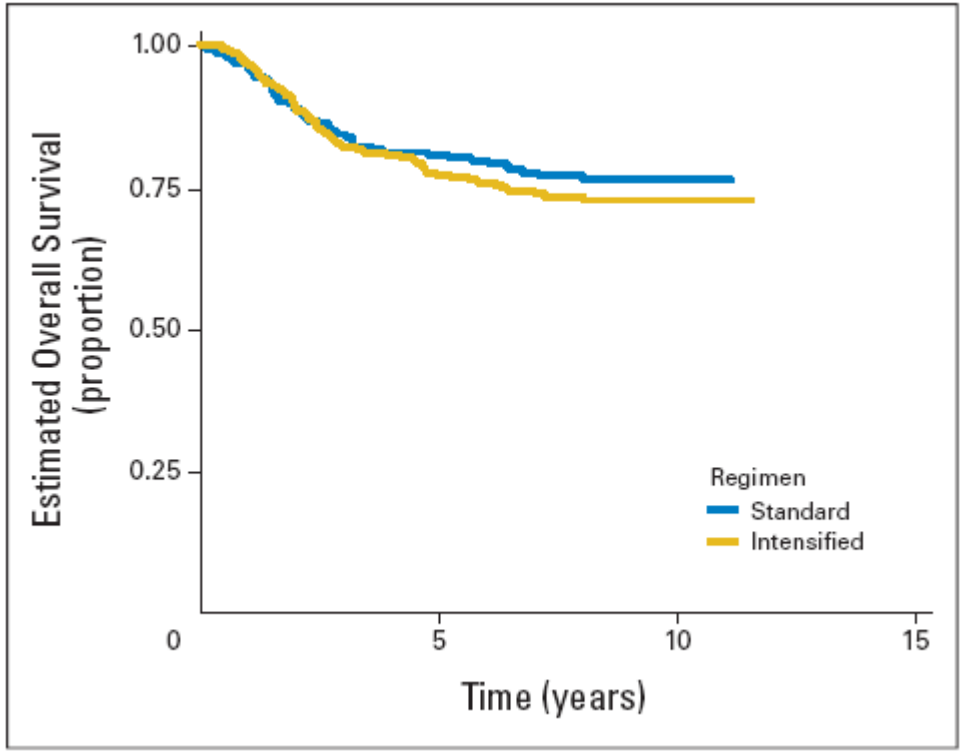
VOLUME 27 · NUMBER 15 · MAY 20 2009

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Dose-Intensified Compared With Standard Chemotherapy for Nonmetastatic Ewing Sarcoma Family of Tumors: A Children's Oncology Group Study





Dose escalation of alkylating agents did not improve the outcome for non metastatic Ewing's Sarcoma patients

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Nonmetastatic Ewing family tumors: high-dose chemotherapy with stem cell rescue in poor responder patients. Results of the Italian Sarcoma Group/ Scandinavian Sarcoma Group III protocol

Chemotherapy Outline

VAC	IVAc	VAC	IE	Local treatment
0	3	6	9	12 week

Good Responders

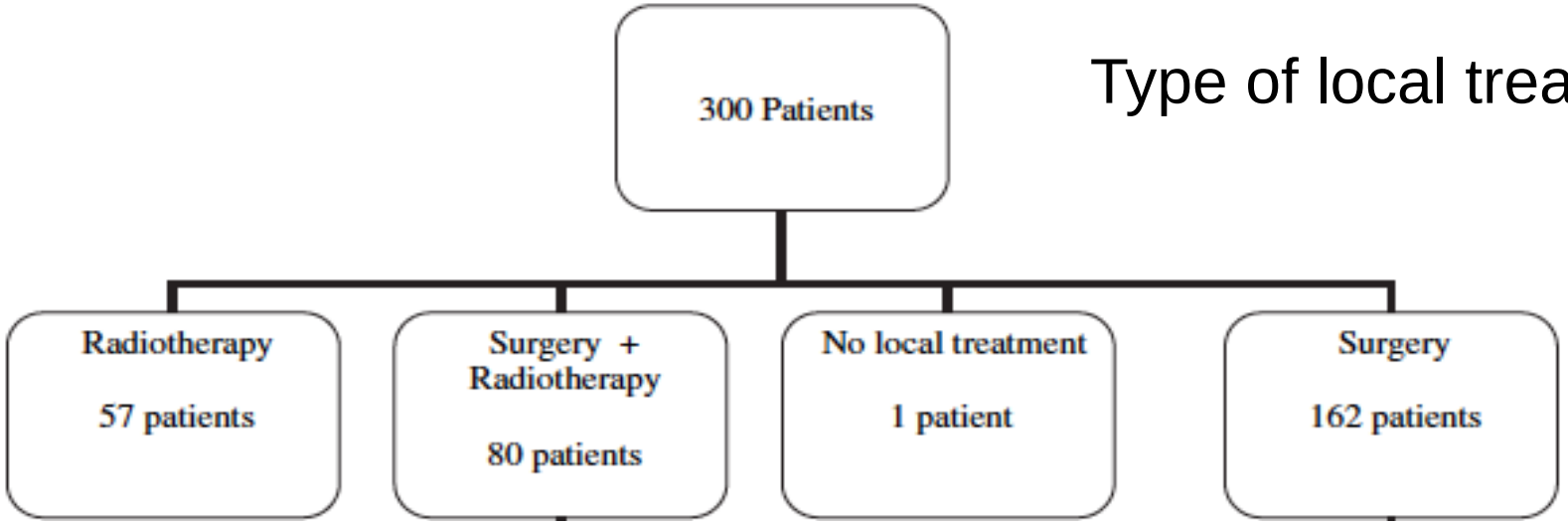
VAC	IVAc	IE	VAC	IVAc	IE	VAC	IVAc	IE	
13	16	19	22	25	28	31	34	37	week

Poor Responders

VAC	CE*	VAC	IE	BuMel
13	16	19	22	25

Characteristics	*n* (%)
Age (years)	
Median (minimum–maximum)	15 (3–40)
Age groups (years)	
3–9	51 (17)
10–17	136 (45)
≥18	113 (38)
Sex	
Male	192 (64)
Female	108 (36)
Site	
Femur	49 (16)
Pelvis	56 (19)
Tibia	38 (12)
Humerus	29 (10)
Rib	26 (9)
Spine	24 (8)
Soft tissues	19 (6)
Scapula	15 (5)
Fibula	14 (5)
Other	30 (10)

Annals of Oncology 22: 1221–1227, 2011



Type of local treatment

	GR (%)	PR (%)	*P* value
Gender			0.04
Male	85 (44)	107 (56)	
Female	61 (56)	47 (44)	
Age (years)			<0.001
3–9	36 (71)	15 (29)	
10–17	74 (54)	62 (45)	
≥18	36 (32)	77 (68)	
Site			0.05
Extremity	86 (54)	73 (46)	
Central	60 (43)	81 (57)	
SAP[a]			0.9
High	14 (48)	15 (52)	
Normal	113 (47)	126 (53)	
LDH[b]			0.3
High	44 (52)	40 (48)	
Normal	81 (45)	100 (55)	

Response to primary chemotherapy according to clinical characteristics

S. Ferrari *Annals of Oncology* 22: 1221–1227, 2011

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- Good Responders: 5-year EFS rate of 75%
- Poor Responders: 5-year EFS rate of 63%
- 28 out of 154 PR patients did not receive HDT
  - ✓ 5-year EFS for the 126 PR with HDT was 72%
  - ✓ 28 PR who were given standard chemotherapy had a 5-year EFS of 33%

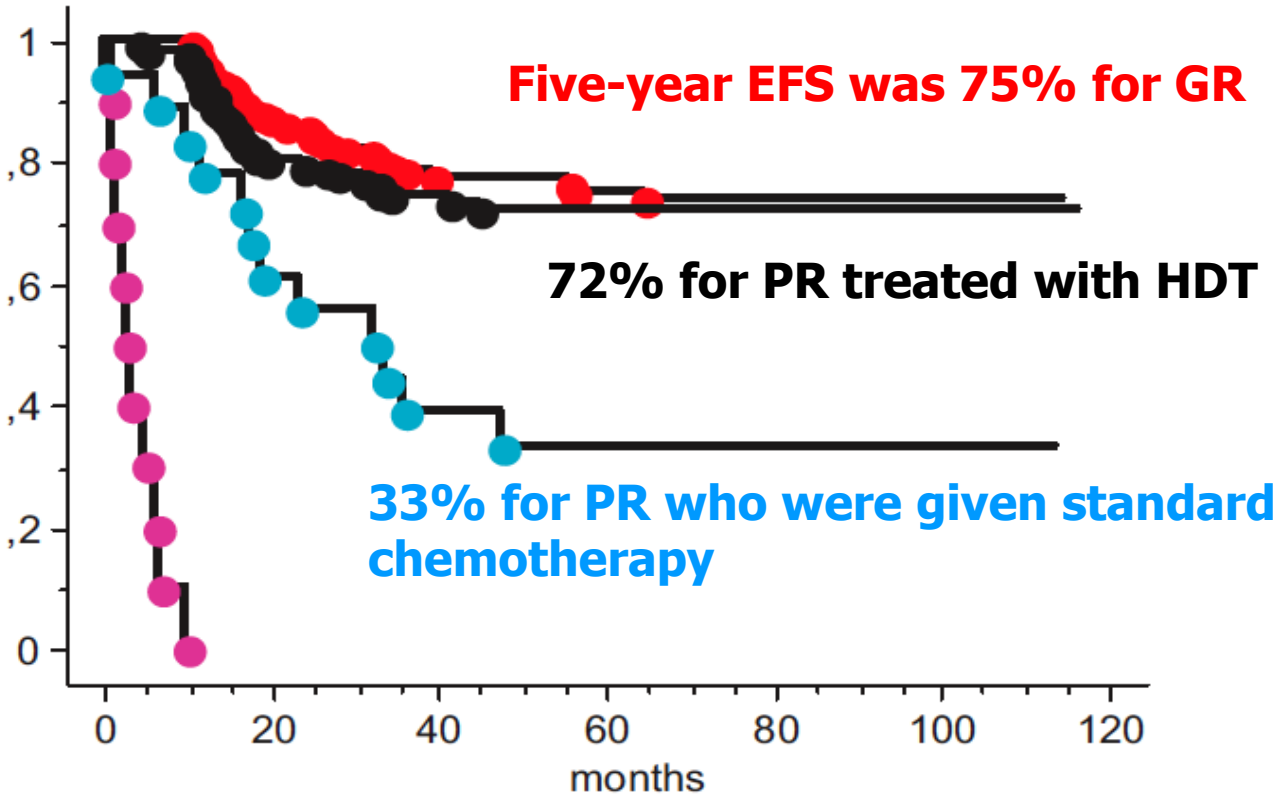

Figure 3. Event-free survival according to response to primary chemotherapy and to high-dose chemotherapy.

Annals of Oncology 22: 1221–1227, 2011

Treatment Principles

- Treatment paradigm

  - Upfront Chemo (CTX) → **Local Therapy** → Consolidation Chemo (CTX)

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Ewing's sarcoma:

Treatment strategies, therapeutic protocols, radiotherapy (techniques, doses, volumes), late effects

Umberto Ricardi

DEPARTMENT OF
ONCOLOGY
UNIVERSITY OF TURIN

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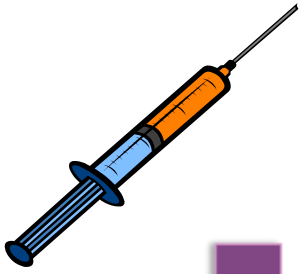
Treatment Principles

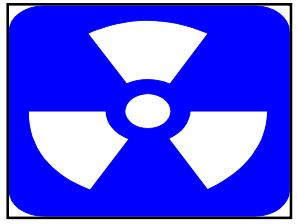
- Treatment paradigm

  - Upfront Chemo (CTX) → **Local Therapy** → Consolidation Chemo (CTX)

Multidisciplinary therapy: local treatment

- ✓ Ability to do a curative resection
- ✓ Size and site of tumor
- ✓ Response to induction chemotherapy (pathological/radiological)
- ✓ Surgical margins status





MDT-based decision

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Surgery

Goal of surgery: clear margins of normal tissue around the entire tumour (“adequate margins”)

Enneking classification of surgical intervention

Intralesional resection	Tumor opened during surgery, or surgical field contaminated, or microscopic or macroscopic residual disease
Marginal resection	Tumor removed en bloc, however, resection throught the pseudocapsule of the tumor; microscopic residual disease likely
Wide resection	Tumor and its pseudocapsule removed en bloc, surrounded by healthy tissue, within the tumor-bearing compartment
Radical resection	The whole tumor-bearing compartment removed en bloc (e.g. above the knee amputation for a lower leg tumor)

Enneking et al., Clin Orthop Rel Res, 1980

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Adequate margins status (COG)

✓*Complete resection is defined as a minimum of 1 cm margin (and ideally 2-5 cm) around the involved bone*

✓*The minimum soft tissue margin for fat or muscle planes is at least 5 mm and for fascial planes at least 2 mm*

References	Margins	Local control	Event-free survival	Overall survival
Ozaki et al. [4]	Adequate	96%		
	Inadequate	88%		
		($P = 0.045$)		
Bacci et al. [5]	Adequate	93%	69.5%	
	Inadequate	81%	50% ($P < 0.001$)	
		($P = 0.001$)		

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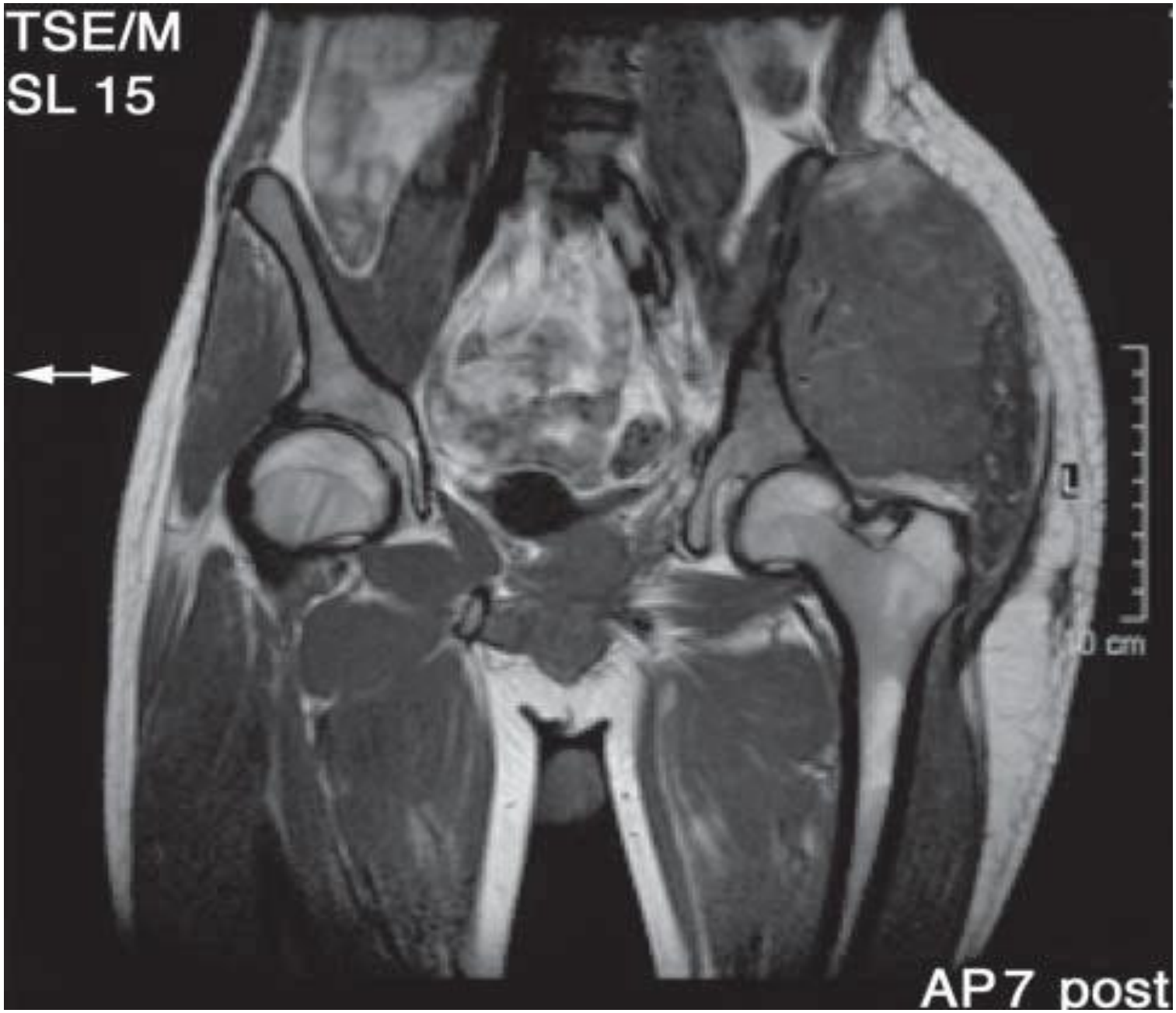
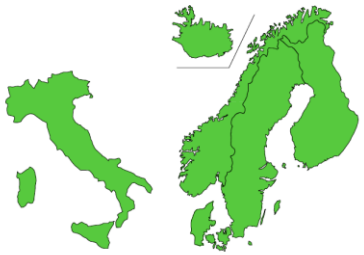
Treatment Principles: Local Therapy

- Surgery more feasible in small lesions in "expendable" bones
  - Hands, feet, fibula, lower sacrum, ribs, clavicle, scapula
- Innovative surgical techniques and cytoreductive CTX allowing for more resections

LESIONS UNRESECTABLE WITH CLEAR MARGINS





Local treatment in ISG-SSG III protocol

ISG-SSG III, 6/1999 – 12/2007
Pts: 284

		LOCAL TREATMENT vs SITE		
	(%)	Extr.	Other	Pelvis
Surgery	(54)	82%	32%	31%
Surgery + Radiotherapy	(25)	12%	36%	16%
Radiotherapy	(21)	6%	32%	53%

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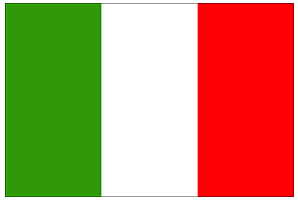

Evolution of local treatment in Italian experience

years	RT %	Surgery %	Surgery&RT %
1972-78	65	11	24
1979-83	53	20	28
1984-90	16	65	19
1991-99	24	52	24
1999-07	21	62	17

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Local treatment

- *Is surgery always better than radiotherapy?*

- *Does combined local therapy (surgery plus pre- or post-operative RT) improve treatment results in high-risk patients?*

Local Treatment

Surgery vs RT: Multicentric Studies

Study	Type of local therapy	N	Local failure rate (%)
ET 1 [1] (1978–1986)	Surgery (±post-operative XRT)	34	10
	Radiotherapy alone	108	33
POG 8346 [2] (1983–1988)	Surgery (±post-operative XRT)	37	12
	Radiotherapy alone	104	35
ET 2 [3] (1987–1993)	Surgery	114	10
	Surgery + post-operative XRT	20	0
	Radiotherapy alone	56	12
SSG IX [4] (1990–1999)	Amputation	8	0
	Wide resection, no XRT	35	11
	Marginal/unradical resection + XRT	17	6
	Radiotherapy alone (inoperable tumors)	28	13
CESS 81/CESS 86/EICESS 92 [5] (1981–1999)	Surgery	237	5
	Surgery + post-operative XRT	298	5
	Pre-operative XRT plus surgery	240	6
	Radiotherapy alone	264	29

✓ *Surgery yields better overall local control as compared to radiotherapy*

✓ *Surgery with clear margins, where feasible, is regarded as the best modality of local control*

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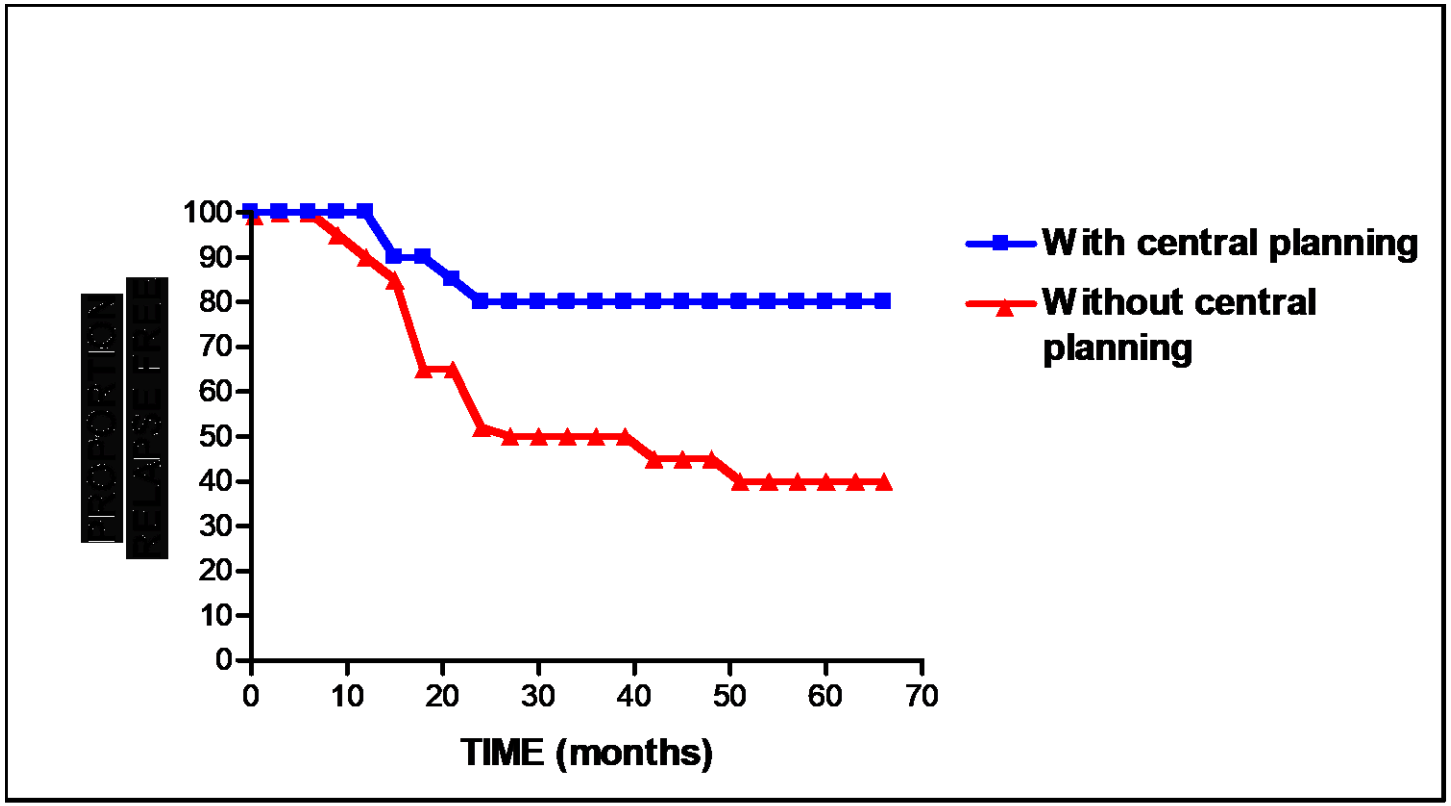
Treatment Principles: Local Therapy

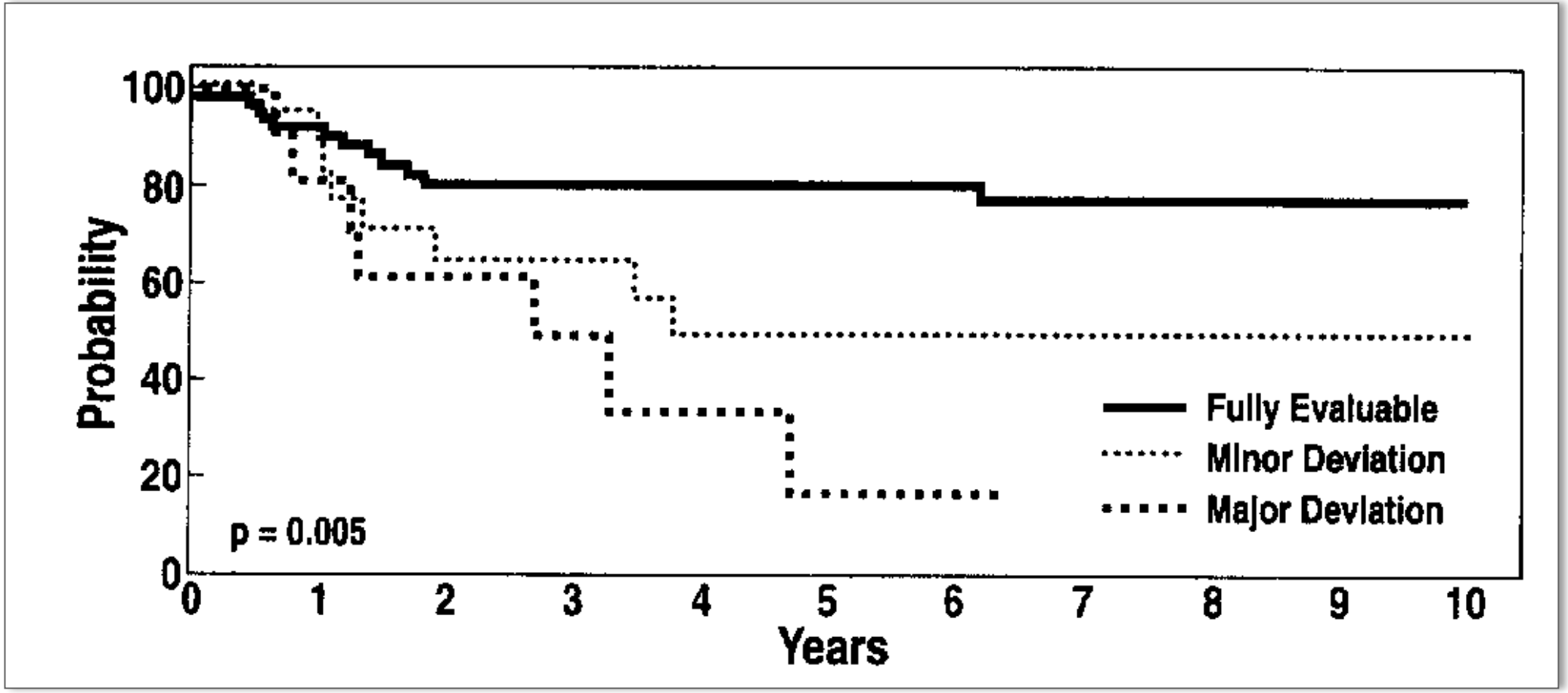
- No prospective randomized data comparing surgery to radiation
- Selection bias confounds the data
  - Central and larger tumors with poorer prognosis more likely to receive RT
  - Local failure after RT alone 20% or more
  - Some data favors surgery due to inadequate RT doses or lack of QA in RT planning

Radiation Technique is of Critical Importance in the Treatment of Ewing's Sarcoma (CESS-81)

(Sauer et al., Radiotherapy and Oncology, 1987)



POG 8346



Local control correlates with quality of RT

DEFINITIVE RADIOTHERAPY AS LOCAL TREATMENT

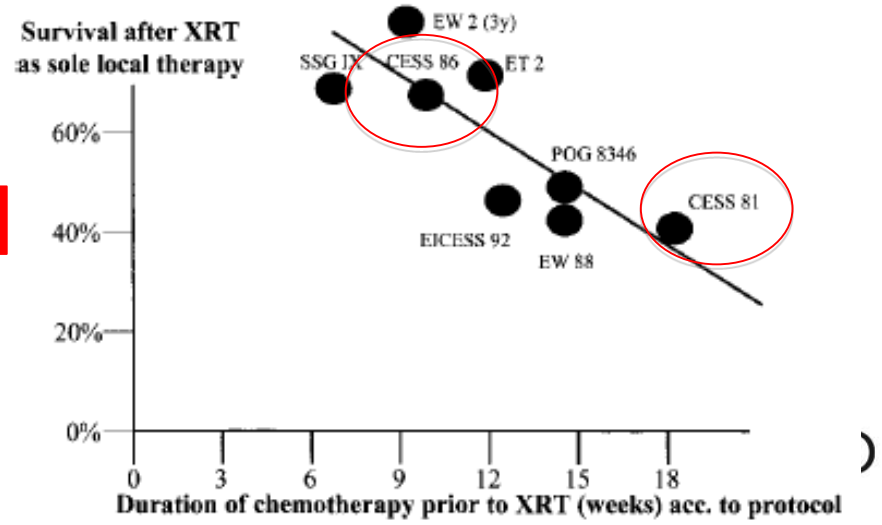
Indications

- *Lesions that are considered not resectable with clear margins (spine, skull) or in which surgery would be extremely mutilating (pelvis, head and neck)*
- *Definitive RT is indicated when only an intralesional resection is possible*

Timing of RT

- *The results of RT are dependent on how RT is incorporated in multimodal treatment concepts*

Association between delay of RT (time interval between CT start and RT start) and survival



Local control and risk groups

Surgery and/or Radiation therapy

Resectable lesions	Irradiated lesions
Usually small	Often large
Peripheral in location	Central in location
Good response to induction chemotherapy	Poor response to induction chemotherapy

Patients who receive radiotherapy as the only single local therapy modality usually represent an unfavorably selected group of patients

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Identification of Patients With Localized Ewing Sarcoma at Higher Risk for Local Failure: A Report From the Children's Oncology Group

Safia K. Ahmed

Int J Radiation Oncol Biol Phys, Vol. 99, No. 5, pp. 1286–1294, 2017

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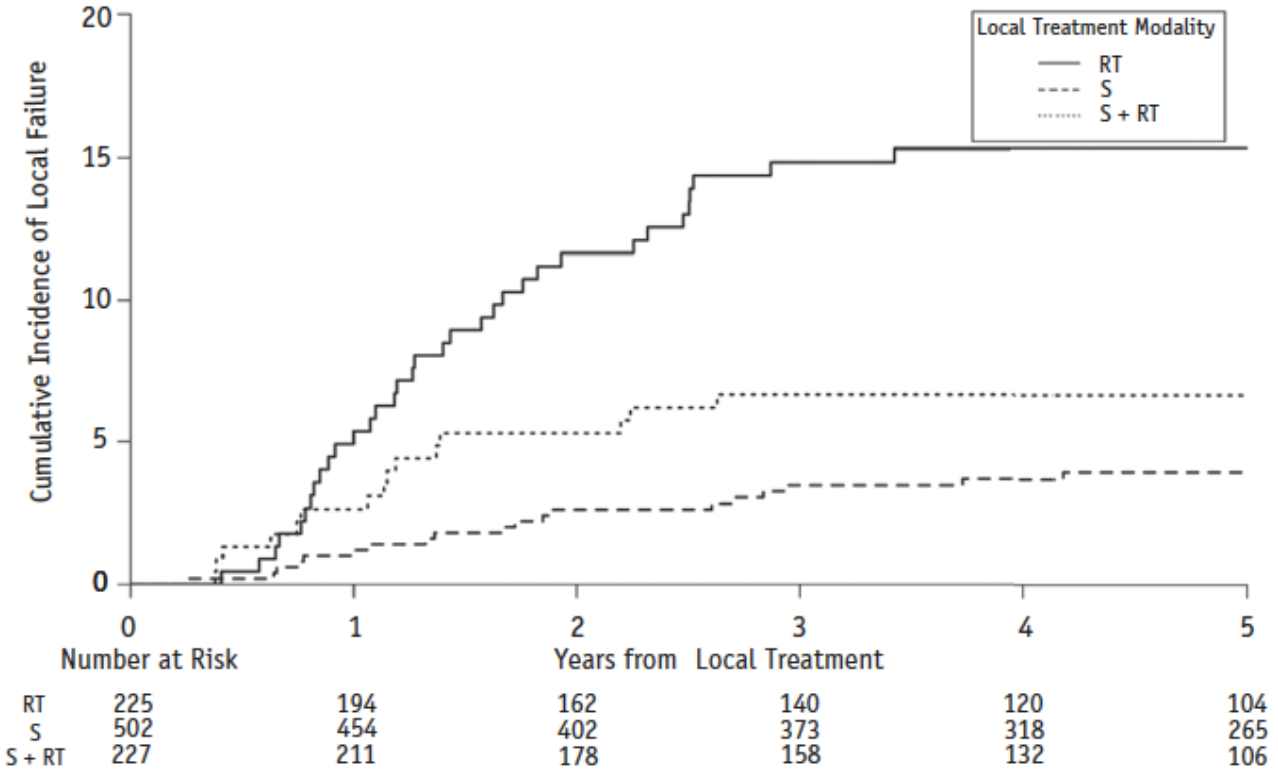

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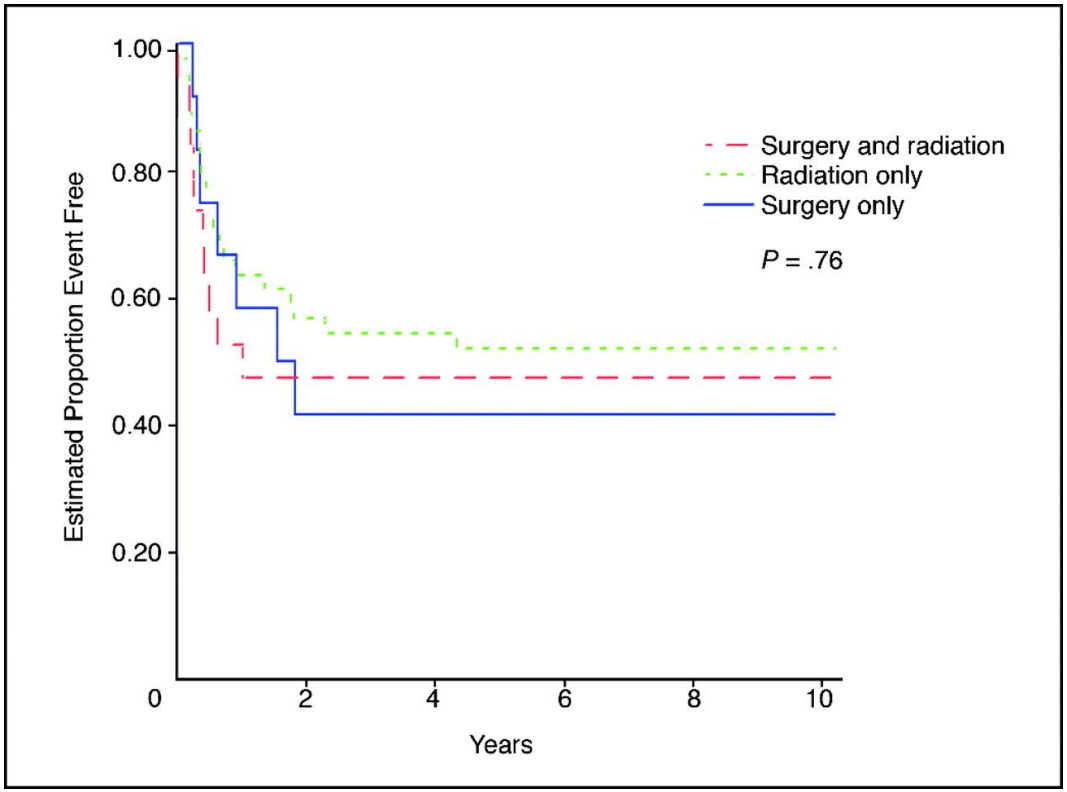
VOLUME 24 · NUMBER 24 · AUGUST 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Local Control in Pelvic Ewing Sarcoma: Analysis From INT-0091—A Report From the Children's Oncology Group

Torunn I. Yock, Mark Krailo, Christopher J. Fryer, Sarah S. Donaldson, James S. Miser, Zhengjia Chen, Mark Bernstein, Fran Laurie, Mark. C. Gebhardt, Holcombe E. Grier, and Nancy J. Tarbell



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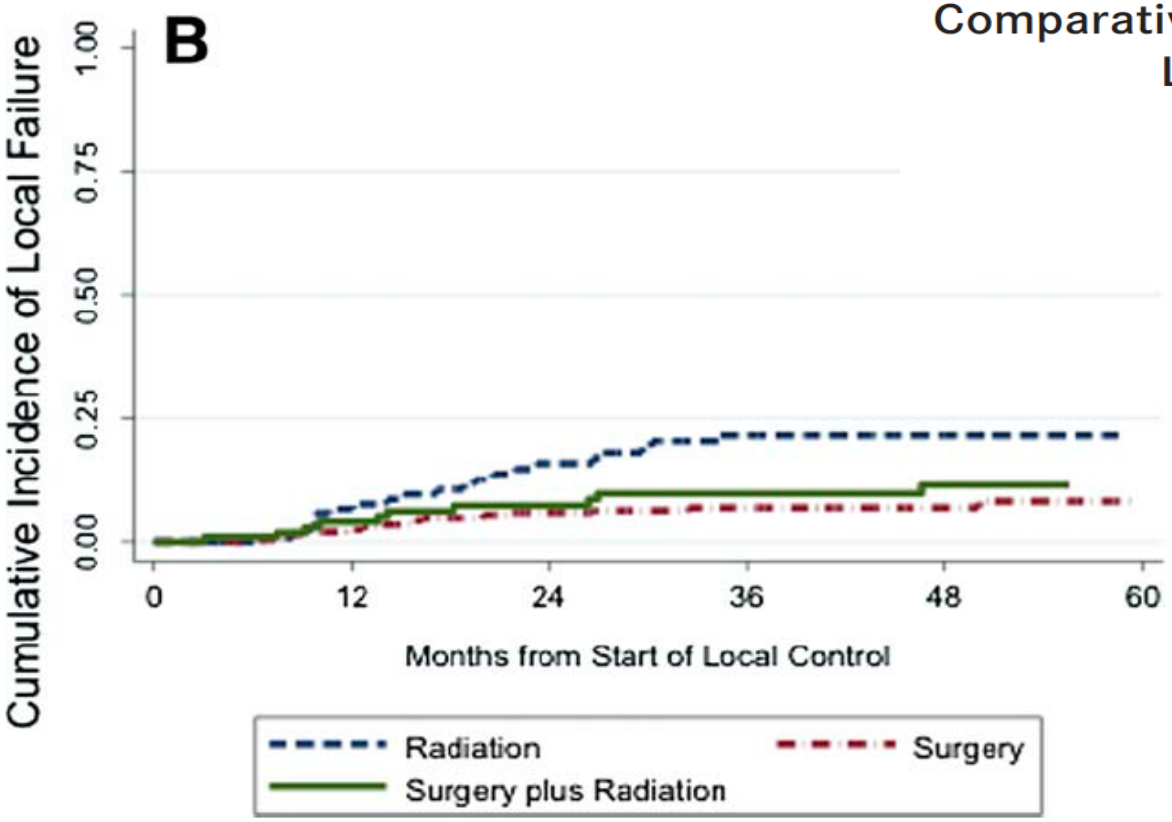

Comparative Evaluation of Local Control Strategies in Localized Ewing Sarcoma of Bone

A Report From the Children's Oncology Group

Cancer Month 00, 2014

Steven G. DuBois

- ✓ In this large group of similarly treated patients (465 pts), choice of the mode of local control was not related significantly to EFS, overall survival, or distant failure, **although the risk of local failure was greater for radiation compared with surgery**

- ✓ These data support surgical resection when appropriate, whereas radiotherapy remains a reasonable alternative in selected patients

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ADJUVANT RADIOTHERAPY

Is combined local treatment better than surgery alone?

- There are no randomized studies on the question of whether combined local treatment (surgery plus radiotherapy) offers an advantage over surgery alone

- The data from major studies demonstrate that the local control rate after surgery plus radiotherapy was better that after surgery alone

- Combined local treatment improves local control and survival **in patients who are at high risk for local failure after resection**

Type of surgery and Histologic Response to induction chemo

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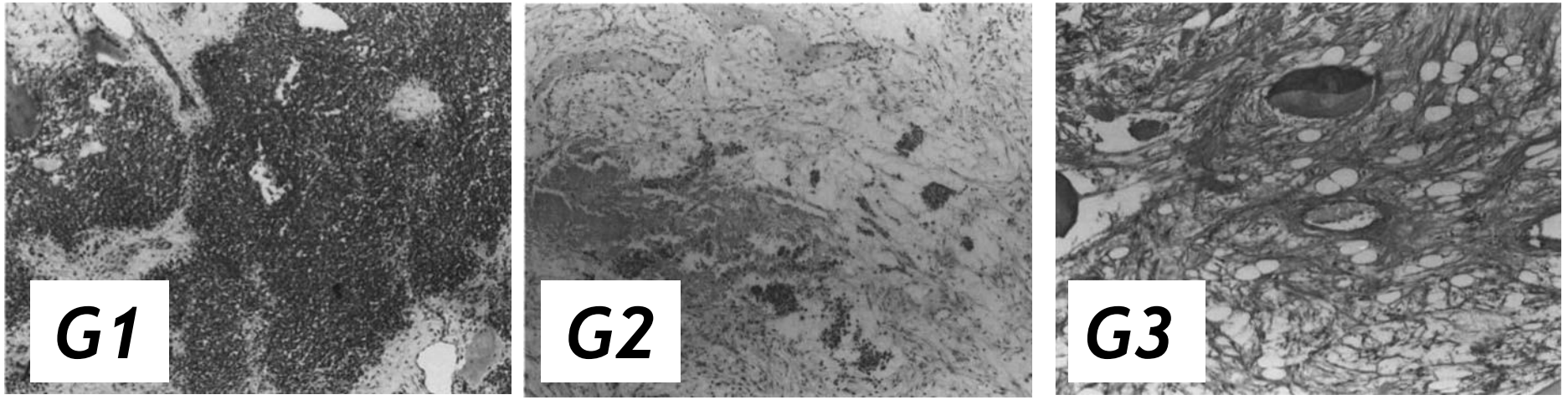
Comparison of Local Therapies

- Post-op RT improved LC over surgery alone if:
  - **Resection with gross or microscopic positive margins**
  - **Wide resection and poor histologic response**



Macroscopic foci of viable tumor cells (>10 x field)

Isolated microscopic foci of viable tumor cells (<10 x field)

No viable tumor

Pediatr Blood Cancer 2008;51:575–580

REVIEW

Post-Operative Radiotherapy for Ewing Sarcoma: When, How and How Much?

S. Laskar, MD,* I. Mallick, MD, T. Gupta, MD, and M.A. Muckaden, MD

INDICATIONS	**Gross or microscopic positive margins** **Clear margins but poor histopathological response to chemotherapy (necrosis <90% is the suggested minimum threshold, but <95-99% may be used based on istitutional practice)**
TIMING	Within 6-8 weeks of surgery (though there is no evidence to suggest that a further delay lesds to inferior outcome)
DOSE	45 Gy to prechemotherapy volume 10.8 Gy by boost to areas of gross tumor residual
FRACTIONATION	Standard daily fractionaction of 1.8 Gy per fraction
TARGET VOLUME	Initial phase (45 Gy): pre chemotherapy tumor volume on MRI with 1.5-2 cm margins. Appropriate modifications should be made in tumors expanding into cavities or the lung Boost phase (10.8 Gy): post-operative gross residul disease with 1.5-2 cm margins

Dose Response and Local Control Using Radiotherapy in Non-Metastatic Ewing Sarcoma

Radiotherapy dose was found to influence local control. Patients who received doses > 49 Gy for tumor size < 8 cm and > 54 Gy for tumor size > 8 cm had improved local control

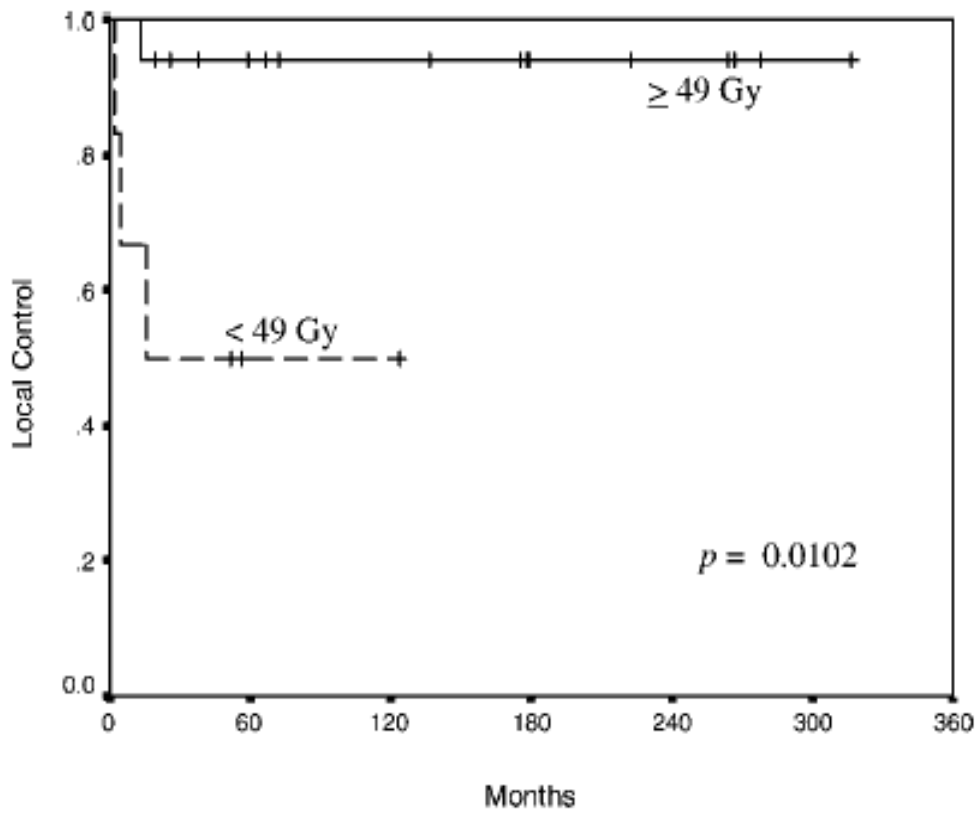


Fig. 1. Local control in tumors ≤8 cm (n = 23) according to radiotherapy dose.

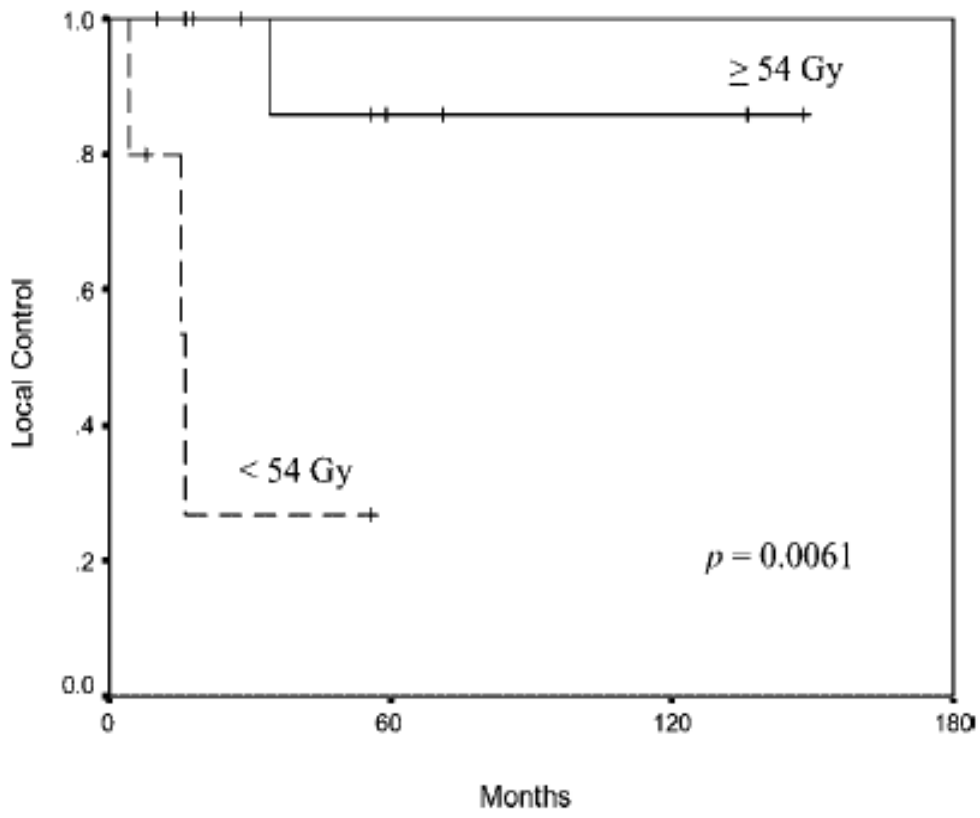


Fig. 2. Local control in tumors >8 cm (n = 17) according to radiotherapy dose.

Arnold C. Paulino, Pediatr Blood Cancer 2007;49:145–148

Radiation Doses

The total dose of radiation depends on the extent of resection (if any), status of margins, as well as the histological response to chemotherapy

Intralesional resection or definitive radiotherapy	55.8 Gy
Microscopic residual disease	45-50 Gy
Surgery with clear margins and poor histological response to chemotherapy	45 Gy

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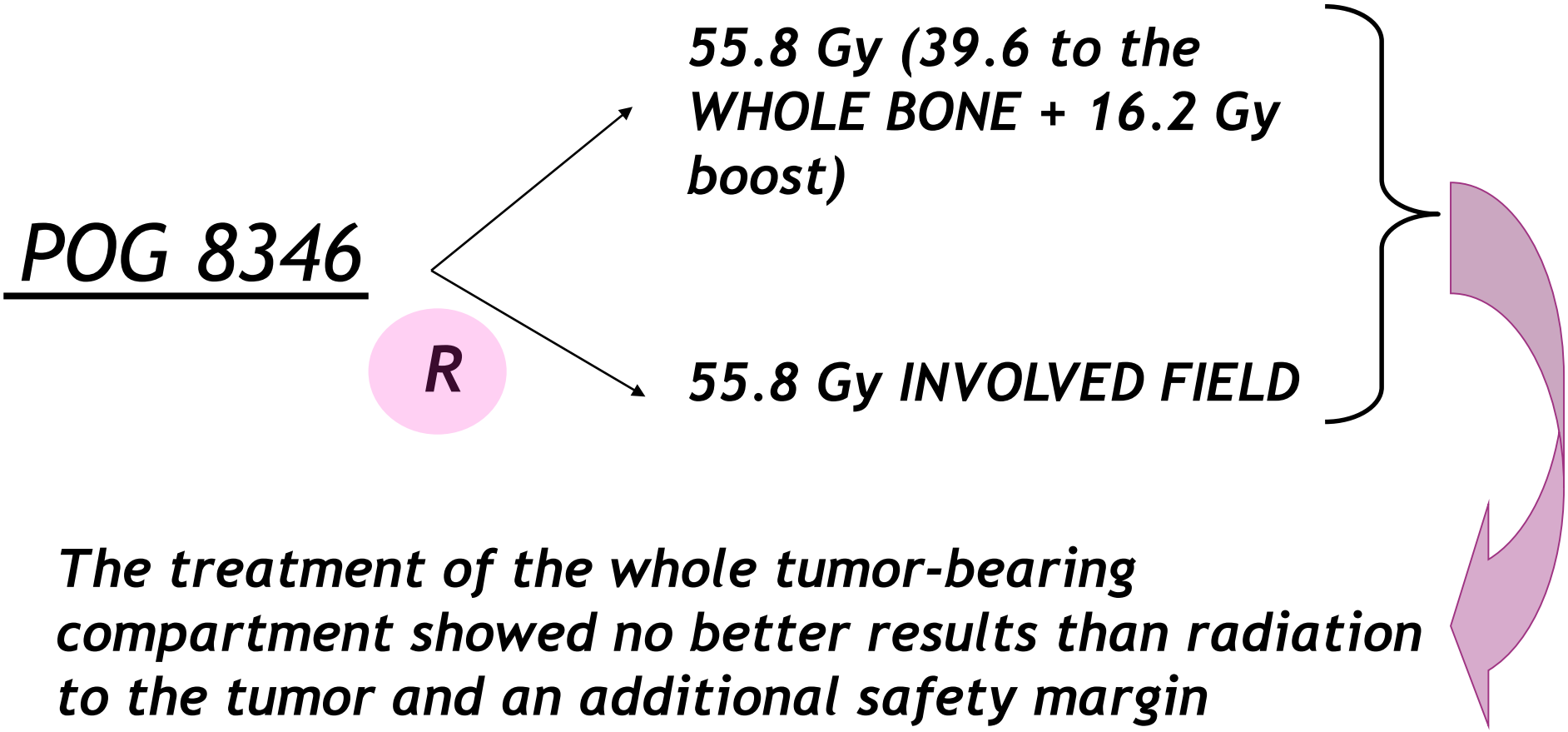
RT Volumes

- Originally encompassed entire medullary cavity: whole bone +boost to primary
- Later data showed comparable results with tailored fields

Radiation Volumes
Whole bone or involved field?



The treatment of the whole tumor-bearing compartment showed no better results than radiation to the tumor and an additional safety margin

The site of majority of failures was central, within RT fields

Donaldson S., IJROBP 1998

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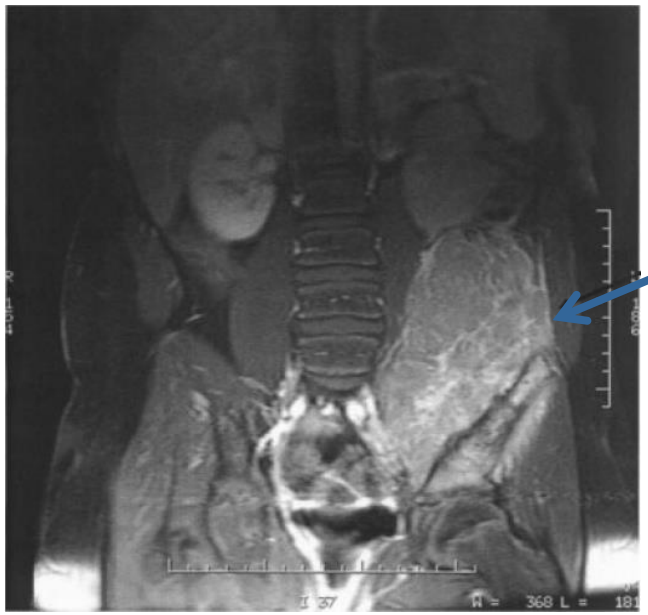
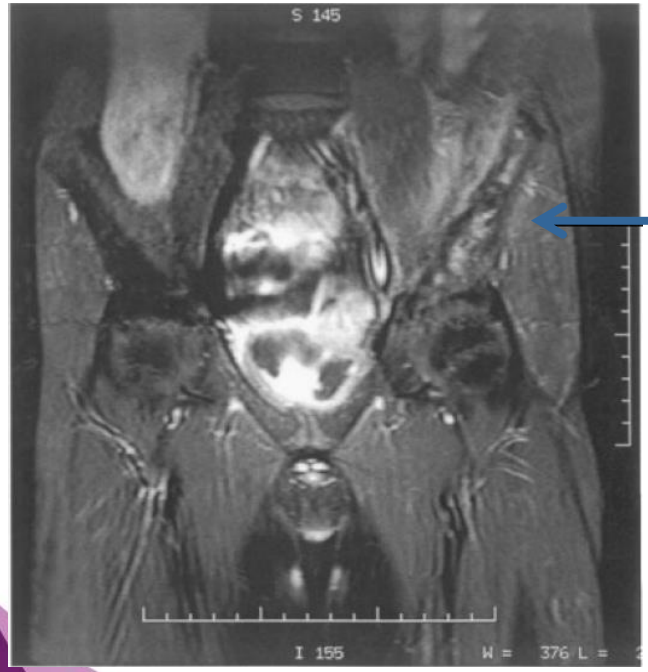
Radiation Volumes



❖ **Initial phase:**

❑ **GTV_1**: pre-chemotherapy tumor volume



❖ **Boost phase:**

GTV_2: includes pre-treatment abnormalities in bone and post-chemo gross tumor in soft tissue

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Radiation Dose – Current COG Protocol

- GTV1, CTV1, and PTV1 are defined
  - 45 Gy in 1.8 Gy are delivered based on pre-chemo extent
- GTV2 defined as residual visible or palpable tumor by imaging or physical exam
  - For unresected or partially resected tumors, GTV2 includes pre-treatment abnormalities in bone and gross tumor in soft tissue post-chemo
  - CTV2=GTV2 + 1 cm
  - PTV2 = 10.8 Gy for total of 55.8 Gy
- Post-op RT: 50.4 Gy for R1 and 55.8 Gy for R2

Current RT Volume Recommendations

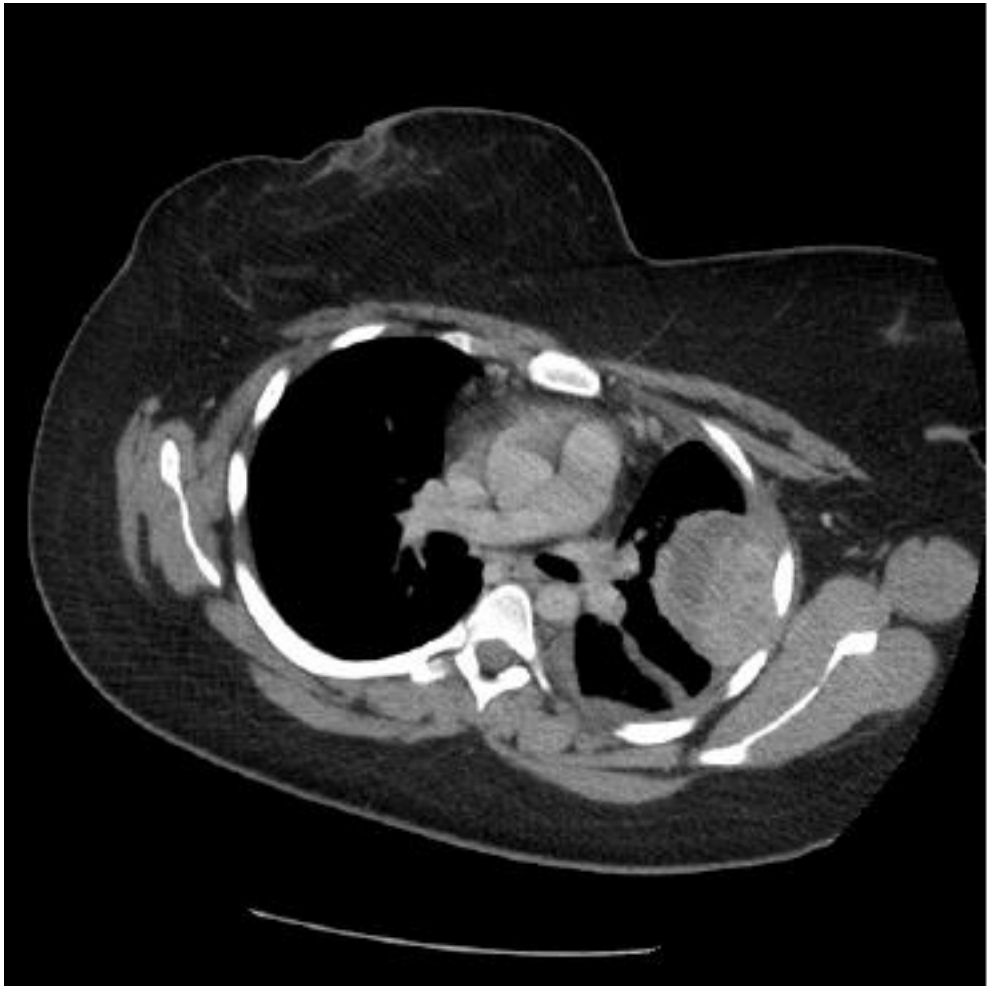
- Use MRI to identify extent of bony and soft tissue disease

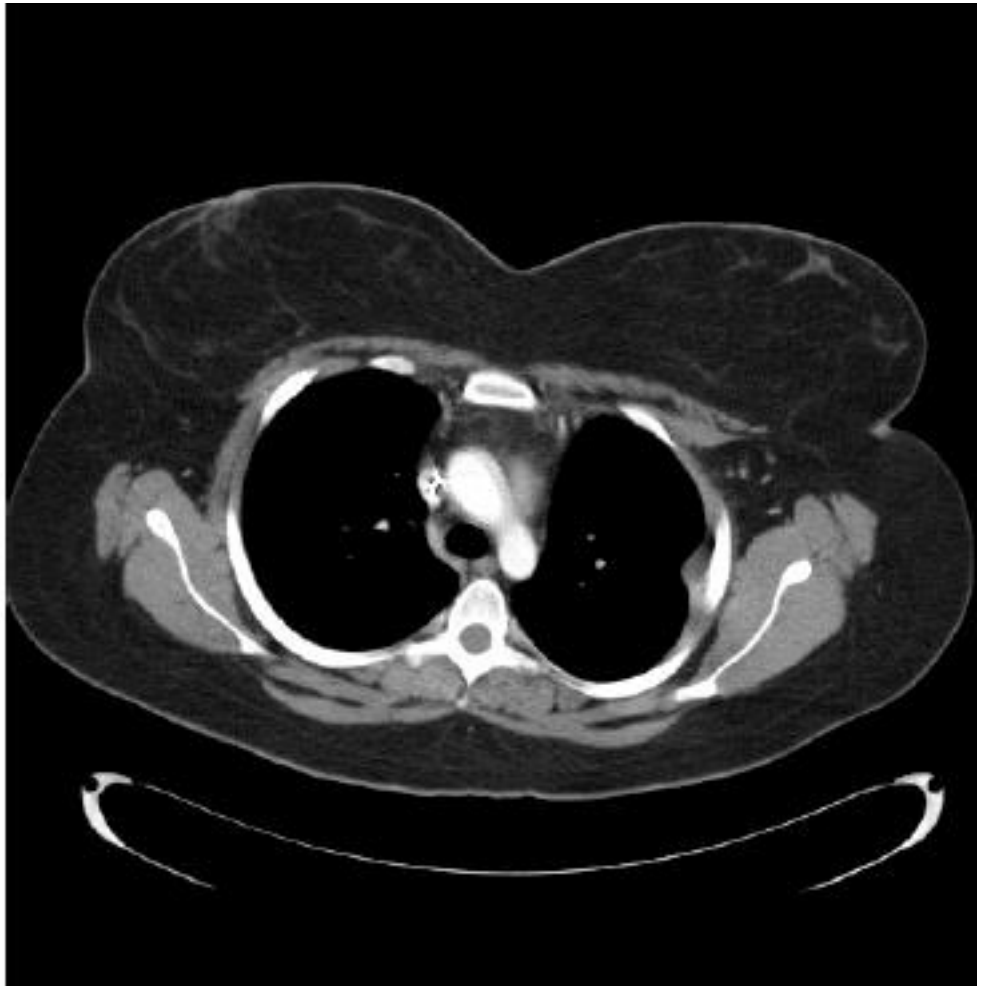
- GTV takes into account pre-chemo extent of disease

- CTV 1.0-1.5cm margin, plus PTV margin
  - Except for large soft tissue mass extending into a body cavity which responds to CTX and allows normal tissues to shift back into position

  Appropriate modifications in tumors expanding into anatomical cavities (thorax, pelvis) without infiltration

- Post-op RT
  - Not as well defined
  - Pre-op tumor bed with margins, c/d to any residual





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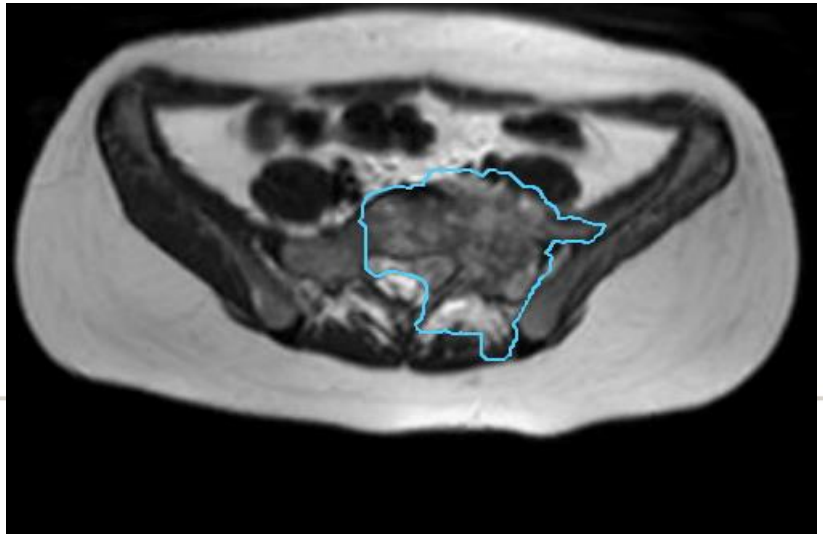
Regions of interest (ROI)

Use **MRI** to identify extent of bony and soft tissue disease

Target volumes	Definition	Mean dice coefficient
GTV_1	Initial extent of the disease	
GTV_2	Initial extent of bony disease but postchemotherapy extent for soft tissue disease extending into the pelvis	
CTV_1	GTV_1 +1.0 cm	
CTV_2	GTV_2 +1.0 cm	



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Target Volumes: Definitive RT

- GTV1 = Pre-chemo bone and soft tissue disease
- GTV2 = Pre-chemo bone and post-chemo soft tissue disease
- Donaldson et al 2004
  - GTV1 + 2-2.5cm to PTV1
  - GTV2 + 1.5-2cm to PTV2
- AEWS 0031
  - GTV1 + 1.5cm CTV1 + ≥ 0.5cm PTV1
  - GTV2 + 1cm CTV2 + ≥ 0.5cm PTV2
- AEWS 1031, AEWS 1221
  - GTV1 + 1cm CTV1 + ≥ 0.5cm PTV1
  - GTV2 + 1cm CTV2 + ≥ 0.5cm PTV2
- St Jude Phase II 2016
  - GTV = gross tumor, initially involved bone, adjacent soft tissue initially infiltrated (eg fascia) that did not regress with soft tissue mass regression
  - CTV1 = GTV + 1cm
  - CTV2 = no expansion in GTV
  - PTV = 0.5-1cm

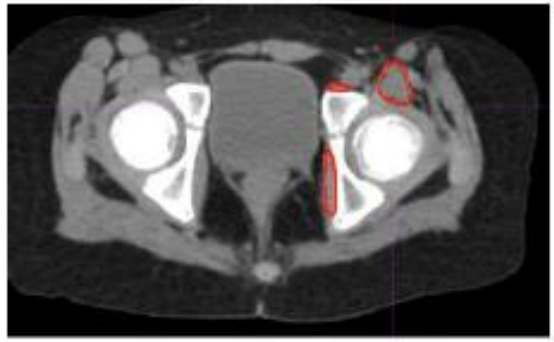
Further reduction of volumes on recent protocols

- St Jude ESFT13 protocol

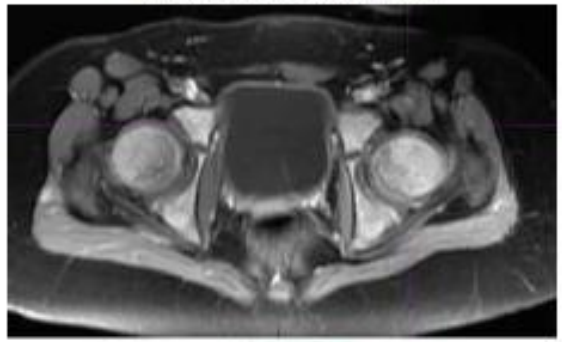
For definitive RT:

- GTV
  - Gross tumor
  - Residual post-chemotherapy soft tissue mass defined by MR
  - Bone initially involved
- CTV1
  - 0.5 cm expansion on GTV, respecting anatomic barriers
  - Tissue that harbored gross disease that now has no visible gross disease.
  - The operative bed in patients that had resection
- No expansion for boost phase (GTV = CTV2)
- Total dose 55.8 to 64.8 Gy

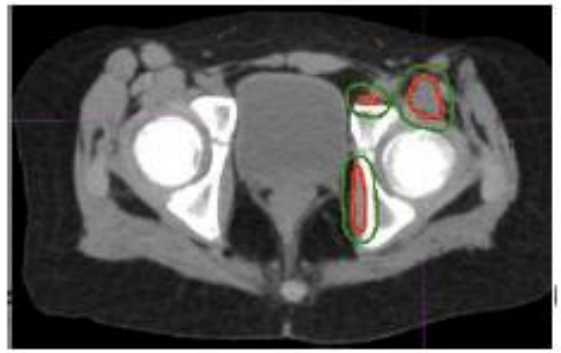
GTV =CTV2

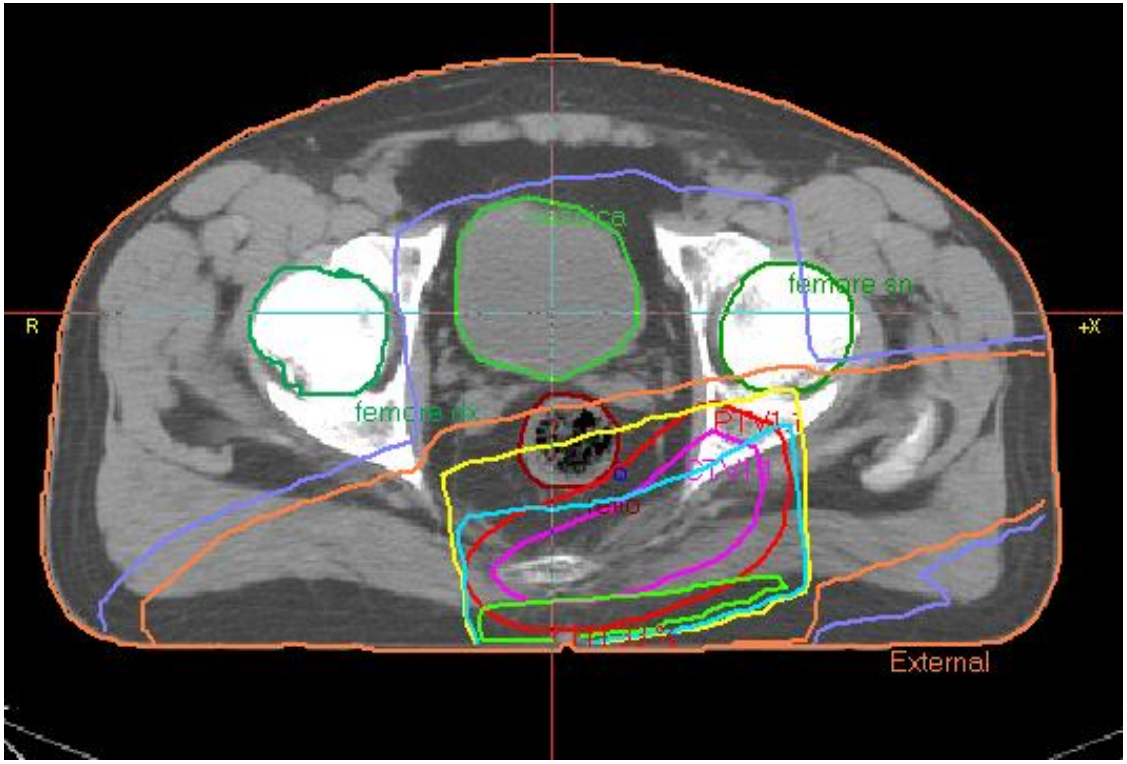


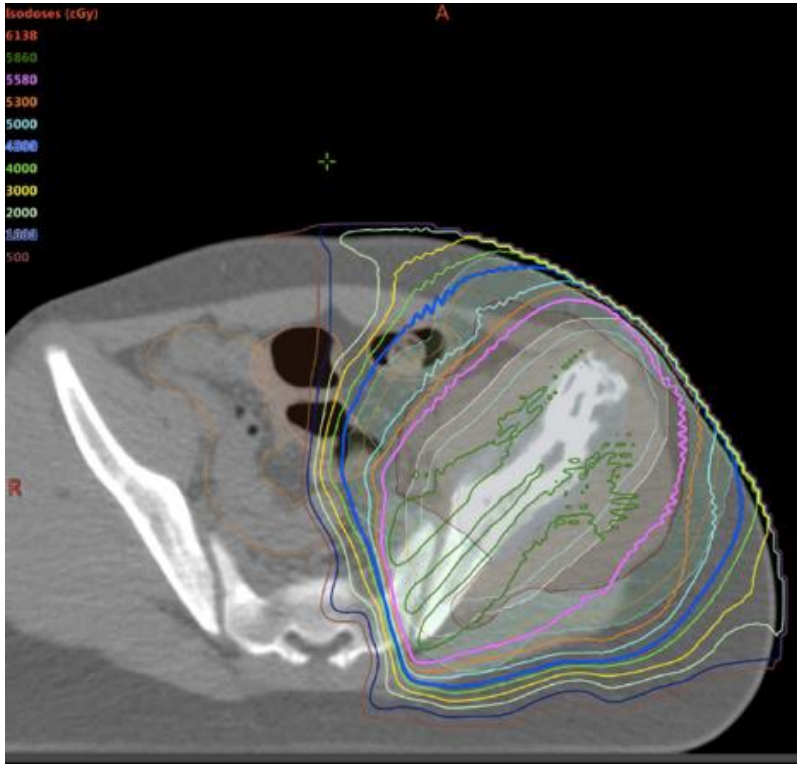
Post-Induction MRI



PTV2







3DCRT

VMAT

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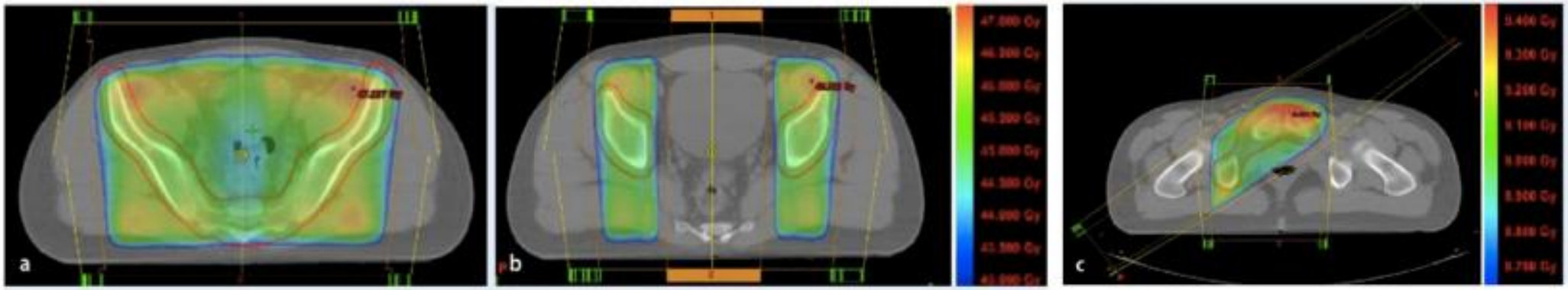
3DCRT v IMRT

- 3DCRT v IMRT comparison study (Mounessi 2013)
- N=8 pelvic EWS, 2 PORT, 6 definitive
- 3DCRT opposing-, 3- or 4-field arrangement
  - PTV1 (whole pelvis, pre-chemo tumor+2cm) 45 Gy
  - PTV2 (pre- or post-chemo tumor +2cm) 54 Gy
  - PTV3 (post-chemo tumor) 59.4 Gy



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3DCRT v IMRT

- 3DCRT v IMRT comparison study (Mounessi 2013)
- PTV V_{95} >98% for both
- IMRT ⇧conformity and bowel-sparing (D_{mean}, $V_{10, 20, 40, 50}$)
- No significant difference in bladder dose
- Significantly higher low dose (2 Gy) volume with IMRT
  - For long-term survivors, SMN from 1% → 1.75%

Mean Value	V_2 (cc)	V_{30} (cc)
IMRT	11,753	3,026
3DCRT	9,655	3,895
P-value	0.05	0.017

SPINAL AND PARASPINAL EWING TUMORS

DANIEL J. INDELICATO, M.D.,*† SAMEER R. KEOLE, M.D.,*† AMIR H. SHAHLAEE, M.D.,‡
CHRISTOPHER G. MORRIS, M.S.,*† C. PARKER GIBBS, JR., M.D.,§ MARK T. SCARBOROUGH, M.D.,§
DAVID W. PINCUS, M.D., PH.D.,¶ AND ROBERT B. MARCUS, JR., M.D.*†

Departments of *Radiation Oncology,‡Pediatrics,§Orthopedic Surgery,and ¶Neurosurgery, University of Florida College of Medicine, Gainesville, FL; and †University of Florida Proton Therapy Institute, Jacksonville, FL

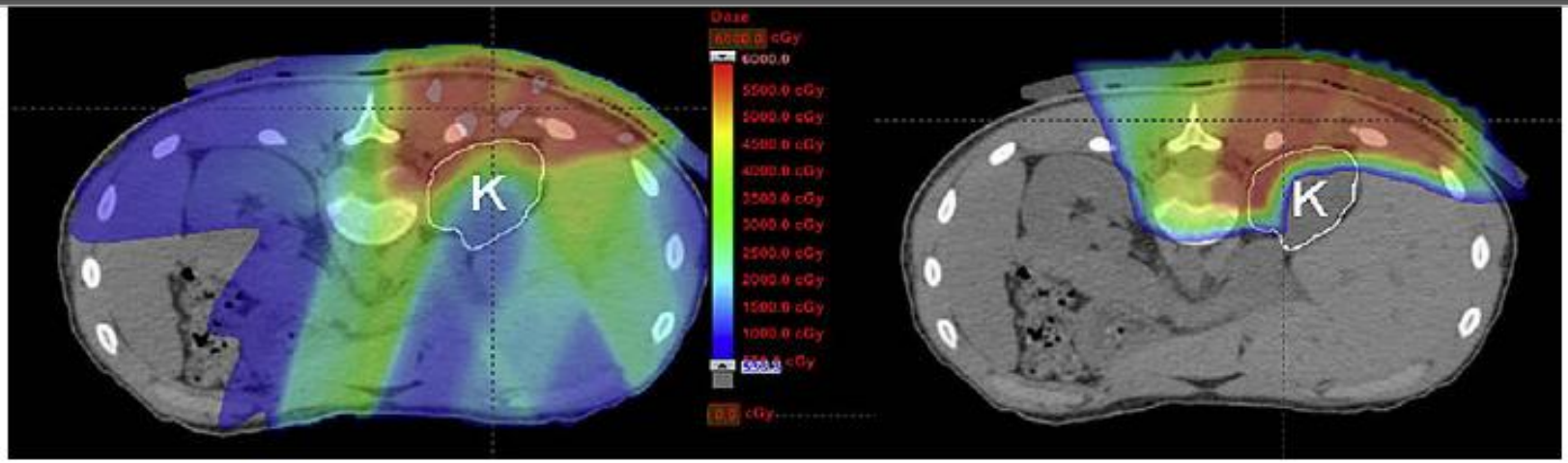


Fig. 3. Dose distribution comparison between (a) photon intensity-modulated radiotherapy plan and (b) proton three-dimensional conformal plan in 16-year-old patient with paraspinal Ewing tumor treated at University of Florida Proton Therapy Institute. Note, difference in low-dose distribution, kidney (K) dose, and dose homogeneity.

PROTON RADIOTHERAPY FOR PEDIATRIC EWING'S SARCOMA: INITIAL CLINICAL OUTCOMES

BARBARA ROMBI, M.D.,* THOMAS F. DELANEY, M.D.,† SHANNON M. MACDONALD, M.D.,† MARY S. HUANG, M.D.,‡ DAVID. H. EBB, M.D.,‡ NORBERT. J. LIEBSCH, M.D., PH.D.,† KEVIN. A. RASKIN, M.D.,§ BEOW Y. YEAP, M.D.,‖ KAREN J. MARCUS, M.D.,¶ NANCY J. TARBELL, M.D.,† AND TORUNN I. YOCK, M.D., M.C.H.†

*ATreP (Provincial Agency for Proton Therapy), Trento, Italy; Departments of †Radiation Oncology, ‡Pediatric Hematology and Oncology, §Orthopaedic Surgery, and ‖Medicine, Massachusetts General Hospital–Harvard Medical School, Boston, MA; and ¶Division of Radiation Oncology, Children's Hospital Boston, MA

- Retrospective analysis
- Median dose 54 Gy RBE
- Median follow-up 38.4 months

-30 patients with EWS, treated between 2003 and 2009 with proton radiotherapy

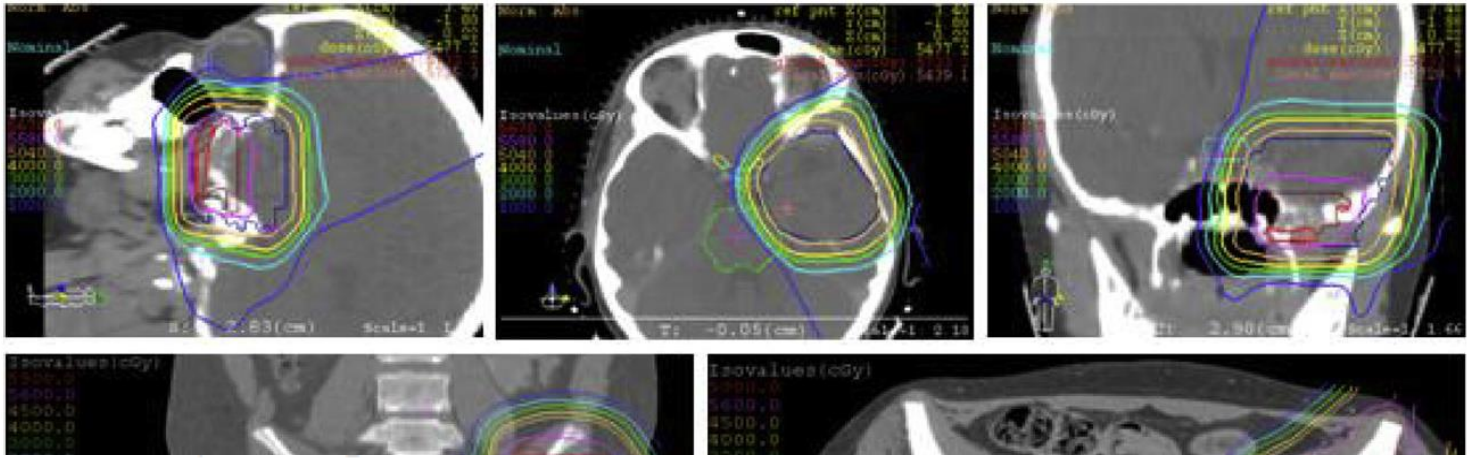
Table 1. Patient characteristics

Patient ID	Disease site treated	Sex	Age at PT	Surgery type (STR, NGTR, GTR, Bx only)	CTV1 Gy (RBE)	CTV2 Gy (RBE)	Total dose Gy (RBE)
1	Lumbar spine and paraspinal	M	17.9	STR	45.0		45.0
2	Pelvic mass, left ileum	F	11.6	Bx only	45.0	12.6	57.6
3	Pelvic mass, left iliopsoas muscle	M	16.6	Bx only	45.0	10.8	55.8
4	Thoraco-lumbo-sacral spine and paraspinal	F	2.6	STR	45.0		45.0
5	Cervico-thoracic and paraspinal	F	3.5	STR	43.2	12.6	55.8
6	Parieto-occipital bone	F	4.8	GTR	45.0		45.0
7	Thoracic paraspinal region	M	4.3	Bx only	43.2	9.6	52.8
8	Base of skull with intracranial extension	M	6.5	Bx only	45.0	10.8	55.8
9	Left chest wall	F	9.2	Bx only	50.4		50.4
10	Upper lung, neck and paraspinal	F	3.7	NGTR	30.6	19.8	50.4
11	Base of skull	F	7.4	STR	54.0		54.0
12	Left orbit, nasal cavity and maxillary sinus	F	15.4	STR	45.0	14.4	59.4
13	Thoraco-lumbar and paraspinal	F	15.2	Bx only	45.0		45.0
14	Base of tongue	F	1.8	Bx only	39.6	16.2	55.8
15	Ethmoid sinus invading orbit	M	17.7	Bx only	45.0	10.8	55.8
16	Thoracic spine and paraspinal	F	11.8	Bx only	46.8		46.8
17	Thoraco-lumbar spine	F	3.1	NGTR	45.0		45.0
18	Lumbar spine	F	13.0	GTR	50.4	5.4	55.8
19	Thoraco-lumbar spine	M	10.1	Bx only	43.2	7.2	50.4
20	Occipital region	M	2.3	Bx only	55.8		55.8
21	Temporal bone	M	11.8	Bx only	50.4	5.4	55.8
22	Pelvic mass, ischium	M	10.1	Bx only	45.0	10.8	55.8
23	Lumbo-sacral spine/pelvis	M	4.2	Bx only	45.0	5.4	50.4
24	Medial right orbit	M	14.8	STR	54.0		54.0
25	Thoracic spine and paraspinal, recurrent*	F	16.1	Bx only	45.0	5.4	50.4
26	CNS metastasis, recurrent*	F	14.5	STR	51.0	5.4	56.4
27	Pelvis	F	9.7	Bx only	45.0	10.8	55.8
28	Lumbo-sacral spinal and paraspinal, recurrent*	M	21.0	STR	45.0	5.4	50.4
29	Lumbar spine	M	11.5	STR	45.0	5.4	50.4
30	Base of skull, sphenoid body and wing	M	9.8	Bx only	50.0	8	58.0

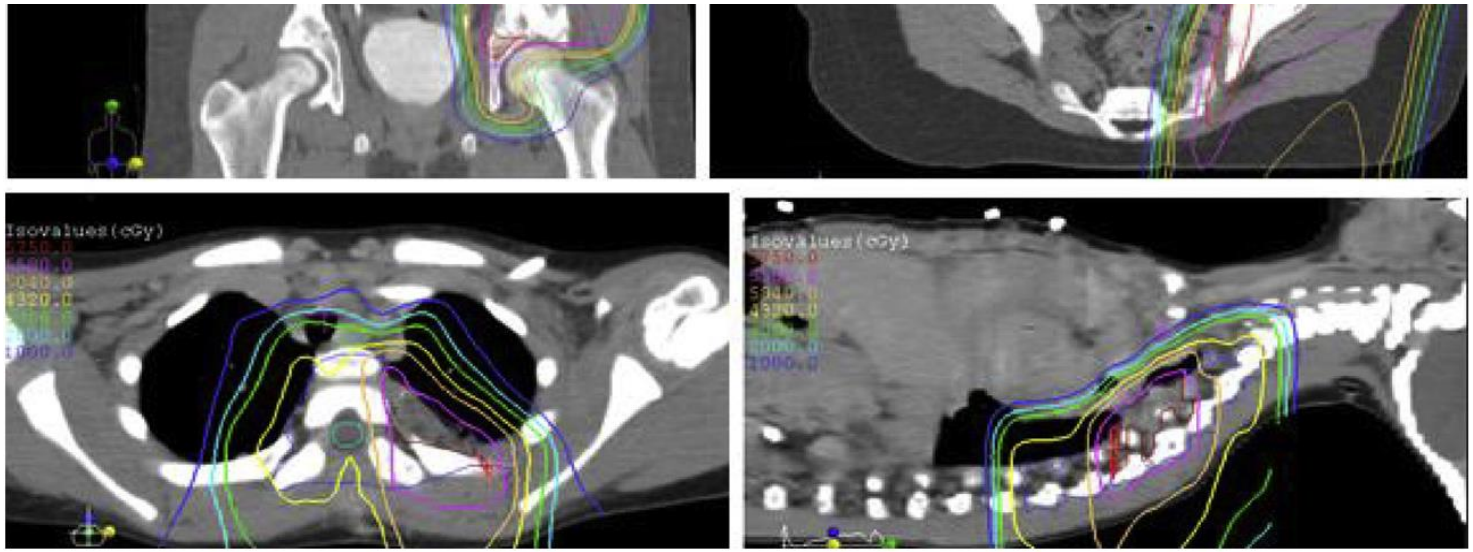
Abbreviations: ID= identification; PT= Proton therapy; STR= subtotal resection; NGTR= near gross total resection; GTR= gross total resection; Bx: biopsy; CTV1= clinical target volume 1; CTV2= CTV= clinical target volume 2; Gy (RBE)= Gray Radiobiologic Equivalent; M= male; F= female; CNS = central nervous system.

* Patients had been treated with surgery and/or PT to the primary lesion; PT was delivered to the site of recurrence.

PROTON RADIOTHERAPY FOR PEDIATRIC EWING'S SARCOMA: INITIAL CLINICAL OUTCOMES



Conclusions: Proton radiotherapy was well tolerated, with few adverse events. Longer follow-up is needed to more fully assess tumor control and late effects, but the preliminary results are encouraging.



BARBARA ROMBI

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 3, pp. 1142–1148, 2012

ESTRO School

Role of Radiotherapy in metastatic ES

✓ Irradiation of primary site (as in localized disease)

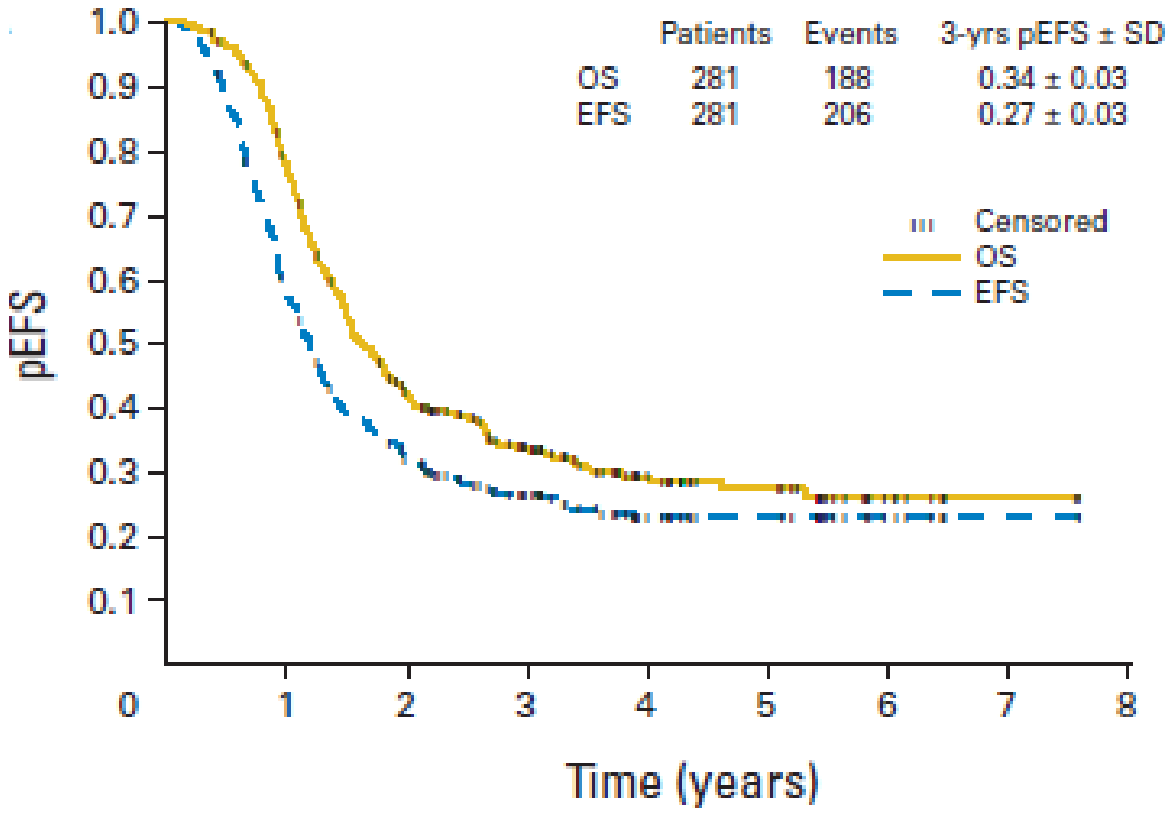
✓ Solitary or limited bony metastases treatment

✓ Pulmonary irradiation (WLI)

JOURNAL OF CLINICAL ONCOLOGY VOLUME 28 · NUMBER 20 · JULY 10 2010

Primary Disseminated Multifocal Ewing Sarcoma: Results of the Euro-EWING 99 Trial

Ruth Ladenstein, Ulrike Pötschger, Marie Cécile Le Deley, Jeremy Whelan, Michael Paulussen, Odile Oberlin, Henk van den Berg, Uta Dirksen, Lars Hjorth, Jean Michon, Ian Lewis, Alan Craft, and Heribert Jürgens



- 3-year EFS rate: 27%
- 3-year OS rate: 34%

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The Value of Local Treatment in Patients With Primary, Disseminated, Multifocal Ewing Sarcoma (PDMES)

Cancer January 15, 2010

Julia Haeusler, MD[1]; Andreas Ranft, PhD[1]; Tobias Boelling, MD[2]; Georg Gosheger, MD[3]; Gabriele Braun-Munzinger, MA[1]; Volker Vieth, MD[4]; Stefan Burdach, MD, PhD[5]; Henk van den Berg, MD, MMed, PhD[6]; Heribert Juergens, MD[1]; and Uta Dirksen, MD, PhD[1]

First report to analyze the role of local treatment in patients with primary disseminated disease

EURO-EWING 99 trial arm R3

Induction chemotherapy	*Local treatment*	***Adiuvant chemotherapy***
VIDE x 6		*high dose CT: Bu-Mel/ Bu-VP16 followed by reinfusion of PBSC*

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Cancer January 15, 2010

The Value of Local Treatment in Patients With Primary, Disseminated, Multifocal Ewing Sarcoma (PDMES)

Julia Haeusler, MD[1]; Andreas Ranft, PhD[1]; Tobias Boelling, MD[2]; Georg Gosheger, MD[3]; Gabriele Braun-Munzinger, MA[1]; Volker Vieth, MD[4]; Stefan Burdach, MD, PhD[5]; Henk van den Berg, MD, MMed, PhD[6]; Heribert Juergens, MD[1]; and Uta Dirksen, MD, PhD[1]

- *April 1998 –July 2006*

120 patients with extrapulmonary, primary, disseminated, multifocal Ewing sarcoma (PDMES)

- *Median follow up 1.38 years (0.8 – 3 years)*

Total no. of patients	120
Males	66 (55%)
Females	54 (45%)
Median age, y	16.2 (4.2-54.1)
Median tumor volume	346 mL (21-1978)
Primary tumor	
Central	82 (68.3%)
Peripheral	34 (28.3%)
Unknown	4 (3.3%)
Metastases	
Bone	97 (78.3%)
1 lesion	11(9.2%)
2-5 lesions	30 (25.0%)
>5 lesions	53 (44.2%)
Unknown	3 (2.5%)
Bone marrow	49 (38.3%)
Additional pulmonary	47 (39.2%)
Lymph node	26 (21.7%)
Liver	11 (9.2%)
CNS	1 (0.8%)
Other	10 (8.3%)

Patients' Characteristics

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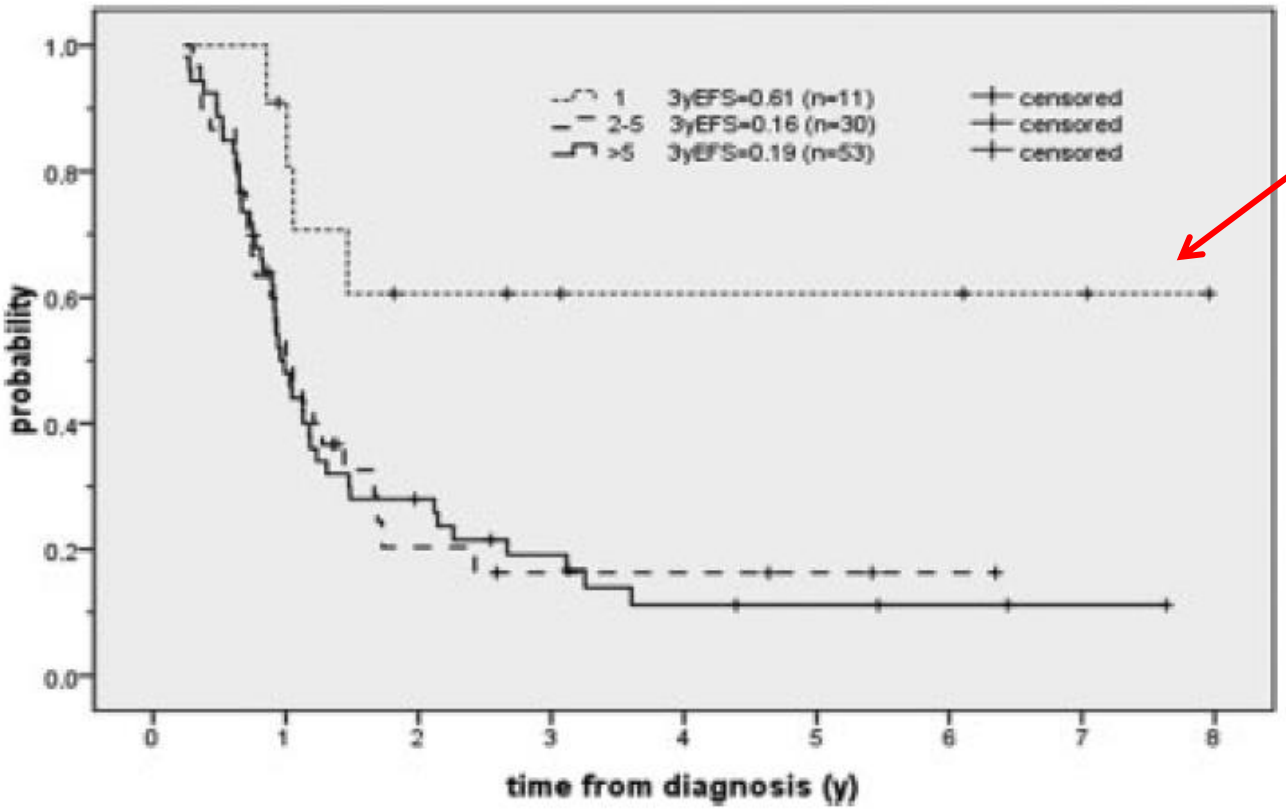
UNIVARIATE ANALYSIS



1 single metastases

Event-free survival according to the number of bone metastases at the time of diagnosis

NUMBER OF BONE METASTASES *was a significant prognostic factor for 3-year EFS:*

- ***1 SINGLE METASTATIC LESION:*** *3-YEAR* ***EFS 0.61***
- *more than 1 bone metastasis (2-5 lesions): 3-year EFS 0.19*
- *>5 lesions: 3-year EFS 0.16 (p< .001*

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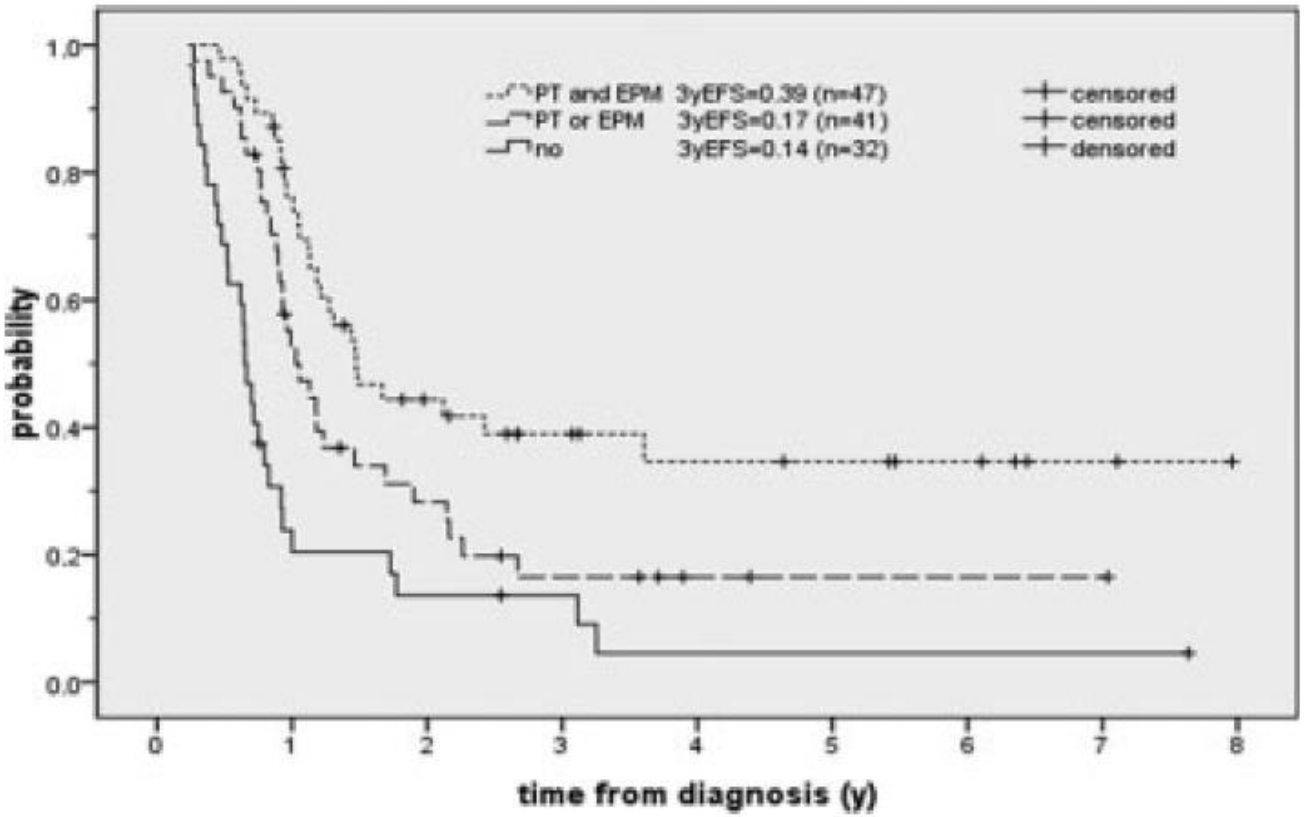

EFS according to local therapy of the primary tumor and/or extrapulmonary metastases

TREATMENT OF PRIMARY and/or EXTRAPULMONARY METASTASES	3-year EFS
Combined treatment	0.39
Local or extrapulmonary treatment alone	0.17
No local treatment	0.14

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MULTIVARIATE ANALYSIS

Variable	Label	Risk Ratio (n1)	*P*	Risk Ratio (n2)	*P*
Local therapy	PT and PDMES	1		1	
(*P* = .001[n1];.046[n2])	PT or PDMES	1.36 (0.72-2.56)	.341	1.78 (0.93-3.43)	.082
	No	3.14 (1.72-5.74)	.000	2.21 (1.10-4.47)	.027
High-dose chemotherapy	No	3.45 (1.92-6.17)	.000	1.54 (0.71-3.35)	.275
Age, y	>15	1.10 (0.68-1.79)	.695	1.03 (0.61-1.75)	.903
Tumor volume	>200 ml	1.65 (0.93-2.94)	.088	1.56 (0.84-2.89)	.158
Bone metastases	No	1		1	
(*P* = .152[n1];.175[n2])	1	0.48 (0.15-1.47)	.199	0.74 (0.23-2.39)	.616
	>1	1.29 (0.67-2.47)	.450	1.68 (0.80-3.53)	.170

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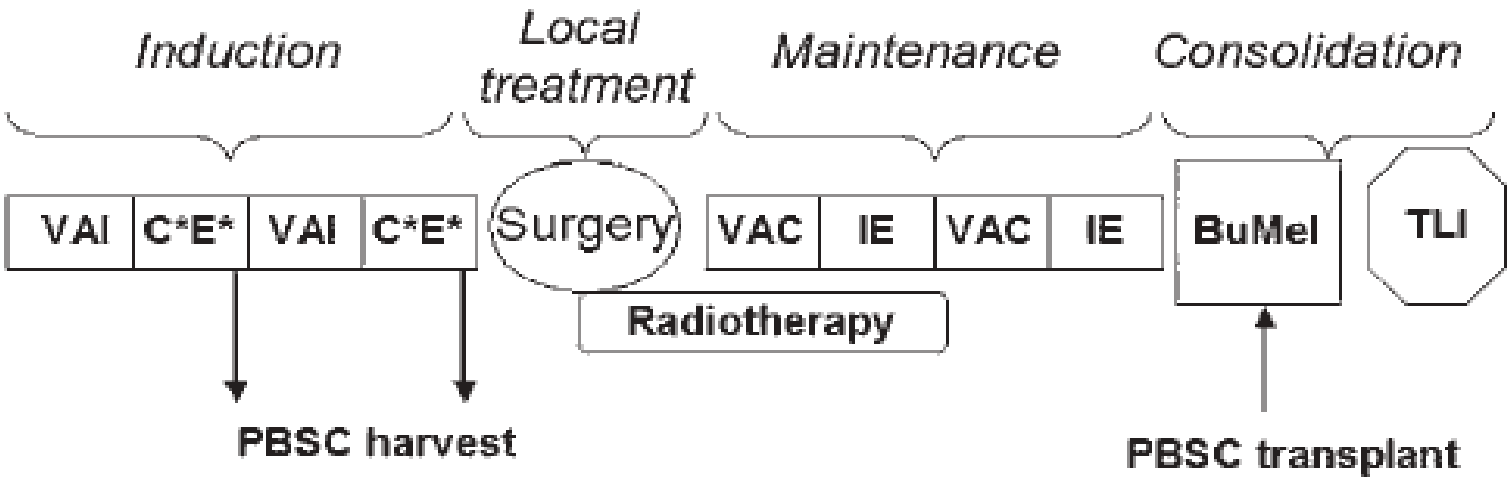
Whole Lung Irradiation in patients with pulmonary metastases from Ewing Sarcoma

- ✓ Although there has never been a randomized trial evaluating the efficacy of WLI, some studies (EICESS-92) have retrospectively shown an improvement in survival

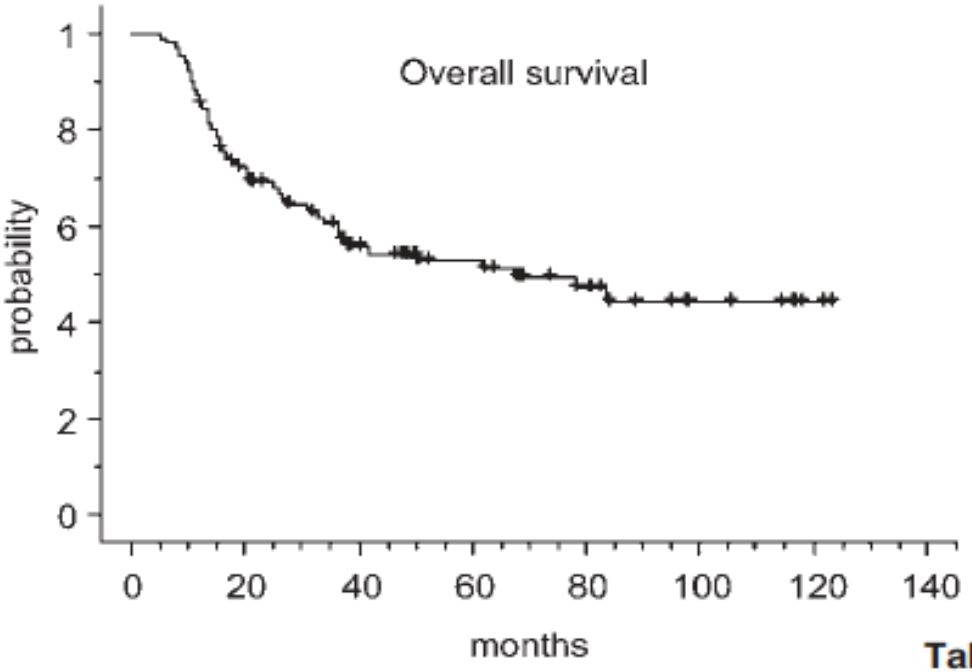
- ✓ As part of the curative intent of treatment of stage IV disease, the standard of care for ES with pulmonary metastases is to deliver low-dose (15 Gy) whole lung irradiation (WLI)

Primary metastatic Ewing's family tumors: results of the Italian Sarcoma Group and Scandinavian Sarcoma Group ISG/SSG IV Study including myeloablative chemotherapy and total-lung irradiation

Background: The Italian Sarcoma Group and the Scandinavian Sarcoma Group designed a joint study to improve the prognosis for patients with Ewing's family tumors and synchronous metastatic disease limited to the lungs, or the pleura, or a single bone.



Annals of Oncology 23: 2970–2976, 2012



Characteristic	No. of patients	Percentage
Age at diagnosis		
Median (years)	16	
Range (years)	2–40	
Sex		
Male	64	63
Female	38	27
Age groups (years)		
≤14	34	33
15–17s	25	24
≥18	43	43

- This intensive approach is feasible and long-term survival is achievable in 50% of patients
- New treatment approaches are warranted for patients responding poorly to primary chemotherapy

Table 3. Multivariate analysis of survival for patients with lung-only metastases

Prognostic factor	Relative risk (95% confidence interval)	*P*
Poor radiological/histological response of primary tumor after induction	3.4 (1.32 to 14.1)	0.004
Partial/no response of lung metastases after induction	2.6 (1.32 to 3.9)	0.01
Primary tumor volume ≥ 200 ml	1.46 (0.46 to 9.7)	0.19
High lactate dehydrogenase value	1.22 (0.47 to 7.58)	0.93

Annals of Oncology 23: 2970–2976, 2012

Strahlentherapie
und Onkologie

Supplement Article

Radiation Toxicity Following Busulfan/Melphalan High-dose Chemotherapy in the EURO-EWING-99-trial: Review of GPOH Data

Tobias Bölling[1], Uta Dirksen[2], Andreas Ranft[2], Iris Ernst[1], Heribert Jürgens[2], Normann Willich[1]

High-dose chemotherapy (HDT) with busulfan/melphalan (Bu-Mel) may yield benefits for patients suffering from metastasized Ewing tumors compared with conventional chemotherapy

In late 2003, there was an alert concerning severe complications after BuMel HDT and irradiation of the spinal cord

Subsequently an amendment with a restriction of the radiation dose to the spinal cord of 30 Gray (Gy) after BuMel HDT and a warning regarding radiotherapy to central axial sites following BuMel HDT was established within the study protocol

In 2005, two reports from France described severe gut toxicity after BuMel HDT and high dose radiotherapy in the pelvis

Absence of severe toxicity problems in Germany

VOLUME 32 · NUMBER 21 · JULY 20 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Breast Cancer After Chest Radiation Therapy for Childhood Cancer

Chaya S. Moskowitz, Joanne F. Chou, Suzanne L. Wolden, Jonine L. Bernstein, Jyoti Malhotra, Danielle Novetsky Friedman, Nidha Z. Mubdi, Wendy M. Leisenring, Marilyn Stovall, Sue Hammond, Susan A. Smith, Tara O. Henderson, John D. Boice, Melissa M. Hudson, Lisa R. Diller, Smita Bhatia, Lisa B. Kenney, Joseph P. Neglia, Colin B. Begg, Leslie L. Robison, and Kevin C. Oeffinger

Purpose

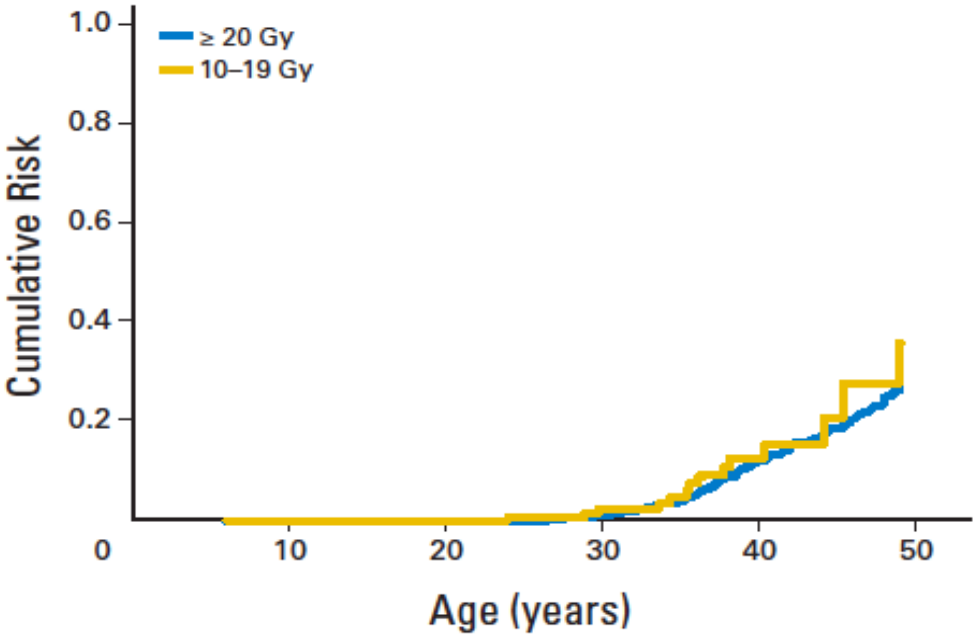
The risk of breast cancer is high in women treated for a childhood cancer with chest irradiation. We sought to examine variations in risk resulting from irradiation field and radiation dose.

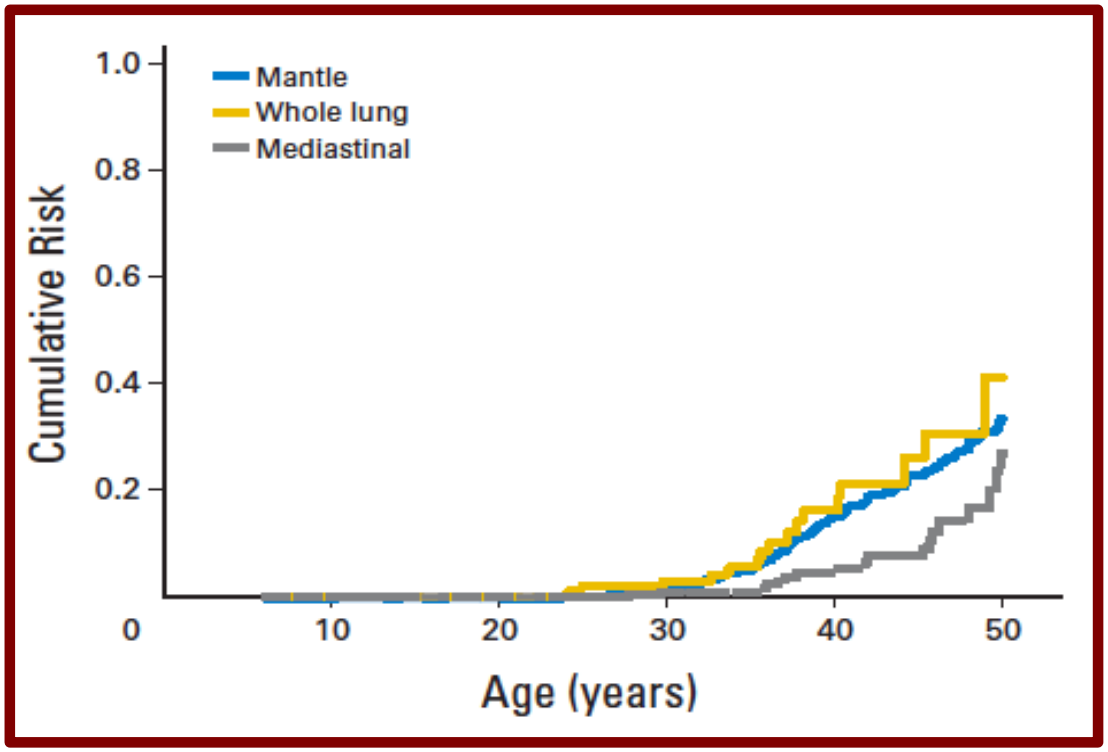
Patients and Methods

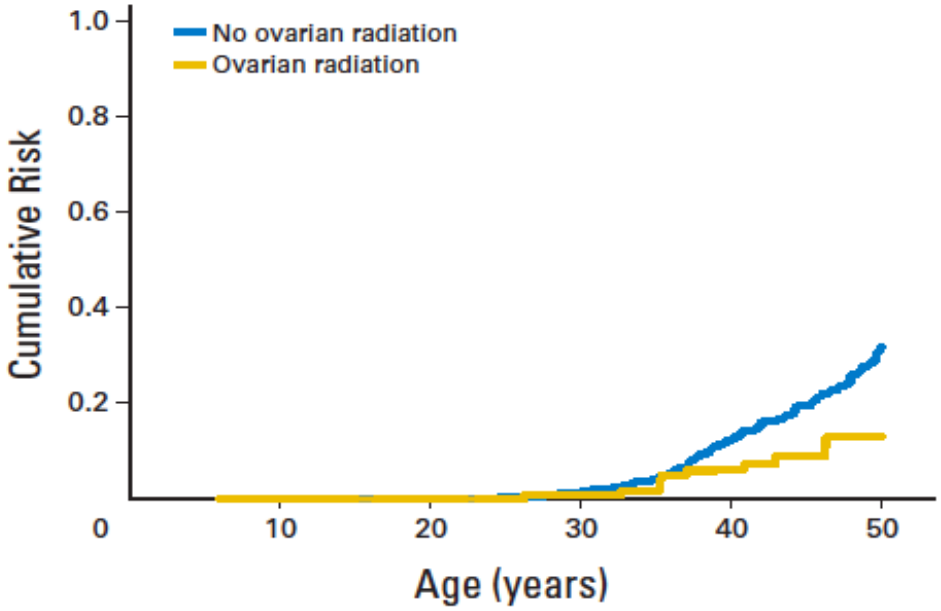
We evaluated cumulative breast cancer risk in 1,230 female childhood cancer survivors treated with chest irradiation who were participants in the CCSS (Childhood Cancer Survivor Study).

Conclusion

Among women treated for childhood cancer with chest radiation therapy, those treated with whole-lung irradiation have a greater risk of breast cancer than previously recognized, demonstrating the importance of radiation volume. Importantly, mortality associated with breast cancer after childhood cancer is substantial.







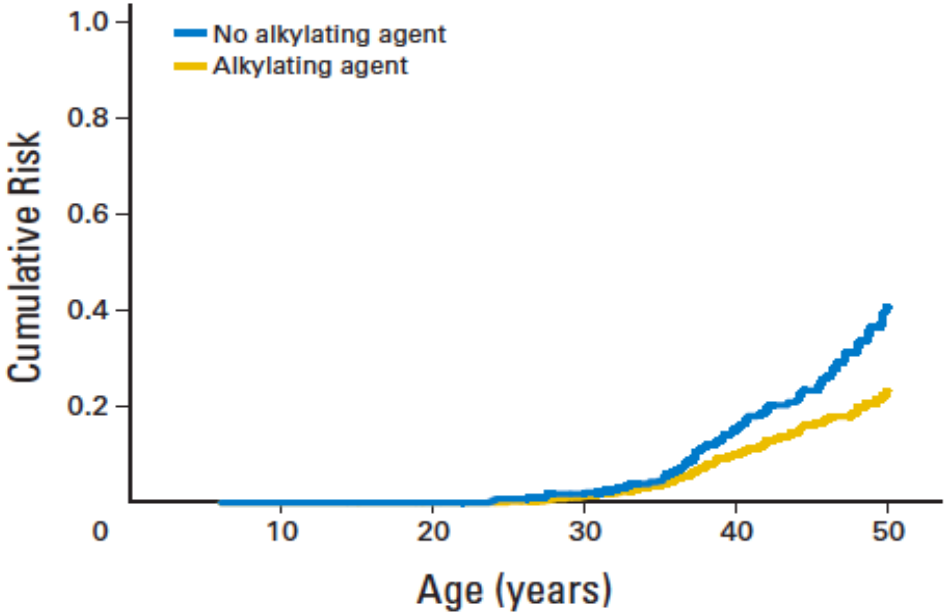


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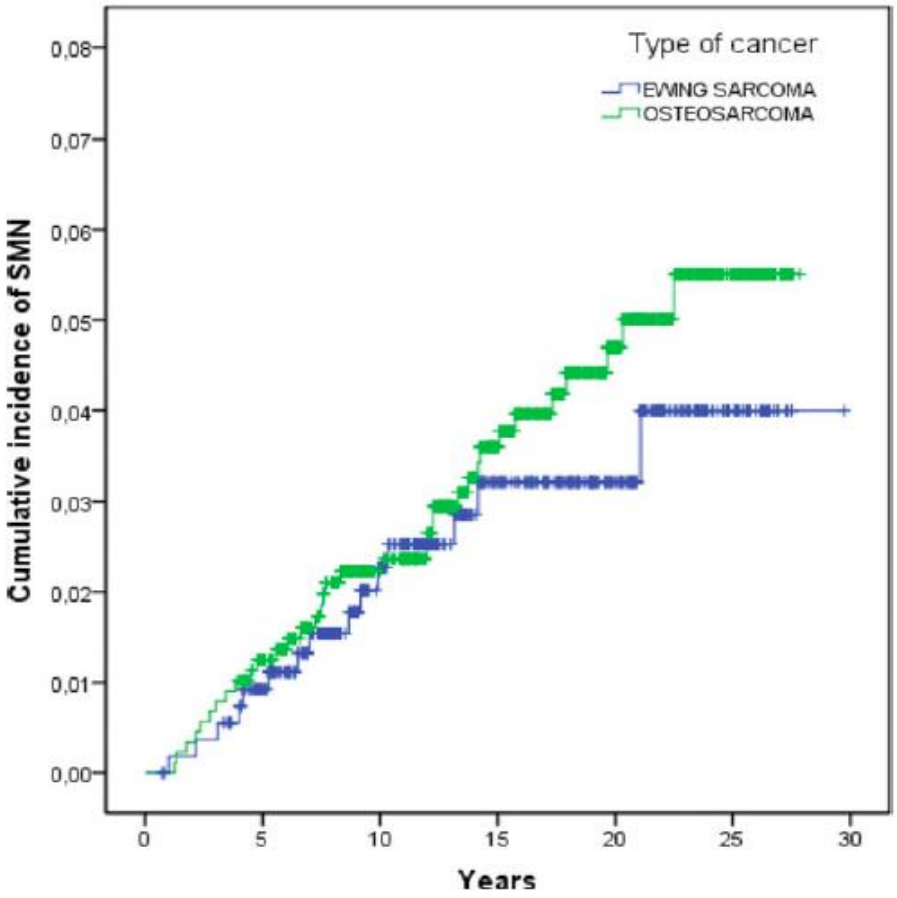
Table 2. SIRs of Breast Cancer by Childhood Cancer Diagnosis and Treatment

Characteristic	No. of Participants	No. of Person-Years of Risk	No. of Breast Cancer Cases		SIR	95% CI
			Observed	Expected		
Total group	1,230	23,920	203	9.3	21.9	19.1 to 25.2
Primary field of chest irradiation, dose in Gy						
Mantle (median, 40; range, 5 to 54)	603	12,012	156	6.5	24.2	20.7 to 28.3
Mediastinal (median, 30; range, 3 to 54)	239	4,732	20	1.5	13.0	8.4 to 20.2
Whole lung (median, 14; range, 2 to 20)	116	2,198	17	0.4	43.6	27.1 to 70.1
Total body (median, 12; range, 4 to 16)	69	1,118	4	0.2	19.3	7.3 to 51.5
Abdominal (median, 20; range, 4 to 40)*	77	1,579	2	0.2	10.8	2.7 to 43.2
Posterior chest (median, 31; range, 6 to 54)†	54	982	0	0.2	0.0	—
Other one-sided anterior (median, 41; range, 10 to 61)	53	1,073	3	0.3	9.9	3.2 to 30.6
Dose of radiation to chest, Gy						
10-19‡	159	2,939	15	0.5	30.6	18.4 to 50.7
≥ 20	916	18,211	179	8.5	21.2	18.3 to 24.5
Ovaries irradiated						
No	1,102	21,259	193	8.1	23.7	20.6 to 27.3
Yes	128	2,661	10	1.1	8.8	4.7 to 16.4
Alkylating agents						
No	418	8,782	89	4.1	22.7	18.4 to 28.0
Yes	805	14,997	113	4.0	21.4	17.8 to 25.8
Childhood cancer group						
Hodgkin lymphoma	678	13,533	167	7.2	23.1	19.8 to 26.8
Other cancer	552	10,387	36	2.0	17.8	12.9 to 24.7
Age at diagnosis, years						
0-9	402	7,983	11	0.7	14.8	8.2 to 26.8
10-14	353	6,864	66	2.4	27.5	21.6 to 35.0
15-20	475	9,031	126	6.1	20.6	17.3 to 24.6

Abbreviation: SIR, standardized incidence ratio.
*Abdominal field extending above diaphragm.
†Posterior thoracic or paravertebral fields.
‡Irradiation fields represented in this group include mantle (n = 3), mediastinal (n = 30), whole lung (n = 46), hemithorax (n = 4), total body (n = 43), paravertebral/posterior chest (n = 11), and abdominal (n = 22).

Late Effects of Chemotherapy and Radiotherapy in Osteosarcoma and Ewing Sarcoma Patients

The Italian Sarcoma Group Experience (1983-2006)



Data were available on 883 patients with osteosarcoma and 543 patients with Ewing sarcoma

Cumulative 10-year and 20-year incidence of an SMN was 4.9% and 6.1%, respectively, in the osteosarcoma group, and **3.4% and 4.7%, respectively, in the Ewing sarcoma group**

Most common SMN in the osteosarcoma group was breast cancer , and **radiotherapy-induced osteosarcoma in ES group**

Permanent sterility was more common in males than in females ; Doxorubicin cardiotoxicity occurred in 18 patients with osteosarcoma (2%) and in 7 patients with Ewing sarcoma (1.3%)

-SJCRH Data base including 266 survivors of Ewing's sarcoma: 16 second malignancies (6.0%) (median follow-up 9.5 years)
- Median latency to the diagnosis of the second malignancy = 7.6 years (range, 3.5 to 25.7).

- The **cumulative incidence rate of secondary sarcoma was radiation dose-dependent** (P = .002):
• no secondary sarcomas in children with Ewing's sarcoma who received dose <48 Gy.
• the absolute risk of developing a secondary sarcoma after doses of 48–59.99 Gy was 24.9 cases/10,000 person-years; for doses of 60 Gy, it was 131 cases/10,000 person-years

Second malignancies after Ewing's sarcoma: radiation dose-dependency of secondary sarcomas.
Kuttesch et al, J Clin Oncol, 1996

Longitudinal Follow-Up of Adult Survivors of Ewing Sarcoma: A Report From the Childhood Cancer Survivor Study

Neyssa M. Marina, MD, MS[1]; Qi Liu, MS[2]; Sarah S. Donaldson, MD[3]; Charles A. Sklar, MD[4]; Gregory T. Armstrong, MD, MSCE[5]; Kevin C. Oeffinger, MD[4]; Wendy M. Leisenring, PhD[6]; Jill P. Ginsberg, MD, MS[7]; Tara O. Henderson, MD, MS[8]; Joseph P. Neglia, MD, MPH[9]; Marilyn A. Stovall, PhD[10]; Yutaka Yasui, PhD[5]; R. Lor Randall, MD[11]; David S. Geller, MD[12]; Leslie L. Robison, PhD[5]; and Kirsten K. Ness, PhD[5]

Cancer July 1, 2017

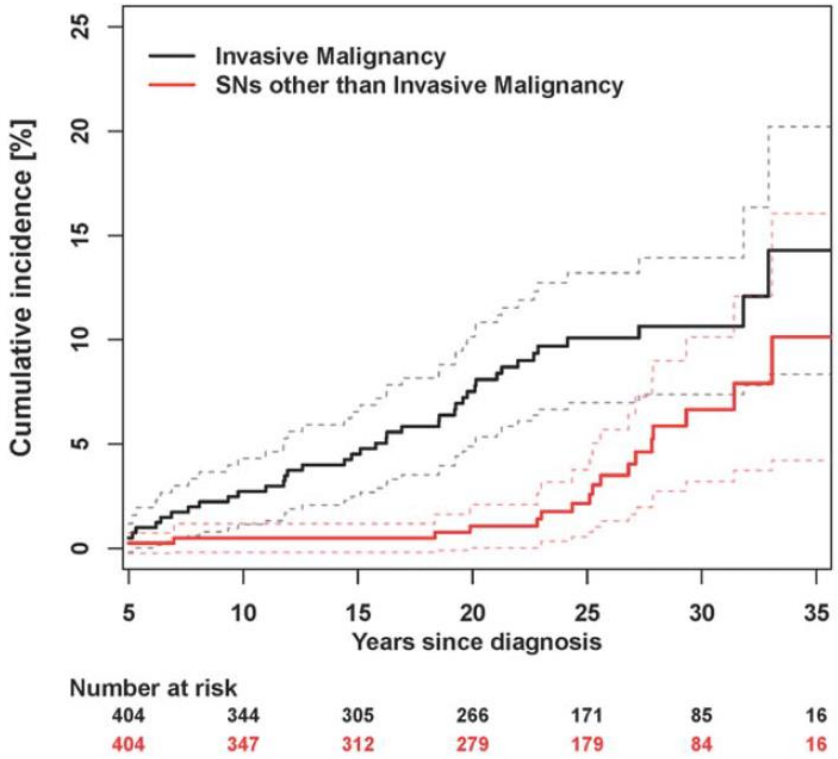


Figure 1. Cumulative incidence of subsequent neoplasms (SNs): malignant and nonmalignant.

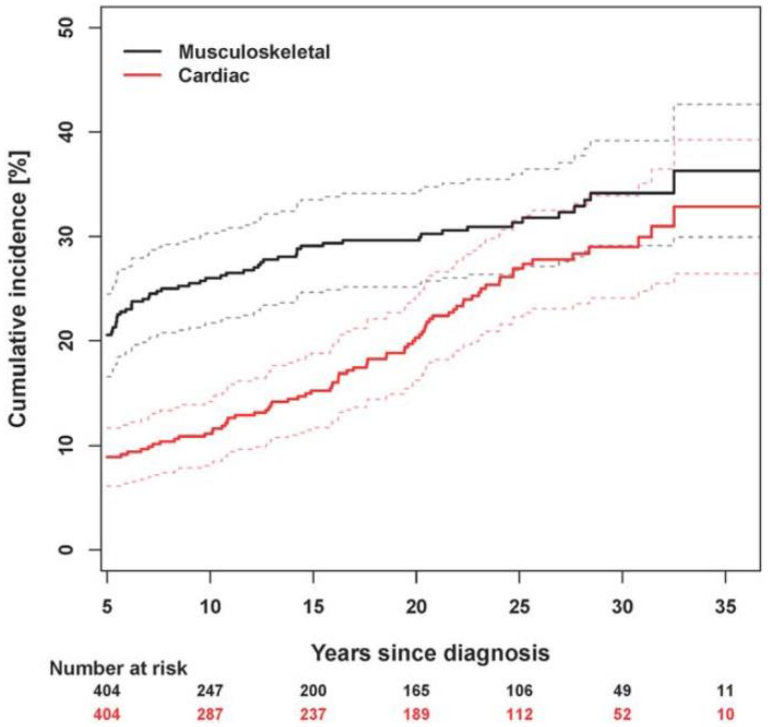


Figure 2. Cumulative incidence of musculoskeletal and cardiac complications.

spectively. **CONCLUSIONS:** With extended follow-up, ESSs' risk for late mortality and SNs does not plateau. Treatment-related chronic conditions develop years after therapy, and this supports the need for lifelong follow-up. ***Cancer* 2017;123:2551-60**. © *2017 American Cancer Society.*

VOLUME 35 · NUMBER 15 · MAY 20, 2017

JOURNAL OF CLINICAL ONCOLOGY

Quality of Survivorship in a Rare Disease: Clinicofunctional Outcome and Physical Activity in an Observational Cohort Study of 618 Long-Term Survivors of Ewing Sarcoma

Andreas Ranft, Corinna Seidel, Christiane Hoffmann, Michael Paulussen, Ann-Christin Warby, Henk van den Berg, Ruth Ladenstein, Claudia Rossig, Uta Dirksen, Dieter Rosenbaum, and Herbert Juergens

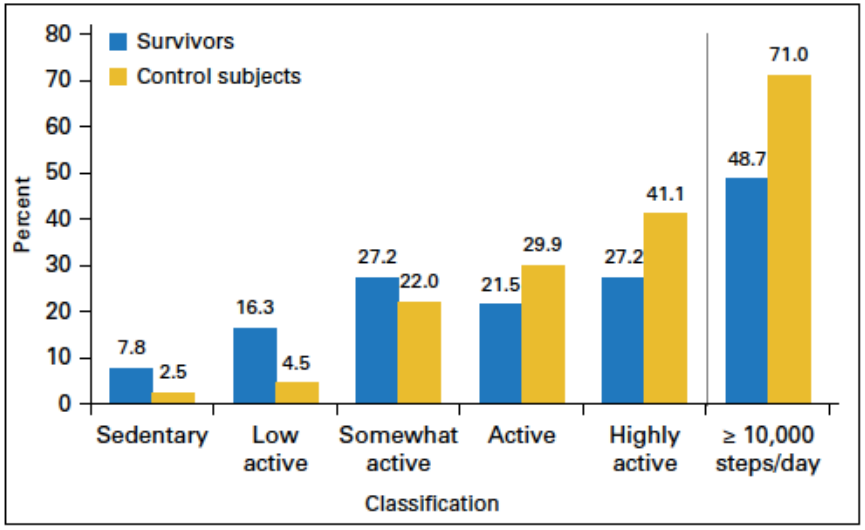


Fig 3. Step measurement classification and percentage of survivors and control subjects within each. Sedentary, < 5,000 steps/day; low active, 5,000 to 7,499 steps/day; somewhat active, 7,500 to 9,999 steps/day; active, 10,000 to 12,499 steps/day; and highly active, ≥ 12,500 steps/day.

Conclusion

Survivors of Ewing sarcoma apparently returned to a normal life with minor limitations. Observed reductions in physical scores should be a focus in future research to optimize treatment strategies to reduce a negative impact on the quality of survivorship.

Summary and conclusions

- ✓ ES are the second most frequent primary bone cancer, affecting primarily patients in the second and third decades of life
- ✓ Patients presenting with localized disease have an approximately two thirds chance of being cured
- ✓ Those whose disease is initially systemic have a much worse outcome (30-40% EFS rate with isolated pulmonary mets, less than 20% chance of cure with bone or bone marrow involvement)
- ✓ No chance of cure in relapsing patients
- ✓ New therapeutic approaches required to cure refractory diseases and/or to reduce late effects

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Conclusion

- For a disease that is certainly uncommon, a concerted effort is required to capture these patients in clinical trials to systematically address questions regarding biological factors and therapeutic strategies to improve survival

- Importance of local treatment → MDT

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WWW.ESTRO.ORG/SCHOOL

WILMS TUMOR: COG CONCEPTS

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MD Anderson Cancer Center
Houston, Texas USA

MD Anderson Cancer Center

ESTRO School

Goals and Objectives

At the end of the presentation, the participant should be able to

1. Discuss the epidemiology, presentation and work-up for children with Wilms' tumor
2. Discuss the COG approach to Wilms' tumor staging and treatment
3. Discuss the indications for radiotherapy in Wilms' tumor and other related renal tumors

Historical Background


MAX WILMS (1867 - 1918)

1814 Rance – first case (Case of fungus haematodes of the kidnies)

1828 Gairdner – second case (Agnes B)

1899 Max Wilms - (Die Mischgeschwuelste)

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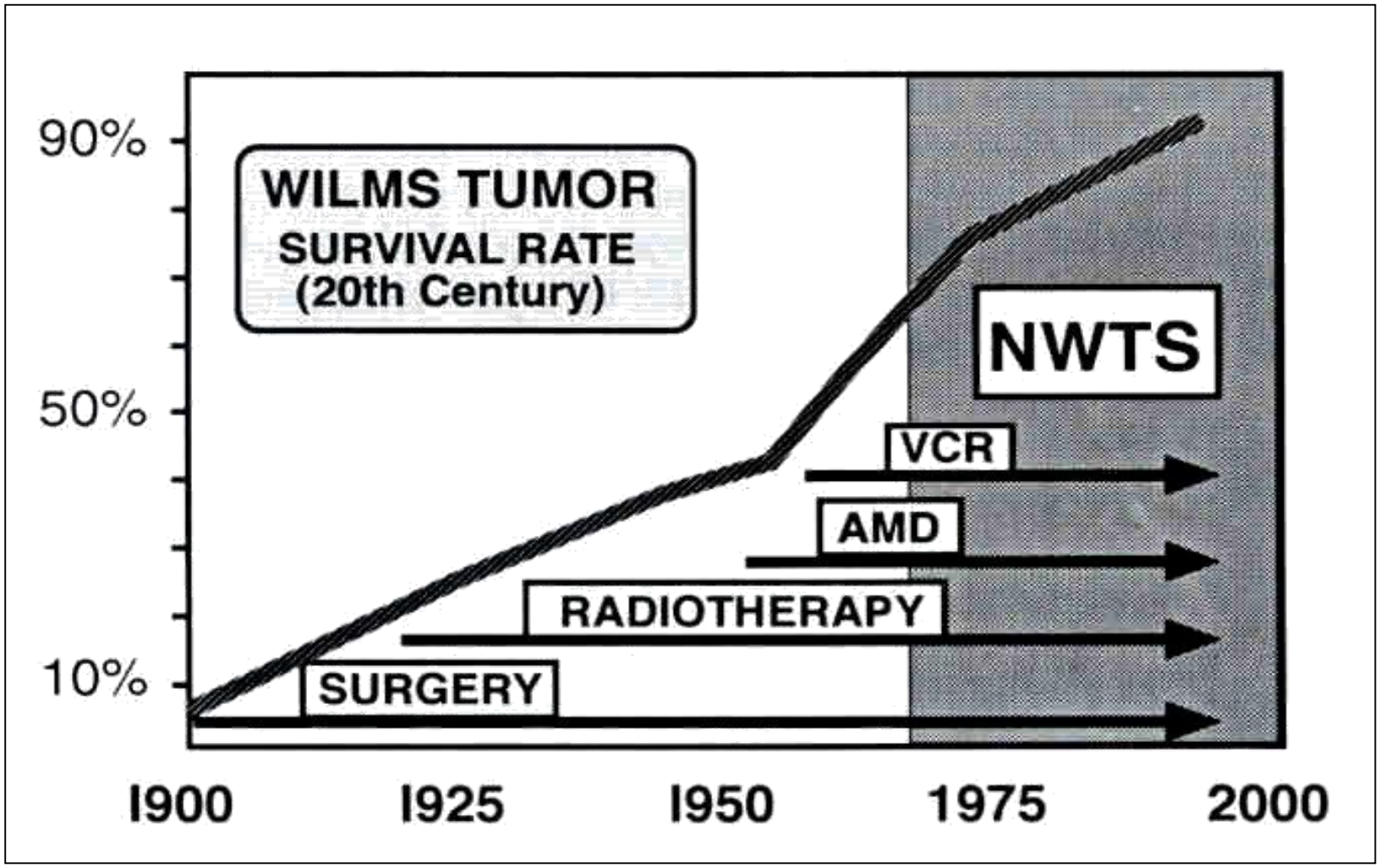
Historical Background



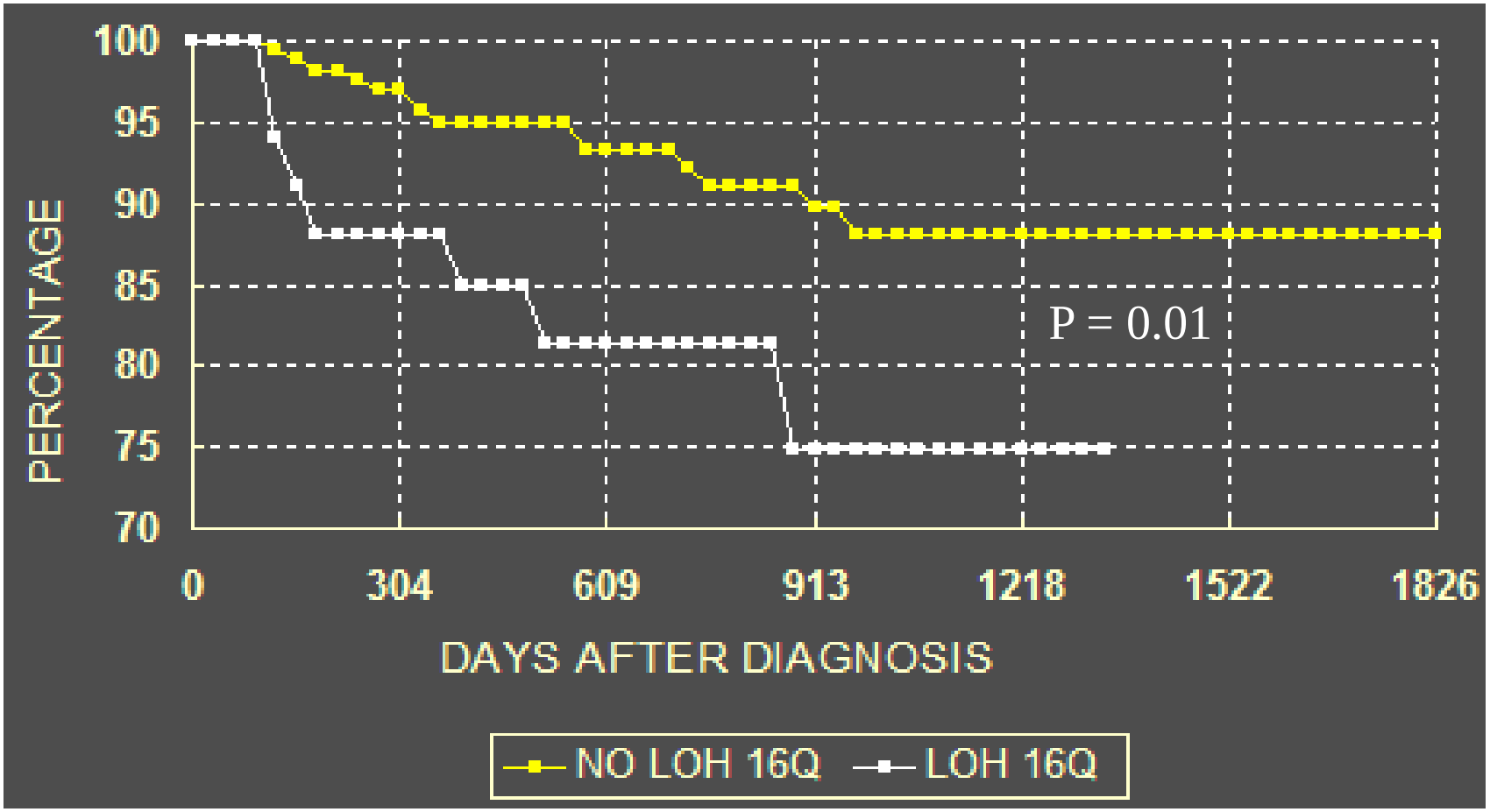
Incidence

- 450 cases/ year in the U.S.
- 7 cases per million children in the U.S.
- Most common abdominal tumor of childhood
- Sex ratio 0.92:1(M:F)
- Median age: 3.5 years

Congenital Syndromes

Syndrome	Presentation	Genetic Change	Incidence of Wilms' Tumor
WAGR	**Aniridia, genitourinary anomalies, mental retardation**	**Monoallelic deletion at chromosome 11p13**	**> 30%**
Denys-Drash	**Intersexual disorders, nephropathy**	**WT1 point mutation**	**> 90%**
Beckwith-Wiedemann	**Macroglossia, organomegaly, neonatal hypoglycemia, gigantism**	**Duplication of paternal allele**	**< 5%**

Loss of Heterozygosity at 16q



Grundy P et al. Cancer Res 1994; 54:2331-3

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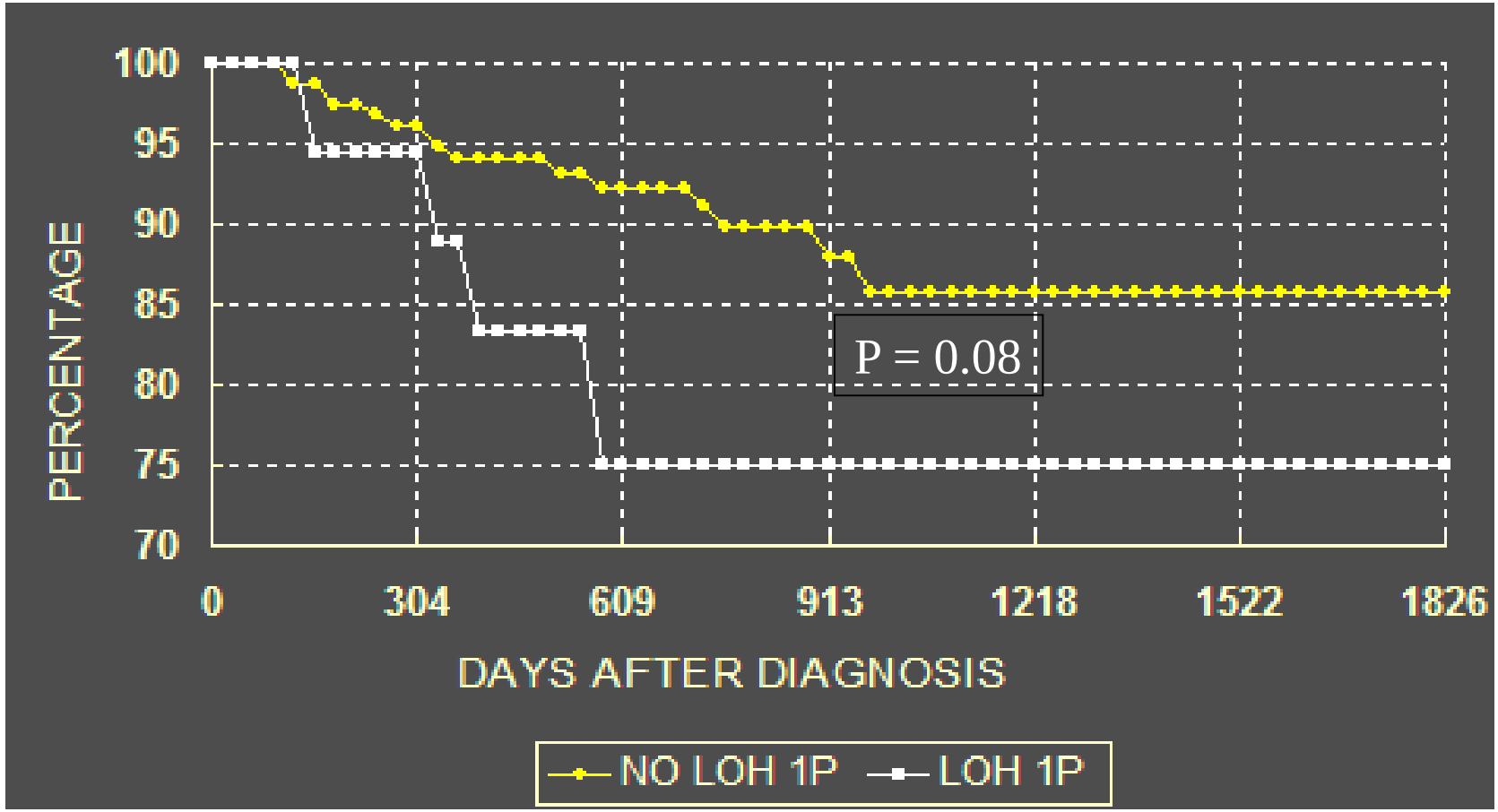
Loss of Heterozygosity at 1p



Grundy P et al. Cancer Res 1994; 54:2331-3

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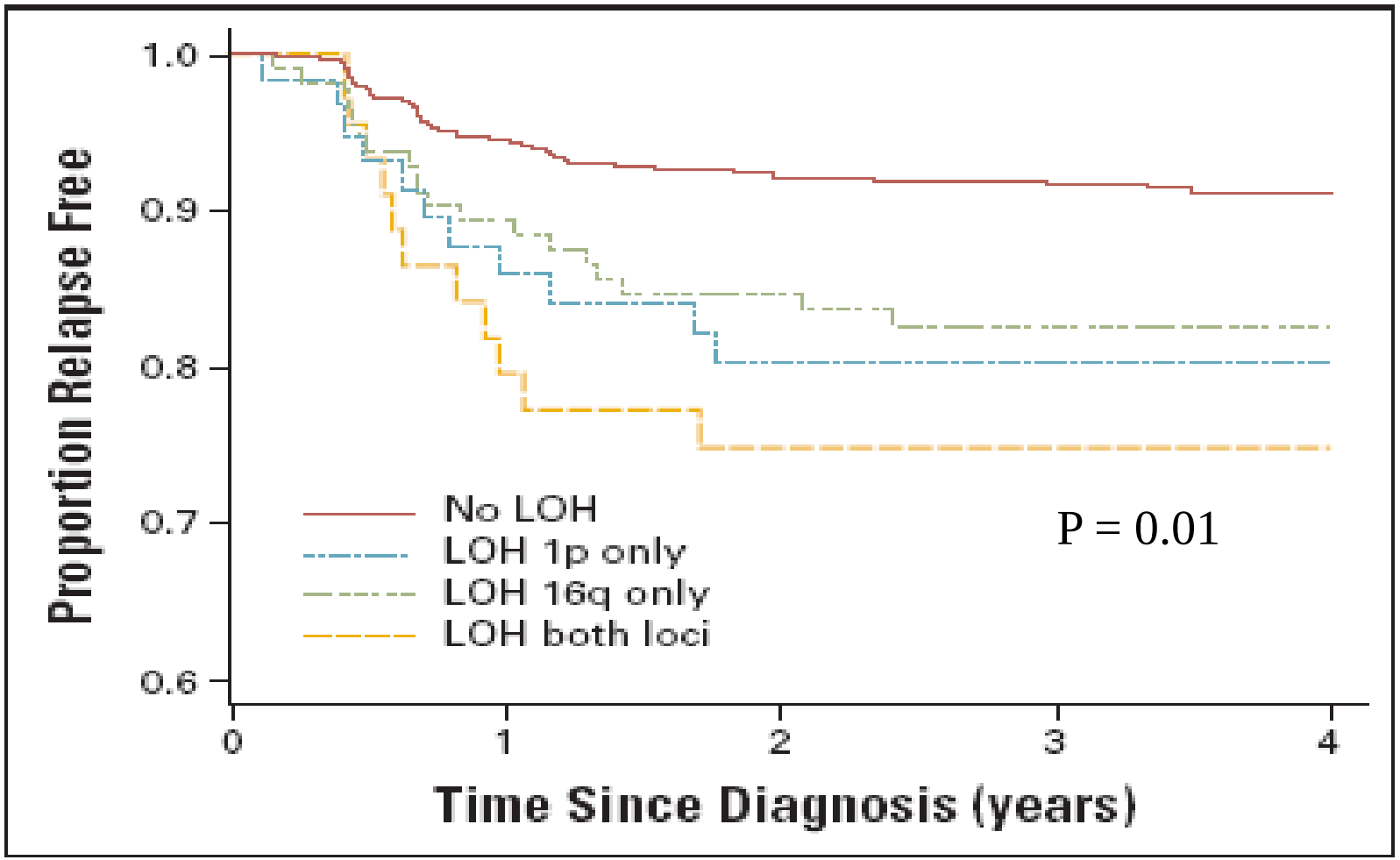
LOH 1p and 16 q (Stage I/II FH, NWTS-5)



Grundy PE et al. J Clin Oncol 2005; 23:7312-21

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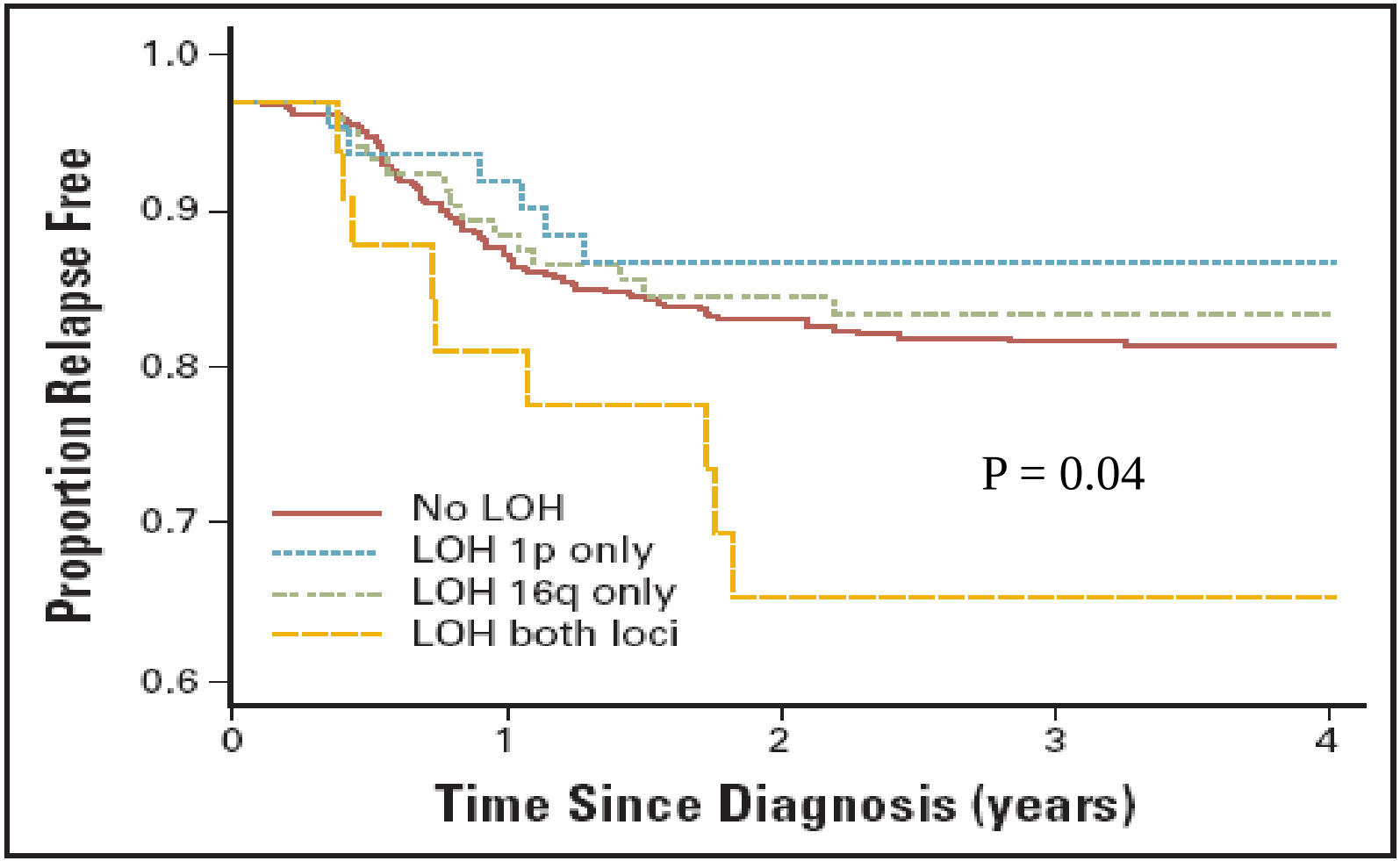
LOH 1p and 16 q (Stage III/IV FH, NWTS-5)



Grundy PE et al. J Clin Oncol 2005; 23:7312-21

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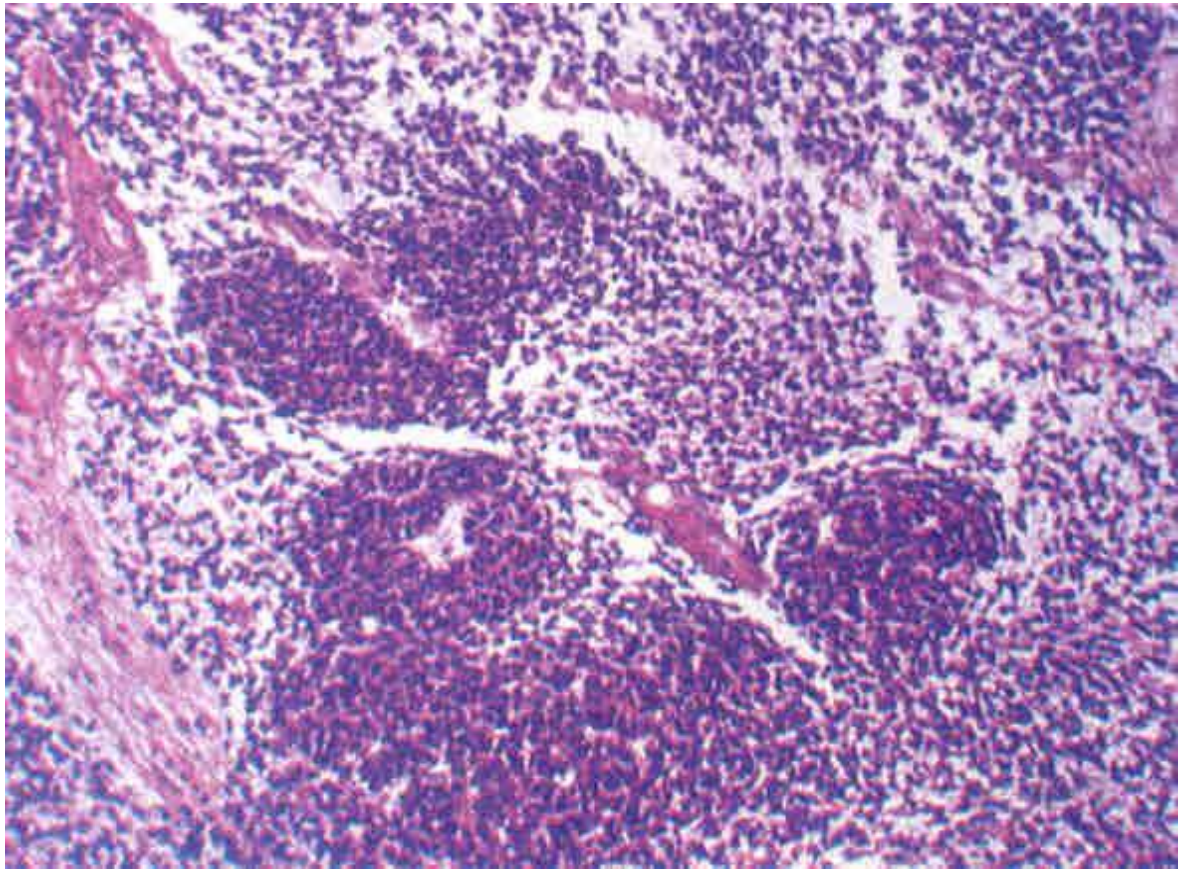
Work-up of Wilms tumor

- Computed tomography of abdomen and pelvis
- Computed tomography of chest
- Skeletal survey (CCSK only)
- Radionuclide bone scan (CCSK only)
- MRI of brain (CCSK and Rhabdoid tumor)
- Bone marrow aspiration and biopsy (CCSK only)

Favorable Histology



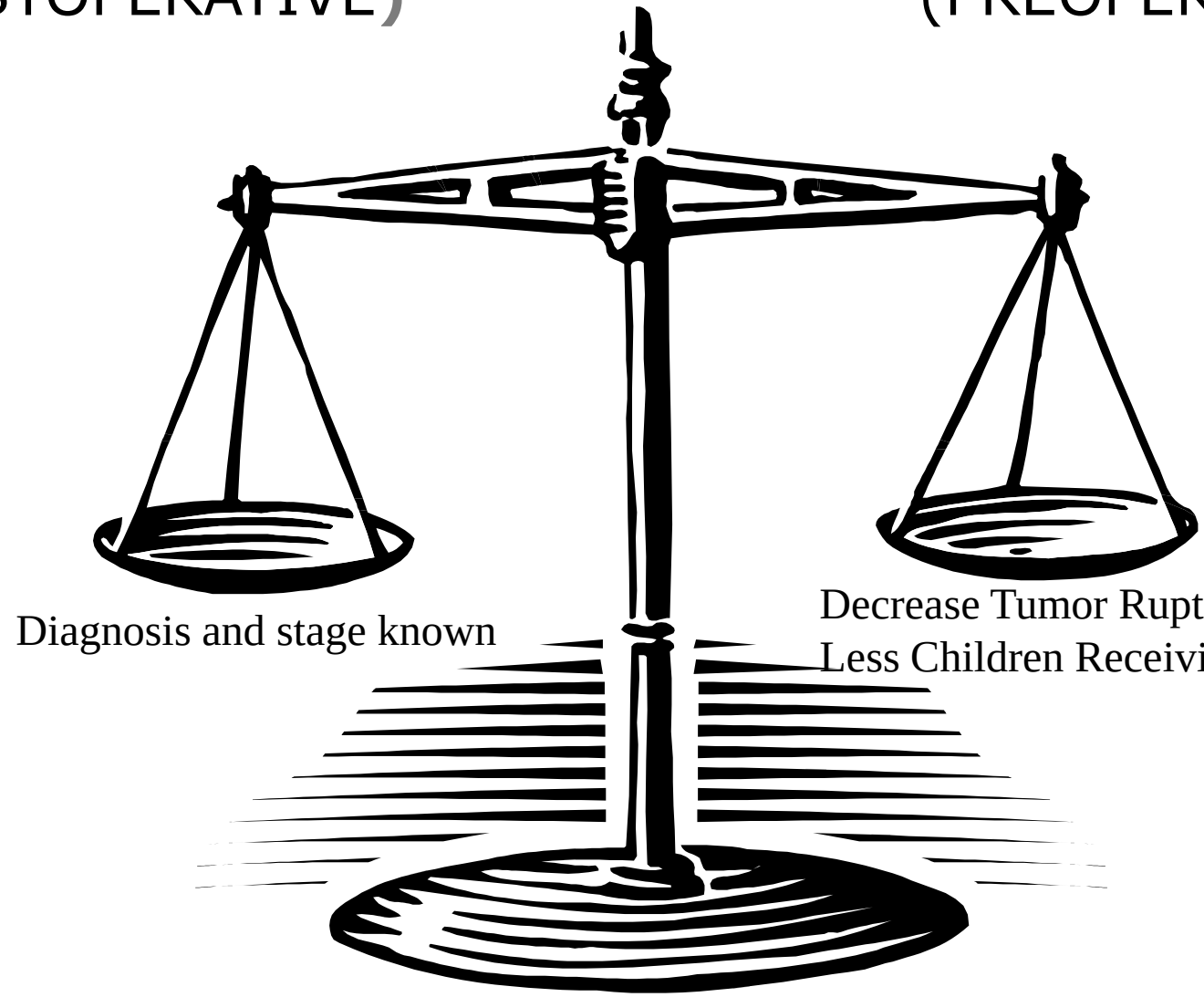
Stromal

Epithelial

Blastemal

NORTH AMERICAN
(POSTOPERATIVE)

EUROPEAN
(PREOPERATIVE)



Diagnosis and stage known

Decrease Tumor Rupture/Spillage
Less Children Receiving Radiotherapy

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Staging System for Wilms Tumor

I Tumor confined to kidney and completely resected. No penetration of the renal capsule or involvement of renal sinus vessels

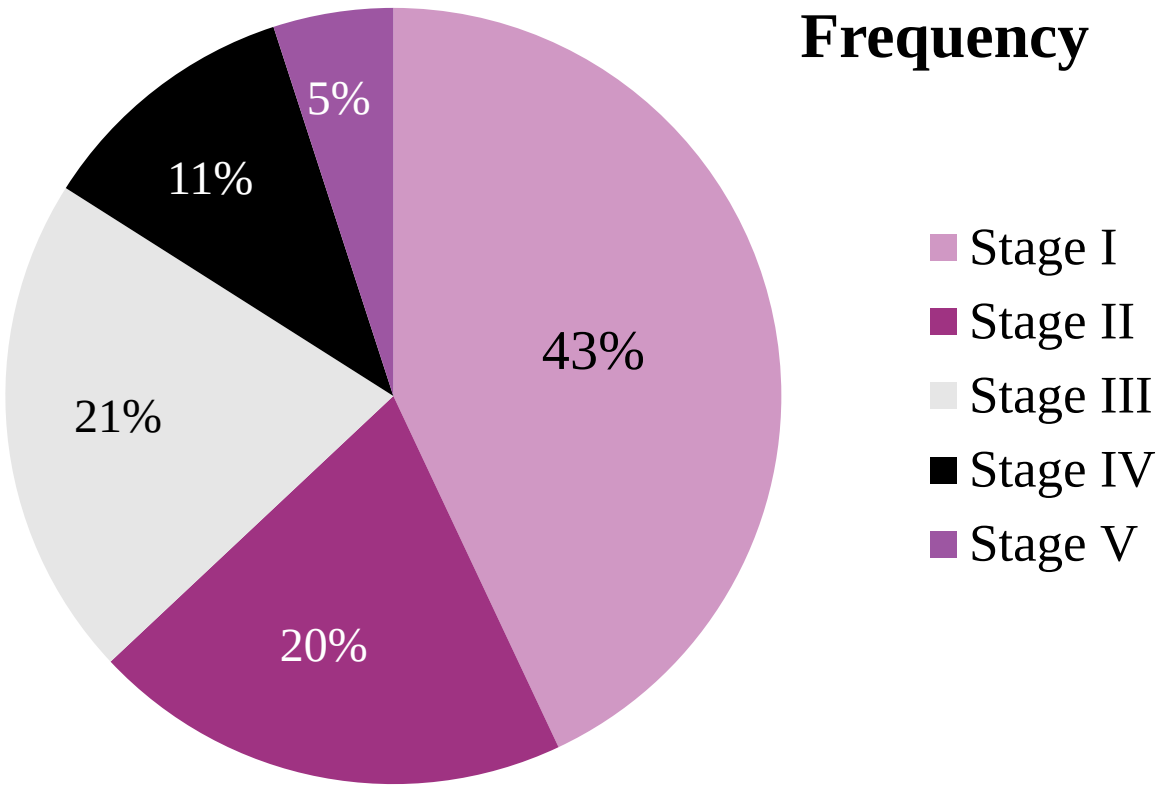
II Tumor extends beyond kidney but completely resected. (a) penetration of renal capsule (b) invasion of renal sinus vessels

III Gross or microscopic residual remains postoperatively (inoperable tumor, positive surgical margins, tumor spillage either before or during surgery, regional lymph node metastases, tumor is removed greater than one piece, penetration through peritoneal surface)

IV Hematogenous or lymph node metastases outside abdomen

V Bilateral Wilms' tumor at onset

Stage Distribution



Wilms Tumor
Stage I, Favorable Histology

NWTS-1

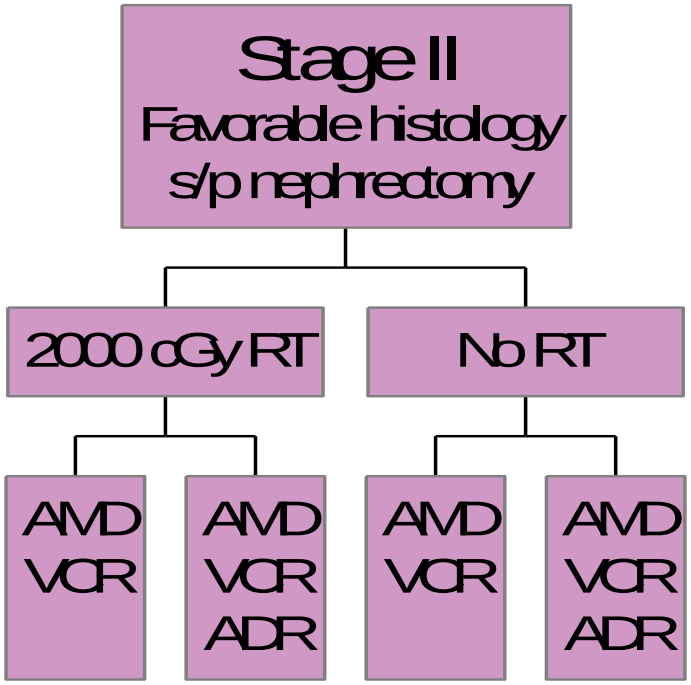
- Radiotherapy not necessary for Group 1 Wilms' tumor < 2 years of age
- There was a benefit for radiotherapy for Group 1 Wilms' tumor $\geq$ 2 years of age (2 yr DFS: 77% vs. 58%, p = 0.04). These pts were treated with Regimen A (AMD alone)

NWTS-2

- Radiotherapy not used in Group I patients. VCR was added to regimen. Randomization was 6 mos vs. 15 mos. Of AMD + VCR. 3-yr RFS was 89% and 84% respectively

D'Angio GJ et al. Cancer 1976,
D'Angio et al. Cancer 1981

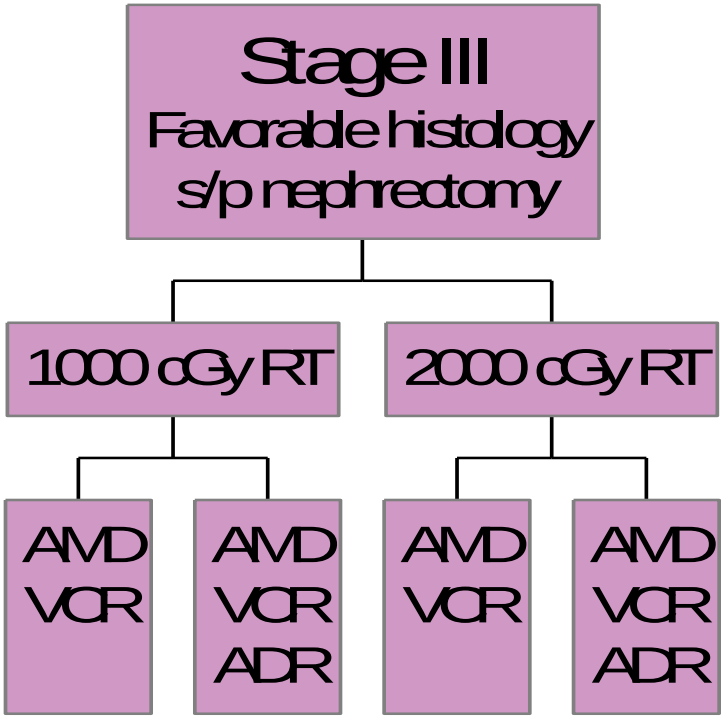
Wilms Tumor
Stage II, Favorable Histology



NWTS-3 Treatment	Percent alive at 2 years
AMD + VCR	98.6%
AMD + VCR + 2000 cGy	98.4%
AMD + VCR + ADR	95.5%
AMD + VCR + ADR + 2000 cGy	93.5%

D'Angio GJ et al. Cancer 1989; 64:349-60

Wilms Tumor
Stage III, Favorable Histology



NWTS-3 Treatment	Percent alive at 2 years
AMD + VCR + 1000 cGy	88.3%
AMD + VCR + 2000 cGy	91.0%
AMD + VCR + ADR + 1000 cGy	92.7%
AMD + VCR + ADR + 2000 cGy	93.1%

D'Angio GJ et al. Cancer 1989; 64:349-60

Spill and Local Recurrence: The Case for Radiation Therapy

	Stage II	Stage III
No Spill	RR = 1.0	RR = 1.0
Spill	RR = 4.5	RR = 1.9

Shamberger RC et al. Ann Surg 1999; 229:292-7

Intraoperative Spill

- 135/1131 (11.9%) of unilateral Wilms tumor on AREN03B2 had intraoperative spillage of tumor
- 110 were secondary to the primary tumor while 20 occurred due to renal vein thrombectomy
- Two factors associated with intraoperative spill: tumor size $\geq$ 12 cm and right laterality

Gow KW et al. J Pediatr Surg 2013; 48:34-8

Local Recurrence Risk Factors (NWTS-1)

Delay	Favorable Histology	Unfavorable Histology	P-value
≤ 10 days	13/220 (6%)	2/29 (7%)	0.25
> 10 days	2/53 (4%)	6/15 (40%)	0.001

Tefft M et al. Int J Radiat Oncol Biol Phys 1980; 6:663-7

Local Recurrence Risk Factors (NWTS-2)

Factor	Intraabdominal Relapse	No Intraabdominal Relapse	P-value
Unfavorable histology	6/10 (60%)	25/249 (10%)	0.001
Field size too small	4/10 (40%)	17/249 (59%)	0.004
Delay ≥ 10 days from surgery	8/10 (80%)	91/249 (37%)	0.005

Thomas PRM et al. J Clin Oncol 1984; 2:1098-101

RT Treatment Delay

- Final pathology and stage needed within a few days to determine if child needs RT
- Need time to do simulation
- Younger children may need anesthesia
- Simulating all children with renal masses seem to be inappropriate

RT Treatment Delay (NWTS-3 & 4)

- Total of 1226 children with Stage II-IV FH children received flank or abdominal RT
- Mean RT delay: 10.9 days (median: 9 days)
- 59% had RT delay between 8 to 12 days
- 8-year flank/abdominal recurrence rates were 1.9/4.8% for delay $\leq$ 10 days and 1.2/5.3% for delay > 10 days (p = n.s.)

Kalapurakal JA et al. Int J Radiat Oncol Biol Phys 2003; 57:495-9

Pulmonary Lesions and RT

- Chest X-ray has traditionally been used to stage patients
- CT scan better in detecting nodules
- Not all nodules are metastatic Wilms' tumor although lungs are most common site of metastasis

DIFFERENTIAL DIAGNOSIS

Wilms' tumor metastasis
Atelectasis
Round pneumonia
Intrapulmonary Lymph Node
Histoplasma capsulatum
Hamartoma
Pseudotumor

St. Jude Study (+ lung mets on CT only)

- 11/124 (9%) of Wilms' tumor pts had negative CXR and positive chest CT
- Treated according to local stage (I.e. no lung RT)
- 4/11 (36%) relapsed – all pulmonary

Wilimas JA et al. J Clin Oncol 1988; 6:1144-6

NWTS-3 (+ lung mets on CT only)

		Relapses		Deaths	
	N	N(r)	% RFS	N (d)	% Survival
Lung RT	18	2	88.1	1	94.0
No RT	9	1	88.9	1	88.0
			P = .95		P = .63

Green DM et al. J Clin Oncol 1991; 9:1776-81

NWTS-3 and –4 Update

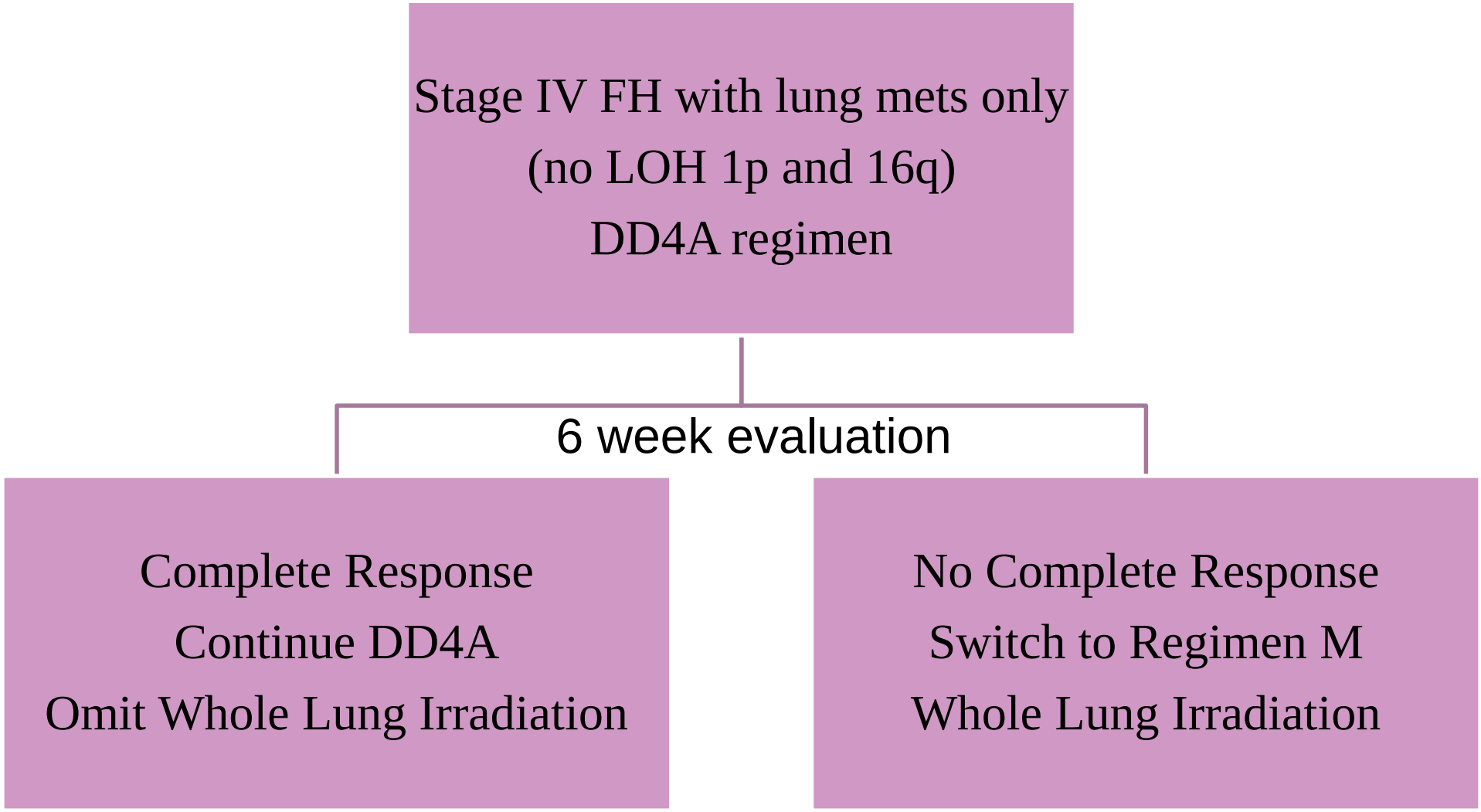
	N	N (relapsed)	4-yr EFS	N (died)	4-yr OS
RT	53	7	89%	6	91%
No RT	37	7	80%	5	85%
		P =.23		P=.41	

Meisel JA et al. Int J Radiat Oncol Biol Phys 1999; 44:579-85

CT Only Lung Mets (NWTS-4 and -5)

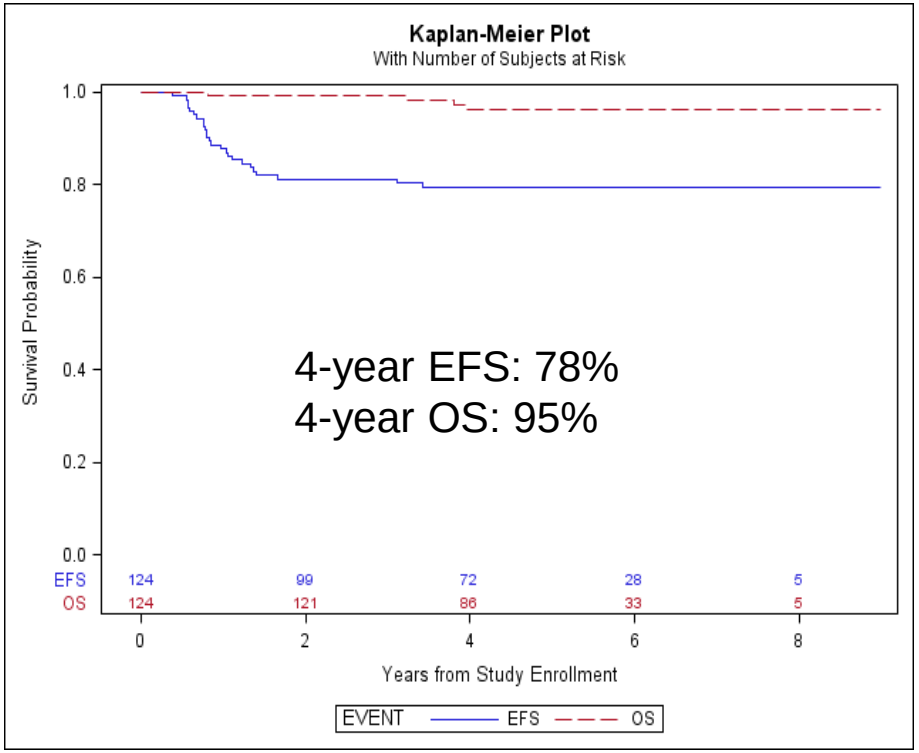
Chemotherapy	**No. of pts**	**2 year RFS (%)**	**5 year RFS (%)**	**P-value**
Actinomycin-D and Vincristine	39	58.1	54.4	0.01
Actinomycin-D Vincristine and Doxorubicin	145	84.2	79.7	
Radiotherapy	**No. of pts**	**2 year RFS (%)**	**5 year RFS (%)**	**P-value**
Whole Lung Radiotherapy	67	89.0	84.6	0.38
No Whole Lung Radiotherapy	91	73.2	69.6	

AREN0533: Stage IV FH with lung mets

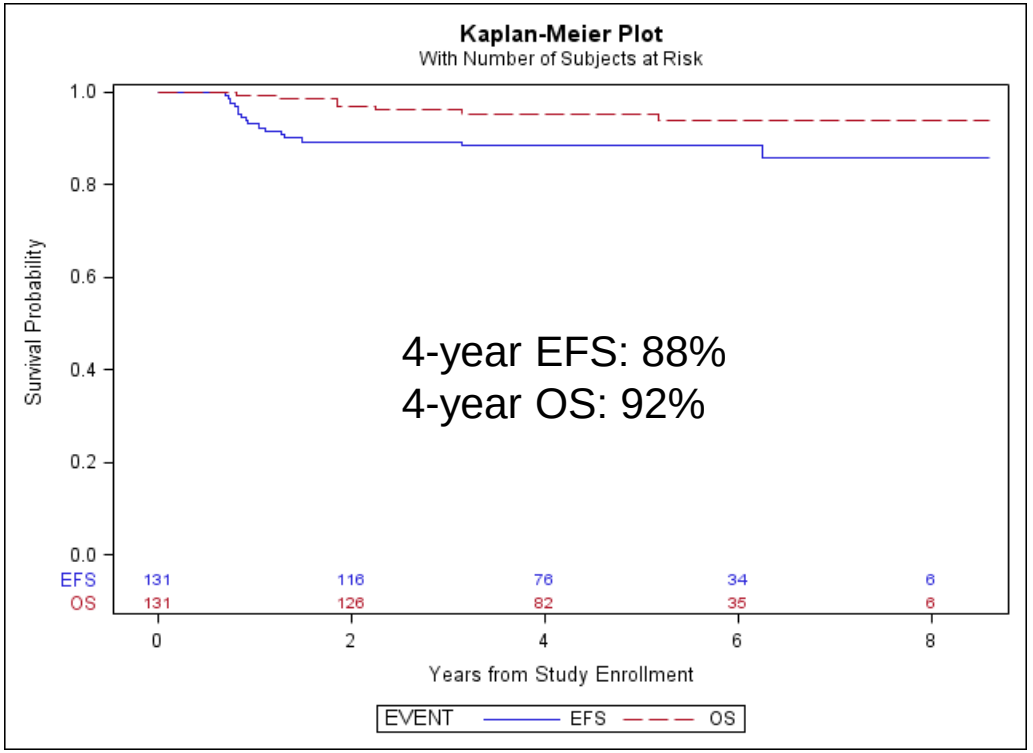


AREN0533: Stage IV FH, Lung Mets only

Complete Response



Incomplete Response



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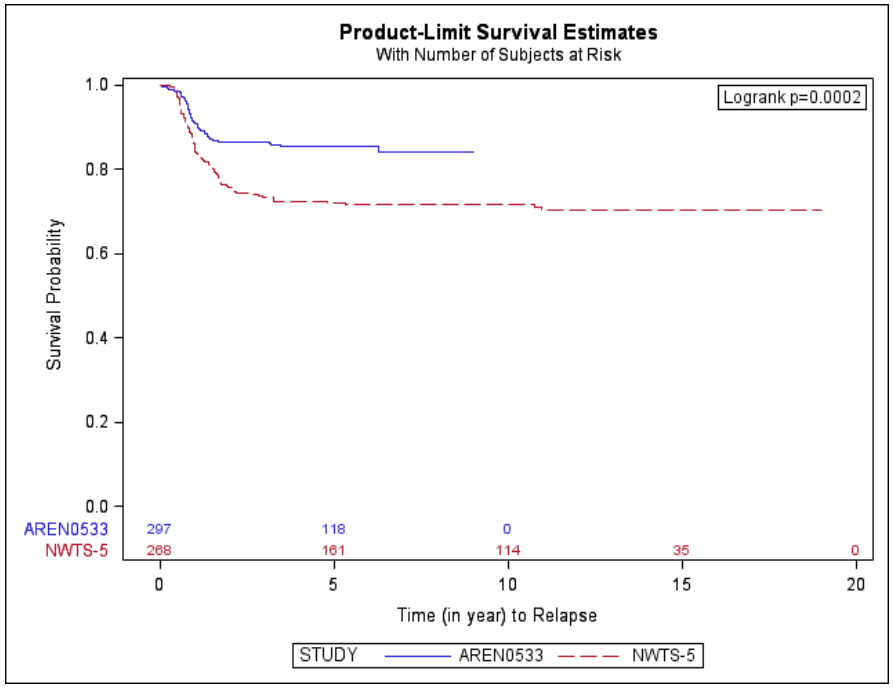
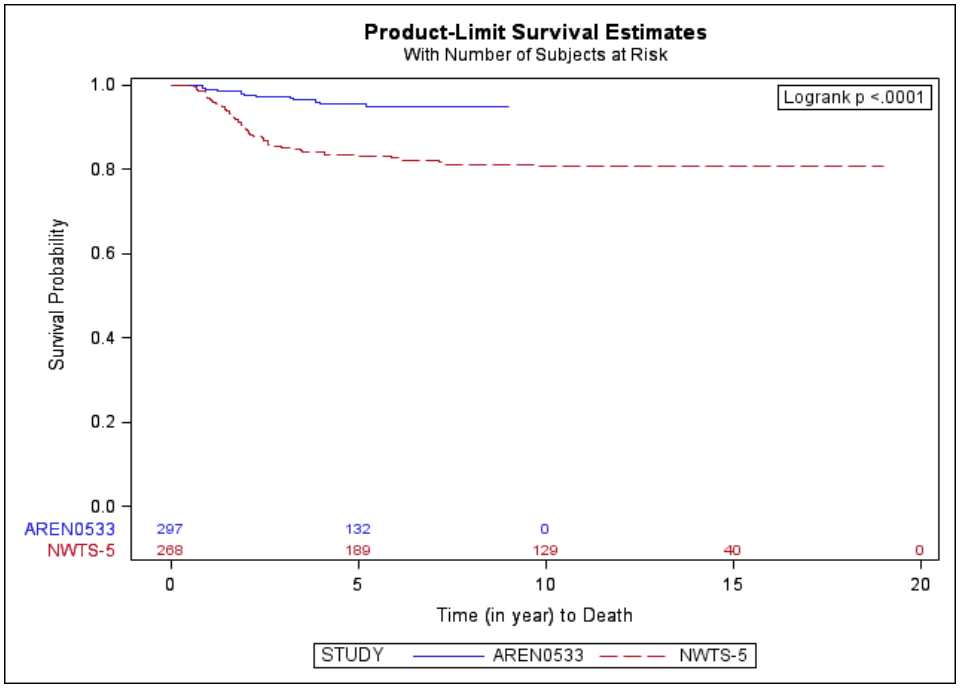
AREN0533 and NWTS-5: Stage IV, FH





NWTS-5: Impact of 1q Gain According to Stage

Table 1. Eight-Year EFS and OS Stratified by Disease Stage and 1q Status

Disease Stage	No. (% of stage group)	8-Year EFS (95% CI)	*P* (EFS)	8-Year OS (95% CI)	*P* (OS)
Stage I (n = 241, 21.6%)					
1q gain	46 (20)	85 (72 to 98)		90 (80 to 100)	
No 1q gain	195 (80)	95 (91 to 99)	.0052	98 (96 to 100)	.0015
Stage II (n = 382, 34.3%)					
1q gain	98 (26)	81 (71 to 91)		94 (87 to 100)	
No 1q gain	284 (74)	87 (83 to 92)	.0775	97 (94 to 99)	.1917
Stage III (n = 358, 32.1%)					
1q gain	115 (32)	79 (70 to 87)		91 (85 to 97)	
No 1q gain	243 (68)	89 (84 to 94)	.0100	95 (91 to 98)	.3335
Stage IV (n =133, 11.9%)					
1q gain	58 (44)	64 (48 to 79)		74 (60 to 88)	
No 1q gain	75 (56)	91 (83 to 99)	.0004	92 (84 to 99)	.0110

Abbreviations: EFS, event-free survival; OS, overall survival.

Gratias EJ et al. J Clin Oncol 2016; 34:3189-94

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NWTS-5: EFS and OS according to 1q gain

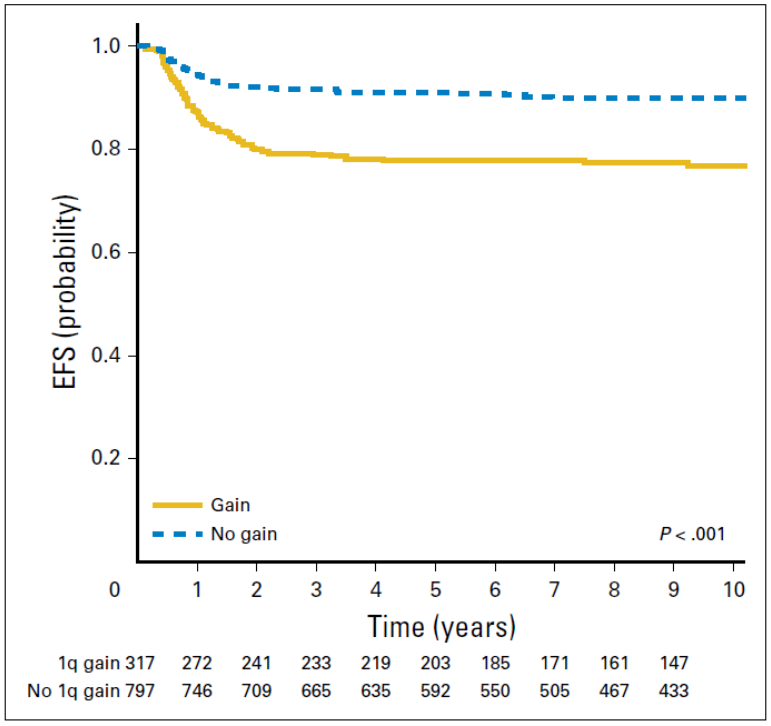

Fig 1. Event-free survival (EFS) stratified for 1q gain.

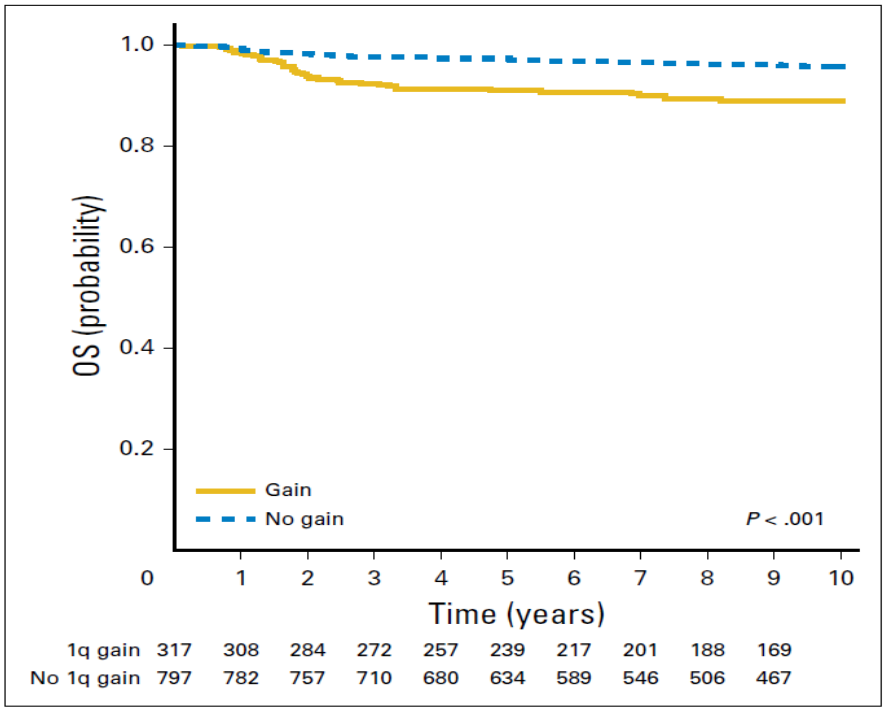

Fig 2. Overall survival (OS) stratified for 1q gain.

Gratias EJ et al. J Clin Oncol 2016;
34:3189-94

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NWTS-5: LOH 1p/16q and 1q Status

Table 2. Eight-Year EFS Stratified by 1q Status and LOH 1p/16q Status

1q Status	1p or 16q Call	No. of Patients	8-Year EFS (95% CI)
No gain	No loss	715	91 (88 to 93)
No gain	Loss	82	84 (74 to 93)
Gain	No loss	174	77 (69 to 84)
Gain	Loss	143	78 (70 to 87)

Abbreviation: EFS, event-free survival; LOH, loss of heterozygosity.

Gratias EJ et al. J Clin Oncol 2016;
34:3189-94

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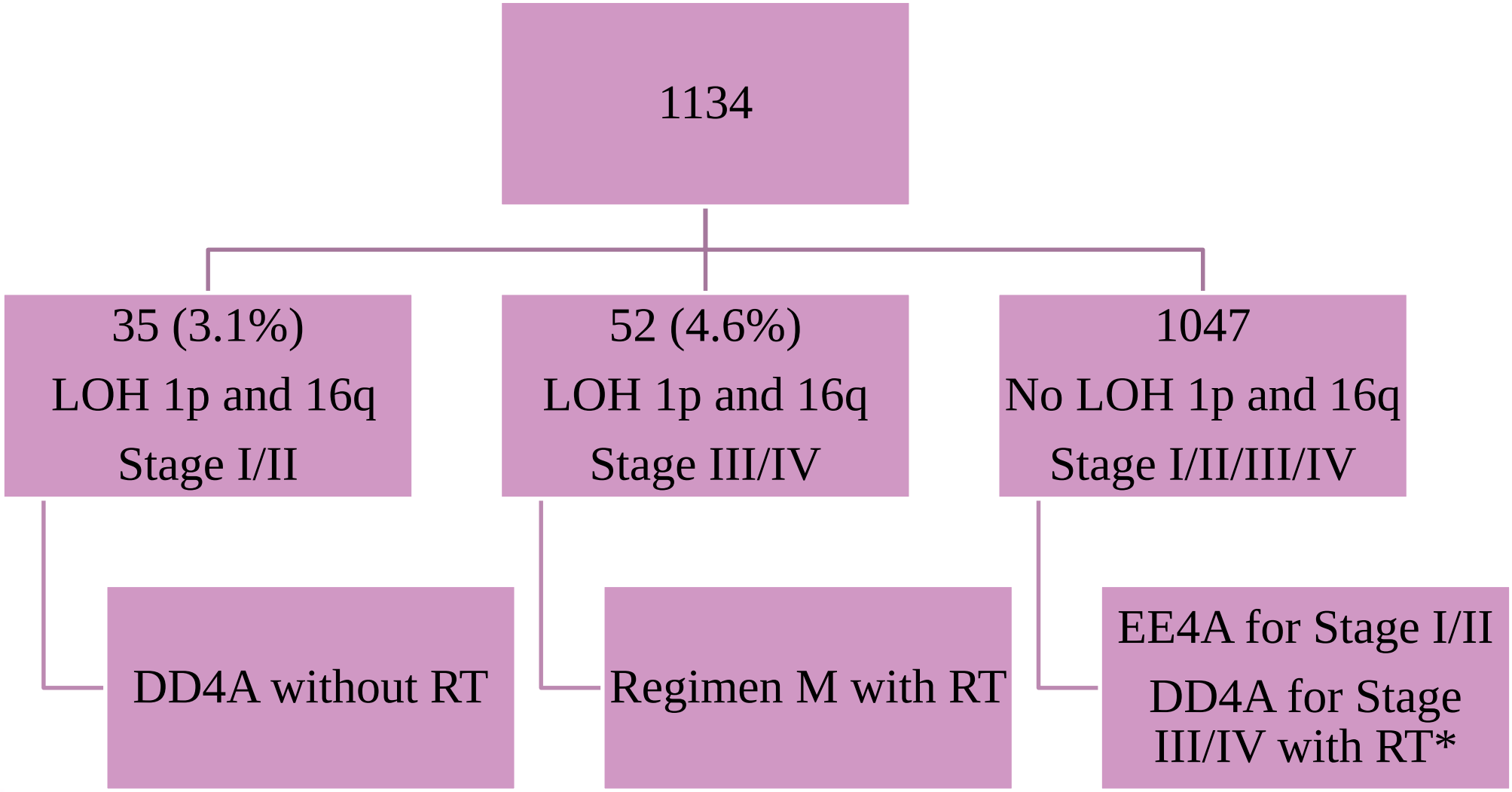
AREN0532/AREN0533



Dix DB et al. J Clin Oncol 33, 2015 (suppl; abstr 10009)

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AREN0532: Stage III FH Tumors

- 583 eligible patients met COG Stage III criteria; 40 pts excluded from analysis secondary to combined LOH 1p and 16 q
- All received DD4A chemotherapy (vincristine, dactinomycin, doxorubicin)
- Median follow-up: 42 months

AREN0532- Stage III FH

The 4-year EFS and OS estimates were 88% and 96% respectively

		N	EFS	P value	OS	P value
Lymph nodes	Negative	237	95%	< 0.01	98%	0.18
	Positive	152	83%		95%	
Gross residual disease	Negative	394	89%	0.14	97%	0.39
	Positive	134	85%		93%	
LOH	Neither	382	92%	< 0.01	97%	0.55
	16q only	99	83%		97%	
	1p only	56	74%		93%	

Fernandez CV et al. J Clin Oncol 33 (suppl; abstr 10010)

AREN0532/AREN0533: 4-year EFS

	NWTS-5	AREN0532/ AREN0533
Stage I/II LOH	74.9%	83.9%
Stage III/IV LOH	65.9%	91.5%

Grade 3 or higher hematological toxicity seen with Regimen M in 60% of patients

Conclusion: Regimen M therapy improved EFS for Stage III/IV FH with LOH 1p and 16q compared to historical comparison group treated with DD4A. The benefit of DD4A for Stage I/II FH LOH 1p and 16q is less clear.

Dix DB et al. J Clin Oncol 33, 2015 (suppl; abstr 10009)

Current COG Guidelines

Stage	Chemotherapy	Radiotherapy
Stage I, FH, age < 2 years with tumor and kidney weight < 550 grams	None	None
Stage I and II, FH with no LOH 1p and 16q	VCR and AMD (Regimen EE4A)	None
Stage I and II, FH with LOH at 1p and 16q	VCR, AMD and DOX (regimen DD4A)	None
Stage III, FH with no LOH at 1p and 16q	VCR, AMD and DOX (Regimen DD4A)	Abdominal/Flank RT
Stage III, FH with LOH at 1p and 16q	VCR, AMD, DOX, CPM, VP16 (Regimen M)	Abdominal/Flank RT
Stage IV, FH with no LOH at 1p and 16q	VCR, AMD and DOX (Regimen DD4A)	Abdominal/Flank RT if Local Stage III Lung XRT if Lung Mets not CR
Stage IV, FH with LOH at 1p and 16q	VCR, AMD, DOX, CPM, VP-16 (Regimen M)	Abdominal/Flank RT if Local Stage III Lung XRT if Lung Mets

COG RT Guidelines for FH Wilms Tumor

Disease Extent	RT Volume	Dose
Hilar lymph nodes/ Gross or microscopic residual confined to flank/ Local spill	Tumor bed, crossing midline to include entire vertebral bodies	1080 cGy/ 6 fx
Para-aortic lymph nodes	Include bilateral para-aortic chains	1080 cGy/ 6 fx
Peritoneal seeding, Preoperative peritoneal rupture, Diffuse operative spill	Whole abdomen	1050 cGy/ 7 fx

COG RT Guidelines for Metastasis

Disease site	RT Field	RT Dose
Liver	Involved portion + 2 cm margin	1980 cGy/11 fx
Lung, age ≥ 18mos	Bilateral lung	1200 cGy/8 fx
Lung, age < 18 mos	Bilateral lung if no response to chemo	900 cGy/ 6 fx
Lymph nodes (Gross tumor, not resected)	Involved nodes	1980 cGy/ 11 fx
Brain	Whole brain +/- boost	2160 cGy/ 17 fx (WB) 1080 cGy/6 fx (boost) if < 16 yrs 3060 cGy/ 17 fx (WB, if ≥ 16 yrs)
Bone	Lesion + 3 cm margin	2520 cGy/14 fx (< 16 yrs) 3060 cGy/17 fx (≥ 16 yrs)

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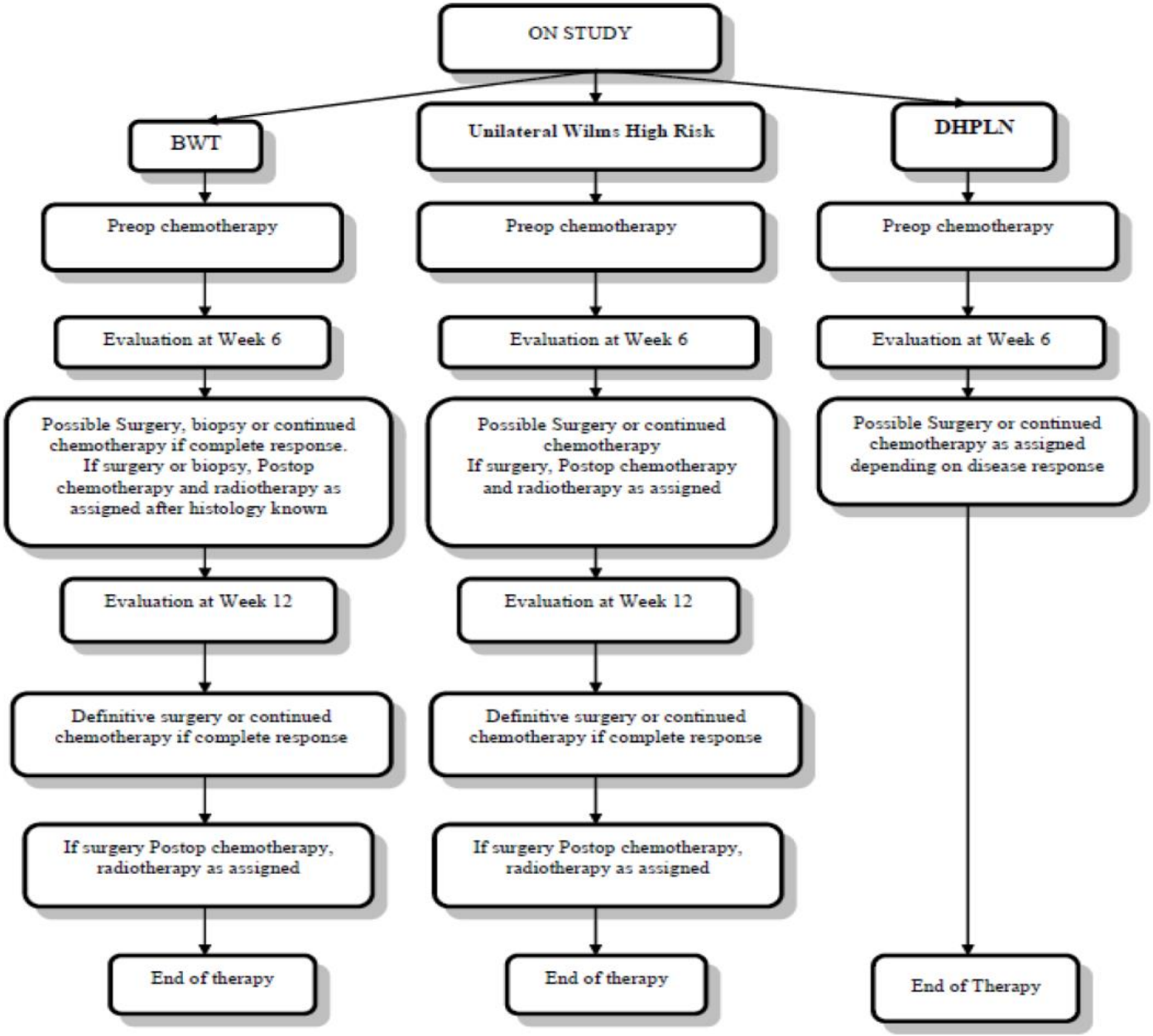
Bilateral Wilms Tumor

	Synchronous	Metachronous
NWTS-1	33/606 (5.4%)	20/606 (3.3%)
NWTS-2 and 3	145/3300 (4.4%)	
St. Jude	29/328 (8.8%)	7/328 (2.1%)
SIOP 1, 2, 5	42/1043 (4.0%)	25/1043 (2.4%)

Synchronous Bilateral Wilms' Tumor

	SURVIVAL		
	2 years	5 years	10 years
NWTS-2 and –3 Montgomery BT et al. J Urol 1991; 146:514-8	83%	73%	70%
SIOP 1,2,5 Coppes MJ et al. J Clin Oncol 1989; 7:310-5	NA	NA	69%
St. Jude Paulino AC et al. Int J Radiat Oncol Biol Phys 1996; 36:541-8	81%	74%	NA

AREN0534



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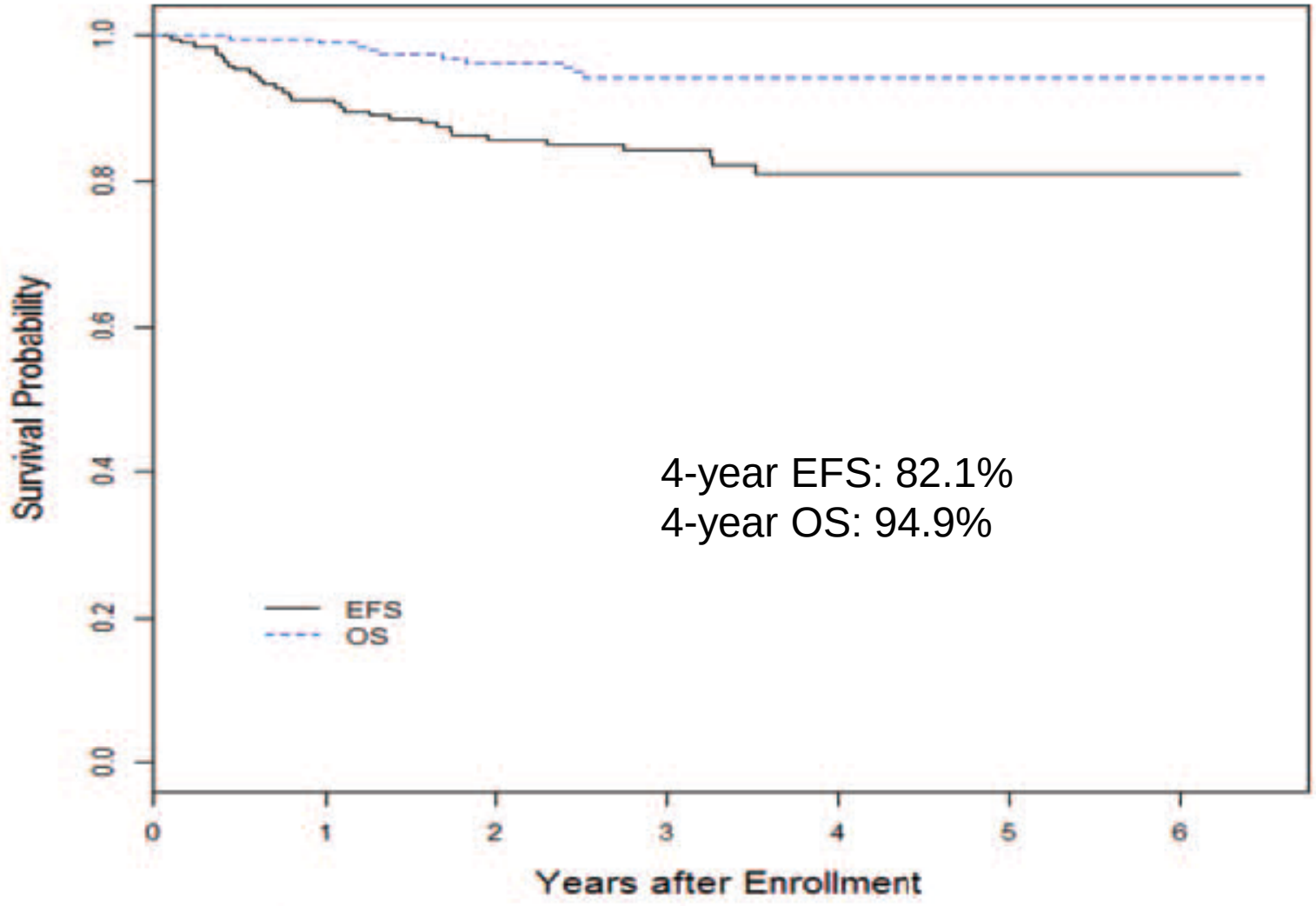
COG AREN0534: Bilateral Wilms Tumor



Ehrlich P et al. Ann Surg 2017; 266: 470-8

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Metachronous Bilateral Wilms Tumor

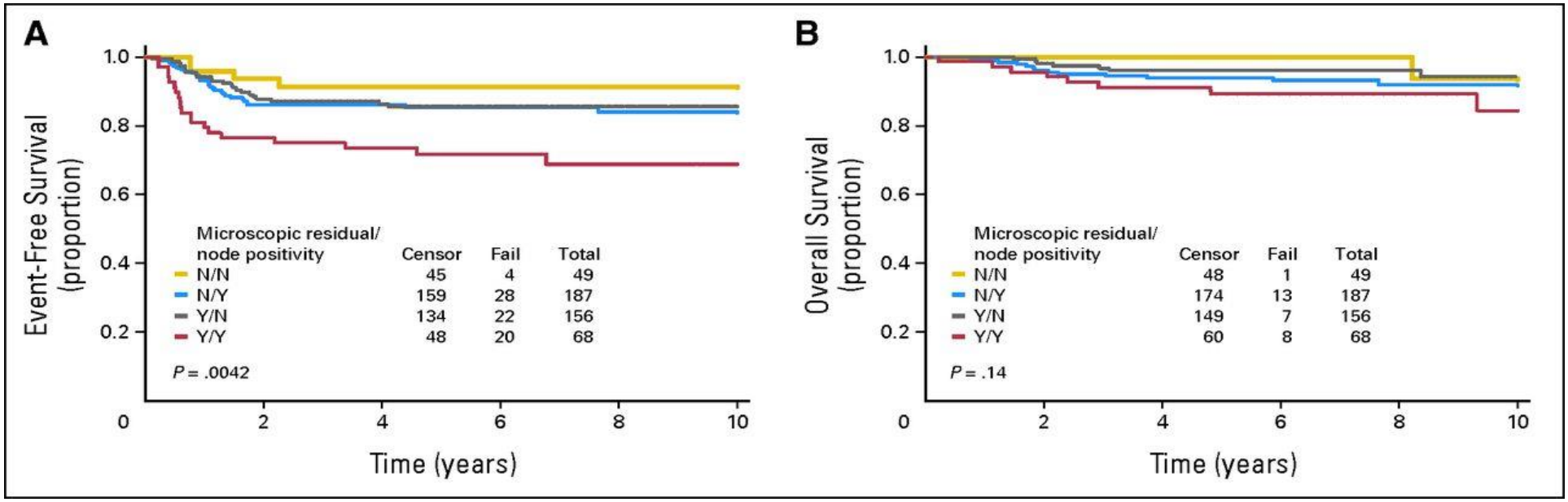
- Review of 108 cases from 30 studies from 1950-1996
- 5- and 10-year overall survivals were 49.1% and 47.2%
- More than 95% of contralateral tumors occur within 60 months (median 23.1 months)
- Better survival with contralateral tumors appearing ≥ 18 months from initial ipsilateral tumor (10 yr survival 55.2% vs. 39.6%)

Paulino AC et al. Cancer 1998; 82:415-20

Relapsed Wilms' Tumor

	N	Survival	
		3 years	5 years
Grundy et al. NWTS-2 and -3	367	30%	NA
Dome et al. St. Jude Children's Hospital	54	NA	21% (prior to 1984) 64% (after 1984)
Groot-Loonen et al. UKCCSG WT-1 Study	71	24%	NA
Paulino et al. University of Iowa	21	38%	33%
Tannous et al. CCG-4921/POG-9945 HRisk	66	52%	NA

Predictors of Relapse: Stage III FH Wilms Tumor



Kaplan-Meier curves for (A) event-free and (B) overall survival for local stage III favorable-histology Wilms tumor by microscopic disease, nonmetastatic only.

Ehrlich P F et al. JCO 2013;31:1196-1201

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Patterns of Failure: NWTS-2 and 3

Site	Frequency
Lung only	58%
Abdomen +/- lung	29%
Other	13%

Grundy PE et al. J Clin Oncol 1989; 7:638-47

Anaplastic Wilms' Tumor

- Unfavorable histology found in 4 to 5% of NWTS and SIOP studies
- Uncommon in infants, but found in about 10% of patients > 5 years of age
- Anaplasia refers to significant enlargement of nuclei in stromal, blastemal or epithelial components to at least 3X, hyperchromatism of enlarged nuclei and multiple mitotic figures

Anaplastic Wilms' Tumor

	Focal anaplasia				Diffuse anaplasia			
Stage	No.	Rel/died	% RF[a]	% 4 yr[b]	No.	Rel/died	% RF[a]	% 4 yr[b]
I	12	1/0	92	100	9	0/0	100	100
II	12	1/1	92	90	45	22/20	51	55
III	7	2/0	71	100	34	18/17	46	45
IV	8	0/0	100	100	23	22/22	4	4
Total	39	4/1	90	97	121	62/59	49	50
				p (relapses) = 0.0001				
				p (deaths) = 0.0001				

Rel, relapses; RF, relapse-free.

[a] Percent relapse-free after 2 years (no first relapse occurred later than 2 years).

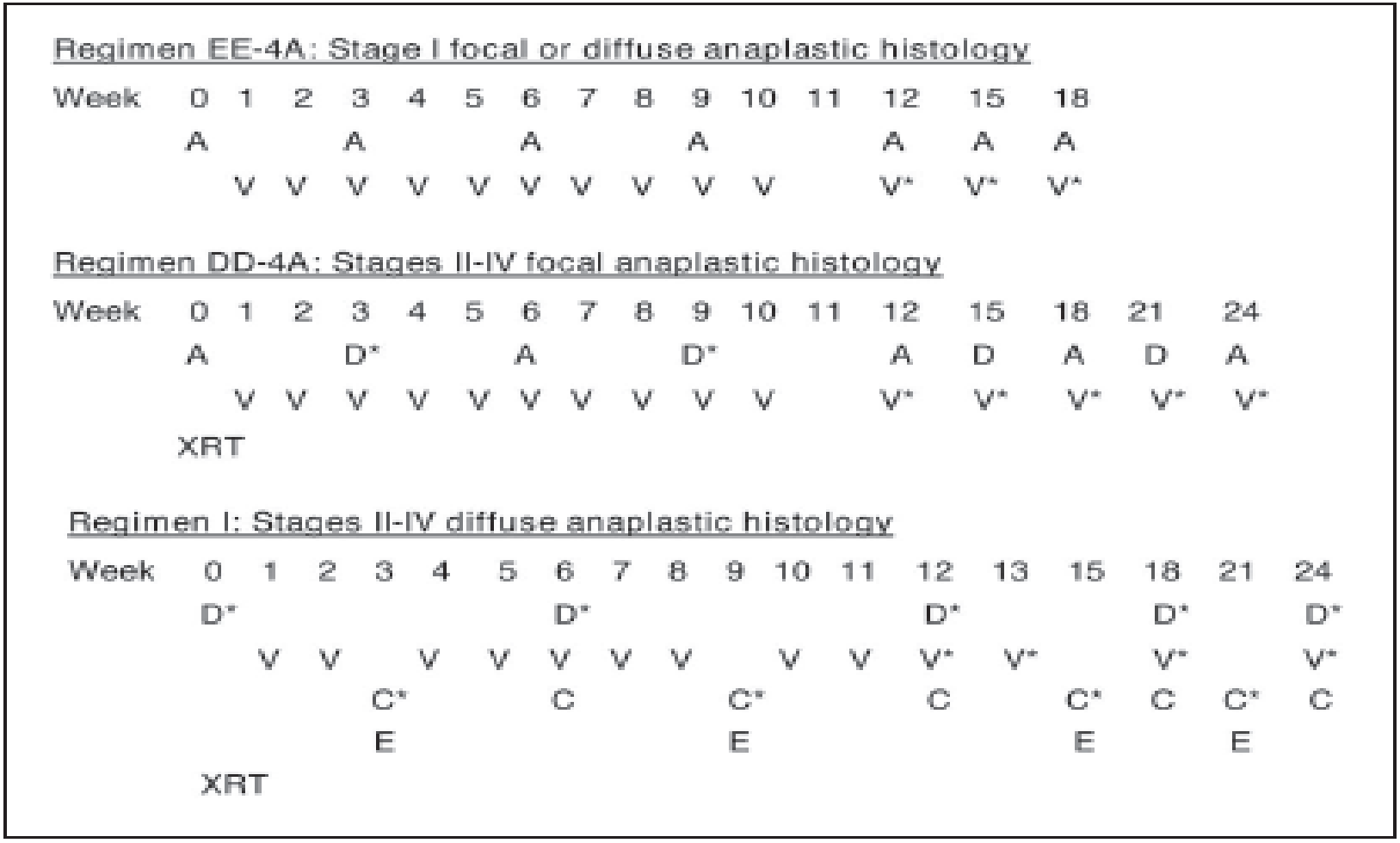
[b] Four-year survival percent. Three patients who died without evidence of tumor (two toxic deaths and one traumatic) were censored from survival calculations.

Faria P et al. Am J Surg Pathol 1996; 20:909-20

Anaplastic Wilms' Tumor

- In NWTS-4, Stage I AH pts were treated with AMD and VCR and had 2-yr overall survival estimates of 85.5% to 93.3% depending on AMD administration regimen
- Stage II to IV AH pts were treated with AMD, VCR and DOX and had 4-yr overall survival rate of 27.1% without CPM and 52.2% with CPM ($p = 0.04$)

Anaplastic Wilms' Tumor (NWTS-5)



Dome JS et al. J Clin Oncol 2006; 24:2352-8

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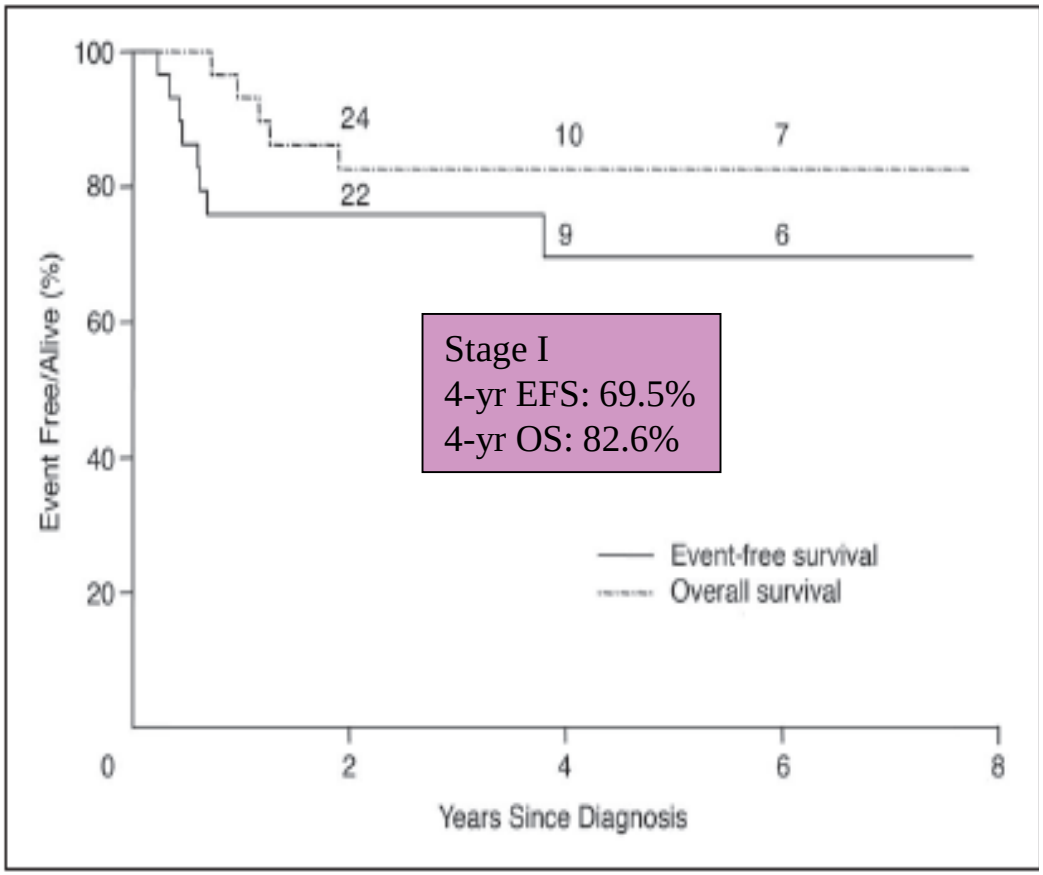
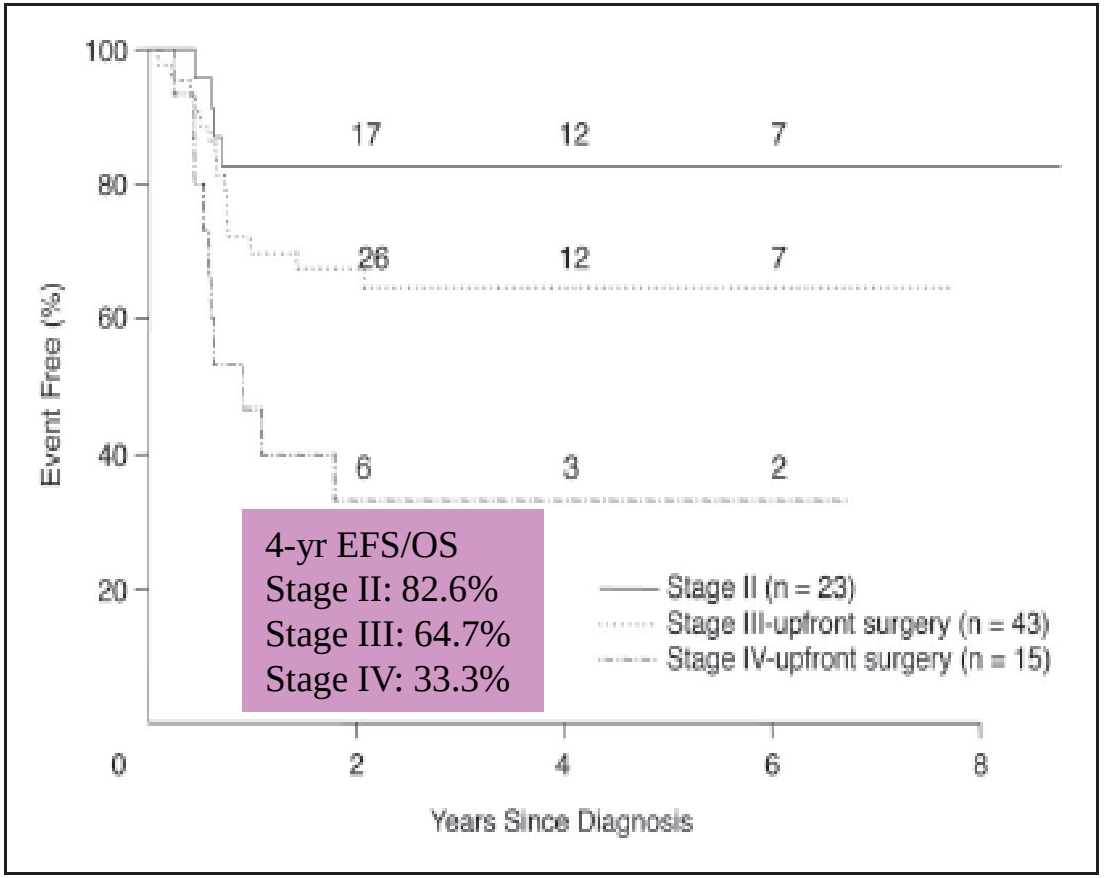
Anaplastic Wilms' Tumor (NWTS-5)





Dome JS et al. J Clin Oncol 2006; 24:2352-8

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RT Dose in Anaplastic Wilms Tumor

Dose (Gy)	N	No. of Tumor Bed Relapses	4-Year Tumor Bed Relapse-free Survival (%)
0 – 18.0	8	1	85.7
18.01-21.6	8	0	100.0
21.61-27.0	4	1	50.0
27.01-32.4	11	1	90.0
32.41-37.8	28	2	89.5
> 37.8	7	0	100.0 p=0.56

Green DM et al. J Clin Oncol 1994; 12:2126-31

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Survival for Anaplastic Wilms Tumor

	Relapse-Free Survival	Overall Survival
Stage I, FA/DA	69%	83%
Stage II, FA	80%	80%
Stage II, DA	83%	82%
Stage III, FA	71-88%	71-100%
Stage III, DA	46-65%	53-67%
Stage IV, FA	61%	72%
Stage IV, DA	31-33%	33-44%
Stage V, FA/DA	44%	55%

NCI PDQ Summary

Clear Cell Sarcoma of Kidney

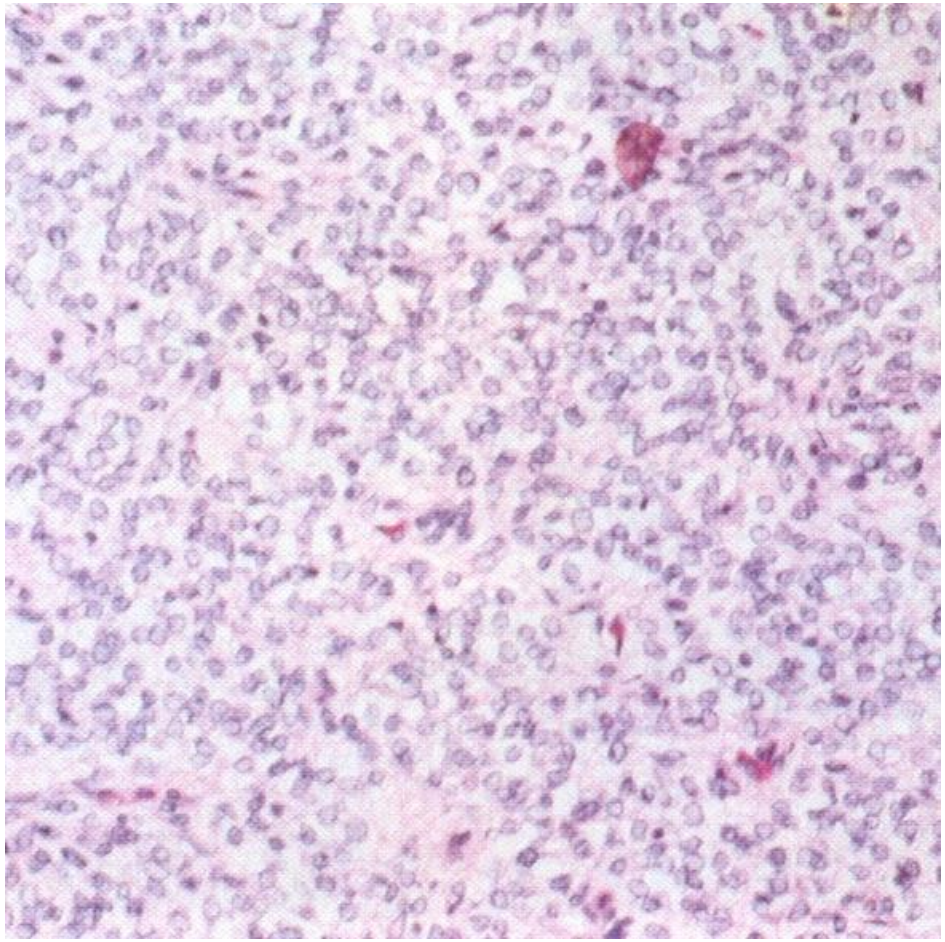
First reported by Kidd in 1970

20 cases each year in the US (4-5% of all renal tumors)

2:1 M:F ratio

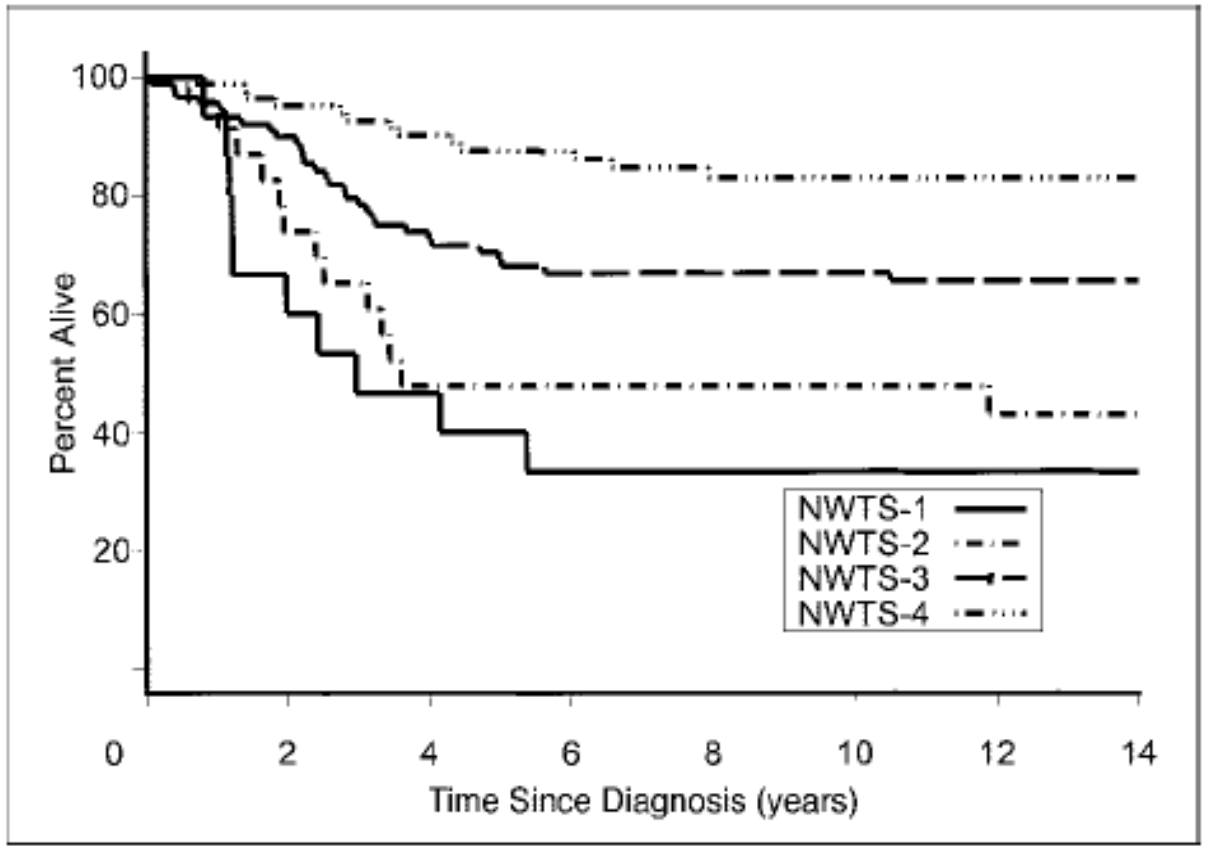
29% lymph node mets at presentation

Most common site of recurrence is bone and lung, followed by abdomen and brain



Argani P et al. Am J Surg Pathol 2000; 24:4-18

Clear cell Sarcoma of Kidney



	N	8-yr RFS	8-yr OS
NWTS-4	86	71.6%	83.0%
NWTS-3	90	60.2%	66.9%

Seibel NL et al. J Clin Oncol 2004; 22:468-73

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RT Dose in Clear Cell Sarcoma

Dose (Gy)	N	No. of Tumor Bed Relapses	4-Year Tumor Bed Relapse-free Survival (%)
0 – 18.0	16	0	100.0
18.01-21.6	18	2	85.9
21.61-27.0	21	0	100.0
27.01-32.4	21	0	100.0
32.41-37.8	15	1	91.7
> 37.8	8	1	83.3 p=0.56

Green DM et al. J Clin Oncol 1994; 12:2132-7

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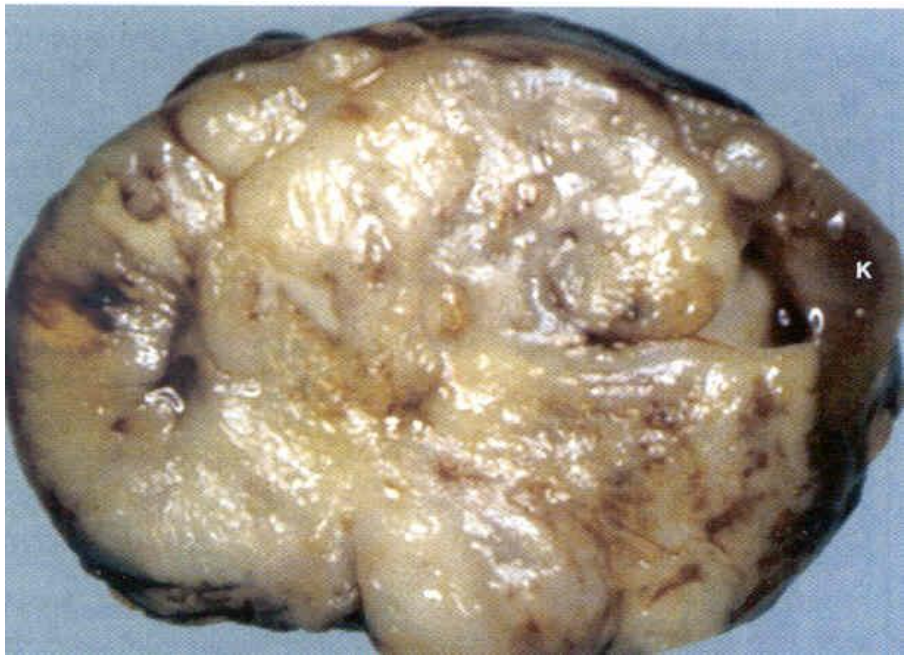
Rhabdoid Tumor

- 2% of all renal tumors
- 80% < 2 years old
- 1.5:1 M:F ratio
- Characterized by INI-1 gene mutation
- Association with primary intracranial mass or brain metastasis
- Worst prognosis for renal tumors



Rhabdoid Tumor

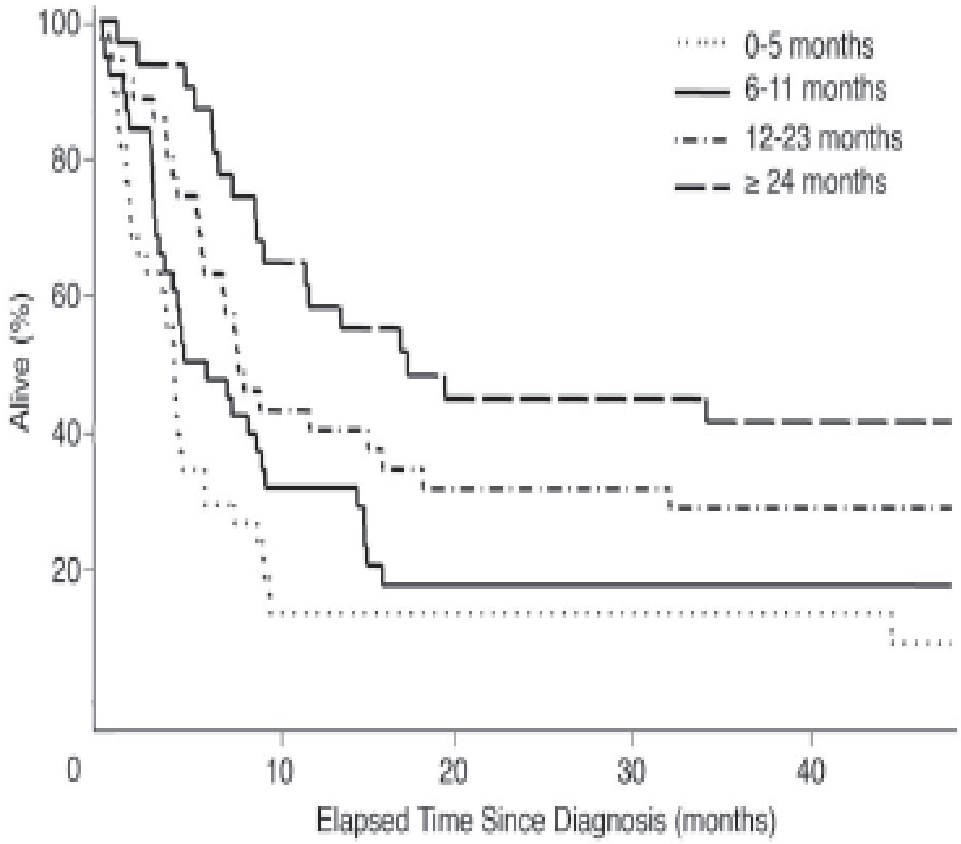


Table 1. Overall Survival by Age Category for NWTS 1-5 RTK Patients

Age at Diagnosis (months)	No. of Patients	No. Deaths		Survival at 4 Years (%)	RR	95% CI
		Obs.	Exp.			
0-5	38	34	19.1	8.8	1.00	—
6-11	38	31	25.6	17.2	0.67	0.41 to 1.08
12-23	35	26	30.4	28.6	0.47	0.28 to 0.78
≥ 24	31	18	33.9	41.1	0.29	0.16 to 0.51

NOTE. Global likelihood ratio test (df = 3), $P = .0001$. Log-rank trend test (df = 1), $P < .0001$.

Abbreviations: NWTS, National Wilms' Tumor Study; RTK, rhabdoid tumor of the kidney; RR, relative risk of death.

Tomlinson GE et al. J Clin Oncol 2005; 23:7641-5

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Rhabdoid Tumor

Table 2. Effect of RT to Renal Fossa for All Patients

RT Dose	No. Patients	No. of Deaths		Survival at 4 Years (%)	RR	95% CI	*P*
		Obs.	Exp.				
No RT	41	36	27.5	10.7	1.00	—	—
0-1,500 Gy	36	25	23.9	30.6	0.79	0.48 to 1.32	.37
1,500 Gy-2,500 Gy	34	29	22.4	14.7	0.98	0.60 to 1.61	.95
≥ 2,500 Gy	25	13	29.1	52.0	0.33	0.17 to 0.63	.001

NOTE. Global likelihood ratio test (df = 3), $P = .001$. Log-rank trend test (df = 1), $P = .003$.
Abbreviations: RT, radiotherapy; RR, relative risk of death.

Tomlinson GE et al. J Clin Oncol 2005; 23:7641-5

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Current COG Guidelines

Stage	Chemotherapy	Radiotherapy
Stage I-III, FA Stage I, DA	VCR, AMD and DOX (Regimen DD4A)	Abdominal/Flank RT
Stage IV, FA Stage II-IV, DA (with no measurable disease) Stage IV, CCSK Stage I-IV, RTK	VCR,AMD, DOX, CPM, VP16, CARBO (Regimen UH-1)	Abdominal/Flank RT Lung RT if lung mets
Stage IV, DA (with measurable disease)	VCR, AMD, DOX, CPM, VP16, CARBO, IRINOTECAN	Abdominal/Flank RT Lung RT if lung mets
Stage I-III CCSK	VCR, AMD, DOX, CPM, VP16 (Regimen I)	Abdominal/Flank RT except Stage I CCSK

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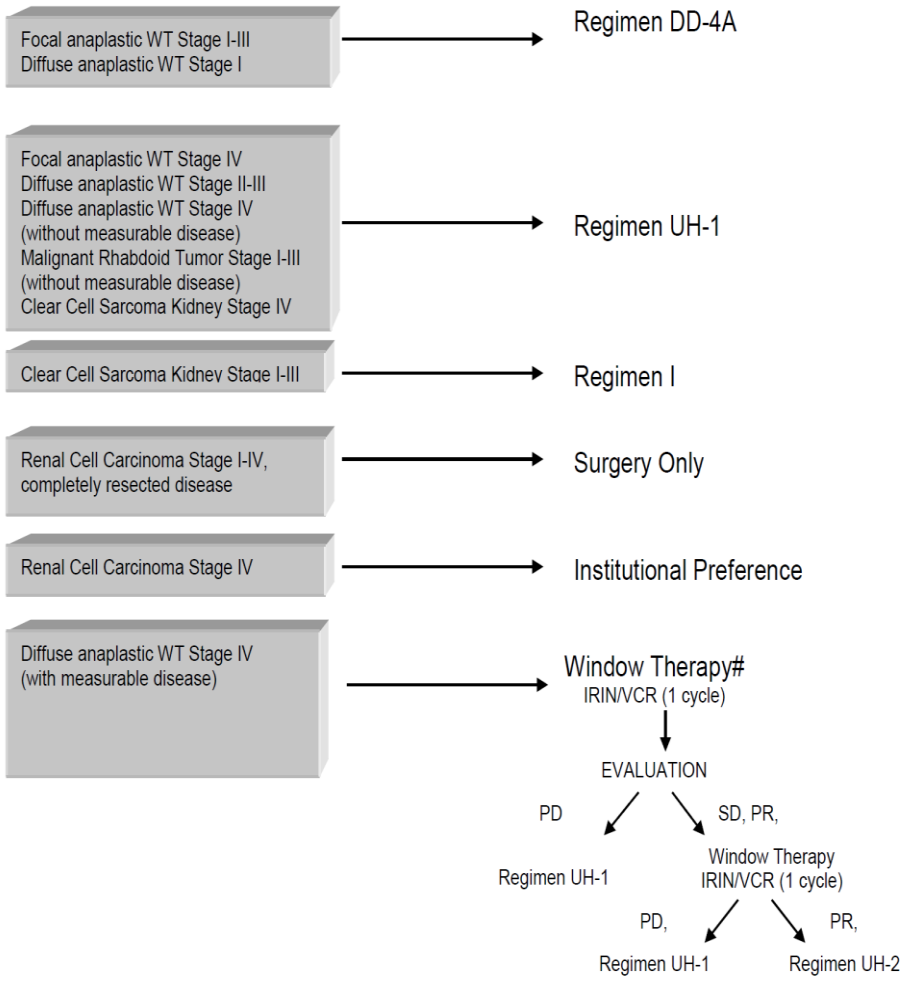
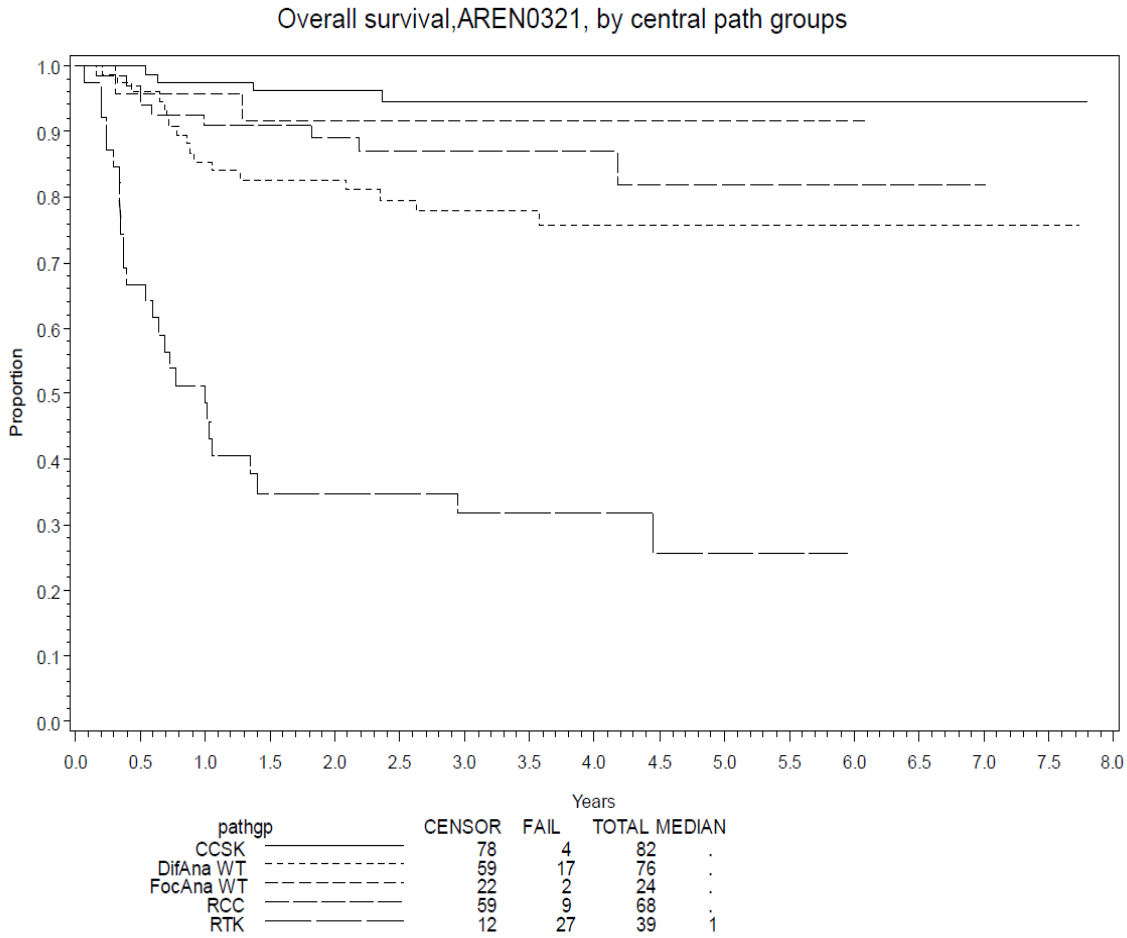
Current COG Guidelines

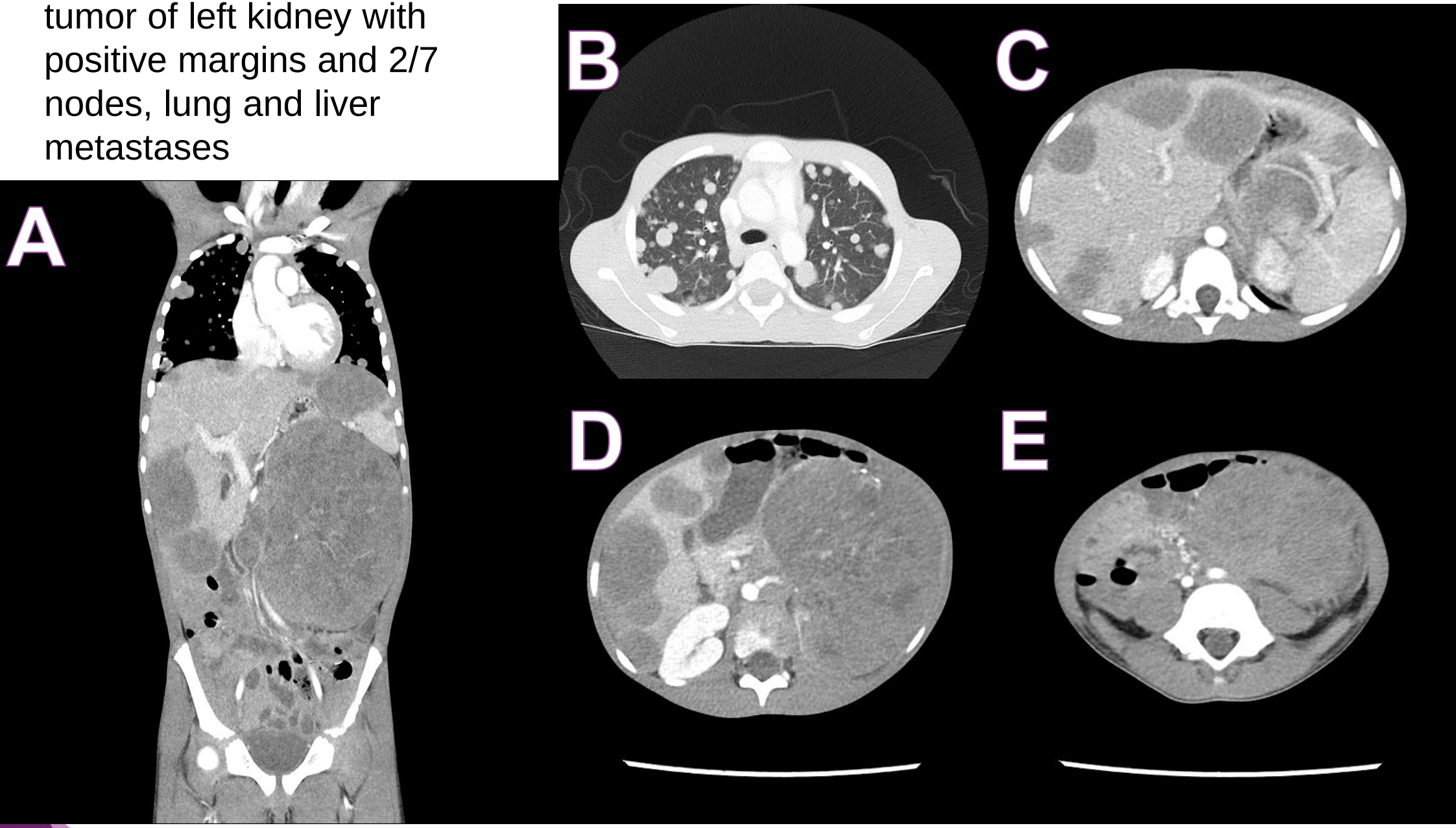
Stage	Radiotherapy Dose
Stage I, CCSK	No RT
Stage I-III, FA Stage I-II, DA Stage II-III, CCSK RTK, < 1 year old	10.8 Gy in 6 fractions Abdominal/Flank RT
Stage III DA RTK, > 1 year old	19.8 Gy in 11 fractions Abdominal/Flank RT
FA, DA, CCSK, RTK	12 Gy in 8 fractions Lung Mets

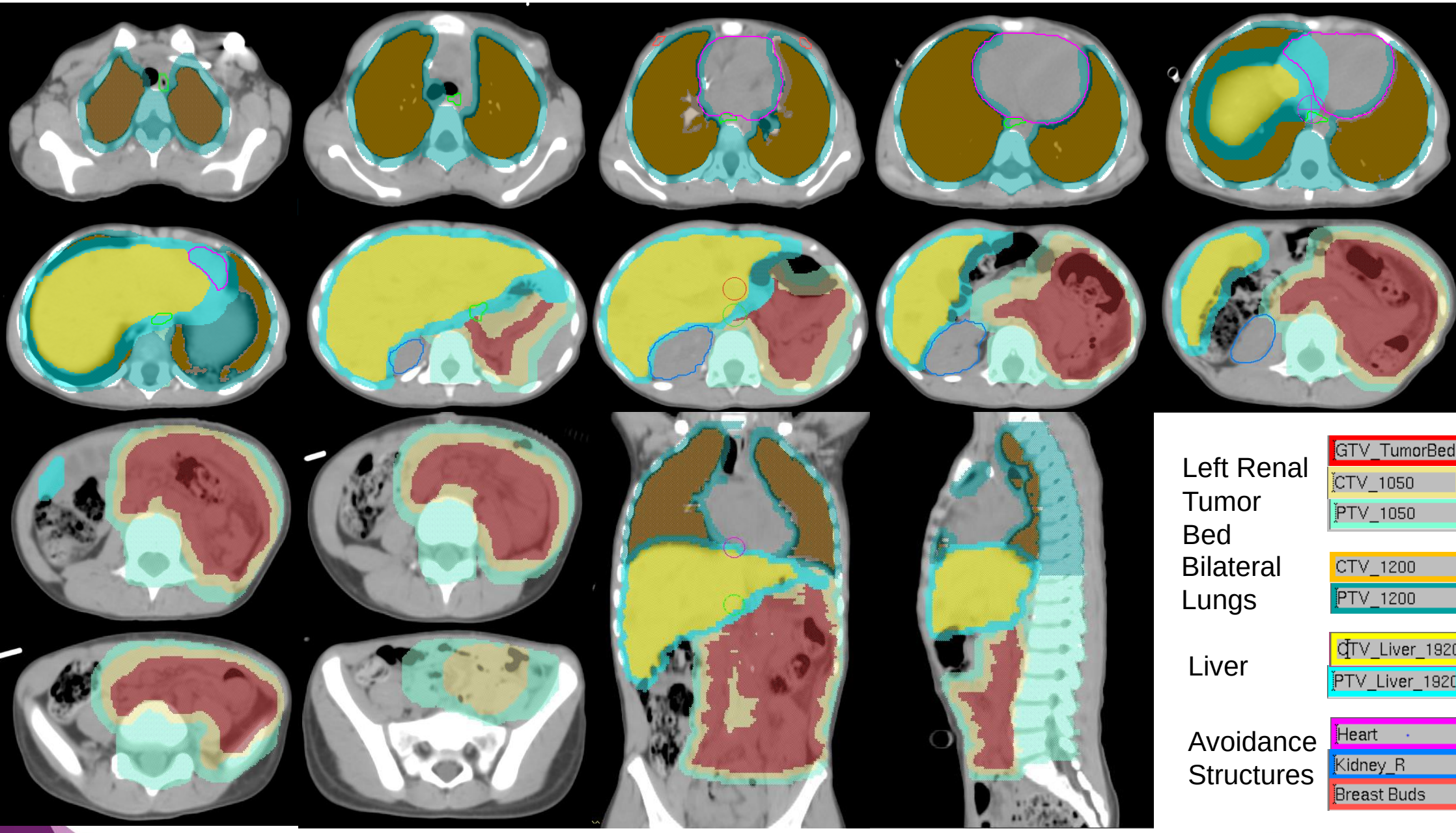
AREN0321


Focal anaplastic WT Stage I-III
Diffuse anaplastic WT Stage I
Regimen DD-4A
Focal anaplastic WT Stage IV
Diffuse anaplastic WT Stage II-III
Diffuse anaplastic WT Stage IV
(without measurable disease)
Malignant Rhabdoid Tumor Stage I-III
(without measurable disease)
Clear Cell Sarcoma Kidney Stage IV
Regimen UH-1
Clear Cell Sarcoma Kidney Stage I-III
Regimen I
Renal Cell Carcinoma Stage I-IV,
completely resected disease
Surgery Only
Renal Cell Carcinoma Stage IV
Institutional Preference
Diffuse anaplastic WT Stage IV
(with measurable disease)
Window Therapy#
IRIN/VCR (1 cycle)
EVALUATION
PD
SD, PR,
Regimen UH-1
Window Therapy
IRIN/VCR (1 cycle)
PD,
PR,
Regimen UH-1
Regimen UH-2


Overall survival,AREN0321, by central path groups
Proportion
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0
Years
pathgp CENSOR FAIL TOTAL MEDIAN
CCSK 78 4 82 .
DifAna WT 59 17 76 .
FocAna WT 22 2 24 .
RCC 59 9 68 .
RTK 12 27 39 1

Favorable histology Wilms tumor of left kidney with positive margins and 2/7 nodes, lung and liver metastases





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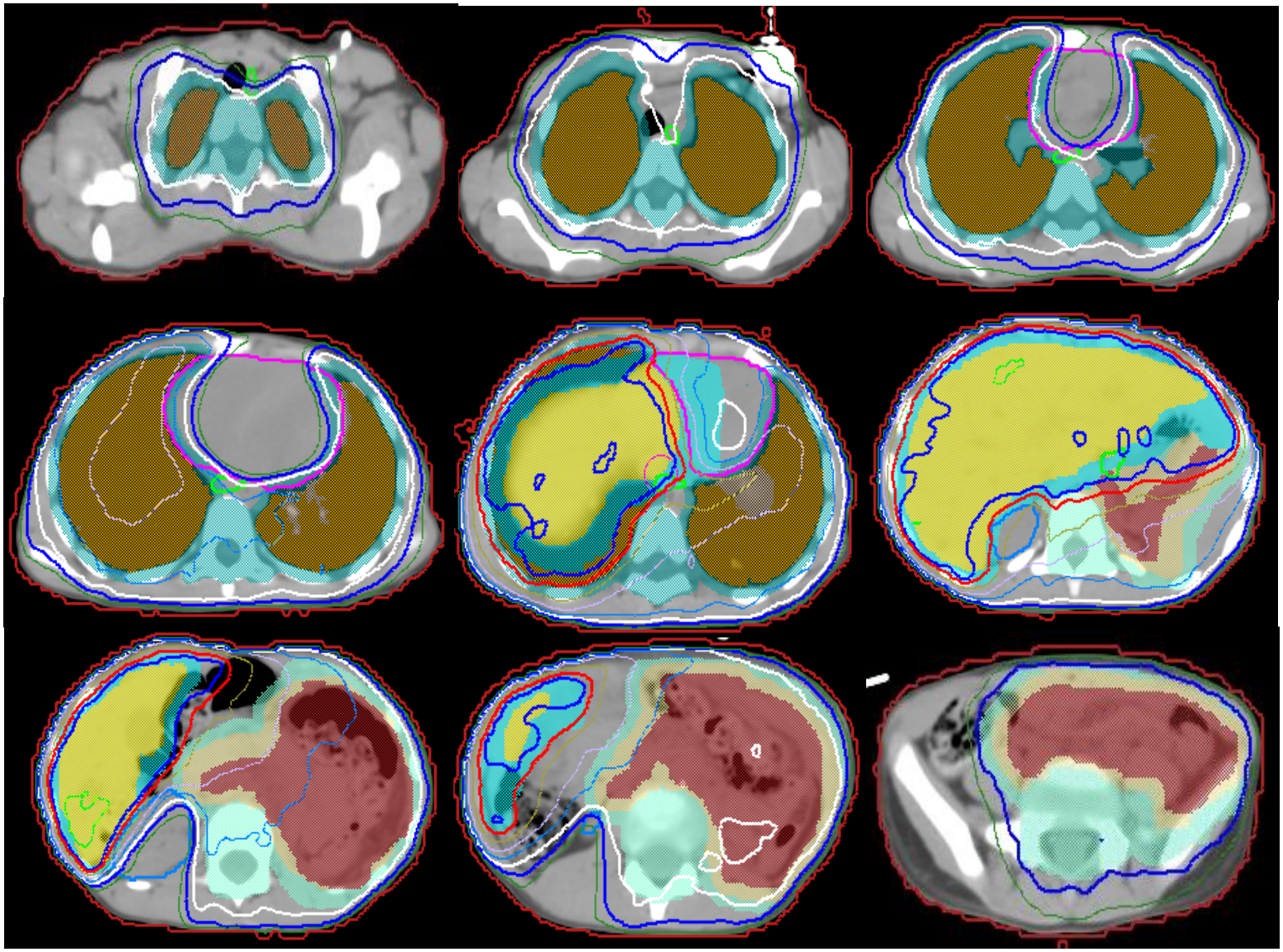
Prescribed Doses:

1050 cGy Left Renal Tumor Bed

1200 cGy Bilateral Lungs

1920 cGy Liver



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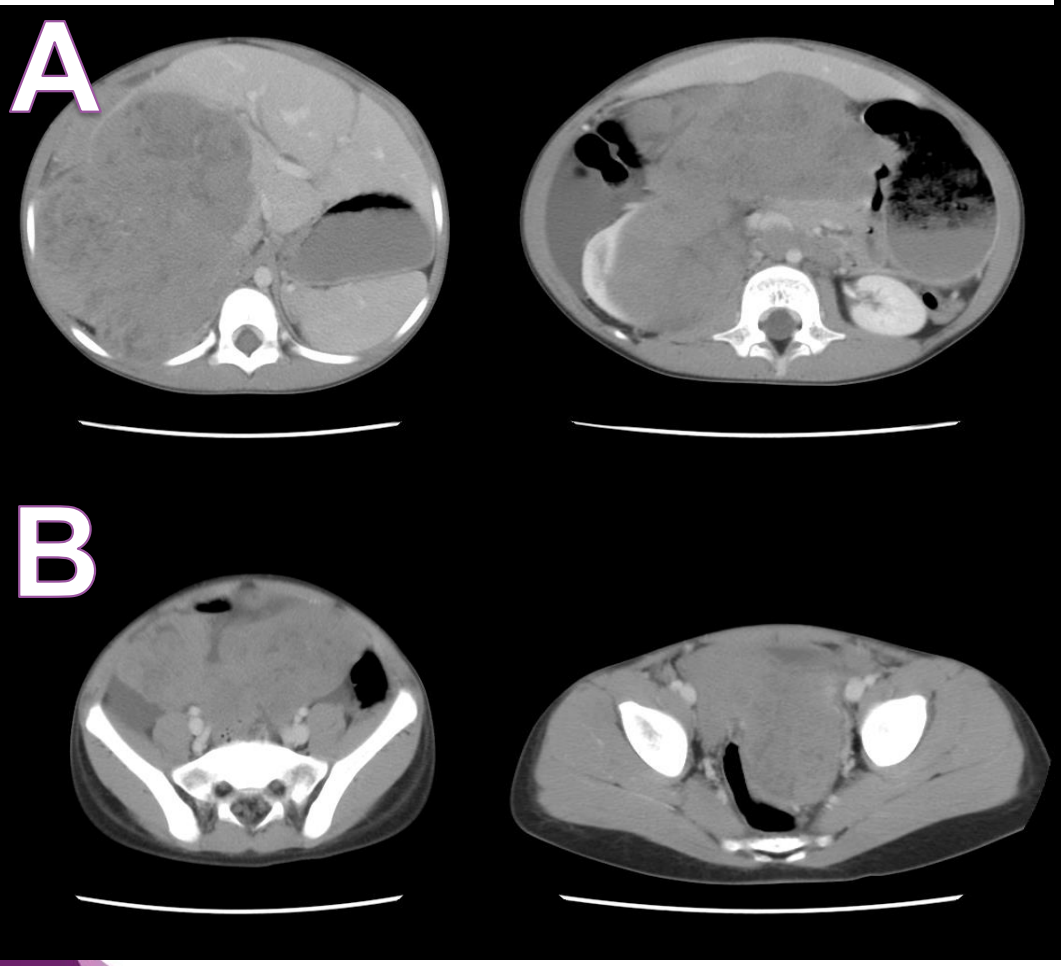
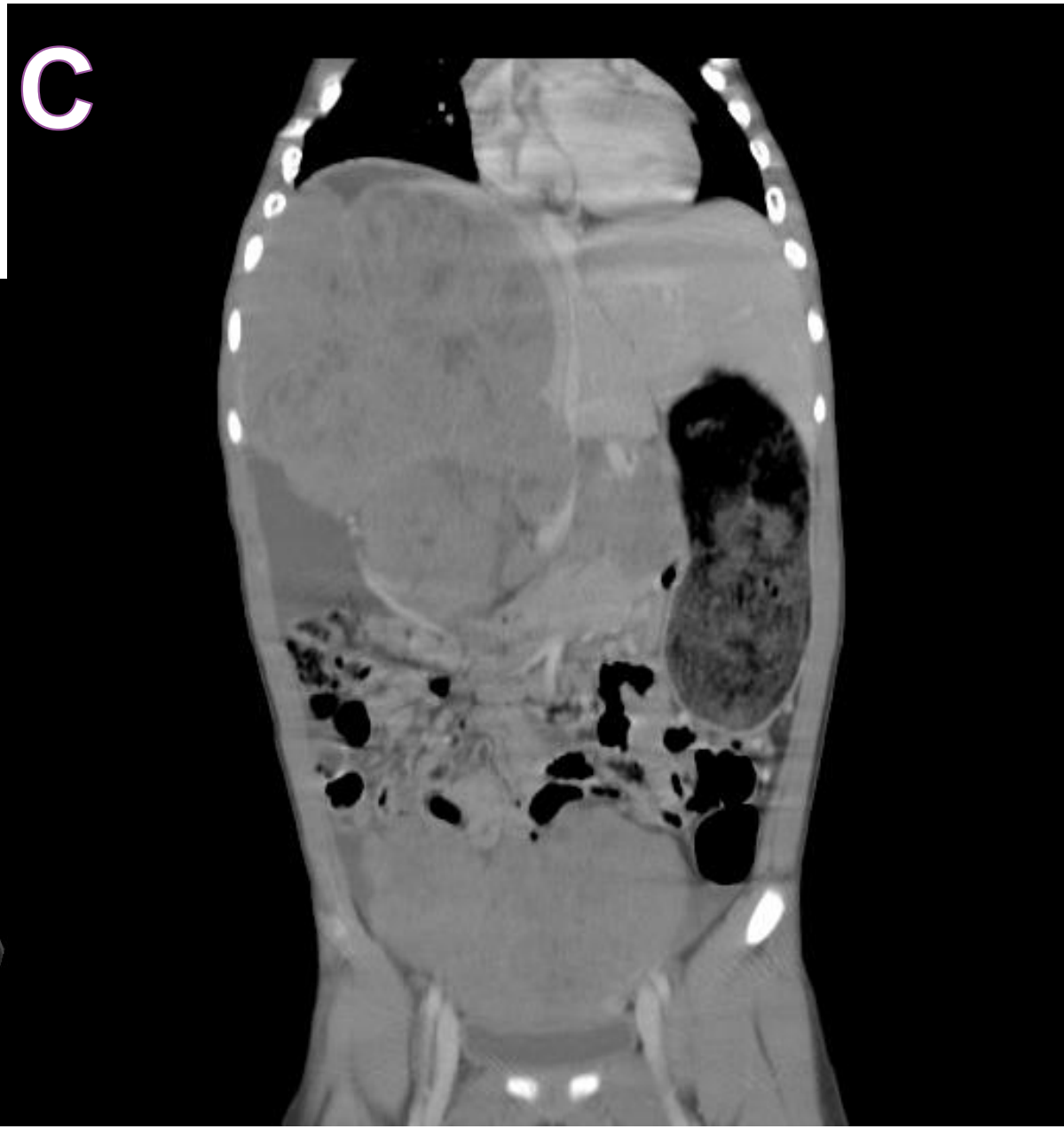
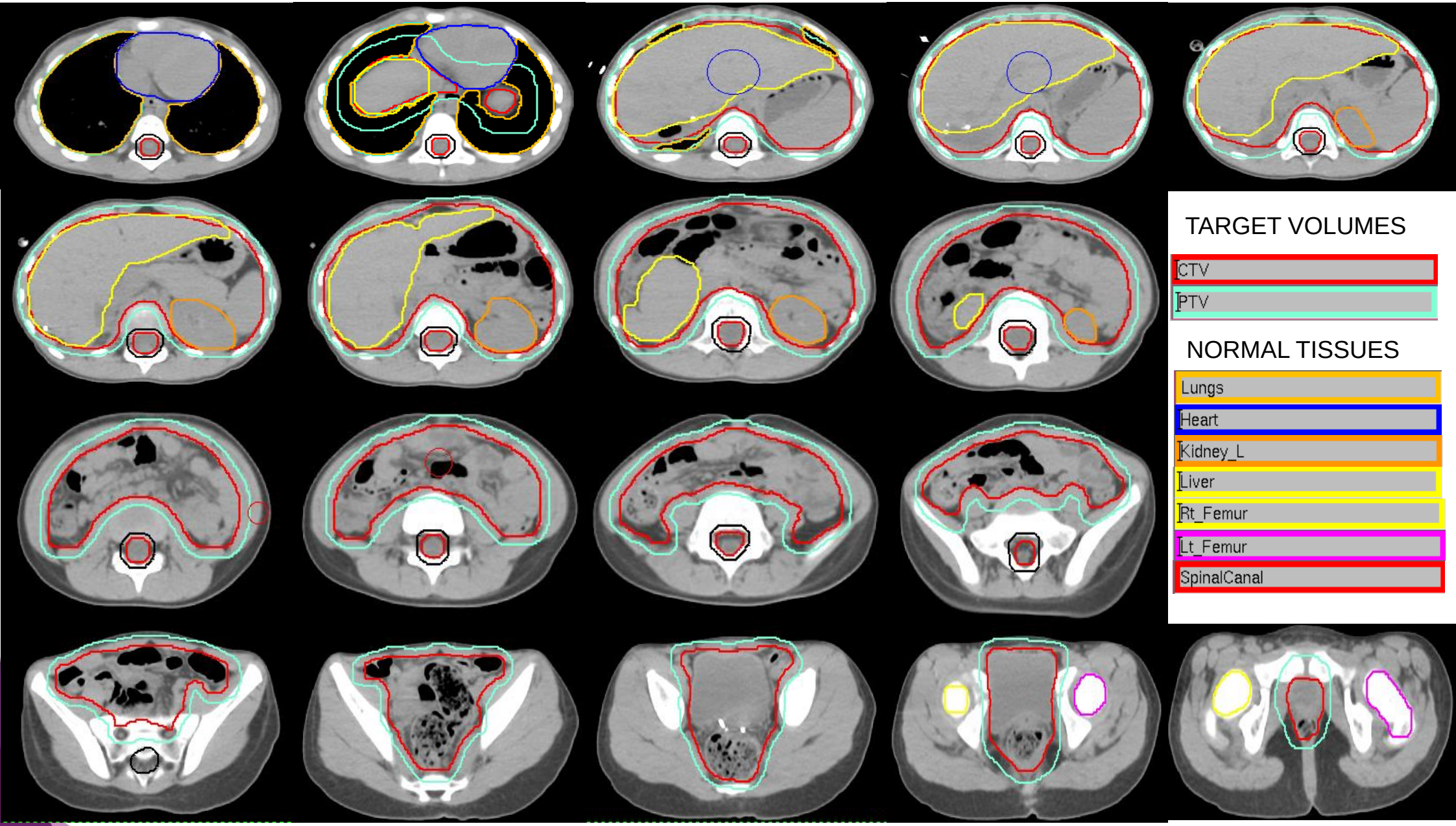
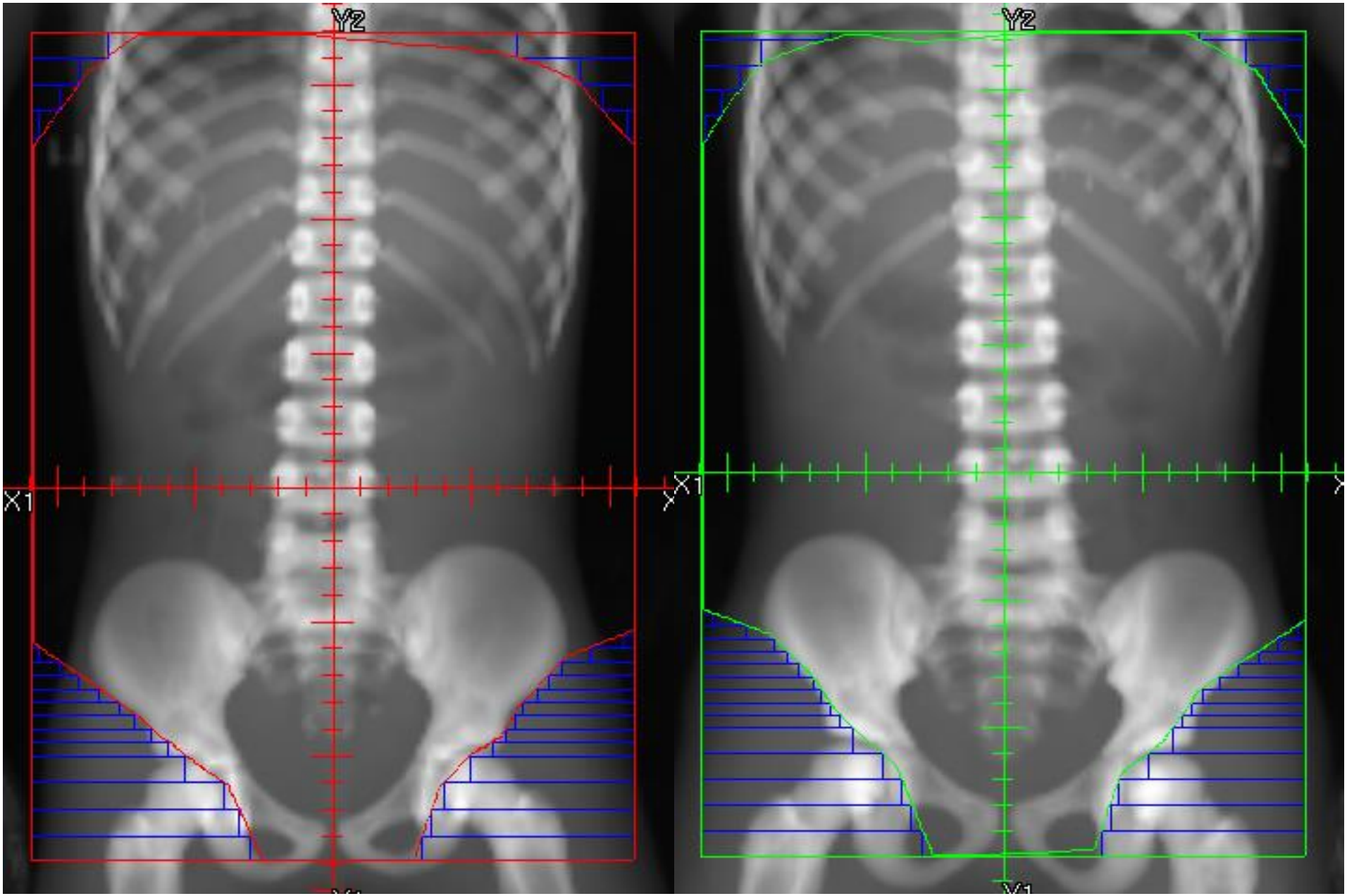
Favorable histology Wilms tumor of right kidney with peritoneal metastasis






TARGET VOLUMES
CTV
PTV
NORMAL TISSUES
Lungs
Heart
Kidney_L
Liver
Rt_Femur
Lt_Femur
SpinalCanal



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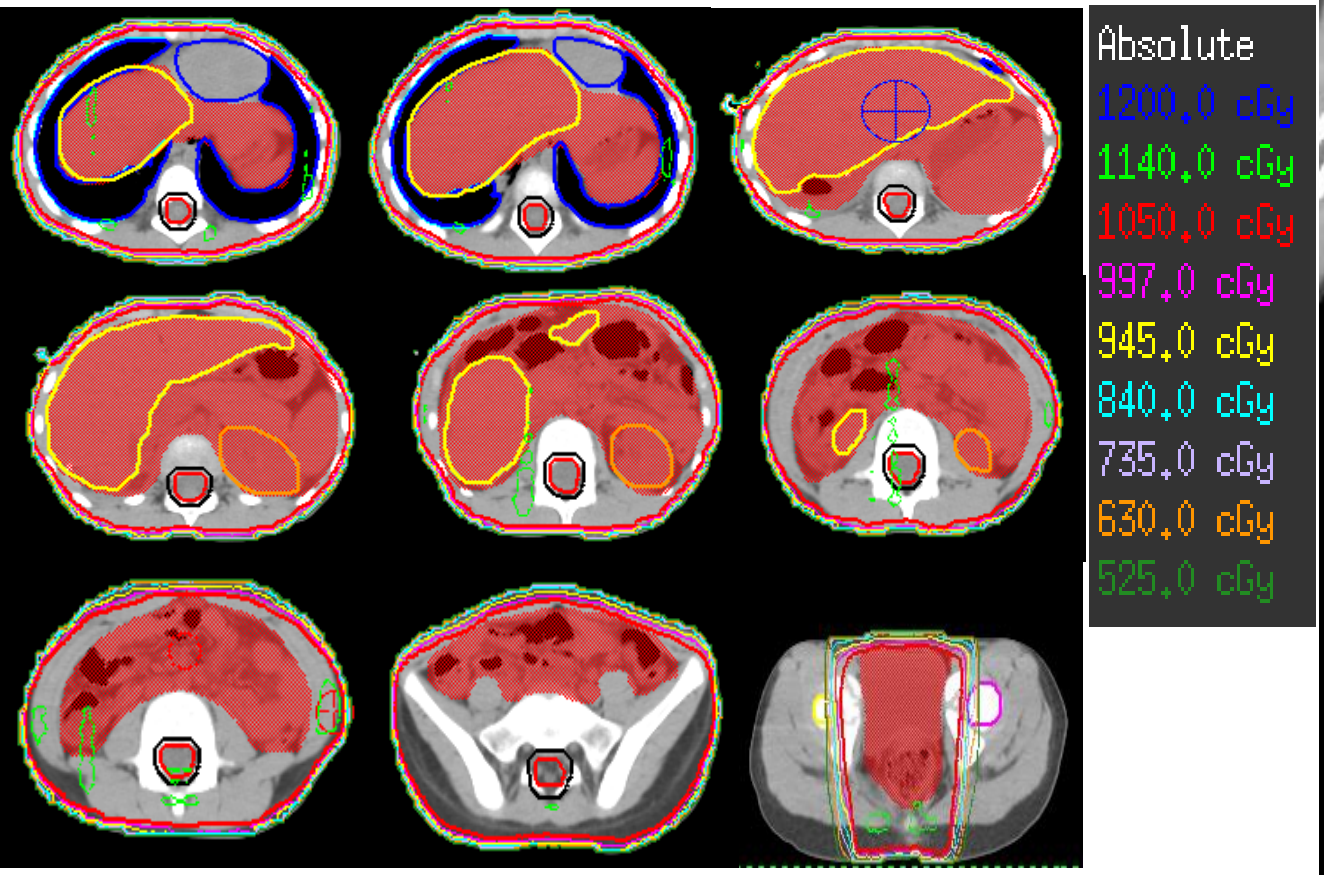

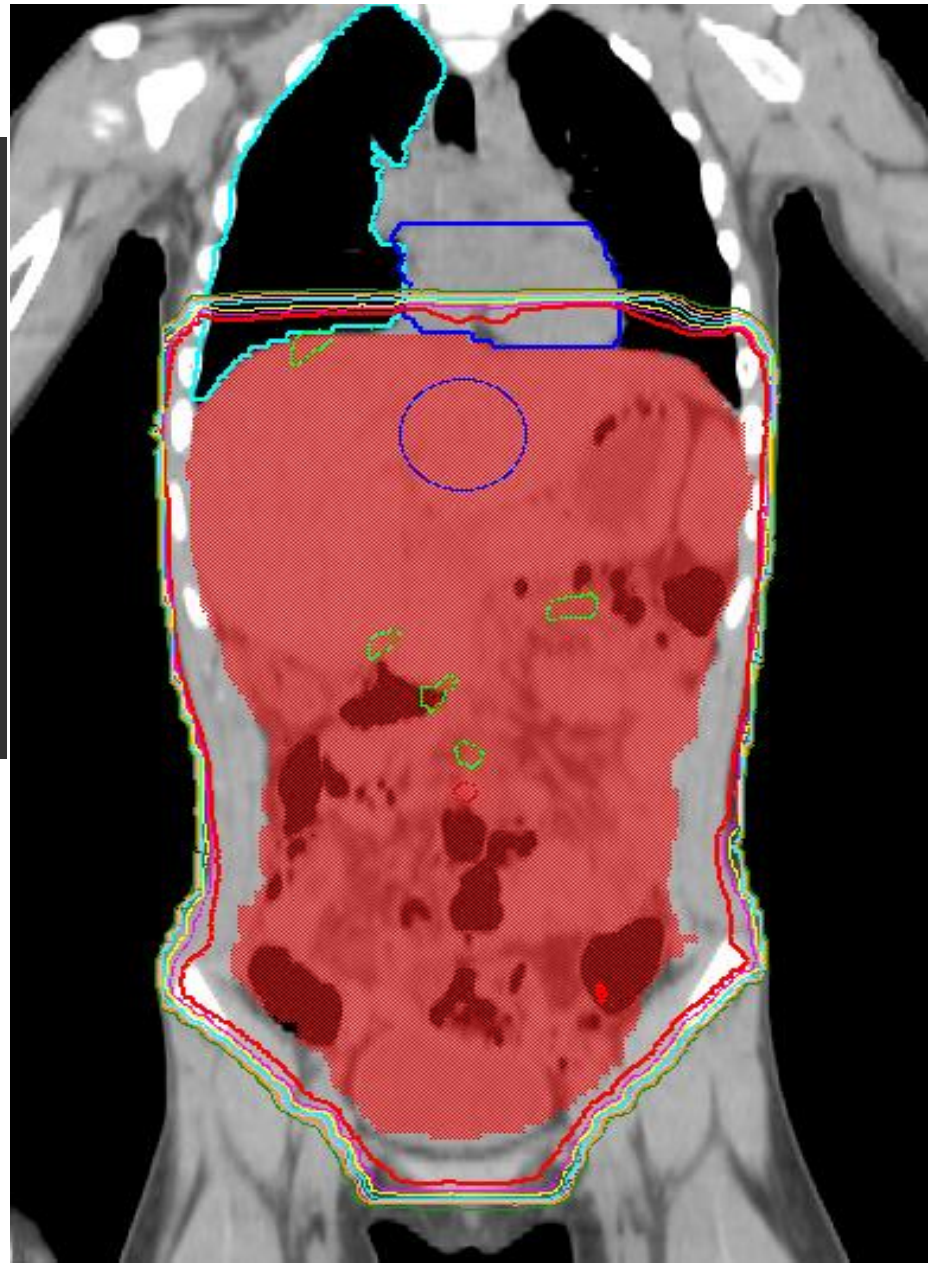

Prescription Dose to Whole Abdomen:
1050 cGy in 7 fractions

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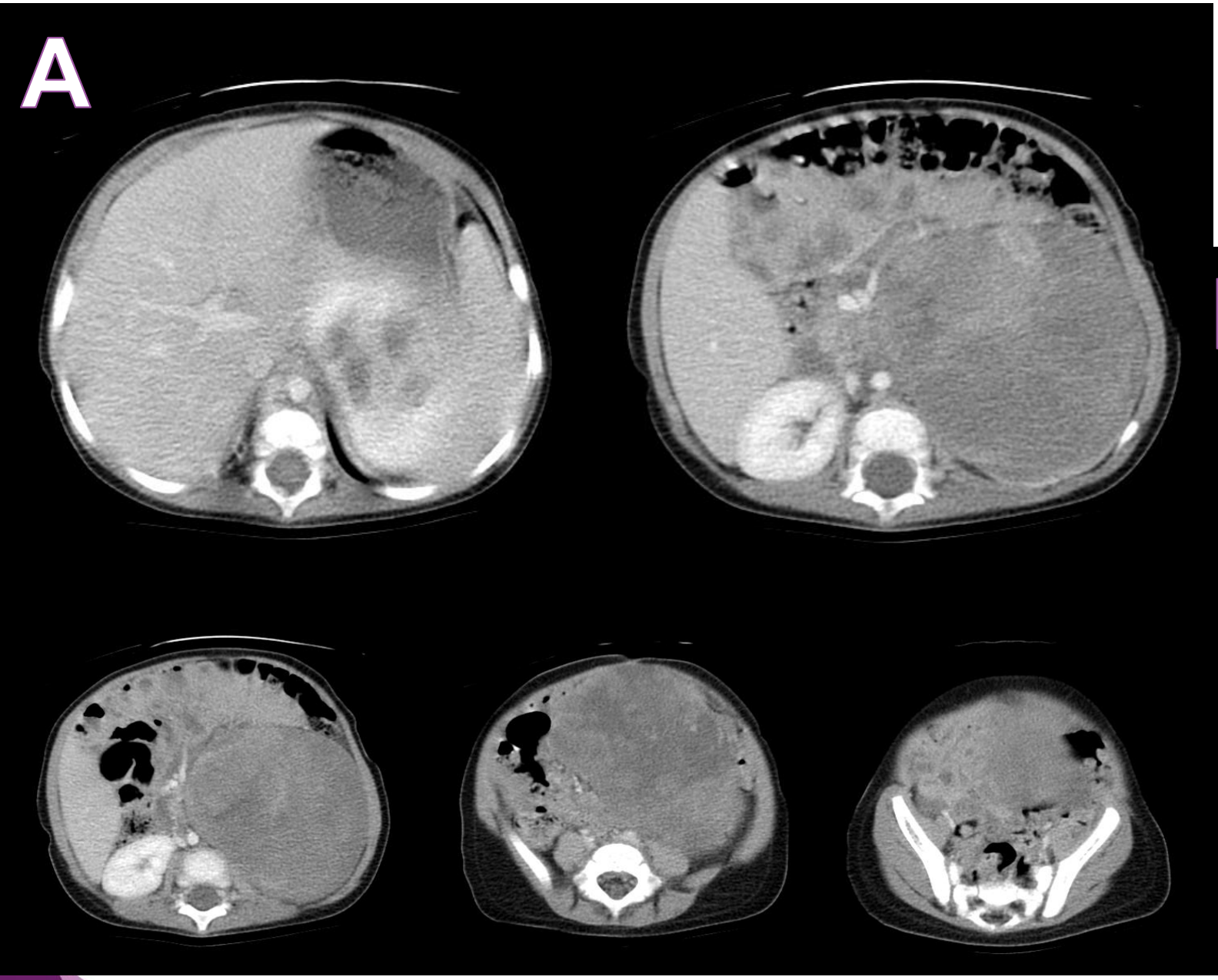
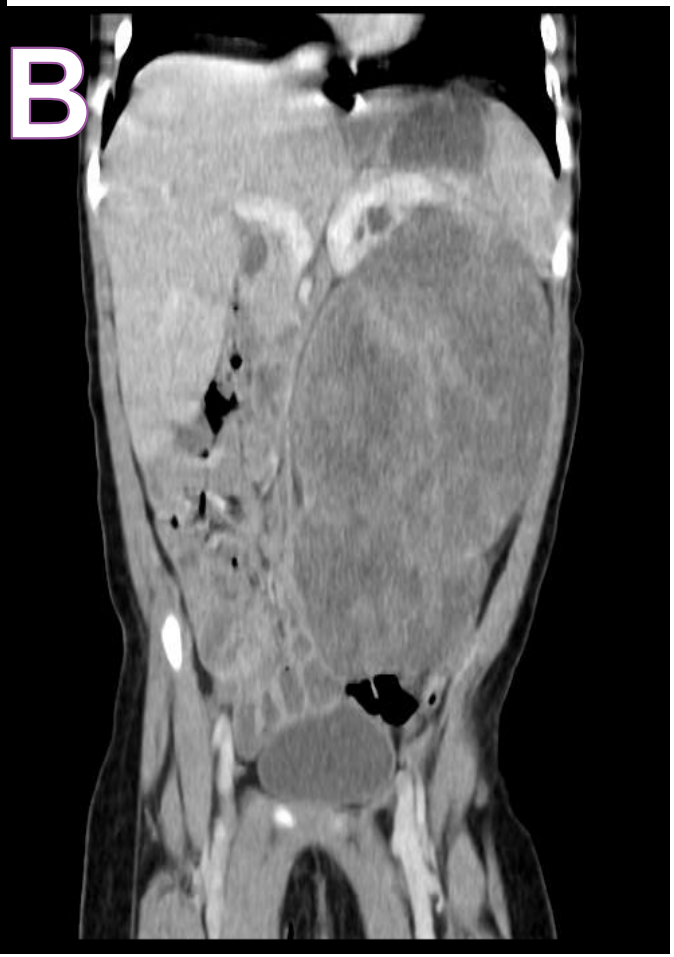
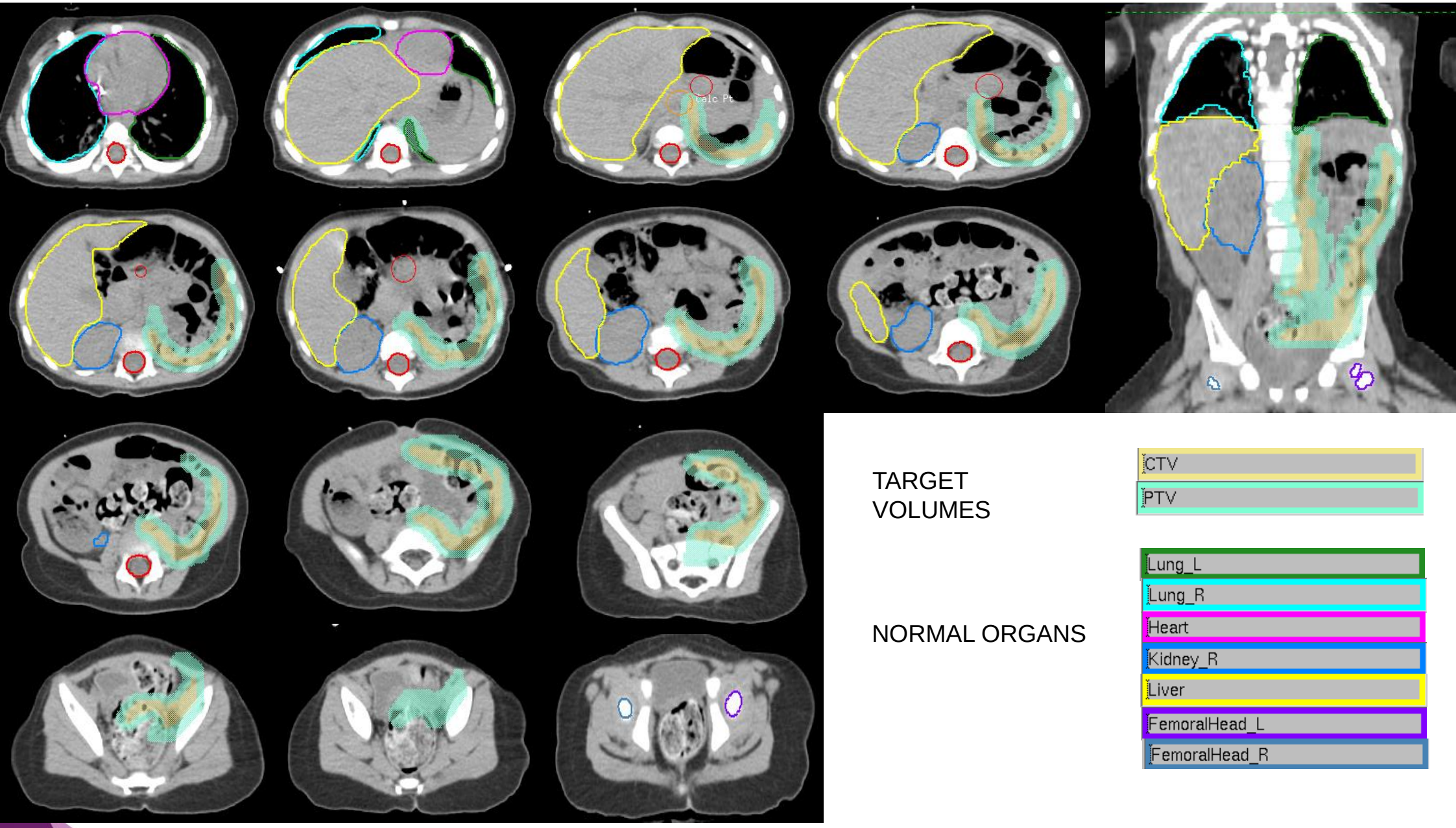


Stage II Clear Cell Sarcoma of Left Kidney





TARGET VOLUMES

CTV

PTV

NORMAL ORGANS

Lung_L

Lung_R

Heart

Kidney_R

Liver

FemoralHead_L

FemoralHead_R

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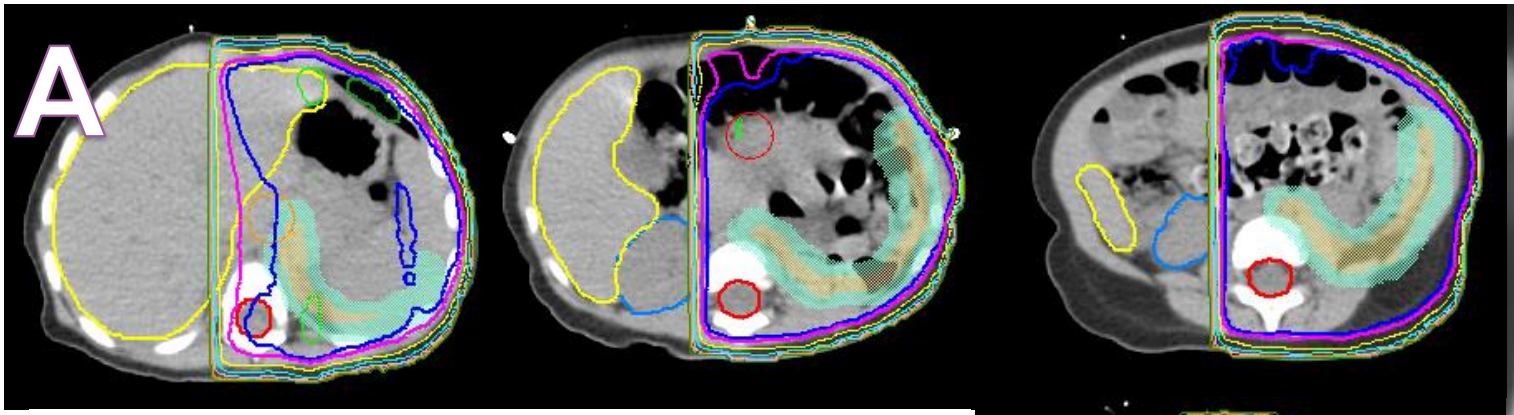

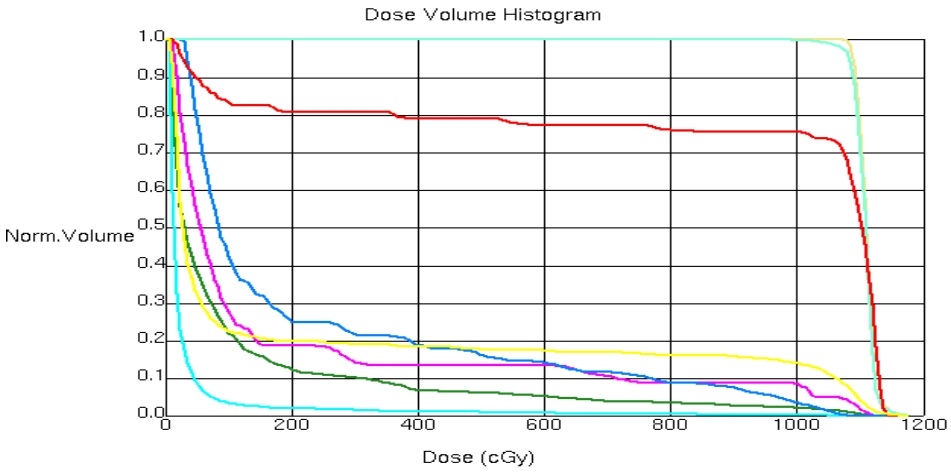

ROI Statistics

Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.
	Lung_L	AP Approved	4.8	1120.9	107.0	206.9
	Lung_R	AP Approved	6.1	1049.9	29.2	76.7
	Heart	AP Approved	9.8	1124.8	181.0	306.2
	Kidney_R	AP Approved	25.7	1083.0	223.9	287.9
	CTV	AP Approved	1031.1	1168.4	1109.0	12.9
	PTV	AP Approved	551.9	1176.7	1106.2	19.2

Prescription Dose:
1080 cGy to left hemiabdomen

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Conclusions

Current survival rates for most children with Wilms' tumor are excellent

Successive trials have reduced the number of children who will require radiotherapy for Wilms tumor

Tumors with LOH 1p AND 16q have a worse prognosis and are currently being treated with more aggressive therapy

Tumors with 1q gain will be treated more aggressively in the next COG studies

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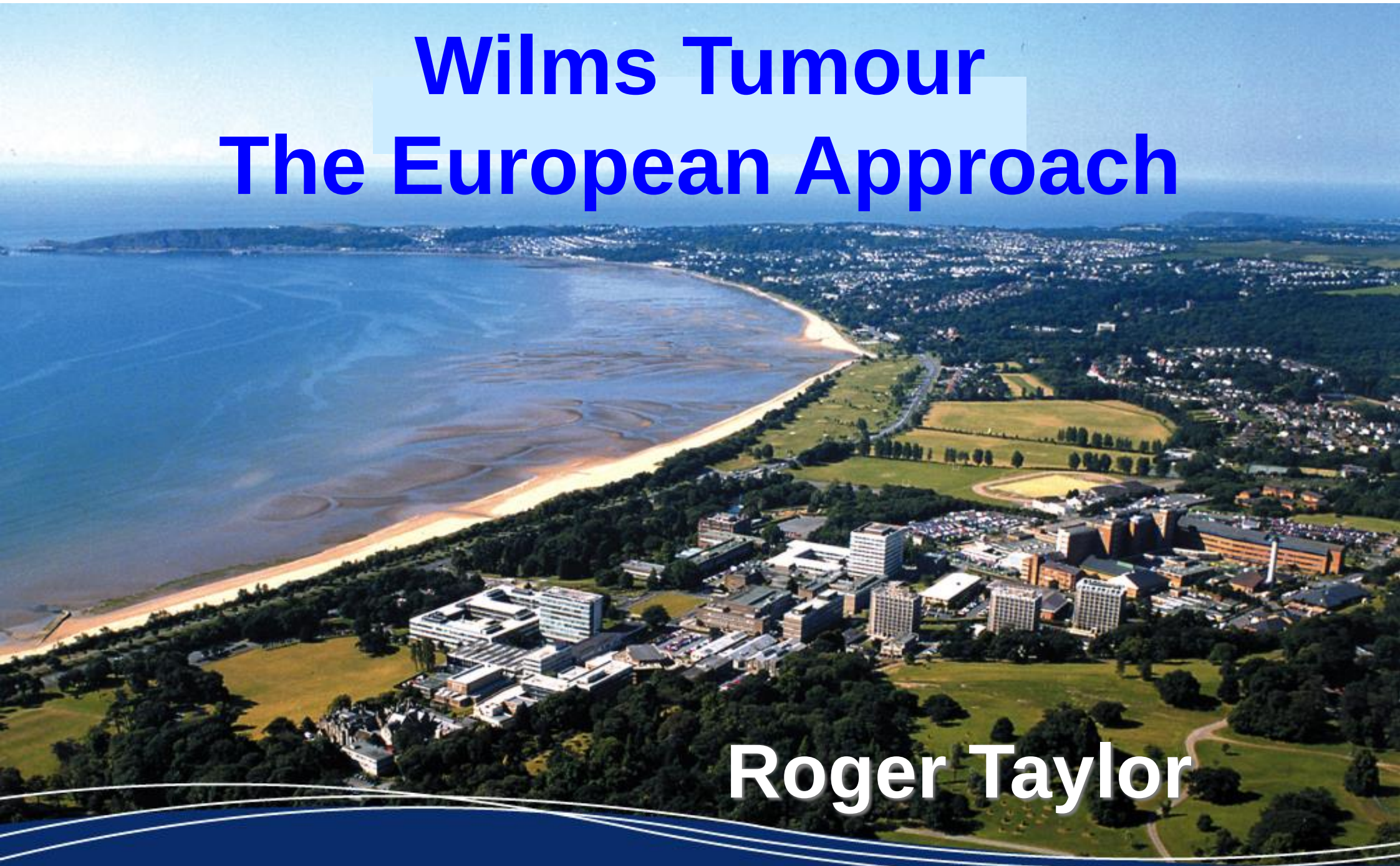
Wilms Tumour
The European Approach

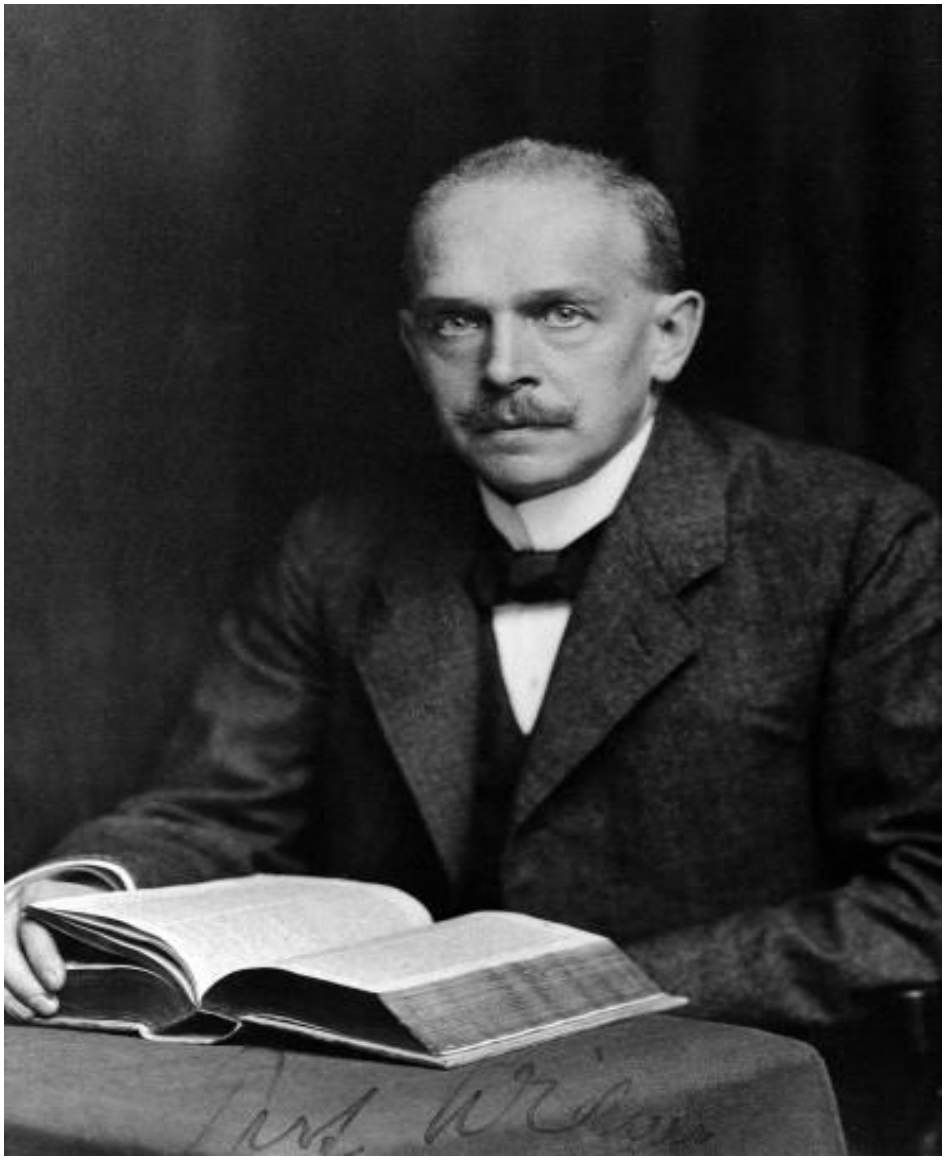


Roger Taylor

SWANSEA UNIVERSITY
PRIFYSGOL ABERTAWE

SOUTH WEST WALES CANCER CENTRE

Max Wilms 1867 - 1918



DIE MISCHGESCHWÜLSTE

Von

Dr. M. WILMS

DOCENT FÜR CHIRURGIE IN LEIPZIG

HEFT 1:

DIE MISCHGESCHWÜLSTE DER NIERE

LEIPZIG

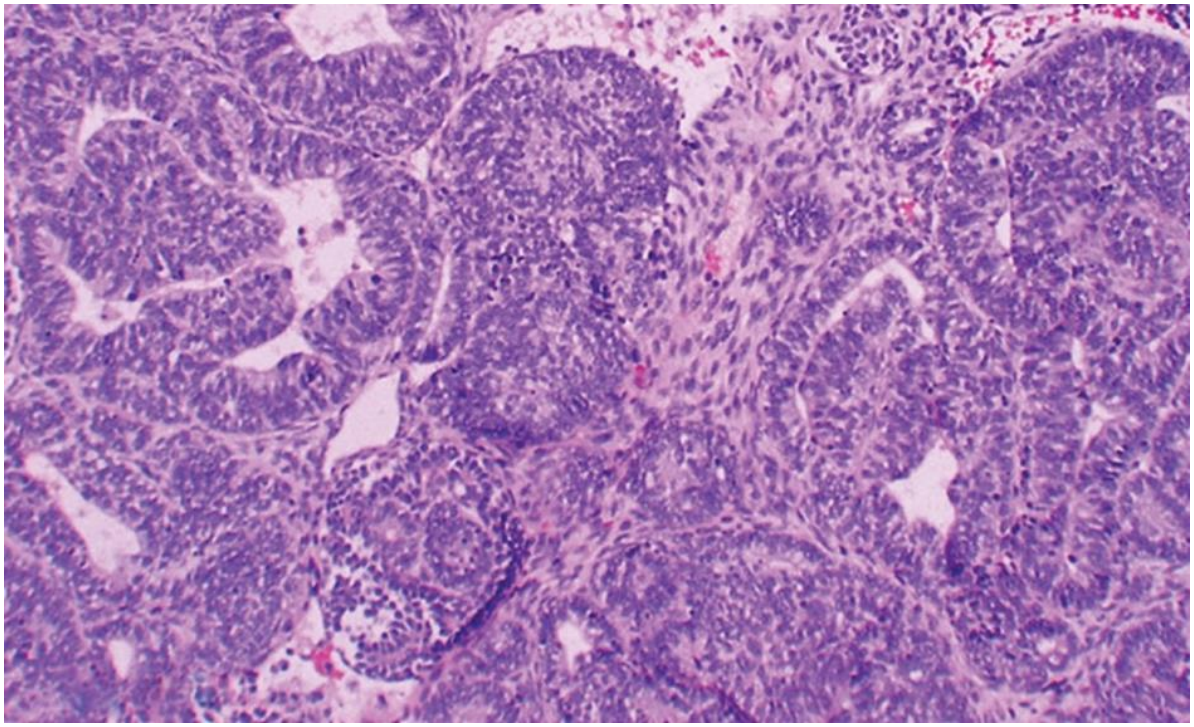
VERLAG VON ARTHUR GEORGI

1899.

Introduction/Epidemiology

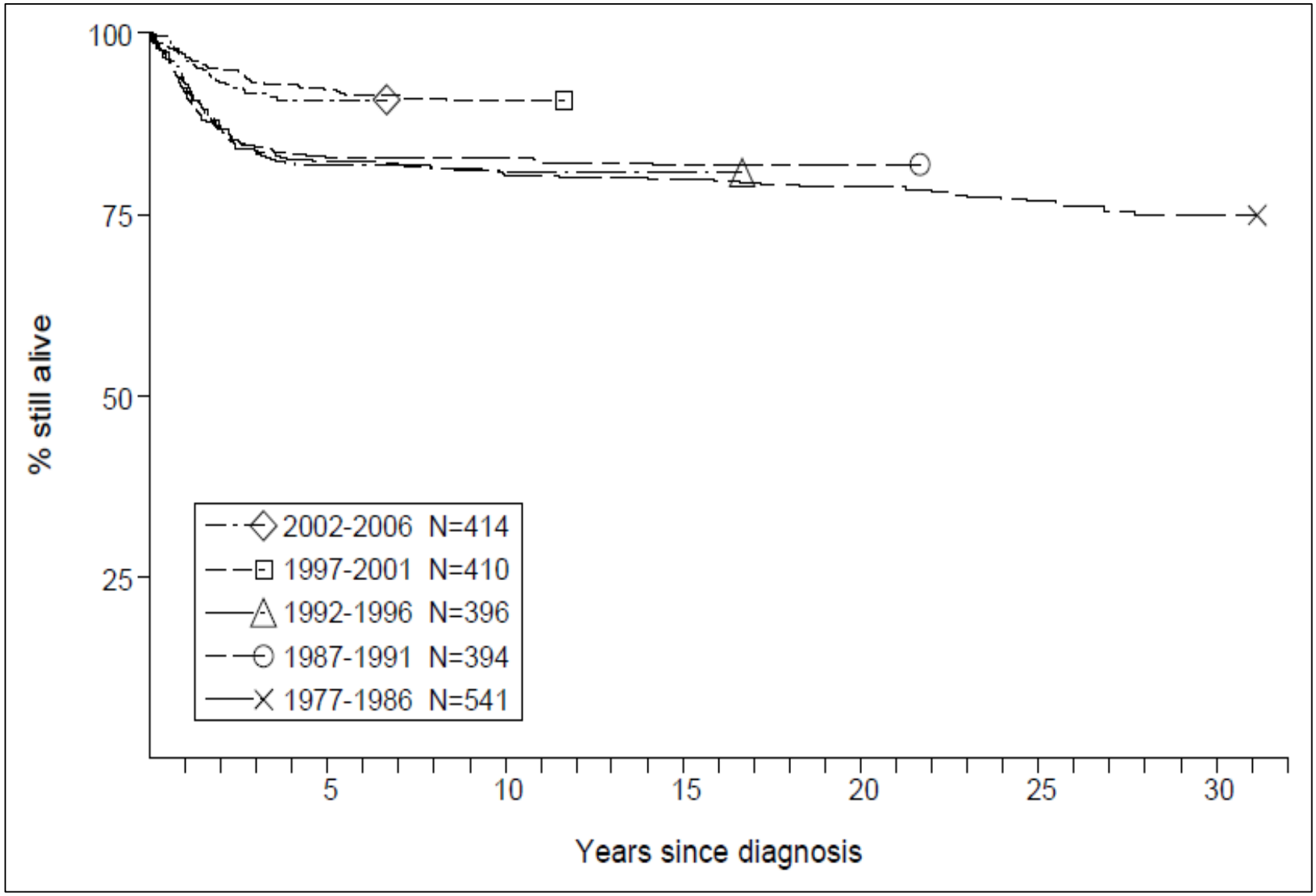
- 6% of paediatric cancers
- M:F ratio – 0.92
- Median age at diagnosis - 3.5 years
- Bilateral in 4-8% of cases
- Associated with congenital abnormalities in 10-13% of cases
  - Aniridia 1%
  - Hemihypertrophy 2-3%
  - Genitourinary abnormalities 5%

Pathology



- Triphasic tumour
  - Blastemal
  - Epithelial
  - Stromal
- Anaplasia in 4-5% of patients (10% of over 5 years of age)
- Nuclear enlargement, hyperchromatism, multiple mitotic figures
- Diffuse anaplasia – noted in > 10% HPF

Wilms' Tumour
Survival of UK Patients



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Wilms' Tumour Staging

- Stage 1: confined to kidney, completely resected
- Stage 2: extension beyond kidney, completely resected
- Stage 3: residual abdominal disease: involved margins, gross residue or nodes, gross rupture, intra-abdominal spread
- Stage 4: haematogenous metastases
- Stage 5: bilateral

Management - Europe

SIOP 1

- 1971 – 1974
- Pre-op RT
- Major difference (p = 0.001) in risk of tumour rupture during surgery

SIOP-5

- 1977-1979

- Is chemotherapy alone as good as chemo-RT?
- Randomisation was to preop chemo-RT (20 Gy) with act-D or to chemotherapy alone using act-D/VCR
- Postop RT omitted in stage 1
- Both arms equivalent in terms of tumour rupture

European Approach
SIOP-Europe 2001 - 2009

NEPHROBLASTOMA
(Wilms tumour)

CLINICAL TRIAL AND STUDY

SIOP WT 2001

SOCIÉTÉ INTERNATIONALE
D'ONCOLOGIE PÉDIATRIQUE
SIOP
INTERNATIONAL SOCIETY
OF PAEDIATRIC ONCOLOGY

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Wilms Tumour
SIOP 2001 Trial

- Pre-operative chemotherapy:
- Vincristine/Actinomycin-D for 4 weeks

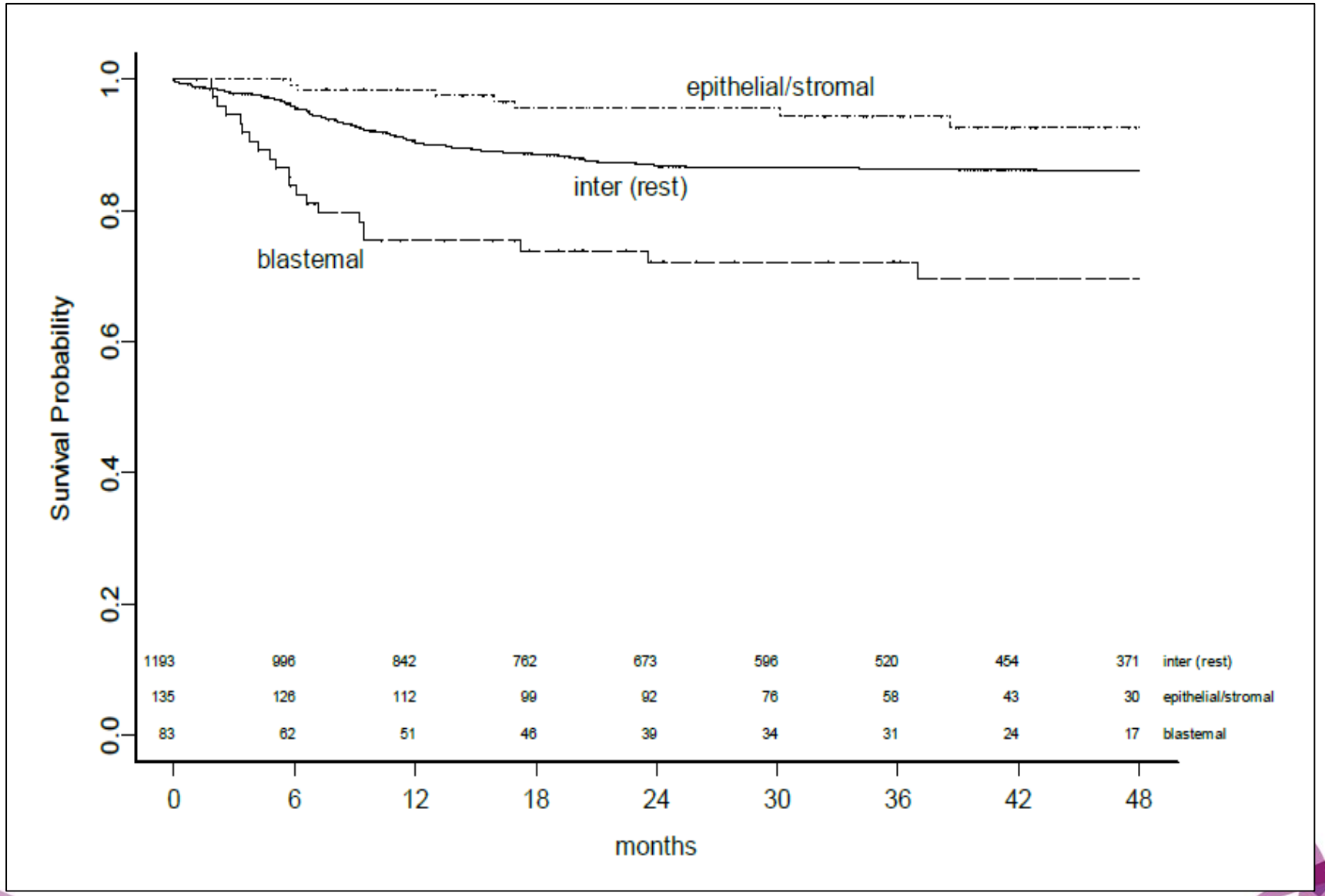
- Surgery - nephrectomy

- Stratification according to risk status based on histology - selection of post-operative therapy

Classification of Renal Tumours of Childhood (SIOP)

- **Low Risk**
  - Mesoblastic nephroma
  - Cystic partially differentited nephroblastoma
  - Completely necrotic nephroblastoma
- **Intermediate Risk**
  - Nephroblastoma, epithelial type
  - Nephroblastoma, stromal type
  - Nephroblastoma, mixed type
  - Nephroblastoma, regressive type
  - Nephroblastoma, focal anaplasia
- **High Risk**
  - Nephroblastoma, blastemal type
  - Nephroblastoma, diffuse anaplasia
  - Clear cell sarcoma
  - Rhabdoid tumour

SIOP Intermediate Risk
Influence of Post-Chemo Histology



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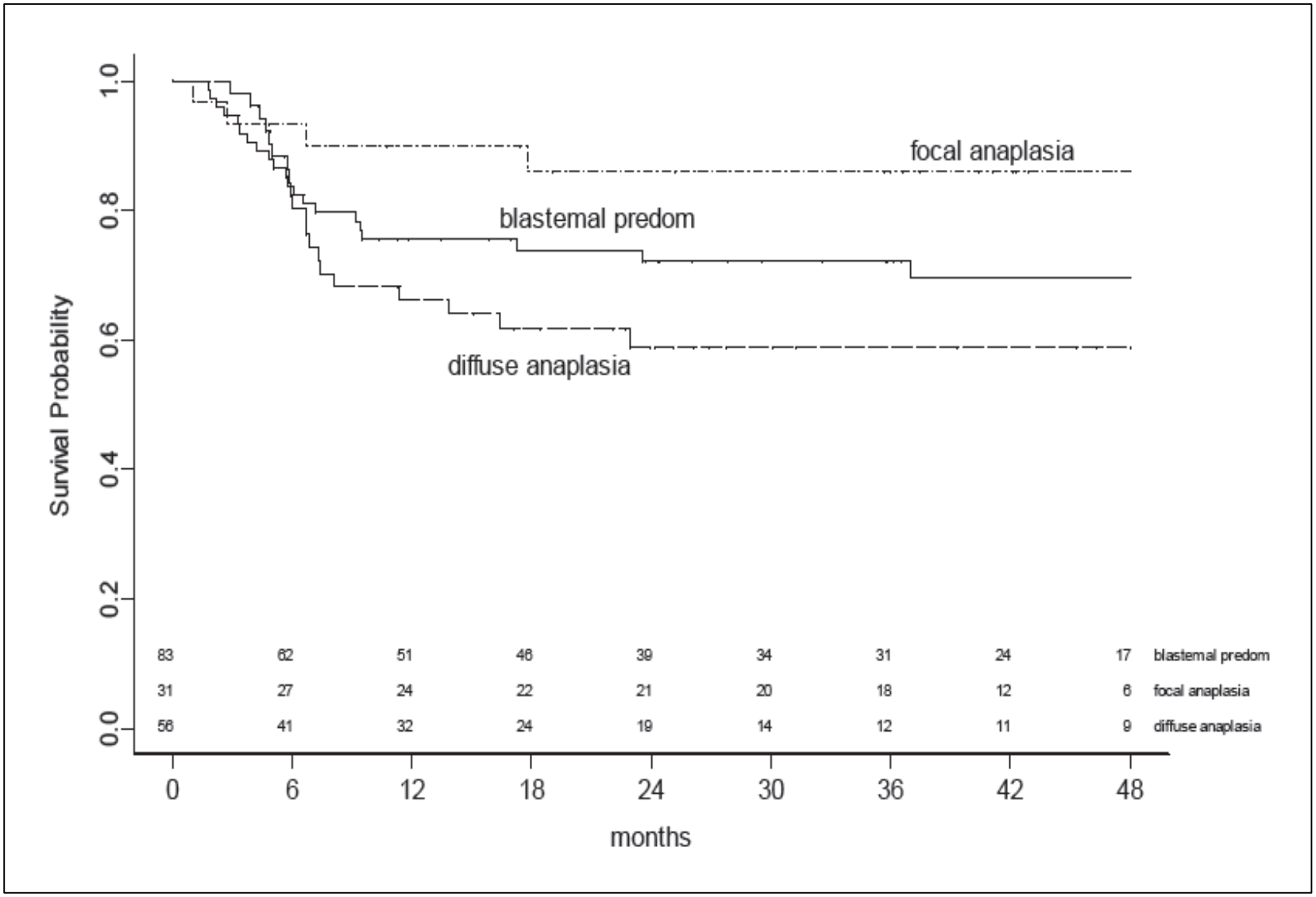
SIOP High Risk
Influence of Histology



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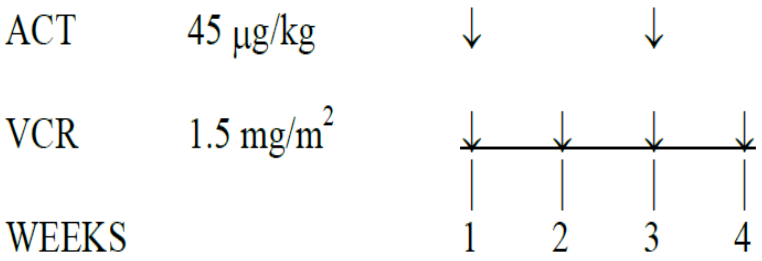
SIOP WT 2001
Post-Chemotherapy Management of Localised Disease

PRE-OPERATIVE TREATMENT



	STAGE I	STAGE II	STAGE III
LOW RISK	NO FURTHER TREATMENT	AV-2	AV-2
INTERMEDIATE RISK	AV-1	R < DOX + / DOX -	R < RT / DOX + / RT / DOX –
HIGH RISK	AVD	HIGH RISK + RT	HIGH RISK + RT

SIOP – Stage 3 Intermediate Histology

STAGE III, INTERMEDIATE RISK, POST-OPERATIVE TREATMENT

REGIMEN AVD

ACT 45 µg/kg ↓ ↓ ↓

VCR 1.5 mg/m^2 ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓

DOX 50 mg/m^2 ↓ ↓ ↓

RT

WEEKS ♦1 2<------3--------4------>5 6 7 8 9 10 11 12 13 14 15 16

17 18 19 ♦20 21 22

23 24 25 26 27 ♦

R

♦ = Echocardiogram (ECHO)* AVD -at start of treatment, prior to wk 20, and end of treatment. AV2 - baseline echocardiogram at start of treatment. *if ECHO is abnormal, see Section 8.3

REGIMEN AV-2

ACT 45 µg/kg ↓ ↓ ↓

VCR 1.5 mg/m^2 ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓

RT

WEEKS ♦1 2<------3--------4------>5 6 7 8 9 10 11 12 13 14 15 16

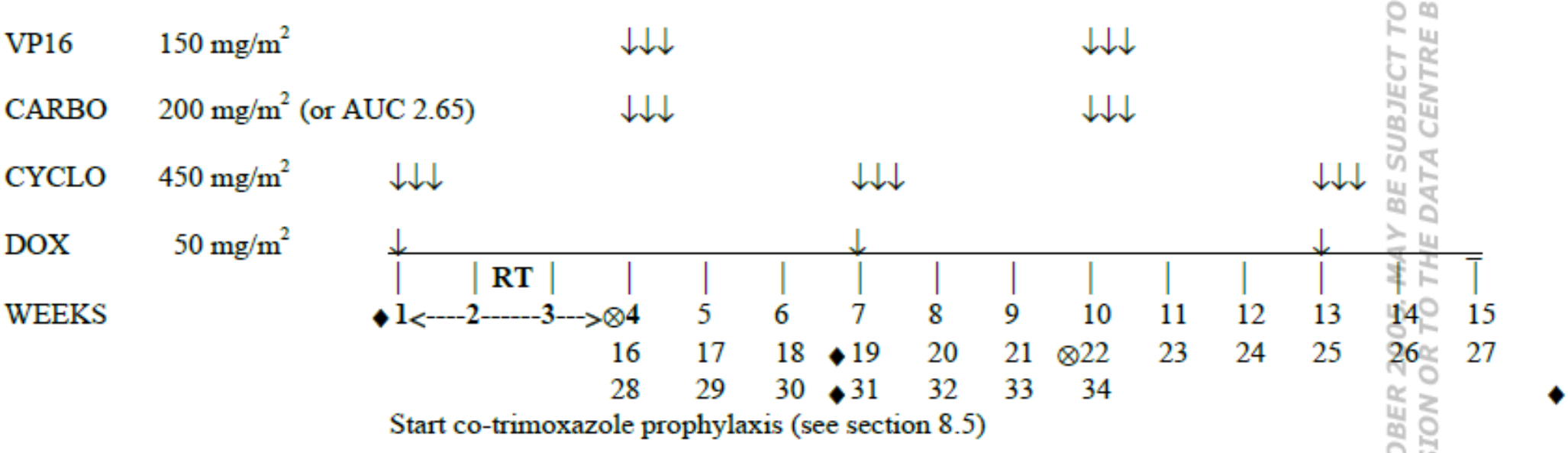
17 18 19 20 21 22

23 24 25 26 27

ACT = actinomycin D = 45 µg/kg/i.v. bolus injection (max 2 mg!)
VCR = vincristine = 1.5 mg/m^2/i.v. bolus injection (max 2 mg!)
DOX = doxorubicin = 50 mg/m^2/i.v. 4-6 hours
If body weight < 12 kg: dose reduction to 2/3 for each drug. If age <6 months: dose reduction to 50% for each drug.
Major intolerance: reduce doses on the next course to 2/3 (see section 8).
Post-operative chemotherapy must start within 21 days of last dose of pre-operative chemotherapy.

SIOP – Stage 3 High Risk Histology

STAGE III, HIGH RISK, POST-OPERATIVE TREATMENT



◆ = Echocardiogram (ECHO)* -at start of treatment,prior to wks 19, 31 and end of treatment. *if ECHO is abnormal, see Section 8.3

⊗ = GFR (measure at every third course, or more frequently if there is evidence of renal dysfunction.)

VP16	= etoposide	=	150 mg/m^2/i.v./in 1 hour
CARBO	= carboplatin	=	200 mg/m^2/i.v./in 1 hour (or AUC = 2.65, see section 8.1e and appendix 11)
CYCLO	= cyclophosphamide	=	450 mg/m^2/i.v./in 1 hour
DOX	= doxorubicin	=	50 mg/m^2/i.v./in 4-6 hours, just after the first CYCLO administration

SIOP WT 2001

Pritchard-Jones et al SIOP Abstract 2011
Pediatric Blood and Cancer 57 (5), 741, 2011

- Can doxorubicin be safely omitted from chemotherapy for stage II/III, intermediate risk WT?
- SIOP multicentre trial (28 countries, 261 centres)
- 4 weeks pre-op VCR /ActD, delayed nephrectomy
- Stage II/III intermediate risk WTs were randomized between 26 weeks AV or AVD (total Doxo 250 mg/m2)
- Stage III tumours received 14.4 Gy flank RT

SIOP WT 2001

Pritchard-Jones et al SIOP Abstract 2011

Pediatric Blood and Cancer 57 (5), 741, 2011

- 583 patients randomized between 2001–2009
- 341 stage II , 242 stage III
- Median FU 39 months
- 22 events (20 relapses)/9 deaths among 291 randomised to AVD and 34 events (27 relapses)/7 deaths among 292 randomised to AV
- 2 yr EFS of 92% (95%CIs: 89–96%) and 89% (95%CIs: 85–93%) (p 0.06) and 5 yr OS 96% (95%CIs: 94–99) and 96% (95%CIs: 93– 99) (p 0.61)
- HR for any event by 5 yrs in the experimental AV arm compared to standard AVD chemotherapy was 1.67 (95%CIs: 0.98– 2.85, p 0.058)

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General Management - Europe

- AV (without dox) now standard therapy in Europe for stage 2/3 intermediate histology

EUROPEAN JOURNAL OF CANCER 42 (2006) 2554–2562

ELSEVIER

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journal homepage: www.ejconline.com

Immediate nephrectomy versus preoperative chemotherapy in the management of non-metastatic Wilms' tumour: Results of a randomised trial (UKW3) by the UK Children's Cancer Study Group

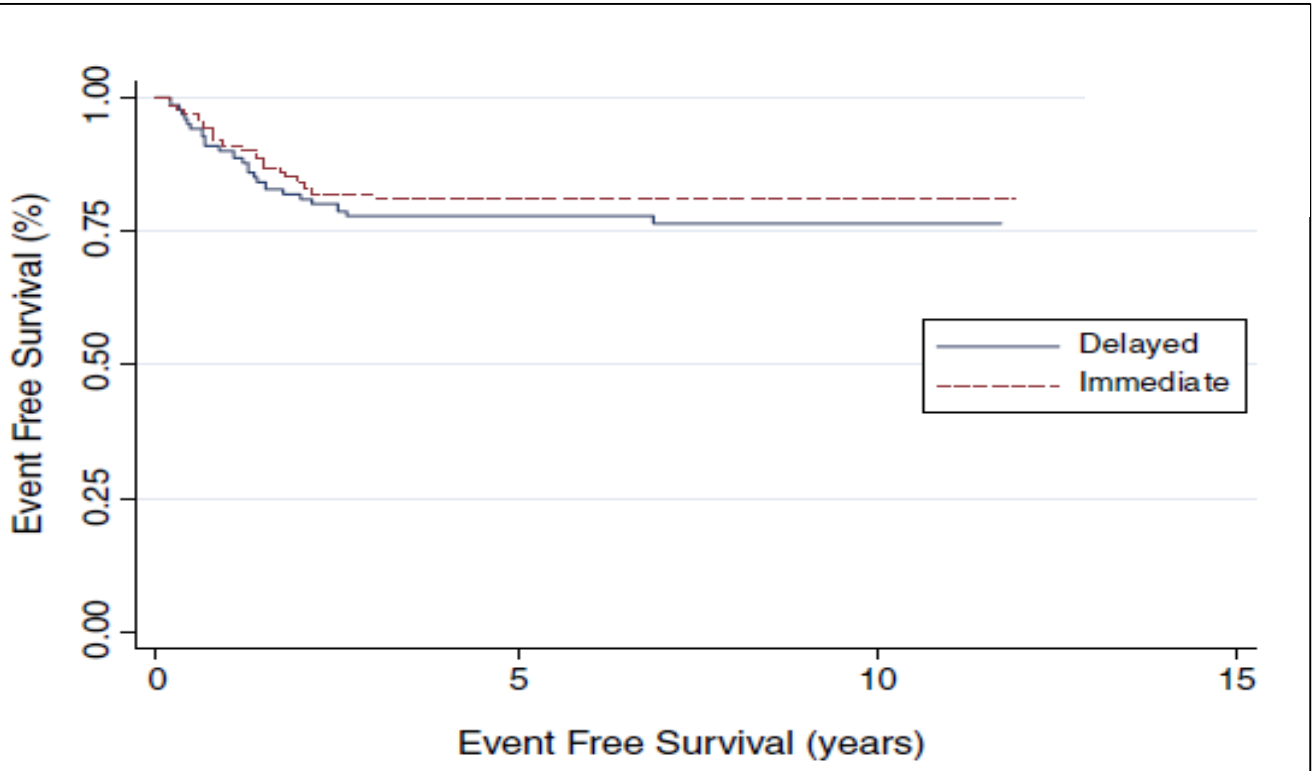
Christopher Mitchell[a,*], *Kathy Pritchard-Jones*[b], *Rosemary Shannon*[c], *Carolyn Hutton*[d], *Suzanne Stevens*[d], *David Machin*[d], *John Imeson*[d], *Anna Kelsey*[e], *Gordan M. Vujanic*[f], *Peter Gornall*[g], *Jenny Walker*[h], *Roger Taylor*[i], *Pat Sartori*[j], *Juliet Hale*[k], *Gill Levitt*[l], *Boo Messahel*[b], *Helen Middleton*[d], *Richard Grundy*[m], *Jon Pritchard*[n], *For the United Kingdom Cancer Study Group*

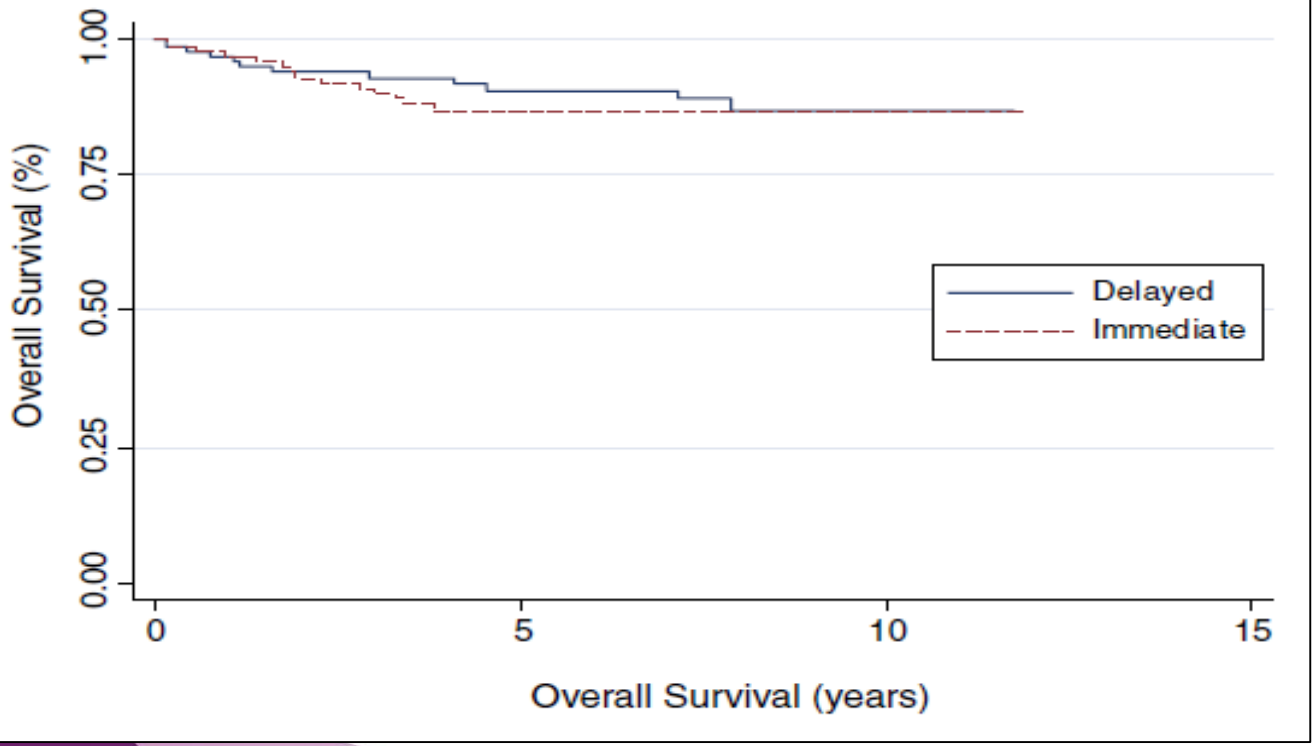
Wilms' Tumour
Radiotherapy in UKW3

- UKW3 (1992-2001)
- Randomised study comparing immediate nephrectomy with pre-operative chemotherapy and delayed nephrectomy
- Abdominal RT for stage III
- 20 Gy for FH, 30 Gy for UH
- Lung RT for patients presenting with lung metastases, 12 Gy in 8 fractions

UKW3

- 1991 – 2001 - 186 patients with non-metastatic WT
- Randomised to either immediate surgery or to 6 weeks preoperative chemotherapy (VCR/ActD) and then delayed surgery
- Post-op chemotherapy according to tumour stage and histology determined at the time of nephrectomy
- Significant improvement in the stage distribution for patients receiving delayed surgery (P 0.008)
- Stage I: 65.2% versus 54.3%
- stage II: 23.9% versus 14.9%
- stage III: 9.8% versus 29.8%
- 20% fewer children receiving radiotherapy or doxorubicin
- EFS and OS at 5 years of 79.6% and 89.0%, respectively, similar in the two groups





UKW3

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Wilms' Tumour
Radiotherapy Issues

Wilms' Tumour Radiotherapy

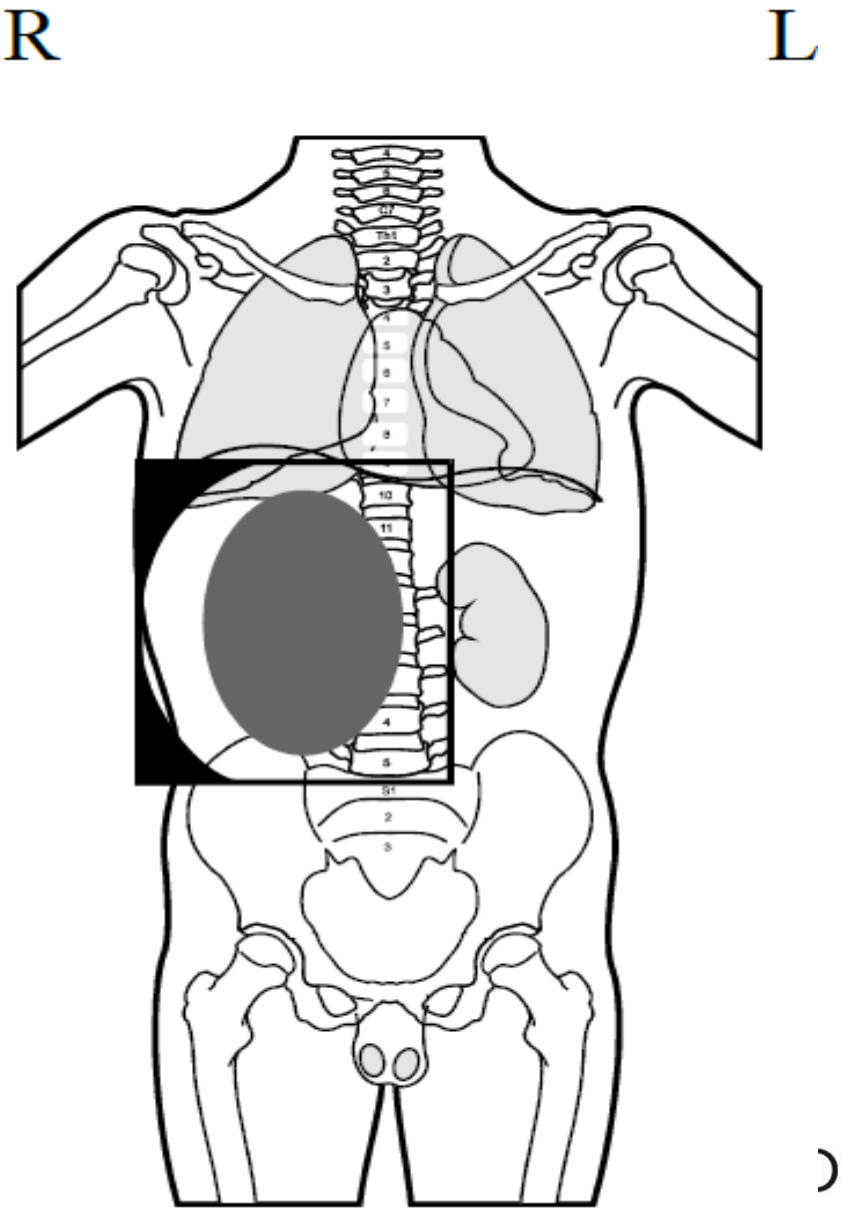
- Radiosensitivity of Wilms' Tumour
- Abdominal RT improved cure rate in Boston series from 32% (1931-1939) to 47% (1940-1947)
- Doses as low as 10.8 - 12.0 Gy have been shown to have an effect on subclinical disease

SIOP - Indications for Flank RT

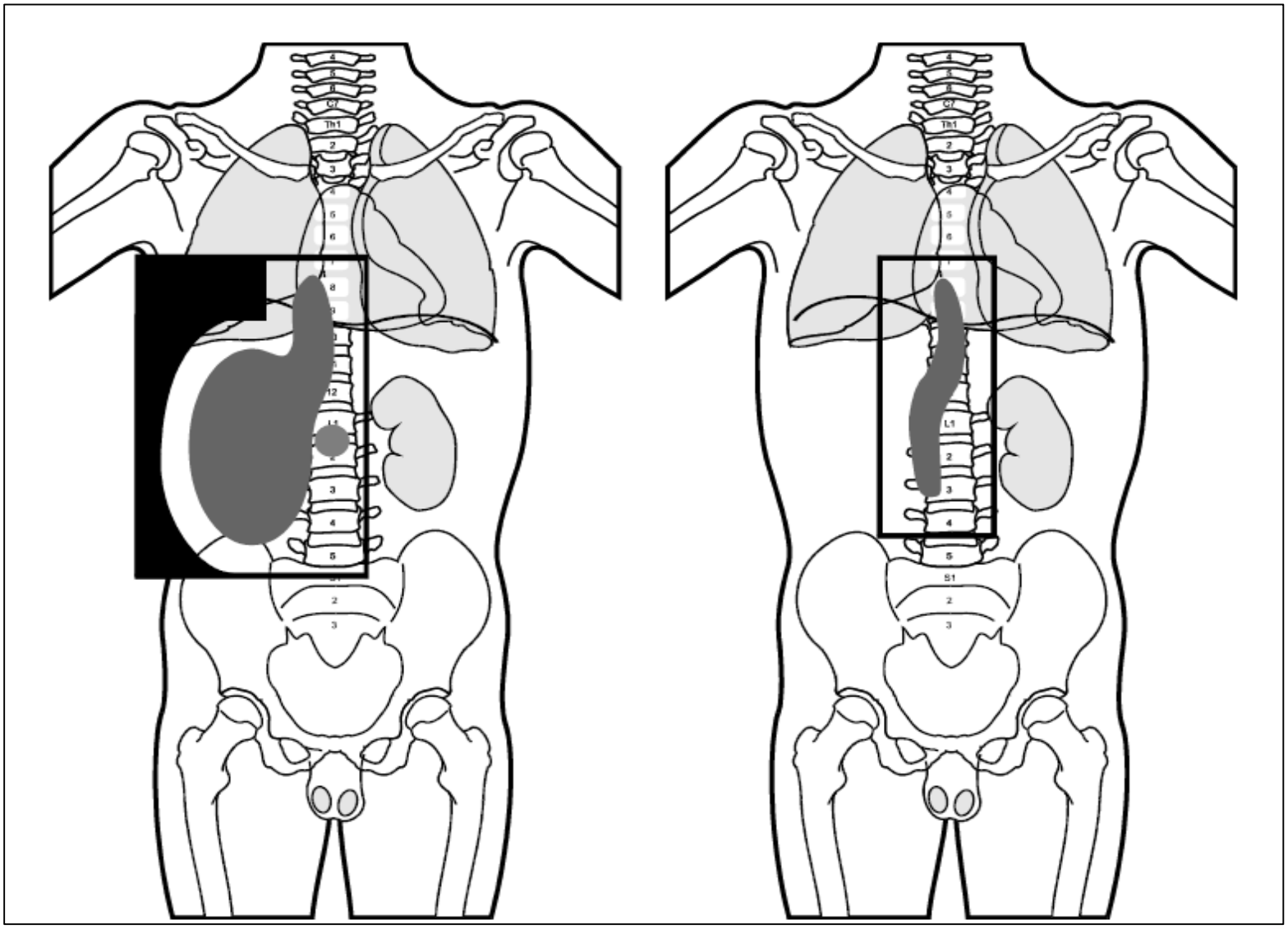
- High risk stage 2 (except blastemal type)
- Stage 3 with intermediate- or high-risk
  - positive margins
  - localised residual tumour
  - localised tumour rupture
  - lymph node positivity
- Stage 4 – abdominal RT indicated according to the local stage (1,2 or 3) of primary tumour and post-op histology

SIOP – RT Volumes

- Encompasses the tumour bed and immediately surrounding area, and the renal hilar and adjacent para-aortic lymph node areas



Flank RT with Boost to Nodes and Tumour Thrombus



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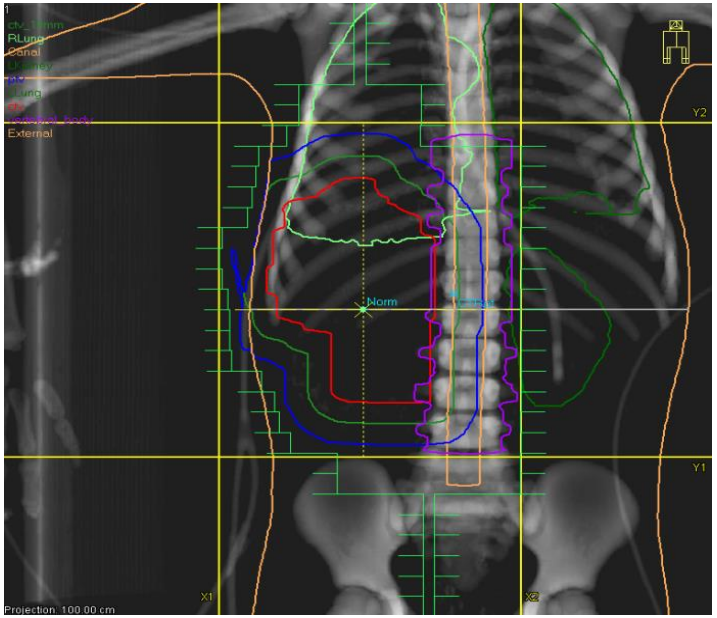
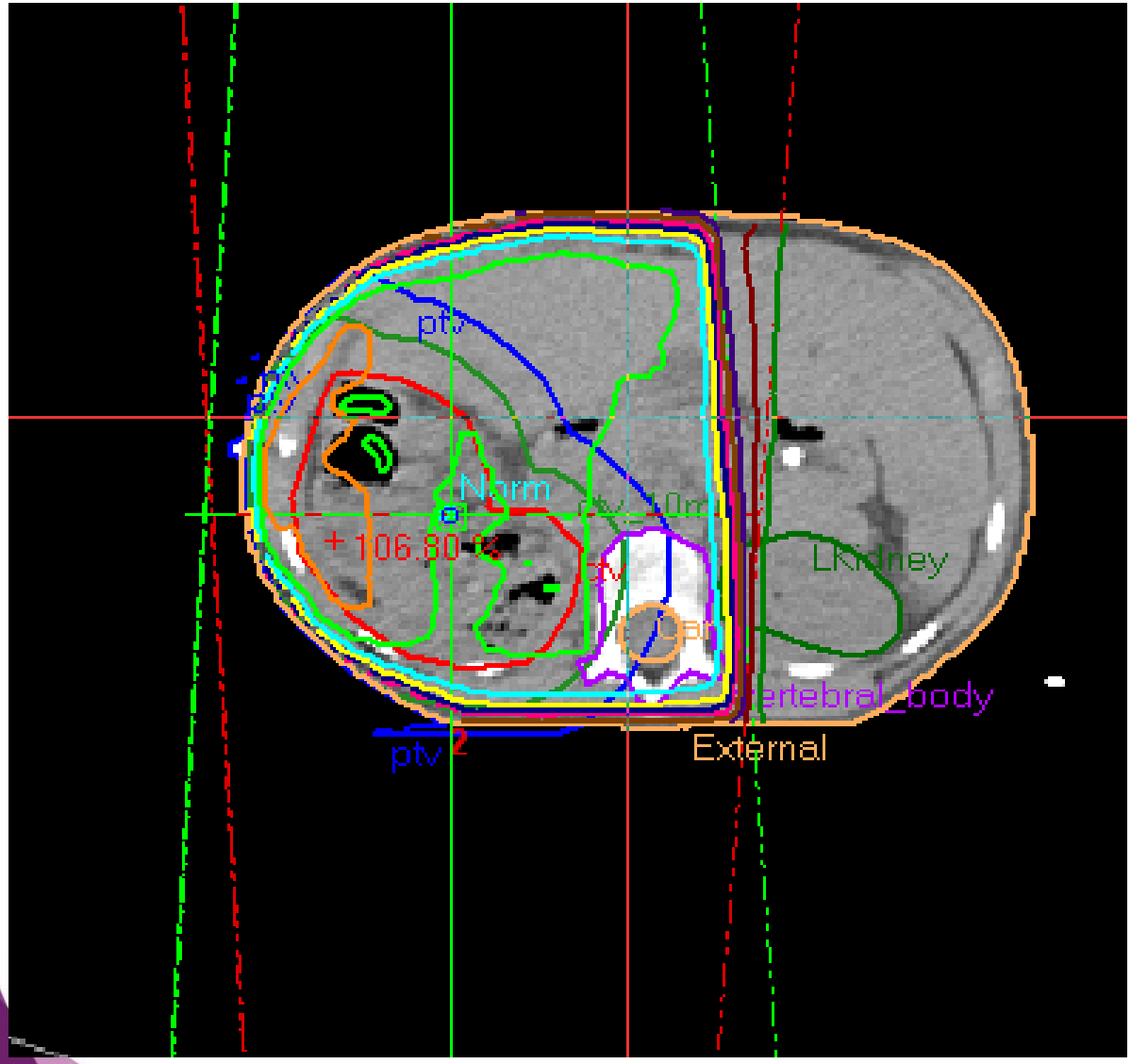
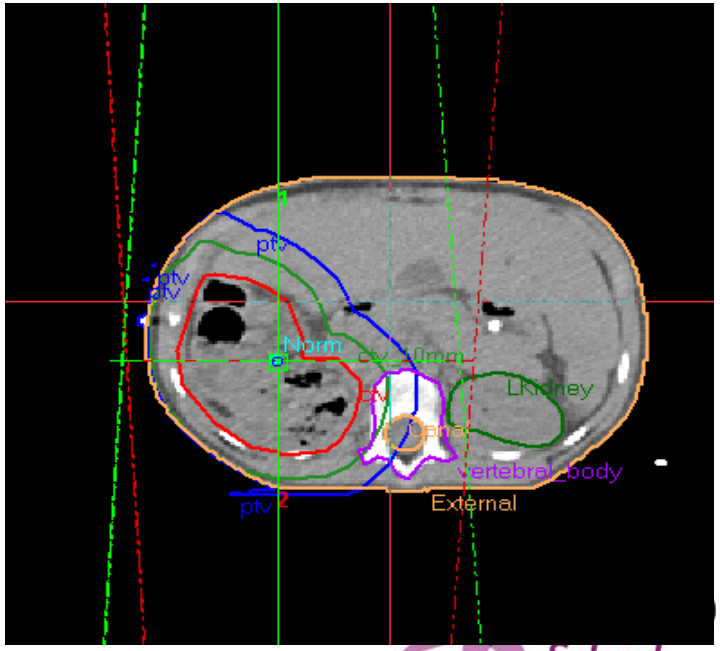
Flank RT


External
Norm
Projection 100.00 cm

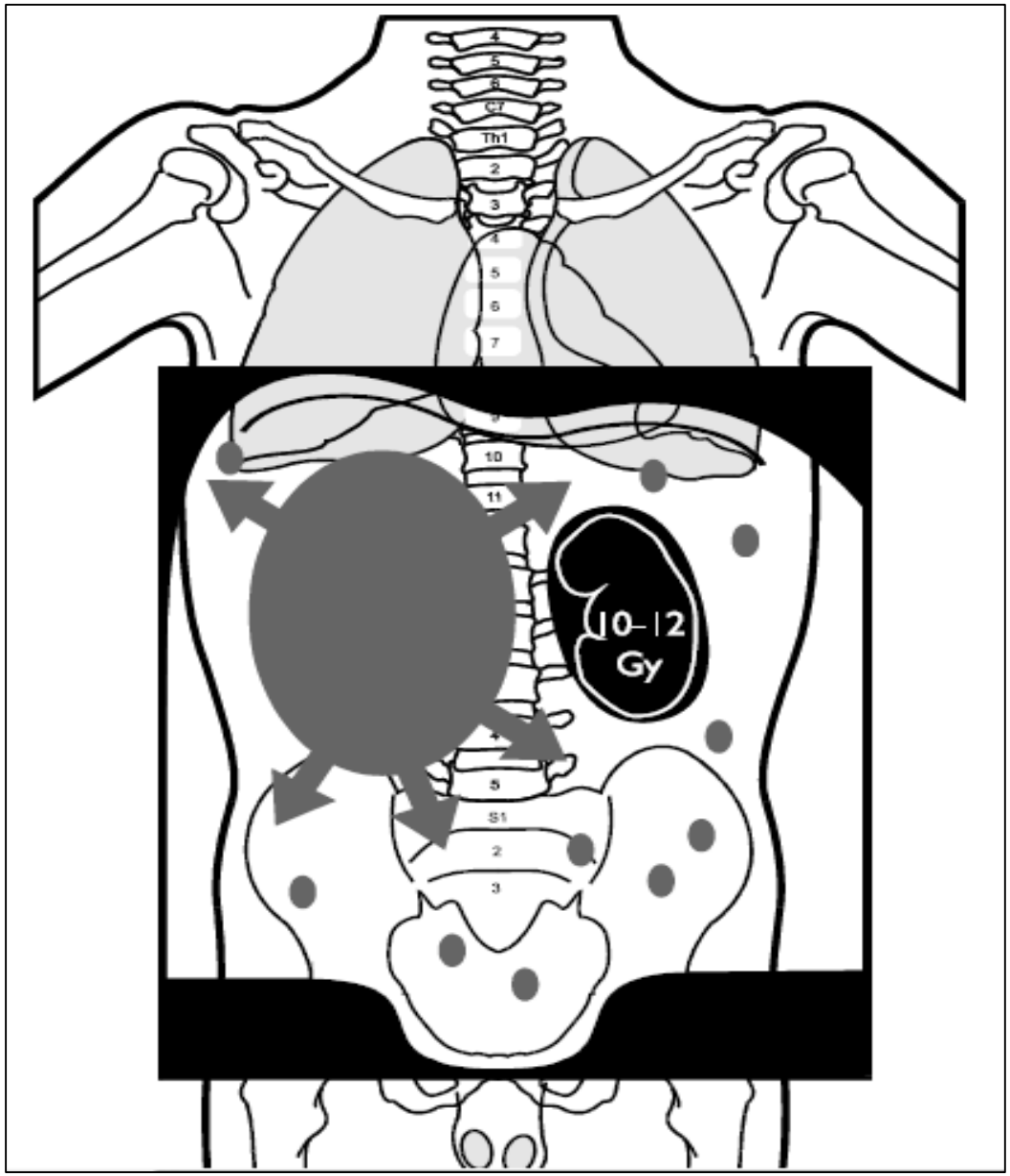

ptv
Norm
+106.80
LKidney
Vertebral_body
ptv 2
External


ptv
Norm
LKidney
Vertebral_body
ptv 2
External

SIOP – Indications for WART

- Gross intra-abdominal contamination:
  - pre-operative or intra-operative tumour rupture
  - diffuse intraperitoneal spread

WART - SIOP Protocol



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SIOP – Indications for WLRT

- WLRT reserved for patients who have failed to achieve CR to induction chemotherapy, and where necessary and feasible, surgical removal of metastases

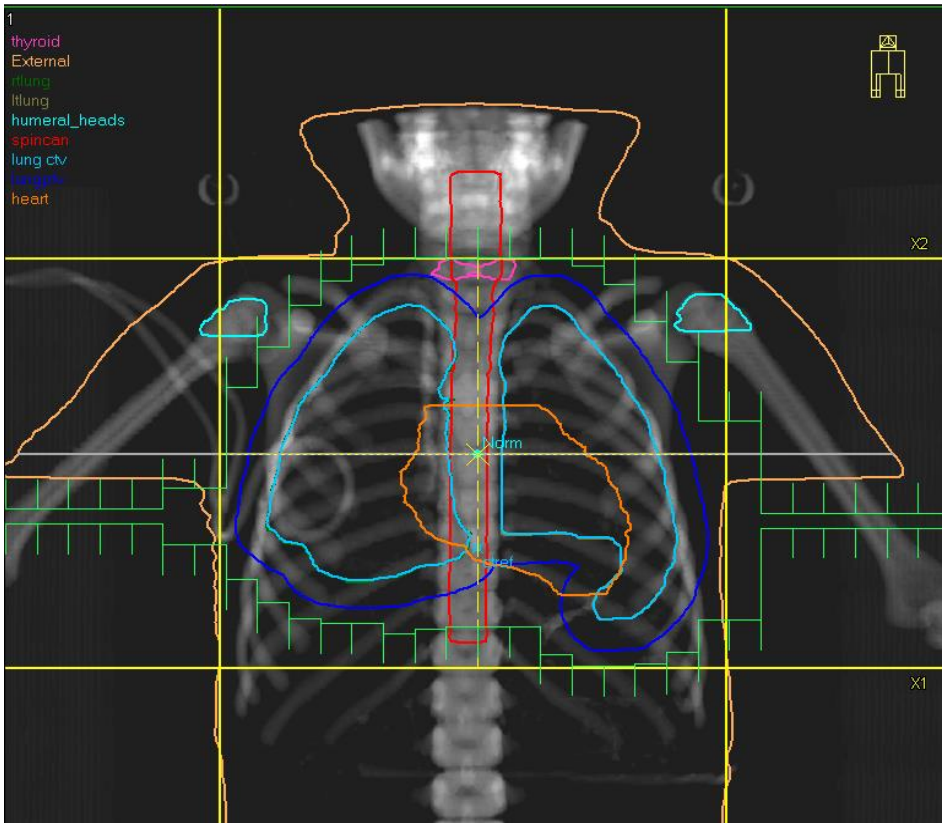
- Review of 234 Stage IV patients, 14% required WLRT - EFS 73%, OS 82%

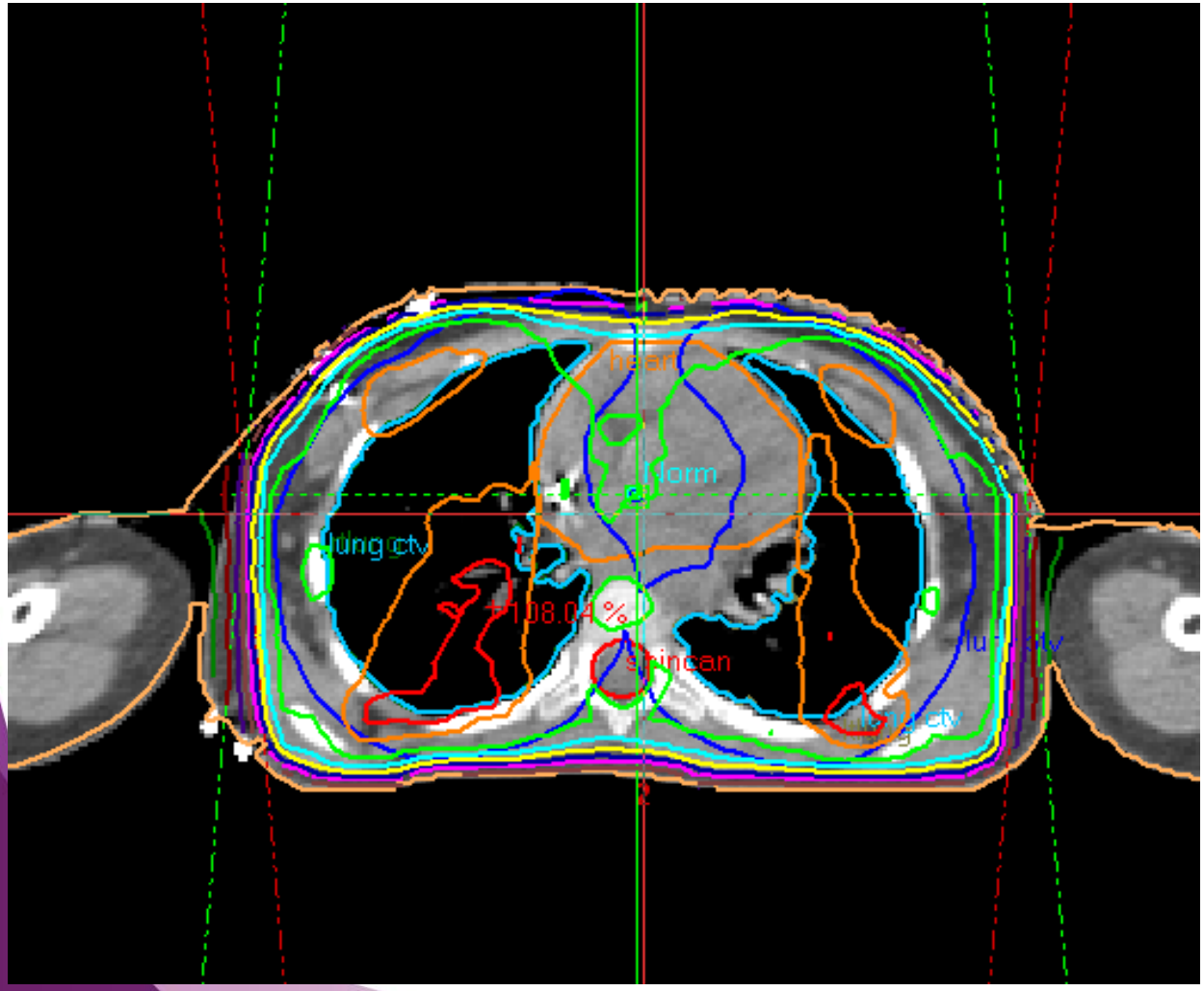
SIOP – RT for Metastases

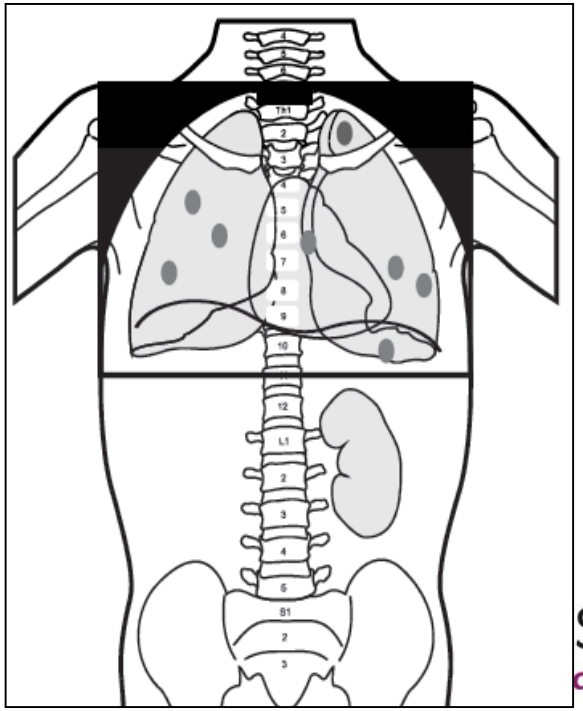
- Liver - residual liver lesions after chemotherapy and surgery

- Other metastatic sites, e.g. bone or brain, regardless of the response to chemotherapy and, if feasible, surgery

Whole Lung RT







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chool

SIOP 2001 RT Doses

- Flank: 1.8 Gy per fraction
- Intermediate risk: 14.4 Gy
- High risk: 25.2 Gy
- Boost to macroscopic residue and/or nodes 10.8 Gy
- WART: 21 Gy in 15 fractions of 1.5 Gy, children aged <1, 10-12 Gy
- WLRT: 15 Gy in 10 fractions with homogeneity correction
- Brain 25.2 Gy, Liver 20 Gy, Bone 30 Gy

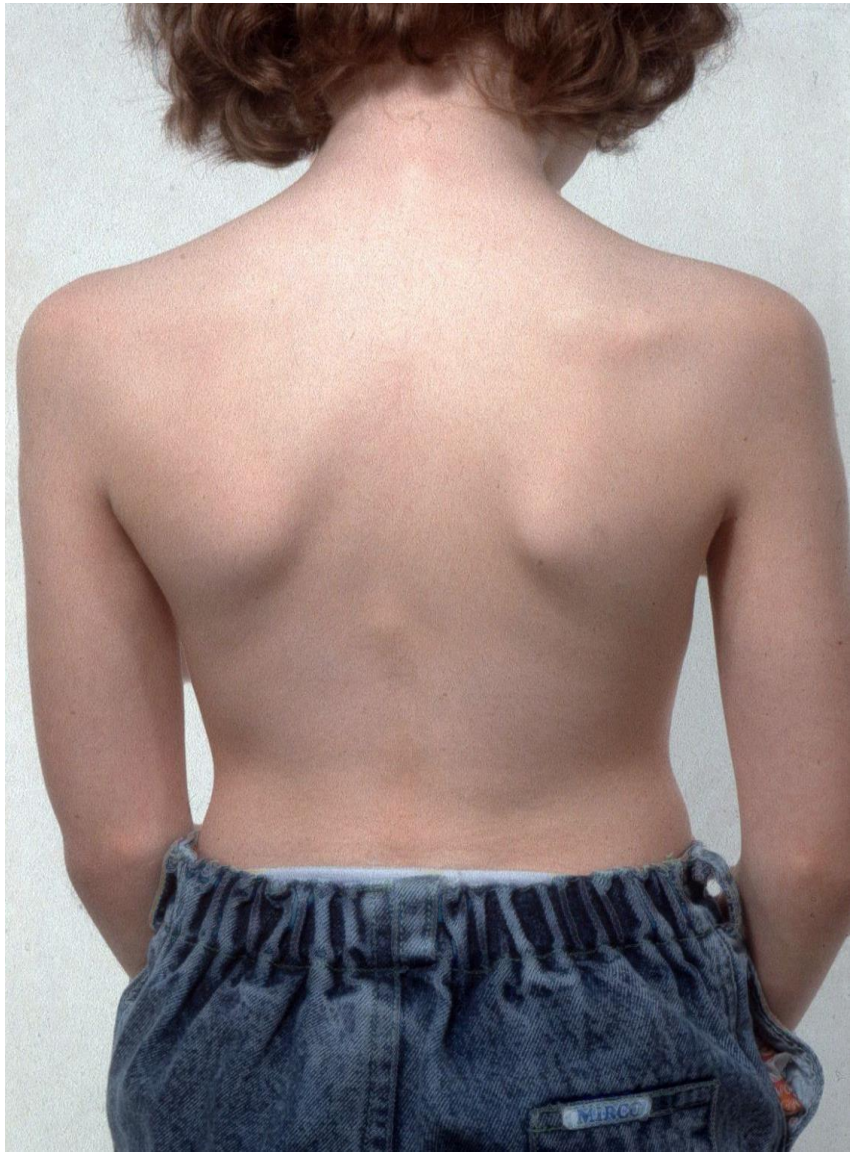
RT for Relapsed Disease

- Feasibility of treatment for relapse depends on initial stage and treatment intensity
- Approximately half of relapsed stage 1 patients can be successfully treated (evidence from difference between relapse-free and overall survival)
- RT plays an important role in treatment of relapse, taking into account OAR tolerances

Stage 5 Disease

- Following chemotherapy and surgery for Stage V disease, RT is usually given according to the local extent of tumour on each side taking into account renal tolerance
- Consider impact of hypertrophy of remaining renal tissue
- Solitary remaining kidney tolerance ~ 12 Gy
- Remaining renal tissue after partial nephrectomy (+ contralateral nephrectomy) tolerance ~ 10 Gy

Wilms' Tumour Abdominal Radiotherapy Long-Term Effects - Thin Waist



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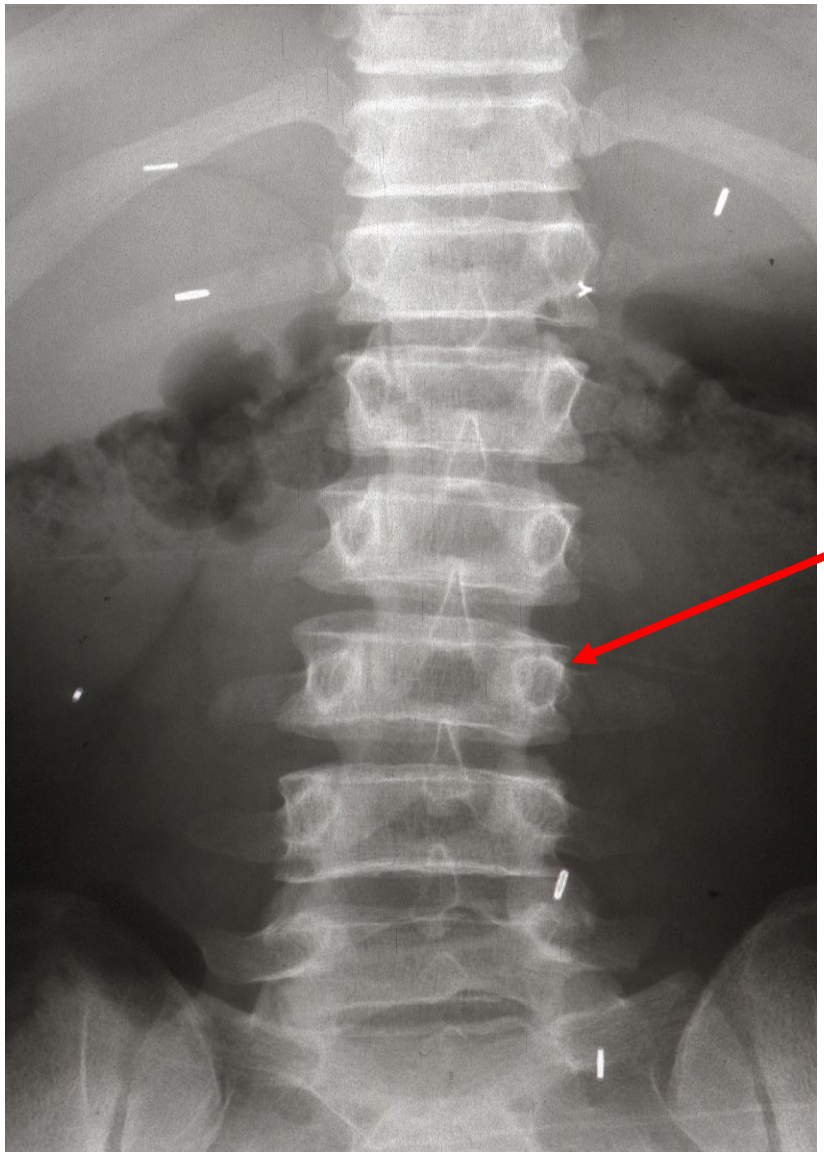
Wilms' Tumour Radiotherapy
Long-Term Effects



Impaired Vertical Growth of Vertebrae

Late Effects

- Second malignancy
- Congestive heart failure
- Adverse pregnancy outcomes
- Improved late effects outcomes:
  - Reduction in proportion of irradiated patients irradiated through risk stratification
  - Reduction of RT dose
  - Better definition of target volumes and avoidance of OARs

Current Developments

IMPORT Study (UK)

- Prospective clinical study (not RCT)
- Aims to improve outcomes for WT and other childhood renal tumours by testing the feasibility of a more 'personalised' approach to risk stratification
- Identification and refine new biomarkers (molecular, proteomic and imaging defined) for the management of the whole spectrum of childhood renal tumours
- Biological characterisation of tumour, blood and urine samples
- Central review of pathology and imaging
- Treatment according to recently closed phase III SIOP Renal Tumours Study Group
- Will inform design of future SIOP clinical trial, which will incorporate a more personalised assessment of relapse risk versus first line therapy burden

SIOP UMBRELLA Future Study

- PROTOCOL + DATA COLLECTION
- Evolved from SIOP 2001
- Reduction of high dose volume with IGRT + IMRT
- Evolution to retroperitoneal volume rather than parallel opposed.
- Delineate bowel and pancreas as well as more “conventional” OARs
- Surgical clips to facilitate delineation of GTV and ITV
- GTV = surgical bed (retroperitoneal)

SIOP UMBRELLA Protocol

Figure 1 | **The UMBRELLA SIOP-RTSG 2016 protocol logo.** The UMBRELLA signifies the ambitious aim to collect information concerning all paediatric primary renal tumours in a comprehensive multidimensional data registry, which includes embedded review of diagnostics, standardized biobanking, and treatment recommendations. CCSK, clear cell sarcoma of the kidney; MRTK, malignant rhabdoid tumour of the kidney; CMN, congenital mesoblastic nephroma; RCC, renal cell carcinoma.

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SIOP UMBRELLA Protocol

CONSENSUS STATEMENT

OPEN

POSITION PAPER

Rationale for the treatment of Wilms tumour in the UMBRELLA SIOP–RTSG 2016 protocol

Marry M. van den Heuvel-Eibrink[1], Janna A. Hol[1], Kathy Pritchard-Jones[2], Harm van Tinteren[3], Rhoikos Furtwängler[4], Arnauld C. Verschuur[5], Gordan M. Vujanic[6], Ivo Leuschner[7], Jesper Brok[2], Christian Rübe[8], Anne M. Smets[9], Geert O. Janssens[1,10], Jan Godzinski[11,12], Gema L. Ramírez-Villar[13], Beatriz de Camargo[14], Heidi Segers[15], Paola Collini[16], Manfred Gessler[17], Christophe Bergeron[18], Filippo Spreafico[16] & Norbert Graf[4] on behalf of the International Society of Paediatric Oncology — Renal Tumour Study Group (SIOP–RTSG)

Nature Review Urology 2017; Online 31st October

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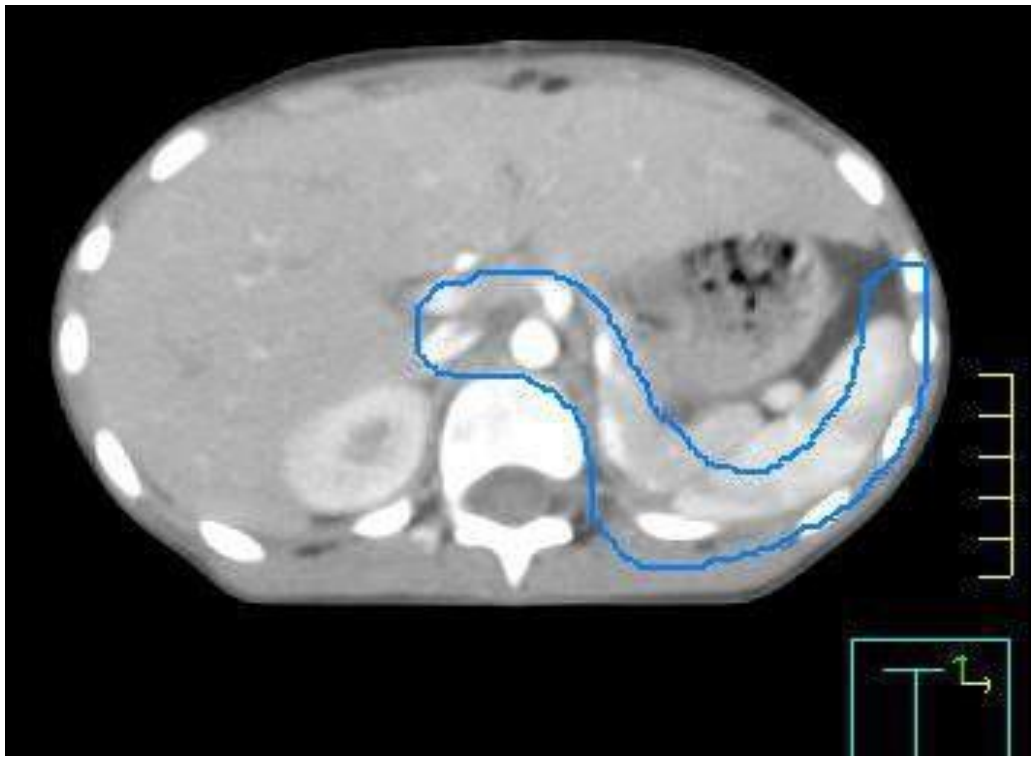
SIOP UMBRELLA – RT
Target Volume Definition

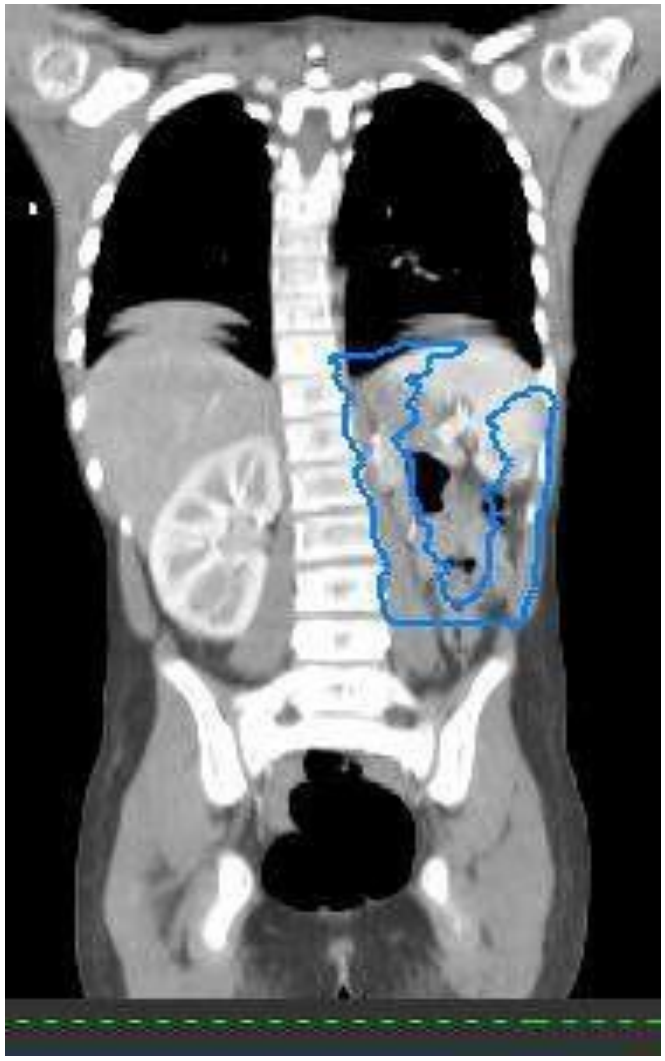
- GTV: based on the combination of pre-operative imaging, (clips?) and the reports by the surgeon and pathologist. Includes the contact zone of the pre-surgery tumour

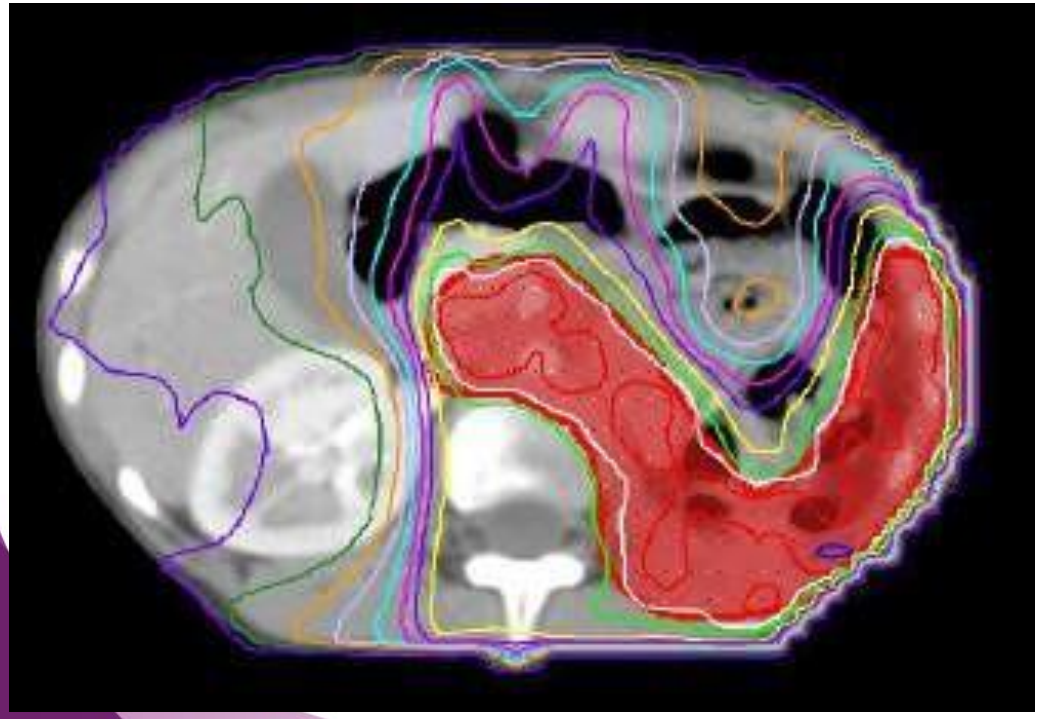
- CTV: Expanded GTV with an anatomically confined margin of 5-10 mm (without expansion into the intestines) including the para-aortic lymph node chain in case of lymph node involvement

UMBRELLA Protocol – RT Target Volume Definition

- ITV: based on the observations of clip motion with 4D-CT-imaging
- PTV: includes ITV with 5-10 mm margin to account for movement and set-up variability
- PTV margin depends on IGRT frequency and immobilization. Daily online position verification is recommended if kV imaging techniques are available. In this case CTV to PTV expansion may be reduced to 5 mm







UMBRELLA
Retroperitoneal CTV

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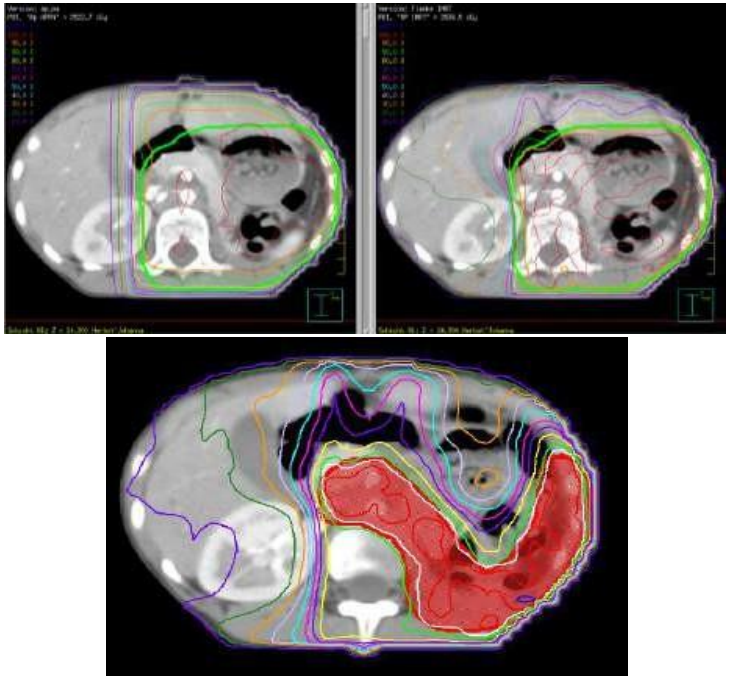
Results - Patterns of abdominal recurrences



„Infield“

Diaphragm (1)

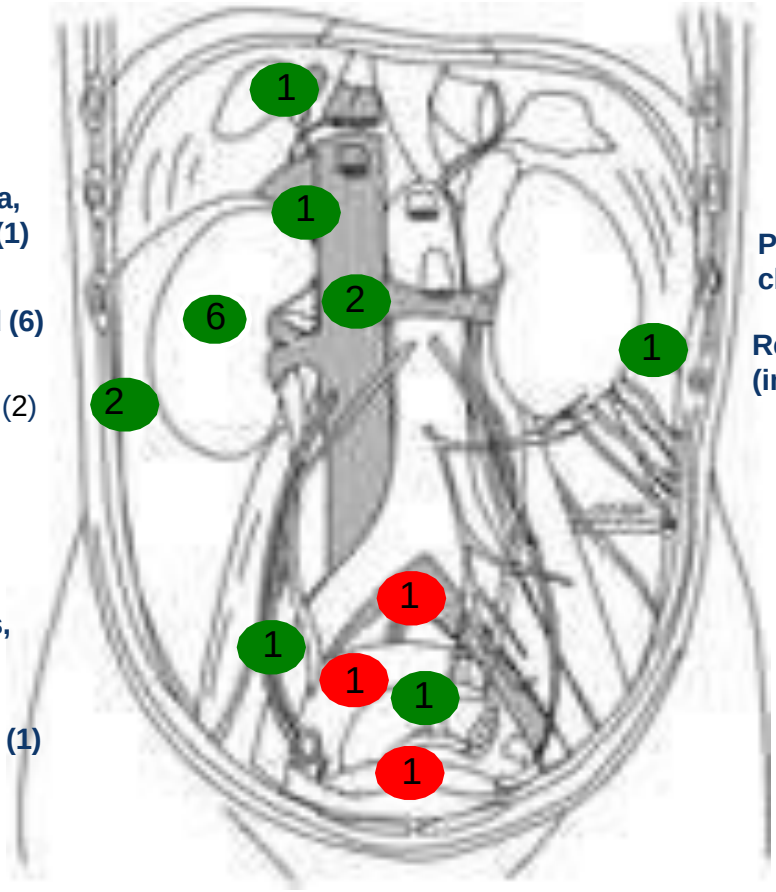
V. portae, V.cava, V. mesenterica (1)

Renal tumour bed (6)

Lateral abdominal wall (2)

Different regions (pelvis: (retrovesical & Mm. Psoas, peritoneal carcinosis) (1)

Pelvis beyond the flank (1)



Paraaortic lymphnode chain (2)

Retrogastric/spleen (infralienal) (1)

Pelvis, Aortic-bifurcation (3)

„Outfield“

	„Infield“ (15)	„Outfield/Beyond Flank“ (3)
IR	*5 (RT+) / 4 (RT-)*	*-*
HR	*4 (RT+) / 2 (RT-)*	*3 (RT+)*

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Courtesy – Dan Saunders

UMBRELLA Study – RT Doses

- Flank 1.8 Gy x 8 fractions – 14.4 Gy (as before)
- 10.8 Gy boost to residual disease (as before)
- No nodal boost for N+ (departure from SIOP 2001)
- Whole abdominal RT for major preoperative or intraoperative tumour rupture, or macroscopic peritoneal deposits
- WLRT – 12 Gy in 8 fractions (corrected)
- Gradient < 3Gy across vertebral bodies

Thank you for your attention

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WWW.ESTRO.ORG/SCHOOL

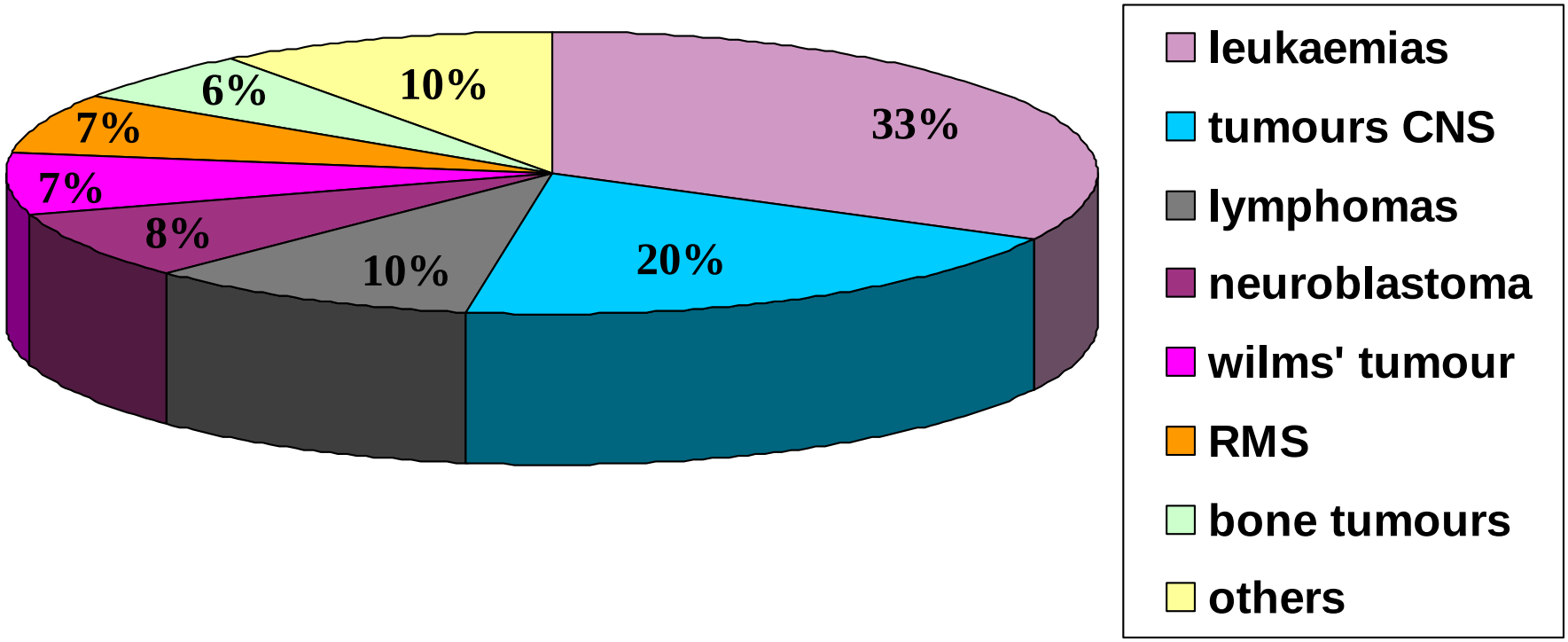
RadiationTherapy in Neuroblastoma

Christian Carrie
Centre Leon Berard - Lyon
France

ESTRO School

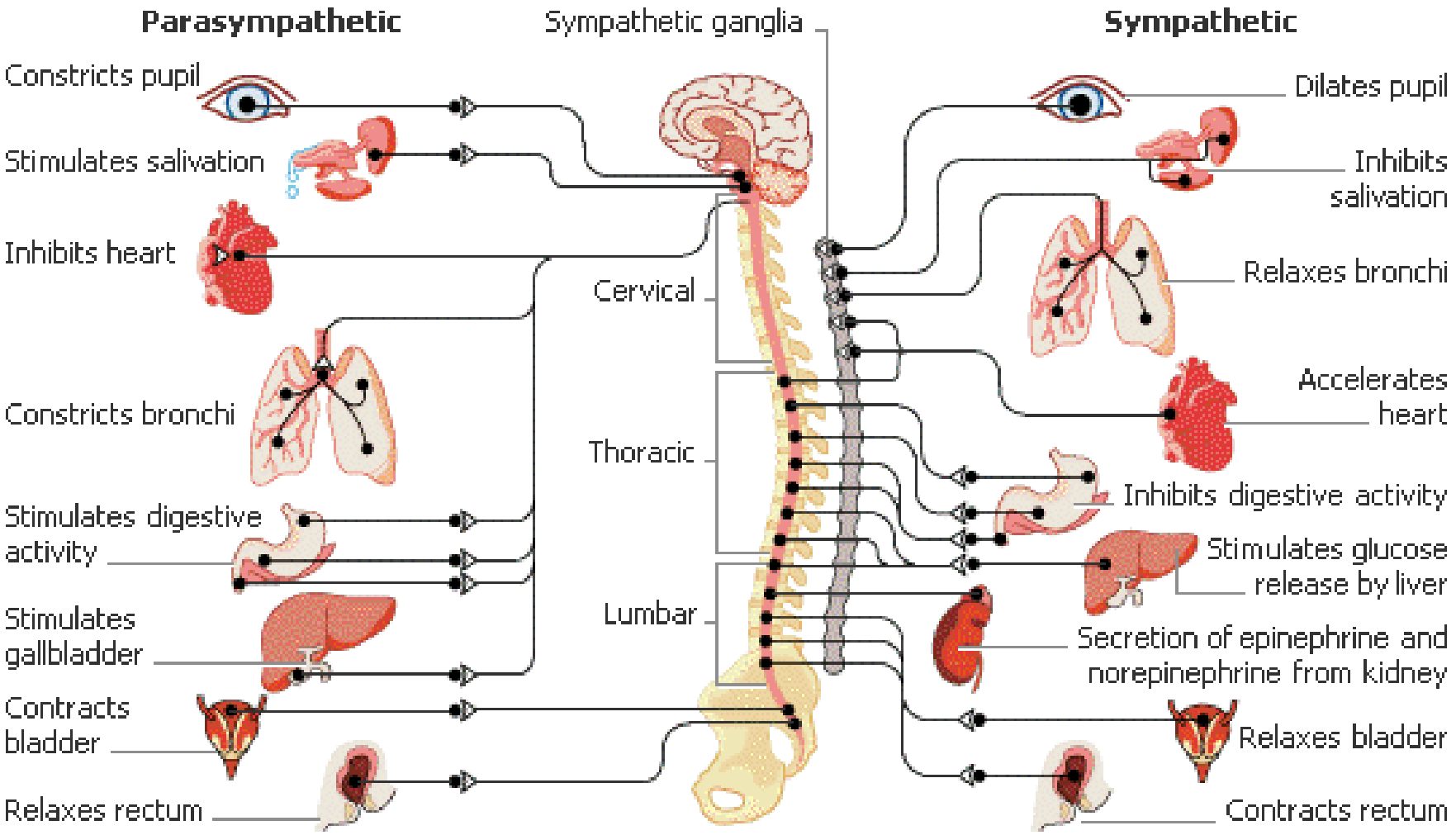
No relevant financial relationship(s) exist

5-10% of childhood tumours



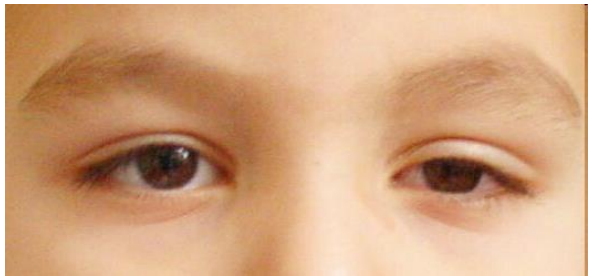
but 15% of death

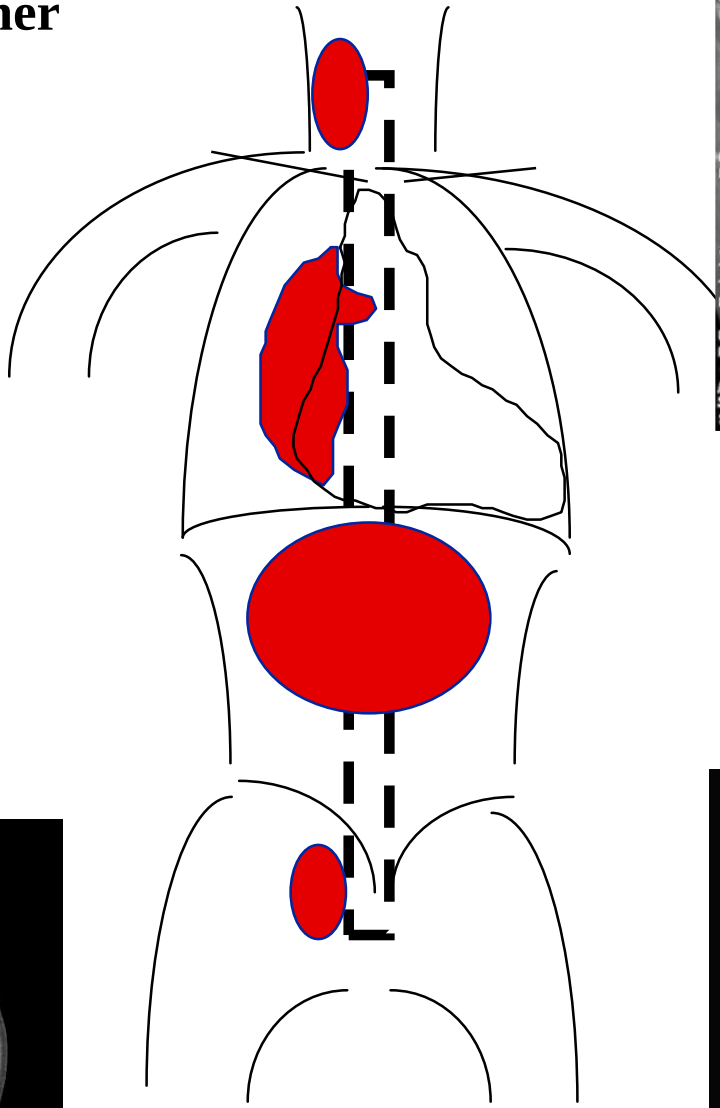
*"**Neuroblastoma** is a **malignant (cancerous) tumor** that develops from **sympathetic nerve tissue**."*

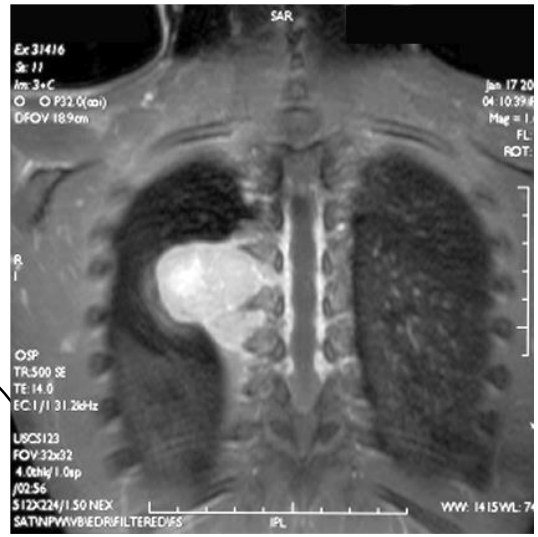


5 % cervical

!!! Claude Bernard Horner

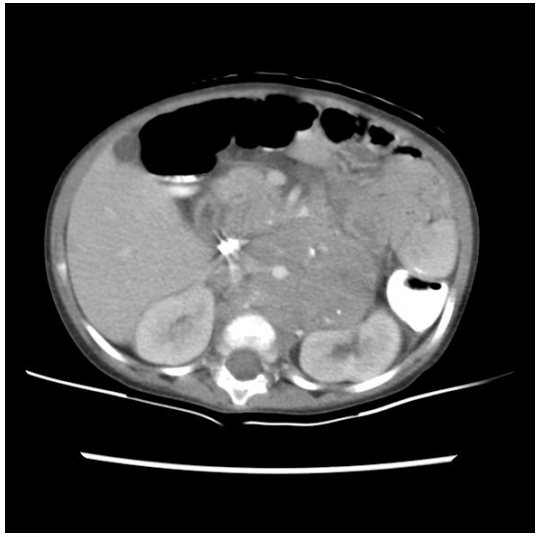






60 % abdominal (rétroperitonéal)

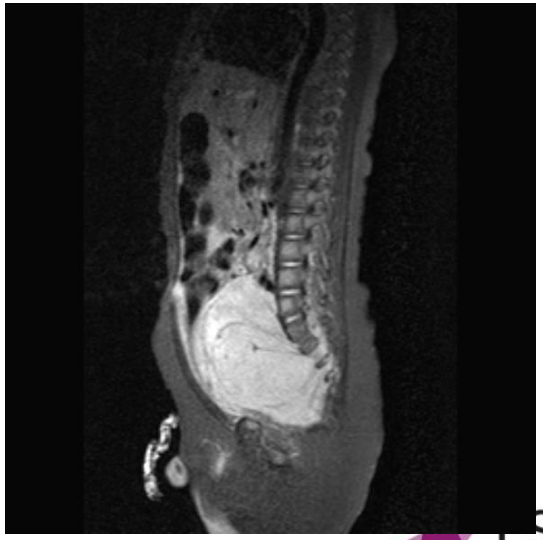
Blood pressure



5 % pelvic

Sphincter dysfunction

30 % thoracic Spinal cord compression



Clinical features

- Most common non-CNS pediatric solid tumor: 10% of all pediatric neoplasms (30% of infantile tumors)
- Most common sites of origin:

  Adrenals (48%) : often painless abdominal mass)• Extra-adrenal retroperitoneum (25%)

  Chest (16%)
- Paraneoplastic syndromes

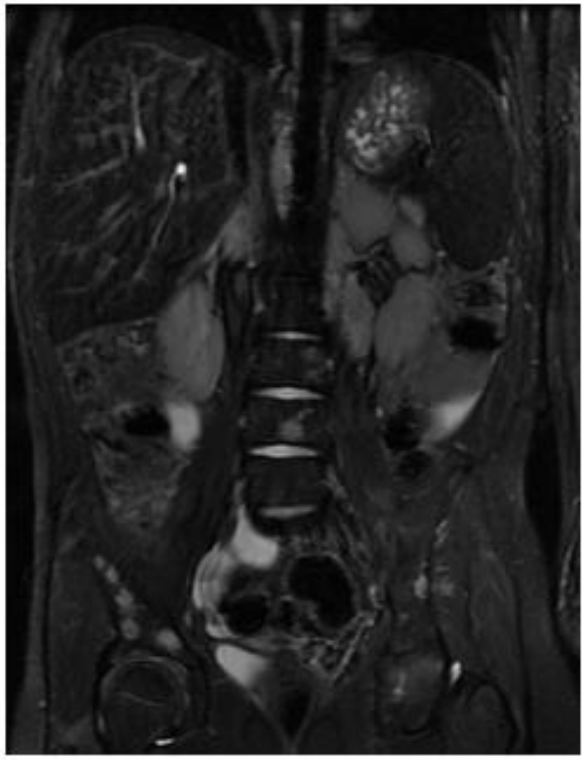
  Opsoclonus/myoclonus (~25%)
- Hypertension 10% due to high VMA/cathecholamines
- Imaging:

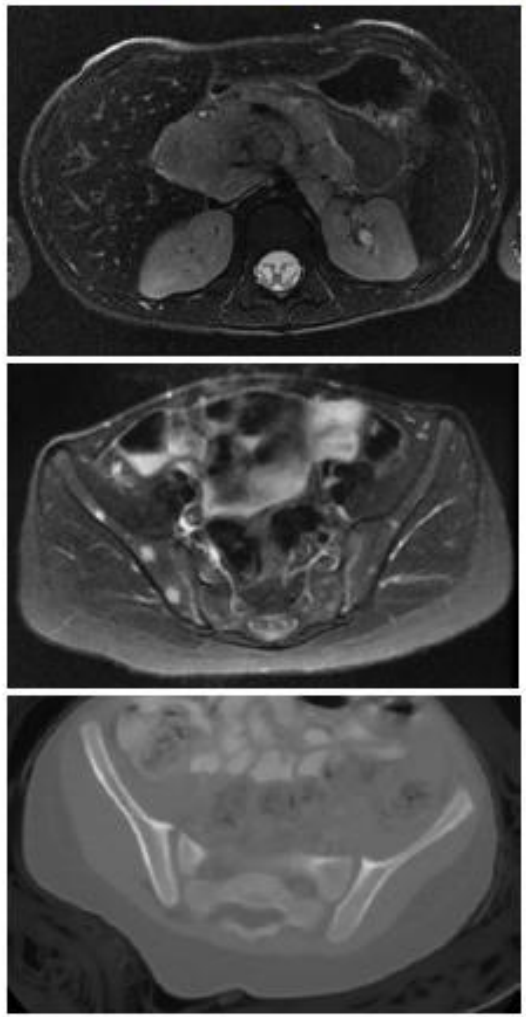
  Extrarenal, fine calcifications (85%)

  No definite capsule, encases vessels, intraspinal extension

  Mets: Bone/marrow, lymph nodes, liver, skin

Neuroblastoma Staging: MRI, CT & MIBG





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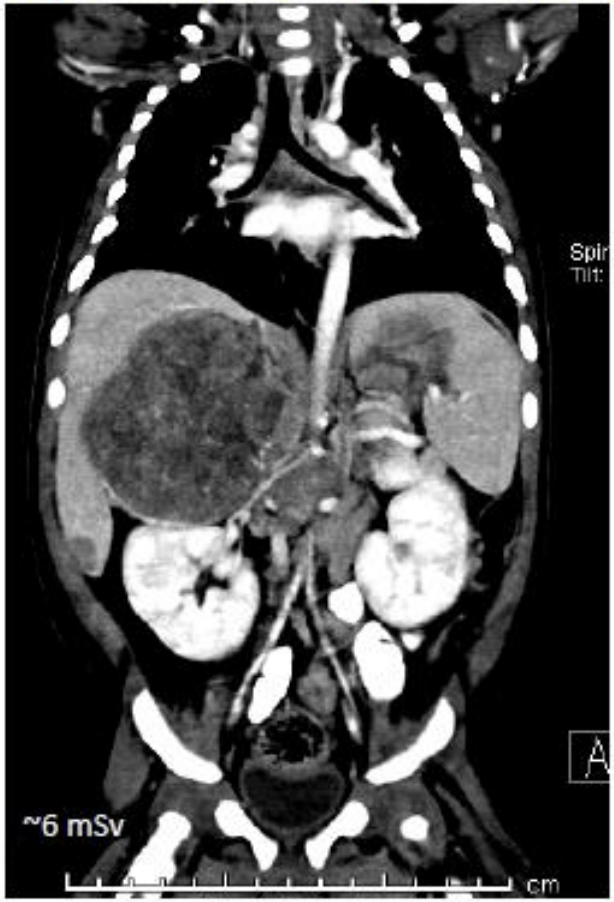
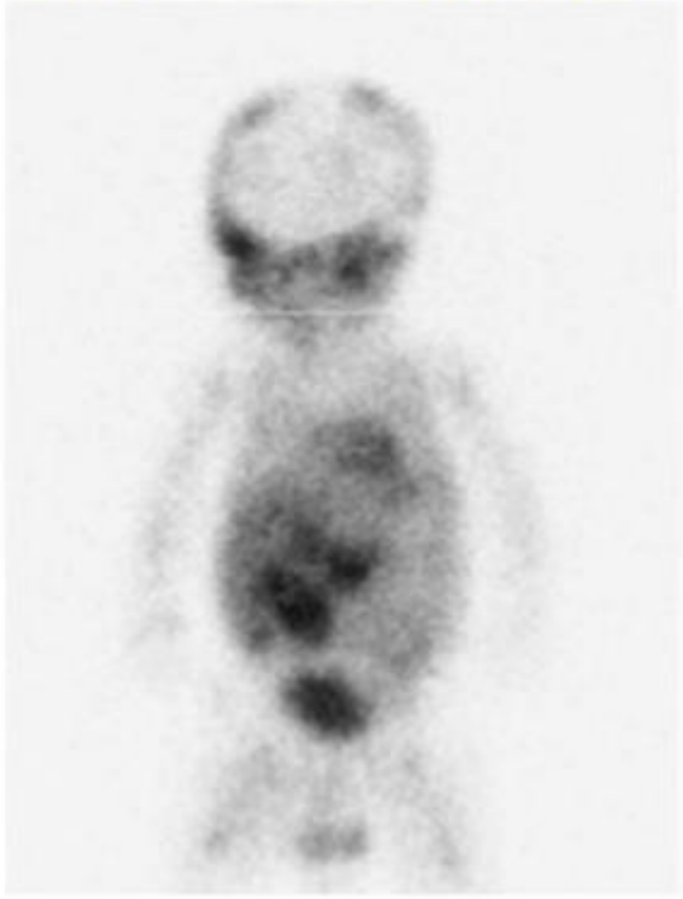
MRI vs sub-sec CT: decreased exposure and reduction in sedation





- ^{99m}Tc-MDP Bone Scan can be omitted from staging algorithm
  - 132 pts
  - No impact on clinical staging
  - Majority of stage 4 pts MIBG^{+}/BS^{+}
  - Only 3 pts MIBG^{-}/BS^{+}
  - Supports new INRG criteria, omitting bone scan

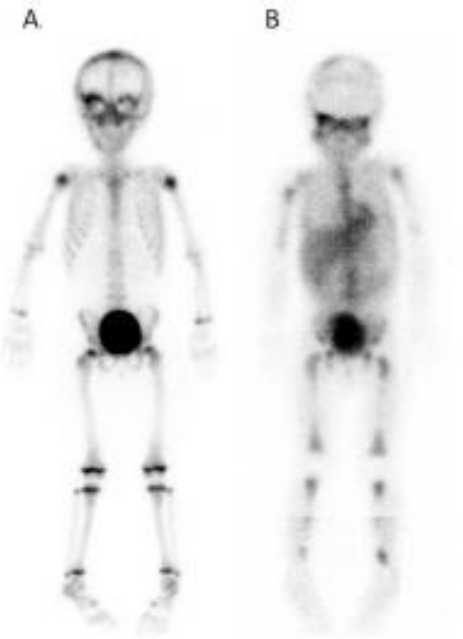


TABLE 2 Comparison of skeletal MIBG vs bone scan uptake in stage 4 patients

Stage 4 patients	Bone scan (+)/MIBG(+)	Bone Scan (−)/MIBG(+)	Bone scan (+)/MIBG(−)	Bone scan (−)/MIBG(−)
N = 78	58	5	3	12
Relative quantification of sites of skeletal uptake				
Bone scan < MIBG	25			
Bone scan = MIBG	31			
Bone scan > MIBG	2			
Bone marrow positive	51	3	2	4

Gauguet et al. PBC, 2017

^{18}F-FDG PET/CT vs MIBG in NBL

- FDG:
  - Superior at depicting Stage 1/2 disease, when FDG+
  - May need MIBG to exclude higher stage
  - Comparable to MIBG in stage 3 patients
    - 33% MIBG only; 27% FDG only; 13% both; 27% neither
  - **Useful in MIBG-negative tumors**
  - False (+) uptake at sites of BM recovery
  - More accurate where MIBG and CIM are discrepant (Melzer et al, EJNMMI, 2011)
- MIBG
  - Superior in evaluating stage 4 disease
  - Superior to FDG-PET for lesion detection at relapse
  - Currently inferior to FDG for quantitative imaging (SUV)

Sharp S. et al. J. Nucl Med, 2009
Taggart et al. JCO, 2001

Stadification

- Neuroblastoma Staging - INSS
- **International Neuroblastoma Staging System (INSS)**
- 1 Localized tumor with complete gross resection
  No regional lymph node involvement
- 2 Localized tumor with incomplete gross resection without
  Ipsilateral lymph node involvement (2A) or with Ipsilateral lymph node involvement (2B)
- 3 Tumor crossing midline and/or contralateral lymph node involvement
- 4 Tumor with distant metastases
- 4s Patient <12 months with localized tumor and metastases confined to liver, skin and/or marrow

Ref : Brodeur GM, et al. JCO **1988 & 1993**

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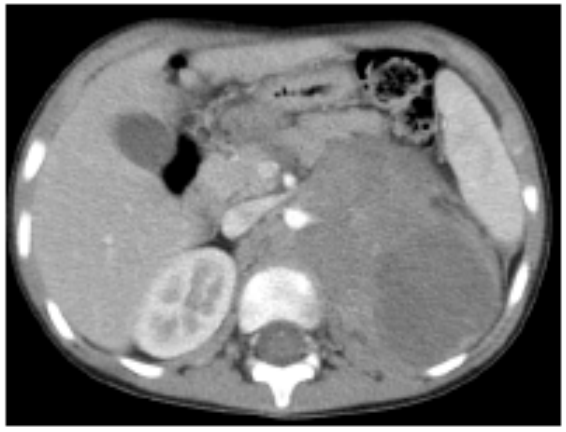
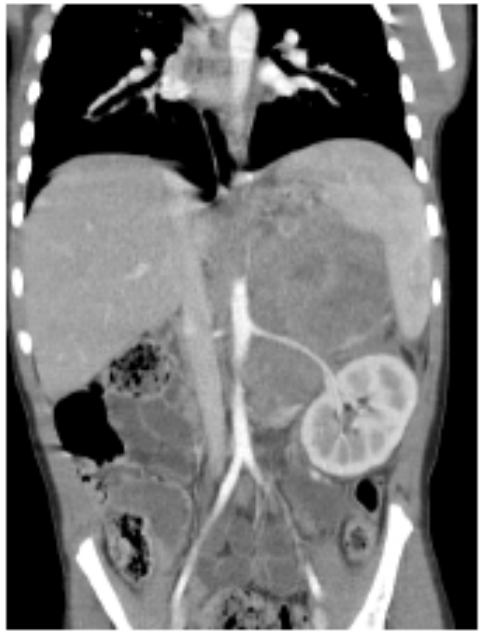
Image Defined Risk Factors – IDRF's

- Surgical risk factors
- Identified by imaging, at Dx, before treatment
- Based on imaging criteria
- International consensus
- Goal:
  - Uniform reporting
  - Prognostic factors

- L1: IDFR = 0
- L2: IDRF ≥ 1
- M: Metastatic disease
- MS: 4S criteria, now age 18 mo





Monclair T, et al. JCO **2009**,
Brisse H, et al. Radiology **2011**

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(life threatening symptoms)

The presence of any of these symptoms is an indication for chemotherapy.

Intraspinal neuroblastoma See appendix 12

- With no symptoms but > 50% tumour presence within spinal canal.
- With signs and/or symptoms related to spinal cord compression.

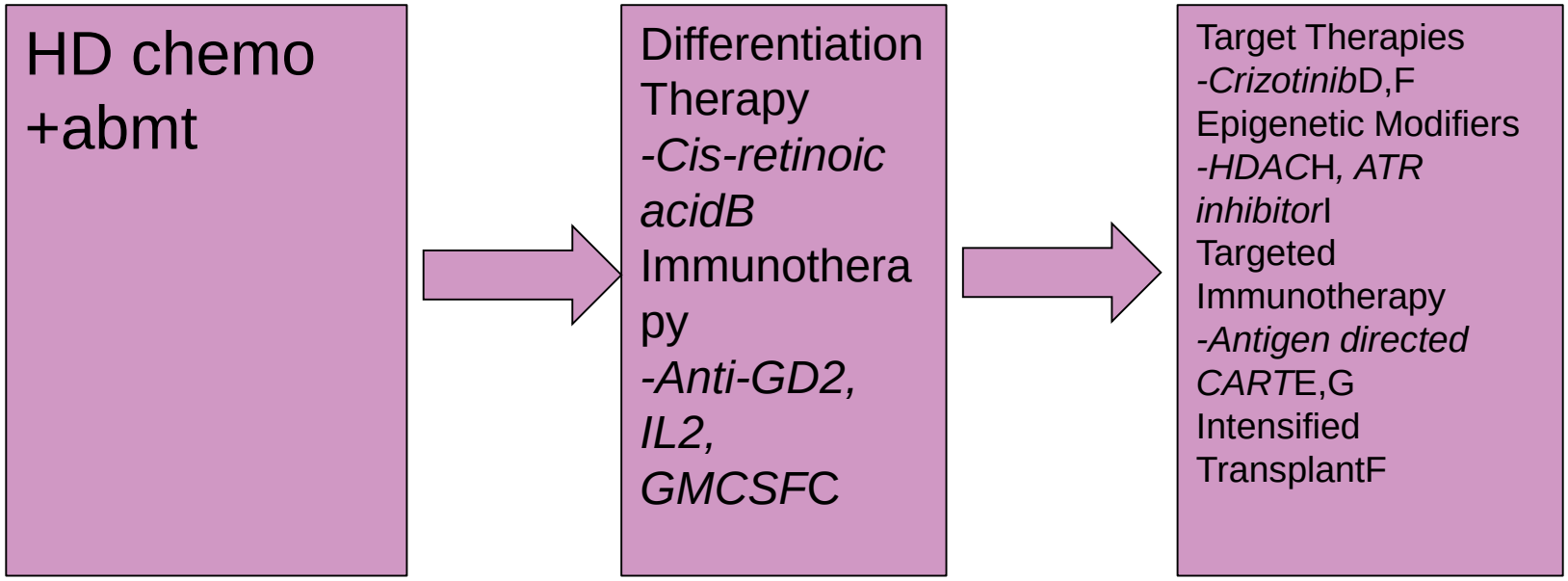
Systemic upset

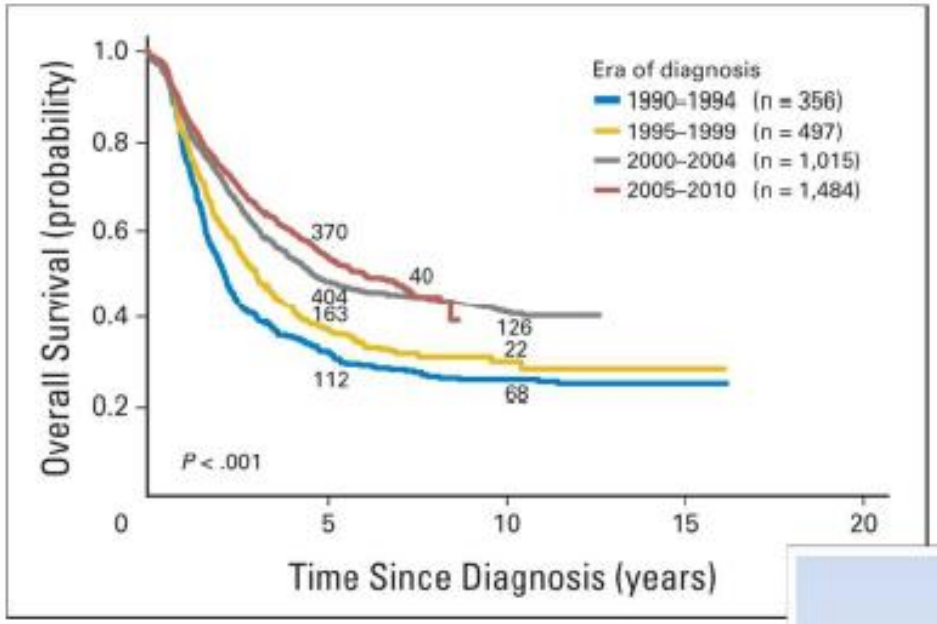
- **Pain requiring opiate treatment**
- **Gastrointestinal**
  - Vomiting needing nasogastric/IV support
  - Weight loss >10% body weight

  NB diarrhoea with VIP does not respond to chemotherapy and is a definite indication for surgery
- **Respiratory**
  - Respiratory distress without evidence of infection
    - Tachypnoea >60
    - Oxygen need
    - Ventilatory support
- **Cardiovascular System**
  - Hypertension
  - IVC compression +/- leg oedema
- **Renal**
  - Impaired renal function, creatinine increased x 2 ULN[1]
  - Poor urine output, less than 2mls/kg/day
  - Hydroureter/hydronephrosis
- **Hepatic**
  - Abnormal liver function >2 ULN
  - Evidence of DIC
  - Platelets <50 x 10^9/l
- **Bladder/Bowel dysfunction** secondary to a mass effect.

Disease stage	Age	*MYCN* status/ Ploidy	Life threatening symptoms	Segmental chromosome alterations *	Study Group (LINES)	Study eligibility
Neonatal adrenal masses	<90 days	-				O-NAM
L1 - INSS 1	Any	non Amp Amp and Pseudo-triploid				LNESG 2
L2	≤18 months	non Amp	No	no	1	Low Risk
				yes	3	
			Yes	no	2	
				yes	3	
Ms	≤12 months	non Amp	No	no	4	Low Risk
				yes	6	
			Yes	no	5	
				yes	6	
L2 Differentiating histology	> 18 months	non Amp			7	Intermediate risk
L2 Poorly/undifferentiated histology	> 18 months	non Amp			8	Intermediate risk
L1 - INSS 1	Any	Amp and Diploid/Tetraploid			9	Intermediate Risk
M	≤12 months	non Amp			10	Intermediate Risk
M	> 12 months	non Amp				High Risk
Ms	> 12 months	non Amp				High Risk
L1 INSS stage 2 L2, M, Ms	Any	Amp				High Risk

Contemporaneous Evolution of Systemic Therapy in High Risk Neuroblastoma





Sequential Improvement in Survival in Stage 4 pts

- HDT and Stem Cell Rescue (2000)
- ImmunoRx and Cytokines (2005-2010)
- Post consolidation immunoRx
- Radiotherapy (^{131}I-MIBG)

Pinto NR, et al. JCO **2015**

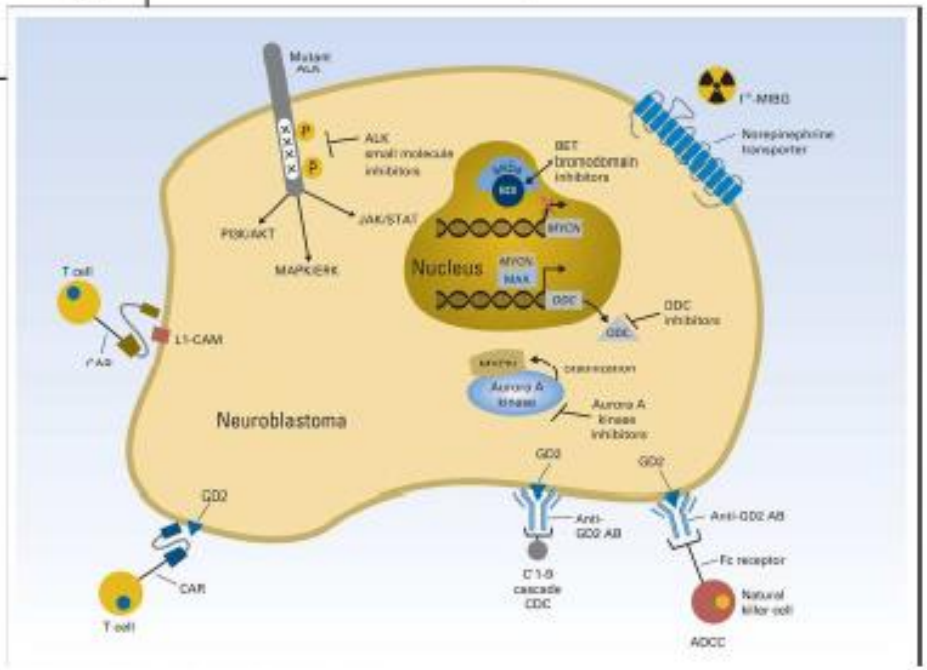
New Horizons:

Targeted Therapies

- Alk inhibitors, e.g Crizotinib

Receptor Targeting:

- ^{177}Lu DOTATATE: SSTR2
- ^{131}I-MIBG: NER tranport



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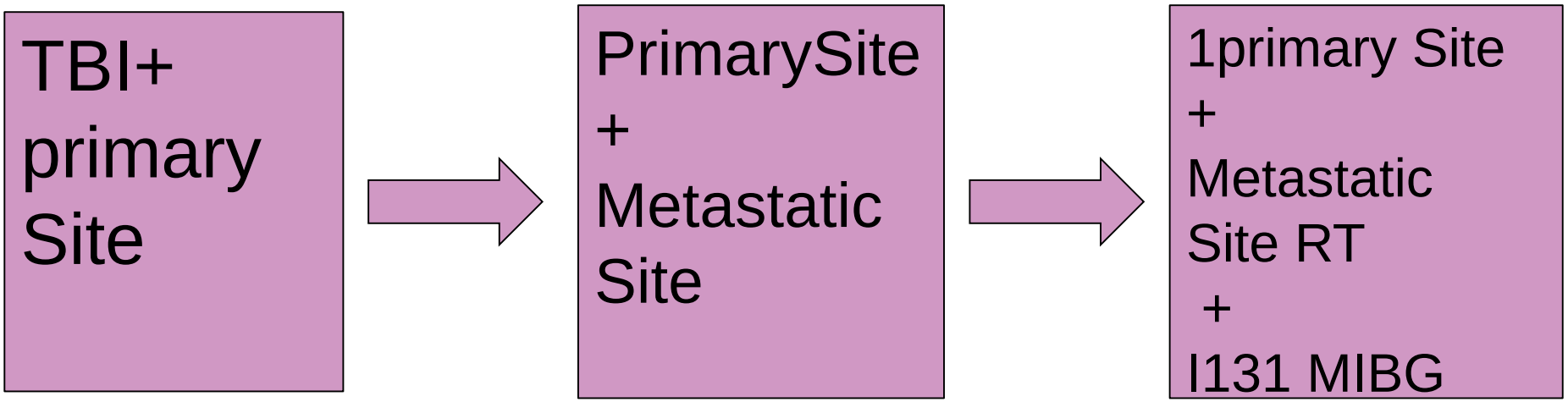
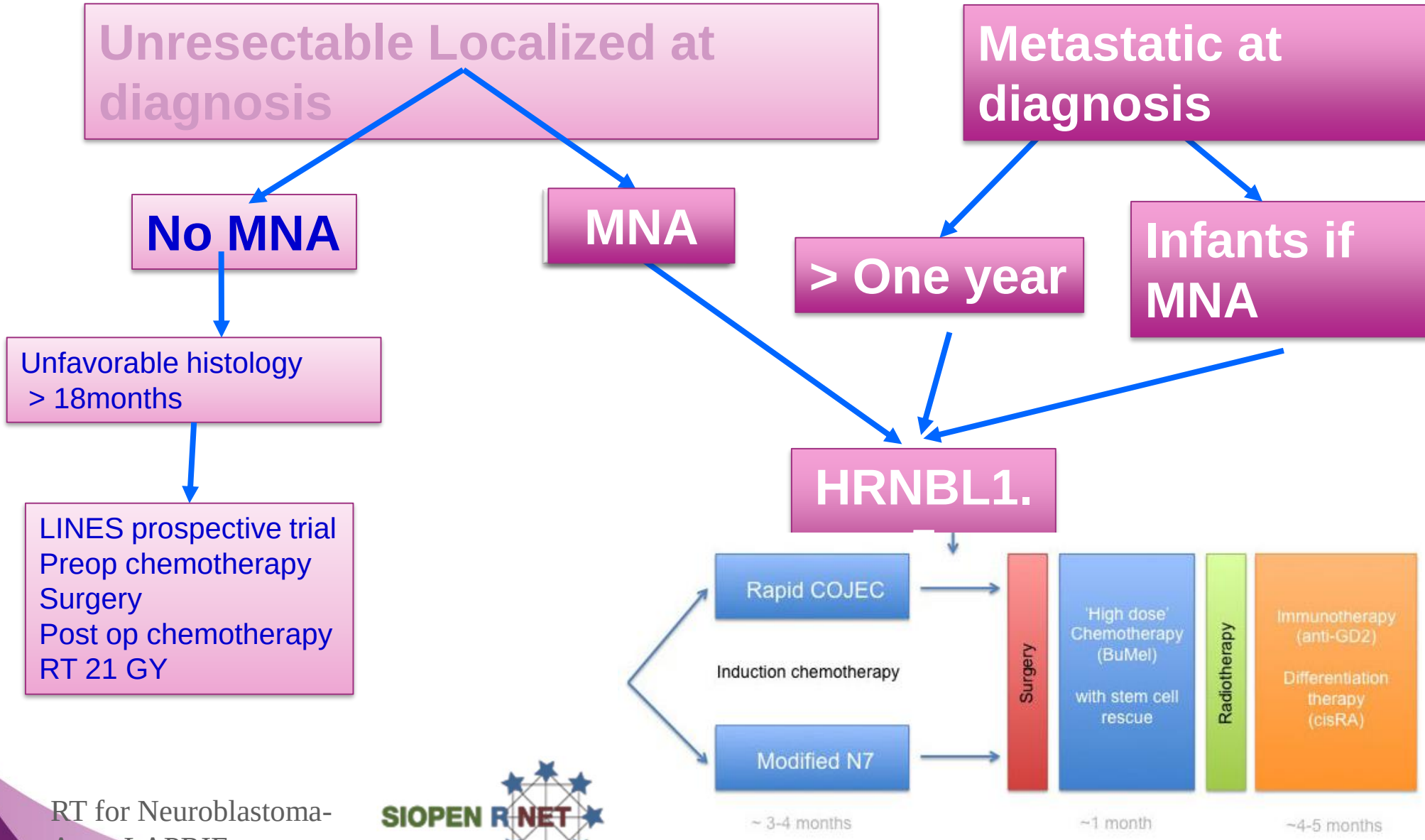
Role of RT : evolution of concept



High risk neuroblastoma : Local RT Indications



SIOPEN R-NET

MNA = MYCN amplification

Radiotherapy on primary site

- **Volume defined by the post chemo / pre surgery volume**
- **Diagnostic CT**
  - Easily available
  - Short examination time (small children)

- **Diagnostic MRI is superior to CT if**
  - pelvic tumors
  - metastatic marrow disease,
  - chest wall invasion and
  - spinal canal involvement
  - long examination in small kids
- **Preoperative surgical planning : CT contrast-enhanced images**
  - the solid portions of the mass are easier to define than on MRI
  - the extent of calcification, which increases after treatment is more easily characterised.
  - Better to delineate the vasculature
  - particularly important when the mass is known to be encasing major vessels

Radiotherapy and local control

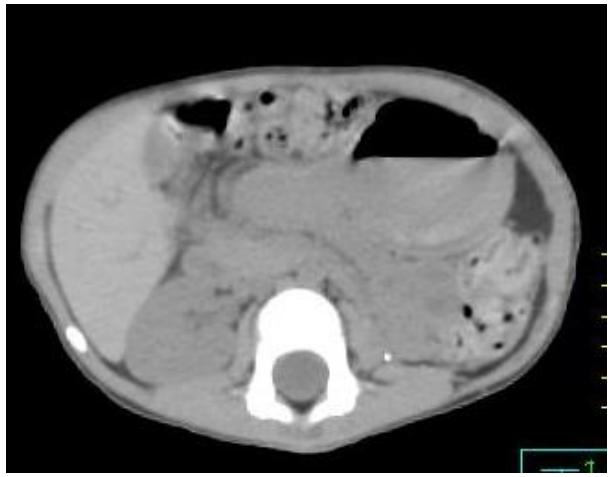
	No rt	rt
Rosen 84	81	32
Castelberry 94	54	21
West 93	33	8
Mattay 93	31	26

RT for high risk localized RT

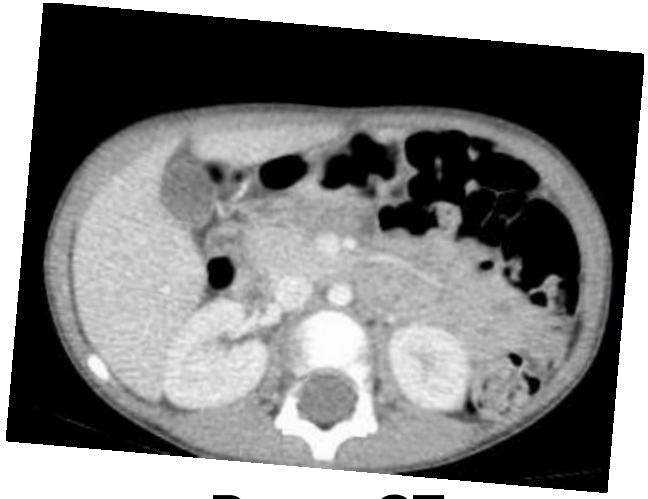
Studies	n	Dose	Fractionation	Volume	Relapse rate Local/metastasis/both/total
Wolden et al. IJROBP 2000 Kushner et al. JCO 2001	99	21Gy	1.5Gy BID	Extent of tumor at diagnosis + 3 cm + lymph nodes	10/45/55
Laprie et al. Cancer 2004	32	24 Gy or 34 Gy	1.5Gy/day	Preoperative volume + 2cm	0/0/1/1
Haas-kogan et al. IJROBP 2003	31	10 Gy TBI + 10 Gy or 20 Gy	2 Gy/Day	Preoperative volume + 2cm	22% failure rate
Bradfield et al. Cancer 2004	17	21 Gy +/- 9Gy	1.5 Gy/day	Preoperative volume + 2cm	1/6/0/7
Ducassou et al, Strahlen Onkol 2015	35	24 Gy or 34 Gy	1.5 Gy/day	Preoperative volume + 2cm	69% local control at 15 years
Casey et al, ASTRO 2016	246	21Gy	1.5 Gy/day		3%local failure at 5 years

Target volume = preoperative volume

registration with preoperative CT or MRI



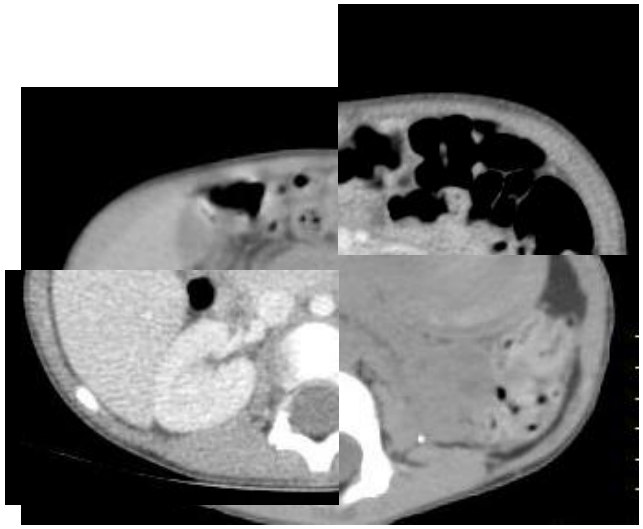
Planning CT

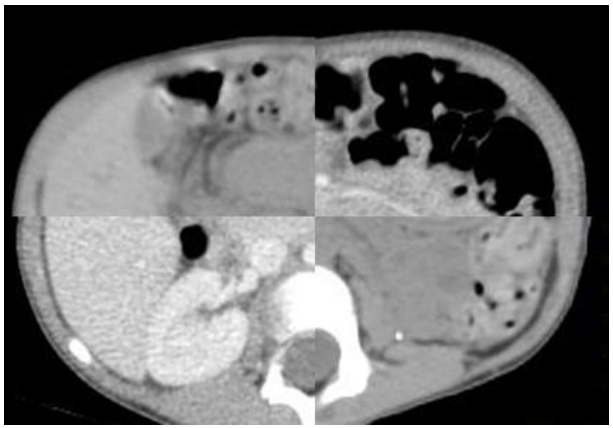


Preop CT

Target volume = preoperative volume

coregistration with preoperative CT or MRI





CoRegistered CT

Use coregistration with great caution

CT or MRI are not performed in treatment position

Organs have moved

Priority to

Radiologist report/discussion

Surgeon's report/discussion+ Clips

Anatomopathology report

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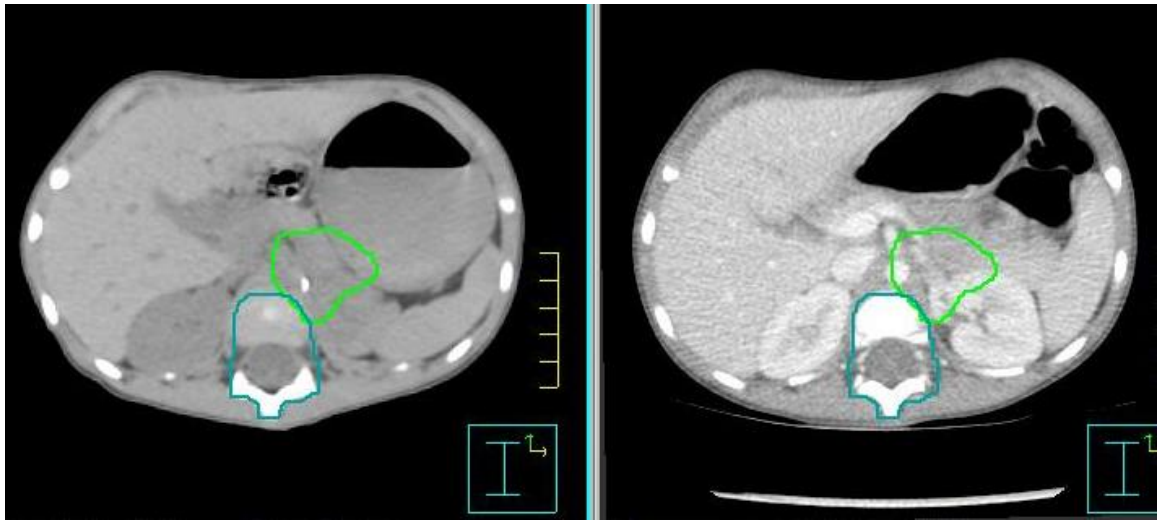
Target Volumes and organs at risk

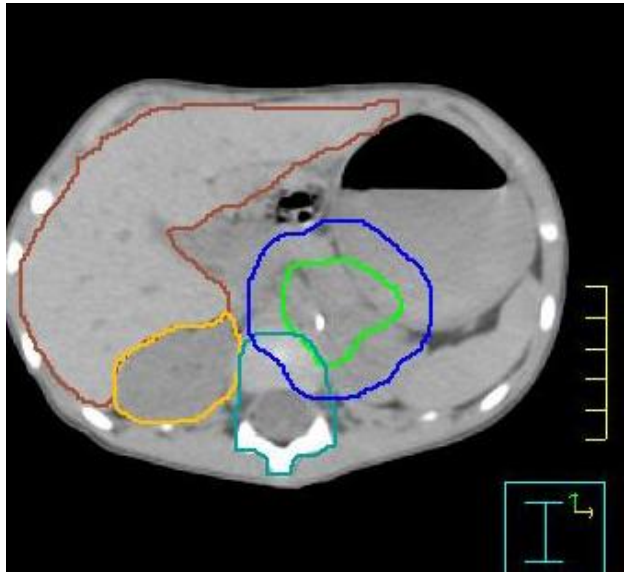


Margins

CTV = GTV + 0,5
(+1 in LINES with avoidances)
PTV = CTV + 0,5-1cm
depending on age,location,contention

Organs at risk

- Vertebras
- Abdominal organs
  - Liver, kidney(s), Spleen, Pancreas, small bowel
- Thoracic organs
  - lung, heart
- Pelvic organs
  - bladder, rectum, bones, ovaries, testicles



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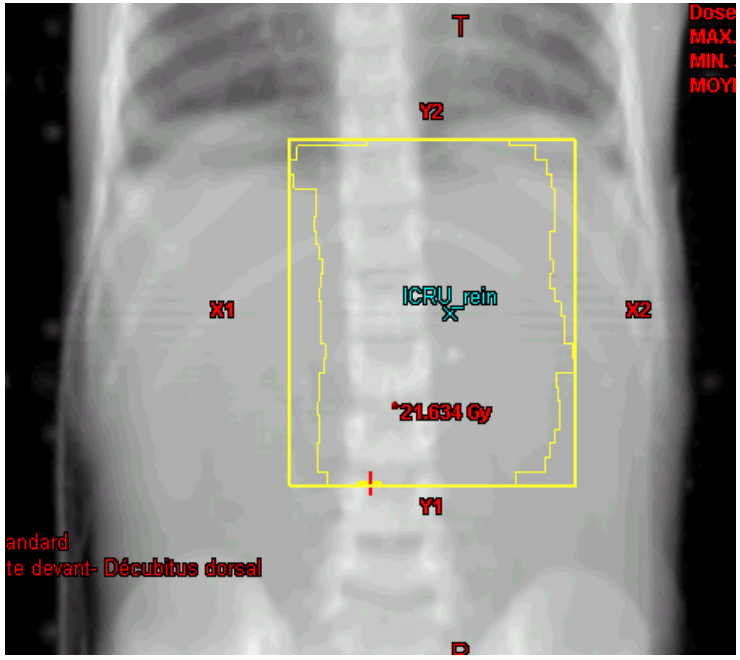
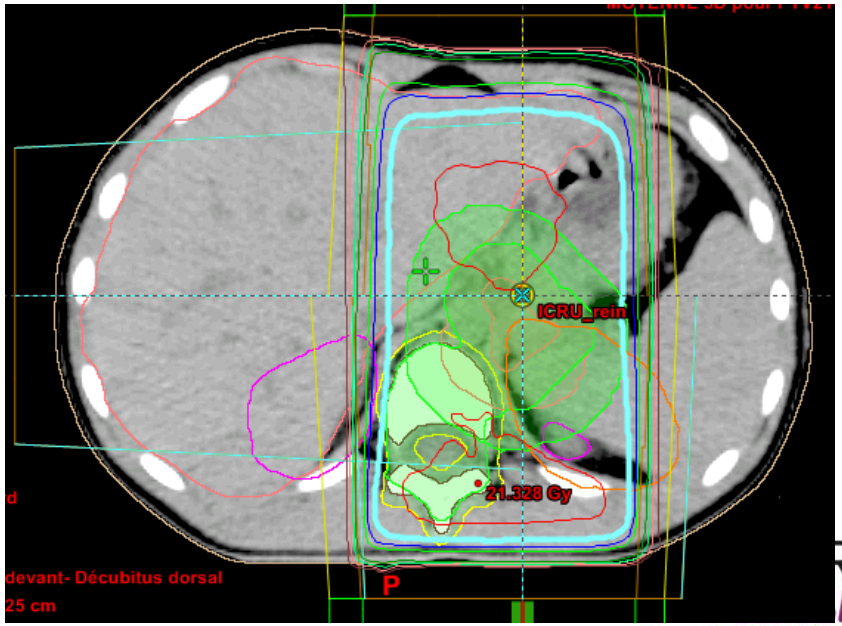
Radiotherapy in SIOPEN HR NBL 1.5

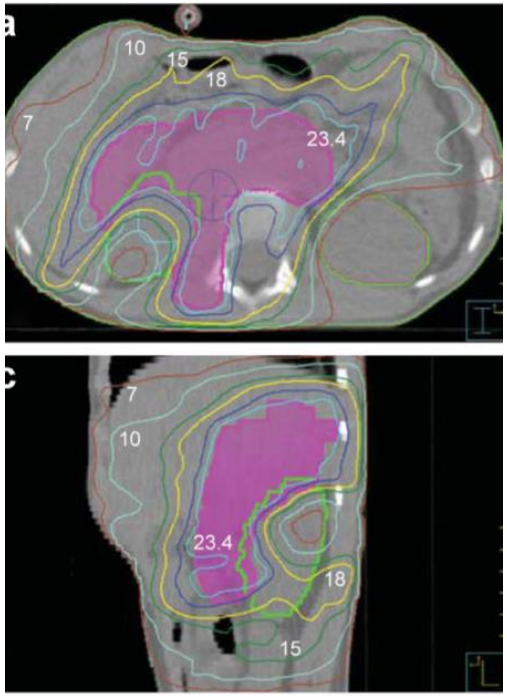
- Dose
  - 21 GY / 1,5 GY
  - 14 fractions
  - 21 days maximum
- PRV vertebras = Vertebras + 3mm
- kidney
  - Median constraint dose 15 Gy
  - OK 21 Gy if remaining kidney is not irradiated
  - PRV around remaining kidney
- AP-PA or slightly obliques
- Repositioning with Kv/KV is fine





IMRT/VMAT for neuroblastoma ?

- Advantages
  - Better conformality
  - best method of RT delivery in midline tumors with respect to kidney doses,
- But
  - at a cost of a higher mean dose to the liver, stomach, spleen
  - Always compare with standard RT
  - Don’t forget the rules on vertebras and bones :
    - contour vertebras in field and outside of field
    - prescribe constraints in field and out of field
    - be very careful.
  - Theoretically increase of risk of second cancers



Panandiker et al, 2012

IMRT was not found to be better than the conventional AP/PA field for lateralized tumors.

Paulino et al. Pediatric Blood Cancer 2006
Plowman et al. Pediatric Blood Cancer 2007

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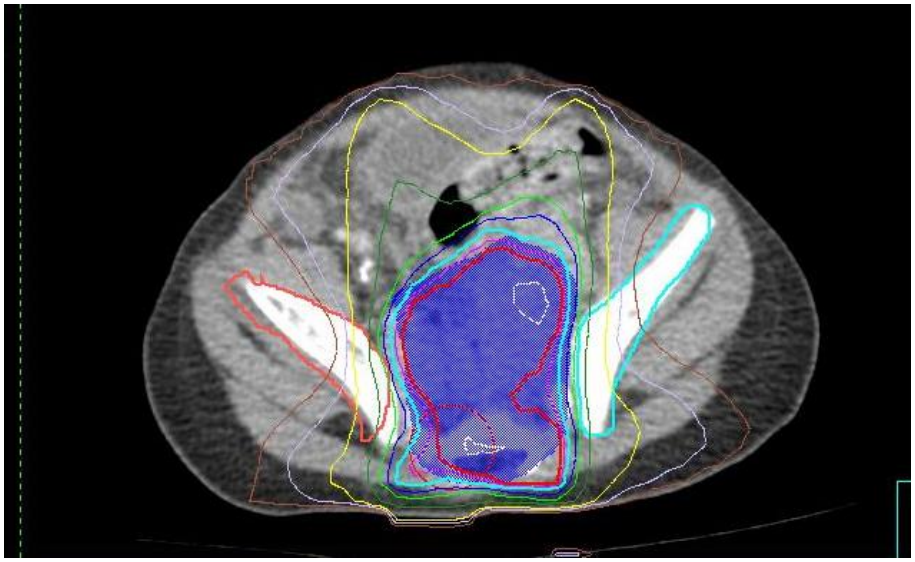
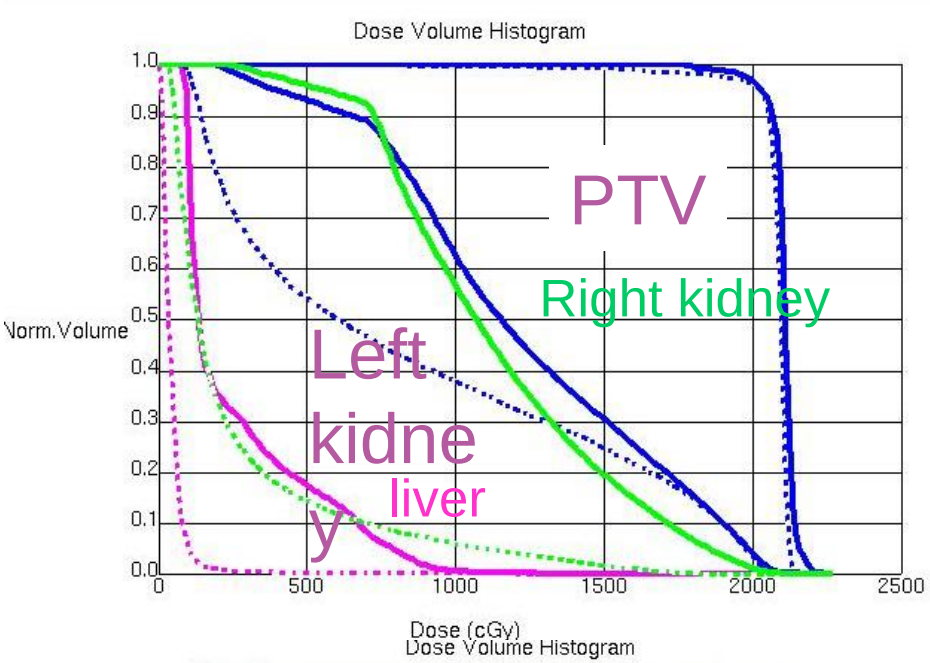
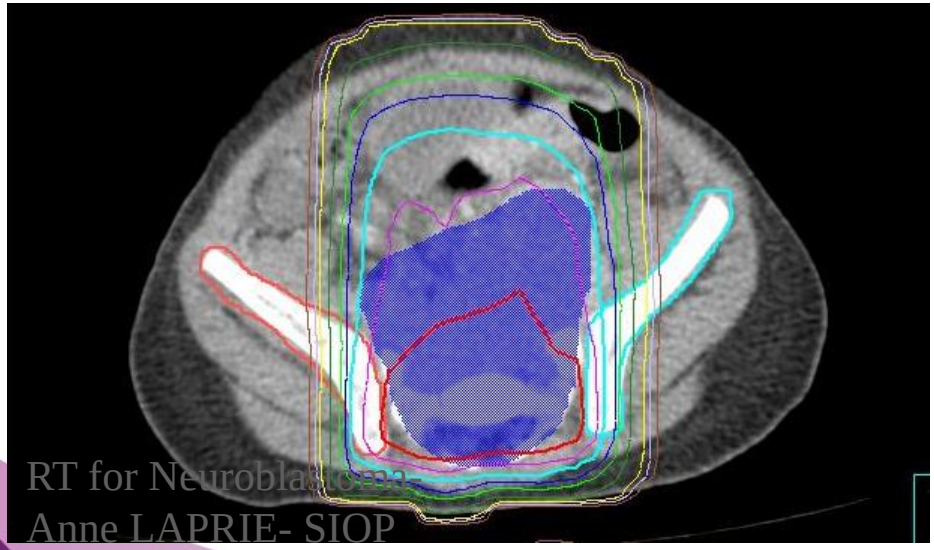
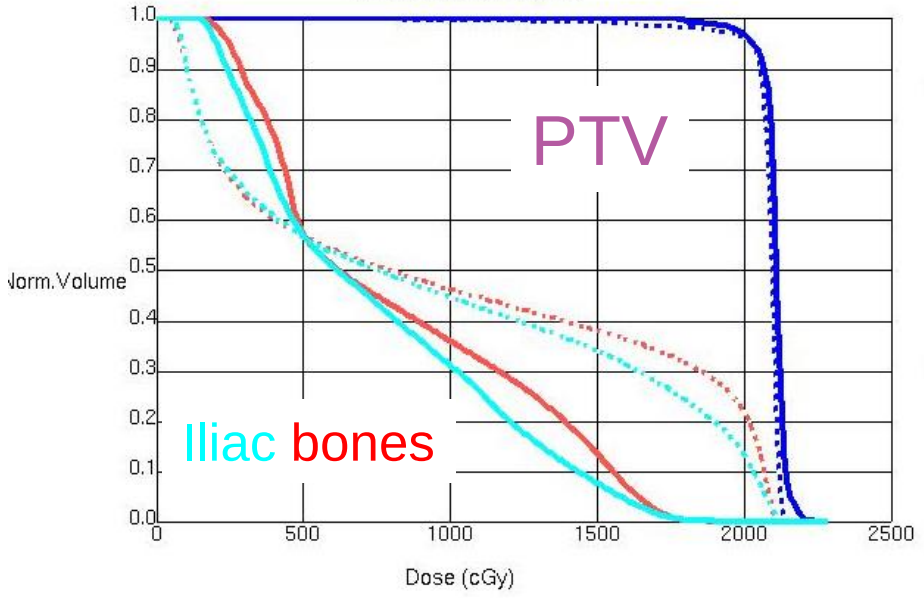
Comparison 3D ---versus IMRT —







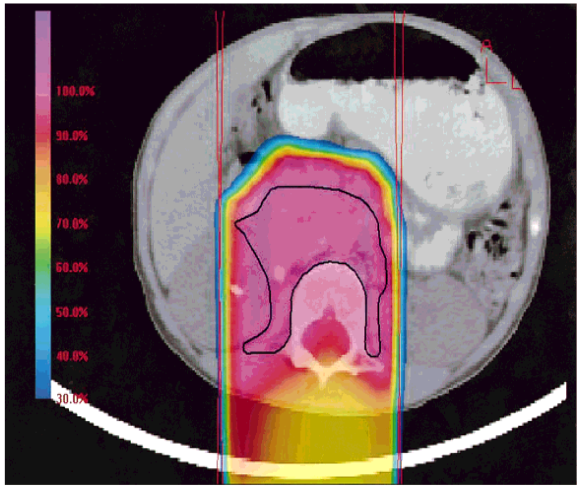


Future : protontherapy for neuroblastoma ?

Outstanding balistic precision

Target volumes located anterior and posterior to the kidney can be encompassed without significant likelihood of renal toxicity.

Close Proximity of vertebras need for homogeneous dose



HUG et al 2001

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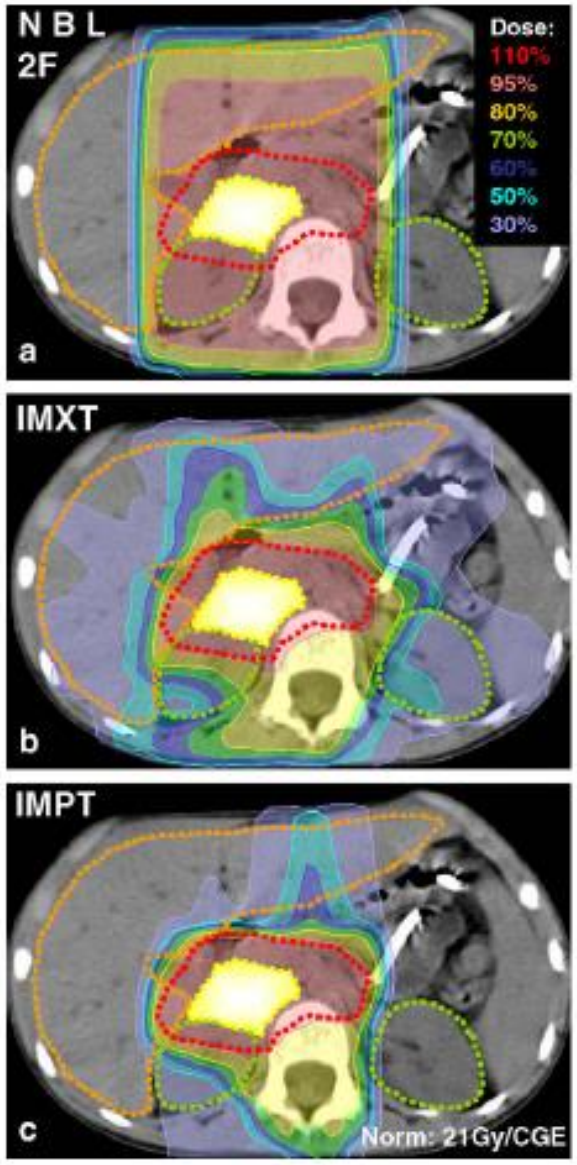
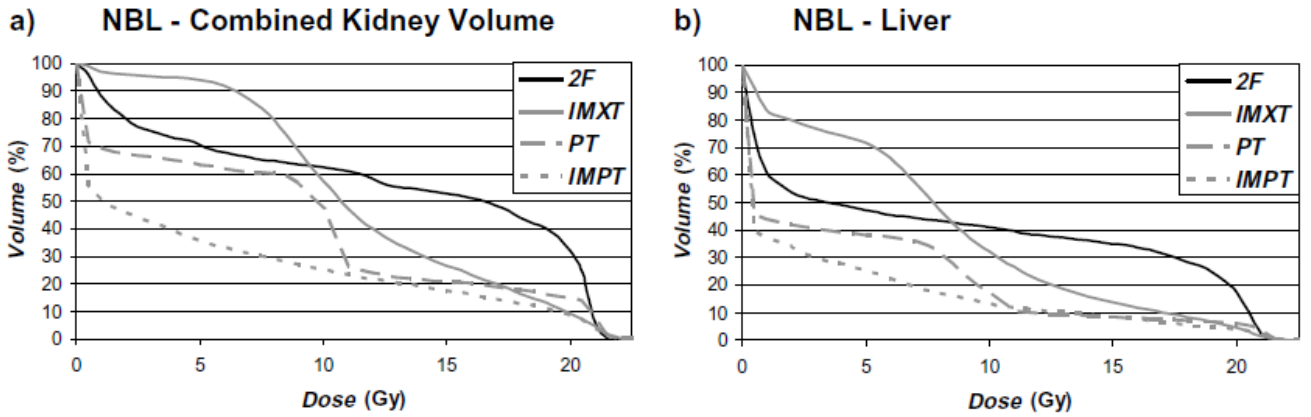
Comparison APPA-IMRT-PT-IMPT



	Goal	2F	IMXT	PT	IMPT
Conformity		0.30 ± 0.04	0.70 ± 0.09 ($p < 0.01$)	0.62 ± 0.06 ($p < 0.01$)	0.79 ± 0.08 ($p < 0.01$)
Homogeneity	>0.86	0.96 ± 0.02	0.89 ± 0.09 ($p = 0.03$)	0.89 ± 0.06	0.92 ± 0.06
$D_{1\%}$ (Gy/CGE)	<23.1 Gy	21.2 ± 0.4	22.2 ± 0.3 ($p = 0.02$)	21.7 ± 0.1	21.6 ± 0.3
$D_{99\%}$ (Gy/CGE)	>18.9 Gy	20.4 ± 0.2	19.7 ± 0.6	19.3 ± 1.3	19.8 ± 1.3
D_{mean} (Gy/CGE)	21 Gy	20.9 ± 0.4	21.1 ± 0.1	21.1 ± 0.1	21.1 ± 0.3
$D_{80\%}$ spinal bones (Gy/CGE)	$D_{80\%}$ > 16.8 Gy	20.3 ± 0.4	17.5 ± 0.4 ($p < 0.01$)	17.5 ± 0.5 ($p < 0.01$)	17.3 ± 0.2 ($p < 0.01$)



M. Hillbrand et al. / Radiotherapy and Oncology 89 (2008) 141–149

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Long term effects

- Main potential late effects ?
  - Musculoskeletal
  - Metabolic syndrome
  - Renal failure
  - Fertility
  - Second cancers

Limits of doses to OAR for neuroblastoma

Organ	Dose	complications
Ovaries	2-5 Gy	Ovarian failure
Uterine	2-5 Gy	Uterine dysfunction
Bone and muscles	10-20 Gy	Bone and muscular hypoplasia
Bladder	30 gy/ 45 Gy	Hemorragic cystitis/fibrosis
Vagina, uterthra	40 Gy	stenosis
bowel	50 – 55 Gy	Bowel obstruction
Rectum	60 Gy	proctitis
Bone	60 Gy	Osteonecrosis, fracture

Paulino, SIOP 2016

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Vertebras

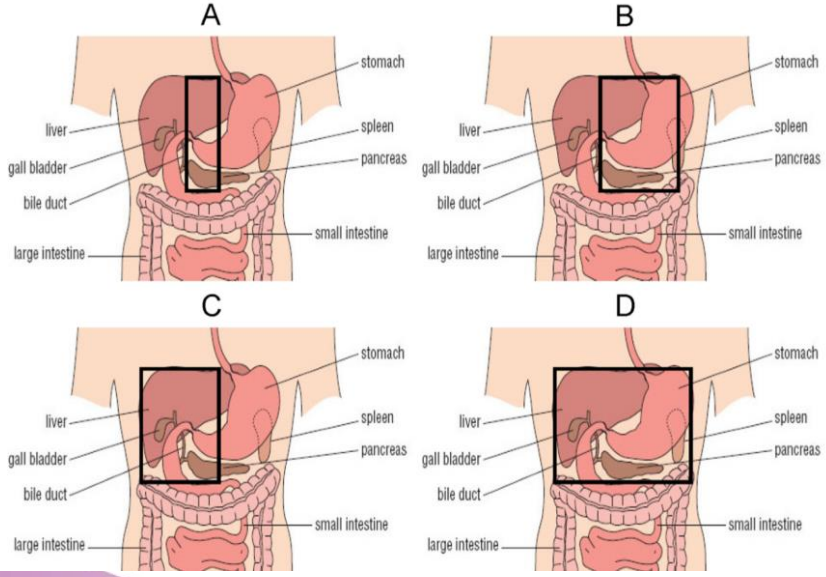
- models to predict height
  - Krasin et al IJROBP 2005
- The height of children with neuroblastoma is significantly affected by RT.
  - Depending on the number of irradiated vertebrae (>6)
  - The use of TBI
  - changes in both signal and shape on MRI.
    - Hua et al, IJROBP 2007
    - Hartley et al, IJROBP 2008
    - Yu et al, radiotherapy and oncology

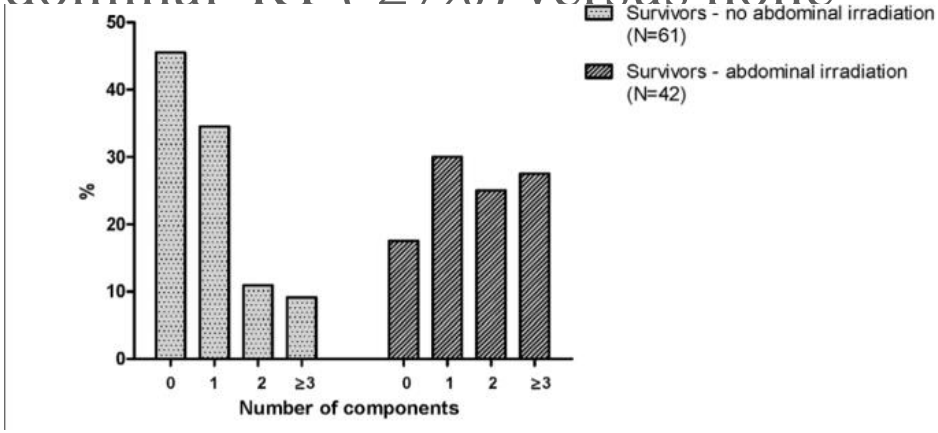
Treated at 4 for stage 4
21 Gy
10 vertebras treated
Now 14, heighth -3DS

COURTESY OFAnne LAPRIE- SIOP

Metabolic syndrome

- Survivors treated for neuroblastoma and nephroblastoma (n=67) were compared with controls (n=61)
- 26 years follow -up
- Components : Higher blood pressure, triglycerides, LDL-C, free fatty acids
- Total percentage fat instead of Lower waist circumference as not reliable as can be decreased due to RT
- Three times more frequent if abdominal RT (27%) versus none





Van Waas PlosOne2012

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Long term sequelae

- **Stage IV :**
  - **31 patients : « More than 50% of children with stage 4 NB may survive.**
  - **high incidence of severe long-term sequelae 98% ».**

Perwein et al, Pediatr Blood Cancer 2011

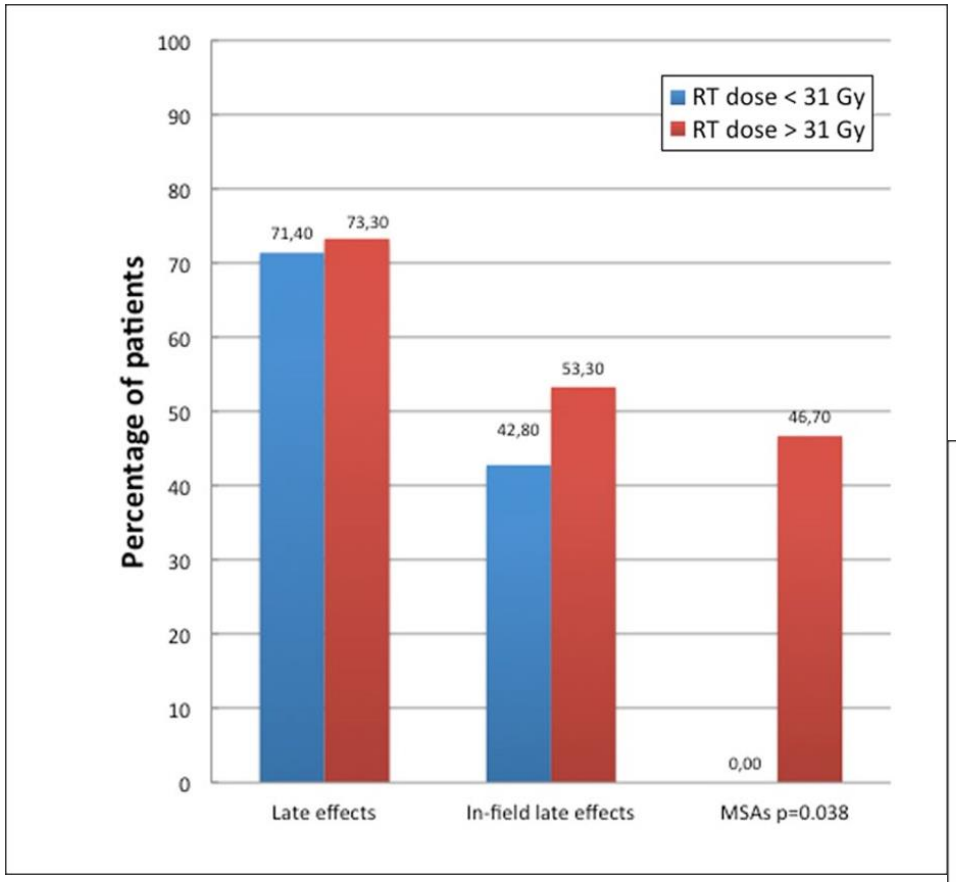
  - **153 patients Only 34% of patients with stage IV NB survived.**
  - **44% of survivors experienced late morbidity .**

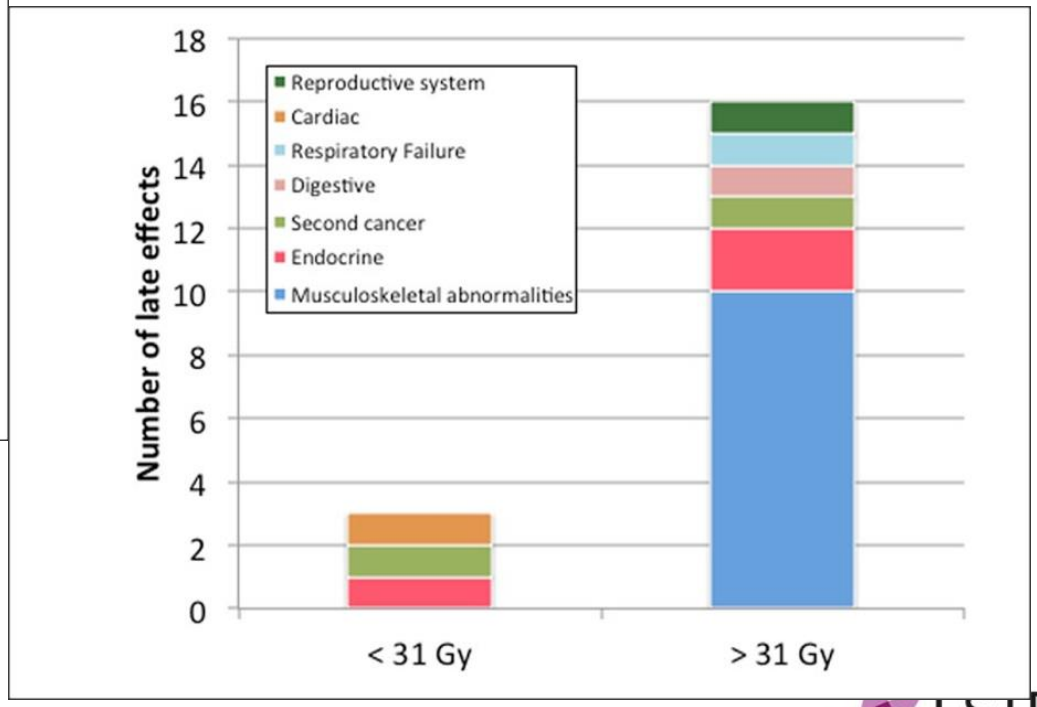
Escobar et al, JPEd Surg 2006

- **Localized high risk**
  - **Very few results as they are usually mixed with stage IV.**
  - **35 patients : 73% toxicity - 45 % within RT fields , long follow up : median 14 years**

Ducassou et al, 2015, Strahlen Onkol

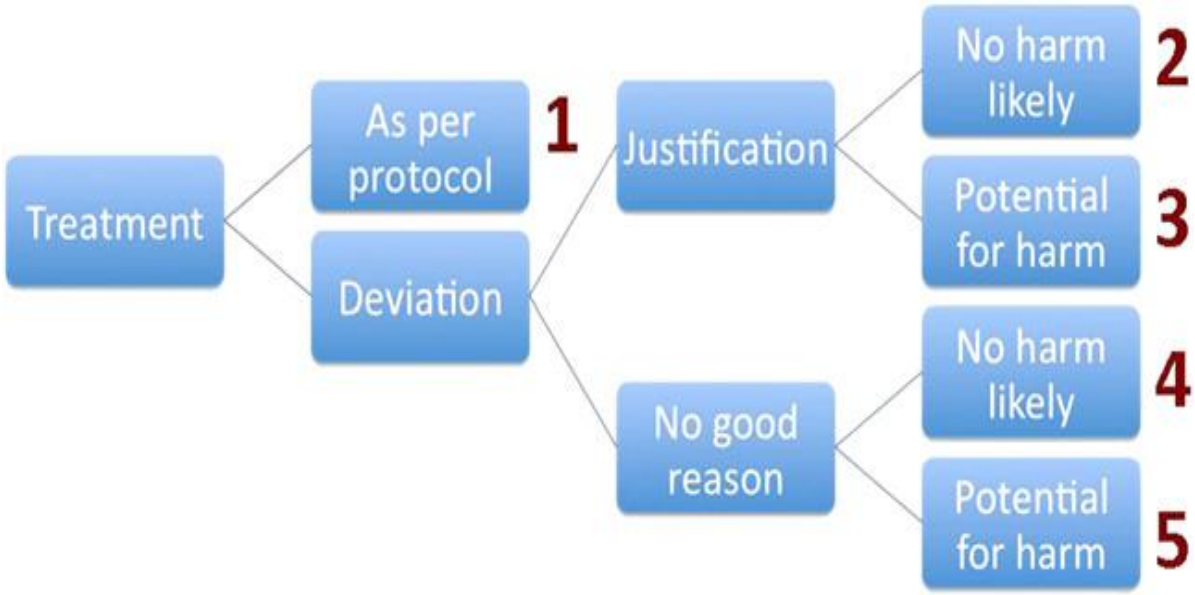
Late toxicity of conformal RT after surgery and chemo and/or high dose chemo for localized HR NB





Ducassou et al, Strahlen Onkol 2015

Centralised quality control of radiotherapy planning



882 patients in the database
<u>100 files could be analysed</u>

48 treatments as per protocol

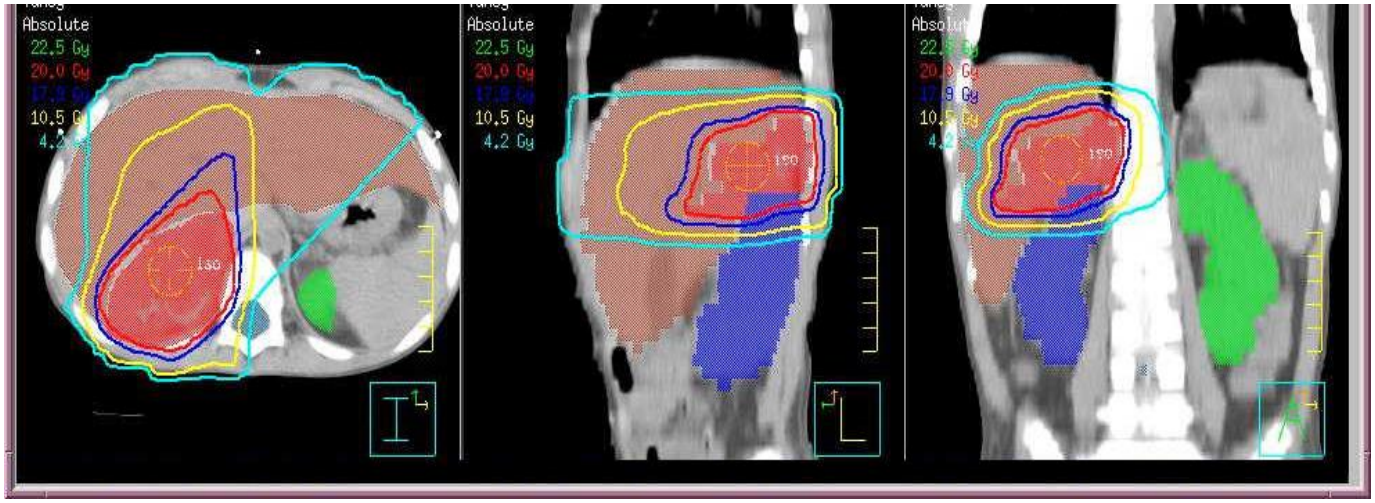
29 Justified deviations without potential harm
5 justified deviations with potential harm
17 unjustified deviations with potential harm

impact on survival and sequelaes ?

Gaze et al, IJROBP 2012

Centralised quality control of radiotherapy planning

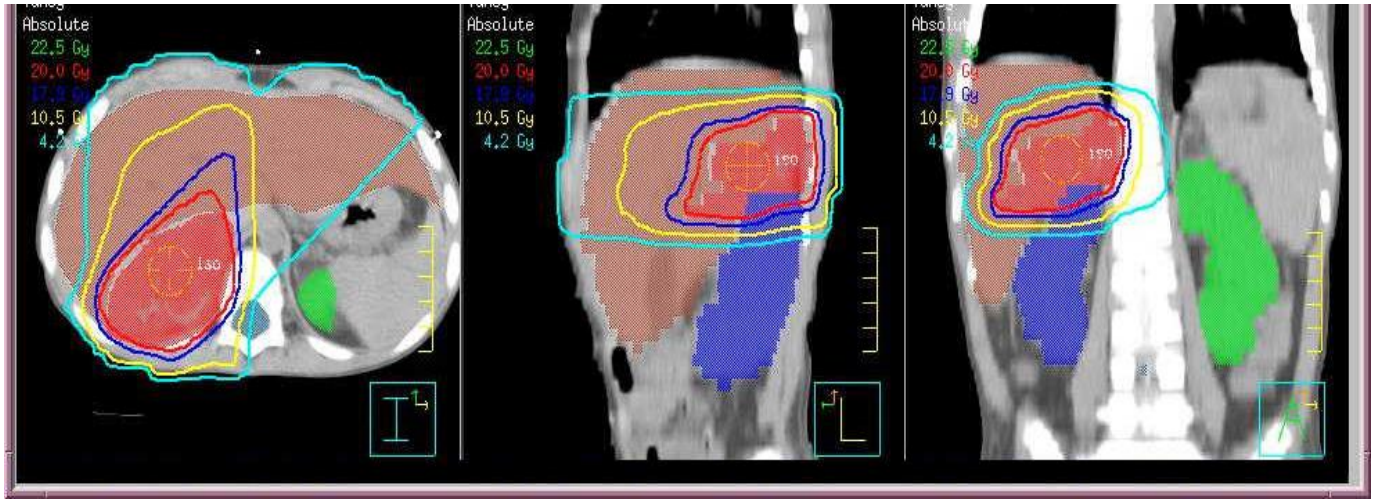
Example of unjustified deviations
WHERE ?



Centralised quality control of radiotherapy planning

Example of unjustified deviations

- Risk of avoidable morbidity
  - Irradiation of part of a vertebra
  - CTV not extended to cover full vertebral width
- Risk of failure of disease controle
  - failure to cover involved lymph nodes



Quality control impact on pronostic

- Higher failure rates and worse overall survival in review of literature of several multicenter clinical trials

Fairchild et al, IJROBP 2013

Peters et al, JCO 2010

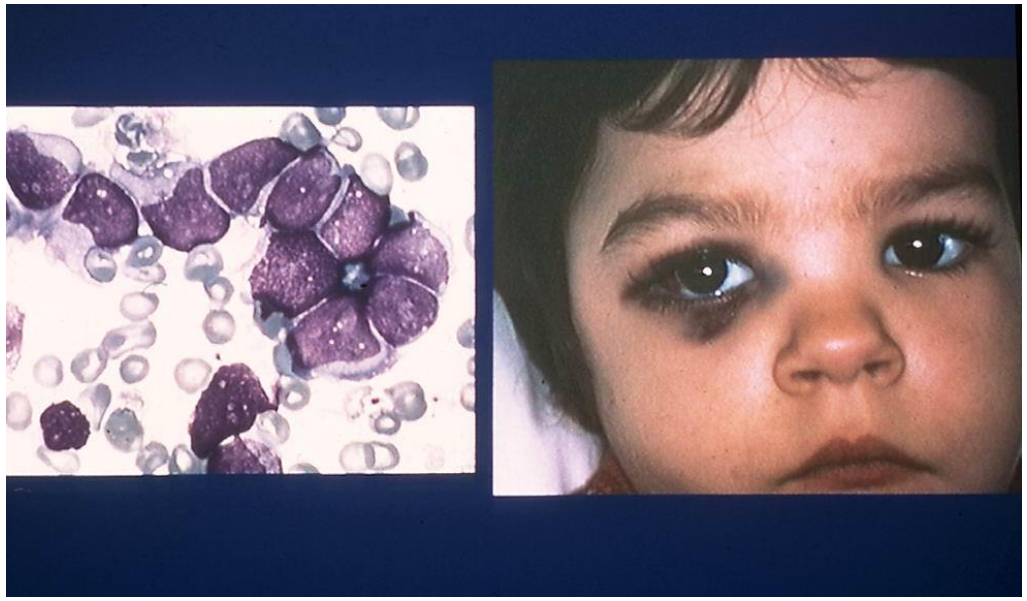
Carrie et al, JCO 2009

- Meta analysis of RT-protocol deviations : occurred in 8–71% of cases, and were associated with a ~75% increased risk of treatment failure and overall mortality

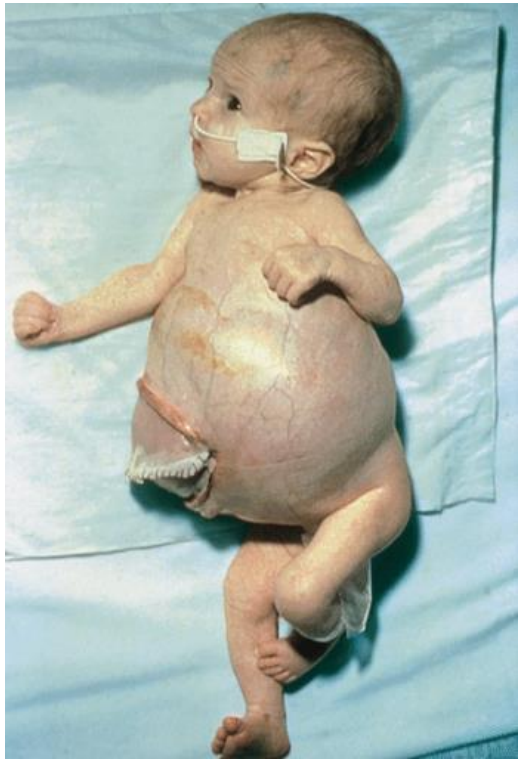
Ohri et al, JNCI 2013

- Use rapid web-based prospective online quality control

Place of RT in metastatic neuroblastoma



Hutchinson



Pepper syndrome

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Indications

- As symptomatic treatment :
  - Pain
  - Compression
  - Esthetic
  - Short duration : 12 to 20 gy /5 fr or 23 gy /1,8gy/fr

Or as an integrated global strategy

Issues with Application of Metastatic Site RT within a global strategy

- Why? : Survival is driven by metastatic site failure and durability of systemic therapy is transient

Author	Rt modality	Sites treated	lf@rt	lf@nonRt
Gatcombe	ebrt	Post induction	1/6	
Bradfield	ebrt	diag	1/17	4/4
Sibley	Tbi+ebrt	Post -SCT	1/10	
Polishchuck	ebrt	Post induction	3/19	128/506
Kandula	ebrt	Post induction	3/13	

Pmid :2523825;28068235;7607934;15022296;19211198

Issues with Application of Metastatic Site RT?

- Currently

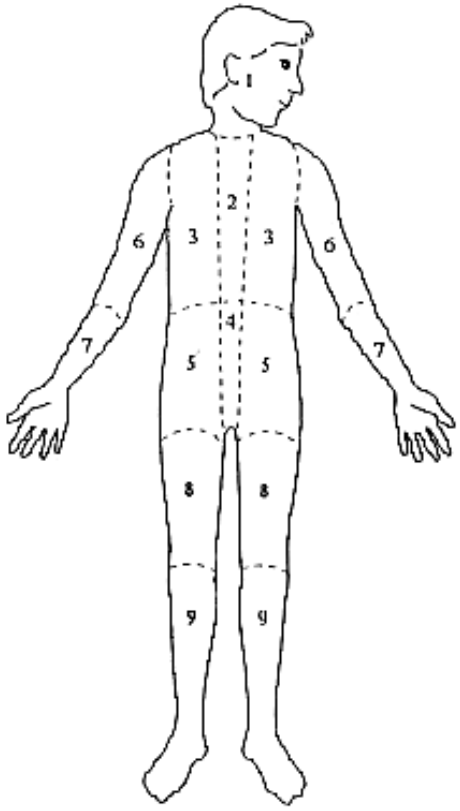
  Persistently MIBG-Avid lesions post induction or residual soft tissue disease

- Future
  - All neuroendocrine cells with active NE transporter
  - Active NB with active NE transporter
  - Persistently MIBG-Avid lesions post induction
  - Residual soft tissue disease

Curie score

- 10 segments (1 soft tissue)
- Each segment scored 0-3.
- Summate scores. Max = 30
- Skeletal score (per segment)
- 1 = 1 distinct lesion
- 2 = 2 distinct lesions
- 3 = ≥ 50% of a segment.
- Soft tissue scoring

- 1 = 1 MIBG avid ST lesion
- 2 = > 1 MIBG avid ST lesion
- 3 = occupies ≥ 50% region
- (chest or abd-pelvis)



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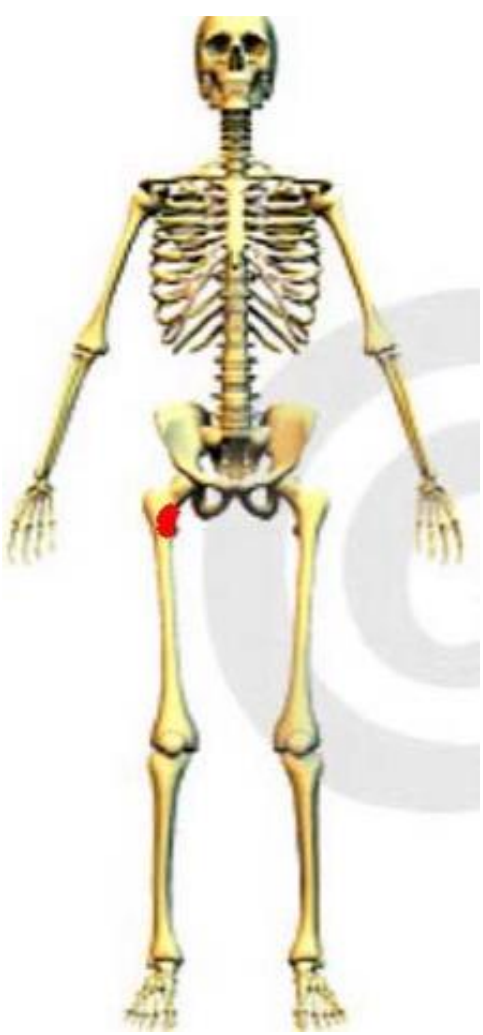
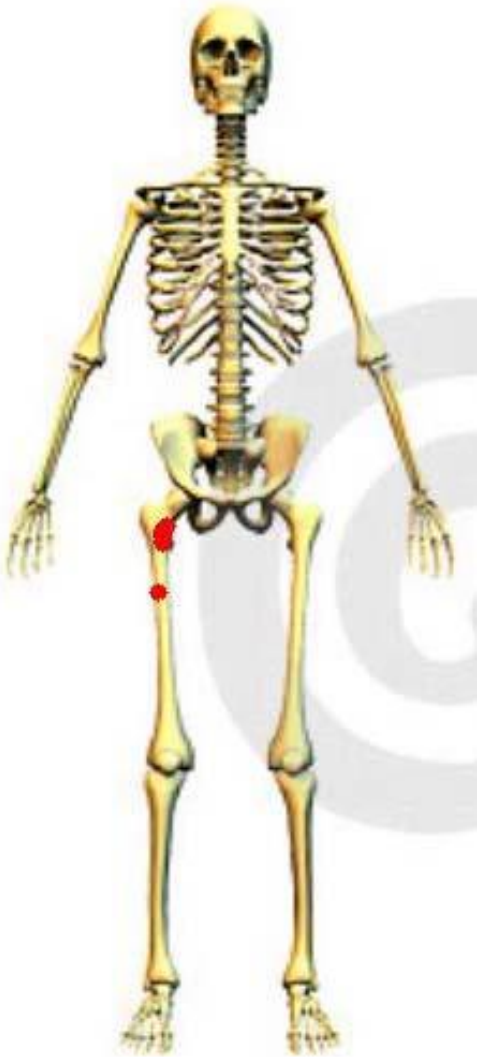
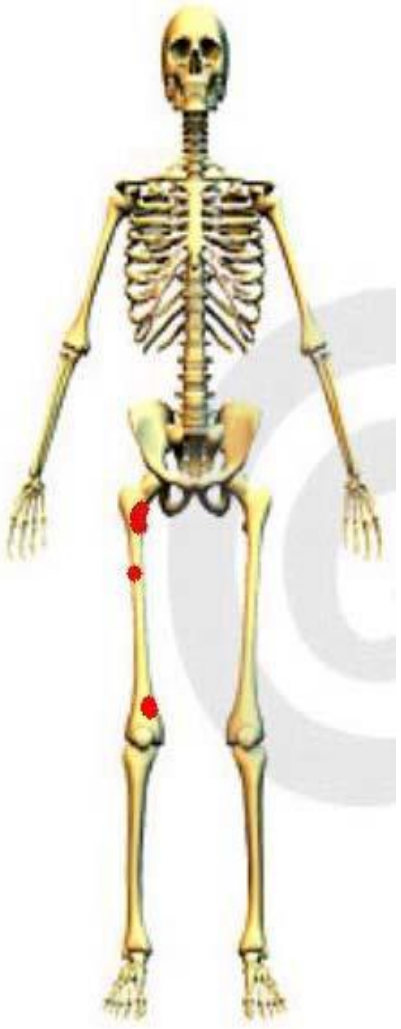
COG Scoring



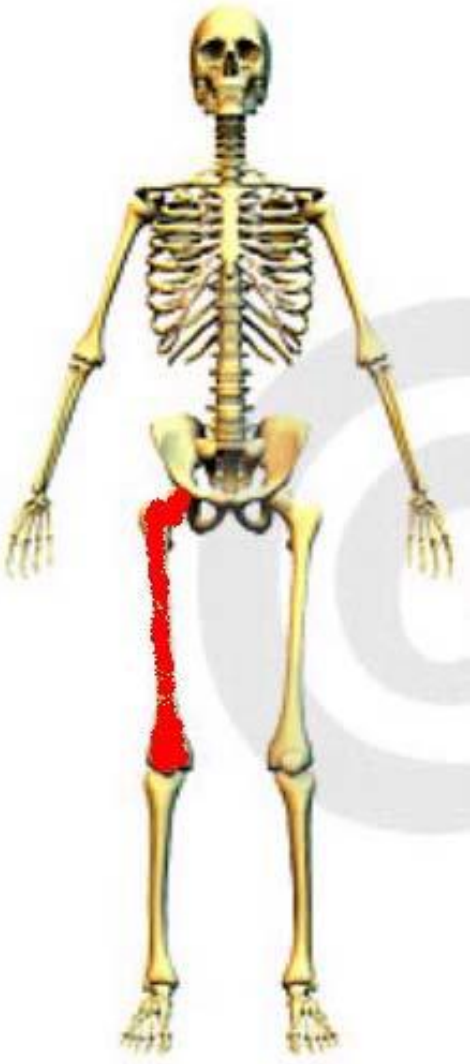
Curie 1



curie2



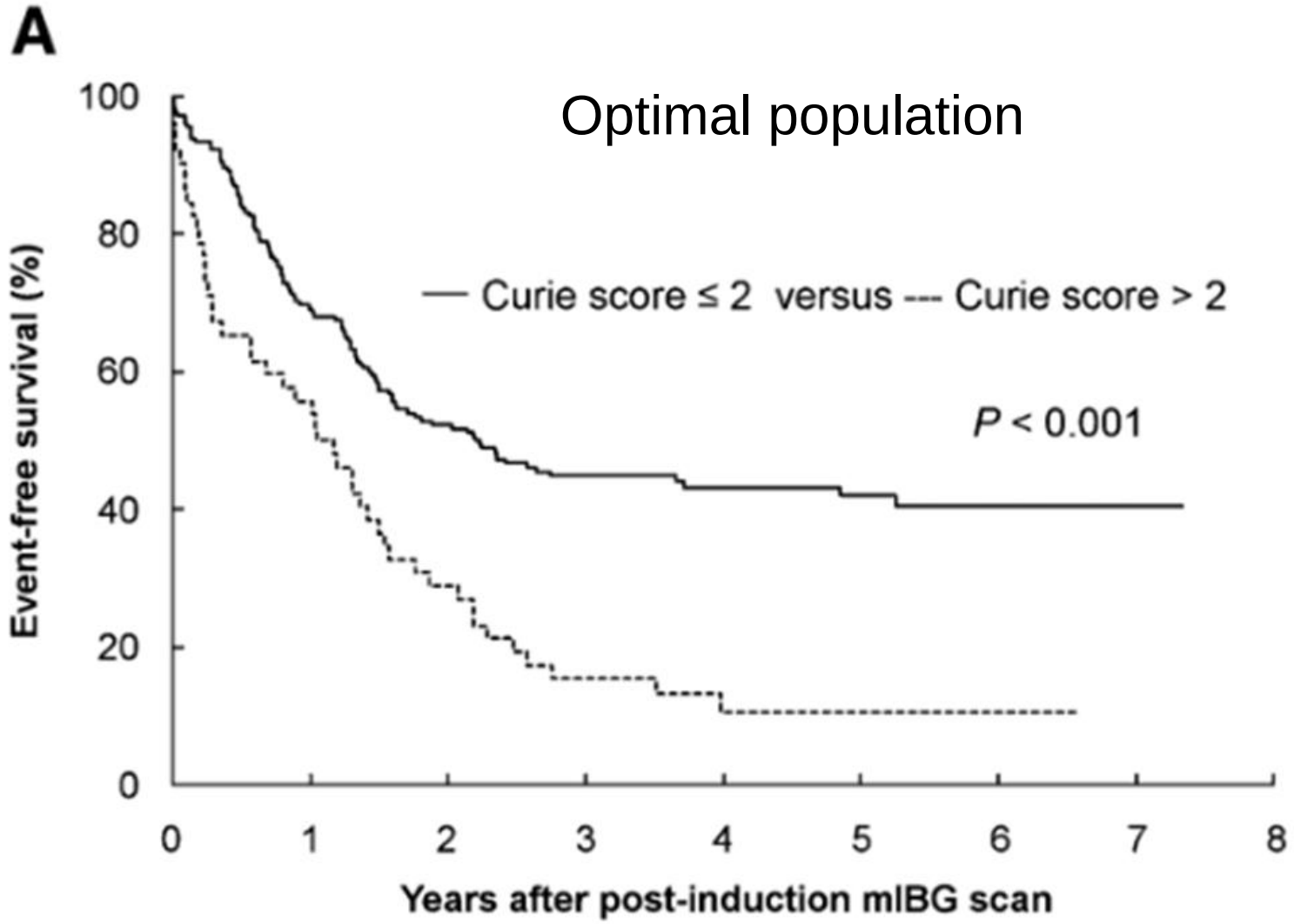
curie2



Curie3

Courtesy of Parisi

Issues with Application of Metastatic Site RT?



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SJCRH study (Lucas)

- Prognostic relevance of Curie score with advances in systemic therapy requires
- ***re-evaluation***
- • ***Early*** metastatic site failure is usually at a ***new*** site while ***prior/old*** MSF usually occurs ***later***
- • ***Inability to complete systemic therapy & presence of lung metastases*** are risk factors for progression at ***new metastatic sites***
- • ***Persistent MIBG avid disease is insufficiently controlled*** with adjuvant doses
- (21.6-23.4 Gy)
- • ***MIBG avidity is a reasonable way to select high risk sites*** for recurrence

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NEXT EUROPEAN PROTOCOL

- Possible (randomised) radiotherapy questions
- Determining the need for RT post complete resection
- Determining the benefit of dose escalation for residual disease
- ? The role for RT in oligometastatic disease
- Prospective RTQA with Quartet

Take home messages for radiotherapy of neuroblastoma

- Second most frequent indication for pediatric RT in very young children
- Standard remains AP-PA
- Less indications of IMRT - Protontherapy is promising
- Be careful with bone irradiation as main late effects are musculoskeletal
- Treat within prospective trials
- Go for online quality control
- Probably a place for metastatic site RT

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Thanks

- Special thanks to :
- J T Lucas : St Judes
- French Society of children's Cancer and the radiotherapy group
  - Anne Laprie, Valérie Bernier, Line Claude, Stéphane Supiot, Jean-Louis Habrand, Claire Alapetite, Anne Ducassou Sylvie Helfre, and many more
- SIOPEN group and the RT group
  - Tom Boterberg, Mark Gaze, Henry Mandeville, Karin Dieckmann, Sylvie Helfre and many more

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WWW.ESTRO.ORG/SCHOOL

IMRT in CHILDREN

Christian Carrie
Centre Leon Berard
Lyon FRANCE

Radiotherapy and childhood

- 1/250 chidren will be diagnosed with a cancer before age of 20
- 50% of chidren with cancer will receive radiation therapy
- More than 75% will be cured and exposed to late effect due to treatment ,not only radiation
- 10450 cases/y in Usa in 2014

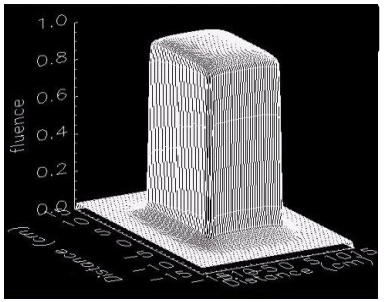
- 1/530 Young adult is a cancer survivor

What does cure mean for a child ?

- Not only cure of cancer but restoration of health
- San Fillipo 2015 :late mortality declined in paediatric cancer from 12 to 6 % between 1970 and 1994
- Amstrong report (astro 2015):
  - 3958/34033 children less than 20 at diagnosis but free of disease after 5 y died
    - 46% of secondary cancer
    - 15% heart disease
    - 8 %Lung disease

Decline in late morbidity due to more selected therapy

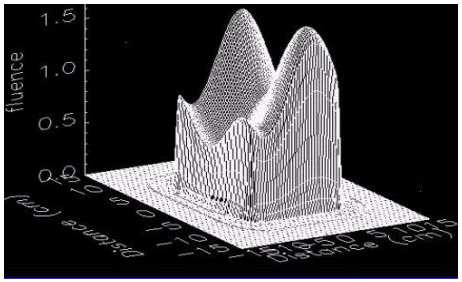
Radiotherapy techniques



CONFORMAL RADIATION : **Homogeneous beams**

INTENSITY MODULATED RADIATION THERAPY (IMRT)

- **Variations of beams intensity**
- **Each beam is split into several fragments**
- **Each fragment delivers different dose**



- **Complex dose distribution**
- **Higher conformity to target volumes and to critical organs**
- **Time consuming**
- **Quality control**
- **cost**

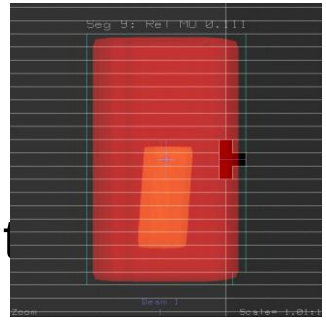
INTENSITY MODULATED RADIATION THERAPY

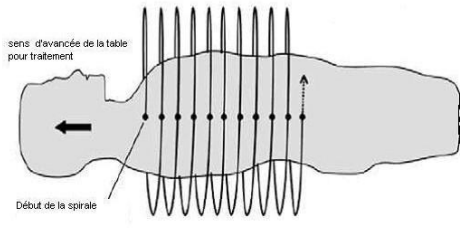
IMRT with fixed beams on LINAC

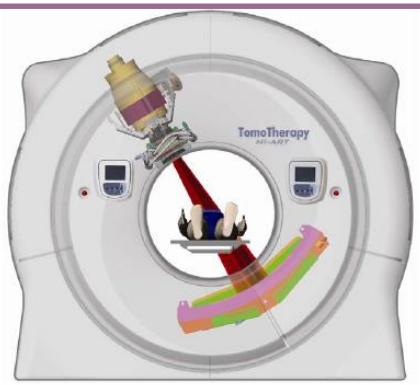
Linac arm is motionless

Leafs are moving during t

Dose rate is constant







Delivery of RT is coupled to a continue table motion

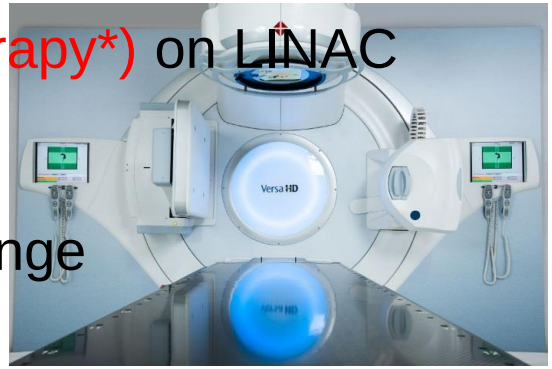
VMAT (Volumetric Modulated Arc Therapy*) on LINAC

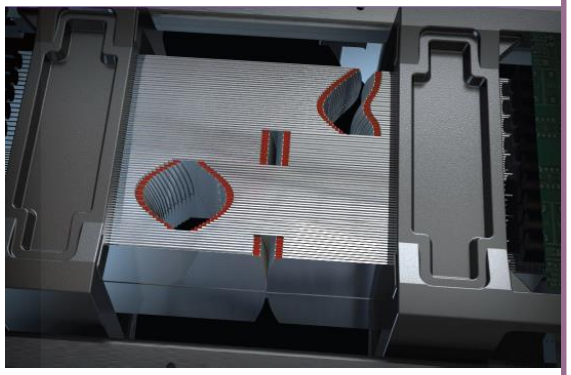
During RT :

Speed and angles of rotation arm change

Dose rate varies

Leafs in motion





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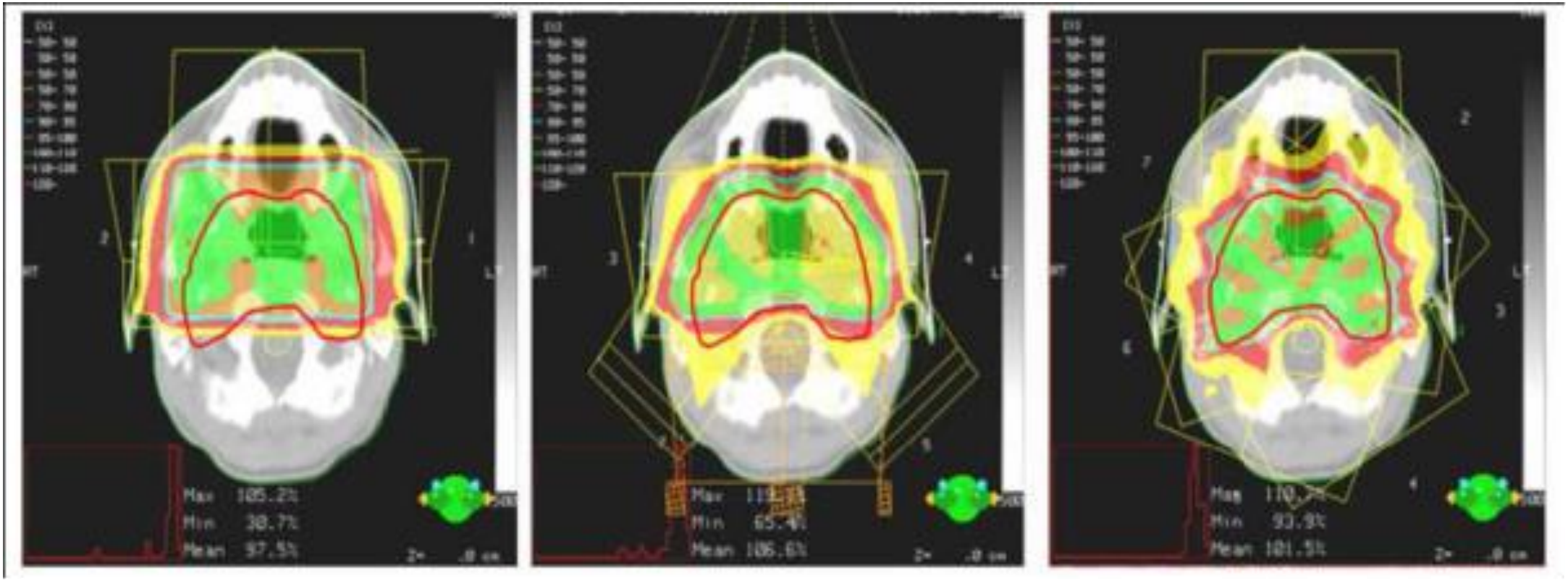
Theoritical advantages



Spare surrounding structures , homogeneity in PTV

“It is intuitively obvious that _____are/is better/ Why would anyone not select a superior dose distribution? Clinical trials are unnecessary/immoral.

- **Protons**
- **IMRT**
- **IGRT**
- **Brachytherapy**

- **Does it mean imrt for everybody ?**

Halperin siop 2012

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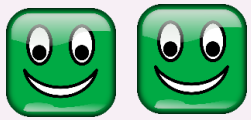
Conformal RT versus IMRT versus PROTONS

	Tomotherapy	VMAT	Conformal	Protons
Target conformation				
Low doses in large volumes				
Easy to treat large volumes				
Sparing of critical organs				
Treatment duration				

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IMRT is Standard of care for adults

1. Prostate
2. Head and neck
3. Sarcoma
4. Brain tumors
5. Gyne

Benefit proved for acute side effect or sequellae (hyposialie , rectitis , brain necrosis) but marginal for local control or OS except in case of dose escalation ex for Nasopharyngeal carcinoma

Benefit of IMRT in UCNT : local control and survival (Adults)

	N	Time of RT	5 y Local Control	5-y DFS	5-y OS	Benefit
Peng, Radiother Oncol. 2012	CRT: 306	2003-2008	84.7% (T4 62%)		67.1%	
	IMRT : 310		90.5% (T4 81%)		79.6%	
Chen, Oncotarget 2017	CRT: 377	2004-2006	76.6%	71.8%		Advanced disease ++
	IMRT : 481		87.6%	82.3%		T4 ++
Zhang, Eur J Cancer 2015	CRT: 4836	2002-2012	90.8%	76.6%	84.5%	Both advanced and
	IMRT : 2245		95.6%	82.1%	87.4%	early disease

- Randomized study in adults := better LC : + 6-11% DFS/OS : +5-12%
- Better target coverage using IMRT
- Advanced disease especialy : T4, N2, Stage III ++)

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Benefit of IMRT in UCNT : local control and survival (children)

	N	Time of RT	5 y Local Control	5-y DFS	5-y OS
Laskhar, Int J Radiat Oncol Biol Phys 2008	CRT: 17	2003-2006	68.2% (2-y)		
	IMRT : 19		84.2% (2-y)		
Qiu, J Cancer Res Clin Oncol2017	**CRT: 74**	**2003-2013**	**88.3%**	**71.2%**	**76.1%**
	IMRT : 102		**97.9%**	**85.7%**	**90.4%**
Liu, Radiat Oncol 2014	CRT: 103	1990-2011	No difference	No difference	
	IMRT : 55				

- No randomized study in childhood

- The most recent large retrospective study confirms the benefit in term of :
  - Local control : + 9%
  - Survival +14%

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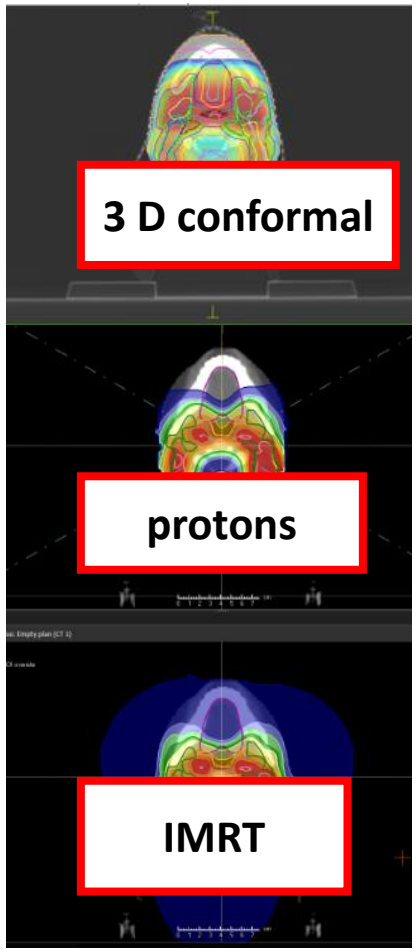
IMRT for all children ?

- As for adulte , better dose distribution does not mean better outcome
- No randomized studies
- As for adults better potential benefit if high dose has to be done close to critical structures (Ex : intra cranial GCT) or complex shape

SPECIFICITY OF PAEDIATRIC RT

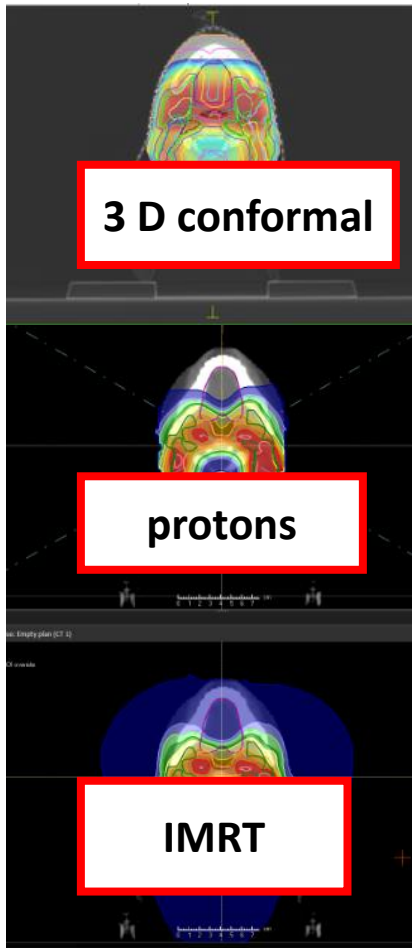
- High cure rate
- Often lower dose than adults
- But often larger volume (CSI, Flank , WART)
- Need of symetric irradiation for young
- Specific radiosensibility (Recklinghausen , Li fraumeni ..)
- Don’t need of dose escalation in most cases

Target coverage



Planning target volume 48 Gy (prophylactic)	Planning target volume 54 Gy (intermediate)	Planning target volume 60 Gy (high risk)
95%	95%	88%
99%	99%	99%
99%	99%	99%

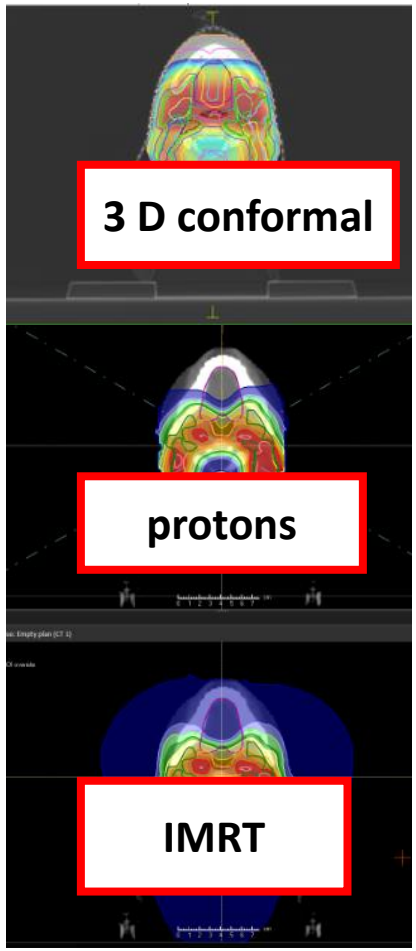
Doses to main critical organs



COCHLEA RIGHT LEFT	LARYNX	PAROTIDE GLANDS RIGHT LEFT	THYROID	PINEAL GLAND	BRAIN STEM	ORAL CAVITY
Max 57 Gy 57 Gy	Max 71 Gy	Mean 60 Gy Gy	Mean 48 Gy	Mean 46 Gy	Max 56 Gy 60 Gy	Mean 45 Gy
Max 51 Gy 43 Gy		an Gy Gy	Mean 43 Gy	Mean 47 Gy	Max 48 Gy	Mean 30 Gy
Max 52 Gy 42 Gy	Max 51 Gy	Mean 28 Gy 30 Gy	Mean 43 Gy	Mean 49 Gy	Max 50 Gy	Mean 33 Gy

NO OR SMALL BENEFIT OF IMRT AND PROTONS

Doses to main critical organs



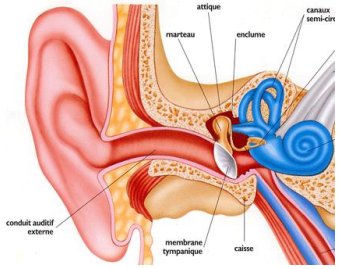
COCHLEA RIGHT LEFT	LARYNX	PAROTIDE GLANDS RIGHT LEFT	THYROID	PINEAL GLAND	BRAIN STEM	ORAL CAVITY
Max 57 Gy 57 Gy	Max 71 Gy	Mean 60 Gy 60 Gy	Mean 48 Gy	Mean 46 Gy	Max 56 Gy 60 Gy	Mean 45 Gy
Max 51 Gy 43 Gy	Max 48 Gy	Mean 20 Gy 27 Gy	**MAJOR EXPECTED BENEFIT OF IMRT AND PROTONS**		Max 48 Gy	Mean 30 Gy
Max 52 Gy 42 Gy	Max 51 Gy	Mean 28 Gy 30 Gy	43 Gy	49 Gy	Max 50 Gy	Mean 33 Gy

Main studies in children

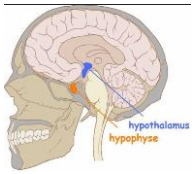
- **Huang** (ijrobp 2002) : dose to inner ear for medulloblastoma decrease from 54 gy to 36,7 gy **but** boost not restricted to tumor bed
- **Parker** (ijrobp 2007) : imrt for csi decrease the V10 gy but increase integral dose
- **Wolden** (ijrobp 2005) :28 RMS treated with IMRT ; 1 local relapse , no secondary tumor
- **Schroeder** (ijrobp 2015) :22 ependymomas .no marginal failures .No grd >2 after 36 m FU
- **La** (ijrobp 2006) : 26 ewing sarcoma : no differences for LC with 3 or 2 D but allow dose escalation without toxicites

The choice must be done on what it is expected at long term

HEARING LOSS

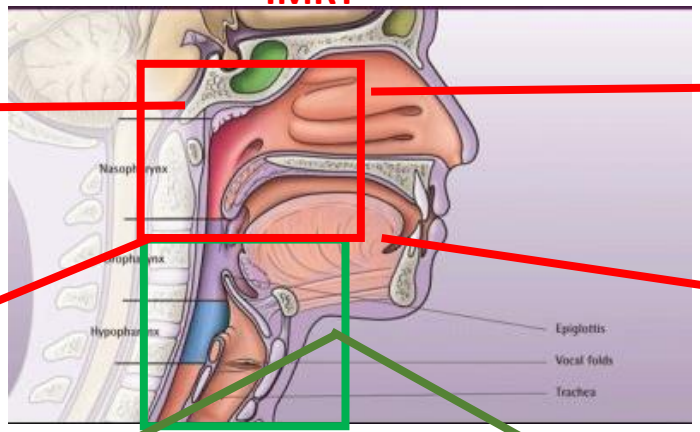


14 - 63 % (Gr. 1-2)
5% severe (Gr 3-4)
< 30% Gr ½ with IMRT



GROWTH and/or Brain RETARDATION

2-35%
No known impact of IMRT

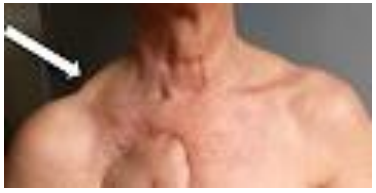


TRISMUS

Up to 50%
IMRT : less than 10%

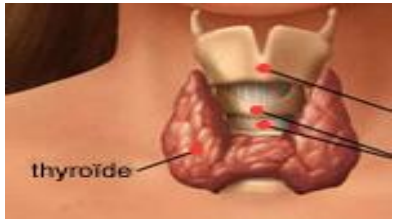
XEROSTOMIA

50-95% Gr 1-2
(< 50 with IMRT)
4 - 10% Gr 3
(<5% with IMRT)

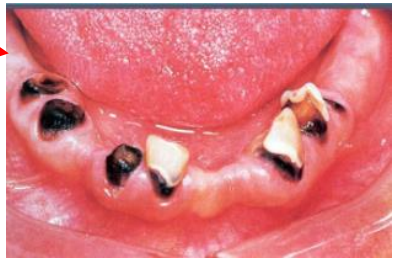


NECK FIBROSIS

40-75%
IMRT : 20-40%
(gr1-2)



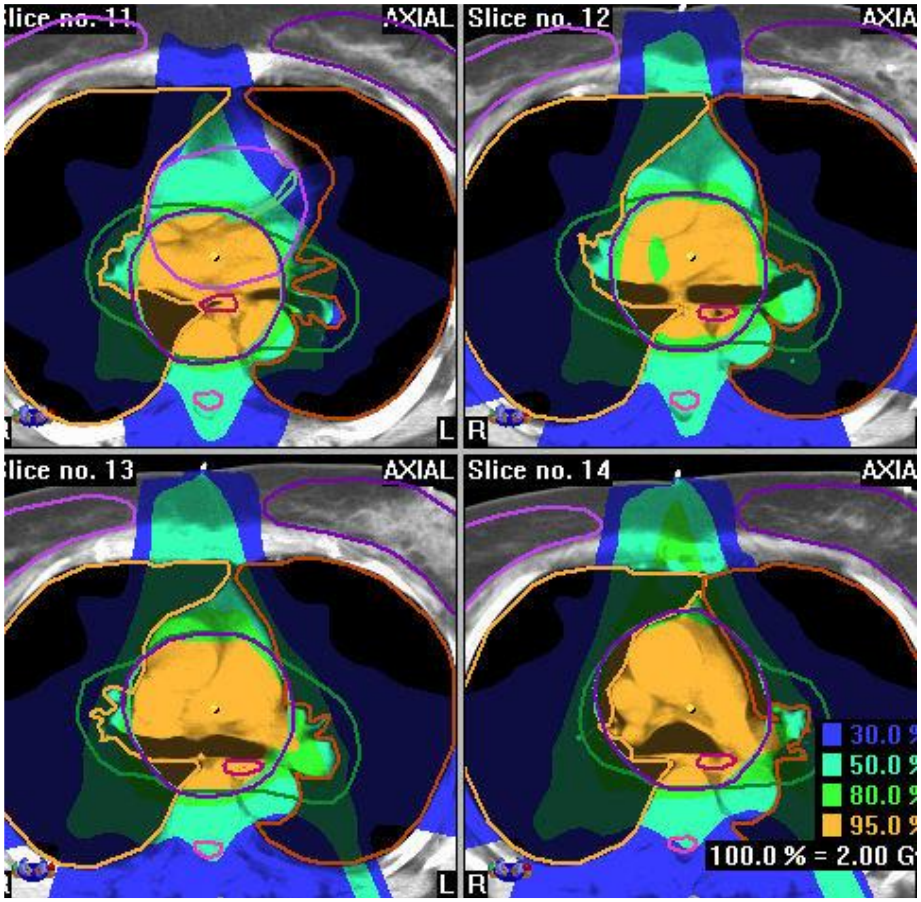
25-82%
RELATIVE RISK > 14
NO IMPACT OF IMRT

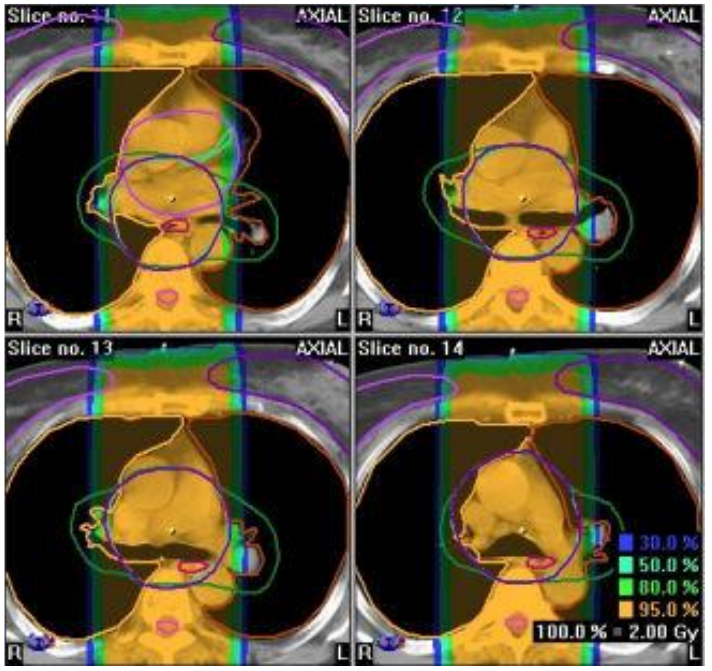


CAVITIES

Up to 65%
< 25% with IMRT

Left coronary artery : 2D APPA / 4field IMRT /7field IMRT





50% less dose to LCA with IMRT

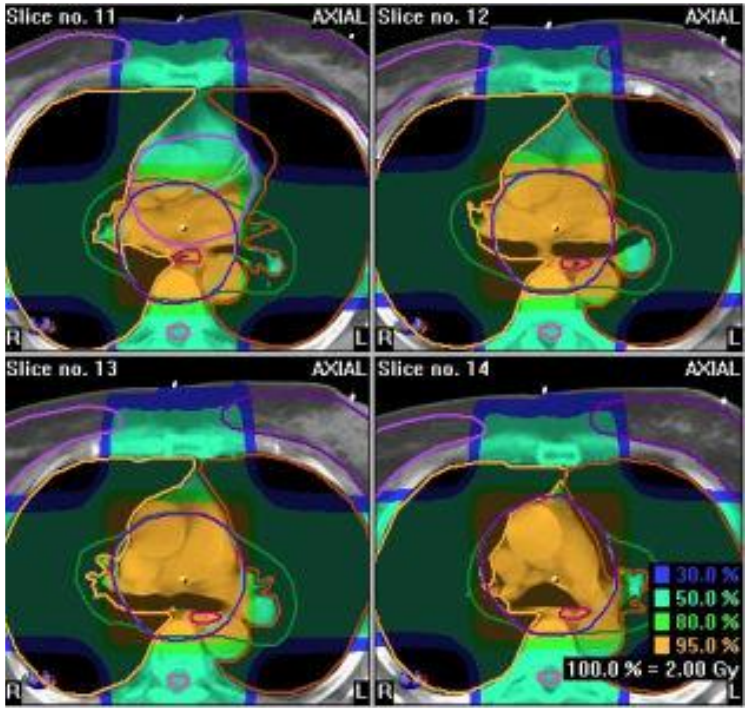


Table 3. Incidence and Relative Risk of a First Cardiac Disease Following Anthracycline and Heart Radiation Dose

Anthracycline Use	Heart Radiation Dose, Gy	Patients	Cardiac Disease: All Grades (n=234) Cases	Incidence at Age 40 (95% CI)	Relative Risk* (95% CI)	Cardiac Disease: Grade 3+ (n=156) Cases	Incidence at Age 40 (95% CI)	Relative Risk* (95% CI)
No								
	None or <0.1	684	5	1.1 (0.3–4.6)	1†	3	0.4 (0.1–0.3)	1†
	<1	594	9	1.5 (0.6–3.7)	3.7 (1.2–11.1)	5	1.2 (0.4–3.1)	2.8 (0.7–12.2)
	1–5	316	15	5.0 (2.7–9.3)	5.5 (2.0–15.4)	4	1.2 (0.3–4.6)	1.9 (0.4–8.8)
	5–15	219	7	3.3 (1.3–7.7)	4.4 (1.4–14.2)	5	1.8 (0.6–5.7)	4.6 (1.1–19.4)
	15–30	239	25	15.3 (10.1–22.9)	18.9 (7.1–50.2)	17	10.4 (6.2–17.3)	19.5 (5.6–67.8)
	30+	113	45	41.3 (30.8–53.7)	60.4 (22.4–163.0)	37	35.8 (25.9–48.1)	75.2 (21.6–1261.2)
Yes								
	None or <0.1	433	40	15.5 (11.0–21.7)	18.4 (7.1–48.0)	31	10.8 (6.9–16.6)	29.2 (8.5–99.7)
	<1	300	30	14.3 (9.6–21.0)	15.0 (5.6–40.2)	13	7.7 (4.3–13.7)	15.4 (4.2–56.0)
	1–5	78	15	26.3 (16.2–41.1)	30.8 (10.9–86.7)	10	18.6 (10.0–33.1)	40.9 (10.9–153.0)
	5–15	51	7	46.8 (18.1–86.3)	26.7 (8.3–85.9)	5	44.4 (15.8–86.5)	37.5 (8.7–161.7)
	15–30	107	28	38.0 (25.9–53.4)	47.1 (17.7–125.5)	18	24.5 (15.5–37.5)	59.5 (16.9–209.6)
	30+	28	8	54.1 (28.7–83.4)	61.5 (19.6–192.8)	8	54.1 (28.7–83.4)	110.7 (28.4–432.4)

CI indicates confidence interval.

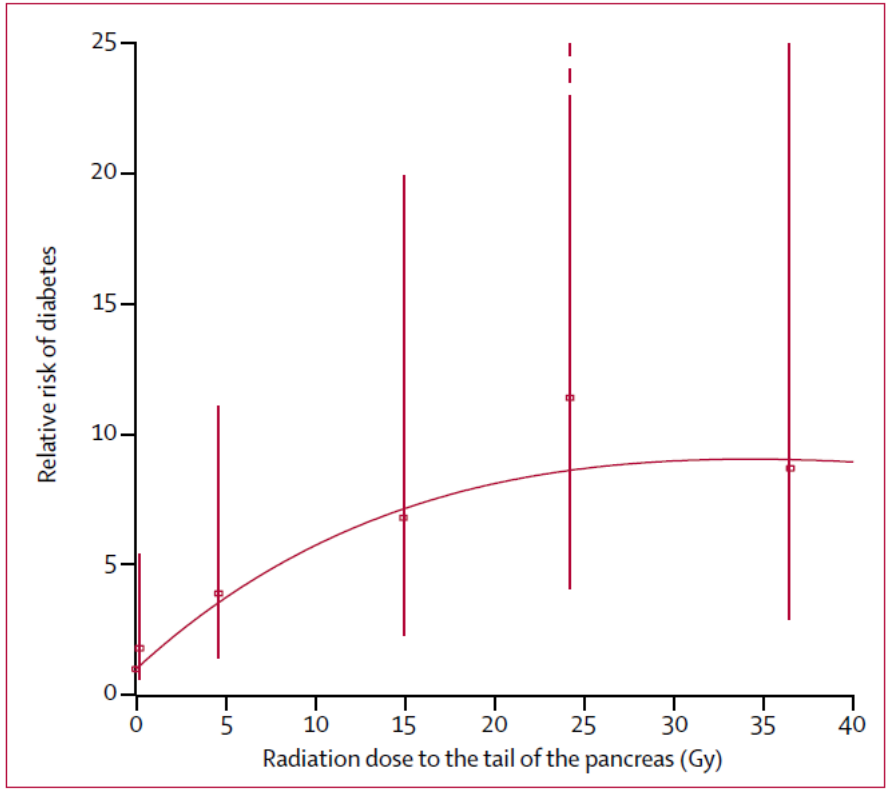
*Cox model using attained age as the timescale, age at first cancer plus 5 years as the entry time adjusted for age, and year at diagnosis of cancer, sex, type of first cancer chemotherapy, and brachytherapy.

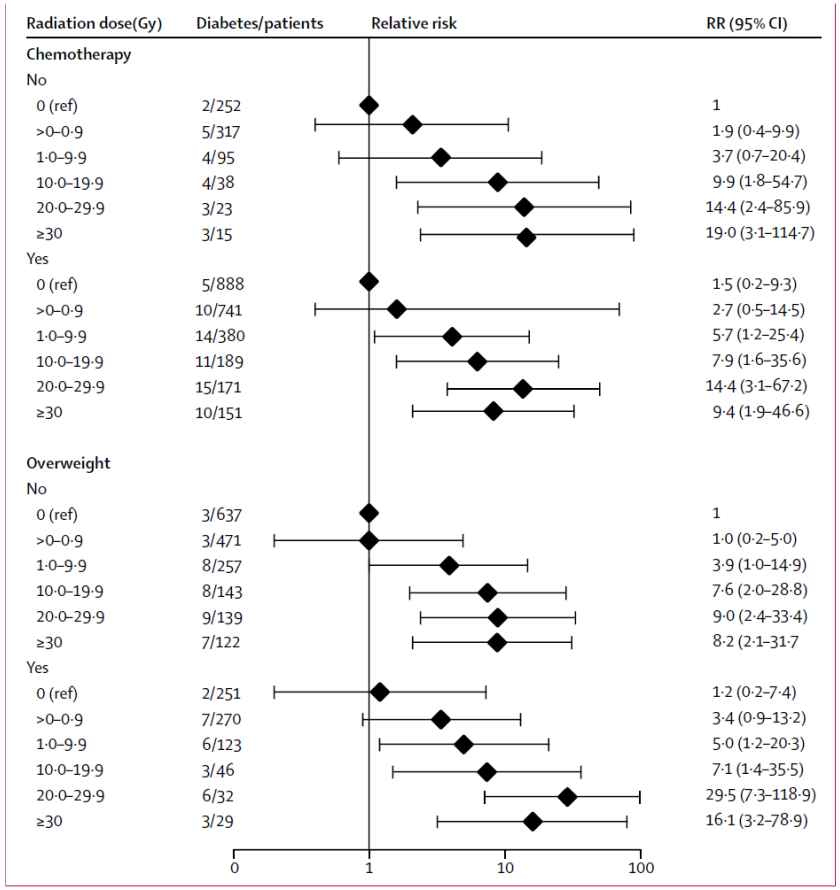
†Reference group.

Haddy N, Diallo S, El-Fayech C, Schwartz B, Pein F, Hawkins M, Veres C, Oberlin O, Guibout C, Pacquement H, Munzer M, N'Guyen TD, Bondiau PY, Berchery D, Laprie A, Scarabin PY, Jouven X, Bridier A, Koscielny S, Deutsch E, Diallo I, de Vathaire F. Cardiac Diseases Following Childhood Cancer Treatment: Cohort Study. Circulation. 2016 Jan 5;133(1):31-8

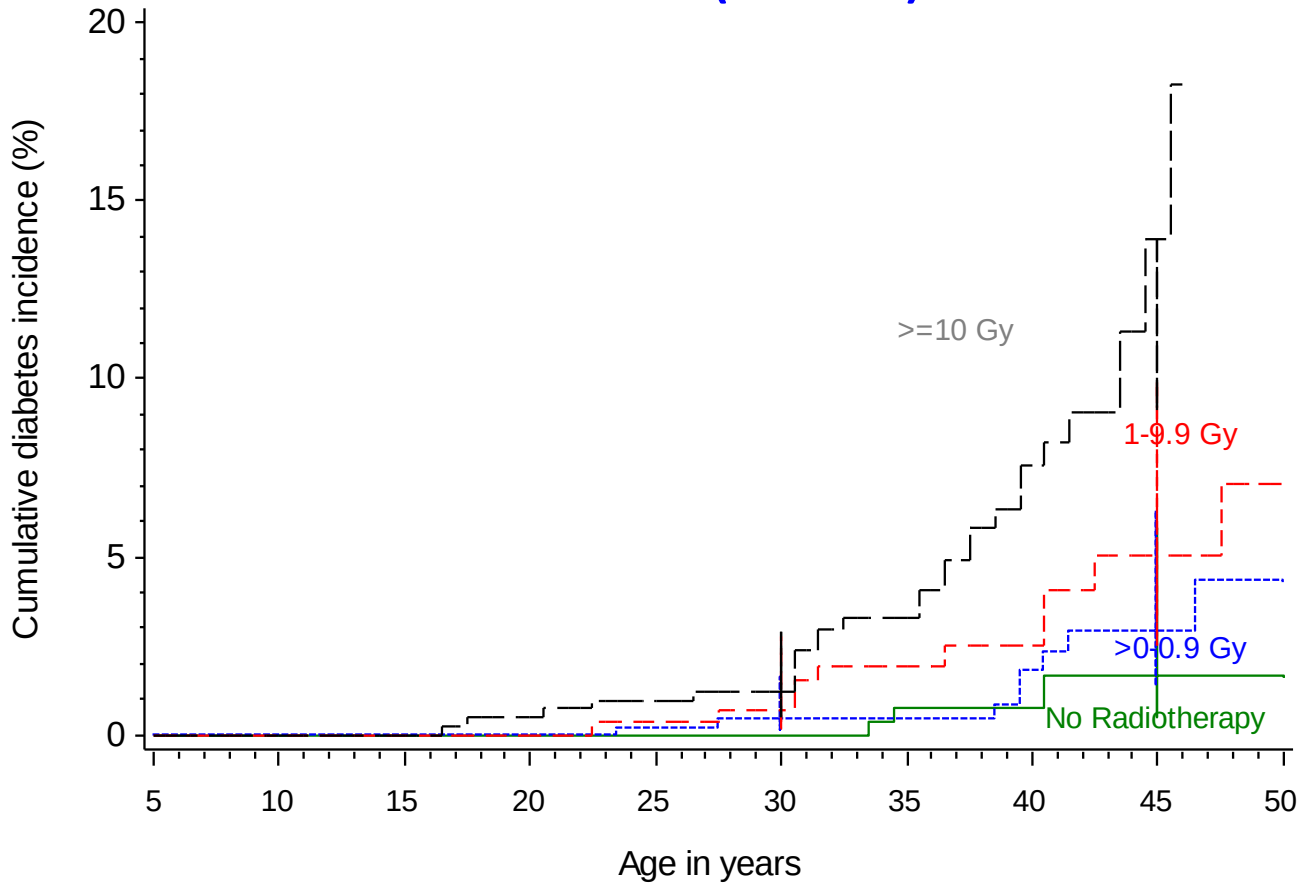
Radiation dose to the pancreas and risk of diabetes mellitus in childhood cancer survivors: a retrospective cohort study

Florent de Vathaire, Chiraz El-Fayech, Faten Fedhila Ben Ayed, Nadia Haddy, Catherine Guibout, David Winter, Cécile Thomas-Teinturier, Cristina Veres, Angela Jackson, Hélène Pacquement, Martin Schlumberger, Mike Hawkins, Ibrahima Diallo, Odile Oberlin





Radiation dose to the left of the pancreas and diabetes incidence (n=56)



4500pts treated between 1985 and 1995.F De Vathaire

Case-control study on cerebrovascular diseases following childhood cancer : France, UK, the Netherlands

253 cases of permanent stroke and 253 individually matched controls

- 72 cases and 72 controls from the UK, from the BCCSS (UB, UK, M Hawkins)
- 153cases and 153 controls, from the FCCSS (INSERM, France, F de Vathaire).
- 28 cases and 28 controls from the DOG Later cohort (AMD, The Netherlands, AMD, L Kremer)

Matching criteria

- Cohort
- Gender
- Age at first primary cancer diagnosis (+/- 1 year)
- Calendar year at first primary cancer diagnosis (+/- 3 years)
- Length of follow-up

A control can serve as a control for more than one case. In addition, control from one matched set may later be found to be a case, at which point the appropriate control will be selected for the new set.

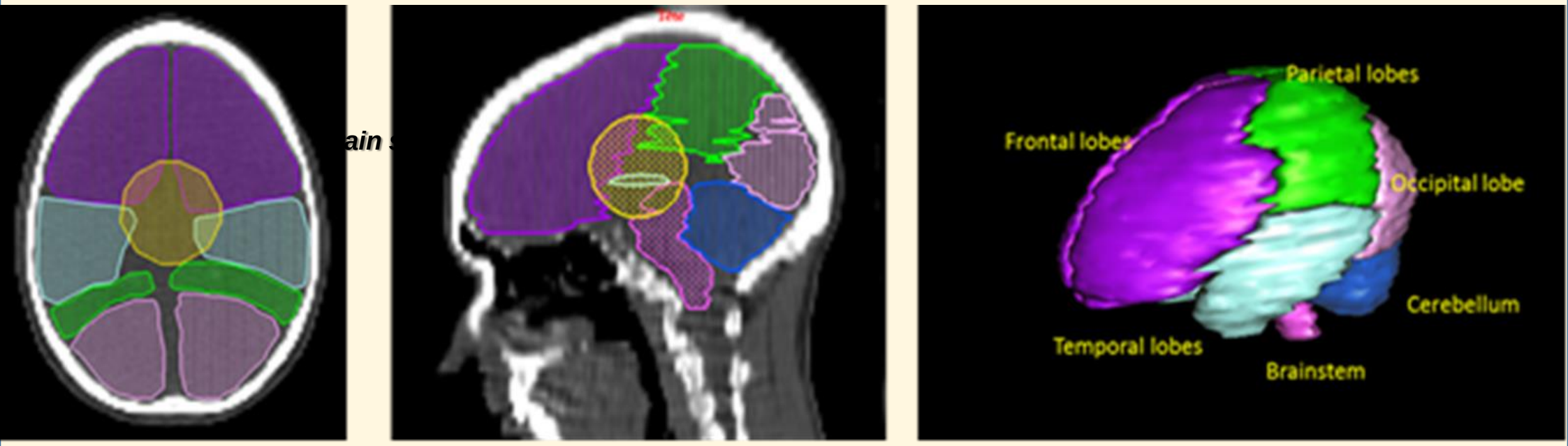


Figure 1-1 3D representation of the voxels available at brain level for the calculation of the brain sub- structures doses distributions in the case of a 17 years aged male patient

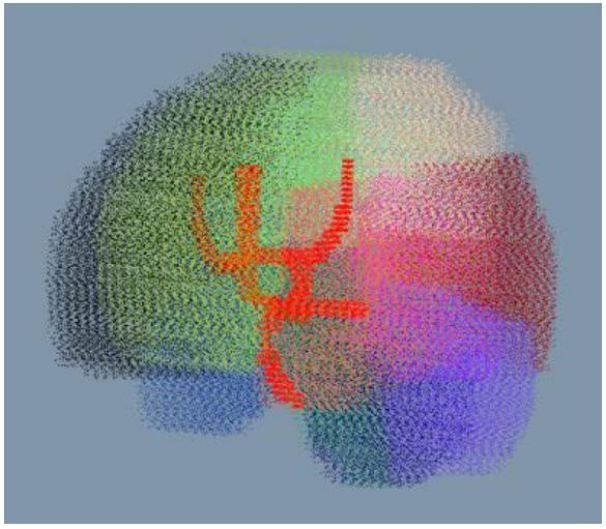


Table 1-3 - Frequency distribution of number of voxels by cerebral sub-region in a 17 years aged male patient.

BRAIN SUB-STRUCTRURE	Number of voxels	BRAIN SUB-STRUCTRURE	Number of voxels
ANTERIOR CEREBRAL ARTERY LEFT	191	MENINGE PARIETAL AREA RIGHT	615
ANTERIOR CEREBRALARTERY RIGHT	196	MENINGE TEMPORAL AREA LEFT	1 252
ANTERIOR COMMUNICATING ARTERY	40	MENINGE TEMPORAL AREA RIGHT	1 125
BASILAR ARTERY	177	MIDDLE CEREBRAL ARTERY LEFT	146
BRAINSTAIN	9 502	MIDDLE CEREBRAL ARTERY RIGHT	146
CEREBELLUM LEFT	17 048	OCCIPITAL LOBE LEFT	15 715
CEREBELLUM RIGHT	14 066	OCCIPITAL LOBE RIGHT	16 616
FRONTAL LOBE LEFT	37 571	PARIETAL LOBE LEFT	20 609
FRONTAL LOBE RIGHT	35 262	PARIETAL LOBE RIGHT	18 534
HYPOPHYSIS	148	POSTERIOR CEREBRAL ARTERY LEFT	135
HYPOTHALAMUS	432	POSTERIOR CEREBRAL ARTERY RIGHT	142
INTERNAL CAROTID ARTERY LEFT	10	POSTERIOR COMUNICATING ARTERY LEFT	98
INTERNAL CAROTID ARTERY RIGHT	17	POSTERIOR COMUNICATING ARTERY RIGHT	96
MENINGE FRONTAL AREA LEFT	1 710	TEMPORAL LOBE LEFT	25 771
MENINGE FRONTAL AREA RIGHT	1 867	TEMPORAL LOBE RIGHT	23 737
MENINGE OCCIPITAL AREA LEFT	749	THALAMUS LEFT	671
MENINGE OCCIPITAL AREA RIGHT	723	THALAMUS RIGHT	727
MENINGE PARIETAL AREA LEFT	689	TOTAL NUMBER OF VOXELS FOR THE WHOLE BRAIN	246 533

All strokes
Comparison between average radiation dose and dose volume approachs

	Average radiation dose to the cerebral arteries	% of volume of cerebral arteries having received
	OR (95%CI)	OR (95%CI)
0 (no Rt)	1 (reference)	1 (reference)
< 1 Gy	1.7 (0.8-3.6)	1.7 (0.8-3.5)
1 – 4.99 Gy	4.6 (1.8-11.7)	9.7 (2.5-38.2)
5 -19.99 Gy	6.5 (3.1-13.3)	4.2 (1.2-15.2)
20 -39.99 Gy	14.5 (6.7-31.4)	15.9 (4.7-47.4)
40 or + Gy	43.9 (7.3-263)	55.3 (11.5-264)

Protons are not magic bullets

- IJROBP Nov 2017 ;St Kralik

- 6,7% (5/75) children treated for brain tumors with protons had **large** vessels radio induced vasculopathy
- 4/5 major strokes
- mean : 1,5 y after ttt.
- Age and dose not of pronostic significance

Pernin et al., J
Leuk 2014, 2:4

Can we Reduce the Toxicity of the Mediastinal Irradiation Using New Highly Conformal Techniques?

Victor Pernin, Sofia Zefkili, Dominique Peurien, Alain Fourquet and Youlia M Kirova*
Department of Radiation Oncology, Institute Curie, Paris, France

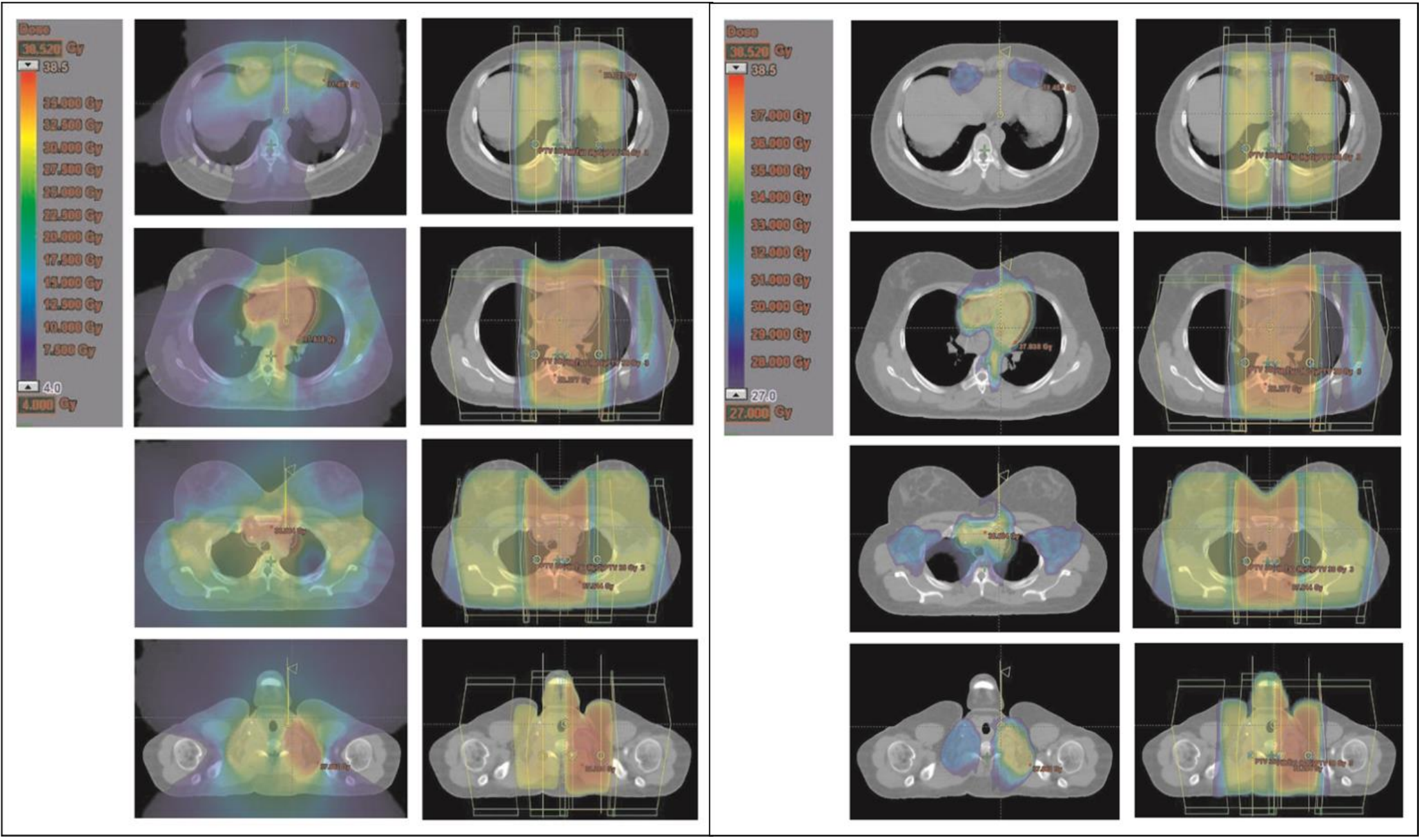
Abstract

Objectives: Three-Dimensional Conformal Radiotherapy (3DCRT) has been successfully used to treat Hodgkin's Lymphoma (HL) but treatment delivery is often complex and requires large fields that may result in significant exposure of normal tissues to ionizing radiation. The present study was undertaken to compare the dosimetry of Involved Field (IF) 3DCRT to HT in female patients treated for HL.

Materials/Methods: A total of 10 young female patients affected with early stage mediastinal HL and treated with IF radiotherapy after chemotherapy were selected from our database. For each patient, 3DCRT and HT plans were designed to deliver 30 Gy to the target volume and 36 Gy in case of residual masses. HT planning solutions were optimized by inverse planning with specific dose-volume constraints on OAR (breasts, lungs, heart). Dose-Volume Histograms (DVHs) were calculated and then compared, both for target and OAR by a statistical analysis (Wilcoxon's Test).

Results: Mean doses to the PTV were almost identical for all plans. Conformity index was better with HT and homogeneity index didn't differ. **Mean dose to the breasts were increased with HT compared to 3DCRT** (right breast: 3.28 vs 2.19, $p<0.05$; left breast: 3.76 vs 2.81, $p<0.05$) whereas no difference in mean doses appeared for heart, coronary arteries, lungs, thyroid and normal tissue. Maximal doses were reduced with HT for breasts (right breast: 19.9 vs 28.87, $p<0.05$; left breast: 24.76 vs 30.29, $p<0.05$) and spinal cord (20.87 vs 33.88, $p<0.05$). Volume exposed to high doses was smaller with HT whereas volume exposed to low doses was smaller with 3DCRT. Pronounced benefits of HT in terms of heart sparing were observed for patients with lymph nodes anterior to the heart.

Conclusions: Although high dose to organ at risk was reduced with HT, increasing low dose especially to the breasts must be taken into account for IF HT. HT may be considered for large PTV



Hodgkin disease

Isodose 4 gy : tomo/3D

Isodose 27 gy :Tomo vs 3D

Pernin et al., J Leuk 2014, 2:4

Are low dose really of concern ?

What is low dose ? Defined by the academy of science biological effect of ionizing radiation (BEIR) based of life span of Bomb A survivor except breast and thyroid (which are based on medically exposed cohort)

For epidemiologist :

- low dose is< 2gy(mainly estimated on Bomb A survivors)
- High dose is > 5gy
- Low dose given by IMRT are in fact high dose for analysis

Berrington de Gonzalez et al (IJROBP, 2012)

- **Second Cancer Radiation Dose-Response Studies**
- **Direct comparaison of ERR/GY from dose>5gy with lower acute exposure<2gy**
- **§ 28 published matched case-control studies**
- **§ 18 Childhood cancer studies**
- **§ 3400 Patients with 2nd cancers**
- **§ Matched to controls without 2nd cancer**
- **§ Individual dose reconstruction to location of**
- **2nd cancer**
- **§ Requires full radiotherapy planning record**
- **& medical physicists**

ESTRO School

Second malignancies :Adulte and child

- Probably **the dose response is linear** with no downturn in risk when the dose increase even after 60 gy except for thyroid with down turn after 20gy ; (Berrington)

- After high dose exposure (> 5gy) Excess of risk is 10 times lower than risk after low dose exposure (2 gy)) for Breast :role of fractionation and perhaps dose to the ovary done for infradiaphragmatique Rt in HD before 2000

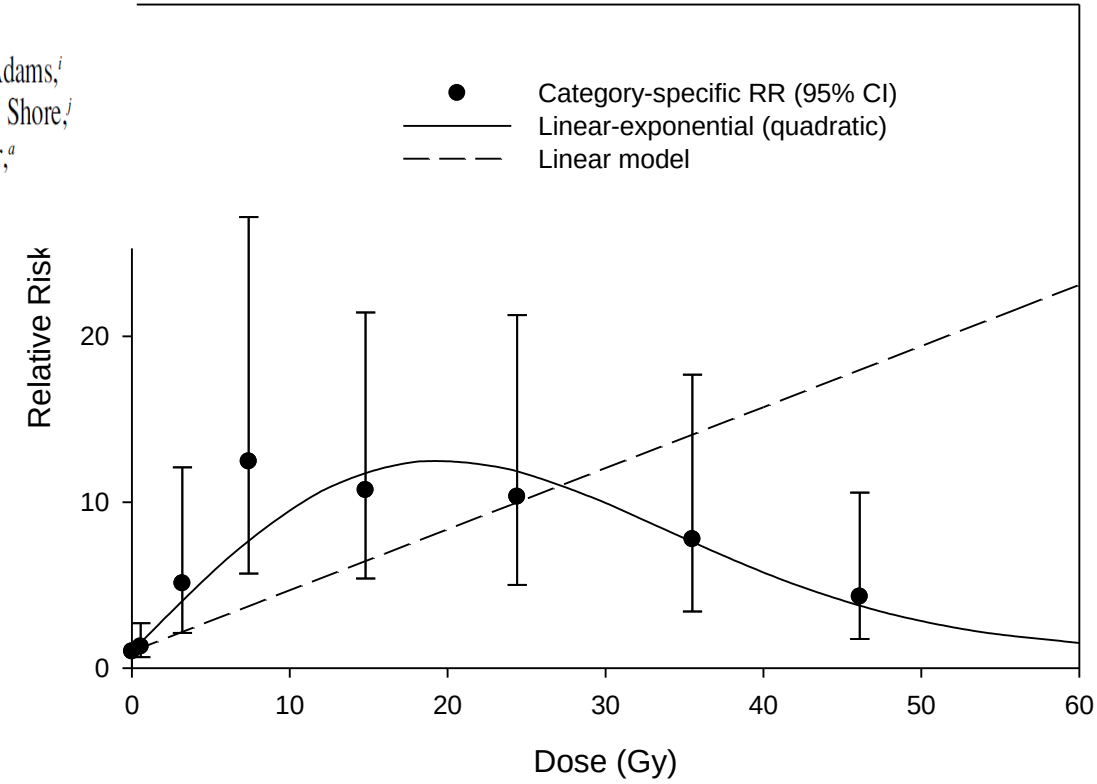
RADIATION RESEARCH 185, 000–000 (2016)
0033-7587/16 $15.00

DOI: 10.1667/RR14213.1

Thyroid Cancer after Childhood Exposure to External Radiation: An Updated Pooled Analysis of 12 Studies.

Lene H. S. Veiga,[a,c] Erik Holmberg,[d] Harald Anderson,[e,f] Linda Pottern,[g] Siegal Sadetzki,[h] M. Jacob Adams,[i] Ritsu Sakata,[j] Arthur B. Schneider,[k] Peter Inskip,[a] Parveen Bhatti,[l] Robert Johansson,[m] Gila Neta,[b] Roy Shore,[j] Florent de Vathaire,[n] Lena Damber,[m] Ruth Kleinerman,[a], Michael M. Hawkins,[o] Margaret Tucker,[a] Marie Lundell[p] and Jay H. Lubin[a,1]

Pooled fitted dose-response



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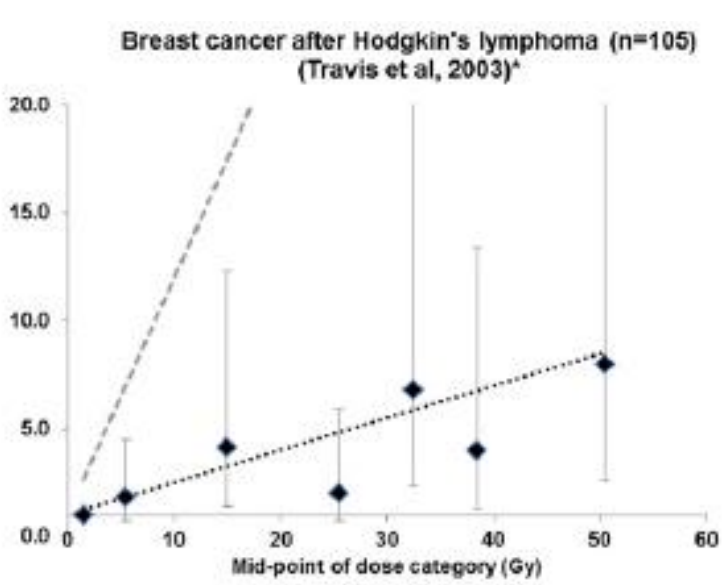
Brain :

ERR/gy higher for meningiomas (10*/glioma)

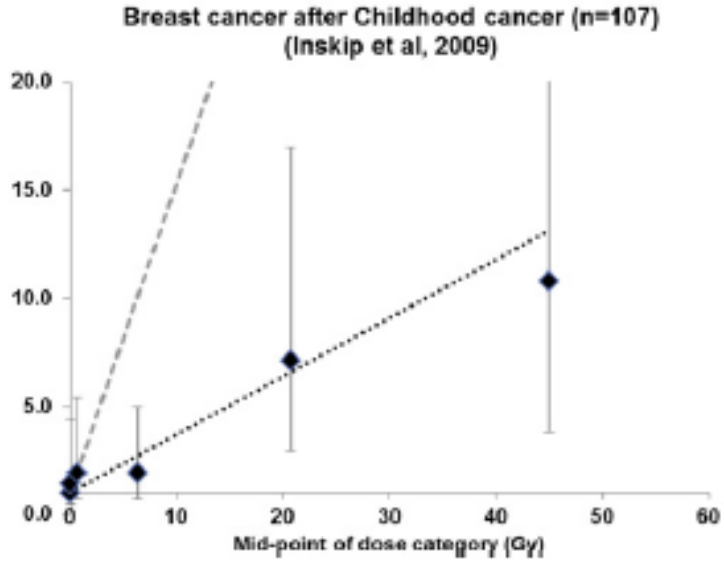
Breast Cancer :

- The ERR/Gy varied from 0,13 to 0,27 : that mean 5 to 16 fold lower than after Bomb A

Second Breast Cancer After Childhood Radiotherapy:– Linear dose-response



ERR/Gy = 0.15
Japanese A-bomb = 1.10
RaBo = 7.3



ERR/Gy = 0.27
Japanese A-bomb = 1.43
RaBo = 5.3

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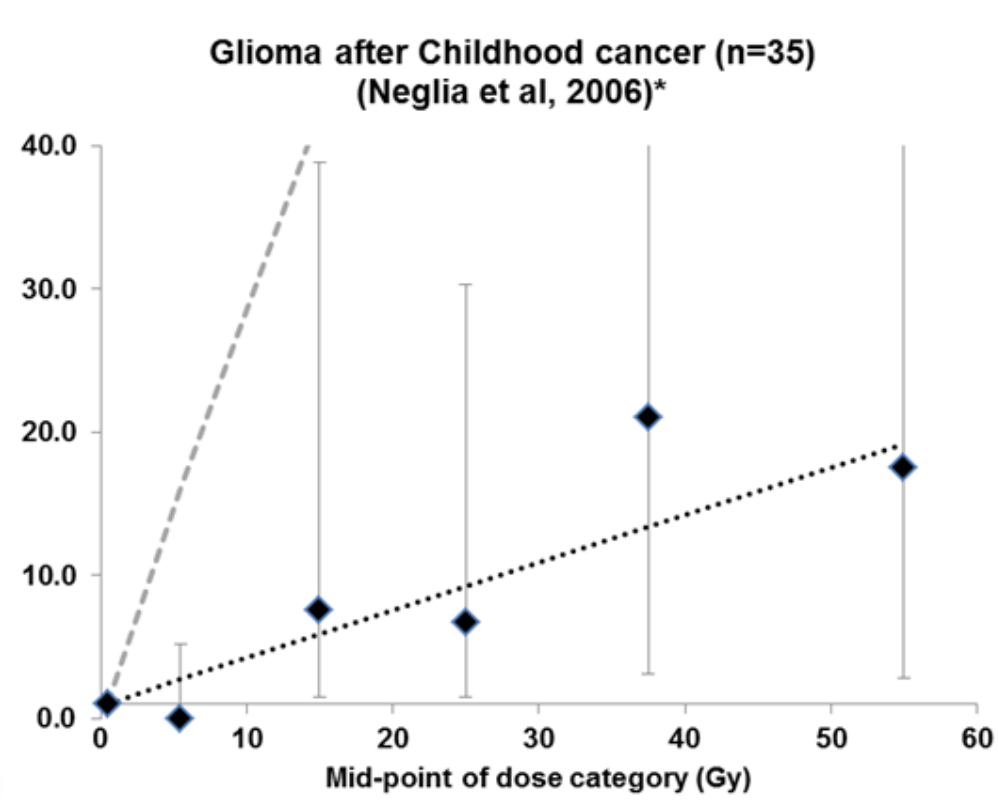
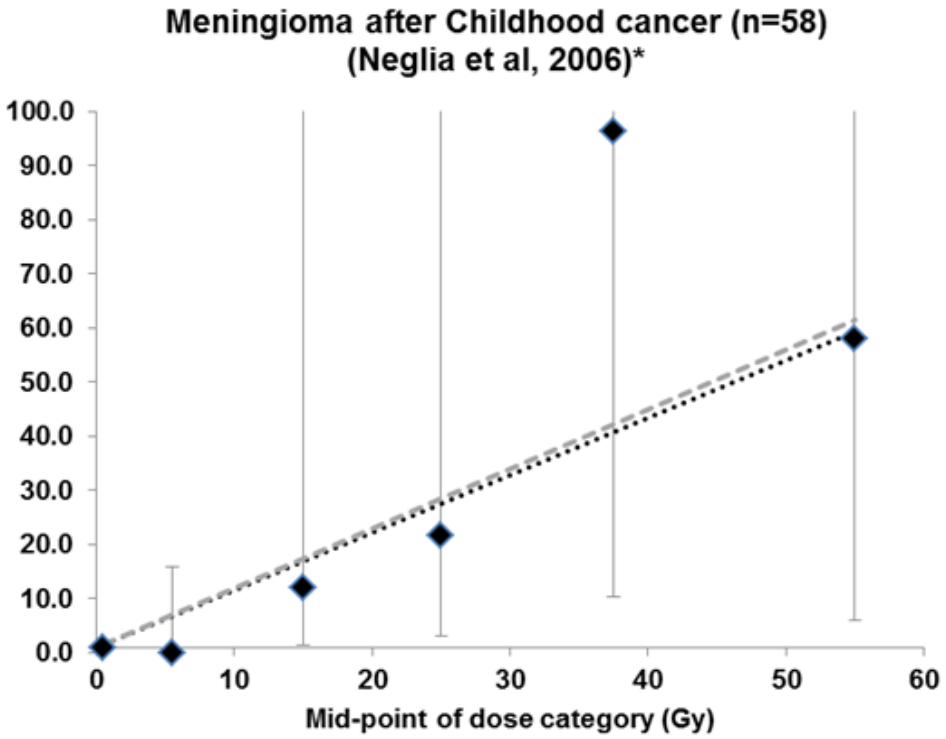
Second Brain Cancer After Childhood Radiotherapy





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Finally

No increase of Second malignancies after IMRT (-27904 cases) compare to 11124 cases treated with 3D for prostate cancer

(Journy Jama 2016)

Y TSENG :IJROBP nov 2017 .Review of SM after lymphoma : no differences according dosimetry.Potential benefit for proton

Need of FU for all children (proton or not)

Summary 1

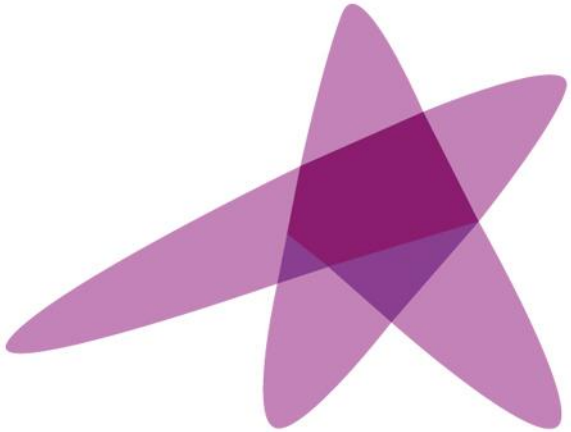
- **Second Cancer Radiation Dose-Response Studies:-**
- § **Linear dose-response**
- § **Exception thyroid cancer**
- § **Risks 5-10x lower than from acute exposure**
- § **Risks highest for youngest children**
- § **Radiation-related cancers take 10+yrs to occur**
- § **Excess risk persists throughout lifetime**
- § **Cumulative absolute risk can be high**

Summary 2

- **IMRT does not make sens**
  - Short life expectancy
  - No acute effect expected
- **IMRT is clearly of high value for**
  - Complex shape
  - High dose combined with close very critical organs : brain tumor, sarcoma
- **Must be carefully evaluated**
  - For very sensitive tumors with high cure rate
  - Large volume treated with low dose (wilms tumors ,hodgkin) because the volume receiving low dose (<2gy) become really significant

Summary 3

- IMRT is efficient to prevent severe organ dysfunction (heart, pancreas, ear, parotid etc etc) when a treshold is defined
- Low dose bath given by IMRT is not the low dose as defined by epidemiologist
- No evidence that IMRT will reduce or increase the risk of secondary cancer



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WWW.ESTRO.ORG/SCHOOL

Proton Therapy in childhood tumors (CNS)

Beate Timmermann

Essen, Germany

ESTRO School

Today‘s Topics

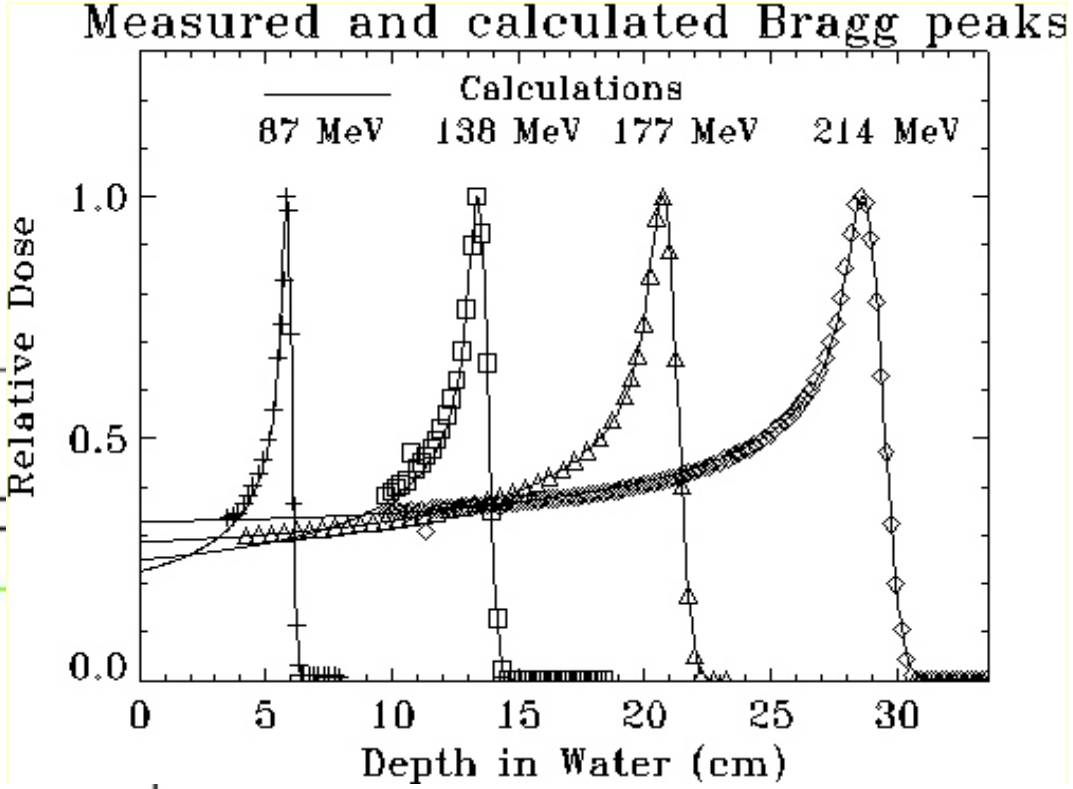
Proton Beam Therapy

- Background
- Experiences
- WPE – West German Proton Center Essen
- Retinoblastoma
- Conclusion

Proton Beam Therapy

- **Background**
- Experiences
- WPE – West German Proton Center Essen
- Restinoblastoma
- Conclusion

Proton therapy



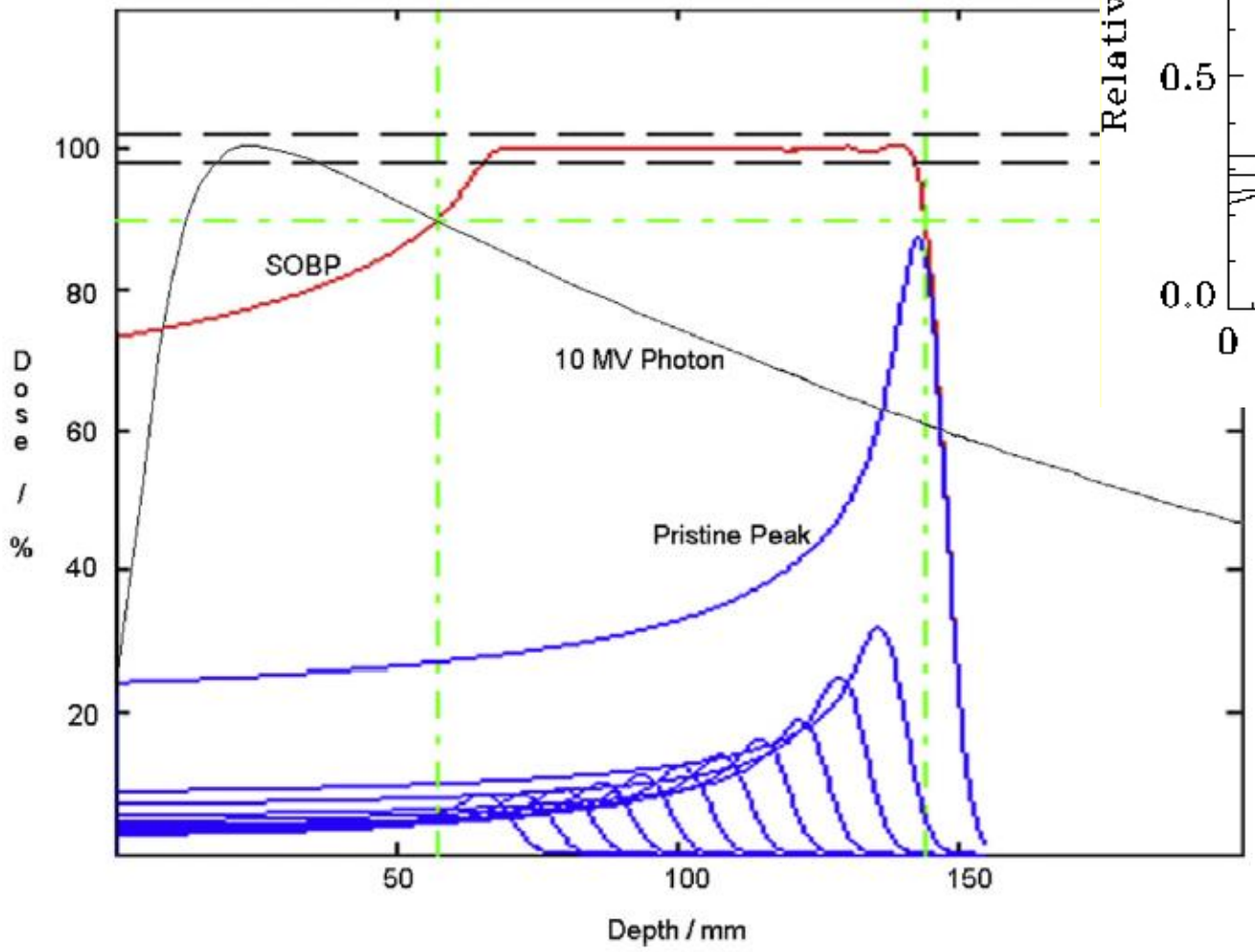


Fig. 1. Proton Bragg peaks of increasing energy and range (courtesy of Hanne Kooy, PhD, Massachusetts General Hospital, Boston, MA).

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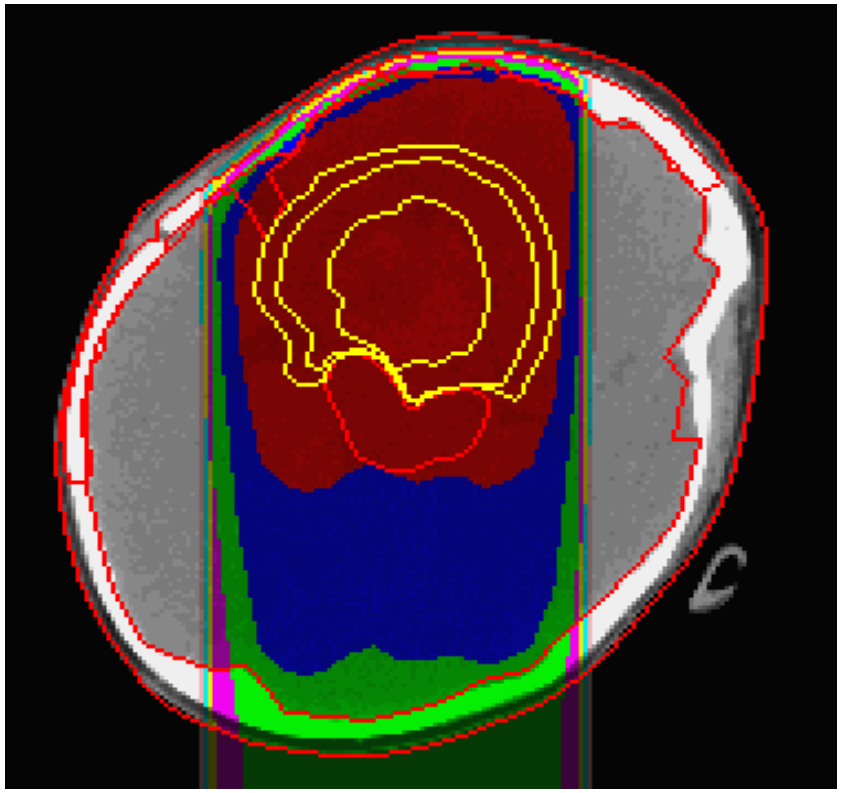
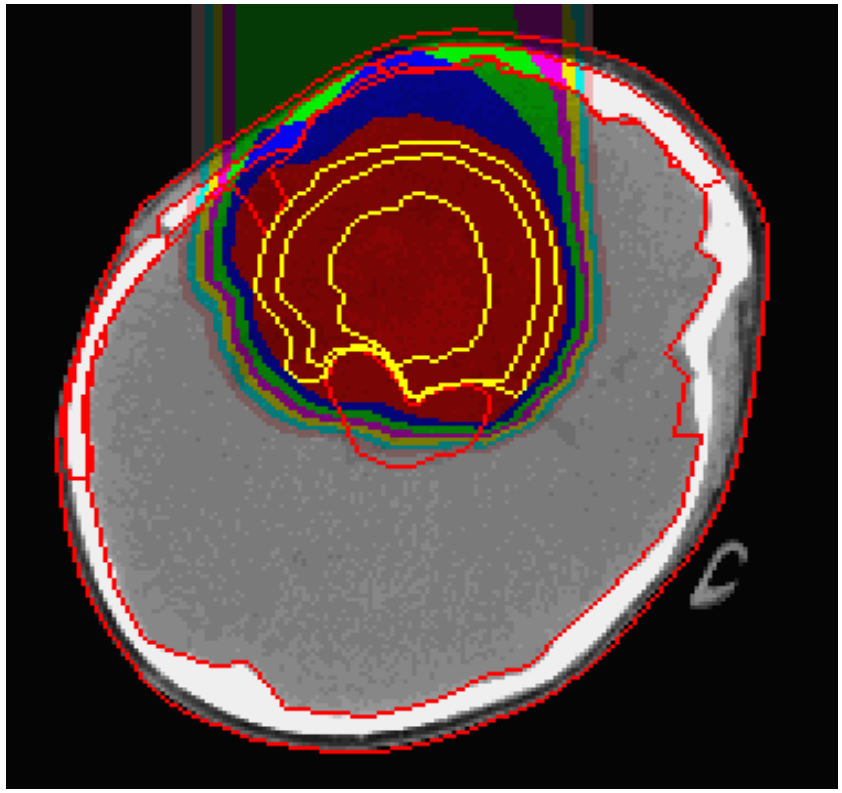
Proton therapy

XRT



Protons



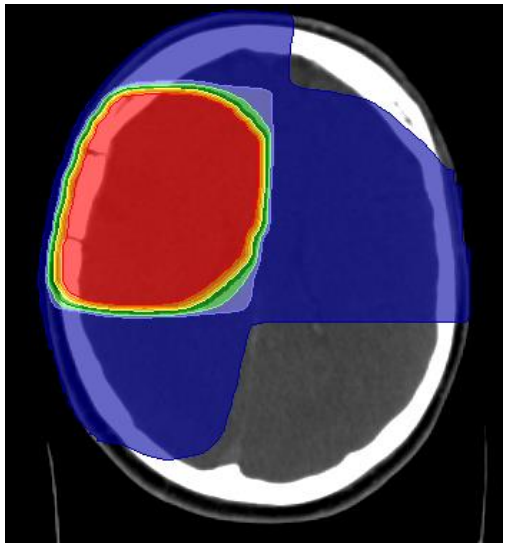
(each 1 field)

Tony Lomax, PSI

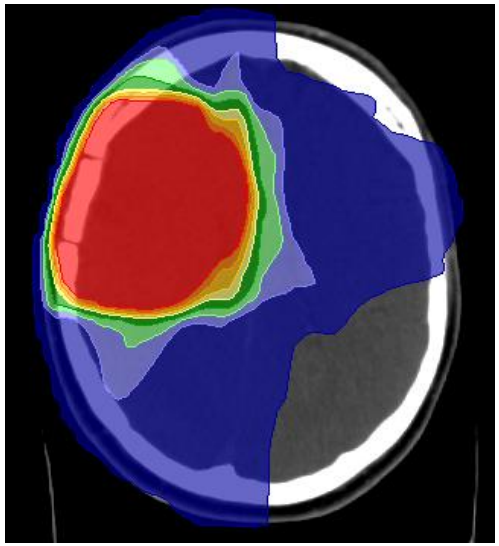
WPE Plan Comparison - Gliomas

4 plans for 8 patients with st gliomas

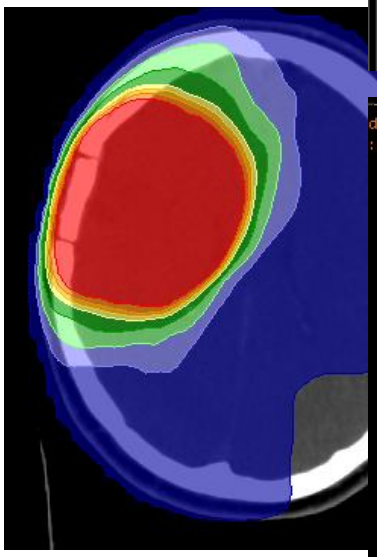
- IMPT-Plan
- 3D-conformal Plan
- IMRT-Plan
- RayArc-Plan



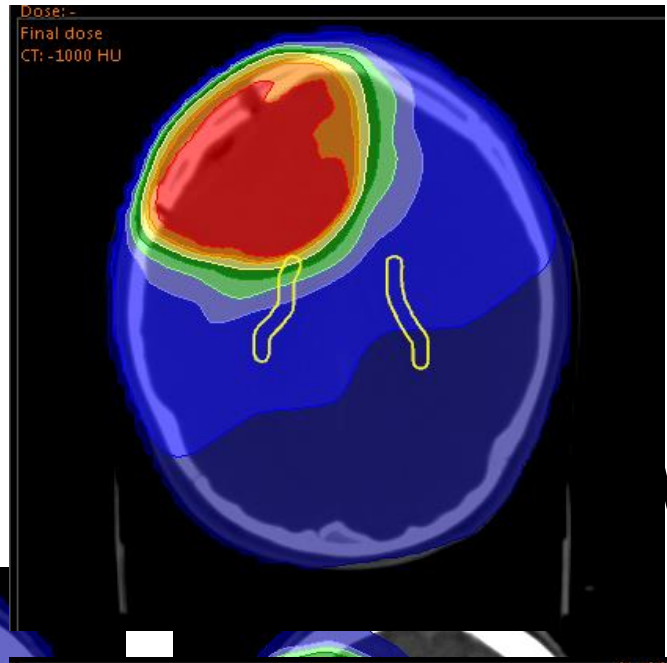
3-D

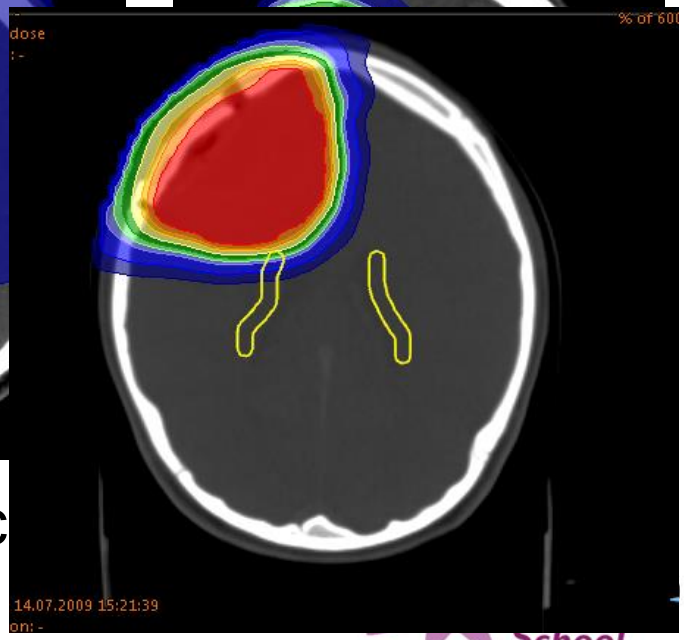


IMRT



RayArc





Merchant et al. 2008

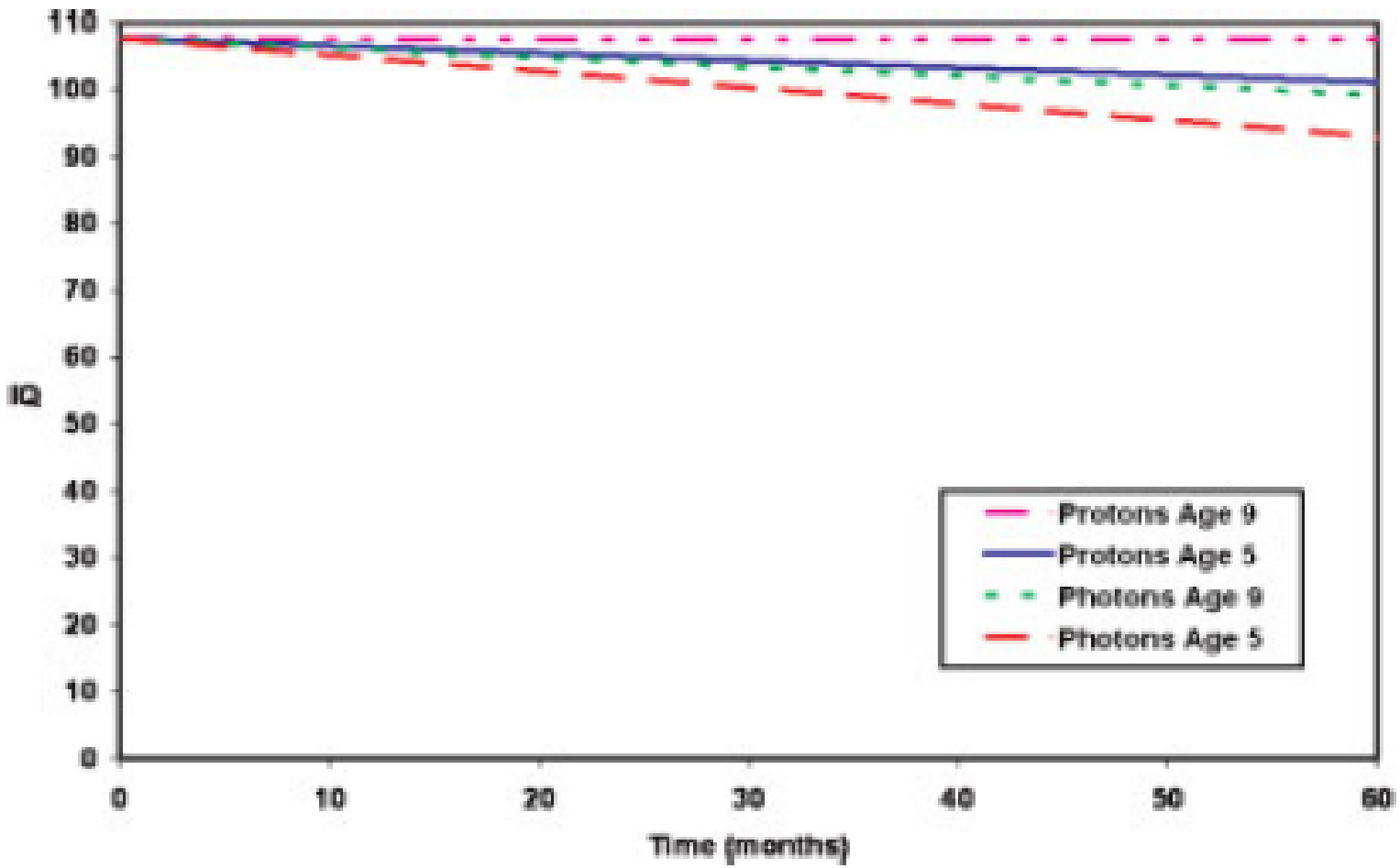


Fig. 5. Estimated IQ for patients ages 5 and 9 with craniopharyngioma planned for treatment with scanning proton beam therapy and conformal photon radiation therapy. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Pediatr Blood Cancer DOI 10.1002/pbc

Fig. 2.
line) do
availabl

Principle of Benefit

From first principles, it would follow that the largest benefit for protons will be in the youngest patients (at risk for late RT effects for the longest period of time) with potentially curative (either localised or oligometastatic) tumours, requiring RT to large target volumes (where a larger normal tissue volume would be spared exit dose) or to a large proportion of a critical organ (i.e. eye, liver, and spinal cord) to high RT doses.

T. Delaney & R. Haas, 2016

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PT and SMN

Lower integral dose with protons could also reduce the risk of RT associated secondary malignancies.

- *Chung et al. 2013*:

compared 558 proton patients with 558 matched patients (mainly adults), med. FU 6.7. and 6.0 years. **On multi-variable analysis, PRT was associated with a decreased risk of SMN** [adjusted hazard ratio, 0.52, $p = 0.009$]

- *Sethi et al. 2014:*

SMN among patients treated PT or XRT for RB, med. FU 6.9 for PT/ 13.1 years for XRT, the 10-year cumulative incidence of **RT-induced SMN was significantly less among the proton cohort** (0 vs. 14%, p = 0.015)

ESTRO School

Front Oncol. 2015; 5: 261.
Published online 2015 Nov 26. doi: 10.3389/fonc.2015.00261
PMCID: PMC4

Secondary Malignancy Risk Following Proton Radiation Therapy

Bree R. Eaton,[1,†*] Shannon M. MacDonald,[1] Torunn I. Yock,[1] and Nancy J. Tarbell[1]

Table 1

Secondary malignancy outcome data in pediatric patients treated with proton radiotherapy.

Reference	Diagnosis	*N*	Follow-up median (range)	Secondary solid tumor incidence (%)
Yock et al. (31)	Medulloblastoma	59	7 years (3.9–10.3)	0
Greenberger et al. (35)	Low-grade glioma	32	7.6 years (3.2–18.2)	0
Sethi et al. (33)	Retinoblastoma	55	6.9 years (1.0–24.4)	5[a]
MacDonald et al. (34)	Ependymoma	70	3.8 years (1–11.7)	0
Ladra et al. (37)	Rhabdomyosarcoma	57	3.9 years (1.2–8.5)	0
Rombi et al. (36)	Ewings sarcoma	30	3.2 years (1.5–7.4)	0[b]

[a]*One patient with bilateral retinoblastoma developed a non-metastatic osteosarcoma of the femur.*

[b]*Four patients developed secondary hematologic malignancies.*

- **Modelling studies**:

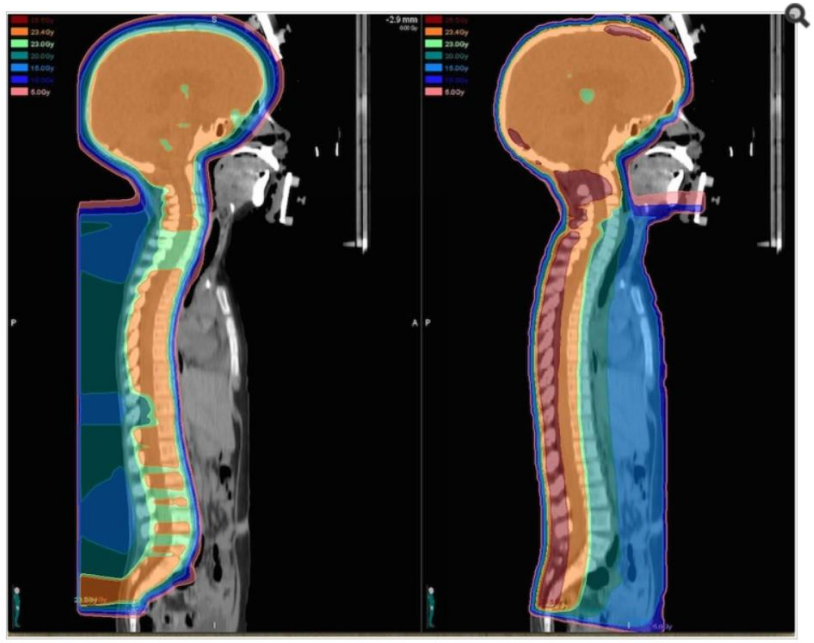
suggest a significant reduction in the risk of SMN.

For a paediatric patient with an orbital RMS by a factor of 2 *[Miralbell 2002, Paganetti 2012, Taddei 2015]*.

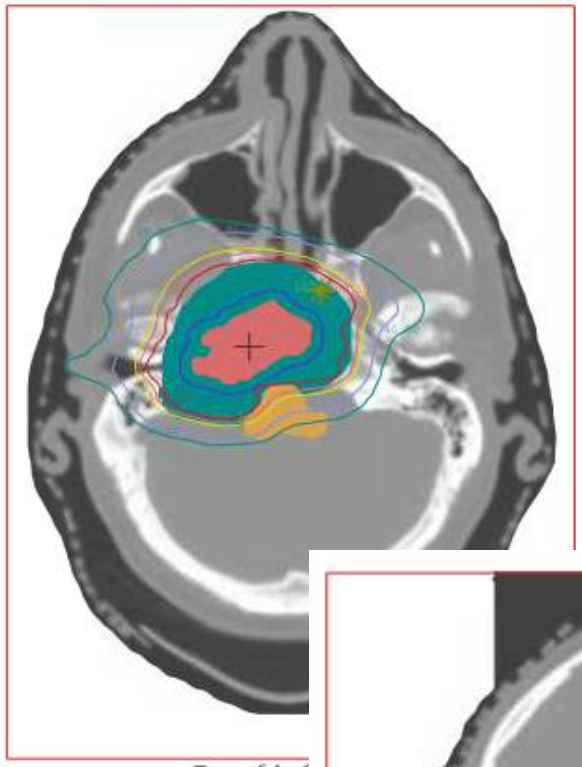
and

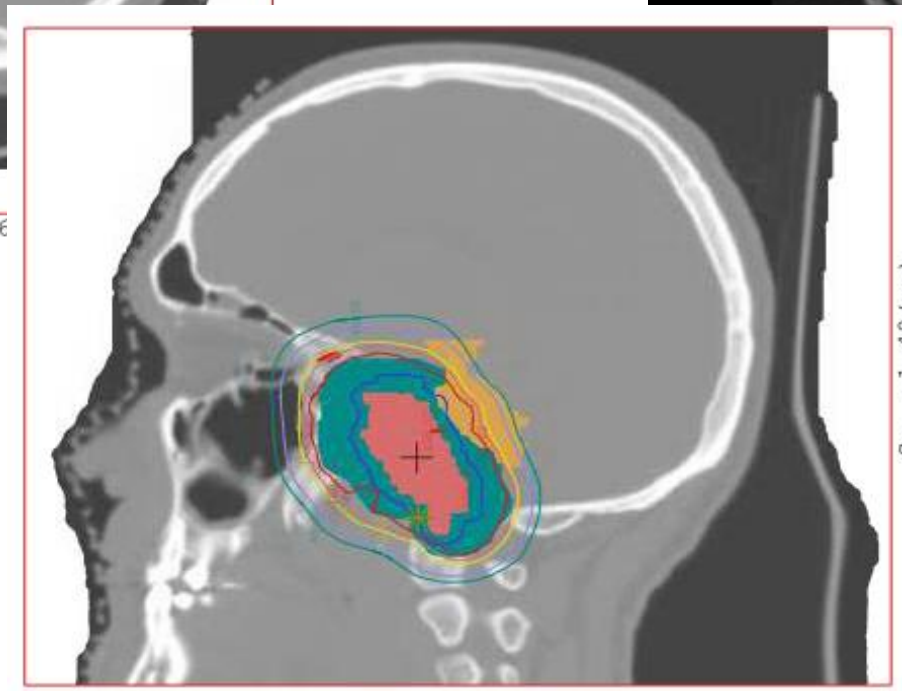
for a MB case undergoing CSI by a factor of 8-15 when compared with IMRT or XRT *[Miralbell 2001]*.

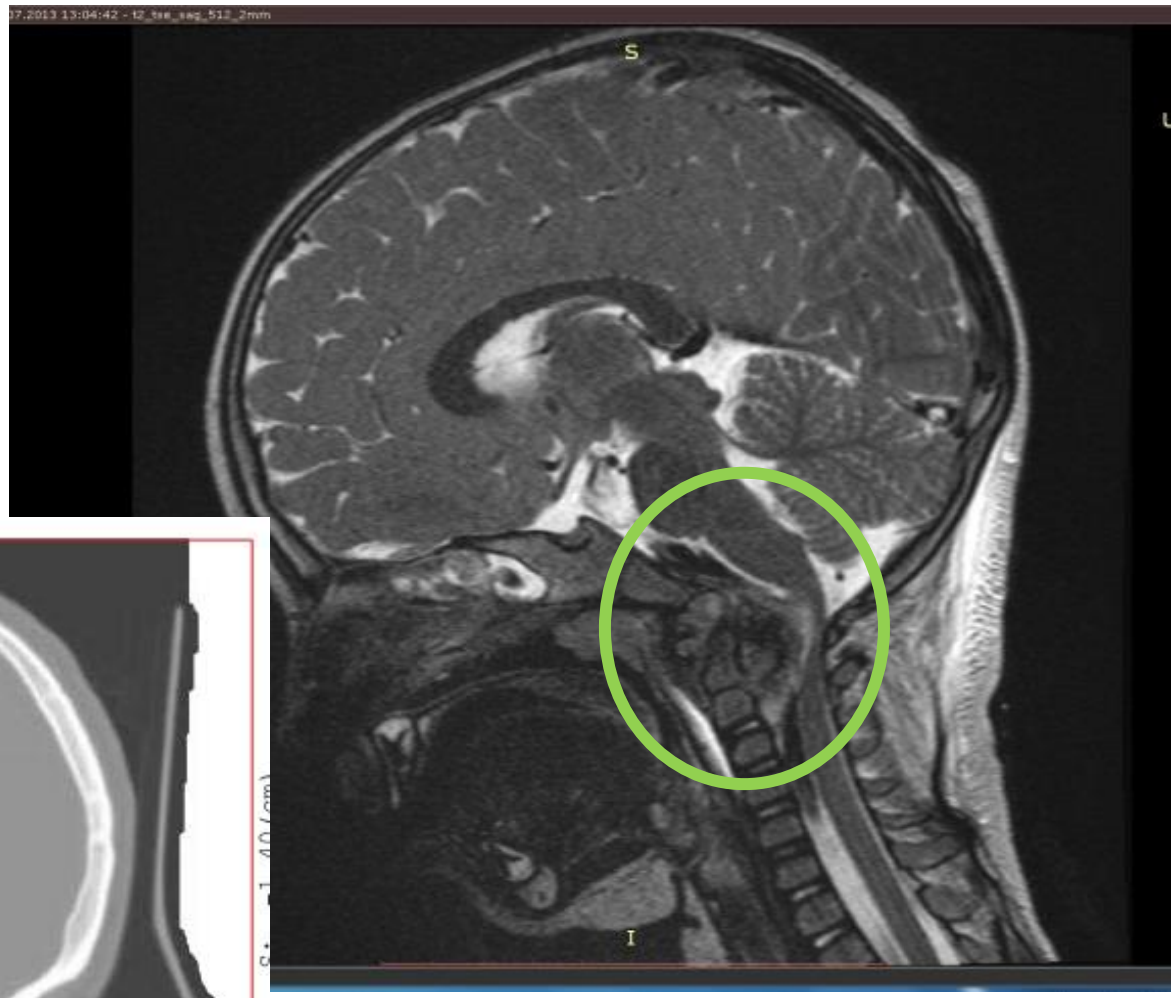
Notably, protons provided more risk reduction for larger than smaller RT volumes.



Fist PT-experiences: Chordomas of the base of skull







PT
74 CGE

PT - Chordomas / Chondrosarcomas

Table 1. Treatment results and late toxicity rates after radiotherapy (RT) of chordomas (CH) and chondrosarcomas (CS). FSRT: fractionated stereotactic radiotherapy; n.i.: no information provided; TL injury: temporal lobe injury.

Tabelle 1. Therapieergebnisse und Spättoxizitätsraten nach Strahlentherapie (RT) von Chordomen (CH) und Chondrosarkomen (CS). FSRT: frak tionierte stereotaktische Strahlentherapie; n.i.: keine Informationen vorliegend; TL injury: Temporallappenläsion.

Author, year	Patients (n)	RT modality	Tumor dose (GyE)	Local control	Late toxicity rate grade 3–4
Catton et al., 1996 [4]	48	Photons	50 (median)	23%/3 y (CH)	n.i.
Romero et al., 1993 [34]	18	Photons	50.1 (mean)	17%/5 y (CH)	n.i.
Debus et al., 2000 [8]	45	Photon (FSRT)	66.6 (median, CH) 64.9 (median, CS)	50%/5 y (CH) 100%/5 y (CS)	2.2%
Munzenrider & Liebsch, 1999 [27]	519	Protons + photons Protons + photons	66–83	73%/5 y (CH 98%/5 y (CS)	13% TL injury 4.4% optic neuropathy
Hug et al., 1999 [14]	58	Protons	70.7 (mean)	79%/5 y (CH) 100%/5 y (CS)	7%
Noel et al., 2001 [30]	45	Protons + photons	67 (median)	83%/3 y (CH) 90%/3 y (CS)	4.4%
Benk et al., 1995 [1]	18	Protons + photons	69 (median)	63%/5 y (CH)	5.5% TL injury
Castro et al., 1994 [3]	223	Helium ions	65 (median)	63%/5 y (CH) 78%/5 y (CS)	20%
Present series	67	Carbon ions	60 (median)	87%/3 y (CH) 100%/3 y (CS)	5.9% TL injury 1.4% optic neuropathy

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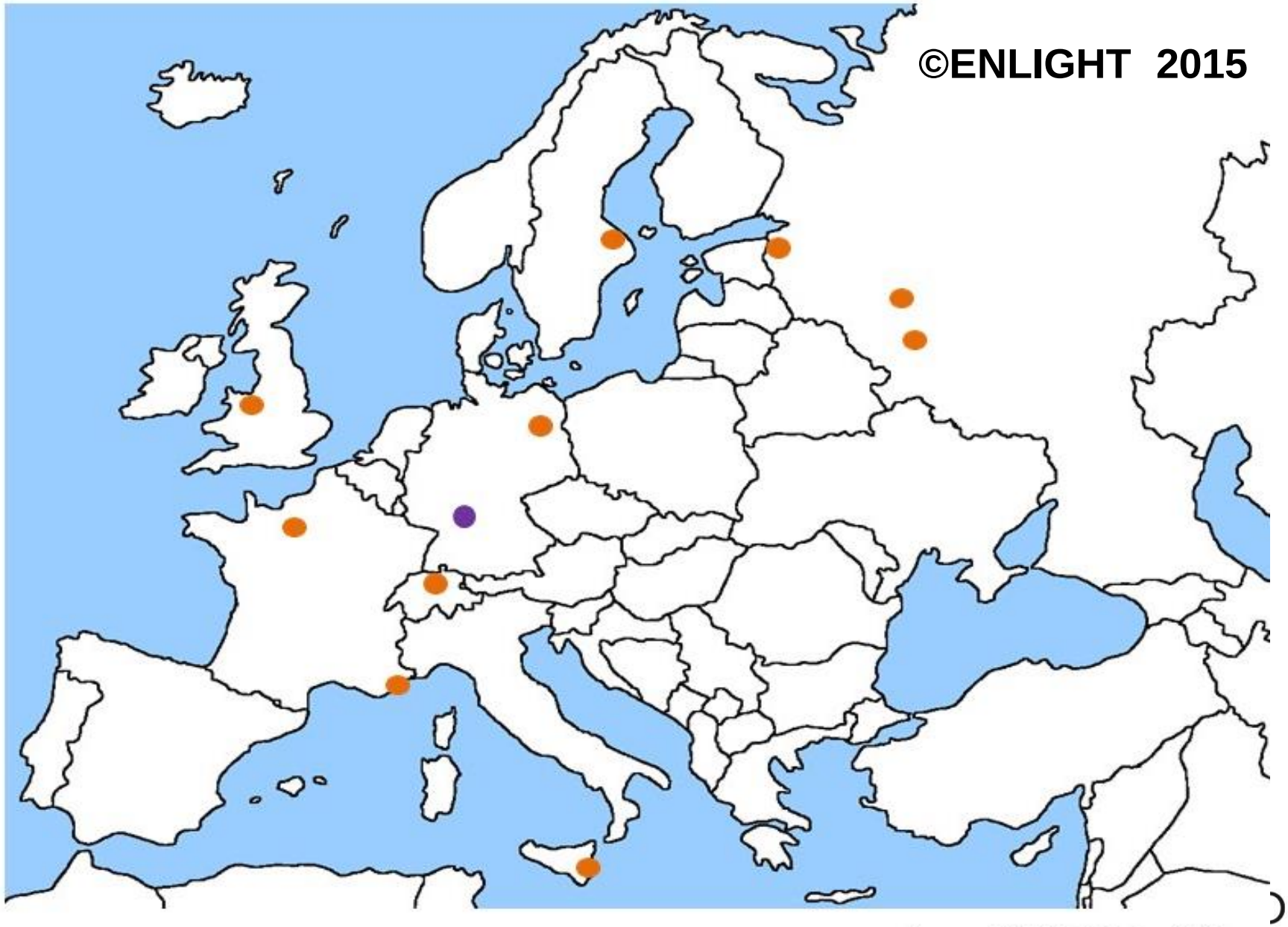
Particle Therapy Centres in Europe - 2002

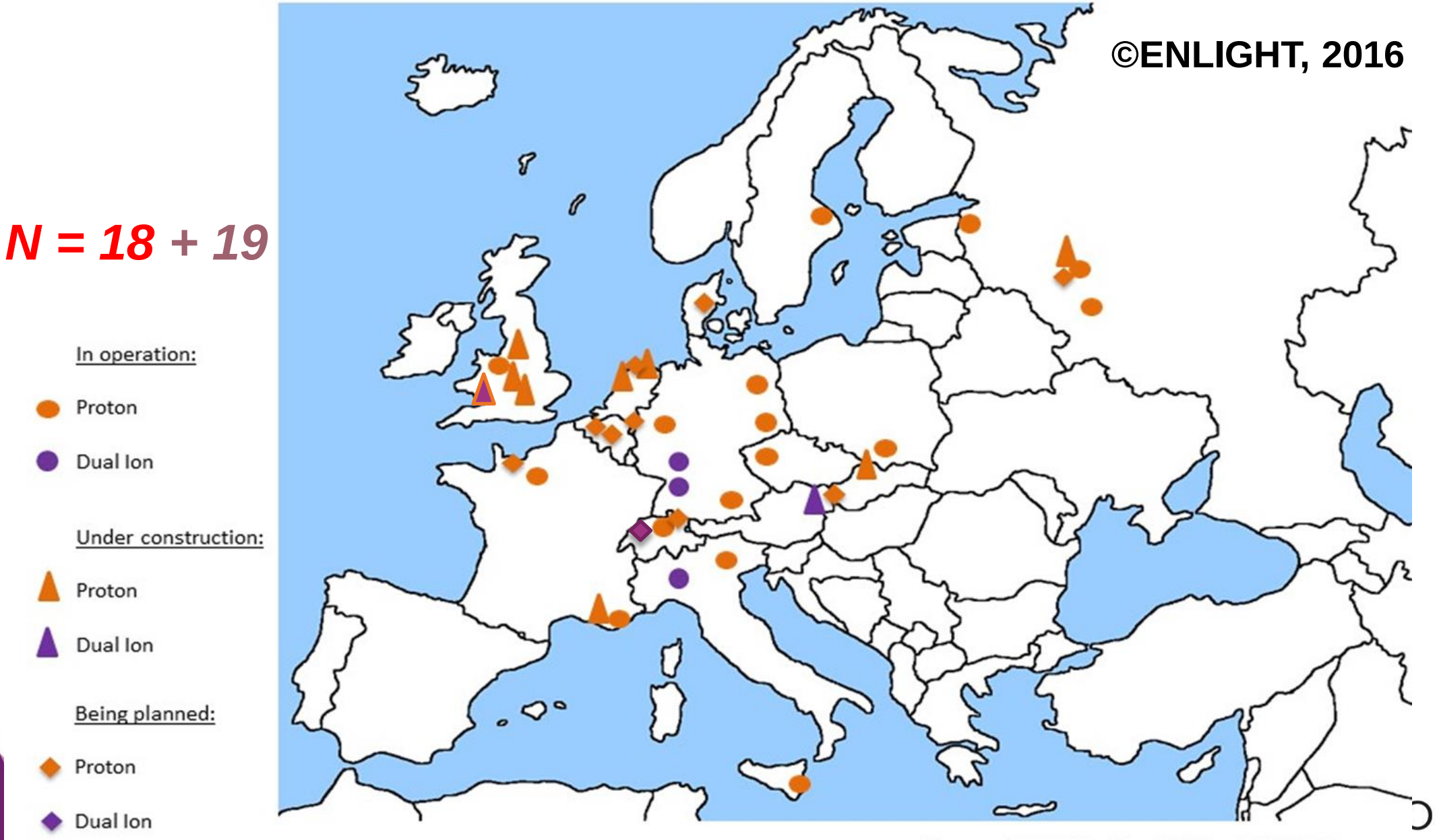
N = 11



Source: PTCOG, October 2015

Particle Therapy Centres in Europe - 2016

N = 18 + 19



PT facilities in EU

• **D:**	**RPTC/München**	(Protons, + Eyes)
	HIT/Heidelberg	(Carbons, Protons)
	WPE/Essen	(Protons, + Eyes)
	Dresden	(Protons)
	Marburg	(Carbons, Protons)
	HMI/Berlin	(P-Eyes)
• **CH:**	**PSI/Villigen**	(Protons)
• **UK:**	**Clatterbridge**	(P-Eyes)
• **A:**	**Vienna Neustadt**	(Protons, Carbons)
• **F:**	**Nice**	(P-Eyes, Protons)
	CPO/Orsay	(P-Eyes, Protons)
• **PL:**	**Krakow**	(P-Eyes, Protons)
• **I:**	**Catania**	(P-Eyes)
	Trento	(Protons)
	Pavia	(Carbons, Protons)
• **SE:**	**Uppsala**	(Protons)
• **CZ:**	**Prague**	(Protons)
• ***Future Projects:***	***I, PL, NL, UK, DK, BE, NO etc.***	

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Proton Beam Therapy

- Background
- **Experiences**
- WPE – West German Proton Center Essen
- Retinoblastoma
- Conclusion

by up to 3×.

Table 2. Description of Proton *versus* IMRT dosimetric re-planning comparisons on paediatric CNS patients. [Key: ASC—Astrocytoma, CRA—Craniopharyngioma, EPE—Ependymoma, LGG—Low Grade Gliomas, MED—Medulloblastoma, OGL—Optic Glioma].

Study	"*n*" of Patients	Age Range (Yr.)	Years	Radiotherapy Technique Protons	IMRT	Diagnosis	Target Dose Px	Main Findings
Bishop *et al.* [11]	52	8.9 median	1996–2012	various	various	CRA	50.4 Gy (RBE)/50.4 Gy	PBT and IMRT produced equivalent outcomes related to survival and solid and cystic disease control.
Boehling *et al.* [12]	10	5–14	2007–2009	3 fields	5–7 fields	CRA	50.4 Gy	Proton therapy resulted in significant sparing of normal tissues.
Brower *et al*								Proton therapy is an effective modality for reducing the dose deposition to non-target tissues.
Moteabbed *et*								Choosing proton therapy for paediatric patients with brain tumors is highly beneficial when considering second malignancies.
Paganetti *et a*								Proton therapy shows an overall advantage when estimating the risk for developing a second malignancy within the irradiated area.
Merchant *et a*								A reduction in the mean dose from protons would have long-term clinical advantages for children with MED, CRA and OG.
Athar *et al.* [6]	6	0.75–14	2010	6 fields	6 fields	Cranial region	54 Gy	Protons can offer the advantage of a lower integral dose compared with IMRT.
Brodin *et al.* [17]	10	4–15	2007–2009	3 fields	2 Arc fields	MED	23.4 and 36 Gy	IMPT plans, including secondary neutron dose contribution, compared favourably to the photon techniques in terms of all radiobiological risk estimates.

Findings:
- Similar chance for local control
- Significantly lower dose to non-target tissue
- Lower integral dose
- Advantage when estimating risk for SMN, even when considering neutron contribution

Cancers **2015**, *7*,

Review

Dosimeti
Outcome
or IMRT

Kris S. Armo

Park et al. Radiation Oncology (2015) 10:135
DOI 10.1186/s13014-015-0441-5

RADIATION ONCOLOGY

RESEARCH Open Access

Differential dosimetric benefit of proton beam therapy over intensity modulated radiotherapy for a variety of targets in patients with intracranial germ cell tumors

Jeonghoon Park[1†], Younghee Park[2†], Sung Uk Lee[1], Taeyoon Kim[1], Yun-Kyung Choi[1] and Joo-Young Kim[1,3*]

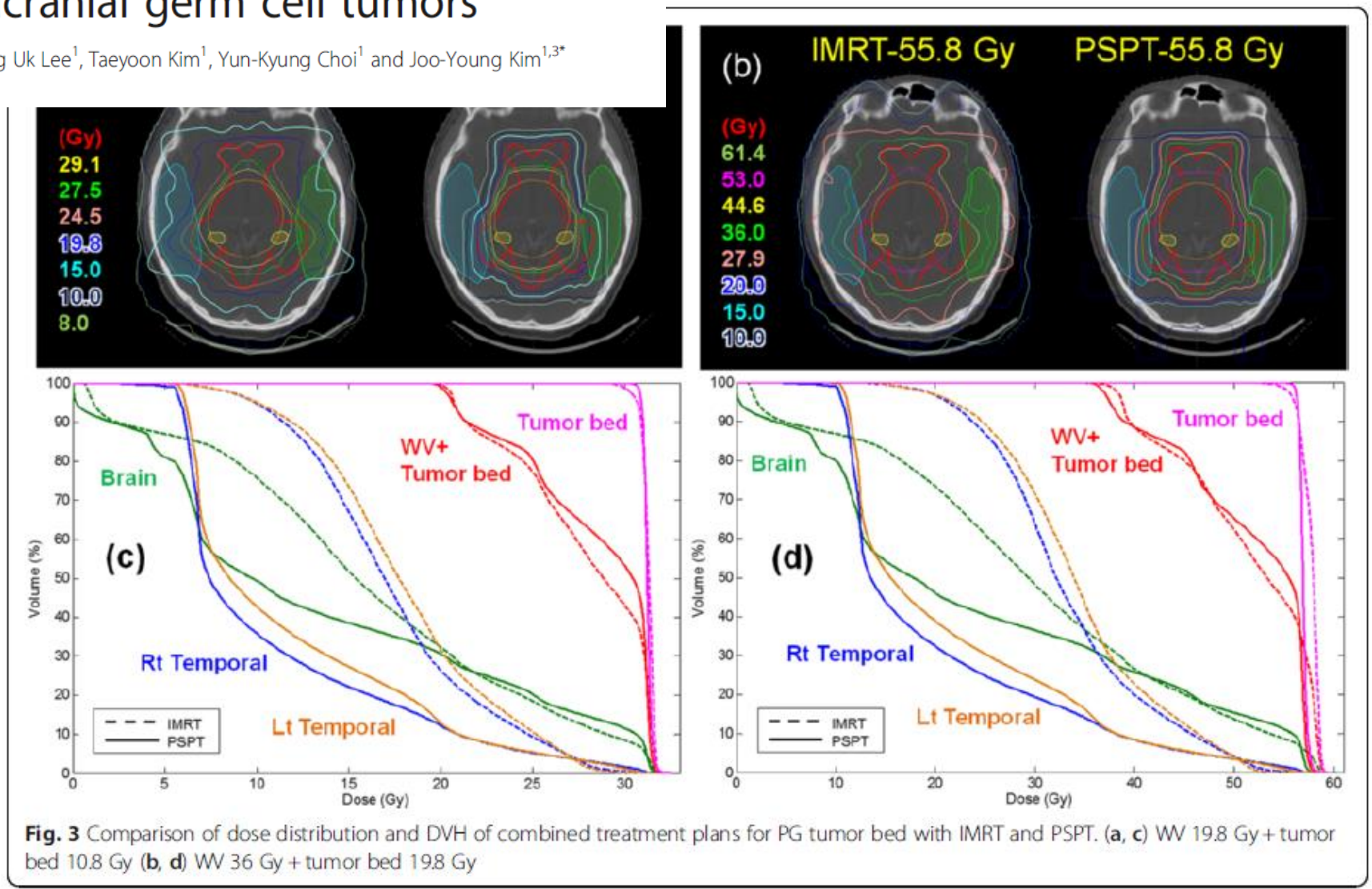

Fig. 3 Comparison of dose distribution and DVH of combined treatment plans for PG tumor bed with IMRT and PSPT. (**a**, **c**) WV 19.8 Gy + tumor bed 10.8 Gy (**b**, **d**) WV 36 Gy + tumor bed 19.8 Gy

Clinical Evidence – PT in children

September 2017

	Autor	Jahr	Diagnose	n	U in Monate	retro/pros	Diagnose	Titel
Jun 17	Antonini	2017	CNS	39	42,1	pros	Brain tumors	Attention, processing speed, and executive functioning in pediatric brain tumor survivors treated with proton beam radiation therap
Jun 17	Weber	2017	Sarcomas	38	49,6	retro	Ewing Sarcoma	Pencil beam scanned protons for the treatment of patients with Ewing sarcoma
May 17	Indelicato	2017	CNS	166	30	retro	CNS tumors	Clinical outcomes following proton therapy for children with central nervous system tumors referred overseas
May 17	Fukushima	2017	Others	32	63	pros	Cancer of the brain, head, or neck	Co-morbidity and quality of life in childhood cancer survivors treated with proton beam therapy
Mar 17	MacEwan	2017	CNS	6	162	retro	Medulloblastoma	Effects of vertebral-body-sparing proton craniospinal irradiation on the spine of young pediatric patients with medulloblastoma.
Jan 17	Park	2017	CNS	20	15	pros	IGCT (Intracranial Germ Cell Tumor)	Neurocognitive and Psychological Functioning of Children with an Intracranial Germ Cell Tumor
Dez 16	Mizumoto	2016	Others	62	97,2	retro	Different	Long-term follow-up after proton beam therapy forpediatric tumors: a Japanese national survey
	Weber							ients Treated a
	Bartelh							
	Wray							
	Mizumo							
	Leiser							rapy
	Ares							
	Yock							
	Eaton							Therapy: A Co
	Kahalle							Brain Tumors
	Rotond							ical prognostic
	Eaton							
	Mizumo							
	Weber							chemo-radiat
Okt 15	Weber							ients Treated a
	Eaton							
	Rosen							er
	Rieber							
	Pulsife							umors
	Lucas							
	Kralik							
	Gunthe							pared to Intens
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	Watts							
	Indelic							
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	Sethi							effectiveness
	Song							craniospinal ir
	McGov							system
	Ladra							ts enrolled on a
	Yock							
	Greenb							gliomas
	Bishop							l analysis of ou
	Fuji							
	Jimene							
	MacDo							
	De Am							ors
	Suneja	2013	CNS	46		retro	CNS	Acute toxicity of proton beam radiation for pediatric central nervous system malignancies
	Mizumoto	2013	CNS	26	19,4	retro		
	Rombi	2013	CH/CS	26	46	pros	Chordoma/Chondrosarkoma	Spot-scanning proton radiation therapy for pediatric chordoma and chondrosarcoma: clinical outcome of 26 patients treated at pa
	Oshiro	2013	Others	14	36	retro		
	Rombi	2012	Sarcomas	30	38,4	retro	EWING Sarcoma	Proton radiotherapy for pediatric Ewing's sarcoma: initial clinical outcomes
	Amchaush	2012	CNS	8	26	pros	Ependymoma	Proton therapy for spinal ependymomas: planning, acute toxicities, and preliminary outcomes

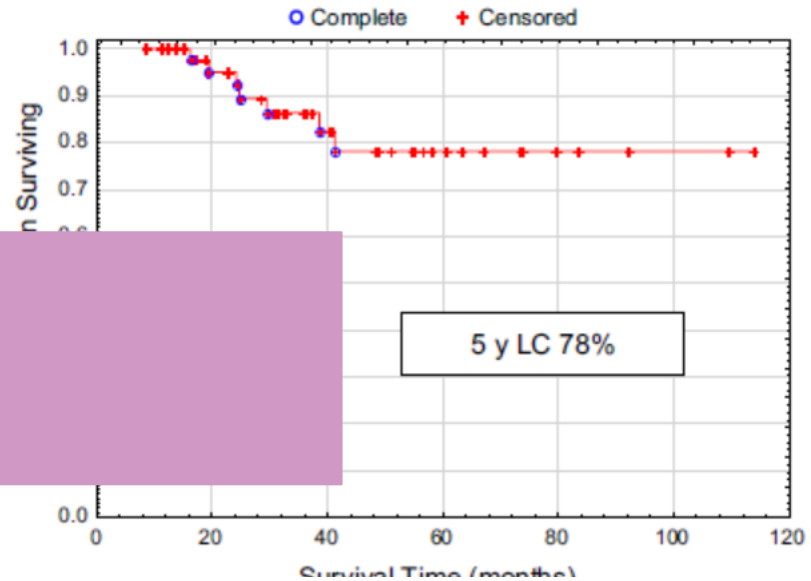
Diagnosis	reports, n	Patients, n	FUs (months)
CH/CS	7		
CNS	44		
Sarcomas	11		
Others	13		
1995-2017	75 total	3328 total	
	18 prospective	44.4 mean	41.8 mean

J Neurooncol (2016) 128:137–145
DOI 10.1007/s11060-016-2090-4

CLINICAL STUDY

Pencil beam scanning proton therapy for pediatric intracranial ependymoma

Carmen Ares[1,2] · Francesca Albertini[1] · Martina Frei-Welte[3] · Alessandra Bolsi[1] · Michael A. Grotzer[4] · Gudrun Goitein[1] · Damien C. Weber[1,5]



Findings:
- high local control
- good feasibilty

- N = 50
- Med. age 2.6 yrs. 17 x STR
- Med. dose 59.4 Gy
- Med. FU 43.4 mo
- 7 local failures, 5 dod
- 2 unilateral deafness,
  1 brainstem necrosis

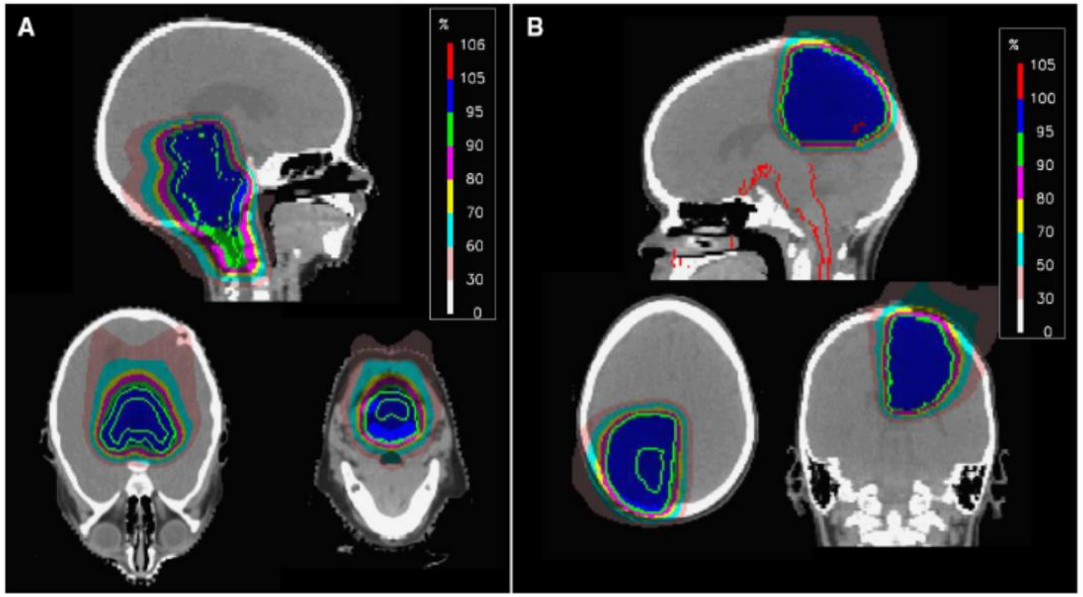
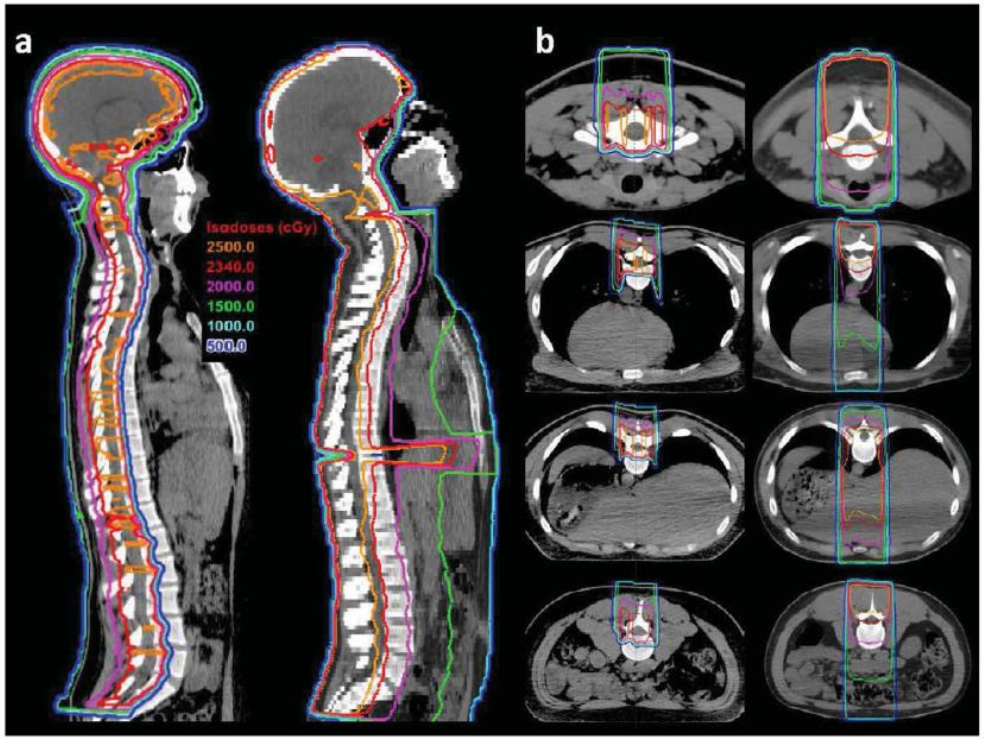


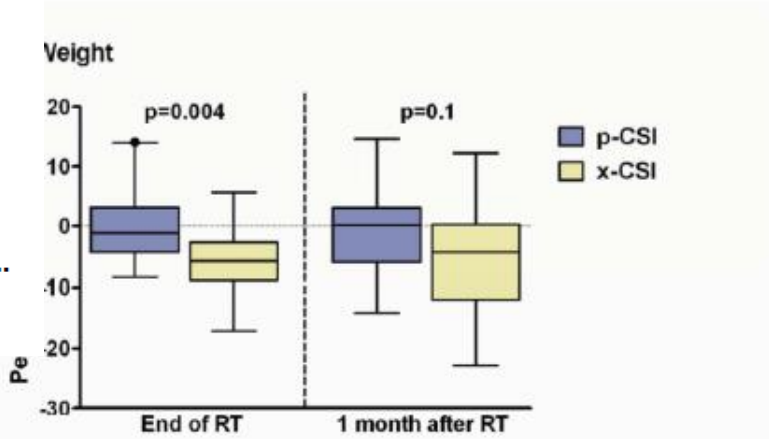
Fig. 2 Representative spot-scanning PT plan for a infratentorial and b supratentorial epemdymoma

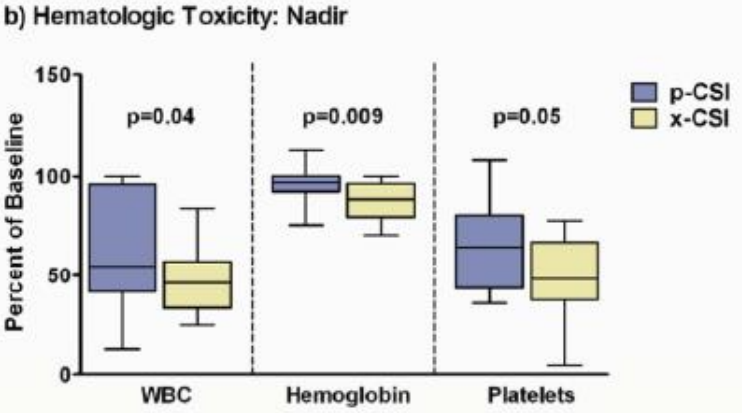
Int J Radiat Oncol Biol Phys. 2013 June 1; 86(2): 277–284. doi:10.1016/j.ijrobp.2013.01.014.

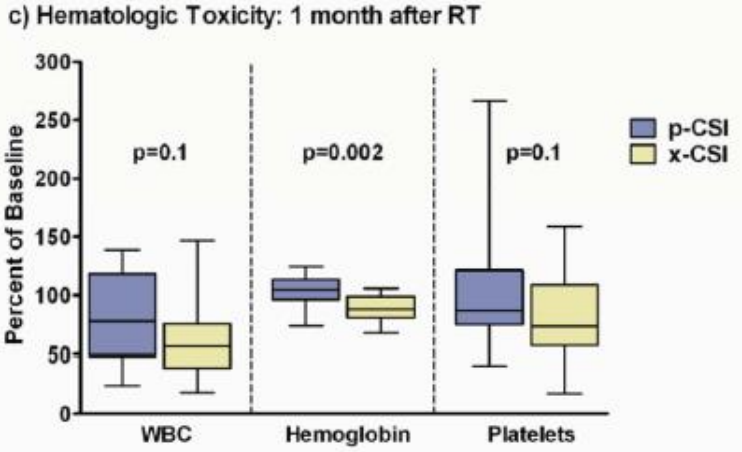
Proton Beam Craniospinal Irradiation Reduces Acute Toxicity for Adults with Medulloblastoma

Aaron P. Brown, M.D.[a], **Christian L. Barney, B.S.**[e], **David R. Grosshans, M.D., Ph.D.**[a], **Mary Frances McAleer, M.D., Ph.D.**[a], **John F. de Groot, M.D.**[b], **Vinay K. Puduvalli, M.D.**[b], **Susan L. Tucker, Ph.D.**[d], **Cody N. Crawford, C.M.D.**[a], **Meena Khan, C.M.D.**[a], **Soumen Khatua, M.D.**[c], **Mark R. Gilbert, M.D.**[b], **Paul D. Brown, M.D.**[a], and **Anita Mahajan, M.D.**[a]









Cancers **2015**, *7*, 706-722; doi:10.3390/cancers7020706

OPEN ACCESS
cancers
ISSN 2072-6694
www.mdpi.com/journal/cancers

Review

**Dosimetric Comparison and Potential for Imp
Outcomes of Paediatric CNS Patients Treated
or IMRT**

Kris S. Armoogum [1,†,*] and Nicola Thorp [2,†]

Findings:
- HRQoL better in the proton cohort (local fields, in part + CSI)
- Potential to reduce radiogenic cancer and cardiac toxicity (CSI)

Table 1. Description of Proton *versus* IMRT patient outcome studies on paediatric CNS patients. [Key: EPE—Ependymoma, LGG—Low Grade Gliomas, MED—Medulloblastoma].

Study	"*n*" of Patients	Age Range (Yr.)	Years	Radiotherapy Technique Protons	IMRT	Diagnosis	Target Dose Px	Main Findings
Yock *et al.* [9]	120 (57/63)	2–18	(Protons) 2004–2009 (Photons) 2001–2002	various	various (not all IMRT)	MED EPE LGG	50–54 Gy	Health Related Quality of Life (HRQoL) for the proton cohort was 5 points less than the healthy population, whereas the photon cohort was 15.5 points lower. Proton CSI has the potential to reduce the risk of radiogenic 2nd cancers and cardiac mortality by up to 6× and 2nd cancer mortality by up to 3×.
Zhang *et al.* [10]	17	2–18	2007–2009	3–5 fields	3–4 fields	MED	23.4 Gy (RBE)/23.4 Gy	

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Pediatric Brain tumors: Quality of Life and Protons

Yock TI et al.
Quality of life outcomes in proton and photon treated pediatric brain tumor survivors.
Radiother Oncol. 2014 Oct; 113 (1):89-94

- **57 PT vs. 63 XRT**
- **Ped. Brain tumours**
- **PedsQL Tests after 3 years**

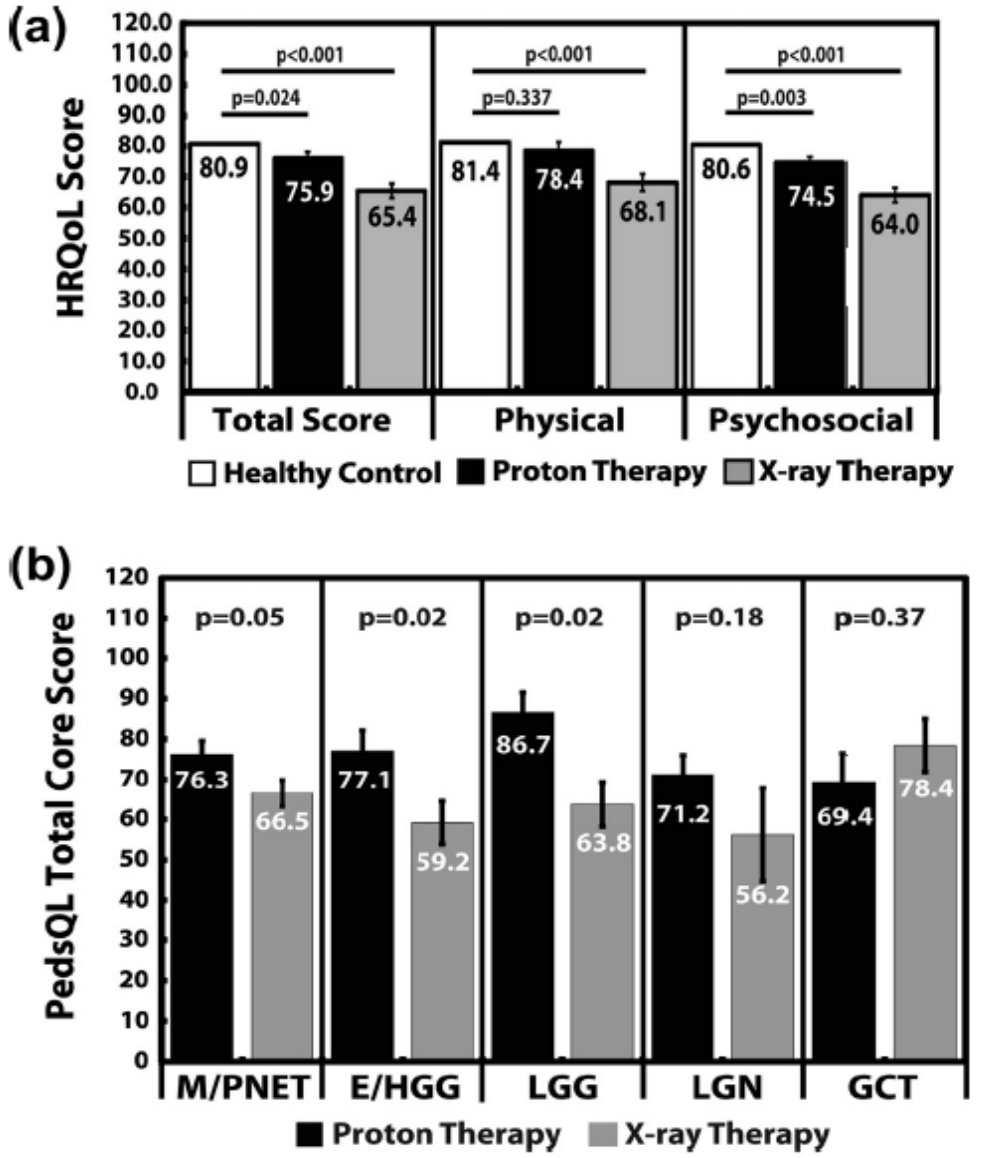

Fig. 1. (a) PedsQL scores in the proton, photon and normative cohorts. (b) Total PedsQL core scores by diagnostic group and radiation type in MGH proton and LPCH photon cohorts. The bars represent the SEM (standard error of the mean).

Clinical Investigation

Early Cognitive Outcomes Following Proton Radiation in Pediatric Patients With Brain and Central Nervous System Tumors

Margaret B. Pulsifer, PhD,* Roshan V. Sethi, MD,†
Karen A. Kuhlthau, PhD,‡ Shannon M. MacDonald, MD,†
Nancy J. Tarbell, MD,† and Torunn I. Yock, MD†

*Departments of *Psychiatry, †Radiation Oncology, and ‡Pediatrics, Massachusetts General Hospital, Boston, Massachusetts*

Received Mar 13, 2015, and in revised form May 7, 2015. Accepted for publication Jun 8, 2015.

Summary

Radiation therapy for CNS tumors is associated with negative cognitive sequelae in intelligence (IQ) and specific cognitive domains. Proton radiation therapy (PRT), which limits dose to normal tissue, could improve cognitive outcome. This study assessed 60 pediatric patients aged ≥6 years at PRT initiation and a mean of 2.5 years thereafter. No significant change was seen in IQ, Verbal Comprehension, Perceptual Reasoning, or Working Memory, but Processing Speed scores declined, especially for younger subjects.

- N=60 patients with CNS disease
- 53% partial CNS PT
- 47% full CNS/CSI PT
- Med. age 12.3 yrs
- Med. FU 2.5 yrs

Neuro-Oncology

Neuro-Oncology 18(6), 881–887, 2016
doi:10.1093/neuonc/nov302
Advance Access date 19 December 2015

Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma

Bree R. Eaton, Natia Esiashvili, Sungjin Kim, Briana Patterson, Elizabeth A. Weyman, Lauren T. Thornton, Claire Mazewski, Tobey J. MacDonald, David Ebb, Shannon M. MacDonald, Nancy J. Tarbell, and Torunn I. Yock

- All CSI pts., +CTX
- PT (40) and XRT (37)
- Med. age; 6.2/8.3 yrs
- Endocrine screening
- Med FU; 5.8/7.0 yrs

ıe outcomes according to

Outcome	Model	PRT vs XRT Odds Ratio (95% CI) or Parameter Estimate (95% CI)	*P*
Hypothyroidism	PS adjusted	0.13 (0.04–0.42)	<.001
	IPTW	0.13 (0.05–0.38)	<.001
	1:1 Matching	0.07 (0.01–0.54)	.011
Sex hormone deficiency	PS adjusted	0.07 (0.01–0.73)	.026
	IPTW	0.07 (0.01–0.70)	.023
	1:1 Matching	N/A[a]	
Endocrine replacement therapy	PS adjusted	0.36 (0.12–1.08)	.068
	IPTW	0.35 (0.13–0.93)	.036
	1:1 Matching	0.25 (0.05–1.18)	.080
Height SDS[b]	PS adjusted	0.82 (0.13–1.51)	.020
	IPTW	0.82 (0.18–1.46)	.012
	1:1 Matching	0.86 (0.15–1.56)	.017

Consequently, PT increasingly used in Germany and worldwide…

- In **very young**
- **Predominantly for localized CNS disease** (Ependymome. LGGs. Craniopharingiomas. ATRTs. CNS PNETs) due to still limited availability of CSI-PT
- PT used for **WVI** (whole ventricular system irradiation)
- PT for **CSI** (whole CNS treatment) less often available. currently but increasing

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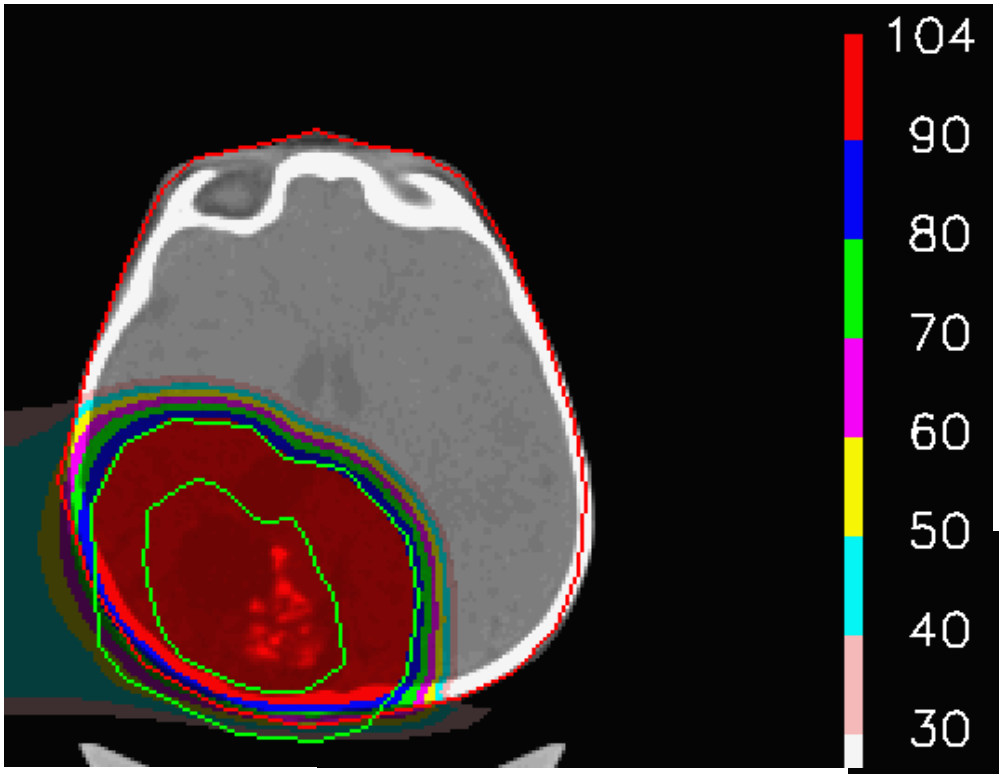
Benefit for

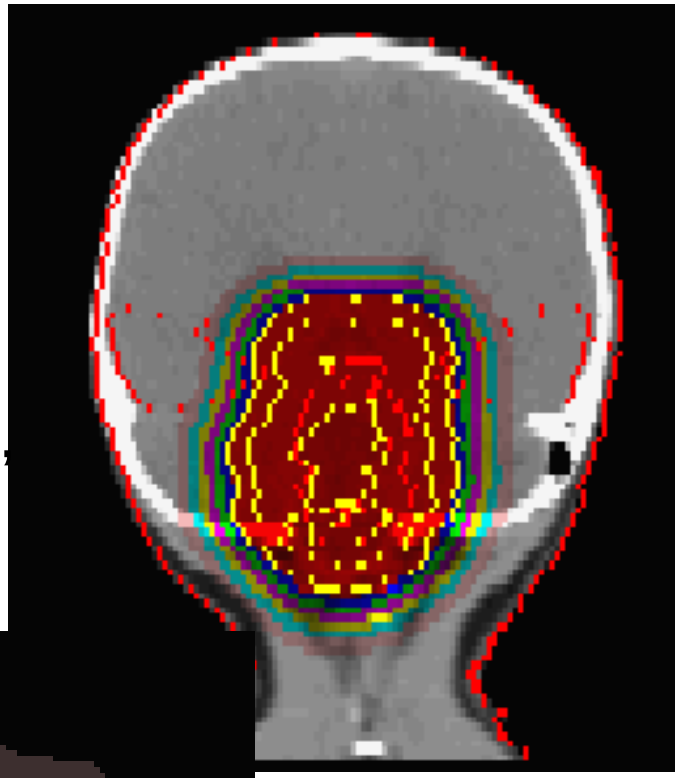
In childhood CNS tumors

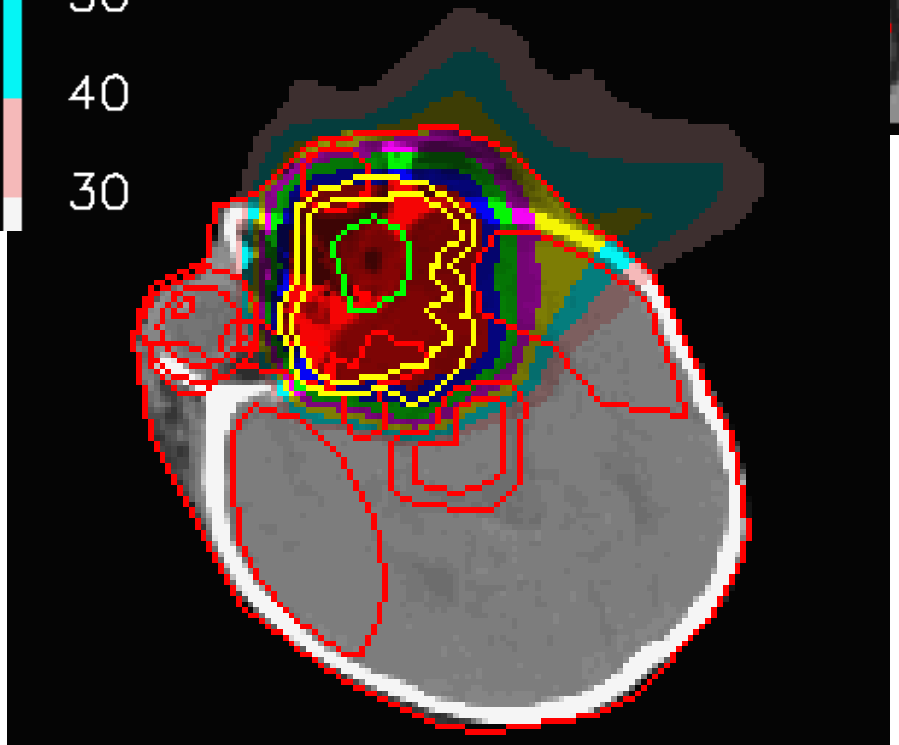
Uninvolved brain,



temporal lobes, hippocampus, cochlea

contralateral side, i.e. parotic, eye; brainstem





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CAVEAT

Imaging changes
and necrosis following PT
in pediatric brain tumors?

Clinical Investigation

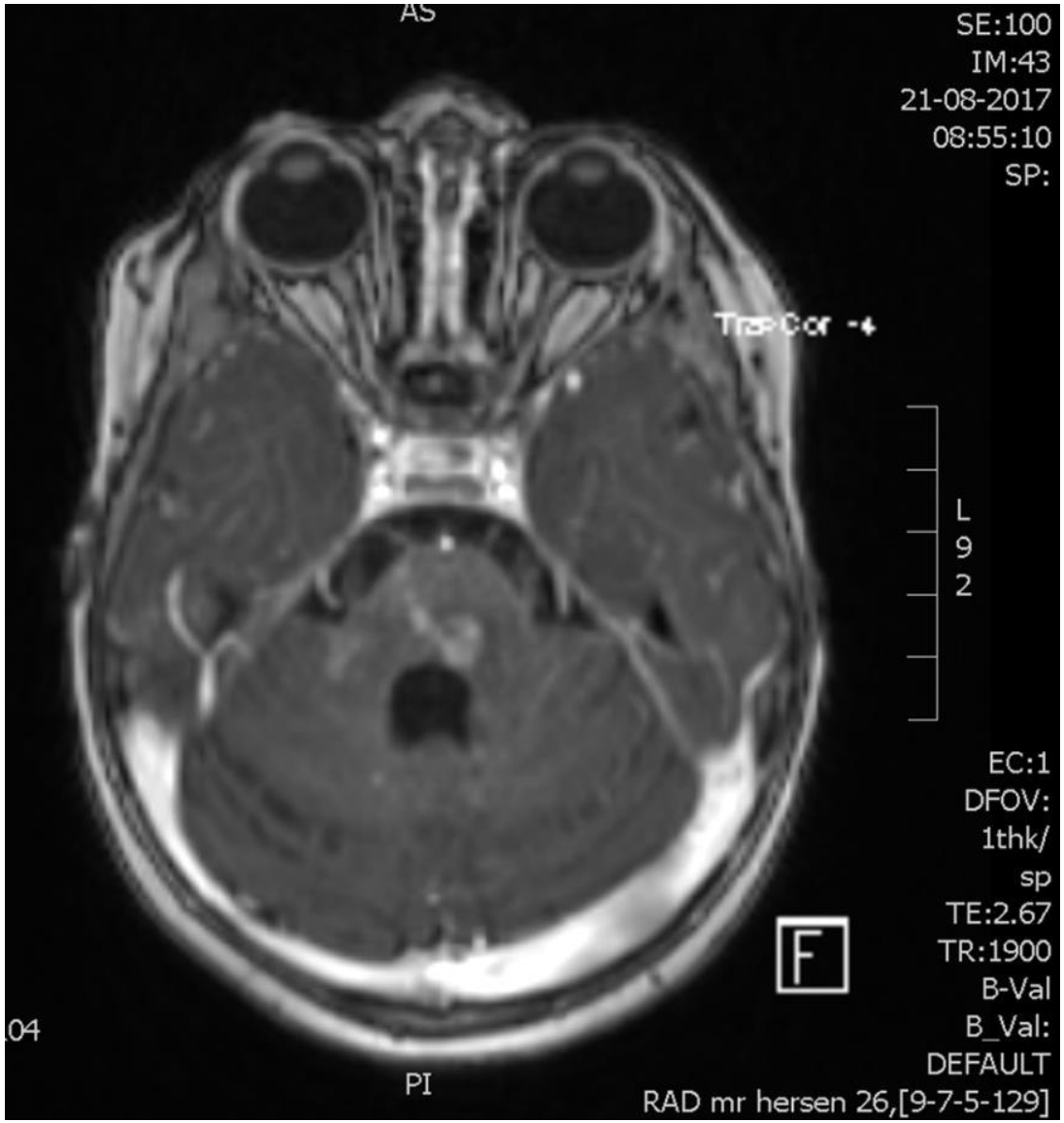
Imaging Changes in Pediatric Intracranial Ependymoma Patients Treated With Proton Beam Radiation Therapy Compared to Intensity Modulated Radiation Therapy

Jillian R. Gunther, MD, PhD,* Mariko Sato, MD, PhD,†
Murali Chintagumpala, MD,† Leena Ketonen, MD, PhD,‡
Jeremy Y. Jones, MD,§ Pamela K. Allen, PhD,* Arnold C. Paulino, MD,*,†
M. Fatih Okcu, MD,† Jack M. Su, MD,† Jeffrey Weinberg, MD,‖
Nicholas S. Boehling, MD,* Soumen Khatua, MD,¶
Adekunle Adesina, MD,# Robert Dauser, MD,**
William E. Whitehead, MD,** and Anita Mahajan, MD*

Risk: Younger age. higher dose. short recovery time after surgery

Conclusions: Postradiation MRI changes are more common with PBRT and in patients less than 3 years of age at diagnosis and treatment. It is difficult to predict causes for development of imaging changes that progress to clinical significance. These changes are usually self-limiting, but some require medical intervention, especially those involving the brainstem.

Reasons, Solutions?



Better consider carefully:

- Uncertainties

(metal. cysts growth…)

- Spot positioning
- RBE
- Individual technical conditions & risk factors

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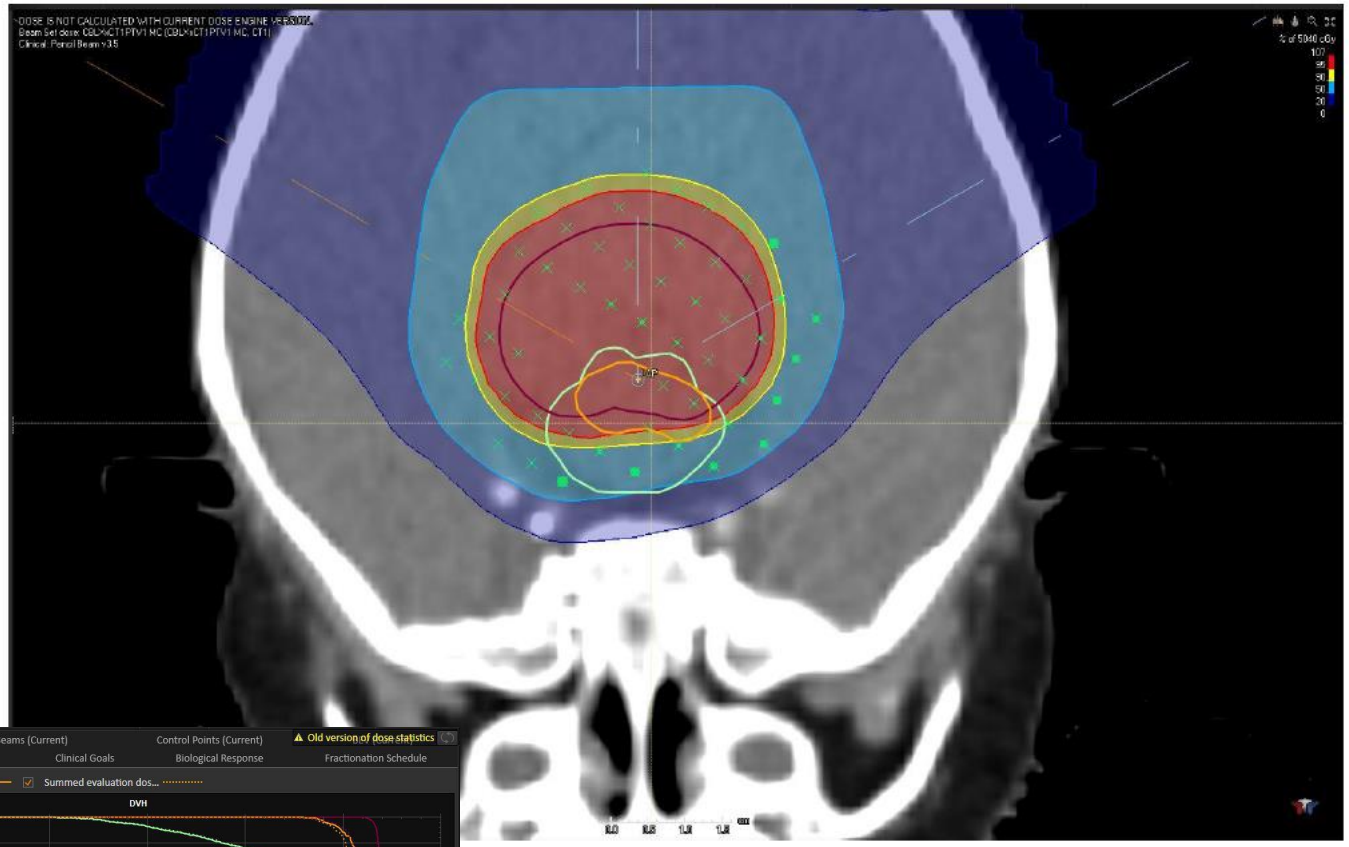
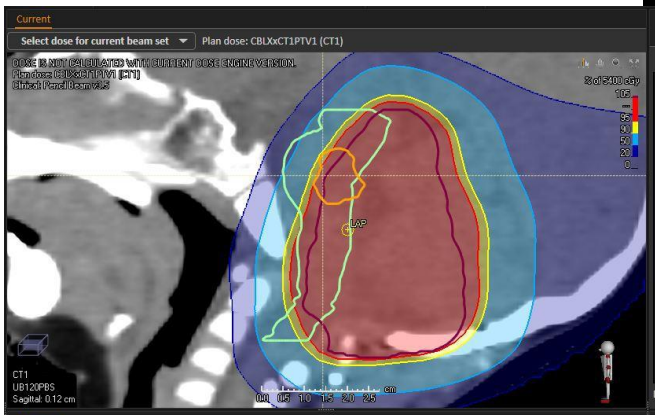
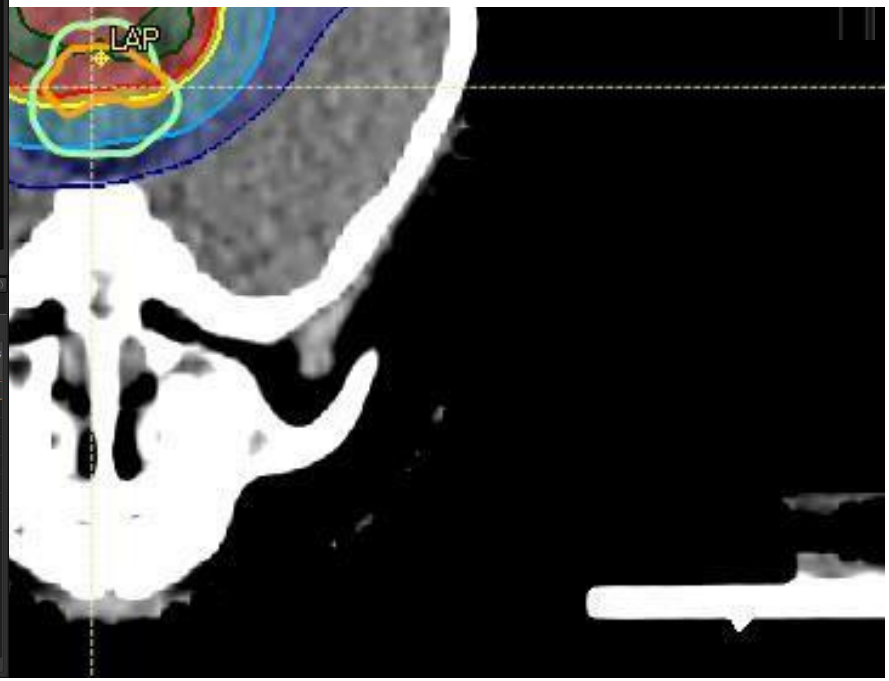
- Check for spot positions
- Monte Carlo Plan verification





Dose	ROI	ROI vol. [cm³]	Dose [cGy] D99	D98	D95	Average	D50	D2	D1	% outs
Plan dose: CBLXxCT1P...	BS_finding	1.7	4764	4811	4983	5305	5373	5416	5422	0 %
Summed evaluation d...	BS_finding	1.62	4732	4788	4924	5208	5255	5324	5330	0 %
Plan dose: CBLXxCT1P...	Hirnstamm	10.91	2483	2656	3155	4938	5325	5417	5423	0 %
Summed evaluation d...	Hirnstamm	10.76	2440	2678	3221	4850	5200	5325	5337	0 %
Plan dose: CBLXxCT1P...	OncoGeometry	10800.79	0	0	0	0	0	0	1	0 %
Summed evaluation d...	OncoGeometry	10838.64	0	0	0	1	1	5	5	0 %
Plan dose: CBLXxCT1P...	PTVB1	53.89	5282	5310	5345	5398	5400	5460	5469	0 %
Summed evaluation d...	PTVB1	53.75	4745	4869	5027	5229	5259	5360	5375	0 %



Proton Beam Therapy

- Background
- Experiences
- **WPE – West German Proton Center Essen**
- Retinoblastoma
- Conclusion

Registry study for children (KiProReg) at WPE

- **Standardized prospective Registry**
- Enrollment of children <18 years since September 2013
- **Data collection:**
  - **Diagnoses & treatment**
  - **PT Radiation data**
  - **Early and late toxicities**
  - **Tumor Status**
- **Treatment concept according to he respective multidisciplinary Protocols (EURO Ewing. CWS guidance. EURHAB etc)**

Children with CNS tumors treated at West German Proton Therapy Center Essen 20013-2017

	No./years
Patients in total	282
female	119
male	163
Median age (range)	5.8 (0.9 - 17.9)
PT under sedation	170 (60%)
Concomitant CTx	84 (30%)
Median FU (yrs) (range) since 1. Dx	1.5 (0.2 - 12.4)

24.11.2017

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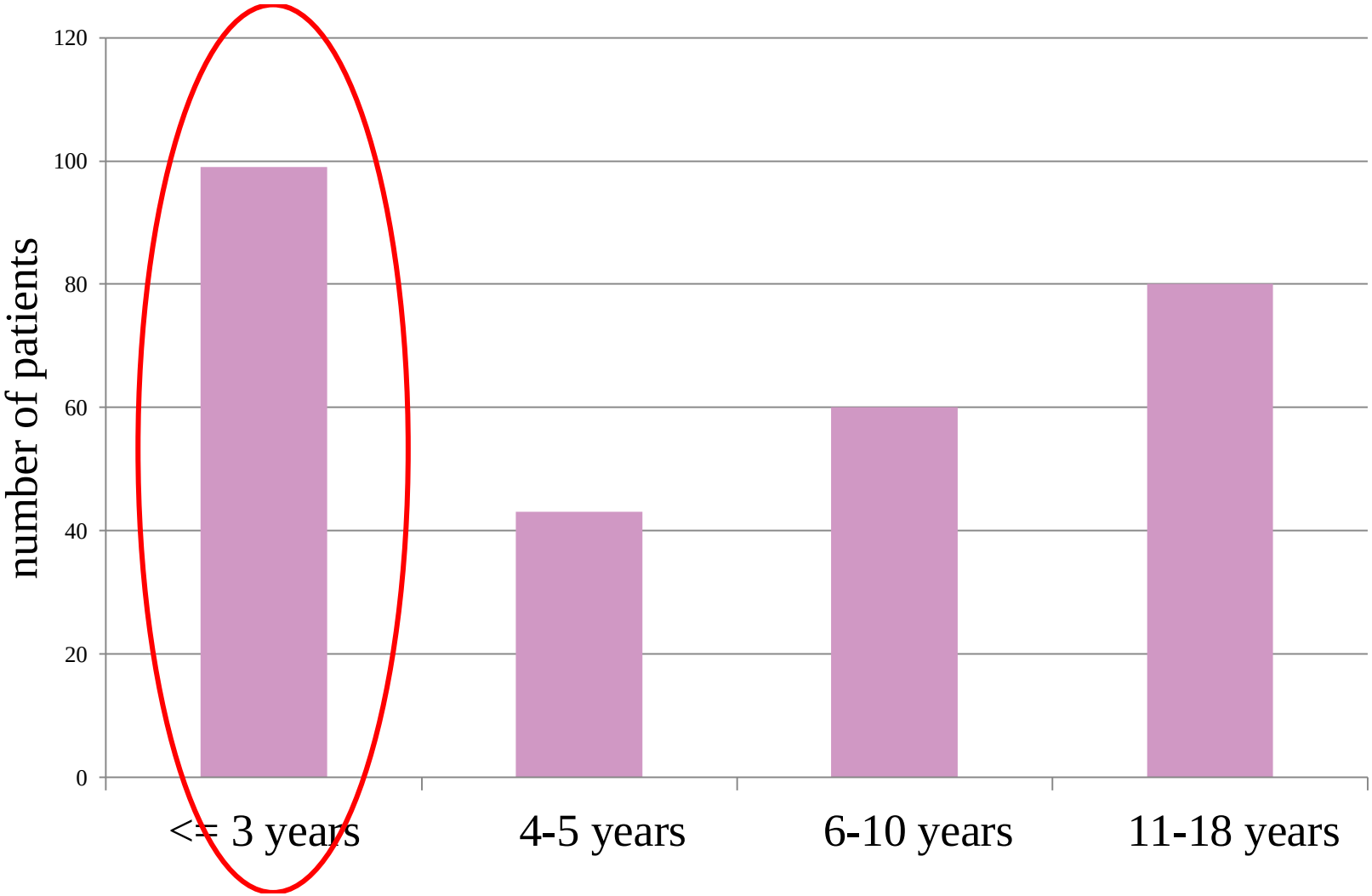
Age distribution



Histopathology

	%
Ependymoma	**31.6%**
Medulloblastoma	**19.1%**
Glioma	**15.6%**
Astrocytoma, Glioma, Glioblastoma, Oligodendroglioma etc	
AT/RT	**11.3%**
Craniopharyngeoma	**8.9%**
GCT (CNS)	**5.0%**
Retinoblastoma	**4.6%**
Meningeoma	1.1%
CPT	1.1%
ETANTR/EZTMR	0.7%
Pineoblastoma	0.7%
Neurocytoma	0.4%
total	100%

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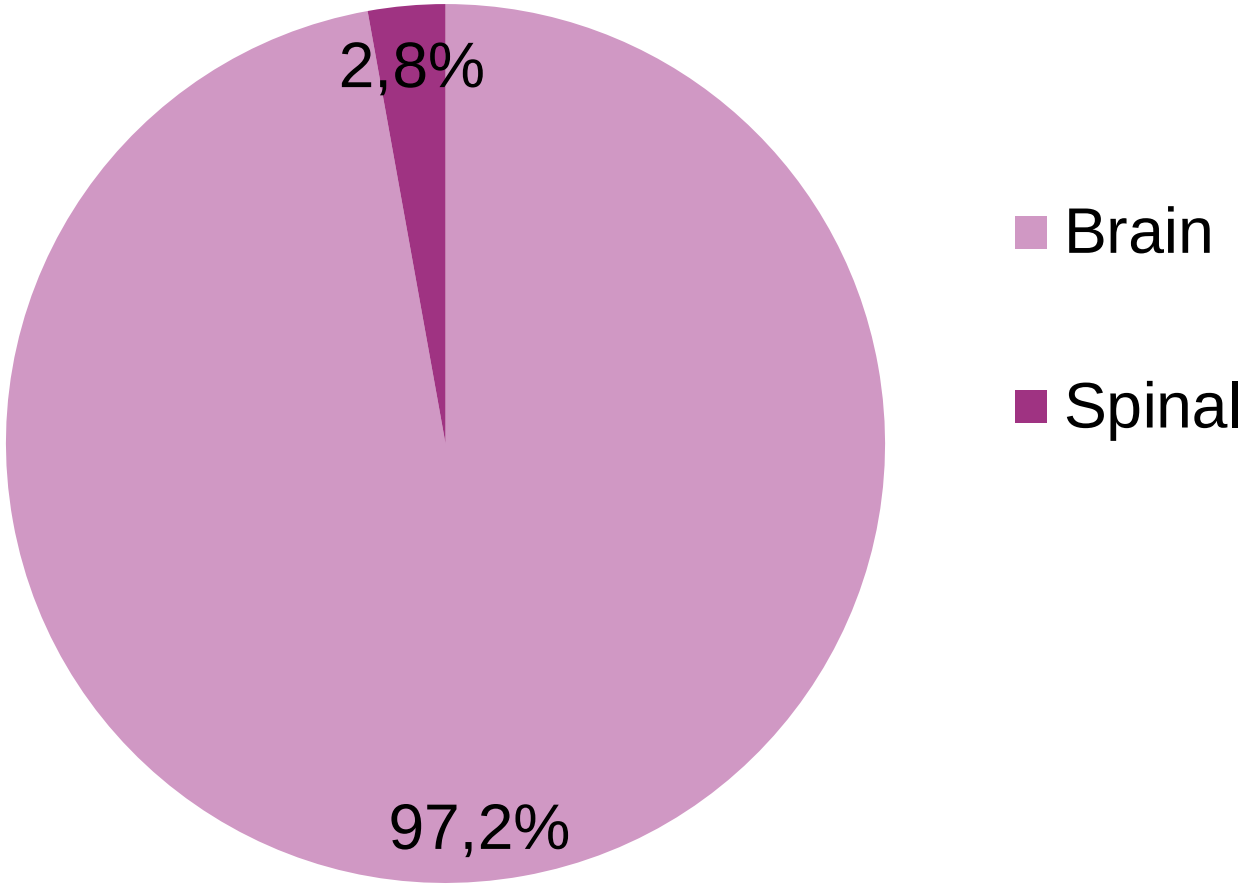
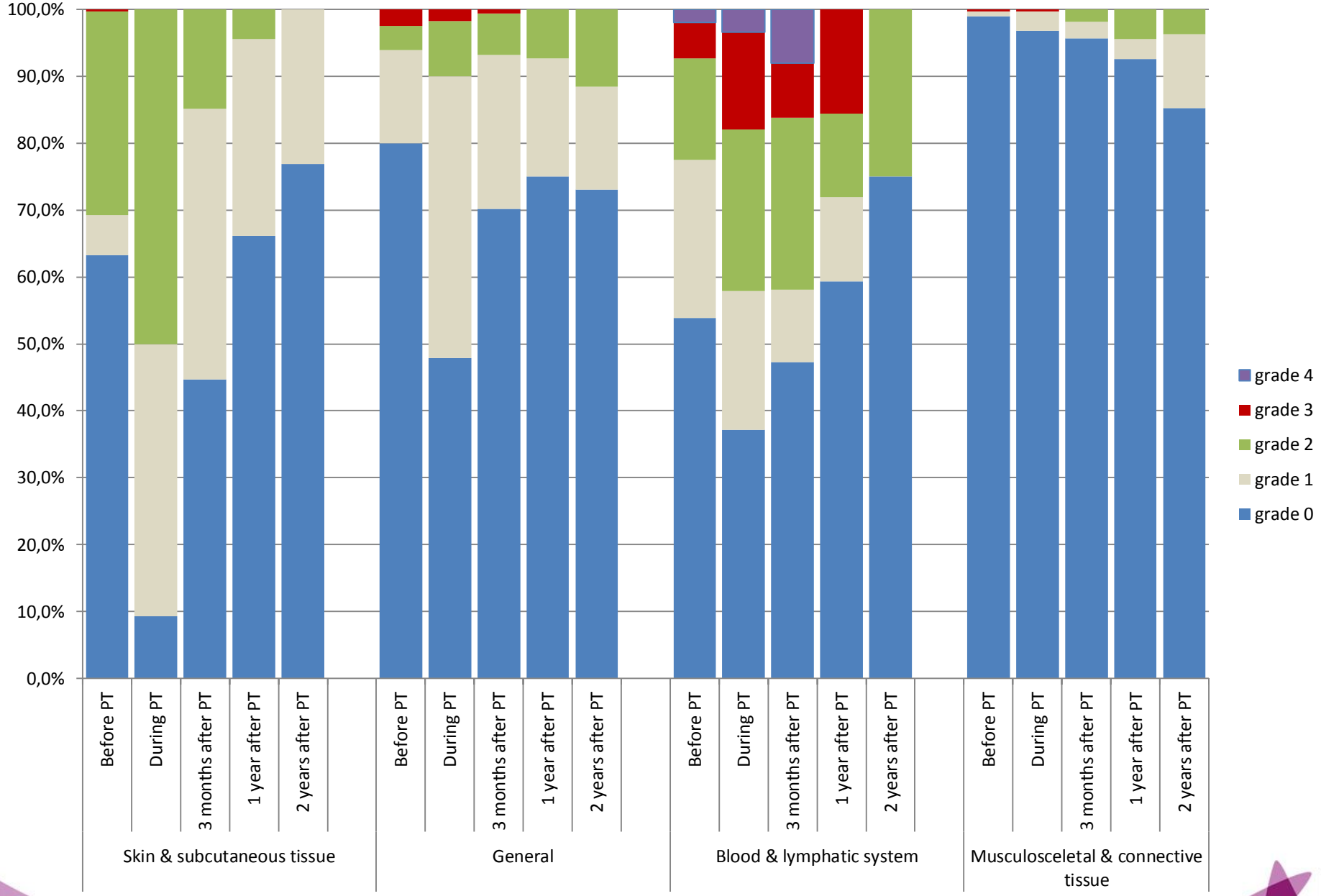
Tumor site



Adverse events - example



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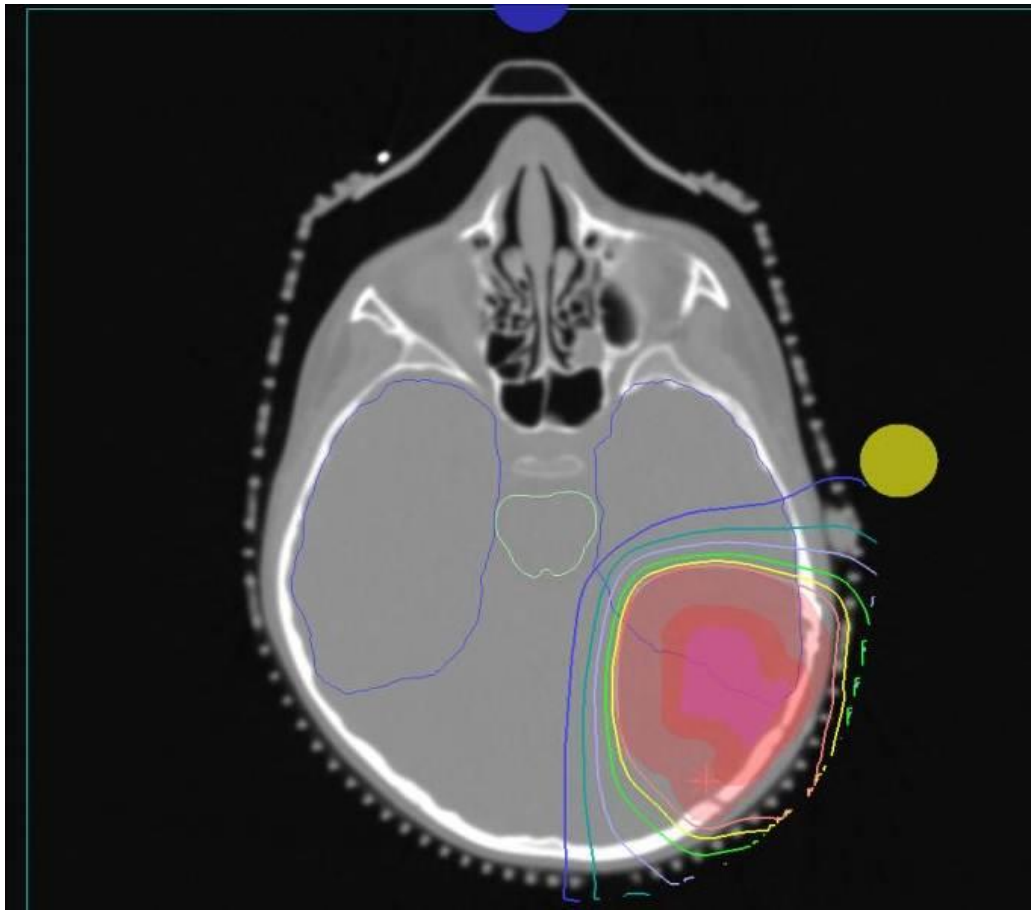
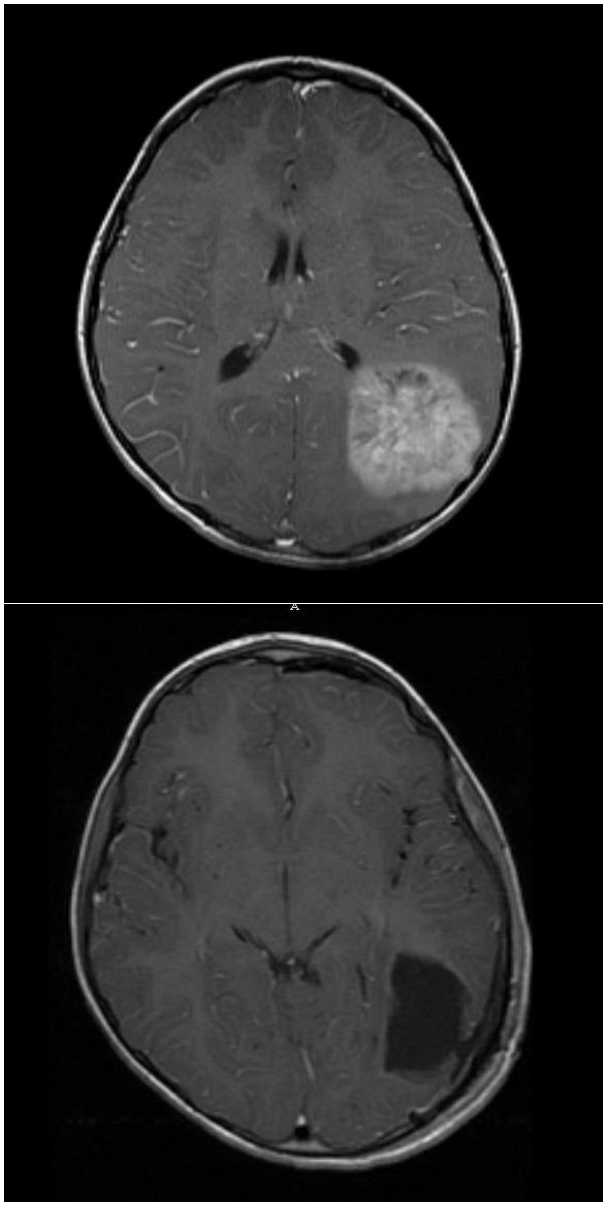
supratentorial ependymoma





PT dose plan:
Maximal sparing of
non-involved
CNS structures!

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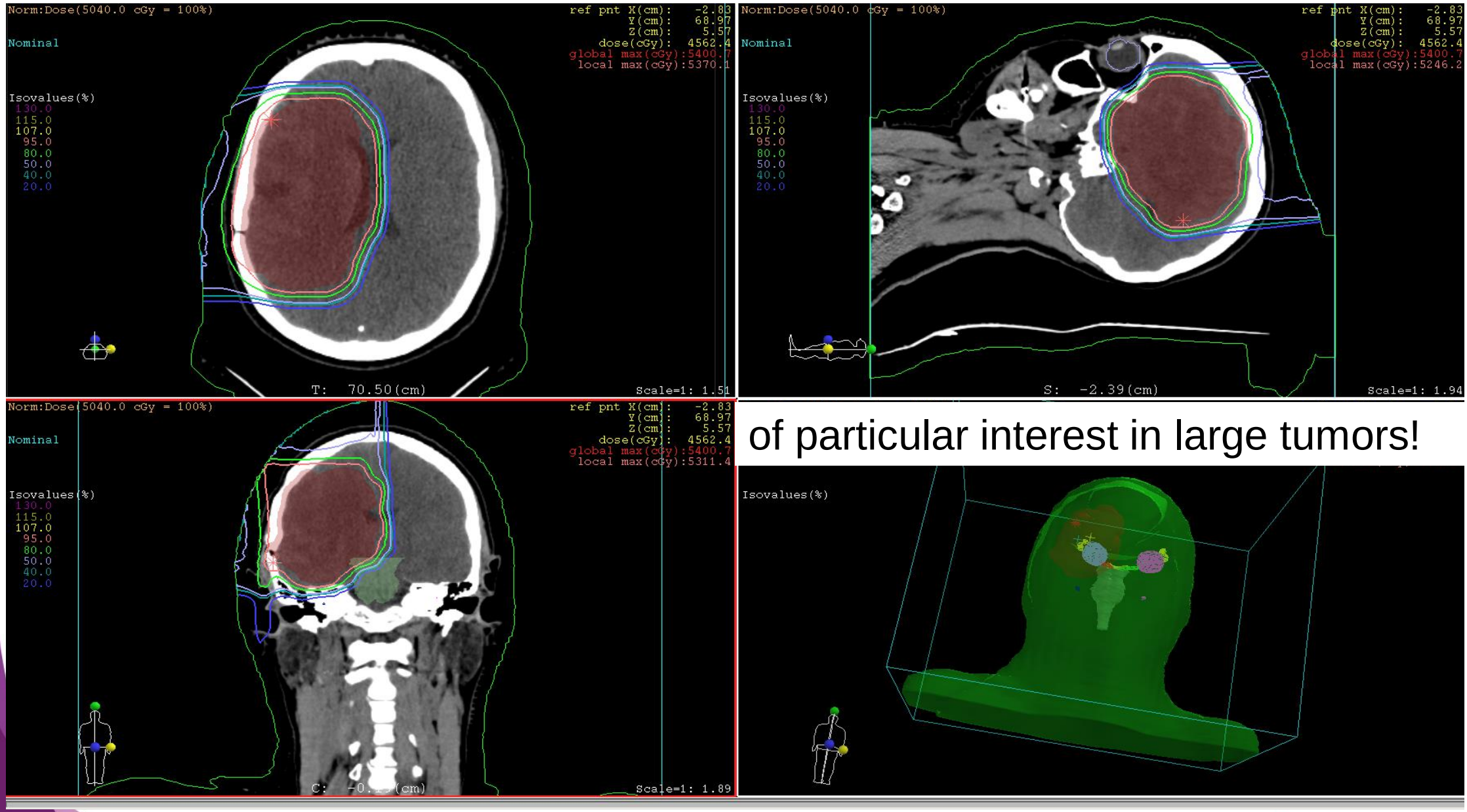
Huge glioma



of particular interest in large tumors!

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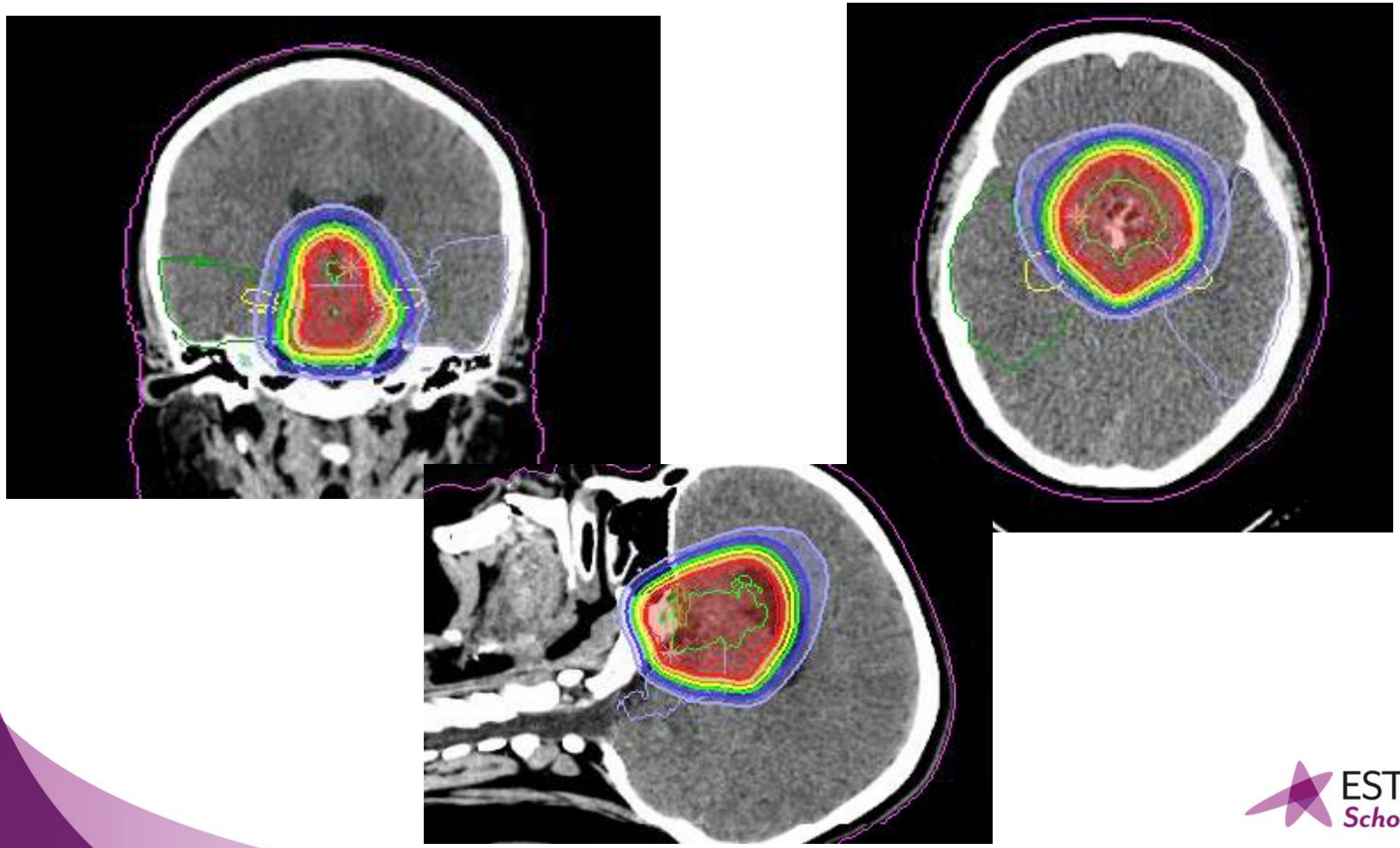
Craniopharyngioma



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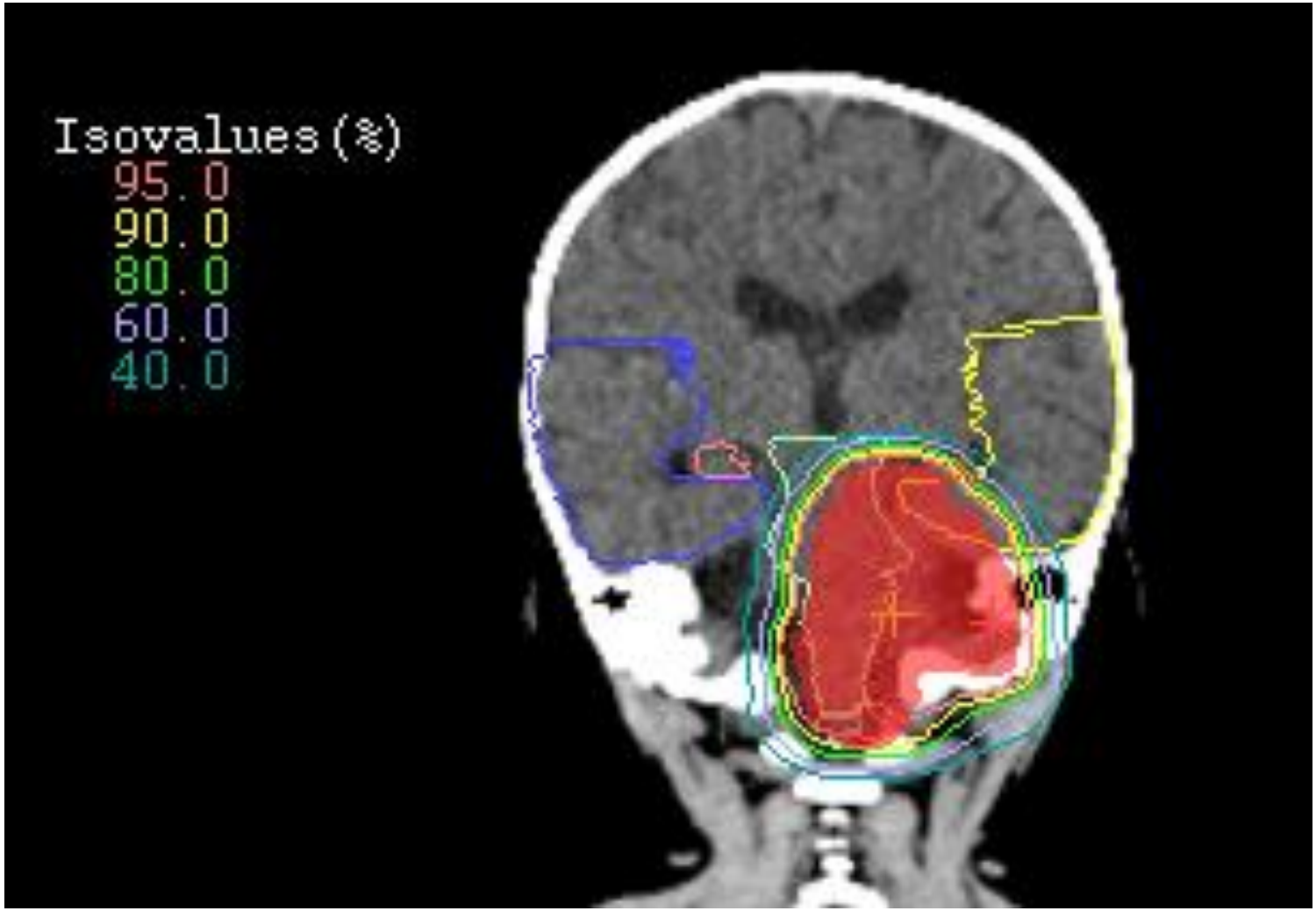
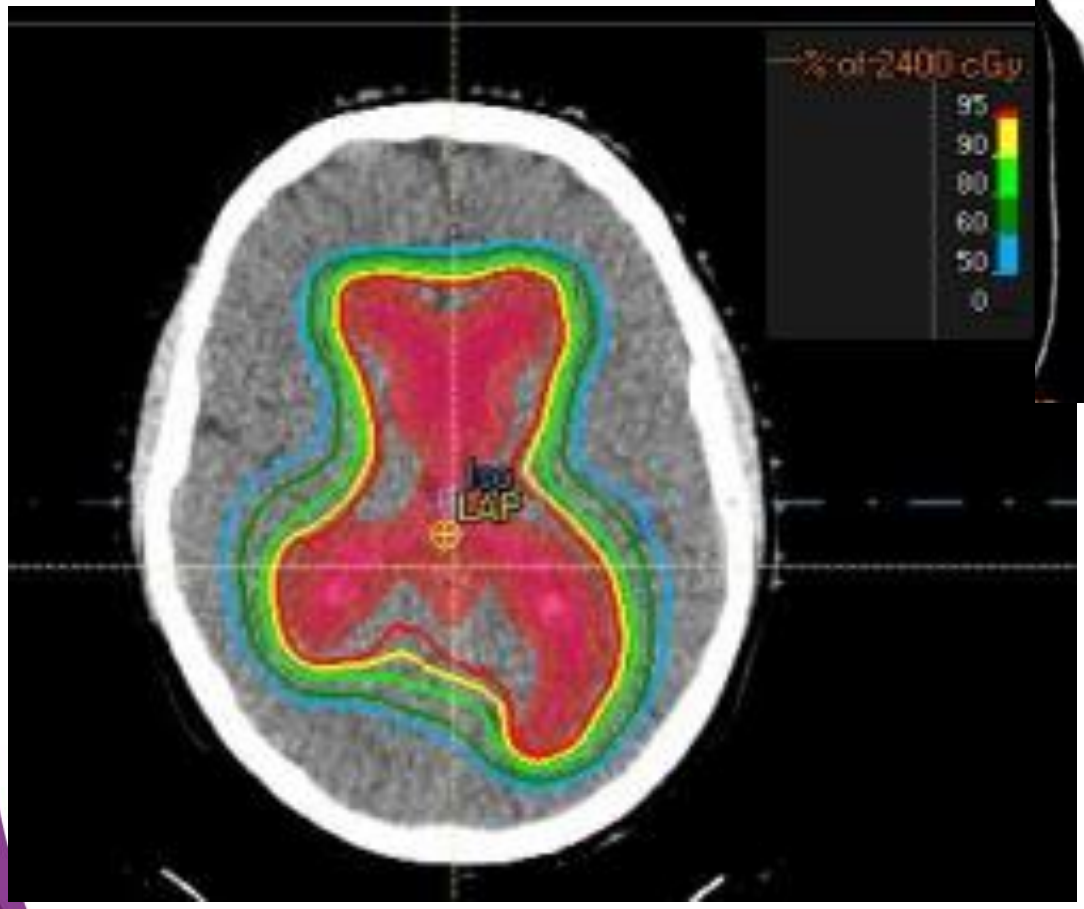
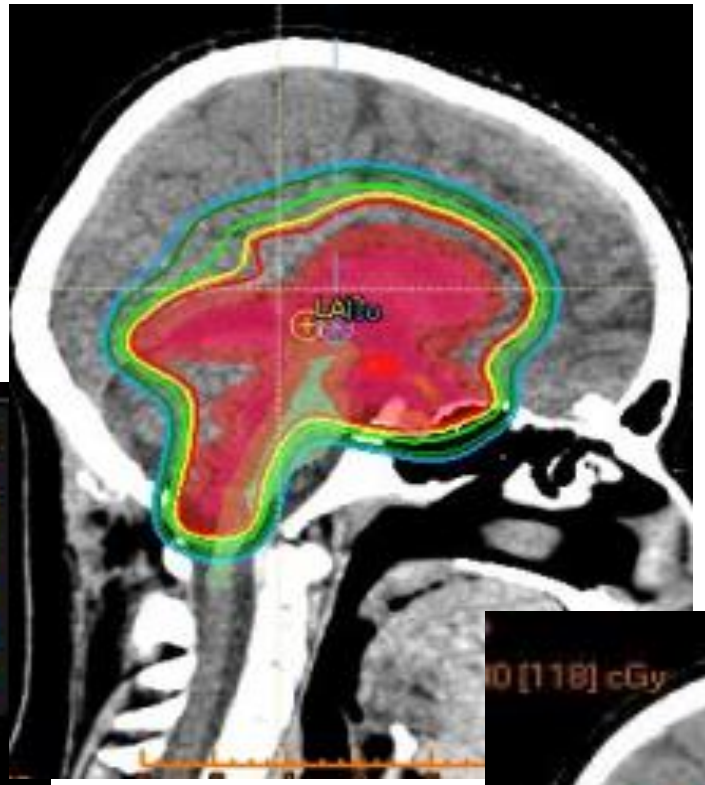
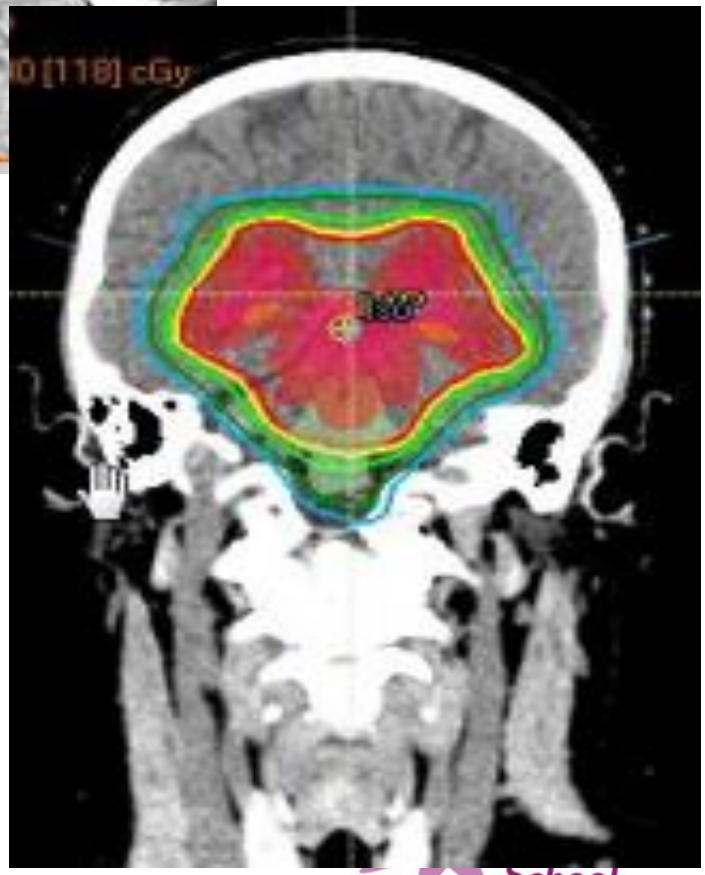
Infratentorial ATRT



Whole Ventricular Irradiation - IMPT

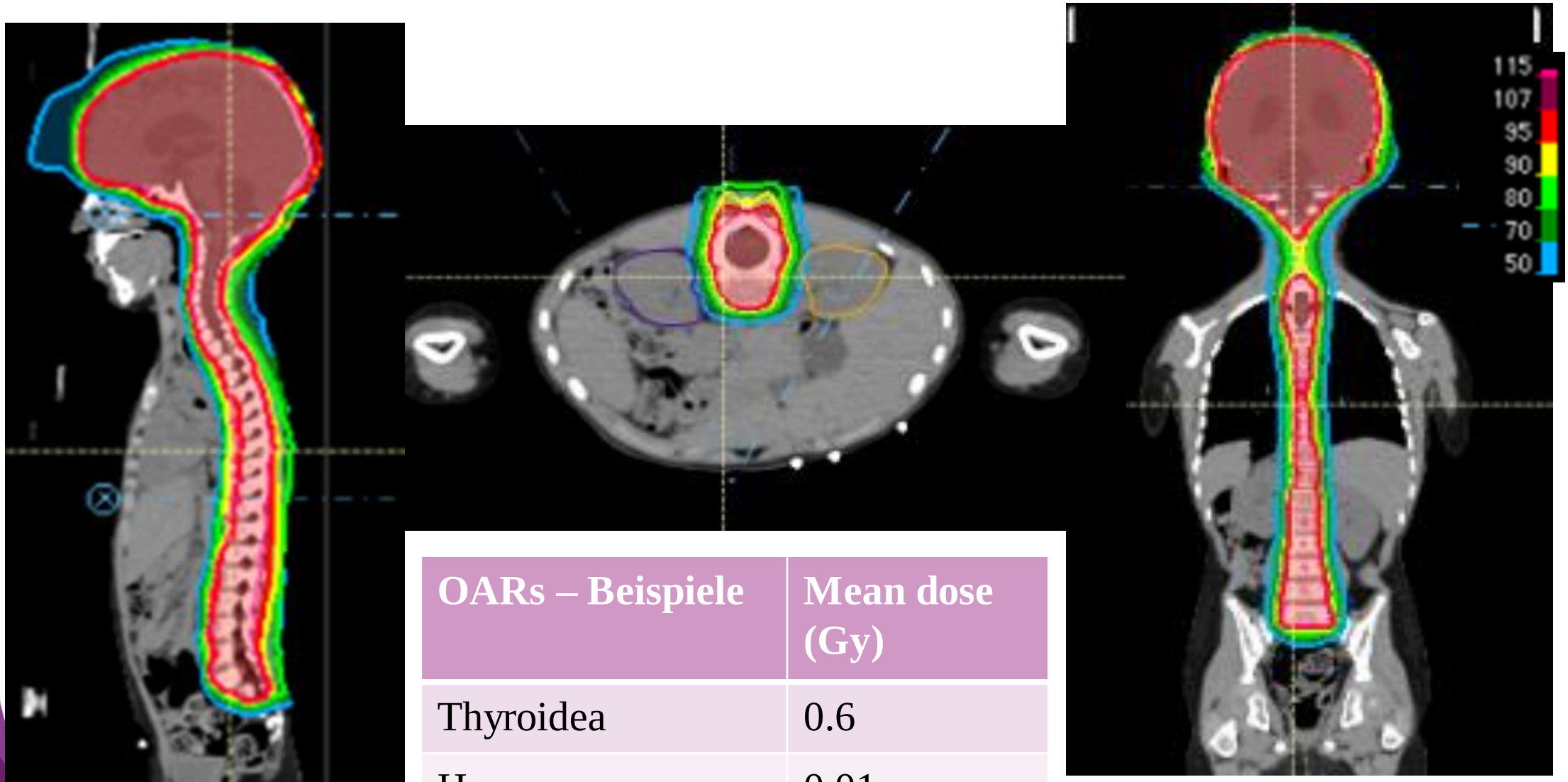






WVI: 24Gy/1.6Gy

CSI - IMPT



OARs – Beispiele	Mean dose (Gy)
Thyroidea	0.6
Herz	0.01
Lunge	0.28

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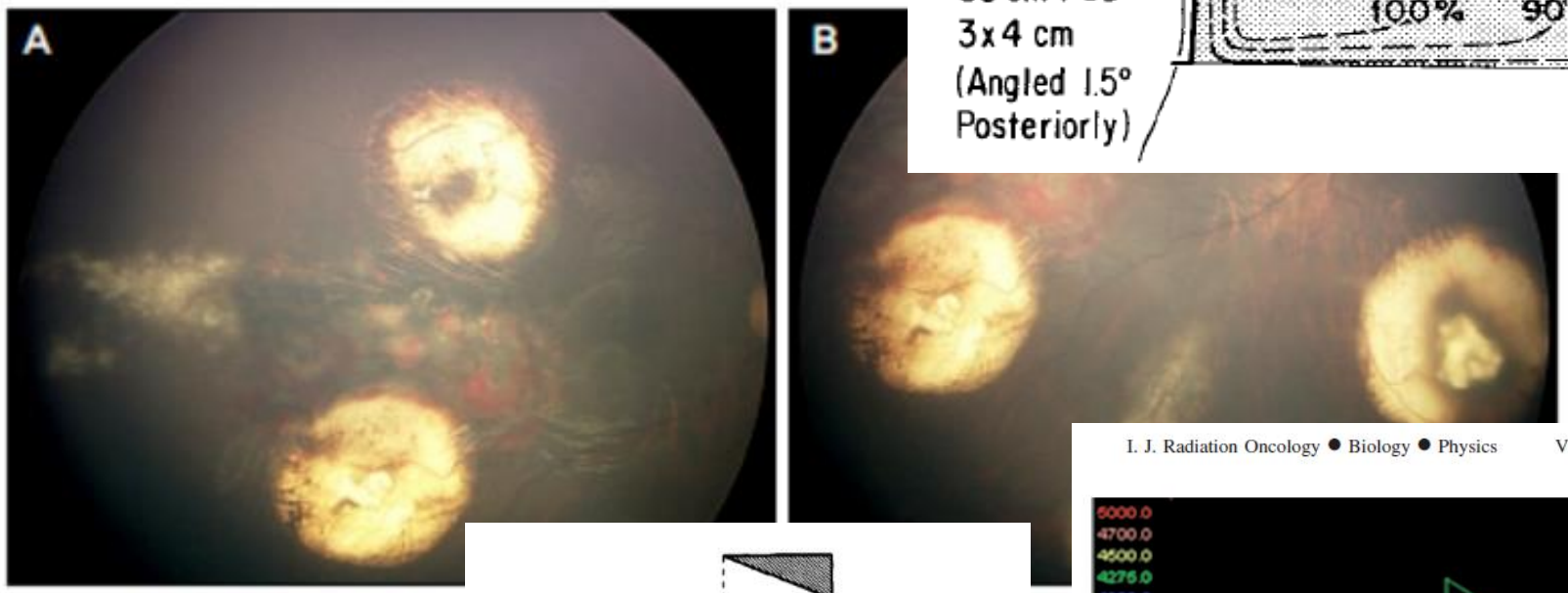
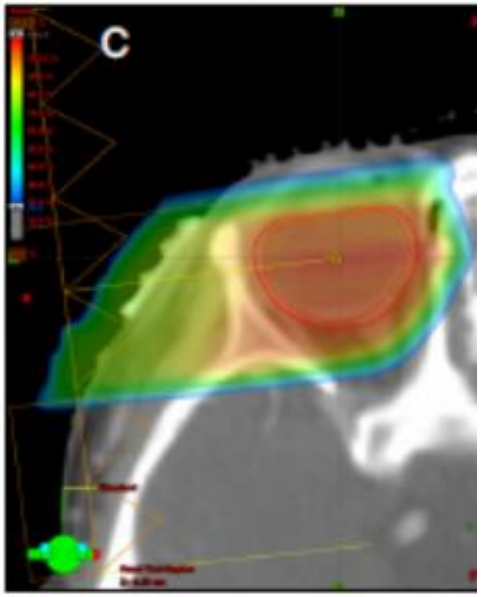
Proton Beam Therapy

- Background
- Experiences
- WPE – West German Proton Center Essen
- **Retinoblastoma**
- Conclusion

Korean J Ophthalmol Vol.25, No.6, 2011





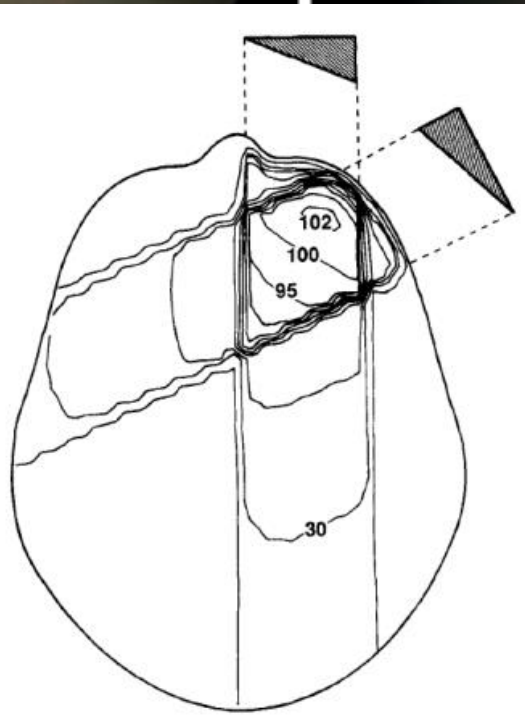
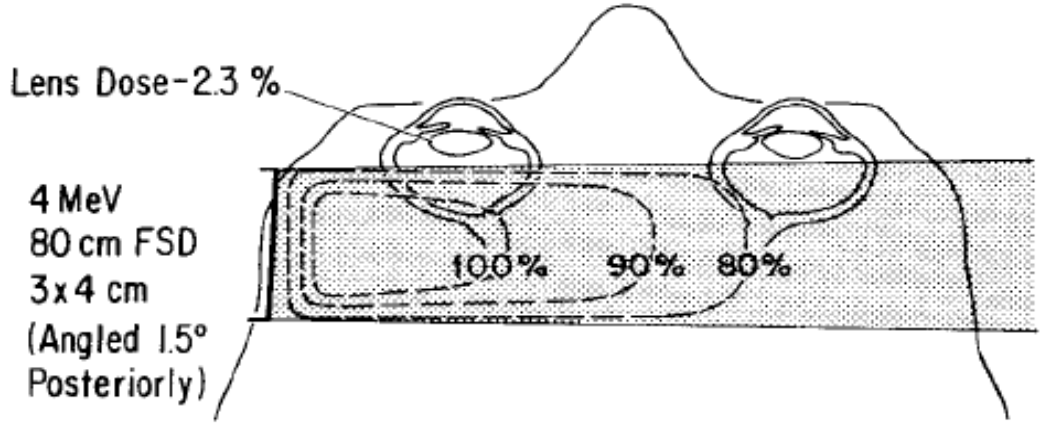


FIG. 1. Isodose distribution. Anterior and lateral wedge pair with a 5° obliquity to spare opposite lens.



I. J. Radiation Oncology ● Biology ● Physics Volume 67, Number 3, 2007

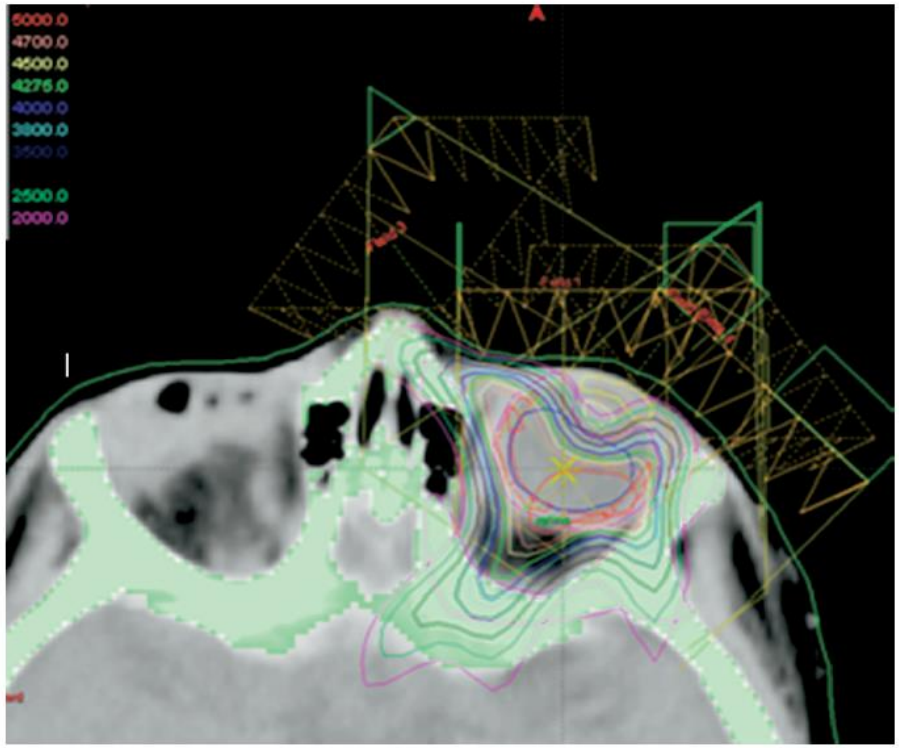


Fig. 2. Isodose curves of intensity-modulated radiotherapy technique.

Pediatric Blood & Cancer

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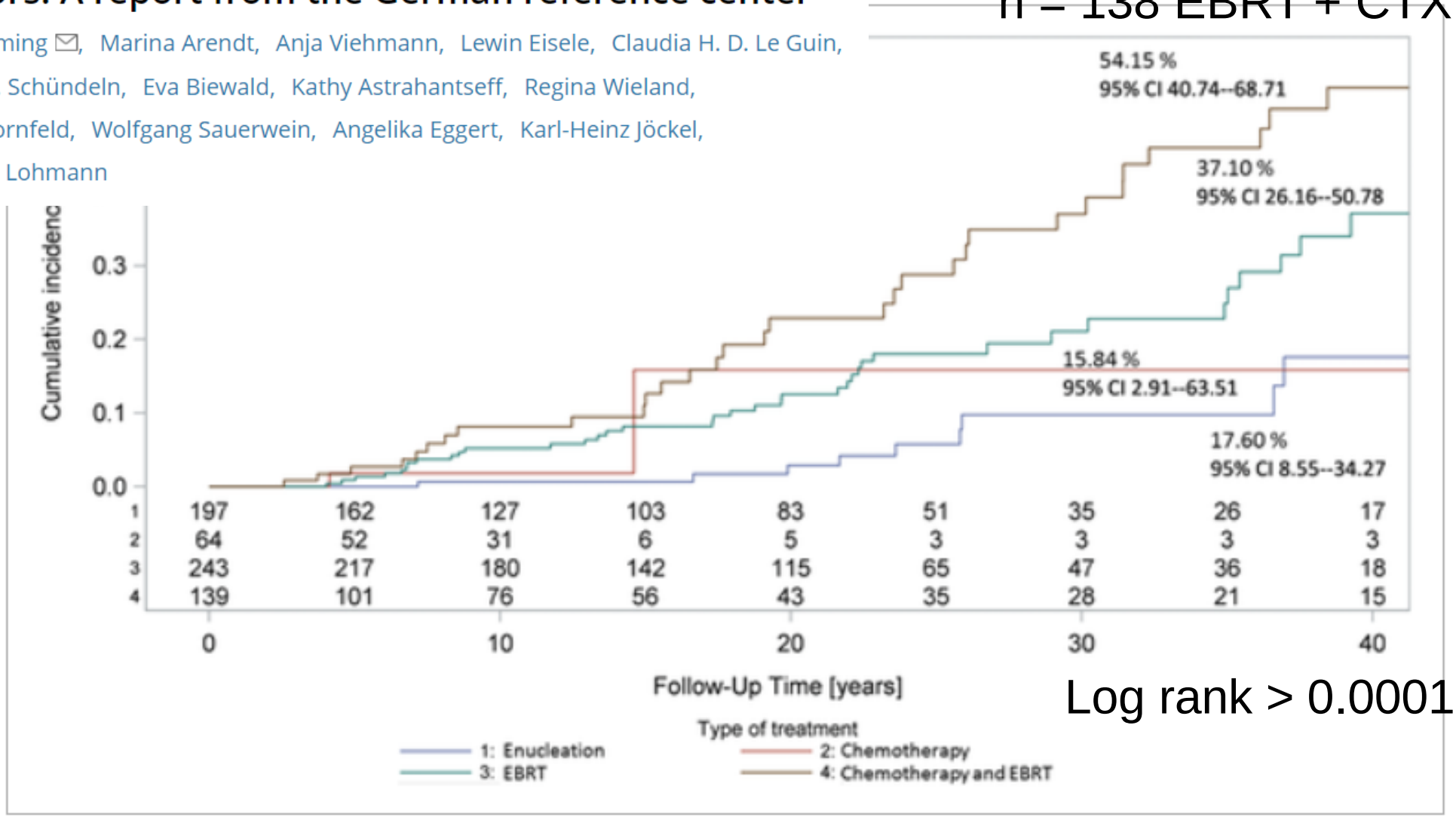
Research Article

Incidence of second cancers after radiotherapy and systemic chemotherapy in heritable retinoblastoma survivors: A report from the German reference center

Petra Temming ✉, Marina Arendt, Anja Viehmann, Lewin Eisele, Claudia H. D. Le Guin, Michael M. Schündeln, Eva Biewald, Kathy Astrahantseff, Regina Wieland, Norbert Bornfeld, Wolfgang Sauerwein, Angelika Eggert, Karl-Heinz Jöckel, Dietmar R. Lohmann

n = 1194 RB registered
n = 648 heritable
n = 197 OP
n = 64 CTX
n = 243 EBRT only
n = 138 EBRT + CTX

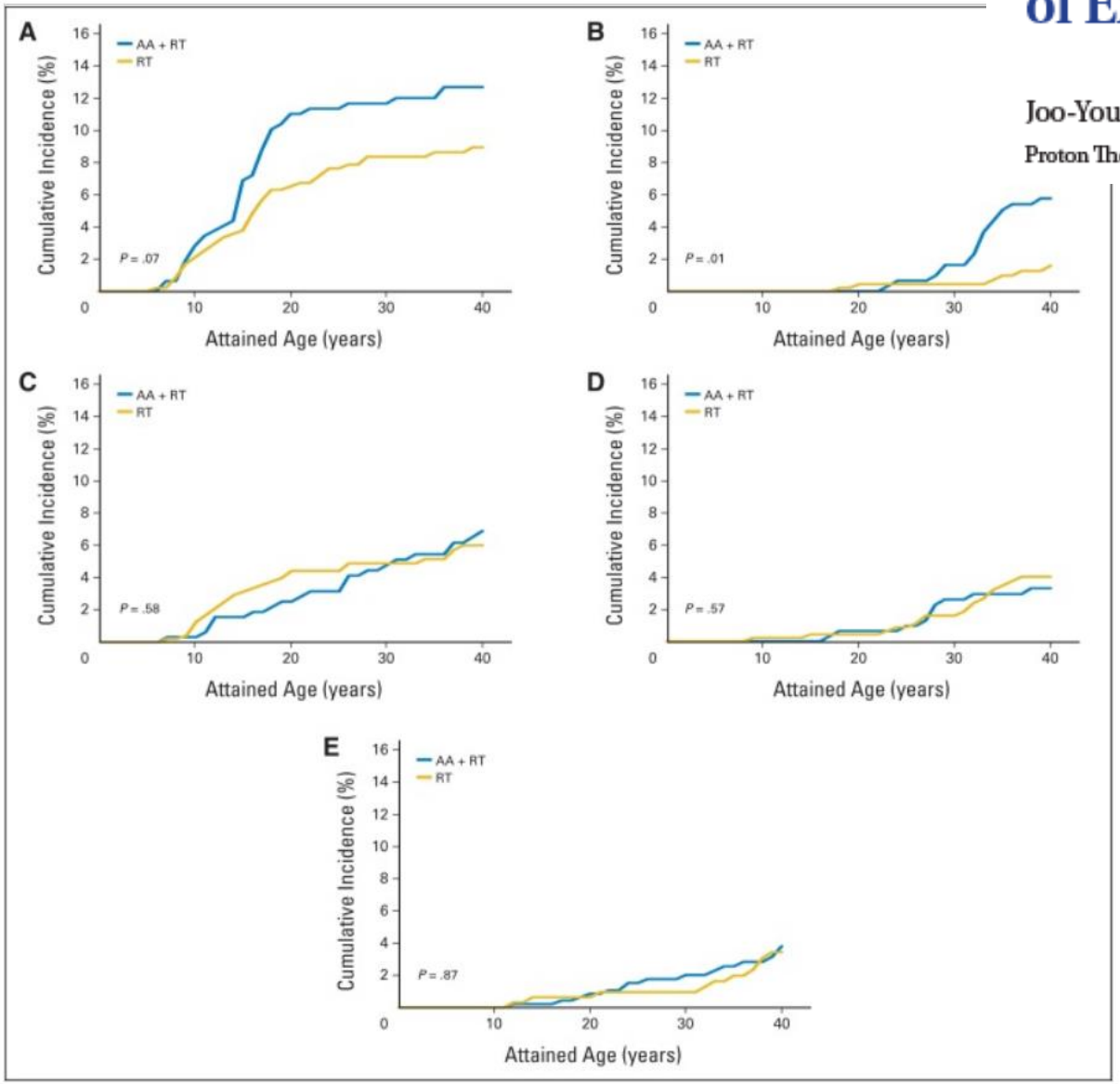


Log rank > 0.0001

Review Article
Yonsei Med J 2015 Nov;56(6):1478-1491
http://dx.doi.org/10.3349/ymj.2015.56.6.1478

Treatment of Retinoblastoma: The Role of External Beam Radiotherapy

Joo-Young Kim and Younghee Park*
Proton Therapy Center, National Cancer Center, Goyang, Korea.



90% treated with RT,

40% treated with alkylating agents

Cumulative Incidence for SMN:

- Bone sarcoma
- Leiomyosarcoma
- Other sarcoma
- Melanoma
- Epithelial tumors

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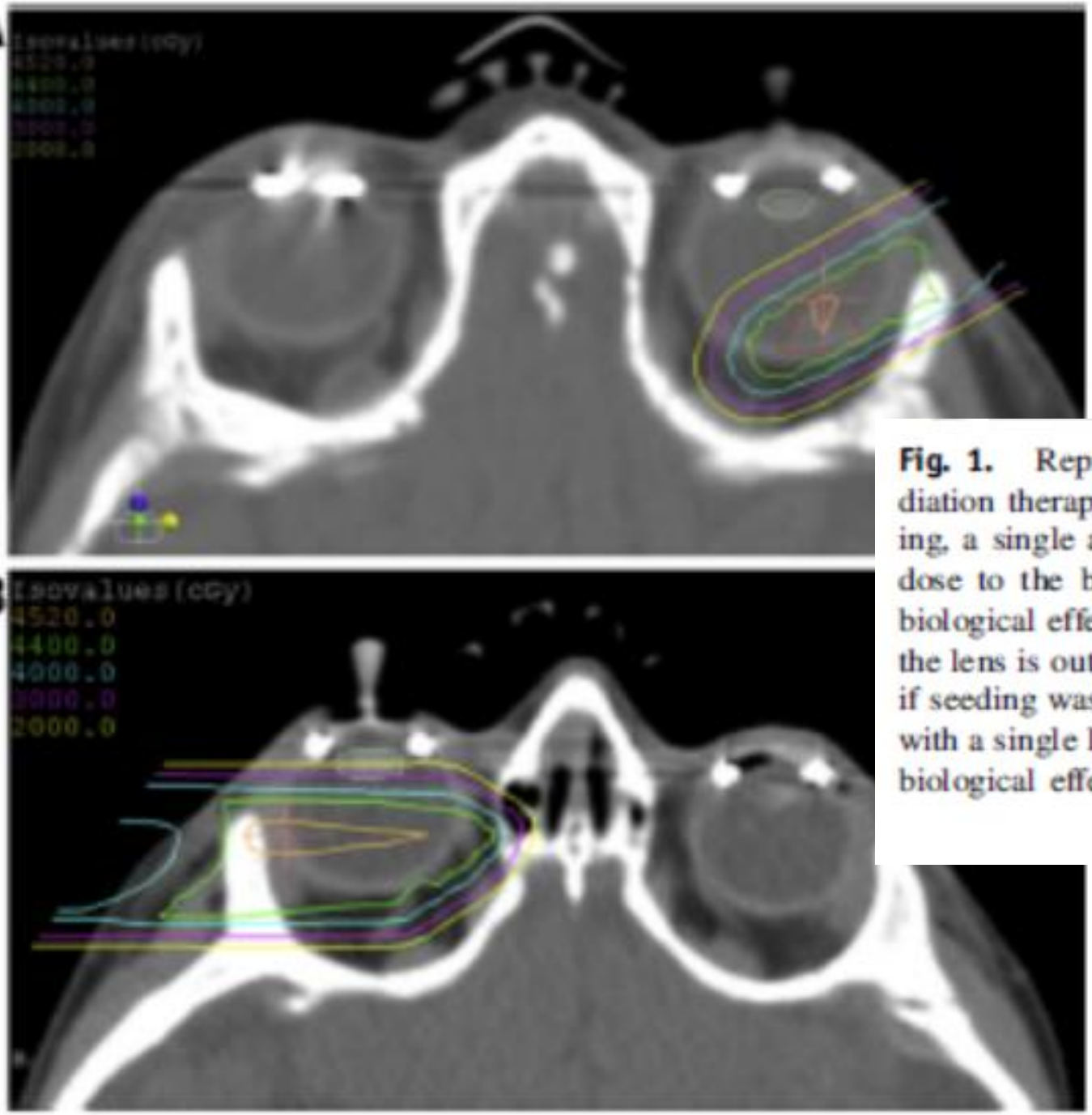

Fig. 1. Representative axial CT slice from 2 proton radiation therapy plans. (A) For small tumors without seeding, a single anterior oblique beam was used to minimize dose to the bony orbit (prescription dose 44 Gy[relative biological effectiveness]). The tumor is outlined in red, and the lens is outlined in pale green. (B) For larger tumors, or if seeding was present, the posterior chamber was targeted with a single lateral beam (prescription dose 45 Gy[relative biological effectiveness]).

Review Article
Yonsei Med J 2015 Nov;56(6):1478-1491
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Treatment of Retinoblastoma: The Role of External Beam Radiotherapy

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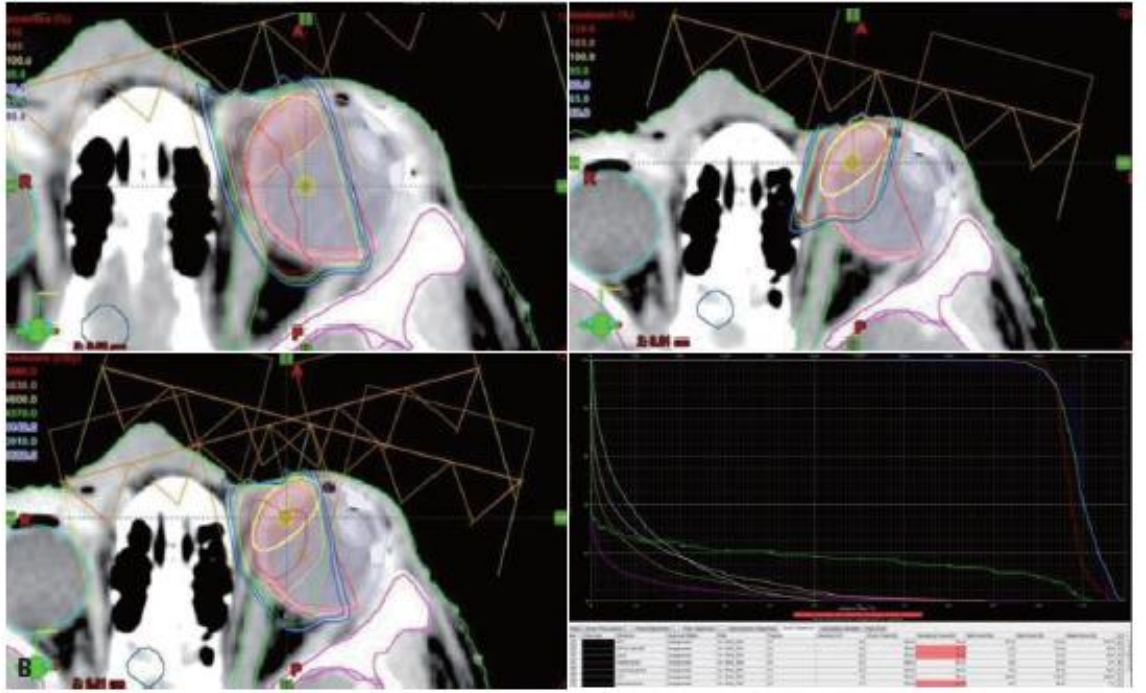
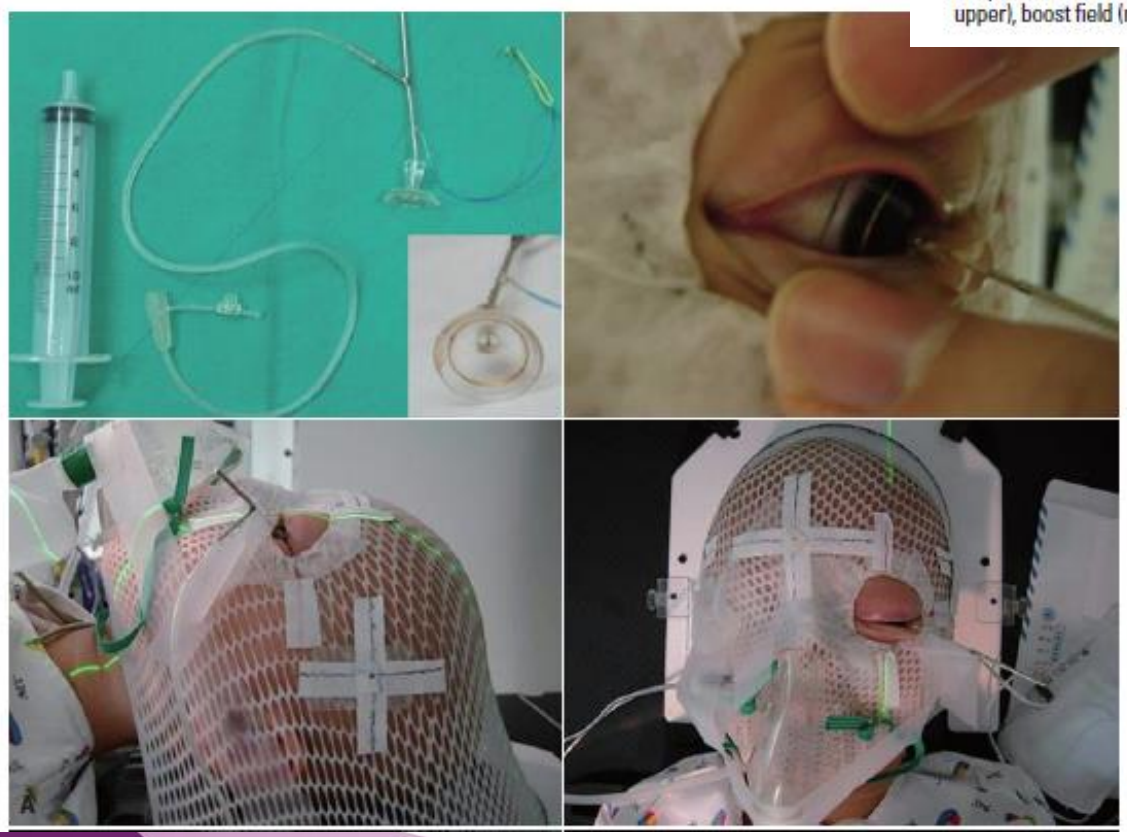


Fig. 2. Practices at National Cancer Center, Korea. (A) Under anesthesia, a small suction cup is placed on the cornea and the eyeball is rotate the proton beam can maximally avoid the orbital bone while covering the retinal target. (B) Dose distribution in proton beam therapy–initial upper), boost field (right upper), summation of both fields (left lower) and corresponding dose volume histogram for the entire plan (right lowe



- PT &
- Suction cup

->

- Avoding bone/soft tissue

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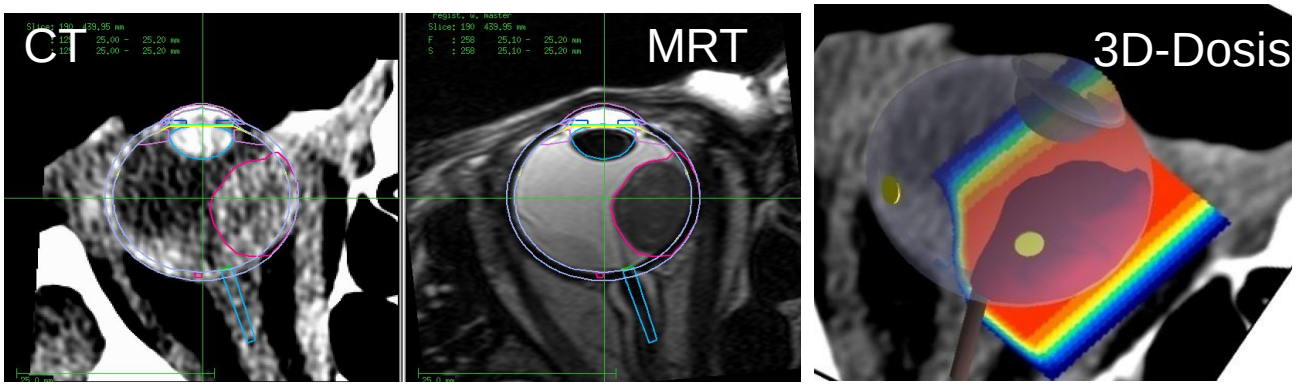
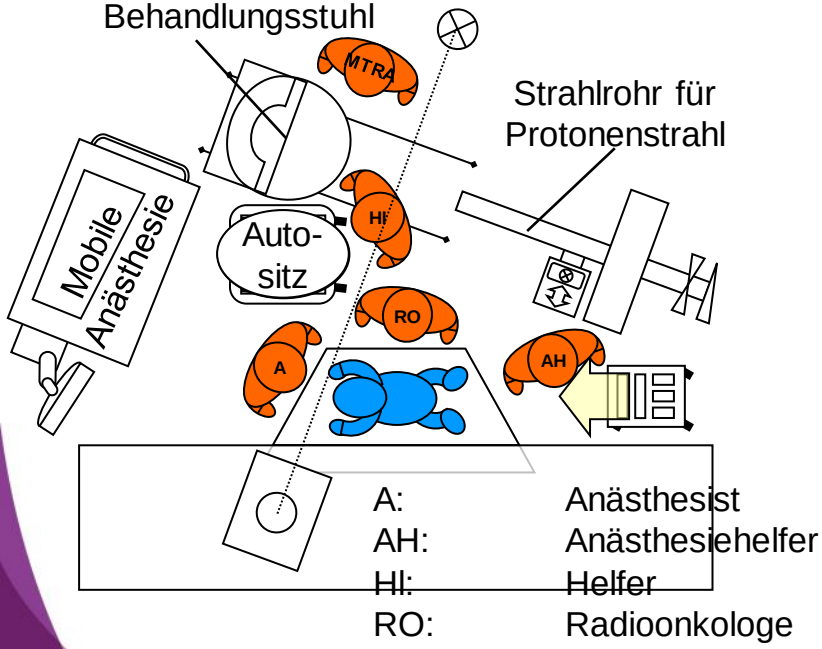
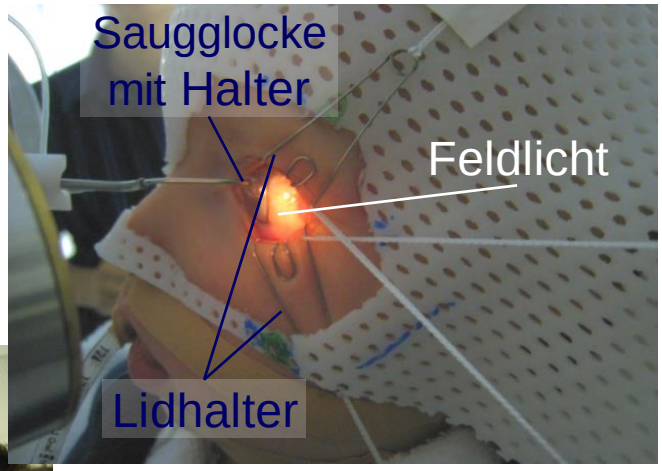
Focal PT in Berlin for RBs







@
Jens Heufelder
Charite, Berlin

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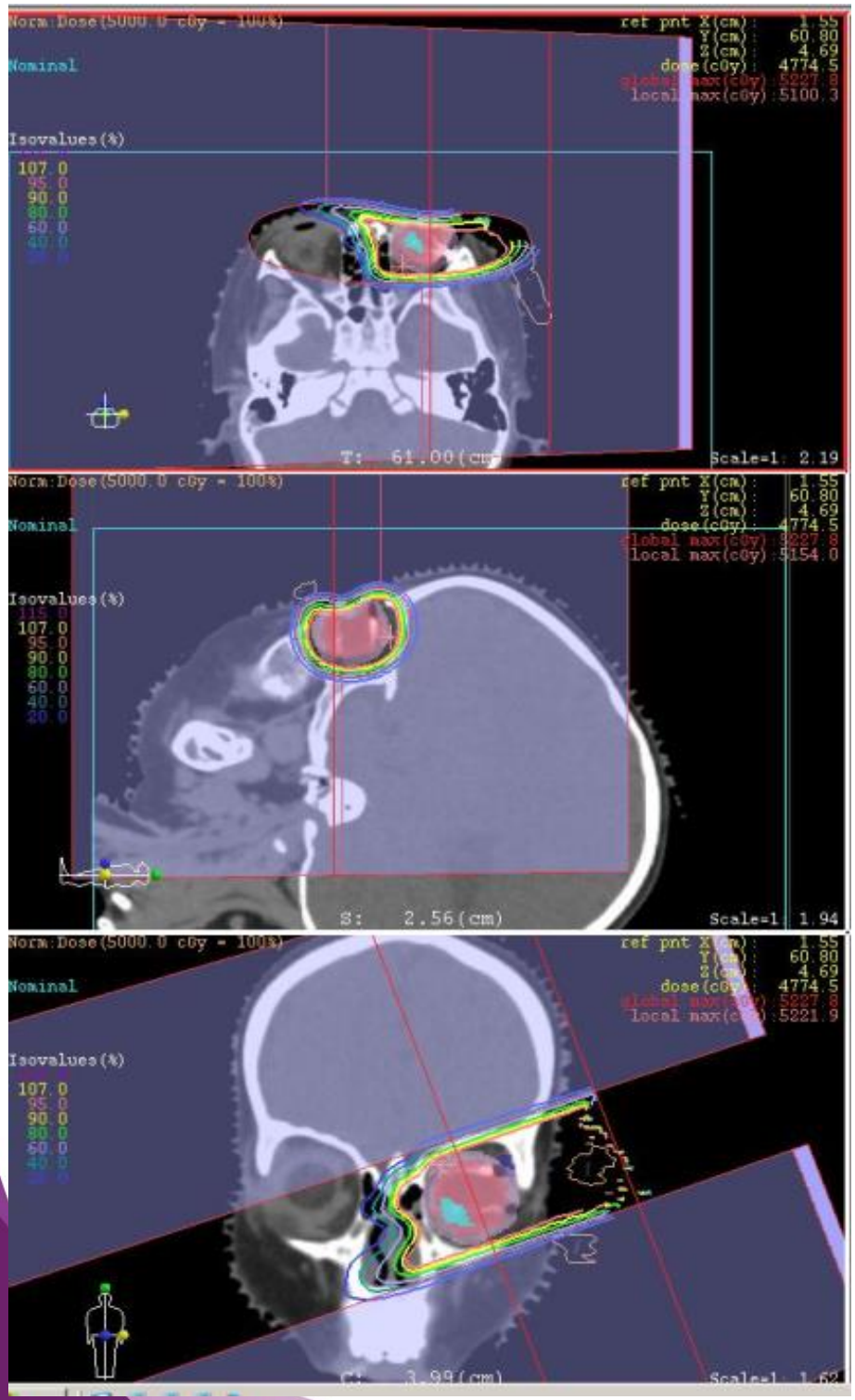
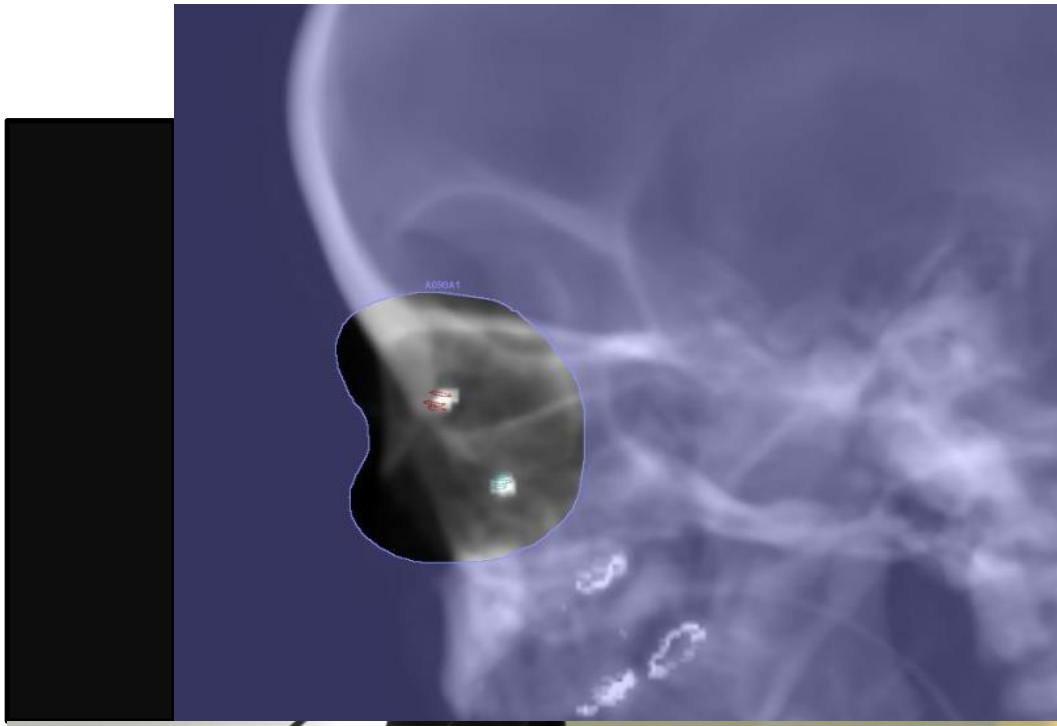
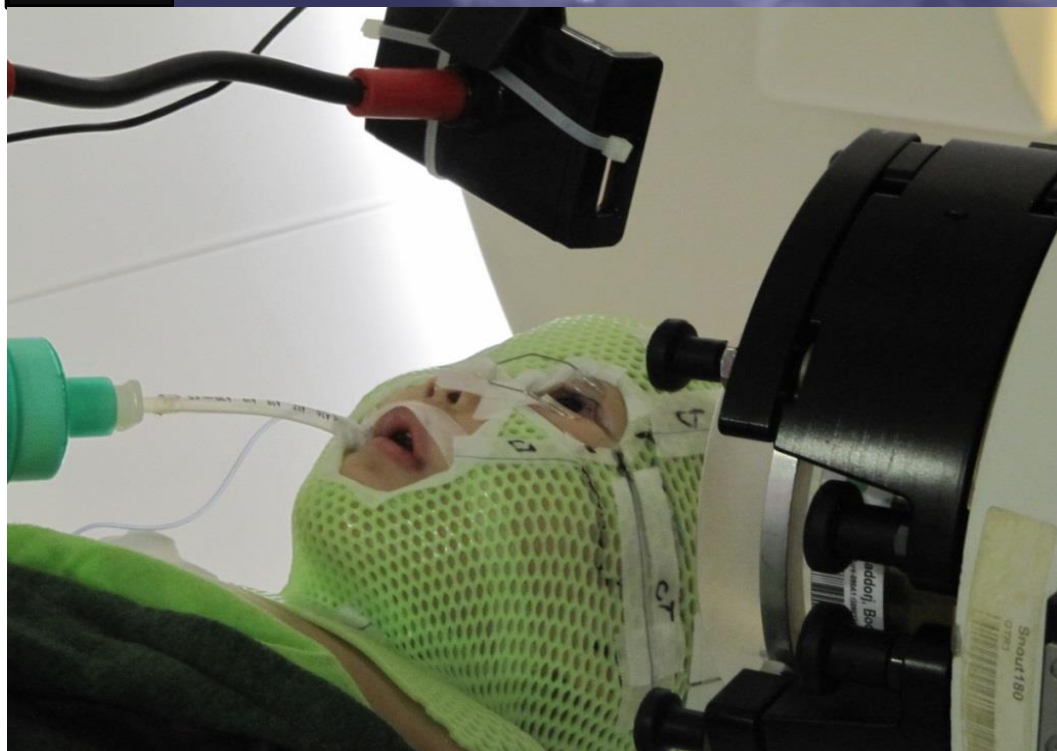
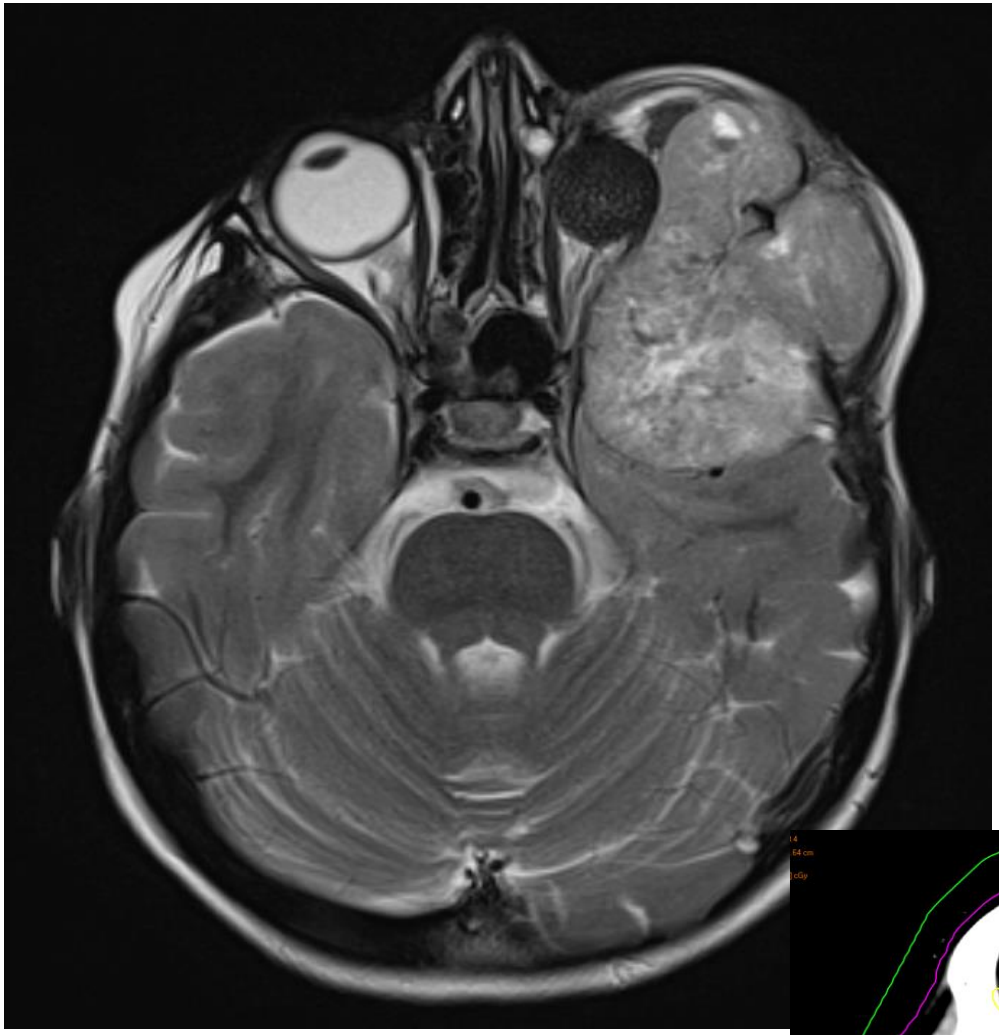


RETINOBLASTOMA @ WPE

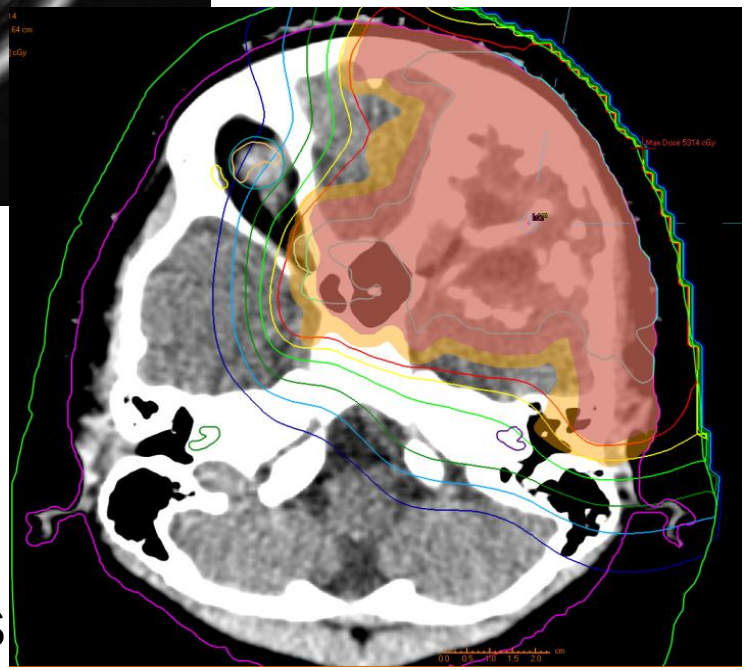


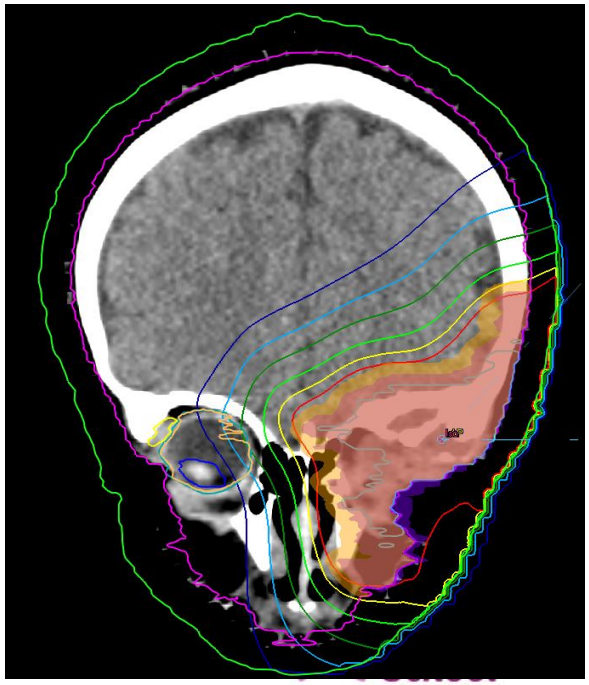




RB Case at WPE

- ♀ 7.5 years old
- 11-2008: D/ Bilateral RB
  R/ Enucleation left eye
  2 x Chemotherapy
  XRT right eye (50Gy/2Gy)





2015:
Swelling left para-ocular region

D/ undiff. Sarkoma

R/Chemotherapy following CWS

Treating RB at WPE

- Secondary sarcoma after XRT (of the contralateral side!)

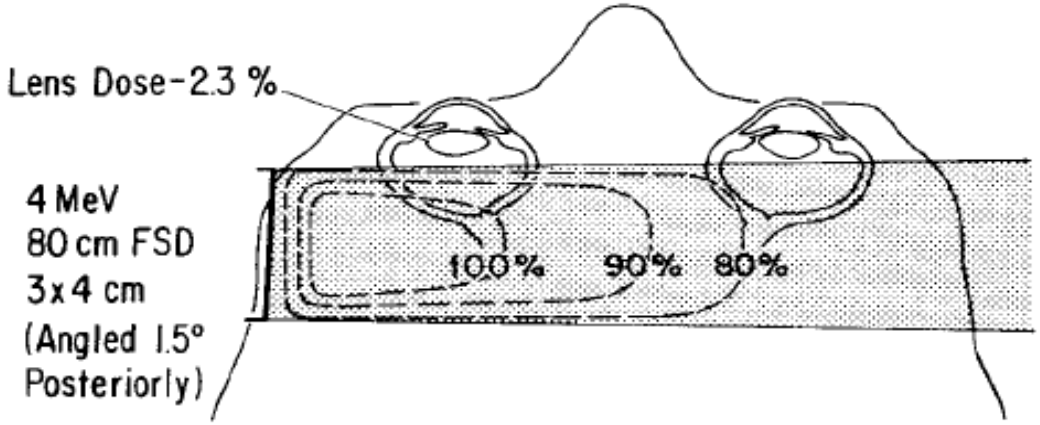
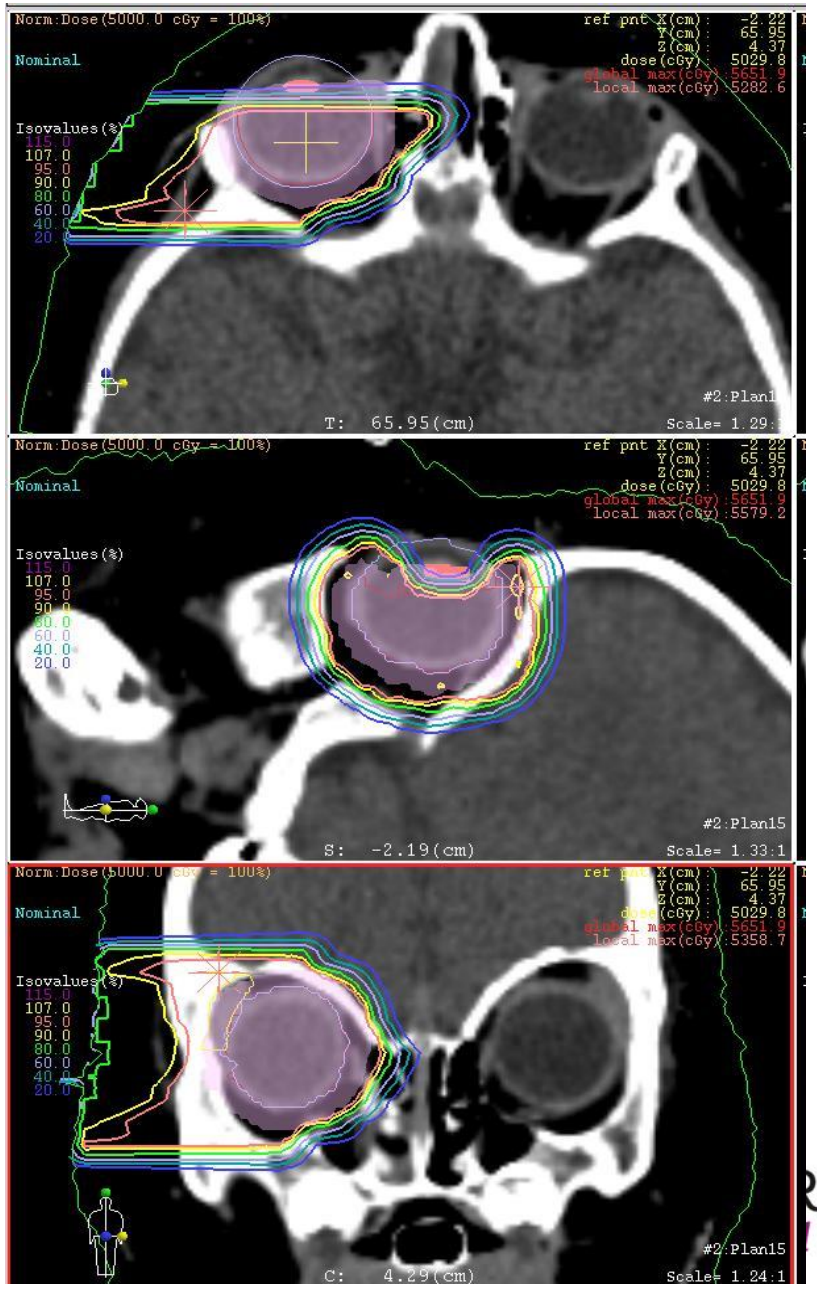


Fig. 2. Computer-calculated isodose distribution for a single 3 × 4-cm lateral field using a 4 MeV Varian linear accelerator. The anterior beam edge is placed at the bony canthus and the beam angled 1.5° posteriorly if the contralateral eye remains in place. Ipsilateral lens dose is estimated using a Li_2BO_4 thermal luminescent dosimeter.



Proton Beam Therapy

- Background
- Experiences
- WPE – West German Proton Center Essen
- Retinoblastomas
- **Conclusion**

Conclusion

- **Proton therapy offers a CHANCE** for improved sparing of normal tissue (or dose intensification)
- Aim to **reduce adverse events and SMN** (less often for intensification in the pediatric cohorts)
- **Increasing role in children** worldwide
- Growing experiences in **CNS tumours and others**
- Advantage greater **for large target volumes, in high doses and in very young**
- To be implemented into **multidisciplinary framework/trials** (SIOP, GPOH…)
- At WPE/Essen particular focus on children
- **Increasing capacity** in Europe
- **Data** on PT (as on any other technique!) to be collected and evaluated (toxicity/TU but also QoL & neuropsych.)
- **Education & training extremely important**

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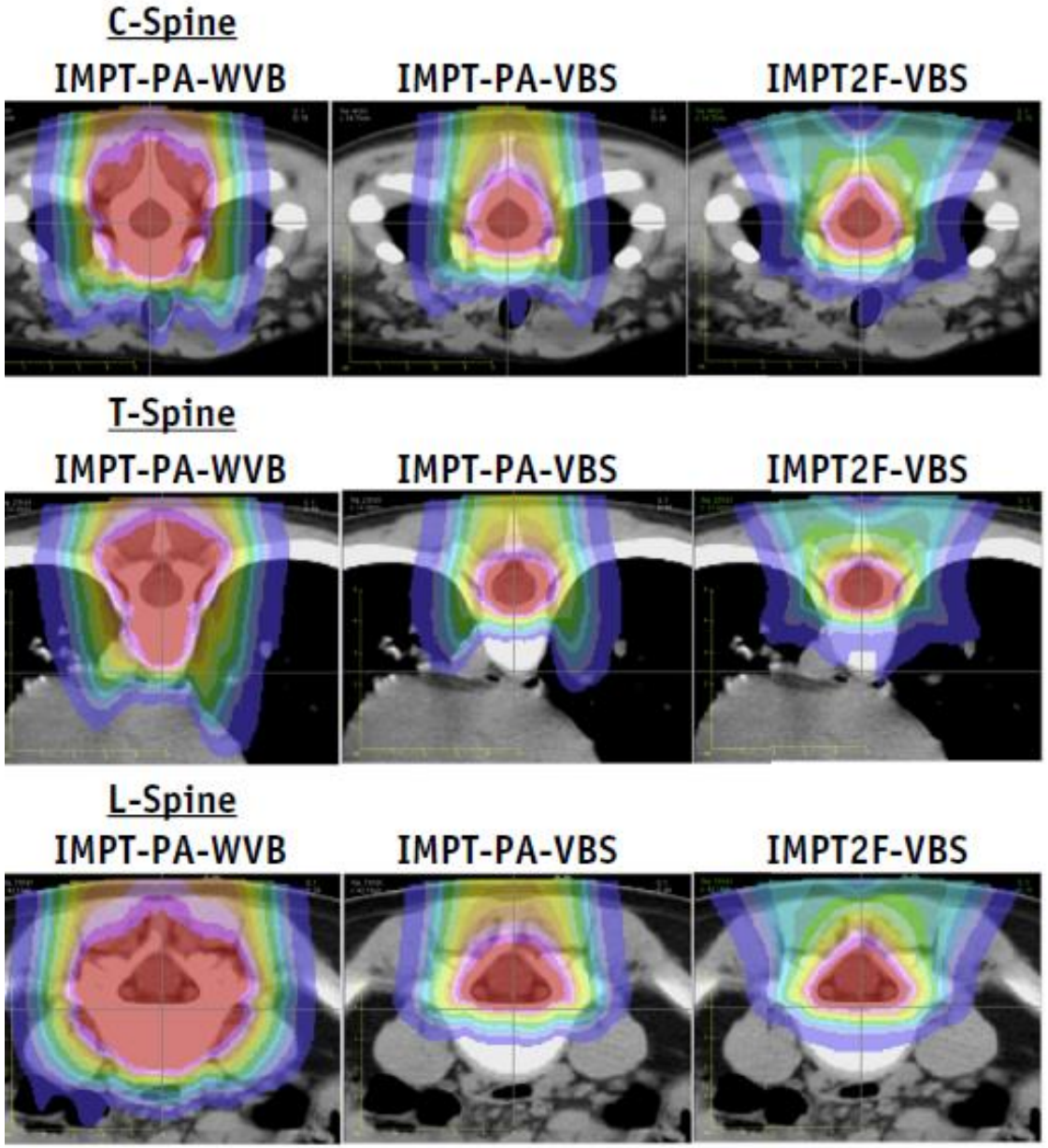
New considerations

- Using IMPT to spare bone at the anterior and posterior vertrebral body and reducing dose to the spinal canal only?



Vertebral sparing craniospinal irradiation 39

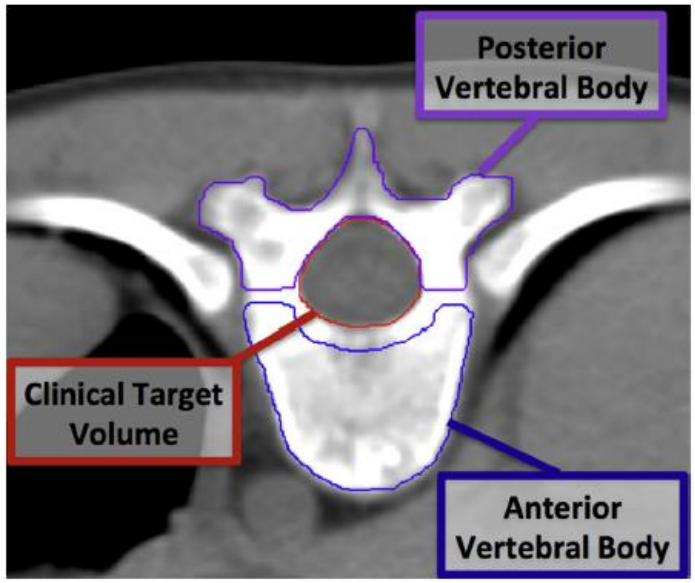


Fig. 1. Vertebral body contouring, including the clinical target volume (red line) and anterior (blue) and posterior (purple) vertebral body. (A color version of this figure is available at www.redjournal.org.)

Giantsoudi et al, IJROBP 2017

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Recommendation for Literature

Cite this article as: Chhabra A, Mahajan A. Treatment of common pediatric CNS malignancies with proton therapy. Chin Clin Oncol 2016;5(4):49. doi: 10.21037/cco.2016.06.02

Review Article

Treatment of common pediatric CNS malignancies with proton therapy

Arpit Chhabra[1], Anita Mahajan[2]

Cancers **2015**, *7*, 706-722; doi:10.3390/cancers7020706

Review

Dosimetric Comparison and Potential for Improved Clinical Outcomes of Paediatric CNS Patients Treated with Protons or IMRT

Kris S. Armoogum [1,†,*] and Nicola Thorp [2,†]

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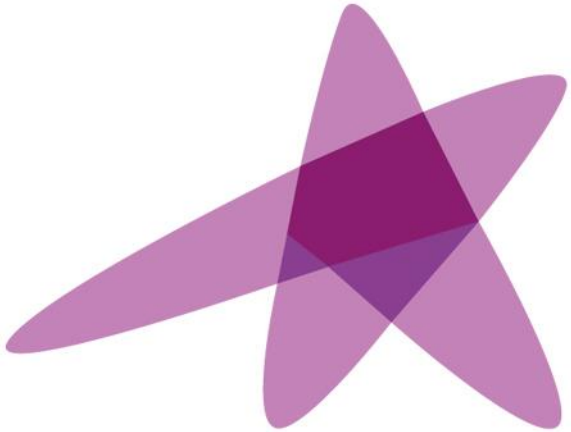
THANK YOU!

To
Team WPE/UK Essen
DKKS
HIT Study Group
Cooperating Partners

Relaxing and enjoying holidays after PT for an Ependymoma at WPE…



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Proton Therapy in childhood tumors (non - CNS)

Beate Timmermann

Essen, Germany

ESTRO School

Today‘s Topics

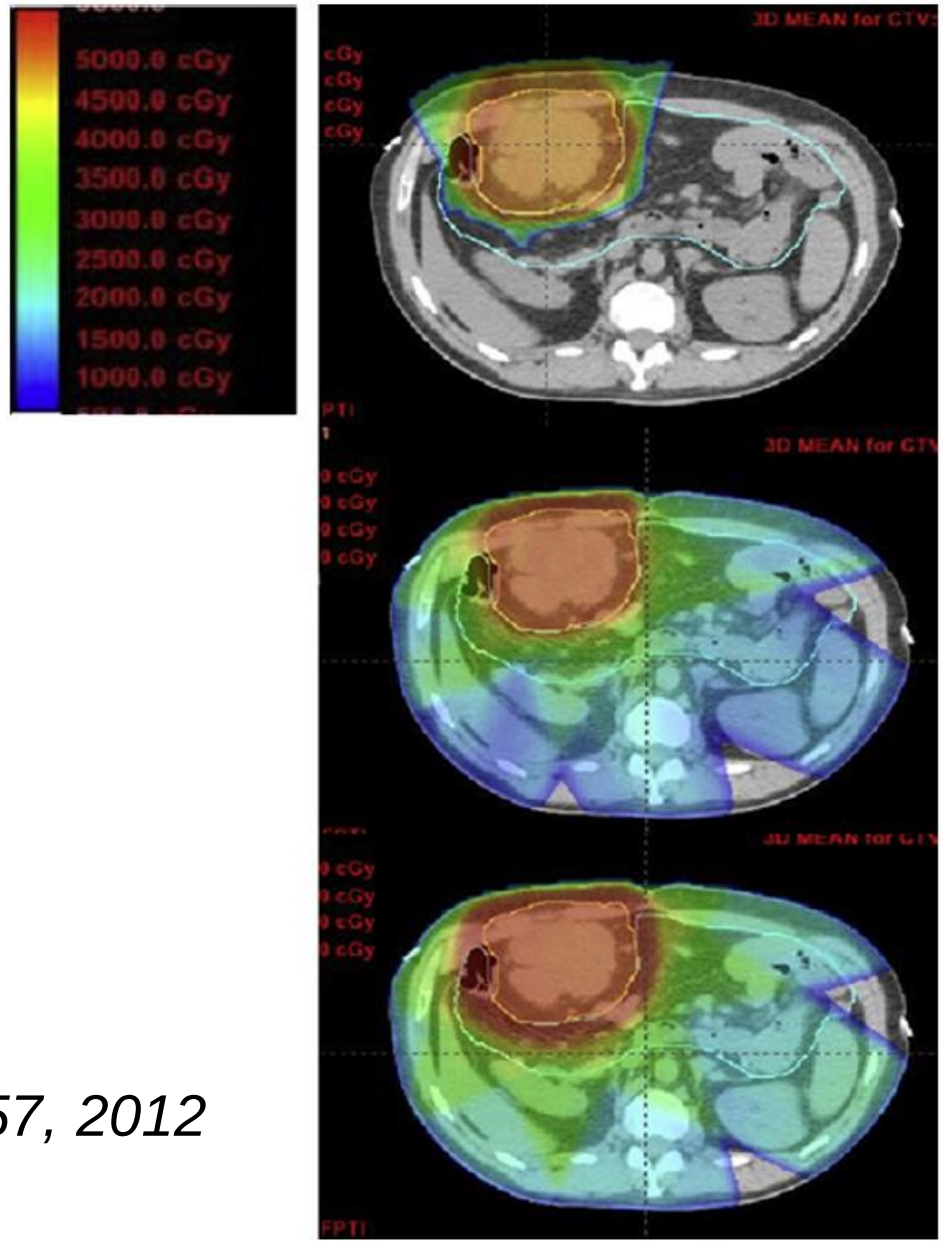
Proton Beam Therapy

- Background
- Experiences (with special emphasis on sarcomas, neuroblastomas, nephroblastomas & lymphomas)
- Experiences at WPE – the West German Proton Center Essen
- Conclusion

Proton Beam Therapy

- **Background**
- Experiences
- WPE – West German Proton Center Essen
- Conclusion

Plan Comparison

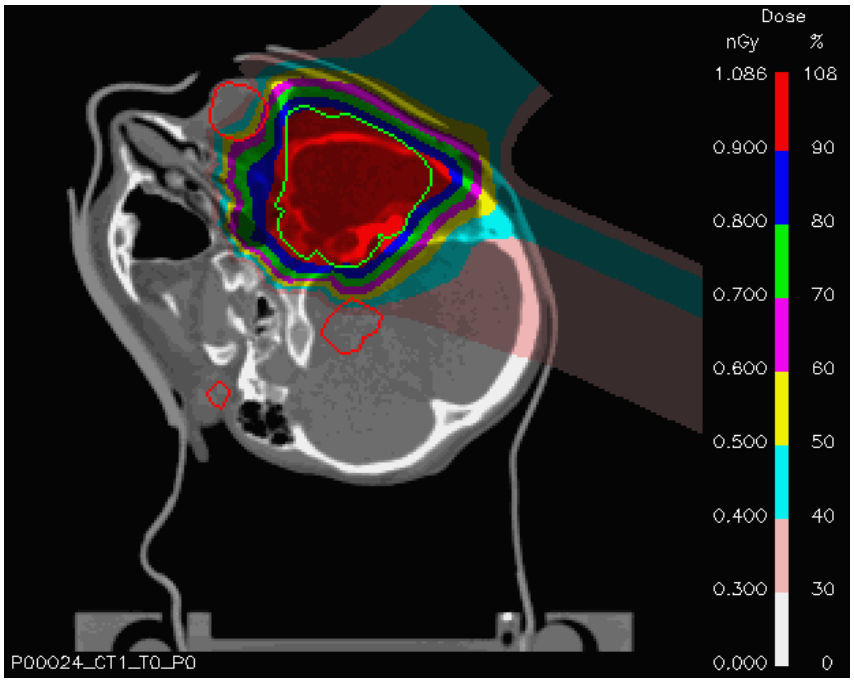


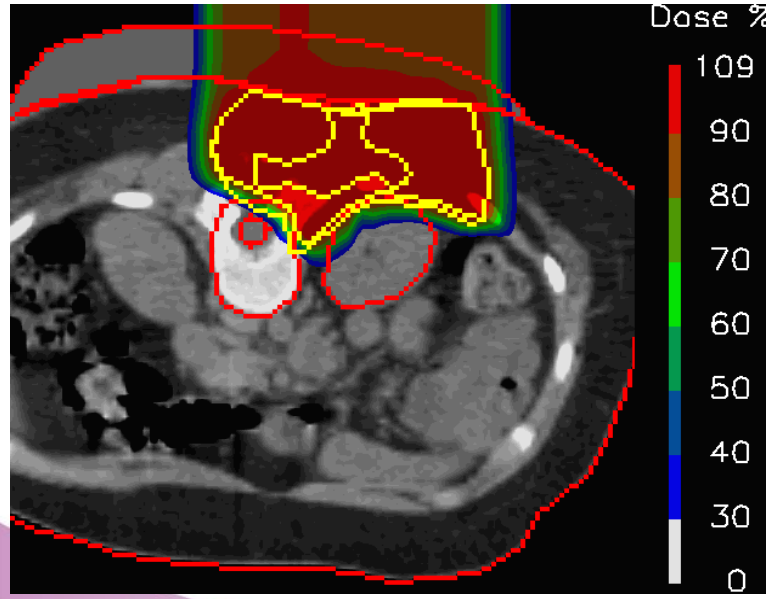
- PT is highly conformal
- Few fields needed
- Small irradiated volume

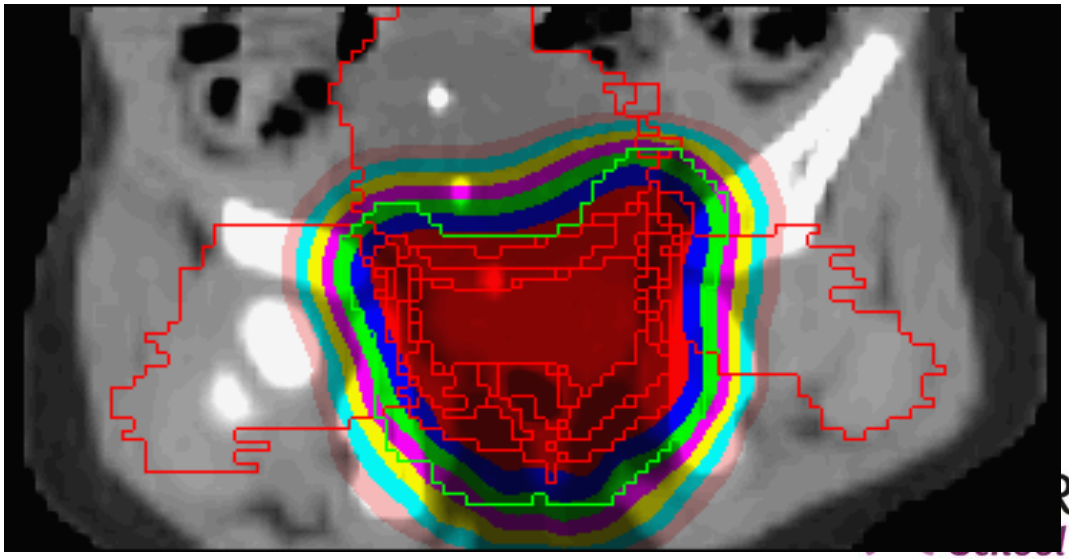
Swanson et al., IJROBP 83, 1549-57, 2012

PT in childhood sarcomas

PAUL SCHERRER INSTITUT
PSI







Proton Beam Therapy

- Background
- **Experiences**
- WPE – West German Proton Center Essen
- Conclusion

Evidence – PT in children

September 2017

	Autor	Jahr	Diagnose	n	U in Monate	retro/pros	Diagnose	Titel
Jun 17	Antonini	2017	CNS	39	42,1	pros	Brain tumors	Attention, processing speed, and executive functioning in pediatric brain tumor survivors treated with proton beam radiation therap
Jun 17	Weber	2017	Sarcomas	38	49,6	retro	Ewing Sarcoma	Pencil beam scanned protons for the treatment of patients with Ewing sarcoma
May 17	Indelicato	2017	CNS	166	30	retro	CNS tumors	Clinical outcomes following proton therapy for children with central nervous system tumors referred overseas
May 17	Fukushima	2017	Others	32	63	pros	Cancer of the brain, head, or neck	Co-morbidity and quality of life in childhood cancer survivors treated with proton beam therapy
Mar 17	MacEwan	2017	CNS	6	162	retro	Medulloblastoma	Effects of vertebral-body-sparing proton craniospinal irradiation on the spine of young pediatric patients with medulloblastoma.
Jan 17	Park	2017	CNS	20	15	pros	IGCT (Intracranial Germ Cell Tumor)	Neurocognitive and Psychological Functioning of Children with an Intracranial Germ Cell Tumor
Dez 16	Mizumoto	2016	Others	62	97,2	retro	Different	Long-term follow-up after proton beam therapy forpediatric tumors: a Japanese national survey
	Weber							ients Treated a
	Bartelh							
	Wray							
	Mizumo							
	Leiser							rapy
	Ares							
	Yock							
	Eaton							Therapy: A Co
	Kahalle							Brain Tumors
	Rotond							ical prognostic
	Eaton							
	Mizumo							
	Weber							chemo-radiat
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	Bishop							l analysis of ou
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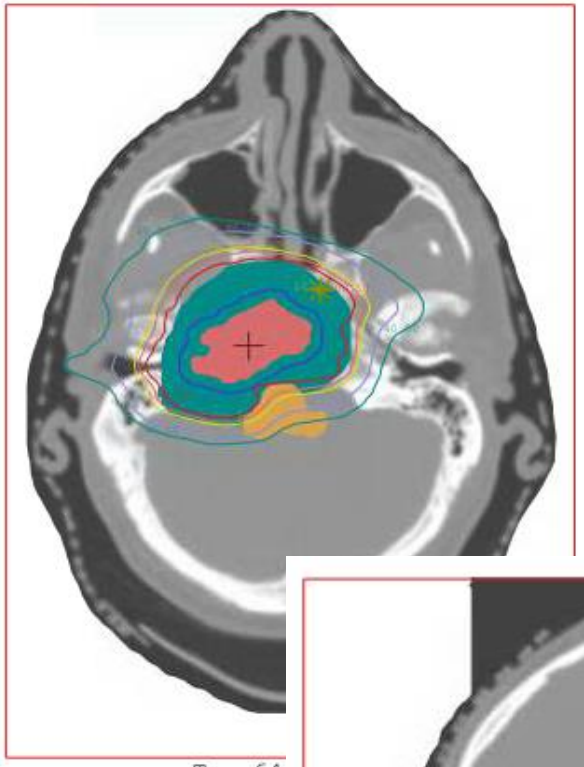
	Jimene							
	MacDo							
	De Am							ors
	Suneja	2013	CNS	46		retro	CNS	Acute toxicity of proton beam radiation for pediatric central nervous system malignancies
	Mizumoto	2013	CNS	26	19,4	retro		
	Rombi	2013	CH/CS	26	46	pros	Chordoma/Chondrosarkoma	Spot-scanning proton radiation therapy for pediatric chordoma and chondrosarcoma: clinical outcome of 26 patients treated at pa
	Oshiro	2013	Others	14	36	retro		
	Rombi	2012	Sarcomas	30	38,4	retro	EWING Sarcoma	Proton radiotherapy for pediatric Ewing's sarcoma: initial clinical outcomes
	Amchaush	2012	CNS	8	26	pros	Ependymoma	Proton therapy for spinal ependymomas: planning, acute toxicities, and preliminary outcomes

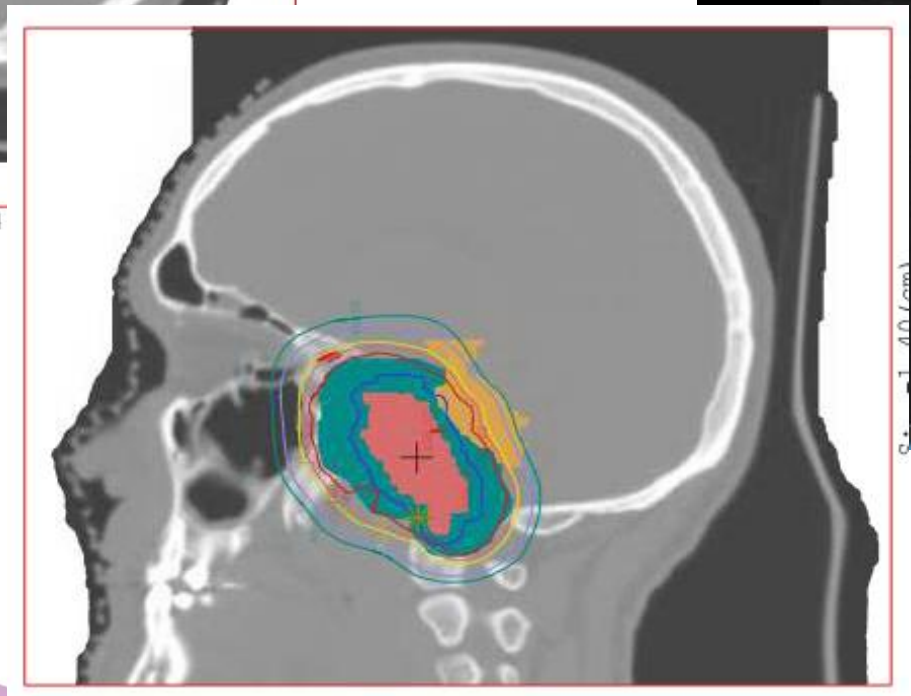
Diagnosis	reports, n	Patients, n	FUs (months)
CH/CS	7		
CNS	44		
Sarcomas	11		
Others	13		
1995-2017	75 total	3328 total	
	18 prospective	44.4 mean	41.8 mean

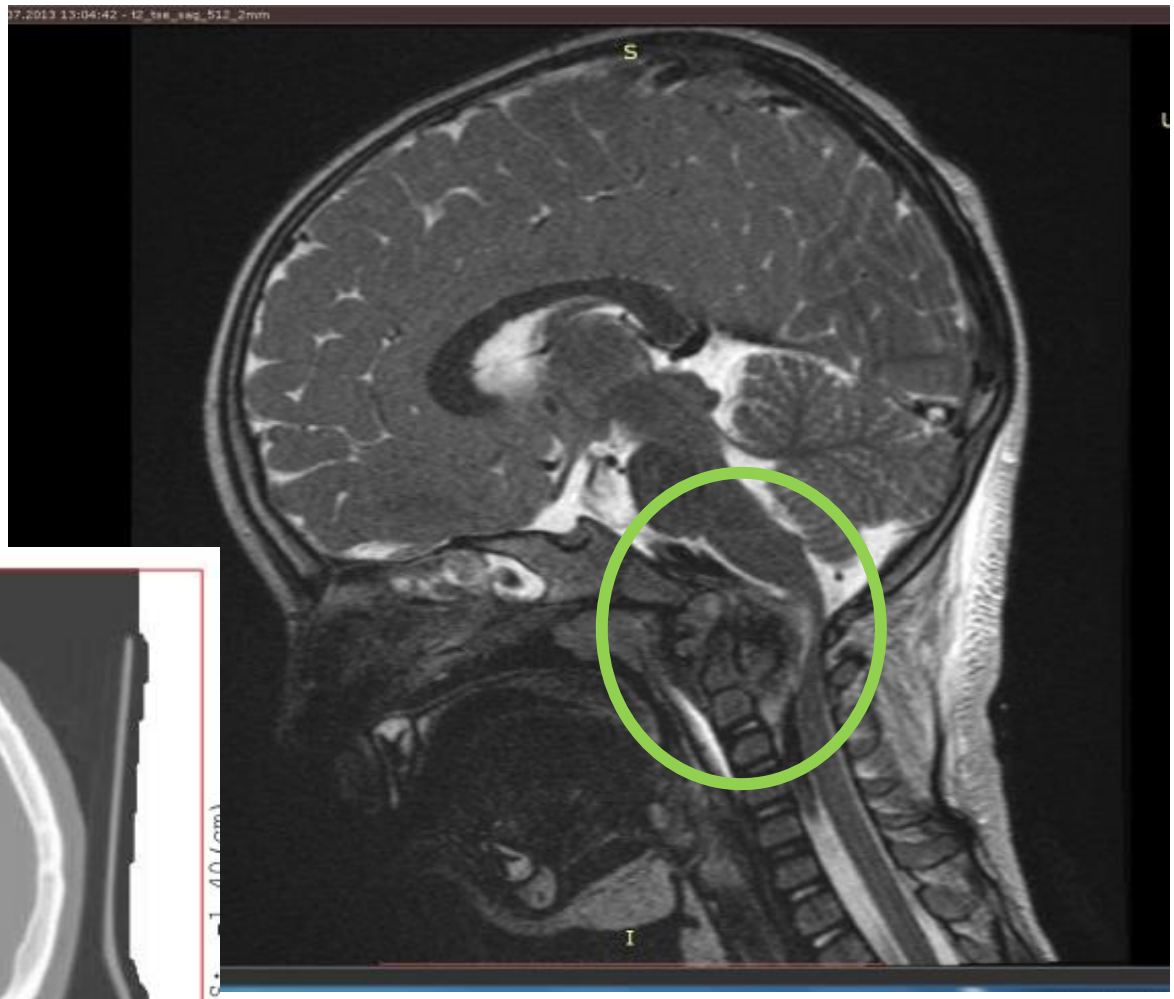
Evidenz PT | Evidenz IMPT

School

Standard: PT in Chordomas / Chondrosarcomas







PT on chordomas

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Table 1. Treatment results and late toxicity rates after radiotherapy (RT) of chordomas (CH) and chondrosarcomas (CS). FSRT: fractionated stereotactic radiotherapy; n.i.: no information provided; TL injury: temporal lobe injury.

Tabelle 1. Therapieergebnisse und Spättoxizitätsraten nach Strahlentherapie (RT) von Chordomen (CH) und Chondrosarkomen (CS). FSRT: fraktionierte stereotaktische Strahlentherapie; n.i.: keine Informationen vorliegend; TL injury: Temporallappenläsion.

Author, year	Patients (n)	RT modality	Tumor dose (GyE)	Local control	Late toxicity rate grade 3–4
Catton et al., 1996 [4]	48	Photons	50 (median)	23%/3 y (CH)	n.i.
Romero et al., 1993 [34]	18	Photons	50.1 (mean)	17%/5 y (CH)	n.i.
Debus et al., 2000 [8]	45	Photon (FSRT)	66.6 (median, CH) 64.9 (median, CS)	50%/5 y (CH) 100%/5 y (CS)	2.2%
Munzenrider & Liebsch, 1999 [27]	519	Protons + photons Protons + photons	66–83	73%/5 y (CH 98%/5 y (CS)	13% TL injury 4.4% optic neuropathy
Hug et al., 1999 [14]	58	Protons	70.7 (mean)	79%/5 y (CH) 100%/5 y (CS)	7%
Noel et al., 2001 [30]	45	Protons + photons	67 (median)	83%/3 y (CH) 90%/3 y (CS)	4.4%
Benk et al., 1995 [1]	18	Protons + photons	69 (median)	63%/5 y (CH)	5.5% TL injury
Castro et al., 1994 [3]	223	Helium ions	65 (median)	63%/5 y (CH) 78%/5 y (CS)	20%
Present series	67	Carbon ions	60 (median)	87%/3 y (CH) 100%/3 y (CS)	5.9% TL injury 1.4% optic neuropathy

Chordomas / Chondrosarcomas

In children LCR up to 90-100% LC (Orsay & PSI !)

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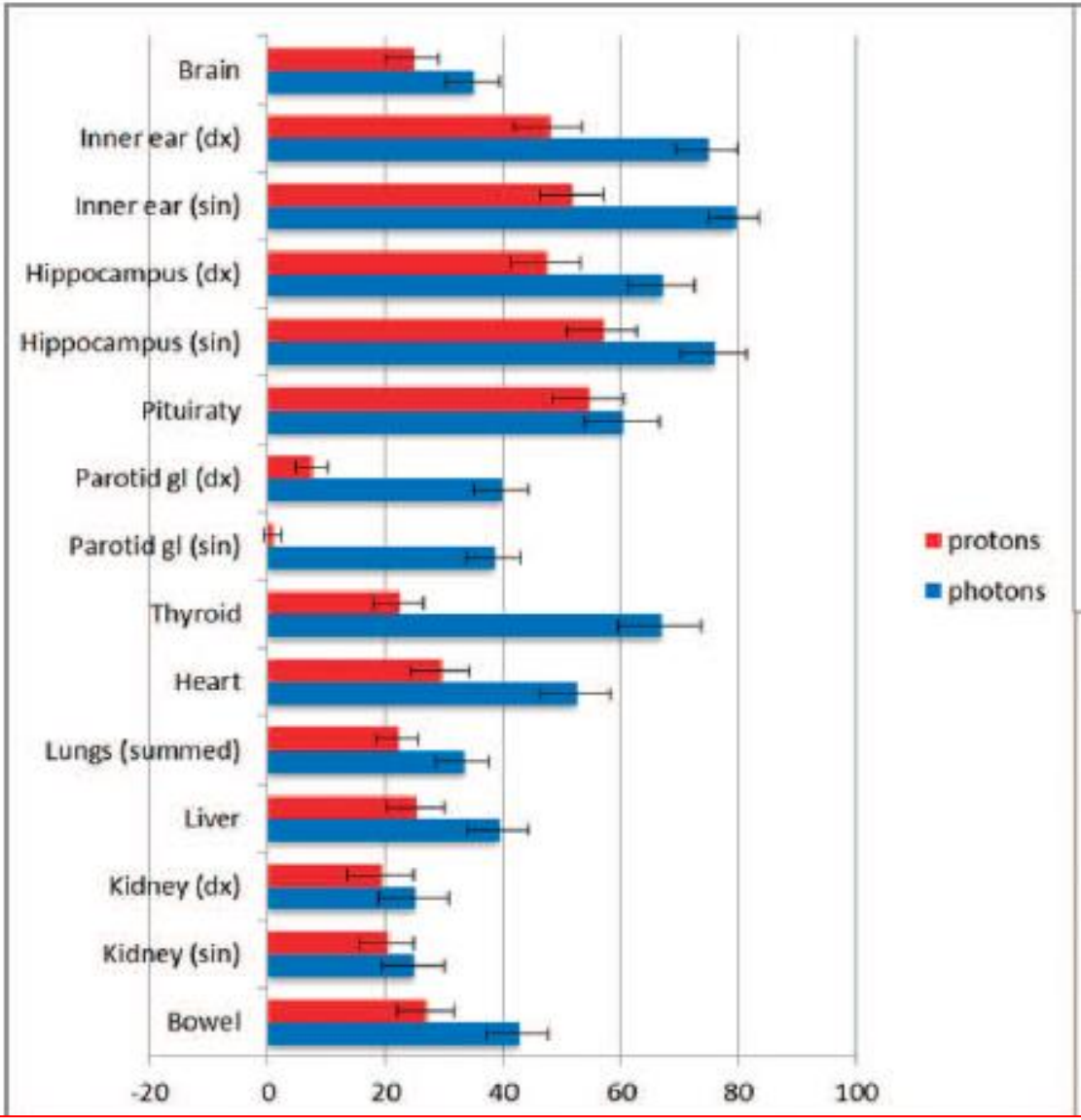
Table 1. Diagnoses, treatment areas, and prescribed doses.

Diagnosis	No. of cases	Area of treatmer (No. of cases)	Prescribed dose, Gy(RBE)
ALL	2	CNS (2)	12, 12
AML	1	Thorax (1)	24
Bladder cancer	1	Abdomen (1)	45
Ependymoma	4	CNS (4)	54, 54.6, 54, 54
Ewing sarcoma	5	Thorax (2), abdomen (3)	54, 45, 54, 63, 54
Giant cell tumor in sella turcica	1	CNS (1)	50.4
Glioma	2	CNS (2)	50.4, 54
Hodgkins disease	3	H&N (1), thorax (2)	19.8, 19.8, 19.8
Medulloblastoma (boost)	3	CNS (3)	21.6, 32.4, 32.4
Neuroblastoma	3	Abdomen (3)	21, 21, 21
Neurocytoma	1	CNS (1)	50.4
Peripheral nerve sheath tumor	1	Abdomen (1)	32.4
Plexus papilloma (boost)	1	CNS (1)	19.8
Pontine glioma	7	CNS (7)	54, 49.7, 49.8, 54, 55.8, 54, 54
Rhabdomyosarcoma	3	H&N (2), abdomen (1)	41.4, 41.4, 32.4
Sarcoma	4	H&N (2), abdomen (2)	45, 54, 54, 25.5
Wilms tumor	3	Thorax (1), abdomen (2)	10, 16.5, 36
Total	45		

Abbreviations: RBE, relative biological effectiveness; ALL, acute lymphocytic leukemia; CNS, central nervous system; AML, acute myeloid leukemia; H&N, head and neck.



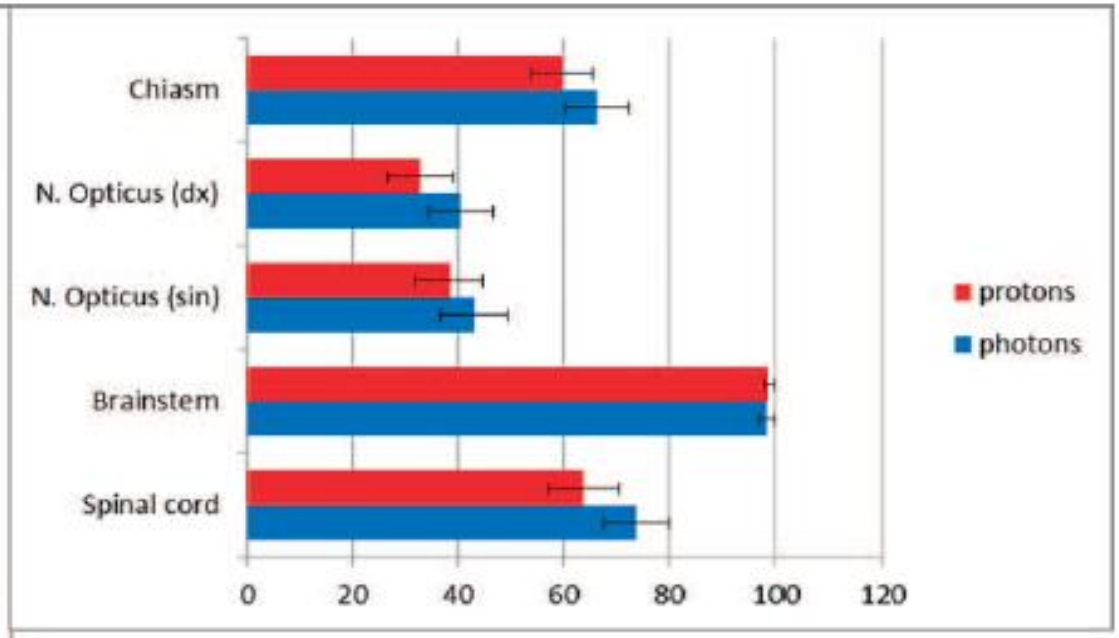


Figure 3. Doses to OARs. Mean doses (left panel) and $D_{2\%}$ (near maximum doses, right panel) in % of the prescribed target dose. Error bars are ± 1 SE.

Conclusions

From this study, we conclude that most pediatric/adolescent patients will gain from protons. Less gain is seen for whole brain, whole lung, whole abdomen or flank treatment.

Radiother Oncol. 2015 August ; 116(2): 309–315. doi:10.1016/j.radonc.2015.07.022.

Proton versus Conventional Radiotherapy for Pediatric Salivary Gland Tumors: Acute Toxicity and Dosimetric Characteristics

Stephen R. Grant, BS[1], **David R. Grosshans, MD, PhD**[2], **Stephen D. Bilton, CMD**[2], **John A. Garcia, CMD**[2], **Mayank Amin, CMD**[2], **Mark S. Chambers, DMD, MS**[2], **Susan L. McGovern, MD, PhD**[2], **Mary F. McAleer, MD, PhD**[2], **William H. Morrison, MD**[2], **Winston W. Huh, MD**[3], **Michael E. Kupferman, MD**[4], and **Anita Mahajan, MD**[2,*]

Table 2

Acute toxicities by CTCAE 4.0 (Grade II/III)

	All patients	Photon/electron therapy n=11 (%)	Proton therapy n=13 (%)	*P* value
Dermatitis *	13 (54)	6 (55)	7 (54)	1.00
Dysphagia‡	3 (13)	3 (27)	0	0.08
Otitis externa€	3 (13)	2 (18)	1 (8)	0.58
Mucositis§	16 (67)	10 (91)	6 (46)	<0.05

* grade II/III dermatitis=brisk erythema, moderate edema, or moist desquamation

‡ grade II/III dysphagia= pain requiring change in diet and/or nutritional support

€ grade II/III otitis= discharge from ear canal

§ grade II/III mucositis= patchy or confluent ulcerations

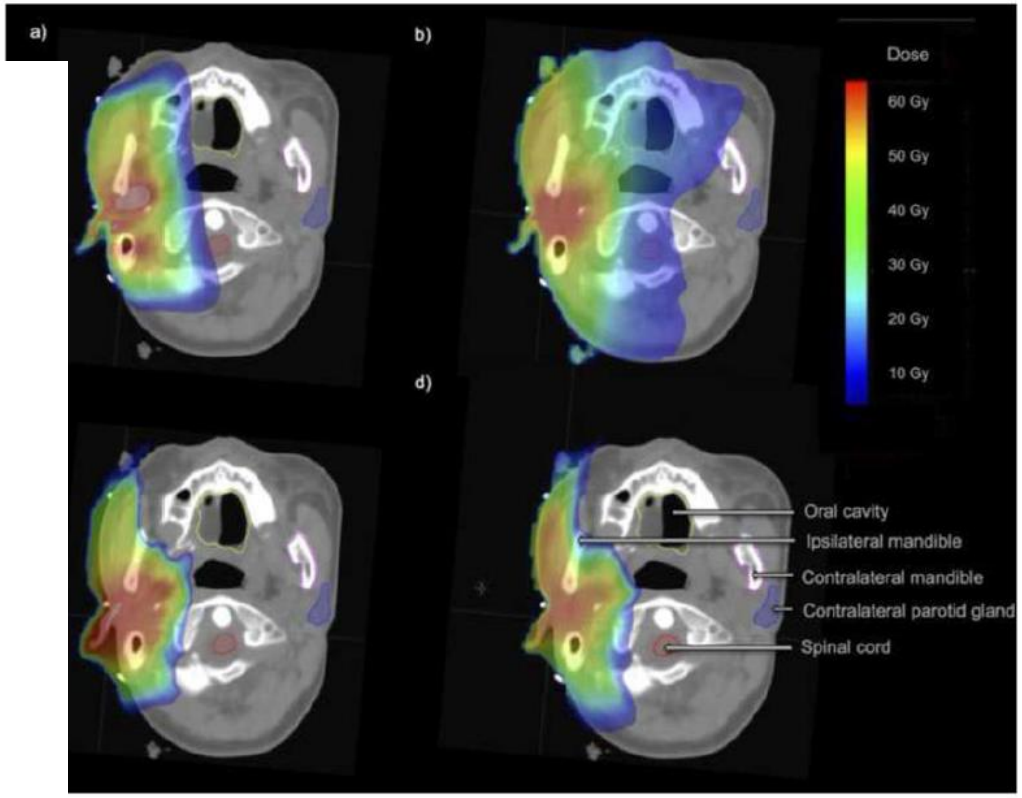
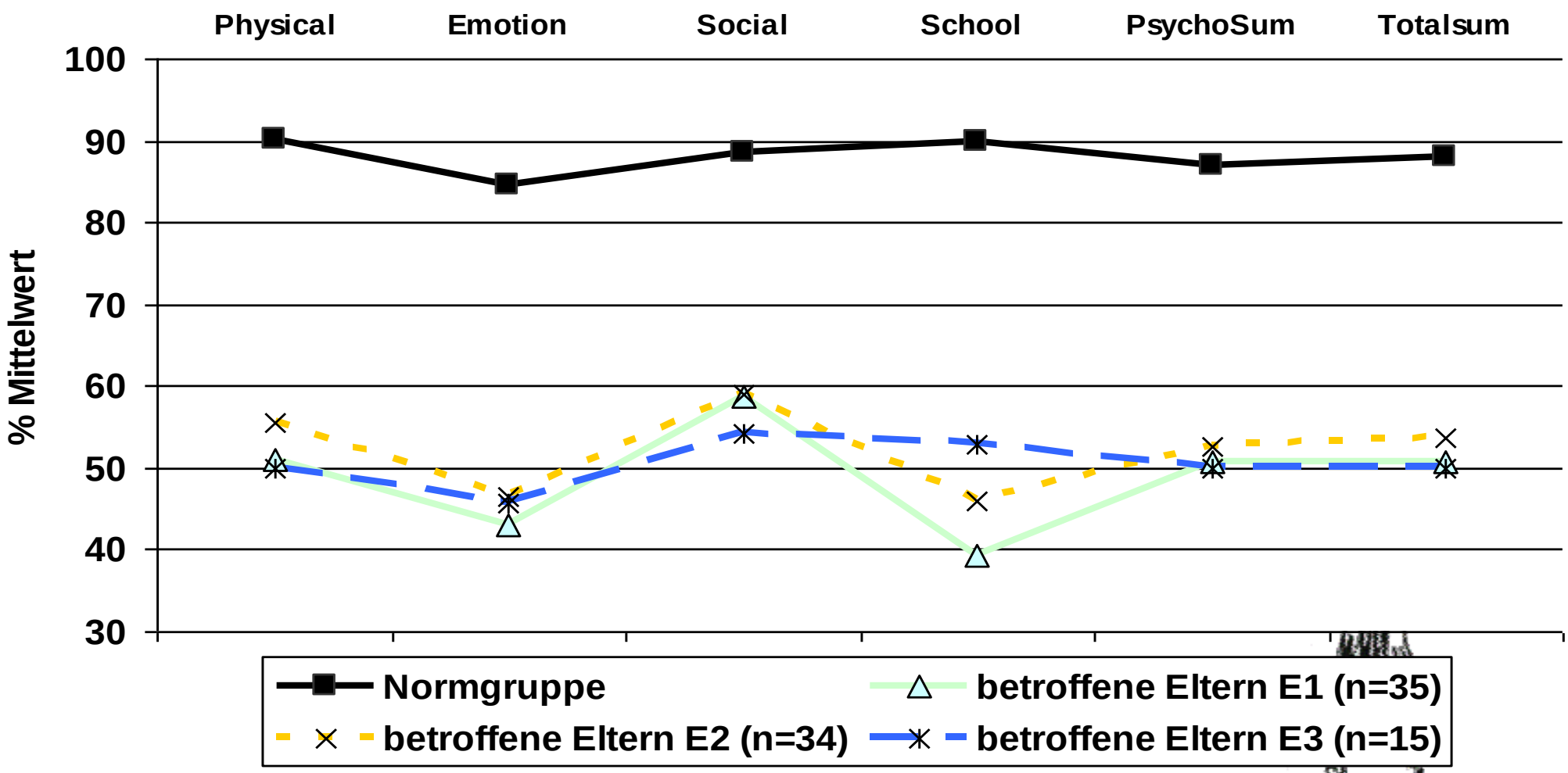


Figure 2.
Isodose line comparison of treatment plans for a patient with a right parotid gland tumor. The patient was treated with electron beam therapy (panel a), and post hoc plans were created for intensity-modulated radiotherapy (b), passive scatter proton radiotherapy (c), and intensity-modulated proton radiotherapy (d). The inhomogeneity coefficients for the respective plans were 1.21 (EBT), 1.02 (IMRT), 1.06 (PSPT), and 1.06 (IMPT).

Can PT improve QoL ?

PedsQL™ proxy-report: parents on infants



Timmermann/Calaminus 2011, unpublished

oncosuisse

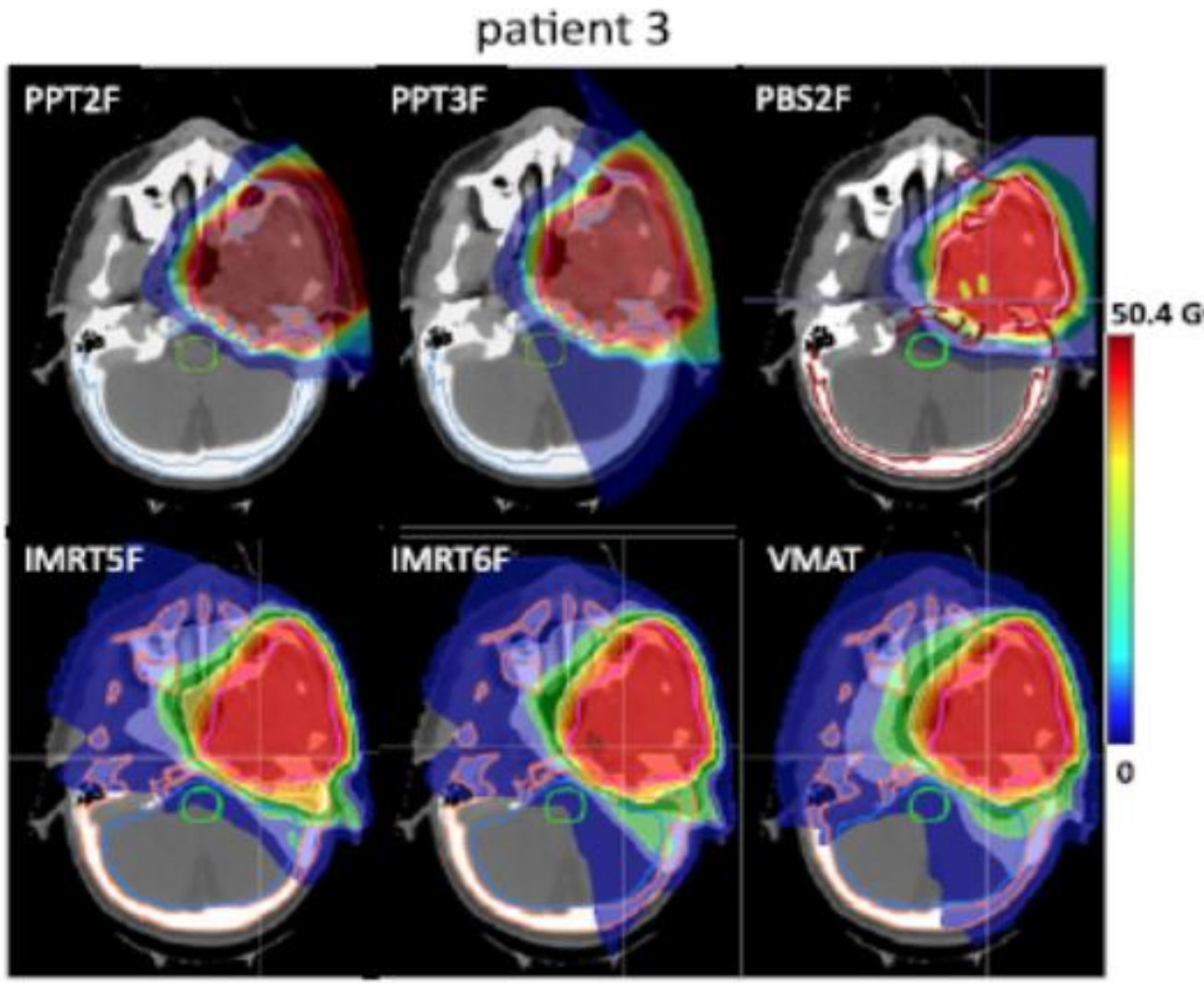
RO School

The risk of radiation-induced second cancers in the high to medium dose region: a comparison between passive and scanned proton therapy, IMRT and VMAT for pediatric patients with brain tumors

ys Med Biol 2014

Maryam Moteabbed[1,2], Torunn I Yock[1,2] and Harald Paganetti[1,2]

[1] Massachusetts General Hospital, Boston, MA 02
[2] Harvard Medical School, Boston, MA 02115, US



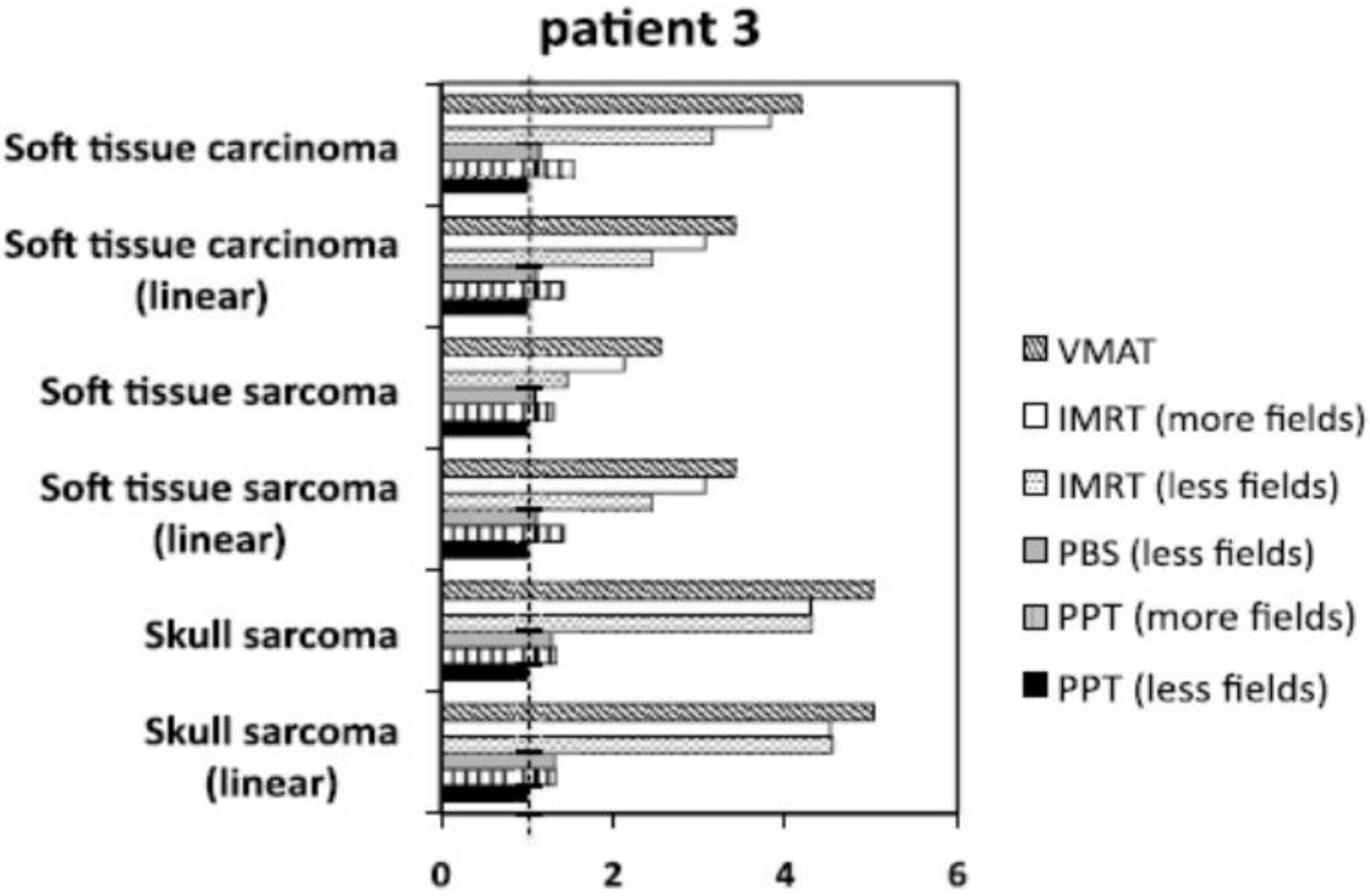


Figure 5. rLAR (ratio of lifetime attributable risk for any modality relative to protons with lesser number of fields) for all tissues/models and modalities for all patients.

Indication for PT

If

- Curative intent
- Very young age

Used in

- CNS and sarcomas
- Sometimes neuroblastomas
- Sometimes neproblastomas
- Sometimes Lymphomas (caveat: motion)

!Restrictions:

- Poor performance status, palliative intent
- Target motion – compensation methods available?
- Metal implants – uncertainties?

Sarcoma

JCO 2014

Preliminary Results of a Phase II Trial of Proton Radiotherapy for Pediatric Rhabdomyosarcoma

Matthew M. Ladra, Jackie D. Szymonifka, Anita Mahajan, Alison M. Friedmann, Beow Yong Yeap, Claire P. Goebel, Shannon M. MacDonald, David R. Grosshans, Carlos Rodriguez-Galindo, Karen J. Marcus, Nancy J. Tarbell, and Torunn I. Yock

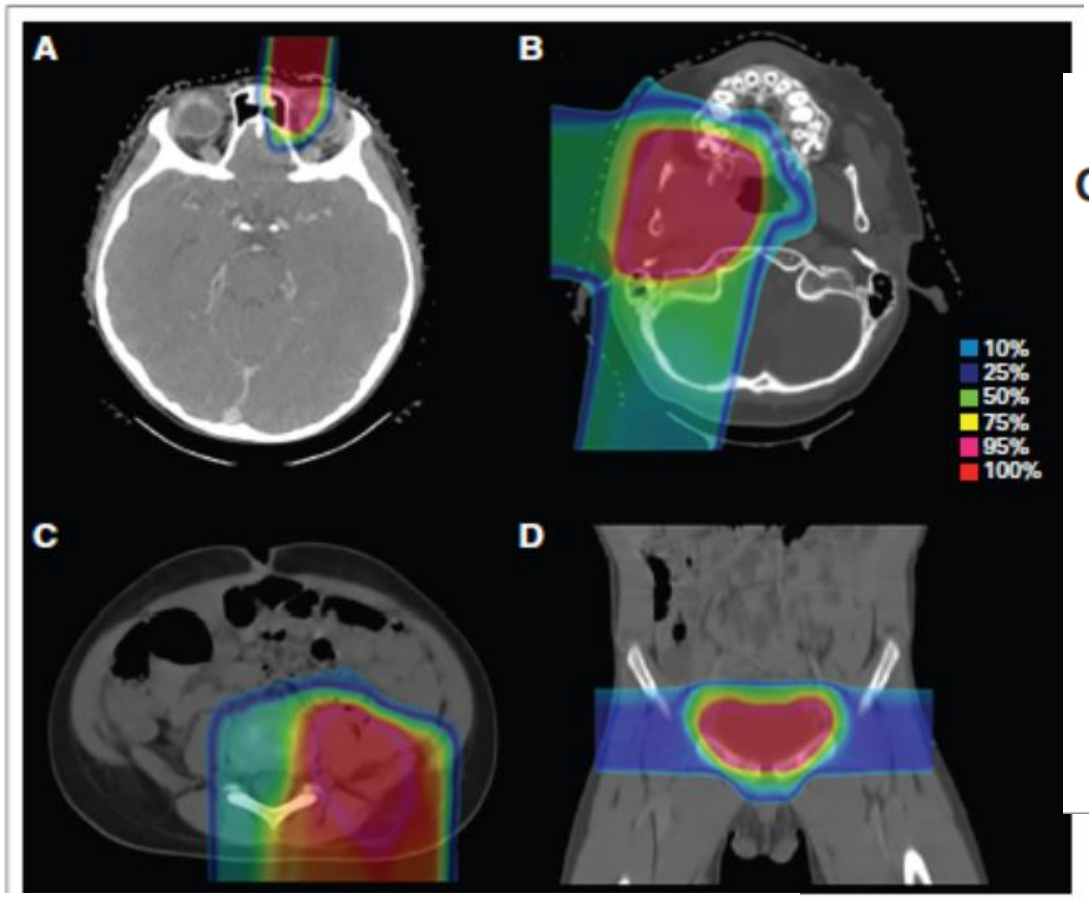
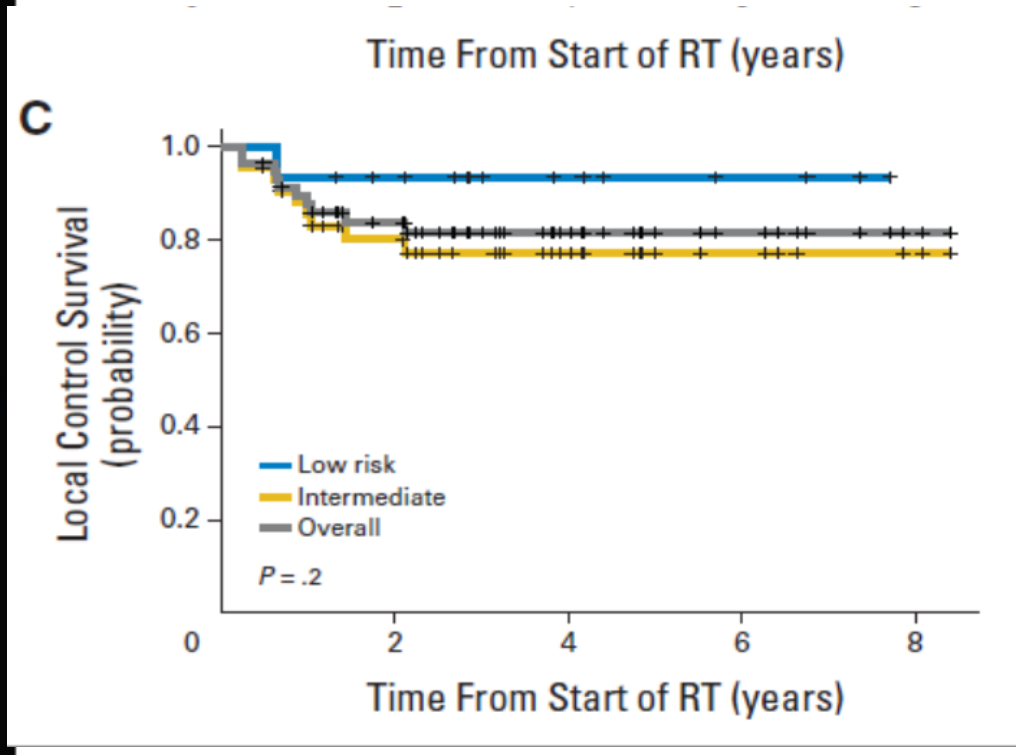


Fig 1. Proton treatment plans for patients with primaries at (A) orbital, (B) paramenin-geal, (C) trunk, and (D) prostate sites.



- FU 47 months (range, 14-102)
- Grade 3 acute tox in 11/35 pat.
- Grade 3 late tox in 3/35 pat.

IJROBP 2(

Critical Review

Proton Therapy in Children: A Systematic Review of Clinical Effectiveness in 15 Pediatric Cancers

Roos Leroy, PhD,* Nadia Benahmed, MSc,* Frank Hulstaert, MD,* Nancy Van Damme, PhD,† and Dirk De Ruysscher, PhD‡

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Received Apr 8, 2015, and in revised form Oct 5, 2015. Accepted for publication Oct 13, 2015.

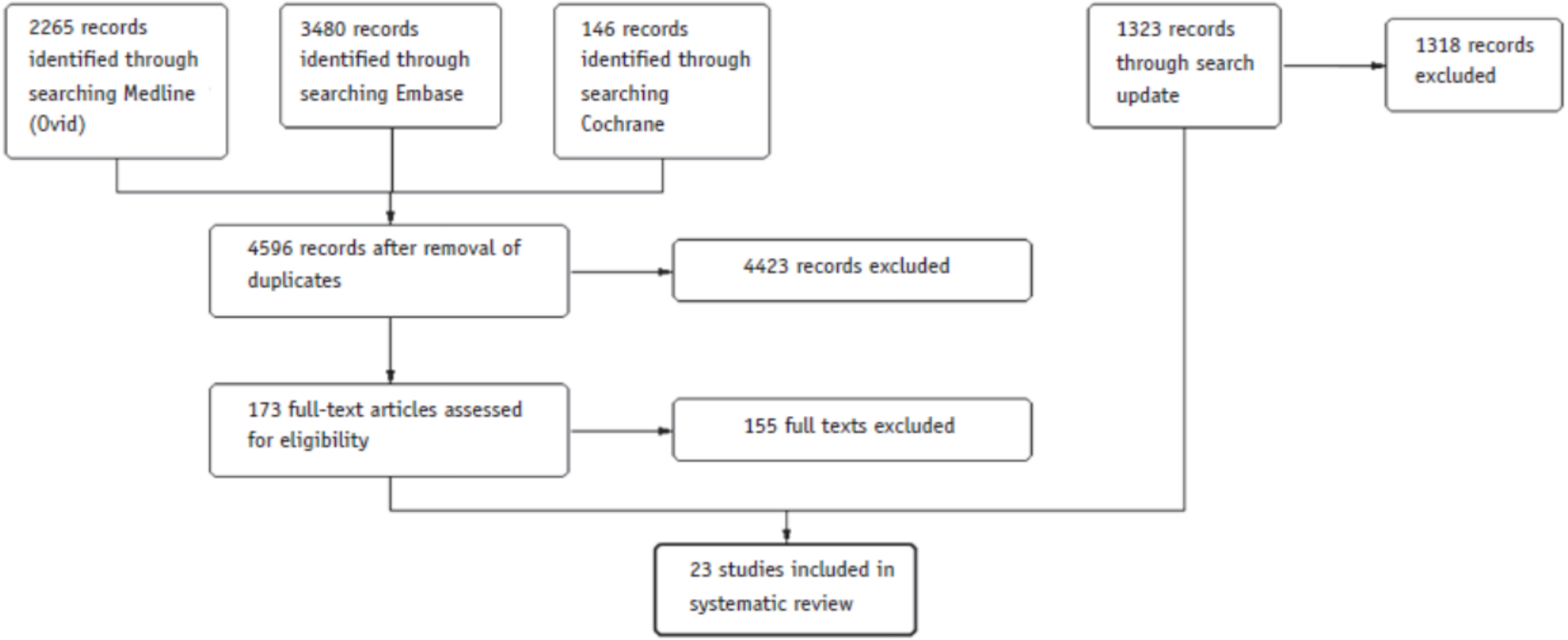


Fig. 1. Flow chart of study selection.

CH/CS

Study	Method	FU
Skull base chondrosarcoma (1 study)		
Rombi et al 2013; Villigen, Switzerland	Retrospective; case series; enrollment: 2000-2010; n = 7; age: 3.7-20.8 y (whole sample, including n = 19 with chordoma)	4.5-126.5 mon (whole sam
Skull base and (para)spinal chordoma (2 studies)		
Rombi et al 2013; Villigen, Switzerland	Retrospective; case series; enrollment: 2000-2010; n = 19; age: 3.7-20.8 y (whole sample, including n = 7 with chondrosarcoma)	4.5-126.5 mon (whole sam
Habrand et al 2008; Orsay, France	Retrospective; case series; enrollment: 1996-2006; n = 26; age: 6-17 y (whole sample, including n = 3 with chondrosarcoma and n = 1 with chondroma)	5-102 months

Conclusions

At present insufficient clinical evidence to support or refute

At present insufficient clinical evidence to support or refute

Rhabdomyosarcoma (5 studies)

Fukushima et al, 2015: Tsukuba, Japan	Retrospective; case series; enrollment: 2007-2013; n = 5 (genitourinary/ pelvic RMS); age: 0.6-4.4 y	10-92 months	Variable† (including chemotherapy, photon RT, and surgery)	No	• CoR: 4/5 (80%) • CR: 4/5 (80%)
Ladra et al, 2014; Boston and Houston, USA	Prospective; case series; enrollment: 2005-2012; n = 57**; age: 0.6-19.5 y	14-102 months	Variable† (including chemotherapy and surgery)		• OS (3 y): 81% (95% CI: 67-89%) • OS (5 y): 78% (95% CI: 63-87%) • EFS (3 y): 73% (95% CI: 59-83%) • FS (5 y): 69% (5% CI: 54-81%) CR (3 y): 81%

RMS

At present insufficient clinical evidence to support or refute

Table 2 *(continued)*

Study	Method				Reported outcomes
Timmerman et al, 2007; Villigen, Switzerland	Retrospective; case series; enrollment: 1997-2005; n = 16 (n = 12 with RMS); age: 0.9-12.1 y	4.3-		and surgery)	• OS‖ (1 y): 90.9% (95% CI NR) • OS‖ (2 y): 69.3% (95% CI NR) • PFS‖ (1 y): 81.8% (95% CI NR) • PFS‖ (2 y): 71.6% (95% CI NR) • RpR: StD: 6/12; PR: 3/12; CoR: 3/12 • RcR (LR): 2/12 (17%)

Osteosarcomas, others

Nonresectable osteosarcoma (1 study)

Ciernik et al, 2011; Boston, USA	Retrospective; case series; enrollment: 1983-2009; n = 55; age: 2-76 y (n children NR)	0-196 months	Variable† (including chemotherapy,	No	• OS (2 y): 84% (95% CI: 69-92%) (5 y): 67% 5% CI: 47-80%) S (2 y): 68% 5% CI: 53-80%)

At present insufficient clinical evidence to support or refute

Pelvic sarcomas (ie, non-rhabdomyosarcoma, no

Pineal parenchymal tumors (no studies with child

PNET (no studies with children included)

Authors suggest *comparative (?!) trials*, large European registries and linking to US pediatric proton consortium registry

In German STS/Bone tumor studies…

Like CWS/STS, Ewing, Osteosarcoma study:

- Proton therapy is allowed
- It is even strongly recommended to be considered for
  - young patients,
  - parameningeal/craniofacial sites,
  - Spinal/paraspinal sites and
  - pelvic sites

Neuroblastoma

Oshiro et al. Radiation Oncology 2013, 8:142
http://www.ro-journal.com/content/8/1/142

RADIATION ONCOLOGY

RESEARCH Open Access

Clinical results of proton beam therapy for advanced neuroblastoma

- N = 14, med age 3 yrs (1-6 yrs)
- FU 21 mo (5 mo-24 yrs)
- 8 alive, NED – 5 DOD
- 1 alive with mets.

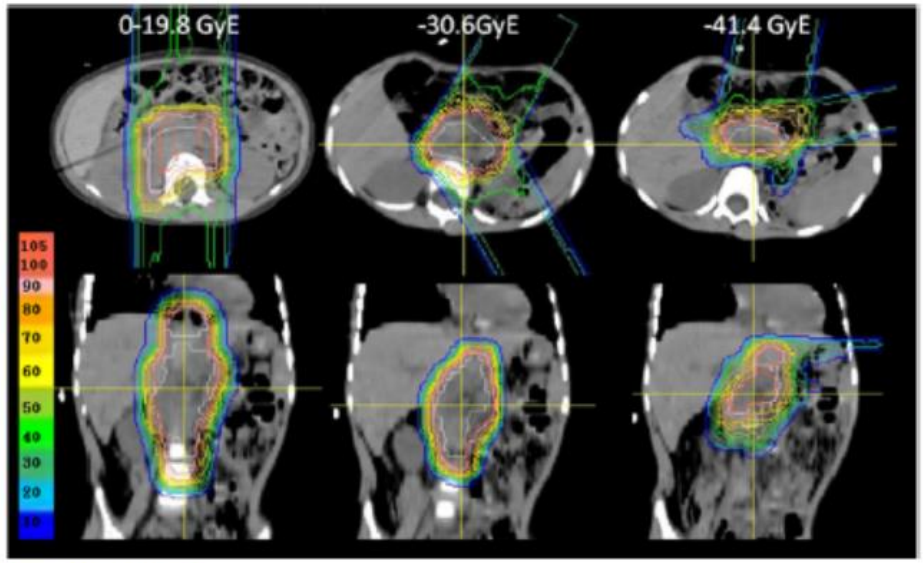
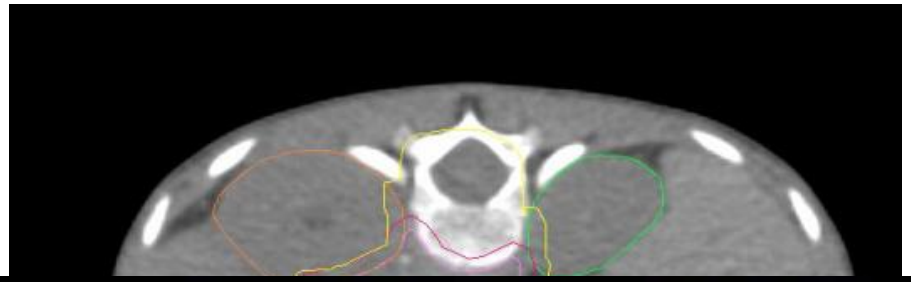


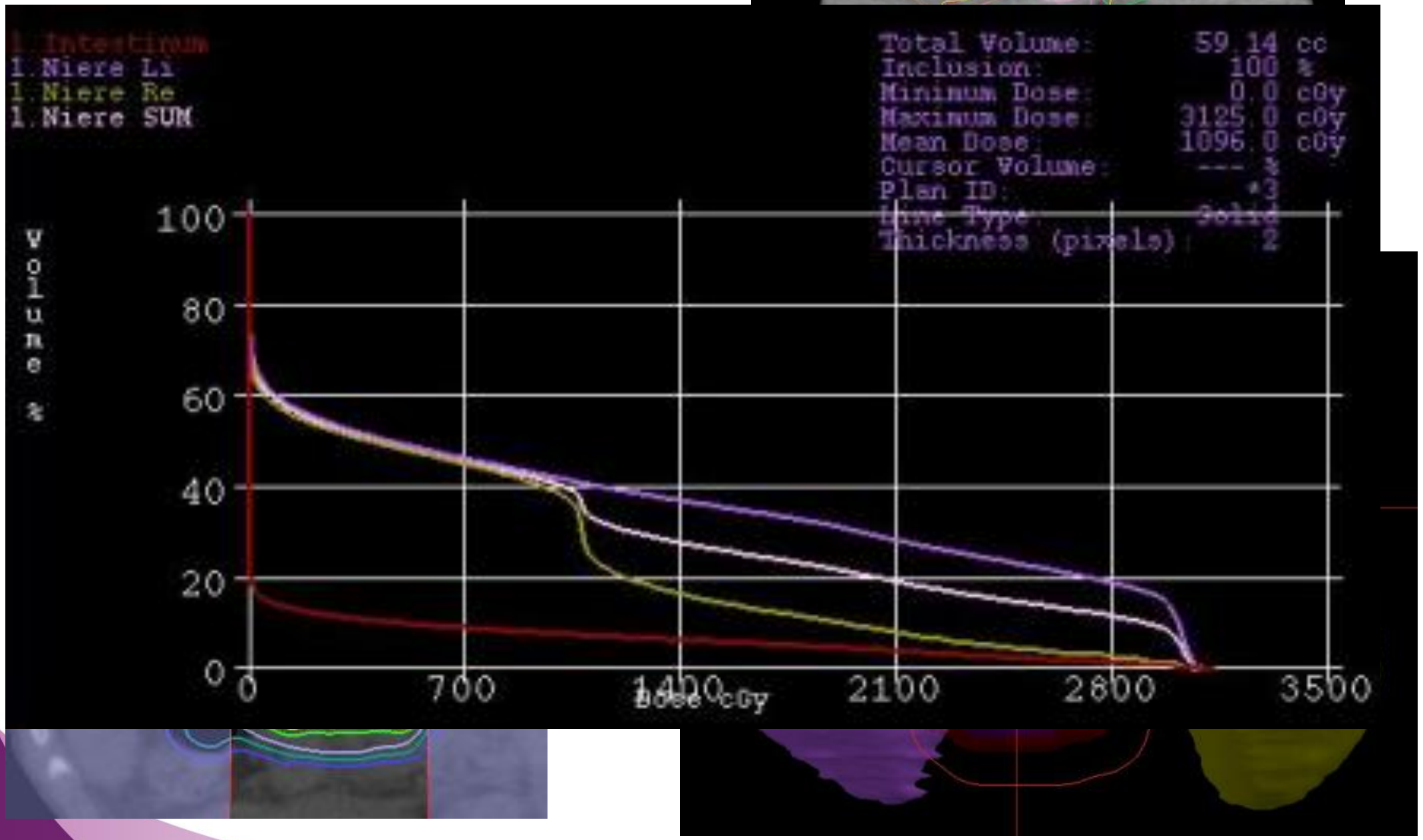
Figure 2 Dose distribution for patient No.12.

Late toxicity*
vertebral growth retardation, narrowed aorta
none
none
None
None
G1 skin pigmentation
none
thin hair
none
none
none
none
-
none

on morbidity scoring scheme of the Radiation

NB: 21.6 + 9 Gy = 30.6 Gy





Lymphoma

Proton therapy in a pediatric patient with stage III Hodgkin lymphoma

Table I. Mean dose to organs at risk.

	3DCRT	IMRT	PT*	3DCRT-PT		IMRT-PT		3DCRT-IMRT	
	Mean dose	Mean dose	Mean dose	RR	AR (Gy)	RR	AR (Gy)	RR	AR (Gy)
Body (J)**	185	201	101	45%	84	50%	100	−8%	−16
Breasts (Gy)	8.2	7.5	1.8	78%	6.4	76%	5.7	9%	0.7
Heart (Gy)	16.7	16	12.3	26%	4.4	23%	3.7	4%	0.7
Lungs (Gy)	12.6	14.1	9.4	25%	3.2	33%	4.7	−12%	−1.5
Stomach (Gy)	21.7	19.9	12.2	44%	9.5	39%	7.7	8%	1.8
Bowel (Gy)	11.2	10.2	4.7	58%	6.5	54%	5.5	9%	1
Esophagus (Gy)	18	17.9	16.2	10%	1.8	9%	1.7	1%	0.1
Liver (Gy)	3.8	6.2	0.3	92%	3.5	95%	5.9	−63%	−2.4

AR, absolute reduction; Gy, Gray; IMRT, intensity-modulated radiation therapy; J, Joule; RR, relative reduction; 3DCRT, three-dimensional conformal radiotherapy.
*PT represented in terms of relative biologic effectiveness.
**Body reflects integral dose measured in joules.

dimensional conformal radiotherapy (3DCRT), (B) intensity-modulated radiotherapy (IMRT), and (C) proton therapy (PT) plans. The clinical target volume (CTV), breasts, heart, and liver are outlined in red, pink, green and yellow, respectively.

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International Journal of Radiation Oncology biology • physics

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Critical Review

Evidence-based Review on the Use of Proton Therapy in Lymphoma From the Particle Therapy Cooperative Group (PTCOG) Lymphoma Subcommittee

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*Department of Radiation Oncology, University of Washington, Seattle Cancer Care Alliance Proton Therapy Center, Seattle, Washington; †Nuffield Department of Population Health, University of Oxford, Oxford, UK; ‡Department of Radiation Oncology, University of Pennsylvania, Philadelphia, Pennsylvania; §Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey; ‖Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York; ¶Miami Cancer Institute at Baptist Health South Florida, Miami, Florida; #Proton Therapy Department, Proton Therapy Center, Prague, Czech Republic; **Department of Radiation Oncology, Emory University School of Medicine, Atlanta, Georgia; ††Department of Radiation Oncology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan City, Taiwan; ‡‡Department of Radiation Oncology, Mayo Clinic Arizona, Scottsdale, Arizona; §§Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland; ‖‖Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, Maryland; ¶¶Department of Radiation Oncology, Institut Curie, Paris, France; ##Department of Radiation Oncology, Stanford University, Stanford, California; ***Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, Florida; †††University of Florida Health Proton Therapy Institute, Jacksonville, Florida; ‡‡‡Northwestern Medicine Chicago Proton Center, Warrenville, Illinois; and §§§Department of Oncology, University of Turin, Turin, Italy

CrossMark

Recent review paper, 2017

- Better sparing of OARs
- Few clinical data
- Randomized trials not going to happen
- PT should be considered in appropriately selected patients

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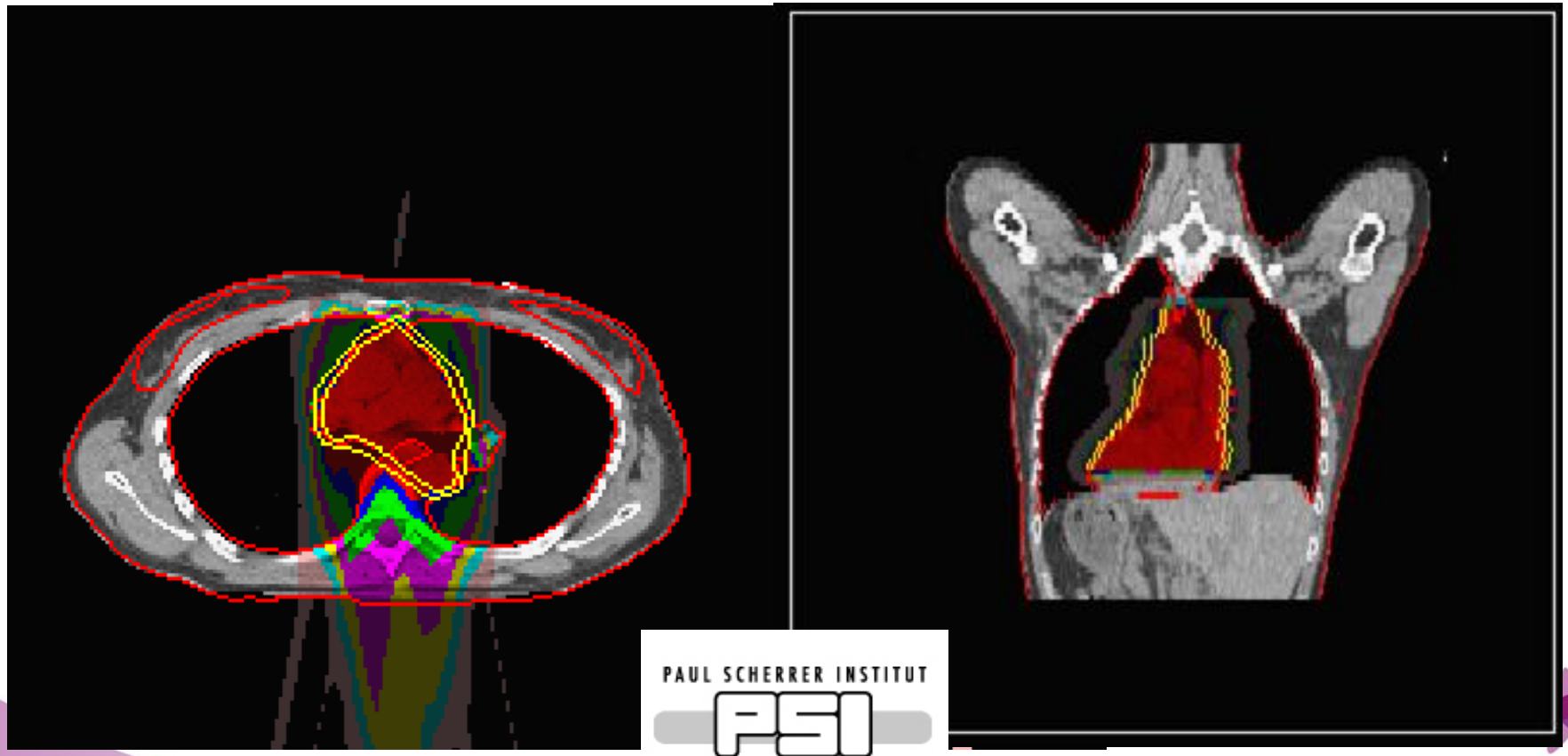
M. Hodgkin, mediastinum

- Attractive to spare female breast and potentially reduce risk for SMN!
- Caveat – Moving target in mediastinal sites



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Nephroblastoma

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DOI: 10.1002/pbc.26176

RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer

Pencil beam scanning proton therapy for treatment of the retroperitoneum after nephrectomy for Wilms tumor: A dosimetric comparison study

Jennifer Vogel[1] | Haibo Lin[1] | Stefan Both[2] | Zelig Tochner[1] | Frank Balis[3] | Christine Hill-Kayser[1]

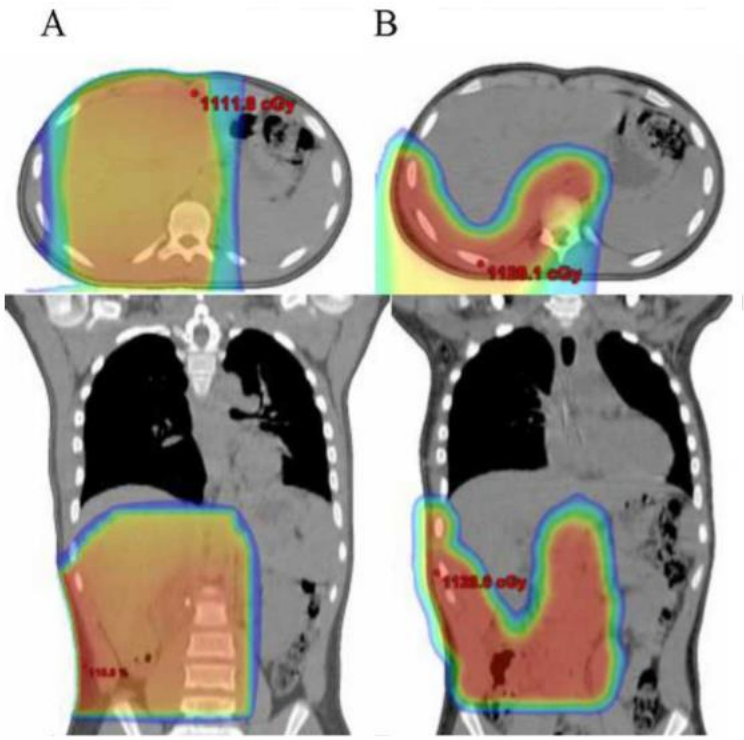


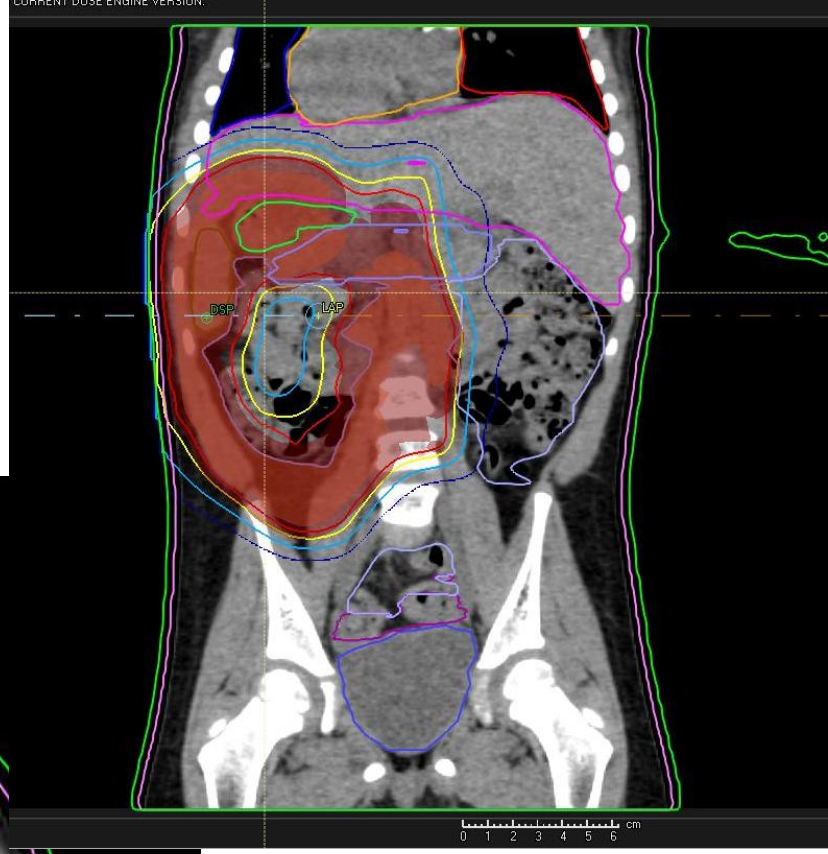
FIGURE 2 AP–PA photon (A) and PBS (B) plans for postoperative flank irradiation.

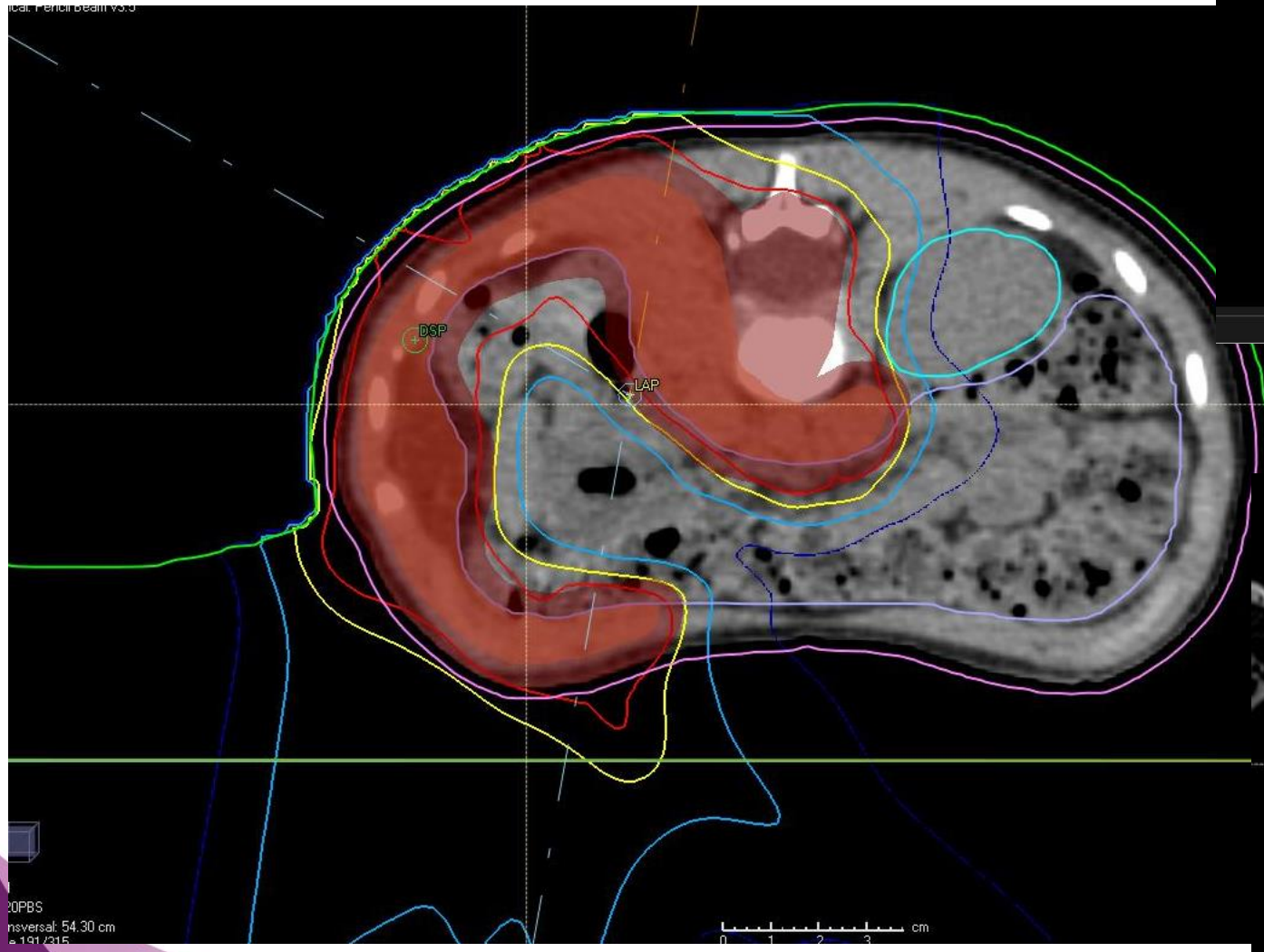
TABLE 3 Dosimetric comparisons

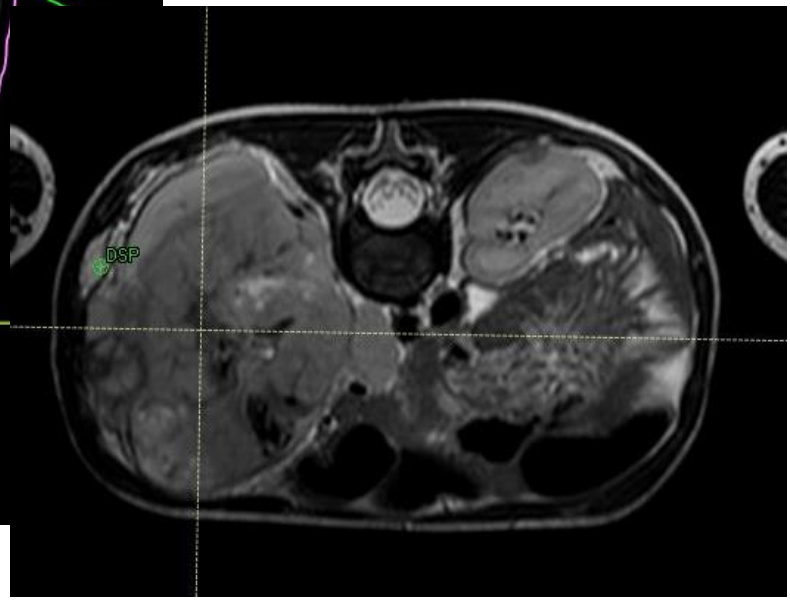
	PBS (cGy RBE)		3DCRT (cGy)		
	Median	Range	Median		
Kidney D20	96	35–297	139	5	
Kidney D50	5	0–40	78	3	
Kidney mean	52	0.6–138	135	21–259	0.009
Bowel D20	1,062	636–1,114	1,107	963–1,156	0.04
Bowel D50	47	4–999	979	114–1,129	0.004
Mean bowel	379	252–703	639	428–870	0.001
Liver D20	1,075	3–1,107	1,077	104–1,164	0.02
Liver D50	132	0–800	1,013	38–1,146	0.4
Mean liver	411	36–626	755	166–1,080	0.02
Pancreas D20	1,110	1,075–1,117	1,107	881–1,130	0.36
Pancreas D50	1,099	787–1,109	1,086	500–1,108	0.39
Mean pancreas	1,030	712–1,108	943	587–1,096	0.32
Integral dose	1,442 Gy RBE × cc	828–2,115	2,130 Gy × cc	1,158–2,792	0.05

PBS, pencil beam scanning; cGy, centiGray; 3DCRT, three-dimensional conformal radiation therapy; RBE, relative biological effectiveness.

Case from WPE – flank PT



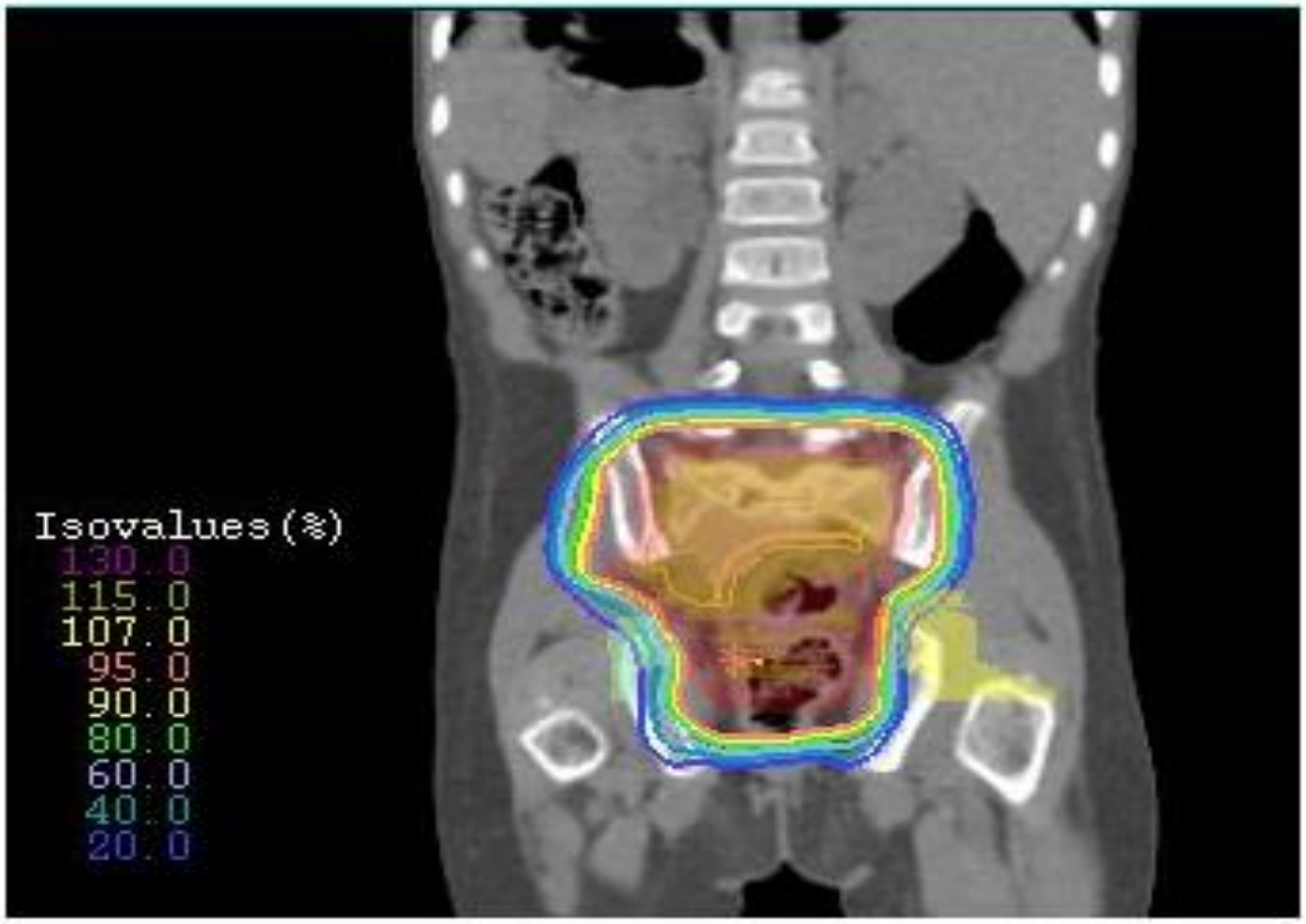




Proton Beam Therapy

- Background
- Experiences
- **WPE – West German Proton Center Essen**
- Conclusion

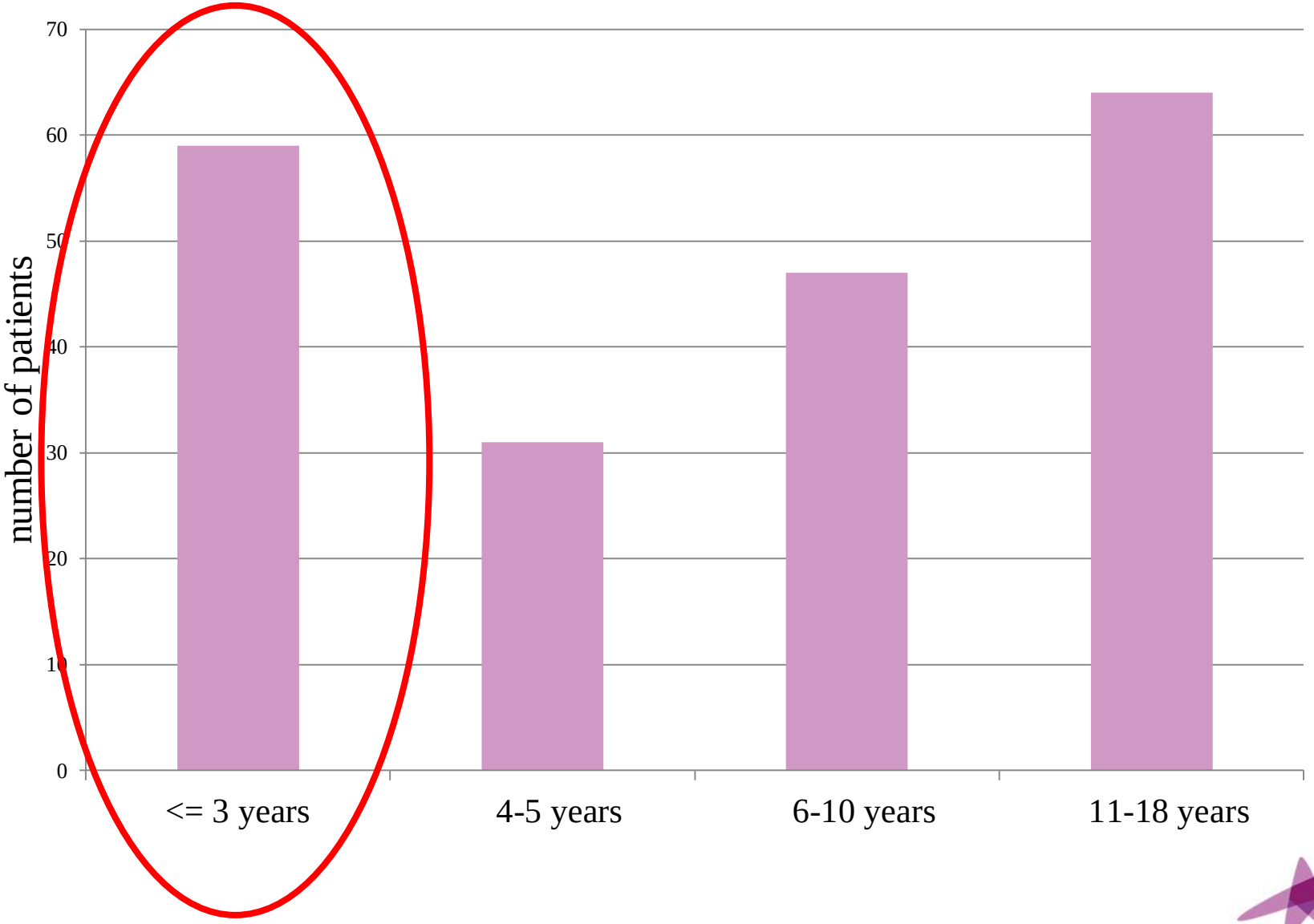
- Children



Children & non-CNS tumors at WPE (pospective „KiProReg“ data), 2013-2017

	No./years
Patients in total	201
female	95
male	106
Median age (range)	6.7 (0.9-17.9)
PT under sedation	108 (54%)
Concomitant CTx	134 (67%)
Median FU (yrs) (range) since first diagnosis	1.6 (0.2-11.7)
Median FU (yrs) (range) since last Fx	0.9 (0.0-3.5)

Age distribution, children with non-CNS tumors



Histopathologies

Neuroblastoma	6%
Extracranial germ cell tumor	4%
Malignant rhabdoid tumor	3%
Lymphoepithelial carcinoma	2%
HL / NHL (Lymphoma)	1%
Wilms tumor	1%
Nerve sheath tumor	1%
Others (each 1)	5%
Total	21%

	No. (%)
Rhabdomyosarcoma	45%
Ewing sarcoma	16%
Chordoma/Chondrosarcoma	6%
Undifferentiated sarcoma	3 %
Synovial sarcoma	2%
Osteosarcoma/-blastoma	2%
pPNET	1%
Fibromyxoid sarcoma	1%
Sarcoma (NOS)	1%
Angiosarcoma	1%
Epitheloid sarcoma	1%
Total	79%

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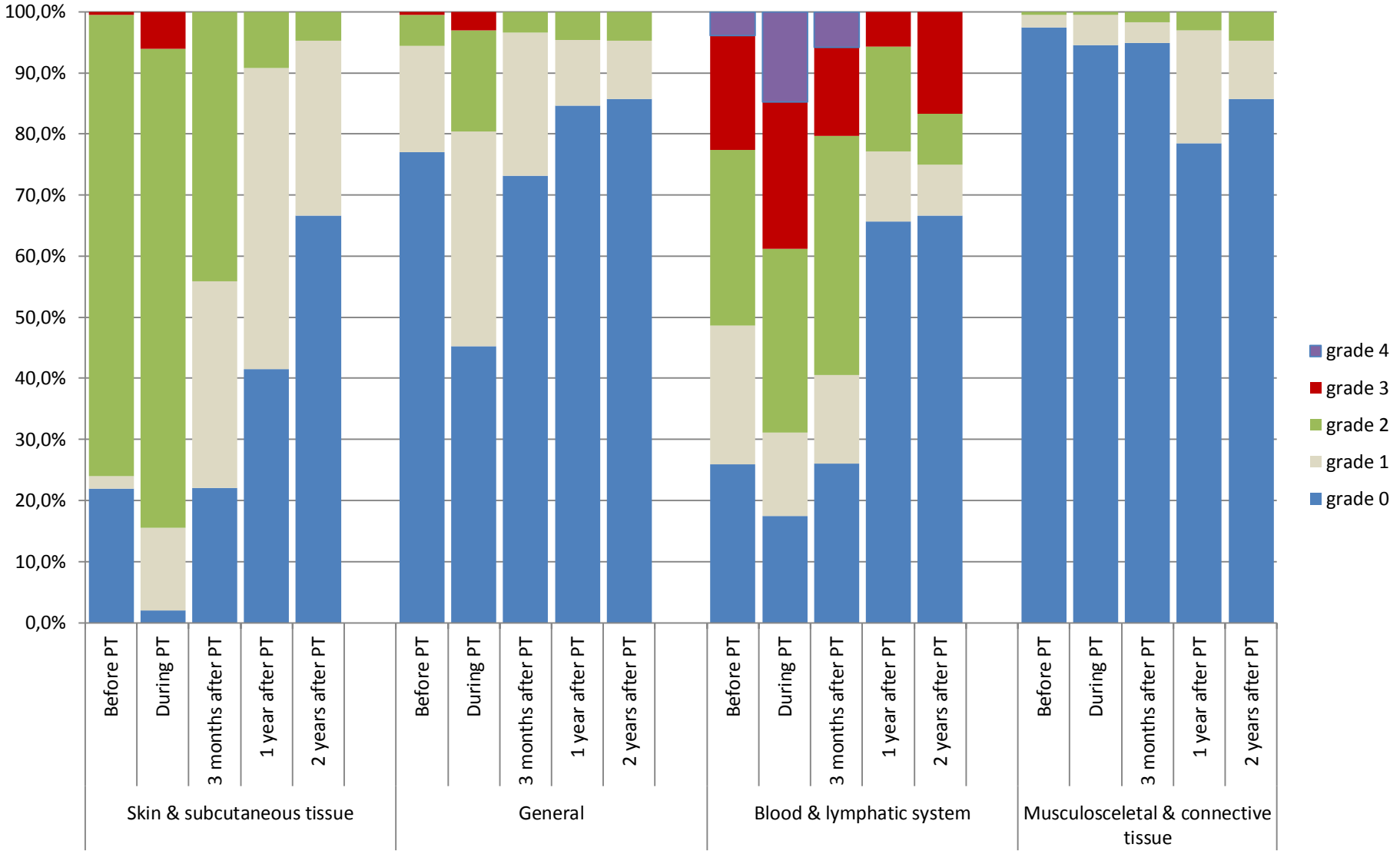
Pretreatment & PT dose

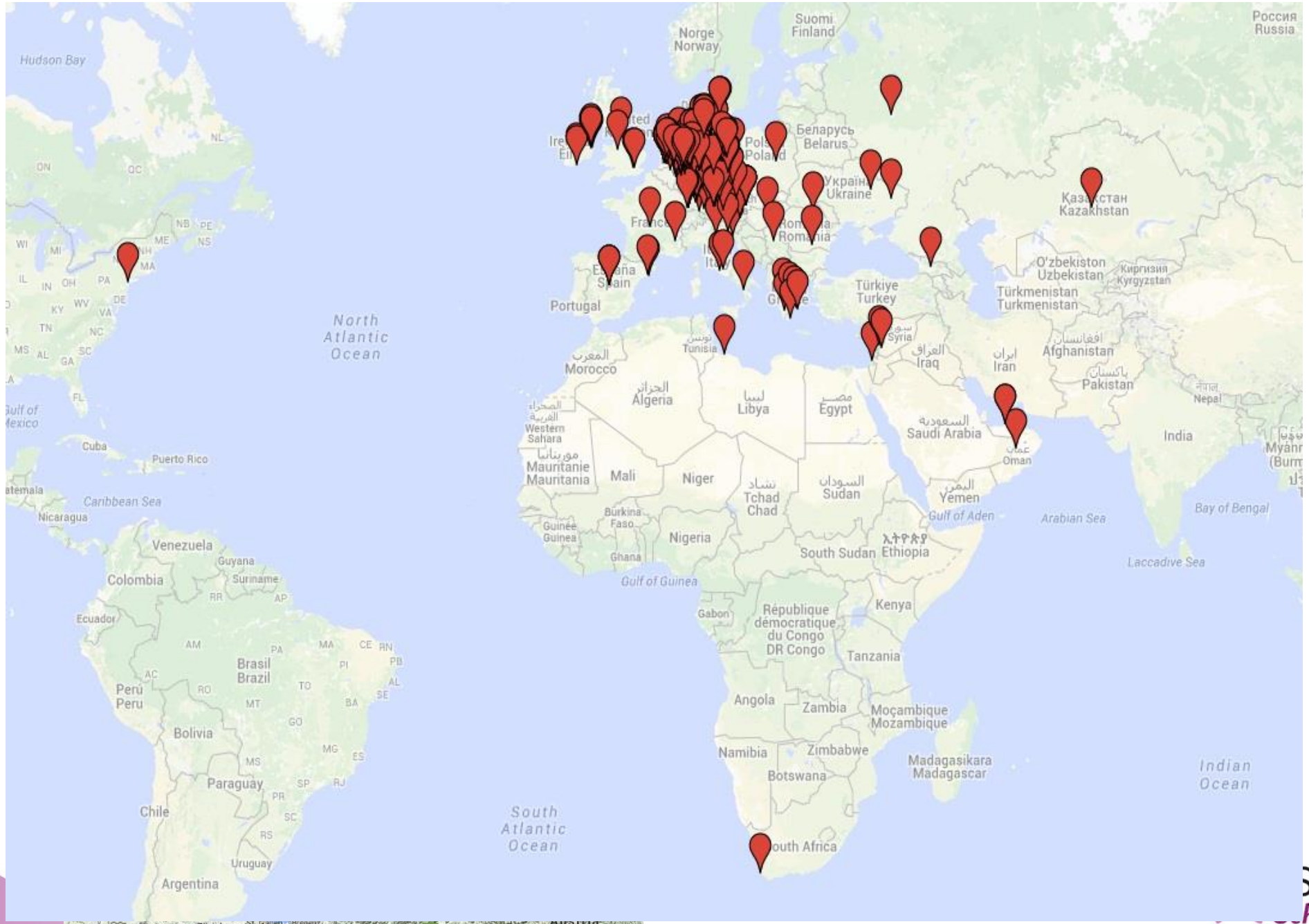
Pre-treatment	%
Surgery before PT	
GTR	21.4%
STR	26.4%
no/biopsy only	52.2%
CTx before PT	89.6%
RTx before PT	5.0%

PT at WPE	median	range
No. of Fx	30	8-41
Fraction dose (Gy)	1.8	1.5-2.5
Total dose (Gy)	54.0	12-74

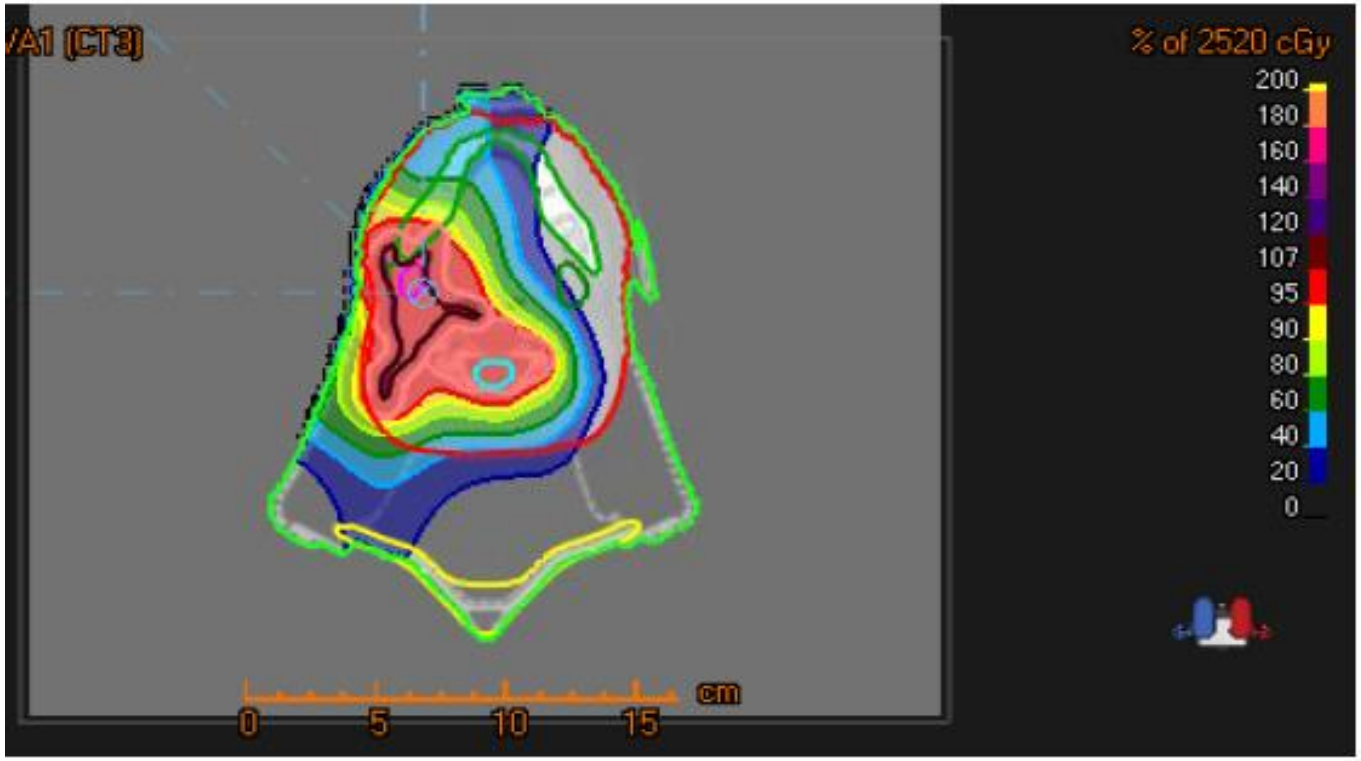
Adverse events - examples

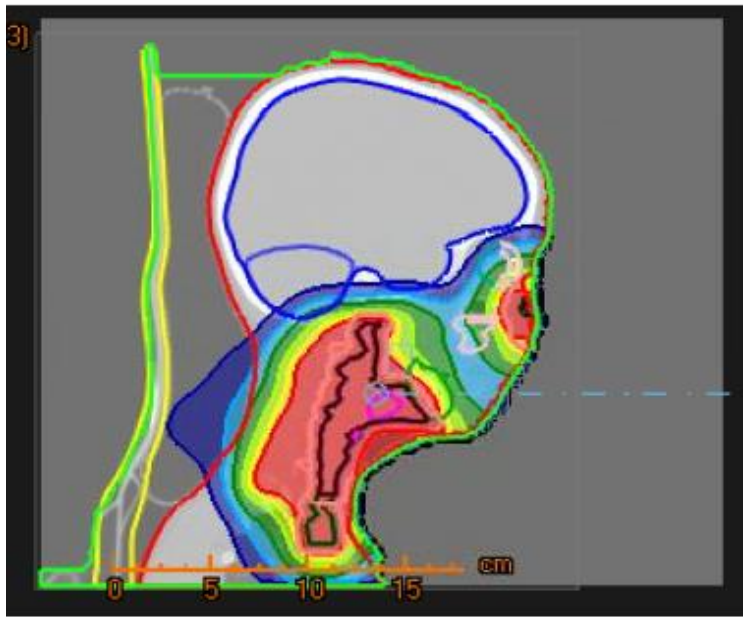


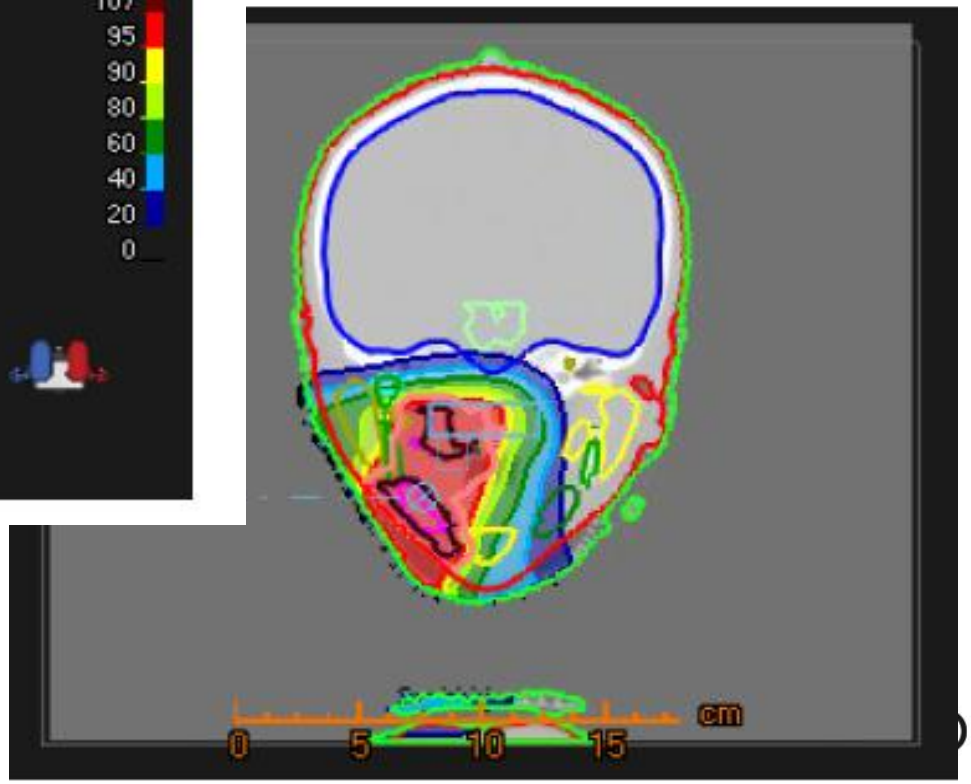
External Partners – FU?!



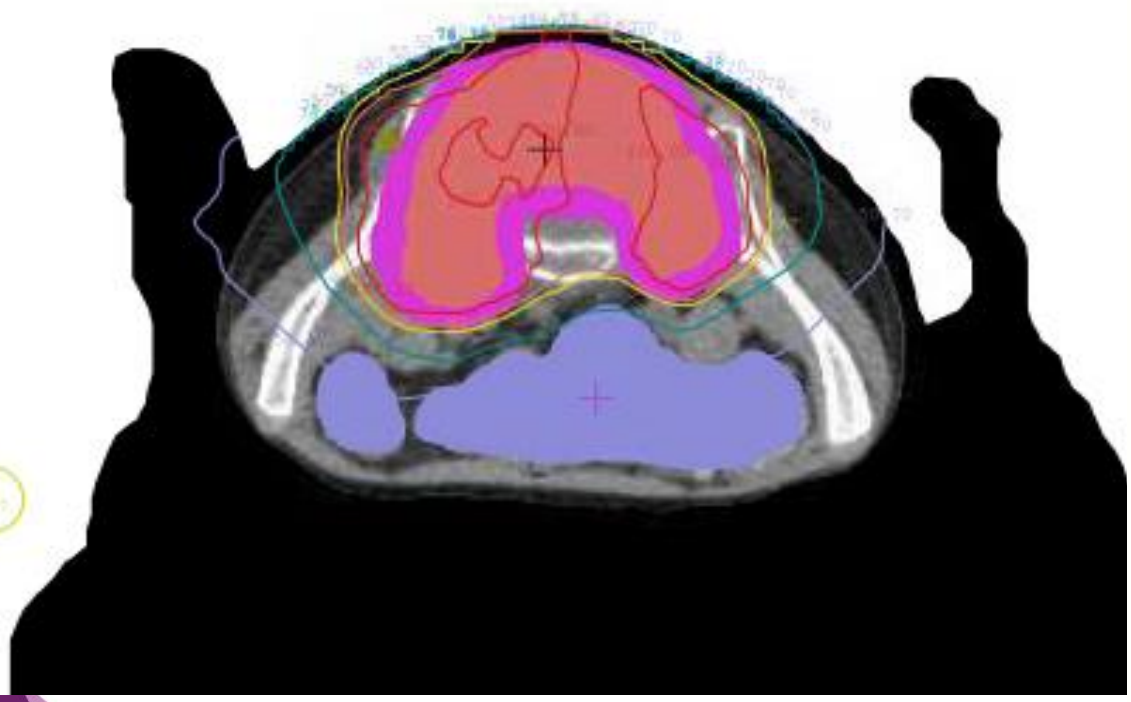
WPE – RMA (f, 7.5 yrs) pm/orbit + cervical LN with IMPT

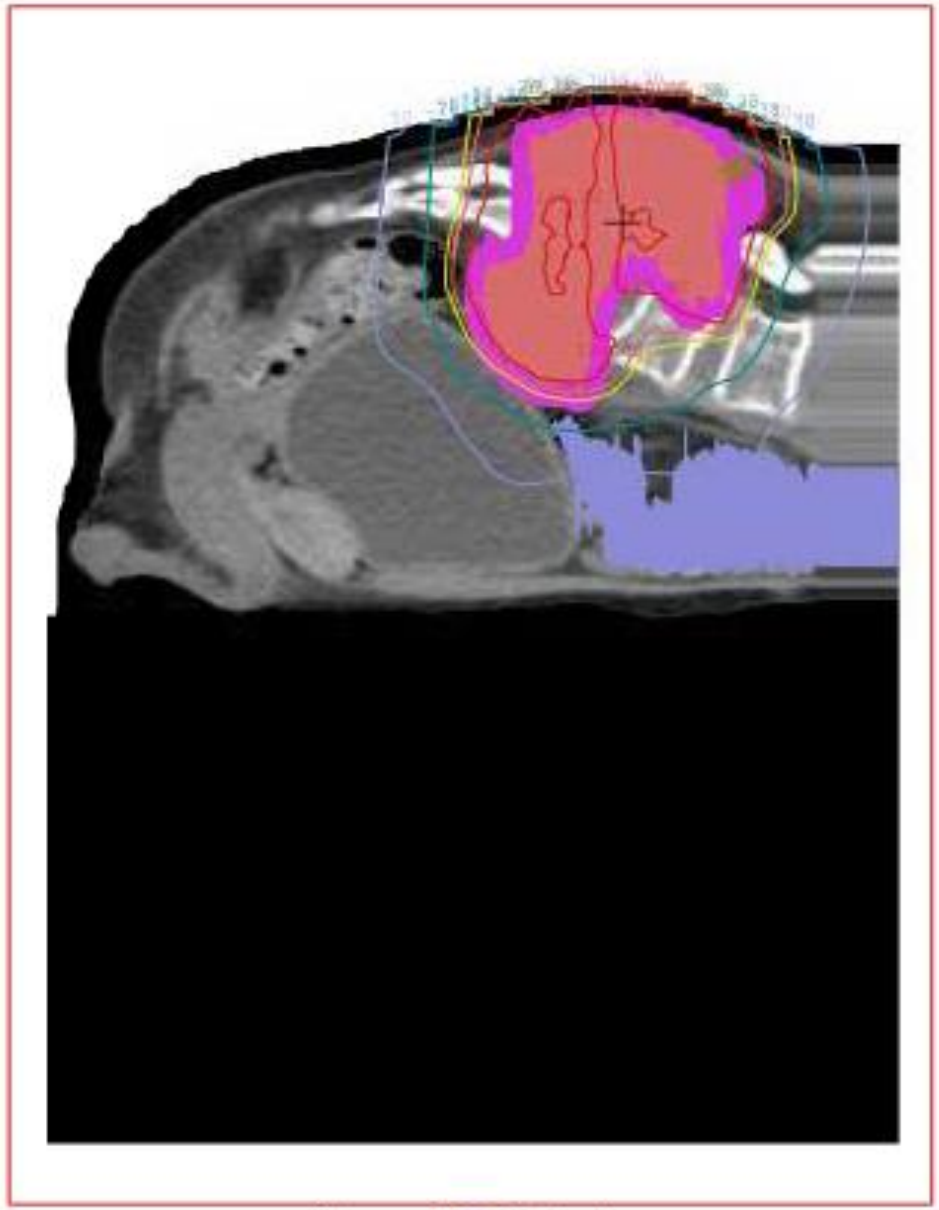






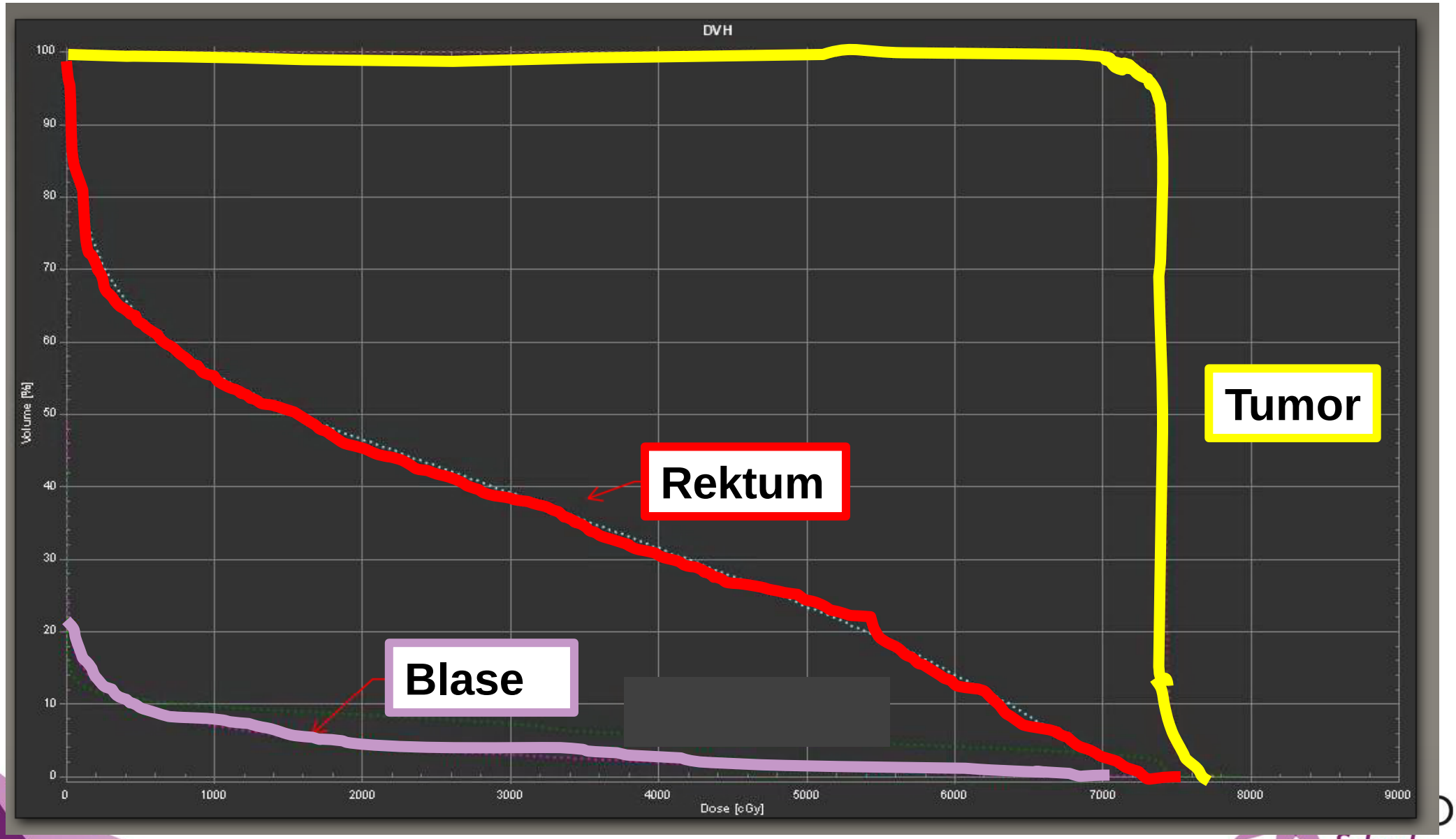
WPE - Osteosarcoma (70 Gy)





WPE – Chordoma (74 Gy)

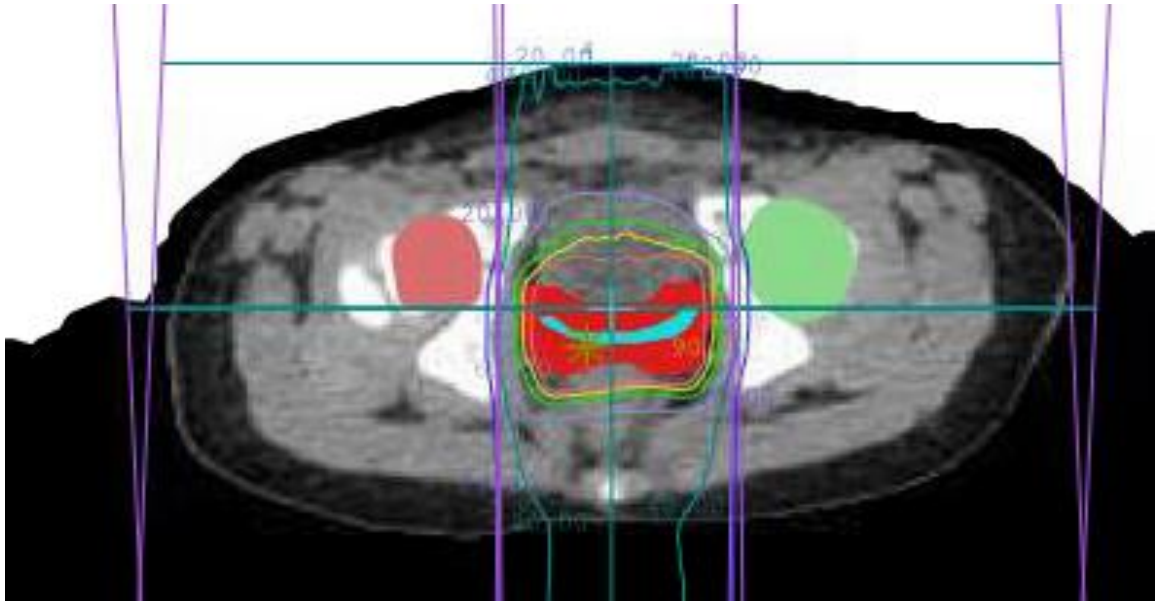
WPE – Chordoma

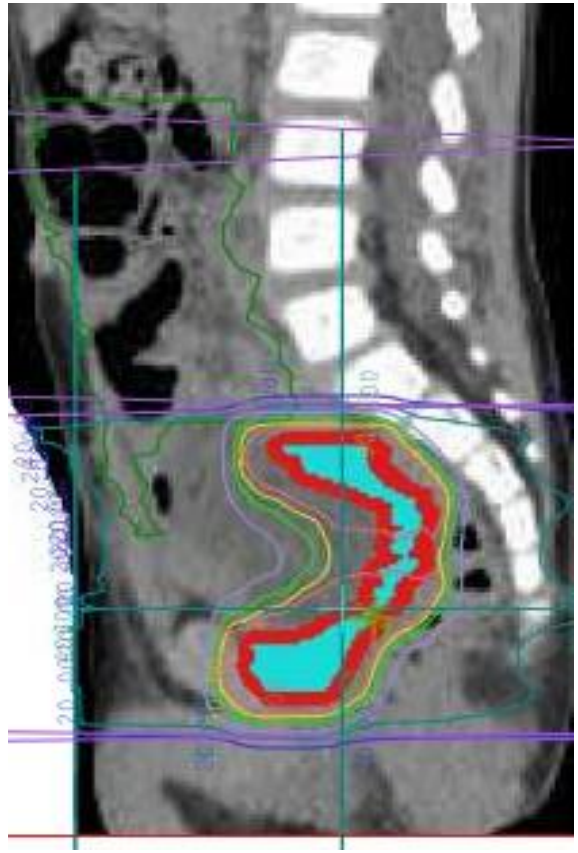


VOLUME

DOSE

WPE – RME (50.4 Gy) pelvis (m, 2.5 yrs)





Proton Beam Therapy

- Background
- Experiences
- WPE – West German Proton Center Essen
- **Conclusion**

Conclusion

- **Proton therapy offers a CHANCE** for improved sparing of normal tissue (or dose intensification)
- Advantage greater **for large target volumes, in high doses and in very young**
- **Increasing role in children** worldwide
- Experiences in on-CNS tumours: **mainly Sarcomas**, …
- Increasingly **neuroblastomas, nephroblastomas, lymphomas**
- To be implemented into **multidisciplinary framework/trials** (SIOP, GPOH…)
- Increasing capacity in Europe and elsewhere
- At WPE/Essen particular focus on children
- **Data** on PT (as on any other technique!) to be collected and evaluated (toxicity/TU but also QoL & neuropsych.)

Thanks for your Attention!

beate.timmermann@uk-essen.de

ESTRO School

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Updates from ESTRO School

Umberto Ricardi

Presidential representative within
ESTRO Educational Council

ESTRO MEMBERSHIP MAY 2017

ESTRO European Society for RADIOTHERAPY & ONCOLOGY

MEMBERS

TOTAL: 6,795

- Individual members: 4,401 — 65%
  - Full: 2,682 — 40%
    - Active — 39%
    - Supporting Ambassador — 1%
  - Associate: 1,719 — 25%
    - Affiliate — 19%
    - In training — 5%
    - Honorary — 1%
- Dual members: 887 — 13%
  - Dual: CARO - ISCO - JASTRO - KOSRO - RANZCR - SEAROG — 10%
  - Dual Young: AIRO GIOVANI - ISCORT - BVRO / ABRO - SEOR - YRROG — 3%
- RTT Alliance members: 63 — 1%
  Austria - Bulgaria - Croatia - Italy - Malta - Portugal - Serbia - Spain - Turkey
- Institutional members: 1,264 — 18%
  45 institutes
- Corporate members: 174 — 3%
  30 companies: 9 Gold members - 21 regular members

RETENTION RATE

- 59% MEMBERS 2012 RENEWED IN 2013
- 65% MEMBERS 2013 RENEWED IN 2014
- 67% MEMBERS 2014 RENEWED IN 2015
- 61% MEMBERS 2015 RENEWED IN 2016
- 64% MEMBERS 2016 RENEWED IN 2017 (MAY)

- % membership categories 2016 that renewed in 2017 (May):
  - Full members — 72%
  - Associate members — 72%
  - Dual members — 67%
  - Institutional members — 89%
- Members 2015 & 2016 renewed in 2017 (May) — 78%
- 75 out of 945 trial members 2016 became regular ESTRO 2017 members

EVOLUTION MEMBERSHIP

- 5,608 IN 2013
- 5,830 IN 2014
- 6,647 IN 2015
- 6,742 IN 2016
- 6,795 IN MAY 2017

INSTITUTIONAL MEMBERSHIP

1,264 institutional members
from 45 institutes - 7 new institutes

- Active — 63%
- In training — 21%
- Affiliate — 13%
- Supporting Ambassador — 3%

YOUNG MEMBERS

822 Young members

- 356 Individual in training — 43%
- 277 Institutional in training — 34%
- 189 Dual young — 23%

ESTRO ACTIVITIES

Participants to activities that are members

- 2017 ESTRO courses — 73%
- ESTRO 36 — 60%
- 6th ICHNO — 22%

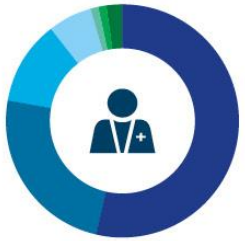
Proportion of members participating to activities

- 2017 ESTRO courses — 12%
- ESTRO 36 — 34%
- 6th ICHNO — 3%

GREEN JOURNAL

- Paper subscription — 18%
- Electronic subscription — 82%

SPECIALTY DISTRIBUTION



- 51% Radiation oncologist
- 23% Medical physicist
- 11% RTT - Dosimetrist
- 6% Clinical oncologist
- 1% Radiobiologist
- 1% Industry Representatives
- 2% Other medical specialties

GEOGRAPHICAL DISTRIBUTION

- 75% Europe
- 8% Asia
- 5% Oceania
- 2% Africa and Middle East
- 9% America

Top 10 member countries 2017	Members	
The Netherlands	13%	822
Germany	8%	518
United Kingdom	7%	456
Italy	7%	445
Canada	5%	331
Belgium	4%	300
Australia	4%	293
Spain	4%	288
Switzerland	4%	254
Denmark	3%	226

SOLIDARITY FUND

90 supporting ambassador members financed

- 9 in training memberships
- 9 ESTRO 36 registrations
- 5 affiliate members
- 6 ESTRO course registrations
- 10 educational grants

ESTRO VISION 2020

Every cancer patient in Europe will have access to state of the art radiation therapy, as part of a multidisciplinary approach where treatment is individualized for the specific patient's cancer, taking into account the patient's personal circumstances

Radiotherapy & Oncology 103(2012) 99-101

Education – one of the pillars of ESTRO

ESTRO School

ESTRO School over the years

A few milestones:

1984 ESTRO ETC created

1991 First ESTRO CC

2005 ESTRO School created

2006 Core ETC to develop long-term strategy and set priorities for the School

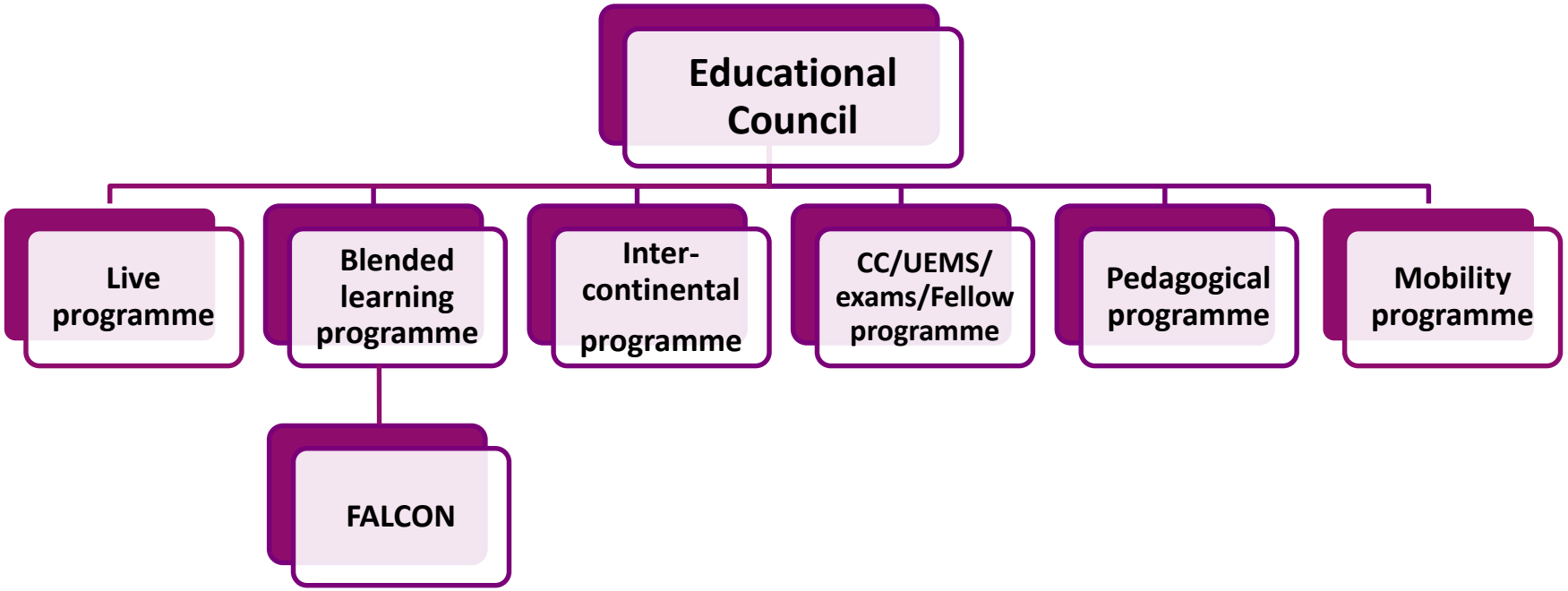
2008 Mission Statement of ESTRO School

2016 Educational council created

First ESTRO Course: ”Radiation physics for clinical Radiotherapy”, Leuven 1985

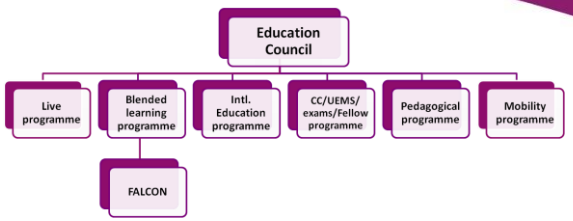
ESTRO School

Educational Council and programmes



ESTRO School

Educational Council



1. Director (professional) - **JG Eriksen**
2. Director (admin + educational) – **C Verfaillie**
3. Presidential representative - **U Ricardi**
4. Progr. Leader Live Group – **JG Eriksen**
5. Progr. Leader Blended Group – **M Leech**
6. Progr. Leader Intl Group – **R Poetter**
7. Progr. Leader CC/UEMS Group – **K Benstead**
8. Progr. Leader Mobility Group – **MC Vozenin**
9. Progr. Leader Pedagogic Group - **C Verfaillie**
10. ESTRO Office – **V VanEgten**

Representation from all groups (RTT, Phys, RB, GEC, ACROP, yESTRO) + IAEA

M Kamphuis – P Hoskin– N Jornet – C Belka – JE Bibault - B Heijmen – E Zubizarretta

ESTRO School

ESTRO School: Where do we stand?

- Live courses
  - ~ 40.000 participants in ~ 460 ESTRO live courses
  - 62 outside Europe
  - > 40 different course topics
  - ~ 50 course directors and 217 teachers in 2016

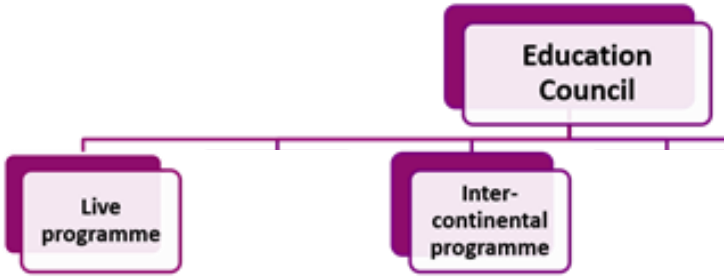
- FALCON
  - > 6400 RO professionals did FALCON contouring (live courses, congress WS, online WS)

- DOVE
  - Online library DOVE with > 14.000 scientific/educational publications
  - Course material in flipping book format

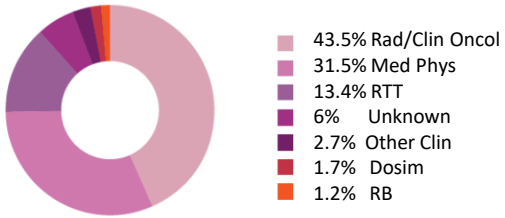
- 231 mobility grants awarded

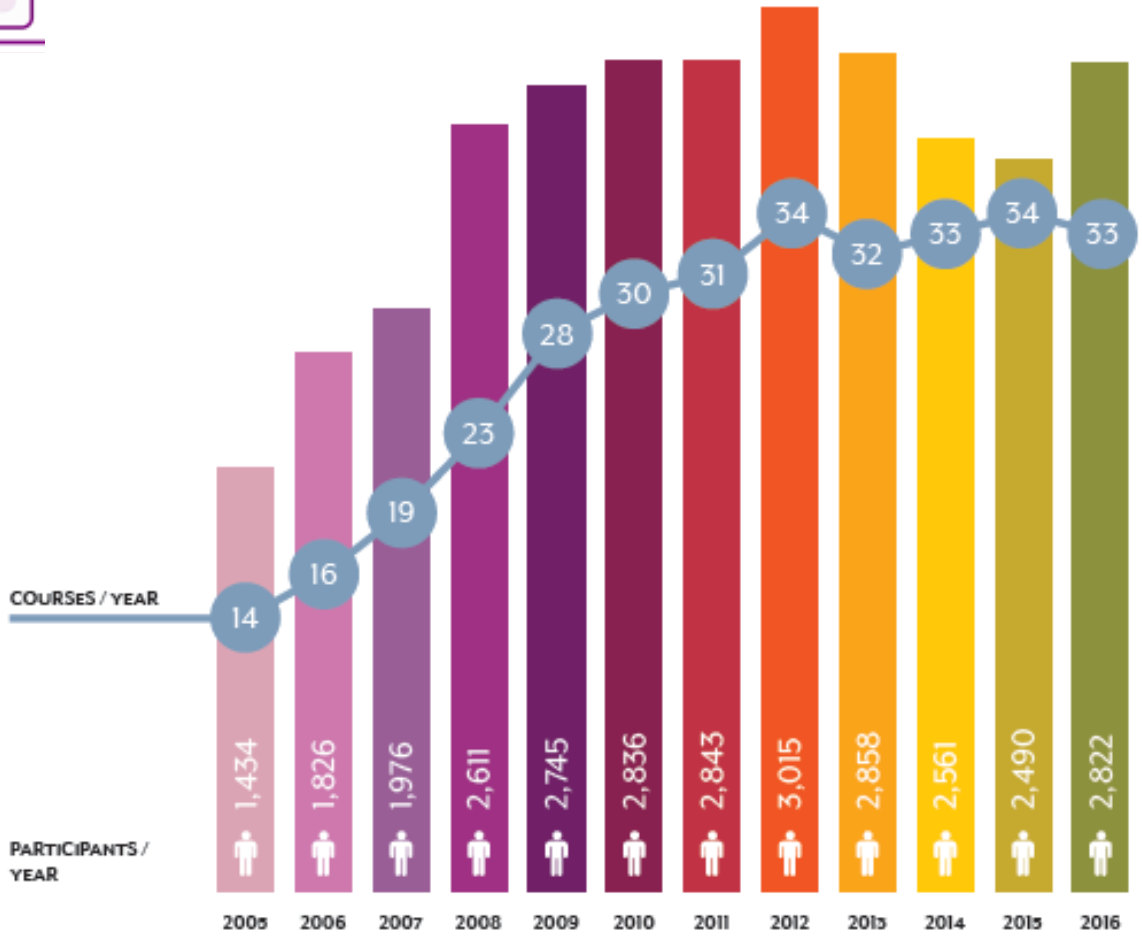
ESTRO School

ESTRO School – live courses



Discipline

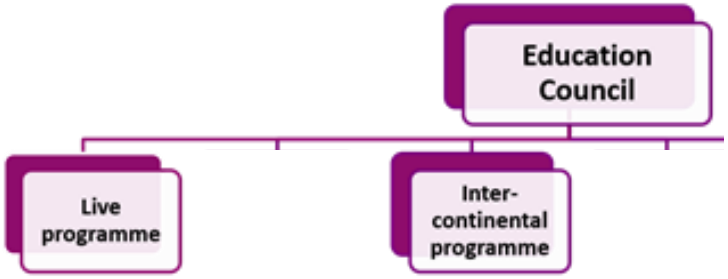




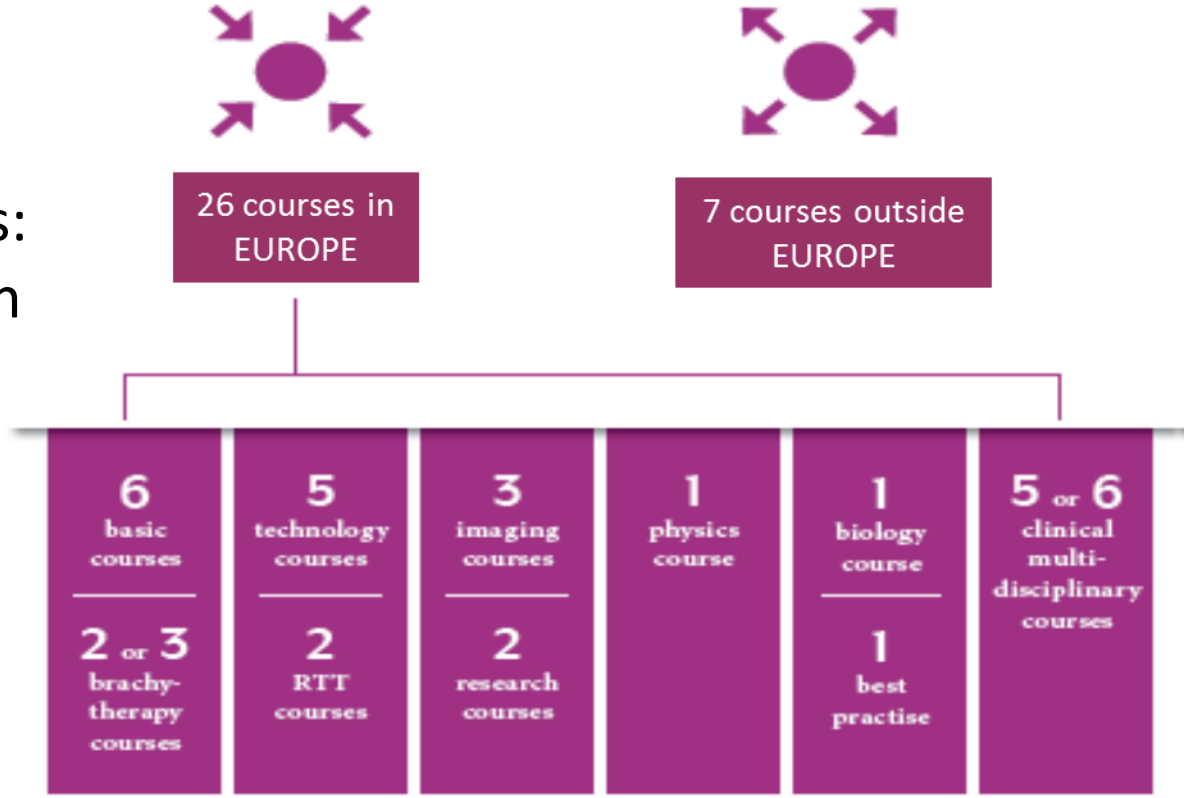
Live courses and participants over the years

ESTRO School

ESTRO School 2016 – live courses

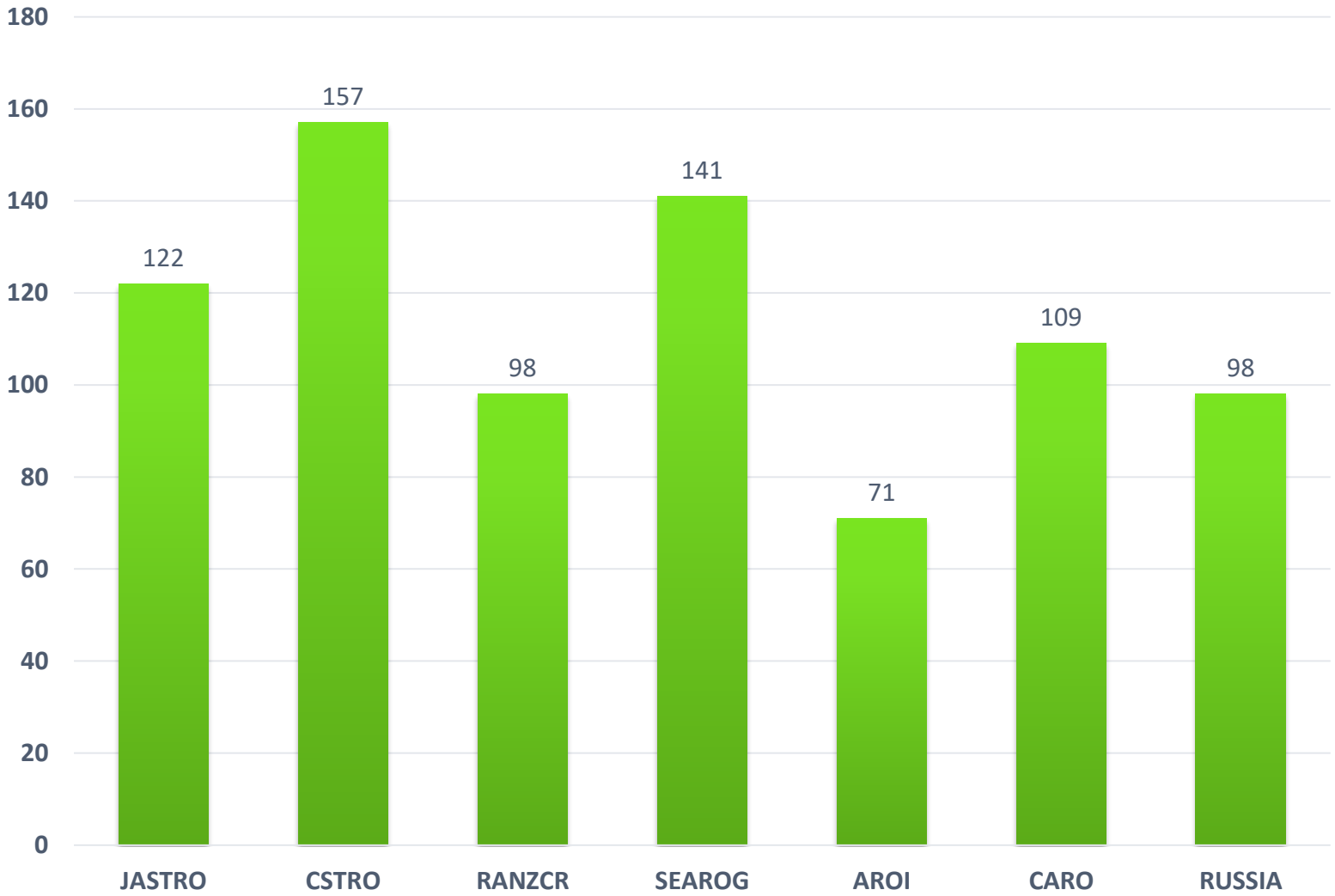


ESTRO non-members: significant proportion



ESTRO School

LIVE COURSES OUTSIDE EUROPE 2016



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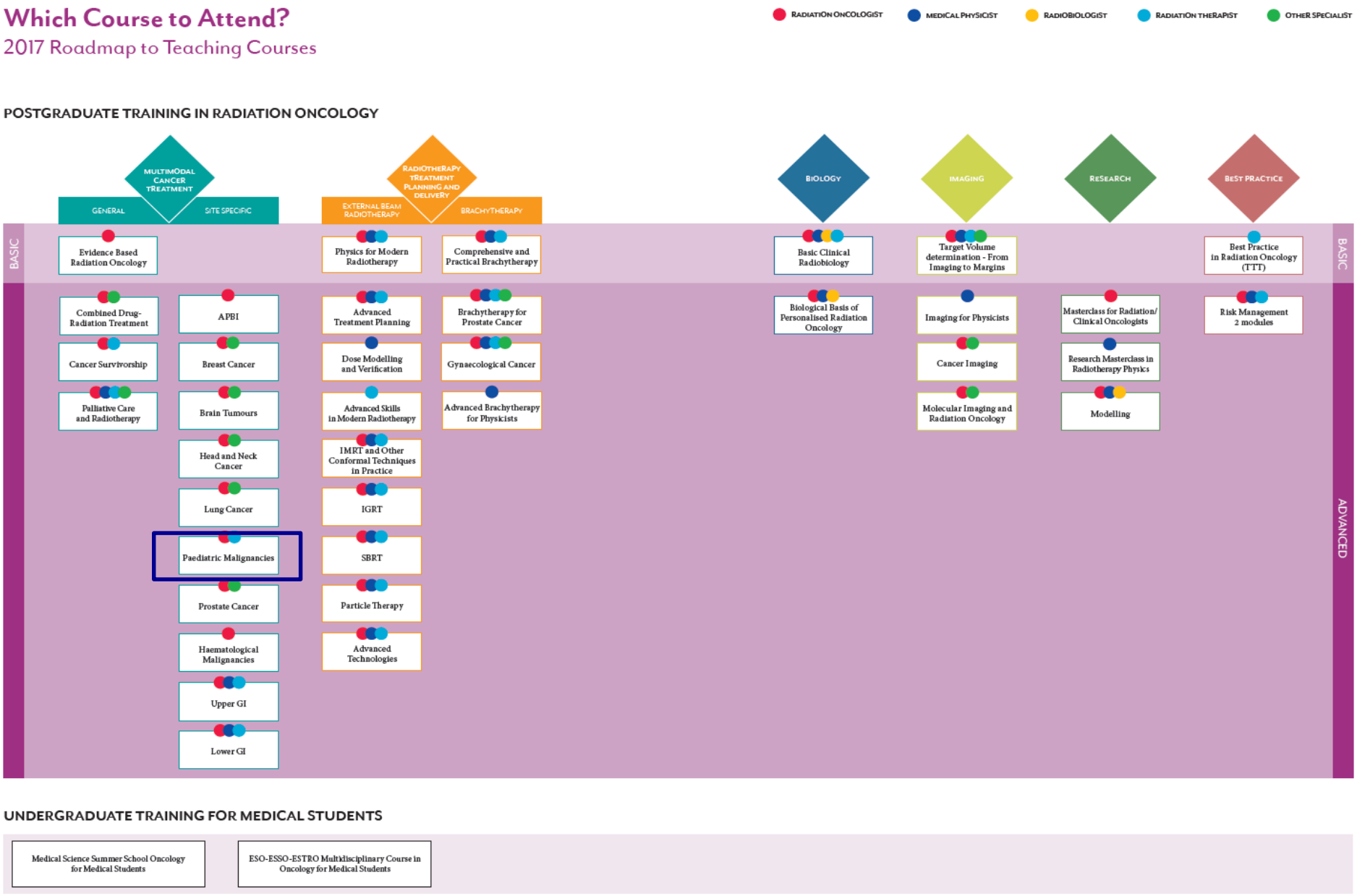
ESTRO School 2017 – live courses

Which Course to Attend?

2017 Roadmap to Teaching Courses



ESTRO SCHOOL OF RADIOTHERAPY AND ONCOLOGY

WWW.ESTRO.ORG

2017

ESTRO School

POSTGRADUATE COURSES IN EUROPE

Comprehensive and Practical Brachytherapy
5-8 March 2017 | Budapest, Hungary

Particle Therapy
6-10 March 2017 | Essen, Germany

Lower GI: Technical and Clinical Challenges for Radiation Oncologists
22-24 March 2017 | Rome, Italy

Upper GI: Technical and Clinical Challenges for Radiation Oncologists
25-28 March 2017 | Rome, Italy

Dose Modelling and Verification for External Beam Radiotherapy
2-6 April 2017 | Warsaw, Poland

IMRT and Other Conformal Techniques in Practice
9-13 April 2017 | Madrid, Spain

ESTRO/ESMIT Course on Molecular Imaging and Radiation Oncology
10-13 April 2017 | Bordeaux, France

Cancer Survivorship
21-23 May 2017 | Brussels, Belgium

Multidisciplinary Management of Prostate Cancer
21-25 May 2017 | Porto, Portugal

Physics for Modern Radiotherapy
4-8 June 2017 | Bucharest, Romania

Advanced Skills in Modern Radiotherapy
11-15 June 2017 | Prague, Czech Republic

Evidence Based Radiation Oncology
11-16 June 2017 | Ljubljana, Slovenia

Combined Drug-Radiation Treatment: Biological Basis, Current Applications and Perspectives
15-18 June 2017 | Milan, Italy

Target Volume determination - From Imaging to Margins
25-28 June 2017 | Lisbon, Portugal

Brachytherapy for Prostate Cancer
29 June - 1 July 2017 | Brussels, Belgium

Advanced Treatment Planning
3-7 September 2017 | Barcelona, Spain

Clinical Practice and Implementation of Image-Guided Stereotactic Body Radiotherapy
3-7 September 2017 | Budapest, Hungary

Palliative Care and Radiotherapy
7-9 September 2017 | Brussels, Belgium

Multidisciplinary Management bof Breast Cancer
10-13 September 2017 | Dublin, Ireland

Research Masterclass in Radiotherapy Physics
10-13 September 2017 | Florence, Italy

Basic Clinical Radiobiology
16-20 September 2017 | Paris, France

Comprehensive Quality Management in Radiotherapy
2-5 October 2017 | Brussels, Belgium

Quantitative Methods in Radiation Oncology: Models, Trials and Clinical Outcomes
8-11 October 2017 | Maastricht, The Netherlands

Best Practice in Radiation Oncology - Train the RTT Trainers
16-18 October 2017 | Vienna, Austria

Multidisciplinary Management of Brain Tumours
22-24 October 2017 | Vienna, Austria

Image-Guided Radiotherapy and Chemotherapy in Gynaecological Cancer: Focus on MRI Based Adaptive Brachytherapy
22-26 October 2017 | Prague, Czech Republic

Image Guided Radiotherapy in Clinical Practice
29 October - 2 November 2017 | Athens, Greece

ESTRO/ESOR Multidisciplinary Approach of Cancer Imaging
2-3 November 2017 | Rome, Italy

Imaging for Physicists
5-9 November 2017 | Malaga, Spain

Paediatric Radiotherapy
30 November - 2 December 2017 | Brussels, Belgium

POSTGRADUATE COURSES OUTSIDE EUROPE

Transition from Conventional 2D to 3D Radiotherapy with a special emphasis on Brachytherapy in Cervical Cancers
8-11 March 2017 | Bengaluru, India

ESTRO-KOSRO GI: Technical and Clinical Challenges for Radiation Oncologists
2-4 June 2017 | Seoul, South Korea

Comprehensive Quality Management in Radiotherapy
5-9 July 2017 | Chengdu, China

Multidisciplinary Management of Head and Neck Oncology
9-13 December 2017 | Singapore, Republic of Singapore

PRE-MEETING COURSES

Five Pre-Meeting Courses at ESTRO 36
5 May 2017 | Vienna, Austria

UNDERGRADUATE COURSES

Medical Science Summer School Oncology for Medical Students (Vienna/Groningen)
10-21 July 2017 | Vienna, Austria

Eso-esso-estro Multidisciplinary Course in Oncology for Medical Students
28 August - 8 September 2017 | Antwerp, Belgium

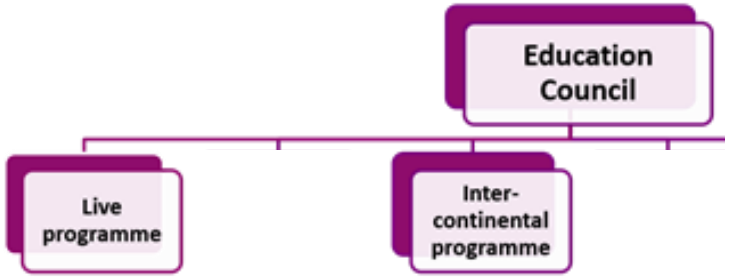
MULTIMODAL CANCER TREATMENT · RADIOTHERAPY TREATMENT PLANNING AND DELIVERY · BIOLOGY · IMAGING · RESEARCH · BEST PRACTICE

ESTRO School

Pediatric Radiation Oncology ESTRO-PROS Course

- 2009: Brussels
- 2011: Brussels
- 2013: Brussels
- 2015: Izmir
- 2016: Bangkok (SEAROG)
- 2017: Brussels

2018: 36 live courses



New in 2018

- ✓ Positioning and immobilisation for radiation therapy
- ✓ Non-melanoma skin cancer
- ✓ Communication in oncology workshop
- ✓ Leadership skills for radiation oncology

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2018
ESTRO SCHOOL
LIVE COURSE

NEW
COURSE

Foundations of Leadership in Radiation Oncology

A Joint ESTRO-CARO-RANZCR Course

20 April 2018 | Barcelona, Spain

Online sessions from March to May 2018

—

Special format: an online programme combined with live sessions at ESTRO 37.

2018
ESTRO SCHOOL
LIVE COURSE

Basic Clinical Communication in Oncology

15 - 17 June 2018 | Brussels, Belgium

—

How to combine efficiency, empathy, information giving and shared decision-making in oncology encounters? The course will provide you with situational training and inspire post-course self-training.

2018
ESTRO SCHOOL
LIVE COURSE

NEW
COURSE

Multidisciplinary Management of Non-melanoma Skin Cancer

4-6 October 2018 | Brussels, Belgium

—

You will benefit from increased understanding of multimodality management of non-melanoma skin cancer. Your clinical daily work will improve due to more awareness of best practices with the patients benefiting from the best possible treatment.

2018
ESTRO SCHOOL
LIVE COURSE

NEW
COURSE

Positioning and Immobilisation for Radiotherapy

3-4 November 2018 | Vienna, Austria: practical sessions
From October to November 2018: online sessions

—

The course provides you with the necessary theory and practical skills to effectively position and immobilise patients for modern radiotherapy techniques. Its online nature offers you flexibility to learn at a time and place that suits you before the two-day live meeting.

2018
ESTRO SCHOOL
LIVE COURSE

AROI Course in Collaboration with ESTRO on Advanced Technologies

Endorsed by ESTRO

2018 | India

—

The course will provide a great opportunity to see how clinicians from different specialities and countries manage and treat thoracic tumours, giving you the possibility to improve your own individual approach to patients.

BLENDED LEARNING

EAGLE

FALCON

Fellowship in Anatomic deLineation & CONtouring

DOVE

ESTRO School

FALCON

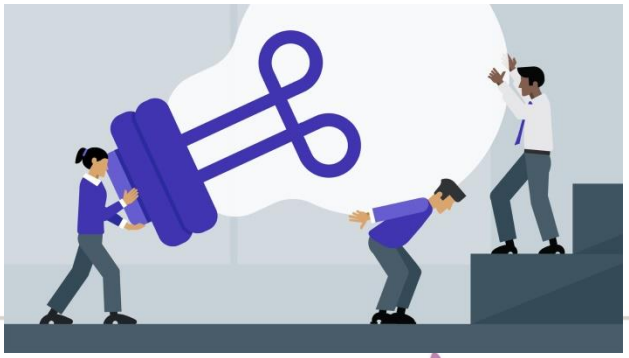
***F**ellowship in **A**natomic de**L**ineation & **CON**touring*

ESTRO's contouring platform:

→ improve your delineation skills, online/onsite

→ see what's in common between your contours and:

- ESTRO guideline contours
- Contours from experts in the field



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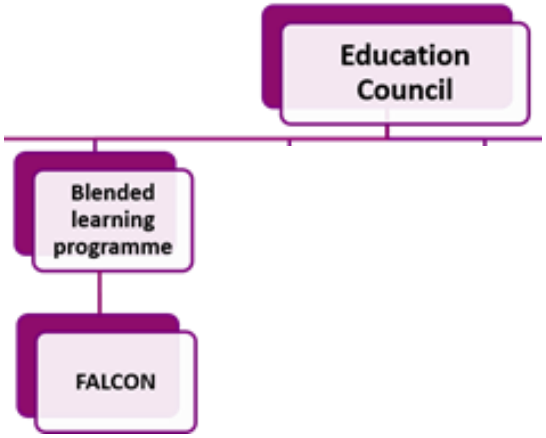
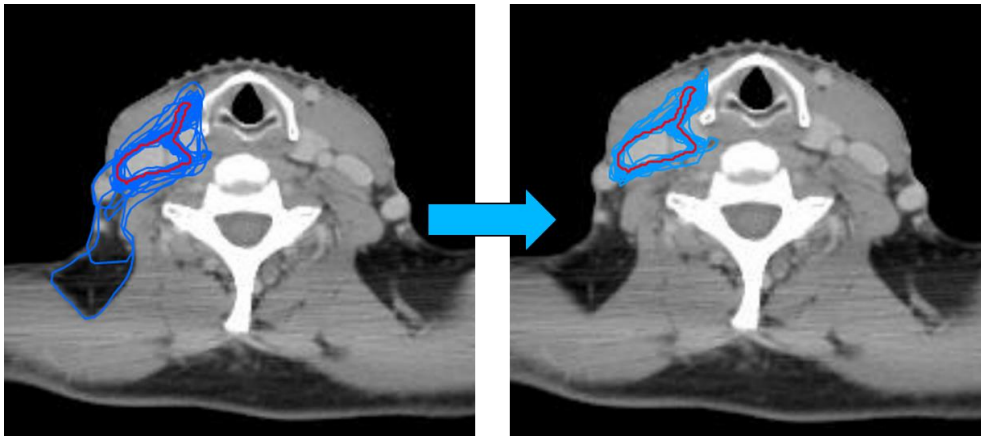
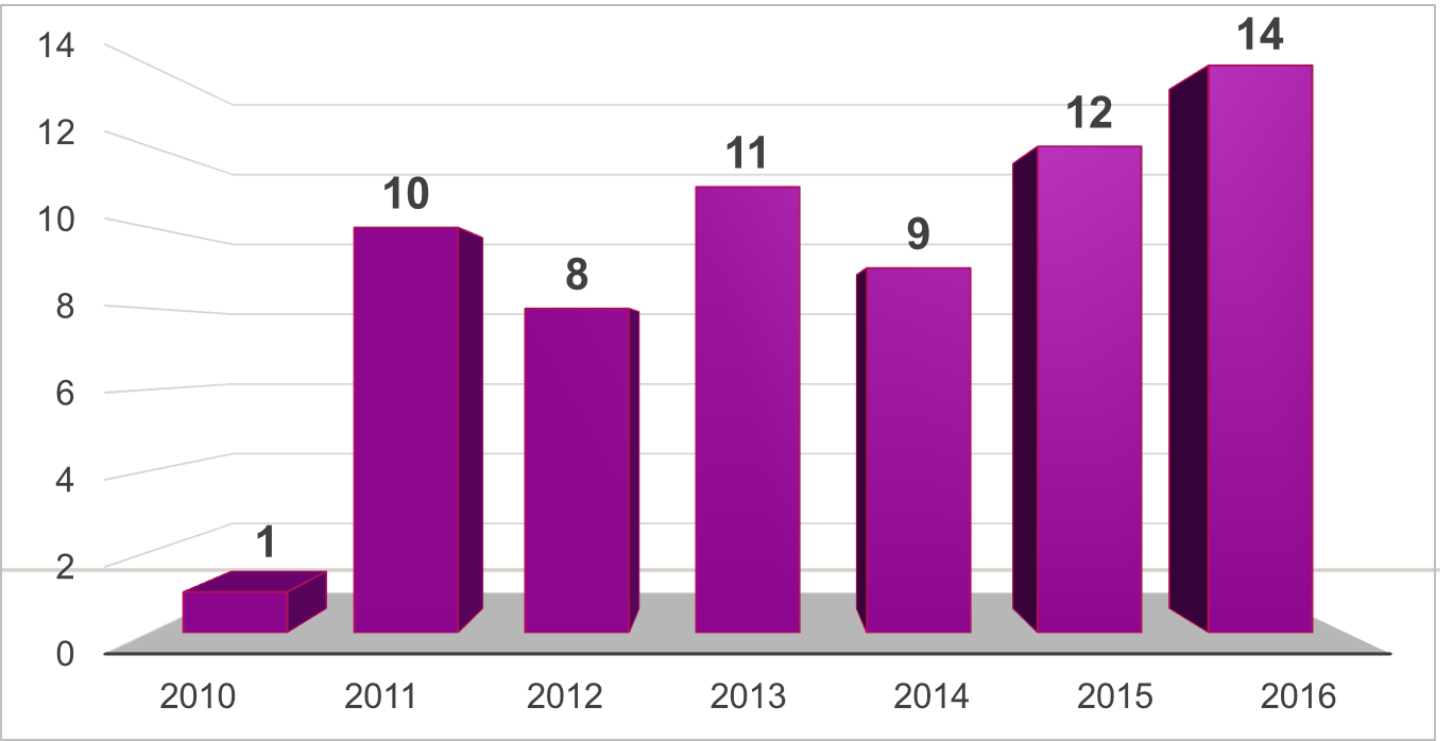
FALCON in live courses



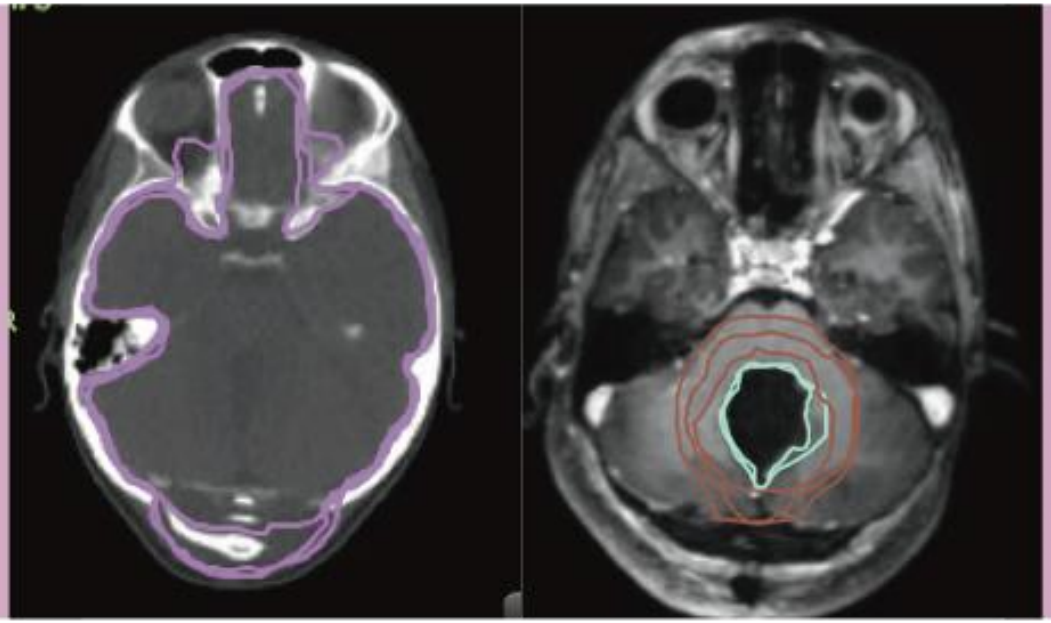




ONLINE CONTOURING WORKSHOP

Paediatric Workshop

5, 12 and 19 December 2017

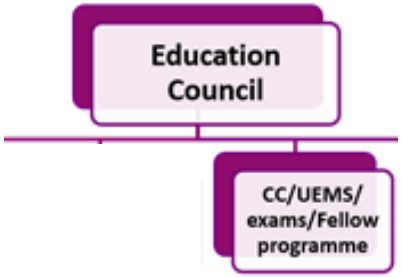


Three online sessions:

- 5 December 2017 - 18.00 > 19.00 CET
- 12 December 2017 - 18.00 > 20.00 CET
- 19 December 2017 - 18.00 > 19.30 CET

Register now on ESTRO.ORG/SCHOOL

ESTRO Core Curricula



lots of new developments and competencies

Radiotherapy and Oncology 103 (2012) 103–108

Contents lists available at SciVerse ScienceDirect

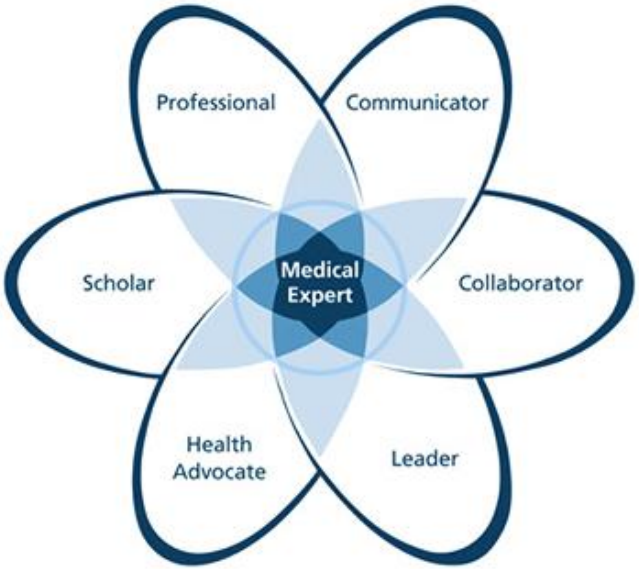
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ESTRO Core Curricula

The updated ESTRO core curricula 2011 for clinicians, medical physicists and RTTs in radiotherapy/radiation oncology

Jesper G. Eriksen [a,*], Andrew W. Beavis [b], Mary A. Coffey [c], Jan Willem H. Leer [d], Stefano M. Magrini [e], Kim Benstead [f], Tobias Boelling [g], Marie Hjälm-Eriksson [h], Guy Kantor [i], Boguslaw Maciejewski [j], Maris Mezeckis [k], Angelo Oliveira [l], Pierre Thirion [m], Pavel Vitek [n], Dag Rune Olsen [o], Teresa Eudaldo [p], Wolfgang Enghardt [q], Pascal François [r], Cristina Garibaldi [s], Ben Heijmen [t], Mirjana Josipovic [u], Tibor Major [v], Stylianos Nikoletopoulos [w], Alex Rijnders [x], Michael Waligorski [y], Marta Wasilewska-Radwanska [z], Laura Mullaney [aa], Annette Boejen [ab], Aude Vaandering [ac], Guy Vandevelde [ad], Christine Verfaillie [ae], Richard Pötter [af]



CanMEDS

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UNION EUROPÉENNE DES MÉDECINS SPÉCIALISTES
EUROPEAN UNION OF MEDICAL SPECIALISTS

Association internationale sans but lucratif — *International non-profit organisation*

AVENUE DE LA COURONNE, 20
BE- 1050 BRUSSELS
www.uems.net

T +32 2 649 51 64
F +32 2 640 37 30
info@uems.net

Training Requirements for the Specialty of Radiation Oncology

European Standards of Postgraduate Medical Specialist Training

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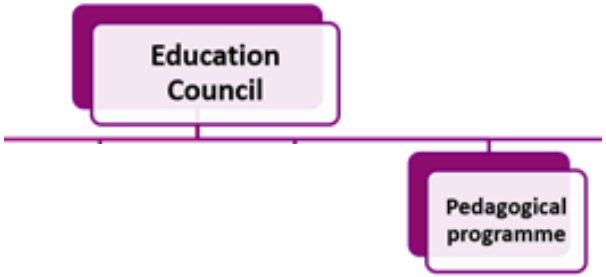
Pedagogical program



- ✓ Educational activities for teachers (Course Directors meeting and Teachers retreat)
- ✓ Implementation of blended learning and focus on how blended is used
- ✓ Collaboration with educationalists for assessment

Travel grants 2016

YOUNG ESTRO

Adapting new technologies in breast brachytherapy

Karolis Ulinskas and Kestutis Akelaitis

HOST INSTITUTE:
National Institute of Oncology
Budapest, Hungary

29 February - 18 March 2016

KAROLIS ULINSKAS

KESTUTIS AKELAITIS

The National Institute of Oncology in Budapest is one of the main brachytherapy centres in Europe treating a large number of patients (around 9,000 new patients per year). The centre employs highly qualified and experienced physicians and physicists, and the centre's large number of clinical trials and publications highlights its significant scientific contribution. The head of the Department of Radiotherapy, Professor Csaba Polgár, is a leading and highly respected breast brachytherapy specialist worldwide, and we felt honoured to have this opportunity to visit the Department.

Brachytherapy is often used for breast cancer treatments, but in our department this technique is not applied yet, due to a lack of technical practice and knowledge. For this reason, we decided to join the Hungarian institution for a period of training and education in order to develop our experience as radiation oncologists and medical physicists.

The main objective of our visit was to learn how to improve our approaches to breast brachytherapy. We also wanted to learn more about patient selection criteria and eligibility for accelerated partial breast irradiation (APBI) using interstitial brachytherapy, and to collaborate in ▼

Dr Karolis Ulinskas and Dr Peter Agostin at the National Institute of Oncology in Budapest, Hungary

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MULTIDISCIPLINARY ONCOLOGY COURSES FOR MEDICAL STUDENTS

New on the ESTRO School programme since 2016:

2 undergraduate initiatives

1. The medical science summer school in oncology for medical students (Vienna/Groningen)
2. The ESO/ESSO/ESTRO multidisciplinary course for medical students

AIM:

- encourage medical students to have an overview on all aspects of oncology disciplines

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ESTRO School staff

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Education Manager

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Anna Lesi
Administrative Coordinator

Mika Palmu
Project Manager

Melissa Vandeviji
Project Manager

Jesper Eriksen – Chair ESTRO Education Council
Christine Verfaillie – Managing Director Education & Science
Viviane Van Egten – Education Manager

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ESTRO 37

20-24 April 2018
Barcelona, Spain

Innovation for Value and Access

DEADLINES

Abstract submission:
23 October 2017

Early registration:
17 January 2018

Late breaking abstract submission:
22 January 2018

Late registration:
21 March 2018

Desk registration:
as of 22 March 2018

WWW.ESTRO.ORG

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European SocieTy for
RADIOTHERAPY
& ONCOLOGY

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Contouring a Madeulloblastoma Clinical case

Chiara Valentini

Klinik und Poliklinik für Strahlentherapie und Radioonkologie

Universitätsklinikum Carl Gustav Carus an der Technischen

Universität Dresden

Dr. Silvia Scoccianti (Radiation Oncology Unit, Azienda Ospedaliera Universitaria Careggi Firenze, Italy) provided the clinical case

From Florenz...

...to Elbflorenz

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Introduction

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Aim of the session

Discussion on:

- contouring a Medulloblastoma's clinical case
    - Target Volumes and Organs at Risk

- Tips on how to recognize critical structures

- Hands-on: Group recontouring with final discussion

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Programm of the session

1. Short introduction of Falcon and Clinical case presentation
2. Collegial discussion of submitted contours
3. Hands on… Time to recontour
4. Discussion of new submitted contours.

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FALCON

***F**ellowship in **A**natomic de**L**ineation & **CON**touring*

ESTRO's contouring platform:

→ improve your delineation skills, online/onsite

→ see what's in common between your contours and:

- ESTRO guideline contours
- Contours from experts in the field

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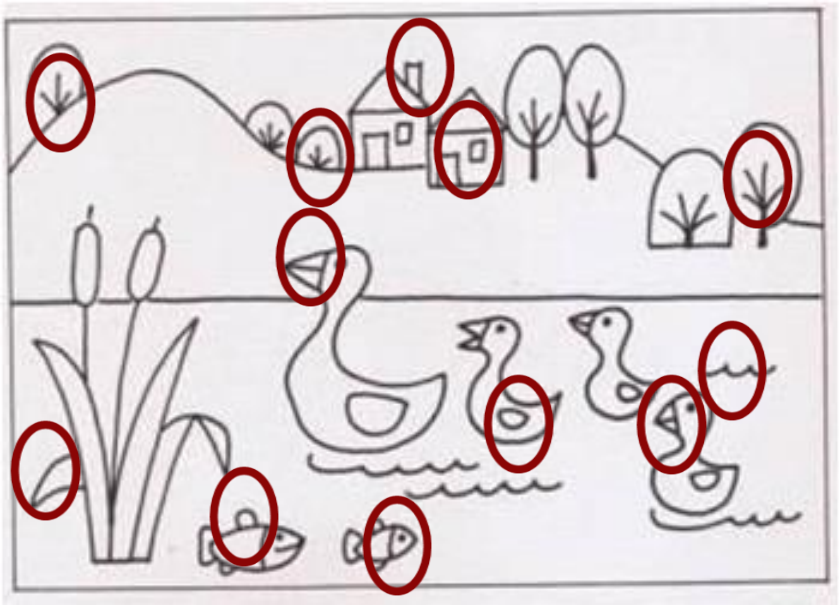
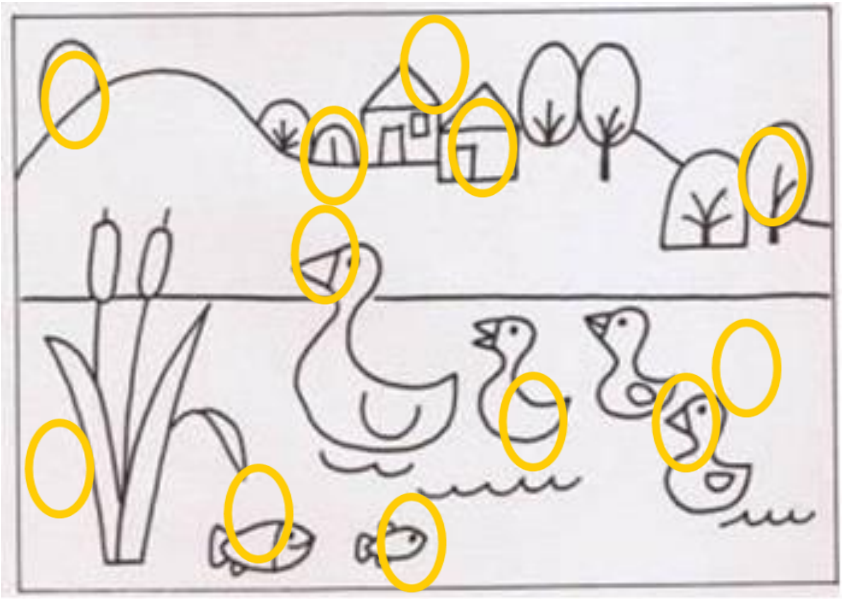
Similarity evaluation methods





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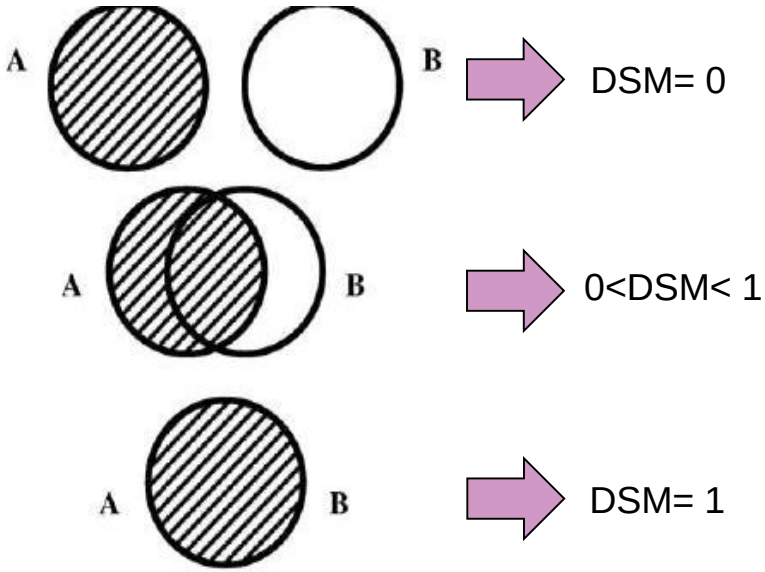
DICE Similarity Metric (DSM)

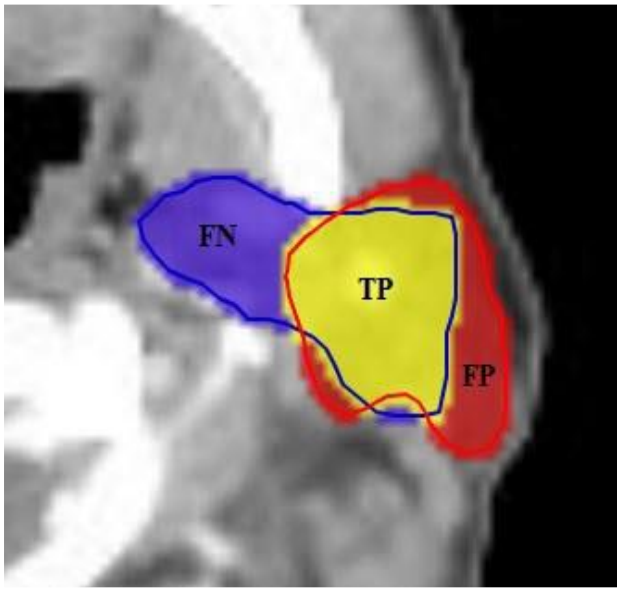
Assessment agreement (True Positive area, TP)
between Participant and Reference contours

$$\frac{2\,|A \cap B|}{|A| + |B|}$$

$$DSM = 2 \times \frac{TP}{(FN + TP) + (FP + TP)}$$



Acad Radiol. 2004 Feb; 11(2): 178–189



Educase User Guide, Jan 2014

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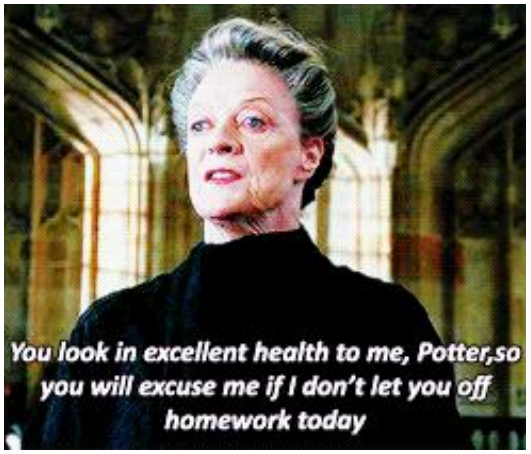
Homeworks have been sent 3 wks before the course



Time for discussion

Time to try again

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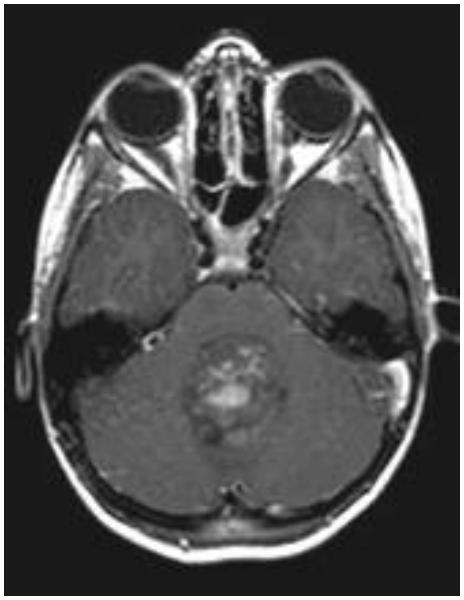
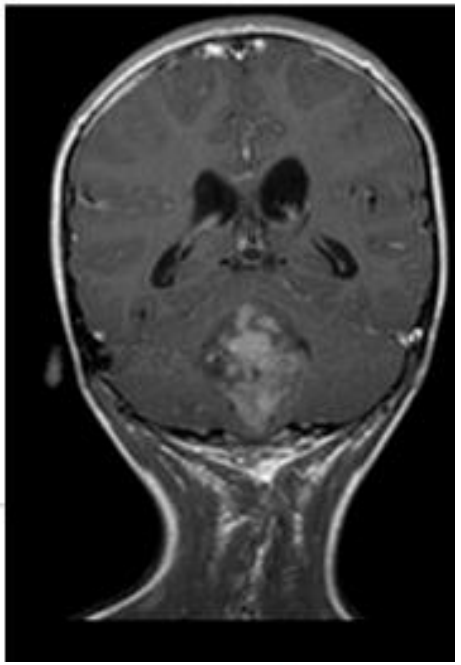
Clinical case description

Case description

Patient: M.B.; female; d.o.b. 23/02/2006
Diagnosis: **Medulloblastoma**





- *April 2015* headache with photophobia, and, then, persistent vomiting
- *09th Apr 2015* **Brain MRI with contrast**
- *09th Apr 2015* **Spine MRI with contrast**: No leptomeningeal dissemination.

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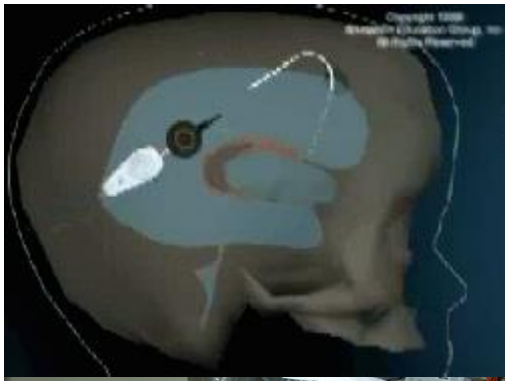
Case description

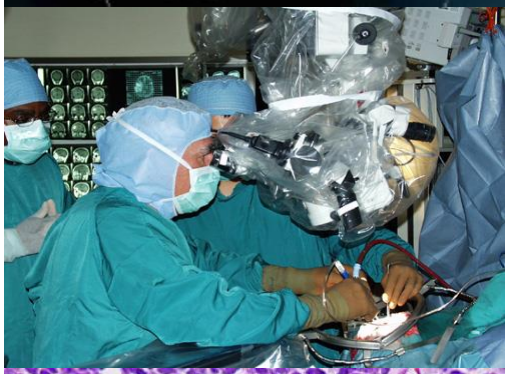
09th Apr 2015 **Ventriculo-cisternal shunt**
09th Apr 2015 **Gross total removal of the lesion**
as shown by **Postoperative MRI** (16/04)

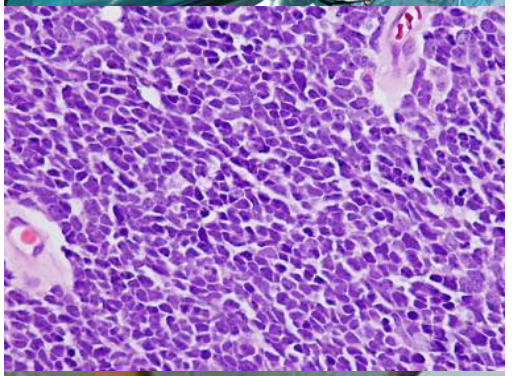
Pathology report: Classic medulloblastoma, N-MYC amplification negative, beta-catenin IHC negative.

CSF cytology: negative.

Referred to Radiation Oncologist for adjuvant treatment







Case description

Referred to Radiation Oncologist for adjuvant treatment

Prescription dose (PNET 4)

CSI	23.4 Gy
Posterior fossa	54 Gy

@ Home Homework: Target volumes

<table>
<tr><th colspan="2">Target volumes</th></tr>
<tr><td colspan="2">CSI CTV</td></tr>
<tr><td rowspan="2">Boost</td><td>Posterior fossa volume</td></tr>
<tr><td>Tumor bed CTV</td></tr>
</table>

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@ Home Homework: Organs at Risk

Intracranial organs at risk	Extracranial organs at risk
ocular globes	parotid glands
lenses	jaw
lacrimal glands	thyroid
pituitary gland	heart
optic nerves	pericardium
optic chiasma	liver
hippocampi	kidneys
cochleas	lungs
brainstem	ovaries or testicles

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Target volumes		Mean Dice Coefficient Score	How many participants drew it
CSI CTV	WB volum Spine volu		13/64
Posterior fossa CTV			2/64
Tumor bed GTV			11/64
Organs at risk			
R Optic nerve			16/64
Optic chiasm			10/64
R Cochlea			12/64
R Hippocampus			3/64
Brainstem			18/64
R Lacrimal gland			3/64
Pituitary gland		0,71	12/64
Heart		0,84	16/64

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„There is no more useless answer to an ever-formulated question“

(Prof. Dr. Dr. J. Debus)

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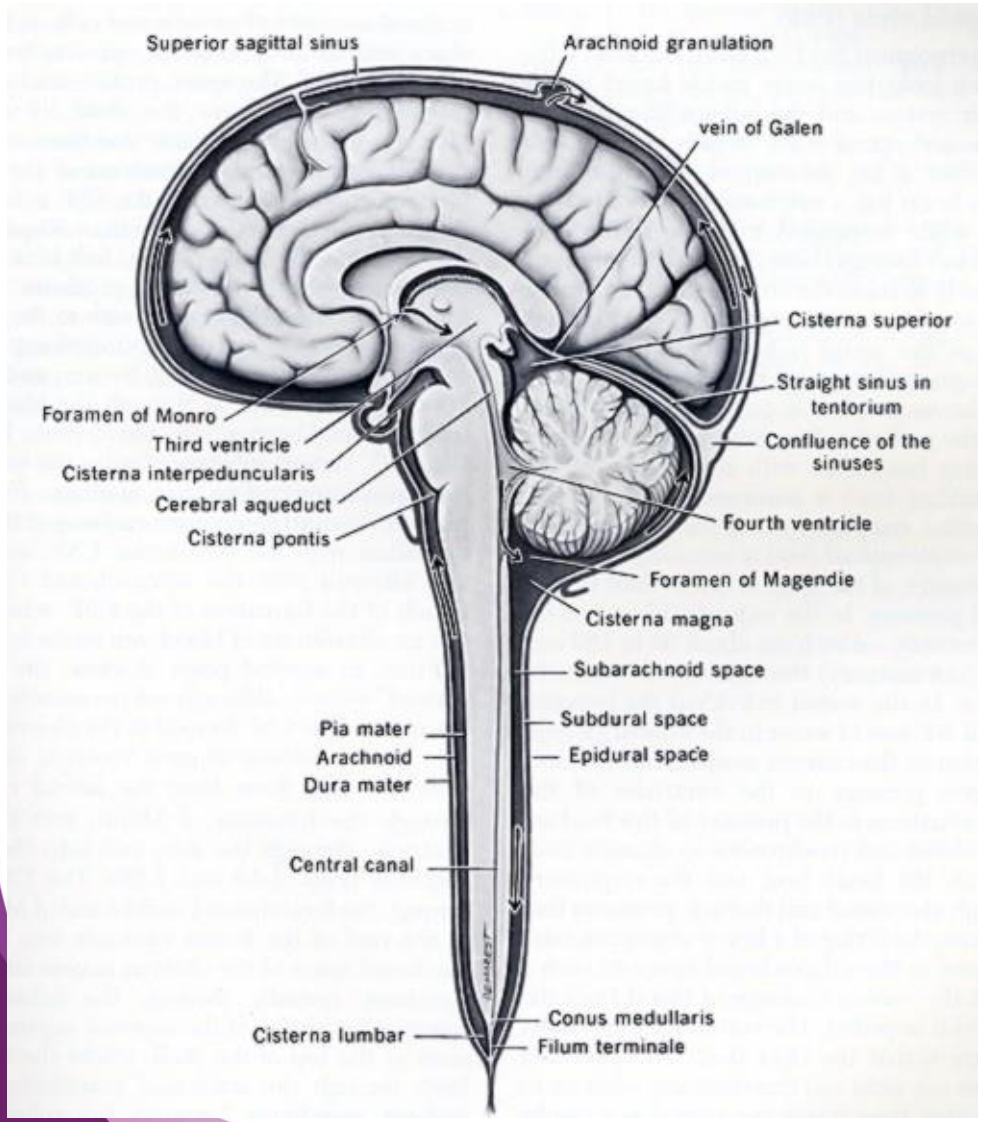
Craniospinal axis



1. Whole Brain
2. Spinal cord
3. Thecal sac

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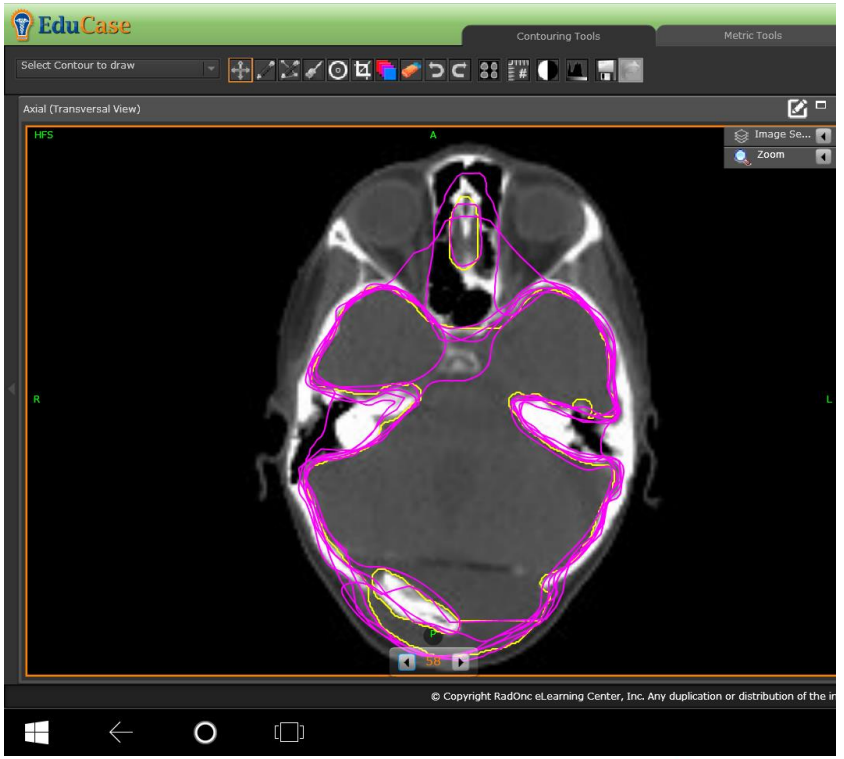
Whole Brain: cribrate plate region

To which extent has to be contoured?



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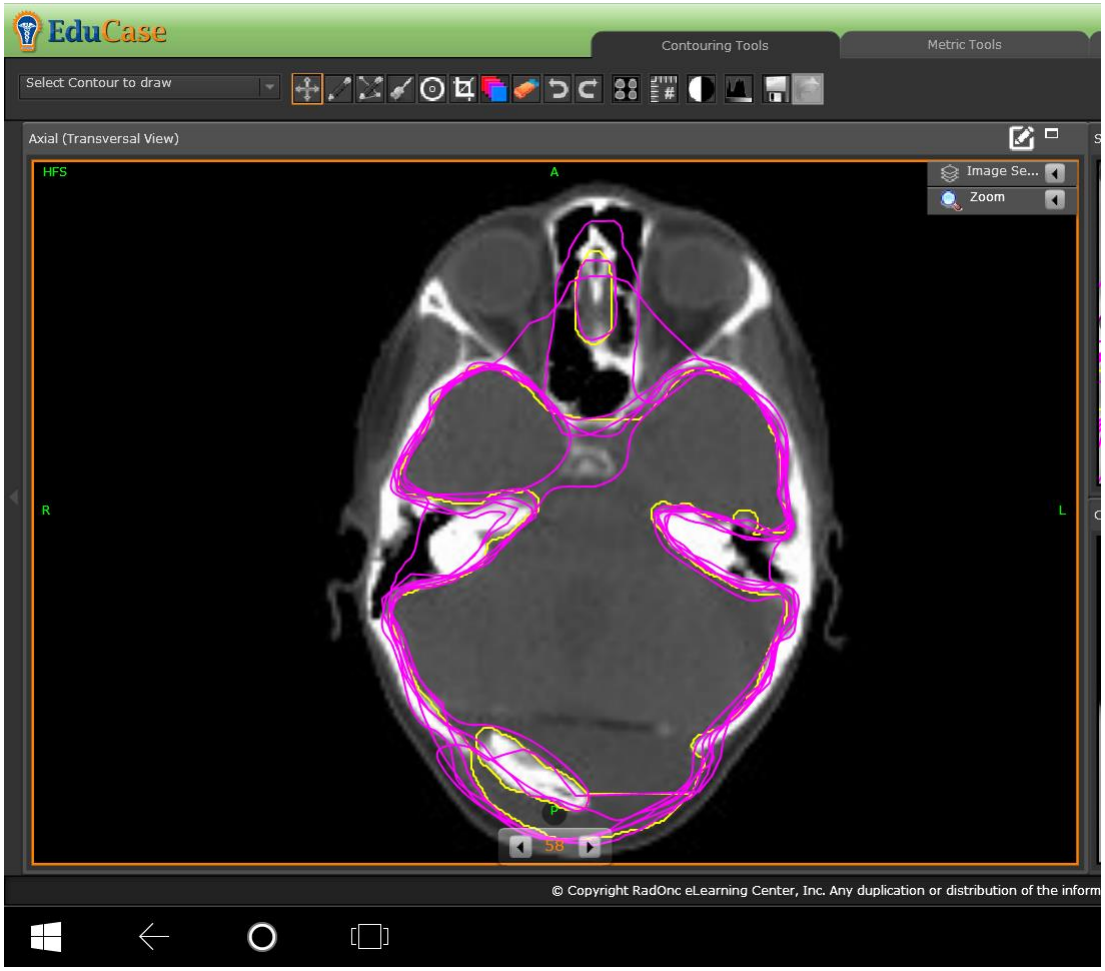
Whole Brain: **petrous bone**

Does it has to be included in our CTV?



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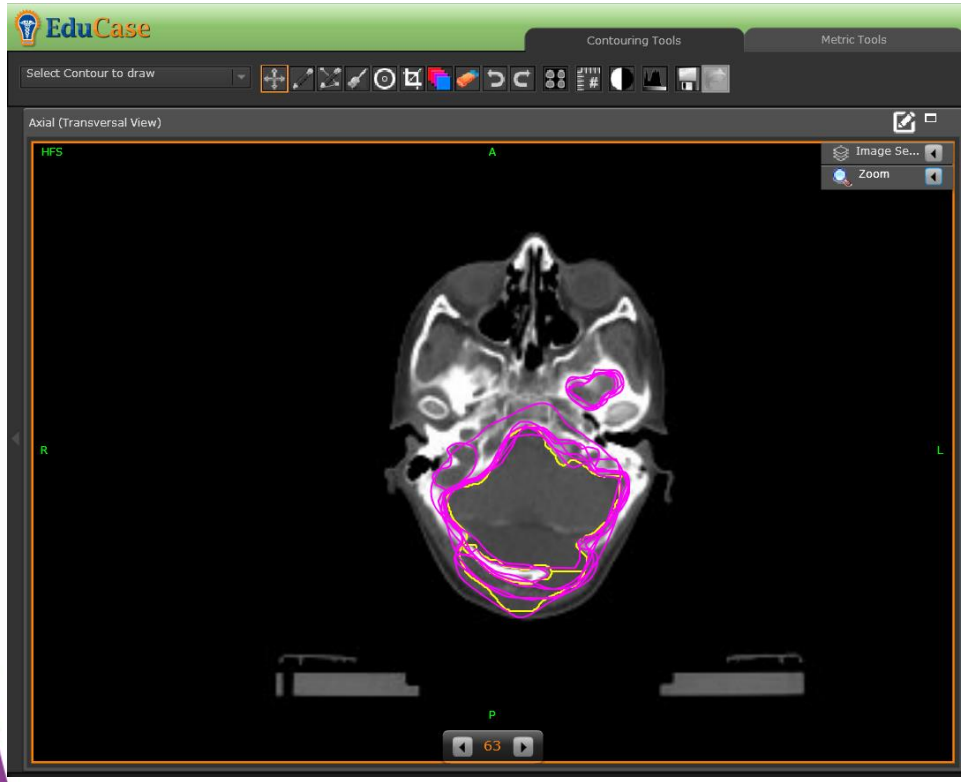
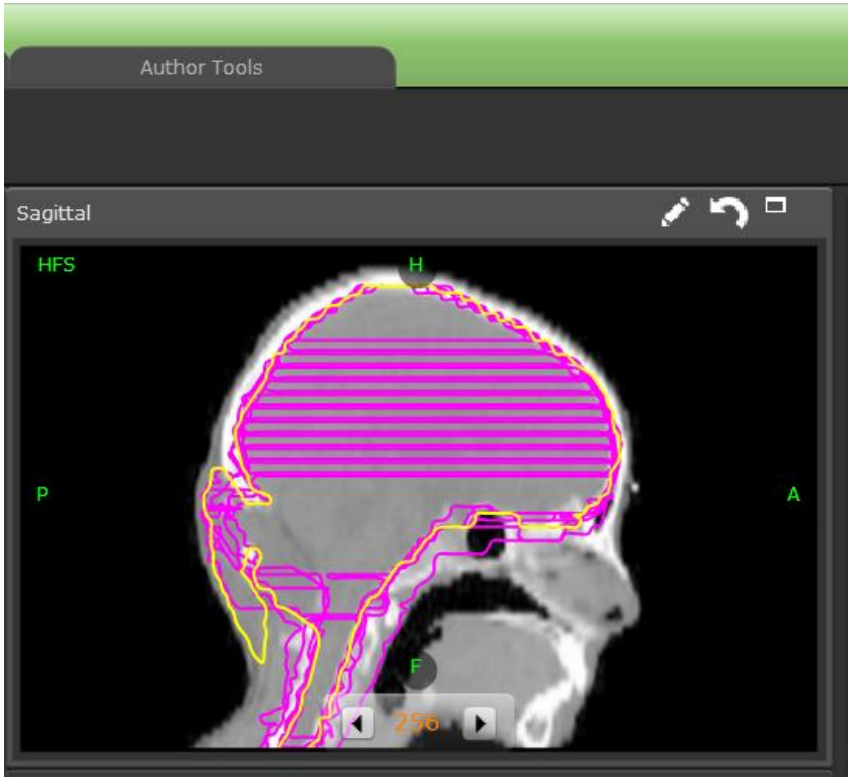
Whole Brain:
pseudomeningocoele's extent





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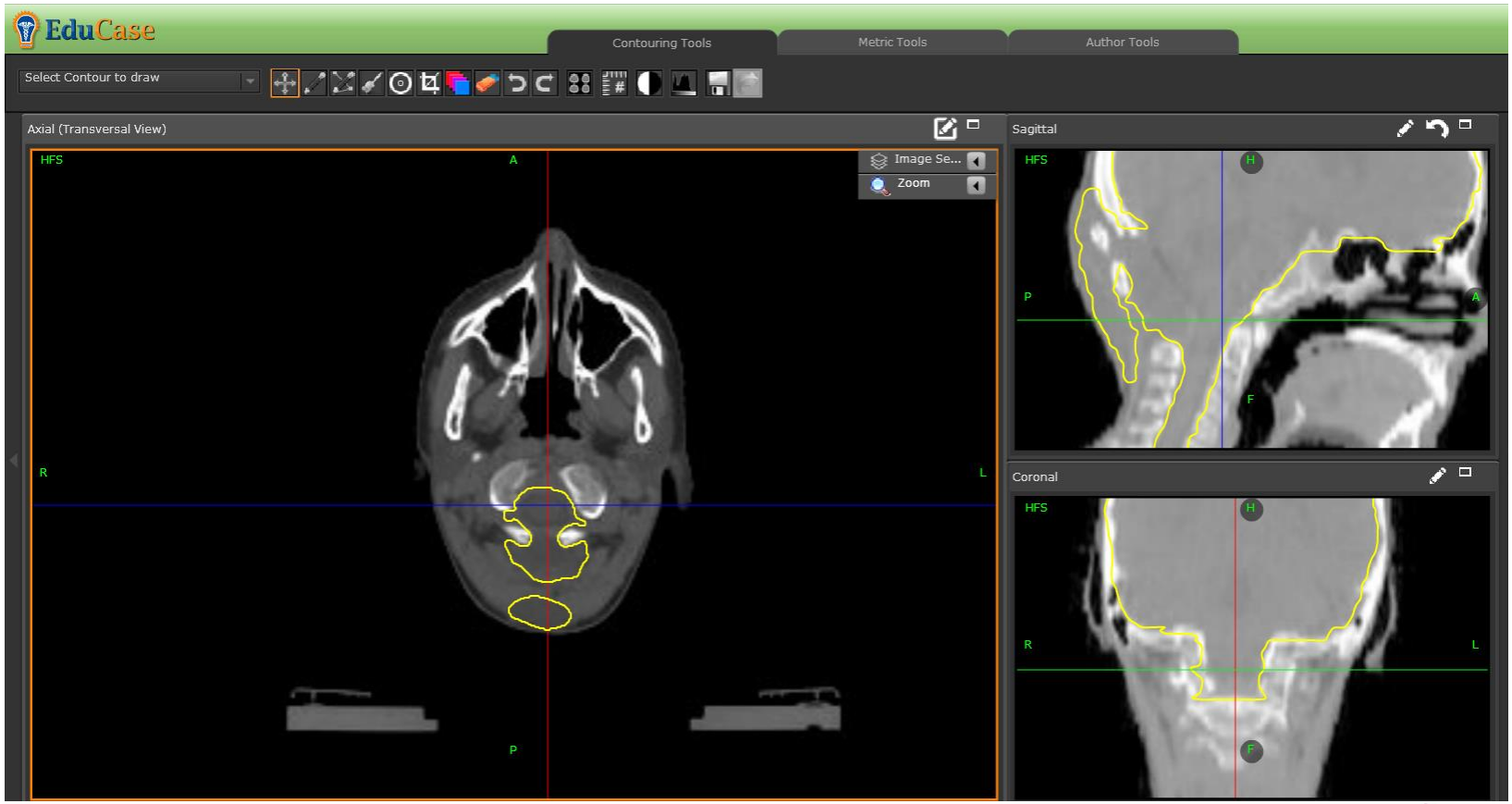
Whole Spine CTV: first root and lateral extent:

Do we have to encompass the lateral foramina? And the subarachnoidal space?



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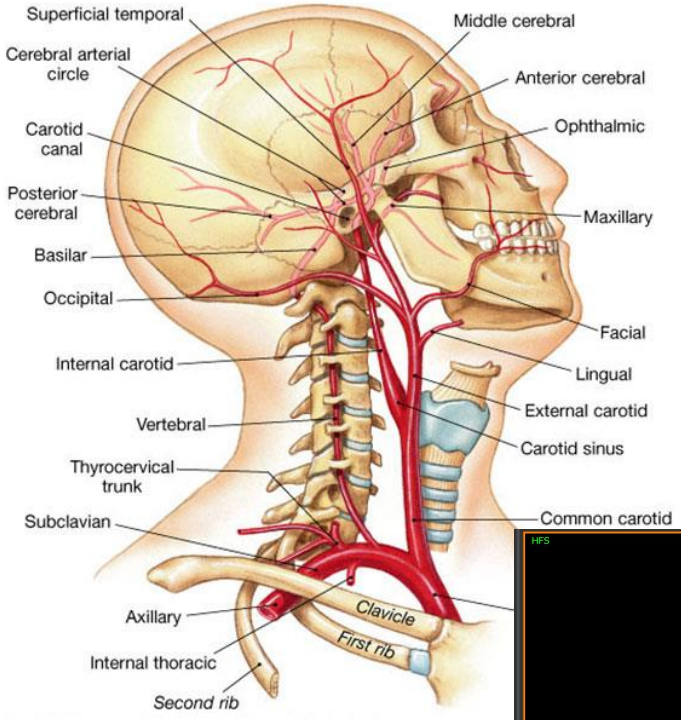
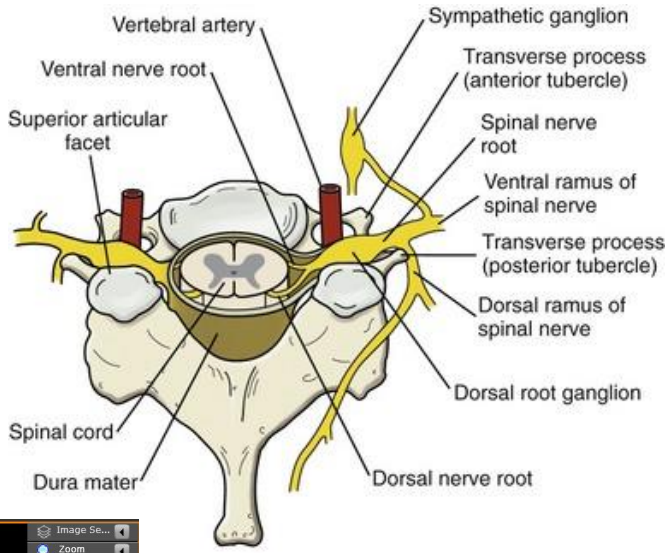
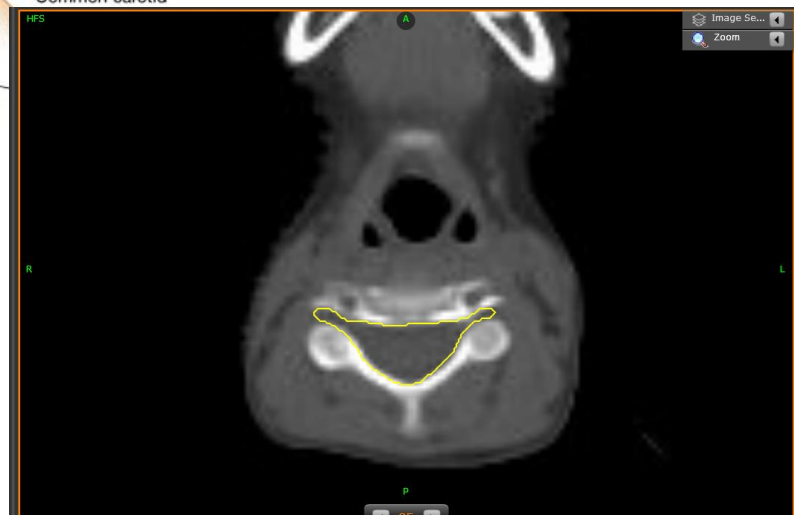
Whole Spine CTV: cervical region

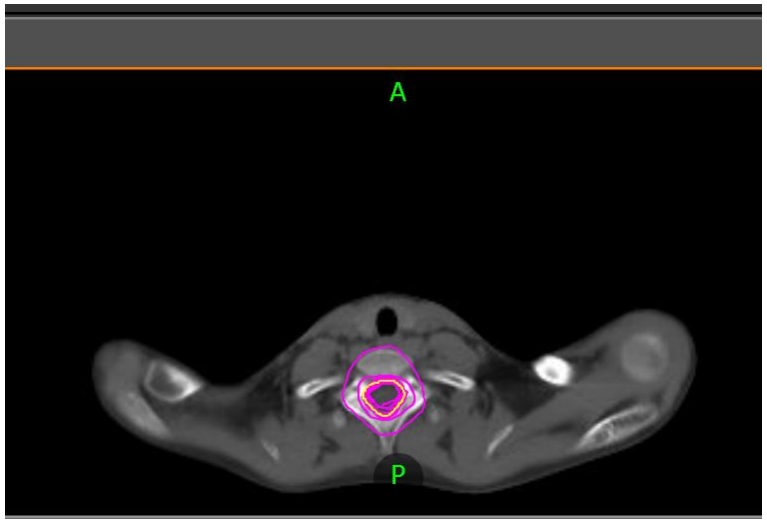
What do we have to include in our CTV?

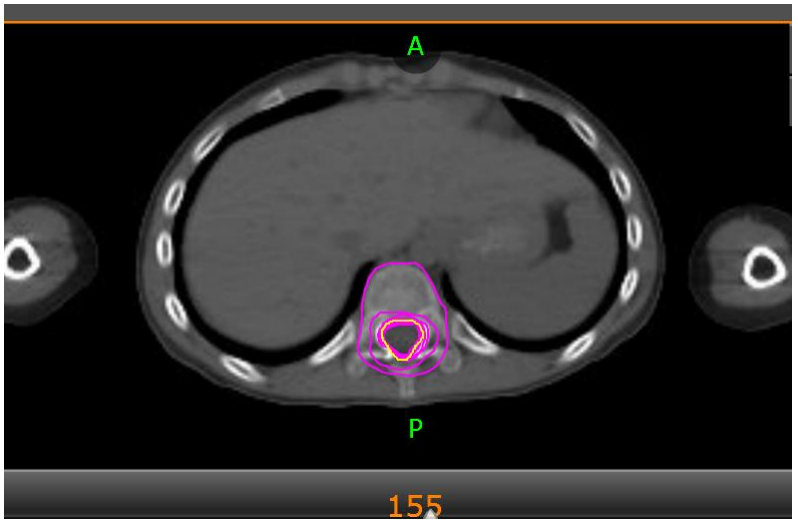


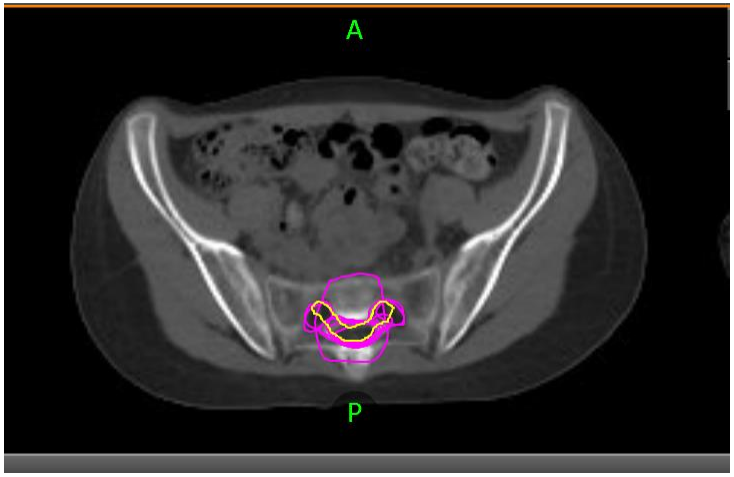




Whole Spinal CTV:
do we have to include the entire vertebral body?







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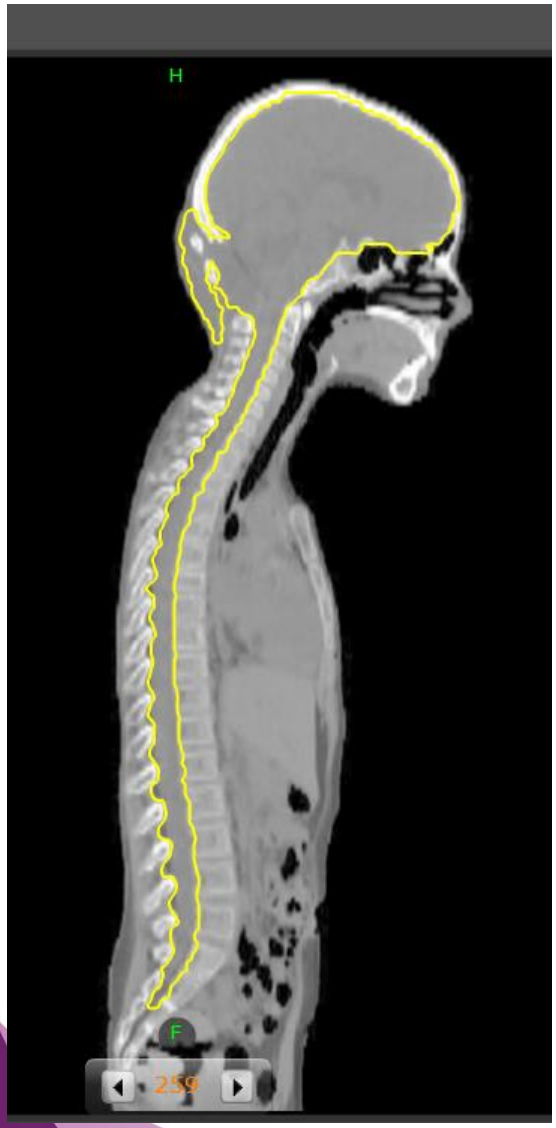
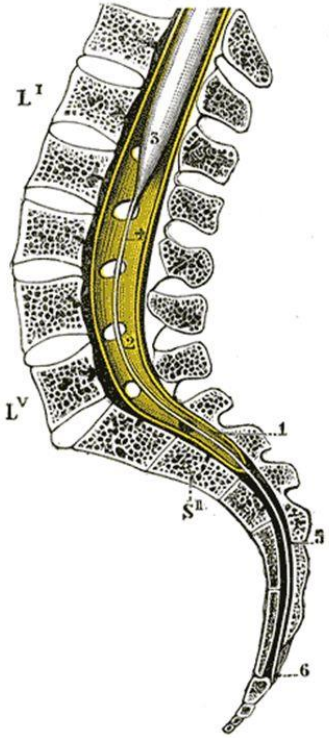
Whole Spinal CTV: lower limit

Which kind of imaging could help us?





Spinal Meninges

The arachnoid is only loosely related to the underlying pia mater.

- the spinal cord ends at L2
- the dural sac and arachnoid end at S2

As a result there is a large space between the arachnoid and pia in the lumbar region:

Lumbar Cistern:

Lower limit to S2 covers 83% of patients

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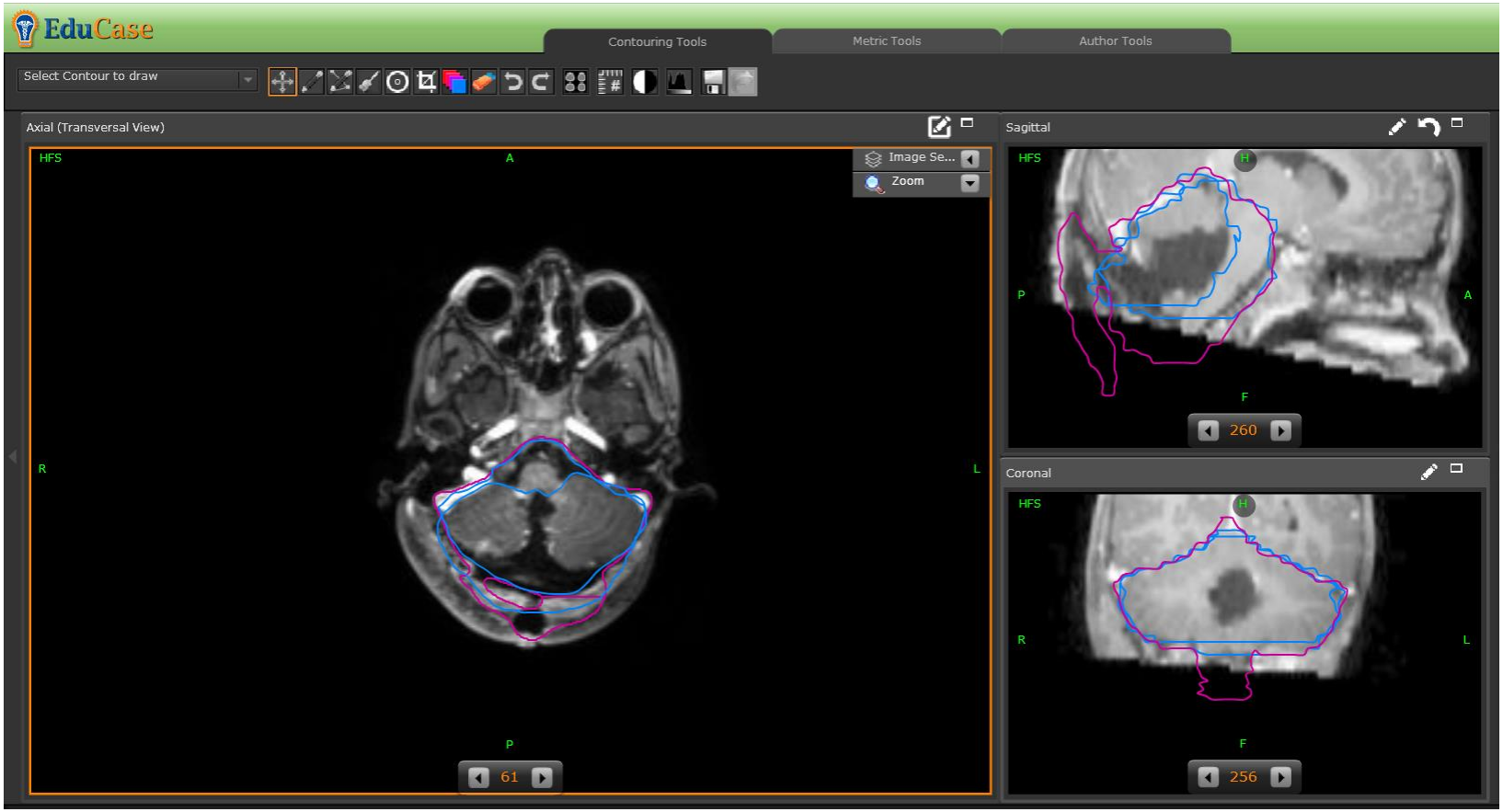
Posterior Fossa:

Which are the limits?

Which kind of imaging could help us?



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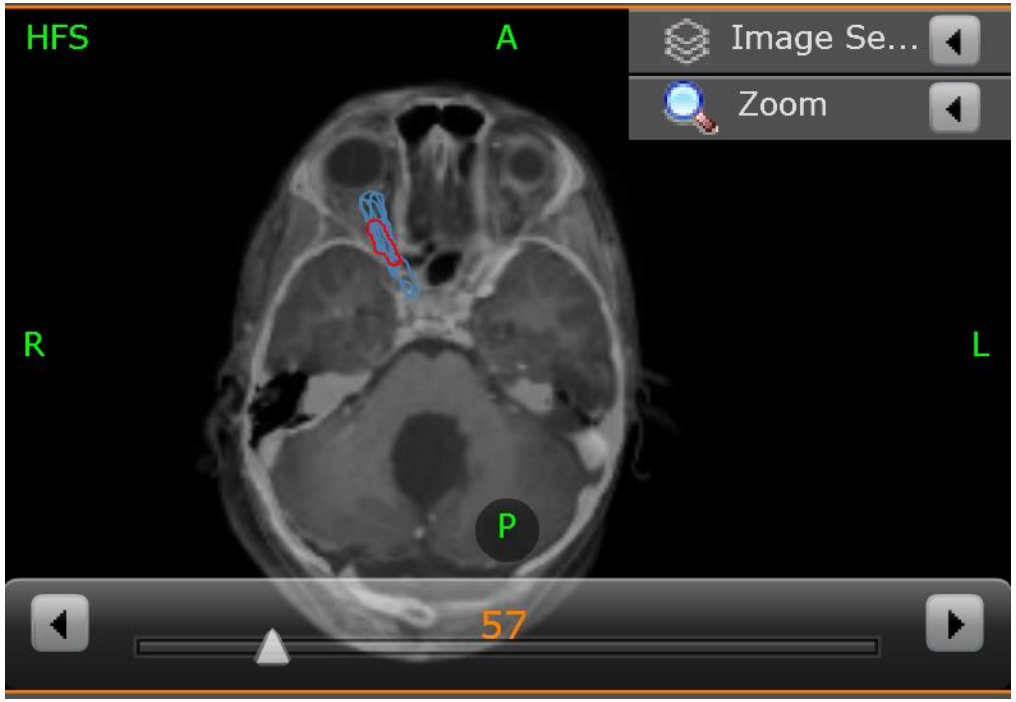
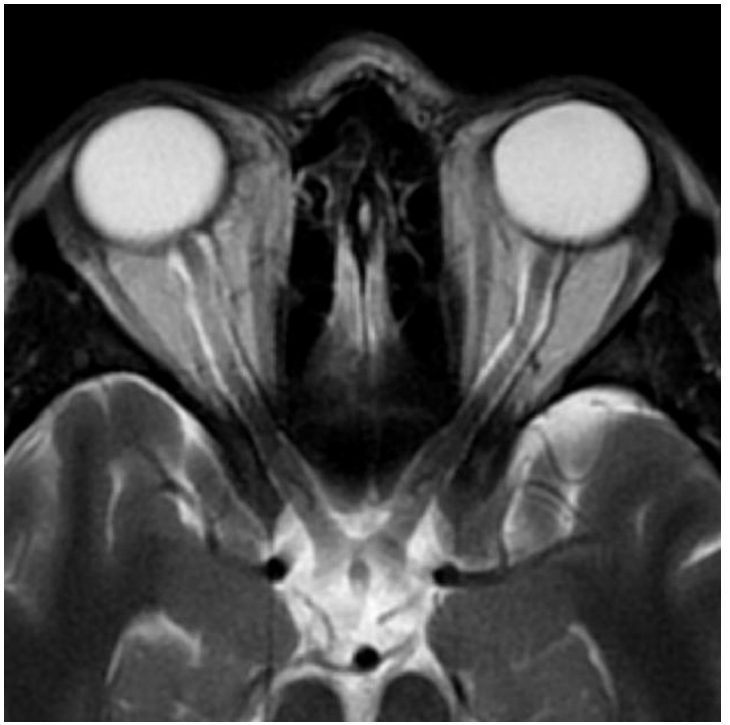
Optic nerve:
How to identify its extent?





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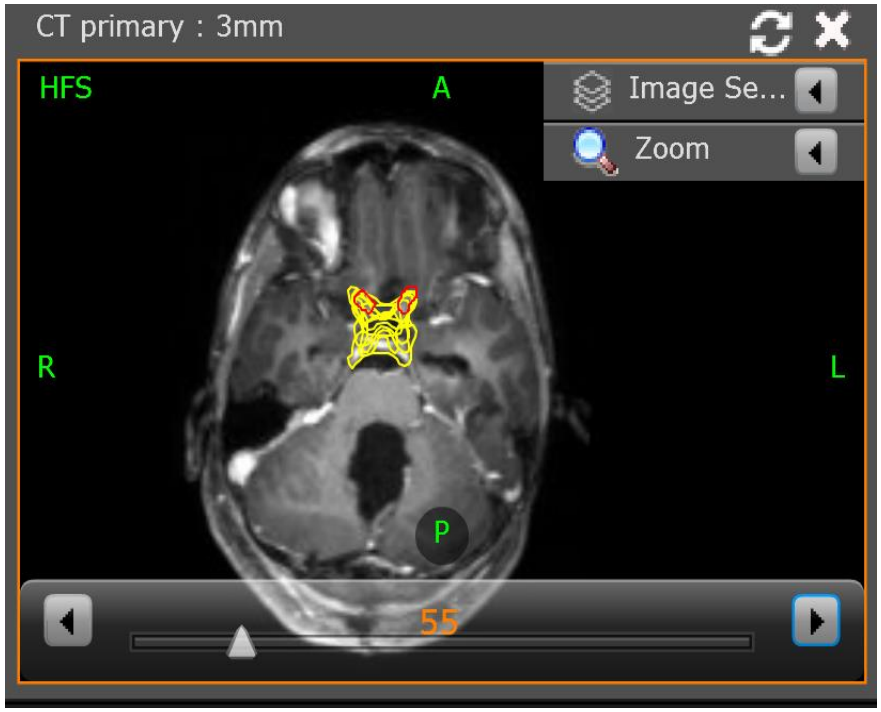
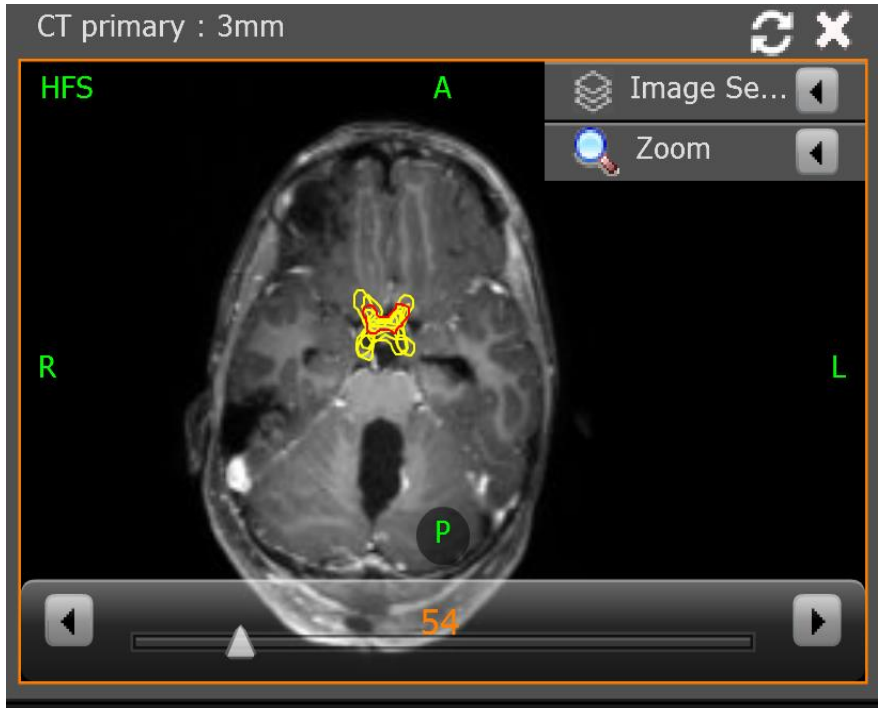
Chiasma:
How to identify its extent?





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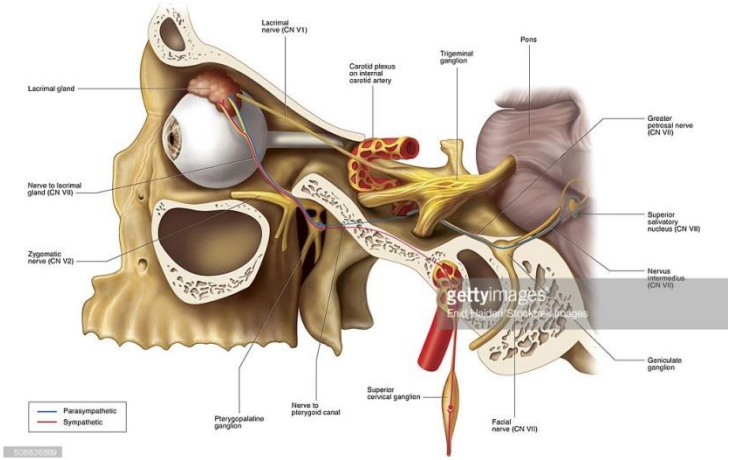
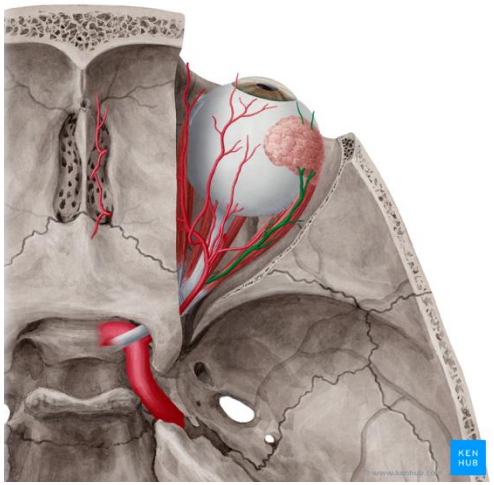
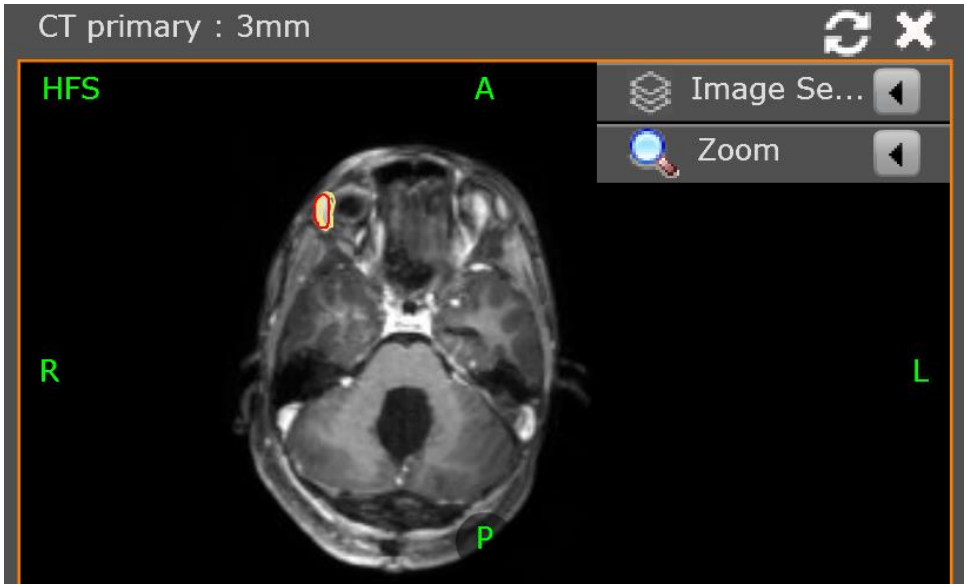
Lacrimal gland

Which kind of imaging could help us?

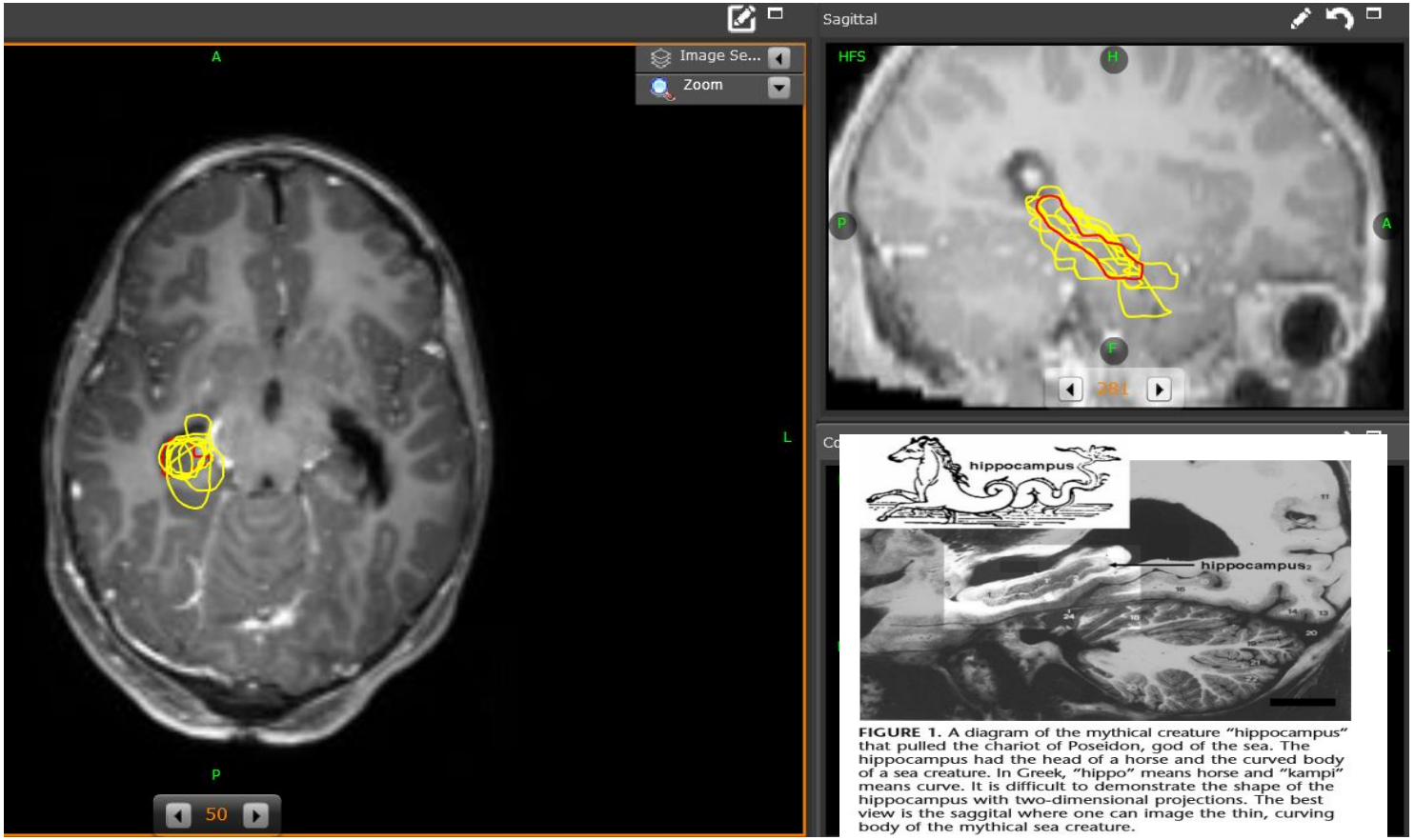






Hippocampi

Which kind of imaging could help us?
Which projection should we look at?



Chera S, et al, Am J Cl Oncol, 2009

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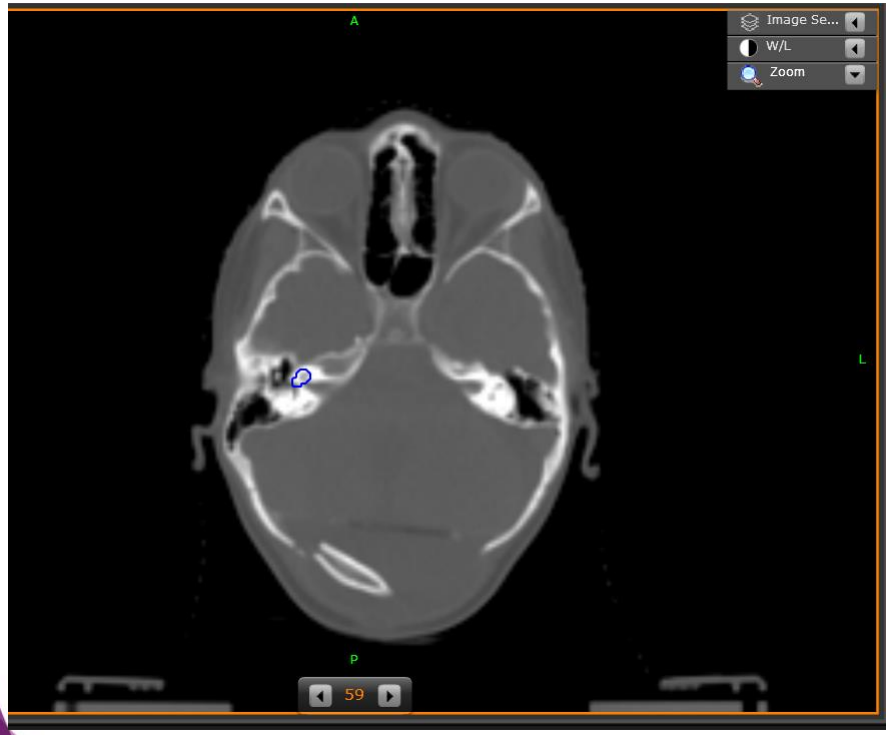
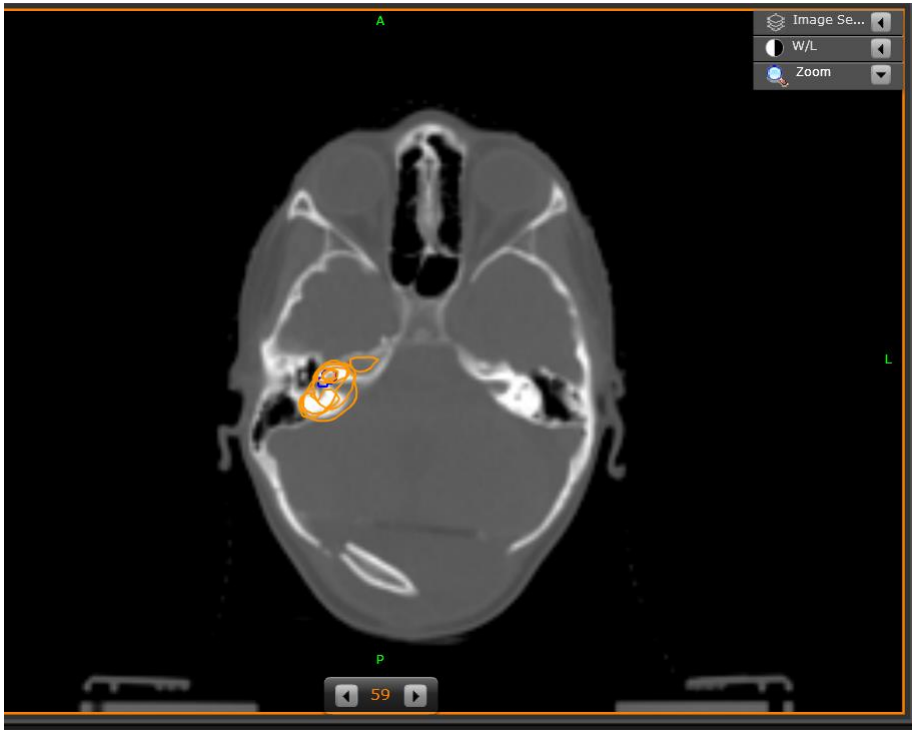
Cochlea

Which kind of imaging could help us?
Which anatomical structures could be helpful?





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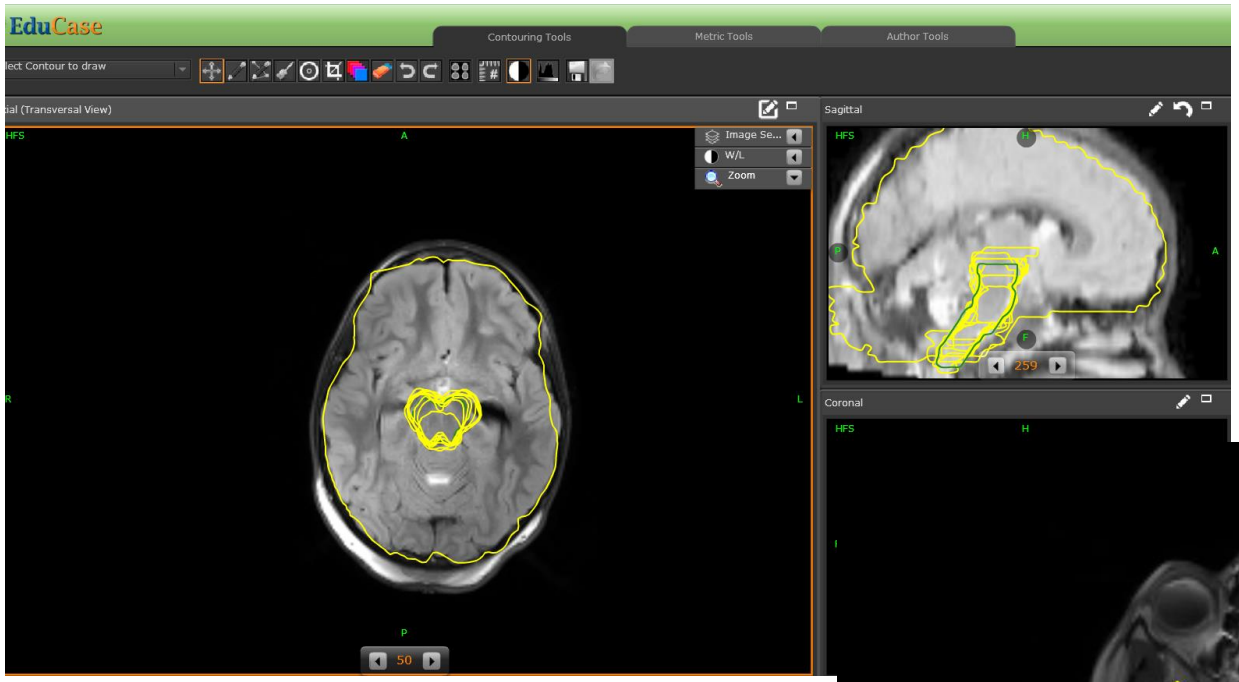
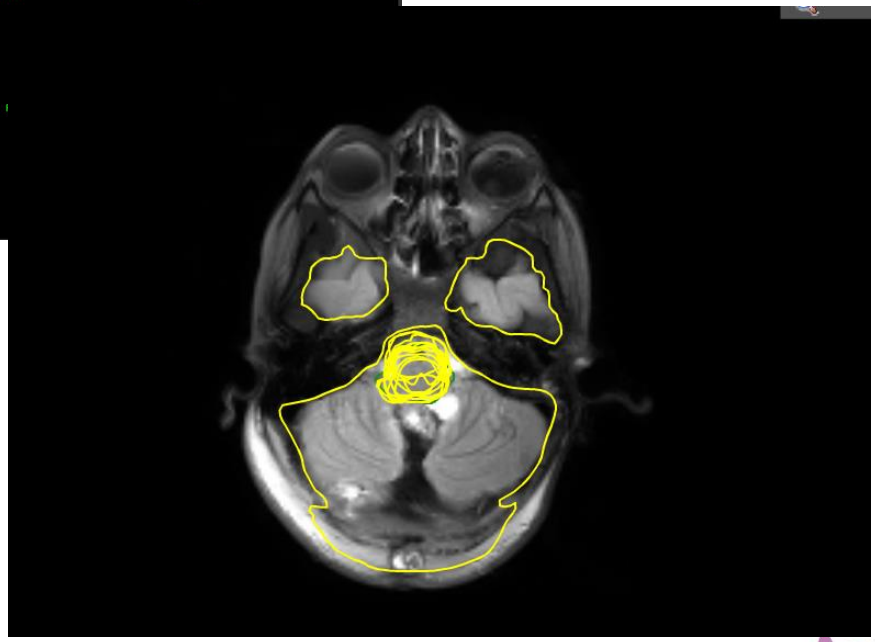
Brainstem:
How to identify its extent?





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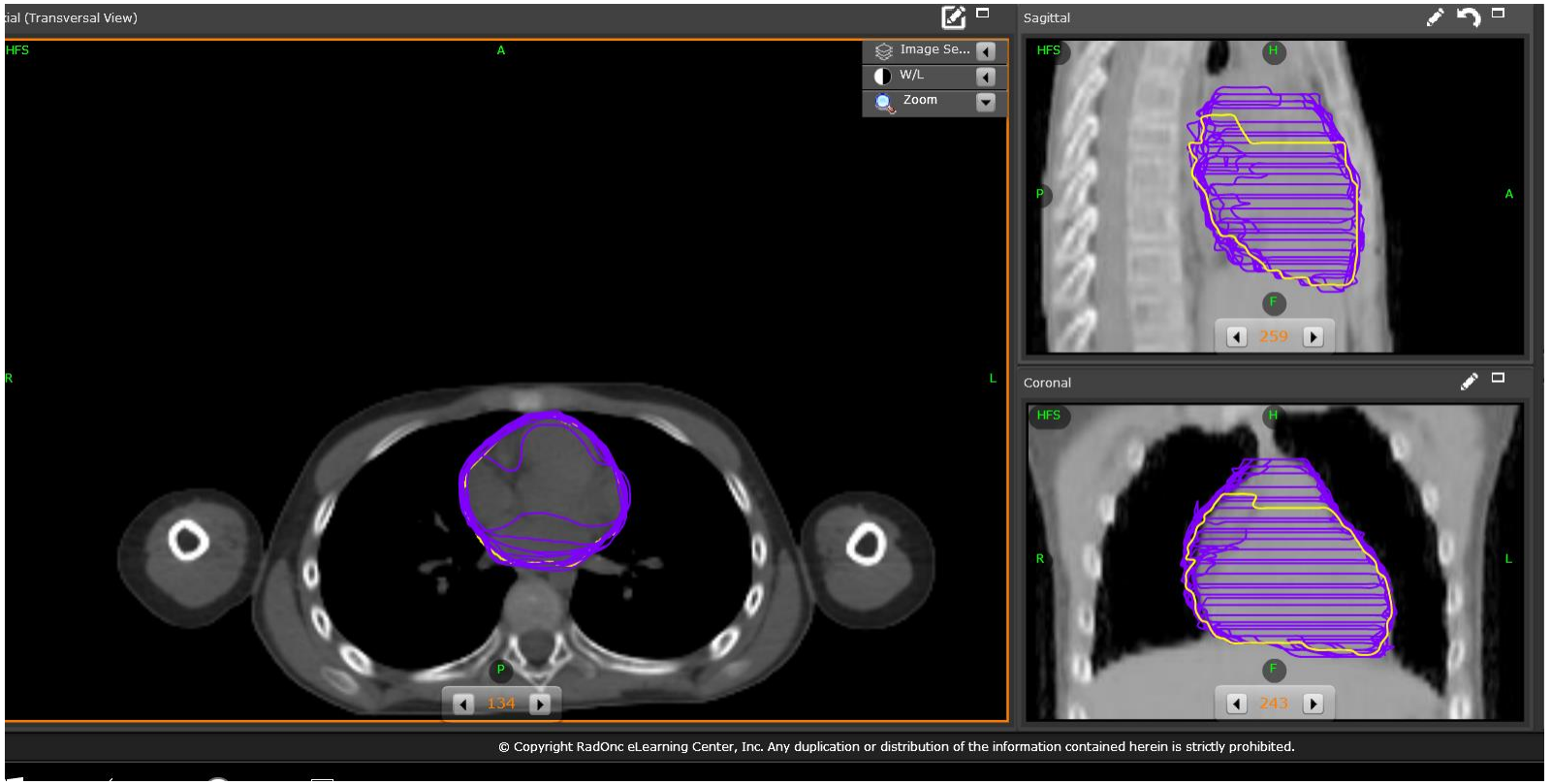
Heart:

Which is its superior limit?



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Group	Structures	Teachers
Group 1	Whole Brain + ***posterior fossa+tumor bed GTV***	*T. Jaspan, C. Valentini*
Group 2	Whole Brain + ***optic nerves***	*R.-D. Kortmann, C. Carrie, R. Taylor*
Group 3	Whole Brain + ***hippocampi***	*U. Ricardi, K. Dieckmann, D. Walker*
Group 4	Whole Brain + ***cochlea***	*A. Paulino, B. Timmermann*
Group 5	Whole Brain + ***spinal axis***	*T. Jaspan, C. Valentini*
Group 6	Whole Brain + ***chiasma***	*R.-D. Kortmann,, C. Carrie, R. Taylor*
Group 7	Whole Brain + ***heart***	*U. Ricardi, K. Dieckmann, D. Walker*
Group 8	Whole Brain + ***lacrimal glands***	*A. Paulino, B. Timmermann*
Group 9	Whole Brain + ***brainstem***	*T. Jaspan, C. Valentini*

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Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study

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Summary

Background Therapy for ependymoma includes aggressive surgical intervention and radiotherapy administered by use of methods that keep the risk of side-effects to a minimum. We extended this treatment approach to include children under the age of 3 years with the aim of improving tumour control.

Methods Between July 11, 1997, and Nov 18, 2007, 153 paediatric patients (median age 2·9 years [range 0·9–22·9 months]) with localised ependymoma were treated. 85 patients had anaplastic ependymoma; the tumours of 122 were located in the infratentorial region, and 35 had received previous chemotherapy. Patients received conformal radiotherapy after definitive surgery (125 patients had undergone gross total, 17 near total, and 11 subtotal resection). Doses of 59·4 Gy (n=131) or 54·0 Gy (n=22) were prescribed to a 10 mm margin around the target volume. Disease control, patterns of failure, and complications were recorded for patients followed over 10 years. Overall survival, event-free survival (EFS), cumulative incidence of local recurrences, and cumulative incidence of distant recurrences were assessed. Variables considered included tumour grade, tumour location, ethnic origin, sex, age when undergoing conformal radiotherapy, total radiotherapy dose, number of surgical procedures, surgery extent, and preradiotherapy chemotherapy.

Findings After a median follow-up of 5·3 years (range 0·4–10·4), 23 patients had died and tumour progression noted in 36, including local (n=14), distant (n=15), and combined failure (n=7). 7-year local control, EFS, and overall survival were 87·3% (95% CI 77·5–97·1), 69·1% (56·9–81·3), and 81·0% (71·0–91·0), respectively. The cumulative incidences of local and distant failure were 16·3% (9·6–23·0) and 11·5% (5·9–17·1), respectively. In the 107 patients treated with immediate postoperative conformal radiotherapy (without delay or chemotherapy), 7-year local control, EFS, and overall survival were 88·7% (77·9–99·5), 76·9% (63·4–90·4), and 85·0% (74·2–95·8), respectively; the cumulative incidence of local and distant failure were 12·6% (5·1–20·1), and 8·6% (2·8–14·3), respectively. The incidence of secondary malignant brain tumour at 7 years was 2·3% (0–5·6) and brainstem necrosis 1·6% (0–4·0). Overall survival was affected by tumour grade (anaplastic *vs* differentiated: HR 3·98 [95% CI 1·51–10·48]; p=0·0052), extent of resection (gross total *vs* near total or subtotal: 0·16 [0·07–0·37]; p<0·0001), and ethnic origin (non-white *vs* white: 3·0 [1·21–7·44]; p=0·018). EFS was affected by tumour grade (anaplastic *vs* differentiated: 2·52 [1·27–5·01]; p=0·008), extent of resection (gross total *vs* near total or subtotal: 0·20 [0·11–0·39]; p<0·0001]), and sex (male *vs* female: 2·19 [1·03–4·66]; p=0·042). Local failure was affected by extent of resection (gross total *vs* near total or subtotal: 0·16 [0·067–0·38]; p<0·0001), sex (male *vs* female: 3·85 [1·10–13·52]; p=0·035), and age (<3 years *vs* ≥3 years: 3·25 [1·30–8·16]; p=0·012). Distant recurrence was only affected by tumour grade (anaplastic *vs* differentiated: 4·1 [1·2–14·0]; p=0·017).

Interpretation Treatment of ependymoma should include surgery with the aim of gross-total resection and conformal, high-dose, postoperative irradiation. Future trials might consider treatment stratification based on sex and age.

Funding American Cancer Society and American Lebanese Syrian Associated Charities (ALSAC).

Introduction

Newer methods of delivering radiotherapy combined with advances in neurosurgery have increased tumour control and reduced side-effects in paediatric patients with localised ependymoma. Preliminary findings from contemporary series using conformal, intensity-modulated, and proton-beam radiotherapy support this conclusion, with reduced side-effects and improved rates of local tumour control, event-free survival (EFS), and overall survival.[1–4] These results are especially relevant because ependymoma is commonly diagnosed in young patients and radiotherapy avoidance has had limited success.[5–7] Fear of radiation-related side-effects has driven radiotherapy avoidance and the use of chemotherapy in young children. Recent data suggest that 42% of patients might avoid irradiation for up to 5 years after diagnosis by use of chemotherapy.[5] Others suggest that fewer than 22% might benefit from this approach[6] and that the role of chemotherapy is unproven.[8] At stake is overall survival and functional outcome; patients treated with post-operative radiotherapy have better EFS and overall survival than those treated with chemotherapy.

Improved disease control provides a new opportunity to assess prognostic factors, patterns of failure, and late effects of treatment. We previously reported on the use of conformal radiotherapy for ependymoma in a

prospective trial that included 88 paediatric patients treated by use of a 10 mm margin around the target volume with a median follow-up of 38 months.[4] The 3-year EFS estimate was 74·7% (95% CI 63·5–85·9), median age at irradiation was 3 years (range 1·1–22·9), and few side-effects were noted. In the current report, we describe our findings with extended follow-up of these original patients and extend our single-institution series to now include a total of 153 patients.

Methods

Patients

Between July 11, 1997, and Nov 18, 2007, 153 patients were treated with conformal or intensity-modulated radiotherapy, with written informed consent from a parent or guardian. The data presented were current on April 20, 2008. The initial 88 patients were prospectively treated in a phase II trial, approved by the institutional review board (IRB), between July 11, 1997, and Feb 5, 2003. The study was amended, with IRB approval, to included similarly treated patients who were enrolled for prospective follow-up once they completed treatment using the same target volume guidelines during the time period from Feb 5, 2003, through to Nov 18, 2007. Eligibility criteria included localised ependymoma without evidence of dissemination (ie, negative for metastases within 3 weeks of irradiation by use of MRI of the brain and spine and CSF cytology) or previous radiotherapy. The minimum age at the time of irradiation was 12 months until Feb 5, 2003, after which it was removed as an eligibility requirement. Previous treatment with chemotherapy was allowed and there was no limit for the interval from time of first surgery to irradiation.

Surgery and imaging follow-up

Neurosurgery was routinely consulted before irradiation to assess eligibility for additional tumour resection. Gross-total resection was defined as intraoperatively assessed macroscopically complete resection and no evidence of residual tumour on MRI. Near-total resection was defined as less than 5 mm residual tumour in greatest dimension. Subtotal resection included all other cases. Imaging follow-up included brain MRI every 3 months for the first 2 years (1997–2002) or every 4 months for the first 3 years (2003–07), then every 6 months up to 5 years, and then annually. Spinal MRI was done annually unless symptoms developed.

Conformal radiotherapy

We have used the term conformal radiotherapy to refer to conformal and intensity-modulated radiotherapy. The latter was used selectively for supratentorial tumours to reduce the dose to the orbit and for infratentorial tumours to reduce the dose to the cochleae. CT planning was used for all patients and postoperative MRI data (postcontrast T1 and T2-weighted sequences) were registered to CT data beginning in 1998. MRI was done in the treatment position using a dedicated magnetic resonance system beginning in 2004, which improved registration, in particular of the anatomy of the upper cervical spinal cord and lower brainstem in patients with infratentorial tumours treated in the prone position. The advent of transferable digital imaging from referring institutions during the past 3 years of the study allowed registration of preoperative imaging data to further assist in target-volume definition. Vacuum moulds were constructed to immobilise patients treated prone; those treated supine had a customised thermoplastic mask with or without radiocamera monitoring. About 70% of children under the age of 7 years needed general anaesthesia (propofol was administered intravenously).

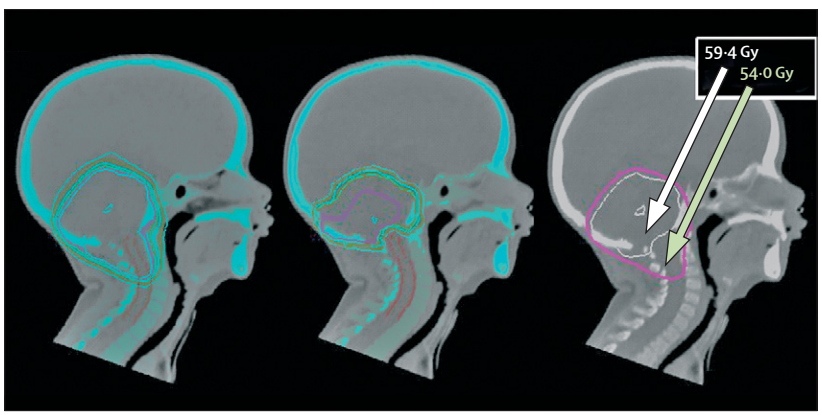

Figure 1: **Sagittal CT reconstruction showing 0–54 Gy (left), 54–59·4 Gy (centre), and composite (right) radiation dose contours for a case of infratentorial ependymoma**

Definitions from the International Commission on Radiation Units and Measurements report 50 were used for target-volume definitions.[9] The description of gross tumour volume (GTV) was modified to include gross residual tumour, or the postoperative tumour bed, or both. The clinical target volume (CTV) was a 10 mm anatomically confined expansion of the GTV. The planning target volume (PTV) was a 3–5 mm geometric expansion of the CTV. Treatment methods included multifield non-coplanar step and shoot using multileaf collimation (5–10 mm). Target volume coverage was –5% and +10%. There were no dose-volume limits for the brainstem and the dose to the spinal cord and optic chiasm were limited to about 54 Gy for the first 30 fractions and were allowed to be less than 70% of the prescribed dose for the remaining three fractions (figure 1). The prescribed dose was 59·4 Gy for all patients except those under the age of 18 months who achieved gross-total resection and selected patients early in our series who received 54 Gy.

Statistical analysis

We assessed overall survival, EFS, cumulative incidence of local recurrences, and cumulative incidence of distant recurrences. Variables included tumour grade, tumour location, ethnic origin, sex, age when undergoing

conformal radiotherapy, total radiotherapy dose, number of surgical procedures, surgical extent, and preradiotherapy chemotherapy. Overall survival was defined as the time interval from the initiation of conformal radiotherapy to death from any cause or last known date of survival. EFS was defined as the time interval from the initiation of conformal radiotherapy to date of tumour progression (determined by MRI), death without tumour progression, or last MRI follow-up, whichever occurred first; patients alive at last follow-up were censored. Kaplan-Meier survival estimates were obtained;[10] standard errors were calculated using the method described by Peto and colleagues.[11,12] Local control time was from the initiation of conformal radiation to recurrences, death, or last follow-up, whichever occurred first. Local only recurrences were events; patients free of local only recurrences were censored at the time of local and distant recurrences, distant recurrences, death, or last follow-up. In the univariate analysis of overall survival and EFS, survival distributions in the groups of each variable were compared by use of Mantel-Haenszel statistics,[13] and hazard ratios (HR) were estimated by use of the Cox proportional hazards model.[14] Multiple regression analysis of overall survival and EFS were done by use of the Cox proportional hazards model. The cumulative incidence function for local or distant tumour progression was estimated using the methods of Kalbfleisch and Prentice.[15] Local failure included only local tumour progression or combined local and distant tumour progression. The length of time for risk of local failure was determined from the start date of conformal radiotherapy to the date of MRI identification of any component of local failure. Distant tumour progression without local progression and death from other causes were considered competing events. Local failure was considered a competing event in the estimation of cumulative incidence of distant tumour progression without local progression. In the univariate analysis of cumulative incidence for local or distant tumour progression, Gray's method[16] was used to compare the cumulative incidence functions between subgroups within each variable. Multiple regression analysis of cumulative incidence functions was done based on Fine and Gray's estimator with the incorporation of competing events.[17] The survival and incidence were reported in the format of estimates (95% CI). The level of significance was set at 0·05 and all p values reported are for two-sided tests. No adjustment was made for multiple comparisons. Analyses were done using SAS (version 9.1.3) and S-plus (version 7.0 for Windows).

	Patients (N=153)
Age at CRT (years)	
Mean (SD)	4·9 (4·4)
Median (range)	2·9 (0·9–22·9)
Age at diagnosis (years)	
Mean (SD)	2·9 (4·4)
Median (range)	2·4 (0·0–22·7)
Elapsed days of CRT	
Mean (SD)	44 (2·5)
Median (range)	44 (37–56)
Age (years), n (%)	
<3	78 (51·0)
≥3	75 (49·0)
Tumour grade, n (%)	
Differentiated	68 (44·4)
Anaplastic	85 (55·6)
Tumour location, n (%)	
Infratentorial	122 (79·7)
Supratentorial	31 (20·3)
Ethnic origin, n (%)	
White	126 (82·4)
Black	19 (12·4)
Hispanic	6 (3·9)
Asian	2 (1·3)
Sex, n (%)	
Female	58 (37·9)
Male	95 (62·1)
Total dose (Gy), n (%)	
54	22 (14·4)
59·4	131 (85·6)
Number of surgical procedures, n (%)	
1	87 (56·9)
2	51 (33·3)
3	11 (7·2)
4	4 (2·6)
Surgical extent, n (%)	
GTR	125 (81·7)
NTR	17 (11·1)
STR	11 (7·2)
Pre-CRT chemotherapy, n (%)	
Yes	35 (22·9)
No	118 (77·1)

CRT=conformal radiotherapy. GTR=gross-total resection. NTR=near-total resection. STR=subtotal resection.

Table 1: **Patient characteristics**

Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of this report. The corresponding author had full access to all of the study data and had final responsibility for the decision to submit for publication.

Results

Clinical and treatment characteristics are shown in table 1. All patients were treated with postoperative conformal radiotherapy. 35 of 153 patients (22·9%) received chemotherapy before conformal radiotherapy and 11 of 153 patients (7·2%) had a delay before treatment of more than 4·4 months because of complications, parental

indecision, or planned observation. Two patients treated with chemotherapy and two observed after first surgery had local progression and underwent resection before conformal radiotherapy. Only 21 of 153 patients (13·7%) had their initial surgery done at our institution, and most of those who needed second surgery had definitive resection done at LeBonheur Children's Medical Center in Memphis, TN, USA. Chemotherapy was administered with the intent of improving second surgery in two patients; the remaining patients received chemotherapy on the basis of the preference of the referring institution to administer chemotherapy to very young children, the perceived high-risk status based on extent of resection, or other reasons including a lack of experience of conformal radiotherapy in young children. Various chemotherapy regimens were used. The most common regimen was cisplatin–cyclophosphamide–etoposide–vincristine (n=10) or the same combination substituting cisplatin with carboplatin (n=9). Regimens of cisplatin and carboplatin with various combinations of etoposide and vincristine were used to treat seven patients. The remainder received various combinations of agents. Only five patients who received chemotherapy did not receive a platinum-containing agent. None of the patients received chemotherapy after conformal radiotherapy. The interval from first surgery to conformal radiotherapy was 7·0 months for patients treated with chemotherapy compared with 1·7 months for those who did not receive chemotherapy. No patient with newly diagnosed localised ependymoma referred to our institution during the time of this study was excluded from this series.

The clinical factors presented in table 1 were independent of one another, except tumour grade, which was associated with tumour location (a higher percentage of differentiated tumours were located in the infratentorial region [60 of 122] than in the supratentorial region [eight of 31]; p for association=0·019).

After a median follow-up of 5·3 years (range 0·4–10·4), 23 patients had died; tumour progression was noted in 36, including local failure in 14 patients, distant failure in 15 patients, and combined local and distant failure in seven patients. All local failures were confined to the 95% isodose volume determined by image registration. Spinal metastatic failure was diagnosed only in symptomatic patients or those assessed at the time of intracranial failure. Spinal metastatic failure as a component of failure occurred in 13 patients: seven patients that had combined local and distant failure, two that had both spinal and intracranial metastases, and four that had isolated spinal metastases. Four female patients, with a primary tumour in the infratentorial region, had a second tumour. Three of these four cases were attributed to radiotherapy, including one case of papillary thyroid cancer at 7 years after radiotherapy and two cases of fatal high-grade glioma involving the brainstem or cerebellum at 60 and 66 months after radiotherapy, respectively. One patient developed a low-grade glioma of the cerebral cortex at 24 months unrelated to conformal radiotherapy. The tumour was resected and the patient remains disease-free 10 years after conformal radiotherapy. All patients with second tumours were under the age of 4 years at the time of irradiation and two had previous exposure to chemotherapy. Excluding the unrelated low-grade glioma, the cumulative incidence of a secondary malignancy at 7 years was 4·1% (95% CI 0·0–8·7) and of a malignant glioma at 7 years was 2·3% (0·9–5·6).

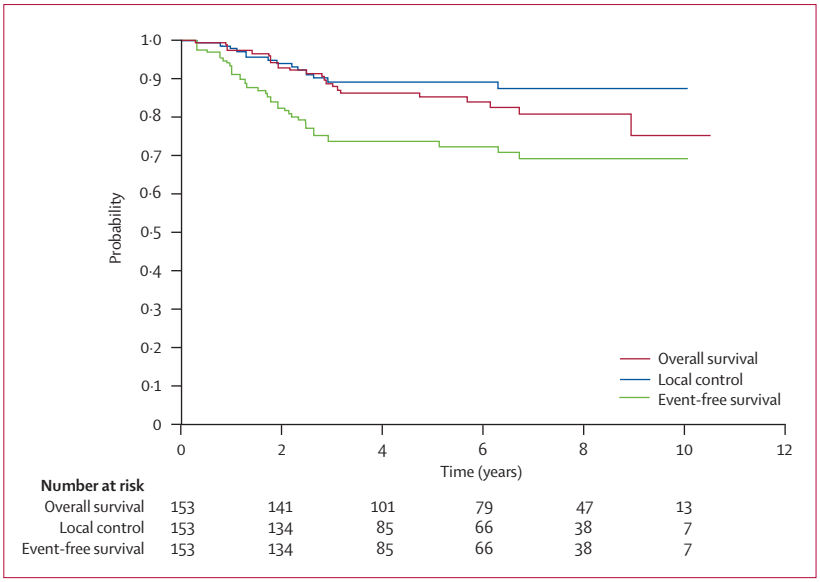

Figure 2: **Event-free survival, overall survival, and local control for 153 patients with localised ependymoma treated with conformal radiotherapy**

There were four cases of clinically significant cervical subluxation. Three cases have required surgical stabilisation. All were in patients with infratentorial ependymoma treated with more than one surgical resection and who had cervical laminotomy of at least one level. Necrosis of the brainstem, as determined by MRI and clinical signs and symptoms, was noted in two patients with infratentorial ependymoma at 9 and 12 months, respectively, after the initiation of conformal radiotherapy. Both were treated with corticosteroids and hyperbaric oxygen therapy. The patient that presented earliest died from necrosis. The patient that presented later was stabilised and remains progression-free 4 years after conformal radiotherapy. This patient is functional with moderate to severe unilateral cranial nerve, motor, and cerebellar deficits. Another patient died within 3 weeks of completing radiotherapy after a seizure; autopsy showed residual tumour and signs of ischaemia and necrosis within the brainstem attributed to an evolving brainstem stroke that occurred during the first of two surgical procedures 6 months earlier. The patient needed mechanical ventilation and was an inpatient during radiotherapy. All three patients were African-American, had infratentorial tumour location, had substantial perioperative morbidity, including evidence

	N	Event-free survival (%)				Overall survival (%)			
		5 years (95% CI)	7 years (95% CI)	HR (95% CI)	p	5 years (95% CI)	7 years (95% CI)	HR (95% CI)	p
Tumour grade									
Differentiated	68	86·4 (76·8–96·0)	79·2 (66·1–92·3)	1·0	0·005	91·9 (84·3–99·5)	89·4 (79·6–99·2)	1·0	0·006
Anaplastic	85	61·3 (46·4–76·2)	61·3 (38·8–83·8)	2·58 (1·30–5·12)	..	78·3 (66·3–90·3)	71·8 (52·6–91·0)	3·56 (1·37–9·22)	..
Tumour location									
Infratentorial	122	71·1 (60·5–81·7)	65·8 (52·7–78·9)	1·0	0·16	84·0 (75·6–92·4)	80·5 (69·5–91·5)	1·0	0·6
Supratentorial	31	82·9 (66·6–99·2)	82·9 (57·6–100·0)	0·52 (0·20–1·32)	..	89·5 (76·8–100·0)	83·1 (59·4–100·0)	0·75 (0·25–2·22)	..
Ethnic origin									
White	126	75·5 (66·3–84·7)	70·4 (57·7–83·1)	1·0	0·26	87·7 (80·6–94·8)	84·5 (74·7–94·3)	1·0	0·017
Other	27	64·5 (30·8–98·2)	64·5 (30·8–98·2)	1·55 (0·71–3·38)	..	72·9 (44·9–100·0)	60·7 (27·4–94·0)	2·84 (1·16–6·92)	..
Sex									
Female	58	84·7 (73·9–95·5)	81·0 (66·3–95·7)	1·0	0·018	91·8 (83·8–99·8)	88·6 (76·8–100·0)	1·0	0·091
Male	95	66·7 (53·4–80·0)	61·0 (43·4–78·6)	2·40 (1·13–5·06)	..	81·1 (70·1–92·1)	76·0 (61·1–90·9)	2·20 (0·86–5·61)	..
Age at CRT (years)									
≥3	75	79·0 (66·8–91·2)	69·4 (52·2–86·6)	1·0	0·37	90·1 (81·1–99·1)	81·7 (68·0–95·4)	1·0	0·46
<3	78	68·6 (55·7–81·5)	68·6 (52·1–85·1)	1·34 (0·71–2·52)	..	80·4 (69·8–91·0)	80·4 (66·1–94·7)	1·37 (0·60–3·12)	..
Total dose (Gy)									
54	22	80·7 (61·5–99·9)	70·6 (44·1–97·1)	1·0	0·67	85·4 (68·9–100·0)	77·7 (53·8–100·0)	1·0	0·82
59·4	131	72·4 (62·4–82·4)	68·8 (55·5–82·1)	1·04 (0·87–1·24)	..	85·0 (77·0–93·0)	81·6 (70·8–92·4)	0·98 (0·80–1·19)	..
Number of surgical procedures									
1	87	79·7 (69·3–90·1)	74·4 (60·3–88·5)	0·55 (0·29–1·02)	0·056	90·1 (82·7–97·5)	83·9 (72·3–95·5)	0·56 (0·24–1·26)	0·15
2–4	66	65·6 (49·5–81·7)	62·0 (41·2–82·8)	1·0	..	78·4 (64·5–92·3)	78·4 (60·6–96·2)	1·0	..
Surgical extent									
GTR	125	81·5 (72·7–90·3)	77·3 (65·0–89·6)	0·21 (0·11–0·40)	<0·0001	93·0 (87·3–98·7)	88·0 (78·8–97·2)	0·16 (0·07–0·36)	<0·0001
NTR or STR	28	41·0 (17·7–64·3)	34·2 (12·1–56·3)	1·0	..	52·4 (25·5–79·3)	52·4 (25·5–79·3)	1·0	..
Pre-CRT chemotherapy									
Yes	35	59·4 (39·6–79·2)	48·7 (26·0–71·4)	1·0	0·008	73·6 (55·6–91·6)	66·9 (43·0–90·8)	1·0	0·038
No	118	78·1 (68·3–87·9)	75·9 (62·8–89·0)	0·43 (0·22–0·81)	..	88·6 (81·3–95·9)	85·3 (75·1–95·5)	0·42 (0·18–0·98)	..

HR=hazard ratio. CRT=conformal radiotherapy. GTR=gross-total resection. NTR=near-total resection. STR=subtotal resection.

Table 2: **Univariate analysis of event-free survival and overall survival according to different variables**

of brainstem ischaemia on postoperative T2-weighted MRI, required tracheostomy, and had postoperative hypertension needing medication. Two of the three also had a history of a postoperative seizures. There were no other cases of necrosis and no other patients had a similar constellation of clinical signs and symptoms before or during radiotherapy. Including all three cases of necrosis, the cumulative incidence of brainstem necrosis at 7 years was 2·5% (95% CI 0·0–5·2); excluding the patient who died after a seizure, it was 1·6% (0·0–4·0).

Seizure disorders required chronic medication in five patients with supratentorial tumour location. Two needed surgery for epilepsy and were able to reduce or stop medication. There was one case of radiation-related cerebral vasculopathy in a patient with infratentorial tumour location that required revascularisation surgery. The patient was aged 12 months at the time of irradiation and the high-dose volume encompassed the Circle of Willis.

7-year estimates of local control, EFS, and overall survival were 87·3% (95% CI 77·5–97·1), 69·1% (56·9–81·3), and 81·0% (71·0–91·0), respectively (figure 2). Median time to progression was 22·5 months (range 5·0–90·9) from diagnosis and 20·3 months (3·1–75·4) from the start of conformal radiotherapy.

Univariate analyses of overall survival by various clinical variables are presented in table 2. Multiple regression analysis showed overall survival was affected by tumour grade, extent of resection, and ethnic origin: gross-total resection was associated with a lower risk of death from any cause than was near-total or subtotal resection (HR 0·16 [95% CI 0·07–0·37]; p<0·0001), while the risk of death was greater in patients with anaplastic tumours than in those with differentiated tumours (HR 3·98 [1·51–10·48]; p=0·0052) and in non-white patients versus white patients (HR 3·0 [1·21–7·44]; p=0·018). However, death from necrosis accounted for the lower overall survival in non-white patients, compared with white patients: when we excluded the two patients who died of necrosis, the comparison of ethnic origin was not significant for overall survival (HR 2·1 [0·8–5·7]; p=0·16 by univariate analysis). The use of chemotherapy before conformal radiotherapy was associated with a lower overall

survival than with no use of chemotherapy in the univariate analysis (66·9% [95% CI 43·0–90·8] *vs* 85·3% [75·1–95·5]; p=0·038), but not in the multiple regression analysis, possibly because of a correlation between chemotherapy before conformal radiotherapy and extent of resection: a smaller proportion of patients had chemotherapy before conformal radiotherapy in the gross-total resection group than in the near-total or subtotal resection groups (24 of 125 patients *vs* 11 of 28; p=0·022).

Univariate statistics of EFS by clinical factor are presented in table 2. Multiple regression analysis showed that EFS was affected by tumour grade, extent of resection, and sex: gross-total resection was associated with a lower risk of death from any cause than near-total or subtotal resection (HR 0·20 [95% CI 0·11–0·39]; p<0·0001), while the risk of progression was greater in patients with anaplastic tumours than in those with differentiated tumours (HR 2·52 [1·27–5·01]; p=0·008) and in male patients versus female patients (HR 2·19 [1·03–4·66]; p=0·042). The use of chemotherapy before conformal radiotherapy was associated with a lower EFS than no use of chemotherapy in the univariate analysis (48·7% [95% CI 26·0–71·4] *vs* 75·9 [62·8–89·0]; p=0·008), but not in the multiple regression analysis. The latter might be explained, as before, by the correlation between chemotherapy before conformal radiotherapy and extent of resection. Although EFS was better in those patients with fewer surgical procedures before irradiation than in those who had more, this effect was not significant (p=0·056; table 2). There was no difference in 3-year EFS when comparing patients treated from July 11, 1997, to Feb 4, 2003, with those treated from Feb 5, 2003, to Nov 18, 2007 (79·0% [69·0–89·0]) *vs* 81·0% [63·2–98·8]; respectively; p=0·98).

The cumulative incidence of local failure was 16·3% at 7 years. Multiple regression analysis showed that the cumulative incidence of local failure was affected by the extent of resection, sex, and age at the time of irradiation. Gross-total resection was associated with a lower risk of local failure (HR 0·16 [95% CI 0·067–0·38]; p<0·0001) compared with near-total or subtotal resection. The risk of local failure was greater in male patients than in female patients (HR 3·85 [1·10–13·52]; p=0·035). Patients under the age of 3 years at the time of conformal radiotherapy had a greater risk of local failure (HR 3·25 [1·30–8·16]; p=0·012) than older patients. Despite 18 of the 22 children treated with 54 Gy being under the age of 3 years at the time of irradiation, there was no difference in local failure by total dose. The cumulative incidence of distant-only failure at 7 years (11·5% [95% CI 5·9–17·1]) was affected by tumour grade (cumulative incidence at 7 years was 17·1% [8·1–26·1] for anaplastic tumours *vs* 5·2% [0–11·0] for differentiated tumours; HR 4·1 [1·2–14·0]; p=0·017), but not by tumour location, sex, ethnic origin, age, or extent of resection.

In view of the favourable prognostic factors of female sex and gross-total resection in the setting of 59·4 Gy, restricting analyses to this population indicates an overall survival of 7 years of 90·3% (95% CI 77·8–100·0) with a cumulative incidence of any failure or local failure of 15·2% (3·8–26·6) and 5·1% (0·0–12·2), respectively. Excluding patients with anaplastic tumours and those who had previous treatment with chemotherapy results in even higher survival and disease control (data not shown).

In a separate analysis, we excluded patients who had been treated with any previous chemotherapy or who had incurred a delay from first surgery to irradiation. The resulting 107 patients treated with postoperative radiotherapy within a median time of 1·5 months (range 0·6–4·4) from first surgery. Within this group of patients, clinical factors presented in table 1 were independent of one another, except for infratentorial tumour location (associated with anaplastic ependymoma [p=0·031]) and age under 3 years at the time of irradiation (p=0·006). Overall survival at 5 and 7 years was 88·6% (95% CI 81·0–96·2) and 85·0% (74·2–95·8), respectively; EFS at 5 and 7 years was 79·2% (69·2–89·2) and 76·9% (63·4–90·4). Local control at 5 and 7 years was 91·4% (84·3–98·5) and 88·7% (77·9–99·5), respectively. Multiple regression analysis showed that overall survival and EFS were lower in patients with anaplastic ependymoma than in those with differentiated ependymoma (overall survival: HR 5·41 [1·39–21·15]; p=0·015; EFS: 4·28 [1·54–11·91]; p=0·005) and higher after gross-total resection than after near-total or subtotal resection (overall survival: 0·17 [0·05–0·56]; p=0·004; EFS: 0·15 [0·06–0·36]; p<0·0001); overall survival was lower in non-white patients than in white patients (3·70 [1·05–13·01]; p=0·041). By contrast with the overall population, sex was not significantly associated with overall survival, EFS, or local failure, and age was not associated with local failure.

In univariate analyses of the subpopulation of 107 patients, EFS was 88·2% [95% CI 73·3–100·0] in females compared with 69·2% [49·0–89·4] in males (HR 2·74 [95% CI 0·92–8·17]; p=0·07). The cumulative incidence of local recurrence was 12·6% (5·1–20·1) when measured at 7 years. This was affected by extent of resection (7·8% (0·5–15·0) for gross-total resection *vs* 40·0% (13·9–66·1) for near-total or subtotal resection; HR 0·11 [0·04–0·38]; p=0·004). The cumulative incidence of distant failure was 8·6% (2·8–14·3) when measured at 7 years, and was affected by tumour grade (2·2% [0·0–6·6] for differentiated ependymoma *vs* 14·6% [4·4–24·8] for anaplastic ependymoma; HR 6·2 [0·8–55·5]; p=0·082). The difference in tumour grade was significant using the log-rank test (p=0·039).

Discussion

This study highlights the long-term benefits—in terms of local tumour control, EFS, and overall survival—of gross-total resection (including undergoing second surgery as a requisite for patients with macroscopically incomplete resection after initial surgery) and high-dose postoperative radiotherapy for the treatment of children

	Time period	Patients, n	5-year EFS	10-year EFS	5-year OS	10-year OS
Merchant (present)	1997–2007	153	74%	69%	85%	75%
Akyuz[18]	1972–91	62	..	36%	..	50%
Perilongo[19]	1977–93	92	..	35%	..	56%
Shu[20]	1980–2000	49	41%	31%	66%	56%
Oya[21]	1961–99	48	42%	42%	62%	47%
Pollack[22]	1975–93	40	46%	36%	57%	45%
Jaing[23]	1985–2002	43	46%	..	54%	..
Van Veelan-Vincent[24]	1980–99	83	48%	46%	73%	51%
Robertson[25]	1986–92	32	50%	..	64%	..
Mansur[26]	1964–2000	60	58%	46%	71%	55%

EFS=event-free survival. OS=overall survival.

Table 3: **Event-free survival and overall survival estimates from selected radiotherapy series reporting 5-year and 10-year outcomes**

with localised ependymoma, even for those who are younger than 3 years. Although it is important to understand the pitfalls that limit a comparison between this and other series, including the high rate of gross-total resection, the single institution nature of the study, and modern staging and surgical procedures to exclude patients with metastatic disease and increase the rate of gross-total resection, suggest the need to identify subclinical metastatic disease, develop new strategies to treat disseminated disease, and find ways to prevent adverse events including second tumours.

Our findings also show the highest rates of overall survival and EFS in childhood ependymoma depend on treatment with gross-total resection and lower tumour grade. A higher EFS was also noted in female patients than in male patients. Local tumour control was greatest in female patients treated with gross-total resection and those older than 3 years of age at the time of irradiation. These findings further support the known prognostic factors of extent of resection and tumour grade, and provide further evidence that the independent clinical factors of sex and age are prognostic for EFS and local tumour control. Indeed, the treatment protocol used here reduces the number of prognostic factors: age is no longer a prognostic factor for EFS and overall survival when chemotherapy is not given and treatment delays are not incurred. Although disease control for all patients remains the primary objective, treatment of paediatric patients places heavy emphasis on keeping therapy to a minimum whenever possible, and on the identification of favourable groups; the three prognostic factors of extent of resection, tumour grade, and sex identified here provide an opportunity for risk stratification and could help to identify such groups.

The improved EFS and overall survival in our study, compared with historical series, are probably due to increased local tumour control. While local control was improved with this treatment protocol, metastatic failures increased relative to local failures and accounted for nearly half of all failures. Patients with metastatic failure were treated with various treatment approaches. Because we have not noted sequential local failure in these patients, it could be concluded that the development of metastatic disease was not related to the inability of radiotherapy to achieve disease control at the primary site. The overall proportion of metastatic failures seemed to depend on the number of patients with anaplastic tumours. Although the potential benefit from craniospinal irradiation has been discounted in historical series due to the high rate of local failure, future treatment strategies should focus on identifying patients with subclinical metastatic disease or anaplastic tumours who might benefit from systemic therapy or craniospinal irradiation.

Available data on local tumour control for ependymoma are limited because most series have not differentiated between local and distant failure in their estimates of EFS. Local failure has been the greatest obstacle to improving overall survival in ependymoma; previous reports show the proportion of patients with local failure to be between 59% and 97%.[18–25] Isolated local failure accounted for 39% of failures in our series. Local failure might be attributed to various factors; our results show that the extent of resection is an important contributing factor. Our estimates of local tumour control exceed those expected from contemporary series using prescribed doses of 54 Gy or more, and with similar rates of gross-total resection.[1–3] This is probably due to the prospective nature of this work, systematic targeting with conformal radiotherapy, our procedures (image registration, rigorous immobilisation, use of general anesthesia, non-coplanar and multifield delivery, and small number of elapsed treatment days), and the relatively high prescribed radiation doses and healthy tissue tolerances that we allowed the spinal cord, brainstem, and optic chiasm to receive. Future efforts to increase local tumour control in ependymoma should prioritise increasing the rate of gross-total resection, using second surgery when needed, and avoiding treatment delays. Consideration should also be given to higher total doses of radiotherapy and combining synergistic agents with irradiation, since the cumulative incidence of local failure remains high at 16%. Future studies should also consider reducing the margin around the target volume from 10 mm to 5 mm to limit the dose to healthy tissues and improve the safety of high-dose irradiation. The limited invasive nature of ependymoma should make further volume reduction feasible.

Series comprised of adequate patient numbers and follow-up (table 3) have reported EFS after irradiation ranging from 41–58% when measured at 5 years to 31–46% at 10 years.[4,18–26] Overall survival has ranged from 54–73% at 5 years to 45–56% at 10 years. Our EFS and overall survival estimates at 5 years were 74% and 85%, respectively. Although these differences might be attributable to treatment era and the distribution of major prognostic factors, the improved outcome persists when

considering the most favourable patients, including those treated with gross-total resection, early postoperative irradiation, and prescribed doses of 54 Gy or more: patients treated in our series with gross-total resection had 5-year EFS estimates of 82%, rising to almost 85% when patients treated with immediate postoperative irradiation, and without chemotherapy, were considered.

The benefits of improved disease control might be realised only if the rate and magnitude of clinically significant side-effects and adverse events is reasonable, as determined on an individual basis as well as from the entire patient cohort. Because of the large number of patients treated over a relatively short period of time, strict compliance to protocol-directed follow-up, and the extended period of assessment, we had the opportunity to document the incidence and time course of a broad range of treatment-related side-effects and to note various rare adverse events. We have reported separately the neurological, endocrine, and cognitive effects in this patient cohort.[27–29] Our recent report assessing the academic abilities of these patients is contemporary with this paper, and highlights the vulnerability of reading ability compared with other academic skills.[28]

A potential limitation to our study is the fact that some of the patients were initially treated elsewhere, before being referred to us. Referral from beyond the geographical region is nearly always associated with bias toward more difficult cases (initial subtotal resection), aggressive tumours (anaplastic ependymoma), and younger patients. However, with an annual US incidence of 0·76 cases per 100 000 individuals aged 0–19 years, and fewer than 274 000 individuals in this age group, the immediate locale of St Jude would be expected to yield less than one case of ependymoma or anaplastic ependymoma per calendar year. Patients were thus recruited for treatment on this protocol from 37 of the 50 States of the USA and from two countries other than the USA. Furthermore, although the absence of a required time interval from first surgery to irradiation aided recruitment, it might also have contributed to a referral bias and affected selection—ie, patients were selected with a more difficult to treat disease than normal. St Jude accepts regional patients for treatment irrespective of disease status; however, those from beyond the immediate geographical region were required to fulfil the enrolment criteria for our protocol to be accepted for treatment.

Although we have reported overall survival as a measured outcome, this endpoint might not be a suitable measure of success, because patients who fail radiotherapy have limited curative options and overall survival is dependent on the pattern of failure and subsequent aggressive management. We have had some success with surgery and a second course of irradiation in selected cases;[30] the paucity of side-effects from limited-volume irradiation could provide new salvage options for these patients. Our data indicate that failure after 3 years is infrequent; 3-year EFS could thus serve as a better measure of success. Of course, late failures are known to occur, and patients in our series have shown rare, but clinically significant, somatic effects and second malignancies. Nonetheless, the relatively low rate of local failure seen here, compared with historical series, combined with an estimated rate of distant-only failure exceeding 10%, suggests that improving the detection of subclinical metastases at the time of diagnosis should be given priority.

Radiotherapy for childhood ependymoma will continue to evolve even as investigators search for means to reduce local and neuraxis treatment failure. Newer methods of delivering radiotherapy promise further reductions in the dose to healthy tissues and increased conformity of the highest doses to the target volume. New methods will also allow for modulation of toxicity based on improved understanding of the relation between dose, irradiation volume, and clinically significant side-effects. In the absence of objective information about healthy tissue dose constraints in this patient cohort, we applied dose limits only for irradiation of the optic chiasm and cervical spinal cord. With long-term follow-up, we are modelling dose, volume, and healthy tissue effects longitudinally with the hope to further optimise treatment.[31]

Contributors

TEM was principal investigator of the study and participated in the concept and design, collection and assembly of data, data analysis and interpretation, manuscript writing, and editing. CL and XX participated in the concept and design, collection and assembly of data, and data analysis and interpretation. LEK, FAB, and RAS participated in the provision of study materials, patients, and editing of the manuscript. All authors participated in the final approval of the manuscript.

Conflicts of interest

The authors declared no conflicts of interest.

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PLOS ONE

RESEARCH ARTICLE

Integrating Tenascin-C protein expression and 1q25 copy number status in pediatric intracranial ependymoma prognostication: A new model for risk stratification

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Abstract

Purpose

Despite multimodal therapy, prognosis of pediatric intracranial ependymomas remains poor with a 5-year survival rate below 70% and frequent late deaths.

Experimental design

This multicentric European study evaluated putative prognostic biomarkers. Tenascin-C (TNC) immunohistochemical expression and copy number status of 1q25 were retained for a pooled analysis of 5 independent cohorts. The prognostic value of TNC and 1q25 on the

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overall survival (OS) was assessed using a Cox model adjusted to age at diagnosis, tumor location, WHO grade, extent of resection, radiotherapy and stratified by cohort. Stratification on a predictor that did not satisfy the proportional hazards assumption was considered. Model performance was evaluated and an internal-external cross validation was performed.

Results

Among complete cases with 5-year median follow-up (n = 470; 131 deaths), TNC and 1q25 gain were significantly associated with age at diagnosis and posterior fossa tumor location. 1q25 status added independent prognostic value for death beyond the classical variables with a hazard ratio (HR) = 2.19 95%CI = [1.29; 3.76] (p = 0.004), while TNC prognostic relation was tumor location-dependent with HR = 2.19 95%CI = [1.29; 3.76] (p = 0.004) in posterior fossa and HR = 0.64 [0.28; 1.48] (p = 0.295) in supratentorial (interaction p value = 0.015). The derived prognostic score identified 3 different robust risk groups. The omission of upfront RT was not associated with OS for good and intermediate prognostic groups while the absence of upfront RT was negatively associated with OS in the poor risk group.

Conclusion

Integrated TNC expression and 1q25 status are useful to better stratify patients and to eventually adapt treatment regimens in pediatric intracranial ependymoma.

Introduction

Ependymoma is the second most common malignant brain tumor in children. Half of the cases are diagnosed before the age of 5, two thirds arising in the posterior fossa. This disease comprises several entities, each with its own molecular pathogenesis, strongly influenced by age and location [1–7]. While supratentorial ependymomas are driven by specific translocations [5,6], infratentorial ependymomas are not and can be distinguished by their DNA methylation pattern [4,7]. Albeit molecularly heterogeneous, ependymomas share common biological and phenotypic characteristics, beyond histological features, for example Notch-1 pathway activation [2] or putative cell of origin [3]. The latest WHO classification update has individualized one of these entities, i.e the supratentorial ependymomas with RELA fusion, considering that the other subgroups could not be distinguished based on standard histology and molecular pathology [8]. Despite their grouping into 9 different entities in the latest publication [7], all ependymomas are actually still treated with the same protocol irrespective of their location. Pediatric ependymomas currently represent a therapeutic challenge, being incurable in at least one third of the cases despite multimodal therapy. However, some children can be cured without recourse to radiotherapy [9,10], while other will experience recurrence regardless of the use of optimal radiotherapy [11]. The extent of resection has been regularly found as the most important prognostic factor [9–11]. Several prognostic biomarkers for ependymoma have been identified in single reports but none of them has been validated prospectively for treatment stratification [12]. Grading according to the current World Health organization (WHO) classification has proved difficult to standardize [13] but has shown prognostic impact in some studies [11,13,14].

Previous studies in pediatric ependymoma reported, at recurrence, frequent gains of chromosome 9q33-34 region, i.e. the genomic region of *NOTCH1* and *Tenascin-C* (TNC), associated with the overexpression of TNC [2,15,16]. TNC is a large hexameric extracellular glycoprotein, with little or no expression detected in healthy adult tissues, and a known Notch-1 target. It is transiently re-expressed upon brain injury and down regulated after tissue repair is complete. TNC is involved in the generation of neural stem-cell niches, modulates matrix-cell interactions and in several types of cancer has been associated with increased vascularity, decreased survival and short time to relapse [17]. Evidence also supports its key role in the maintenance of a metastatic "niche" that would allow for the survival of disseminated tumor cells by activating NOTCH and WNT pathways [18]. TNC expression by immunohistochemistry (IHC) has been shown, specifically in ependymomas, to be associated with higher grade [15] and inferior event-free survival in small retrospective series [16,19]. Among two prognostic molecular groups of posterior fossa ependymoma identified, tumors from the group with poor prognosis were more frequently positive for TNC [4]. TNC expression is also more frequent in ependymomas of children than in those of adults [4,15].

Many studies have also reported chromosome 1q gain to be associated with worse prognosis in ependymoma but neither a candidate gene at 1q nor a definite biological explanation has been clearly identified so far [14,20–22].

Extent of resection and radiotherapy are the most important prognostic factors whatever the location or the subtype of the ependymoma [9–12]. The aim of this study was to provide a prognostication tool for all intracranial ependymomas that could be used to stratify every patient enrolled in an international trial. Biological prognostic markers, TNC and 1q25 gain, were added to the clinical and therapeutic parameters to improve the predictive accuracy of this prognostication tool.

Materials and methods

Patients

From the SIOP Ependymoma Biology Working Group BIOMECA (BIOlogical Markers for Ependymomas in Children and Adolescents), 595 patients from 5 national trial cohorts (France (FR) (n = 93), United Kingdom (UK) (n = 105), Italy (IT) (n = 62), Germany GPOH HIT 2000 trial (n = 139), and Heidelberg group (n = 196)) were identified. All patients included in the study were under 18 years, had a histologically confirmed newly diagnosed ependymoma that was centrally reviewed nationally according to WHO 2007 guidelines before selection of the patient samples for confection of tissue microarray (TMA) blocks. Patients without clinical records of treatment and comorbidities and without sufficient follow-up were excluded from the final analysis. All patients were treated by surgery. Upfront adjuvant radiotherapy (RT) +/- chemotherapy (CT) was administered for patients aged older than 3 and 5 years according to the country and regardless the extent of resection. Patients under 3–5 years were treated by chemotherapy as first line treatment. Treatments were defined by the national protocols listed in Section A in S1 File.

The studies were approved by the internal review boards of the sponsoring institutions in each country according to the regulation in place at the time of the conduct of the clinical study (see the initial publications of the trials in which the patients were enrolled, Section A in S1 File). Informed consent for these studies was obtained from the parents and guardians within the frame of a clinical research protocol when applicable or within a dedicated study for scientific purpose. (See S2 File for an example of the consent signed by the family of French patients).

Specimen characteristics

Analyses were performed in formalin fixed paraffin embedded ependymoma samples from patients at first surgery before CT or RT, included in TMA blocks (Section A in S1 File).

Assay methods

Preliminary studies in the consortium and extensive literature review led us to choose TNC and 1q25 to be evaluated as prognostic biomarkers in this collaborative endeavor [12]. TNC IHC was performed according to techniques described in Section A in S1 File. As previously described by Puget and coworkers [2], TNC IHC in ependymoma stained the extracellular matrix, and was generally not observed in individual cells, neither in the nucleus nor in the cytoplasm. Two main patterns (perivascular and intercellular) or a combination of both were observed (Fig A in S3 File). In some cases, TNC staining was heterogeneous within different regions of a same tumor. Immunohistochemical staining for TNC was scored based on staining intensity, as follows: 0: no staining; 1: weak staining; 2: moderate to strong staining (Fig A in S3 File). Scoring was based on most positive areas. For statistical analyses, moderate and strong staining was considered as overexpression (positive), compared to absent and weak staining (negative). Immunostains for TNC were performed using the same techniques and scored independently using the proposed scheme described above, by three observers. Reproducibility of staining and scoring for TNC was tested in the UK cohort by two independent observers, blindly, with excellent reproducibility (kappa = 0.91) (Section A in S1 File).

Chromosome 1q25 status was also studied on the same TMA material using FISH techniques (France, UK, Heidelberg), or on whole slides (IT) as previously described [19,20]. Cases from GPOH, had their 1q25 status analyzed by multiplex ligation-dependent probe amplification (MLPA) employing the SALSA MLPA P303 probemix (MRC Holland, Amsterdam, the Netherlands) (Section A in S1 File).

RELA-fusion positive supratentorial ependymomas were identified by one of the recognized methods to detect these fusions, i.e. FISH [5], RNAseq [6] or immunohistochemistry [5], depending on the material available and the cohort (Section A in S1 File).

Study design

We collected all data concerning patients from the 4 countries included in various trials (Section A in S1 File) [9,10,22,23,24] and from one single center previously used for biomarker discovery [4]. TMA slides included tumor tissue appropriate to analyze TNC and 1q25 gain for most patients (Fig B in S3 File) and were used for IHC and FISH, respectively.

The median follow-up was estimated using the reverse Kaplan-Meier method. The endpoint was overall survival (OS), defined as the time from the date of diagnosis to the date of death from any cause. Survivors were censored at the date of their last follow-up. The cut-off date of this analysis was January 1st, 2009.

Statistical analysis

The baseline characteristics (sex, age at diagnosis ($<, \geq$ 36 months), tumor location (posterior fossa, supratentorial), grade (II, III), extent of resection (incomplete, complete), upfront adjuvant RT, RELA-fusion (negative, positive) and the 2 markers (TNC and 1q25 gain) were described overall and by cohort. The association between the 2 markers (TNC and 1q25 gain) and the covariates was tested after adjusting for cohort (Cochran-Mantel-Haenszel test). The association with OS was tested using the log rank test comparing the unadjusted survival Kaplan-Meier curves. We reported 5-year OS and its 95% confidence interval (CI) estimated

using Rothman's method. The core model was a multivariable Cox model stratified by cohort and including age, tumor location, grade, extent of resection and treatment. This selection was based on established clinical knowledge. Sex was not a candidate variable. The prognostic value of each marker (TNC and 1q25 gain) was evaluated in adding one at a time and both in the core model [25]. These models were compared using Akaike criterion (AIC) for goodness-of-fit and integrated AUC (iAUC) for discriminant ability. This latter is defined by the integral of Area Under Curve and we fixed a time interval of 3 years (value close to 1 indicate a good discrimination). The proportional hazards (PH) assumption was tested for the selected model using Schoenfeld residuals with a global test and the model was stratified by some covariates if needed. A list of clinical interactions pre-specified by the clinicians (including interaction with cohort to measure the between-cohort heterogeneity) was tested one at a time. Significant interactions were included in the model and the stability of the final model was evaluated using bootstrap resampling [26]. From the final model, we derived a prognostic score, its distribution was reported and risk groups with different prognosis were created using a non-data-driven method [27]. Calibration was evaluated by estimating the agreement between predicted and observed probability of death. The performance validation used the internal-external cross validation approach proposed by Royston et al. [28]. All analyses were conducted on complete cases. In addition, we also performed subgroups analyses (posterior fossa and supratentorial apart) to describe the patients' characteristics and evaluated the association between the two markers (TNC and 1q25 gain) and OS, to justify the use of one single model to predict outcome on the entire population of pediatric intracranial ependymomas. The nominal alpha level, within the pooled analysis, was p = 0.05. We used SAS 9.3 (SAS Institute Inc., Cary NC) and R packages (survival, survAUC and rms) for statistical analyses. Results were reported according to the REMARK recommendations [25]. More details on statistical analyses performed are given in the appendix (Section B in S1 File).

Results

Patient description

From the 595 pediatric patients with intracranial ependymomas identified, 478 patients (FR (n = 64), UK (n = 88), IT (n = 28), GPOH (n = 134) and Heidelberg (n = 164)), with complete data (= 80%) including results for both TNC and chromosome 1q25 gain were selected for the principal analysis (Fig B in S3 File). Median follow-up was 5.0 years [range: 0.0; 17.0]. Patients were predominantly male (61%), older than 36 months (63%), with grade III histology (71%), with tumors located in posterior fossa (69%), and treated with radiotherapy as first line therapy (with or without chemotherapy) (65%) (Table A in S4 File). As expected, children older than 36 months received post-operative radiation therapy with or without chemotherapy (81%) more often than younger patients (38%) ($p<0.0001$). Patients not irradiated at diagnosis were systematically irradiated at the time of relapse. The five-year OS of the entire population was 71%, not significantly different in the 5 cohorts (logrank test p-value = 0.26) (Fig C in S3 File). The median overall survival was 9.94 years with a minimum value for the FR cohort (7.66 years).

The baseline characteristics were comparable with those of patients either without material for TNC and/or chromosome 1q25 gain analysis (n = 91) or with material but missing clinical characteristics (n = 23) (Table B in S4 File). The following analyses were based on the complete data set (n = 470) excluding 6 patients with missing extent of resection and 2 with missing information on treatment.

Association between Tenascin-C, 1q25 gain and covariates

Positivity for TNC was significantly more common in patients under 36 months (76% vs 45%, $p<0.0001$) and in posterior fossa tumors (69% vs 30%) ($p<0.0001$), while 1q25 gain was significantly more common in older patients (22% vs 13%, $p<0.01$) and in posterior fossa tumors (21% vs 13%, $p<0.05$). The 2 markers were not correlated ($p = 0.79$) (Table C in S4 File). None of these two biomarkers was correlated with RELA status (Table C in S4 File).

Univariate analysis

Twenty-eight percent (131/470) of patients died during follow up. Patients without TNC overexpression had a longer OS (median: 12.5 years 95%CI = [9.1; NE]) compared to patients with TNC overexpression (median: 7.8 y [6.4; NE]) ($p = 0.012$) (Fig 1A). The 5-year OS was 79.6% [72.1; 85.5] and 61.2% [53.7; 68.2] in patients with tumors negative and positive for TNC, respectively. Similar results were observed for 1q25 gain with a median OS of 12.5 y [9.9; NE] and 4.6 y [4.0; 7.8] in patients with negative and positive status, respectively ($p<0.0001$) (Fig 1B). The 5-year OS was 74.3% [68.5; 79.4] and 48.8% [36.7; 61.0] in patients with negative and positive 1q25 gain status, respectively.

Model building

From the core model using clinical variables and grading (model 1), we constructed 3 models by adding TNC alone (model 2), 1q25 gain alone (model 3) and the 2 markers (model 4). Model 3 showed a better goodness-to-fit, i.e lower AIC (AIC = 969,7) and a better discriminant ability, ie higher iAUC (iAUC = 0.70) than model 1 and 2 AIC = 992.8 and 991.0, iAUC = 0.63 and 0.64, respectively) (Table D in S4 File). Model 4 with TNC and 1q25 did not give additional information with a difference between AIC lower than 3 (AIC: 967.8, iAUC = 0.70) even if TNC was marginally significant with HR = 1.49 [0.99; 2.22] ($p = 0.051$).

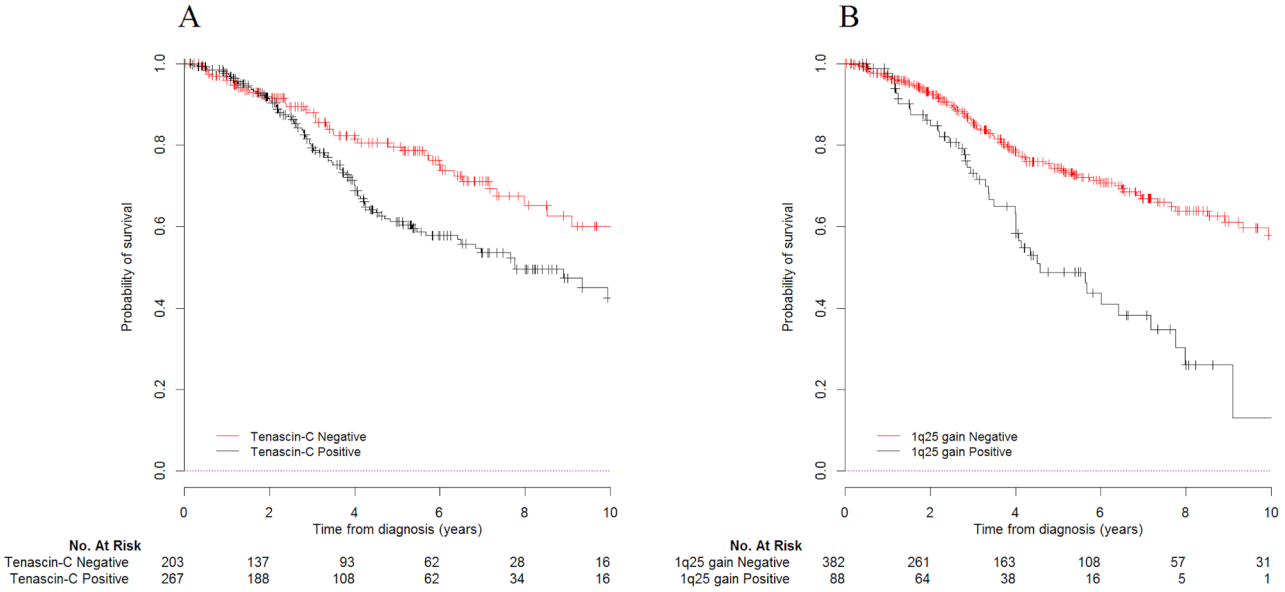

Fig 1. Kaplan-Meier-based overall survival curves according to Tenascin-C (negative (43%), positive (57%)) (A) and 1q25 gain (negative (81%), positive (19%)) (B) (n = 470). The hazard ratios (HR) and 95% confidence intervals, estimated through a univariate Cox model stratified by cohort, were for TNC: $HR_{pos\ vs\ neg} = 1.586$ [1.105; 2.277] ($p = 0.012$) and for 1q25 gain: $HR_{pos\ vs\ neg} = 2.490$ [1.721; 3.605] ($p<0.0001$).

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In model 3, the hazard ratio (HR) for patients with positive 1q25 gain was $HR_{pos\ vs\ neg}$ = 2.83 [1.93; 4.16] ($p<0.0001$). Grade and extent of resection were also significantly associated with OS ($p<0.05$). The global test of PH assumption was significant (p = 0.0055) with a high violation of PH assumption by RT (p = 0.0139). The association of upfront RT with overall survival is time-dependent; this means that the advantage of receiving upfront RT is only significant during the first 3 years after diagnosis (data not shown). After stratification on RT covariate as a time-dependent variable, the global test of PH assumption was no longer significant (p = 0.338). This stratification enables to define a baseline hazard related to upfront RT and also having a more stable model regarding the correlation between upfront RT and age. The results are reported in the second column of Table E in S4 File.

The next step in building the model was to evaluate some pre-specified interactions listed in Table C in S4 File. No heterogeneity of the effect of TNC and 1q25 gain across trials was observed. The significant interactions (age x grade, tumor location x TNC and tumor location x 1q25) were included and only tumor location x TNC (p = 0.014) was retained in the final model (Table E in S4 File). This model leads to a better AIC compared to the model without interaction (817.4 vs 823.8) with a slightly better discriminant ability (iAUC = 0.70 vs 0.68). In terms of HR, a statistically significant deleterious effect of positive TNC was observed in patients with posterior fossa tumors ($HR_{pos\ vs\ neg}$ = 2.19 [1.29; 3.76] (p = 0.004) while no significant effect was observed in patients with supratentorial tumors ($HR_{pos\ vs\ neg}$ = 0.64 [0.28; 1.48] (p = 0.295) (interaction test p = 0.015). HR of 1q25 gain did not change substantially compared to the ones estimated from model 3 ($HR_{pos\ vs\ neg}$ = 2.97 [1.99; 4.43] ($p<0.0001$). RELA-fusion was not included in the final model because of the exclusion of 45% of data (RELA is only defined in the supratentorial ependymomas).

Pediatric Intracranial Ependymomas Score (PIES), risk stratification and calibration

From the final model (Table E in S4 File), we developed a prognostic score called Pediatric Intracranial Ependymomas Score (PIES) for OS with a mean (standard deviation) of 2.52 (0.67) (Fig 2A). PIES was calculated, for each patient, as a weighted sum of the covariates in the final model, where the weights are the regression coefficients (Table 1). Three risk groups were defined by cut-points placed at the 27 and 73 percentile of the PIES (cut-points = 1.943 and 2.991): poor risk group includes patients with grade III (93%), incomplete extent of resection (80%), positive TNC (82%) and 1q gain (48%), good risk group includes patients $\geq$36 old months (78%), with grade II (68%), complete extent of resection (77%) and absence of 1q25 gain (100%).

Fig 2B shows the Kaplan-Meier estimation of OS for the 3 risk groups with a good separation: $HR_{intermediate\ vs\ good}$ = 2.39 [1.44; 3.97] and $HR_{poor\ vs\ good}$ = 5.36 [3.21; 8.96]. The 5-year OS was 85.1% [76.5; 90.9] in the good prognosis group (n = 126), 72.3% [64.1; 79.3] in the intermediate group (n = 219) and 44.0% [33.2; 55.4] in the poor prognosis group (n = 125). No heterogeneity of the risk group (poor, intermediate, good) was observed across national cohorts (p = 0.146) and the separation is globally well maintained across the cohorts. The agreement between predicted and observed probability of death at 5 years (calibration) is represented in Fig 2C with groups of approximately 80 patients to have reliable estimate. The figure shows an acceptable calibration. We observed a significant association between upfront RT and OS in poor risk group (HR = 0.377 [0.158, 0.898] (p = 0.028) while no significant difference is observed in good risk group (HR = 2.074 [0.611, 7.035]; p = 0.242) and intermediate risk group (HR = 1.042 [0.486, 2.233]; p = 0.916) (Fig D in S3 File). HRs of upfront RT were

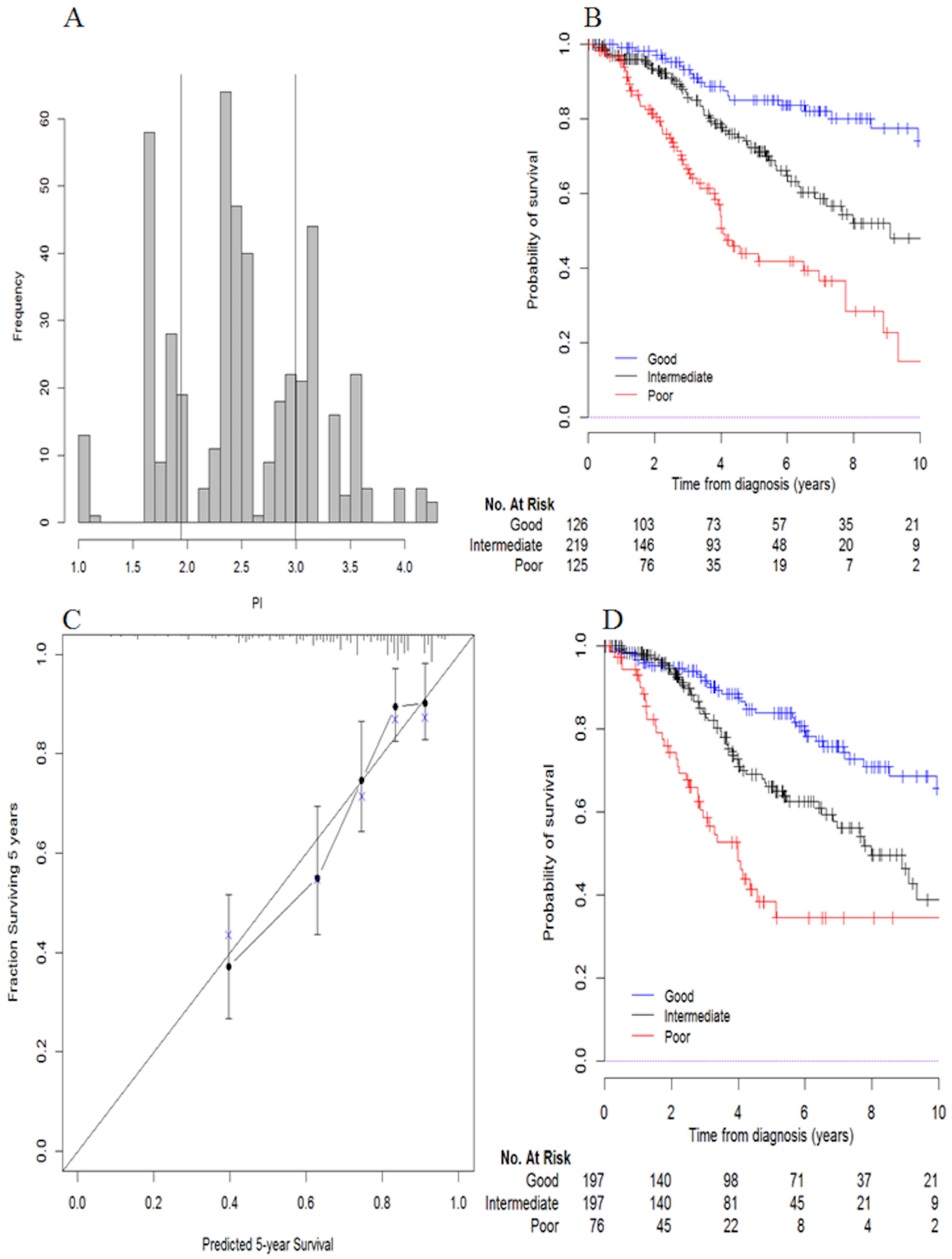

Fig 2. A) Histogram of Pediatric Intracranial Ependymomas Score (PIES), B) Kaplan-Meier-based overall survival curves of 3 risk groups, C) Agreement between predicted and observed probability of death at 5 years and D) Kaplan-Meier-based overall survival curves of 3 risk groups using internal-external cross-validation approach.

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Table 1. Regression coefficients of Pediatric Intracranial Ependymomas Score (PIES).

Prognostic factor		B
Age at diagnosis	$\geq$ 36 months vs <36months	-0.08818
Tumor location	Posterior fossa vs supratentorial	0.61200
Grade	III vs II	0.66265
Extent of resection	Complete vs Incomplete	-0.57949
Tenascin C	Posterior fossa: Positive vs Negative	0.78724
	Supratentorial: Positive vs Negative	-0.44741
1q25 gain	Positive vs Negative	1.08820

PIES was calculated, for each patient, as follows: $PIES = \beta_1\ I(age \geq 36) + \beta_2\ I(tumor\ location = supratentorial) + \beta_3\ I(grade = III) + \beta_4\ I(extent\ of\ resection = complete) + \beta_5\ I(Tenascin\ C = positive, tumor\ location = posterior\ fossa) + \beta_6\ I(Tenascin\ C = positive, tumor\ location = supratentorial) + \beta_7\ I(1q\ gain = positive)$
with $I(x) = 1$ *if* x *is true*, 0 *otherwise*
and a patient is classified in one risk group as follows:
if $PIES < 1.943$ (27*th percentile*) *then risk = good*
else if $1.943 \leq PIES \leq 2.991$ (73*th percentile*) *then risk = intermediate*
else if $PIES > 2.991$ *then risk = poor*

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estimated from a Cox model stratified on cohort and controlling for age, tumor location, grade, extent of surgery, TNC, TNC x tumor location interaction and 1q25 gain.

Model validation

An internal-external cross validation approach was used to validate our PIES [27]. After omitting one cohort, fitting the model (Table E in S4 File) on 4 other cohorts and calculating the 27 and 73 percentiles of PIES (to define the cut-offs), we calculated PIES for patients from the omitted cohort and classified them into good, intermediate or poor prognosis according to these cut-offs. After repeating these steps for each cohort, we can estimate the Kaplan-Meier OS curves for the 3 risk groups including all patients. Fig 2D shows a good discrimination between the three groups. We ended up model validation by calculating iAUC using the same approach. The values of iAUC (>0.62) estimated on independent cohort were good with small difference from the ones estimated on the training set. The discriminant ability appears to replicate well from the set of cohort omitting one (iAUC: from 0.67 to 0.73) and the remaining cohort (iAUC: 0.63 to 0.73).

Posterior fossa and supratentorial subgroups

Although potential possible heterogeneity between these two biological entities has been captured by adding interaction terms between tumor localization and covariates for developing model in the pooled analysis, we described the patients' characteristics and performed a multivariable analysis for these 2 entities, separately.

When the multivariable analysis was restricted to posterior fossa ependymomas, grade III, extent of resection, TNC immunopositivity and 1q25 gain were associated with OS (Table 2, See Table G in S4 File for description).

Fig 3 shows the OS curves for the whole group of posterior fossa ependymoma, and according to cohort, 1q25 status and TNC immunopositivity.

When the multivariable analysis was restricted to supratentorial ependymomas, only 1q25 gain remained significantly associated with OS (Table 3, See Table H in S4 File for description).

Table 2. Multivariable model for overall survival in patients with posterior fossa ependymomas (N = 325). The multivariable Cox regression model is stratified by cohort and radiotherapy‡.

Prognostic factors		Hazard Ratio	95% confidence interval	p-value
Age at diagnosis	<36months	1		0.1662
	≥ 36 months	0.685	[0.402; 1.170]	
Grade	II	1		0.0283
	III	1.710	[1.059; 2.761]	
Extent of resection	Incomplete	1		0.0043
	Complete	0.525	[0.338; 0.817]	
Tenascin-C	Negative	1		0.0184
	Positive	1.941	[1.118; 3.367]	
1q25 gain	Negative	1		0.0001
	Positive	2.491	[1.561; 3.976]	

‡: RELA is not evaluated in the posterior fossa

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When RELA-fusion status was added in the multivariable model, it was not retained as significant (Table 4):

Fig 4 shows the OS curves for the whole group of supratentorial ependymoma, and according to cohort, 1q25 status and TNC immunopositivity.

Discussion

This is the first study to propose an integrated score, combining clinical and pathological covariates with biomarkers for prognostication of pediatric ependymoma across multiple national cohorts. This unique and largest pooled analysis published so far allows to study interactions between covariates predicting overall survival. We choose to model the overall survival since progression-free survival would have been too much influenced by the initial treatment; indeed, young children were not treated with radiation and were therefore more prone to early relapses. In this respect, the association of upfront RT with OS could be specifically assessed since the various trials used different strategies with or without RT included in the first line treatment. Biomarkers chosen had been previously recognized but not completely validated. We showed that (i) the model performance including 1q25gain (model 3) is better than the models with no marker (model 1) and with TNC (model 2) and (ii) the model performance including both markers (model 4) did not improve substantially the performance of model 3. We, however, report that taking into account the interaction between TNC and tumor location (last column of Table E in S4 File) improved the performance of models 3 and 4. This is due to the fact that the prognostic effect of TNC was different according to tumor location. We decided to develop one model for all intracranial ependymoma and not 2 models (one for posterior fossa and one for supratentorial) in order to maximize the ability to study the interactions in the largest cohort possible. This approach was considered appropriate since treatment strategies are presently not stratified by location. When the analyses were restricted to the posterior fossa or supratentorial ependymomas, similar effect on overall survival were observed for 1q25 gain and TNC immunopositivity, but with limited power compared to the pooled population irrespective of the location.

Taking into account the major subtypes of ependymomas in each location, ie RELA-fusion positive or negative supratentorial tumors and PFA or PFB tumors, would also be of importance. Due to the retrospective nature of the study and the difficulty to obtain the methylation profile for all the samples, we could not incorporate it in the scoring. Moreover, this

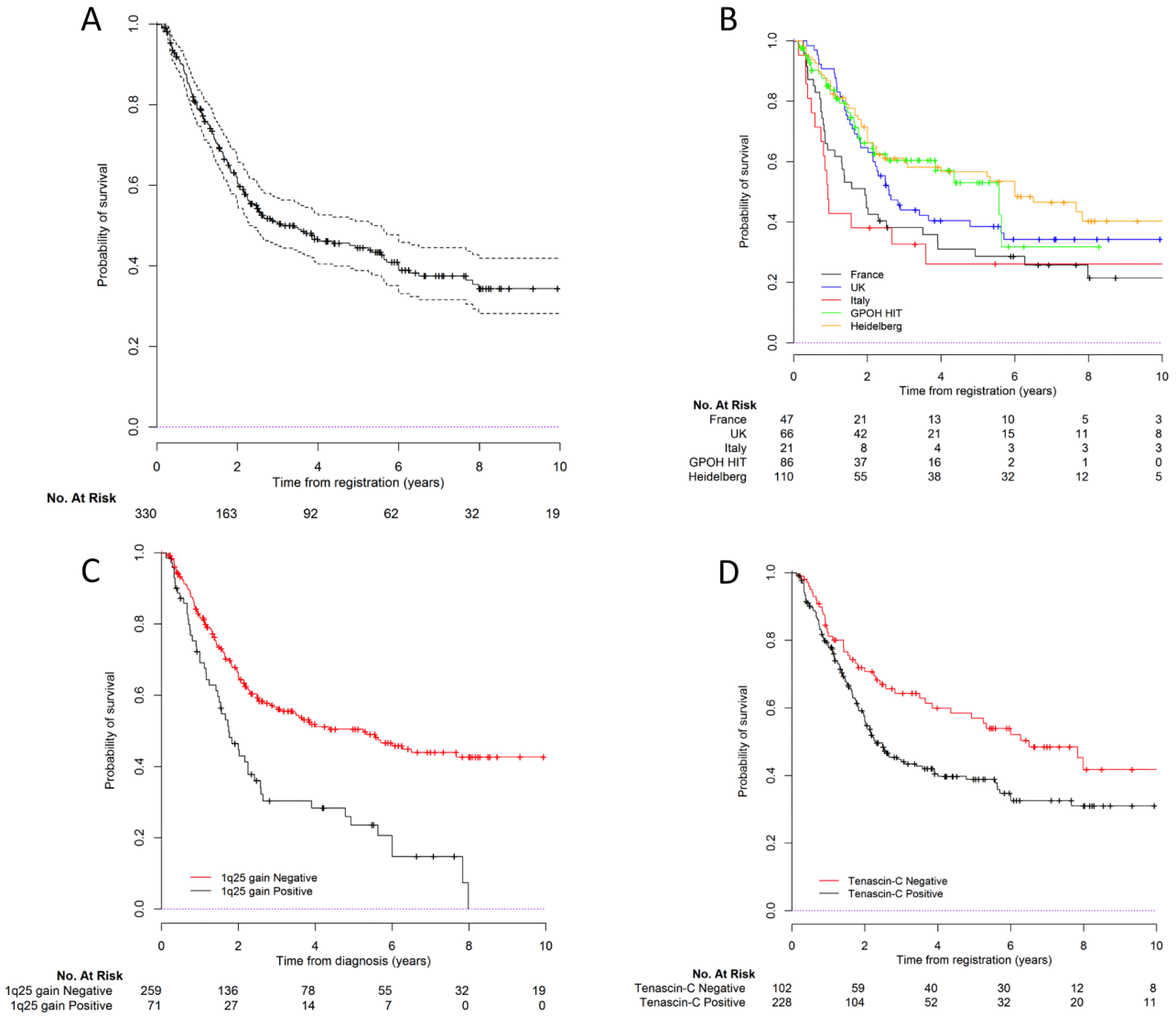

Fig 3. Survival curves for posterior fossa tumor patients. A) Global overall survival; B) Overall survival by cohort; C) by 1q status and D) by TNC expression.

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Table 3. Multivariable model for overall survival in patients with supratentorial ependymomas (N = 145). The multivariable Cox regression model is stratified by cohort and radiotherapy.

Prognostic factors		Hazard Ratio	95% confidence interval	p-value
Age at diagnosis	<36months	1		0.1617
	≥ 36 months	2.881	[0.655; 12.680]	
Grade	II	1		0.0613
	III	4.787	[0.928; 24.676]	
Extent of resection	Incomplete	1		0.1871
	Complete	0.565	[0.242; 1.319]	
Tenascin-C	Negative	1		0.1149
	Positive	0.474	[0.188; 1.199]	
1q25 gain	Negative	1		0.0067
	Positive	3.261	[1.389; 7.658]	

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Table 4. Multivariable model for overall survival in patients with supratentorial ependymomas with available RELA-fusion status (N = 72). The multivariable Cox regression model is stratified by cohort and radiotherapy.

Prognostic factors		Hazard Ratio	95% confidence interval	p-value
Age at diagnosis	<36months	1		0.1612
	≥ 36 months	4.281	[0.560; 32.752]	
Grade	II	1		0.1161
	III	8.835	[0.583; 133.789]	
Extent of resection	Incomplete	1		0.8723
	Complete	1.100	[0.344; 3.515]	
Tenascin-C	Negative	1		0.1811
	Positive	0.427	[0.122; 1.487]	
1q25 gain	Negative	1		0.0666
	Positive	3.586	[0.916; 14.032]	
RELA	Negative	1		0.5777
	Positive	0.669	[0.163; 2.750]	

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methylation profile may be difficult to obtain prospectively in every center because of costs and the recent change of the array version (450K to 850K) may need a re-validation of the results. Presently, there are two types of posterior fossa ependymomas defined by methylation profiling, PFA and PFB. These entities largely corresponding to pediatric and adult ependymomas, respectively, could also be distinguished by IHC as shown by Witt and coworkers [4]. Indeed, most PFA identified with methylation profiling (i.e 94%) were in fact positive for TNC while only 11% of PFB ependymomas were in fact positive for TNC. We could therefore assume that TNC IHC could be a simple surrogate for methylation profiling of PF ependymomas. The impact of TNC on overall survival is limited to the posterior fossa tumors in which its positivity is significantly more frequent.

The reproducibility of the IHC for TNC was validated in the study, including its scoring, and this has still to be proven for methylation studies. As the derived PIES score is a powerful tool to stratify the outcome of patients, it would be interesting to study in the future if the methylation profiling improves the performance of this prognostic score. Regarding supratentorial ependymomas, RELA-fusion status could be obtained in 72 out of 145 tumors. The presence of the RELA-fusion was correlated neither with TNC immunopositivity, nor with 1q25 gain. When the RELA-fusion status was incorporated in the multivariable model of overall survival in supratentorial ependymomas, it was not retained as significant besides 1q25 gain.

While controversial results have been reported on the prognostic significance of WHO histological grade in pediatric ependymoma [13,14,20], we found that histological grade III was significantly correlated with worse OS as reported by Merchant and coworkers [11] In our series, this prognostic effect remains homogeneous across cohorts (interaction p-value = p = 0.756). Despite a well-known heterogeneity of grading reported by different pathologists and cohorts,[13] in this large series grade remains a strong prognostic factor. Indeed, criteria used for grading are associated with tumor aggressiveness even if their reproducibility may vary among pathologists [13]. Thus, although the assignment of a given tumor to a given grade may be less reliable than other prognostic variables used in the model (e.g. location or age), the impact of the grade has still to be considered for prognostication in a multivariate approach.

A meta-analysis has shown that 1q gain is the most frequent genetic alteration in childhood ependymoma. Different studies report the gain of 1q as a marker of poor prognosis in ependymoma [14,20,22,23,29,30], and one publication has included part of the patients of the present series [21]. In the paper by Witt and colleagues including posterior fossa ependymoma from

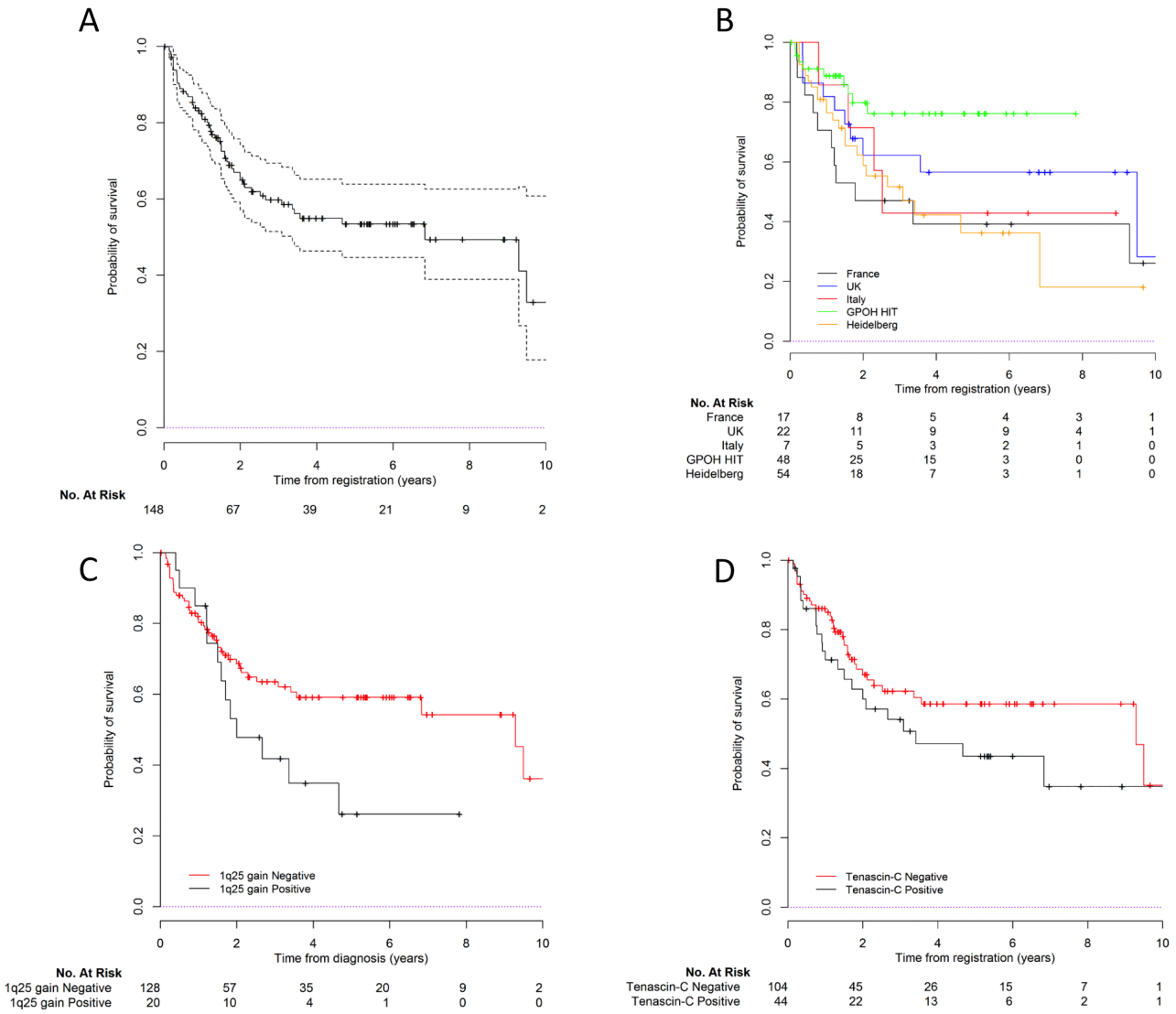

Fig 4. Survival curves for supratentorial tumor patients. A) Global overall survival; B) Overall survival by cohort; C) by 1q status and D) by TNC expression.

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all ages, as observed for TNC, 1q gains had a higher occurrence in group A, and shared the association with worse prognosis. Interestingly, in the validation of the gene expression data performed on an independent cohort, patients from group A with 1q gains assessed by FISH exhibited no difference in survival compared with other group A patients, whose tumors did not display this aberration [4]. This is not surprising, if one considers that TNC is also overexpressed in group A patients and independently from 1q25 gain. In fact, only 19% of patients showed 1q25 gains while TNC overexpression was observed in 57%; consequently, the model incorporating the two risk factors was more effective to describe the prognosis of the whole population. In the recent study by Pajtler and coworkers [7], 1q gain was a strong prognostic factor across all subgroups of ependymomas, irrespective of their location.

Although a significant difference was observed between upfront RT and no upfront RT in high risk group only, caution about this finding is required due to possible bias because (i) this

study was not designed to evaluate RT effect and (ii) even if the association between RT and overall survival was estimated from a multivariable model it is possible that confounders affecting both the administration of RT and overall survival were not captured even if we believe that their impacts are marginal. The finding that omitting to give radiotherapy as part of the first treatment was only detrimental for the high risk patients may challenge its systematic use in low-risk tumors, especially in young children.

Our data with simple and reproducible assays support the prospective assessment of these two biomarkers in clinical practice. They confirm, on a large multi-centric cohort of almost 500 children, the single center results from Austria where TNC and 1q25 gain were also shown to be prognostic in a series of 52 posterior fossa ependymomas [31]. IHC and FISH techniques are widely available as standard techniques in diagnostic neuropathology laboratories, and are already part of the regular assessment of other pediatric brain tumors such as medulloblastomas. The PIES score should be easily performed in current practice and represents a potential tool to stratify patients in randomized trials. In case new biomarkers would be identified, the same methodology would be applicable to see if their incorporation in the survival prediction model would improve its performance.

Supporting information

S1 File. Supplementary text. —Section A. Patients, Immunohistochemistry, 1q status assessment; **Section B.** Details of the statistical analyses.
(DOCX)

S2 File. Informed consent sample (French patients).
(DOCX)

S3 File. Supplementary figures. —Fig A. TNC immunostaining in pediatric ependymoma. Upper panel: qualitative aspects of TNC staining: (A) Perivascular staining; (B) Perivascular and intercellular staining. Lower panel: TNC scoring: most positive areas were analyzed and scored for intensity of staining as shown. Only moderate and strong staining were considered as overexpression; **Fig B. Flow chart; Fig C. Kaplan-Meier-based overall survival curves overall** (dashed lines represent the 95% confidence bands) and by cohort (n = 478); **Fig D. Kaplan-Meier-based overall survival by radiotherapy, for good (A), intermediate (B) and poor (C) risk groups.**
(ZIP)

S4 File. Supplementary tables. —Table A. Baseline characteristics, by cohort and for all patients; **Table B.** Patient and tumor characteristics for patients with and without TNC and 1q25 gain results; **Table C.** Correlation between Tenascin-C and 1q25 gain and baseline characteristics in all patients—complete cases analysis; **Table D.** Analysis of overall survival (OS) using a multivariable Cox regression model stratified by cohort in complete cases; **Table E.** Analysis of overall survival (OS) using a multivariable Cox regression model without and with interaction between TNC and tumor location stratified by cohort and radiotherapy in complete cases; **Table F.** P-values of pre-specified interaction terms; **Table G.** Baseline characteristics, by cohort and overall in posterior fossa patients; **Table H.** Baseline characteristics, by cohort and overall in supratentorial patients.
(ZIP)

S5 File. Individual patient database from all cohorts, anonymized.
(XLS)

S6 File. Statement necker hospital brain tumor collection.
(PDF)

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CLINICAL INVESTIGATION **Brain**

INTRACRANIAL EPENDYMOMAS IN CHILDREN: SOCIETY OF PEDIATRIC ONCOLOGY EXPERIENCE WITH POSTOPERATIVE HYPERFRACTIONATED LOCAL RADIOTHERAPY

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Purpose: To prospectively investigate the role of local hyperfractionated radiotherapy (RT) after surgical resection in the treatment of intracranial ependymomas in children.

Patients and Methods: Postoperative local hyperfractionated RT was proposed for every child (>5 years old at diagnosis) with localized intracranial ependymoma. The planned dose was 60 Gy after complete resection (CR) and 66 Gy after partial resection, delivered in two daily fractions of 1 Gy, according to the early postoperative imaging findings.

Results: Between November 1996 and December 2002, 24 children with infratentorial (n = 20) or supratentorial (n = 4) intracranial ependymoma were included. The median age was 8.6 years (range, 5–17). The World Health Organization grade was anaplastic in 10 of the 24 patients (not assessable in 1). After a retrospective central review, a CR was reported in 16 patients, partial resection in 4, and doubtful resection in 4. The radiation dose was 60 Gy in 18 cases (one partial resection), 66 Gy in 5 cases (one CR), and 54 Gy in 1 case (CR). The 5-year overall survival rate was 74.8%, and the progression-free survival rate was 54.2%. Of the 24 patients, 11 developed a relapse: 7 local only and 4 metastatic and local. The histological grade and extent of resection were not prognostic factors. More than 3 in 4 children had no sequelae of RT at a median follow-up of 7 years (95% confidence interval, 66.4–90.0 months).

Conclusion: The results of our study have shown that hyperfractionated RT is safe but provides no outcome benefit compared with other strategies of RT such as standard fractionated regimens. © **2009 Elsevier Inc.**

Ependymoma, Bifractionated radiotherapy, Long-term effects, Children.

INTRODUCTION

Ependymomas (EPs) account for 6–12% of all primary central nervous system tumors occurring in children. The mean age at diagnosis is 3 years, and one-half of cases occur before 5 years old (1). More than 90% of childhood EPs are intracranial, and two-thirds occur below and one-third above the tentorium (2). The main signs and symptoms are not specific and depend on the tumor location and the associated increased intracranial pressure (3). The management of EP is one of the most controversial issues in pediatric oncology, because most of our knowledge has been derived from single-institutional series spanning many years. For older children, because EP is classically considered a chemoresistant (4) ''local'' disease, surgery and postoperative local radiotherapy (RT) are considered essential for successful treatment. Research has thus focused on precision RT techniques enabling local dose escalation to increase local control. The aim of hyperfractionated RT (HFRT) is to improve the therapeutic ratio, by enhancing the antitumor effect without increasing the incidence of late effects. Some studies have reported promising results with HFRT for medulloblastoma (5) and EP (6). For children <5 years old, because RT, in particular, results in the risk of side effects that negatively affect cognition, as

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Conflict of interest: none.

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well as endocrine and neurologic function (7), strategies to delay or avoid RT have been reported (8–10). The present study focused on strategies combining surgery and HFRT that were investigated prospectively in children >5 years at diagnosis.

PATIENTS AND METHODS

Patient eligibility

Postoperative local HFRT was offered to all children with localized intracranial EP seen between November 1996 and December 2002 in centers affiliated with the French Society of Pediatric Oncology. The criteria for enrollment included age of 5–17 years at diagnosis, EP of any pathologic grade, and written informed consent. The criteria for exclusion were spinal primary EP, disseminated EP, previous chemotherapy or RT, relapse, associated disease, refusal, or impossible follow-up. Patients with ependymoblastoma were not included in this study. The findings were prospectively recorded. The primary objective was to determine the 5-year overall survival (OS) of the patients after surgery and HFRT. Secondary objectives were to determine the response rate to HFRT when applicable, identify the prognostic factors (especially the value of grading) and patterns of relapse, and define the rate of sequelae in a homogeneous group of patients.

Histologic slides of all patients were reviewed by a qualified pediatric neuropathologist panel (M.M. Ruchoux, A. Lellouch-Tubiana, and A. Jouvet) and classified as Grade 2 (classic) or Grade 3 (anaplastic) according to the absence or presence of signs of malignancy (*i.e.,* mitoses, necrosis, and neovascularization) according to the World Health Organization criteria (11).

Treatment characteristics

The extent of resection was rated by the surgeon as incomplete (biopsy or remaining tumor of >1.5 cm^3), subtotal (remaining tumor <1.5 cm^3), or total (no recognizable residue), as recommended by the International Society of Pediatric Oncology Brain Tumor Subcommittee for the reporting of trials (12). The extent of resection was rated by the radiologist as complete (CR), partial, or doubtful as determined from the findings on postoperative craniospinal magnetic resonance imaging (MRI) or computed tomography (CT) performed as soon as possible (24–48 h) after surgery. The ratings were reviewed retrospectively by a panel of experts (A. Geoffray and P. Thiesse).

In the case of a CR, 60 Gy HFRT in two daily fractions of 1 Gy (separated by ≥6 h) was performed. The target volume was the preoperative tumor volume plus a 1-cm safety margin. RT could be conformational or not, at the discretion of the group. The photon energy was ≥8 MeV. No more than 44 Gy was delivered to areas in the occipital region and no more than 60 Gy if more than one-third of the brain was involved. A customized immobilization device was used for each patient. The clinical target volume was defined on CT, with MRI fusion for the last patients treated, when this procedure was available.

In the case of partial removal, second-look surgery was discussed before RT. If the second surgical resection was complete, the patients were treated as described for those with a CR. Otherwise, an extra boost of 6 Gy was delivered to the residual volume, in addition to the 60-Gy dose already described. No patient received chemotherapy in this first line of treatment, because the place of chemotherapy for this disease is still debated (4).

For patients in relapse, repeat surgery was performed whenever feasible, unirradiated areas were irradiated, and inclusion in a protocol of oral etoposide was encouraged.

The rules to stop the study at 2 years were defined as follows: >30% of relapses among patients with CR and >50% of relapses or progressive disease in patients with incomplete resection.

Evaluation procedures

The initial screening included brain MRI with and without contrast, and three-dimensional measurements of the tumor. Spinal MRI was performed if the tumor was located in the posterior fossa. Examination of the cerebrospinal fluid was mandatory only if lesions were found on spinal MRI. The quality of the resection was evaluated using early postoperative imaging by the local physician during treatment and was centrally reviewed retrospectively.

The clinical examination and MRI were repeated 6 weeks after treatment to assess the response rate. The response to RT corresponded to a reduction in the size of the residual tumor surface by >50% on imaging (12). MRI was repeated every 4 months for 2 years, every 6 months during the third year, and every year for 5 years. Long-term effects (*e.g.,* audiometric, endocrinal, or psychometric impairment and school or professional difficulties) were recorded each year.

Statistical analysis

The OS rates, estimated using the Kaplan-Meier method, were calculated from the date of surgery to death or the date of the last follow-up visit for patients who were still alive. The progression-free survival (PFS) rates were estimated from the date of surgery to the time of documented failure (date of progression for patients whose disease progressed before achieving complete remission, date of relapse or date of death for others) or to the date of the last follow-up visit for those remaining in their first complete remission. The median follow-up was estimated using the method of Schemper and Smith (13). Statistically significant differences in OS and PFS were tested using the two-tailed log–rank test. Statistical analyses were performed using Statistical Package for Social Sciences, version 11.5 (SPSS, Chicago, IL).

RESULTS

Study population

A total of 24 patients from nine Society of Pediatric Oncology centers were included. Ten patients were registered but not included for the following reasons: previous chemotherapy in 1, relapse in 5, nonbifractionated RT in 1, age <5 years in 2, and wrong histologic type in 1 (medulloepithelioma). Because of the low rate of inclusion, the study was stopped before it reached the expected number for inclusion ($n = 40$).

The median age was 8.6 years (range, 5–17). Of the 24 patients, 16 were boys and 8 were girls. The tumor location was the posterior fossa in 20 patients and supratentorial in 4. Among the 20 patients with infratentorial EP, 19 underwent spinal MRI; all findings were considered normal. The histologic grade could be assessed in 23 of the 24 patients; 13 tumors were classified as Grade 2 (classic) and 10 as Grade 3 (anaplastic).

Surgery

Surgical resection, as reported by the neurosurgeon, was total in 15 patients, subtotal in 8, and partial in 1. One patient underwent second-look surgery for resection of a postoperative residual mass, after which the surgery was considered

complete. Another patient considered to have undergone partial resection underwent placement of a ventriculoperitoneal shunt. Severe acute complications developed in 6 patients consisting of cranial nerve paralysis with swallowing difficulties in 3, akinetic mutism in 1, both disturbances in 1, and hemiplegia in association with an intracranial postoperative hematoma in 1.

Central radiologic review

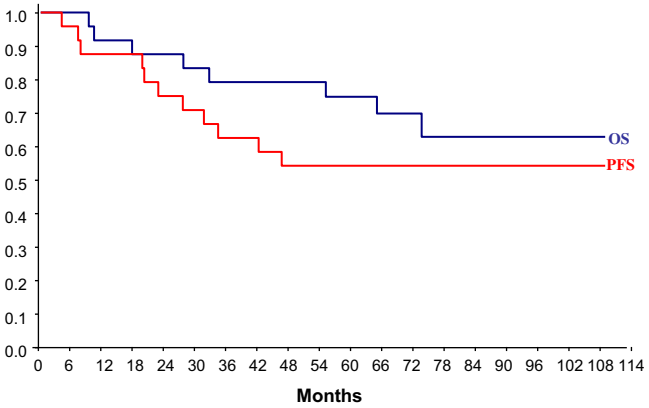
Both postoperative CT and MRI were performed in 11 cases, MRI only in 11 cases, and CT only in 2. At the central radiologic review, the resection was considered complete in 16 of the 24 patients and doubtful or partial in 4 each.

Of the 20 patients with infratentorial EP and the 4 patients with supratentorial EP, 14 and 2, respectively, underwent CR. In 6 children with infratentorial tumors, a discrepancy was found between the operative report and the early postoperative imaging results. The central radiologic review showed radiologic residual disease in 1 case that had been considered a CR by the surgeon. In contrast, no residual mass was found in 5 patients for whom the neurosurgeon had reported subtotal surgery.

Only the extent of resection as defined by the panel of experts was considered for statistical analysis.

Radiotherapy

Radiotherapy was performed in all patients, a median of 31 days (range, 20–97) after surgery. In 5 cases, RT was started >40 days after surgery. In 1 case, the interval was as long as 97 days because of second-look surgery. That patient was considered to have undergone a CR before the initiation of RT. For all patients, the mean interval between RT sessions was ≥6 h. The energy was >8 MeV in 22 cases and equal to 6 MeV in 2. Of the 24 children, 18 received 60 Gy. Of these 18 patients, 14 had undergone a CR, 1 an incomplete, and 3 a doubtful resection, as determined after central review. Another 5 children received 66 Gy. Of these 5, 1 had undergone a CR, 3 an incomplete, and 1 a doubtful resection. One patient with a CR received 54 Gy owing to a protocol violation. HFRT was conformational in 20 patients. Of the 4 patients with measurable residual disease, 3 had an objective response to HFRT. No severe acute complications of HFRT were reported.



3-year OS: 79.2%, IC95% [63.9; 95.4]; 3-year PFS: 62.5%, IC95% [43.1; 81.9]

5-year OS: 74.8%, IC95% [57.3; 92.3]; 5-year PFS: 54.2%, IC95% [34.2; 74.1]

Fig. 1. Overall survival (OS) and progression-free survival (PFS) rates of 24 patients with intracranial ependymoma.

PFS and OS

The median follow-up was 87.5 months (95% confidence interval, 66–90). Of the 24 patients, 8 died, all of neoplastic evolution. The estimated 3- and 5-year OS rate was 79.2% and 74.8%, respectively (Fig. 1). The 3- and 5-year PFS rate was 62.5% and 54.2%, respectively.

Prognostic factors analysis

Tumor grade and extent of resection were selected to be tested as potential prognosis factors. The extent of resection was assessed by the central radiologic review committee. The two-tailed test failed to find any statistically significant difference (Table 1).

Patterns of failure

At the last follow-up visit, 12 patients were in their first complete remission, 2 were in their second or greater

Table 1. Univariate analysis of correlation between selected parameters and estimated PFS and OS rates

Characteristic	*n*	5-y PFS (%)	*p*	5-y OS (%)	*p*
Grade			.849		.833
2	13	53.8 (24.8–76.0)		76.2 (42.7–91.7)	
3	10	50.0 (18.3–75.3)		70.0 (25.3–82.7)	
Location			.465		.854
Supratentorial	4	75.0 (12.8–96.1)		75.0 (12.8–96.1)	
Infratentorial	20	50.0 (27.1–69.2)		74.7 (49.3–86.6)	
Extent of resection*			.842		.269
Complete	16	56.3 (29.5–76.2)		81.3 (52.4–93.5)	
Partial or doubtful	8	50.0 (15.3–77.5)		62.5 (29.9–86.0)	
Radiation dose (Gy)			.561		.991
≤60	19	52.6 (28.7–71.9)		73.7 (47.9–88.1)	
66	5	80.0 (20.3–96.9)		80.0 (20.3–96.9)	

Abbreviations: PFS = progression-free survival; OS = overall survival.
Data in parentheses are 95% confidence intervals.
* As assessed by central radiologic review.

Table 2. Pattern of failures

Variable	Local (n = 7)	Distant (n = 1)	Distant and local (n = 3)
Grade			
2 (n = 6)	3	1	2
3 (n = 5)	4	0	1
Location			
Infratentorial (n = 10)	6	1	3
Supratentorial (n = 1)	1	0	0
Extent of resection			
Complete (n = 7)	5	0	2
Partial (n = 2)	0	1	1
Doubtful (n = 2)	2	0	0

complete remission, 1 had stable disease, and 1 had disease progression.

Relapse developed in 11 patients. The rates of relapse were similar between patients with Grade 2 and Grade 3 tumors (6 of 13 vs. 5 of 10, respectively; Table 2). The patient whose histologic grade was not assessable did not develop a relapse. One-half of the patients with infratentorial and the one-fourth of patients with supratentorial EP developed a relapse. The rate of relapse was similar among the patients with CR, incomplete resection, or doubtful resection (7 of 16, 2 of 4, and 2 of 4, respectively). Disease recurred once in 8 patients, twice in 2, and five times in 1 patient. The median time to the first relapse was 22 months (range, 4–46). Seven patients had only local failure; one had an isolated distant failure; and three had combined failure (Table 2). Of the 10 local relapses, 9 were infield relapses and 1 occurred outside the radiation field.

The treatment of failure was surgery alone in 1 patient, chemotherapy alone in 2, RT alone in 1, surgery and chemotherapy in 3, surgery, RT, and chemotherapy in 3, and palliative treatment in 1 patient. The median survival after relapse was 12.5 months (range, 0–44).

Long-term side effects

The long-term side effects among the 16 patients alive at completion of the study are reported in Table 3. Three-fourths of the patients had normal psychomotor development, as assessed by the local physician. Of the 16 patients, 9 underwent an IQ test. Wechsler scale III or IV were used, depending on the age of the patient. After a median follow-up of 41 months (range, 7–66), the mean verbal IQ was 93 (range, 54–130), and the mean performance IQ was 88 (range, 42–111). Two patients required placement in a special school, and two were ≥2 years behind at school. One patient had transient growth hormone deficiency requiring growth hormone supplementation with rapid normalization of the size. No other endocrine disorder was reported, but 4 of the 24 patients were in prepuberty stage. Their size was normal (with −1 to +1 standard deviation for age and gender) in all patients. One patient with a supratentorial tumor had a severe decrease of visual acuity secondary to high intracranial pressure with optic atrophy and required adapted schooling.

DISCUSSION

Treatment of EP is one of the most controversial issues in pediatric oncology. The published data in the field have mostly been mono- or oligocentric studies and mainly retrospective. Few randomized studies have been reported. The prognostic factors and oncologic strategies are a matter of debate. CR is usually shown as the main prognostic factor (2, 14, 15), although some series (6), including ours, have failed to confirm this finding. In most series, CR was obtained in about one-half of patients, although surgery is generally less successful in patients with infratentorial lesions (14). Pathologic grading is a matter of major debate. Some series have described it at a major prognostic factor (16–18), and others have failed to show any difference with grade (9, 19–21). The results obtained in our series failed to show any difference. Whether this was a result of the low number of patients included or differences in the grading assessment remains to be demonstrated. Recently, discrepancies between histologic assessments have been reported in infants (9, 10). Whether this applies only to infants or also is true for older children remains unresolved. An international panel of experts is currently reviewing such cases to answer this question.

Table 3. Long-term side effects among 16 living patients

Variable	Patients evaluated (n)	Sequelae
Auditory	15	
Normal		12
Loss <40 dB at 1,000–8,000 Hz on one ear		1
Loss >40 dB at 1,000–8,000 Hz or <40 on both ears		2
Schooling	16	
Normal school or university (possibly 1 y behind)		12
Normal school but >2 years behind		2
Special school and currently employed		1
Special school and currently unemployed		1
Vision	16	
Normal		9
Diplopia		5
Mild decrease of visual acuity		1
Severe decrease of visual acuity		1
Psychomotor development	16	
Normal		12
Mild retardation		2
Severe retardation		2
Endocrine deficit	16	
None		15
Hypothyroidism		0
Growth hormone deficiency		1
Premature or delayed puberty		0*

* Four in prepubertal stage.

Table 4. Comparison of six different treatment strategies for intracranial EP after surgery

Investigator	Patients (*n*)	Complete resection (%)	Median age (y)	Radiation dose and type (*n*)	Adjuvant chemotherapy (*n*)	OS	PFS
Timmermann *et al*. (21)	55 (5)	51	6.2	54 Gy conventional and focal (13) 35 Gy CSI + 20 Gy focal boost (40) Not irradiated (2)	55	3 y, 76%	3 y, 59%
Merchant *et al*. (26)	88 (0)	84	2.8	59.4 Gy conformal and focal (NI) 54 Gy for children <18 mo (NI)	5	NA	3 y, 75%
Massimino *et al*. (16)	63 (1)	73	NA	70 Gy bifractionated and focal (46) 54 Gy conventional and focal (12) 35 Gy CSI + bifractionated boost (1) Not irradiated (4)	14	5 y, 75%	5 y, 56%
Needle *et al*. (6)	19 (0)	47	7.5	70.7 Gy bifractionated and focal (14) 35 Gy bifractionated CSI + 35 Gy boost (2) 45 Gy conventional and focal (1) 36 Gy CSI + 18 Gy focal boost (1) 36 Gy WBI + 18 Gy focal boost (1)	16	NA	5 y, 74%
Agaoglu *et al*. (27)	40 (7)	50	5.5	54 Gy conventional and focal (15) 35 Gy CSI + 20 Gy focal boost (23) Not irradiated (2)	22	5 y, 65%	5 y, 51%
Present study	24 (0)	67	9	60 Gy bifractionated and focal (18) 60 Gy bifractionated and focal + 6 Gy focal boost (5) 54 Gy bifractionated and focal (1)	None	3 y, 79.2% 5 y, 74%	3 y, 62.5% 5 y, 54.2%

Abbreviations: EP = ependymoma; OS = overall survival; PFS = progression-free survival; CSI = craniospinal irradiation; NI = no information; WBI = whole brain irradiation; NA = not available.

In children >5 years of age at diagnosis, the standard postoperative treatment includes local RT. The rationale is that more than one-half of EP patients relapse locally (14). Major debates are ongoing concerning the type of RT (*e.g.,* standard, conformational, hyperfractionated), the fields (local, craniospinal) and doses to be used. Craniospinal RT is no longer advocated for localized EP, unlike for medulloblastoma (21–23). A dose–effect relationship has been suggested by a retrospective analysis (23). A consensus for delivering doses >50 Gy is emerging (14). HFRT involves giving a smaller dose per fraction, with RT fractions administered at least twice each day. The total radiation dose is increased and the total treatment duration remains approximately the same. Small doses given more than once a day, usually 6–8 h apart, produce a redistribution of proliferating tumor cells, with some cells entering a radiosensitive stage. Other nonproliferating or dose-limiting tissues, such as normal brain, will potentially be spared by this effect of redistribution. HFRT exploits the differences in repair capacity between tumor and late-responding normal tissues. To maintain an isoeffect in tissues, owing to the sparing effect of smaller fractions (the molecular mechanism of which is still hypothetical), the total dose must be increased (24). The efficacy of HFRT has been shown in medulloblastoma (5), and the results of the randomized primitive neuroectodermal tumor IV study are pending. HFRT has never been reported as the sole treatment of EP. Most series have used it in combination with chemotherapy (6, 16, 25). Encouraging results have been reported by Needle *et al*. (6) for a short series of 19 children >5 years of age. The 5-year PFS rate was 74% when chemotherapy

(*i.e.,* carboplatin, etoposide, vincristine, and ifosfamide) was followed by 70.7-Gy bifractionated RT. Similarly, Massimino *et al.* (16) reported on the Associazione Italiana di Ematologia-Oncologia Pediatrica strategy using vincristine, etoposide, and cyclophosphamide with HFRT at a dose of 70.4 Gy, with a 5-year OS rate of 75% and a PFS rate of 56%. Their results were also very encouraging, with 9 of 12 responses to RT and 15 of the 23 relapses being local. In the present study, the 5-year OS (74.8%) and PFS (54.2%) rates were roughly similar, despite lower radiation doses (range, 60–66 Gy) and the lack of associated chemotherapy. The rate of response to RT was 3 of 4 and most (10 of 11) relapses were local. However, the administration of HFRT is more complicated than standard RT. Only one-third of our patients could receive RT within the first 30 days after surgery. This delay was not just related to postoperative complications. Whether monofractionated RT would have resulted in shorter delays is not clear. Most recent studies have used standard local or craniospinal (21) or conformal RT (26). The 5-year OS rate was 65–76%, and the PFS rate was 50–75% (16, 18, 21, 27–29). The results of the five major studies are reported in Table 4. The most encouraging results have been reported by Merchant *et al.* (26). This unicentric study also included young patients (median age, 2.8 years). The high rate of complete surgical removal obtained in the present study might have been because of the high number of second-look surgeries. The rate and type of postoperative complications have not been clearly reported. The 1-cm safety margin is small and requires perfect immobilization of the patient. The RT procedures are very sophisticated and thus often require general anesthesia, which can be difficult to perform in a multi-institutional setting. The 3-year PFS findings have been reported, and longer follow-up is needed to ensure that relapse will not occur. Whether such encouraging results will be confirmed by the multi-institutional ACNS 0121 Children's Oncology Group study remains to be demonstrated. The major concern with RT delivered to young children is long-term neuropsychological and endocrine sequelae. It is difficult to compare series that do not always prospectively report such complications and for which no follow-up data are available. Grill *et al.* (30) reported that 11 patients with EP who underwent local RT of the whole posterior fossa at 55 Gy had a mean full-scale IQ of 84.2, with the verbal IQ superior to performance IQ. Of these 11 patients, 94% were able to attend normal schooling (30). Our series showed that about three-quarters of long-term survivors were free of neuropsychological, endocrine, or hearing troubles and have normal school results. The visual sequelae are mostly strabismus, which is more likely a result of surgery than to RT.

CONCLUSION

The results of the present study have demonstrated that local HFRT is feasible for the treatment of EP. Whether the low rate of long-term sequelae resulted from the procedure remains to be demonstrated. Only one-half of the children treated were cured. Whether standard 59.4 Gy will result in greater PFS at 5 years also remains to be clarified. Moreover, the role of adjuvant treatment by chemotherapy or innovative treatments deserves additional randomized evaluation.

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Primary postoperative chemotherapy without radiotherapy for intracranial ependymoma in children: the UKCCSG/SIOP prospective study

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Summary

Background Over half of childhood intracranial ependymomas occur in children younger than 5 years. As an adjuvant treatment, radiotherapy can be effective, but has the potential to damage the child's developing nervous system at a crucial time—with a resultant reduction in IQ and cognitive impairment, endocrinopathy, and risk of second malignancy. We aimed to assess the role of a primary chemotherapy strategy in avoiding or delaying radiotherapy in children younger than 3 years with intracranial ependymoma.

Methods Between December, 1992, and April, 2003, we enrolled 89 children with ependymoma who were aged 3 years or younger at diagnosis, of whom nine had metastatic disease on pre-operative imaging. After maximal surgical resection, children received alternating blocks of myelosuppressive and non-myelosuppressive chemotherapy every 14 days for an intended duration of 1 year. Radiotherapy was withheld unless local imaging (ie, from the child's treatment centre) showed progressive disease.

Findings 50 of the 80 patients with non-metastatic disease progressed, 34 of whom were irradiated for progression. The 5-year cumulative incidence of freedom from radiotherapy for the 80 non-metastatic patients was 42% (95% CI 32–53). With a median follow-up of 6 years (range 1·5–11·3), overall survival for the non-metastatic patients at 3 years was 79·3% (95% CI 68·5–86·8) and at 5 years 63·4% (51·2–73·4). The corresponding values for event-free survival were 47·6% (36·2–58·1) and 41·8% (30·7–52·6). There was no significant difference in event-free or overall survival between complete and incomplete surgical resection, nor did survival differ according to histological grade, age at diagnosis, or site of disease. In 47 of 59 (80%) patients who progressed, relapse resulted from local control only. The median time to progression for the 59 patients who progressed was 1·6 years (range 0·1–10·2 years). The median age at irradiation of the whole group was 3·6 years (range 1·5–11·9). For the 80 non-metastatic patients, the 23 who achieved the highest relative dose intensity of chemotherapy had the highest post-chemotherapy 5-year overall survival of 76% (95% CI 46·6–91·2), compared with 52% (33·3–68·1) for the 32 patients who achieved the lowest relative dose intensity of chemotherapy.

Interpretation This protocol avoided or delayed radiotherapy in a substantial proportion of children younger than 3 years without compromising survival. These results suggest, therefore, that primary chemotherapy strategies have an important role in the treatment of very young children with intracranial ependymoma.

Introduction

Over half of childhood intracranial ependymomas occur in children under 5 years of age, and the effective treatment of these patients remains one of the more difficult tasks in paediatric oncology.[1] The success of any treatment strategy in this age group has to be measured not only in terms of event-free or overall survival, but also in terms of the potential for serious or irreversible damage to the developing brain.

Most childhood ependymomas arise in the posterior fossa, are large, and are difficult to resect. There is general acceptance that adjuvant therapy is required even when complete resection is achieved.[2–7] Choices over adjuvant therapy are difficult, and to an extent, have depended on the underlying philosophies of national groups and institutions. Radiotherapy is effective, but its delivery is complicated by the vulnerability of an immature CNS to radiation damage. Although the degree of functional impairment depends on field size, radiation dose, and age at treatment, most long-term survivors have multiple problems including a global reduction in IQ and more specific cognitive defects such as short-term memory loss.[8–11] Preliminary studies suggest that conformal radiotherapy to the posterior fossa in children older than 12 months might not result in severe neurocognitive damage, at least in the short term.[4] However, there are other serious delayed effects from radiotherapy, such as neuroendocrine sequelae and second cancers which could adversely affect the child's quality of life.[12–14]

The perception of unacceptable side-effects of cranial radiotherapy in young children led a number of institutions and national groups to adopt chemotherapy-based strategies designed to avoid or delay irradiation.[2,3,5,6,15]

The United Kingdom Children's Cancer Study Group/International Society of Paediatric Oncology (UKCCSG/SIOP) undertook study CNS9204, a clinical trial of combined adjuvant treatment strategy in children younger than 3 years with malignant brain tumours, with the aim of using primary chemotherapy to minimise the risk of drug resistance, maximise intensity of treatment, and avoid or at least delay radiotherapy. Based on this strategy, radiotherapy was reserved only for those with resistant recurrent tumours. This study included children with any malignant brain tumours; however, because outcomes vary by histological subtype,[3,5] in this article, we report only on intracranial ependymoma.

This study was intended to differ from other contemporaneous studies in its rapidly changing schedule of agents, which alternated myelosuppressive with non-myelosuppressive chemotherapy.[16] Furthermore, patients were irradiated only at the time of disease progression or at the time of a relapse.

Methods

Participants

Criteria for inclusion were diagnosis of a primary intracranial tumour, histological diagnosis of ependymoma, being aged 3 years or younger at diagnosis, and not having had previous adjuvant cytotoxic drug or radiation treatment. Figure 1 shows the trial profile. The trial was approved by UKCCSG/SIOP and national ethical approval was obtained. Informed consent was obtained from parents or guardians of each child, in accordance with national guidelines at the time of this trial, and noted in the hospital records.

Procedures

After maximal surgical resection, the chemotherapy schedule comprised blocks of myelosuppressive treatment (carboplatin and cyclophosphamide), alternated with non-myelosuppressive treatment (cisplatin and high-dose methotrexate] at 14-day intervals to produce a high-intensity regimen with modest individual drug-dose intensity (table 1).

The chemotherapy schedule comprised four courses of alternating myelosuppressive and non-myelosuppressive drugs repeated every 56 days for a total of seven cycles: course 1, carboplatin (550 mg/m² or 20 mg/kg) over 4 h and vincristine (1·5 mg/m² or 0·05 mg/kg) intravenous bolus; course 2, methotrexate (8000 mg/m² or 250 mg/kg) and vincristine (1·5 mg/m² or 0·05 mg/kg); course 3, cyclophosphamide (1500 mg/m² or 50 mg/kg) over 4 h with prehydration and mesna; course 4, cisplatin (40 mg/m² for 48 h or 1·3 mg/kg). Further details of administration are given in table 1. 10% of the total dose of methotrexate was given over the first hour then the remaining 90% was given intravenously over 23 h. Hydration with 0·18 % NaCl+2·5% dextrose+$NaHCO_3$ 50 mmol/L+KCl 20 mmol/L was given before, during, and for at least 48 h after the methotrexate infusion was completed. Methotrexate serum concentration was measured at 24 h, 48 h, and 72 h post infusion. Folinic acid rescue was 15 mg fixed dose and was started 36 h after start of methotrexate infusion 3-hourly for five doses, then 6-hourly until serum methotrexate concentration was under 0·1 µmol/L ($<1\times10^{-7}$ molar). Mesna was given alongside the cyclophosphamide (1800 mg/m² or 60 mg/kg) and was given intravenously commencing with prehydration, continuing through 4-h cyclophosphamide infusion and ending 12 h after completion of cyclophosphamide infusion. For cisplatin administration, prehydration included 0·45% saline+2·5% dextrose, 200 mL/m² for 3 h. Hydration during and for 6 h post cisplatin was 0·45% saline+2·5% dextrose+KCl 20 mmol/L +mannitol 12g/L. Total intravenous infusion rate was equal to 125 mL/m²/h for 48 h.

Drugs chosen had different mechanisms of cytotoxic action in an attempt to prevent the early emergence of drug resistance. Children weighing up to 10 kg were dosed according to weight, and those heavier than 10 kg were dosed on a surface-area basis. Chemotherapy was to start within 4 weeks of surgery, and continued for 1 year unless there was unacceptable toxicity (determined by the treating physician), or until disease progression. Haematological toxicity alone was not an indication to delay treatment.

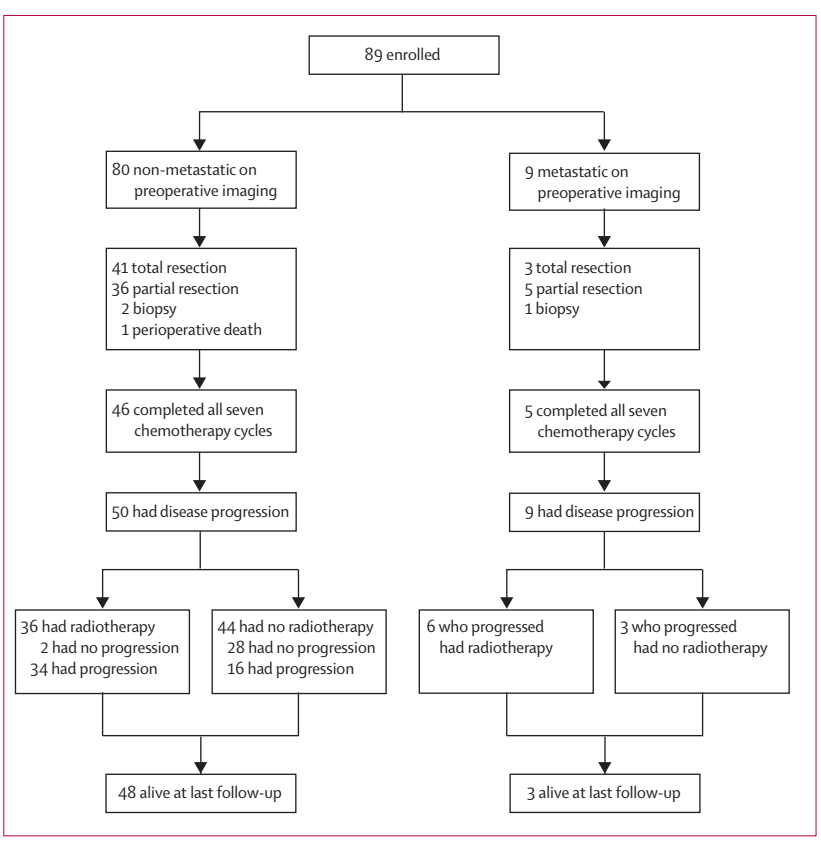

Figure 1: **Patient flow**
Two children were treated on protocol following diagnosis just after their third birthday based on the philosophy of minimising neurocognitive and other late effects of radiotherapy.

	Children weighing up to 10 kg (dose by weight)	Children weighing more than 10 kg (dose by surface area)
Course 1 (day 0)		
Vincristine (IV bolus)	0·05 mg/kg	1·5 mg/m²
Carboplatin (IV over 4 h)	20 mg/kg	550 mg/m²
Course 2 (day 14)		
Vincristine (IV bolus)	0·05 mg/kg	1·5 mg/m²
Methotrexate	250 mg/kg	8000 mg/m²
Folinic acid	15 mg fixed dose	15 mg fixed dose
Course 3 (day 28)		
Vincristine (IV bolus)	0·05 mg/kg	1·5 mg/m²
Cyclophosphamide	50 mg/kg	1500 mg/m²
Mesna	60 mg/kg	1800 mg/m²
Course 4 (day 42)		
Cisplatin (continuous infusion for 48 h)	1·3 mg/kg×2 days	80 mg/m² in two divided doses

IV=intravenous. There were seven cycles in total, each cycle was delivered over 56 days.

Table 1: **Chemotherapy schedule**

	Metastases at diagnosis*	
	No	Yes
Study population	80	9
Male sex	54	4
Younger than <1 year at diagnosis	11	3
Median age (range) in years	1·93 (0·05–3·16)	1·36 (0·24–2·25)
Infratentorial ependymoma	69	7
Supratentorial ependymoma	11	2
Central review histology as classic (II)	54	5
WHO classified as anaplastic (III)	26	4

*Based on preoperative MRI.

Table 2: **Patient characteristics at diagnosis**

	Number of patients (n=89)
Haematological	
Grade 3	6
Grade 4	83
Renal	
Grade 3	3
Grade 4	0
Audiological	
Grade 3	3
Grade 4	2
Gastrointestinal	
Grade 3	23
Grade 4	3
Other	
Grade 3	27
Grade 4	3

Table 3: **Cumulative toxicity**

Radiotherapy was withheld unless there was progressive disease defined on local imaging—age did not determine whether radiotherapy was given. For localised, non-metastatic tumours, 50 Gy in 25 daily fractions of 2 Gy per fraction, 5 days per week, was prescribed for the radiologically defined macroscopic tumour plus a margin of 2 cm. Whole neuroaxis radiotherapy was recommended for metastatic disease: for children aged 3 years and older, 35 Gy in 21 daily fractions of 1·67 Gy per fraction was prescribed to the whole neuroaxis. This was followed by a boost to the primary tumour of 20 Gy in 12 daily fractions of 1·67 Gy per fraction given to the initial tumour volume, plus a margin of 2 cm. For infants younger than 3 years, the whole neuroaxis dose was reduced to 25 Gy in 20 daily fractions of 1·25 Gy per fraction. The boost dose to the primary tumour was 20 Gy in 12 daily fractions of 1·67 Gy per fraction (ie, as for the older children).

Assessment

Patients were staged by full neuraxis imaging, postoperative scans (within 48 h) were recommended, but for various reasons this was achieved in most but not all cases. All patients underwent primary surgery with the aim of achieving maximal surgical resection. A complete resection was recorded when there was no visible tumour documented by the surgeon at the end of operation, a subtotal resection when visible tumour remained, and a biopsy when only sufficient tumour for diagnosis was removed. The operative notes and postoperative scans were reviewed centrally (JAGP, CM). Central radiological review of the extent of the surgical resection on postoperative scans was done according to SIOP criteria (CM, TC, WKC, RG).[17] Routine scans were requested at day 112, 224, and the end of the chemotherapy schedule. 6-monthly post-treatment scans were recommended. MRI scans of children on long-term follow-up of more than 4 years post-surgery were reviewed centrally for evidence of leucoencephalopathy as determined by white matter changes acting as a surrogate marker for methotrexate neurotoxicity. Minimum criteria for this review included T1-weighted and T2-weighted MRI scans with gadolinium enhancement. Cerebrospinal fluid sampling before chemotherapy was recommended.

Histological slides from all patients were reviewed by DE and JI. Tumours were classified as grade II or III according to WHO criteria.[18] Ependymoblastomas, which are now classified with other primitive neuroectodermal tumours, were excluded.[18] Toxicity was assessed by the treating physician and coded in the CCLG data centre. The UKCCSG shortened listing of National Cancer Institute common toxicity criteria version 2.0 were used.

Statistical analysis

Standardised received dose of chemotherapy (SRDChemo) was calculated for each patient as the

proportion of the cumulative dose of the chemotherapy regimen actually received relative to that defined in the protocol (table 1). These proportions were then averaged over all patients receiving the regimen. The relative dose intensity (RDIChemo) adjusted the individual patient SRDChemo by the ratio of the time the regimen took to be given, divided by the corresponding protocol-defined time. These are then averaged for all patients to give the regimen RDIChemo.

After surgery, patients were classified into four groups: those who (A) continue to be alive without progression and without radiotherapy; (B) have disease progression, or die without progression first being documented, but who do not receive radiotherapy; (C) receive elective radiotherapy without documentation of progression; or (D) receive radiotherapy after progression.

Of the corresponding survival times in these groups, those in A were censored for all events, whereas those for B, C, and D represent times to competing events. A competing event is one which, if it occurs, prevents another event from being observed. In the presence of competing risks, the cumulative incidence method[19] estimates the cumulative probability for each cause of failure for B, C, or D in the presence of all risks to the patients concerned. If the radiotherapy-free survival (RADFS) rate is calculated, which adds all the event types together, then (1–RADFS) is the sum of the three separate cumulative incidences.

Event-free survival was defined as the time from date of surgery to the date of the first event—ie, a recurrence or death. When death followed recurrence, the event was the recurrence. Overall survival was calculated as the time from the date of surgery to death from any cause. Patients still alive were censored at the date last seen. Survival probabilities were calculated using the Kaplan-Meier method. The hazard ratios and 95% CIs for comparing metastatic and non-metastatic patients were estimated using the Cox proportional hazards model. The potential influences of age, sex, histology, tumour site, and extent of resection on the hazard ratio were also investigated with the Cox model.[20]

The effect of the RDIChemo was assessed by calculating the residual overall survival time from 1-year after the start of chemotherapy.[21]

The protocol of this trial is currently under review to ensure it complies with good clinical practice, and the revised protocol will be registered in a publicly accessible database upon completion.

Role of the funding source

The sponsor of the study had no role in the study design, conduct of the study, data collection, data management, data analysis, data interpretation, preparation of the report, review of the report, or approval of the report. RGG, SAW, CLW, KR, JI, TC, WKC, NT, DWE, and DM had full access to all of the raw data and RGG had final responsibility to submit for publication.

Results

89 patients with a diagnosis of intracranial ependymoma from 21 participating centres were registered to the study between Dec 1, 1992, and April 31, 2003. Of these, 80 (90%) presented without metastatic disease and nine (10%) with imaging evidence of primary dissemination. Of the children with metastatic disease, three had nodular spinal leptomeningeal dissemination (M3), three had cerebral nodules (M2), and three had cranial and spinal disease (M3) present on pre-operative MRI images. Table 2 shows patients' characteristics. The children were predominantly male (58 [66%]). 76 (85%) had infratentorial tumours. Pre-chemotherapy assessment was done consistent with a Lansky play scale of 70–90%.

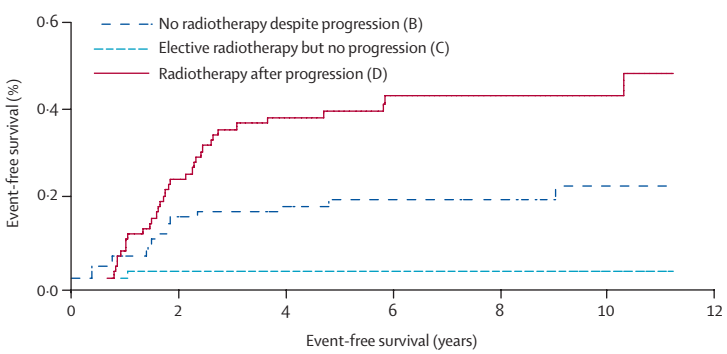

Figure 2: **Competing risks analysis for patients with non-metastatic ependymoma**

	Number of relapses (n=59)	5-year overall survival from the date of relapse (95% CI)
Relapse site		
Local relapse site	47	26 (13-41)
Local and metastatic relapse	6	Too early to tell
Metastatic relapse only	4	Too early to tell
Unknown	1	0
Perioperative death	1	0
WHO grade		
WHO primary tumour grade II	37	30 (13-48)
WHO primary tumour grade III	22	25 (8-47)
Surgery		
No surgery after relapse	28	24 (8-44)
Surgery after relapse	30	31 (13-51)
Perioperative death	1	0
Radiotherapy		
No radiotherapy after relapse	18	Too early to tell
Radiotherapy without surgery	17	20 (5-43)
Radiotherapy with surgery	23	32 (11-55)
Perioperative death	1	0

Table 4: **Outcome in patients with a first relapse after primary treatment**

After a central review, 59 (66%) of cases were designated classic (WHO grade II) ependymoma. The local histopathological grade was changed in 26 (29%) tumours—14 cases changed from grade II to III, and from grade III to II in 12. Cerebrospinal fluid (CSF) cytology was examined in 37 patients (42%), with no malignant cells detected.

44 (49%) had a complete resection of the primary tumour, 41 (46%) had subtotal resection, and biopsy only was done in three (3%), and one (1%) died perioperatively. The concordance between the surgical report and central radiology review with respect to completeness of resection was 68%.

The median start of chemotherapy was 23 days (range 0–81) after surgery. Five patients had a delay of more than 50 days (range 52–81). One patient had chemotherapy after delayed second-look surgery. 51 (57%) completed all seven cycles of chemotherapy. A further ten patients stopped protocol treatment as they had been on treatment for over 1 year without completing all cycles, nine were in remission, and one had stable residual disease. Chemotherapy was stopped early in 27 patients: 11 had disease progression, ten had unacceptable toxicity, one had residual disease and was irradiated, one patient had no tumour on imaging, whereas for four patients no specific reason was given. There was one postoperative death. Haematological toxicity was the most common treatment-related problem, with either grade 3 or 4 occurring in all patients (table 3). Only two, one metastatic and one non-metastatic, patients had grade 4 audiological toxicity.

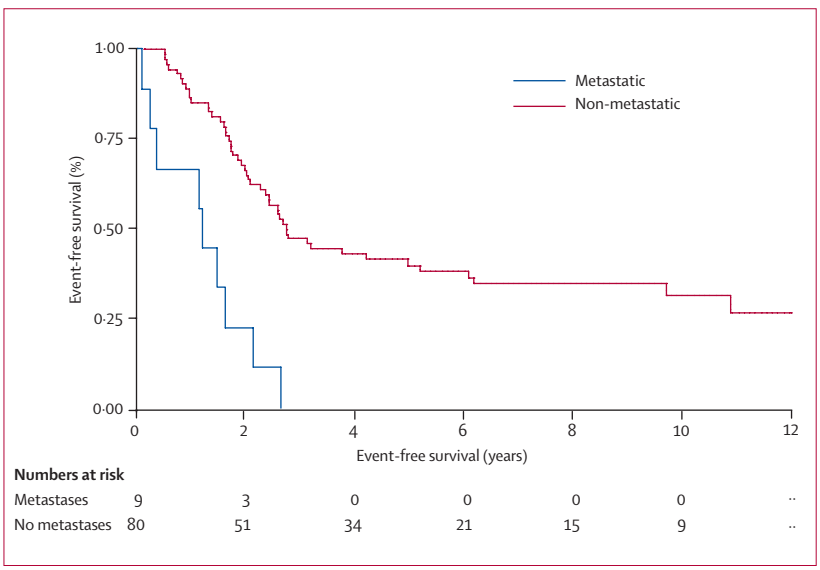

Figure 3: **Event-free survival by presence or absence of metastases at diagnosis**

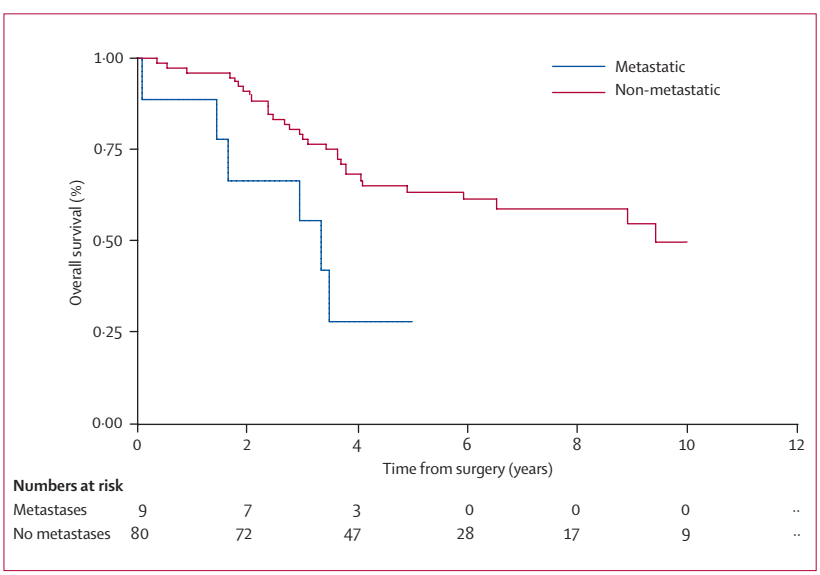

Figure 4: **Overall survival by presence or absence of metastases at diagnosis**

50 of the 80 patients with non-metastatic disease progressed, of whom 34 were irradiated for progression (figure 1); eight were aged less than 3 years), and 16 patients with progressive disease were not irradiated for reasons determined by the physician or parent. In addition, two were irradiated (one younger than 2·5 years) despite no progression being reported. Thus, 44 (55%) patients with non-metastatic disease were not irradiated. All nine patients who had metastatic disease at diagnosis progressed. Six of these nine patients were irradiated. As would be anticipated, the radiotherapy rate was lower in those with a complete tumour resection: 18 of 44 (41%) compared to 24 of 44 (55%) of those not fully resected.

Given that not all patients who progressed were irradiated, to reflect more accurately the need for radiotherapy, we used cumulative incidence methodology (CIM)[19] to calculate radiotherapy-free survival. For all 89 patients, the 3-year and 5-year cumulative radiotherapy rates were 44·6% (95% CI 34·5–56·2) and 49·3% (38·8–61·0), respectively. The median time from surgery to radiotherapy was 20·3 months (range 7·8–123·6) and median age at irradiation was 3·6 years (range 1·5–11·9). In non-metastatic patients, combining all who were irradiated with those that were eligible for this treatment modality (but did not receive it) perhaps reflects more accurately the success of this chemotherapy protocol in avoiding radiotherapy. The 5-year cumulative incidence rate of freedom from radiotherapy for non-metastatic patients was 42% (95% CI 32–53; 1-sum of all the curves in figure 2).

In total, 59 patients including all nine with metastatic disease progressed, 37 of whom subsequently died. 47 relapsed locally, four at a metastatic site, six at both local and metastatic sites, one was unknown, and one child died during surgery. In all 40 patients who received radiotherapy for their progression, 23 also had surgery. Of the remainder who did not receive radiotherapy, seven patients underwent surgery alone, two received alternative chemotherapy, one was treated under a palliative care regimen, eight had no further treatment, and one died perioperatively (table 4).

Median time to progression for the 59 patients who progressed was 1·6 years (range 0·1–10·2). The 3-year event-free survival for all 89 patients was 42·7% (95% CI 32·2–52·8) and 5-year 37·5% (27·3–47·7) (figure 3). As would be anticipated, event-free survival was poorer for those with metastatic disease (HR 4·1, 95% CI 2·0–8·7, p<0·0001) with all progressing within 3 years. In the non-metastatic patients, the 3-year and 5-year event-free survival was 47·6% (36·2–58·1) and 41·8% (30·7–52·6). No significant difference was seen in event-free survival at 5 years between non-metastatic patients with WHO grades II and III disease: 38·4% (95% CI 26·6–50·0) and 41·7% (15·3–66·5), respectively.

For the 51 patients alive at last follow-up, the median follow up was 6·0 years (range 1·5–11·3). 38 patients died: 34 due to tumour, four from post–surgical complications. The 3-year overall survival for the whole group was 76·8% (95% CI 66·4–84·4) and the 5-year overall survival was 60·0% (95% CI 48·4–69·7). As expected, survival was poorer for those with metastatic disease (hazard ratio [HR] 3·0 [95% CI 1·2–7·3], p=0·016) (figure 4). In the non-metastatic patients, the 3-year and 5-year overall survival was 79·3% (95% CI 68·5–86·8) and 63·4% (51·2–73·4), respectively. Although the numbers were small, 14 children, those younger than 1 year at diagnosis, seemed to have the poorest survival, although this was not significant: 44% were alive at 5 years compared with 65% for those aged between 2 and 3 years at diagnosis (HR 1·4 [95% CI 0·9–2·2]; p=0·18; table 5). Whether the patient was male or female did not seem to affect outcome. Tumour location in the supratentorium was associated with a better survival than for patients with infratentorial tumours (83% *vs* 56%), but this comparison was not significant (HR 3·1 [95% CI 0·8–12·5]; p=0·12; table 5). The 5-year overall survival for grade II disease was 61·5% (95% CI 48·2–72·4) and 66·7% (33·7–86·0) for grade III.

Patients with a complete resection, based on neurosurgical review, had better 5-year event-free survival (48·9% [95% CI 33·8–62·8]), than those with partial resection or biopsy alone (25·8% [13·7–39·6]). Importantly, there was a difference in 5-year overall survival (68·1% [51·2–80·2] *vs* 51·8% [35·6–65·8]) for complete versus incomplete resection, although this is not firmly established with our study sample size (p=0·07; figure 5). Overall survival based on the radiological assessment of residual tumour showed that complete resection did not confer a better outcome (p=0·28). From our analysis neurosurgical rather than radiological assessment of completeness of resection was a more powerful predictor of outcome (data not shown).

The actual distribution of the SRDChemo achieved from the combination chemotherapy schedule of table 1 varied according to the total number of cycles received by each patient. There was a tendency towards lower SRDChemo in those who had the fewest cycles, whereas in those who had all seven cycles, the distribution is skewed towards higher values. The median SRDChemo achieved was 0·97, very close to the protocol ideal of unity, but ranged from 0·59 (a patient receiving cycle 1 only) to 1·46 (a patient receiving all seven cycles who was

	N	HR for death (95% CI)	p
Age <1 year at diagnosis	14	1·4 (0·9-2·2)	0·18
Female sex	31	1·1 (0·5-2·1)	0·13
Infratentorial ependymoma	76	3·1 (0·8-12·5)	0·12
WHO III histology	30	1·6 (0·8-3·2)	0·15
Partial resection (judged by neurosurgeon)	45	1·8 (0·9-3·6)	0·07
Partial resection (judged by radiological review)	55	1·5 (0·7-3·0)	0·28
Dose intensity <0·8	32	1·6 (1·0-2·7)	0·04

Table 5: **Risks from different potential prognostic variables**

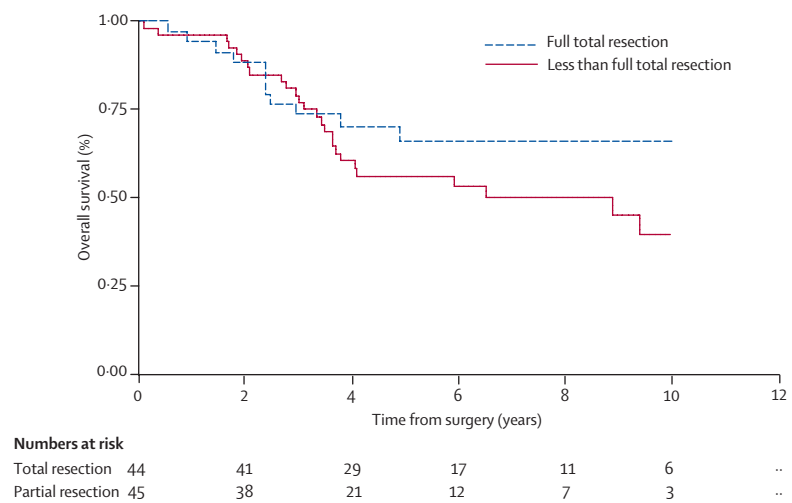

Figure 5: **Overall survival based on neurosurgical assessment of the extent of resection at the end of surgery**

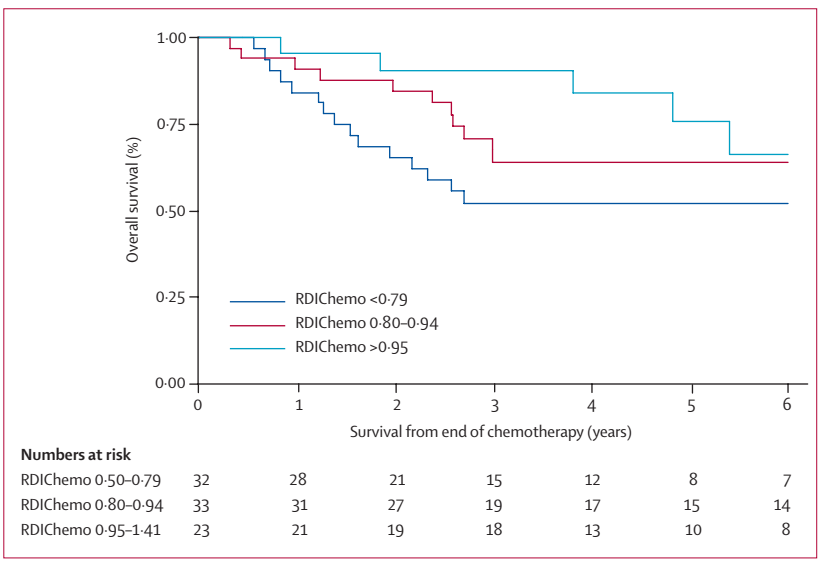

Figure 6: **Overall survival from end of chemotherapy by relative dose intensity chemotherapy (RDIChemo) received**

	n	Event-free survival (%)		Overall survival (%)		"Radiotherapy-free" survival
		3-year	5-year	3-year	5-year	
Pediatric Oncology Group[3,22]	48	46*	27	58*	40·5	0
Children's Cancer Group[6]	15	26	18	NA	NA	NA
SFOP[2]	73	40*	22	68*	52	22
CCG-9921	74	50*	32	65	59	40
St Jude[4]	48	69·5	55†	NA	NA	0
This study	89	48	42	79·3	63	42

NA=not available. *Estimated on the basis of exponential survival using the quoted 5-year rates. †Projected survival, assuming exponential survival rates. The German Paediatric brain tumour studies are not included as they only include anaplastic (grade III) tumours on Hirntumor Säuglinge und Kleinkinder (HIT-SKK) protocols.

Table 6: **Outcomes of major studies of ependymoma in young children**

given more drug than the dose calculated based on their body-surface area). The median of the ratio between actual time and protocol-dictated length of a cycle (56 days per cycle) was 1·09, which is close to the protocol ideal of unity, and ranged from 0·79 to 1·63. 1·63 was for a patient receiving six cycles over an extended duration.

Combining the dose and relative time elements into the RDIChemo resulted in a median of 0·87 or about 90% of that intended. About one-third of the patients achieved an RDIChemo of less than 0·78 (minimum 0·53) and about one-third more than 0·93 (maximum 1·41). The overall survival achieved by these groups (after rounding to convenient boundary values) suggests that those with the highest-achieved RDIChemo tended to have longer survival times post completion of chemotherapy (figure 6). The 3-year postchemotherapy overall survival was 52·1% (95% CI 33·5–67·9), 64·0% (44·3–78·3), and 90·7% (67·6–97·6) for the three RDIChemo groups, respectively. These rates will be affected to a greater or lesser extent by subsequent treatment, including radiotherapy, and the effect of these on overall survival will increasingly affect the ultimate shape of the survival curves as the interval from the end of chemotherapy increases. Patients achieving the highest RDIChemo (calculated from the relative time it took to administer the chemotherapy against the protocol specification) had a postchemotherapy 5-year overall survival of 76% (95% CI 46·6–91·2) compared with 64% (44·6–78·4) and 52% (33·3–68·1) in those in the intermediate and lower dose-intensity groups, respectively (p=0·04).

The MRI scans of the 40 patients who had survived 4 years beyond treatment were reviewed, 19 had received radiotherapy. Subtle white matter changes were noted in two non-metastatic patients, one of whom had received radiotherapy. 33 children of this subgroup are still alive, six of whom seem to have stable residual disease at the end of treatment.

Discussion

Our results show that after primary postoperative chemotherapy, children younger than 3 years had a 5-year overall survival of 63·4%, without the use of radiotherapy in 42% of those treated for non-metastatic disease. For those with and without metastases at diagnosis, the median delay to radiotherapy was 20·3 months, and the median age at irradiation was 3·6 years. This study did not identify age or histological grading as prognostic factors, but did identify that metastatic disease predicted poor survival. Finally, in contrast to several other reports, completeness of surgical resection was not identified as a significant predictor for survival.

There are several possible explanations for the relative success of this primary chemotherapy strategy. Treatment intensity of the chemotherapy could be important. The treatment schedule specified a 14-day treatment interval, irrespective of blood count. During the planned 1-year protocol period, there was one peri-operative death, four patients progressed and died, while ten others relapsed; in all, 11 patients progressed on treatment. Of the 84 survivors, those achieving optimum RDIChemo had a post chemotherapy 5-year survival of 76% compared with 52% in those not achieving optimum RDIChemo (p=0·04). The effect of non-chemotherapy events, such as postsurgical neurotoxicity, intercurrent infections, shunt malfunction and treatment, might have contributed to the cause of decreases in RDIChemo inferring that avoidance of these events by enhanced attention to supportive and preventive care might benefit patients by permitting optimum RDIChemo to be achieved in a higher proportion. This highlights the importance of an integrated and holistic approach to patient care aimed at maximising nutrition, infection prevention, and optimisation of surgical approaches to minimise neurological risks. The role of dose intensity in the management of ependymoma deserves further study.

Comparison of survival results of our study against those reported by other national trials groups using primary chemotherapy showed that our study had better outcomes than the French Society of Pediatric Oncology (SFOP) study (table 6). Our study achieved an event-free survival of 64·4% and 44·9% at 2 and 4 years for non-metastatic patients, compared with 33% (95% CI 23–44) and 22% (13–34) at the same time points in the SFOP study.[2] Comparisons in overall survival between these studies showed less marked differences: 5-year overall survival of 63·4% (52–73) in our trial, compared with 52% (38–65) in the SFOP series.[2] Such contrasting results between event-free survival and overall survival reflect the efficacy of salvage therapies after primary chemotherapy. Our results were better than those from the US Pediatric Oncology Group (POG) 8633 study in which chemotherapy was delivered to delay, but not avoid, radiotherapy.[3,22] Finally, comparison to the US Children's Cancer Group (CCG)-9921 study shows similar overall survival (59% at 5 years).[5] The effect of age in this very young cohort upon survival was non-significant, in contrast with the POG study[3,22] and other groups.[2,4,5] The very young age group, limited age range studied, and small numbers of patients in cohorts

precludes strong conclusions, although immaturity and tumour biology are likely to affect outcome.

Comparison of event-free survival in cohorts receiving primary radiotherapy with overall survival in those receiving primary chemotherapy and delayed radiotherapy when necessary can be justified since radiotherapy is used in both, but delayed or avoided in some depending on the efficacy of the primary surgery and chemotherapy.[2,23] The 3-year overall survival of 79·3% of this UK study was higher than the St Jude study (3-year progression-free survival 69·5%)[4] and higher than other primary radiotherapy studies.[24] Critical to the interpretation of this data is the proportion receiving radiotherapy and the number of patients who were not irradiated despite progression, through parental or physician choice. The approach used here for calculating cumulative incidence of radiotherapy, using the competing risks methodology, reflects more accurately the need for radiotherapy, justifying our conclusion that 42% of patients studied are true radiotherapy-free survivors.

Comparisons between these relatively small studies highlight inconsistencies in methods of reporting, and the effect of tumour and patient factors such as age, histological grading, and surgical resection upon primary outcomes, making direct comparison problematic. The current international effort using meta-analysis to arrive at a clinical and scientific consensus on the optimum stratification of patients for the next era of clinical trials in this diagnostic group is therefore justified as the most important next step for testing of the next generation of treatments.[25]

Consistent application of histological grading of malignant ependymomas using the WHO 2000 classification,[18] identifies classic ependymoma (grade II) and anaplastic ependymoma (grade III). Differentiation between these categories requires the recognition and interpretation of a spectrum of pathological features. In this cohort, 59 (66%) of 89 had WHO grade II histology, whilst the SFOP reported 60 (88%) of 68 as grade III.[2] Some reports, including ours, did not identify histological grade as prognostic,[3,26–30] whilst others did.[2,4,31–33] An international consensus on the interpretation of histological grade and its true value as a prognostic factor is required.

Nine (10%) of 89 children in this cohort had metastatic disease, and all nine progressed. Metastatic disease has been reported in 7–12% of patients with ependymoma.[22,26,27] Although two studies found no effect of metastatic disease on outcome,[22,27] four studies (including ours) did detect an effect.[5,26,34]

Compliance with CSF cytological examination in this study was relatively poor, with results in just over 40% of cases. However, recent evidence suggests that this investigation was not helpful in predicting those patients who would subsequently have a relapse in the spinal cord.[35] The use of CSF cytology in determining outcome in ependymoma seems therefore to be limited, although a larger multicentre assessment is needed to clarify this. The lack of CSF cytology to determine M1 status in our study, although a deficiency, is probably of lesser importance than the detection of leptomeningeal deposits on MRI scanning in terms of patient outcome.

This study was mainly devised to investigate whether chemotherapy can avoid or delay radiation in young children with malignant brain tumours. Assessing tumour response to chemotherapy was not a principal component of the study. It is now accepted that assessing chemotherapy response in ependymoma is a considerable challenge. Several factors can confound radiological review, for example, changes in the contrast uptake by the tumour, the use of surgicell as an adjunct to stopping tumour-bed haemorrhage, the timing of the scan, and residual anatomical abnormality after surgery. The role of more sophisticated imaging methods such as PET or magnetic resonance spectroscopy now need to be investigated.[36]

The selection of drugs in this study was determined by a combination of factors predictive of tumour sensitivity and myelotoxicity to create a time-intensive schedule. Methotrexate was selected because of the high-level folate receptor expression in ependymoma cells, thereby providing a mechanism to maximise drug accumulation into the tumour.[37] The Children's Cancer and Leukaemia Group have just initiated a phase II study investigating the single-agent activity of high-dose methotrexate in children with incompletely resected ependymoma. The group continues to use this chemotherapy protocol for children with completely resected disease, but now recommend conformal radiotherapy using multiple fields and a dose of 59·4 Gy to the tumour bed. Cisplatin doses in this study were higher than those in the SFOP protocol and vincristine was used in three of four courses of each cycle. Cisplatin ototoxicity is well recognised, but the incidence of grade IV ototoxicity in this study was reassuringly low. Future strategies to improve outcome could include the use of granulocyte-colony stimulating factor to maintain dose intensity and etoposide in combination with either cisplatin or carboplatin. Scheduling and sequencing of chemotherapy drugs could also be important, since the 14-day schedule might have acted through antiangiogenic mechanisms and the predicted cytotoxic effects.

We delayed radiotherapy to avoid damaging the developing CNS at a crucial point in its maturation. This protocol began in an era in which the longitudinal follow-up of patients was not considered as crucial as it now is, and neuropsychological assessment was not an intrinsic part of this study as this cohort was recruited as part of a study seeking to establish the role of chemotherapy for children younger than 3 years with a variety of brain tumours. However, data on neuropsychological outcome of nine children, none of whom had been irradiated, from a single UK centre treated on this protocol have recently been reported.[38] At a mean age at diagnosis of 22 months and a mean time from diagnosis of 75 months, all children had full-scale IQ

(103), verbal (105) IQ, and performance (non-verbal) (99) IQ within the normal range.

There is a clear association between methotrexate and acute and late neurotoxicity, the severity and nature of which are dependent on the dose and mode of administration of the drug, folinic acid rescue, and the concomitant use of radiotherapy.[39–41] Evidence of late CNS damage by high-dose methotrexate comes from the presence of leucoencephalopathy. Only two of our long-term survivors had subtle white-matter changes on MRI. Similar low incidence rates of this abnormality have been reported by Kellie and co-workers.[42] The risk factors for leucoencephalopathy due to methotrexate include highest doses (>10 000 mg/m²) and frequent administration (7–10 day intervals).[40,41] The methotrexate dose (8000 mg/m²) and interval (8 weeks) in our study were less than this. The report describing the use of intraventricular and intravenous methotrexate in children younger than 3 years with medulloblastoma is also reassuring as although leucoencephalopathy was detected, its presence did not predict for worse neurocognitive outcomes within the treatment cohort, except when cranial radiotherapy was also used. The cognitive outcomes were, however, worse than a normal comparative group.[43] The risk of neurocognitive late effects from high-dose methotrexate in children with brain tumours would therefore seem to be acceptable,[40,42,44] but requires monitoring prospectively in future studies with neuropsychological assessment. We conclude that the risk of neurotoxicity from this protocol is acceptable given the serious nature of the presenting clinical problem and the multimodal therapy required for successful outcomes.

The extent of surgical resection is the most consistently reported prognostic factor affecting both progression-free and overall survival both in single centre,[4,27,30,45] and multi-centre studies.[2,3,5] A few single-centre retrospective studies have found no survival advantage to complete resection.[29,46,47] However, the proportion of cases in which a complete surgical resection is obtained varies from around 50% in most studies,[2,3,27,34] to 85%.[4] We have shown that the neurosurgical assessment of the extent of surgery more closely reflected outcome than did radiology review. Our study showed that whilst there was an indication of a better event-free survival for children who had a complete resection compared with those with less complete resection, this did not translate into an improved overall survival. The lack of evidence for surgical resection predicting outcome could be due to the confounding effect of surgical toxicity compromising delivery of effective chemotherapy, or effective chemotherapy and stratified radiotherapy diluting out the effect of enhanced surgical resection. There is no doubt that optimised uncomplicated primary resection is an excellent start for the management of childhood ependymoma.[1] Whether centralised specialist surgical centres or vigorous training and multicentre audits can best deliver low surgical toxicity rates in health systems is yet to be established.

The original aim of avoiding or delaying radiotherapy in these children without compromising outcome has been achieved. Our results confirm a role for primary chemotherapy in young children with intracranial ependymoma. The results reported here will contribute further to the impetus for collaborative studies in Europe and the US in this very young age group. The establishment of a clinical scientific consensus on risk stratification factors is the first, and most important, next step. Despite these advances, the long-term outlook for children with ependymoma remains unacceptably poor and further therapeutic advances will only come through a better understanding of the underlying tumour biology.

Contributors

RGG, SW, and MWE were responsible for data analysis and data interpretation. CW and DM undertook the statistical analysis and interpretation. KR was the trial coordinator, and was responsible for data management. JI and DWE undertook the central neuropathology review. TC and WKC did the central radiological review. JP and CM did the neurosurgical review and assessment. RG, RHAC, DAW, JP, CCB, and LSL designed the trial. NT did the trial radiotherapy review. RG and LSL wrote the report. SP, MWE, DAW, and LSL reviewed the report. LSL also contributed to data assessment.

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Denmark: University Hospital, Copenhagen.
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England: Addenbrooke's Hospital, Cambridge; Birmingham Children's Hospital; Bristol Children's Hospital; St James' University Hospital, Leeds; Great Ormond Street Hospital for Children, London; The Royal Manchester Children's Hospital; Queen's Medical Centre, Nottingham; Royal Victoria Infirmary, Newcastle upon Tyne; John Radcliffe Hospital, Oxford; Sheffield Children's Hospital; Southampton General Hospital; Royal Marsden Hospital, Sutton.
Northern Ireland: The Royal Hospital for Sick Children, Belfast.
Scotland: Royal Hospital for Sick Children; Edinburgh.
Sweden: Queen Silvia's Hospital for Children, Gothenburg.
The Netherlands: Emma Kinderziekenhuis, Amsterdam.
Wales: The Children's Hospital for Wales, Cardiff.

Conflicts of interest

The authors declared no conflicts of interest.

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CLINICAL INVESTIGATION **Brain**

PROTON RADIOTHERAPY FOR CHILDHOOD EPENDYMOMA: INITIAL CLINICAL OUTCOMES AND DOSE COMPARISONS

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Purpose: To report preliminary clinical outcomes for pediatric patients treated with proton beam radiation for intracranial ependymoma and compare the dose distributions of intensity-modulated radiation therapy with photons (IMRT), three-dimensional conformal proton radiation, and intensity-modulated proton radiation therapy (IMPT) for representative patients.

Methods and Materials: All children with intracranial ependymoma confined to the supratentorial or infratentorial brain treated at the Francis H. Burr Proton Facility and Harvard Cyclotron between November 2000 and March 2006 were included in this study. Seventeen patients were treated with protons. Proton, IMRT, and IMPT plans were generated with similar clinical constraints for representative infratentorial and supratentorial ependymoma cases. Tumor and normal tissue dose–volume histograms were calculated and compared.

Results: At a median follow-up of 26 months from the start date of radiation therapy, local control, progression-free survival, and overall survival rates were 86%, 80%, and 89%, respectively. Subtotal resection was significantly associated with decreased local control ($p = 0.016$). Similar tumor volume coverage was achieved with IMPT, proton therapy, and IMRT. Substantial normal tissue sparing was seen with proton therapy compared with IMRT. Use of IMPT will allow for additional sparing of some critical structures.

Conclusions: Preliminary disease control with proton therapy compares favorably with the literature. Dosimetric comparisons show the advantage of proton radiation compared with IMRT in the treatment of ependymoma. Further sparing of normal structures appears possible with IMPT. Superior dose distributions were accomplished with fewer beam angles with the use of protons and IMPT. © 2008 Elsevier Inc.

Ependymoma, Pediatric brain tumors, Proton beam radiation.

INTRODUCTION

Ependymomas are relatively rare malignancies accounting for 8–10% of intracranial pediatric tumors, with most cases occurring in children younger than 4 years (1, 2). One third of intracranial childhood ependymomas occur in the cerebral hemispheres. The remaining two thirds occur in the posterior fossa, arising along the lining of the fourth ventricle (3, 4). Standard treatment for patients with both supratentorial and infratentorial ependymoma consists of maximal surgical resection followed by radiation therapy (1, 5, 6). Critical structures, including the brainstem, cranial nerves, cochlea, and brain, lie in close proximity to treatment volumes, which, in addition to very young age at diagnosis, makes a highly conformal treatment most desirable.

Excellent control rates have been achieved with radiation therapy to the initially involved area of disease, which is now the accepted standard of care (7–11). Despite this reduction in treatment volume compared to historical radiation volumes, healthy uninvolved tissues receive radiation. In addition, because ependymomas occur in the very young, these patients can expect to experience worse adverse late effects from radiation therapy to the brain compared to older children or adults. Because morbidities are related to the normal tissues irradiated in the process of treating the tumor, it is of critical importance to improve dose conformity to the tumor bed. Complications of central nervous system (CNS) radiation in the pediatric population are well documented and include developmental and neurocognitive deficits, neuroendocrine

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dysfunction, growth abnormalities, sensorineural hearing loss, vascular events, and second malignancies (12–15). These late effects of treatment are a substantial source of morbidity and mortality, can impair quality of life, and affect the ability to function normally in society.

The unique characteristics of proton therapy offer major advantages in optimizing prescription dose to tumor volumes while sparing normal tissues. The chief advantage of proton radiotherapy is the sparing of normal tissue through the elimination of exit dose and reduction in entrance dose.

Currently, the majority of proton therapy is delivered through passive beam-scattering methods by using range compensators and apertures, which are custom designed to deliver a homogeneous dose distribution conforming to the distal edge of the target for each field (16). Intensity-modulated proton therapy (IMPT) refers to plans that deliver the dose to the target by the superimposition of individually *inhomogeneous* fields (17–19). The IMPT allows for increased dose-shaping capabilities with improved conformity not only at the distal region of the target, but also to the proximal target edge from a given field. At the present time, IMPT cannot be delivered efficiently with passive scattering beams alone and requires implementation of active scanning methods, which have the additional advantage of reduced neutron contamination, which may drive down the risk of second malignancy compared with passively scattered techniques (20, 21).

In this study, we report early clinical outcomes, including LRF, DFS, overall survival, and toxicities for patients with childhood ependymoma treated with three-dimensional (3D) conformal proton therapy. This represents the first report of clinical outcomes using proton radiation for pediatric CNS ependymoma. Similar to other comparative planning studies, we show the dosimetric advantage of proton radiotherapy over intensity-modulated radiation therapy (IMRT) for the treatment of childhood ependymoma by comparing dose–volume histograms for tumor volumes and normal tissues (22–24). In addition, we show that further tissue sparing may be achieved for selected patients when the techniques of intensity modulation are applied to proton therapy.

METHODS AND MATERIALS

Patients

All patients with supratentorial and infratentorial CNS ependymoma treated at the Francis H. Burr Proton Facility and Harvard Cyclotron between November 2000 and March 2006 were included in this retrospective study. Seventeen patients were identified. A dedicated planning contrast-enhanced computed tomography (CT) scan was obtained. Patients were immobilized with a custom Aquaplast facemask (WFR Aquaplast, Wyckoff, NJ). A separate high-definition magnetic resonance image (3-mm slices, no skip) was performed, and the T1 postgadolinium and/or flair sequence was anatomically registered to the CT scan by using CMS Focal Fusion software to facilitate volume definition. The tumor bed and residual tumor were contoured as the gross tumor volume. Several patients were coenrolled on the Children's Oncology Group ACNS 0121 ependymoma trial, and a 1-cm margin was added to the gross tumor volume for clinical tumor volume (CTV) as required for the protocol. For some earlier patients not on protocol, the CTV was defined as the tumor bed at risk and any area judged at risk of microscopic extension, which generally comprised a margin around that tumor bed of 1–1.5 cm. An additional margin of 8–10 mm was added around the CTV to account for both penumbra and planning target volume together, which accounts for a setup margin of approximately 3 mm. Brass apertures and Lucite compensators were custom made for each field. Daily positioning was achieved based on bony landmarks with diagnostic-quality orthogonal X-rays compared with digitally reconstructed radiographs. A computer program assists therapists in making patient couch shifts in 6 *df* to more accurately align patients (16).

The proton dose was prescribed in cobalt gray equivalent (CGE) using the relative biologic effectiveness value of 1.1 (25). Critical normal tissues were contoured for each patient. These included brainstem, optic chiasm, optic nerves, lenses, cochlea, pituitary gland, hypothalamus, temporal lobes, and whole brain. Generally accepted tolerance doses were used. If tumor was adjacent to or involving the brainstem, a small volume was permitted to exceed 54 CGE. Field arrangements were chosen to minimize dose to critical structures while maximizing target coverage. Most patients were treated with a three- or four-field technique. For infratentorial tumors, patients generally were treated with posterior-anterior, RPO, and LPO fields with a superior field only if it improved coverage and/or avoidance of such critical structures as brainstem. For supratentorial tumors, a variety of field arrangements were used depending on the location of the tumor. Only 3 patients had a cone down or boost for the purpose of decreasing the volume of brainstem receiving a dose greater than 54 CGE.

Dosimetric comparisons

For two representative cases, we compared IMRT, 3D conformal proton beam, and IMPT radiation treatment plans for a posterior fossa ependymoma occupying the fourth ventricle and extending along the right foramen of Luschka and a supratentorial ependymoma. Both patients were treated with conformal proton radiation with a rotational gantry system.

Standard proton planning was performed with XiO planning software (CMS Inc., St. Louis, MO). The Francis H. Burr Proton Therapy Center provides a rotational gantry system and maximum proton beam energy of 231 MeV. A four-field technique was used in both cases using superior, posterior-anterior, right lateral oblique, and left lateral oblique beam directions. The CTV prescription was 55.8 CGE.

To create the IMPT plan, CT data and contours were transferred to the inverse treatment planning system, KonRad Pro, developed at the German Cancer Research Center, Germany (18, 26). The scientific version of KonRad used in the present work allows optimization of dose distributions not only for photon, but also for proton radiation and carbon beam therapy. Plan optimization is performed for several irradiation fields simultaneously by using the inverse planning technique based on the Newton gradient method (27). In this study, the IMPT plan was optimized for discrete pencil beam spots by using three coplanar beam orientations with beam angles of 140, 180, and 220 for the infratentorial case. These fields were adopted from the 3D proton plan. The superior field was omitted because it did not add to the quality of the IMPT plan. Three fields were also used for the supratentorial IMPT plan. The IMRT plans were generated for both patients, again using the Konrad planning system.

Statistical analysis

Rates of local control, progression-free survival, and overall survival were estimated by using the Kaplan-Meier method.

Follow-up was measured from the initiation of proton radiotherapy until local recurrence, distant failure, or death; patients who had not reached the event of interest were censored at their last follow-up. Log-rank test was used to compare local control rates by the extent of surgical resection; the exact two-sided p value was computed by using StatXact 6 (Cytel, Cambridge, MA).

Ethical considerations

Institutional review board approval was obtained before record and plan review. Complete anonymity of names and medical record numbers was maintained.

RESULTS

Seventeen patients (six males, 11 females) were treated with proton radiotherapy between November 2000 and March 2006. Median prescribed dose was 55.8 CGE (range, 52.2–59.4 CGE). Age at diagnosis ranged from 13 months to 12.8 years, with a median age of 3.6 years. Thirteen patients had a gross total resection before radiation therapy, and 4 were considered to have a subtotal resection. Thirteen patients had infratentorial tumors and 4 had supratentorial tumors. Seven patients had Grade III ependymoma, and 10 patients had Grade II ependymoma. Seven patients were enrolled on the Children's Oncology Group protocol ACNS 0121. Four patients received chemotherapy. Chemotherapy was delivered after resection and before radiation therapy for 3 of the 4 patients because of gross residual disease. The other received chemotherapy after subtotal resection and was considered to have a complete response after chemotherapy; no adjuvant radiation was given at this time. This patient experienced recurrence 2 years later. At the time of recurrence, she underwent a GTR and received radiation. At a median follow-up of 26 months from the start date of radiation therapy (range, 43 days to 78 months), local control, progression-free survival, and overall survival rates were 86% ± 9% (SE), 80% ± 10%, and 89% ± 10%, respectively. Two patients experienced local recurrence and 1 patient failed distally in the thoracic spine; all other patients remain disease free. Both patients who failed locally had infratentorial tumors and subtotal surgical resections; 1 patient had a Grade III ependymoma, the other had a Grade II tumor. Subtotal surgical resection was associated significantly with worse local control ($p = 0.016$). In 1 patient, local recurrence ultimately led to death after subtotal resection and more chemotherapy. In the other patient, recurrence was diagnosed radiographically and the patient is living with the recurrent/persistent disease after radiosurgery and is on chemotherapy. The patient, who failed distally in the thoracic spine, had a Grade III tumor. This patient underwent gross total resection followed by adjuvant local field radiation therapy and currently is without evidence of disease. Endocrine, auditory, and neurocognitive data were collected for most patients. Although no late toxicity was reported to date, it is too early to conclusively report late toxicity for this group of patients.

For dosimetric comparison, two representative cases (supratentorial and infratentorial) were selected. The IMRT and IMPT plans were generated and compared with standard proton plans. All plans were normalized so that 55.8 Gy/CGE covered 95% of the CTV. Comparable tumor volume coverage was achieved with IMPT, standard (3D-conformal) proton therapy, and IMRT. Substantial normal tissue sparing was seen with the proton therapy compared with IMRT. Use of IMPT allowed for additional sparing of critical structures (Tables 1 and 2; Figs. 1 and 2). For the supratentorial plan, improvement in organ sparing with IMPT was most pronounced in the dose to the hypothalamus. Both infratentorial and supratentorial plans showed improved sparing of whole brain and temporal lobes with protons compared with IMRT. The IMPT provided further sparing of these structures. This was achieved with a decreased number of treatment fields; four with standard proton therapy and only three with IMPT.

Tables 1 and 2 list doses received by 5%, 50%, and 90% of each structure, as well as the mean dose for each structure. Figures 1 and 2 show dose–volume histograms for tumor volumes and normal structures for the infratentorial and supratentorial plans, respectively. Proton radiation therapy decreased dose to all normal structures evaluated. Less benefit was derived for normal structures directly adjacent

Table 1. Comparison of plans (IMPT, protons, and IMRT) for a representative patient with an infratentorial ependymoma

	IMPT				Protons				IMRT			
	Mean	D_5	D_{50}	D_{90}	Mean	D_5	D_{50}	D_{90}	Mean	D_5	D_{50}	D_{90}
Whole-brain CTV	6	45	<0.1	<0.1	9	48	<0.1	<0.1	13	54	2	0.4
Temporal lobe	2	13	<0.1	<0.1	4	21	<0.1	<0.1	16	48	11	1
Brainstem	24	57	16	< 0.1	33	56	37	4	39	57	47	7
Pituitary	<0.1	<0.1	<0.1	<0.1	<0.1	0.2	<0.1	<0.1	12	16	12	7
Optic chiasm	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	6	17	4	3
Left cochlea	<0.1	0.1	<0.1	<0.1	2	5	2	1	37	38	37	36
Right cochlea	29	34	29	24	35	43	36	26	43	45	43	41
Hypothalamus	<0.1	<0.1	<0.1	<0.1	0.2	1	0.1	<0.1	11	25	10	3
CTV	57	58	57	56	57	58	57	56	57	58	57	56
GTV	57	58	57	56	57	58	57	56	57	58	57	56

Abbreviations: IMPT = intensity-modulated proton therapy; IMRT = intensity-modulated radiation therapy; CTV = clinical tumor volume; GTV = gross tumor volume; D_x = Dose in gray to structures for x% of tissue volume.

Table 2. Comparison of plans (IMPT, protons, and IMRT) for a representative patient with a supratentorial ependymoma

	IMPT				Protons				IMRT			
	Mean	D_5	D_{50}	D_{90}	Mean	D_5	D_{50}	D_{90}	Mean	D_5	D_{50}	D_{90}
Whole-brain CTV	5	27	0	<0.1	7	37	0.2	<0.1	12	45	3	0.5
Temporal lobe	8	19	8	<0.1	11	30	14	<0.1	23	47	23	3
Brainstem	21	57	4	<0.1	22	56	7	<0.1	23	58	8	2
Pituitary	<0.1	<0.1	<0.1	<0.1	<0.1	0.1	<0.1	<0.1	2	3	2	2
Optic chiasm	<0.1	<0.1	<0.1	<0.1	0.1	0.3	<0.1	<0.1	3	4	3	2
Left cochlea	<0.1	<0.1	<0.1	<0.1	<0.1	0.1	<0.1	<0.1	3	4	3	2
Right cochlea	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	2	2	2	1
Hypothalamus	15	47	13	0.3	22	49	20	4	22	50	22	6
CTV	56	57	56	56	56	57	56	56	57	58	57	56
GTV	57	57	57	56	56	56	56	56	57	58	57	56

Abbreviations: IMPT = intensity-modulated proton therapy; IMRT = intensity-modulated radiation therapy; CTV = clinical tumor volume; GTV = gross tumor volume; D_x = Dose in gray to structures for x% of tissue volume.

to or encompassed by the CTV. The IMPT provided further normal tissue sparing for most structures.

Figure 3 shows axial views of the IMRT, proton, and IMPT plans for treatment of an infratentorial ependymoma. Dose distributions are shown at the level of the cochlea and temporal lobes. For the infratentorial plan, the left cochlea received a mean dose of 37 Gy with IMRT, 2 CGE with protons, and less than 0.1 CGE with IMPT. Mean dose received by the

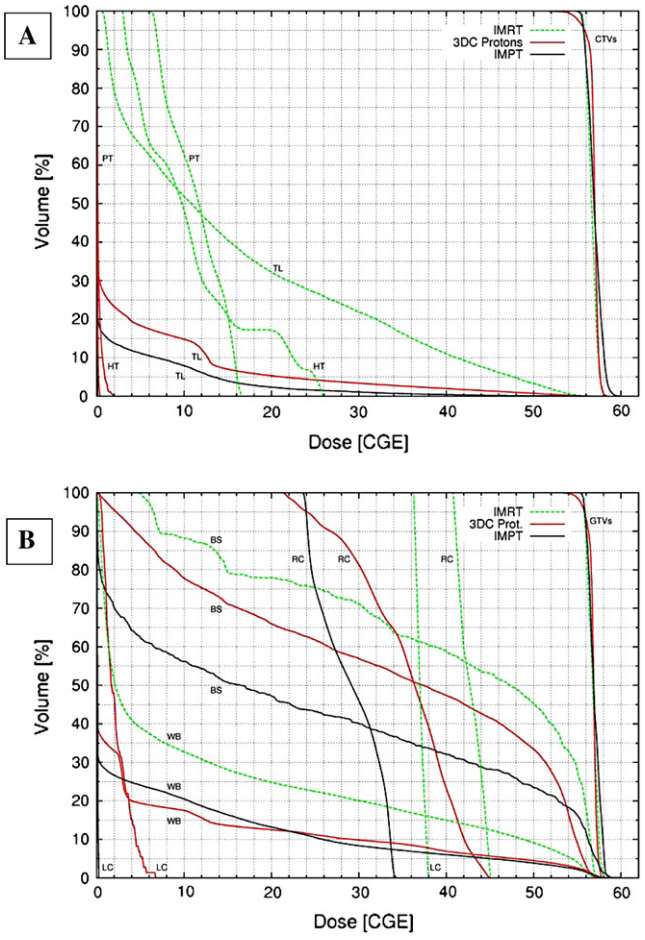

Fig. 1. Comparison dose–volume histogram (DVH) for intensity-modulated radiation therapy (IMRT), proton (3DC proton), and intensity-modulated proton therapy (IMPT) plans for infratentorial ependymoma: (A) clinical tumor volume (CTV), temporal lobes (TL), pituitary (PT), hypothalamus (HT), (B) gross tumor volume (GTV), right cochlea (RC), left cochlea (LC), brainstem (BS), and whole brain (WB).

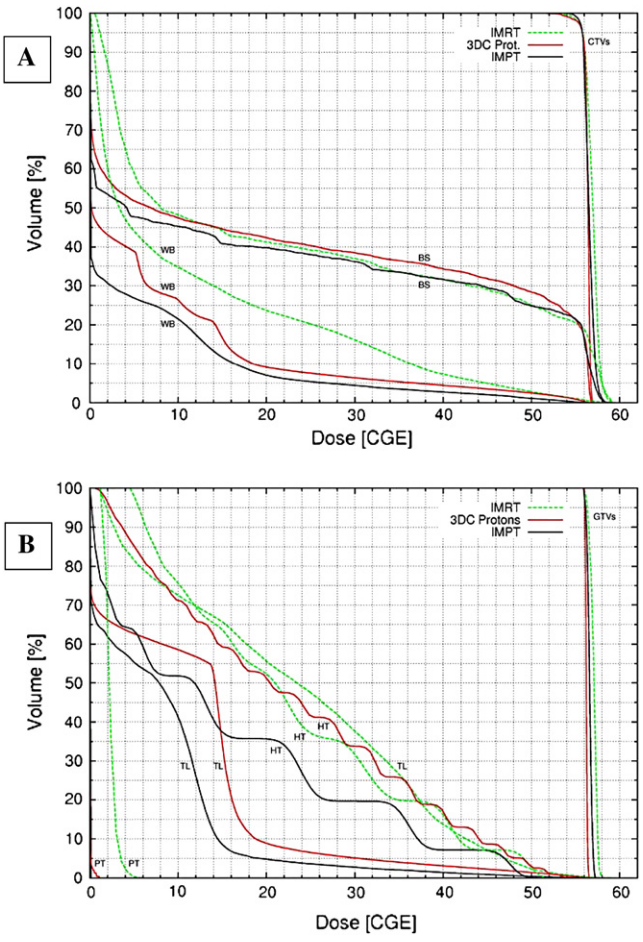

Fig. 2. Comparison dose–volume histogram (DVH) for intensity-modulated radiation therapy (IMRT), proton (3DC Prot.), and intensity-modulated proton therapy (IMPT) plans for supratentorial ependymoma: (A) clinical tumor volume (CTV), brainstem (BS), whole brain (WB), (B) gross tumor volume (GTV), temporal lobes (TL), pituitary (PT), and hypothalamus (HT).

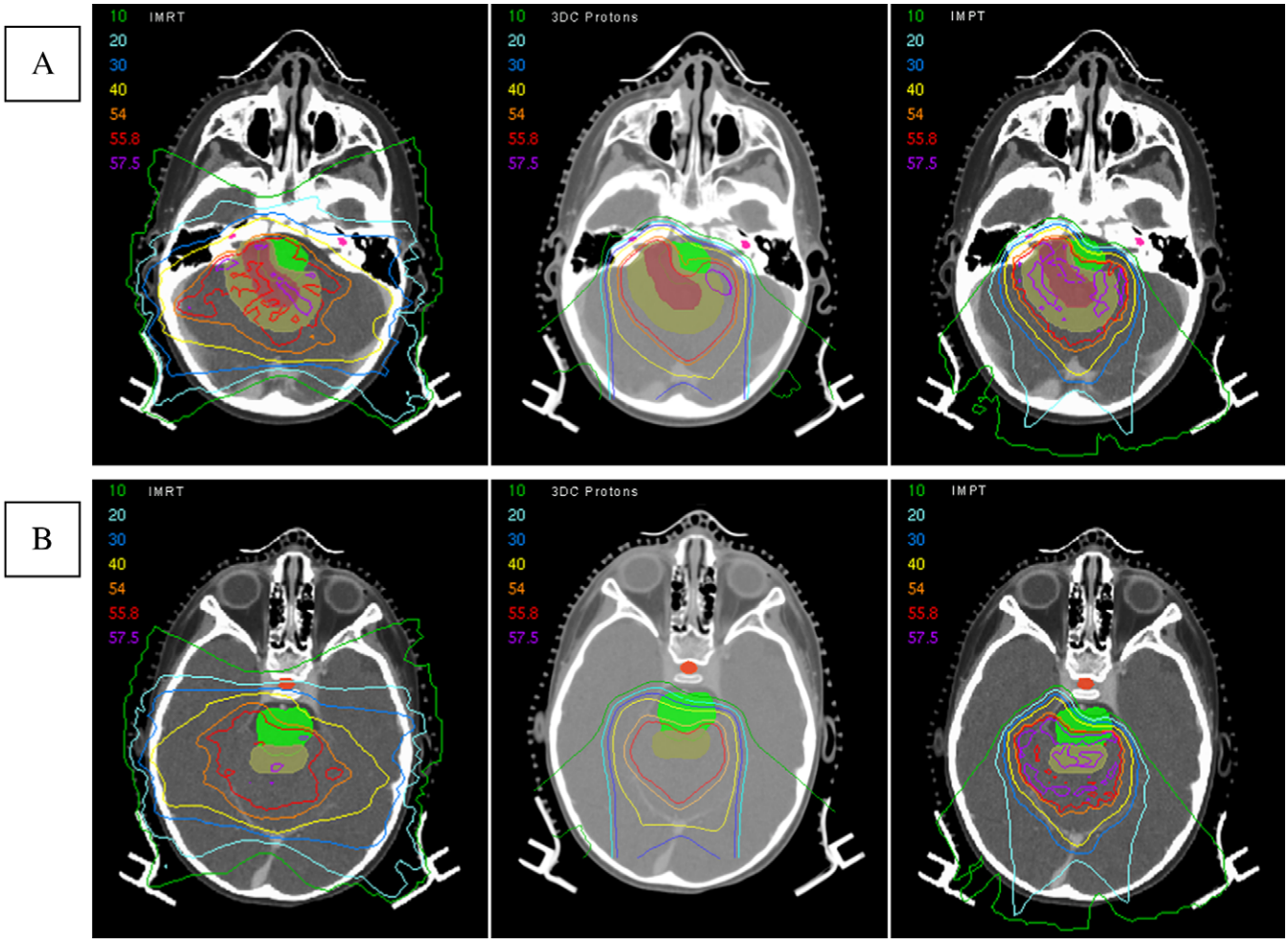

Fig. 3. Intensity-modulated radiation therapy (IMRT), proton, and intensity-modulated proton therapy (IMPT) plans shown in the axial plane at the level of the (A) cochlea and (B) temporal lobes and pituitary gland. Gross tumor volume (GTV) is shown in red, and clinical tumor volume (CTV) is shown in yellow. Protons show improved sparing of the cochlea, cerebellum, pituitary gland, and temporal lobes. The IMPT plan shows superior proximal target conformity and further sparing of structures.

temporal lobes was 16 Gy with IMRT. This was reduced to 4 CGE with protons and 2 CGE with IMPT. A similar benefit was seen with the dose received by the whole brain. Five percent and 50% of the pituitary received 16 and 12 Gy with IMRT, respectively. The dose to 5% and 50% of this structure with both proton and IMPT plans was less than 1 CGE in each case. The hypothalamus received a mean dose of 10.7 Gy with IMRT. For protons, mean dose was 0.2 CGE, and no measurable dose was delivered with IMPT. Similarly, dose to the brainstem was reduced with proton treatment. Dose–volume histograms (Figs. 1 and 2) visibly show the benefit of protons for the brain and other CNS structures. Figure 4 shows sagittal and coronal views and illustrates the rapid dose falloff of proton radiation.

Similar to the infratentorial plan, greater sparing of CNS structures was shown for proton and IMPT planning for the supratentorial case. The hypothalamus was in close proximity to the CTV for this particular case. The IMPT planning provided substantially greater sparing for this particular structure (Fig. 5).

DISCUSSION

This study shows excellent early outcomes using proton radiation for the treatment of patients with localized ependymoma. Consistent with several prior studies, we found a significant correlation between subtotal resection and subsequent local failure (6, 28). No significant late toxicity after radiation was reported to date in patients followed up since 2000. Dose distributions for proton therapy compare favorably with IMRT plans. The IMPT appears to allow for further sparing of some critical structures.

Fortunately, disease control for childhood ependymoma has improved significantly during the past several years, and the 3- to 5-year survival rate range now is 60–80% (7, 29–31). However, late side effects of radiation therapy are still worrisome for this group of patients because of the proximity of these tumors to critical tissues and the exceptionally young age at diagnosis.

Currently, the most widely available technique to minimize toxicity to normal tissue without compromising dose

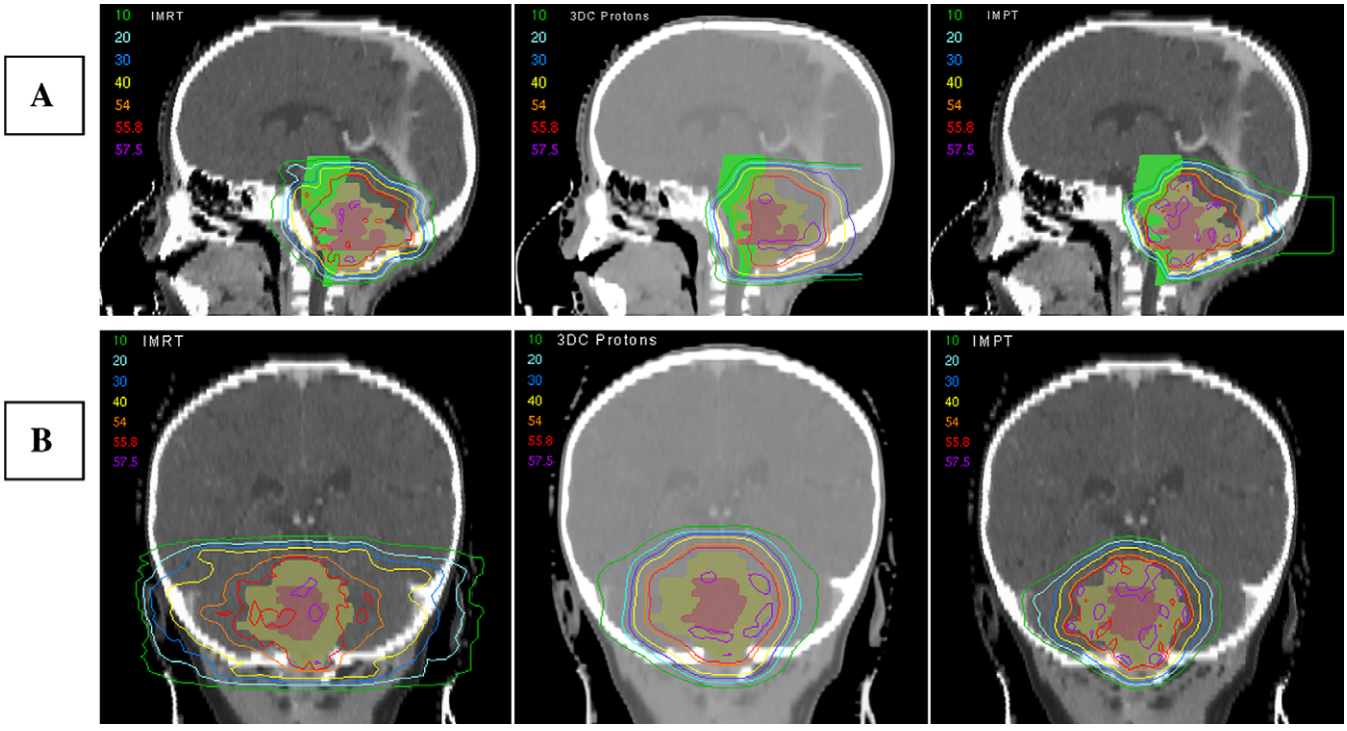

Fig. 4. (A) Sagittal views show increased conformity and complete sparing of the structures anterior to the target volume with protons and intensity-modulated proton therapy (IMPT). The IMPT plan shows further better dose shaping to the proximal target volume. (B) Coronal views show increased sparing of normal tissue lateral and superior to the tumor volume. Gross tumor volume (GTV) is shown in red, and clinical tumor volume (CTV) is shown in yellow.

to the target volume is IMRT. Proton radiation therapy is another modality available at select centers. The distinct physical properties of protons allow for complete sparing of normal tissues beyond the end range of the proton beam, and proton irradiation was shown to provide superior dose distributions for many pediatric and adult malignancies (23, 32, 33). It is accepted as a radiation treatment by many of the pediatric cooperative group trials, and its availability, while still limited, is expanding.

The techniques used for IMRT can also be applied to protons (IMPT), providing even more conformal dose distributions, further minimizing the dose delivered to normal structures and with the added advantage of decreasing neutron scatter. At present, IMPT is available for clinical

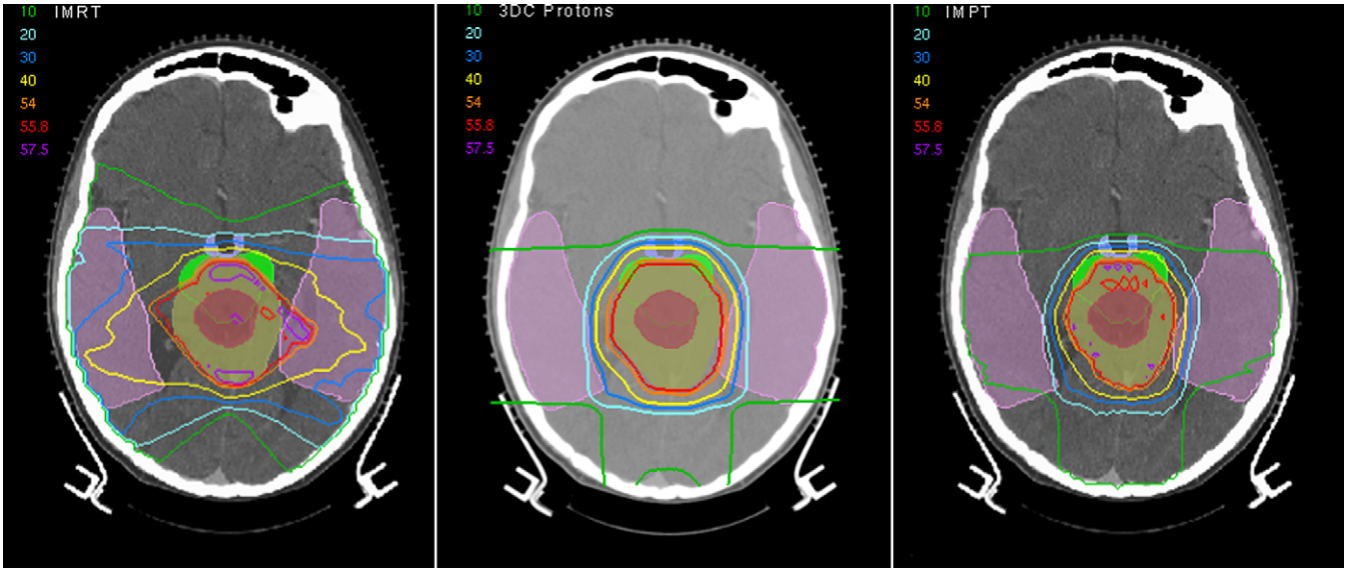

Fig. 5. Axial views at the level of the temporal lobes and hypothalamus of intensity-modulated radiation therapy (IMRT), proton, and intensity-modulated proton therapy (IMPT) plans for a patient with supratentorial ependymoma. Gross tumor volume (GTV) is shown in red, and clinical tumor volume (CTV) is shown in yellow. Protons and IMPT show increased sparing of the temporal lobes. The IMPT plan provides greater sparing of the hypothalamus.

treatment at only one institution in Europe, but its broad application is desirable because it further improves upon that which can be achieved with proton radiotherapy.

Cognitive impairment, a well-documented late toxicity of whole-brain radiation in the pediatric population, was correlated with dose and younger age of the child undergoing irradiation (34, 35). Fewer data are available about the cognitive toxicities associated with 3D conformal irradiation. Merchant *et al.* (36) recently published the effects of conformal radiation therapy on IQ in 88 children with localized ependymoma treated with conformal radiation therapy to a dose of 54–59.4 Gy. This study found that increased irradiation of specific areas of the brain (*i.e.,* supratentorial brain and left temporal lobe) correlated with lower IQ scores. In our study, proton therapy reduced the dose to 5%, 50%, and 90% of the whole brain and temporal lobes compared with IMRT. The IMPT reduced these doses even further. Additional studies are needed to better determine the effects of radiation on particular areas of the brain, but decreasing the amount of normal brain irradiated, particularly in the high-dose regions, appears to minimize neurocognitive effects of radiation.

Neuroendocrine abnormalities are another familiar complication of radiation therapy. Although it is possible for IMRT to provide some sparing of the pituitary and hypothalamus, even small doses can be significant. Reduced growth hormone secretion is the most common endocrinopathy induced by radiation and may be caused by hypothalamic or pituitary dysfunction (37). Growth hormone deficit generally occurs at a minimum hypothalamic dose of 18 Gy, but was reported at doses as low as 10 Gy for a single-fraction treatment and 12 Gy delivered in standard fractionation (38). Dosimetric evaluation of 3D conformal plans shows that although the largest effect of hypothalamic radiation is in the high-dose area, even very low doses of radiation can result in a decrease in growth hormone (39). Improved sparing of the hypothalamus was shown for both comparisons. For the patient with supratentorial ependymoma, differences in dose to the hypothalamus were marked and represented perhaps the greatest advantage for the use of IMPT. Although doses to the hypothalamus were lower for the infratentorial case, improvement was accomplished with protons and IMPT, and differences were in the range that could result in a clinical difference (maximum of 26 Gy for IMRT vs. 2 CGE for protons and 0.0 for IMPT). The typically young age and significant growth potential for children with ependymoma makes any sparing of the hypothalamic-pituitary axis desirable.

It is clear that radiation dose delivered to the cochlea causes sensorineural hearing loss. However, the dose at which this hearing loss occurs is not well documented (14). Merchant *et al.* (40) examined the effect of radiation dose on sensorineural hearing loss and concluded that the average dose to the cochlea should be kept at less than 32 Gy during a 6-week course of radiation, and preferably less than 18–20 Gy. It is possible that with longer follow-up, this dose will be even lower. In this study, we show that a marked decrease in dose to the cochlea can be achieved when proton radiation is used for the treatment of patients with infratentorial ependymoma. Mean dose to the left cochlea was 37 Gy with IMRT. Mean doses delivered to the left cochlea with protons and IMPT were 2 CGE and less than 0.1 CGE, respectively. Although an individual case will determine the amount of sparing that can be achieved of the cochlea, taken in aggregate, proton radiotherapy, with either 3D conformal fixed proton fields or with IMPT, improves upon the sparing of these important structures.

When delivering radiation therapy to the adult population, minimizing the dose to organs that are already below the normal tissue tolerance may not provide a large clinical benefit. However, for the developing pediatric patient who may live several decades after treatment with radiation therapy, the probability of late complications or radiation-induced malignancies is much greater. Miralbell *et al.* (20) assessed the potential influence of improved dose distribution with proton beam radiation and IMPT compared with 3D conformal photon radiation and IMRT on the induction of second malignancies. Treatment plans were compared for 1 patient with rhabdomyosarcoma of the paranasal sinus and 1 patient with medulloblastoma. The risk of second malignancy was estimated with a model based on guidelines from the International Commission on Radiologic Protection. The IMPT was superior to other modalities with regard to reduction in second malignancy risk. The expected risk of radiation-induced malignancy for IMPT was almost 2.4 times less than that for the conformal photon plan and about half the risk expected for IMRT. Protons (with or without intensity modulation) decreased the estimated risk compared with photon planning (with or without intensity modulation). In this study, we show that proton radiotherapy can provide superior normal tissue sparing with a decreased integral dose compared with IMRT. In these plans, IMPT provided a further decrease in the amount of normal tissue receiving radiation through beam optimization and by allowing for omission of the superior field.

Proton therapy provides similar target coverage and greater normal tissue sparing with significantly fewer beam angles. Six beams were used for the IMRT plans, four beams for the conformal proton plans, and three for IMPT plans. Decreasing the number of beam angles used simplifies the delivery of treatment, reduces the time needed for patient setup, and decreases the number of opportunities to introduce error.

The main focus of all technological advances in radiation therapy is to deliver sufficient dose to the target volume while decreasing the amount of normal tissue receiving radiation and the dose to normal tissue exposed. The ability to accomplish this task is dependent on the inherent properties of the type of radiation used and method of delivery. We report early clinical outcomes for patients with childhood ependymoma treated with proton radiation. This study clearly shows the advantages of protons over IMRT for representative patients with supratentorial and infratentorial ependymoma. Increased capabilities of delivering protons with a computer-optimized spot-scanning technique, IMPT, were also shown for these cases. The young age at diagnosis and proximity of critical structures in patients with ependymoma makes the application of proton radiation therapy a very attractive method of delivering treatment.

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CLINICAL INVESTIGATION **Brain**

PROTON RADIOTHERAPY FOR CHILDHOOD EPENDYMOMA: INITIAL CLINICAL OUTCOMES AND DOSE COMPARISONS

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Purpose: To report preliminary clinical outcomes for pediatric patients treated with proton beam radiation for intracranial ependymoma and compare the dose distributions of intensity-modulated radiation therapy with photons (IMRT), three-dimensional conformal proton radiation, and intensity-modulated proton radiation therapy (IMPT) for representative patients.

Methods and Materials: All children with intracranial ependymoma confined to the supratentorial or infratentorial brain treated at the Francis H. Burr Proton Facility and Harvard Cyclotron between November 2000 and March 2006 were included in this study. Seventeen patients were treated with protons. Proton, IMRT, and IMPT plans were generated with similar clinical constraints for representative infratentorial and supratentorial ependymoma cases. Tumor and normal tissue dose–volume histograms were calculated and compared.

Results: At a median follow-up of 26 months from the start date of radiation therapy, local control, progression-free survival, and overall survival rates were 86%, 80%, and 89%, respectively. Subtotal resection was significantly associated with decreased local control ($p = 0.016$). Similar tumor volume coverage was achieved with IMPT, proton therapy, and IMRT. Substantial normal tissue sparing was seen with proton therapy compared with IMRT. Use of IMPT will allow for additional sparing of some critical structures.

Conclusions: Preliminary disease control with proton therapy compares favorably with the literature. Dosimetric comparisons show the advantage of proton radiation compared with IMRT in the treatment of ependymoma. Further sparing of normal structures appears possible with IMPT. Superior dose distributions were accomplished with fewer beam angles with the use of protons and IMPT. © 2008 Elsevier Inc.

Ependymoma, Pediatric brain tumors, Proton beam radiation.

INTRODUCTION

Ependymomas are relatively rare malignancies accounting for 8–10% of intracranial pediatric tumors, with most cases occurring in children younger than 4 years (1, 2). One third of intracranial childhood ependymomas occur in the cerebral hemispheres. The remaining two thirds occur in the posterior fossa, arising along the lining of the fourth ventricle (3, 4). Standard treatment for patients with both supratentorial and infratentorial ependymoma consists of maximal surgical resection followed by radiation therapy (1, 5, 6). Critical structures, including the brainstem, cranial nerves, cochlea, and brain, lie in close proximity to treatment volumes, which, in addition to very young age at diagnosis, makes a highly conformal treatment most desirable.

Excellent control rates have been achieved with radiation therapy to the initially involved area of disease, which is now the accepted standard of care (7–11). Despite this reduction in treatment volume compared to historical radiation volumes, healthy uninvolved tissues receive radiation. In addition, because ependymomas occur in the very young, these patients can expect to experience worse adverse late effects from radiation therapy to the brain compared to older children or adults. Because morbidities are related to the normal tissues irradiated in the process of treating the tumor, it is of critical importance to improve dose conformity to the tumor bed. Complications of central nervous system (CNS) radiation in the pediatric population are well documented and include developmental and neurocognitive deficits, neuroendocrine

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dysfunction, growth abnormalities, sensorineural hearing loss, vascular events, and second malignancies (12–15). These late effects of treatment are a substantial source of morbidity and mortality, can impair quality of life, and affect the ability to function normally in society.

The unique characteristics of proton therapy offer major advantages in optimizing prescription dose to tumor volumes while sparing normal tissues. The chief advantage of proton radiotherapy is the sparing of normal tissue through the elimination of exit dose and reduction in entrance dose.

Currently, the majority of proton therapy is delivered through passive beam-scattering methods by using range compensators and apertures, which are custom designed to deliver a homogeneous dose distribution conforming to the distal edge of the target for each field (16). Intensity-modulated proton therapy (IMPT) refers to plans that deliver the dose to the target by the superimposition of individually *inhomogeneous* fields (17–19). The IMPT allows for increased dose-shaping capabilities with improved conformity not only at the distal region of the target, but also to the proximal target edge from a given field. At the present time, IMPT cannot be delivered efficiently with passive scattering beams alone and requires implementation of active scanning methods, which have the additional advantage of reduced neutron contamination, which may drive down the risk of second malignancy compared with passively scattered techniques (20, 21).

In this study, we report early clinical outcomes, including LRF, DFS, overall survival, and toxicities for patients with childhood ependymoma treated with three-dimensional (3D) conformal proton therapy. This represents the first report of clinical outcomes using proton radiation for pediatric CNS ependymoma. Similar to other comparative planning studies, we show the dosimetric advantage of proton radiotherapy over intensity-modulated radiation therapy (IMRT) for the treatment of childhood ependymoma by comparing dose–volume histograms for tumor volumes and normal tissues (22–24). In addition, we show that further tissue sparing may be achieved for selected patients when the techniques of intensity modulation are applied to proton therapy.

METHODS AND MATERIALS

Patients

All patients with supratentorial and infratentorial CNS ependymoma treated at the Francis H. Burr Proton Facility and Harvard Cyclotron between November 2000 and March 2006 were included in this retrospective study. Seventeen patients were identified. A dedicated planning contrast-enhanced computed tomography (CT) scan was obtained. Patients were immobilized with a custom Aquaplast facemask (WFR Aquaplast, Wyckoff, NJ). A separate high-definition magnetic resonance image (3-mm slices, no skip) was performed, and the T1 postgadolinium and/or flair sequence was anatomically registered to the CT scan by using CMS Focal Fusion software to facilitate volume definition. The tumor bed and residual tumor were contoured as the gross tumor volume. Several patients were coenrolled on the Children's Oncology Group ACNS 0121 ependymoma trial, and a 1-cm margin was added to the gross tumor volume for clinical tumor volume (CTV) as required for the protocol. For some earlier patients not on protocol, the CTV was defined as the tumor bed at risk and any area judged at risk of microscopic extension, which generally comprised a margin around that tumor bed of 1–1.5 cm. An additional margin of 8–10 mm was added around the CTV to account for both penumbra and planning target volume together, which accounts for a setup margin of approximately 3 mm. Brass apertures and Lucite compensators were custom made for each field. Daily positioning was achieved based on bony landmarks with diagnostic-quality orthogonal X-rays compared with digitally reconstructed radiographs. A computer program assists therapists in making patient couch shifts in 6 *df* to more accurately align patients (16).

The proton dose was prescribed in cobalt gray equivalent (CGE) using the relative biologic effectiveness value of 1.1 (25). Critical normal tissues were contoured for each patient. These included brainstem, optic chiasm, optic nerves, lenses, cochlea, pituitary gland, hypothalamus, temporal lobes, and whole brain. Generally accepted tolerance doses were used. If tumor was adjacent to or involving the brainstem, a small volume was permitted to exceed 54 CGE. Field arrangements were chosen to minimize dose to critical structures while maximizing target coverage. Most patients were treated with a three- or four-field technique. For infratentorial tumors, patients generally were treated with posterior-anterior, RPO, and LPO fields with a superior field only if it improved coverage and/or avoidance of such critical structures as brainstem. For supratentorial tumors, a variety of field arrangements were used depending on the location of the tumor. Only 3 patients had a cone down or boost for the purpose of decreasing the volume of brainstem receiving a dose greater than 54 CGE.

Dosimetric comparisons

For two representative cases, we compared IMRT, 3D conformal proton beam, and IMPT radiation treatment plans for a posterior fossa ependymoma occupying the fourth ventricle and extending along the right foramen of Luschka and a supratentorial ependymoma. Both patients were treated with conformal proton radiation with a rotational gantry system.

Standard proton planning was performed with XiO planning software (CMS Inc., St. Louis, MO). The Francis H. Burr Proton Therapy Center provides a rotational gantry system and maximum proton beam energy of 231 MeV. A four-field technique was used in both cases using superior, posterior-anterior, right lateral oblique, and left lateral oblique beam directions. The CTV prescription was 55.8 CGE.

To create the IMPT plan, CT data and contours were transferred to the inverse treatment planning system, KonRad Pro, developed at the German Cancer Research Center, Germany (18, 26). The scientific version of KonRad used in the present work allows optimization of dose distributions not only for photon, but also for proton radiation and carbon beam therapy. Plan optimization is performed for several irradiation fields simultaneously by using the inverse planning technique based on the Newton gradient method (27). In this study, the IMPT plan was optimized for discrete pencil beam spots by using three coplanar beam orientations with beam angles of 140, 180, and 220 for the infratentorial case. These fields were adopted from the 3D proton plan. The superior field was omitted because it did not add to the quality of the IMPT plan. Three fields were also used for the supratentorial IMPT plan. The IMRT plans were generated for both patients, again using the Konrad planning system.

Statistical analysis

Rates of local control, progression-free survival, and overall survival were estimated by using the Kaplan-Meier method.

Follow-up was measured from the initiation of proton radiotherapy until local recurrence, distant failure, or death; patients who had not reached the event of interest were censored at their last follow-up. Log-rank test was used to compare local control rates by the extent of surgical resection; the exact two-sided p value was computed by using StatXact 6 (Cytel, Cambridge, MA).

Ethical considerations

Institutional review board approval was obtained before record and plan review. Complete anonymity of names and medical record numbers was maintained.

RESULTS

Seventeen patients (six males, 11 females) were treated with proton radiotherapy between November 2000 and March 2006. Median prescribed dose was 55.8 CGE (range, 52.2–59.4 CGE). Age at diagnosis ranged from 13 months to 12.8 years, with a median age of 3.6 years. Thirteen patients had a gross total resection before radiation therapy, and 4 were considered to have a subtotal resection. Thirteen patients had infratentorial tumors and 4 had supratentorial tumors. Seven patients had Grade III ependymoma, and 10 patients had Grade II ependymoma. Seven patients were enrolled on the Children's Oncology Group protocol ACNS 0121. Four patients received chemotherapy. Chemotherapy was delivered after resection and before radiation therapy for 3 of the 4 patients because of gross residual disease. The other received chemotherapy after subtotal resection and was considered to have a complete response after chemotherapy; no adjuvant radiation was given at this time. This patient experienced recurrence 2 years later. At the time of recurrence, she underwent a GTR and received radiation. At a median follow-up of 26 months from the start date of radiation therapy (range, 43 days to 78 months), local control, progression-free survival, and overall survival rates were 86% ± 9% (SE), 80% ± 10%, and 89% ± 10%, respectively. Two patients experienced local recurrence and 1 patient failed distally in the thoracic spine; all other patients remain disease free. Both patients who failed locally had infratentorial tumors and subtotal surgical resections; 1 patient had a Grade III ependymoma, the other had a Grade II tumor. Subtotal surgical resection was associated significantly with worse local control ($p = 0.016$). In 1 patient, local recurrence ultimately led to death after subtotal resection and more chemotherapy. In the other patient, recurrence was diagnosed radiographically and the patient is living with the recurrent/persistent disease after radiosurgery and is on chemotherapy. The patient, who failed distally in the thoracic spine, had a Grade III tumor. This patient underwent gross total resection followed by adjuvant local field radiation therapy and currently is without evidence of disease. Endocrine, auditory, and neurocognitive data were collected for most patients. Although no late toxicity was reported to date, it is too early to conclusively report late toxicity for this group of patients.

For dosimetric comparison, two representative cases (supratentorial and infratentorial) were selected. The IMRT and IMPT plans were generated and compared with standard proton plans. All plans were normalized so that 55.8 Gy/CGE covered 95% of the CTV. Comparable tumor volume coverage was achieved with IMPT, standard (3D-conformal) proton therapy, and IMRT. Substantial normal tissue sparing was seen with the proton therapy compared with IMRT. Use of IMPT allowed for additional sparing of critical structures (Tables 1 and 2; Figs. 1 and 2). For the supratentorial plan, improvement in organ sparing with IMPT was most pronounced in the dose to the hypothalamus. Both infratentorial and supratentorial plans showed improved sparing of whole brain and temporal lobes with protons compared with IMRT. The IMPT provided further sparing of these structures. This was achieved with a decreased number of treatment fields; four with standard proton therapy and only three with IMPT.

Tables 1 and 2 list doses received by 5%, 50%, and 90% of each structure, as well as the mean dose for each structure. Figures 1 and 2 show dose–volume histograms for tumor volumes and normal structures for the infratentorial and supratentorial plans, respectively. Proton radiation therapy decreased dose to all normal structures evaluated. Less benefit was derived for normal structures directly adjacent

Table 1. Comparison of plans (IMPT, protons, and IMRT) for a representative patient with an infratentorial ependymoma

	IMPT				Protons				IMRT			
	Mean	D_5	D_{50}	D_{90}	Mean	D_5	D_{50}	D_{90}	Mean	D_5	D_{50}	D_{90}
Whole-brain CTV	6	45	<0.1	<0.1	9	48	<0.1	<0.1	13	54	2	0.4
Temporal lobe	2	13	<0.1	<0.1	4	21	<0.1	<0.1	16	48	11	1
Brainstem	24	57	16	< 0.1	33	56	37	4	39	57	47	7
Pituitary	<0.1	<0.1	<0.1	<0.1	<0.1	0.2	<0.1	<0.1	12	16	12	7
Optic chiasm	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	6	17	4	3
Left cochlea	<0.1	0.1	<0.1	<0.1	2	5	2	1	37	38	37	36
Right cochlea	29	34	29	24	35	43	36	26	43	45	43	41
Hypothalamus	<0.1	<0.1	<0.1	<0.1	0.2	1	0.1	<0.1	11	25	10	3
CTV	57	58	57	56	57	58	57	56	57	58	57	56
GTV	57	58	57	56	57	58	57	56	57	58	57	56

Abbreviations: IMPT = intensity-modulated proton therapy; IMRT = intensity-modulated radiation therapy; CTV = clinical tumor volume; GTV = gross tumor volume; D_x = Dose in gray to structures for x% of tissue volume.

Table 2. Comparison of plans (IMPT, protons, and IMRT) for a representative patient with a supratentorial ependymoma

	IMPT				Protons				IMRT			
	Mean	D_5	D_{50}	D_{90}	Mean	D_5	D_{50}	D_{90}	Mean	D_5	D_{50}	D_{90}
Whole-brain CTV	5	27	0	<0.1	7	37	0.2	<0.1	12	45	3	0.5
Temporal lobe	8	19	8	<0.1	11	30	14	<0.1	23	47	23	3
Brainstem	21	57	4	<0.1	22	56	7	<0.1	23	58	8	2
Pituitary	<0.1	<0.1	<0.1	<0.1	<0.1	0.1	<0.1	<0.1	2	3	2	2
Optic chiasm	<0.1	<0.1	<0.1	<0.1	0.1	0.3	<0.1	<0.1	3	4	3	2
Left cochlea	<0.1	<0.1	<0.1	<0.1	<0.1	0.1	<0.1	<0.1	3	4	3	2
Right cochlea	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	2	2	2	1
Hypothalamus	15	47	13	0.3	22	49	20	4	22	50	22	6
CTV	56	57	56	56	56	57	56	56	57	58	57	56
GTV	57	57	57	56	56	56	56	56	57	58	57	56

Abbreviations: IMPT = intensity-modulated proton therapy; IMRT = intensity-modulated radiation therapy; CTV = clinical tumor volume; GTV = gross tumor volume; D_x = Dose in gray to structures for x% of tissue volume.

to or encompassed by the CTV. The IMPT provided further normal tissue sparing for most structures.

Figure 3 shows axial views of the IMRT, proton, and IMPT plans for treatment of an infratentorial ependymoma. Dose distributions are shown at the level of the cochlea and temporal lobes. For the infratentorial plan, the left cochlea received a mean dose of 37 Gy with IMRT, 2 CGE with protons, and less than 0.1 CGE with IMPT. Mean dose received by the

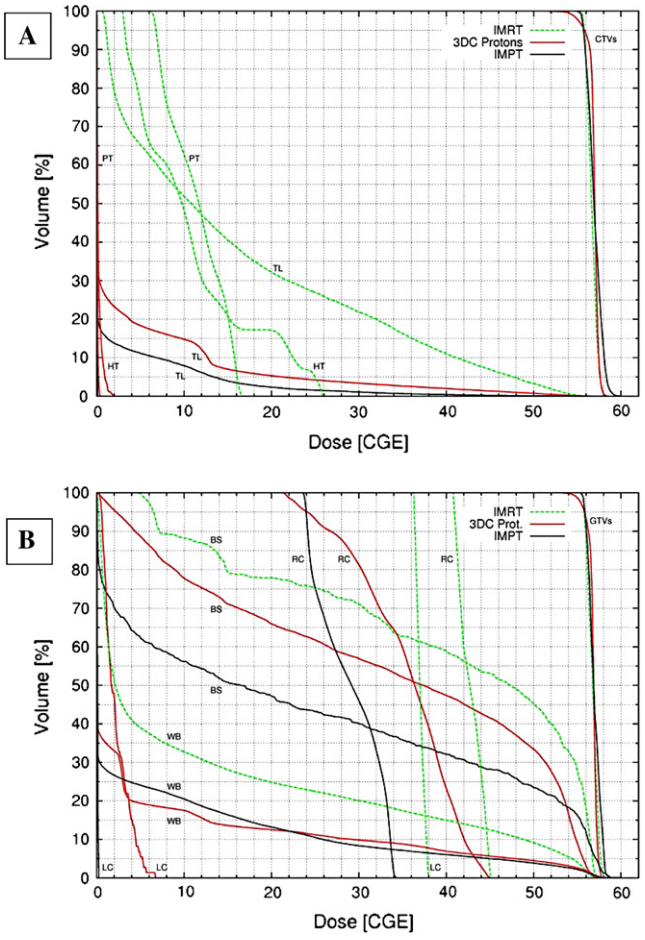

Fig. 1. Comparison dose–volume histogram (DVH) for intensity-modulated radiation therapy (IMRT), proton (3DC proton), and intensity-modulated proton therapy (IMPT) plans for infratentorial ependymoma: (A) clinical tumor volume (CTV), temporal lobes (TL), pituitary (PT), hypothalamus (HT), (B) gross tumor volume (GTV), right cochlea (RC), left cochlea (LC), brainstem (BS), and whole brain (WB).

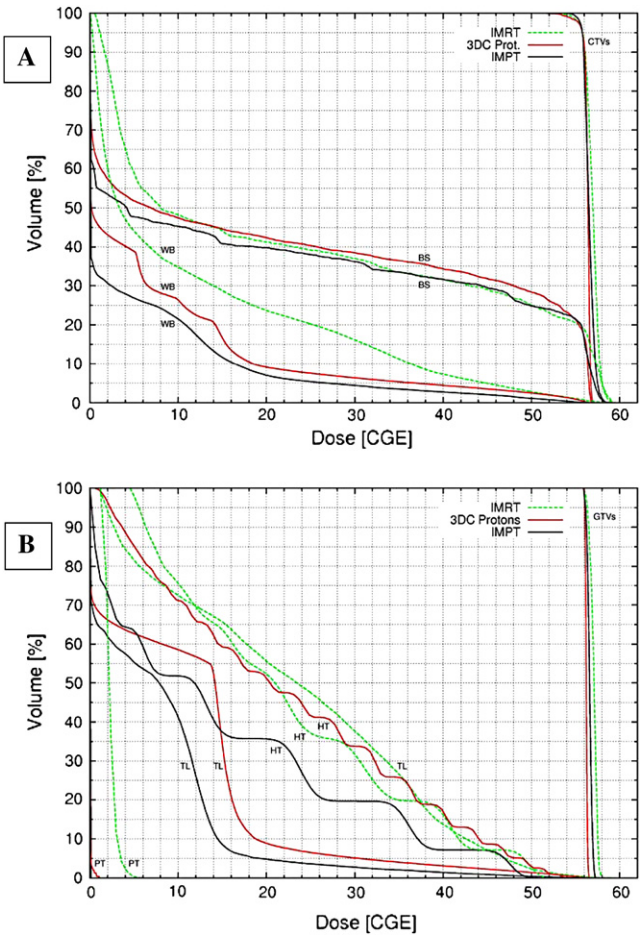

Fig. 2. Comparison dose–volume histogram (DVH) for intensity-modulated radiation therapy (IMRT), proton (3DC Prot.), and intensity-modulated proton therapy (IMPT) plans for supratentorial ependymoma: (A) clinical tumor volume (CTV), brainstem (BS), whole brain (WB), (B) gross tumor volume (GTV), temporal lobes (TL), pituitary (PT), and hypothalamus (HT).

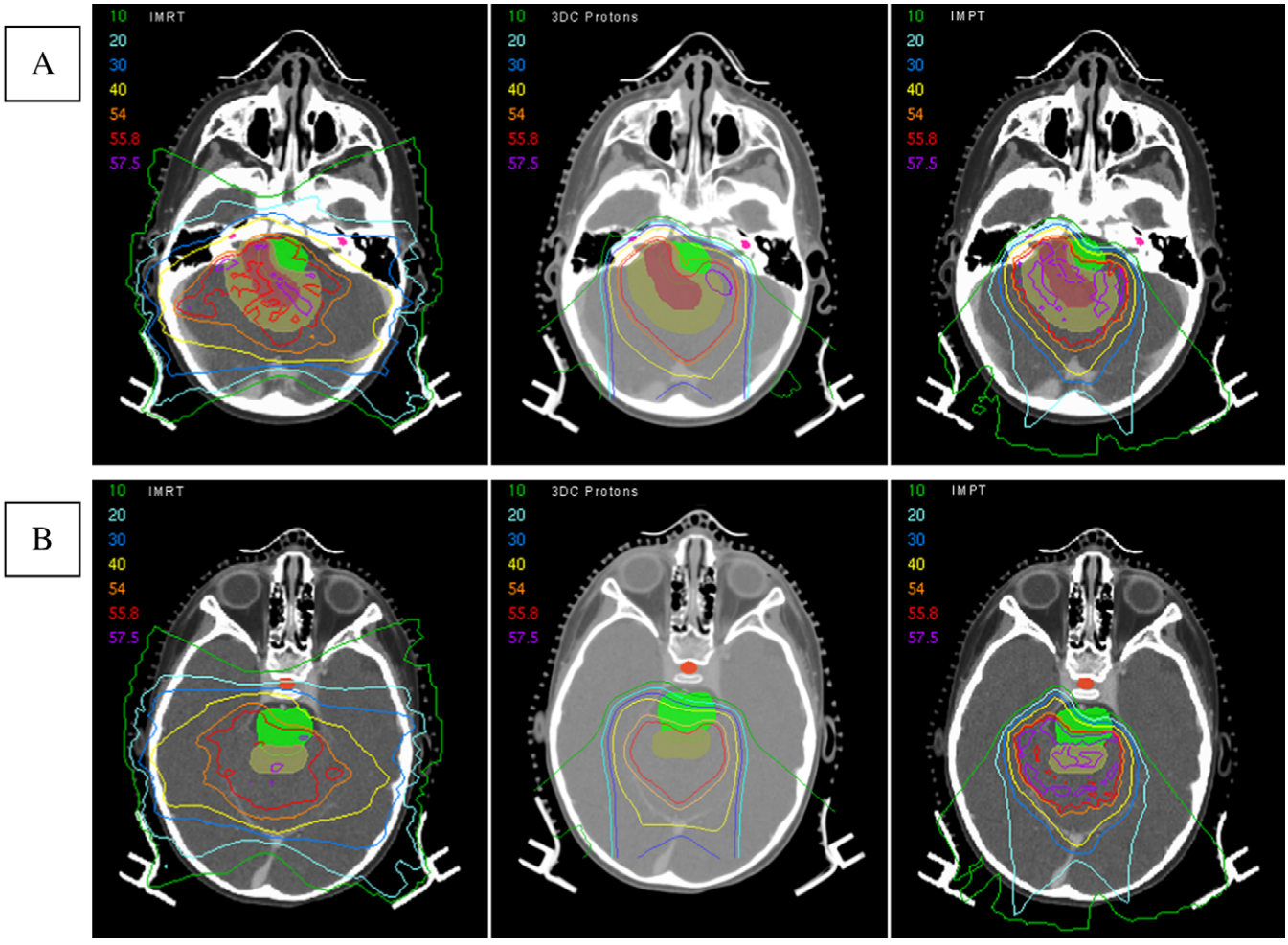

Fig. 3. Intensity-modulated radiation therapy (IMRT), proton, and intensity-modulated proton therapy (IMPT) plans shown in the axial plane at the level of the (A) cochlea and (B) temporal lobes and pituitary gland. Gross tumor volume (GTV) is shown in red, and clinical tumor volume (CTV) is shown in yellow. Protons show improved sparing of the cochlea, cerebellum, pituitary gland, and temporal lobes. The IMPT plan shows superior proximal target conformity and further sparing of structures.

temporal lobes was 16 Gy with IMRT. This was reduced to 4 CGE with protons and 2 CGE with IMPT. A similar benefit was seen with the dose received by the whole brain. Five percent and 50% of the pituitary received 16 and 12 Gy with IMRT, respectively. The dose to 5% and 50% of this structure with both proton and IMPT plans was less than 1 CGE in each case. The hypothalamus received a mean dose of 10.7 Gy with IMRT. For protons, mean dose was 0.2 CGE, and no measurable dose was delivered with IMPT. Similarly, dose to the brainstem was reduced with proton treatment. Dose–volume histograms (Figs. 1 and 2) visibly show the benefit of protons for the brain and other CNS structures. Figure 4 shows sagittal and coronal views and illustrates the rapid dose falloff of proton radiation.

Similar to the infratentorial plan, greater sparing of CNS structures was shown for proton and IMPT planning for the supratentorial case. The hypothalamus was in close proximity to the CTV for this particular case. The IMPT planning provided substantially greater sparing for this particular structure (Fig. 5).

DISCUSSION

This study shows excellent early outcomes using proton radiation for the treatment of patients with localized ependymoma. Consistent with several prior studies, we found a significant correlation between subtotal resection and subsequent local failure (6, 28). No significant late toxicity after radiation was reported to date in patients followed up since 2000. Dose distributions for proton therapy compare favorably with IMRT plans. The IMPT appears to allow for further sparing of some critical structures.

Fortunately, disease control for childhood ependymoma has improved significantly during the past several years, and the 3- to 5-year survival rate range now is 60–80% (7, 29–31). However, late side effects of radiation therapy are still worrisome for this group of patients because of the proximity of these tumors to critical tissues and the exceptionally young age at diagnosis.

Currently, the most widely available technique to minimize toxicity to normal tissue without compromising dose

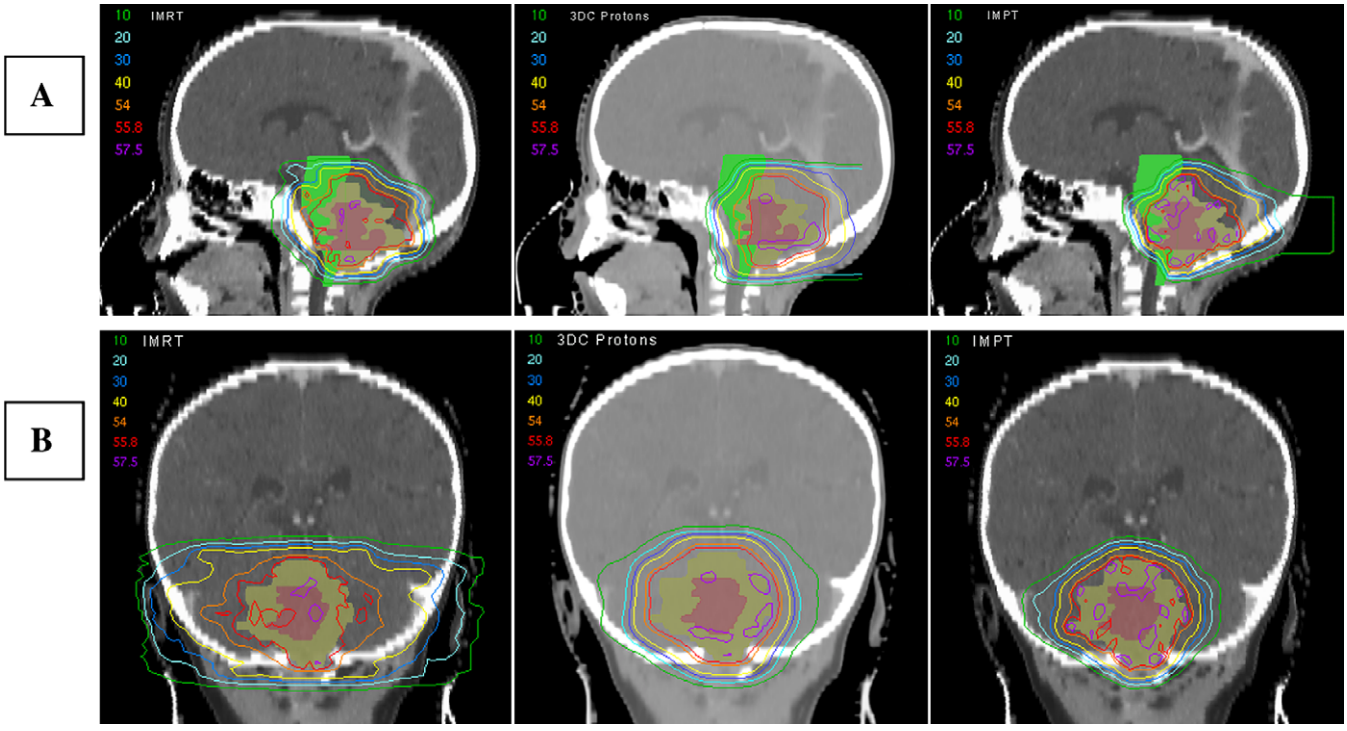

Fig. 4. (A) Sagittal views show increased conformity and complete sparing of the structures anterior to the target volume with protons and intensity-modulated proton therapy (IMPT). The IMPT plan shows further better dose shaping to the proximal target volume. (B) Coronal views show increased sparing of normal tissue lateral and superior to the tumor volume. Gross tumor volume (GTV) is shown in red, and clinical tumor volume (CTV) is shown in yellow.

to the target volume is IMRT. Proton radiation therapy is another modality available at select centers. The distinct physical properties of protons allow for complete sparing of normal tissues beyond the end range of the proton beam, and proton irradiation was shown to provide superior dose distributions for many pediatric and adult malignancies (23, 32, 33). It is accepted as a radiation treatment by many of the pediatric cooperative group trials, and its availability, while still limited, is expanding.

The techniques used for IMRT can also be applied to protons (IMPT), providing even more conformal dose distributions, further minimizing the dose delivered to normal structures and with the added advantage of decreasing neutron scatter. At present, IMPT is available for clinical

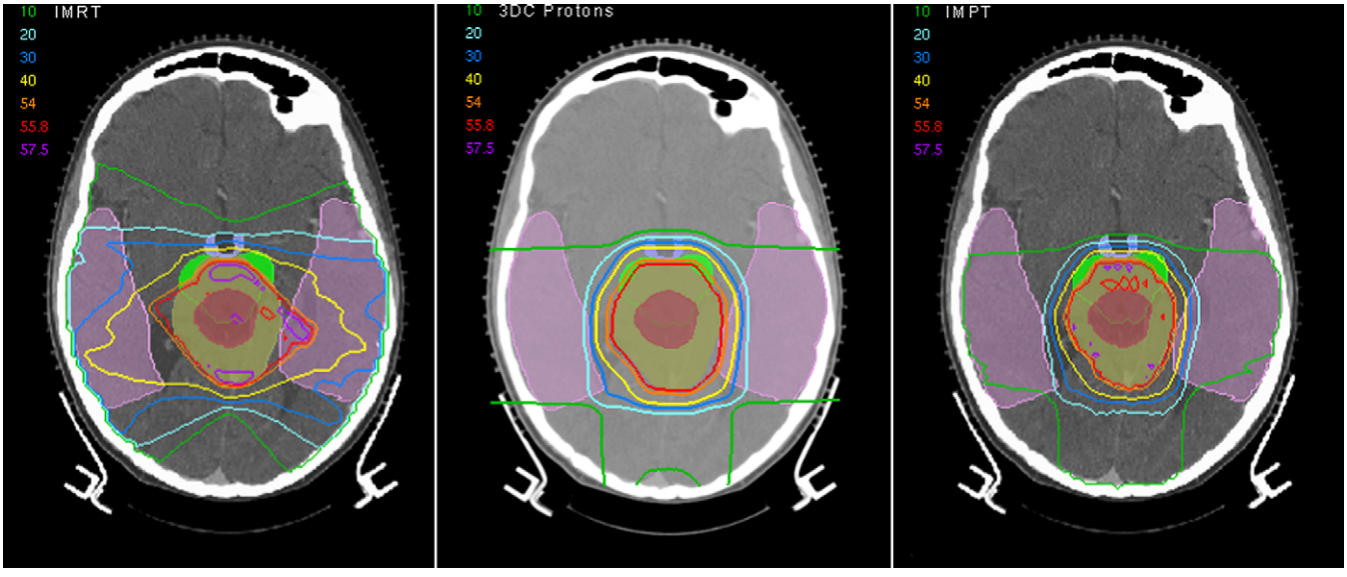

Fig. 5. Axial views at the level of the temporal lobes and hypothalamus of intensity-modulated radiation therapy (IMRT), proton, and intensity-modulated proton therapy (IMPT) plans for a patient with supratentorial ependymoma. Gross tumor volume (GTV) is shown in red, and clinical tumor volume (CTV) is shown in yellow. Protons and IMPT show increased sparing of the temporal lobes. The IMPT plan provides greater sparing of the hypothalamus.

treatment at only one institution in Europe, but its broad application is desirable because it further improves upon that which can be achieved with proton radiotherapy.

Cognitive impairment, a well-documented late toxicity of whole-brain radiation in the pediatric population, was correlated with dose and younger age of the child undergoing irradiation (34, 35). Fewer data are available about the cognitive toxicities associated with 3D conformal irradiation. Merchant *et al.* (36) recently published the effects of conformal radiation therapy on IQ in 88 children with localized ependymoma treated with conformal radiation therapy to a dose of 54–59.4 Gy. This study found that increased irradiation of specific areas of the brain (*i.e.,* supratentorial brain and left temporal lobe) correlated with lower IQ scores. In our study, proton therapy reduced the dose to 5%, 50%, and 90% of the whole brain and temporal lobes compared with IMRT. The IMPT reduced these doses even further. Additional studies are needed to better determine the effects of radiation on particular areas of the brain, but decreasing the amount of normal brain irradiated, particularly in the high-dose regions, appears to minimize neurocognitive effects of radiation.

Neuroendocrine abnormalities are another familiar complication of radiation therapy. Although it is possible for IMRT to provide some sparing of the pituitary and hypothalamus, even small doses can be significant. Reduced growth hormone secretion is the most common endocrinopathy induced by radiation and may be caused by hypothalamic or pituitary dysfunction (37). Growth hormone deficit generally occurs at a minimum hypothalamic dose of 18 Gy, but was reported at doses as low as 10 Gy for a single-fraction treatment and 12 Gy delivered in standard fractionation (38). Dosimetric evaluation of 3D conformal plans shows that although the largest effect of hypothalamic radiation is in the high-dose area, even very low doses of radiation can result in a decrease in growth hormone (39). Improved sparing of the hypothalamus was shown for both comparisons. For the patient with supratentorial ependymoma, differences in dose to the hypothalamus were marked and represented perhaps the greatest advantage for the use of IMPT. Although doses to the hypothalamus were lower for the infratentorial case, improvement was accomplished with protons and IMPT, and differences were in the range that could result in a clinical difference (maximum of 26 Gy for IMRT vs. 2 CGE for protons and 0.0 for IMPT). The typically young age and significant growth potential for children with ependymoma makes any sparing of the hypothalamic-pituitary axis desirable.

It is clear that radiation dose delivered to the cochlea causes sensorineural hearing loss. However, the dose at which this hearing loss occurs is not well documented (14). Merchant *et al.* (40) examined the effect of radiation dose on sensorineural hearing loss and concluded that the average dose to the cochlea should be kept at less than 32 Gy during a 6-week course of radiation, and preferably less than 18–20 Gy. It is possible that with longer follow-up, this dose will be even lower. In this study, we show that a marked decrease in dose to the cochlea can be achieved when proton radiation is used for the treatment of patients with infratentorial ependymoma. Mean dose to the left cochlea was 37 Gy with IMRT. Mean doses delivered to the left cochlea with protons and IMPT were 2 CGE and less than 0.1 CGE, respectively. Although an individual case will determine the amount of sparing that can be achieved of the cochlea, taken in aggregate, proton radiotherapy, with either 3D conformal fixed proton fields or with IMPT, improves upon the sparing of these important structures.

When delivering radiation therapy to the adult population, minimizing the dose to organs that are already below the normal tissue tolerance may not provide a large clinical benefit. However, for the developing pediatric patient who may live several decades after treatment with radiation therapy, the probability of late complications or radiation-induced malignancies is much greater. Miralbell *et al.* (20) assessed the potential influence of improved dose distribution with proton beam radiation and IMPT compared with 3D conformal photon radiation and IMRT on the induction of second malignancies. Treatment plans were compared for 1 patient with rhabdomyosarcoma of the paranasal sinus and 1 patient with medulloblastoma. The risk of second malignancy was estimated with a model based on guidelines from the International Commission on Radiologic Protection. The IMPT was superior to other modalities with regard to reduction in second malignancy risk. The expected risk of radiation-induced malignancy for IMPT was almost 2.4 times less than that for the conformal photon plan and about half the risk expected for IMRT. Protons (with or without intensity modulation) decreased the estimated risk compared with photon planning (with or without intensity modulation). In this study, we show that proton radiotherapy can provide superior normal tissue sparing with a decreased integral dose compared with IMRT. In these plans, IMPT provided a further decrease in the amount of normal tissue receiving radiation through beam optimization and by allowing for omission of the superior field.

Proton therapy provides similar target coverage and greater normal tissue sparing with significantly fewer beam angles. Six beams were used for the IMRT plans, four beams for the conformal proton plans, and three for IMPT plans. Decreasing the number of beam angles used simplifies the delivery of treatment, reduces the time needed for patient setup, and decreases the number of opportunities to introduce error.

The main focus of all technological advances in radiation therapy is to deliver sufficient dose to the target volume while decreasing the amount of normal tissue receiving radiation and the dose to normal tissue exposed. The ability to accomplish this task is dependent on the inherent properties of the type of radiation used and method of delivery. We report early clinical outcomes for patients with childhood ependymoma treated with proton radiation. This study clearly shows the advantages of protons over IMRT for representative patients with supratentorial and infratentorial ependymoma. Increased capabilities of delivering protons with a computer-optimized spot-scanning technique, IMPT, were also shown for these cases. The young age at diagnosis and proximity of critical structures in patients with ependymoma makes the application of proton radiation therapy a very attractive method of delivering treatment.

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Final results of the second prospective AIEOP protocol for pediatric intracranial ependymoma

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Background. This prospective study stratified patients by surgical resection (complete = NED vs incomplete = ED) and centrally reviewed histology (World Health Organization [WHO] grade II vs III).

Methods. WHO grade II/NED patients received focal radiotherapy (RT) up to 59.4 Gy with 1.8 Gy/day. Grade III/NED received 4 courses of VEC (vincristine, etoposide, cyclophosphamide) after RT. ED patients received 1–4 VEC courses, second-look surgery, and 59.4 Gy followed by an 8-Gy boost in 2 fractions on still measurable residue. NED children aged 1–3 years with grade II tumors could receive 6 VEC courses alone.

Results. From January 2002 to December 2014, one hundred sixty consecutive children entered the protocol (median age, 4.9 y; males, 100). Follow-up was a median of 67 months. An infratentorial origin was identified in 110 cases. After surgery, 110 patients were NED, and 84 had grade III disease. Multiple resections were performed in 46/160 children (28.8%). A boost was given to 24/40 ED patients achieving progression-free survival (PFS) and overall survival (OS) rates of 58.1% and 68.7%, respectively, in this poor prognosis subgroup. For the whole series, 5-year PFS and OS rates were 65.4% and 81.1%, with no toxic deaths. On multivariable analysis, NED status and grade II were favorable for OS, and for PFS grade II remained favorable.

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Conclusions. In a multicenter collaboration, this trial accrued the highest number of patients published so far, and results are comparable to the best single-institution series. The RT boost, when feasible, seemed effective in improving prognosis. Even after multiple procedures, complete resection confirmed its prognostic strength, along with tumor grade. Biological parameters emerging in this series will be the object of future correlatives and reports.

Keywords: boost, ependymoma, grade, prognosis, surgery.

While genomic, transcriptomic, and epigenetic research has recently identified particular molecular characteristics and subtypes of ependymoma that correlate with patients' clinical features, such as age and site,[1–5] clinical trials conceived and reported to date are still based on clinically prognostic factors like the extent of resection and—for some, but not all trials—patients' age and tumor grade.[6–8] The potential for developing targeted, risk-adapted therapies based on recent biological discoveries will probably be exploited over the next few years. While we await the best stratification for the future, we report here on the results obtained in 160 consecutive children between 2002 and 2014 in the second trial on intracranial ependymoma conducted by the Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP). The therapeutic strategy was based on previously obtained results[6] and aimed to improve patient outcome, focusing particularly on the subgroups with the worst prognosis.

Materials and Methods

Patient Eligibility

Children with infratentorial or supratentorial ependymoma were eligible for the study if they met the following criteria: (i) age over 3 and under 21 years old; (ii) histologically confirmed ependymoma; (iii) no prior exposure to chemotherapy (other than steroids) or radiotherapy; (iv) normal cardiac, hepatic, and renal function; (v) Lansky score >30; and (v) more than one surgical procedure before enrollment was accepted and considered part of the design to maximize resection before adjuvant treatment. In July 2006, the protocol was amended to include diagnoses in children between 12 months and 3 years of age. A second and last amendment in April 2009 prolonged patient accrual beyond 5 years. The protocol and its amendments were approved by the AIEOP and by the independent scientific and/or ethical committees of all the 17 institutions treating the children. Parents or guardians provided written consent to the children's participation in the study.

Study Design

This was a prospective, multi-institutional, nonrandomized study. The treatments administered depended on surgical outcomes and histological grade for patients with no postoperative residual disease (Fig. 1).

Pathology Review

Histological examination was centralized for all cases before patients were assigned to any treatment arm. Subependymomas were not considered in this study. Cases were reviewed according to the World Health Organization (WHO)[9] criteria by 2 of the authors (F.G., M.A), who had already provided revision for the previous series.[6]

Treatment Regimens

All patients were to undergo maximal resection. All surgical reports were reviewed centrally. Resection was deemed complete when the neurosurgeon confirmed the absence of macroscopic residual tumor at the end of the procedure and imaging

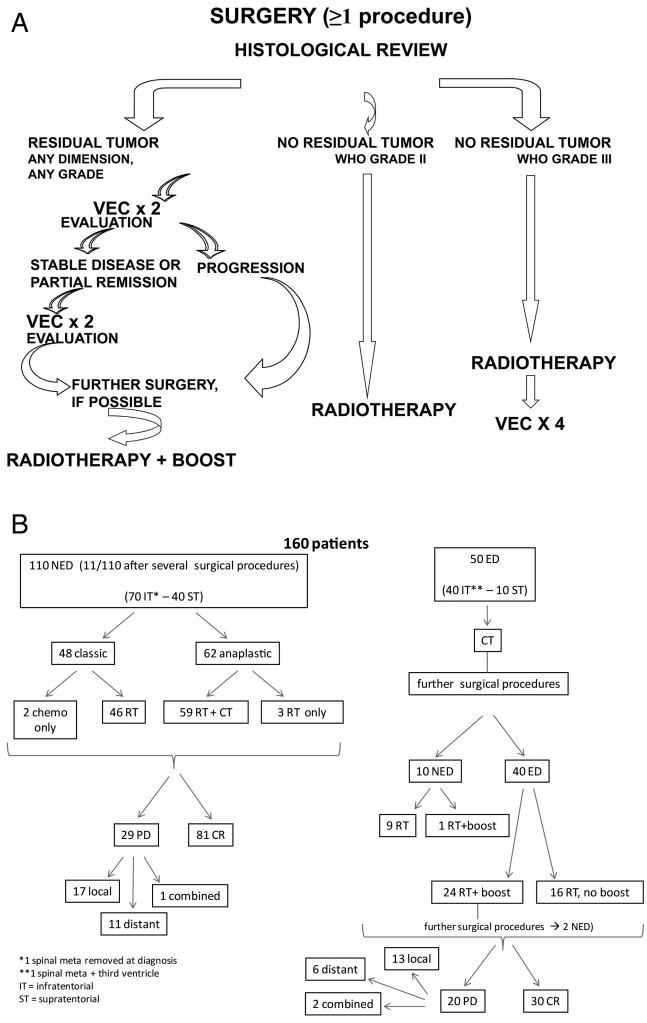

Fig. 1. (A) Treatment diagram and (B) patient flow during treatment.

documented complete/near-complete resection, essentially as it was described also in Merchant's papers on the St Jude series,[7,8] namely: gross total resection was defined as neurosurgical judgment of macroscopically complete resection and no evidence of residual tumor on MRI; near-total resection was defined as <5 mm of residual tumor in greatest dimension; and all other cases were considered as subtotal resections. Patients were then divided into 2 treatment groups by the absence or presence of visible residual disease (at least 5 mm in size) on MRI performed as soon as possible after surgery. A further stratification, identifying a third treatment arm, was applied to patients with no residual tumor, based on tumor grade (ie, WHO grade II or grade III).

(1) The aim was to start adjuvant treatment preferably within 4 weeks after surgery, but there was no time limit to begin adjuvant treatment after surgery. Three different treatment programs were adopted, depending on the extent of residual disease after surgery and on the results of upfront central pathology review, as shown in Fig. 1A. Patients achieving a gross or near-gross total excision (no evidence of disease = NED) of grade II tumors were to receive focal radiotherapy (RT) using a 3D-conformal technique, with 1.8 Gy daily up to 59.4 Gy.
(2) If patients were NED but had grade III tumors, they were also given 4 courses of vincristine, etoposide, and cyclophosphamide (VEC) chemotherapy after the same RT.
(3) Patients with residual disease (evidence of disease = ED) after surgery received a maximum of 4 VEC courses, the main aim of which was to bridge to a second-look surgery whenever possible, and received 59.4 Gy of RT followed by an 8-Gy boost in 2 fractions of 4 Gy each on any residual disease still measurable in 3 planes on MRI after chemotherapy and/or further surgery.

Since July 2006, children over 1 and under 3 years of age received the same treatment, except that the total radiation dose was lowered to 54 Gy for patients younger than 18 months, and patients with grade II tumors who were unequivocally NED after surgery could be given only 6 courses of VEC and a strict follow-up, at the local center's discretion.

The VEC regimen consisted of vincristine (1.5 mg/m^2, day 1), cyclophosphamide (1 g/m^2 infused in 1 h for 3 doses, 3 h apart, day 1), and etoposide (100 mg/m^2 infused in 2 h, days 1, 2, and 3). VEC was delivered every 3–4 weeks both before and after RT according to the general treatment plan. The use of granulocyte colony stimulating factor as a supportive treatment was optional. A central venous catheter was used to administer the chemotherapy, which was to be discontinued in the event of disease progression or unacceptable toxicity. RT was delivered using at least a 3D-conformal treatment plan and delivery technique (all intensity-modulated RT techniques, including tomotherapy and volumetric modulated arc therapy allowed). The target volumes were: the postoperative tumor bed at the primary site ± residuals after surgery for gross tumor volume (GTV); the GTV plus an anatomically confined margin of 1 cm for the clinical target volume (CTV); and a 0.3–0.5 cm geometrical expansion of the CTV for the planned target volume (PTV). The GTV had to include the edge of the resection cavity with the anatomically involved tissues, and gross residual tumor was assessed on postoperative MRI, on the sequence where it was more properly appreciated judging from its preoperative MRI features: T1 sequence ± gadolinium enhancement, T2, or (most frequently) fluid attenuated inversion recovery.

For the RT boost, the GTV coincided with all pathological tissue still measurable after surgery and chemotherapy; the CTV overlapped the GTV; and the PTV was a 0.2–0.3 cm geometrical expansion of the CTV/GTV. The boost was planned to be delivered soon after completion of the full conformal treatment.

For infratentorial tumors extending beyond the foramen magnum, the corresponding spinal cord was excluded on reaching a cumulative physical dose of 54 Gy. In all other cases, the cervical spinal cord that might be included in the PTV was excluded on reaching a cumulative physical dose of 50 Gy. Children had to be treated supine using megavoltage photons with a nominal energy ≥6 MV. Based on local policies, immobilization devices were used for all patients to ensure treatment reproducibility.

Staging and Imaging Follow-up

Disease extent at diagnosis was assessed by means of a spinal MRI and CSF cytology in all patients. If more than 4 weeks elapsed between the postoperative scan and the start of adjuvant therapy, another radiological assessment was required. For patients receiving only RT as adjuvant treatment after surgery, MRI was performed 6 weeks after RT was completed. In cases with residual disease, MRI was repeated after the first 2 courses of chemotherapy, before RT, after completing RT and before the boost, if feasible, and 6 weeks afterward. In cases undergoing second-look surgery, MRI was repeated as soon as possible after the surgical procedure. For patients with no residual disease given chemotherapy after RT, MRI was repeated after 2 courses of VEC and again 1 month after completing the treatment.

Radiological follow-up included MRI every 3 months for the first 2 years after completing the treatment, then every 4 months in the third and fourth years, and then every 6 months thereafter.

Statistical Methods

All patients were included in our analysis, regardless of whether or not they were compliant with the treatment program. The main endpoints of the study were overall survival (OS) and progression-free survival (PFS) for the whole case series. We also assessed local tumor control for the 3 treatment subgroups: (i) after conformal RT, (ii) chemotherapy and/or second-look surgery followed by RT ± boost, and (iii) chemotherapy after conformal RT. The OS time was computed as the time elapsing from the date of the first diagnostic radiological exam to the date of death due to any cause, censoring at the time of the latest follow-up for patients still alive. The PFS time was computed as the interval between the date of the first diagnostic radiological exam and the date when progression (local or distant, whichever occurred first) was identified, censoring at the latest follow-up for patients remaining in first complete remission. OS and PFS curves were estimated using the Kaplan–Meier method and compared with the log-rank test. We also separately estimated the cumulative incidence

of local and distant progression, conducting the analyses in a competing risks framework: local progression concurrent with distant progression was classified as distant progression, and the cumulative incidence curves were estimated and compared using Gray's test.[10]

Multivariable analyses were run to investigate the joint prognostic effect on OS and PFS of patient- and tumor-related characteristics, such as patients' gender and age, tumor site and grade, need for a shunt, residual tumor after first surgery, residual tumor after second-look surgery (ie, before RT), and interval between surgery and chemotherapy. For both of the endpoints investigated, the number of events (deaths or disease progressions) for each predictor variable was very low, and this hampered the reliability of the results emerging from the multivariable regression model.[11] To select the most informative variables from among the previously defined set of predictors, we therefore resorted to using "component-wise gradient boosting,"[12] as implemented in the R library "mboost,"[13] which is a machine learning method for optimizing prediction accuracy and selecting variables during the fitting process.

The association between pairs of categorical variables or between continuous and categorical variables was assessed using Fisher's exact test or the Mann-Whitney-Wilcoxon test, respectively.

Results

Patients

Between January 2002 and December 2014 (when patient accrual was stopped), 160 consecutive children with a median age of 4.9 years (range, 1–17.8 y) entered the protocol. All histological diagnoses were obtained at the local pathology service, and all tumor samples were centrally reviewed (as explained above), and treatments were tailored in the light of said review. The main characteristics of the patients in this series are given in Table 1, as a whole and by extent of resection, which was complete for 110 patients.

Tumor Location

Tumors originated supratentorially in 50 children and infratentorially in the remaining 110. At diagnosis, distant spread was identified in 2 patients with completely resected infratentorial tumors: one had further nodules in the third ventricle, the conus medullaris, and the spine at T6; the other had a cauda nodule that was removed soon after first excision of the primary tumor. Their CSF cytological examinations were negative for tumor cells, thus confirming the doubtful utility of this common diagnostic procedure.[14,15]

Extent of Resection

After initial surgery, residual tumor was documented in 50/160 (31%) children, based on combined neurosurgical reports and postoperative imaging studies.

Eleven children had achieved a complete resection after 2 surgical procedures (including the girl with the cauda metastasis). A significant association emerged between tumor location and extent of resection: residual tumor was detected in 40/110 (36.4%) infratentorial tumors, and in 10/50 (20.0%) supratentorial neoplasms ($P = .044$).

Table 1. Main patient and tumor characteristics

	Patients with NED ($N = 110$)	Patients with ED ($N = 50$)	Total Patients ($N = 160$)
Gender			
Female	46 (41.8%)	14 (28.0%)	60 (37.5%)
Male	64 (58.2%)	36 (72.0%)	100 (62.5%)
Age			
Median, y (interquartile range)	5.3 (2.8–9.3)	4.2 (2.7–7.2)	4.9 (2.8–9.1)
Under 3 y	31 (28.2%)	14 (28.0%)	45 (28.1%)
3 y or over	79 (71.8%)	36 (72.0%)	115 (71.9%)
Tumor location			
Supratentorial	40 (36.4%)	10 (20.0%)	50 (31.2%)
Infratentorial	70 (63.6%)	40 (80.0%)	110 (68.8%)
WHO grade			
Grade II/classic	48 (43.6%)	28 (56.0%)	76 (47.5%)
Grade III/anaplastic	62 (56.4%)	22 (44.0%)	84 (52.5%)
Ventricular shunt			
No	84 (76.4%)	16 (23.6%)	100 (62.5%)
Yes	26 (23.6%)	34 (68.0%)	60 (37.5%)

In 60/160 children, a permanent ventricular shunt was needed to manage hydrocephalus, and this was significantly associated with tumor location: a shunt was needed for 51/110 (46.4%) patients with infratentorial tumors, and 9/50 (18.0%) patients with supratentorial disease ($P = .001$).

Histology

Seventy-six tumors (47.5% of the sample) were defined as "classic" (WHO grade II) ependymomas, while 84 (52.5%) were "anaplastic" (WHO grade III).

The percentage of anaplastic ependymomas differed at the 2 locations: 49/110 (44.5%) tumors arising infratentorially and 35/50 (70%) of supratentorial tumors were anaplastic ($P = .004$). There was no significant difference in tumor histology between the group of NED patients, 62/110 (56.4%) of whom had anaplastic tumors, and the ED group, where 22/50 (44.0%) had the anaplastic form ($P = .173$).

Patients' Gender and Age

Gender was not significantly associated with tumor origin, extent of resection, tumor grade, or need for a shunt (data not shown).

Age was significantly associated with tumor origin: the percentage of patients with infratentorial tumors was higher among those aged <3 years (40/45 [88.9%] vs 70/115 [60.9%] patients ≥ 3 y old; $P = .001$). Age was also significantly associated with tumor grade ($P = .034$), the percentage of patients with grade III tumors being higher among those aged <3 years (30/45 [66.7%] vs 54/115 [47.0%] patients aged ≥ 3 y). The proportion of patients needing a ventricular shunt was also significantly higher among the younger patients (23/45 [51.1%] vs 37/115 [32.2%]; $P = .030$). Age was not significantly associated with the extent of resection, however ($P = .999$).

Adjuvant Treatment

Figure 1B shows the treatment diagram for the series as a whole.

Of the 110 NED children, 3 with grade III anaplastic ependymoma did not receive chemotherapy after radiation due to a local physician violating the protocol (in 2 cases) or to the patient's poor neurological conditions (in 1). Two children under 3 years of age at diagnosis with a grade II classic histology received only VEC chemotherapy after complete resection.

Of the 50 ED patients, 27 underwent further surgical procedure(s) after 1–4 courses of VEC. Number of VEC courses was not compulsory because the main chemotherapy aim, in patients with residual disease, was to bridge to second-look surgery. Complete resection was achieved in 10 cases. Another 2 patients were submitted to complete resection of tumor residuals after RT, as will be below further described.

Second-look surgery

Including second-look procedures performed soon after a first excision, before any adjuvant treatment, a total of 100 procedures were performed in 46/160 children (28.8%), with 40 patients undergoing surgery twice, 5 children 3 times, and 1 child 5 times. One of these patients had second-look surgery during RT on a cystic mass, while residual tumor was removed in 2 children 10 and 14 months after they had received the RT boost. This approach achieved an additional 23 complete resections with respect to the status after the first surgical procedure.

Of the 40 patients still with ED when their RT started, 24 had RT boosts, as per our protocol, after completing conformal RT. In one other child, a neurosurgeon prescribed the RT boost on what he contoured as an area of microscopic residual disease, even though second-look surgery had been judged complete (so this RT boost went against the protocol). Sixteen remaining children with ED did not receive the boost for the following reasons: (i) at the radiotherapist's discretion, due to a large residual tumor or anatomical constraints in 9 cases; (ii) because no residual tumor was clearly identifiable after chemotherapy in 6; and (iii) due to metastatic disease in 1.

Of the 158 patients given adjuvant radiotherapy after surgery, 140 received 59.4 Gy, another 8 children under 18 months of age at diagnosis received 54 Gy, and 8 patients received doses of 50.5–57.6 Gy, with a median of 55.8 Gy. The 2 patients with metastatic disease were treated differently. The patient with the complete resection of both the primary tumor and the spinal metastasis, who was 12 years old, received craniospinal irradiation at a total dose of 36 Gy, in 20 daily fractions of 1.8 Gy, with a boost up to 54 Gy on the primary tumor bed and up to 50.4 Gy on the secondary site. The other child, 6 years old at diagnosis, received 59.4 Gy on the primary tumor bed because the other sites were not ascertained for sure to be metastases, thereafter, when they did grow, he had surgery on the spinal nodules and received 59.4 Gy on the third ventricle metastasis and 36 Gy on the spine.

The PFS and OS of the 16 patients receiving different radiation doses on their primary tumors did not differ statistically from the other 141 patients.

Of the 2 children receiving only chemotherapy as adjuvant treatment, one was alive in continuous remission at 77 months after diagnosis, while the other had a local relapse after 19 months, was reoperated on and irradiated at the total dose of 59.4 Gy, and was alive in second remission at 118 months at the time of this report.

Treatment Toxicity

At least one neurological deficit and/or hemorrhagic or infectious episode was reported in 63/160 patients after surgery. Among those, gastrostomy or a nasogastric tube was to be put in place in 5 patients and tracheostomy in 3, while postsurgical mutism was detected in 3 cases. Adjuvant treatment began more than 6 weeks after surgery for 63/160 patients. In 36 cases, this was due to recovery from postsurgical complications, mainly low cranial nerve deficits and CSF dynamic alteration, while in the remaining 27 patients it was a referral delay. None of the patients had to abandon the adjuvant treatment due to these events. For the sample as a whole, the time elapsing between surgery and adjuvant treatment ranged from 11 to 210 days, median 42 days. This interval had no prognostic impact.

None of the children died due to adjuvant treatment.

Second-look surgery was followed by a deterioration in neurological cerebellar and lower cranial nerve function in 4/46 patients and by bleeding in 1. At the time of this report, all neurological impairments had reportedly improved.

Chemotherapy-related toxicity overlapped with the situation seen in the previous protocol when it was used before RT,[6] and did not differ when the 4 VEC schedules were administered after RT.

Progression-free Survival and Overall Survival

The median follow-up was 67 months (95% CI: 59–78 mo; interquartile range: 41–110 mo). For the whole series, the 5-year PFS and OS were respectively 65.4% (95% CI: 57.7%–74.0%) and 81.1% (95% CI: 74.6%–88.2%) (Fig. 2). The

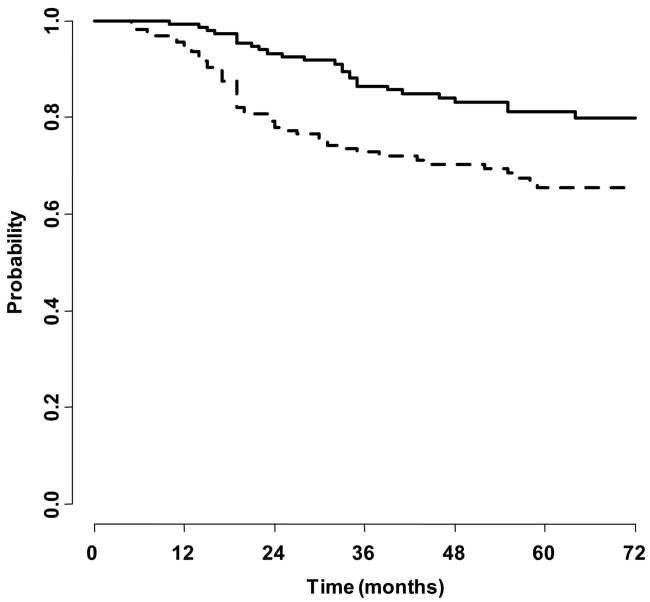

Fig. 2. Kaplan–Meier PFS and OS curves for the whole series.

5-year probability of local relapse was 20.7% (95% CI: 14.8%–29.1%) and for distant metastasis it was 13.9% (95% CI: 9.2%–21.0%). Combined relapses were detected in 3 cases, as shown by Fig. 1B.

The median time to progression was 19 months (4–103 mo), 23 months for local, and 17 months for distant relapse.

Based on the surgical results at the time of starting adjuvant treatment, the 5-year PFS and OS rates were respectively 70.8% (95% CI: 66%–75.6%) and 86.6% (95% CI: 82.9%–90.3%) for patients without residual disease, and 53% (95% CI: 39.7%–71%) and 68.6% (95% CI: 55.7%–84.6%) for patients with residual disease.

Table 2 shows the 5-year PFS and OS estimates by the different prognostic variables. Female patients had a significantly better PFS ($P = .005$) and OS ($P = .031$) than males. Having found significant results for PFS, we separately estimated the cumulative incidence of local and distant relapse. The local relapse rate was significantly lower in females (5-year cumulative incidence estimate: 3.4%; 95% CI: 0.9%–13.3%) than in males (31.8%; 95% CI: 22.9%–44.0%; $P < .0001$), while for distant metastases there was no significant difference between the 2 groups, with 16.3% (95% CI: 8.8%–30.1%) in females, and 12.4% (95% CI: 7.1%–21.7%) in males ($P = .597$).

There were no significant differences in PFS by patients' age, but the 2 groups (<3 vs ≥3 y old) differed significantly in terms of OS (Table 2). PFS did not differ significantly by tumor location either (infratentorial vs supratentorial), whereas OS did ($P = .039$). PFS was significantly better for grade II tumor patients without residual disease than for grade III tumor patients with or without residues, while the latter shared much the same PFS (Fig. 3A; $P = .025$); the OS also differed significantly between these 3 groups (see different curves in Fig. 3B; $P = .007$). Figure 1B shows the pattern of tumor relapse: there was no significant difference as regards local relapse ($P = .309$; Supplementary Fig. S1), but patients with residual disease after surgery had the highest incidence of local recurrence (5-year estimate: 28.9%; 95% CI: 17.6%–47.4%), followed by grade III tumor patients without residues (19.4%; 11.3%–33.5%) and grade II patients without residues (13.5%; 5.8%–31.7%). Distant relapses were significantly more common among patients with grade III tumors—whether they were without residues (18.7%; 10.8%–32.1%) or with residual disease (17.9%; 9.4%–34.1%)—than in grade II patients without residues (2.3%; 0.3%–16.9%) ($P = .048$). Considering grade influence on patients' PFS and OS according to tumor location, neither PFS nor OS was influenced in supratentorial tumor patients. There was instead a statistically significant difference for patients whose tumor originated infratentorially in both PFS (5-year estimate: 73.3%, 95% CI: 61.0%–88.2% if grade II; and 47.8%, 95% CI: 35.0%–65.2% if grade III, $P = .0047$) and OS (5-year estimate: 89.7%, 95% CI: 81.5%–98.7% if grade II; and 65.1%, 95% CI: 52.1%–81.4% if grade III, $P = .009$).

Considering the patients' status before RT, with a further 10 patients becoming disease free after chemotherapy and second-look surgery, the PFS and OS differed statistically between the 120 patients who were NED and the 40 who were still ED. The 5-year estimates for local relapse were 16.9%

Table 2. Kaplan–Meier PFS and OS

	PFS		OS	
	5-y Estimate (CI)	*P* (log-rank)	5-y Estimate (CI)	*P* (log-rank)
Gender		.005		.031
Female	80.3% (70.4%–91.6%)		89.3% (81.5%–97.8%)	
Male	55.8% (45.9%–67.9%)		75.7% (66.6%–86.0%)	
Age		.164		.035
<3 y	57.6% (43.1%–77.2%)		70.3% (56.3%–87.8%)	
≥3 y	67.9% (59.3%–77.8%)		84.8% (77.9%–92.3%)	
Tumor location		.116		.039
Infratentorial	60.9% (51.4%–72.2%)		77.7% (69.4%–87.0%)	
Supratentorial	73.8% (61.9%–87.9%)		88.1% (78.8%–98.6%)	
Residual disease after surgery		.025		.007
No residual grade II	84.1% (72.9%–97.0%)		97.6% (93.1%–100.0%)	
No residual grade III	61.9% (50.3%–76.1%)		79.1% (68.6%–91.2%)	
Residual, any grade	53.1% (39.7%–71.0%)		68.6% (55.7%–84.6%)	
Status before radiation therapy		.011		.001
NED	72.1% (63.8%–81.5%)		87.8% (81.5%–94.6%)	
ED	45.3% (30.9%–66.2%)		61.2% (46.5%–80.5%)	
WHO grade		.018		.031
Grade II/classic	75.3% (64.9%–87.3%)		90.5% (83.4%–98.1%)	
Grade III/anaplastic	57.0% (46.7%–69.6%)		73.3% (63.5%–84.6%)	
Ventricular shunt		.349		.019
No	68.9% (59.8%–79.4%)		85.7% (78.4%–93.6%)	
Yes	58.4% (45.5%–74.9%)		72.5% (60.6%–86.6%)	

(95% CI: 10.8%–26.4%) in NED patients and 32.5% (95% CI: 19.5%–54.0%) in still-ED patients ($P = .119$). The corresponding cumulative incidence estimates for distant metastases were 11.1% (95% CI: 6.5%–18.9%) and 22.3% (95% CI: 11.9%–41.9%) ($P = .105$).

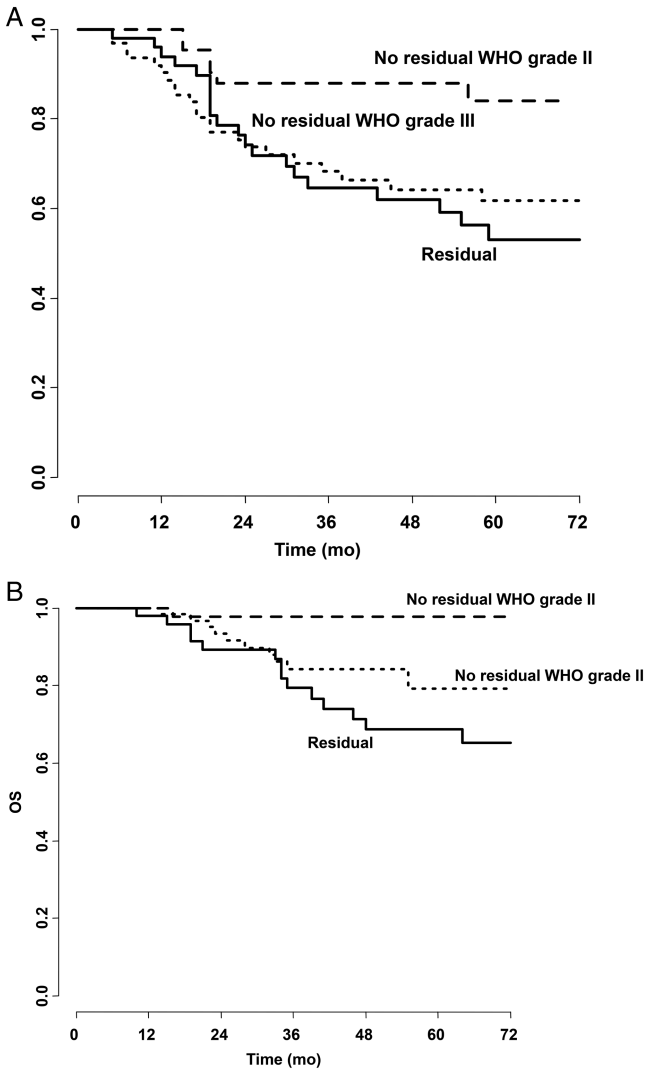

Fig. 3. (A) Kaplan-Meier PFS and (B) OS curves by outcome of first surgery.

When the 2 children who achieved NED status after RT boost were included, there were 23 patients who came to have NED after accrual thanks to multiple surgical procedures and chemotherapy; their prognoses, in terms of both PFS and OS, were much the same as for patients who had NED after a single excision (data not shown).

Among the 40 patients with ED before RT, 24 received the prescribed boost after the standard course of radiation (Fig. 1B): the 5-year estimates for PFS were 58.1% (95% CI: 39.1%–86.4%) for the latter 24 patients, and 43.0% (95% CI: 43.0%–78.6%) for the 16 not given the boost ($P = .344$), while the OS estimates were 68.7% (95% CI: 50.5%–93.4%) versus 50.2% (95% CI: 29.8%–84.6%) ($P = .346$). A WHO grade II classic ependymoma was associated with the best PFS and OS in our sample: the PFS was 75.3% (95% CI: 64.9%–87.3%) and 57.0% (95% CI: 46.7%–69.6%) for grade II and grade III tumor patients, respectively ($P = .018$); and the OS was 90.5% (95% CI: 86.8%–98.1%) and 73.3% (95% CI: 63.5%–84.6%) for grade II and grade III tumor patients, respectively ($P = .031$). The 5-year estimates for local relapse were 17.3% (95% CI: 9.6%–31.0%) in the grade II subgroup and 23.7% (95% CI: 15.6%–35.9%) for patients with ED ($P = .281$). The corresponding cumulative incidence estimates for distant metastases were 7.4% (95% CI: 3.2%–17.5%) and 19.3% (95% CI: 12.1%–30.6%) ($P = .052$). Among the 45 patients aged below 3 years at diagnosis, 16 had grade II tumors. Differently from older children, their PFS and OS were not significantly better than those of children with grade III tumors.

Table 3 shows the results of Cox's multivariate analysis, after selecting prognostic variables with the boosting algorithm. The most influential variables identified by the algorithm were the same on both of the endpoints considered, but tumor grade had the most influence on PFS, followed by gender, NED/ED status before RT, and tumor location; as for OS, the most influential variable was NED/ED status before RT, followed by tumor grade, tumor location, and gender.

Discussion

After the previous Italian experience showing quite a good prognosis for completely resected classic ependymoma,[6]

Table 3. Cox multivariate model analyses of PFS and OS

	PFS		OS	
	Hazard Ratio (CI)	*P* (Wald test)	Hazard Ratio (CI)	*P* (Wald test)
Gender		.063		.251
Male vs female	1.93 (0.96, 3.86)		1.72 (0.68, 4.37)	
Tumor location		.186		.076
Infratentorial vs supratentorial	1.59 (0.80, 3.14)		2.47 (0.91, 6.72)	
Status before radiation therapy		.058		.009
ED vs NED	1.78 (0.98, 3.22)		2.73 (1.28, 5.83)	
WHO grade		.012		.009
Grade III vs II	2.20 (1.19, 4.06)		3.03 (1.31, 6.98)	

efforts were made to improve the strategies for patients with residual disease and for the children whose prognoses remained poor even after a complete resection, that is, those with anaplastic ependymoma.[8,16] Given the renewed interest in RT in recent years, with the advent of more sophisticated RT planning and delivery techniques, allowing a dose reduction to normal tissues and improving clinical results (as described mainly in several publications by T. Merchant and colleagues[7,8]), including a reasonably satisfactory neurocognitive outcome even in the pluri-operated and the youngest children,[17] we applied the same approach to children under 3 years old.

As already reported,[18] second-look surgical procedures were undertaken on a national scale in both the first[6] and this subsequent protocol, achieving a complete resection rate of 75% without significant additional morbidity. This percentage comes very close to the 125/158 cases reported by Merchant in 2009[8] and compares favorably with other experiences,[19–21] raising hopes that a larger percentage of children may be cured. Optimal local tumor control was further pursued by using higher doses of radiation and adding hypofractionated 8-Gy boosts to local residues after surgery. At the time of writing the protocol, and more recently too, some authors were beginning to demonstrate the activity of high-dose local radiation in a few patients with residual or recurrent ependymoma. They reported achieving local control rates as high as 70%, albeit always with short follow-ups and smaller series than the one described here.[22–25] In our series, the 24 patients receiving the RT boost had a 5-year PFS higher than 58% and, for the whole group of patients with ED, it was over 53% compared with 35% in our previous report,[6] 41% for the St Jude series,[8] and <30% with the Children's Cancer Group protocol 9942,[21] which are the largest and most recent series. The difference vis-à-vis the patients achieving a complete resection persisted, however, on univariate analysis for both PFS and OS, and on multivariate analysis for OS.

We added VEC chemotherapy after RT for patients with completely resected anaplastic ependymomas, who had a worse prognosis than those with completely resected classic WHO grade II tumors in our own previous series and in those of others.[8,26] The German Hirntumoren (HIT) trials had obtained the best results in this subset of patients by using adjuvant chemotherapy with sandwich or post-RT courses.[26] Our protocol was not as successful in the 2 subgroups of patients with different tumor grades but the same surgical results: the outcome for the 2 populations remained significantly different. The role of adjuvant chemotherapy in ependymoma will only be definitively ruled out, however, after the completion of the randomized trial by the International Society of Paediatric Oncology (SIOP), which is investigating this issue.

The prognosis for children under 3 years old did not differ significantly, in terms of PFS, from that of older children treated according to the same protocol, but their OS was lower. This may be because the younger children were offered a less aggressive second treatment at relapse, whereas nowadays there is a tendency to perform further excisions and to repeat irradiation.[27–29] The use of chemotherapy-only protocols in young patients achieved very low PFS and high re-treatment rates,[19,30,31] and—barring exceptional cases—it should be abandoned, especially now that experiences of good neurofunctional outcomes after first-line irradiation have been confirmed.[8]

The better prognosis for female patients had already been noted[8,32] and correlated with a lower local relapse rate, but not with any other significant prognostic factors. A better prognosis for female patients had already been described in high-grade glioma.[33] To our knowledge, this rather peculiar difference in outcome has yet to be studied, but a correlation with still hidden biological differences between the genders has been hypothesized.

As in our previous protocol and subsequent papers,[6,20,34] we again found a strong prognostic impact of tumor grade, even on multivariate analysis. Despite inconsistency in other national series, the prognostic significance of tumor grade in our previous series was also confirmed in a multinational pathological review.[16] It is now clear that the impact of histology can emerge only if well-characterized clinical cohorts of sufficient size are selected, and relevant and reproducible histological criteria are adopted.[16,35,36] In particular, given the efforts to provide optimal adjuvant radiotherapy, it is tempting to speculate that the impact of histology detected in Italian series may relate to different radiosensitivity of WHO grade II versus grade III ependymoma.

In conclusion, in a national multi-institutional setting, and in the largest sample of ependymoma patients to be included in a prospective trial to date, we have demonstrated the feasibility of multiple surgical procedures followed by a novel radiotherapeutic approach, with a trend to outcome amelioration in children with residual disease, a patient group that carries a poor prognosis. A limitation of this study is the lack of complete observations on neurocognitive outcome, even if some evaluations have been published.[37] The recently opened SIOP trial will try, as did the previously open COG-ACNS0831 trial, to shed light on the usefulness of adjuvant chemotherapy in patients with completely resected tumors. The significance of factors repeatedly shown to be prognostic will be further analyzed in the light of genomic and molecular studies on the same series of patients in an effort to elucidate how they may be subgrouped differently, also with a view to sparing certain patient categories from adjuvant treatment.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Journal* online (http://neuro-oncology.oxfordjournals.org/).

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Conflict of interest statement. None to declare by any author.

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CLINICAL INVESTIGATION **Brain**

HYPERFRACTIONATED RADIOTHERAPY AND CHEMOTHERAPY FOR CHILDHOOD EPENDYMOMA: FINAL RESULTS OF THE FIRST PROSPECTIVE AIEOP (ASSOCIAZIONE ITALIANA DI EMATOLOGIA-ONCOLOGIA PEDIATRICA) STUDY

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Purpose: A postsurgical "stage-based" protocol for ependymoma was designed.

Methods and Materials: Children were given: (*1*) focal hyperfractionated radiotherapy (HFRT) if with no evidence of disease (NED), or (*2*) 4 courses with VEC followed by HFRT for residual disease (ED). HFRT dose was 70.4 Gy (1.1 Gy/fraction b.i.d.); VEC consisted of VCR 1.5 mg/m^2 1/w, VP16 100 mg/m^2/day × 3, CTX 3 g/m^2 d 1. When feasible, second-look surgery was recommended.

Results: Sixty-three consecutive children were enrolled: 46 NED, 17 ED; the tumor was infratentorial in 47 and supratentorial in 16, with spinal metastasis in 1. Of NED patients, 35 of 46 have been treated with HFRT; 8 received conventionally fractionated radiotherapy, and 3 received no treatment. Of the 17 ED patients, 9 received VEC + HFRT; violations due to postsurgical morbidity were as follows: HFRT only (2), conventionally fractionated radiotherapy (3) + VEC (2), and no therapy (1). Objective responses to VEC were seen in 54%; objective responses to RT were seen in 75%. Overall survival and progression-free survival at 5 years for all 63 children were 75% and 56%, respectively; for the NED subgroup, 82% and 65%; and for the ED subgroup, 61% and 35%, respectively. All histologies were centrally reviewed. At multivariate analysis, grading, age, and site proved significant for prognosis.

Conclusions: HFRT, despite the high total dose adopted, did not change the prognosis of childhood ependymoma as compared to historical series: New radiotherapeutic approaches are needed to improve local control. Future ependymoma strategies should consider grading when stratifying treatment indications. **© 2004 Elsevier Inc.**

Childhood ependymoma, Adjuvant therapy for ependymoma, Hyperfractionated radiotherapy in ependymoma.

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INTRODUCTION

Ependymoma accounts for 10% of childhood central nervous system tumors, with half the cases presenting in children below 3 years of age, and 10% to 15% as spinal tumors (1–3). Most of our knowledge derives from single-institutional series spanning many years, so it is not surprising that the conclusions of some reports are partially in conflict. Some of the many questions still under debate concern the optimal radiotherapy volumes, doses, and techniques; the usefulness of chemotherapy as adjuvant treatment; and the prognostic impact of histologic grading, patient's age, tumor site, and persistent hydrocephalus (4–7). In 1993, based on a retrospective national survey that enabled a relatively large series of ependymomas to be collected (5), a prospective single-arm study was launched with treatment stratification based on the completeness of surgical resection. Moreover, the effects of postoperative hyperfractionated radiotherapy (HFRT) were to be investigated in all patients, along with the possible role of a chemotherapy schedule containing cyclophosphamide, etoposide, and vincristine administered in children with postoperative residual disease before irradiation. Between October 1993 and May 2001, this observational protocol accrued 63 pediatric patients, and the results achieved are reported in this article.

METHODS AND MATERIALS

Patient eligibility

Children with posterior fossa or supratentorial ependymoma fulfilling the following criteria were eligible for the study: (*1*) age over 3 years and below 21; (*2*) histologically proven ependymoma; (*3*) no prior exposure to chemotherapy (except for steroids) or radiotherapy; (*4*) normal cardiac, hepatic, and renal function; (*5*) a Lansky score exceeding 30; (*6*) more than 1 surgical operation was accepted to maximize resection before adjuvant treatment. This protocol was approved by the Italian Association for Pediatric Hematology-Oncology and by the scientific and ethical committees of each institution treating the children. Children's parents or guardians provided written consent for participation in the study.

Pathology review

Histologic centralization was performed for all cases.

Ependymoblastoma, mixopapillary ependymoma, and subependymoma were not included in this study.

The cases were reviewed according to the World Health Organization criteria (8) by one of the authors (F.G.) with no information about the clinical course. For the purposes of the analysis, ependymomas were divided into Grade 2 and Grade 3 lesions, i.e., classic and anaplastic ependymoma. Grade 2 ependymoma was defined according to the microscopic features described by Wiestler *et al.* (8). Anaplastic features were defined as increased cellularity, cytologic atypia, and microvascular proliferation. Necrosis, although more frequently observed in anaplastic lesions, was not uncommon in classic Grade 2 neoplasms. Figure 1 shows the most relevant aspects of the adopted criteria.

Surgery and staging

All patients were to undergo maximal surgical resection. All operative reports were reviewed centrally. Resection was deemed complete when the neurosurgeon confirmed the absence of residual tumor at the end of the procedure, and imaging documented complete/near complete resection, according to the guidelines of the International Society of Pediatric Oncology (9), namely R1 (no visible tumor on early postoperative CT or MRI with and without contrast

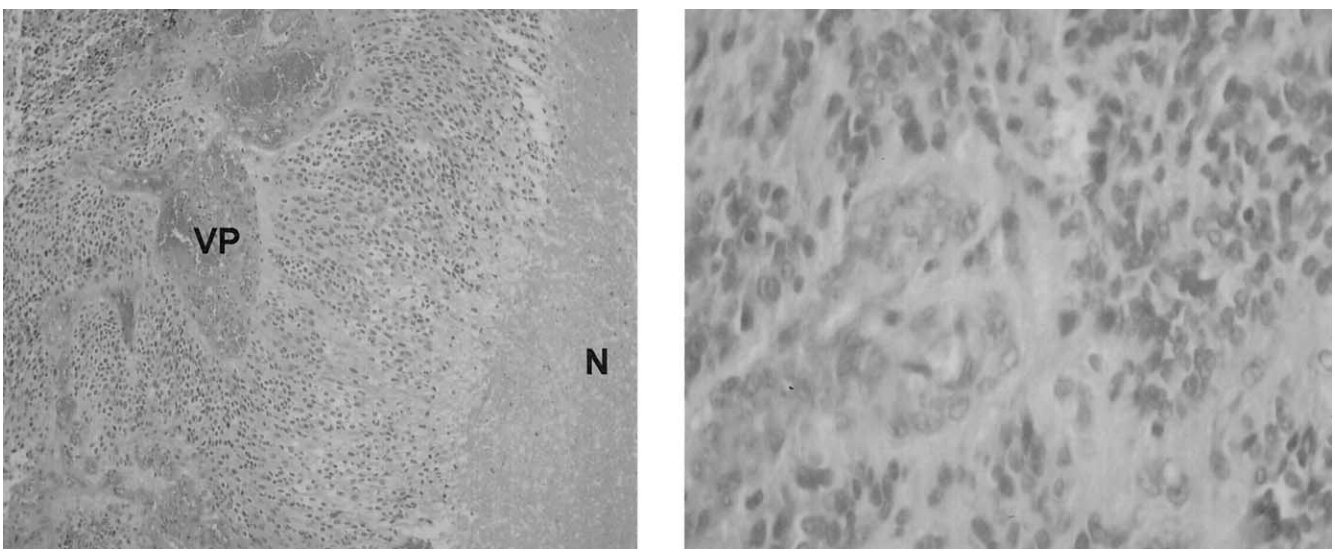

Fig. 1. (Left) Anaplastic ependymomas characterized by high cellularity and vascular proliferation (VP); necrosis (N) was not a requisite for anaplasia (H&E staining 100× power fields). (Right) Anaplastic ependymoma; focal vascular proliferation in a high cellularity area (H&E staining 400× power fields).

injection) and R2 (rim enhancement at the operation site). Patients were thereafter divided into two treatment groups according to the absence or presence of visible ($\geq$1.5 cm^2) residual disease before or after contrast enhancement on CT scan or MRI performed as soon as possible after surgery. Disease extent at diagnosis was assessed by means of a spinal MRI and cephalo-spinal fluid cytology. If more than 4 weeks had elapsed between postoperative scan and the beginning of adjuvant therapy, a new radiologic evaluation was required.

Magnetic resonance imaging evaluation was repeated after the first two courses and at the end of chemotherapy, if prescribed, before radiotherapy, and 6 weeks after its end. Tumor response evaluation followed International Society of Pediatric Oncology criteria (9), but disease reduction inferior to 50% (minor response) was included also in the amount of objective responses. Partial remissions and minor responses were defined altogether as volume reduction.

Radiologic follow-up included MRI every 3 months for the first 2 years after treatment, every 4 months for the third and the fourth year, and then every 6 months.

Treatment regimens

Adjuvant treatment was intended to be started within 4 weeks of surgery and followed two different treatment programs, according to extent of disease after surgery. Patients with postsurgical evidence of residual disease measuring at least 1.5 cm^3 received 4 monthly cycles of chemotherapy followed by HFRT, whereas children with no residual disease were given HFRT alone. Chemotherapy consisted of the vincristine, etoposide, cyclophosphamide (VEC) regimen, with vincristine (1.5 mg/m^2, Day 1; repeated on Days 8, 15, and 22 of the first and third course), cyclophosphamide (1 g/m^2 infused in 1 h for 3 doses, Day 1), and etoposide (100 mg/m^2 infused in 2 h, Days 1, 2, and 3). The use of granulocyte colony-stimulating factor as supportive treatment was optional. A central venous catheter was required for the administration of chemotherapy. MRI evaluation was repeated after the first 2 courses, before radiotherapy, and 6 weeks after its end. Chemotherapy was discontinued if disease progression or unacceptable toxicity occurred. Radiotherapy was delivered to a volume including the preoperative tumor extent plus a margin of 2 cm in all directions. The prescribed total dose of radiation was 70.4 Gy in 64 fractions of 1.1 Gy administered twice daily with a minimum 6-h interval between fractions, for a total of 32 treatment days. For tumors extending below the foramen magnum, the total dose to the spinal cord was maintained below 55 Gy. Children had to be treated with high-energy photon beams. Immobilization devices, according to local policies, were required for all patients to guarantee treatment reproducibility. Two-dimensional or three-dimensional computerized treatment plans to optimize dose distribution around the target volume were strongly recommended. Craniospinal irradiation was given exclusively in the case of proven distant spread and never for prophylactic purposes.

Statistical analyses

This observational protocol was stopped to accrual on May 2001, when the target number of 60 patients was reached. The major end points of the study were to estimate overall survival (OS) and progression-free survival (PFS) rates for the entire case series and for the two subgroups of patients with and without disease after surgery. In addition, local tumor control after high-dose HFRT was assessed, as well as tumor response to the adopted chemotherapy regimen.

All patients were included in the analysis according to the "intention to treat principle," regardless of whether they were compliant with the planned treatment program.

Overall survival rates were estimated using the Kaplan-Meier product-limit method from the day of the first radiologic diagnostic examination up until death, or to the date of the latest follow-up visit for patients who were still alive. PFS rates were estimated from the day of the first radiologic diagnostic examination up to the time of progression or the date of the latest follow-up visit for patients remaining in first complete remission (CR) (10).

The null effects hypothesis concerning the differential effect of some prognostic factors in univariate analysis was tested by means of the log–rank test (11), and all p values were two-tailed. In addition, the joint effects of the prognostic indicators—extent of residual disease and classes of age, tumor site, ventricular shunt, and grading—were investigated by a Cox regression model (12) using a backward selection procedure that retained only the variables that reached the conventional significance of 5% level. The null hypothesis of the regression analysis was tested by Wald test (13). The relative risks were estimated as hazard ratios (HR).

Follow-up data were updated as of December 31, 2002.

RESULTS

Patients

Between October 1993 and June 2001, 66 consecutive children entered the first Italian Association for Pediatric Hematology-Oncology cooperative protocol for the treatment of intracranial ependymoma. All histologic diagnoses were performed at the local pathology service, but all tumor samples were centrally reviewed by one of the authors (F.G.). Three patients were excluded because of misdiagnosis (glioblastoma multiforme in 2 patients and primitive neuro-ectodermal tumor [PNET] in 1 patient).

This group of 63 eligible patients represented an annual accrual rate of 9.3 patients, corresponding to more than 70% of all children in Italy from this age group with intracranial ependymoma.

The main characteristics of the patients are described in Table 1.

Tumor location

The tumor originated supratentorially in 16 children and in the posterior fossa in the remaining 47. In an examination

Table 1. Patient characteristics

Characteristics	Patients without residual disease (46)	Patients with residual disease (17)	Total (63)
Supratentorial	12	4	16
Infratentorial	34	13	47
Grade 2	32	11	43
Grade 3	14	6	20
Over 6 years	29	6	35
Under 6 years	17	11	28
No ventricular shunt	36	8	44
Ventricular shunt	10	9	19

of this latter group of patients, the tumor was described as adhering to the cerebellopontine angle in 27 cases and intraventricular in 17, whereas in another 3, the surgeon reported being unable to identify the origin of the tumor. At diagnosis, distant spread was found in only 1 patient with a completely resected supratentorial tumor and a spinal node located at D7. In another 2 patients, the tumor extended from the supratentorial site to the posterior fossa in 1, and from the posterior fossa to D7 in the other.

Extent of resection

After surgery, residual tumor was documented in 17 of 63 (27%) children, as assessed by combined neurosurgical reports and postoperative imaging studies.

In 16 of 46 completely resected cases, the posterior fossa tumor had reached the spine at C2.

Three children achieved complete removal of the tumor through 2 (2 cases) and 3 (1 case) operations. No significant correlation was found between tumor location and the extent of resection: Residual tumor was detected in 13 of 47 (28%) of the infratentorial tumors and in 4 of 16 (25%) of the supratentorial neoplasms.

In 19 of 63 children, a permanent ventricular shunt was needed to manage hydrocephalus. This occurred more frequently in patients less than 6 years of age (13/28 or 46%) than in older children (6/35 or 17%, $p < 0.04$).

Histology

All slides were centrally reviewed, and 43 tumors were defined as "classic" (Grade 2) tumors (68%), whereas 20 (32%) were "anaplastic" (Grade 3) according to the World Health Organization classification (8). When the reviewed diagnoses were compared with the original ones, the tumor was downgraded in three cases from Grade 3 to Grade 2 ependymoma. Concordance therefore reached 95%.

The percentage of anaplastic tumors differed at the two locations: 12 of 47 (25%) tumors arising in the posterior fossa and 8 of 16 (50%) supratentorial tumors were anaplastic. There was no difference between the group of patients completely resected, where 14 of 46 (30%) had anaplastic tumors, and the group with residual disease, where 6 of 17 (35%) had anaplastic tumors.

Treatment feasibility and compliance

We examined whether the treatment guidelines had been applied correctly. The interval between surgery and adjuvant treatment (HFRT and VEC) ranged between 23 and 130 days with a median of 41 days. This interval was not statistically different between the group of patients without (range, 24–130 days; median, 48 days) and the group with (range, 23–130 days; median, 35 days) residual disease after surgery. In some patients, a longer interval was needed to ameliorate postsurgical conditions before any adjuvant treatment was delivered; in one child included in the study, no adjuvant treatment was possible, because he suffered a basilar vein thrombosis soon after surgery and remained comatose for 73 months. Another 8 children had major postsurgical sequelae: 6 needed a permanent tracheostomy, accompanied by a percutaneous gastrostomy in 1 case; 1 suffered from iatrogenic diabetes insipidus and 1 from monolateral deafness. The scheduled chemotherapy was not adopted in 3 patients, based on the local physician's judgment that the patients' performance status was too poor, and modified (delivering oral VP16 for 4 monthly courses) in 1 child with a hematologic syndrome (protein C deficiency).

Radiotherapy was not administered to 4 of 63 patients. In 2 cases, poor postsurgical conditions prevented any adjuvant treatment; in the cases of 2 children with nonanaplastic supratentorial ependymomas, the local physician decided that surgical resection had been adequate. In 46 of 59 children, the prescribed HFRT was administered. In 13 children, a conventional fractionation (1 fraction a day, conventionally fractionated radiotherapy [CRT]) was adopted. In 2 cases, the parents refused hyperfractionation; in the patient with spine metastasis, craniospinal irradiation at 36 Gy was adopted, whereas the boost at the primary site followed the HFRT schedule at a total dose of 70.4 Gy. In the remaining 10 cases, there were logistic problems, mainly because of the young age of the patients requiring general anesthesia, in the delivery of 2 fractions per day. The median dose of CRT to tumor bed was 54 Gy.

Compliance in patients without residual tumor

When this subgroup of 46 patients is considered in detail, the main treatment violations consist of (*a*) the adoption of a CRT schedule in 8 cases, and (*b*) the omission of any adjuvant radiotherapy in another 3 cases.

The 3 children who did not receive radiotherapy were a boy with a tracheostomy and 2 children with completely resected Grade 2 supratentorial tumors, mentioned earlier, whose local oncologist decided to omit irradiation. Overall, 35 of 46 children (76%) without residual disease were correctly treated with HFRT, including 4 children who received also VEC for referral center decision.

Compliance in patients with residual tumor

As already mentioned, the proposed chemotherapy schedule was applied in full in 12 of 17 cases. In 3 children, no chemotherapy was delivered, because of postsurgical complications. In 1 child, a different schedule (oral VP16) was used, because of a preexisting protein C deficiency; in 1 patient, the second course was suspended as a result of inappropriate ADH secretion and a disturbed cardiac rhythm. One patient received 8 VEC courses for massive postsurgical residual disease. HFRT was given to 11 patients, whereas 5 were treated with CRT; 1 was not irradiated at all, because he was comatose. In all, 9 of 17 (53%) children fully complied with the protocol guidelines.

Of the 12 patients evaluable for the effect of radiotherapy—being 1 in CR after VEC and 3 after second-look surgery, as will be detailed in a further paragraph—6 had CR and 3 volume reduction (objective responses, 9/12), 1 had stable disease, and 2 revealed tumor progression at the first radiologic reevaluation.

Response to chemotherapy

We report here the response evaluated after the first 2 courses and after all the four scheduled courses. All 13 of 17 patients with residual disease treated with VEC were evaluated for tumor response to chemotherapy with MRI as scheduled. Seven of 13 had tumor volume reduction after the first two courses, and the response continued to be appreciable after the subsequent two courses, reaching a CR in 1 of 13. Five had stable disease during the first two courses and after the whole chemotherapy phase; 1 had progressive disease after the first two courses. The objective response rate was 54% (95% confidence interval [CI], 25%–81%).

Chemotherapy toxicity

In all, 48 complete 3-day chemotherapy courses were administered to 13 patients. The weekly administrations of vincristine after the first day of the first and third courses amounted to 94 of 130, and 12 of 94 were reduced to 75% of the full dose, because of peripheral neurotoxicity. Another 12 of 94 (13%) doses of weekly vincristine were reduced, because of prior severe constipation or peripheral neuropathy. Neutropenia Grade 4 NCI/CTC was reported after 11 courses, which required precautionary or therapeutic hospitalization in 9 of 11 patients; Gram+ bacteriemia was documented in only 1 patient. Seven platelet transfusions were required for piastrinopenia Grade 4 in 2 patients, and 27 packed red cell transfusions were given to 8 patients. Inappropriate antidiuretic hormone secretion and postvincristine intestinal ileum complicated the second chemotherapy course in 1 patient. None of the patients suffered toxic death after chemotherapy.

Second-look surgery

Five of the 17 patients with residual disease underwent resurgery for potentially resectable tumor after chemotherapy. Second surgery was performed after two courses in 1 patient and after all the scheduled chemotherapy in the other 4 children. Three patients consequently became disease free: In 2 cases, the tumor location was supratentorial; in 1, a spinal metastatic nodule was resected. In 2 other cases (1 stable disease after 4 courses, 1 tumor progression), the neurosurgeon achieved only a cytoreductive surgery. None of these resections was followed by permanent morbidity.

Overall survival and progression-free survival

The median follow-up of the survivors in this series was 5 years (range, 1.5–9 years). The PFS rate for all patients at 5 years was 56% (95% CI, 41%–70%) with a rate of 65% (95% CI, 49%–82%) for patients without residual disease and 35% (95% CI, 10%–61%, $p = 0.05$ [Fig. 2]) for patients with residual disease after surgery.

The OS rate for the whole series at 5 years was 75% (95% CI, 62%–88%), being 82% for patients without residual disease (95% CI, 68%–97%) and 61% (95% CI, 36%–86%, $p = 0.03$ [Fig. 2]) for patients with residual disease after surgery.

A total of 23 patients have relapsed so far at a median time of 21 months from diagnosis. Of the 12 relapses occurring in children without residual disease after surgery, 4 were local recurrence only (4 in the posterior fossa, and 1 was supratentorial). Seven relapses were outside the original site, namely in the dorsal spine (3 cases), lateral ventricle (2), basal nuclei (1), and frontal lobe (1). One local failure in the posterior fossa was accompanied by synchronous dissemination with s.c. and cervical spine nodules. Ten of the 11 children with residual disease recurred locally, 1 in the cauda. Overall, 8 of 23 (35%) relapses were remote, corresponding to 13% of the whole patient population. Table 2 analyzes relapses according to patients' characteristics, revealing a trend toward distant relapses in patients without residual disease after surgery. Mean time to local and distant failure was 25 and 22 months, respectively. The treatment protocol did not include a strategy for relapse, so salvage therapy followed the local pediatric oncologists' indications. Eleven of the 23 relapsing patients are still alive, 3 of 11 in second or further remission. Median survival after relapse is 15 months, with a range from 1 to 34 months.

Survival analyses

The results of the univariate analyses of PFS and OS are listed separately in Table 3 for the entire case series. In the entire case series, residual disease after surgery and Grade 3 were associated with a significantly higher risk of both relapse and death, whereas ventricular shunting influenced only progression-free survival, and age <6 years negatively affected overall survival. Figure 3 depicts the PFS and OS for patients with classic (Grade 2) and anaplastic (Grade 3) tumors, showing that anaplastic tumors are at significantly higher risk of both disease progression ($p = 0.0008$) and death ($p < 0.0001$). Of note, the presence of anaplasia was able to negatively influence treatment outcome in children both with and without residual disease after surgery.

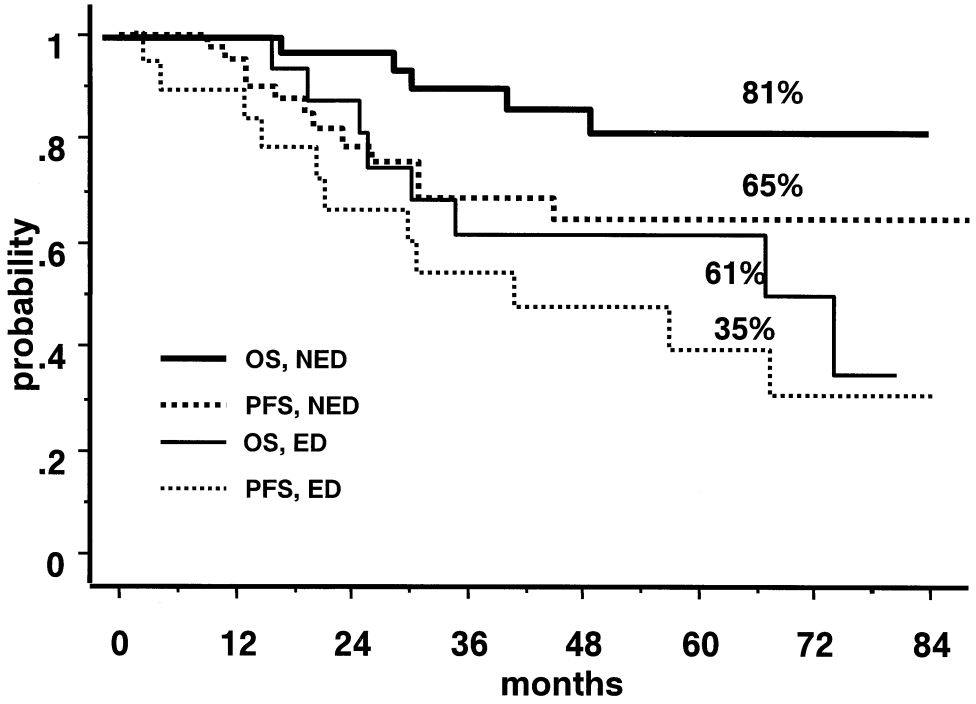

Fig. 2. Overall survival (OS) and progression-free survival (PFS) at 5 years for patients without (NED) and with (ED) evidence of residual disease

The final model of the regression analysis revealed that PFS was significantly affected by the presence of anaplastic subtype (HR: 4.9, 95% CI, 2.1–11.5; $p = 0.002$) and tumor located in the posterior fossa (HR: 4.2, 95% CI, 1.22–14.3; $p = 0.02$). The presence of anaplastic subtype influenced significantly OS (HR: 8.2, 95% CI, 2.4–27.8; $p = 0.0008$), as did age <6 years (HR: 3.8, 95% CI, 1.2–13.9; $p = 0.05$). In both models, the presence of residual disease showed only a nonsignificant trend ($p = 0.11$ and $p = 0.13$, respectively) for a higher risk of both disease progression and death.

Table 2. Main characteristics in relapsed patients

Characteristics (23)	Local failure (14)	Distant failure (8)	Local + distant (1)
Patients without residual disease (12)	4	7	1
Patients with residual disease (11)	10	1	0
Grade 2 (11)	8	3	0
Grade 3 (12)	6	5	1
Over 6 yr (9)	4	4	1
Under 6 yr (14)	10	4	0
No ventricular shunt (12)	6	5	1
Ventricular shunt (11)	8	3	0
Supratentorial (3)	3	0	0
Infratentorial (20)	11	8	1

DISCUSSION

The management of intracranial ependymoma is still a controversial topic in pediatric neuro-oncology and may range among institutions from surgery alone to a combination of surgery, radiotherapy, and chemotherapy (2, 3, 7, 14–16). The lack of uniformity is partially justified by the disappointing results reported by the majority of series. The 5-year survival for children with ependymoma ranges between 30% and 50% with a worse prognosis for patients with residual disease after surgery. In many series reported so far, the annual accrual rate does not exceed 3 to 8 patients, and this paucity contributes to uncertainties regarding the optimal treatment.

The main challenge in treating ependymoma is local relapse, which accounts for the vast majority of failures. Ependymoma has consequently been considered a “surgical disease” where completeness of excision can be reached in about half of the cases (3, 5, 6, 14). After reviewing and reporting on an Italian series of 92 children treated over 17 years, we were retrospectively able to identify the presence of residual disease as the only prognostic factor at multivariate analysis. Overall survival was 70% for patients who were disease free after surgery and 57% for patients who had residual disease; PFS was 32% and 11%, respectively (5).

The present protocol was therefore designed with two different treatment strategies for patients with and without residual disease. The addition of radiotherapy for all patients was based mainly on historical data that left many questions still unanswered (3, 7, 17). Considering the results

Table 3. Five-year overall survival and progression-free survival rates for all patients (*p* values are two-tailed according to log–rank test)

	n	%PFS (95% CI)	*p*	%OS (95% CI)	*p*
Residual disease after surgery					
Absent	46	65 (49–82)	0.05	82 (69–97)	0.031
Present	17	35 (10–61)		61 (36–86)	
Age					
>6 years	35	64 (45–83)	0.07	85 (70–100)	0.02
<6 years	28	46 (25–68)		64 (43–84)	
Site					
Supratentorial	16	76 (52–99)	0.08	84 (63–100)	0.24
Infratentorial	47	48 (30–65)		71 (55–87)	
Ventricular shunting					
No	44	66 (50–82)	0.05	78 (62–94)	0.08
Yes	19	36 (11–60)		68 (45–91)	
Grading					
Grade 2	43	66 (50–83)	0.0008	87 (76–99)	<0.0001
Grade 3	20	30 (5–55)		40 (10–69)	
Total	63	56 (41–70)		75 (62–88)	

Abbreviations: PFS = progression-free survival; OS = overall survival.

reported by Vanuystel and Brada (18), concluding that the risk of spinal seeding was uninfluenced by the extent of radiotherapy volume (local vs. craniospinal radiotherapy), we opted for local radiotherapy, which has become a standard postoperative treatment in the majority of institutions (14, 19, 20) Hyperfractionated radiotherapy was adopted in the attempt to increase the chances of local tumor control in both treatment groups throughout the delivery of a higher total dose (70.4 Gy) as compared with conventional treatments (54–56 Gy), without increasing late damages on normal brain tissues. The preliminary results reported by Needle *et al*. on a monoinstitutional series of 19 patients were indeed very favorable, with a PFS of 72% at 5 years after systemic chemotherapy and HFRT at a total dose of 72 Gy (21).

As for chemotherapy, the only randomized study published to date, which adopted vincristine and lomustine, concluded that this regimen did not improve survival (22). Among other drug combinations, the "8 in 1" regimen, MOPP and etoposide-carboplatin, have been disappointing (3, 23), whereas the best response rate so far has been reported by Duffner *et al*. with the Pediatric Oncology Group (POG) "baby brain" protocol (24): The combination of vincristine plus cyclophosphamide, alternating with eto-

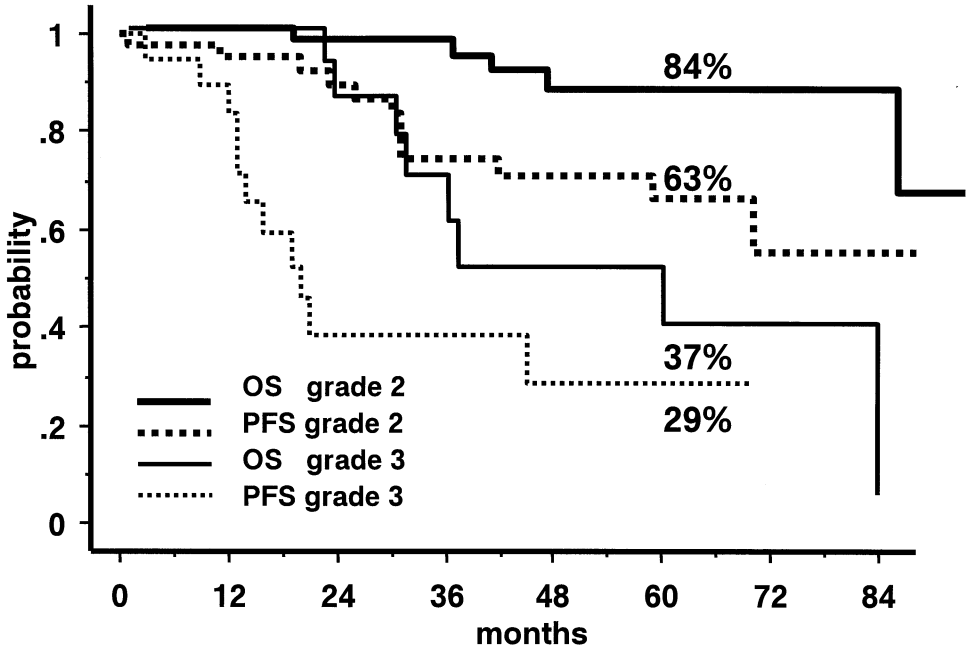

Fig. 3. Overall survival (OS) and progression-free survival (PFS) at 5 years for patients with Grade 2 and Grade 3 subtypes.

poside and cisplatin, obtained an objective response of 48%. In said study, moreover, delaying radiotherapy until after quite a long chemotherapy schedule (12–24 months) did not seem to interfere with the outcome of radiotherapy. We have adopted a schedule with a higher dose of cyclophosphamide, aiming to improve dose intensity and thus overcoming the chemoresistance of ependymoma (4) and obtaining a better local control in children with residual disease.

Our series compares fairly well with the largest reported so far, with an annual accrual rate of over 9 patients, even excluding children below 3 years of age (1, 3, 5, 7, 17).

The tumors completely or nearly resected amounted to more than 70%, and this proportion is among the highest currently reported (17). This difference in comparison to other series can be explained by the strong inclination among neurosurgeons to remove the tumor completely, much of the disease prognosis being dependent on optimal excision (26). The goal of complete tumor removal was therefore pursued, with even second-look resections being adopted either after an early postoperative scan or later on, after chemotherapy and before radiotherapy. This approach is, in other authors' opinions as well as ours, wiser than a single "heroic" and probably more harmful surgery that can lead to severe sequelae (27–29). In our series, 4 children received no therapy after surgery, because of "first-line" surgical morbidity, whereas none of the 8 second-look operations were complicated by sequelae. Ventricular shunting was necessary in about 30% of patients to manage hydrocephalus, even in the presence of complete resection. The number of shunts directly correlated with the patient's age, being more numerous in children under 6 years old. When dealing with ependymoma, complete resectability depends on the skill of the operator, of course, but also on the characteristics of the tumor itself (27, 30, 31): In fact, infratentorial ependymoma in more than 50% of cases (32, 33) (54% in our series) involves the cerebellopontine angle intimately related with the cranial nerves. Finally, the resectability of ependymoma may reflect also a favorable tumor biology determining a noninfiltrating growth pattern (17, 30, 34).

One-third of the tumors were classified as Grade 3 or anaplastic. In the literature, the histologic distribution is very heterogeneous, with some series containing a high percentage of anaplastic tumors (6, 17), especially if they include children below 3 years of age, whereas other series reported only Grade 2 tumors (21, 25, 34, 35). In our series, a centralized review of the specimens revealed a good consistency among pathologists (95%).

When we considered patients who received chemotherapy, whose activity in patients with evidence of disease was one of the end points of the strategy adopted, our results documented a potential role of VEC in ependymoma with an objective response rate reaching 54%. The role of chemotherapy in newly diagnosed ependymoma remains a matter of debate, however. As Duffner *et al.* (24, 36, 37) have already pointed out, the real question is related not to the chemo-sensitivity of this tumor, which we and other authors have identified (38–40), but to the curative capability of chemotherapy, because children with ependymoma tend to develop progressive disease after several years, in striking contrast to other pediatric tumors, which usually recur early. Most studies employing chemotherapy, however, have contributed little to our understanding of the activity of the drugs adopted, because the drugs were used soon after radiotherapy (16, 21, 43), or regardless of the presence of measurable disease (5, 22). A recent hypothesis, also stemming from the issue of the "baby" protocols (6, 37), is that chemotherapy could facilitate a subsequent second surgical approach, not only because of reduction or stabilization of tumor volume, but also for the time left to the recovery from postsurgical morbidity (4, 23, 41) and maybe because the residual tumor becomes more circumscribed and amenable to resection (28), i.e., less infiltrating vital structures.

Radiotherapy achieved a response in 9/12 evaluable patients. These results confirm the effect of radiation treatment in ependymoma (42) and also in the presence of residual disease. Local failures have not been prevented by adopting the hyperfractionated schedule, however, or by delivering a high total dose in the vast majority of cases. Despite several studies supporting a dose–response relationship in radiation therapy for ependymoma (19, 25, 27), the schedule we adopted has not dramatically improved local control compared to historical series, especially in patients with residual disease and anaplastic histology.

Thirteen percent of all patients relapsed outside the radiotherapy fields; in 7 of 8 of these cases, the primary tumor had been completely resected. Isolated metastatic relapses have been reported by other authors in 3% to 15% of cases (3, 14, 24, 43), despite the adoption of craniospinal radiotherapy (15, 16) and despite different total radiotherapy doses and fractionations (44–46).

An infratentorial origin and age less than 6 years were associated with a worse prognosis. These clinical features are recognized as risk variables, regardless of tumor malignancy and extent of resection, by other authors, as well (15, 29, 45, 47). In our series, age correlated with the need for ventricular shunting, maybe as a result of the more difficult surgical approach in smaller patients, because of a "plastic" tumor growing peripherally, displacing or involving vessel and nerve structures in the subarachnoid space (32, 33, 48).

Anaplastic subtype and posterior fossa origin indicated higher risk of relapse and death. The standard grading criteria for ependymoma in the literature are controversial, and their prognostic significance remains debatable (1, 5, 7, 14, 24, 46). In a recent comment on histologic classification and prognostic criteria, Packer (49) observed that the lack of an accepted grading system prevents any conclusions as to the histologic features that are more prognostic. In our series, histologic grading was the most powerful prognostic indicator: Grade 2 tumors obtained a PFS of 66% and an OS of 87%, whereas anaplastic ependymoma reached only 29% and 37% for PFS and OS, respectively. The same pathologic criteria, adopted in a recent paper by Merchant *et al.* on a

retrospective series, revealed the same prognostic impact of grading (50).

The different prognostic criteria adopted in the classification of risk categories for intracranial ependymoma have contributed in the past to determining very different treatment approaches in the few prospective studies published so far. There are patients whose treatment has been tailored according to tumor grade, resulting in more aggressive strategies being adopted for the anaplastic histotype (16); other patients are treated according to the tumor's site of origin (2, 34) or the patient's age at diagnosis (6, 24). Some children are treated on the basis of surgical results, as they are in our series (27). It may be that each of these approaches determines a different trend in the natural history of the disease or, more probably, that we are dealing with different diseases, all grouped under the same name, ependymoma. We would argue that, based on what molecular biology has revealed for other pediatric cancers, e.g. acute leukemia or neuroblastoma, cytogenetic and molecular biology studies might disclose new features of this tumor. With that event, we will be able to consider new, more reliable features for modeling more satisfactory treatment strategies, in addition to the various clinical and histologic aspects already outlined, for intracranial ependymoma.

We conclude that, to the best of our knowledge to date, surgery remains the main treatment tool for ependymoma, but it should be modeled in a prospective setting to suit the patient's neurologic conditions, in one or more operations, to avoid losing the chance to implement subsequent treatment for the morbid effects of surgery. VEC chemotherapy could be more widely explored, considering its at least partial efficacy in the small series of patients that we have treated. VEC features a substantial lack of severe toxicity and the possibility of rendering a second surgical approach more successful in terms of patient morbidity, though this result has been proven in only a minority of patients. The VEC schedule, like other chemotherapy regimens adopted so far, is not, however, the key to the cure of ependymoma. As for radiotherapy, HFRT does not seem to have had a determinant therapeutic impact as compared to historical controls. New radiotherapy treatment techniques such as three-dimensional conformal radiotherapy may allow the delivery of high radiation doses focused to small volumes while sparing significantly the surrounding normal brain and improving the therapeutic ratio; therefore, patients with poor prognosis should benefit from the application of these techniques (19, 42, 46).

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Both Location and Age Predict Survival in Ependymoma: A SEER Study

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Background. Studies have suggested that supratentorial ependymomas have better survival than infratentorial tumors, with spinal tumors having the best prognosis, but these data have been based on small samples. Using a population-based registry of ependymomas, we analyzed how age, gender, location, race and radiotherapy influence survival in children. ***Methods.*** We queried the Surveillance Epidemiology End Results database (SEER-17) from 1973 to 2003, strictly defining ependymomas by histology. Site codes were used to distinguish between supratentorial, infratentorial, and spinal tumors when available. Outcomes were compared by location, age, gender, race and radiotherapy, using Kaplan–Meier analysis and logrank tests. Cox regression was completed, incorporating all significant covariates from univariate analysis. ***Results.*** Six hundred thirty-five children were identified with an overall 5-year survival of 57.1 ± standard error (SE) 2.3%. Increasing age was associated with improved survival ($P < 0.0001$). Five-year survival by location was 59.5 ± SE 5.5% supratentorial, 57.1 ± SE 4.1% infratentorial and 86.7 ± SE 5.2% spinal. Radiotherapy of the infratentorial tumors resulted in significantly improved survival in both univariate analysis (logrank $P < 0.018$) and multivariate analysis restricted to this tumor location ($P = 0.033$). Using multivariate analysis that incorporated all tumor locations, age ($P < 0.001$) and location ($P = 0.020$) were significant predictors for survival. ***Conclusions.*** Age and location independently influence survival in ependymoma. Spinal tumors are associated with a significantly better prognosis than both supratentorial and infratentorial tumors, and may represent a distinct biological entity. Radiotherapy appears beneficial for survival in patients with infratentorial ependymoma. Pediatr Blood Cancer 2009;52:65–69. © 2008 Wiley-Liss, Inc.

Key words: brain tumor; ependymomas; epidemiology; pediatric oncology; survival

INTRODUCTION

Brain tumors currently occur at an annual rate reported as high as 4.3 per 100,000 person-years in children, with ependymomas comprising 8–10% of these neoplasms [1–7]. Ependymoma continues to be associated with significant mortality with 5-year overall survival reported about 65% [6,8]. Opinions vary regarding which factors influence outcome.

Younger children are generally thought to have a poorer prognosis [9,10], and survival rates appear to be lower in children than adults [6]. Although radiotherapy is the standard of care for adults, current treatment recommendations for children vary and are often limited by the significant neurotoxicity associated with radiation [11]. Survival has also been reported to vary by tumor location: supratentorial tumors lead to higher survival rates than infratentorial tumors, and spinal tumors have the best prognosis [1–3,12].

Unfortunately, many studies reporting these survival trends are based on small samples and single-institution experiences. Thus, there is a need for more complete and definitive analysis based upon a larger sample in a population-based cancer registry. This study sought to analyze how age, gender, location, race, and radiotherapy influence survival in ependymoma, using such a comprehensive database.

METHODS

The Surveillance Epidemiology End Results Program (SEER-17) was used to identify all ependymoma cases diagnosed at age 18 or younger in 17 United States cancer registries from 1973 to 2003 [13]. The National Cancer Institute's SEER database is an authoritative source of United States population-based data, incorporating both historical and current cases, and now draws a representative 26% of the population [13]. Approval for research was granted by the Stanford Panel on Human Subjects in Medical Research. Cases were selected from the SEER-17 if there was a diagnosis of ependymoma defined by the International Classification of Disease (ICD-0-3) histology codes 9391, 9392, 9393, and 9394 (ependymoma, anaplastic ependymoma, papillary ependymoma and myxopapillary ependymoma). The SEER database captures institutional diagnoses and does not centrally review pathology. Primary tumor locations were distinguished by ICD-0-2 site codes and defined as supratentorial (700, 702–714), infratentorial (716-717), or spinal (720-721, 701, 725). Those tumors identified as ventricle, overlapping brain, brain not otherwise specified, overlapping or not otherwise specified (715, 718, 719, 728, and 729) were excluded from location analysis because of the inability to assign the tumor to one of the three strata.

Survival was defined as the time from diagnosis until death due to all causes. Overall survival was calculated by Kaplan–Meier analysis. Treatments coded as beam radiation, radioactive, and radiation were classified as "radiotherapy" while those labeled as none or refused were classified as "no radiotherapy." Outcomes were compared by age, location, gender, race (blacks and whites), and radiotherapy using univariate logrank tests.

Cox proportional hazards multivariate regression was subsequently used to incorporate all significant covariates from univariate analysis (i.e., location, age, radiotherapy). A pre-planned multivariate analysis was completed for the subgroup of infratentorial tumors incorporating the significant univariate covariates age and

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TABLE I. Patient Characteristics, n = 635

Characteristic	n	%
Gender		
Male	370	58.3
Female	265	41.7
Age at initial diagnosis, years		
0–4	329	51.8
5–8	104	16.4
9–12	80	12.6
13–15	67	10.5
16–18	55	8.6
Mean ± standard deviation	6.33 ± 5.45	
Median	4	
Histologic diagnosis (ICD-0-3 code)		
Ependymoma (9391)	511	80.5
Anaplastic ependymoma (9392)	119	18.7
Papillary ependymoma (9393)	1	0.2
Myxopapillary ependymoma (9394)	4	0.6
Primary tumor site		
Supratentorial	106	16.7
Infratentorial	193	30.4
Spinal	55	8.7
Other	281	44.3
Race		
White	510	80.3
Black	77	12.1
Other	48	7.5
Treatment		
Radiotherapy	358	56.4
No radiotherapy	254	40.0
Unknown	23	3.6

n, number of children.

radiotherapy. Hazard ratios and 95% confidence intervals were calculated. An interaction term was created for location and age in order to test for effect modification between the two independent variables. All statistical analyses were completed using SPSS (version 15.0, Chicago, IL).

RESULTS

The characteristics of the 635 patients identified from the SEER database are listed in Table I. Most tumors, 80.5%, were classified as well-differentiated, or unspecified, ependymoma (9391) while the remaining included anaplastic, papillary and myxopapillary ependymomas. Mean age was 6.3 ± standard error 0.22 years and median age 4 years. Overall, a majority of patients were male and the predominant race was white. Most patients (56.4%) were reported to have received radiotherapy. The most common identified tumor location was infratentorial.

Univariate comparisons of survival based upon age, race, gender, and treatment appear in Table II. Radiotherapy was associated with significantly increased survival compared with no treatment (logrank $P = 0.022$). There was no significant difference in survival by gender or race, although there were trends toward improved survival among females compared with males and whites compared with blacks. Increasing age was associated with improved survival (logrank $P < 0.0001$).

Tumor location was classified into spinal, supratentorial, and infratentorial according to Figure 1. Three hundred fifty-four tumors were included in the location analysis. Univariate analysis demonstrated a significant difference in survival among the three tumor locations, with improved survival among spinal tumors (logrank $P = 0.001$; Fig. 2). There was no difference in 5-year survival between supratentorial and infratentorial locations. Specific 5-year survival data for the three locations appear in Table III. Even when survival analyses for location were repeated by including the indeterminate location cases with classification as all supratentorial or all infratentorial, our findings were unchanged (data not shown).

Radiotherapy for the individual tumor locations was also compared (Table IV). Using univariate analysis, radiotherapy did not significantly affect survival in spinal or supratentorial tumors. Radiotherapy appeared to convey a significant survival improvement for infratentorial tumors compared to no treatment in both univariate analysis (logrank $P = 0.018$, Fig. 3) and subgroup multivariate analysis restricted to infratentorial tumors ($P = 0.033$). Using multivariate analysis for all tumor locations,

TABLE II. Univariate Comparison of Survival by Gender, Race, and Treatment

	n	Median survival (months)	5-year survival (%)	SE (%)	*P*-value*
Gender					0.97
Male	370	97.0	56.4	3.0	
Female	265	154	54.9	3.6	
Race					0.20
White	510	154	56.7	2.5	
Black	77	53.0	45.1	6.7	
Treatment					0.022
Radiotherapy	358	154	56.8	3.0	
No radiotherapy	254	91.0	53.6	3.6	
Age					
0–4	329	43.0	45.5	3.1	<0.0001
5–8	104	145	56.5	6.1	
9–12	80	268	63.3	6.5	
13–15	67	—	75.8	6.1	
16–18	55	—	77.0	7.0	

n, number of children; SE, standard error. *Logrank Test.

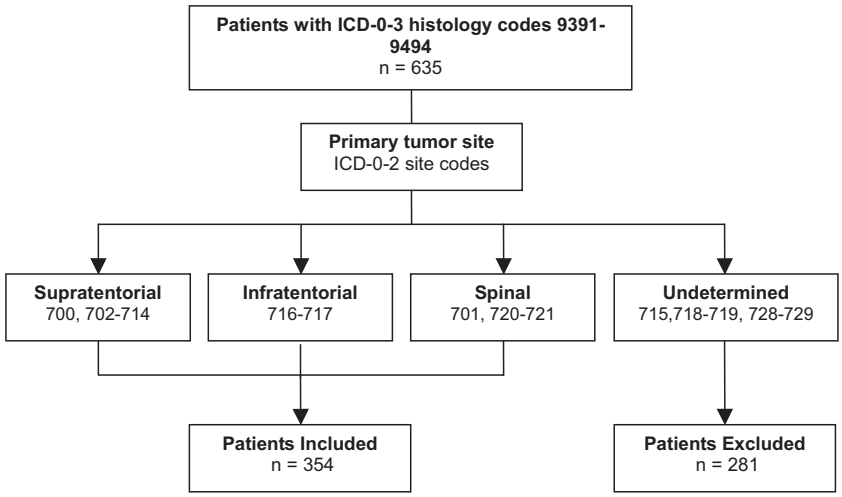

Fig. 1. Patient selection for primary tumor site analysis. n, number of children.

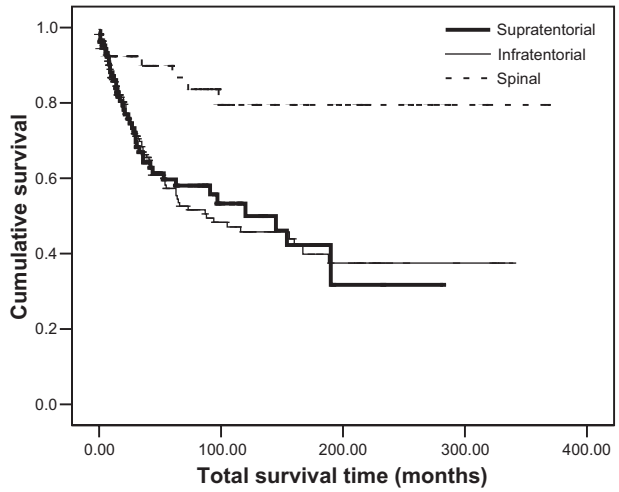

Fig. 2. Survival by primary tumor site. Total number of patients = 354. Number of patients in each arm: supratentorial = 106, infratentorial = 193, spinal = 55. Logrank Test, $P = 0.001$.

both location ($P = 0.020$) and age ($P < 0.001$) remained as significant predictors of survival among pediatric ependymomas, while radiotherapy did not retain significance. There was no interaction between age and location.

DISCUSSION

Our study draws a large sample of 635 patients with ependymomas from a population-based cancer registry. Both age and location directly influence survival in children, consistent with prior research [1–3,8–10,12].

Although the current therapy for ependymomas in children often includes surgery followed by radiotherapy, variations in treatment plans using or not using radiotherapy have occurred because of concerns about neurotoxicity in young children [11]. Chemotherapy may be provided to delay the radiation therapy until older age, and sometimes children did not receive any irradiation for infratentorial ependymomas [14,15]. Specifically, Grundy et al. [16] found that among children less than 3 years without metastases from ependymoma, chemotherapy alone following maximal surgery provided an effective 42% 5-year cumulative incidence of freedom from radiotherapy. Duffner et al. [15], however, recorded excessive relapses in infants with an approach to defer radiotherapy by chemotherapy alone longer than 12 months. Furthermore, Merchant et al. reported that conformal irradiation in children achieves 74.7% progression free survival at 3 years from diagnosis. Among patients less than age 3 at time of irradiation, 3-year progression free survival was not significantly different at 69.5% with normal neurocognitive outcome scores [17]. In our study, radiotherapy was associated with improved outcomes, consistent with recent work by Shu et al. [8] that analyzed the treatment of 61 patients and found improved survival among children with higher radiation dose. However, following stratification, our study demonstrated a survival benefit of

TABLE III. Five-Year Univariate Survival Estimates by Primary Tumor Site

Primary tumor site	n	5-year survival (%)	SE (%)	95% confidence interval
Supratentorial	106	57.8	5.5	(47.0, 68.6)
Infratentorial	193	54.4	4.2	(46.1, 62.6)
Spinal	55	86.6	5.2	(76.4, 96.8)

n, number of children; SE, standard error.

TABLE IV. Univariate Comparison of Survival by Radiotherapy for Each Primary Tumor Site, n = 339

	Radiation				No radiation				
	n	Median (mo)	5-year survival (%)	SE (%)	n	Median (mo)	5-year survival (%)	SE (%)	*P*-value*
Supratentorial	65	120.0	54.0	7.0	38	190.0	68.0	8.6	0.95
Infratentorial	116	116.0	57.1	5.2	68	43.0	48.2	7.1	0.018
Spinal	20	—	95.0	4.9	32	—	80.0	8.4	0.82

n, number of children; mo, months, SE, standard error. *Logrank Test.

radiation only for infratentorial tumors, while radiotherapy was not associated with a difference in survival for spinal and supratentorial tumors. While our data are retrospective and treatments were not assigned randomly, radiotherapy appears beneficial for infratentorial ependymoma, counter to some prior speculation [14].

Recent work by Taylor et al. [18] suggests that specific progenitor cells may contribute to the formation of the distinct tumor types occurring in the supratentorial, infratentorial and spinal regions. Our study found spinal tumors were associated with a significantly better prognosis than both supratentorial and infratentorial tumors, but no difference was observed when comparing supratentorial to infratentorial tumors. Similar findings suggesting no difference in survival among supratentorial and infratentorial locations were shown in a recent study by Shu et al. [8] Together these findings suggest that spinal tumors may represent a distinct biological entity, but are not particularly supportive of infratentorial and supratentorial tumors as entirely distinct.

One limitation of our study was the inability to specify location for tumors identified as ventricle, overlapping brain, brain not otherwise specified, overlapping, or not otherwise specified (715, 718, 719, 728, and 729). When analyzing how location affects survival, these specific cases were eliminated because of the inability to assign them to supratentorial, infratentorial, or spinal. In order to ensure that there was no systematic error associated with this determination, univariate location analysis was repeated with all the indeterminate cases included and classified as infratentorial. The result was compared to a second univariate analysis completed with all the indeterminate cases classified as supratentorial. Because there was no statistically significant difference in the two results, the lack of site classification was judged to be random and made exclusion of these cases from any analysis examining location reasonable.

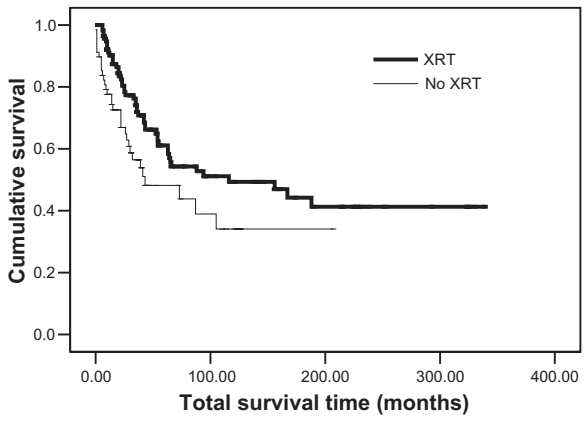

Fig. 3. Comparison of survival by radiotherapy for infratentorial tumors. XRT = radiotherapy. Total number of patients = 184. Number of patients in each arm: XRT = 116, no XRT = 68. Logrank Test, $P = 0.018$.

In a retrospective, observational study, it is always possible that other confounding variables were not incorporated into the analysis and influenced the results. Potential prognostic factors such as stage, extent of surgical resection, histologic grade, and specific details of all treatments are not consistently available over three decades in the SEER database, and therefore could not be included in our multivariate analysis. Specifically, histologic grade was not analyzed in our study because there is wide variation among institutions in tumor grading and most registrars encode ependymomas as ''ependymomas,'' regardless of whether well-differentiated or anaplastic. Finally, advances in medicine, including new surgical technologies, evolution of computed tomography and then magnetic resonance imaging as well as revision of pathology classification schema, have occurred during the time period examined and may lead to reporting bias.

Despite these limitations, our study demonstrates how survival varies by age, location, and radiotherapy. Understanding these trends may help us further understand the biology and guide refinements in the treatment of ependymoma. Distinct knowledge of how radiation and tumor location relate to survival may guide clinical management of ependymoma in these populations, perhaps leading to modification of treatment guidelines for young children.

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INVITED PAPER

Three-dimensional conformal radiation therapy for ependymoma

Thomas E. Merchant

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Abstract
Introduction The application of conformal radiation therapy in the treatment of pediatric ependymoma is a success story resulting from advances in radiation therapy planning and delivery. These advances occurred at a time when clinical trial results confirmed that radiotherapy avoidance strategies were unsuccessful.
Discussion Investigators have been keen to confirm the promise of newer radiation therapy methods even for the youngest children. When preliminary results suggested that high-dose focal irradiation could be safely administered through systematic targeting and that cognitive function could be preserved, investigators moved to include conformal therapy in the frontline management of children regardless of age. The results with postoperative conformal radiation therapy were further enhanced when neurosurgeons increased the rate of gross-total resection and recognized that second surgery could be safely accomplished after incomplete initial resection. With more than a decade of experience, the role of conformal radiation therapy in the treatment of childhood ependymoma has been firmly established as investigators consider new trials to increase disease control and improve functional outcomes.

Keywords Radiation therapy · Pediatrics · Ependymoma · Brain tumor

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Purpose

Ependymoma describes a diverse group of central nervous system (CNS) tumors for which the very young are disproportionably represented; nearly half of pediatric cases occur in children under the age of 4 years [1]. The factor of age is a critical point for successful treatment of ependymoma that requires aggressive surgery and high-dose postoperative radiation therapy. Incomplete resection and high rates of local failure characterize past institutional and cooperative group series for older children [2–10]. When radiation therapy avoidance was the hallmark of clinical trials for younger children, results were inferior to those achieved when radiation therapy was administered as a part of frontline management [11–14].

Two decades ago, radiation therapy for ependymoma consisted of craniospinal irradiation with or without chemotherapy. Long-term event-free survival was less than 40% [15]. Patients experienced tumor progression at the primary site because most had measurable residual tumor at the time of irradiation. Because of concern about neuraxis dissemination, especially in patients with high-grade tumors, craniospinal and boost irradiation of the primary site was administered postoperatively. Those who survived suffered debilitating side effects. Recognition that primary site irradiation was equivalent to craniospinal irradiation occurred at a time when radiotherapy avoidance was becoming the regimen of choice for younger patients and the advantage of focal treatment, even using conventional techniques, could not be realized because of the persistently high rates of local failure [16].

Three-dimensional conformal radiation therapy trials were developed in the early 1990s at major medical centers in the USA. Supported by government contracts, these trials showed that radiation dose to prostate, head and neck, and

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lung tumors could be safely escalated to increase tumor control. Most convincing was the noticeable reduction in acute side effects leading radiation oncologists to consider the application of the same techniques in pediatric CNS tumors.

The advent of conformal radiation therapy set the stage for a renewed look at the role of radiation therapy in the treatment of children with ependymoma. A prospective phase II trial (RT-1) was conducted at St. Jude Children's Research Hospital between 1997 and 2003. The primary goals were to objectively document the side effects of radiation therapy and to demonstrate that tumor control with a 10-mm clinical target volume margin was equivalent to conventional radiation therapy. Eighty-eight patients with ependymoma were enrolled during a 5-year period and most were under the age of 3 years at the time of irradiation. For the first time, radiation therapy was a component of frontline management in a clinical trial for children under the age of 3 years. The rate of gross-total resection (GTR) exceeded 85% as patients were systematically referred for second surgery prior to radiation therapy to minimize the amount of residual tumor. Through this process, the feasibility and safety of second surgery were demonstrated. The reported 3-year progression-free survival was 75% and the 3-year cumulative incidence of local failure was 15% [17]. These results were attributed to the high rate of gross-total resection, newer radiation planning and delivery methods, the relatively high dose tolerances for the cervical spinal cord and optic chiasm, and a cumulative planning target volume dose of 59.4 Gy with 100% coverage. As presented in the same report, the side effects of radiation therapy were found to be limited in this vulnerable patient population. Baseline and longitudinal testing using the prospective battery of neurologic, endocrine, and cognitive testing continue to demonstrate that most long-term survivors function within the range of normal. Radiation dosimetry was found to correlate with functional outcomes supporting the goal of target volume reduction in this vulnerable group of patients [18]. The results of this study were widely accepted as a major advance, especially for very young children. As these results were unfolding, investigators in the Children's Oncology Group (COG) supported the development and implementation of the ACNS0121 protocol which was based on the concepts of conformal therapy developed at St. Jude Children's Research Hospital. The COG protocol was activated in August 2003, widely accepted, and reached its goal of 350 eligible patients in 4 years [19].

In early 2009, an update in the series of patients treated at St. Jude Children's Research Hospital was published that included 153 patients [20]. With a median follow-up of 62 months (range 3–112 months) from the initiation of radiation therapy, the 7-year event-free and overall survivals were 69% and 81%, respectively The 7-year local control rate was 87%. A subset of patients treated with immediate postoperative radiation therapy were found to have even high rates of local control (89%), event-free (77%), and overall survival (85%) when estimated at 7 years. Extent of resection and tumor grade remain important prognostic factors. Among the patients with differentiated ependymoma treated with GTR and 59.4 Gy, there were very few failures. These data define potential groups for treatment intensification or reduction.

More than a decade later, sufficient experience has been gained to confirm the promise of conformal radiation therapy in pediatric CNS tumors and document improvements in disease control and preservation of functional outcomes in childhood ependymoma. In this report, we will summarize the data available from the treatment and follow-up of children irradiated using conformal radiation therapy including information on side effects.

Materials and methods

Conformal radiation therapy is defined as forward planned three-dimensional conformal radiation therapy or inverse planned intensity-modulated radiation therapy (IMRT) using photons. The goal of treatment is to achieve conformity of the prescription dose to the targeted volume and to spare normal tissues including the noninvolved brain, brainstem, spinal cord, optic chiasm, hypothalamus, and functional subunits of the cerebral hemispheres or cerebellum. The nomenclature used to define target volumes for conformal radiation therapy were first issued by the International Commission on Radiation Units and Measurements (ICRU) in 1993 and first used in a clinical trial for ependymoma beginning in 1997 [21, 22]. The ICRU defines the gross tumor volume (GTV) as the imaging visible residual tumor or volume of greatest tumor burden. The clinical target volume (CTV) is defined by a margin surrounding the GTV that includes microscopic tumor extension and depends on the tumor. The planning target volume (PTV) is an additional margin surrounding the CTV that is meant to account for variability in patient positioning. To date, these definitions have been used with one modification: The GTV has been defined to include residual tumor and/or the tumor bed. This modification fits with the concept of greatest tumor burden. Recent trials have prescribed CTV margins of 10 mm and PTV margins of 3–5 mm (Fig. 1).

Conformal radiation therapy requires specialized hardware and software. Both are now widely available. The first step in conformal therapy planning is computed tomography (CT) imaging in the treatment position. CT is the fundamental data set for three-dimensional treatment

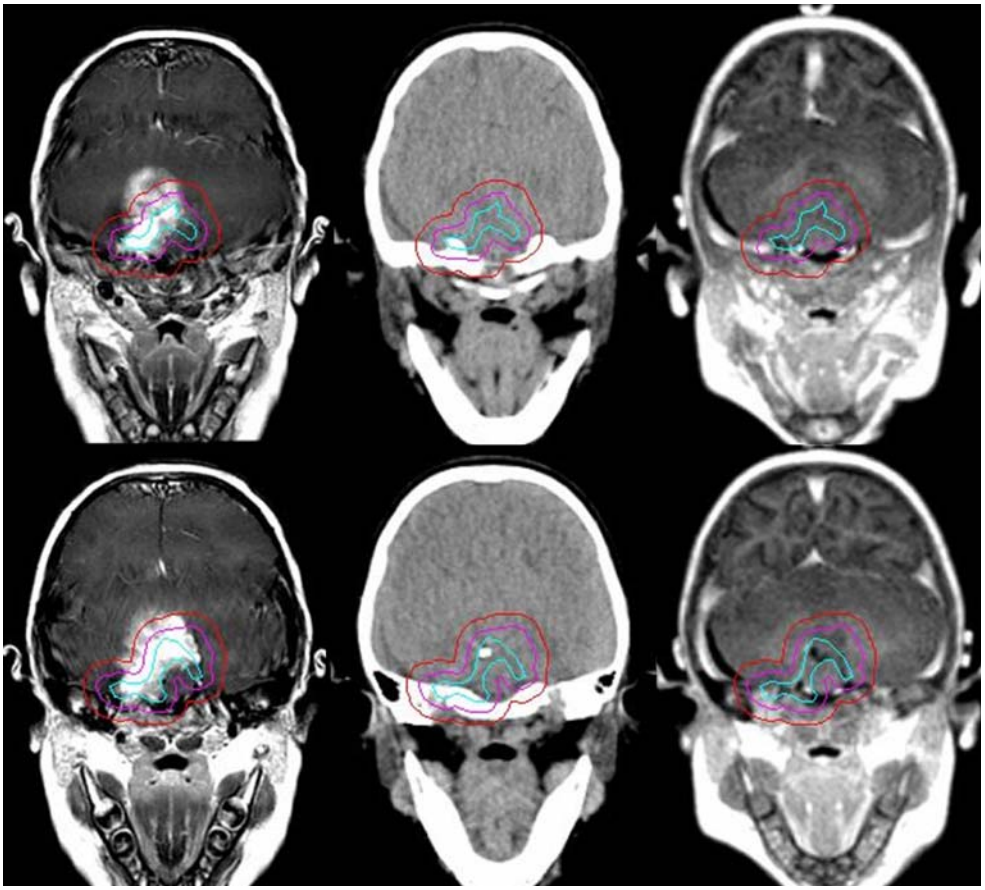

Fig. 1 Axial preoperative (*left*) and postoperative treatment planning (*right*) postcontrast T1-weighted MR and treatment planning (*center*) CT images of a patient with posterior fossa ependymoma. Gross target volume (*blue*), clinical target volume (*magenta*), and planning target volume (*red*) contours are shown on all images

planning. The Houndsfield unit represents tissue density for radiation dose calculation. The CT defines the coordinate system for radiation therapy which can be verified using the kilo- or megavoltage imaging systems which are part of the modern linear accelerator. Early on, target volumes and normal tissue contours were drawn directly on CT data using dedicated treatment planning computers. More recently, planning systems are capable of incorporating and registering multiple sets of pre- and postoperative magnetic resonance (MR) imaging and other data including PET.

The use of MR imaging to define target volumes and normal tissue contours refined the treatment of ependymoma for most patients have posterior fossa tumors where the performance of CT is limited. The superior contrast of MR has allowed investigators to define and differentiate residual tumor from postoperative change and has increased the accuracy of the definition of functional subunits of the brain. The use of MR imaging in treatment planning has revealed that changes in the position of normal tissue volumes may occur as a function of time after surgery and that MR imaging should coincide with radiation therapy planning. Further, the position of the patient for the MR study is critical, especially for patients with posterior fossa tumors, where differences in flexion and extension of the head may impact the position of the spinal cord. Regardless of whether the patient is treated in the prone or supine position, state-of-the-art radiation therapy planning therefore requires MR imaging to be performed in the same position as the treatment planning CT study (Fig. 2).

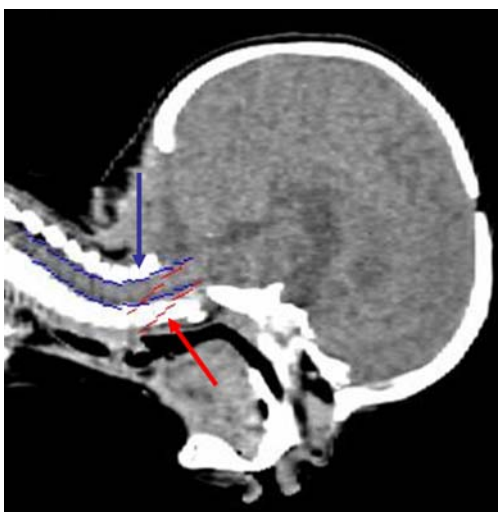

Fig. 2 Sagittal digitally reconstructed treatment planning CT data with spinal cord contour (*blue arrow*) and contour of diagnostic MR spinal cord contour (*red arrow*) to demonstrate potential registration errors when MR is not performed in the position of treatment delivery

Forward planned three-dimensional radiation therapy follows target and normal tissue volume contouring with beam's eye view treatment planning and the placement of multiple, noncoplanar individually shaped treatment beams pointed at the target yet avoiding critical normal tissues when feasible. The positioning of the beams, the number, shape and weight of beams, the exposure of normal tissues, and the accepted level of conformity is empiric yet limited by tumor size, location, patient positioning, and other factors coincident with the overall treatment plan. Intensity-modulated radiation therapy follows the same process before arriving at the iterative process of inverse planning to achieve predetermined levels of target volume coverage and adhere to operator imposed normal tissue constraints.

Fifty-four grays has been widely considered as the minimum dose required for local tumor control with gross residual and tumor bed concentrations of microscopic disease; higher doses are considered to be more efficacious based on first principles of radiation therapy and our understanding that local failure dominates as a component of first failure. More recent series have employed 59.4 Gy at 1.8 Gy/day for all patients except those under the age of 18 months who have undergone gross-total resection who have been treated with 54 Gy. These dose requirements question the utility of craniospinal irradiation for metastatic ependymoma given that neuraxis doses are limited to 36–39.6 Gy. Most would consider that there is a difference in the level of microscopic tumor concentration in the subclinically involved neuraxis versus the resected tumor bed which requires a higher dose.

The treatment planning objectives for conformal radiation therapy are to ensure target volume (PTV) coverage, minimize inhomogeneity, respect normal tissue tolerances, and c, and hypothalamic-pituitary unit. The full spectrum of conformal treatment techniques including forward or inversely planned conformal radiation therapy (intensity-modulated radiation therapy) is capable of achieving these goals. Proton beam radiation therapy also falls under the same rubric.

Patients who receive conformal radiation therapy may be treated in the supine or prone position. A treatment planning CT is required and contrast is optional. The planning procedure should be performed as close to the start of treatment as possible because the possibility of postoperative changes in normal tissues. The CT scan should be of high resolution, certainly smaller section thickness that the planning target volume margin. In 2009, ≤2 mm is considered the standard. Registration of MR to CT is now a requirement for treatment planning to determine the extent of disease and to visualize the postoperative tumor bed, especially for posterior fossa tumors where the performance of CT is low. Because ependymoma has variable enhancement pre- and postoperative three-dimensionally acquired post-Gd T1-weighted data and thin section T2-weighted MR imaging data sets formatted in the transverse plane and registered to the CT study enable the radiation oncologist to contour the preoperative extent of disease and the postoperative tumor bed appreciating the full extent of disease and the postoperative shift of normal tissues. Other data sets representing alternative MR sequences may be registered and used as needed. It has also been found useful to repeat MR imaging immediately prior to radiation therapy which can be useful to clarify significant changes noted on the MRI obtained immediately postoperatively. The MR studies for RT planning, whenever feasible, should be obtained as close as possible to the start of treatment and about the time of simulation to account for changes in ventricular volumes, the operative site, and extra-axial fluid collections.

The CT scan is the primary data set for radiation therapy planning and required to account for tissue heterogeneity in the planning process. We also suggest that the cochleae, spinal cord, and skin contour originate from the CT scan owing to the small size (cochleae) or critical nature (spinal cord) of these structures. The MR data set is used for the target volumes (GTV, CTV, PTV) and critical normal tissue structures in the head and neck (thyroid) and the entire brain, eyes, optic nerves, optic chiasm, pituitary, hypothalamus, and temporal lobes [23].

Radiation oncologists generally accept the need for higher doses of radiation to treat ependymoma but remain concerned about normal tissue effects. Indeed, the dose to the spinal cord and brainstem are first among concerns when irradiating young children. Other normal tissue volumes or critical structures include the cochlea, hypothalamic-pituitary unit, optic chiasm, and temporal lobes.

In recent years, algorithms for handling dose to these critical structures and defined dose limits have become available. For the purposes of treatment planning an infratentorial tumor, the upper aspect of the spinal cord begins at the inferior border of the foramen magnum and should be contoured on the treatment planning CT. For consistency in reporting the spinal cord should be contoured on a number of images to be determined by the image section thickness. We have recommended 30 images at 2 mm section thickness. The treatment should be planned without compromising the dose prescription and to minimize inhomogeneity that would have the spinal cord receiving >1.8 Gy/day. If the cumulative treatment dose may exceed 54 Gy to more than 10% of the protocol defined spinal cord structure, the spinal cord should be excluded from the treatment after 54 Gy and receive no more than 1.25 Gy per fraction at any point. No myelopathy has been reported using these guidelines [24].

The optic chiasm dose should be managed in a very similar fashion to the spinal cord and should be defined on CT or MR and appearing on at least two successive images. If the cumulative treatment dose may exceed 54 Gy, the chiasm should be excluded from the treatment after 54 Gy and receive no more than 1.25 Gy per fraction at any point. These guidelines also allow for the coverage of the target volumes to be compromised after 54 Gy in selected cases.

Each cochlea should be contoured separately on the CT data as a circular structure within the petrous portion of the temporal bone. The size and position of the contoured cochlea should be confirmed by viewing the structures in three dimensions using the treatment planning system and on two successive CT images. The mean dose to the cochleae should be limited to 35 Gy. At these levels, the risk of hearing loss is less than 5% [25].

The brainstem is central to the irradiated volume in patients with posterior fossa tumors, and while major side effects from radiation therapy have not been widely reported, investigators remain very concerned about the long-term effects of irradiation especially for children who suffer neurological effects from tumor and surgery. Recent data suggest that factors impeding neurologic recovery in children with ependymoma treated with high-dose postoperative radiation therapy do not include radiation dose, rather, the volume of tumor and clinical and treatment factors related to tumor and surgery. Given the safety profile of radiation therapy as administered in recent trials and plans to further reduce the target volume for radiation therapy, the risk of side effects involving the brainstem should be further diminished [26].

Temporal lobe and whole brain doses of radiation therapy are correlated with cognitive outcome corrected for the age of the patient at the time of irradiation. This important knowledge has driven investigators to find new ways to reduce dose to normal tissues (shrinking target volume margins) or this high-dose volume of irradiation using conformal methods. Evaluating patients with ependymoma and considering radiation effects should not be absent the potential effects of hydrocephalus [18, 27].

Hypothalamic dose volume effects have been modeled for patients with ependymoma suggesting that the risk of endocrinopathy is low for most patients and that while even low doses to the hypothalamus result in a risk for growth hormone deficiency, other endocrinopathies are even less common if baseline assessments prove to be normal. Preexisting endocrine deficiencies in these children correlate with ventricle size (hydrocephalus) at diagnosis [28, 29].

Result

The peer-reviewed scientific literature contains numerous references to highly focused focal irradiation for intracranial ependymoma in children; however, there is only one perspective conformal series. The primary measure of success for conformal radiation therapy is local tumor control corrected for extent of resection which is the most important prognostic factor. There are several contemporary series that utilized fully or to a large extent conformal radiation therapy. Local tumor control has been estimated at 68–89% when measured at 3–5 years (Table 1) [18, 30–32]. The rates of local control in the modern series are considerably higher than those inferred from historic series where event-free survival and not local control rates have been reported (Table 2) [2–10].

IMRT

The use of IMRT in very young children has raised concern about extraneous dose to normal tissues. Mansur et al. [33] found that IMRT lowered peripheral doses near the target. This was attributed to reduced internal scatter due to smaller effective field sizes. The thyroid was given as an example of a critical peripheral organ near to the targeted volume. The peripheral dose was similar for both IMRT and three-dimensional CRT indicating that peripheral dose was difficult to predict by monitor units which are often significantly greater for IMRT.

Table 1 Local tumor control estimates from contemporary reports using postoperative irradiation

Series	Time period	Patients	GTR (%)	Local control
MacDonald-PBRT	2000–2006	17	76	86% at 2 years
Schroeder-IMRT	1994–2005	22	77	68% at 3 years
Massimino-HFRT	1993–2001	46	74	70% at 4 years
Merchant-CRT/IMRT	1997–2007	153	85	89% at 5 years

PBRT proton beam radiation therapy, *IMRT* intensity-modulated radiation therapy, *HFRT* hyperfractionated radiation therapy, *CRT* conformal radiation therapy, *GTR* gross-total resection

Table 2 Event-free and overall survival estimates from selected radiotherapy series reporting 5 and 10 year outcomes

Series	Time period	Patients	5-year EFS	10-year EFS	5-year OS	10-year OS
Akyuz	1972–1991	62	–	36%	–	50%
Perilongo	1977–1993	92	–	35%	–	56%
Shu	1980–2000	49	41%	31%	66%	56%
Oya	1961–1999	48	42%	42%	62%	47%
Pollack	1975–1993	40	46%	36%	57%	45%
Jaing	1985–2002	43	46%	–	54%	–
V. Veelan	1980–1999	83	48%	46%	73%	51%
Robertson	1986–1992	32	50%	–	64%	–
Mansur	1964–2000	60	58%	46%	71%	55%
Merchant	1997–2007	153	74%	69%	85%	75%

EFS event-free survival, *OS* overall survival

FSRT

Coombs et al. [34] used fractionated stereotactic radiotherapy to treat intracranial ependymoma in young children. Their success rate was comparable to conventional irradiation using a total dose of 54 Gy that was administered in two phases involving, first, the posterior fossa and, second, the tumor bed. Progression-free survival at 5 years was reported to be 64%. Murthy and others [35] compared dosimetry for posterior fossa ependymoma based on treatment strategies. Target and normal structures contoured included the normal brain, brainstem, cochleae, optic chiasm, hypothalamic axis, supratentorial brain, and the temporal lobes. They found that a six-field technique was optimal irrespective of the size of the target volumes, especially for tumors located anterior to the brainstem.

SRS

Stereotactic radiosurgery (SRS) has been used adjuvantly after surgery alone or in combination with fractionated external beam irradiation for residual disease [36–41]. Stereotactic radiosurgery has also been used as a salvage treatment with or without addition resection for patients who fail fractionated irradiation. In a series by Lo et al. [36] that included the aforementioned clinical scenarios, among the five patients treated with surgery and fractionated external beam who experienced treatment failure, three were salvaged with stereotactic radiosurgery using approximately 14 Gy with a median follow-up of 30 months. Necrosis was observed and successfully managed. Both patients treated with postoperative fractionated irradiation and focal SRS boost for residual disease were controlled during the same time frame. Jawahar et al. [37] assessed the role of stereotactic radiosurgery to treat locally progressive ependymoma in adults and children. Their series included 22 patients. The mean tumor volume was 13.7 cm^3 and the mean maximal and median margin doses were 32.3 and 16.1 Gy. With a median follow-up of 21 months, 68% responded to treatment and 41% developed distant metastasis. Median survival was 2.2 years.

Craniospinal RT

The series by Timmermann et al. [42] included 55 children with anaplastic ependymoma with 28 treated with GTR and various methods of irradiation. All received chemotherapy. Median follow-up was 38 months; local disease progression occurred in 20 of 53 irradiated patients. The overall survival rate at 3 years after surgery was 75.6%. This value is considered low but includes patients with metastatic disease. The 3-year event-free survival was 66% for localized tumors. Irradiation volume and other clinical factors did not influence survival. McLaughlin et al. [43] is a classic series where patients with anaplastic tumors received craniospinal irradiation and those with differentiated tumors were treated focally. The differences in outcome are difficult to measure based on the high rate of local recurrence. Among 32 intracranial tumors, 21 suffered recurrence at the primary site. Overall and relapse-free survival rates were 51% and 46%, respectively, at 10 years. Tumor site was prognostic for absolute survival ($p=$

Table 3 Event-free survival estimates for favorable patients from selected radiotherapy series reporting 5-year outcomes

Series	Time period	GTR/patients	5-year OS (%)	5-year EFS (%)
Massimino	1993–2001	46/63	82	65
Shu	1980–2000	30/49	83	61
Mansur	1964–2000	14/60	84	69
Merchant	1997–2007	125/153	93	86

GTR gross-total resection, *EFS* event-free survival, *OS* overall survival

0.0004): 45% for infratentorial and 20% for supratentorial tumor location.

Conclusion

The advent of conformal radiation therapy has provided a renewed interest in radiation therapy for the frontline management of ependymoma, especially for younger patients. Selected contemporary series report high rates of tumor control and overall survival (Table 3) for favorable patients now confirmed with longer-term data. These data provide a basis for future studies that will attempt to improve upon the results achieved with modern surgery and radiation therapy using additional forms of adjuvant and possibly systemic therapy.

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ORIGINAL REPORT

Preliminary Results From a Phase II Trial of Conformal Radiation Therapy and Evaluation of Radiation-Related CNS Effects for Pediatric Patients With Localized Ependymoma

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ABSTRACT

Purpose
We conducted a phase II trial of conformal radiation therapy (CRT) for localized childhood ependymoma to determine whether the irradiated volume could be reduced to decrease CNS-related side effects without diminishing the rate of disease control.

Patients and Methods
Between July 1997 and January 2003, 88 pediatric patients (median age, 2.85 ± 4.5 years) received CRT in which doses (59.4 Gy to 73 patients or 54.0 Gy after gross-total resection to 15 patients younger than 18 months) were administered to the gross tumor volume and a margin of 10 mm. Patients were categorized according to extent of resection (underwent gross total resection, n = 74; near-total resection, n = 6; subtotal resection, n = 8), prior chemotherapy (n = 16), tumor grade (anaplastic, n = 35), and tumor location (infratentorial, n = 68). An age-appropriate neurocognitive battery was administered before and serially after CRT.

Results
The median length of follow-up was 38.2 months (± 16.4 months); the 3-year progression-free survival estimate was 74.7% ± 5.7%. Local failure occurred in eight patients, distant failure in eight patients, and both in four patients. The cumulative incidence of local failure as a component of failure at 3 years was 14.8% ± 4.0%. Mean scores on all neurocognitive outcomes were stable and within normal limits, with more than half the cohort tested at or beyond 24 months.

Conclusion
Limited-volume irradiation achieves high rates of disease control in pediatric patients with ependymoma and results in stable neurocognitive outcomes.

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INTRODUCTION

Ependymoma is a rare brain tumor that occurs in very young children: fewer than 150 cases per year occur in the United States among persons younger than 14 years.[1] Surgery and postoperative radiation therapy are essential to the successful management of ependymoma, but those who receive radiation therapy are at risk of side effects that negatively affect cognitive, endocrine, and neurologic function.[2] The specter of radiation-related side effects, which is most ominous for those who are very young at the time of treatment, has motivated investigators to test strategies to delay or avoid the use of radiation in young children. However, cooperative group trials testing the use of chemotherapy to delay irradiation have met with limited success, reporting results inferior to those achieved for patients treated with immediate postoperative radiation therapy.[3-5]

Conformal radiation therapy (CRT) is a spectrum of radiation treatment planning and delivery techniques developed to focus radiation and limit the highest doses to the

volume at risk of recurrence while sparing normal tissues. These techniques incorporate three-dimensional imaging (computed tomography and magnetic resonance imaging) into the planning process and use sophisticated software to delineate and display the treatment volume and important normal tissue structures for selective targeting and optimization of dosimetry. Initially developed for the treatment of adults with prostate and head and neck cancer, CRT has been successful in reducing side effects and improving tumor control[6,7] and holds the promise of reducing radiation-related treatment effects in children with brain tumors, although no long-term clinical trials have yet been reported. The successful application of CRT to ependymoma in children may improve outcomes by reducing side effects and thereby permit the reintroduction of radiation therapy as a treatment option for very young children. Nevertheless, guidelines for the use of CRT will be needed to ensure that the appropriate volume receives the prescription dose and that disease control is not compromised.

We designed and conducted a phase II trial to test the hypothesis that irradiation of a smaller-than-conventional treatment volume reduces side effects without affecting the rate of tumor control or local pattern of failure. We selected an anatomically confined margin of 10 mm around the tumor, tumor bed, or both as the clinical target volume for a prospective phase II trial. These guidelines were used prospectively to treat 88 pediatric patients with ependymoma, the largest trial to date for such patients. The neurocognitive function of these patients was evaluated before and after CRT in a comprehensive manner that has not been previously reported in the literature.

PATIENTS AND METHODS

Patients

From July 1997 through January 2003, 88 pediatric patients with intracranial ependymoma were enrolled onto a phase II trial approved by the institutional review board. Criteria for enrollment included age between 1 and 21 years at the time of irradiation; histologic confirmation of intracranial ependymoma; no evidence of dissemination; no prior irradiation; no ongoing chemotherapy; adequate performance status; and written informed consent. The protocol was amended to allow enrollment of patients as old as 25 years; only one patient older than 21 years entered the study. Sixteen patients received chemotherapy before irradiation; most received multiagent chemotherapy including cyclophosphamide, cisplatin or carboplatin, etoposide, and vincristine.

Extent of Resection Definitions

All patients underwent resection before radiation therapy. Gross-total resection was defined as resection after which the only tumor cells that remained were visible with the use of the operating microscope; patients for whom this type of resection was achieved had no evidence of disease on postoperative neuroimaging. Near-total resection was defined as resection after which only residual tumor $<$ 5-mm thick was visible on postoperative neuroimaging. Subtotal resection was defined as resection that left behind residual tumor $>$ 5-mm thick on postoperative neuroimaging. Further surgery was systematically applied to maximize the extent of resection before irradiation.

CRT

Target volume definitions and planning and treatment parameters have been previously described.[8] The gross tumor volume (GTV) contained the tumor bed, residual tumor, or both. The clinical target volume (CTV) contained the GTV with an added margin of 10 mm, which was included so that subclinical microscopic disease beyond the GTV could be treated. The CTV was anatomically confined; that is, it was limited by normal tissue structures through which tumor extension was unlikely. The planning target volume included the CTV surrounded by an additional margin of 3 to 5 mm expanded in three dimensions to account for uncertainty in patient positioning and image registration. Conventional fractionation (1.8 Gy per day) was used to treat all patients, and the prescribed dose was 59.4 Gy. Exceptions included children younger than 18 months and three children older than 18 months who received 54.0 Gy after gross-total resection.

Neurocognitive Testing

Neurocognitive testing was performed before (baseline) and 6, 12, 24, 36, 48, and 60 months after the start of CRT. Baseline testing was delayed slightly if the institution of CRT was given logistic priority. Age-appropriate tests included those for cognitive development (Bayley Scale of Infant Development–II,[9] Wechsler Preschool and Primary Scales of Intelligence–Revised,[10] Wechsler Intelligence Scale for Children–III,[11] and Wechsler Adult Intelligence Scale III[12]), verbal memory and recall (California Verbal Learning Test: Child and Adult versions[13,14]), academic achievement (Wechsler Individual Achievement Test,[15]) activities of daily living (Vineland Adaptive Behavior Scale Survey[16]), and visual-auditory paired associate learning (Visual-Auditory Learning Test[17]). All tests have well-documented reliability and validity and result in age-corrected standard scores. The testing regimen was based on patient age. When more than one instrument was age-appropriate for a patient, the selection of instrument reflected the desire to maintain consistency in the use of consecutive instruments and to conduct at least two evaluations by using the same instrument. Clinical judgment was used to select the instrument with which the child was expected to achieve the most valid performance.

Statistical Methods

Progression-free survival (PFS) was measured from the initiation of radiation therapy to the neuroimaging documented time of tumor recurrence, where tumor recurrence included local-only failure, distant-only failure, or simultaneous local and distant failure. One patient who died of reasons unrelated to radiation therapy was censored at the date of death in the estimate of PFS. The rate of local failure was monitored by using group sequential boundaries obtained according to the sequential conditional probability ratio tests.[18] Patients were followed every 3 months for 2 years and every 6 months thereafter. PFS was estimated by using the Kaplan-Meier method.[19] Estimates based on categoric clinical variables were compared by using the log-rank test,[20] and estimates based on continuous clinical variables were compared by using Cox regression analysis.[21] Variables for which $P < .10$ in the univariate analysis were included in a Cox regression model.[21] Local control was estimated using cumulative incidence methods,[22] with distant tumor recurrence and death (one patient

Table 1. Demographic and Clinical Variables of Patients Categorized According to Age at Irradiation

Patient Characteristic	Age ≥ 3 Years (n = 40)		Age < 3 Years (n = 48)		P
	No. of Patients	%	No. of Patients	%	
Length of follow-up, months					
Median	34.7		25.6		
Range	1.3-60.5		6.1-59.8		
Sex					
Female	19	47.5	22	45.8	.88
Male	21	52.5	26	54.2	
CSF shunting					
No	31	77.5	28	58	.057
Yes	9	22.5	20	42	
Pre-CRT chemotherapy					
No	35	87.5	37	77	.21
Yes	5	12.5	11	23	
Extent of resection					
Gross-total	34	85	40	83.3	.83
Near-total	2	5	4	8.3	
Subtotal	4	10	4	8.3	
Tumor grade					
Anaplastic	13	32.5	22	45.8	.20
Differentiated	27	67.5	26	54.2	
Tumor location					
Infratentorial	26	65	42	87.5	.012
Supratentorial	14	35	6	12.5	
No. of pre-CRT resections					
1	26	65	30	63	.45
2	14	35	14	29	
3			2	4	
4			2	4	
Hydrocephalus					
No	16	46	8	17	.014
Yes	24	60	40	83	

Abbreviation: CRT, conformal radiation therapy.

whose death was not attributed to disease progression or radiation therapy) as competing risks. The longitudinal trends in neurocognitive outcomes were estimated by using linear mixed models with random coefficients.[23] SAS software was used for all analyses.[24] Data analyses were performed by the biostatistical coauthors.

RESULTS

Clinical and treatment characteristics of the study patients are presented in Table 1. To identify similarities and differences among the patients, we categorized them according to age (younger than 3 years or ≥ 3 years) for comparison. Older patients were more likely to have supratentorial tumors ($P = .012$), and the younger patients were more likely to have hydrocephalus ($P = .014$) and require CSF shunting ($P = .057$). Larger proportions of the younger patients received preirradiation chemotherapy and had anaplastic tumors at diagnosis. However, these proportions were not significantly different from those of the older patients.

Disease Control

The median length of follow-up was 38.2 months (range, 12.4 to 75.6 months); 20 patients experienced disease progression, and the median time to progression for those patients was 14 months (range, 6 to 26 months). Failures were characterized as local (n = 8), local + distant (n = 4), and distant (n = 8). There were no marginal failures. The cumulative incidence of local failure estimate at 3 years was 14.8% ± 4.0%. The actuarial PFS estimate at 3 years was 74.7% ± 5.7% (Fig 1). Thirteen of the failures occurred among the 48 children younger than 3 years at the time of irradiation. One patient died whose death was not attributed to radiation therapy. He was censored at the time of death when autopsy showed stable residual tumor. Univariate analysis identified statistically significant differences in actuarial 3-year event-free survival estimates based on extent of resection (gross-total resection *v* near-total resection/subtotal resection; 77.6% ± 5.8% *v* 42.9% ± 16.2%;

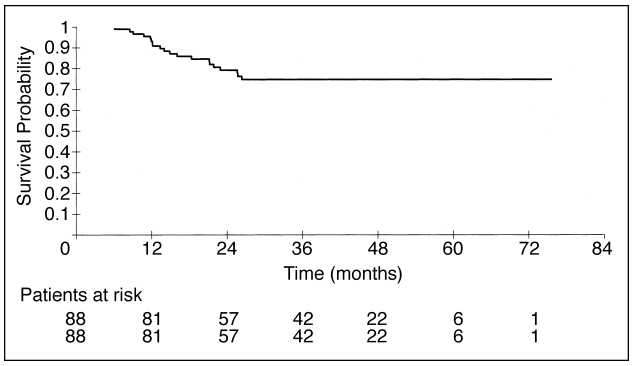

Fig 1. Event-free survival estimates for patients treated with postoperative conformal radiation therapy.

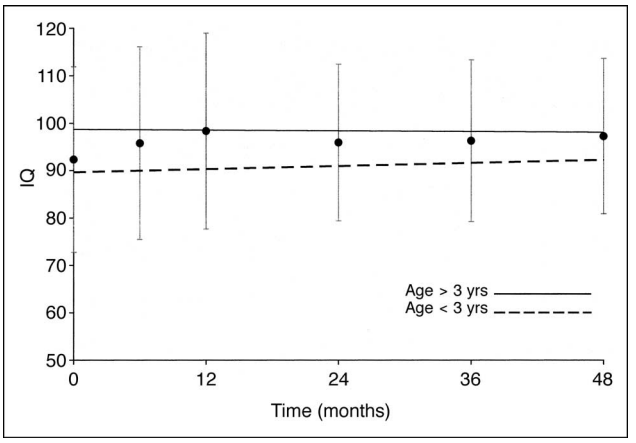

Fig 2. Estimated mean intelligence quotient (IQ) before and after conformal radiation therapy.

$P = .0031$), tumor grade (differentiated versus anaplastic; 90.3% ± 4.6% *v* 43.7% ± 12.4%; $P < .0001$), and history of preirradiation chemotherapy (no chemotherapy *v* chemotherapy, 78.1% ± 6.0% *v* 60.0% ± 14.3%; $P = .0446$). There was no difference in PFS estimates between patients older than 3 years and those younger at the time of irradiation (80.8% ± 7.2% *v* 69.5% ± 8.6%; $P = .23$) or between those with infratentorial tumors and those with supratentorial tumors (74.9% ± 6.3% *v* 71.4% ± 13.5%; $P = .86$). PFS estimates were not influenced by the intervals between the time of symptom appearance and diagnosis, the interval between diagnosis and the start of CRT, and the number of elapsed treatment days. High tumor grade ($P < .0001$) and less than gross-total resection ($P = .001$) negatively affected outcome and the hazard ratio for PFS in a multivariate analysis.

Neurocognitive Effects

The patients underwent a total of 316 neurocognitive examinations to evaluate changes in intelligence quotient (IQ), memory, academic achievement, adaptive behavior, and visual-auditory learning. There was no statistically significant change in the measures of these features for patients who completed evaluation 24 months after the initiation of CRT (more than half of the cohort; Figs 2 through 4). However, patients younger than 3 years at the time of CRT had a significantly lower mean IQ at the start of CRT than did patients older than 3 years (89.7 ± 2.8 *v* 98.7 ± 3.1; $P = .034$), but the IQ of those younger than 3 years improved over time. There was no statistically significant difference in IQ scores for patients comparing infratentorial and supratentorial tumor location. At the most recent follow-up, mean scores on all neurocognitive outcomes were within normal limits (ie, no more than +10 points from the normative mean for the appropriate age group).

DISCUSSION

The purpose of this study was to test the hypothesis that irradiation of a smaller-than-conventional treatment volume reduces side effects without affecting the rate of tumor control or local pattern of failure. The results of this study demonstrated a 3-year PFS estimate of 74.7% ± 5.7% for patients with ependymoma treated with CRT using an anatomically confined CTV whose 10-mm margin surrounded the postoperative tumor bed. The rate of failure in the study is less than those of other studies, which have yielded 2- to 5-year PFS estimates of only 50% to 67%.[25-30]

Of the 20 patients who experienced recurrence or progression, none had marginal failures; however, the relatively large proportion of patients experiencing relapse with disease in the neuraxis but not at the primary site after treatment was both disappointing and informative. This proportion was higher than the expected proportion, which is based on lower rates reported in some series,[31] and may indicate that the overall pattern of

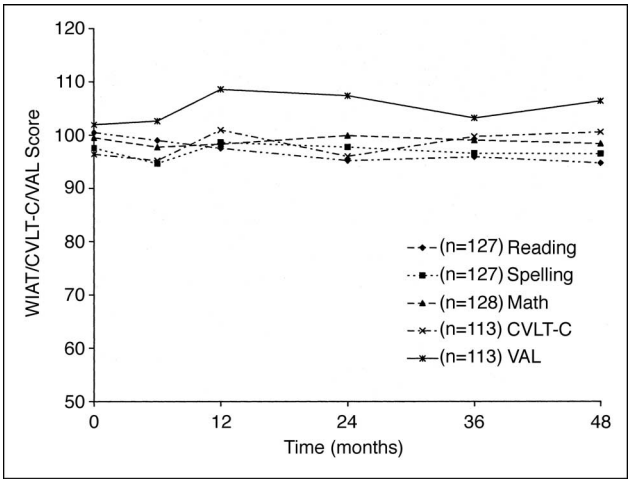

Fig 3. Mean Wechsler Individual Achievement Test (WIAT) scores before and after conformal radiation therapy. CVLT-C, California Verbal Learning Test: Child; VAL, visual-auditory learning test.

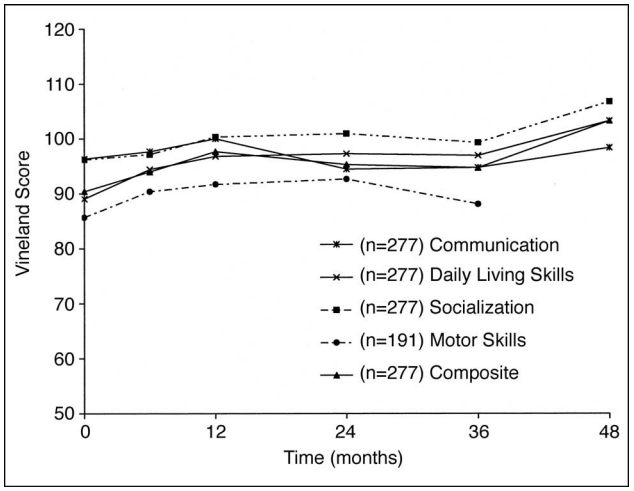

Fig 4. Mean Vineland Adaptive Behavior Scale scores before and after conformal radiation therapy.

failure changed as a result of the high rate of local tumor control and gross-total resection.[30]

The improved rate of disease control in this study may be attributable to factors that include the high proportion of cases in which gross-total resection was done, systematic targeting with three-dimensional imaging, and the relatively high prescribed total dose. Gross-total resection was performed in 84% of cases, near-total resection in 7%, and subtotal resection in 9%; the average volume of residual disease was only 1.2 cm^3. The percentage of cases in which gross-total resection was conducted in this study was higher than the national average, which has ranged from 40% to 60%.[32,33]

We evaluated CNS effects in a rigorous, consistent manner, using widely accepted tests to identify the effects of radiation on cognitive, endocrine, and neurologic function. The most encouraging finding from this study was the level of function and lack of treatment-related effects in a young and vulnerable group of children treated with high-dose irradiation. Only a limited comparison of neurocognitive effects can be made between patients from this study and those treated conventionally, because prospective data from a similarly well-characterized group of pediatric patients with ependymoma are not available. After correcting for other factors responsible for neurocognitive function in pediatric patients with CNS tumors, other investigators found that the dose and volume of irradiation seem to play a role in altering neurocognitive status or intellectual outcome. In a study that included 59 pediatric patients with medulloblastoma and 37 with posterior fossa ependymoma (including 14 patients younger than 3 years at the time ependymoma was diagnosed), 90% of those with ependymoma, which was treated with irradiation to the posterior fossa, maintained an IQ greater than 90 at 5 to 10 years after treatment.[34] In the group with medulloblastoma, which was treated with craniospinal irradiation and a boost to the posterior fossa, only 20% of patients had an IQ greater than 90 at 5 years, and the proportion decreased to 10% at 10 years. In a separate publication, a review of multiple studies compared the IQ of pediatric patients treated postoperatively with craniospinal irradiation, focal irradiation of the primary site, or no irradiation.[35] Patients who received craniospinal irradiation had significantly lower IQs than those who did not receive such treatment; however, those treated with focal irradiation had IQ values comparable to those who received no irradiation. These results support efforts to reduce the volume of irradiation. Much of the fear instilled in those who treat young children with brain tumors may be derived from reports about children with medulloblastoma for whom a persistent and early decline in intellectual outcome is anticipated after craniospinal irradiation.[36] Perhaps the most direct comparison of the present neurocognitive outcomes can be made with the results from the study of Grill et al,[37] who reported a mean IQ of 85.3 (standard deviation, $\pm$ 13.6) for 12 long-term survivors of ependymoma treated with conventional posterior fossa irradiation at age $\geq$ 5 years. Spiegler et al[38] recently reported on four patients with ependymoma and 30 with medulloblastoma in a study that was meant to show change over time and the onset of stability for IQ measured after radiation therapy. Because of the small number of serial evaluations, their modeling was limited to 17 patients evaluated within 6 months from diagnosis and followed for a median of 3.3 years. They found that patients evaluated early in their treatment course experienced a steep decline with eventual leveling in the pattern of a quadratic function.

Our study is unique because it includes children younger than 3 years at the time of irradiation. The age of 3 years has been used to define those who are at greatest risk of the effects of irradiation and for whom trials have been designed in an effort to delay or avoid irradiation. Age at the time of diagnosis has also been described as an important prognostic factor. In the present study, 13 of the 48 patients younger than 3 years experienced disease progression. Children in this age group in earlier studies had a worse prognosis than older patients, possibly because of more aggressive tumor biology, reluctance to give postoperative radiation therapy, or use of lower doses of radiation.[29,39,40] The first infant study by the Pediatric Oncology Group attempted to delay radiation therapy by using postoperative chemotherapy and showed a significant difference in outcome based on age.[3,41] The 5-year PFS estimate was 12.7% $\pm$ 8% for the 31 patients between the ages of 0 and 23 months treated with chemotherapy for 2 years, whereas the 17 patients who were 24 to 36 months old treated with chemotherapy for 1 year had an estimate of 54.8% $\pm$ 15%. The age-related differences remained even when the analysis was limited to those without metastases who had undergone gross-total resection: the 5-year PFS estimates were

37.5% ± 17% for the eight patients who were 0 to 23 months of age and 87.5% ± 12% for the eight patients who were 24 to 36 months old. Their findings suggested that the poor survival estimates frequently reported for young children were probably related to the delay in the administration of radiation therapy, although tumor location and extent of resection were important cofactors.

Preirradiation chemotherapy was shown to marginally effect PFS by univariate statistics in this report. The PFS after radiation therapy has been shown to be shorter for those treated with chemotherapy compared with those not treated with chemotherapy.[42,43] In the prospective Pediatric Oncology Group study,[3] those who received chemotherapy for 2 years had a worse PFS when compared with those who received chemotherapy for 1 year; however, because the Pediatric Oncology Group study did not have a radiation control arm, the effect seemed to be age-related. In our study, we had a sufficient number of young patients who did and did not receive chemotherapy so that we were able to perform univariate and multivariate analyses to show that age was not a factor and that preirradiation chemotherapy affects PFS by univariate statistics. The marginal significance of this result leads us to believe that the 7-week course of chemotherapy for incompletely resected patients on the current Children's Oncology Group study will not compromise PFS.

The French Society of Pediatric Oncology conducted a study to determine whether postoperative chemotherapy and additional surgery at the completion of chemotherapy or time of progression could replace radiation therapy as treatment for ependymoma in 73 children younger than 5 years.[5] PFS estimates at 2 and 4 years were 33% and 22%, respectively; 50% of patients experienced relapse during the planned chemotherapy course. Radiation therapy was ultimately delivered to 39 patients (53%), but nearly 72% of patients with relapsed disease required further surgery and irradiation. At the time of their report, 34 patients (47%) had avoided irradiation, but only 11 were without evidence of disease and remained at high risk of progression.

The median age of patients enrolled on the present study was 2.85 years, and their outcome has raised further questions about the necessity of chemotherapy and of efforts to delay or avoid irradiation. On the basis of our findings, the use of radiation therapy for pediatric patients of all ages (1 to 21 years) has been adopted by investigators from the Children's Oncology Group. The current national trial for pediatric patients with localized ependymoma uses the targeting guidelines from this study and seeks to increase the proportion of cases in which gross-total resection is achieved, through the use of second surgery (Children's Oncology Group ACNS0121).

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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CLINICAL INVESTIGATION **Brain**

A RETROSPECTIVE STUDY OF SURGERY AND REIRRADIATION FOR RECURRENT EPENDYMOMA

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Purpose: To report disease control for patients with recurrent ependymoma (EP) treated with surgery and a second course of radiation therapy (RT_2).
Patients and Methods: Thirty-eight pediatric patients (median age, 2.7 years) with initially localized EP at the time of definitive RT underwent a second course of RT after local (n = 21), metastatic (n = 13), or combined (n = 4) failure. Reirradiation included radiosurgery (n = 6), focal fractionated reirradiation (n = 13), or craniospinal irradiation (CSI; n = 19).
Results: Initial time to failure was 16 months, and median age at second treatment was 4.8 years. Radiosurgery resulted in significant brainstem toxicity and one death (median dose, 18 Gy). Progression-free survival ratio was greater than unity for 4 of 6 patients; there was one long-term survivor. Three of 13 patients treated using focal fractionated reirradiation (median combined dose, 111.6 Gy) experienced metastasis. The CSI was administered to 12 patients with metastatic failure, 3 patients with local failure, and 4 patients with combined failure. The 4-year event-free survival rate was 53% ± 20% for 12 patients with metastatic failure treated with CSI. Failure after CSI was observed in 1 of 3 patients with a history of local failure and 3 of 4 patients with a history of combined failure.
Conclusion: Patients with locally recurrent EP experience durable local tumor control, but remain at risk of metastasis. Patients with metastatic EP failure may receive salvage therapy that includes a component of CSI. Durability of disease control and long-term effects from this approach require further follow-up. © 2008 Elsevier Inc.

Radiotherapy, Re-treatment, Ependymoma, Pediatrics, CNS neoplasms, Toxicity.

INTRODUCTION

Children with ependymoma (EP) for which treatment fails after surgery and radiation therapy (RT) have few options: chemotherapy may prolong survival, but is not curative, and surgeons are reluctant to approach recurrent disease without the backing of effective adjuvant salvage therapy.

Fractionated reirradiation may be a potential treatment for these patients. However, guidelines have not been established, relative benefits and risks are unknown, and most reported reirradiation series included patients with diverse diagnoses and combined adult and pediatric patients (1, 2). Single-fraction radiosurgery was used in selected patients with locally recurrent or metastatic EP with mixed results. Morbidity was high, and durable disease control was not clearly shown (3, 4). Fractionated reirradiation has not been systematically explored for patients with EP, mainly because these patients tend to be young and pediatric oncologists are not familiar with reirradiation as a treatment option.

We identified 38 patients with EP recurrent after previous surgery and conventionally fractionated RT and subsequently treated with radiosurgery, focal fractionated reirradiation (FFRT), or craniospinal irradiation (CSI) at our institution. We reviewed treatment and outcomes for these patients with the hope of developing guidelines for reirradiation or highlighting the relative risks based on clinical information. From a review of the data, three groups emerged to focus our effort to outline strategies for the use of radiation as a salvage therapy for patients with EP.

PATIENTS AND METHODS

Thirty-eight patients with EP recurrent after surgery and RT and subsequently treated by using single-fraction radiosurgery (n = 6), FFRT (n = 13), and CSI (n = 19) were identified for an institutional review board–approved retrospective review.

Review of patient information included, at a minimum, date of birth, diagnosis, surgery, chemotherapy, RT, disease progression

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after initial irradiation (the first course of irradiation [RT_1]) and reirradiation (the second course of irradiation [RT_2]), follow-up, and death. Patient sex, extent of resection, tumor grade at initial and subsequent resections, sites of relapse, radiation dose and volume, chemotherapy agents, major toxicities, use of hyperbaric oxygen therapy (HBOT), and disease status (no evidence of disease, stable disease, and progressive disease) were recorded.

RT_2 techniques

In a nonrandomized manner, patients were offered one of three reirradiation methods: radiosurgery, FFRT, and CSI. Treatment selection was driven by treatment era, cumulative experience, and, more recently, patient age. Radiosurgery was considered for some of the earliest patients treated in this series to limit dose to normal tissue. These patients were treated by using conventional irradiation that included substantial normal tissue irradiation. With the observed toxicity of radiosurgery, FFRT was explored and found to be tolerable. Considering the very limited volume of normal tissue currently irradiated using three-dimensional treatment techniques and our three-dimensional understanding of the distribution of dose, CSI was explored as a last resort in children with metastatic disease or older patients with local failure, considering their risk of future metastatic failure. The CSI was administered with some modification of the standard technique to patients with metastatic disease and a cohort of patients with local failure. Modifications were limited to patients with a history of previous infratentorial irradiation, and for the lateral cranial fields, included customized cerrobend blocking that followed the cranial outline from the temporal bone to the occiput and shielding of the previously irradiated upper cervical spinal that received approximately more than 30% of the previous prescription dose, or about 16.2 Gy. This level of shielding was empirically chosen to limit the combined cord dose to approximately 16.2 + 39.6 = 55.8 Gy. All craniospinal treatments were photon based, with dose prescribed at the midplane (cranium) and anterior aspect of the spinal canal (spine). Supplemental treatment of metastatic sites generally included forward-planned conformal RT targeting the tumor and/or tumor bed that was then expanded by a margin of 5 mm to form the planning target volume. Focal fractionated irradiation included forward-planned conformal RT in which the gross tumor volume included the tumor and/or tumor bed that was expanded by 5 mm, edited at anatomic boundaries to form a clinical target volume, and then geometrically expanded an additional 3–5 mm to form the planning target volume. All patients were treated with 4- or 6-MV photons. An example of FFRT for local failure is shown in Fig. 1, and an example of CSI after metastatic failure and metastasectomy is shown in Fig. 2. With reference to Table 1, treatment details for the 6 patients treated with radiosurgery at the time of failure include the following: Patient 1, Gamma Knife, 20 Gy to 50% using 8-mm collimator and one shot; Patient 2, stereotactic radiosurgery (SRS), 17.5 Gy to 90% using 25-mm collimator; Patient 3, SRS, 16.5 Gy to 90% using 25-mm collimator; Patient 4, Gamma Knife, 15 Gy to 50% using 8- and 4-mm collimators and six shots; Patient 5, SRS, 18 Gy to 90% using 25-mm collimator; and Patient 6, SRS, 18 Gy to 90% using a 30-mm collimator.

Analysis

Analysis included descriptive statistics and Kaplan-Meier progression-free survival (PFS) statistics. Results were presented primarily with study patients separated into three groups representing those treated at relapse with SRS, FFRT, and CSI, including sequential focal boost treatment of sites of relapse.

Definitions

Local failure included failure at the primary site with no evidence of metastasis. Metastatic failure included failure at sites not previously involved with tumor with no evidence of recurrence at the primary site. Combined failure included simultaneous local recurrence and metastasis. The RT_1 was defined as the first course of RT, and RT_2 was defined as the second course of RT.

RESULTS

Study group

Relevant patient information and outcomes are listed in Tables 1, 2, and 3. The study group included 24 male and 14 female patients with a median age at diagnosis of 2.5 years (range, 0.6–15.0 years), median age at time of RT_1 of 2.7 years (range, 1.1–15.3 years), and median age at time of RT_2 of 4.8 years (range, 2.0–16.9 years). No study patient had evidence of metastatic disease at the time of diagnosis. Eight patients had a supratentorial primary tumor location. Before the initiation of RT_1, 16 patients underwent chemotherapy and the extent of resection was recorded as gross total

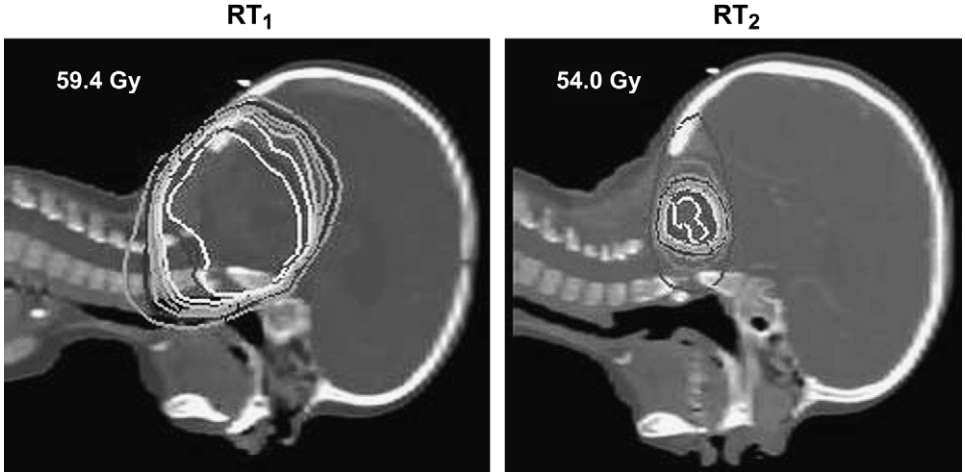

Fig. 1. Example of focal reirradiation (second course of radiotherapy [RT_2]) for ependymoma after prior focal radiation therapy (RT_1). The central isodose line (white) represents the prescription dose.

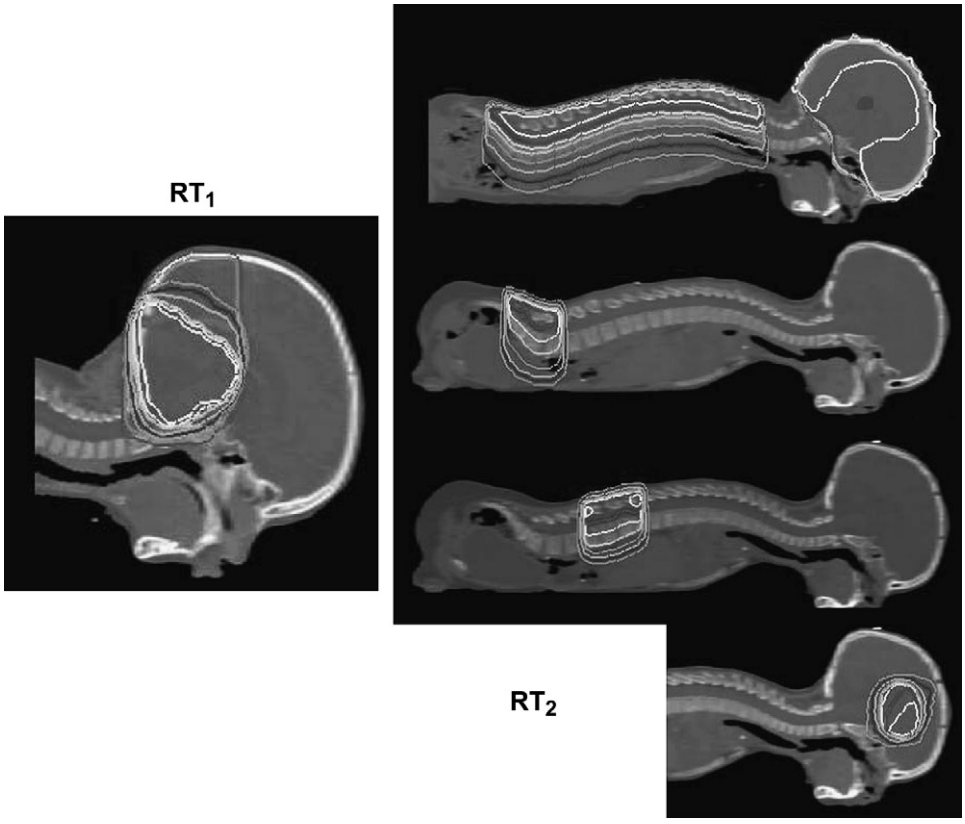

Fig. 2. Example of craniospinal and metastatic site dosimetry (second course of radiotherapy [RT_2]) for ependymoma after prior focal radiation therapy (RT_1). The central isodose on the RT_1 plan (white) represents the prescription dose of 59.4 Gy.

resection (GTR) in 26, near-total resection (NTR; ≤5 mm thickness residual) in 6, and subtotal resection (STR) in 5 patients. Seventeen patients had anaplastic tumor grade, 6 were found to have focal anaplasia, and the remainder had differentiated EP.

RT_1: initial irradiation

A variety of dose, volume, and fractionated regimens were used for the initial treatment. Thirty-six patients were treated by using conventional fractionation (1.6–2.0 Gy/d) to 60.4 (n = 1), 59.4 (n = 22), 55.8 (n = 2), 54 (n = 5), 50.4 (n = 2), 50 (n = 1), 48 (n = 1), 40 (n = 1), and 37.8 Gy (n = 1). Two patients were treated by using hyperfractionated irradiation (1.2 Gy/d) to 69.6 Gy. Three patients were treated with supplemental radiosurgery as part of their initial management: 1 with 8 Gy after fractionated 40 Gy, 1 with 9 Gy after fractionated 54 Gy, and 1 with 15 Gy after fractionated 59.4 Gy. One patient received CSI to 30.4 Gy followed by focal fractionated irradiation to 48 Gy as a part of initial management. All patients were treated with 4- or 6-MV photons.

Failure after RT_1 and treatment before RT_2

Median time to failure after RT_1 was 19 months (range, 3–73 months). Local failure (n = 21) occurred with a median time of 20 months (range, 9–73 months), metastatic failure (n = 13) occurred with a median time of 22 months (range, 3–62 months), and combined local and metastatic failure (n = 4) occurred with a median time of 10 months (range, 7–26 months; Fig. 3). At the time of RT_1 relapse, 2 patients were treated briefly with chemotherapy (ifosfamide, carboplatin, and etoposide for two cycles) and 35 of 38 patients were treated with additional surgery. All 4 patients with combined local and metastatic failure underwent attempted resection of local and metastatic disease (one to four metastatic sites/patient), and GTR was achieved in 2 patients. Twelve of 13 patients with metastatic failure underwent metastasectomy (one to three metastatic sites/patient). The extent of resection was characterized as GTR in 7, NTR in 3, and STR in 2 patients. Nineteen of 21 patients with local failure underwent GTR (n = 12), NTR (n = 4), or STR (n = 3).

RT_2: radiosurgery

Six lesions in 6 patients were treated by means of radiosurgery using a median dose of 18 Gy (range, 15–20 Gy). Lesions in 5 patients were entirely within the high-dose volume of previous treatment; the lesion in the sixth patient was an isolated metastasis to the lateral ventricle. Median time from initiation of RT_1 to RT_2 was 21.9 months (range, 7.5–67.7 months), and from RT_1 failure to RT_2, 1.4 months (range, 0.4–2.3 months). Four patients underwent surgery before RT_2, resulting in GTR (n = 2) or STR (n = 2). Two patients experienced progression with local failure at 6.3 and

Table 1. Clinical and salvage treatment information for study patients

Patient	Reirradiation volume	Lesions/ surgery sites	Resection or metastasectomy results	Interval RT1 RT2 (mo)	RT age (Y)	CSI dose (Gy)	RT2 irradiation sites			Maximal reirradiation dose (Gy) and site	RT2 failure
							Site 1 (Gy)	Site 2 (Gy)	Site 3 (Gy)		
1	SRS	1/1	—	10.7	2.0	—	Plneal(17.7)	—	—	Pineal (48)+17.5 SRS	Combined
2	SRS	1/1	STR	21.9	6.0	—	CP angle (16.5)	—	—	Cerebellum/stem (50.4) + 16.5 SRS	Local
3	SRS	1/1	STR	29.8	5.3	—	4^{th} ventricle (15.0)	—	—	Cerebellum/stem (60.4) + 15 SRS	Local
4	SRS	1/1	GTR	37.4	9.7	—	4^{th} ventricle (18.0)	—	—	Cerebellum/stem (69.6) + 18 SRS	
5	SRS	1/1	GTR	67.7	7.3	—	Obex (18.0)	—	—	Cerebellum/stem (50.4) + 18 SRS	
6	SRS	1/1	—	7.5	3.3	—	4^{th} ventricle (20.0)	—	—	no overlap	Combined
7	local	1/1	GTR	75.7	10.1	—	4^{th} ventricle (50.4)	—	—	Cerebellum/stem (90.4) + SRS	
8	local	1/1	NTR	10.5	4.3	—	4^{th} ventricle (54.0)	—	—	Cerebellum (113.4)	
9	local	1/1	—	14.1	9.5	—	Temporal (50.6)	—	—	Temporal (108.4)	Metastases
10	local	1/1	NTR	14.1	10.8	—	Foramen rotundum (52.2)	—	—	Cerebellum/stem (111.6)	Metastases
11	local	1/1	GTR	14.7	3.1	—	4^{th} ventricle (54.0)	—	—	Cerebellum/stem (113.4)	
12	local	1/1	NTR	17.1	6.2	—	4^{th} ventricle (52.2)	—	—	Cerebellum/stem (111.6)	Metastases
13	local	1/1	STR	23.1	5.3	—	Left sylvlan issue (50.6)	—	—	frontotemporal(101.0)	
14	local	1/1	GTR	25.2	3.5	—	CP angle (54.0)	—	—	Cerebellum/stem (109.4)	
15	local	1/1	GTR	25.9	4.1	—	4^{th} ventricle (54.0)	—	—	Cerebellum/stem (113.4)	
16	local	1/1	GTR	22.0	3.5	—	4^{th} ventricle (54.0)	—	—	Cerebellum/stem (113.4)	
17	local	1/1	GTR	24.6	3.6	—	4^{th} ventricle (52.2)	—	—	Cerebellum/stem (111.6)	
18	local	1/1	GTR	82.2	9.9	—	4^{th} ventricle (50.4)	—	—	Cerebellum/stem (120.0)	
19	local	1/1	GTR	77.8	13.5	—	4^{th} ventricle (54.0)	—	—	Cerebellum/stem (108.0)	
20	CSI	3/3	GTR	10.7	14.1	41.4	Frontal midline (57.6)	Occipital (57.6)	Parasagittal (57.6)	Frontal (111.6)	Combined
21	CSI	5/3	STR	17.6	6.2	41.4	4^{th} ventricle (54.0)	Lateral ventricles (54)	L2L3 (54.0)	Cerebellum/stem (113.4) + SRS	Local
22	CSI	2/2	STR	20.1	16.9	39.6	Parietal (57.6)	—	—	Parietal (117.0)	Metastases
23	CSI	2/2	GTR	33.9	4.8	35.2	Cerebellum (48.6)	T4 (45.4)	—	Cerebellum/stem (86.4)	
24	CSI	1/1	GTR	50.9	10.0	38.6	Coolpital (59.4)	—	—	Occipital (113.4)	Local

(*Continued*)

Table 1. Clinical and salvage treatment information for study patients (*Continued*)

Patient	Reirradiation volume	Lesions/ surgery sites	Resection or metastasectomy results	Interval RT1 RT2 (mo)	RT age (Y)	CSI dose (Gy)	RT2 irradiation sites			Maximal reirradiation dose (Gy) and site	RT2 failure
							Site 1 (Gy)	Site 2 (Gy)	Site 3 (Gy)		
25	CSI	1/1	NTR	29.9	6.6	39.6	4^{th} ventricle (54.0)	—	—	Cerebellum/stem (113.4)	
26	CSI	1/1	GTR	35.7	5.1	39.6	4^{th} ventricle (54.0)	—	—	Cerebellum/stem (113.4)	
27	CSI	1/1	GTR	4.2	5.4	39.6	L36 S1 (59.4)	—	—	Cerebellum/stem (99.0)	
28	CSI	4/3	STR	13.0	5.8	39.6	Lateral ventricles (59.4)	Conus (54)	Sacrum (59.4)	Cerebellum/stem (99.0)	Metastases
29	CSI	1/1	GTR	22.3	4.7	39.6	Infundibular recess (54.0)	—	—	Cerebellum/stem (99.0)	
30	CSI	3/1	GTR	20.5	4.0	39.6	Lateral ventricles (59.4)	—	—	Cerebellum/stem (99.0)	
31	CSI	2/2	GTR	32.5	5.8	37.6	Frontal (55.8)	Finecal sac (57.6)	—	Cerebellum/stem (93.6)	
32	CSI	3/3	GTR	23.1	9.3	39.6	Foramen rotundum (54.0)	L1 (54.0)	C7 (52.2)	Parietal (93.6)	
33	CSI	1/1	GTR	23.6	4.2	41.4	Lateral ventricle (54.0)	—	—	Cerebellum/stem (99.0)	
34	CSI	1/1	GTR	24.3	4.8	39.6	Ca update (59.4)		—	Cerebellum/stem (99.0)	
35	CSI	5/3	GTR	25.3	13.3	39.6	T6 (54)	T12 (54.0)	—	Cerebellum/stem (99.0)	
36	CSI	1/1	GTR	28.0	3.7	39.6	Sylvian fissure (59.4)	—	—	Cerebellum/stem (99.0)	Metastases
37	CSI	2/2	GTR	43.7	10.2	39.6	Cervicomodullary (57.6)	Conus (57.6)	—	Parietal (93.6)	Metastases
38	CSI	1/1	STR	63.3	8.5	39.6	Fontal (59.4)	—	—	Cerebellum/stem (99.0)	

Abbreviations: SRS = stereotactic radiosurgery; CSI = craniospinal irradiation; NTR = near-total resection; GTR = gross total resection; STR = subtotal resection; RT = radiation therapy; RT1= initial radiotherapy; RT2 = reirradiation; CP = cerebellopontine.

Table 2. Patient disease control intervals and outcomes according to reirradiation volume and initial pattern of failure.

Patient	Reirradiation volume	Initial pattern of failure	PFS, RT1 (months)	PFS, RT2 (months)	PFSRT1/PF SRT2	RT2 progression	Disease status	Overall survival (months)
1	SRS	Local	10	18.50	1.80	Yes	DOD	65.5
2	SRS	Local	20	6.23	0.31	No	DOD	57.5
3	SRS	Local	27	11.90	0.43	Yes	DOD	65.1
4	SRS	Local	37	40.53	1.11	Yes	DOC	79.0
5	SRS	Local	66	125.27	1.89	No	NED	194.6
6	SRS	Metastatic	6	8.27	3.28	Yes	DOD	24.7
7	Local	Local	9	76.83	8.44	No	NED	190.2
8	Local	Local	9	1.43	0.15	No	SD	13.5
9	Local	Local	10	4.10	0.41	Yes	DOD	48.6
10	Local	Local	13	7.70	0.58	Yes	DOD	26.3
11	Local	Local	14	38.63	2.85	No	NED	60.7
12	Local	Local	15	6.07	0.41	Yes	DOD	46.2
13	Local	Local	16	136.33	8.72	No	NED	169.8
14	Local	Local	16	2.63	0.16	No	NED	35.7
15	Local	Local	19	4.43	0.23	No	NED	33.1
16	Local	Local	21	8.67	0.42	No	NED	34.5
17	Local	Local	23	41.10	1.77	No	NED	69.1
18	Local	Local	59	78.47	1.33	No	NED	169.2
19	Local	Local	73	29.87	0.41	No	NED	109.6
20	CSI	Metastatic	3	22.17	7.15	No	SD	31.5
21	CSI	Combined	7	6.80	1.01	Yes	DOD	24.2
22	CSI	Combined	10	9.63	0.99	Yes	DOD	35.0
23	CSI	Metastatic	11	19.03	1.74	Yes	PD	71.2
24	CSI	Metastatic	17	24.30	1.40	No	NED	51.8
25	CSI	Metastatic	18	18.97	1.07	No	NED	39.7
26	CSI	Combined	19	8.53	0.45	Yes	DOD	37.1
27	CSI	Metastatic	22	69.73	3.24	No	NED	103.2
28	CSI	Metastatic	22	40.70	1.89	No	SD	139.9
29	CSI	Metastatic	22	49.50	2.23	No	NED	75.1
30	CSI	Metastatic	23	4.43	0.19	No	NED	29.8
31	CSI	Metastatic	25	2.53	0.00	No	SD	35.5
32	CSI	Combined	26	261.03	10.21	No	NED	303.9
33	CSI	Metastatic	26	40.67	1.56	Yes	PD	77.6
34	CSI	Local	27	6.03	0.23	Yes	DOD	70.0
35	CSI	Local	28	14.87	0.53	No	SD	49.3
36	CSI	Local	35	13.30	0.38	No	NED	59.3
37	CSI	Metastatic	43	32.40	0.76	Yes	PD	78.4
38	CSI	Metastatic	62	19.30	0.31	No	SD	92.9

Abbreviations: SRS = stereotactic radiosurgery; CSI = craniospinal irradiation; PFS = progression-free survival; RT1 = initial radiation therapy; RT2 = reirradiation; DOD = dead of disease; DOC = dead of other causes; NED = no evidence of disease; SD = stable disease.

11.9 months and died, 2 experienced progression with combined local and distant recurrence at 8.3 and 18.5 months and died, 1 died of radiation necrosis at 40 months, and 1 patient remains without evidence of disease 10 years after SRS, but required surgery and HBOT 8 years after SRS for necrosis. Notably, all 4 patients who experienced disease progression and died had neuroimaging or pathologic evidence of necrosis. Despite the poor outcome, the progression-free survival of second radiation course/progression-free survival of first radiation course (PFS_{RT2}/PFS_{RT1}) ratio was greater than unity for 4 of 6 patients and was 1.89 for the only survivor, whose initial recurrence was experienced 66 months after her initial treatment with GTR and 50 Gy.

RT_2: FFRT

Thirteen patients with local failure were treated by using FFRT to a median dose of 52.2 Gy (range, 50.4–54 Gy). Median combined total dose was 111.6 Gy (range, 98.4–120 Gy). Median time from initiation of RT_1 to RT_2 was 23 months (range, 10–82 months), and from RT_1 failure to RT_2, 4 months (range, 1–66 months). Twelve of 13 patients underwent repeated resection at the time of RT_1 failure. The group was composed of 11 patients with an infratentorial primary tumor location. Surgery was not performed in 1 of 2 patients with a supratentorial primary tumor location. Two patients underwent multiple attempts at resection and chemotherapy regimens before RT_2, which facilitated the two longest delays from RT_1 failure to RT_2 of 23.4 and 66 months. Three patients in this group experienced progression with metastatic failure at 4, 6, and 7 months and subsequently died at 10, 17, and 20 months after RT_2 despite additional therapy. Widespread metastatic disease, including metastatic disease in the region of the primary site, made it difficult to determine the durability of local control. The remaining 10

Table 3. Clinical and initial treatment information for study patients

Patient	Reirradiation volume	IT (or) ST	Initial tumor Grade	Chemotheraphy	Surgery extent	RT/ age (Y)	Dose (Gy)	Pattern of Failure POF
1	SRS	ST	AEP	Yes	GTR	1.1	48 (30.4 Gy CSI)	Local
2	SRS	IT	EP	Yes	GTR	4.2	50.4	Local
3	SRS	IT	EP	Yes	NTR	2.8	60.4	Local
4	SRS	IT	EP	No	NTR	6.6	69.6	Local
5	SRS	IT	EP	No	GTR	1.8	50.0	Local
6	SRS	IT	AEP	No	NTR	2.7	54(+9 +Gy SRS)	Metastatic
7	Local	IT	FAEP	Yes	STR	3.9	40(+8 +Gy SRS)	Local
8	Local	IT	EP	No	GTR	3.4	59.4	Local
9	Local	ST	AEP	No	GTR	6.3	55.8	Local
10	Local	IT	AEP	Yes	NTR	9.7	59.4	Local
11	Local	IT	AEP	No	GTR	1.9	59.4	Local
12	Local	IT	FAEP	Yes	NTR	4.6	59.4	Local
13	Local	ST	AEP	Yes	GTR	3.4	50.4	Local
14	Local	IT	AEP	Yes	STR	1.4	55.8	Local
15	Local	IT	AEP	No	GTR	2.0	59.4	Local
16	Local	IT	EP	Yes	GTR	1.7	59.4	Local
17	Local	IT	FAEP	No	GTR	1.5	59.4	Local
18	Local	IT	AEP	No	GTR	3.1	69.6	Local
19	Local	IT	EP	No	GTR	7.1	54.0	Local
20	CSI	ST	AEP	Yes	GTR	13.2	54.0	Combined
21	CSI	IT	EP	No	STR	4.7	59.4 (+15Gy SRS)	Combined
22	CSI	ST	AEP	No	GTR	15.3	59.4	Combined
23	CSI	IT	EP	Yes	STR	2.0	37.8	Combined
24	CSI	ST	FAEP	No	GTR	5.9	54.0	Local
25	CSI	IT	EP	Yes	NTR	4.2	59.4	Local
26	CSI	IT	FAEP	Yes	GTR	2.2	59.4	Local
27	CSI	IT	AEP	No	GTR	5.1	59.4	Metastatic
28	CSI	IT	FAEP	No	GTR	4.8	59.4	Metastatic
29	CSI	IT	AEP	No	GTR	2.9	59.4	Metastatic
30	CSI	IT	FAEP	No	GTR	2.3	59.4	Metastatic
31	CSI	IT	FAEP	No	GTR	3.1	59.4	Metastatic
32	CSI	ST	AEP	Yes	GTR	7.4	59.4	Metastatic
33	CSI	IT	AEP	No	GTR	2.3	59.4	Metastatic
34	CSI	IT	AEP	No	GTR	2.8	59.4	Metastatic
35	CSI	IT	AEP	Yes	NTR	11.2	59.4	Metastatic
36	CSI	IT	EP	No	GTR	1.4	59.4	Metastatic
37	CSI	ST	AEP	No	GTR	6.6	54.0	Metastatic
38	CSI	IT	EP	Yes	STR	3.3	59.4	Metastatic

Abbreviations: SRS = stereotactic radiosurgery; CSI = craniospinal irradiation; AEP = anaplastic ependymoma; EP = differentiated ependymoma; FAEP = ependymoma with focal anaplasia; GTR = gross total resection; NTR = near-total resection; STR = subtotal resection; RT = radiation therapy; IT = Infratentorial; ST = Supratentorial.

patients had no evidence of disease, with a median follow-up of 30 months (range, 2–136 months) after RT_2. The PFS_{RT2}/PFS_{RT1} ratio was greater than unity for 5 of 10 patients.

RT_2: CSI

Nineteen patients with previous combined (n = 4), local (n = 3), or metastatic (n = 12) failure received CSI after aggressive attempts to resect locally recurrent and/or metastatic disease. Considering the 4 patients with a history of combined failure, 3 experienced relapse at 7, 8, and 9 months, and 1 was the longest survivor in this reirradiation series. The longest survivor experienced concurrent primary site relapse and metastasis to the thoracic spine after previous treatment with subtotal resection and 37.8 Gy. This patient underwent GTR at both sites in 1985, received CSI (35.2 Gy) and boost treatment (48.6 Gy metastasis; 45.4 Gy primary site), and remains disease free more than 20 years later.

Three patients with local failure received CSI for salvage therapy. One patient experienced relapse with metastatic disease after 6 months and died despite subsequent chemotherapy. Follow-up for the remaining 2 patients was 13 and 14 months.

There were 12 patients with metastatic failure after RT_1 who received CSI. All these patients were treated with metastasectomy of spinal, intracranial, or intraventricular disease. Resection was attempted for all lesions except isolated 3-mm spinal lesions in 2 patients that were considered too small to merit additional surgery. Three of 12 patients experienced progression at 19, 32, and 40 months. The remaining 9 patients were followed up without disease progression for a median of 22 months (range, 3–69 months). The PFS_{RT2}/PFS_{RT1}

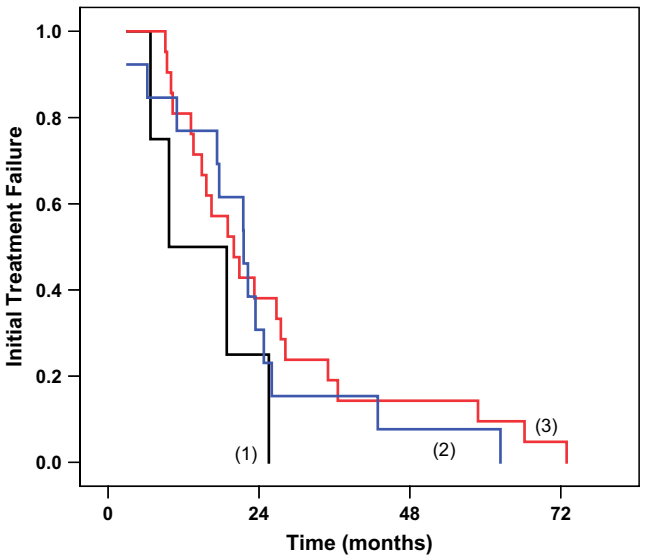

Fig. 3. Initial rates and patterns of failure after surgery and radiation therapy. Combined local and metastatic failure (black–(1)), local failure (red–(3)), and metastastic failure (blue–(2)).

ratio was greater than unity for 6 of 9 patients who have disease control, with a median index of 1.4 (range, 0.1–7.2).

Two of the 3 patients with progressive disease experienced failure at metastatic sites in the brain or spine that were aggressively resected and treated with supplemental irradiation to 59.4 Gy after high-dose CSI.

For patients with metastatic disease treated by using CSI, there was 1 case each of documented secondary malignancy, necrosis, and myelopathy. The patient with the longest PFS in this subgroup developed a histologically confirmed high-grade secondary glial neoplasm that arose 5 years after irradiation to a site of metastatic disease in the supratentorial brain. Total dose to this site was 59.4 Gy. The patient with the shortest interval from initiation of RT_1 to initiation of RT_2, 4 months, developed necrosis at the site of previous focal treatment that was included in the CSI volume. This patient received focal irradiation to the fourth ventricle after GTR and experienced progression with metastatic disease at L_3–S_1 only 10 weeks after completing his first treatment course. After resection, CSI (39.6 Gy) with boost treatment of L_3–S_1 (59.4 Gy) was delivered. Necrosis occurred in the cerebellum approximately 6 months after completing RT_2 and subsequently was treated by using resection and HBOT. The region of necrosis received approximately 99 Gy. The patient remains with neurologic deficits and no evidence of progressive disease 2 years after completion of salvage therapy. The other case was a patient with a history of supratentorial EP treated by using previous focal irradiation. This patient experienced failure with metastases to Meckel's cave, the cervical spine, and conus medullaris. The patient underwent metastasectomy of the intracranial metastases and cervical spinal cord metastasis. After GTR, this patient received CSI to 39.6 Gy and focal treatment to all known sites of metastases, including 54 Gy to the cervical spinal cord. The patient was seen in follow-up for her 2-year evaluation after initiation of RT_2 and was noted to have bilateral lower-extremity weakness. Magnetic resonance imaging of the spinal cord showed extensive T2 changes at the level of previous resection. The HBOT was administered, and 1 year later, the patient returned to her asymptomatic baseline and imaging changes resolved. The PFS for subsets of reported patients is shown in Fig. 4. Median combined total dose at any point of overlap in the brain was 99 Gy (range, 86.4–117 Gy).

Overall survival for three subsets of reported patients is shown in Fig. 5. None of the 12 patients with initial metastatic failure treated by using CSI died despite progression in 3 patients. There were three deaths in the 13 patients with initial local failure treated with FFRT. The overall survival estimate for this subset was 67% ± 16% at 5 years. There was only one survivor in the patients treated with radiosurgery after local failure. The 5-year overall survival estimate was 20% ± 18%.

DISCUSSION

Children with EP tend to be young, with more than 50% of cases diagnosed in patients younger than 3 years. Children in this age range are most vulnerable to the effects of RT, and its use in frontline management is both recent and experimental. Historically, the pattern of failure for children with EP treated with surgery and RT was local. With improving rates of GTR and image-guided high-dose irradiation to 59.4 Gy, the pattern of failure has become mixed, with a greater proportion of patients experiencing failure with metastatic disease (5). The combination of young age and metastatic failure are two prominent factors that drive investigators to test

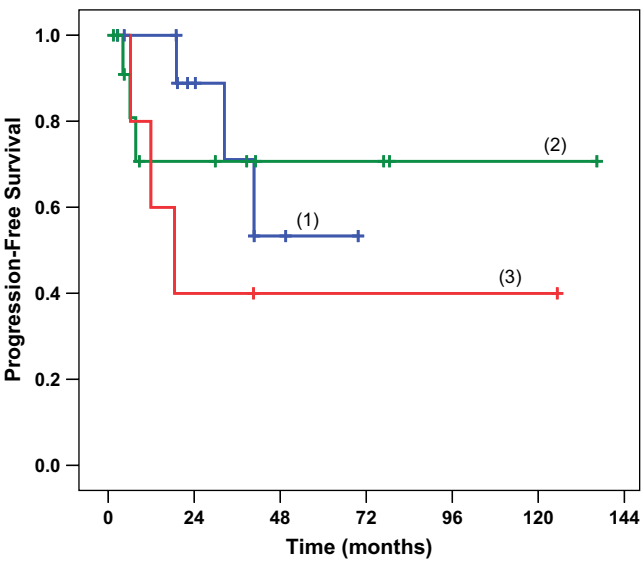

Fig. 4. Progression-free survival after reirradiation according to treatment method and initial tumor pattern failure (blue (1) = 12 patients with metastatic failure treated with craniospinal reirradiation; green (2) = 13 patients with local failure retreated with focal fractionated irradiation; red (3) = 5 patients with local failure treated with radiosurgery).

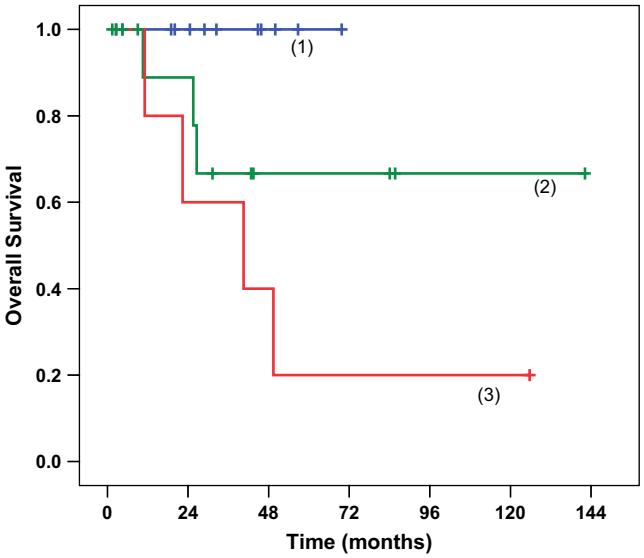

Fig. 5. Overall survival dated from the start of reirradiation according to treatment method and initial tumor pattern failure (blue (1) = 12 patients with initial metastatic failure treated with craniospinal reirradiation; green (2) = 13 patients with local failure retreated with focal fractionated irradiation; red (3) = 5 patients with local failure treated with radiosurgery).

experimental systemic therapies instead of reirradiation for this patient population.

The recent use of conformal RT for the treatment of children with EP has decreased the volume of normal tissues receiving the highest doses and increased our knowledge of dose to normal tissues volumes, leaving open the possibility for reirradiation in the setting of failure after conventional treatment. We have taken advantage of this information to perform additional surgery and reirradiation by using a fractionated treatment approach.

We attempted to present results of this series according to RT_2 type: SRS, FFRT, and CSI, with additional subgroup analysis according to RT_1 failure type. The major findings from this review are the lack of long-term disease control and morbidity of patients undergoing SRS, the durability of disease control and lack of major toxicity for patients undergoing CSI, and the excellent rate of disease control for patients with local recurrences re-treated by using fractionated therapy.

The effectiveness of reirradiation is ultimately measured by the rate of long-term disease control and functional outcome. Although this series spans nearly 20 years, 28 of 32 patients had their RT_2 administered during the past 10 years, making the results preliminary. In this preliminary series, the PFS_{RT2}/PFS_{RT1} ratio was greater than unity for 20 of 38 patients, including 4 of 6 SRS patients, 5 of 13 patients with local failure treated by using FFRT, and 8 of 12 patients with metastatic failure treated by using CSI.

Exploring normal tissue tolerance with reirradiation can lead to lethal complications or tremendous morbidity. This is readily apparent from the SRS group and remains a concern for patients treated by using fractionated reirradiation regardless of the follow-up interval. Although changes in imaging and, to a lesser extent, symptoms were apparent within 6 months of RT in the SRS group, their persistence resulted in morbidity and mortality even years after treatment. Two patients treated by using CSI experienced signs and symptoms suggestive of necrosis. As noted, 1 patient experienced progression to necrosis in the cerebellum requiring surgery and HBOT. This case was notable because the event might have been predicted based on the short interval between the RT_1 and RT_2 treatment courses. However, because our technique of reirradiation using a combination of CSI and boost treatment seeks comprehensive coverage of the neuraxis, shielding large volumes of previously irradiated tissue invites reseeding. The other case was a patient who underwent metastasectomy of a cervical spinal cord metastasis and developed signs of myelopathy. She was successfully treated by using HBOT.

The interval between courses of radiation is recognized, along with such other clinical factors as the specific region of the brain or spinal cord, as an important variable to consider when offering re-treatment (6). Although investigators showed by experimentation or in clinical studies that the spinal cord may tolerate reirradiation to relatively high doses (7, 8), we restricted re-treatment to the spinal cord when administering CSI to patients who had undergone previous infratentorial irradiation that involved the upper cervical spinal cord. The addition of CSI to a dose of 39.6 Gy and to regions treated to less than 30% of the previously prescribed 54 Gy achieves a biological equivalant dose (BED) of approximately 96 Gy_2, whereas overlap of the entire cervical cord with the combined doses of 54 and 39.6 Gy would achieve a biological equivalent dose (BED) of approximately 246 Gy_2. The former value is within the lower range and the latter is within the upper range of the previously reported cumulative spinal cord doses of 102–181.5 Gy_2, for which the risk of myelopathy was estimated at 25%. In our patients, categorized as intermediate risk based on cumulative dose, the BED of the first course of treatment was about 129 Gy_2 (8).

Indications for reirradiation require exploration. In addition, guidelines need to be established with regard to dose and volume. Patients who experience progression with combined local and metastatic failure after previous RT fare poorly with RT_2 and should be considered for experimental therapy or a combined-modality approach involving CSI. Patients who experience progression with metastatic disease, but remain controlled at the primary site, should be considered for aggressive metastasectomy and CSI, with attention given to the timing of reirradiation, normal tissue tolerances, and adequate treatment of the volume at risk. Progression at sites of metastasectomy and high-dose irradiation with durable control at the primary site suggest the need for more aggressive surgery to achieve negative margins, greater cumulative doses of radiation to the metastatic site, or a combined-modality approach that would include agents synergistic with RT.

Patients who experience progression with local failure require careful neuraxis surveillance for metastatic disease and aggressive local resection with definitive evidence that

the recurrence was local. The nature and timing of the local failure may provide helpful clues about the risk of neuraxis dissemination and move caregivers to recommend focal or craniospinal treatment. The specter of metastatic disease may be decreased in a patient who experiences disease progression where residual tumor was known to remain after initial surgery or in a patient who develops obvious local failure relatively late, longer than 3 years after RT. Clinical condition and age of a patient also require consideration; very young or debilitated patients may not fare well with CSI. We do not propose a lower age cutoff for CSI, but consider it to be an option in children older than 3 years because patients of a similar age with medulloblastoma continue to undergo high-dose CSI as a front-line treatment option.

The role of radiosurgery is difficult to define from our series because of the small number of patients and preponderance of treatment sites that involve the brainstem. Although it might be considered a better option for patients with supratentorial local or metastatic disease, these patients tend to have operable disease that may be removed and simplify follow-up, which, after radiosurgery, is often complicated by changes in the treated volume and normal tissues. Even with radiosurgery, some normal brain is irradiated. High-dose single-fraction treatment can be harmful, especially when such a critical structure as the brainstem is involved.

Reirradiation for recurrent primary brain tumors has been a long-standing treatment option, with investigators cognizant of the attendant risks of necrosis or neurologic complication (9). One published series reported a 9% risk of necrosis and overall complication rate of 29% in 34 patients with primary brain tumors, including children, undergoing fractionated reirradiation to a median combined dose of 79.7 Gy (range, 43.2–111 Gy) (1). This series showed only a modest palliative and survival benefit in a diverse group of patients. A more specific evaluation of combined reirradiation and lomustine therapy was conducted in a small cohort of patients with high-grade glioma, showing a median overall survival of 13.7 months. The reirradiation dose was limited to 34.5 Gy in 23 fractions, with a median interval between first and second courses of irradiation of 14 months (10). With the advent of conformal RT, investigators attempted to minimize the dose to normal tissues when reirradiation was attempted. One series included 20 patients with primary brain tumors unsuitable for brachytherapy or radiosurgery, predominantly high-grade glioma. With a median reirradiation dose of 36 Gy (range, 30.6–59.4 Gy) and combined dose range of 80.6–119.4 Gy, neurologic improvement and stabilization of disease was observed in more than 67% of patients (11). Different dose and fractionated schemes were attempted for similar patients. For example, low-dose (36 Gy) fractionated reirradiation was applied successfully to predominantly adult patients with low- and high-grade astrocytoma. The lack of observed toxicity might be attributable to the long interval between courses (median, 50 months) for patients with low grade and relatively short time to progression for patients with high grade (12, 13). Similar low hypofractionated doses were applied in patients with high-grade glioma (14) and EP (15) with modest results. The FFRT and radiosurgery for medulloblastoma appears to be safe, provided doses are relatively low, and locally effective. However, overall results are poor in a tumor system prone to metastatic failure, not unlike EP (2).

The patients in this report continue to be followed up for treatment-related side effects involving neurologic, endocrine, and cognitive function. None was lost to follow-up. Of the 23 patients for whom salvage therapy did not fail, 4 have notable disabilities, including the 2 patients alive and without disease progression after necrosis (1 radiosurgery patient and 1 patient treated with CSI), 1 patient who was functionally disabled by surgery before reirradiation, and the patient who is the longest survivor in our series (>20 years) who lives with parents and is simply employed. The rest of the children continue to be followed up, and the magnitude of side effects has been greatest in children treated with CSI. Given the very small volume targeted for FFRT, barring structure damage to the brainstem, the risks of endocrinopathy, ototoxicity, and cognitive decline for these patients do not appear to be significantly greater than those observed after their initial treatment course.

In summary, reirradiation with curative intent should be considered for patients with recurrent EP after previous adjuvant focal irradiation. Aggressive attempts to resect local and metastatic disease are favored in this approach. Patients treated in this manner require careful surveillance for side effects of this combined salvage treatment approach.

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CONSENSUS PAPER

The current consensus on the clinical management of intracranial ependymoma and its distinct molecular variants

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Abstract Multiple independent genomic profiling efforts have recently identified clinically and molecularly distinct subgroups of ependymoma arising from all three anatomic compartments of the central nervous system (supratentorial brain, posterior fossa, and spinal cord). These advances motivated a consensus meeting to discuss: (1) the utility of current histologic grading criteria, (2) the integration of molecular-based stratification schemes in future clinical trials for patients with ependymoma and (3) current therapy in the context of molecular subgroups. Discussion at the meeting generated a series of consensus statements and recommendations from the attendees, which comment on the prognostic evaluation and treatment decisions of patients with intracranial ependymoma (WHO Grade II/III) based on the knowledge of its molecular subgroups. The major consensus among attendees was reached that treatment decisions for ependymoma (outside of clinical trials) should not be based on grading (II vs III). Supratentorial and posterior fossa ependymomas are distinct diseases,

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although the impact on therapy is still evolving. Molecular subgrouping should be part of all clinical trials henceforth.

Keywords Ependymoma · Subgroups · RELA · YAP1 · Treatment · Trial · Posterior fossa

Introduction

Ependymoma is a histologically defined intrinsic tumor that involves the three major anatomic compartments (supratentorial brain, posterior fossa, and spinal cord) of the central nervous system and affects both children and adults. The current standard of care therapy for patients with intracranial ependymoma remains surgical resection combined with radiotherapy. The survival benefit of chemotherapy for ependymoma and the prognostic ability of histopathological grading criteria to risk-stratify patients are still both inconclusive and contentious. No molecular or tumor-specific immunohistochemical markers are in routine current clinical use for ependymoma. Recent advances in the biological characterization of ependymal tumors have demonstrated the existence of nine clinically, demographically, and molecularly distinct entities, with three occurring in each anatomic compartment. These findings offer new opportunities to create a precise, reliable, and objective platform for stratification of ependymoma patients, and the potential for altering therapeutic decisions based on molecular features. Herein, we discuss the current consensus on the molecular subgroups of intracranial ependymoma (WHO Grade II/III) in children and adults, as well as recommendations for integration into future clinical trial designs. These discussions and recommendations were made by a collection of neuro-oncologists, neurosurgeons, neuro-pathologists, radiation oncologists, and basic scientists, meeting at the global ependymoma consensus conference (Huntsville, Ontario, Canada in September 2015) (Fig. 1).

The utility of histologic grading of ependymoma in a molecular era

Ependymomas from throughout the central nervous system are currently sub-divided by three histology-based grades used to predict the natural course of the disease and patient outcome [19]. However, the utility of histological grading of ependymoma for risk stratification has been controversial and without consistent associations of tumor grade with patient outcome. The World Health Organization (WHO) Grade I tumors include myxopapillary ependymoma, which typically occurs in the spine, as well as subependymoma, which is usually intracranial. Grade I ependymomas are relatively easier to distinguish, occur predominantly in adults, and are associated with favorable clinical outcomes [19]. Conventional ependymomas are divided between WHO Grade II and WHO Grade III (anaplastic) tumors, the latter showing elevated mitotic activity, microvascular proliferation, and tumor necrosis. Analysis of multiple cohorts of intracranial ependymoma highlights a wide variance in the utility of the Grade II versus Grade III distinction as a robust prognostic marker [9]. Furthermore, the utility of conventional histologic grading may be confounded by the anatomic compartment [29, 37]. These considerations have raised significant questions as to whether the grading criteria should stratify patients into different therapeutic regimens. It was therefore agreed upon that: (1) treatment decisions for ependymoma should not be based on classification and grading that is solely based on histopathological characteristics (especially, the distinction of Grade II versus Grade III tumors) and (2) central and combined histologic–molecular review and classification should be a principal and integral component of any future clinical trial. Indeed, the updated 4th edition of the WHO classification of central nervous system tumors recognizes the supratentorial molecular variant, ST-EPN-RELA (see next section), as a distinct biological and clinical disease entity

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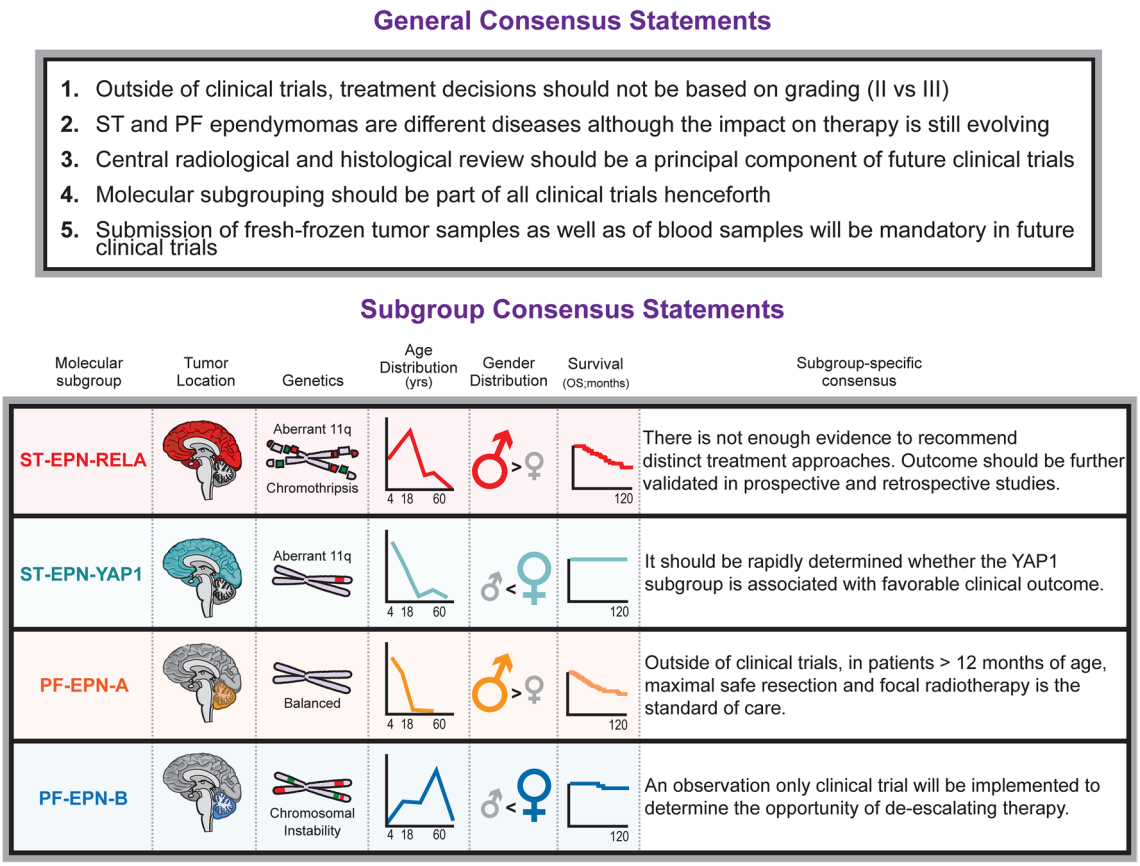

Fig. 1 General and molecular subgroup specific consensus statements on the clinical management of intracranial ependymoma

[20]. Integrated histo-molecular analyses of ependymal tumors from clinically well-annotated prospective international trial cohorts hold promise for inclusion of additional molecular ependymoma 'entities' into the upcoming 5th edition of the WHO classification of CNS tumors.

Molecular subgroups of ependymal tumors in the central nervous system

Although molecular subgroups of ependymoma arising in different anatomical sites exhibit histopathological similarities, their molecular profiles are easily discernable, owing to diverse genetic, transcriptional, and epigenetic programs [7, 8, 18, 22, 24, 30, 36, 37]. Functional cross-species analyses have provided evidence that these molecular differences may be reflective of discrete developmental and cellular origins [16, 30, 33]. Based on demographic, clinical, and molecular data, supported in multiple independent cohorts [23, 29–31, 36, 37], a full consensus was reached that: posterior fossa and supratentorial ependymoma are biologically different diseases both treated by surgery and radiotherapy. Future molecular characterization and clinical trials will assess whether posterior fossa and supratentorial ependymoma may benefit from different forms of therapy. A recent international collaborative study identified nine molecular subgroups of ependymal tumors, three in each anatomical compartment of the central nervous system, spine (SP), posterior fossa (PF), and supratentorial region (ST) [29]. One of the subgroups within each compartment was enriched with WHO Grade I subependymomas (SE), named ST-SE, PF-SE, and SP-SE. These molecular subependymomas occurred in adults only. The two other molecular subgroups within the spine predominantly matched the histopathology-based diagnoses of myxopapillary ependymoma (SP-MPE) and (WHO Grade II/III) ependymoma (SP-EPN). The remaining two molecular types of ependymoma occurred in the posterior fossa, termed PF-EPN-A and PF-EPN-B or alternatively posterior fossa Group A and B, and were independently identified in retrospective studies [36, 37]. PF-EPN-A tumors occur predominantly in infants and young children. Due to their predominant lateral localization, PF-EPN-A tumors are often difficult to completely resect and are associated with high recurrence rates [37]. Conversely, PF-EPN-B tumors occur largely in adolescents and young adults and are associated with a

more favorable prognosis. More than 70% of supratentorial ependymomas are characterized by fusions between *C11ORF95* and the *RELA* gene, and were recently termed ST-EPN-RELA [29, 30]. While ST-EPN-RELA tumors may occur in both children and adults, the remaining molecular subgroup of supratentorial ependymoma harbors recurrent fusions to the oncogene *YAP1* and is enriched in the pediatric population [29, 30]. Since preliminary evidence of a small retrospective cohort indicates that patients with YAP1 fusions have an excellent prognosis, it was agreed upon that the international community should move rapidly toward determining whether ST-EPN-YAP1 is a subgroup with an extremely favorable clinical outcome and therefore might benefit from careful therapy de-escalation within the setting of a clinical trial. Retrospective classification of clinically well-annotated supratentorial ependymomas, which have been treated in clinical trials, is expected to give more detailed information on outcome within this subgroup in the near future. No consensus was made upon morphologically diagnosed ST-ependymomas without RELA/YAP1 fusion. It was felt that further investigation was needed for this apparently heterogeneous group of tumors. It was acknowledged that such issues could be addressed with a DNA methylation-based molecular classification for ependymal tumors that represents an unbiased, robust, and uniform scheme that adequately reflects the full biological, clinical, and histopathological heterogeneity across all age groups, grades, and major anatomical CNS compartments. The clinical feasibility of this platform is supported by multiple components: (1) low sample input and DNA requirements, (2) robust results from formalin-fixed paraffin-embedded (FFPE) tissue, and (3) minimal batch effects and assay consistency between different clinical-genomic facilities. In addition to DNA methylation patterns, DNA copy number profiles can be derived from this analysis. It is important to note that chromosome 1q gain has been shown to be an independent prognostic factor that occurs in a subset of PF-EPN-A, PF-EPN-B, and ST-EPN-RELA tumors [12, 17, 24, 29, 32, 37]. Future integrated molecular efforts will explore the integration of molecular subgroup, copy number alterations (namely chromosome 1q gain), and their impact on patient outcome.

Molecular sub-classification is expected to significantly support treatment decisions and simplify risk stratification processes in the immediate future, and should impact clinical trial design and operation in both children and adults. A complete consensus was reached that molecular subgrouping should be a part of all clinical trials moving forward. It was agreed that certification of diagnostic assays for molecular subgroup detection is of high importance. However, it was acknowledged that there were differences between countries regarding certifying agencies and regulations, and therefore most attendees felt that it was not reasonable and feasible to generate a consensus statement on certification processes. To further improve molecular diagnostics and identify new prognostic factors and therapeutic targets, optimal tissue material for ongoing and future biologic discovery studies is required. The great majority of attendees agreed that submitting fresh-frozen samples should be mandatory within upcoming clinical trials for ependymoma. Although DNA methylation profiling can be performed with FFPE-derived tissue, frozen samples would provide optimal material for use in future applications, such as genome sequencing. The interpretation of any tumor sequencing (from a limited gene panel up to whole genome) would dramatically benefit from a matched control to correct for aberrations inherent to the germline. As such, an agreement among most attendees was established that submission of blood samples should also be mandatory for enrollment in a clinical trial. It should be recognized that arguments were made against the mandate of fresh-frozen tissue, owing to the logistical issues of collection, storage, and submission, particularly in small community centers. Additionally, there were ethical concerns regarding the mandated submission of blood. Attendees recognized that efforts would need to be established to create standard operating procedures in smaller centers to enable reliable collection and submission of frozen tissue. Many of those agreeing on a mandate of frozen tissue and blood argued that given the rapid developments in the field of molecular genetics, with the emergence of increasingly powerful analytical devices and computational tools, the time is now to collect tissue specimens in combination with high-quality clinical data. This would enable the use of such advances to improve the care of future ependymoma patients.

Clinical management of intracranial ependymoma in the context of molecular subgroups

Clinical management of intracranial ependymomas (WHO Grade II/III) is challenging and the optimal treatment strategy is contentious. Intracranial ependymoma, particularly before administration of any therapy, demonstrates predominantly locally invasive growth patterns and has only very low metastatic potential. Surgery plays a primary role for local tumor control and the extent of neurosurgical resection has been the most consistent independent prognostic factor reported in the last decades [5, 6, 34]. The favorable outcome of patients without residual disease and the large difference in event-free and overall survival between patients with complete versus incomplete resection (up to 50% in some series) have led to the concepts of aggressive de-bulking and second-look surgery. Such neurosurgical procedures may be performed immediately following incomplete initial resection or after a short course

of chemotherapy and is currently being systematically evaluated in clinical trials. A comprehensive radiological assessment of the residual disease status is expected to give the highest degree of information to base potential secondary neurosurgical intervention decisions. Attendees agreed that central radiological review of pre- and post-surgical imaging should be a principal component of every clinical trial enrolling patients with ependymoma henceforth.

In addition to surgery, post-operative field radiotherapy dosed at 54–59.4 Gy is considered the standard of care for patients with non-disseminated ependymoma to lower the risk of local recurrence [25]. Radiation margins around the target volume have also decreased from 2.0 to 1.0 cm, with no evidence of increased frequency of tumor relapse [25]. Owing to the challenging localization of ependymoma, particularly in the case of laterally located infant posterior fossa tumors, proton therapy has been explored as a radiation modality to spare proximal neurological structures [21]. In the case of recurrent ependymoma, a retrospective analysis demonstrated that the efficacy of re-irradiation, however, was associated with a decline in patient intellectual function [4].

It should be emphasized that all prior studies that evaluated the therapeutic value of neurosurgical interventions and external beam radiation in posterior fossa ependymoma have not accounted for molecular subgroup affiliation and might therefore be confounded by clinical differences in response to therapy between these subgroups. Data from a current retrospective study on four independent non-overlapping cohorts of posterior fossa ependymomas ($n = 820$ cases) found that patients with either PF-EPN-A or PF-EPN-B tumors benefit from gross total resection, with the survival rates being particularly poor for sub-totally resected PF-EPN-A, even in the setting of radiation therapy [31]. Participants at the conference concluded that for PF-EPN-A tumors in patients older than 12 months of age who are treated outside of clinical trials, maximal safe surgical resection and focal radiotherapy should be defined as the standard of care. Owing to the challenging localization of PF-EPN-A tumors, attendees acknowledged that patients would benefit from being treated in specialized centers by experienced neurosurgeons. Since the study strongly demonstrates that a large subset of patients with PF-EPN-B tumors who received a gross total resection did not recur, even in the absence of radiotherapy, it was agreed that a randomized clinical trial for newly diagnosed and gross totally resected PF-EPN-B ependymoma comparing observation versus standard upfront radiation should be considered. Such a trial would test the possibility of therapy to be de-escalated in some patients with PF-EPN-B ependymoma.

Observation for gross totally resected supratentorial ependymomas has also been advocated based on retrospective series that were not molecularly characterized. For example, a retrospective, multicenter study comprising 92 patients (median age was 17.5 years, range 1–83 years) with gross totally resected and non-anaplastic supratentorial ependymal tumors did not find evidence of decreased progression-free or overall survival with the omission of external beam radiation [11]. The 5–10 year Kaplan–Meier estimated overall survival for the overall cohort was 83.2 and 84.1%, respectively. Another retrospective review of only ten patients (median age 5.6 years, range 1.8–15.6 years), which also included ependymomas diagnosed as WHO grade III, found that in some children with completely resected supratentorial ependymoma, surgery alone may be an acceptable treatment option [35]. The outcomes in the aforementioned series differed from the largest cohort published to date comprising 122 supratentorial ependymal tumors that were classified according to their DNA methylation profiles as ST-EPN-RELA, ST-EPN-YAP1 and ST-SE [29]. Tumors harboring *C11ORF95* gene fusions to *RELA* accounted for more than 70% of supratentorial ependymomas (median age 8 years, range 0–69 years) and were associated with a poor prognosis with 5-year progression-free and overall survival of 29 and 75%, respectively. Interestingly, the level of resection did not significantly affect the outcome within the ST-EPN-RELA-positive subgroup in this retrospective analysis in patient samples collected over a long period of time (>20 years). The two remaining supratentorial subgroups, ST-SE and ST-EPN-YAP1, were restricted only to adults (median age 40 years, range 22–76 years) and predominantly to children (median age 1.4 years, range 0–51 years), respectively, with both of these variants showing an excellent prognosis. As the cited studies and other available collections of single cases markedly differ regarding age distribution, therapy modalities and availability of molecular data, variations in outcome cannot be reliably linked to specific treatment approaches or molecular subgroups. It was, therefore, concluded that there was not enough evidence yet to recommend distinct treatment approaches for ST-EPN-RELA ependymoma. Molecular analyses of supratentorial ependymomas from clinically well-annotated international trial cohorts as well as from large retrospective cohorts with long-term follow-up have now been initiated. The authors expect that this approach will help to clarify questions about the clinical outcome of the molecular variants of supratentorial ependymoma and result in explicit therapy recommendations.

In contrast to surgery and radiotherapy, the role of chemotherapy in the management of ependymoma remains unproven despite extensive investigation. Cohorts of pediatric or adult patients in which the role of chemotherapy was retrospectively analyzed either failed to demonstrate a survival advantage or showed substantial variation between individual patients [3, 13, 28]. Two international randomized trials in children are currently comparing

post-irradiation chemotherapy to observation only, SIOP Ependymoma II (Europe) and ACNS0831 (USA). In an attempt to delay radiotherapy in very young children, driven by concerns about long-term treatment toxicity, several groups used post-operative chemotherapy approaches in children under 3 years with 42% being the highest rate of 5-year progression-free survival reached to date [14, 15, 40]. In marked contrast, extension of immediate post-operative high-dose conformal radiotherapy to children under the age of 3 years led to 7-year progression-free survival rates of 77%, albeit long-term follow-up for toxic effects on development are still pending [25]. For this reason, radiotherapy deferral strategies that use chemotherapy have been abandoned in most institutions for children >12 months of age. Initial responses to chemotherapy after subtotal resection have been demonstrated [10] and the ependymoma trial ACNS0831 is currently assessing the role of neoadjuvant chemotherapy and second-look surgery, with a combined chemotherapy regimen of vincristine, cisplatin, etoposide, and cyclophosphamide. To date, there is no chemotherapeutic regimen that can routinely be recommended outside the context of a clinical trial. Since the consensus for therapeutic management in the molecularly well-defined PF-EPN-A subgroup does not include any systemic therapy, it will definitely open new avenues for rather rapid implementation of innovative trials for this devastating disease.

Model development and novel therapeutics

Because of the recognition that ependymal tumors comprise molecularly distinct subtypes, with potentially distinct clinical management, the generation of subgroup-specific pre-clinical models for the development and assessment of novel therapies is required. The identification of candidate cells of origin for ependymoma has permitted the generation of novel mouse models that can be leveraged for novel therapeutic discovery and evaluation [1, 16, 27, 30]. Ephrin receptor B2 (*EPHB2*)-driven ST ependymoma models—also highly expressed in ST-EPN-RELA tumors—have pinpointed 5-fluorouracil treatment as a potential cytotoxic therapy with efficacy in murine models and is currently being evaluated in early phase ependymoma clinical trials [1, 16, 38]. Owing to the clear genetic drivers of ST-EPN-RELA and ST-EPN-YAP1, transcriptionally faithful mouse models are currently generated, which will create similar opportunities to identify druggable targets against these specific subtypes of ependymoma [30]. In parallel, patient-derived xenograft (PDX) models have been established, permitting further therapeutic evaluation of novel drugs and compounds against ependymoma [2, 26, 39]. In the case of PF-EPN-A, the absence of a clear genetic driver has hampered efforts to create genetic mouse models of the disease. Moving forward, it will be important that pre-clinical models are developed in the context of ependymoma subgroups, such that molecular stratification of these tumors is paired with specific therapeutic targets.

Conclusions

We now recognize that ependymal tumors from different compartments of the central nervous system are biologically distinct and there are phenotypically divergent subgroups within each anatomic compartment. Future clinical trials, the development of pre-clinical model systems, and the identification and testing of subtype-specific therapeutics must accompany molecular classification to be useful to ependymoma patients and to the neuro-oncology community. The differentiation between histologically defined grade II versus grade III/anaplastic ependymomas is problematic and of limited utility for clinical decision-making, and therefore should be used with great caution outside the setting of a clinical trial. For patients with PF-EPN-A ependymoma over the age of 12 months of age, the recommended standard of care is maximal safe micro-neurosurgical removal followed by local radiotherapy, but probably does not include the routine use of chemotherapy outside the setting of a clinical trial. A subset of PF-EPN-B ependymoma patients who undergo gross total micro-neurosurgical resection are likely cured in the absence of radiotherapy, and a clinical trial to test the possibility to avoid radiotherapy in the context of complete resection for PF-EPN-B patients is indicated. The characteristics and heterogeneity between molecular subgroups of supratentorial ependymoma require additional study before specific treatment recommendations can be made. The division of an already uncommon entity ("ependymoma") into nine new entities will necessitate great co-operation and international collaboration with the pediatric and adult neuro-oncology community if clinical trials are to be properly and expeditiously completed.

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Therapeutic Impact of Cytoreductive Surgery and Irradiation of Posterior Fossa Ependymoma in the Molecular Era: A Retrospective Multicohort Analysis

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ABSTRACT

Purpose
Posterior fossa ependymoma comprises two distinct molecular variants termed EPN_PFA and EPN_PFB that have a distinct biology and natural history. The therapeutic value of cytoreductive surgery and radiation therapy for posterior fossa ependymoma after accounting for molecular subgroup is not known.

Methods
Four independent nonoverlapping retrospective cohorts of posterior fossa ependymomas (n = 820) were profiled using genome-wide methylation arrays. Risk stratification models were designed based on known clinical and newly described molecular biomarkers identified by multivariable Cox proportional hazards analyses.

Results
Molecular subgroup is a powerful independent predictor of outcome even when accounting for age or treatment regimen. Incompletely resected EPN_PFA ependymomas have a dismal prognosis, with a 5-year progression-free survival ranging from 26.1% to 56.8% across all four cohorts. Although first-line (adjuvant) radiation is clearly beneficial for completely resected EPN_PFA, a substantial proportion of patients with EPN_PFB can be cured with surgery alone, and patients with relapsed EPN_PFB can often be treated successfully with delayed external-beam irradiation.

Conclusion
The most impactful biomarker for posterior fossa ependymoma is molecular subgroup affiliation, independent of other demographic or treatment variables. However, both EPN_PFA and EPN_PFB still benefit from increased extent of resection, with the survival rates being particularly poor for subtotally resected EPN_PFA, even with adjuvant radiation therapy. Patients with EPN_PFB who undergo gross total resection are at lower risk for relapse and should be considered for inclusion in a randomized clinical trial of observation alone with radiation reserved for those who experience recurrence.

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INTRODUCTION

Ependymoma is the third most common posterior fossa tumor of childhood and a major cause of morbidity and mortality in pediatric oncology, occurring across the entire age spectrum.[1-16] Current therapy for posterior fossa ependymoma in children is aggressive surgical resection followed by involved-field radiation, resulting in 7-year event free-survival of 65%.[12,15] Despite the high mortality rate, trials of cytotoxic chemotherapy have failed to reveal a clear survival benefit for chemotherapy over surgery and radiation alone, although definitive pediatric randomized trials of maintenance chemotherapy are still recruiting through cooperative groups (ClinicalTrials.gov identifiers: NCT01096368 and NCT02265770).[1,5,17] In adults, posterior fossa ependymoma is frequently treated with surgery alone.[18]

Numerous publications have suggested that the most powerful prognostic factor for posterior fossa ependymoma is the extent of surgical resection or, more appropriately, the amount of residual tumor after surgery. This has entailed an aggressive surgical approach, with some oncologists and surgeons tolerating serious neurologic deficits, including the need for tracheostomies and gastrostomy tubes, as an inevitable cost in the attempt to achieve tumor-free survival, including potentially morbid second-look surgery.

Because the majority of ependymomas within the neuroaxis are histologically similar, historically they had been thought to compose one disease, but they were subsequently recognized to be biologically distinct in the supratentorial, posterior fossa, and spinal compartments of the CNS.[19] More recently, integrated genomic approaches have clearly shown the existence of the following three distinct molecular variants of posterior fossa ependymoma: EPN_PFA, EPN_PFB, and subependymoma. EPN_PFA occurs primarily in infants and young children, whereas EPN_PFB occurs primarily in older children and adults.[20-23] Subependymomas are grade 1 tumors with an excellent prognosis restricted to older adults. Patients with EPN_PFB have an excellent outcome, with survival rates in excess of 90%, whereas patients with EPN_PFA have a poor outcome. Curiously, neither EPN_PFA nor EPN_PFB has any recurrent somatic single nucleotide variants, and both demonstrate a low rate of mutation across the genome.[21] The complete lack of recurrent somatic single nucleotide variants implies that targeted therapy using small molecules directed against recurrent mutations is unlikely to be a successful strategy for patients with posterior fossa ependymoma. EPN_PFA is characterized by relatively increased DNA methylation compared with EPN_PFB, and preclinical studies suggest that epigenetic modulating agents might be beneficial for patients with EPN_PFA.[21]

All prior studies of the therapeutic value of cytoreductive surgery and external-beam radiation done in the premolecular era have not accounted for subgroup affiliation and might therefore be confounded by clinical differences in response to therapy between EPN_PFA and EPN_PFB. In addition to extent of resection and provision of radiotherapy, age at presentation was a strong posterior fossa ependymoma risk factor in the premolecular era literature. It is unclear whether younger age is an independent risk factor or is merely a reflection of the enrichment of patients with EPN_PFA in younger cohorts. Thus, it is unclear whether older patients with EPN_PFA will do well, whereas younger patients with EPN_PFB will do poorly. Previous studies from our group and others have suggested that the two posterior fossa ependymoma subgroups may have disparate responses to therapy.[20,21] To determine the true value of extent of resection, radiation therapy, and age at presentation as biomarkers in the molecular era, we present the largest retrospective cohort of posterior fossa ependymomas ever assembled and determine the validity and strength of known biomarkers after accounting for molecular subgroup.

METHODS

Three hundred five posterior fossa ependymomas were obtained from the Hospital for Sick Children and from collaborating centers from around the world through the Global Ependymoma Network of Excellence (GENE) consortium from 1990 to 2014. Samples were all collected in accordance with the approval of the Hospital for Sick Children Research Ethics Board and local institutional research ethics boards. To account for unobserved variables, three independent nonoverlapping validation cohorts were assembled from the prospective St Jude Children's Research Hospital (n = 112, RT1 cohort), the Collaborative Ependymoma Research Network (n = 121, CERN cohort), and the German Cancer Research Center/Burdenko Neurosurgical Institute (n = 261, Burdenko cohort). Full details of the cohorts, sample processing, collection of clinical annotations, and statistical analysis are found in the Appendix (online only).

RESULTS

Demographics of Posterior Fossa Ependymoma Cohorts

Posterior fossa ependymomas from all four cohorts had molecular subgroup determined using unsupervised hierarchical clustering of genome-wide methylation arrays, as recently described.[23] In total, we analyzed 820 posterior fossa ependymomas, which were subsequently found to include 678 EPN_PFAs and 142 EPN_PFBs, with EPN_PFBs more highly enriched in the CERN and Burdenko cohorts, as reflected by the median age (Table 1). Demographics and treatment details of each of the four cohorts are listed in Table 1. Grade was not included as a variable because a previous reanalysis of several prospective cohort studies showed the existing WHO histologic classification to be unreliable as a result of profound intraobserver variability, confounding its utility in clinical risk stratification.[24] The median age of patients with EPN_PFA was almost identical across all four cohorts, with a combined median age of 3 years (Appendix Fig A1, online only; overall age range, 0 to 77 years; GENE: median, 3.6 years; range, 0 to 72 years; St Jude RT1: median, 2.38 years; range, 0.62 to 22.76 years; CERN: median, 4 years; range, 0 to 67 years; Burdenko: median, 4 years; range, 0 to 65 years). Children younger than age 5 years almost exclusively had EPN_PFA (three EPN_PFB tumors in patients < 5 years old); however, 45% of pediatric patients age 10 to 17 years had EPN_PFB tumors. Adults largely had EPN_PFB, although 11% of adults had EPN_PFA tumors. Overall, 236 deaths and 420 progression events were observed, and median follow-up time of the entire cohort was 6.7 years (95% CI, 6.0 to 7.2 years).

Subgroup Affiliation Is the Most Powerful Prognostic Marker for Posterior Fossa Ependymoma

To determine the prognostic value of ependymoma subgroups, we performed a Cox proportional hazards regression model across

Table 1. Demographic and Treatment Characteristics of All Four Cohorts

Characteristic	No. of Patients (%)			
	GENE (n = 326)	St Jude's RT1 (n = 112)	CERN (n = 121)	Burdenko (n = 261)
Median age, years (interquartile range)	3.6 (1.87-7.45)	2.38 (1.57-4.99)	4 (2-25.5)	4 (2-8.5)
Male sex	175 (53.6)	61 (54.5)	63 (52.1)	152 (58.2)
GTR	221 (68.9)	92 (82.1)	68 (56.7)	138 (53.3)
Adjuvant first-line radiation	250 (78.6)	112 (100)	72 (59)	196 (75.1)
Adjuvant chemotherapy	138 (44.5)	0	42 (34.7)	164 (62.8)
Disease progression	148 (45.7)	40 (35.7)	72 (59.5)	146 (55.9)
Dead	104 (31.9)	41 (33.9)	28 (25)	63 (24.2)
Subgroup				
EPN_PFA	275 (84.4)	104 (92.9)	86 (71.1)	213 (81.6)
EPN_PFB	51 (15.6)	8 (7.1)	35 (28.9)	48 (18.4)

NOTE. Data were missing for the following: GTR: GENE, n = 4; CERN, n = 1; Burdenko, n = 2; adjuvant first-line radiation: GENE, n = 8; adjuvant chemotherapy: GENE, n = 16; disease progression: GENE, n = 2; and sex: Burdenko, n = 16.
Abbreviations: CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence; GTR, gross total resection (< 5 mm residual disease).

all four cohorts incorporating age, extent of surgical resection, adjuvant external-beam irradiation, subgroup, and cohort stratification (Table 2, Appendix Tables A1-A3, online only). No significant predictor-cohort interaction was identified for any of these variables with the exception of adjuvant radiation, which had a stronger effect in the GENE cohort; thus, we proceeded to pool all four cohorts in a multivariable analysis (Appendix Table A4, online only). After accounting for treatment variables, subgroup affiliation remained a highly significant predictor of progression-free survival (PFS; hazard ratio [HR], 2.14; 95% CI, 1.31 to 3.49; $P = .002$, Table 2; Appendix Tables A1 and A3 report each cohort individually) and overall survival (OS; HR, 4.30; 95% CI, 1.88 to 9.87; $P < .001$; Table 2; Appendix Tables A1 and A3 report each cohort individually). Administrative censoring at 10 years did not significantly alter the multivariable analysis (Appendix Tables A2 and A3). The HR for subgroup affiliation (HR, 4.30) was the highest of the examined biomarkers. Extent of resection, adjuvant external-beam irradiation, and male sex were also significant independent predictors of PFS and OS, whereas age at diagnosis and delivery of chemotherapy were not. We then evaluated the survival of patients with EPN_PFA versus EPN_PFB in each cohort individually. Across the four cohorts, EPN_PFA had significantly worse PFS and OS compared with EPN_PFB (Table 2; Appendix Fig A2, online only; Appendix Tables A1 and A2).

Table 2. Multivariable Cox Proportional Hazards Regression Model of Progression-Free and Overall Survival

Variable	Hazard Ratio	95% CI	*P*
Progression-free survival (n = 777)			
Age	0.99	0.98 to 1.00	.13
Male	1.25	1.02 to 1.54	.03
Incomplete resection	1.84	1.49 to 2.28	< .001
Adjuvant first-line radiation	0.63	0.49 to 0.79	< .001
Chemotherapy	1.04	0.81 to 1.34	.76
EPN_PFA subgroup	2.14	1.31 to 3.49	.002
Overall survival (n = 778)			
Age	0.98	0.96 to 1.00	.12
Male	1.41	1.97 to 1.85	.01
Incomplete resection	2.13	1.60 to 2.82	< .001
Adjuvant first-line radiation	0.52	0.38 to 0.72	< .001
Chemotherapy	0.90	0.65 to 1.26	.54
EPN_PFA subgroup	4.30	1.88 to 9.87	< .001

EPN_PFA Carries a Poor Prognosis Independent of Age at Diagnosis

In the premolecular era, age was an important prognostic factor for patients with posterior fossa ependymoma. We assessed the relative hazard for EPN_PFA and EPN_PFB depending on age and found that the relative risk of an EPN_PFA tumor is relatively constant across all age groups with a slight decrease for adults and is consistently higher than for EPN_PFB across the entire age spectrum (Appendix Fig A3, online only). We restricted our survival analysis to patients older than age 10 years, and EPN_PFA remained a significant predictor of poor outcome for both 10-year PFS ($P = .001$) and 10-year OS ($P < .001$; Appendix Fig A4 and Appendix Table A5, online only). Finally, to determine whether older children with EPN_PFA have a poor outcome, we stratified age as less than or greater than 10 years and found no significant difference in either PFS or OS, confirming that the poor prognosis attributed to EPN_PFA is not solely a result of the young age of the cohort (Fig 1). A similar analysis was done for EPN_PFB, where survival was stratified as greater than or less than 18 years with no significant difference in survival, further reaffirming that EPN_PFB is a favorable-risk group independent of age at diagnosis (Fig 1). As such, we conclude that the poor prognosis of EPN_PFA and the excellent prognosis of EPN_PFB are independent of age at diagnosis, confirming the results of the multivariable Cox regression analysis.

Surgical Cytoreduction of EPN_PFA Is Prognostic Independent of Subgroup

Extent of resection is identified in multiple publications as the single most important predictor of outcome for patients with posterior fossa ependymoma. However, poor-prognosis EPN_PFA tumors are a difficult surgical challenge as a result of their lateral location and occurrence in small infants who have a small blood volume, whereas good-prognosis EPN_PFB tumors are comparatively straightforward to resect as a result of their midline location and occurrence in an older age group. We hypothesized that the

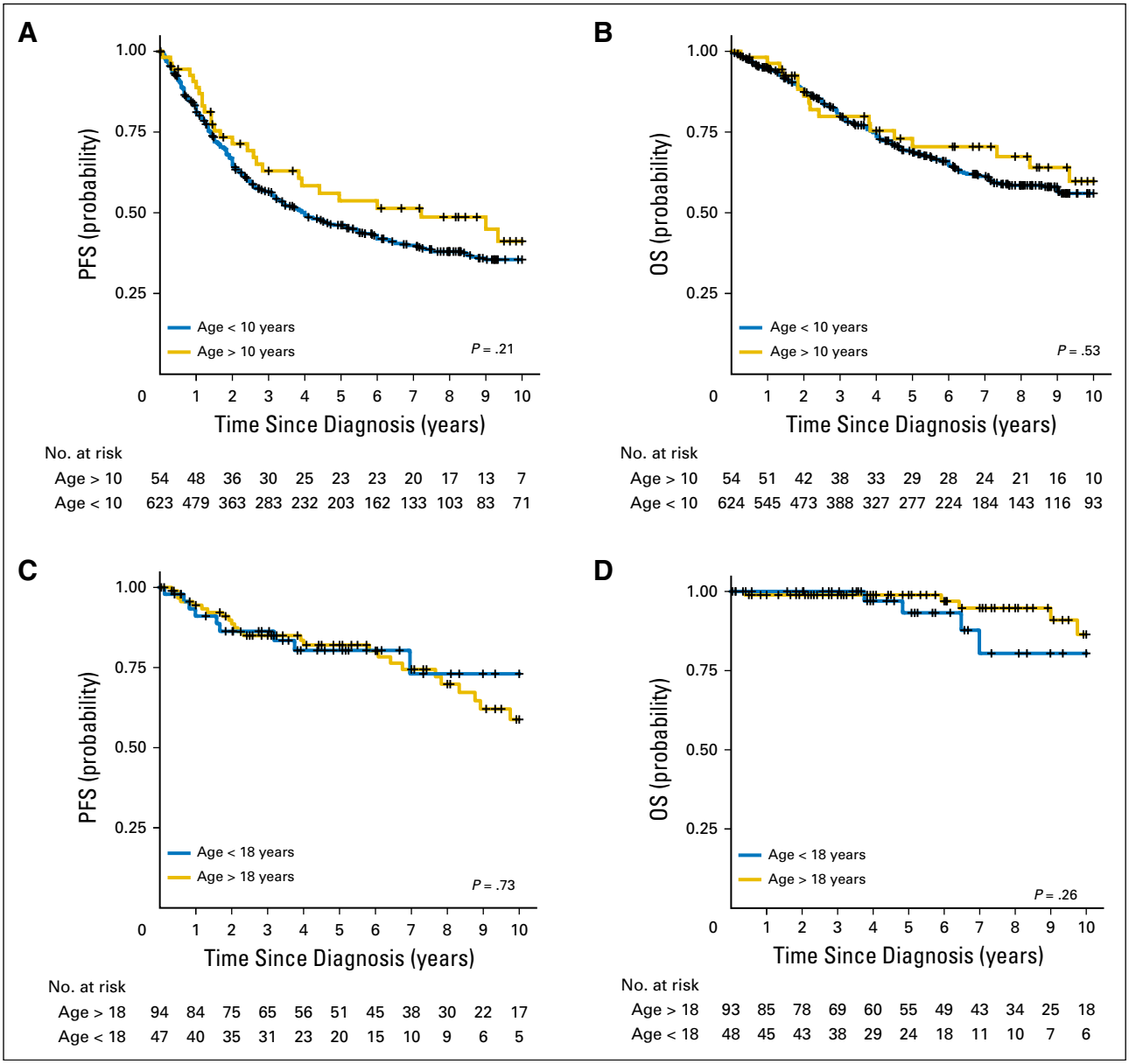

Fig 1. Survival of EPN_PFA and EPN_PFB stratified by age. (A) Progression-free survival (PFS) and (B) overall survival (OS) of EPN_PFA stratified by age greater than or less than 10 years. (C) PFS and (D) OS of EPN_PFB stratified by age greater than or less than 18 years. *P* values determined using log-rank test.

previously observed therapeutic value for surgical cytoreduction was confounded by the poor natural history of EPN_PFA tumors, which are difficult to resect, compared with the benign natural history of EPN_PFB tumors, which are less difficult to resect.

To determine the relationship between subgroup and extent of resection after accounting for molecular subgroup, we compared PFS and OS in each subgroup individually stratified by extent of resection. When comparing subtotal resection (STR) versus gross total resection (GTR) in EPN_PFA, STR was highly predictive of a dismal PFS and OS (Fig 2 and Appendix Table A6, online only). In a multivariable Cox proportional hazards model that included adjuvant chemotherapy and radiation, survival remained dismal for STR EPN_PFA (Appendix Tables A7 and A8, online only). Although we observed some variability in the effect of extent of resection across the four cohorts, we did not observe a statistically significant difference in or heterogeneity of the effect of extent of resection in EPN_PFA across cohorts (interaction $P = .80$ for PFS, $P = .53$ for OS). Male sex was a significant independent predictor of poor outcome across all four cohorts in GTR in a multivariable analysis restricted to EPN_PFA, although STR is a high-risk group in both male and female patients (Appendix Fig A5, online only, and Appendix Table A7). Within EPN_PFA, female patients with a GTR had a 5-year PFS of 0.652 (95% CI, 0.581 to 0.732), whereas male patients with a GTR had a 5-year PFS of 0.455 (95% CI, 0.393 to 0.527).

The value of first-line (adjuvant post-surgical) radiotherapy could only be compared with no radiation in the GENE, CERN, and Burdenko cohorts, because all patients in the prospective

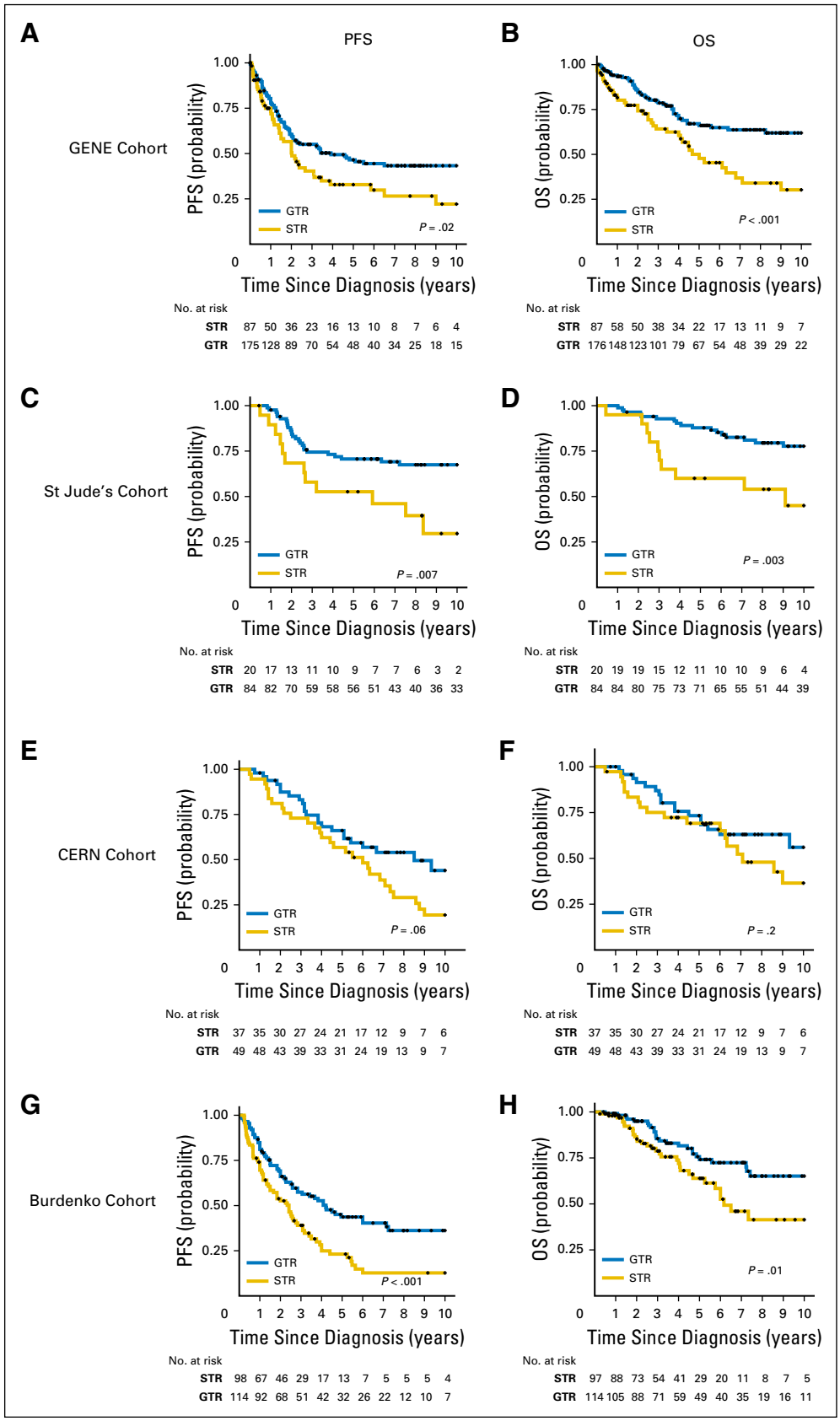

Fig 2. (A, C, E, and G) Progression-free survival (PFS) and (B, D, F, and H) overall survival (OS) of EPN_PFA stratified by extent of resection across all four cohorts. CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence; GTR, gross total resection; STR, subtotal resection (> 5 mm residual disease). *P* values determined using log-rank test.

St Jude RT1 cohort received adjuvant postoperative radiation. Strikingly, survival for STR EPN_PFA was not different between those who received first-line external-beam radiation and those who did not in the CERN and Burdenko cohorts (Appendix Fig A6, online only). In the GENE cohort, there was a statistically significant difference by a univariable analysis in patients who did not receive radiation; however, survival remains poor even in patients with subtotal resections who received external-beam irradiation. These data suggest that the benefit of post-surgical first-line adjuvant external-beam irradiation for patients with EPN_PFA is limited in the face of a subtotal resection and that these patients should be prioritized for clinical trials of novel therapy.

Patients With GTR EPN_PFB Have an Excellent Prognosis

As a result of limited patient numbers, we combined patients with EPN_PFB from the GENE, St Jude RT1, and CERN cohorts and demonstrated that STR results in a high risk of relapse (10-year PFS for GTR, 0.740; 95% CI, 0.550 to 0.859; 10-year PFS for STR, 0.50; 95% CI, 0.271 to 0.692). These findings were confirmed in a cohort of patients with EPN_PFB treated at the Burdenko Institute (Fig 3). As a result of the similar behavior of the two cohorts and the relatively small number of patients with EPN_PFB in each cohort, we combined all patients in our subsequent multivariable analysis. In a multivariable analysis restricted to EPN_PFB, a similar

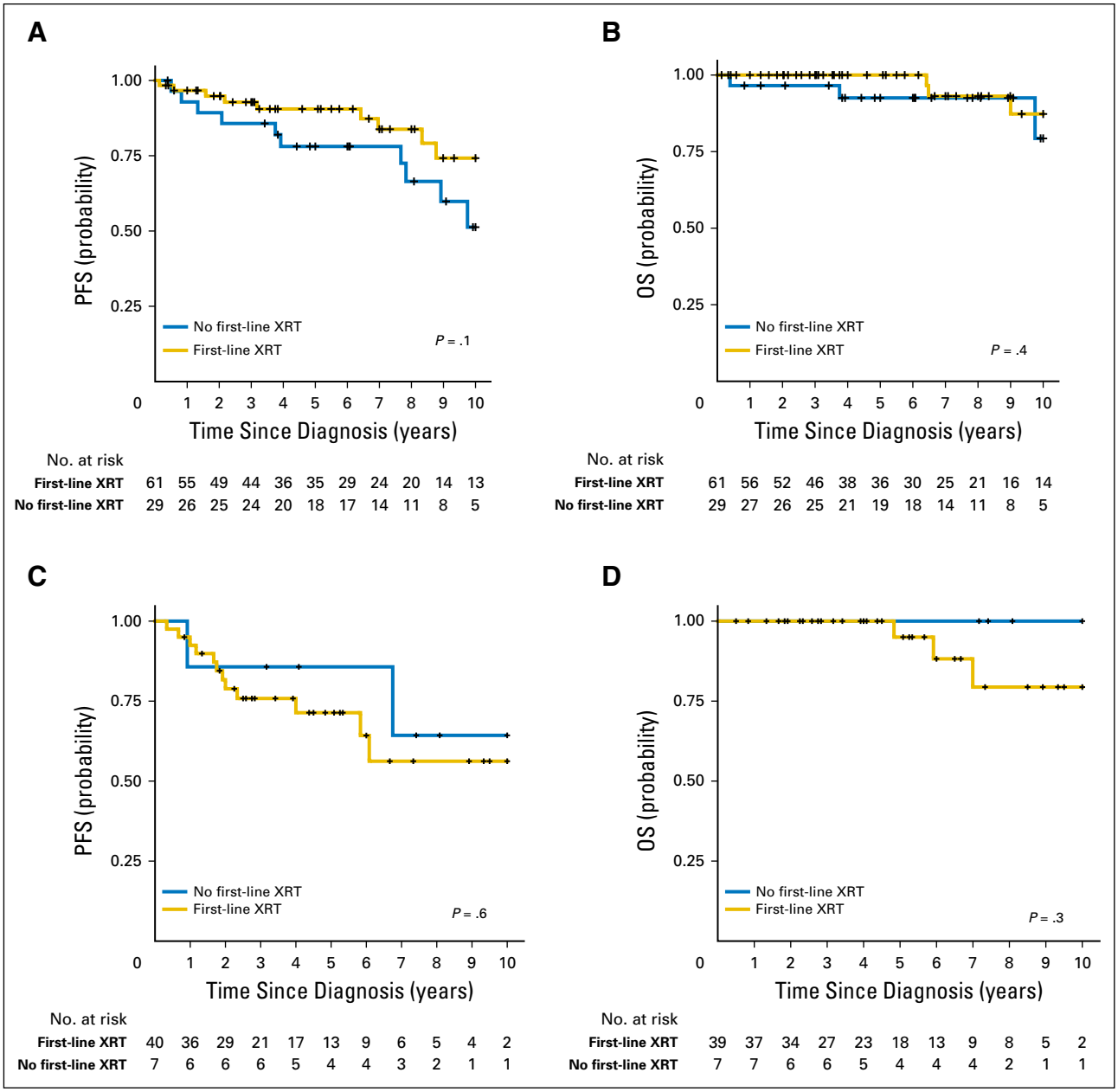

Fig 3. Value of adjuvant post-operative first-line external-beam irradiation (XRT) in EPN_PFB. (A) Progression-free survival (PFS) and (B) overall survival (OS) of EPN_PFB across the Global Ependymoma Network of Excellence, St Jude's, and Collaborative Ependymoma Research Network cohorts. (C) PFS and (D) OS of EPN_PFB across the Burdenko cohort. *P* values determined using log-rank test.

pattern emerges, where an incomplete resection is an independent predictor of both PFS and OS (Appendix Tables A9 and A10, online only). However, OS for patients with GTR EPN_PFB is extremely favorable, with a 10-year OS of 0.961 (95% CI, 0.753 to 0.994), compared with patients with STR EPN_PFB, who had a 10-year OS of 0.667 (95% CI, 0.308 to 0.870; Appendix Fig A7, online only). Interestingly, the PFS for patients with EPN_PFB who did not receive external-beam irradiation was 0.451 (95% CI, 0.216 to 0.661); however, the OS was 0.823 (95% CI, 0.519 to 0.943). These data suggest that a subset of patients with EPN_PFB can be cured by surgery alone after GTR (Fig 3). Of the three nonirradiated patients with EPN_PFB who died, two had an STR and one had a GTR. A substantial portion of patients with EPN_PFB who experience recurrence after initially withholding radiation can potentially be successfully treated by repeat surgery and delayed delivery of radiation (Fig 3). Indeed, the effect of a GTR versus an STR in EPN_PFB was significant for both the three combined cohorts and for the Burdenko cohort (P = .02 in univariable Cox regression

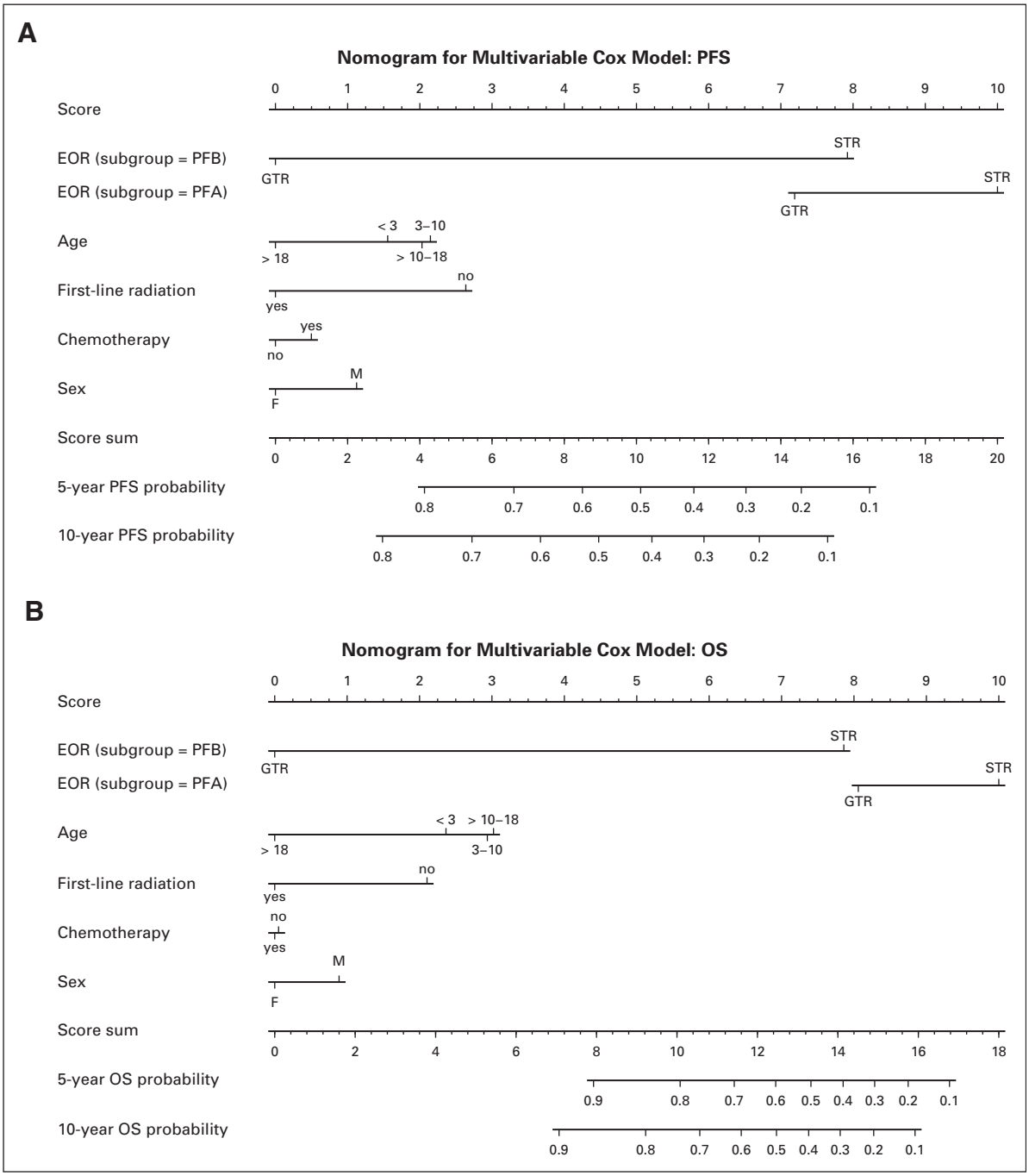

Fig 4. Nomogram of (A) progression-free survival (PFS) and (B) overall survival (OS) of posterior fossa ependymoma based on the multivariable Cox proportional hazards model. Each effect is translated into a risk score. The individual risk scores need to be totaled by the reader. The score sum can be translated into predicted 5- and 10-year PFS and OS probabilities. EOR, extent of resection; F, female; GTR, gross total resection; M, male; STR, subtotal resection.

analysis). Because the long-term effects of radiation for posterior fossa ependymoma in young adults who are cured can be quite severe,[25-28] these data provide the necessary clinical equipoise for initiation of a clinical trial of initial radiation avoidance in patients with GTR EPN_PFB ependymoma.

DISCUSSION

We have defined the demographic and prognostic properties of the two subgroups of posterior fossa ependymoma across the largest cohort of posterior fossa ependymoma assembled to date. Although three of the cohorts consist of retrospective data, the St Jude RT1 cohort was prospectively followed and homogeneously treated. The cohort is of such a large size that it will not likely be repeated in our lifetime, nor is a prospective clinical trial randomly assigning extent of resection in posterior fossa ependymoma patients likely.

We have shown that although EPN_PFA occurs primarily in infants and EPN_PFB is diagnosed primarily in adults, in children age 10 to 17 years, there is equal representation of both subgroups. Moreover, in adults, approximately 11% of patients have EPN_PFA. Across the entire age spectrum, we show that subgroup is the most powerful predictor of outcome, suggesting that in patients older than age 5 years, there is significant information to be gained in routine subgrouping of patients with posterior fossa ependymoma. Extent of resection, although no longer the most powerful predictor of outcome, remains prognostic in both subgroups. In particular, patients with STR EPN_PFA constitute a high-risk group with a poor outcome. Finally, we have shown that a subset of patients with EPN_PFB can be treated with surgery alone without external-beam irradiation, suggesting a trial of observation alone may be warranted in this subset of patients. Overall, in a prediction model of subgroup, treatment, and extent of resection as depicted in a nomogram, we find that EPN_PFA is the strongest predictor of poor outcome (Fig 4). Male sex was also an independent predictor of poor outcome in our analysis across all four cohorts, which is consistent with previous reports.[12] Interestingly the survival advantage in females is most pronounced in the setting of GTR EPN_PFA. A more comprehensive integrated genomic study will likely be required to clarify this association; however, it is noteworthy that females with a GTR have 10-year survival rates approximately 15% higher than males.

Our finding that patients with STR EPN_PFA have a dismal outcome has significant implications to the design of future clinical trials. Although a simple proximate solution would be to suggest GTR in all patients, this is frequently not possible as a result of brainstem invasion. Additionally, this subset of EPN_PFA seems to confer the least benefit from adjuvant external-beam irradiation and could potentially benefit from novel therapies. Previous studies of chemotherapy have shown only limited activity against posterior fossa ependymoma, with high-dose chemotherapy with autologous stem-cell support resulting in 3-year event-free survival of less than 30%, consistent with the survival we observed.[29,30] The role of adjuvant chemotherapy will require completion and reporting of long-term outcomes in the open studies of both the European Society of Pediatric Oncology (SIOPe) and the Children's Oncology Group (ACNS0831), where patients are randomly assigned to maintenance chemotherapy. Our findings across four independent cohorts of posterior fossa ependymoma suggest that STR EPN_PFA should be prioritized for first-line investigational agents, such as DNA demethylase inhibitors and EZH2 inhibitors, to provide an opportunity to assess activity of these agents prior to radiation.[21] Indeed, even patients with GTR EPN_PFA have OS rates of close to 50%, suggesting aggressive surgeries are not curative, and novel approaches would benefit this group as well.

We also find that STR confers a significantly poorer prognosis in EPN_PFB. Considering that the 10-year OS for EPN_PFB is greater than 85% with a complete resection, we feel that a GTR should be attempted where possible. The EPN_PFB data are limited by small numbers of STR patients and, as such, warrant some caution in interpretation. Major limitations of our study are a lack of central review of postoperative imaging in the three retrospective cohorts, retrospective design of the study without uniform follow-up imaging to identify progression, and treatment heterogeneity. Indeed, nonenhancing residual tumor can be missed even with modern postoperative magnetic resonance imaging. A large prospective radiographic study using modern three-dimensional magnetic resonance imaging volumetrics with a receiver operating curve will be needed to determine precisely how much residual tumor is truly predictive of a poor prognosis.

Finally, our finding that EPN_PFB can potentially be cured without external-beam irradiation has profound implications. Across the EPN_PFB cohort, we demonstrate many patients who have not experienced recurrence despite the lack of radiation therapy. Therefore, our data suggest that radiation in EPN_PFB can be initially withheld and that patients who experience recurrence can potentially be treated with salvage reresection and radiation. The ability to successfully treat patients with EPN_PFB with repeat surgery and radiation therapy is demonstrated by the large difference between PFS and OS in this patient population. Considering that the majority of adult posterior fossa ependymoma patients are not treated on open protocols, prospective evaluation will be crucial to determine the optimal treatment approach. We feel that our data support consideration of a prospective clinical trial of observation alone for GTR EPN_PFB, which could potentially spare patients the toxic effects of radiation.[31] The age group in which this could confer the highest benefit would be the older pediatric and adolescent population, in whom radiation has significant effects on learning and memory, and this approach could significantly improve long-term quality of life in this subset of patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Appendix

Methods

Patient Cohort

All frozen samples were snap frozen and stored at −80°C. Both frozen and formalin-fixed paraffin-embedded (FFPE) samples were collected from diagnosis and, in four instances, from relapse. Criteria for inclusion were an institutional histologic diagnosis of grade 2 or greater ependymoma and location within the posterior fossa. FFPE tissue was collected as scrolls or unstained slides. The Global Ependymoma Network of Excellence cohort was deemed the discovery cohort. Samples from three additional cohorts were collected and processed in an identical manner, including central pathologic review by a single pathologist in each of the three cohorts. Patients from the three additional cohorts have been partially reported in other cohort studies.[12,23,24] Subtotal resection was defined as greater than 5 mm of postoperative residual disease in at least two planes on postoperative magnetic resonance imaging or postoperative contrast-enhanced computed tomography scan as per the guidelines of the Children's Oncology Group based on institutional radiologic reports. A gross total resection was defined as less than 5 mm of postoperative residual disease on postoperative magnetic resonance imaging or postoperative contrast-enhanced computed tomography based on institutional radiologic reports. Assessment of clinical variables pertaining to treatment and survival were performed at local institutions blinded to the molecular subgrouping. Grading was not included as a variable as a result of previous reports showing the extreme interobserver variability of this measure.[24]

DNA Extraction

Fresh-frozen posterior fossa ependymomas were stored at −80°C before processing for extraction of DNA. For frozen samples, DNA extraction was performed using a proteinase K digestion and phenol:chloroform:isoamyl alcohol extraction and ethanol precipitation.[25] FFPE samples were processed using the Qiagen DNeasy FFPE extraction kit (Qiagen, Hilden, Germany), as per the manufacturer's instructions.[26] Samples were quantified using Picogreen (Life Technologies, Waltham, MA).

Genome-Wide DNA Methylation Profiling

All samples were analyzed on the Illumina Infinium HumanMethylation450 BeadChip (Illumina, San Diego, CA) at the Princess Margaret Genomics Centre (Toronto, Ontario, Canada), the St Jude Children's Research Hospital (Memphis, TN), or the German Cancer Research Center (Heidelberg, Germany) according to the manufacturer's instructions and as previously described. All analysis was conducted in the R Statistical Environment (v3.1.3; www.r-project.org). Raw data files (.idat) were processed as previously described, and ependymoma subgroup affiliation was assigned as per a recently released classifier using unsupervised hierarchical clustering.[23] Thirty-five grade 1 ependymomas (myxopapillary and subependymomas) were excluded from the analysis based on this classifier. Eleven samples diagnosed as ependymomas by local institutions did not cluster with posterior fossa ependymoma and were removed from the analysis.

Statistical Analysis

Progression-free survival and overall survival were right censored at 10 years and analyzed using the Kaplan-Meier method, and *P* values were determined using the log-rank test. Administrative censoring at 10 years was performed to ensure a reasonable completeness of follow-up across all four cohorts as a result of declining patient numbers at longer follow-up times. Administrative censoring resulted in only 1.6% of additionally censored patients at the end of the follow-up period for overall survival. As such, both continuous and censored data are presented. Survival data are presented as survival estimates including 95% CIs. A progression event was defined as the earliest time point between two assessment times with clear radiologic progression as reported by the local institution, and progression-free survival was defined as the interval between the initial diagnosis (typically surgery) and the progression event. Overall survival was calculated as the time from surgery to the time of death from any cause as reported by the referring institution. Associations between covariates and risk groups were tested using the Fisher's exact test. Univariable and multivariable Cox proportional hazards regression was used to estimate hazard ratios including 95% CIs. In pooled analysis, cohort was included as a stratification variable in the Cox model. In some EPN_PFB subgroup analysis, Firth correction was applied as a result of monotone likelihoods.[27] Age-dependent relative hazards for PFA/PFB subgroups were estimated from a Cox model with

age and subgroup interaction and a restricted cubic spline function with three knots for age to allow for a nonlinear relationship. All *P* values reported are two-sided. All statistical analyses were performed in the R statistical environment (v3.1.2), using R packages of survival (v2.37-7), rms (4.3-1), Coxphf (v1.1), and ggplot2 (v1.0.0).

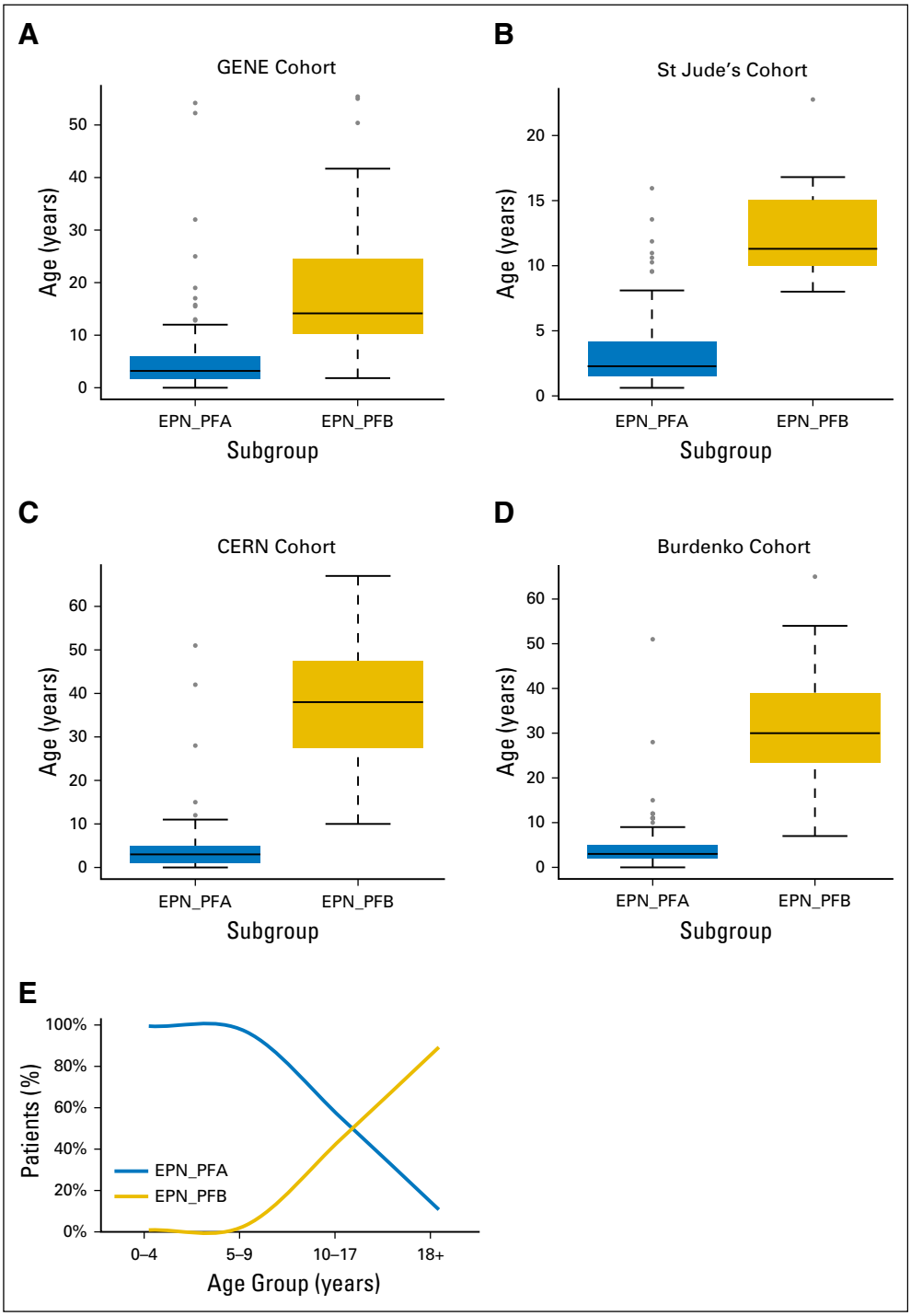

Fig A1. (A-D) Boxplots of the age distribution of EPN_PFA and EPN_PFB, where boxes represent median and interquartile range and whiskers represent 95% CIs. (E) Proportion of patients with EPN_PFA and EPN_PFB in each age group. CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence.

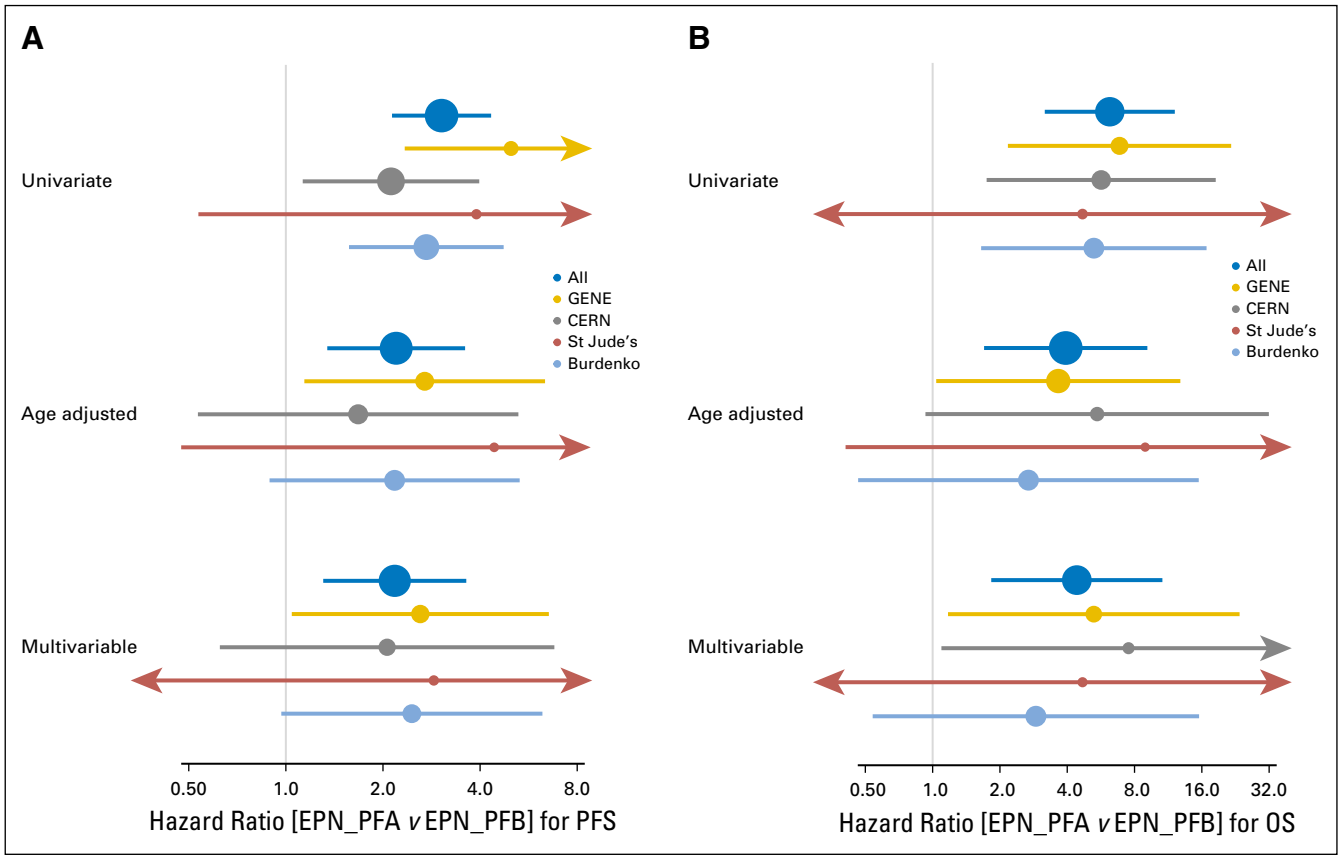

Fig A2. Forest plots of EPN_PFA versus EPN_PFB across all cohorts and each cohort individually as a univariate analysis, age-adjusted univariate analysis, and multivariable analysis for (A) progression-free survival (PFS) and (B) overall survival (OS). CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence.

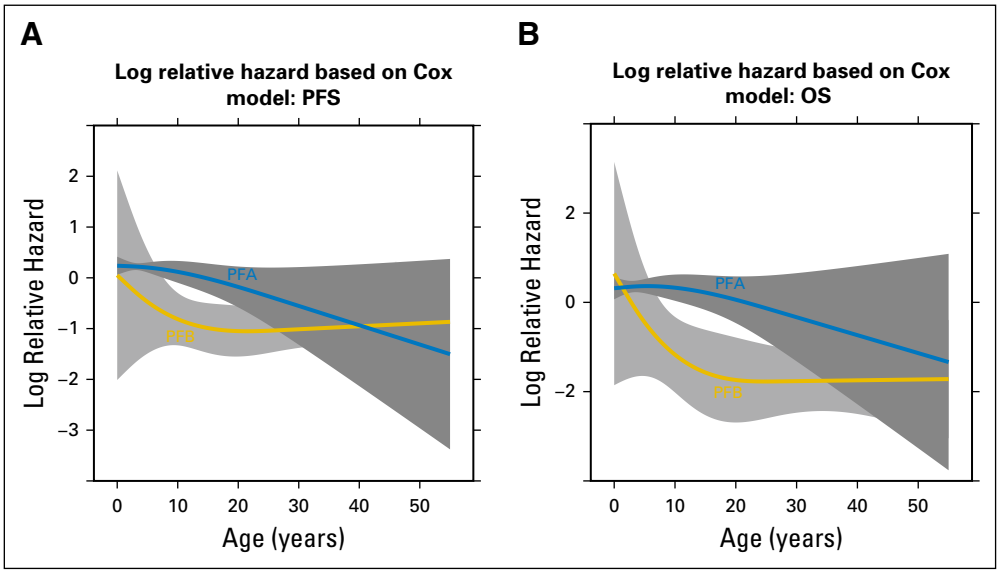

Fig A3. Plot of age at diagnosis as a function of the log10 of the hazard ratios of EPN_PFA versus EPN_PFB for (A) progression-free survival (PFS) and (B) overall survival (OS).

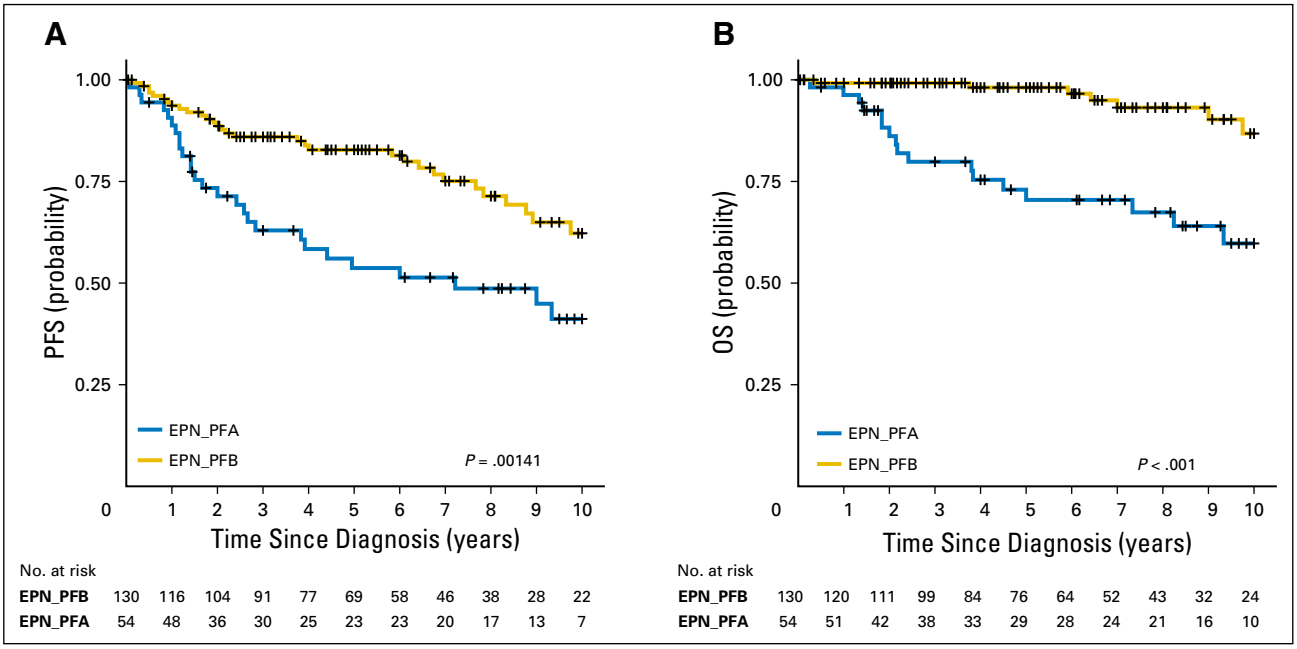

Fig A4. Survival by subgroup in patients with an age at diagnosis of greater than 10 years for (A) progression-free survival (PFS) and (B) overall survival (OS).

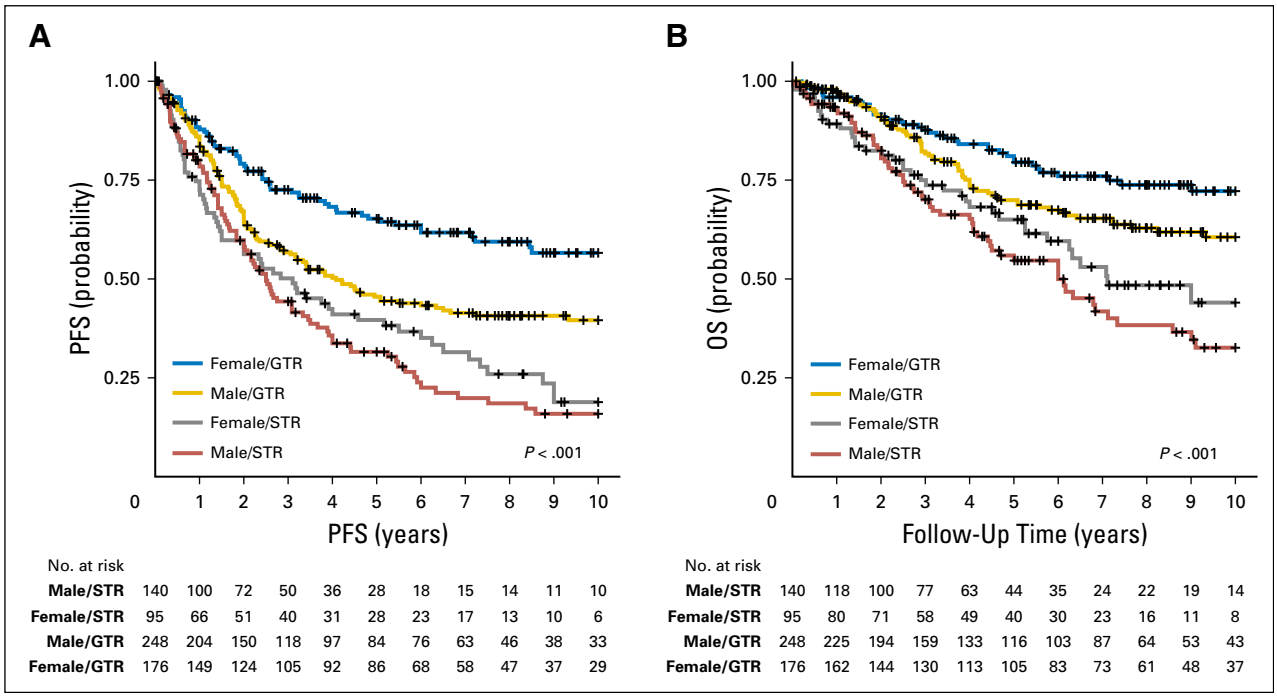

Fig A5. Sex as a function of extent of resection in EPN_PFA for (A) progression-free survival (PFS) and (B) overall survival (OS). *P* values were determined using the log-rank test. GTR, gross total resection; STR, subtotal resection.

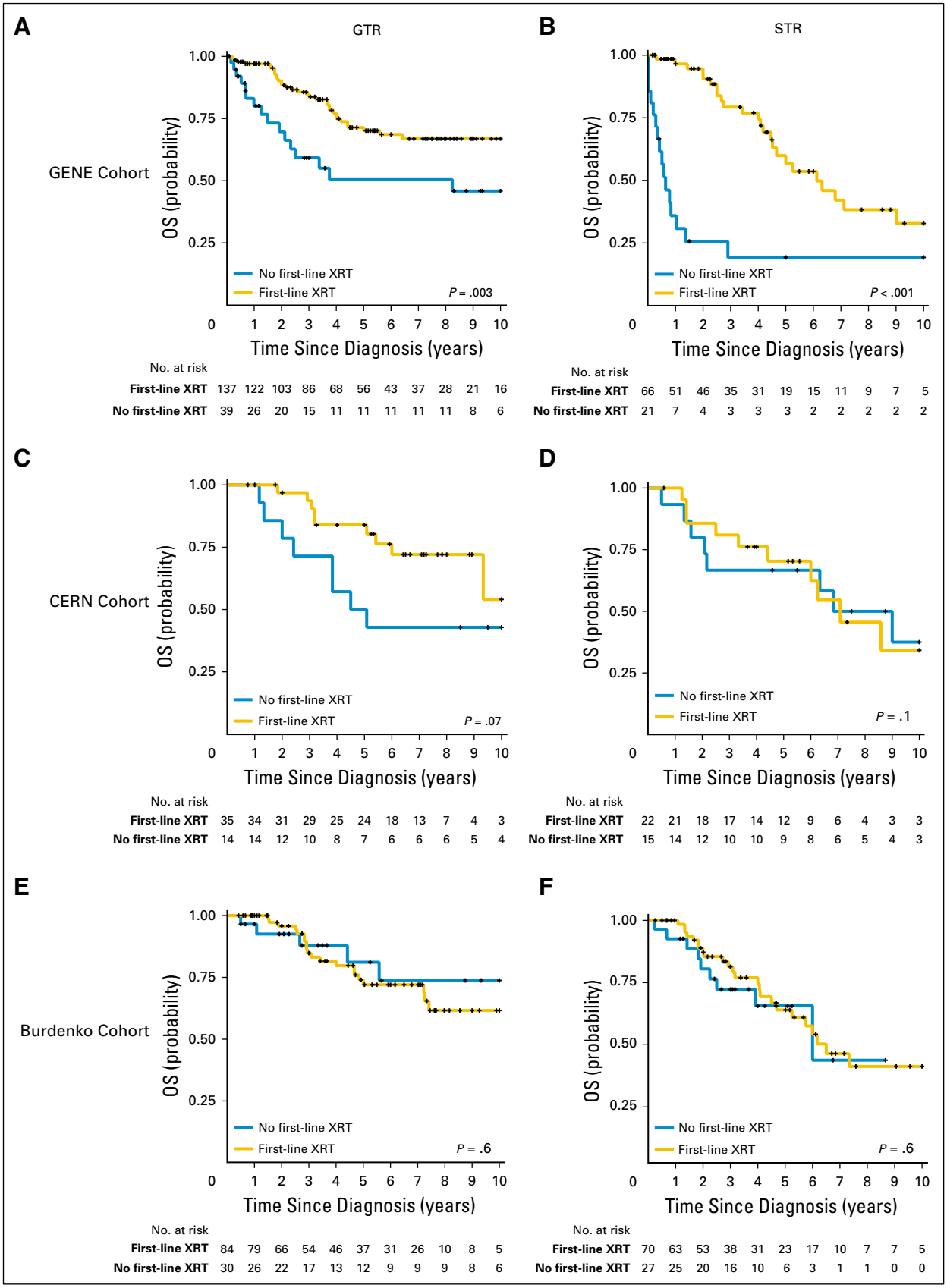

Fig A6. Overall survival (OS) of EPN_PFA for the four cohorts divided by (A, C, and E) gross total resection (GTR) and (B, D, and F) subtotal resection (STR). *P* values were determined using the log-rank test. CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence; XRT, radiotherapy.

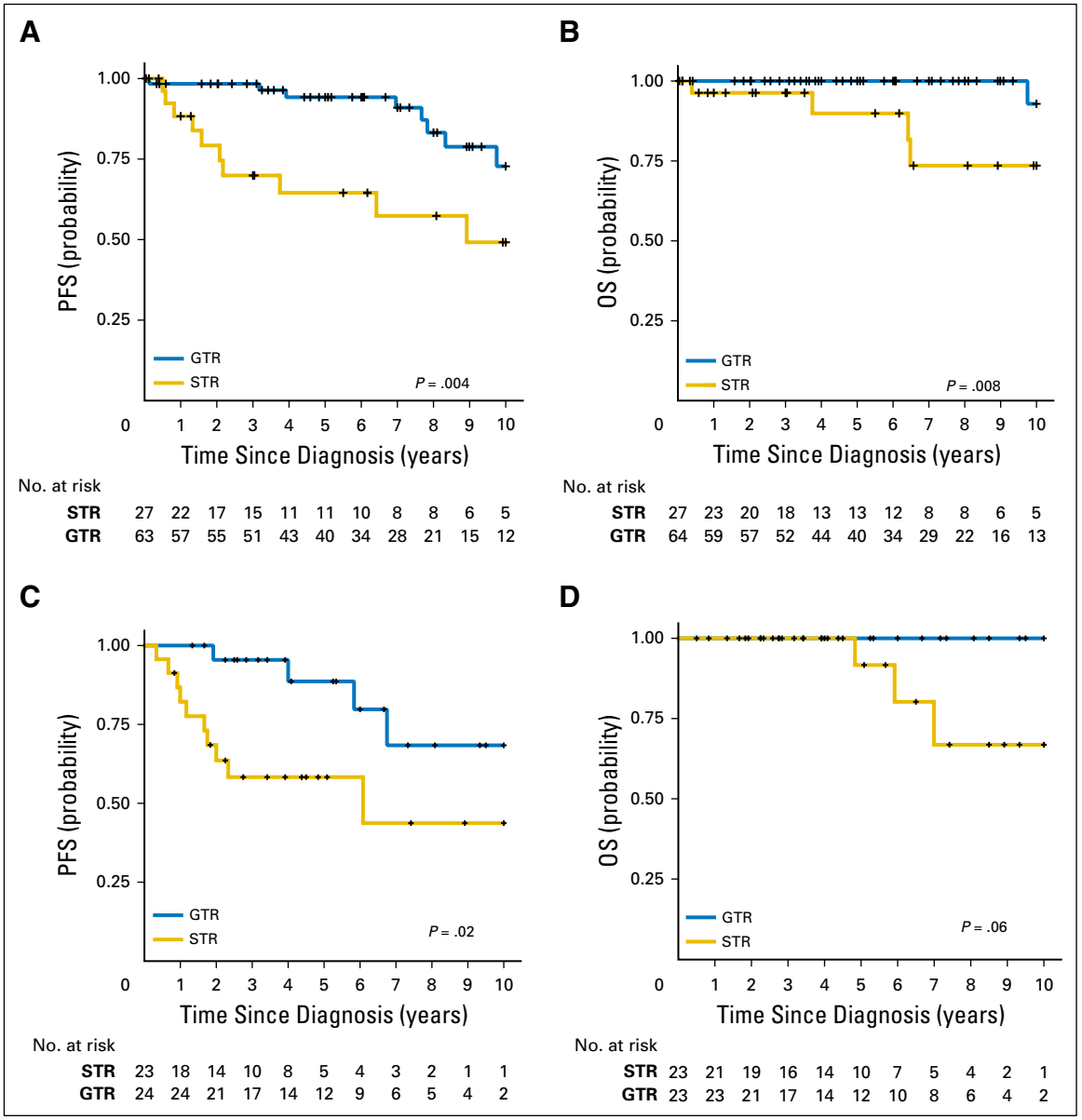

Fig A7. Progression-free survival (PFS) and overall survival (OS) EPN_PFB stratified by extent of resection for (A and B) the combined Global Ependymoma Network of Excellence (GENE), St Jude's, and Collaborative Ependymoma Research Network (CERN) cohorts and (C and D) the Burdenko Cohort. GTR, gross total resection; STR, subtotal resection.

Table A1. Multivariable Cox Proportional Hazards Model of Survival Across All Posterior Fossa Ependymomas

Variable	PFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
GENE cohort (PFS, n = 304; OS, n = 305)				
Subgroup EPN_PFA	2.66 (1.14 to 6.23)	.02	6.11 (1.38 to 27.01)	.02
Age	0.97 (0.95 to 0.99)	.008	0.96 (0.93 to 0.99)	.02
Incomplete resection	1.87 (1.31 to 2.67)	< .001	2.37 (1.55 to 3.64)	< .001
Adjuvant first-line radiation	0.30 (0.21 to 0.44)	< .001	0.29 (0.18 to 0.45)	< .001
Adjuvant first-line chemotherapy	1.07 (0.74 to 1.55)	.72	0.75 (0.47 to 1.20)	.23
Male	1.19 (0.86 to 1.66)	.30	1.26 (0.83 to 1.89)	.28
CERN cohort (PFS, n = 120; OS, n = 120)				
Subgroup EPN_PFA	2.08 (0.65 to 6.66)	.22	6.95 (1.13 to 42.71)	.04
Age	1.00 (0.97 to 1.03)	.89	1.01 (0.97 to 1.05)	.73
Incomplete resection	1.59 (0.91 to 2.79)	.10	1.79 (0.87 to 3.70)	.12
Adjuvant first-line radiation	0.70 (0.43 to 1.14)	.15	0.62 (0.33 to 1.17)	.14
Adjuvant first-line chemotherapy	0.95 (0.51 to 1.79)	.88	0.79 (0.37 to 1.72)	.56
Male	1.17 (0.73 to 1.90)	.51	2.12 (1.07 to 4.21)	.03
St Jude RT1 cohort (PFS, n = 112; OS, n = 112)				
Subgroup EPN_PFA	1.40 (0.25 to 7.96)	.70	4.94 (0.43 to 698.63)	.23
Age	0.99 (0.89 to 1.10)	.87	1.05 (0.91 to 1.17)	.51
Incomplete resection	2.75 (1.42 to 5.33)	.003	3.27 (1.47 to 6.90)	.005
Male	2.16 (1.15 to 4.06)	.009	2.72 (1.23 to 6.74)	.01
Burdenko cohort (PFS, n = 241; OS, n = 241)				
Subgroup EPN_PFA	2.49 (0.98 to 6.35)	.06	2.72 (0.51 to 14.67)	.24
Age	0.99 (0.96 to 1.02)	.61	0.98 (0.93 to 1.04)	.49
Incomplete resection	2.03 (1.43 to 2.89)	< .001	2.00 (1.19 to 3.37)	.009
Adjuvant first-line radiation	1.11 (0.74 to 1.66)	.61	1.08 (0.60 to 1.95)	.80
Adjuvant first-line chemotherapy	0.99 (0.65 to 1.49)	.94	1.38 (0.71 to 2.66)	.34
Male	1.10 (0.76 to 1.58)	.62	0.85 (0.50 to 1.45)	.55

Abbreviations: CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Table A2. Multivariable Cox Proportional Hazards Regression Model of 10-Year Progression-Free and Overall Survival

Variable	Hazard Ratio	95% CI	*P*
Progression-free survival (n = 777)			
Age	0.99	0.97 to 1.00	.09
Male	1.25	1.01 to 1.54	.04
Incomplete resection	1.88	1.51 to 2.33	< .001
Adjuvant first-line radiation	0.63	0.50 to 0.81	< .001
Adjuvant first-line chemotherapy	1.02	0.79 to 1.32	.87
EPN_PFA subgroup	2.18	1.31 to 3.62	.003
Overall survival (n = 778)			
Age	0.98	0.96 to 1.00	.13
Male	1.40	1.06 to 1.84	.02
Incomplete resection	2.14	1.61 to 2.84	< .001
Adjuvant first-line radiation	0.52	0.38 to 0.71	< .001
Adjuvant first-line chemotherapy	0.91	0.66 to 1.27	.6
EPN_PFA Subgroup	4.27	1.86 to 9.81	< .001

Table A3. Multivariable Cox Proportional Hazards Model of 10-Year Survival Across All Posterior Fossa Ependymoma

Variable	PFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
GENE cohort (PFS, n = 304; OS, n =3 05)				
Subgroup EPN_PFA	2.61 (1.04 to 6.53)	.04	5.26 (1.17 to 23.60)	.03
Age	0.96 (0.93 to 0.99)	.005	0.96 (0.92 to 1.00)	.03
Incomplete resection	1.90 (1.33 to 2.72)	< .001	2.49 (1.61 to 3.87)	< .001
Adjuvant first-line radiation	0.29 (0.20 to 0.43)	< .001	0.27 (0.17 to 0.43)	< .001
Adjuvant first-line chemotherapy	1.01 (0.69 to 1.47)	.96	0.75 (0.47 to 1.22)	.25
Male	1.16 (0.83 to 1.61)	.40	1.20 (0.79 to 1.82)	.40
CERN cohort (PFS, n = 120; OS, n = 120)				
Subgroup EPN_PFA	2.08 (0.65 to 6.66)	.22	7.52 (1.09 to 51.67)	.04
Age	1.00 (0.97 to 1.03)	.89	1.00 (0.96 to 1.05)	.73
Incomplete resection	1.59 (0.91 to 2.79)	.10	1.82 (0.86 to 3.85)	.12
Adjuvant first-line radiation	0.70 (0.43 to 1.14)	.15	0.67 (0.53 to 1.28)	.22
Adjuvant first-line chemotherapy	0.95 (0.51 to 1.79)	.88	0.77 (0.35 to 1.68)	.51
Male	1.17 (0.73 to 1.90)	.51	2.02 (1.01 to 4.04)	.05
St Jude RT1 cohort (PFS, n = 112; OS, n = 112)				
Subgroup EPN_PFA	2.87 (0.31 to 26.73)	.35	4.68 (0.40 to 662.59)	.25
Age	1.00 (0.90 to 1.11)	1.00	1.05 (0.91 to 1.18)	.47
Incomplete resection	2.77 (1.42 to 5.38)	.003	3.49 (1.56 to 7.45)	.003
Male	2.42 (1.25 to 4.67)	.009	3.16 (1.38 to 8.30)	.006
Burdenko cohort (PFS, n = 241; OS, n = 241)				
Subgroup EPN_PFA	2.46 (0.97 to 6.24)	.06	2.90 (0.54 to 15.55)	.21
Age	0.99 (0.96 to 1.02)	.63	0.98 (0.93 to 1.04)	.52
Incomplete resection	2.00 (1.40 to 2.84)	< .001	2.01 (1.18 to 3.42)	.01
Adjuvant first-line radiation	1.09 (0.73 to 1.64)	.66	1.10 (0.60 to 2.03)	.75
Adjuvant first-line chemotherapy	1.01 (0.66 to 1.54)	.96	1.31 (0.67 to 2.54)	.43
Male	1.10 (0.76 to 1.58)	.62	0.84 (0.49 to 1.42)	.51

Abbreviations: CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Table A4. Predictor-Cohort Interaction Likelihood Ratio Test for Both Progression-Free Survival and Overall Survival

Predictor	*P*	
	PFS	OS
EPN subgroup	.35	.84
Age	.09	.68
Extent of resection	.79	.49
Sex	.37	.14
Adjuvant first-line chemotherapy	.70	.82
Adjuvant first-line radiation	< .001	.009

NOTE. Values represent the *P* values for a likelihood ratio test for predictor-cohort interaction.
Abbreviations: OS, overall survival; PFS, progression-free survival.

Table A5. The 5- and 10-Year Survival of Patients With EPN_PFA and EPN_PFB Older Than Age 10 Years

Survival	EPN_PFA	EPN_PFB
No. of patients	54	128
Median PFS (95% CI)		
5-year PFS	0.537 (0.413 to 0.698)	0.828 (0.761 to 0.900)
10-year PFS	0.412 (0.283 to 0.600)	0.622 (0.513 to 0.756)
Median OS (95% CI)		
5-year OS	0.705 (0.585 to 0.849)	0.981 (0.955 to 1.000)
10-year OS	0.598 (0.458 to 0.780)	0.868 (0.771 to 0.977)

Abbreviations: OS, overall survival; PFS, progression-free survival.

Table A6. The 5- and 10-Year Survival of Patients With EPN_PFA Stratified by GTR and STR Across Four Cohorts

Survival	Median (95% CI)			
	GENE	St Jude's	CERN	Burdenko
GTR				
5-year PFS	0.467 (0.386 to 0.544)	0.707 (0.596 to 0.793)	0.667 (0.515 to 0.781)	0.453 (0.354 to 0.547)
5-year OS	0.688 (0.605 to 0.756)	0.879 (0.786 to 0.933)	0.739 (0.587 to 0.843)	0.781 (0.682 to 0.853)
10-year PFS	0.425 (0.339 to 0.508)	0.676 (0.561 to 0.767)	0.459 (0.299 to 0.606)	0.369 (0.261 to 0.476)
10-year OS	0.628 (0.533 to 0.710)	0.774 (0.660 to 0.854)	0.567 (0.389 to 0.711)	0.661 (0.526 to 0.766)
STR				
5-year PFS	0.370 (0.261 to 0.479)	0.526 (0.287 to 0.719)	0.568 (0.394 to 0.708)	0.261 (0.175 to 0.356)
5-year OS	0.535 (0.413 to 0.643)	0.590 (0.345 to 0.770)	0.681 (0.499 to 0.809)	0.658 (0.540 to 0.753)
10-year PFS	0.259 (0.141 to 0.394)	0.301 (0.102 to 0.531)	0.218 (0.100 to 0.365)	0.143 (0.067 to 0.247)
10-year OS	0.327 (0.194 to 0.467)	0.451 (0.214 to 0.663)	0.401 (0.221 to 0.575)	0.433 (0.280 to 0.577)

Abbreviations: CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence; GTR, gross total resection; OS, overall survival; PFS, progression-free survival; STR, subtotal resection.

Table A7. Multivariable Cox Proportional Hazards Model of Survival in EPN_PFA

Variable	PFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
All cohorts (PFS, n = 645; OS, n = 646)				
Age	0.98 (0.96 to 1.00)	.08	0.99 (0.96 to 1.01)	.26
Incomplete resection	1.71 (1.37 to 2.14)	< .001	2.05 (1.52 to 2.76)	< .001
Adjuvant radiation	0.64 (0.50 to 0.82)	< .001	0.52 (0.38 to 0.72)	< .001
Adjuvant chemotherapy	1.04 (0.81 to 1.35)	.74	0.89 (0.63 to 1.26)	.51
Male	1.31 (1.05 to 1.62)	.02	1.39 (1.04 to 1.85)	.02
GENE cohort (PFS, n = 258; OS, n = 259)				
Age	0.96 (0.93 to 0.99)	.007	0.96 (0.91 to 1.00)	.03
Incomplete resection	1.68 (1.17 to 2.42)	.005	2.26 (1.46 to 3.49)	< .001
Adjuvant radiation	0.31 (0.21 to 0.45)	< .001	0.28 (0.18 to 0.45)	< .001
Adjuvant chemotherapy	1.08 (0.74 to 1.58)	.68	0.78 (0.49 to 1.25)	.30
Male	1.10 (0.79 to 1.55)	.57	1.17 (0.77 to 1.78)	.46
CERN cohort (PFS, n = 86; OS, n = 86)				
Age	1.00 (0.96 to 1.04)	.92	1.01 (0.97 to 1.06)	.53
Incomplete resection	1.63 (0.85 to 3.12)	.14	1.80 (0.83 to 3.88)	.13
Adjuvant radiation	0.73 (0.43 to 1.25)	.25	0.61 (0.31 to 1.18)	.14
Adjuvant chemotherapy	0.89 (0.46 to 1.72)	.73	0.77 (0.35 to 1.67)	.50
Male	1.40 (0.81 to 2.43)	.23	2.51 (1.18 to 5.33)	.02
St Jude's RT1 cohort (PFS, n = 104; OS, n = 104)				
Age	1.00 (0.90 to 1.12)	.94	1.04 (0.91 to 1.19)	.61
Incomplete resection	2.71 (0.40 to 5.26)	.003	3.26 (1.49 to 7.12)	.003
Male	2.42 (1.25 to 4.69)	.009	2.86 (1.21 to 6.77)	.02
Burdenko cohort (PFS, n = 197; OS, n = 197)				
Age	0.99 (0.96 to 1.03)	.77	1.01 (0.96 to 1.06)	.70
Incomplete resection	1.88 (1.30 to 2.71)	< .001	1.84 (1.08 to 3.12)	.02
Adjuvant radiation	1.12 (0.74 to 1.70)	.60	1.02 (0.56 to 1.85)	.94
Adjuvant chemotherapy	0.98 (0.64 to 1.49)	.92	1.42 (0.73 to 2.78)	.30
Male	1.19 (0.81 to 1.77)	.38	0.89 (0.51 to 1.53)	.66

Abbreviations: CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Table A8. Multivariable Cox Proportional Hazards Model of 10-Year Survival in EPN_PFA

Variable	PFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
All cohorts (PFS, n = 645; OS, n = 646)				
Age	0.98 (0.96 to 1.00)	.07	0.99 (0.96 to 1.01)	.26
Incomplete resection	1.74 (1.39 to 2.18)	< .001	2.05 (1.52 to 2.76)	< .001
Adjuvant radiation	0.65 (0.50 to 0.83)	< .001	0.52 (0.38 to 0.72)	< .001
Adjuvant chemotherapy	1.03 (0.80 to 1.34)	.80	0.89 (0.63 to 1.26)	.51
Male	1.31 (1.05 to 1.63)	.02	1.39 (1.04 to 1.85)	.02
GENE cohort (PFS, n = 258; OS, n = 259)				
Age	0.95 (0.92 to 0.99)	.008	0.96 (0.91 to 1)	.03
Incomplete resection	1.74 (1.21 to 2.52)	.003	2.26 (1.46 to 3.49)	< .001
Adjuvant radiation	0.31 (0.21 to 0.45)	< .001	0.28 (0.18 to 0.45)	< .001
Adjuvant chemotherapy	1.03 (0.70 to 1.51)	.88	0.78 (0.49 to 1.25)	.30
Male	1.09 (0.78 to 1.53)	.62	1.17 (0.77 to 1.78)	.46
CERN cohort (PFS, n = 86; OS, n = 86)				
Age	1.00 (0.96 to 1.40)	.92	1.01 (0.97 to 1.06)	.53
Incomplete resection	1.91 (0.98 to 3.75)	.06	1.80 (0.83 to 3.88)	.13
Adjuvant radiation	0.84 (0.47 to 1.48)	.54	0.61 (0.31 to 1.18)	.14
Adjuvant chemotherapy	0.82 (0.42 to 1.61)	.57	0.77 (0.35 to 1.67)	.50
Male	1.46 (0.82 to 2.59)	.20	2.51 (1.18 to 5.33)	.02
St Jude's RT1 Cohort (PFS, n = 104; OS, n = 104)				
Age	1.01 (0.90 to 1.12)	.9	1.04 (0.91 to 1.19)	.61
Incomplete resection	2.77 (1.43 to 5.38)	.003	3.26 (1.49 to 7.12)	.003
Male	2.59 (1.31 to 5.10)	.006	2.86 (1.21 to 6.77)	.02
Burdenko cohort (PFS, n = 197; OS, n = 197)				
Age	0.99 (0.96 to 1.03)	.80	1.01 (0.96 to 1.06)	.70
Incomplete resection	1.84 (1.28 to 2.66)	.001	1.84 (1.08 to 3.12)	.02
Adjuvant radiation	1.10 (0.72 to 1.67)	.66	1.02 (0.56 to 1.85)	.94
Adjuvant chemotherapy	1.00 (0.65 to 1.54)	.99	1.42 (0.73 to 2.78)	.30
Male	1.19 (0.81 to 1.77)	.38	0.89 (0.51 to 1.53)	.66

Abbreviations: CERN, Collaborative Ependymoma Research Network; GENE, Global Ependymoma Network of Excellence; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Table A9. Multivariable Cox Proportional Hazards Model of Survival in EPN_PFB in All Cohorts

Variable	Progression-Free Survival (n = 132)		Overall Survival (n = 132)	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	0.99 (0.97 to 1.02)	.70	0.98 (0.92 to 1.04)	.45
Incomplete resection	3.93 (1.78 to 8.68)	< .001	11.32 (1.28 to 100.41)	.03
Adjuvant radiation	0.49 (0.21 to 1.14)	.10	0.53 (0.09 to 3.06)	.48
Adjuvant chemotherapy	1.64 (0.45 to 5.92)	.45	5.37 (0.45 to 64.12)	.18
Male	0.76 (0.37 to 1.59)	.47	0.76 (0.15 to 3.79)	.74

Abbreviation: HR, hazard ratio.

Table A10. Multivariable Cox Proportional Hazards Model of 10-Year Survival in EPN_PFB in All Cohorts

Variable	Progression Free Survival (n = 132)		Overall Survival (n = 132)	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age	0.99 (0.96 to 1.02)	.52	0.97 (0.91 to 1.04)	.38
Incomplete resection	4.30 (1.89 to 9.77)	< .001	11.06 (1.24 to 98.32)	.03
Adjuvant radiation	0.49 (0.21 to 1.16)	.10	0.51 (0.09 to 2.99)	.45
Adjuvant chemotherapy	1.51 (0.42 to 5.41)	.45	4.93 (0.42 to 58.18)	.20
Male	0.69 (0.32 to 1.47)	.33	0.77 (0.15 to 3.84)	.75

Abbreviation: HR, hazard ratio.

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Ependymoma

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Contents

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Abstract

Ependymomas are rare tumours of neuroectodermal origin classified as myxopapillary ependymoma and subependymoma (grade I), ependymoma (grade II) and anaplastic ependymoma (grade III). The more common location is infratentorial (60%). Age <40 years and extent of surgery appear related to better prognosis, while the role of other prognostic factors, such as tumour grade and tumour site are equivocal. This emphasizes the role of surgery as the standard treatment. Postoperative radiotherapy is indicated in high-grade ependymomas, and is recommended in low-grade ependymomas after subtotal or incomplete resection (confirmed by postoperative MR). Deferral of radiotherapy until recurrence may be considered on an individual basis for patients with MR confirmation of a radical resection. Recommended dose to involved fields is 45–54 Gy for low-grade (grade II) and 54–60 Gy for high-grade ependymomas (grade III). There is no proof that postoperative chemotherapy improves the outcome. At recurrence, platinum-, nitrosourea- or temozolomide-based chemotherapy can be administered, although there is no evidence of efficacy.

Keywords: Ependymomas; Treatment; Prognosis

1. General information

1.1. Definition

Ependymomas are rare tumours of neuroectodermal origin arising from ependymal cells in the obliterated central canal of the spinal cord, the filum terminale, choroid plexus or white matter adjacent to the highly angulated ventricular surface [1]. Additionally, ependymomas can be found in the brain parenchyma as a result of fetal ependymal cell rests migrating from periventricular areas [2].

1.2. Incidence

About 500 new cases of ependymoma are diagnosed in the European Union each year. The annual incidence rate in Europe is around 2 per million [3]. Ependymoma is slightly more frequent in males than females [3] and occurs in all age groups. About 15% of all patients are children of less than 5 years of age [4]. In children and in the countries of Central and South America and Asia, the annual incidence of ependymoma is less than 2 per million [4]. In North America, Oceania and most of Europe, the rate varies between 2 and 4 per million. In Denmark, Sweden, Finland, the former East Germany and Slovenia, the incidence is at least 4 per million.

1.3. Survival

In Europe, 1-year survival for adults diagnosed with ependymoma during 1990–1994 was 82% and 5-year survival 72%, with no difference between men and women [5]. Five-year survival decreased markedly with age from 79% in the youngest (15–45 years), to 44% in the oldest age group (patients 75 years and over) [5]. The 1-year survival for children with ependymoma in Europe, between 1990 and 1994, was 80%, at 5-year 55%. Survival was very poor in infants (24%), then increased with age: in children aged 1–4 years 44%, at 5–9 years 68% and at 10–14 years 75% [6].

1.4. Aetiology and risk factors

Little is known about the aetiology of ependymomas. A possible relationship between the presence of polyomavirus SV40 has been suggested [7,8], but could not be confirmed by other studies [9,10]. From a recent study [10] over a 55-year period (69.5 million person years), cancer incidence was not shown to be associated with exposure to SV40-contamined poliovirus vaccine. Incidence data on ependymoma were carefully reviewed because of an increase in ependymoma incidence among children aged 0–4 years in exposed periods and compared with the incidence in preceding unexposed periods. However, the incidence of ependymoma was relatively low in the years of SV40 contamination, with a highest incidence observed in 1964, when most children were too young to have received the SV40-contaminated vaccine. An increased incidence of ependymomas has also been reported in neurofibromatosis type 2 [11]. An inverse association between maternal consumption of vitamin supplements during pregnancy and brain tumours has been observed in five out of six studies on this subject [12], and one of these studies related specifically to the category of ependymomas [13].

2. Pathology and biology

2.1. Histopathology

According to the World Health Organization (WHO) [14], ependymal tumours are being classified as WHO grade 1: myxopapillary ependymoma (occurring almost exclusively

in the conus-cauda-filum terminale region) and subependymoma, a benign, slowly growing intraventricular lesion with a very favourable prognosis, WHO grade II ependymoma and WHO grade III anaplastic ependymoma. Ependymoblastomas are being classified as primitive neuroectodermal tumours (PNET) and must be distinguished from anaplastic ependymomas.

2.1.1. Myxopapillary ependymoma (WHO grade I)

This entity is characterised by cuboidal tumour cells, with GFAP expression and lack of cytokeratin expression, surrounding blood vessels in a mucoid matrix. Mitotic activity is very low or absent.

2.1.2. Subependymoma (WHO grade I)

Subependymoma has isomorphic nuclei in an abundant and dense fibrillary matrix with frequent microcysts; mitoses are very rare or absent.

2.1.3. Ependymoma (WHO grade II)

This neoplasm has moderate cellularity; mitoses are rare or absent and nuclear morphology is monomorphic. Key histological features are perivascular pseudorosettes and ependymal rosettes [14]. Four histological variants have been described: cellular ependymoma, which has hypercellularity and increased mitotic rate, papillary ependymoma, clear cell ependymoma and tanycytic ependymoma.

2.1.4. Anaplastic ependymoma (WHO grade III)

This tumour is characterised by hypercellularity, cellular and nuclear pleomorphism, frequent mitosis, pseudopalisading necrosis and endothelial proliferation. The latter two criteria do not appear to be independently related to prognosis [15]. Perivascular rosettes are a histological hallmark.

2.2. Immunophenotype

2.2.1. Immunophenotype

Ependymomas typically express GFAP, particularly in pseudorosettes and in grades I–II lesions, S100 protein and vimentin [16,17]. In some cases, focal expression of cytokeratins has been observed [18], while neuronal antigens are never observed. The proliferation index is variable and is higher when anaplastic features are present or the patient is aged

2.3. Genetic features

2.3.1. Genetic features

Data concerning the cytogenetic features of ependymoma are sparse. Approximately two thirds of patients exhibit cytogenetic abnormalities but no primary deletion is evident. The most frequent abnormal cytogenetic features consist of monosomy 22 or in various translocations involving chromosome 22, which have been detected in approximately 30% of cases [19–22]. The absence of a tumour-suppressor gene located on chromosome 22 has been suggested. Aberrations involving chromosomes 1, 6, 7, 9, 10, 11, 12, 13, 16, 17, 19 and 20 have been reported less frequently. Ependymomas are genetically different from astrocytic and oligodendroglial tumours. No mutations or deletions of the tumour suppressor genes CDKN2A and CDKN2B and no amplification of CDK4 or CCND1 or EGFR have been described [23,24]. The p53 gene has only a minor and unclear role in induction of ependymomas [25,26]. However, mdm2 gene amplification has been found in up to 35% of ependymomas [27]. The gene product MDM2 is believed to act as a cellular regulator of p53-mediated tumour growth. MDM2 immunopositivity was detected in 96% of specimens, suggesting not only a role of mdm2 amplification in the tumorigenesis of ependymoma but also the presence of a mechanism of MDM2 overexpression other than gene amplification [27]. Analyses of mutations of the NF2 suppressor gene yielded conflicting results [28,29]. It is likely that NF2 mutations are related to spinal ependymomas only [30], which constitute a molecular variant, while a tumour-suppressor gene, independent of the NF2 gene, might be implicated in the genesis of cerebral ependymomas [31]. The cytogenetic aberrations seem to differ between tumours from adult and younger patients, and between intracranial and spinal ependymomas [32].

3. Diagnosis

3.1. Clinical presentation

Clinical presentation is non-specific, and depends on the size, location and malignancy of the tumour. Anaplastic ependymomas give rise to signs and symptoms more rapidly. Intraventricular ependymomas often cause headache, nausea and vomiting, papilloedema, ataxia, and vertigo due to increased intracranial pressure and hydrocephalus. The compression of posterior fossa structures leads to visual disturbances, ataxia and hemiparesis, dizziness and neck pain. Patients with extraventricular supratentorial ependymomas may show forgetfulness, behavioural changes and lethargy with signs like seizures and focal neurological deficits. Spinal cord lesions are typically associated with back pain of long duration, and motor or sensory deficits of lower and upper extremities.

3.2. Localisation

Ependymomas are more commonly infratentorial (60%), particularly in the fourth ventricle, and in 50% of cases can extend into the subarachnoid space of the cisterna magna or the cerebello-pontine angle, or involve the medulla and upper cervical cord [33,34]. The second most common location is the spinal cord, followed by the lateral ventricles and the third ventricle. Approximately one-half of supratentorial ependymomas are parenchymal and one-half are primarily intraventricular, arising more often (75%) in the lateral ventri-

cles than in the third ventricle. Myxopapillary ependymomas are typically and almost exclusively located in the conus – cauda equina – filum terminale region. Rarely, they have been observed in the upper spinal cord, in the lateral ventricles or in the brain parenchyma. Subependymomas are typically located in the fourth and in the lateral ventricles.

3.3. Diagnostic criteria

Ependymoma appears as a well-circumscribed lesion with varying degrees of contrast enhancement, which is more pronounced in anaplastic tumours and can be absent in subependymomas, on either MRI or CT scanning. A cystic component, the presence of calcium, and intra-tumoural haemorrhage are occasionally observed, while oedema and brain infiltration are infrequent. Surgical exploration and biopsy are essential for the selection of appropriate treatment.

4. Staging

4.1. Staging procedures

The staging work-up should include a careful history, physical examination and magnetic resonance imaging of the brain and the spinal cord. Examination of the CSF for cytological evidence of malignancy is essential. The incidence of spinal seeding is 1.6% for supratentorial tumours, 9.7% for infratentorial lesions, 8.4–20% for high-grade tumours, and 2–4.5% for low-grade lesions [34,35]. The highest incidence is observed among high-grade infratentorial ependymomas.

4.2. Staging system

The UICC/AJC classification [36] is applied to all brain tumours and distinguishes between supratentorial and infratentorial locations. However, this classification is rarely used and the nodal and distant metastases categories very rarely occur in ependymomas.

4.3. Restaging procedures

Restaging should include all the diagnostic procedures that were positive at the time of diagnosis and of initial staging. Spinal seeding rate is consistently different among reported series, most likely due to different diagnostic criteria and whether either clinical or pathologic seeding was considered—the latter being almost 10 times more frequent than the former [37]. The most important determinants of the risks on spinal seeding are tumour grade and localisation [35]; 0–12.5% of patients with high-grade supratentorial lesions developed spinal seeding, whereas 0–38% of those with high-grade infratentorial tumours developed spinal dissemination [33,35,38,39]. For low-grade tumours, 0–7% of patients with supratentorial lesions developed seeding compared with 0–40% for those with infratentorial lesions [33,35,37–39]. The incidence of spinal seeding was related directly to local tumour control, regardless of tumour grade. The incidence of spinal dissemination was significantly lower in locally controlled patients than in those with uncontrolled primary lesions (3.3% versus 9.5%) [35].

5. Prognosis

5.1. Natural history

Grades I–II tumours, which are slowly growing gliomas, disseminate infrequently to brain parenchyma, nerve roots, bones and CSF; they are sometimes asymptomatic and are found incidentally at autopsy [40]. Anaplastic ependymomas exhibit a more rapid growth pattern and are occasionally invasive. They may occasionally be the result of malignant progression from grade II tumours, and tend to spread into the CSF more frequently, particularly if located in the posterior fossa.

5.2. Prognostic factors

Most reported series of ependymomas are retrospective and, include only a small number of patients, due to the low incidence of this tumour type. Moreover, these studies span several decades which hampers the interpretation of the results due to changes in grading systems and diagnostic and therapeutic policies, and with limited statistical power. Consequently, generally accepted prognostic factors are lacking. The prognostic significance of tumour grade is not universally accepted, most likely due to the varying definitions of anaplasia [41–43], to the large number (69%) of discrepancies between local pathology diagnosis and those reported on centralised review [44], and to the fact that classical histological features of anaplasia seem to be unrelated to the biological behaviour of ependymomas [40]. Another confounding factor is that most series fail to distinguish patients with malignant ependymomas from those with ependymoblastomas which have an especially poor prognosis. According to some authors, tumour grade is the most important determinant of prognosis [34,35,45–49], whereas others did not find any correlation between survival and histologic grade suggesting that the outcome is influenced by anatomical location, which dictates resectability, rather than by pathological features [37,38,50–53]. The 5-year survival for patients with low-grade tumours ranges from 55% to 87%, whereas for anaplastic ependymomas it varies between 10% and 47% [34,39,47,54]. A direct correlation between age and better prognosis has been suggested. The small number of patients, the different definitions of paediatric age among series (ranging from 12 to 20 years), and the heterogeneity of histological grade and tumour location [34,49,54–57] between the compared groups preclude reliable conclusions. Ependymomas are uncommon in adults, and it is difficult to clearly assess outcome in a strictly adult population as most of the published series mainly relate to paediatric patients. Adult patients

may have a somewhat better prognosis with 5-year survivals of 55–90% as compared to paediatric patients, i.e.14–60% [38,39,46,52,58]. In general, the younger the child the worse the prognosis [38,45,47,53]. It has been suggested that paediatric ependymomas may behave more aggressively, based on the more immature neural tissue of the children [38,58]. Different patterns in cytogenetic aberrations between younger and older patients may underlie the age-related outcome [32]. The role of tumour location is also controversial. If spinal lesions are related to the most favourable outcome, things are less clear for intracranial tumours. Some authors reported no prognostic impact of this variable [37,39,49,54,55]. According to others, supratentorial ependymomas are related to a worse prognosis because they more often exhibit peripheral infiltrative growth into the brain parenchyma and are less often entirely encapsulated rendering surgical resectability troublesome [33,34,38,46,59]. Furthermore, infratentorial tumours show a lower mitotic activity than supratentorial tumours [60,61]. Conversely, other authors claimed a worse prognosis for ependymomas arising from the posterior fossa, which occur in younger patients [45] and invade the brainstem, the floor of the fourth ventricle or cranial nerves of the cerebellopontine angle through the foramen of Luschka, precluding complete resection [38,53]. The 5-year survival ranges between 35% and 76% for supratentorial, 40% and 59% for infratentorial, and 57% and 100% for spinal ependymomas [33,39,46,49,62]. The extent of resection has been proposed as an independent prognostic factor. Gross total resection achieves a better 5-year survival than a subtotal removal or biopsy [52,63,64]. In some cases, the benefit of complete resection was limited to low-grade tumours [55]. However, most authors failed to find any significant survival advantage related to the extent of resection [34,38,49,53,57]. The lack of evidence for the impact of surgery on survival could be related to the unreliability of subjective assessment of the degree of surgical ablation [65]. By contrast, the degree of resection, when assessed by postoperative imaging, revealed a significant difference in 5-year freedom from progressive disease in a small series of 19 patients [65]. Female gender was reported to show better survival than male gender in one single series [55].

6. Treatment

6.1. Surgery

Surgery represents the standard treatment for ependymoma; it provides tissue for histologic diagnosis, may re-establish cerebrospinal fluid flow, and permits debulking or total resection of the tumour. Maximal surgical resection can be of paramount importance and should be carried out whenever possible, without compromising neurological function, and a positive relation between extent of imaging-based surgical resection and outcome has been suggested [65]. Postoperative magnetic resonance imaging allows a better evaluation of the degree of resection and may also identify cases in whom immediate second-look surgery might be useful. Significant improvements in neurosurgical techniques and neuro-anesthesia have facilitated a reduction of operative mortality of 25–50% for infratentorial and of 6–22% for supratentorial ependymomas to less than 5% of cases [38,47,52,56]. Incomplete resection is the rule because ependymomas usually grow in highly specialised areas of the central nervous system. The frequency of complete resections is higher in surgical series than in radiotherapy series and ranges from 25% to 93% for supratentorial ependymomas [33,39,66,67] and from 5% to 72% for infratentorial ependymomas [33,38,39,44,46,49,52,54,67]. The rate of gross total resections in infratentorial tumours depends on their location, being up to 100% in the roof of the fourth ventricle, 86% in mid-floor tumours and 54% in the lateral recesses [52]. Spinal cord tumours, which in the majority are low-grade lesions, can often completely be removed, and without functional sacrifice in 27–45% of cases [33,34,46,47,49,68–70].

6.2. Radiation therapy

Postoperative radiotherapy (RT) is the standard treatment on a type C basis in high-grade ependymomas, and on a type 3 basis in low-grade ependymomas. Five-year survival rates for patients with intracranial ependymomas have increased from 0–27% [71] to 36.5–87% since the use of systemic irradiation [25,34,39,46,47,54–56,62,63,67,68,70,72–74]. However, data on survival after surgery alone are limited in modern series and a clear impact of radiotherapy on the outcome is not supported by consistent statistical data because no randomised trials have been carried out. The non-significant prolonged survival with postoperative irradiation as observed in retrospective series was either uncontrolled or compared with historical controls [45,54,72] while in the single series reporting a significant benefit, the comparison was biased due to inclusion of patients experiencing progressive disease during postoperative chemotherapy, or patients younger than 3 years of age in the control arm [63]. Notwithstanding these considerations, particularly since failure to control local disease remains the most significant factor contributing to recurrence and a poor survival, there is a consensus that radiotherapy should be part in the standard of care for the majority of patients. More recently, some small series reported a remarkably good outcome in children with low-grade intracranial ependymoma and did not receive irradiation after a gross total resection [45,65–68,70,73,75,76]. The option of a close observation and delaying radiation until signs of tumour progression may be relevant, since late effects as cognitive deterioration, endocrine dysfunction in small children or dementia in the elderly constitute major concerns in patients who are potential long-term survivors of brain tumours. So, reserving RT for relapses appears to be an attractive strategy in these patients. It may also be considered as a therapeutic option for patients with a subtotal resection of low-grade ependymomas, assuming that the behaviour of

these tumours may be similar to low-grade gliomas, where no untoward impact on overall survival has been observed following a 'wait and see' policy following surgery [77]. On the other hand, no data about the impact of delaying RT on tumour control and survival are available for adult patients with totally resected low-grade ependymomas, and thus the best postoperative policy remains controversial. The option of a close observation and delaying irradiation until tumour progression seems appropriate for individual clinical use on type R basis for selected subsets of patients, such as those with totally resected low-grade tumours. The standard treatment volume should be defined according to modern conformational techniques and is limited to the pre-surgical tumour bed with an added margin of 1–2 cm [73,78], on a type C basis in all low-grade lesions [34,35,49,55,56], and on a type R basis in high-grade supratentorial lesions [33,54–56,64,79]. Craniospinal irradiation should be reserved for patients with evidence of cranio-spinal seeding [33,59,61] and is suitable for individual clinical use on type R basis in high-grade infratentorial lesions [33,34,53,56,64,80,81], based on their high potential of tumour spread into the ventricular system and into the spinal subarachnoid space] [81]. However, prophylactic spinal irradiation did not seem to modify patterns of failure [33,34,39,49,54,65,71,80,81] for high-grade lesions, which disseminated into the spine in 8–9.4% of patients treated with and in 6.6–10% without craniospinal irradiation [35,55]. Moreover, local recurrence is the predominant pattern of failure for both low-grade and high-grade ependymomas [33,47,56,80–82], and the lack of local control represents the main risk factor for subarachnoid seeding [49], which rises from 3.3–5% to 8.5–10% based on either the absence or presence of local recurrence [65,80]. Finally, no survival advantage has been demonstrated for craniospinal irradiation [49,73,78,80], and the rate of spinal seeding among high-grade tumours may be overestimated since most authors have not excluded ependymoblastomas, and treatment-related toxicity remains a serious concern, especially in small children [35,80]. Little is known about the optimal radiation schedules dose to be employed. Doses >45 Gy [46,49,56,64,67] or >50 Gy [34,54] have been shown to be superior to lower doses. Other authors did not observe differences in outcome using doses of 40–50 Gy or of 50–55 Gy [35]. A standard dose, on type R basis, of 54–60 Gy, should be delivered to the tumour bed. Whenever possible, the dose to the optic chiasm should be limited to 55.8 Gy, to the upper cervical spinal cord to 54 Gy and to the optic nerves to 50.4 Gy [83]. Recently, the issue of treatment duration was addressed in a series of 34 patients collected over e period of 33 years [57]. The authors concluded that treatment duration was the most important prognostic factor.

6.3. Chemotherapy

Information concerning the activity of chemotherapy in ependymoma is very limited. The role of postoperative chemotherapy has been assessed in a randomised phase III trial of children with infratentorial ependymoma, without evidence of survival benefit [84]. Currently, there is no proof that the addition of chemotherapy to radiotherapy improves outcome and application of adjuvant chemotherapy should not be recommended as standard treatment and should be restricted to investigational trials [44,63].

6.4. Treatment of recurrent disease

A standard salvage therapy for recurrent ependymoma has not been identified. Second surgery and re-irradiation can be suitable for individual clinical use. Patients with ependymoma failure provide an important opportunity for prospective investigation of potentially effective drugs, and their inclusion in investigational multi-centre clinical trials should strongly be encouraged. Cisplatin and carboplatin are the most extensively tested single agents, showing response rates of 31% and 13%, respectively, in a total of about 30 patients [85]. Therefore, chemotherapy including cisplatin may be suitable for individual clinical use. Among the other few agents which have been assessed in 10 cases or more, are ifosfamide, thiotepa, arizidinybenzoquinone, dibromodulcitol, idarubicin and PCNU. None of these has achieved a better than 10% response rate [85]. Anecdotal experiences with procarbazine, vincristine and cytarabine have not been encouraging, while etoposide achieved two responses in nine cases [85]. A few combinations of agents have been investigated, mainly in infants and young children. There are only a few trials including more than 20 cases, in which 48% of 25 children, under 3 years of age responded to a combination of vincristine and cyclophosphamide [86], and 55% of 21 cases responded to a combination of procarbazine, ifosfamide, etoposide, high-dose methotrexate, cisplatin and cytarabine [87]. High-dose chemotherapy has also undergone limited clinical investigation in children, without proven benefits and up to 33% treatment-related fatal toxicities [85,88,89]. To date this approach should be considered not recommended.

6.5. New active drugs and therapeutic options

Since the inability to eradicate the primary tumour in both low- and high-grade ependymomas is the single most important factor of treatment failure [55], more aggressive local therapies are being assessed in clinical trials to improve tumour control. Stereotactic radiosurgery has given favourable results in small series as a first-line [90] and as a salvage treatment [91,92] and deserves further evaluation. Conformational radiotherapy as hyperfractionated dose schedules have also been explored, and may help decreasing local failure rate in subtotally resected patients [33,83]. Among the new drugs, topotecan and paclitaxel have been investigated, however without evidence of activity [93], while preliminary experience with temozolomide, as reported in abstract form, seems somewhat more encouraging [94]. The use of temozolomide should be further examined in the context of a clinical trial.

7. Late sequelae

7.1. Long term sequelae

Cognitive and focal neurological deficits may have a great impact on long term survivors of brain tumours, regardless of the histology and grade of the tumour. Memory loss, apathy, concentration difficulties and personality changes may have a profound effect, even in those patients who appear to have a Karnofsky performance status of 90 or 100. Surgery in the so-called silent areas may contribute to cognitive deficits. Less clear are the late effects of radiation therapy on cognitive function. Radiotherapy is known to cause the early somnolence syndrome, but may also cause late sequelae, in particular delayed leuko-encephalopathy with cognitive dysfunction and radiation necrosis [95–97]. In individual patients, it is difficult however to entangle the direct effects of the tumour on cognition from late effects of treatment. A recent survey on cognitive deficits in progression free survivors of low-grade glioma failed to confirm the generally assumed untoward relation between radiotherapy and cognitive deficits [98]. Only in those patients who had been treated with fraction of 2 Gy or more, evidence of increased cognitive dysfunction has been observed. The only other association with cognitive deficits was treatment with anti-epileptic drugs. Prior studies have suggested that whole brain radiotherapy may be associated with more cognitive deficits than involved field irradiation, although today involved field radiotherapy is standard practice [99]. Radiation therapy may also affect cranial nerves, or induce endocrine dysfunction even in case of tumours distant from the hypothalamus-pituitary region [100]. Seizures may have a great impact on the quality of life even in patients with well-controlled tumours. Newer anti-epileptic drugs may have less side-effects and should be considered, especially in those patients using a multi-drug regimen. Apart from cognitive deficits, a risk of death of 2.5% at 2 years has been reported for doses of 50.4 Gy. A risk of radionecrosis up to 5% at 5 years may occur after 60 Gy to one third, or 50 Gy to two thirds of the brain volume, and with 50–53 Gy to brain stem with a similar risk for blindness after 50 Gy to the optic chiasm. Also chemotherapy may induce late sequelae such as lymphoma, leukemia or solid tumours, as well as lung fibrosis, infertility, renal failure, and signs of neurotoxicity of the peripheral nervous system.

8. Follow-up

8.1. Follow up

No general guidelines for the follow-up of *ependymomas* can be given, these should be tailored to the individual patient and taking into account tumour grade, previously administered treatment and independent prognostic factors as age and the functional status of the patient. Low-grade glioma patients should be followed, even with stable lesion since many years. At some point in time, progression will inevitably occur and treatment should be installed before irreversible deficits has developed.

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ORIGINAL PAPER

Spinal myxopapillary ependymoma outcomes in patients treated with surgery and radiotherapy at M.D. Anderson Cancer Center

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Abstract This study was undertaken to determine the disease outcomes in patients treated with surgery alone or surgery and adjuvant radiotherapy (RT) for myxopapillary ependymoma (MPE) of the spine. The medical records of 35 patients with MPE treated at The University of Texas M.D. Anderson Cancer Center between December 1968 and July 2002 were reviewed. The endpoints analyzed were progression-free survival (PFS), overall survival, and local control. The median age of patients was 35 years (range, 14–63 years), and the male to female ratio was 2.5:1. In total, 21 (60%) patients underwent a gross total resection, 13 (37%) a subtotal resection, and 1 (3%) a biopsy only; 22 of them (63%) also received adjuvant RT. The median follow-up was 10.7 years. The 10-year overall survival, PFS, and local control rates for the entire group were 97%, 62%, and 72%, respectively. Of 11 patients, 5 (45%) who had undergone gross total resection alone had recurrence. A total of 12 (34%) patients had disease recurrence, all in the neural axis; 8 of them had treatment failure at the primary site only, 3 in the distant neural axis only, and 1 at the primary site and in the distant neural axis. Patient age (> 35 years; $P = 0.002$) and adjuvant RT ($P = 0.04$) significantly affected PFS. The long-term patient survival duration for MPE managed with surgery and adjuvant RT is favorable. Regardless of the extent of resection, adjuvant RT appears to significantly reduce the rate of tumor progression. Failures occurred exclusively in the neural axis, mainly at the primary site.

Keywords Myxopapillary ependymoma · Ependymoma · Spinal tumor · Surgery · Radiotherapy

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Introduction

Ependymomas are the most common intraspinal tumors [1], representing 15% of spinal cord tumors and up to 60% of spinal cord gliomas [2, 3]. Myxopapillary ependymomas (MPEs), first described in 1932 by Kernohan [4], are a distinctive variant of ependymomas both clinicopathologically and genetically [5, 6]. According to the World Health Organization classification of central nervous system tumors, MPEs are grade I tumors [7]. MPEs are usually histologically benign, often encapsulated, and slow-growing tumors with a long disease course. The incidence of MPE is low; in a large series of cases of ependymomas, only 13% were found to be of the myxopapillary type [8]. Most MPEs occur in the lumbosacral/cauda equina region. Occasionally, MPEs arising from other sites in the spinal cord, from the intracranial region, or from the subcutaneous soft tissues in the sacrococcygeal region have been described [9–13].

Most spinal ependymoma series published in the literature have included only patients with spinal

ependymomas, although a few have also included patients with MPEs [14–18]. According to these reports, the mainstay of spinal ependymoma treatment is surgery to obtain a histologic diagnosis and resect as much of the tumor as possible. Postoperative radiotherapy (RT) has also been advocated as an additional mean of controlling spinal ependymomas in patients who undergo subtotal resection (STR) [14–18]. However, the respective roles of surgery and adjuvant RT in the treatment of spinal ependymomas require further study. For ependymomas, some investigators have advocated minimal surgery and adjuvant RT, whereas others have reported good clinical outcomes with gross total resection (GTR) alone [19–23]. These viewpoints are not necessarily relevant to the management of MPE, however, which represents a more favorable, histopathologic variant of ependymoma with a distinct clinical course.

In this paper, we report the outcomes from a single institutional experience with 35 spinal MPEs treated with either surgery alone or surgery and adjuvant RT.

Patients and methods

Study group

This study involved 35 patients with histologically verified spinal MPE treated at The University of Texas M.D. Anderson Cancer Center between 1968 and 2002. The institutional review board at M.D. Anderson Cancer Center approved the study design, which involved a retrospective review of the patients' medical records and a waiver of informed consent. The information necessary for the study was obtained through this review. The current vital status of all 35 patients was obtained from the M.D. Anderson Cancer Center tumor registry, the United States Social Security database, mailed questionnaires, and telephone interviews. Follow-up data of varying duration were available for all patients in this study.

Surgical treatment

The extent of surgery was determined from the surgical reports and/or postoperative imaging studies. The surgery was classified as a GTR if the surgeon had described a complete removal of the tumor or if there was no evidence of tumor on scans from postoperative computed tomography (CT) or magnetic resonance imaging (MRI). The surgery was classified as a STR if the surgeon had observed unresected tumor in the operative bed or if a tumor was visible on follow-up imaging studies.

Radiation treatment

All patients were treated with either linear accelerators that used 6 MV or 18 MV energies or a ^{60}Co machine (for patients treated during the earlier part of the study). The most common technique used was a single posterior–anterior field (in 86% of the patients); although 14% of the patients received RT with 3-dimensional treatment planning. The RT treatment volume was the primary tumor plus a 3–5 cm margin based on the imaging results and the treating physician's preferences. The cone-down field encompassed the primary tumor with a 2 cm margin.

Chemotherapy

No patient in this study received initial or adjuvant chemotherapy. Four patients received salvage chemotherapy due to recurrence of leptomeningeal disease.

Functional evaluation

Neurologic function was evaluated by use of a Frankel classification system (A = Complete motor and sensory loss, B = Preserved sensation only, C = Motor and sensory incomplete function, D = Useful motor function, E = No motor or sensory function disorder) [24]. Grades were assigned before adjuvant RT and last follow-up visits.

Statistical analysis

Data analysis was performed by using Stata 9.0 statistical software (Stata, College Station, TX). The Pearson's χ^2 test was used to assess measures of association in frequency tables. The survival function was determined by using Kaplan–Meier estimates. The log-rank test was used to assess the equality of the survival function across groups. The equality of means for continuous variables was assessed by using the *t*-test. Statistical tests were based on a two-sided significance level, and a *P* value of 0.05 or less was considered to be statistically significant.

The survival time was calculated from the diagnosis date to the first occurrence of the considered event (i.e., local spine recurrence alone, distant spinal failure alone, or any recurrence). More specifically, overall survival (OS) was the time from diagnosis to death

from any cause, progression-free survival (PFS) the time from diagnosis to a first recurrence of disease (i.e., local or distant metastasis), and local tumor control (LC) the time from diagnosis to first local failure.

Results

Patient characteristics

Patient characteristics are summarized in Table 1. Of the 35 patients, 25 were males. The median age at diagnosis was 35 years. The most common presenting symptom was low back pain (94%). The median duration of symptoms before diagnosis was 12 months. The median KPS was 80. The most common initial imaging modality was MRI in 29 patients (83%). In 21 patients (60%) tumor location was lumbosacral/cauda equina region.

Table 1 Patient characteristics and treatment details

Variable	Number[a]
Number of patients	35
Age, years	
Median	35
Range	14–63
KPS[b]	
Median	80
Range	50–100
Gender	
Female/Male	10/25
Symptoms	
Low back pain	33 (94%)
Extremity numbness	15 (43%)
Extremity weakness	6 (17%)
Urinary dysfunction	5 (14%)
Abnormal gait	3 (9%)
Symptom duration, months	
Median	12
Range	1–84
Imaging modality	
Myelography	5 (14%)
CT	1 (3%)
MRI	29 (83%)
Tumor location	
Thoracolumbar	14 (40%)
Lumbosacral/cauda equina	21 (60%)
Extent of surgery	
Gross total resection	21 (60%)
Subtotal resection	13 (37%)
Biopsy only	1 (3%)
Primary treatment	
Surgery	13 (37%)
Surgery + RT	22 (63%)

[a]Data are presented as number of patients unless otherwise indicated

[b]KPS, Karnofsky performance status

Treatment results

Surgery was the initial treatment in all patients. GTR was achieved in 21 patients (60%), STR in 13 (37%), and a biopsy only in 1 patient (3%). A total of 13 patients were observed after their surgery. These patients included 11 patients who underwent GTR and 2 who underwent STR.

RT was given adjuvantly after surgery to 22 patients (63%) and as salvage treatment of recurrent disease to 7 (20%). The median time to the start of adjuvant RT from the date of surgery was 47 days (range, 21–140 days). The total RT dose ranged from 44.3 to 56 Gy (median, 50.4 Gy), and the dose per fraction ranged from 1.5 Gy to 2 Gy (median, 1.8 Gy). In 13 patients, a cone-down field was used for the last median 9 Gy (range, 3.6–13.5 Gy).

A total of five patients underwent craniospinal irradiation (CSI) prescribed to a median dose of 39.6 Gy (range, 39.6–41 Gy) plus a median 10.8 Gy (range, 9–13.5 Gy) boost to the tumor bed for leptomeningeal disease (LMD). One of the patients received CSI at the time of diagnosis of LMD. The remaining four patients had initially received local RT to the spine at diagnosis and subsequently were retreated with CSI due to recurrence of LMD.

Survival and local control

The median follow-up time was 10.7 years (range, 3–33 years). The OS rate at both 5 and 10 years was 97% (Fig. 1). Three patients died during the follow-up period. One died of MPE and the others of unknown causes 15 years after the initial diagnosis. There were 12 (34%) recurrences in the study population. The median time to disease recurrence was 65 months (range, 5–378 months). The 5- and 10-year PFS rates were 70% and 62%, respectively (Fig. 2), and 5- and 10-year LC rates were 76% and 72%, respectively.

The influence on survival of both clinical and treatment variables was also examined. The prognostic variables we studied included age, Karnofsky performance status, duration of symptoms prior to diagnosis, tumor location, extent of surgery, initial treatment modality, and total RT dose. There were no statistically significant associations between the prognostic variables and OS rate. However, older patient age (≤35 years vs. >35 years) ($P = 0.002$) and initial treatment modality (surgery vs. surgery + adjuvant RT) significantly affected PFS (Fig. 3; $P = 0.04$) for the entire study group. The 5- and 10-year PFS rates for all patients who received adjuvant RT were 82% and

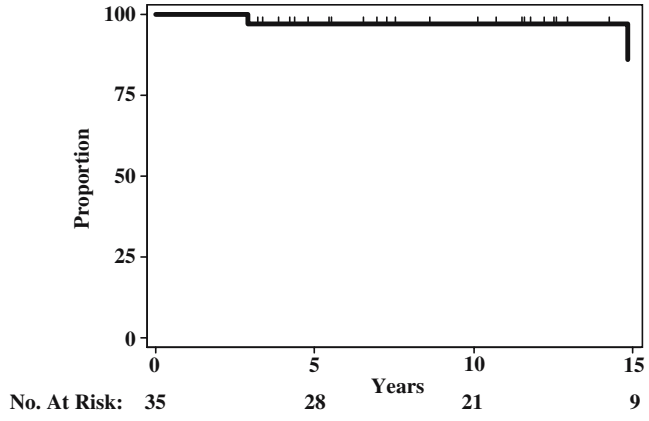

Fig. 1 Overall survival for the entire group

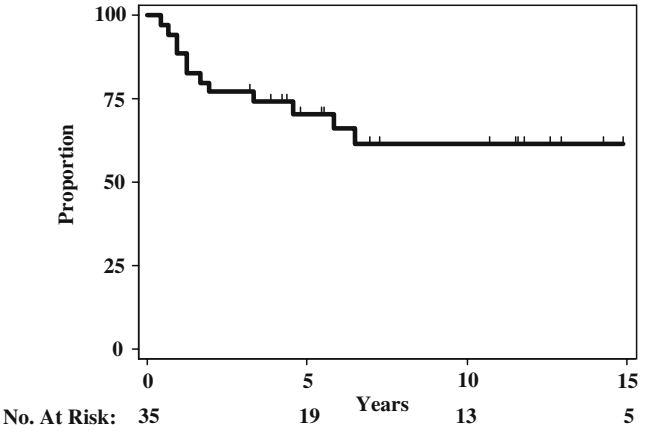

Fig. 2 Progression-free survival for the entire group

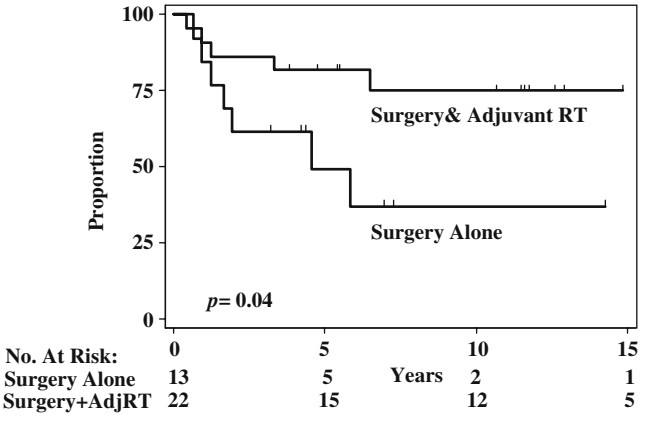

Fig. 3 Progression-free survival according to initial treatment groups (i.e., surgery alone vs. surgery and adjuvant radiotherapy, $P = 0.04$)

75%, respectively, and for those treated by any surgery alone 49% and 37%, respectively.

Adjuvant radiation was associated with higher LC. The 10-year LC rates with or without adjuvant RT were 86% and 46%, respectively ($P = 0.03$). Regarding the extent of surgery, the 10-year LC rate for patients who had GTR with and without adjuvant RT were 90% and 58%, respectively ($P = 0.01$). The LC rate for patients who underwent STR plus adjuvant RT was 90% at 10 years, whereas two patients who had STR alone experienced local recurrence.

Patterns of failure

Table 2 shows the primary tumor site and the initial and salvage treatments used. All 12 recurrences were in the neural axis, and most were within the primary site. Overall, eight patients had failures within the primary site alone, three in the distant neural axis only, and one at the primary site and in the distant neural axis. Regarding the extent of surgery, disease recurrence was experienced by 5 (45%) of 11 patients who had GTR alone, 1 (10%) of 10 patients who had GTR plus adjuvant RT, 2 (100%) of 2 patients treated with STR alone, and 4 (33%) of 12 patients treated with STR plus adjuvant RT.

Of the 12 patients, 8 (67%) with treatment failures underwent successful salvage therapy with further surgery, RT, and/or chemotherapy (2 patients received oral 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosurea (CCNU) 130 mg/m^2 monthly for 12 courses, one received intrathecal mafosfamide 5 mg monthly for 18 courses, and one received oral procarbazine 125 mg/m^2 monthly for 6 courses). Three of these patients were alive with disease at last follow-up, at 4–21 years following their relapse.

Neurologic functional outcome after adjuvant RT

All patients tolerated RT completing their prescribed therapy without interruption. The median follow-up time for patients undergoing adjuvant RT was 11.5 years (range, 2.9–33 years). Before adjuvant RT, 7 patients (32%) were classified as Frankel grade E, 13 patients (59%) as grade D, and 2 patients (9%) as grade C. There was no patient classified as grade A or B before adjuvant RT. Ten patients (45%) maintained their pretreatment neurological status up to the last follow-up visit (7 patients were grade E, 2 were grade D and 1 was grade C). Eleven patients (50%) experienced improved neurologic function after treatment (10 patients changed from grade D to E, 1 patient from grade C to D). One patient (5%) with grade D changed to grade B after multiple surgeries for tumor progression (Fig. 4).

Table 2 Patients who failed the primary treatment

Patient	Age (years)	Tumor location	Primary treatment	Site of recurrence	Time to recurrence (months)	Salvage therapy/outcome (survival duration after salvage)
1	22	L1–4	STR[a] and local RT	Distant	78	Surgery, CSI, and CHT/Dead-unknown (27 years)
2	14	T6–L4	GTR and local RT	Local	15	Surgery/NED (10 years)
3	27	L1–3	STR and local RT	Distant	11	Surgery, whole spine RT, and CHT/AWD (21 years)
4	31	L3–4	STR	Local	20	Surgery and local RT/NED (19 years)
5	20	L1–3	Bx and local RT	Local	40	Surgery/NED (5 years)
6	16	L2	GTR	Local	5	Surgery and RT/NED (10 years)
7	28	L2	STR	Local	55	Surgery and RT/NED (10 years)
8	19	T5–7/T12–L1	GTR	Distant and local	11	CSI and CHT/AWD (11 years)
9	35	T12–L3/L5–S1	GTR	Distant	8	CSI/NED (7 years)
10	33	S1–5	GTR	Local	70	RT/NED (6 years)
11	60	T12–L4	STR and CSI	Local	5	CHT/DOD (2.5 years)
12	26	T9–L2	GTR	Local	23	RT/AWD (4 years)

[a]STR = Subtotal resection; RT = Radiotherapy; CSI = Craniospinal irradiation; CHT = Chemotherapy; GTR = Gross total resection; NED = No evidence of disease; AWD = Alive with disease; BX = Biopsy; DOD = Dead of disease

Discussion

In our study, patients treated for histologically proven MPE had excellent long-term survival rates: the 10-year OS rate was 97%, and the 10-year PFS and LC rates were 62% and 72%, respectively. Most recurrences occurred within the primary site of disease. No recurrences occurred outside the neural axis. Most importantly, our data support the notion that patients who initially receive adjuvant radiotherapy to maximize local control have improved PFS rates.

Our results compare favorably with those of other series in the literature that have focused on spinal ependymomas, including MPEs. For example, 10-year survival rates of 75% to 100% have been reported by other authors [9, 14, 16, 18, 25–27] (Table 3).

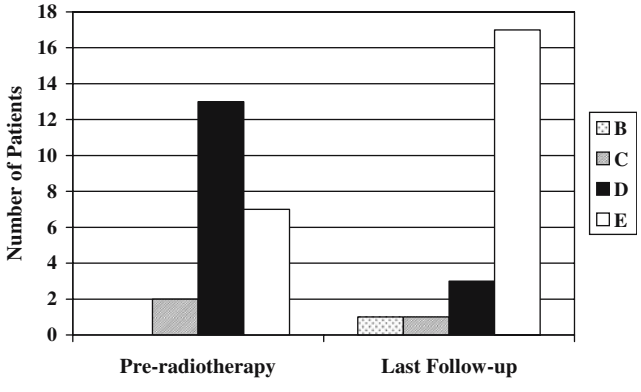

Fig. 4 Neurologic function according to Frankel classification

In the current study, no significant effect of the different initial surgical extents on OS or PFS was found. However, in patients who had either GTR or STR, adjuvant radiotherpy showed better LC rates (90% for both) at 10 years, compared with GTR or STR alone (58% and 0%, respectively). This result was comparable to that reported by Waldron et al. [18], who likewise observed no influence of the extent of resection. These authors also showed no recurrences in 11 patients with low-grade tumors treated with GTR and adjuvant RT; similarly, in our study, only 1 (10%) of 10 patients who had GTR plus adjuvant RT had disease recurrence. Furthermore, Shaw et al. [25] observed recurrences in three (44%) of seven patients treated with GTR and postoperative RT. In a Mayo Clinic series on MPEs, only 7 (16%) of the 45 patients who underwent GTR had recurrences [14]. Several authors have demonstrated the importance of the extent of surgical resection in determining recurrence patterns and do not support the use of adjuvant RT after GTR in spinal ependymoma [20, 23, 28, 29].

In our experience, MPEs can be technically tricky to resect completely because of the anatomic complexity of the cauda equina. Intraoperative ultrasonography can be quite helpful in disclosing occult foci hiding behind the cauda equina [19]. The main asset to a safe and effective operation in this disease, however, remains an experienced, persistent, technically skillful surgeon [30]. Recently, the use of monitoring techniques, such as the recording of somatosensory evoked potentials, and the earlier diagnosis made possible by CT and MRI have made tumors (including MPEs)

Table 3 Treatment characteristics and incidence of recurrence in selected spinal MPE series

Reference	Number of cases	Time period	Mean age (years)	E/MPE[a]	GTR/STR-Bx	Adjuvant RT (%)	Mean follow-up (month)	Relapse rate (%)	OS rate at 10 years (%)
Sonneland et al. [9]	77	1924–1985	36.7	0/77	45/32	46	N/A	17	N/A
Shaw et al. [25]	22	1963–1983	47	12/10	8/14	100	156	31.8	95
Whitaker et al. [16]	58	1950–1987	40	34/24	14/44	74	70	22.4	100
Waldron et al. [18]	59	1958–1987	37	43/16	16/43	100	130	18.7	75
Wen et al. [27]	20	1960–1984	36	20/9	7/13	65	N/A	30	86
Schild et al. [14]	35	1963–1994	33.5	23/12	10/25	100	124.8	N/A	100[b]
Clover et al. [26]	11	1971–1990	36	11/6	1/10	73	88	50[c]	80
Present study	35	1968–2002	33	0/35	21/14	63	127	34	97

[a]E/MPE = Ependymoma/myxopapillary ependymoma; GTR = Gross total resection; STR = Subtotal resection; Bx = Biopsy; RT = Radiotherapy; OS = Overall survival; N/A = Not available

[b]5-year OS rate for MPE subgroup

[c]Relapse rate for MPE subgroup

amenable to complete resection in up to 94% of cases [19, 30, 31]. In our study, GTR was possible in a somewhat smaller percentage of patients with MPE, in keeping with the more irregular shape of MPEs and their contact with multiple nerve roots. However, in MPE patients in our study undergoing GTR, the data suggest that GTR alone may not be sufficient, and that adjuvant RT should be given and is indicated even in the setting of GTR. This is in contrast to spinal ependymoma in which GTR without RT may be deemed sufficient treatment.

In this study, 12 patients (34%) experienced disease recurrence, 8 at the local site alone (10-year LC rate was 72%). A similar pattern of failure has been noted in other retrospective series. Whitaker et al. [16] showed that in 43 patients treated with postoperative radiation, 6 of 8 with recurrent tumors had failures at the primary site. Similarly, of the 22 patients who underwent surgery and postoperative RT in the study by Shaw et al. [25], 6 of 7 failures were at the primary site.

We did not observe any extraneural metastases in our study but did observe four recurrent tumors that were distant from the site of the primary tumor. Two patients had recurrences in the brain. Although rare, this pattern of failure has been noted in other series. Whitaker et al. [16] found a 5.8% incidence of cranial relapse in 259 patients with spinal ependymomas; the pattern of failure in our series support the use of local field irradiation for localized spinal MPE, regardless of the extent of the resection.

In our current study, the addition of postoperative RT to surgery was associated with significantly better 10-year PFS rates (75% for surgery + RT vs. 37% for surgery alone, $P = 0.04$) and 10-year LC rates (86% for surgery + RT versus 46% for surgery alone, $P = 0.03$). Several authors have similarly reported improved survival rates and decreased recurrences in patients treated with postoperative RT after STR or GTR in various series of spinal ependymoma or MPE [8, 13, 15, 17, 26, 30, 32].

The optimal dose of radiation for spinal ependymomas has been debated in the literature. This has been extrapolated to MPE, which is usually located in the cauda equina. Most authors recommend doses of 40–50 Gy [16, 26, 27, 29]. In a study by Garcia et al. [33], a dose–response effect was seen. Patients who received doses greater than 40 Gy had significantly improved PFS rates. Similarly, Marks and Adler [32] recommended a dose of 40-Gy for totally resected MPEs. In our study, which analyzed the effect of total radiation dose using 45 Gy as the cutoff dose; we did not find any significant differences between the two dose groups, most likely because most patients received 50 Gy to the tumor site, and only four patients received doses equal to or less than 45 Gy.

In conclusion, the long-term survival for spinal MPE managed with surgery and adjuvant radiotherapy is favorable. Failures occur exclusively in the neural axis, mainly in the primary site. Regardless of the extent of surgery, adjuvant RT to the primary disease site appears to significantly reduce the rate of tumor progression.

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● *Clinical Investigation*

THE RESULTS OF RADIOTHERAPY FOR EPENDYMOMAS: THE MAYO CLINIC EXPERIENCE

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Purpose: This analysis was performed to examine the outcome of patients with histologically confirmed ependymomas of the brain or spinal cord who received postoperative radiotherapy.

Methods and Materials: Eighty patients with histologically confirmed ependymomas were evaluated retrospectively. All were treated with various combinations of surgery, radiotherapy (RT), and chemotherapy. Follow-up ranged from 5 to 30 years (median 10.4 years).

Results: The 5- and 10-year survival rates for the entire study group were 79% and 73%, respectively. Patients with low-grade (1 and 2 of 4) tumors had a 5-year survival rate of 87% as compared to 27% for those with high-grade (3 and 4 of 4) tumors ($p < 0.0001$). Patients with tumors of the spine had a 5-year survival rate of 97% as compared to 68% for those with infratentorial tumors, and 62% for those with supratentorial tumors ($p = 0.03$). Patients with myxopapillary ependymomas of the spine had a 5-year survival rate of 100% as compared with 76% for patients with other histological subtypes of ependymoma ($p = 0.02$). Multivariate analysis revealed that the survival rate was independently associated with tumor grade ($p = 0.0007$) and histological subtype ($p = 0.02$). Twenty-eight patients (35%) experienced local failure and 10 patients (13%) developed leptomeningeal seeding. The 5-year leptomeningeal failure rate was 10% in patients with low-grade tumors as compared to 41% for patients with high grade tumors ($p = 0.01$).

Conclusion: Patients with low-grade tumors, especially those with myxopapillary subtypes, have high 5-year survival rates when treated with post-operative radiotherapy. High grade ependymomas are associated with a much poorer outcome. New forms of therapy are required to improve the outcome of patients with high-grade ependymomas. © **1998 Elsevier Science Inc.**

Ependymoma, Surgery, Radiation therapy, Chemotherapy introduction.

INTRODUCTION

Ependymomas arise from ependymal cells forming the lining of the ventricles and central canal of the spinal cord. It is estimated that 17,600 primary central nervous system (CNS) tumors were diagnosed in the United States during 1997 (1). Ependymomas represented 40–60% of the 2,700 primary spinal cord tumors and 1–8% of the 14,900 primary brain tumors (2).

Intracranial ependymomas occur primarily in children and spinal ependymomas are more common in adults. In general, grading of ependymomas has been based upon a number of characteristics including cellularity, cytologic atypia, mitotic activity, vascular proliferation, and necrosis. These tumors are graded based primarily on mitotic activity and endothelial proliferation. Low-grade ependymomas are more common than high-grade tumors. The various histologic subtypes include classic, papillary, clear cell, tanycytic, pigmented (melanotic), and myxopapillary forms (3). Myxopapillary ependymomas are low-grade tumors found in the cauda equina region, where most arise from the filum terminale. The most characteristic histologic feature of myxopapillary tumors is the abundance of intercellular and perivascular mucin. Cytogenetic studies indicate that ependymomas frequently show abnormalities occurring on chromosome 9, 11, or 22 (4).

Treatment usually includes maximal resection followed by radiotherapy. Chemotherapy is usually reserved for recurrent tumors. However, recent clinical trials in children with high-grade tumors include chemotherapy as a component of initial therapy with surgery and radiation. (5, 6)

The present analysis was undertaken to define the long-term outcome of patients with ependymomas. Treatment options and prognostic factors were evaluated to clarify their relationship to survival and disease control. These factors are evaluated to provide treatment recommendations and explore avenues of further research.

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Table 1. Tumor grade and site of origin

Tumor grade	Brain	Spine	Total
1–2	36	34	70
3–4	9	1	10
Total	45	35	80

Table 2. Tumor type and site of origin

Tumor type	Brain	Upper spine	Lumbar spine	Total
Myxopapillary	0	0	12	12
Other types	45	16	7	68
Total	45	16	19	80

METHODS AND MATERIALS

Study group

Between 1963 and 1994, 80 patients with ependymomas were identified from the Radiation Oncology Tumor Registry. The outcome of therapy was retrospectively analyzed. Included in the study were 33 females and 47 males ranging in age from 1 to 69 years, with a median age of 33.5 years.

Statistical methods

Survival and local control rates were the principle endpoints of the analysis. Local failure was defined as progression of local symptoms or as tumor growth documented on neuroimaging studies. Survival and local control rates were determined with the Kaplan-Meier product limit method. The statistical significance of differences between the curves was determined by the log-rank test. Multivariate analysis was performed with the Cox proportional hazards model. Follow-up ranged from 5 to 30 years, with a median follow-up of 10.4 years.

Surgery and pathologic features

Primary sites included the supratentorial brain in 13 patients, infratentorial brain in 32 patients, and spinal cord in 35 patients. Seventy patients were found to have low-grade (1 and 2) tumors and 10 had high-grade (3 and 4) tumors. The distribution of tumor grade, sub-type, and site of origin are found in Tables 1 and 2. Myxopapillary tumors were uniformally grade 1 tumors found in the lumbar spine region. The following studies were performed to assess for seeding of the central nervous system (CNS): myelography in 40 patients, MRI in 21 patients, CT scans in 25 patients, and CSF cytology in 24 patients. Based on the findings of clinical studies (myelography, MRI, CT, or CSF cytology), 4 patients (6%) were found to have seeding of the CNS at the time of diagnosis, including 2 of 70 (3%) with low-grade tumors and 2 of 10 (20%) with high-grade tumors.

The extent of tumor resection was determined by a careful review of operative reports. Gross total resections were performed in 17 (21%) patients, subtotal resections in 57 (71%) patients, and biopsy alone in the remaining 6 (8%) patients (Table 3). Of the 45 patients with tumors arising in the brain, gross total resections were performed in 7 (16%), subtotal resections in 36 (80%), and biopsies in 2 (4%). Of the 35 patients with tumors arising in the brain, gross total resections were performed in 10 (29%), subtotal resections in 21 (67%), and biopsies in 4 (11%).

Tumors were graded on a 4 grade scale: grade 1 lesions lacked mitotic activity; grade 2 lesions exhibited occasional mitoses; grade 3 lesions showed brisk mitotic activity, and often some endothelial proliferation; grade 4 tumors showed high mitotic indices and prominent endothelial proliferation. As a rule, high-grade (3 and 4) were markedly cellular and often showed nucleolar prominence. Palisading necrosis was most often seen in grade 4 lesions. Cellular pleomorphism and simple non-palisading necrosis were not considered useful grading parameters.

Post-operative therapy

All 80 patients underwent radiation therapy as a portion of their initial treatment sequence (Table 3). The most common indication for radiotherapy was the presence of residual tumor in 63 patients. The remaining 17 patients received adjuvant therapy following gross total resection, 78 of whom received treatment at Mayo Clinic and 2 at other institutions. Treatment was delivered with 4, 6, or 10 MV photons. Radiotherapy was delivered to the craniospinal axis in 20 patients, to the whole brain in 3 patients, to the total spine in 6 patients, and to the primary tumor bed (brain or spine) alone in the remaining 51 cases. Doses administered to the primary tumor bed and to areas of gross disease ranged from 24 to 59.4 Gy (median 49.7 Gy) in 1.8–2.0 Gy fractions. Twenty-five (31%) of the 80 patients received doses less than 45 Gy to the primary tumor bed. Prophylactic doses administered to uninvolved regions ranged from 28.5 to 40.0 Gy. The doses delivered and the field arrangements used were based on the treating physician's preferences.

Table 3. Summary of therapy

	Surgery			Radiotherapy			
Tumor grade	Biopsy	STR	GTR	Local field	WBRT/WSRT	CSRT	Adjuvant chemotherapy
1–2	6	49	15	49	8	13	1
3–4	0	8	2	2	1	7	0

STR = subtotal resection; GTR = gross total resection; WBRT = whole brain radiotherapy; WSRT = whole spine radiotherapy; CSRT = craniospinal radiotherapy.

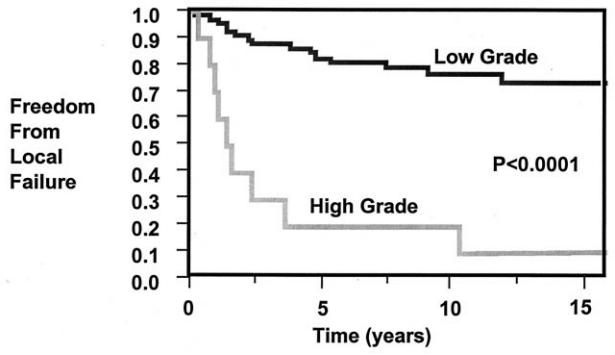

Fig. 1. Freedom from local failure by tumor grade (1 and 2 vs. 3 and 4).

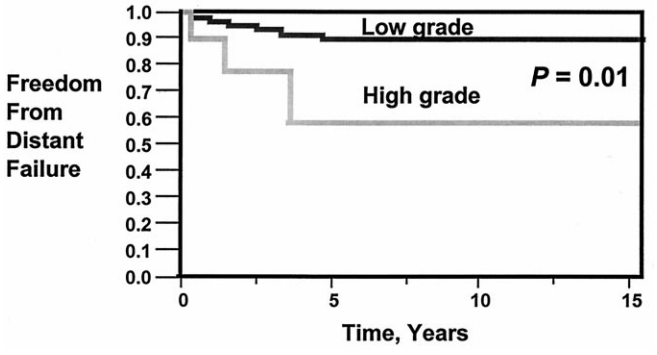

Fig. 3. Freedom from leptomeningeal failure by tumor grade (1 and 2 vs. 3 and 4).

One patient received chemotherapy as a component of initial treatment (dianhydrogalactitol, triazinate, etoposide, Table 3). Salvage chemotherapy was administered to 8 patients when disease progression was documented after initial treatment. Various combinations of the following agents were administered: dianhydrogalactitol, triazinate, etoposide, semustine, procarbazine, diaziquone, vincristine, prednisone, cis-platin, and methotrexate.

RESULTS

Patterns of failure

Local control rates at 5 and 10 years were 75% and 70%, respectively. The 5-year local control rates were 83% for patients with low-grade tumors as compared to 20% for those with high-grade tumors ($p < 0.0001$) (Fig. 1). Patients with primary tumors measuring less than 3.5 cm in diameter had a 5-year local control rate of 80% as compared to 70% for larger tumors ($p = 0.049$) (Fig. 2). Additional factors evaluated and not significantly associated with local control included the extent of resection, radiation dose, field arrangement, patient age, sex, or the histologic subtype (myxopapillary vs. others).

Leptomeningeal dissemination following therapy occurred in 7 of 70 patients (10%) with low-grade tumors and 3 of 10 patients (30%) with high-grade tumors. The actuarial 5-year leptomeningeal failure rates were 10% for patients with low-grade tumors as compared to 41% for those with high-grade tumors ($p = 0.01$) (Fig. 3). Radiotherapy field arrangement did not significantly alter the risk of leptomeningeal seeding. The 5-year leptomeningeal failure rate was 9% for those treated with local fields, 11% for those treated with whole brain or whole spine fields, and 24% for those treated with craniospinal axis fields ($p = 0.4$). Patterns of failure for both low- and high-grade tumors were evaluated in detail (Table 4). The predominant pattern of failure was local failure, which was sometimes accompanied by leptomeningeal failure. Isolated leptomeningeal failures were uncommon, occurring in only 5% of patients. Only one patient failed in non-CNS sites (scalp, lungs, and kidneys). This individual developed leptomeningeal seeding prior to widespread metastases.

Survival

Actuarial 5-, 10-, and 15-year survival rates for the entire study group were 79%, 73%, and 61%, respectively (Fig. 4). Tumor size, patient age, sex, radiotherapy field arrangement, and radiation dose were not significantly associated

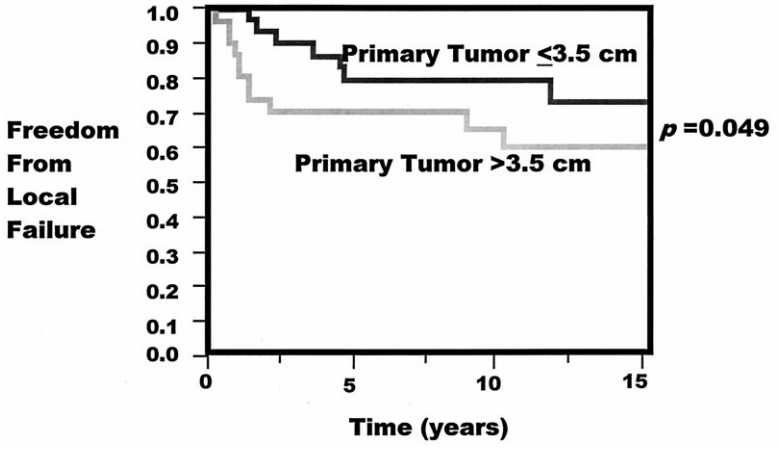

Fig. 2. Freedom from local failure by tumor size.

Table 4. The effect of tumor grade on patterns of failure

Low-grade (1–2) tumors (n = 70)			
Patterns of failure	Local failure	Local control	Total
Distant failure	3 (4%)	4 (6%)	7 (10%)
Distant control	16 (23%)	47 (67%)	63 (90%)
Total	19 (27%)	51 (73%)	70 (100%)
High-grade (3–4) tumors (n = 10)			
Patterns of failure	Local failure	Local control	Total
Distant failure	3 (30%)	0	3 (30%)
Distant control	6 (60%)	1 (10%)	7 (70%)
Total	9 (90%)	1 (10%)	10 (100%)
All patients (n = 80)			
Patterns of failure	Local failure	Local control	Total
Distant failure	6 (7.5%)	4 (5%)	10 (12.5%)
Distant control	22 (27.5%)	48 (60%)	70 (87.5%)
Total	28 (35%)	52 (65%)	80 (100%)

Patients are categorized into various groups by tumor grade and the subsequent pattern of failure, including both local failures and distant (leptomeningeal) failures.

with survival. More extensive tumor resection was associated with a non-significant trend favoring survival. The 5-year survival rates were 94% for patients having gross-total resections, 76% for those having subtotal resections, and 67% for those having only biopsies ($p = 0.2$).

Univariate analysis (log-rank test) revealed that the following factors were associated with survival: tumor grade, location, and histologic type. Patients with low-grade tumors had a 5-year survival rate of 87% as compared to 27% for those with high-grade tumors ($p < 0.0001$) (Fig. 5). Patients with tumors of the spine had a 5-year survival rate of 97% as compared to 68% for those with lesions of the infratentorial brain and 62% for those with lesions of the supratentorial brain ($p = 0.03$) (Fig. 6). Patients with the myxopapillary subtype had a 5-year survival rate of 100% as compared to 76% for patients with other histological subtypes of ependymoma ($p = 0.02$) (Figs. 7 and 8). Multivariate analysis revealed that survival was independently associated with both grade ($p = 0.0007$) and histological subtype ($p = 0.02$), but not tumor location ($p = 0.07$).

DISCUSSION

The present analysis was performed to define the long-term outcome of patients with ependymomas. The ideal preoperative staging work-up should include a careful history and physical examination, magnetic resonance imaging (MRI) of the clinically involved CNS site, and a CSF cytology. Clinically uninvolved CNS sites should also be imaged with MRI because of the risk of meningeal seeding. In our series, 6% of patients were found to have CNS seeding prior to therapy and 16% following treatment.

Prognostic factors associated with survival on univariate analysis included tumor grade, location, and histologic type (myxopapillary vs. other subtypes). Both tumor grade and histologic type were associated with survival on multivariate analysis. The importance of tumor grade as a determinant of survival has been observed by other investigators (7–13). Tumor grade is the most consistently reported prognostic factor in the literature.

Post-operative radiotherapy resulted in a high (87%) 5-year survival rate for those with low-grade tumors. Our data suggests that survival is improved when there is resection of as much tumor as is safely possible. For patients having residual disease detected intraoperatively or with a postoperative MRI scan, moderate dose radiotherapy to the tumor bed is indicated. Garrett and Simpson reported a dose-response for patients with ependymomas. Of their patients who received ≤ 45 Gy, 5 of 18 (28%) were alive at

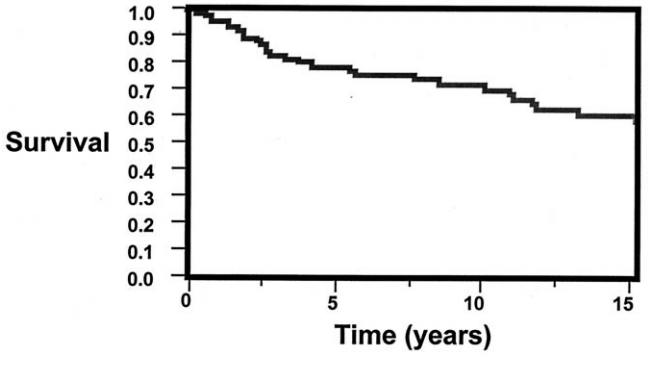

Fig. 4. Overall survival for the entire group of patients.

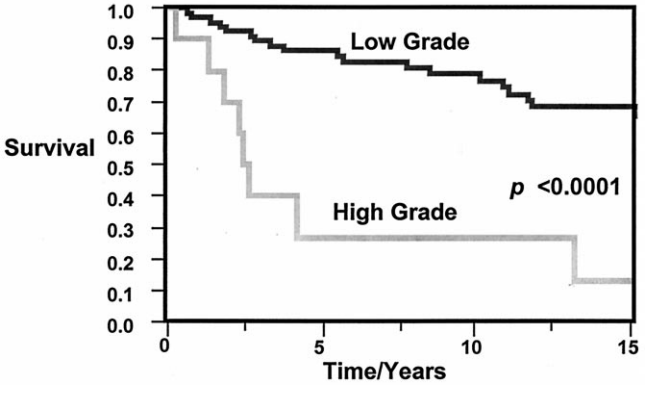

Fig. 5. Overall survival by tumor grade (1 and 2 vs. 3 and 4).

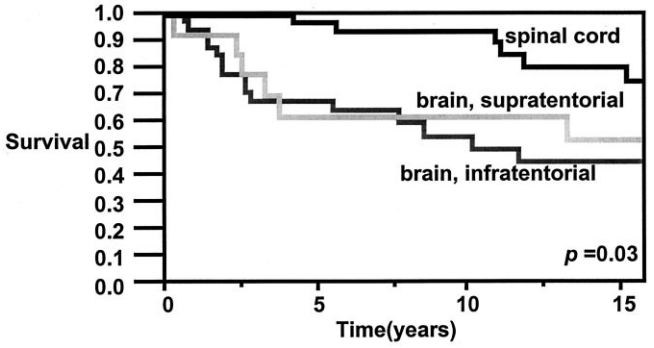

Fig. 6. Overall survival by primary tumor location.

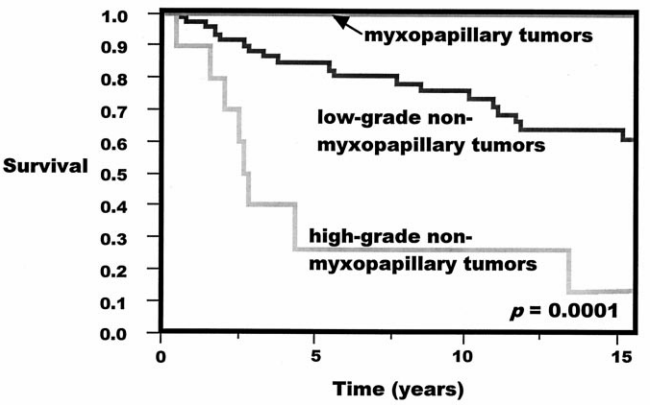

Fig. 8. Overall survival of patients with myxopapillary ependymomas (all considered grade 1) as compared to those with other tumor types divided by grade.

last follow-up as compared to 49 of 73 (67%) patients who received a higher dose (2). Stuben *et al.* reported a similar dose-response; patients that received doses greater than 45 Gy had significantly improved progression free survival rates (14). We did not observe a dose-response; therefore, a total dose of 50.4 Gy in 28 fractions is reasonable. There are series reporting favorable outcomes for patients with low-grade (including myxopapillary) tumors of the lumbar spine or cauda equina having undergone en bloc complete resection alone (15–19); therefore, the option of observation following en bloc complete resection for patients with low-grade spinal tumors is a reasonable one. In this setting, it is advisable to obtain a post-operative MRI to verify the absence of locally persistent tumor before withholding radiotherapy (20).

In the present series, the survival rate of patients with high-grade tumors was quite poor (27% at 5 years). Fortunately, only a minority of patients present with high-grade lesions. Potential methods of improving radiotherapy include modifications of field designs, doses, and fractionation pattern. Regarding field designs, craniospinal axis radiotherapy is reasonable for those with high-grade ependymomas because of their high risk of leptomeningeal failure (41% in our series). Although we were unable to show that craniospinal irradiation provided a survival advantaged, the number of patients (10) with high-grade tumors was too small to clearly examine this issue, and 7 of the 10 did receive craniospinal irradiation. Vanuytsel *et al.* reported that craniospinal irradiation was associated with better survival rates for patients with high-grade tumors (11). Our finding that 9 of the 10 patients with high-grade tumors developed local failure indicates that the radiation doses used (24–55.2 Gy in patients with high-grade tumors, median 43 Gy) were insufficient to achieve local control. The dose of radiation administered to the primary site could potentially be increased above conventional levels (to 59.4–64.8 Gy) with the following RT techniques: 3-D treatment planning utilizing small conformal beams, dynamic conformal RT, or stereotactic RT. The use of systemic therapy can be also considered in patients with high-grade tumors. Bloom *et al.* found that the use of chemotherapy improved survival rates in this setting (21). It is possible that combinations of conventional therapy or possibly novel therapies will result in more favorable outcomes.

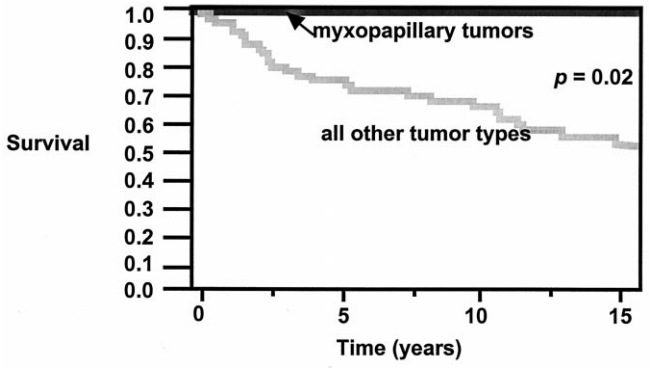

Fig. 7. Overall survival by histologic type of tumor.

Major limitations of this study are biases which may have been introduced by the retrospective nature of the data collection and the relatively small number of patients with high-grade tumors. However, this is one of the larger studies in the literature and it has long-term follow-up (median follow-up was greater than 10 years).

In summary, ependymomas are uncommon gliomas affecting all levels of the central nervous system. Low-grade tumors are more common than high-grade lesions. The present study indicates that postoperative radiotherapy of low-grade lesions resulted in high survival rates. The 5-year and 10-year actuarial survival rates were 87% and 79%, respectively. Myxopapillary ependymomas occurred in the lumbar spine region and were associated with an excellent prognosis; the 5-year survival rate was 100%. Patients with high-grade lesions had a poor prognosis due to a high risk of both local failure and craniospinal axis seeding. The results of aggressive therapy with resection and craniospinal irradiation were unfavorable in this group; therefore, new forms of therapy will be required to improve the prognosis of patients with high grade ependymomas.

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CLINICAL–PATIENT STUDIES

Long term outcome with post-operative radiation therapy for spinal canal ependymoma

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Abstract
Purpose A retrospective study was performed to evaluate the long term efficacy and safety of post-operative radiation therapy in the management of spinal canal ependymoma at our institution.
Methods and materials Between 1954 and 1997, 22 patients with spinal canal ependymoma were treated with post-operative radiotherapy at our institution. The median age at diagnosis was 34.7 years (range 9.8–56.1 years). All patients underwent open biopsy with histologic diagnosis: 13 patients (59%) had ependymoma (WHO Grade II) and 9 patients (41%) had myxopapillary ependymoma (WHO Grade I). The median tumor size was 4.0 cm (range 1.5–15.0 cm). Twenty patients received subtotal resection and 2 patients received gross-total resection. Median radiation dose was 45.0 Gy.
Results The median follow up for surviving patients was 11.4 years (range 0.6–37.0 years). An 80% progression-free-survival (PFS) was observed for all patients at 5-, 10- and 15-year endpoints. All recurrences were within 3 years of treatment. The 5-, 10- and 15-year overall-survivals (OS) for all patients were 85%, 78% and 64%, respectively. Patients with tumors larger than 6.0 cm at time of presentation demonstrated 5- and 10-year PFS of 58.3% compared to 92.3% for patients with tumors 6.0 cm or smaller ($P = 0.047$). There was no significant correlation between tumor size and OS.
Conclusions Post-operative radiation after subtotal resection is safe and offers durable tumor control and long term patient survival.

Keywords Ependymoma · Radiation · Spinal canal · Spinal cord

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Introduction

Primary spinal canal tumors comprise approximately 15% of all primary central nervous system (CNS) tumors [1]. Ependymomas are the most common neuroepithelial neoplasm in the spinal canal, comprising 50–60% of spinal gliomas [2]. Spinal canal ependymomas have long been characterized as slow-growing tumors with a predominantly local growth pattern, a high rate of local recurrence and a favorable long term survival. Ependymomas are classified by histologic grade as subependymoma (WHO Grade I), myxopapillary ependymoma (WHO Grade I), ependymoma (WHO Grade II); and anaplastic ependymoma (WHO Grade III) [3].

Without prospective randomized trials on this rare tumor, management of primary spinal canal ependymomas is largely based on single institution historical data. Surgery is generally the first line of therapy, and serves the dual purpose of tissue diagnosis and gross tumor excision. The use of adjuvant therapy varies by institution due to uncertainty with regard to the need

for radiation after gross total resection, the influence of histology on recurrence patterns, the optimal radiation dose, and the role of chemotherapy. A retrospective study was performed to evaluate the long term efficacy and safety of post-operative radiation therapy in the management of spinal canal ependymoma at our institution.

Methods and materials

This retrospective study was conducted with approval from the Human Studies Committee of the Washington University School of Medicine. Between 1954 and 1997, 22 patients with spinal canal ependymoma were treated with post-operative radiation therapy at our institution.

The median age at diagnosis was 34.7 years (range 9.8–56.1 years). There were 8 (36%) male and 16 (64%) female patients. Duration of symptoms ranged from 1 to 48 months, with a median of 10 months. Common symptoms included back pain (91%), numbness (55%), gait disturbance (32%), radiculopathy (32%), paresthesias (27%) and urinary retention (27%). Common clinical signs included paresis (77%) and hyperreflexia (36%).

Diagnostic evaluation included conventional myelogram only (12 patients), conventional and CT myelogram (7 patients), myelogram and MRI (3 patients) and MRI alone (2 patients). CSF evaluation was negative in 9 patients and not performed in 13 patients. All patients underwent open biopsy with histologic diagnosis: 13 patients (59%) had ependymoma (WHO Grade II) and 9 patients (41%) had myxopapillary ependymoma (WHO Grade I) [3]. The median tumor size was 4.0 cm (range 1.5–15.0 cm). The tumor locations and characteristics are listed in Table 1. Twenty patients (90%) received subtotal resection (STR) and 2 patients (10%) received gross-total resection (GTR). Twenty patients (91%) received radiation therapy after surgical treatment. Two patients (9%) received salvage radiation therapy for recurrence after treatment with surgery alone (GTR in one case and STR in the other). Median dose of radiation prescribed was 45.0 Gy (range 30.0–54.0 Gy). Median daily fraction size was 1.8 Gy (range 1.5–2.5 Gy). Radiation treatment parameters are listed in Table 2. None of the patients received chemotherapy as part of initial management.

After completion of treatment, patients were followed at 3 month intervals for the first 2 years, then every 6–12 months for 5 years and sporadically thereafter. Evaluations at the time of follow-up consisted of a history and physical examination. Computed tomography (CT) scans or magnetic resonance imaging (MRI) of the spinal canal were only conducted if indicated by patient symptoms or signs. Patients were considered to have local failure if there were clinical, radiographic, or histologic evidence of recurrence. Duration for endpoints was calculated from the date of completion of radiation therapy.

StatView software (SAS Institute, Cary, NC) was used to calculate survival rates based on the Kaplan–Meier method. Univariate analyses were conducted by the log-rank test. A P value of ≤ 0.05 was considered statistically significant.

Table 1 Subsites of involved disease

Spinal subsite	Number of patients (percent of total)	WHO grade (percent within subsite)	Range of tumor size (cm)
Cauda Equina	6 (27.3)	Grade I: 4 (66.6) Grade II-2 (33.3)	2.0–8.0 (mean 5.2)
Cervical	4 (18.2)	Grade I-1 (25.0) Grade II-3 (75.0)	1.5–15.0 (mean 9.0)
Lumbar	3 (13.6)	Grade I-3 (100.0)	2.5–12.0 (mean 8.5)
Filum Terminale	3 (13.6)	Grade II-3 (100.0)	2.0–4.0 (mean 3.0)
Thoracic	2 (9.1)	Grade II-2 (100.0)	3.0–10.0 (mean 6.5)
Conus Medullaris	2 (9.1)	Grade I-1 (50.0) Grade II-1 (50.0)	3.0
Cerivcomedullary	1 (4.5)	Grade II-1 (100.0)	4.0
Deposits ≥ 1 Subsite	1 (4.5)	Grade II-1 (100.0)	2.5 (largest deposit)

Table 2 Radiation treatment parameters

	Number of patients (Percent)
Radiation field	
Local field	13 (59.1)
Whole spine	6 (27.3)
Craniospinal	3 (13.6)
Energy	
Cobalt	9 (40.9)
>6 MV (including mixed low/high energy)	7 (31.8)
≤6 MV	3 (13.6)
Orthovoltage	3 (13.6)

Results

The median follow up for all patients was 10 years (range 0.4–37.0 years). The median follow up for

surviving patients was 11.4 years (range 0.6–37.0 years). An 80% progression free survival (PFS) was observed for all patients at 5-, 10- and 15-year endpoints (Fig. 1). Of the 4 patients (18.1%) who recurred: 2 patients recurred within the radiation fields 17- and 28-months after treatment; one patient recurred in the spine outside of the treatment field 20 months after treatment; and one patient recurred in the treatment field as well as in the untreated cranium 5 months after treatment. Mean time to recurrence was 17 months. All recurrences were within 3 years of treatment. The 5-, 10- and 15-year overall survivals (OS) for all patients were 85%, 78% and 64%, respectively (Fig. 2). Four patients died of disease, 2 patients died of inter-current disease, and 16 patients were censored at last follow up without evidence of disease.

Six patients (27%) demonstrated long term neurologic deficits after treatment. Symptoms included paresis (2 patients), urinary retention (2 patients), urinary incontinence (1 patient) and arachnoiditis (1 patient). All patients had complaints prior to the start of radiation, suggesting that the symptoms were sequelae of tumor invasion or surgical resection, however contribution from radiation cannot be excluded.

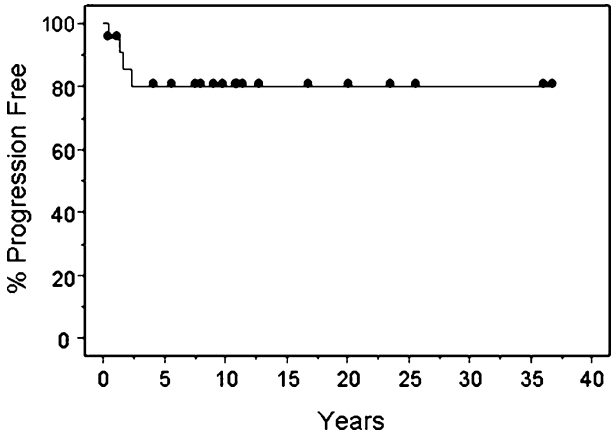

Fig. 1 Progression-free survival for all patients

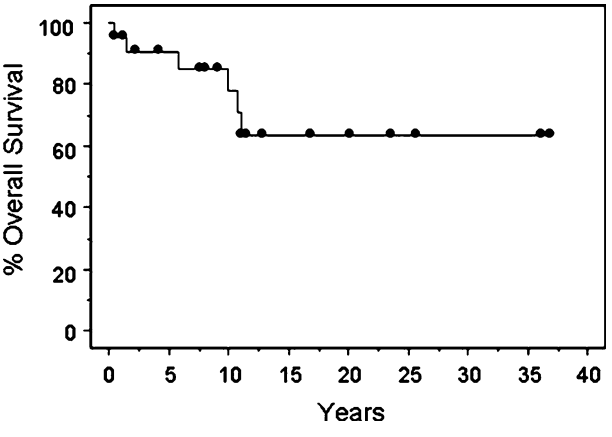

Fig. 2 Overall survival for all patients

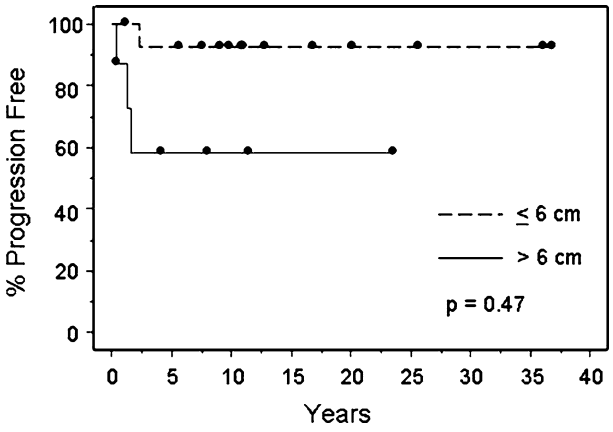

Fig. 3 Progression-free survival for patients with tumors ≤6 cm or >6 cm

Various patient, tumor and treatment factors were examined to determine their influence on prognosis. A worse outcome was observed with larger tumors (Fig. 3). Patients with tumors greater than 6 cm at time of presentation demonstrated 10-year PFS of 58.3% compared to 92.3% for patients with tumors 6 cm or smaller. This difference was statistically significant ($P = 0.047$). There was no significant correlation between tumor size and OS. In this retrospective series, no prognostic value was noted for gender, age, dose prescribed, volume of irradiation, histologic grade, extent of surgery, timing of radiation or era of treatment.

Discussion

Reported survival rates for patients with spinal canal ependymoma after surgery and post-operative radiation range from 68 to 95% at 10 years [4–13]. The median follow up of 11.4 years obtained with this series is quite lengthy with respect to prior studies and provides further evidence of a sustained favorable outcome for these patients.

Institutional reports suggest the potential for excellent control rates with surgery alone for low grade lesions that are completely removed [14–19]. However, progression rates after partial or subtotal tumor removal range from 20 to 50% at 5 years [10, 13, 19–21]. Despite the fact that 90% of the patients in our study

received only subtotal resection, an 80% local control rate was maintained at 15 years with the use of radiation therapy, suggesting that post-operative radiation is effective and should be considered after incomplete resection of tumor. Recurrence rates in series that include high grade tumors (current WHO Grade III) range from 16 to 37% even after documented GTR [9–11], supporting the use of adjuvant radiation for high grade lesions irrespective of the degree of resection.

It is difficult to draw conclusions on the prognostic value of patient, tumor or treatment variables given the small sample size in our series. Our data suggest a PFS advantage with tumors 6 cm or less. Other reports have suggested improved outcome with younger age [13], smaller tumor size [9], distal spinal disease [22], myxopapillary histology [12], low tumor grade [13, 23], gross total resection [8, 10], post-operative radiation [12] and radiation dose above 50 Gy [9].

Our study does not demonstrate a dose response relationship for tumor control. Some investigators have observed a trend towards improvement with doses of 50 Gy or higher and advocate for treatment to 55 Gy, with the last 5 Gy given to a boost volume [9]. A dose range of 45–50 Gy has been used historically as the threshold dose beyond which the incidence of radiation myelopathy is thought to increase significantly. Current models of spinal cord tolerance suggest that up to 55 Gy in conventional fractions (2 Gy or less per day) can be delivered safely with a less than 2% risk of causing radiation myelopathy [24–29]. Nevertheless, in the absence of strong evidence for a dose–response, most institutions remain cautious about escalating dose beyond 50 Gy and continue to recommend doses in the range of 40–50 Gy [11–13, 22, 30–32]. Only 2 patients in our series were treated beyond 50 Gy (both received 54 Gy in 1.8 Gy fractions). Radiation therapy did not seem to cause treatment related late effects within our population, suggesting that the doses used in our study (range 30 Gy–54 Gy; median 45 Gy) can be delivered safely.

Only 1 patient in our series failed outside of the localized treatment field. The vast majority of spinal ependymoma recurrences occur at or near the primary site. Of those patients who fail at distant sites in the CNS, many do so despite the addition of cranio-spinal irradiation (CSI) [13, 30]. Whereas the increased morbidity associated with CSI is well established, there is little evidence in the literature that whole-CNS or whole-spinal irradiation adds tumor control or survival advantage for non-disseminated lesions. The role of large volume irradiation should therefore be limited to patients with disseminated disease.

Chemotherapy has a limited role in the management of spinal ependymomas. There is no data to suggest a benefit for chemotherapy in the initial treatment of adults. Treatment of very young patients is individualized and sometimes utilizes chemotherapy in an attempt to delay radiation. Several prospective randomized trials of chemotherapy in intracranial ependymoma have failed to demonstrate a local control or survival advantage [33–35]. The efficacy of chemotherapy continues to be investigated in clinical trials.

Improvement in both surgical and radiation treatments is expected to have occurred over the time course of this study. Although we did not find a difference in outcome of our patients by year of treatment, other investigators have shown improved outcome with later eras of treatment [13]. Improved microsurgical techniques and earlier diagnosis through CT and MR imaging have contributed to improved chances of GTR at first presentation. The use of three dimensional imaging for radiation treatment planning allows for more conformal radiation delivery in the modern era. New treatment modalities such as intensity modulated radiation therapy, image guided radiation therapy, stereotactic radiosurgery and helical tomotherapy will theoretically allow for improvement in the therapeutic ratio.

Conclusions

Post-operative radiation after subtotal resection is safe and offers durable tumor control and long term patient survival.

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PART OF PROCEEDINGS
Review of Radiotherapy Dose and Volume for Intracranial Ependymoma†

Roger E. Taylor, MA, FRCP, FRCR*

Background. Radiotherapy (RT) is well established in the management of intracranial ependymoma (EP) and post-operative RT is employed for the majority of patients. There are no randomised trials of RT in EP and evidence for dose and volume relies on retrospective single institution series, usually comprising a heterogeneous mix of relatively small numbers of patients recruited over several decades. ***Procedure.*** The literature including RT dose and response data reported since the early 1990s was reviewed. ***Results.*** Five-year overall survival (OS) ranges from 40 to 79%. There is some evidence of a dose response relationship from <45 Gy to >50 Gy. In the majority of series outcome is related to WHO grade and extent of resection. There is no evidence of benefit for 'prophylactic' craniospinal RT (CSRT). In all series there is a significant risk of local recurrence, usually within the target volume. Early results of conformal RT have suggested that a margin for CTV of 1 cm around the post-operative tumour bed and any residual GTV is feasible. ***Conclusions.*** The main aims of future studies will be to maximise the number of patients achieving complete resection, and RT dose escalation. Hyperfractionated radiotherapy (HFRT) has been employed in some studies and results are awaited. The role of CSRT needs to be evaluated further for patients presenting with leptomeningeal metastases. Multi-institutional and international studies are necessary to improve understanding of the clinical behaviour, biology and management of EP. Pediatr Blood Cancer 2004;42:457–460.

Key words: dose-response; ependymoma; prognosis; radiotherapy; volume

INTRODUCTION

Ependymomas are relatively uncommon, accounting for 5–10% of brain tumours in the paediatric age group. They arise from the ependymal lining of the ventricular system. They can occur at any site within the ventricular system or in the spinal canal. Approximately two-thirds are infratentorial, usually arising in the ependymal lining of the 4th ventricle. Patients with tumours arising in the posterior fossa generally present with signs and symptoms of raised intracranial pressure. Extension of a 'tongue' of tumour through the foramen magnum and into the upper cervical region occurs in approximately 50% of patients with posterior fossa tumours. Patients with supratentorial tumours generally present with focal neurological symptoms and signs. Spread of EP is primarily local. Although gadolinium-enhanced MRI of the craniospinal axis and CSF cytology are essential components of the work-up for these patients, the risk of leptomeningeal seeding at diagnosis is low, generally of the order of 5–10%.

The following histological subtypes of EP [1] are seen:

myxopapillary ependymoma (WHO Grade I),
ependymoma (WHO Grade II),
anaplastic ependymoma (WHO Grade III).

Myxopapillary EP are slowly growing lesions that are almost exclusively located in the conus and filum terminale region of the spinal cord and are the most common spinal cord tumour in this location.

For many years radiotherapy (RT) has been established as an important modality in the treatment of intracranial EP. The evidence for the benefit of post-operative RT compared with surgery alone is based on a number of retrospective series [2,3]. The benefit for post-operative RT compared with surgery alone has also been demonstrated in several more recent series, 45% versus 0% 5-year event-free survival (EFS) [4] and 51–70% versus 13% 5-year progression-free survival (PFS) [5]. This study reports a review of the more recent literature since the early 1990s which includes data on dose and volume for RT for EP. Interpretation of the literature is confounded by the lack of randomised studies, with the literature consisting mainly of single institution retrospective comparisons of different dose/fractionation regimens. In these series, patients have been accrued usually over several decades. Most series are small, comprising a

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heterogeneous mix of tumour parameters and prognostic factors, including extent of resection and grade.

DOSE-RESPONSE RELATIONSHIP

When interpreting retrospective data it is difficult to rule out selection for lower RT dose based on adverse prognostic features e.g. age and tumour size, with lower dose RT being employed for younger patients and those with larger target volumes. It is also difficult in some studies to analyse the impact of dose on response when a dose-fractionation regimen has been uniformly applied, or when there is a high local relapse rate.

This review includes 11 series of patients reported since the early 1990s [4–14] and comprises 526 patients, involving treatment over time periods between 14 and 38 years. In these series the mean number of patients treated per institution per year was 1.8. This reflects the low incidence of EP. Overall 5-year survival varied from 40 to 79%. Seven of the 11 series demonstrated that the outcome was related to grade [4,7,9,11–14] and 7 series demonstrated the outcome related to the extent of surgical resection [4–7,9,13,14]. For incompletely resected tumours 5-year OS varied from 22 to 64.1%, whereas for completely resected tumours this was from 61 to 80%.

DOSE-RESPONSE DATA

Table I shows outcome data from 11 series reported since the early 1990s, in which information on dose-response has been given. Although data is inconclusive, there is some evidence of a dose-response effect, either for >45 Gy versus <45 Gy or >50 Gy versus <50 Gy.

ROLE OF HYPERFRACTIONATED RADIOTHERAPY (HFRT)

There is no data on the radiobiology of EP. Thus consideration of the potential benefit for HFRT relies on the empirical analysis of series of patients treated by HFRT. In the Pediatric Oncology Group (POG) 9132 study, in 15 patients who had incomplete resection a HFRT dose of 69.6 Gy given in 58 twice daily fractions resulted in a 3-year EFS of 52% [15]. This compared favourably with a similar group treated in an earlier study with conventional fractionation, who had a 5-year EFS of 27%. Several other studies have explored the role of HFRT in ependymoma and results are awaited.

ROLE OF DURATION OF RT

In one study [16] the impact on outcome of prolongation of the duration of RT has been examined. In this study in patients for whom the RT treatment duration was <50 days, the 5-year OS was 85.5% compared with 45.5% for 50 days or greater ($P = 0.01$). The 5-year local control rate for patients whose treatment duration was <50 days was 70.6% compared with 45.5% for 50 days or greater ($P = 0.05$). In this type of analysis it is important to rule out an impact of other prognostic factors. However, this study is of interest and for future analyses of outcome of RT for

TABLE I. Influence of Radiotherapy (RT) Dose on Outcome

Author [reference]	Institution	Dates	No. of patients	RT dose			
				<45 Gy	≥45 Gy	<50 Gy	≥50 Gy
Goldwein et al., 1990 [6]	Philadelphia	1970–1988	51	18% 5Y OS 0% 5Y PFS	51% 5Y OS 32% 5Y PFS		
Vanuytsel et al., 1992 [7]	Royal Marsden	1952–1988	93			53% 5Y OS (<=50 Gy)	55% 5Y OS (>50 Gy)
Chiu et al., 1992 [8]	MD Anderson	1955–1986	25			33% 5Y OS	58% 5Y OS
Rousseau et al., 1994 [4]	IGR, Paris	1975–1989	65			51% 5Y OS	69% 5Y OS
Carrie et al., 1995 [9]	Lyon	1974–1993	37			6/12 (50%) relapsed (<50 Gy)	6/16 (37.5%) relapsed (>50 Gy)
Pollack et al., 1995 [5]	Pittsburgh	1975–1993	37			Routinely applied to a dose >=50 Gy)	
Stuben et al., 1997 [10]	Essen	1963–1995	41	36% 5Y PFS (≤45 Gy)	45% 5Y PFS (>45 Gy)		
Schild et al., 1998 [11]	Mayo clinic	1963–1994	45		'No dose response'		
Mc Laughlin et al., 1998 [12]	Gainesville	1966–1989	32		N/A (high loc rec rate)		
Paulino et al., 2002 [13]	Iowa	1965–1997	52		GTR + >45 Gy LC 76.9%		
Oya et al., 2002 [14]	Kyoto	1961–1999	48			Uniformly applied, modified according to tumour size, no association (<55 Gy vs. >=55 Gy)	

PFS, progression-free survival; OS, overall survival; GTR, gross total resection; LC, local control.

TABLE II. Pattern of Recurrence

		Pattern of recurrence		
Series	Number of patients	Local	Distant	Local + Distant
Goldwein	51	29 (56.9%)	1 (2.0%)	
Vanuytsel	88	45 (51.1%)	2 (2.3%)	5 (5.7%)
Chiu	25	12 (48.0%)	2 (8.0%)	
Rousseau	65	20 (30.8%)	10 (15.4%)	3 (4.6%)
Carrie	37	14 (37.8%)	4 (10.8%)	
Pollack	37	17 (45.9%)	2 (5.4%)	
Stuben	41	7 (17.1%)	7 (17.1%)	
Schild	45 (incl spine)	(35%)	(13%)	
McLaughlin	32	20 (62.5%)		1 (3.1%)
Paulino	52	17 (32.7%)		4 (7.7%)
Oya	48	20 (41.7%)	6 (12.5%)	

EP it would be worthwhile to include duration of RT together with other RT parameters.

PATTERN OF RECURRENCE

Table II summarises the pattern of recurrence from 11 series. The pattern of recurrence is predominantly local, with a low risk of leptomeningeal relapse.

RT VOLUME

In a literature review, there was no evidence to support the use of extended field or craniospinal RT [7]. Further series provide further confirmation of this view (Table III). In one series, for eight patients presenting with leptomeningeal metastases a 5-year PFS of 37% was reported [5] and in another series three of six [14] have remained disease free after CSRT. The role of CSRT for patients presenting with leptomeningeal relapse needs further evaluation.

For patients treated by local RT there has been no consistent recommendation for extent of CTV around the PTV and margins for CTV have generally varied from approximately 1 to 2 cm, and sometimes the whole posterior fossa. In a report from St. Jude's Children's Hospital, 64 patients with EP have been included in a study of conformal RT using a margin of 1 cm for CTV around the GTV [17]. With a follow-up of 17 months (range 3–43 months) there have been six recurrences. Failure occurred within the CTV for five patients including three with concurrent leptomeningeal relapse. One patient developed metastatic disease with no evidence of local failure. In this series treatment of a CTV encompassing 1.0 cm of brain around the margin of resection and/or any residual tumour on MR scan appeared to be safe. Whether this guideline is suitable for determination of the CTV in a multi-institutional setting will be the subject of the planned COG study.

MANAGEMENT OF ANAPLASTIC EPENDYMOMA

The majority of series report a worse outcome for anaplastic (WHO grade III) compared with WHO grade II EP. The majority of these series are from single

TABLE III. Influence of Extent of RT Volume on Outcome

	Outcome	
Author [reference]	Local RT	Craniospinal RT
Goldwein et al., 1990 [6]	31% 5-Year PFS	27% 5-Year PFS
Vanuytsel et al., 1992 [7]	38% 5-Year PFS	46% 5-Year PFS
Chiu et al., 1992 [8]	1/12 Leptomeningeal relapses	0/7 Leptomeningeal relapses
Rousseau et al., 1994 [4]	40% 5-Year EFS	49% 5-Year EFS
Carrie et al., 1995 [9]	0/5 Relapses	7/11 Relapses
Pollack et al., 1995 [5]	70% 5-Year PFS	51% 5-Year PFS
Stuben et al., 1997 [10]	58% 5-Year PFS	45% 5-Year PFS
Schild et al., 1998 [11]	9% Leptomeningeal relapses	24% Leptomeningeal relapses
McLaughlin et al., 1998 [12]	1/17 Leptomeningeal relapses	0/15 Leptomeningeal relapses
Paulino et al., 2002 [13]	80.8% 5-Year OS	71.4% 5-Year OS
Oya et al., 2002 [14]	3/37 Leptomeningeal relapses	1/10 Leptomeningeal relapses

OS, overall survival; EFS, event-free survival; PFS, progression-free survival.

institutions. However, a multi-institutional series has been reported from the German HIT group [18]. In this series of 55 patients, supratentorial tumours received 54 Gy local RT and infratentorial tumours received CSRT 35.2 Gy in 1.6 Gy fractions with a local 20 Gy boost. All patients received chemotherapy. Three year OS was 75.6%. The extent of resection was significant, with a 3-year PFS of 83.3% for completely resected compared with 38.5% for incompletely resected tumours. Overall 40 patients had CSRT. Of 25 relapses 20 were local, 3 distant and 2 local + distant. As with other studies [19,20], the predominant pattern of relapse was local and anaplastic EP, although associated with a worse outcome should probably be treated according to the same guidelines as grade II EP.

CONCLUSIONS

The data on RT dose response relationships in the literature on the management of EP are difficult to interpret. The majority of studies have shown a major impact of extent of resection and histology on outcome. There have been inadequate patient numbers to perform reliable multivariate analyses. There is some evidence of dose response relationship from <45 up to >50 Gy. In most series the predominant pattern of relapse in all series is local, even after gross total resection and post-operative RT. There is no evidence of benefit for extended field or craniospinal RT. The priority for future studies is to maximise the probability of local tumour control. Measures might include increasing the proportion with complete resection, possibly with use of chemotherapy and 'second look surgery' for those with initial incomplete resection. It may also be possible to enhance the benefit for RT, by dose escalation with conventionally fractionated conformal RT. This will be the subject of the planned Children's Oncology Group study. The role of HFRT may justify further evaluation and results of completed studies are awaited.

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CLINICAL INVESTIGATION **Brain**

COMBINED POSTOPERATIVE IRRADIATION AND CHEMOTHERAPY FOR ANAPLASTIC EPENDYMOMAS IN CHILDHOOD: RESULTS OF THE GERMAN PROSPECTIVE TRIALS HIT 88/89 AND HIT 91

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Purpose: To evaluate the outcome in children with anaplastic ependymomas after surgery, irradiation, and chemotherapy; and to identify prognostic factors for survival.

Methods and Materials: Fifty-five children ($n = 27$ girls, 28 boys; median age at diagnosis, 6.2 years) with newly diagnosed anaplastic ependymomas were treated in the multicenter, prospective trials HIT 88/89 and HIT 91. Macroscopic complete resection was achieved in 28 patients; 27 patients underwent incomplete resection. All patients received chemotherapy before ($n = 40$) or after irradiation ($n = 15$). The irradiation volume encompassed either the neuraxis followed by a boost to the primary tumor site ($n = 40$) or the tumor region only ($n = 13$). No radiotherapy was administered in two patients.

Results: Median follow-up was 38 months. The overall survival rate at 3 years after surgery was 75.6%. Disease progression occurred in 25 children with local progression occurring in 20. The median time to disease progression was 45 months. The only significant prognostic factor was the extent of resection (estimated progression-free survival [EPFS] after 3 years was 83.3% after complete resection and 38.5% after incomplete resection) and the presence of metastases at the time of diagnosis (0% vs. 65.8% 3-year EPFS in localized tumors). Age, sex, tumor site, mode of chemotherapy, and irradiation volume did not influence survival.

Conclusions: Treatment centers should be meticulous about surgery and diagnostic workup. Because the primary tumor region is the predominant site of failure it is important to intensify local treatment. Dose escalation by hyperfractionation or stereotactic radiotherapy might be a promising approach in macroscopically residual disease. The role of adjuvant chemotherapy requires further study. © 2000 Elsevier Science Inc.

Anaplastic ependymoma, Children, Radiotherapy, Chemotherapy.

INTRODUCTION

The incidence of ependymomas in the pediatric age group is low, constituting usually less than 10% of all intracranial tumors, with an incidence of 2.2 to 2.7/100,000 per year (1). Two-thirds of low- and high-grade ependymomas localize infratentorially and about one-third localize supratentorially. This tumor carries the risk of meningeal dissemination, which occurs in 2% to 30% of patients (2). Previous series, most of them retrospective, have shown a probability of recurrence after 5 years of 50%, with the majority of failures occurring at the site of the primary disease (3, 4).

Over the past 25 years, there has been progressive improvement in treatment results, stemming from advances in neuroradiological imaging, neurosurgical techniques, postoperative care, and the precision of radiotherapy. However, predictive factors are still controversial, and there is no agreement on standard therapy.

During the past several decades, prophylactic irradiation of the neuraxis was recommended following surgical resection of the tumor (4–6). Nearly all authors have agreed with the importance of achieving macroscopically complete tumor resection (7–10). In contrast, the role of adjuvant chemotherapy in the treatment regimen has not been defined. We present the results from an analysis of patients with anaplastic ependymomas treated in two prospective multicenter trials undertaken to evaluate survival after combined therapy and the validity of prognostic factors for survival.

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METHODS AND MATERIALS

In 1988, the German Pediatric Society for Hematology and Oncology (GPOH) initiated a cooperative multicenter trial in Germany and Austria to evaluate the treatment of malignant brain tumors in childhood. The goals of the studies were to determine the efficacy of adjuvant chemotherapy before irradiation, and to identify prognostic factors for survival. The study plan was tested in 147 patients in a pilot trial from March 1989 to February 1990. Since August 1991, 515 children were enrolled in the randomized trial, which was closed in December 1997.

Eligibility

Children between 3 and 18 years of age with newly diagnosed intracranial medulloblastomas and anaplastic ependymomas were included in the study; 73 centers participated. Diagnosis was made by the institutional pathologist according to the World Health Organization (WHO) classification of brain tumors (11), but a central review was also required. Informed consents for all children were signed by their parents or legal guardians.

Evaluation of disease

Prior to surgery, the children had computed tomography (CT) or magnetic resonance imaging (MRI) scans of the brain and entire spine as well as neurologic examinations. Postoperatively, CT or MRI scans were performed within 72 hours of resection, and the cerebrospinal fluid (CSF) was evaluated before the start of the adjuvant regimen. MRI or CT scans were obtained again after radiotherapy and chemotherapy and 4 months after the completion of treatment. Thereafter, imaging was performed every 6 months. Neuroradiologic imaging findings were also submitted to a central review committee.

Treatment protocol

Surgery. The resection was performed as totally as possible without risking major impairment. Verification of histologic diagnosis was mandatory.

Chemotherapy. In HIT 88/89, the children were treated postoperatively with preirradiation ("sandwich") chemotherapy. In HIT 91, children were randomized to receive either immediate radiotherapy followed by maintenance chemotherapy or preirradiation chemotherapy followed by radiotherapy (Fig. 1).

Maintenance chemotherapy. During irradiation, vincristine (VCR) was administered intravenously once a week (1.5 mg/m^2). Chemotherapy was started 6 weeks after the end of irradiation and consisted of eight cycles given every 6 weeks. The chemotherapy comprised cisplatin (70 mg/m^2 iv on day 1), CCNU (75 mg/m^2 orally on day 1), and VCR (1.5 mg/m^2 iv on days 1, 8, and 15).

Preirradiation ("sandwich") chemotherapy. Chemotherapy was administered starting 14 days after surgery. It was given in two cycles and consisted of the following agents: ifosfamide (3 g/m^2 iv on days 1–3) and etoposide (150 mg/m^2 iv on days 1–3) during weeks 3 and 10, methotrexate (MTX) (5 g/m^2 iv continuously), and citrovorum-factor (CF-rescue) during weeks 5, 6, 12, and 13 and cisplatin (40 mg/m^2 iv days 1 to 3) and cytarabine (400 mg/m^2 iv days 1 to 3) during weeks 7 and 14. In the event of disease progression during chemotherapy, radiotherapy was started immediately. Otherwise, radiotherapy was started 3 weeks after the last day of chemotherapy.

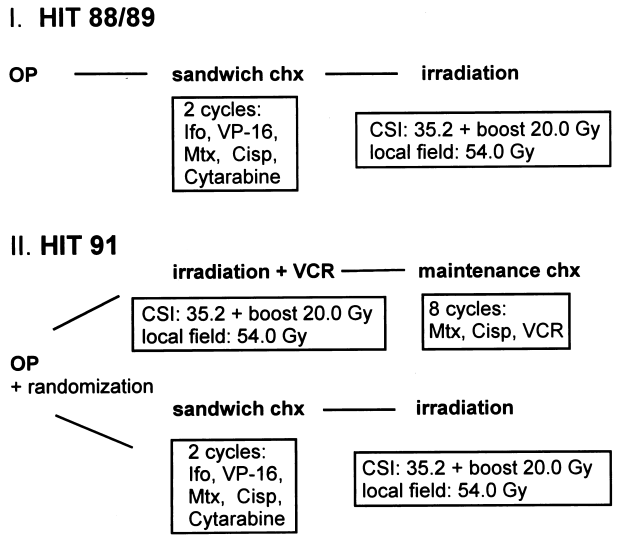

Fig. 1. Treatment schedules of chemotherapy and radiotherapy in trials HIT 88/98 and HIT 91. OP, resection; chx, chemotherapy; Ifo, ifosfamide; VP-16, etoposide; Mtx, Methotrexate; Cisp, Cisplatin; CSI, craniospinal irradiation; VCR, vincristine.

Radiotherapy. All infratentorial and metastatic tumors were to be treated by irradiation of the neuraxis followed by an additional boost to the posterior fossa. For supratentorial ependymomas, the treatment volume was to encompass the tumor site only, unless the tumor was in contact with the ventricular system. Radiotherapy was started 4 weeks after "sandwich" chemotherapy or 3 weeks after surgery.

The prescribed total dose for the neuraxis was 35.2 Gy (1.6 Gy per fraction, five times per week). The posterior fossa was to receive a boost dose of 20.0 Gy given in 2.0-Gy fractions. Lesions in patients with spinal metastases were to be irradiated with a total dose of 50.0 Gy. No increase in dose was recommended for patients with positive CSF cytologic findings. In the event of a limited-volume irradiation, the tumor site was to receive a total dose of 54.0 Gy at 2.0 Gy per fraction.

Statistical considerations

The data for patients with anaplastic ependymomas, as confirmed by the treating center and in part validated by the reference pathology, included in the HIT 88/89 and HIT 91 trials, served as the basis for the statistical evaluation of the prognostic factors for survival. These patients were treated by 33 centers between 1989 and 1997. The documentation of disease in patients was performed by the treating centers; the center monitoring the clinical data was the Children's

Hospital, University of Würzburg, Würzburg, Germany. Additional data about radiotherapy were collected and monitored by the Department of Radiooncology, University of Tübingen, Tübingen, Germany. The follow-up period was defined as extending from the date of surgery to the date of last patient contact or last event. The length of survival was calculated from the date of surgery. Terminal events were defined as the date of death from any cause (overall survival), the date of progression (progression-free survival), or the date of diagnosis, progression, or death (event-free survival). For all patients alive without events, the length of survival for the statistical analysis was considered the last date of the documented contact with the patient. Data for patients who died without evidence of progression were censored.

The Kaplan-Meier method was used to estimate survival, and the log-rank test was used for the statistical comparison of survival estimates. We planned to perform a multivariate analysis (Cox regression) only if more than one of the potential prognostic factors showed a remarkable influence in the univariate analysis ($p < 0.1$) and a minimum of 10% of the patients had one of these risk factors. All statistical analyses in this study were done for descriptive purposes. Data are presented with nominal two-tailed *p* values (unadjusted for multiple comparisons) and 95% confidence intervals. All analyses were carried out with the SAS system for Windows 6.1 software (SAS Institute, Cary, NC).

Table 1. Characteristics of 55 children with anaplastic ependymomas treated in Germany and Austria, 1988–1997

Characteristic	No. of patients	Percentage
Median age (range): 6.2 years (3–16)		
Sex		
Male	28	50.9
Female	27	49.1
Site		
Infratentorial	29	52.7
Supratentorial	26	47.3
Metastases		
M0	50	91.0
M1	3	5.4
M2/3	2	3.6
Surgery		
Incomplete resection	27	49.1
Complete resection	28	50.9
HIT		
88/89	18	32.7
91	37	67.3
Chemotherapy		
Maintenance	15	27.3
Sandwich	40	72.7
Radiotherapy*		
CSI	40	72.7
Local field	13	23.6

CSI = craniospinal irradiation.
* 2 children received no irradiation.

RESULTS

Patient population

Seventy-one children were treated for anaplastic ependymoma. Pathologic findings were reviewed in 51 (71.8%) children. Sixteen children were excluded from evaluation because the pathologic results of the review committee revealed low-grade ependymoma ($n = 1$), ependymoblastoma ($n = 5$), primitive neuroectodermal tumor ($n = 2$), astrocytoma ($n = 1$), medulloblastoma ($n = 5$), or glioblastoma ($n = 2$). Of 55 patients eligible for the study (27 females and 28 males; age range 3.0–16.6 years; median, 6.2 years), pathologic review was performed in 35 children. In 26 patients, the tumor site was supratentorial (47.3%); in 29 children, the tumor site was infratentorial (52.7%) (Table 1).

In 20 patients, leptomeningeal dissemination was evaluated by CSF cytologic studies at presentation. Four patients had positive CSF cytology findings; in 35 children, no CSF findings were available, but the children underwent craniospinal MRI. Metastases to the central nervous system (CNS) were found in 2 children: 1 child had a spinal tumor in the lumbosacral region, and the other child had cerebral dissemination as well as positive CSF findings. No metastases outside the CNS were found (Table 2).

Treatment

Surgery. All children underwent surgery. The extent of resection was assessed by postoperative CT/MRI and was considered macroscopically complete in 28 children and incomplete in 27.

Chemotherapy. Eighteen children in HIT 88/89 and 37 children in HIT 91 were treated. In the HIT 91 trial, 81% of the patients were randomized; the parents of 7 children refused randomization. All patients received adjuvant chemotherapy; maintenance chemotherapy was performed in 15 children and sandwich chemotherapy in 40 children.

Radiotherapy. Thirteen children were irradiated at the primary tumor site only. The median total dose was 54.0 Gy (1 patient received a dose of 55.8 Gy). The median dose per fraction was 2.0 Gy (range, 1.8–2.0 Gy).

Forty children received craniospinal irradiation with an additional boost to the posterior fossa. The median total dose to the neuraxis was 35.2 Gy (range, 24.0–39.6 Gy); 15.0% of the patients received a dose of less than 30.0 Gy.

Table 2. Pattern of dissemination at time of diagnosis in 5 children

Age (years), sex	Primary tumor site	CSF positive	Distant metastases	M stage
3.4, F	Infratentorial	Yes	No	M1
5.3, F	Supratentorial	Yes	No	M1
4.0, F	Infratentorial	Yes	No	M1
7.9, M	Infratentorial	Yes	Cerebral	M2
8.7, M	Infratentorial	Unknown	Lumbosacral	M3

CSF = cytologic analysis of cerebrospinal fluid.

Table 3. Patient characteristics according to treatment volume

Variable	CSI (n = 40)	Local irradiation (n = 13)
Median age (range)	7.2 yr (3.6–8.8 yr)	5.3 yr (3.0–16.6 yr)
Tumor site		
Infratentorial	28	1
Supratentorial	12	12
Resection		
Complete	20	6
Incomplete	20	7
M-Stage		
M0	35	13
M1–3	5	0

CSI = craniospinal irradiation. yr = years.

The median single dose was 1.6 Gy (range, 1.5–1.6 Gy). The median boost dose was 20.0 Gy with a median single dose of 2.0 Gy (range, 1.5–2.0 Gy). The cumulative median dose to the posterior fossa was 55.2 Gy (range, 42–56 Gy); 10% of the children had a cumulative dose of less than 50 Gy; 2.5% of the children had a dose of more than 55.2 Gy.

Eleven children with supratentorial primary tumors underwent craniospinal irradiation because the tumor had infiltrated the ventricular system, and 1 child underwent this treatment because of dissemination of the disease. The parents of 2 children refused irradiation. Both children had localized supratentorial primary tumors and underwent complete resection plus sandwich chemotherapy, according to the design of the HIT 91 trial.

Table 3 shows patient characteristics according to the volume of radiotherapy.

Survival

Follow-up ranged from 5 to 106 months (median, 38 months). The 3-year-estimated overall survival rate and progression-free survival rate were 75.6% and 59.7%, respectively (Fig. 2). The pathologic findings were not evaluated by the review committee in 20 patients included in the analysis. We estimated the overall and progression-free survival rates in the reviewed children separately and found

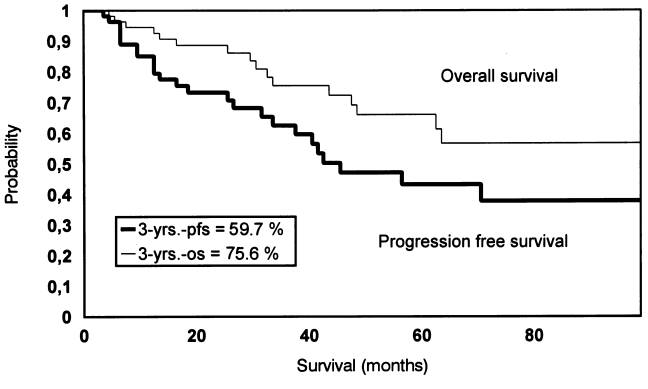

Fig. 2. Kaplan-Meier plots of the estimated overall and progression-free survival rates of 55 children.

Table 4. Univariate analyses of the correlation between selected parameters and estimated progression-free survival rate in 55 children with anaplastic ependymomas

Parameter	No. of patients (n = 55)	3-yr Progression-free survival rate (%)	95% CI	p Value
Age (years)				
1–6	26	66.2	46.8–85.6	0.63
> 6	29	58.4	37.6–79.2	
Sex				
Male	28	67.5	42.9–80.9	0.35
Female	27	57.1	36.1–78.1	
Tumor site				
Infratentorial	29	53.1	33.1–73.1	0.71
Supratentorial	26	72.4	52.8–92.0	
Metastases				
Yes	5	0	0–35.1	0.0001*
No	50	69.0	51.3–80.3	
Resection				
Complete	28	83.3	68.2–98.4	0.0043*
Incomplete	27	38.5	16.2–60.8	
Chemotherapy				
Maintenance	15	61.9	35.6–88.2	0.25
Sandwich	40	63.7	47.6–79.8	
Treatment volume				
CSI	40	56.3	39.8–72.8	0.44
Involved field	13	92.3	77.8–100	

CSI = Irradiation of craniospinal axis.
* Significant.

no difference (76% and 62%, respectively). Sixteen (29%) children died of recurrent disease. One child died of severe septic complications after salvage surgery. No other deaths occurred.

Patterns of failure

At the time of the last follow-up, 30 children were free of disease, and 25 patients showed progression. Disease recurred at the primary tumor site only in 20 patients (36.4% of all patients, 80% of failures). Disease disseminated within the CNS in 3 (5.5%) children: 1 case was meningeal and intracranial, 1 case was intracranial, and 1 case was in the thoracic spinal canal. Two children (3.6%) suffered from combined distant (1, intracranial; 1, not specified) and local failure.

Impact of clinical variables on outcome

Table 4 summarizes the correlations between the clinical variables and both the estimated overall and progression-free survival rates. Of the factors associated with both the overall and progression-free survival rates, leptomeningeal dissemination or solid metastases at the time of diagnosis were found to be significant. All 5 children with positive CSF cytology findings (n = 4) or spinal metastases (n = 2) died within 2 years of surgery. In contrast, children with localized tumors achieved a progression-free survival rate of 65.8% at 3 years (Fig. 3). Neither age, sex, or tumor site showed an impact on treatment outcome. The relationship

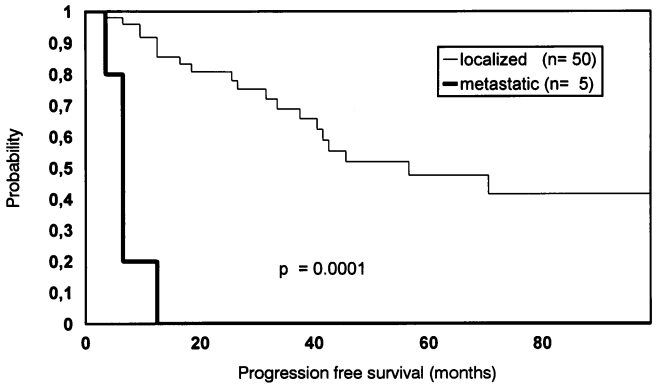

Fig. 3. Relationship between initial dissemination and the estimated progression-free survival rate.

between the tumor site and the progression-free survival rate is shown in Fig. 4.

Impact of treatment variables on outcome

The treatment-related variables associated with progression-free survival are also summarized in Table 4. The patients with macroscopically complete resection ($n = 28$) fared significantly better, with an estimated overall survival rate of 91.5% at 3 years, than those who underwent incomplete resection ($n = 27$), with an estimated overall survival rate of 56.1% ($p = 0.046$). The estimated progression-free survival was also significantly better for children with completely resected tumors (Fig. 5).

The maintenance chemotherapy or sandwich chemotherapy did not alter the prognosis. Specifically, children who were treated for disease in the neuraxis with an additional boost to the tumor site showed no difference in outcome compared with the children who were treated with irradiation at the tumor site only. Of the children who did not receive any radiotherapy, 1 is alive after 5 years (her tumor specimen was not reviewed) and 1 died of local and distant disease progression after 1.5 years.

The distribution of risk factors in patients with supratentorial tumors given radiotherapy to the craniospinal axis or the tumor region is shown in Table 5, and the survival rate

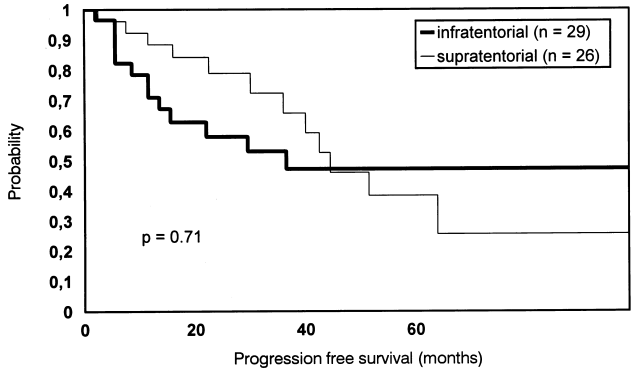

Fig. 4. Relationship between tumor site and estimated progression-free survival rate.

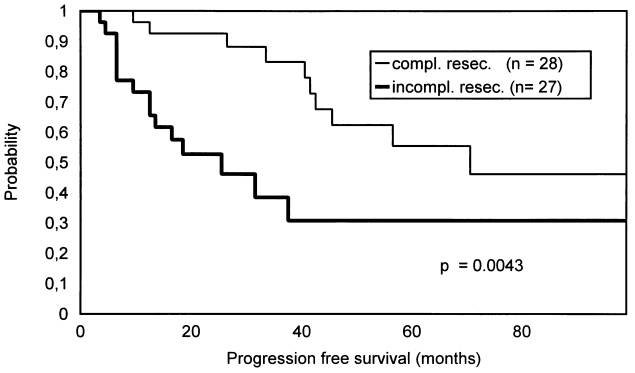

Fig. 5. Relationship between the extent of resection and the estimated progression-free survival rate. compl. resec, complete resection; incompl. resec., incomplete resection.

distribution is shown in Fig. 6. Because of very uniformly administered radiotherapy, it is difficult to draw conclusions; however, we did not find an impact of fraction size or total dose on the survival rate.

DISCUSSION

Ependymomas account for 3% to 4% of childhood cancers (1). There is little information on the outcome of different treatments for ependymomas and still no consensus on the optimal therapy. Most studies have investigated low- and high-grade ependymomas, despite several reports about a worse outcome in patients with anaplastic ependymomas (12–15). Only WHO grade III ependymomas were included in the two German brain tumor trials described here.

The outcome in patients with ependymomas remains suboptimal, although the survival rates have increased from 24% (16) to 60% and 70% (12, 17). Regardless of the therapy administered in the patients in the present study, those with unfavorable factors, such as incomplete resection and tumor dissemination, had a poor outcome, with progression-free survival at 3 years of 38% and 0%, respectively. Disease recurrence at the primary site is still the main obstacle to cure, occurring in 88% of all cases of progression in our study. Similar rates have been observed in other

Table 5. Characteristics of 24 supratentorial ependymomas according to treatment volume*

Variable	CSI	Local field
Total number* of tumors	12	12
Resection		
Complete	4	6
Incomplete	8	6
M stage		
M0	11	12
M1–3	1	0

* Of the 26 children with supratentorial ependymomas, 2 were not irradiated.

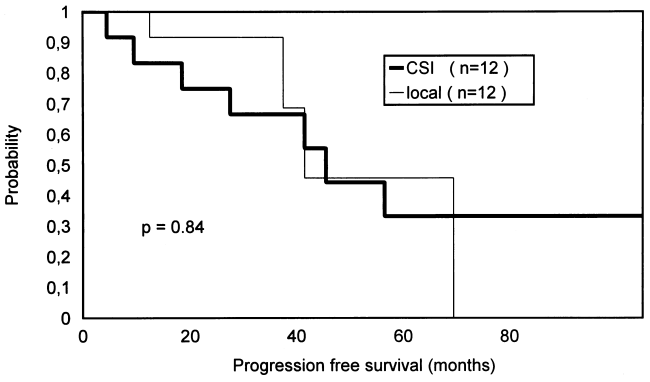

Fig. 6. Relationship between treatment volume and estimated progression-free survival rate for all 24 supratentorial ependymomas. CSI, craniospinal irradiation; local, tumor region only.

studies (2, 6, 15, 18–21). We also observed that the frequency of leptomeningeal seeding after therapy (9.1%) is similar to those reported previously, ranging from to 0% to 50% in clinical and autopsy studies (4, 22–28).

Kun *et al.* (29) and Shaw *et al.* (14) reported failures occurring shortly after treatment, with a median time to failure of 18 months. In our study, despite the short follow-up period, the majority of failures occurred after 3 years, with an estimated median time of 45 months to disease progression. This finding might be an effect of the long duration of combined treatment, ranging from about half a year in the preirradiation arm to 1 year in the maintenance arm. Merchant *et al.* (15) reported a median time of 37 months to disease progression with 61% of the patients receiving preirradiation or maintenance chemotherapy.

Our study results indicate that, age, sex, and tumor site do not influence outcome, in contrast to findings in other series.

Age

In previous studies, younger children had a lower survival rate than older patients (2, 13, 19, 24, 30, 31). However, Salazar *et al.* (21) found a reverse trend; in their study, patients older than 12 years fared worse than the younger children. We, on the other hand, found no impact of age on the survival rate, but this may be related to the fact that only children older than 3 years of age were enrolled in our trials. Foreman *et al.* (20) also observed no age-related effect on survival.

Sex

Only a few studies have analyzed the prognostic influence of sex on outcome in patients with ependymomas. Some authors have reported a worse prognosis in male patients (3, 32). In contrast, Shaw *et al.* (14), Foreman *et al.* (20), and Zorlu *et al.* (33) did not find any significant difference, as confirmed by our analysis.

The ratio of infratentorial to supratentorial anaplastic ependymomas is 1:1 (15).

Tumor site

The impact of the tumor site on outcome is controversial. For example, Foreman *et al.* (20) observed a survival advantage in patients with supratentorial ependymomas, though the difference was not significant. Needle *et al.* (34), on the other hand, observed a significant survival advantage in patients with supratentorial ependymomas, but there were only 9 such patients with anaplastic tumors in their series. A worse prognosis for patients with supratentorial tumors was attributed to a higher rate of anaplastic histology (10, 16, 29) or less gross total resection (15). Differences in outcome according to tumor site have been attributed to perioperative mortality (16, 28, 31, 35). No association of outcome with tumor site was described by Salazar (36). Read (37) and Vanuytsel *et al.* (3) observed no association between tumor site and survival, but they did observe a higher rate of spinal seeding in infratentorial tumors. Our study results showed no impact of tumor site on treatment outcome.

Dissemination

Most studies have not analyzed the influence of tumor dissemination at presentation. A reason for this may be that insufficient staging techniques may very rarely identify spread. Pollack *et al.* (2), however, surprisingly found no correlation between the rate of tumor dissemination and prognosis. They thought that this finding might be due to the fact that they diagnosed spread on the basis of cytologic, rather than gross, evidence of spread or to the fact that they used more aggressive therapy. We also had cytologic evidence of dissemination in 3 of 5 children, and all 5 children were treated with irradiation of the neuraxis with an additional boost to the primary tumor site. However, all children died in less than 2 years after surgery and had a significantly worse outcome in our analysis. But it must be considered that many children in our study did not undergo a cytologic analysis of the CSF; it therefore is possible that some children with disseminated disease may still be alive, which would mean that the outcome in such patients in our series was actually better than our data showed. In addition, negative cytology findings are no absolute proof for an absence of tumor cells in the CSF, a possibility that could also mean that the outcome was actually better than we observed.

Extent of resection

In the Italian Pediatric Neurooncology Group series of 93 children (38), the completeness of resection emerged as the most significant predictor of outcome. Many studies have shown such an influence of total resection (7, 8, 13, 15, 18, 30, 32, 39). However, some studies failed to show an advantage for complete resection (34, 36). In the present series, total macroscopic removal was associated with considerably improved progression-free and overall survival rates. In addition, the rate of total or gross total resections has improved over time with total resection in half the patients in our study versus lower rates in previous studies. Vanuytsel *et al.* (3) described 72 incomplete resections in 93 (77.2%) children treated between 1952 and 1988. The pre-

viously reported perioperative mortality rate of 17% (24, 40) was diminished to 0% in our study.

Chemotherapy

The effectiveness of adjuvant chemotherapy is difficult to assess in our study because all patients received either maintenance or sandwich chemotherapy. However, former trials have failed to show a survival advantage for chemotherapy, including the SIOP (Societé Internationale Oncologie Pediatrique) and the Children's Cancer Study Group trials (7, 16, 24, 37, 41, 42), but many patients with low-grade ependymomas also were enrolled in these studies, which could influence the results. Ependymomas have been shown to respond to chemotherapy (43–46). In particular, Needle *et al.* (34) reported in 1997 a survival benefit for adjuvant chemotherapy consisting of carboplatin, vincristine, ifosfamide, and etoposide, though they also included hyperfractionated radiotherapy in their treatment strategy. Kühl *et al.* (47) reported a combined partial and complete response of 55% for patients with anaplastic ependymomas in the HIT88/89 trial. However, the chemotherapy administered in our study population, which consisted of different agents given in different schedules, did not alter the prognosis in our patients.

Irradiation

Since postoperative irradiation started to be used, the survival rate has improved from 20% to 60% (5, 6, 9, 16, 48, 49). There is now uniform agreement that craniospinal radiotherapy is indicated for anaplastic ependymomas (21, 50) and useful in preventing spinal seeding (51). However, because some authors have reported that spinal seeding occurs only in infratentorial ependymomas (36, 52), others have prescribed craniospinal irradiation only for disseminated and infratentorial tumors. This was the strategy in our trial and was based on these experiences. According to our findings, irradiation of the tumor region was sufficient for localized supratentorial tumors, and the distribution of risk factors was equivalent in both groups. At present, many oncologic centers treat localized infratentorial tumors with limited-volume irradiation to reduce toxicity. The impact of this approach on the risk of spinal failure is unclear. However, the low spinal relapse rate observed in our study does not support this strategy since irradiation of the neuraxis was an essential part of treatment. An additional consideration in interpreting the findings from previous studies is that many low-grade ependymomas and also many adults have been included in some of these series and only a few children with infratentorial anaplastic ependymomas treated with local fields were observed for more than 5 years.

In our series, radiotherapy of the craniospinal region in disseminated disease could not prevent progression despite irradiation of the neuraxis, thereby suggesting a need to intensify treatment.

Another irradiation parameter is the dose level. Retrospective series indicate that doses greater than 45 Gy have to be delivered to the primary site (48, 49, 52, 53). Merchant *et al.* (15), who studied exclusively anaplastic ependymomas, found that by increasing the dose to the primary site, the outcome was positively influenced. We were unable to analyze the dose–response relationship for survival, however, because the majority of the children were treated with a very small dose range (42–55.8 Gy) to the primary site, similar to the treatment approach used in the study of Rousseau *et al.* (6), who also could not demonstrate a difference. Recent advances in radiotherapy techniques have as their aim improvements in the therapeutic ratio in childhood brain tumors by adding potentially more effective strategies that increase tumor control and limit radiation toxicity. For example, hyperfractionated radiotherapy has the potential of safely increasing the dose to the tumor while sparing late effects (54). Pilot studies of hyperfractionated radiotherapy in medulloblastomas have revealed excellent tumor control of up to 95% in such patients with acceptable acute toxicity (55, 56). A Children's Cancer Group Phase I/II trial investigated the effectiveness of hyperfractionated radiotherapy in brainstem gliomas with total doses of 78 Gy (57); although the survival rate remained poor, the treatment modality was tolerated relatively well with a prolonged need for steroid treatment and intralesional necrosis the only drawbacks. Another advance in radiotherapy is fractionated stereotactic irradiation, which focuses the dose on the tumor while sparing surrounding normal tissue, thus allowing better local dose escalation. Local dose intensification by radiosurgery might be a valuable approach, although data for children with CNS malignancies are scant . Grabb *et al.* (58) evaluated the role of stereotactic radiosurgery in 25 children with inoperable brain tumors, of whom 7 had ependymomas. The results in these patients with ependymomas were discouraging, but the authors (58) proposed that the therapy might be more effective if administered as part of primary treatment. Loeffler *et al.* (59) performed radiosurgery in 2 patients with ependymomas, both of whom were in complete remission 13 and 5 months after therapy.

CONCLUSIONS

The multimodal regimen used in the present study, consisting of adjuvant combined irradiation and chemotherapy, is effective in the treatment of anaplastic ependymomas in childhood. The predominant site of failure is the region of the primary tumor. The only significant predictive factors for overall and progression-free survival are the extent of resection and the dissemination of tumor at presentation. Therefore, exact staging techniques, including MRI of the brain and spine and cytologic studies of the CSF, are indispensable. Irradiation of the tumor site is sufficient for the treatment of localized supratentorial tumors. Whether this procedure is also sufficient for infratentorial ependymomas requires further studies to reduce toxicity. The prognosis remains very poor for patients with residual disease. In addition, because of the high frequency of local recurrence, it might be appropriate to intensify local treatment by using, for example, hyperfractionated schedules or a stereotactic

radiotherapy boost. The role of chemotherapy in anaplastic ependymomas in childhood has to be determined in prospective trials that focus on children with anaplastic ependymomas classified according to the WHO criteria.

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Phase II trial

Role of radiotherapy in anaplastic ependymoma in children under age of 3 years: Results of the prospective German brain tumor trials HIT-SKK 87 and 92☆

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Abstract

***Background and purpose*: To evaluate the outcome of very young children with anaplastic ependymoma after delayed or omitted radiotherapy (RT).**

***Materials and methods*: Children under age of 3 years with anaplastic ependymoma were enrolled in the HIT-SKK 87 trial from 1987. After surgery, low-risk patients (R0, M0) received maintenance chemotherapy until elective RT at age of three. In high-risk patients (R+, M+) intensive induction chemotherapy was followed by maintenance chemotherapy and subsequently delayed RT. If there was, progression radiotherapy started immediately. In the HIT-SKK 92, trial MTX-based chemotherapy was applied. RT was administered in non-responders only.**

***Results*: Thirty-four children with anaplastic ependymoma were eligible (age 1.0–33.0 months). All children received chemotherapy. In 13 children, no RT was administered. Preventive RT after chemotherapy was given in nine, and salvage RT in 12 children. OS and PFS rates after 3-year were 55.9 and 27.3%, respectively. Twenty-five children relapsed. Positive impact on survival was observed in children with higher age, M0-stage, complete resection, and treatment with radiotherapy. Without RT only 3/13, children survived.**

***Conclusion*: Delaying RT jeopardizes survival even after intensive chemotherapy. Predominant site of failure is the primary tumor site. RT of the neuraxis should be omitted in localized disease.**
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Keywords: Very young children; Ependymomas; Radiation therapy; Chemotherapy

Ependymomas comprise between 5 and 10% of childhood brain tumors [37]. The peak incidence is in the first 3 years of life, where ependymoma account for up to 30% of childhood brain tumors [27,49]. In children, therapy requires a careful balance between toxicity and efficacy. In younger children, the developing brain is very sensitive to any insult. This may lead to severe late sequelae [6,16,19,22,23,32,42]. On the other hand, the prognosis in very young children is particularly poor [7,11,45].

Many attempts have been made to increase survival while reducing adverse side effects. Surgical resection of brain tumors in babies and infants is often difficult [5]. The risk of side effects of radiotherapy correlates inversely to the age of the child [42,43]. In the past postoperative radiotherapy of the whole central nervous system was standard treatment for ependymoma [27,40]. In 1985, van Eys et al. reported the use of postoperative chemotherapy to avoid radiotherapy for infants [46]. Even though their results were not very promising, many study groups started to delay radiation therapy by early administration of chemotherapy.

We present an analysis of infants and babies enrolled in prospective trials with postoperative chemotherapy. The purpose of the report is to present the disease control results for the very young children treated prospectively with postoperative chemotherapy in an effort to delay or avoid irradiation.

Materials and methods

In 1987, the German Pediatric Society for Hematology and Oncology (GPOH) initiated a cooperative multi-institutional

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trial to evaluate delaying or omitting radiation therapy by administering intensive chemotherapy after surgery in very young children with malignant brain tumors. The aim was to reduce potential injury of the developing central nervous system. The study plan was tested in the Pilot trial HIT-SKK 87 from March 1987 to October 1992 and continued in HIT (HirnTumor; in English: 'braintumour')-SKK (Säuglinge und KleinKinder; English 'infants and babies') 92 trial until December 1997.

Patient eligibility

Children younger than 3 years of age with newly diagnosed malignant brain tumors were accrued to the study. Several German and Austrian institutes participated. Diagnosis was made by the institutional pathologist according to the World Health Organization classification of brain tumors [24]. Central review for histology was also recommended. The subgroup of patients with an anaplastic ependymoma was included in the present analysis only.

Evaluation of disease

Prior to surgery, computed tomography or magnetic resonance imaging scans of the brain and entire spine were recommended. Repetition of imaging was obtained after surgery and every 10 weeks during the therapy course. Neurological examinations and evaluation of cerebrospinal fluid were also advocated. After completion of therapy, neuroradiologic imaging was performed every 6 months.

Evaluation of toxicity and quality of life

At the beginning of the protocol, no prospective standardized tests for evaluation of radiotherapy toxicity and late effects were implemented. However, data about late toxicity were collected by the Department of Radiooncology, University of Tübingen, Germany, by sending letters and contacting responsible clinicians on the telephone.

Treatment protocol

Surgery

Maximum achievable resection was recommended, without risking major impairment. Confirmation of histological diagnosis was mandatory. Extent of resection, either subtotal or complete, was estimated from the operative report and postoperative imaging.

Chemotherapy

Two to 4 weeks after surgery, all children received chemotherapy according to the HIT-SKK 87 or 92 trial (Fig. 1).

HIT-SKK 87

Low risk patients (complete resection, no dissemination of disease) received maintenance chemotherapy until radiotherapy at the age of 3 years or progression.

High risk patients (subtotal resection, metastatic disease), as well as children between age of 2.5 and 3.0, received induction chemotherapy after surgery given in two cycles (Fig. 2). Subsequently, maintenance chemotherapy followed until radiotherapy was initiated at the age of three. If there was progression or recurrence, chemotherapy was interrupted and radiotherapy was given immediately.

HIT-SKK 92

Three cycles of postoperative chemotherapy were given with intervals of 3 weeks (Fig. 2). If there was complete remission, no radiotherapy was recommended. If there was progression or tumor recurrence before 18 months of age, an

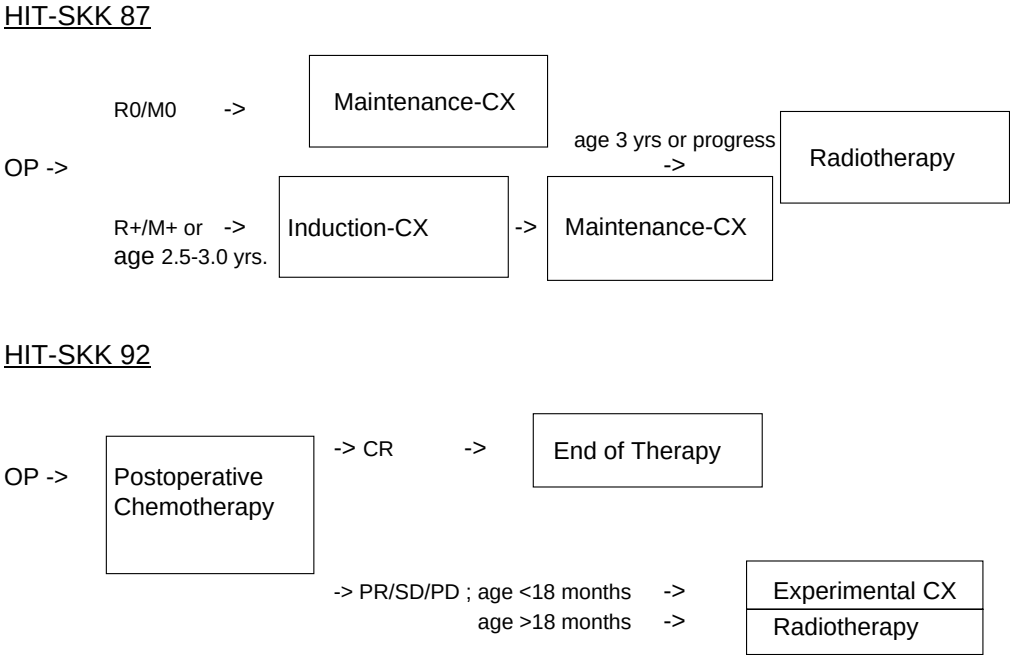

Fig. 1. Treatment schema.

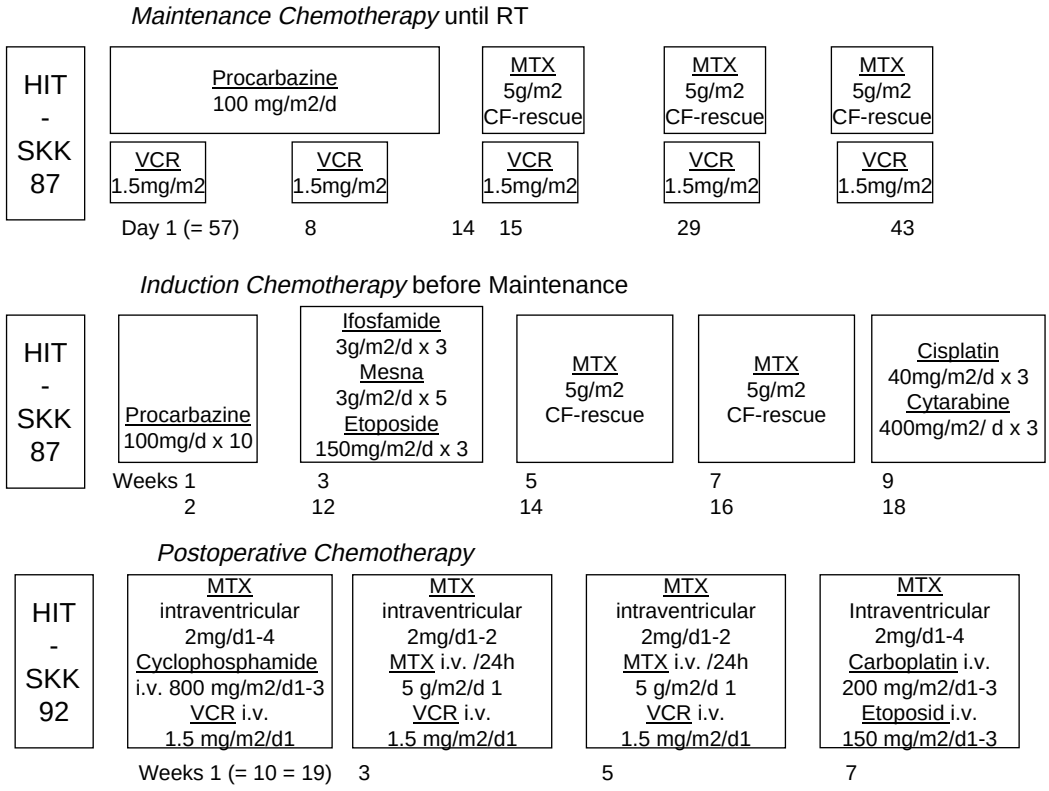

Fig. 2. Chemotherapy schedules.

experimental chemotherapy was recommended to follow, and radiotherapy was recommended for children older than 18 months.

Radiotherapy

Infratentorial and metastatic tumors were to be treated by irradiation of the neuraxis, followed by a boost to the posterior fossa. For supratentorial ependymoma, treatment volume should encompass the primary tumor site only, unless the tumor was involving the ventricular system.

The prescribed total dose for the neuraxis covering the whole subarachnoidal space was 35.2 Gy (1.6 Gy per fraction, five times weekly). The posterior fossa was to receive a boost dose of 20.0 Gy (2.0 Gy per fraction, five times per week). For local radiotherapy, the prescribed total dose was 54.0 Gy (2.0 Gy per fraction). The PTV should encompass the primary tumour volume plus additionally a 2 cm safety margin. For children without any residual disease or dissemination, total dose to the neuraxis was allowed to be reduced to 24.0 Gy. The choice was at the discretion of the local radiotherapist.

At the time of onset of the HIT-SKK trial no further detailed guidelines for radiotherapy were included. In 1991, the guidelines were specified and a quality assurance program was integrated. Methods and results have been published already elsewhere [25,26]

Statistical considerations

The data of children with anaplastic ependymoma, as confirmed by the institutional pathologists, included in the HIT-SKK87 and 92 trials served as basis for statistical evaluation of prognostic factors and survival. Patients were treated in 23 centers.

Documentation of disease was performed by the treating centers. The clinical data was monitored at the Children's Hospital, University of Würzburg, Germany. Additional data on radiotherapy was collected and monitored by the Department of Radio-Oncology, University of Tübingen, Germany.

The follow-up period was defined as extending from the date of surgery to the latest patient contact or event. The length of survival was calculated from the date of surgery. Terminal events were defined as date of death from any cause (overall survival) or the date of first progression or relapse after surgery (progression-free survival (PFS)). For all patients alive without events, the length of survival was censored for the statistical analysis as the last date of documented contact with the patient. Data for patients who died without evidence of progression was censored.

The Kaplan–Meier method was used to estimate overall survival, and the log-rank test was applied for statistical comparison of survival estimates. Data is presented with nominal two-tailed p-values and 95% confidence intervals. All analysis was carried out with the SAS Institute system for Windows, version 8 software (SAS Institute, Cary, NC).

Results

Patient population

Thirty-four children with ependymoma were eligible (median age, 20.5 months). Histopathologic findings were

Table 1
Characteristics of the 34 children with ependymoma

Characteristics	No. of patients	(%)
Age (months)		
Median		20.5
Range		1.0–33.0
Sex		
Male	18	52.9
Female	16	47.1
Site		
Infratentorial	31	91.2
Supratentorial	3	8.8
Spinal	0	0
Metastases		
M0/Mx	29	85.3
M1	3	8.8
M2/3	2	5.9
Resection		
Complete	18	52.9
Incomplete	16	47.1
Chemotherapy		
SKK 87	15	44.1
SKK 92	19	55.9
Radiotherapy		
CSI+boost	11	32.4
Local field	10	29.4
None	13	38.2
Radiotherapy		
Preventive	12	35.3
Salvage	9	26.5
None	13	38.2

reviewed in 17 children. In 31 children, the tumor site was infratentorial. No patient with spinal ependymoma was included in the study.

In 23 patients,CSF cytologic studies for evaluation of leptomeningeal dissemination were available at presentation. Three children had positive CSF cytological findings (13%); in 11 children, CSF-samples were not available, but all children underwent craniospinal imaging. Solid metastases to the CNS were found in two children (5.9%). Twenty-nine children (85.3%) did not present with any metastases (Table 1).

Treatment

Surgery

All children underwent surgery. Extent of resection was assessed by postoperative CT/MRI, and was considered to be macroscopically complete in 18 children.

Chemotherapy

In HIT-SKK 87 trial, 15 children and, in HIT-SKK 92, 19 children were treated. All children received adjuvant chemotherapy.

Radiotherapy

Thirteen children did not receive any radiotherapy (38.2%). Ten children were irradiated at the primary tumor site only. Eleven children received craniospinal irradiation with an additional boost to the tumor. The median cumulative total dose to the tumor was 54.0 Gy (range, 20.8–56.4 Gy). The median total dose to the neuraxis was 35.2 Gy (range, 24.0–39.6 Gy). The median dose per fraction was 1.8 Gy (range, 1.4–2.2 Gy). In 12 children, radiotherapy was given immediately after completion of chemotherapy without any sign of recurrence or progression of disease. In nine children, radiotherapy was delayed and, administered only in case of recurrence or progression as salvage therapy. Median time interval between surgery and start of irradiation was 11 months (range, 4–34 months).

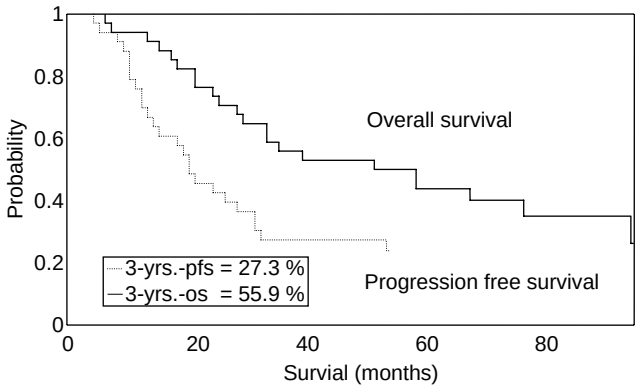

Fig. 3. Kaplan–Meier plots of overall survival and PFS.

Survival

Follow-up for all patients ranged from 7 to 146 months. In survivors, the median time of follow-up was 76.5 months (range, 53–146). For all patients, the 3-year estimated overall survival rate and 3-year PFS rate were 55.9% (confidence interval (=CI) 39.2–72.6) and 27.3% (CI 12.1–42.5), respectively (Fig. 3). For histologically reviewed children ($n=17$), PFS rates were estimated separately, but no difference could be detected (3-year overall survival and PFS of 58.8% (CI 35.4–82.2) and 25% (CI 3.8–46.2), respectively). Twenty-one children died of recurrent disease. One chemotherapy-related death occurred. There were no other causes of death. For patients who failed, median time to progression was 8 months and median time to death was 29.5 months (range, 7–95 months).

Patterns of failure

At last follow-up, nine children were free of disease, and 25 children showed progression (73.5%). Nineteen children (76.0%) failed at the tumor site only. Six children (24%) developed dissemination within the CNS (four of them intracranial, one spinal, and one both intracranial and spinal); all of those six patients had local failures also.

Late effects

At last follow-up, in five survivors information about late toxicity was available. In two children, growth retardation, pituitary insufficiency and need for hormonal replacement were reported. In one other child, retardation in language and mental development was described. One more child had motor deficits in the left upper arm, and one child suffered from cerebellar ataxia.

Table 2
Univariate analysis of the correlation between patient and treatment parameters and estimated PFS in 34 children with ependymoma

Parameter	No. of patients ($n=34$)	3-Year PFS rate (%)	95% CI	*P*-value
Age				
<18 months	13	16.8	0-37.9	0.23
>18 months	21	33.3	13.2-53.5	
Sex				
Male	18	17.7	0-35.9	0.26
Female	16	37.5	13.8-61.2	
Metastases[a]				
M0	19	33.4	11.6-55.2	0.11
M1/2/3	5	0	0-0	
Resection				
Complete	18	41.2	17.8-64.6	0.07
Incomplete	16	12.5	0-28.7	
Schedule				
SKK 87	15	40.0	15.2-64.8	0.15
SKK 92	19	16.7	0-33.9	
Histology				
Reviewed	17	25.0	3.8-46.2	0.84
Not rev.	17	29.4	7.7-51.1	

[a] Children without CSF examination were excluded from this analysis.

Table 3
Univariate analysis of the correlation between radiotherapy parameters and overall survival

Parameter of radiotherapy	No. of patients	3-Year OS rate (%)	95% CI	*P*-value
Given	21	66.7	46.5-86.8	
Not given	13	38.5	12.0-64.9	0.21
Preventive	12	66.7	40.0-93.3	
Salvage	9	66.7	35.9-97.5	0.62
CSI + boost	11	54.5	25.1-83.9	
Local fields	10	80.0	55.2-100	0.69

Prognostic factors

Treatment related and clinical variables, which correlate with overall survival and PFS, are listed in Table 2. Among the factors associated with PFS, younger age, male gender, incomplete resection (Fig. 4) and the presence of metastases at time of diagnosis showed a negative trend, which did not reach statistical significance. The children treated according to HIT-SKK 87 fared better than those included in HIT-SKK 92. Among the factors associated with overall survival, administration of radiotherapy showed a positive trend without statistical significance (Table 3). Administering radiotherapy for prevention or salvage did not show correlation with overall survival either. Nine children received radiotherapy after progression or recurrence had occurred; only two of them survived without further progression. Six children died in spite of salvage irradiation; one is living with local recurrence and is receiving salvage chemotherapy. Target volume of radiotherapy was not found to impact survival either. However, in the six children with dissemination during or after chemotherapy, none received craniospinal radiotherapy before dissemination; two failed after local irradiation. In 13 children, radiotherapy was omitted and only chemotherapy was given; three of them survived. In these 13 children even after progression in nine children either parents had refused treatment or, responsible clinicians stated that general condition contradicted further treatment. In metastatic ependymoma ($n=5$), two received craniospinal irradiation, one local radiotherapy, and in two children no irradiation was administered. Only one child survived, who received craniospinal radiotherapy.

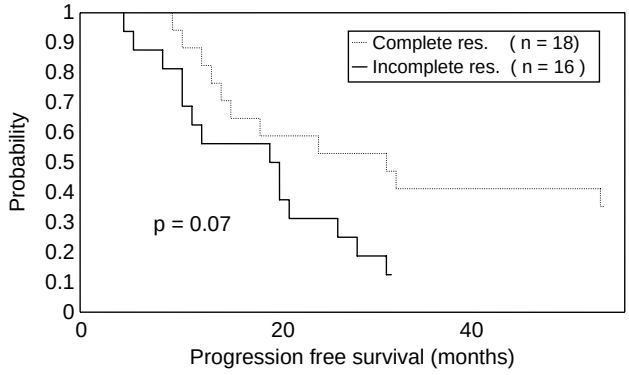

Fig. 4. Extent of resection and PFS.

Discussion

Ependymomas in childhood are rare. However, ependymoma has a peak incidence in infants and babies [27]. Only a few large series refer to ependymoma in early infancy. As in the German HIT trials, in most of the previous series all malignant brain tumors were treated with the same strategy. Different cut-off ages were chosen in those series and no analysis focused on anaplastic ependymoma in infancy only. In the HIT trials only anaplastic ependymomas were included.

The current gold standard for treating ependymoma in early infancy is hard to define. Until the early eighties standard treatment was surgery followed by craniospinal or focal radiotherapy [4,5,11,40]. Because of severe adverse effects that may occur when irradiating the central nervous system in young children [6,42,43], alternative treatment approaches have been introduced by adding intensive chemotherapy in order to delay or omit radiotherapy [20,46]. Treatment results have been disappointing with survival rates between 20 and 50% [12,28,49].

Our strategy, including early postoperative chemotherapy and selective radiotherapy when appropriate, resulted in 3-year overall survival and PFS rates of 55.9 and 27.3%, respectively, for all patients. These results are similar to those previously reported. Geyer et al. observed a 3-year PFS rate of 26% in 15 infants less than 18 months with ependymomas after postoperative 'eight-in-one' chemotherapy with a subset of about 20% not receiving

radiotherapy [12]. Six of the total 15 children had anaplastic histology and no further specific clinical parameters were listed separately for ependymoma patients. In the series of White et al., 5/14 children younger than 4 years of age with ependymomas survived after receiving a VETOPEC-based early chemotherapy [49]. All patients had M0 stage though, and information about the proportions of anaplastic tumors and irradiated patients is missing in the report. Radiotherapy was reserved for relapse in the report of Ater et al., who administered MOPP-Chemotherapy to infants less than 3 years of age [1]. Five ependymomas were included, two survived; one of them received salvage radiotherapy.

Local control is the most important aspect of treatment in ependymomas; most treatment failures occur locally. Several trials have shown that complete surgery is a strong prognostic factor in these tumors [3,18,29,33,34,36,44,47]. In Children's Cancer Group (CCG) Protocol 921, patients with gross total resection had a 5-year progression free survival of 66%, compared to 11% for those with residual disease [39]. In the analysis of the German HIT trials for children with anaplastic ependymoma above 3 years of age, a 3-year PFS of 83.3% could be achieved after complete resection, compared to only 38.5% after incomplete surgery [44]. In our analysis, babies and infants receiving complete surgery also show an advantage, with 3-year PFS of 41.2%, compared to only 12.5% after incomplete resection. Still, the importance of the operative procedure is very clear and there have been groups reporting successful treatment of intracranial ependymoma with surgery alone [21]. Palma et al. reported that six out of 12 children survived without any adjuvant therapy; only one child experienced late recurrence [35]. In young children omission of adjuvant, therapy could significantly reduce the risk of late morbidity, thus, potentially favoring an attempt to remove remaining tumor at second surgery. On the other hand, the risks of aggressive surgery are high in young children [5] and the role of surgery without adjuvant radiation is still uncertain. Ependymomas have not been supposed to be very chemo-responsive in the past. In a randomized CCG trial for children over 3 years of age, vincristine and lomustine were found to be of no benefit for ependymoma [10]. In the CCG trial for infants, including five children with measurable postoperative disease, no child with intracranial ependymoma achieved complete or even partial response after receiving chemotherapy [12]. Response rates reported in other retrospective studies range from 0 to 48% [9,15]. In the Australia–New Zealand trial, seven children were evaluable for response to chemotherapy, and six achieved either complete or partial response, but only five of 14 children with ependymoma survived, none of those with initial dissemination [49]. Duffner et al. concluded from her re-analysis of the Baby-POG I trial that ependymoma might be chemo-sensitive, but not chemo-curable, because long delay of radiotherapy reduced survival rates despite intensive interposed chemotherapy [8]. In our series, only three out of 13 children treated with chemotherapy alone survived.

Historically, surgery alone resulted in 5-year survival rates of less than 30%, comprising all ranges of histological grade and degree of surgery [27]. After employing adjuvant irradiation routinely, survival could be improved significantly, with survival rates of up to 60% in older children [4,31,40,41,48]. The irradiation volume encompassed the whole neuraxis in most of the children, which led to significant late sequelae [16,17,19,22,23]. Later trials attempted to delay or omit radiation therapy in infants. The Baby-POG I trial treated 48 children with intracranial ependymoma under the age of 3 years. First analysis resulted in promising 3-year overall survival rates of 61.8% [9]. These findings did not persist. The children developed late recurrences and new analysis revealed the benefit of not delaying radiotherapy for any longer than 1 year, with 5-year overall survival rates of 63.3%. When radiotherapy was delayed for 2 years, 5-year overall survival rate was only 25.7% [8]. They concluded that delay of radiotherapy of more than 1 year adversely affected survival. Several trials tried to delay or avoid radiotherapy: the CCG trial by administering postoperatively the 'eight-in-one' regimen, the M.D. Anderson Cancer Center study MOPP chemotherapy, and the Australia–New Zealand study by giving Vincristine, etoposide and intensive cyclophosphamide. But all of these studies included only 5–15 children and could not lead to strong conclusions regarding radiotherapy [1,12,49]. In our trial, the 3-year overall survival rate of 21 children who were irradiated was 66.7%, compared to only 38.5% for those receiving no radiotherapy. We failed to answer the question if radiotherapy can be delayed until recurrence. However, only two of nine children receiving radiotherapy after developing progression survived without any further progression. Nowadays, the irradiation of intracranial ependymoma without dissemination has changed significantly. Most of the brain tumor groups recommend encompassing the tumor bed only, because as with our findings, no benefit could be detected of irradiating the whole CNS of patients with non-disseminated ependymoma [2,40]. This reduction of irradiated central nervous tissue will lead to reduction of the risk of late sequelae. The efficacy of chemotherapy is still unclear and the predominance of local failures indicates the need for local treatment approaches. Therefore, we feel that the avoidance or long delay of local radiotherapy even in young children with ependymoma is not yet justified. This is in accordance with the current Children's Oncology Group trial (COG ACNS0121) implementing RT even for very young children with localized ependymoma [30]. Regarding the optimal doses for radiotherapy, we cannot draw any conclusion from our analysis because of the small group and inhomogeneous treatments. Retrospective series indicate that total doses greater than 45 Gy must be delivered to the tumor site [13,48]. Merchant et al. studied anaplastic ependymoma and found a positive influence of increasing the local dose [29].

There is consensus that local relapse is the major cause of failure in ependymoma [3,18,29,33,34,36,44,47]. In accordance in our analysis, all children failed locally and, in 76% of the cases, the site of failure was solely local.

Age at diagnosis was found to be an important prognostic factor for ependymomas. In previous studies, children below 3–6 years had a lower survival rate than older patients [14,33,38]. There is little data concerning the impact of age in the subgroup of infants and babies. Duffner et al. revealed a significant difference between the two age groups (A: 0–24 months vs. B: 24–36 months) with 5-year survival rates of 25.7% compared to 63.3%, but the younger children had a

longer delay of radiotherapy [8]. We observed a trend for better outcome in children older than 18 months. However, in accordance with Duffner et al. we also delayed radiotherapy for a longer period in younger children.

Conclusion

In ependymomas local control is the most important prognostic factor for treatment outcome. Therefore, optimization of local modalities seems to be most promising in order to improve prognosis. This may lead to more aggressive surgical procedures or second surgery in patients with residual disease. In localized disease, restriction of target volume to the primary tumor site only can achieve tumor control and, reduce the risk of long-term toxicity. Omission or long delay of radiotherapy should be avoided as it jeopardizes survival, even if intensive chemotherapy has been given. In very young children (e.g. less than 12–18 months), however, new approaches should be investigated in order to postpone focal radiotherapy. Monitoring of toxicity and late effects needs to become an essential part of all studies dealing with young children.

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Impairment of intellectual functions after surgery and posterior fossa irradiation in children with ependymoma is related to age and neurologic complications

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Abstract

Background: To investigate the neuropsychological outcome of children treated with surgery and posterior fossa irradiation for localized infratentorial ependymoma.

Methods: 23 patients (age 0.3 – 14 years at diagnosis) who were treated with local posterior fossa irradiation (54 Gy) underwent one (4 patients) or sequential (19 patients) neuropsychologic evaluation. The last evaluation was performed at a median of 4.5 (1 to 15.5) years after RT.

Results: Mean last full scale IQ (FSIQ), verbal IQ (VIQ) and PIQ were 89.1, 94.0, and 86.2 respectively. All patients had difficulties with reading, and individual patients showed deficits in visuospatial, memory and attentional tasks. There was no trend for deterioration of intellectual outcome over time. All 5 children with IQ scores ≤ 75 were under the age of four at diagnosis. There was a significant association between the presence of cerebellar deficits and impaired IQ (72.0 vs 95.2, p < 0,001). The absence of hydrocephalus was an indicator of better neuropsychologic outcome (mean FSIQ of 102.6 vs 83.9, p = 0.025).

Conclusion: Within the evaluated cohort, intellectual functions were moderately impaired. Markedly reduced IQ scores were only seen with early disease manifestation and treatment, and postoperative neurological deficits had a strong impact on intellectual outcome.

Background

Within the posterior fossa, ependymoma is the second most common malignant tumour in children [1]. As with other paediatric central nervous system (CNS) tumours, finding the balance between effective treatment and preservation of psychomotor development is challenging. Modern approaches aim at maximizing surgical resection while reducing the volume of irradiation since complete tumour removal is the main prognostic factor [2-4].

As a consequences of brain damage caused by the tumor itself and the surgery, some children develop neurologic deficits such as cerebellar dysfunction and cranial nerve palsies [5]. Indeed, radiation therapy rarely causes neurologic damage in the absence of complications such as radionecrosis or stroke. More aggressive surgery may thus increase the risk of neurologic damage.

Progressive intellectual impairment is a serious side effect of whole brain irradiation [6-9], the extent to which intellectual capacities are also diminished due to local radiation to the posterior fossa remains to be determined. Intellectual quotient (IQ) is preserved in patients with ependymoma after posterior fossa irradiation only, compared to children with medulloblastoma who received craniospinal irradiation (CSI) [10]. Furthermore preliminary data suggest that there may be only limited decline in neurocognitive functions after local posterior fossa irradiation [3,11].

To determine the risk factors for intellectual impairment and to define the neuropsychological profile of long term survivors of localised infratentorial ependymoma we analysed the long-term neuropsychological outcome of children who received posterior fossa radiotherapy in a cohort of patients treated between 1986 and 2003 either at diagnosis (in children over 5 years of age) or after first relapse following chemotherapy in younger children. Patients who were diagnosed 1998 and later were evaluated prospectively.

All potential risk factors for intellectual impairment [12] were studied, including pre-operative complications such as hydrocephalus, surgical complications and persistent cerebellar deficits, age, and radiation volume (conformational versus whole posterior fossa)

Methods

Patients

Patients were included in this study if they (i) were diagnosed and operated on a localised infratentorial ependymoma, (ii) received local posterior fossa irradiation at the Institute Gustave-Roussy in Villejuif between 1986 and 2003, as initial treatment or after chemotherapy according to the BBSFOP protocol (Carboplatin/Procarbazin; Etoposide/Cisplatin; Vincristine/Cyclophosphamide) [13], (iii) had at least one standardised neuropsychologic evaluation, and (iii) had no abnormal premorbid psychomotor development as reported by the parents.

Twenty-three patients fulfilled these criteria. Informed consent was obtained from all patients. Patient characteristics are shown in table 1. Age at diagnosis ranged between 0.3 and 14.2 years (median 7.2). Of ten patients who were under the age of five at diagnosis, eight were irradiated under the age of five, three of them were irradiated before the age of three. There was a male predominance with 17 boys within the group. 16 patients were presenting with signs of intracranial pressure at disease manifestation. All patients had surgical resection with gross total resection achieved in 18 patients. Four patients received postoperative chemotherapy according to the French BBSFOP protocol [13] and commenced to radiotherapy due to progression of residual tumour or relapse.

Radiotherapy

All patients were treated using megavoltage equipments (4.5 to 20 MV photons of a linear accelerator). Total dose ranged between 50 and 62 Gy, administered in 5 weekly sessions of 1.8 Gy per day, with each beam treated every day. The highest doses correspond to patients with gross residual disease present at the time of radiations. A computerized dose-distribution was made available in all patients using the DOSIGRAY® software. In early patients, it was based on radiographic simulation films with hand-drawn tailored shieldings, based on physician knowledge of the anatomical landmarks, and tumour characteristics. More recently, a 3D high definition CT-scan based representation of dose-distribution superimposed with the posterior fossa structures, and tumour contour was made available. Dose-volume histograms for structures of interest were also generated. As far as technical considerations, early patients were treated in a straightforward approach

Table 1: General characteristics of 23 patients included in the study.

Age at diagnosis	0.3 – 14.2 y (median 7.2)
Male gender	17
Pts under 5 y at diagnosis	10
Pts under 5 y at irradiation	8
Preradiation chemotherapy	4
Hydrocephalus at presentation	16
Gross total resection at 1st surgery	18
Second surgery	4
Radiation therapy dose	50–62 Gy
Opposite lateral beams	12
Conformal irradiation	11
Postoperative cerebellar mutism	0
Postoperative cerebellar syndrome	15
Severe	3
Moderate	7
Mild	5
Cerebellar syndrome at last IQ evaluation	6
Severe	2
Moderate	2
Mild	2
Interval between RT and last IQ evaluation	1–15.5 y (median 4.5)
Age at last IQ evaluation	4.5–19.6 y (median 13.2)

RT = Radiotherapy.
IQ = Intellectual Quotient.
Pts = Patients.
Gy = Gray.
y = years.

combining two opposed laterals; recent 3D simulation, allowed conformation to the target with optimal sparing of adjacent organs (mainly pituitary, cochleas, chiasm). The gross tumour volume (GTV) for the primary site boost included the postoperative tumor bed. The clinical target volume (CTV) included the GTV, with an anatomically confined margin of 2 cm in the adjacent brain, whereas the planned target volume (PTV) expanded the CTV with a geometric margin of 1 cm. Multiple beams arrangements were used, ie 2 to 4 wedge anterior and/or posterior obliques. The early approach induced full dose of radiations in the entire posterior fossa, along with occipital and posterior temporal lobes. Only pituitary located at anterior margin, was kept to an acceptable level. The recent approach allowed marked reduced maximal dose to most structures outside the posterior fossa, including cochleas occipital and parietal lobes. The reverse side is that doses to the pituitary as well as integral dose to the temporal lobes were slightly increased due to beams exits.

Neuropsychologic evaluation

A battery of age adapted standard neuropsychological tests was applied to all patients. This included an IQ measure using Wechsler scales WAIS-R for adults, WISC-III for children ≥ 7 years and WPPSI-R for children aged < 7 years [14,15]. WISC-III consists of 10 obligatory and 3 optional subtests with a range of test scores between 1 and 19 (average: 10). Complementary tests were used to describe patients neurocognitive abilities as previously described by our group [16]. Additionally reading skills were measured by using the test of the alouette [17]. Executive functions were evaluated using the Wisconsin card sorting test (WCST). The evaluation was completed by the judgment of line orientation [18], facial recognition [19], a copy of the Rey – Osterrieth complex figure for children over 7 and analysis of fine motor skills with the Purdue pegboard test [20]. This latter test evaluates fine motor speed with the dominant and non-dominant hand both separately and together. The tests were timed, and a period of three hours was allowed for the entire evaluation. They were always performed in the same order. Information regarding school placement, both before disease onset and at the time of the neuropsychological evaluation, was also collected from parent's interview.

Tests were performed longitudinally in 19 patients. Of them 13 patients were evaluated prospectively and had baseline evaluation within the first year after the completion of radiotherapy. One of them was too young for WPPSI-R and received K-ABC [21]. Six patients were first tested >1 year after completion of radiotherapy (1.1–11.6 years, median 7.6). Four patients had only one neuropsychological evaluation between 3.9 and 8.6 years after completion of RT (median 7).

Presence of cerebellar syndrome (Ataxia, Dysmetria, Nystagmus) was graduated as mild, moderate, or severe according to the impact on daily activities by an independent physician unaware of the neuropsychological performance using Riva's rating scale [22].

All patients were regularly screened for endocrinologic deficits and hearing impairment.

Statistical Analysis

Statistical analysis was conducted using SPSS software (12.0 Version). Test results of the neuropsychological test (except IQ measures and subgroups) were normalised and transferred into Z-scores where score >= 2 corresponds to a probability of 95% to be outside of normal distribution.

The neuropsychologic profile was analysed descriptively based on the results of Wechsler subtests and the above mentioned additional test.

For analysis of risk factors for intellectual impairment, patients were divided into groups according to: age at radiotherapy (<5 y vs. ≥ 5 y); cerebellar syndrome, fine motor achievment; hydrocephalus at presentation, radiotherapy volume (conformal vs. posterior fossa). For each patient the result of the last FSIQ test was used. Comparison was done using Mann-Whitney-U test for non-parametrical data.

The age limit of 5 years was chosen due to reasons of clinical practice. Patients below 5 years of age were eligible for adjuvant BBSFOP chemotherapy [13]. Patients aged 5 or older would receive immediately adjuvant radiotherapy according to our institutional standard. Influence of age at RT was also analysed using linear regression.

Due to the small group size a multivariable analysis of risk factors was not reasonable and was therefore omitted.

Longitudinal data of achievment (FSIQ and reading) were analysed descriptively. Due to the small sample size and limited reliability of potential findings a random coefficient model was not used.

Results

The last neuropsychologic evaluation was done at a median of 4.5 years after the completion of radiotherapy (range 1 – 15.5 years). At the last testing mean full scale intelligence quotient (FSIQ), verbal IQ (VIQ) and performance IQ (PIQ) were 89.1 (standard deviation SD 14.6), 94.0 (SD 12.4), and 86.2 (SD 16.1). Of the 23 evaluable patients FSIQ was 90 or above in 10 patients (43%), between 80 and 90 in eight patients (35%), and below 80 in five patients (22%).

Profile of neuropsychological evaluation

In most of the WISC III subtests, scores were within average limits with mean scores above or equal 8 in 10 of 13 subtests (norms are 10 +/- 2 for each subtest). None of the patients showed a significant (≤ 2 SD) impairment of VIQ. Of the VIQ subtests 2 children achieved low test scores in the "information" subtest testing general knowledge. Four patients showed significant impairments in the optional memory subtest. PIQ was below VIQ in 17 patients with a mean difference of 7.8 points and a significant impairment in 6 patients. A marked impairment was seen in the chessboard/coding subtest and limited impairments in object assembly, symbols and picture arrangement, subtests evaluating speed of written performance and the capacity of visuo-spatial observation and organisation, respectively. Mean processing speed was also reduced. Table 2 shows the IQ subtest scores.

All of the 12 tested patients showed impairment in their reading skills, with a lag of 1 to 5 years between "reading age" and chronological age (median 3.8 years). The discrepancy was growing with time in all 8 patients with sequential testing (figure 1). Concerning visuospatial capacities, 3 of 16 patients had severe difficulties in reproducing the Rey-Osterrieth complex figure (mean Z-score of the whole group being -1.01 SD) while none of 11 patients tested had severe difficulties with the benton line orientation test (mean Z-score of the whole group being 0.56 SD). Short term memory measured by digit span was

Table 2: Wechsler scale (WISC-III) subtest results of 23 patients.

	Number of patients with scores below minus 2 SD	mean
Full scale IQ	2/23	89.1
Verbal IQ	0/23	94.0
Performance IQ	6/23	86.2
Verbal comprehension	2/22	94.5
Perceptive organization	1/22	92.1
Speed	4/22	86.6
Verbal subtests		
Information	2/23	8.4
Similarities	0/23	9.3
Arithmetics	0/23	9.8
Vocabulary	0/23	9.1
Comprehension	1/23	9.4
Memory	4/22	8.0
Performance subtests		
Picture completion	3/23	9.4
Codes	6/22	5.9
Picture arrangement	2/22	8.2
Block design	2/22	8.5
Object assembly	5/21	7.9
Mazes	1/22	9.6
Symbols	3/22	7.9

SD = standard deviation.
IQ = Intellectual Quotient

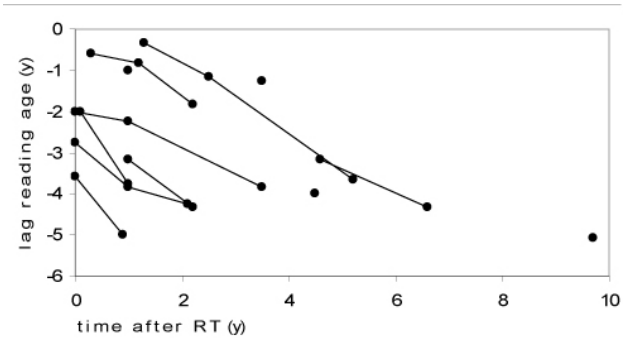

Figure 1
Reading performances. Differences between chronological age and reading age in years of 12 patients at different time points after therapy (4 had one test, 8 had sequential testing); Results of individual patients are connected with lines.

significantly diminished in 1 of 10 tested patients (mean Z-score of the whole group being-0.62 SD) and long term memory measured by word list was significantly diminished in 3 of 19 tested patients (mean Z-score of the whole group being -0.92 SD). Overall results of 12 patients who received the wisconsin card sorting test (WSCT) were within average limits, but 7 of these 12 showed attentional deficits with slow adaption, the tendency to keep one strategy, difficulties with reasoning, and problems to maintain the intentional thread. Difficulties within the WSCT were not correlated to the IQ scores.

Except reading skills, none of the tests showed declining results over time after therapy.

Risk factor analysis (see table 3)

Age

Low IQ results occurred mainly in the young age group. Figure 2 shows the distribution of FSIQ values at last evaluation and age at irradiation. Comparing the IQ results of children younger than 5 years at irradiation with children who were older at the time of irradiation, the difference failed significance but there was a trend for poorer outcome in younger children. Mean FSIQ was 82.7 (n = 8, SD 17.2), and 92.5 (n = 15, SD 12.8) respectively (p = 0.1).

Interval since RT and FSIQ

Of 13 patients with a baseline evaluation, 10 patients were tested before the start of irradiation and three patients within the first year after completion of radiotherapy. One of these patients was below 3 years of age at diagnosis, therefore he received age adapted tests without IQ testing. Of the remaining 12 patients mean baseline FSIQ, VIQ and PIQ (SD) was 91.6 (10.6), 98.4 (8.9) and 85.8 (13.6). The only patient with a baseline FSIQ below 75 was diagnosed at 2.5 years and received delayed RT

Table 3: Medical history of the patients and full scale IQ scores at last evaluation.

pt	age	location	hydroc.	shunt	surg.	complications	age at RT	last test	neurology	last IQ
1	13.7 y	FV, obex	yes	no	GTR	no	14 y	17.8 y	normal	84
2	4.3 y	FV, obex	yes	VCS	GTR	no	5.8 y	11.1 y	CS grade 2	83
3	1.5 y	FV, right angle	yes	VCS	GTR	no	2.6 y	4.5 y	normal	85
4	7.7 y	FV	yes	EVD	GTR	no	7.8 y	10.1 y	normal	108
5	13.8 y	FV, obex	yes	EVD	GTR	no	13.8 y	16.2 y	normal	86
6	8.8 y	FV, roof	yes	EVD	STR	no	9.3 y	12.7 y	normal	81
7	14.2 y	FV, angles	no	no	GTR	no	14.4 y	19.7 y	normal	82
8	4.1 y	right angle	no	no	GTR	infection	4.3 y	14.9 y	normal	112
9	10.9 y	FV	yes	VCS	GTR	no	11 y	13.2 y	normal	93
10	3.5 y	FV	yes	no	GTR	no	3.7 y	12.3 y	normal	83
11	8.2 y	right angle	no	no	GTR	no	8.3 y	12 y	paresis VI+VII	93
12	3.7 y	FV, obex	yes	VP	STR	no	3.8 y	10.7 y	CS grade 1	68
13	3.2 y	FV	yes	no	STR	no	3.3 y	17.5 y	normal	104
14	2.5 y	FV	yes	VP	GTR	no	2.7 y	18 y	CS grade 2	70
15	13.5 y	FV	yes	VCS	GTR	no	13.7 y	17.7 y	normal	90
16	0.3 y	FV	yes	no	GTR	no	1.3 y	16.9 y	CS grade 3	75
17	2.5 y	FV, brainstem	yes	no	GTR	no	6.2 y	10.7 y	CS grade 3	71
18	4.5 y	FV	no	no	STR	no	4.6 y	15.8 y	normal	115
19	9.8 y	FV	yes	VP	GTR	no	10 y	15.1 y	ptosis	97
20	2.9 y	FV, right angle	yes	EVD	GTR	subdural eff.	3 y	10.3 y	CS grade 1	65
21	6.8 y	FV to C4	no	no	GTR	no	6.9 y	7.9 y	normal	86
22	8.2 y	FV to C2	no	no	GTR	no	8.3 y	12.8 y	nystagmus	111
23	12.5 y	FV	no	no	GTR	no	12.6 y	14.8 y	normal	108

RT = radiotherapy; IQ = Intellectual Quotient; Hydroc. = hydrocephalus. Presence of hydrocephalus was noted in patients with clinical signs of raised intracranial pressure associated with enlarged lateral ventricles and/or bulging of the third ventricle.
Surg. = extent of surgery; C2–C4 = 2nd and 4th cervical vertebra; EVD = external ventricle drainage; VCS = ventriculocisternostomy; VP = ventriculo-peritoneal shunt; GTR = gross total resection; STR = subtotal resection.
CS = cerebellar signs; presence of cerebellar syndrome (Ataxia, Dysmetria, Nystagmus) was graduated as mild, moderate, or severe according to the impact on daily activities by an independent physician unaware of the neuropsychological performance using Riva's rating scale [22].

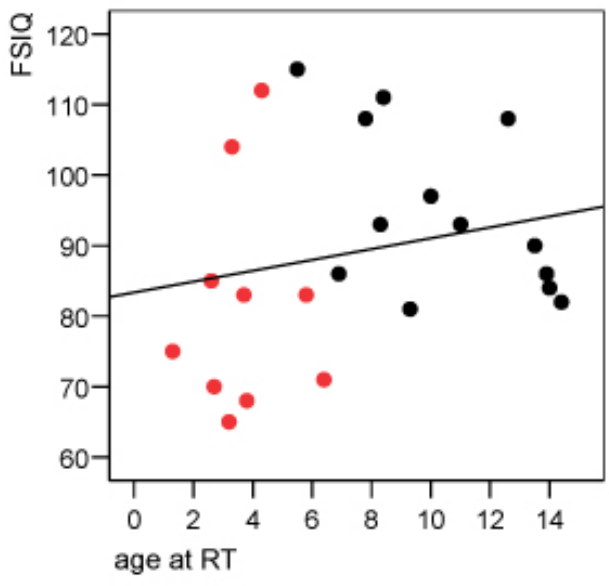

Figure 2
Of ten patients with age < 5 years at diagnosis, eight were irradiated before the age of 5. Regression line is also indicated (r = 0.22; p = 0.3). Black circles = patients > 5 y at diagnosis. Red circles = patients < 5 y at diagnosis.

with neuropsychological evaluation and onset of irradiation at 5.9 years.

In the longitudinal analysis there was no trend for loss of intellectual capacity over time after completion of irradiation. Figure 3 shows FSIQ scores of the sequential evaluations over time. There were six patients showing a decline in the measured IQ results, while five were gaining points. Of 11 patients who had baseline IQ testing and evaluation 2–5 years after radiotherapy (median 3.5 years) mean FSIQ (SD) at baseline and at last evaluation were 91.9 (11.0) and 91.3 (13.2), respectively. The difference between evaluations ranged between -10 to +12 points, with a median difference of 0.

Cerebellar syndrome and other influencing factors

At the time of last neuropsychological evaluation 6 patients had a cerebellar syndrome. There was a strong correlation with decreased IQ scores. Mean FSIQ (SD) was 72.0 (6.3) within the group of children with persisting cerebellar syndrome compared to 95.2 (12.0) within the group of children showing no signs of cerebellar syndrome. This difference was highly significant ($p < 0.001$) (figure 4). Hand motor speed measured by Purdue pegboard evaluation was also highly correlated with FSIQ

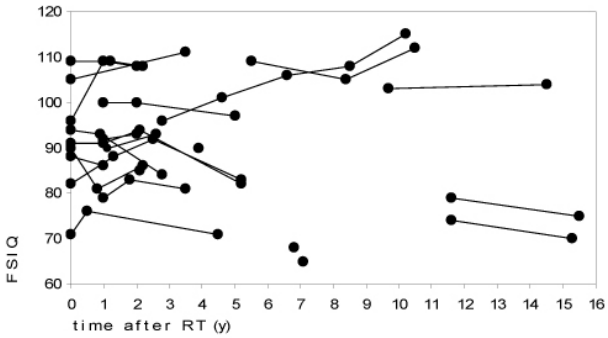

Figure 3
FSIQ of the 23 patients at different time points after RT. Results of individual patients are connected with lines.

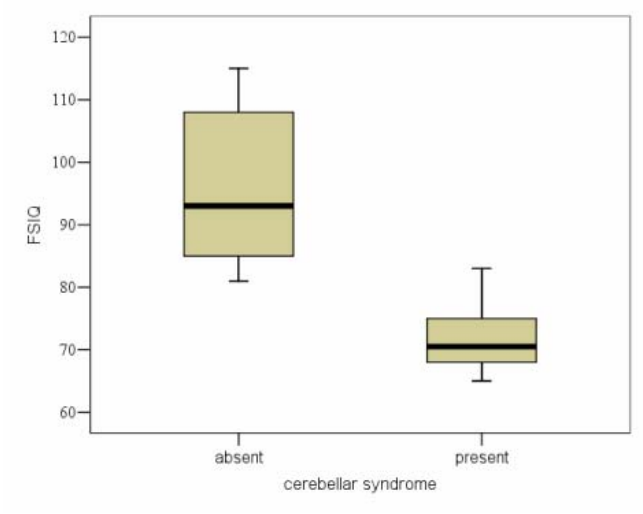

Figure 4
FSIQ with absent (n = 16) and present (n = 6) cerebellar syndrome (CS) at time of neuropsychological evaluation. Representation of the results is given as a Tukey and Cleveland's box-plot. The box represents the 5 principal centiles, ie 50% of the distribution. The line in the middle of the box represents the median. The line on top of the box joins the 90th centile. The line below the box joins the 10th percentile. Circles indicate the extreme values.

results (p = 0.003). With only 5 patients showing no signs of elevated intraventricular pressure (IVP) at initial presentation, the negative influence of elevated IVP was however significant (p = 0.025). Mean FSIQ with and without IVP at presentation was 83.9 (SD12.5) and 102.6 (SD14.4), respectively.

Patients with opposite lateral beams radiotherapy showed a lower mean FSIQ (SD) of 86.2 (16.7) compared to patients with conformal radiotherapy with FSIQ (SD) of 92.4 (12.6). The difference did not reach significance (p = 0.21).

Schooling

Three patients attended a regular school but had a delay of 2 or more years. One patient visited a special institute. The other patients were attending regular schools with no more than one year delay.

Endocrine deficits

Four patients had endocrinologic deficits which needed substitution (precocious puberty 2, growth hormone deficit 2). None of the patients had severe hearing impairment.

Discussion

We conducted neuropsychological evaluations in patients with localised infratentorial ependymoma who received surgery and irradiation limited to the posterior fossa. Mean IQ scores evaluated with Wechsler IQ tests showed an overall moderate impairment but mean FSIQ remained in the normal range. While some patients had significant impairments in their PIQ scores, no significant impairment was seen in the VIQ score. Compared to previously published outcome scores of children who received whole brain irradiation these impairments were limited [16]. In our study IQ measures showed a high variability at all evaluated time points. Within the group which could be evaluated longitudinally (19/23), there was no trend for deterioration of intellectual functioning over time. This finding is in contrast to studies on medulloblastoma patients receiving CSI, who showed a deterioration of intellectual functions for years after the completion of therapy [7,23-25], and it is supporting the data by Merchant et al, who evaluated the influence of conformal RT for the treatment of ependymoma to intellectual outcome. With radiation limited to the tumour volume, they described stable intellectual functions with a median follow up of 3 years [3]. A recent report from Fouladi et al. also showed no significant longitudinal decline of IQ measures of patients with infratentorial tumours who received local RT compared to CSI [26].

With local posterior fossa irradiation, large parts of the supratentorial hemispheres and white matter are spared from irradiation, which might explain that there is no gradual IQ drop as it is seen after whole brain irradiation. Our data support this hypothesis since children receiving conformal RT tended to show a better outcome than those treated with opposite lateral beams. Merchant et al analysed with radiation dosimetry models that volume and dose of irradiation of the supratentorial brain was predictive for IQ in localised infratentorial ependymoma [27], which supports the above mentioned concept.

In our study very low IQ results were only observed in young children, but there was no statistical significant correlation between age at irradiation and intellectual outcome within our limited study population. While in different studies on patients who received CSI the progressive deterioration of neuropsychological functions was more pronounced in younger children [28,29], in our study there was no significant age dependent decrease of intellectual functions, and IQ results achieved at baseline evaluation and at follow up evaluations showed no difference. There was however a trend for worse outcome in younger children. But larger sample may be necessary to show a clear difference in outcome. Therefore we suppose that local posterior fossa RT is unlikely to be the only factor causing worse neuropsychological outcome in young children. As in our study, there were only 3 children, who were treated with radiotherapy before the age of 3, we are not able to draw definite conclusion about the role of very young age in the intellectual deficit after posterior fossa RT.

The intellectual deficits reported in our study might reflect also damages accrued by the disease and surgical therapy. This concept is supported by studies showing that IQ is impaired in survivors of posterior fossa tumours even in the absence of radiotherapy [22,30,31] suggesting contributing factors of the disease itself and surgical therapy on neuropsychological outcome.

Looking for other factors which could predict for low IQ performance we found a strong correlation of IQ and cerebellar damage, measured by the presence of cerebellar syndrome at the time of neuropsychological evaluation. A pivotal role of cerebellar damage for the presence of intellectual deficits was described recently by our group in a study evaluating 76 children with posterior fossa tumours, where disease factors and surgical complications were exceeding the negative effects of adjuvant therapy. Interestingly persistent cerebellar syndrome was more frequent in the latter described study population (51%) which consisted mainly of medulloblastoma patients, compared to this study (26%) [32].

Another factor which showed a trend to negatively influence the intellectual outcome in our study was hydrocephalus at presentation. Merchant et al analysed ventricular enlargement by MRI at different time points in patients with infratentorial ependymoma. They stated a relevant influence of hydrocephalus on intellectual achievement, while they postulated that the negative influence of ventricular enlargement was reversible if ventricular size decreases over time [33]. Since there was no regular longitudinal measurement in our cohort, we could not evaluate the influence of change in ventricular size.

Concerning the neuropsychological profile, the subtest analysis of the Wechsler IQ test showed impairments concerning processing speed and visual motor skills. Individual patients had reduced scores in subtests reflecting visual perceptive and memory problems, whereas the overall performance on these tasks was just slightly decreased. The impaired reading capacities may reflect problems with speed and possibly also visual problems. The battery of additional tests showed an increase of the lag between reading age and chronological age over time since therapy in all tested patients, which is likely due to a reduced rate of skill acquisition. This highlights that tests exploring reading skills are usefull read-outs for the monitoring of the outcome of these children. Furthermore there were individual deficits in visuospatial capacities, in attention and in memory functions. Similar deficits are described in patients suffering cerebellar astrocytoma [34-36] and medulloblastomas [16]. Although there seems to be a common spectrum of deficits, we like to emphasis, that there was a wide variability and that we couldn't detect a clear pattern of impairment. Possibly the diversity of impairments reflects the differing influence of perioperative and intraoperative damage done to the brain.

Conclusion

In conclusion, our data show that intellectual functions are moderately impaired in survivors of infratentorial ependymoma. Compared to children who received CSI, neuropsychological outcome was favourable in children who received only local posterior fossa radiotherapy.

There was a wide variability of the level of intellectual achievements and specific impairments. The high variability is likely to be caused by cerebellar and cerebral damage reflecting the influence of disease and surgery-related factors. Studies looking at therapy optimization should include neurological and cognitive evaluations to further describe the influencing factors and possible mechanisms of intellectual impairment. This report also indicates that further refinement of adjuvant therapy for ependymoma should include means to deliver radiation with limited fields and better chemotherapies to defer radiotherapy in the youngest patients. Children should also be always monitored for neurological and neuropsychological outcome to ensure that they get the necessary support for rehabilitation.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

KVH participated in the design of the study, collected the data, performed the statistical analysis and drafted the manuscript.

VK conceived the study, participated in its design and coordination, performed and evaluated the neurocognitive tests, and helped in drafting the manuscript.

JLH participated performed the irradiation and evaluated the radiotherapy files.

CK conceived the study and followed the patients clinically.

GD conceived the study, participated in its design and coordination.

JG conceived the study, participated in its design and coordiantion, helped to collect the data, to perform the statistical analysis, and to draft the manuscript.

All authors read and approved the final manuscript.

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NEURO-ONCOLOGY

A new approach to ependymoma subtyping

Trimethylation of lysine 7 on histone H3 (H3K27me3), as detected by immunohistochemistry, can differentiate subgroups of childhood ependymomas with markedly different prognoses, according to new research published in *Acta Neuropathologica*. This relatively simple test could aid the tailoring of treatment to ensure that children with low-risk tumours are not subjected to unnecessarily aggressive therapy.

"Childhood posterior fossa ependymomas (EPN_PF) are molecularly segregated into group A and group B on the basis of DNA methylation signatures," explains Sriram Venneti, who led the new study with Alexander Judkins. "Patients with EPN_PFA exhibit a dismal prognosis and respond best to complete resection combined with radiotherapy, whereas patients with EPN_PFB have a better prognosis and do not show recurrence even without radiotherapy."

Currently, these tumour subtypes can only be reliably distinguished through the use of DNA methylation arrays, which are expensive and require specialist resources. By contrast, the new approach was based on immunohistochemistry, which is available in most clinical laboratories. Judkins, Venneti and colleagues had previously observed global loss of H3K27me3 in a subset of EPN_PF that carried a poor prognosis, and they hypothesized that H3K27me3 might serve as a surrogate measure of tumour methylation status.

H3K27me3 immunohistochemistry was initially performed on tumour sections from 112 patients, 72 with EPN_PFA and 40 with EPN_PFB. The assessors were blinded to the methylation status of the tumour, and H3K27me3 positivity was defined as staining in more than 80% of cells. The researchers found that all the EPN_PFA tumours were H3K27me3-negative, and 97.5% of the EPN_PFB tumours were H3K27me3-positive.

The team went on to test tumour samples from 230 patients with EPN_PF to explore the prognostic value of H3K27me3 status. Negativity for H3K27me3 was shown to be associated with a significant reduction in overall and progression-free survival, providing further evidence that H3K27me3 is a viable stratification marker for EPN_PF.

"Our work provides evidence that global reduction in H3K27me3 is a robust and cost-effective molecular surrogate for EPN_PFA," concludes Venneti. "H3K27me3 immunohistochemistry could be implemented to guide molecular-based therapies, reducing morbidity in children with low-risk tumours while identifying patients who require more-intensive treatment."

Heather Wood

> "H3K27me3 immunohistochemistry could be implemented to guide molecular-based therapies"

ORIGINAL ARTICLE Panwalkar, P. *et al.* Immunohistochemical analysis of H3K27me3 demonstrates global reduction in group-A childhood posterior fossa ependymoma and is a powerful predictor of outcome. *Acta Neuropathol.* http://dx.doi.org/10.1007/s00401-017-1752-4 (2017)

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Clinical Investigation

Neuropsychological Outcome of Children Treated for Standard Risk Medulloblastoma in the PNET4 European Randomized Controlled Trial of Hyperfractionated Versus Standard Radiation Therapy and Maintenance Chemotherapy

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HC-C and AR are co-first authors.

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Summary

In the PNET4 randomized controlled treatment trial, cognitive performance of children and young adults with standard risk medulloblastoma allocated to undergo hyperfractionated radiation therapy (HFRT) followed by standard chemotherapy was compared to that of subjects allocated to receive standard radiation therapy (STRT) followed by standard chemotherapy regimen. Treatment with HFRT was associated with a trend toward better verbal outcomes in children younger than 8 years of age at diagnosis, but no significant differences in other cognitive measurements.

Purpose: In the European HIT-SIOP PNET4 randomized controlled trial, children with standard risk medulloblastoma were allocated to hyperfractionated radiation therapy (HFRT arm, including a partially focused boost) or standard radiation therapy (STRT arm), followed, in both arms, by maintenance chemotherapy. Event-free survival was similar in both arms. Previous work showed that the HFRT arm was associated with worse growth and better questionnaire-based executive function, especially in children <8 years of age at diagnosis. Therefore, the aim of this study was to compare performance-based cognitive outcomes between treatment arms.

Methods and Materials: Neuropsychological data were collected prospectively in 137 patients. Using the Wechsler Intelligence Scales, Kaufman Assessment Battery for Children, and Raven's Progressive Matrices, we estimated full-scale intelligence quotient (FSIQ) and, when available, verbal IQ (VIQ), performance IQ (PIQ), working memory index (WMI), and processing speed index (PSI).

Results: Among the 137 participants (HFRT arm n = 71, STRT arm n = 66, 63.5% males), mean (±SD) ages at diagnosis and assessment respectively were 9.3 (±3.2) years of age (40.8% < 8 years of age at diagnosis) and 14.6 (±4.3) years of age. Mean (±SD) FSIQ was 88 (±19), and mean intergroup difference was 3.88 (95% confidence interval: −2.66 to 10.42, $P = .24$). No significant differences were found in children >8 years of age at diagnosis. In children <8 years of age at diagnosis, a marginally significant trend toward higher VIQ was found in those treated in the HFRT arm; a similar trend was found for PSI but not for PIQ, WMI, or FSIQ (mean intergroup differences were: 12.02 for VIQ [95% CI: 2.37-21.67; $P = .02$]; 3.77 for PIQ [95% CI: −5.19 to 12.74; $P > .10$]; 5.20 for WMI [95% CI: −2.07 to 12.47; $P > .10$]; 10.90 for PSI [95% CI: −1.54 to 23.36; $P = .08$]; and 5.28 for FSIQ [95% CI: −4.23 to 14.79; $P > .10$]).

Conclusions: HFRT was associated with marginally higher VIQ in children <8 years of age at diagnosis, consistent with a previous report using questionnaire-based data. However, overall cognitive ability was not significantly different.

Introduction

Extensive research has consistently recognized longitudinal impairments associated with medulloblastoma (MB), the most frequent malignant brain tumor of the central nervous system (CNS) during childhood (1-3). Standard treatment includes surgical resection, postoperative radiation therapy (RT) and adjuvant chemotherapy. MB survivors experience significant health-related problems, namely endocrine and growth morbidity and reduced fertility (4, 5), second tumors (6), hearing loss (7), and long-term neurological deficits (8-10). Among the major complications arising from the tumor and its treatment, predominantly RT and especially when given with chemotherapy, are the high rate of neurocognitive deficits, possibly attributable to the deleterious effects of radiation on white matter development (11, 12). MB survivors typically achieve scores below the mean for age-matched peers in measurements of intelligence quotient (IQ), verbal and performance IQ (VIQ, PIQ), processing speed index (PSI), working memory index (WMI), and sustained attention (13-16). Importantly, deficits in these core cognitive domains tend to worsen over time (16-18). To improve tumor control and quality of survival, hyperfractionated RT (HFRT) capitalizes on the fact that proliferating tumor cells are more sensitive than normal tissue to a given dose of RT if it is administered in a larger number of fractions of smaller size. This enhances the antitumor effects of RT while sparing normal tissues (19-22). Compared with standard fractionated RT (STRT), HFRT can be used either to maintain a given antitumor effect while decreasing unwanted effects on the CNS or to increase the antitumor effect without increasing unwanted effects on the CNS. Previous uncontrolled studies by Carrie et al (22) and Gupta et al (23) reported higher posttreatment full-scale IQ in patients receiving twice-daily HFRT than that in historical controls receiving once-daily STRT. However, using historical controls instead of a controlled experimental randomized design limits interpretation of these data.

Furthermore, we could hypothesize that the lack of a significant IQ decline could be related to improved quality of posterior fossa irradiation, even in STRT, with less radiation to the temporal and occipital lobes.

The HIT-SIOP PNET4 phase 3 European randomized controlled treatment trial (RCT) for MB was designed to investigate the hypothesized biological advantage of HFRT relative to STRT. Five-year event-free survival was similar between the 2 arms (24). A subsequent cross-sectional study

(25) assessed quality of survival through use of questionnaires of executive function, health status, behavior, health-related quality of life (HRQoL), and growth. That study indicated significantly better executive functioning for children and young adults treated with HFRT than those treated with STRT, in accordance with the reports by Carrie et al (22) and Gupta et al (23). No other significant advantage of HFRT was observed for health status, behavior, or HRQoL, and patients receiving HFRT had significantly greater deficit in height gain from diagnosis. Differences between treatment arms regarding executive functioning and growth impairment were significantly greater in patients less than 8 years of age at diagnosis (25). The present study aimed to complement these findings by examining effects of HFRT and STRT on cognitive outcomes in PNET4 survivors as assessed directly using age-appropriate measurements of intellectual ability.

Methods and Materials

Patients

A population of 338 participants (4-21 years of age) from 10 countries was randomly assigned to either HFRT or STRT for M0 MB between 2001 and 2006.

STRT consisted of 23.4 Gy to the craniospinal axis and 54 Gy to the posterior fossa given over 42 days in 30 daily fractions of 1.8 Gy for 5 days per week. HFRT was given in 68 fractions: 1.0 Gy twice per day with an 8-hour interval between fractions, given over 48 days. In the HFRT arm, the total craniospinal dose was 36 Gy, and the whole posterior fossa dose was 60 Gy, with a further focused boost of 8 Gy to the tumor bed. In both arms, a maximum of 8 doses of vincristine, 1.5 mg/m^2 (maximum 2 mg), was given once per week during RT, followed by adjuvant chemotherapy. Eight cycles of cisplatin, 70 mg/m^2 intravenously, lomustine, 75 mg/m^2 on day 1, and vincristine, 1.5 mg/m^2 intravenously, on days 1, 8, and 15, began 6 weeks after the end of RT, with a 6-week interval between each cycle (24).

Neuropsychological assessment was not part of the original PNET4 protocol, which consisted of questionnaire assessments alone. Four of the original 10 participating countries had collected prospective or cross-sectional data regarding cognitive outcomes between 2004 and 2013. The 216 event-free patients from France, Germany, Italy, and Sweden who remained in remission during the 9-month period of the cross-sectional follow-up study conducted by Kennedy et al (25) were eligible for the present analyses, and of these subjects, 137 (63.4%) had data regarding cognitive outcomes (71 of 107 [66.4%] HFRT; 66 of 109 [60.6%] STRT). A subgroup of 35 of 137 participants (25.6%) had had at least 2 assessments of the same cognitive outcomes (mean delay between evaluations was 2.9 years). For this subgroup, the results of the last assessment were considered for the cross-sectional analyses.

Procedure

The present study conformed to ethical requirements of all participating countries. Written consent was obtained by the treating clinician to conduct cognitive assessments.

Measurements

Cognitive measurements differed according to participants' ages and countries. Patients were generally evaluated with age-appropriate Wechsler Intelligence Scales (26-29). In Germany, age-appropriate Raven's Coloured Matrices (30) and Standard Progressive Matrices (31), the vocabulary subtests of the Wechsler Scales or Kaufmann Assessment Battery for Children (K-ABC I-II, Riddles subtest), and the Number Recall test of the K-ABC I-II were used to assess children's performance and verbal and working memory abilities, respectively (32). Five measurements of cognitive ability were derived from these assessments: Full Scale IQ (FSIQ), VIQ, PIQ, WMI, and PSI (for France, Italy, and Sweden only).

In addition, an adapted version of the Medical Examination form (33) addressed to the clinicians and information from the Medical Educational Employment and Social (MEES) questionnaire addressed to parents and adult participants (33) provided information on participant's baseline demographics and secondary outcomes.

Statistical analysis

Effects of treatment allocation on cognitive measurements were evaluated through regression models: first for the whole group and, second, by age category at diagnosis (<8 or ≥ 8 years of age), similar to those in the study by Kennedy et al (25). At each step, sex, interval between diagnosis and assessment, presence of postoperative complications (or, alternatively, presence of cerebellar mutism) were introduced in the regression models, together with treatment allocation.

Statistical significance testing was 2-tailed with a .003 significance level to adjust for multiple testing (Bonferroni correction). However, results with a P value of $<.05$ and a P value of $>.003$ were categorized as marginally significant. For longitudinal analyses, mean differences between first and second assessments were compared to zero using paired Student t tests.

Results

Group comparisons between participants and nonparticipants

Participants with cognitive outcomes and nonparticipants were similar regarding sex, treatment allocation, and interval between diagnosis and cognitive assessment.

However, nonparticipants tended to be older at diagnosis (mean = 11.89 vs 9.31, $P<.01$), suggesting that older participants had a lower probability of receiving a cognitive assessment.

Demographic and baseline characteristics for participants

Participants who received HFRT and STRT were similar regarding sex, age at diagnosis, age at assessment, and interval between diagnosis and assessment (Table 1). Regarding pre- and postoperative characteristics, the 2 groups were also similar except that a slightly higher rate of postoperative complications and extraocular movement deficits were observed in participants receiving HFRT compared to those receiving STRT.

Cognitive outcomes at posttreatment evaluation for the whole group of participants

Distribution of the 5 cognitive outcomes indicated considerable variability, with scores ranging from 40 to 145. Using a cutoff point of −2 SD, 12.4% of the FSIQ, 8% of VIQ, 12.5% of PIQ, 7% of WMI, and 33.7% of PSI scores were in the lower extreme range.

Cognitive outcomes were similar according to sex, country, age at diagnosis, age at assessment, and interval between diagnosis and assessment. Mean scores tended to be lower ($P<.05$ in all cases) in the presence of postoperative ataxia: FSIQ (85.01 versus 94.52), VIQ (89.76 versus 99.4), WMI (89.34 versus 95.29) and PSI (73.82 versus 85.54). Postoperative cerebellar mutism was associated with lower mean PIQ (79.33 versus 89.09) and PSI (65.83 versus 81), and extra ocular movements deficits were associated with lower mean VIQ (90.37 versus 98.27, $P<.05$ in all cases). The presence of any perioperative complications, including cerebellar mutism, was also associated with lower mean scores of PSI (68.75 versus 81.14, $P=.04$). No other differences were observed for the remaining postoperative characteristics. Due to these associations, the effects of perioperative complications (or alternatively, cerebellar mutism) were controlled for in the regression analyses described below.

Effects of treatment on cognitive outcomes

Country by treatment interactions were not significant. In univariate analyses, all cognitive outcomes were similar between HFRT and STRT arms (Table 2). However, PSI tended to be higher in the HFRT arm (difference of 7.9 [95% confidence interval [CI]: −0.14 to 15.9], $P=.05$). In younger participants (<8 years of age at diagnosis), VIQ tended to be higher in the HFRT arm (difference of 12.02 [95% CI: 2.4-21.7], $P=.02$). For the remaining measurements, no other differences were observed between arms when age at diagnosis was considered.

The results of regression analyses paralleled those of univariate analyses described above. In the full sample, allocation to HFRT showed a marginally significant trend to higher PSI scores ($F = 4.74$, $P=.03$), and in participants whose age at diagnosis was <8 years, it showed a marginally significant association with higher VIQ scores ($F = 7.1$, $P=.01$). No other significant effect or strong trend associated with treatment allocation was found on the remaining cognitive outcomes, either for the total sample or for the subgroup of participants whose age at diagnosis was >8 years. These same analyses were redone after exclusion

Table 1 Descriptive statistics of the study's participants according to treatment allocation

	HFRT				STRT			
	N	M	±SD	Range	N	M	SD	Range
Demographic characteristic (ref)								
Age at diagnosis (y)*	71	9.1	3.23	4-17.6	66	9.5	3.14	4.3-17.3
Age at diagnosis (<8 y) (%)†	31	(43.7)	-	-	25	(37.9)	-	-
Age at assessment*	71	14.3	4.48	6.2-24.9	66	14.9	4.11	6.1-24.7
Interval from diagnosis (y)*	71	5.2	2.81	0.08-9.9	66	5.4	2.53	0.58-10.5
No. of males (%)†	46	(64.8)	-	-	41	(62.1)	-	-
No. of premorbid developmental impairments (%)†	2	(2.8)	-	-	4	(6.1)	-	-
Postoperative status								
No. of postoperative complications (%)†	10	(14.1)	-	-	3	(4.6)	-	-
No. with impaired consciousness (%)†	0	(0)	-	-	2	(3.1)	-	-
No. with impaired nerve III (%)†	35	(53)	-	-	23	(37.7)	-	-
No. with ataxia (%)†	34	(58.6)	-	-	36	(64.3)	-	-
No. with cerebellar mutism (%)†	6	(8.5)	-	-	3	(4.6)	-	-

Abbreviations: HFRT = hyperfractionated radiation therapy; M = mean; SD = standard deviation; STRT = standard radiation therapy.

* Student *t* test.

† Khi-2 de Mantel-Haenszel.

of participants with perioperative complications and cerebellar mutism, and results remained unchanged.

Longitudinal analyses

Thirty-five participants (25.6%) underwent 2 cognitive assessments. These participants were characterized by longer intervals between diagnosis and the last assessment ($P = .01$) and higher rates of cerebellar mutism ($P = .03$). None of the remaining baseline characteristics was different between participants with cognitive assessment performed at 2 time points and those who had data at 1 time point. The last assessment was performed at a mean interval from the first evaluation of 2.9 years, with the mean interval being similar in both arms.

Cognitive measurements did not differ significantly between time point 1 and time point 2 (Table 3). However, there was a tendency for PIQ to increase from the first to the second assessment (difference of 5.9 [95% CI: 1.1-10.7], $P = .019$).

Moreover, the difference between cognitive outcomes on the 2 occasions of testing, derived by [Time 2 − Time 1] did not differ between HFRT and STRT arms (Table 4).

Discussion

The results suggest that treatment allocation contributed to explain specifically the VIQ scores of participants less than 8 years of age at diagnosis. For this subgroup, those allocated to the HFRT arm had higher VIQ scores than participants in the STRT arm. Those allocated to HFRT also had a strong trend, falling short of statistical significance, to higher PSI scores in the reduced number of participants completing this test, both in the sample as a whole and in those less than 8 years of age at diagnosis. These effect sizes were large for VIQ and medium for PSI. Other differences between treatment arms for the remaining cognitive measurements were small and nonsignificant. Longitudinal results, although unpowered, indicated no significant effects of treatment allocation on the cognitive outcomes, neither at Time 1 and Time 2, nor from the first to the second assessment.

In the present study, treatment was randomly allocated, and follow-up rates for the cognitive assessment were reasonable (63%), which allowed composition of 2 heterogeneous groups regarding IQ outcomes. However, some limitations should be taken into account. The measurements used to assess cognitive performance differed according to country and, thus, might reflect distinct underlying constructs of cognitive ability. This limitation justifies caution in the interpretation of the results and generalization of these findings. Importantly, these results highlight the urgent need for an international consensus in the measurements used to assess cognitive ability (34). Moreover, participants were slightly younger at diagnosis than nonparticipants. However, this difference is not likely to have biased our results, as the only significant differences were observed for the subgroup of participants with younger age at diagnosis. Furthermore, the analysis per age category had not been planned in the initial protocol but was carried out in order to bring complementary information to confirm or refute the observation by Kennedy et al (25) of benefits of HFRT to executive function. Finally, results of the regression analyses remained unchanged even when controlling for the marginally significant excess of perioperative complications, namely cerebellar mutism in the HFRT arm.

Table 2 Mean differences in cognitive outcomes according to treatment allocation and age at diagnosis

	HFRT				STRT				
Outcome	N	M	SD	Range	N	M	SD	Range	P*
FSIQ	71	90.3	19.7	40-137	66	86.4	18.9	40-122	.24
FSIQ (age >8)	40	90.7	21.8	40-137	41	87.6	19.3	40-118	.49
FSIQ (age <8)	31	89.7	16.8	65.5-128.5	25	84.5	18.6	40-122	.27
VIQ	58	96.3	17.1	55-128	55	92.4	20.6	43-145	.28
VIQ (age >8)	31	95.8	17.4	55-128	34	97.1	22.1	47-145	.79
VIQ (age <8)	27	96.8	17.1	60-126	21	84.8	15.7	43-112	.02
PIQ	70	89.7	21	40-140	66	87.1	17.1	40-122	.43
PIQ (age >8)	39	90.4	24.6	40-140	41	88.3	16.8	40-118	.66
PIQ (age <8)	31	88.9	15.8	65-128.5	25	85.1	17.7	41-122	.40
WMI	68	92.3	13.8	55-124	61	89.1	15.3	55-120	.21
WMI (age >8)	38	90	14.8	55-124	39	88.6	16.1	56-120	.69
WMI (age <8)	30	95.2	11.9	65-118	22	90	14.2	55-110	.16
PSI	29	83.3	14.7	50-112	28	75.4	15.5	50-100	.05
PSI (age >8)	18	81.1	15.6	50-112	17	75.1	16.3	50-100	.27
PSI (age <8)	11	86.8	13.1	62-103	11	75.9	14.8	50-96	.08

Abbreviations: FSIQ = full scale intelligence quotient; PIQ = performance intelligence quotient; PSI = processing speed index; VIQ = verbal intelligence quotient; WMI = working memory index. Other abbreviations as in Table 1.

* Student t test.

Table 3 Time interval and differences in cognitive outcome scores between first and second assessments

	Time 2 to Time 1				
Parameter	N	Mean	±SD	Range	*P**
Interval between assessment (y)	32	2.9	1.8	0.92-7	-
FSIQ	33	0.18	10.3	−23 to 18	.92
VIQ	34	−1.7	13.7	−31 to 25	.47
PIQ	35	5.9	14.4	−25 to 26	.02
PSI	26	−3.1	12.8	−28 to 20	.22

Abbreviations are as in Table 2.
Due to missing data, WMI was not considered in these analyses.
* Paired Student *t* test.

The encouraging survival rates of patients treated for MB (24) has led researchers to focus on long-term consequences of these tumors and their treatment on neurocognitive performance, most often focused on overall intellectual ability. Previous research has reported that MB survivors are at increased risk for cognitive impairment, with progressive decline in IQ stabilizing typically within 1 to 2 SD below the mean of typical age-matched developing peers 5 years after treatment (13, 17, 35, 36). Results of the present study align well with those of previous reports. Collectively, the mean scores of all the survivors' IQ measurements allocated either to STRT or HFRT arms fell 1 SD below the mean, and approximately 10% of the participants showed performances 2 SD below the mean regardless of treatment. MB survivorship carries lingering effects on the patient's intellectual functioning, with significant implication for other domains of quality of survival, namely academic achievement (36, 37). An evidence-based conceptual model in which IQ deficits of MB survivors arise secondary to underlying impairments in core cognitive skills such as attention, processing speed, and working memory (36, 37) has been proposed. Deficits observed in PSI for the full sample support this contention and suggest that these core cognitive skills might represent developmental precursors to overall delays in general cognitive ability. However, the considerable variability of FSIQ (range, 40-140, 25% of survivors with IQ $\geq$ 100) implies that some patients do not follow the expected pathway of neurocognitive impairment in accordance with Palmer's conclusion (37).

PNET4 is the first RCT comparing IQ outcomes between patients who received HFRT versus those who received STRT, and this study aimed to explore further the effect of treatment on cognitive function recently reported by Kennedy et al in PNET4 participants (25). Our findings provide support for their observation that the effect of RT on executive function is moderated according to treatment because cognitive skills pertaining to information processing speed, working memory, and attention represent the core developmental precursors of later intellectual and academic function (37).

Taken together with those of Kennedy et al, our findings suggest that the HFRT arm might result in more preserved cognitive function in children less than 8 years of age at diagnosis as suggested by previous reports of the greater vulnerability of these children to the adverse effects of treatment on neurocognitive outcomes (17, 36). These results also parallel those reported by Carrie et al (22) and Gupta et al (23) that children treated with HFRT displayed more preserved cognitive functions compared with those of historical controls. IQ deficits in MB survivors are probably due to a diminished ability to acquire new information, rather than the loss of previously acquired knowledge (15). Applied to our results, the diminished impact of HFRT on young children's ability to acquire new information represents a plausible explanation for their superior VIQ scores compared with those of STRT. Moreover, we also must account for the fact that differences between the 2 arms were not only the fractionation but also the partially more focused boost in the HFRT arm, which could possibly have led to an increased protection of the temporal and occipital lobes. The more focused posterior fossa and primary site boost will most likely become a standard procedure (38).

Moreover, our results extend the findings reported by Kennedy et al (25), who presented evidence that survivors allocated to HFRT arm showed better scores on the Behavior Rating Inventory of Executive Function (BRIEF) global executive composite score than the group that had received STRT. Interestingly, Vriezen and Pigott (39) reported a significant correlation between VIQ and the Metacognition index of the BRIEF questionnaire, (ie the cognitive subscales of this questionnaire), in a group of children with traumatic

Table 4 Mean comparisons of time 1 and time 2 cognitive outcomes by treatment allocation

	Time 1						Time 2						Time 2 - Time 1						
	HFRT			STRT			HFRT			STRT			HFRT			STRT			
Outcome	N	M	SD	N	M	SD	N	M	SD	N	M	SD	N	M	SD	N	M	SD	*P**
FSIQ	16	95.3	14.9	18	86.4	13.9	16	96.8	19.1	17	86.5	15.6	16	1.6	12.3	17	−1.1	8.2	.47
VIQ	16	103.6	15.1	18	90.8	15	16	101.2	17.8	18	89.7	20	16	−2.4	15.1	18	−1.1	12.8	.78
PIQ	16	88.4	16.9	19	85.5	14.9	16	98.7	19	19	87.8	11.9	16	10.3	14.7	19	2.3	13.4	.10
PSI	13	89.5	17.7	13	84.3	16.4	14	86.8	13.9	14	77	15.9	13	−1.1	11.9	13	−5.2	13.8	.42

Abbreviations are as in Table 2.
* Paired Student *t* test.

brain injury. However, as argued by Kennedy et al (25), although HFRT survivors obtained higher executive functioning scores than STRT survivors, self- or parental reports of behavioral adjustment, HRQoL, or health status were comparable between treatment groups. As concluded by Chevignard et al (40), although the use of questionnaires might complement information about executive functioning, they might rely on a more global frame of everyday functioning and provide less information regarding core cognitive processes. Furthermore, in the previous study (25), HFRT survivors presented a greater decrement in height and reported more use of hearing aids. Differences in the use of hearing aids does not allow us to rule out the hypothesis that the better VIQ scores of young children allocated to HFRT could be attributed to more appropriate referrals to health services in case of hearing loss.

The longitudinal analyses indicated that IQ outcomes were not significantly different between the first and the second assessments, neither for the full sample nor for each treatment group. On one hand, these results follow the findings of Gupta et al (25), who indicated the absence of any decreasing trend on measurements of FSIQ, VIQ, and PIQ for patients allocated to HFRT, compared with those of historical controls. On the other hand, the results of the analyses performed with the full sample contrasts with an established body of literature documenting an IQ decline in MB survivors (22, 37), suggesting a possible overall improvement of MB treatments, regardless of RT fractionation, as suggested earlier regarding the protection of the temporal and occipital lobes. Nevertheless, our results should be interpreted with caution. The small number of patients with 2 available assessments collected prospectively (mostly in 2 countries) coupled with the short time between assessment and diagnosis limited the ability of the study to detect clinically important differences between treatment arms, especially when considering subgroups according to the age at diagnosis.

Conclusions

In conclusion, this study provides some support to previous observations in the same RCT regarding possible benefits of HFRT, compared to STRT in the PNET4 study, on young children's verbal ability. Although it does not demonstrate a clear advantage of HFRT in the regimen used, that regimen, in comparison to STRT, was designed to be more effective on tumor cells and iso-effective in its effects on the CNS. The hypothesis that a lower dose regimen of HFRT—designed to be iso-effective on tumor cells with decreased adverse effects on the CNS—would bring clinically important benefits deserves further exploration, with children less than 8 years of age at diagnosis being the group most likely to benefit. Furthermore, this study reports detailed findings in patients treated with STRT, against which newer treatment approaches could be compared, such as lower craniospinal irradiation doses and a tumor bed rather than whole posterior fossa boost.

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Quality of Survival and Growth in Children and Young Adults in the PNET4 European Controlled Trial of Hyperfractionated Versus Conventional Radiation Therapy for Standard-Risk Medulloblastoma

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Summary

We report on quality of survival in the PNET4 RCT

Purpose: To compare quality of survival in "standard-risk" medulloblastoma after hyperfractionated radiation therapy of the central nervous system with that after standard radiation therapy, combined with a chemotherapy regimen common to both treatment arms, in the PNET4 randomised controlled trial.

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comparing hyperfractionated radiation therapy with standard radiation therapy, combined with a chemotherapy regimen common to both treatment arms, in children and young adults with medulloblastoma. We observed a possible benefit of hyperfractionated radiation therapy to executive function but greater restriction of spinal growth and no significant benefit to health status, behavior, or quality of life.

Methods and Materials: Participants in the PNET4 trial and their parents/caregivers in 7 participating anonymized countries completed standardized questionnaires in their own language on executive function, health status, behavior, health-related quality of life, and medical, educational, employment, and social information. Pre- and postoperative neurologic status and serial heights and weights were also recorded.

Results: Data were provided by 151 of 244 eligible survivors (62%) at a median age at assessment of 15.2 years and median interval from diagnosis of 5.8 years. Compared with standard radiation therapy, hyperfractionated radiation therapy was associated with lower (ie, better) *z*-scores for executive function in all participants (mean intergroup difference 0.48 SDs, 95% confidence interval 0.16-0.81, $P = .004$), but health status, behavioral difficulties, and health-related quality of life *z*-scores were similar in the 2 treatment arms. Data on hearing impairment were equivocal. Hyperfractionated radiation therapy was also associated with greater decrement in height *z*-scores (mean intergroup difference 0.43 SDs, 95% confidence interval 0.10-0.76, $P = .011$).

Conclusions: Hyperfractionated radiation therapy was associated with better executive function and worse growth but without accompanying change in health status, behavior, or quality of life.

Introduction

Survivors of childhood central nervous system (CNS) tumors have shown impairments of quality of survival (QoS) in multiple domains of function, persisting or worsening many years after completion of treatment (1-5). Medulloblastoma survivors, particularly if treated before age 8 years, have impaired health-related quality of life (HRQoL)—a multidimensional concept that includes physical, social, cognitive, and emotional functioning (6-8), with underlying difficulties in neurocognition, attention, executive function (9-13), growth, fertility, thyroid function (14-18), educational attainment, employment, and formation of long-term relationships. Rates of stroke, second tumors, and premature aging are increased (14, 19-25).

The HIT-SIOP PNET4 phase 3 European randomized controlled treatment trial (RCT) for medulloblastoma compared hyperfractionated radiation therapy (HFRT) comprising 2 smaller fractional doses of 1 Gy per day, separated by an interval of at least 8 hours, with conventionally fractionated standard treatment (STRT) of 1 1.8-Gy fraction per day. Smaller fractional radiation therapy doses produce a redistribution of proliferating tumor cells, with some cells entering a radiosensitive stage and thus providing a better tumor cell kill. Nonproliferating tissues, such as normal brain, should be spared this effect of redistribution and thereby potentially be protected by HFRT according to a linear-quadratic formula relating fraction size to biological effect (26). This sparing effect of HFRT may account for the higher full-scale intelligence quotient after treatment with twice-daily HFRT without chemotherapy than that observed in historical controls treated with once-daily STRT previously reported by Carrie et al (27) and Gupta et al (28) in medulloblastoma survivors (29). These studies were not, however, experimental in design and relied on historical controls, rather than random allocation of treatment, to provide comparison groups.

The HFRT regimen used in PNET4 was predicted to be biologically more effective in its effects on tumor tissue than STRT, but this was not supported by a 5-year event-free survival rate (0.79 ± 0.02) in both treatment arms (30). It was also predicted that the HFRT in PNET4 would produce long-term CNS effects that were either similar or possibly, by reduction of the posterior fossa HFRT boost outside the tumor bed, less deleterious than those observed after STRT.

In-depth assessment of CNS outcomes in multicenter clinical trials has typically been associated with ascertainment rates below 30% (31) and attrition bias (1). Booklets of standardized questionnaires for completion by participants and parents, however, achieved ascertainment rates of 73% in United Kingdom survivors enrolled in the PNET3 study of medulloblastoma at 7 years from diagnosis (32). PNET4 provided an opportunity to establish whether cross-cultural adaptations of the same questionnaires could be applied across Europe. We report here on a cross-sectional follow-up study of the CNS and endocrine outcomes in surviving PNET4 participants.

Methods and Materials

Patients

Between 2001 and 2006, 338 participants aged 4-21 years in 10 countries had been randomly allocated to receive either HFRT or STRT treatment trial for M0 medulloblastoma in PNET4. Standard radiation therapy comprised 23.4 Gy to the craniospinal axis and 54 Gy to the posterior fossa and was given over 42 days in 30 daily fractions of 1.8 Gy for 5 days per week. Hyperfractionated radiation therapy was given in 68 fractions: 1.0 Gy twice per day with an 8-hour interval between fractions, given over 48 days. The total craniospinal dose was 36 Gy, and the whole posterior fossa dose was 60 Gy, with a further boost to 68 Gy to the tumor bed. In both treatment arms a maximum of 8 doses of vincristine 1.5 mg/m^2 (maximum 2 mg) was given once per week during radiation therapy and adjuvant chemotherapy. Eight cycles of cisplatin 70 mg/m^2 intravenously, lomustine 75 mg/m^2 on day 1, and vincristine 1.5 mg/m^2 intravenously on days 1, 8, and 15, began 6 weeks after the end of RT, with a 6-week interval between each cycle (30). The 244 survivors from France, Germany, Italy, The Netherlands, Spain, Sweden, and the United Kingdom who remained in remission during the 2010-2011 9-month cross-sectional follow-up study period in the QoS study were eligible for the present QoS study.

Procedure

Written consent for QoS data collection had been obtained as part of the PNET4 treatment trial by the treating clinician, who provided

age-appropriate booklets of questionnaires to eligible participants. The study was approved by ethics committees in all participating countries.

Outcome measures

The 4 principal QoS outcome measures were z-scores on standardized age-appropriate questionnaires. These assessed executive function in everyday life, health status, behavioral difficulties, and HRQoL. In participants aged <18 years at assessment, the questionnaires were parent-report versions of the Behavior Rating Inventory of Executive Function (BRIEF) (33); the Health Utilities Index (HUI3) (34); the Strengths and Difficulties Questionnaire (SDQ) (35); the Pediatric Quality of Life Inventory (PedsQL) (36); and, if aged 11-17 years, self-report versions of the HUI3, SDQ, and PedsQL. Survivors aged ≥18 years provided self-report versions of the BRIEF, the HUI3, and the 30 core question version of the European Organization for Research and Treatment of Cancer Quality of Life measure (QLQ-C30) (37).

Reduction in height z-score compared with that at diagnosis, known to vary with radiation treatment dose (38), was the prespecified principal endocrine outcome. Height, weight, and mid-parental height were expressed as z-scores, age- and sex-standardized against United Kingdom British 1990 growth reference values (39) to allow inter- and intragroup comparisons. Baseline demographic and secondary outcome information was provided by clinicians using adapted versions of the Medical Examination Form (40) and by adult participants and parents of child participants using the Medical, Educational, Employment and Social questionnaire (40).

Statistical analysis

Univariate analyses of HFRT and STRT group scores were conducted using Mann-Whitney U tests or t tests. Quality of survival questionnaire scores in age-specific subgroups, governed by the age ranges of questionnaires, were converted to a single dataset of z-scores in all participants where mean = 0, SD = 1 for scores of all study participants on that measure. Proxy-report z-scores for children and self-report z-scores for adults for BRIEF and HUI3 were thus used to create a single "executive function z-score" variable and a single "health status z-score" variable, respectively. Proxy-report SDQ z-scores, available only in participants aged <18 years, provided behavioral difficulties z-scores. Finally, child self-report z-scores for PedsQL and adult self-report z-scores for the QLQ-C30 were used to create a single "HRQoL z-score" variable. Statistical analysis of QoS was thus simplified into 4 analyses relating to these 4 prespecified principal QoS outcomes. Analyses of questionnaire subscales were conducted only when total scores differed.

A regression model, including sex, younger age (3-7.9 years) or older age (8.0-20.8 years) at diagnosis, and cerebellar mutism (or, in an alternative model, perioperative complications including cerebellar mutism), was used to increase the precision of the estimate of the effect of treatment on principal QoS outcomes and on decrement since diagnosis in height z-score. Sensitivity analyses were used to examine possible confounding by baseline characteristics. Statistical significance testing (SPSS version 19.0; SPSS, Chicago, IL) was 2-tailed with a 1% significance level to adjust for multiple testing (41).

Results

Baseline characteristics

Outcomes were ascertained in 151 of 244 eligible survivors (61.9%) (74 of 117 [63.2%] and 77 of 127 [60.6%] that had received HFRT and STRT, respectively) at a median interval from diagnosis of 5.8 (range, 4.2-9.9) years. Participants and nonparticipants in the QoS study receiving HFRT were similar with respect to sex, age at diagnosis, pre- and postoperative characteristics, chemotherapy received, and interval between diagnosis and assessment of QoS to those receiving STRT; there was a small excess of neurologic deficits of extraocular movement in those allocated to HFRT and of premorbid developmental impairment in those allocated to STRT (Table 1). The radiation therapy actually delivered to PNET4 QoS study participants corresponded well to that prescribed in both treatment arms: quality assurance included both fields (checked in at least 68 of 151 [45%]) and dose delivered (checked in at least 51 of 151 [34%]).

Outcomes at posttreatment evaluation

There were significant ($P<.01$) correlations between all of the outcome measures, including strong positive correlations (0.58-0.80) between proxy- and self-report scores, between health status and HRQoL scores, and between executive function and behavioral difficulties scores (Supplementary Table e1, available online). Female participants had poorer HRQoL z-scores than males (group mean difference 0.48, 95% confidence interval [CI] 0.13-0.84, $P=.008$) but were similar to males with respect to executive function, health status, and behavioral difficulties.

Effect of HFRT on executive function, behavior, health status, and HRQoL

Scores in subgroups governed by questionnaire age ranges showed no statistically significant differences between treatment arms other than lower (better) adult self-report BRIEF executive function scores in those aged ≥18 years at assessment (Fig. 1). In the merged single dataset of z-scores for all participants for the 4 principal outcome measures, executive function (BRIEF) z-scores were significantly lower (better) after HFRT than after STRT (group mean difference 0.48, 95% CI 0.16-0.81, $P=.004$) (Table 2), but health status, behavioral difficulties, and HRQoL of all participants were similar in the 2 treatment arms (group mean z-score differences 0.26, 0.23, and 0.14, respectively, with 95% CIs including the null point, $P\geq.25$) (Table 2). The intergroup differences in executive function (BRIEF) Global Executive Composite z-scores seemed to be general effects reflected in statistically significant intergroup differences for both the Behavioral Regulation Index, carried by inhibition, shift, and emotional control subscales, and also for the Meta-cognitive Index, carried by monitoring, working memory, and planning/organizing subscores (Supplementary Table e2).

Effect of HFRT on growth

Compared with STRT, the mean group decrement since diagnosis in height z-score after HFRT was greater by 0.43 (95% CI

Table 1 Demographic characteristics and postoperative neurology in participants and nonparticipants by treatment

Characteristic	Participants			Nonparticipants		
	n1, n2 (HFRT, STRT)	HFRT	STRT	n1, n2 (HFRT, STRT)	HFRT	STRT
Demographic characteristics	(74, 77)			(43, 50)		
Median [range] age at diagnosis (y)	74, 77	8.7 [3.2-20.8]	9.7 [3.3-20.4]	43, 50	9.0 [4.2-17.6]	8.5 [5.0-17.8]
Median [range] age at assessment (y)	74, 77	14.9 [7.5-29.9]	15.9 [8.6-29.6]	43, 50	15.1 [9.1-26.4]*	14.5 [10.6-23.6]*
Median [range] interval from diagnosis (y)	74, 77	5.7 [4.2-9.9]	5.8 [4.1-9.8]	43, 50	7.1 [4.2-9.9]*	6.5 [4.2-9.9]*
Males, n (%)	74, 77	51 (69)	46 (60)	43, 50	25 (58)	29 (58)
Midparental height *z*-score (SD)	68, 71	0.09 (0.80)	-0.10 (0.90)	4, 10	NT	NT
Premorbid developmental impairment, n (%)	47, 49	1 (1)	5 (6)	11, 18	2 (5)	0
Postoperative neurology, n (%)†	(74, 77)			(43, 50)		
Impaired consciousness	72, 74	1 (1)	2 (3)	41, 50	2 (5)	2 (4)
Impaired nerves III, IV, VI	70, 71	32 (46)	22 (29)	37, 45	16 (37)	13 (26)
Ataxia	64, 68	36 (49)	37 (48)	29, 39	19 (44)	23 (46)
Cerebellar mutism	74, 77	6 (8)	4 (5)	43, 50	6 (14)	3 (6)

Abbreviations: HFRT = hyperfractionated radiation therapy (see Patients and Methods); NT = not tabulated as insufficient data; STRT = standard radiation therapy (see Methods and Materials).

* For nonparticipants, median age at assessment and interval from diagnosis was estimated using January 1, 2011, the midpoint of the assessment period, as the notional assessment date.

† Percentages are expressed as a percentage of total number of participants or nonparticipants, using conservative assumption that the feature was not present in cases not reported.

0.10-0.76, $P=.011$) (Fig. 2, Table 2), without a difference between treatment arms in weight decrement (Table 2). The mean group decrement from mid-parental height *z*-score (ie, genetic target) was also significantly greater after HFRT, by 0.55 (Fig. 2).

Impact of demographic characteristics and clinical events

After adjustment in a regression model for age, sex, and the presence of cerebellar mutism (or, alternatively, all perioperative complications), the association between HFRT and lower (ie, better) executive function *z*-scores in participants of all ages was unchanged (adjusted mean intergroup difference 0.48, 95% CI 0.15-0.80, $P=.005$). In a sensitivity analysis, exclusion of the 6 participants with premorbid developmental impairment did not materially alter the effect size of treatment allocation on executive function (mean intergroup *z*-score difference 0.44, 95% CI 0.11-0.77, $P=.01$).

We looked for an interaction between age category (see Patients and Methods) and the effect of treatment allocation on the principal outcomes. These interactions, which the study was not powered to detect, fell short of statistical significance but were substantial for the outcomes in which a main effect of treatment allocation was found (interaction estimates 0.62, 95% CI −0.07 to 1.30, $P=.077$ for executive function *z*-score; 0.48, 95% CI −0.20 to 1.16, $P=.16$ for height decrement *z*-score). When younger and older participants were analyzed separately because of these interactions, the effects of treatment allocation on executive function and height decrement *z*-scores were 3-fold larger in the younger group (<8.0 years at diagnosis) (Table 3). As with the unstratified analysis, mean intergroup *z*-score differences were not appreciably altered by adjustment for sex and cerebellar mutism or by exclusion of the 6 patients with premorbid developmental impairment. The differences in executive function *z*-score were not, however, supported by any significant differences between treatment groups at any age with respect to scores on cognition-related subscale measures of health status (HUI3 cognition) or quality of life (PedsQL school functioning, QLQ-C30 cognitive functioning) (not shown).

Hormone and other therapies, ototoxicity, and adult social and employment outcomes

Approximately half of participants in each arm had received growth hormone (GH) and thyroxine replacement therapies (Table 4). In both treatment arms, state benefits were being claimed in one-third, special educational support was required in more than half, and the majority used therapy services and reported problems with their appearance (Table 4). Compared with those receiving STRT, use of hearing aids was reported in a significantly higher percentage in the HFRT group (10% and 23%, respectively; Table 4). This difference was, again, clearer in the group aged <8 years at diagnosis (6 of 40 [15%] after STRT, 10 of 30 [33%] after HFRT) than in those older at diagnosis (4 of 51 [7.8%] after STRT, 6 of 40 [15%] after HFRT). However, neither the HUI3 hearing attribute (mean rank single attribute function scores 54.4 and 51.7 in the HFRT and STRT groups, respectively) nor the previously reported audiogram data from this study (see

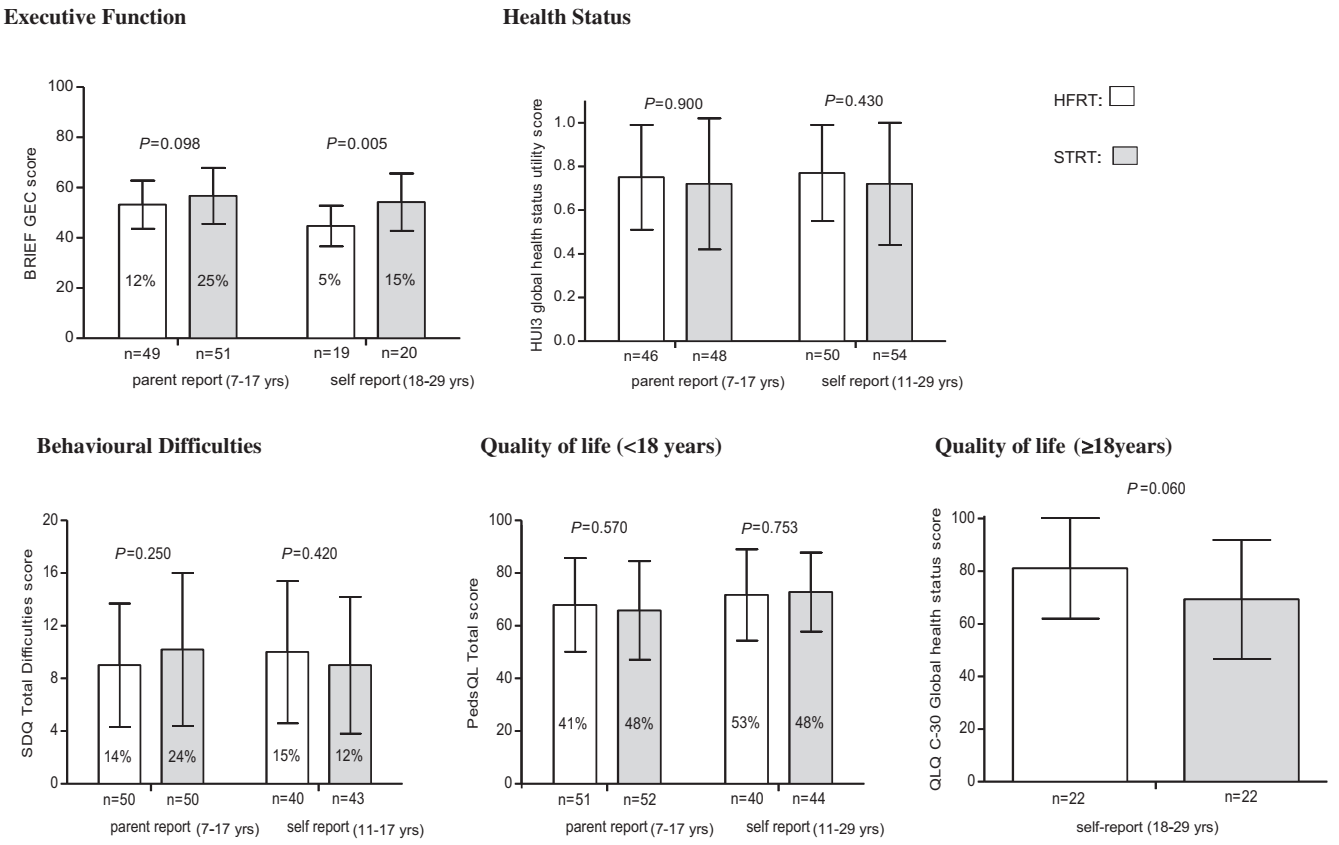

Fig. 1. Scores on age-appropriate measures of quality of survival by treatment allocation. Error bars indicate SDs. Executive Function: Higher scores indicate worse function. Percentages within bars refer to abnormally elevated scores. BRIEF GEC = Behavior Rating Inventory of Executive Function Global Executive Composite. Health Status: Higher scores indicate better health. HUI = Health Utilities Index. Behavioral Difficulties: Higher scores indicate worse function. Percentages within bars refer to borderline or abnormal scores. SDQ = Strengths and Difficulties Questionnaire. Quality of life: Higher scores indicate better quality. Percentages within bars refer to "at risk" scores. PedsQL = Quality of Life Inventory; QLQ-C30 = core 30-question version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. HFRT = hyperfractionated radiation therapy; STRT = standard radiation therapy.

Discussion) suggested a higher incidence of ototoxicity after HFRT. Self-reported social and employment outcomes, only applicable to participants whose age at assessment was ≥18 years (all of whom were also aged ≥8 years at diagnosis), seemed to be similar in the 2 treatment arms excepting an excess, in the group allocated to HFRT, of those driving a motor vehicle (Supplementary Table e3).

Discussion

The PNET4 trial is the first clinical RCT of craniospinal HFRT versus STRT for medulloblastoma and the first pediatric brain tumor treatment trial to ascertain QoS information internationally across Europe. Compared with survivors who had received STRT, BRIEF scores for executive function in everyday life suggested a possible benefit to those who had received HFRT 6 years after enrollment in the PNET4 trial, but the fact that this group did not show associated benefits on measures of health status or quality of life is equally important. The HFRT group also suffered a greater decrement from height *z*-score at diagnosis despite GH treatment, and use of a hearing aid was more commonly reported after HFRT.

Because treatment allocation was random, differences in outcomes are inherently unlikely to be attributable to known or unknown differences in premorbid characteristics. Exclusion from the analysis of participants reported to have premorbid developmental impairment did not alter the findings. The similarity of nonparticipant and participant baseline characteristics in both treatment arms makes attrition bias unlikely, and the retention rate for QoS follow-up information at 4-9 years from diagnosis of 62% is high relative to a rate of <30% (31) in other pediatric neuro-oncology studies and a mean rate of 68% (range, 41-100%) at 1 year follow-up in RCTs for pediatric chronic conditions (42). A system is now in place to include in future trials the option of direct entry of patients' responses to electronic versions of these questionnaires on personal computers or other devices with Internet access, but its effect on ascertainment in this context remains to be determined. Radiation therapy fields, as distinct from fractionation schedules, were the same in both treatment arms except for the (small) boost to the tumor bed in HFRT, and there is no reason to suppose that field alignment differed between the 2 arms.

The BRIEF questionnaire, which relates to everyday function, has been widely used in patients with acquired brain injury with

Table 2 Outcome *z*-scores by treatment group in all participants for the 4 principal domains of quality of survival and for decrement since diagnosis in height and weight *z*-score

Outcome	n1, n2	Group mean (SD) *z*-scores		Mean intergroup difference (95% CI)	*P*
		HFRT (a)	STRT (b)	(b) − (a)	
Quality-of-survival measures					
Executive Function BRIEF-GEC *z*-score*	68, 71	−0.25 (0.87)	0.24 (1.06)	0.48 (0.16 to 0.81)	.004
Health Status HUI3 *z*-score*	55, 59	0.12 (0.86)	−0.14 (1.18)	−0.26 (−0.65 to 0.12)	.40
SDQ behavioral difficulties *z*-score†	50, 50	−0.11 (0.89)	0.11 (1.10)	0.23 (−0.17 to 0.63)	.25
Quality of Life *z*-score‡	62, 66	0.07 (1.02)	−0.07 (0.98)	−0.14 (−0.49 to 0.21)	.42
Height and weight§					
Height decrement from diagnosis	59, 56	−1.27 (0.90)	−0.84 (0.87)	0.43 (0.10 to 0.76)	.011
Weight decrement from diagnosis	59, 60	−0.42 (1.02)	−0.21 (0.91)	0.20 (0.15 to 0.55)	.27

Abbreviations: BRIEF-GEC = Behavior Rating Inventory of Executive Function Global Executive Composite; CI = confidence interval; HUI = Health Utilities Index; SDQ = Strengths and Difficulties Questionnaire. Other abbreviations as in Table 1.

* By proxy-report if aged <18 years; by self-report if aged ≥18 years. Higher BRIEF-GEC scores indicates worse executive function. Higher HUI3 scores indicate better health status.

† By proxy-report if aged <18 years; not available if aged ≥18 years. Higher SDQ scores indicate worse behavior.

‡ By self-report Quality of Life Inventory if aged <18 years; by self-report Core 30-item version of Quality of Life questionnaire, if aged ≥18 years. Higher scores indicate better quality of life.

§ Expressed as a *z*-score where mean = 0, SD = 1 for the healthy United Kingdom population. More negative scores indicate greater decrement in height and weight *z*-scores between dates of diagnosis and follow-up.

good psychometric properties in this population and provides information that is complementary to but different from performance measures (43-46), but its use as the only measure of executive function is a limitation of the present study. The relatively low (10-23%) rates of BRIEF scores in the clinical range for executive dysfunction are similar to those observed using a 25-item neurocognitive questionnaire, based on the BRIEF, in the Childhood Cancer Survivor Study and contrast with estimates of 64-85% rates of impaired executive function obtained by direct assessment in adult survivors of medulloblastoma (7, 8, 24). This discrepancy does not bias or explain the observed intergroup differences. The better BRIEF subscale scores for behavioral regulation and metacognition underlying the differences in global scores for executive function, after HFRT relative to STRT, could indicate a decrease of deficits in working memory, attention, and processing speed that have been previously reported after STRT (6-8, 10-12).

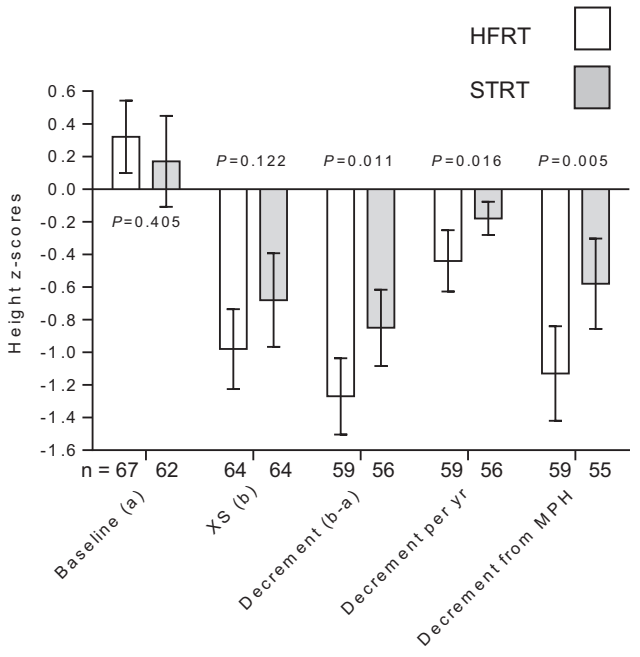

Fig. 2. Group mean height *z*-scores by treatment allocation. Height *z*-scores (see Patients and Methods) (a) at baseline, (b) at cross-sectional (XS) follow-up, (c) decrement = (b) minus (a), (d) decrement per year, (e) decrement from mid-parental height *z*-score (MPH). Error bars indicate 95% confidence intervals.

The 3-fold greater differences in executive function and growth decrement *z*-scores between treatment arms in study participants aged 3-8 years at diagnosis is consistent with previous observation of the greater effects of radiation, especially in combination with chemotherapy, on the CNS (9, 13) and on bony growth in this age group but must be treated with caution because stratification by age was an unplanned, exploratory post hoc analysis in the present study. The greater incidence of reported use of hearing aids after HFRT than after STRT is a concern but of uncertain significance because previously reported audiogram data from this study (30) were similar in the 2 treatment arms. Alteration of fields to spare the cochlea has become standard of care subsequent to the radiation therapy used in this study.

Time from diagnosis, both to height measurement and also to GH replacement therapy, patient ages and genetic height potential, and numbers receiving GH and thyroid hormone were similar between the 2 treatment arms. Evidence of an additional central GH or thyroid hormonal secretory deficit associated with HFRT was lacking and, unlike spinal damage (47, 48), is reversible with hormone therapies (15, 16). The greater height decrement from diagnosis observed after HFRT is therefore likely to be due to relatively greater spinal shortening from radiation damage to both bony matrix and growth plate (48-50) and unlikely to result from differences in skeletal maturity or, thence, time to final adult height. This could be attributable to the higher biologically effective craniospinal dose of HFRT on bone, as predicted for a "late reacting" tissue (see next paragraph), a greater than predicted

Table 3 Outcome z-scores by treatment group in all participants stratified by age into those aged <8.0 years and those aged ≥8.0 years at diagnosis

	<8.0 y at diagnosis					≥8.0 y at diagnosis				
Outcome	n1, n2	HFRT	STRT	Intergroup mean difference (95% CI)	*P*	n1, n2	HFRT	STRT	Intergroup mean difference (95% CI)	*P*
Executive function (BRIEF)	29, 24	−0.45 (0.83)	0.39 (1.11)	0.84 (0.31 to 1.38)	.003	39, 47	−0.09 (0.88)	0.16 (1.03)	0.25 (−0.17 to 0.67)	.24
Health status (HUI3)	26, 21	0.14 (0.76)	−0.09 (1.13)	0.23 (−0.32 to 0.79)	.41	29, 38	0.10 (0.94)	−0.17 (1.22)	0.27 (−0.28 to 0.82)	.33
Behavioral difficulties (SDQ)	31, 23	−0.18 (0.75)	0.30 (1.17)	0.48 (−0.09 to 1.04)	.10	19, 27	−0.02 (1.09)	−0.05 (1.03)	0.03 (−0.61 to 0.67)	.93
Quality of life (PedsQL and QLQ-C30)	20, 17	0.18 (1.04)	−0.06 (1.01)	0.23 (−0.45 to 0.92)	.50	42, 49	0.02 (1.01)	−0.07 (0.98)	0.10 (−0.32 to 0.51)	.64
Height decrement from diagnosis	23, 17	−1.62 (0.85)	−0.91 (0.84)	−0.71 (−1.26 to −0.17)	.012	36, 39	−1.05 (0.88)	−0.82 (0.89)	−0.23 (−0.64 to 0.18)	.26
Weight decrement from diagnosis	24, 19	−0.23 (1.13)	0.02 (1.04)	−0.25 (−0.92 to 0.43)	.47	35, 41	−0.53 (0.93)	−0.31 (0.84)	−0.21 (−0.62 to 0.19)	.30

Abbreviations: PedsQL = Quality of Life Inventory; QLQ-C30 = core 30-item version of the Quality of Life Questionnaire. Other abbreviations as in Tables 1 and 2.
Values are mean (SD).

tendency for epiphyseal tissue to respond to HFRT as an "early reacting" tissue, or both. An interaction between the effect of HFRT and its use in combination with chemotherapy cannot be ruled out.

Table 4 Secondary quality-of-survival outcomes by treatment group: Hormone replacement, use of therapy services, hearing aids, state benefits, and cosmetic outcome

Outcome	n1, n2 (HFRT, STRT)	HFRT	STRT
Mean (SD) years to growth hormone replacement	27, 19	2.98 (0.7)	2.88 (0.6)
Growth hormone replacement therapy	72, 75	39 (54)	37 (49)
Thyroxine replacement therapy	71, 76	36 (51)	34 (45)
Physiotherapy	73, 77	46 (63)	56 (73)
Occupational therapy	73, 77	16 (22)	15 (19)
Speech and language therapy	73, 77	26 (36)	23 (30)
Psychology	73, 77	29 (40)	40 (52)
Special educational support	72, 77	36 (50)	46 (60)
Educational provision not suited to child's needs	60, 66	16 (27)	13 (20)
Uses a hearing aid	70, 74	16 (23)*	7 (10)*
In receipt of state benefits	71, 72	28 (40)	26 (36)
Problems with appearance	71, 74	45 (63)	46 (62)
Hair thinning, patchy hair loss, or no hair	69, 71	58 (84)	52 (73)

Abbreviations as in Table 1.
Values are number (percentage) except where noted. Differences between treatment arms did not approach statistical significance ($P>.1$) except where indicated.
* χ^2 4.81, $P=.028$ for intergroup difference.

The estimated biologically equivalent dose (BED) of HFRT relative to STRT on the CNS was calculated on the assumption, based on rates of radiation-induced necrosis within the CNS, that $\alpha/\beta = 2$ for the linear (α) and quadratic (β) components of increase in the radiation dose per fraction on the CNS in the linear-quadratic radiobiological model (26). On this calculation, the BED at 2 Gy of HFRT for the CNS was 21.4% higher for the craniospinal dose outside the boost field (27.0 vs 22.2 Gy BED), unchanged for the tumor bed (51.0 vs 51.8 Gy BED), and 15% lower in the remaining posterior fossa boost field, which included areas of the cerebral cortex adjacent to the cerebellum (45.1 vs 51.8 Gy). The effect on CNS outcomes of these interarm differences is difficult to predict. The better executive function reported here is consistent with the encouraging cognitive function reported in previous uncontrolled studies (27, 28), but the absence of differences in health status, behavior, and QoL suggests similarity of treatment arms with respect to effects on the CNS. Neither the absence of difference between treatments in PNET4 with respect to Event free survival (EFS) (30) nor the greater decrement in height after HFRT reported here were predicted in advance of PNET4.

In conclusion, this study highlights the uncertainty of radiobiological assumptions with respect to early- and late-reacting tissue components in the normal CNS and bony spine. Although the present study suggests some benefit to executive function associated with HFRT, it also showed an absence of associated benefit to behavior, health status, or quality of life and does not enable us to reach a final conclusion on whether HFRT was of greater overall benefit than STRT to QoS. Collation of neuropsychometric testing, collected within some participating national groups on PNET4 survivors, into an international dataset is in progress. If the neuro-psychometric data also show an association between HFRT and better cognitive function, a further trial of HFRT might be discussed. Stratification of HFRT dose by age and biological risk factor would need to be guided by the present

study, the neuro-psychometric data, and the PNET5 study in progress.

Future studies should include both a more global overview of executive function by assessing it not only in everyday life, as we did here, but also in the testing situation and also more detailed auxology, including sitting height and pubertal staging.

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ORIGINAL REPORT

Growth Hormone Secretion After Conformal Radiation Therapy in Pediatric Patients With Localized Brain Tumors

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See accompanying editorial on page 4743

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ABSTRACT

Purpose
Growth hormone deficiency (GHD) after radiation therapy negatively affects growth and development and quality of life in children with brain tumors.

Patients and Materials
Between 1997 and 2008, 192 pediatric patients with localized primary brain tumors (ependymoma, n = 88; low-grade glioma, n = 51; craniopharyngioma, n = 28; high-grade glioma, n = 23; and other tumor types, n = 2) underwent provocative testing of GH secretion by using the secretogogues arginine and L-dopa before and after (6, 12, 36, and 60 months) conformal radiation therapy (CRT). A total of 664 arginine/L-dopa test procedures were performed.

Results
Baseline testing revealed preirradiation GHD in 22.9% of tested patients. On the basis of data from 118 patients, peak GH was modeled as an exponential function of time after CRT and mean radiation dose to the hypothalamus. The average patient was predicted to develop GHD with the following combinations of the time after CRT and mean dose to the hypothalamus: 12 months and more than 60 Gy; 36 months and 25 to 30 Gy; and 60 months and 15 to 20 Gy. A cumulative dose of 16.1 Gy to the hypothalamus would be considered the mean radiation dose required to achieve a 50% risk of GHD at 5 years ($TD_{50/5}$).

Conclusion
GH secretion after CRT can be predicted on the basis of dose and time after irradiation in pediatric patients with localized brain tumors. These findings provide an objective radiation dose constraint for the hypothalamus.

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INTRODUCTION

Growth hormone deficiency (GHD) is the first and most common adverse effect of hypothalamic irradiation in brain tumor survivors.[1] A pooled prevalence of 35.6% has been estimated from studies evaluating GHD in survivors of childhood cancer. GHD is an important and well-documented etiology of poor growth, abnormal body composition, altered energy metabolism,[2] poor overall health, and diminished quality of life. Recent evidence suggests that GHD increases cardiovascular risk factors[3,4] and contributes to cognitive impairment,[5-7] adding to the importance of the problem and our need to understand the risk factors for GHD, including the specific contribution of cranial irradiation.

Our understanding of the contribution of radiation dose and time after treatment to the development of GHD has relied on retrospective information obtained from patients treated to regional or whole-brain volumes from which reasonable estimates of doses to the hypothalamus-pituitary axis were obtained. Stem-cell transplantation regimens using total-body irradiation yield a 25% incidence at 5 to 10 years for 8 to 12 Gy and a 50% incidence at 10 years for 14.4 Gy.[8] Cranial irradiation regimens using doses of more than 24 Gy yield a 66% incidence,[9,10] and regimens using doses of more than 30 Gy lead to incidences as high as 80% by 10 years.[11] In one series of optic pathway tumors, doses in excess of 45 Gy resulted in a 100% incidence of GHD within 2 years.[12] These same studies have confirmed that increasing cranial radiation dose and time after treatment are the main risk factors.[13]

There is a need for well-designed studies to accurately determine the prevalence of endocrinopathies in cancer survivors treated with radiation therapy. We performed prospective serial tests of endocrine function in children with localized brain tumors treated with conformal radiation therapy

(CRT) including intensity-modulated radiation therapy. This report describes the results from serial growth hormone (GH) testing in a cohort of patients up to 5 years after the initiation of radiation therapy. The results have applicability in the treatment of children with CNS tumors and patients in whom the hypothalamus-pituitary unit is included in the irradiated volume.

PATIENTS AND METHODS

Pediatric patients (n = 192) with localized primary brain tumors including ependymoma (n = 88), low-grade glioma (n = 51), craniopharyngioma (n = 28), high-grade glioma (n = 23), and other tumor types (n = 2) underwent provocative testing of GH secretion before and after CRT or intensity-modulated radiation therapy. All patients signed consent forms that were approved by the institutional review board.

Endocrine Testing

The arginine tolerance/L-dopa (AT/L-dopa) test was performed before (baseline) and at 6, 12, 36, and 60 months after the initiation of CRT. No patients were receiving dexamethasone or enzyme-inducing antiepileptic drugs at the time of testing. The clinical measure of GH secretory capacity was the peak GH value as determined by chemiluminescence. Patients were determined to have GHD if the peak GH response to the AT/L-dopa test was less than 7 ng/ml. Details regarding this procedure have been described previously.[14]

CRT and Hypothalamic Dose-Volume Data

The method of CRT has been previously described.[15,16] Except for patients with high-grade glioma who were treated by using a 2-cm clinical target volume margin, all patients were treated by using a 1-cm clinical target volume margin surrounding the gross residual tumor or the tumor bed. Patients younger than age 7 years undergoing treatment had general anesthesia. Patients were immobilized with a relocatable stereotactic head frame, a thermoplastic face mask, or a molded vacuum bag.

To assist in the planning process and identification of normal tissue structures, all patients underwent magnetic resonance imaging (MRI) scans to obtain a 3-dimensionally acquired contrast-enhanced T1-weighted data set. The resultant images were registered to the treatment planning computed tomography data set obtained with the patient in the treatment position. The hypothalamus was contoured from the MRI data, and the distribution of the dose through the hypothalamus was calculated for each patient. The mean dose to the hypothalamus was used for the analysis.

Statistical Analysis

Two analyses were carried out for this study. The first was to characterize the baseline peak GH levels, estimate the proportion of patients with GHD before irradiation, and identify clinical factors associated with pre-existing GHD. The second was to characterize the longitudinal trends of peak GH after CRT, estimate the rate of change in peak GH values during the first 5 years after CRT, and quantify the influence of radiation dose and other clinical factors on the rate of change.

A mixed effects (random and fixed effects) model was used for the analysis.[17,18] The peak GH, measured by the AT/L-dopa test, was the response variable for the model. The peak GH values were log transformed to achieve the best fit. In the model for the longitudinal analysis, the log peak GH value was modeled as a function of time for the evaluation of each patient and was used to create a regression line. The intercept of the line was the baseline (pre-CRT) log peak GH value, and the slope of the line was the rate of change for the log peak GH value. The intercept and slope of individual patient regression lines were considered random effects and were used to estimate the regression curve for the patient population. The effect of irradiation on the longitudinal trend of peak GH value was estimated from the contributive factor of the mean dose to the hypothalamus in the model. The total effect of CRT on the hypothalamus was modeled as a linear combination of the effects of different levels of radiation dose. The resulting model with estimating parameters was used to predict the longitudinal change in peak GH level.

To estimate the risk of GHD (the probability that the peak GH was lower than 7 ng/mL) for a given mean radiation dose at a specific time after CRT, we assumed that log peak GH was normally distributed with a mean predicted by equation 2 (see Results) and that the standard deviation was 0.64 on the basis of the estimated standard deviation for the log peak GH at baseline in all patients. We assumed that for a subgroup receiving the same mean radiation dose, the mean log peak GH level would change with time but that the standard deviation of the log peak GH level would remain the same.

RESULTS

Pre-Irradiation GHD

Baseline testing was performed on 180 patients. To conservatively estimate the incidence of pre-existing GHD, we excluded eight patients with baseline values ≥ 3 ng/mL and less than 7 ng/mL when subsequent testing showed that peak GH levels at later times recovered to levels ≥ 7 ng/mL. On the basis of this possibility, we excluded one patient who underwent only baseline testing with peak GH ≥ 3 ng/mL and less than 7 ng/mL. None of the patients with baseline values less than 3 ng/mL showed evidence of recovery to the normal range of ≥ 7 ng/mL on subsequent testing; thus, those with only one baseline evaluation value less than 3 ng/mL were included in the analysis of preirradiation GHD. Finally, we excluded the test results for one patient who had a longstanding history of selective serotonin reuptake inhibitor use. Among the 170 patients who were included in the analysis of baseline test results, 39 (22.9%) had preirradiation GHD. Peak GH was less than 3 ng/mL in 25, less than 5 ng/mL in 33, and less than 7 ng/mL in 35 patients.

Pre-CRT GHD could not be predicted significantly by sex, history of pre-CRT chemotherapy, age at the time of CRT, or time interval from diagnosis to CRT. Pre-CRT GHD was less likely in white patients (relative risk [RR], 0.325; $P = .0213$) than in black patients; in diagnoses other than craniopharyngioma, including ependymoma and both high- and low-grade glioma, the RRs were 0.017, 0.011, and 0.043, respectively ($P < .001$); and in patients with infratentorial tumors compared with those with supratentorial tumors, the RR was 0.142 ($P < .001$). Patients who qualitatively appeared to have hydrocephalus were not more likely to have pre-CRT GHD; however, those who required cerebrospinal fluid (CSF) shunting did have a higher risk (RR, 2.085; $P = .0480$).

Longitudinal Effect of CRT on GH Secretion

The longitudinal change in peak GH values was modeled by using data from 118 patients, including those who did not have preirradiation GHD and who were able to undergo baseline and at least one subsequent evaluation. The number of baseline and subsequent evaluations totaled 469: baseline (n = 118), 6 months (n = 110), 12 months (n = 113), 36 months (n = 72), and 60 months (n = 56).

The longitudinal trend of peak GH level was modeled with the time variable (time after the start of irradiation) and clinical variables, including the mean radiation dose to the hypothalamus (mean dose), the presence or absence of CSF shunting before irradiation (CSF shunt), the baseline value of peak GH (bGH), and tumor location. There was an association between mean dose and CSF shunt ($P = .0253$), mean dose and tumor location ($P < .001$), and mean dose and the time interval from diagnosis to CRT ($P = .0025$). Patients with a CSF shunt had lower baseline levels of peak GH than patients without shunts ($P = .5830$), and

patients with supratentorial tumors had lower baseline levels than those with infratentorial tumors ($P = .1667$). The mean dose to the hypothalamus was higher in patients with a longer interval from diagnosis to the start of irradiation ($P = .0025$).

There was a statistically significant ($P < .001$) exponential decline in peak GH values after the start of irradiation (equation 1), shown by a model with only time as the predictor. The paired interactions of time and mean dose ($P < .001$), time and CSF shunt ($P < .0022$), and time and bGH ($P = .0484$) were significant by a model that included time and mean radiation dose as predictors (equation 2). The exponential decline in peak GH with time is shown by using curves that represent dose at intervals of 10 Gy (Fig 1).

All possible interactions of the four clinical variables were considered in model fitting; the best model is delineated in equation 3. In that model, the interaction between time and mean radiation dose was the most significant ($P < .001$), followed by time and bGH ($P = .0029$), and time and CSF shunt ($P = .0350$). In the composite model, patients without CSF shunts had higher longitudinal values of peak GH. Patients with higher baseline values of peak GH had a greater rate of decline in longitudinal values. Increasing mean dose was inversely correlated with longitudinal peak GH.

$$peak\ GH \times \exp[2.5928 - (0.02088 \times time)] \quad (1)$$

$$peak\ GH = \exp(2.5947 + \{time \times [0.0019 - (0.00079 \times mean\ dose)]\}) \quad (2)$$

$$peak\ GH = \exp([0.7774 + (0.08769 \times CSF\ shunt) + (0.63 \times bGH)] + \{time \times [0.02926 + (0.014 \times CSF\ shunt) - (0.0138 \times bGH) - (0.00092 \times mean\ dose)]\}) \quad (3)$$

Considering attrition from disease progression and the initiation of replacement therapy in those who developed clinically significant GHD during the first years after irradiation (Appendix, online only), we performed a similar analysis by using a data set that was limited to peak GH values obtained through 36 months. In this subset analysis, the interaction between time and mean dose remained highly significant, and the model showed a steeper decline in peak GH as a function of time and dose.

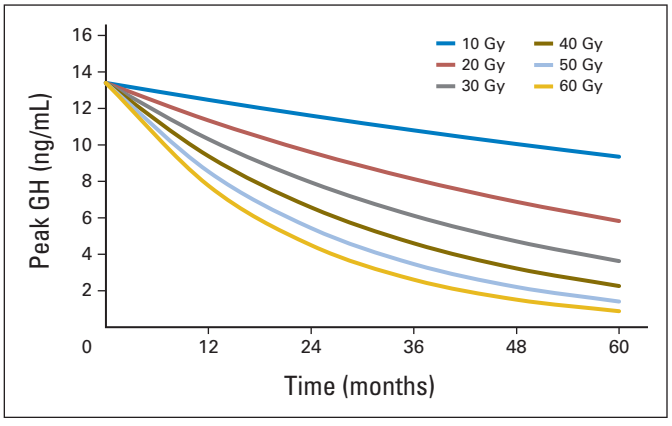

Fig 1. Peak growth hormone (GH) according to hypothalamic mean dose and time after start of irradiation. According to equation 2, *peak GH* = exp{2.5947 + *time* × [0.0019 − (0.00079 × *mean dose*)]}.

Probability of GHD by Time and Dose

By using the estimating equation that included time and mean dose to the hypothalamus (equation 2), and assuming a standard deviation similar to that of our cohort at baseline, we calculated the probability of GHD (ie, probability of a peak GH lower than 7 ng/mL) at 12, 36, and 60 months after irradiation (Table 1) for each given level of mean radiation dose (5 Gy, 10 Gy, …, 60 Gy). A similar analysis was performed by using the data set for 0 to 36 months. The average patient was predicted to develop GHD with the following combinations of time after CRT and mean dose to the hypothalamus: 12 months and more than 60 Gy, 36 months and 25 to 30 Gy, and 60 months and 15 to 20 Gy.

Complication Probabilities: $TD_{5/5}$ and $TD_{50/5}$

The $TD_{5/5}$ and $TD_{50/5}$ represent the minimum (5% risk) and maximum (50% risk) radiation dose tolerance estimated at 5 years. These estimates consider conventional fractionated radiation therapy to the organ at risk by using clinical regimens of 1.8 to 2.0 Gy per day administered 5 days per calendar week. Assuming the standard deviation of the baseline value of log peak GH in our cohort as that for the log peak GH for any given pair of time and mean dose, and assuming a normal distribution for this value, we determined that all patients would have at least a 5% risk of having a peak GH level less than 7 ng/mL, regardless of their mean doses.

By using the same method, we determined that for patients to have less than a 50% risk of peak GH below 7 ng/mL at 5 years, the mean dose to the hypothalamus should not exceed 16.1 Gy over the course of 6 to 6.5 weeks based on the 60-month data set and 12.6 Gy over the course of 6 to 6.5 weeks based on the 36-month data set.

DISCUSSION

GHD after therapeutic cranial irradiation is a treatable late effect of successful cancer therapy that might be reduced or eliminated through careful treatment planning or new methods. Our results suggest that when the mean dose to the hypothalamus can be reduced to less than 16.1 Gy, half the surviving children may be spared from GHD during the first 5 years after treatment. Considering that GHD results from damage to the neurons in the hypothalamus that are considered most sensitive to the effects of irradiation,[19] it follows that the incidence of other endocrine deficiencies might also be reduced if and when this threshold dose is observed. Reducing hypothalamic irradiation should be feasible when treating children with brain tumors if the targeted volume is not immediately adjacent to the hypothalamus and when advanced methods of photon or proton therapy are used. That our patients received 30 to 33 fractions of 1.8 Gy over the course of 6 to 6.5 weeks should be considered in the interpretation of these results, since the fractional dose threshold is 0.49 to 0.54 Gy per fraction or 27% to 30% of the prescribed daily dose.

The criteria for diagnosis of GHD vary by institution. Children without any tumor history are often considered to have GHD and qualify for GH therapy when their peak stimulated GH is less than 10 ng/mL. This study provides firm estimates of the radiation dose required to induce GHD by using a more conservative diagnostic level of 7 ng/mL. However, it is clear that other factors in addition to radiation dose contribute to this endocrine deficit. In our study, the incidence of GHD before irradiation was related to CSF shunting, which is

Table 1. Probability of GHD by Mean Dose to the Hypothalamus and Time After Irradiation Using Peak GH Data Through 36 and 60 Months After Conformal RT

		36-Month Data (GH, ng/mL)*			60-Month Data (GH, ng/mL)†		
Time After RT Start (months)	Mean Dose to Hypothalamus (Gy)	Probability of < 7	Probability of < 3	Predicted Mean Peak	Probability of < 7	Probability of < 3	Predicted Mean Peak
12	5	0.15	0.0093	13.55	0.16	0.0107	13.07
	10	0.18	0.0120	12.73	0.18	0.0130	12.46
	15	0.20	0.0154	11.96	0.20	0.0157	11.89
	20	0.23	0.0196	11.23	0.23	0.0189	11.34
	25	0.26	0.0247	10.55	0.25	0.0226	10.81
	30	0.29	0.0309	9.92	0.27	0.0269	10.31
	35	0.33	0.0383	9.32	0.30	0.0318	9.83
	40	0.36	0.0472	8.75	0.32	0.0375	9.38
	45	0.40	0.0576	8.22	0.35	0.0439	8.94
	50	0.44	0.0697	7.73	0.38	0.0513	8.53
	55	0.48	0.0837	7.26	0.41	0.0595	8.13
	60	0.52	0.0998	6.82	0.44	0.0688	7.76
36	5	0.19	0.0135	12.36	0.18	0.0131	12.44
	10	0.28	0.0274	10.25	0.25	0.0227	10.79
	15	0.38	0.0518	8.50	0.32	0.0377	9.36
	20	0.50	0.0910	7.05	0.41	0.0599	8.12
	25	0.61	0.1486	5.85	0.50	0.0912	7.04
	30	0.72	0.2267	4.85	0.58	0.1332	6.11
	35	0.81	0.3237	4.02	0.67	0.1869	5.30
	40	0.88	0.4346	3.33	0.74	0.2524	4.60
	45	0.93	0.5508	2.77	0.81	0.3282	3.99
	50	0.96	0.6628	2.29	0.86	0.4119	3.46
	55	0.98	0.7620	1.90	0.91	0.4998	3.00
	60	0.99	0.8426	1.58	0.94	0.5877	2.60
60	5	0.23	0.0193	11.28	0.21	0.0160	11.84
	10	0.40	0.0569	8.26	0.33	0.0379	9.34
	15	0.59	0.1369	6.04	0.47	0.0800	7.37
	20	0.76	0.2720	4.42	0.61	0.1504	5.82
	25	0.89	0.4526	3.24	0.75	0.2533	4.59
	30	0.95	0.6437	2.37	0.85	0.3844	3.62
	35	0.99	0.8039	1.74	0.92	0.5305	2.86
	40	1.00	0.9104	1.27	0.96	0.6725	2.25
	45	1.00	0.9664	0.93	0.98	0.7931	1.78
	50	1.00	0.9898	0.68	0.99	0.8825	1.40
	55	1.00	0.9975	0.50	1.00	0.9403	1.11
	60	1.00	0.9995	0.37	1.00	0.9731	0.87

Abbreviations: GH, growth hormone; GHD, growth hormone deficiency; RT, radiation therapy.
*36-month model: $peak\ GH = \exp(2.6518 + \{time \times [0.001385 - (0.00104 \times mean\ dose)]\})$.
†60-month model: $peak\ GH = \exp(2.5947 + \{time \times [0.0019 - (0.00079 \times mean\ dose)]\})$.

standard in the sequelae and treatment of severe hydrocephalus. Pre-existing GHD was also related to tumor diagnosis and tumor location. These variables are often correlated, considering the singular suprasellar location of craniopharyngioma and the fact that the diencephalon or optic pathway is the most commonly irradiated site in childhood low-grade glioma. Because these tumors are intimately associated with the hypothalamus, these patients have a high likelihood of postradiation GHD if it is not already present before irradiation. All factors considered, our data suggest a need for early evaluation and intervention in these patients.

Children with ependymoma often present with obstructive hydrocephalus originating in the posterior fossa. The direct effect of hydrocephalus on the hypothalamus from increased intracranial pressure and expansion of the ventricular system should not be underestimated. Although tumor resection may relieve the obstruction, permanent CSF shunting is required for the most severe cases. In addition to radiation dose to the hypothalamus, CSF shunting is an important risk factor for GHD both before and after irradiation.

Endocrine deficiencies cannot always be predicted by tumor location. This observation highlights the contribution of scattered radiation[20] and the need for more accurate estimates of hypothalamic radiation dose. Clinical data describing neuroendocrine effects of irradiation have been derived by using generalized estimates of radiation dose under conditions in which the dose to the hypothalamic-pituitary axis was generally homogeneous and discrete. Examples include patients treated with single-dose or fractionated total-body irradiation (8 to 14 Gy), those given cranial irradiation for acute lymphoblastic leukemia (18 Gy and 24 Gy), and those with tumors of the sella or parasellar region in which the hypothalamic-pituitary axis was uniformly included in the volume of prescribed dose (> 50 Gy). Radiation is a significant contributor to neuroendocrine complications commonly observed after treatment for brain tumors and tumors of the

head and neck when the hypothalamus is subtended by the irradiated volume.[21] Similar complications are observed when the hypothalamus is incidentally irradiated in the treatment of nasopharyngeal cancer, retinoblastoma, Hodgkin's lymphoma, and pediatric sarcomas of the head and neck.[22]

For other diseases, the hypothalamus may have been located within the irradiated volume for part or all of the treatment or in the gradient of dose (dose falloff), receiving only a fraction of the daily dose administered. These circumstances make it difficult to assign a dose to the hypothalamus and to determine the risk for late effects. These difficulties are present when the patient is seen by an endocrinologist years after treatment and retrospective dose calculations may be difficult to perform. Newer radiation techniques use 3-dimensional imaging (computed tomography and MRI) and allow for more accurate dose calculation and reporting. Correlated with objective measures of endocrine effects, dosimetry of hypothalamic irradiation will become increasingly valuable in predicting the incidence of specific endocrinopathies.

In pediatric radiation oncology, reducing adverse effects of treatment is an important goal. Reducing adverse effects can be achieved primarily by limiting CNS irradiation to patients for whom the indications are clear and the benefits outweigh the risks. The risk for endocrine-related complications should be carefully considered in planning radiation therapy but should not be used as a reason to avoid curative therapy. Careful follow-up and surveillance will lead to earlier intervention and mitigation of the consequences of cranial radiation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Clinical Investigation

Critical Combinations of Radiation Dose and Volume Predict Intelligence Quotient and Academic Achievement Scores After Craniospinal Irradiation in Children With Medulloblastoma

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Summary

The effects of radiation dose and volume in patients with medulloblastoma are largely understood in terms of the prescribed dose to the neuraxis. This research demonstrates an association between radiation dose to specific subvolumes of the brain and decline in longitudinal cognitive scores, supporting the need to further reduce radiation dose and volume or modify the distribution of dose in these patients.

Purpose: To prospectively follow children treated with craniospinal irradiation to determine critical combinations of radiation dose and volume that would predict for cognitive effects.

Methods and Materials: Between 1996 and 2003, 58 patients (median age 8.14 years, range 3.99-20.11 years) with medulloblastoma received risk-adapted craniospinal irradiation followed by dose-intense chemotherapy and were followed longitudinally with multiple cognitive evaluations (through 5 years after treatment) that included intelligence quotient (estimated intelligence quotient, full-scale, verbal, and performance) and academic achievement (math, reading, spelling) tests. Craniospinal irradiation consisted of 23.4 Gy for average-risk patients (nonmetastatic) and 36-39.6 Gy for high-risk patients (metastatic or residual disease >1.5 cm^2). The primary site was treated using conformal or intensity modulated radiation therapy using a 2-cm clinical target volume margin. The effect of clinical variables and radiation dose to different brain volumes were modeled to estimate cognitive scores after treatment.

Results: A decline with time for all test scores was observed for the entire cohort. Sex, race, and cerebrospinal fluid shunt status had a significant impact on baseline scores. Age and mean radiation dose to specific brain volumes, including the temporal lobes and hippocampi, had a significant impact on longitudinal scores. Dichotomized dose distributions at 25 Gy, 35 Gy, 45 Gy, and 55 Gy were modeled to show the impact

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of the high-dose volume on longitudinal test scores. The 50% risk of a below-normal cognitive test score was calculated according to mean dose and dose intervals between 25 Gy and 55 Gy at 10-Gy increments according to brain volume and age.
Conclusions: The ability to predict cognitive outcomes in children with medulloblastoma using dose-effects models for different brain subvolumes will improve treatment planning, guide intervention, and help estimate the value of newer methods of irradiation. © 2014 Elsevier Inc.

Introduction

The cognitive effects of craniospinal irradiation (CSI) have been a primary concern for investigators and caregivers involved in the treatment of children with medulloblastoma (MB) (1-5), the most common malignant brain tumor in children. Until 25 years ago the standard of care for all patients included 36 Gy CSI followed by irradiation of the posterior fossa to a cumulative dose ≥54 Gy. To reduce treatment complications, CSI dose levels are now limited to 23.4 Gy for patients with minimal residual disease and no evidence of neuraxis metastases, whereas 36 Gy remains the standard for other patients, including those with residual disease ≥1.5 cm^2 or documented metastases; those treated with 23.4 Gy CSI require adjuvant chemotherapy to achieve the same level of disease control observed with higher doses (6). Craniospinal irradiation includes supplemental "boost" irradiation of the primary site. Until recently the anatomic posterior fossa has been the target volume for patients with MB (7). Further reducing craniospinal dose and testing the feasibility of focal irradiation of the primary site, in lieu of posterior fossa irradiation, has been the objective of recent and ongoing institutional and cooperative group studies (8, 9).

Despite these changes the gains have been small, leading investigators to question whether further reductions in dose and volume are warranted or whether they are likely to result in an improvement over past results (10, 11).

There are limited data correlating regional or volumetric effects of irradiation in children with MB. Investigators from the Childhood Cancer Survivor Study attempted to associate region-specific radiation dose and neurocognitive and quality-of-life outcomes in adult survivors of central nervous system malignancies, including those with MB (12). High-dose irradiation of the temporal region was associated with memory impairment compared with nonirradiated patients; however, no association between dose and outcome was observed for other regions. We were the first to report a volumetric association between radiation dose and cognitive effects in children with MB (13). We observed, in a series of children who were prospectively followed after risk-adapted postoperative CSI and adjuvant chemotherapy, that radiation dose to the entire brain was associated with longitudinal intelligence quotient (IQ) scores. Although the volume receiving the highest dose had the greatest impact, there was a similar decline in IQ for each gray of exposure. These results supported further reductions in radiation dose and volume, with an emphasis on reducing the volume that receives the highest dose, especially for young patients who are at greatest risk for cognitive effects.

In this report we explore the association between 3-dimensional brain dose and cognitive effects in children with MB. We evaluate toxicity thresholds according to dose, volume, and age. We extend our prior results in a larger cohort of children and add academic achievement as a response variable in the models. We have included the dose information about the hippocampus. This has been viewed as a critical functional volume related to neurogenesis and subsequent cognitive effects (14). The goal of this research was to estimate critical combinations of radiation dose and volume resulting in cognitive impairment. Understanding dose and volume effects will improve radiation therapy planning and our understanding of partial organ tolerances to the effects of irradiation beyond those already published (15).

Methods and Materials

The study cohort included 58 patients (median age at diagnosis 8.14 years, range 3.99-20.11 years) treated between 1996 and 2003 diagnosed with MB and longitudinally followed after surgery, radiation therapy, and postirradiation chemotherapy with multiple (>2) cognitive evaluations. The group was further characterized by sex (male, n = 40; female, n = 18); race/ethnicity (white, n = 47; black, n = 9; Hispanic, n = 2); extent of resection (gross total resection [GTR], n = 47; <GTR, n = 11); risk-classification (average, n = 34; high, n = 24); cerebrospinal fluid (CSF) shunt (present, n = 8; absent, n = 50); and 10 patients had more than 1 surgery. At the time of diagnosis, 50 of 58 patients were right-handed, 6 of 58 were left-handed, and 2 of 58 were ambidextrous. After surgery, 1 right-handed patient became left-handed and 1 ambidextrous patient became right-handed.

The treatment protocol included resection followed by risk-adapted, postoperative CSI and postirradiation chemotherapy, as described elsewhere (16). Average-risk patients received 23.4 Gy CSI, 36 Gy conformal posterior fossa irradiation, and 55.8 Gy primary site irradiation using a 2-cm clinical target volume (CTV) margin. High-risk patients received 36-39.6 Gy CSI, followed by 55.8 Gy primary site irradiation using a 2-cm CTV margin. When the posterior fossa was irradiated to 36 Gy after 23.4 Gy CSI, the CTV for that volume was the anatomic posterior

fossa. Composite radiation dose data were assembled for all patients, and normal tissue volumes were systematically contoured on MR imaging data registered to the treatment planning CT. Dose-volume data for each of the normal tissue structures was extracted in differential form for integration. The median and mean doses were determined for each brain region (Table 1).

Patients underwent serial cognitive testing at baseline (after surgical resection) and annually after the start of CSI. The cognitive tests for this study included IQ and academic achievement. Intelligence quotient was estimated according to the Information, Similarities, and Block Design subtests from the age-appropriate Wechsler scale (Wechsler Preschool and Primary Scales of Intelligence, Revised [17], Wechsler Intelligence Scale for Children, Third Edition [18], and Wechsler Adult Intelligence Scale, Revised [19]) using a formula presented by Sattler (20). This method for estimating IQ correlates highly with IQs derived from full administration ($r=0.93$). Age-based scaled scores, with a mean of 100 and standard deviation of 15, were derived using each standardization sample. Academic testing consisted of 3 subtests from the Wechsler Individual Achievement Test (Word Reading, Spelling, and Math Reasoning) (21). These subtests are content representative, reliable, and have good convergent/discriminant validity. Performance on each subtest was converted to an age-standardized score with a mean of 100 and standard deviation of 15.

A linear mixed model with random coefficients was used to estimate the impact of the specific clinical variables and nonoverlapping dose-volume intervals on the longitudinal trend of the cognitive scores after the start of CSI. A variety of clinical variable were included in the modeling process. Dose variables included mean dose to the contoured normal tissue volumes and dichotomized the dose distributions. We generated pairs of dose-volume variables: V0_25 Gy and V25 Gy+, V0_35 Gy and V35 Gy+, V0_45 Gy and V45 Gy+, and V0_55 Gy and V55 Gy+. We then fit a random coefficient model to investigate the effect of dose-volumes on the longitudinal trend of cognitive scores over time. Because of the small volume for the hippocampus, it was not treated with volumetric dose data. We modeled the combined effect of radiation dose and volume and age at the time of irradiation. We then calculated the TD 50/5. The TD 50/5 is the tolerance dose for a given normal tissue that within 5 years will cause a maximal (unacceptable) 50% complication rate. To estimate the TD 50/5 for the normal tissue volumes included in this study, we fixed the level of our response variables (cognitive scores) to 85 and dose in 5-Gy increments and determined the threshold volume corresponding to a particular dose that would result in a score below 85. For each model the estimating equation developed by the mixed-model procedure was examined for direction of slope (positive or negative), magnitude of the specific dose-volume coefficients, and the P value of each coefficient. For each fitted model, only the factors significant at $P<.10$ were included in the final estimating equation. The P values were not adjusted for multiple testing. All analyses were performed using SAS (SAS Institute, Cary, NC).

Results

Longitudinal trends in cognitive scores

The longitudinal trends in cognitive scores were modeled during the first 5 years after radiation therapy (RT). The linear models showed that baseline evaluations for IQ and academic achievement were within the range of normal. Longitudinally, there was a statistically significant decline (points per year) in all scores (Table 2).

Impact of clinical variables on longitudinal trends in cognitive scores

We then investigated the impact of clinical variables on the longitudinal trend of cognitive scores by adding 1 clinical variable at a time. For significant changes in longitudinal scores we note P values and absolute differences in the annual rate of change, comparing high- and low-impact variables, as follows. Risk classification: Estimated IQ (EIQ) ($P=.0347$, 1.93 points per year [pts/y]) and math scores ($P=.0050$, 2.87 pts/y) declined at a higher rate in high-risk patients. Sex: Spelling scores declined at a higher rate in female patients ($P=.0207$, 2.06 pts/y). Race: EIQ was lower in black patients at baseline ($P=.0151$, 14.93

Table 1 Radiation dose to different brain volumes in 58 patients with medulloblastoma

Normal tissue volume of interest	Dose (cGy)				
	Mean	SD	Median	Minimum	Maximum
Brain total	4034	528.7	3797	3336	5006
Left hippocampus	5219	421.9	5379	3749	5892
Right hippocampus	5189	420.6	5286	4110	5885
Infratentorial	5688	159.6	5678	5349	6167
Supratentorial	3814	596.4	3596	3006	4865
Left temporal	4558	450.7	4462	3600	5507
Right temporal	4529	422.0	4436	3749	5462

Abbreviation: SD = standard deviation.

Table 2 Longitudinal models of cognitive scores through 5 years after craniospinal irradiation in patients with medulloblastoma

Psychology test	No. of patients	Baseline	5-y Score	Δ Points/y
Estimated IQ	58	93.44	89.35	−0.82
WIAT Math	52	94.50	84.11	−2.08
WIAT Reading	52	94.99	83.48	−2.30
WIAT Spelling	52	93.28	82.84	−2.09

Abbreviations: IQ = intelligence quotient; WIAT = Wechsler Individual Achievement Test.
Cognitive test score = baseline value + Δ points/y × time in years.

Table 3 Effect of increasing mean dose on cognitive test scores by brain volume

	Estimated IQ		WIAT math		WIAT reading		WIAT spelling	
Normal tissue volume	−	+	−	+	−	+	−	+
Entire brain	.0121	<.0001	.0096	.0007	n.s.	<.0001	n.s.	.0002
Supratentorial brain	.0161	<.0001	.0251	.0009	n.s.	<.0001	n.s.	.0002
Temporal lobe (left)	.0032	<.0001	.0184	.0013	n.s.	<.0001	n.s.	.0002
Temporal lobe (right)	.0005	<.0001	.0053	.0009	.0184	<.0001	n.s.	<.0001
Hippocampus (left)	.0751	<.0001	n.s.	.0025	n.s.	<.0001	n.s.	.0001
Hippocampus (right)	.0130	<.0001	n.s.	.0016	n.s.	<.0001	n.s.	<.0001
Infratentorial brain	.0002	<.0001	n.s.	.0034	n.s.	<.0001	n.s.	.0001

Abbreviation: n.s. = not significant. Other abbreviations as in Table 2.
P values are grouped in columns according to the inclusion (+) or exclusion (−) of age in the model.

pts). Cerebrospinal fluid shunt: EIQ was higher at baseline (12.58 pts) in patients who did not have a CSF shunt ($P = .0478$), and those without CSF shunts had a lower rate of decline in math ($P = .0025$, 4.79 pts/y) and reading scores ($P = .0319$, 2.32 pts/y). Extent of resection: Baseline math scores were higher in patients who underwent < GTR ($P = .0091$, 9.97 pts). Gross total resection was associated with a slower rate of decline in reading scores ($P = .0269$, 2.25 pts/y) than in those who underwent < GTR. Age at RT: With the exception of math and reading scores, age (time of diagnosis or irradiation) had a highly significant impact on the rate of decline in all test scores (EIQ, $P = .0141$; Math, $P = .1832$; Reading, $P = .0688$; Spelling, $P = .0424$).

Impact of mean radiation dose on longitudinal trends in cognitive scores

The longitudinal trends in cognitive scores were modeled by time since irradiation and mean dose. Increasing mean dose to all volumes had a statistically significant negative impact on EIQ. Increasing mean dose to all normal tissue volumes except for the infratentorial brain and hippocampi had a statistically significant negative impact on math scores. Increasing mean dose to the right temporal lobe had a statistically significant negative impact on reading scores. The impact of increasing mean dose to the right hippocampus was borderline significant. When age was included,

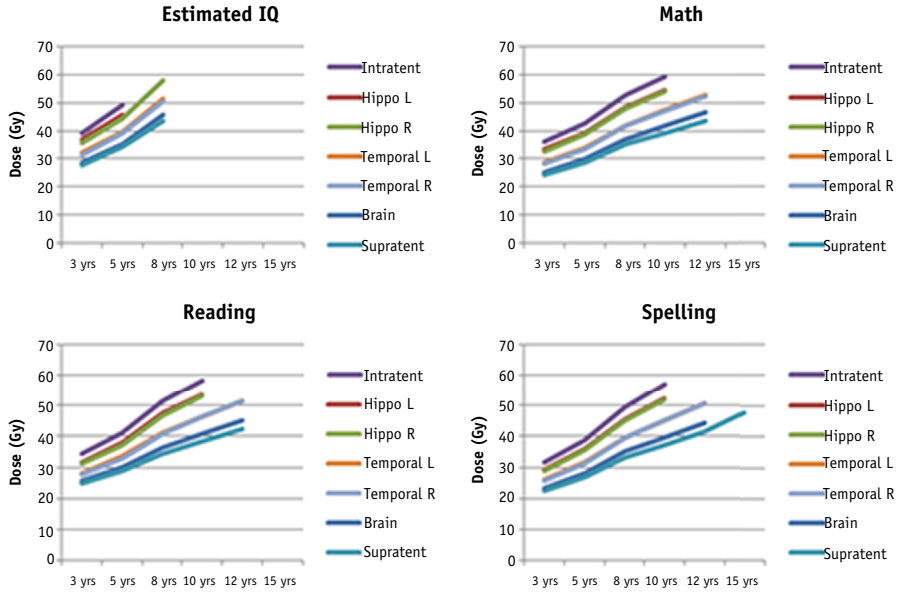

Fig. 1. Estimated iso-effect curves of mean dose by brain volume and age at the time of irradiation representing a probability of below-average IQ or academic achievement 5 years after treatment. Each graph represents a different cognitive test, and each curve represents a different normal tissue volume. Missing estimates indicate that the model calculated a dose that was outside the range of dose used to generate the models. Brain = entire brain volume; EIQ = estimated intelligence quotient; Hippo L = left hippocampus; Hippo R = right hippocampus; Infratent = infratentorial brain; Math = Wechsler Individual Achievement Test (WIAT) math scores; Reading = WIAT reading scores; Spelling = WIAT spelling scores; Supratent = supratentorial brain; Temporal L = left temporal lobe; Temporal R = right temporal lobe.

Table 4 Statistical significance of dose-volume intervals on longitudinal cognitive scores after craniospinal irradiation

		Cut point V25 Gy		Cut point V35 Gy		Cut point V45 Gy		Cut point V55 Gy	
Volume	Test	V <2 Gy	V >25 Gy	V <35 Gy	V >35 Gy	V <45 Gy	V >45 Gy	V <55 Gy	V >55 Gy
Brain	EIQ	n.s	.0079	n.s.	.0027	n.s.	.0140	n.s.	.0185
	Math	n.s.	<.0001	n.s.	<.0001	n.s.	.0010	n.s.	n.s.
	Reading	n.s.	<.0001	n.s.	<.0001	n.s.	.0252	n.s.	n.s.
	Spelling	n.s.	.0003	n.s.	.0001	n.s.	n.s.	n.s.	n.s.
Supratentorial	EIQ	n.s.	.0077	n.s.	.0028	n.s.	.0153	n.s.	n.s.
	Math	n.s.	.0001	n.s.	<.0001	n.s.	.0032	.0403	n.s.
	Reading	n.s.	<.0001	n.s.	<.0001	n.s.	.0177	.0051	n.s.
	Spelling	n.s.	.0002	n.s.	<.0001	.0486	n.s.	.0024	n.s.
Infratentorial	EIQ	n.s.	n.s.	n.s.	n.s.	.0483	.0144	.0018	.0002
	Math	n.s.	.0002	n.s.	.0003	n.s.	<.0001	n.s.	<.0001
	Reading	n.s.	<.0001	n.s.	<.0001	n.s.	<.0001	n.s.	<.0001
	Spelling	n.s.	<.0001	.0309	<.0001	n.s.	<.0001	n.s.	<.0001
Temporal Left	EIQ	n.s.	.0362	.0152	.0010	n.s.	.0016	n.s.	.0167
	Math	n.s.	.0001	n.s.	<.0001	n.s.	<.0001	.0590	n.s.
	Reading	n.s.	<.0001	n.s.	<.0001	n.s.	<.0001	.0063	n.s.
	Spelling	n.s.	<.0001	n.s.	<.0001	n.s.	.0035	.0033	n.s.
Temporal Right	EIQ	n.s.	.0413	.0094	.0006	.0203	.0003	n.s.	.0019
	Math	n.s.	.0004	n.s.	<.0001	n.s.	<.0001	n.s.	n.s.
	Reading	n.s.	<.0001	n.s.	<.0001	n.s.	<.0001	.0282	.0201
	Spelling	n.s.	<.0001	n.s.	<.0001	n.s.	.0006	.0234	n.s.

Abbreviations: EIQ = estimated intelligence quotient; Math = WIAT math scores; Reading = WIAT reading scores; Spelling = WIAT spelling scores. Other abbreviations as in Table 2.

it had a significant impact on longitudinal scores in all models (Table 3). The *P* values are included in Table 3 to show the presence or absence of an association and the relative significance. Appendix 1 (available online) includes the full models.

TD 50/5 for below-average IQ and academic achievement according to mean normal tissue dose

We calculated the mean dose required for a child to have a 50% risk of a below-average IQ or academic achievement test score 5 years after irradiation. The calculation was performed using age-adjusted mean dose models. The estimated mean doses are presented as iso-effect curves in Figure 1. The larger-volume normal tissue structures required a lower dose to achieve the same effect as the smaller-volume normal tissue structures.

Impact of radiation dose intervals on longitudinal trends in cognitive scores

Using the cut points of 25 Gy and 35 Gy, the higher dose interval had a consistent and statistically significant impact on the longitudinal trend in cognitive test scores, whereas the lower dose interval did not. A similar finding was observed for the infratentorial and temporal lobe volumes at 45 Gy. For the other normal tissue volumes evaluated at 45 Gy and all normal tissue volumes at 55 Gy, the impact of dose was significant only when the dose interval (high or low) included the majority of the volume (data not shown). The only exception was for EIQ. At the high-dose cut points of 45 Gy and 55 Gy, the higher-dose term was smaller than the lower-dose term and retained statistical significance (Table 4). The *P* values are included in Table 4 to show the presence or absence of an association and the relative significance. Appendix 2 includes the full models.

TD 50/5 for below-average IQ and academic achievement according to radiation dose intervals

For the entire brain and left and right temporal lobes we calculated, according to the age of the patient at the time of RT, the threshold volumes receiving dose in excess of 25 Gy, 35 Gy, 45 Gy, and 55 Gy that would have 50% of cognitive scores falling below 85 for EIQ 5 years after RT. The results show that no additional dose to the entire brain above a specified level would be required for patients with the specified ages or younger to have a 5% probability of EIQ <85 at 5 years: age 8 years and 25 Gy, age 12 years and 30 Gy, age 15 years and 35 Gy. For both the left and right temporal lobes these values were age 8 years and 25 Gy, age 8 years and 30 Gy, age 10 years and 35 Gy, age 12 years and 40 Gy, age 12 years and 45 Gy, and age 15 years and 50 Gy. The results show that there is a <50% probability of an EIQ <85 for the following combination of brain dose and age: <25 Gy and ≥8 years, <30 Gy and ≥12 years, and <35 Gy and ≥15 years. The probability of an EIQ <85 at 5 years is <50% for the following combinations of left and right temporal lobe dose: <25 Gy and

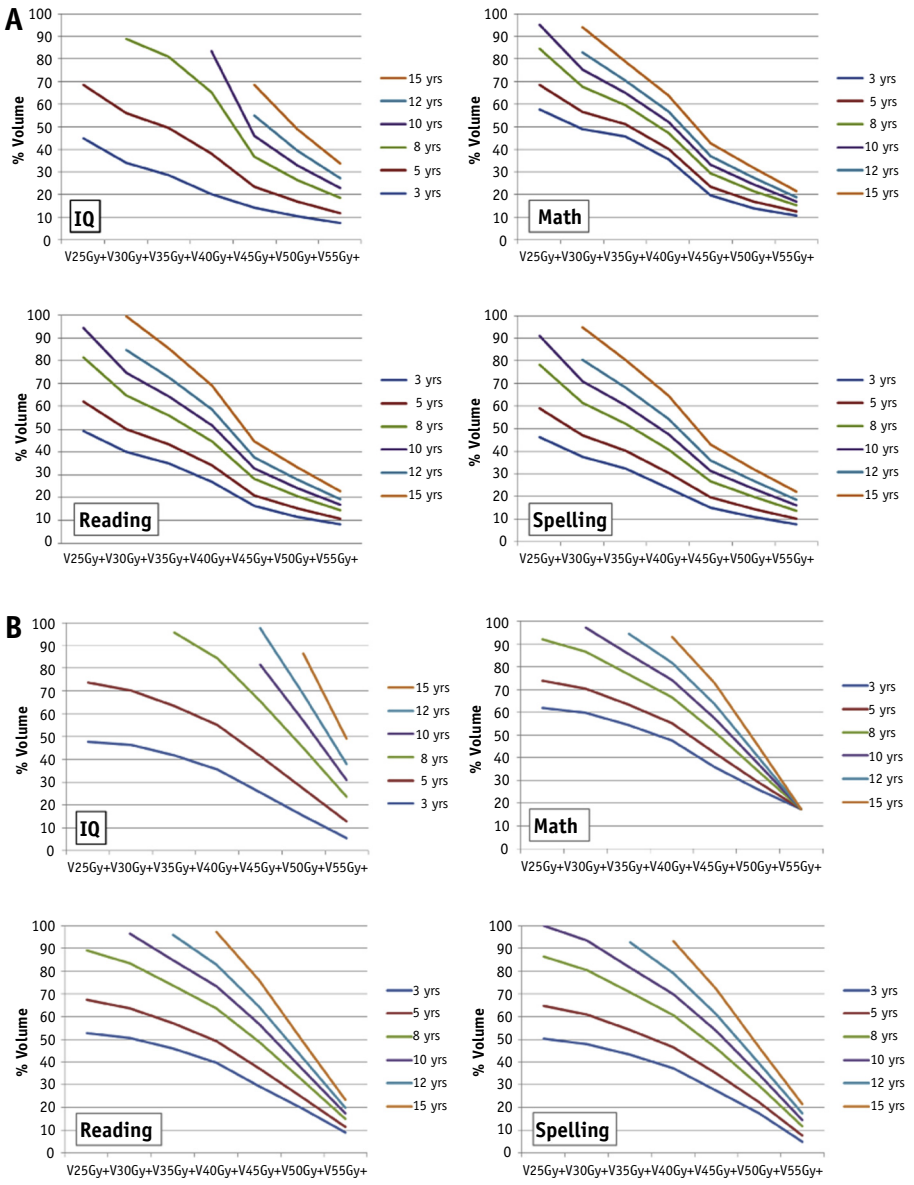

Fig. 2. Iso-effect curves of age at the time of irradiation modeled according to the percentage of a specific brain region receiving a mean dose in excess of a specified amount. V25 Gy + represents the percent volume of the brain receiving dose in excess of 25 Gy. TD 50/5 (tolerance dose for a given normal tissue that within 5 years will cause a maximal [unacceptable] 50% complication rate) for brain (a), left temporal lobe (b), and right temporal lobe (c).

8 years, <30 Gy and 8 years, <35 Gy and 10 years, and <40 Gy and 12 years (Fig. 2a-c).

Discussion

Patients with MB treated with postoperative CSI and postirradiation chemotherapy experience a decline in cognitive test scores during the first 5 years after treatment, and a variety of clinical variables contributed to the baseline scores or decline. The presence of CSF shunt, sex, and race had the greatest impact on baseline IQ scores. High-risk classification, female sex, the presence of CSF shunt, and the extent of resection had a significant impact on decline in scores. Depending on the outcome measure, the decline exceeded 4 points per year in some cases. As anticipated, age had a significant impact on decline in all measures, and the rate of decline was inversely proportional to age at the time of irradiation.

The most important information from this study was the association between radiation dose and cognitive test scores. Similar to our previous work, we were able to show regional differences in radiation dose and effect (13). In this study we expanded the association between dose, volume, and outcome measures to include additional structures and academic achievement. Increasing mean dose to all volumes except for the left hippocampus impacted IQ. Increasing mean dose to all volumes except the infratentorial brain and

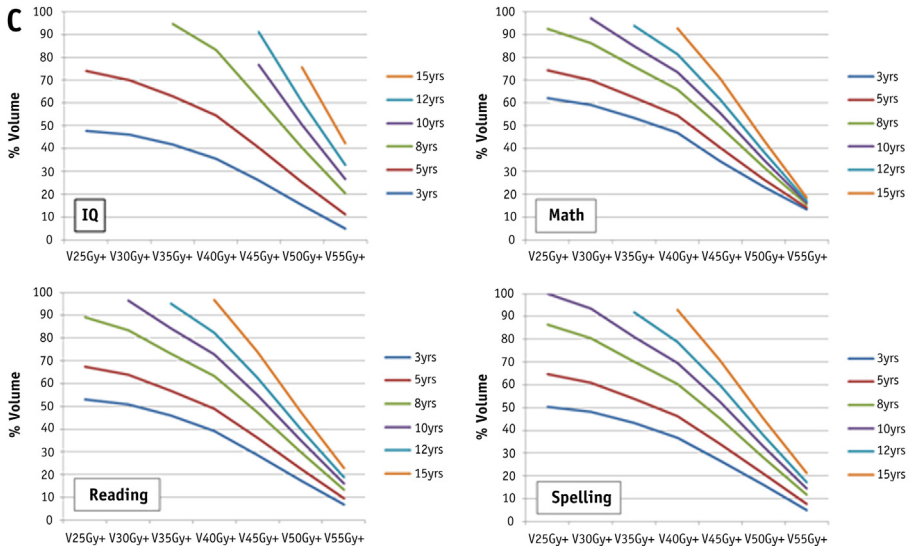

Fig. 2. (*Continued*).

either hippocampus had an effect on math scores. Increasing mean dose only to the right temporal lobe had a significant impact on reading scores. There was no association between spelling scores and radiation dose for this cohort. Increasing mean dose to all volumes affected all scores when age was included in the model. This is one of the first-large scale studies to demonstrate an effect between hippocampus dose and cognitive outcome in children, although many have supported hypotheses surrounding this association. Age at the time of irradiation, when incorporated into the model, increased the significance of the aforementioned interactions between mean dose and time and contributed additional correlations between radiation dose, all measures of academic achievement, and the normal tissue volumes under evaluation. The latter finding suggests the importance of including clinical variables in the models.

Understanding the association between radiation dose and outcome is important. Most radiation oncologists prefer a simplified approach to treatment optimization, relating risk of complications to a specific dose. The calculated TD 50/5 estimates in this report provide this type of data reduction. We estimated that when the brain dose exceeds 25 Gy for a patient aged <8 years, 30 Gy for a patient aged <12 years, and 35 Gy for a patient aged <15 years, there is a 50% probability of below-average IQ 5 years after treatment.

The infratentorial brain seems to be the most tolerant normal tissue volume among those assessed for the outcomes of IQ and academic achievement, followed by the temporal lobes and associated hippocampi, and finally the supratentorial brain. The implication of this information is that for the given combinations of dose and volume it may be difficult to reduce side effects. In the setting in which CSI is administered, measures taken to reduce dose to normal tissues in the boost phase of treatment might have little impact. This finding supports the need to further reduce or eliminate the use of CSI wherever possible.

The iso-effect curves presented have several dimensions: patient age at irradiation, radiation dose parameter, brain volume at risk, and psychology outcome measure. The information in the iso-effect plots may be used as a threshold in the treatment planning process, to evaluate risk of cognitive decline in assessing the potential benefit of delaying irradiation, and to design interventions for populations at risk.

The effects of CSI in long-term survivors of MB are historic (22) and are motivation for investigators to test alternatives, including modifications in the sequencing of therapy (23) or general radiation therapy parameters of total dose and fractionation (24). New information about the biology of MB may identify selected patients for CSI dose reductions or elimination. This information is currently being used to select favorable-risk patients for CSI doses as low as 15 Gy (25). As proton therapy promises to further reduce the dose to normal tissue associated with the boost phase of treatment, it is conceivable that with more advanced forms of proton therapy, including intensity modulated proton therapy (26), selectively reducing dose to critical volumes of the brain during CSI, especially those associated with neurogenesis, might be feasible and safe. Future treatment of children with embryonal tumors may be preferentially administered using proton therapy. Optimally planned intensity modulated proton therapy might be able to limit the high-dose volume and associated collateral dose to the infratentorial space. This could advantageously limit the dose to the supratentorial structures, including the temporal lobes and hippocampal subvolumes, to the prescribed CSI dose or below the threshold of effect and lead to improved outcomes (27).

There are limitations to the present study: the number of patients, the number of clinical factors that might affect baseline and longitudinal measures, and the measures themselves, which include only global intelligence and academic achievement. The study cohort was treated and followed on a

protocol that limited prospective follow-up to 5 years and included patients with high-risk features. There are a number of clinical factors that strongly influence baseline and longitudinal cognition, including the effects of age (28), tumor (hydrocephalus), and surgery (29, 30). Accounting for these factors and the development of comprehensive parametric models, including dose, requires more patients.

In summary, there are strong associations between radiation dose, irradiated volume, and cognitive outcomes as measured by standardized tests. When modeling the effect of radiation dose, clinical factors that affect baseline and longitudinal measures should be considered. Future research should be focused on assessing larger datasets, inclusion of patients treated with a wider range of CSI dose, and the development of multiparametric models.

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Clinical Investigation

Effect of Cerebellum Radiation Dosimetry on Cognitive Outcomes in Children With Infratentorial Ependymoma

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Summary

This study associates longitudinal deficits in intelligence quotient (IQ) and academic achievement with collateral irradiation of the posterior cerebellum in children with infratentorial ependymoma. To further reduce cerebellum-linked neurocognitive deficits, radiation dose to the posterior cerebellum should be avoided in treatment planning and delivery. Advanced methods of radiation therapy may be used to further optimize treatment of these patients.

Purpose: Cognitive decline is a recognized effect of radiation therapy (RT) in children treated for brain tumors. The importance of the cerebellum and its contribution to cognition have been recognized; however, the effect of RT on cerebellum-linked neurocognitive deficits has yet to be explored.

Methods and Materials: Seventy-six children (39 males) at a median 3.3 years of age (range, 1-17 years old) were irradiated for infratentorial ependymoma from 1997 to 2008. The total prescribed dose was 54 to 59.4 Gy administered to the postoperative tumor bed with 5- or 10-mm clinical target volume margin. Age-appropriate cognitive and academic testing was performed prior to the start of RT and was then repeated at 6 months and annually throughout 5 years. The anterior and posterior cerebellum and other normal brain volumes were contoured on postcontrast, T1-weighted postoperative magnetic resonance images registered to treatment planning computed tomography images. Mean doses were calculated and used with time after RT and other clinical covariates to model their effect on neurocognitive test scores.

Results: Considering only the statistically significant rates in longitudinal changes for test scores and models that included mean dose, there was a correlation between mean infratentorial dose and intelligence quotient (IQ; −0.190 patients/Gy/year; $P = .001$), math (−0.164 patients/Gy/year; $P = .010$), reading (−0.137 patients/Gy/year; $P = .011$), and spelling scores (−0.147 patients/Gy/year; $P = .012$), where Gy was measured as the difference between the mean dose received by an individual patient and the mean dose received by the patient group. There was a correlation between mean anterior cerebellum dose and IQ scores (−0.116 patients/Gy/year; $P = .042$) and mean posterior cerebellum dose and IQ (−0.150 patients/Gy/year; $P = .002$), math

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(−0.120 patients/Gy/year; $P = .023$), reading (−0.111 patients/Gy/year; $P = .012$), and spelling (−0.117 patients/Gy/year; $P = .015$) scores.
Conclusions: Sparing portions of the cerebellum should be considered in RT planning for children with infratentorial ependymoma because of the potential impact of radiation dose on cognitive function.

Introduction

Neurocognitive impairment after irradiation is a major concern when treating children with brain tumors, especially those who share the prospect of long-term survival. Measures to reduce radiation dose to the normal brain have been successful to the extent that even very young children with localized brain tumors are offered irradiation as a part of initial management in clinical trials (studies ACNS0121 [NCT00027846], ACNS0831 [NCT01096368], and A9934 [1]).

Reducing radiation dose to normal brain has been achieved through target volume reduction and by reducing the total prescribed dose. Newer methods of irradiation have been investigated, including conformal and intensity modulated photon and proton therapy. These methods rely on a detailed understanding of radiation dose-volume effects which link the incidence and severity of neurocognitive impairment to specific volumes of normal brain, defined by their function.

Our team was among the first to describe the association between radiation dose distributions and longitudinal cognitive measures in low-grade glioma (2), medulloblastoma (3), ependymoma (4), and craniopharyngioma (5). Children with ependymoma show remarkable resiliency and preservation of cognition as determined by longitudinal measures of intelligence, memory, attention, and behavior (6-8).

Possible explanations for preservation of cognition include the resiliency of the cerebellum or its contribution to cognitive processes. Cognition in humans has been thought to involve frontal and tempoparietal lobes, the hippocampus-mammillary complex, and other supratentorial regions. There is increasing evidence to suggest a role for the cerebellum in complex cognitive operations like language function, working memory, executive function, and emotion (9-11). Investigations suggest the posterior cerebellum has a role in cognition and that the anterior cerebellum appears to contribute to sensorimotor function (10, 12). Cognitive deficits in children with cerebellar tumors treated with surgery alone have been reported (13-19). It remains unclear whether cerebellar irradiation affects cognitive function.

The impact of irradiation on the cerebellum has become relevant in the current era, as the posterior fossa has become one of the most commonly irradiated sites. Understanding the effect of radiation dose will improve our ability to selectively spare the cerebellum in the process of treatment planning and help us to further understand the neurobiological mechanisms underlying cognitive deficits.

We investigated the association between radiation dose to the cerebellum and the time course of cognitive change after irradiation. Children enrolled in our prospective trials using RT for infratentorial ependymoma provided a group from which prospective neurocognitive assessments have been performed and a unique opportunity to explore the correlation between cerebellar irradiation and cognition.

Methods and Materials

Patients

Seventy-six pediatric patients (39 males), median age 3.3 years (range 1-17 years) with diagnoses of localized infratentorial ependymoma and enrolled in a phase 2 trial of conformal radiation therapy (CRT) between 1997 and 2008 were included. Patients included in this investigation had a minimum of two neurocognitive assessments. Details of the trial and results were reported earlier (20). None of the participants had tumor recurrence prior to the neurocognitive assessments, and none was censored because of a decline in function. Institutional Review Board approval was obtained, and data were managed according to the Health Insurance Portability and Accountability Act of 1996. Written, informed consent was required.

Radiation treatment planning, cerebellar contouring, and radiation dose

All patients received conformal or intensity modulated RT using conventional fractionation of 1.8 Gy per day. The total dose was 54 or 59.4 Gy administered 5 days per week. The lower dose was used for children younger than 18 months treated with gross-total resection. The gross tumor volume included the postoperative tumor bed and residual disease. The clinical target volume (CTV) margin (5 or 10 mm) surrounded the gross tumor volume to account for subclinical tumor extension. This volume was confined at non-neural interfaces. The CTV was surrounded geometrically by the planning target volume (PTV) margin (3-5 mm) to account for variability in positioning. Treatment was prescribed such that 100% of the PTV received at least 95% of the protocol-specified dose.

The supratentorial and infratentorial brain and anterior and posterior cerebellar lobes were contoured on postoperative T1-weighted magnetic resonance images (3D-acquired MP RAGE postcontrast with in-plane resolution of 1 mm) obtained immediately prior to RT and

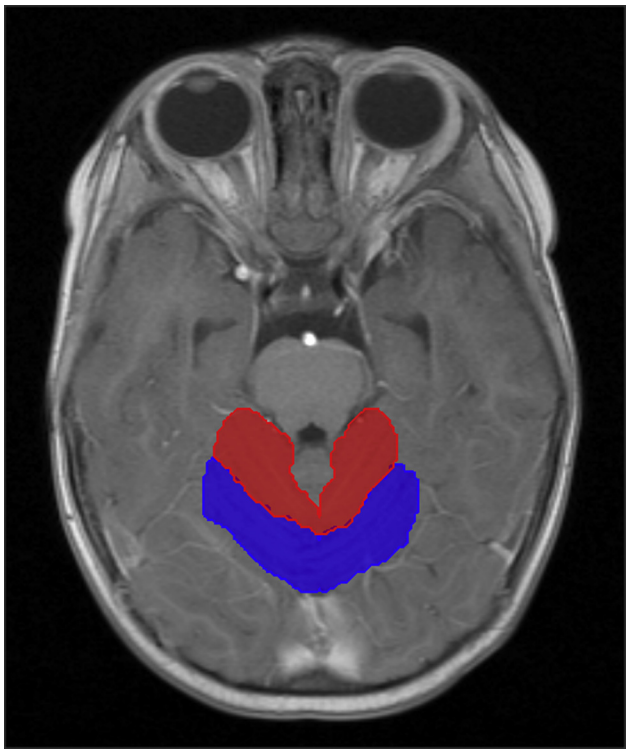

Fig. 1. Axial postcontrast T1-weighted MR image showing representative anterior (red) and posterior (blue) cerebellar contours. A color version of this figure is available at www.redjournal.org.

coregistered to the computed tomography dataset used for dose calculation (Fig. 1). The infratentorial brain included the entire brainstem and cerebellum. The cerebellum was segmented into anterior and posterior lobes according to the magnetic resonance imaging atlas outlined by Schmahmann et al (21). The primary fissure was identified in the midsagittal plane and was used as a landmark for segmenting the anterior and posterior cerebellar lobes. Lobules I to V were included in anterior cerebellar lobes, and lobules VI to X were included in posterior cerebellar lobes. Differential dose-volume histograms were calculated for the normal tissue volumes. For purposes of analysis, the left and right cerebellar lobes were combined because it was assumed that irradiation of the other lobe would have a similar effect and taken as the error term in the model and reduce the power of the statistical test. The mean doses were highly correlated between the anterior cerebellum left 5679.6 ± 479.8 cGy and right 5676.9 ± 411.6 cGy and the posterior cerebellum left 5060.7 ± 582.9 cGy and right 5030.8 ± 635.3 cGy.

Surgery and chemotherapy

All patients underwent resection prior to RT. Ventriculoperitoneal cerebrospinal fluid (CSF) shunting was performed as required, in 24 patients. Twelve patients received chemotherapy prior to irradiation, using cyclophosphamide and cisplatin or carboplatin, etoposide, and vincristine.

Cognitive outcomes intelligence quotient, academic tests, and visual-auditory learning scores

Patients underwent age-appropriate prospective neurocognitive assessment at the outset of treatment, after the initial surgery and usually prior to irradiation but otherwise within 3 months, 6 months, and annually through 5 years. Intelligence quotient (IQ) was measured using the mental index of Bayley scales or derived from the Information, Similarities and Block Design subtests from the age-appropriate Wechsler scale (22, 23). Academic testing included three subsets from Wechsler Individual Achievement Test (WIAT), namely, the WIAT Word Reading, Spelling, and Math Reasoning (24). Visual learning was assessed with the Visual-Auditory Learning (VAL) test from Woodcock-Johnson Tests of Cognitive Ability (revised) (25). The VAL test is an associative learning task of word-symbol pairings. Each subset score was converted to an age-standardized score based on a large, representative, normative sample with a mean of 100 and a standard deviation of 15.

Statistical analysis

A mixed-effects model with random coefficients for intercept and slope was used for the analysis. The intercept was the estimate of the baseline scores; the slope was the rate of change for the population average scores on the specific neurocognitive test and measured the magnitude of the effect of the independent variable. The *P* value of the coefficient was considered for comparative significance relative to the mean for the patient group. Longitudinal trends of population average scores were first estimated with time as the only covariate. The following covariates were then used in the multivariate analysis: age at the time of irradiation based on the mean of 4.8 years (younger, <4.8 years; older, >4.8 years); sex, race, presence of a CSF shunt, the use of preirradiation chemotherapy, gross tumor volume, CTV and PTV; and mean dose to the supratentorial brain, infratentorial brain, anterior cerebellum, and posterior cerebellum and left and right hippocampi. To analyze the effect of radiation dose, differences in mean dose from the population average were used as covariate. The number of tests contributing to the analysis included IQ (n = 559), WIAT Math scores (n = 365), WIAT Reading scores (n = 363), WIAT Spelling scores (n = 361), and VAL (n = 292). Differences in the number of evaluations were attributed to age at the time of testing and the appropriateness of the measure. All analyses were performed using SAS version 9.2 software (Cary, NC).

Results

Mean doses (±standard error [SE]) to the supratentorial brain (14.04 ± 3.24 Gy), infratentorial brain (52.13 ± 4.50 Gy), anterior cerebellum (56.78 ± 4.32 Gy), and

posterior cerebellum (50.6 ± 5.82 Gy) were calculated. Baseline mean neurocognitive scores were within the normal range (mean ± SE) for WIAT reading (103.60 ± 1.53), WIAT math (98.62 ± 1.93), WIAT spelling (102.30 ± 2.21), VAL (94.66 ± 2.54), and IQ, which was below average (96.59 ± 1.78). Based on longitudinal observations through the first 5 years after irradiation, improvement was observed in IQ and VAL scores at the rate of 0.1803 ± 0.246 points/year ($P = .467$) and 1.361 ± 0.371 points/year ($P \leq .001$), respectively. Among the academic achievement scores, WIAT math scores remained unchanged over time, whereas a modest but statistically significant decline was observed in WIAT reading scores at the rate of −0.96 ± 0.24 points/year ($P \leq .001$) and in WIAT spelling scores of −0.85 ± 0.35 points/year ($P = .019$) (Table 1).

The association between clinical variables and baseline cognitive scores was investigated. There was a negative correlation between baseline scores and the presence of a CSF shunt for all of the cognitive measures. This correlation was statistically significant for IQ (−11.55, $P = .002$), WIAT reading (−8.17, $P = .003$), WIAT math (−7.15, $P = .036$), WIAT spelling (−6.08, $P = .057$), and VAL (−9.05, $P \leq .037$). There was a positive correlation with age at the time of irradiation and baseline IQ scores (1.31 patients/1 year-age-difference [yad]; ie, difference between the age of the individual patient and group mean; $P = .006$) and VAL scores (2.24 patients/yad, $P \leq .001$) and negative correlation between age and baseline WIAT reading scores (−0.91 patients/yad, $P \leq .001$). The use of preirradiation chemotherapy had no impact on baseline scores. None of the clinical variables of age at irradiation, CSF shunt, or preirradiation chemotherapy impacted longitudinal change in neurocognitive scores.

Effect of cerebellar dosimetry on longitudinal IQ scores

When IQ scores were estimated using a mixed model equation adjusted for time since irradiation, there was a significant association between IQ scores and infratentorial, anterior cerebellar, and posterior cerebellar mean doses and time after treatment. The magnitude of the effect ranged from −0.150 patients/Gy/year for the posterior cerebellum to −0.190 patients/Gy/year for the infratentorial brain.

Effect of cerebellar dosimetry on longitudinal WIAT reading, math, and spelling scores

When WIAT Reading, Math, and Spelling scores were estimated individually by using mixed model equations, adjusted for time since irradiation, infratentorial and posterior cerebellar mean doses were found to have significantly negative effects on the longitudinal trend of all WIAT academic scores, ranging from −0.111 patients/Gy/year for the posterior cerebellum on WIAT reading scores to −0.164 patients/Gy/year for the infratentorial brain on WIAT math scores (Table 2).

Effect of tumor volume, surgery, and RT parameters

There was an association between the gross tumor volume and longitudinal VAL scores. The magnitude of the effect was −0.0729 patients/mL/year ($P = .0222$). There was no association between number of surgery procedures or preirradiation extent of resection and longitudinal scores. Fifty-one patients had 1 surgery, 21 patients had 2 operations, and 4 patients underwent 4 attempts at resection prior to irradiation. The preoperative extent of resection was gross-total resection (GTR) in 61, near total resection (NTR) in 11 and subtotal resection (STR) in 4. There was an association between mean dose to the left hippocampus and longitudinal IQ (−0.0558 patients/Gy/year; $P = .0305$) and VAL (−0.0517 patients/Gy/year; $P = .0063$) scores. There was an association between mean dose to the right hippocampus and VAL (−0.0683 patients/Gy/year; $P = .0024$) scores. There was no association between cumulative total dose (54 Gy vs 59.4 Gy) and longitudinal cognitive scores. Eight patients received 54 Gy, and the remainder received 59.4 Gy.

Table 1 Baseline and longitudinal trends in cognitive tests scores in 76 children with infratentorial ependymoma treated with postoperative irradiation

		Baseline (intercept)*			Slope†		
Cognitive test	No. of evaluations	Estimate	SE	*P*	Estimate	SE	*P*
IQ	559	96.5869	1.7809	<.0001	0.1803	0.2460	.4671
WIAT reading	363	103.60	1.5313	<.0001	−0.9639	0.2458	.0004
WIAT math	365	98.6237	1.9306	<.0001	0.3460	0.3249	.2918
WIAT spelling	361	102.30	2.2108	<.0001	−0.8536	0.3463	.0190
VAL	292	94.6609	2.5354	<.0001	1.3610	0.370	.0009

Abbreviations: IQ = intelligence quotient; VAL = visual-auditory learning; WIAT = Wechsler Individual Achievement Test.

* Intercept scores represent neurocognitive scores at conformal radiation therapy baseline. Scores are reported as standard scores, which have a normative mean of 100 and a standard deviation of 15.

† Slope represents change in neurocognitive scores in standard points per year.

Table 2 Longitudinal effect of mean radiation dose on cognitive test scores in 76 children with infratentorial ependymoma

Test and site	Slope[†]		
Brain subvolume	Estimate[*]	SE	*P* value
IQ			
Infratentorial brain	−0.190	0.055	.001
Anterior cerebellum	−0.116	0.055	.042
Posterior cerebellum	−0.150	0.047	.002
Supratentorial brain	0.057	0.076	.451
WIAT reading			
Infratentorial brain	−0.137	0.052	.011
Anterior cerebellum	−0.073	0.048	.134
Posterior cerebellum	−0.111	0.043	.012
Supratentorial brain	0.039	0.066	.557
WIAT math			
Infratentorial brain	−0.164	0.062	.010
Anterior cerebellum	−0.056	0.062	.368
Posterior cerebellum	−0.120	0.052	.023
Supratentorial brain	0.053	0.083	.528
WIAT spelling			
Infratentorial brain	−0.147	0.057	.012
Anterior cerebellum	−0.028	0.054	.608
Posterior cerebellum	−0.117	0.047	.015
Supratentorial brain	0.021	0.073	.779
VAL			
Infratentorial brain	−0.148	0.070	.040
Anterior cerebellum	0.061	0.062	.338
Posterior cerebellum	−0.136	0.059	.026
Supratentorial brain	−0.050	0.090	.585

Abbreviations: IQ = intelligence quotient; NS = not significant; SE = standard error; VAL = visual-auditory learning; WIAT = Wechsler Individual Achievement Test.

[*] Estimate represents the additional rate of change in neurocognitive outcome contributed by the mean radiation dose in points/Gy/year. It is calculated according to the differences of radiation dose deviated from the population average.

[†] Slope represents rate of change in neurocognitive scores in standard points per year.

Discussion

Ependymoma is the third most common brain tumor in children, and overall survival rates exceed 70% when measured at 5 years in patients receiving immediate postoperative irradiation (20). Most children with ependymoma have infratentorial tumor location and excellent functional outcomes after standard treatment; however, among those who experience cognitive decline, younger age at the time of irradiation, multiple and extensive surgery, hydrocephalus, and chemotherapy have been implicated, in addition to dose and volume of irradiation (6, 26-32). Although our analysis identified factors associated with cognitive decline, the associated risk was small. This study is a step forward in our understanding of the effects of irradiation in a functional subvolume of the normal brain with results that associate cerebellar irradiation with specific cognitive effects in children with ependymoma. High-dose irradiation of the infratentorial brain was associated with a steeper decline in multiple cognitive domains. The negative effect on IQ was contributed by both anterior and posterior cerebellar mean doses; whereas, the decline in academic achievement scores was primarily attributed to the mean posterior cerebellar doses. These results suggest that sparing of the cerebellar volume should be considered during radiation planning and that smaller target volumes should be considered when feasible.

The cerebellum has been thought to be involved in regulation of motor coordination, balance, and motor speech (9, 33, 34). In the past 2 decades, neuroanatomical studies have shown reciprocal connectivity of cerebellum with cerebral frontal, parietal, and temporal associative areas involved in higher cognitive functioning (9, 12). Numerous functional neuroimaging studies showed activation of cerebellum during cognitive tasks like language, executive function, and working memory (9, 12). According to the functional dichotomy of cerebellum (12, 33), anterior cerebellum having reciprocal connection to cerebral motor cortex and spinal cord is thought to be involved in sensorimotor functions and posterior lobe, defined as the region posterior and inferior to primary fissure and comprising lobules VI to X, to be involved in cognitive domains (11, 33). The association of higher-than-population-average posterior cerebellar doses with declines in the cognitive outcomes, namely, IQ, reading, math, and spelling scores, replicates this functional topography to some extent. Negative effect of anterior cerebellar mean doses with estimated IQ may reflect the effect of anterior cerebellar irradiation on the timed motor component of this assessment (eg, although performing the block design subset, the child is required to place the blocks as per a specific design within a limited time period, thus relying on a child's speed with motor abilities).

Contrary to the studies evaluating cognitive outcomes in children receiving whole-brain irradiation (26, 35, 36) and consistent with reports of children treated with limited irradiation (4, 26, 31), average IQ scores of our cohort after 5 years of CRT fall within the range of population norms. IQ is a complex cognitive construct that involves anatomically distributed regions of the brain, including a variety of supratentorial and infratentorial brain subvolumes like frontal, parietal gray matter volume, and putamen and the entire cerebellar volume (37). Although a recent study of children treated for ependymoma with proton RT failed to indicate a decline in intellectual or adaptive functioning, the sample size was small (n = 14 and n = 28, respectively), and the follow-up time was short (average of 2 years), precluding conclusions or comparison with current findings (38). Although we are not clear about relative contributions of different brain regions involved in this complex cognitive ability, the sparing effect of newer methods on IQ or greater IQ decline observed in those treated with cranial irradiation (26) can be hypothesized to be secondary to the additive effects of tumor and other treatments, most notably surgery to the functional subunits that may be distant but anatomically connected through white matter bundles. This

is supported by the fact that global white matter changes reflecting demyelination and thus disrupting trans-synaptic communications have been implicated as a possible mechanism underlying postirradiation brain injury causing cognitive deficits (39, 40). Similarly, a diffusion tensor imaging-based study in children with posterior fossa tumors revealed that disruption of cerebellothalamocerebral pathways following irradiation were associated with poorer working memory, a core cognitive skill involved in complex cognitive functions including IQ and academics (41). The same authors stated that diffuse white matter changes in the posterior fossa following irradiation and disruption of multiple other pathways connecting cerebellum to supratentorial structures may have been responsible for deficits.

Linguistic skills such as reading and spelling were more vulnerable than math skills in our cohort as shown by the decline in these group mean scores over time. This finding is contrary to the greater math impairment observed in children treated with cranial irradiation (42) but may reflect greater specificity of localized cerebellar insult following irradiation (43). The frontal, parietal, temporal, and occipital regions have been reported to be activated in response to tasks eluding orthographic, phonological, and semantic processes involved in reading (44). The posterior cerebellar regions have now been added to this list (44, 45). Cerebellar hemispheric regions adjacent to posterior superior fissure are bilaterally being activated during phonological assembly and deep nuclear regions on the right activated during semantic processing (44). Riva et al (46) in their study of children with cerebellar tumors reported poor naming and comprehension abilities that were more pronounced in right cerebellar lesions. Most of our patients had midline tumors. Minimal dose differences in right and left cerebellar hemispheres limited our ability to test this lateralization effect (6).

Cerebellar involvement in mathematical calculations has been documented and is thought to rely on its connectivity with frontal brain regions (47). WIAT math mean scores on follow-up, however, were unchanged as reported earlier (6), but children receiving higher-than-average population mean doses to infratentorial brain and more specifically to posterior cerebellum had steeper declines in all three academic achievement scores over time, showing a deleterious effect of higher cerebellar doses on these skills.

Among the various clinical covariates studied, younger children had lower baseline IQ scores, but age effect was not evident at 5 years after CRT, which could be attributed to the sparing effect of conformal irradiation that probably does not halt their recovery from perioperative insults (6, 26, 29). Consistent with earlier reports, the deleterious negative association of severe hydrocephalus on cognition was evident and the reversible nature of this effect was replicated by the loss of this negative association with the longitudinal trends (29). IQ scores are age standardized to account for change in performance associated with typical development. The positive correlation between age at time of irradiation and baseline IQ scores likely reflects the protective effect of age with respect to potential insults encountered prior to irradiation (eg, surgical interventions, chemotherapy).

Although mean supratentorial doses were not found to affect any longitudinal cognitive trend in this analysis, we cannot outwardly refute this aspect as cranial doses as low as 18 Gy have been implicated in effects on cognition in children with acute lymphoid leukemia (48), and mean supratentorial dose for our cohort was approximately 14 Gy. Our previous analysis revealed that supratentorial volumes receiving doses as low as 0 to 5 Gy have negative effects on IQ (4). This difference could have been because of the different parameter used in present analysis (ie, mean dose as opposed to the volume receiving dose between 0 and 5 Gy) (4). Long-term detrimental effects of surgery cannot be completely excluded. Associations of long term cognitive deficits with postoperative acute cerebellar insults like cerebellar mutism have been suggested in the literature (13, 16, 31). We realize that the academic performances assessed are known to be influenced by other behavioral and environmental factors such as prolonged school absences which could not be accounted for but would not be expected to affect academic domains differentially.

Conclusions

In this relatively homogenous cohort, we were able to demonstrate that high-dose cerebellar irradiation negatively influenced the longitudinal trend of multiple cognitive measures and mirrored the functional topography of cerebellum. Our goal was not to prove whether the cerebellum was directly involved in cognition but rather to determine the contribution of cerebellar irradiation on long-term cognitive effects realizing that the cerebellum is part of a neural network.

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ORIGINAL REPORT

Impact of Craniospinal Dose, Boost Volume, and Neurologic Complications on Intellectual Outcome in Patients With Medulloblastoma

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See accompanying editorial on page 1749; listen to the podcast by Dr Armstrong at www.jco.org/podcasts

A B S T R A C T

Purpose

To examine the impact of radiation (ie, craniospinal irradiation [CSR] dose and boost volume) and complications (ie, hydrocephalus and other neurologic complications, including mutism) on patterns of change in intellectual functioning in medulloblastoma survivors.

Patients and Methods

We conducted a retrospective review of 113 patients treated for medulloblastoma between 1983 and 2011 who were seen for neuropsychological assessment, including longitudinal follow-up of intellectual function. Patients were treated with either standard-dose CSR with a posterior fossa (PF) boost (n = 51), standard-dose CSR plus tumor bed (TB) boost (n = 9), reduced-dose CSR plus PF boost (n = 28), or reduced-dose CSR plus TB boost (n = 23), with or without chemotherapy. A subset of patients developed hydrocephalus that required cerebrospinal fluid (CSF) diversion (n = 54) and/or other neurologic complications (n = 40), more than half of which were postoperative mutism (n = 25). Growth curve analysis was used to determine stability or change in intelligence scores over time.

Results

Patients treated with reduced-dose CSR plus TB boost showed stable intellectual trajectories, whereas patients treated with higher doses and larger boost volumes experienced intellectual declines. Presence of complications was associated with worse intellectual outcome; however, hydrocephalus requiring CSF diversion and mutism differed in their pattern of decline.

Conclusion

These results improve our understanding of factors that impair intellectual outcome in patients treated for medulloblastoma. Lower doses of CSR and smaller boost volumes seem to mitigate intellectual decline. Our findings validate the use of TB boost and suggest PF boost should be reconsidered.

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INTRODUCTION

Medulloblastomas are the most common malignant CNS tumors in childhood, accounting for 50% of all posterior fossa (PF) tumors.[1] Current treatment protocols include surgery, craniospinal irradiation (CSR) with a boost to the tumor site, and chemotherapy—a lifesaving combination that unfortunately contributes to long-term physical, endocrine, and neuropsychological impairments in survivors[2]; > 90% percent of survivors require long-term special education services and have reduced rates of high school graduation and employment.[3] Treatment with CSR after surgical resection of medulloblastoma results in a decline in neuropsychological functioning over time.[4-7] However, much less is known about the mediating impact of specific radiation doses and boost volumes on changes in intellectual outcome. Neurologic complications can also have deleterious effects on cognitive function.[8] It is crucial to understand the relationship between radiation dose/exposure and complications on the time course of intellectual change after treatment, because this will help to inform current protocol selection as well as the nature and design of future treatment protocols and may identify time windows for the delivery of protective or rehabilitative interventions. To address these critical issues, we examined patterns of change in intellectual

functioning for patients with medulloblastoma as a function of radiation dose and boost volume and, separately, as a function of neurologic complications.

Patients with medulloblastoma are currently stratified into average- or high-risk disease groups.[1] Average-risk disease is defined by a lack of neuraxis dissemination and/or no minimal residual tumor after surgery.[9] Radiation dose de-escalation has been adopted for average-risk patients, because they have more favorable disease outcomes. Typically, these patients are treated with reduced-dose CSR (ie, 23.4 Gy to neuraxis), whereas high-risk patients receive standard-dose CSR (ie, 36 Gy).[1] As new stratification and dose de-escalation strategies are considered in the treatment of medulloblastoma, it is important to establish the effect of different CSR doses and boost volumes on intellectual functioning.

The premise of dose de-escalation is that delivering less radiation to the brain should result in more favorable outcomes. Several cross-sectional studies have suggested treatment with reduced-dose CSR and a PF boost may result in less cognitive impairment than treatment with standard-dose CSR,[10-12] but this has not always been observed.[13] In fact, impairments were still observed across all studies. Moreover, patients treated with reduced-dose CSR and a PF boost exhibited intellectual declines over time.[7,14] PF boost volume may be critical in determining outcome. A PF boost delivers substantially more radiation to structures located outside the targeted area, including the cochlea, temporal lobes, and parotid glands, than a boost limited to the tumor bed (TB).[15] To date, one study has suggested preserved intelligence after treatment with reduced-dose CSR and sequential focal conformal boosts to the PF and TB.[16] However, TB boost is not as yet a part of standard care. A boost to the entire PF is included in at least one treatment arm in most ongoing clinical trials for medulloblastoma, including the ACNS 0331 and SIOP (International Society of Paediatric Oncology)/PNET (Primitive Neuroectodermal Tumor) 4 trials. The SJMB (St Jude Medullablastoma) trials, where a TB boost has been used exclusively since 1996, are an exception. Of the trials that compare PF with TB boost (eg, ACNS 0331), the focus is on event-free survival rather than cognitive outcome. To our knowledge, our study is the first to directly compare intellectual outcome in patients treated with different clinically relevant CSR dose and boost volume combinations. Our first goal was to examine the rate of change over time in intelligence scores in patients with medulloblastoma as a function of CSR dose and boost volume.

Radiation is not the only insult to the brain with the capacity to affect intellectual functioning. We recently showed that patients with any of the following complications—motor deficits, cranial nerve deficits, mutism, and/or meningitis—had greater impairment in information processing speed than patients without such complications.[13] However, the impact of specific neurologic complications on the evolution of intellectual development remains unknown. Longitudinal studies are ideally suited to monitor this evolution, because they provide information regarding the timing of onset and trajectory of intellectual decline. Although each CNS complication has a unique potential to negatively affect intelligence, hydrocephalus and mutism are potentially the most debilitating[14,17-20] and warrant individual attention.

Hydrocephalus is characterized by accumulation of cerebrospinal fluid (CSF) in the CNS ventricular system, resulting in increased intracranial pressure,[21] and has been correlated with lower intellectual functioning and academic skills in survivors of pediatric brain tumors.[18,19,22-25] Most patients present with hydrocephalus, but some require intervention to divert CSF. The impact of hydrocephalus requiring treatment on intelligence has not been studied longitudinally in patients with medulloblastoma. Cerebellar mutism is an acute complication characterized by diminished speech output, linguistic difficulties, and dysarthria, affecting nearly one quarter of all patients with medulloblastoma.[17] Recent research has suggested mutism is associated with poor intellectual outcome.[14,20] Our second goal was to longitudinally evaluate the impact of hydrocephalus requiring CSF diversion and mutism on intellectual outcome.

To address these goals, we retrospectively evaluated intelligence scores for $\leq$ 14 years for 113 patients diagnosed with medulloblastoma. Information gleaned from this study will improve our understanding of the factors affecting long-term intellectual outcome in patients treated for medulloblastoma.

PATIENTS AND METHODS

Patients

A total of 113 patients treated for medulloblastoma between August 1983 and January 2011 at the Hospital for Sick Children (Toronto, Ontario, Canada) were seen for neuropsychological assessment. (This represents 53% of all patients with medulloblastoma treated in the same time period; we note our sample represents 79% of all patients treated and available for neuropsychological assessment since systematic monitoring was instituted in 1995. Patients who experienced early relapse and subsequently died [19%] did not undergo follow-up with neuropsychological assessments. Other factors that reduced our evaluation rate included geographic distance and parent refusal of clinical neuropsychology services. Before 1995, resource limitations at our institution did not allow routine assessment of all patients, but there was no systematic bias toward who was or was not referred. Finally, access to neuropsychological evaluation was not related to ability to pay). Patient characteristics, including incidence of hydrocephalus, mutism, and other neurologic complications, are summarized in Table 1. Patients treated with CSR received either standard- (ie, 30.6 to 39.4 Gy) or reduced-dose (ie, 18 to 23.4 Gy) radiation to the entire brain and spine. Because of changes in the treatment protocol used at our institution, patients seen before 2006 received a boost to the entire PF, whereas those seen from 2006 onward were treated on the SJMB 03 protocol and received a focal conformal boost with a margin of 1 cm around the TB; in both cases, total boost volume dose was 45 to 55.4 Gy.

Materials and Procedures

There is variability in both the number of times patients in our sample were assessed and the number of years over which they were assessed. All patients were seen after a single course of CSR. (Three patients initially treated without radiation were assessed after recurrence and treatment with CSR.) Assessment details are summarized in Table 1. The Full Scale Intelligence Quotient (FSIQ) is a reliable measure of overall cognitive functioning; the Verbal Comprehension Index (VCI) measures verbal reasoning and conceptualization abilities; the Perceptual Reasoning/Organization Index (PRI) evaluates the ability to interpret and organize visually presented nonverbal information.[26] The Working Memory/Freedom From Distractibility Index (WMI) measures attention abilities, and the Processing Speed Index (PSI) evaluates the speed of graphomotor and mental processing.[26] Research ethics board approval was obtained before data extraction from clinical records.

Statistical Analyses

First, χ^2 analyses were conducted to compare patient and sample cohorts and patients in each treatment arm. Second, mixed-model growth curve analyses were used to determine the stability/change in intelligence scores over time as a function of: one, radiation dose and boost volume while controlling for hydrocephalus requiring CSF diversion and mutism; and two, individual

Table 1. Patient Characteristics, Medical Variables, and Assessment Details

Characteristic	Total (N = 113)		Standard-Dose CSR + PF Boost (n = 51)		Standard-Dose CSR + TB Boost (n = 9)		Reduced-Dose CSR + PF Boost (n = 28)		Reduced-Dose CSR + TB Boost (n = 23)		*P**
	No.	%	No.	%	No.	%	No.	%	No.	%	
CSR	111	98.2									
Chemotherapy†	102	90.3	41	80.4	9	100.0	27	96.4	23	100.0	.017
Protocol											
A	3		2				1				
B	21		20				1				
C	24		4				20				
D	17		14		1		2				
E	30		1		8				21		
F	2						2				
G	4						1		2		
H	1										
Deceased	22	19.5	12	23.5	3	33.3	6	21.4	1	4.3	.17
Gross total resection‡	83	73.5	30	58.8	7	77.8	24	85.7	20	87.0	.12
Clinical risk (average risk)	67	59.3	17	33.3	4	44.4	23	82.1	22	95.7	< .001
Hydrocephalus											
Presence at diagnosis	90	79.6	39	76.5	5	55.6	25	89.3	19	82.6	.16
Requiring CSF diversion	54	47.8	18	35.0	5	55.6	14	50.0	15	65.2	.10
Third ventriculostomy	6	5.3	2	3.9	0	0.0	1	3.6	3	13.0	.32
EVD only	18	15.9	2	3.9	3	33.3	5	17.9	8	34.8	.004
VPS	30	26.5	14	27.5	2	22.2	8	28.6	4	14.4	.78
≥ 1 revision	17	15.0	9	17.6	2	22.2	3	10.7	3	13.0	.79
Mutism§	25	22.1	7	13.7	2	22.2	9	32.1	6	26.1	.26
Motor deficits‖	18	15.9	8	15.7	2	22.2	3	10.7	5	21.7	.71
Cranial nerve deficits¶	2	1.8	2	3.9	0	0.0	0	0.0	0	0.0	.49
Meningitis	9	8.0	5	9.8	1	11.1	2	7.1	0	0.0	.47
Male sex	79	69.9	39	76.5	8	88.9	19	67.9	11	47.8	.049
Age at diagnosis, years											.29
Mean	7.51		7.89		8.44		6.54		7.48		
SD	3.37		3.69		3.69		3.32		3.47		
Range	1.09-14.95		1.92-14.54		3.53-14.48		1.69-13.64		1.09-14.95		
Time from diagnosis to first assessment, years#											.13
Mean	1.21		1.61		0.82		0.93		0.77		
SD	1.68		2.16		0.93		1.14		0.95		
Range	0.05-8.73		0.05-8.73		0.08-2.48		0.10-5.33		0.05-4.11		
Time from diagnosis to last assessment, years											< .001
Mean	6.06		7.28		3.2		6.8		3.26		
SD	3.42		3.49		1.17		3.42		1.51		
Range	1.47-14.16		1.63-14.16		2.05-5.17		2.25-12.39		1.47-5.63		
No. of assessments											.34
Average	3		3		2		3		2		
Range	1-7		1-7		1-6		1-7		1-6		
Patients seen for a single assessment	32	28.3	17	33.3	4	44.4	3	10.7	8	34.8	.60

NOTE. Test versions used to assess intellectual functioning included: Wechsler Intelligence Scale for Children (eds 3 and 4), Wechsler Preschool and Primary Scale of Intelligence (revised and ed 2), Wechsler Abbreviated Scale of Intelligence, and Wechsler Adult Intelligence Scale (eds 3 and 4).

Abbreviations: CSF, cerebrospinal fluid; CSR, craniospinal irradiation; EVD, external ventricular drain; PF, posterior fossa; SD, standard deviation; TB, tumor bed; VPS, ventriculoperitoneal shunt.

*P values reflect χ^2 analyses conducted between four radiation treatment groups.

†Chemotherapy protocols and associated agents are as follows: A, Baby POG (cyclophosphamide, vincristine, cisplatin, and etoposide); B, ICE (ifosfamide, carboplatin, and toposide); C, CCG 9961 (vincristine, lomustine/cyclophosphamide, and cisplatin); D, POG 9631 (etoposide, cisplatin, cyclophosphamide, and vincristine); E, SJMB 03 (vincristine, cisplatin, and cyclophosphamide); F, ACNS 0331 (vincristine, cisplatin, lomustine, and cyclophosphamide); G, 99703 (cisplatin, vincristine, cyclophosphamide, and etoposide); and H, MOPP (mechloroethamine, vincristine, procarbazine, and prednisone). Patients who did not receive chemotherapy were treated before 1999.

‡Data unavailable for one patient.

§Patients classified as having mutism if they had diminished speech output, linguistic difficulties, or dysarthria after surgery.

‖Patients classified as having motor deficits if they had ataxia, dysmetria, or hemiparesis on neurologic examination.

¶Patients classified as having cranial nerve deficits if they had any cranial nerve palsy on neurologic examination (eg, seventh nerve palsy as diagnosed by facial weakness).

#Seventy-six patients assessed within 12 months from diagnosis.

Table 2. CSR Dose and Boost Volume

Index	Total Patients				Intercept		Slope			
	No.	Mean	SE	Comparison *P*	Estimate	SE	Estimate	SE	*P*	Comparison *P*
FSIQ										
Growth curve analysis										
Reduced + TB boost	19	91.97	4.22	.13 × .31 × .11*	93.02	3.53	1.12	1.55	.39	.04 × .19 × .04†
Reduced + PF boost	27	83.93	2.57	.13 × .75 × .87*	97.29	2.86	−2.18	0.88	.01	.04 × .78 × .89†
Standard + TB boost	7	84.98	8.35	.31 × .75 × .55*	101.24	5.19	−2.96	2.78	.23	.19 × .78 × .75†
Standard + PF boost	49	82.90	2.00	.11 × .87 × .55*	95.78	1.90	−2.05	0.54	< .001	.04 × .89 × .75†
Single–time point analysis				.06						—
Reduced + TB boost	8	91.25	6.17		—	—	—	—	—	
All other treatments	65	78.65	2.17		—	—	—	—	—	
PSI										
Growth curve analysis				.75						.45
Reduced + TB boost	18	83.07	4.29		90.74	3.40	−1.14	1.63	.47	
All other treatments	80	80.41	1.26		92.63	1.71	−2.38	0.38	< .001	
Single–time point analysis				.07						—
Reduced + TB boost	5	89.20	6.81		—	—	—	—	—	
All other treatments	57	76.11	2.02		—	—	—	—	—	
PRI										
Growth curve analysis				.07						.03
Reduced + TB boost	19	95.95	4.49		96.17	3.49	1.40	1.64	.38	
All other treatments	89	85.30	1.62		98.56	1.73	−2.20	0.46	< .001	
Single–time point analysis				.096						—
Reduced + TB boost	8	92.50	6.43		—	—	—	—	—	
All other treatments	64	80.98	2.27		—	—	—	—	—	
WMI										
Growth curve analysis				.40						.18
Reduced + TB boost	18	93.04	5.15		96.02	3.66	0.30	1.82	.86	
All other treatments	81	87.37	1.56		99.75	1.87	−2.15	0.45	< .001	
Single–time point analysis				.04						—
Reduced + TB boost	5	100.20	7.72		—	—	—	—	—	
All other treatments	59	83.31	2.25		—	—	—	—	—	
VCI										
Growth curve analysis				.27						.14
Reduced + TB boost	20	93.66	3.83		95.04	3.14	0.64	1.42	.64	
All other treatments	87	87.24	1.36		96.39	1.57	−1.48	0.39	< .001	
Single–time point analysis				.12						—
Reduced + TB boost	8	93.50	5.61		—	—	—	—	—	
All other treatments	65	84.03	1.97		—	—	—	—	—	

Abbreviations: FSIQ, Full Scale Intelligence Quotient; PF, posterior fossa; PSI, Processing Speed Index; TB, tumor bed; VCI, Verbal Comprehension Index; WMI, Working Memory/Freedom From Distractibility Index.
*Mean comparison.
†Slope comparison.

complications (ie, hydrocephalus, other neurologic complications, and mutism alone). The mixed-model technique can handle unbalanced and missing data, a common phenomenon in clinical samples, and can account for the different times since diagnosis assessments were conducted.[27] Linear and curvilinear (ie, quadratic) models were generated for all indices of intellectual functioning, and the curvilinear model was reported when both models were significant. (A significant curvilinear term reflects curvature in the slope of the modeled function representing change over time; for indices that decline over time, it indicates that the rate of decline from year to year decreases as time increases.) The intercept produced by the model estimates group functioning at the beginning of the modeled time period, which was shortly after tumor resection in our sample. This mixed-model technique was applied using the PROC MIXED procedure in SAS software (version 9.1; SAS Institute, Cary, NC). In mixed-model approaches, single–time point data were included, because these contribute to overall group means and add stability to the overall model but do not contribute to slope. Furthermore, a univariable analysis was conducted to examine intellectual outcome as a function of radiation dose and volume at a single time point, approximately 5 years after diagnosis. For all analyses, results were considered significant if $P < .05$. Finally, a Kaplan-Meier survival plot was generated to display overall survival for patients separated by treatment group. Because our groups did not correspond to specific treatment arms, the plot was not used for statistical analysis.

RESULTS

Patient and Sample Cohort Comparisons

First, we compared patients treated before and after 1995 on factors that might contribute to cognitive risk. The cohorts did not differ in age at diagnosis ($P = .72$), rate of hydrocephalus requiring CSF diversion ($P = .95$), or mutism ($P = .08$). Patients treated before 1995 had a longer average time from diagnosis to first

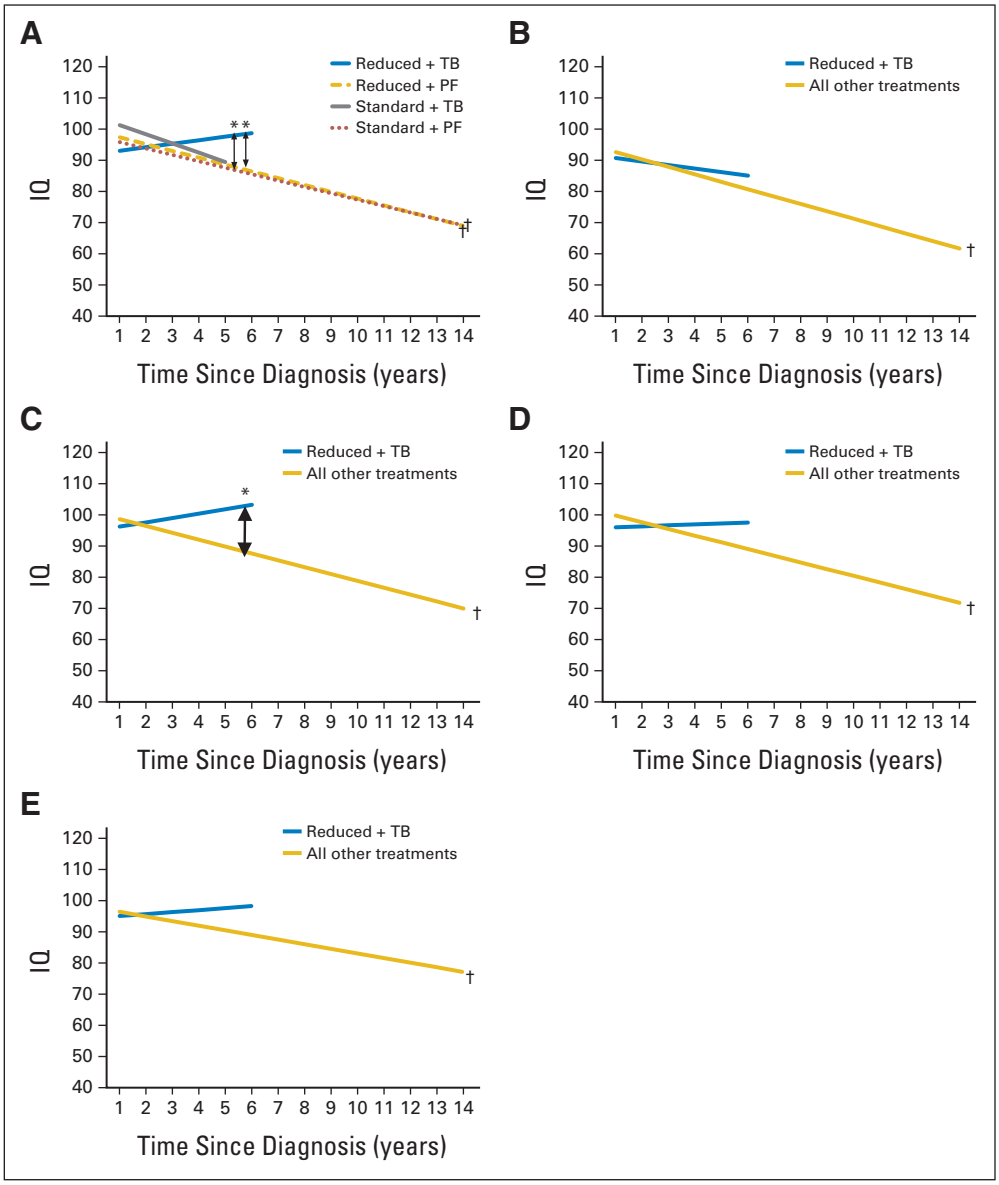

Fig 1. Estimated declines in (A) Full Scale Intelligence Quotient (IQ) score over time for patients in each of four treatment groups (reduced-dose craniospinal irradiation [CSR] + tumor bed [TB] boost, n = 19; reduced-dose CSR + posterior fossa [PF] boost, n = 27; standard-dose CSR + TB boost, n = 7; and standard-dose CSR + PF boost, n = 49) in linear-term model and (B) Processing Speed Index, (C) Perceptual Reasoning/Organization Index, (D) Working Memory/Freedom From Distractibility Index, and (E) Verbal Comprehension Index for patients treated with either reduced-dose CSR plus TB boost (n = 18 to 20) or any of other three treatments (n = 80 to 89) in linear-term models. NOTE. Lower limit of *y*-axis was not set to 0, because lowest obtainable IQ score is 40. (*) Significant difference in mean slope ($P < .05$) (†) Significant negative slope ($P < .001$).

assessment ($P = .01$), and the cohorts differed in CSR treatment received ($P = .002$).

Second, for patients diagnosed after 1995, we compared the cohort included in our sample with those who were not included. The groups did not differ in age at diagnosis ($P = .16$) or rate of hydrocephalus requiring CSF diversion ($P = .57$). Patients not included in our sample had a shorter time from diagnosis to death ($P < .001$) and more deaths ($P < .001$). Furthermore, patients not included in our sample had a lower incidence of mutism ($P = .01$), and more patients received standard-dose CSR plus PF boost ($P = .001$).

Finally, patients who had their first assessment within 1 year (n = 76) had higher initial FSIQ and greater decline than those who had their first assessment after 1 year post-treatment (n = 37; all $P < .02$), presumably because patients in the latter group experienced significant declines before their first assessment. Slopes for PRI, PSI, VCI, and WMI did not differ between groups (all $P > .05$).

CSR Dose and Boost Volume

We compared the four radiation treatment groups (summarized in Table 1) while controlling for the most prevalent and potentially debilitating complications: hydrocephalus requiring CSF diversion and mutism. Patients treated with reduced-dose CSR plus TB boost showed stable FSIQ scores (Table 2; Fig 1A). Strikingly, individual patient trajectories in this group indicated that the majority of patients treated with reduced-dose CSR plus TB boost had stable or improved performance over time (Fig 2A), whereas decreases were seen in patients treated with a PF boost (Fig 2B). Patients treated with standard-dose CSR plus PF boost and reduced-dose CSR plus PF boost showed declines of at least 2 FSIQ points per year (all $P < .05$; Table 2; Fig 1A). Declines were also evident in patients treated with standard-dose CSR plus TB boost, but the small sample size (n = 9) and limited longitudinal data (n = 2) precluded statistical significance (Table 2). The FSIQ slope for patients receiving reduced-dose CSR plus TB boost

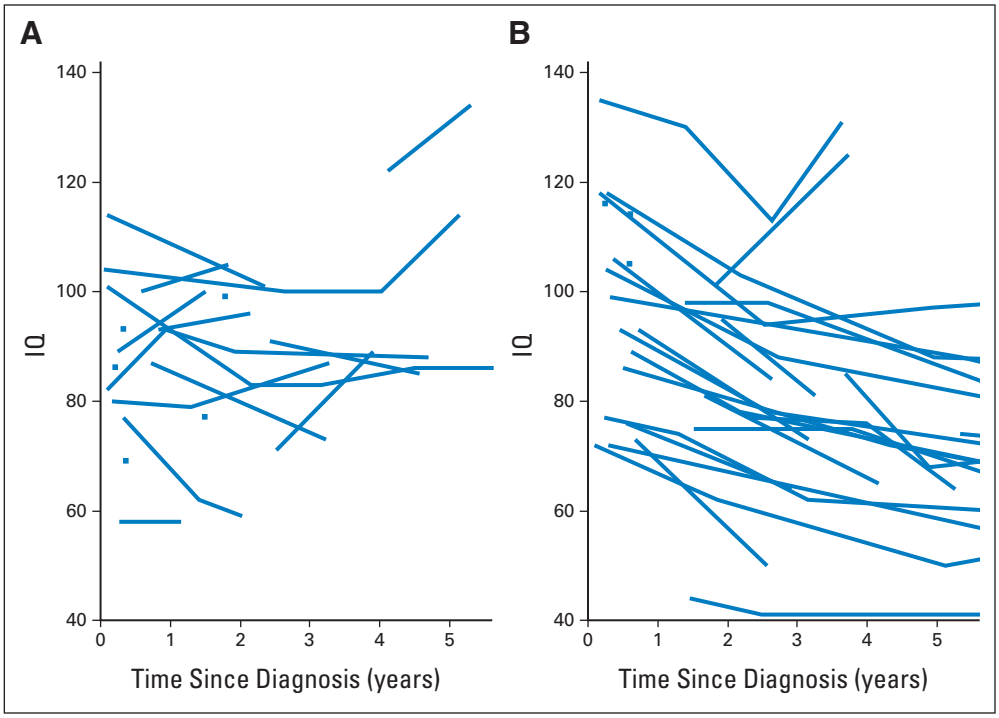

Fig 2. Observed Full Scale Intelligence Quotient (IQ) scores in comparable timeframe for patients treated with (A) reduced-dose craniospinal irradiation (CSR) plus tumor bed boost (n = 19) and (B) reduced-dose CSR plus posterior fossa boost (n = 28). Each line represents patient seen for serial intellectual assessment; each square represents patient seen once.

differed from those of patients receiving reduced-dose CSR plus PF boost and standard-dose CSR plus PF boost (all $P < .05$; Table 2; Fig 1A). Because patients treated with reduced-dose CSR plus TB boost did not show FSIQ declines, whereas all other treatment groups did, and because there were no mean slope differences between patients treated with standard-dose CSR plus PF boost, reduced-dose CSR plus PF boost, and standard-dose CSR plus TB boost, all subsequent analyses compared patients in these three treatment groups considered together (ie, all-other-treatments group) with patients treated with reduced-dose CSR plus TB boost.

Patients treated with reduced-dose CSR plus TB boost showed stable trajectories for all IQ indices (Table 2; Figs 1A to 1E). In contrast, PSI, PRI, WMI, and VCI declined by at least 1.4 points per year over the modeled time period (all $P < .001$; Table 2; Fig 1C) for patients in the all-other-treatments group. Finally, the PRI slope differed between the reduced-dose CSR plus TB boost and all-other-treatments groups ($P = .03$; Table 2; Figs 1B to 1E).

Furthermore, we examined outcomes between the two groups at the latest time point for which we had maximal intelligence data, approximately 5 years after diagnosis (n = 79; mean, 5.26 years; standard deviation, 1.82). Patients treated with reduced-dose CSR plus TB boost had higher WMI scores than patients in the all-other-treatments group ($P = .04$), and FSIQ, PRI, and PSI scores trended toward significance (all $P < .10$; Table 2).

Neurologic Complications

FSIQ, PSI, PRI, and WMI declined by at least 1.5 points per year regardless of hydrocephalus status (all $P < .01$; Table 3). The slope for PRI differed between patients treated for hydrocephalus and those who did not require treatment ($P = .02$; Table 3). Furthermore, VCI declined by 4.2 points per year for patients with hydrocephalus requiring treatment ($P = .001$). Patients who were treated for hydrocephalus did not have lower intelligence intercepts than patient not requiring treatment for hydrocephalus but showed lower mean FSIQ, PRI, WMI, and VCI scores across the modeled time period (all $P < .05$; Table 3).

Patients who experienced neurologic complications—motor deficits, cranial nerve deficits, meningitis, or mutism—had lower intercepts (all $P < .005$) and lower means (all $P < .005$) on all IQ indices compared with patients without complications. Likewise, when mutism was considered alone, patients with mutism had lower intercepts for FSIQ, PSI, WMI, and VCI (all $P < .05$; Table 3) and lower means for all IQ indices (all $P < .05$; Table 3) than patients without mutism. Notably, FSIQ, PSI, and PRI declined by at least 2.2 points per year in patients with and without mutism (all $P < .005$), and mean slope did not differ for any IQ index (Table 3).

Survival Plot

Kaplan-Meier survival plot revealed that patients treated with reduced-dose CSR plus TB boost did not show worse survival than patients in the all-other-treatments group (Fig 3).

DISCUSSION

We compared patterns of change in intellectual functioning for patients treated with different clinically relevant CSR dose and boost volume combinations and for patients with neurologic complications. Our findings demonstrate that patients treated with reduced-dose CSR plus TB boost experience stable intelligence trajectories and that both hydrocephalus requiring CSF diversion and mutism are associated with poor intellectual functioning but show distinctive trajectories of decline.

Table 3. Neurologic Complications

Index	Total Patients				Intercept			Slope				Quadratic		
	No.	Mean	SE	Comparison *P*	Estimate	SE	Comparison *P*	Estimate	SE	*P*	Comparison *P*	Estimate	SE	*P*
FSIQ														
Hydrocephalus*				.001			.24				.06			
Yes	47	80.63	2.36		91.77	2.26		−5.80	1.28	< .001		0.43	0.12	< .001
No	57	87.55	2.00		95.17	2.87		−2.84	0.92	.003		0.12	0.08	.04
Mutism				< .001			.02				.39			
Yes	23	77.67	3.11		87.93	2.77		−5.12	1.57	.002		0.36	0.15	.01
No	81	86.68	1.74		95.58	3.20		−3.57	0.85	< .001		0.18	0.08	.02
PSI														
Hydrocephalus*				.16			.38				.40			
Yes	43	77.46	1.96		87.47	2.07		−2.72	0.65	< .001		—	—	—
No	55	82.28	1.53		89.83	2.65		−2.05	0.46	< .001		—	—	—
Mutism				.003			.004				.91			
Yes	23	74.55	2.36		82.79	2.38		−2.24	0.74	.003		—	—	—
No	75	82.58	1.41		91.17	2.80		−2.34	0.44	< .001		—	—	—
PRI														
Hydrocephalus*				< .001			.41				.02			
Yes	50	82.18	2.51		95.38	2.28		−7.23	1.37	< .001		0.56	0.13	< .001
No	58	90.22	2.15		97.79	2.95		−3.24	0.99	.002		0.18	0.09	.045
Mutism				< .001			.06				.15			
Yes	24	80.26	3.44		91.73	2.87		−6.72	1.65	< .001		0.55	0.15	< .001
No	84	88.50	1.94		98.04	3.29		−3.98	0.91	< .001		0.21	0.08	.01
WMI														
Hydrocephalus*				.03			.20				.22			
Yes	45	82.60	2.27		92.86	2.25		−2.68	0.72	< .001		—	—	—
No	54	90.59	1.85		96.61	2.89		−1.57	0.54	.005		—	—	—
Mutism				.002			< .001				.17			
Yes	24	83.31	2.92		86.98	2.60		−0.96	0.87	.27		—	—	—
No	75	88.96	1.71		98.01	3.06		−2.36	0.50	< .001		—	—	—
VCI														
Hydrocephalus*				.009			.50				.09			
Yes	50	84.41	2.03		93.21	2.17		−4.19	1.23	.001		0.28	0.12	.02
No	57	90.62	1.75		95.10	2.80		−1.56	0.91	.09		0.05	0.08	.52
Mutism				.02			.01				.87			
Yes	24	83.10	2.69		87.69	2.25		−1.25	0.78	.12		—	—	—
No	83	89.18	1.52		94.33	2.61		−1.40	0.45	.002		—	—	—

Abbreviations: FSIQ, Full Scale Intelligence Quotient; PRI, Perceptual Reasoning/Organization Index; PSI, Processing Speed Index; VCI, Verbal Comprehension Index; WMI, Working Memory/Freedom From Distractibility Index.

*Refers to hydrocephalus requiring treatment to divert cerebrospinal fluid.

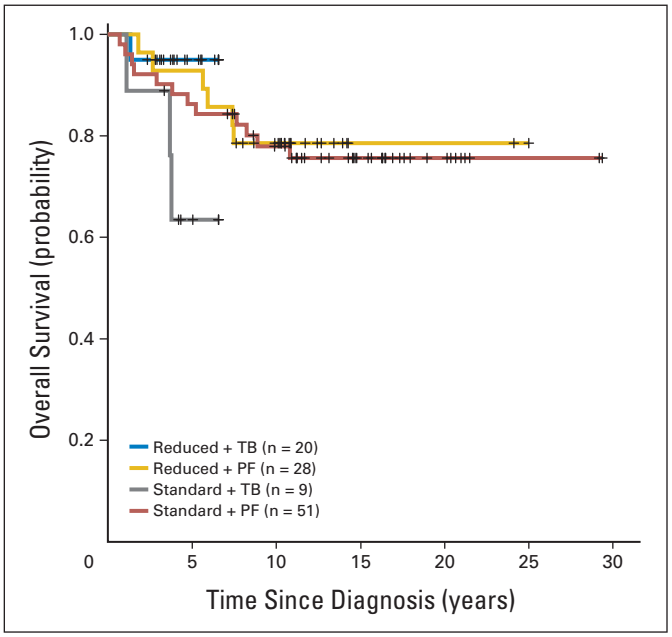

Fig 3. Kaplan-Meier plot showing overall survival probability for patients with medulloblastoma separated by treatment group. PF, posterior fossa; TB, tumor bed.

All patient groups had intercepts that were below the normative mean, indicating all patients with medulloblastoma remain vulnerable to intellectual impairment. However, we found that patients treated with reduced-dose CSR plus TB boost showed stable intelligence beyond their initial impairment and did not experience worse survival. Patients treated with reduced-dose CSR plus PF boost, standard-dose CSR plus PF boost, and standard-dose plus TB boost all declined similarly. Our findings suggest that limiting the boost volume to TB is critical for mitigating adverse intellectual outcome in patients with medulloblastoma who are eligible for treatment with reduced-dose CSR.

We showed that patients requiring treatment for hydrocephalus had comparable intercepts for PRI but declined more quickly than patients who did not require CSF diversion. In contrast, patients with mutism displayed lower intercepts, but their subsequent declines across all IQ indices paralleled patients without mutism. These unique trajectories may reflect the distinct mechanism of injury associated with each complication.

In patients with PF tumors, hydrocephalus typically arises because the tumor blocks CSF flow within the ventricular system.[28] CSF accumulation increases intracranial pressure and produces mechanical stress that decreases cerebral blood flow, reduces the availability of neurotransmitters, damages axons and myelin, and renders neurons dysfunctional.[29] The time course of intellectual impairment we observed suggests that hydrocephalus produces a sustained injury. Additionally, shunting procedures cause direct structural damage and increase the risk of postoperative complications.[30] Thus, patients with hydrocephalus may receive several cumulative insults to the brain, rendering them susceptible to continued intellectual impairment. Patients with hydrocephalus may therefore benefit from increased neuropsychological monitoring and rehabilitation strategies designed to help compensate for an ongoing injury.

The underlying cause of mutism is largely unknown, but mutism has been most commonly observed in children with large, aggressive tumors that require radical resection.[17,31] The time course of intellectual decline and profile of patients who developed mutism in our sample suggest the impairment results from acute effects of the tumor and surgery. Thus, patients with mutism may benefit from vigilant neuropsychological monitoring immediately after treatment and rehabilitation strategies focused on acute injury recovery.

Our findings should be considered in light of some limitations. First, the use of different test versions to assess intelligence over time is not optimal; however, we were limited to the versions available in the patient records, and these changed with time. Furthermore, our sample size was smaller for certain IQ indices because of lack of availability from some measures (eg, WASI). Second, it would have been preferable to include cognitive outcome measures other than IQ. Future studies seeking to characterize the cognitive domains most compromised by treatment and complications would benefit from using specific measures of neuropsychological function. Third, chemotherapy protocols, surgical practice, and supportive care have changed over the time period studied and may have been confounding factors in outcome. Finally, our finding that patients treated with reduced-dose CSR plus TB boost showed stable intelligence after treatment should be interpreted with caution, because their follow-up time was shorter than that for patients treated with a PF boost. Declines may emerge over a longer time period not captured in our investigation.

With biologically based strategies presently well positioned to guide treatment de-escalation in medulloblastoma, our findings are timely. For instance, patients with WNT medulloblastoma have excellent disease prognosis and are ideal candidates for therapy de-escalation.[32] We have demonstrated that lower CSR dose and smaller boost volume lead to stable intellectual trajectories without seeming to worsen survival. As a result, we suggest that PF boost be reconsidered in the treatment of medulloblastoma. We also showed that hydrocephalus requiring CSF diversion and mutism worsen intellectual outcome but show different trajectories. Establishing the impact of specific neurologic complications and delineating the time course of impairment are essential to identifying time windows for the delivery of protective or rehabilitative intervention. Our findings improve our understanding of the factors that impair intellectual outcome in patients with medulloblastoma and stress the importance of longitudinal studies in the development of time-sensitive intervention strategies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Provision of study materials or patients: Eric Bouffet, Michael D. Taylor, Normand Laperriere, Brenda J. Spiegler, Laura Janzen, Donald Mabbott
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Data analysis and interpretation: Iska Moxon-Emre, Michael D. Taylor, Normand Laperriere, Donald Mabbott

Manuscript writing: All authors

Final approval of manuscript: All authors

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Clinical Investigation: Pediatric Tumor

A 5-Year Investigation of Children's Adaptive Functioning Following Conformal Radiation Therapy for Localized Ependymoma

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Summary

A prospective trial showed that conformal radiation therapy spared adaptive behavior in children with ependymoma. The study cohort included a vulnerable population including children as young as 12 months of age at the time of irradiation. Although immediate postoperative radiation therapy has been adopted as a standard of care for these patients, these findings secure the ability of advanced methods of irradiation and target volume reduction to reduce or eliminate cognitive effects in children with brain tumors.

Purpose: Conformal and intensity modulated radiation therapies have the potential to preserve cognitive outcomes in children with ependymoma; however, functional behavior remains uninvestigated. This longitudinal investigation prospectively examined intelligence quotient (IQ) and adaptive functioning during the first 5 years after irradiation in children diagnosed with ependymoma.

Methods and Materials: The study cohort consisted of 123 children with intracranial ependymoma. Mean age at irradiation was 4.60 years (95% confidence interval [CI], 3.85-5.35). Serial neurocognitive evaluations, including an age-appropriate IQ measure and the Vineland Adaptive Behavior Scales (VABS), were completed before irradiation, 6 months after treatment, and annually for 5 years. A total of 579 neurocognitive evaluations were included in these analyses.

Results: Baseline IQ and VABS were below normative means ($P<.05$), although within the average range. Linear mixed models revealed stable IQ and VABS across the follow-up period, except for the VABS Communication Index, which declined significantly ($P=.015$). Annual change in IQ ($-.04$ points) did not correlate with annual change in VABS ($-.90$ to $+.44$ points). Clinical factors associated with poorer baseline performance ($P<.05$) included preirradiation chemotherapy, cerebrospinal fluid shunt placement, number and extent of surgical resections, and younger age at treatment. No clinical factors significantly affected the rate of change in scores.

Conclusions: Conformal and intensity modulated radiation therapies provided relative sparing of functional outcomes including IQ and adaptive behaviors, even in very young children. Communication skills remained vulnerable and should be the target of preventive and rehabilitative interventions. © 2012 Elsevier Inc.

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Introduction

Ependymoma accounts for approximately 5%-7% of all pediatric brain tumors and is diagnosed most frequently in children 4 years of age or younger (1). Optimal treatment outcomes generally result from gross total resection and subsequent irradiation (2), with resulting 3-year disease-free survival rates approaching 75% (3). The use of postoperative conformal and intensity modulated radiation therapy has become the standard of care for ependymoma because the prescription dose can be precisely shaped to the targeted volume, reducing the dose to normal, uninvolved tissue. This treatment approach is not without functional risks: children who receive treatment for ependymoma and other posterior fossa tumors are at risk for parenchymal and vascular damage, endocrinopathy, and cognitive deficits (2). Given the high survival rates associated with ependymoma and the generally young age at diagnosis, it is important to understand the functional outcomes these children can expect in order to prepare families appropriately and design interventions to ameliorate deficits.

Children who receive treatment for brain tumor including radiation therapy, chemotherapy and surgery are at risk for cognitive late effects, such as global declines in intellectual function and academic achievement (4-8), with resulting concerns about overall quality of life and the ability to function independently at older ages. Radiation dose to normal brain tissue has been identified as a direct predictor of postirradiation intelligence quotient (IQ) in ependymoma (9). Furthermore, ependymoma survivors exhibit greater stability in IQ scores after treatment with focally administered conformal and intensity modulated irradiation than children with similarly located tumors, including medulloblastoma, who are treated with craniospinal irradiation (8). Additional evidence of spared verbal learning ability (10) and academic skills including math and spelling (6) suggests progress toward reducing late effects; however, this progress is not global. Continued declines are noted in reading ability, with younger age at treatment conferring additional risk (6). Measures of academic achievement offer a glimpse into real-world performance, yet further investigation of functional outcomes following newer methods of irradiation is needed.

Adaptive functioning, or the ability to perform the tasks of daily living at an age-appropriate level, has not been thoroughly examined in this population. In typically developing individuals, correlations between adaptive and intellectual functioning are small to moderate (11), suggesting that these measures identify related but not identical constructs. Few studies have examined adaptive functioning in children with brain tumors. In heterogeneous samples of children with brain tumors, declines in adaptive functioning have been found in children undergoing surgery only (12) and in those receiving conventional radiation therapy and chemotherapy (13, 14). Children without brain tumors who receive low-dose whole-brain irradiation and subsequent bone marrow transplantation also experience a decline in global adaptive function (15). Hydrocephalus, a common complication of ependymoma, confers independent risk for adaptive deficits, and children with congenital hydrocephalus perform below age-level expectations on daily living skills and communication skills as adults (16). Despite these risks, no studies to our knowledge have explicitly examined adaptive functioning after newer methods of irradiation in this population.

Children with ependymoma are at risk for a host of cognitive and functional sequelae as a result of disease- and treatment-related factors, given the young age at diagnosis, the need for aggressive resection, and potential risks associated with hydrocephalus. Based on emerging literature suggesting relative sparing of some cognitive skills in this population with advanced treatment techniques, the need to examine outcomes in daily functioning is paramount. This study capitalized on the availability of a large sample of children whose disease was homogenously diagnosed and treated, permitting greater reliability and generalizability of findings. Aims of the study were to examine the trajectory of adaptive behavior scores in children treated with conformal irradiation for localized ependymoma; to compare the rate of change in IQ and adaptive behavior scores; and to identify clinical, demographic, and treatment-related variables that influence the change in scores over time. We hypothesized that this cohort would experience a decline in adaptive functioning over time and that the change in adaptive behaviors would correspond with a change in IQ scores.

Table 1 Baseline demographic and clinical characteristics (n = 123)

Variable	Mean no. of patients (95% CI)	Range
Age at RT	4.60 (3.85-5.35)	1.02-17.64
Sex		
Male	61	50
Female	62	50
Race		
African-American	10	8
Caucasian	107	87
Other	6	5
Tumor location		
Infratentorial	98	80
Supratentorial	25	20
Number of surgeries		
1	78	63
2	36	29
3 or more	9	7
Extent of pre-RT surgery		
Biopsy only	0	0
STR	13	11
NTR	9	7
GTR	101	82
Pre-RT chemotherapy	29	24
Hydrocephalus	80	65
Shunt placement	46	37

Abbreviations: CI = confidence interval; GTR = gross total resection (macroscopic complete); NTR = near total resection (≤5-mm residual disease); RT = conformal or intensity modulated radiation therapy; SD = standard deviation; STR = subtotal resection (>5-mm residual disease).
Percentages may not total 100% due to rounding procedures.

Methods and Materials

Participants

This study enrolled 123 children in a single-institution phase II trial of conformal radiation therapy for localized ependymoma between July 1997 and January 2008 (3). Study entry criteria for the phase II

Table 2 Baseline and longitudinal neurocognitive scores

Variable	Baseline (n = 85) mean (95% CI)	P*	Correlation with baseline IQ Pearson r (P)†	Annual change	P‡	Correlation with IQ change Pearson r (P)§
EIQ	95.75 (91.52-99.98)‖	.023	-	−0.04	.898	-
VABS Com	96.93 (93.72-100.14)‖	.026	.39 (<.0001)‖	−0.90‖	.015	.04 (.6715)
VABS DL	92.62 (89.25-95.99)‖	<.001	.46 (<.0001)‖	+0.44	.265	.14 (.1336)
VABS Soc	97.54 (94.71-100.37)‖	.043	.41 (<.0001)‖	+0.39	.322	−.10(.2604)
VABS ABC	92.73 (89.17-96.29)‖	<.001	.52 (<.0001)‖	+0.30	.468	.04 (.7006)

Abbreviations: ABC = Adaptive Behavior Composite; CI = confidence interval; Com = Communication Index; DL = Daily Living Skills Index; EIQ = estimated IQ; Soc = Socialization Index; VABS = Vineland Adaptive Behavior Scales.
Models are valid for up to 5 years after irradiation.
* Compared with normative mean of 100 (±15 SD).
† Pearson correlation between baseline IQ score (first row) and VABS indices.
‡ Significant decline over time.
§ Pearson correlation between change in IQ (slope) and change in VABS indices.
‖ Significant at a P level of <.05.

trial included age between 1 and 25 years at time of treatment, histologic confirmation of ependymoma, no evidence of disseminated disease, no ongoing chemotherapy, no previous irradiation, and adequate performance status (ie, according to Eastern Cooperative Oncology Group Grade 0-2 criteria) (17). Additionally, participants must have completed at least 2 serial neurocognitive assessments, which required English as the primary language, and have no sensory or motor impairment that prohibited neurocognitive testing. Parents provided consent for this investigation, which was approved by the institutional review board.

Medical treatment and clinical factors

All patients underwent surgical resection before irradiation, with additional surgery performed as needed to maximize extent of resection before treatment. Children who received chemotherapy before irradiation typically received cyclophosphamide, cisplatin, or carboplatin, etoposide, and vincristine. Hydrocephalus was identified by neuroimaging at diagnosis. Radiation treatment parameters have been described previously (6, 9, 18). All participants received conformal (n = 115) or intensity modulated radiation therapy (n = 8) at St. Jude Children's Research Hospital, using conventional fractionation (1.8 Gy per day) with a prescribed dose of 59.4 Gy. The dose was attenuated to 54.0 Gy for children younger than 18 months of age after gross total resection. The irradiated clinical target volume included a 10-mm margin surrounding the tumor and/or tumor bed to control microscopic disease and an additional 3- to 5-mm margin expansion in 3 dimensions to form the planning target volume and account for uncertainty in patient positioning and image registration.

Neurocognitive assessment

Participants underwent serial neurocognitive assessment at pre-irradiation baseline 6 months after treatment and annually thereafter for 5 years. Intellectual function was assessed using the

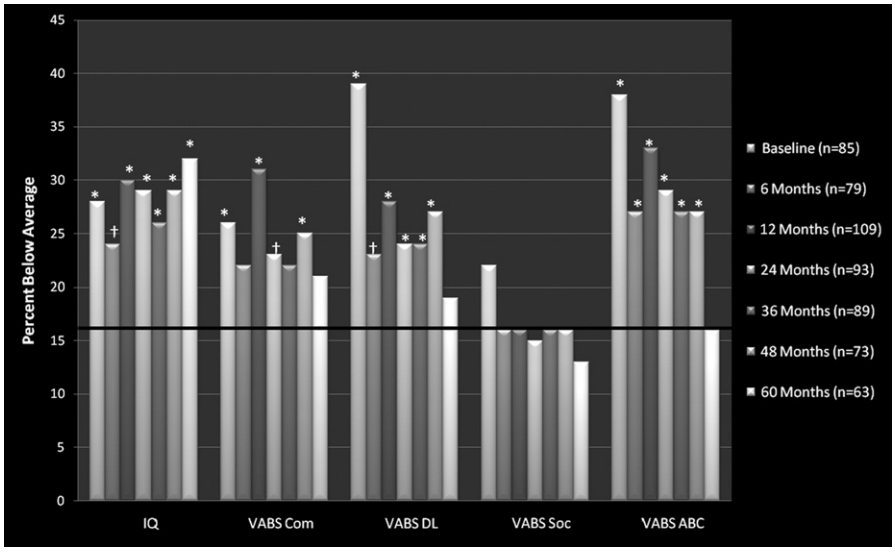

Fig. Percentage of IQ and adaptive behavior scores falling below the average range (<85) at each time point. Solid line at 16% denotes the expected proportion of below-average scores based on a normally distributed population estimate. ABC = Adaptive Behavior Composite; Com = Communication Index; DL = Daily Living Skills index; Soc = Socialization index; VABS = Vineland Adaptive Behavior Scale. *Significantly greater than 16% is indicated at P<.05; †nonsignificant trend at P<.10.

Table 3 Clinical and demographic variables affecting baseline performance

Variable	EIQ		VABS Com	
	Intercept (95% CI)	*P*	Intercept (95% CI)	*P*
Age at RT*	87.14 (82.22-92.06)	<.001‡	96.86 (92.90-100.82)	.986
No. of surgeries†	104.44 (95.80-113.08)	.036‡	108.35 (102.45-114.25)	<.001‡
Sex		.495		.118
Male	94.52 (89.50-99.54)		94.83 (91.11-98.55)	
Female	97.05 (91.86-102.24)		99.09 (95.31-102.87)	
Extent of surgery		.999		.628
STR	95.59 (84.30-106.88)		93.81 (85.62-102.00)	
NTR	95.74 (82.06-109.42)		94.57 (83.83-105.31)	
GTR	95.76 (91.76-99.76)		97.59 (94.65-100.53)	
Pre-RT chemotherapy		.020‡		.006‡
Yes	87.84 (80.41-95.30)		90.34 (85.09-95.59)	
No	98.04 (94.02-102.06)		99.03 (96.05-102.01)	
Shunt placement		<.001‡		<.001‡
Yes	86.46 (80.58-92.34)		90.17 (85.94-94.40)	
No	100.67 (96.51-104.83)		100.82 (97.68-103.96)	

Abbreviations: ABC = Adaptive Behavior Composite; CI = confidence interval; Com = Communication Index; DL = Daily Living Skills Index; EIQ =estimated IQ; GTR = gross total resection macroscopic complete); NTR = near total resection (≤5-mm residual disease); RT = conformal and intensity modulated radiation therapy; SEM = standard error of the mean; Soc = Socialization Index; STR = subtotal resection (>5-mm residual disease); VABS = Vineland Adaptive Behavior Scales.
Clinical and demographic variables are included in this table if their relationship with IQ and VABS scores was significant or trended toward significance in univariate models.

* Younger age at RT was associated with lower scores, such that scores increased significantly with each additional year of age at the time of RT for EIQ, VABS DL, VABS Soc, and VABS ABC.

† More than one surgery was associated with significantly lower scores across EIQ and all VABS indices, where scores worsened with each additional surgery.

‡ Significant at a *P* value of <.05.

§ Nonsignificant trend at a *P* value of <.10.

Bayley Scales of Infant Development, second edition (children < 4 years of age) (19), and the Block Design, Similarities, and Information subtests from the age-appropriate Wechsler scale (children 4 years and older) (20-22). Abbreviated Wechsler IQ scores were derived from a formula provided by Sattler (23), which yields an estimated IQ (EIQ) that correlates highly (r=0.93) with IQ scores obtained from full administration. All measures yield an age-normed standard score with a mean of 100 and a standard deviation of 15.

Adaptive functioning was assessed with the Vineland Adaptive Behavior Scales (VABS) (11), which is a psychometrically validated parent interview administered by a trained psychological examiner that assesses adaptive behaviors at developmental levels from birth through adulthood. Several domains are assessed, yielding index scores for Communication, Daily Living Skills, Socialization, and Motor Skills (for children up through age 5). An overall Adaptive Behavior Composite is obtained. All index scores have an age-referenced mean of 100 and a standard deviation of 15, where higher scores reflect better skills. A reduced number of children received Motor Skills Index scores at each time point due to the age constraints for the scale; therefore, it was not included in analyses.

Analyses

Descriptive analyses were conducted to characterize the clinical, demographic, and neurocognitive features of the study group at baseline. Frequencies were calculated to determine proportions of the sample with EIQ and VABS standard scores below average (<85) at each time point. Longitudinal changes in EIQ and adaptive functioning were examined using linear mixed models. The intercept served as the standard score at baseline, and the slope represented the mean change in score per month. Pearson correlations were then used to investigate the relationships between changes (ie, slope values) in EIQ and VABS index scores over the 5-year follow-up period. Finally, univariate linear mixed models were used to examine the effects of demographic, clinical, and treatment-related variables on changes in adaptive functioning.

Results

Demographic, clinical, and treatment-related characteristics of the study cohort are presented in Table 1. Mean age at irradiation was 4.60 years (95% confidence interval [CI], 3.85-5.35), and the group was balanced with respect to sex. Most participants underwent near total or gross total resection, and 37% required more than one surgery. In 80%, tumors were located within the posterior fossa. Approximately 24% received preirradiation chemotherapy, and nearly 65% experienced hydrocephalus as a complication of their disease. There was a strong association between age at diagnosis (P=.001) or age at the time of irradiation (P=.0240) and the use of preirradiation chemotherapy. The patients treated by pre-CRT chemotherapy were younger than those not treated by pre-CRT chemotherapy.

Participants completed a total of 579 neurocognitive evaluations. All 123 participants completed at least 2 VABS; 117

Table 3 (*continued*)

VABS DL		VABS Soc		VABS ABC	
Intercept (95% CI)	*P*	Intercept (95% CI)	*P*	Intercept (95% CI)	*P*
86.95 (83.11-90.79)	<.001‡	93.82 (90.49-97.15)	.003‡	88.09 (83.90-92.28)	.004‡
102.48 (96.07-108.89)	.001‡	106.09 (100.70-111.48)	.001‡	105.76 (99.21-112.31)	<.001‡
	.057§		.480		.222
89.94 (86.04-93.84)		96.69 (93.38-100.00)		90.89 (86.73-95.05)	
95.38 (91.42-99.34)		98.40 (95.03-101.77)		94.60 (90.39-98.81)	
	.046‡		.463		.195
82.79 (74.44-91.14)	-	93.69 (86.48-100.90)		84.94 (75.94-93.94)	
96.92 (85.87-107.97)	.048	95.11 (85.39-104.83)		91.78 (79.98-103.58)	
93.59 (90.59-96.59)	.019	98.16 (95.55-100.77)		93.79 (84.79-102.79)	
	.008‡		<.001‡		<.001‡
85.96 (80.43-91.49)		89.94 (85.45-94.43)		83.16 (77.48-88.64)	
94.77 (91.63-97.91)		100.00 (97.43-102.57)		95.80 (92.57-99.03)	
	<.001‡		<.001‡		<.001‡
83.84 (79.51-88.17)		91.17 (87.41-94.93)		82.73 (78.24-87.22)	
97.53 (94.34-100.72)		101.07 (98.33-103.81)		98.32 (95.01-101.63)	

participants completed at least two EIQ measures. Incomplete evaluations resulted from patient illness/fatigue, parental refusal, treatment/travel scheduling conflicts, and failure to attend evaluation appointments. Baseline EIQ and VABS scores are presented in Table 2. Group means were below normative means ($P<.05$) for EIQ and all VABS indices; however, none was outside of the average range (85-115). The proportion of the sample with EIQ and adaptive behavior scores falling below the average range at each time point was calculated. Based on the normal distribution of these scores in the general population, it was anticipated that 16% of the sample would score less than 85 on any given index. Significantly more ($P<.05$) than 16% of the sample scored below average on EIQ and VABS Communication, Daily Living Skills, and Adaptive Behavior Composite indices across nearly all time points during the first 4 years. Proportions of VABS indices falling below average returned to expected levels at Year 5. In contrast, the proportion scoring below average on the VABS Socialization Index never exceeded population expectations. Results for all indices across time points are shown in Fig.

Linear mixed models revealed the trajectory of change in EIQ and adaptive scores over the 5-year follow-up period. Only the VABS Communication Index declined significantly at a loss of nearly 1 standard score point per year ($P=.015$). Pearson correlations performed on the slopes for each index score revealed no significant ($P>.05$) correlations between change in EIQ and change in VABS indices over time.

Univariate linear mixed models were used to examine the effects of clinical, demographic, and treatment-related factors on change in adaptive behaviors over time. Several variables exerted significant impact on baseline EIQ and adaptive behavior scores (Table 3). Younger age at irradiation, chemotherapy prior to irradiation, and cerebrospinal fluid shunt placement resulted in lower baseline scores across nearly all indices ($P<.05$). Extent of preirradiation surgical resection affected baseline VABS Daily Living Skills Index ($P=.046$); near total or gross total resection was associated with higher baseline scores. A trend was noted for the effect of sex on daily living skills, where girls had higher baseline scores than boys ($P=.057$). No variables significantly affected the rate of change in EIQ or any VABS indices.

Discussion

Contrary to predictions, children treated with conformal and intensity-modulated radiation therapy for localized ependymoma experienced relative stability in their adaptive functioning over the 5-year follow-up period. These results provide novel and clinically meaningful information about the ability of these patients to perform developmentally appropriate tasks of daily living and add to the existing literature that suggests relative stability in IQ (8), verbal learning (10), and academic skills including math and spelling (6). These ependymoma survivors demonstrated less pronounced cognitive and functional effects up to 5 years after treatment relative to those of an older cohort of medulloblastoma survivors who received craniospinal irradiation (24). Prior reports have suggested that the use of craniospinal irradiation to treat medulloblastoma is the primary risk factor differentiating these 2 groups (24), indicating that the use of conformal radiation therapy

may play a large role in sparing healthy brain tissue, resulting in better functional performance.

In this cohort, baseline scores were below population means, suggesting deleterious effects of preirradiation factors on developmental progress that must be considered in addition to the effects of radiation therapy. Indeed, young age at treatment, the need for a shunt to manage hydrocephalus, preirradiation chemotherapy, and multiple surgical resections required to obtain minimal residual disease before treatment were related to lower baseline performance on nearly all IQ and adaptive behavior indices. It should be noted that young age and preirradiation chemotherapy are highly related, given that chemotherapy is often administered in order to delay irradiation for very young children. Tumor growth alone is likely to disrupt functional outcome; however, additional clinical factors prior to irradiation must be considered. Despite the significant impact on baseline scores, these factors were not found to significantly affect the trajectory of change over time. Children who begin the treatment course with lower scores may remain at lower performance levels but are not predicted to experience any more significant decline than children who performed at higher levels before treatment.

The trajectory of change in adaptive behaviors was not associated with the rate of change in IQ scores, suggesting that adaptive functioning is a unique outcome that warrants continued assessment. Measures of adaptive behavior and IQ are modestly correlated in typically developing individuals and those diagnosed with intellectual impairment (11); however, acquired brain injuries and other neurologically based disorders (eg, attention-deficit/hyperactivity disorder) have a less predictable effect on this relationship (25). Physical factors such as motor impairment, decreased balance, and sensory deficits may all play a moderating role in adaptive outcomes following treatment for ependymoma and warrant further investigation. Likewise, psychosocial factors such as exposure to developmentally appropriate tasks and parental expectations of performance, which are known to be altered in childhood cancer survivors (26), may also affect adaptive functioning in this population.

While this sample exhibited general stability in their adaptive performance across time, the VABS Communication Index declined significantly over the 5-year study period. It is important to note that the Communication Index encompasses skills that may be uniquely affected by tumors in the posterior fossa. For example, speech production in general can be impacted by postoperative posterior fossa syndrome, and the effects of this syndrome on language production and organization can linger indefinitely, even if productive, intelligible speech improves (27). At older ages, items comprising the Communication Index include writing and advanced reading skills. These have been shown to be diminished in ependymoma survivors (6), and thus their emergence as weaknesses in more functional settings is not surprising.

It is notable that, while group mean scores remained within the average range across indices, a larger-than-expected proportion of children exhibited scores below the average range. Based on the normal distribution of IQ and adaptive scores in the general population, approximately 16% of the population can be expected to score below 85; yet, scores for a greater proportion of this sample fell below the average range on most scores at nearly all time points. The proportion of children with scores below average appeared to diminish at the 5-year point for all VABS indices. In contrast, the proportion of the cohort with below-average EIQ scores remained high across time. This dissociation between intellectual and adaptive functioning warrants further scrutiny to determine which factors promote buffering of adaptive functions. Interestingly, the proportion of children with below-average scores on the VABS Socialization Index never exceeded population expectations. This may be due to the ongoing social exposure that is inherent in receiving cancer treatment at a children's hospital, suggesting less disruption to these developmental skills. Continued longitudinal follow-up is needed to determine whether these trends continue.

Young age at treatment has been identified as a prominent risk factor for more significant cognitive late effects, possibly due to disrupted exposure to developmentally appropriate material during critical periods (eg, learning to read) or to more pronounced liabilities in attention and executive function, making new learning more difficult across domains. These deficits are suspected to be heavily related to disrupted neural development of white matter in early childhood. Following central nervous system-directed therapies, reduced normal-appearing white matter volumes are overwhelmingly correlated with performance on measures of attention, impulsivity, and processing speed (28). However, much of what is known about these late effects stems from research into the use of craniospinal irradiation for treatment of medulloblastoma (29). In this sample of children with ependymoma, younger age at treatment was associated with lower baseline scores but not with the rate of change in IQ or adaptive scores. This finding is consistent with those of other reports of young ependymoma survivors that suggest stable intellectual (18), memory (10), and math and spelling skills (6), lending support for the early treatment of very young children with focal irradiation as a conservative yet effective measure of disease control.

Although these findings are promising with regard to functional outcomes following focused irradiation, they are not without some important limitations. The VABS is a widely used measure of adaptive functioning, but its reliance on parent report is subject to bias. Scores obtained using this measure, although reliable and generally stable, rely on a child's opportunity to demonstrate skills at an age-appropriate level, and this is sometimes affected by factors unrelated to treatment (eg, parental expectations, socioeconomic limitations). Clinician observation of tasks of daily living might provide a less biased assessment of skills but would certainly add a burden to research that might prohibit large-scale investigations. Results related to IQ change across time may be affected by changes in IQ instruments at different age levels. When changing from a measure of infant IQ to one for preschoolers or older children, variations in scoring criteria and normative samples may eclipse true IQ findings or add variability that is a result of the psychometric properties of the test. This may be addressed with more consistent measures across the age range in future studies. Finally, these results are based on group performance across time, thereby limiting the predictive power of results for individual patients. Future research might approach the development of predictive algorithms that could provide specific individual risks for patients based on their clinical and demographic histories.

Conclusions

In summary, these findings suggest relative stability of IQ and adaptive behaviors following treatment for ependymoma with conformal radiation therapy methods. Behaviors most likely to decline include communication skills, which may be affected by tumor location in the posterior fossa and cannot be easily separated

from academic skills such as reading and writing. Future directions include the development of patient-specific risk models to help inform parents about appropriate expectations, supports, and behavioral demands. Given the lack of a strong relationship with the trajectory of change in IQ, these results highlight a need to continue evaluating adaptive functioning as a separate yet important functional outcome for survivors of ependymoma. Further follow-up 5 to 10 years postirradiation will be needed to examine whether functional performance remains stable. These findings suggest that baseline performance and preirradiation factors may prove to be the strongest predictors of functional outcome.

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Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology Group trial A9961

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The purpose of the trial was to determine the survival and incidence of secondary tumors in children with medulloblastoma receiving radiotherapy plus chemotherapy. Three hundred seventy-nine eligible patients with nondisseminated medulloblastoma between the ages of 3 and 21 years were treated with 2340 cGy of craniospinal and 5580 cGy of posterior fossa irradiation. Patients were randomized between postradiation cisplatin and vincristine plus either CCNU or cyclophosphamide. Survival, pattern of relapse, and occurrence of secondary tumors were assessed. Five- and 10-year event-free survivals were 81 ± 2% and 75.8 ± 2.3%; overall survivals were 87 ± 1.8% and 81.3 ± 2.1%. Event-free survival was not impacted by chemotherapeutic regimen, sex, race, age at diagnosis, or gender. Seven patients had disease relapse beyond 5 years after diagnosis; relapse was local in 4 patients, local plus supratentorial in 2, and supratentorial alone in 1. Fifteen patients experienced secondary tumors as a first event at a median time of 5.8 years after diagnosis (11 >5 y postdiagnosis). All non-CNS solid secondary tumors (4) occurred in regions that had received radiation. Of the 6 high-grade gliomas, 5 occurred >5 years postdiagnosis. The estimated cumulative 10-year incidence rate of secondary malignancies was 4.2% (1.9%–6.5%). Few patients with medulloblastoma will relapse ≥5 years postdiagnosis; relapse will occur predominantly at the primary tumor site. Patients are at risk for development of secondary tumors, many of which are malignant gliomas. This may become an increasing issue as more children survive.

Keywords: chemotherapy, medulloblastoma, radiotherapy, secondary tumors.

Reported figures on event-free survival (EFS) and overall survival (OS) have slowly risen over the past 2 decades in pediatric cases of medulloblastoma, with multiple studies reporting 3- to 5-year EFS and OS rates of >70% in children with nondisseminated disease at time of diagnosis.[1–5] Potential reasons for this apparent improvement in survival have been the routine employment of more aggressive surgery; more refined preoperative evaluations, resulting in a more pristine group of children with nondisseminated disease; and the use of adjuvant chemotherapy during and after radiotherapy.[1–5] In past reports, especially those describing children receiving radiotherapy alone, late relapses, arbitrarily those occurring >5 years following diagnosis, were frequently reported.[6–8] In addition, the frequency and impact of secondary tumors on both EFS and OS have been poorly characterized in children surviving medulloblastoma.[6–8]

In 2006, the results were reported of a phase III study of reduced-dose craniospinal radiation therapy (2400 cGy), standard local boost radiotherapy (total dose 5580 cGy), and adjuvant chemotherapy consisting of vincristine during radiotherapy and 1 of 2 cisplatin-containing postradiotherapy regimens.[1] Five-year EFS and OS in this cohort of 379 patients were >80%, and the chemotherapy regimen received did not affect outcome. Since this initial report, both secondary

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tumors and late relapses have been encountered in children treated in this study. Reported for this patient population are long-term EFS, OS, pattern of disease relapse, and occurrence of secondary tumors.

Methods

Between December 1996 and December 2000, 421 patients with medulloblastoma were entered on our study. To be eligible, patients had to have histologically confirmed medulloblastoma and be between the ages of 3 and 21 years, inclusive, at the time of diagnosis.[1] Patients were to have no evidence of disseminated disease on MRI of the entire brain and spine performed pre- or postoperatively or on cytological examination of lumbar cerebrospinal fluid performed between 5 days of surgery and the onset of radiation. Patients were to have <1.5 cm^2 of residual tumor on postoperative imaging performed within 21 days, preferably within 72 h, of surgery. Patients with brainstem involvement were eligible for the study. Treatment must have begun within 31 days of definitive surgery. All institutions participating in this study had received approval from their institutional review boards, and age-appropriate informed consent/assent was obtained from each patient/parent/guardian.

Preoperative and postoperative MRI studies were centrally analyzed for 409 (97%) of the 421 patients for evaluation of extent of disease and amount of postoperative residual disease. Eligibility was based on institutional review, except when central review revealed unequivocal evidence of dissemination or excess residual disease, in which case, for analysis, patients were considered ineligible. If, on central review, studies were considered incomplete or not interpretable because of movement or other artifacts, patients were considered incompletely assessable but remained eligible for analysis. Central pathologic review was performed on 358 (85%) of the cohort by 1 of 2 neuropathologists.

After central review, 379 patients (including 66 who, on evaluation, had no evidence of excess residual or metastatic disease but whose studies could not be fully evaluated because of poor quality or incompleteness of submission) were deemed eligible for analysis. Patient characteristics have been noted in a previous report.[1]

Two hundred twenty-three patients were male and 156 were female. Seventeen percent of patients ($n = 65$) were 3–4 years of age, 51% ($n = 193$) were 5–9 years of age, and 32% ($n = 121$) were >15 years of age.

Treatment

A dose of 2340 cGy of craniospinal radiation with a posterior fossa boost of 3240 cGy (total dose 5580 cGy) was prescribed in fractions of 180 cGy per day, 5 days per week. Treatment to the craniospinal axis was not to exceed 20 days, and the entire treatment was to be completed within 51 days. The boost volume included the entire posterior fossa with a 1-cm margin around the tentorium or the tumor. Both parallel opposing fields and conformal radiation therapy techniques were allowed. Spinal treatment was as outlined previously.[1]

After surgery, eligible patients were randomized to receive either 8 cycles of regimen A or regimen B of chemotherapy, as previously described (see Fig. 1). Patients on both regimens were treated with weekly vincristine during radiotherapy (1.5 mg/m^2, maximum 2 mg, maximum 8 doses). Regimen A consisted of CCNU, cisplatin, and vincristine. Regimen B consisted of cisplatin, cyclophosphamide, and vincristine. Dose modifications for toxicity were as have been previously published.[1]

Statistical Consideration

Patients were randomly assigned to 1 of the 2 experimental regimens at the time of study enrollment, stratified by age and brainstem involvement. The primary endpoint for analysis was time to a treatment-failure event (EFS) measured from the time of study enrollment. An *event* was defined as death from any cause, or the first occurrence of relapse, progressive disease, or development of a secondary tumor. The secondary endpoint was time to death from any cause or the first occurrence of, from which actuarial survival probability was computed. (Refer to the original article for details of statistical design of the trial.) Nonparametric EFS and survival curves were computed using product-limit (Kaplan–Meier) estimates, with standard errors via the Greenwood formula. Cumulative incidence of secondary tumors over time was calculated by the method proposed by Gray. Fisher's exact test was used to detect

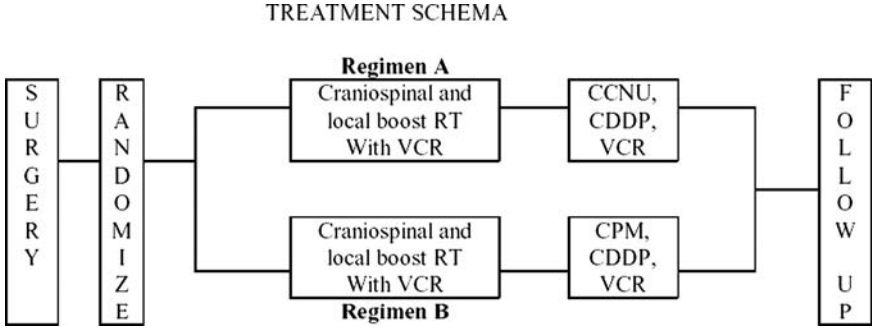

Fig. 1. Treatment schema.

the relationship between years of relapse and the type of relapse.

Secondary tumors and relapse determinations.— Patients were considered to have relapse or secondary tumors based on institutional determinations. All neuroradiographic studies demonstrating relapse or secondary tumors were centrally received. Pathologic confirmation of a secondary tumor was mandatory for inclusion, but pathologies were not centrally reviewed. As regards determining tumor relapse, pathologic confirmation was not mandatory and relapse could be diagnosed based on neuroradiographic interpretation by the treating institution.

Results

Overall Outcome

Data collection was halted 10 years after entry of the last patient on study. At time of analysis of the 379 eligible patients, the median follow-up for the 312 patients who were alive was 9.7 years (range, 0.2–13.7 y). Sixty-eight patients experienced tumor progression and 5 had death as first event; 58 have died to date. Late disease progression occurring 5 years after treatment occurred in 7 patients, 6 of whom died. The mean age at initial diagnosis of those developing late tumor relapse was 6.8 years. Two relapsed at an age later than their age at diagnosis plus 9 months. Fifteen developed secondary tumors—of these, 11 occurred more than 5 years after diagnosis, and 9 patients died (see Table 2).

For the cohort of 379 patients, 5- and 10-year EFSs were $81 \pm 2.0\%$ and $75.8 \pm 2.3\%$, respectively. Five- and 10-year OSs were $87 \pm 1.8\%$ and $81.3 \pm 2.1\%$, respectively (see Fig. 2). As noted in the original article, EFS did not differ between patients treated with regimen A and those treated with regimen B (see Fig. 3)—10-year EFS for regimen A was $74 \pm 3\%$ compared with $78 \pm 3.2\%$ for regimen B ($P = .24$). Moreover, EFS and OS were not impacted by sex, race, age at diagnosis, gender, brainstem involvement, extent of resection, or histologic evidence of diffuse or focal anaplasia.

Pattern of Disease Relapse

The pattern of disease relapse in patients on this study is as noted in Table 1. In the 7 patients with late relapse, pattern of relapse, as determined by the treating institution, was local in 4, local plus supratentorial in 2, and supratentorial alone in 1. Of these patients at time of initial entry to study, 5 had "total" resections and 2 "subtotal" resections. Of the 2 with subtotal initial resections, 1 failed locally and distally, and the second distally alone. On central review, the patient with a supratentorial-alone relapse had findings (radiographic) consistent with infiltrating glioma; however, the patient was not biopsied at relapse. For the purposes of this report, the patient is still considered a "late" relapse, as patients were classified per treating-institution diagnosis, unless there was clear pathologic evidence to document a different histology. In contrast, patients who relapsed earlier than 5 years from diagnosis had predominantly at least some component of disseminated relapse, with only 16% of patients having local relapse alone compared with 57% of patients with late relapse (Fisher's exact test $P = .029$). Spinal involvement, either alone or in combination with local relapse, which was commonly seen in those relapsing before 5 years of age, was not seen in those relapsing later.

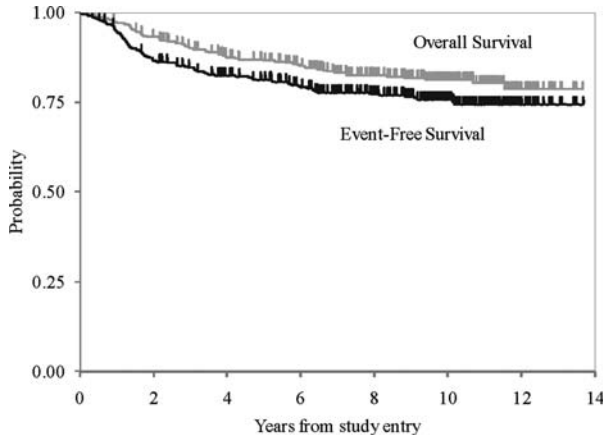

Fig. 2. Overall and event-free survival.

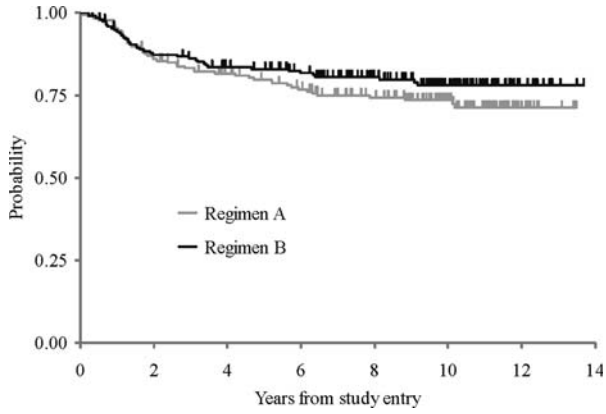

Fig. 3. Event-free survival by regimen.

Table 1. Pattern of relapse

Type of Relapse	≤5 y	>5 y
Local alone	10 (16%)	4 (57%)
Not local alone	51 (84%)	3 (43%)
Total	61	7

Fisher exact test $P = .029$, percent of total cases in age range are given in parentheses.

Table 2. Secondary tumors

Time of Secondary Tumor	Time after Treatment[a] (y)	Regimen	Secondary Tumor Type	Life Status	Time since Last Seen[b] (y)
<5 y	3.2	B	Precursor T-cell lymphoblastic leukemia	Dead	0.27
	3.7	A	Glioblastoma, NOS	Dead	0.32
	4.7	B	Basal cell carcinoma, NOS (Gorlin's)	Alive	8.16
	4.8	A	Spindle cell carcinoma	Alive	1.67
>5 y	5.3	A	Glioma, malignant	Dead	0.68
	5.3	A	Glioblastoma, NOS	Dead	0.56
	5.7	A	Osteosarcoma, NOS	Dead	1.28
	5.8	A	Myelodysplastic syndrome, NOS	Dead	6.87
	6.4	B	Myelodysplastic syndrome, NOS	Alive	0.76
	6.5	B	Pilocytic astrocytoma	Dead	0.85
	8.2	B	Papillary adenocarcinoma, NOS (thyroid)	Alive	1.07
	9.2	B	Glioblastoma multiforme	Dead	2.37
	9.2	B	Glioblastoma multiforme	Alive	1.18
	10.1	A	Papillary carcinoma, follicular (thyroid)	Alive	2.79
	10.3	A	Glioma, malignant	Dead	0.51

Abbreviation: NOS, not otherwise specified.
[a]Time between initial diagnosis and development of the secondary tumor.
[b]Time between diagnosis of the secondary tumor and when last seen.

Secondary Tumors

Fifteen patients experienced secondary tumors as a first event; 8 were on regimen A and 7 on regimen B. The median time to secondary tumor was 5.8 years; 4 occurred <5 years and 11 >5 years postdiagnosis, as shown in Table 2. Patients with secondary tumors were diagnosed at a median of 5.6 years postdiagnosis (range, 3.1–16.8 y). There was no significant difference in the incidence of secondary tumors in children older than 5 years at diagnosis compared with younger children. There was also no significant difference between the 2 randomized arms. The estimated cumulative incidence rate of secondary tumors at 5 and 10 years for the entire cohort was 1.1% (95% CI: 0.0%–2.3%) and 4.2% (95% CI: 1.9%–6.5%), respectively (see Fig. 4). Nine patients with secondary tumors died; 6 of the 9 were on regimen A (the CCNU-containing arm). One child with glioblastoma multiforme, who was alive at the time of this report, had been followed for 1.18 months and had been treated in the cyclophosphamide arm of the study. One child, diagnosed with a secondary "pilocytic astrocytoma" of the brainstem, died secondary to the tumor within 1 year of diagnosis (central histopathologic review was not performed). The child with basal cell carcinomas developing within the radiotherapy field was diagnosed with Gorlin's syndrome at time of development of the basal cell tumors. Of the 4 patients with non-CNS solid tumors, 2 had thyroid-region tumors, 1 had an osteosarcoma in the temporal bone, and 1 had a spindle cell sarcoma in the nasal region. Thus, all developed solid tumors in regions that would have received at least scatter radiation.

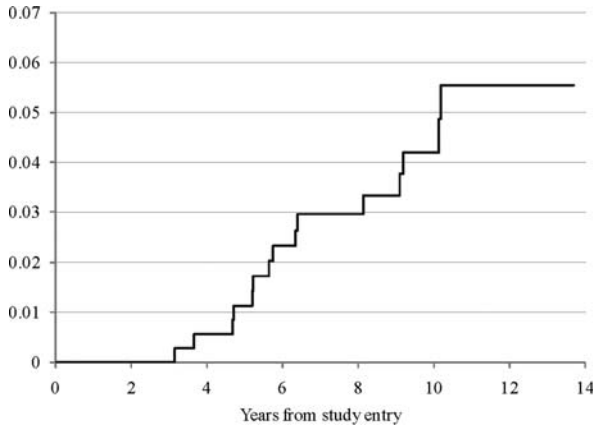

Fig. 4. Cumulative incidence of secondary tumors.

Discussion

The long-term results seen in this group of patients receiving radiotherapy and adjuvant chemotherapy, during and following radiotherapy, are both reassuring and cautionary. Ten-year EFS and OS rates of ~75%–80% are encouraging and compare favorably with survival rates reported in series utilizing radiation therapy alone or preradiation chemotherapy.[2,4,5,9] Prospective randomized trials comparing radiation therapy alone to radiation plus chemotherapy have not been performed; however, the best reported survival rates at 5 and 10 years for children with nondisseminated medulloblastoma receiving radiotherapy alone have ranged between 50% and 65%, even with the use of higher

doses of craniospinal radiation (3600 cGy).[4,7,10] Studies utilizing preradiation chemotherapy followed by higher doses of craniospinal radiation have disclosed 5-year survival rates of ~60%–65%.[9,11] Also reassuring is the stability of the survival curves after the multimodal treatment used in this study, which included a "reduced dose" of 2400 cGy of craniospinal radiation. In the few series that have reported long-term survival in children with medulloblastoma treated predominantly with radiation therapy alone, there has been no clear-cut plateauing of the survival curve, with some reporting a 10%–20% fall in survival between years 5 and 10.[7,10] The data from this randomized prospective study show few relapses after 5 years, possibly due to the addition of adjuvant chemotherapy. The majority of relapses in our series occurred within 2 years of diagnosis, with approximately one-third of relapses occurring in years 3 to 5, but only in 7 of 68 after year 5.

The pattern of relapse also differed in those children who relapsed within the first 5 years of diagnosis compared with those who relapsed later. Excluding the 1 child who was considered to have an isolated supratentorial relapse by the treating institution and, in retrospect, may have had an infiltrating cortical glioma, all "late" relapses occurred with some component of local disease; none had spinal disease either in isolation or as a component of initial relapse. A similar pattern was reported by von Hoff for the HIT99 trial.[12] Children in the Children's Oncology Group study who relapsed <5 years postdiagnosis overwhelmingly were likely to have some component of disease dissemination, as only 10 of the 61 had local relapse alone. Relapse outside the primary tumor site within 5 years of diagnosis, without any evidence of local relapse, occurred in 24 patients (40%), including 7 with spinal disease alone. This disseminated dominant pattern of failure with "early" relapse has also been found by others.[12–14] There does not seem to be a strong rationale, given these results, to continue surveillance studies of the spine in children who have survived >5 years with medulloblastoma treated with radiation and 1 of the 2 chemotherapeutic regimens used in this study. However, although surveillance studies after 5 years of disease control are unlikely to show recurrent disease, the increasing incidence of secondary tumors gives more credence to their use. A limitation of our data is that it is unknown whether the 7 children with relapse >5 years postdiagnosis were symptomatic at time of relapse or were identified solely by surveillance studies.

The 4.2% 10-year cumulative incidence of secondary tumors is quite worrisome, although the confidence intervals range between 2% and 6.5%. After closure of the database, another secondary presumed high-grade glioma of the brainstem (unbiopsied at the treating physician's discretion) occurred in a 9-year survivor. Direct comparison with other series is difficult because in most series, information was not gathered prospectively but rather was obtained from retrospective reviews and registries. There seems to be no question that radiotherapy is associated with increased relative risk for development of secondary tumors in children with brain tumors and leukemia, especially secondary malignant brain tumors >5 years from diagnosis and treatment.[15–18] In our series, all solid non-CNS secondary tumors occurred either within the radiation therapy portal or in regions where scatter radiation was likely (thyroid, nasal region, and temporal bone). However, the exact incidence of these secondary tumors is difficult to glean from studies, and for children with medulloblastoma, the incidence has been estimated to be in the 1%–2% range.[2,10] In retrospective reviews, the incidence of secondary tumors has been noted to be somewhat less after radiation therapy alone (in the 1% range at 10 years) or is not mentioned at all.[4,7,10] In a recent prospective series from Germany of 280 patients administered either sandwich pre- and postradiation chemotherapy or postradiation chemotherapy, 12 patients developed secondary tumors, including 3 with high-grade gliomas;[12] 8 of the 12 tumors were noted in patients who received the more aggressive sandwich chemotherapy, using similar drugs to those used in this series. In an analysis of the Surveillance Epidemiology and End Results data, a higher incidence of secondary tumors was noted in children surviving brain tumors treated after 1985 compared with those treated between 1979 and 1984, even when controlling for the use of radiation.[15] The authors suggest that this might be due to the use of more aggressive chemotherapy in the later eras. The Childrens Cancer Survivor Study found a trend but not a statistically significant relationship between an increased occurrence of secondary tumors and treatment in the later era, compared with those treated earlier.[16] It should be noted that although chemotherapy was used to some extent in the early 1980s, it has been increasingly employed since and is now considered by most a standard component of treatment for all children >3 years of age with medulloblastoma. Also, chemotherapeutic regimens employing potentially mutagenic alkylating agents, including in some cases etoposide, have been intensified over the past decade, raising the possibility that more secondary tumors may occur.[3,12] On the other hand, those same studies used lower-dose craniospinal radiotherapy, and increased total doses of radiotherapy have been related to a higher incidence of secondary brain cancer.[16] It remains to be seen whether the use of more focused radiotherapeutic techniques, such as proton beam irradiation, will in the future reduce the incidence of radiation-associated non-CNS secondary tumors.

Younger age at time of radiation has been related to a higher likelihood of development of a secondary tumor, but the results of this study do not show a relationship.[16] Patients specifically developing high-grade gliomas were a median of 5.8 years of age at initial diagnosis (range, 3.7–10.8 y).

In the cohort of patients treated in this study, the majority of secondary tumors, especially those occurring >5 years postdiagnosis, have been highly aggressive, with 5 malignant gliomas, 1 osteosarcoma, and 2 myelodysplastic syndromes. The literature and our experience would suggest that those patients with high-grade gliomas will rarely respond to treatment or survive,

making occurrence of this complication even more devastating.[12,18] Diagnosis of secondary malignant brain tumors in children with medulloblastoma is challenging, especially when they occur in the brainstem or similar deep-seated areas, and distinction between tumor recurrence and a secondary tumor can be impossible without histologic confirmation. Complicating diagnosis further is the difficulty of distinguishing small-cell gliomas from medulloblastomas that have undergone extensive glial differentiation, even when tissue is available for analysis. With all these considerations, it is impossible to determine whether this worrisome incidence of secondary tumors in this and other series evaluating patients with medulloblastoma receiving radiotherapy and chemotherapy is due to a true rise in incidence or better ascertainment. Also, in the present series, no meningiomas have been noted, and it is likely that as the survivor cohort ages, this tumor type will become prevalent.[16,19,20]

In conclusion, the updated results of this study demonstrate that the vast majority of children with nondisseminated medulloblastomas treated with radiation and receiving the chemotherapeutic regimens used in this study, during and after radiation therapy, will survive relapse-free. A small proportion of patients will relapse ≥ 5 years postdiagnosis, and in almost all, relapse will occur at the primary site. Patients are also at risk for development of secondary tumors including, but not limited to, tumors of the central nervous system, and long-term follow-up strategies must take this into account.

Conflict of interest statement. None declared.

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ORIGINAL REPORT

Processing Speed, Attention, and Working Memory After Treatment for Medulloblastoma: An International, Prospective, and Longitudinal Study

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See accompanying editorial on page 3480

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ABSTRACT

Purpose
The current study prospectively examined processing speed (PS), broad attention (BA), and working memory (WM) ability of patients diagnosed with medulloblastoma over a 5-year period.

Patients and Methods
The study included 126 patients, ages 3 to 21 years at diagnosis, enrolled onto a collaborative protocol for medulloblastoma. Patients were treated with postsurgical risk-adapted craniospinal irradiation (n = 36 high risk [HR]; n = 90 average risk) followed by four cycles of high-dose chemotherapy with stem-cell support. Patients completed 509 neuropsychological evaluations using the Woodcock-Johnson Tests of Cognitive Abilities Third Edition (median of three observations per patient).

Results
Linear mixed effects models revealed that younger age at diagnosis, HR classification, and higher baseline scores were significantly associated with poorer outcomes in PS. Patients treated as HR and those with higher baseline scores are estimated to have less favorable outcomes in WM and BA over time. Parent education and marital status were significantly associated with BA and WM baseline scores but not change over time.

Conclusion
Of the three key domains, PS was estimated to have the lowest scores at 5 years after diagnosis. Identifying cognitive domains most vulnerable to decline should guide researchers who are aiming to develop efficacious cognitive intervention and rehabilitation programs, thereby improving the quality of survivorship for the pediatric medulloblastoma population.

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INTRODUCTION

In contrast to their healthy peers, children who have been treated for medulloblastoma exhibit a decreased ability to acquire new information and skills at a comparable rate.[1] Declines in academic performance and overall intellect have long been identified as serious disease and treatment-related sequelae.[2,3] Recent studies have also revealed that children treated for medulloblastoma experience deficits in more key cognitive skills.[4-10]

A retrospective examination of 70 patients treated for a brain tumor found deficits in speed of processing, attention, memory, and academic performance at approximately 3 to 4 years after diagnosis.[4] A study of cognitive skills among a group of survivors of pediatric leukemia and brain tumor found that treatment with cranial irradiation was associated with slowed information processing and difficulties with working memory (WM).[11] Given the retrospective nature, cross-sectional design, and the mixed diagnoses included in these studies, questions remain with regard to the manifestation of the cognitive deficits over time experienced by patients who receive cranial irradiation for medulloblastoma.

From studies of healthy children, it is known that the ability to process information efficiently improves rapidly at an early age and continues to show improvement throughout childhood, eventually reaching adult levels of performance during late adolescence.[12] An extensive review among healthy children concluded that WM ability follows a similar course of development.[13]

Using standardized cognitive testing, the current study aimed to prospectively measure three key cognitive skills of children treated within a risk-based trial for pediatric medulloblastoma, from the point of diagnosis forward. Processing speed (PS), broad attention (BA), and WM were examined relevant to demographic and treatment risk factors. It was hypothesized that patients who were older at the time of diagnosis and treated as average risk (AR) would maintain function over time, whereas younger and high-risk (HR) patients would show declines in function over time. Identifying which patients are at risk for deficits in key cognitive skills and the time course on which they may manifest will provide important information for those seeking to develop and test empirically based intervention programs.

PATIENTS AND METHODS

Patients and Procedures

From 2003 to 2011, 318 patients age 3 to 21 years with histologically proven medulloblastoma tumors were enrolled onto a collaborative treatment protocol (SJMB03; NCT00085202; see Appendix for list of collaborating sites).[14] The institutional review board–approved informed consent was obtained on all patients before starting protocol therapy.

All sites followed the same protocol-driven medical treatment. Patients with M0 disease with no brainstem invasion, in whom gross total resection was achieved, were classified as AR; otherwise patients were classified as HR. Treatment between AR and HR patients was identical with the exception of postoperative radiation therapy, initiated within 31 days of definitive surgery. AR patients received 23.4 Gy of craniospinal irradiation and 55.8 Gy of conformal primary site boost (+1 cm margin). HR patients received 36 to 39.6 Gy of craniospinal irradiation and 55.8 Gy of conformal primary site boost. Chemotherapy was initiated 6 weeks after the completion of radiation therapy and included four cycles of dose-intensive cyclophosphamide, cisplatin, and vincristine. Patients were observed every 3 months for 2 years and every 6 months thereafter. Audiograms and endocrine testing were routinely conducted with hearing aids and appropriate replacement therapy offered as necessary. Patients also received vision testing throughout the study.

Of the 318 patients with medulloblastoma enrolled at the time of the current analyses, 75 patients were excluded as a result of posterior fossa syndrome that restricted valid assessment at baseline. Others were excluded for the following reasons: enrolled at a site that did not participate in neurocognitive testing (n = 19), lack of fluency in English (n = 12), medical status restricting assessment (n = 8), parents had refused testing (n = 12), scheduling conflicts (n = 8), died of disease (n = 2), progressive disease and off study (n = 2), and patient was found to have significant pre-existing learning deficits (n = 1). An additional 53 patients were excluded as a result of having only a single evaluation. The final study group consisted of 126 patients from eight collaborative sites (Appendix). As part of a separate study, a subgroup of patients from the primary site (St Jude Children's Research Hospital) were randomly assigned to receive either a computer-based reading intervention (n = 33) or standard of care (n = 28). The aim of the reading intervention was to improve reading decoding ability, which was found to be vulnerable in a previous study.[2]

The 126 patients included in the final analysis had an average age at diagnosis (AgeDx) of 9.82 years (standard deviation [SD], 4.39 years; Table 1). Parents provided demographic information, including marital status (n = 111; Table 1) and years of education (n = 107). Parents attended school for a median of 14 years (mean, 14.3 years; SD, 2.5 years; range, 8 to 20 years).

Table 1. Demographic Characteristics of Patients With Medulloblastoma (N = 126) and Their Parents (N = 111) by Risk Status

Characteristic	Average-Risk Patients		High-Risk Patients		All Patients	
	No.	%	No.	%	No.	%
Sex						
Female	34	69.4	15	30.6	49	38.9
Male	56	72.7	21	27.3	77	61.1
Race						
Aboriginal	1	100.0	—	—	1	0.8
Asian	4	80.0	1	20.0	5	4.0
Black	8	72.7	3	27.3	11	8.7
Black and white	1	100.0	—	—	1	0.8
Other	4	100.0	—	—	4	3.1
Unknown	3	100.0	—	—	3	2.4
White	69	68.3	32	31.7	101	80.2
Age at diagnosis, years						
Mean					9.82	
Standard deviation					4.39	
Parent marital status (N = 111)						
Divorced	8	66.7	4	33.3	12	10.8
Married	60	70.6	25	29.4	85	76.6
Separated	7	77.8	2	22.2	9	8.1
Single	5	100.0	—	—	5	4.5
Years of education of parents						
Mean					14.3	
Standard deviation					2.5	

Neurocognitive Assessment

Patients completed 509 assessments between 0 and 5 years from diagnosis (median, three assessments per patient; range, two to seven assessments). Neurocognitive testing was scheduled after surgical resection (baseline; shortly after the time of enrollment) and at 1, 3, and 5 years after diagnosis. At the primary site (St Jude Children's Research Hospital), every attempt was made to evaluate patients after completion of radiation treatment and annually from time of diagnosis. To be included in the study, patients needed to complete a protocol-driven evaluation of cognitive function using the Woodcock-Johnson Tests of Cognitive Abilities Third Edition[15] at baseline and at least one other time point. Patients were also examined via the Woodcock-Johnson Tests of Achievement Third Edition,[16] and those results will be reported separately. The country-specific edition of the Woodcock-Johnson battery was used at the Australian collaborative sites.

Three key cognitive skills were of particular interest for the current study: PS, BA, and WM. Age-adjusted standard scores have a population mean of 100 and an SD of 15. Standard scores of 90 to 110 are considered average, 80 to 89 low-average, 70 to 79 low, and ≤ 69 very low.[15,16] (See Appendix for subtest information).

Statistical Analysis

Linear mixed effects models (LMEMs) were used to estimate change in each cognitive function separately over time.[17,18] LMEMs allow estimation of the overall, group-level, and patient-level parameter estimates including rate of change (slope) over time.[19-24] Profile plots with spline smoothing were created as part of exploratory data analysis to identify outliers and to visually inspect patterns of change in each outcome. No deviations from linearity were apparent, and the number of observations per patient was not large enough to reliably model nonlinear change.

As reported previously,[2] examining cognitive outcomes within this population via single-variable analyses masks important results that manifest themselves differently in patient subgroups. Hence, our models are multivariable in nature. The following variables and their interaction with time were considered for inclusion in the LMEMs: AgeDx (years), risk group (AR and HR), sex, race (white and other), randomly assigned intervention group status (intervention or standard of care), baseline performance (standard scores), parent marital status (married and other), and parental education (years). Parent marital status and parental education were included as surrogate variables for socioeconomic status. We have previously shown that patients with

higher baseline values may be more vulnerable to deterioration in their cognitive functioning.[3] Therefore, baseline performance was included as a covariate rather than simply as the earliest value in the longitudinal sequence. To explain the variability in baseline scores, we used general linear models (GLMs) to study associations of the same set of covariates mentioned earlier with the baseline score.

A backward elimination approach was used both for GLMs and LMEMs to remove nonsignificant variables from the full model. On the basis of the F statistic *P* values, variables were removed from the model one at a time starting with the largest *P* value, until the final model was achieved for each outcome. Consistent with the hierarchy principle if a variable was included as part of an interaction term, its main effect was also included in the model regardless of significance. All models were fitted using PROC GLM and PROC MIXED in SAS Release 9.2 (SAS Institute, Cary, NC). All tests were two-tailed, and a significance threshold of $P = .05$ was used. No adjustments were made for the number of tests performed.

RESULTS

Race and intervention group status of the patient were not significantly associated with baseline scores or change in PS, WM, and BA scores over time. Therefore, they were removed from the models. Sex, AgeDx, risk status, parent education, parent marital status, and baseline scores were found to have significant associations that varied by outcome as described in the following sections.

PS

Observed PS scores at baseline were in the low-average range (mean, 88.06; SD, 20.43). In an effort to understand what impacts baseline performance, we used GLM. Only AgeDx was found to be significantly associated with baseline PS scores, where older patients had lower baseline scores compared with younger patients ($P = .0176$; Table 2).

The examination of change over time using LMEMs revealed that younger AgeDx ($P < .001$), HR disease ($P = .0025$), and higher baseline scores ($P = .0095$) were associated with slower PS over time (Table 3). The intercept term estimated by this model has significant associations with sex and, by design, with baseline PS performance. Results for the subtests contributing to PS can be found in the Appendix.

Table 2. Observed Baseline Standard Scores and Final GLMs for Baseline Scores by Neurocognitive Outcome

Outcome and Covariate	Observed Baseline Score		GLM Baseline Estimates	
	Mean	SD	Coefficient Estimate	*P*
Processing speed	88.06	20.43		
Intercept			98.337	< .001
AgeDx			−1.018	.0176
Working memory	102.40	16.95		
Intercept			82.244	< .001
AgeDx			−1.306	.0015
Parent education			2.066	.0013
Parent marital status (married)			6.077	.0895
Broad attention	98.35	16.87		
Intercept			78.797	< .001
AgeDx			−1.330	.0017
Parent education			1.964	.0029
Parent marital status (married)			8.707	.0189

Abbreviations: AgeDx, age at diagnosis; GLM, generalized linear model; SD, standard deviation.

Table 3. Final Linear Mixed Effects Models by Neurocognitive Outcome

Outcome and Covariate	Coefficient Estimate	*P*
Intercept		
PS		
Intercept	17.7137	< .001
Sex (female)	2.3943	.0343
AgeDx	0.0569	.6550
Risk (AR)	−1.6766	.1871
Baseline PS	0.8056	< .001
WM		
Intercept	11.7845	.0032
Risk (AR)	0.07723	.9561
Baseline WM	0.8889	< .001
BA		
Intercept	7.7564	.0352
Risk (AR)	1.1723	.3732
Baseline BA	0.9130	< .001
Slope		
PS		
Time	−1.9084	.4863
AgeDx × time	0.4700	< .001
Risk (AR) × time	3.2377	.0025
Baseline PS × time	−0.05897	.0095
WM		
Time	7.1803	.002
Risk (AR) × time	2.4886	.0036
Baseline WM × time	−0.09911	< .001
BA		
Time	6.4692	.0353
Risk (AR) × time	3.1663	.006
Baseline BA × time	−0.1007	< .001

Abbreviations: AgeDx, age at diagnosis; AR, average risk; BA, broad attention; PS, processing speed; WM, working memory.

Our population-level model for PS is given below where the terms with significant *P* values are in bold print. In this model, I_{AR} is an indicator function for risk ($I_{AR} = 1$ for AR patients and 0 otherwise), and I_S is an indicator function for sex ($I_S = 1$ for female patients and 0 otherwise). Time and AgeDx were treated as continuous variables and were measured in years:

$$\begin{aligned} PS = {} & \mathbf{17.714} + \mathbf{2.394} \times \mathbf{I_S} - 1.677 \times I_{AR} + 0.057 \times AgeDx \\ & + \mathbf{0.806} \times \mathbf{PS_{baseline}} - 1.908 \times time + \mathbf{0.470} \times \mathbf{AgeDx} \times \mathbf{time} \\ & + \mathbf{3.238} \times \mathbf{I_{AR}} \times \mathbf{time} - \mathbf{0.059} \times \mathbf{PS_{baseline}} \times \mathbf{time} \end{aligned}$$

Using this equation, we estimated PS scores at 5 years after diagnosis assuming a baseline PS value of 88.06, which was the observed average value in our cohort. Patients who were 6 years of age at diagnosis and HR had estimated mean scores in the very low range, whereas their older counterparts had estimated scores in the low to low-average range (Fig 1). Patients who were AR fared better, with estimated mean PS scores in the low-average range only for patients age 6 years at diagnosis, whereas older patients were in the average range (Fig 1). Our model also suggests that even if the baseline PS value

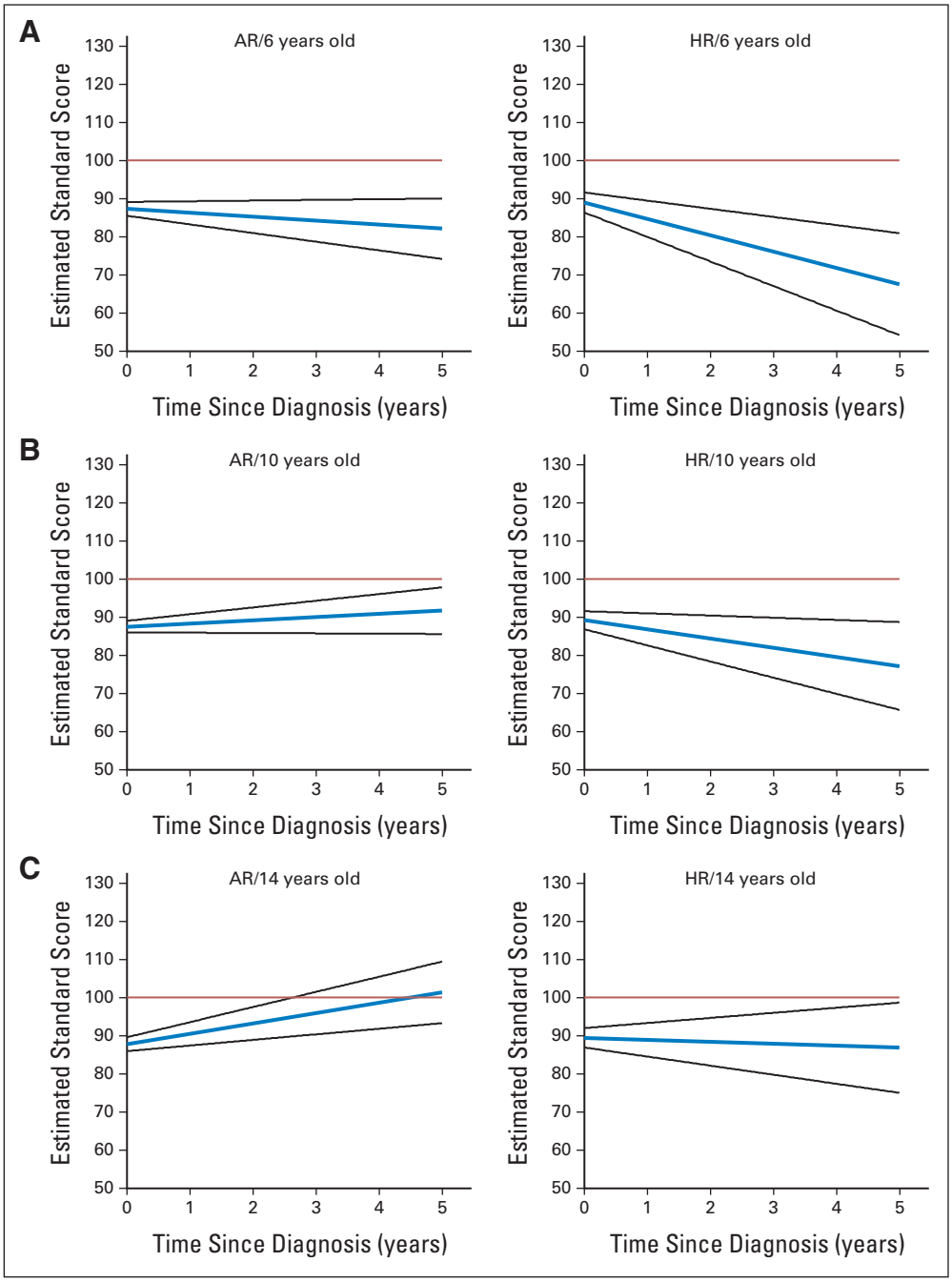

Fig 1. Estimated change in processing speed standard score (blue line; 95% CI, black lines) over time (years) for patients diagnosed at (A) 6, (B) 10, and (C) 14 years old with either average-risk (AR) or high-risk (HR) medulloblastoma. Population mean, 100 (red line).

is 100 (healthy population average), the estimated 5-year average PS value in the younger HR group remains in the low to very low range. Although sex was significant as part of the intercept term, the estimated 5-year mean PS values were not notably different between male and female patients.

WM

Observed WM scores at baseline were in the average range (mean, 102.40; SD, 16.95). Using GLM, results suggested lower baseline WM scores for patients diagnosed at an older age and higher baseline scores for patients whose parents were better educated and married (Table 2).

Time, risk, and baseline score were the only significant variables in our longitudinal model for WM scores. HR patients and patients with higher baseline scores exhibited less favorable outcomes (Table 3). Results for subtests contributing to WM can be found in the Appendix.

The following equation represents our population-level model for WM where the variables are defined as previously stated. The coefficients in bold are statistically significant:

$$\mathrm{WM} = \mathbf{11.785} + 0.077 \times \mathrm{I_{AR}} + \mathbf{0.890} \times \mathrm{WM_{baseline}} + \mathbf{7.180} \times \mathrm{time} + \mathbf{2.489} \times \mathrm{I_{AR}} \times \mathrm{time} - \mathbf{0.099} \times \mathrm{WM_{baseline}} \times \mathrm{time}$$

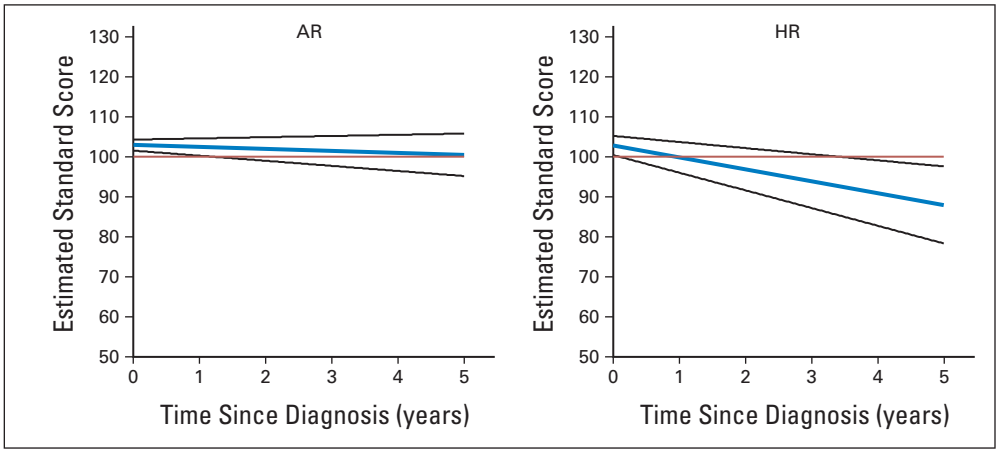

Fig 2. Estimated change in working memory standard score (blue line; 95% CI, black lines) over time (years) for patients diagnosed with either average-risk (AR) or high-risk (HR) medulloblastoma. Population mean, 100 (red line).

On the basis of this equation, mean WM scores for AR and HR patients are estimated to be in the average and low-average range at 5 years after diagnosis, respectively (Fig 2).

BA

Observed BA scores at baseline were in the average range (mean, 98.35; SD, 16.87). Younger patients and patients whose parents were married and better educated had higher baseline BA scores (Table 2).

Our longitudinal model results for BA were similar to the ones for WM where time, risk, and baseline BA scores were the only variables that were associated with change in BA over time. However, HR patients and patients with higher baseline scores had less favorable outcome (Table 3). Results for subtests contributing to BA can be found in the Appendix.

The following is our population-level model for BA where the variables are defined as before and bold indicates significant associations:

$$BA = \mathbf{7.756} + 1.172 \times I_{AR} + \mathbf{0.913} \times WM_{baseline} + \mathbf{6.469} \times time + \mathbf{3.166} \times I_{AR} \times time - \mathbf{0.101} \times WM_{baseline} \times time$$

On the basis of this equation, the average BA scores for both AR and HR patients were estimated to be in the average and low-average range at 5 years after diagnosis, respectively (Fig 3).

DISCUSSION

The current study is a comprehensive prospective comparison of key cognitive functions among a group of patients treated with risk-adapted therapy. Change in PS, WM, and BA was examined over time. Using the derived equations to estimate scores at 5 years after diagnosis, PS was found to have the lowest scores, especially for those who were younger at diagnosis and had HR disease. These patients had estimated average PS scores in the low to very low range, BA scores in the low-average to low range, and WM scores in the low-average range. These findings are similar to those from Mabbott et al[5] who studied cognitive function of pediatric patients who were treated for a brain tumor and evaluated 4 to 6 years after diagnosis. The lowest scores for all patients were found on information PS. BA and WM results were at or above what was expected for a healthy population.

Slowed processing of information may contribute to impaired learning of new information, especially in an academic setting. For school-aged children, necessary modification strategies may include eliminating timed testing and reducing the number of assignments. Although accommodations and modifications are a necessary step in supporting patients after treatment for pediatric medulloblastoma, there is a critical need to provide empirically

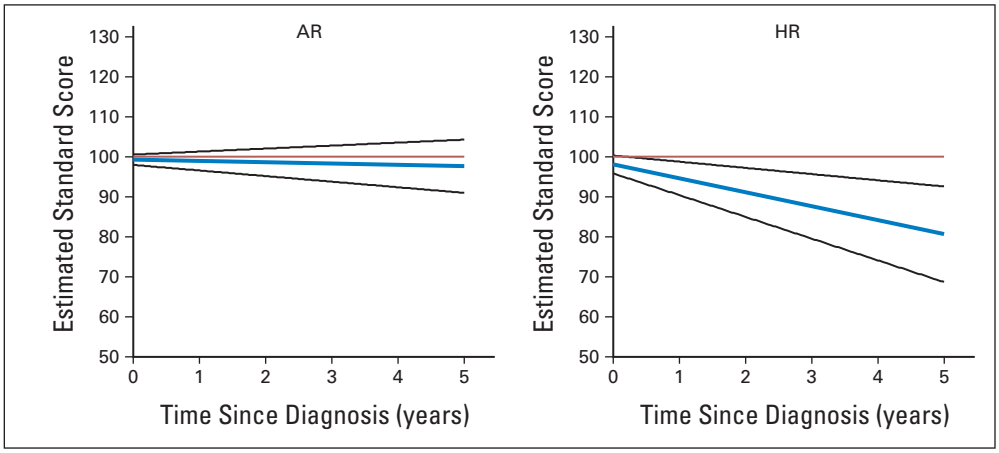

Fig 3. Estimated change in broad attention standard score (blue line; 95% CI, black lines) over time (years) for patients diagnosed with average-risk (AR) or high-risk (HR) medulloblastoma. Population mean, 100 (red line).

tested cognitive remediation and intervention programs. Results from the current study suggest that interventions that focus on improving PS hold merit. A pilot study aimed at improving cognitive skills among children with cancer-related brain injury reported that although the participants required longer than expected to complete the intervention, the group showed improved PS scores after intervention.[25] Additional studies report evidence of improved cognitive processes among populations experiencing learning difficulties.[26,27]

Of the variables tested, AgeDx, risk status, and baseline performance were found to be significantly associated with change in PS. Several studies have revealed that young age of the patient at the time of diagnosis is a prominent risk factor for cognitive late effects,[1,3,10] but few studies have been able to examine how age and risk may interact. The uniform patient population, treatment regimen, and number of observations included in the present study allowed for such examination. As hypothesized, those who were youngest at diagnosis and those who were treated as HR showed the greatest vulnerability. The declines experienced by this group may be related to the white matter injury documented after diagnosis.[28-32]

The process of myelination within the white matter continues into the third decade of life.[33] In healthy individuals, cortical white matter tracts normally complete myelination by age 3 or 4 years, followed by cerebellar connectivity, and full completion into the late 20s.[34] The presence of disease may delay maturation.[35,36] Radiation can cause interference in postnatal endothelial and glial cell cycles, depressed postnatal neurogenesis of subependymal glial and hippocampal neuroblast stem cells, and immune-mediated radiotherapy associated inflammatory processes.[37-40] Tumor compression of surrounding white matter and additional treatment with chemotherapy are alternate explanatory factors for white matter changes.[41,42]

Although the current study includes several cognitive assessments per patient among a consistently treated group of patients, with a median of three assessments per patient (range, two to seven assessments), no nonlinear trend was apparent and the data were not sufficient to reliably explore nonlinear models. Those with higher baseline values were shown to have steeper declines over time. This finding is similar to a study of general intellect, where those with higher baseline values were also found to have steeper declines over time.[3] Without extended long-term follow-up to reveal potential nonlinear patterns, questions remain with regard to when the declines eventually cease and whether or not the impact of baseline scores is potentially a regression to the mean effect.

Older patients were found to have lower PS, WM, and BA scores at baseline, a finding that was counterintuitive. Tumor location and PFS were examined for potential relation to AgeDx, but results failed to offer any explanation. Future studies that assess more specific pretreatment variables, such as symptom duration (ie, time from symptom onset to diagnosis) or symptom severity, may offer greater insight.[43]

Similar to a previous study of general intellect,[44] the current results showed higher parent education to significantly relate to higher patient baseline WM and BA scores. In addition, children from families with married parents also showed higher baseline BA and WM scores. Education and marital status may be acting as proxy variables for family environment, which has been shown to be related to recovery in pediatric studies of traumatic brain injury.[45] However, no such relationship to change in performance over time was found in the current study. Therefore, for a more complete understanding of potential impact, family environment should be explored in more detail in future studies. Long-term memory processes, involving the encoding, retrieval, and consolidation of information in memory, and executive functions were also not measured in this study, yet are related to late effects of radiation as well as posterior fossa brain tumor effects on cognition.[46,47] The same specificity of longitudinal change in relation to age, disease risk, and dose burden should be examined in relation to other key cognitive processes that affect learning and adaptation to the environment.

The present study shows that patients treated for medulloblastoma are especially vulnerable to change in PS ability, especially for those who are younger and HR. Concentrating efforts to remediate PS may support the maintenance of collateral processes. The current results should guide researchers to develop efficacious cognitive intervention programs, thereby improving the quality of survivorship for the pediatric medulloblastoma population.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Manuscript writing: All authors
Final approval of manuscript: All authors

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Appendix

Methods

Participating sites. From 2003 to 2011, 318 patients age 3 to 21 years with histologically proven medulloblastoma tumors were enrolled onto a collaborative treatment protocol (SJMB03; NCT00085202). The primary site was St Jude Children's Research Hospital (Memphis, TN). Collaborative sites included Children's Hospital of Philadelphia (Philadelphia, PA), Duke University Medical Center (Durham, NC), Hospital for Sick Children (Toronto, Ontario, Canada), Royal Children's Hospital Brisbane (Brisbane, Australia), Royal Children's Hospital Melbourne (Melbourne, Australia), Sydney Children's Hospital (Sydney, Australia), and Texas Children's Cancer Center (Houston, TX).

Neurocognitive assessment. Processing speed (PS) refers to the ability to efficiently absorb and cognitively manage presented information. Patients completed the following two subtests that, when combined, derive the PS composite score: decision speed, developed to test processing of semantic information; and visual matching, developed to test speed of processing visual perceptual information. Working memory (WM) is the temporary storage and manipulation of information necessary for the completion of various cognitive tasks. Patients completed the following two WM-related subtests: numbers reversed, a task of holding a span of presented numbers in short-term memory while reversing the sequence; and auditory working memory, a task of holding a mixed set of numbers and words in short-term memory while reordering into two sequences. Scores from the following four subtests were combined to derive the composite measure of broad attention (BA): numbers reversed and auditory working memory (described earlier); auditory attention, a test designed to measure speech sound discrimination amid increasing background noise; and pair cancellation, a task measuring concentration ability by rapidly identify visually presented repeated patterns.

Results

Decision speed. Using linear mixed effects models, age at diagnosis ($P = .0062$), risk status ($P = .0250$), and baseline performance ($P < .001$) were found to be significantly associated with change in decision speed over time (Table 2). Younger, high-risk patients and those with higher baseline scores experienced steeper declines in decision speed.

General linear model (GLM) analysis revealed that race was significantly associated with decision speed scores at baseline ($P = .0154$). Patients who were white had higher PS baseline scores than other races (Appendix Table A1).

Visual matching. Linear mixed effects models revealed that age at diagnosis was significantly associated with changes of visual matching scores over time ($P < .001$). Risk ($P = .0019$) and baseline performance ($P = .008$) were also significantly associated with the changes in visual matching scores over time (Appendix Table A2). Younger, high-risk patients and those with higher baseline WM scores experienced steeper declines in visual matching. GLM analysis showed that risk status and age of the patient at diagnosis were significantly associated with baseline visual matching scores (Appendix Table A1).

Numbers reversed. Age at diagnosis and parent education were significantly associated with scores at baseline ($P = .0037$ and $P = .0039$, respectively; Appendix Table A1). Baseline performance and risk status were associated with changes in numbers reversed scores over time ($P < .001$ and $P = .0491$, respectively), with those classified as high risk and who had higher scores at baseline experiencing steeper declines over time (Appendix Table A2).

Auditory working memory. GLM revealed that age at diagnosis ($P = .0023$) and parent education ($P = .006$) were significantly associated with the auditory working memory scores at baseline (Appendix Table A1). Linear mixed effects models revealed that risk status ($P < .001$) and baseline performance ($P < .001$) were significantly associated with changes in auditory working memory scores over time (Appendix Table A2). High-risk patients and those with higher baseline scores experienced steeper declines in auditory working memory.

Auditory attention. Parent marital status ($P = .0263$) was significantly associated with auditory attention at baseline (Appendix Table A1). Risk ($P = .0152$), baseline performance ($P < .001$), and parent education ($P = .0182$) were significantly associated with change in auditory attention over time (Appendix Table A2).

Pair cancellation. Age at diagnosis was significantly associated with pair cancellation at baseline ($P < .001$; Appendix Table A1). Risk ($P = .0321$) and baseline performance ($P = .0036$) were significantly associated with the changes in pair cancellation scores over time (Appendix Table A2). High-risk patients and those with higher baseline scores experienced steeper declines in pair cancellation.

Table A1. Observed Baseline Standard Scores and Final GLMs for Baseline Scores by Neurocognitive Outcome

Outcome and Covariate	Baseline Score		GLM Estimates	
	Mean	SD	Coefficient Estimate	*P*
Decision speed	91.17	17.87		
Intercept			101.351	< .001
Race (nonwhite)			−9.919	.0154
AgeDx			−0.815	.0279
Visual matching	87.98	20.49		
Intercept			101.137	< .001
Risk (AR)			−6.838	.0878
AgeDx			−1.482	.0011
Parent marital status (married)			7.217	.0978
Numbers reversed	100.49	15.54		
Intercept			88.452	< .001
AgeDx			−1.097	.0037
Parent education			1.677	.0039
Auditory working memory	104.68	15.94		
Intercept			87.874	< .001
AgeDx			−1.180	.0023
Parent education			1.717	.0060
Parent marital status (married)			6.500	.0629
Auditory attention	101.72	13.22		
Intercept			94.423	< .001
Parent marital status (married)			7.933	.0263
Pair cancellation	90.95	13.59		
Intercept			103.345	< .001
AgeDx			−1.148	< .001

Abbreviations: AgeDx, age at diagnosis; AR, average risk; GLM, generalized linear model; SD, standard deviation.

Table A2. Final Linear Mixed Effects Models by Neurocognitive Outcome

Outcome and Covariate	Coefficient Estimate	*P*
Intercept		
DS		
Intercept	18.2232	< .001
Sex (female)	3.2390	.009
Risk (AR)	−0.9460	.4953
AgeDx	0.01305	.9253
Baseline DS	0.8044	< .001
VM		
Intercept	17.3422	< .001
AgeDx	0.1729	.1880
Risk (AR)	−1.9544	.1254
Baseline VM	0.8078	< .001
NR		
Intercept	16.9023	.0003
Risk (AR)	1.9593	.1917
Baseline NR	0.8275	< .001
AWM		
Intercept	19.1009	< .001
Risk (AR)	−2.8034	.0684
Baseline AWM	0.8359	< .001
AA		
Intercept	35.8948	< .001
Risk (AR)	−0.4888	.7707
Baseline AA	0.6472	< .001
Parent education	0.07832	.7877
PC		
Intercept	6.9547	.0627
Risk (AR)	1.3093	.2586
Baseline PC	0.9071	< .001
Slope		
DS		
Time	4.2792	.1899
Risk (AR) × time	2.6263	.0250
AgeDx × time	0.3226	.0062
Baseline DS × time	−0.09653	< .001
VM		
Time	2.3106	.2701
AgeDx × time	0.08636	< .001
Risk (AR) × time	0.8310	.0019
Baseline VM × time	0.01905	.0080
NR		
Time	11.2763	< .001
Risk (AR) × time	1.8564	.0491
Baseline NR × time	−0.1341	< .001
AWM		
Time	8.1587	< .001
Risk (AR) × time	3.1648	< .001
Baseline AWM × time	−0.1099	< .001
AA		
Time	5.1546	.2667
Risk (AR) × time	3.3908	.0152
Baseline AA × time	−0.1746	< .001
Parent education × time	0.5637	.0182
PC		
Time	10.3868	.0226
Risk (AR) × time	3.0545	.0321
Baseline PC × time	−0.1383	.0036

Abbreviations: AA, auditory attention; AgeDx, age at diagnosis; AR, average risk; AWM, auditory working memory; DS, decision speed; NR, numbers reversed; PC, pair cancellation; VM, visual matching.

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Association between radiation dose to neuronal progenitor cell niches and temporal lobes and performance on neuropsychological testing in children: a prospective study

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Background. Neurocognitive toxicity from radiation therapy (RT) for brain tumors may be related to damage to neural progenitor cells that reside in the subventricular zone and hippocampus. This prospective study examines the relationship between RT dose to neural progenitor cell niches, temporal lobes, and cerebrum and neurocognitive dysfunction following cranial irradiation.

Methods. Standardized assessments of motor speed/dexterity, verbal memory, visual perception, vocabulary, and visuospatial working memory were conducted in 19 pediatric patients receiving cranial RT and 55 controls at baseline and 6, 15, and 27 months following completion of RT. Prescription doses ranged from 12 Gy to 59.4 Gy. Linear mixed effects regression model analyses were used to examine the relationships among neuropsychological performance, age, and radiation dose to the subventricular zone, hippocampus, temporal lobes, and cerebrum.

Results. Performance on all neuropsychological tests, except vocabulary, was significantly reduced in patients relative to controls, particularly among younger children. Performance on motor speed/dexterity decreased with increasing dose to hippocampus ($P < .05$) and temporal lobes ($P < .035$). There was also a significant relationship between (i) reduced performance on verbal learning and increasing dose to the cerebrum ($P = .022$) and (ii) reduced performance on visual perception and increasing dose to the left temporal lobe ($P = .038$). There was no association between radiation dose to evaluated structures and performance on vocabulary or visuospatial working memory.

Conclusions. These prospective data demonstrate a significant association between increasing RT dose to hippocampus and temporal lobes and decline in neurocognitive skills following cranial irradiation. These findings have important implications for trials, including RTOG 0933 (hippocampal-sparing whole brain radiation therapy for brain metastases).

Keywords: brain irradiation, brain tumor, neural progenitor cell niches, neuropsychological performance.

Radiation therapy (RT) is integral to the management of a wide variety of both pediatric and adult brain tumors. However, RT to the brain is associated with neurocognitive toxicity.[1–7] The etiology of radiation injury to the brain is likely multifactorial, but data suggest that injury to neural progenitor cells (NPCs) plays a role.[8–14]

Within the mammalian brain, NPCs are known to reside in 2 areas, or NPC niches: the subventricular

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zone (SVZ) of the lateral ventricles and the dentate gyrus of the hippocampus.[15–17] NPCs are critical to recovery of the CNS from damage, including RT-associated injury.[18,19] However, NPCs and their progenitor stem cell populations are highly radiosensitive.[8,20–22] Emerging data suggest that the human brain has neurogenic areas similar to the rodent brain[17] that may be associated with neurocognitive toxicity following RT and chemotherapy.

Limited retrospective human studies suggest an association between radiation dose to the hippocampus and temporal lobes and neurocognitive deficits following cranial irradiation.[23–25] The relationship between radiation dose to the SVZ and neurocognitive sequelae remains controversial. Although prophylactic intrathecal methotrexate administration in children with acute lymphoblastic leukemia has been associated with neurologic toxicity,[26–29] suggesting a potential relationship with injury to cells immediately adjacent to the ventricle,[30] retrospective data have not demonstrated a correlation between RT dose to the SVZ and neurocognitive decline following radiation therapy.[31]

We present one of the first prospective studies to examine the relationship between RT dose to NPC niches, temporal lobes, and cerebrum and neurocognitive dysfunction in children following cranial irradiation for brain tumors. The a priori hypothesis of this study was that increased radiation dose to the temporal lobes and NPC-containing niches would be associated with decreased performance on follow-up neurocognitive testing, specifically on tests of memory, executive function, and motor dexterity.

Materials and Methods

Study Population and Eligibility

Children ($n = 19$) ages 1–18 years at the time of radiation to the brain for tumors of any histology or prophylactic cranial irradiation were eligible for enrollment in this prospective study approved by the institutional review board at The Johns Hopkins Hospital. Procedures were followed in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association. Written consent was obtained prior to enrollment in the study. The comparison group ($n = 55$) were healthy, typically developing children with no history of psychiatric disorder, neurologic illness, or learning disability.

Radiation Dose to Brain Structures

The SVZ, hippocampus, temporal lobes, and cerebrum were manually contoured using the treatment-planning CT scan and co-registered T1-weighted postgadolinium contrast and fluid attenuated inversion recovery (FLAIR) MRIs. The SVZ was defined as a 5-mm region adjacent to the lateral wall of the lateral ventricle. The contours of the hippocampus, temporal lobes, and cerebrum were delineated using an online radiographic atlas as a reference (http://headneckbrainspine.com). To minimize interindividual differences in measurement, all contours were drawn by a single physician. The initial contours were then reviewed by a second physician to confirm their accuracy. Figure 1 shows representative contours of the hippocampus on an axial T1-weighted MRI postgadolinium contrast that has been fused to the treatment-planning CT scan. The mean radiation dose to each of these structures was calculated from the dose volume histogram of the restored radiation treatment plan using the Pinnacle planning system (Philips).

Neuropsychological Measures

The neuropsychological assessment was designed to provide a delineation of selected neurobehavioral functions, using nationally standardized tests with good test-retest reliability that have been validated in the age range of interest. For this prospective study, we emphasized assessment of memory and motor speed, considered to be most sensitive to radiation effects to NPCs in the hippocampus and SVZ, respectively. Testing was performed by a trained master's-level psychology associate or postdoctoral neuropsychology fellow under the supervision of a board-certified neuropsychologist in an outpatient clinic. Control participants were screened for psychiatric disorders using the Diagnostic Interview for Children and Adolescents, Fourth Edition.[32] Neuropsychological testing was performed at baseline and at approximately 6, 15, and 27 months following completion of RT in patients and at matched time points for controls. Not all patients were evaluated on all tests at all time points, and missing patients varied among time points. Additionally, some of the youngest patients were not tested until the later time points. The neuropsychological protocol was as follows:

Verbal memory was assessed using the Memory for Words Test,[33] a measure of short-term auditory verbal memory/learning. Tests of declarative learning and recognition vocabulary are considered to be dependent on the integrity of subcortical systems, including the thalamus and hippocampus.

Vocabulary was measured via the Peabody Picture Vocabulary Test, third edition,[34] which requires the participant to identify a picture that best describes a word by pointing to it or verbalizing its number. Tests of vocabulary are considered to be dependent on temporal lobe functioning, particularly that of the left temporal lobe.

Working memory was assessed using (i) the Bead Memory Test,[35] a measure of visual-spatial working memory in which participants look at a picture of beads in a given pattern and then reproduce the pattern from memory; and (ii) the Auditory Working Memory assessment (Woodcock Johnson version III [WJ-III]), a measure of auditory verbal memory in which patients are asked to repeat lists of unrelated words. Working memory tests are considered to be

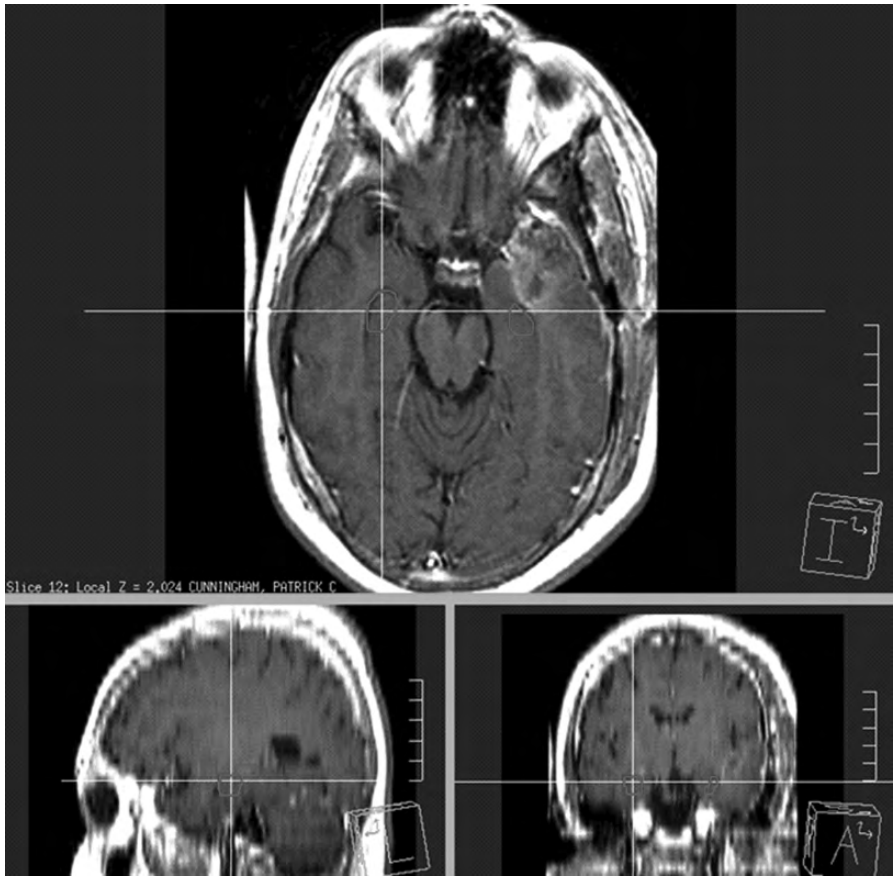

Fig. 1. Representative contours of the hippocampus on an axial (top image) T1-weighted MRI postgadolinium contrast and on the sagittal (bottom left) and coronal reconstructions (bottom right). The T1 postgadolinium and FLAIR-sequence MRIs were fused to the RT-planning CT scan to allow calculation of the doses to contoured structures.

dependent on dorsolateral prefrontal-striatal circuitry, potentially disrupted following damage to the SVZ.

Motor speed was assessed using Purdue Pegboard,[36] which measures the time it takes to place pegs into a board with 25 parallel holes. The 2-Hand trial was analyzed for the present study. Measures of motor speed are considered to be dependent on frontostriatal circuitry involving the motor circuit including the putamen, which may be disrupted secondary to damage to the SVZ.

Visual perception[37] required the participants to match 2-dimensional line drawings to a model. Performance on the visual perception test has been shown to be associated with temporal lobe volumes.[38]

Data Analysis

Linear mixed effect (LME) regression analyses were used to examine differences in neuropsychological test scores between patients and controls ("group"), with moderating variables including age at the time of the baseline visit ("age_0") and time since baseline ("time"). Main effects and their 2- and 3-way interactions were used in the analyses of the raw scores of the neuropsychological tests. Two-way interaction terms included $Age_0 \times$ Time, which examined the change in test score with age over time; Group $\times$ Age_0, which examined differences in test scores with age between the groups; and Group $\times$ Time, which examined differences in test scores with time between the groups. A 3-way interaction term (Group $\times$ $Age_0 \times$ Time) was used to examine whether the neuropsychological scores changed differently with age and over time between patients and controls. For LME analyses showing a significant term "time," a general linear model ANOVA with Fisher's least significant difference was used as a post-hoc test to evaluate the differences in neuropsychological performance between patients and controls at individual time points (visits 1–4).

In patients, LME analyses were also used to evaluate the overall relationship between the raw scores of the neuropsychological tests and regional radiation doses ("dose") to SVZ, hippocampus, temporal lobes, and cerebrum. The analyses controlled for age at the time of irradiation (age_{RT}) and for the presence or absence of concurrent chemotherapy. For presentation of the results in the Figures, *Z*-scores were used to account for the effect of age on neuropsychological performance. Because we hypothesized that higher radiation doses to specific brain regions in patients would result in a more pronounced impairment on specific neuropsychological tests, no corrections for multiple comparisons were performed. Statistical significance was set to $P < .05$.

Results

Table 1 shows patient demographic information and treatment characteristics, and Table 2 shows control demographic information. The mean age at cranial irradiation was 11.8 years (range 1.1–18.6). The primary site was infratentorial in 5/19, supratentorial in 12/19, and leukemia in 2/19. Radiation treatment plans were craniospinal, $n = 8$; whole brain radiation, $n = 3$; and 3-dimensional or intensity-modulated RT, $n = 9$. Mean prescription dose was 42.9 Gy (range 12 Gy–59.4 Gy). Eight patients (42%) received concurrent chemotherapy, most commonly (87.5%) vincristine based. The neuropsychological evaluation was completed by the following number of patients: baseline, $n = 13$ (time between diagnosis and baseline testing: range 14–2284 days, median 127 days); 6-month follow-up, $n = 13$; 15-month follow-up, $n = 14$; 27-month follow-up, $n = 10$; and by the following number of controls: baseline, $n = 55$; 6-month follow-up, $n = 43$; 15-month follow-up, $n = 38$; 27-month follow-up, $n = 37$.

Table 1. Patient and treatment characteristics

	n	%
Gender		
Male	12	63
Female	7	37
Age at diagnosis		
0–4 y	4	21
5–9 y	3	16
10–14 y	8	42
15–19 y	4	21
Ethnicity		
Caucasian	13	68
African American	4	21
Other	2	11
Handedness		
Right	18	95
Left	1	5
Diagnosis		
Glioma	4	21
Medulloblastoma/PNET	5	26
Germinoma	3	16
Leukemia	2	11
Nongerminoma germ cell tumor	2	11
Pineoblastoma	1	5
Craniopharyngioma	1	5
Ependymoma	1	5
RT technique		
Craniospinal	8	42
Whole brain	3	16
3D conformal or IMRT	8	42
Radiation dose		
0–20 Gy	2	11
21–49 Gy	3	16
50–60 Gy	14	74
Primary site		
Supratentorial	14	74
Infratentorial	5	26
Concurrent chemotherapy		
Yes	8	42
No	11	58

Abbreviations: PNET, primitive neuroectodermal tumor; IMRT, intensity-modulated RT.

Group Differences in Neuropsychological Performance

Fig. 2 shows overall changes in neuropsychological test scores over time in the patient and control groups, and Fig. 3 shows the differences in the mean test scores at individual visits. The main LME analysis indicated that patients tended to have a significantly lower (worse) overall performance on motor dexterity (group, $P = .015$; Group × Time, $P = .027$), verbal learning (group, $P = .001$; Group × Age_0, $P = .003$), visuospatial working memory (group–trend, $P = .057$; Group × Age_0, $P = .047$; Group × Time, $P = .003$), and visual perception (group, $P < .0001$; Group × Age_0, $P < .0001$; Group × Time, $P = .018$; Group × Age_0 × Time, $P = .015$). Patients had poorer neuropsychological performance than controls as early as baseline, with significantly lower test scores on motor dexterity (Purdue Pegboard, $P = .008$) and verbal learning (Memory for Words, $P = .003$) (Fig. 3). Performance improved with age in both groups on motor dexterity (Purdue Pegboard, Fig. 2A), verbal learning (Memory for Words, Fig. 2B), visuospatial working memory (Bead Memory, Fig. 2C), and visual perception (visual perception test, Fig. 2D) (all tests, $P < .0001$). However, different rates of change in test performance were found with age, such that neuropsychological deficits relative to controls—in particular verbal learning, visuospatial working memory, and visual perception—were more pronounced in younger patients (Fig. 2). In

Table 2. Control characteristics

	n	%
Gender		
Male	30	55
Female	25	45
Age at enrollment		
0–4 y	0	0
5–9 y	19	35
10–14 y	21	38
15–19 y	15	27
Ethnicity		
Caucasian	26	47
African American	24	44
Other	5	9
Handedness		
Right	44	80
Left	11	20

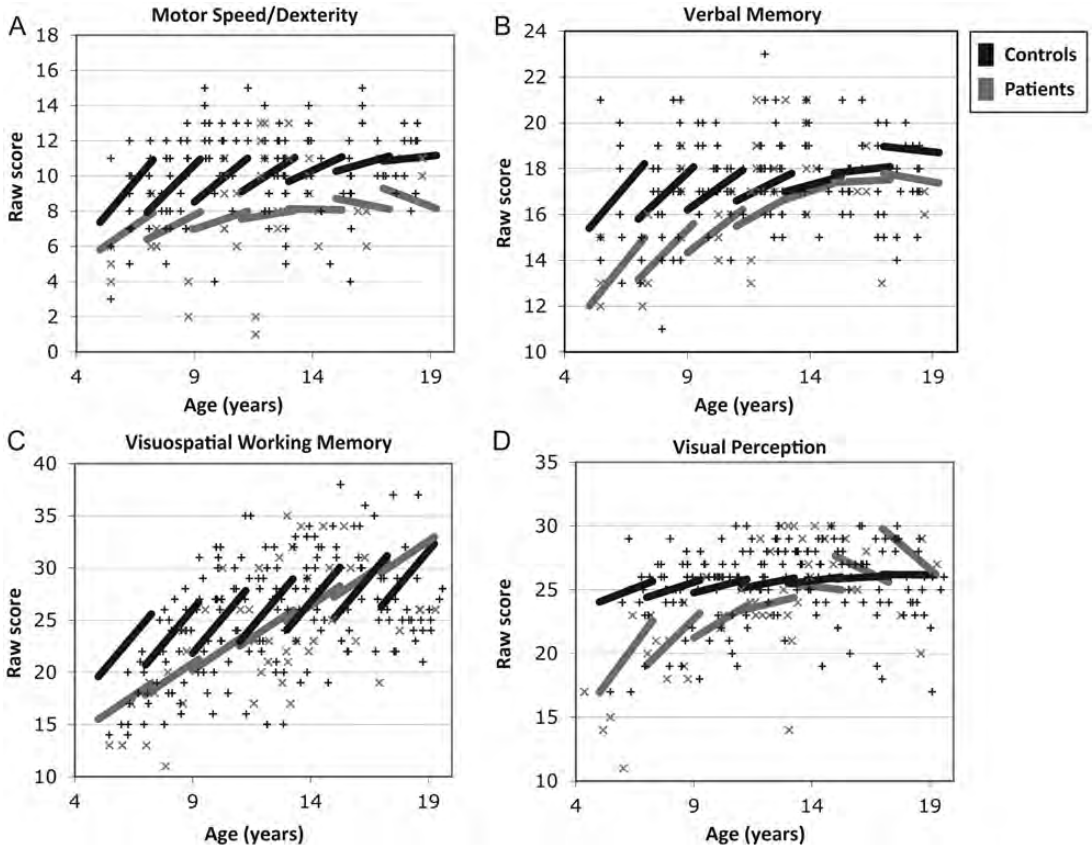

Fig. 2. Age- and time-related changes in neuropsychological performance (raw scores) in patients and controls. The black "+" symbols represent individual control data points and the gray "×" symbols represent individual patient data points. The results of the LME regression analyses of age- and time-related differences in test scores between patients and controls are presented as solid lines. The individual lines represent changes in test scores over time (27 mo) for patients (gray lines) and controls (black lines) of different ages. Raw scores in both groups increased with age on the Purdue Pegboard 2-Hand test (1A), WJ-III Memory for Words (1B), Bead Memory (1C), and visual perception test (1D) (all $P < .001$). Improvement in test performance on the Purdue Pegboard 2-Hand, WJ-III Memory for Words, and visual perception tests over the 27-mo period was most prominent in younger children. However, despite overall improvement over time, younger patients had more pronounced cognitive deficits.

addition, different rates of change in test performance were found over time in patients versus controls, such that the performance of patients improved toward normal over time. For example, the improvement over time was faster for patients than for controls on verbal memory but slower for patients than for controls on motor speed/dexterity.

No significant group- or age-related differences were revealed for recognition vocabulary (these results are not included in Figs 2 and 3).

Effect of Radiation Dose on Neuropsychological Performance

Motor speed and dexterity (Purdue Pegboard 2-Hand).—Among patients, motor speed and dexterity decreased with increasing mean radiation dose to the hippocampus (main LME analyses: left hippocampus, dose: $P = .049$, visit: $P = .023$; right hippocampus, dose: $P = .032$, visit: $P = .014$). Test performance also decreased with increasing mean dose to the temporal lobes (main LME analysis: left temporal lobe, dose: $P = .033$, visit: $P = .021$; right temporal lobe, dose: $P = .015$, visit: $P = .017$). At 6-month follow-up, raw scores decreased with increasing doses to the left and right hippocampi and temporal lobes (for all, $P < .045$). At 15-month follow-up, the relationship was significant for the temporal lobes (left, $P = .020$; right, $P = .010$) and at 27-month follow-up, for the right hippocampus ($P = .036$). Figures 4 and 5 illustrate decreased motor speed/dexterity with increasing radiation doses to the hippocampi and temporal lobes, respectively, at 6-month follow-up. There was no significant effect of mean dose to cerebrum ($P = .46$) or SVZ ($P > .3$) on performance. There was no significant difference in performance on the test of motor speed between patients with infratentorial versus supratentorial tumors ($P = .37$ at 6 mo, $P = .55$ at 15 mo, and $P = .59$ at 27 mo).

Verbal learning (WJ-III Memory for Words).—Although the main analysis for verbal learning indicated an overall effect of dose to cerebrum on test performance (dose, $P = .022$; visit, $P = .013$; $Age_{RT} \times$ Dose,

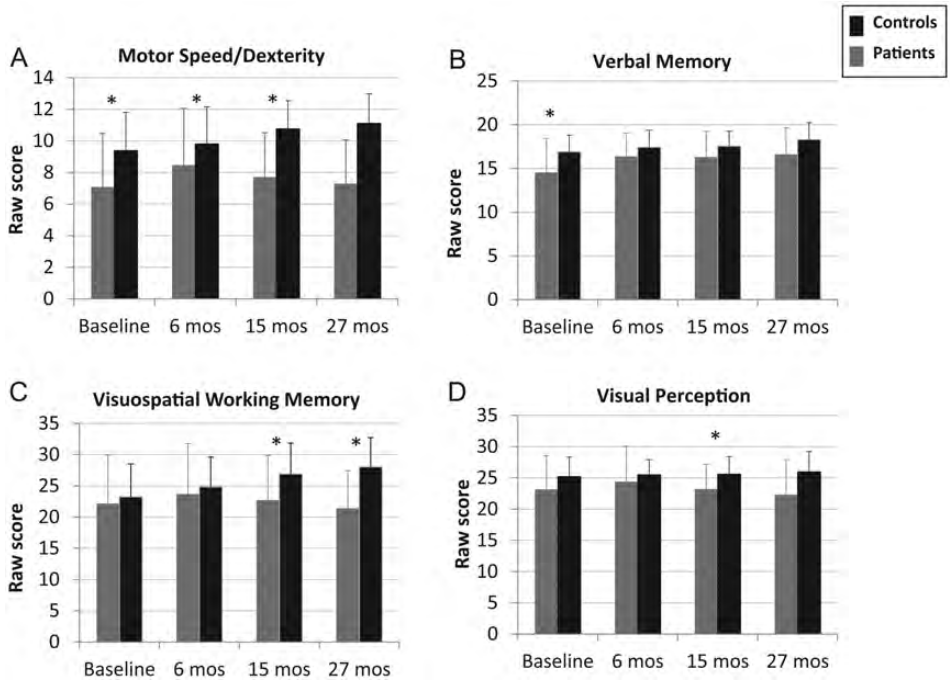

Fig. 3. Performance of patients vs controls at all time points on the Purdue Pegboard 2-Hand (2A), WJ-III Memory for Words (2B), Bead Memory (2C), and visual perception tests (2D). The data represent mean raw scores and SDs. Asterisk (*) indicates significant group differences detected in post-hoc analyses.

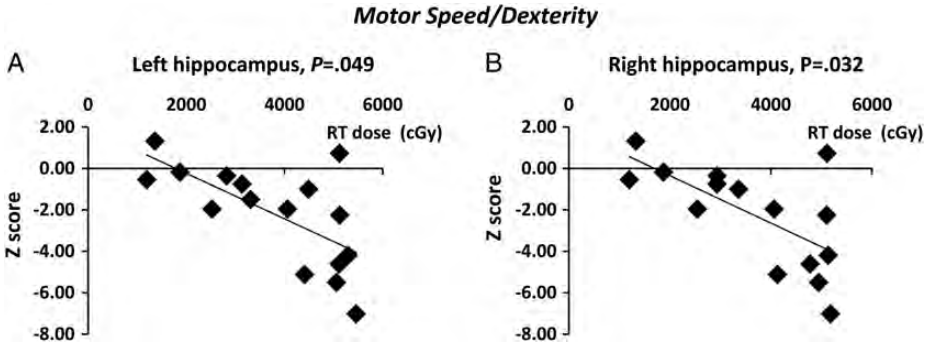

Fig. 4. Performance on Purdue Pegboard 2-Hand test (Z-scores) at 6 mo following completion of RT relative to (A) mean left hippocampal radiation dose, $P = .049$, and (B) mean right hippocampal radiation dose, $P = .032$. Standardized scores were used in this analysis to account for the impact of age on test performance.

$P = .033$; Dose × Visit, $P = .050$), no significant relationships were detected at the individual follow-up visits (dose, all $P > .10$). On verbal learning, there was no significant effect of dose to the left or right hippocampus ($P > .24$), temporal lobes ($P > .6$), or SVZ ($P = .10$).

Visual perception.—The main analysis of the visual perception test indicated an overall tendency for decreased scores with increasing dose to the left temporal lobe (dose, $P = .038$; Age_{RT} × Dose, $P = .041$). No significant findings were detected at follow-up visits (dose, all $P > .14$). There was no significant relationship between performance on visual perception and mean dose to the cerebrum ($P = .062$), SVZ ($P > .08$), right temporal lobe ($P = .067$), and left and right hippocampi ($P > .07$). There was no difference in performance on this test between left- and right-handed individuals ($P = .52$ at 6 mo, $P = .89$ at 15 mo, and $P = .49$ at 27 mo).

Vocabulary (Peabody Picture Vocabulary Test).—Analyses of vocabulary indicated slight differences in the relationship between the test scores and radiation dose to the right temporal lobe (dose, $P = .23$; Dose × Visit, $P = .024$) and left temporal lobe (dose, $P = .30$; Dose × Visit, $P = .058$) among visits. The significance of the interaction term Dose × Visit was likely due to a weak relationship between the test scores and radiation doses at visits 3 and 4 ($P = .15$ and .18, respectively). There was no association between radiation dose to

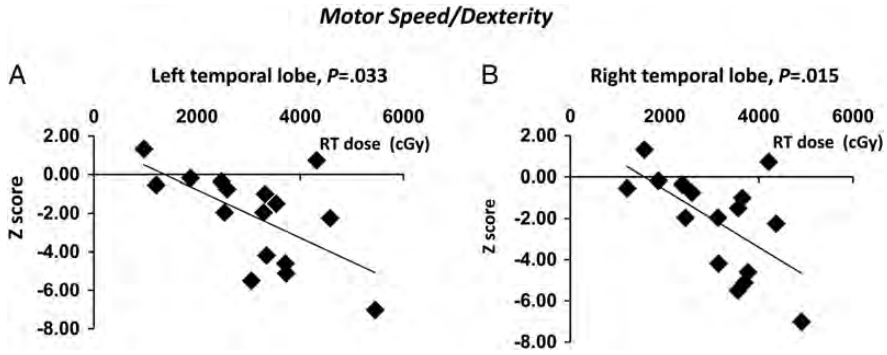

Fig. 5. Performance on Purdue Pegboard 2-Hand test (*Z*-scores) at 6 mo following completion of RT relative to (A) mean left temporal lobe radiation dose, $P = .033$, and (B) mean right temporal lobe radiation dose, $P = .015$. Standardized scores were used in this analysis to account for the impact of age on test performance.

the left or right hippocampus (dose, $P \geq .2$), cerebrum ($P = .22$), or SVZ ($P \geq .21$) and performance on the vocabulary test.

Visuospatial working memory (Bead Memory).—There was no relationship between mean radiation dose to the left or right hippocampus ($P \geq .66$), temporal lobes ($P \geq 0.87$), SVZ ($P \geq 0.18$), or cerebrum ($P \geq .25$) and performance on the spatial working memory test.

Discussion

We present a prospective study examining the relationship between radiation dose to NPC-containing niches, temporal lobes, and cerebrum and neurocognitive function following RT. We demonstrate a significant association between increasing mean RT dose to the hippocampus and temporal lobes and decline in select neurocognitive skills following cranial irradiation, but no association between mean dose to SVZ or cerebrum and test performance. This is one of the first human studies to corroborate animal data suggesting a relationship between radiation-induced damage to the hippocampus and neurocognitive dysfunction.[8–14]

These prospective data are consistent with prior retrospective studies on long-term cancer survivors that have demonstrated a significant association between radiation dose to the temporal lobes and neurocognitive dysfunction.[25,39] A prior prospective study found that patients receiving >43.2 Gy to 13% of the volume of the left temporal lobe were significantly more likely to demonstrate a >10% decline in performance in full-scale IQ.[24] An analysis of patients with nasopharyngeal carcinoma reported significantly lower cognitive functioning scores in patients with a mean dose to the temporal lobes of >36 Gy.[23]

Changes in the development of neuropsychological skills (especially motor speed, declarative memory, and visuoperceptual skills) following cranial irradiation may result from radiation-induced structural damage to the brain. For example, Nagel et al[40] demonstrated that the volume of both the right and left hippocampi decreased during the first 2–3 years following craniospinal radiation for medulloblastoma. Diffusion tensor MRI has been used to detect increased diffusion of water molecules in the hippocampus of patients receiving RT.[41] Similarly, changes in white matter integrity[42] and volume[43] occur following cranial irradiation, and reduced volumes of the cerebellar vermis predict reduced performance on neuropsychological testing.[44] Future studies will be critical in gaining additional insight into the mechanism of radiation-induced structural changes in the brain and its relationship to neurocognitive dysfunction.

Our study did not demonstrate a relationship between RT dose to the SVZ and neurocognitive function, a finding that is consistent with a prior study.[31] Improved neurocognitive performance has also been reported in patients with central nervous system germ cell tumors treated with whole ventricle irradiation compared with craniospinal RT,[45] suggesting that the most critical areas for neurocognitive dysfunction are likely to reside outside of the SVZ.

There are several limitations to our study. First, although hippocampal and temporal lobe functions are classically associated with declarative memory and learning, the most significant relationship between radiation dose to these areas and reduced performance was on the test of motor speed, which may reflect the sensitivity of tests of motor function to neural dysfunction outside the frontally mediated motor systems. These changes to motor function may reflect earlier effects on more widespread subcortical white matter pathways involved in the development of motor speed. In addition, the test of motor function is the only timed measure included in this battery, and the results may therefore reflect a difference in processing speed. Performance on the test of motor speed may also have been impacted by radiation dose to other structures, such as the cerebellum, which received a mean dose of 29.5 Gy (range 2–50.4 Gy). Although the relatively large percentage of patients with infratentorial tumors could have confounded our results, there was no significant difference

in performance on the test of motor speed between patients with infratentorial versus supratentorial tumors at any time point.

There was a significant relationship between radiation dose to the left temporal lobe and performance on the visual perception test. However, the effect was very small and may not be clinically significant. There was no difference in performance on this test between left- and right-handed individuals at any time point.

The absence of a significant association between radiation dose to the hippocampi/temporal lobes and performance on tests of verbal learning and memory, visuospatial working memory, and vocabulary may be due to low statistical power in detecting a difference, since the motor function and spatial perception tests are dependent on a complex interplay among multiple neural pathways and may be more sensitive than the other tests examined in this study.

Second, given the relatively small number of patients enrolled in this study, we were not able to perform a detailed analysis of all potential variables that might contribute to cognitive outcomes. For example, confounding variables such as tumor location, recurrence patterns, and surgical interventions may have contributed to the changes in neurocognitive function that we report. Our data suggest potential recovery in function over time from tumor and surgery-related intervention. The relationships among other disease- or treatment-related factors beyond radiation dose to the structures evaluated remain unclear. Future studies enrolling a larger and potentially more homogeneous patient population would be helpful in further evaluating this interaction. Similarly, longer-term follow-up will be important in ascertaining whether the changes reported in this study were impacted by acute effects associated with the disease, surgery, and adjuvant therapy rather than strictly cognitive late effects of radiation.

In addition, although the eligibility criteria for study entry were comparable for both the patient and control groups, there were no children age 0–4 years in the control group, whereas this age group comprised 21% of the patient group. Because we used standardized, age-adjusted scores for our analysis of the neurocognitive tests, we would not expect this difference to have an impact upon our results. Similarly, there were a larger percentage of African Americans in the control group than in the patient group, but we are not aware of evidence to suggest that this would impact upon test performance or interpretation of results.

Third, our series contains missing data, in that not all patients were evaluated on all tests at all time points, and missing patients varied among time points. This limitation may be in part related to the poor prognosis and severity of illness in our patients as well as the complex social situations of families of pediatric cancer patients, which may have limited their ability to present for all scheduled appointments. Additionally, some of the youngest patients were not tested until the later time points. Our analyses presume that the existing data are reflective of the entire group, but future studies with potentially more complete datasets will be important to provide confirmation.

In addition, while our data suggest that limiting radiation dose to the temporal lobe and hippocampus is important in reducing the neurocognitive sequelae of radiation to the brain, we do not have sufficient data to determine a safe radiation tolerance of these structures. In order to effectively spare these areas using techniques such as intensity-modulated RT, it will be critical to better define the radiation tolerance and dose response of these structures. Similarly, further evaluation for a dose-volume effect in these structures will be important.

Finally, we report results on a limited number of neurocognitive tests, and our analysis includes radiation dose to only a limited number of brain structures. Analysis of a broader spectrum of neurocognitive functions and CNS anatomy in future studies will be important. It is possible that the associations we report are confounded by radiation dose to adjacent structures that were not included in this analysis.

To conclude, we report a significant relationship between radiation dose to the hippocampus and temporal lobes and performance on select neurocognitive tests but do not find a relationship between RT dose to the SVZ and neurocognitive function. To our knowledge, this study is one of the first prospective studies to date to examine the relationship between radiation dose to NPC-containing niches and neurocognitive function. Our results have important implications for ongoing clinical trials such as RTOG 0933, which is a phase II trial of hippocampal avoidance during whole brain RT for brain metastases and has a primary objective of performance on a test of verbal learning and memory.

Conflict of interest statement. None declared.

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Pediatr Blood Cancer 2013;60:1350–1357

Intellectual and Academic Outcome Following Two Chemotherapy Regimens and Radiotherapy for Average-Risk Medulloblastoma: COG A9961

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Purpose. Assess the intellectual and academic outcomes as well as risk factors associated with treatment for average-risk medulloblastoma in childhood using 23.4 Gy of craniospinal radiotherapy plus adjuvant chemotherapy. ***Methods.*** From an overall sample of 379 enrolled in the parent study (COG A9961), 110 patients received a total of 192 assessments over more than 5 years with standardized IQ and academic achievement tests. Random coefficient models of the various outcomes were developed that incorporated covariates including chemotherapy regimen, age at diagnosis, sex, initial Full Scale IQ, and mutism. ***Results.*** Participants in this study were found to be comparable to the overall sample in all demographic, disease, and treatment factors, except there were more gross total resections in the subsample undergoing intellectual and academic assessment. Major findings include significant decline in both intellectual and academic domains over time that were greater in children who were younger at diagnosis and had higher initial intelligence test scores. Children with mutism were at higher risk for initial effects on intelligence. No effects of sex were found. ***Conclusion.*** These results show progressive decline over several years post-treatment in standardized intellectual and academic scores. Despite recent improvements in therapies for these children, most notably a decrease dose of craniospinal radiation, they remain at risk. The pursuit of less toxic treatments, particularly for younger children, should continue. Neuropsychological surveillance should be routine at centers treating children with brain tumors. Pediatr Blood Cancer 2013;60:1350–1357.

Key words: academic; brain tumor; cognitive; intellectual; medulloblastoma; pediatric

INTRODUCTION

Treatment for children 3 years or greater with non-disseminated totally or near totally resected medulloblastoma, so-called average-risk disease, has evolved over the past decade [1]. Because of neurodevelopmental risks associated with what was once standard (36 Gy) craniospinal radiotherapy, and evidence that treatment with lower doses of craniospinal radiotherapy (23.4 Gy) plus chemotherapy during and after radiotherapy, results in survival rates that compare favorably to treatment with higher dose radiotherapy with or without chemotherapy, accepted treatment consists of lower-dose craniospinal radiotherapy and chemotherapy. Reducing damage to healthy surrounding tissue has also been a focus of more recent therapeutic approaches. Focal and conformal radiotherapy to more precisely target diseased tissue, as well as new technologies (e.g., proton beam radiotherapy) have become increasingly utilized in attempts to spare healthy tissue. In addition to providing comparable disease control and survival, there is evidence of less neurocognitive morbidity in children treated with lower doses [2,3]. Ris et al. [2] reported an estimated loss of 4.3 Full Scale IQ points per year, while Mulhern et al. [3] estimated that there was a 10–15 IQ point benefit to younger children treated with the reduced dose craniospinal radiation.

Neurocognitive effects have been linked to both gross [4] and microscopic [5] changes in white matter integrity. Mulhern et al. [4] found that the amount of normal appearing white matter correlated inversely with cognitive functioning, including IQ, in a sample of 42 patients treated with craniospinal radiotherapy. Mabbott et al. [5] found multiple areas of cerebral white matter damage after treatment with craniospinal radiotherapy, and this was associated with lower IQ. The pathophysiology of long-term disturbances in neuropsychological functioning and development is not limited to white matter injury. Although incompletely understood, it probably involves apoptotic cell death and secondary cell death mediated by hypoxic-ischemic and inflammatory responses, culminating in damage to the intimal lining of the cerebral vasculature, disruption of the blood–brain barrier, and direct damage to cerebral white matter as well as damage to neural progenitor cells in neuronal niches [6,7]

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Effects on intellectual development are associated with both radiation dose and age, with younger children treated with higher doses being most at risk for eventual declines in IQ up to 4 years post-treatment [8]. One study reported different trajectories in intellectual development for older and younger patients [9]. Older patients (mean age at diagnosis = 11 years) showed early preservation followed by later decline while younger patients (mean age at diagnosis = almost 6 years) showed early decline followed by later stabilization of IQ.

Research on cerebellar mutism suggests that this may be a heretofore underappreciated factor in accounting for late effects. Cerebellar mutism is characterized by acute onset of mutism 1–2 days after surgery, ataxia, emotional lability, irritability, and high pitched cry. Robertson et al. [10] found that the incidence of mutism following surgery for medulloblastoma may be as high as 24%. In some cases recovery is slow and incomplete, and Grill et al. [11] reported lower Verbal IQ, Performance IQ, and fine motor deficits in patients with mutism compared to those without mutism.

This study contributes to a growing literature describing outcomes associated with modern RT protocols involving reduced craniospinal dose. The uniquely large sample and application of sophisticated multivariate modeling also allowed a simultaneous investigation of multiple putative predictors, such as age, sex, mutism, and baseline functioning. We hypothesized that: (1) our sample of patients treated for average-risk medulloblastoma would show an overall decline in IQ and achievement scores over time; (2) younger patients at treatment would show more decline than older patients; and (3) those exhibiting mutism would have poorer IQ and achievement outcomes than those without mutism. Although not posing specific hypotheses, we were also interested in exploring other possible predictors of outcome, such as sex and baseline level of functioning.

PATIENTS AND METHODS

The joint Pediatric Oncology Group/Children's Cancer Group (now the Children's Oncology Group: COG) prospective phase III clinical trial (A9961) of craniospinal radiotherapy (CSR) and adjuvant chemotherapy opened for enrollment in December 1996. It provided an ideal opportunity to prospectively study neurocognitive late effects in the largest sample yet reported of children treated with 23.4 Gy CSR. Children ages 3–21 years of age newly diagnosed with Average Risk Medulloblastoma (3 years of age or older with totally or near totally resected, nondisseminated disease) were eligible, and the study accrued 421 patients. All patients were treated with craniospinal dose of 23.4 Gy with a 32.4 Gy boost to the posterior fossa. Concomitant vincristine was administered during radiation therapy (RT), and patients were randomized to one of two adjuvant chemotherapy regimens beginning 6 weeks post-RT. Regimen A consisted of oral lomustine (CCNU), intravenous cisplatin (CDDP), and intravenous vincristine (VCR). Regimen B included intravenous cyclophosphamide (Cyclo), CDDP, and intravenous VCR. The 5-year progression-free survival rates for the treatment approaches were 82 ± 2.8% for regimen A, and 80 ± 3.1% for regimen B, which compares favorably with those reported in conventional therapy [1].

Sample

The neurocognitive component of A9961 was conducted on a subset of Pediatric Oncology Group and Children's Cancer Group member institutions that had identified psychologists and agreed at the outset of the trial to complete the study measures. Four hundred twenty-one patients were enrolled on A9961 with 42 subsequently excluded following central review. Of the 379 remaining patients, 110 (26%) had at least baseline intellectual testing completed and 75 (18%) had at least a baseline assessment of academic achievement and are included in the intellectual testing study sample (ITSS) and academic achievement study sample (AASS), respectively. Table I shows the frequency of evaluations for the ITSS and AASS groups. Clinical and demographic characteristics for ITSS and AASS are summarized in Table II. None of these characteristics were significantly associated with therapeutic regimen ($P > 0.05$). In most respects, the study samples were representative of the overall sample. However, the ITSS had significantly more gross total resections resulting in no residual tumor compared to those excluded from the analysis who had a larger percentage of radical subtotal resections (>95% of the tumor resected), resulting in slightly more residual tumor (<1.5 cm^2; $P = 0.025$). Of the 379 eligible patients, few had brain stem involvement (15%) and significantly fewer of these were part of ITSS and AASS ($P = 0.003$ and $P = 0.042$, respectively). Parents provided consent for the testing as part of the overall consent to participate in COG protocol A9961 in

TABLE I. Frequency and Timing of Intellectual and Academic Achievement Assessments

Number of times assessed	Intellectual testing, N (%)	Academic achievement, N (%)	Timing of assessments in years from completion of radiation ±6 months	Intellectual testing, N (%)	Academic achievement, N (%)
1	52 (47)	37 (49)	Baseline[a]	110 (57)	75 (59)
2	35 (32)	25 (33)	1	10 (5)	7 (6)
3	22 (20)	12 (16)	2	37 (19)	15 (20)
4	1 (1)	1 (2)	3	5 (3)	3 (2)
			4	7 (4)	3 (2)
			5	15 (8)	11 (9)
			6	8 (4)	3 (2)

[a]Diagnosis to 9 months post-radiation.

TABLE II. Comparison of Demographic and Clinical Characteristics in the Intellectual Testing Subsample and Academic Achievement Subsample Versus the A9961 Patients Who Did Not Participate

	At least baseline intellectual testing, included in analysis (N = 110)	No baseline intellectual testing, not included in analysis (n = 269)	At least baseline academic achievement testing, included in analysis (n = 75)	No baseline academic achievement testing, not included in analysis (n = 304)
Sex				
Male				
N	57	166	42	181
Percent	51.8	61.7	56.0	59.5
Female				
N	53	103	33	123
Percent	48.2	38.3	44.0	40.5
Treatment regimen				
A				
N	57	130	41	146
Percent	51.8	48.3	54.7	48.0
B				
N	53	139	34	158
Percent	48.2	51.7	45.3	52.0
Extent of resection				
No tumor sampling/no surgery				
N	0	1	0	1
Percent	0	0.4	0	0.3
Subtotal resection				
N	2	10	2	10
Percent	1.8	3.7	2.7	3.3
Radical subtotal resection				
N	12	60	9	63
Percent	10.9	22.3	12.0	20.7
Gross total				
N	96	198	64	230
Percent	87.3	73.6	85.3	75.7
Amount of residual tumor				
None/not visible				
N	90	182	59	213
Percent	81.8	67.7	78.7	70.1
$\leq$1.5 cm^2				
N	10	53	7	56
Percent	9.1	19.7	9.3	18.4
$>$1.5 to $\leq$3.0 cm^2				
N	0	1	0	1
Percent	0	0.4	0	0.3
Tumor present, but not measurable				
N	4	17	4	17
Percent	3.6	6.3	5.3	5.6
Equivocal for tumor				
N	6	16	5	17
Percent	5.5	5.9	6.7	5.6
Cerebellar mutism syndrome				
Yes				
N	24	60	13	71
Percent	21.8	22.3	17.3	23.4
No				
N	84	203	60	227
Percent	76.4	75.5	80.0	74.7
Unknown				
N	2	6	2	6
Percent	1.8	2.2	2.7	2.0
Brain stem involvement				

(*Continued*)

TABLE II. (*Continued*)

	At least baseline intellectual testing, included in analysis (N = 110)	No baseline intellectual testing, not included in analysis (n = 269)	At least baseline academic achievement testing, included in analysis (n = 75)	No baseline academic achievement testing, not included in analysis (n = 304)
Yes				
N	6	47	5	48
Percent	5.5	17.5	6.7	15.8
No				
N	104	222	70	256
Percent	94.5	82.5	93.3	84.2
Age at diagnosis				
Median	7.38	8.14	8.16	7.79
Min	3.44	3.10	4.28	3.10
Max	16.82	19.49	16.17	19.49

accordance with each institution's Institutional Review Board requirements.

Intellectual and Academic Achievement Testing

The A9961 neurocognitive assessment schedule called for an evaluation to be completed between 3 and 6 months post-RT, as well as two follow-up assessments completed at 2 and 5 years post-study entry. During the study, some of the assessments were taken according to the planned schedule and others were taken at varying time points. In order to make maximum use of the available data, analyses included patients who had at least one assessment between diagnosis and 9 months after completion of radiation (the baseline test). This is justified on the basis of research showing the emergence of significant late-effects of radiation after 9 months post-RT (Ris et al.[2]). The number of times assessed and timing of these assessments are contained in Table I. Table III shows the observed scores for each year after radiation therapy.

The test battery in the original COG A9961 protocol included age-appropriate, gold standard measures of general intellect (Wechsler Preschool and Primary Scales of Intelligence-Revised, Wechsler Intelligence Scale for Children-Third Edition, Wechsler Adult Intelligence Scale-Revised, Wechsler Adult Intelligence Scale-Third Edition), academic achievement (Wide Range Achievement Test-Third Edition), visuomotor integration (Beery Visual Motor Integration Test), adaptive functioning (Vineland Adaptive Behavior Scale), and social-emotional status (Child Behavior Checklist). However, the most complete data were for the intellectual tests and academic measures and so this report will concentrate on only Full-Scale IQ (FSIQ), Performance IQ (PIQ), and Verbal IQ (VIQ) outcomes from the intellectual tests and reading, spelling, and arithmetic outcomes from the academic achievement tests. Per protocol, intellectual testing was completed first followed by academic testing. However, adherence to this order was not specifically documented as testers were free to use clinical discretion to maximize the validity of the results.

Statistical Methods

Differences in demographic and clinical characteristics were investigated using exact chi-squared tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Random coefficient models [12] (RCMs) were used to estimate the change in neurocognitive outcomes over time and to investigate the effect of covariates on the estimated change. RCMs are an approach for analyzing multiple assessments on each patient over time. These models take into account that measurements on the same patient are correlated. RCMs allow for unbalanced data and use all available data. Although this study planned assessments at 3–6 months post-radiation and at 2 and 5 years after study enrollment, patients were assessed at a variety of times during the study. Time of the

TABLE III. Observed Intellectual and Achievement Scores

Timing of assessments in years from completion of radiation ±6 months	FSIQ[a] mean (SD)	VIQ mean (SD)	PIQ mean (SD)	Reading mean (SD)	Spelling mean (SD)	Arithmetic mean (SD)
Baseline[b]	96.2 (16.9)	98.6 (16.0)	93.2 (17.4)	98.8 (16.6)	97.1 (17.3)	94.7 (18.6)
1	96.0 (21.3)	100.0 (23.1)	92.5 (17.9)	98.0 (18.8)	102.4 (15.4)	96.0 (20.8)
2	90.1 (17.4)	91.5 (17.6)	90.8 (16.5)	97.8 (15.9)	96.8 (16.3)	93.7 (17.4)
3	99.5 (15.8)	99.6 (11.0)	97.3 (18.4)	92.7 (13.3)	93.0 (14.9)	105.0 (8.5)
4	79.6 (14.9)	83.0 (11.8)	79.4 (19.3)	103.0 (1.73)	93.0 (12.7)	95.7 (23.2)
5	93.5 (13.5)	94.5 (15.2)	92.7 (15.0)	94.0 (17.8)	88.4 (14.9)	92.2 (10.5)
6	75.6 (12.4)	79.9 (12.1)	78.0 (13.1)	78.5 (21.9)	75.0 (12.5)	68.0 (3.0)

[a]Intellectual and achievement scores presented as standardized scores with mean of 100 and SD of 15; [b]Diagnosis to 9 months post-radiation.

assessment used in the analysis was calculated in years from the end of radiation. All assessments were used in the model construction.

Separate models were created for each neurocognitive outcome. Treatment regimen, sex, and cerebellar mutism were treated as dichotomous variables in the models. Age at diagnosis was analyzed both as a continuous covariate and as a categorical variable divided at the age of 7 to enhance comparison with previous studies. Profile plots with spline smoothing were created prior to analysis to identify outliers and to visually inspect patterns in the change in outcome over time. We focused on the pattern of change in the first 2 years as 75% of the data was within this interval. There was no evidence of deviations from linearity that caused concern, so for all outcomes a linear change was assumed. Patients that had only the baseline measurement (i.e., only one score) were not excluded, although these patients only contributed to the estimation of the intercept. Statistical significance for an intercept or slope term was set at $P < 0.05$. The analyses for this study were carried out using PROC MIXED in the SAS statistical package, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Results from the longitudinal models revealed significantly lower FSIQ (96.0 points; $P = 0.020$), PIQ (93.5 points; $P = 0.0002$), and arithmetic scores (94.9 points; $P = 0.021$) at baseline compared to the normative mean of 100. Further there was a significant decrease in the FSIQ following radiation (−1.9 points/year; $P \leq 0.0001$), as well as significant declines in Verbal IQ (VIQ; −1.9 points/year; $P \leq 0.0001$), Performance IQ (PIQ; −1.7 points/year; $P \leq 0.001$), Reading (−1.5 points/year; $P = 0.047$), and Spelling (−2.1 points/year; $P = 0.004$).

Chemotherapy regimen B was significantly associated with worse scores at baseline compared with regimen A for FSIQ (92.3 vs. 99.6, $P = 0.028$), VIQ (94.2 vs. 102.1, $P = 0.013$), and Reading (94.1 vs. 102.4, $P = 0.033$), but there were no significant differences in slope. To investigate whether the difference in chemotherapy regimens at baseline was an artifact of extreme outliers, the data were reanalyzed without these scores and there was no longer a significant difference in the FSIQ estimated baseline, but there remained significant differences at the intercept for VIQ and Reading. Further, children treated with regimen A experienced a significant decline in Math scores over time (A: −2.7 points/year vs. B: −0.29 points/year, $P = 0.050$).

Because the difference at baseline was unexpected, the differential early toxicities in these two regimens were explored as they may have accounted for these differences in test scores. For the purposes of these analyses, toxicities were categorized as hematologic, nervous system, performance score, and infection using CTCAE (Common Terminology Criteria for Adverse Events) grades for the chemotherapy course closest to the timing of the baseline assessment. For each toxicity categorization, a toxicity was defined as occurring if the patient experienced any grade. The results of these analyses indicate that nervous system toxicity was strongly related to baseline intellectual and achievement scores ($P = 0.0068$ and $P = 0.0030$ for Full Scale IQ and Reading, respectively). However, when the random coefficient models were re-run with nervous system toxicity as a covariate, treatment regimen remained significantly correlated with baseline scores in most models. It cannot be ruled out, as well, that the significant relationship between nervous system toxicity and baseline scores merely reflects neurologic deficits that these patients had at baseline that were not chemotherapy toxicities, *per se*. Therefore, since differences in treatment groups at baseline could not be accounted for, all subsequent models controlled for regimen.

TABLE IV. Demographic and Clinical Predictors of Intellectual Outcomes

	FSIQ					VIQ					PIQ				
		Intercept		Slope			Intercept		Slope			Intercept		Slope	
	N[a]	Estimate	SE	Estimate	SE	N[a]	Estimate	SE	Estimate	SE	N[a]	Estimate	SE	Estimate	SE
Overall sample	106	96.0	1.7	−1.9[b]	0.45	109	98.3	1.6	−1.9[b]	0.42	109	93.5	1.7	−1.7[b]	0.48
Sex															
Female	51	97.1	2.4	−2.2[b]	0.63	52	98.8	2.3	−2.1[b]	0.59	53	94.5	2.4	−2.0	0.68
Male	55	95.0	2.3	−1.6[b]	0.65	57	97.7	2.2	−1.5[b]	0.60	56	92.8	2.3	−1.4[b]	0.72
Mutism															
Yes	23	89.1[c]	3.5	−2.8[b]	0.86	23	92.9	3.4	−2.6[b]	0.78	24	86.5[c]	3.5	−2.2[b]	0.95
No	81	97.8	1.9	−1.6[b]	0.53	84	99.9	1.8	−1.6[b]	0.51	83	95.4	1.9	−1.5[b]	0.59
Baseline FSIQ															
<100	61	84.3[c]	1.3	−1.0	0.53	64	88.6[c]	1.5	−0.72	0.49	64	82.3[c]	1.4	−1.2	0.61
≥100	45	111.8	1.6	−2.7[b,c]	0.58	45	111.5	1.8	−2.8[b]	0.53	45	110.0	1.7	−2.8[b]	0.66
Age															
<7	48	94.0	2.5	−2.9	0.63	49	94.8	2.3	−2.6[b]	0.58	49	92.4	2.5	−3.1[b,c]	0.67
≥7	58	97.9	2.3	−0.96	0.60	60	100.9	2.1	−1.0	0.58	60	94.5	2.3	−0.50	0.64
Extent of resection															
Gross total	93	96.0	1.8	−2.0[b]	0.38	95	98.6	1.7	−1.9[b]	0.36	95	93.3	1.8	−1.8[b]	0.42
Subtotal/radical subtotal	13	98.0	4.9	−1.6	0.91	14	96.5	4.6	−1.3	0.87	14	97.8	4.9	−1.5	1.0

SE, standard error. [a]Small differences in sample sizes reflect missing data preventing derivation of all scores for a participant; [b]Statistically significant decline compared to zero (no decline) at the $P < 0.05$ level; [c]Statistically significant difference between the two groups at the $P < 0.05$ level.

Analysis of Intellectual Performance

Table IV reports the results of univariate analyses investigating the effects of demographic and clinical characteristics on intellectual performance after adjusting for differences due to treatment regimen. Patients who experienced some level of mutism had a significantly lower estimated FSIQ and PIQ baseline compared to patients without mutism ($P = 0.039$ and $P = 0.036$, respectively) and experienced significant declines in all three intellectual outcomes although not significantly different at the $P = 0.05$ level from those with no mutism. FSIQ, VIQ, and PIQ scores of younger patients decreased faster than the older patients ($P = 0.014$, $P = 0.012$, $P = 0.023$, respectively). Age at diagnosis divided at the age of 7 years showed similar results, although when age was categorized in this way, the slope for VIQ did not attain significance. Patients with a higher baseline FSIQ score showed a significantly faster rate of decrease in FSIQ ($P = 0.047$). There were no significant differences in the estimated baseline scores or slopes by gender or extent of resection.

Analysis of Academic Achievement

Patients with mutism experienced significant declines in all three academic achievement outcomes, and Reading scores declined significantly faster than for those with no mutism (−4.3 points/year vs. −0.49 points/year, $P = 0.012$). Age at diagnosis as a continuous variable was significantly correlated with changes in Reading scores with younger patients experiencing a steeper decline over time ($P = 0.016$). Younger patients experienced significant declines in Spelling scores although not statistically significant from older patients. Table V displays results of academic achievement outcomes by age at diagnosis divided at the age of 7 years. There were no significant sex or extent of resection effects.

DISCUSSION

The results of this study indicate significant decline in intellectual functioning over 5 years of an estimated 1.7 points per year in this sample of children treated for average-risk medulloblastoma. This is approximately half the rate of decline reported in another, non-overlapping sample from the Children's Cancer Group (CCG) [2]. This may be accounted for by differences between these two studies, including both a younger mean age and greater variability in IQ instruments used in the 2001 study. Furthermore, the current findings derive from a much larger sample, and the rate of decline reported here is in close agreement with that reported by Mulhern et al. [13].

Similar to the IQ scores, declines in standardized academic achievement scores were found. Confirming our hypothesis, a risk factor for declines included younger age at treatment (FSIQ, VIQ, PIQ, and Reading). Higher baseline IQ (FSIQ) was also associated with greater decline. Sex was not associated with declining intellectual or academic scores. Chemotherapy regimen (FSIQ, VIQ, and Reading) and mutism (FSIQ, PIQ) were associated with differences at baseline. The latter finding suggests that children who experience post-surgery mutism are at increased risk for initial effects with the rate of decline thereafter being consistent with that of children who do not experience mutism. Mutism, though, may place children at risk for later decline in reading skills, providing partial support for our hypothesis. This finding contributes to a growing literature identifying mutism, which was found in 22% of our sample, as an important risk factor in neurocognitive outcome [11,14]. It is important to note that verbal skills were not selectively impacted by mutism. In fact, non-verbal abilities reflected in PIQ were most affected and may relate to associated symptoms of mutism, such as attentional dysregulation and executive dysfunction. Age at diagnosis was confounded with

TABLE V. Demographic and Clinical Predictors of Academic Achievement

	Reading					Spelling					Arithmetic				
		Intercept		Slope			Intercept		Slope			Intercept		Slope	
	N[a]	Estimate	SE[b]	Estimate	SE	N[a]	Estimate	SE	Estimate	SE	N[a]	Estimate	SE	Estimate	SE
Overall sample	74	98.8	1.9	−1.5	0.73	71	97.8	1.9	−2.1	0.69	75	94.9	2.1	−1.3	0.76
Sex															
Female	32	98.9	2.9	−1.2	1.2	33	99.0	2.9	−2.3[c]	1.0	33	95.1	3.2	−2.1	1.1
Male	42	97.7	2.6	−1.6	1.0	38	96.1	2.7	−1.8	1.0	42	94.1	2.8	−0.43	1.0
Baseline FSIQ															
<100	43	91.9[d]	2.2	−0.81	0.87	41	91.1[d]	2.4	−1.8	0.89	43	87.1[d]	2.5	−0.33	0.94
≥100	31	107.2	2.7	−2.6	1.2	30	106.1	2.8	−2.4	1.2	32	104.6	2.9	−2.1	1.2
Mutism															
Yes	12	99.9	4.9	−4.3[c,d]	1.3	12	96.1	5.0	−3.0[c]	1.2	13	87.6	4.8	−2.6[c]	1.3
No	60	97.4	2.3	−0.49	0.73	58	97.8	2.3	−1.6[c]	0.80	60	96.7	2.3	−1.0	0.89
Age															
<7	21	95.1	3.5	−2.6[c]	1.2	20	93.3	3.7	−2.4	1.1	22	92.2	3.9	−1.5	1.1
≥7	53	99.2	2.2	0.63	0.94	51	99.0	2.3	−1.8	0.96	53	95.2	2.6	−0.76	1.1
Extent of resection															
Gross total	63	98.3	2.2	−1.7[c]	0.75	61	97.9	2.2	−2.2[c]	0.72	64	95.1	2.3	−1.4	0.84
Subtotal/radical subtotal	11	98.7	5.2	−0.19	1.5	10	96.1	5.5	−1.2	1.8	11	91.8	5.6	0.15	1.9

[a]Small differences in sample sizes reflect missing data preventing derivation of all scores for a participant; [b]SE, standard error; [c]Statistically significant decline compared to zero (no decline) at the $P < 0.05$ level; [d]Statistically significant difference between the two groups at the $P < 0.05$ level.

mutism as those with mutism tended to be somewhat younger than those without mutism (although not significantly so). This study did not have sufficient power to parse the variance attributable to these two factors.

The difference at the end of RT between the two chemotherapy regimens is difficult to explain. Regimen B was associated with greater toxicity (hematologic and infection) throughout treatment [1], and it was this regimen that had the lower baseline score. Since chemotherapy was initiated 6 weeks post-RT and baseline measurements were taken between diagnosis and 9 months post-RT, differential toxicities could conceivably account for this initial difference in IQ. However, post hoc analyses of the full range of toxicities and their relation to baseline testing did not support this conclusion. Statistical artifact was also explored by removing extreme scores, which resulted in some (FSIQ) but not all (VIQ and Reading) outcomes failing to reach significance. Therefore, the question of why there was a difference in scores at baseline remains unanswered although it may be a failure of random assignment to equate the two chemotherapy groups on initial intellectual and academic functioning.

As was reported by Ris et al. [2], higher intellectual functioning at the time of treatment was associated with greater decline, although these children maintained higher scores over follow-up than did those with lower intellectual functioning. This is consistent with the buffering effect of cognitive reserve as formulated by Dennis [15] and Stern [16], that is, outcome following an insult to the brain is maximized in the context of higher premorbid cognitive abilities. Younger age at treatment has been found to be a robust risk factor in the late-effects literature and our findings reemphasize the importance of developing effective treatments for this disease that are less toxic to the developing central nervous system. While the reduced dose of CSR used in this study (23.4 Gy) in comparison to higher doses used in other studies would appear to attenuate intellectual decline, the estimated loss of over half a standard deviation by 5 years post treatment is still substantial and associated with academic and, likely, a cascade of neurobehavioral morbidity later in life.

Some differences in our findings compared to those of another report on a similar sample [13] bear explanation. While Mulhern et al. [13] failed to find a significant difference in IQ between average-risk (treated with 23.4 Gy CSR) and high-risk (treated with 39.6 Gy CSR) groups, and no statistically significant decline in IQ in the average-risk group, patients in the Mulhern et al. study were treated with three-dimensional conformal radiotherapy while nearly all of our patients were treated with conventional two-dimensional radiotherapy. Therefore, our patients may have received somewhat higher doses to larger volumes in the posterior fossa.

The limitations of our study include low rate of testing of eligible participants in A9961, variability in both follow-up and timing of completed assessments, and age-related variance in the testing instruments. Low testing rates are attributable to several factors including failure to refer to a psychologist/neuropsychologist at centers lacking comprehensive brain tumor clinics, failure of third party payers to cover the costs of the evaluation, and decreased motivation on the part of the family with increased time from treatment. Still, the overall sample size of 110 undergoing a total of 192 assessments is an unusually large, homogeneous sample of children with average-risk medulloblastoma receiving contemporary treatments.

Multivariate techniques, such as random coefficient modeling used here, are able to make maximum use of the available data despite a high rate of missingness. Straightforward interpretation of such results, though, requires the assumption that missingness is independent of outcome, an assumption that cannot be confirmed. For example, it may be that those patients who return for testing have suffered either more or less impairment than those who were not available for testing, in which case missingness and outcome would be related. Alternatively, it may be that other factors, such as the availability of a psychologist/neuropsychologist to do the testing at a particular institution determined whether follow up testing was completed, in which case missingness and outcome would be unrelated.

Another challenge in longitudinal research is measurement error introduced by transitions in tests as the sample ages. In the current study, out of 20 such transitions, the majority (60%) consisted of changing from the WPPSI-R to the WISC-III. However, since the WISC-III tends to yield slightly higher IQ scores than the WPPSI-R [17] the effect would be null biasing (i.e., to underestimate decline over time).

In conclusion, while the current study was restricted to patients with average-risk medulloblastoma, all of whom received 23.4 Gy CSR, these results add to the growing empirical support for the neurocognitive benefits of reduced dose protocols. Most of what we know about long-term neurobehavioral toxicities of RT is based on therapies in which larger volumes of brain are exposed to higher doses. Conclusions drawn from this literature my have limited generalizability to contemporary and future cohorts of children treated for brain tumors. For younger children and infants, in particular, who are at higher risk for such complications, deferred radiotherapy [18,19], lower doses of craniospinal radiotherapy, hyperfractionated radiotherapy [20], and proton beam therapy further limiting the volume of local boost radiotherapy and scatter to the temporal lobes [21] offer the promise of further reduction in adverse late effects.

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Differences in Brainstem Fiber Tract Response to Radiation: A Longitudinal Diffusion Tensor Imaging Study

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Summary

Longitudinal diffusion tensor imaging data from 42 medulloblastoma patients were analyzed to assess regional differences in structural integrity changes of brainstem white matter tracts after radiation therapy. These changes were not uniform across the brainstem despite similarities in the distribution of dose, suggesting that the radiation-induced changes in brainstem may be tract dependent.

Purpose: To determine whether radiation-induced changes in white matter tracts are uniform across the brainstem.

Methods and Materials: We analyzed serial diffusion tensor imaging data, acquired before radiation therapy and over 48 to 72 months of follow-up, from 42 pediatric patients (age 6-20 years) with medulloblastoma. FSL software (FMRIB, Oxford, UK) was used to calculate fractional anisotropy (FA) and axial, radial, and mean diffusivities. For a consistent identification of volumes of interest (VOIs), the parametric maps of each patient were transformed to a standard brain space (MNI152), on which we identified VOIs including corticospinal tract (CST), medial lemniscus (ML), transverse pontine fiber (TPF), and middle cerebellar peduncle (MCP) at the level of pons. Temporal changes of DTI parameters in VOIs were compared using a linear mixed effect model.

Results: Radiation-induced white matter injury was marked by a decline in FA after treatment. The decline was often accompanied by decreased axial diffusivity, increased radial diffusivity, or both. This implied axonal damage and demyelination. We observed that the magnitude of the changes was not always uniform across substructures of the brainstem. Specifically, the changes in DTI parameters for TPF were more pronounced than in other regions ($P<.001$ for FA) despite similarities in the distribution of dose. We did not find a significant difference among CST, ML, and MCP in these patients ($P>.093$ for all parameters).

Conclusions: Changes in the structural integrity of white matter tracts, assessed by DTI, were not uniform across the brainstem after radiation therapy. These results support a role for tract-based assessment in radiation treatment planning and determination of brainstem tolerance.

Introduction

Therapy-induced injury to the normal brainstem is a concern in the treatment of common childhood brain tumors. Injury to the brainstem may cause deficits in motor and sensory capabilities and coordination functions, which can compromise the quality of life of long-term survivors.

Current data on brainstem toxicity are limited and are based on subjective or categoric scoring methods (1). Because of the

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lack of tools for assessing substructures, the brainstem has often been regarded as a single organ, and the dose constraint has been determined without considering the regional sensitivity within the brainstem. Some studies have placed separate limits on the maximum dose to the "center" and "surface" of the brainstem (2), but the rationale for this practice is not clear, and no systematic evaluation has been reported as far as we are aware.

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that provides a quantitative assessment of microscopic injuries in the white matter after radiation therapy (3, 4). DTI-derived parameters reflect radiation-induced histologic changes (5) and neurologic dysfunctions (6). These findings support the use of DTI as a surrogate marker of brainstem integrity.

Our previous study (7) showed that radiation-induced white matter injury in the brainstem can be detected by DTI-derived parameters. Longitudinal evolution of parameters showed individually distinctive patterns, implying different responses to brainstem injury. In the present work, we extended the previous study, using a larger patient population and longer follow-up times, to investigate whether radiation-induced white matter injury is uniform within the brainstem. Additional substructures were analyzed, and an extended number of DTI-derived parameters were used. Our previous study included patients with 4 types of brain tumors; the present work included only patients with medulloblastoma to minimize variation in the patient group with regard to treatment and statistical group analysis.

Methods and Materials

Participants

Between July 2003 and June 2008, 121 pediatric patients diagnosed with central nervous system embryonal tumors (medulloblastoma, primitive neuroectodermal tumor, or atypical teratoid rhabdoid tumor) were enrolled on a prospective institutional protocol. DTI data were acquired for the patients at postoperative baseline, at the completion of radiation therapy, and every 6 months thereafter up to 72 months. Of the 84 medulloblastoma patients, we selected 42 for the present study, who had follow-up DTI data for more than 48 months (median, 66 months), did not experience necrosis or MRI-proven abnormality in the brainstem, and presented DTI images free of severe artifacts caused by metallic dental braces or surgical hardware. Patients younger than 6 years were excluded from this study because of the unavailability of age-matched control individuals. The median age at baseline was 10 years (range, 6-20 years).

Another set of DTI data acquired from 52 healthy volunteers (age 6-24 years) was used to distinguish pathologic changes in patients from normal age-related changes. Healthy volunteers were enrolled in an institutional functional imaging protocol between October 2007 and April 2011. Two consecutive annual MRI scans were performed on the volunteers.

All protocols were compliant with the Health Insurance Portability and Accountability Act and were approved by our institutional review board. Written informed consent and assent were obtained according to institutional policy.

Treatment

Patients underwent surgical resection, craniospinal irradiation, and chemotherapy as previously described (7). Risk-adapted radiation therapy was administered, and all patients received adjuvant chemotherapy 6 weeks after the completion of radiation therapy (Table 1).

MRI data acquisition

MRI scans on patients were performed on a 1.5T MR scanner (Symphony or Avanto; Siemens Medical Solutions, Enlargen, Germany). DTI data were acquired by a double spin-echo pulse sequence, using the following parameters: repetition time = 10,000 ms; echo time = 100 ms; field of view = $230 \times 230\ mm^2$; matrix = 128×128; and slice thickness = 3 mm (no gap). Diffusion encoding was applied along either 6 or 12 directions with a diffusion weighting factor (b) of 1000 s/mm^2. One reference image was acquired without the diffusion encoding gradient (b = 0 s/mm^2). The DTI scan was repeated 4 times to increase the signal-to-noise ratio. In addition to DTI, a T1-weighted anatomic image with a high resolution ($1.25 \times 0.82 \times 0.82\ mm^3$) was acquired for the use of spatial registration with computed tomography (CT) and the associated dose distribution. DTI scans on healthy volunteers were performed on a 3T MR scanner (Siemens Tim Trio) in accordance with the functional imaging study protocol. Consequently, a few imaging parameters were different from those of patients: repetition time = 6500 ms; echo time = 120 ms; field of view = $192 \times 192\ mm^2$; and b = 700 s/mm^2. Statistical analysis was designed in such a manner that the potential bias in DTI data between the 2 groups was compensated.

Table 1 Characteristics of participants

Characteristic	Medulloblastoma patients	Healthy volunteers
Total number	42	52
M	25	31
F	17	21
Baseline age (y)		
Median	10	12
Range	6-20	6-24
Risk classification		
Average-risk group	32	-
High-risk group	10	-
Radiation treatment		
Craniospinal irradiation (Gy)	23.4-39.6	-
Boost to primary site (Gy)	16.2-32.4	-
Total dose to primary site (Gy)	55.8	
Chemotherapy	4 cycles of high-dose cyclophosphamide, cisplatin, and vincristine	-
Extent of resection		-
Gross total resection	37	-
Near-total resection (>90%)	5	-

Image processing

A total of 469 DTI data sets were processed from the 42 patients, using FSL (FMRIB, Oxford, UK). All diffusion-weighted images (ie, with nonzero b value) were affine-registered to the reference image with a b value of 0 to remove the effects of patient motion and eddy current-induced image distortion. Then, the diffusion tensor was estimated for each voxel, from which 4 DTI-derived parameters ("DTI parameters" hereafter for simplicity) were calculated: fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD). For an efficient and consistent regional analysis of the large volume of data, DTI parameter maps were spatially normalized to a standard space (MNI152) by a nonlinear deformation algorithm provided by FSL, so that volumes of interest (VOIs) identified in the standard space could be commonly used for all patient images. Eigenvectors were also normalized via diffusion tensor reorientation (8), and all normalized FA and primary eigenvector images were averaged to generate a standard color-coded FA map (Fig. 1). The CT and the associated dose distribution of each patient were also spatially normalized to the MNI152 space. They were first registered to the T1-weighted image, followed by nonlinear deformation to the standard space.

Volumes of interest

First, the midbrain and pons were delineated on axial images of the standard color-coded FA map (Fig. 1). The midbrain volume of interest (VOI) extended in the cranial direction until the thalamus started to appear and to the caudal direction before the transverse pontine fiber (TPF) started to appear. The pons VOI covered axial images showing the TPF. A gap of the DTI slice thickness (3 mm) between the midbrain and pons was not included in the VOIs to avoid the partial volume effect. The corticospinal tract (CST), medial lemniscus (ML), transverse pontine fiber (TPF), and middle cerebellar peduncle (MCP) were further identified at the level of pons. The TPF VOI was separated into 2 compartments: ventral TPF (vTPF) and dorsal TPF (dTPF). It should be noted that the VOIs were named for simplicity, and they may include tracts other than the tract referred to by the name; for instance, the ML VOI may include the spinothalamic tract, the central tegmental tract, or the rubrospinal tract in addition to the medial lemniscus.

Statistical analysis

The mean DTI parameter values at each VOI were calculated, and a statistical analysis was performed to investigate their temporal changes. A mixed effect model was used to analyze the temporal change of the DTI parameter: $\mathrm{DTI} = \alpha_0 + \alpha_1 \times \mathrm{age} + \alpha_2 \times \mathrm{t} \times \mathrm{group} + \alpha_3 \times \mathrm{dose} + \alpha_4 \times \mathrm{group}$. Here, t is the time from the baseline (in year), group is a dummy variable indicating whether the data are from the patient (group = 1) or healthy volunteer (group = 0), and the Greek letters with subscripts are fitting coefficients. The first 2 terms model normal age-related change, and the following 2 terms indicate deviation of the patient group from the normal change considering the effect of individual dose differences. The last term, $\alpha_4 \times$group, accounts for potential bias in DTI parameters between the groups at the baseline.

Pairwise comparisons were performed to test whether deviation from the normal pattern in the patient group was the same across different structures. The temporal change from baseline was quantified in terms of the normalized DTI parameter, $\mathrm{nDTI(t)} = \mathrm{DTI(t)/DTI(0)}$, and the ratio of a pair of VOIs, i and j, was modeled by $\mathrm{nDTI_i(t)/nDTI_j(t)} = \beta_0 + \beta_1 \times \mathrm{age_0} + \beta_2 \times \mathrm{t} + \beta_3 \times \mathrm{t} \times \mathrm{group}$. The second term, $\beta_1 \times \mathrm{age_0}$, accounts for individual differences in baseline age, $\mathrm{age_0}$. This term was included in the model when it was significant. The estimated coefficient β_3 in the last term indicates how much decline (when $\beta_3 < 0$) or increase (when $\beta_3 > 0$) VOI i shows in the DTI parameter compared with VOI j.

All statistical analyses were performed using the software R (Wirtschaftsuniverstät Wien Vienna University, Austria). A P value less than .05 was considered statistically significant.

Results

Figure 2 shows the average radiation doses to the VOIs over the 42 patients. They were distributed in accordance with proximity to the primary site. The pons was exposed to a higher dose than was the midbrain for 39 of 42 patients. The average doses in the brainstem substructures ranged from 49.4 Gy (vTPF) to 55.4 (ML) and were ordered as follows: vTPF < CST < dTPF < MCP < ML. The differences between any pair of these were statistically significant (paired t test, $P<.001$), except for dTPF/MCP and MCP/ML.

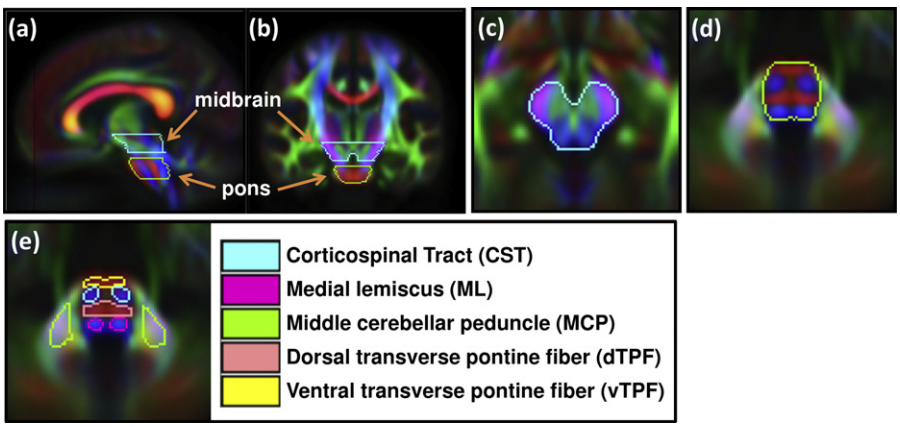

Fig. 1. Volumes of interest drawn on the standard color-coded fractional anisotropy map. (a, b) Sagittal and coronal views of midbrain and pons showing cranial-caudal locations of volumes of interest. (c, d) Axial views of midbrain and pons. (e) Substructures within brainstem.

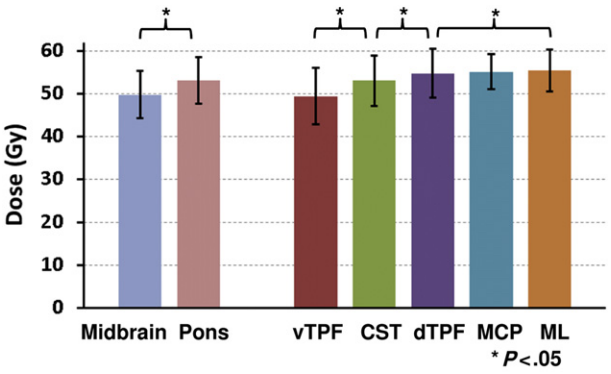

Fig. 2. Average doses in the volumes of interest over the 42 patients. Error bars indicate standard deviation. CST = corticospinal tract; dTPF = dorsal transverse pontine fiber; MCP = middle cerebral peduncle; ML = medial lemniscus; vTPF = ventral transverse pontine fiber.

The DTI parameters showed age-related changes in healthy volunteers. FA increased and RD and MD decreased in all VOIs ($P<.001$). AD in CST and ML did not show significant changes ($P>.126$) but decreased in other regions ($P<.006$). FA of the patient group negatively deviated from the normal age-related change (ie, $\alpha_2 < 0$) and was statistically significant in the entire pons, dTPF, vTPF, and MCP ($P<.004$). AD and RD also showed negative deviations for all VOIs ($P<.034$) except for dTPF and vTPF, where RD deviated positively ($\alpha_2 > 0$, $P<.023$). The deviation from the normal pattern was not strongly dependent on individual differences of dose (ie, $\alpha_3 \times$ dose was not significant) for most VOIs. Only CST showed a significant relation between AD reduction and dose ($\alpha_3 < 0$, $P=.03$).

The pairwise comparison between the pons and midbrain showed that the decrease of FA in the pons was more pronounced than that in the midbrain (Fig. 3a). The ratio of the normalized FA between the pons and midbrain showed a negative trend ($\beta_3 = -0.065$, $P<.001$). The ratios of the normalized AD and MD also showed significantly negative trends ($P<.001$).

Further pairwise comparisons on substructures revealed that the temporal changes of DTI parameters were not uniform within the pons. Figure 4 shows the FA maps of the pons for a patient at baseline and the 2 follow-up times. The decrease of FA in TPF was manifested 18 and 45 months from the baseline. By contrast, FA in the CST and ML showed smaller reductions at 18 months and recovered to the baseline level at 45 months. Figure 5 shows comparisons of the temporal changes of the normalized FA of the CST and dTPF for all 42 patients. In most cases, dTPF showed a greater drop than CST and remained at the lower value, whereas CST either showed a smaller reduction or eventually recovered to the baseline level.

The statistical analysis confirmed that the ratio of normalized FA between the dTPF and CST showed a significantly negative trend ($\beta_3 = -0.135$, $P<.001$) (Fig. 3b). The analysis with other DTI parameters was consistent with this result. Taken together, these results suggest that compromised structural integrity is more pronounced in the dTPF than in CST: dTPF showed more significant decrease in AD, increase in RD, and increase in MD than did the CST ($P<.001$ for all comparisons) (Fig. 3b). Similar results were found when the dTPF was compared with the ML or the MCP (Fig. 3c, d). On the other hand, no significant differences were observed for the pairs dTPF/vTPF, ML/CST, and MCP/CST in any of the DTI parameters (Fig. 3e-g). In summary, the TPF showed more changes reflecting white matter injury than did the CST, ML, and MCP at the level of pons, regardless of dorsal or ventral compartments, whereas there were no significant differences among the other 3 VOIs.

This regional variation of the temporal changes could not be explained unequivocally by the dose distribution. Although

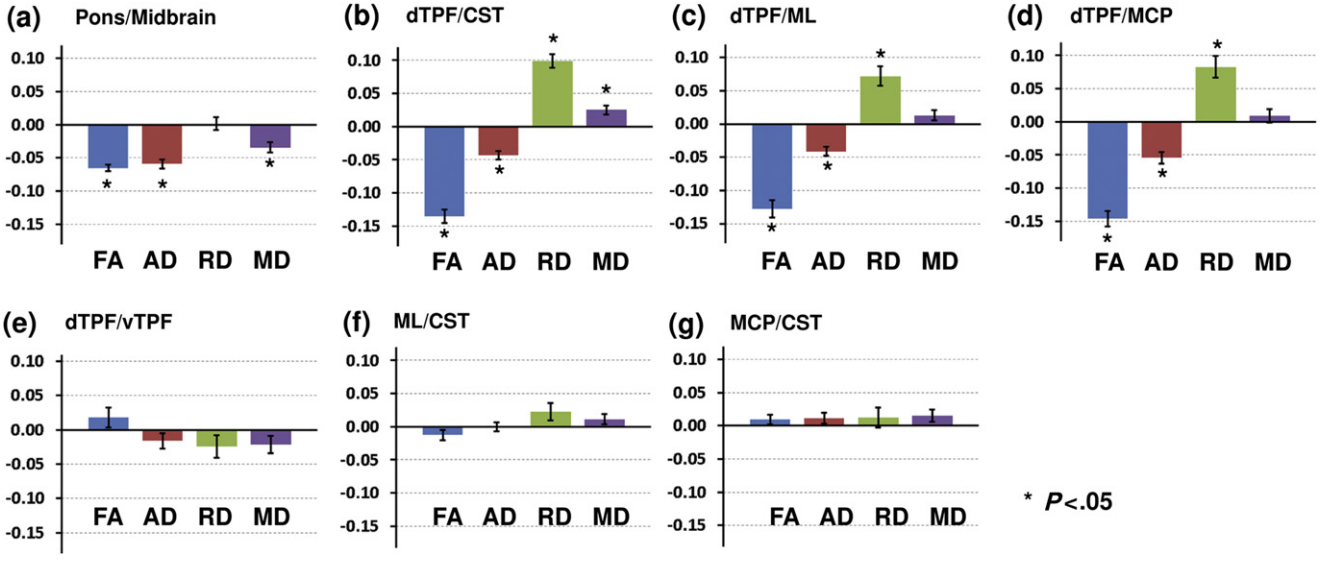

Fig. 3. Pairwise statistical comparison of the temporal changes of diffusion tensor imaging parameters between pairs of volumes of interest. Comparisons between (a) Pons and Midbrain, (b) dTPF and CST, (c) dTPF and ML, (d) dTPF and MCP, (e) dTPF and vTPF, (f) ML and CST, and (g) MCP and CST are presented. The number in the ordinate is β_3 in the statistical model equation (see text) that indicates the temporal change of the volume of interest in numerator with respect to the one in denominator. Error bars indicate standard error. AD = axial diffusivity; CST = corticospinal tract; dTPF = dorsal transverse pontine fiber; FA = fractional anisotropy; MCP = middle cerebral peduncle; MD = mean diffusivity; ML = medial lemniscus; RD = radial diffusivity; vTPF = ventral transverse pontine fiber.

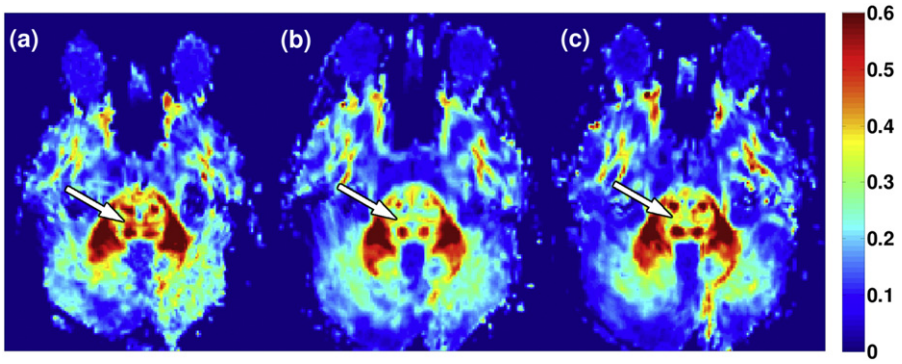

Fig. 4. Fractional anisotropy maps of a medulloblastoma patient (male, baseline age 11 years) acquired at baseline (a) and the 2 follow-up times of 18 months (b) and 45 months (c) from baseline. White arrows indicate dorsal transverse pontine fiber showing more pronounced fractional anisotropy reduction than in the other regions.

the TPF (either dorsal or ventral) received a smaller dose than the ML (Fig. 2), the TPF showed greater changes than did the ML (Fig. 3c). We found significant differences between the dTPF and CST (Fig. 3a) but not between the ML and CST (Fig. 3f) or between the MCP and CST (Fig. 3g), which have similar or even greater dose differences. To further investigate the effect of dose on the regional differences in DTI parameter changes, we repeated the pairwise comparison with an additional term, $\beta_4 \times \text{dose}_i/\text{dose}_j$, in the mixed effect model. Here, $\text{dose}_i/\text{dose}_j$ is the ratio of dose delivered to VOIs i and j, respectively. We found that this term was not significant ($P>.05$) for all pairs of comparisons with all DTI parameters.

Discussion

In this study, we analyzed the temporal changes in DTI parameters measured in the brainstem of patients with medulloblastoma. These changes in patients deviated from the normal age-related changes and suggested white matter injury. This result confirms our previous findings and supports the use of DTI for studying therapy-induced alteration in the brainstem. In addition, we found that the temporal changes in DTI parameters were not always uniform throughout the brainstem.

The normal changes occurring with age in DTI parameters were consistent with previous reports (7, 9). The reduced RD and

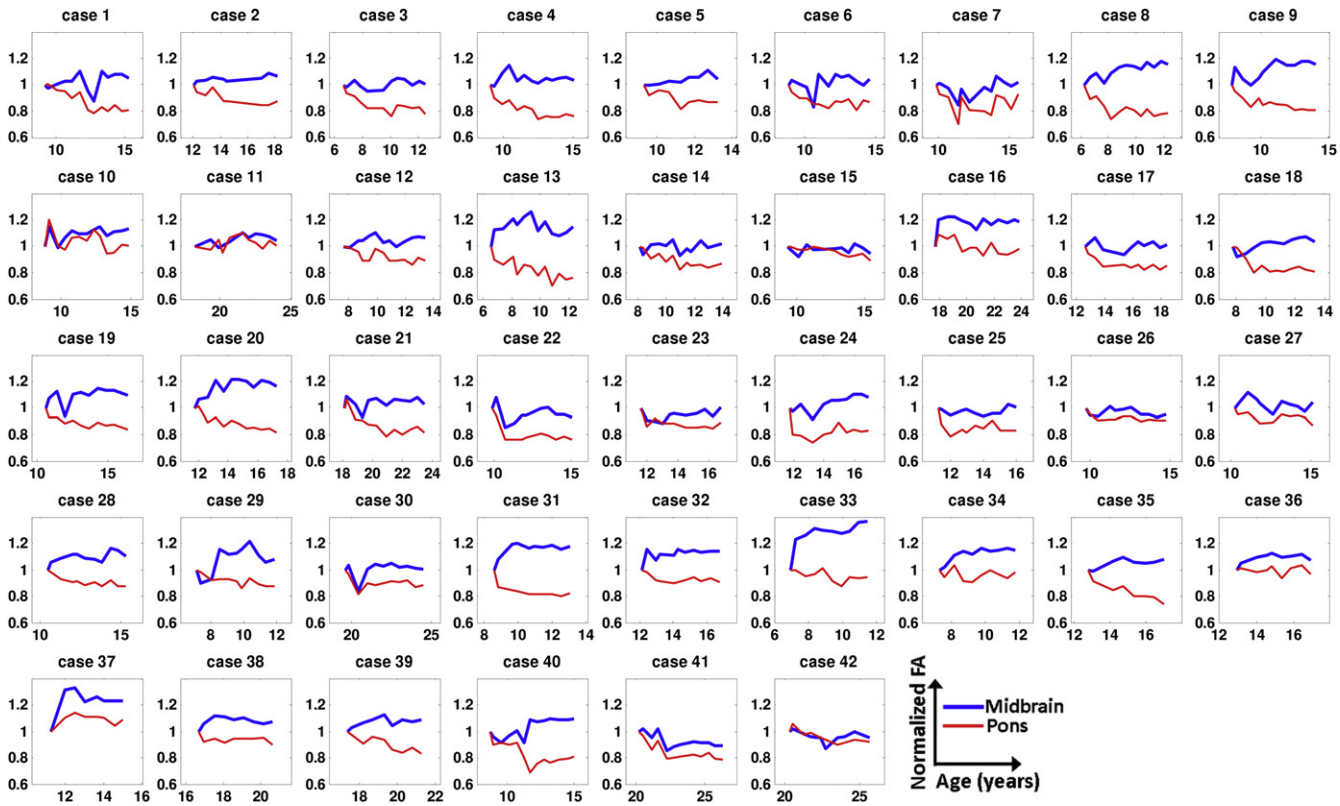

Fig. 5. Temporal plots of fractional anisotropy in corticospinal tract and dorsal transverse pontine fiber for all 42 patients. Each fractional anisotropy value was normalized by the corresponding baseline value.

AD reflect thickening of myelin and increased axonal caliber or number of brain fibers (9). The deviation from the normal pattern for the patient group was prominent in the dTPF and vTPF. The negative and positive deviations of AD and RD in the TPF imply axonal degeneration and demyelination in this structure, respectively. Pairwise comparisons confirmed that the temporal change in the TPF was different from those in other regions.

The differences of DTI parameter changes either across individual patients or different regions were not strongly related to the variation of dose. This is possibly because the dose was narrowly distributed (Fig. 2). One consequent implication is that the radiation-induced white matter changes are contributed to by factors other than dose. We speculate that the regional intrinsic features of fiber tracts are associated with the response to radiation. However, to fully understand tract-specific response to radiation, other clinical factors such as tumor mass, surgical procedure, and existing condition also need to be accounted for.

Regional sensitivity to radiation therapy has been previously reported. White matter tends to be more sensitive to radiation than gray matter (10) at the same dose level, possibly because of the smaller vascular density of the white matter. For white matter regions, an animal model study showed that the lateral spinal cord is more radiosensitive than the central part in terms of the occurrence of necrosis or hemorrhage (11). Another study on pediatric medulloblastoma patients found more significant changes in FA in the frontal white matter than in the parietal region (12). The pathophysiology of therapy-induced white matter injury has been understood in the context of ischemic effects caused by vascular abnormalities or the dysfunction of oligodendrocytes (10, 13). The regional variation of white matter injury has been accordingly explained in terms of the regional differences in vascularity (12) or migration of oligodendrocyte progenitor cells (11). Thus, it would be useful to investigate whether that vascularity or oligodendrocyte cell population in the TPF is different from those in other regions.

The TPF is a part of the cortico-ponto-cerebellar tract, which is a major pathway for the motor cortex to communicate with the cerebellum. This tract conveys the information used in the planning and initiation of movement from the cortex to neurons in the pontine gray and subsequently to the cerebellum. White matter injury in TPF may result in symptoms such as ataxia. In the future, we will conduct a correlation study with neurologic examinations to understand the clinical impact of changes in DTI parameters. It is intriguing that the MCP did not show the structural changes that the TPF did, even though these 2 structures belong to the same fiber tract. The insensitivity of the MCP to radiation therapy has been observed in medulloblastoma and pilocytic astrocytoma patients (14) and has been explained by the extracerebellar localization of the cell bodies of the axons within the MCP.

The dorsal TPF is located approximately in the central area of the pons. Thus, our data partially support the conventional belief that the "center" of the pons is more vulnerable than the "surface." However, the ventral TPF near the brainstem surface also had a similar response, suggesting that tract-based assessment may provide important insights into determining regional brainstem sensitivity to radiation. This may lead to an adjustment in planning constraints used to minimize brainstem toxicity and associative studies with tract-specific neurologic deficits.

The echo-planar imaging in the brainstem region is prone to the effects of magnetic susceptibility differences and pulsation from blood or the cerebrospinal fluid. Recent advances in DTI have allowed high-resolution imaging in localized regions, which is less sensitive to susceptibility variations and motion without compromising the signal-to-noise ratio (15). Such imaging methods would enable the study of additional smaller fiber tracts that were not covered in this work.

In summary, this study showed that radiation-induced white matter changes assessed by DTI were not always uniform within the brainstem. The inspection with the dose distribution suggested that this regional difference may be contributed to by factors other than dose. Although the clinical impact will be further investigated, we believe this study provides a new insight into planning and evaluation of radiation treatment.

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