ESTRO School

ESTRO Course Book

Evidence Based Radiation Oncology

11 - 16 June, 2017
Ljubljana, Slovenia

NOTE TO THE PARTICIPANTS

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Faculty

Christopher Cottrill

Disclaimer

EUROPEAN ACCREDITATION COUNCIL
FOR CONTINUING MEDICAL EDUCATION
Institution of the UEMS

The faculty of the teachers for this event has disclosed any potential conflict of interest that the teachers may have.

Evidence-based Radiation Oncology

Chris Cottrill

St Bartholomew's Cancer Centre London

Blood-letting

Blood-letting

Used by the Persians in Babylon in 500 BC

van Helmont recommended a randomised trial in 1662

Practice shown to be harmful in 1820

Practice ceased about 1910

van Helmont JA (1662) Lodowick Loyd, London

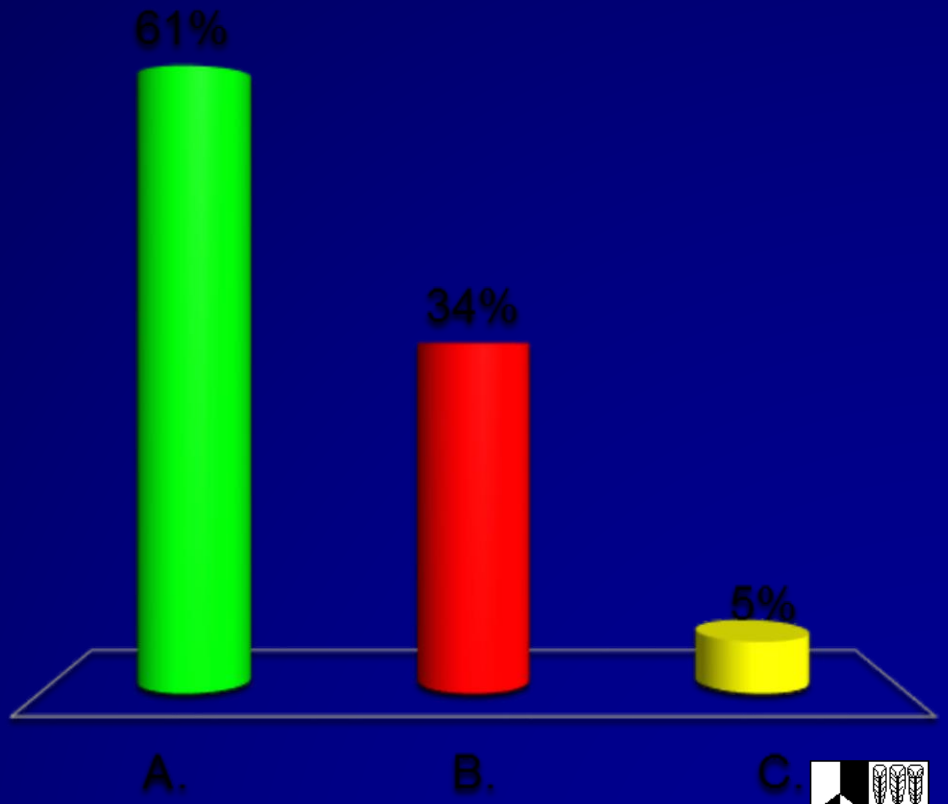
EMINENCE-based medicine

Making the same mistakes with an ever increasing degree of certainty!

EVIDENCE-based medicine

"Evidence-based medicine is destined to replace individual clinical judgement"

A. Agree
B. Disagree
C. Don't know



Evidence-based medicine

Integrating

individual clinical judgement

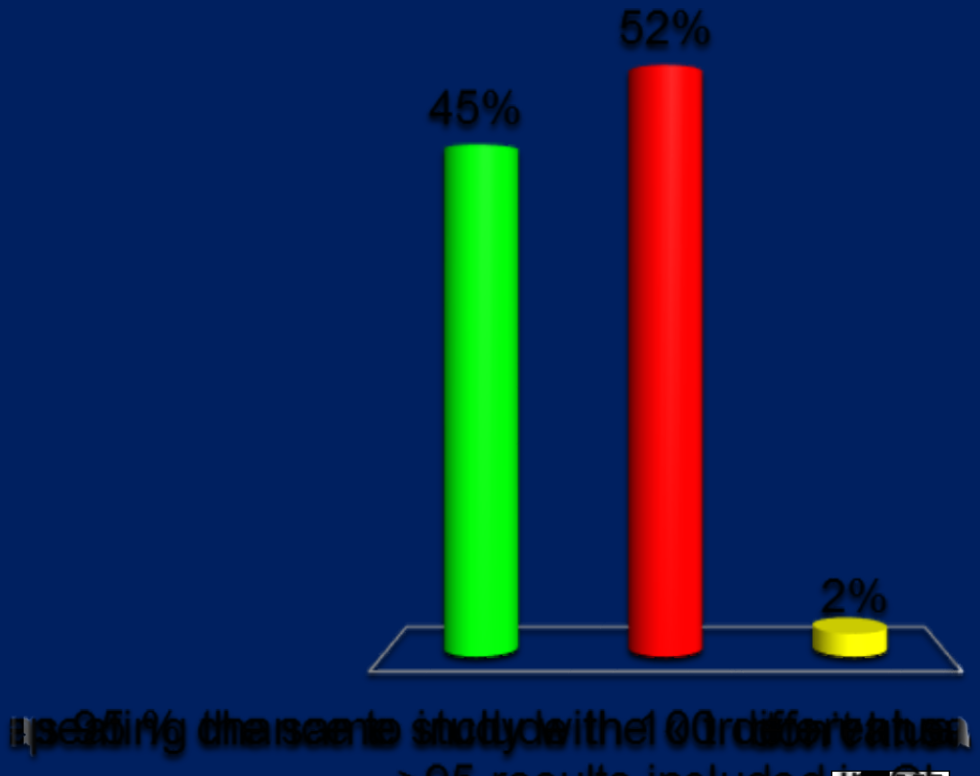
and best available evidence

Evidence-based medicine

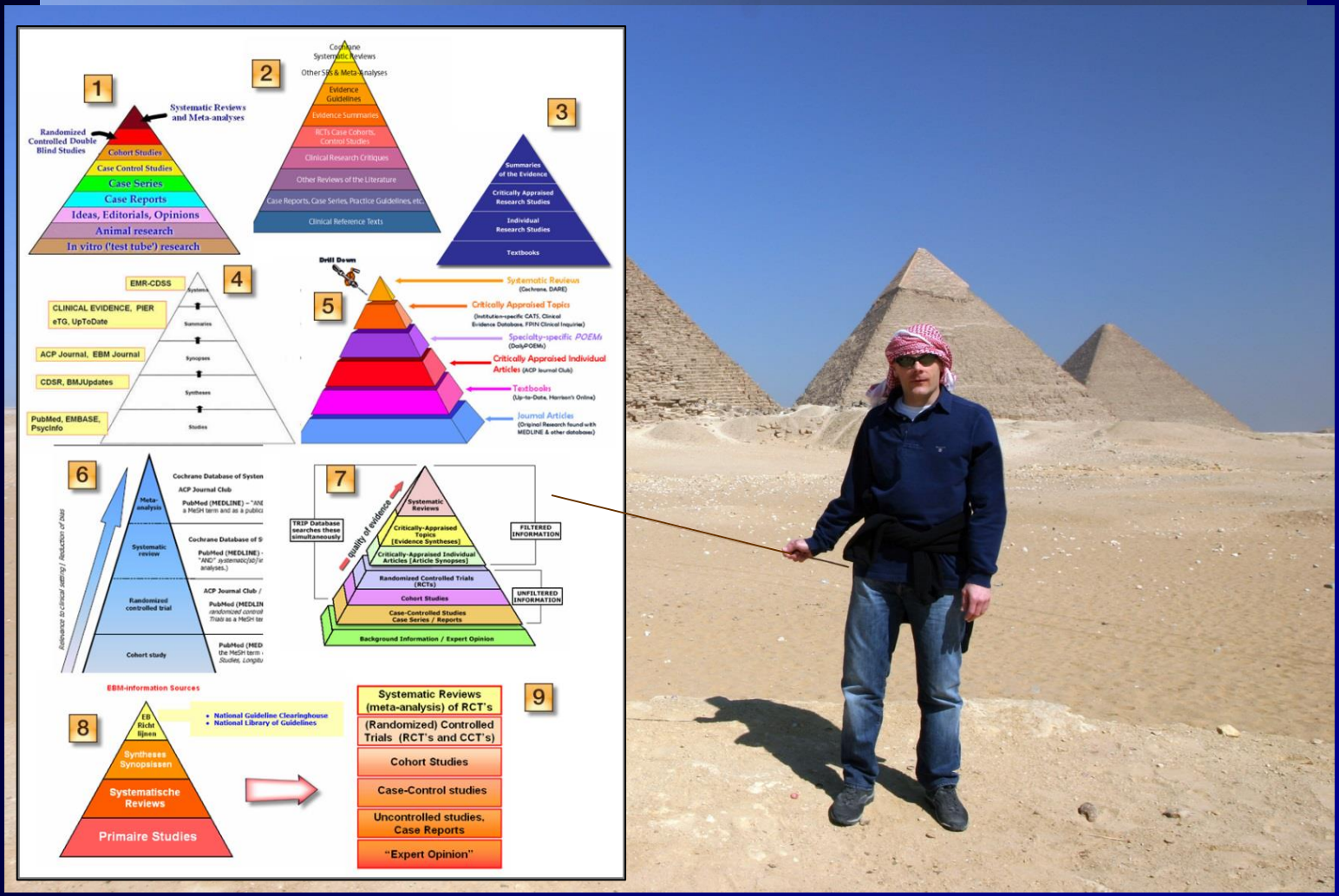
The use of mathematical estimates of the likelihood of benefit and the risk of harm, derived from high quality research on population samples, to inform decision-making in the diagnosis, investigation or management of individual patients

Confidence interval

A. has 95 % chance to include the « true » value
B. repeating the same study with 100 different samples would yield >95 results included in CI
C. don’t know

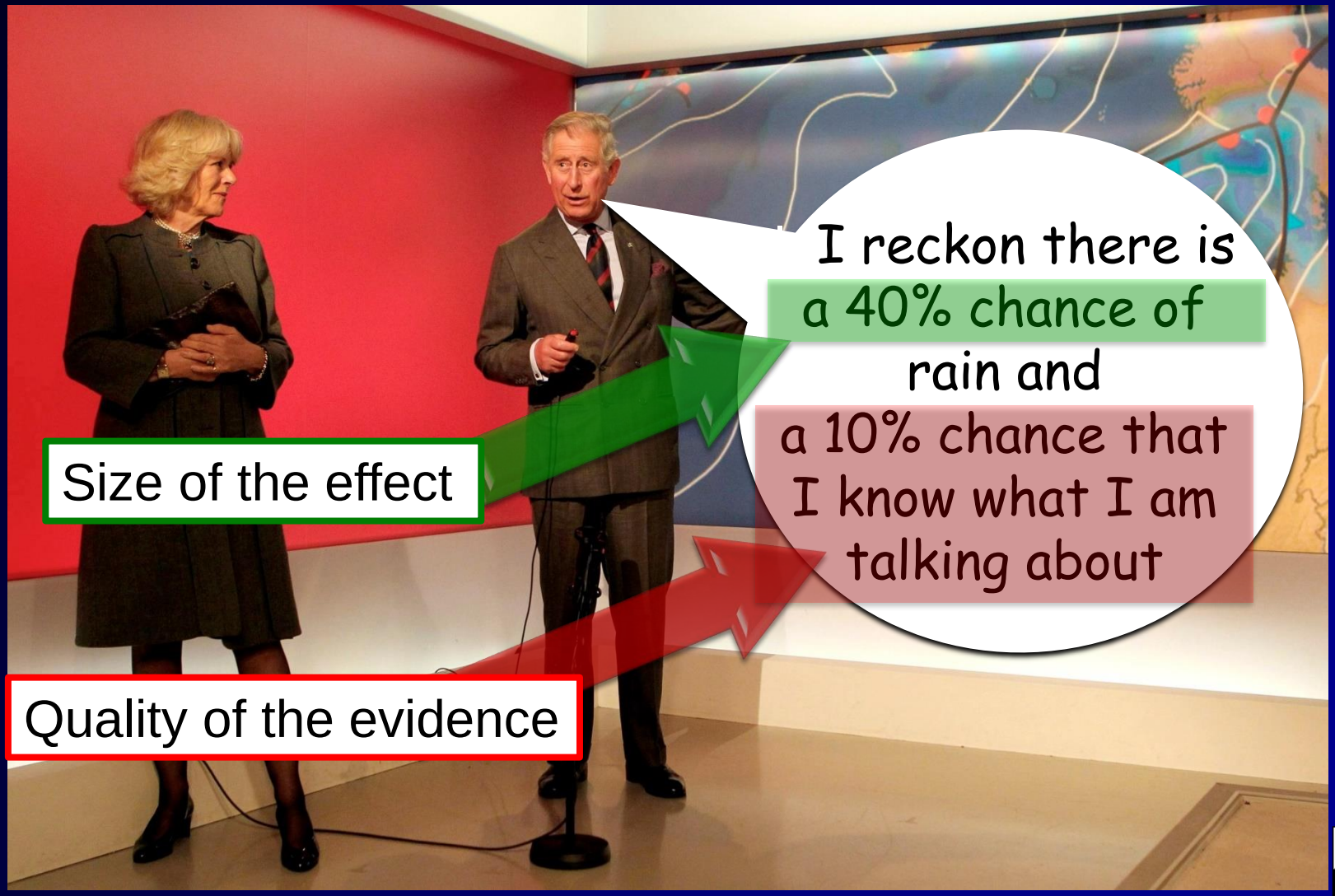


Let’s go to the pyramids !



Levels of Evidence

How do we judge the evidence?



The GRADE approach

GRADE

- GRading of recommendations, Assessment, Development and Evaluations Working Group
- Systematic and explicit approach to preparing evidence-based systematic reviews and clinical guidelines

GRADE categorises the quality of the evidence

- Study limitations
- Inconsistency of results
- Indirectness of evidence
- Imprecision
- Publication bias

Large magnitude of effect
Plausible biases would reduce effect
Dose-response gradient

Guyatt British Medical Journal 2008

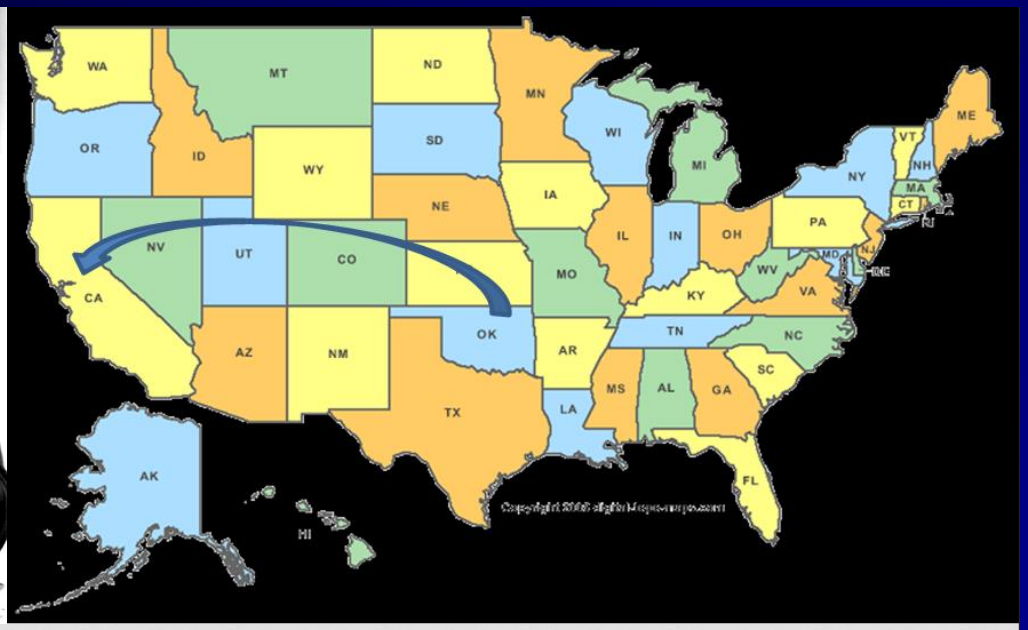
The GRADE approach

GRADE categorises the strength of the recommendations

- Balance between desirable and undesirable effects
- Quality of evidence
- Values and preferences
- Costs (resource allocation)

Guyatt British Medical Journal 2008

The Will Rogers Phenomenon



"When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states."

Will Rogers

The Will Rogers Phenomenon

Old staging process				New staging process				Result
Stage	N	Alive	6/12 surv.	Stage	N	Alive	6/12 surv.	6/12 surv.
I	42	32	76%	I	24	22	92%	92%
				II	1	1	100%	
				III	17	9	55%	
II	25	17	68%	II	18	13	72%	72%
				III	8	5	63%	
III	64	23	36%	III	89	37	42%	42%
Total	131	72	55%		131	72	55%	55%

Feinstein A R *et al* (1985) N Engl J Med 312:1604-8

The Will Rogers Phenomenon

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Volumes

- Gross Tumour Volume (GTV)
- Clinical Target Volume (CTV)
- Planning Target Volume (PTV)
- Treated Volume
- Irradiated Volume
- Planning Organ at Risk Volume (PRV)

GTV

- Extent and location of malignant disease
- Clinical examination and / or imaging

  Primary tumour

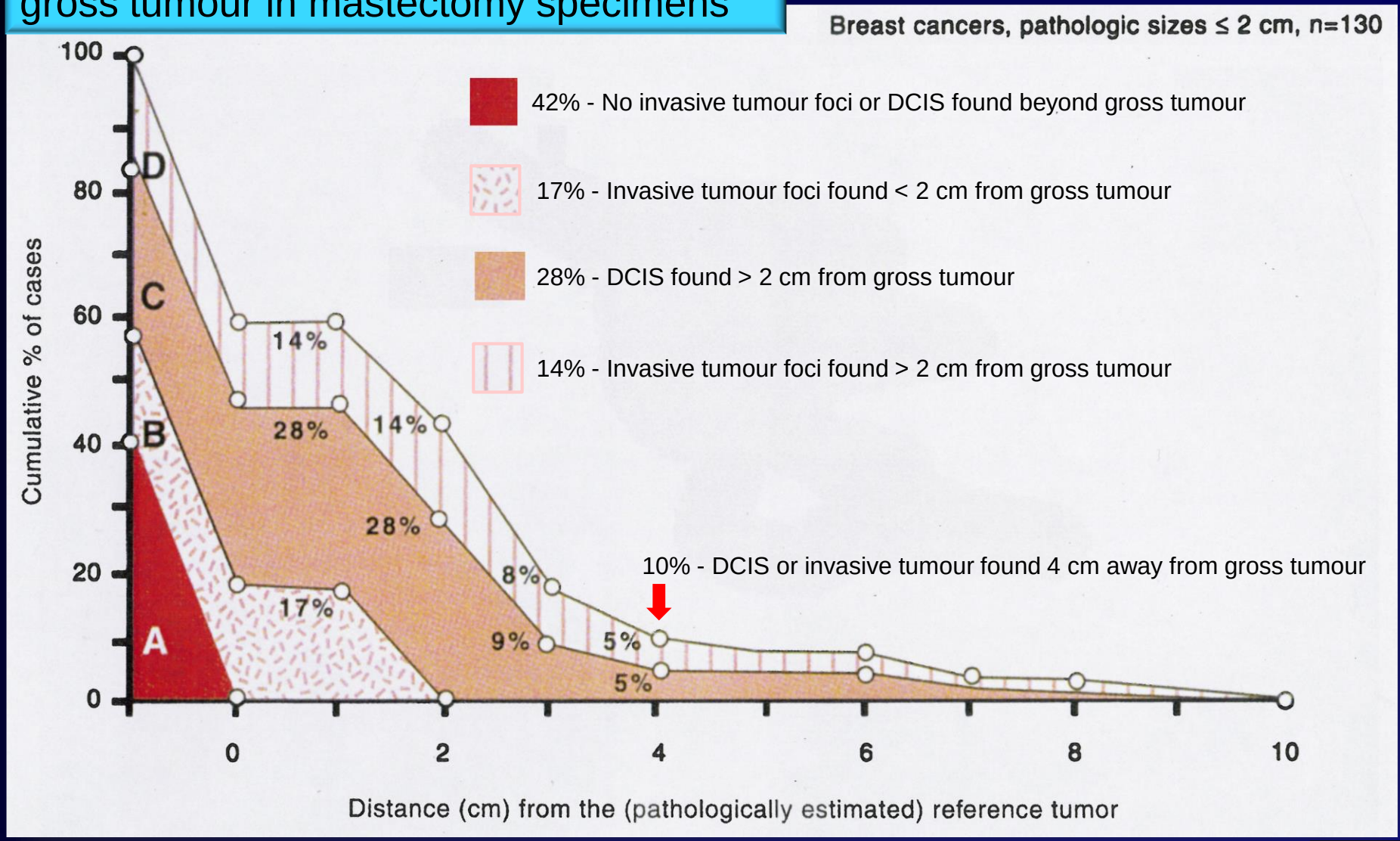
  ± macroscopic lymph node metastases

  ± other metastases
- Highest tumour cell density
- None after R0 surgery / CR to chemo

CTV

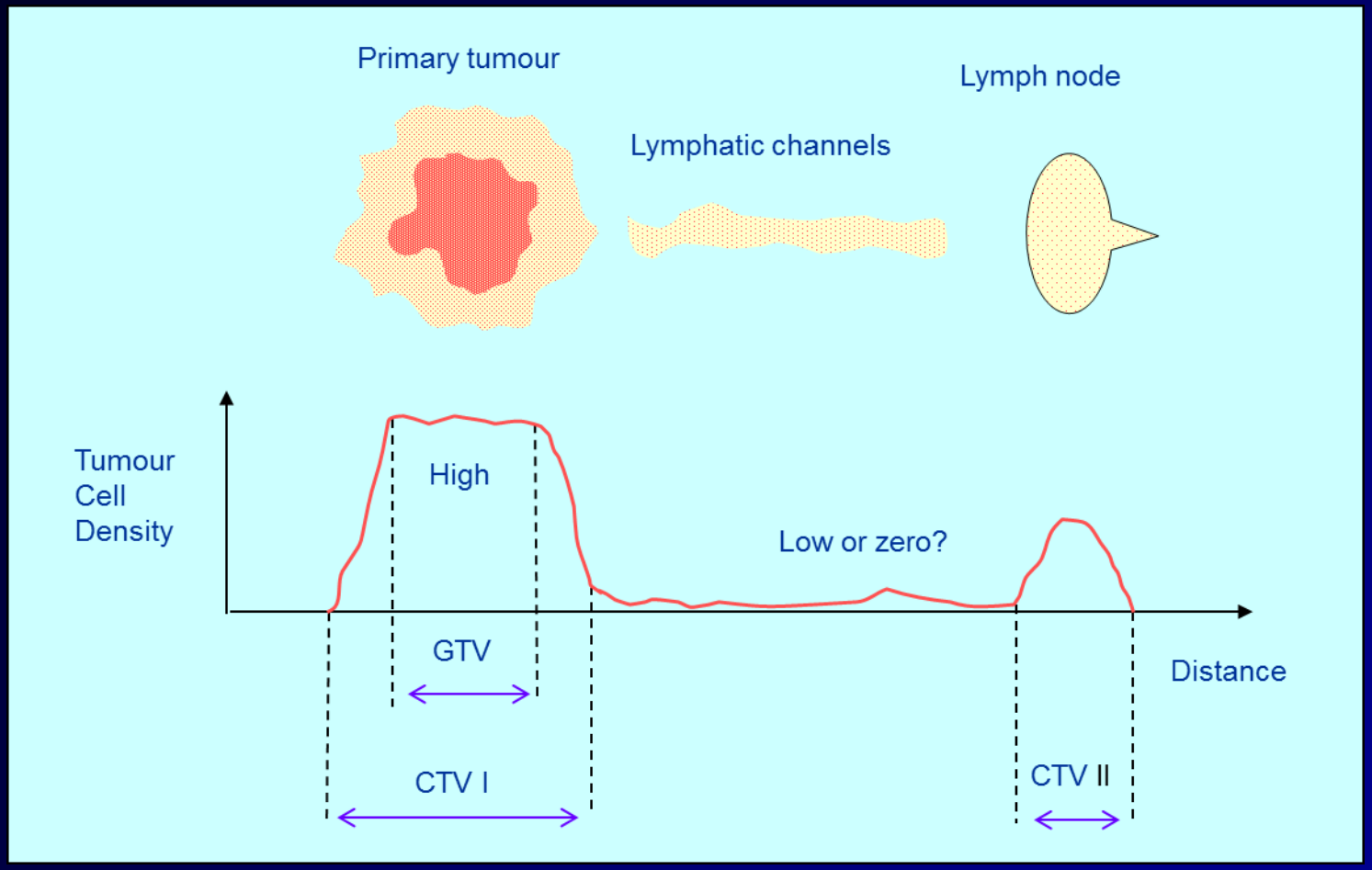
- The sites at risk of relapse if untreated
- Includes undetectable (“subclinical”) disease
- Estimate of risk
  - clinical experience
  - pathological
  - documented treatments and follow-up

Clinical example: tumour foci beyond gross tumour in mastectomy specimens



Redrawn from Holland R *et al* (1985) Cancer 56:979-990

GTV and CTV



Redrawn from ICRU Report 62 (1999)

PTV

- Geometrical concept used for treatment planning
- Defined to ensure that prescribed dose is actually delivered to CTV
- Includes margin on CTV to account for variations and uncertainties
- Does not exclude OAR
- Does not include penumbra

Organs at Risk

- Critical normal tissues which put constraints on planning
- Location may mean compromise in PTV coverage
- May be *serial* or *parallel*
- May have uncertainties in position, size and shape
- Planning organ at Risk Volume (PRV)

Set-up margin

Accounts for difficulties in delivering the treatment

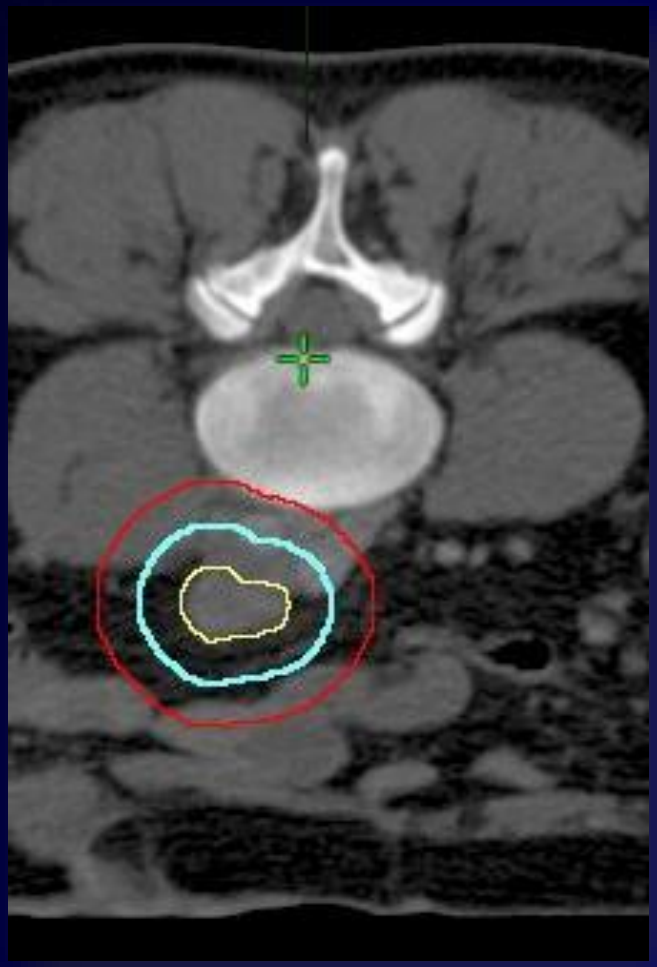
- Reproducing the patient position
- Reproducing the beam alignment
- Mechanical uncertainties
- Dosimetric uncertainties

PTV = ITV + set-up margin

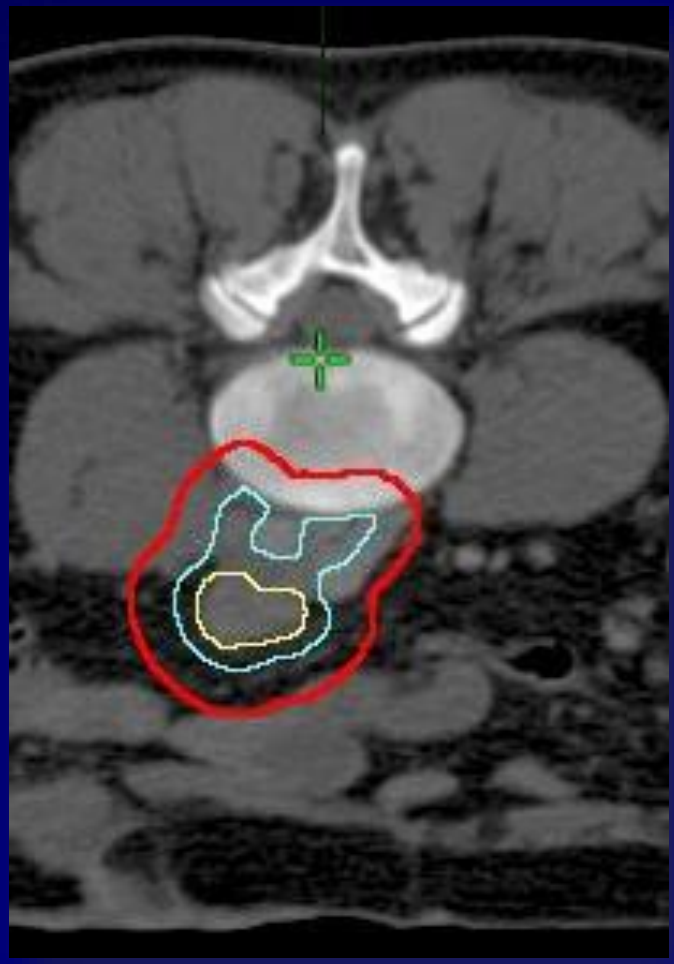
Remember! Remember!

- GTV and CTV are biological
  - margins based on anatomy and pathology
- PTV is geometric
  - margin accounts for positional uncertainties and physics

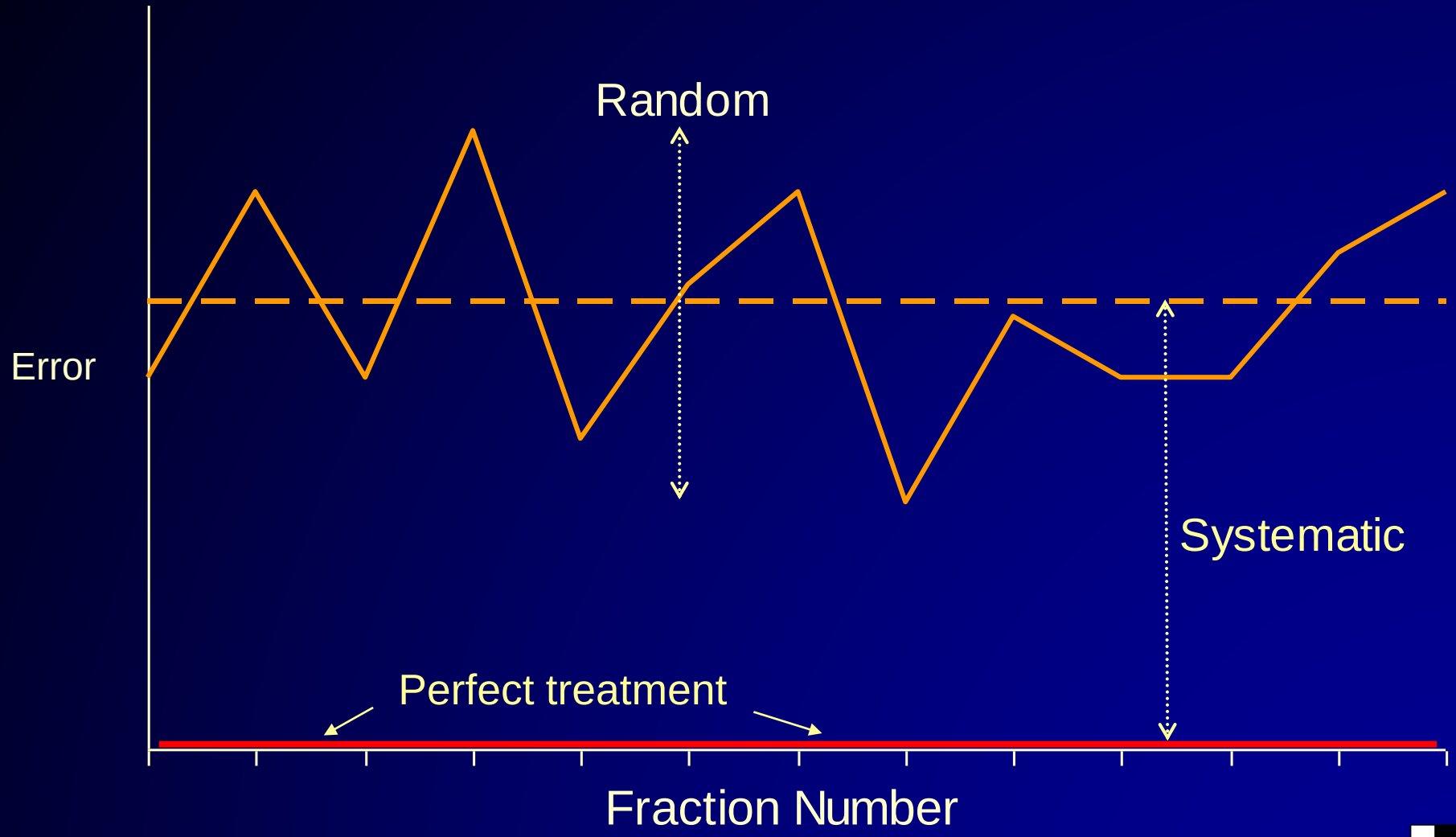
Geometry alone



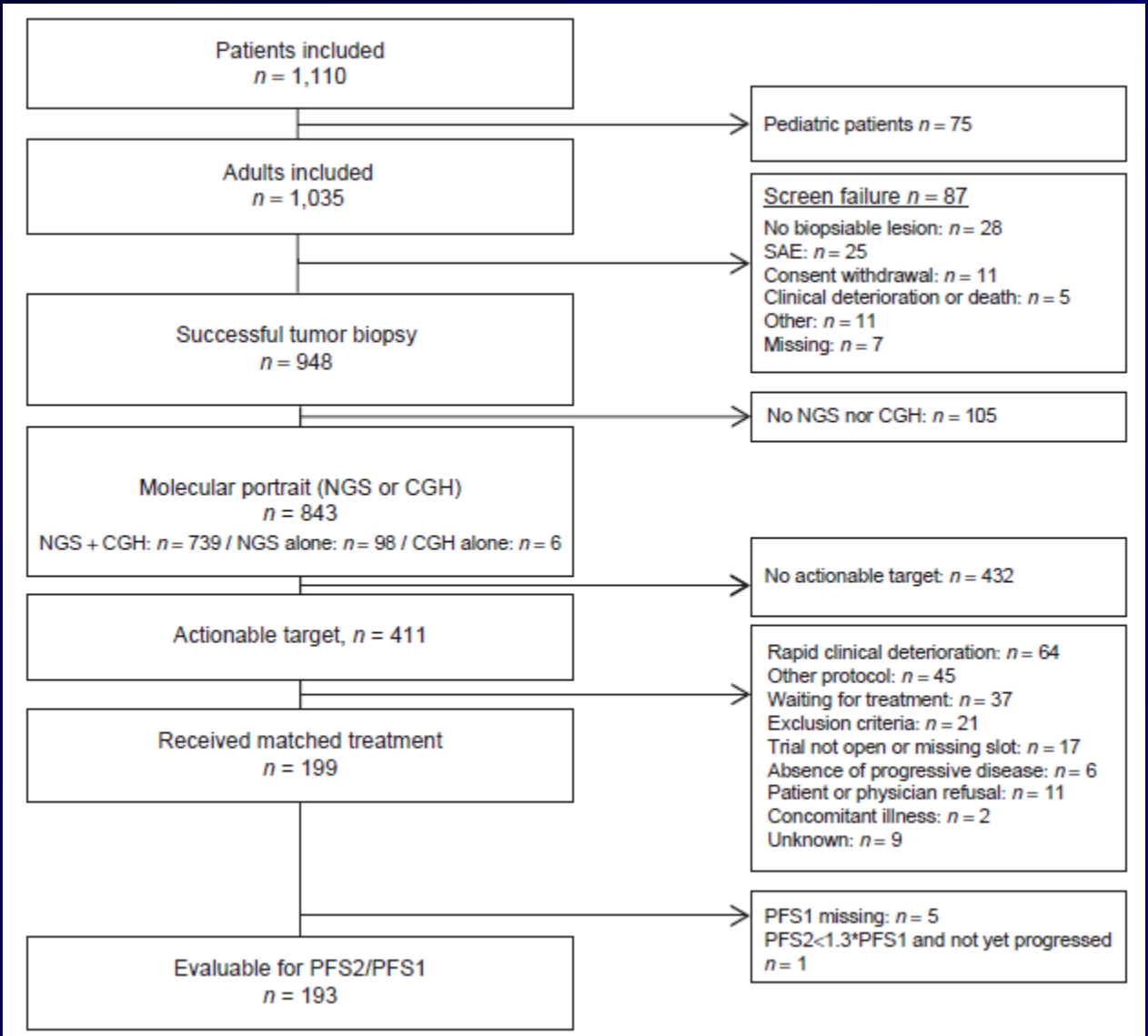
Biology and geometry



Systematic & random errors

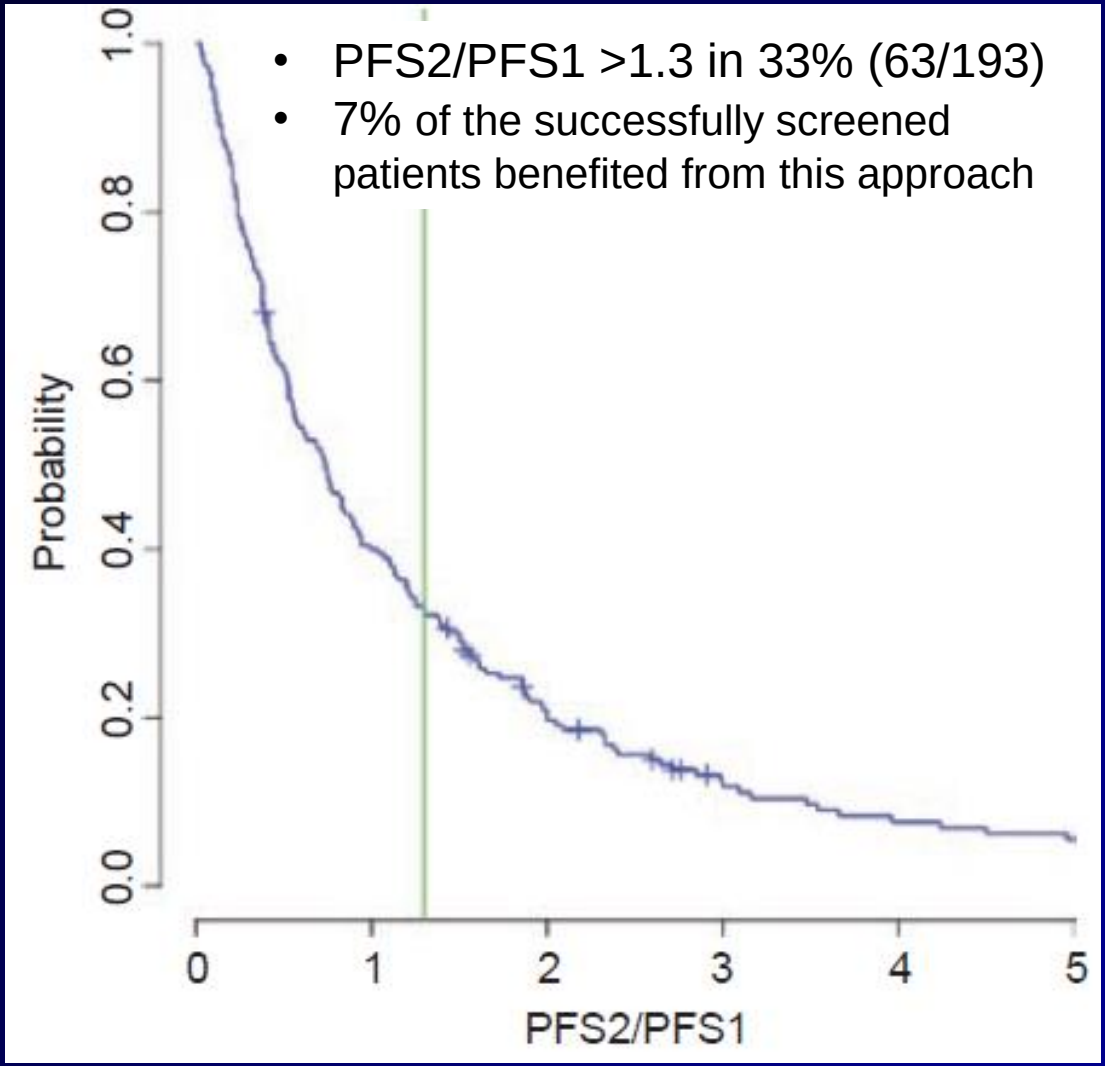


Personalised medicine



Massard Cancer Discov; 2017

Personalised medicine



- PFS2/PFS1 >1.3 in 33% (63/193)
- 7% of the successfully screened patients benefited from this approach

Massard Cancer Discov; 2017

ESTRO: Evidence-based Radiation Oncology

Big Data

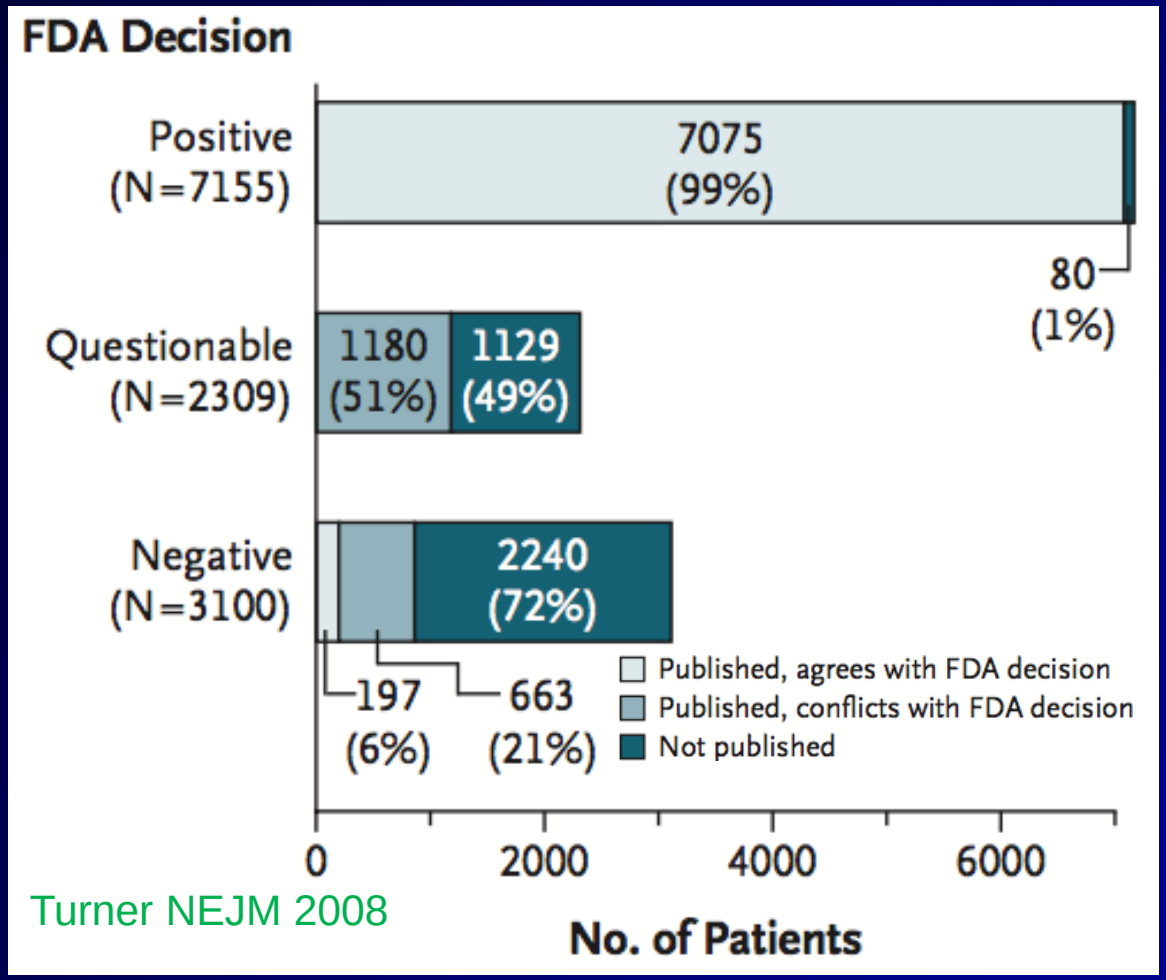
In USA only 3% of the patients‘ data are used in clinical research

Challenges	Big data	Clinical trial
Bias	Disadvantage	Advantage
Detailed relevant data	Disadvantage	Advantage
Sample size	Advantage	Disadvantage
Timely results	Advantage	Disadvantage
“Generalizability”	Advantage	Disadvantage

Chen Int J Radiat Oncol Biol Phys 2016

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.



Turner NEJM 2008

Several problems with research

….high quality research takes time (and resources)

Edgeworth R *et al* (1984) Eur J Phys 5:198-200

One last problem with research ...

Facial appearance affects science communication

Ana I. Gheorghiu[a], Mitchell J. Callan[a], and William J. Skylark[b,1]

[a]Department of Psychology, University of Essex, Colchester CO4 3SQ, United Kingdom; and [b]Department of Psychology, University of Cambridge, Cambridge CB2 3SQ, United Kingdom

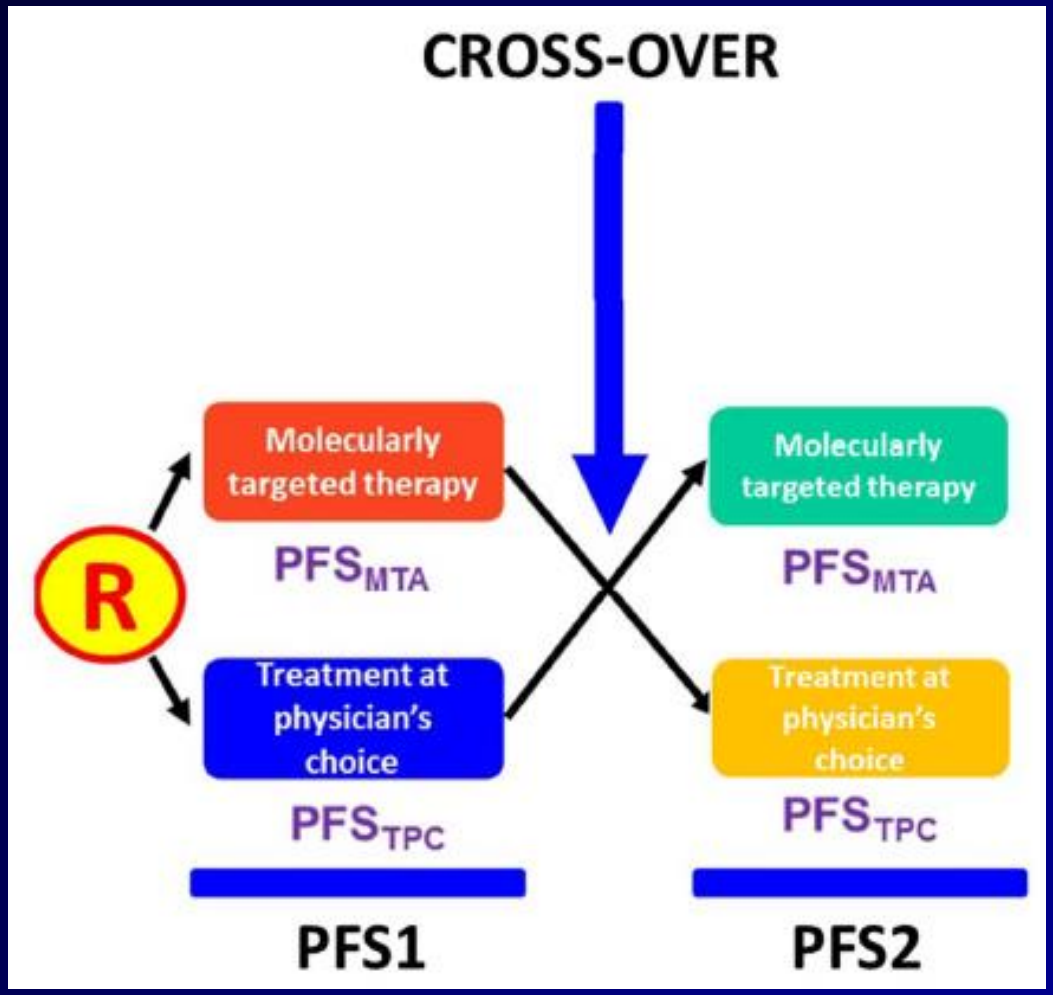
„When judging whether a researcher does “good science,” people preferred scientists who look competent and moral, but also favored less sociable and more physically unattractive individuals“

Gheorghiu PNAS 2017

Conclusion

- a challenging issue
- evidence requires good quality data
- to be estimated
  - size of effect
  - quality of evidence
  - clinical significance

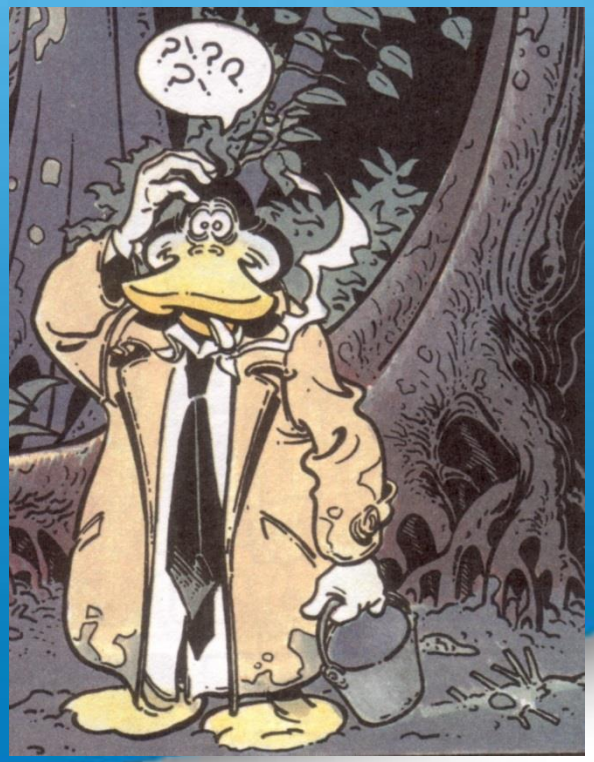
Personalised medicine



ESTRO: Evidence-based Radiation Oncology

Belin Annals Oncol 2016

Statistics for the RadOnc



Testing hypothesis

Cancéropôle Nord-Ouest

litis

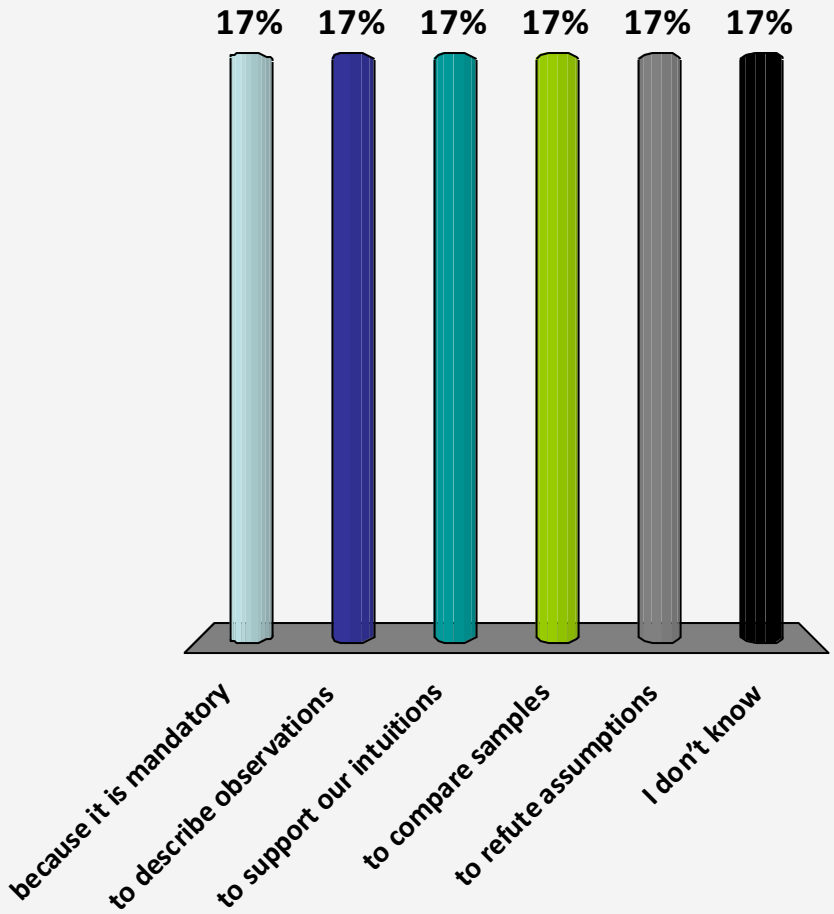
ESTRO European Society for RADIOTHERAPY & ONCOLOGY

UNIVERSITÉ DE ROUEN

CENTRE HENRI BECQUEREL HAUTE-NORMANDIE

Why do we use statistics ?

A. because it is mandatory
B. to describe observations
C. to support our intuitions
D. to compare samples
E. to refute assumptions
F. I don’t know



Phases of clinical research

Phase	Question	Endpoint
I	dose	(early) toxicity
II	activity	response (toxicity)
III	superiority	control survival toxicity

The principle of testing : H0

- H0 : an refutable assumption
- e.g. “all swans are white”

The principle of testing : H0

- H0 : an refutable assumption
- e.g. “all swans are white”

The principle of testing : H0

- In an ideal world
  - H0 : “new treatment cures all patients”
  - if a single failure is observed ...
  - then conclude : “H0 is false”
- In practice
  - H0 : “ new = old / none”
  - if a difference is observed ...
  - isn’t it by chance ?

What is « p » ?

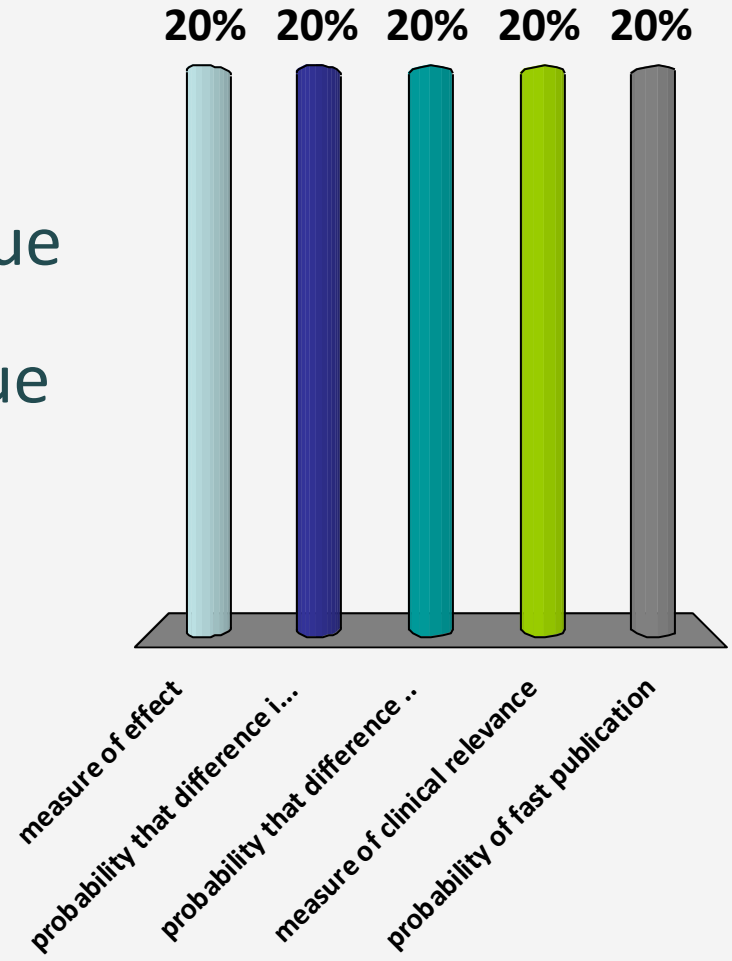
A. measure of effect

B. probability that difference is true

C. probability that difference is due to chance

D. measure of clinical relevance

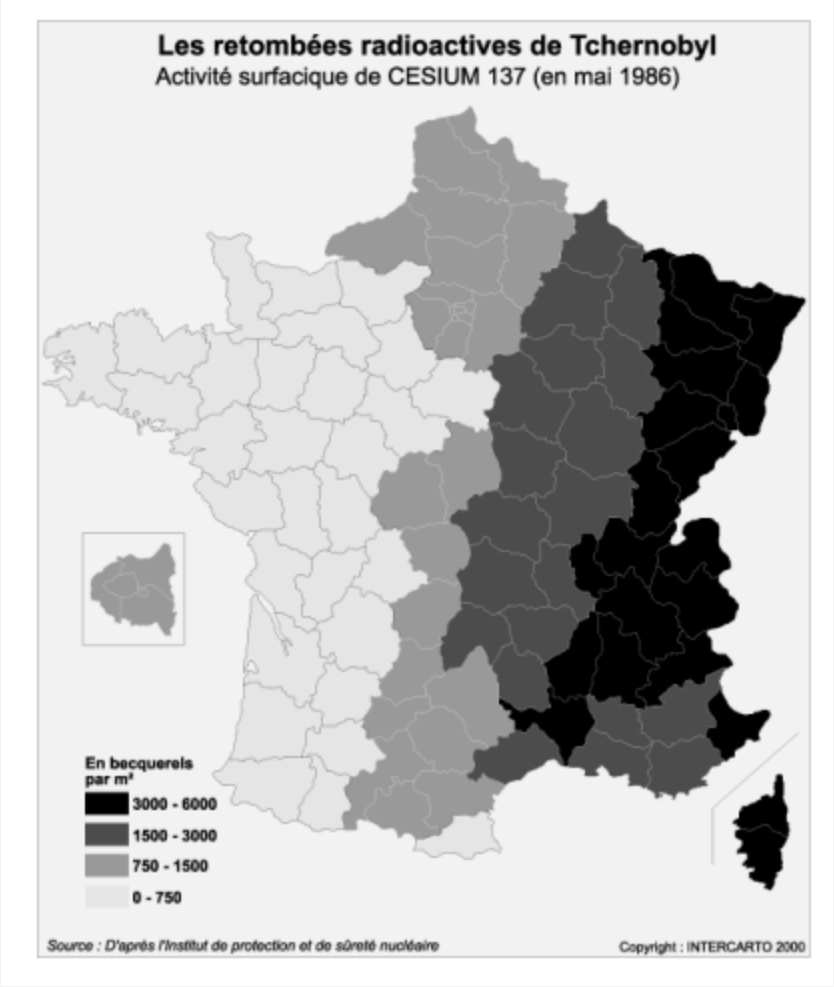
E. probability of fast publication

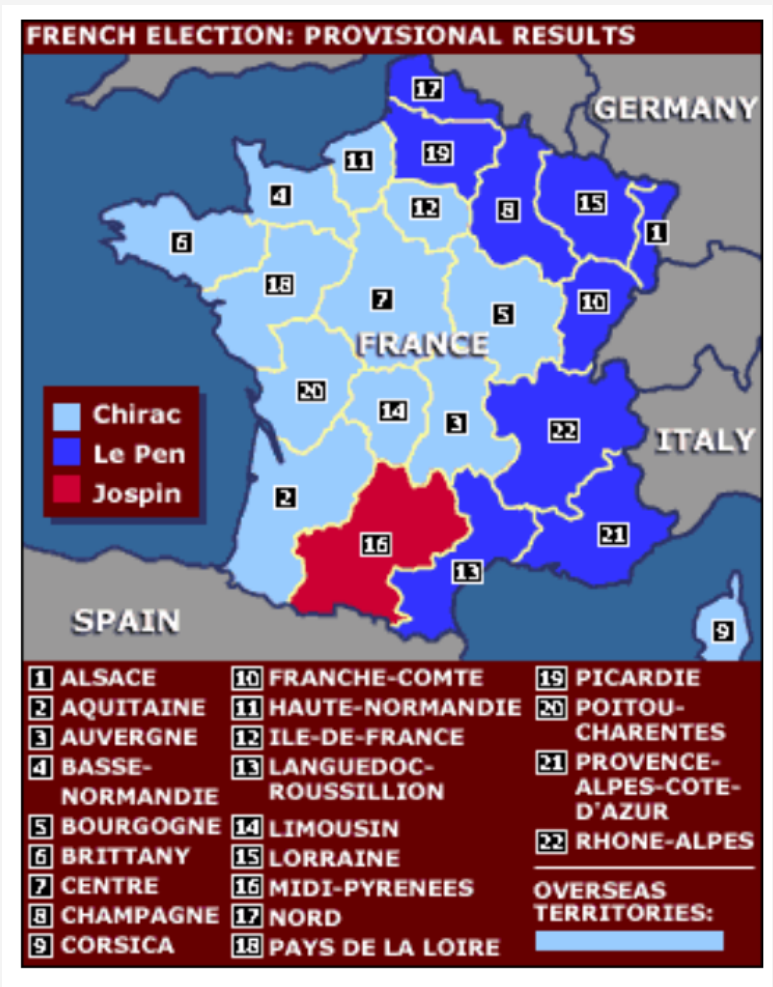


p-value

- Probability that the observed difference is due to chance if H0 holds true
- If $p \geq 0.05$: accept H0
  - the difference has ≥95% risk to be due to chance
- If $p < 0.05$: reject H0
  - the difference has ≤5% risk to be due to chance

Significance is not the same as cause





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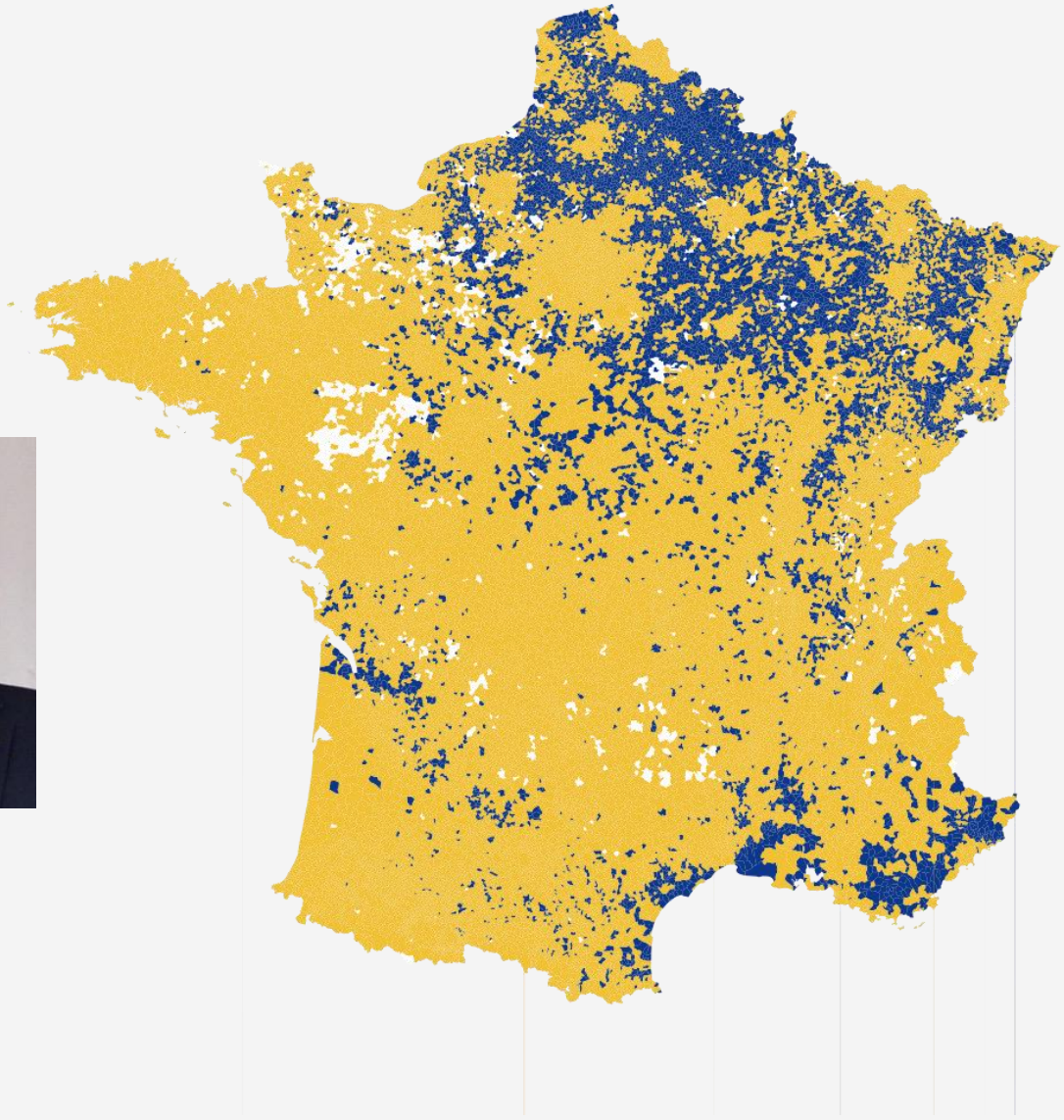


Significance is not the same as cause

2 ways of being wrong

- type I : conclude “A ≠ B” while “A = B”
  - an ineffective treatment is selected
- type II : conclude “A = B” while “A ≠ B”
  - the best treatment is not selected

Both errors are equally disturbing

Errors in clinical trials

Truth	Trial conclusion	
	A = B	A ≠ B
A = B	correct	type I (p = α)
A ≠ B	type II (p = β)	correct (power = 1 - β)

Open access, freely available online

Essay

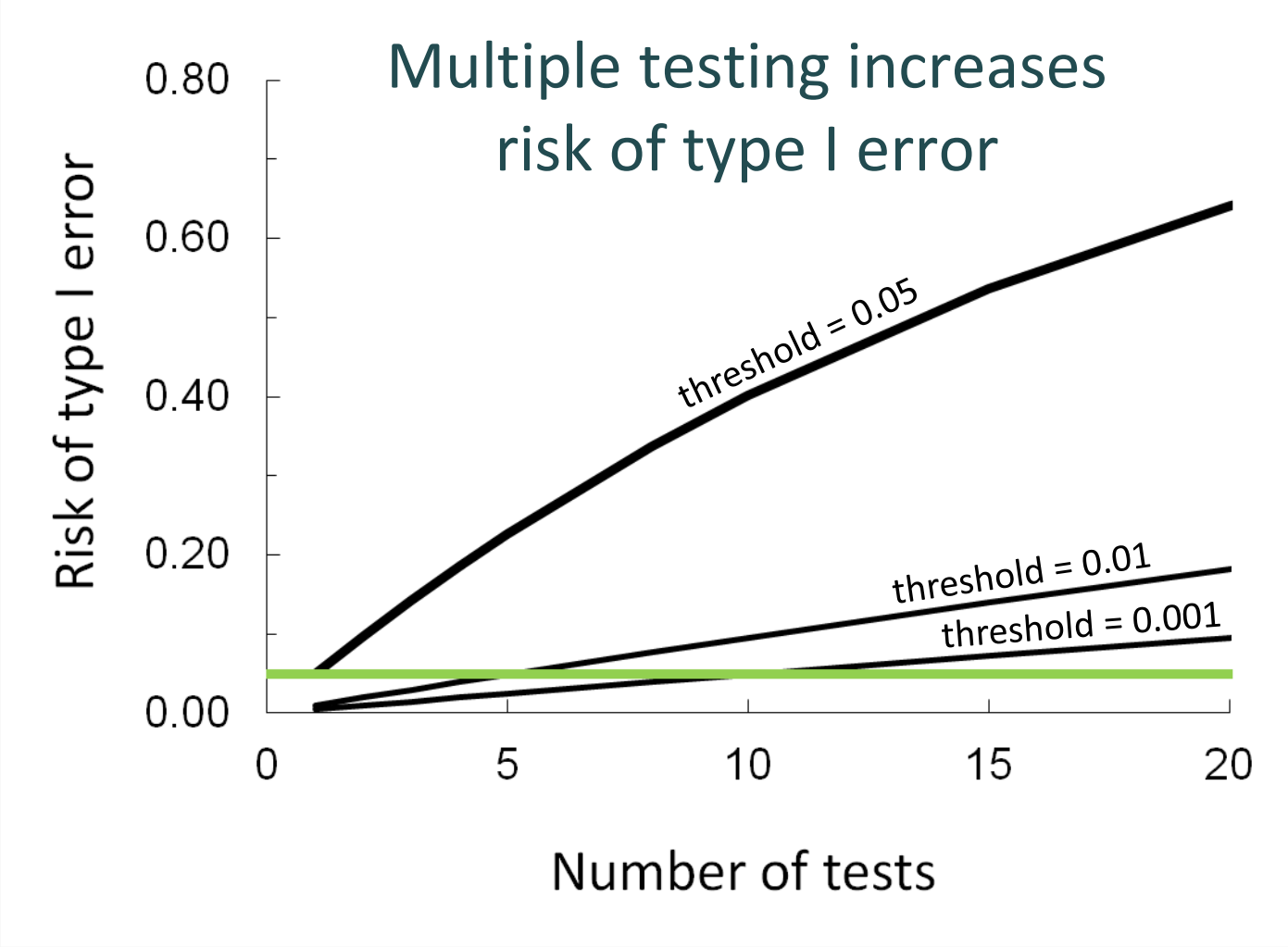
Why Most Published Research Findings Are False

John P. A. Ioannidis

- Lack of power
  - small studies / small effects
  - repeated tests
- Bias (≠ chance variability)
  - patient selection
  - flexibility (design, outcome, analysis)
  - selective reporting / reading

Ioannidis PLOS Med 2005

“Fishing” for significant p-values



Sample size

- A clinician's decision
  - meaningful difference
  - risks of error to be accepted
    - type I error : α
    - type II error : β (1 – power)
- To be calculated BEFORE +++++
  - a non feasible trial ?
  - an underpowered trial ?

Update on Lancaster 1601

Treatment	Scurvy	Total
lemon juice	0	2
rum	2	2
see water	2	2
prayer	2	2

- Observation:
  - P(S/no J) = 6/6 = 1.0 [0.16 – 1.0]
  - P(S/J) = 0/2 = 0.0 [0.0 – 0.46]
- Conclusion
  - p = 0.04
  - reject H0

Update on Lancaster 1601

Treatment	Scurvy	Total
lemon juice	0	2
rum	1	2
rectal enema	2	2
prayer	2	2

- Observation:
  - P(S/ no J) = 5/6 = 0.83 [0.36 – 1.0]
  - P(S/ J) = 0/2 = 0.0 [0.0 – 0.46]
- Conclusion
  - p = 0.11
  - do not reject H0

All tests should be bilateral

Patient informed	Prayer		HR [95% CI]
	Yes	No	
No	52 % (315/604)	51 % (304/597)	1.02 [0.92 – 1.15]
Yes	59 % (352/601)		
HR [95% CI]	1.14 [1.02 – 1.28]		

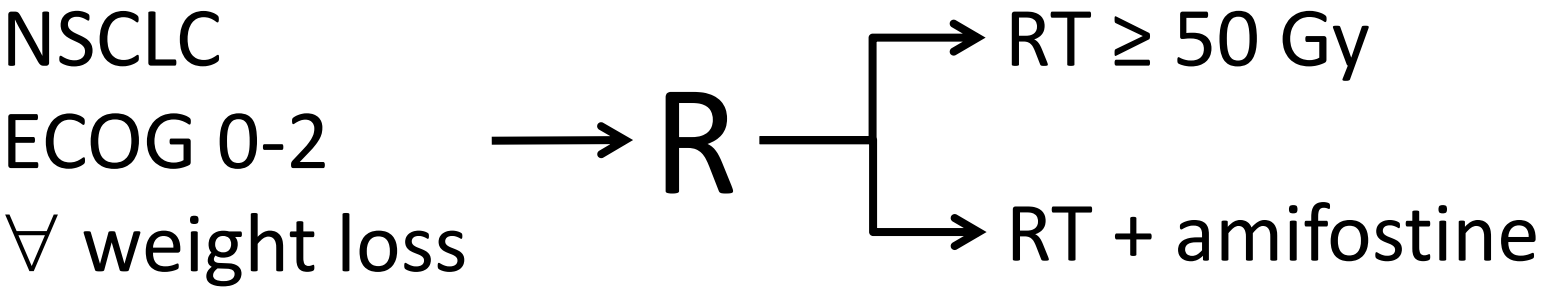
Study of the Therapeutic Effects of Intercessory Prayer (STEP) in cardiac bypass patients: A multicenter randomized trial of uncertainty and certainty of receiving intercessory prayer

Benson Am Heart J 2006

Bias

- factor(s) that produce(s) erroneous findings
  - design
  - data analysis
  - presentation
- e.g. selection bias
  - dose escalation only feasible in smaller tumours
  - frail patients referred to RT instead of surgery
- not to be confused with chance variability
  - findings could be erroneous by chance

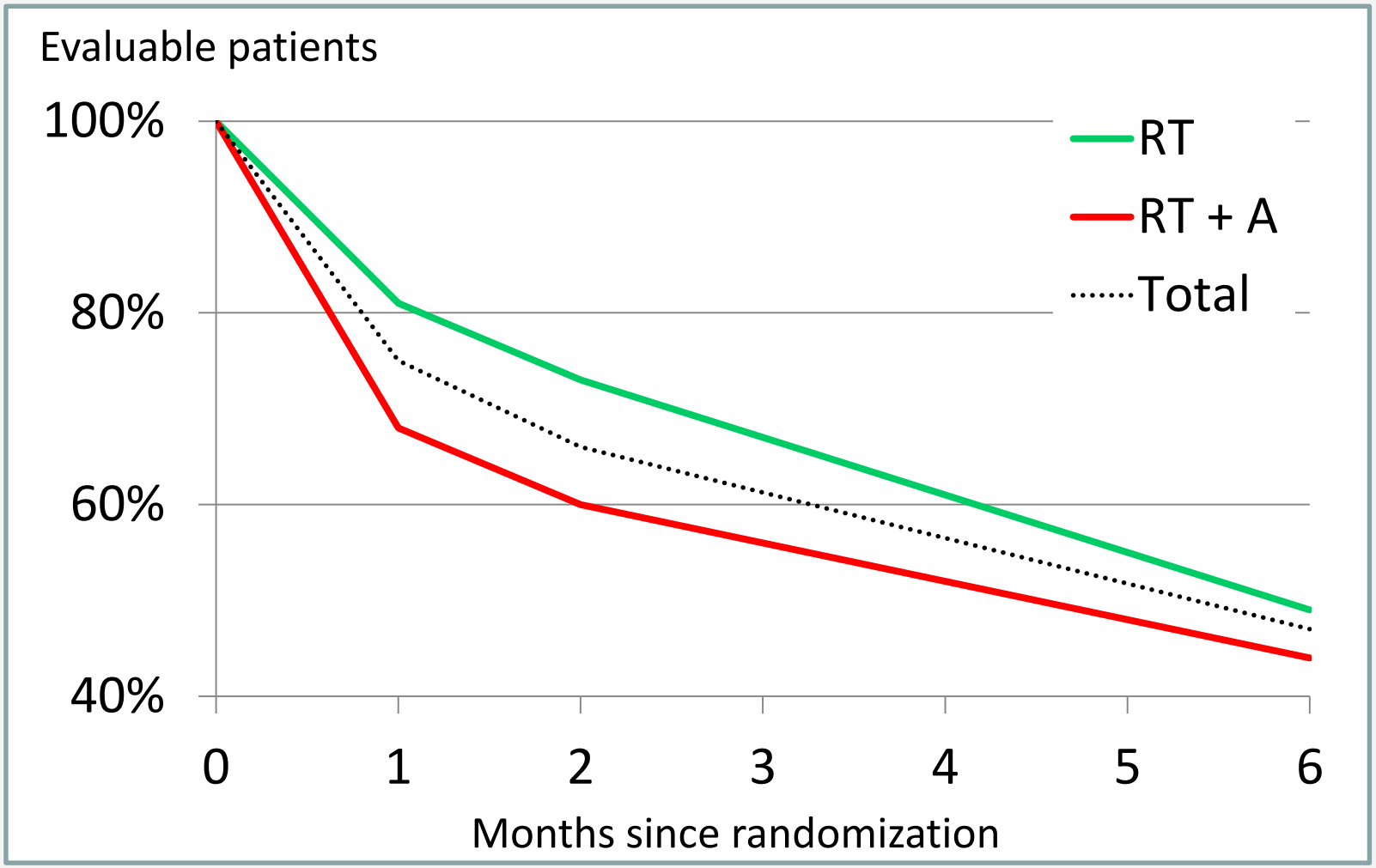
Exclusion of patients



N = 73 / 73

Antonadou IJROBP 2001

(Non-)evaluable patients



Antonadou IJROBP 2001

All patients are important

- lost patients = lost events
  - less power
  - bias
- many ways to lose patients
  - missing data
  - early stopping
  - patients exclusion

A word on ethics

- Randomisation is ethical … if
  - best alternative unknown
  - adequate methodology
  - informed consent

- What is not ethical ?
  - use of treatments without proven superiority
  - inclusion of patients in poor trials
  - diversion of patients eligible for research
  - waste of resources

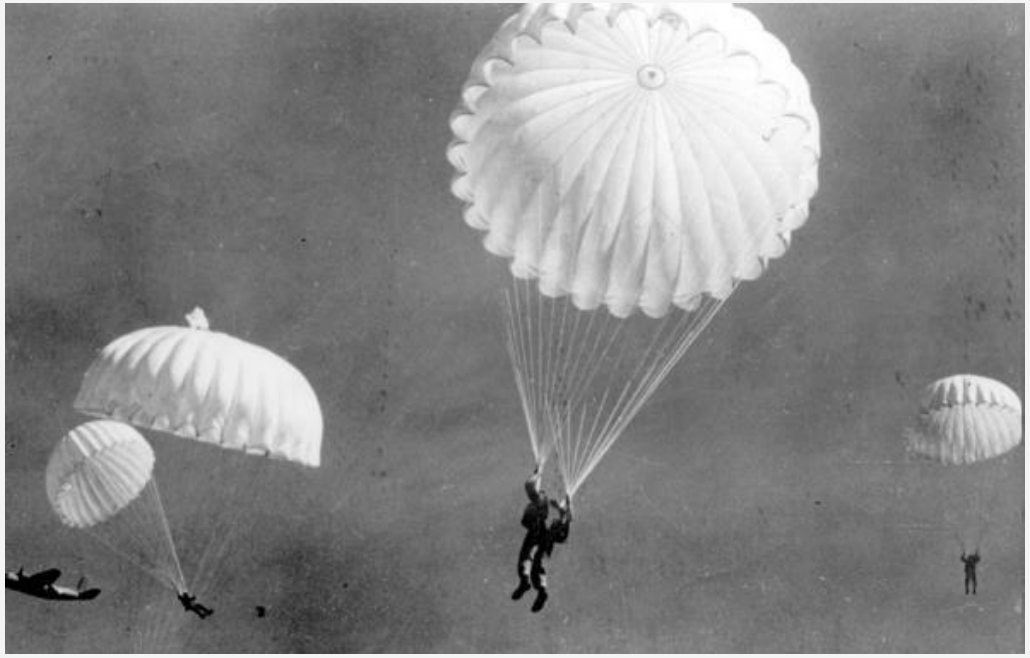
The problems with phase III

- Small effects mean (very …) large trials
  - many questions cannot be addressed
- The results are disappointing
  - 510 phase III @ ASCO 1989-1998
  - 223 (44%) with $p \leq 0.05$
  - 183 (36%) superiority of experimental arm
- The results come too late
  - not relevant for routine patients
  - obtained with obsolete modalities

Krzyzanowska JAMA 2003

Trials that are not feasible

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomized trials



Smith BMJ 2003

Trials that are not feasible

Parachute use to prevent death and major trauma
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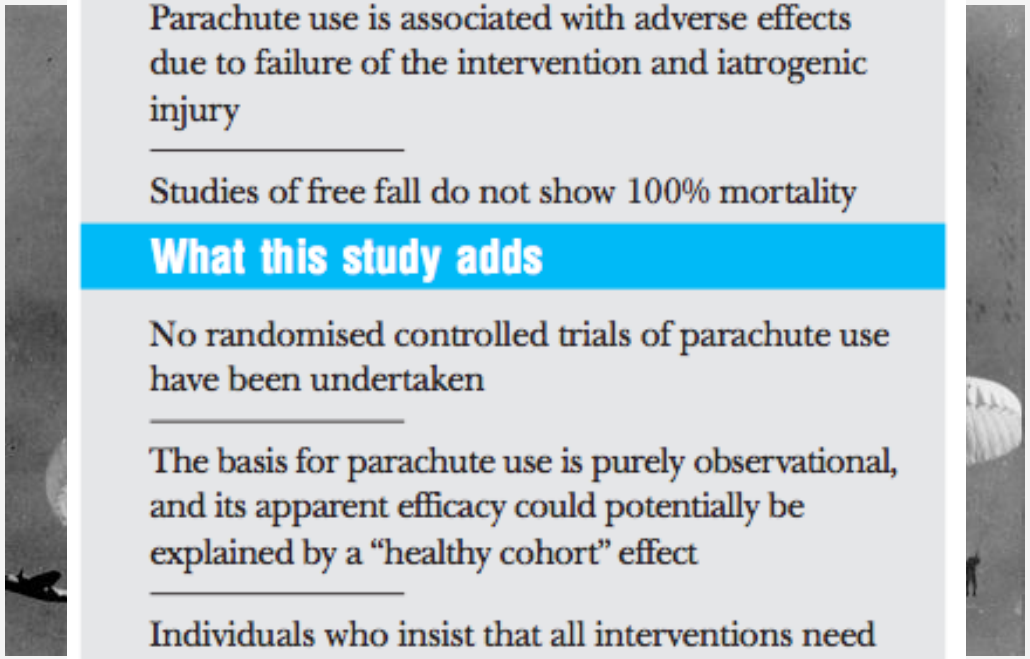


What is already known about this topic

Parachutes are widely used to prevent death and major injury after gravitational challenge

Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury

Studies of free fall do not show 100% mortality

What this study adds

No randomised controlled trials of parachute use have been undertaken

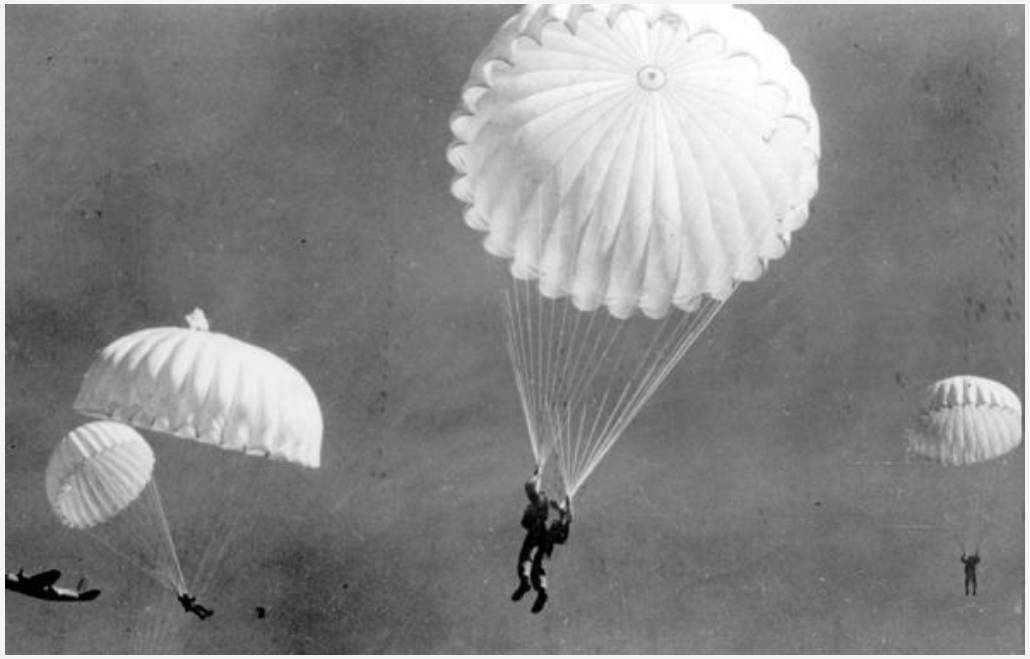
The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect

Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

Smith BMJ 2003

Trials that are not feasible

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised trials

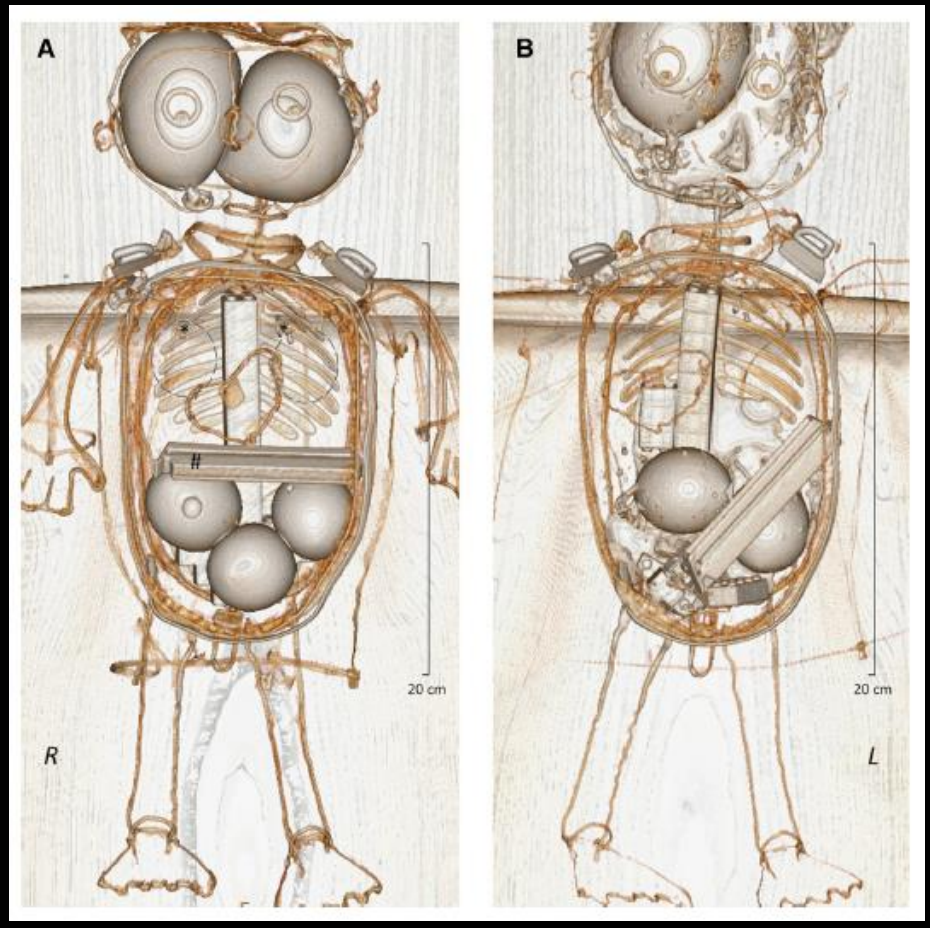


Smith GCS and Pell JP (2003) BMJ 327:1459-1461

Does usage of a parachute in contrast to free fall prevent major trauma?: a prospective randomised-controlled trial in rag dolls

Patrick Czorlich[1] · Till Burkhardt[1] · Jan Hendrik Buhk[2] · Jakob Matschke[3] · Marc Dreimann[4] · Nils Ole Schmidt[1] · Sven Oliver Eicker[1]

Eur Spine J 2016



Does usage of a parachute in contrast to free fall prevent major trauma?: a prospective randomised-controlled trial in rag dolls

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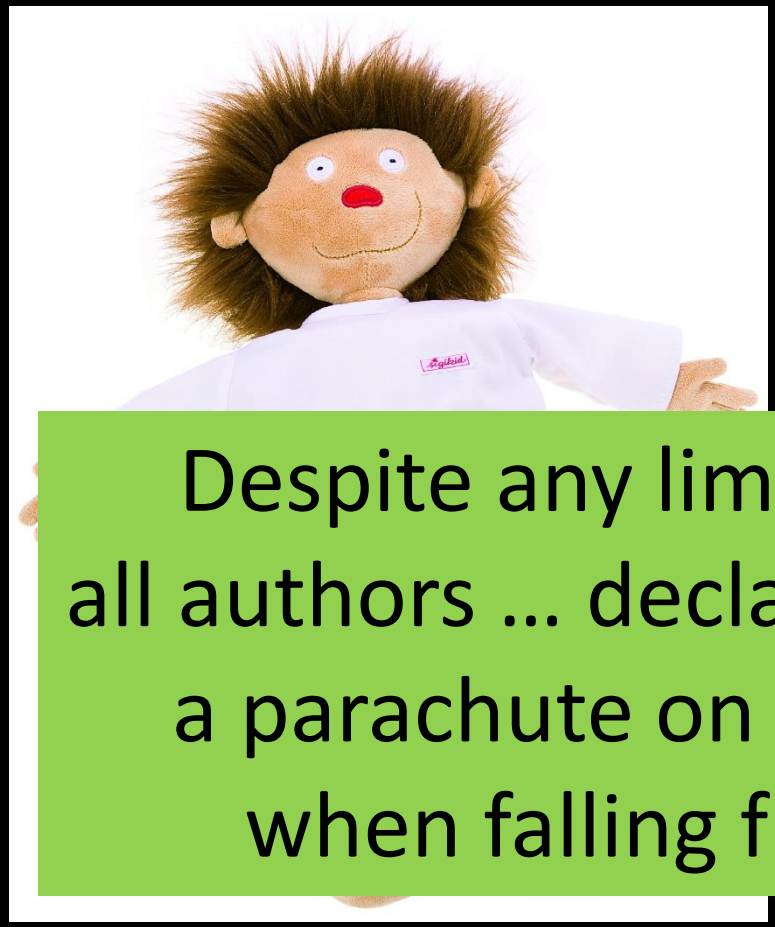
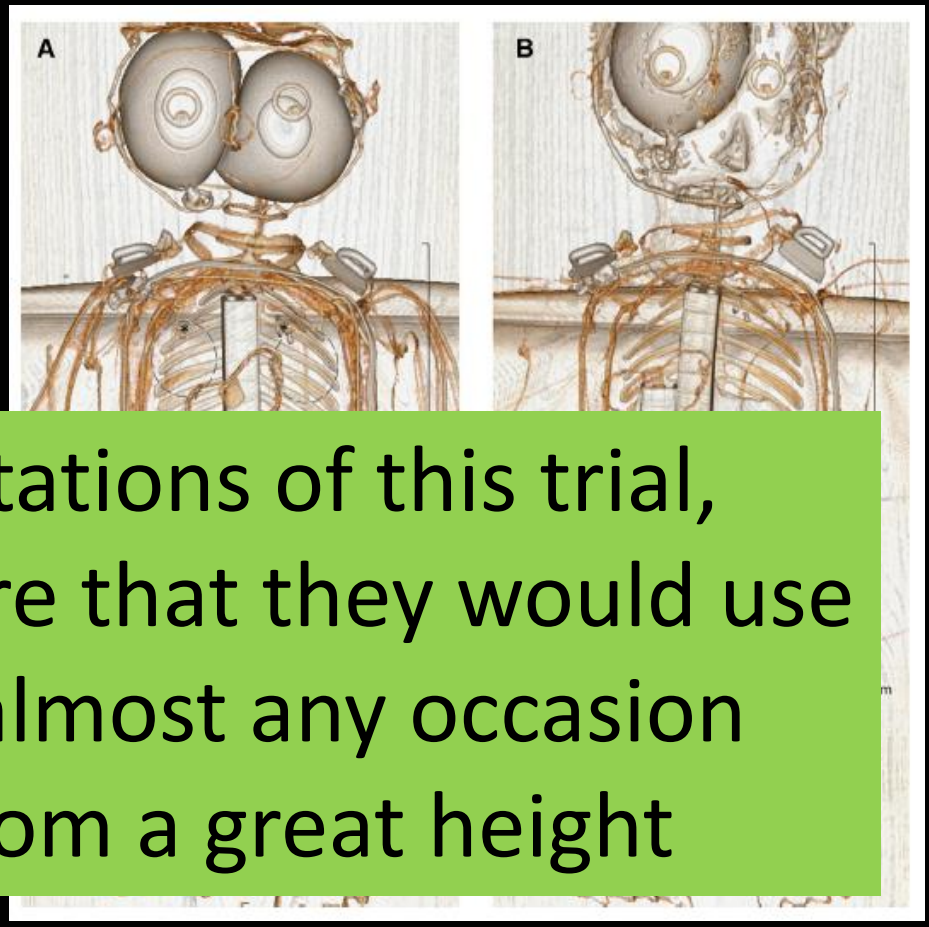




Despite any limitations of this trial,
all authors … declare that they would use
a parachute on almost any occasion
when falling from a great height

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Type of research	Power	True/false	Bias	PPV
Good quality RCT	0.80	1:1	0.10	0.85
Meta-analysis of good quality RCTs	0.95	2:1	0.30	0.85
Meta-analysis of small RCTs	0.80	1:3	0.40	0.41
Phase I/II RCT	0.20	1:5	0.20	0.23
Exploratory epidemiological study	0.80	1:10	0.30	0.20
Exploratory with massive testing	0.20	1:1000	0.80	0.001

Ioannidis PLOS Med 2005

Conclusion

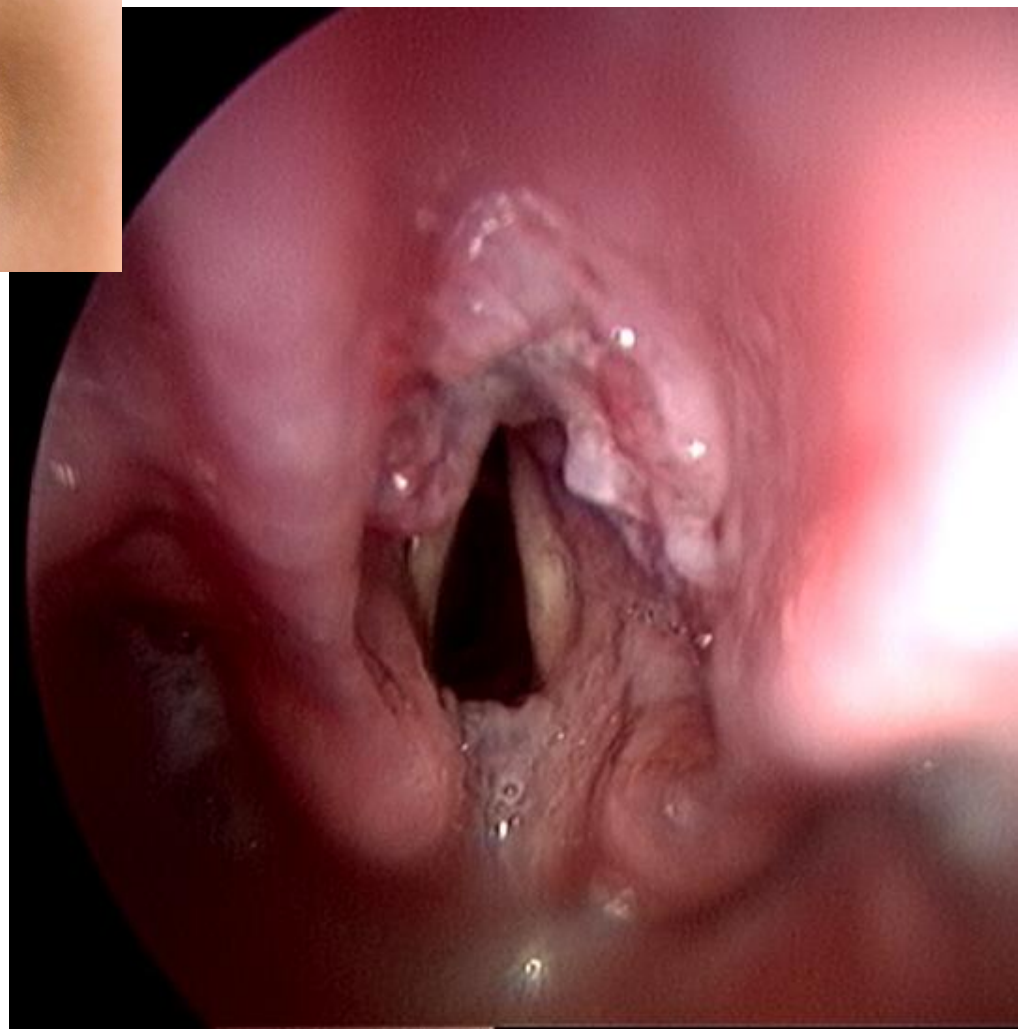
- Good data more important than tests
- Study design
  - KISS: Keep It Simple, Stupid !
  - AGARA: As Good As Reasonably Achievable
- Are the results clinically significant ?

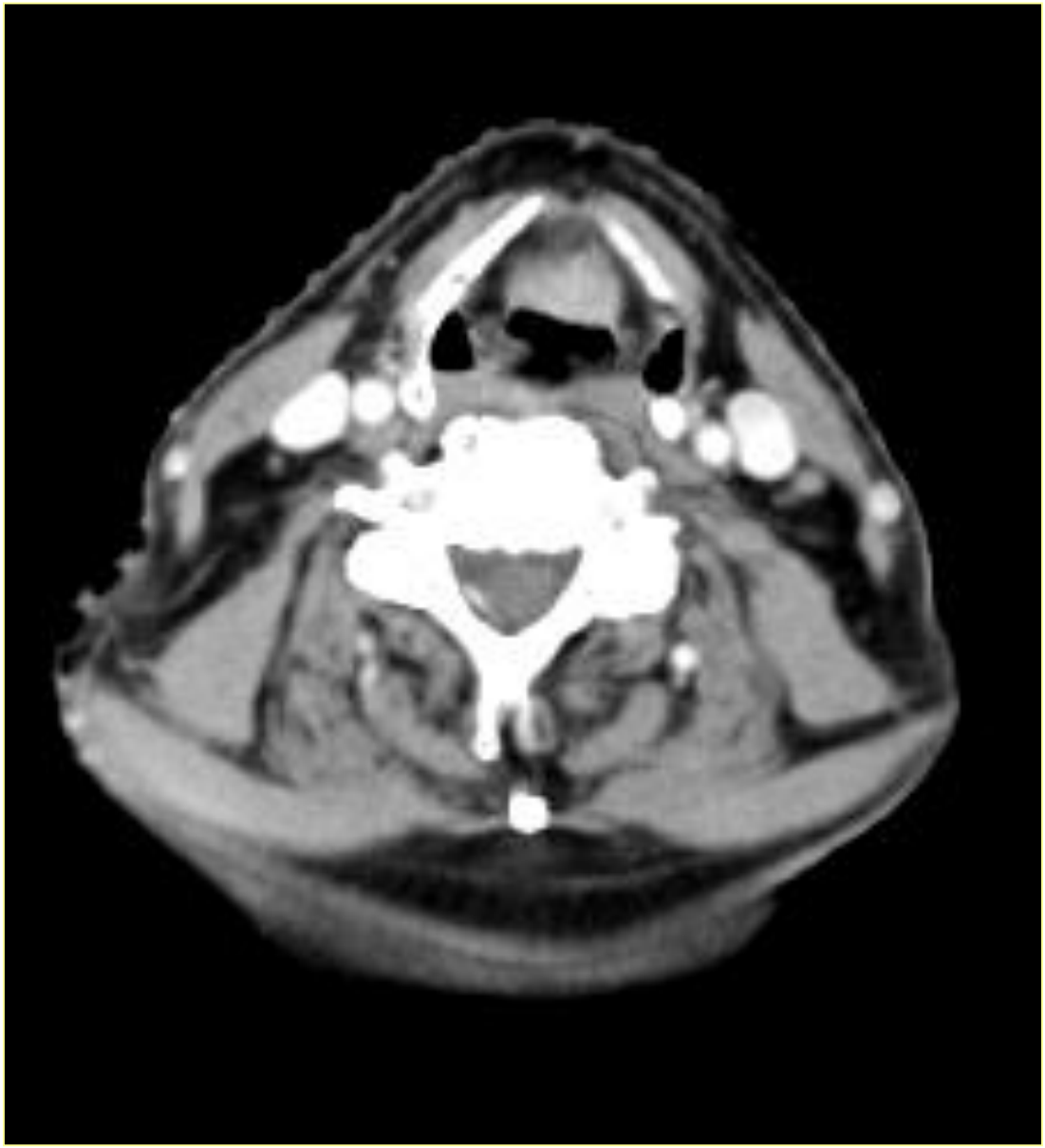
Imaging
in treatment planning and delivery

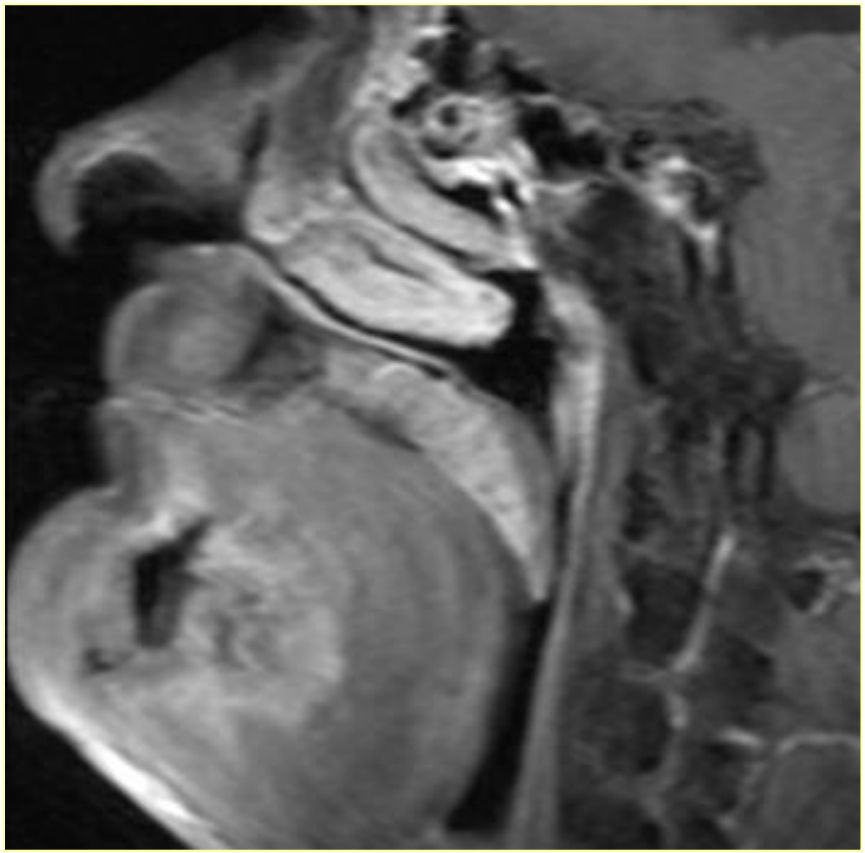
Hans Kaanders
Department of Radiation Oncology
Radboud University Medical Center
Nijmegen, The Netherlands

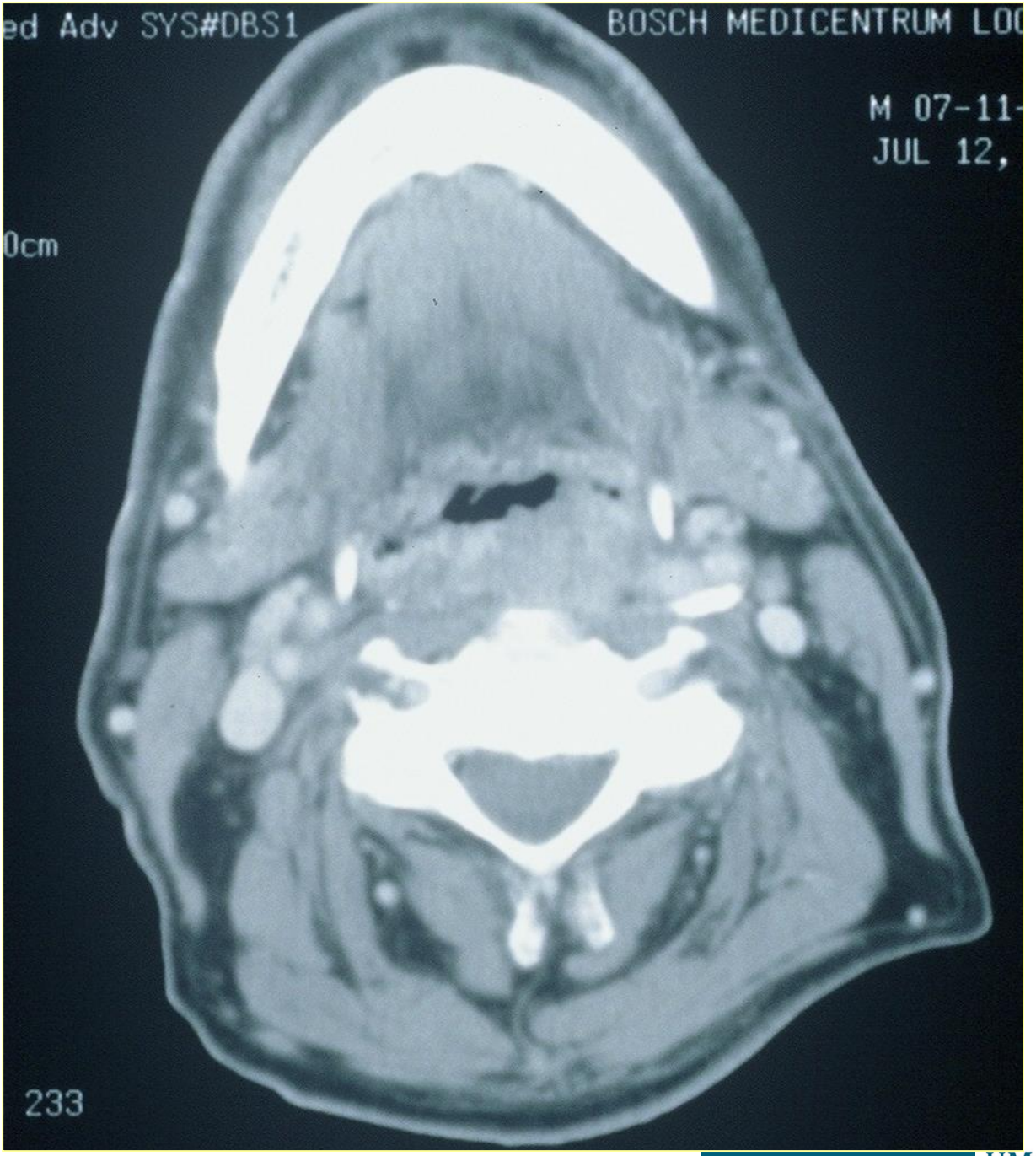
Imaging and radiation oncology

- *Diagnostic stage*
- *Treatment selection*
- *Planning stage*
- *Treatment stage*
- *Follow-up*





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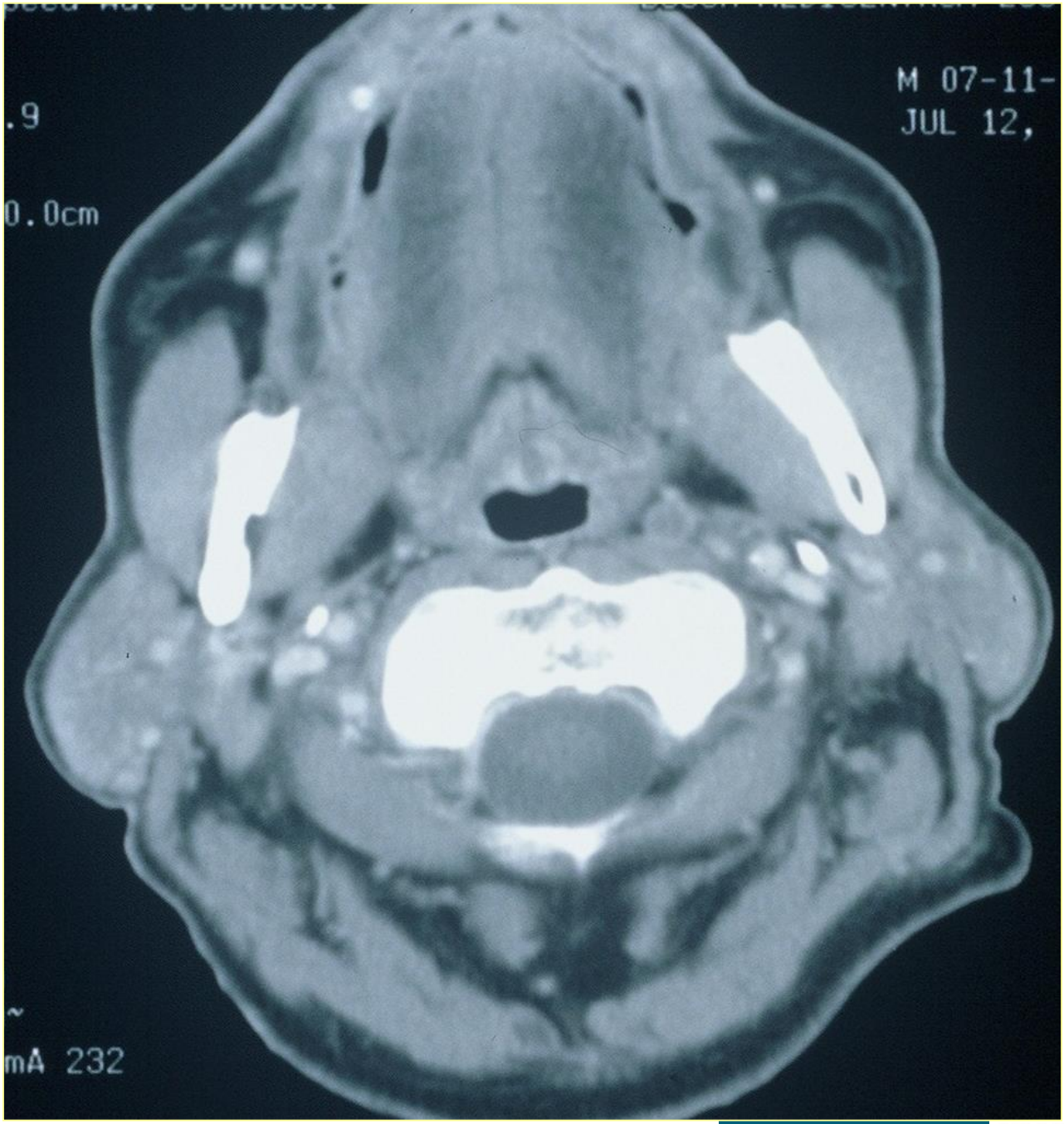
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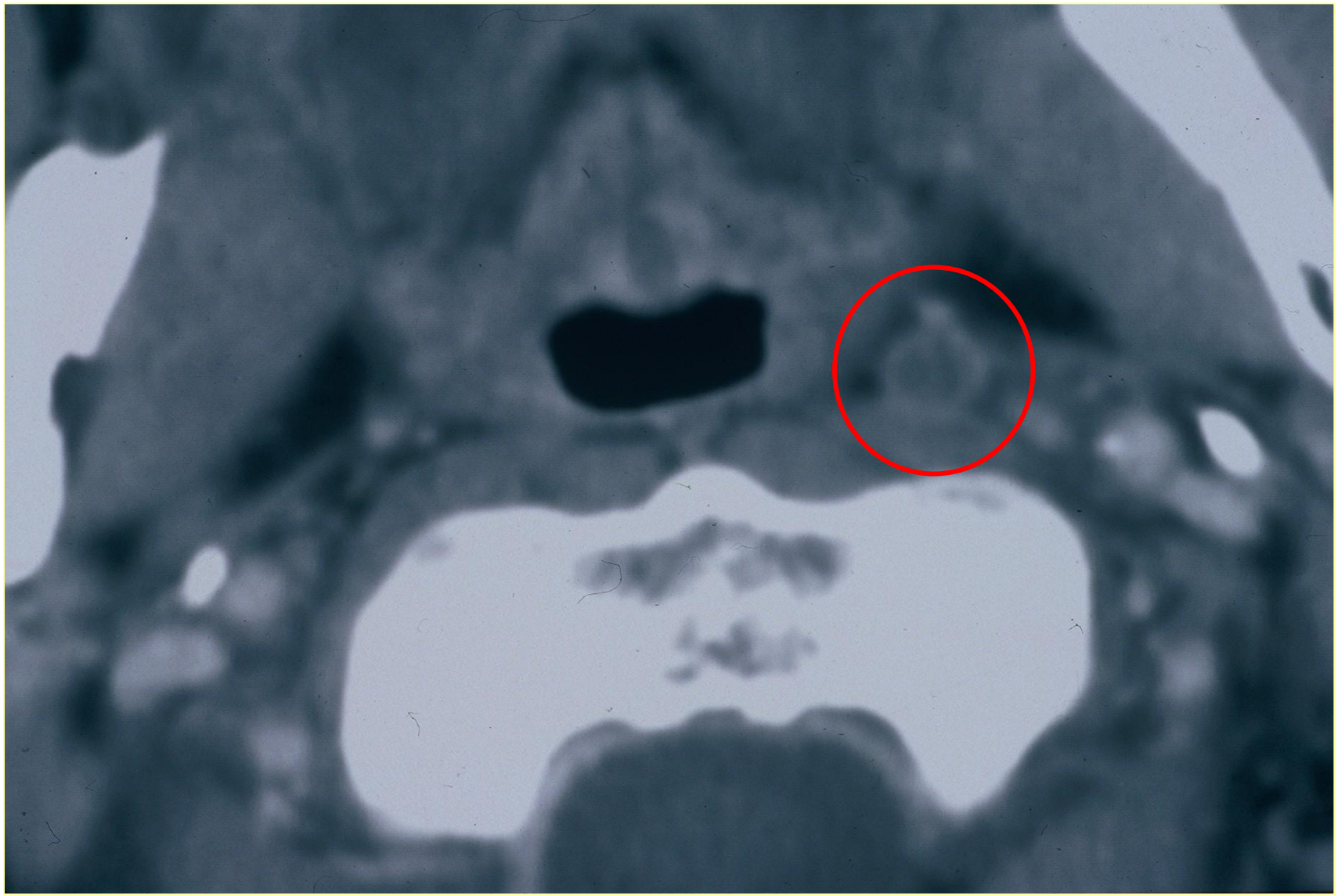
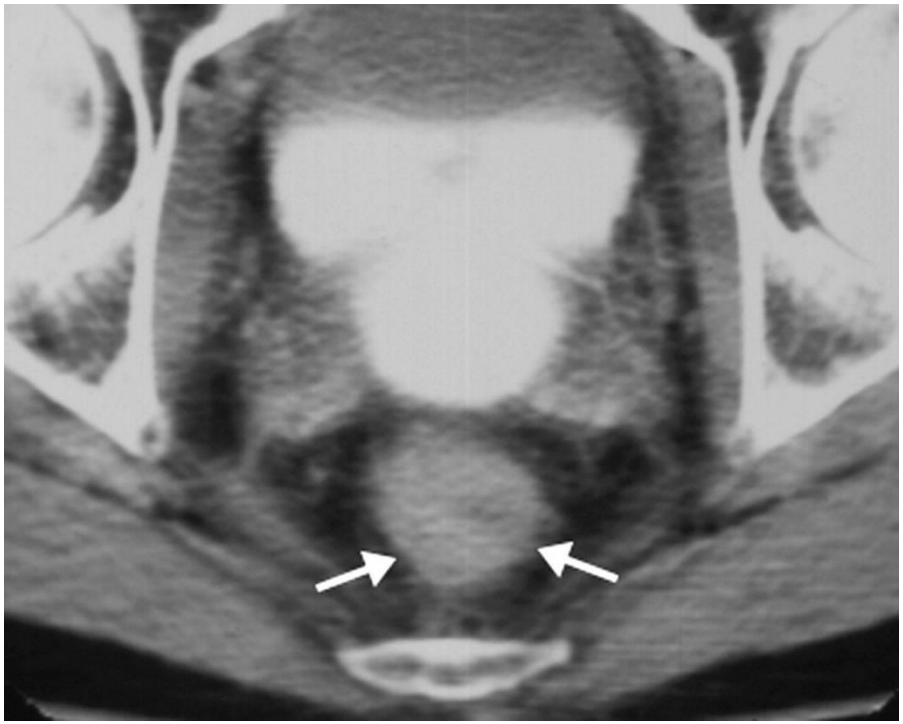
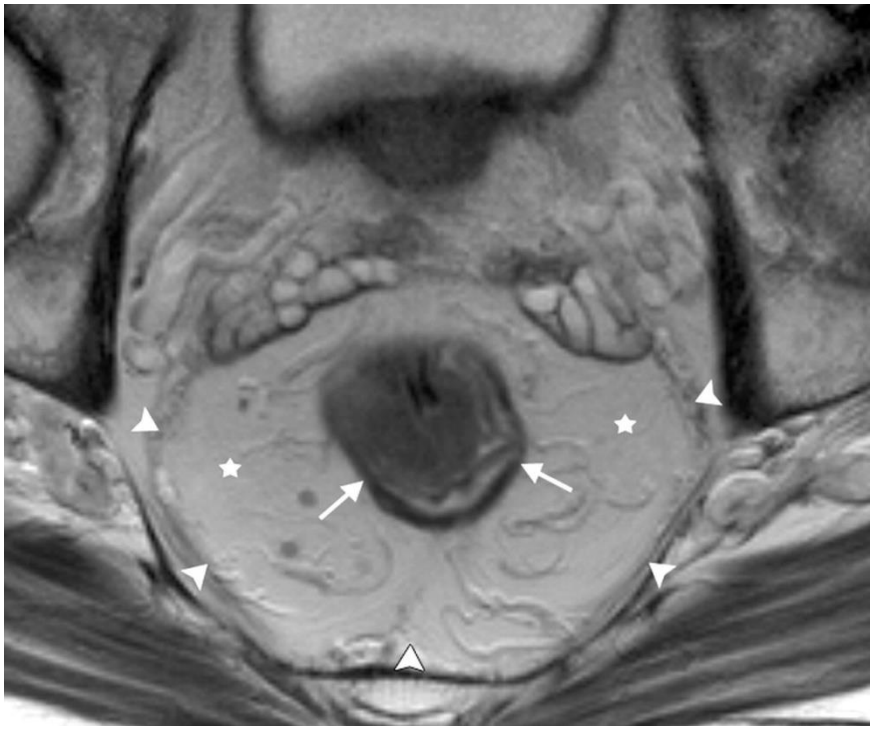


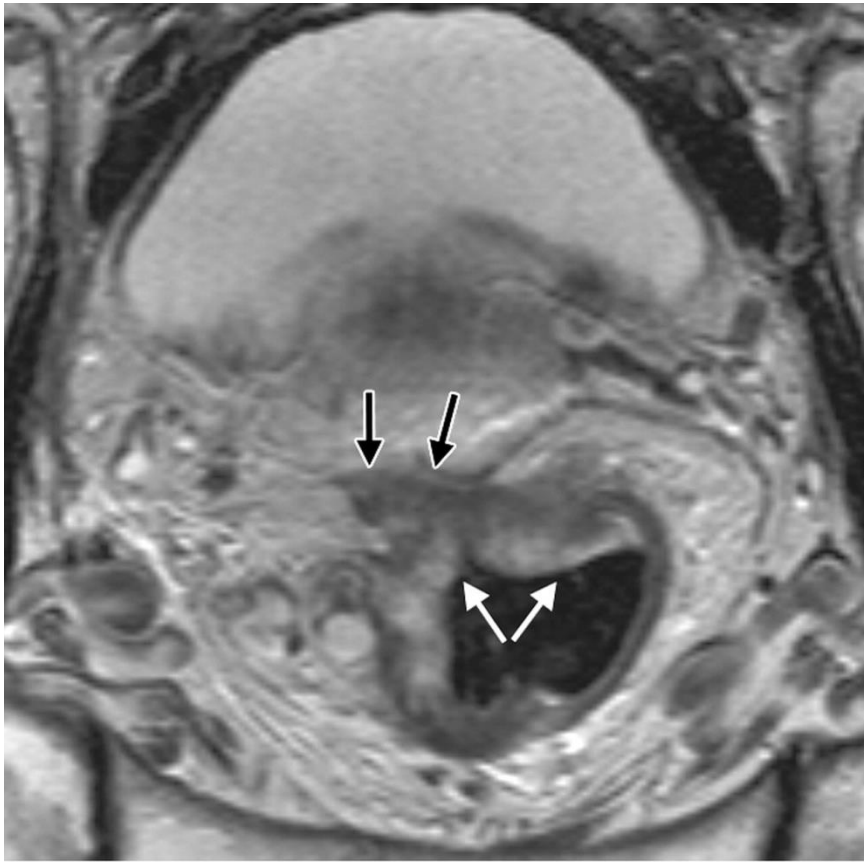
Imaging the pelvis CT vs MRI

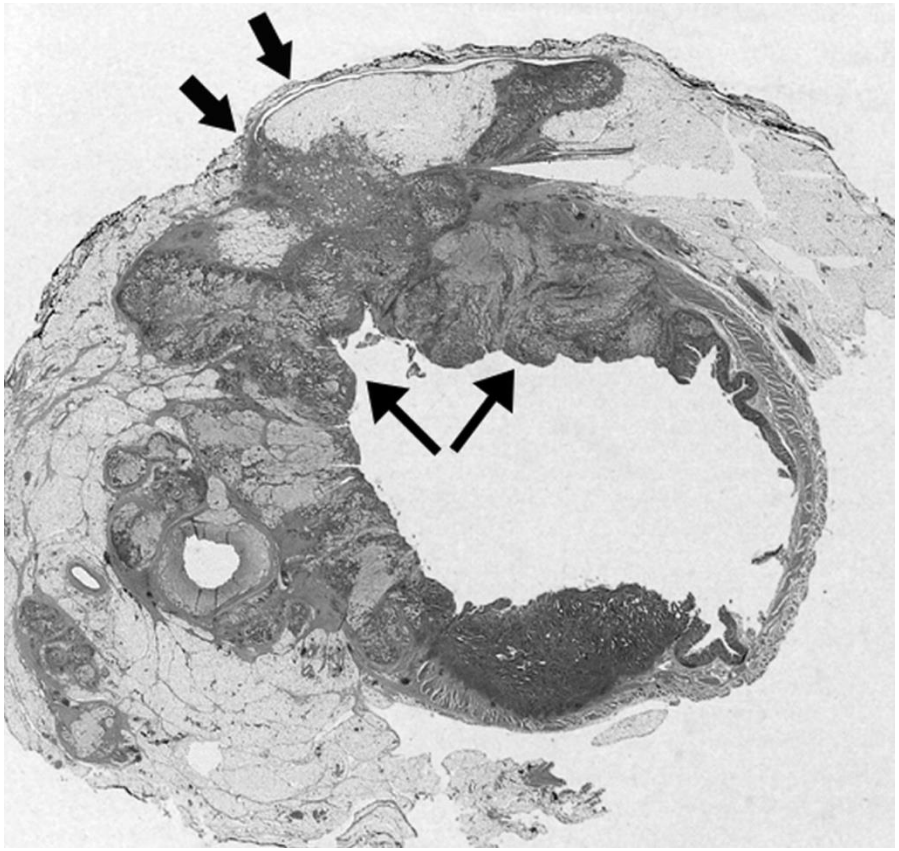




Beets-Tan et al. Radiology 2004

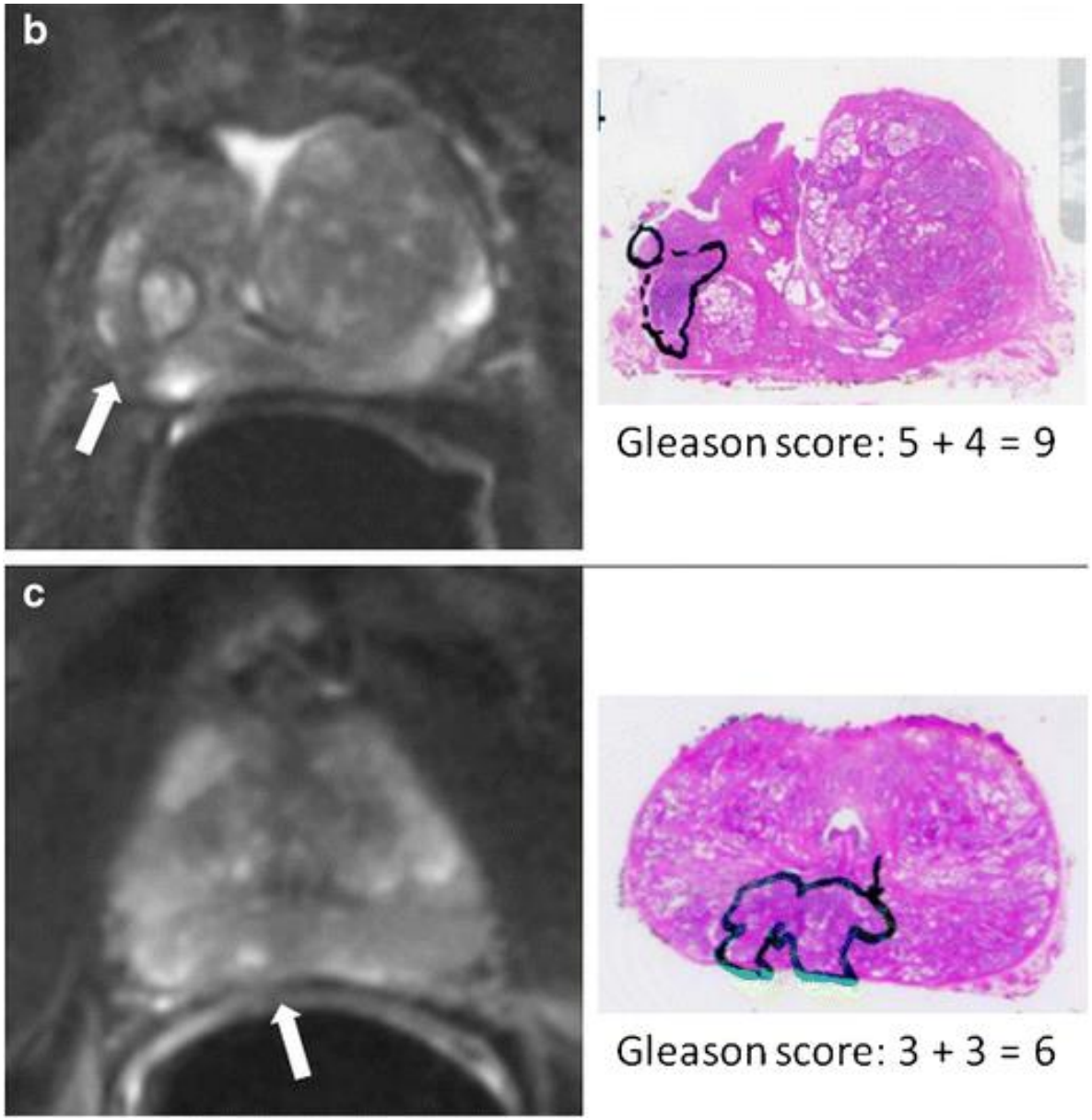
MRI of the pelvis - rectal cancer





Beets-Tan et al. Radiology 2004

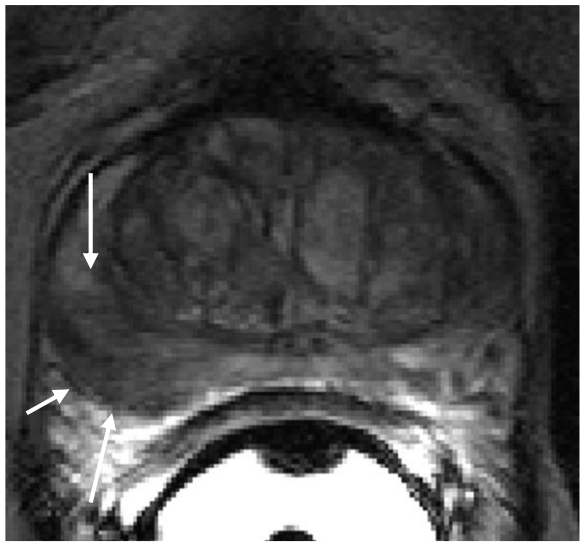
MRI of the pelvis - prostate cancer



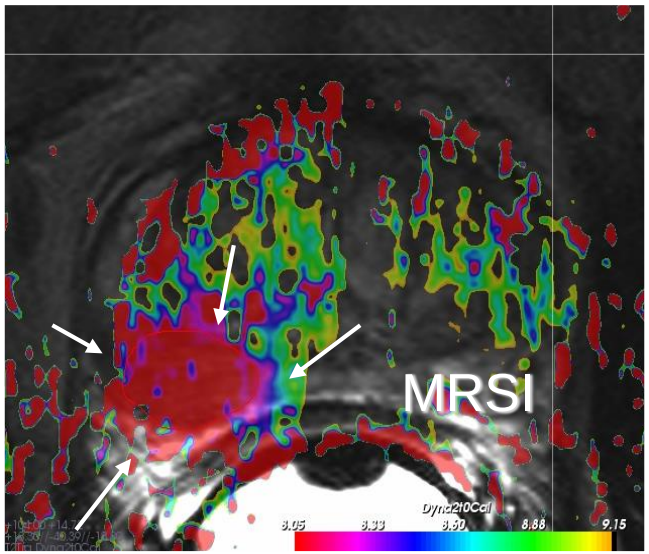
Vos et al. Eur. Radiol. 2014

Identifying high risk areas within the GTV

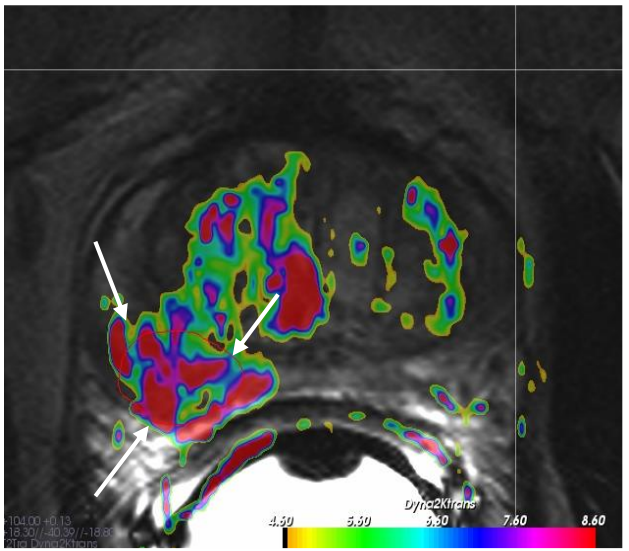
T2



DCE-MRI

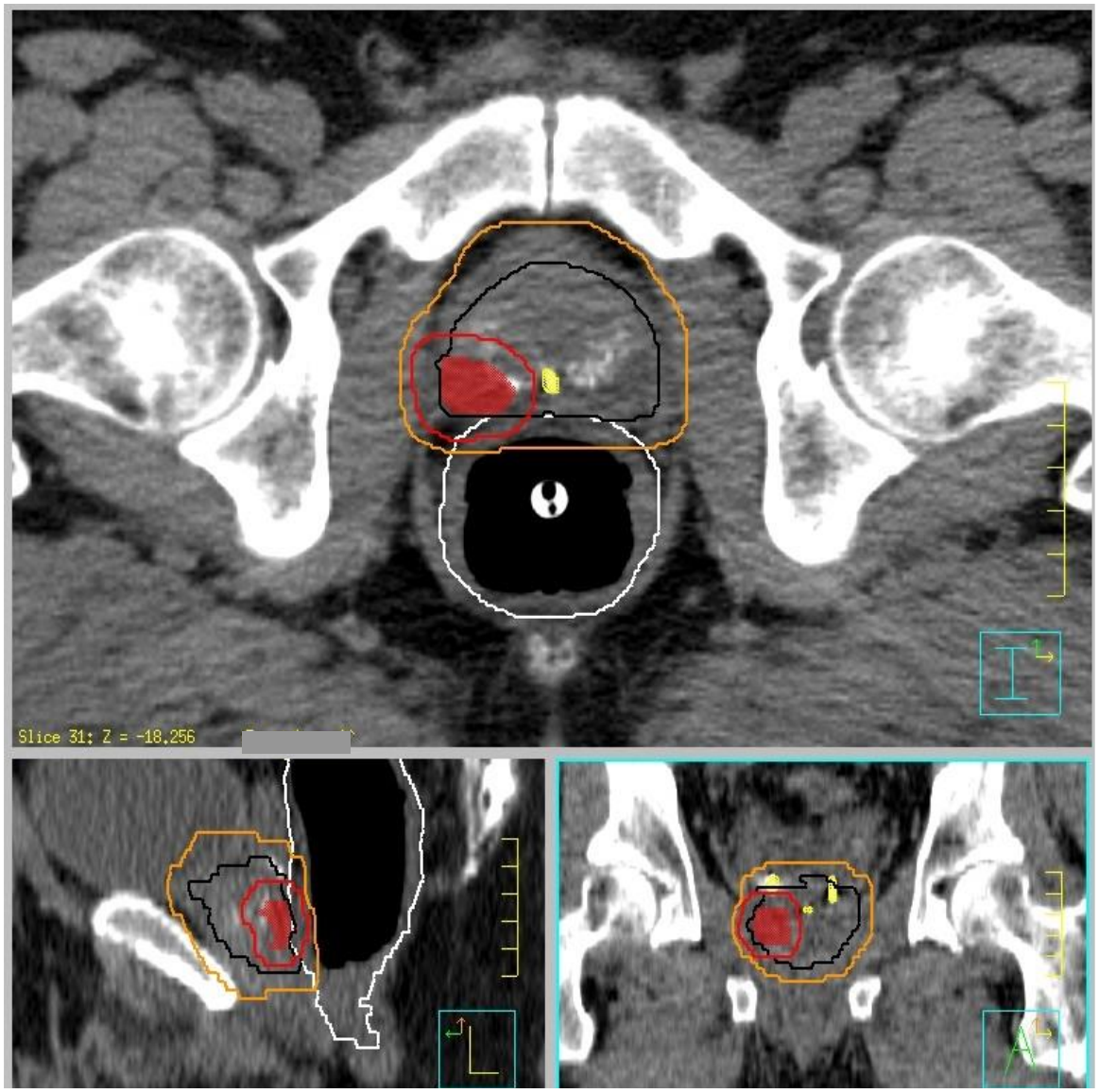


DCE-MRI



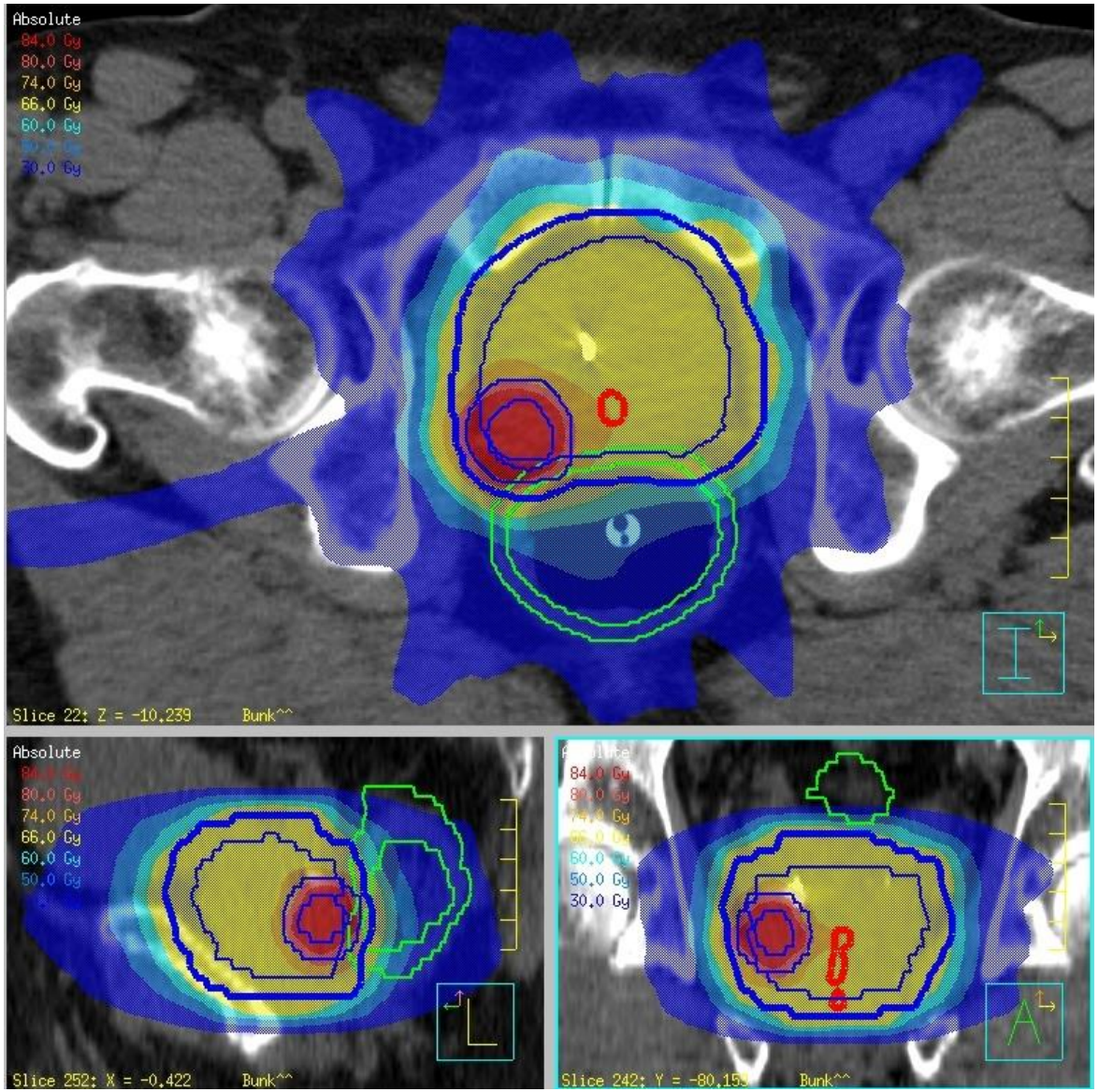
Van Lin, Int J Radiat Oncol Biol Phys 2006

Additional boosting of dominant intraprostatic lesion



Van Lin, Int J Radiat Oncol Biol Phys 2006

70 Gy prostate, 90 Gy dominant intraprostatic lesion

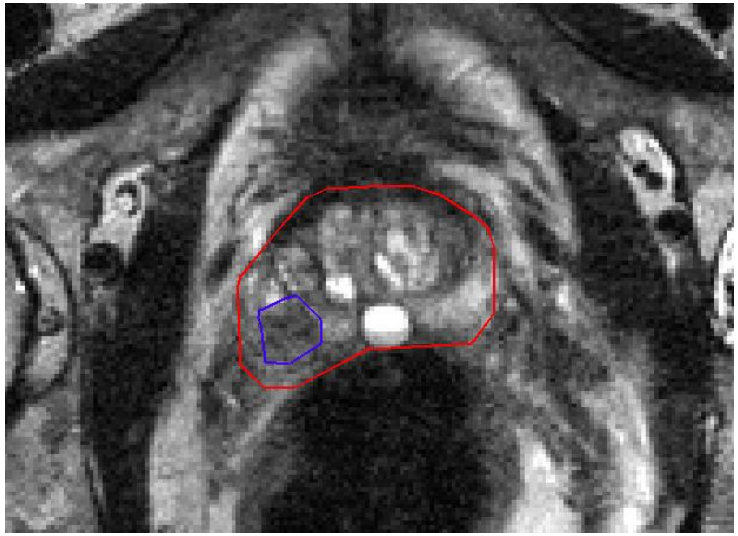


Van Lin, Int J Radiat Oncol Biol Phys 2006

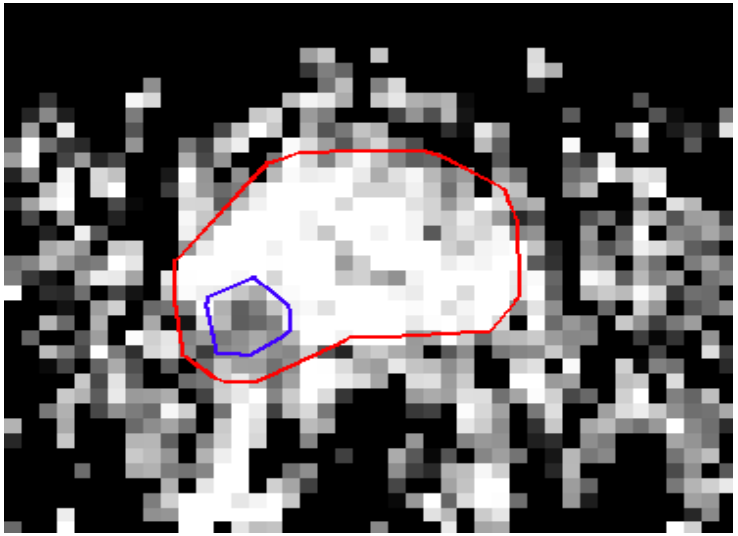
UMC St Radboud

Flame study

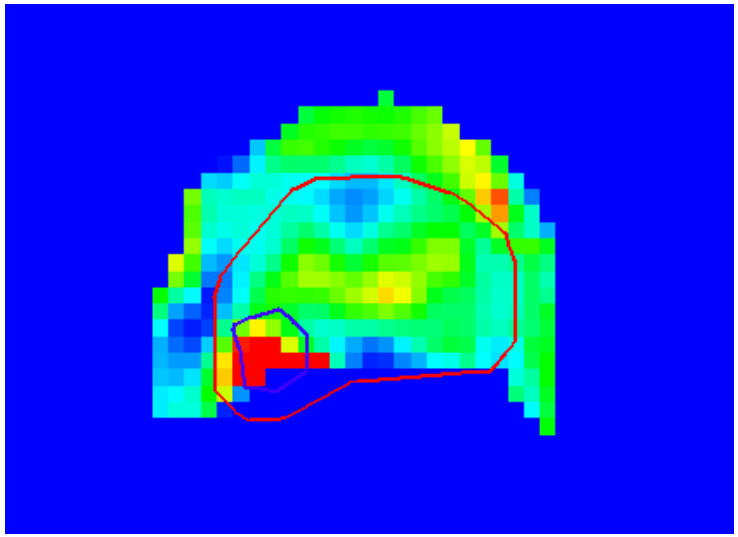
MRI T2-weighted



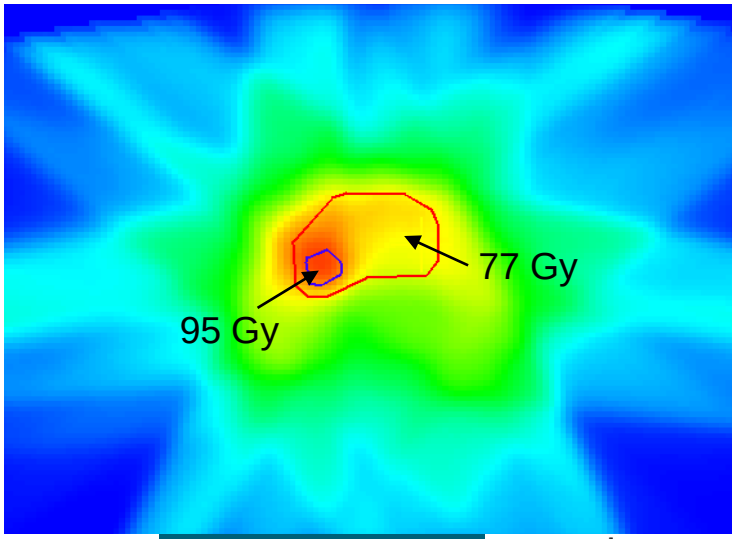
Diffusion-weighted-MRI, ADC-map



DCE-MRI, k-trans map

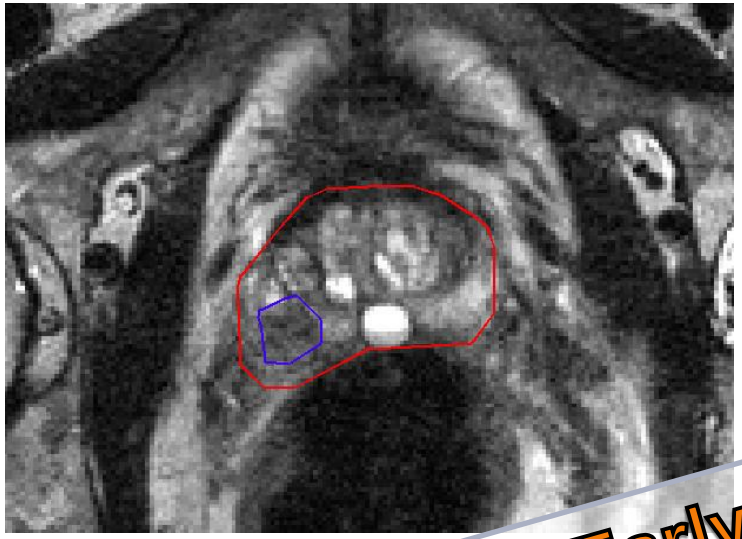


Dose distribution

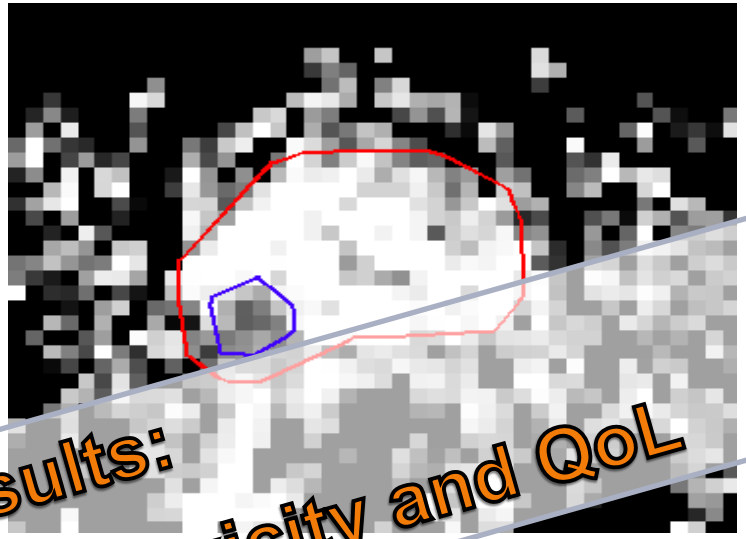


Flame study

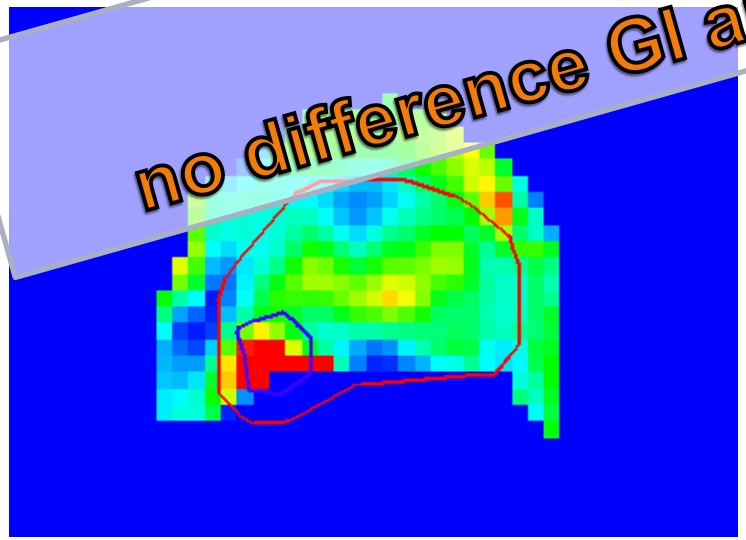
MRI-T2 weighted



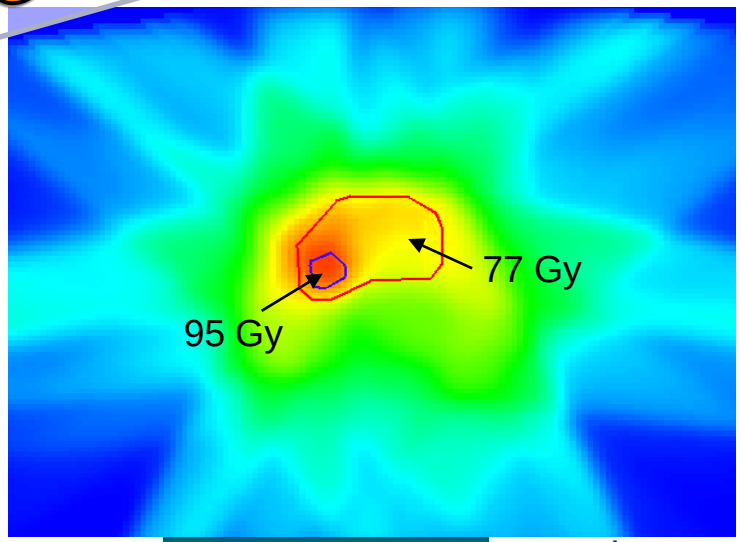
Diffusion-weighted-MRI, ADC-map



DCE-MRI, k-trans map



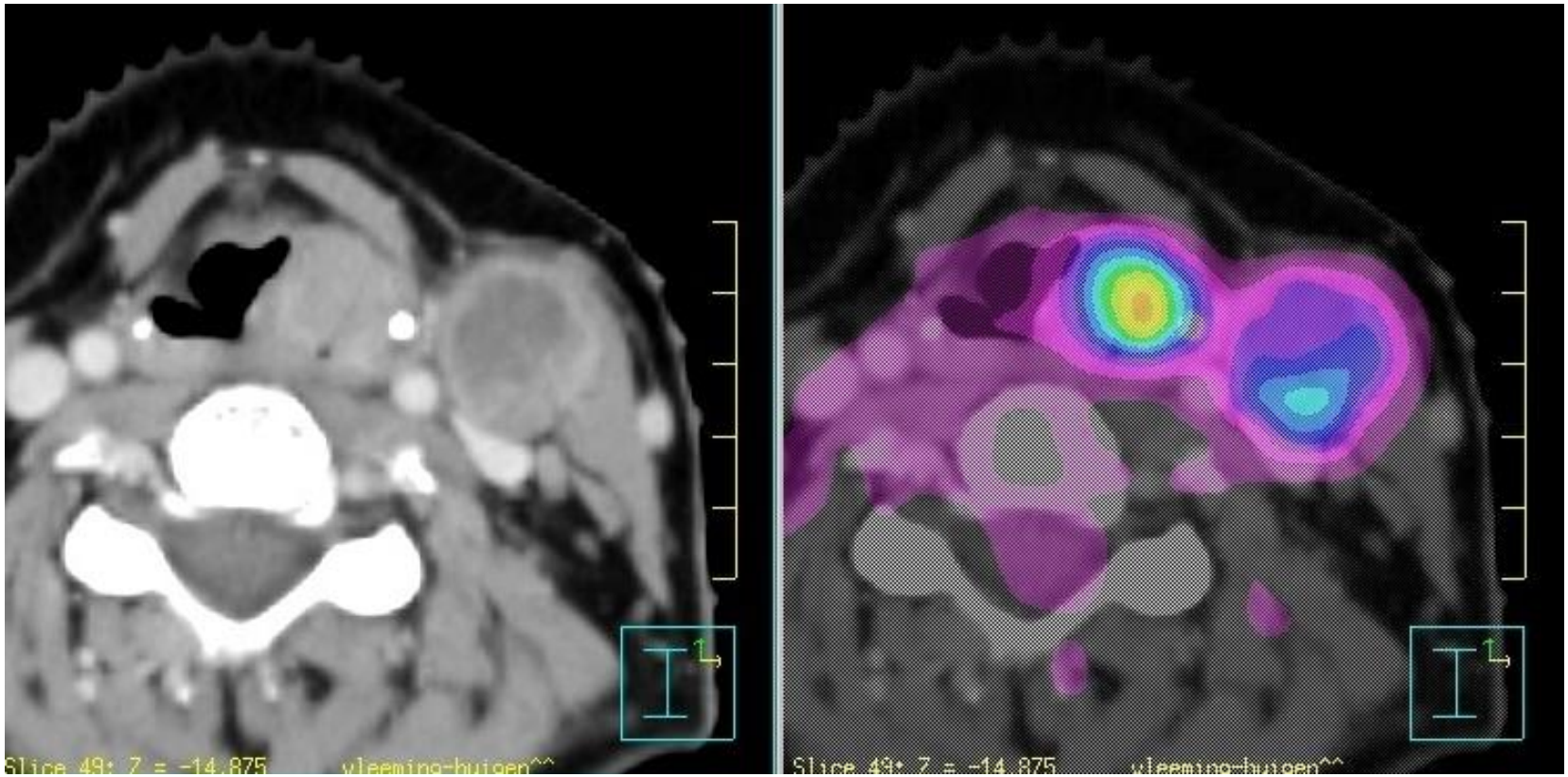
Dose distribution



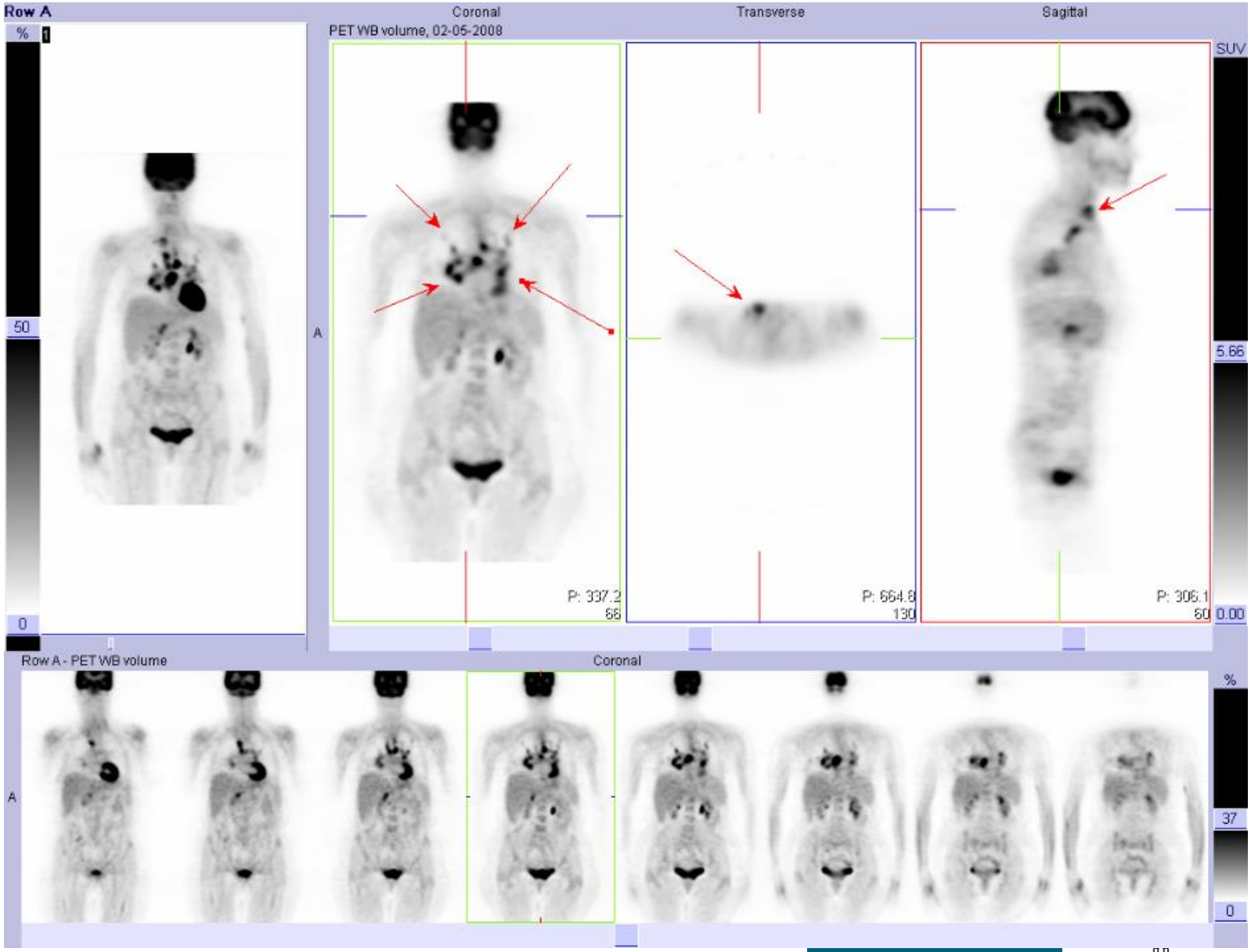
Early results:

no difference GI and GU toxicity and QoL

PET/CT for head and neck cancer



FDG-PET for staging of non-small-cell lung cancer



FDG-PET in the preoperative assessment of suspected non-small-cell lung cancer: PLUS trial

	Conventional workup (n=96)	Conventional workup + PET (n=92)
No thoracotomy	**18 (19%)**	**32 (35%)**
confirmed N2/3	10	18
confirmed distant metastases	1	7
benign primary lesion	2	3
other tumor	2	1
intercurrent morbidity, refusal	3	3
Thoracotomy	**78 (81%)**	**60 (65%)**
non-futile thoracotomy	**39 (41%)**	**41 (44%)**
futile thoracotomy	**39 (41%)**	**19 (21%)**
benign	7	2
explorative thoracotomy	1	1
IIIA-N2	6	4
IIIB	6	2
recurrence or death < 1 year	19	10

Van Tinteren et al. Lancet 2002

FDG-PET
vs
CT, MRI and Ultrasound for staging of the neck

	N	Sensitivity	Specificity	Accuracy
	106			
PET		70%	82%	75%
CT		66%	74%	70%
MRI		64%	69%	66%
Ultrasound		84%	68%	76%

Stuckensen et al. J Cranio-Maxillofac Surg 2000

FDG-PET
vs.
CT, MRI and Ultrasound for staging of the neck
-
Meta-analysis

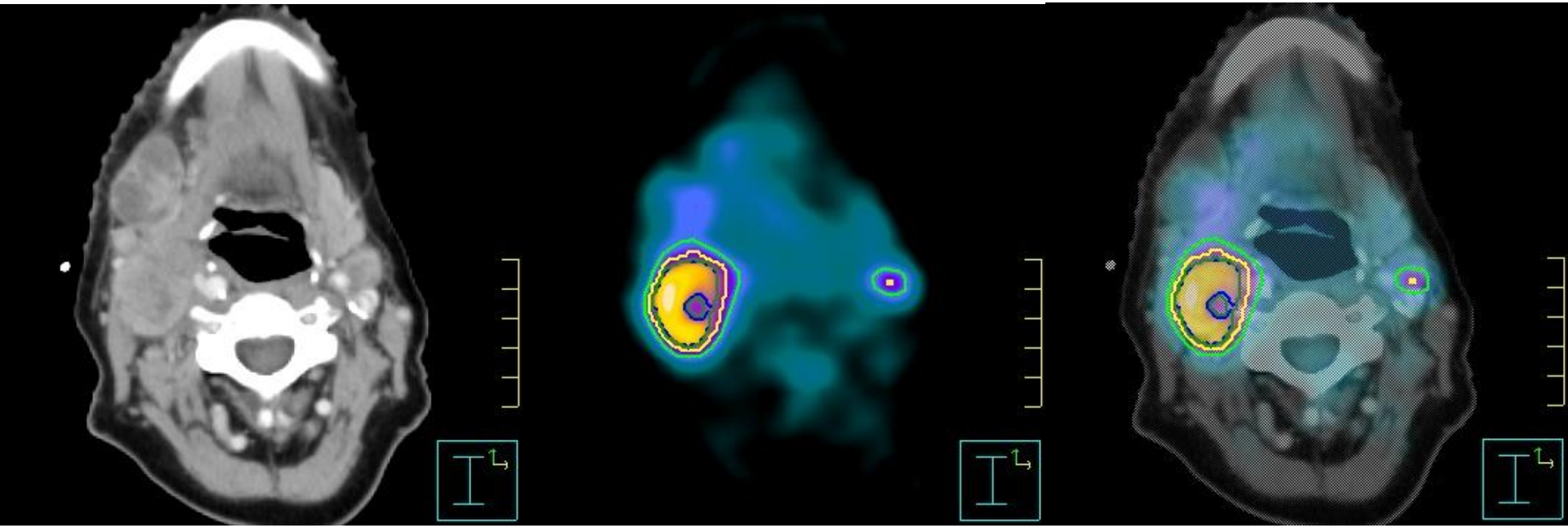
Diagnostic methods compared	Sensitivity	Specificity
CT	74% (61-83)	76% (68-83)
PET	82% (72-89)	86% (78-91)
MRI	78% (54-92)	80% (67-88)
PET	78% (64-87)	85% (79-90)
CT+MRI	66% (44-82)	76% (53-90)
PET	73% (58-84)	89% (84-93)
Ultrasound FNA	42% (10-97)	96% (76-99)
PET	45% (27-64)	88% (76-95)

Kyzas et al. J Natl Cancer Inst 2008

FDG-PET

for identification of lymph node metastases

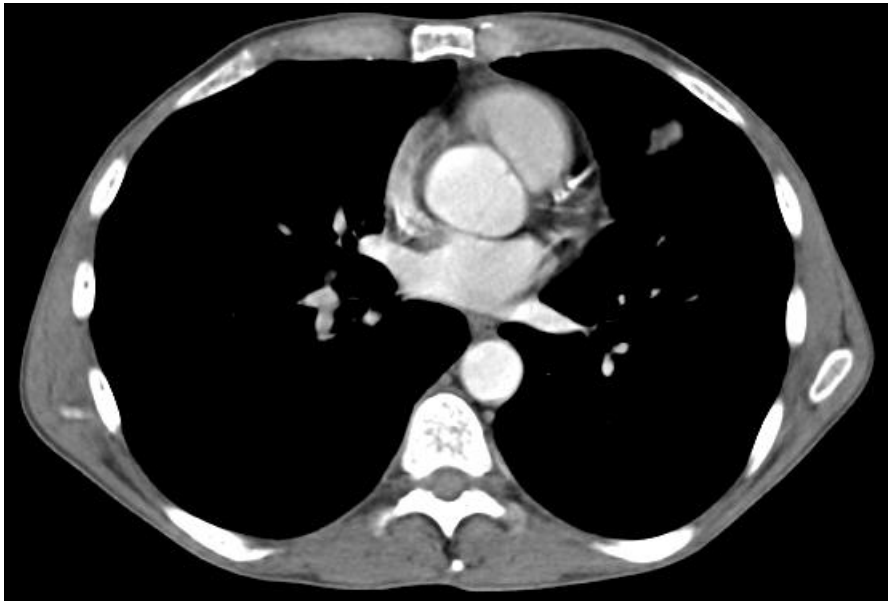
- pitfalls -

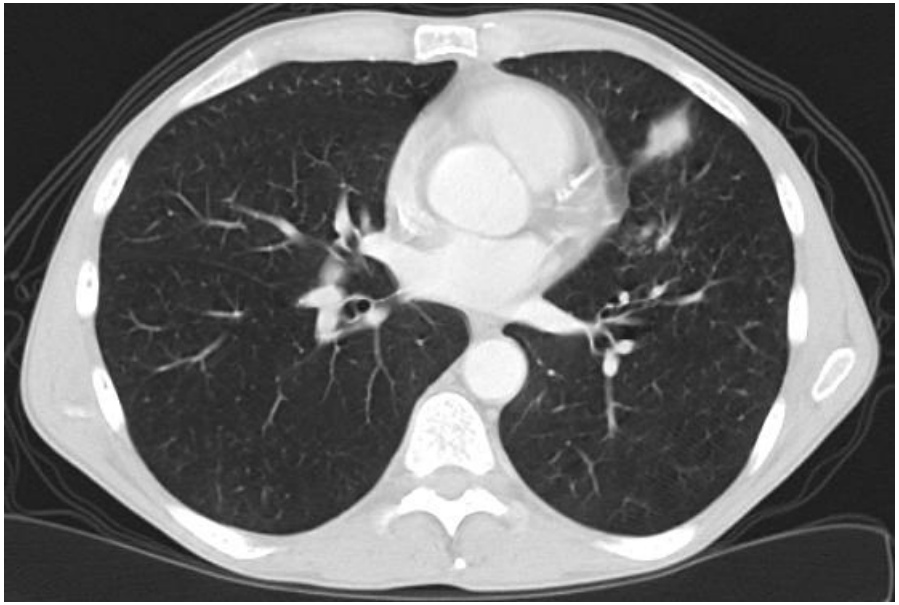


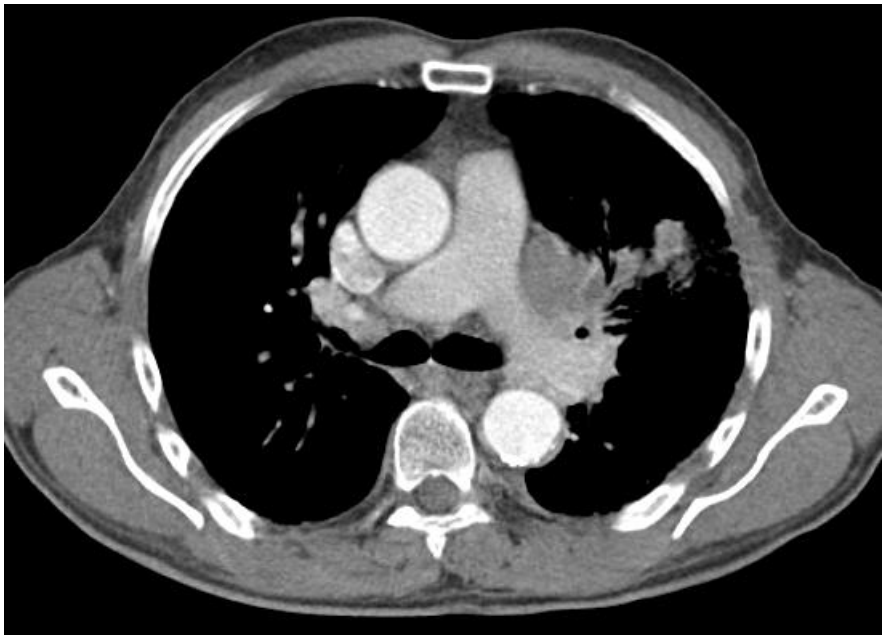
Delineation of target volumes

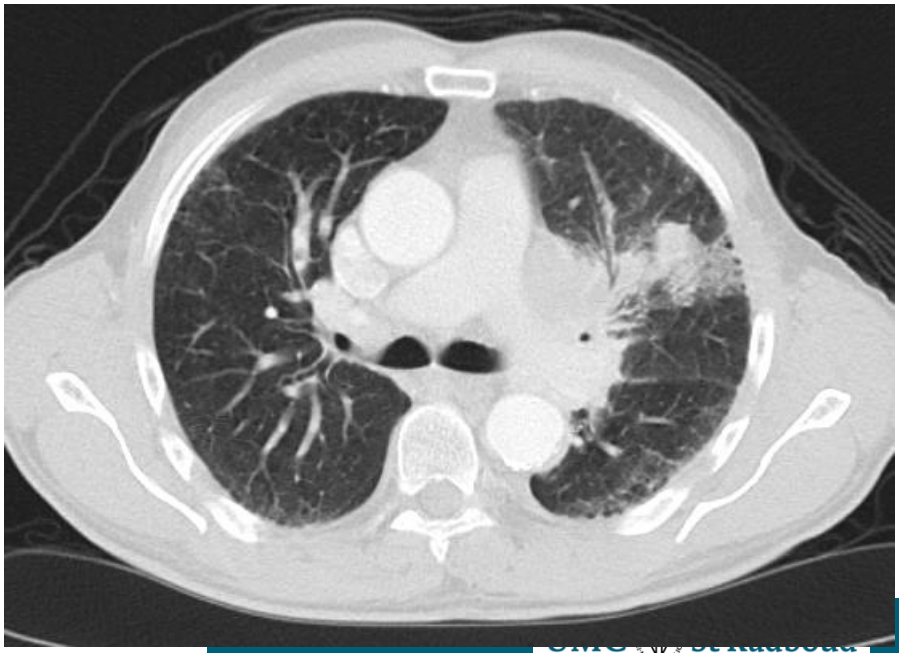
- Imaging modalities
- Inter-observer variations
- Segmentation methods
- Organ motion
- Changes during therapy

Choose the proper window settings

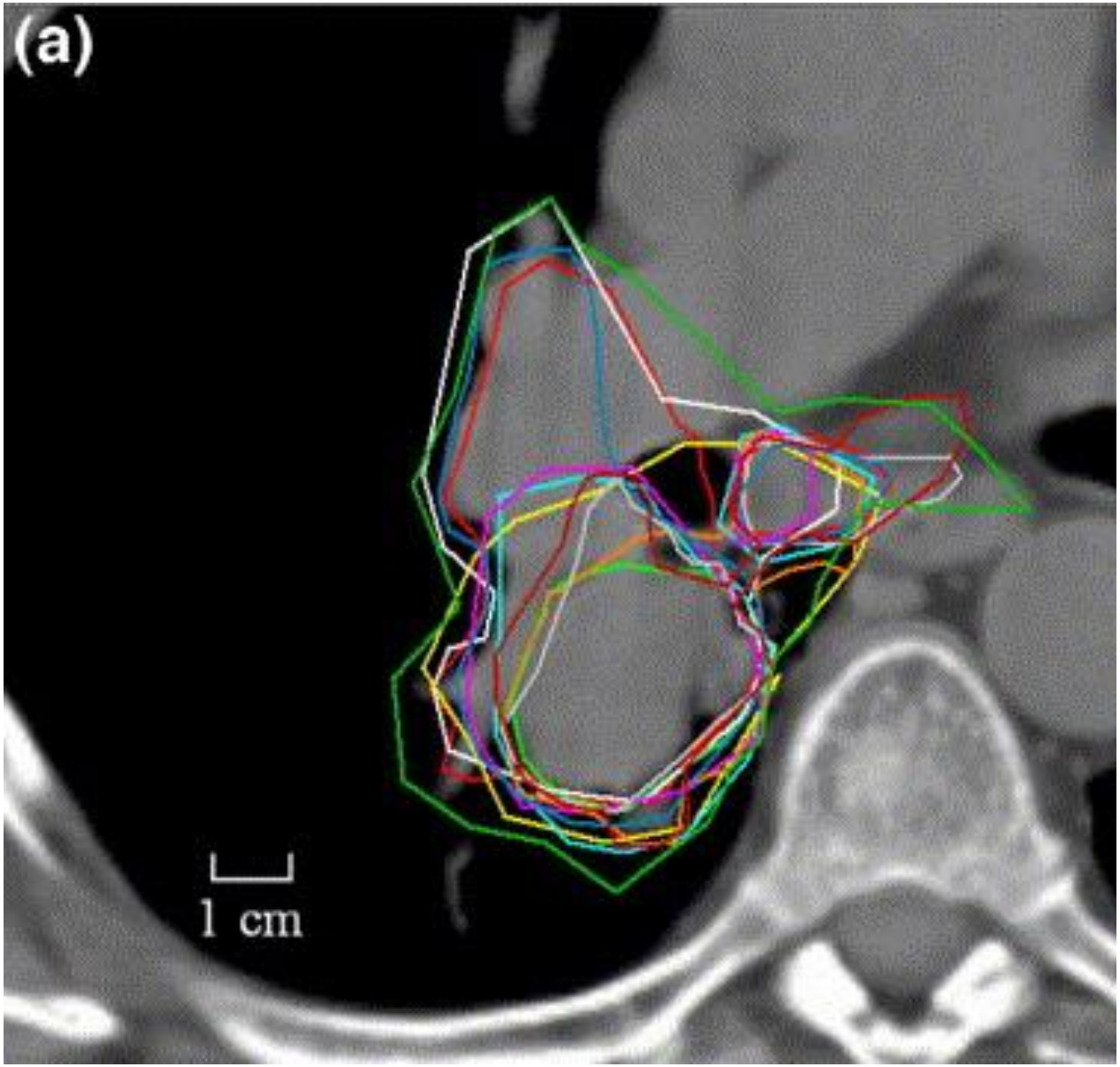






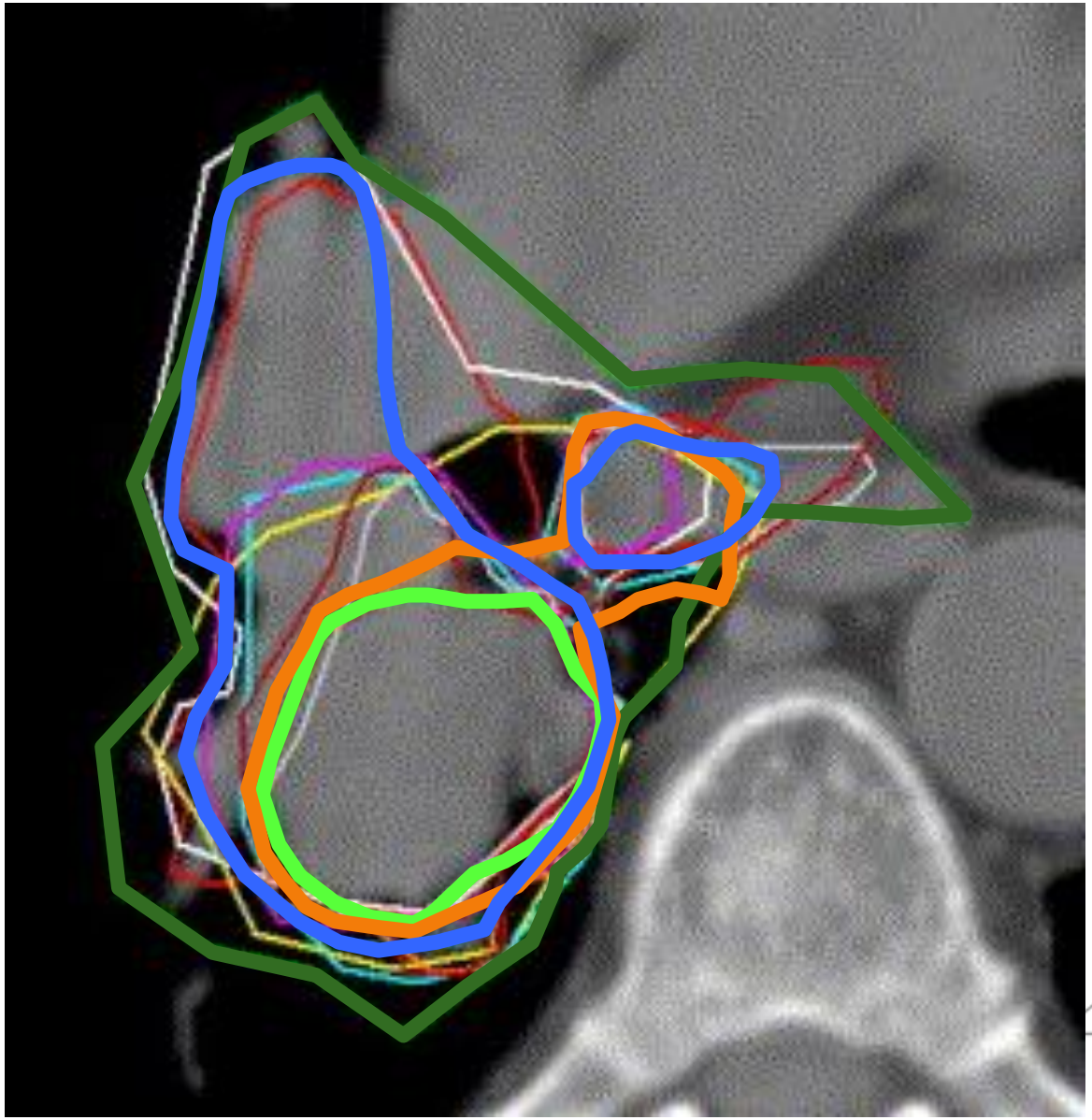


Inter-observer variations



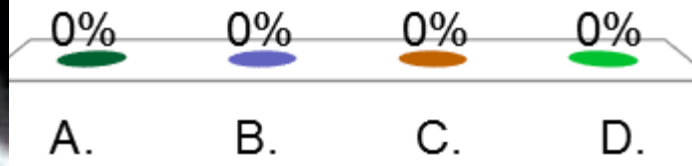
Steenbakkers, Int J Radiat Oncol Biol Phys 2006

Inter-observer variations



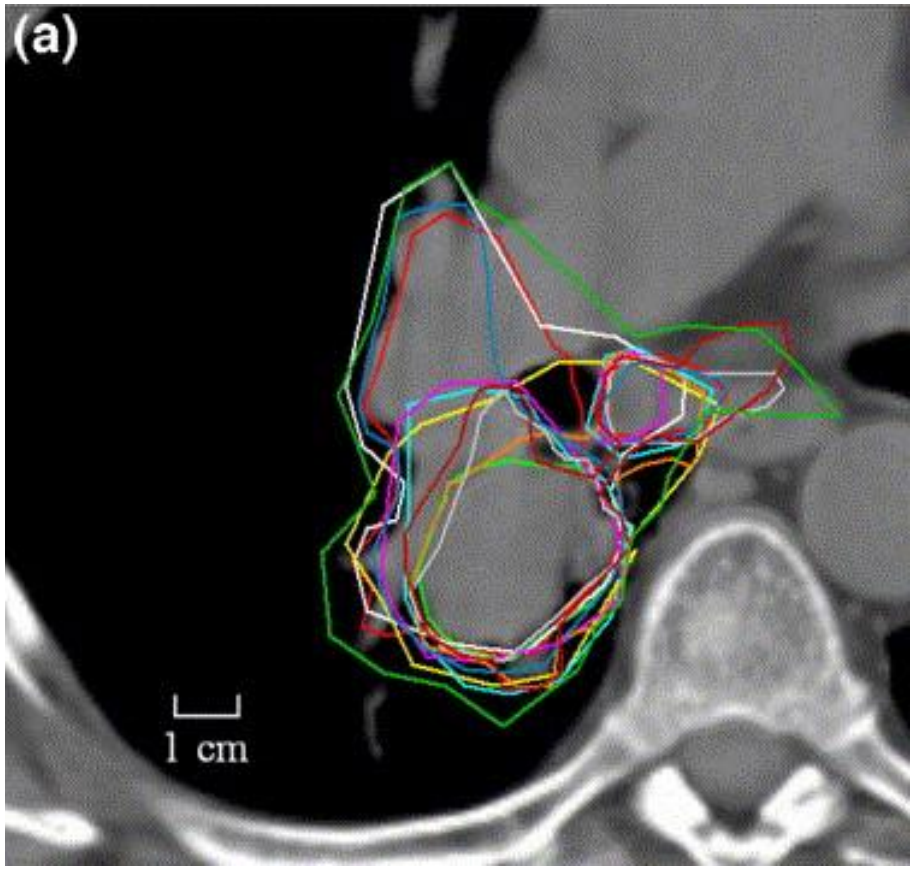
Who is right?

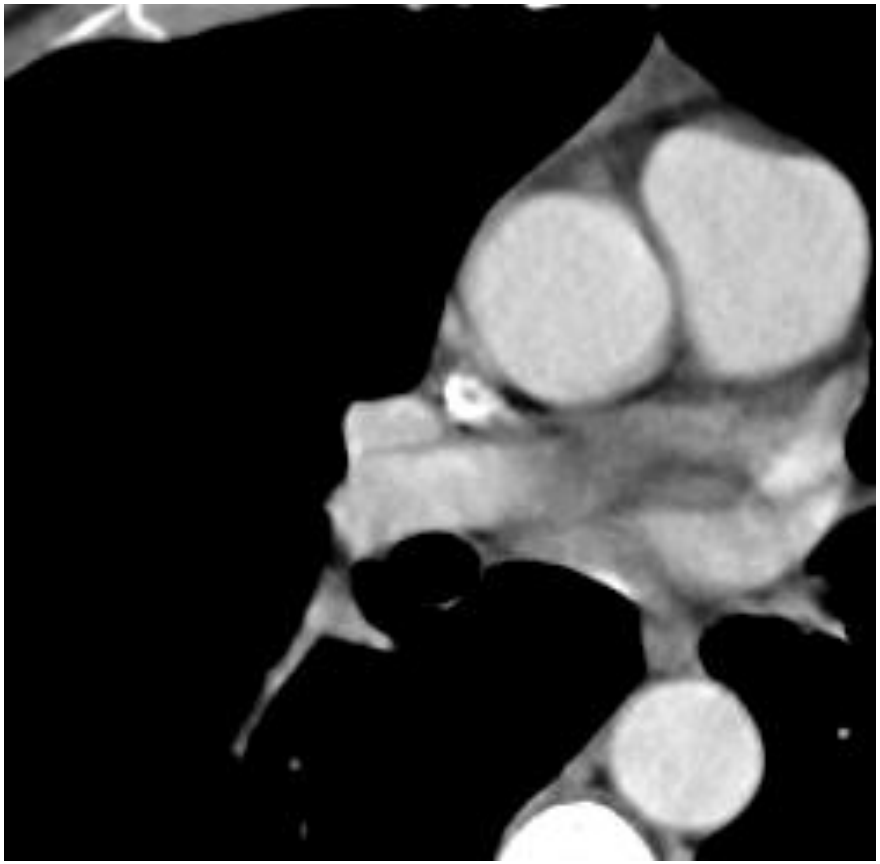
A. Green
B. Blue
C. Orange
D. Light green



Steenbakkers, Int J Radiat Oncol Biol Phys 2006

Inter-observer variations



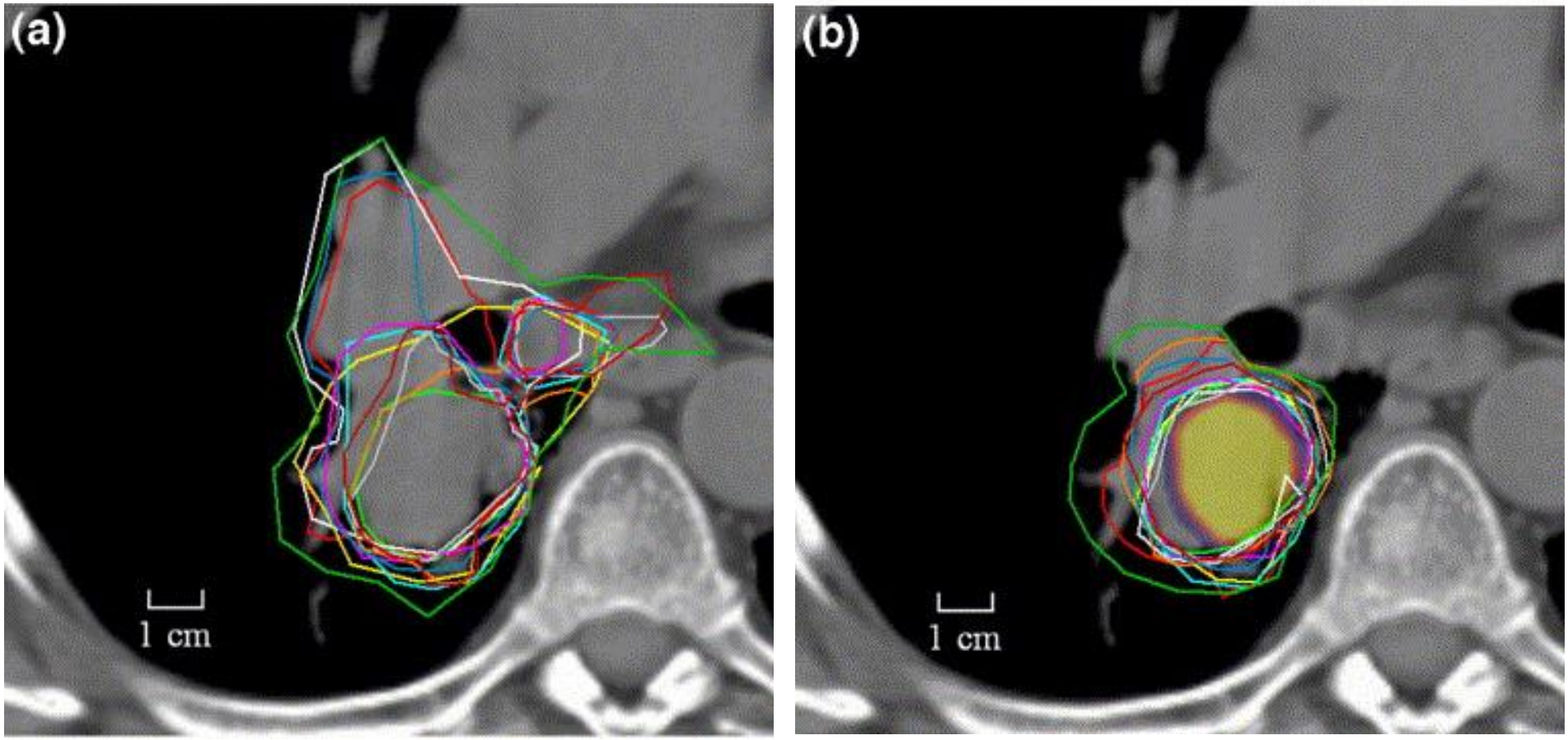


Steenbakkers, Int J Radiat Oncol Biol Phys 2006

Inter-observer variations

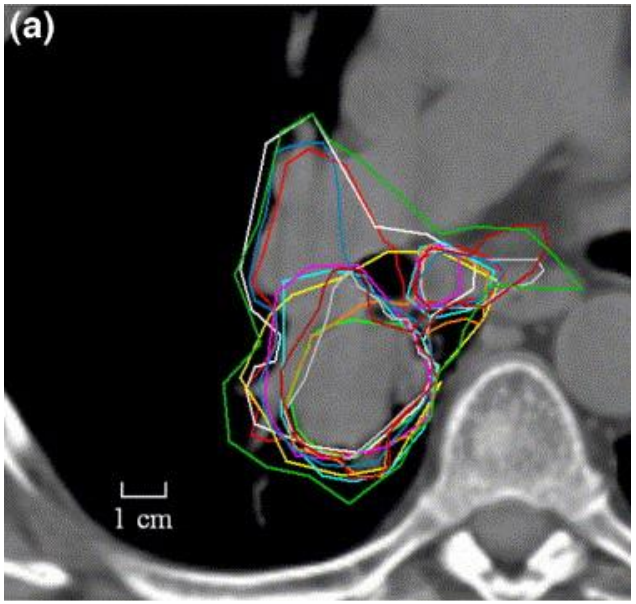
CT

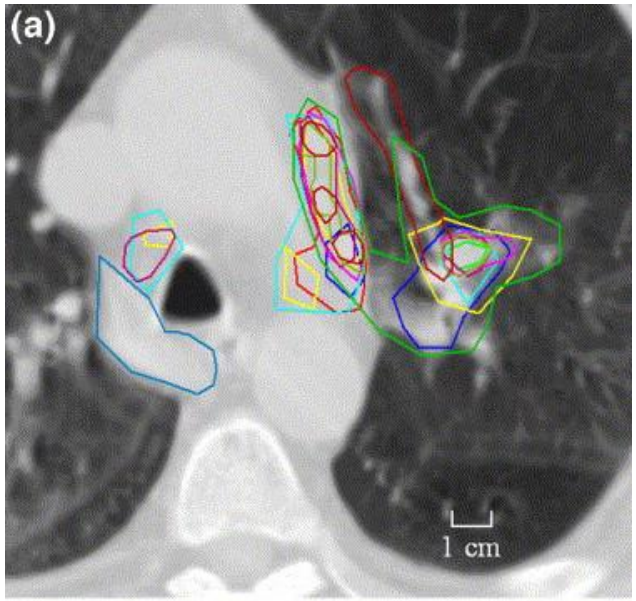
PET/CT



Steenbakkers, Int J Radiat Oncol Biol Phys 2006

Inter-observer variations



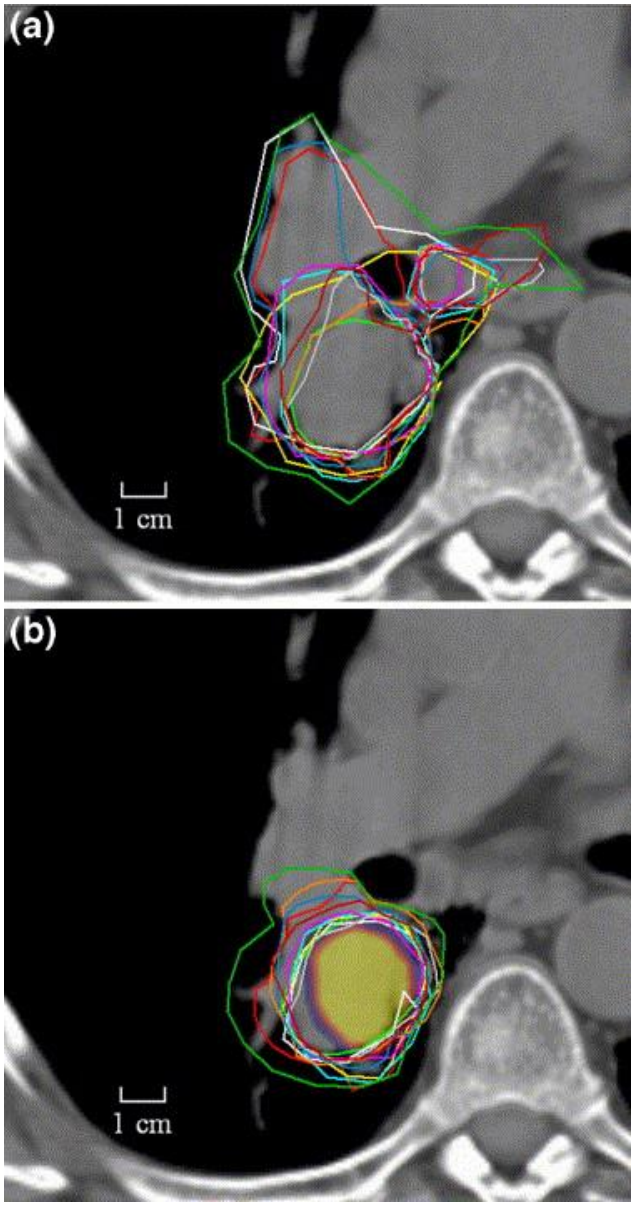


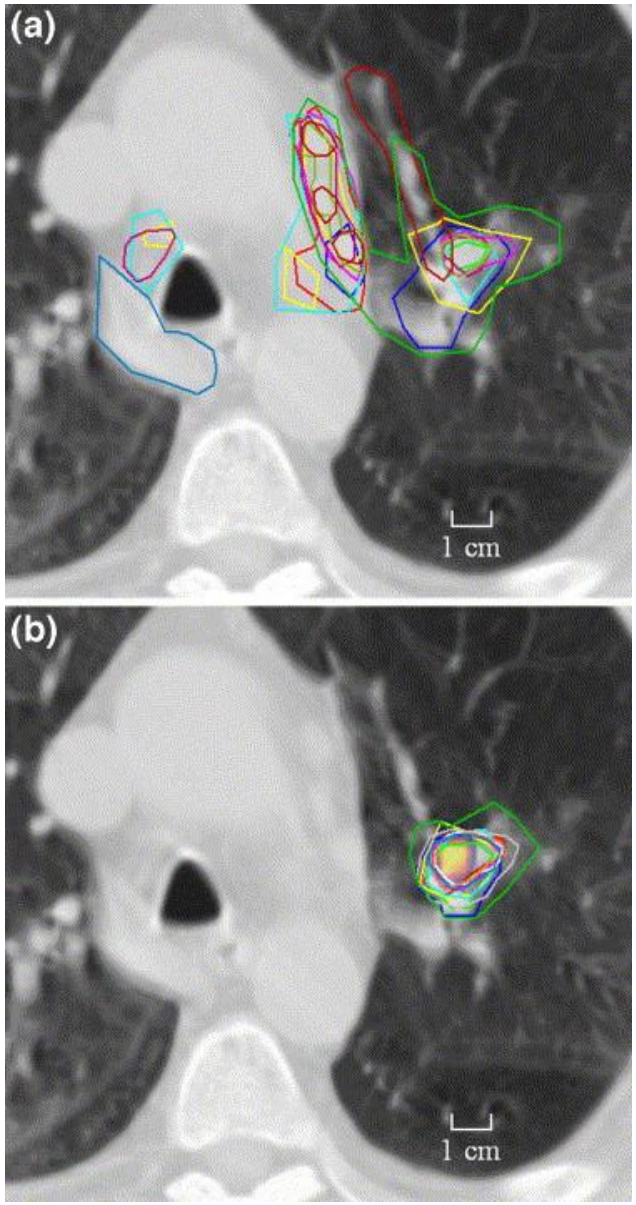
Steenbakkers, Int J Radiat Oncol Biol Phys 2006

Inter-observer variations

CT

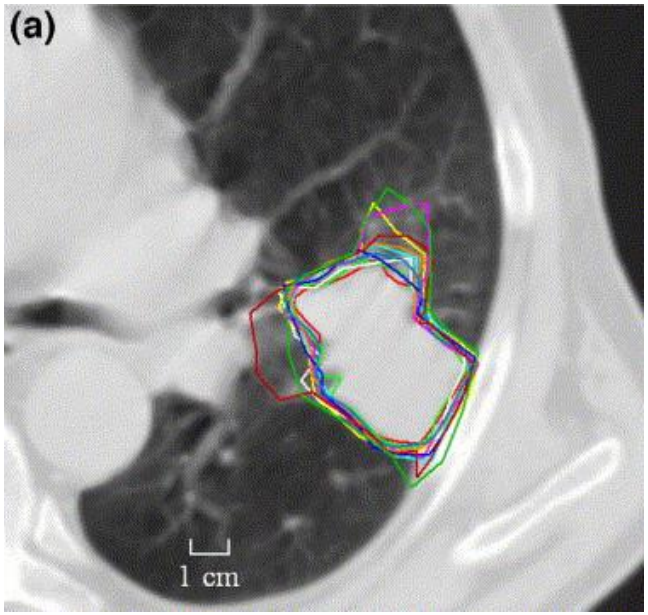
CT + PET





Steenbakkers, Int J Radiat Oncol Biol Phys 2006

Inter-observer variations

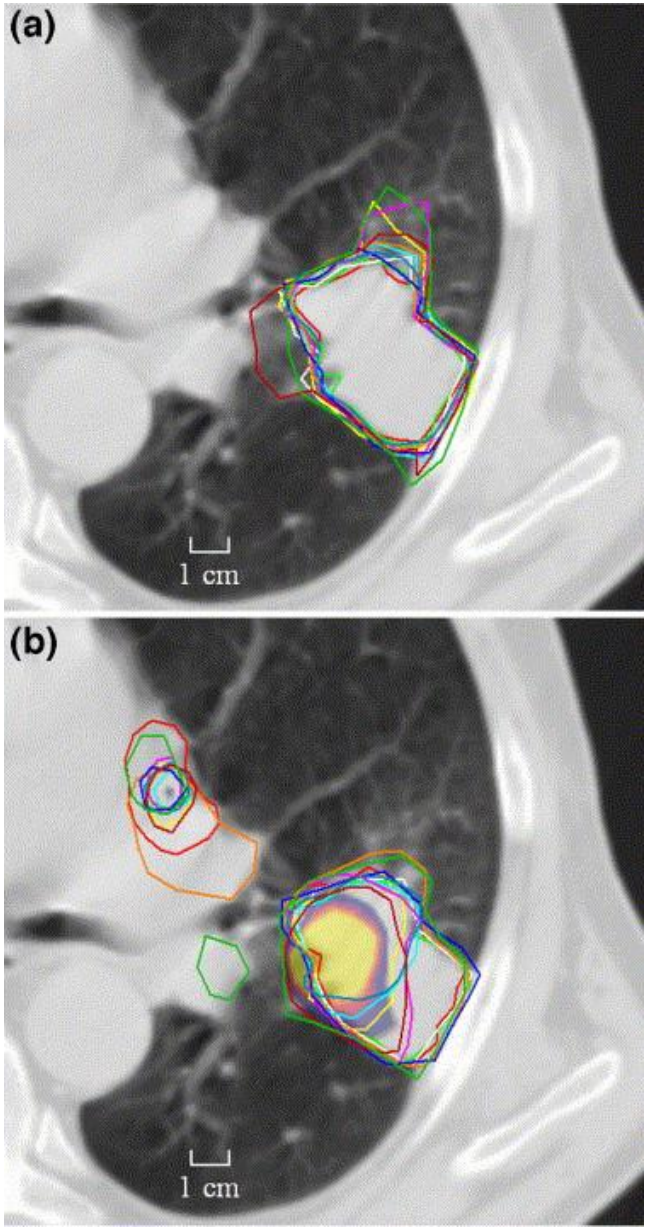


Steenbakkers, Int J Radiat Oncol Biol Phys 2006

Inter-observer variations

CT

CT
+
PET

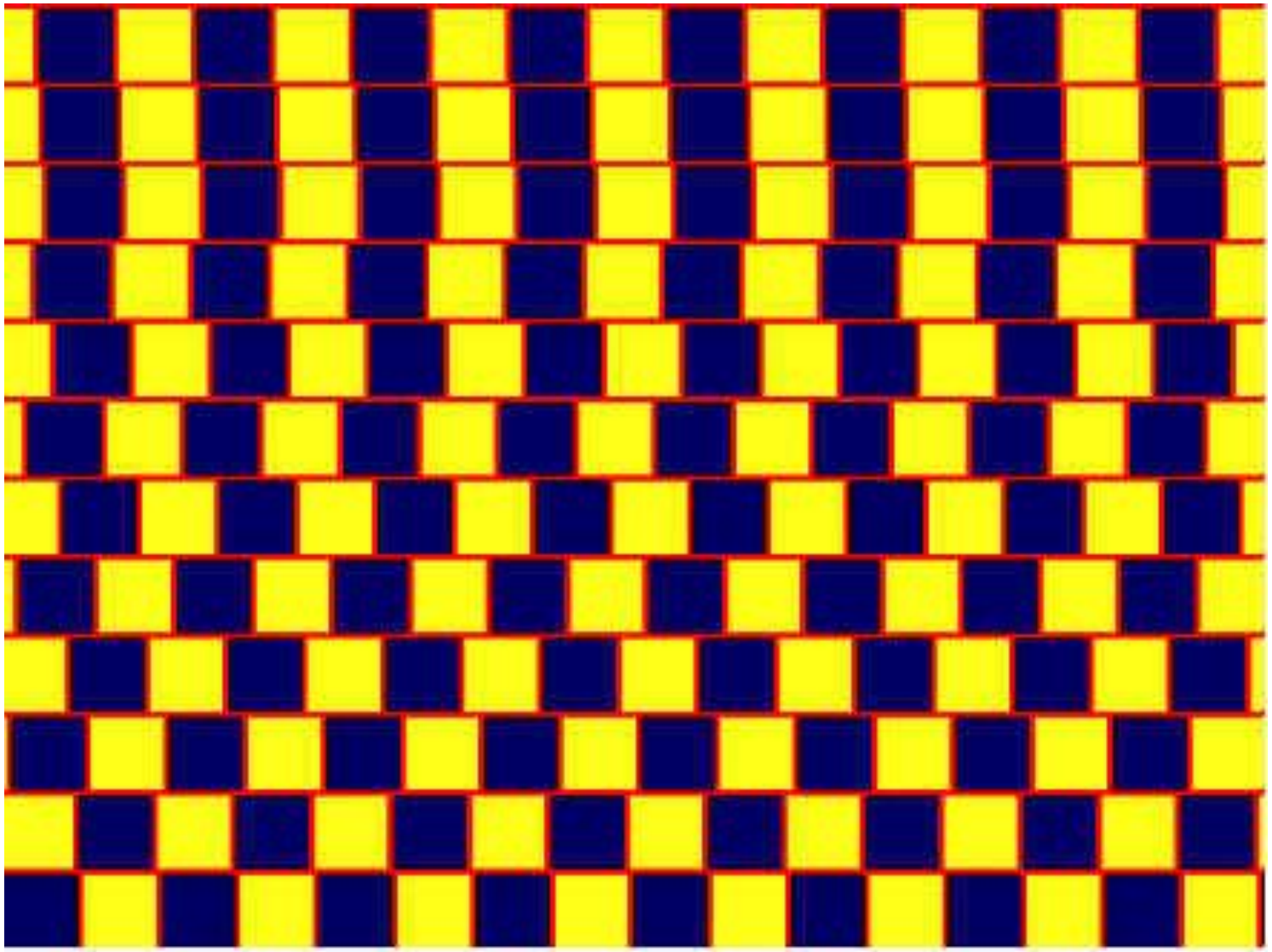


Steenbakkers, Int J Radiat Oncol Biol Phys 2006

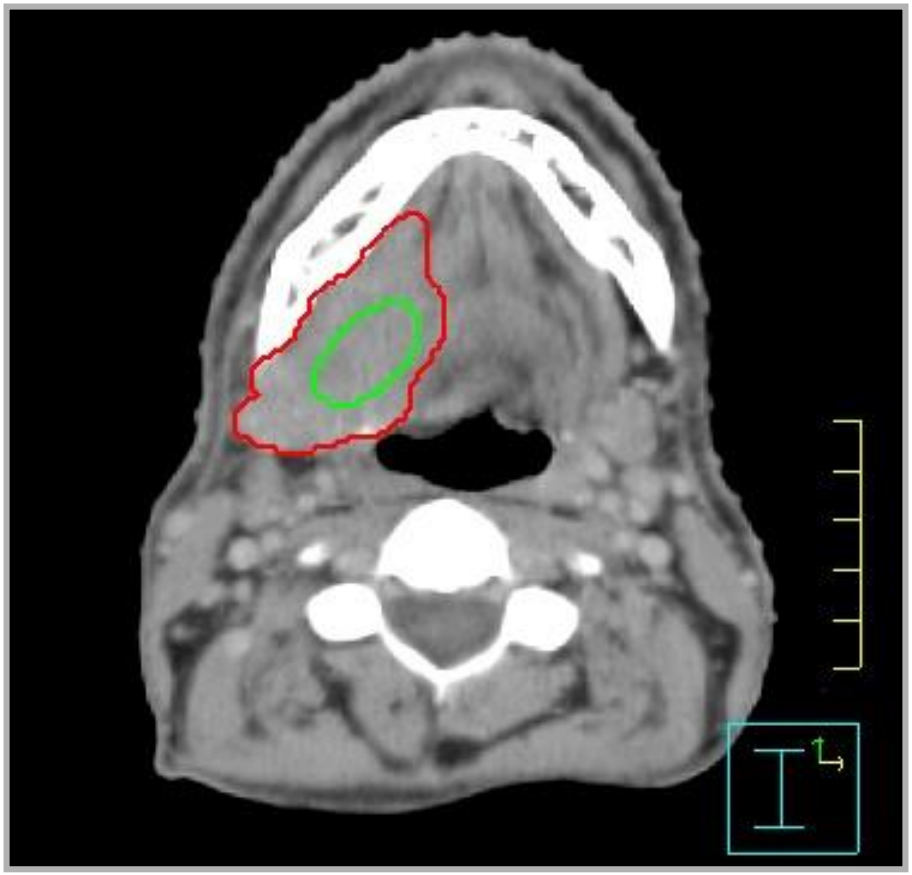
The human brain …

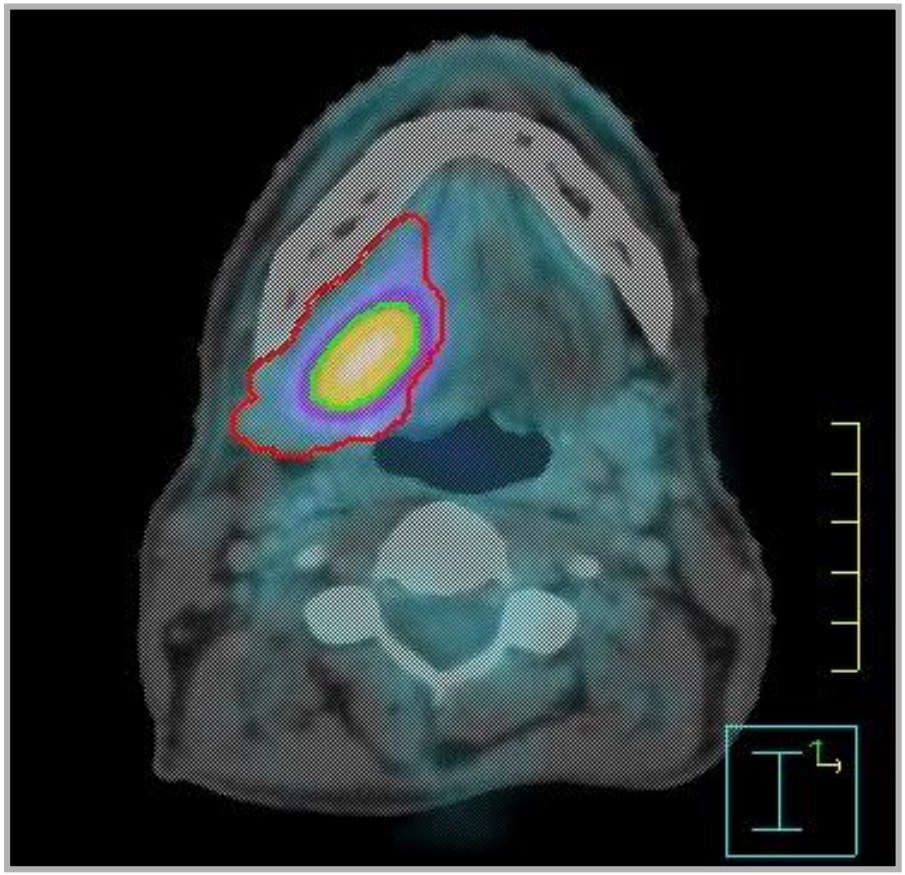
… tricks us whenever it can!

... parallel or not? What is the truth?



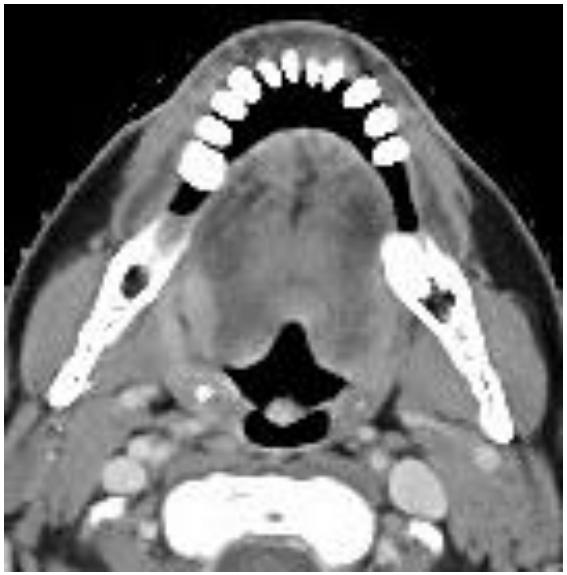
Delineation of tumor: what is the role of FDG-PET/CT?

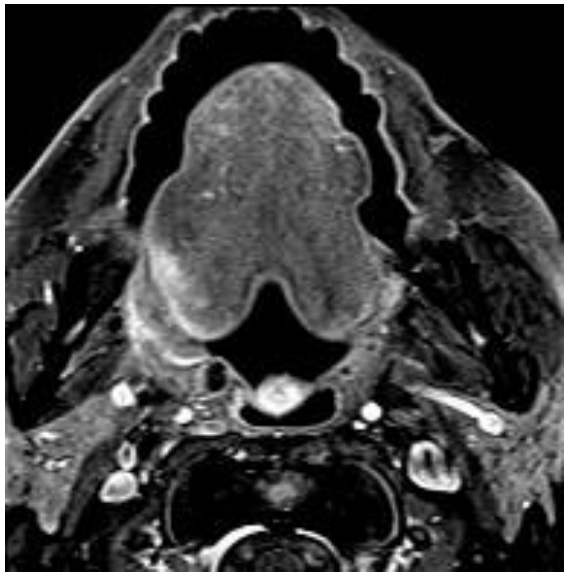


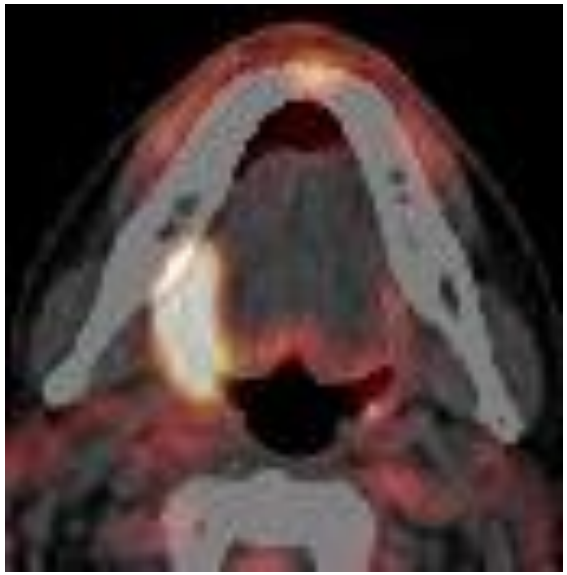


Schinagl et al. Cancer Imaging 2006

Delineation of head and neck tumors:

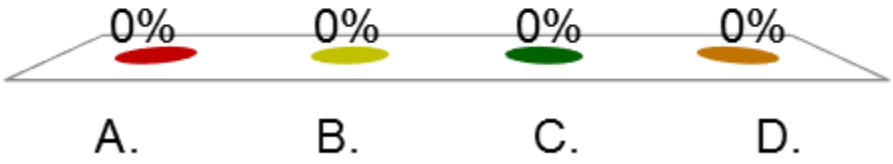






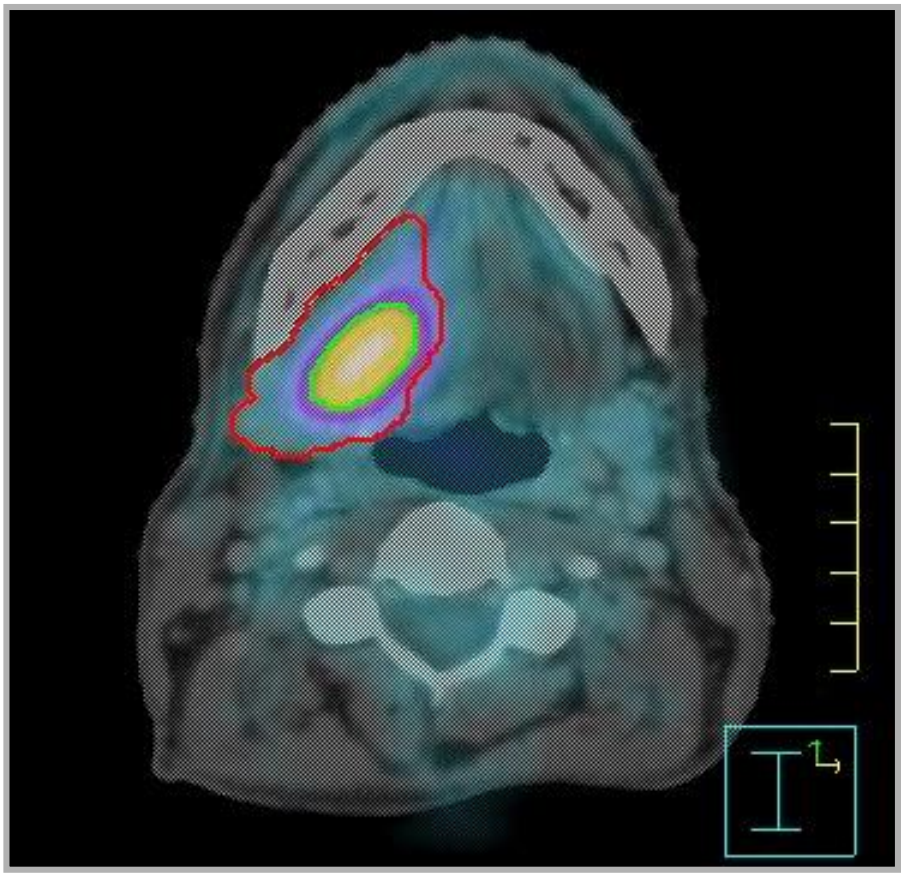
What do you use?

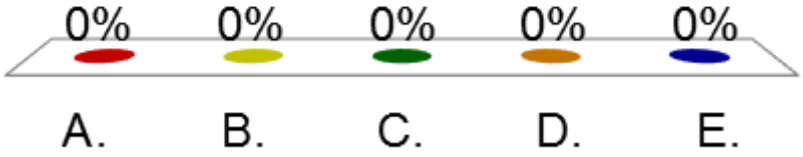
A. CT
B. CT and MRI
C. CT and PET
D. CT, MRI and PET



If you use PET for delineation, which segmentation method do you use?

A. visual
B. GTV - 40% - 50%
C. GTV - SUV
D. GTV - SBR
E. other



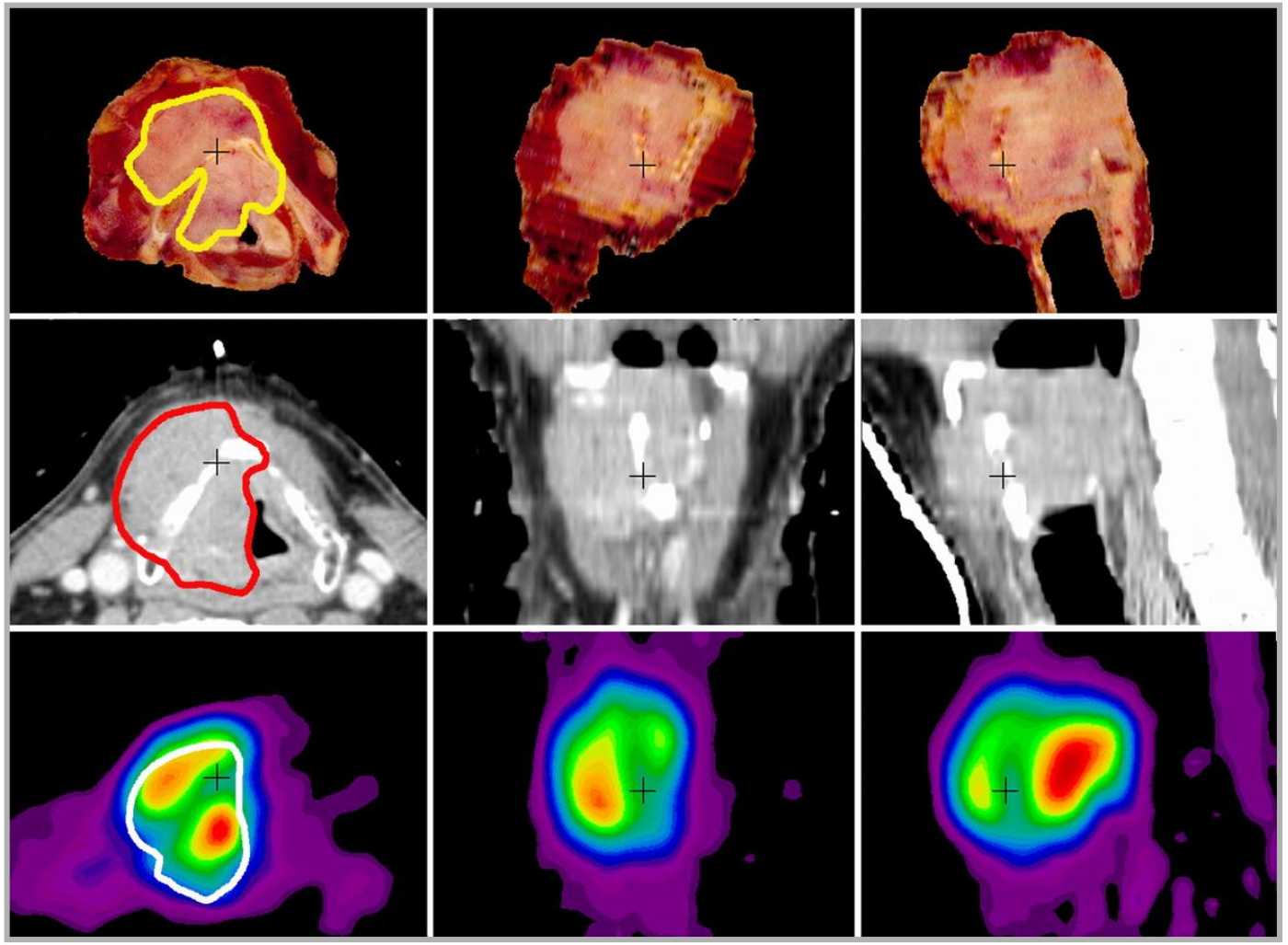


Assessment of tumor volume: validation of CT, MRI and FDG-PET

Surgical specimen

CT-scan

FDG-PET



Daisne, Radiology 2004

Assessment of tumor volume: validation of CT, MRI and FDG-PET

	Mean volume (cm^3)		
	oropharynx	larynx - hypopharynx	surgical specimen available
CT	32.0	21.4	20.8
MRI	27.9	21.4	23.8
PET	20.3	13.4	16.3
Specimen			13.4

In 9 patients for whom a surgical specimen was available, PET was most accurate for volume assessment

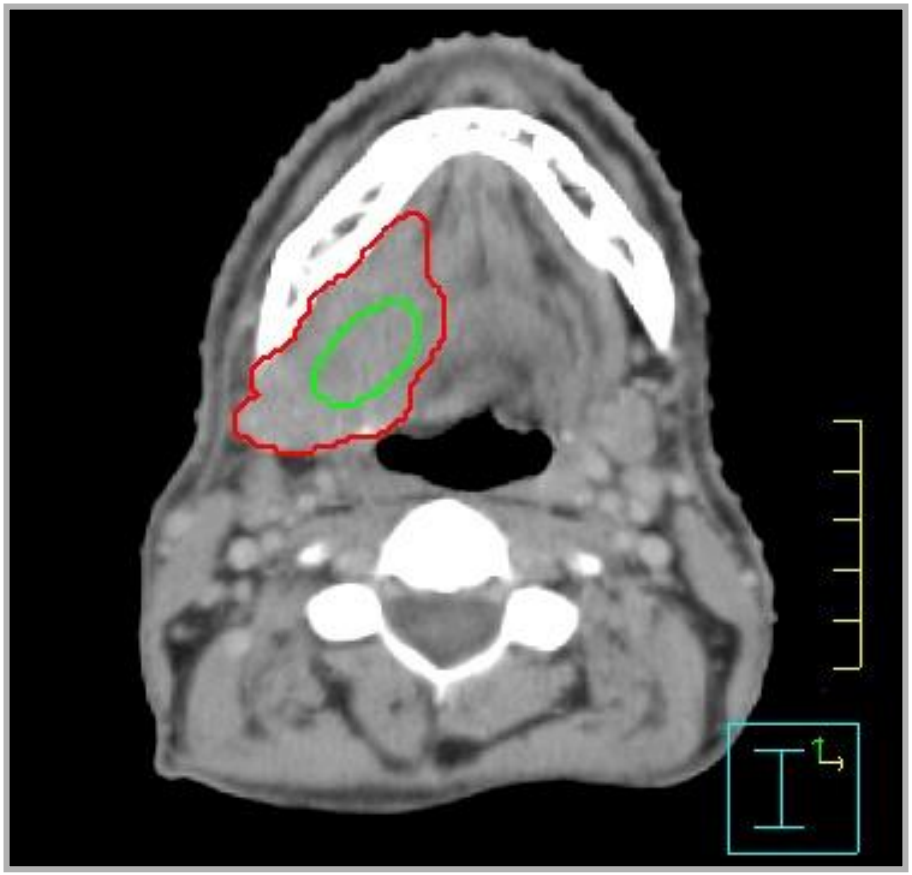
Daisne, Radiology 2004

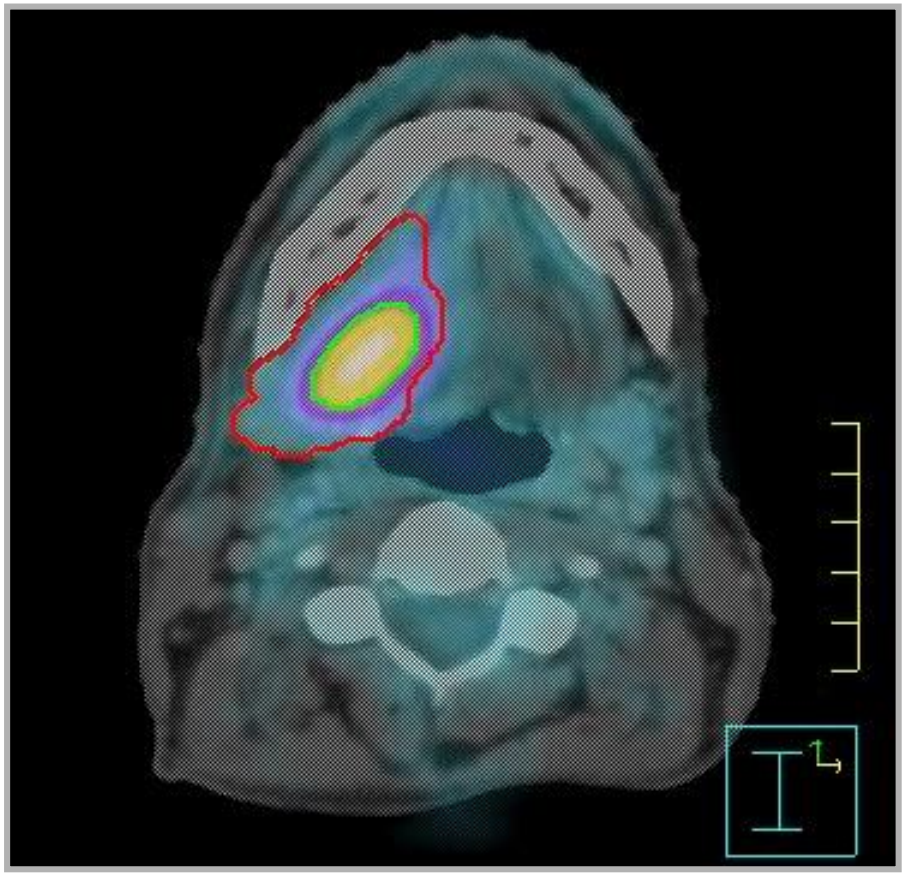
Mismatch of laryngeal tumor GTV's: CT, MRI and FDG-PET vs. surgical specimen

Pair	Volume (%) not identified by imaging study
Specimen to CT	10%
Specimen to MRI	9%
Specimen to PET	13%

Daisne, Radiology 2004

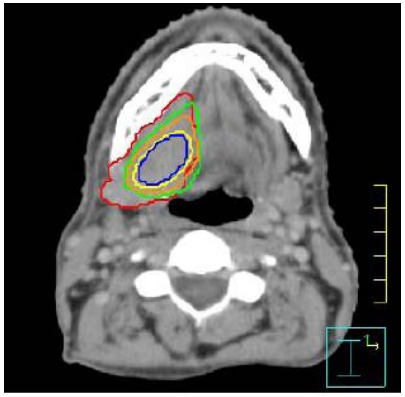
Segmentation of PET signal: which method?

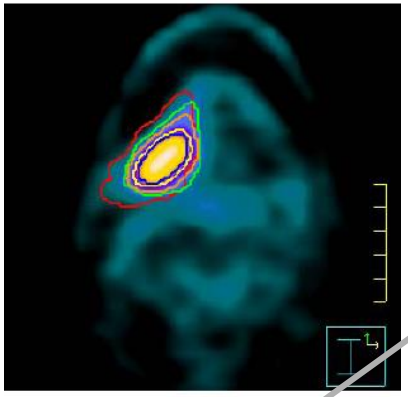


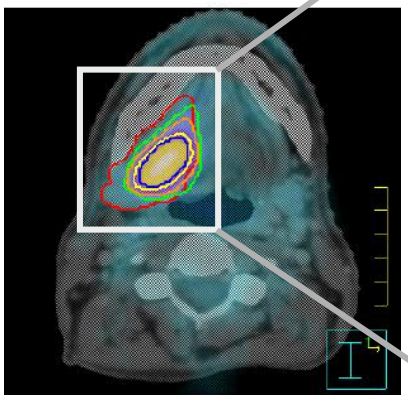


Schinagl et al. Cancer Imaging 2006

Segmentation of PET signal: which method?







Result of target volume definition is dependent on segmentation method:

CT:

GTV - CT 47.5 cm^3 (**red**)

PET:

GTV - visual 43.8 cm^3 (**green**)

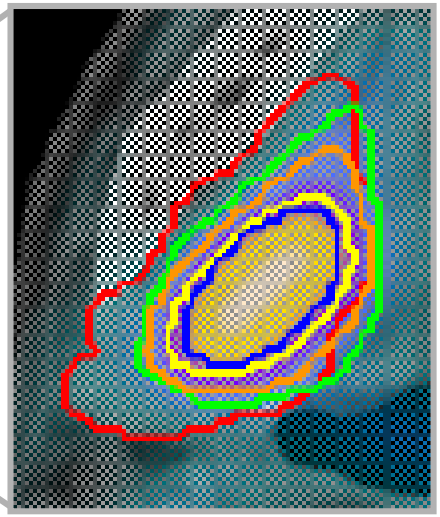
$GTV_{40\%}$ 20.1 cm^3 (**yellow**)

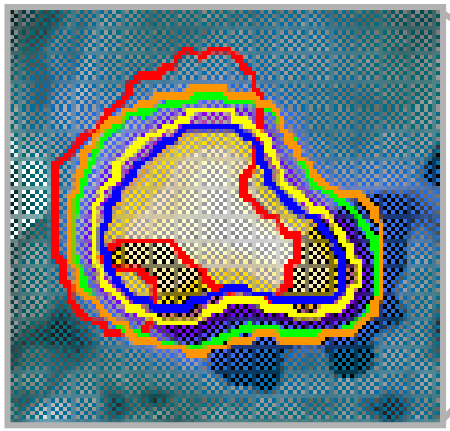
GTV_{SUV} 32.6 cm^3 (**orange**)

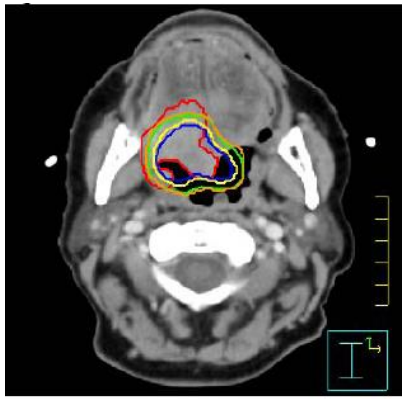
GTV_{SBR} 15.7 cm^3 (**blue**)

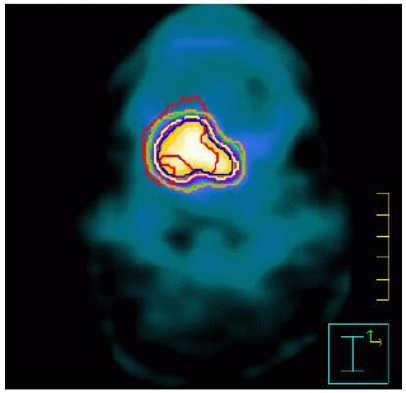
visual

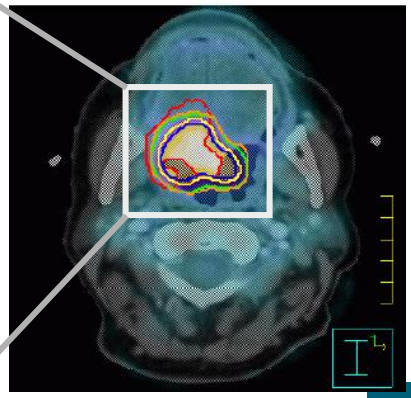
semi-automatic





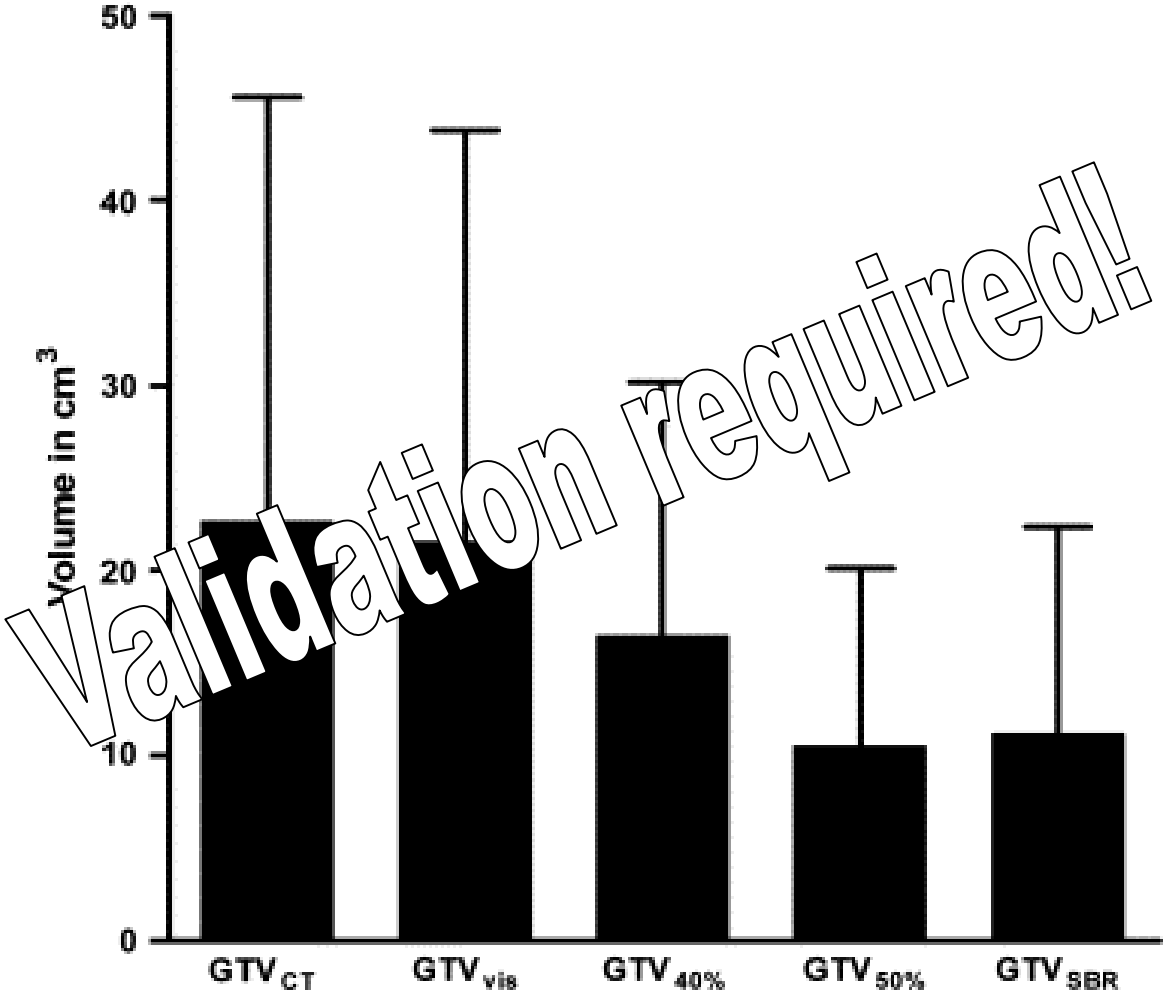






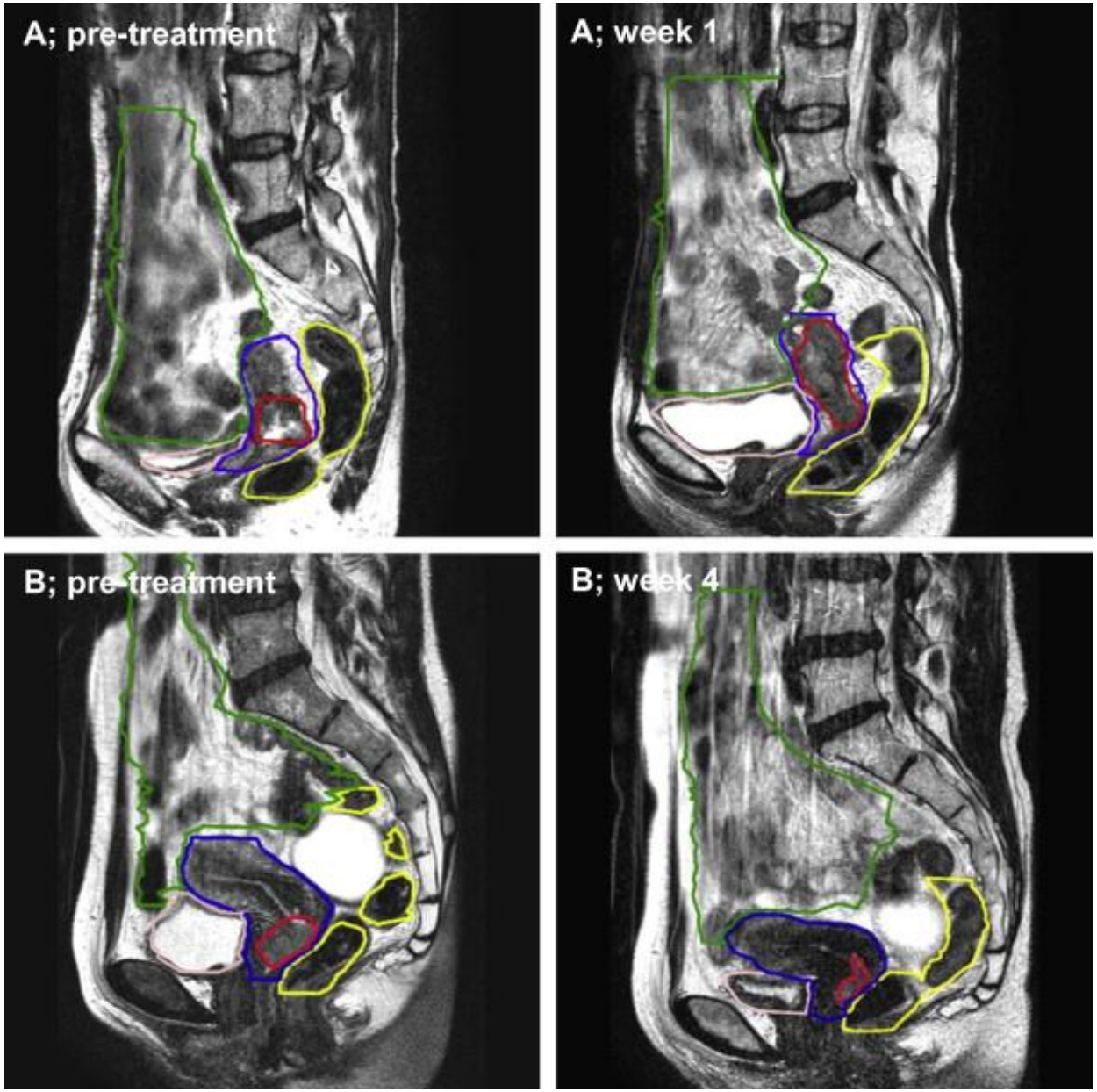
Schinagl, Int J Radiat Oncol Biol Phys 2007

Segmentation of PET signal: which method? significant differences in GTV volume (78 H&N patients)



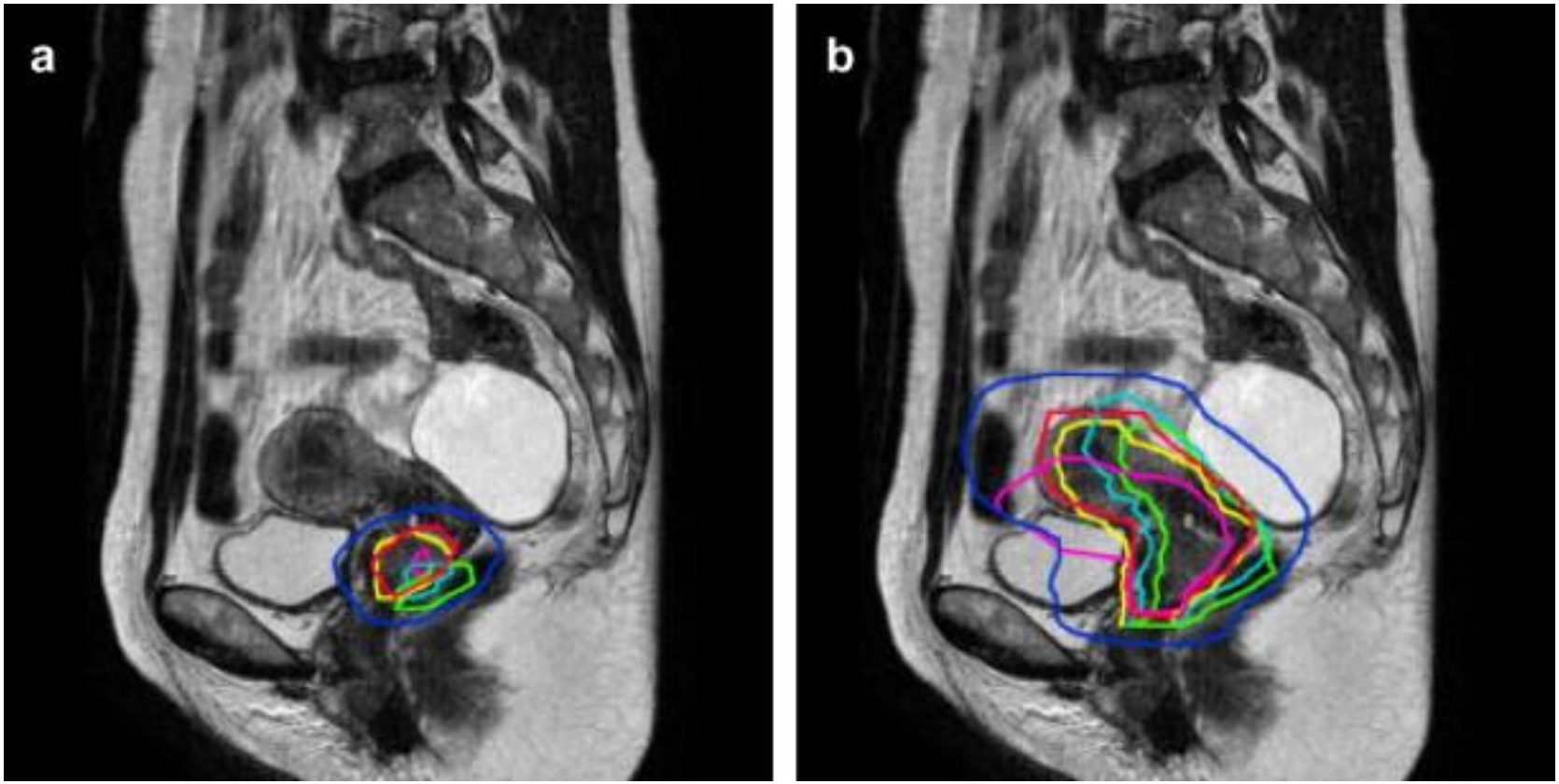
Schinagl, Int J Radiat Oncol Biol Phys 2007

Organ motion in the pelvis



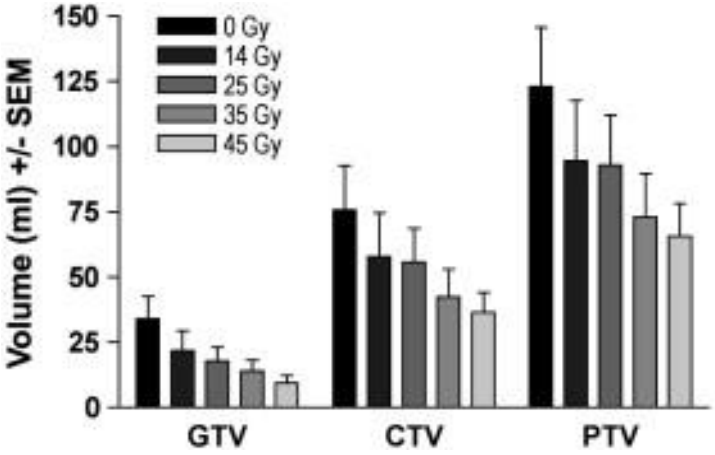
Van de Bunt, Radiother Oncol 2008

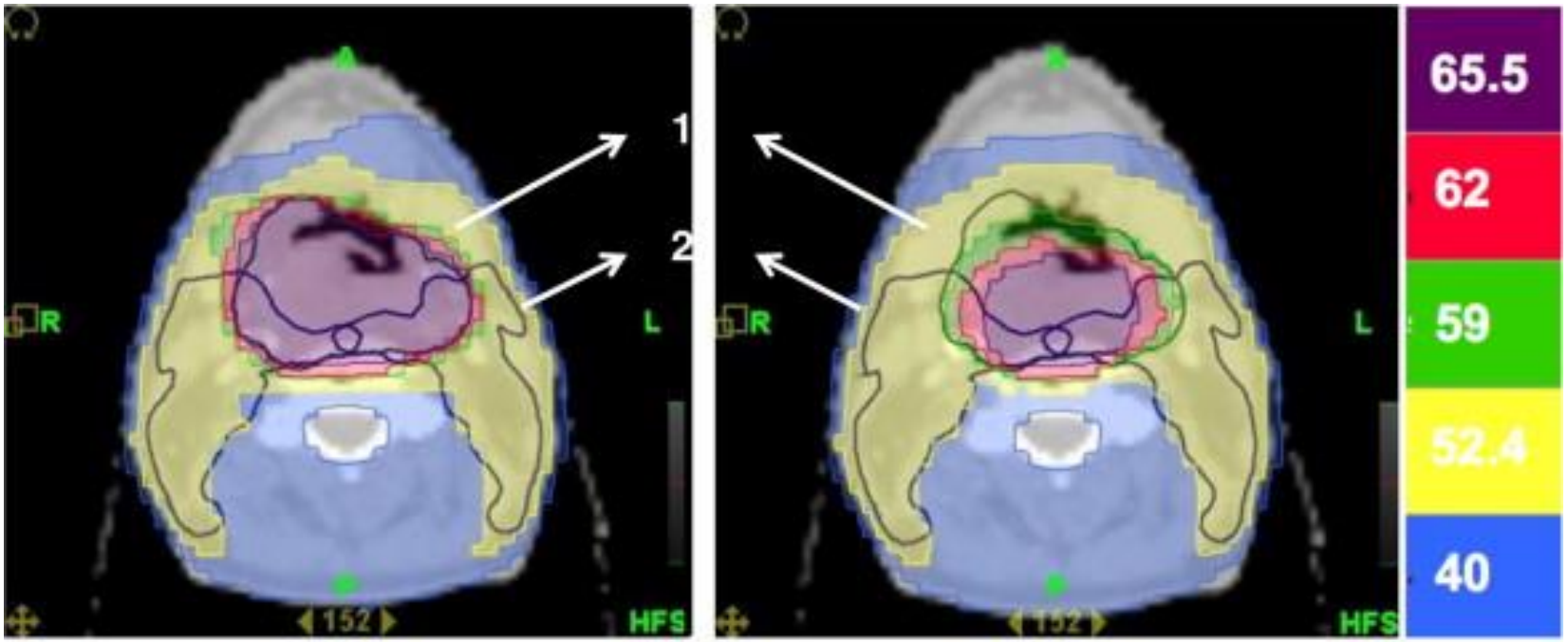
Changes in the (position of the) GTV and CTV during treatment



Van de Bunt, Radiother Oncol 2008

Image guided radiotherapy





1. Prophylactic tumor PTV
2. Prophylactic nodal PTV

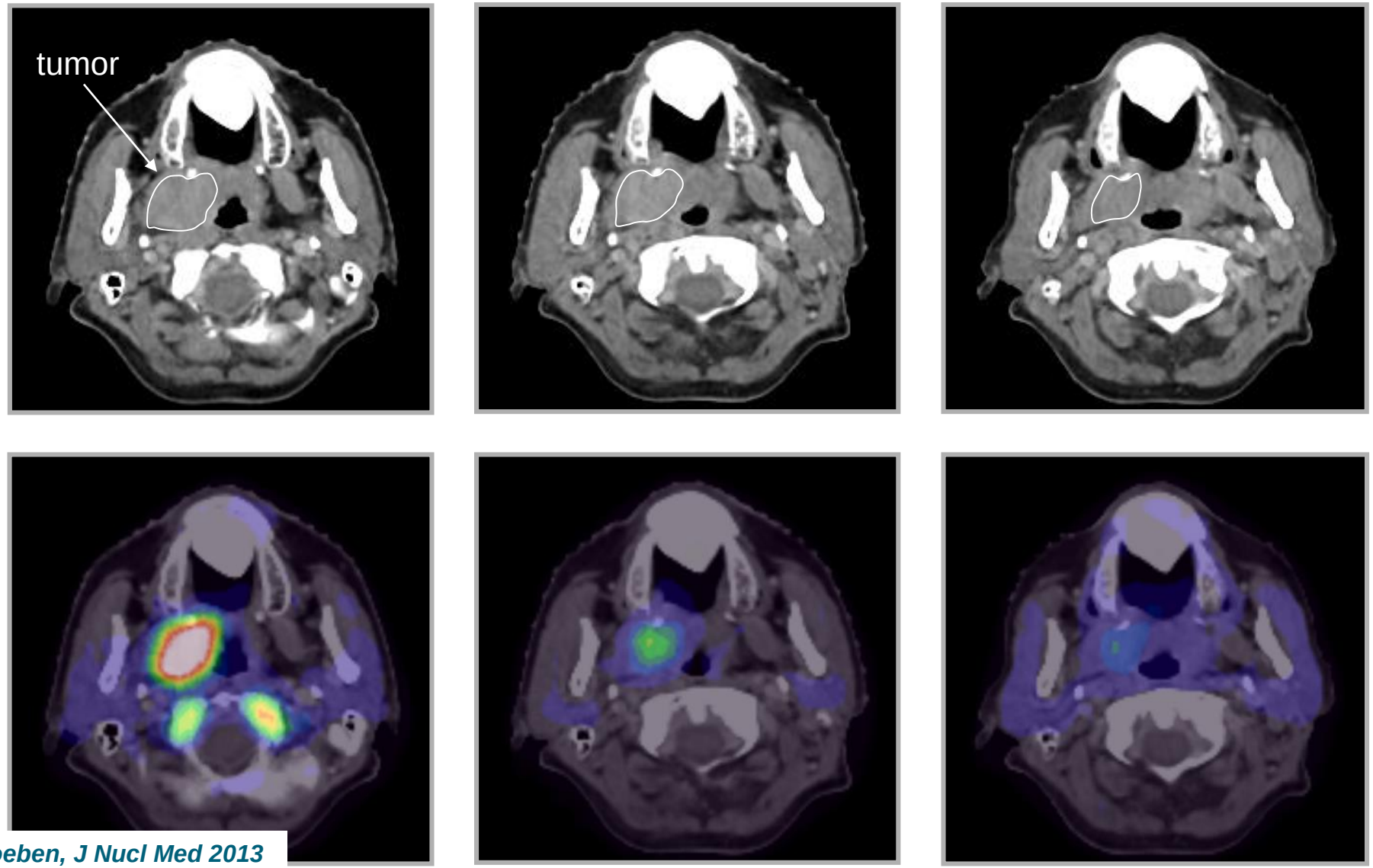
Geets, Radiother Oncol 2007

Functional imaging of proliferation: FLT-PET

before radiotherapy

2nd week of radiotherapy

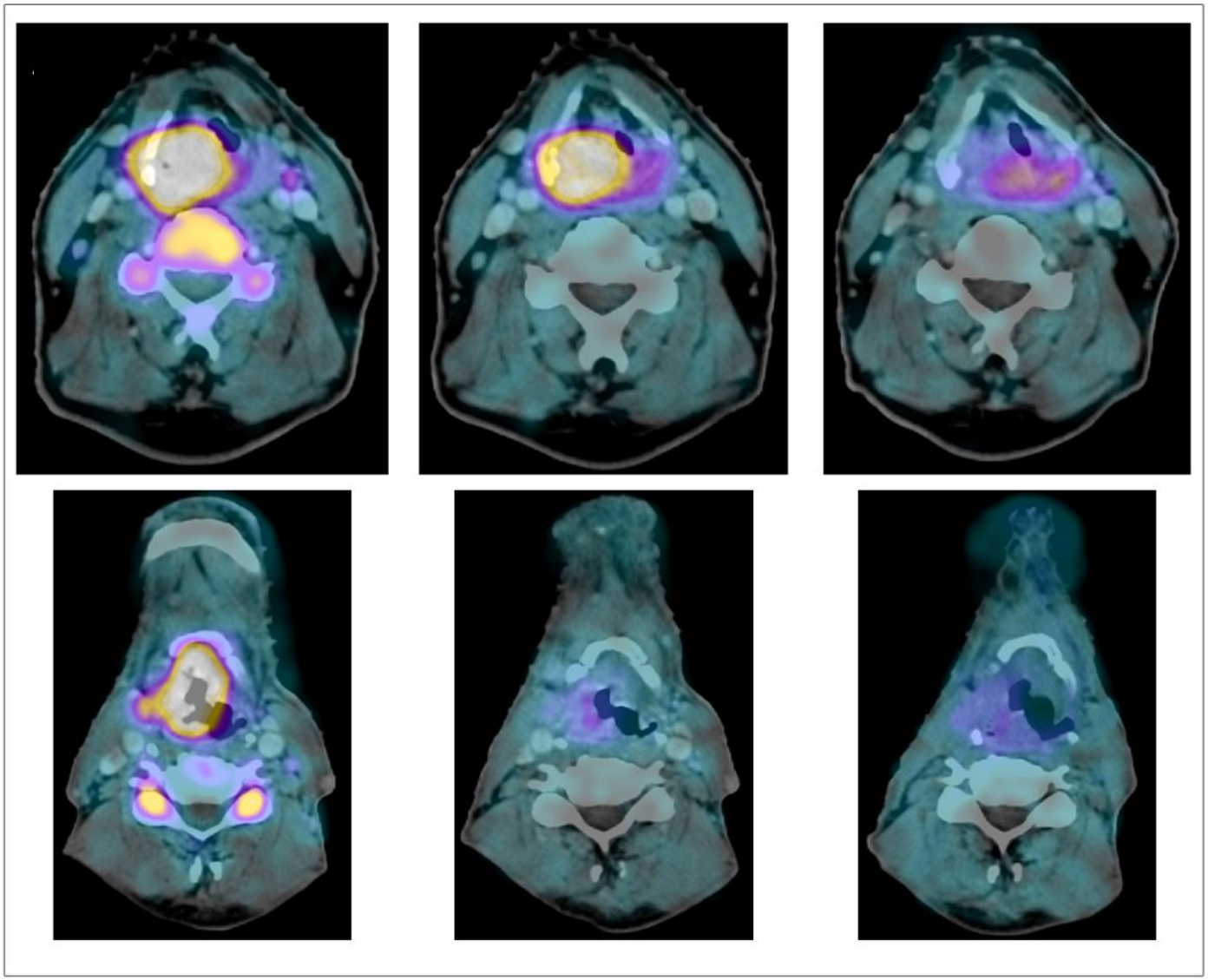
4th week of radiotherapy



Hoeben, J Nucl Med 2013

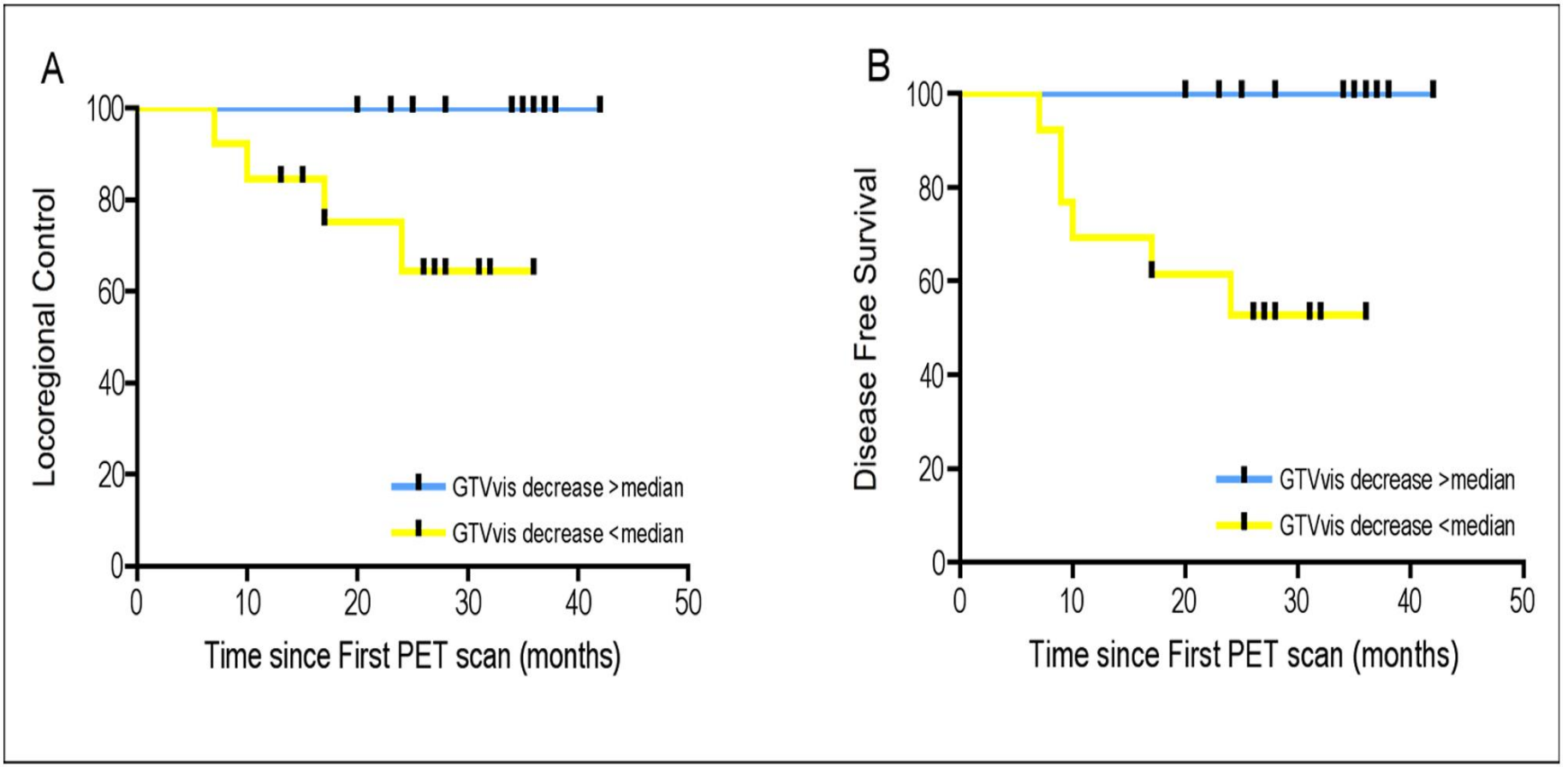
Early response assessment: FLT-PET

baseline week 2 week 4



Hoeben, J Nucl Med 2013

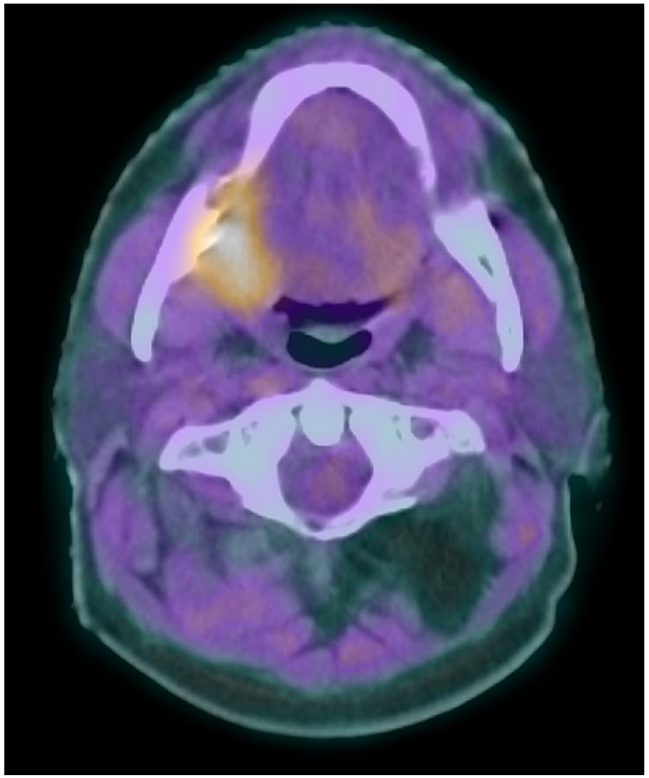
Early response assessment: CT and FLT-PET



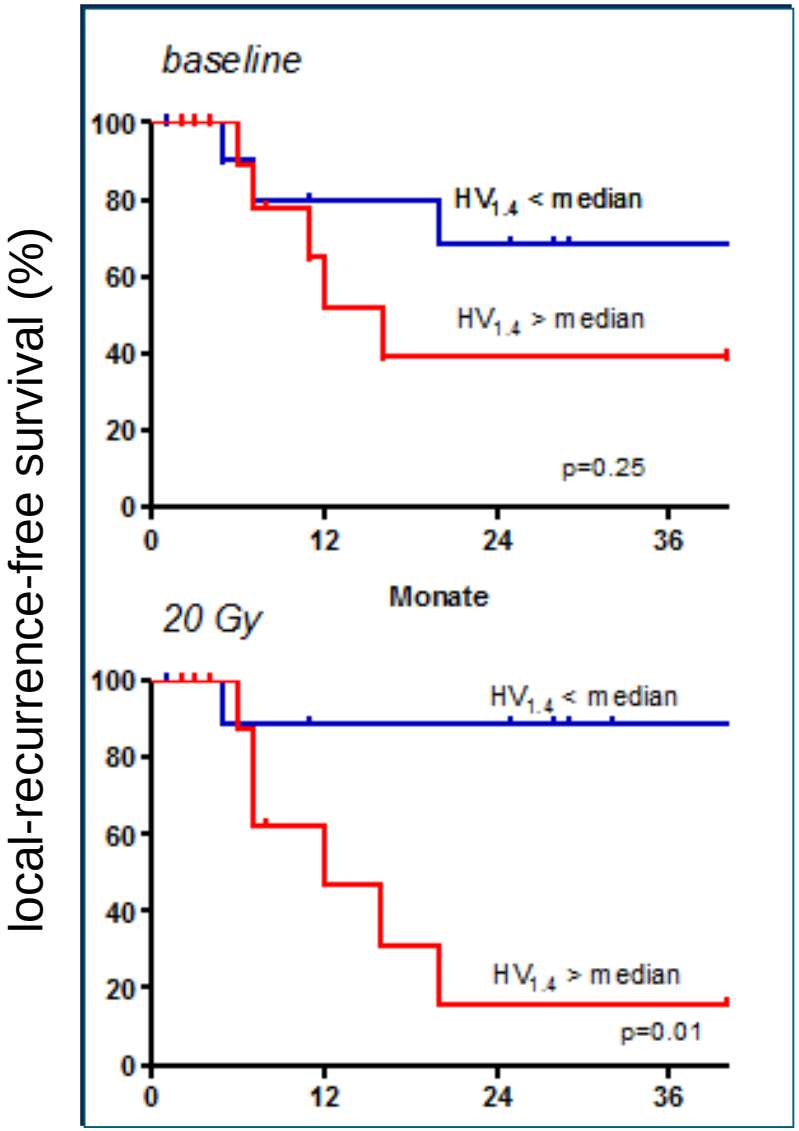
Hoeben, J Nucl Med 2013

Functional imaging of hypoxia (FMISO, FAZA, F-HX4)

F-MISO-PET



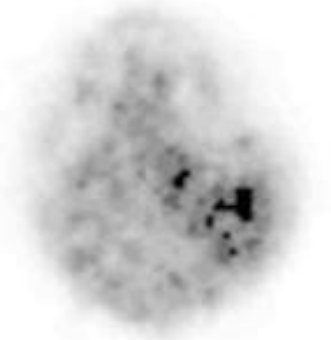
H&N cancer



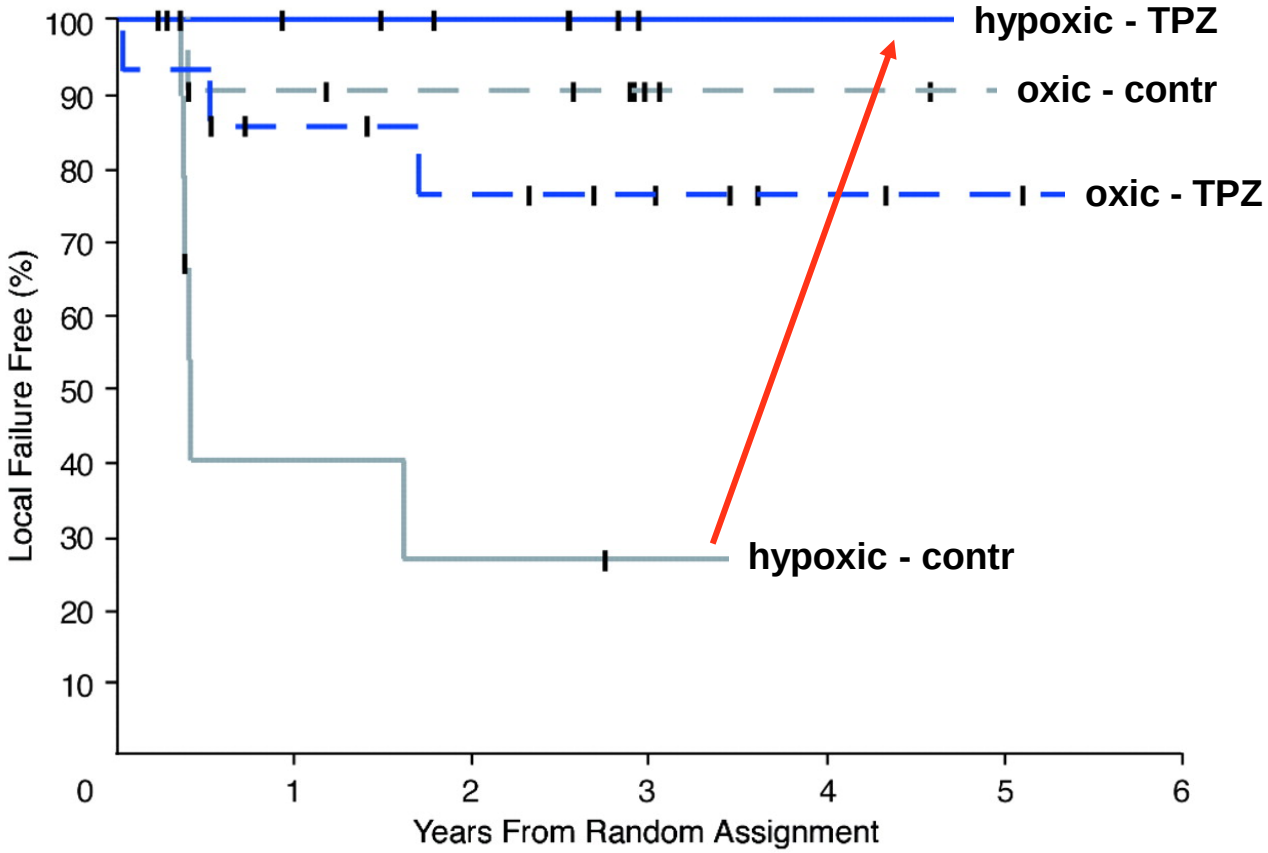
Zips, Radiother Oncol 2012

Local tumor control after radiotherapy + or - tirapazamine: hypoxic versus non-hypoxic tumors

FDG-PET

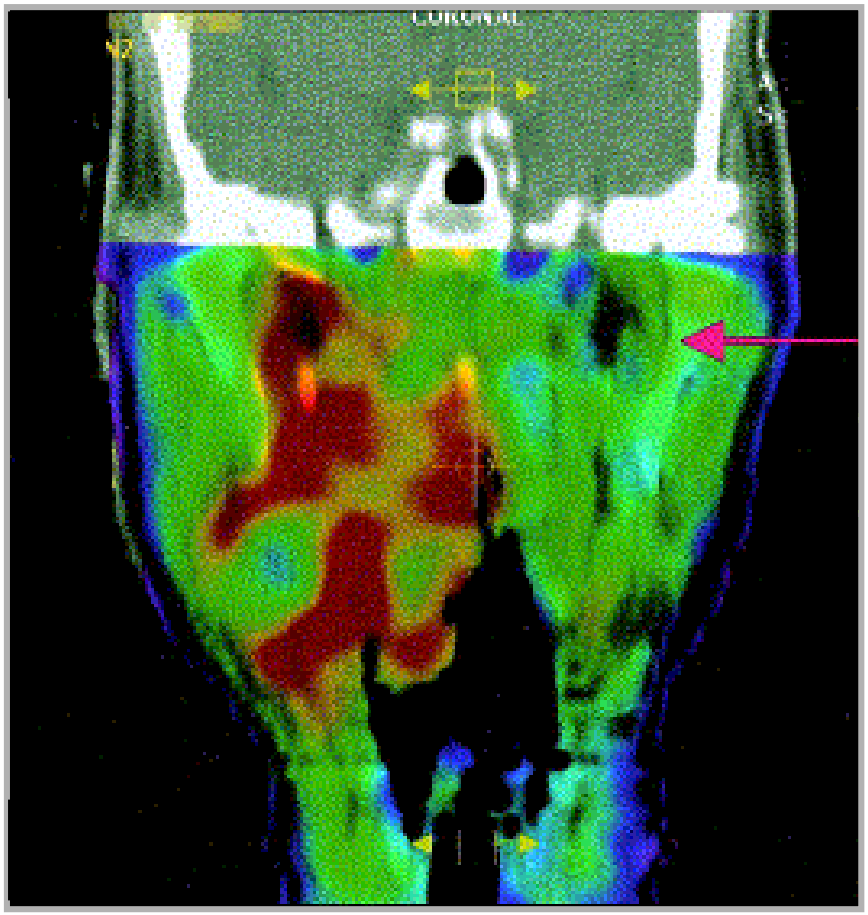


FMISO-PET



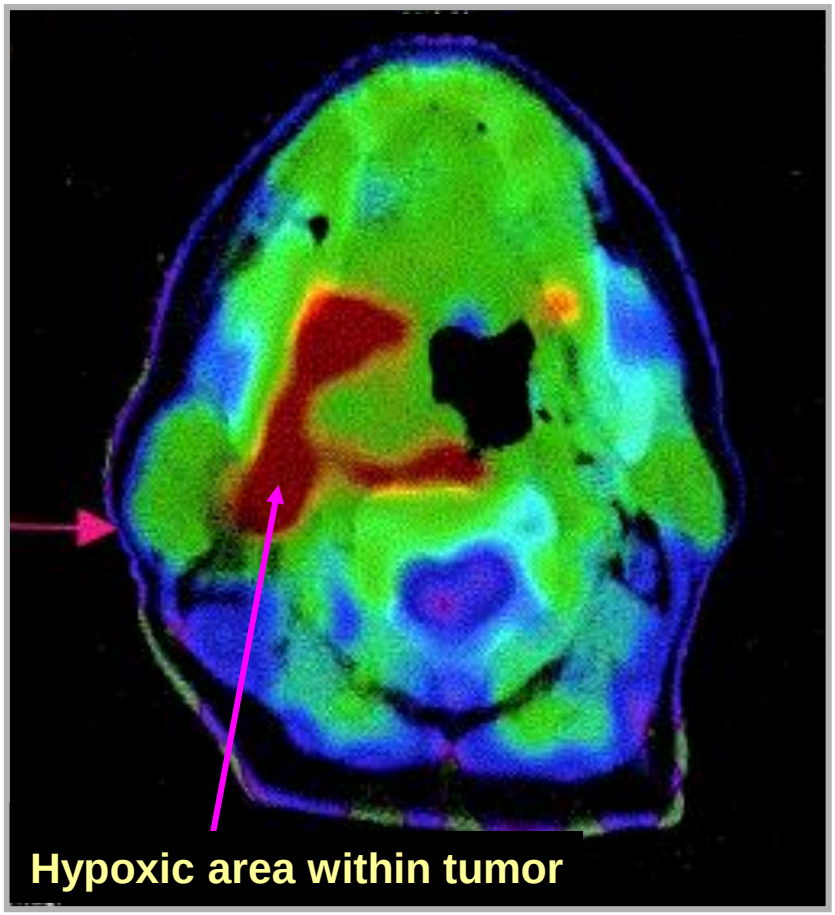
Rischin, J Clin Oncol 2006

Dose painting based on hypoxia imaging (^{64}Cu-ATSM)



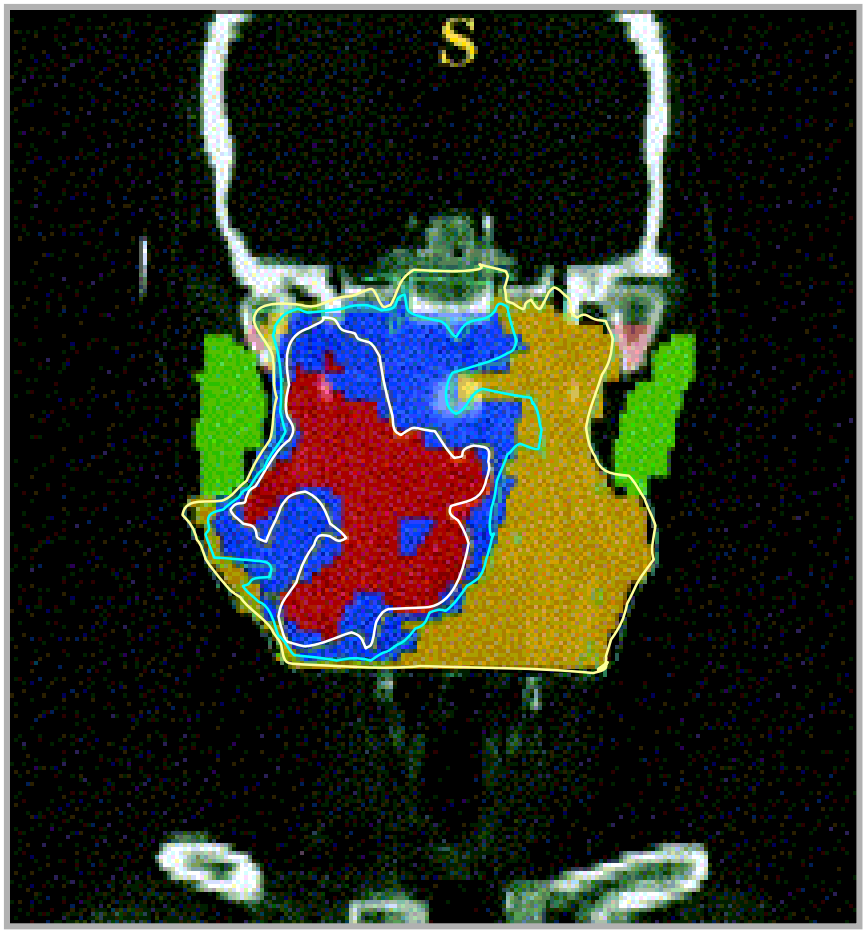
Coronal view

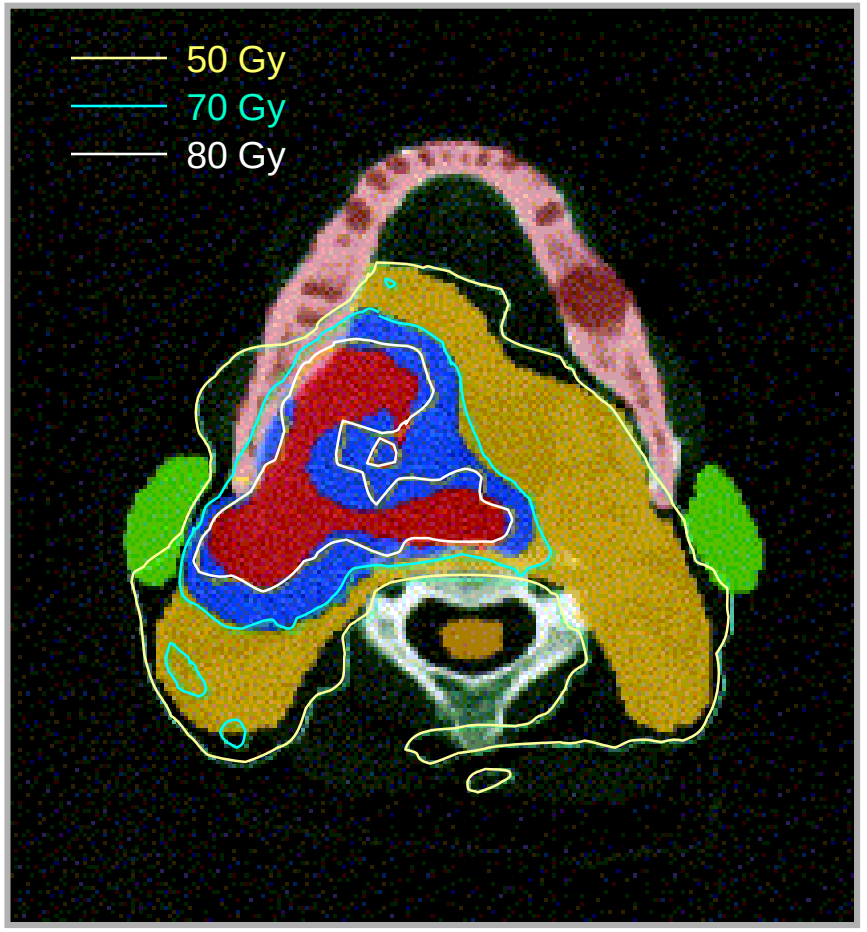
Axial view



Chao, Int J Radiat Oncol Biol Phys 2001

Dose painting based on hypoxia imaging (^{64}Cu-ATSM)





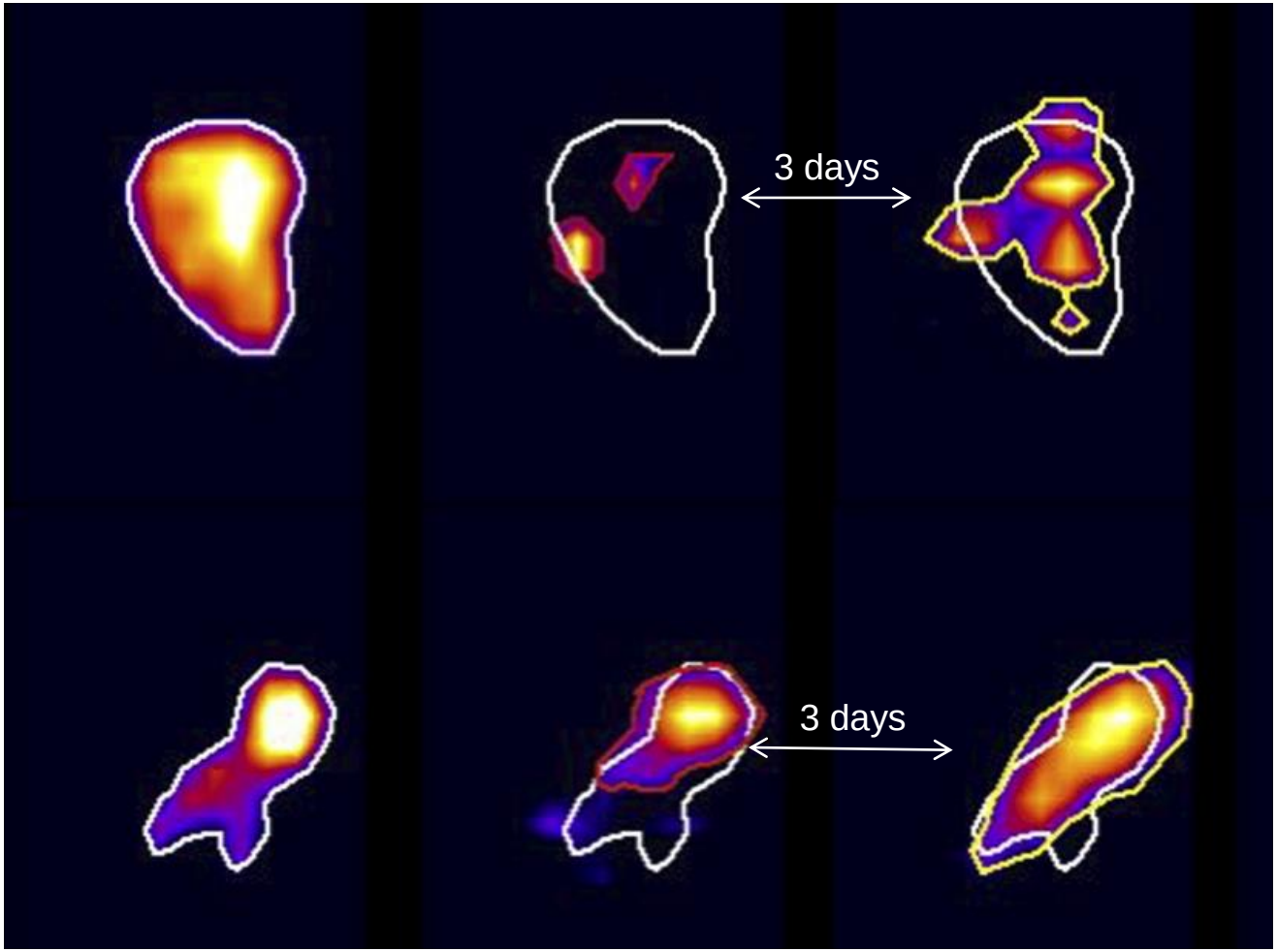
Chao, Int J Radiat Oncol Biol Phys 2001

PET/CT guided intensity-modulated radiotherapy *"dose painting"* – potential limitations

- Chronically hypoxic cells have limited life-span.
- Significant changes in oxygenation status after start of radiotherapy.
- Spatial resolution of PET-scanning and other imaging modalities good enough for dose painting?
- Significant dose escalation (>> 80 Gy) required for large hypoxic subvolumes. May not be feasible.

Temporal and spatial stability…

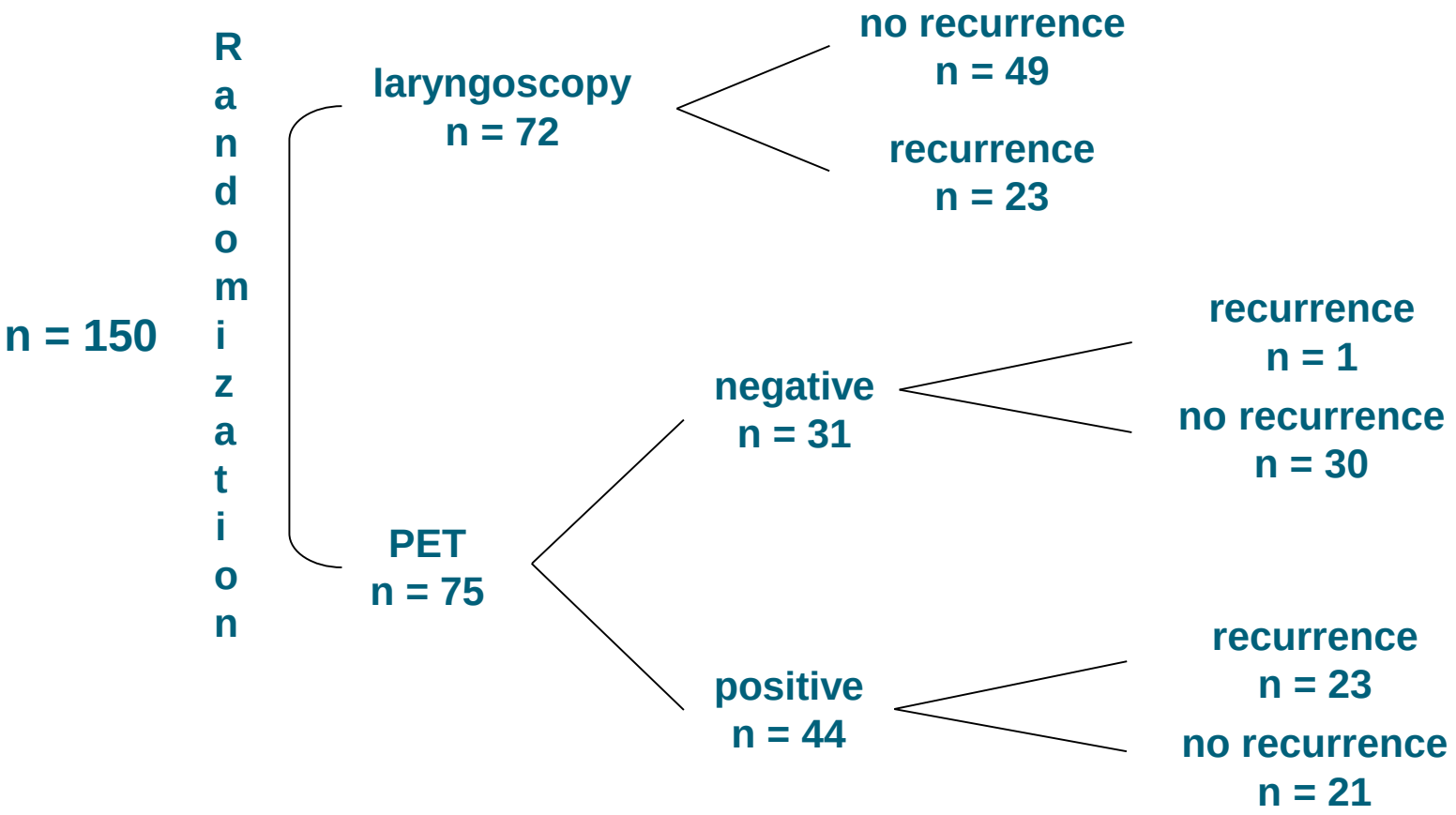
^{18}F-MISO PET



Nehmeh, Int J Radiat Oncol Biol Phys 2008

FDG-PET in follow-up of larynx carcinoma

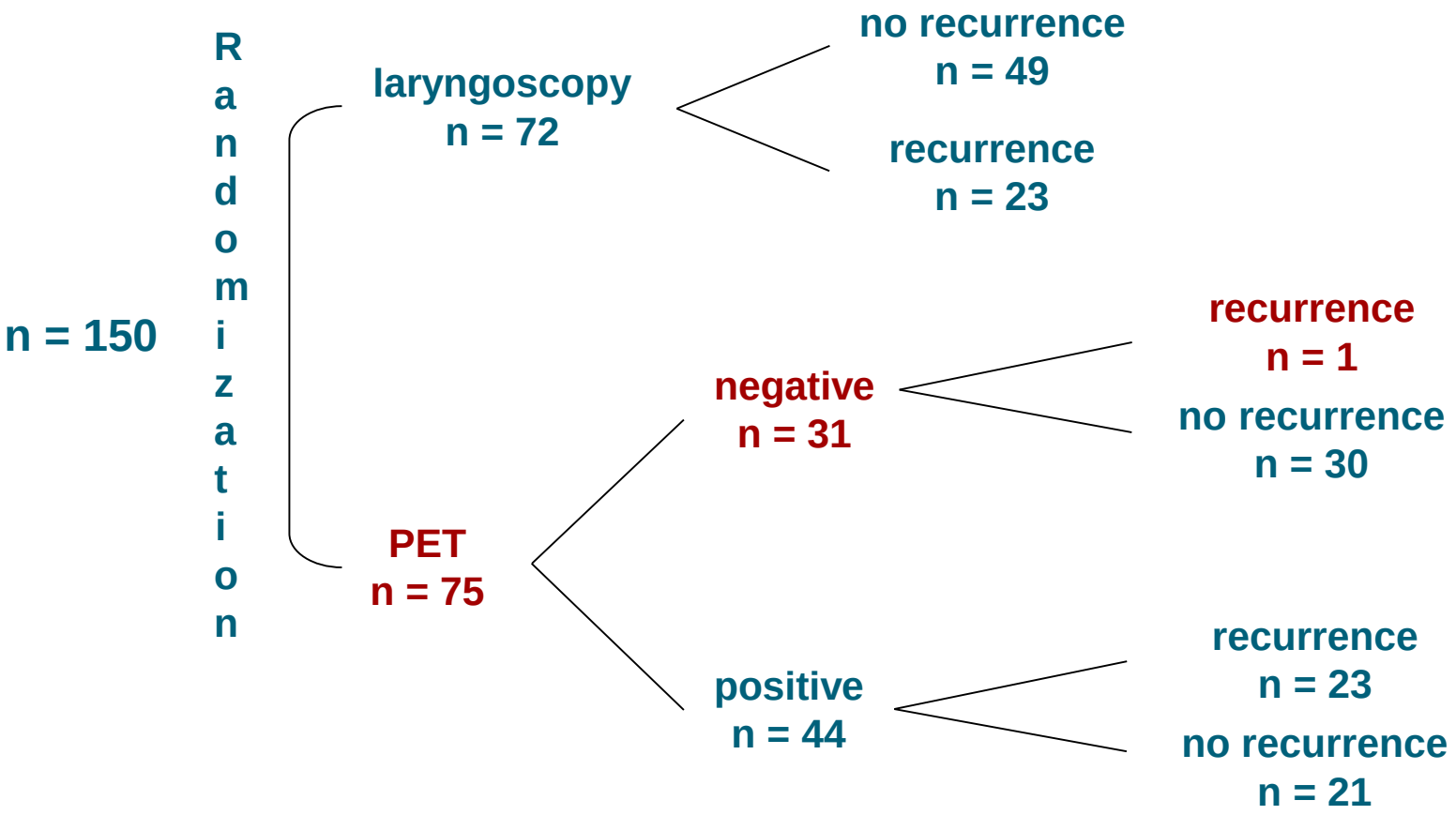
RELAPSE study



de Bree, Radiother. Oncol. 2016

FDG-PET in follow-up of larynx carcinoma

RELAPSE study

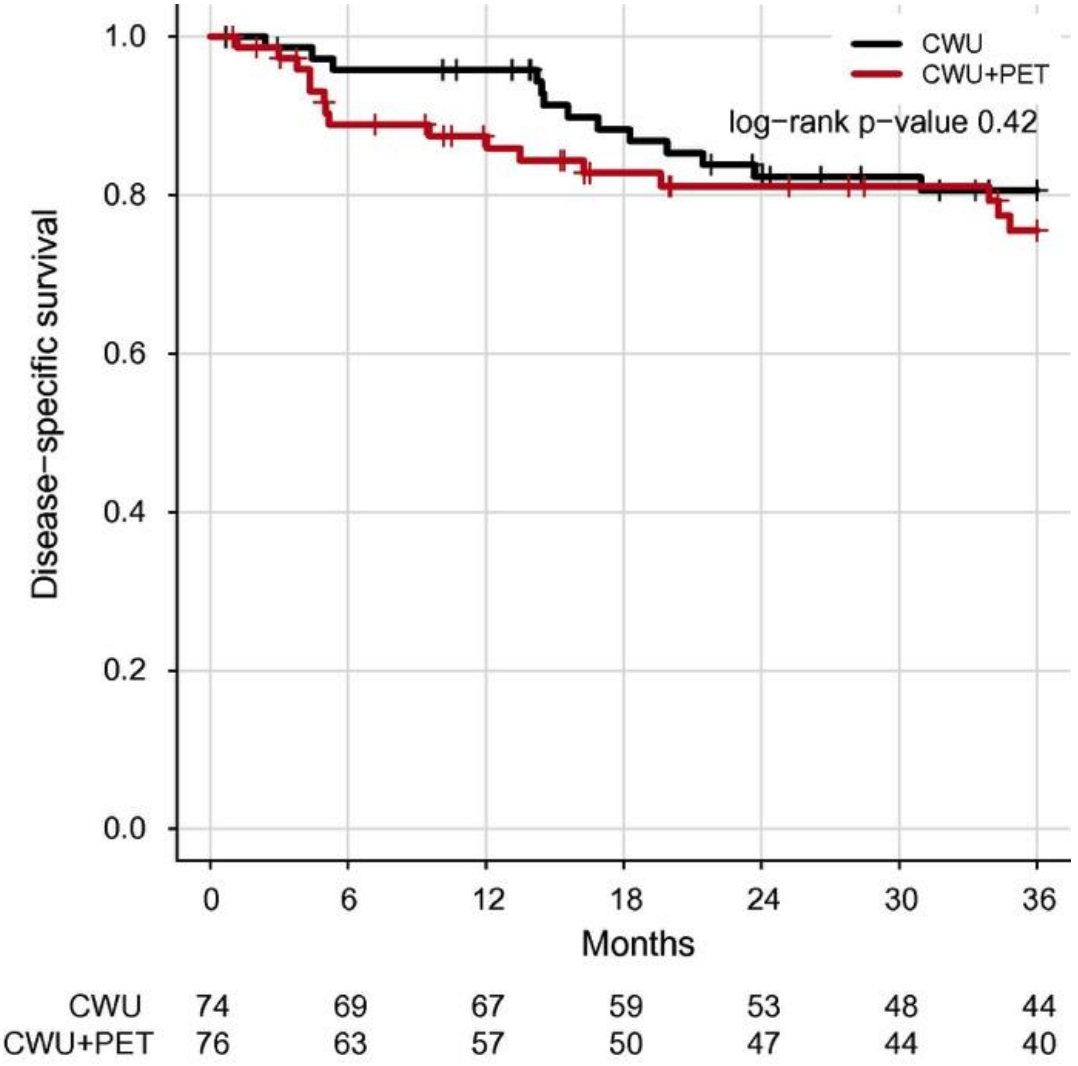


50% less (futile) laryngoscopies

de Bree, Radiother. Oncol. 2016

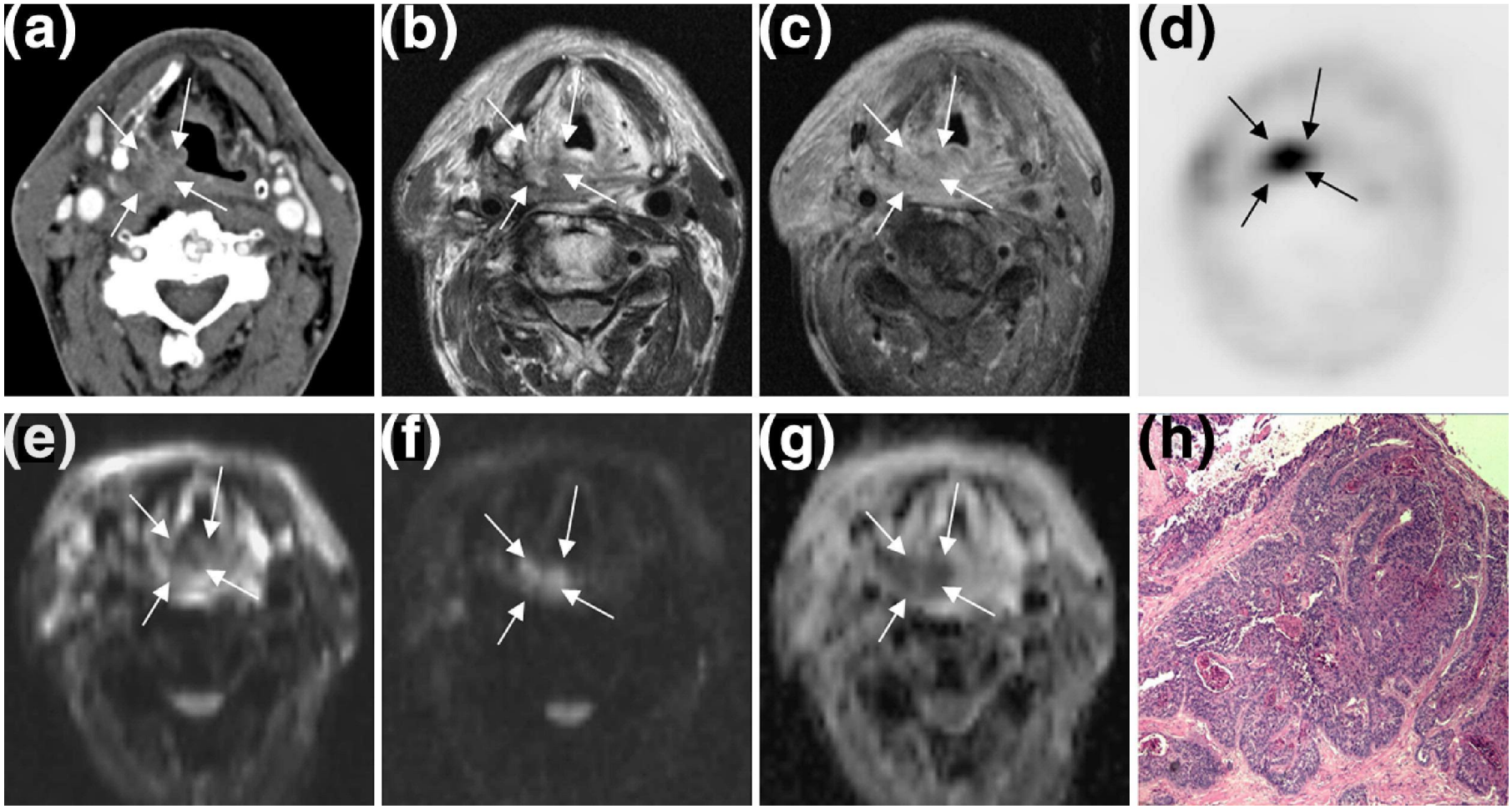
FDG-PET in follow-up of larynx carcinoma

RELAPSE study



de Bree, Radiother. Oncol. 2016

Follow-up: diffusion-weighted MRI after chemoradiotherapy for head and neck cancer

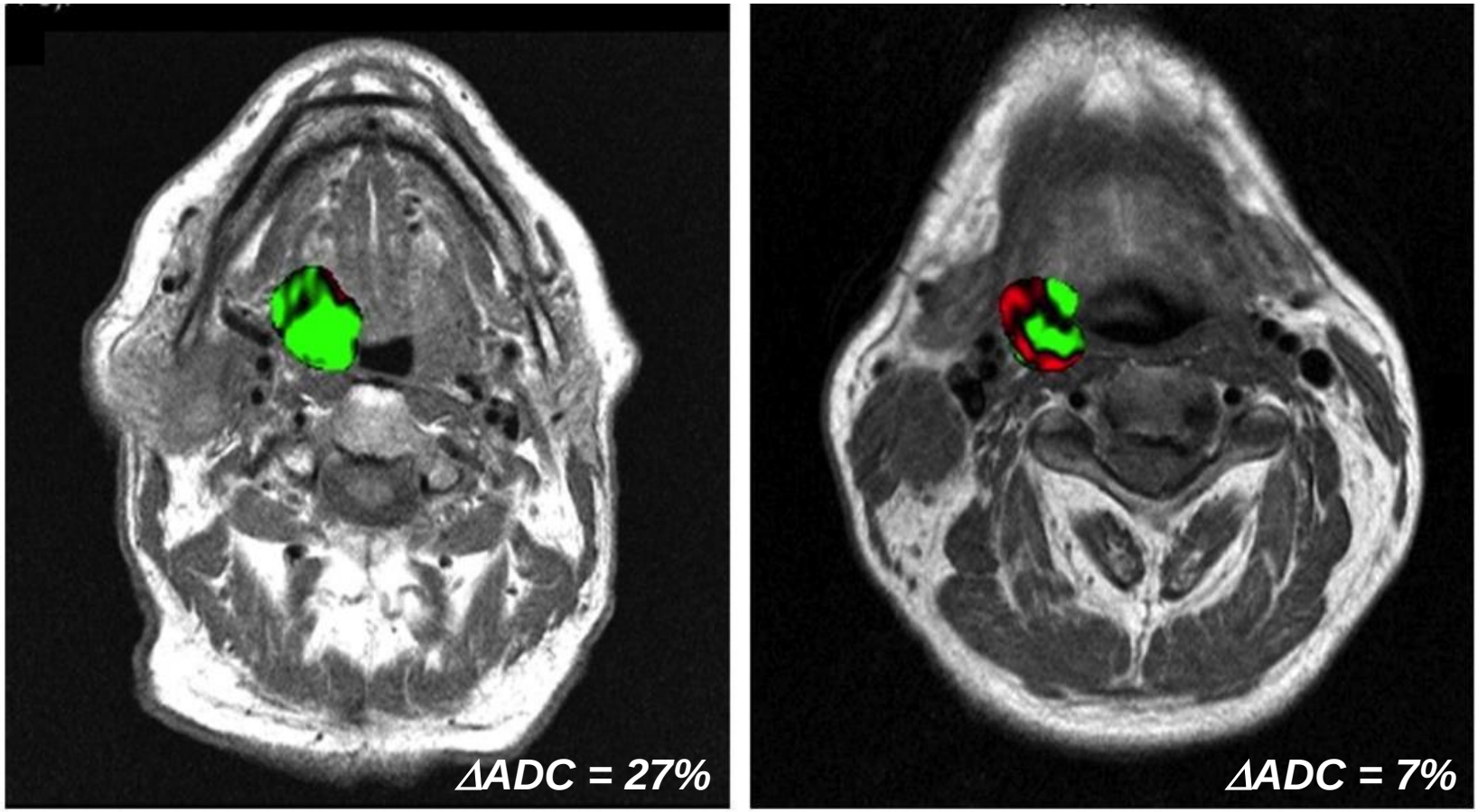


Vandecaveye, IJROBP 2007

Δ apparent diffusion coefficient as predictor of outcome

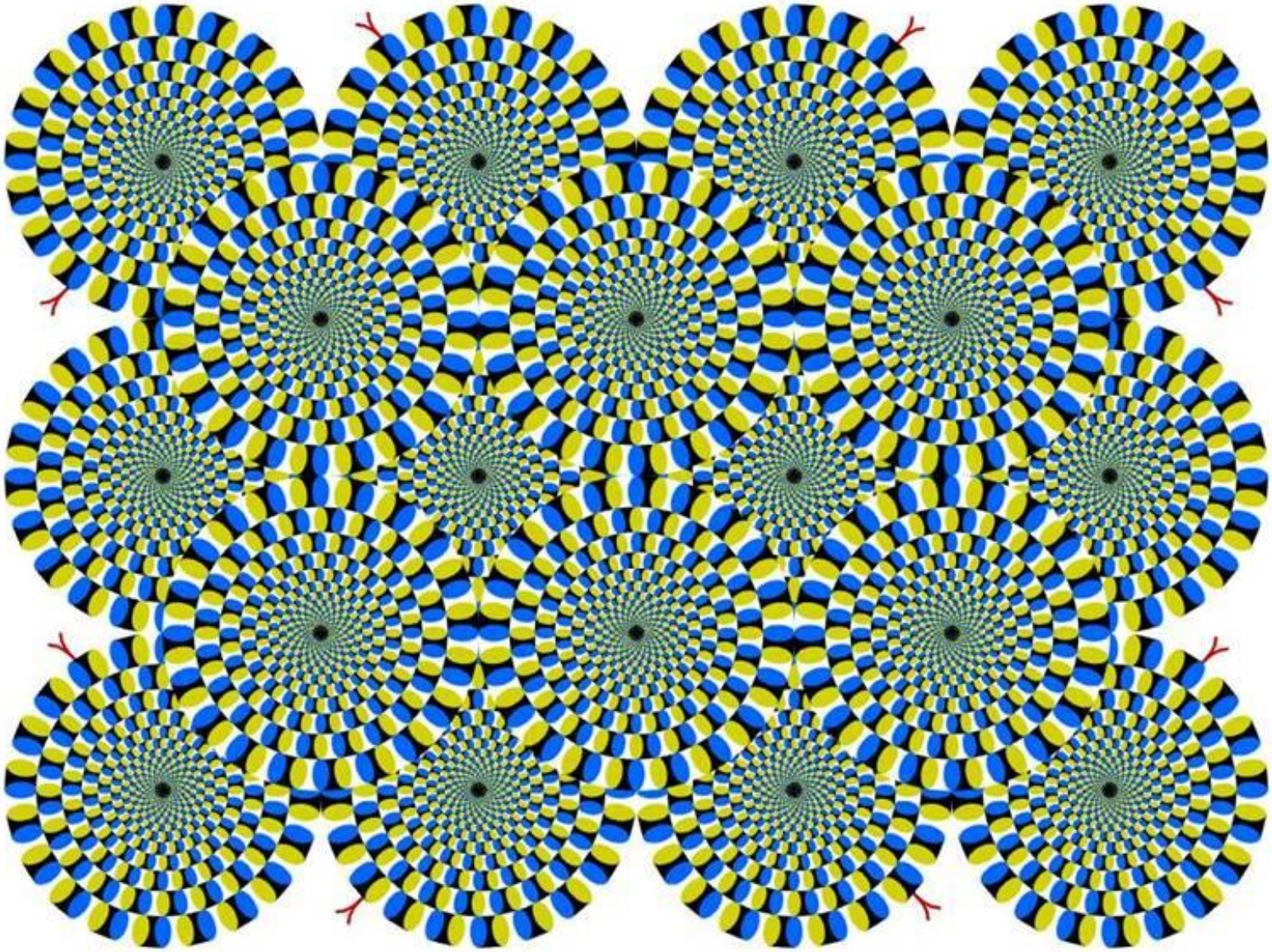
good responder

poor responder



Lambrecht, R&O 2014

If something‘s rotating? – you need a break!



Evidence-based radiotherapy for rectal cancer

Dr Li Tee Tan

Cambridge University Hospitals NHS
NHS Foundation Trust

Levels of evidence

IA	Meta-analysis of randomized controlled trials
IB	At least one randomized controlled trial
IIA	At least one controlled study without randomization
IIB	At least one quasi-experimental study
III	Non-experimental descriptive studies (comparative studies, correlation studies, case-control studies)
IV	Expert opinions

Grades of recommendation

A	Directly based on Level I evidence
B	Directly based on Level II evidence or extrapolated recommendations from Level I evidence
C	Directly based on Level III evidence or extrapolated recommendations from Level I or II evidence
D	Directly based on Level IV evidence or extrapolated recommendations from Level I, II, or III evidence

Levels of evidence

Levels of scientific evidence	
1++	High-quality meta-analyses, high-quality systematic reviews of clinical trials with very little risk of bias.
1+	Well-conducted meta-analyses, systematic review of clinical trials or well-conducted clinical trials with low risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with high risk of bias.
2++	High-quality systematic reviews of cohort or case and control studies; cohort or case and control studies with very low risk of bias and high probability of establishing a causal relationship.
2+	Well-conducted cohort or case and control studies with low risk of bias and moderate probability of establishing a causal relationship.
2-	Cohort or case and control studies with high risk of bias and significant risk that the relationship is not causal.
3	Non-analytical studies, such as case reports and case series.
4	Expert opinion.

Grades of recommendation

Grades of recommendations	
A	At least one meta-analysis, systematic review or clinical trial classified as 1++ and directly applicable to the target population of the guideline, or a volume of scientific evidence comprising studies classified as 1+ and which are highly consistent with each other.
B	A body of scientific evidence comprising studies classified as 2++, directly applicable to the target population of the guideline and highly consistent with each other, or scientific evidence extrapolated from studies classified as 1++ or 1+.
C	A body of scientific evidence comprising studies classified as 2+, directly applicable to the target population of the guideline and highly consistent with each other, or scientific evidence extrapolated from studies classified as 2++.
D	Level 3 or 4 scientific evidence, or scientific evidence extrapolated from studies classified as 2+.

Due to their high risk of bias, studies classified as 1- or 2- should not be used in compiling recommendations

Good Clinical Practice

√[1]	Practice recommended on the basis of clinical experience and consensus by the drafting team

Outline

- Past questions
- Guidelines
- Current questions

Endpoints

- Local control
- Survival
- Toxicity (late ± acute)
- Sphincter preservation

Outline

- Past questions
  - Chemo-RT or RT alone?
  - Pre-op or post-op?
  - Long course or short course?
- Guidelines
- Current questions

Outline

- Past questions
  - **Chemo-RT or RT alone?**
    - **Post-op**
  - Pre-op or post-op?
  - Long course or short course?
- Guidelines
- Current questions

Do you offer post-op RT without chemotherapy in your practice?

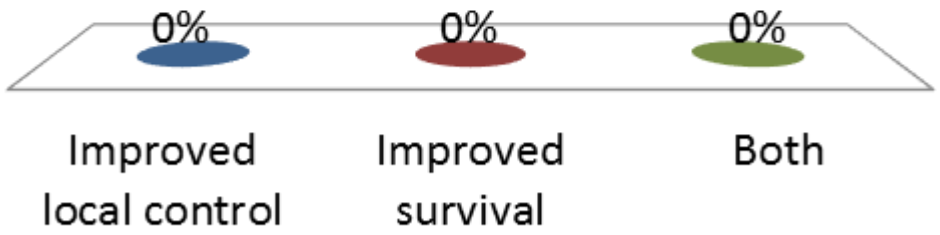
A. Routinely
B. Sometimes
C. Rarely

Do you offer post-op RT with chemotherapy in your practice?

A. Routinely
B. Sometimes
C. Rarely

What are the benefits of adding chemotherapy to RT in the post-op setting?

A. Improved local control
B. Improved survival
C. Both



GITSG 7175 (1975-1980)

Treatment	n	Local recurrence	5-year OS
Surgery alone	58	24%	36%
Post-op RT	50	27%	46%
Post-op chemo	48	20%	46%
Post-op chemo-RT	46	11%	56%
		$p = 0.009$	$p = 0.07$

Gastrointestinal Tumor Study Group. N Engl J Med. 1985;312(23):1465-72

NCCTG 79-47-51 (1980-1986)

- 204 patients

	RT	Chemo-RT	*p value*
5-year LR	63%	41%	0.0016
5-year OS	40%	55%	0.025
Late toxicity	6	7	

- Reduction in death highly significant for LAR (52%, p = 0.0037) but not significant for APR (10%, p = 0.92)

Krook JE et al. N Engl J Med. 1991;324(11):709-15

Acute toxicity

Reaction	Combination Regimen		Radiation Alone (N = 99)	
	Fluorouracil + Semustine (N = 101)	Radiation + Fluorouracil (N = 96)		
	percent of patients			
Nausea	73	38	6	
Severe	10	2		0
Vomiting	54	11	1	
Severe	6	2		0
Diarrhea	76	59	42	
Severe	21	20		5
Stomatitis	23	4	0	
Severe	1	1		0
Dermatitis	0	28	22	
Severe	0	5		0
Alopecia	16	0	0	
Severe	1	0		0
Leukopenia (<4000/μl)	83	78	21	
<2000/μl	15	18		0
Thrombocytopenia (<100,000/μl)	35	9	2	
<25,000/μl	4	0		0

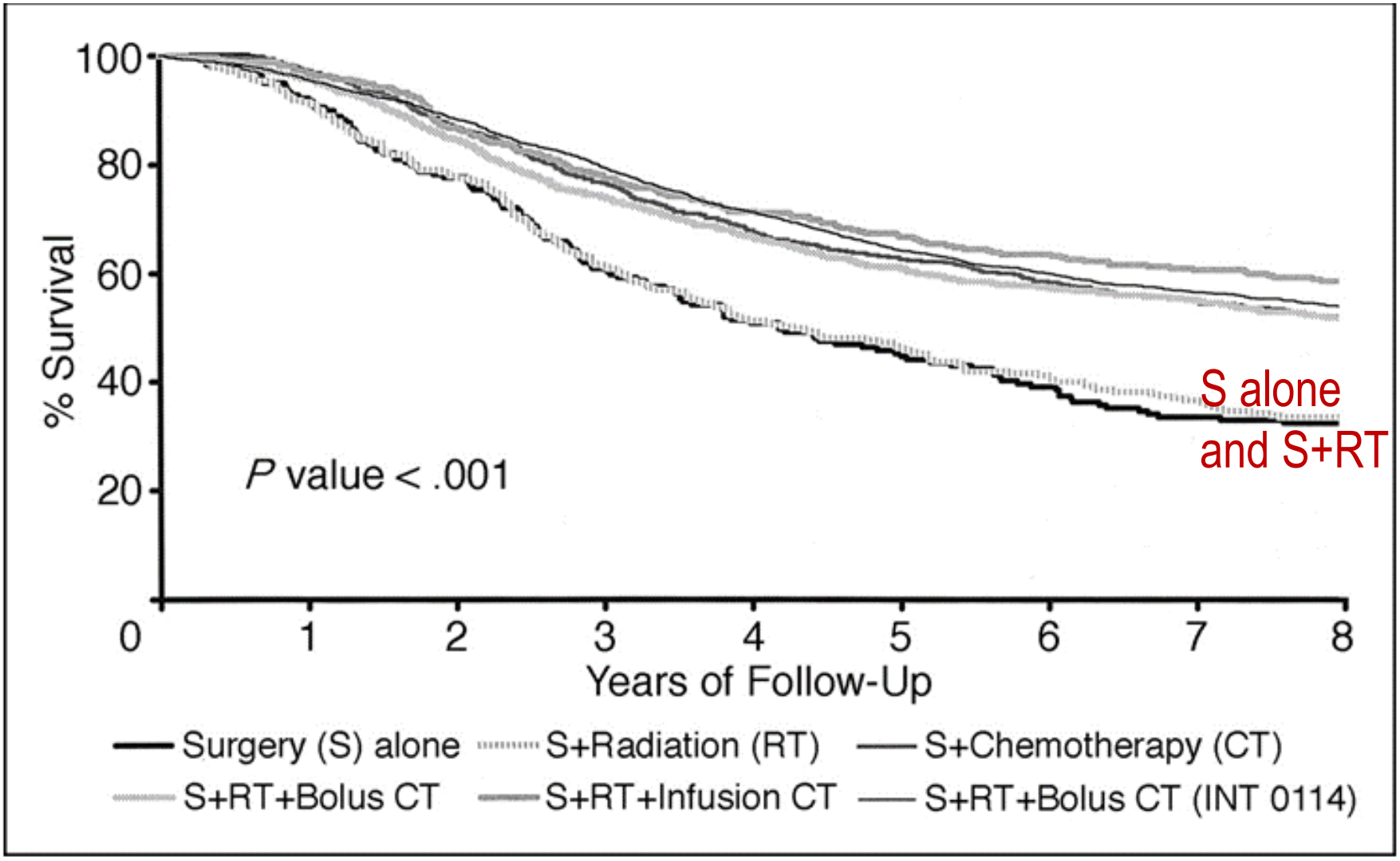
Krook JE et al. N Engl J Med. 1991;324(11):709-15

NCCTG pooled analysis

- 3,791 patients from 5 randomised studies
  - Surgery alone - 179
  - RT alone = 281
  - Chemo-RT = 2799
  - Chemo alone = 532

Gunderson LL et al. J Clin Oncol. 2004;22(10):1785-96

NCCTG pooled analysis



Gunderson LL et al. J Clin Oncol. 2004;22(10):1785-96

Conclusion 1

	Post-op RT	Post-op chemo-RT
Local recurrence	✗	✓
Survival	✗	✓
Toxicity (acute)	✓	✗
Toxicity (late)	=	=
Sphincter preservation		

Outline

- Past questions
  - **Chemo-RT or RT alone?**
    - **Pre-op**
  - Pre-op or post-op?
  - Long course or short course?
- Guidelines
- Current questions

Do you offer pre-op RT without chemotherapy in your practice?

A. Routinely
B. Sometimes
C. Rarely

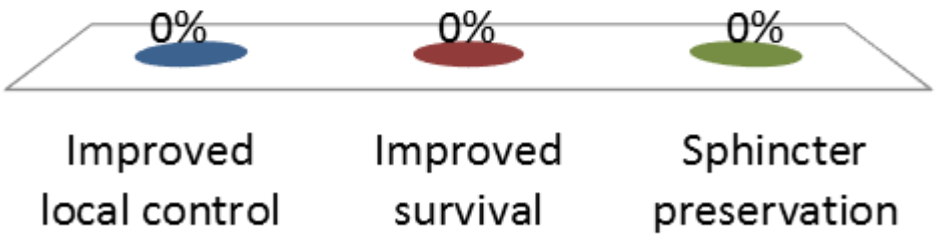
Do you offer pre-op RT with chemotherapy in your practice?

A. Routinely
B. Sometimes
C. Rarely

What are the benefits of adding chemotherapy to long course RT in the pre-op setting?

Select one or more

A. Improved local control
B. Improved survival
C. Sphincter preservation



Cochrane review

- Preoperative chemo-radiation versus radiation alone for stage II and III resectable rectal cancer
- 5 studies
  - 3 studies: RT dose the same in both arms
  - 2 studies: RT alone arm is 25 Gy/5#

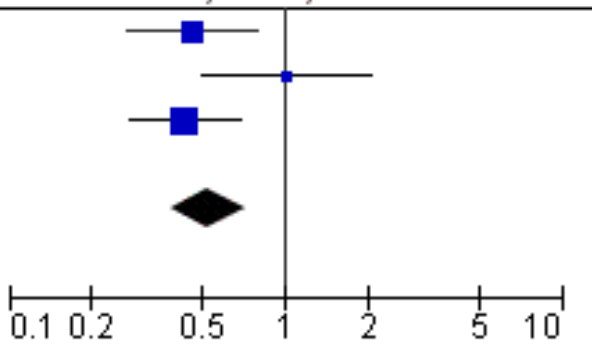
De Caluwé L, Cochrane Database Syst Rev. 2013

Local recurrence

Study or Subgroup	CRT Events	CRT Total	RT Events	RT Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bosset 2006	22	253	43	252	35.2%	0.46 [0.27, 0.80]
Boulis-Wassif 1984	19	126	18	121	14.0%	1.02 [0.51, 2.04]
Gerard 2006	30	375	61	367	50.8%	0.44 [0.27, 0.69]
Total (95% CI)		**754**		**740**	**100.0%**	**0.53 [0.39, 0.72]**
Total events	71		122			

Heterogeneity: Chi² = 4.24, df = 2 (P = 0.12); I² = 53%

Test for overall effect: Z = 4.03 (P < 0.0001)



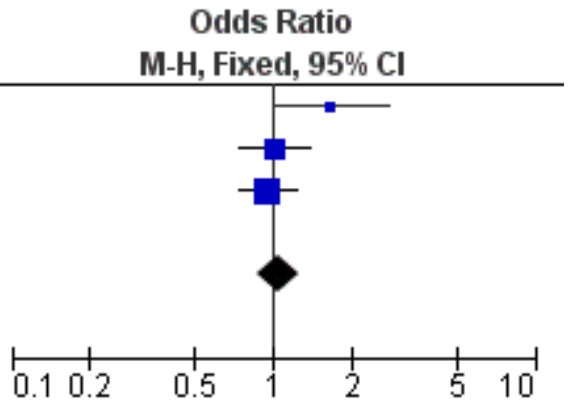
De Caluwé L, Cochrane Database Syst Rev. 2013

Overall survival

Study or Subgroup	CRT Events	CRT Total	RT Events	RT Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Boulis-Wassif 1984	68	126	50	121	10.6%	1.66 [1.01, 2.75]	1984
Gerard 2006	122	375	118	367	36.4%	1.02 [0.75, 1.38]	2006
Bosset 2006	173	506	178	505	53.0%	0.95 [0.74, 1.24]	2006
Total (95% CI)		**1007**		**993**	**100.0%**	**1.05 [0.88, 1.27]**	
Total events	363		346				

Heterogeneity: $Chi^2 = 3.78$, $df = 2$ ($P = 0.15$); $I^2 = 47\%$

Test for overall effect: $Z = 0.55$ ($P = 0.58$)



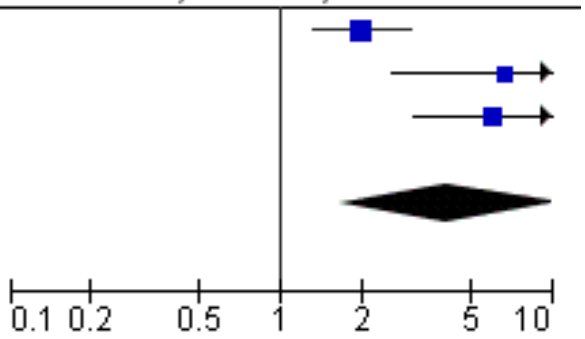
De Caluwé L, Cochrane Database Syst Rev. 2013

G3-4 toxicity (Acute)

Study or Subgroup	CRT Events	CRT Total	RT Events	RT Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosset 2006	67	483	37	495	38.4%	1.99 [1.31, 3.04]
Bujko 2006	29	157	5	155	28.0%	6.80 [2.56, 18.07]
Gerard 2006	55	375	10	367	33.6%	6.14 [3.08, 12.24]
Total (95% CI)		**1015**		**1017**	**100.0%**	**4.10 [1.68, 10.00]**
Total events	151		52			

Heterogeneity: Tau² = 0.49; Chi² = 10.57, df = 2 (P = 0.005); I² = 81%

Test for overall effect: Z = 3.10 (P = 0.002)



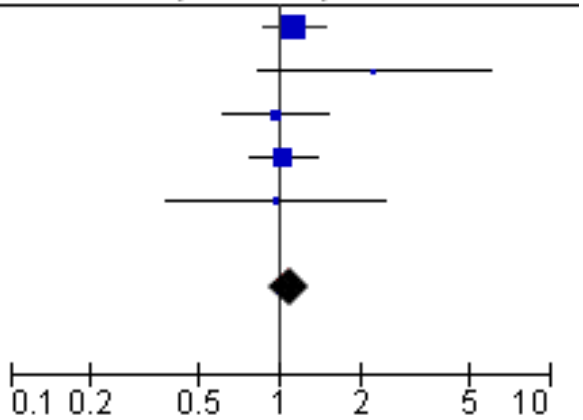
De Caluwé L, Cochrane Database Syst Rev. 2013

Sphincter preservation

Study or Subgroup	CRT Events	CRT Total	RT Events	RT Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosset 2006	263	473	249	475	45.0%	1.14 [0.88, 1.47]
Boulis-Wassif 1984	13	124	6	121	2.9%	2.24 [0.82, 6.11]
Bujko 2006	87	157	87	155	14.7%	0.97 [0.62, 1.52]
Gerard 2006	188	357	185	357	34.1%	1.03 [0.77, 1.39]
Latkauskas 2011	32	46	26	37	3.3%	0.97 [0.38, 2.49]
Total (95% CI)		**1157**		**1145**	**100.0%**	**1.09 [0.92, 1.30]**
Total events	583		553			

Heterogeneity: Tau² = 0.00; Chi² = 2.54, df = 4 (P = 0.64); I² = 0%

Test for overall effect: Z = 1.00 (P = 0.32)



De Caluwé L, Cochrane Database Syst Rev. 2013

Conclusion 2

	Pre-op RT	Pre-op chemo-RT
Local recurrence		
Survival		
Toxicity (acute)		
Toxicity (late)		
Sphincter preservation		

Outline

- Past questions
  - Chemo-RT or RT alone?
  - **Pre-op or post-op?**
  - Long course or short course?
- Guidelines
- Current questions

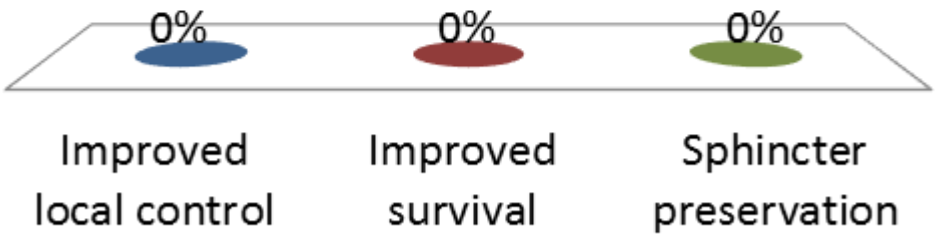
Do you prefer to offer RT before or after surgery?

A. Before
B. After
C. It depends

What are the benefits of pre-op radiotherapy (± chemotherapy) for rectal cancer?

Select one or more

A. Improved local control
B. Improved survival
C. Sphincter preservation



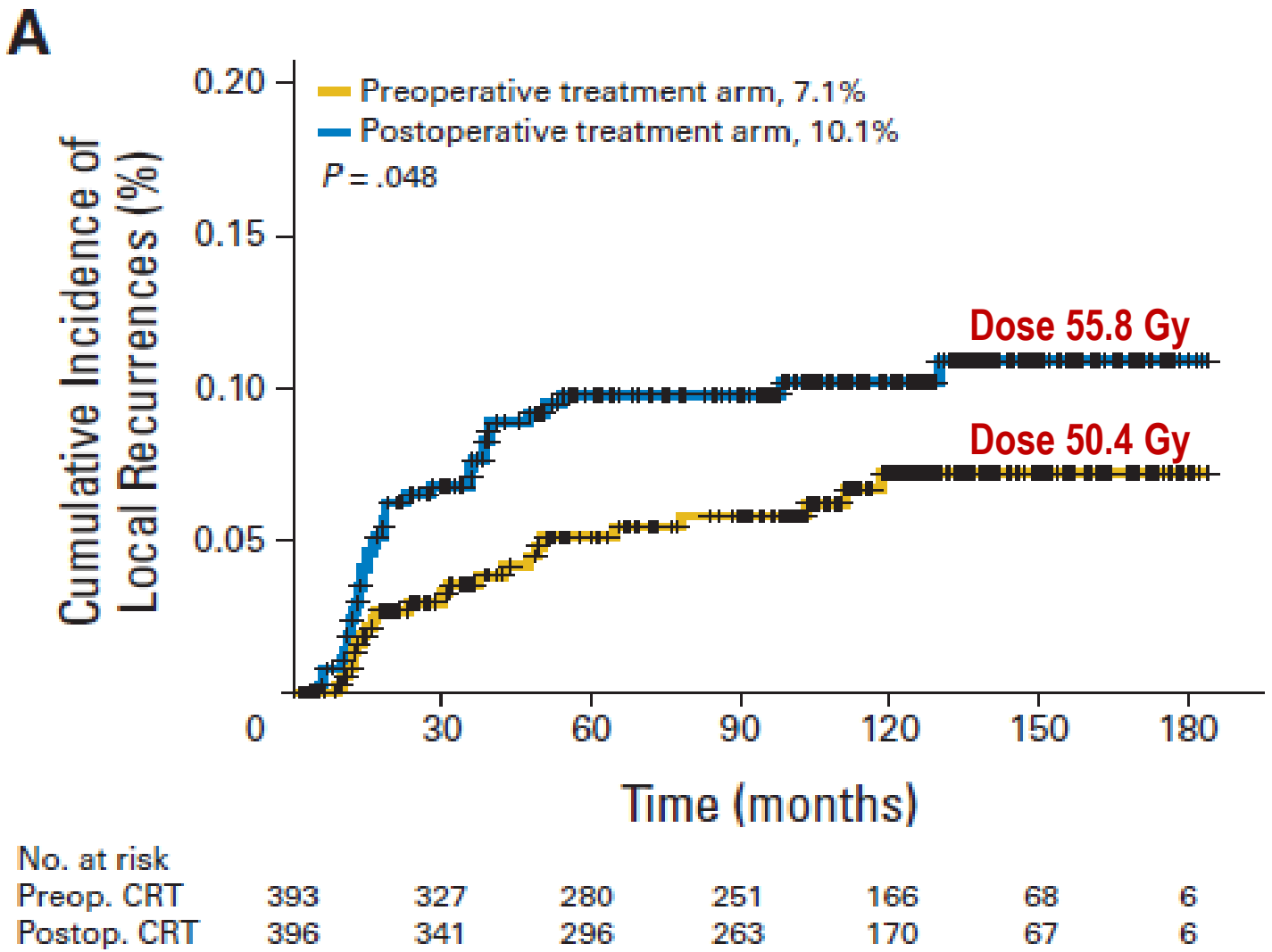
German Rectal Cancer Study CAO/ARO/AIO (1995-2002)

- Study group
  - 823 patients
  - Clinical stage T3-4 or N+ (operable)
  - Inferior margin within 16 mm from anal verge
- Randomisation
  - Chemo-RT (50.4 Gy) + surgery (TME) + 4 x bolus 5-FU
  - Surgery (TME) + chemo-RT (55.8 Gy) + 4 x bolus 5-FU

  (Chemo-RT = 5-FU 1000 mg/m2/d D1-5, weeks 1+5)

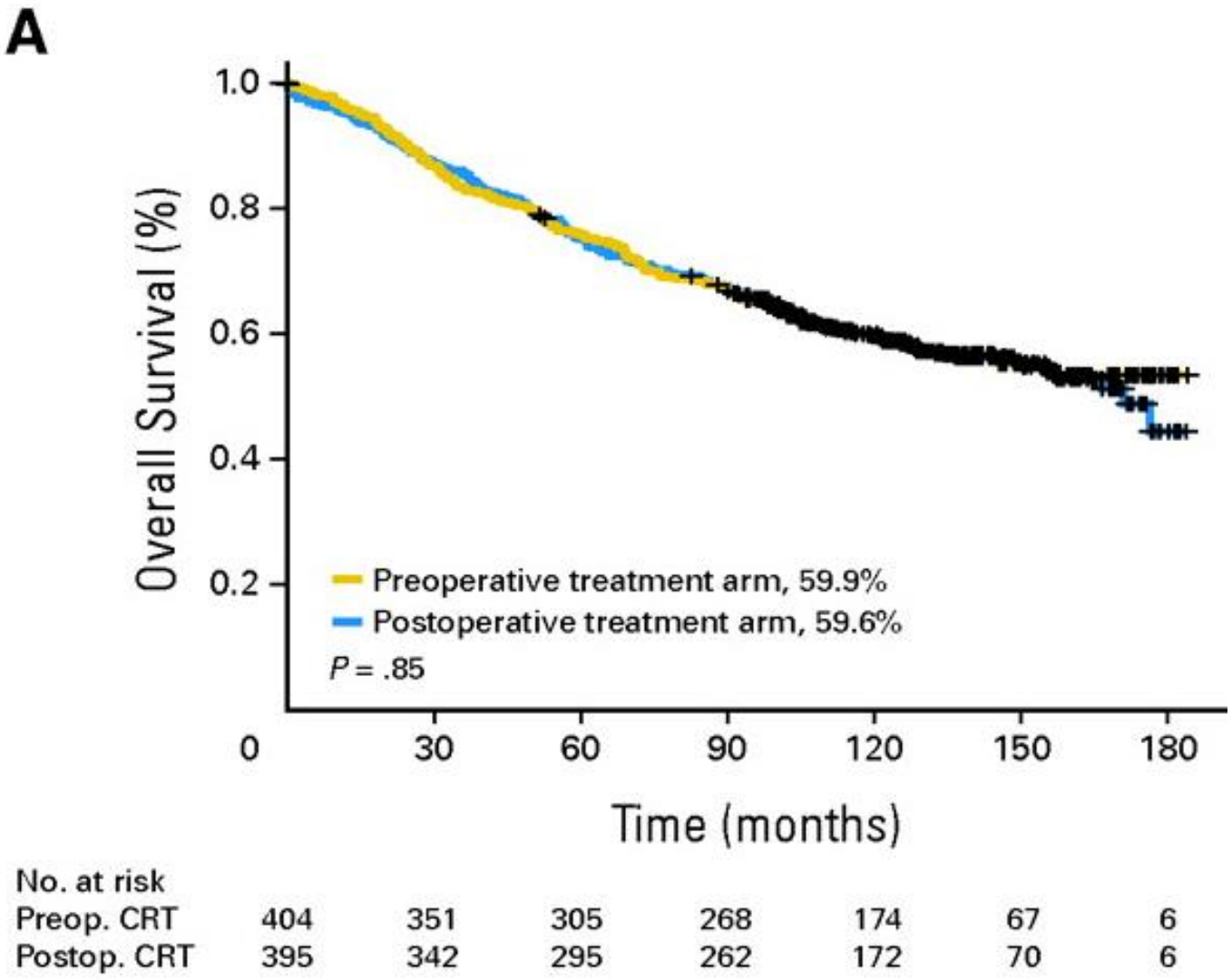
Sauer R, N Engl J Med. 2004;351(17):1731-40

Local recurrence



Sauer R, N Engl J Med. 2004;351(17):1731-40

Overall survival



Sauer R, N Engl J Med. 2004;351(17):1731-40

Toxicity

Table 5. Grade 3 or 4 Toxic Effects of Chemoradiotherapy, According to Actual Treatment Given.*

Type of Toxic Effect	Preoperative Chemoradiotherapy (N=399)	Postoperative Chemoradiotherapy (N=237)	P Value
	% of patients		
Acute			
Diarrhea	12	18	0.04
Hematologic effects	6	8	0.27
Dermatologic effects	11	15	0.09
Any grade 3 or 4 toxic effect	27	40	0.001
Long-term			
Gastrointestinal effects†	9	15	0.07
Strictures at anastomotic site	4	12	0.003
Bladder problems	2	4	0.21
Any grade 3 or 4 toxic effect	14	24	0.01

No difference in surgical complications (36% vs. 34%)

Sauer R, N Engl J Med. 2004;351(17):1731-40

Pre-op RT vs selective post-op [C]RT

Study	n		LR	p	OS
Uppsala	471	25.5 Gy	13%	0.02	No diff
1980-1985		60 Gy RT	22%		No diff
MRC CR07	1350	25 Gy	4%	<0.0001	No diff
1998-2005		45 Gy CRT	11%		No diff
Dutch TME	1861	25 Gy	6%	<0.001	64%
1996-1999		50.4 Gy RT	11%		63%

Frykholm GJ. Dis Colon Rectum. 1993;36(6):564-72

Sebag-Montefiore D, Lancet. 2009;373(9666):811-20

Peeters KC, Ann Surg. 2007 Nov;246(5):693-701

Sphincter preservation
Surgery ± pre-op RT

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Anterior resection or Hartmann's procedure					
Boulis Wassif 1979	15/44	6/46		0.9 %	2.61 [1.12, 6.13]
Cedermark 1995	154/424	154/425		10.8 %	1.00 [0.84, 1.20]
Dahl 1990	52/159	52/140		5.3 %	0.88 [0.65, 1.20]
Gerard 1988a	24/231	40/220		2.6 %	0.57 [0.36, 0.92]
Goldberg 1994b	131/230	136/245		12.0 %	1.03 [0.88, 1.20]
Higgins 1986	7/181	6/180		0.6 %	1.16 [0.40, 3.38]
Illenyi 1994	32/115	44/116		3.9 %	0.73 [0.50, 1.07]
Kapiteijn 2001	629/924	644/937		19.6 %	0.99 [0.93, 1.05]
MRC 1984 (Multi frc)	57/278	74/285		5.4 %	0.79 [0.58, 1.07]
MRC 1984a	59/287	74/285		5.5 %	0.79 [0.59, 1.07]
MRC 1996	46/139	52/140		5.0 %	0.89 [0.65, 1.23]
Petersen 1998	26/47	17/46		2.8 %	1.50 [0.95, 2.36]
Reis Neto 1989	18/34	22/34		3.5 %	0.82 [0.55, 1.22]
Stockholm 1996	99/272	109/285		8.7 %	0.95 [0.77, 1.18]
Swedish RCT 1997	243/585	227/583		13.4 %	1.07 [0.93, 1.23]
Total (95% CI)	**3950**	**3967**		**100.0 %**	**0.96 [0.88, 1.04]**

Total events: 1592 (Treatment), 1657 (Control)
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 23.47$, df = 14 (P = 0.05); $I^2 = 40\%$
Test for overall effect: Z = 1.10 (P = 0.27)

Wong RK et al. Cochrane Database Syst Rev. 2007

Conclusion 3

	Pre-op	Post-op
Local recurrence		
Survival		
Toxicity (acute)		
Toxicity (late)		
Sphincter preservation		

Outline

- Past questions
  - Chemo-RT or RT alone?
  - Pre-op or post-op?
  - **Long course or short course?**
- Guidelines
- Current questions

Do you give short course pre-operative radiotherapy for rectal cancer?

A. Routinely
B. Sometimes
C. Rarely

Polish Colorectal Study Group

- 312 patients.
- Randomisation
  - SCRT 25/5 + early surgery
  - LCRT 50.4/28 + 5-FU/FA + delayed surgery

	SCRT	LCRT	*p value*
Crude LR	9%	14.2%	0.170
4-year OS	67.2%	66.2%	0.96
Acute toxicity	3.2	18.2	< 0.001
Late toxicity	10.1%	7.1%	0.360

Bujko K. Br J Surg. 2006;93(10):1215-23

TROG 01.04
Trans-Tasman Radiation Oncology Group

- 326 patients. T3N0-2 on MRI or US.
- Randomisation
  - SCRT 25/5 + early surgery + 6# chemo.
  - LCRT 50.4/28 + 5-FU + delayed surgery + 4# chemo

	SCRT	LCRT	*p value*
3-year LR	7.5%	4.4%	0.23
Distal tumours (≤5 cm)	6/48	1/31	0.21
5-year OS	74%	70%	0.62
Late toxicity	5.8%	8.2%	0.53

Ngan SY. J Clin Oncol. 2012;30(31):3827-33

Clinical and pathological downstaging

- 83 patients. Resectable stage II and III.
- Randomisation
  - SCRT 25/5 + delayed surgery
  - LCRT 46 Gy + 5-FU + delayed surgery + 4# chemo

	SCRT	LCRT	*p value*
Sphincter preservation	70.3%	69.6%	0.342
Post-op complications	40.5%	26.1%	0.221
R0 resection	86.5%	91.3%	0.734
Pathological downstaging	21.6%	39.1%	0.07

Latkauskas T. Colorectal Dis. 2012;14(3):294-8

Conclusion 4

	SCRT	LCRT
Local recurrence	=	=
Survival	=	=
Toxicity (acute)	✓	✗
Toxicity (late)	=	=
Sphincter preservation	=	=

Summary

For operable rectal cancers

- Compared to post-op RT, post-op chemo-RT reduces LR + improves survival
- Compared to pre-op RT, pre-op chemo-RT reduces LR but does not improve survival
- Compared to post-op (C)RT, pre-op (C)RT reduces LR + reduces toxicity
- Short course RT is equivalent to long course CRT

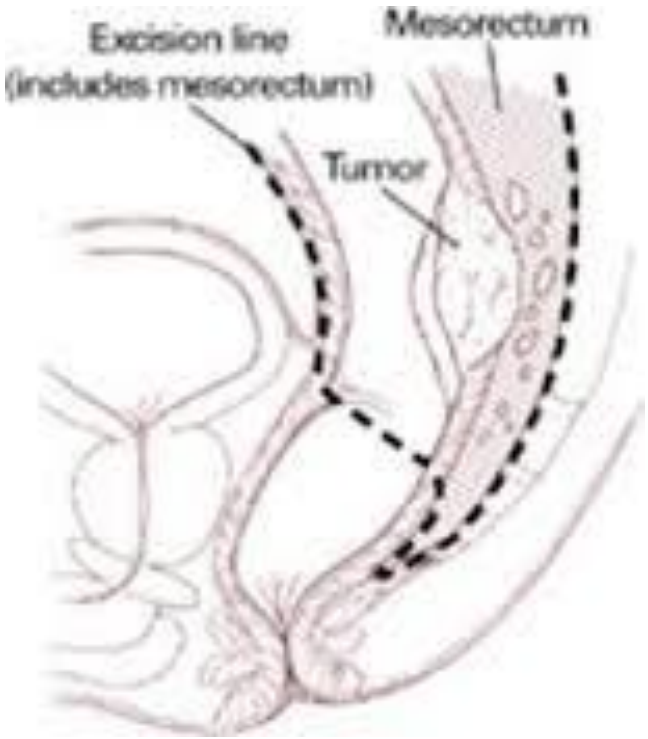
Question

- Why have post-op CRT studies shown a survival improvement whereas pre-op CRT studies have not?

Possible answers

- Post-op studies (older)
  - Pathological information available
  - Poorer prognosis patients selected for evaluation
- Pre-op studies (newer)
  - Better control arms (better training)

Better surgery (TME)

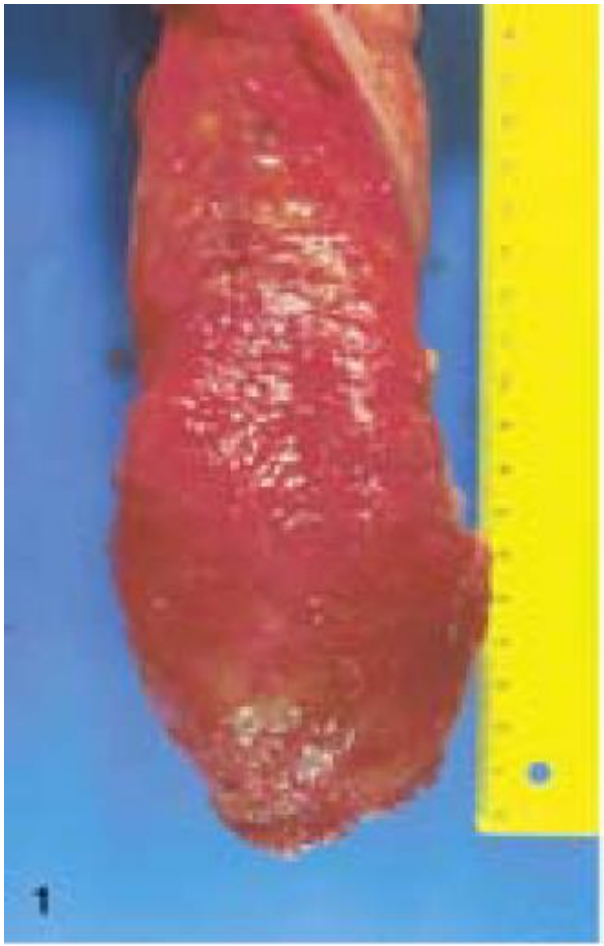


	Good Mesorectal	Intermediate Intra-mesorectal	Poor Muscularis propria
CRM +ve rate	9%	12%	19%

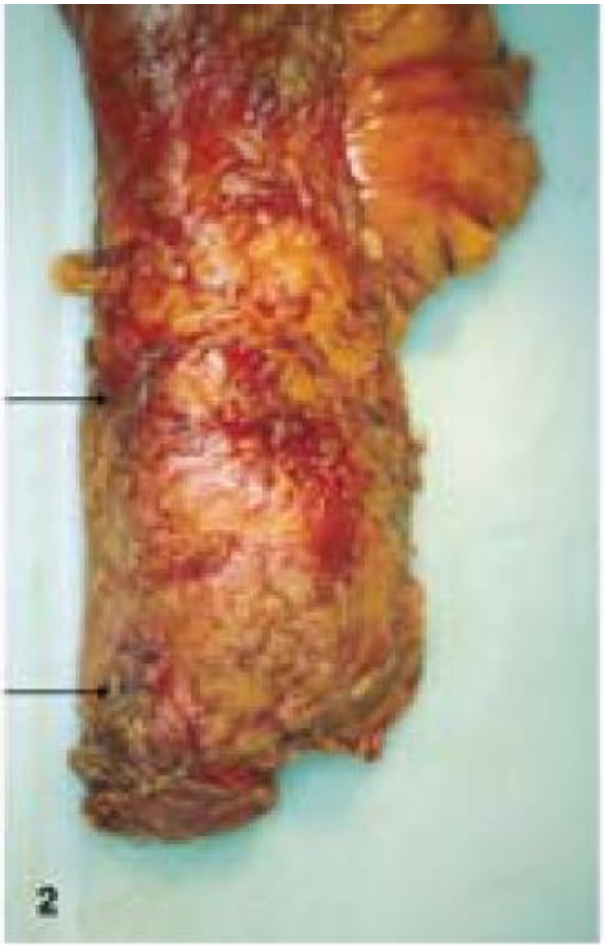
Quirke P, et al. Lancet. 2009; 373(9666): 821–828

Total mesorectal excision

Good



Intermediate



Poor

SCRT studies

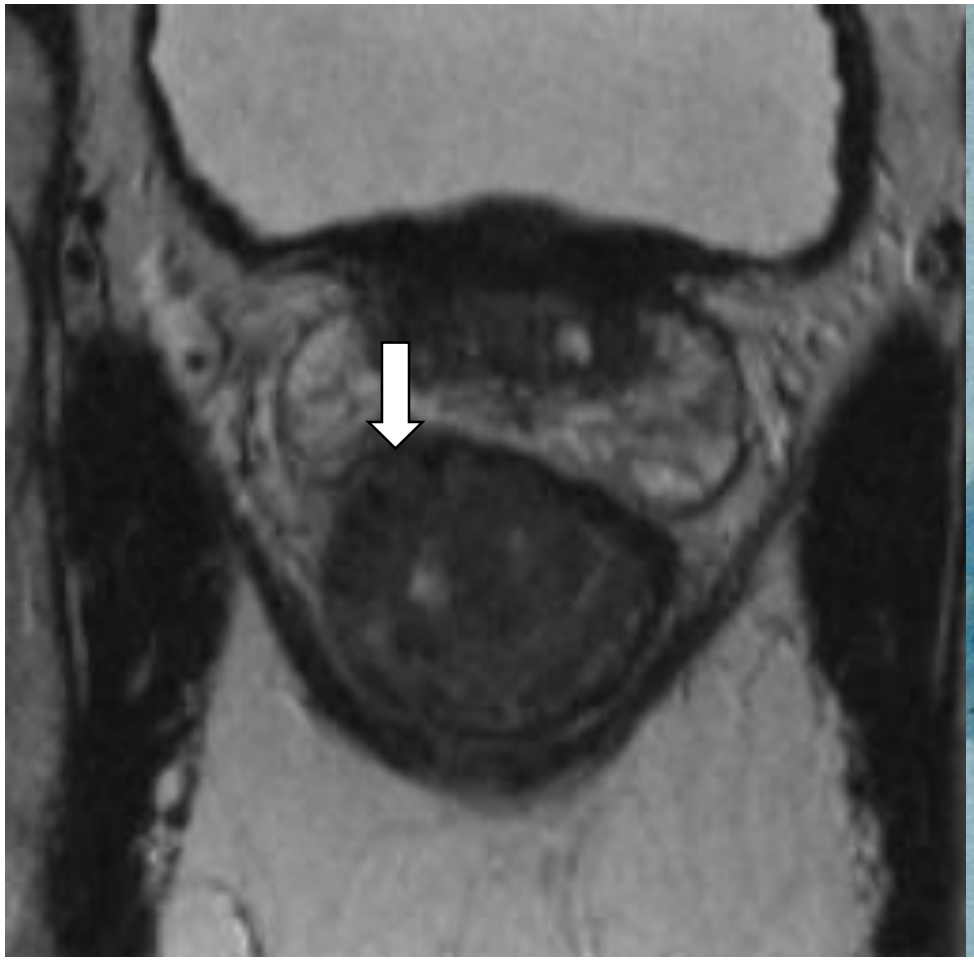
Study	Participants	Good TME	LR
Swedish Rectal Cancer Trial	1987-1990	<10%	19.2% (213/1110)
MRC CR07	1998-2005	51%	7.5% (99/1350)
Dutch TME	1996-1999	56%	7.3% (140/1861)
MERCURY	2002-2003	73%	5.3% (13/246)

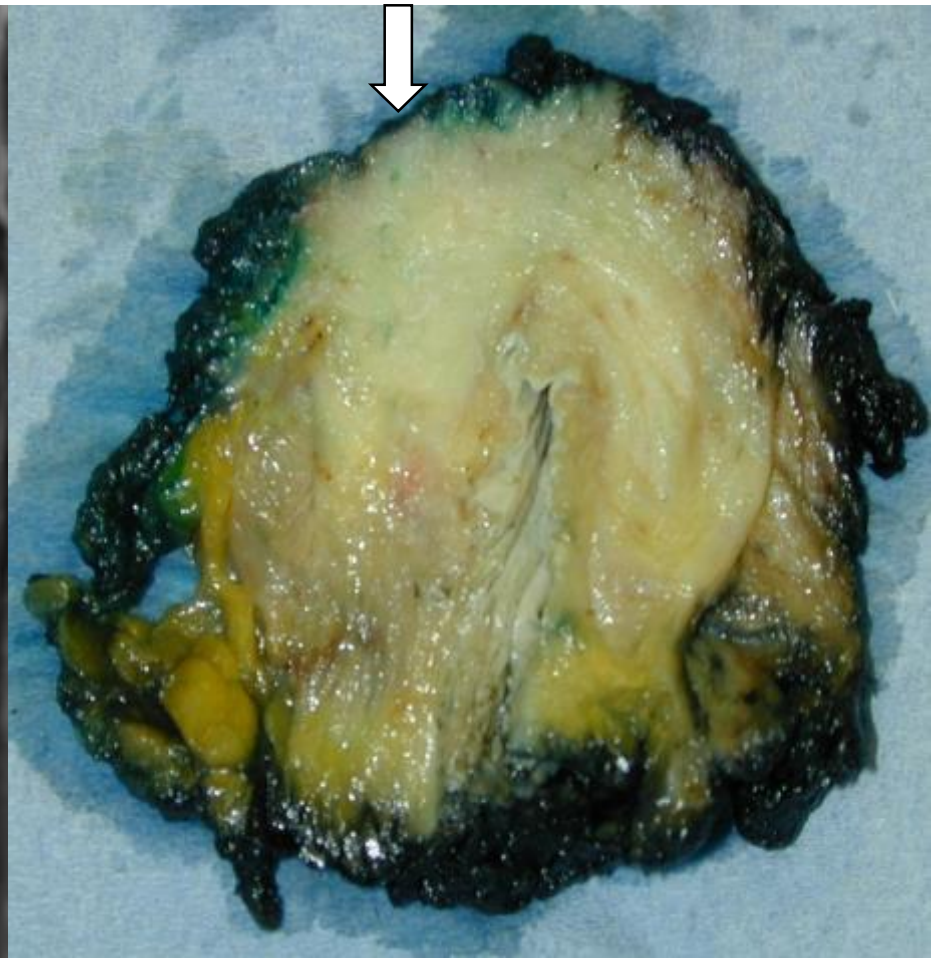
RT does not compensate for poor surgery

	TME		RT + TME	
	n	LR (%)	*n*	LR (%)
>2 mm	483	5.8	504	0.9
1–2 mm	53	14.9	47	0
≤1 mm	120	16.4	107	9.3
Postoperative RT	56	17.3	—	
No postoperative RT	64	15.7	—	
Total	656	8.4	662	2.1

Marijnen CA, et al. Int J Radiat Oncol Biol Phys. 2003;55(5):1311-20

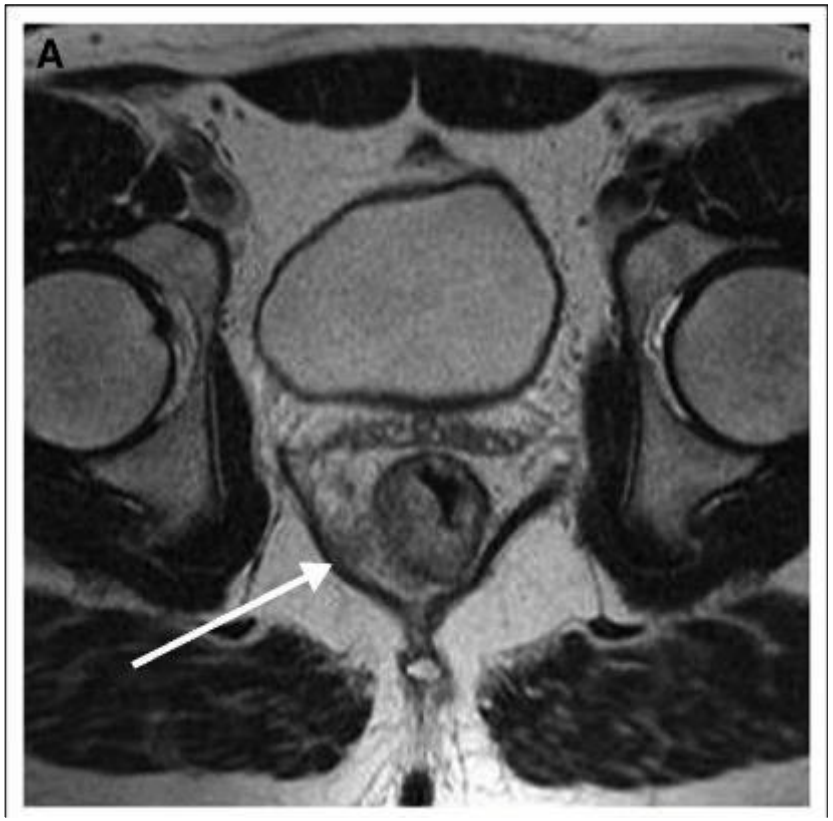
Better pathology

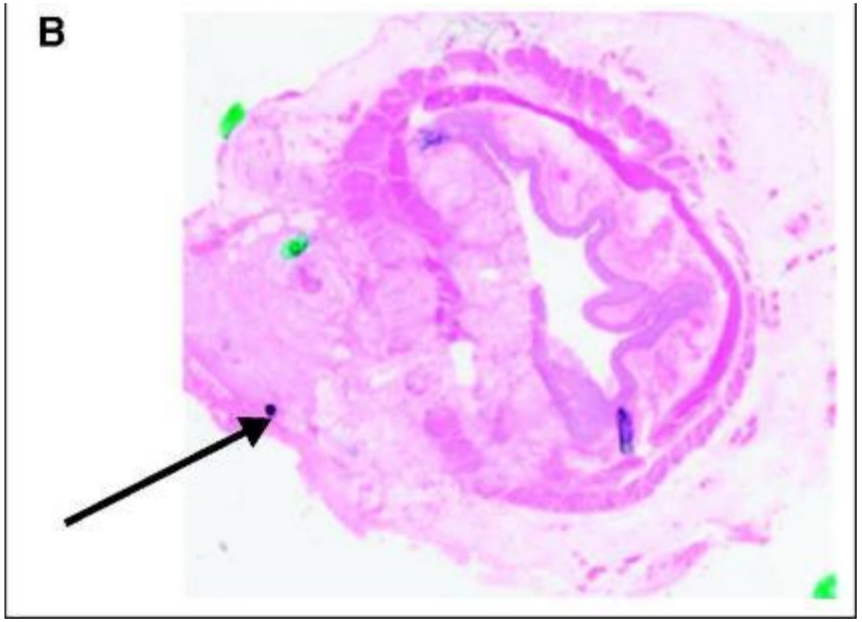




Better imaging

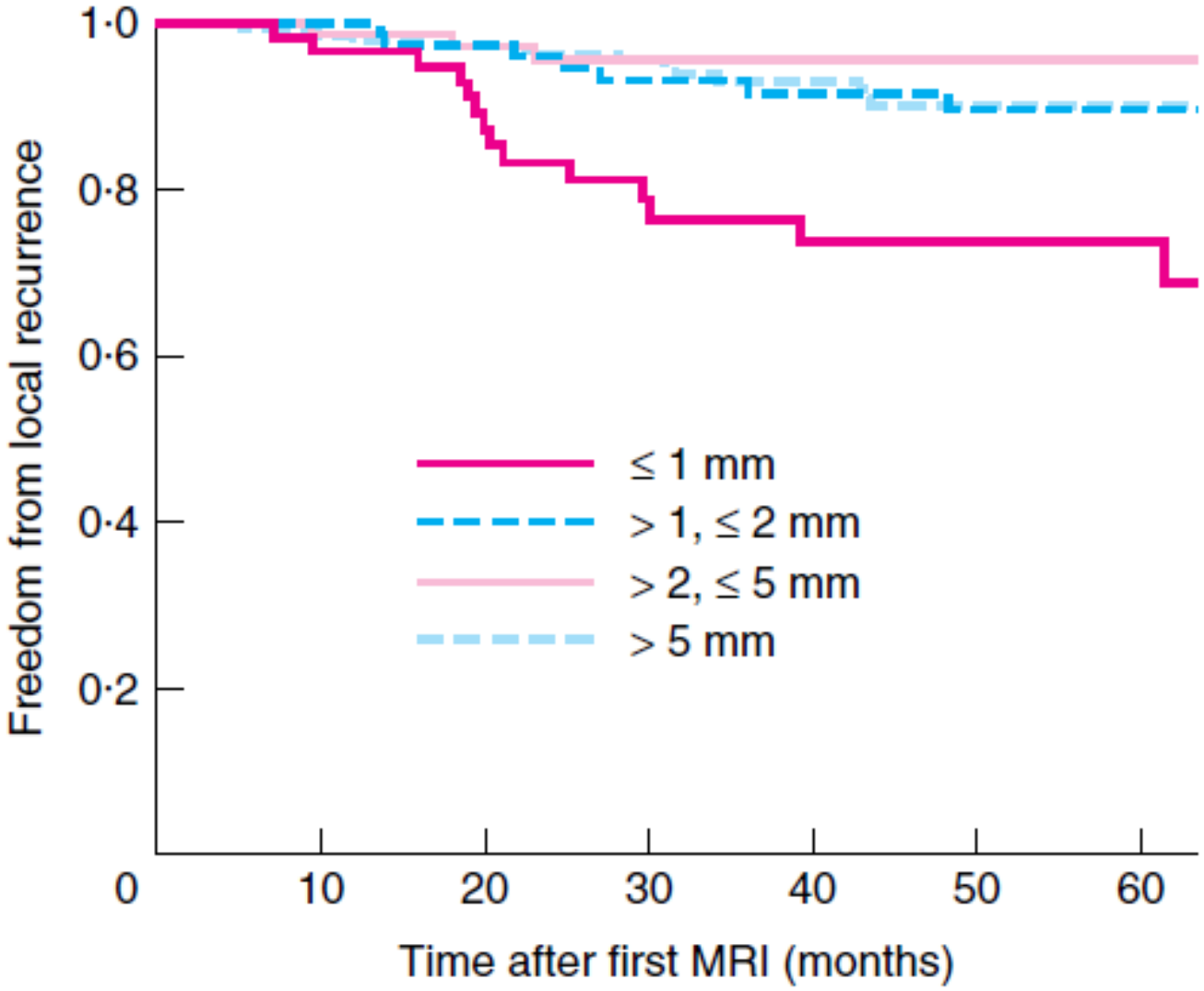
- **M**agnetic R**e**sonance Imaging and **R**ectal **C**ancer E**ur**opean Equivalence Stud**y** (MERCURY)





Taylor FG, et al. J Clin Oncol. 2014;32(1):34-43

MERCURY



Taylor FG, et al. Br J Surg. 2011;98(6):872-9

MERCURY

- Pre-op MRI assessment of CRM predicts DFS + LR

	mCRM clear (n=310)		mCRM involved (n = 64)	
	Clear	Involved	Clear	Involved
(y)pCRM	94%	6%	47%	53%
LR	6%	21%	10%	32%

Under-reporting = 6%, Over-reporting 47%

Taylor FG, et al. J Clin Oncol. 2014;32(1):34-43

Outline

- Past questions
  - Chemo-RT or RT alone?
  - Pre-op or post-op?
  - Long course or short course?
- **Guidelines**
- Current questions

Risk-stratified treatment (pre-op)

- Early ('**Good**')

– surgery alone sufficient

- Intermediate ('**Bad**')

– give pre-op RT (5 × 5 Gy) **or** CRT

- Locally advanced ('**Ugly**')

– CRT needed to achieve high probability of R0 surgery

Glimelius B. Ann Oncol. 2010;21 Suppl 5:v82-6.

TNM 7

Primary Tumor (T)

- **TX** Primary tumor cannot be assessed
- **T0** No evidence of primary tumor
- **Tis** Carcinoma in situ: intraepithelial or invasion of lamina propria[1]
- **T1** Tumor invades submucosa
- **T2** Tumor invades muscularis propria
- **T3** Tumor invades through the muscularis propria into pericolorectal tissues
- **T4a** Tumor penetrates to the surface of the visceral peritoneum[2]
- **T4b** Tumor directly invades or is adherent to other organs or structures[2,3]

Regional Lymph Nodes (N)[4]

- **NX** Regional lymph nodes cannot be assessed
- **N0** No regional lymph node metastasis
- **N1** Metastasis in 1–3 regional lymph nodes
- **N1a** Metastasis in one regional lymph node
- **N1b** Metastasis in 2–3 regional lymph nodes
- **N1c** Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- **N2** Metastasis in 4 or more regional lymph nodes
- **N2a** Metastasis in 4–6 regional lymph nodes
- **N2b** Metastasis in 7 or more regional lymph nodes

MRI staging (ESMO)

- **T3:** tumour invades through the muscularis propria into the subserosa or into non-peritonealised perirectal tissues
  - **T3a:** tumour extends <1 mm beyond muscularis propria [4]
  - **T3b:** tumour extends 1-5 mm beyond muscularis propria [4]
  - **T3c:** tumour extends 5-15 mm beyond muscularis propria [4]
  - **T3d:** tumour extends 15 mm beyond muscularis propria [4]

Glimelius B. Ann Oncol. 2010;21 Suppl 5:v82-6.

MRI staging (RSNA)

Mid to high

T3	Tumor invades through muscularis propria to pericolorectal tissues
a	Tumor < 5 mm into the perirectal fat or extramural
b	Tumor 5–10 mm into the perirectal fat or extramural
c	Tumor > 10 mm into the perirectal fat or extramural

Low

T1	Tumor confined to bowel wall but does not extend through full thickness; intact outer muscle coat
T2	Tumor replaces muscle coat but does not extend into intersphincteric plane
T3	Tumor invades intersphincteric plane or lies within 1 mm of levator muscle
T4	Tumor invades external anal sphincter and is within 1 mm and beyond levator muscle with or without invading adjacent organs

Hussain S. Published December 1, 2009. Updated July 16, 2012

Taylor FG. AJR 2008; 191:1827–1835.

ESMO guidelines

Good 	cT1-2, cT3a (b) if middle or high, N0 (or cN1 if high), mrf-, no EMVI cT3b = ≤5mm
Bad 	cT2 very low, cT3mrf- (unless cT3a(b) and mid- or high rectum), N1-2, EMVI+, limited cT4aN0
Ugly 	cT3mrf+, cT4a,b, lateral node+

Glimelius B. Ann Oncol. 2010;21 Suppl 5:v82-6.

NCCN

CLINICAL STAGE	NEOADJUVANT THERAPY[m]
T3, N0 or T any, N1-2 or T4 and/or locally unresectable or medically inoperable	Chemo/RT • Capecitabine/long-course RT[m] or infusional 5-FU/ long-course RT[m] (category 1 and preferred for both) or • Bolus 5-FU/leucovorin/ long-course RT[m,n] or RT[m] • Short-course RT[o] (not recommended for T4 tumors) or Chemotherapy[p] • FOLFOX (preferred) or CapeOx (preferred) or • 5-FU/leucovorin or capecitabine

NICE CG131 (UK)

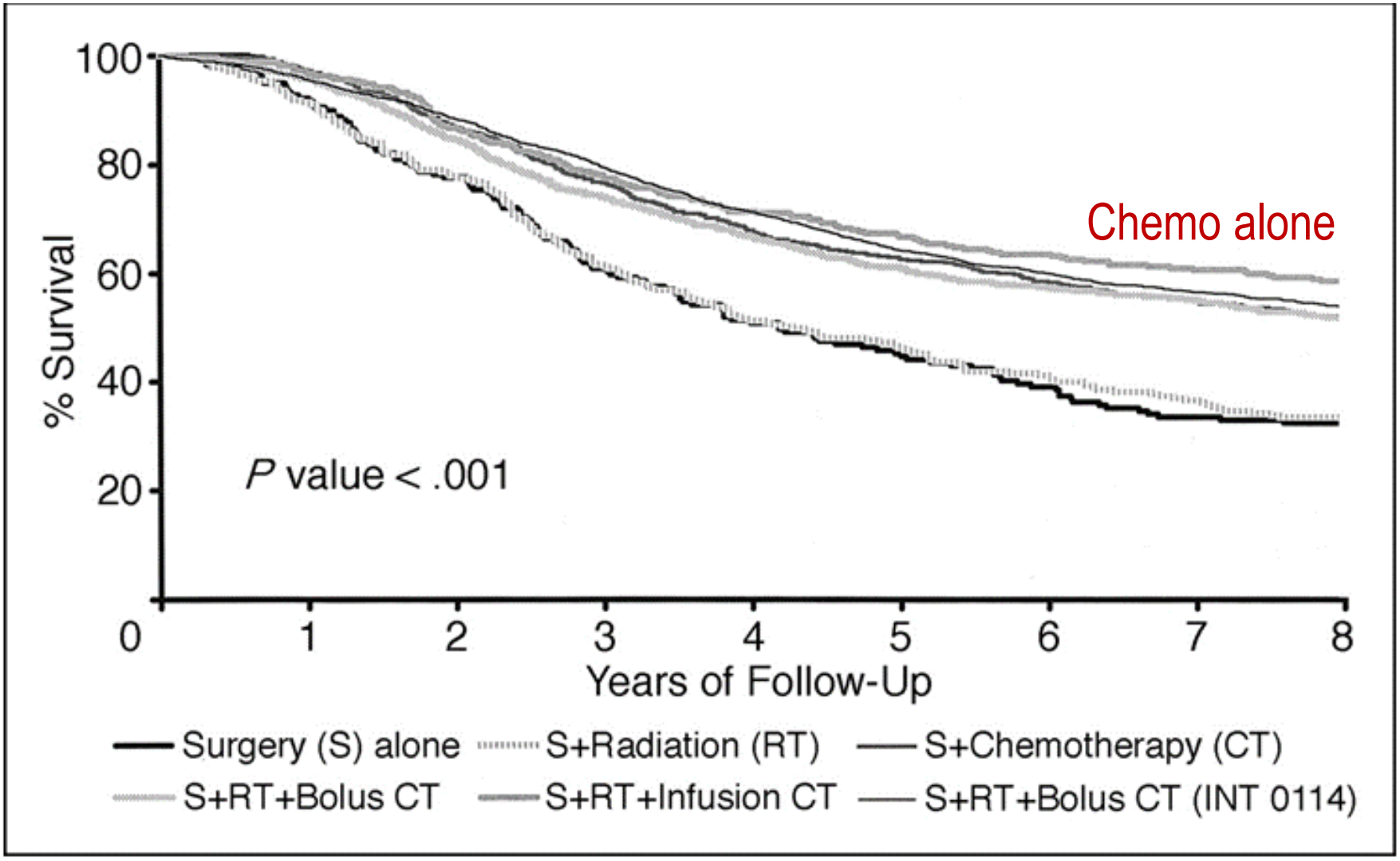
Good 	• cT1 or cT2 or cT3a **and** • No lymph node involvement cT3a = <5mm
Bad 	• Any cT3b or greater, in which the potential surgical margin is not threatened **or** • Any suspicious lymph node not threatening the surgical resection margin **or** • The presence of extramural vascular invasion
Ugly 	• A threatened (<1 mm) or breached resection margin **or** • Low tumours encroaching onto the inter-sphincteric plane **or** with levator involvement

NICE 2014

Indications for post-op CRT

- ESMO
  - CRM+ or N+
- NCCN
  - N+
  - pT3-4, N0
- NICE
  - CRM+

NCCTG pooled analysis



Gunderson LL et al. J Clin Oncol. 2004;22(10):1785-96

Outline

- Past questions
  - Chemo-RT or RT alone?
  - Pre-op or post-op?
  - Long course or short course?
- Guidelines
- **Current questions**

The quest

	Good 	Bad 	Ugly 
Local control	⇔		↑
Survival	⇔	↑	↑
Acute toxicity	↓	⇔	
Late toxicity	↓	⇔	
Sphincter preservation	↑	↑	⇔

Options

- Chemotherapy
  - Drugs
  - Sequencing
- Radiotherapy
  - Sequencing
  - IMRT
  - BT
- Surgery
  - Local surgery
  - No surgery
  - Timing
- Imaging
  - PET-CT
  - Functional

Options

- **Chemotherapy**
  - **Drugs**
  - **Sequencing**
- Radiotherapy
  - Sequencing
  - IMRT
  - BT
- Surgery
  - Local surgery
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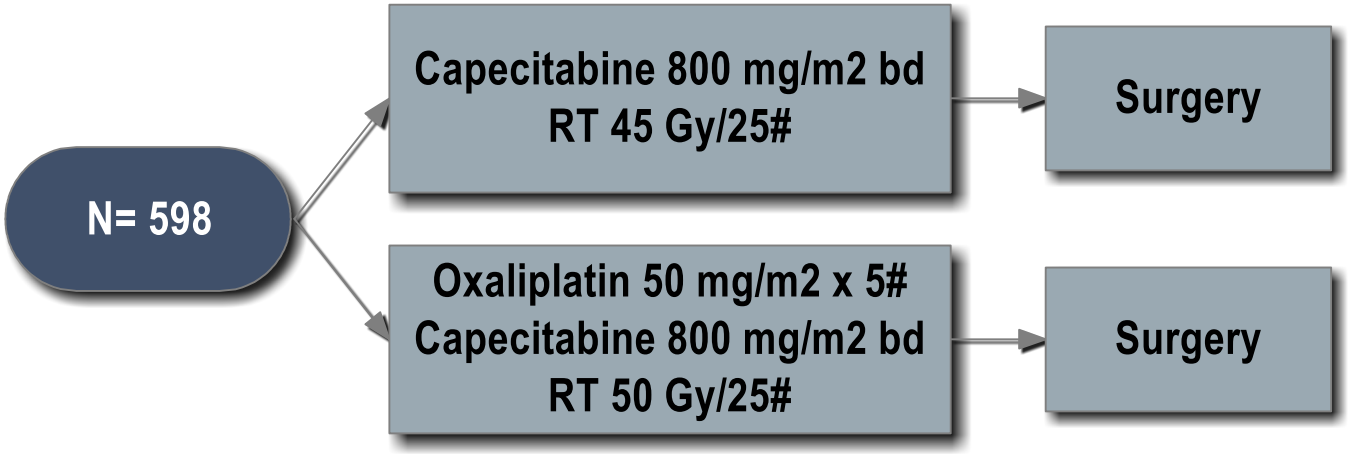
  - Timing
- Imaging
  - PET-CT
  - Functional

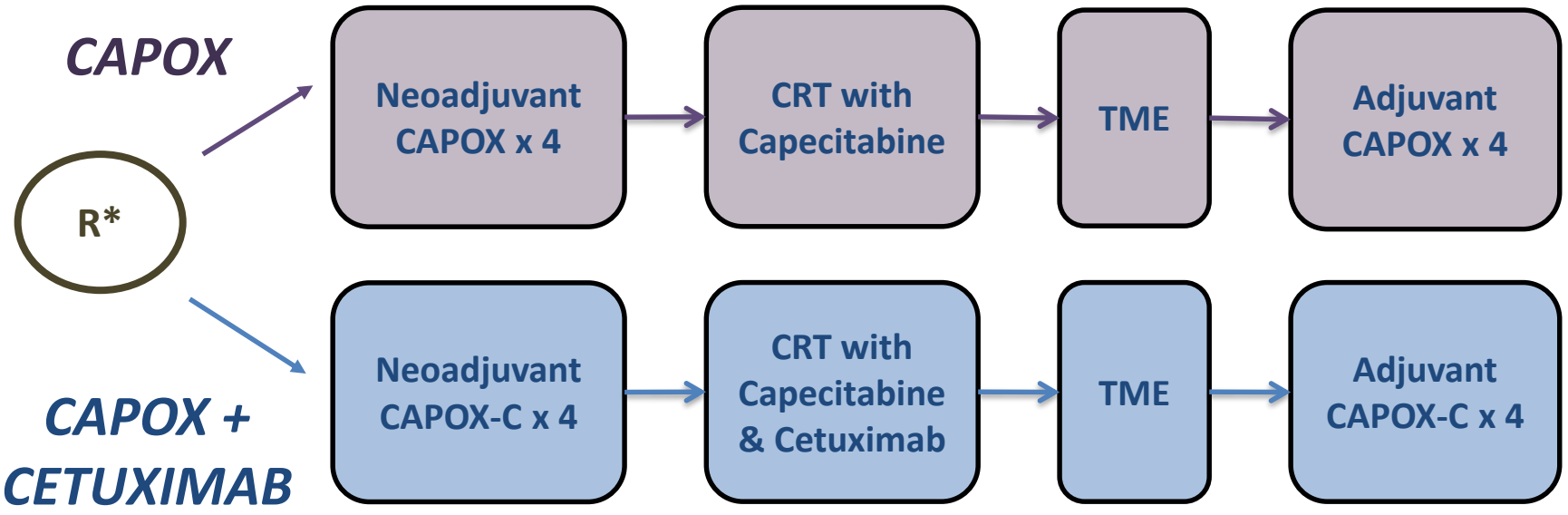
ACCORD 12/0405-Prodige 2



	Cap45	Capox50	*p value*
pCR	13.9%	19.2%	0.09
Sphincter sparing	74.6%	75.4%	
Local recurrence	6.1%	4.4%	
Overall survival	87.6%	88.3%	
Acute G3-4 diarrhoea	3.2%	12.6%	<0.001

Gerard JP, J Clin Oncol. 2010 Apr 1;28(10):1638-44

The EXPERT-C trial – Design



**Patients recruited from 15 European Centres 2005-2008*

Key inclusion criteria:

- Tumours within 1mm of mesorectal fascia
- Tumours extending ≥5mm into peri-rectal fat
- T4 tumours
- Presence of extramural vascular invasion
- T3 tumours at/below levators

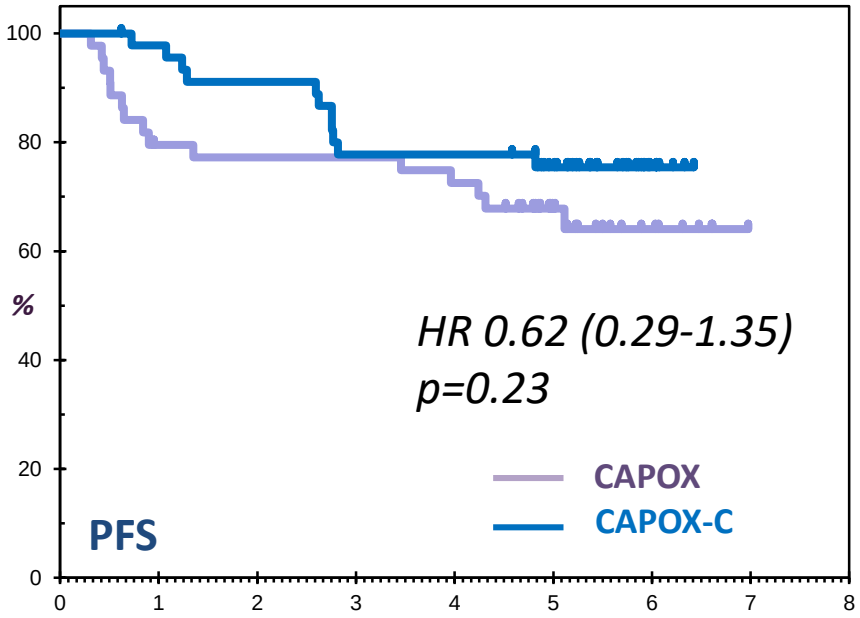
Endpoints

- Primary endpoint:
  CR in *KRAS/BRAF* WT patients
- Secondary endpoints:
  RR, PFS, OS, safety and QoL

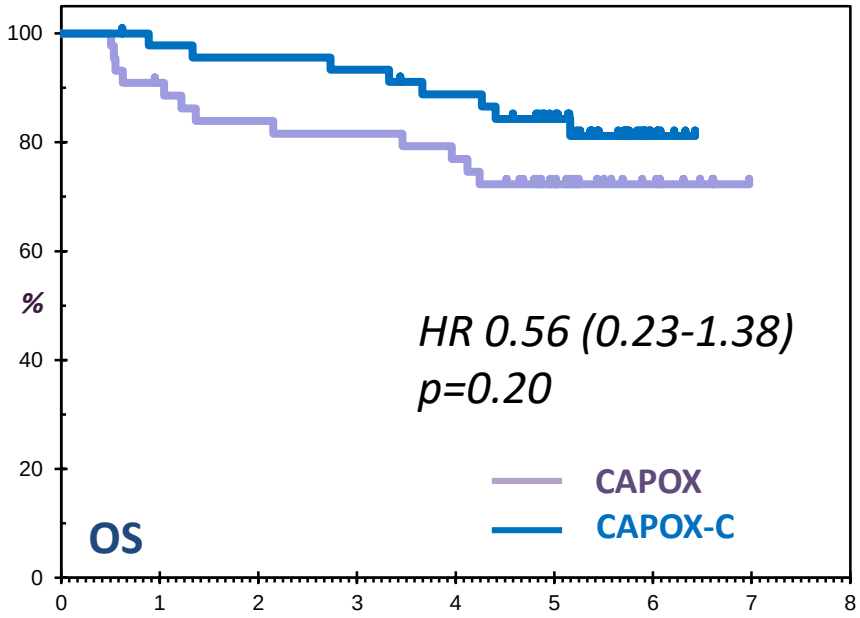
Dewdney, J Clin Oncol 2012

The EXPERT-C trial – Results

- No significant improvement in PFS and OS in the *KRAS/BRAF* WT group (median follow-up 63.8 months)



Time from randomisation (years)



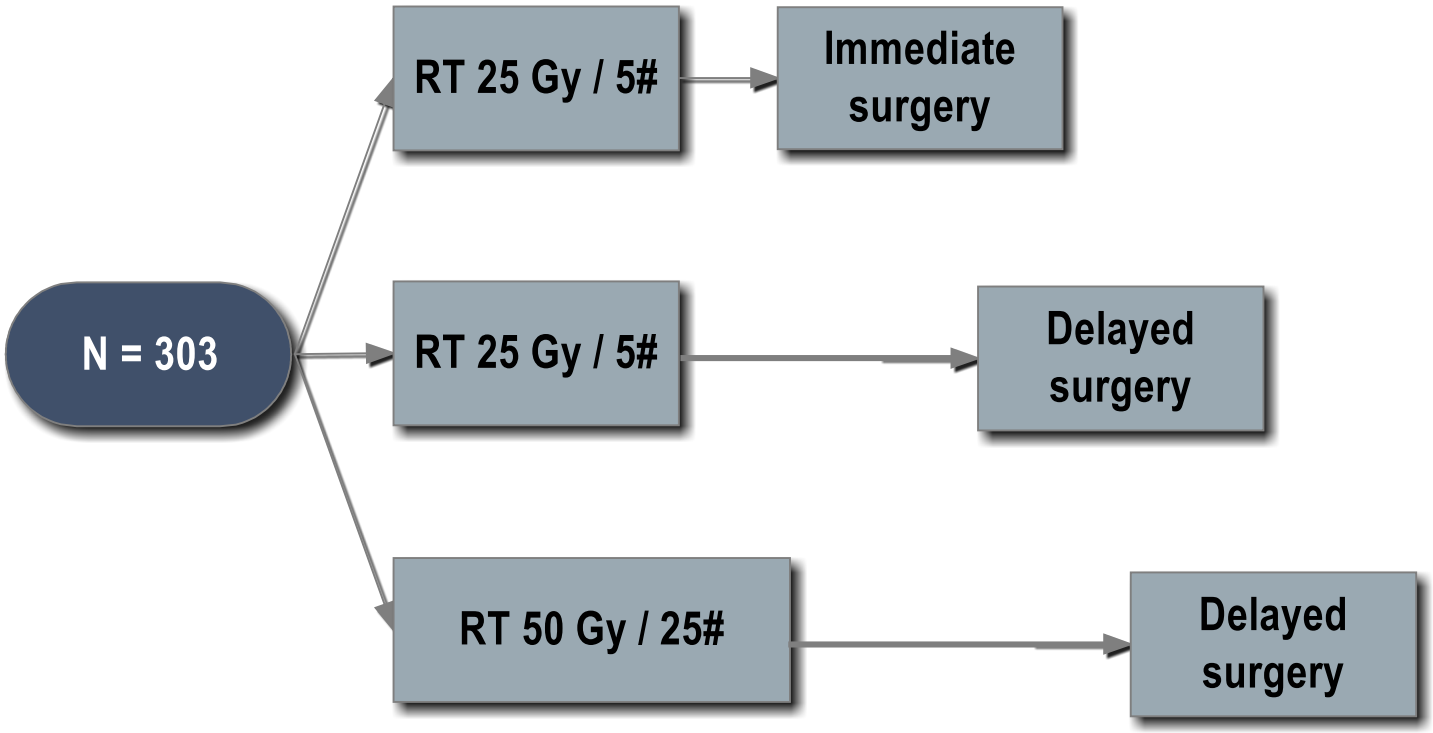
Time from randomisation (years)

Sclafani, ESMO 2013

Options

- Chemotherapy
  - Drugs
  - Sequencing
- **Radiotherapy**
  - **Sequencing**
  - **IMRT**
  - **BT**
- Surgery
  - Local surgery
  - No surgery
  - Timing
- Imaging
  - PET-CT
  - Functional

Stockholm III

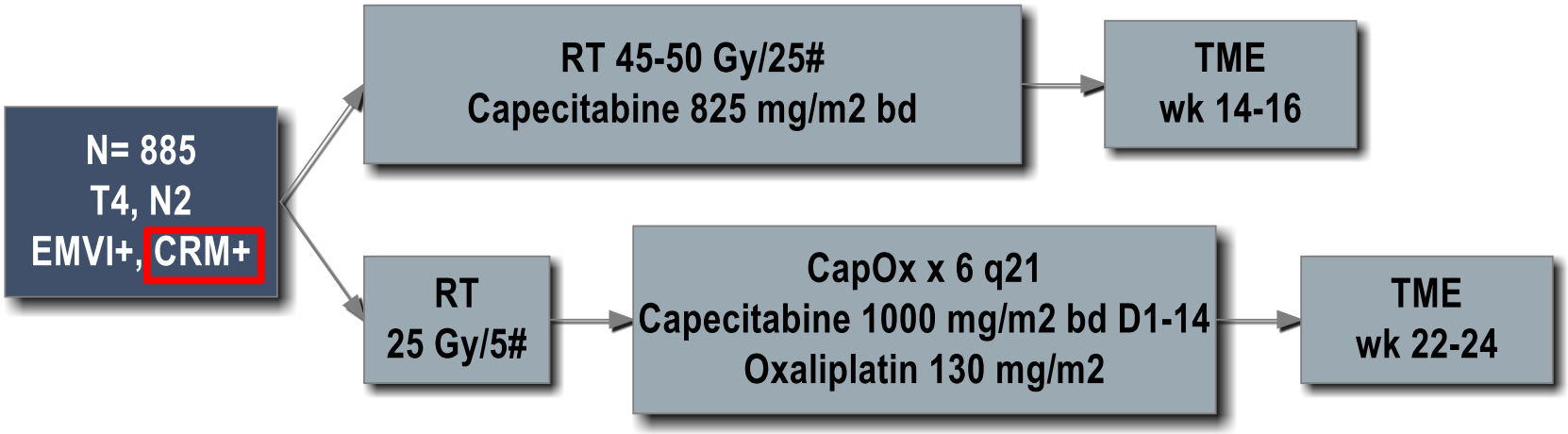


Stockholm III

- Longer delay after SCRT results in
  - Lower ypT categories
  - Higher rate of pathological CR (11·8% vs 1·7%; P = 0·001)
  - More Dworak grade 4 tumour regression (10·1% vs 1·7%; P < 0·001)

Pettersson D. Br J Surg. 2015;102(8):972-8

RAPIDO



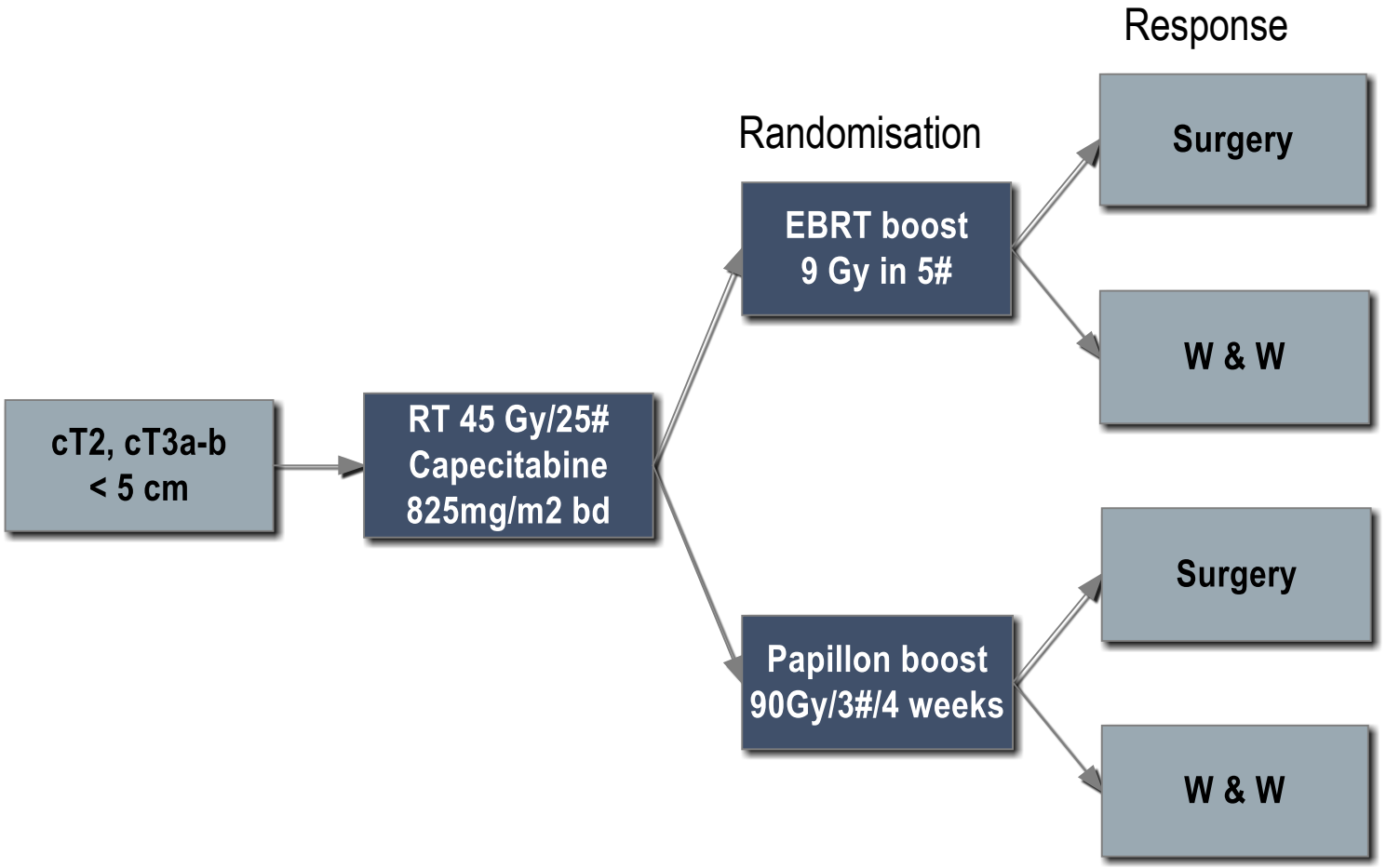
- End points
  - 3-year DFS
  - OS, CRM status, pCR, acute + late toxicity, surgical complications, QoL

Brachytherapy

- 200 patients, T1-T4, Papillon boost (80-110 Gy in 3-4#)
  - CRT = 127 (63%)
  - SCRT = 57 (28%)
  - No EBRT = 16 (8%)
- Results
  - CR = 136 (68%), maintained in 116
  - PR = 64 (34%), 38 immediate surgery, 8 = ypT0
  - Organ preservation = 79%

Sun Myint, ESTRO 35, 2016, Abstract 0283

OPERA study

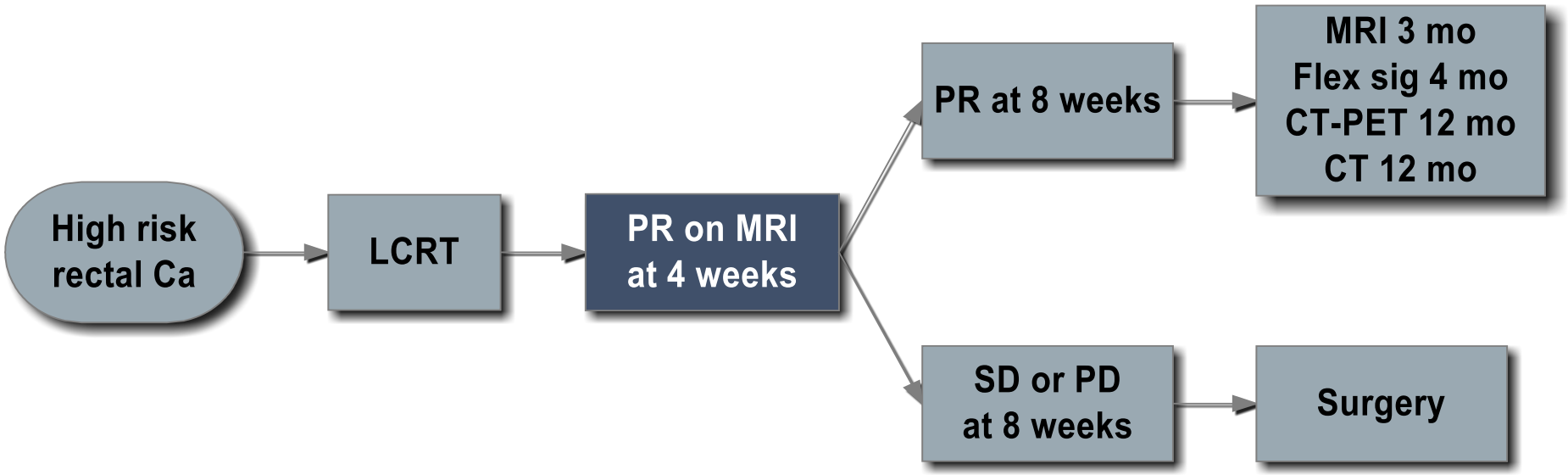

Response
Randomisation
cT2, cT3a-b
< 5 cm
RT 45 Gy/25#
Capecitabine
825mg/m2 bd
EBRT boost
9 Gy in 5#
Papillon boost
90Gy/3#/4 weeks
Surgery
W & W
Surgery
W & W

Options

- Chemotherapy
  - Drugs
  - Sequencing
- Radiotherapy
  - Sequencing
  - IMRT
  - BT

- **Surgery**
  - **Local surgery**
  - **No surgery**
  - **Timing**
- Imaging
  - PET-CT
  - Functional

Royal Marsden Delayed Surgery



Current Status	Open
Closure Date	30/06/2015
Global Sample Size	59
Global Recruitment to Date	118%

MERRION

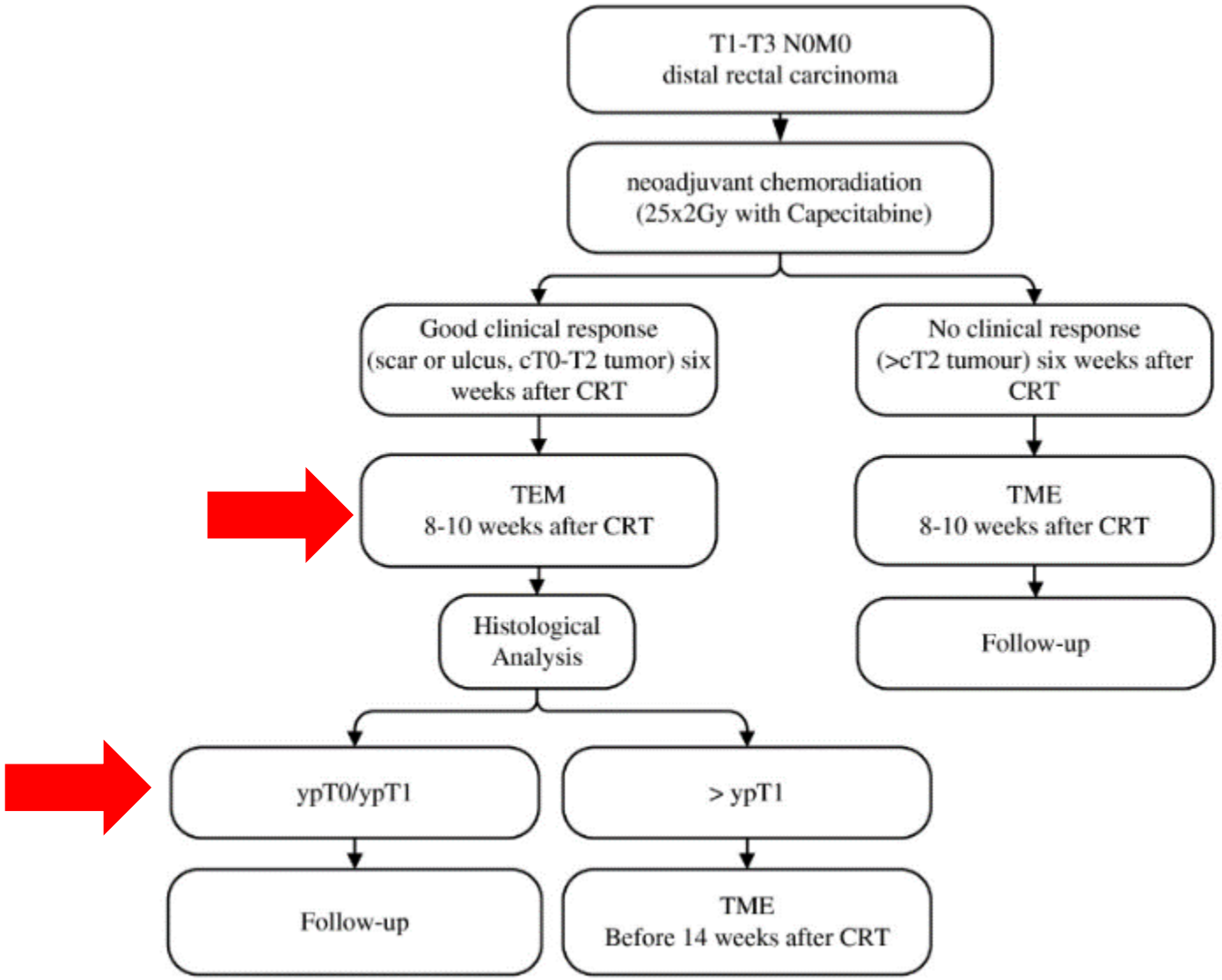
- **M**ulticenter **E**valuation of **R**ectal cancer **R**e**I**maging p**O**st **N**eoadjuvant Therapy

	yMRT Stage		
ypT Stage	**<yMRT4**	**yMRT4**	**Total**
<ypT4	217	27	244
ypT4	6	17	23
Total	223	44	267
Kappa statistic (κ)		0.445	

MR understages 26.1% (6/23) of ypT4 tumors and overstages 11.1% (27/244) of ypT0-3 tumors. The associated κ statistic of 0.445 indicates unacceptable agreement of MR with pathological staging.

Hanly AM, et al. Ann Surg. 2014;259(4):723-7

Dutch CARTS study



Dutch CARTS study

- 55 patients
  - cT1 N0 = 10, cT2 N0 = 29, cT3 N0 =16
- 47 patients had TEM
  - ypT0-1 disease in 30
- Local recurrence developed in 3 of 9 (33%) patients with ypT2 tumours who declined further surgery
- TEM after chemo-radiotherapy enabled organ preservation in one-half of the patients with rectal cancer

Verseveld M, et al. Br J Surg. 2015;102(7):853-60

Dutch CARTS study

- Grade 3 complications = 42%
- Two deaths from toxicity

Verseveld M, et al. Br J Surg. 2015;102(7):853-60

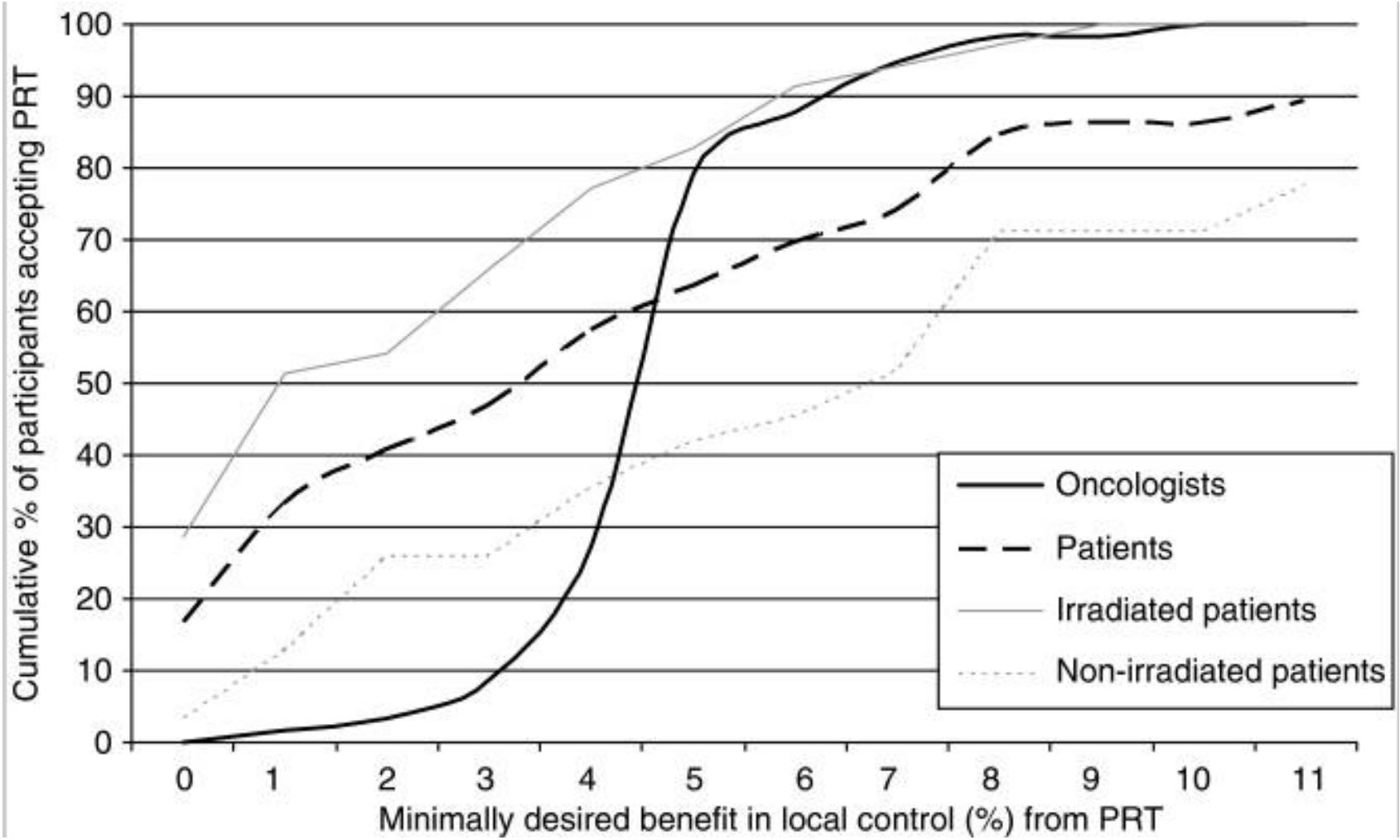
What benefit?

What benefit?

- Interview
  - 66 disease-free patients
  - 60 oncologists (surgical, radiation, medical)
- Outcome measures
  - Survival
  - Local control
  - Faecal incontinence
  - Sexual dysfunction

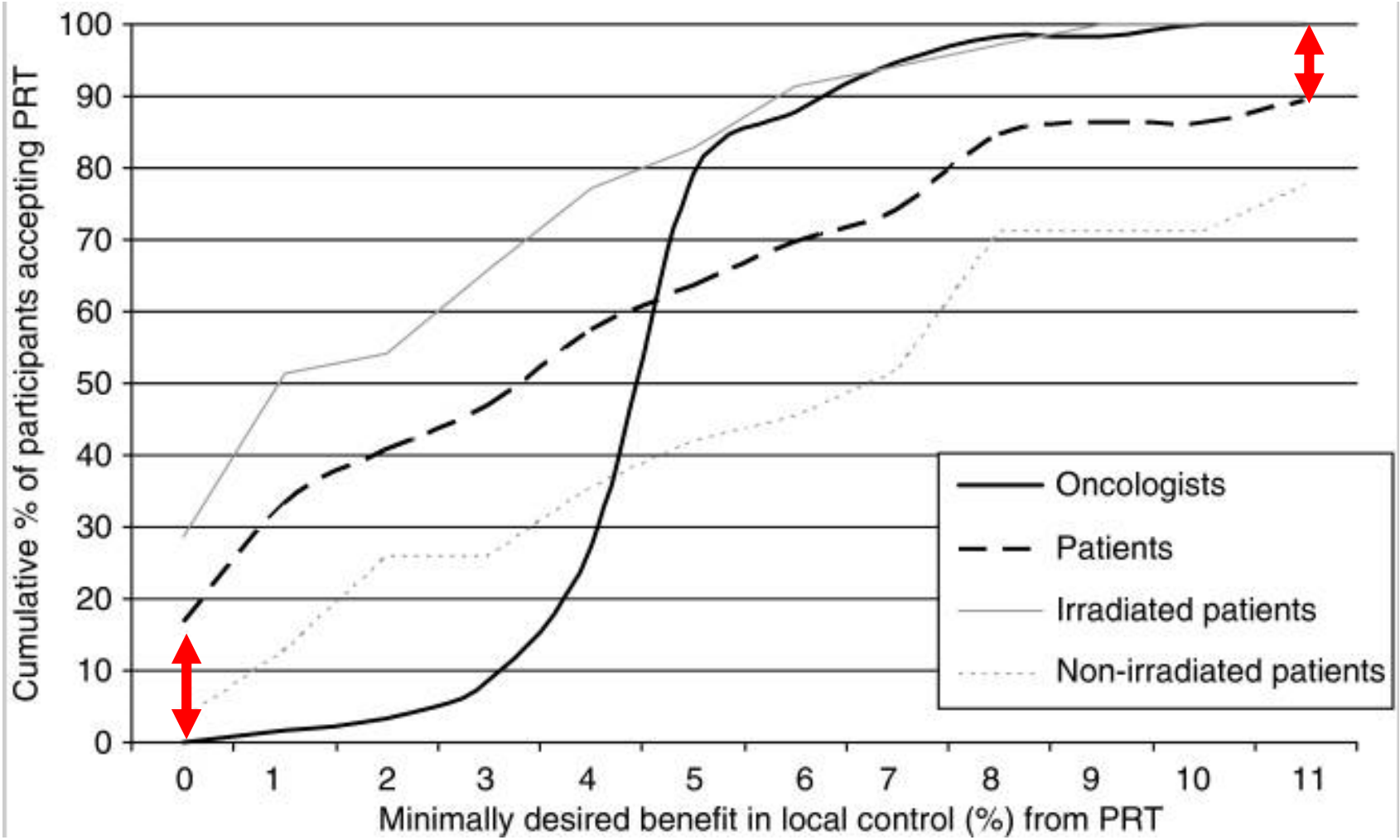
Pieterse AH, et al. Br J Cancer. 2007;97(6):717-24

Pre-op RT for LC



Pieterse AH, et al. Br J Cancer. 2007;97(6):717-24

Pre-op RT for LC



Pieterse AH, et al. Br J Cancer. 2007;97(6):717-24

Pre-op RT for LC

- Radiotherapists considered local control more important than medical oncologists (35±9 vs 24±8, P = 0.02) and surgeons (28±11, P = 0.04).
- Surgeons considered sexual dysfunction more important than radiotherapists (20±9 vs 14±5, P = 0.02).
- Medical oncologists considered survival more important than surgeons (28±9 vs 17±12, P = 0.05).
- Clinicians who had supervised tended to consider local control more important than clinicians who had not (36±9 vs 29±10 P = 0.05)

Pieterse AH, et al. Br J Cancer. 2007;97(6):717-24

Pre-op RT for LC

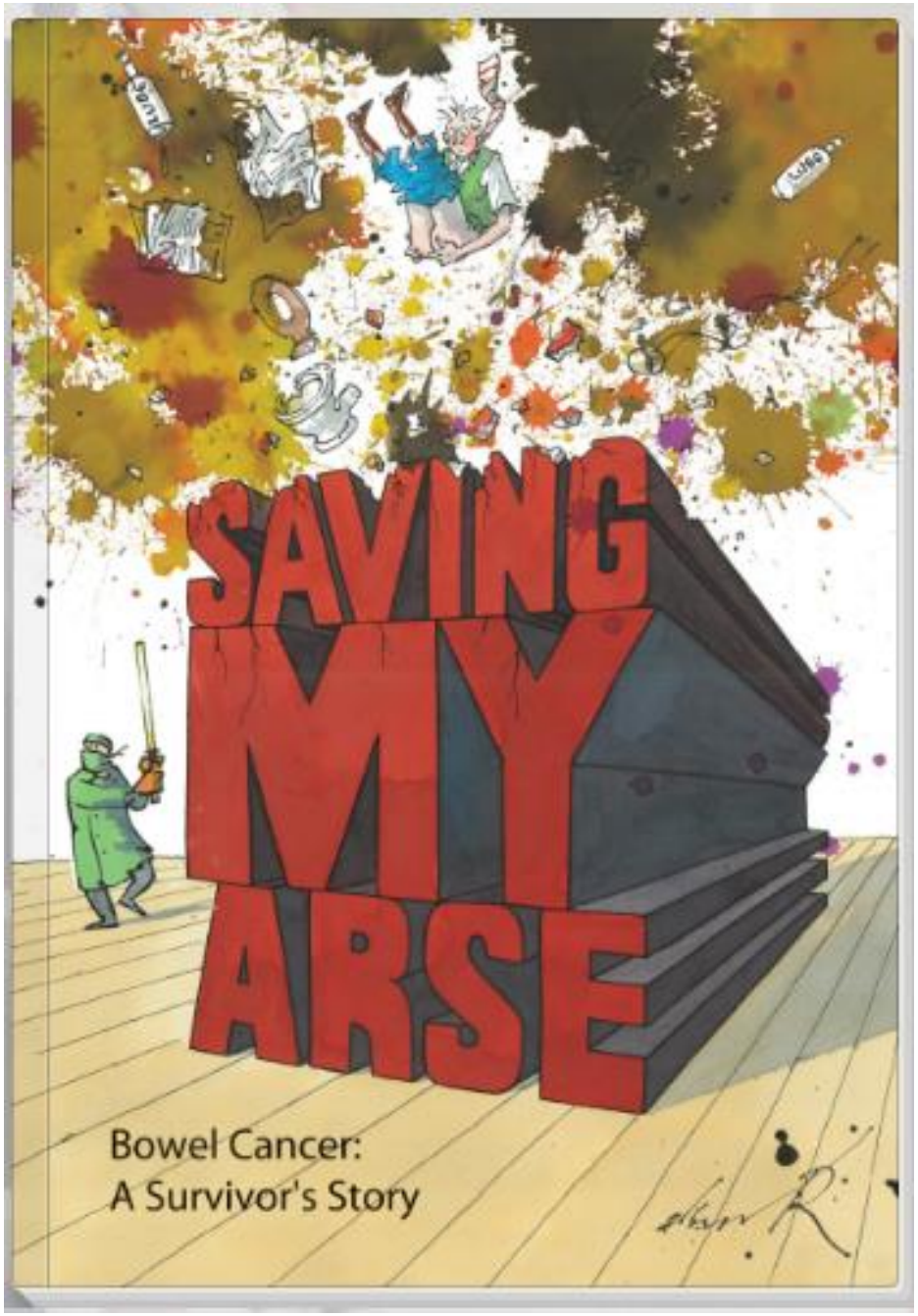
- One medical oncologist would not advise PRT to male patients, and only for a 7% benefit to female patients.
- One surgical oncologist would advise PRT to male patients for 6% benefit, but could not decide for female patients.

Pieterse AH, et al. Br J Cancer. 2007;97(6):717-24

Priority

	Patients	Oncologists	
Incontinence	29 (47%)	24 (41%)	**6%**
Local control	21 (34%)	20 (34%)	**0%**
Survival	7 (11%)	12 (20%)	**9%**
Sexual dysfunction	5 (8%)	3 (5%)	**3%**

Pieterse AH, et al. Br J Cancer. 2007;97(6):717-24


SAVING
MY
ARSE
Bowel Cancer:
A Survivor's Story

Explaining risk benefit

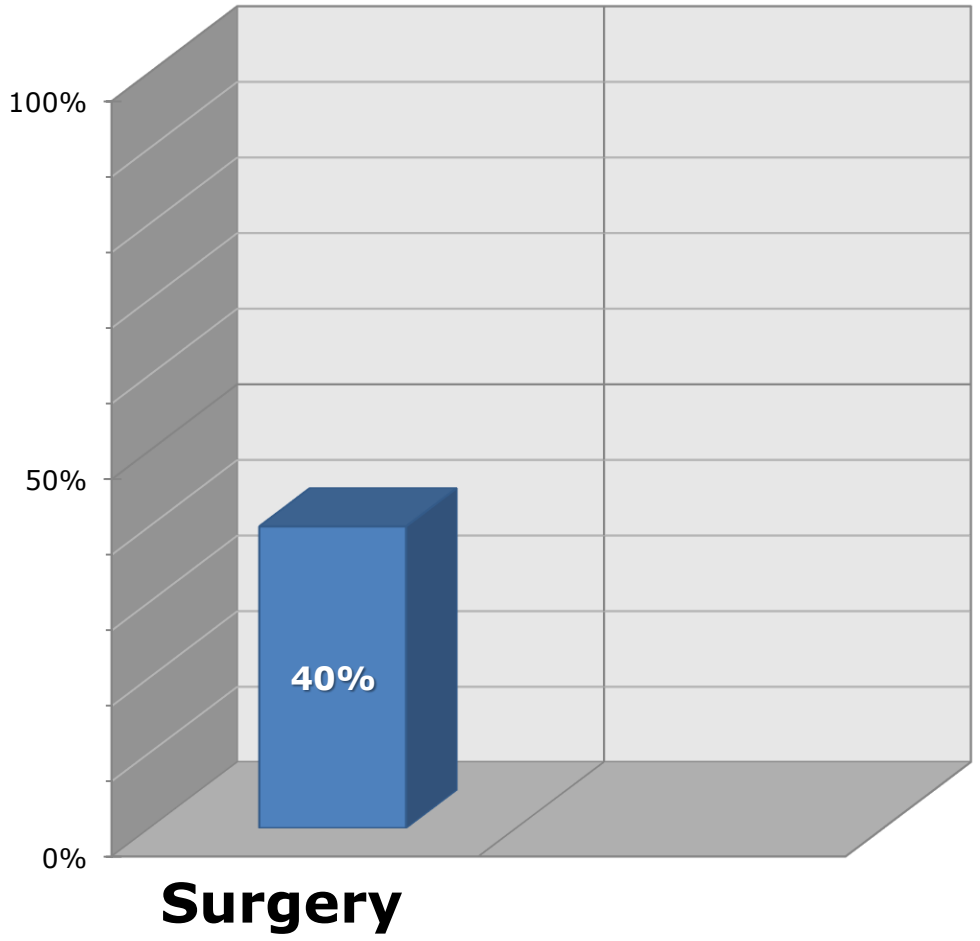
I don't understand?

Those are good results.
Just trust me.

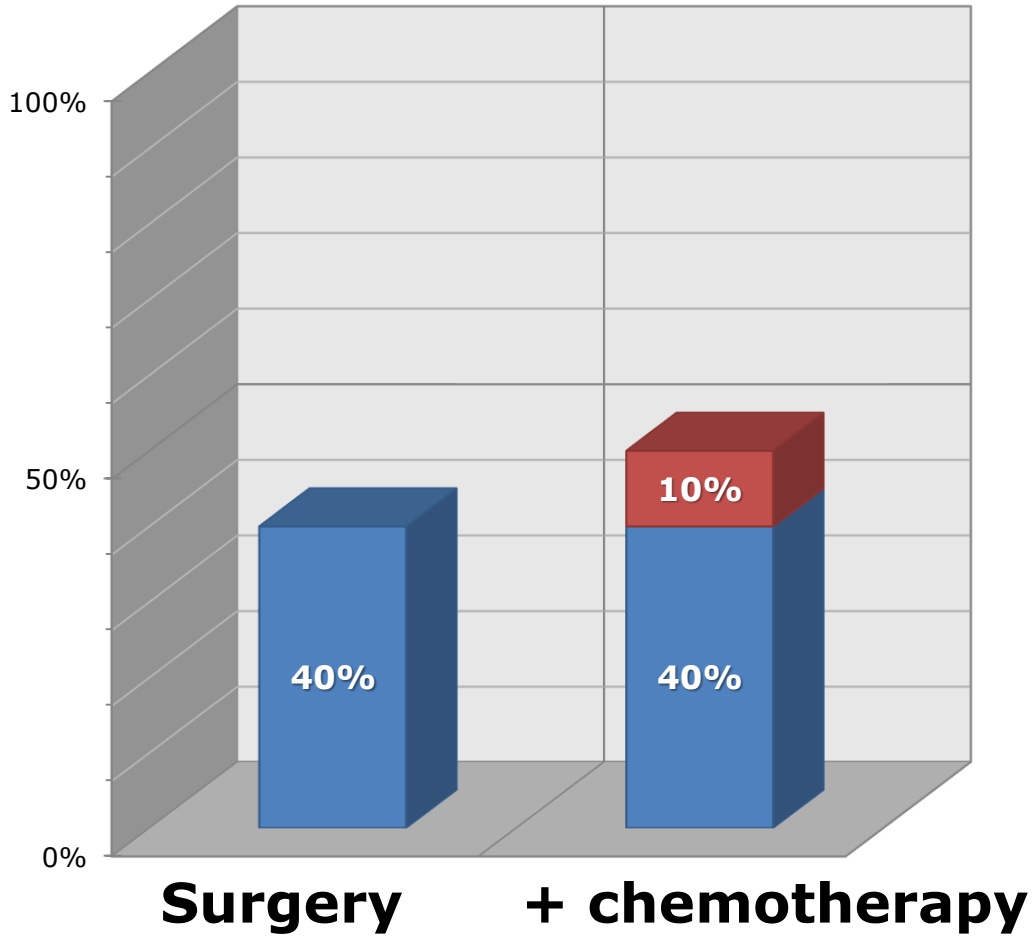
freshspectrum.com

Number needed to treat

Dukes' C colon



Dukes' C colon



10 patients

10 patients

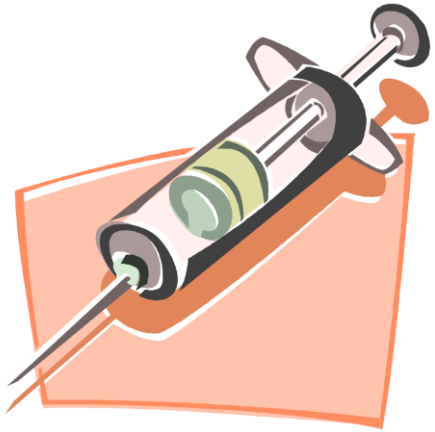
Cured

10 patients

Cured

Not cured

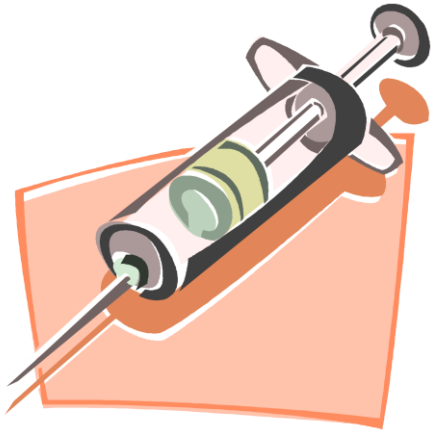
Give chemotherapy



Cured

Not cured

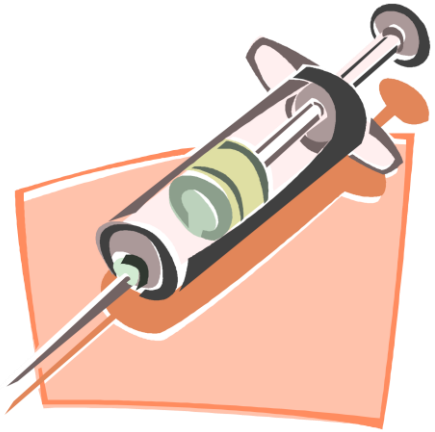
Give chemotherapy



Cured

Not cured

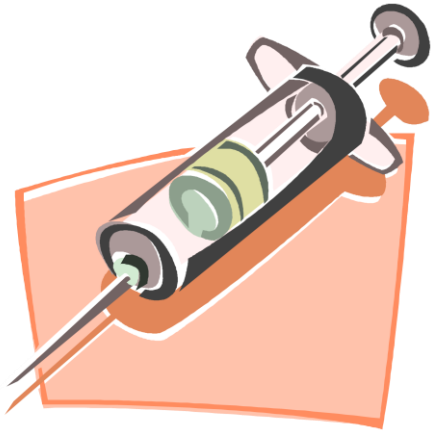
Give chemotherapy



Cured

Not cured

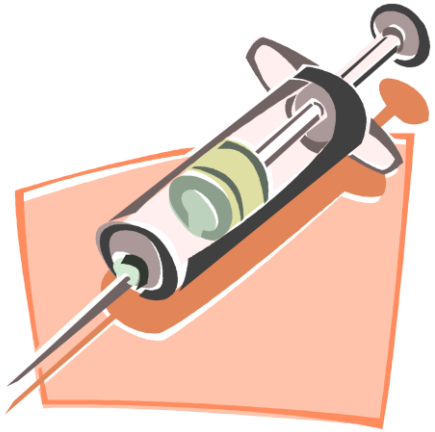
Give chemotherapy



Cured

Not cured

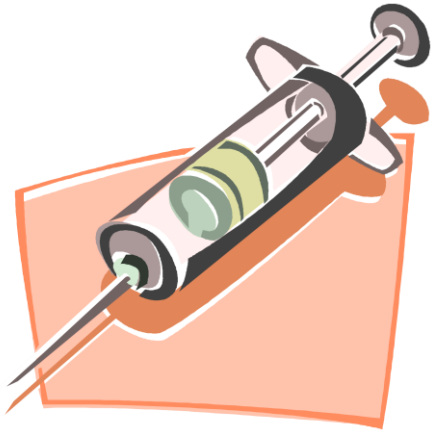
Give chemotherapy

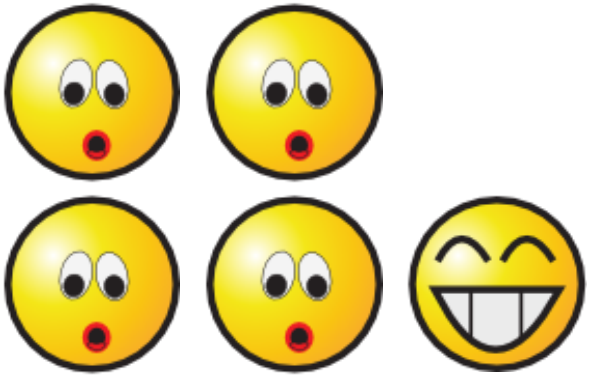


Cured

Not cured

Give chemotherapy

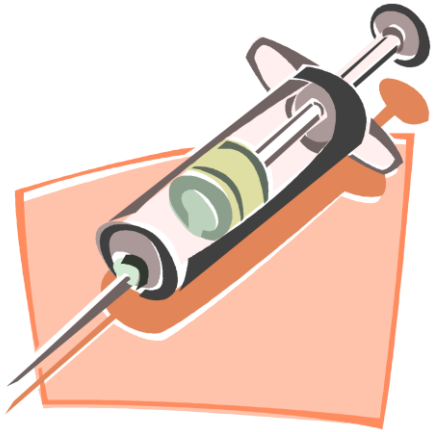


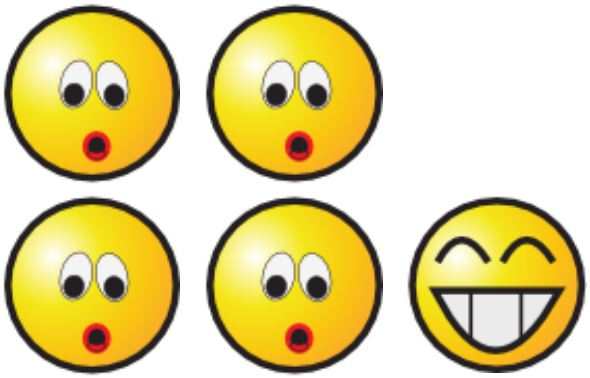


Cured

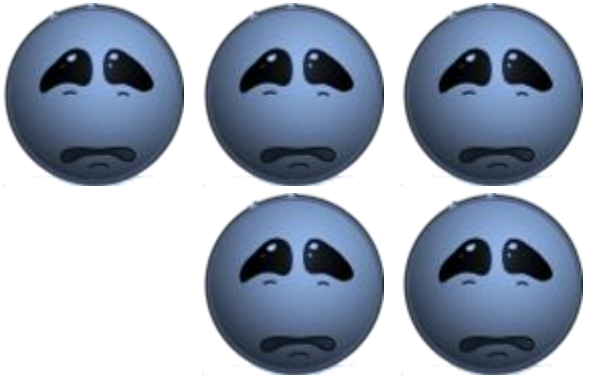
Not cured

Give chemotherapy



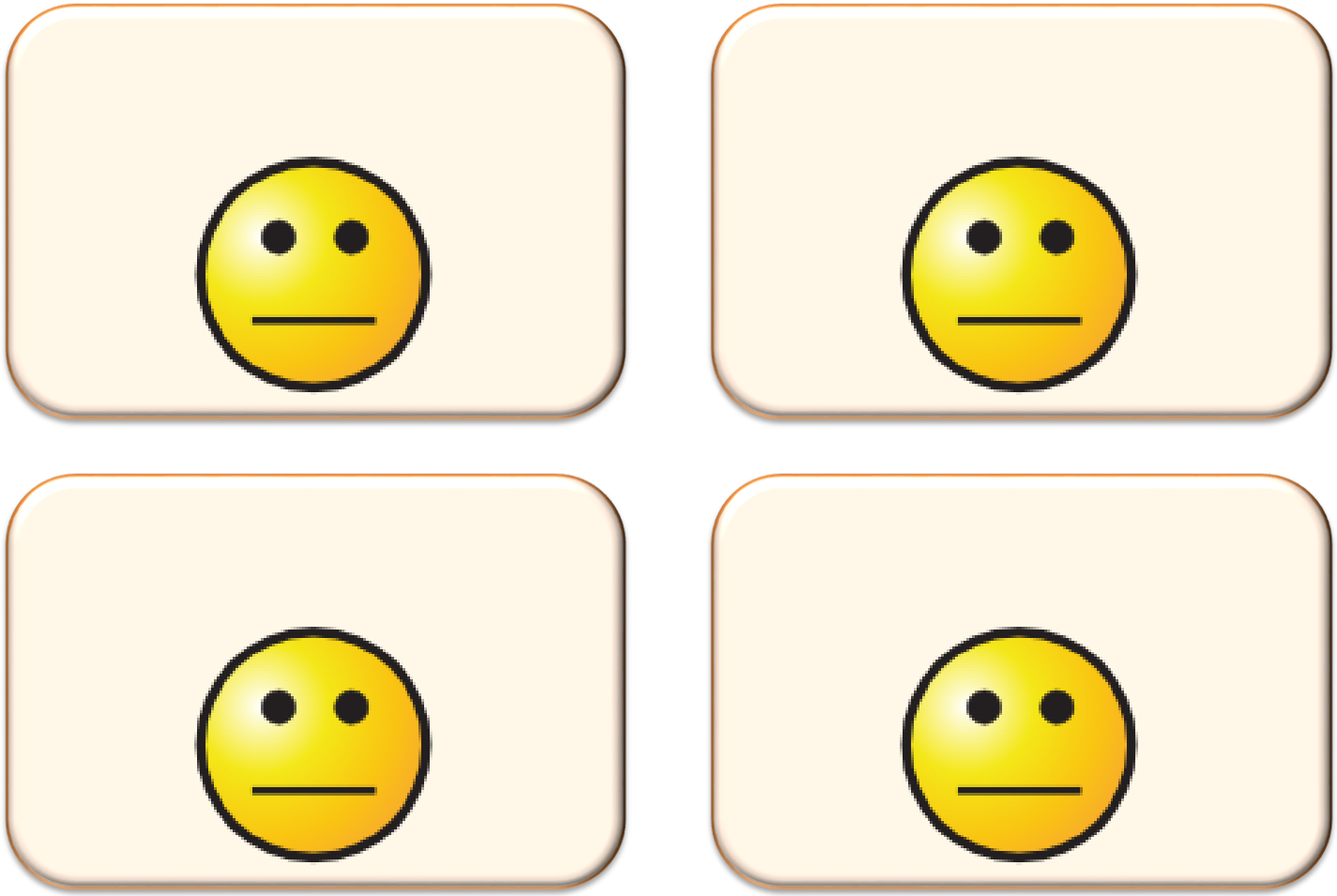


Cured



Not cured

Outcome



Outcome

Cured
No side-effects

Outcome

Cured
No side-effects

Cured
Has side-effects

Outcome

Cured
No side-effects

Cured
Has side-effects

Not cured
No side-effects

Outcome

Cured
No side-effects

Cured
Has side-effects

Not cured
No side-effects

Not cured
Has side-effects

Future

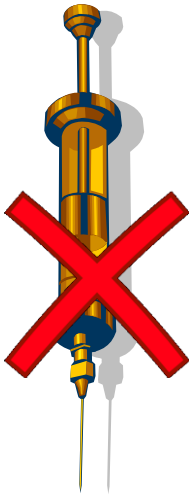
Not cured
Has side-effects

Future

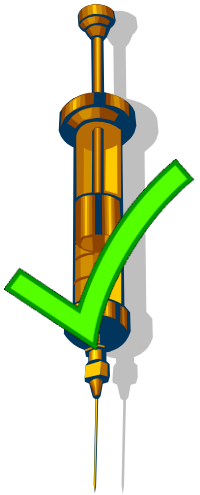
Future

Now

I wish
I hadn't
bothered



At least
I've tried



Future

Evidence-based medicine

Statistics for the RadOnc

Meta-analysis

Cancéropôle Nord-Ouest

litis

ESTRO European Society for RADIOTHERAPY & ONCOLOGY

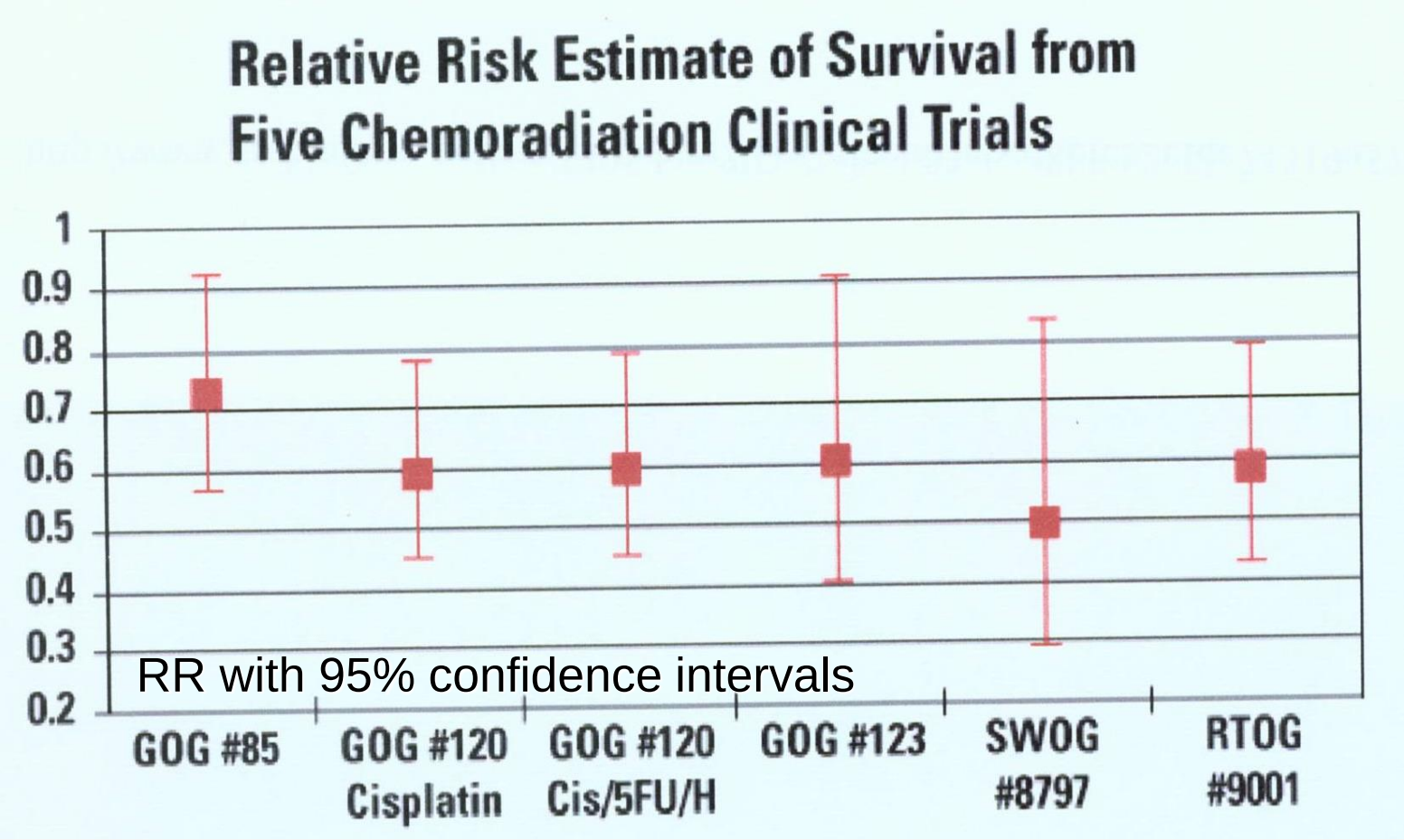
UNIVERSITÉ DE ROUEN

CENTRE HENRI BECQUEREL HAUTE-NORMANDIE

Meta-analysis

- Combined analysis of randomised trials
  - to increase the level of evidence
- What provides the highest level of evidence ?
  - ≥2 randomised trials
    - well-designed
    - well-conducted
    - by independent groups
    - with consistent results
  - or a meta-analysis … ??

Need for meta-analysis ?



研究结论冲突

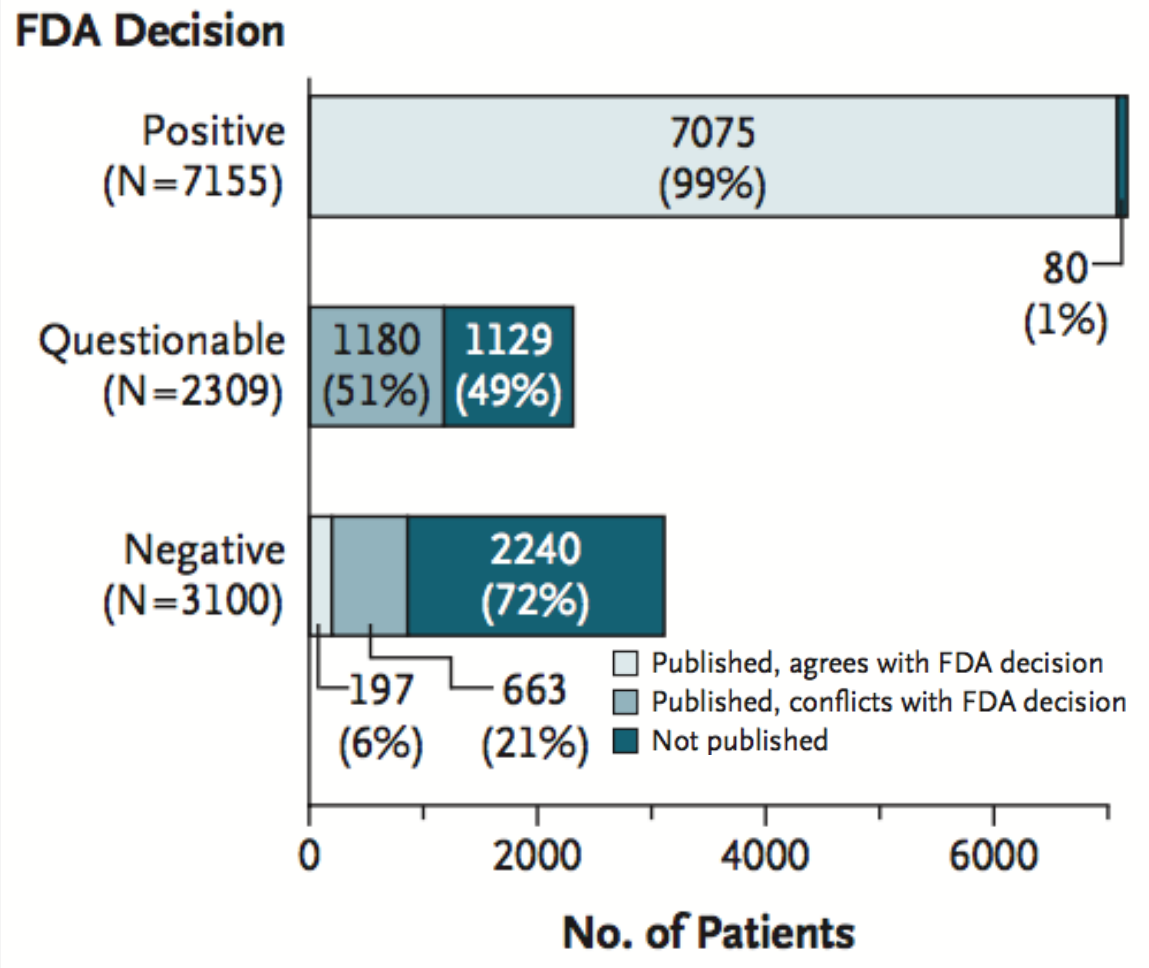

ESTRO
29
ESTRO
WWW.ESTRO.ORG
SEPTEMBER 12-16 < 2010
BARCELONA < SPAIN

We need meta-analysis

- Non significant differences
  - low effect or low power ?
- Estimates of treatment effects
  - inconsistent / contradictory
- “Suboptimal” quality of trials
  - small sample size
  - analysis, reporting

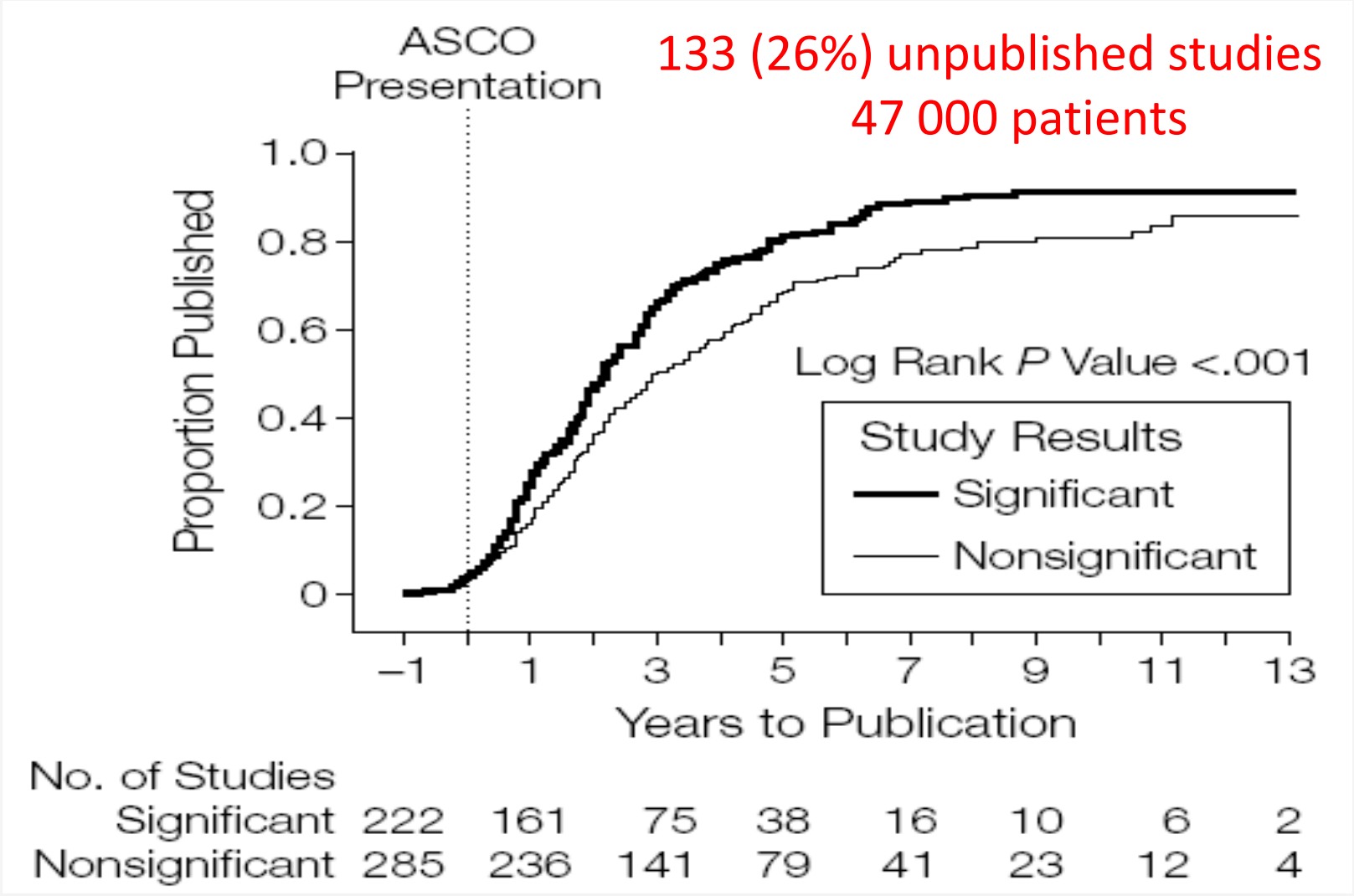
Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.



Turner NEJM 2008

Publication bias



Krzyzanowska JAMA 2003

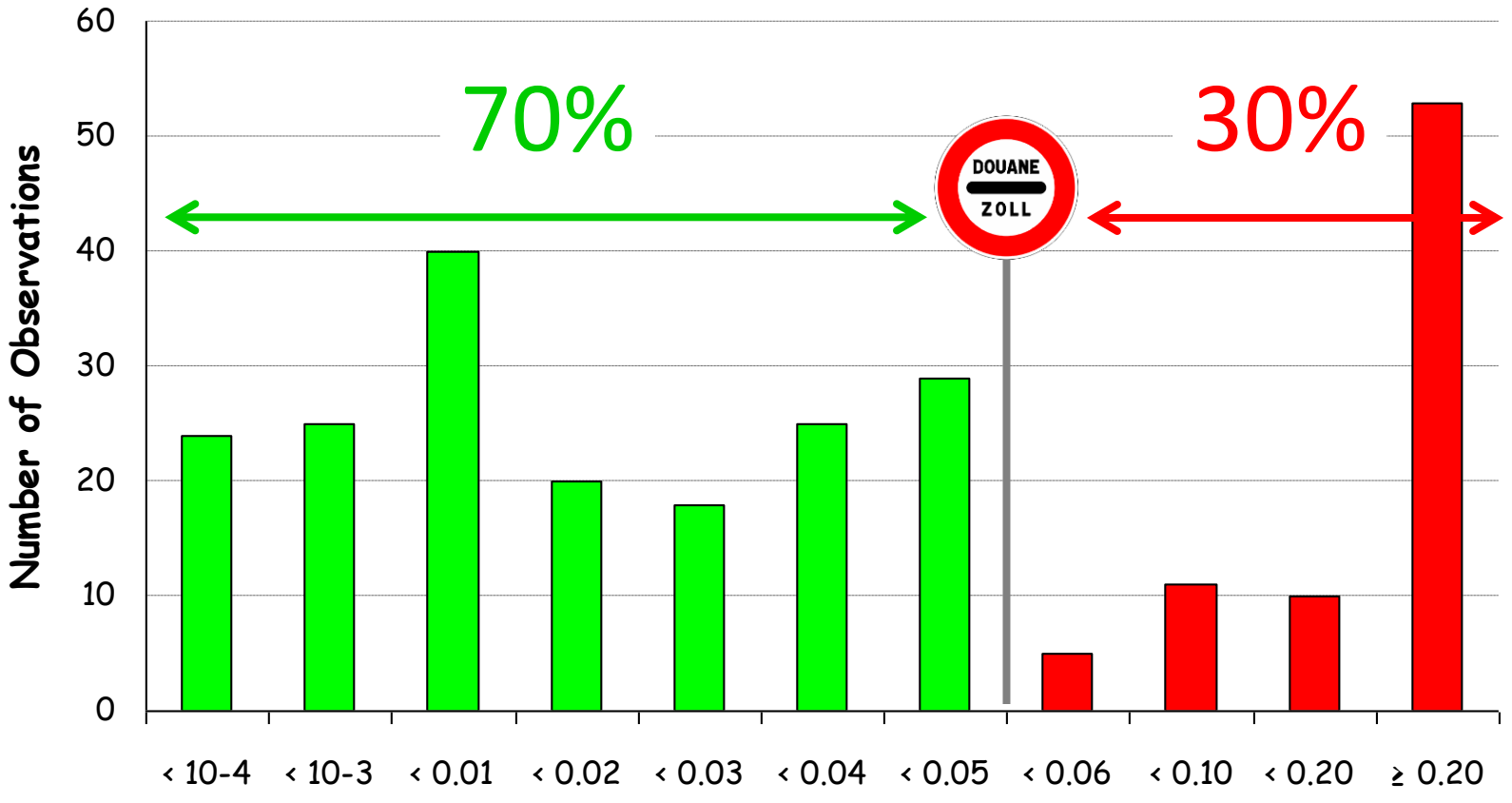
“Tower of Babel” bias

p-value	German (%)	English (%)
≥ 0.05	26 (65)	15 (38)
[0.01, 0.05]	8 (20)	14 (38)
[0.001,0.01]	3 (8)	4 (8)
<0.001	3 (8)	7 (18)
Total	40	40

Papers with p-values < 0.05
more likely to be published in English

Egger Lancet 1997

“Salesmanship”



1rst p-value appearing in abstracts
of 260 RCTs published in 2003

Gøtzsche BMJ 2006

“Salesmanship”

p-value	checked	correct	???	wrong
]0.04 – 0.05]	23/29	8 (35%)	11 (48%)	4 (17%)
]0.05 – 0.06]	4/5	4 (100%)		

- Non-significant difference in abstract ?
  - believe it !

Gøtzsche BMJ 2006

Selective reporting

Outcome	% incompletely reported	
	median	[10% - 90%]
Efficacy	22	48 – 100
Toxicity	25	0 - 100

Toxicity less likely to be reported !

Chan BMJ 2005

Objectives of meta-analysis

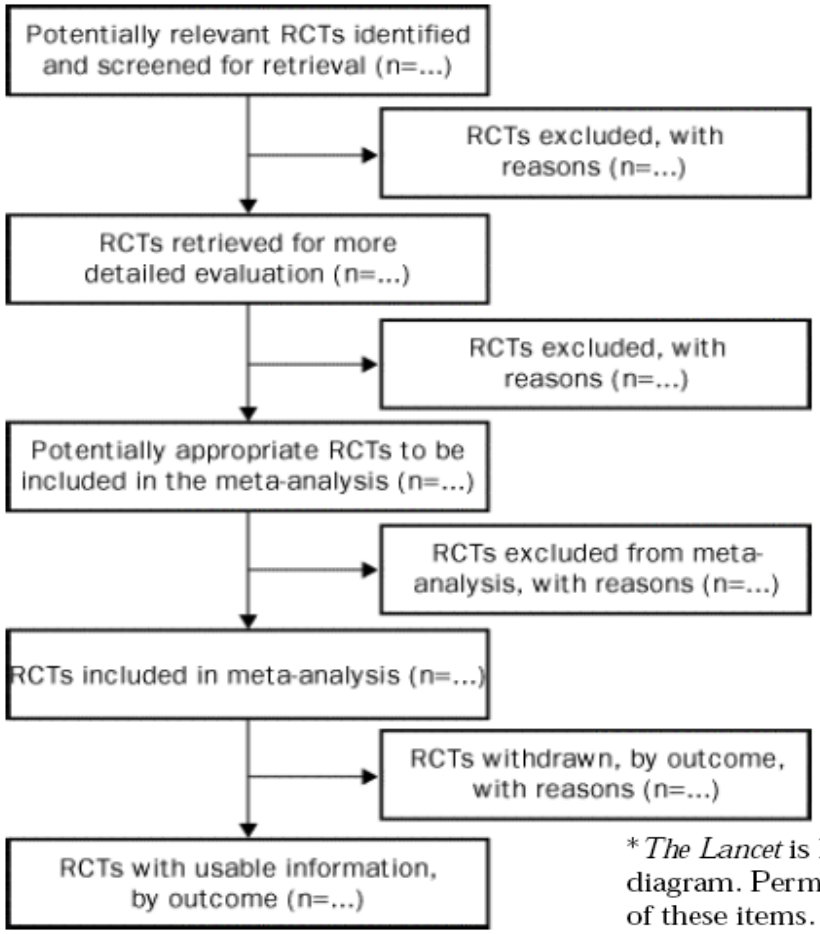
- Increase the level of evidence
  - a more reliable answer
  - a more precise measure of effect
- Generate new hypothesis
  - from differences between trials
  - from subgroup analyses

A scientific methodology

- An explicit (and relevant ...) question
- An exhaustive search of the data
  - avoid publication bias
- Assess the quality of the data
  - trial methodology
- A protocol written a priori
  - including sample size calculation

Data description

Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement flow diagram



* *The Lancet* is happy for readers to make copies of the checklist and flow diagram. Permission need not be obtained from the journal for reproduction of these items.

Hazard ratio

- Ratio of risks of death (event)
  - in « experimental » group
  - vs. in « control » group

Hazard ratio = 1

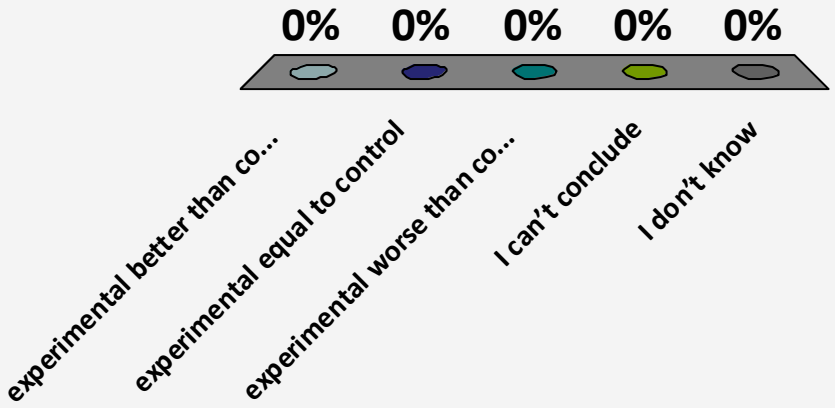
A. experimental better than control

B. experimental equal to control

C. experimental worse than control

D. can’t conclude

E. don’t know



Hazard ratio = 0.63

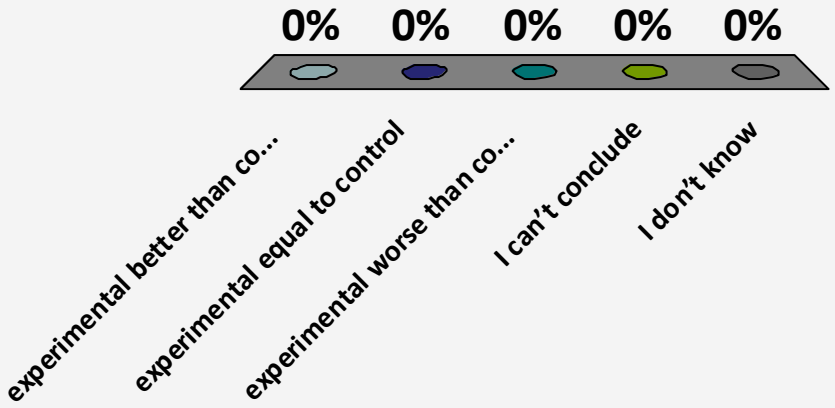
A. experimental better than control

B. experimental equal to control

C. experimental worse than control

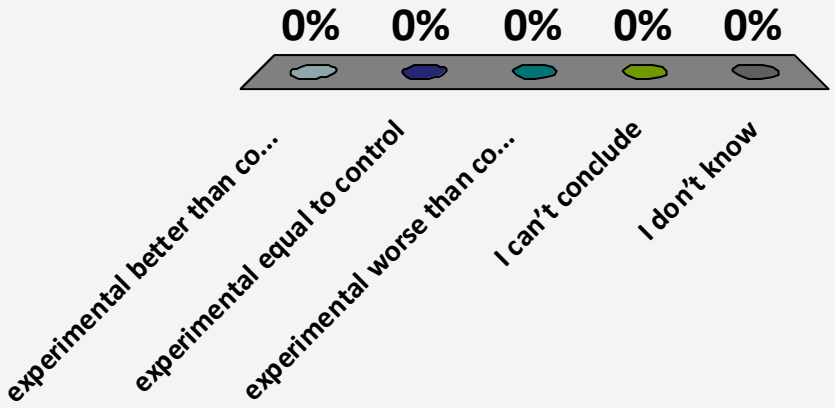
D. can’t conclude

E. don’t know



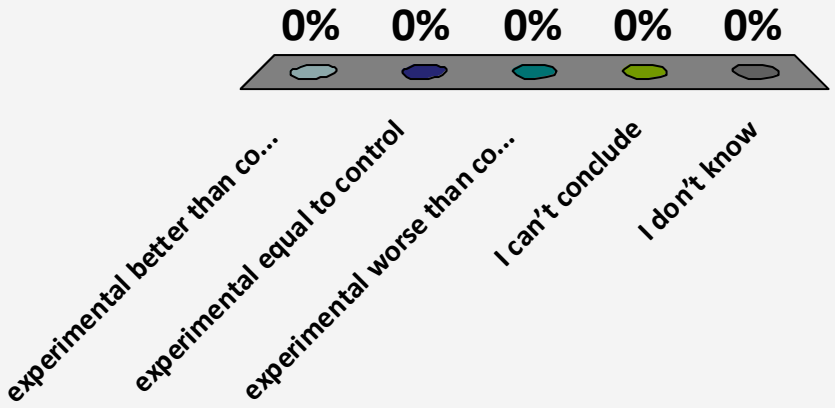
Hazard ratio = 0.63 [0.41 – 0.88]

A. experimental better than control
B. experimental equal to control
C. experimental worse than control
D. can’t conclude
E. don’t know

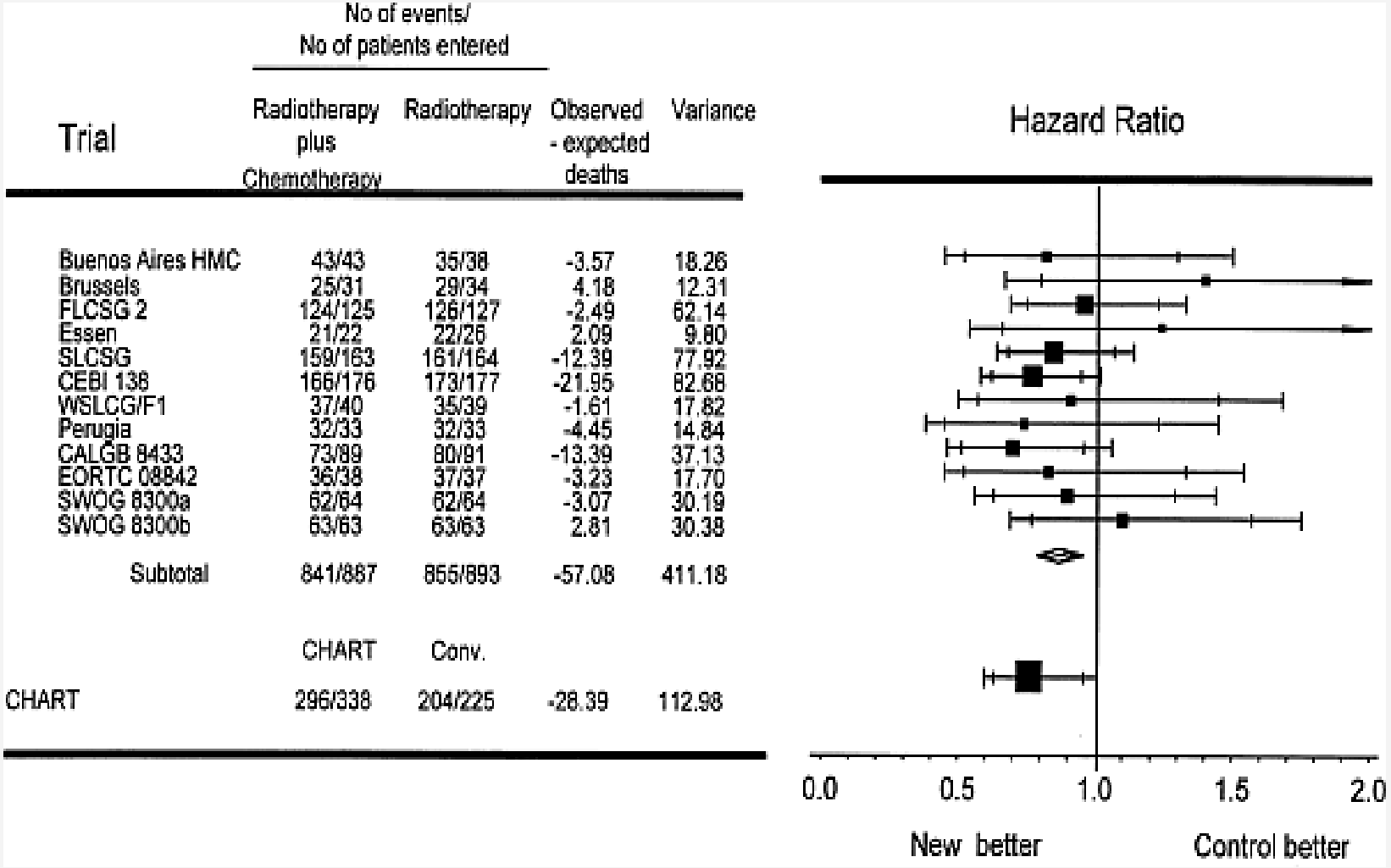


Hazard ratio = 1.74 [0.88 – 3.51]

A. experimental better than control
B. experimental equal to control
C. experimental worse than control
D. can’t conclude
E. don’t know

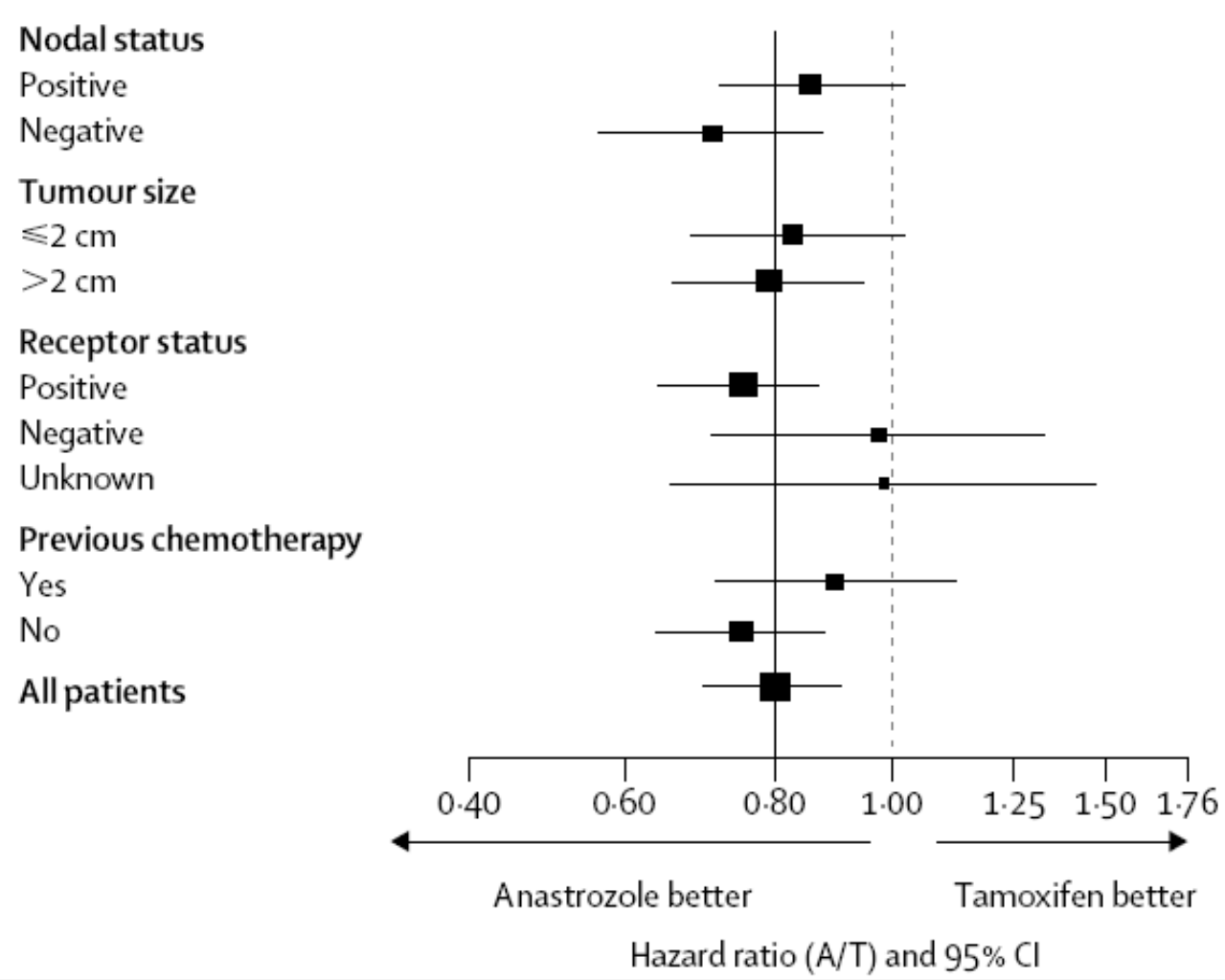


Forest plot



Saunders R&O 1999

Subgroup analysis



ATAC trials, Cuzick Lancet 2005

Additional advantages

- Cheap and quick
  - no need to produce more data
  - finance data retrieval and management
- Homogeneous statistical analysis
  - all eligible data ++++
  - uniform endpoint
  - longer follow-up
  - intent to treat

Prefer individual data

- Improved quality of data
  - check random procedure
  - update follow-up
- Improved analysis
  - uniform endpoint definition
  - intent to treat
  - assess heterogeneity between trials
- Contact with investigators

Amifostine meta-analysis

Ref	First Author	Median follow-up in months	
		Before update	After update
5	Komaki	27	58
6	Leong	74	79
7	Movsas	36	46
9	Brizel	25	29 (45%updated)
10	Bourhis	NA	97
13	Buntzel	NA	73
14	Buntzel	24	85 (60% updated)
16	Braaksma	12	45
17	Giglio	NA	21
22	Gallardo	20	109
20	Kouvaris	NA	24
23	Jellema	NA	37
	Total		45

Tribodet ESTRO 2006, Bourhis JCO 2011

Limits

- No control over previous work
  - selection bias
  - obsolete staging / treatment
  - inadequate evaluation of toxicity
- Trial exclusion = loss of information
- Individual data not available or complete
- Publication bias fully avoided ?

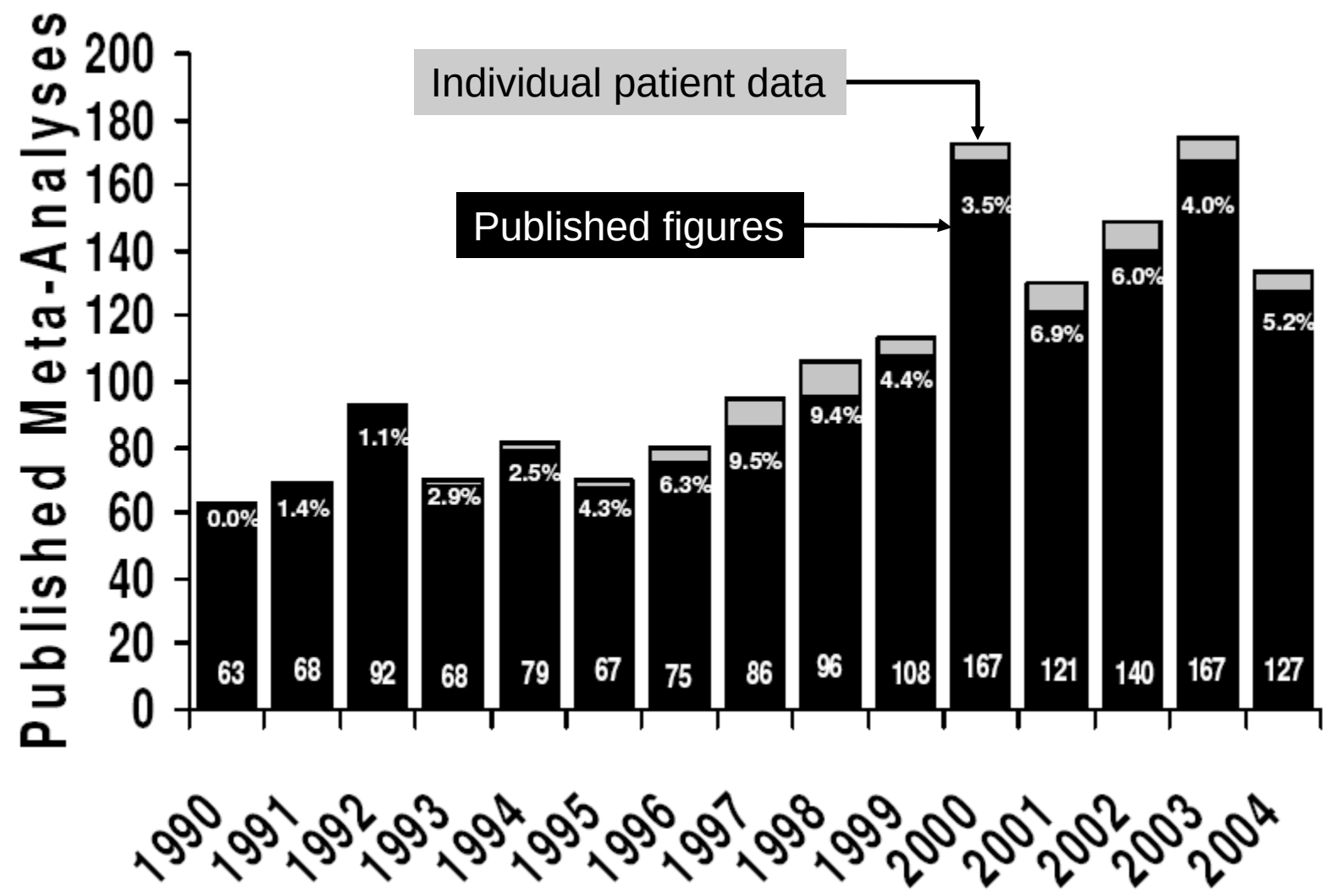
Amifostine phase III trials

Author	Year	Random	Allocation	Withdraw	Intent treat	Placebo	Multicentric	Sponsor
Antonadou	2002	Adequate	Unclear	Yes	Yes	No	No	Unknown
Antonadou	2001	Unclear	Unclear	Yes	Yes	No	No	Pharmaceutical
Antonadou	2003	Adequate	Unclear	Yes	No	No	No	Unknown
Athanassiou	2003	Unclear	Unclear	Yes	Yes	No	Yes	Unknown
Bourhis	2000	Adequate	Adequate	Yes	Yes	No	No	Both
Braaksma	2002	Unclear	Unclear	No	No	No	No	Unknown
Brizel	2000	Adequate	Unclear	Yes	Yes	No	Yes	Pharmaceutical
Bünzel	1998	Unclear	Unclear	No	No	No	No	Both
Komaki	2004	Adequate	Adequate	Yes	Yes	No	No	Both
Koukourakis	2000	Adequate	Unclear	No	No	No	No	Both
Kouvaris	2003	Adequate	Unclear	Yes	No	No	No	Unknown
Liu	1992	Unclear	Unclear	Yes	No	No	Yes	Both
Movsas	2005	Adequate	Adequate	Yes	Yes	No	Yes	Both
Senzer	2005	Unclear	Unclear	No	No	No	No	Unknown

Sasse IJROBP 2006

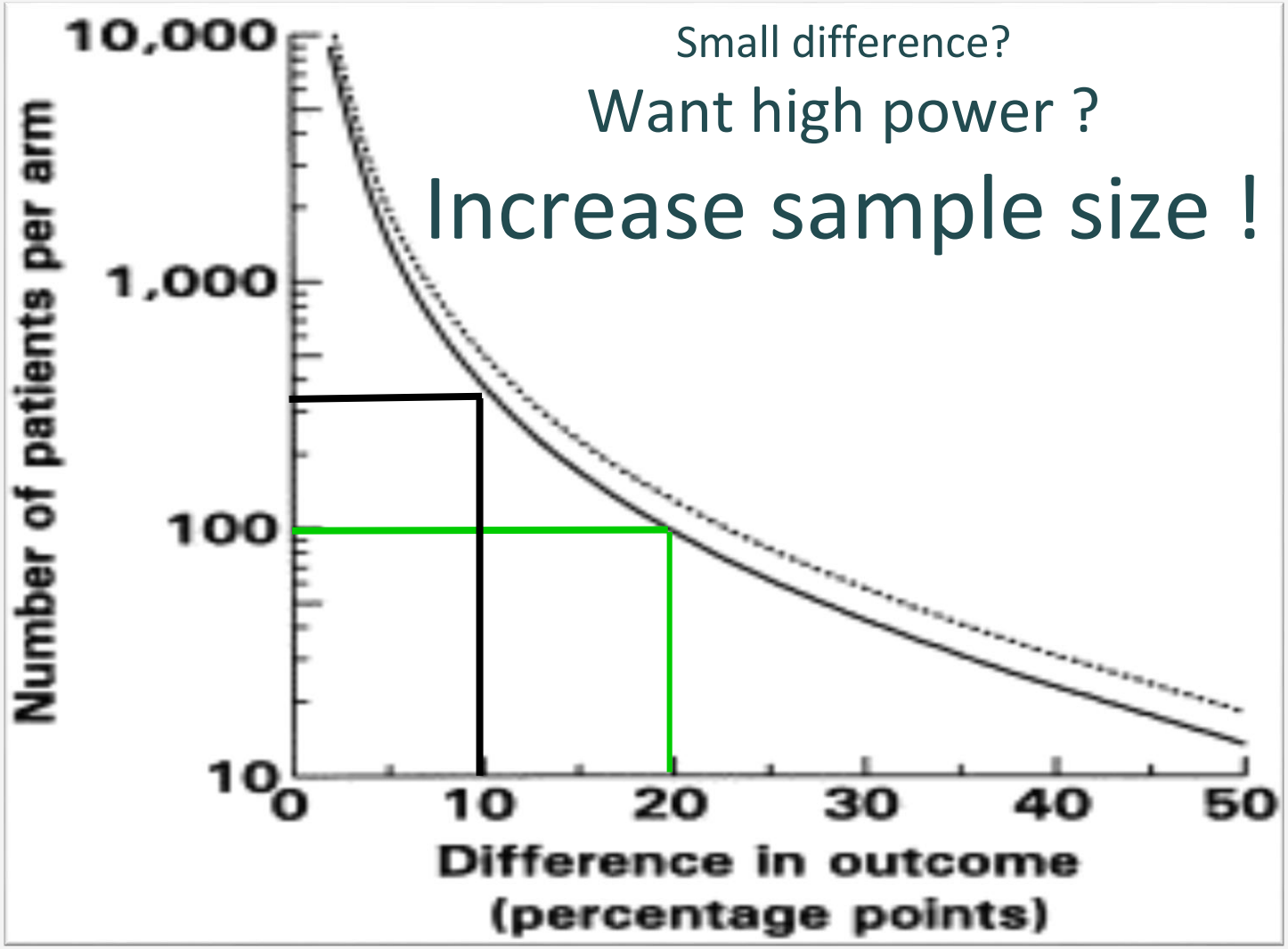
Individual vs. abstracted data

(published cancer-related meta-analyses)

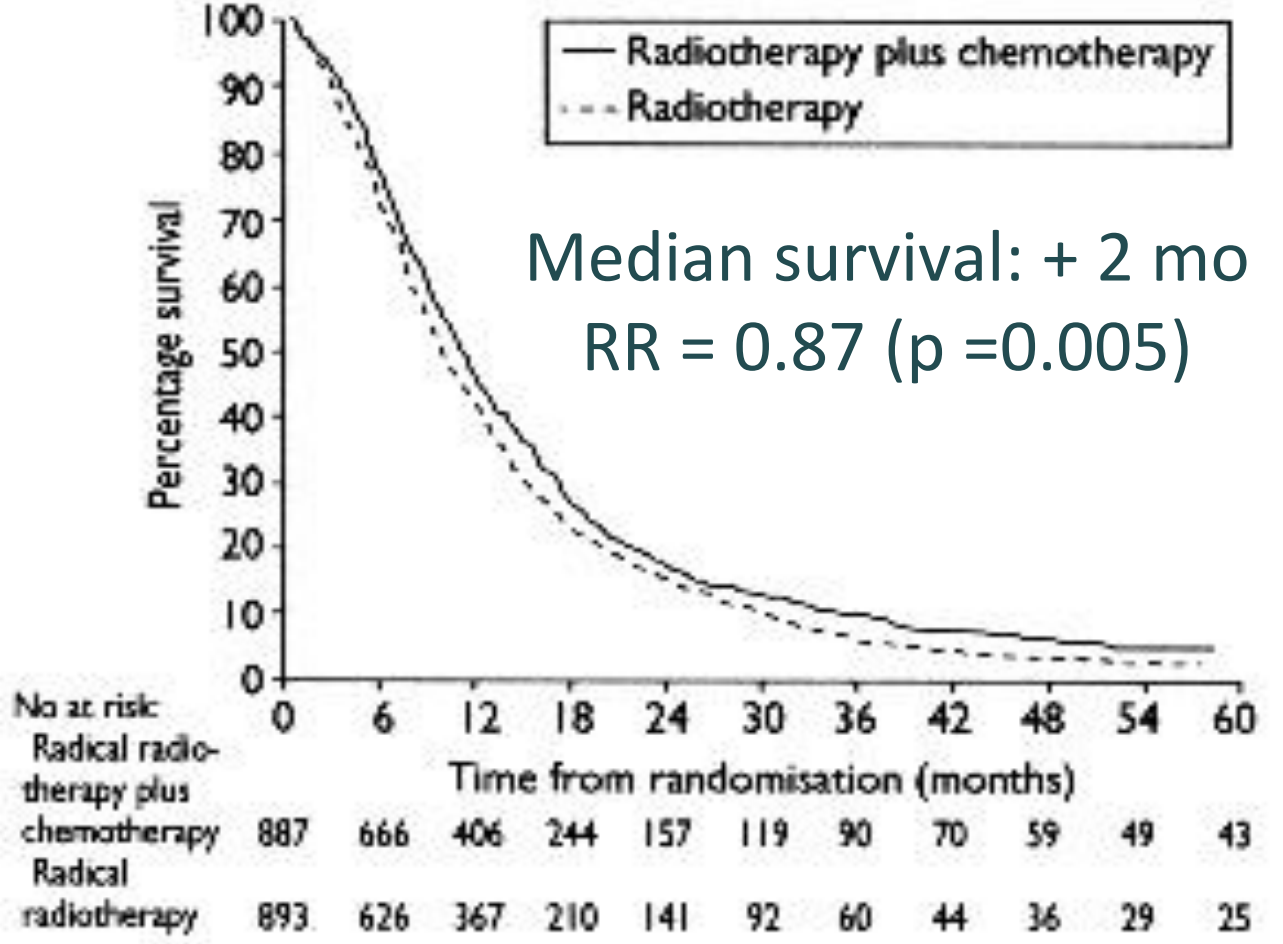


Lyman BMC Med Res Meth 2005

Sample size


Small difference?
Want high power ?
Increase sample size !
10,000
1,000
100
10
Number of patients per arm
0
10
20
30
40
50
Difference in outcome
(percentage points)

Too large a sample size !

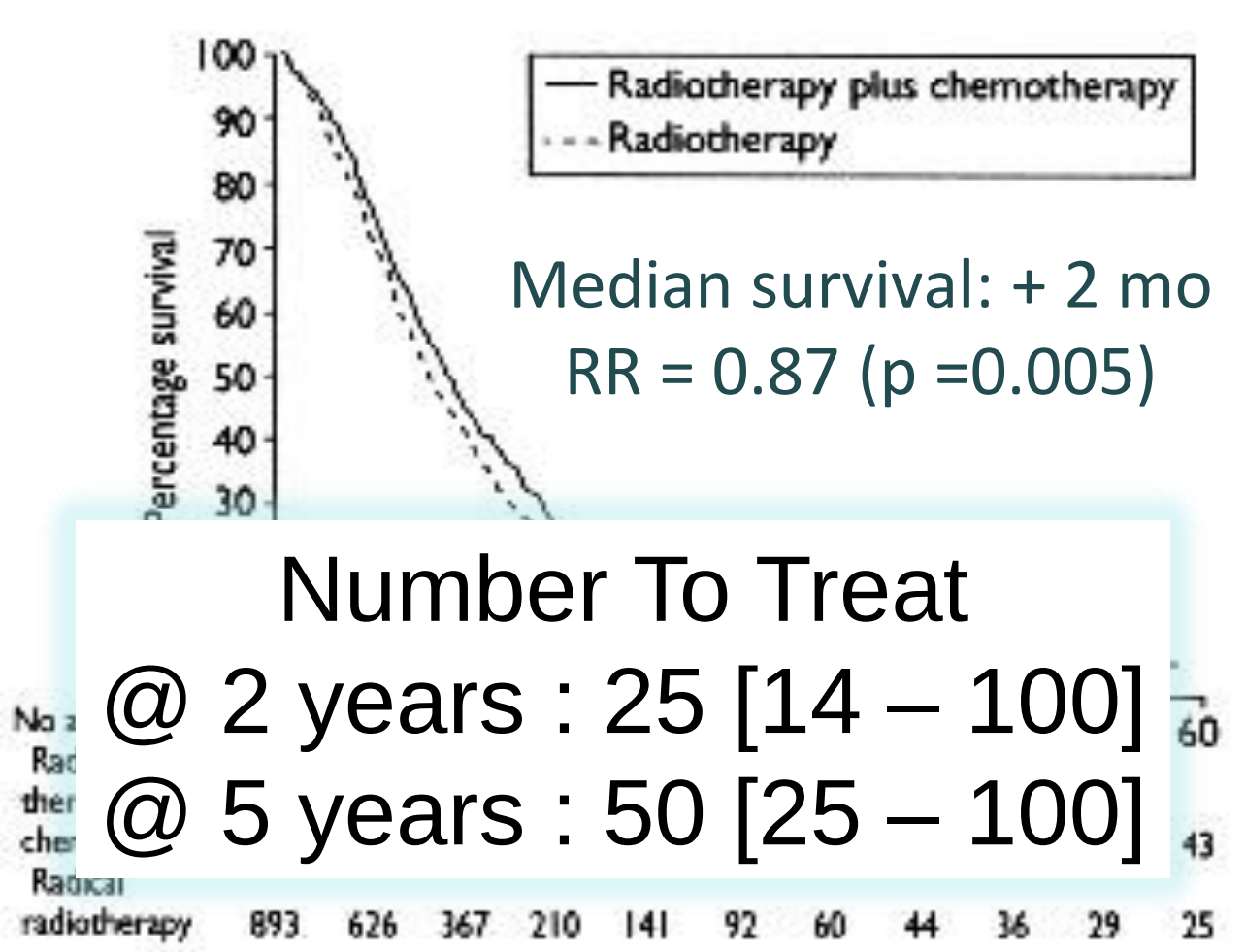


Median survival: + 2 mo

RR = 0.87 (p =0.005)

NSCLC Collaborative Group BMJ 1995

Too large a sample size !



Median survival: + 2 mo

RR = 0.87 (p =0.005)

Number To Treat

@ 2 years : 25 [14 – 100]

@ 5 years : 50 [25 – 100]

NSCLC Collaborative Group BMJ 1995

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Type of research	Power	True/false	Bias	PPV
Good quality RCT	0.80	1:1	0.10	0.85
Meta-analysis of good quality RCTs	0.95	2:1	0.30	0.85
Meta-analysis of small RCTs	0.80	1:3	0.40	0.41
Phase I/II RCT	0.20	1:5	0.20	0.23
Exploratory epidemiological study	0.80	1:10	0.30	0.20
Exploratory with massive testing	0.20	1:1000	0.80	0.001

Ioannidis PLOS Med 2005

Conclusion

- Meta-analyses don’t replace RCTs
- Good data more important than tests
- Beware of zoom effect
- Hypotheses need confirmation

Evidence-based radiotherapy for endometrial cancer

Dr Li Tee Tan

Cambridge University Hospitals NHS
NHS Foundation Trust

Epidemiology

- Most common gynae cancer in western countries
- Confined to the uterus in 75%
  - High risk features in 30%
  - Occult metastatic disease in 15%
- Treatment of choice = surgery

Adjuvant radiotherapy

- Who to treat?
- How to treat?
- What to treat?

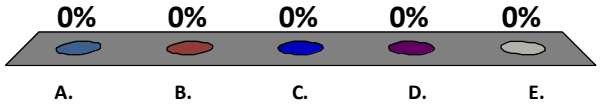
Patient

- Age 55
- LAVH + BSO (no LND) for IbG2 endometrioid ca
- Tumour invades into outer half of myometrium to within 3 mm of serosal surface
- No LVSI

What adjuvant RT would you recommend?

A. None
B. Vault BT
C. Pelvic RT
D. Don't know

- Age 55
- Stage IbG2 (no LND)
- No LVSI



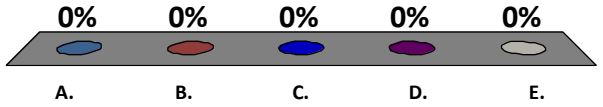
Would your recommendation be different if she was 65 instead of 55?

A. No

B. Yes – recommend more intensive RT

C. Yes – recommend less intensive RT

- Age **65**
- Stage IbG2 (no LND)
- No LVSI



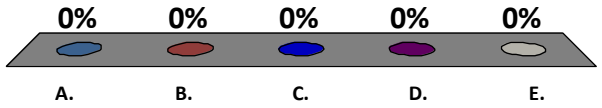
Would your recommendation be different if tumour was G3 instead of G2?

A. No

B. Yes – recommend more intensive RT

C. Yes – recommend less intensive RT

- Age 55
- Stage Ib**G3** (no LND)
- No LVSI

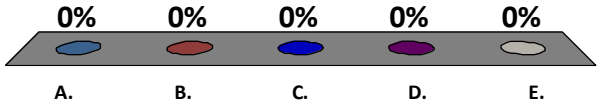


Would your recommendation be different if there was focal LVSI?

A. No

B. Yes

- Age 55
- Stage IbG2 (no LND)
- **Focal** LVSI



FIGO staging 2009

IA	Tumour confined to the uterus, no or < ½ myometrial invasion
IB	Tumour confined to the uterus, > ½ myometrial invasion
II	Cervical stromal invasion, but not beyond uterus
IIIA	Tumour invades serosa or adnexa
IIIB	Vaginal and/or parametrial involvement
IIIC1	Pelvic node involvement
IIIC2	Para-aortic involvement
IVA	Tumour invasion bladder and/or bowel mucosa
IVB	Distant metastases including abdominal metastases and/or inguinal lymph nodes

Adjuvant radiotherapy

- **Who to treat?**
- How to treat?
- What to treat?

PORTEC-1

- Role of RT in Stage I disease (no LND)
- Whole pelvis RT vs. observation
- Inclusion criteria
  - G1, deep (≥50%) invasion (2009 Ib)
  - G2, superficial or deep invasion (2009 Ia + Ib)
  - G3, superficial (<50%) invasion (2009 Ia)

Creutzberg CL, et al. Lancet. 2000 22;355(9213):1404-11

PORTEC-1 results

	RT	Control	*p* value
Local recurrence	4%	14%	<0.001

RT recommended only if two adverse features present: age ≥ 60, deep myometrial invasion, G3.

Other RCTs

Trial	No of pts.	Surgery	Randomization	Local recurrence	Survival
Portec 1	714	TAH-BSO	Obs	14%	85%
2000	Stage IB, G2-3		EBRT	4%	81%
	Stage IC, G1-2			(p<.001)	(n.s.)
GOG-99	392	TAH-BSO &	Obs	12%	86%
2004	Stage IB, IC, IIA	LA	EBRT	3%	92%
				(p<.01)	(n.s.)
ASTEC/EN.5	789	TAH-BSO	Obs	6% (BT50%)	84%
2009	Stage IAB G3	LA optional	EBRT	3% (BT50%)	84%
	Stage IC	(30%)		(p<0.02)	(n.s.)

Adjuvant radiotherapy

- Who to treat?
- **How to treat?**
- What to treat?

PORTEC-2

- Type of RT
- Vaginal BT vs. whole pelvis RT
- Inclusion criteria
  - 1C (deep invasion), G1 or 2, age ≥ 60 (Ib)
  - 1B (superficial invasion), G3 and age ≥ 60 (Ib)
  - 2A, any age, G1 or 2, deep or superficial invasion (Ia + Ib)
  - 2A, any age, G3, superficial invasion (Ia)

Nout RA, et al. Lancet. 2010 6;375(9717):816-23

PORTEC-2 results

	VBT	EBRT	*p* value
Vaginal recurrence	1.8%	1.6%	0.74
Pelvic recurrence	5.1%	2.1%	0.17
Acute GI toxicity	12.6%	53.8%	

VBT is adjuvant treatment of choice for patients with "high-intermediate risk" endometrial Ca

ESMO-ESGO-ESTRO recommendations 2015

4 risk groups

Risk group	Histology	Adjuvant treatment
Low	Ia, G1-2, LVSI -ve	None

Colombo N. Radiother Oncol. 2015;117(3):559-81

ESMO-ESGO-ESTRO recommendations 2015

4 risk groups

Risk group	Histology	Adjuvant treatment
Low	Ia, G1-2, LVSI -ve	None
Intermediate	Ib, G1-2, LVSI -ve	BT or none if <60

Colombo N. Radiother Oncol. 2015;117(3):559-81

ESMO-ESGO-ESTRO recommendations 2015

4 risk groups

Risk group	Histology	Adjuvant treatment	
Low	Ia, G1-2, LVSI -ve	None	
Intermediate	Ib, G1-2, LVSI -ve	BT or none if <60	
		With LND	No LND
High-intermediate	Ib, G1-2, LVSI +ve Ia, G3	BT or none	BT if G3 and LVSI - EBRT if LVSI+

LVSI must be unequivocally positive (not focal)

Colombo N. Radiother Oncol. 2015;117(3):559-81

ESMO-ESGO-ESTRO recommendations 2015

4 risk groups

Risk group	Histology	Adjuvant treatment	
		With LND	No LND
High	Ib G3	EBRT or BT	EBRT (+ chemo)
	II G1-2, LVSI -ve II G3 or LVSI +ve	BT EBRT	EBRT EBRT (+ chemo)
	III	EBRT (+ chemo)	

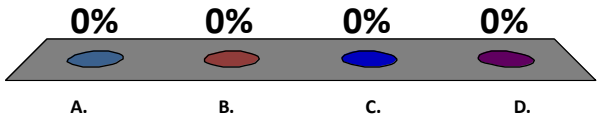
Colombo N. Radiother Oncol. 2015;117(3):559-81

Adjuvant radiotherapy

- Who to treat?
- How to treat?
- **What to treat?**

What is your standard superior border for adjuvant EBRT for endometrial cancer?

A. L5/S1 junction
B. L4/L5 junction
C. Common iliac bifurcation
D. Aortic bifurcation



RTOG consensus guidelines

- “CTV should include the common, external, and internal iliac lymph node regions”
- “Common iliac lymph nodes from 7 mm below L4–L5 interspace”

Small W Jr. Int J Radiat Oncol Biol Phys. 2008;71(2):428-34

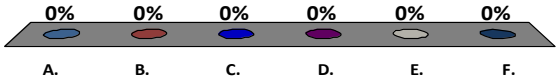
Gynecologic Cancer Intergroup

- Upper border of pelvic field
  - L4/5 = 14
  - L5/S1 = 13
  - Not specified = 6
- Cambridge = L5/S1
  - Common iliac node recurrence rare
  - No survival benefit, limit toxicity

Small W, et al. Int J Gynecol Cancer. 2009;19(3):395-9

What is your treatment length for adjuvant vault brachytherapy?

A. Top 2 cm
B. Top 3 cm
C. Top 4 cm
D. Upper third
E. Upper half
F. Other



Gynecologic Cancer Intergroup

TABLE 5. How much of the vagina do you most often treat?

Response	%
Whole vagina	4.0
Upper one third	28.0
Upper one half	12.0
Upper two thirds	16.0
3.0 cm	16.0
4.0 cm	16.0
5.0 cm	4.0
7.0 cm	4.0

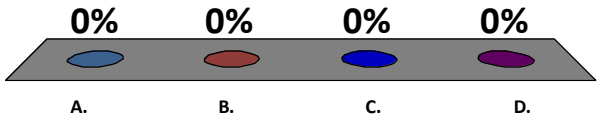
Cambridge: treat top 2 cm only (PORTEC-3 = 2-3 cm)

Local recurrence 2007-2012 = 4.5% (PORTEC-1 = 4%)

Small W, et al. Int J Gynecol Cancer. 2009;19(3):395-9

Where do you prescribe the dose for adjuvant vault brachytherapy?

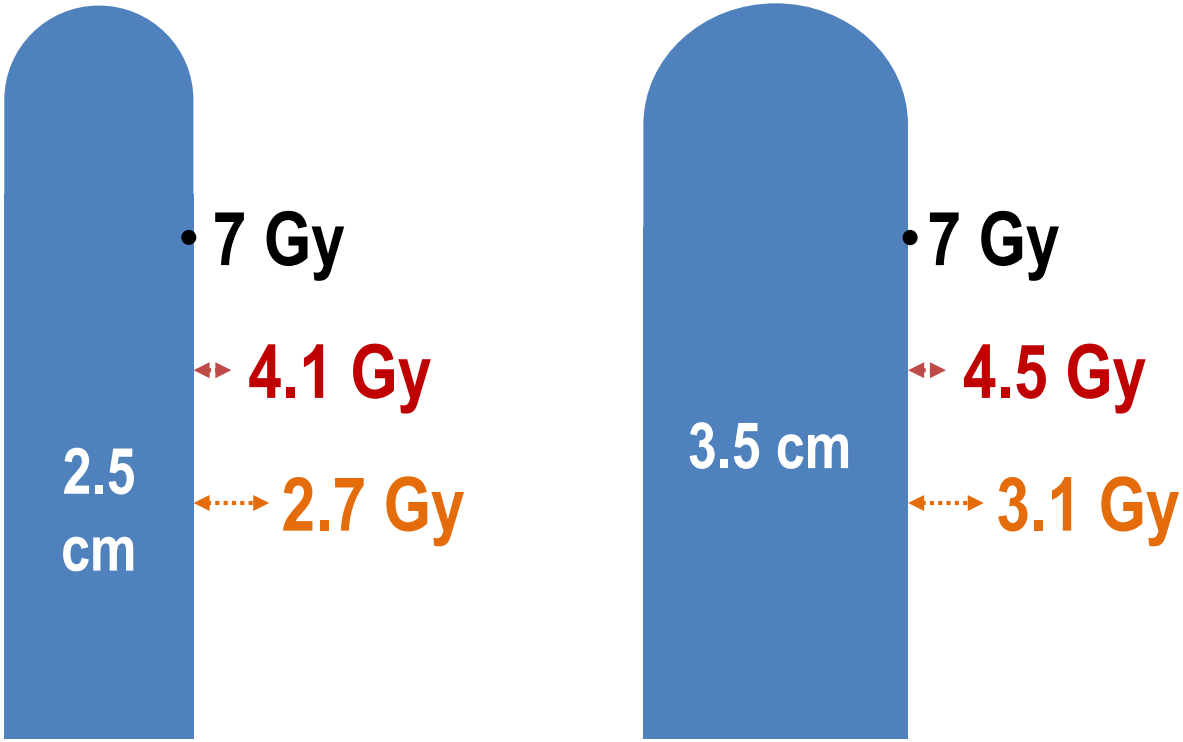
A. Surface of applicator
B. 0.5 cm depth
C. 1 cm depth
D. Other



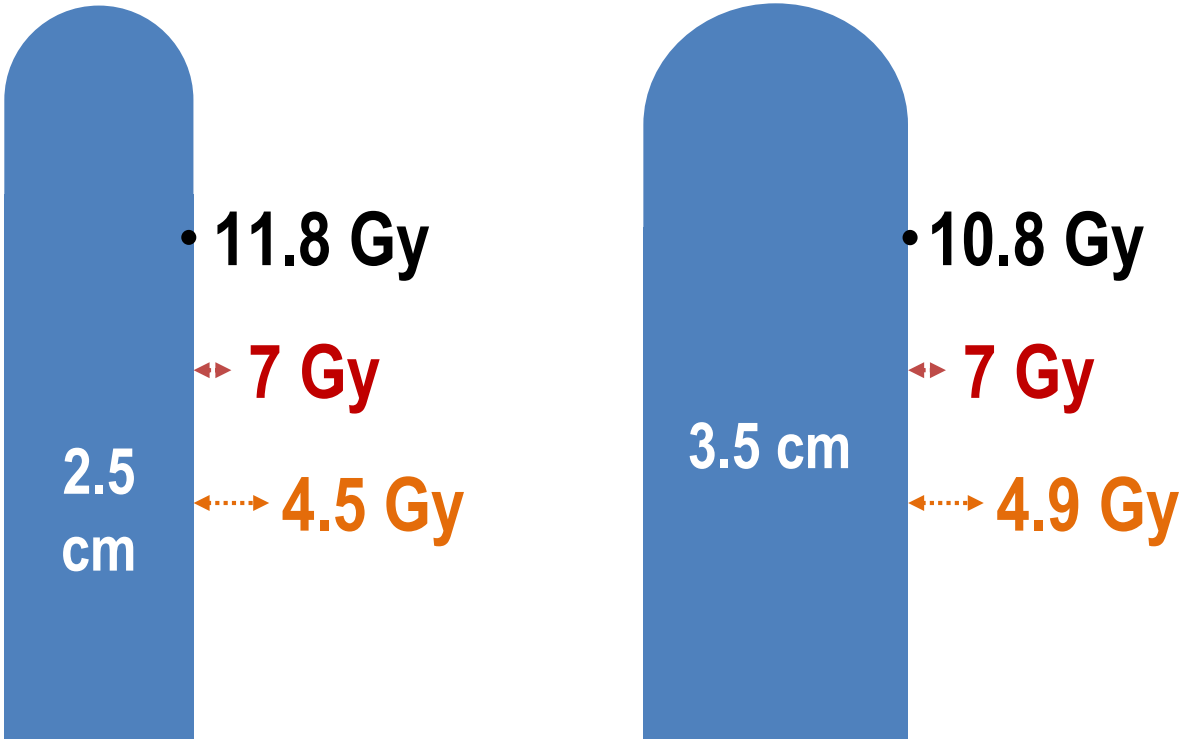
Published schedules for BT alone

Dose/#	Publication	Prescription
7 Gy x 3	Nout *et al*, Lancet 2010 (PORTEC-2)	5 mm
7 Gy x 3	Small *et al*, IJROBP 2005 (ABS)	5 mm
5.5 Gy x 4	Chong & Hoskin, Brachytherapy 2008 (UK)	5 mm
5.5 Gy x 5	Atahan *et al*, Int J Gynecol Cancer 2008 (Turkey)	5 mm
16.2 Gy x 2	Petereit *et al*. Int J Gynecol Cancer 1999 (USA)	0 mm
6 Gy x 6	Ng *et al*, Gynecol Oncol 2000 (Australia)	0 mm

Prescription point



Prescription point



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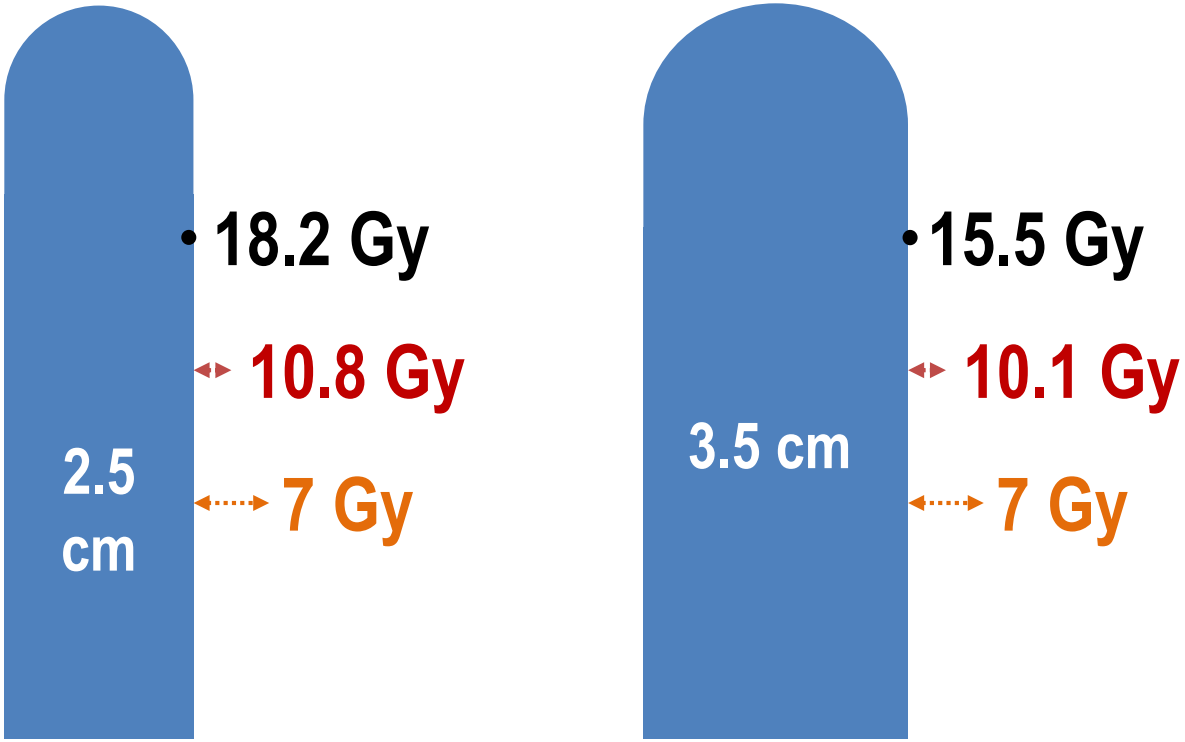
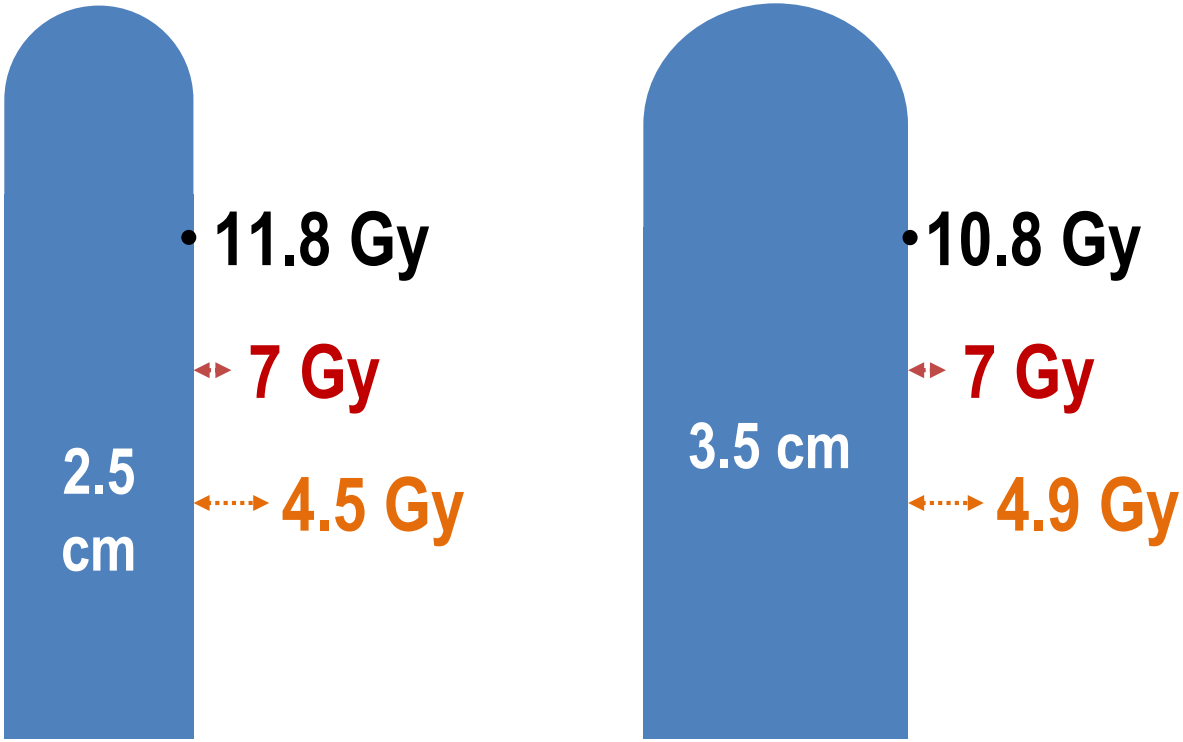


Prescription point

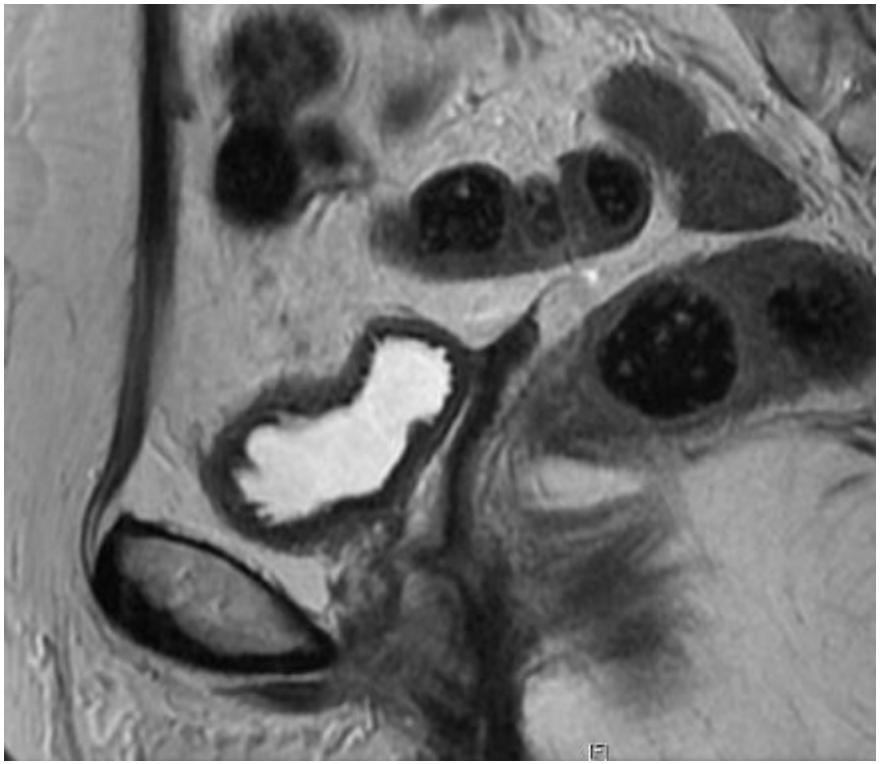


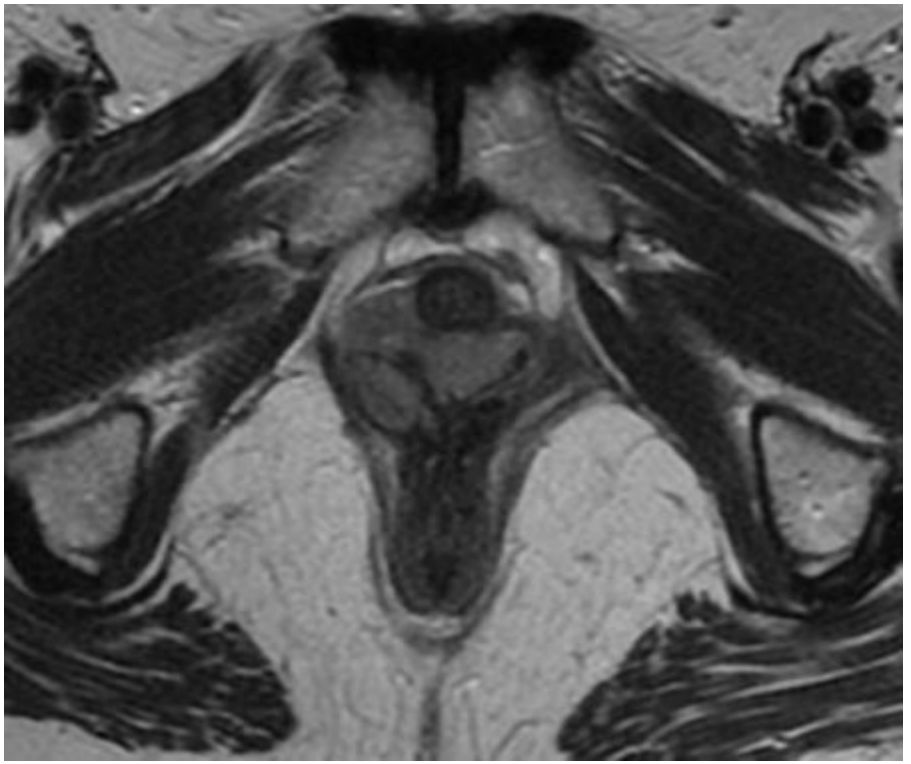
Vaginal wall is ~5 mm thick (ICRU rectal point)

Patient

- Age 55
- LAVH + BSO for IbG2 endometrioid ca
  - Tumour invades into outer half of myometrium to within 3 mm of serosal surface
  - No LVSI
- No post-operative RT
- Isolated vaginal recurrence at 12 months

Patient

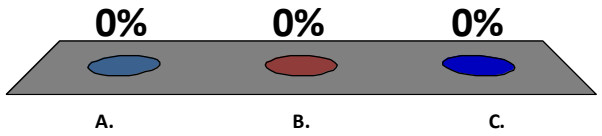




What treatment would you recommend for recurrence?

A. Surgery
B. Radiotherapy
C. Chemotherapy

- Age 55
- Stage IbG2
- No LVSI
- No post-op RT

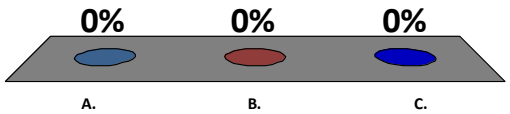


What local control rate would you expect after salvage RT for vault recurrence?

A. 20%

B. 50%

C. 80%

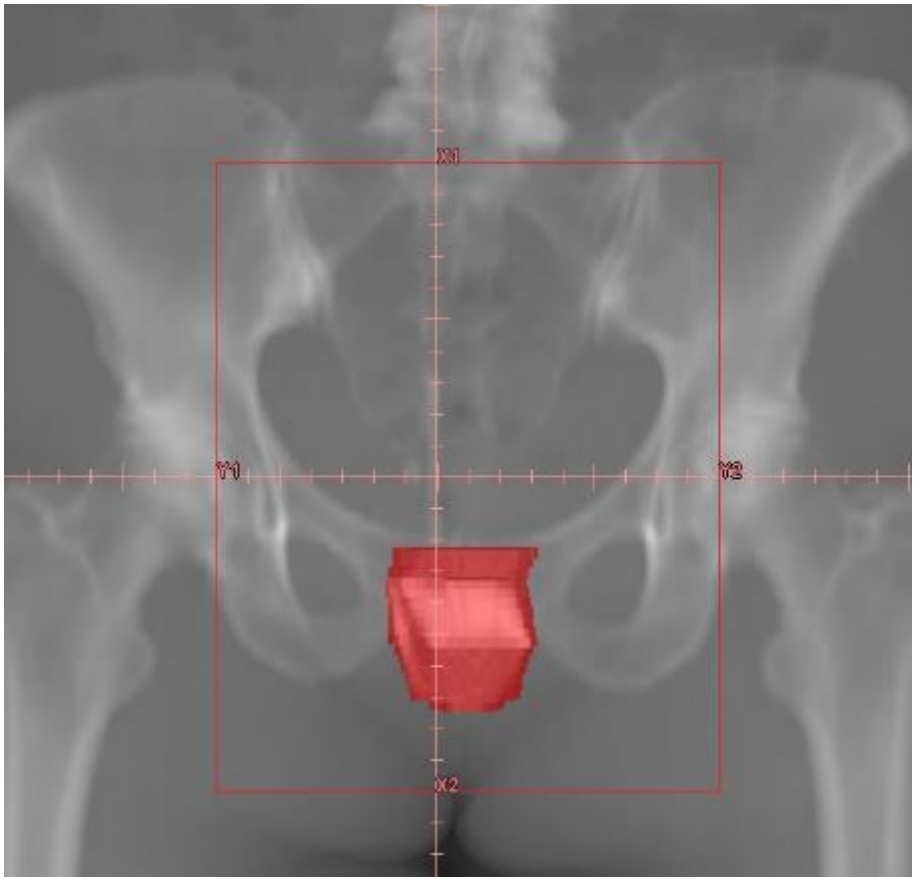


Vault recurrence

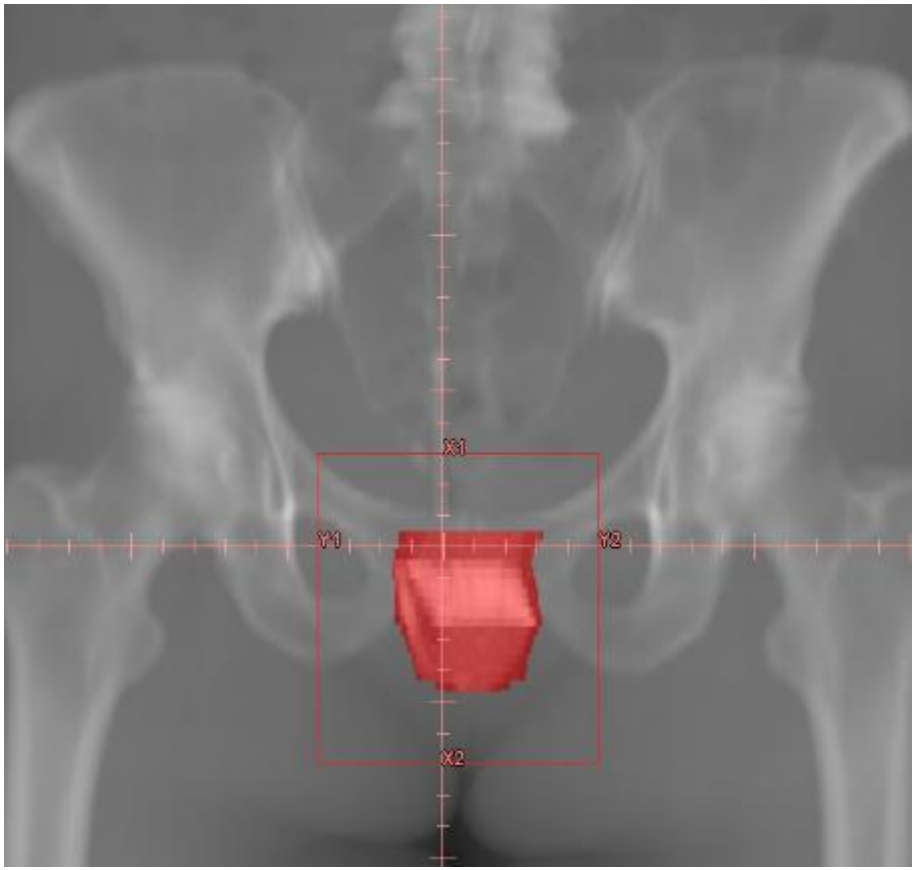
- Danish Endometrial Cancer Study
  - 1166 patients, surgery alone
  - Vaginal recurrence: low risk 6.3%, intermediate risk 22%
  - **Curative treatment: 100% CR, 74% cured**
- Must give sufficient dose (>65 Gy)
  - EBRT boost
  - Interstitial boost
  - IMRT

Ørtoft G, et al. Int J Gynecol Cancer. 2013; 23(8):1429-37

Patient

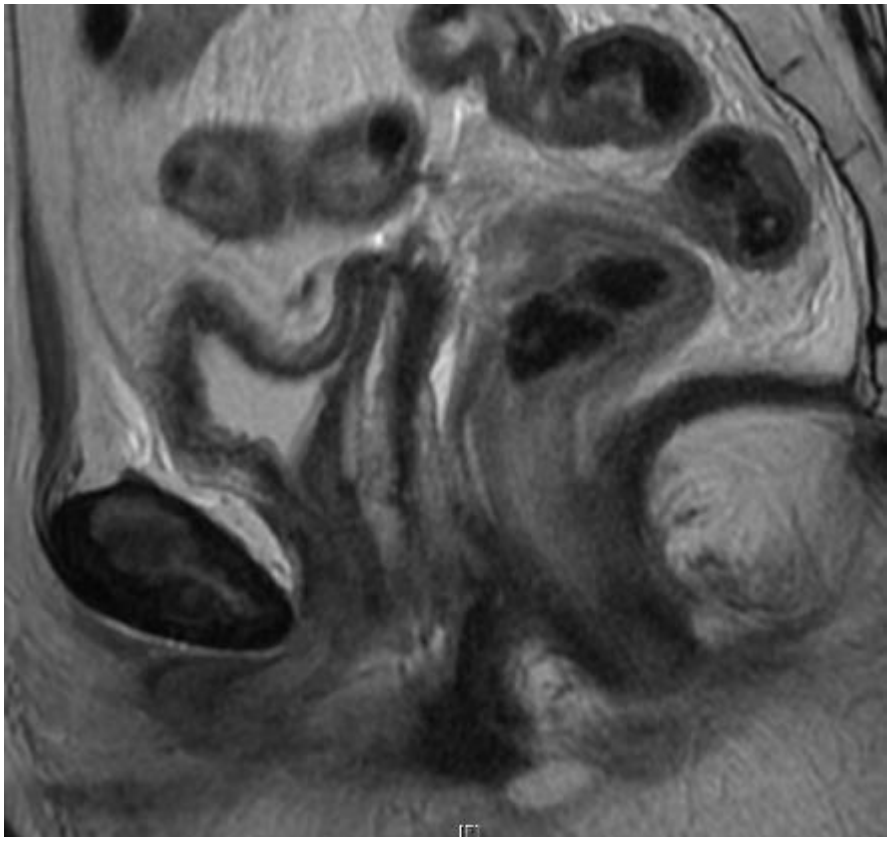


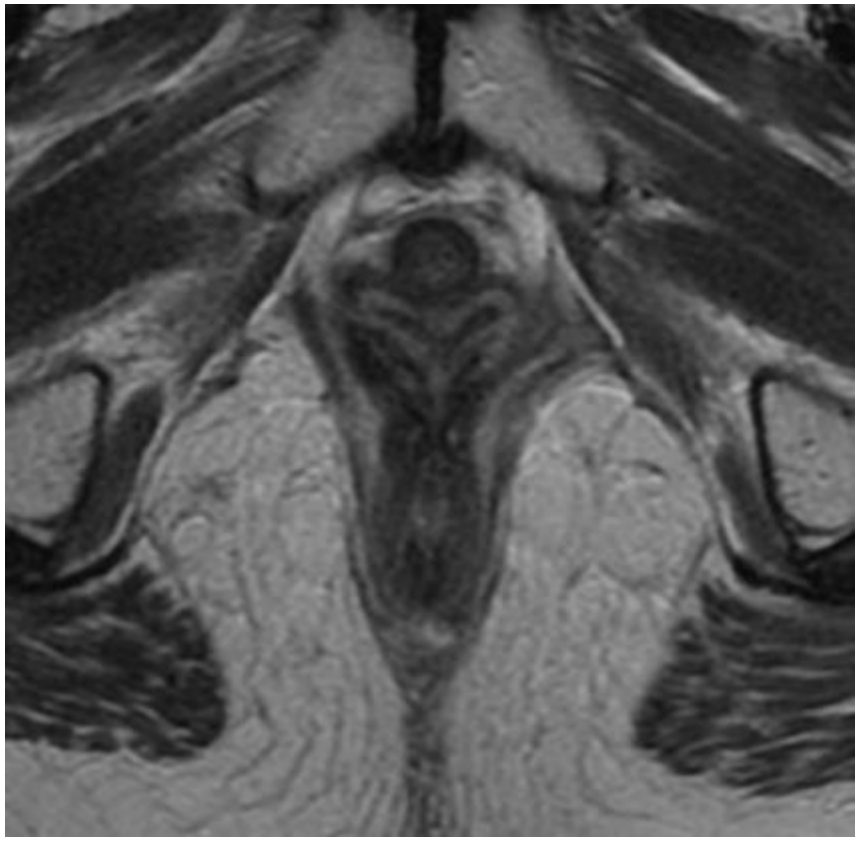
45Gy in 25#



20Gy in 10#

Patient





ESMO-ESGO-ESTRO recommendations 2015

- RT with curative intent is indicated in patients with isolated vaginal relapse after surgery.
- Use of systemic therapy or surgery before RT for vaginal or pelvic node recurrence could be considered in certain patients with more bulky disease.

Colombo N. Radiother Oncol. 2015;117(3):559-81

Evidence-based radiotherapy for cervix cancer

Dr Li Tee Tan

Cambridge University Hospitals NHS
NHS Foundation Trust

Grades of recommendation

Grades of recommendations	
A	At least one meta-analysis, systematic review or clinical trial classified as 1++ and directly applicable to the target population of the guideline, or a volume of scientific evidence comprising studies classified as 1+ and which are highly consistent with each other.
B	A body of scientific evidence comprising studies classified as 2++, directly applicable to the target population of the guideline and highly consistent with each other, or scientific evidence extrapolated from studies classified as 1++ or 1+.
C	A body of scientific evidence comprising studies classified as 2+, directly applicable to the target population of the guideline and highly consistent with each other, or scientific evidence extrapolated from studies classified as 2++.
D	Level 3 or 4 scientific evidence, or scientific evidence extrapolated from studies classified as 2+.

Due to their high risk of bias, studies classified as 1- or 2- should not be used in compiling recommendations

Good Clinical Practice

√[1]	Practice recommended on the basis of clinical experience and consensus by the drafting team

Outline

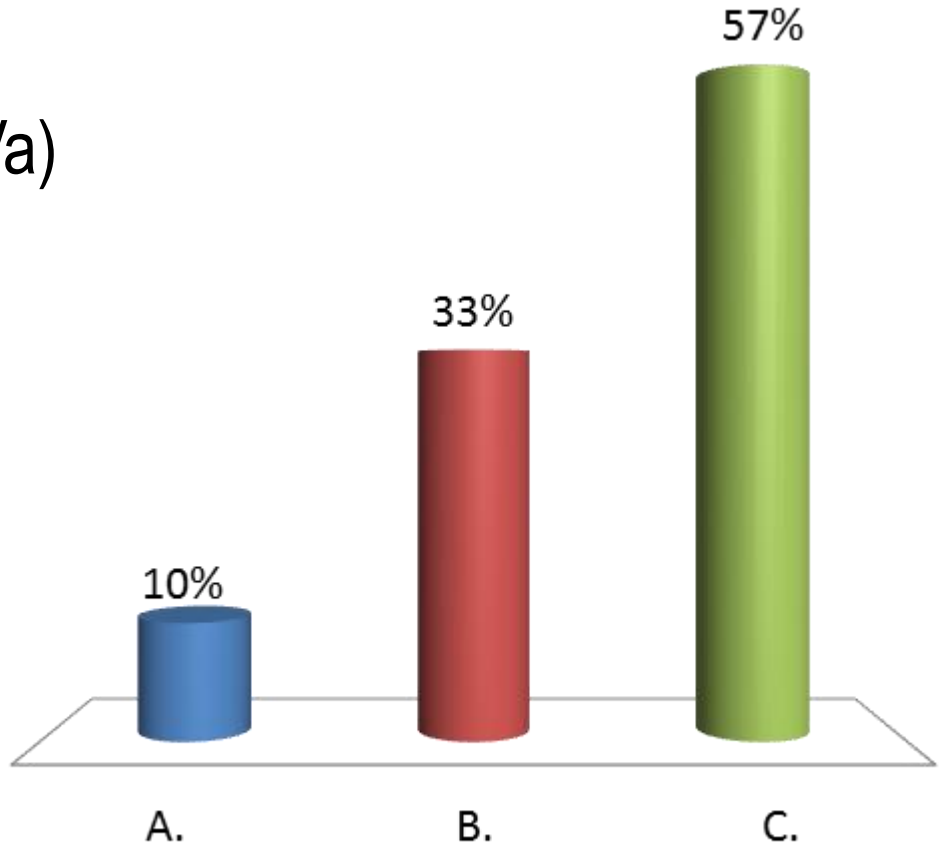
- Radiotherapy
- Brachytherapy
- Combined with chemotherapy
- Combined with surgery

Outline

- **Radiotherapy**
  - **Which stage?**
  - What volume?
  - What technique?
  - What dose?
- Brachytherapy
- Chemotherapy
- Surgery

For which disease stage would you recommend radiotherapy as curative treatment?

A. Early stage (Ib1, IIa)
B. Advanced stage (Ib2, IIb-IVa)
C. Both



Early stage disease

- Level Ib evidence
- Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer
  - 469 women
  - Post-op RT if pT2b or greater, <3 mm uninvolved cervical stroma, involved margin, positive nodes
- Results
  - No difference in OS (84% both groups)
  - More morbidity with surgery (28% vs.12%, p = 0·0004)

Landoni F, et al. Lancet. 1997;350(9077):535-40.

Advanced stage disease

- Level II evidence

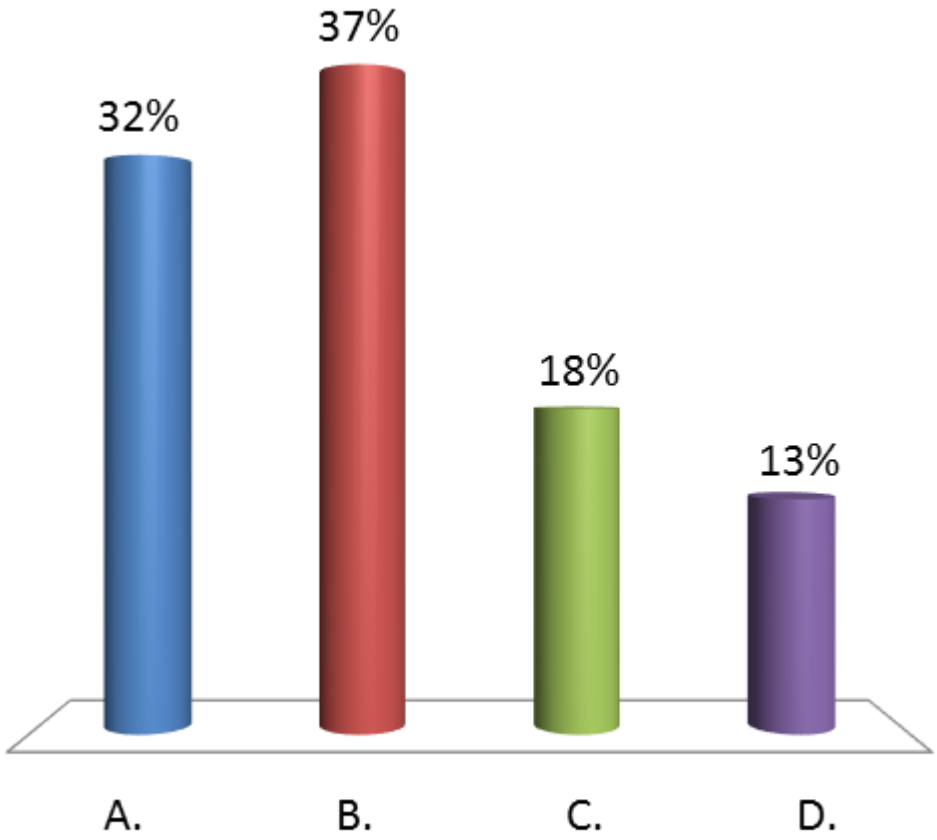
	II		III		IVA	
	S	LC	S	LC	S	LC
FIGO 1987-1989	66%		39%		11%	
PCS 1973	57%		47%			
M.D. Anderson 1975	65%	82%	40%	67%		
Washington University	68%	84%	45%	63%		
French Co-operative Study	76%	80%	50%	57%		

Outline

- **Radiotherapy**
  - Which stage?
  - **What volume?**
  - What technique?
  - What dose?
- Brachytherapy
- Chemotherapy
- Surgery

Where is your standard superior border for EBRT for node-negative cervix cancer?

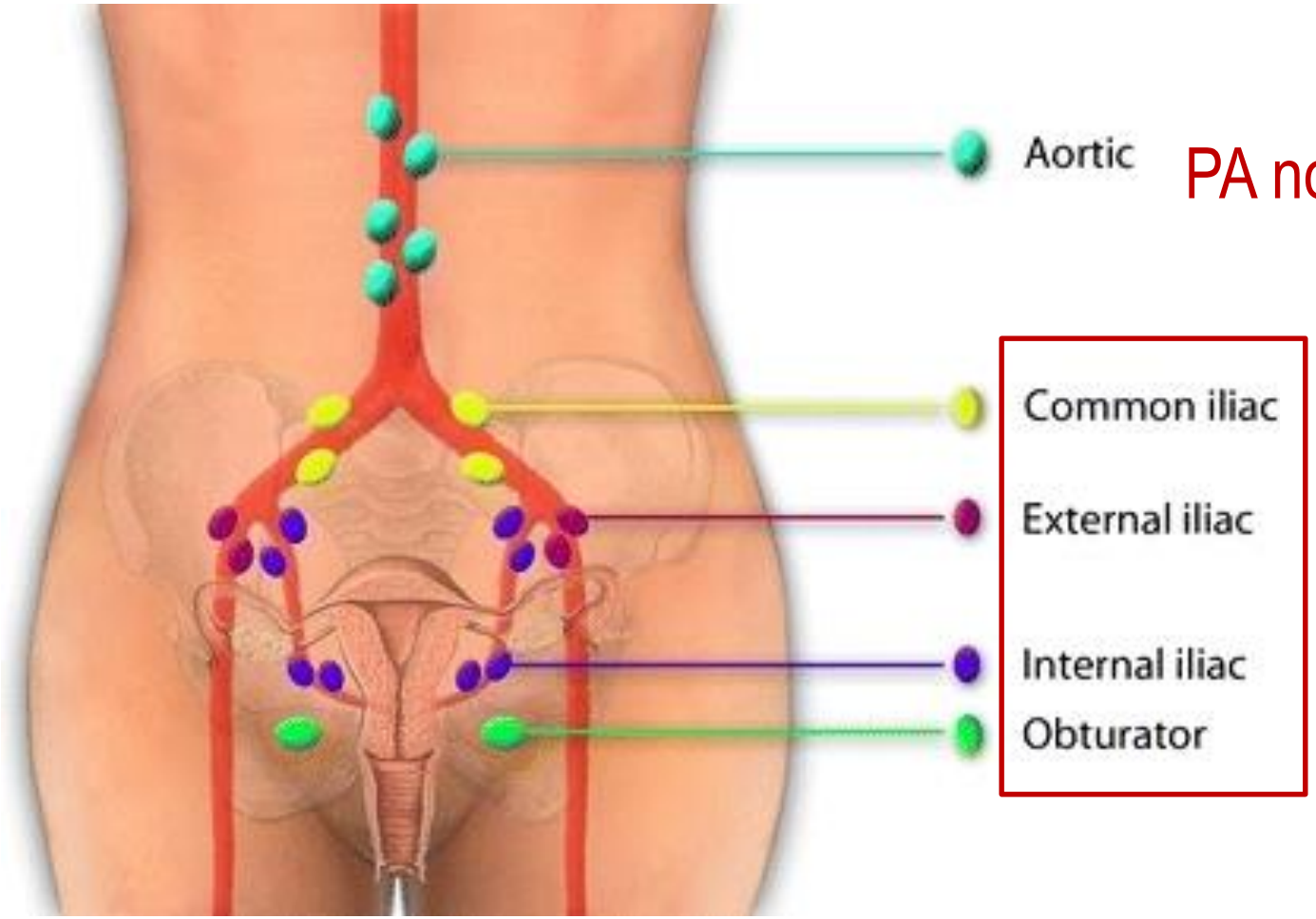
A. L5/S1 junction
B. L4/L5 junction
C. Inferior to L5/S1 junction (individualised)
D. Superior to L4/L5 junction (individualised)



Target volume

- Primary tumour (GTV-T)
- Pathological nodes (GTV-N)
- Elective volume (CTV-E)
  - Uterus
  - Parametria
  - Vagina (2 cm below GTV-T)
  - Regional nodes

Regional nodes

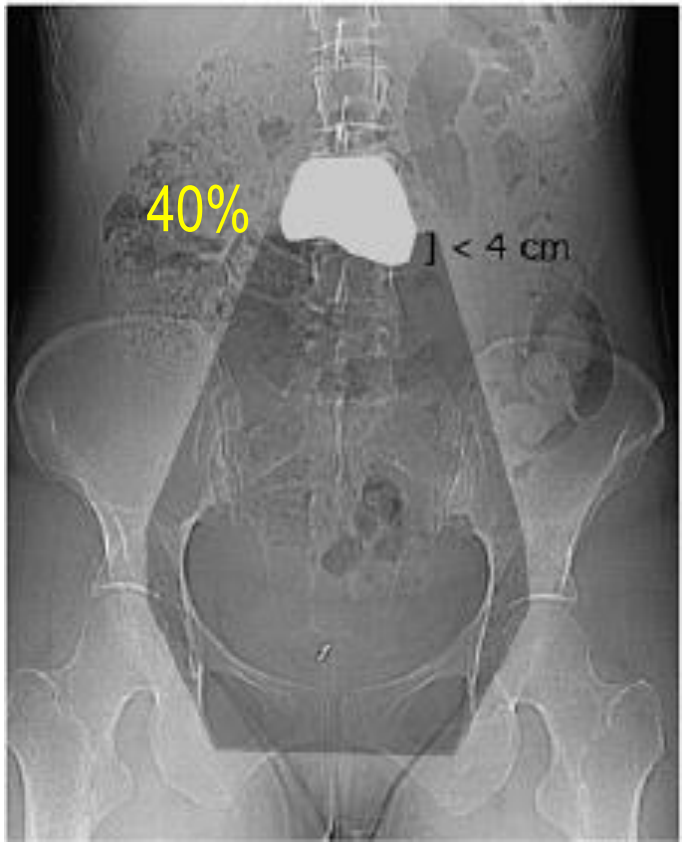


TNM

PA nodes = M1

Patterns of regional failure

- MD Anderson 1980-2000 (1894 patients)
  - 198 regional (no central) recurrences (33% distant mets)

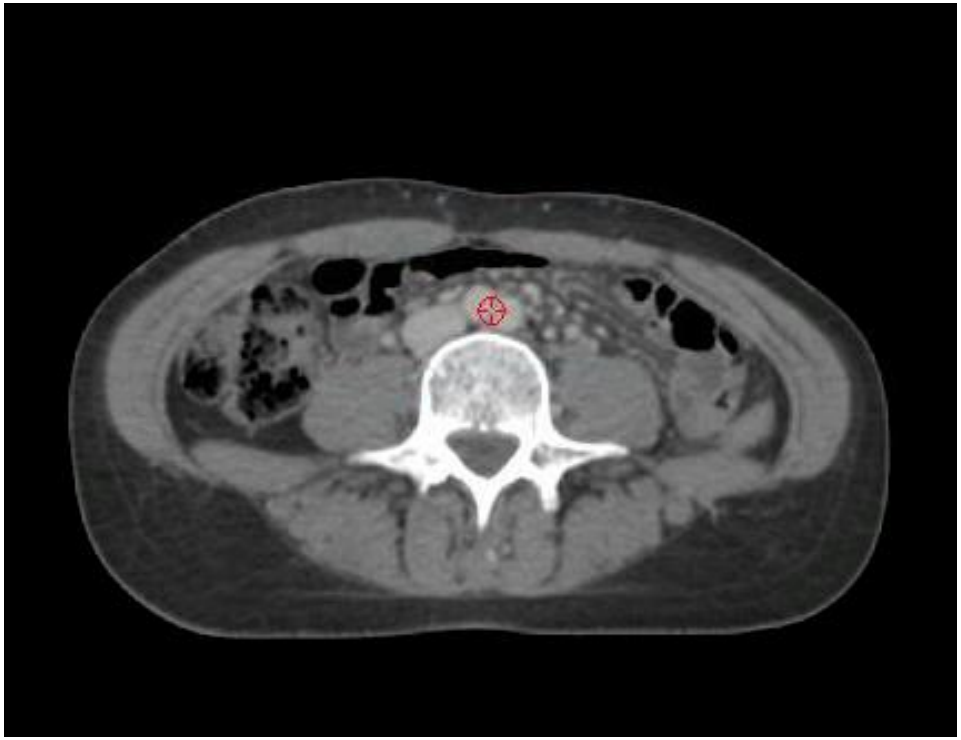


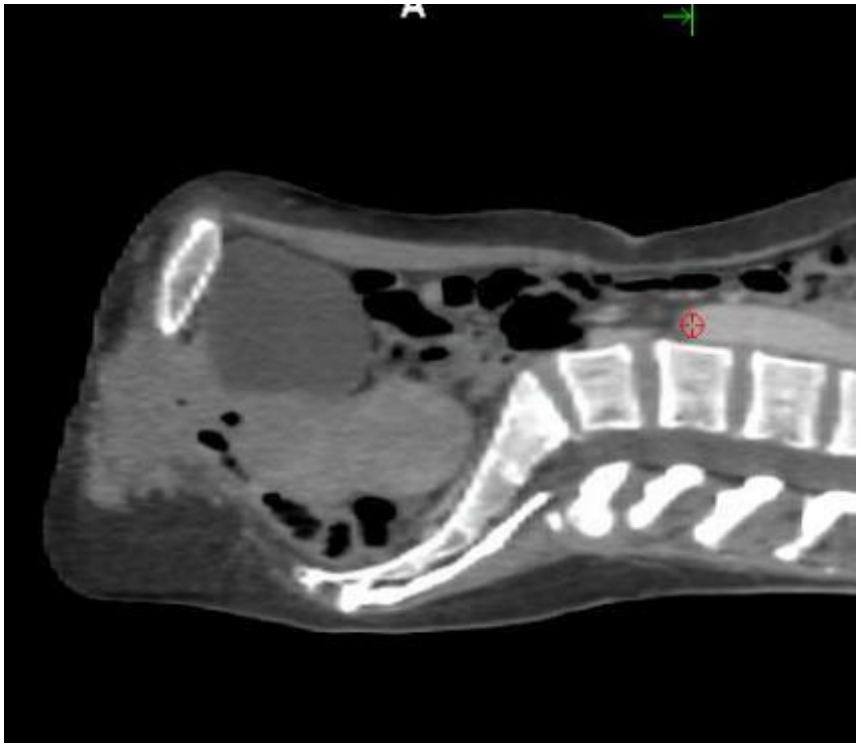
Beadle BM, et al. Int J Radiat Oncol Biol Phys. 2010;76(5):1396-403

Nodal delineation - common iliac

- Taylor A, *et al*. IJROBP, 2005;63:1604–12
  - 7 mm margin round vessels
  - Bifurcation of aorta
  - Extend posterior and lateral borders to psoas and vertebral body
- Small W, *et al*. IJROBP 2008;71:428-434 (RTOG)
  - From 7 mm below L4/5 interspace to bifurcation of common iliac arteries

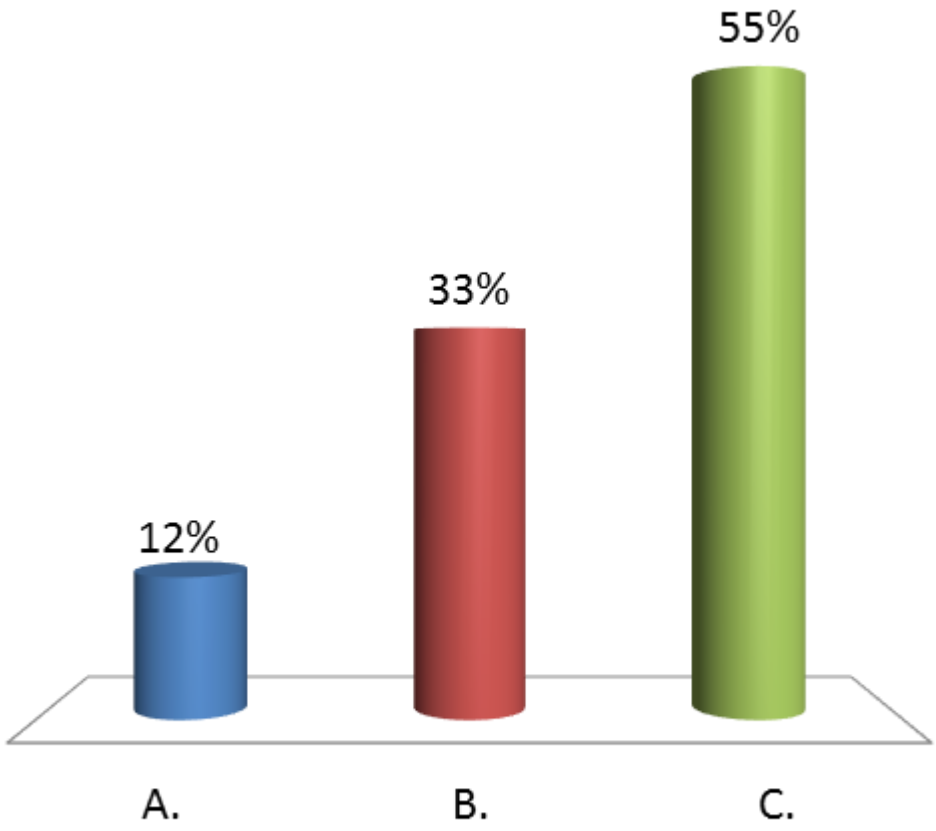
Nodal delineation - common iliac





Are paraaortic node metastases in cervical cancer curable?

A. No
B. Yes, if microscopic
C. Yes, microscopic and macroscopic



PA node irradiation - macroscopic disease

- Level II evidence
- RTOG 92-10
  - 30 patients, Stage I-IV + biopsy-proven PA nodes
  - Hyperfractionated (bd) EBRT + cisplatin/5FU
- Results
  - 4-year OS 29% (median FU = 57 months)

Grigsby PW, et al. Int J Radiat Oncol Biol Phys. 2001;51(4):982-7

PA node irradiation - prophylactic

- Level Ib evidence
- RTOG 79-20
  - 367 patients, Ib2, IIa (> 4 cm), IIb
  - Pelvis vs. pelvis + PA (40-50 Gy, no chemo)
- Results
  - 10-year OS 44% vs. 55% (p = 0.02)

Rotman M, et al. JAMA. 1995;274(5):387-93

PA node irradiation - prophylactic

- 441 patients
  - I-IIb proximal + positive LN, all IIb distal or III
  - Pelvis vs. pelvis + PA (45 Gy)
- Results
  - No significant difference in local control, OS, DFS
    Significantly higher incidence of PA metastases + distant metastases without local recurrence in pelvic RT group
- Patients with high probability of local control can benefit from EFRT

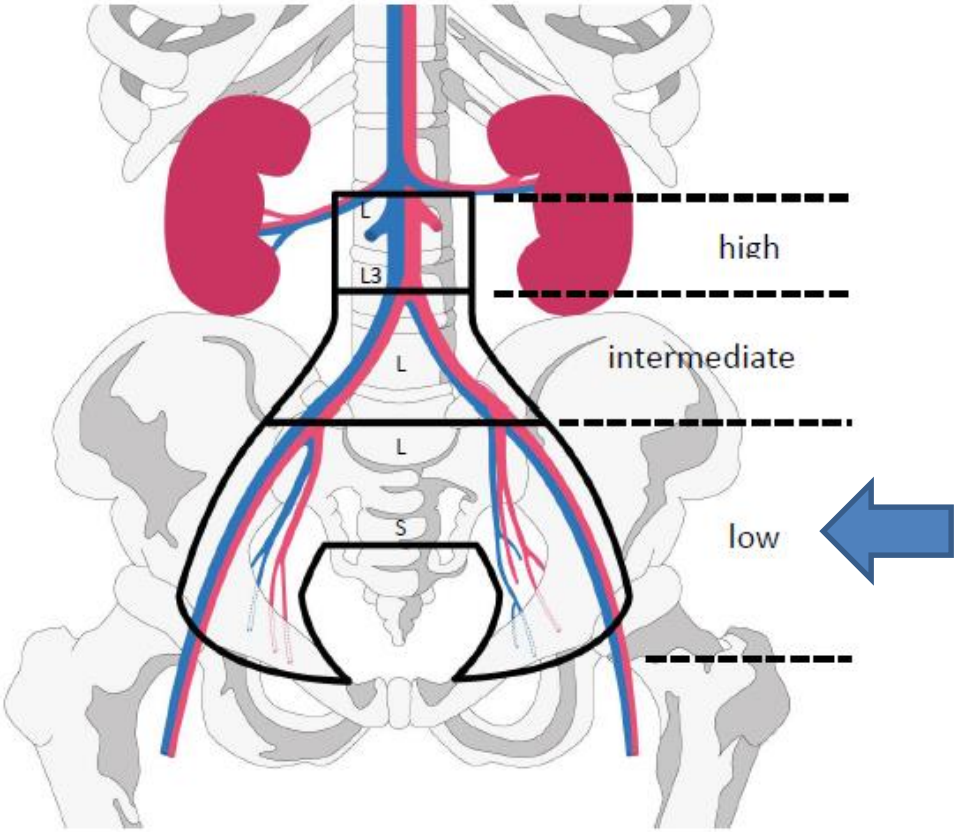
Haie C, et al. Radiother Oncol. 1988 Feb;11(2):101-12

Prophylactic extended field RT

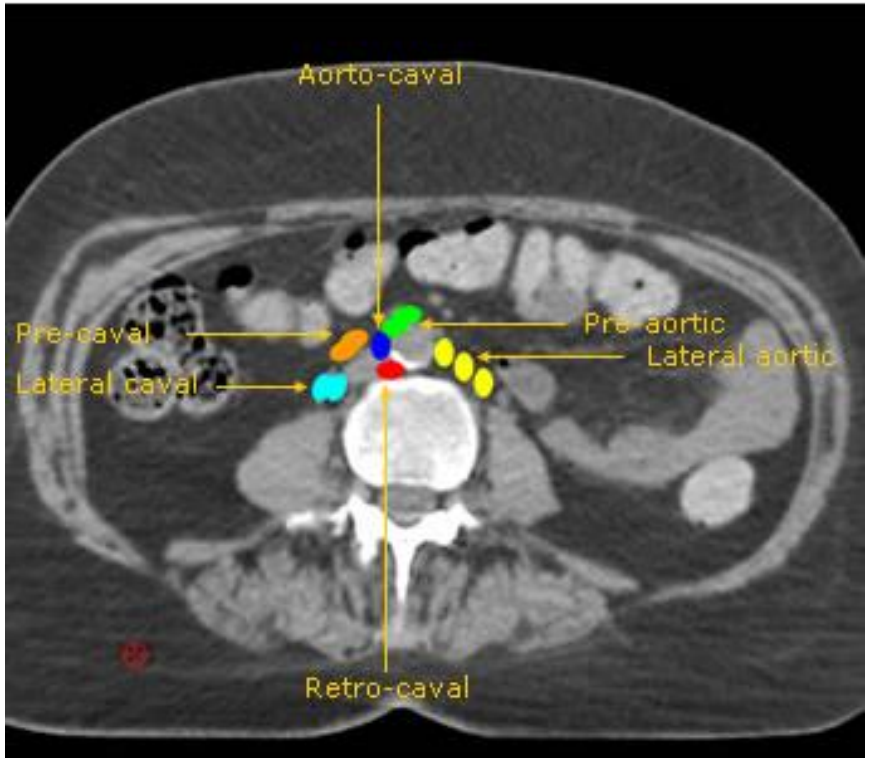
- Which patients?
  - PET-CT (sensitivity 84%, specificity 95%)
  - RPLND
- EMBRACE II criteria
  - Common iliac node or ≥ 3 pelvic nodes
  - Treat to renal vein (PA nodes above renal vessels incurable)

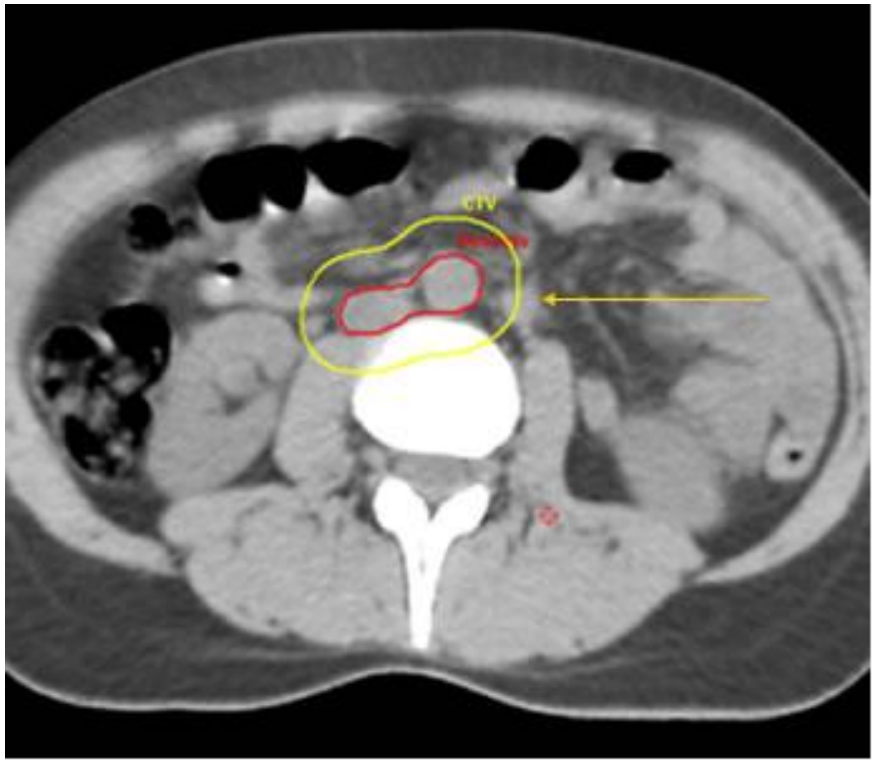
EMBRACE II EBRT CTV

Risk Group LN	Definition
Low Risk (LR LN)	Tumour size ≤4cm AND stage IA/IB1/IIA1 AND N0 AND squamous cell carcinoma AND no uterine invasion
Intermediate Risk (IR LN)	Not low risk No high risk features
High Risk (HR LN)	Based on nodal pathology • ≥ 1 pathologic node at common iliac or above • OR ≥ 3 pathologic nodes



PA node irradiation - contouring





EMBRACE II EBRT CTV

Risk Group LN	Definition
Low Risk (LR LN)	Tumour size ≤4cm AND stage IA/IB1/IIA1 AND N0 AND squamous cell carcinoma AND no uterine invasion
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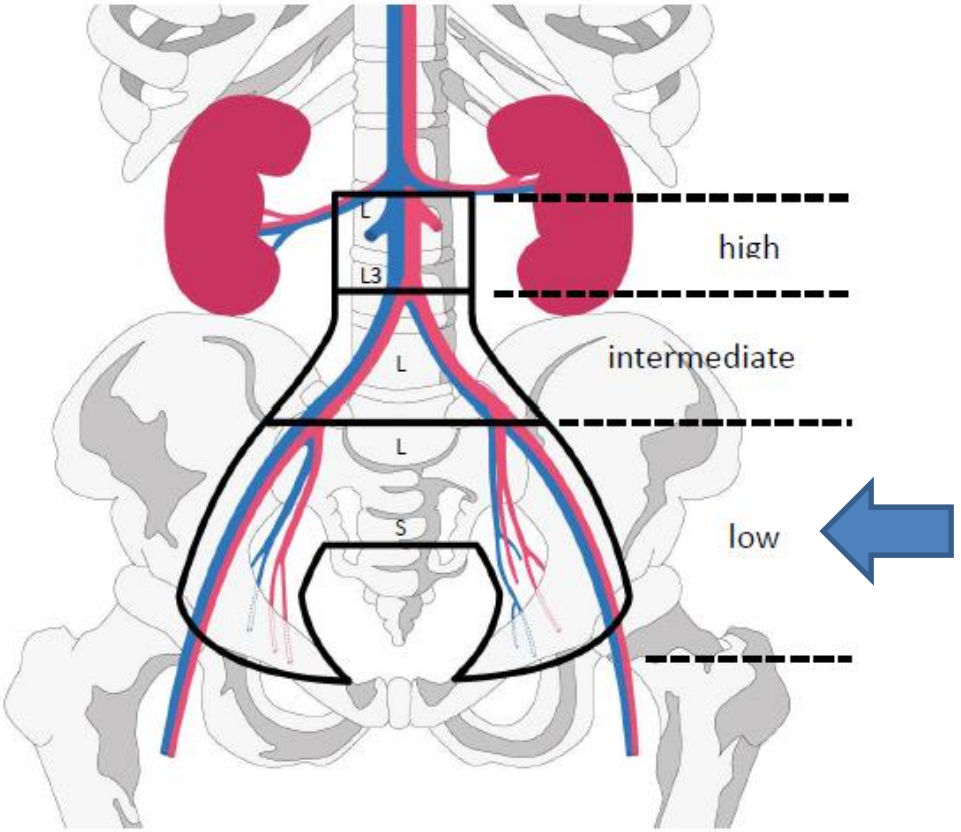
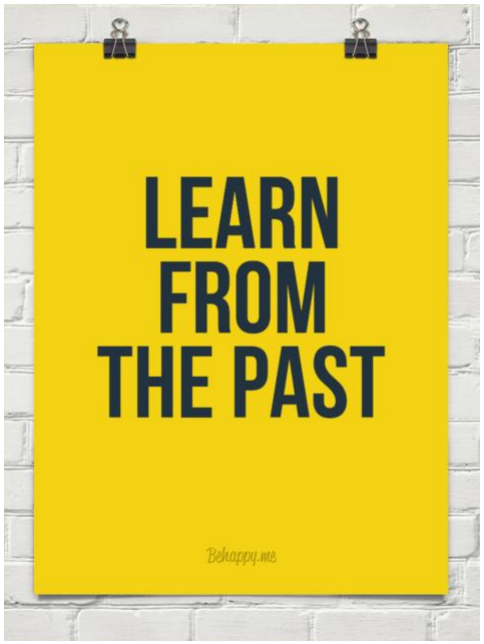
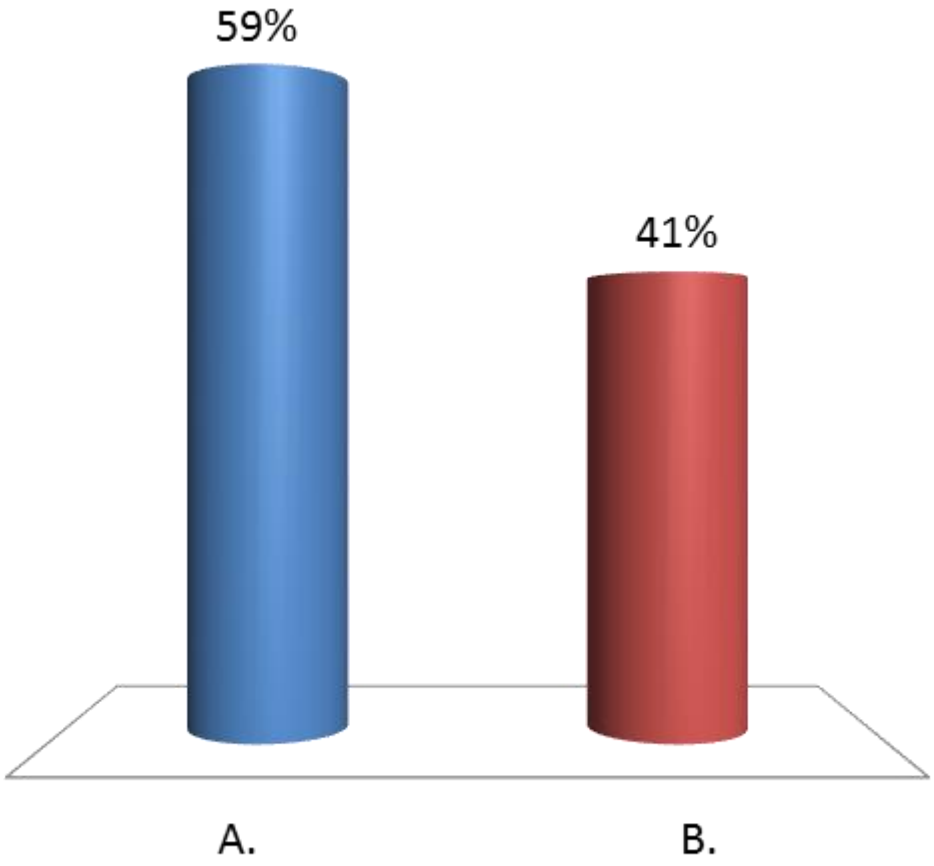


Do you think that decreasing the CTV for low risk tumours is “experimental”?

A. Yes

B. No



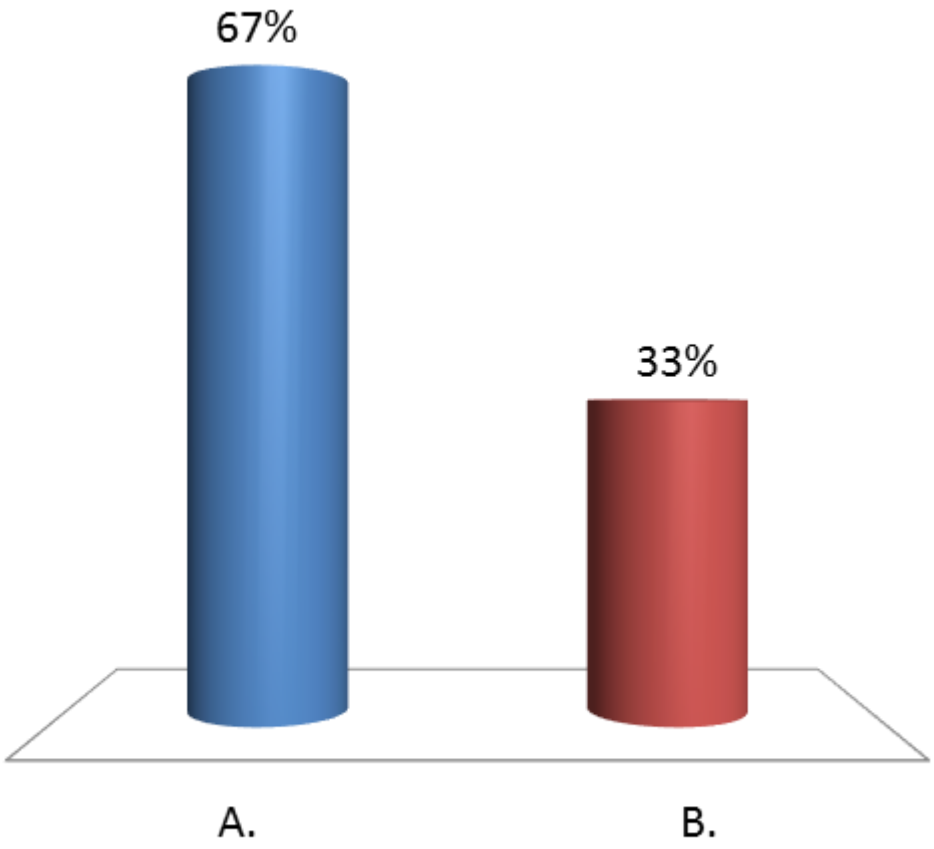


Outline

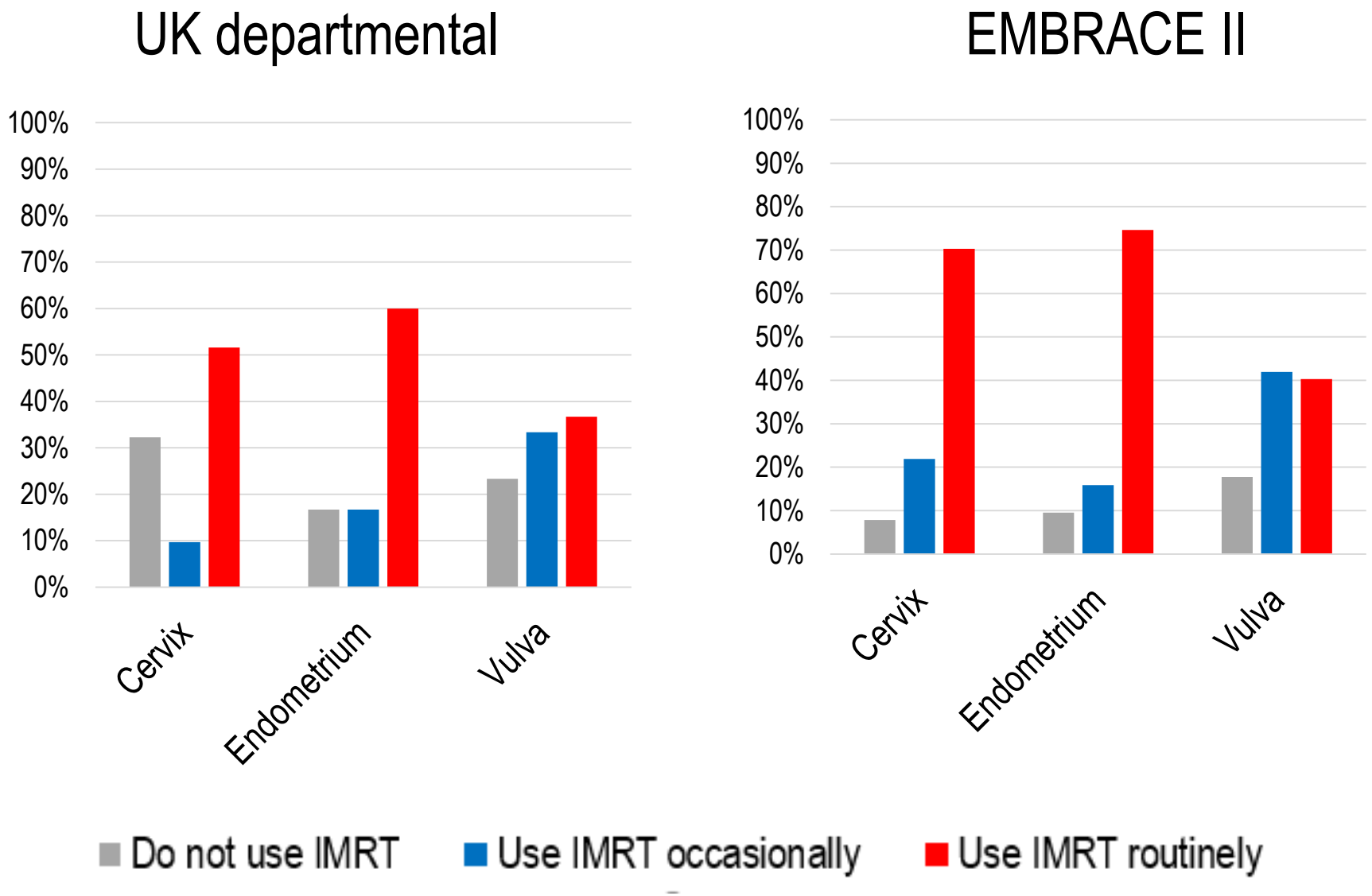
- **Radiotherapy**
  - Which stage?
  - What volume?
  - **What technique?**
  - What dose?
- Brachytherapy
- Chemotherapy
- Surgery

Do you routinely use IMRT for cervical cancer at your centre?

A. Yes
B. No

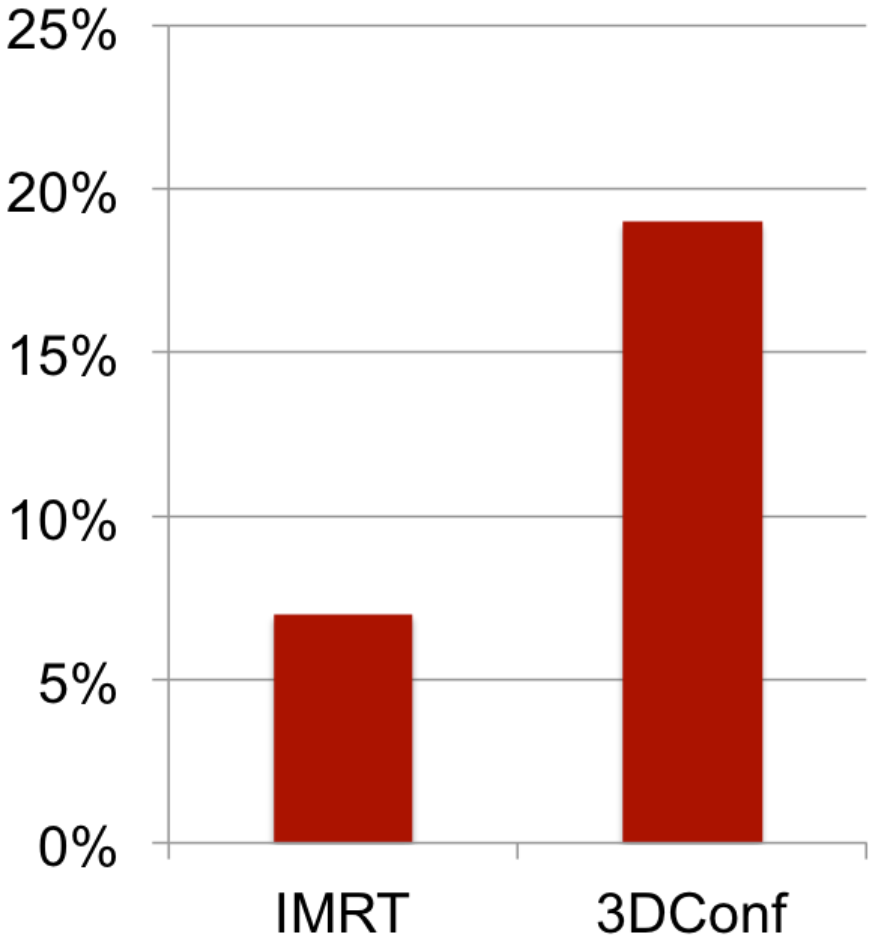


Survey 2016


UK departmental
EMBRACE II
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cervix
Endometrium
Vulva
Do not use IMRT
Use IMRT occasionally
Use IMRT routinely

EMBRACE: QoL, chronic diarrhoea

Not at all
A little
Quite a bit
Very much



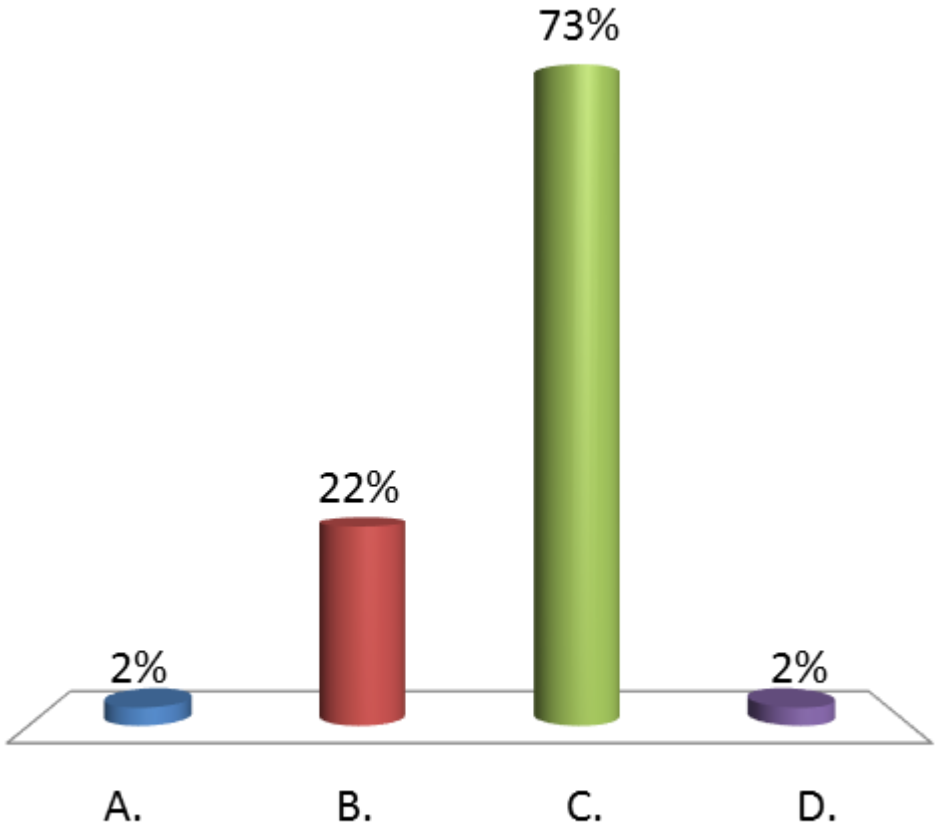
Kirchheiner, EMBRACE Meeting 2014

Outline

- **Radiotherapy**
  - Which stage?
  - What volume?
  - What technique?
  - **What dose?**
- Brachytherapy
- Chemotherapy
- Surgery

What is your standard EBRT dose for radical radiotherapy for cervix cancer?

A. 40 Gy in 20#
B. 45 Gy in 25#
C. 50-50.4 Gy in 25-28#
D. Other



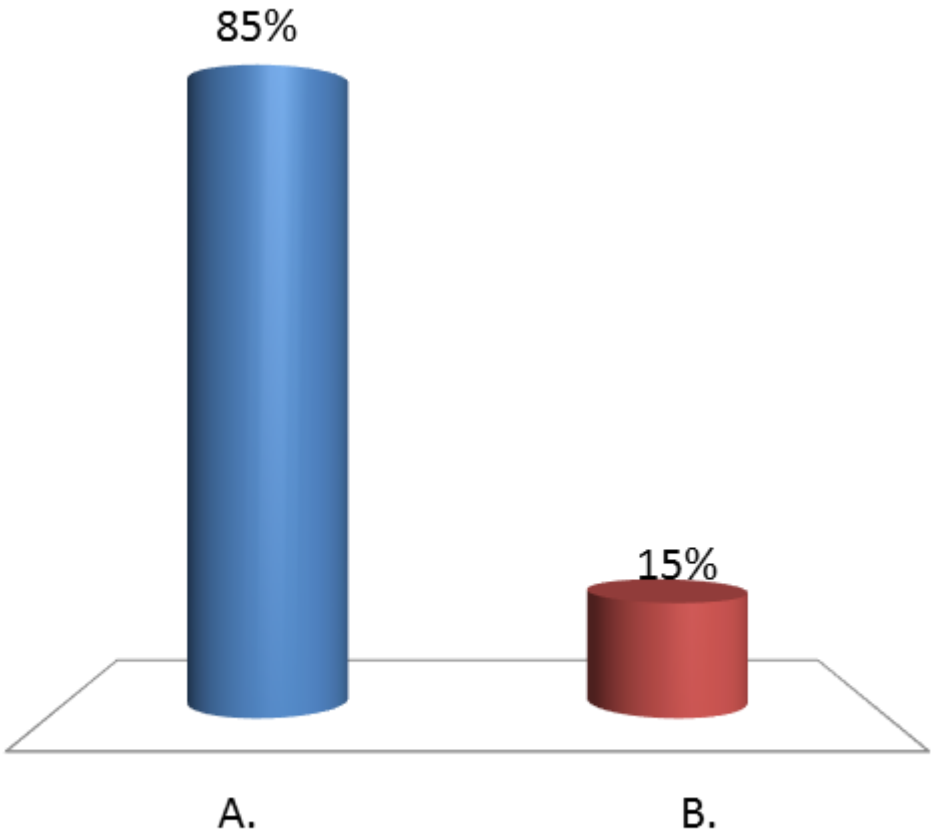
0

EBRT dose

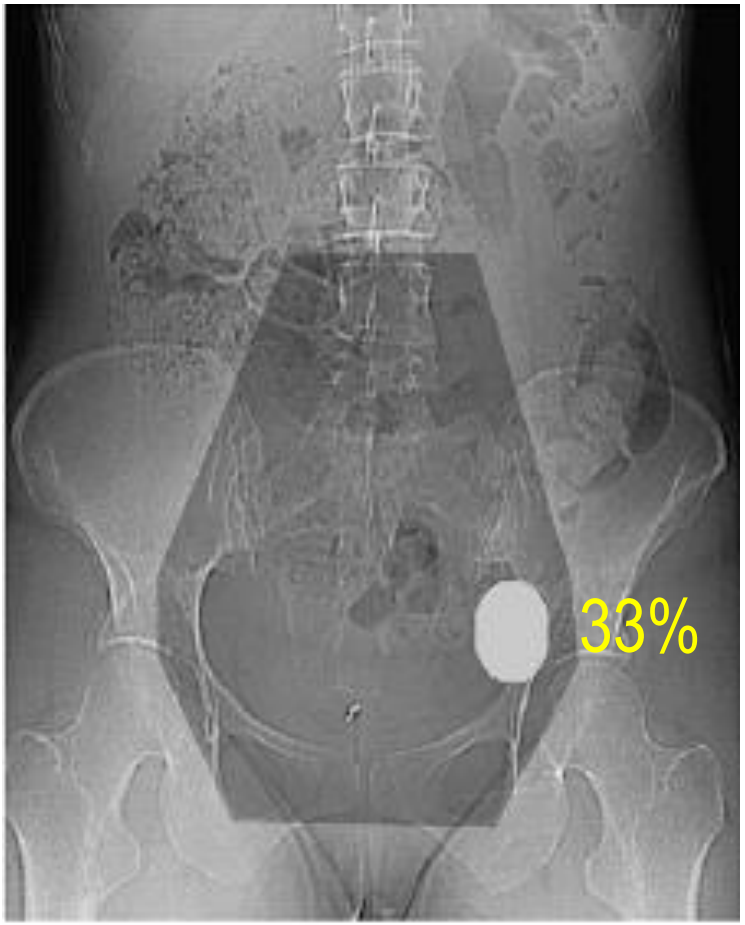
- Level II-III evidence
  - Large cohort studies
  - OAR tolerances

Do you boost the dose to pathological nodes?

A. Yes
B. No

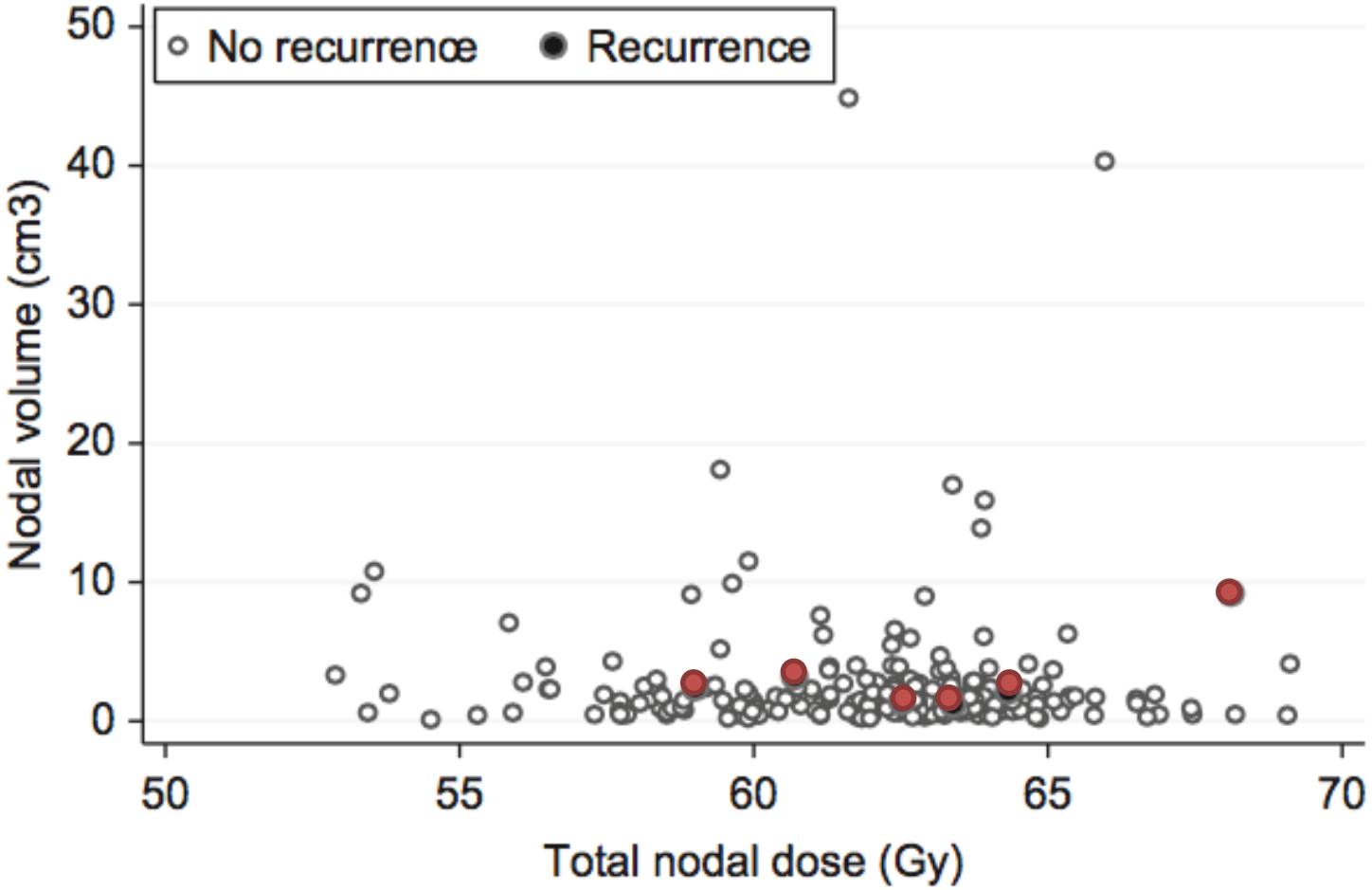


Patterns of regional failure



Beadle BM, et al. Int J Radiat Oncol Biol Phys. 2010;76(5):1396-403

Impact of dose on nodal control



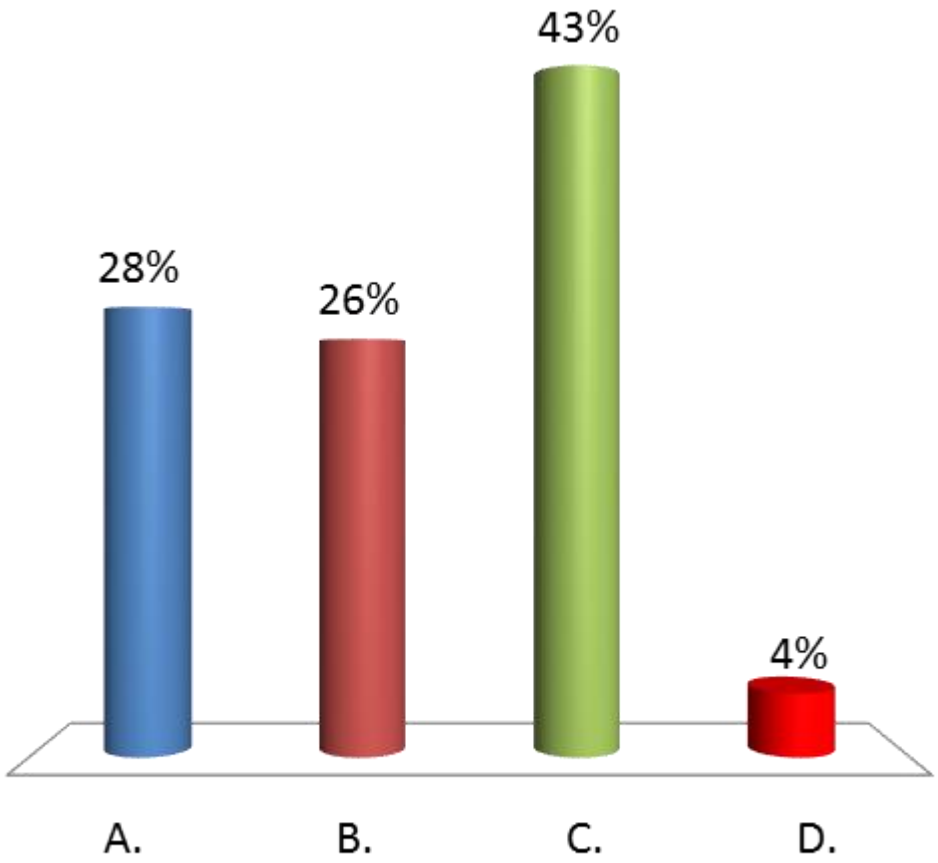
Ramlov A, et al. Acta Oncol. 2015;54(9):1567-73

Outline

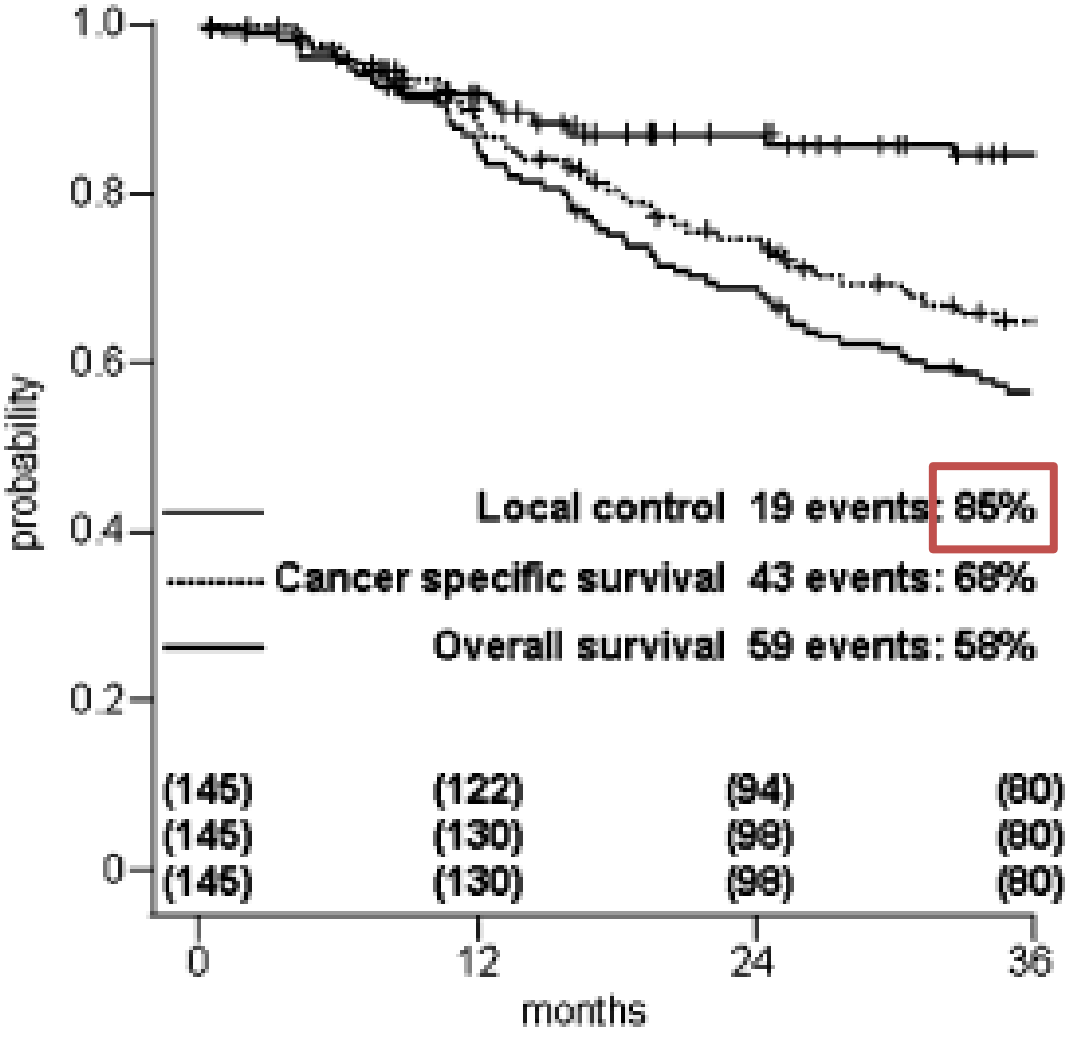
- Radiotherapy
- **Brachytherapy**
- Combined with chemotherapy
- Combined with surgery

Is IGBT for cervix cancer offered at your centre?

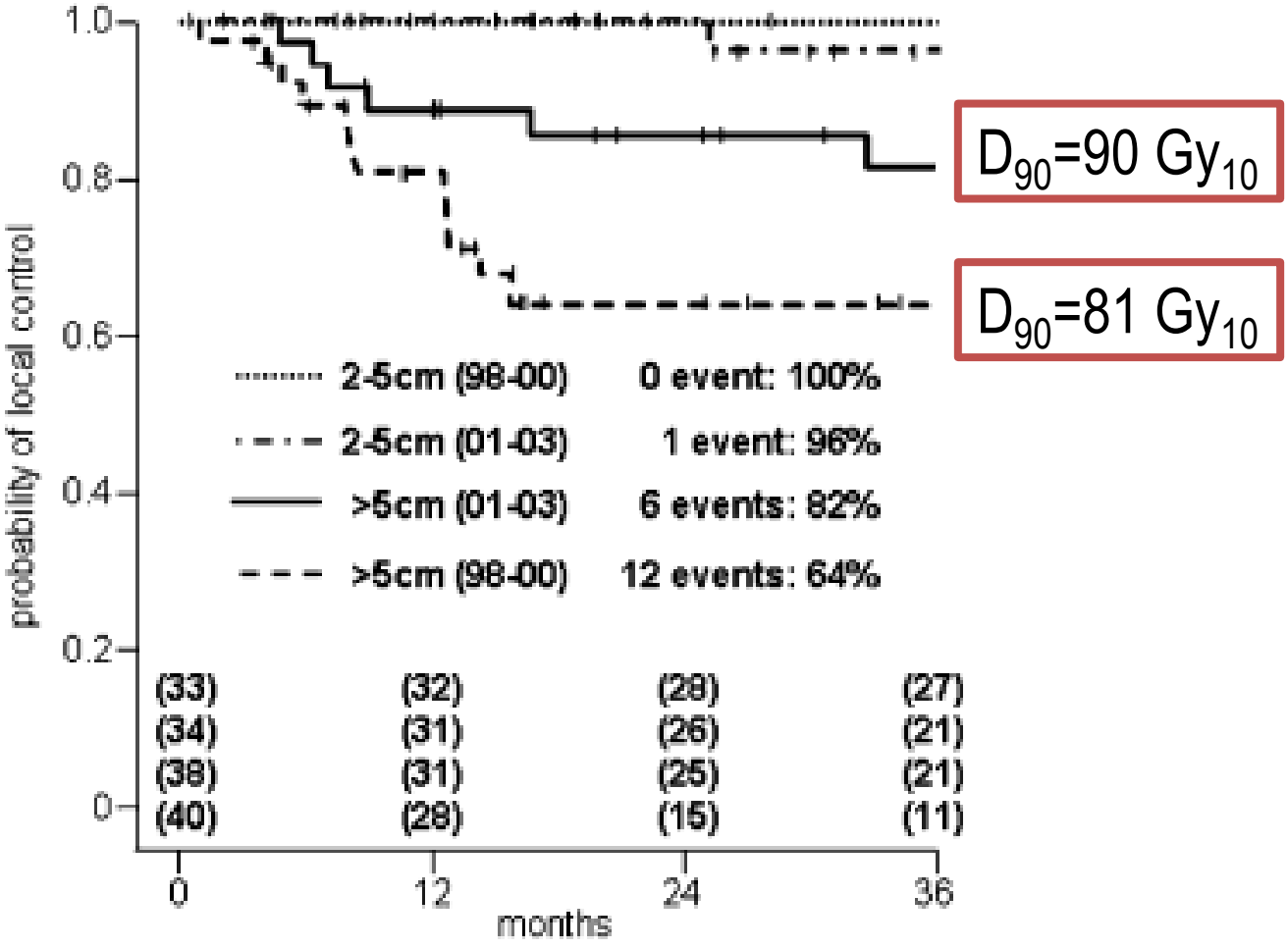
A. No
B. Yes - CT-guided
C. Yes - MRI-guided
D. Yes - US-guided



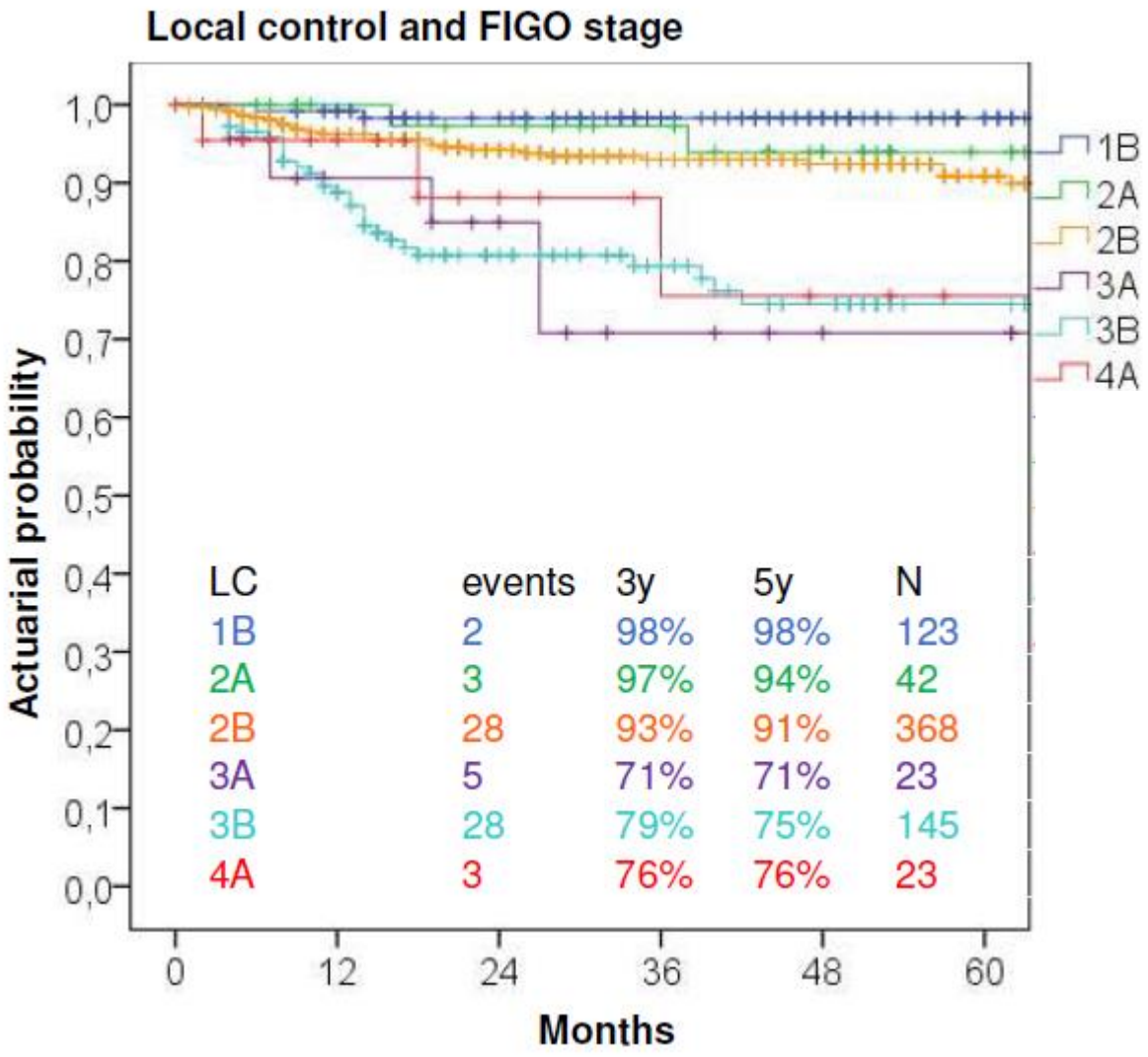
Potter R, *et al.*
Radiother Oncol 2007;83(2):148-55



Potter R, *et al.*
Radiother Oncol 2007;83(2):148-55



Retro-EMBRACE (CT + MRI IGBT)

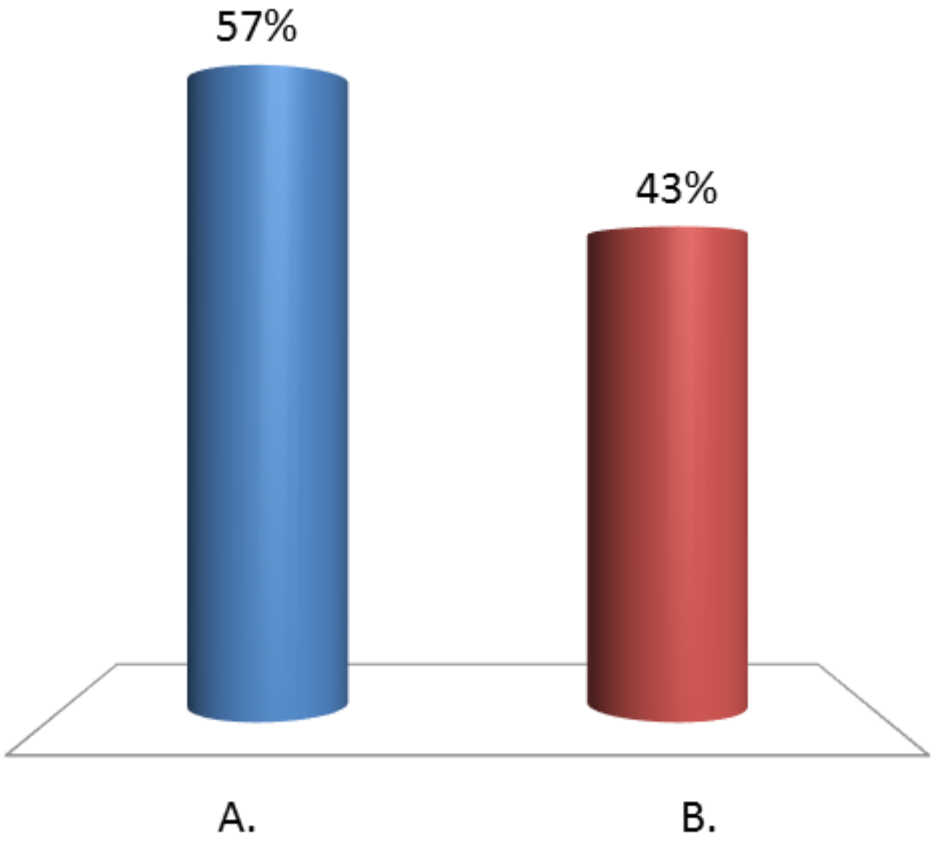


Sturdza A. Radiother Oncol. 2016;120(3):428-433.

Do you offer combined intracavitary-interstitial BT for cervix cancer at your centre?

A. Yes

B. No



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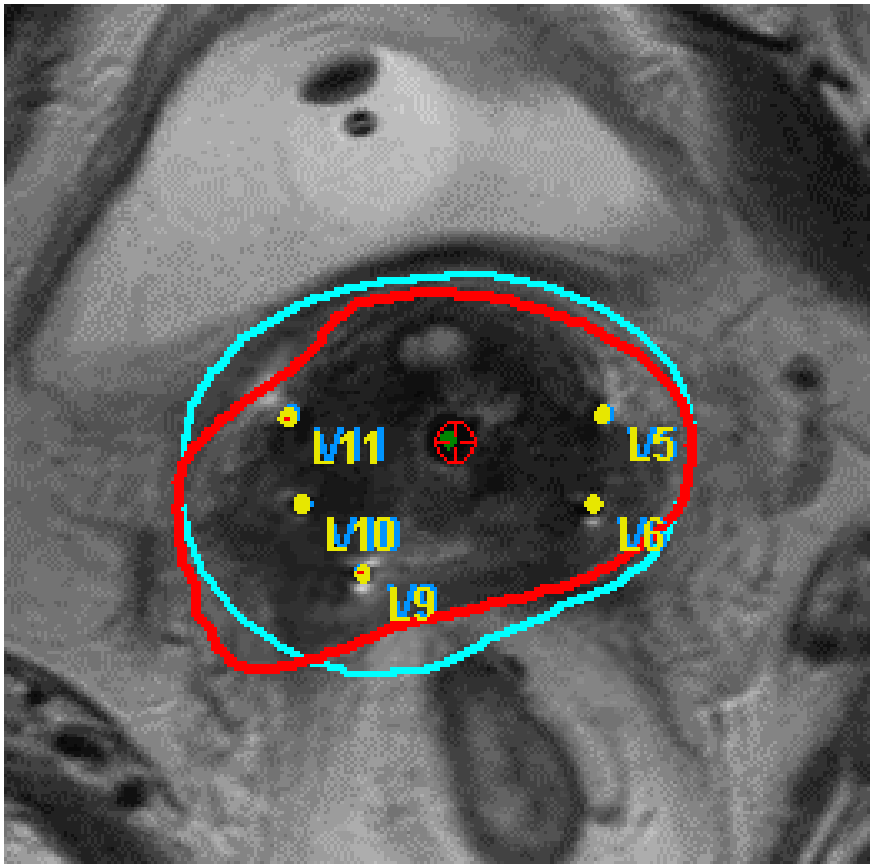
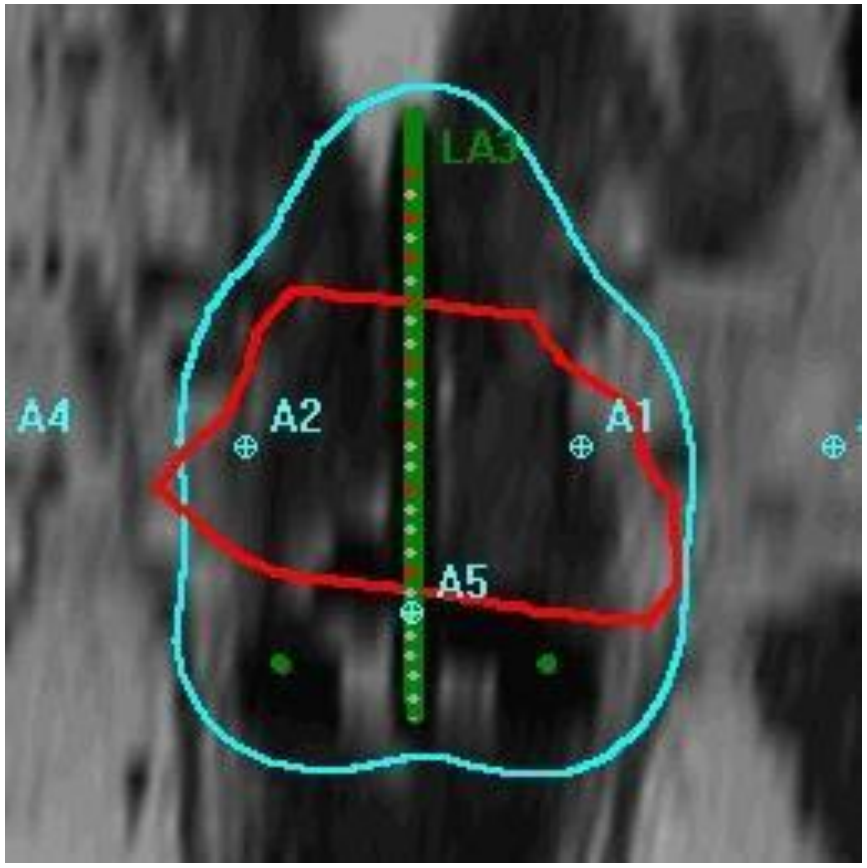
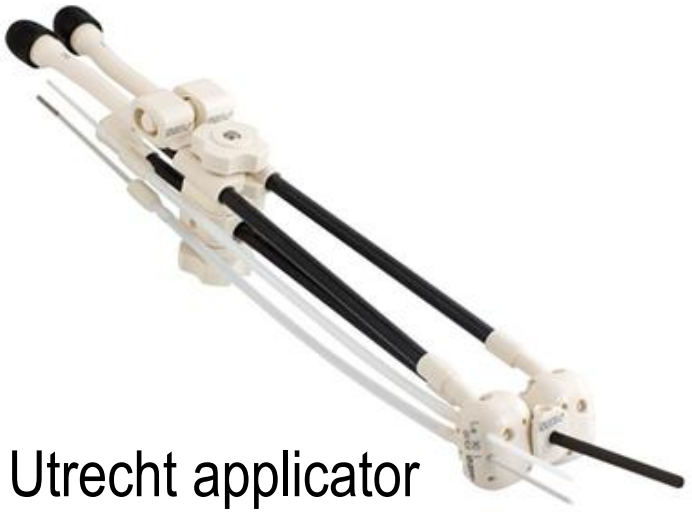
Combined intracavitary/interstitial



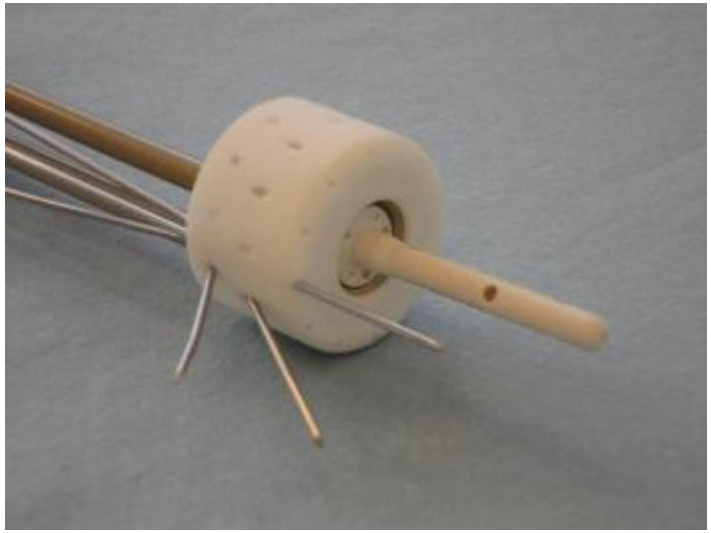


Combined intracavitary/interstitial

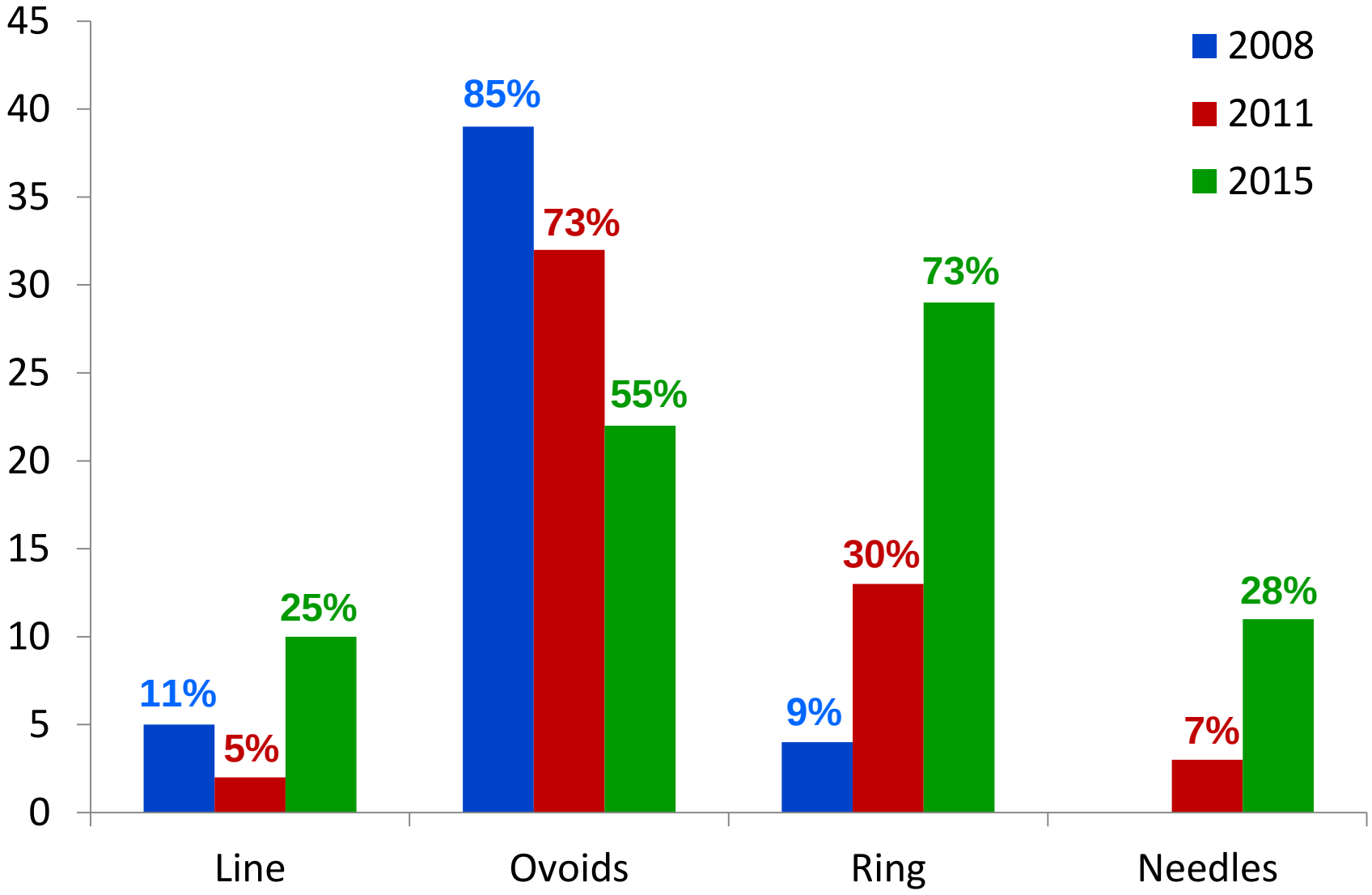
Vienna applicator



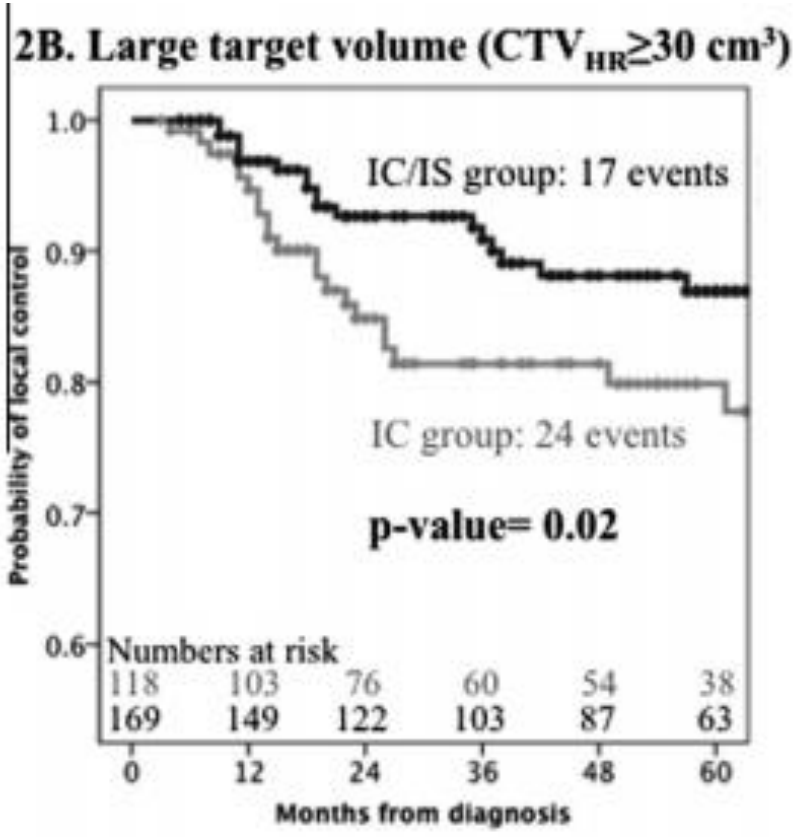
Utrecht applicator

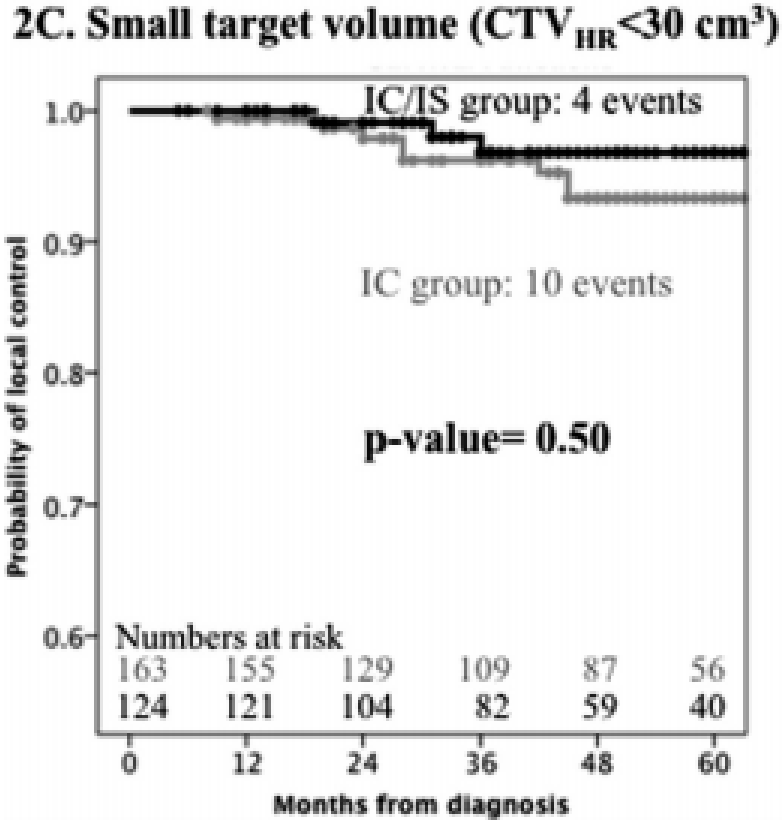


UK survey


45
40
35
30
25
20
15
10
5
0
2008
2011
2015
11%
5%
25%
85%
73%
55%
9%
30%
73%
7%
28%
Line
Ovoids
Ring
Needles

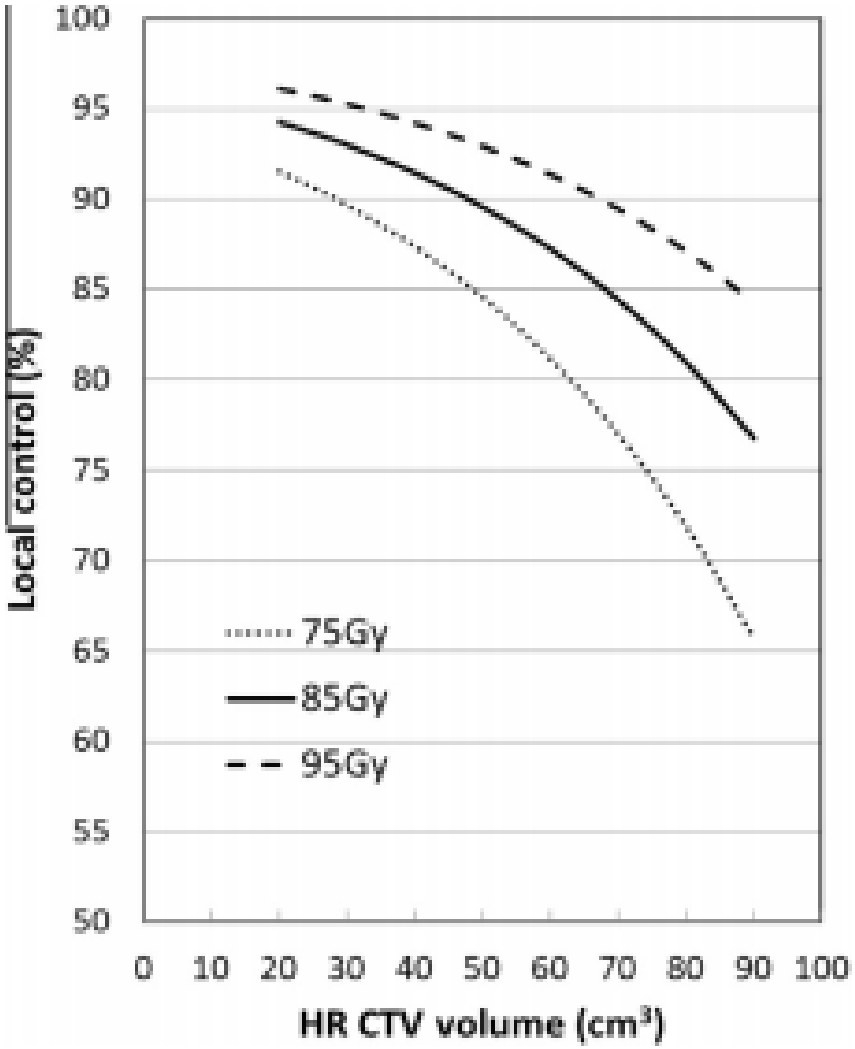
RetroEMBRACE (IC vs IC/IT)





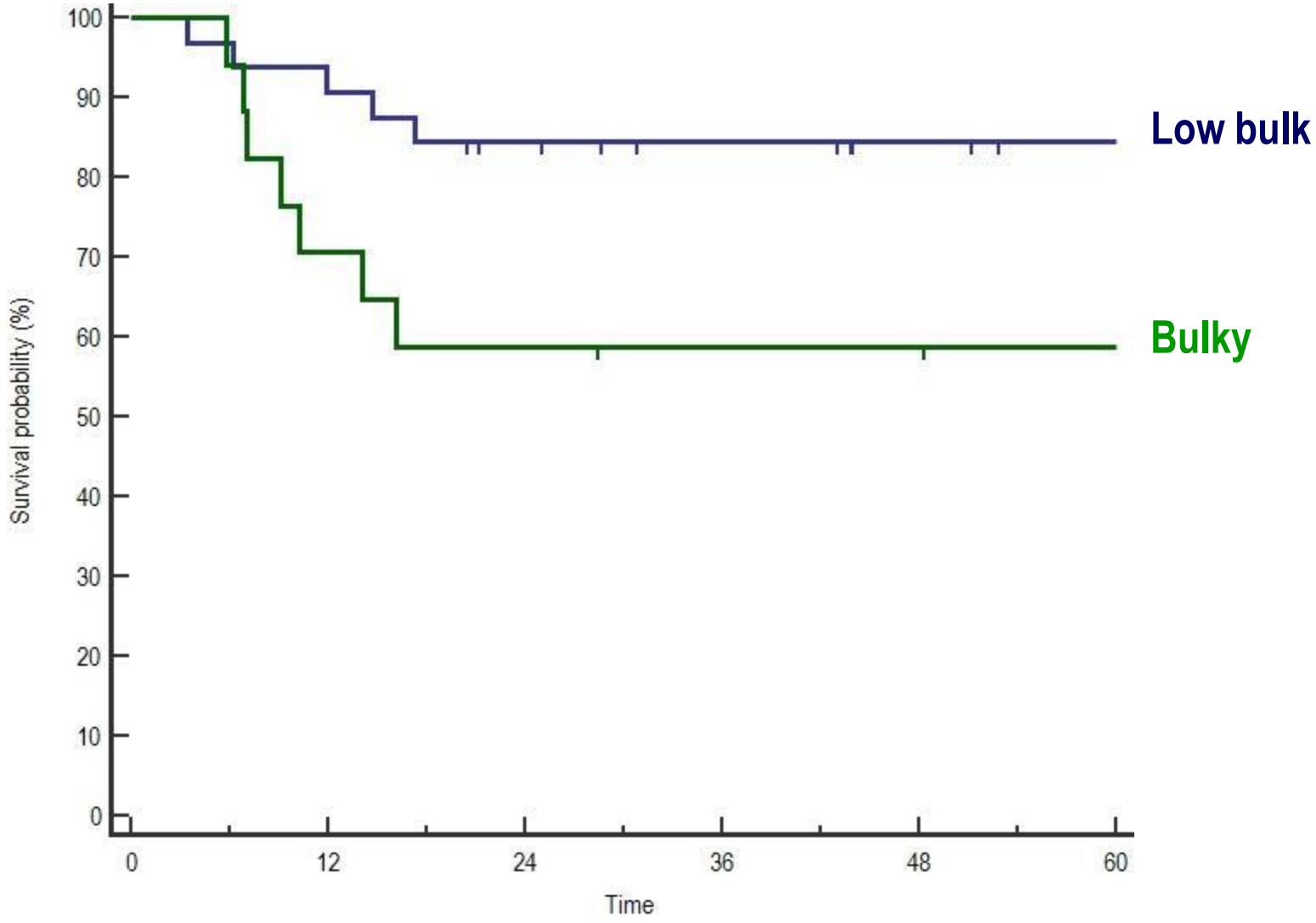
Fokdal L. Radiother Oncol. 2016;120(3):434-440

RetroEMBRACE

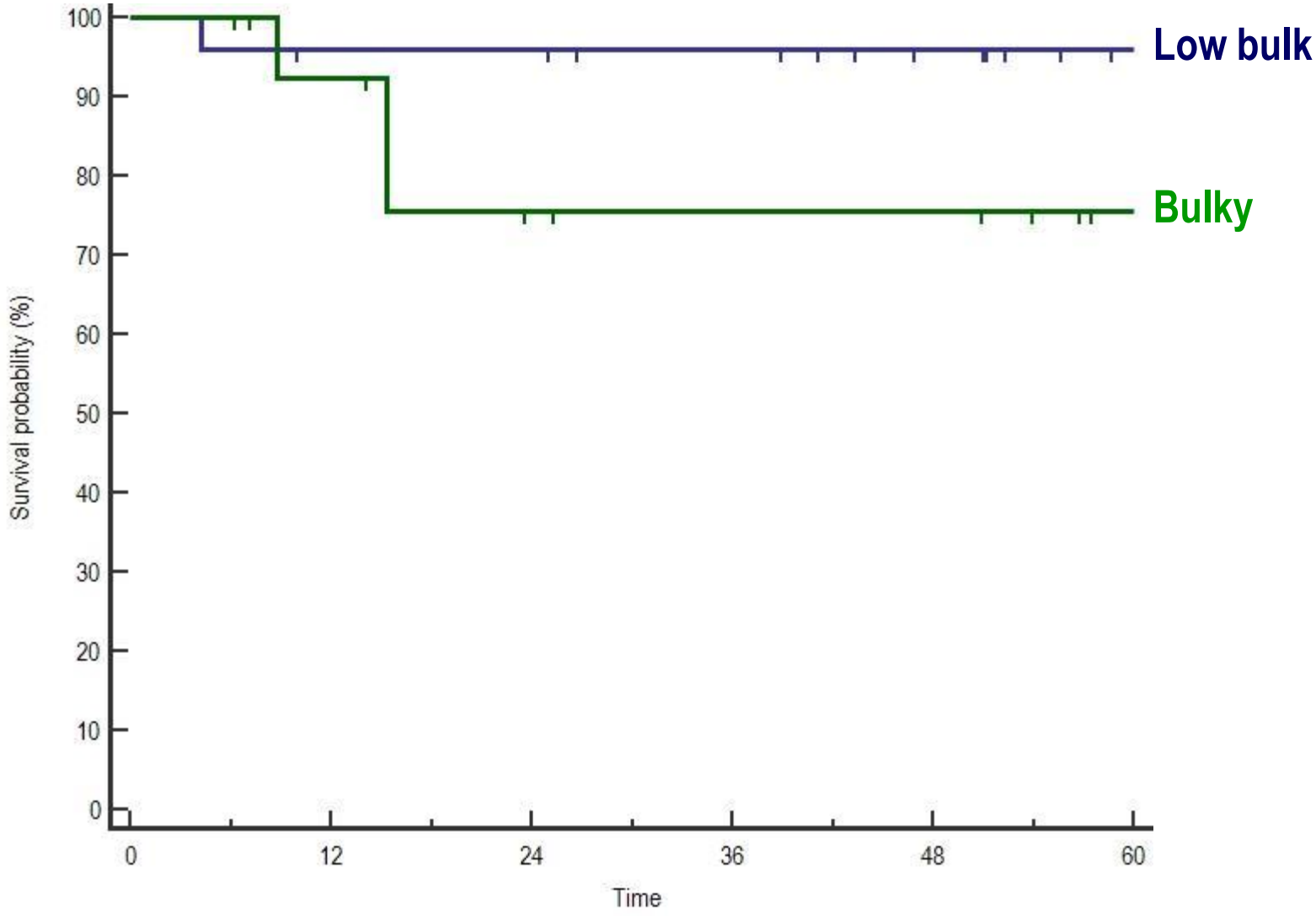


Tanderup K. Radiother Oncol. 2016;120(3):441-446.

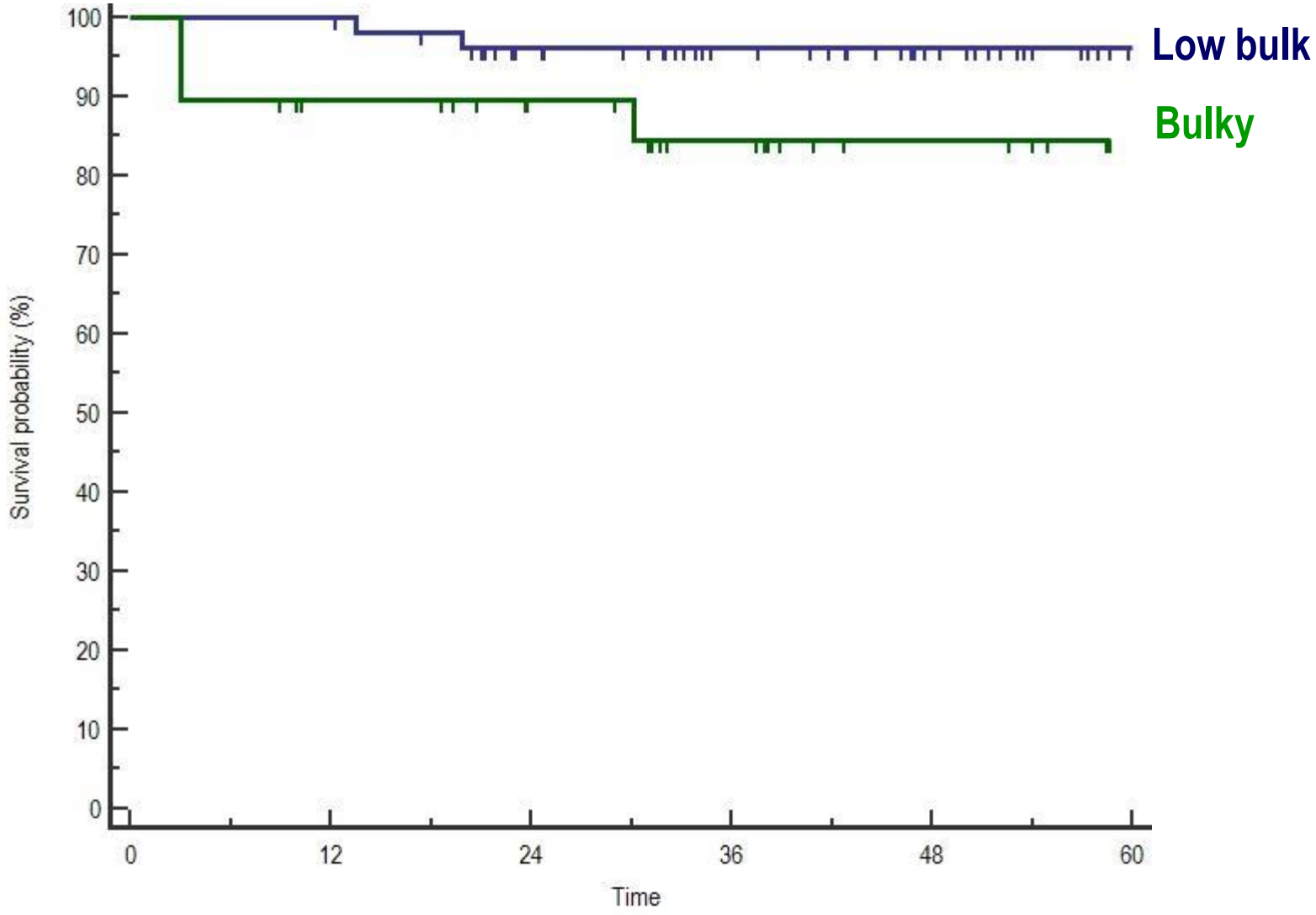
LDR 1999-2004



CT 2005-2008


Low bulk
Bulky
Survival probability (%)
100
90
80
70
60
50
40
30
20
10
0
0
12
24
36
48
60
Time

MRI 2009-2012

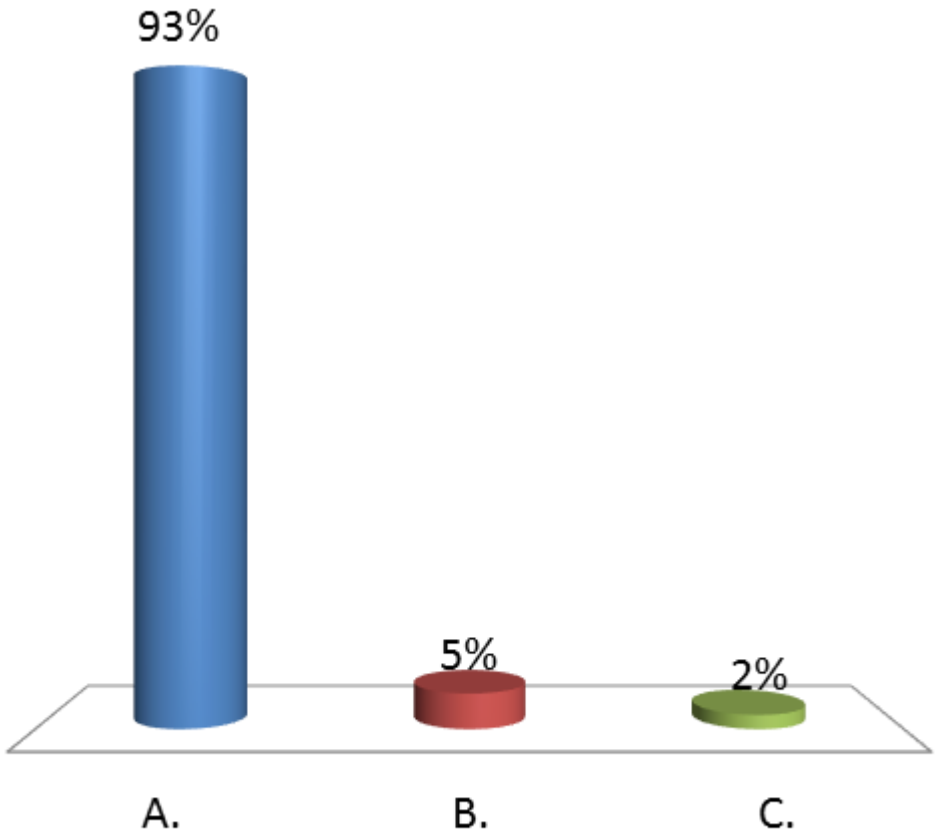


Outline

- Radiotherapy
- Brachytherapy
- **Chemotherapy**
  - **Concomitant**
  - Neoadjuvant
  - ~~Adjuvant~~
- Surgery

Do you routinely give concomitant chemotherapy with radiotherapy for cervix cancer?

A. Yes
B. No
C. Don't treat cervix cancer



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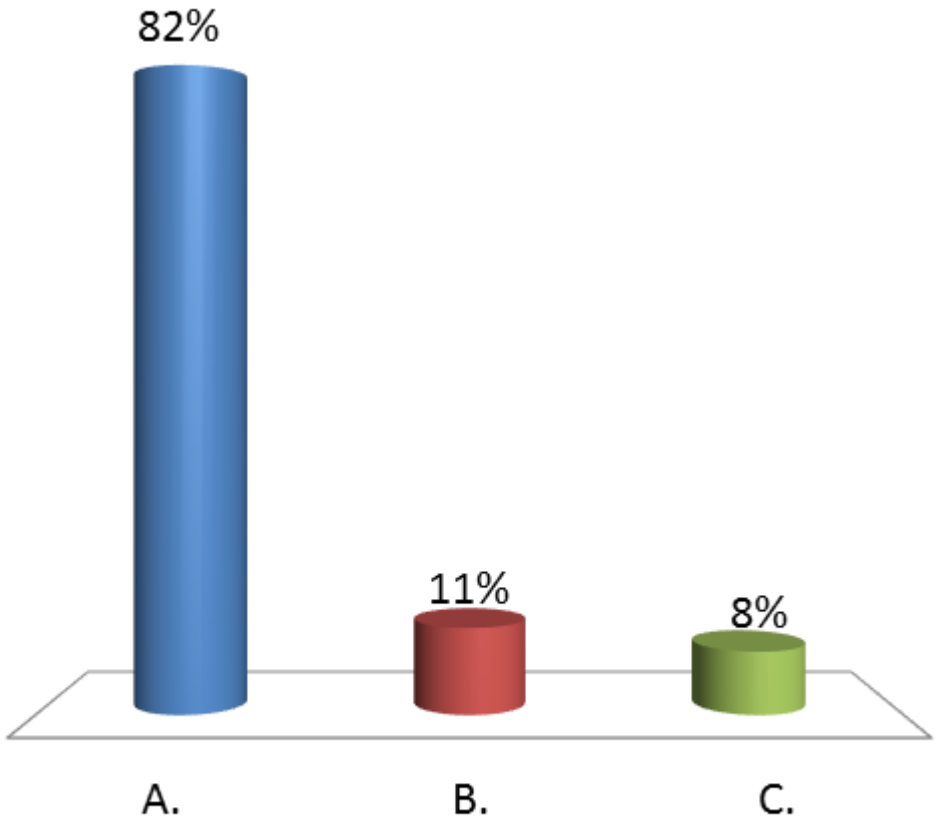
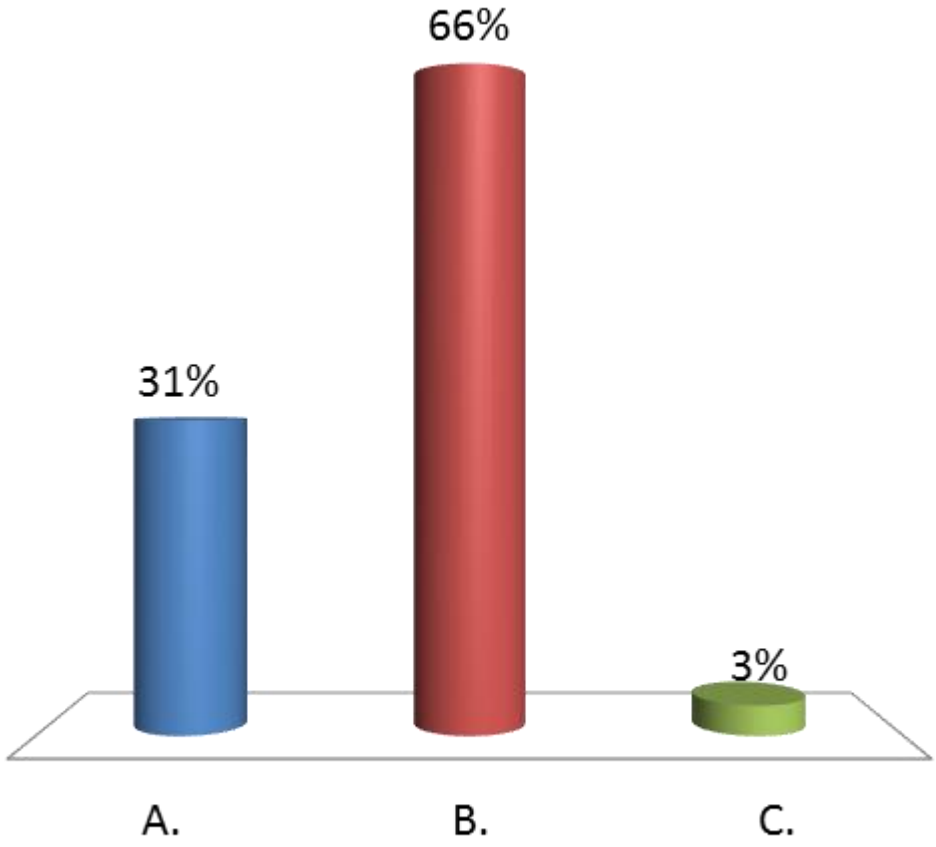
Which concomitant chemotherapy regimen is used at your centre?

A. Weekly cisplatin only
B. Weekly cisplatin and cisplatin-5FU
C. Both platinum and non-platinum regimens



Which FIGO stage would you treat with concomitant chemo-RT?

A. All stages
B. Not Ib1 patients
C. Not IIIb or IVa patients



Evidence

Trial	Publication
GOG 85	Whitney CW, *et al*. J Clin Oncol 1999; 17(5):1339-1348
RTOG 9001	Morris M, *et al*. N Engl J Med 1999; 340(15):1137-1143
GOG 120	Rose PG, *et al*. N Engl J Med 1999; 340(15):1144-1153
SWOG 8797	Peters WA, III, *et al*. J Clin Oncol 2000; 18(8):1606-1613
GOG 123	Keys HM, *et al*. N Engl J Med 1999; 340(15):1154-1161

Benefit

Trial	Patients	Survival gain	*p* value
GOG 85	388	10% at 3 years	0.02
RTOG 9001	403	15% at 5 years	0.004
GOG 120	767	18% at 3 years	0.004
SWOG 8797	268	10% at 4 years	0.007
GOG 123	374	9% at 3 years	0.008

Comparison

Trial	Control	Experimental
GOG 85	RT + HU	CRT
RTOG 9001	EFRT	CRT
GOG 120	RT + HU	CRT ± HU
SWOG 8797	S + RT	S + CRT + CT
GOG 123	RT + S	CRT + S

Chemotherapy

Trial	Regimen
GOG 85	Cisplatin 50 mg/m^2 + 5-FU 4000 mg/m^2
RTOG 9001	Cisplatin 75 mg/m^2 + 5-FU 4000 mg/m^2
GOG 120	Cisplatin 40 mg/m^2 Cisplatin 50 mg/m^2 + 5-FU 4000 mg/m^2 + HU 2 g/m^2
SWOG 8797	Cisplatin 70 mg/m^2 + 5-FU 4000 mg/m^2
GOG 123	Cisplatin 40 mg/m^2

Chemotherapy

Trial	Regimen
GOG 85	Cisplatin 50 mg/m^2 + 5-FU 4000 mg/m^2
RTOG 9001	Cisplatin 75 mg/m^2 + 5-FU 4000 mg/m^2
GOG 120	Cisplatin 40 mg/m^2 Cisplatin 50 mg/m^2 + 5-FU 4000 mg/m^2 + HU 2 g/m^2
SWOG 8797	Cisplatin 70 mg/m^2 + 5-FU 4000 mg/m^2
GOG 123	Cisplatin 40 mg/m^2

Chemotherapy

Trial	Regimen
GOG 85	Cisplatin 50 mg/m^2 + 5-FU 4000 mg/m^2
RTOG 9001	Cisplatin 75 mg/m^2 + 5-FU 4000 mg/m^2
GOG 120	Cisplatin 40 mg/m^2 Cisplatin 50 mg/m^2 + 5-FU 4000 mg/m^2 + HU 2 g/m^2
SWOG 8797	Cisplatin 70 mg/m^2 + 5-FU 4000 mg/m^2
GOG 123	Cisplatin 40 mg/m^2
Pearcey 2002	Pelvic RT ± Cisplatin 40 mg/m^2, 259 pat, ns for OS/LC

Meta-analyses

- **2001 (2005)**

  Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis.

  *Lancet 2001;**358**:781–6*

- **2002**

  Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer--a meta-analysis.

  *Clin Oncol (R Coll Radiol). 2002;**14**:203-12*

- **2008**

  Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomised trials.

  J Clin Oncol. 2008;26:5802-12

Conclusion 1

- Addition of chemotherapy to radiotherapy significantly improves 5-year survival

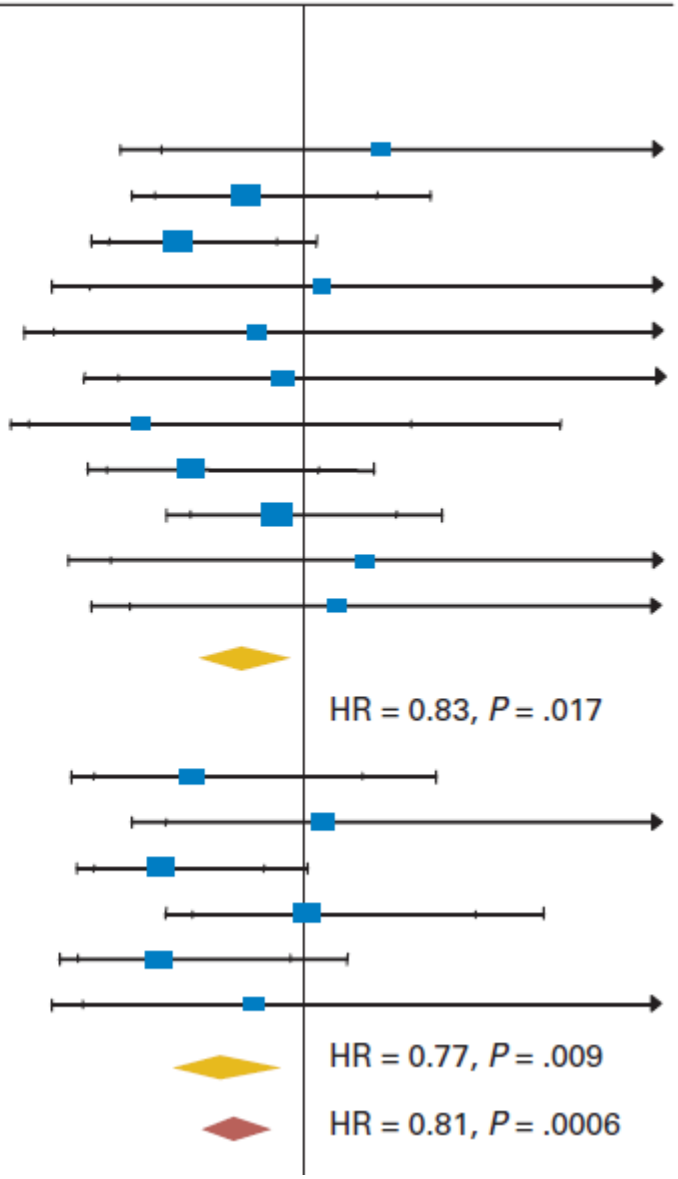
5-year survival

Metaanalysis	Trials	Patients	Increase	HR	*p* value
2001 (2005)	24	4921	10% (7 to 13%)	0.69 (0.61 to 0.77)	<0.00001
2002	8	1065		0.74 (0.64 to 0.86)	0.00006
2008	13	3104	6%	0.81 (0.71 to 0.91)	0.0006

Conclusion 2

- Significant survival benefit for both
  - Platinum-based
  - Non-platinum based

Trial ID	CTRT events	CTRT pts.	Control events	Control pts.	O-E	Variance
Trials of Chemoradiation *v* radiotherapy						
(a) Platinum-based CTRT						
Onishi[44] (CDDP or CDBCA)	16	26	15	23	1.52	7.59
Pearcey[43] (CDDP)	53	130	60	129	-5.00	28.20
GOG0123[6] (CDDP)	49	185	69	189	-12.90	29.38
Chen[23] (a) (CDDP FU VCR)	8	30	8	30	0.21	4.00
Chen[23] (b) (CDDP FU VCR)	6	30	7	30	-0.45	3.25
Pras (CDBCA FU)	17	28	16	26	-0.47	8.15
GOG0165[26] (a) (CDDP)	8	26	12	24	-3.03	4.92
Cikaric[47] (CDDP)	37	100	48	100	-8.02	21.12
Leborgne (CDDP FU)	75	170	85	170	-3.07	39.91
Gariapagaoglu[48] (CDDP)	9	22	8	22	0.70	4.23
Lal[50] (CDDP)	14	94	12	86	0.62	6.49
Sub-total	292	841	340	829	-29.89	157.23
(b) Non–platinum-based CTRT						
Thomas[24] (a) (FU)	24	57	32	58	-5.16	13.83
Thomas[24] (b) (FU)	26	58	25	60	0.71	12.74
Lorvidhaya[25] (a) (MMC FU)	40	233	59	242	-12.52	24.57
Lorvidhaya[25] (b) (MMC FU)	54	230	49	221	0.31	25.67
Roberts[49] (MMC)	25	124	39	124	-8.39	15.92
GOG0165[26] (b) (FU)	11	27	12	24	-0.82	5.55
Sub-total	180	729	216	729	-25.87	98.28
Total	472	1,570	544	1,534	-54.56	251.54



J Clin Oncol. 2008;26:5802-12

Conclusion 3

- No difference in the size of benefit by
  - Radiotherapy dose
  - Chemotherapy dose
  - Chemotherapy regimen

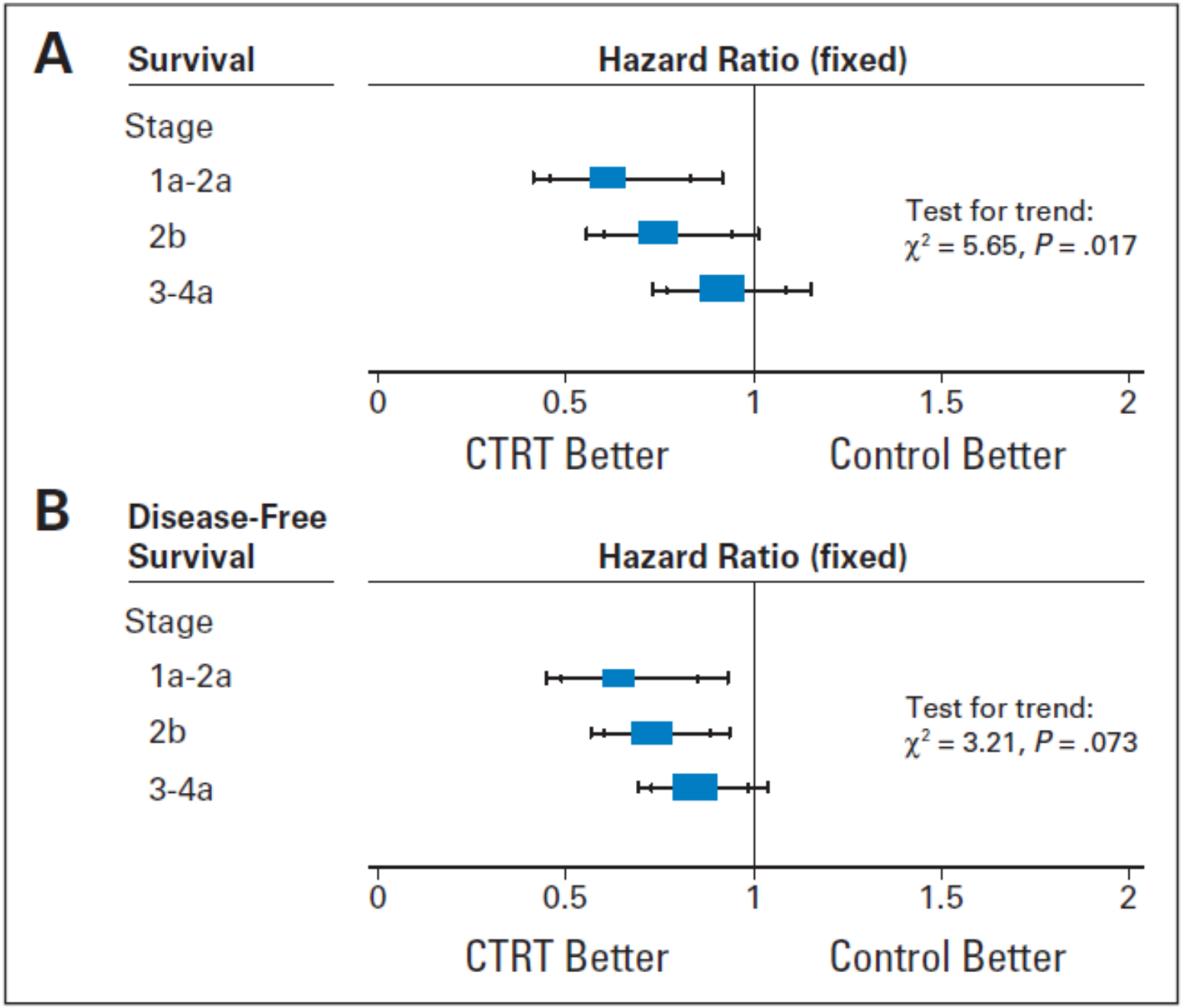
Variable	Main Analysis (13 trials)		
	HR	95% CI	Interaction *P*
Planned radiotherapy dose			
≥ 45 Gy + BRT	0.78	0.68 to 0.89	
< 45 Gy + BRT	0.93	0.70 to 1.24	.26
Planned radiotherapy duration, weeks			
≤ 8	0.83	0.72 to 0.96	
> 8	0.73	0.57 to 0.93	.35
Planned chemotherapy cycle length, weeks*			
≤ 1	0.74	0.60 to 0.92	
> 1	0.95	0.72 to 1.25	.16
Planned cisplatin dose-intensity, mg/m^2/wk*			
≤ 25	0.93	0.70 to 1.24	
> 25	0.76	0.62 to 0.96	.25
Cisplatin regimen*			
Single agent	0.76	0.62 to 0.93	
Combination	0.93	0.70 to 1.24	.25
Chemotherapy regimen			
Single agent	0.75	0.63 to 0.88	
Combination	0.86	0.71 to 1.04	.29

J Clin Oncol. 2008;26:5802-12

Conclusion 4

- Suggestion of difference in size of benefit with tumour stage

J Clin Oncol. 2008;26:5802-12

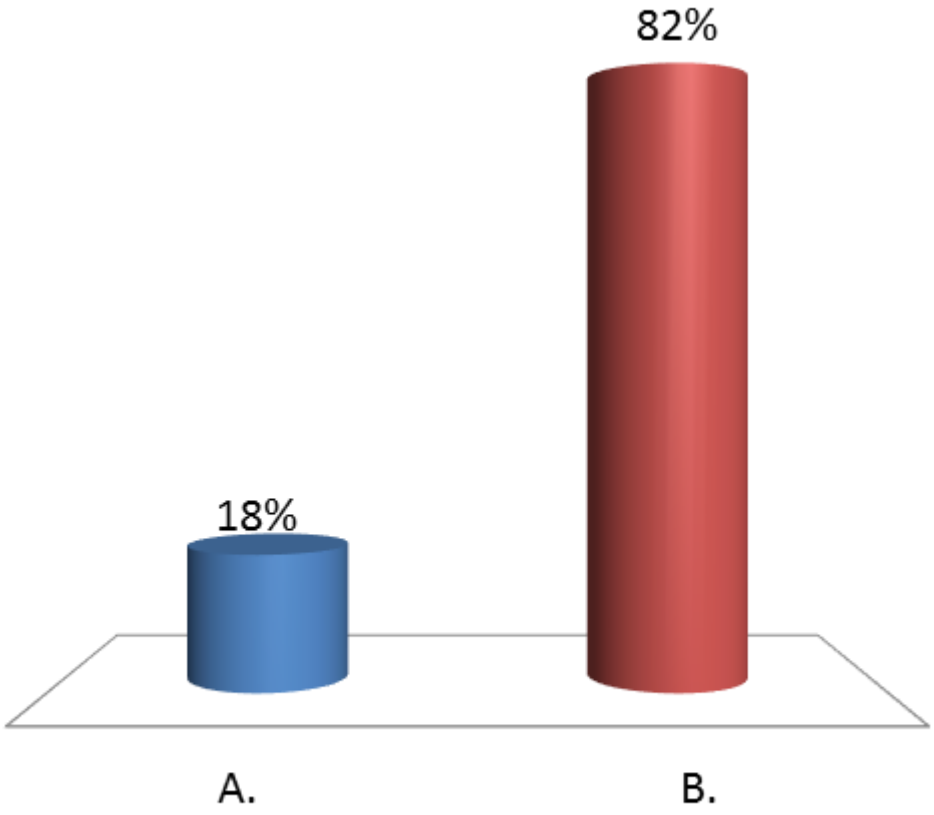


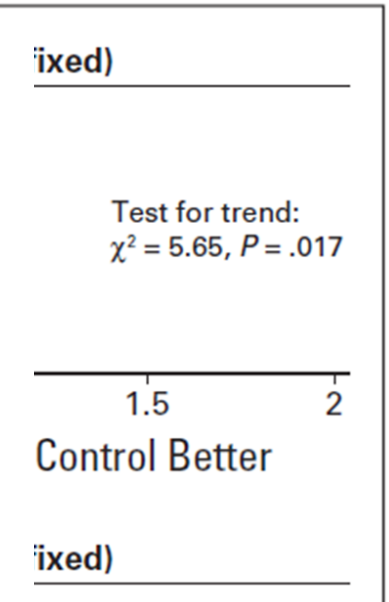
J Clin Oncol. 2008;26:5802-12

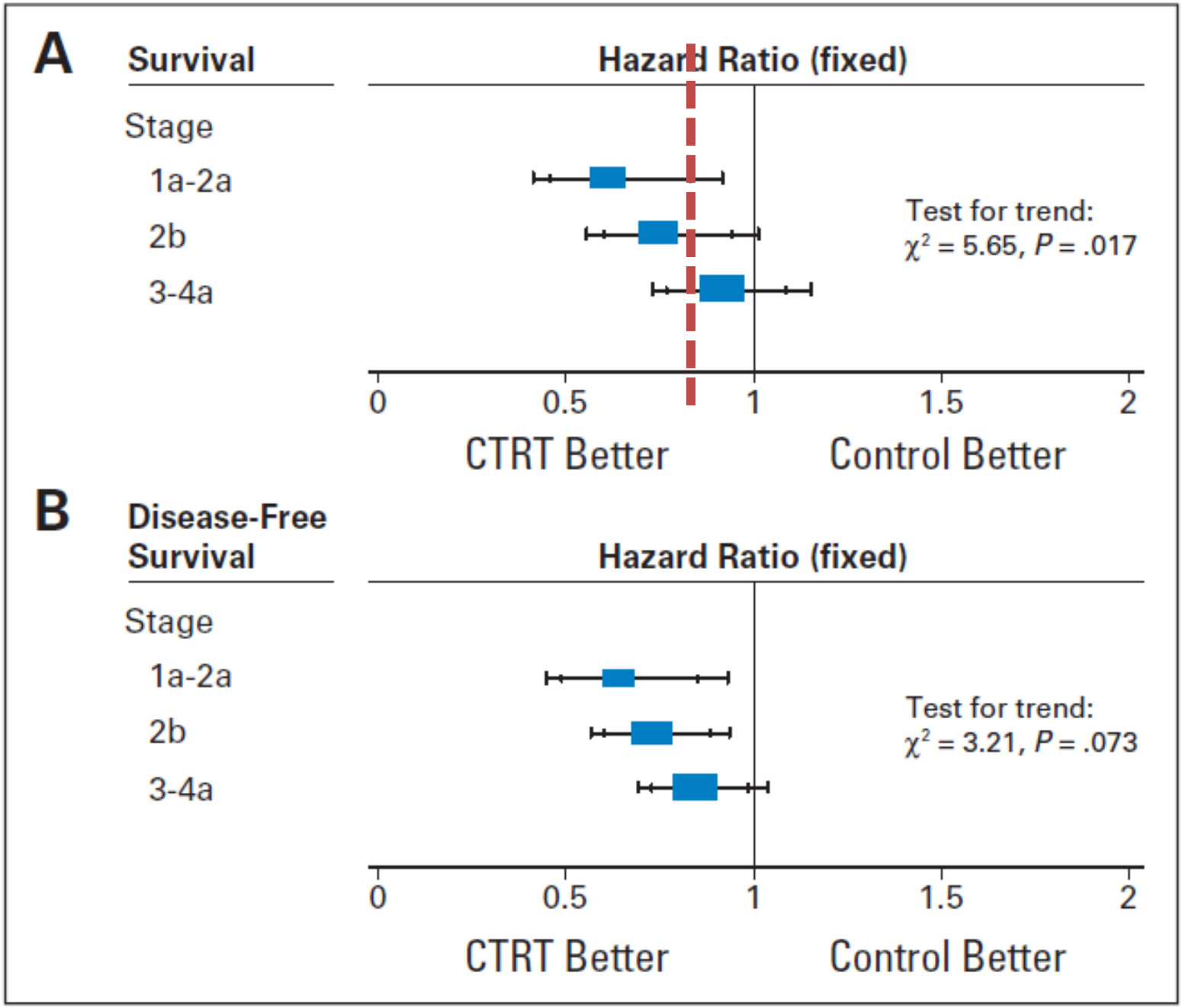
Would you stop offering concomitant chemo Stage III and IVa patients?

A. Yes

B. No

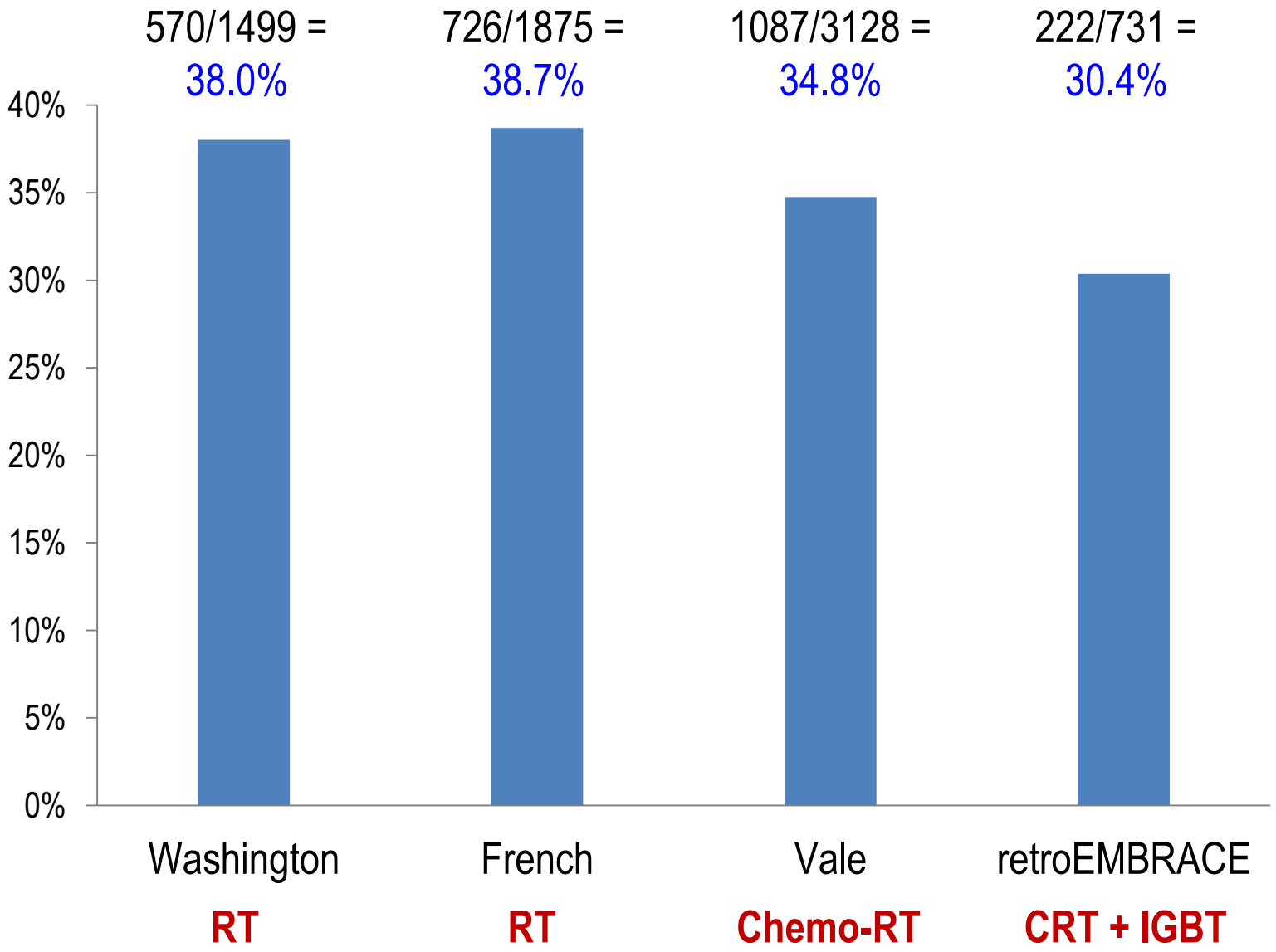




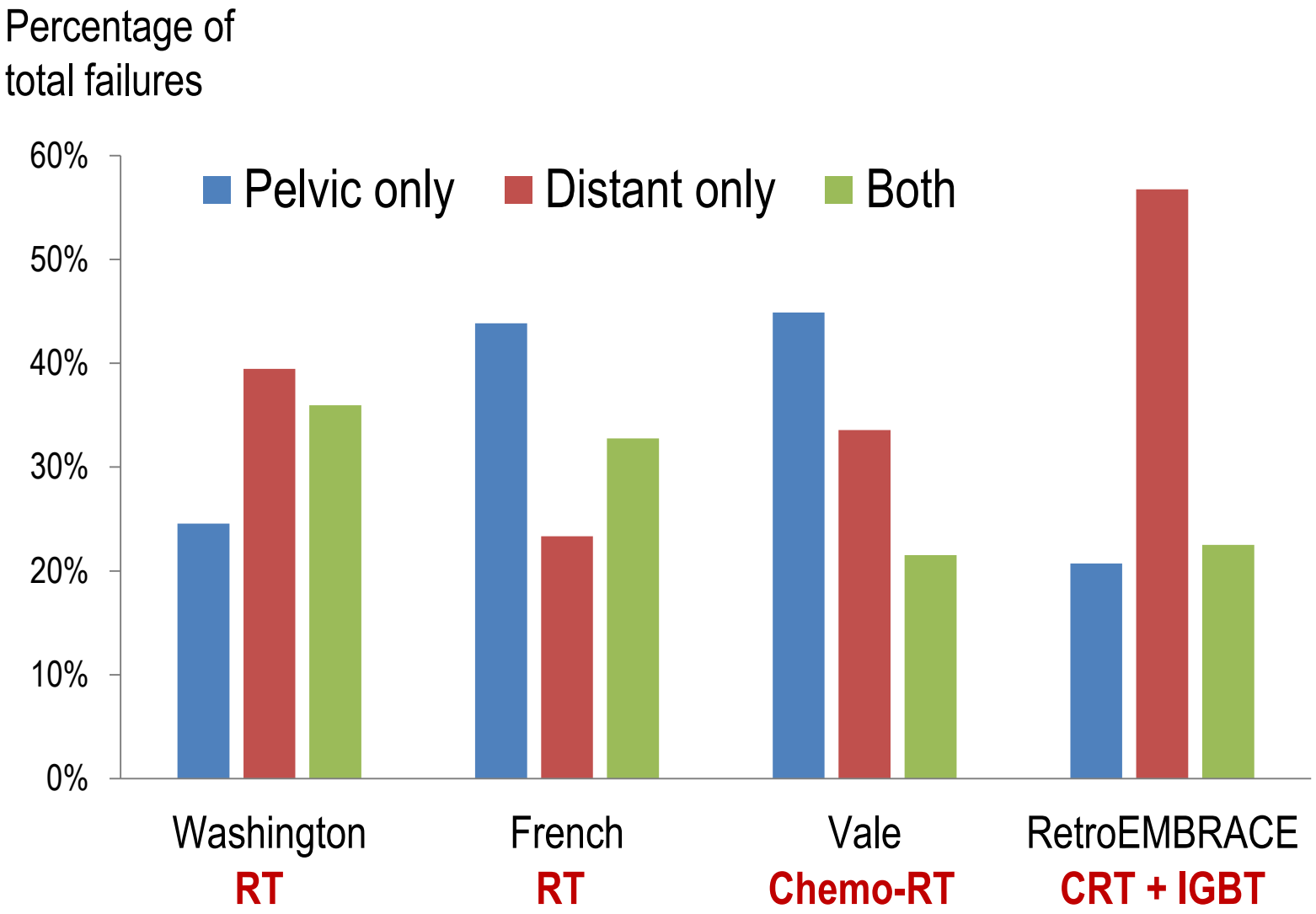


J Clin Oncol. 2008;26:5802-12

Total failures



Patterns of spread

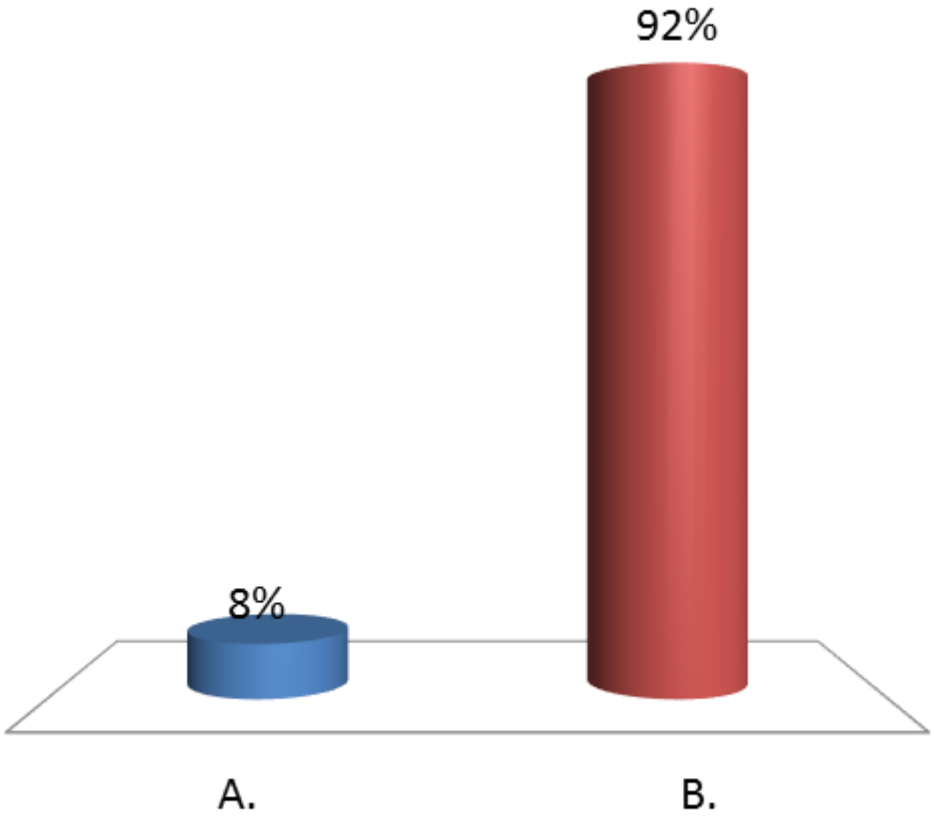


Outline

- Radiotherapy
- Brachytherapy
- **Chemotherapy**
  - Concomitant
  - **Neoadjuvant**
- Surgery

Do you routinely give neoadjuvant chemotherapy before radiotherapy for cervix cancer?

A. Yes
B. No



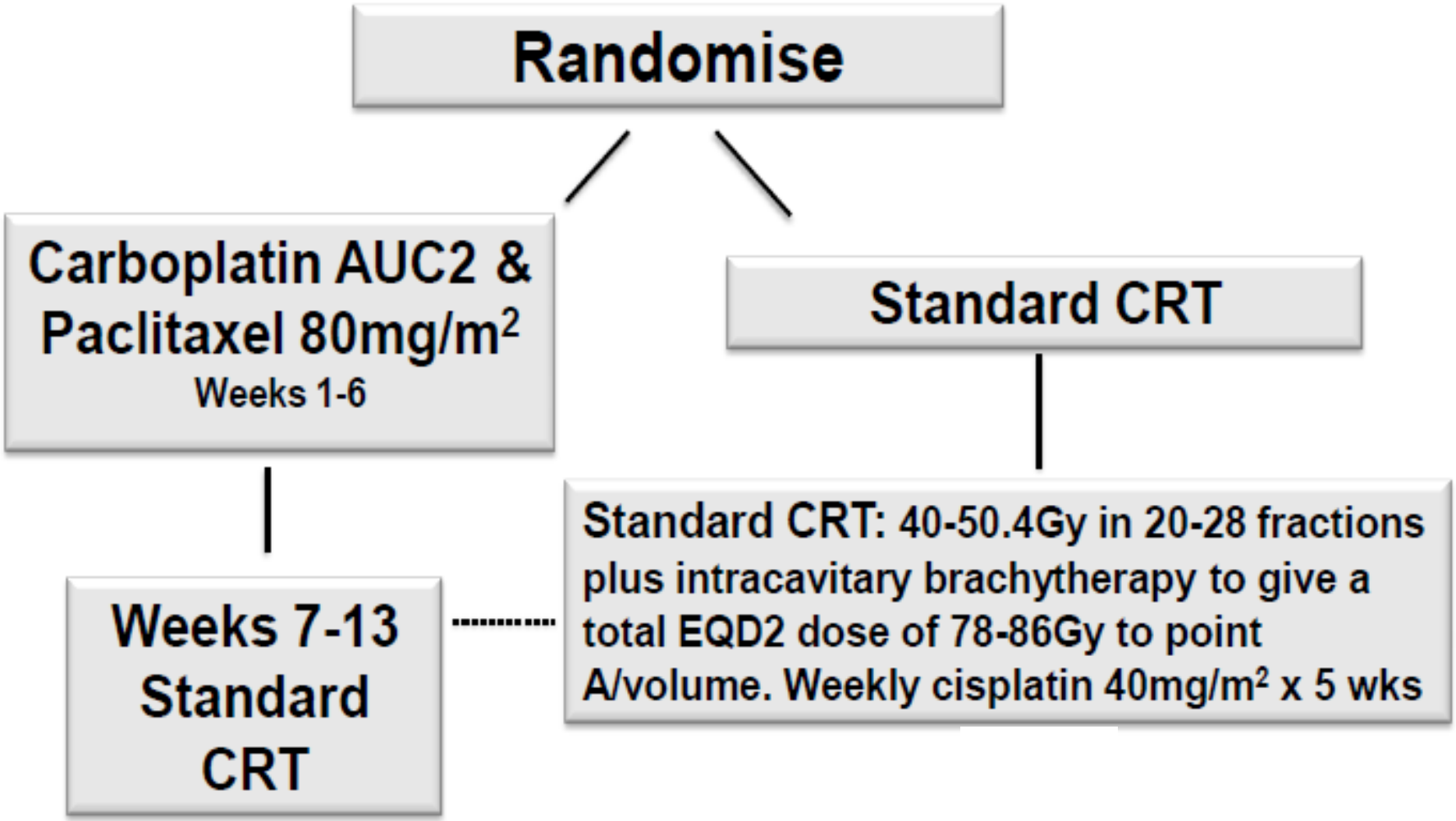
0

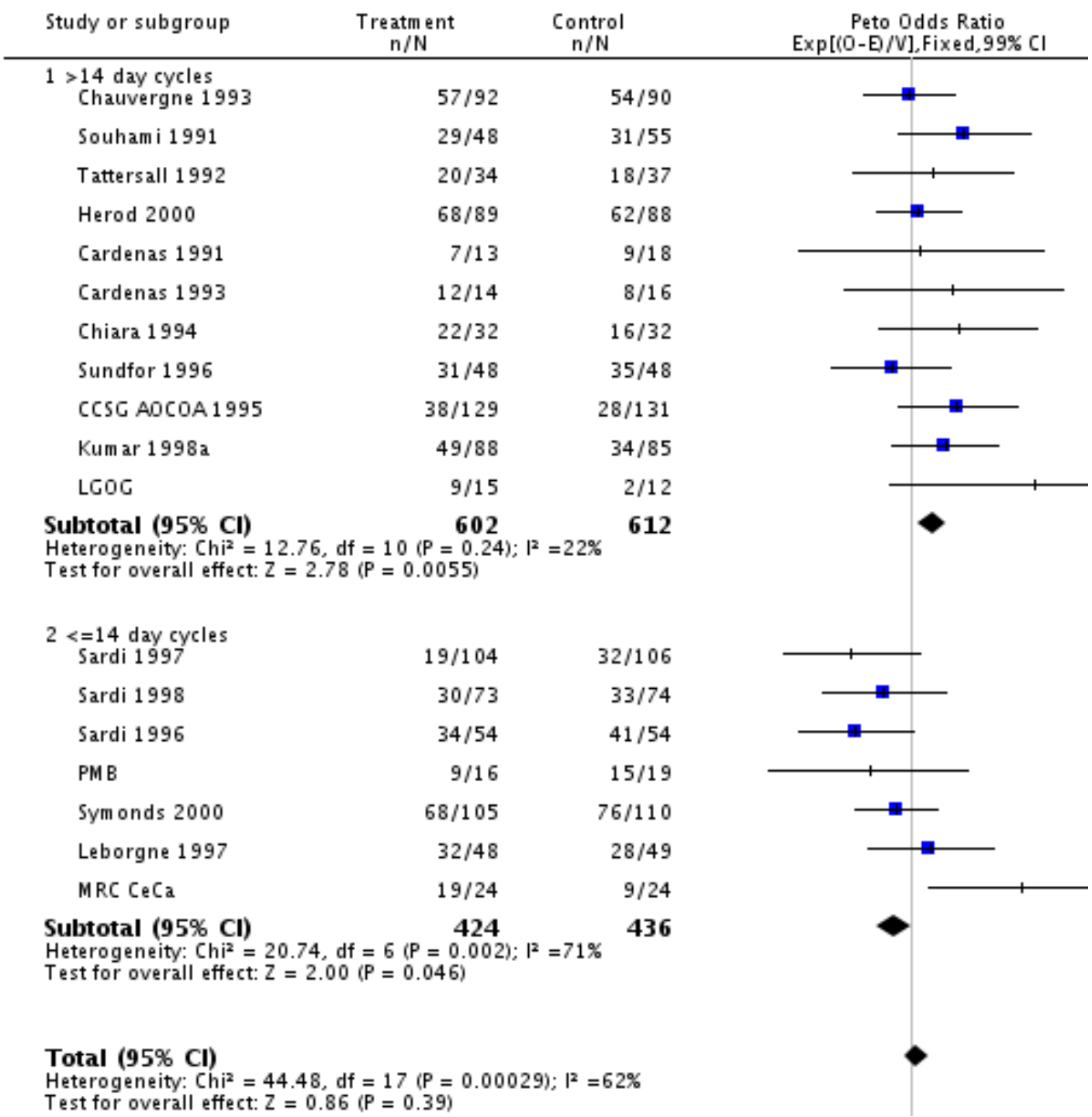
Cochrane review 2004

- 1975-2006
- 18 trials, 2074 patients
- No survival benefit (p = 0.4)

Tierney J. Cochrane Database of Systematic Reviews 2004

UK INTERLACE




Study or subgroup
Treatment n/N
Control n/N
Peto Odds Ratio Exp[(O-E)/V],Fixed,99% CI
1 >14 day cycles
Chauvergne 1993 57/92 54/90
Souhami 1991 29/48 31/55
Tattersall 1992 20/34 18/37
Herod 2000 68/89 62/88
Cardenas 1991 7/13 9/18
Cardenas 1993 12/14 8/16
Chiara 1994 22/32 16/32
Sundfor 1996 31/48 35/48
CCSG ADCOA 1995 38/129 28/131
Kumar 1998a 49/88 34/85
LGOG 9/15 2/12
Subtotal (95% CI) 602 612
Heterogeneity: Chi² = 12.76, df = 10 (P = 0.24); I² =22%
Test for overall effect: Z = 2.78 (P = 0.0055)
2 <=14 day cycles
Sardi 1997 19/104 32/106
Sardi 1998 30/73 33/74
Sardi 1996 34/54 41/54
PMB 9/16 15/19
Symonds 2000 68/105 76/110
Leborgne 1997 32/48 28/49
MRC CeCa 19/24 9/24
Subtotal (95% CI) 424 436
Heterogeneity: Chi² = 20.74, df = 6 (P = 0.002); I² =71%
Test for overall effect: Z = 2.00 (P = 0.046)
Total (95% CI)
Heterogeneity: Chi² = 44.48, df = 17 (P = 0.00029); I² =62%
Test for overall effect: Z = 0.86 (P = 0.39)

Outline

- Radiotherapy
- Brachytherapy
- Chemotherapy
- **Surgery**
  - **Primary surgery + adjuvant RT**
  - RT + adjuvant surgery

GOG 92

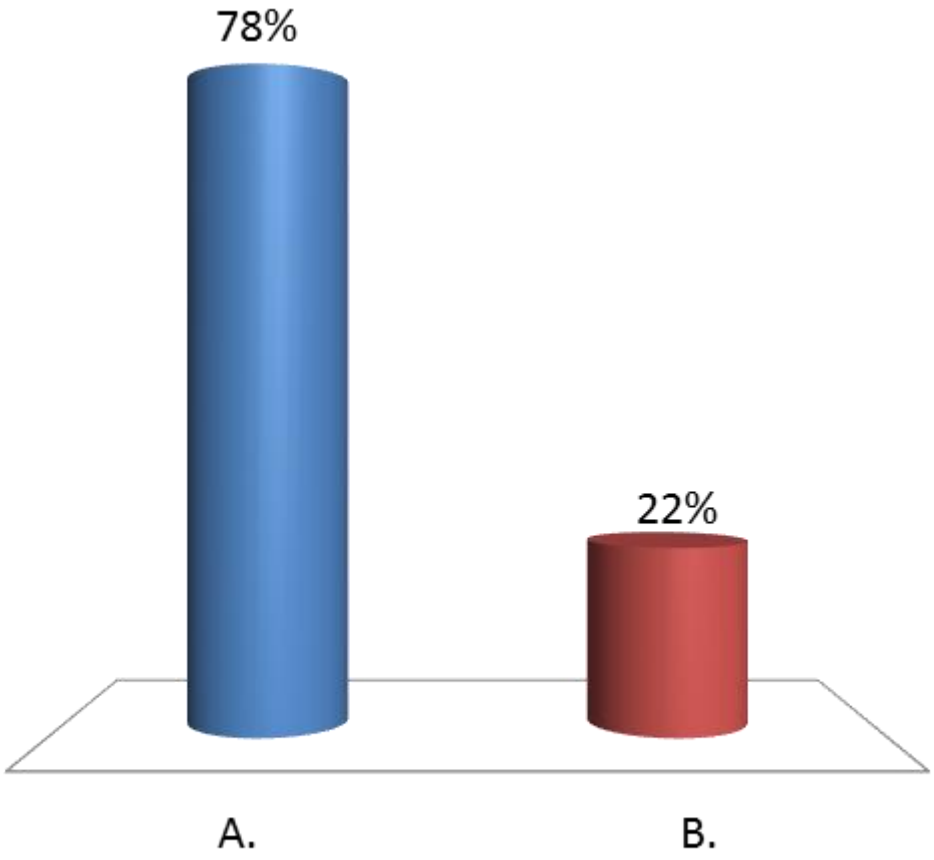
- 277 patients
  - 2 of 3 risk factors:
    - >1/3 stromal invasion
    - LVSI
    - tumour diameter > 4 cm
  - RT vs no RT
- Results
  - Recurrences in 14% (RT) vs 21% (no RT) (p = 0.007)
  - No difference in OS

Sedlis, A, et al. Gynecol Oncol. 1999 May;73(2):177-83

Rotman M, et al. Int J Radiat Oncol Biol Phys. 2006 May 1;65(1):169-76

Do you offer post-op RT for cervix cancer according to GOG 92 criteria?

A. Yes
B. No



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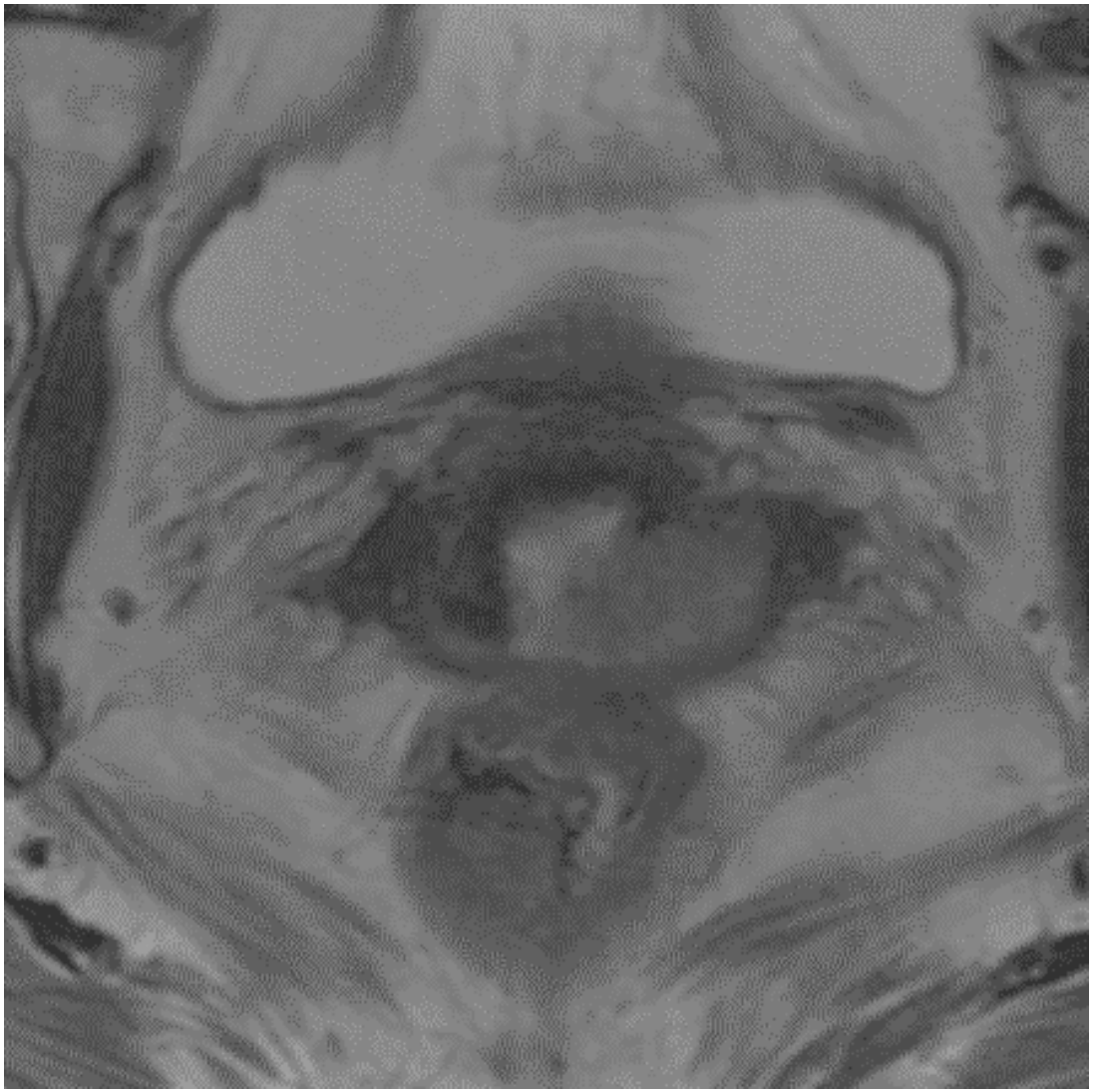


Outline

- Radiotherapy
- Brachytherapy
- Chemotherapy
- **Surgery**
  - Primary surgery + adjuvant RT
  - **RT + adjuvant surgery**

GOG 71 / RTOG 84-12

- 256 patients
  - Tumours ≥ 4 cm
  - RT vs. RT + extrafascial hysterectomy
- Results
  - Fewer relapses in RT + HYST group (at 5 years, 27% vs. 14%) (ns)
  - No difference in survival

Keys HM, et al. Gynecol Oncol. 2003 Jun;89(3):343-53

Summary

Evidence	Radiotherapy	Chemotherapy	Surgery
Level I	Early stage (Prophylactic EFRT)	Concomitant *Neoadjuvant**	Surgery + CRT* *(C)RT + Surgery**
Level II-III	Advanced stage PAN RT (N+) IGBT		
Level IV	Nodal boost		

* Improved LC only

* No benefit

Evidence-based radiotherapy for vulva cancer

Dr Li Tee Tan

Cambridge University Hospitals NHS
NHS Foundation Trust

Epidemiology

- Rare - 3-5% of gynae cancers
- Squamous cell carcinoma in 85-90%
- Elderly patients

Evidence- based RT

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
✓	Recommended best practice based on the clinical experience of the guideline development group

FIGO Staging 2009

IA	≤ 2 cm in size with stromal invasion ≤ 1 mm, negative nodes
IB	> 2 cm in size or with stromal invasion > 1 mm, negative nodes
II	Spread to lower 1/3 urethra, lower 1/3 vagina, anus, negative nodes
III	Positive inguino-femoral lymph nodes
IIIA(i)	1 lymph node metastasis ≥ 5 mm
IIIA(ii)	1-2 lymph node metastasis(es) < 5 mm
IIIB(i)	2 or more lymph nodes metastases ≥ 5 mm
IIIB(ii)	3 or more lymph nodes metastases < 5 mm
IIIC	Positive node(s) with extracapsular spread
IVA(i)	Invades upper 2/3 urethra, upper 2/3, bladder mucosa, rectal mucosa, or fixed to pelvic bone
IVA(ii)	Fixed or ulcerated inguino-femoral lymph nodes
IVB	Any distant metastasis including pelvic lymph nodes

Role of radiotherapy

- Post-operative
- Pre-operative

Post-operative radiotherapy

- Aims
  - Reduce local recurrence
  - Reduce regional recurrence
  - Improve survival
- Questions
  - Does it work?
  - Can it replace groin surgery?
  - Does adding chemotherapy help?

Reduce local recurrence

- 135 patients (observational study)
  - Stage I-II = 110
  - Stage III-IV = 25

Table 14–6. CORRELATION OF SURGICAL MARGIN WITH LOCAL RECURRENCE FOLLOWING SURGICAL THERAPY OF VULVAR CANCER

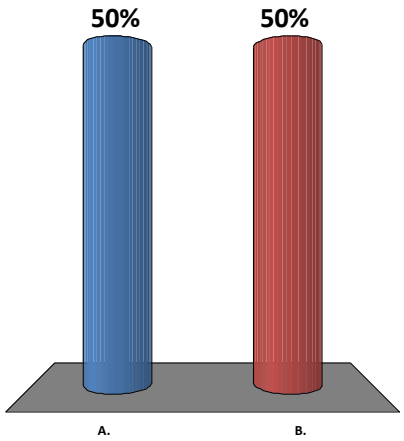
	Surgical Margin < 8 mm (N = 44)	Surgical Margin ≥ 8 mm (N = 91)
Local recurrence	21/44 (48%)	0/91

Heaps JM, et al. Gynecol Oncol. 1990;38(3):309-14

Would you offer post-op RT if margin is <8mm and further excision is not possible?

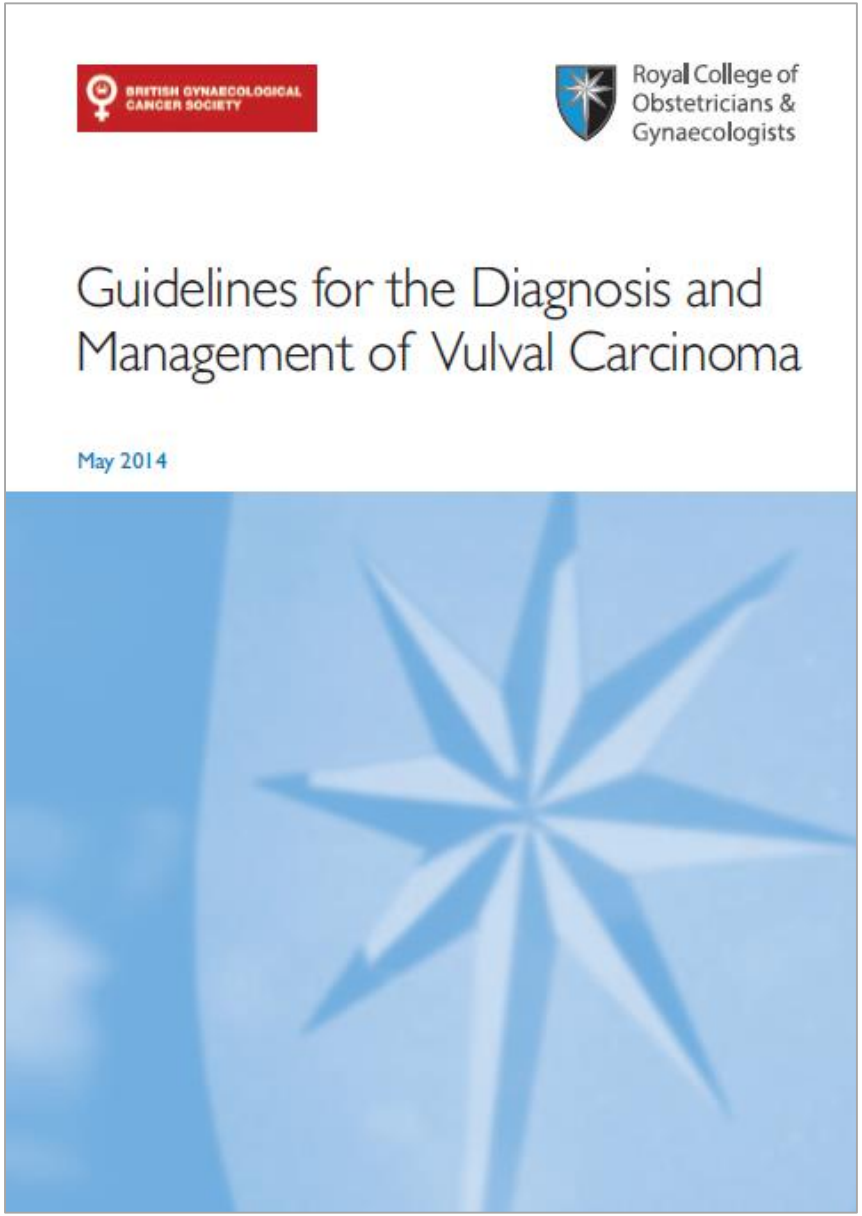
A. Yes

B. No



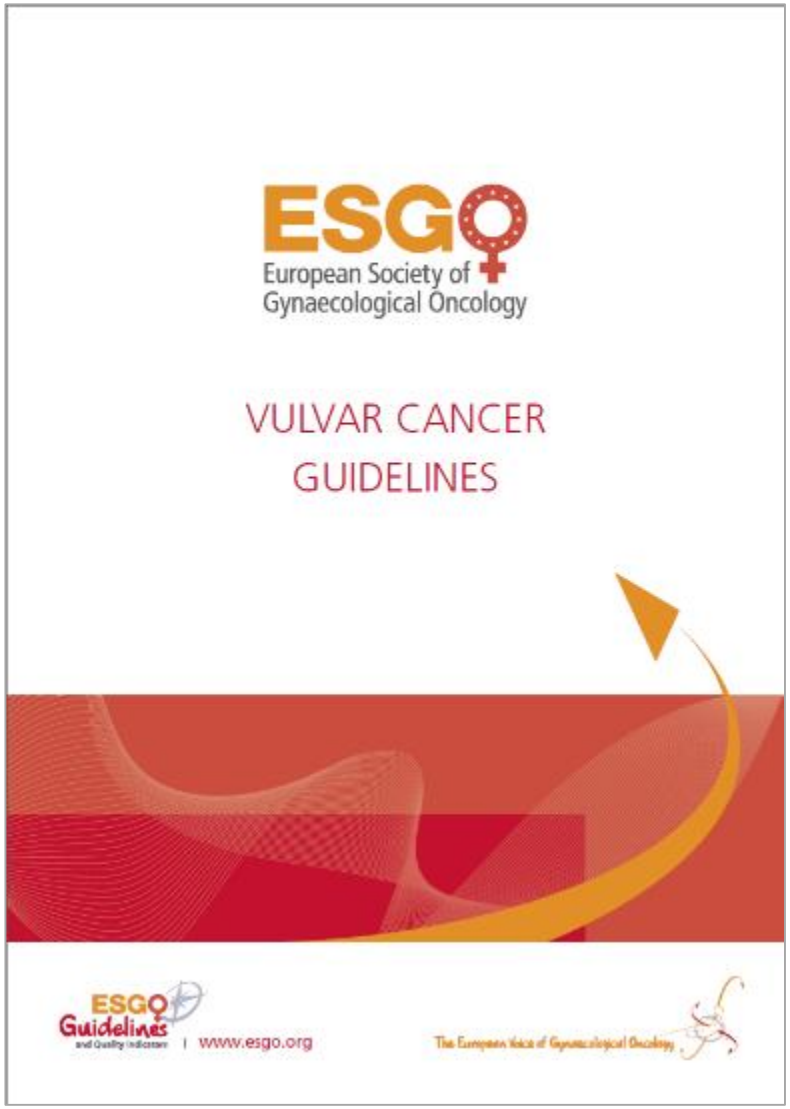
BGCS/RCOG guidelines 2014

"There is not enough evidence to recommend adjuvant local therapy routinely in patients with close surgical margins."



ESGO 2016

- In case of close but clear pathological margins, postoperative vulvar radiotherapy may be considered to reduce the frequency of local recurrences. There is no consensus for the threshold of pathological margin distance below which adjuvant radiotherapy should be advised.



Expert opinion

Reduce regional recurrence
Improve survival

- GOG-37 (RCT)
  - 114 patients
  - Positive inguinal nodes
- Pelvic node dissection vs pelvic RT

	Surgery	Radiotherapy
Regional recurrence	24%	5%
Survival	54%	68%

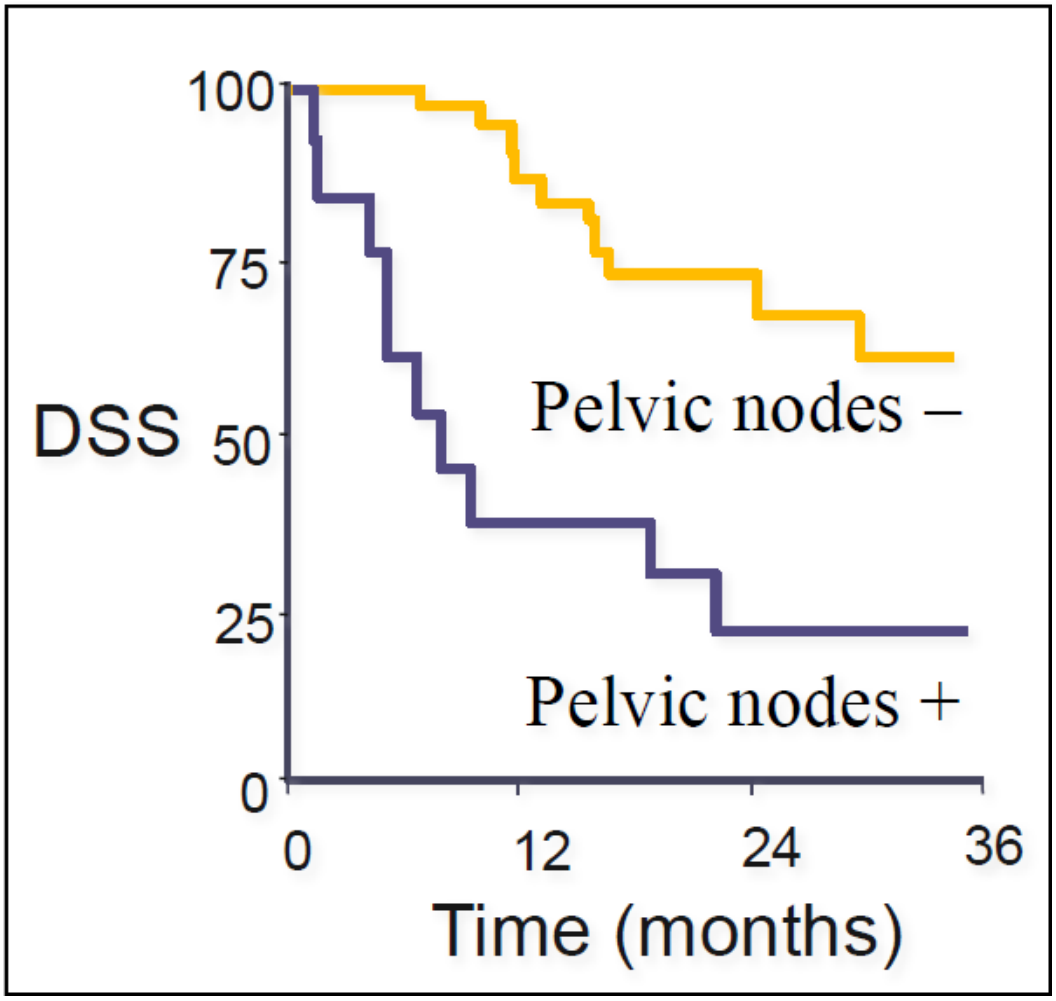
$p = 0.03$

Homesley HD, et al. Obstet Gynecol. 1986;68(6):733-40

Indications for post-operative RT

- 2 or more microscopic nodes
- 1 or more macroscopic node
- Extracapsular disease

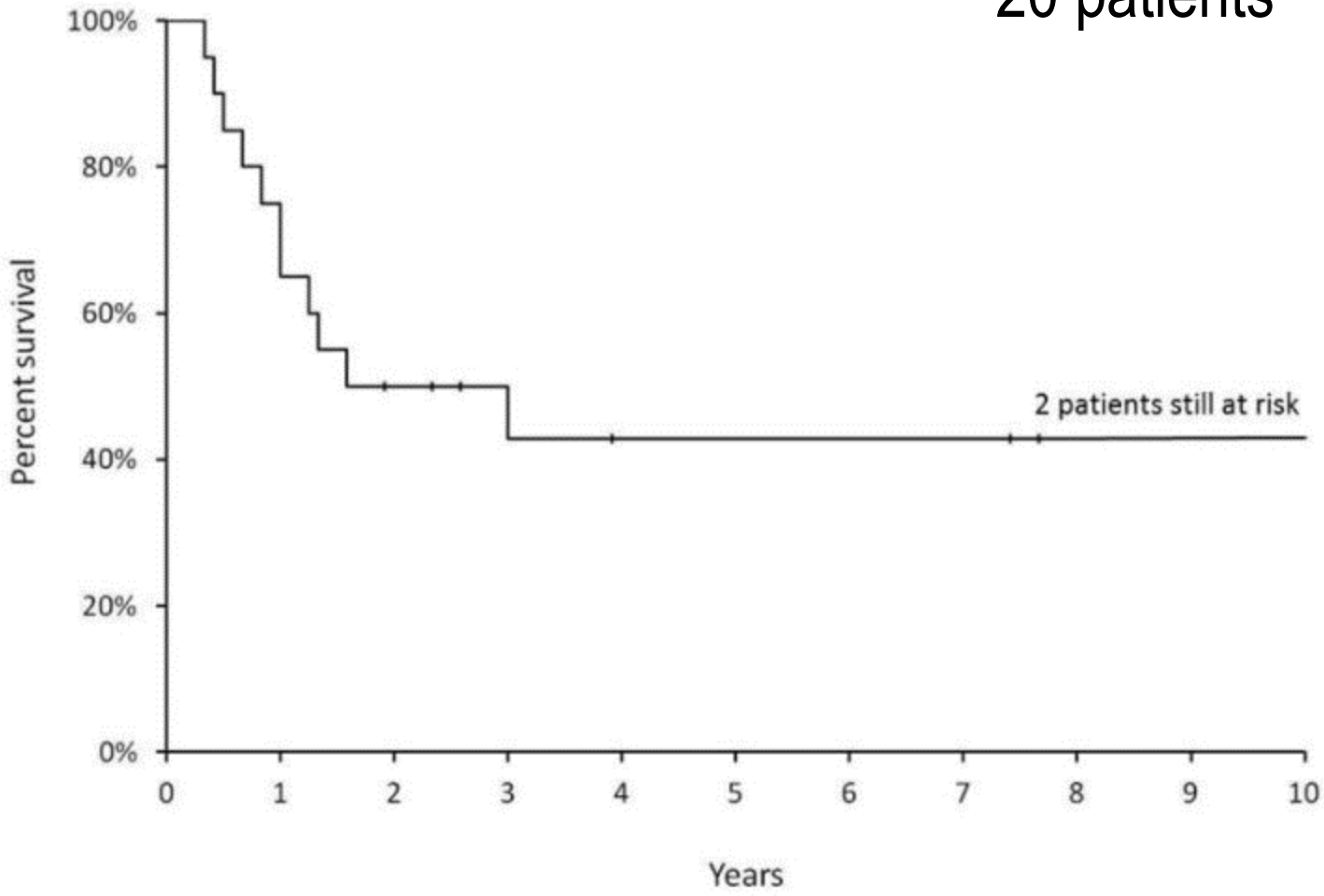
Pelvic nodes = M1



Homesley HD, et al. Obstet Gynecol. 1986;68(6):733-40

Positive pelvic lymph nodes

20 patients



Thaker NG. Gynecol Oncol. 2015;136(2):269-73.

Replace groin surgery

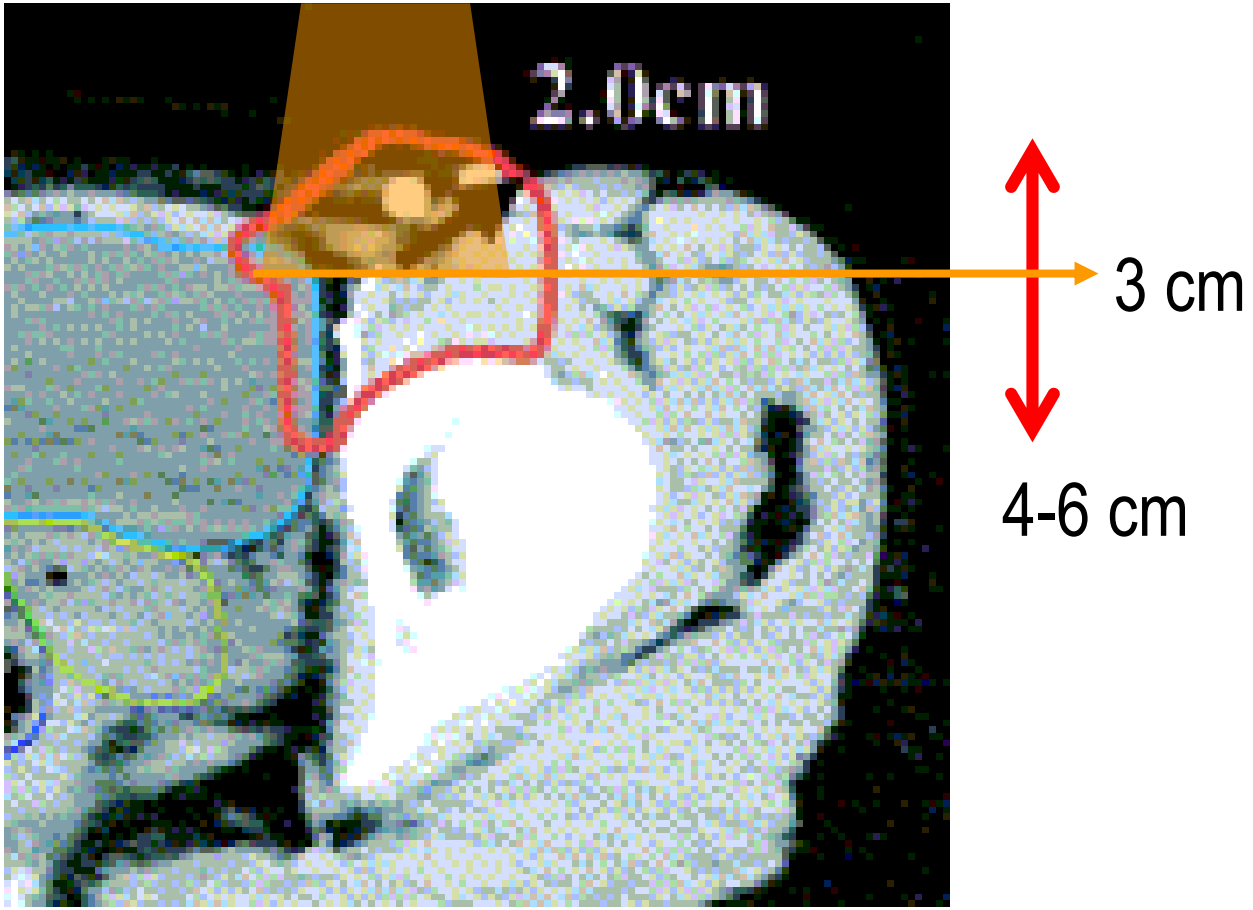
- GOG 88
  - RT vs inguinal node dissection
  - 58 patients
  - T1-3, N0-1, M0

	Surgery	Radiotherapy
Groin relapse	0%	18.5%

Stehman FB, et al. IJROBP 1992. 24:389-396

RT vs nodal dissection

- 50 Gy at 3 cm depth

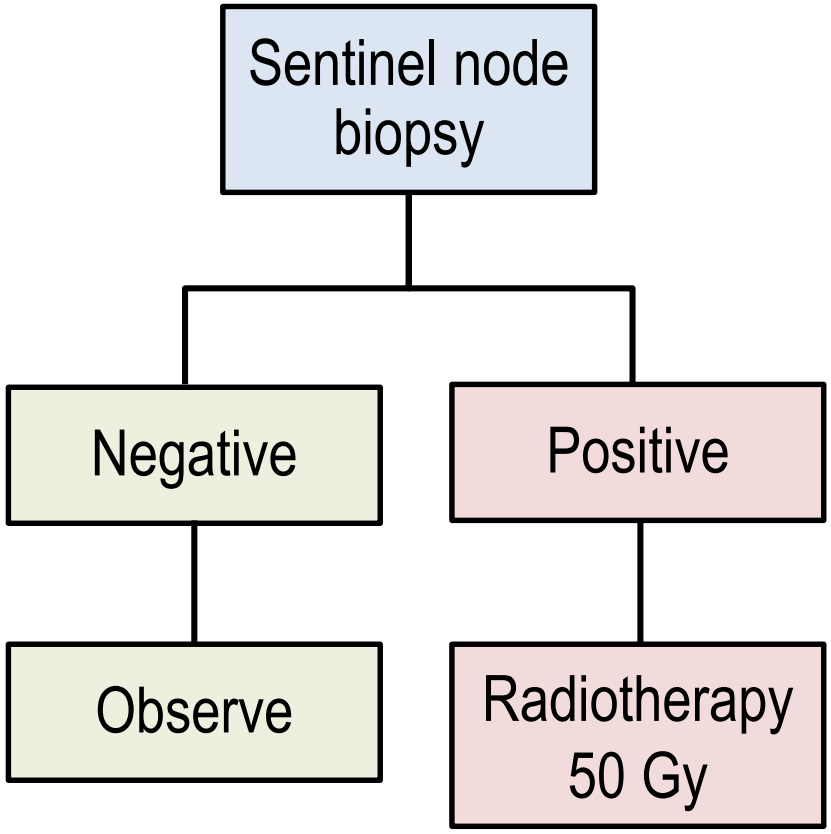


RCOG 2014

- Surgery is the cornerstone of therapy for the groin nodes in women with vulval cancer.
- Individual women who are not fit enough to withstand surgery, even when performed under regional anaesthesia, can be treated with primary radiotherapy.

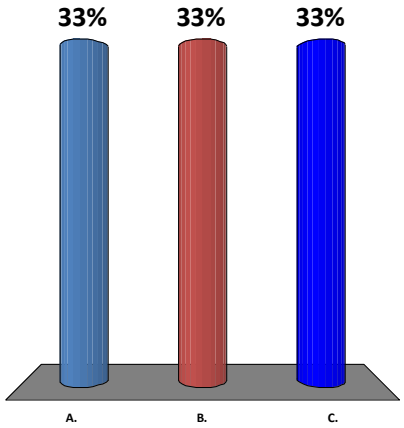
GROINSS-V II

- Observational study
  - T1-T2 < 4 cm
  - No clinical/radiological involved nodes



Do you offer concomitant chemotherapy with adjuvant radiotherapy for vulvar cancer?

A. Usually
B. Sometimes
C. No



GYNECOLOGIC CANCER INTERGROUP

An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

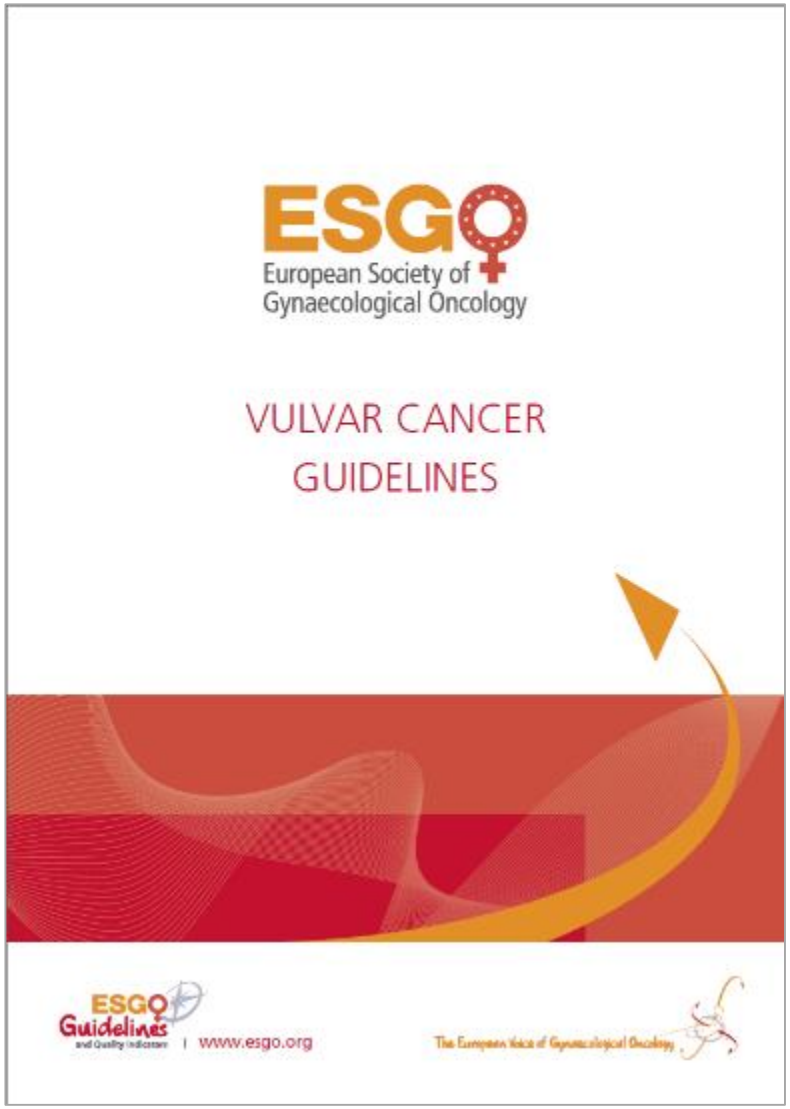
Patterns of Care for Radiotherapy in Vulvar Cancer: A Gynecologic Cancer Intergroup Study

- Use of concomitant chemotherapy
  - No = 50%
  - Yes = 50%
- Regimens
  - Cisplatin 70%
  - Cis + 5FU 20%
  - 5FU + MMC 10%

Gaffney DK, et al. Int J Gynecol Cancer. 2009;19:163-7

ESGO 2016

- Based on evidence from other squamous cell cancers such as cervical, head & neck, and anal cancer, the addition of concomitant, radiosensitising chemotherapy to adjuvant radiotherapy should be considered.



Grade C: Extrapolated evidence from studies rated as 2++

Role of radiotherapy

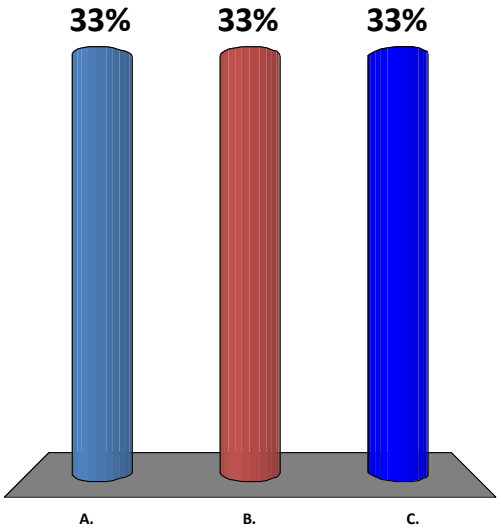
- Post-operative
- **Pre-operative**

Pre-operative

- Aims
  - Downstage disease
  - Avoid mutilating surgery
- Questions
  - Benefit of adding chemotherapy?
  - Avoid all surgery?

Do you offer neoadjuvant chemo-RT for vulvar cancer?

A. Usually
B. Sometimes
C. No



GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Patterns of Care for Radiotherapy in Vulvar Cancer: A Gynecologic Cancer Intergroup Study

- Use of concomitant chemotherapy
  - No = 19%
  - Yes = 81%
- Regimens
  - Cisplatin 55%
  - Cis + 5FU 31%
  - 5FU + MMC 5%
  - Other 9%

Gaffney DK, et al. Int J Gynecol Cancer. 2009;19:163-7

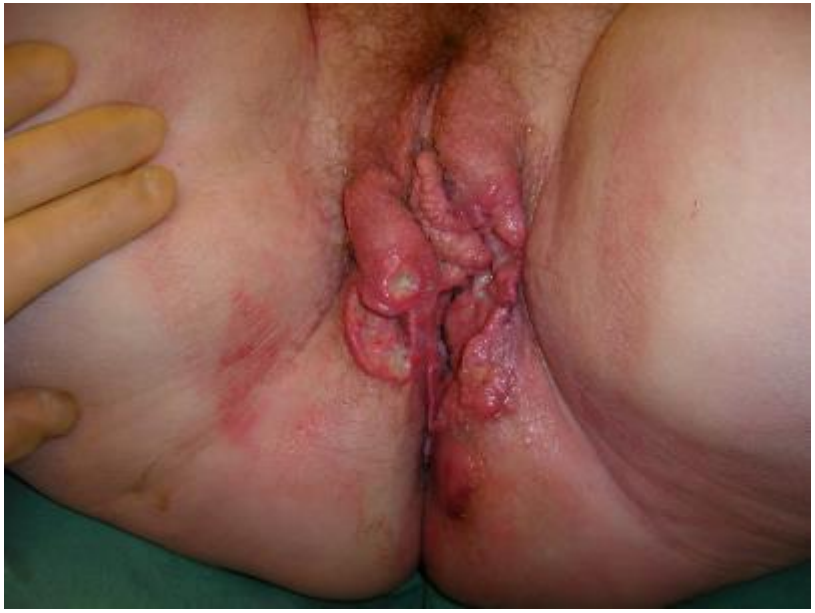
Concomitant chemotherapy

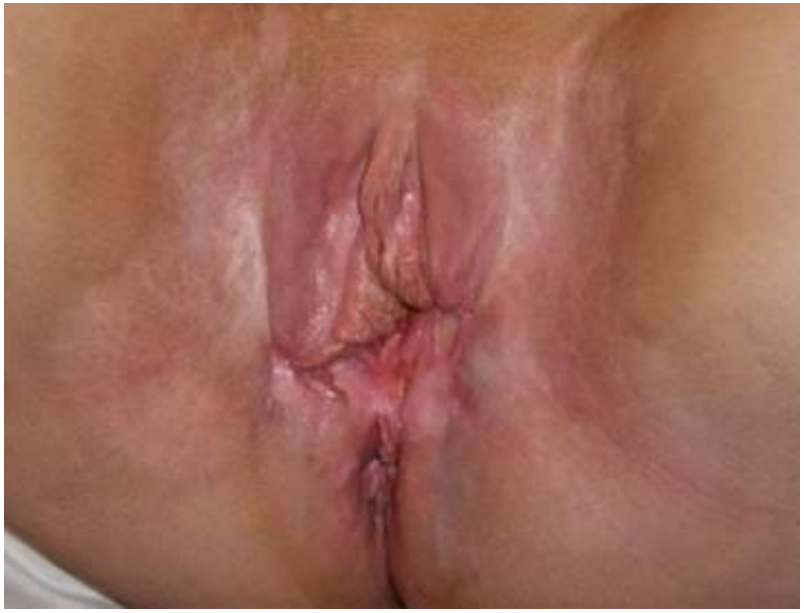
- RCT of neoadjuvant chemoRT vs. surgery
  - 68 patients
  - **Operable cancer**, FIGO Stage II-IV
  - Reported in abstract only (IJGC 2003; Vol. 13 Suppl 1:6)
  - No difference in 5-year survival or morbidity

Maneo A, et al. Cochrane Database of Systematic Reviews 2011

Avoid surgery

- Phase II studies
  - Operability achieved in 63-92% of cases with platinum-based regimens
  - Effective for both primary and nodes



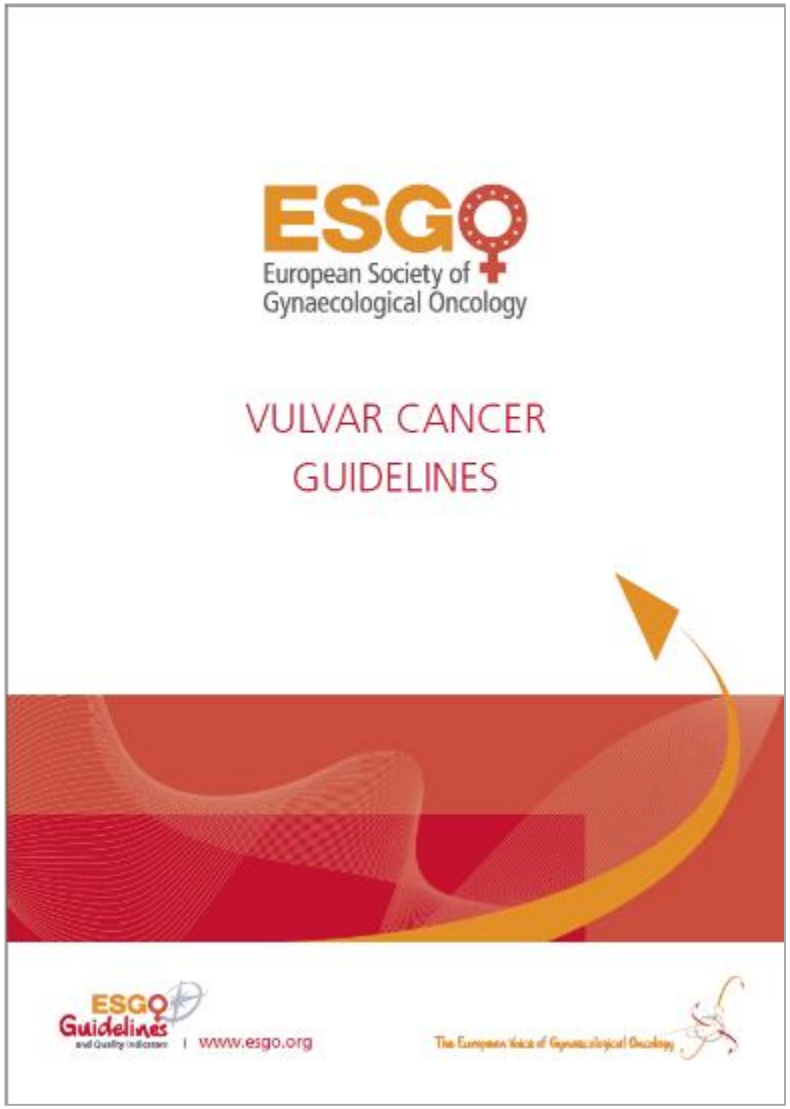


Outcome

- 27-85% of patients died due to treatment-related causes or disease
- Toxicity substantial
  - Severe skin reactions
  - Avascular necrosis
- Different from cervical and anal cancers
  - Less responsive
  - Worse skin reaction c.f. anal Ca - vulva dystrophy?

ESGO 2016

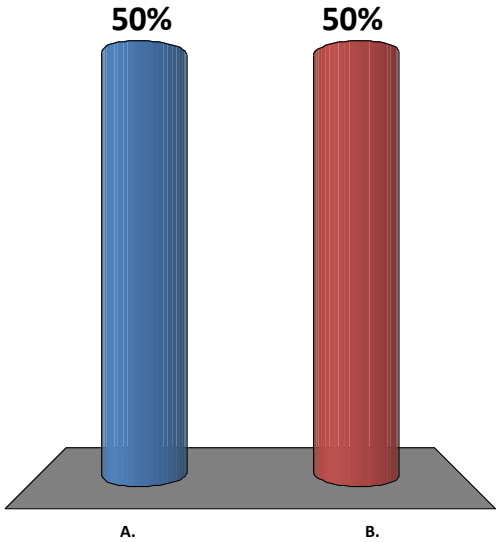
- Definitive chemoradiation (with radiation dose escalation) is the treatment of choice in patients with unresectable disease.
- In advanced stage disease, neoadjuvant chemoradiation should be considered in order to avoid exenterative surgery.



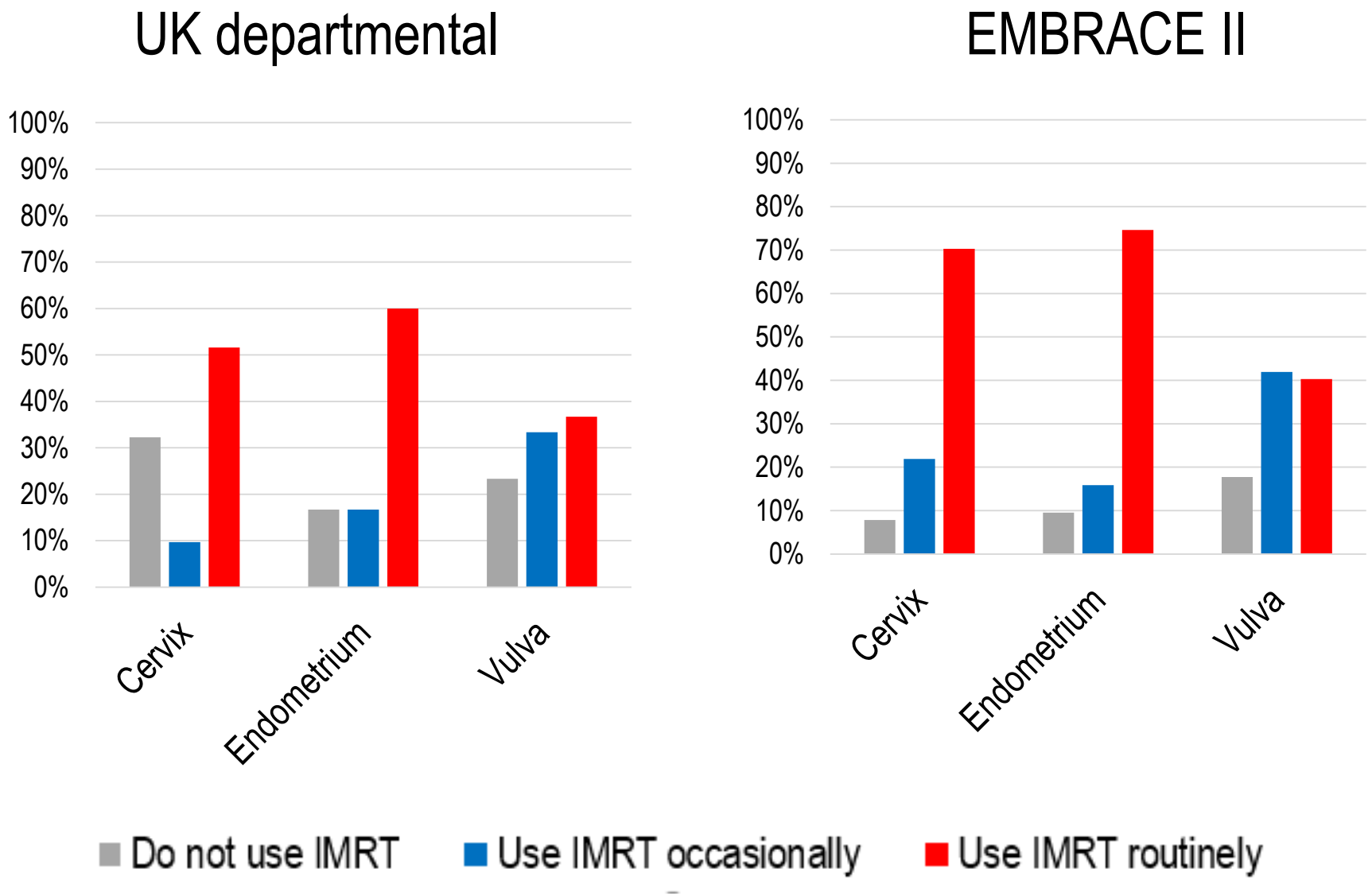
Grade C

Do you routinely use IMRT for vulva cancers?

A. Yes
B. No



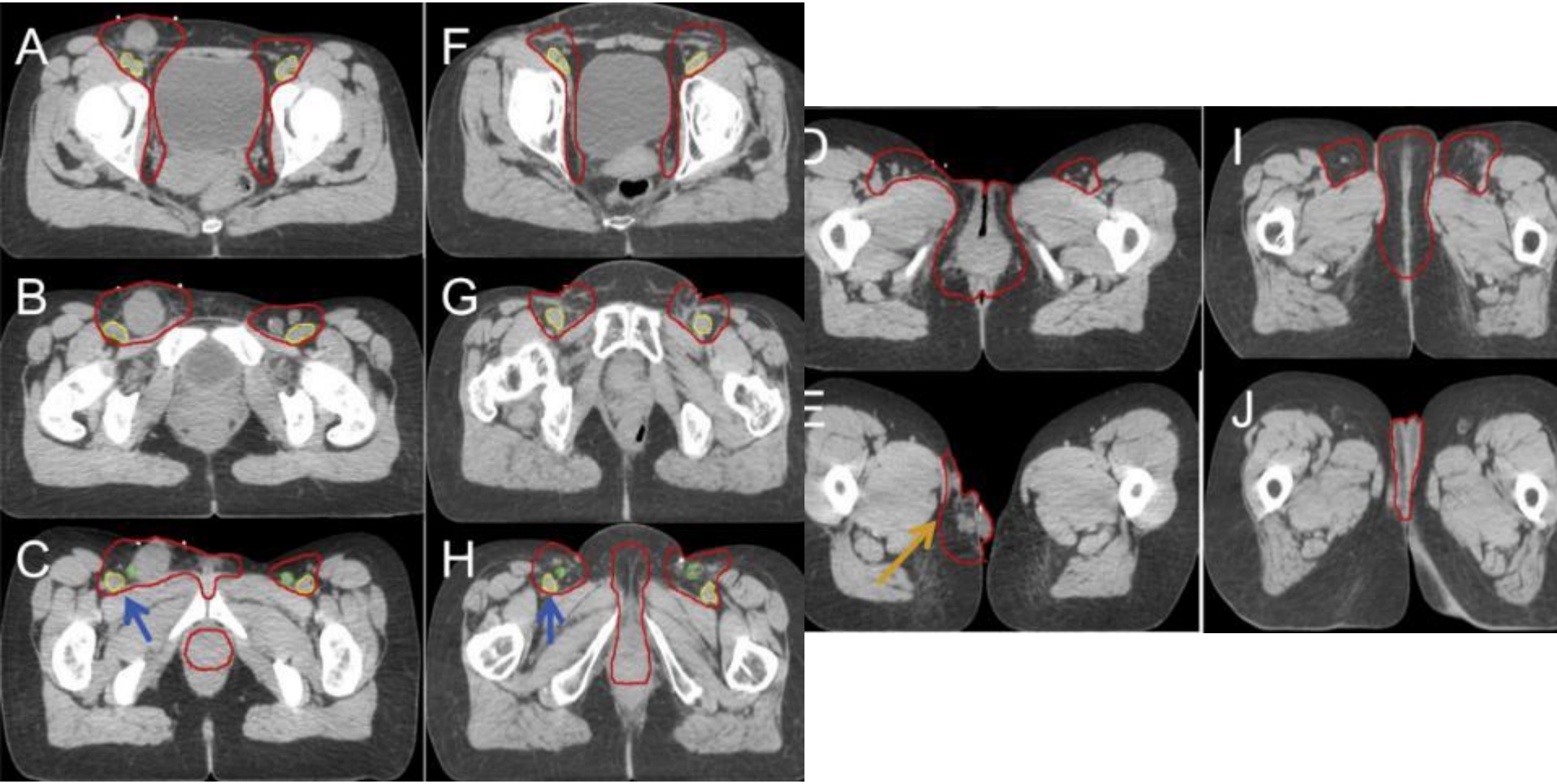
Survey 2016


UK departmental
EMBRACE II
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cervix
Endometrium
Vulva
Do not use IMRT
Use IMRT occasionally
Use IMRT routinely

IMRT Contouring

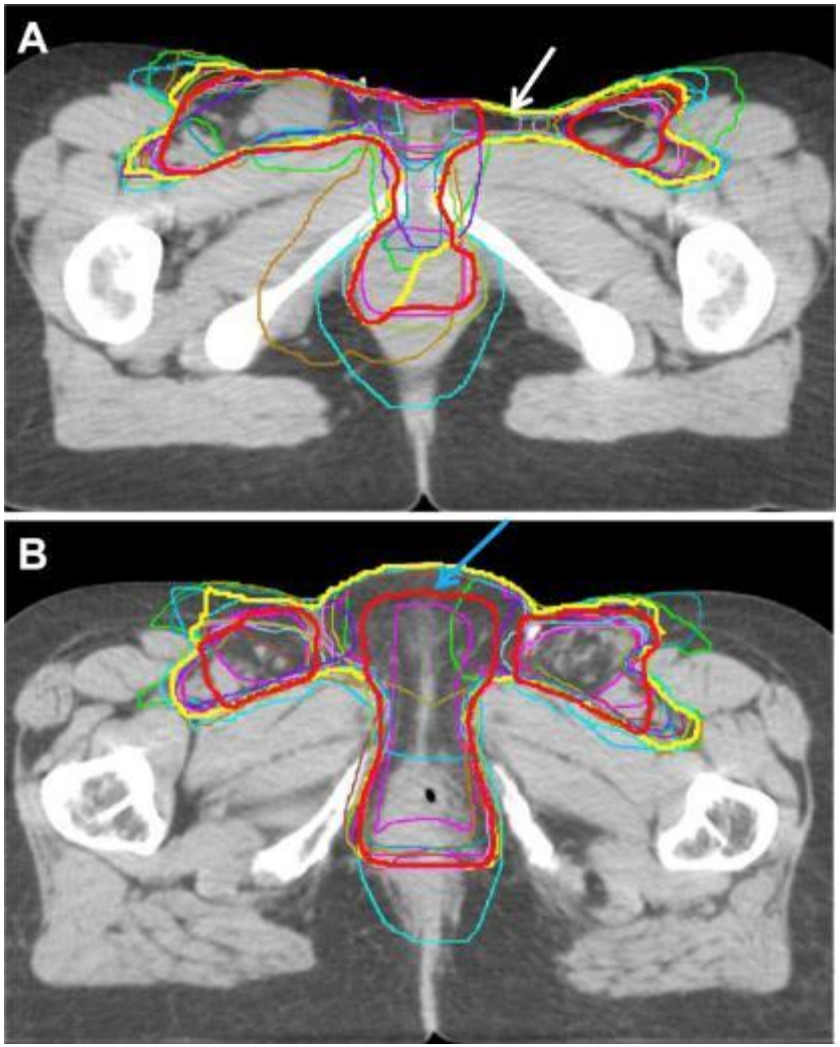
- How high?
- How low?
- What margin round femoral vessels?
- How much vagina?
- Include mons?
- “In transit lymphatics?”

IMRT contouring



Gaffney DK. Int J Radiat Oncol Biol Phys. 2016;95(4):1191-200

IMRT contouring



Gaffney DK. Int J Radiat Oncol Biol Phys. 2016;95(4):1191-200

Contouring inguinal nodes CTV

- Perivascular margin (femoral vessels)
  - Anteromedial ≥35 mm,
  - Anterior ≥23 mm,
  - Anterolateral ≥25 mm,
  - Medial ≥22 mm
- "Lymph node recurrence is not seen posterior or lateral to femoral vessels, thus there is no need to add margins to the vessels in those regions."

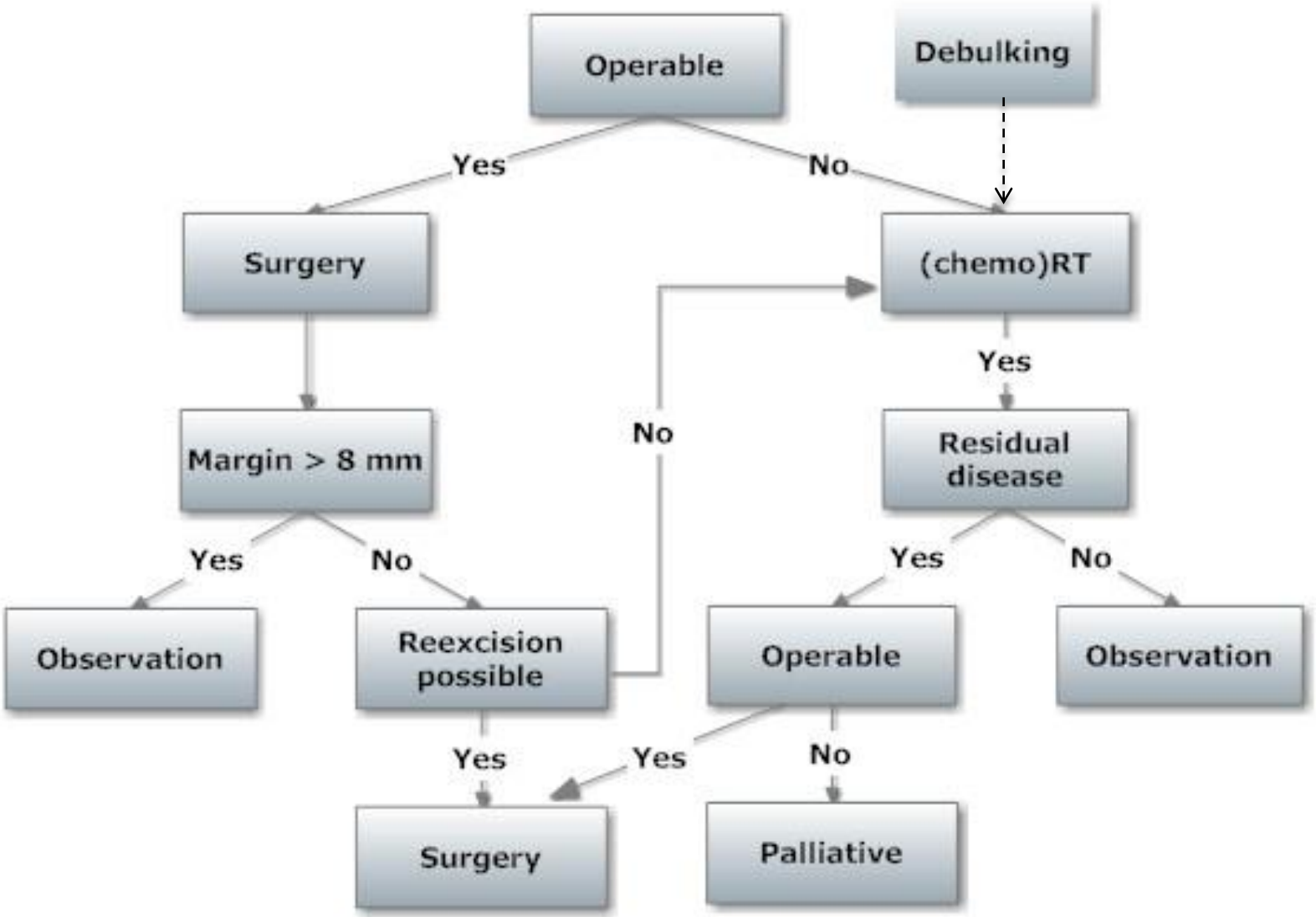
Gaffney DK. Int J Radiat Oncol Biol Phys. 2016;95(4):1191-200

Contouring inguinal nodes CTV

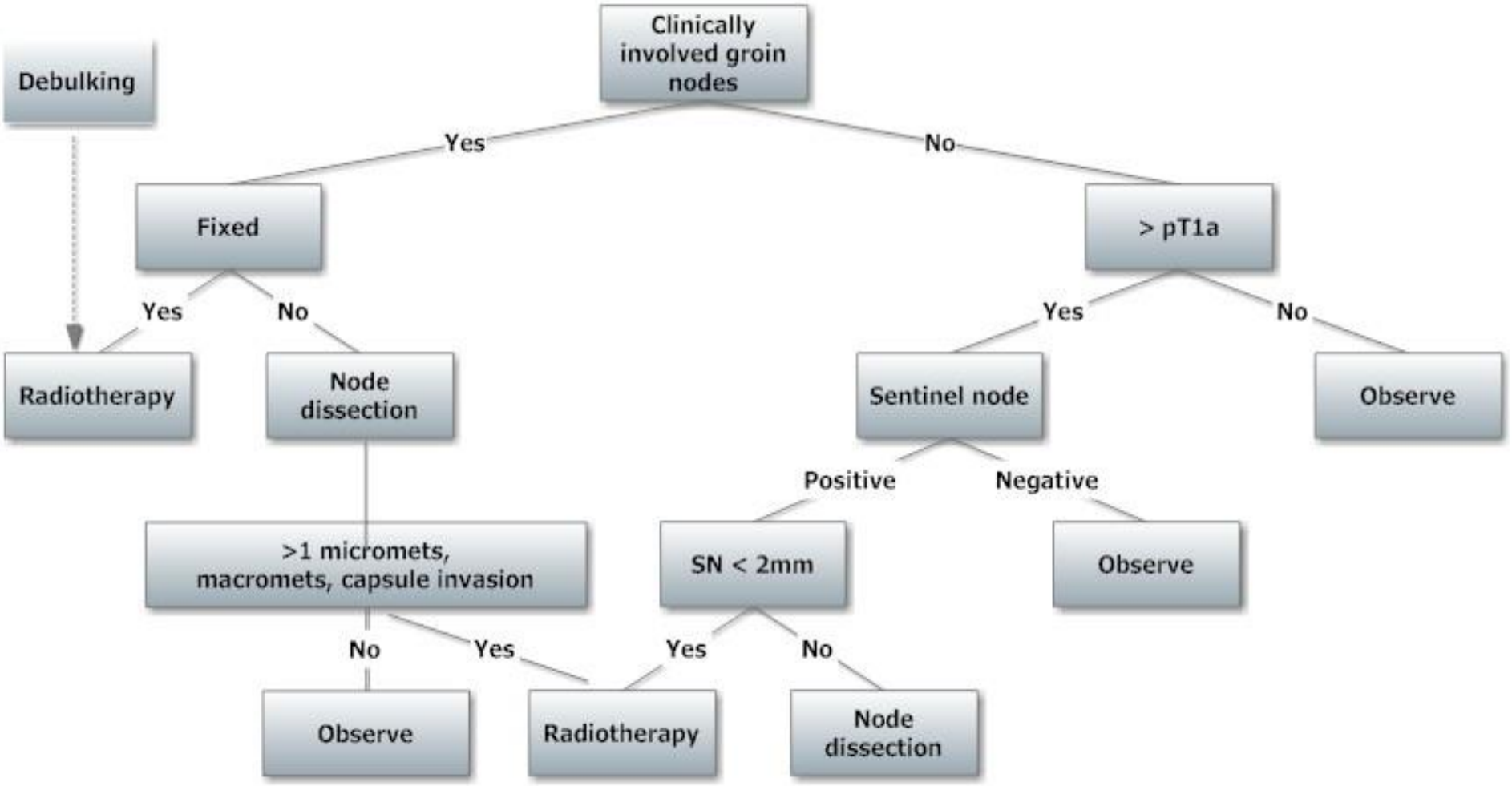
- Inferior border
  - 2 cm below the sapheno-femoral junction
  - Level of the lesser trochanter

Gaffney DK. Int J Radiat Oncol Biol Phys. 2016;95(4):1191-200

Decision tree - vulva



Decision tree - groins



CANCER RESEARCH UK

Imperial College Healthcare NHS Trust

EBRO: CNS Imaging

Ljubljana 2017

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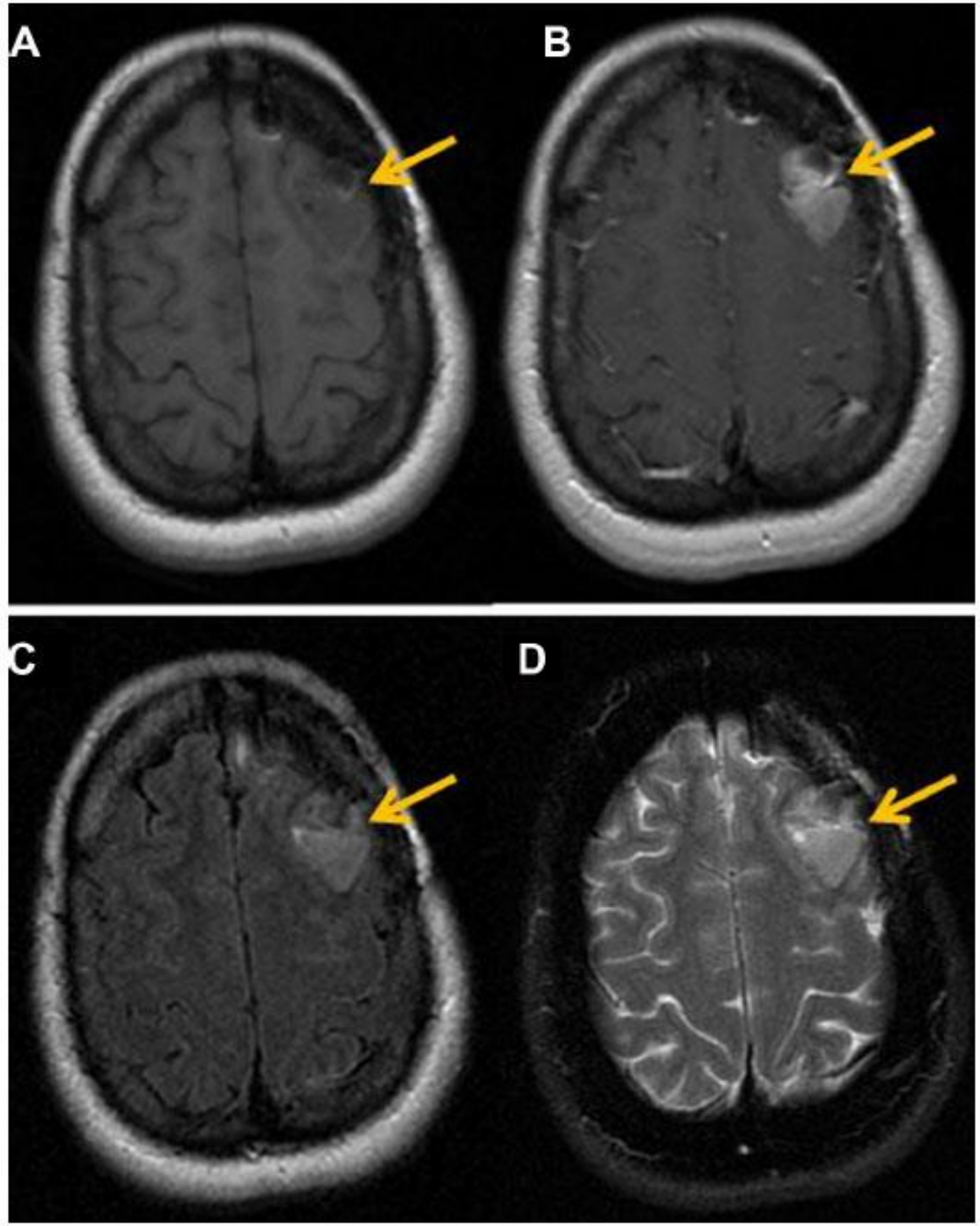
Imperial College London

BTRC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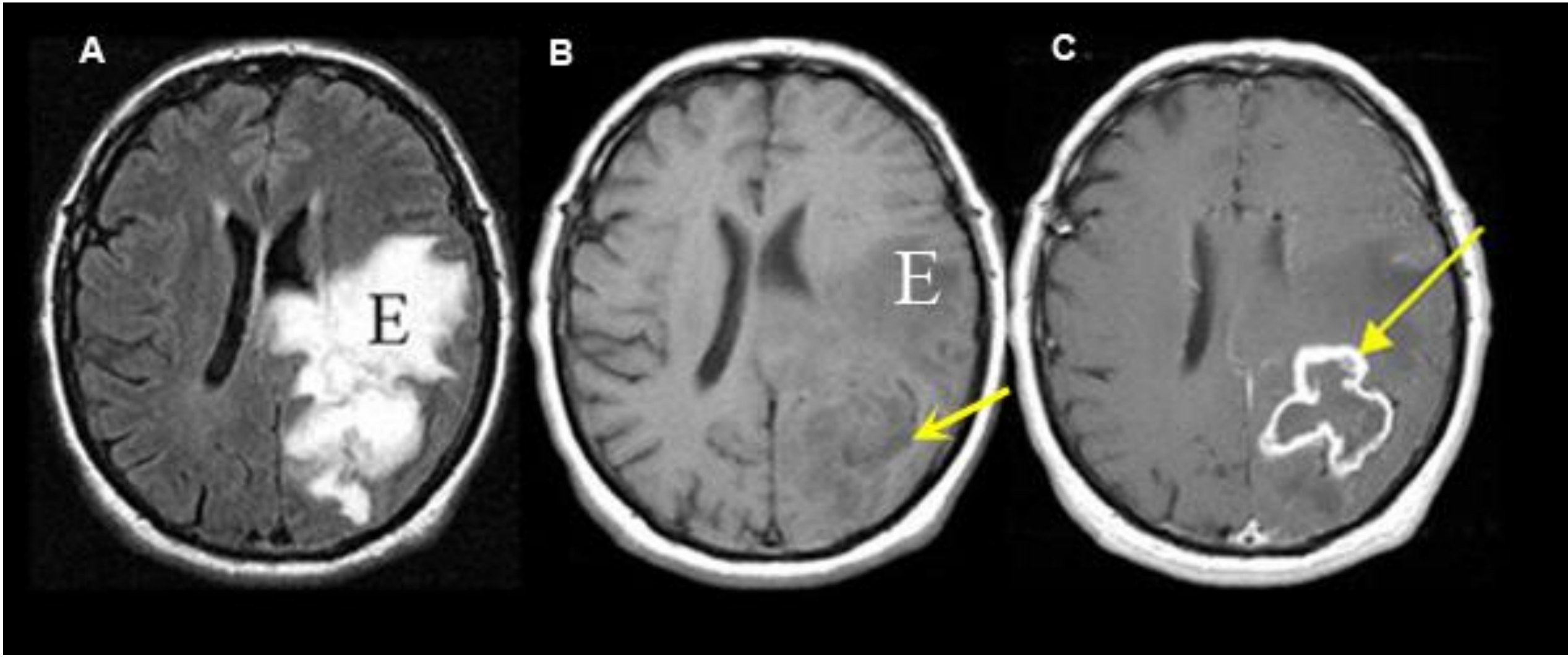
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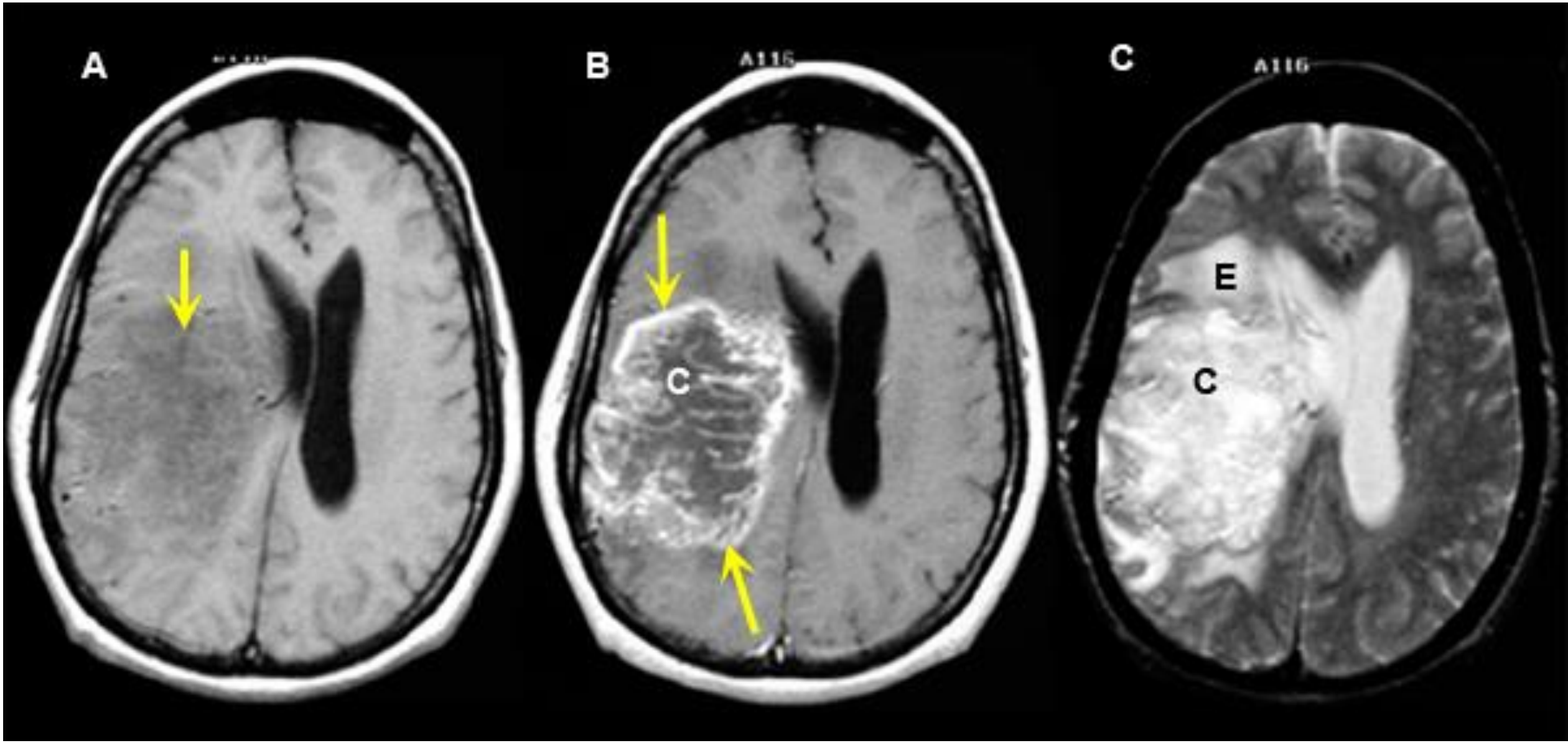
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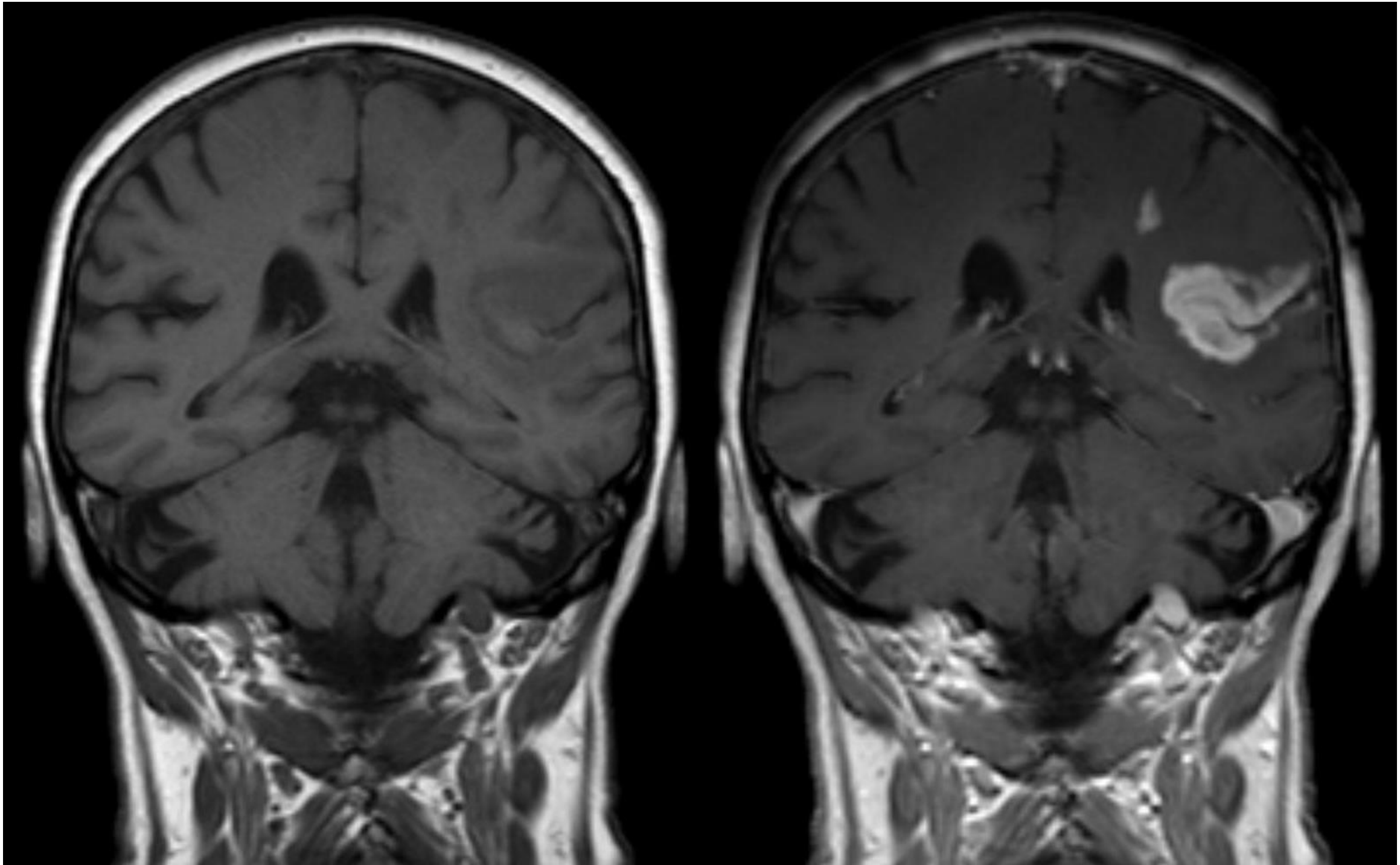

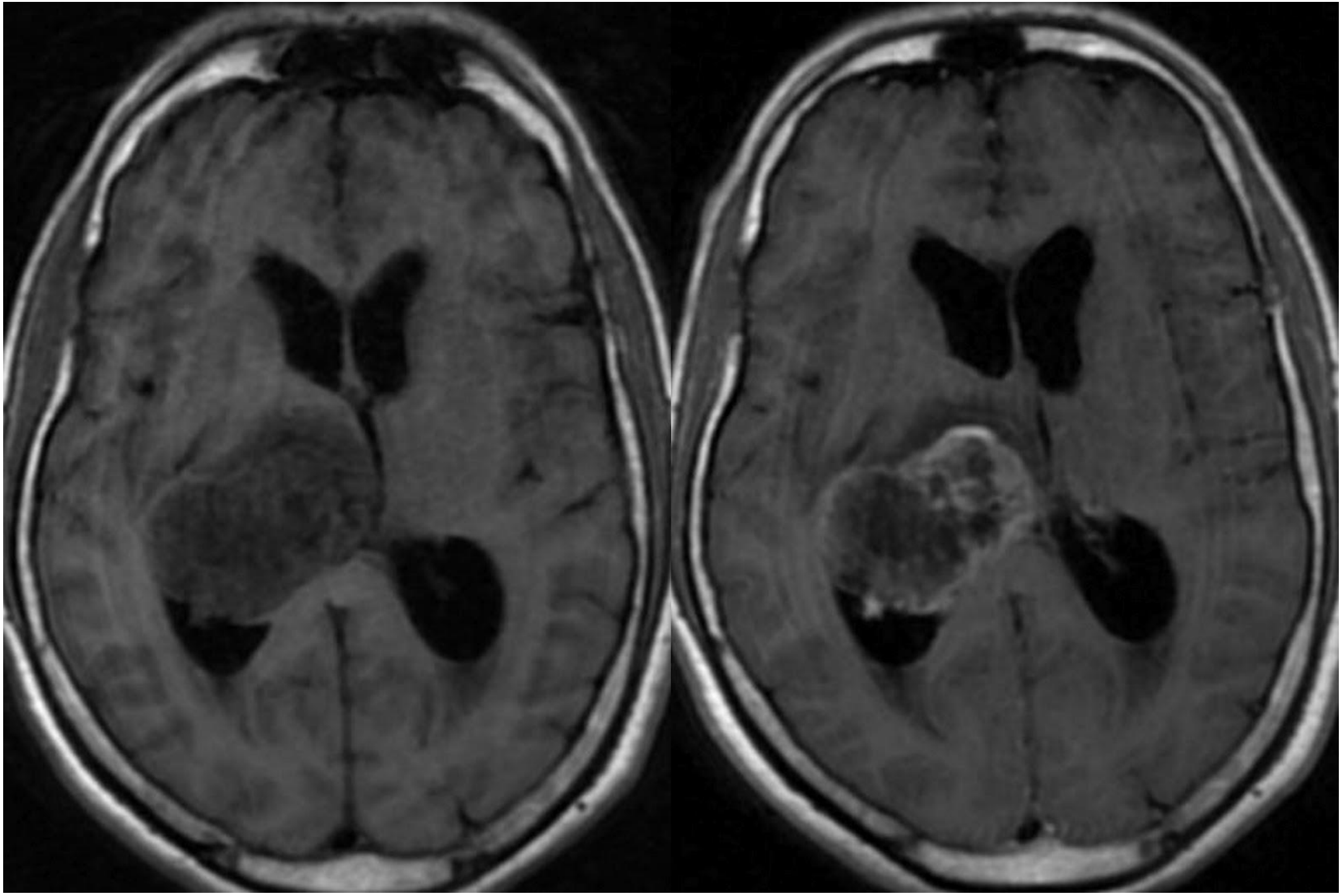

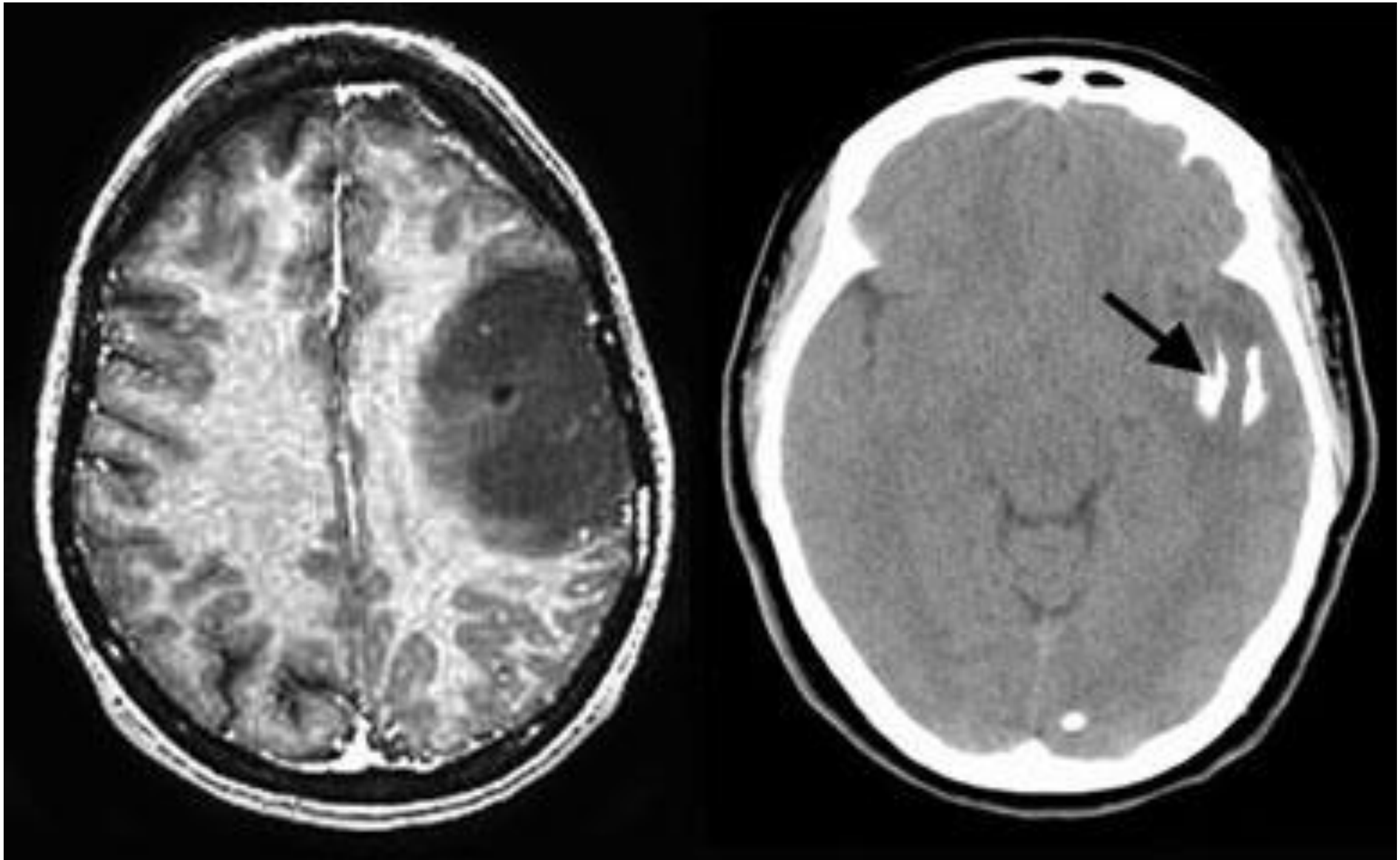

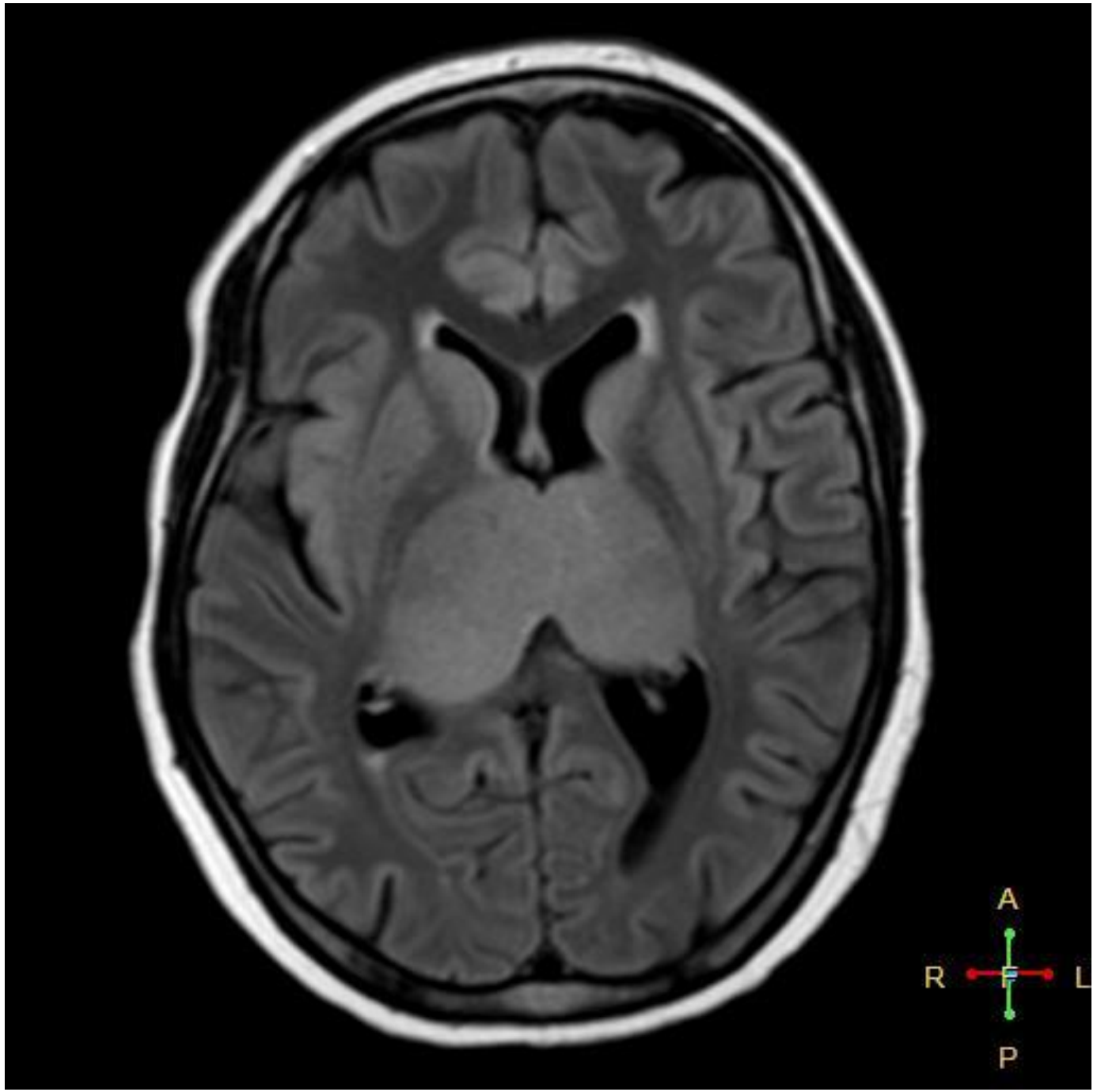
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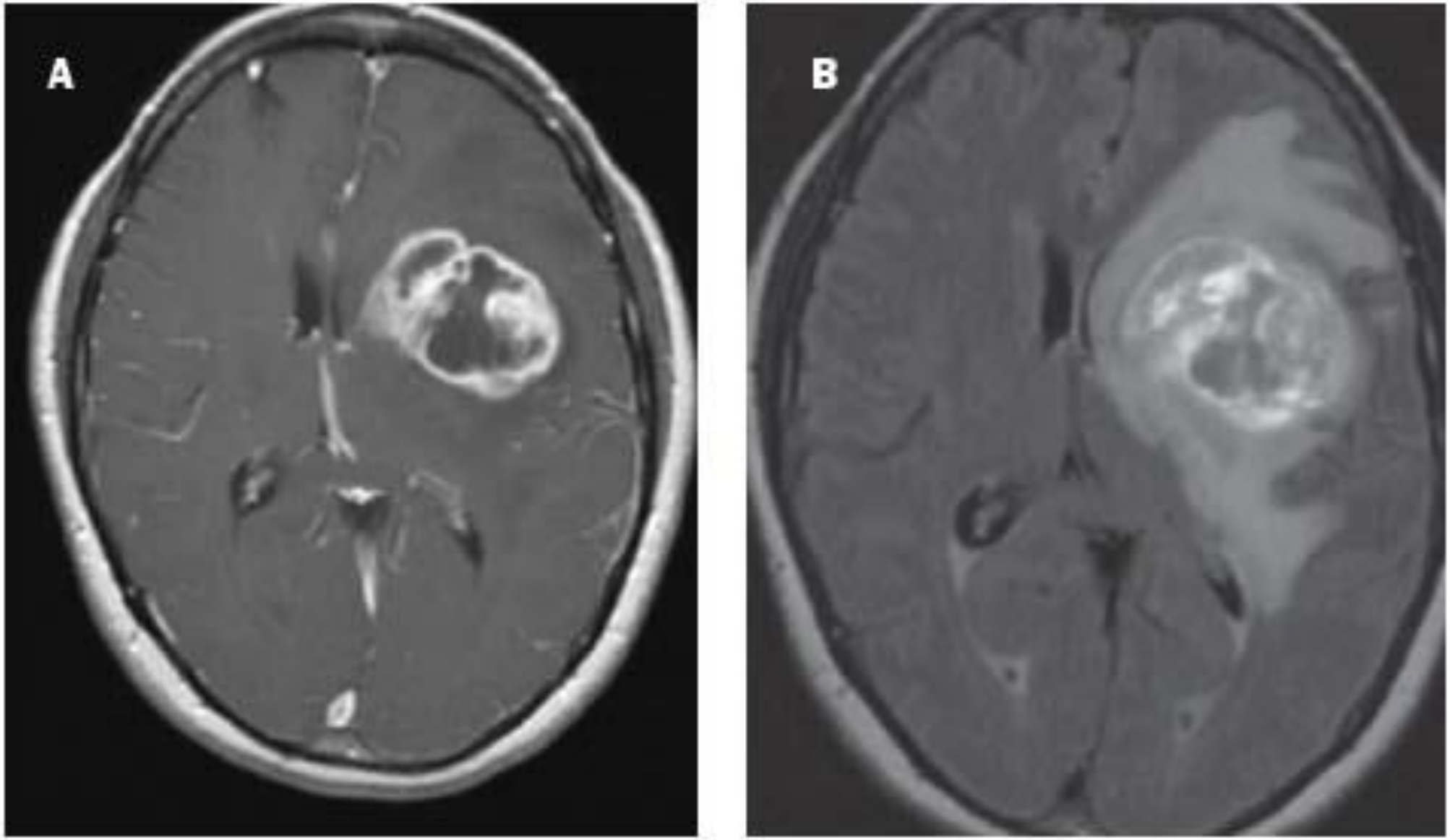
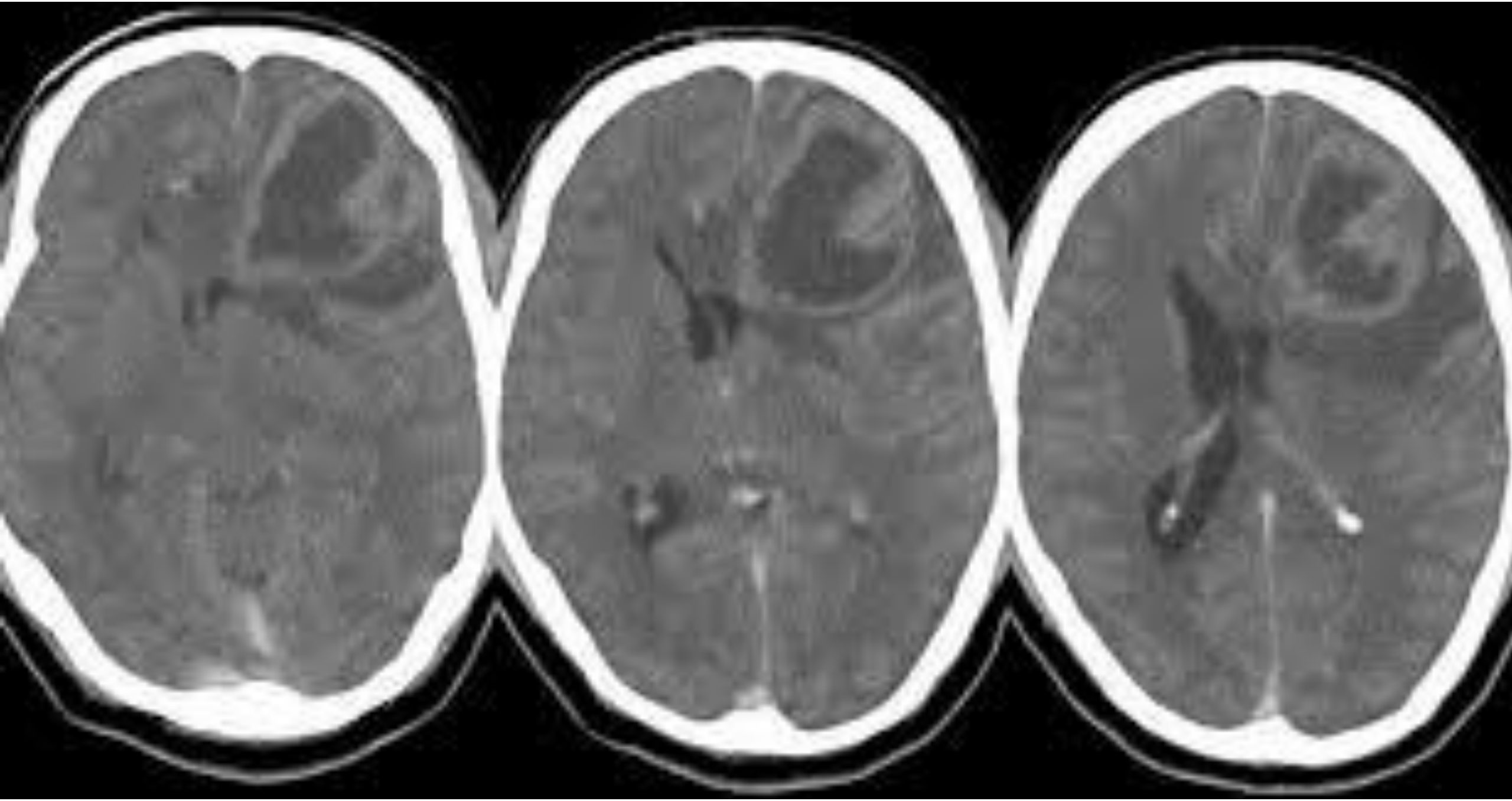
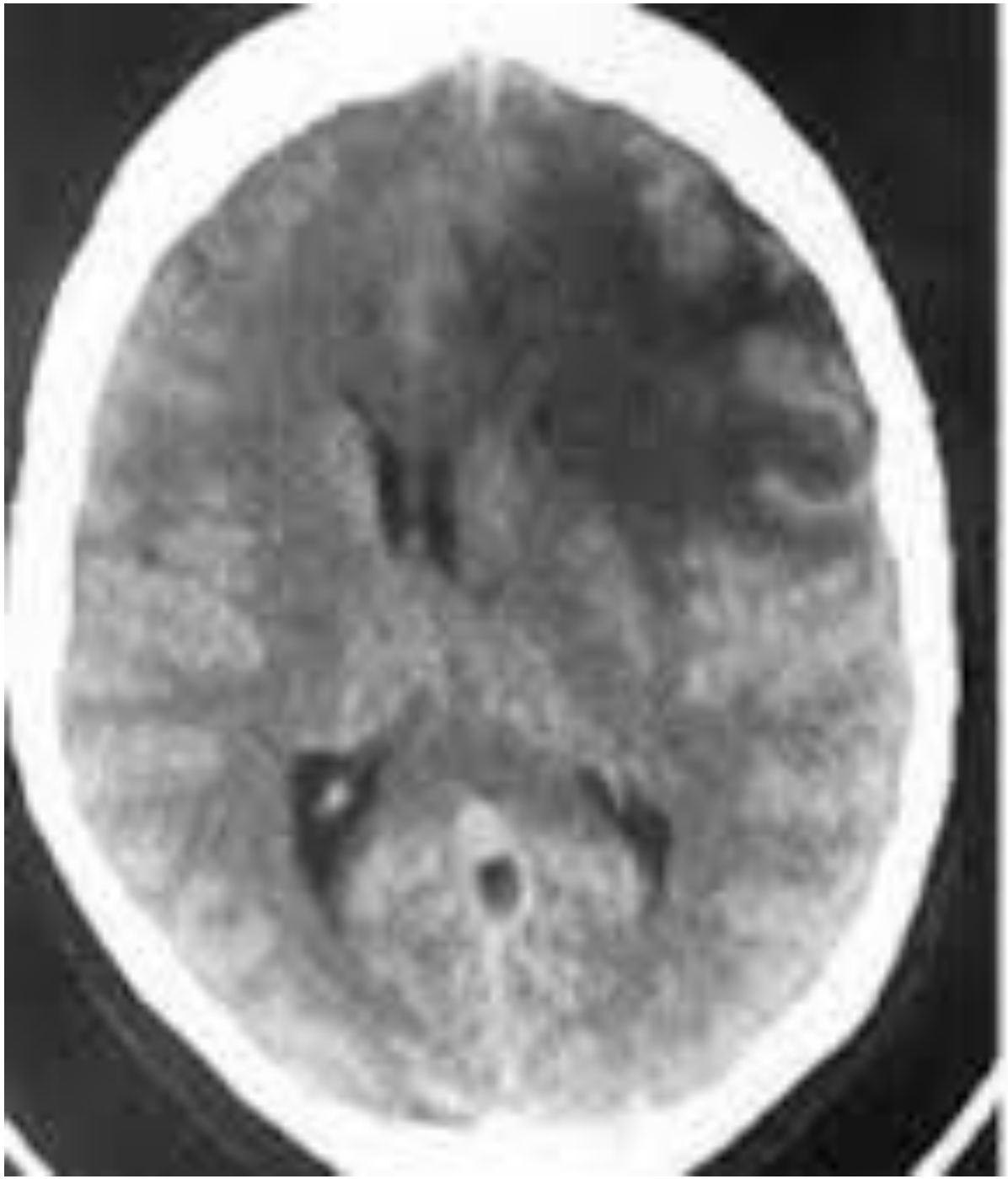
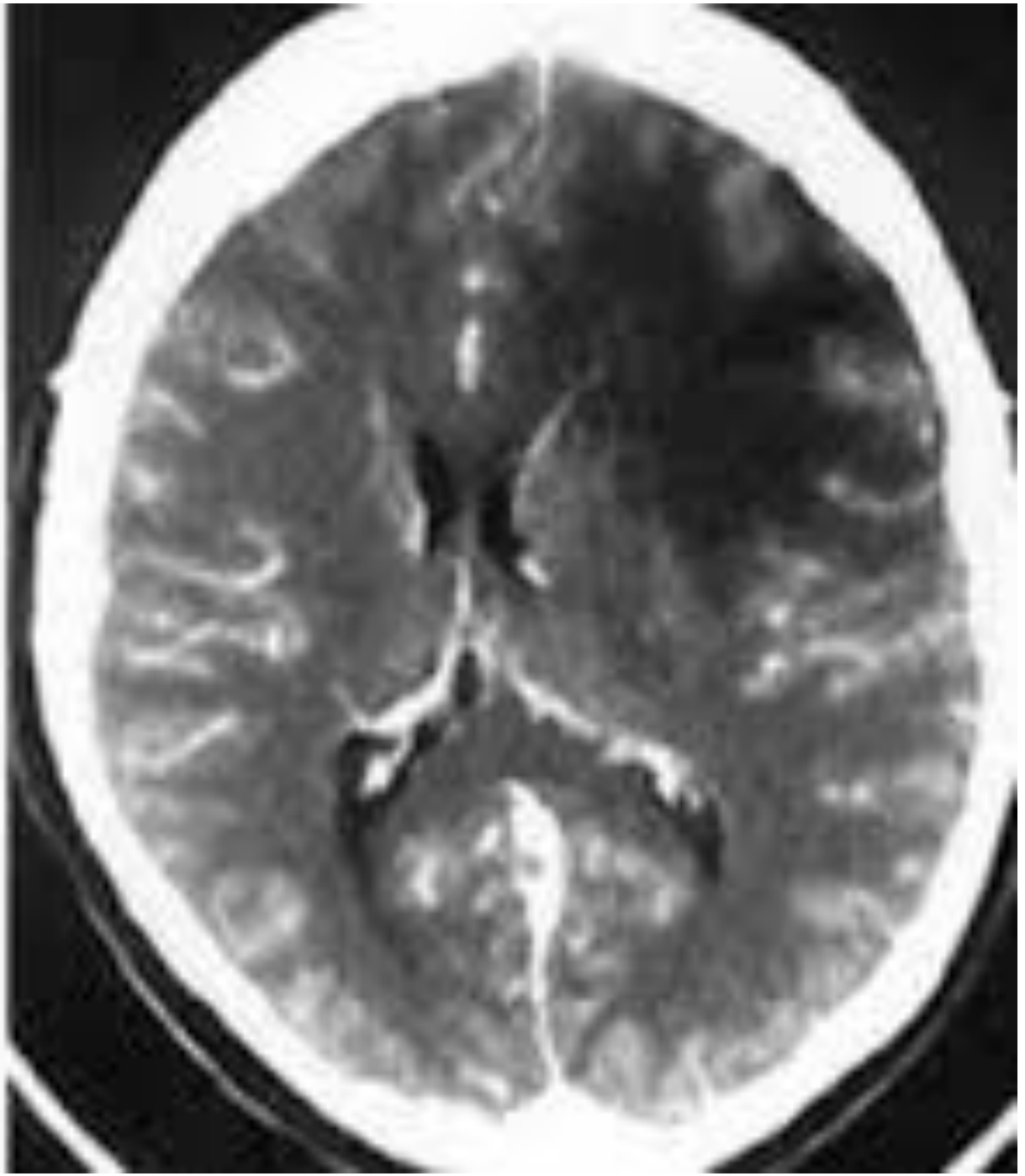
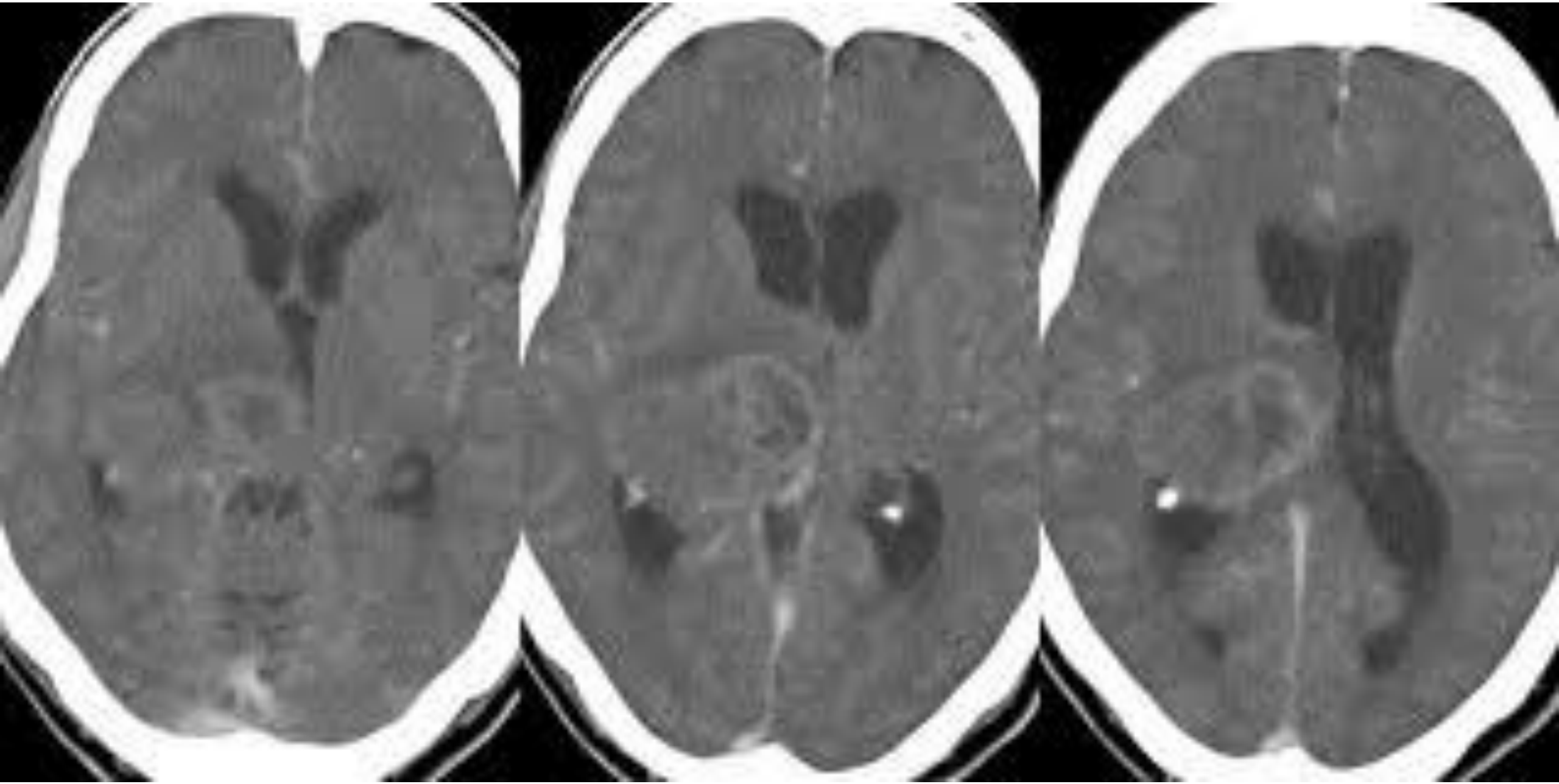


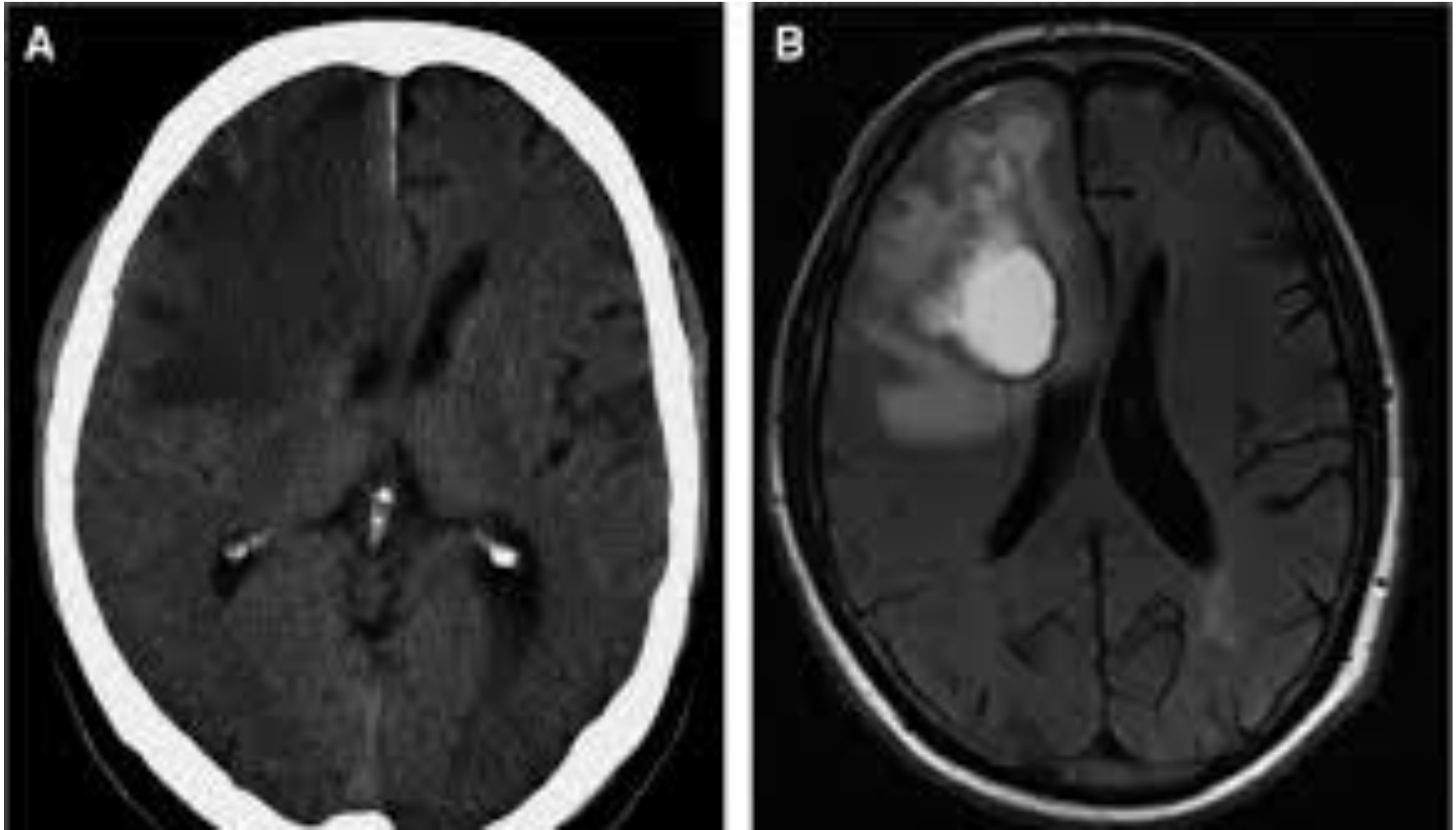
Figure 2. Glioblastoma multiforme. A: Contrast-enhanced T1-weighted image shows enhancing necrotic lesion. B: Contrast-enhanced FLAIR shows enhancing necrotic tumor as well as surrounding vasogenic edema.







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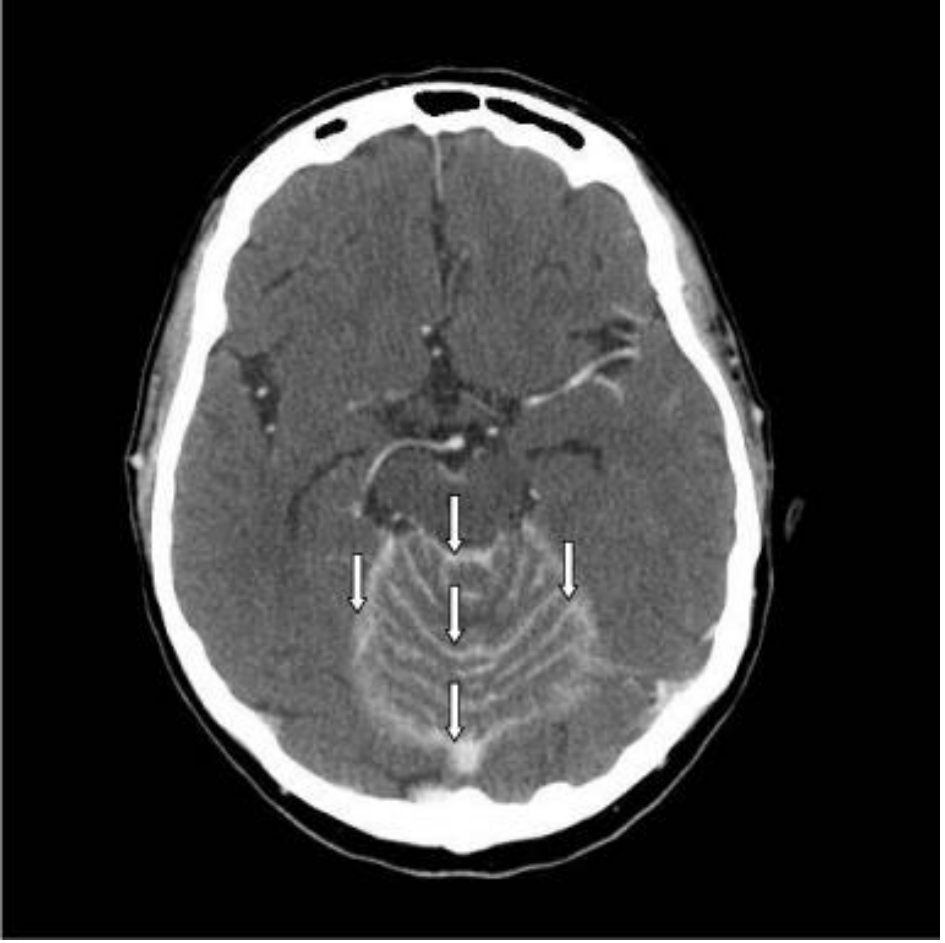

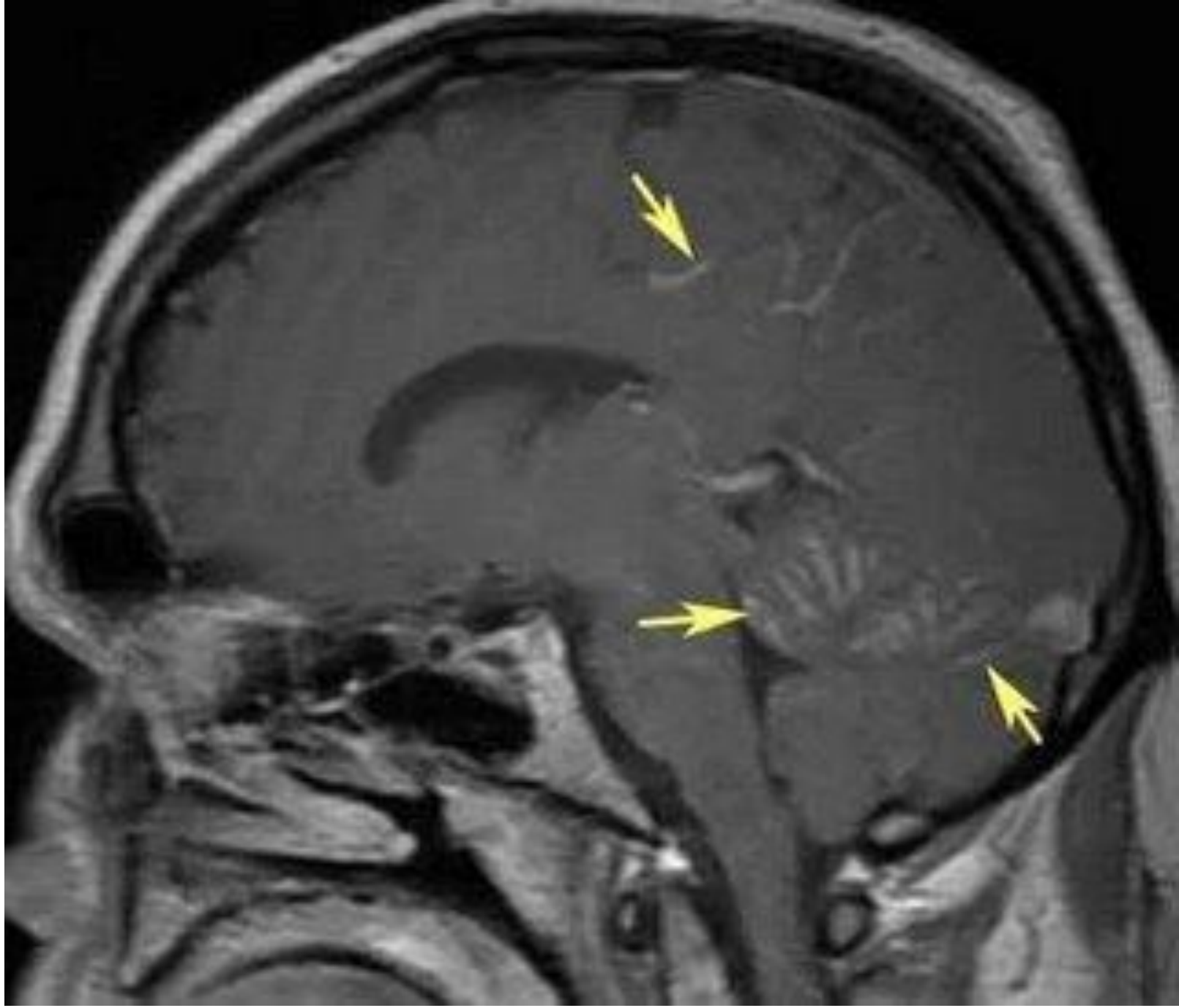

Summary

- T1 with Gad
- T2
  - Flair easier than standard T2

- Check the T1 without Gad as well as the T1 with Gad!
- Practical points:
  - Slice thickness
  - Time between MRI and RT
  - Fusion error

EBRO: CNS Tumours

Ljubljana 2017

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Computational Oncology Group, Imperial College

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Introduction

- Neuro-oncology is a fascinating area
- Rare tumours
- Poor outcomes
- Uneven outcomes

- Gliomas (grade 1 – 4)
- Ependymoma
- Medullblastoma
- Pituitary
- Meningioma

Introduction 2

- Evidence-base is small enough
  - Balancing unequal considerations
    - Early RT in LGG: Seizures:
    - PFS; OS; Cognition; Fatigue

- Good example of both strengths and weaknesses of EBM
  - Meta-analysis showed benefit of chemo in HGG pre-Stupp – not used
  - Much decision-making is non-evidence based
  - Trials are partial, and address only some of the questions
    - Sometimes with long lead times and ignoring other evidence
    - E.g. RTOG 98-02

Cases

- 8 Cases in all
  - 3 HGG
  - 2 LGG
  - 3 Mets

- Most of them are ‘grey’ cases
- I will try and strike a balance between reviewing the evidence and offering some practical suggestions
  - Gaps in the evidence are sources of research
  - Cases get more uncertain as we go on

Some notation

- Intervention A vs B improves OS, but is more likely to lead to grade 3 - 4 toxicity
  - $A >_{OS} B$
  - $A <_{Grade3\text{-}4} B$ (n.b: A < B in the sense that it is worse)

- In patients with disease D, having high F is associated with a better survival than low F.
  - Patients D, High $F >_{OS}$ Low F

Some examples

- In patients with GBM:
  - Chemo-RT leads to a longer survival than RT alone (Stupp, 2005)
  - Chemo-RT is more toxic than RT, esp. haematological toxicity (Stupp, 2005)
  - MGMT-methylation is associated with improved survival (Hegi, 2005)

  - In patients with GBM
    - CRT $>_{OS}$ RT
    - CRT $<_{Grade3\text{-}4}$ RT
    - GBM and CRT; MGMT-meth $>_{OS}$ MGMT-unmeth

Clinical Cases

- What do you see?
- What would you do, and why ?
  - What are the benefits and harms of your approach
- What are the expected outcomes ?
- Can you present the arguments for and against ?
  - Useful to consider dialectical argumentation approach

Recent British Politics

- Recent General Election 2017
- Theresa May is (still) British Prime Minister

- One feature of the British system is that the Prime Minister is just an MP (in this case, Maidenhead)
- But:
  - Her local election gets more interest
  - Anyone may register to stand as local MP
  - So…..


LIVE Maidenhead
ELECTION 2017
GLASGOW SOUTH
Stewart McDonald re-elected
SNP hold
UK SEATS
LAB 157
CON 139
SNP 24
DUP 8
LD 3

Intergalactic space lord, running to be an independent member of parliament for Maidenhead

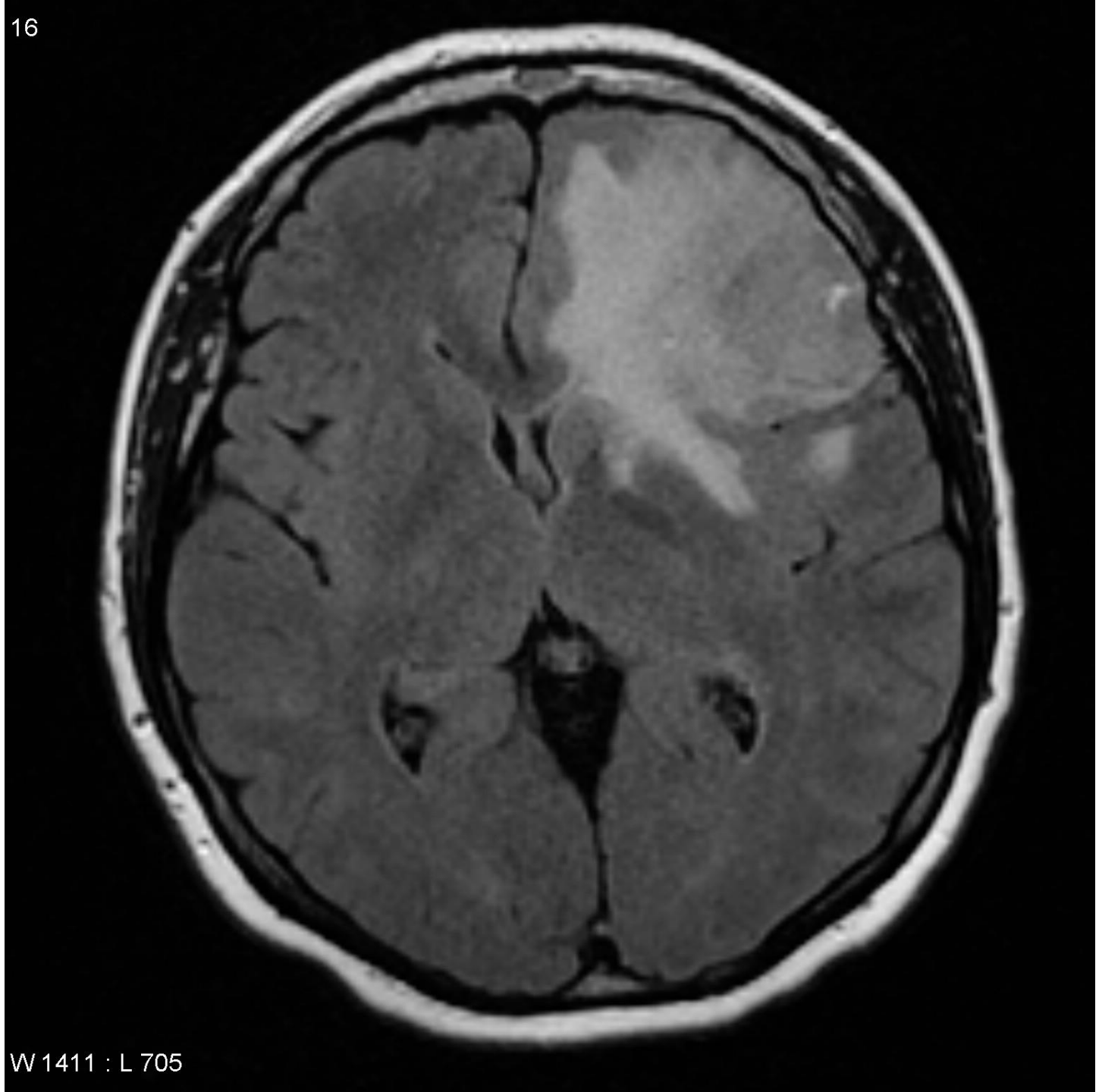
Lord Buckethead

Elmo is a [Muppet](#) character on [Sesame Street](#). He is three-and-a-half years old

Elmo

Case 1

- 59 yr old right-handed man
  - 2 weeks history of increasing headaches
  - Sudden onset speech problems and facial drooping
  - Admitted as ? CVA
  - ECOG PS = 1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High-grade Glioma Background

- High-grade glioma
  - Grade 3 – 4 glioma
  - Astrocytoma and oligodendroglioma
  - Grade 4 astrocytoma = GBM = WHO Grade 4 glioma
    - Debate over GBM-O

  - Rare tumours
  - Poor prognosis
  - Little improvement over time
  - Surgery and RT mainstay of treatment
  - Some role for chemo

Case 1

- Likely to be a GBM
- Operable
- “Optimal” treatment is Surgery, Chemo-RT and adjuvant chemotherapy

Case 1

- Likely to be a GBM
- Operable
- Optimal treatment is Surgery, Chemo-RT and adjuvant chemotherapy
  - What is the benefit of each ?
  - What are the risks of each ?
  - What radiotherapy dose, fractionation and margins, and why ?
  - How long do we continue chemotherapy for ?

- We need to know these to make decisions about what to do for an individual

Case 1

- What are the benefits of surgery?

Case 1

- What are the benefits of surgery?

HUGE! Operate on all of them

None, they all die anyway

Case 1

- Surgery offers:
  - Diagnosis
    - Modern diagnostics often need more than a biopsy
  - Improvement in symptoms
  - Does surgery improve survival ?

Case 1

- Benefits of surgery:
  - No randomised data on the benefit of surgery in newly diagnosed GBM in most patients*
  - Repeated data from retrospective analysis of trial patients
  - Trials of surgical adjuvants (IO-MRI, 5-ALA)
  - Often group patients by extent of resection (GTR; STR; Bx)
  - Consistent message:
    - GTR $>_{OS}$ STR/Bx; GTR $>_{6mPFS}$ STR/Bx
  - Less clear (but perhaps true):
    - GTR $>_{OS}$ STR $>_{OS}$ Bx; GTR $>_{6mPFS}$ STR $>_{6mPFS}$ Bx
  - However, these are all post-hoc analyses
    - What is the obvious confounding factor here ?

*Vuorinen et al. *Acta Neuro. 2003*

Case 1 Pathology

- Which molecular markers are important ?
  - What is their impact ?
  - How would it change your management ?

Case 1 Pathology

- MGMT
- IDH-1
- 1p/19q
- EGFR

- New WHO classification focuses on IDH-1 and 1p/19q
- Doesn’t mention MGMT

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- MGMT
- IDH-1
- 1p/19q
- EGFR

- New WHO classification focuses on IDH-1 and 1p/19q
- Doesn’t mention MGMT

Case 1 Pathology

- MGMT – MGMT Methylation is prognostic and predictive
- IDH-1 – Prognostic and ?predictive
- 1p/19q – Prognostic and predictive
- EGFR - ?Prognostic not predictive; not a target (currently)
  - Multiple attempts to target EGFR-receptors in GBM
  - All failed

Case 1 Pathology

- IDH-wt
- MGMT methylated
- 1p/19q retained

What does this mean ?

Case 1 Pathology

- IDH-wt
- MGMT methylated
- 1p/19q retained

- This is a “GBM”

Case 1 Treatment

- Surgery
- Radiotherapy

Case 1 Treatment

- Surgery
- Radiotherapy
  - But what dose, fractionation, and margins ?

Case 1 Treatment

- Surgery
- Radiotherapy
  - But what dose, fractionation, and margins ?

All so confusing

Case 1 RT Dose

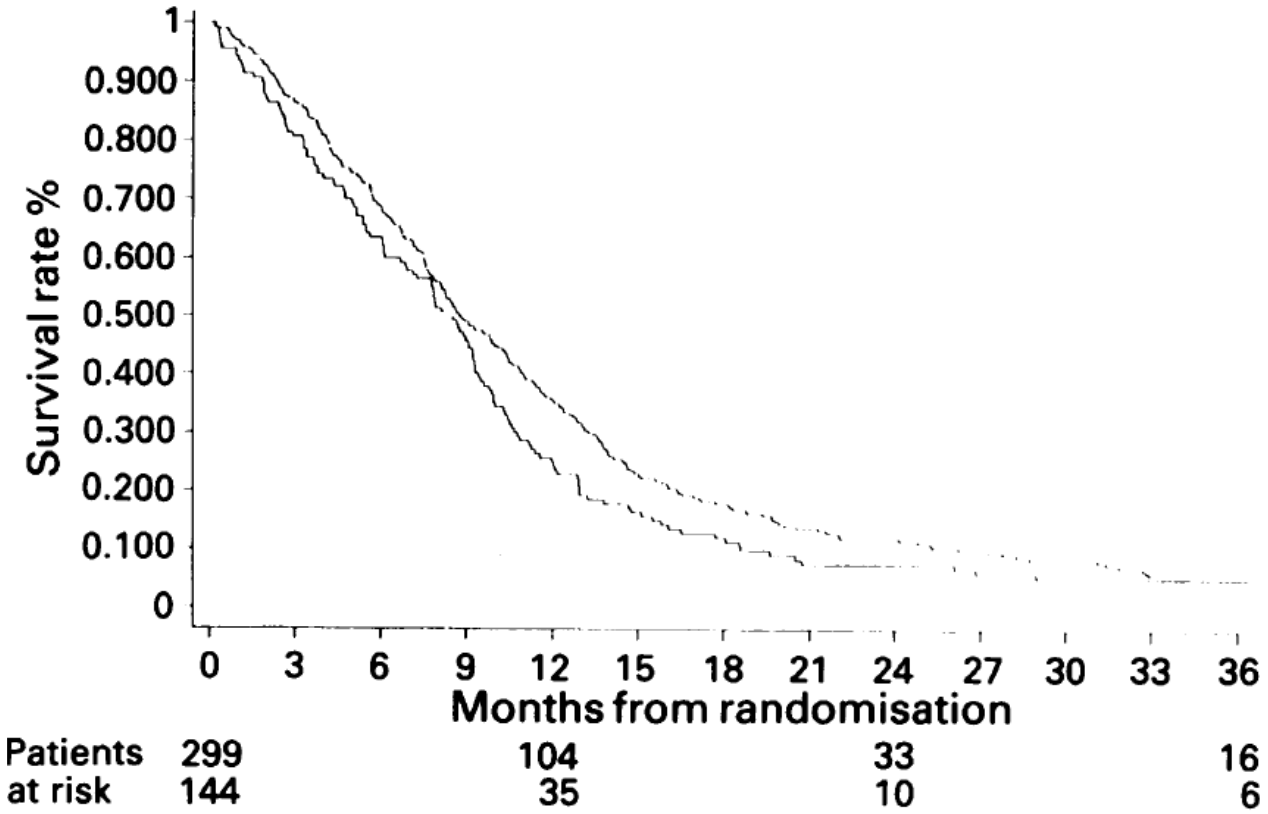

Figure 1 Survival by allocated treatment. —— Group 1 (45 Gy), – – – Group 2 (60 Gy).

Bleehen, BJC 1991

Table VI Definition of prognostic index

Prognostic factor	*Category*	*Score*
Age (years)	⩽44	0
	45–59	6
	⩾60	12
WHO performance status	0–1	0
	2	4
	3–4	8
Extent of neurosurgery	complete resection	0
	partial resection	4
	biopsy	8
History of fits (months)	⩾3	0
	<3	5
	none	10

Prognostic Index = sum of scores for each factor, a low score indicating a better prognosis.

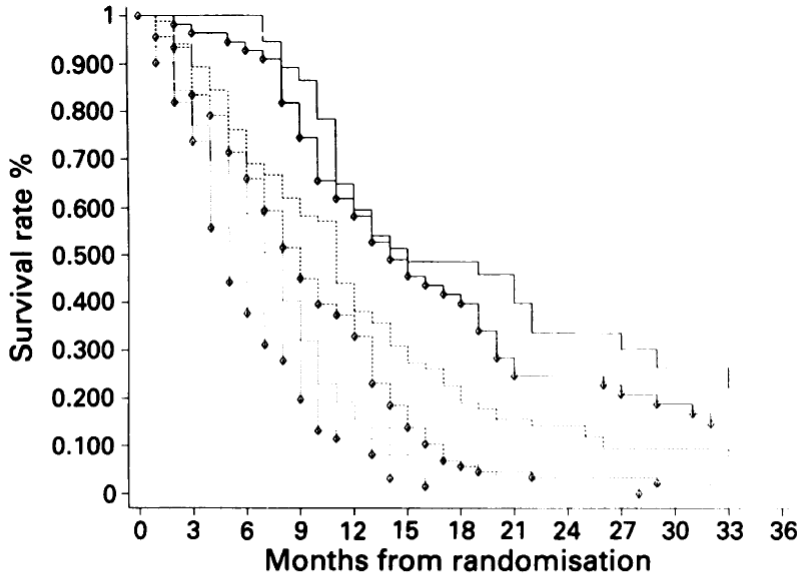

Figure 2 Prognostic groups. Index score: —— 0–10; —◇— 11–15; – – – 16–20; —◇— 21–25; ····· 26–33; ···◇··· 34–38.

Case 1 Treatment:

- Post-op RT
  - Meta-analysis: RR: 0.81
  - 60Gy $>_{OS}$ 45Gy (Bleehan)
  - Persistent failure from benefit of higher doses/ boosts/ etc.

- But what margins ?

Laperriere, RadiotherOncol 2002
Bleehen, BJC 1991
Walker, RedJ, 1979

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  - 60Gy $>_{OS}$ 45Gy (Bleehan)
  - Persistent failure from benefit of higher doses/ boosts/ etc.

- But what margins ?
  - How do we define success in GBM radiotherapy?

Laperriere, RadiotherOncol 2002
Bleehen, BJC 1991
Walker, RedJ, 1979

Case 1 Treatment:

- Post-op RT
  - Non-randomised data
  - Success is local failure
    - Because we know we did not miss
    - Opens up a route to redefining success (pattern of failure vs. OS).

- US vs. Europe
  - Europe – single phase; 2 – 3 cm margins
  - USA – 2 phase, 2 dose levels
  - USA volumes are bigger; no better; more normal tissue irradiated

Case 1 Treatment:

- Post-op RT
- T1 and T2 sequences on MRI
- GTV: T1 contrast enhancing
- CTV: GTV + 2 – 3 cm
  - Make sure it includes T2 abnormality
  - Allow for fusion errors
  - Edit for natural boundaries
  - CTV -> PTV margin

Case 1 Treatment

- Surgery
- Radiotherapy
  - 60Gy/ 30#. 2 – 3 cm CTV. Use MRI for planning
- Chemotherapy

Case 1 Chemotherapy

- Would you suggest chemotherapy?
- Which agents, when and for how long?
- What are the additional toxicities?

Chemotherapy

Table 4. Grade 3 or 4 Hematologic Toxic Effects in Patients Treated with Temozolomide.

Toxic Effect	Concomitant Temozolomide Therapy (N=284)	Adjuvant Temozolomide Therapy (N=223)	Entire Study Period* (N=284)
	number of patients (percent)		
Leukopenia	7 (2)	11 (5)	20 (7)
Neutropenia	12 (4)	9 (4)	21 (7)
Thrombocytopenia	9 (3)	24 (11)	33 (12)
Anemia	1 (<1)	2 (1)	4 (1)
Any	19 (7)	32 (14)	46 (16)

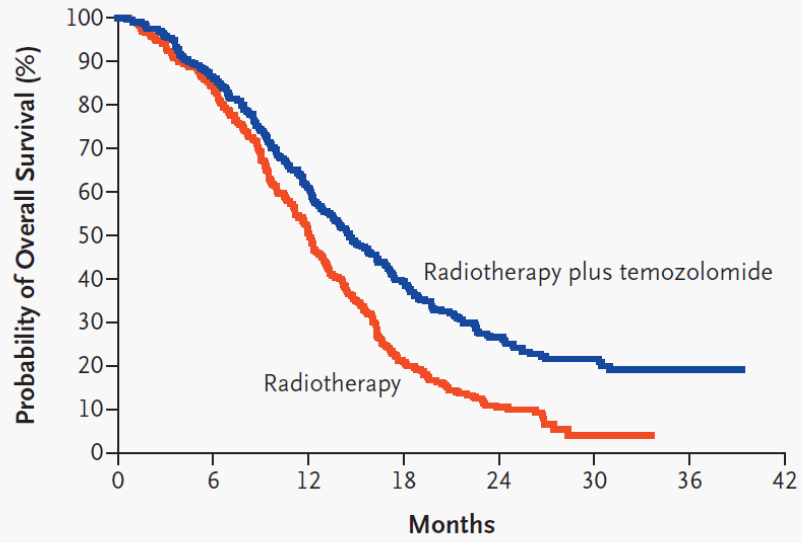
* The entire study period was defined as the period from study entry to seven days after disease progression.

Table 1. Demographic Characteristics of the Patients at Baseline.

Characteristic	Radiotherapy (N=286)	Radiotherapy plus Temozolomide (N=287)
Age — yr		
Median	57	56
Range	23–71	19–70
Age — no. (%)*		
<50 yr	81 (28)	90 (31)
≥50 yr	205 (72)	197 (69)
Sex — no. (%)		
Male	175 (61)	185 (64)
Female	111 (39)	102 (36)
WHO performance status — no. (%)*†		
0	110 (38)	113 (39)
1	141 (49)	136 (47)
2	35 (12)	38 (13)
Extent of surgery — no. (%)*		
Biopsy	45 (16)	48 (17)
Debulking	241 (84)	239 (83)
Complete resection	113 (40)	113 (39)
Partial resection	128 (45)	126 (44)

Stupp, NEJM 2005; LancetOnc 2009

Chemotherapy



No. at Risk							
Radiotherapy	286	240	144	59	23	2	0
Radiotherapy plus temozolomide	287	246	174	109	57	27	4

Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001).

Table 3. Overall and Progression-free Survival According to Treatment Group.*

Variable	Radiotherapy (N=286)	Radiotherapy plus Temozolomide (N=287)
	value (95% CI)	
Median overall survival (mo)	12.1 (11.2–13.0)	14.6 (13.2–16.8)
Overall survival (%)		
At 6 months	84.2 (80.0–88.5)	86.3 (82.3–90.3)
At 12 months	50.6 (44.7–56.4)	61.1 (55.4–66.7)
At 18 months	20.9 (16.2–26.6)	39.4 (33.8–45.1)
At 24 months	10.4 (6.8–14.1)	26.5 (21.2–31.7)
Median progression-free survival (mo)	5.0 (4.2–5.5)	6.9 (5.8–8.2)
Progression-free survival (%)		
At 6 months	36.4 (30.8–41.9)	53.9 (48.1–59.6)
At 12 months	9.1 (5.8–12.4)	26.9 (21.8–32.1)
At 18 months	3.9 (1.6–6.1)	18.4 (13.9–22.9)
At 24 months	1.5 (0.1–3.0)	10.7 (7.0–14.3)

* A total of 160 patients in the radiotherapy group and 60 patients in the radiotherapy-plus-temozolomide group received temozolomide as salvage therapy. CI denotes confidence interval.

Stupp, NEJM 2005; LancetOnc 2009

Case 1 Chemotherapy

MGMT methylated – Prognostic

Predictive

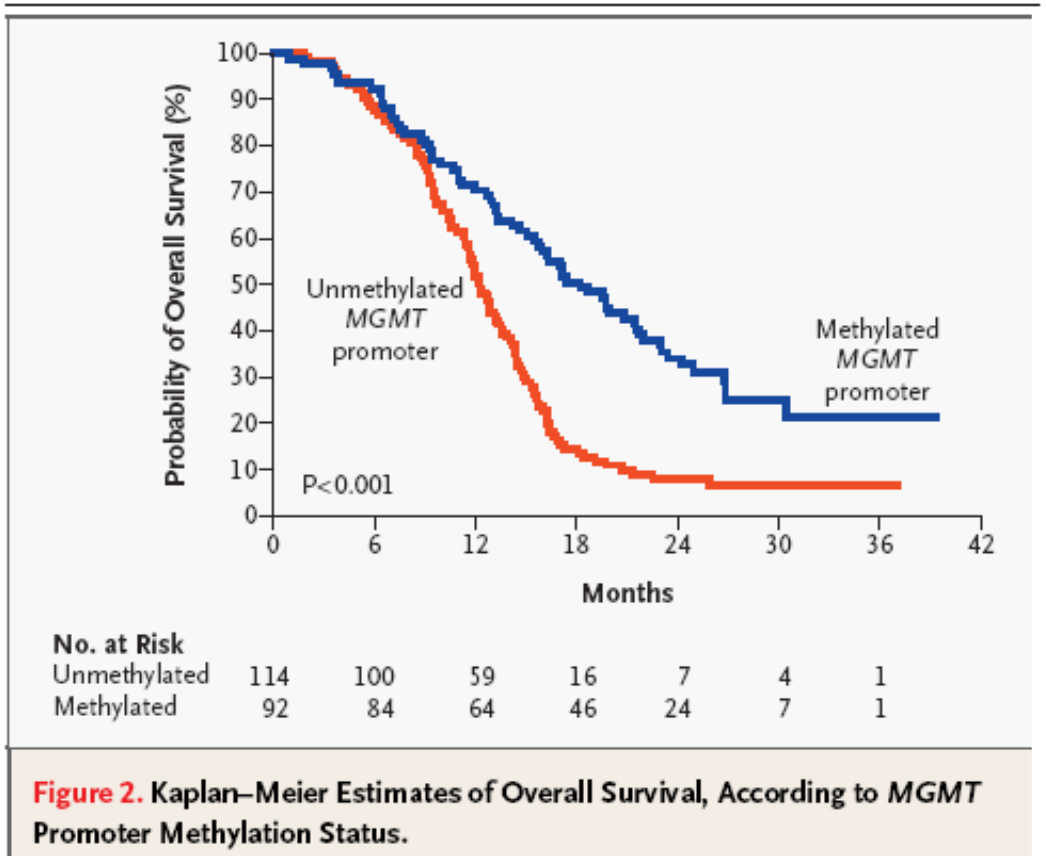
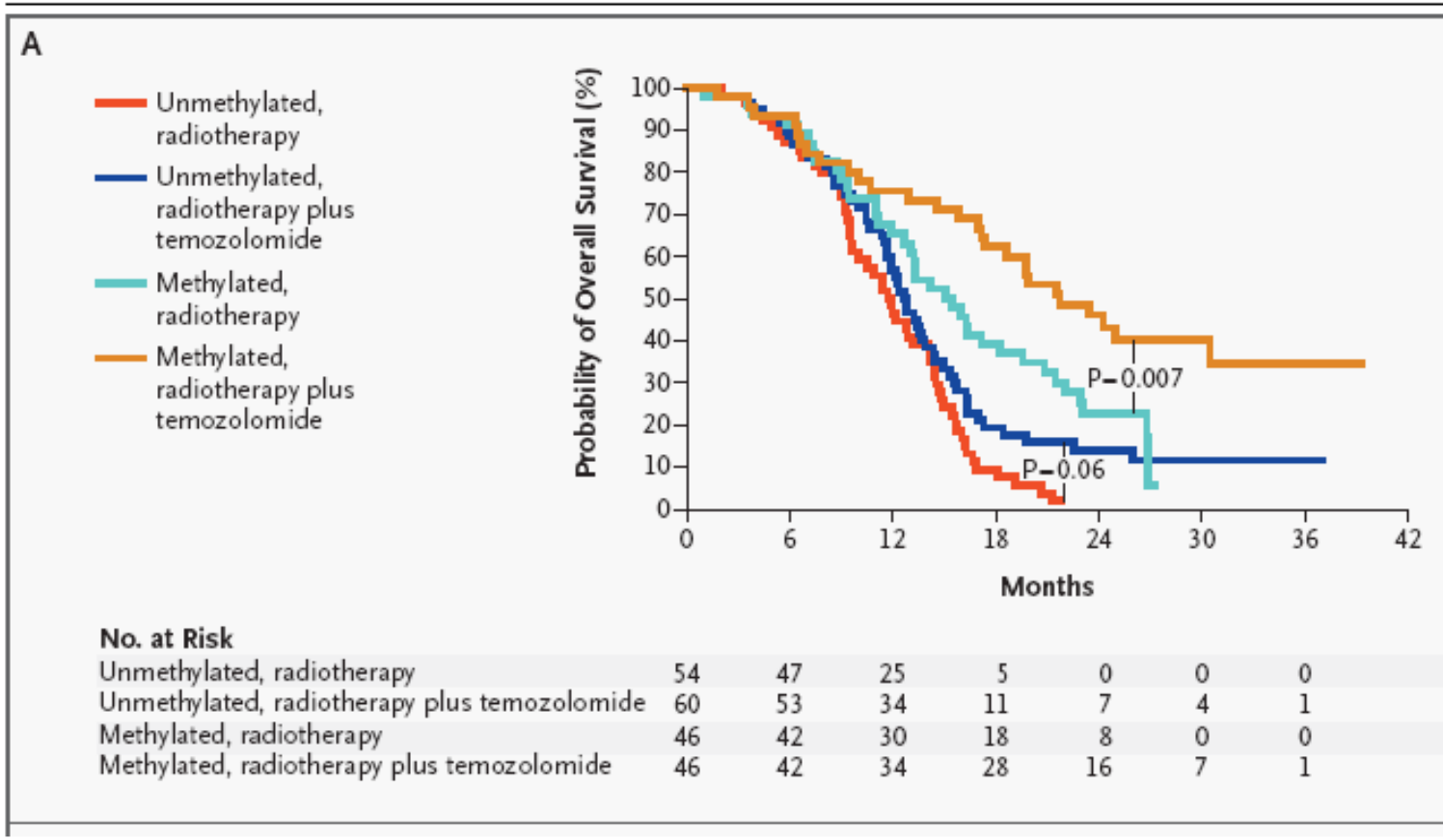


Figure 2. Kaplan–Meier Estimates of Overall Survival, According to *MGMT* Promoter Methylation Status.



Hegi NEJM 2005

Case 1 Chemotherapy

- Would you give chemotherapy without results of the Stupp trial?

Case 1 Chemotherapy

- Would you give chemotherapy without results of the Stupp trial?

Bernard talked about publication bias

Case 1 Chemotherapy

- Multiple trials demonstrate benefit from adjuvant chemotherapy in HGG
- First meta-analysis in 1993
  - 16 trials; 3000 patients; 10% improvement in OS
  - 12 Trials; IPD MA; 3004 patients; Improved Median OS by 2 months
- Phase 2 trial of RT + TMZ

Fine, Cancer 1993
Stewart, Lancet 2002
Athanassiou, JCO, 2005

Case 1 Chemotherapy

- Multiple trials demonstrate benefit from adjuvant chemotherapy in HGG
- First meta-analysis in 1993
  - 16 trials; 3000 patients; 10% improvement in OS
  - 12 Trials; IPD MA; 3004 patients; Improved Median OS by 2 months
- Phase 2 trial of RT + TMZ

What took you so long ?

Fine, Cancer 1993
Stewart, Lancet 2002
Athanassiou, JCO, 2005

Case 1 Chemotherapy

- Better prognosis if MGMT methylated
- Benefit from addition of TMZ
  - 150 – 200mg/m2 d1 – d5
  - For how long?

Case 1 Chemotherapy

- No benefit from extended TMZ on OS
  - Multiple retrospective studies show that those who take TMZ for 12 months live longer than those who take TMZ for 6 months
  - Recent analysis of RCT data suggests maybe PFS improvement but no OS improvement

Blumenthal, NeuroOnc 2017

Case 1 Chemotherapy

- No benefit from extended TMZ on OS
  - Multiple retrospective studies show that those who take TMZ for 12 months live longer than those who take TMZ for 6 months
  - Recent analysis of RCT data suggests maybe PFS improvement but no OS improvement
  - Why is there is difference between retrospective data and RCT?
  - Is PFS worthwhile?

Blumenthal, NeuroOnc 2017

Case 1 Prognosis

- 59 yr old right-handed man
  - 2 weeks history of increasing headaches
  - Sudden onset speech problems and facial drooping
  - Admitted as ? CVA
  - ECOG PS = 1

	Population 1* (n=573, 547 used, 498 deaths)		Radiotherapy alone (n=286, 274 used, 263 deaths)		Population 2† (n=287, 273 used, 235 deaths)		Population 3‡ (n=103, 97 used, 77 deaths)	
	HR (95% CI)	p (% inclusion)	HR (95% CI)	p (% inclusion)	HR (95% CI)	p (% inclusion)	HR (95% CI)	p (% inclusion)
Treatment assignment								
Temozolomide and radiotherapy	1·00	<0·0001 (99·6)	NI	NI	NI	NI	NI	NI
Radiotherapy	1·60 (1·34–1·91)		NI	NI	NI	NI	NI	NI
MGMT promoter methylation status								
Methylated	NI	NI	NI	NI	NI	NI	1·00	..
Unmethylated	NI	NI	NI	NI	NI	NI	2·75 (1·68–4·49)	<0·0001 (92)
Age (years)§								
≤50	..	0·003 (82)		NS (29)	..	0·008 (80)		NS (37)
51–60	1·19 (1·06–1·34)	..	1·12 (0·95–1·32)	..	1·26 (1·06–1·48)	..	1·32 (0·95–1·84)	..
>60	..	..	..	..	..	..	..	..
WHO performance status§								
0	..	NS (48)	..	NS (8)	..	0·006 (78)	..	0·003 (82)
1	1·12 (0·98–1·28)	..	0·98 (0·82–1·19)	..	1·32 (1·08–1·60)	..	1·76 (1·21–2·55)	..
2	..	..	..	..	..	..	..	..
Interaction term between performance status and treatment	0·99 (0·82–1·19)	NS (40)	NI	NI	NI	NI	NI	NI
Extent of surgery§								
Complete resection	..	<0·0001 (96)	..	0·007 (80)	..	0·0004 (75)	..	NS (7)¶
Partial resection	1·33 (1·17–1·52)	..	1·29 (1·07–1·55)	..	1·37 (1·14–1·63)	..	1·03 (0·64–1·64)	..
Biopsy	..	..	..	..	..	..	..	..
Tumour location								
Unilobal	1·00	NS (30)	1·00	NS (13)	1·00	NS (52)	1·00	NS (41)
Central and multilobal	1·17 (0·92–1·50)	..	0·94 (0·66–1·33)	..	1·40 (0·99–1·97)	..	1·62 (0·80–3·29)	..
MMSE score								
27–30	1·00	<0·0001 (98)	1·00	<0·0001 (89)	1·00	0·0009 (79)	1·00	0·008 (81)
<27	1·63 (1·34–1·98)	..	1·71 (1·31–2·24)	..	1·66 (1·25–2·19)	..	1·98 (1·20–3·28)	..
Corticosteroids at randomisation								
No	1·00	0·003 (85)	1·00	0·005 (81)	1·00	NS (33)	1·00	NS (12)
Yes	1·36 (1·11–1·67)	..	1·52 (1·13–2·03)	..	1·19 (0·89–1·59)	..	1·17 (0·70–1·97)	..
Sex								
Women	1·00	NS (51)	1·00	NS (22)	1·00	0·03‖ (55)	1·00	NS (10)
Men	1·16 (0·97–1·40)	..	1·13 (0·88–1·46)	..	1·30 (0·99–1·70)	..	1·10 (0·69–1·77)	..
Haemoglobin								
Low (anaemia)	1·00	NS (9)	1·00	NS (9)	1·00	NS (36)	1·00	NS (21)
Normal	1·06 (0·86–1·31)	..	0·96 (0·72–1·28)	..	1·33 (0·98–1·81)	..	1·44 (0·85–2·46)	..
C-index corrected for optimism	65%		NI		63%		66%	

Case 1 Prognosis

https://www.eortc.be/tools/gbmcalculator/

- 59
- PS 1
- TMZ/RT
- Surgery
  - 12.3 months (Bx)
  - 14.8 (STR)
  - 18.5 (GTR)

- Doesn't include MGMT!

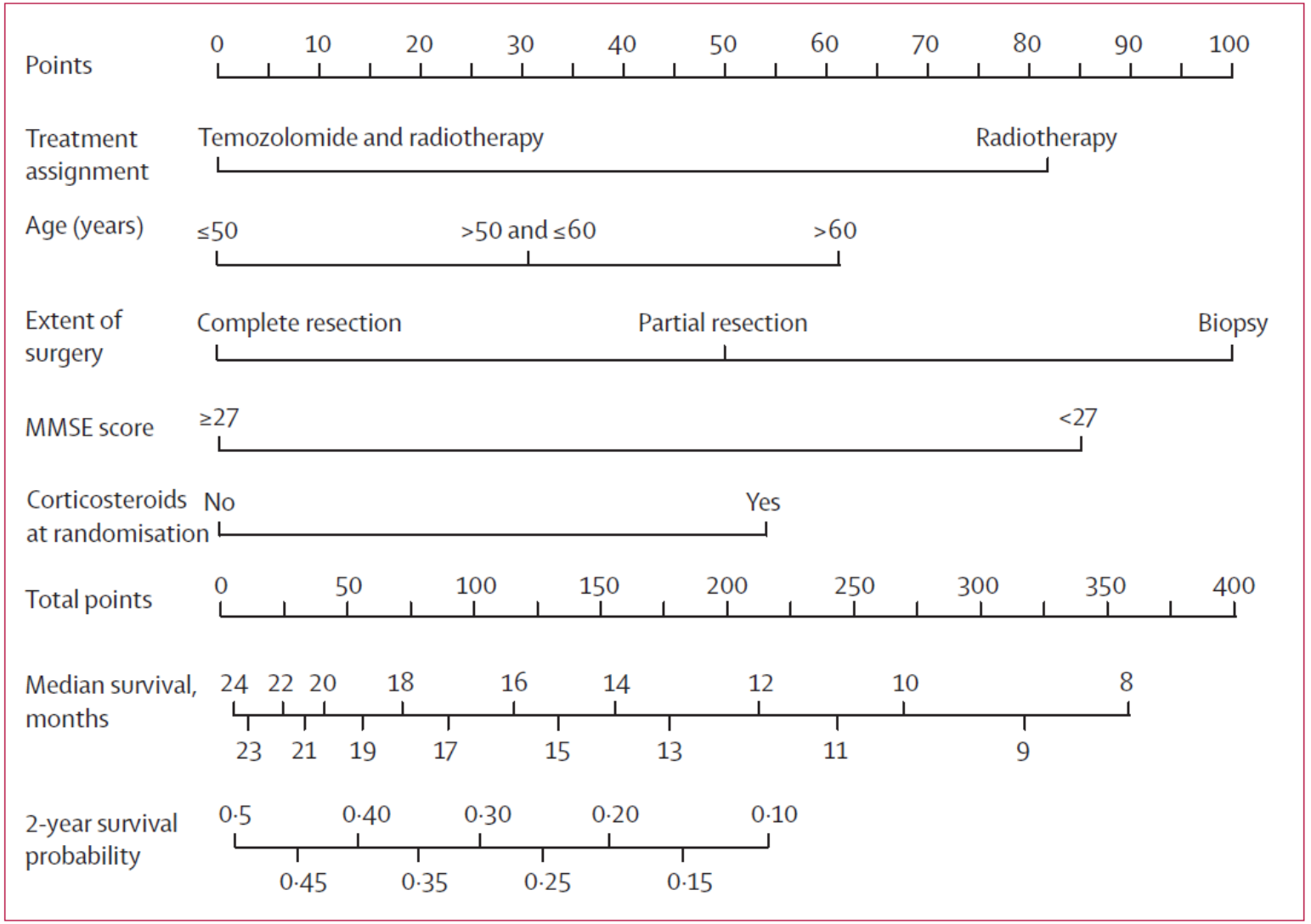
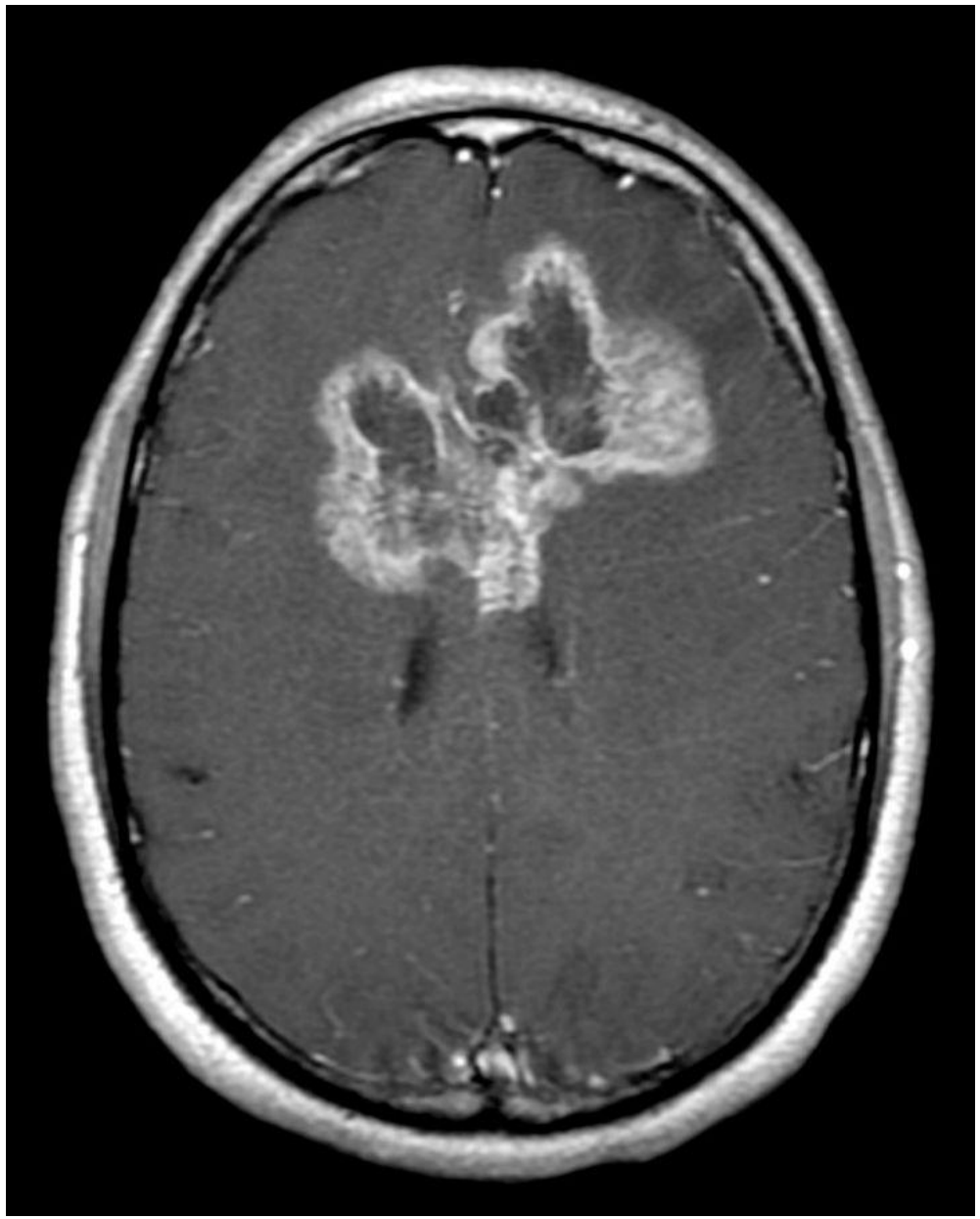


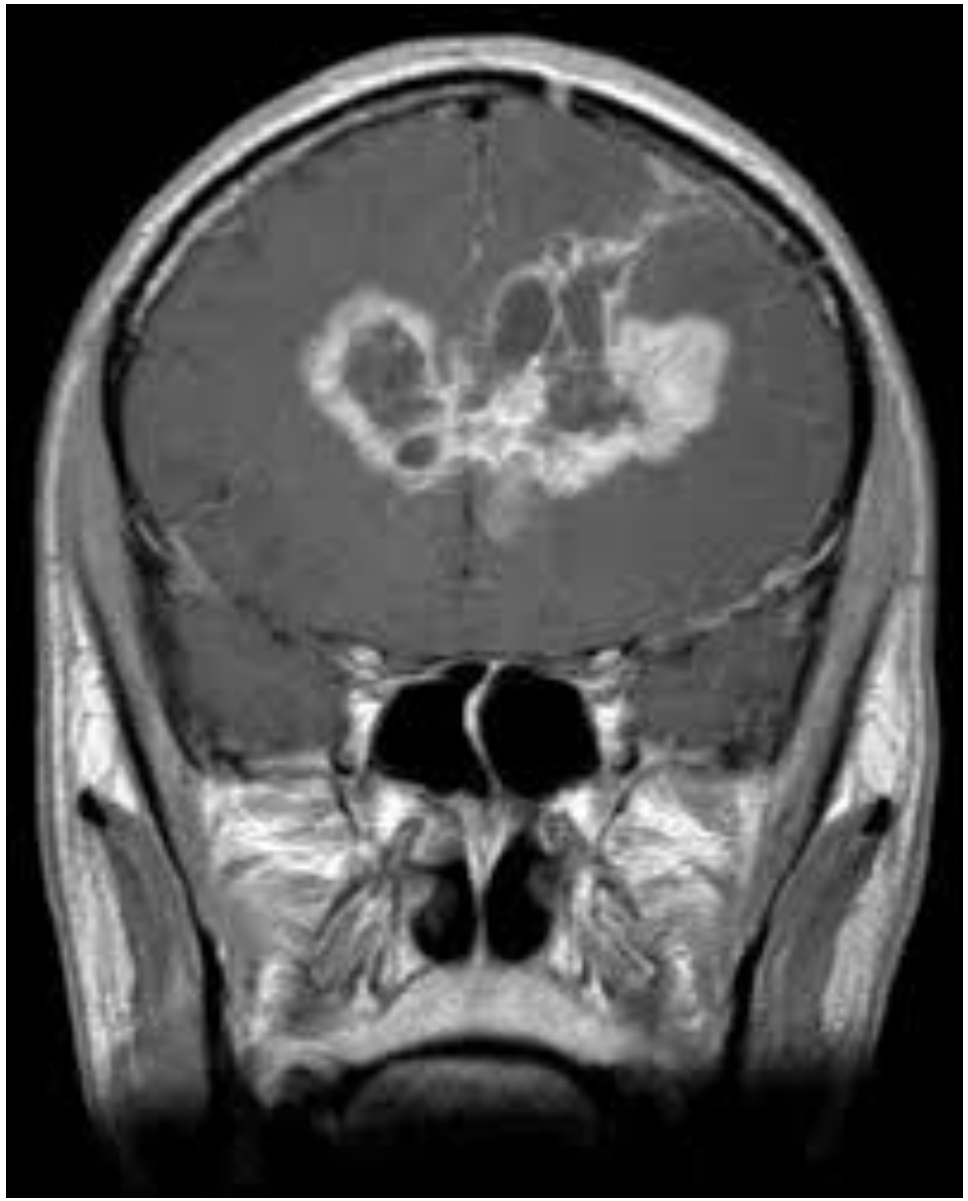
Figure 1: Nomogram for predicting median survival and probability of survival at 2 years in all randomised patients (population 1)

Case 1 Questions ?

Case 2

- 81 yr old man
  - Admitted with problems walking and not coping at home
  - Previously very well
  - ECOG PS = 3
  - Improved with steroids





Case 2

- Role of surgery ?
- Role of RT ?
- Role of chemo ?

Case 2 Surgery

- Is it resectable ?

- Would tissue help otherwise ?

Everything is resectable !

Why put them through a biopsy ?

Role of surgery

- Is the lesion resectable?
  - What would a biopsy accomplish ?
- What are subsequent treatment options ?
- What are the likely outcomes ?
  - 30 day mortality after resection of brain tumours?
  - Functional outcomes ?

Case 2

- Likely to be a GBM
- Prognostic factors in GBM:
  - Age: Elderly $<_{OS}$ Young
  - Surgery: Complete Resection $>_{OS}$ Incomplete Resection $>_{OS}$ Biopsy
  - Performance Status: Good PS $>_{OS}$ Low PS
  - MGMT: MGMT-meth $>_{OS}$ MGMT-unmeth

  - Older literature grouped grade 3 & 4: Grade 3 $>_{OS}$ Grade 4

Case 2: Age

	Patients Age <65 y, *n* = 110	Patients Age ≥65 y, *n* = 42	
Mean age, y (range)	51.6 (23–64)	71.9 (65–83)	$P < .0001$
Median KPS (range)	80 (40–100)	80 (40–100)	$P = .0737$
Extent of operation, *n*			$P = 1.0$
Resection	97 (88%)	37 (88%)	
Biopsy	13 (12%)	5 (12%)	
Initial treatment, *n*			$P = .364$
RT + TMZ	91 (83%)	32 (65%)	
RT alone	19 (17%)	10 (24%)	
MGMT promoter, *n*			$P = .851$
Methylated	39 (35%)	16 (38%)	
Unmethylated	71 (65%)	26 (62%)	

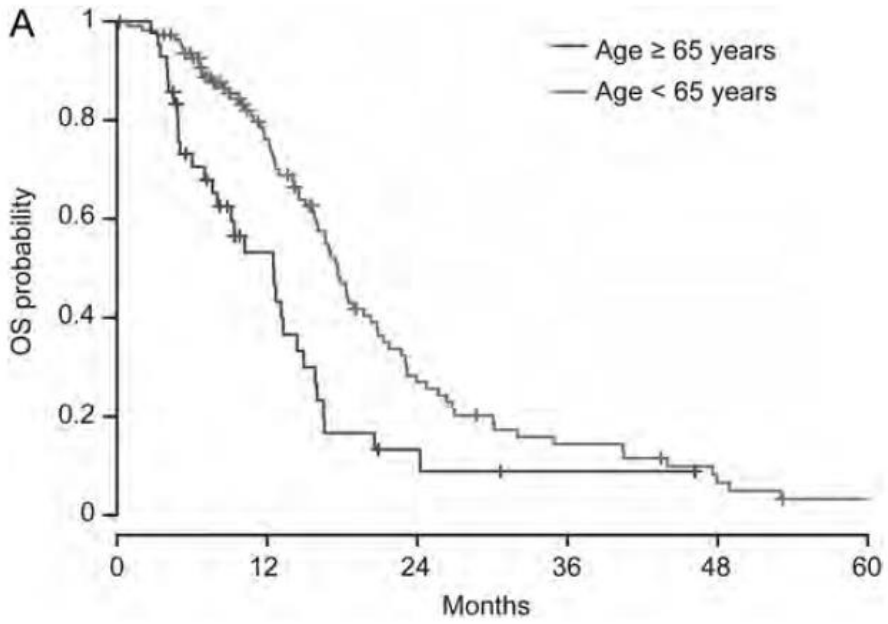


Fig. 3. Survival by age in TCGA collective. (A) OS of G-CIMP–negative patients, stratified by age (<65 vs ≥65 y).

Wiestler, NeuroOnc2013

Case 2: Age

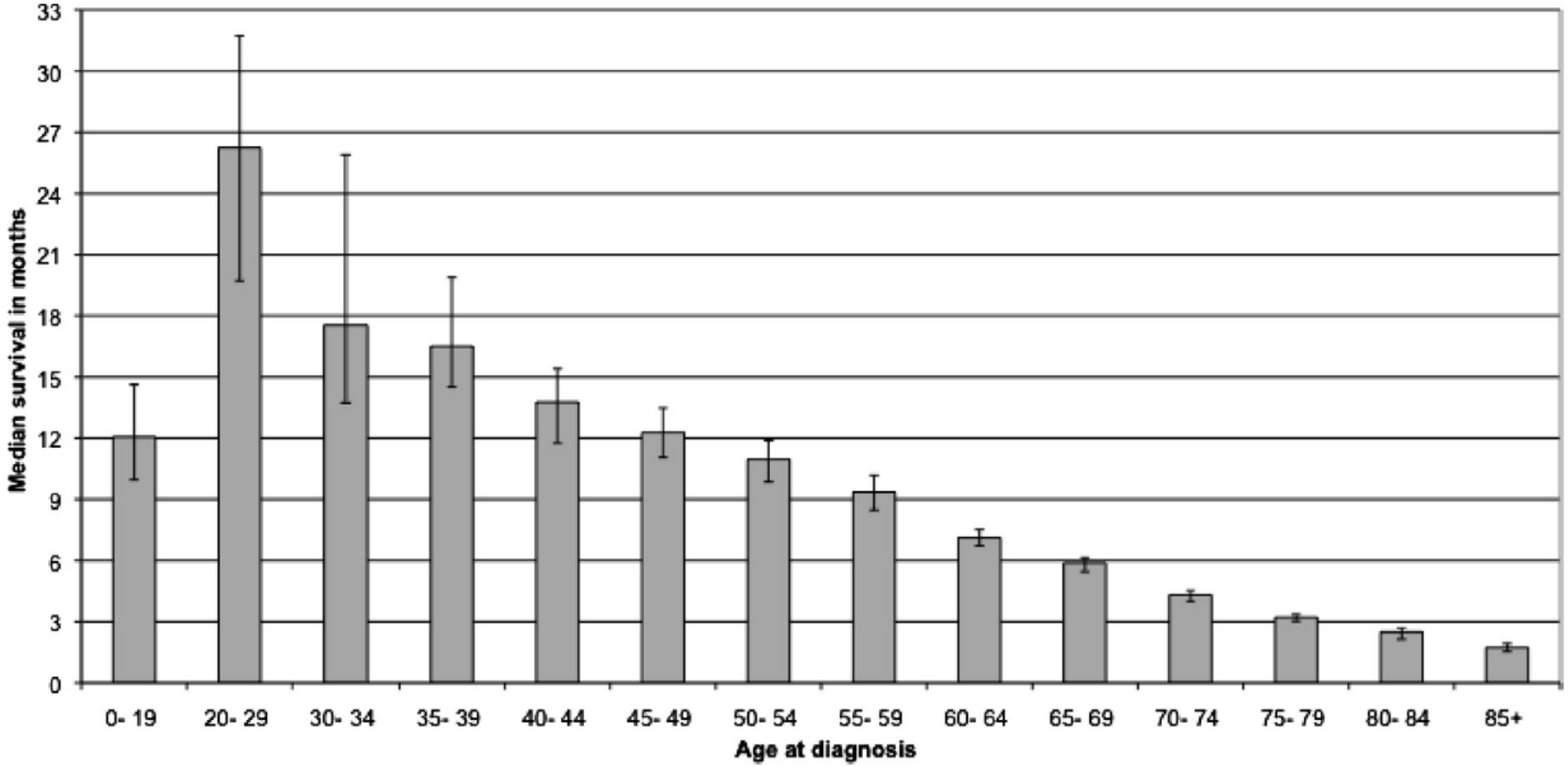


Fig. 4. Median life expectancy in months for patients with a GBM by age. There is a significant stepwise reduction in life expectancy with increasing age $\geqslant$20 years ($p < 0{\cdot}0001$). Bars denote 95% confidence intervals.

Brodbelt, EJC 2015

Case 2

- 81 yr old man with an iresectable GBM
  - Treatment options – RT or chemo
  - Historically, RT has a prognosis of ~ 6/12
    - Probably worse given lack of surgery

- Biopsy allows for MGMT-testing
  - NOA-8 study
  - Nordic

Case 2

- NOA-8 study
  - 412 pts; GBM or G3 Astrocytoma; >65 yr old; Non-inferiority 25% margin
    - TMZ 100mg/m2 d1-7q14 or
    - RT 60 in 30
  - Median OS 8/12
  - 73/209 pts were MGMT-meth
  - MGMT-meth $>_{MedianOS}$ MGMT-non-meth (12 vs 8 months)
  - MGMT-meth & TMZ $>_{EFS}$ MGMT-meth & RT
  - MGMT-non-meth & RT $>_{EFS}$ MGMT-non-meth & TMZ

Wick Lancet Onc 2012

Case 2

- Nordic study
  - 291 pts; GBM; >60 yr old
    - TMZ 200mg/m2 d1-5q28 or
    - RT 60 in 30 or
    - RT 34 in 10
  - Median OS 8/12 with RT_{34} or TMZ (~6/12 with RT_{60})
  - GBM >70yr old; $RT_{34} >_{OS} RT_{60}$
  - GBM >70yr old; TMZ $>_{OS} RT_{60}$
  - GBM >70yr old; $RT_{34} \sim_{OS}$ TMZ
  - Toxicity non-zero (3 deaths ~1%TRM)

Malmstrom LancetOnc 2012

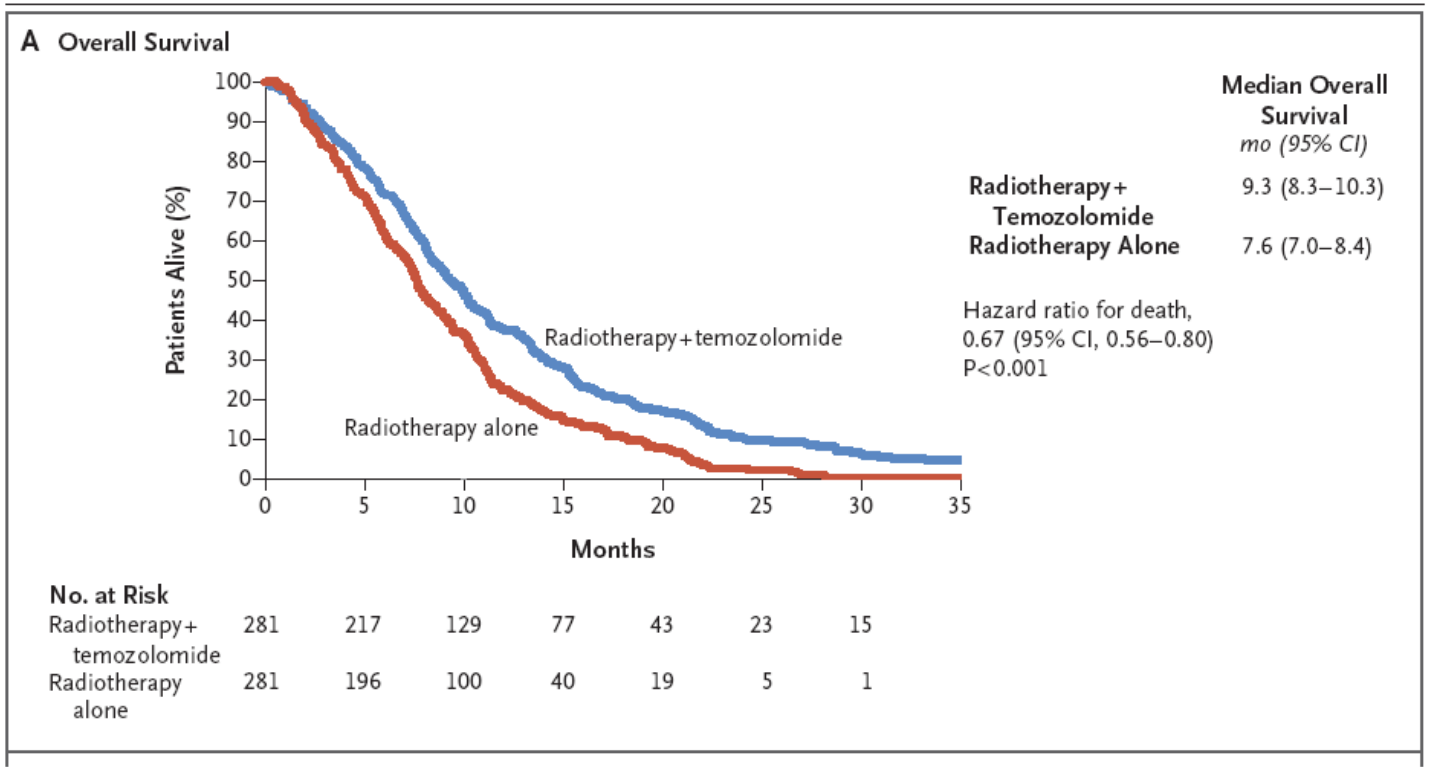
Case 2

- IAEA trial
  - 98 pts; GBM; >50 & KPS 50 – 70; >65 KPS 50 - 100
    - RT 25Gy/5# vs. 40Gy/15#
    - $RT_{25} \sim_{OS} RT_{40}$
    - $RT_{25} \sim_{PFS} RT_{40}$
    - However, not pre-specified non-inferiority trial

Roa JCO 2016

Case 2

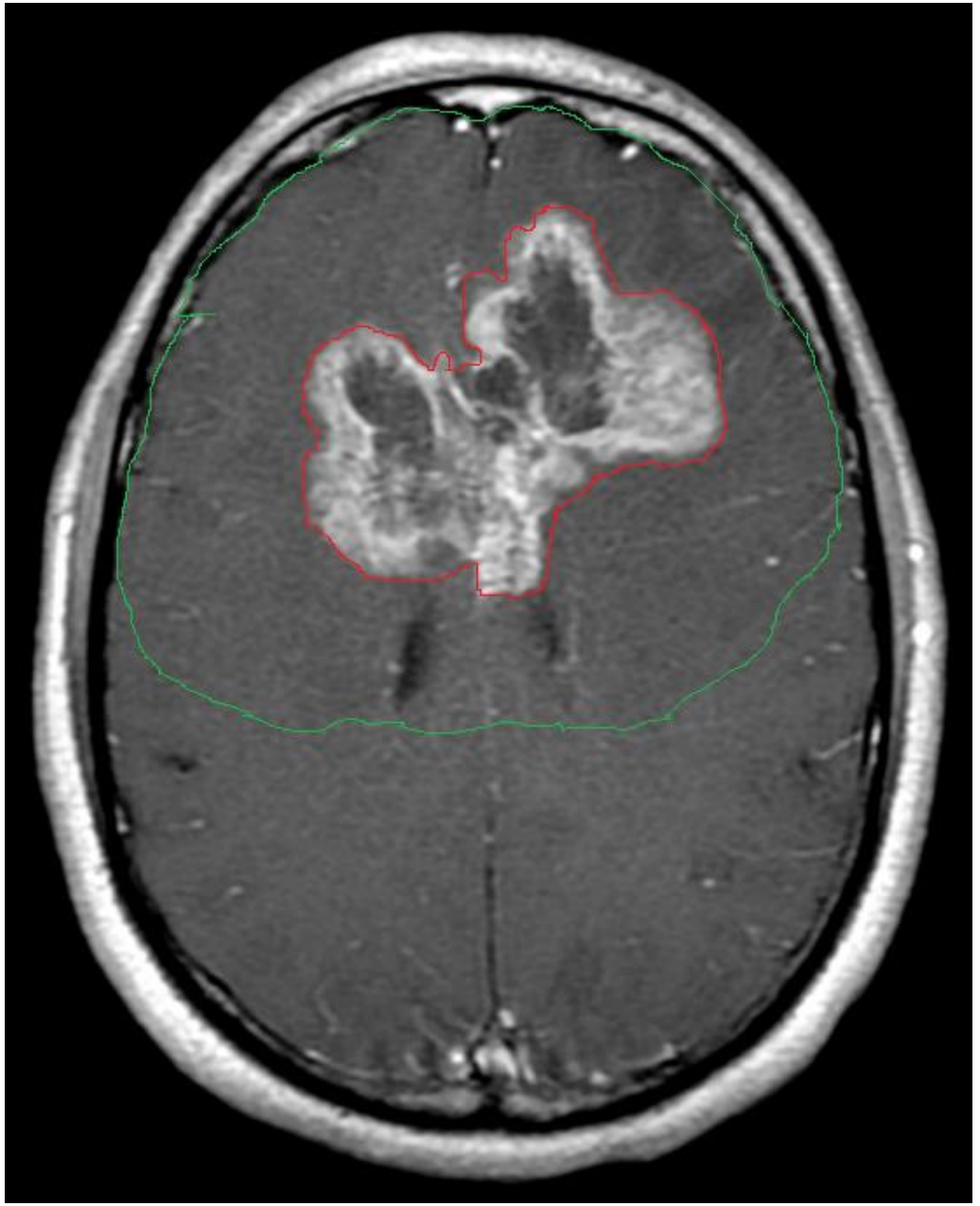
- Chemo-RT in the elderly (>65)
  - 30% > 76 yo
  - ECOG PS 0 - 2



Perry NEJM 2017

RT Margins

- GTV = CE area
- CTV = GTV +2 – 3 cm
  - Check T2 abnormality



Treatment options

- No treatment (BSC) or Treatment
- RT or TMZ
  - 30Gy/6#
  - OR 40/15 with Chemo
  - OR 25/5

Treatment options

- No treatment (BSC) or Treatment
- RT or TMZ
  - 30Gy/6#
  - OR 40/15 with Chemo
  - OR 25/5

This is a mess

What’s the best thing to do ?

Some practical considerations

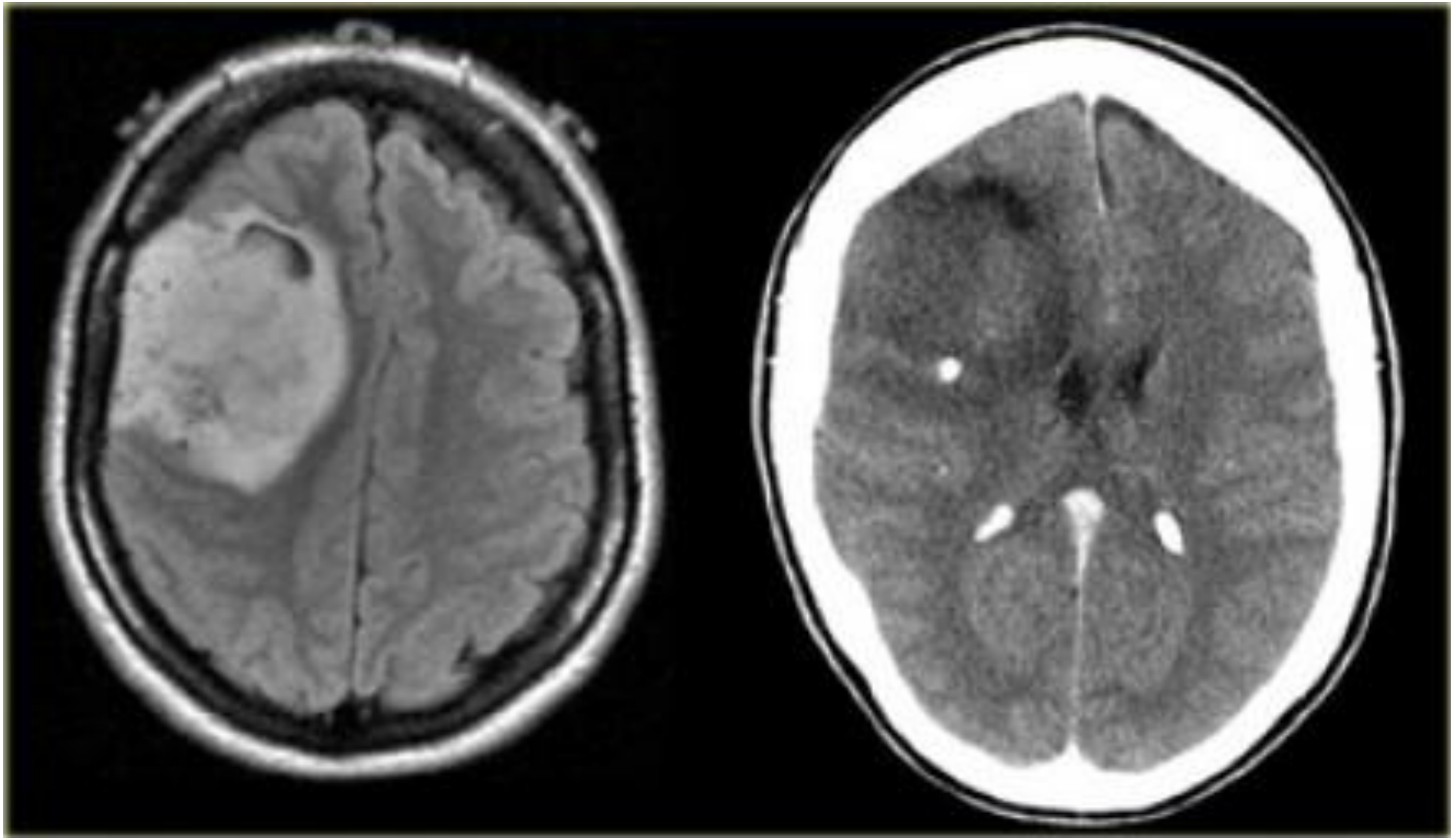
- Biopsy and MGMT testing may take weeks
  - Likely survival is ~4 – 8 months
  - Might get functional improvement with treatment (?how common)
  - May delay functional decline
- We suggest either CRT (if fit) OR surgery and RT OR Nothing

- Simultaneously address:
  - Discharge planning
  - Palliative & End-of-life care
  - Rehabilitation (OT/ PT)

Case 2 Questions ?

Case 3

- 37 yr old left-handed woman
  - Diagnosed with a ‘low-grade glioma’ 8 years ago
  - Well
  - Admitted following a single seizure
  - Clinically well
  - ECOG PS = 0



Case 3

- Lesion is likely to be an intermediate grade tumour
  - Age
  - History
  - Prolonged non-progression

- Historically divided into Grade 2 or Grade 3
  - We have known that they have variable outcomes
  - Age, histology, neurological status, tumour size, grade are prognostic
  - And yet still much variability

Case 3 pathology

- Note that grade is still important
- But for grade 2/3, mol pathology is important
- But there are other factors
  - Age
  - Performance Status
  - Surgical resectability
  - rCBV on perfusion MRI

- We do not yet know how to integrate these
  - Don’t yet appear in the WHO classification

Brief detour

- This is a generic problem
- We know a,b and c are important
- We know how they relate to each other and outcomes
  - Then we show that x and y are more important than a
  - Now we have x and y, b and c
  - But we don’t know how they relate to each other…

  - Updating multi-parameter models with non-independence of parameters
  - Significant underlying technical challenge

Case 3 pathology

- Partial resection
  - ~4cc of tissue
- Molecular pathology shows Grade 3 astrocytoma
  - 1p/19q co-deleted
  - IDH-1 mutated
  - MGMT methylated

Case 3 pathology

- Partial resection
  - ~4cc of tissue
- Molecular pathology shows Grade 3 astrocytoma
  - 1p/19q co-deleted
  - IDH-1 mutated
  - MGMT methylated

What does this mean ?

Case 3 Management

- How would you interpret the pathology ?
- Treatment ?
- Prognosis ?

Case 3 Management

- How would you interpret the pathology ?

A: GBM
B: Anaplastic Astro (Grade 3)
C: Anaplastic Oligo (Grade 3)
D: Anaplastic OligoAstro (Grade 3)
E: Astrocytoma (Grade 2)

(Report: Grade 3 astrocytoma; 1p/19q co-deleted; IDH-1 mutated; MGMT methylated)

Case 3 Pathology

- Molecular pathology shows Grade 3 astrocytoma
  - 1p/19q co-deleted
  - IDH-1 mutated
  - MGMT methylated

- This is a grade 3 oligodendroglioma
  - 1p/19q co-deletion is prognostic AND predictive

Case 3 Pathology

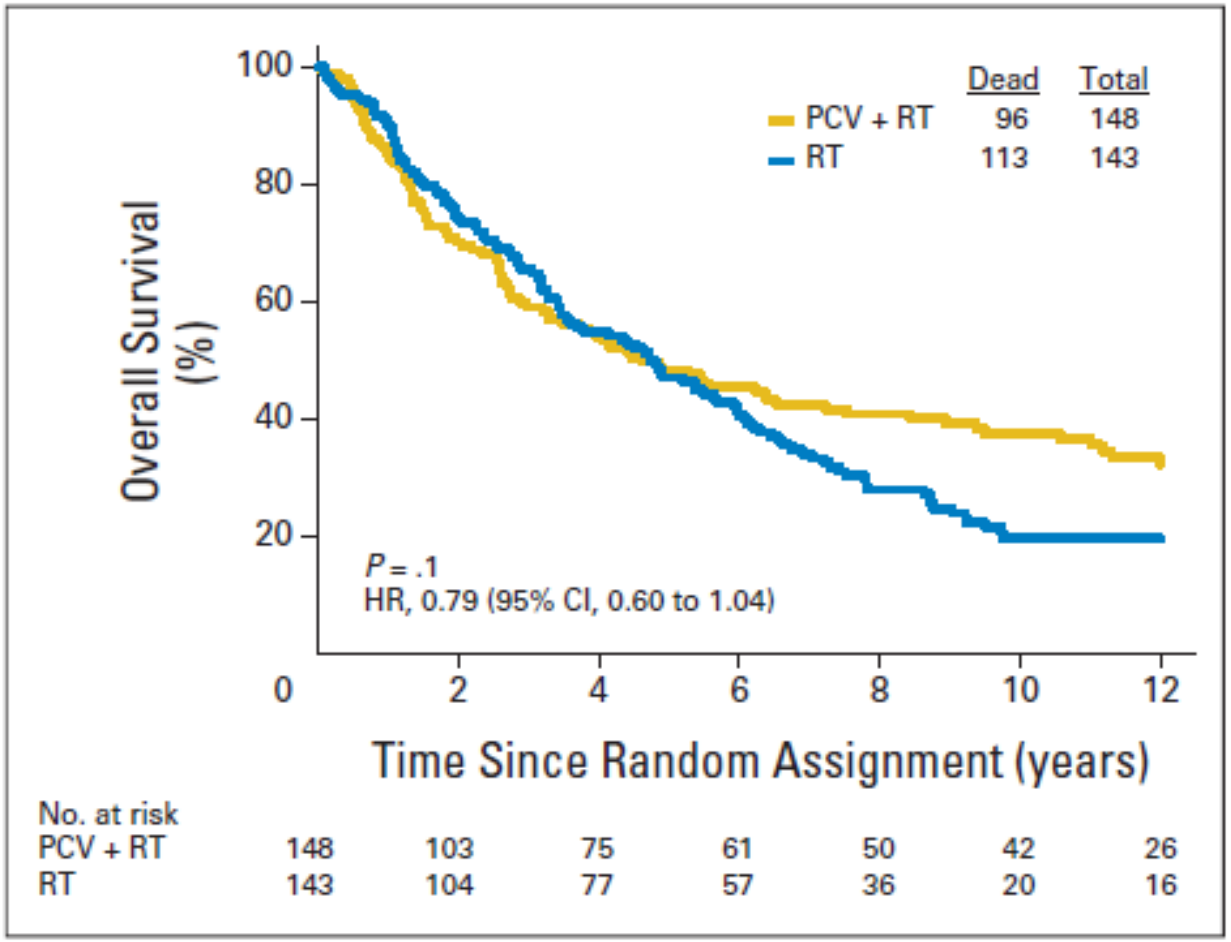


Fig 2. Kaplan-Meier estimates of overall survival by treatment group. The hazard ratio (HR) for survival of patients treated with procarbazine, lomustine, and vincristine (PCV) plus radiotherapy (RT) compared with RT alone was 0.79 (95% CI, 0.60 to 1.04; $P = .1$).

Prognostic – 1p/19q better for both arms

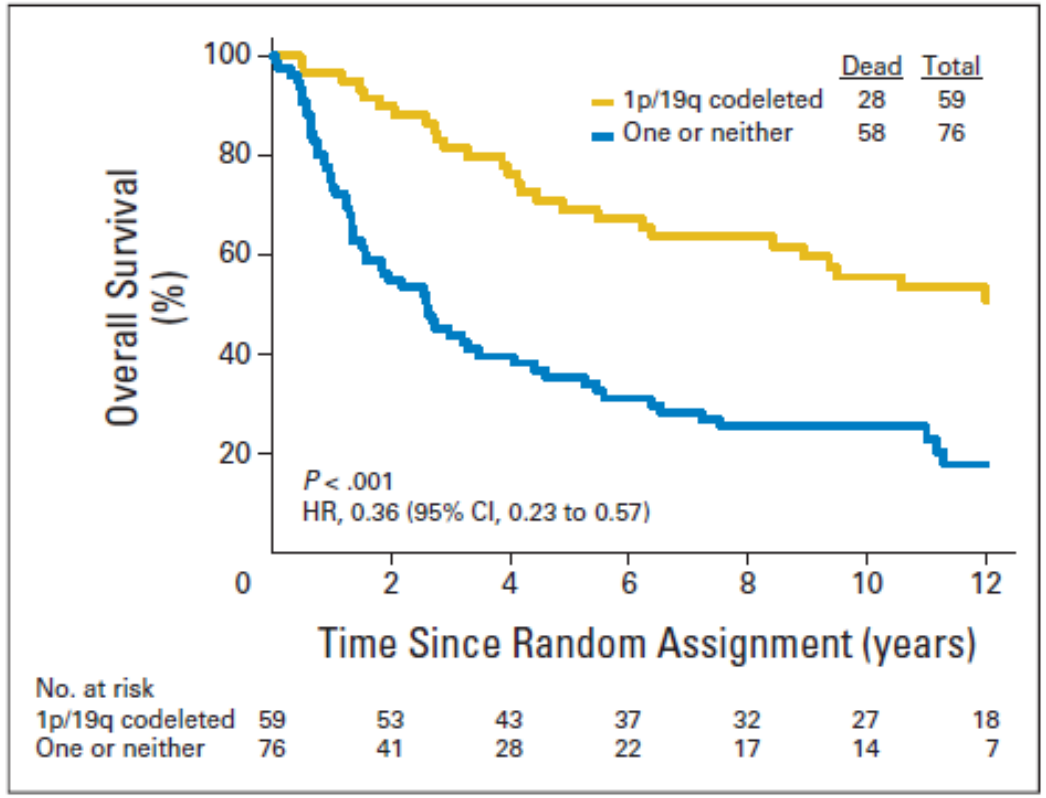


Fig 3. Kaplan-Meier estimates of overall survival by genotype for procarbazine, lomustine, and vincristine plus radiotherapy arm. The hazard ratio (HR) for overall survival of patients with 1p/19q codeleted anaplastic oligodendroglioma (AO)/anaplastic oligoastrocytoma (AOA) compared with those with AO/AOA in whom one or neither allele was deleted was 0.36 (95% CI, 0.23 to 0.57; $P < .001$).

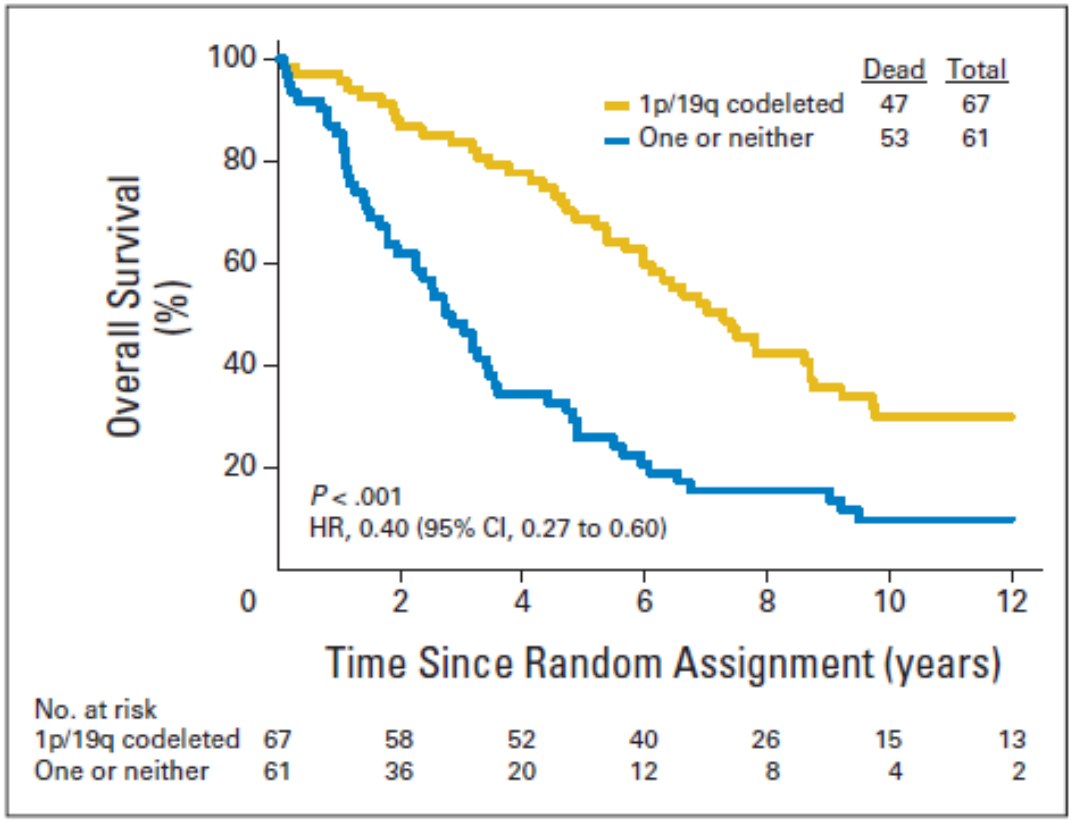


Fig 4. Kaplan-Meier estimates of overall survival by genotype for radiotherapy arm. The hazard ratio (HR) for overall survival of patients with 1p/19q codeleted anaplastic oligodendroglioma (AO)/anaplastic oligoastrocytoma (AOA) compared with those with AO/AOA in whom one or neither allele was deleted was 0.40 (95% CI, 0.27 to 0.60; $P < .001$).

Predictive

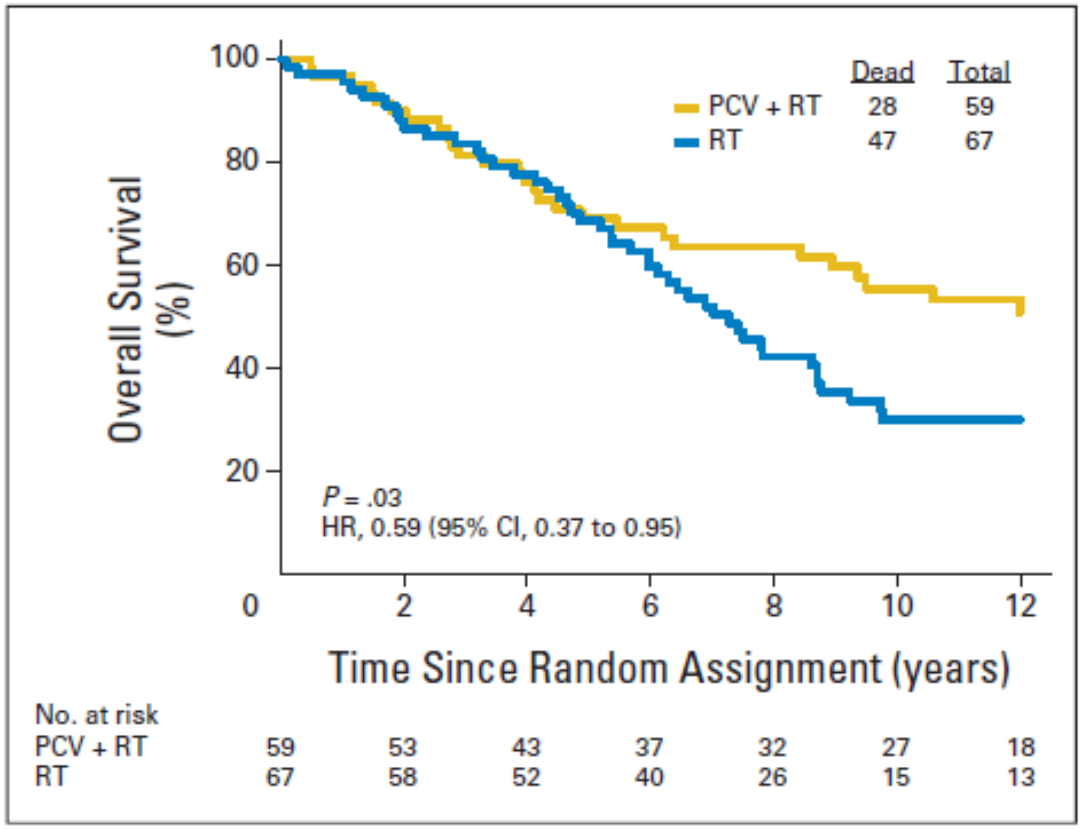


Fig 5. Kaplan-Meier estimates of overall survival by treatment for patients with 1p/19q codeleted anaplastic oligodendroglioma (AO)/anaplastic oligoastrocytoma (AOA). The hazard ratio (HR) for overall survival of patients with codeleted AO/AOA treated with procarbazine, lomustine, and vincristine (PCV) plus radiotherapy (RT) compared with those treated with RT alone was 0.59 (95% CI, 0.37 to 0.95; $P = .03$).

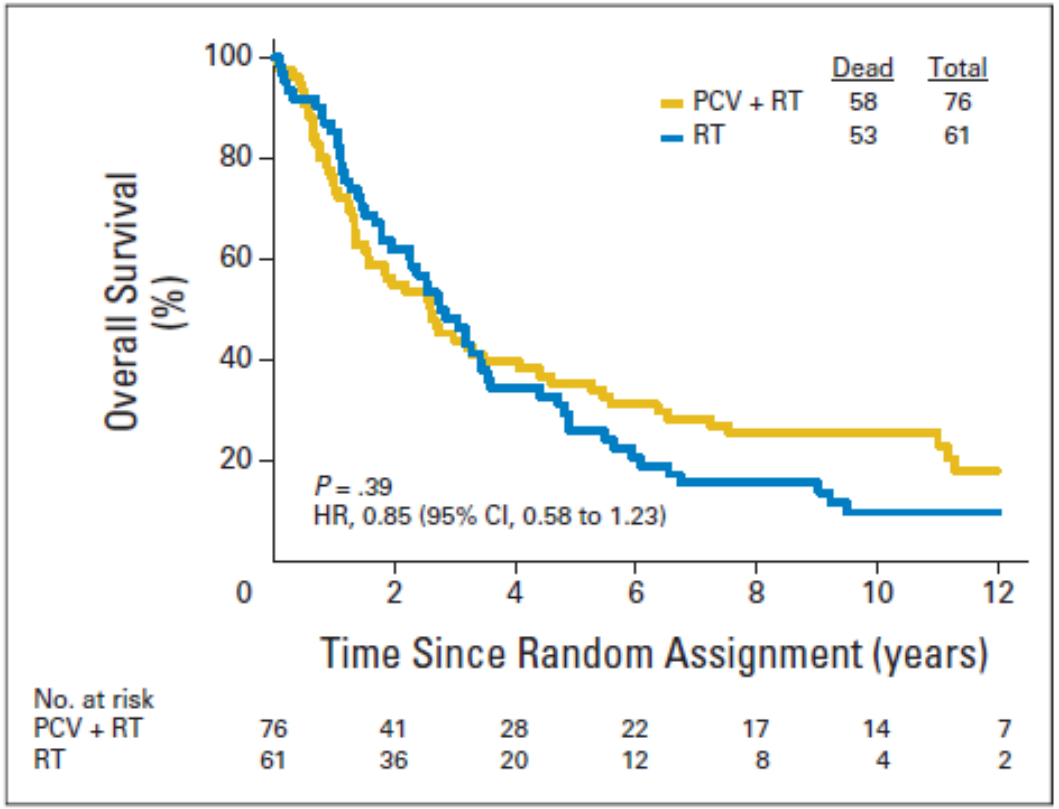


Fig 6. Kaplan-Meier estimates of overall survival by treatment for patients with anaplastic oligodendroglioma (AO)/anaplastic oligoastrocytoma (AOA) in whom one or neither allele (1p or 19q) was deleted. The hazard ratio (HR) for overall survival of those with noncodeleted AO/AOA treated with procarbazine, lomustine, and vincristine (PCV) plus radiotherapy (RT) compared with those treated with RT alone was 0.85 (95% CI, 0.58 to 1.23; $P = .39$).

Case 3 Management

- Treatment:
  - Optimal treatment for G3 oligo is (surgery), RT and chemo
  - G3 ‘oligo’: RT + PCV $>_{OS}$ RT alone
    - 1p/19q is prognostic, as is IDH-1 mutation
    - 1p/19q is also predictive
    - Unclear if there is a role for chemo in non-1p/19q co-deleted tumours

- Prognosis ?

Cainrncross, JCO 2013
van den Bent, JCO 2013

Case 3 Management

- Patient says they will have EITHER RT or chemo, but not both
  - Which would you suggest ?

A: RT
B: Chemo

Case 3 Management

- Patient says they will have EITHER RT or chemo, but not both
  - Which would you suggest ?

  A: RT
  B: Chemo

- NOA-04:
  - RT ~ Chemo (with cross-over)

Wick, JCO 2009

Case 3 Management

- Prognosis ?
  - RT Alone; Chemo alone; RT then chemo
  - Median Survival:

A: <5 Yrs

B: 5 – 10 Yrs

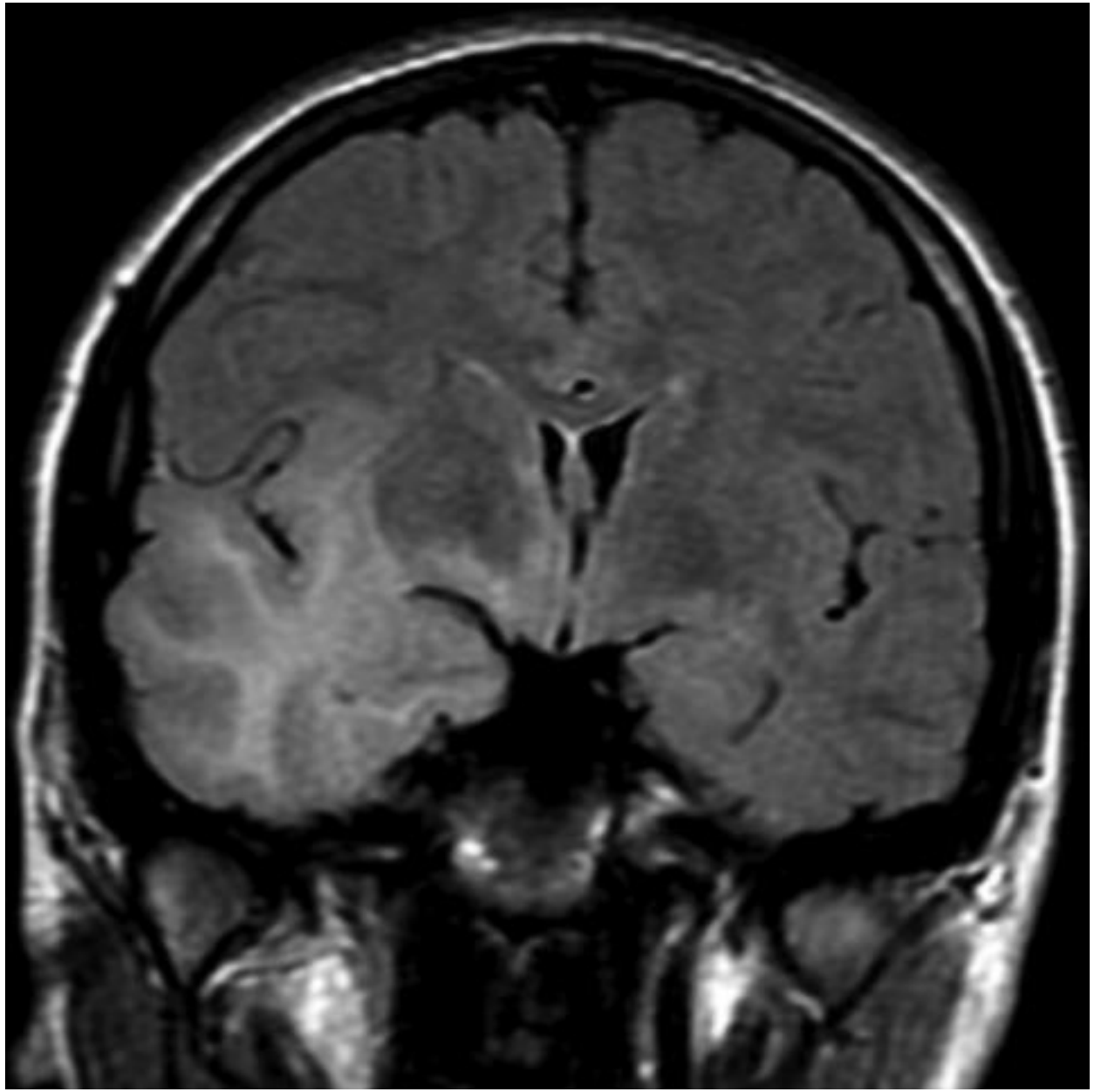
C: 10 – 15 Yrs

D: 15 – 20 Yrs

Case 3 Questions ?

Case 4

- 27 yr old man with increasing sensory symptoms in his left arm
  - Occasionally spreading to left leg and arm
  - Increasing frequency over the last 3 months
  - Otherwise well



Case 4

- What is the likely diagnosis ?
- What is the likely prognosis ?

Case 4 Management

- Young man
- Gradual onset of symptoms
- Imaging more suggestive of low-grade glioma

Case 4 Management

- Most likely to be grade 2 astrocytoma
  - Bx would help
- Prognosis in LGG:

Astrocytoma histology
Age >=40
Tumor >=6 cm
Tumor crossing midline
Neurologic deficit

Risk Group	Score	Median OS
Low risk	0 - 2	7.8 years
High risk	3 - 5	3.7 years

Prognosis in ‘Low risk’ group:
55 yr old, triple-neg
20mm, 4 LN+ve woman with breast cancer

Pignatti, JCO 2002

Case 4 Management

- Most likely to be grade 2 astrocytoma
  - Bx would help
- Prognosis in LGG:

Astrocytoma histology
Age >=40
Tumor >=6 cm
Tumor crossing midline
Neurologic deficit

Risk Group	Score	Median OS
Low risk	0 - 2	7.8 years
High risk	3 - 5	3.7 years

Prognosis in 'Low risk' group:
55 yr old, triple-neg
20mm, 4 LN+ve woman with breast cancer

This is an old study…
Don't you have anything newer ?

Pignatti, JCO 2002

Case 4 Management

- Options:
  - Surveillance
  - Surgery
  - RT
  - Chemo
  - Combination of the above

  - Genuinely think that LGG is one of the most challenging tumours for decision-making
  - Risks of long-term toxicity
  - Under-appreciated impact of tumours

Case 4 Management

- Surgery
  - No randomised data for surgery in LGG
  - Several pieces of evidence favour surgery
    - However, we are balancing OS against functional deficits
    - Very operator and centre dependent
    - Even in large centres, with technology, substantial rates of post-op deficit
  - Early resection hospital $>_{OS}$ Late resection hospital
    - 153 pts from Norway

Jakola, JAMA 2012

Case 4 Management

- Adjuvant therapy
  - RT
  - Chemo
  - Combined
  - Nothing

Case 4 Management

- Early RT $>_{PFS}$ Late RT
- Early RT $\sim_{OS}$ Late RT
- Early RT $\sim_{RiskTrans}$ Late RT

- TMZ ~or $<_{OS}$ RT

- RT + PCV > RT alone
  - RTOG 98-02 (1998 – 2002)
    - RT + PCV $>_{OS}$ RT (13 vs 7 yrs)
    - RT + PCV $>_{PFS}$ RT
- RT + PCV $\sim_{CogFunct}$ RT alone

van den Bent Lancet 2005

Case 4 Management

- RT Dose
  - $RT_{>45} \sim_{OS} RT_{45}$
  - $RT_{>45} <_{Tox} RT_{45}$
- But..
  - RTOG 98-02 used 54/30

Case 4 Management

- Central problem is of risk-stratification
  - JCO risk model
  - EORTC updated risk model
    - Time since first LGG symptoms
    - MRC score
    - Astrocytoma
    - Tumor size >5cm
  - Add other things?
    - Perfusion MRI
    - Etc.

Gorlia, NeuroOnc 2013

Case 4 Management

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  - JCO risk model
  - EORTC updated risk model
    - Time since first LGG symptoms
    - MRC score
    - Astrocytoma
    - Tumor size >5cm
  - Add other things?
    - Perfusion MRI
    - Etc.

This is newer…. But still missing lots of things

Gorlia, NeuroOnc 2013

Case 4 Management

- RTOG 98-02 ‘Low-risk’ group
  - Aged <40 and GTR of tumour (111 pts)
  - 50% PFS at 5 years

Gorlia, NeuroOnc 2013

Case 4 Management

- RTOG 98-02 ‘Low-risk’ group
  - Aged <40 and GTR of tumour (111 pts)
  - 50% PFS at 5 years

That is small group of patients, who have a complete resection

Gorlia, NeuroOnc 2013

Case 4 Pathology

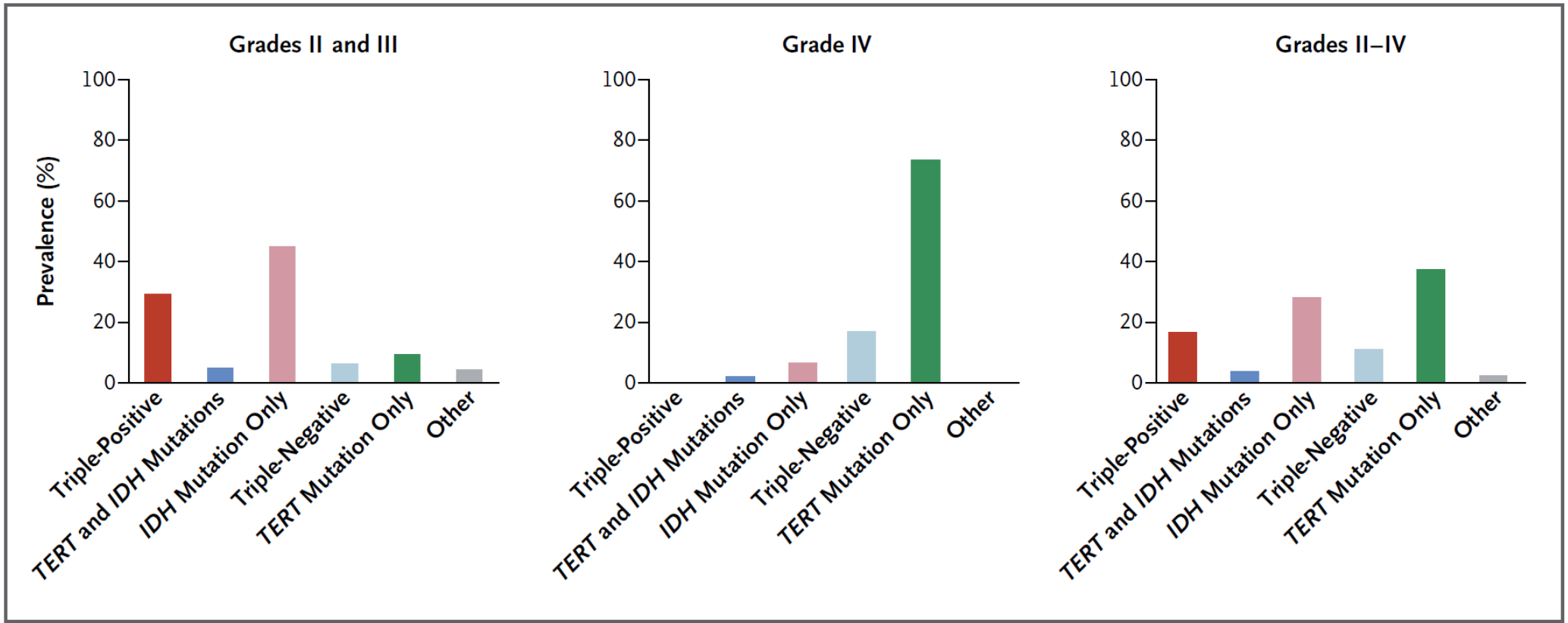
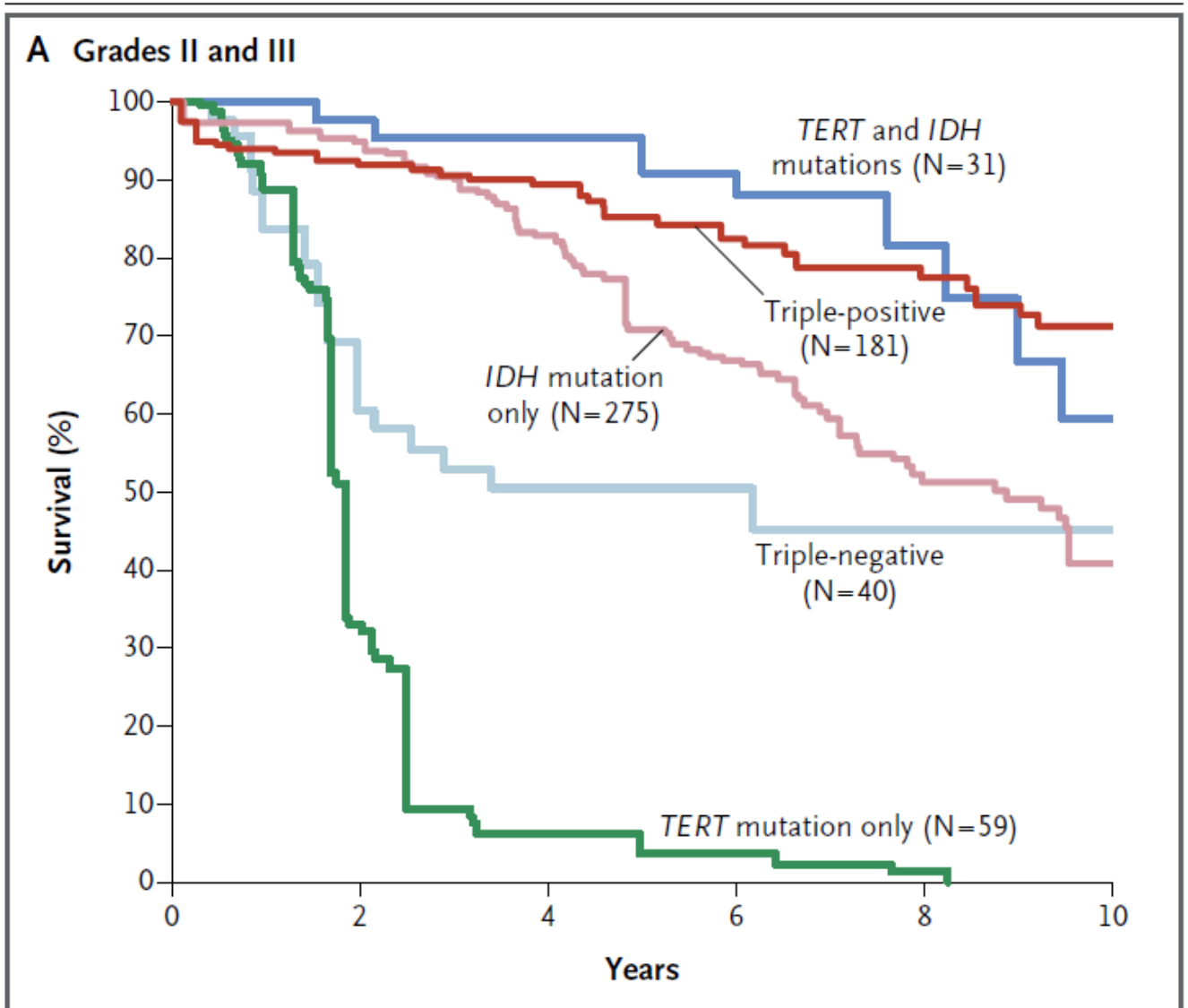


Figure 1. Prevalence of the Glioma Molecular Groups in the Combined Sample.

The prevalence of the molecular groups among gliomas of grade II or III (astrocytomas, mixed oligoastrocytomas, and oligodendrogliomas), grade IV (glioblastoma multiforme), and grades II through IV combined is shown.

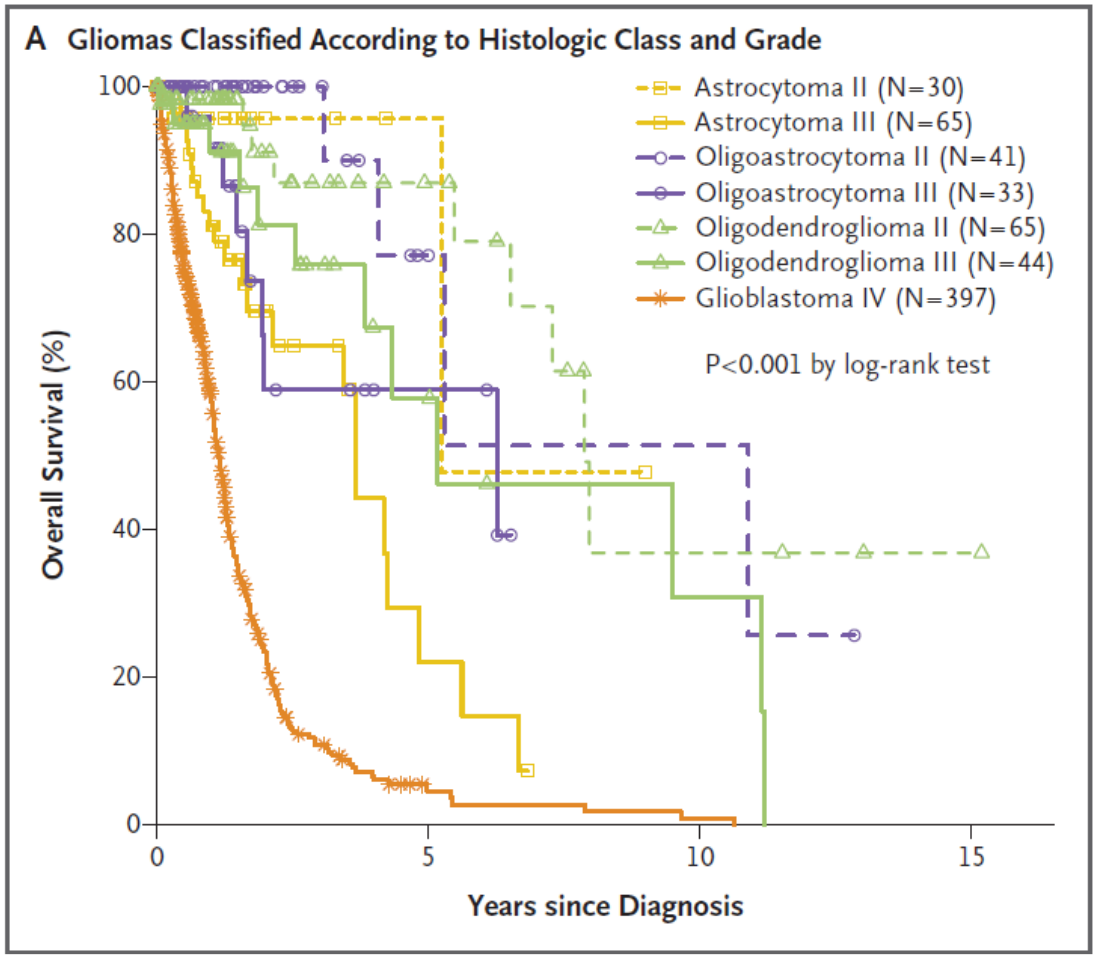
Eckel-Passow NEJM 2015

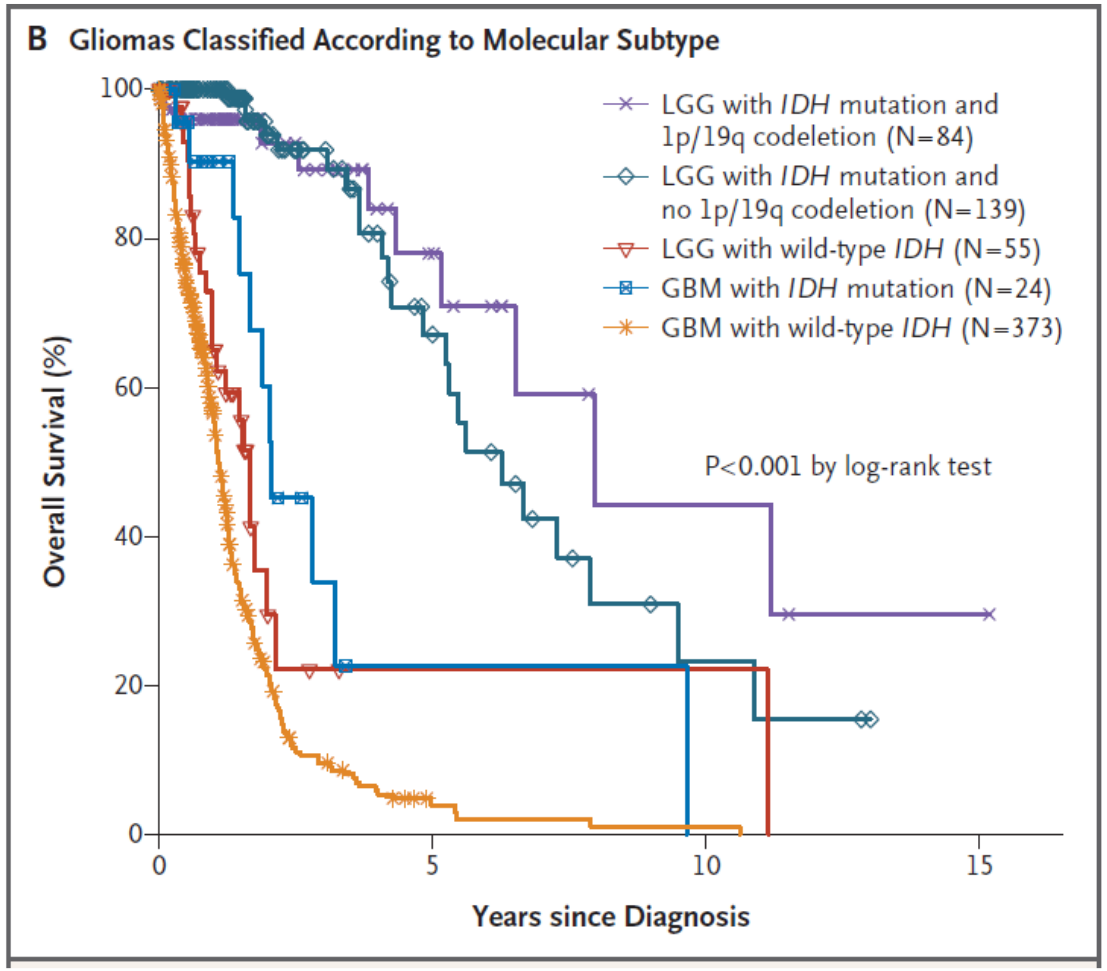
Case 4 Pathology



Eckel-Passow NEJM 2015

Case 4 Pathology





Case 4 Management

- Biopsy shows grade 2 astrocytoma
  - Mol pathology shows:
  - 1p/19q non co-del
  - IDH -1 mutant
  - ATRX wild-type

- Treatment ?
- Prognosis ?

Case 4 treatment

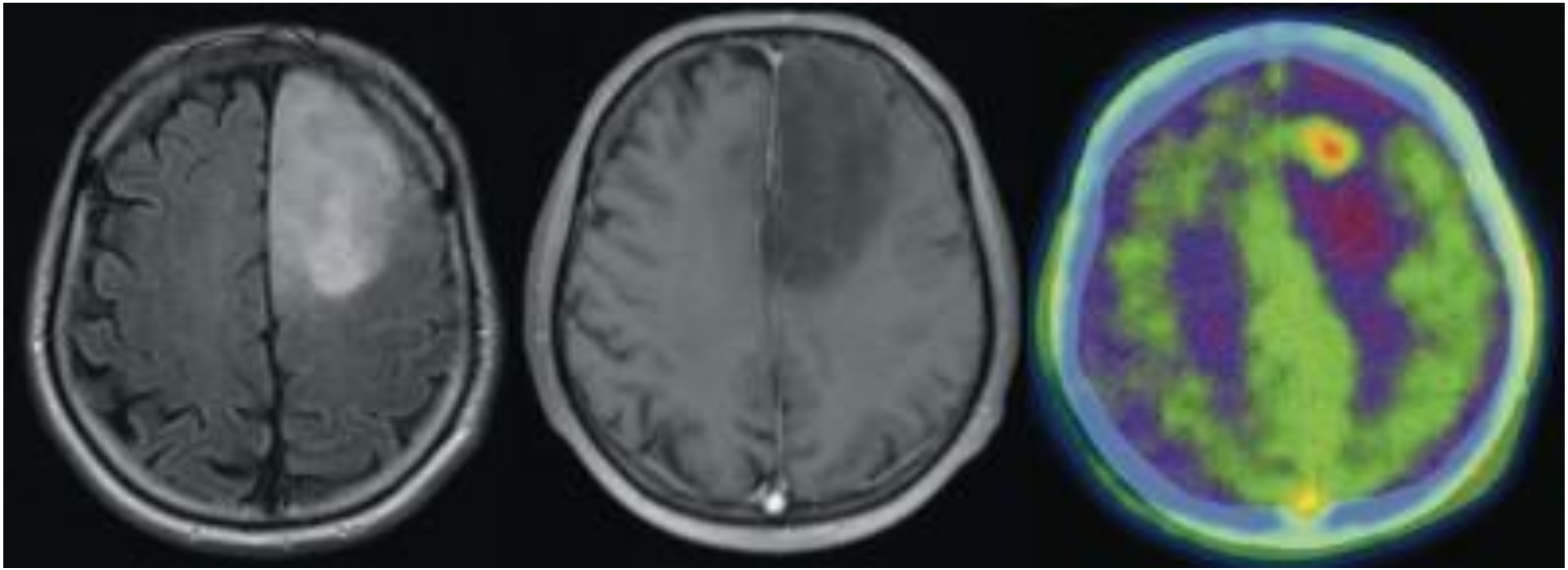
- Suggest Active surveillance
- Biopsy is helpful
- Beware of ‘gentle drift’
  - Often useful to compare imaging over a longer time span

- If we need to treat, then RT + Chemo is better than RT
  - What dose to use ?

Case 4 Questions ?

Case 5

- 55 yr old man
  - Sudden onset facial droop
  - In retrospect, 2 episodes of ‘automatism’ - walked home without remembering it
  - Past history of hypertension and hypercholestrolaemia



Case 5

- What does the imaging suggest ?
- Prognosis ?

Case 5

Astrocytoma histology
Age >=40
Tumor >=6 cm
Tumor crossing midline
Neurologic deficit

Risk Group	Score	Median OS
Low risk	0 - 2	7.8 years
High risk	3 - 5	3.7 years

Time Since first symptoms (30 wks; longer better)

MRC score (No probs/ some or major deficit)

Astrocytoma

Tumour size (5cm)

Case 5

Astrocytoma histology
Age >=40
Tumor >=6 cm
Tumor crossing midline
Neurologic deficit

Risk Group	Score	Median OS
Low risk	0 - 2	7.8 years
High risk	3 - 5	3.7 years

Newer EORTC still doesn't include molecular pathology

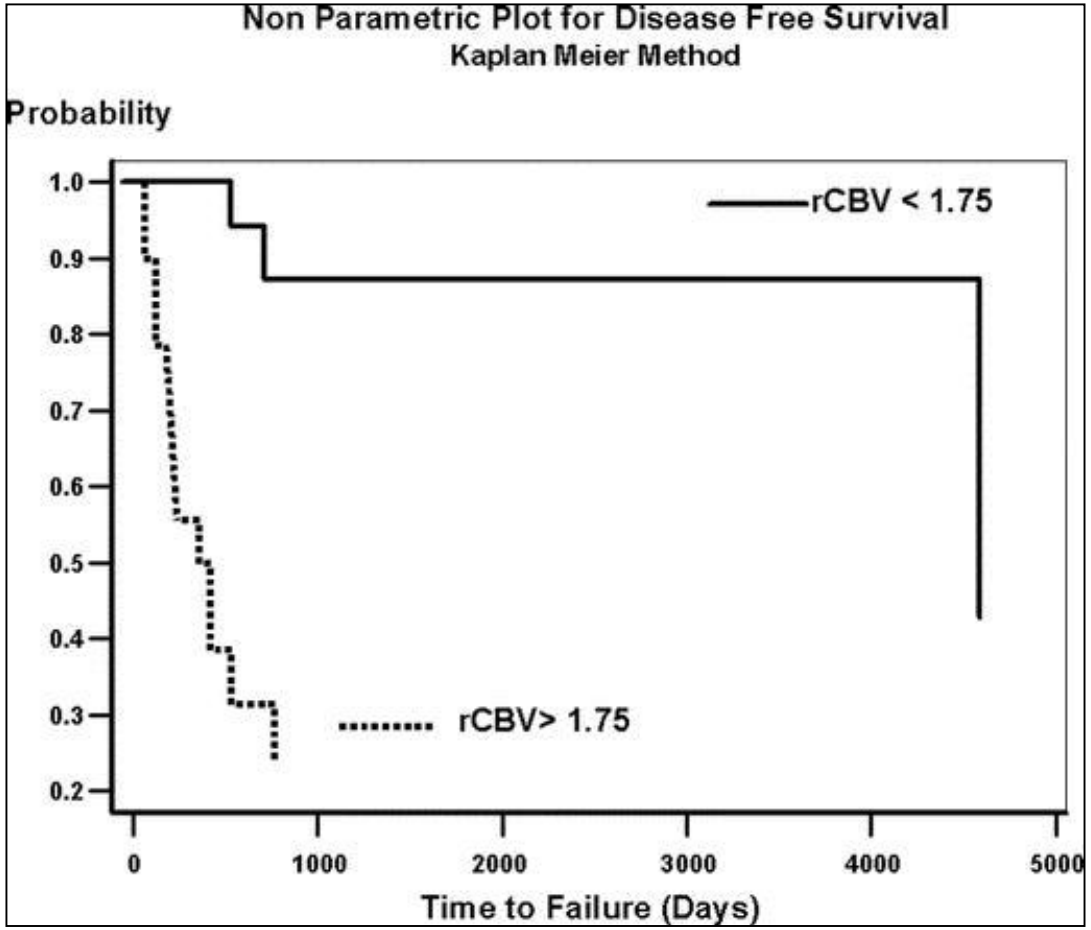
Time Since first symptoms (30 wks; longer better)

MRC score (No probs/ some or major deficit)

Astrocytoma

Tumour size (5cm)

Role of rCBV



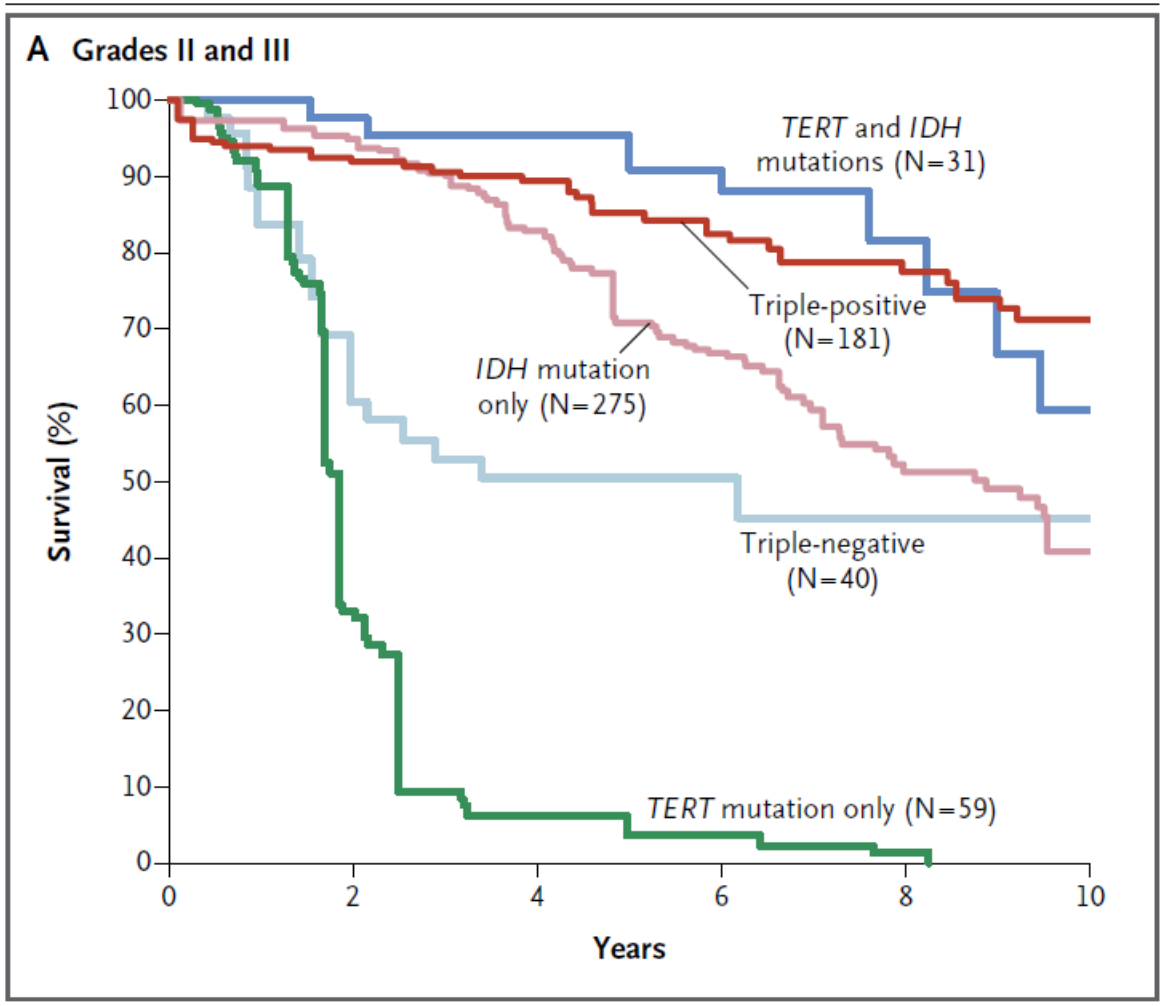
Perfusion Magnetic Resonance Imaging Predicts Patient Outcome as an Adjunct to Histopathology: A Second Reference Standard in the Surgical and Nonsurgical Treatment of Low-grade Gliomas.
Law, Meng; Oh, Sarah; Johnson, Glyn; Babb, James; Zagzag, David; Golfinos, John; Kelly, Patrick

Neurosurgery. 58(6):1099-1107, June 2006.
DOI: 10.1227/01.NEU.0000215944.81730.18

Case 5 Prognosis

- ‘Conventional’ prognosis
- Functional imaging adds to this
  - Also adds info on targeting of surgery

- Bx shows
  - IDH-wt
  - TERT-wt
  - No 1p/19q loss



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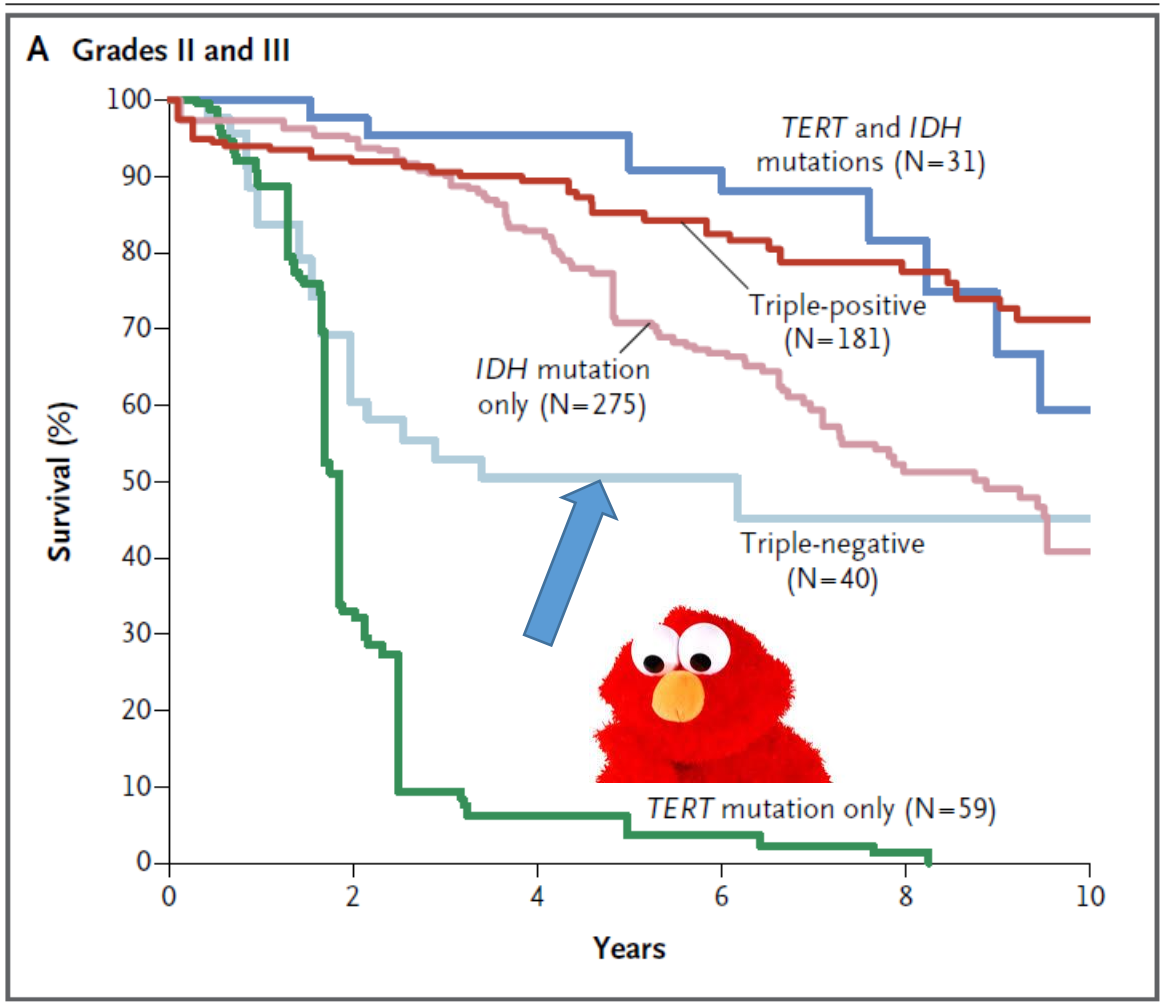


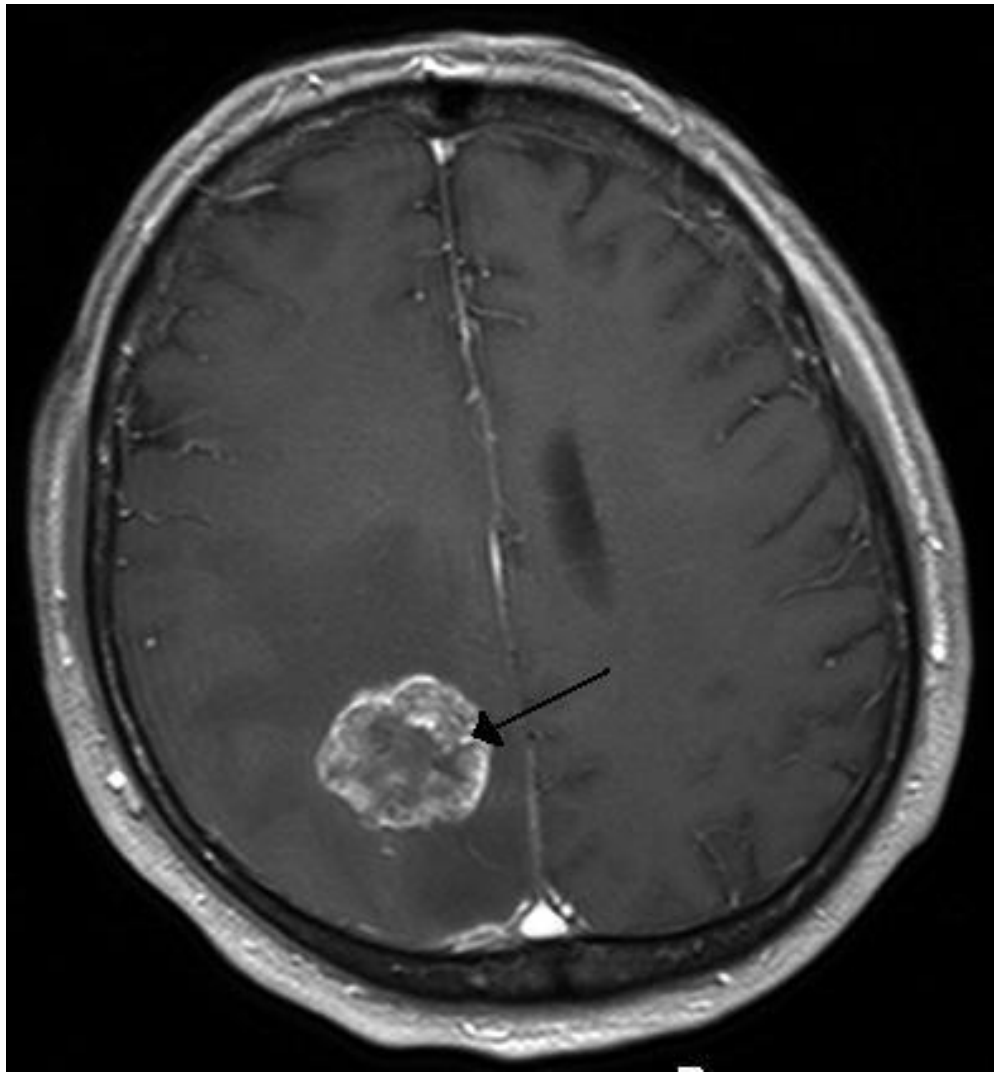
Case 5 Management

- Surgical resection
- Check histology
  - Either RT + PCV (Grade 2 astro)
  - RT + PCV (Grade 3 oligo)
  - RT alone (Grade 3 astro)
    - EORTC 26053-22054: RT +/- TMZ (4-way randomisation)
    - DMSC: Add Adj. TMZ
- Unsatisfactory evidence

Case 5 Questions ?

Case 6

- 56 yr old woman with a history of breast cancer
  - HER-2 positive, ER/PR –ve
  - Surgery, adjuvant RT and adjuvant chemo
  - Ongoing adjuvant Herceptin
  - 3 week history of headache and dizziness
  - Restaging CT shows no evidence of extra-cranial disease



Case 6

- Likely metastatic breast cancer
- Well
- No ECD

- Prognosis ?
- Treatment ?
- Evidence base for treatment ?

Case 6

- Prognosis?

A: <3 months

B: 3 – 9 months

C: 9 – 14 months

D: 14 – 18 months

E: 18 + months

Case 6

- Treatment ?

A: Surgery

B: SRS

C: WBRT

D: Surgery & WBRT

E: SRS & WBRT

Case 6 - prognosis

- Best prognostic tool is dsGPA
  - Better than the RPA
  - dsGPA = 3.5; MedOS ~ 11 months

Case 6 - prognosis

Table 1. Median Survival Time for Patients With Brain Metastases by DS-GPA Score

	Overall			DS-GPA Score															
				0-1.0				1.5-2.0				2.5-3.0				3.5-4.0			
	Survival Time (months)		No. of	Survival Time (months)		Patients		Survival Time (months)		Patients		Survival Time (months)		Patients		Survival Time (months)		Patients		*P*
Diagnosis	Median	95% CI	Patients	Median	95% CI	No.	%	Median	95% CI	No.	%	Median	95% CI	No.	%	Median	95% CI	No.	%	(log-rank)
NSCLC	7.00	6.53 to 7.50	1,833	3.02	2.63 to 3.84	254	14	5.49	4.83 to 6.40	705	38	9.43	8.38 to 10.80	713	40	14.78	11.80 to 18.80	161	9	< .001
SCLC	4.90	4.30 to 6.20	281	2.79	1.83 to 3.12	65	23	4.90	4.04 to 6.51	119	42	7.67	6.27 to 9.13	84	30	17.05	4.70 to 27.43	13	5	< .001
Melanoma	6.74	5.90 to 7.56	481	3.38	2.53 to 4.27	84	17	4.70	4.07 to 5.39	150	31	8.77	6.74 to 10.77	135	28	13.23	9.13 to 15.64	112	23	< .001
RCC	9.63	7.66 to 10.91	286	3.27	2.04 to 5.10	43	15	7.29	3.73 to 10.91	76	27	11.27	8.80 to 14.80	104	36	14.77	9.73 to 19.79	63	22	< .001
Breast cancer	13.80	11.53 to 15.87	400	3.35	3.13 to 3.78	23	6	7.70	5.62 to 8.74	104	26	15.07	12.94 to 15.87	140	35	25.30	23.10 to 26.51	133	33	< .001
GI cancer	5.36	4.30 to 6.30	209	3.13	2.37 to 4.57	76	36	4.40	3.37 to 6.53	65	31	6.87	4.86 to 11.63	50	24	13.54	9.76 to 27.12	18	9	< .001
Other	6.37	5.22 to 7.49	450	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Total	7.16	6.83 to 7.52	3,940	3.10	2.83 to 3.45	545	16	5.40	4.90 to 5.89	1,219	35	9.63	8.74 to 10.58	1,226	35	16.73	14.65 to 18.80	500	14	< .001

Abbreviations: DS-GPA, diagnosis-specific Graded Prognostic Assessment; NSCLC, non–small-cell lung cancer; RCC, renal cell carcinoma; SCLC, small-cell lung cancer.

Case 6 - GPA

Non–small-cell and small-cell lung cancer

Prognostic Factor	GPA Scoring Criteria 0	0.5	1.0	Patient Score
Age, years	> 60	50-60	< 50	____
KPS	< 70	70-80	90-100	____
ECM	Present	—	Absent	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8

Melanoma

Prognostic Factor	GPA Scoring Criteria 0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2

Breast cancer

Prognostic Factor	GPA Scoring Criteria 0	0.5	1.0	1.5	2.0	Patient Score
KPS	≤ 50	60	70-80	90-100	n/a	____
Subtype	Basal	n/a	LumA	HER2	LumB	____
Age, years	≥ 60	< 60	n/a	n/a	n/a	____
Sum total						____

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3

Renal cell carcinoma

Prognostic Factor	GPA Scoring Criteria 0	1.0	2.0	Patient Score
KPS	< 70	70-80	90-100	____
No. of BM	> 3	2-3	1	____
Sum total				____

Median survival (months) by GPA: 0-1.0 = 3.3; 1.5-2.0 = 7.3; 2.5-3.0 = 11.3; 3.5-4.0 = 14.8

GI cancers

Prognostic Factor	GPA Scoring Criteria 0	1	2	3	4	Patient Score
KPS	< 70	70	80	90	100	____

Median survival (months) by GPA: 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.9; 4.0 = 13.5

Case 6

- Best prognostic tool is dsGPA
  - Better than the RPA
  - dsGPA = 3.5; MedOS ~ 11 months

- But still problems in terms of patient cohort and how standard they are
- Decision-making:
  - How is the patient ?
  - How is the disease ?
  - What are the options ?

Case 6

- Patient is well (PS and ECD)
- Disease is limited
  - But large
- Treatment options:
  - WBRT
  - Surgery
  - SRS
  - Or combinations of these

Case 6

- Given good PS and limited disease, focal treatment seems best
  - SRS or surgery
  - Benefits and risks of each

- Argument for adding WBRT

Is Surgery or SRS better ?

Case 6 - WBRT

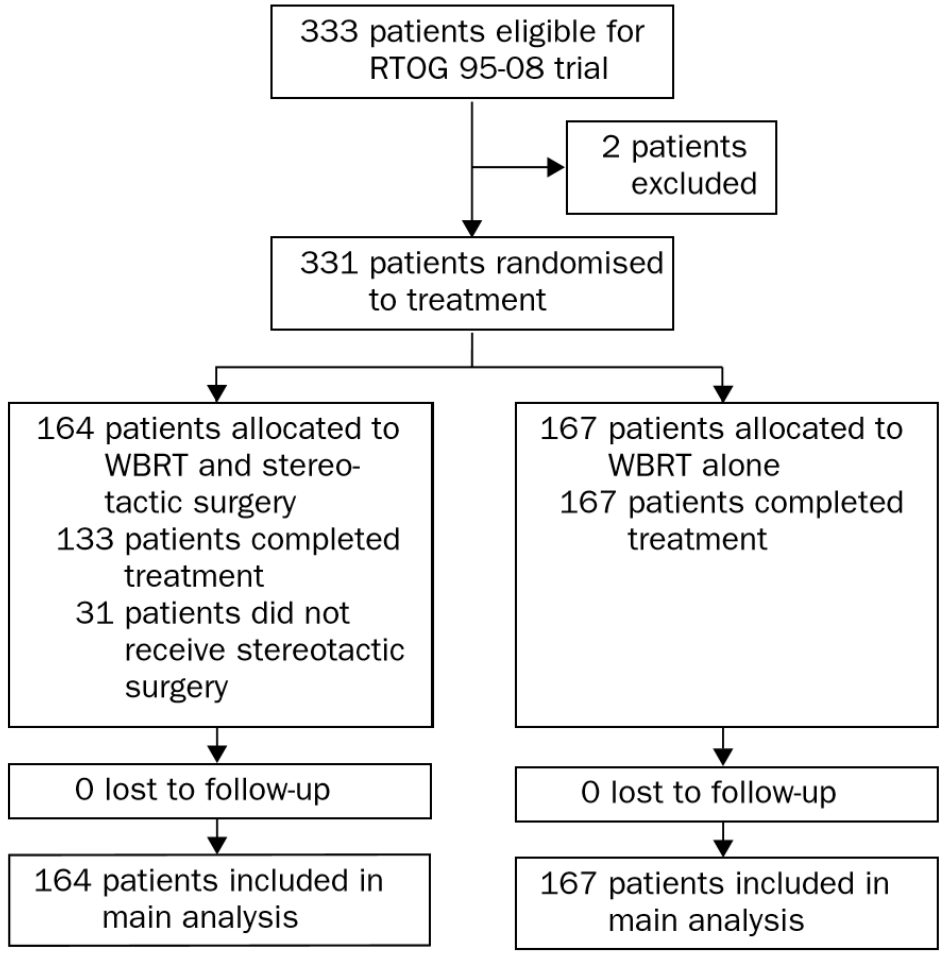
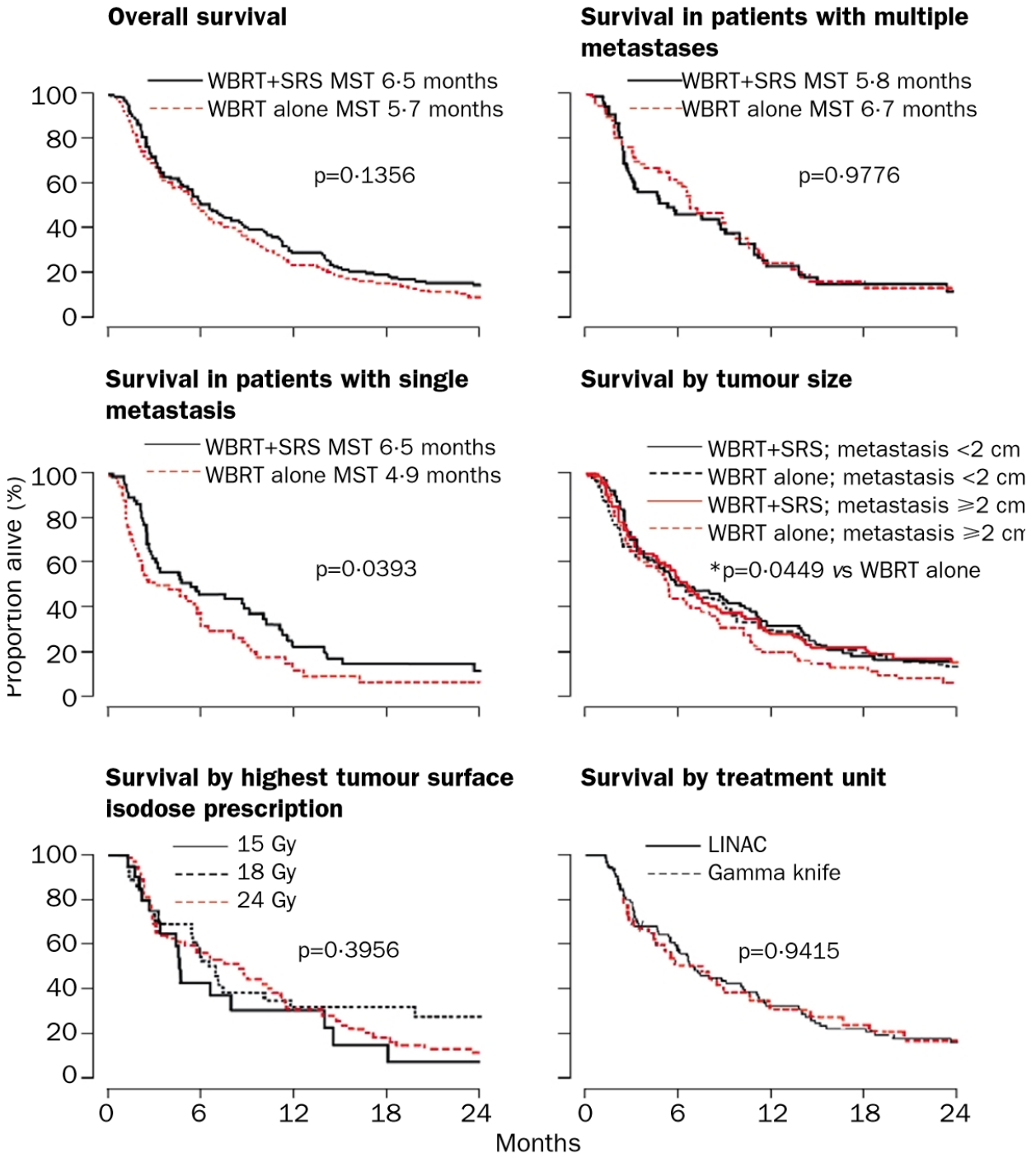
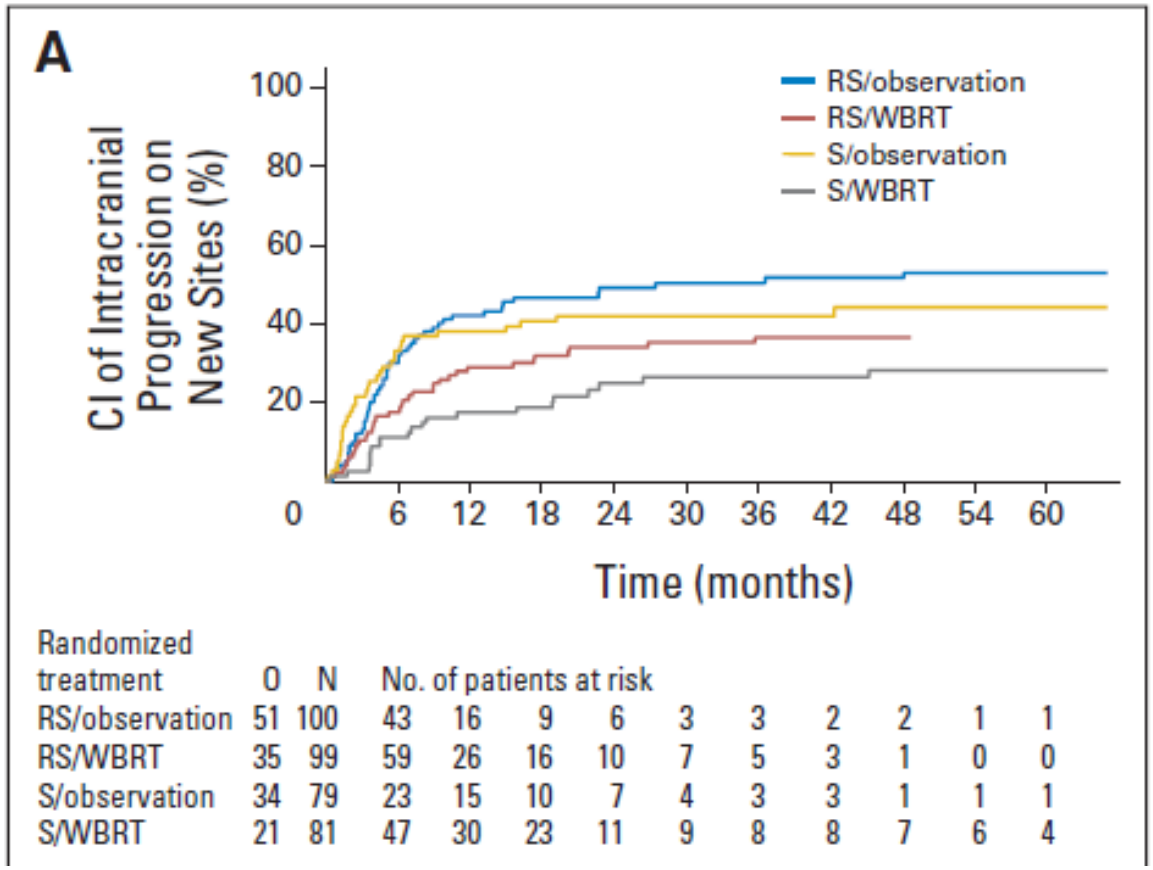


Figure 1: **Trial profile**

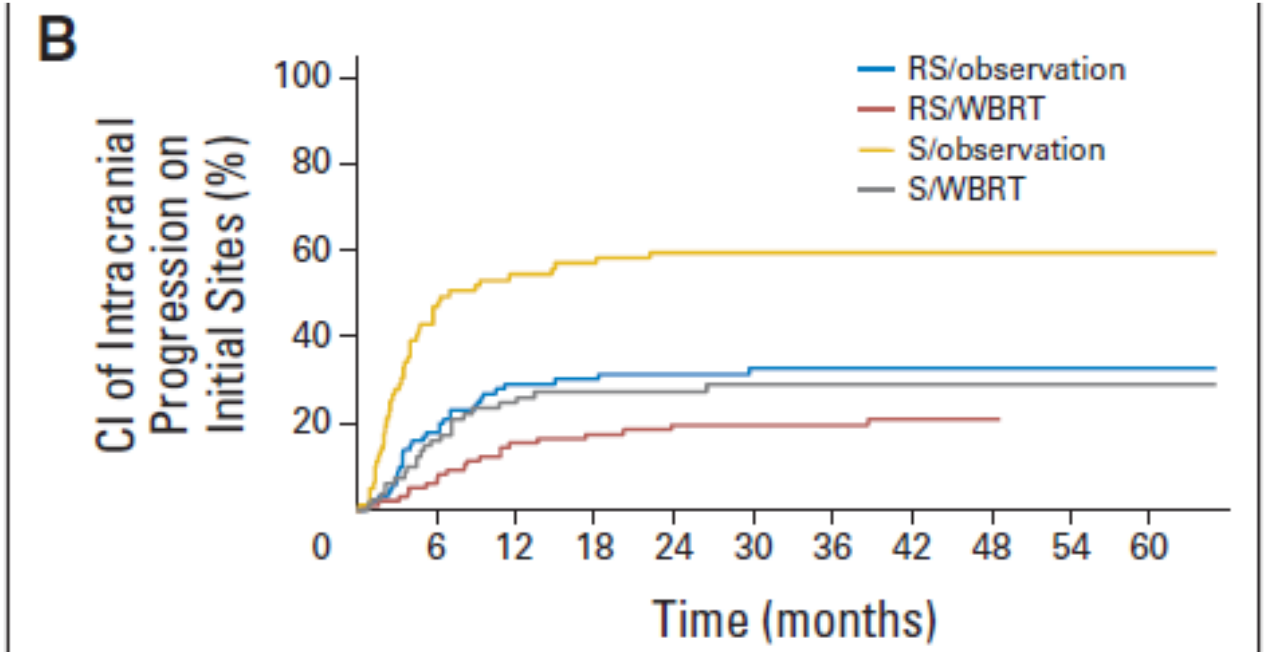
Andrews Lancet 2004



Case 6 - WBRT



Randomized treatment	O	N	No. of patients at risk									
RS/observation	51	100	43	16	9	6	3	3	2	2	1	1
RS/WBRT	35	99	59	26	16	10	7	5	3	1	0	0
S/observation	34	79	23	15	10	7	4	3	3	1	1	1
S/WBRT	21	81	47	30	23	11	9	8	8	7	6	4

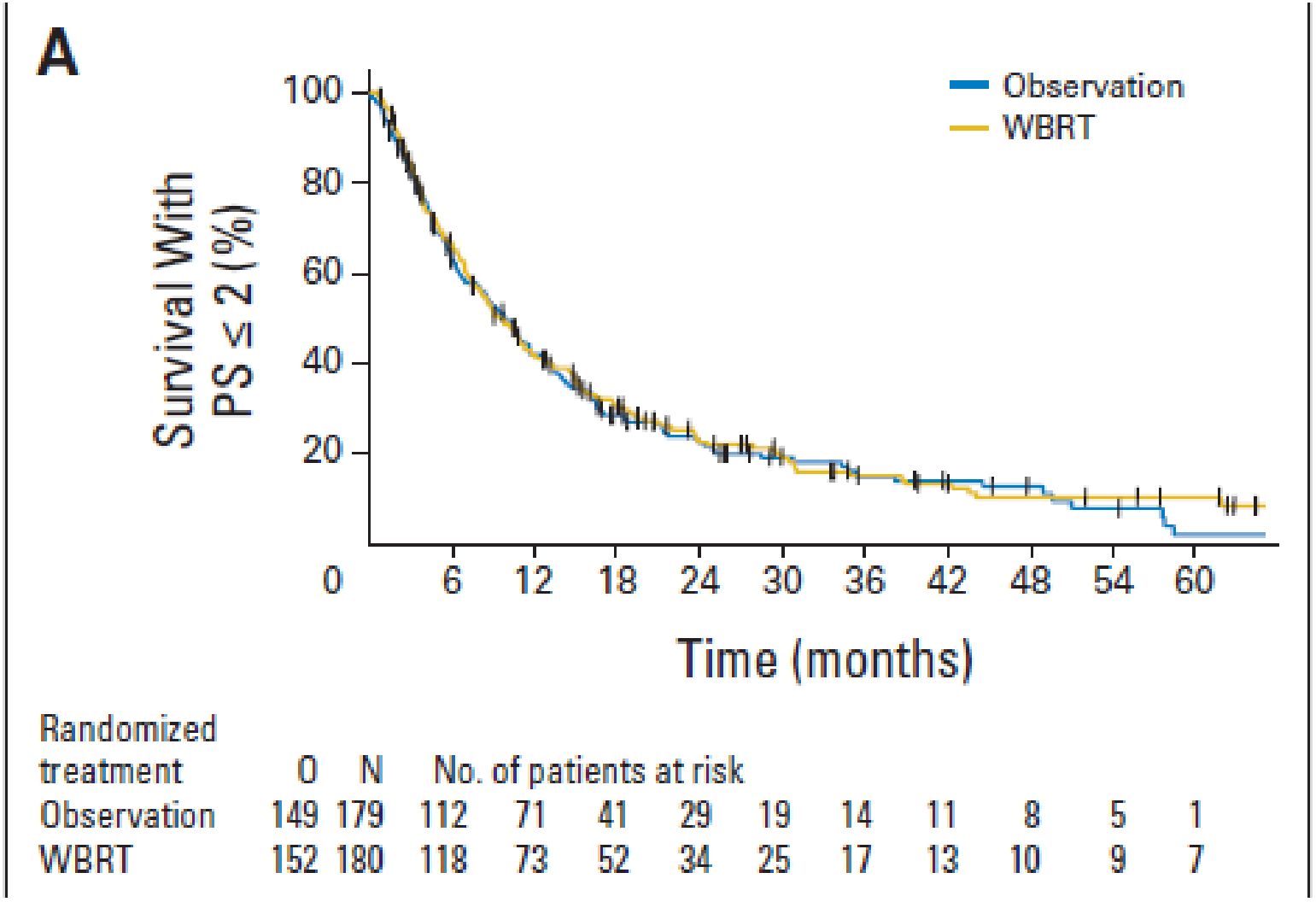


Randomized treatment	O	N	No. of patients at risk									
RS/observation	32	100	43	16	9	6	3	3	2	2	1	1
RS/WBRT	20	99	59	26	16	10	7	5	3	1	0	0
S/observation	47	79	23	15	10	7	4	3	3	1	1	1
S/WBRT	23	81	47	30	23	11	9	8	8	7	6	4

Fig 2. Time to intracranial progression at (A) new sites and (B) initial sites in patients treated initially by radiosurgery (RS) or surgery (S) after observation or adjuvant whole-brain radiotherapy (WBRT). Patients who died before the event (competing risk) were censored. CI, cumulative incidence; O, number of events; N, number of patients.

Kocher JCO 2011

Case 6 - WBRT



Kocher JCO 2011

Case 6 - WBRT

- WBRT reduces intracranial relapse rate
  - But doesn’t improve OS

- This is because brain mets don’t always kill the patient

- Brain mets as a marker of aggressive disease
- Therefore associated with poor survival
  - Not always causal

Case 6

- Role of WBRT
  - Focal Rx +WBRT $\sim_{OS}$ Focal Rx alone
  - Focal Rx +WBRT $>_{IntraCranProg}$ Focal Rx alone
  - Focal Rx +WBRT $\sim_{TimePS2}$ Focal Rx alone

  - SRS + WBRT $<_{CogFunc}$ SRS Alone

  - Is WBRT better in a small subset of patients ?
    - Andrews Lancet 2004 (Single met; SRS + WBRT $>_{OS}$ SRS alone)
    - Sperduto RedJ 2014 (GPA 3.5 – 4; SRS + WBRT $>_{OS}$ SRS alone)
    - Ayoma JAMA 2015 (NSCLC; GPA 2.5 – 4; SRS + WBRT $>_{OS}$ SRS alone)

Case 6

- Surgery or SRS have ~ 50% of Intra-cranial progression
  - Roughly-halved by WBRT
  - WBRT does not increase OS
    - But might do in a small sub-group
    - But these are the one who get neuro-cognitive decline
- Options:
  - Surgery + close surveillance
  - Surgery + WBRT

Case 6

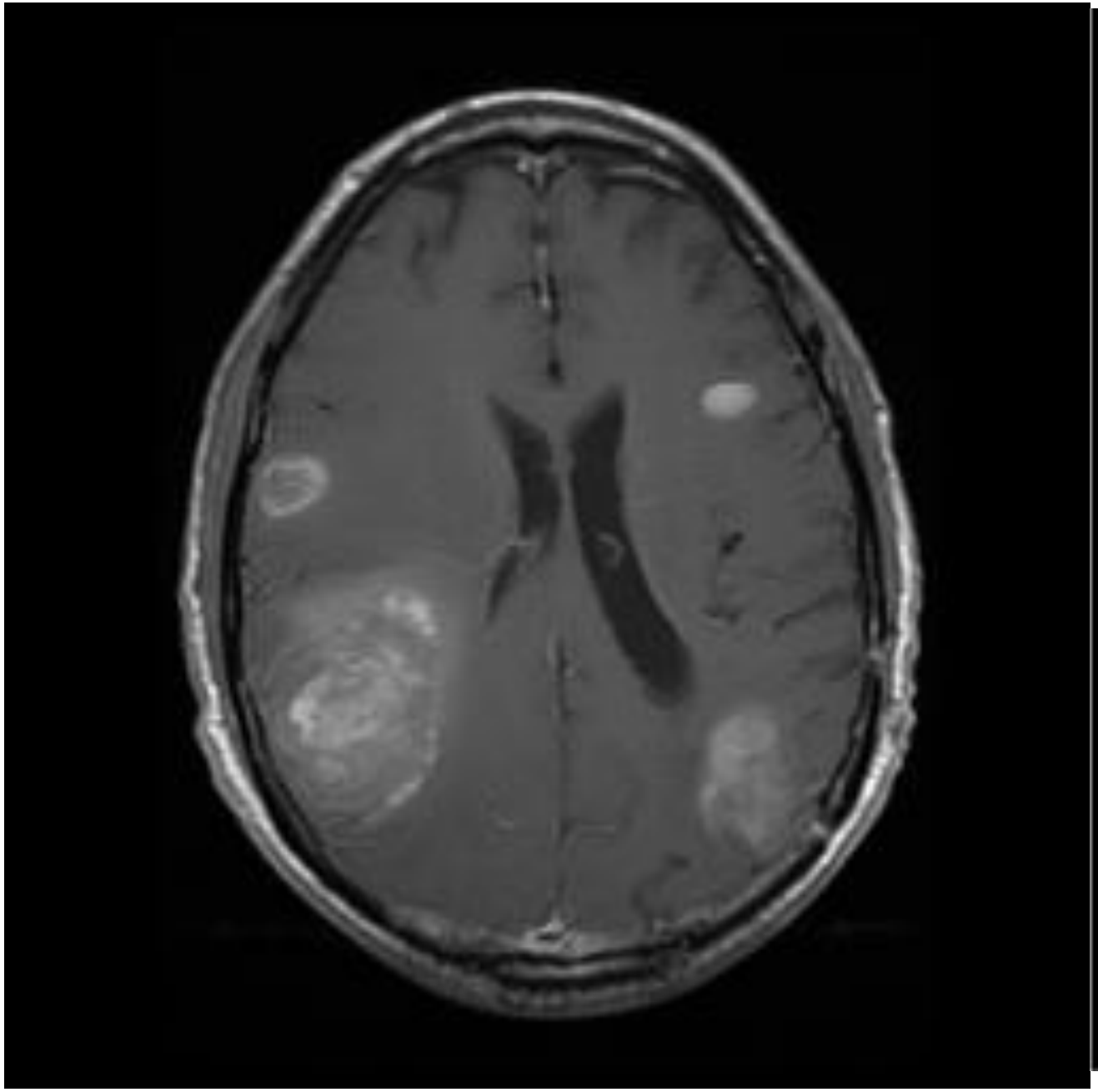
- Potential ideas:
  - HS-WBRT ?
  - Cavity SRS ?
  - Chemo-protection

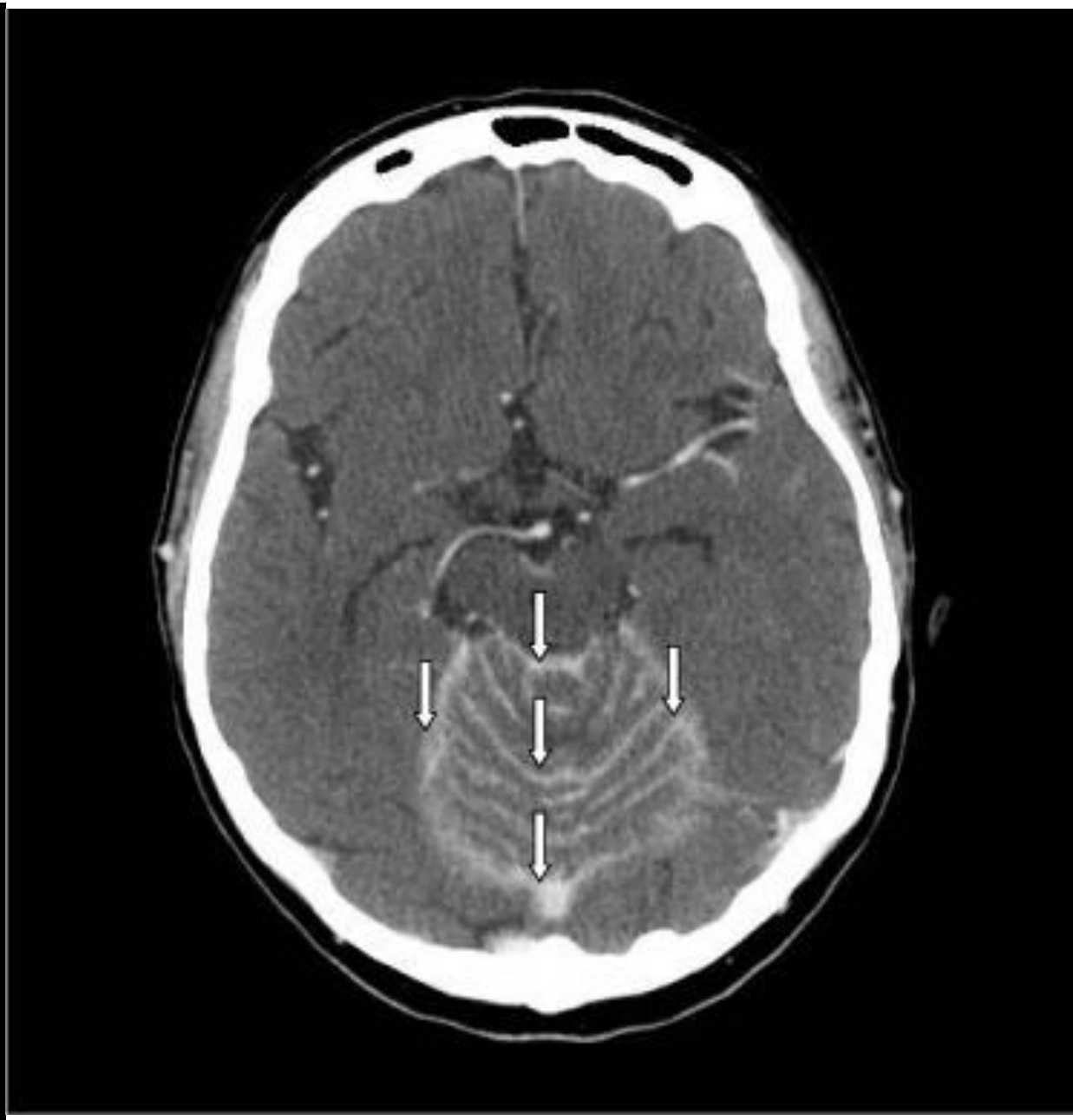
- Relapse on HER-2 targeted agent not uncommon
  - Not a reason to stop HER-2 treatment
  - Careful with TDM-1!

Case 6 Questions ?

Case 7

- 27 yr old woman
  - Excision of a pigmented lesion from her back 3 years ago
  - Told ‘not cancer’
  - 4 week history of headache
  - Collapsed
  - Brought to hospital
  - GCS = 14/15
  - GCS improves to 15/15, ECOG PS = 3





Case 7 imaging

- What is the most important thing you see on the imaging ?

Case 7

- PS = 3
- Multiple mets
- Young
- Imaging shows leptomeningeal disease

- Treatment options ?
- Prognosis ?

Treatment options

- Leptomeningeal disease
- With parenchymal disease
- Therefore argument against focal therapy

- Options are WBRT/ WBRT & focal spinal/ CSRT/ chemo/ IT chemo
  - No clear evidence in favour of any one of them
  - Very little evidence
  - Some very selective case series

Case 7 – Practical aspects

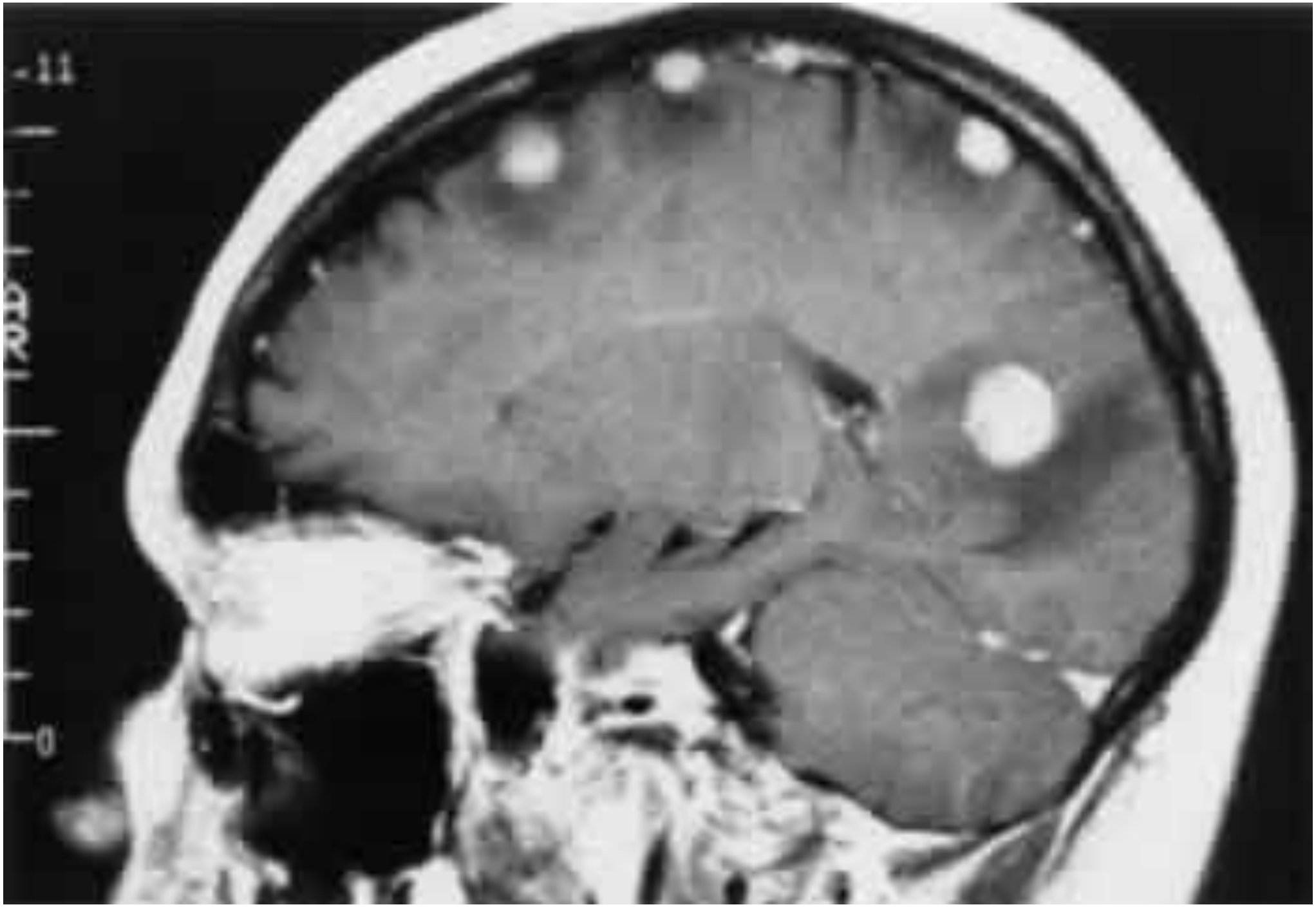
- Prognosis poor
- IT chemo has risks due to poor CSF flow

- I would suggest WBRT or no treatment
  - This patient got no treatment as in ITU and rapid deterioration

Case 7 Questions ?

Case 8

- 44 yr old woman
  - Metastatic lung cancer
  - Progressive liver mets
  - Otherwise well
  - ECOG PS = 1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Case 8

- Met lung cancer
- Progressive ECD
- Well
- Multiple small lesions

- Treatment options ?
- Evidence ?
- Benefits and risks of each ?

Case 8

- NOT going to cover SRS in detail

- SRS feasibility:
  - Conventionally 1 - 3 or 1 – 4 mets
  - 20cc total volume
  - Volume drives toxicity

  - HypoFrac may help with this
  - Do the number of mets matter ?

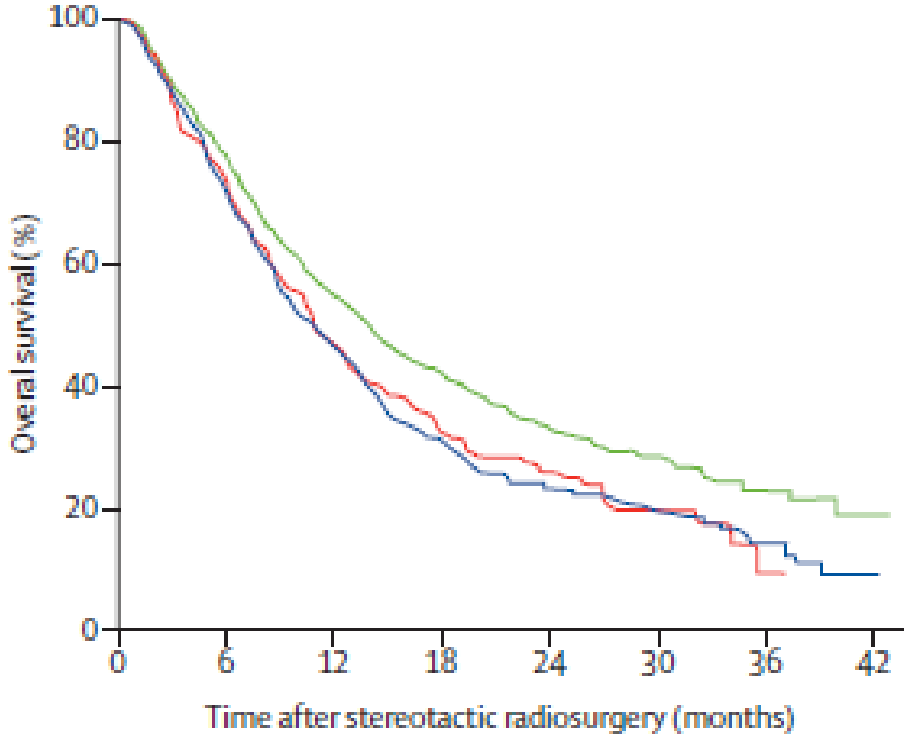
Case 8 - multimets

- GK study across Japan
- 1194 pts in 3 yrs
- 1 – 10 mets
- Total vol <15ml

- Non-inferiority for survival

Yamamoto, LancetOnc 2014

Group	Median overall survival, months (95% CI)	HR (95% CI)	p value
1 tumour	13·9 (12·0–15·6)	0·76 (0·66–0·88)	0·0004
2–4 tumours	10·8 (9·4–12·4)	Reference	
5–10 tumours	10·8 (9·1–12·7)	0·97 (0·81–1·18)	0·78



Number at risk				
1 tumour	455	234	97	22
2–4 tumours	531	215	61	16
5–10 tumours	208	84	31	1

***Figure*: Kaplan-Meier curves of overall survival**
HR=hazard ratio.

Case 8

- Treatment options
  - Surgery or SRS or WBRT
  - Options in favour of each
- Evidence
- However, WBRT seems ‘too much’; Surgery seems ‘unwise’
  - This does NOT come out of the evidence
  - Such decisions are ‘pre-trial’ – and lead to problems with the evidence
  - We need to be careful about how we interpret the evidence

Case 8 Questions ?

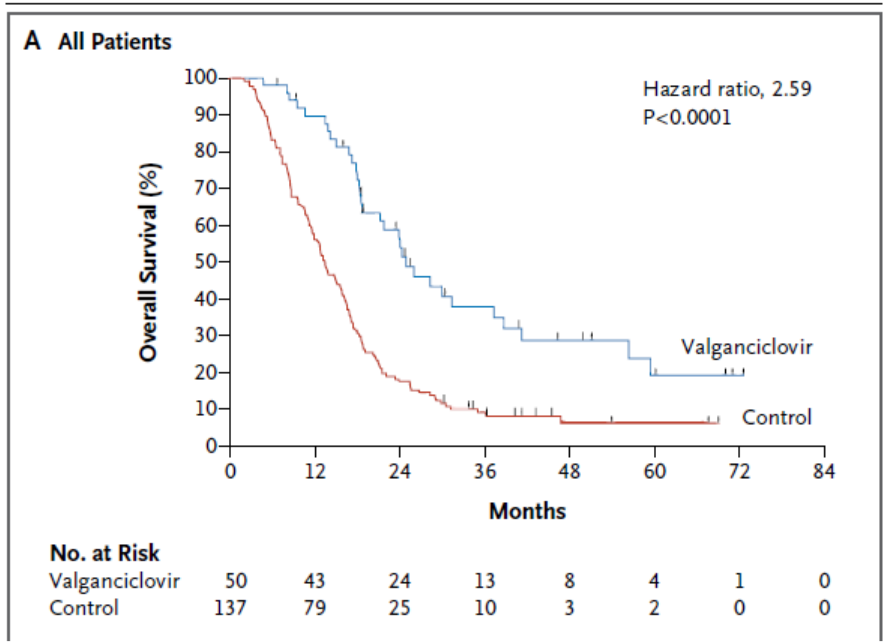
Summary

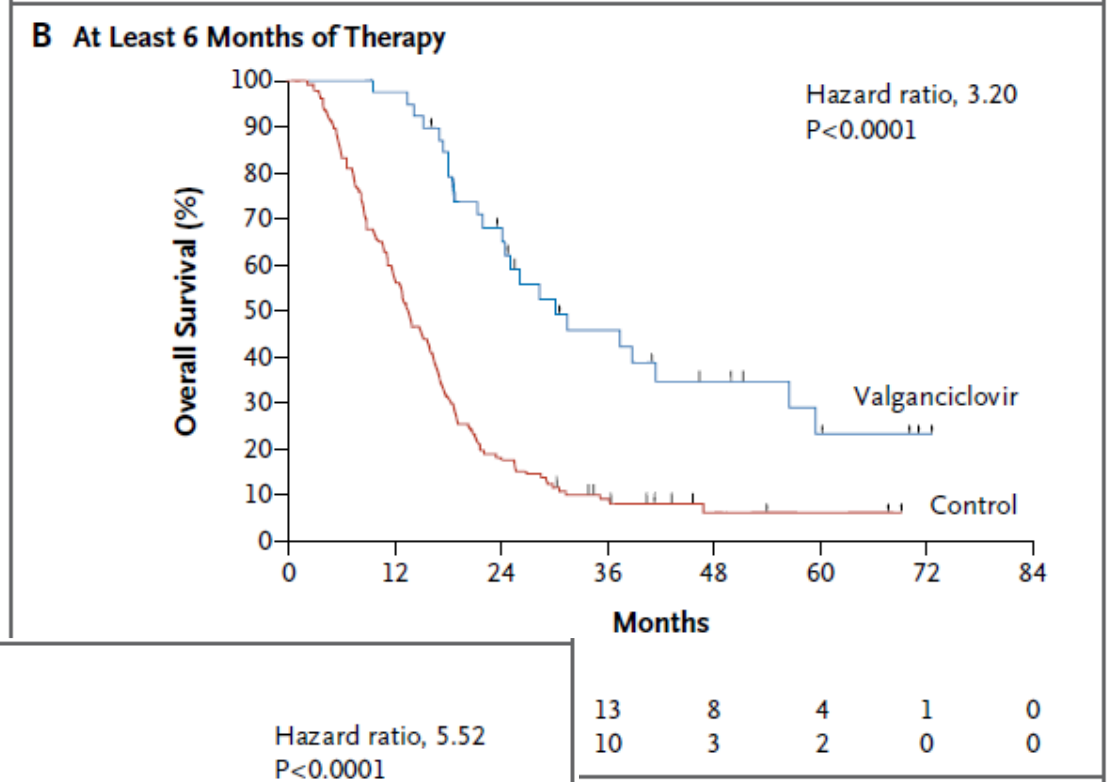
- 3 HGG; 2 LGG; 3 Mets
  - No meningioma, pituitary, medulloblastoma, pilocytic astrocytoma
  - Focus on treatment and prognosis
- For glioma, grade still matters
  - But molecular pathology is becoming more important for risk stratification
  - We are not going to reduce the dose in IDH-mut GBM
- Brain mets – still poor evidence base
- Clinically fascinating area
  - Good mix of technology and humanity

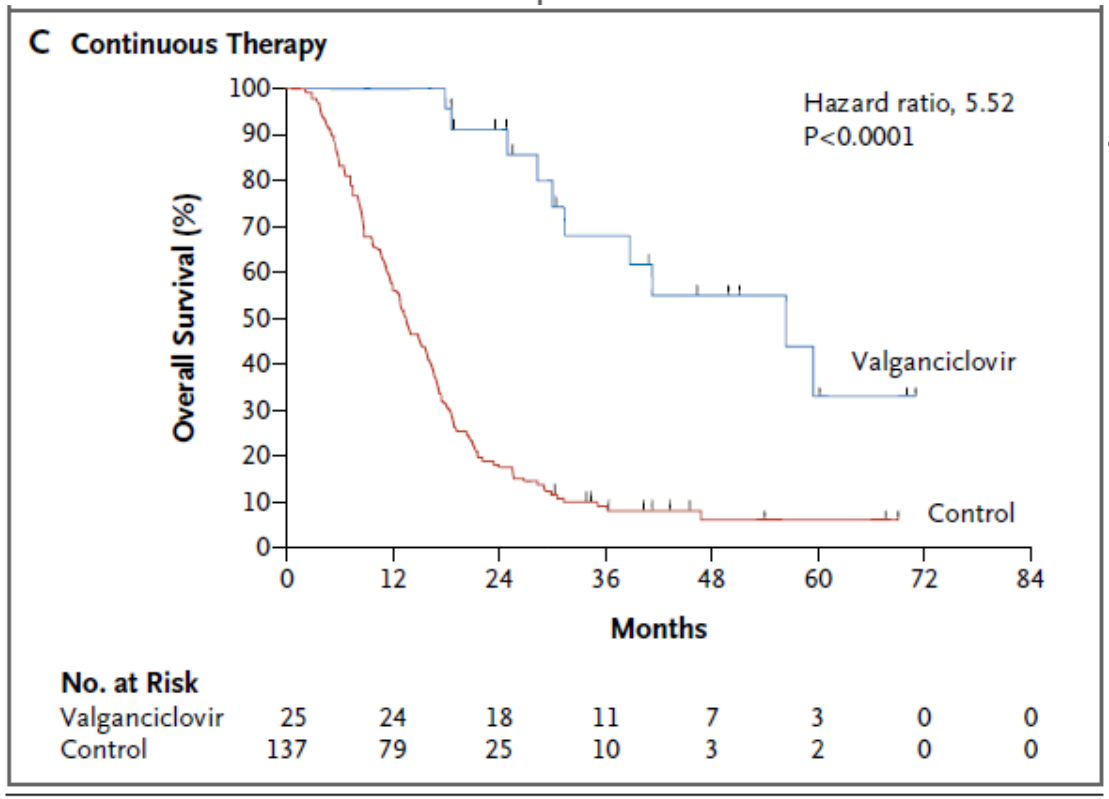
Evidence-based Neuro-oncology

- Brain tumours are devastating
- Patients and families are desperate
  - “Is there anything else I can try?”

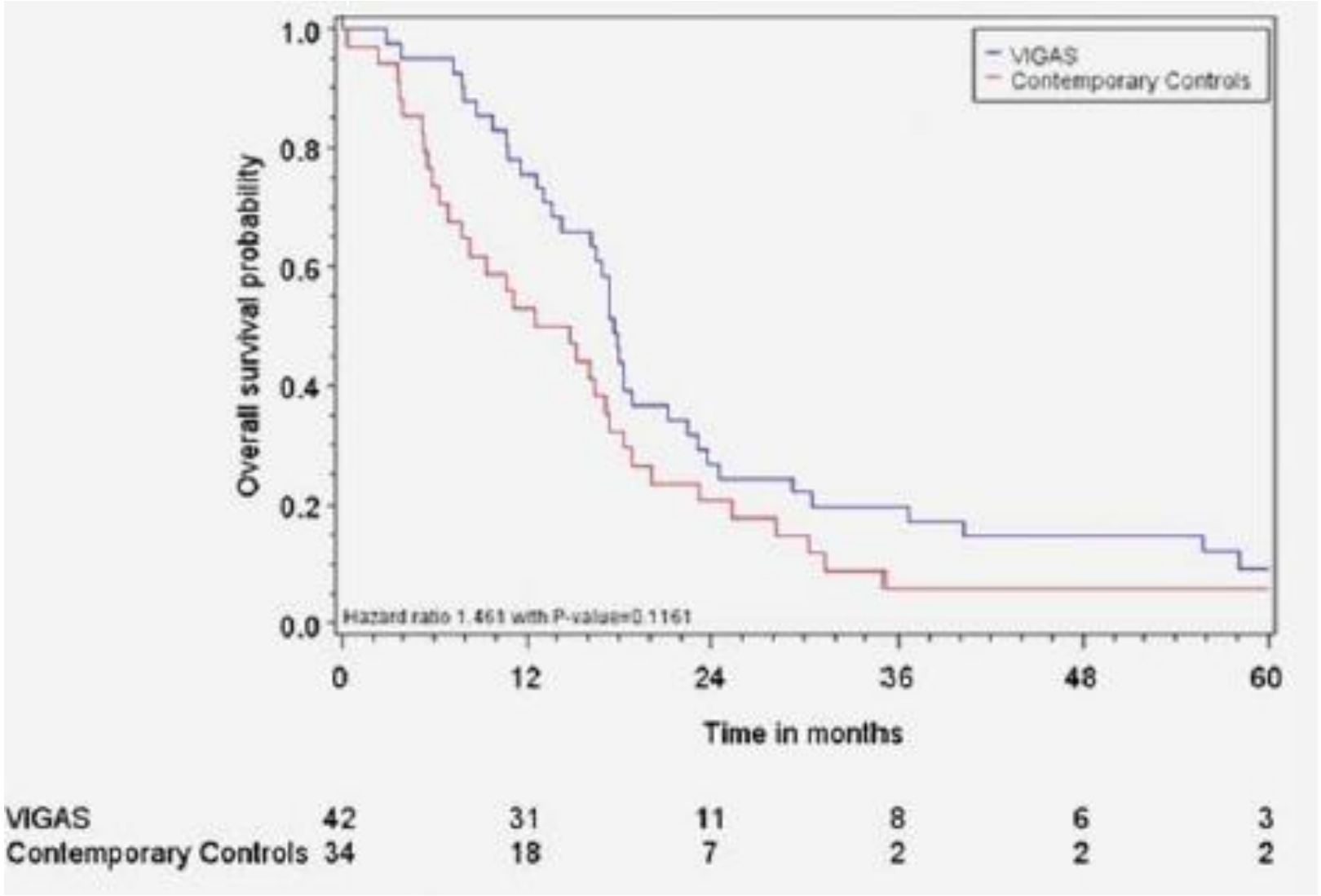
Valgancyclovir in GBM





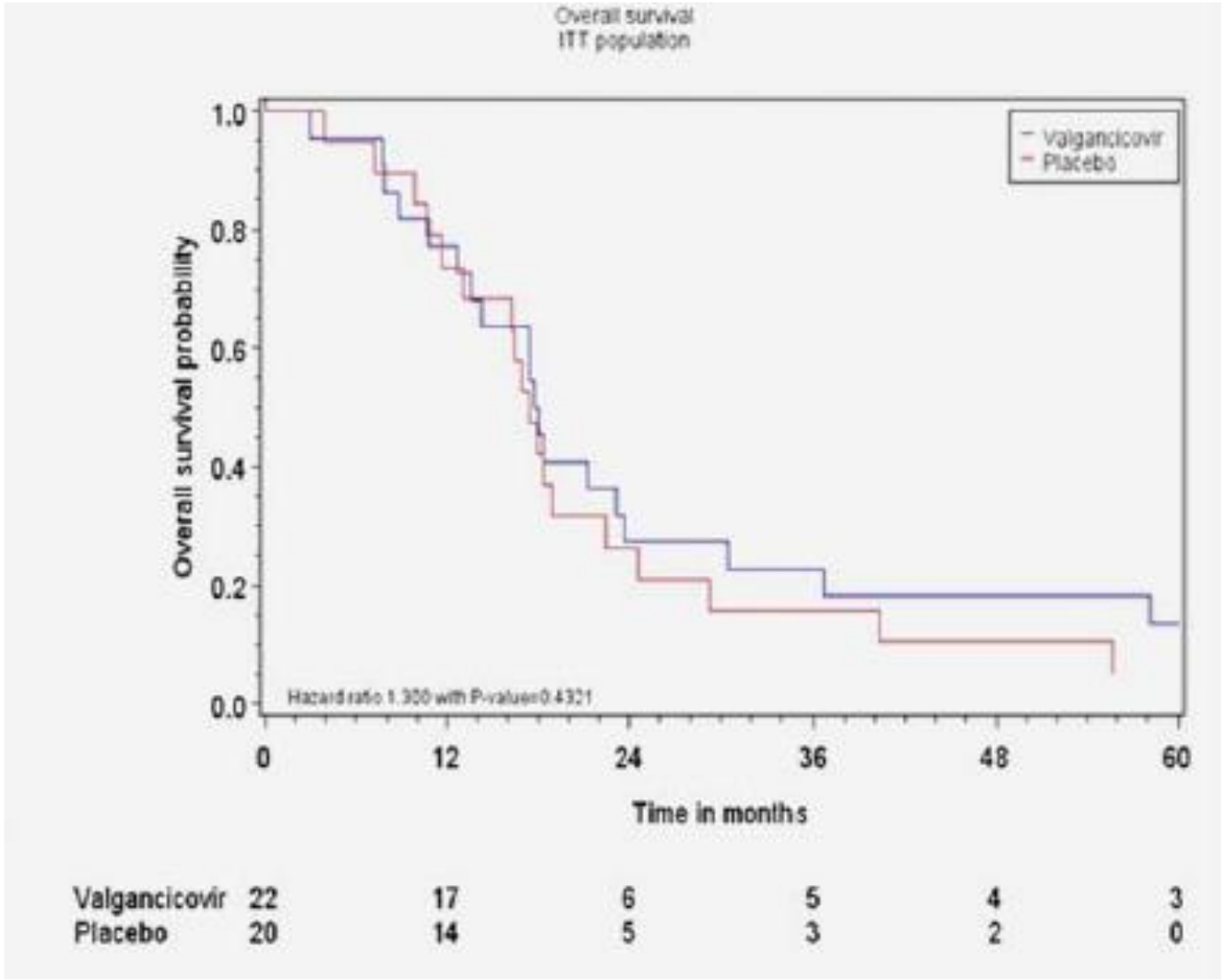


Valgancyclovir and GBM (2)



Stragliotto IJC 2013

Valgancyclovir and GBM (3)



Stragliotto IJC 2013

ACT studies

- ~1/3rd GBM are EGFR+ve
- EGFR+ve GBM have a worse prognosis
- We can target EGFR

ACT studies

- ~1/3rd GBM are EGFR+ve
- EGFR+ve GBM have a worse prognosis
- We can target EGFR

Let’s do a trial !

ACT Phase 2

- New GBM: GTR; No progression after CRT

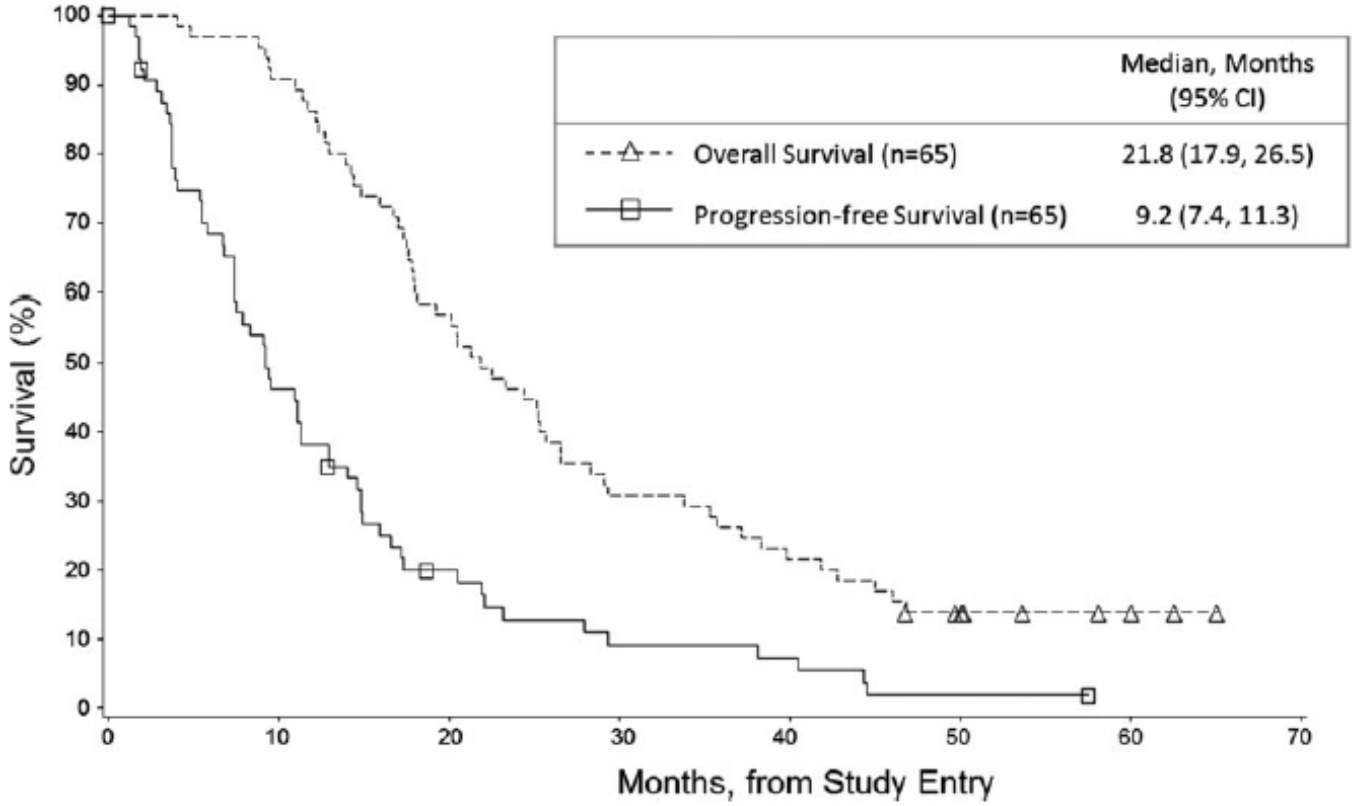


Fig. 2. Kaplan–Meier estimates of PFS and OS. Survival durations are calculated from study entry, representing a median of 3.0 (range, 2.4–4.4) months from diagnosis (as shown in Table 1). Line markers represent censored data.

ACT Phase 2

- New GBM: GTR; No progression after CRT

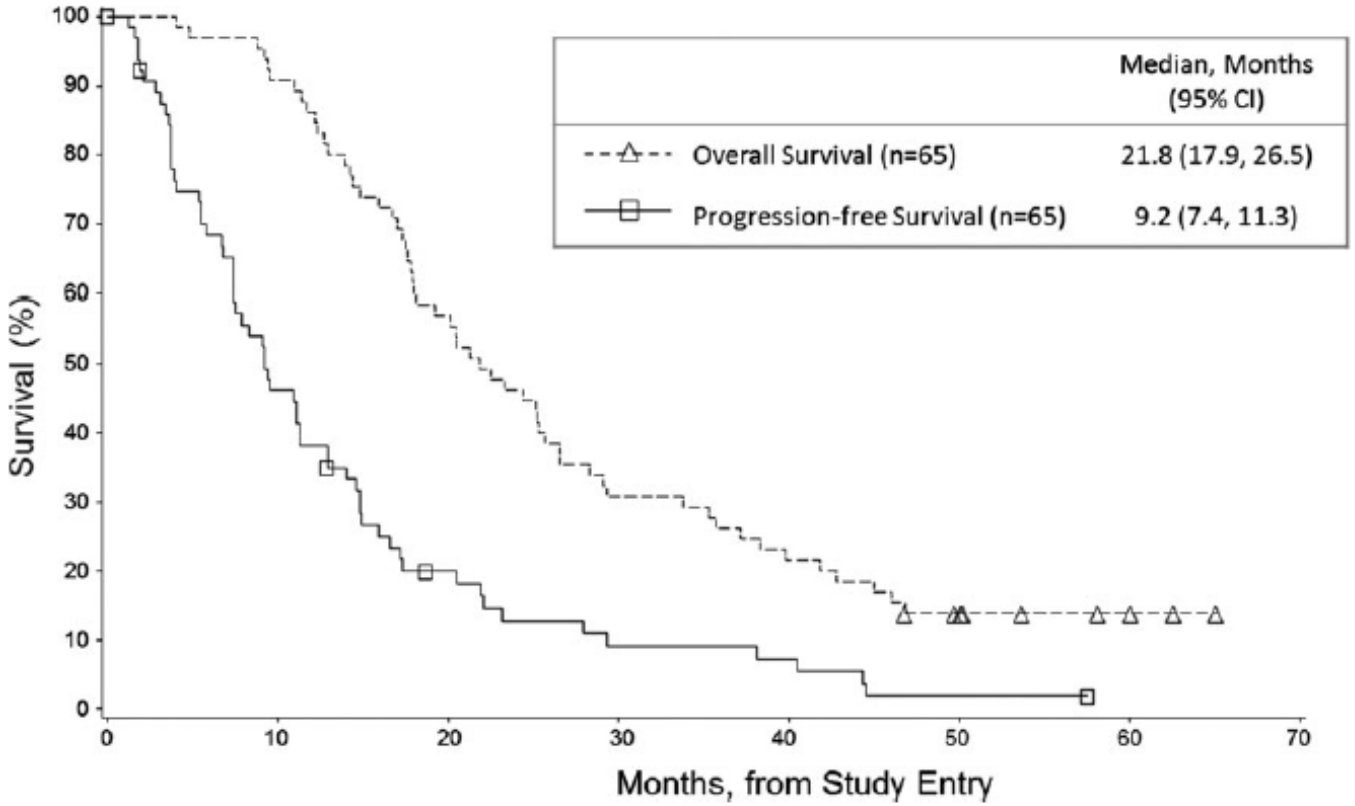


Fig. 2. Kaplan–Meier estimates of PFS and OS. Survival durations are calculated from study entry, representing a median of 3.0 (range, 2.4–4.4) months from diagnosis (as shown in Table 1). Line markers represent censored data.

ACT IV: Phase 3

- 745 pts
- HR = 0.99

- No other data yet available….

ACT IV: Phase 3

- 745 pts
- HR = 0.99

- “the rindopepimut combination showed OS data similar to expectations in the phase III study while patients in the control arm significantly outperformed.”

- Reanalysis of EORTC trial patient who met enrolment criteria showed this better analysis
- RCTs are not perfect…. But better than this

GBM post-2005

- Stupp 2005
- Improved Median OS by 2 months
- Multiple other trials of targeted agents
  - All failed

- Only positive trial: TTF
  - 21 000 Euro/ month

The future

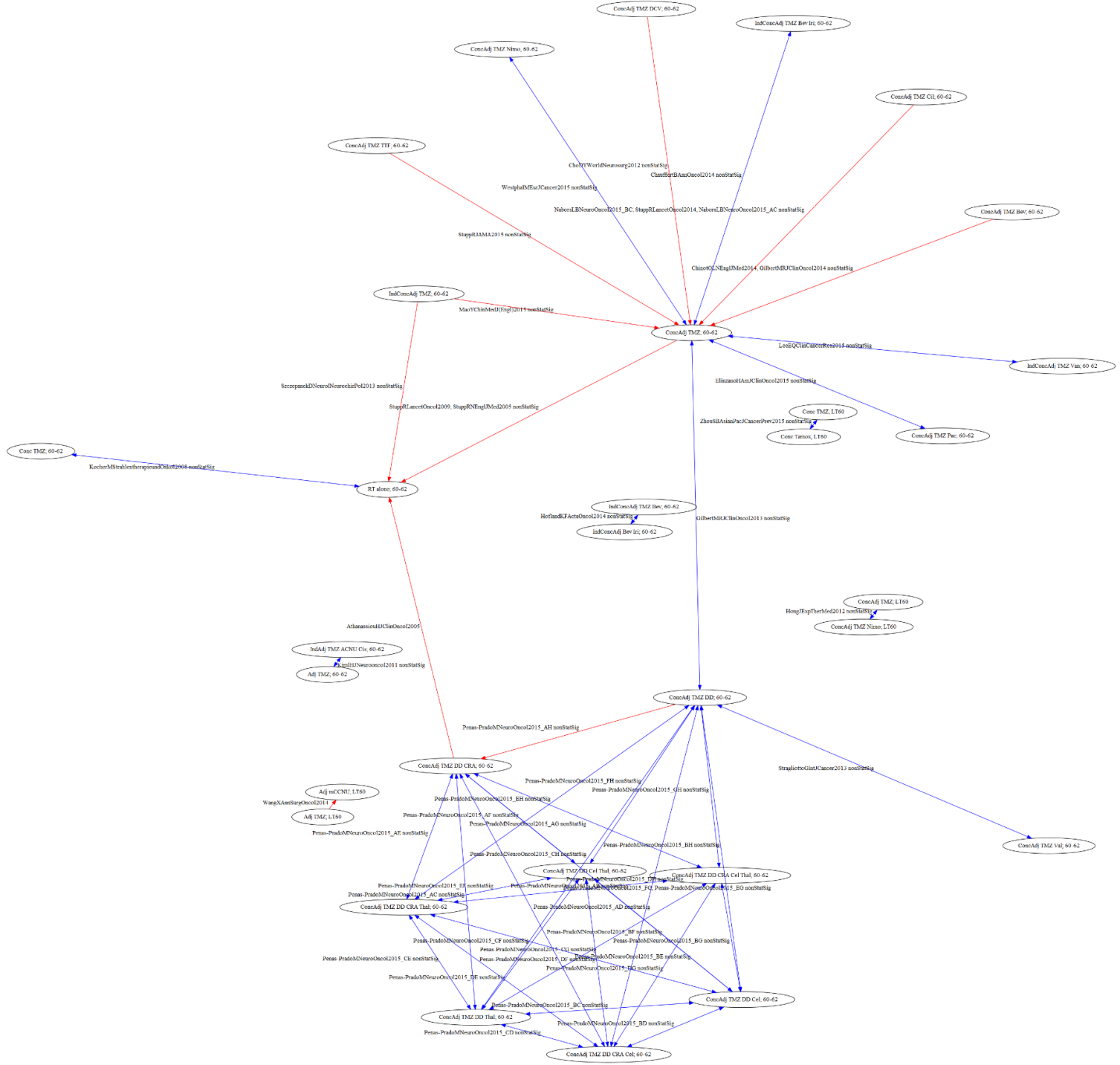
- Better definitions of tumours
  - WHO made a start on this
    - IDH-Mut GBM; H3 K27M mut midline glioma
  - Causes as many problems as it solves
  - Will lead to basket trials

- Randomised Phase 2 trials!

- Better technology gives more options
  - Decision-making is more difficult with more options
- Knowledge is Fractal

Alan Rector

GBM Systematic Review



END

Case 3 pathology notes

- Recent work suggest an integrated pathology approach may help
- The TCGA paper looks at 293 pts with grade 2/3 gliomas. They suggest that LGG with IDH-wild type are essentially GBMs (Fig. 4, Fig. 5B), and are distinct from other LGG, in that they occur in older patients, and in different locations. For these patients, survival is intermediate between 'true' GBM with IDH-wt and GBM with mutated IDH-mutation.
-
- It is work remembering that those with IDH-mut and 1p/19q still only had a median OS of 8 years, which is better - but still worse than many cancers. IDH-wt GBM is still the worst disease - which suggests that grade still plays some role in prognosis.
-
- The Eckel-Passow paper looks at IDH, 1p/19q and TERT promoter mutations. Genetics was associated with survival in Grade 2/3 gliomas, but not in GBM. Tumours with TERT mutations only did really very badly, even if they were grade 2/3 (although most TERT-mut only tumours were GBM).
-
- There are still some significant outstanding issues: data on performance status and treatment is incomplete (and one might think has some impact on outcome), and although the molecular groups segregate well, they are not perfect (e.g. the inverse association by TERT and ATRX - but not in everyone; the idea that IDH-mut is not prognostic in GBM patients with TERT mutations). Some of these are also subject to small-cohort problems.
-
- Nonetheless, I think the data are interesting, but mainly for grade 2/3 tumours (GBMs do badly, and grade still matters). This might end up pushing us towards more tissue sampling in those with lower-grade tumours, in order to risk stratify. The impact on treatment is less clear, although one can make an argument that in someone with a grade II TERT-mut astrocytoma, the outcomes are so poor one should treat them as a GBM. I am not convinced we have the evidence for this yet - the fact they do badly doesn't mean that they do better with CRT.
-
- As ever, I am happy to discuss - although I am not a molecular pathologist!
-

Evidence Based Radiation Oncology: Prostate cancer

De Bari Berardino, MD, fESTRO

Radiation Oncology Dpt.
Centre Hospitalier Régional Universitaire «Jean Minjoz»
France

Evidence Based Radiation Oncology: Prostate cancer

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France

Before to start…

A message to Matt….

Italian Prime Minister 1994-1995 and in 2001 - 2006


MARINE
Présidente

The 5 W and 1 H of EBM

What …. is the Evidence Based Medicine?

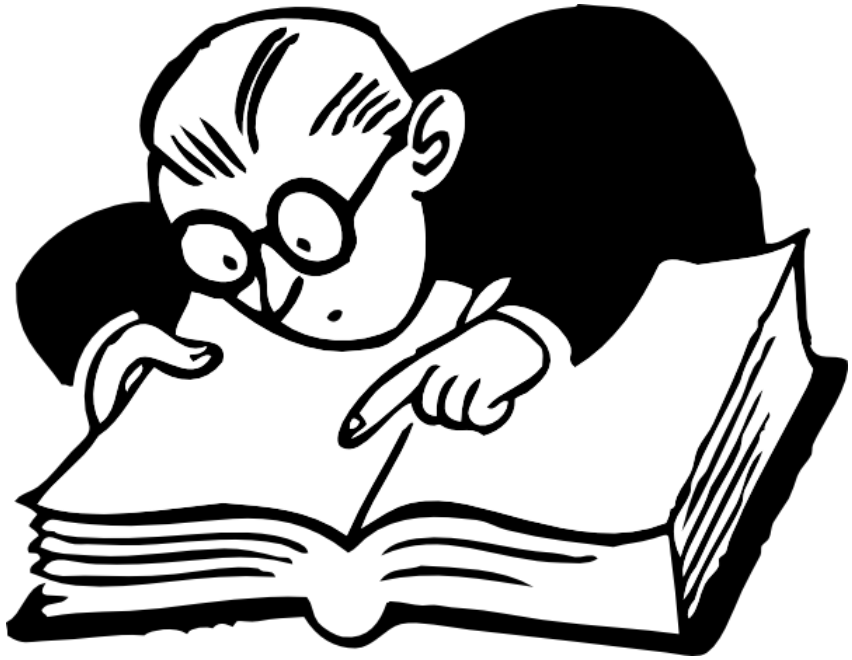
Why …

Which …

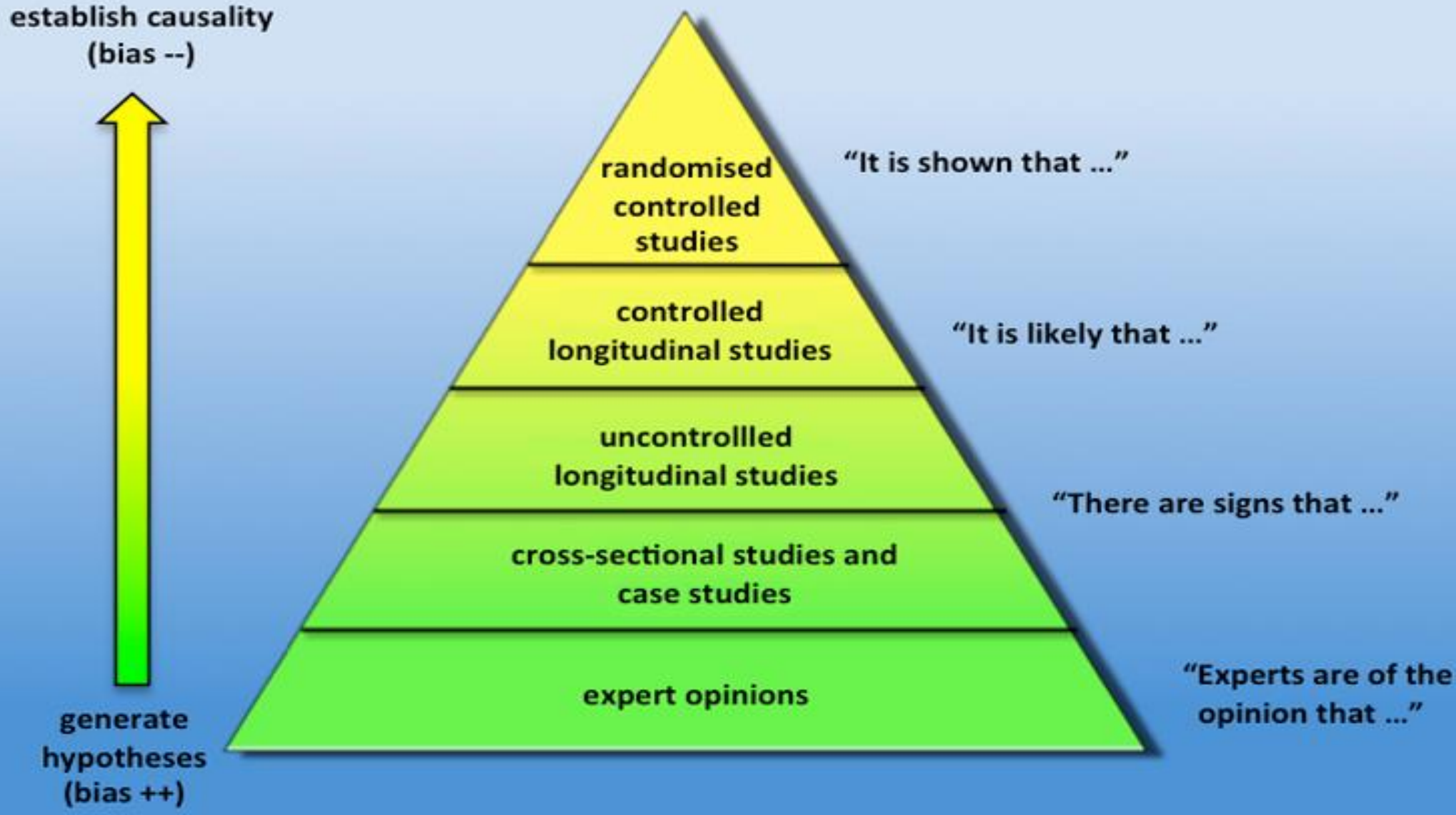
When …

Where …

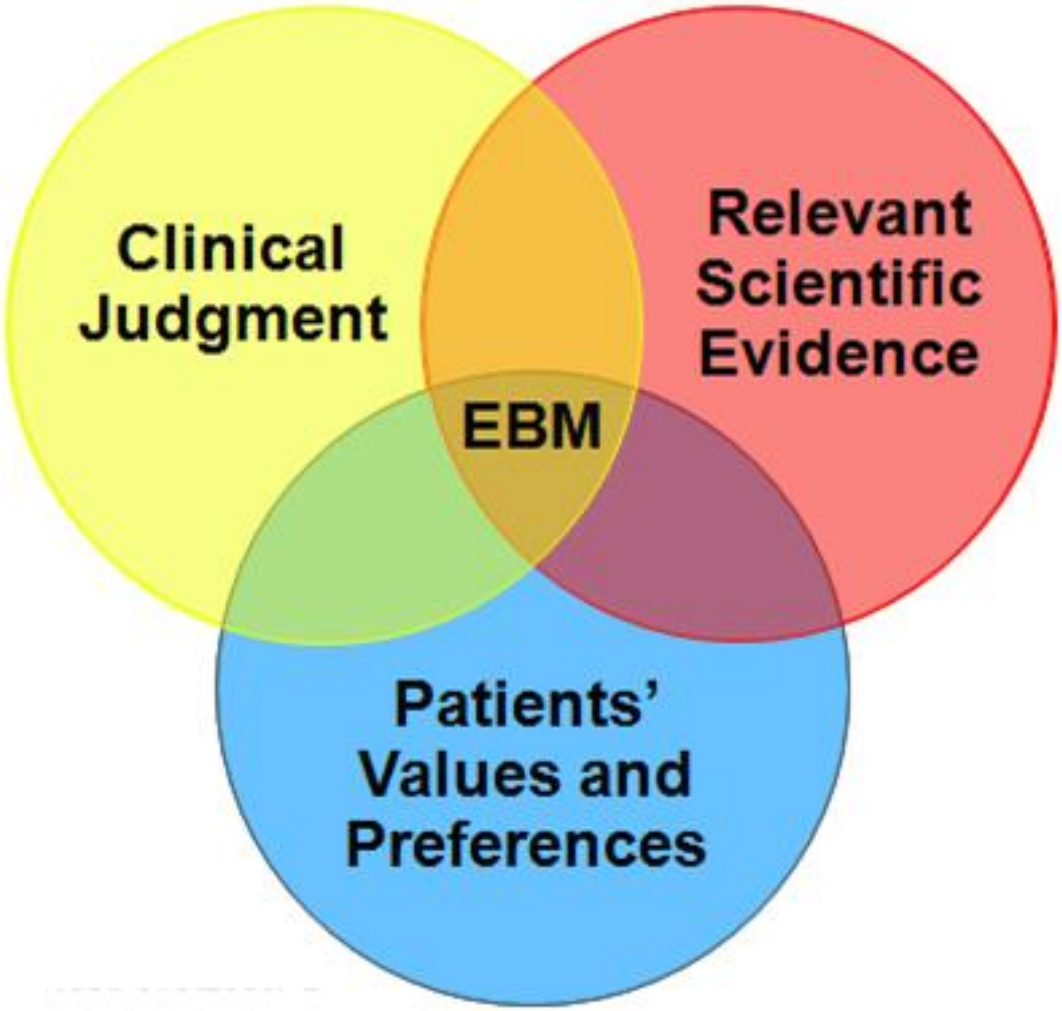
How …



Evidence Based Medicine…A definition



Evidence Based Medicine…A definition



Sacket DL et al. BMJ 1996, 31287023.71-72

The School of Athens (Raffaello, 1509-1511)

Evidence Based Medicine…A definition

Plato

The theory of forms

Aristotle

Empirism

The School of Athens (Raffaello, 1509-1511)

Evidence Based Medicine…A definition

Plato

Eminence Based Medicine

Aristotle

Evidence Based Medicine

The School of Athens (Raffaello, 1509-1511)

The 5 W and 1 H of EBM

What …. is the Evidence Based Medicine?

Why …to discuss of EBRO in PCa?

Which …

When …

Where …

How …

Why …to discuss of EBRO in PCa?

30 years ago…

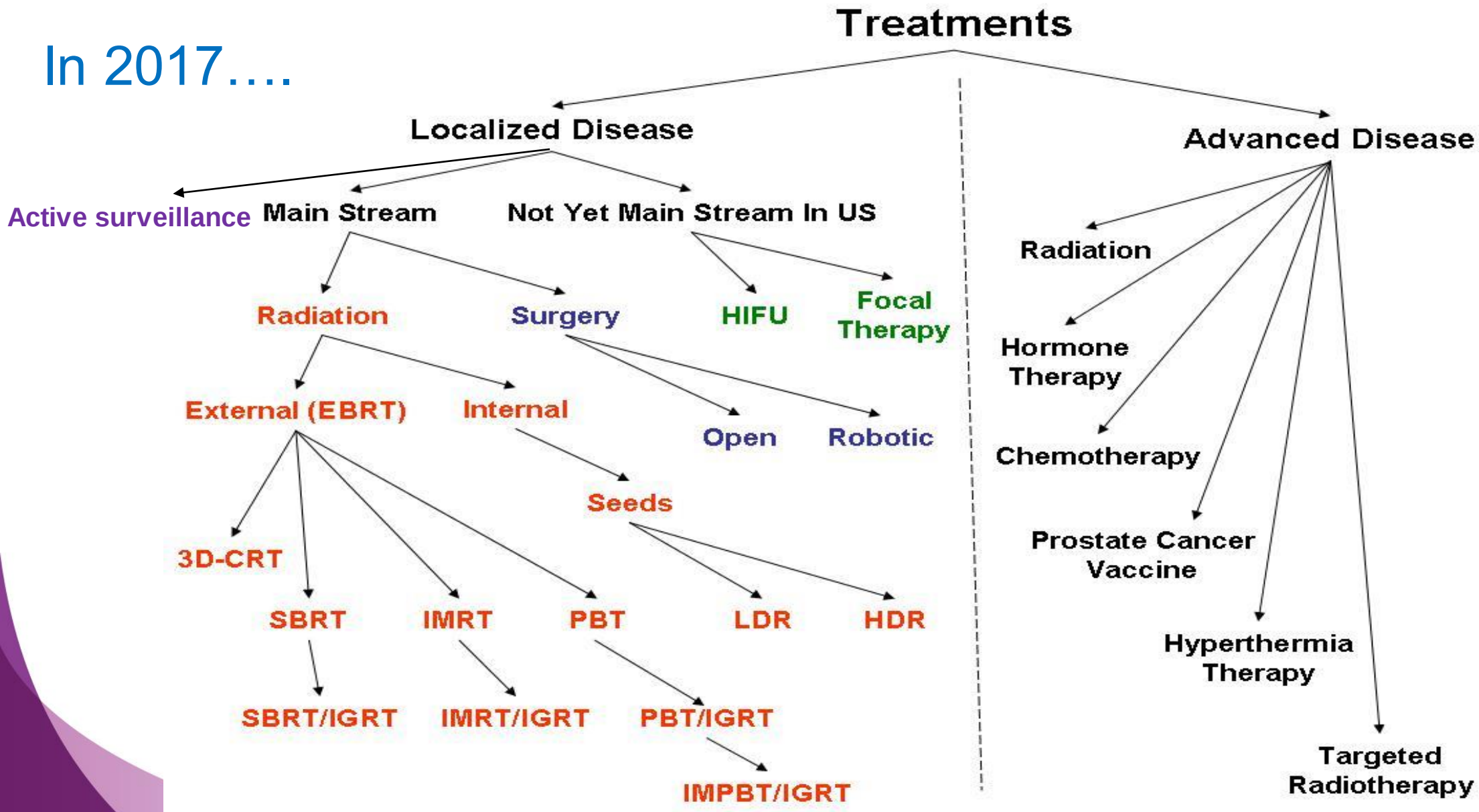
Radical prostatectomy

Vs

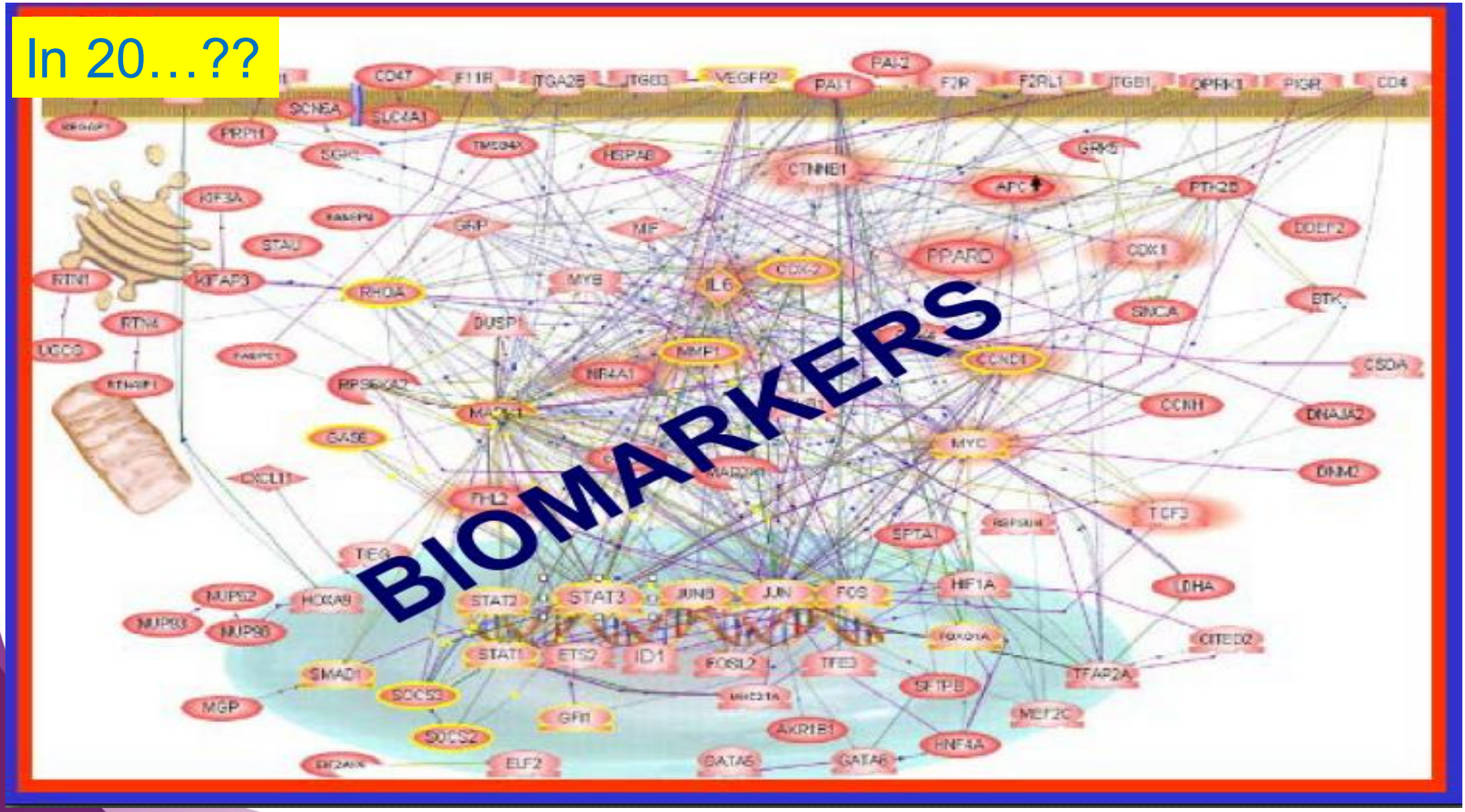
Radiotherapy

Why …to discuss of EBRO in PCa?

In 2017….

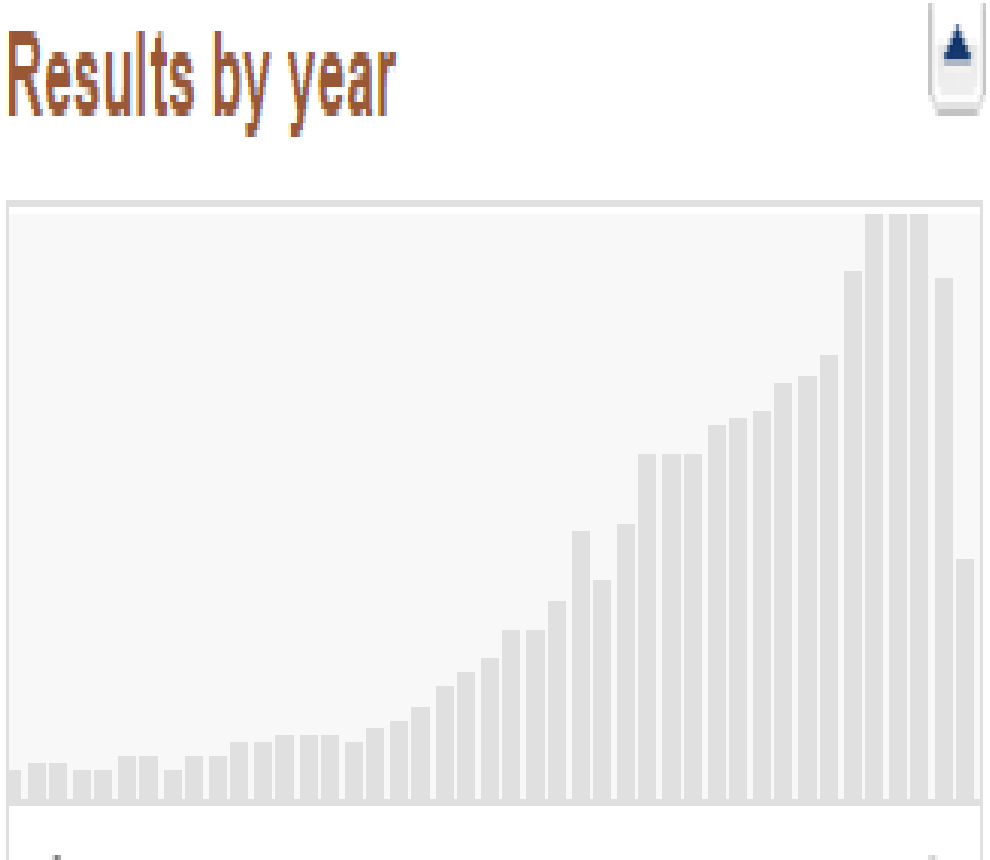


Why …to discuss of EBRO in PCa?



Why …to discuss of EBRO in PCa?

Why …to discuss of EBRO in PCa?



Why …to discuss of EBRO in PCa?

2016

Search results

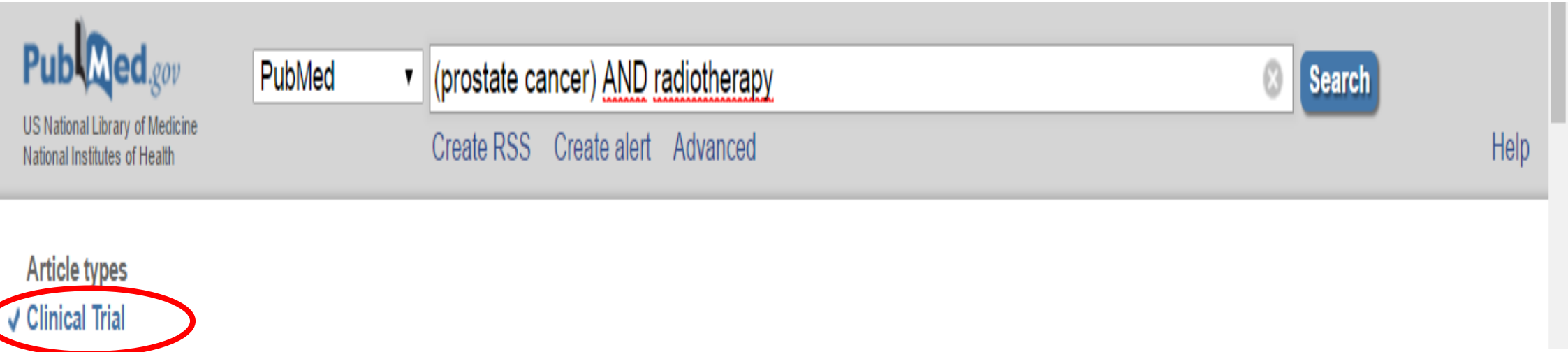
Items: 1 to 20 of 8237

2017

Search results

Items: 1 to 20 of 19553

Why …to discuss of EBRO in PCa?



2016

Search results

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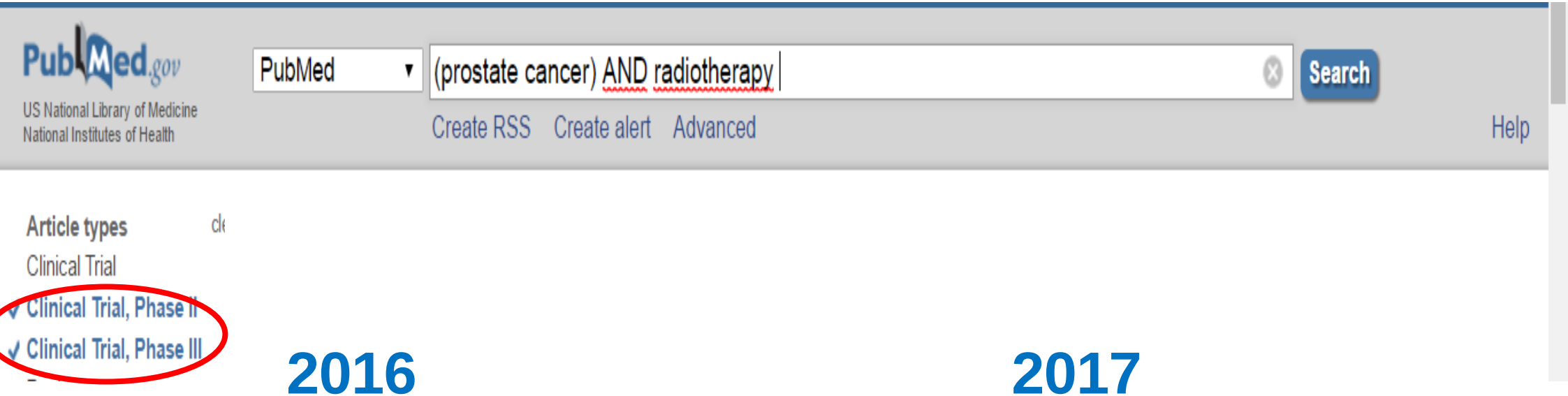
2017

Search results

Items: 1 to 20 of 1804

Why …to discuss of EBRO in PCa?



2016

Search results

Items: 1 to 20 of 323

2017

Search results

Items: 1 to 20 of 499

Why …to discuss of EBRO in PCa?

Prostate Cancer Results Study Group (PCRSG)

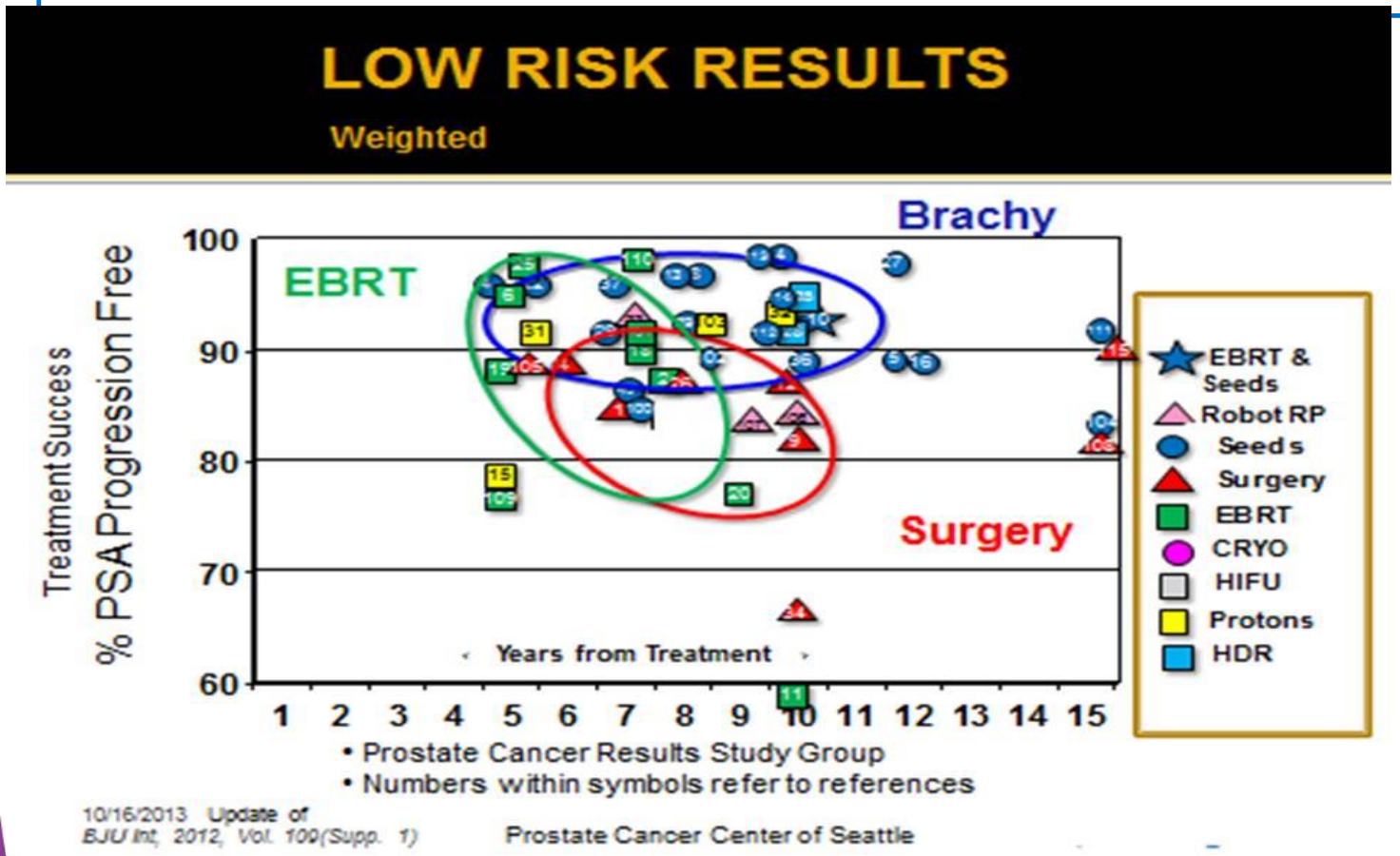
Purpose: to compare and share results for prostate cancer that are understandable to both patients and physicians.

>25,000 articles published from 2000-2012 in peer-reviewed journals.

1066 articles were identified as related to treatment.

http://www.prostatecancertreatmentcenter.com/prostate-cancer/study-group

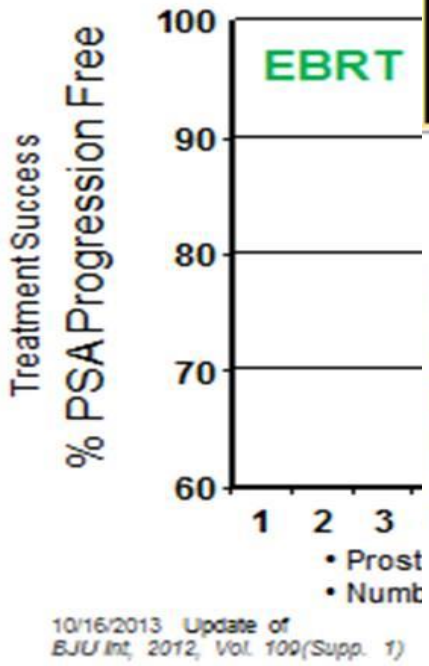
Why …to discuss of EBRO in PCa?



Why …to discuss of EBRO in PCa?

LOW RISK RESULTS

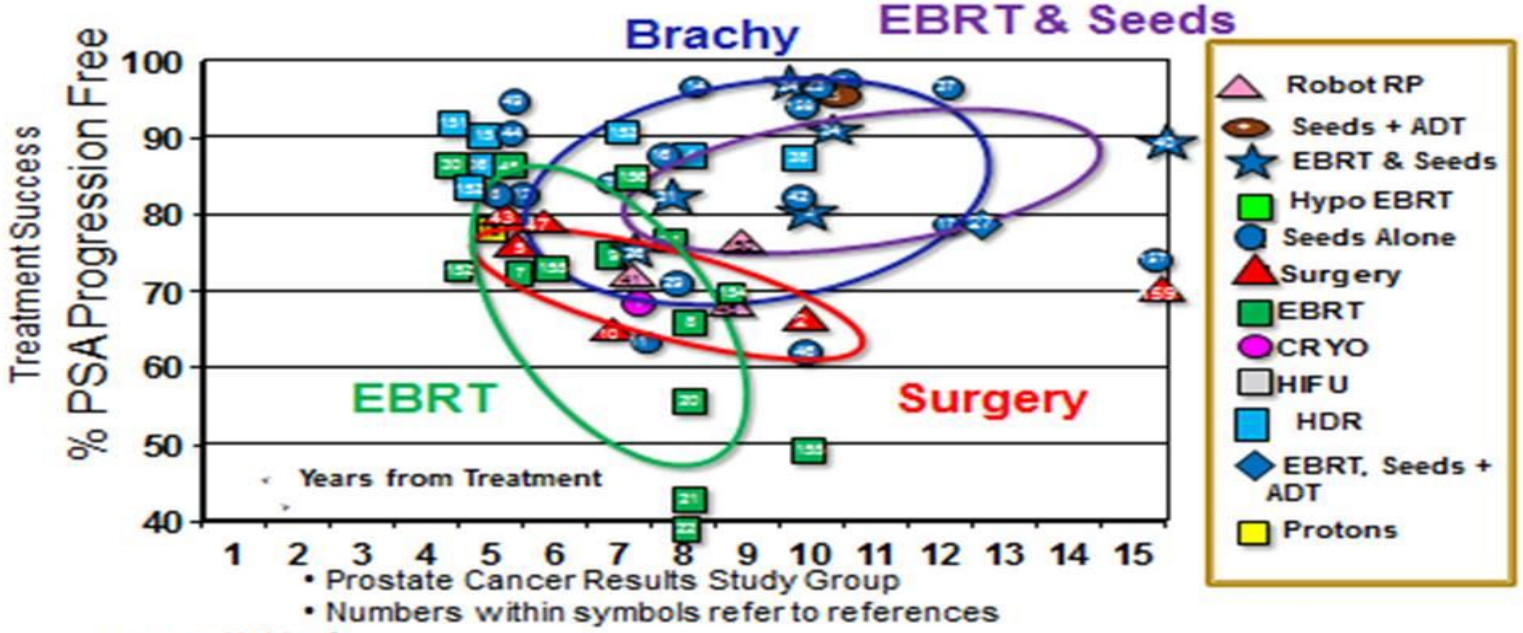
Weighted



10/16/2013 Update of
BJU Int, 2012, Vol. 109(Supp. 1)

INTERMEDIATE RISK RESULTS

Weighted



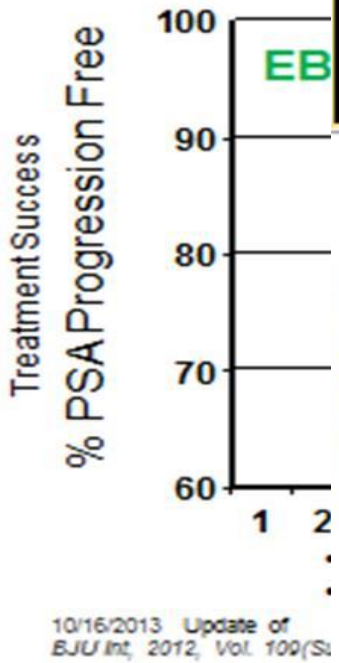
10/16/2013 Update of
BJU Int, 2012, Vol. 109(Supp 1)

Prostate Cancer Center of Seattle

Why …to discuss of EBRO in PCa?

LOW RISK RESULTS

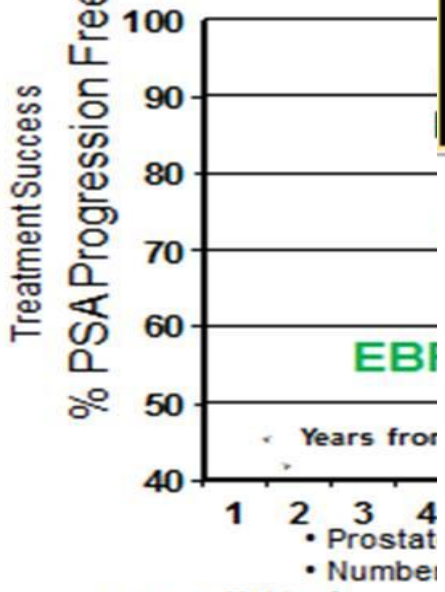
Weighted



10/16/2013 Update of
BJU Int, 2012, Vol. 109(Su

INTERMEDIATE RISK RESULTS

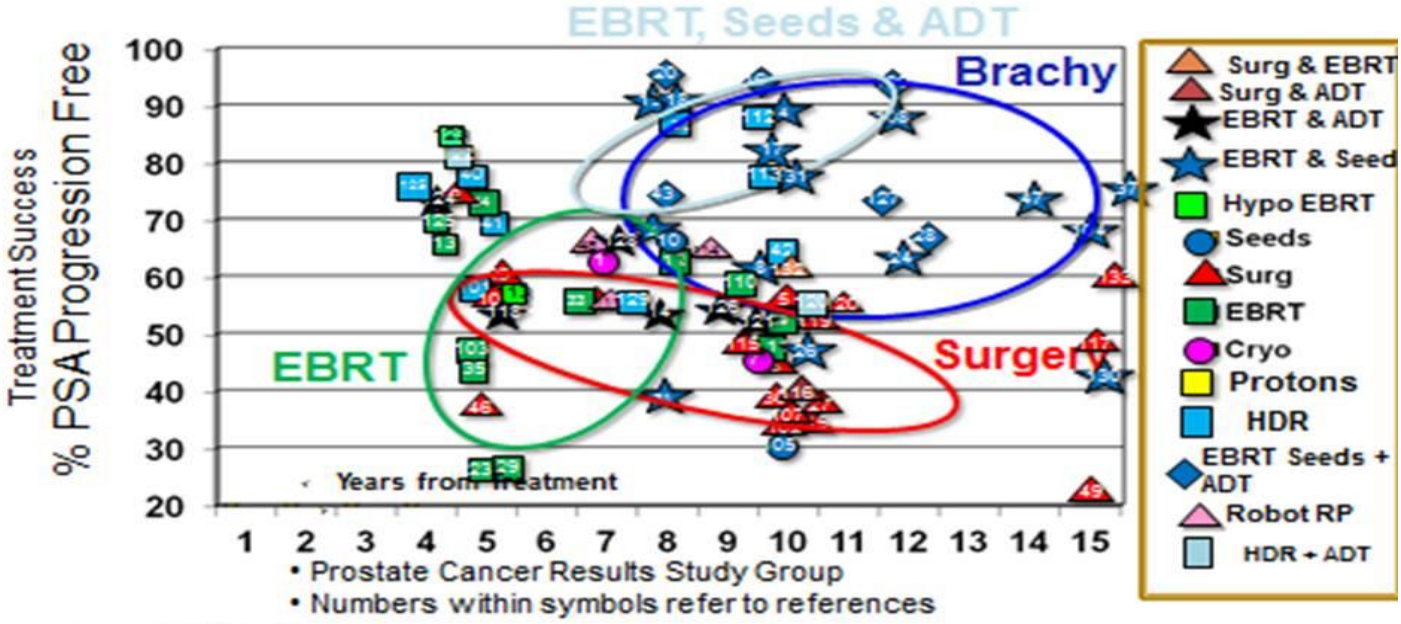
Weighted



10/16/2013 Update of
BJU Int, 2012, Vol. 109(Supp 1

HIGH RISK RESULTS

Weighted



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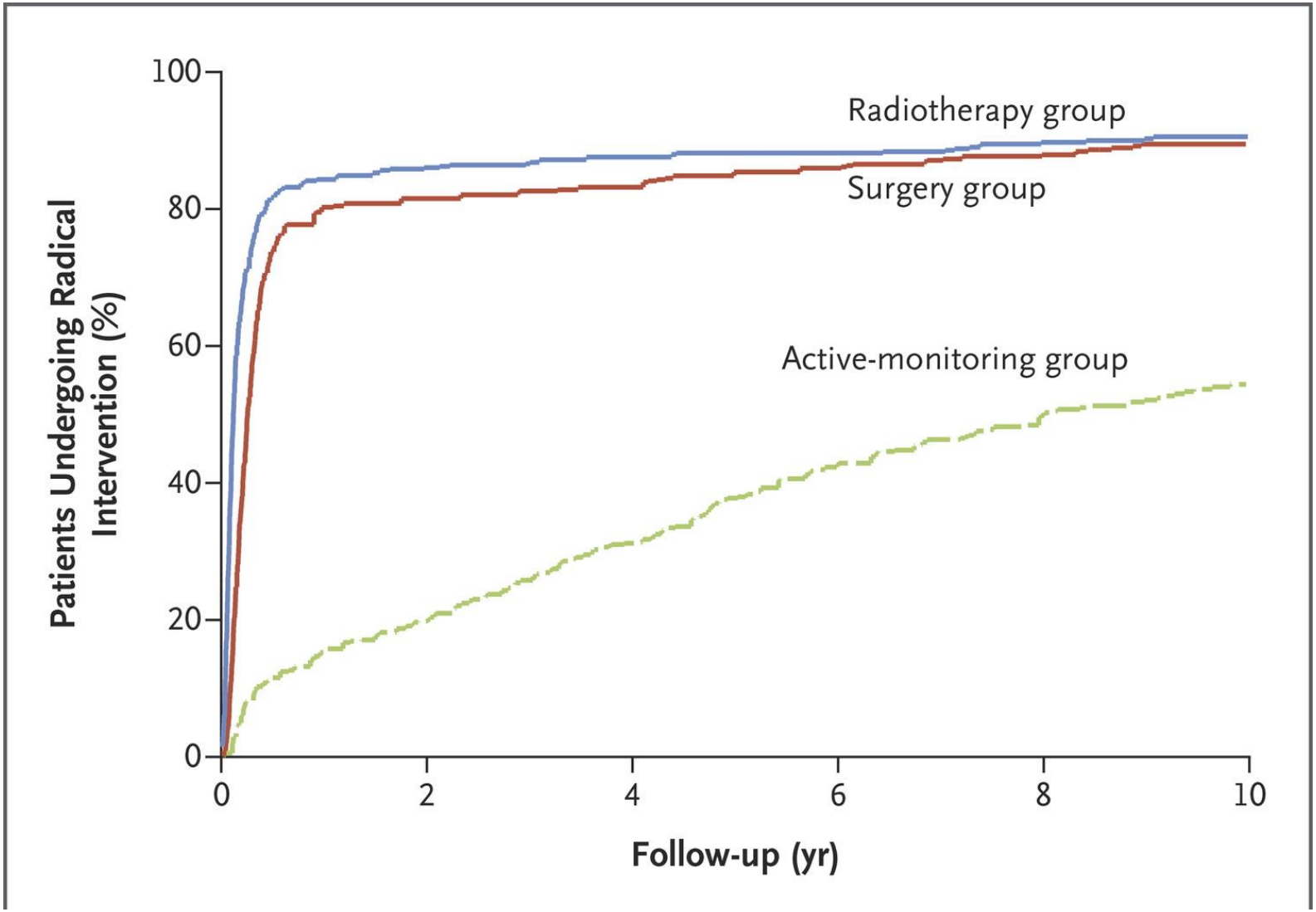
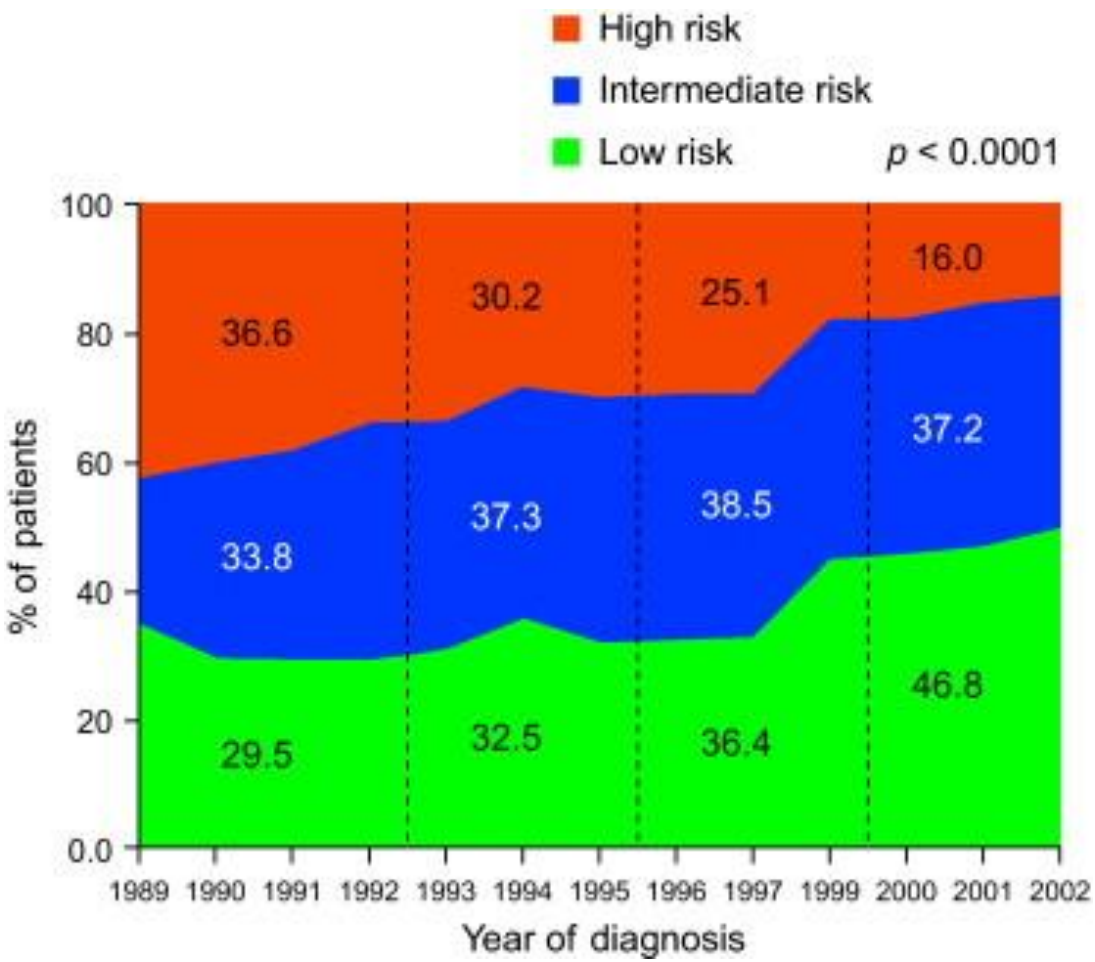


Hamdy et al., N Engl J Med. 2016 Oct 13;375(15):1415-1424

The analysis of the research in PC… Methodological limits

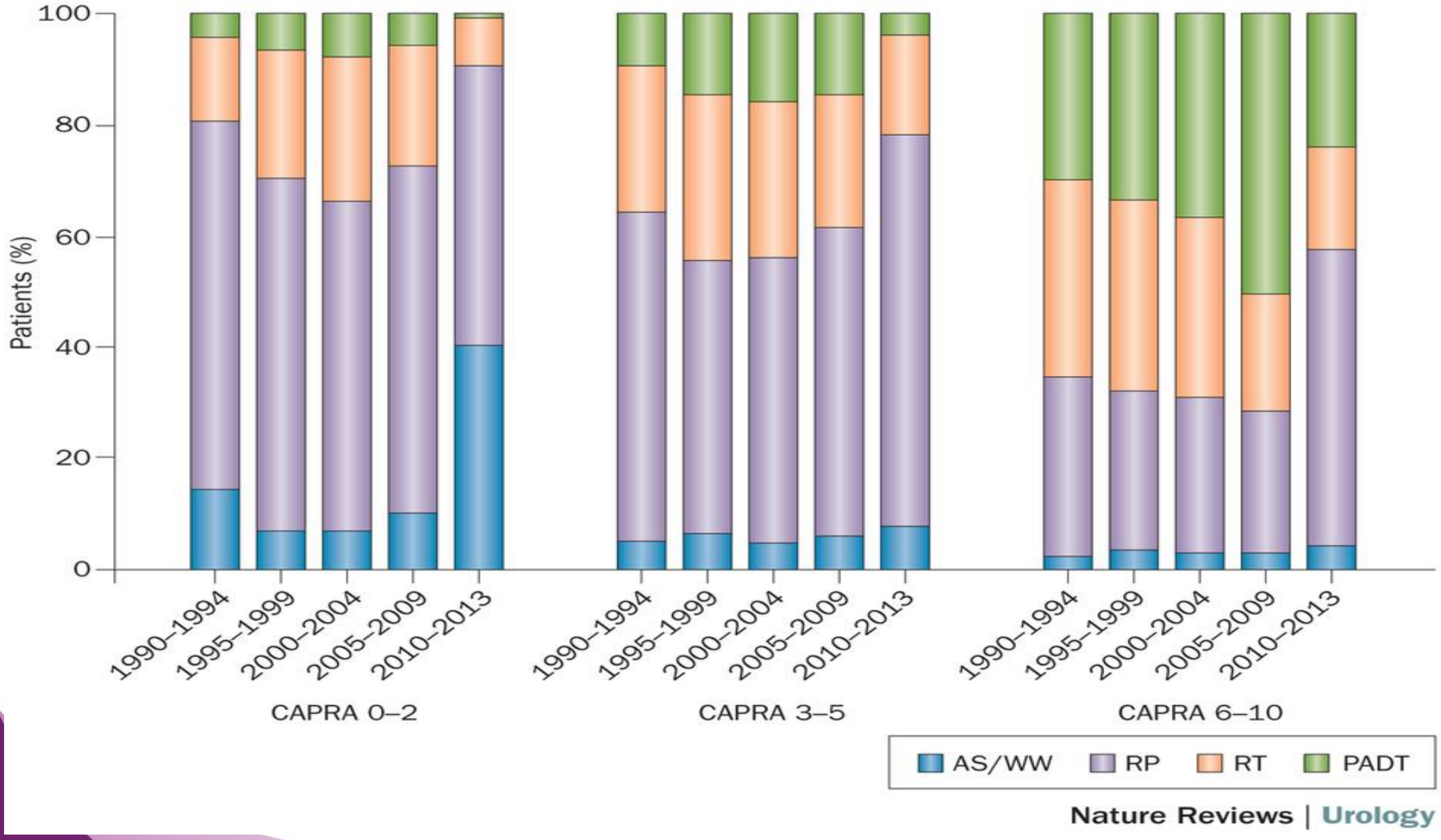


1985: Introduction of the PSA

→ Stage migration
→ Impact on the treatment

Cooperberg MR et al, J Urol. 2003;170:S21-S27

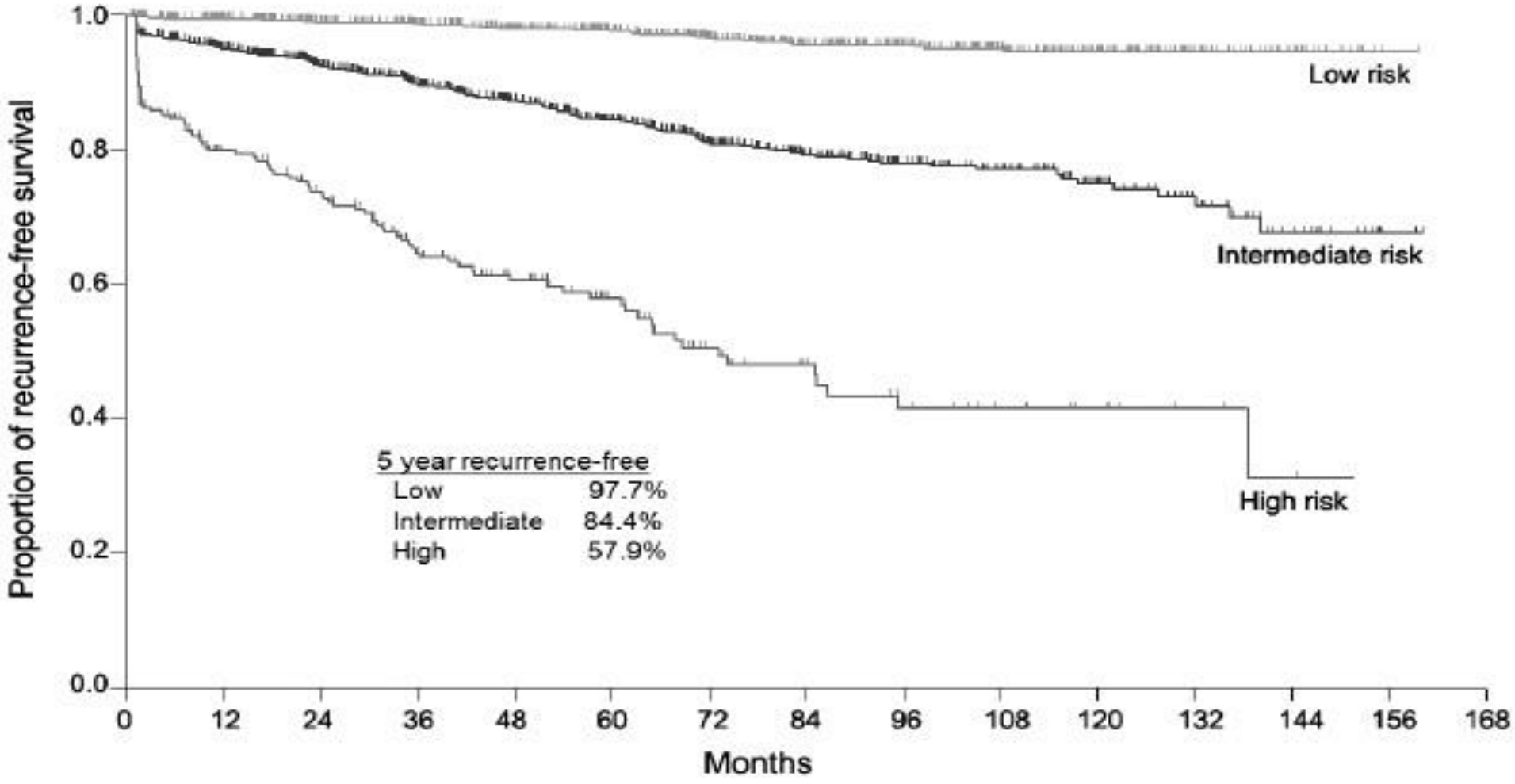
The analysis of the research in PC… Methodological limits



The analysis of the research in PC…
Methodological limits

	Low Risk	Moderate Risk	High Risk
Primary Tumor, cT	cT1 / 2a	cT2b	cT2c[1] / 3
	and	or	or
PSA Value (ng/ml)	≤ 10	> 10 ≤ 20	> 20
	and	or	or
Gleason Score	≤ 6	7	≥ 8

The analysis of the research in PC… Methodological limits



Number at risk

Low	1251	1123	995	901	792	674	547	430	335	251	164	87	38	3
Intermediate	1298	1081	892	751	614	483	364	275	200	143	90	51	24	2
High	263	167	138	102	77	58	41	32	23	17	11	6	3	

The analysis of the research in PC… Methodological limits

A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score

Table 2 – Univariate and multivariable results of Cox proportional hazards regression using varying Gleason grade categorizations

rade	Post-RP Gleason grade						RT Gleason grade without hormone therapy					
Multivariable		Univariate			Multivariable			Univariate			Multivariable		
95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
2.18–2.95	<0.0001	2.66	2.32–3.06	<0.0001	1.94	1.67–2.24	<0.0001	1.47	1.08–2.00	0.014	1.32	0.97–1.81	0.076
4.88–6.67	<0.0001	9.94	8.67–11.40	<0.0001	5.14	4.43–5.97	<0.0001	3.65	2.69–4.95	<0.0001	2.83	2.06–3.88	<0.0001
7.73–10.80	<0.0001	16.76	14.33–19.59	<0.0001	7.99	6.73–9.48	<0.0001	4.26	3.03–6.00	<0.0001	2.87	2.00–4.12	<0.0001
11.53–16.47	<0.0001	33.16	28.73–38.28	<0.0001	11.68	9.92–13.76	<0.0001	7.58	5.58–10.30	<0.0001	4.47	3.17–6.31	<0.0001
Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
2.95–3.89	<0.0001	4.41	3.87–5.02	<0.0001	2.73	2.38–3.13	<0.0001	2.11	1.62–2.76	<0.0001	1.77	1.35–2.33	<0.0001
8.81–11.94	<0.0001	24.06	21.02–27.53	<0.0001	8.50	7.31–9.90	<0.0001	5.78	4.39–7.63	<0.0001	3.43	2.52–4.67	<0.0001

ference; RP = radical prostatectomy; RT = radiation therapy.
eoperative prostate-specific antigen (PSA) and clinical stage (T1 vs T2 vs T3/4), and post-RP Cox model includes preoperative PSA, surgical margin status, and pathology

≤6

3 + 4

4 + 3

8

≥9

Epstein JI et al, Eur Urol. 2016;69:428-465

The analysis of the research in PC… Methodological limits

Heterogeneity of the endpoints:

- OS
- Cancer specific survival
- Clinical relapse
- Biochemical relapse

A definition of relapse based on the PSA… the intrinsic bias….

Defining Biochemical Recurrence of Prostate Cancer After Radical Prostatectomy: A Proposal for a Standardized Definition

Table 3. Outcome of Radical Prostatectomy by BCR Definition

BCR Definition	10-Year PFP		BCR Events	PSA at BCR		Median Time to BCR (months)
	%	95% CI		Median	IQR	
Single PSA ≥ 0.6	72	68% to 75%	349	0.9	0.67-1.40	30
Single PSA ≥ 0.4	69	65% to 72%	416	0.57	0.45-1.00	25
Single PSA ≥ 0.2	63	60% to 67%	557	0.3	0.21-0.51	20
PSA ≥ 0.4 and rising	74	70% to 78%	318	1.00	0.62-1.90	31
PSA ≥ 0.2 and rising	72	68% to 75%	385	0.56	0.35-1.20	27
PSA ≥ 0.1 and rising	69	65% to 73%	436	0.38	0.25-0.91	24
2 successive rises, final ≥ 0.2	68	65% to 71%	458	0.35	0.2-0.9	22
3 successive rises	71	68% to 74%	398	0.47	0.2-1.35	28
3 successive rises of ≥ 0.1	72	69% to 76%	360	0.57	0.3-1.4	29
3 consecutive rises	73	70% to 77%	359	0.56	0.27-1.41	42
ASTRO	79	76% to 82%	359	0.56	0.27-1.41	15

Abbreviations: BCR, biochemical recurrence; PSA, prostate-specific antigen; PFP, progression-free probability; IQR, interquartile range; ASTRO, American Society for Therapeutic Radiation and Oncology.

Stephenson AJ et al, JCO 2006;24:3973-3978


KEEP
CALM
AND
FOCUS
ON
RADIOTHERAPY

The 5 W and 1 H of EBM

What …. is the Evidence Based Medicine?

Why …to discuss of EBRO in PCa?

Which is the better dose?

When …

Where …

How …

High dose versus conventional dose in external beam radiotherapy of prostate cancer: a meta-analysis of long-term follow-up

6 RCTs, 2822 patients
Endpoint: 10-year efficacy of CDRT vs HDRT

- OS = no difference
- PCSS = no difference
- Better BFS : 34.0 vs. 24.7 % ($p < 0.00001$).

- Toxicity: HDRT significantly increased:
  - late Grade 2+ GI tox (28.0 vs. 18.6 %, $p < 0.0001$)
  - late G2+ GU toxicity (22.6 vs. 19.5 %, $p = 0.04$).

Hou Z et al., J Cancer Res Clin Oncol. 2015 Jun;141(6):1063-71

Efficacy and toxicity of external-beam radiation therapy for localised prostate cancer: a network meta-analysis

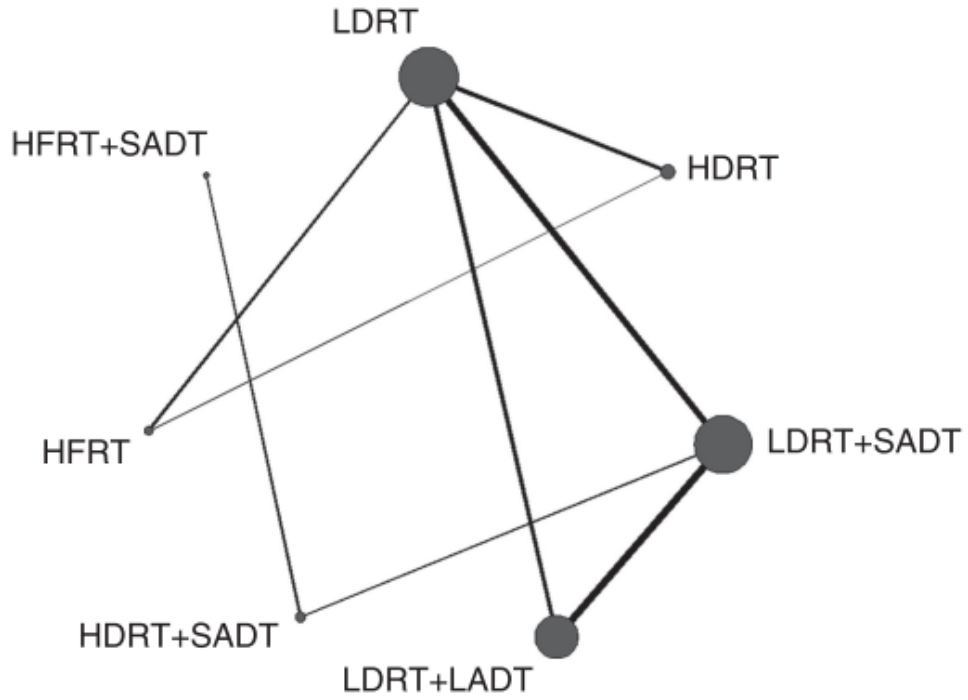
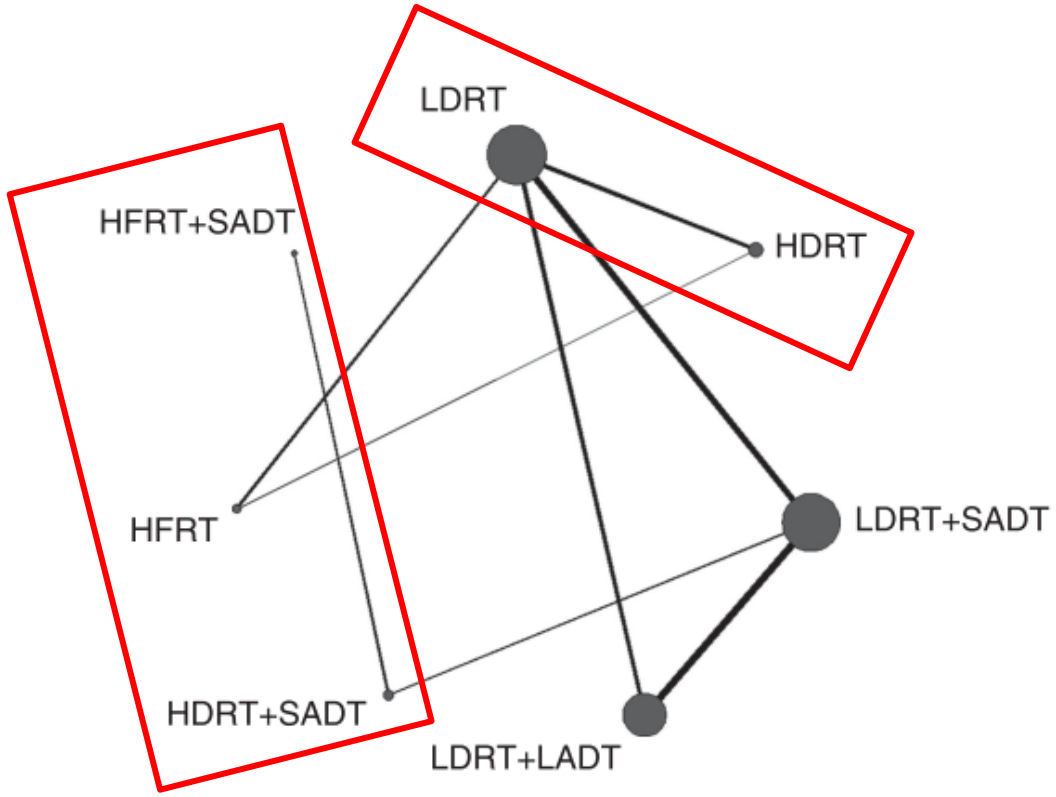


Figure 2. Network of eligible comparisons for the network meta-analysis for efficacy. The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of randomised participants (sample size).

Zhu Z et al., Br J Cancer 2014;110: 2396–2404

Efficacy and toxicity of external-beam radiation therapy for localised prostate cancer: a network meta-analysis



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Zhu Z et al., Br J Cancer 2014;110: 2396–2404

Efficacy and toxicity of external-beam radiation therapy for localised prostate cancer: a network meta-analysis

Table 1. Efficacy in meta-analysis of direct comparisons

	OM				BF				CSM			
	OR	95% CI	P	I^2	OR	95% CI	P	I^2	OR	95% CI	P	I^2
HDRT *vs* LDRT	0.91	0.72–1.14	0.395	0	0.61	**0.49–0.76**	**0.000**	0	0.92	0.67–1.26	0.586	0
LDRT + SADT *vs* LDRT	0.77	**0.66–0.90**	**0.001**	0	0.48	**0.41–0.57**	**0.000**	0	0.51	**0.38–0.67**	**0.000**	0
LDRT + LADT *vs* LDRT	0.65	**0.48–0.87**	**0.004**	28.20%	-	-	-	-	0.56	**0.38–0.83**	**0.004**	44.20%
LDRT + LADT *vs* LDRT + SADT	0.86	0.71–1.06	0.160	30.90%	0.65	**0.44–0.96**	**0.030**	*82.60%*	0.71	**0.53–0.95**	**0.023**	21.60%
HDRT + SADT *vs* LDRT + SADT	1.1	0.72–1.69	0.671		0.64	**0.48–0.83**	**0.001**	0	0.62	0.21–1.81	0.383	43.80%
HFRT *vs* LDRT	0.86	0.62–1.20	0.380	0	0.84	0.67–1.07	0.151	0	0.67	0.34–1.34	0.257	0
HFRT *vs* HDRT	0.94	0.06–15.42	0.962		0.61	0.10–3.82	0.595		-	-	-	-
HFRT + SADT *vs* HDRT + SADT	0.43	0.17–1.12	0.083		0.63	0.28–1.40	0.258		0.28	0.06–1.37	0.144	

Abbreviations: ADT = androgen deprivation; CI = confidence interval; CSM = cancer-specific mortality; HDRT = high-dose radiotherapy; HFRT = hypofractionated radiotherapy; LADT = long-term androgen deprivation therapy; LDRT = low-dose radiotherapy; OM = overall mortality; PSA = prostate-specific antigen failure; OR = odds ratio; SADT = short-term androgen deprivation therapy. Two three-arm studies comparing LDRT with LDRT + SADT and LDRT + LADT were not included in the pair-wise meta-analysis.

Zhu Z et al., Br J Cancer 2014;110: 2396–2404

Efficacy and toxicity of external-beam radiation therapy for localised prostate cancer: a network meta-analysis

Table 1. Efficacy in meta-analysis of direct comparisons

	OM				BF				CSM			
	OR	95% CI	P	I^2	OR	95% CI	P	I^2	OR	95% CI	P	I^2
HDRT *vs* LDRT	0.91	0.72–1.14	0.395	0	0.61	**0.49–0.76**	**0.000**	0	0.92	0.67–1.26	0.586	0
LDRT + SADT *vs* LDRT	0.77	**0.66–0.90**	**0.001**	0	0.48	**0.41–0.57**	**0.000**	0	0.51	**0.38–0.67**	**0.000**	0
LDRT + LADT *vs* LDRT	0.65	**0.48–0.87**	**0.004**	28.20%	-	-	-	-	0.56	**0.38–0.83**	**0.004**	44.20%
LDRT + LADT *vs* LDRT + SADT	0.86	0.71–1.06	0.160	30.90%	0.65	**0.44–0.96**	**0.030**	*82.60%*	0.71	**0.53–0.95**	**0.023**	21.60%
HDRT + SADT *vs* LDRT + SADT	1.1	0.72–1.69	0.671		0.64	**0.48–0.83**	**0.001**	0	0.62	0.21–1.81	0.383	43.80%
HFRT *vs* LDRT	0.88	0.62–1.26	0.480	0	0.84	0.67–1.07	0.151	0	0.67	0.34–1.34	0.257	0
HFRT *vs* HDRT	0.94	0.06–15.42	0.962		0.61	0.10–3.82	0.595		-	-	-	-
HFRT + SADT *vs* HDRT + SADT	0.43	0.17–1.12	0.083		0.63	0.28–1.40	0.258		0.28	0.06–1.37	0.144	

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High-dose radiation therapy was defined as total dose >74 Gy and LDRT as total dose ⩽70 Gy.

Zhu Z et al., Br J Cancer 2014;110: 2396–2404

Efficacy and toxicity of external-beam radiation therapy for localised prostate cancer: a network meta-analysis

Missing trials….

HDRT vs HDRT + SADT

HDRT + LADT vs LDRT + LADT

HDRT vs HDRT + SADT

….

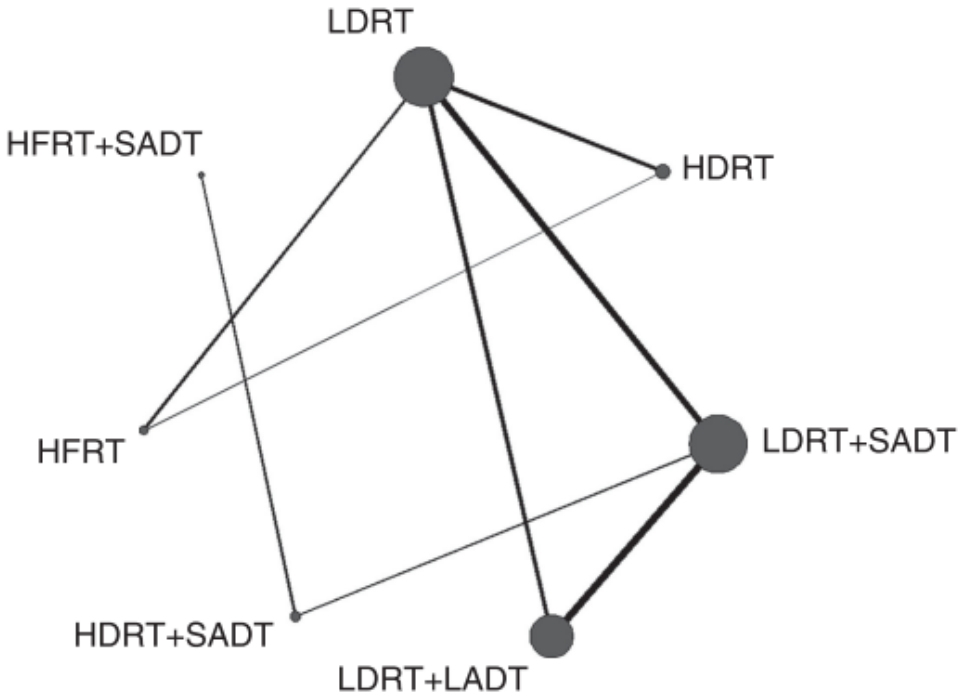


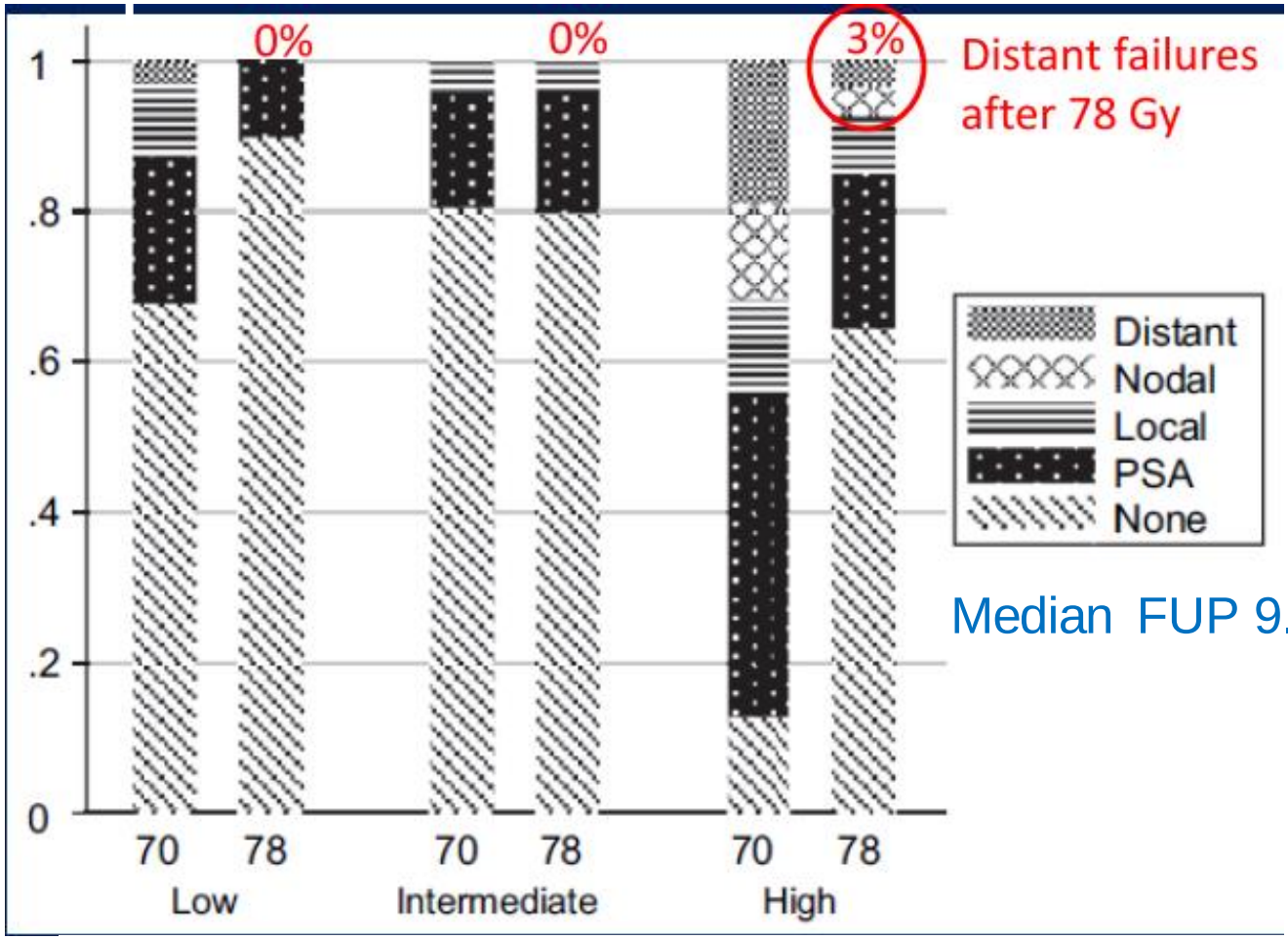
Figure 2. Network of eligible comparisons for the network meta-analysis for efficacy. The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of randomised participants (sample size).

Zhu Z et al., Br J Cancer 2014;110: 2396–2404

Which evidences for dose escalation?

Study (year)	Population	Standard RT	High Dose RT	Results
Beckendolf (2011)	LR – IR – HR	70 Gy	80 Gy	Better BFS
Peeters (2006)	LR – IR – HR	68 Gy	78 Gy	Better BFS in IR and HR
Kuban (2008)	LR – IR - HR	70 Gy	78 Gy	Better BFS
Zietman (2008)	LR – IR	70.2 Gy	79.2 Gy	Better BFS in LR, strong trend in IR
Pollack (2002)	LR – IR - HR	70 Gy	78 Gy	Better BFS in IR and HR

Which evidences for dose escalation?



Median FUP 9.7 years

Kuban et al. Int J Radiat Oncol Biol Phys. 2011 Apr 1;79(5):1310-7

Efficacy and toxicity of external-beam radiation therapy for localised prostate cancer: a network meta-analysis

Missing trials??

HDRT vs HDRT + SADT

HDRT + LADT vs LDRT + LADT

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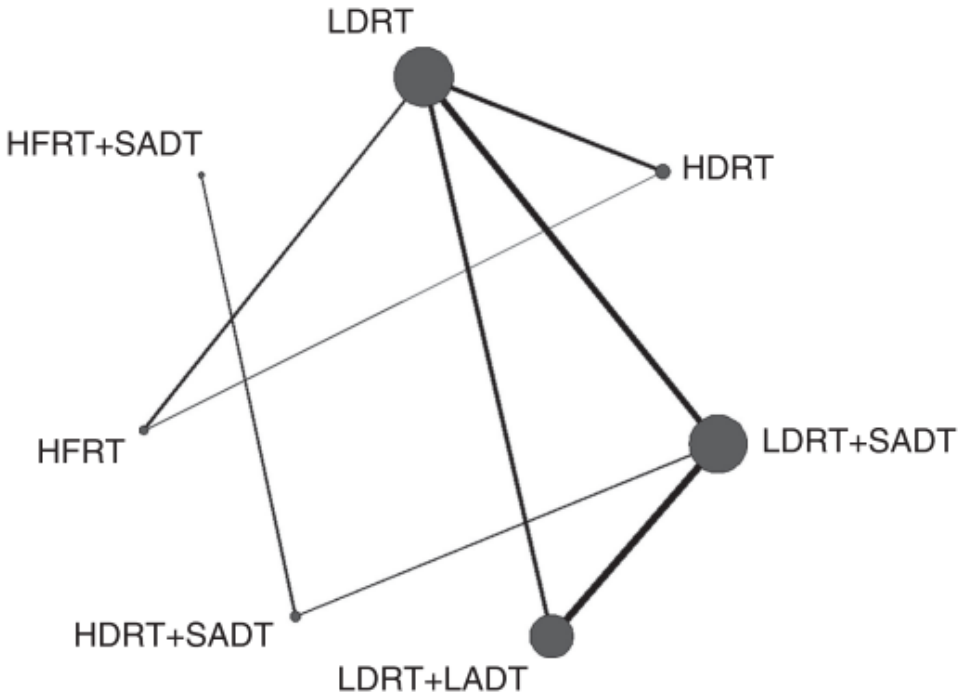

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Zhu Z et al., Br J Cancer 2014;110: 2396–2404

Which evidences for dose escalation?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Prostate Cancer

PRINCIPLES OF RADIATION THERAPY

Primary External Beam Radiation Therapy

- Highly conformal RT techniques should be used to treat prostate cancer.
- Doses of 75.6 to 79.2 Gy in conventional fractions to the prostate (± seminal vesicles for part of the therapy) are appropriate for patients with low-risk cancers. For patients with intermediate- or high-risk disease, doses up to 81.0 Gy provide improved PSA-assessed disease control.

The 5 W and 1 H of EBM

What …. is the Evidence Based Medicine?

Why …to discuss of EBRO in PCa?

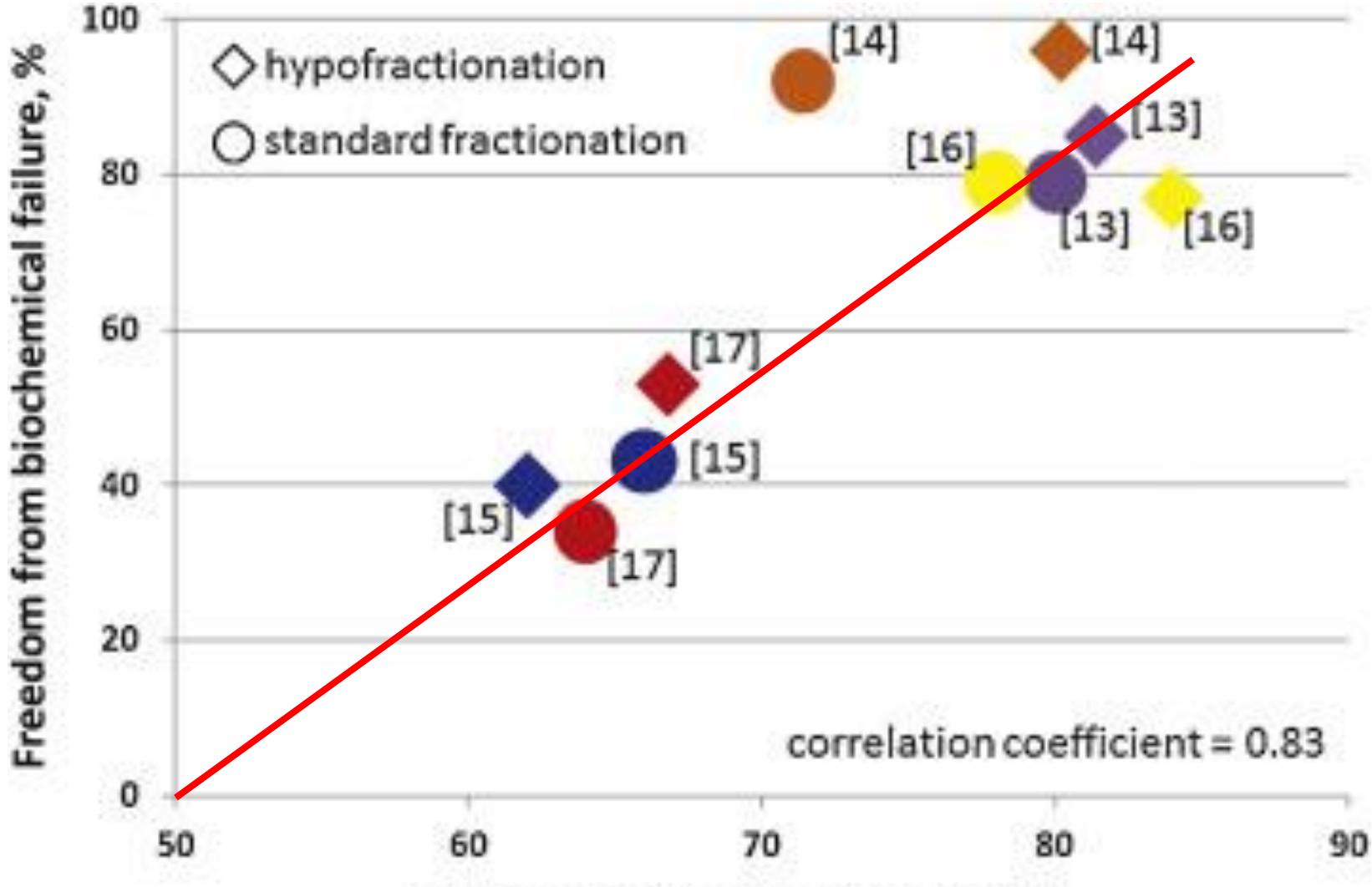
Which is the better dose?

When … treatment duration…dose/fraction

Where …

How …

Any evidence for hypofraction?



Koontz et al, Eur Urol 2015; 68:683–691

Any evidence for hypofraction?

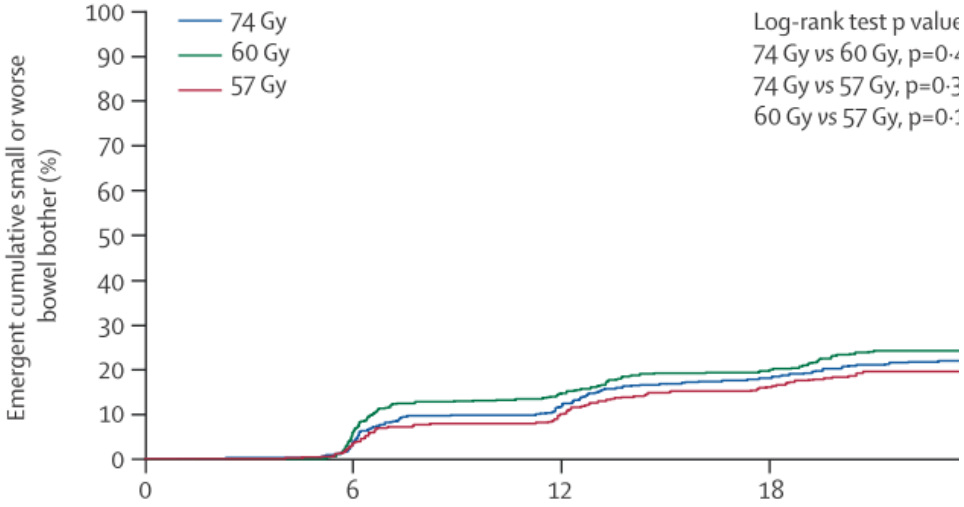
Table 3. Randomized hypofractionation trials: schedules, equivalent doses in 2 Gy fractions and biochemical outcome.

Trial	Patients (n)	Fractionation schedule	RT technique	NTD2/1.5	NTD2/3	Median FUP	% 5y-bRFS
Canada	470 T1-2 466 T1-2	66 Gy/2 Gy/33 f 52.5 Gy/2.62 Gy/20f	2D–3D CRT	66 Gy 62 Gy	66 Gy 59 Gy	47.5 mo	52.9 59.9
Australia	109 T1-2 108 T1-2	64 Gy/2 Gy/32 f 55 Gy/2.75 Gy/20 f	2D-3D CRT	64 Gy 66.8 Gy	64 Gy 63.3 Gy	62.5 mo	56 57
USA	102 LI 102 LI	75.6 Gy/1.8 Gy/42 f 72 Gy/2.4 Gy/30 f	IMRT	71.3 Gy 80.2 Gy	72.6 Gy 77.8 Gy	40 mo	92 96
USA	152 LIH 151 LIH	76 Gy/2 Gy/38 f 70.2 Gy/2.7 Gy/26 f	IMRT	76 Gy 84.2 Gy	76 Gy 80 Gy	60 mo	85.6 86.1
Italy	85 H 83 H	80 Gy/2Gy/40 f 62 Gy/3.1 Gy/20 f	3D CRT	80 Gy 81.5 Gy	80 Gy 74 Gy	70 mo	74 85
UK	153 LI 153 LI 151 LI	74 Gy/2 Gy/37 f 60 Gy/3 Gy/20 f 57 Gy/3 Gy/19 f	IMRT	74 Gy 77.1 Gy 73.3 Gy	74 Gy 72 Gy 68.4 Gy	50.5 mo	–

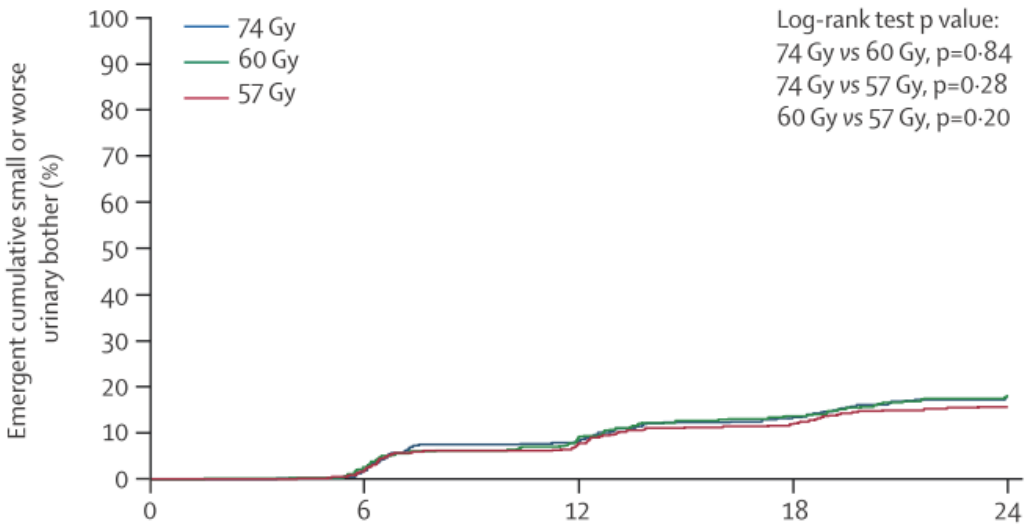
EQD2: Equivalent dose in 2 Gy fractions; FFBF: Freedom from biochemical failure; H: High risk; I: Intermediate risk; IMRT: Intensity modulated radiotherapy; L: Low risk; mo: Months; RT: Radiotherapy.

De Bari B, Expert Rev Anticancer Ther. 2014 May;14(5):553-64.

Hypofractionated radiotherapy versus conventionally fractionated radiotherapy for patients with intermediate-risk localised prostate cancer: 2-year patient-reported outcomes of the randomised, non-inferiority, phase 3 CHHiP trial



Number at risk (events)				
74 Gy	596 (23)	564 (46)	497 (35)	430 (18)
60 Gy	577 (34)	533 (49)	456 (26)	399 (22)
57 Gy	589 (21)	563 (38)	510 (33)	439 (17)

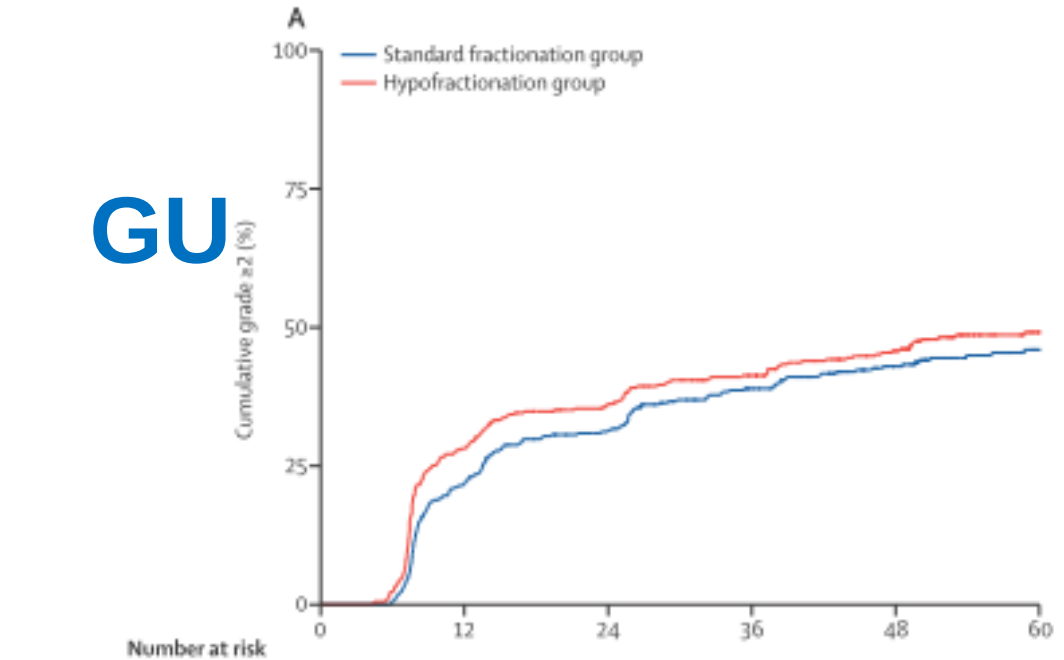


Number at risk (events)					
74 Gy	517 (9)	497 (34)	445 (25)	390 (18)	276
60 Gy	521 (14)	499 (34)	436 (22)	388 (19)	286
57 Gy	522 (11)	505 (30)	461 (21)	399 (17)	293

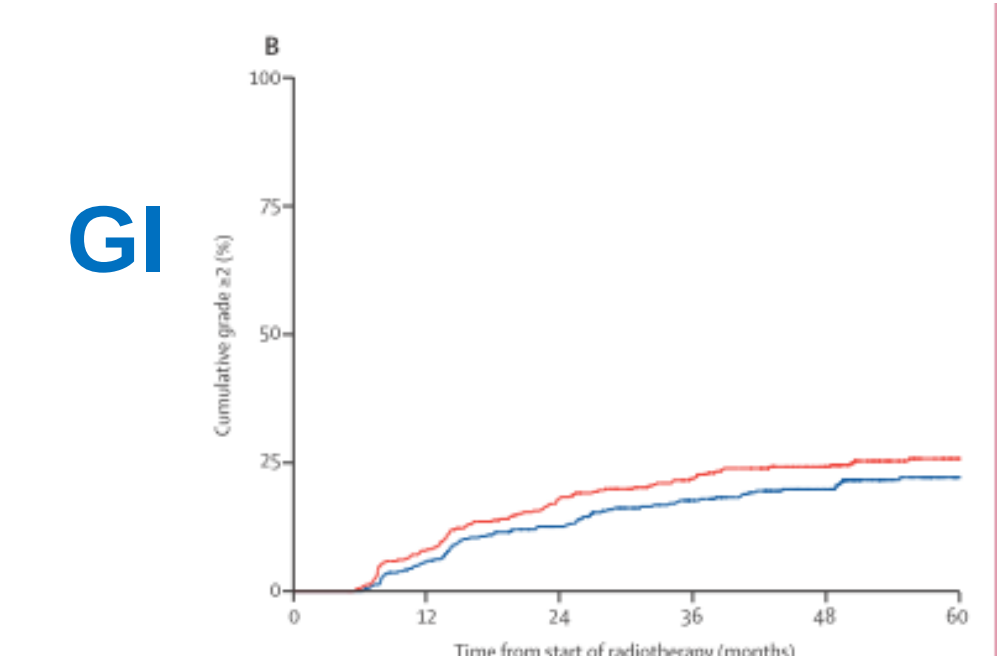
Wilkins A et al., Lancet Oncol. 2015 Dec;16(16):1605-16

Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial

GU



GI



Alluwini S et al., Lancet Oncol. 2015 Dec;16(16):274-283

Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial

	Standard fractionation group (n=390)	Hypo-fractionation group (n=402)	p value
Genitourinary			
Pain needing drugs (grade 2)	14 (4%)	21 (5%)	0·26
Macroscopic haematuria (grade 3)	9 (2%)	15 (4%)	0·24
Increased frequency at day (grade 2)	96 (25%)	100/401 (25%)*	0·92
Increased frequency at night five to seven times (grade 2)	107 (27%)	125/401 (31%)*	0·25
Increased frequency at night >seven times (grade 3)	26 (7%)	46/401 (12%)*	0·019
Incontinence (grade 3)	39/364 (11%)*	49/372 (13%)*	0·30
Gastrointestinal			
Pain needing drugs (grade 2)	18 (5%)	35 (9%)	0·021
Diarrhoea with drugs (grade 2)	19 (5%)	21 (5%)	0·82
Increased frequency ≥six (grade 2)	31 (8%)	58 (15%)	0·0035
Use of pads (grade 3)	22 (6%)	32 (8%)	0·19
Blood or mucous loss (grade 3)	15 (4%)	22 (6%)	0·28

Alluwini S et al., Lancet Oncol. 2015 Dec;16(16):274-283

Any evidence for hypofraction?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Prostate Cancer

- **Moderately hypofractionated image-guided IMRT regimens (2.4–4 Gy per fraction over 4–6 weeks) have been tested in randomized trials reporting similar efficacy and toxicity to conventionally fractionated IMRT. They can be considered as an alternative to conventionally fractionated regimens when clinically indicated.**


AND SBRT???

Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials☆☆

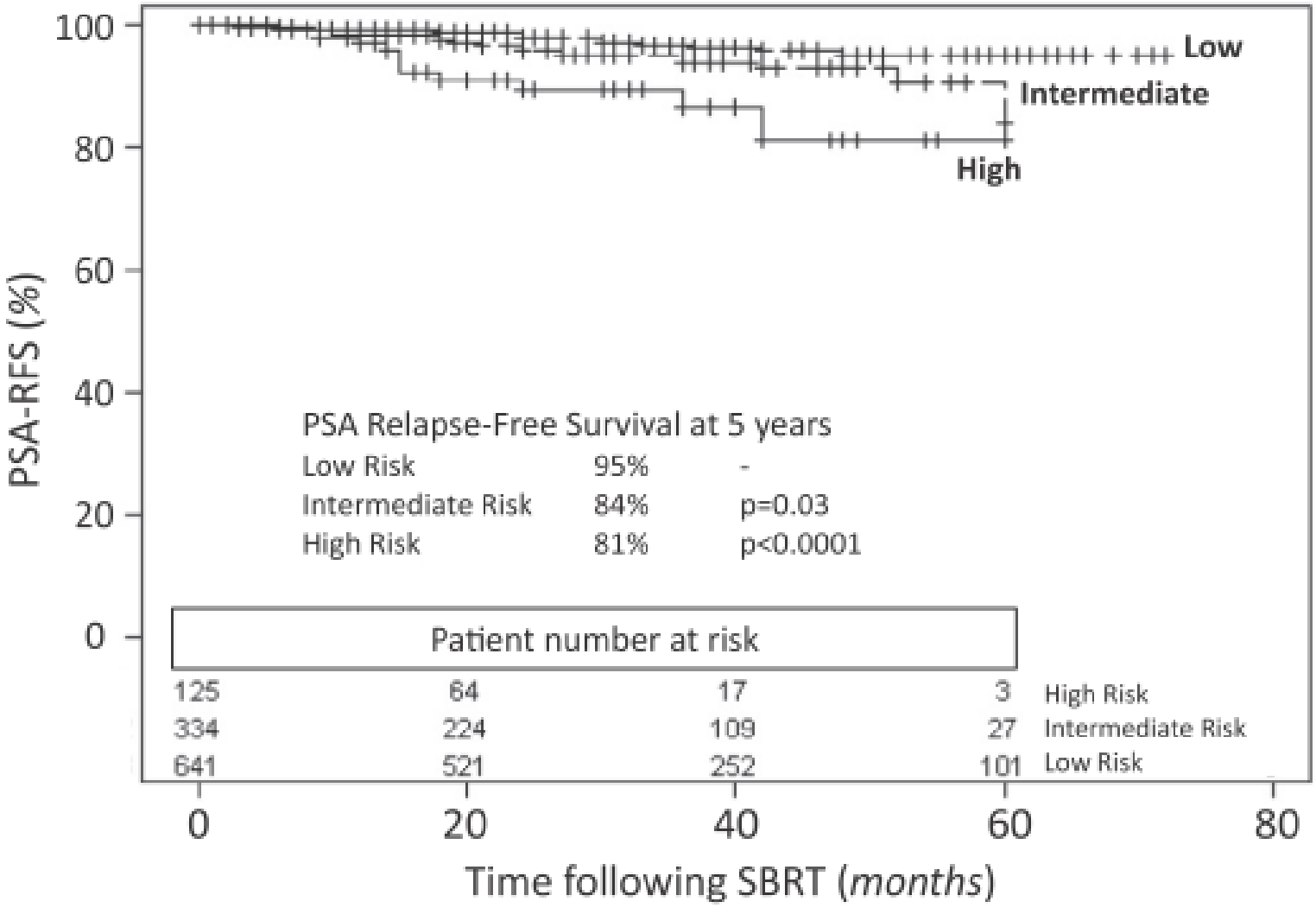
Patient and treatment characteristics ($n = 1100^{\dagger}$).

Risk group	N (%)	35 Gy	36.25 Gy	38–40 Gy	ADT use	FU*
Low	641 (58%)	254 (40%‡)	319 (50%)	68 (11%)	50 (8%)	36
Intermediate	334 (30%)	108 (32%)	188 (56%)	38 (11%)	49 (15%)	30.5
High	125 (11%)	23 (18%)	82 (66%)	20 (16%)	48 (38%)	23
Total	1100	385 (35%)	589 (54%)	126 (11%)	147 (14%)	

Median followup : 36 months…only….

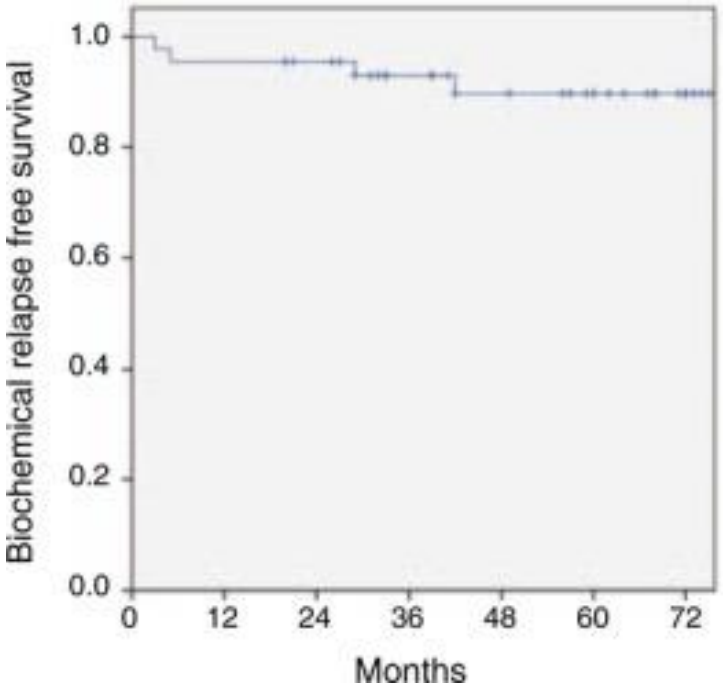
King CR et al., Radioth Oncol 2013, 109. 217–221

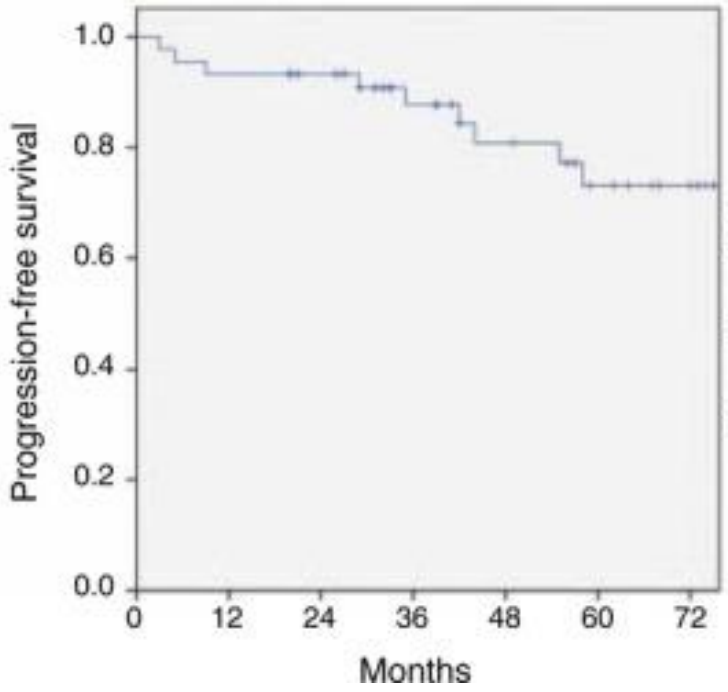
Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials☆☆

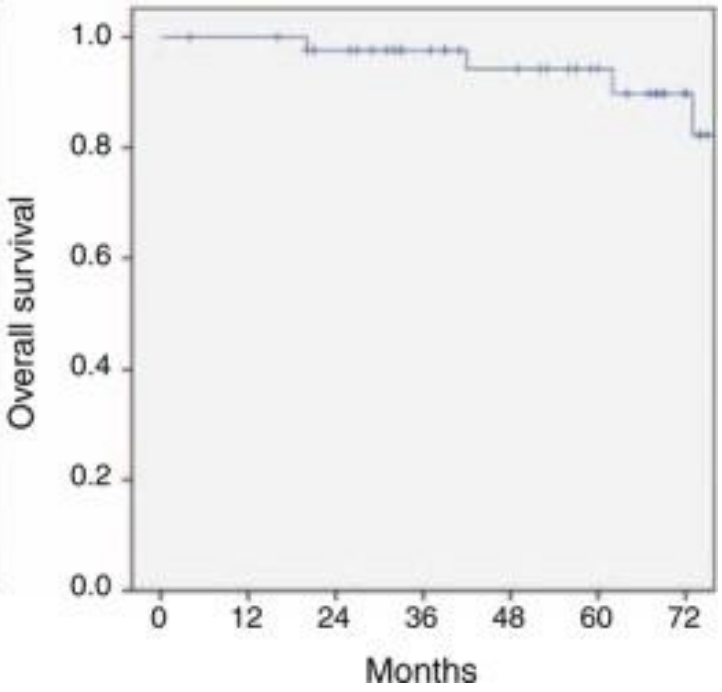


King CR et al., Radioth Oncol 2013, 109. 217–221

Stereotactic body radiotherapy as treatment for organ confined low- and intermediate-risk prostate carcinoma, a 7-year study.







King AJ et al, Front Oncol. 2014 Sep 2;4:240.

Any evidence for hypofraction?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Prostate Cancer

- **Extremely hypofractionated image-guided IMRT/SBRT regimens (6.5 Gy per fraction or greater) are an emerging treatment modality with single institutional and pooled reports of similar efficacy and toxicity to conventionally fractionated regimens. They can be considered as an alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise.**

Ilona Staller (Cicciolina)
member of the Italian Parliament in1987 - 1991

The 5 W and 1 H of EBM

What …. is the Evidence Based Medicine?

Why …to discuss of EBRO in PCa?

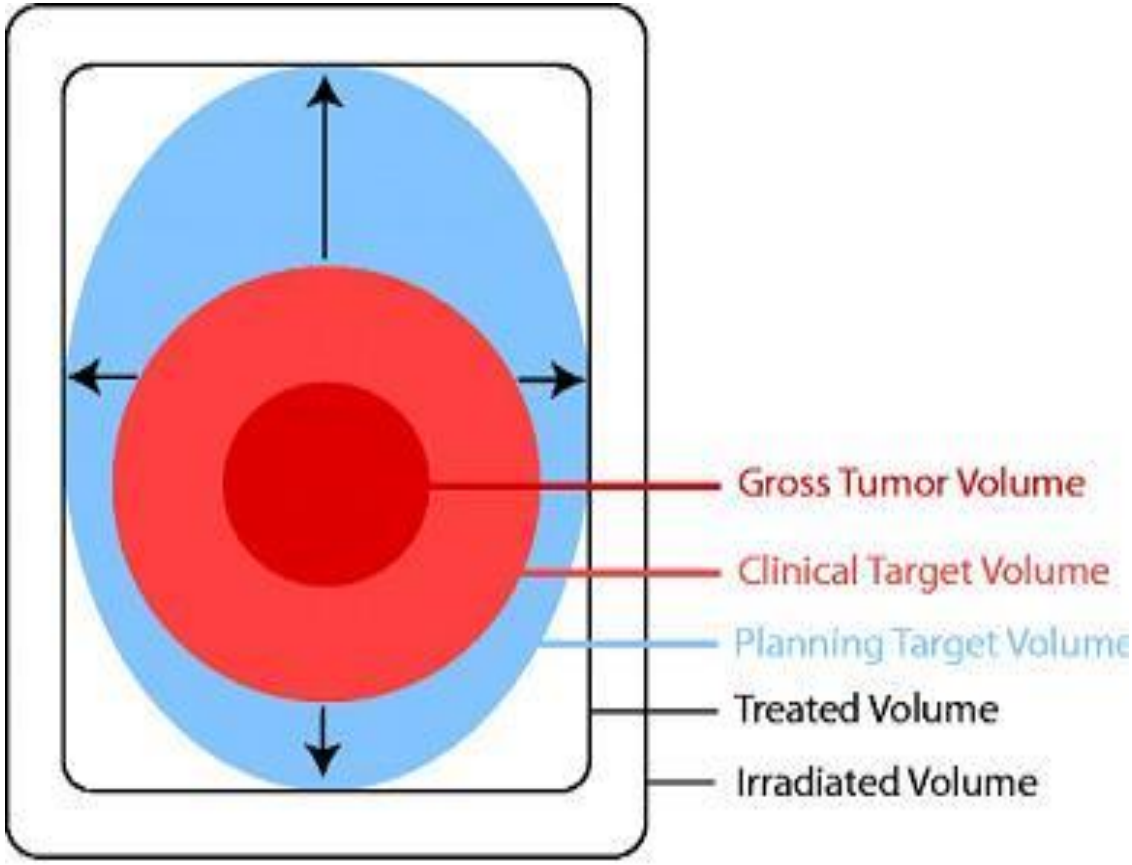
Which is the better dose?

When … treatment duration…dose/fraction

Where … Evidence based volumes

How …

Could treatment volumes be evidence based?



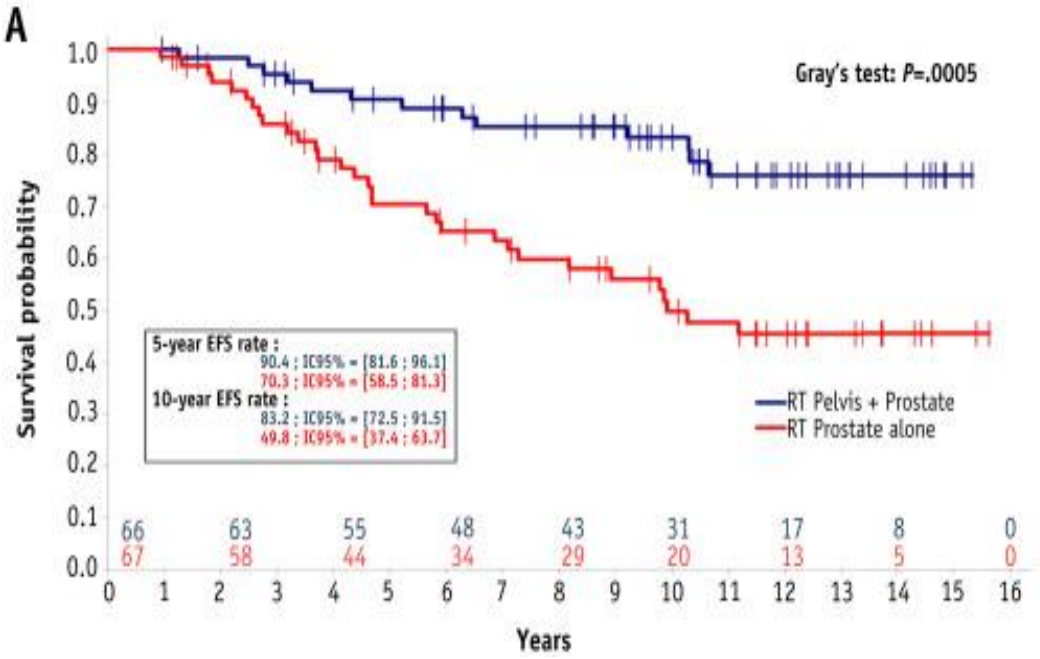
GTV = Almost never contoured in PC RT

CTV = Prostate + extraprostatic spread +/- SV +/- pelvic irradiation

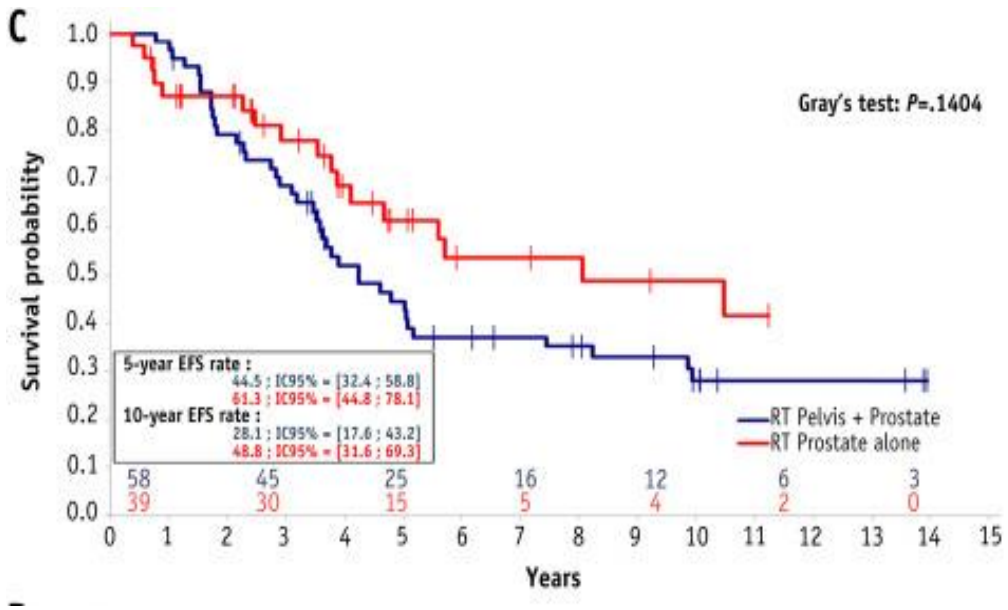
Pelvic irradiation in the randomized trials

Study	Stage	Design	C-C Field Size (cm)	N. Pts	FUP (years)	RFS (bioch or clin)	P-value
RTOG 77-06	T1b, T2	WPRT PORT	Upper border: L5-S1 NA	220 225	12	31 27	NS
RTOG 94-13	All T PSA <100 N+ risk ≥15%	WPRT PORT	16X16 11X11	410 410	7	36 36	NS
RTOG 94-13 (sub-group analysis of patients receiving neoadjuvant HT)	All T PSA <100 N+ risk ≥15%	WPRT PORT	16X16 11X11	322 323	7	40 27	0.023
GETUG 01	T1b-T3, pNx	WPRT PORT	Upper border: S1-S2	225 221	5	66 65.3	NS

Event free survival – GETUG 01 re-analysis



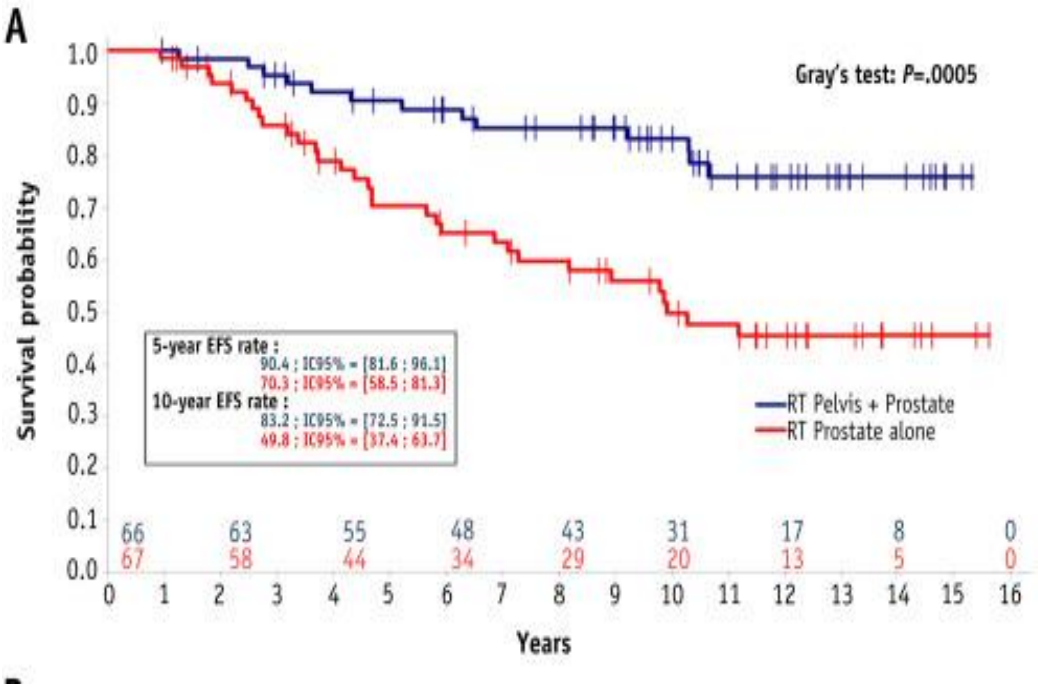
lymph node involvement (LNI) risk <15%



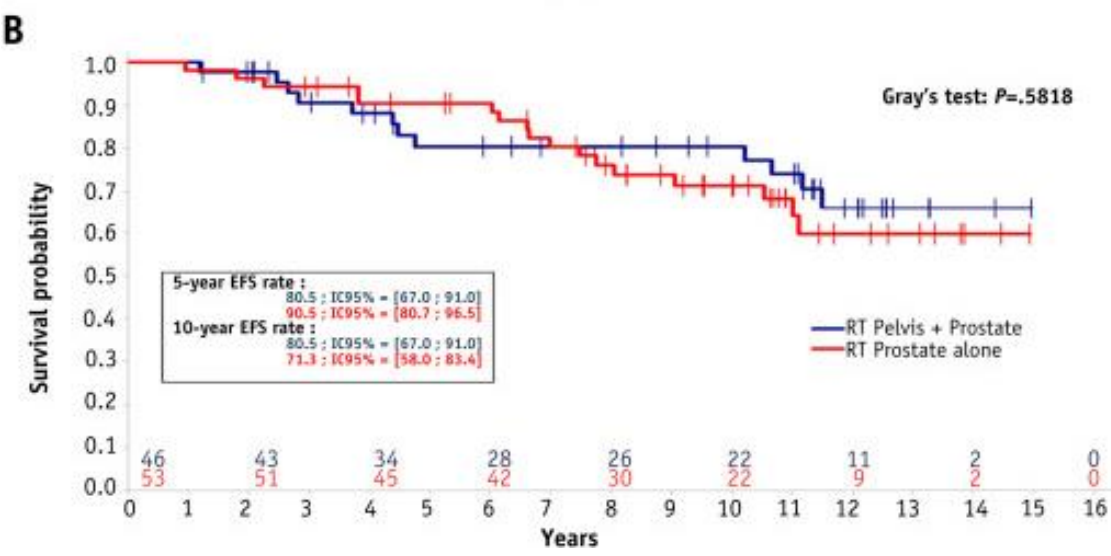
lymph node involvement (LNI) risk ≥15%

Pommier P. et al, Int J Radiat Oncol Biol Phys. 2016 Nov 15;96(4):759-769.

Event free survival – GETUG 01 re-analysis



lymph node involvement (LNI) risk <15%
Without ADT



lymph node involvement (LNI) risk <15%
With ADT

Pommier P. et al, Int J Radiat Oncol Biol Phys. 2016 Nov 15;96(4):759-769.

DISTRIBUTION OF PROSTATE SENTINEL NODES: A SPECT-DERIVED ANATOMIC ATLAS

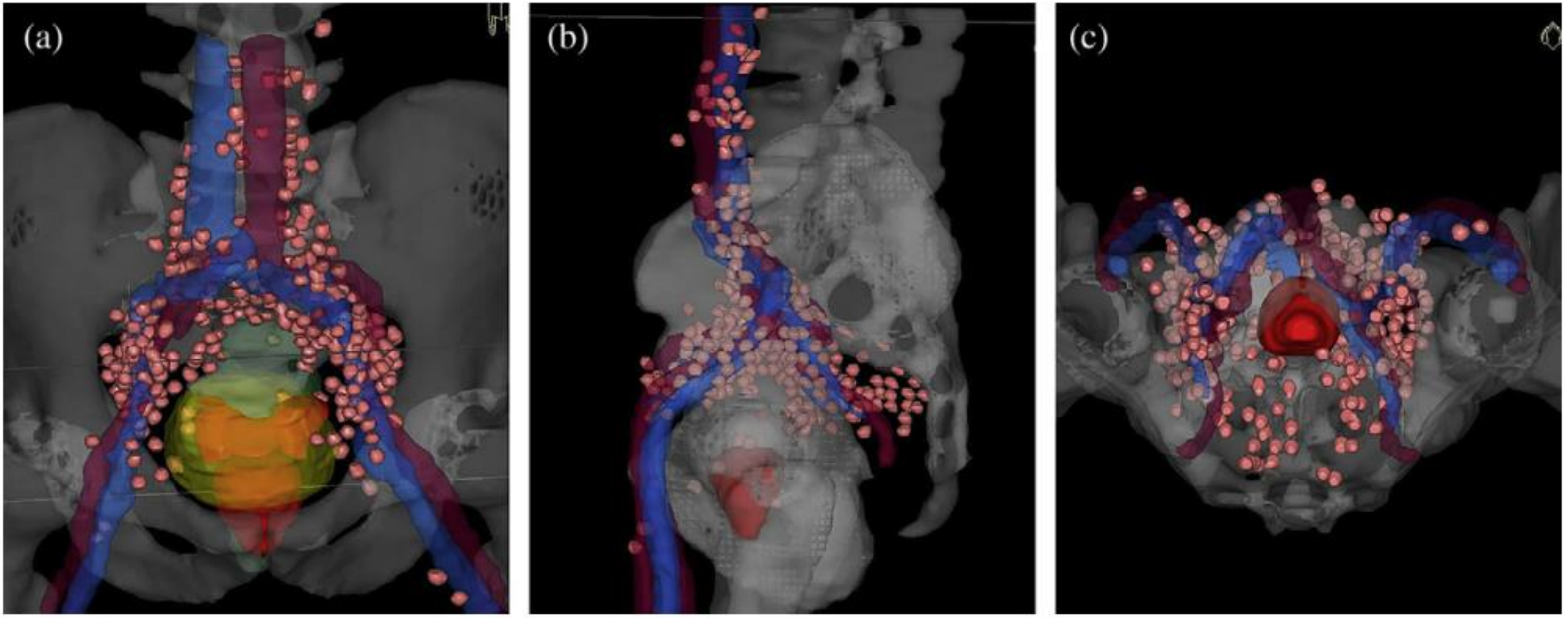


Fig. 2. Cumulative sentinel lymph node distribution (virtual dataset) in 61 patients. A, View from ventral above. B, View from the left side. C, View bottom-up, supine position. Sentinel nodes = pink, prostate = red, bladder = yellow, rectum = green, vessels = blue/red).

Ganswidt U et al., Int j Radiat Oncol Biol Phys 2011 79(5): 1364-72

DISTRIBUTION OF PROSTATE SENTINEL NODES: A SPECT-DERIVED ANATOMIC ATLAS

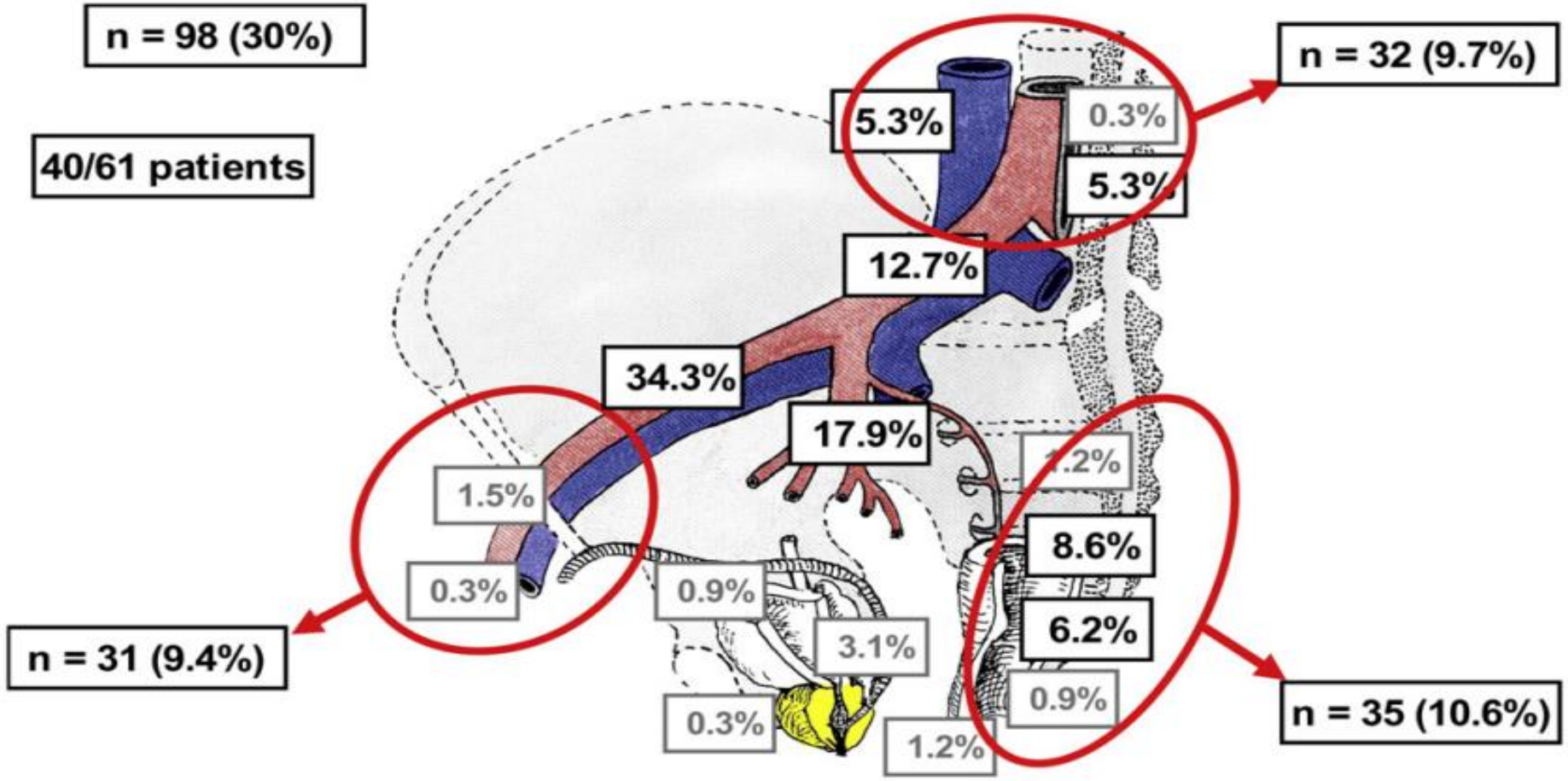


Fig. 3. Areas and anatomic distributions of sentinel lymph nodes with a potential "geographic miss." A geographic miss was observed in 98/324 (30%) sentinel lymph nodes in 40/61 patients (65.6%); for details see Table 3.

Ganswidt U et al., Int j Radiat Oncol Biol Phys 2011 79(5): 1364-72

Target volume definition in high-risk prostate cancer patients using sentinel node SPECT/CT and ^{18}F-choline PET/CT

Table 3 Localization of sentinel lymph nodes in relation to the pelvic CTV

SN	Inside CTV	Outside CTV
SV	2	0
Inguinal	0	1
Pararectal	0	9
Presacral	9	0
Obturator	11	0
Internal iliac	8	0
External iliac	28	0
Distal common iliac	19	0
Left paraaortic	0	8
Right paraaortic	0	9
Total	77	27

Abbreviation: VS: seminal vesicle lymph plexus.

Vees et al, Radiat Oncol. 2012 Aug 8;7:134

Mapping of Pelvic Lymph Node Metastases in Prostate Cancer

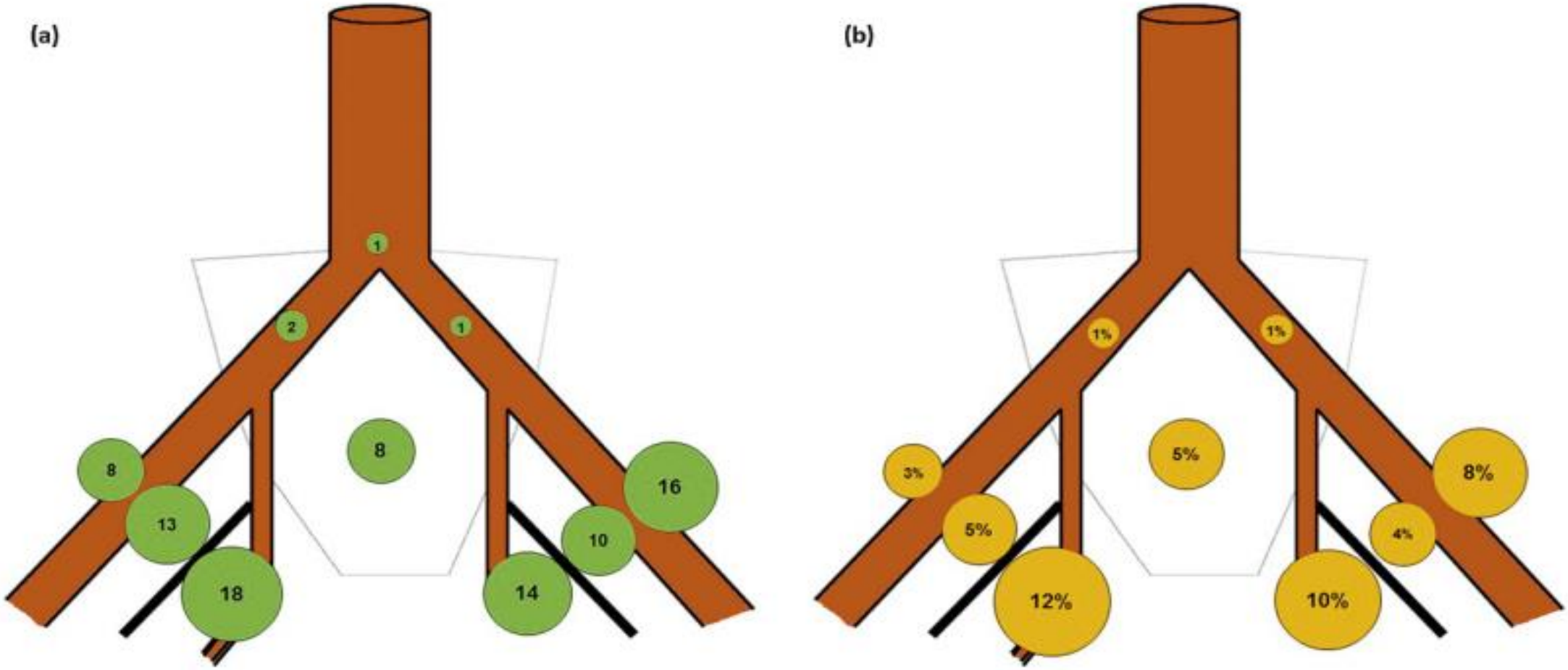


Fig. 5 – (a) Number of positive lymph nodes (LN+) per region and (b) percentage of LN+ of the total number of removed lymph nodes per region in 74 patients. Dimensions of the circles correlate with the numbers.

Joniau S et al, Eur Urol. 2013 Mar;63(3):450-8.

WHOLE-PELVIS, "MINI-PELVIS," OR PROSTATE-ONLY EXTERNAL BEAM RADIOTHERAPY AFTER NEOADJUVANT AND CONCURRENT HORMONAL THERAPY IN PATIENTS TREATED IN THE RADIATION THERAPY ONCOLOGY GROUP 9413 TRIAL

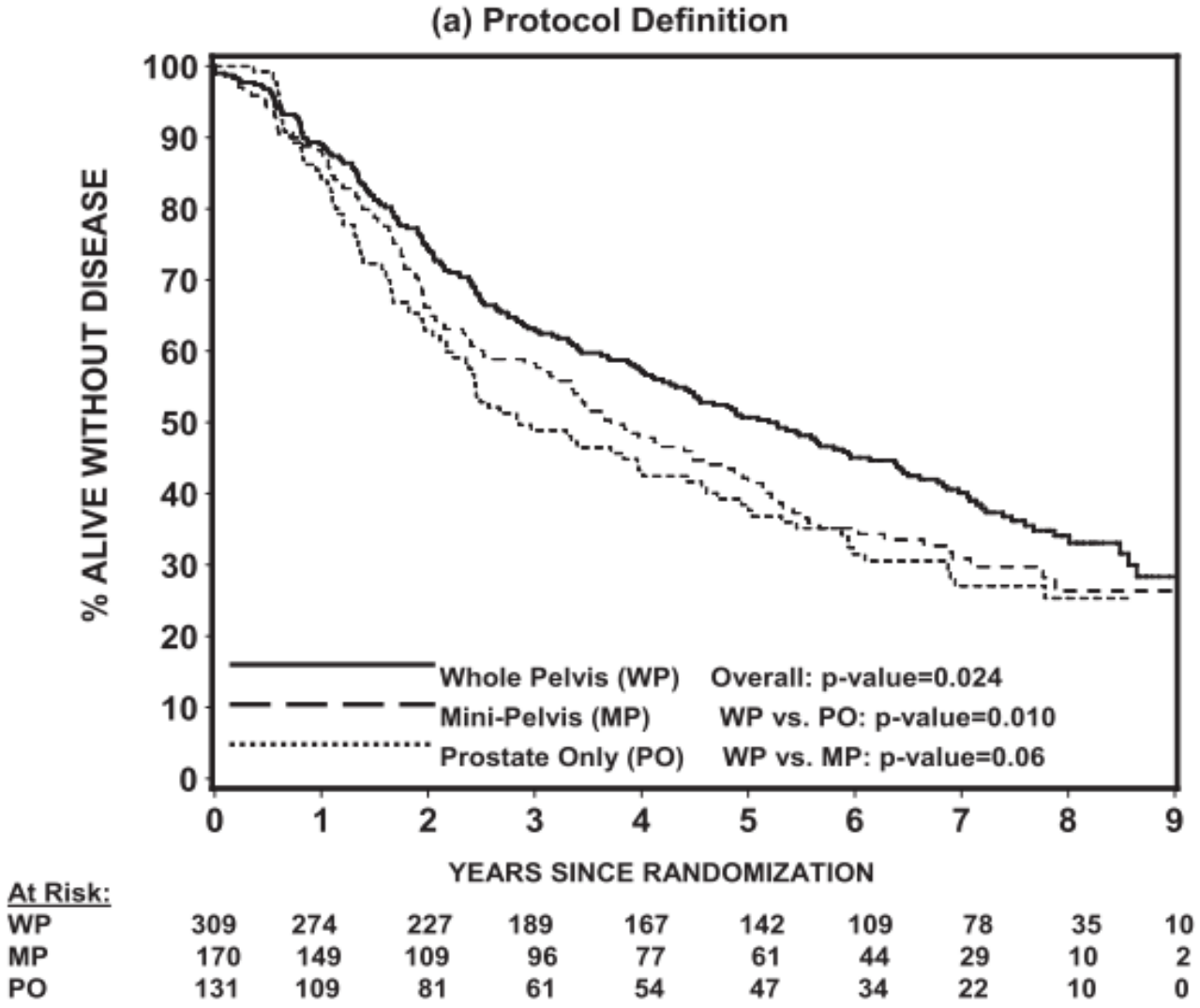
Ad hoc analysis of a randomized trial

3 arms

1. Prostate only field
2. Mini-pelvis (true pelvis) = 10 X 11 cm (C-C direction)
3. Whole pelvis (upper border L5-S1) = 17 X 17 cm (C-C direction)

Roach 3rd et al, IJROBP 2006; 66(3) 647 - 653

WHOLE-PELVIS, "MINI-PELVIS," OR PROSTATE-ONLY EXTERNAL BEAM RADIOTHERAPY AFTER NEOADJUVANT AND CONCURRENT HORMONAL THERAPY IN PATIENTS TREATED IN THE RADIATION THERAPY ONCOLOGY GROUP 9413 TRIAL



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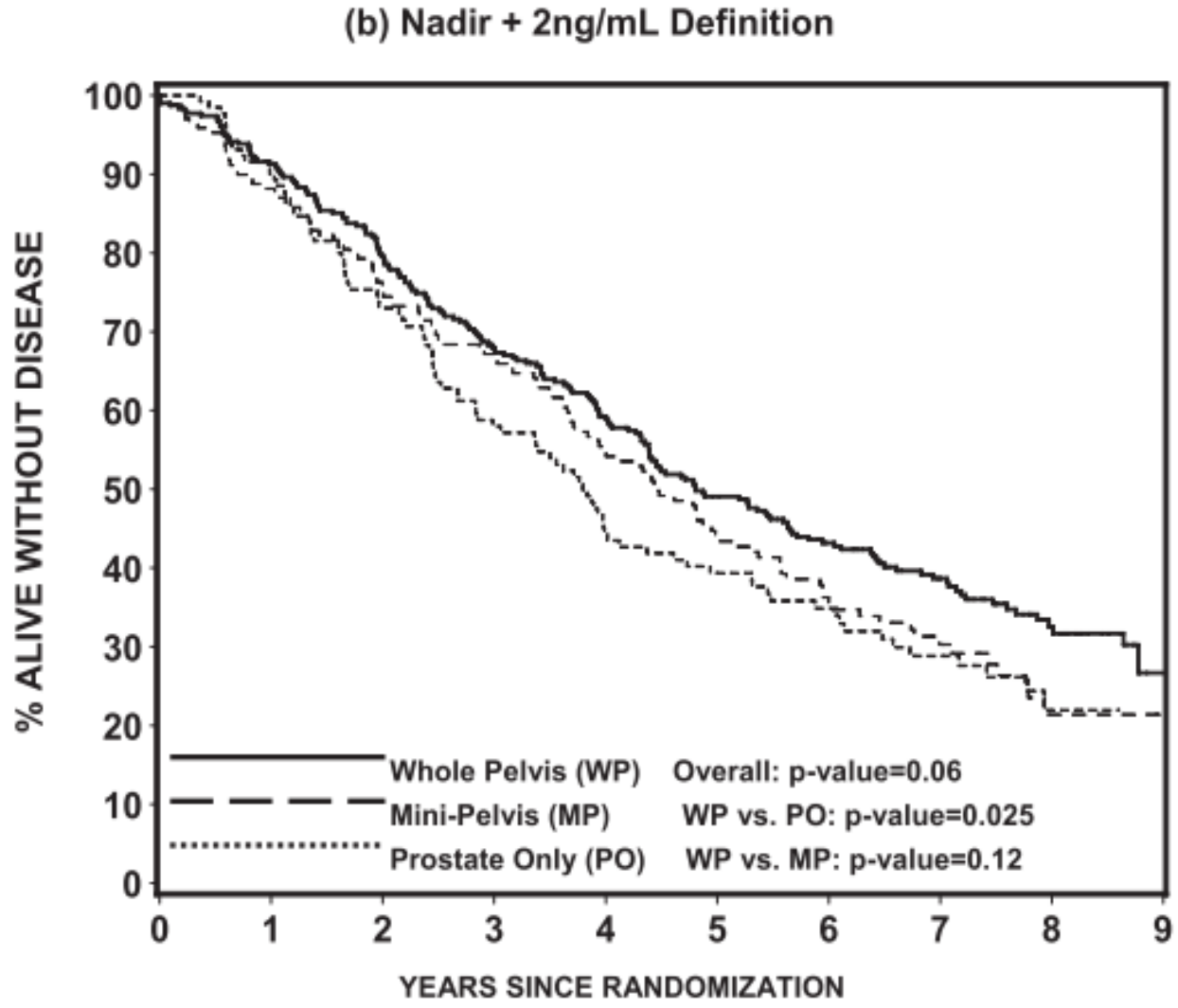
WHOLE-PELVIS, "MINI-PELVIS," OR PROSTATE-ONLY EXTERNAL BEAM RADIOTHERAPY AFTER NEOADJUVANT AND CONCURRENT HORMONAL THERAPY IN PATIENTS TREATED IN THE RADIATION THERAPY ONCOLOGY GROUP 9413 TRIAL



Roach 3rd et al, IJROBP 2006; 66(3) 647 - 653

Is there still a role for pelvic irradiation?

Could these new evidences on the pattern of relapse of PC (at least partially) explain the failure of available RCTs on pelvic irradiation???

The Roach formulas

- Based on PSA, Gleason Score (GS) and the T status;

- Allow a prediction of the risk of:

  - Nodal Involvment (N+)
  - Extracapsular extention (ECE)
  - Non-organ confined disease (NOCD)
  - Seminal Vescicles invasion (SV)

Roach M, Oncol News Int 6(Suppl 3):5-6, 1997

The Roach formulas

- ECE risk = 1.5 x PSA + ([Gleason-3) x 10)[1]
- N+ risk = 2/3 x PSA + ([Gleason-6] x 10)[2]
- SV invasion = PSA +([Gleason -6] x 10) [3]

1. Roach 3rd et al, Semin Urol Oncol. 2000 May;18(2):108-14
2. Roach 3rd et al, Int J Radiat Oncol Biol Phys. 1994 Jan 1;28(1):33-7
3. Diaz et al, Int J Radiat Oncol Biol Phys. 1994 Sep 30;30(2):323-9

The Roach formulas

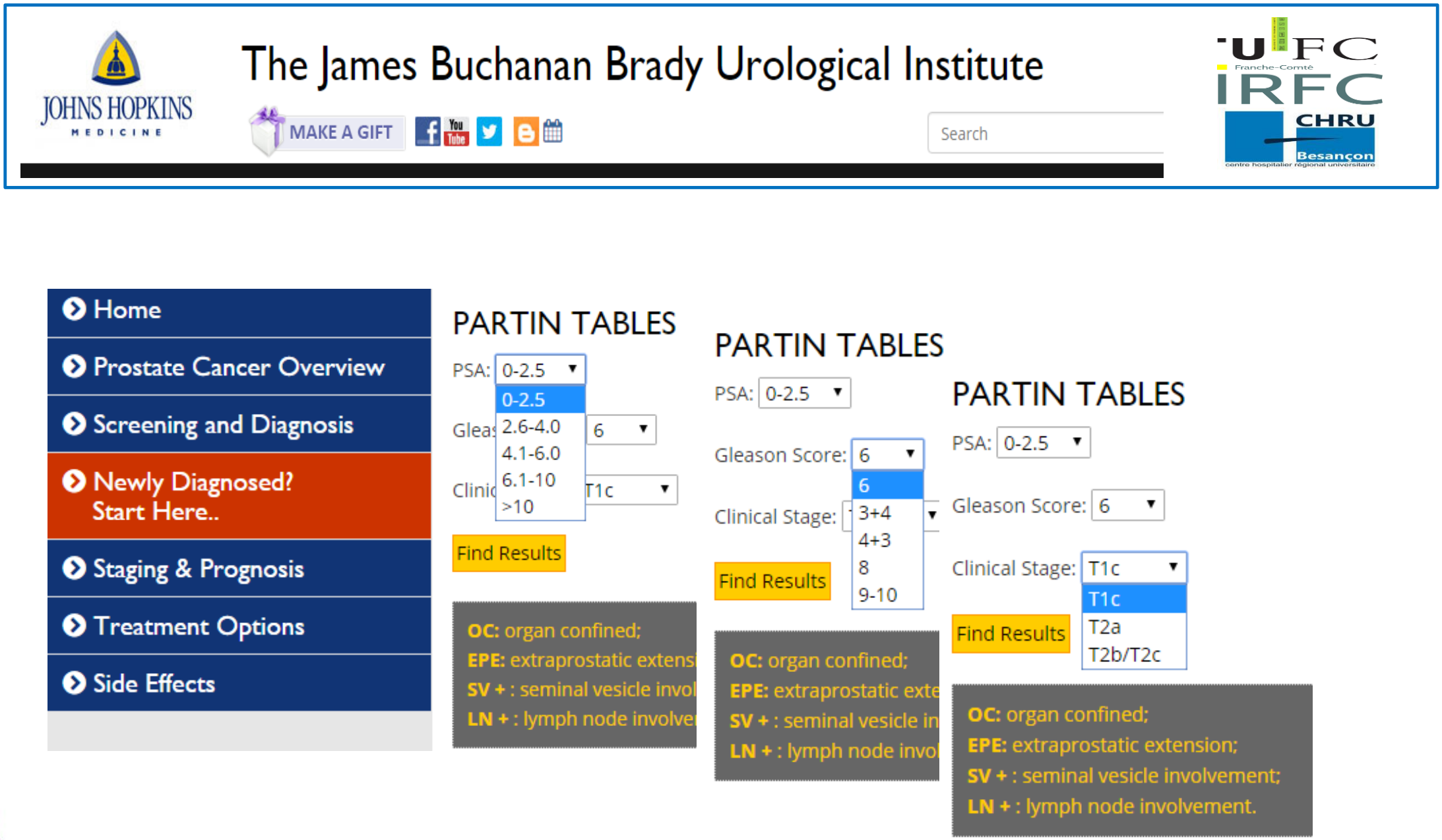
T1a and T1C:	TG = 1
T1b, T2a	TG = 2
T2b, T2c	TG = 2.5
T3a	TG = 3

Roach M, Oncol News Int 1997; 6(Suppl 3): 5-6

The Roach formulas

- ECE risk = (1.5 x PSA) + [(GS - 3) × 10].
- N+ risk = 2/3 PSA [(GS + TG - 8) × 10].
- NOCD risk = 3/2 PSA [(GS + TG - 4) × 10].

Roach M, Oncol News Int 1997; 6(Suppl 3): 5-6



http://urology.jhu.edu/prostate/partintables.php

PATIENTS CARACTERISTICS

Median PSA = 4.9 ng/mL,

63% had Gleason 6 disease, and 78% of men had T1c disease.

73% of patients had OC disease

23% had EPE

3% had SV + but not LN +

1% had LN + disease

And T3 Tumors??

http://urology.jhu.edu/prostate/partintables.php

The next future…the analysis of Big Data?

ORIGINAL ARTICLE

Could Machine Learning Improve the Prediction of Pelvic Nodal Status of Prostate Cancer Patients? Preliminary Results of a Pilot Study

De Bari B et al, Cancer Invest 2015 Jul;33(6):232-40

Seminal vesicles invasion

- 344 radical prostatectomy specimens

- Fifty-one patients (15%) demonstrated SV involvement in 81 SVs
    - 21 unilateral
    - 30 bilateral

Kestin LL et al, IJROBP 2002; 54 (3): 686-697

Seminal vesicles invasion

Table 2. Mean values for selected characteristics by seminal vesicle status

Characteristic	Mean −SV	Mean +SV	*t* test *p* value
Clinical			
Age at diagnosis	65.5 years	66.0 years	0.68
Pretreatment PSA	11.6 ng/mL	22.3 ng/mL	0.001
Biopsy Gleason score	5.7	6.7	<0.001
Clinical T classification	T2a	T2b	<0.001
Alkaline phosphatase	67 U/L	75 U/L	0.21
Pathologic			
Prostate weight	47 g	51 g	0.21
Major Gleason pattern	3.2	4.0	<0.001
Minor Gleason pattern	3.4	4.1	<0.001
Gleason score	6.5	8.1	<0.001
Maximum tumor dimension	1.6 cm	3.2 cm	<0.001
% of gland involved with cancer	19%	64%	<0.001
Length of seminal vesicles	3.3 cm	4.2 cm	<0.001

PSA = prostate-specific antigen; SV = seminal vesicle.

Kestin LL et al, IJROBP 2002; 54 (3): 686-697

Seminal vesicles invasion

Table 2. Mean values for selected characteristics by seminal vesicle status

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Alkaline phosphatase	67 U/L	75 U/L	0.21
Pathologic			
Prostate weight	47 g	51 g	0.21

Patients with only one high-risk feature still demonstrated a 15% risk of SV involvement, whereas 58% of patients with all three high-risk features had positive SVs.

Kestin LL et al, IJROBP 2002; 54 (3): 686-697

Seminal vesicles invasion

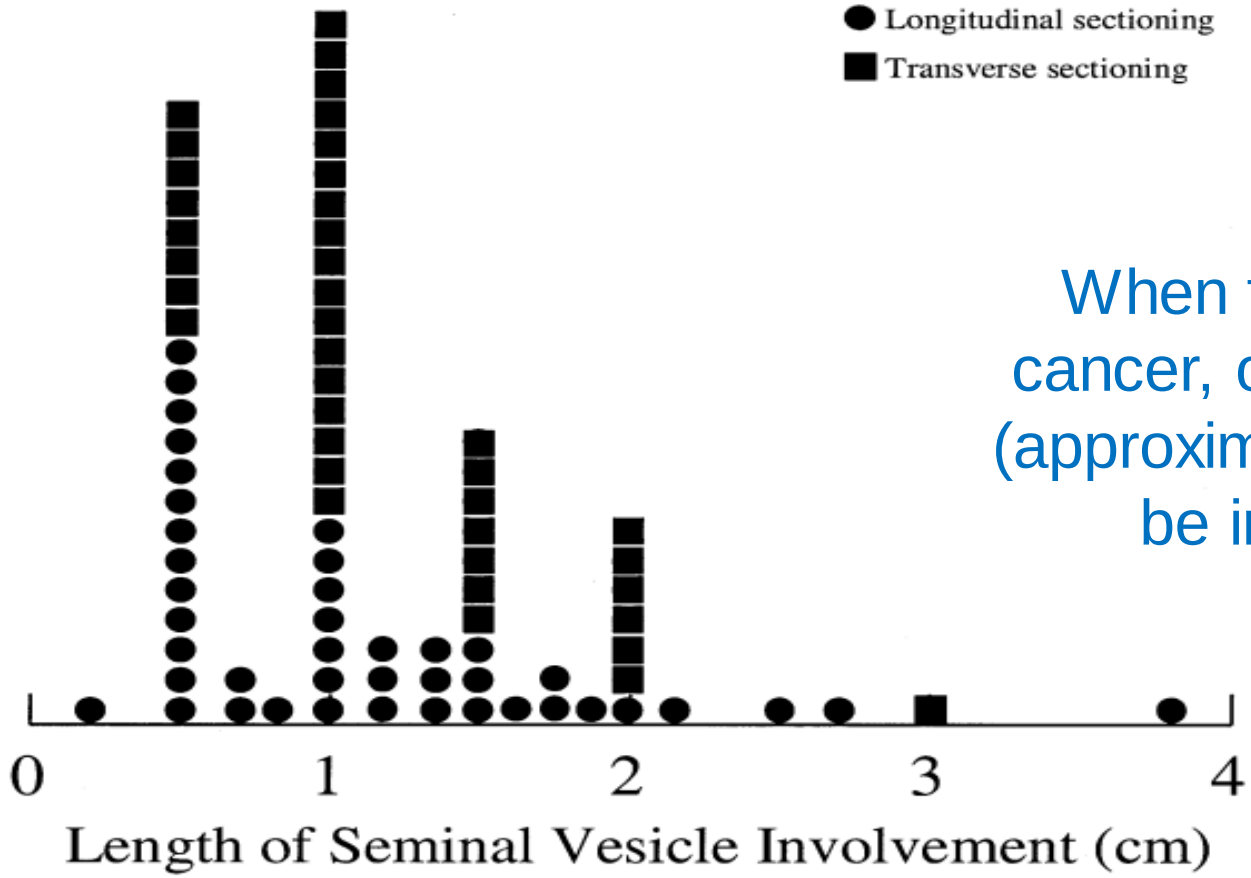


Fig. 3. Distribution of length of seminal vesicle involvement.

When treating the SV for prostate cancer, only the proximal 2.0-2.5 cm (approximately 60%) of the SV should be included within the CTV.

Kestin LL et al, IJROBP 2002; 54 (3): 686-697

The 5 W and 1 H of EBM

What …. is the Evidence Based Medicine?

Why …to discuss of EBRO in PCa?

Which is the better dose?

When … treatment duration…dose/fraction

Where … Evidence based volumes

How … to deliver/to combine

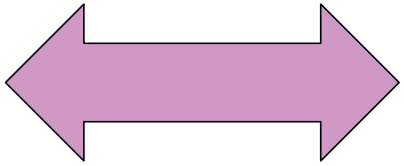
How to deliver

- Role of IMRT
- Role of IGRT
- Role of BRT

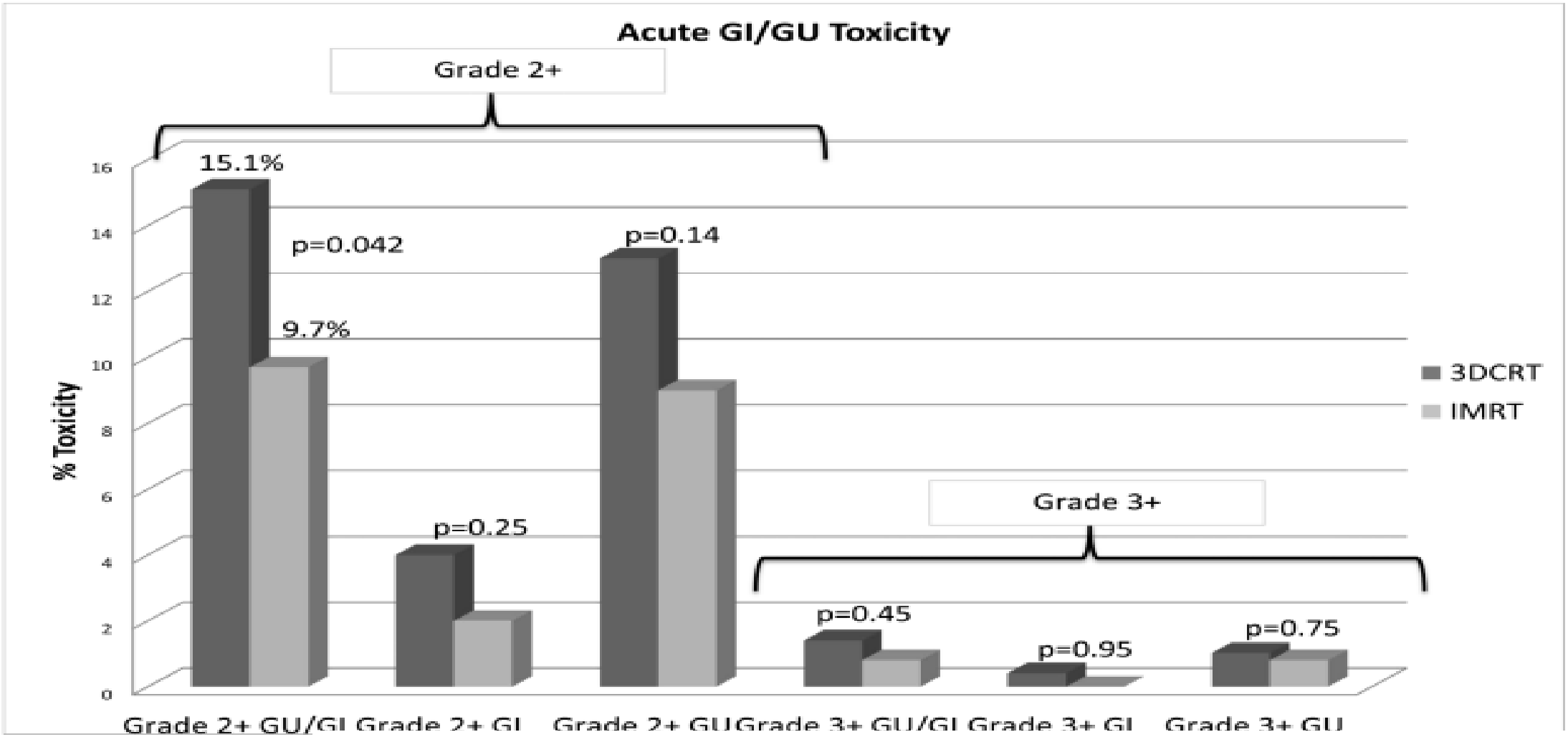
How to deliver

- **Role of IMRT**
- **Role of IGRT**
- **Role of BRT**

Is IMRT in PCa evidence based?



Preliminary Toxicity Analysis of 3DCRT versus IMRT on the High Dose Arm of the RTOG 0126 Prostate Cancer Trial



Michalski JM et al, Int J Radiat Oncol Biol Phys. 2013 Dec 1;87(5):932-8

Preliminary Toxicity Analysis of 3DCRT versus IMRT on the High Dose Arm of the RTOG 0126 Prostate Cancer Trial

Grade 2+ Acute GU/GI Toxicity, Multivariate analysis

Stratified variables	Variable categories	Observed risk	95% Confidence Interval	p-Value
RT Method	3DCRT 79.2Gy	RL	(0.379, 0.999)	0.049
	IMRT	0.615		
Age	≤70 y	RL	(0.361, 0.861)	0.008
	>70	0.558		
Race	White	RL	(0.487,1.519)	0.604
	Non-white	0.860		

RL=reference level

Michalski JM et al, Int J Radiat Oncol Biol Phys. 2013 Dec 1;87(5):932-8

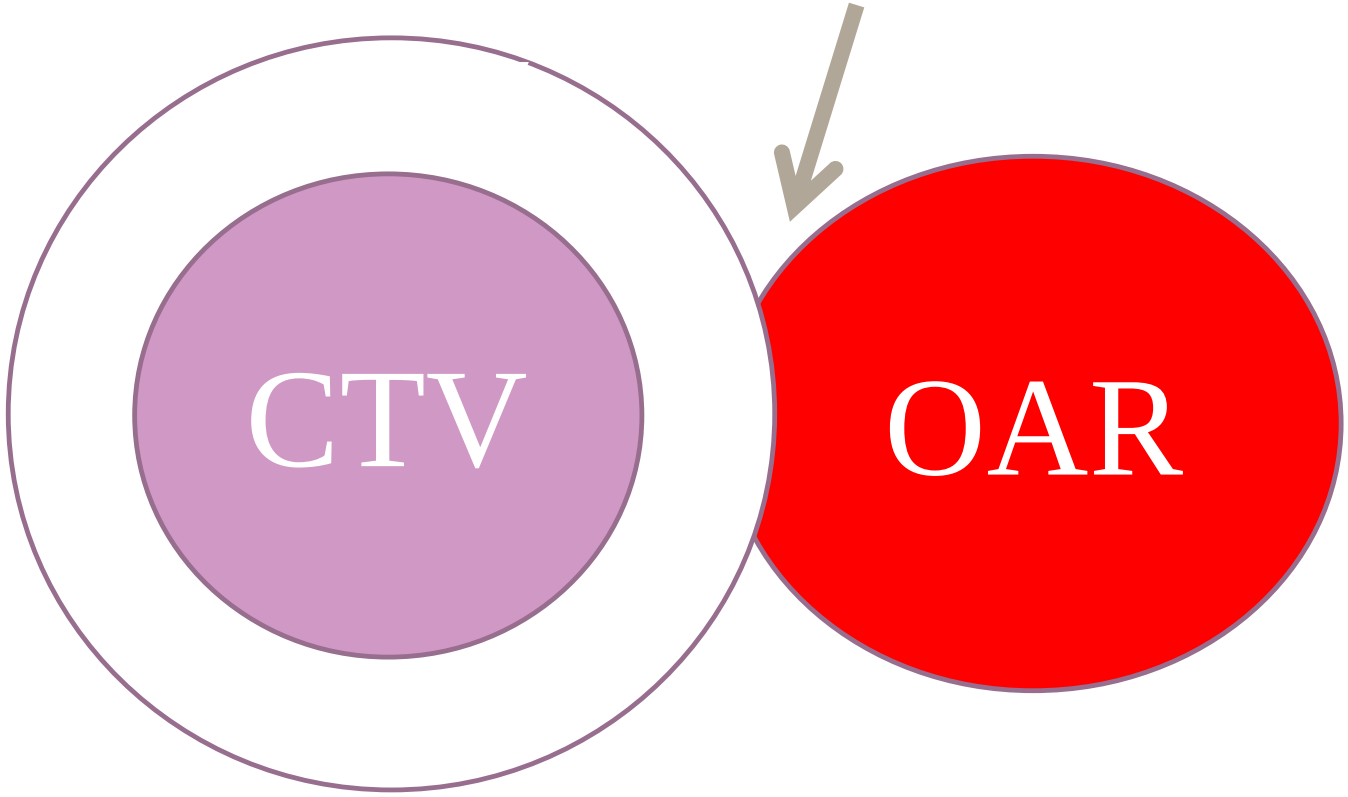
IMRT vs 3D-CRT

Author	n.Pts	Endpoint	IMRT	3D-CRT	P-value
Zelefsky 2008	1571	G2 + tox	5%	13%	<0.001
Jani 2007	IMRT 355 3D-CRT 106	Late GU Late GI tox	54% 65%	61% 85%	NS <0.001
Jacobs 2014	IMRT 11039 3D-CRT 6976	G2 + Late GU G2 + Late GI	30% 25%	32% 30%	NS NS
Goldin 2013	IMRT 457 3D-CRT 557		Propensity score analysis		NS NS

How to deliver

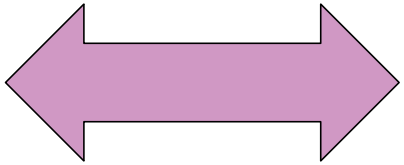
- Role of IMRT
- Role of IGRT
- Role of BRT

Is IGRT in PCa evidence based?

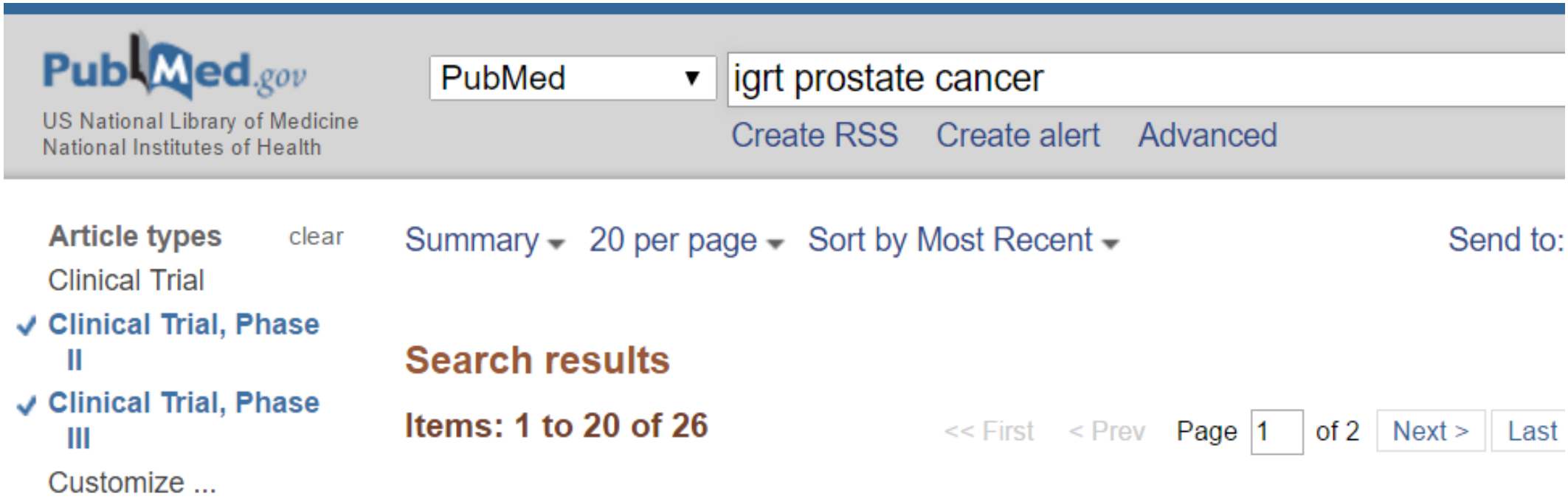


Reduction of toxicities
Dose escalation

Is IGRT in PCa evidence based?



Is IGRT in PCa evidence based?



None of these studies randomizes IGRT vs no-IGRT schedules to assess the clinical impact on PC patients….

Improved Clinical Outcomes With High-Dose Image Guided Radiotherapy Compared With Non-IGRT for the Treatment of Clinically Localized Prostate Cancer

Retrospective analysis

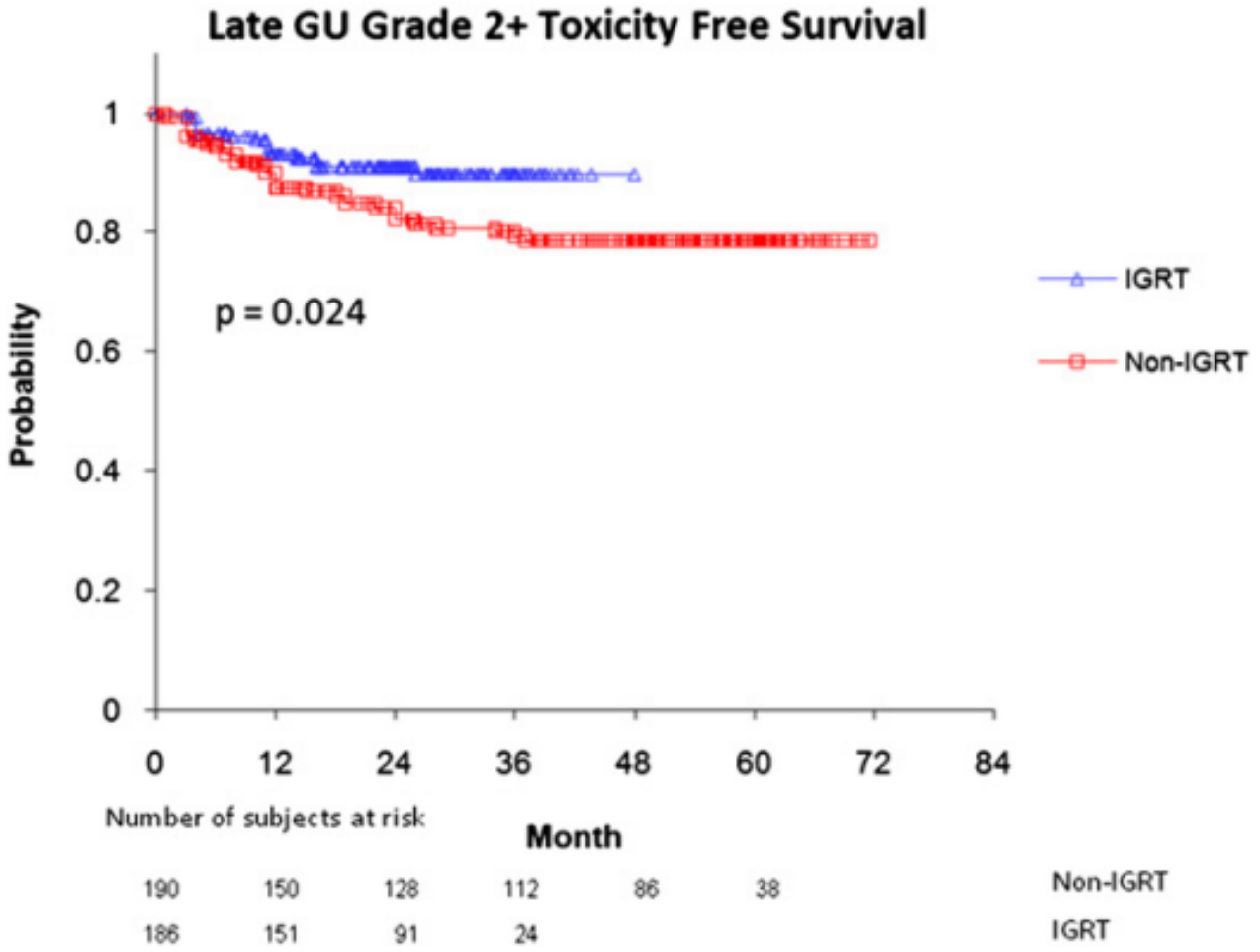
IMRT group = 186 pts
IGRT-IMRT group = 190 pts

IGRT performed with Kv and intraprostatic fiducials

Same total dose = 86.4 Gy

Zelefsky M et al, IJROBP 2012; 84 (1): 125-129

Improved Clinical Outcomes With High-Dose Image Guided Radiotherapy Compared With Non-IGRT for the Treatment of Clinically Localized Prostate Cancer



Zelefsky M et al, IJROBP 2012; 84 (1): 125-129

Improved Clinical Outcomes With High-Dose Image Guided Radiotherapy Compared With Non-IGRT for the Treatment of Clinically Localized Prostate Cancer

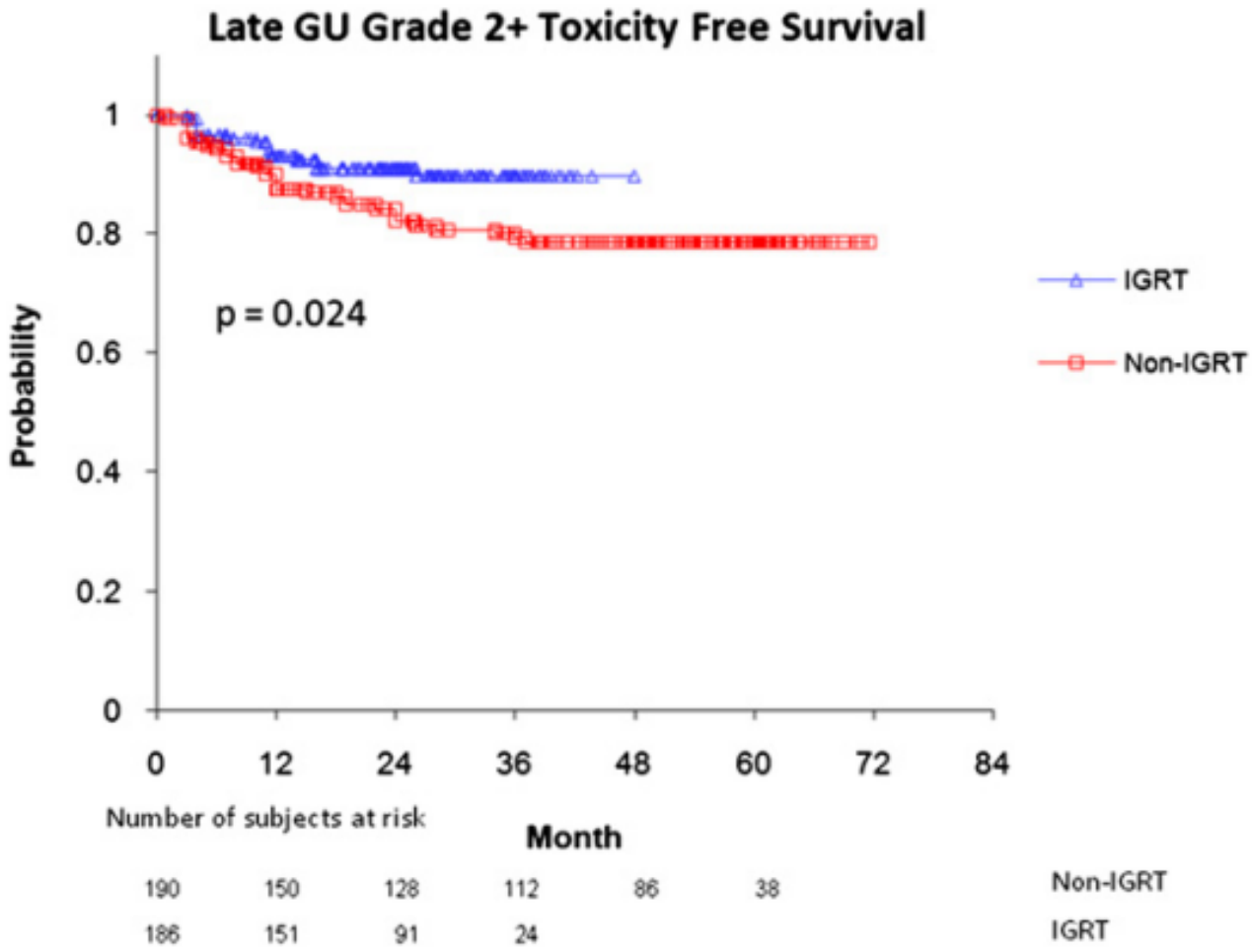
Table 3 Cox regression analysis for predictors of late urinary toxicity

Cox regression	Coefficient	95% CI (±)	SE	*p*	Hazard exponent coefficient
Age	0.028	0.041	0.021	0.183	1.028
Androgen deprivation therapy	0.150	0.566	0.288	0.603	1.161
IGRT	0.711	0.606	0.309	0.021	2.037
Baseline IPSS	0.043	0.036	0.018	0.021	1.044

Abbreviations: CI = confidence interval; IGRT = image-guided radiotherapy; IPSS = International Prostate Symptom Score; SE = standard error.

Zelefsky M et al, IJROBP 2012; 84 (1): 125-129

Improved Clinical Outcomes With High-Dose Image Guided Radiotherapy Compared With Non-IGRT for the Treatment of Clinically Localized Prostate Cancer



No impact on rectal toxicity

Zelefsky M et al, IJROBP 2012; 84 (1): 125-129


No impact on rectal toxicity…WHY???

Improved Clinical Outcomes With High-Dose Image Guided Radiotherapy Compared With Non-IGRT for the Treatment of Clinically Localized Prostate Cancer

PTV = prostate + entire seminal vesicles + a 1-cm margin except posteriorly, where a 0.6-cm margin was used

"…PTV regions receiving less than the prescription routinely included the prostate e rectal interface (to adhere to our rectal dose e volume constraints) and occasionally the superior portion of the seminal vesicles to adequately spare small bowel…."

Zelefsky M et al, IJROBP 2012; 84 (1): 125-129

Improved Clinical Outcomes With High-Dose Image Guided Radiotherapy Compared With Non-IGRT for the Treatment of Clinically Localized Prostate Cancer

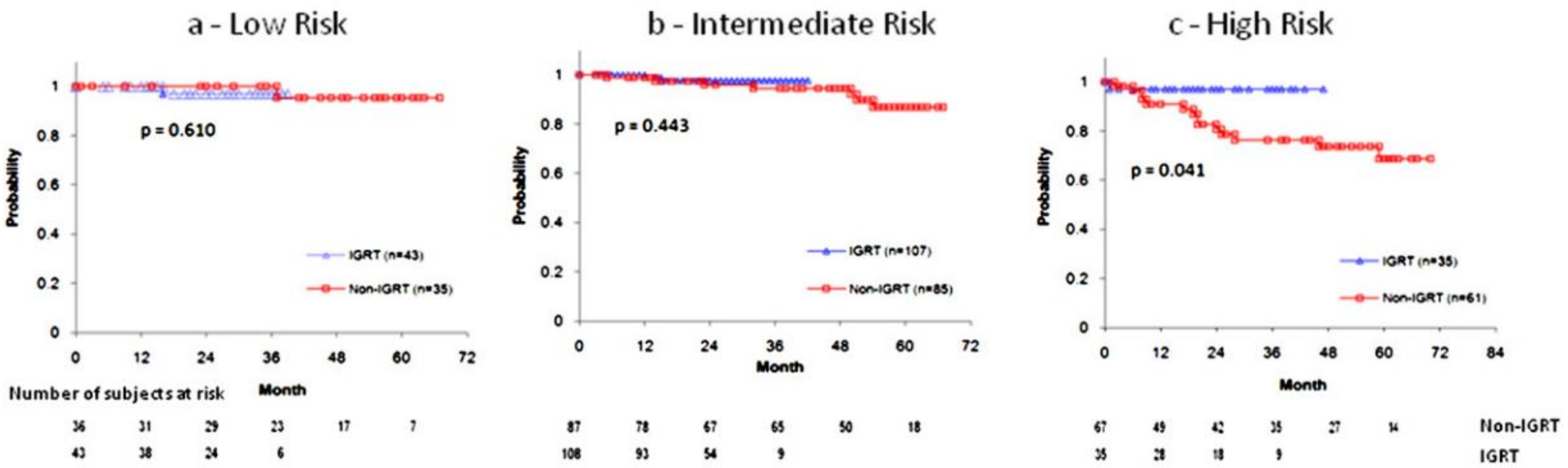


Fig. 2. Comparison of prostate specific antigen relapse-free survival outcomes between patients treated with image-guided radiotherapy (IGRT) to 86.4 Gy and those treated with intensity-modulated radiotherapy to the same dose level.

Zelefsky M et al, IJROBP 2012; 84 (1): 125-129


Better biochemical free survival …WHY???

Improved Clinical Outcomes With High-Dose Image Guided Radiotherapy Compared With Non-IGRT for the Treatment of Clinically Localized Prostate Cancer

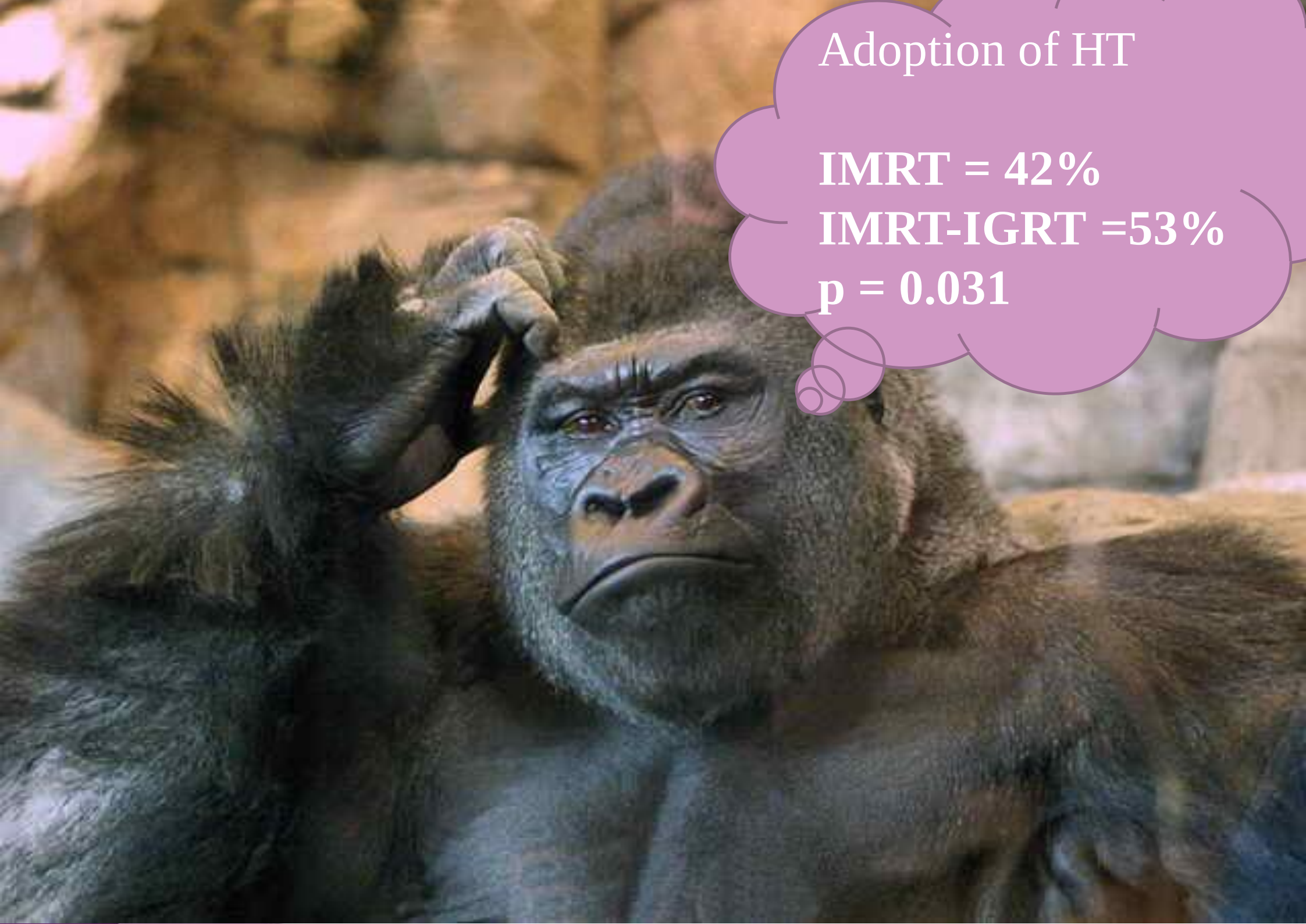
PTV = prostate + entire seminal vesicles + a 1-cm margin except posteriorly, where a 0.6-cm margin was used

"…The enhanced accuracy of IGRT could possibly explain the improved biochemical tumor control observed for high-risk patients with a large volume of disease in whom escalated dose levels are critical for local tumor control…" (Zelefsky et al)

Zelefsky M et al, IJROBP 2012; 84 (1): 125-129


Treatment period
IMRT = 2006-08
IGRT/IMRT = 2007-09


Median follow-up (months)
IMRT = 49
IGRT/IMRT = 24


Adoption of HT
IMRT = 42%
IMRT-IGRT =53%
p = 0.031

Munch, *The Scream, 1893*

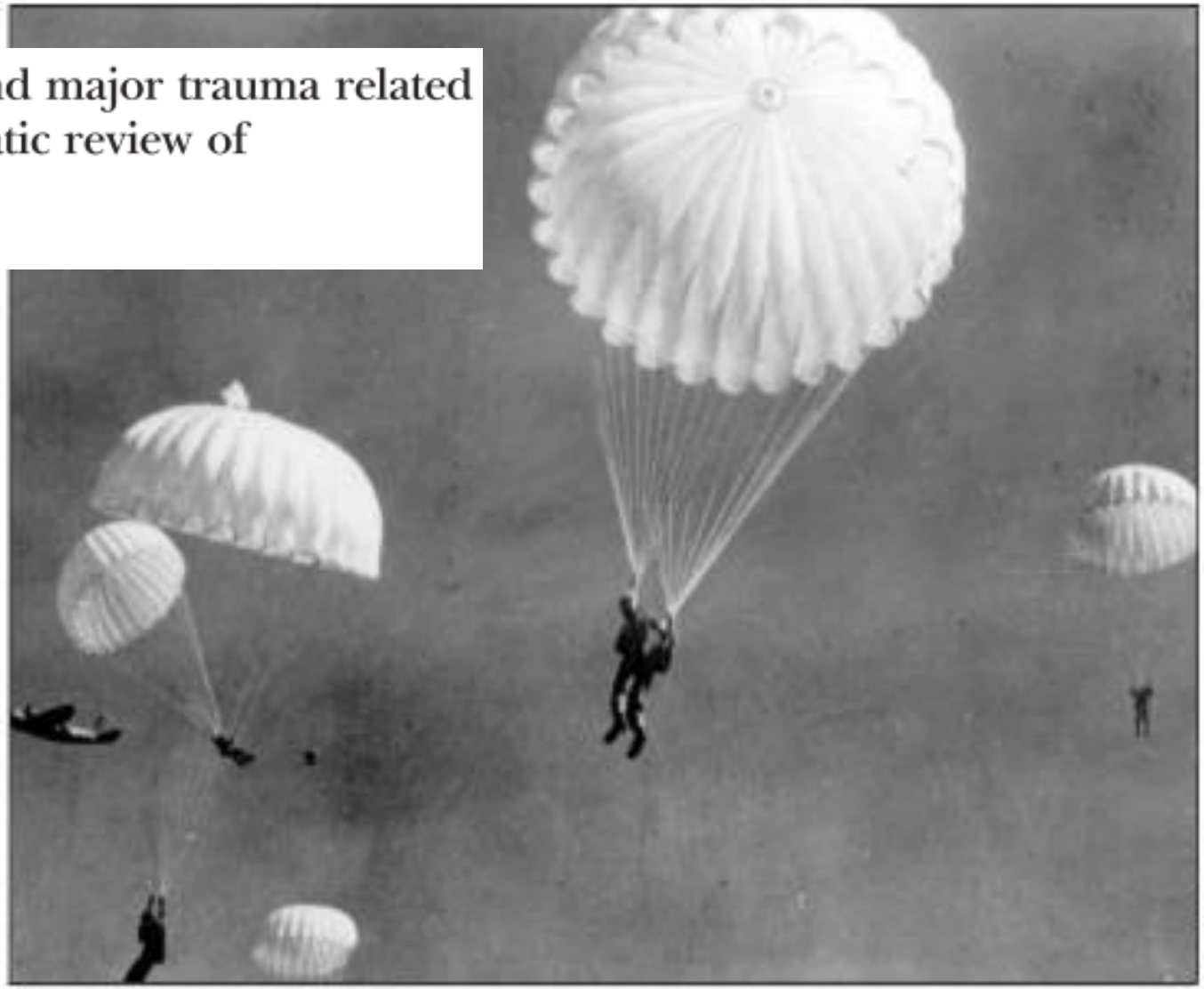
IMRT and IGRT in PCa

Should we forget IMRT and IGRT in the PCa treatment because of the lack of high level randomized trials?

IMRT and IGRT in PCa
…a pragmatic approach…

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell *BMJ* 2003;327:1459–61



Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

IMRT and IGRT in PCa
…a pragmatic approach…

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

BMJ 2003;327:1459–61

What is already known about this topic

Parachutes are widely used to prevent death and major injury after gravitational challenge

Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury

Studies of free fall do not show 100% mortality

What this study adds

No randomised controlled trials of parachute use have been undertaken

The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect

Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

How to deliver

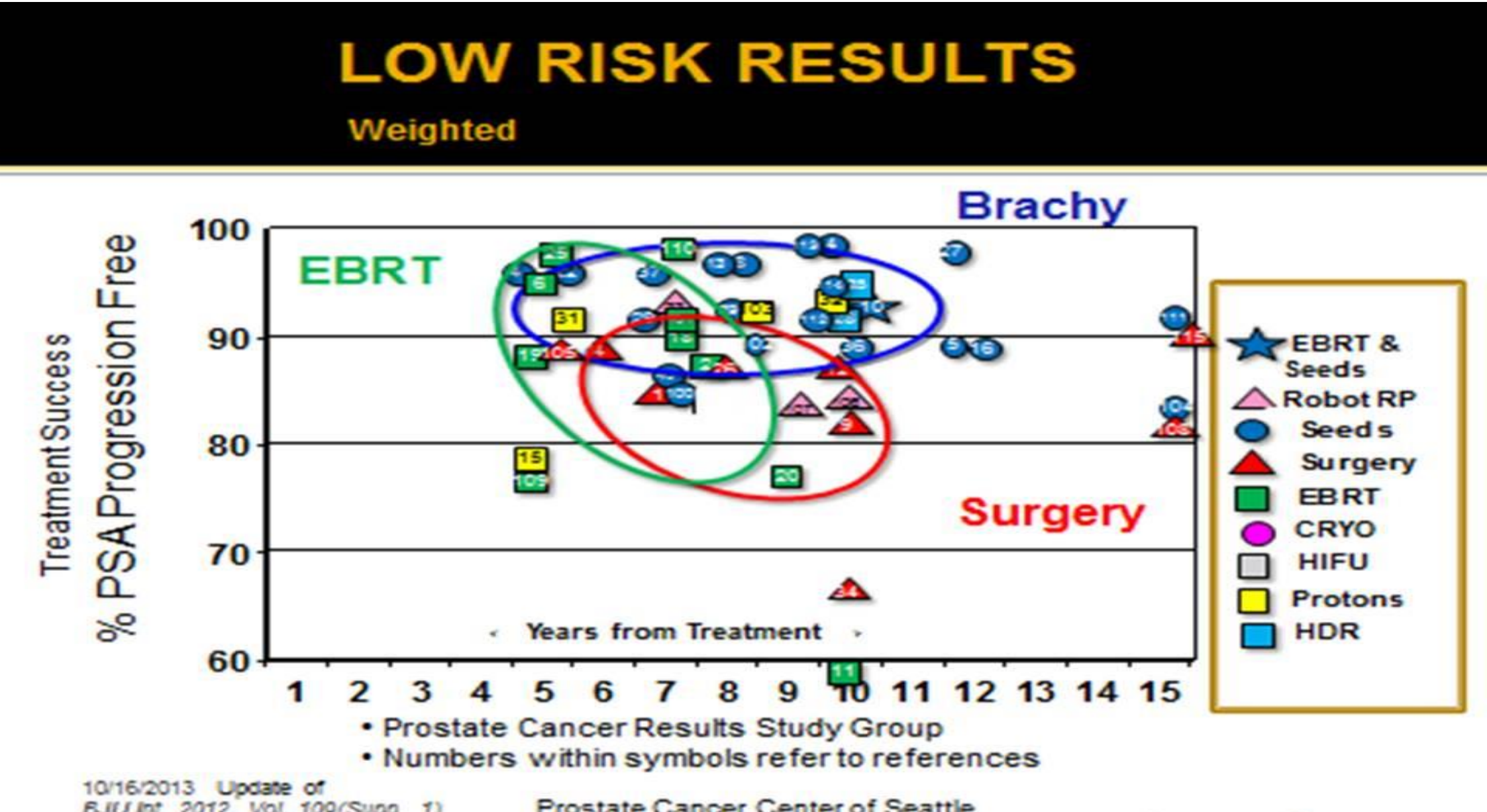
- **Role of IMRT**
- **Role of IGRT**
- **Role of BRT**

Is the adoption of BRT as boost evidence – based? Data from RCTs

Author (year)	Years of enrollement	PTS	BRT schedule	EBRT dose	Risk group	FUP (years)	5-y bRFS (%)
Santhia (2005)	1992-1997	51 53	- 35 Gy (HDR)	66 40	IR HR	8.2	49 71 p = 0.04
Hoskin (2012)	1997-2005	108 110	- 17 X 2 (HDR)	55 (2.75) 35.75 (2.75)	LR IR HR	12	61 75 p = 0.002
RTOG 0232	2003 - 2012	296 292	LDR EBRT + LDR	125-145 45 + 125/145	IR	5	NS

The adoption of BRT as boost could be considered evidence based

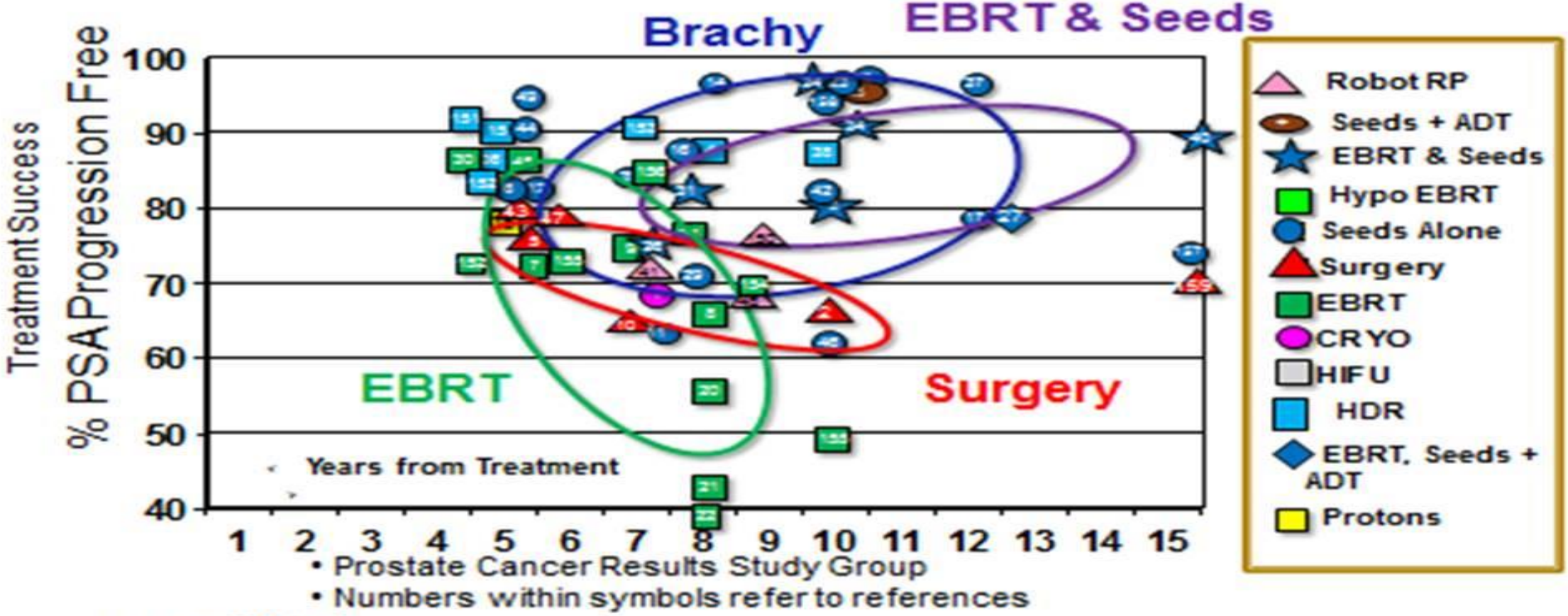
Is the adoption of BRT monotherapy evidence – based?



Is the adoption of BRT monotherapy evidence – based?

INTERMEDIATE RISK RESULTS

Weighted



- Prostate Cancer Results Study Group
- Numbers within symbols refer to references

10/16/2013 Update of
BJU Int, 2012, Vol. 109(Supp 1)

Prostate Cancer Center of Seattle

Is the adoption of BRT monotherapy evidence – based?

Brachytherapy (LDR or HDR) as monotherapy = large but retrospective studies.

Comparable results with RP or EBRT in terms of bRFS rates.

BRT (LDR or HDR) is included in the NCCN guidelines as a standard therapeutic option for low risk PC, BUT high level evidences based on RCTs are still lacking

The 5 W and 1 H of EBM

What …. is the Evidence Based Medicine?

Why …to discuss of EBRO in PCa?

Which is the better dose?

When … treatment duration…dose/fraction

Where … Evidence based volumes

How … to combine with systemic treatments

RCTs for ADT + RT vs RT alone

Table 2: Randomized trials examining the addition of ADT to radiation for high-risk patients.

Trial	Study cohort	Median follow-up	Trial arms	Outcomes
RTOG 85-31 [11, 12]	945 patients T3 (82%) or N1 (18%)	7.6 years	RT versus RT + ADT (44–46 Gy to whole pelvis; 20–25 Gy boost to prostate) ADT: goserelin at least 2 years, preferably until progression	10-year OS (39% versus 49%, $p = 0.002$) 10-year DSS (78% versus 84%, $p = 0.005$) Overall survival benefit limited to patients with Gleason 7–10
RTOG 86-10 [13–15]	456 patients T2-T4, N0-1 with "bulky" disease (palpable ≥ 25 cm^2)	11.9 years	RT versus RT + ADT (44–46 Gy to whole pelvis; 20–25 Gy boost to prostate) ADT: 4 months' goserelin + flutamide, starting 2 months prior to RT	10-year OS (34% versus 43%, $p = 0.12$) 10-year DSS (23% versus 36%, $p = 0.01$) Subset analyses at 8 years showed that benefit was confined to Gleason 2–6 patients. No benefit to ADT in Gleason 7–10
TROG 96-01 [16]	802 patients T2b-T4N0	10.6 years	RT alone versus RT + 3 mo. ADT versus RT + 6 mo. (66 Gy, no pelvic node treatment) ADT: goserelin + flutamide given *neoadjuvantly*	At 10 years, addition of 6 months' ADT improved 10-year OS (70.8% versus 57.5%, $p = 0.0005$) 10-year DSS (48% versus 23%, $p < 0.0001$)
EORTC 22863 [17, 18]	415 patients T1-2N0 grade 3 or T3-4N0-1	9.1 years	RT versus RT + 3 years' ADT (50 Gy to pelvis, 20 Gy boost) ADT: 1 month' cyproterone acetate, goserelin × 3 years starting with RT	10-year OS (40% versus 58%, $p = 0.0004$) 10-year DSS (10% versus 30%, $p < 0.0001$)

OS: overall survival, DSS: disease-specific survival.

Juloori et al, Prostate Cancer. 2016;2016:2420786

RCTs for ADT + RT vs RT alone

Table 3: Randomized trials comparing LTAD and STAD with radiation in high-risk patients.

Trial	Study cohort	Median follow-up	Trial arms	Outcomes
EORTC 22961 [19]	970 patients with T2c-T4 or N1-2	6.4 years	RT + 6 months' ADT versus RT + 36 months' ADT (Prostate dose 70 Gy) ADT: 6 months' CAB (LHRH agonist + antiandrogen) ± 2.5 years' LHRH agonist	5-year OS 81% versus 85% ($p = 0.02$) 5-year DSS 95% versus 97% ($p = 0.002$) QOL measures the same in each arm No difference in cardiac fatal event Increased rates of reported gynecomastia, incontinence, and sexual dysfunction with LTAD
RTOG 92-02 [20, 21]	1514 patients with T2c-T4	11.3 years	RT + 4 months' ADT versus RT + 28 months' ADT (44–50 Gy to whole pelvis, boost to 65–70 Gy prostate) ADT: goserelin + flutamide 4 months total (prior to and during RT) ± 2 years' goserelin	10-year OS 52% versus 54% ($p = 0.25$) 10-year DSS 84% versus 89% ($p = 0.0001$) Gleason 8–10 subset: 10-year OS 32% versus 45% ($p = 0.0061$) Increased grade 3 GI toxicity at 8 years with LTAD (2.9% versus 1.2%, $p = 0.04$)
DART 01/05 Spain [22]	355 patients (47% int.-risk, 53% high-risk)	5.3 years	RT + 4 months' ADT versus RT + 28 months' ADT (76–82 Gy to prostate) ADT: goserelin + antiandrogen for 4 months total (prior to and during RT) ± 2 years' goserelin	5-year OS 86% versus 95% ($p = 0.009$) 5-year BRFS 81% versus 89% ($p = 0.019$) 5-year metastasis-free survival 83% versus 94% ($p = 0.009$)
PCS IV Trial Canada Nabid et al. [23]	630 node-negative, high-risk patients	6.5 years	RT + 18 months' ADT versus RT + 36 months' ADT (44 Gy to whole pelvis, 70 Gy to prostate) ADT: bicalutamide 1 month, goserelin q 3 months for 18 or 36 months	10-year OS 59% versus 62% ($p = 0.28$) 10-year DSS 84.1% versus 83.7% ($p = 0.82$)

LTAD: long-term ADT, STAD: short-term ADT, OS: overall survival, DSS: disease-specific survival, and BRFS: biochemical relapse-free survival.

Combination of androgen deprivation therapy and radiotherapy for localized prostate cancer in the contemporary era

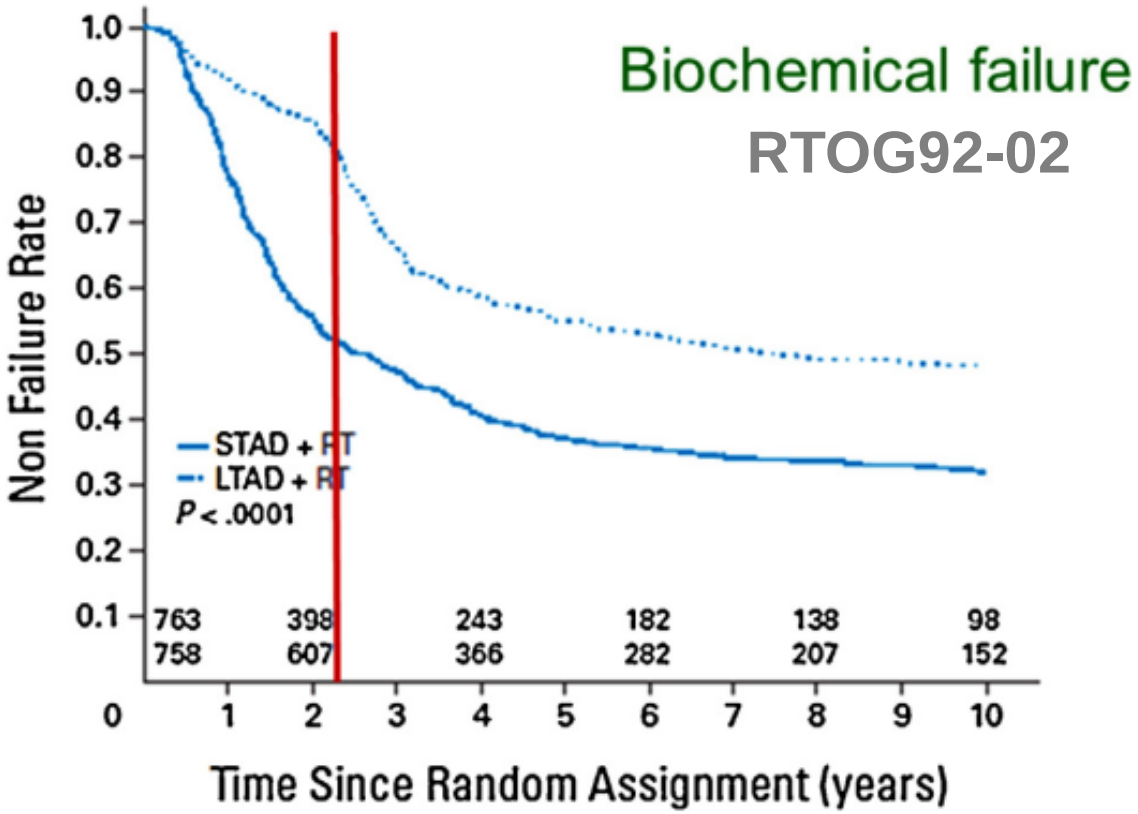
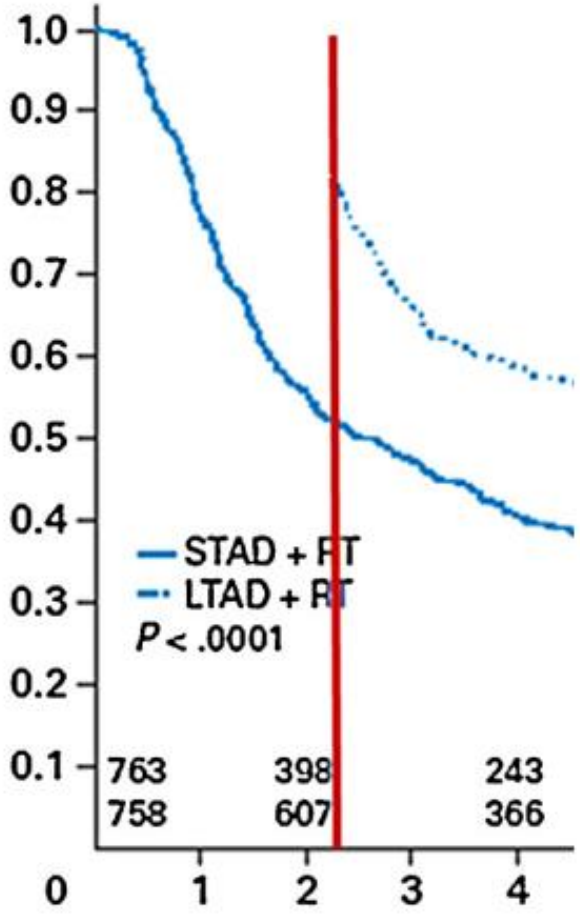


Fig. 1. Biochemical failure in RTOG 92-02 trial (modified from [14]).



D'Angelillo RM et al, Crit Rev Oncol Hematol 2015; 93: 136-148

How to combine…hormonal therapy
An overview of the results of RCTs (neoadjuvant)

Reference	Pts (n)	Risk group	RT (Gy)	Hormonal therapy (HT)	Median follow-up (years)	Scheme (HT months)	Timing of HT			Local failure	Biochemical NED	Overall survival
							Pre-RT (months)	RT (months)	Post-RT (months)			
Pilepich *et al.*, 2001 [39],	456	High	65–70	TAB	13.2	RT alone					20	34
Roach *et al.*, 2008 [40] (RTOG 86-10)		(bulky disease)			11.9	RT + HT (4)	2	2		(10 years, p=0.18[a])	35 (10 years, p=0.0001)	42 (10 years, p=0.12)
Laverdiere *et al.*, 2004 [41]	161	Intermediate	64	TAB	5	RT alone				NR	42	NR
(Quebec L-101)		(~70%)				RT + HT (3)	3				66	
						RT + HT (10)	3	2	5		69 (7 years, p<0.05[b])	
D'Amico *et al.*, 2004 [42],	206	Intermediate	70	TAB	7.6	RT alone				NR	55	61
D'Amico *et al.*, 2008 [43]		(79%)				RT + HT (6)	2	2	2		79 (5 years, p<0.05)	74 (8 years, p=0.01)
Denham *et al.*, 2005 [44]	802	High	66	TAB	5.9	RT alone				28	38	NR
(TROG 96-01)		(84%) Intermediate (16%)				RT + HT (3)	2	5		17	52	
						RT + HT (6)	2	2		12 (5 years, p<0.05[b])	56 (5 years, p<0.05[b])	
McGowan *et al.*, 2009 [38]	1979	Low	66	TAB	9.2	RT alone				39	59	57
(RTOG 94-08)		(35%) Intermediate (54%) High (11%)			9.1	RT + HT (4)	2	2		21 (2 years[c], p=0.001)	74 (10 years, p=0.01)	62 (10 years, p=0.03)

How to combine…hormonal therapy
An overview of the results of RCTs (neoadjuvant)

Reference	*Pts (n)*	*Risk group*	*RT (Gy)*	*Hormonal therapy (HT)*	*Median follow-up (years)*	*Scheme (HT months)*	*Timing of HT*			*Local failure*	*Biochemical NED*	*Overall survival*
							Pre-RT (months)	*RT (months)*	*Post-RT (months)*			
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Roach *et al.*, 2008 [40]		(bulky disease)			11.9	RT + HT (4)	2	2			35	42
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(Quebec L-101)		(~70%)				RT + HT (3)	3				66	
						RT + HT (10)	3	2	5		69	
											(7 years, p<0.05[b])	
D'Amico *et al.*, 2004 [42],	206	Intermediate	70	TAB	7.6	RT alone				NR	55	61
D'Amico *et al.*, 2008 [43]		(79%)				RT + HT (6)	2	2	2		79	74
											(5 years, p<0.05)	(8 years, p=0.01)
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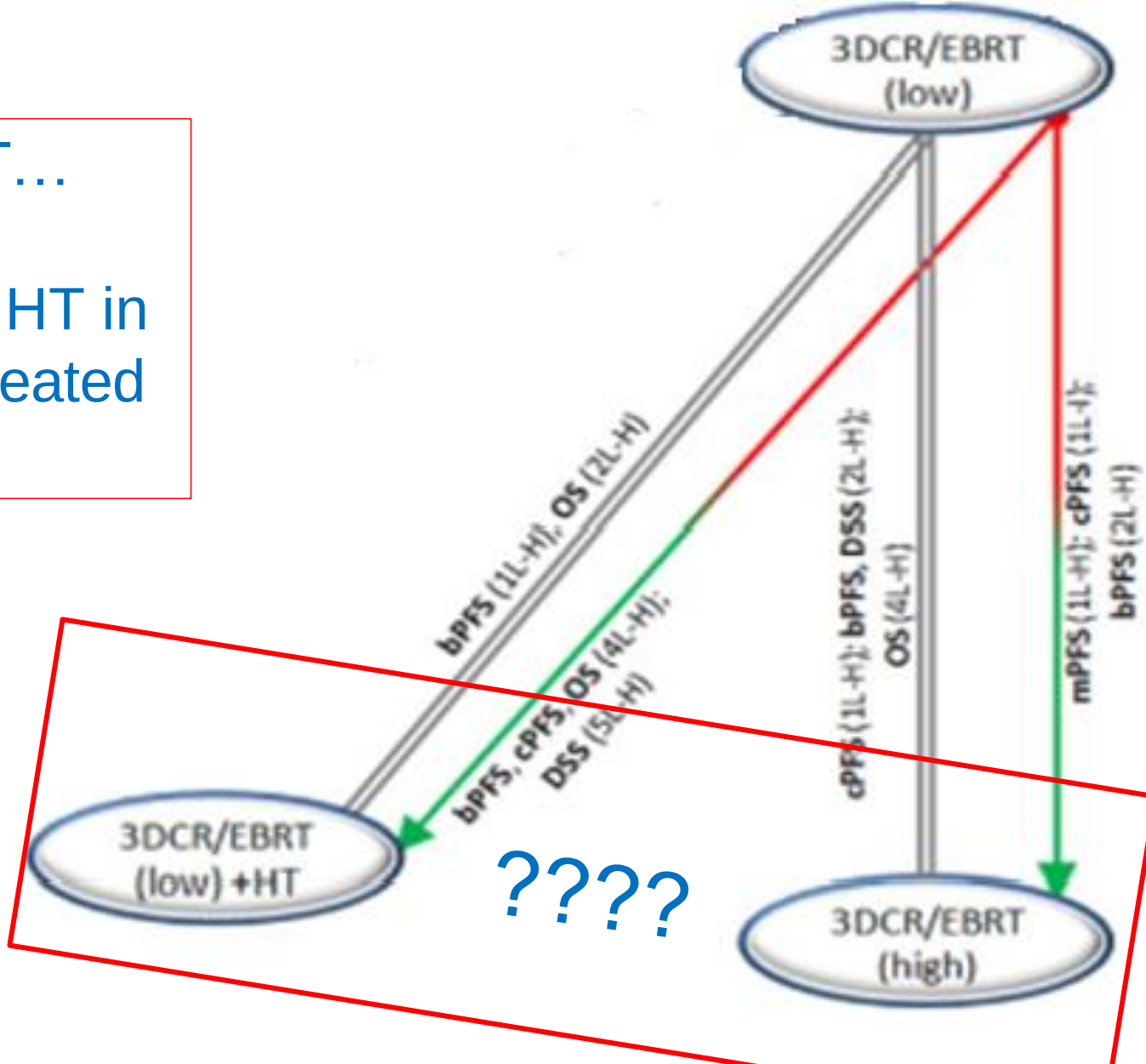
(TROG 96-01)		(84%)				RT + HT (3)	2	5		17	52	
		Intermediate				RT + HT (6)	2	2		12	56	
		(16%)								(5 years, p<0.05[b])	(5 years, p<0.05[b])	
McGowan *et al.*, 2009 [38]	1979	Low	66	TAB	9.2	RT alone				39	59	57
(RTOG 94-08)		(35%)			9.1	RT + HT (4)	2	2		21	74	62
		Intermediate								(2 years[c], p=0.001)	(10 years, p=0.01)	(10 years, p=0.03)
		(54%)										
		High										
		(11%)										

A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer

Wolff RF et al., Eur J Cancer 2015; 51: 2345–2367

No RCTs on HD-RT +/- HT…

Is it a problem in adopting HT in more recent populations treated with higher doses of RT??



How to combine…hormonal therapy

Feng FY et al, Int J Radiat Oncol Biol Phys. 2013 May 1;86(1):64-71

Retrospective analysis of 234 men treated with 75-79.2 Gy and varying ADT

Covariate	Biochemical failure			Metastasis		
	P Value	HR	95% CI	*P* Value	HR	95% CI
PSA (log)	.003	2.7	1.4-5.2	.10	2.2	0.86-5.4
T stage						
T1-T2c	Reference			Reference		
T3-T4	.11	1.5	0.91-2.4	.10	1.8	0.89-3.7
Gleason Score						
2-6	Reference			Reference		
7	.36	1.4	0.67-3.0	.37	1.7	0.55-5.1
8	.14	1.8	0.82-4.1	.19	2.3	0.67-7.7
9-10	.009	3.3	1.3-8.1	<.0001	12.1	3.3-44
ADT group						
None	Reference			Reference		
STAD	.18	0.64	0.34-1.2	.002	0.27	0.11-0.63
LTAD	.03	0.46	0.23-0.93	<.0001	0.10	0.04-0.27
Age	.07	0.97	0.95-1.0	.90	1.0	0.97-1.0
CMI						
None	Reference			Reference		
1	.32	0.8	0.5-1.3	.11	0.5	0.2-1.2
2 or more	.12	0.6	0.3-1.2	.19	0.5	0.2-1.4

>≥1 year

Abbreviations: ADT = androgen deprivation therapy; CI = confidence interval; CMI = Charlson Comorbidity Index; HR = hazard ratio; LTAD = long-term ADT; PSA = prostate-specific antigen; STAD = short-term ADT.

How to combine… chemotherapy and RT

Study	Type of study	n. pts	Inclusion criteria	RT (Gy)	Type of CT	Main Results
Kumar et al	Phase I	22	IR- HR	70.2	Docetaxel	G2 diarrhea = 36% G2 dysuria = 23%
Chen et al	Phase I	18	HR	78 (IMRT)	Docetaxel	Median FUP 26 mo bRFS = 94%.
Marchall et al	Phase I	19	HR	77.4	Docetaxel	Median FUP 41 mo bRFS = 80%. No severe tox.
Sanfilippo et al	Phase I- II	22	HR	63-73.8 Dose escalation	Paclitaxel	Six of the twenty-two patients experienced a PSA relapse at a median follow-up of 38 mo
Perrotti et al	Phase I-II	20	HR	72 (IMRT)	Docetaxel	3 G3 acute tox

How to combine… chemotherapy and RT

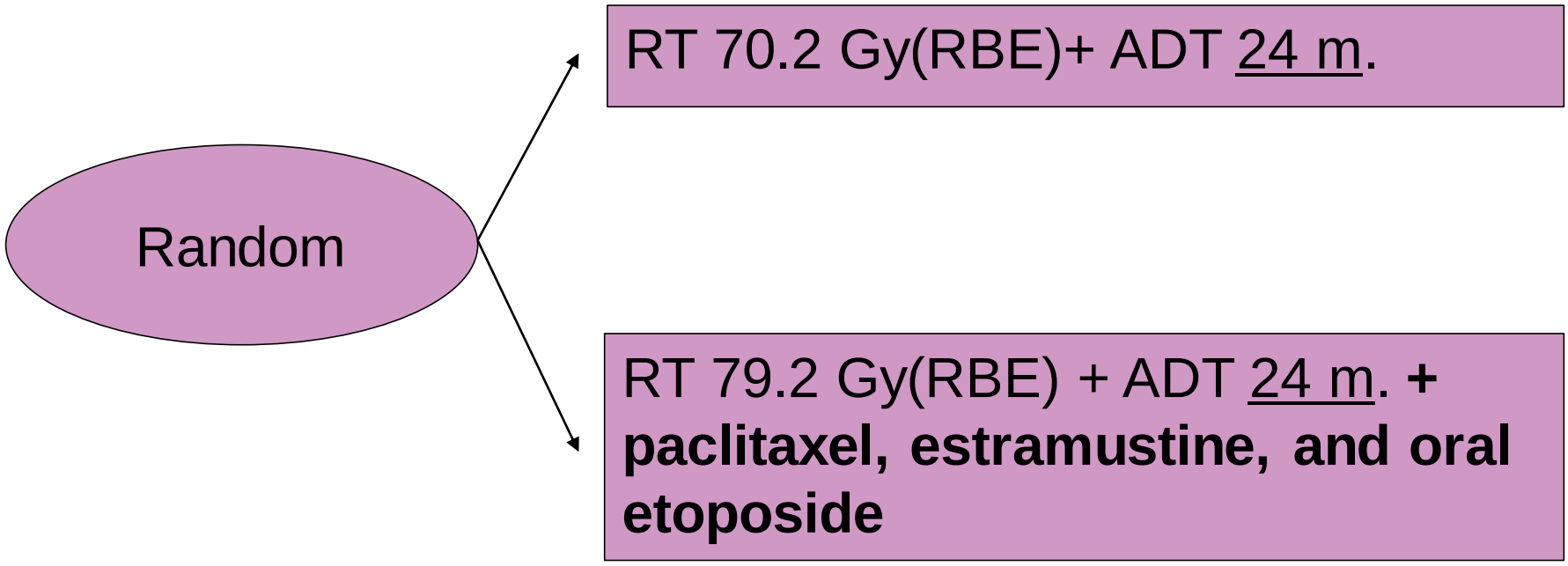
Study	Type of study	n. pts	Inclusion criteria	RT (Gy)	Type of CT	Main Results
SWOG 9024	Phase II	30	T3 +, N0	45 + 25.2	Daily 5-FU	13/30: PSA < 1.0 ng/dL 6/13 negative post-treatment biopsy
Khil et al	Phase II	65	cT2b-c + GS 9-10, cT3, or cTxN1M0	45 + 20-25	Estramustine Phosphate + Vinblastine	undetectable PSA at nadir: 86% biochemical remission: 48%
MSKCC	Phase II	27	High risk and/or N+	75.6	Estramustine Phosphate + Vinblastine	5-y BRFS: 34% Acute G3 GI tox: 35% Acute G3 GI tox: 48%
Khil et al	Phase II	50	IR-HR	70.2	Docetaxel	Median FUP 54 m 5-y bRFS = 66% 5-y OS = 92%

ClinicalTrials.gov

NCT00004054

RTOG-9902: Int J Radiat Oncol Biol Phys. 2015 Oct 1;93(2):294-302

Primary endpoint: 5-year OS



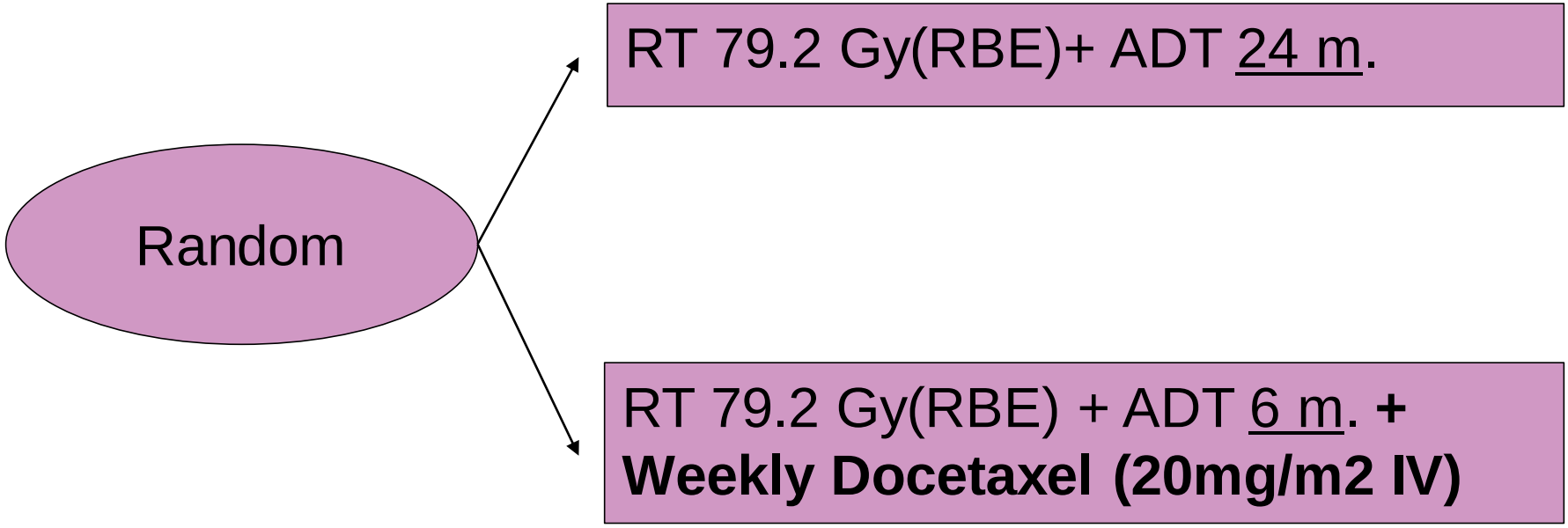
No significant differences in OS, biochemical failure, local progression, distant metastases, or disease-free survival with the addition of adjuvant CT to LT AS þ RT.

ClinicalTrials.gov

NCT01603420

Proton Collaborative Group

Primary endpoint: 5-year Freedom From Failure (FFF) Rates



Trial is completed. Results are pending

ESTRO School

Evidence Based Radiation Oncology: Post-operative radiotherapy in PCa

De Bari Berardino, MD, fESTRO

Radiation Oncology Dpt.
Centre Hospitalier Régional Universitaire «Jean Minjoz»
France

The 5 W and 1 H of EBM

What ….

Why …

Which…

When …

Where …

How …

The 5 W and 1 H of EBM

What ….is the role of RT in the postop setting?

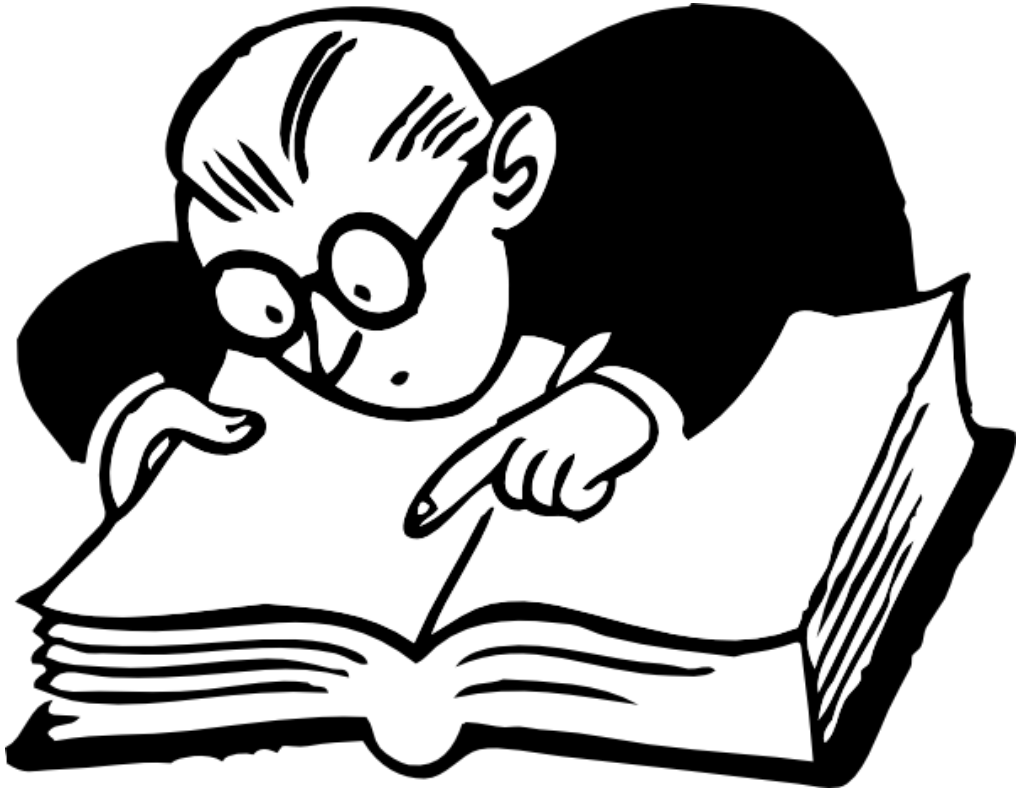
Why …

When …

Which…

Where …

How …



What are the evidences in the postoperative setting PC?

Table 1
Characteristics of eligible trials

Trial descriptors	EORTC 22911	SWOG 8794	German Cancer Society ARO 96-02 and AUO AP 09/95
Eligibility criteria	At least one of: extraprostatic extension, seminal vesicle invasion, or positive surgical margins (pT2 N0 M0 R1 or pT3 N0 M0 R0-1) WHO PS 0-1 Age ⩽75 yrs	At least one of: extraprostatic extension, seminal vesicle invasion, or positive surgical margins (pT2 N0 M0 R1 or pT3 N0 M0 R0-1) SWOG PS 0-2 Negative pelvic lymphadenectomy[a]	Extraprostatic extension or seminal vesicle invasion with or without positive surgical margins (pT3 N0 R0-1) Undetectable PSA following RP
Median age	65 yrs	64.9 yrs	NR
Stratification variables	Institution; pT3a (present vs. absent); R0 vs. R1; pT3b (present	Tumour extent (pT3a or R1 vs. pT3b vs. R1 and pT3b); NADT (present vs.	Gleason score (2–6 vs. 7–10); R0 vs. R1; pT3a vs. pT3b; NADT
Number randomized	1005	431	307
Number eligible	968	425	300

Morgan et al, Radiother Oncol. 2008 Jul;88(1):1-9

What are the evidences in the postoperative setting PC?

Table 1
Characteristics of eligible trials

Trial descriptors	EORTC 22911	SWOG 8794	German Cancer Society ARO 96-02 and AUO AP 09/95
Time from RP until start of adjuvant RT	<16 weeks	<18 weeks	8–12 weeks
Adjuvant RT dose–fractionation	60 Gy in 30 fractions	60–64 Gy in 30–32 fractions	60 Gy in 30 fractions
Median follow-up	5 years	10.6 years	4.5 years
Primary endpoint	Biochemical progression-free survival	Metastasis-free survival	Biochemical progression-free survival
Definition of biochemical progression	An increase of more than 0.2 μg/L over the lowest postoperative value measured on three occasions at least 2 weeks apart.	For men with a postsurgical PSA ⩽0.4 ng/mL, the first occurrence of PSA >0.4 ng/mL	PSA increase from undetectable to detectable level, with confirmation by further increase at least 3 months later

Morgan et al, Radiother Oncol. 2008 Jul;88(1):1-9

What are the evidences in the postoperative setting PC?

Reference	N	Inclusion criteria	Dose (Gy)	Follow-up median (years)	10-year BPFS ART vs. NFT	10-year OS ART vs. NFT	10-year toxicity rate (%) ART vs. NFT
Thompson et al. (5)	425	pT3 cN0/pN0 R0/R1	60–64	12.7	52 vs. 26% $p < 0.001$	74 vs. 66% $p = 0.023$	GI, G3 = 3.3 vs. 0 GU, G3 17.8 vs. 9.5
Bolla et al. (4)	1005	pT2–3 pN0 R0/R1	60	10.6	60 vs. 41% $p < 0.0001$	77 vs. 81% $p = 0.2$	GU > G2 = 21.3 vs. 13.5 ($p = 0.003$) GI > G2 = 2.5 vs. 1.9 ($p = 0.47$)
Wiegel et al. (6)	388 (307)	pT3 pN0 R0/R1 PSA 0	60	9.3	56 vs. 35% $p < 0.0001$	84 vs. 86% $p = 0.59$	ART: GU, G3 = 1 patient, G2 = 2 patients, GI, G2 = 2 patients

BPFS, Biochemical progression-free survival; OS, overall survival; ART, adjuvant radiation therapy; NFT, no further therapy; GU, genitourinary; GI, gastro-intestinal; G, grade.

Herrera F et al. Front Oncol. 2016 May 9;6:117

What are the evidences in the postoperative setting PC?

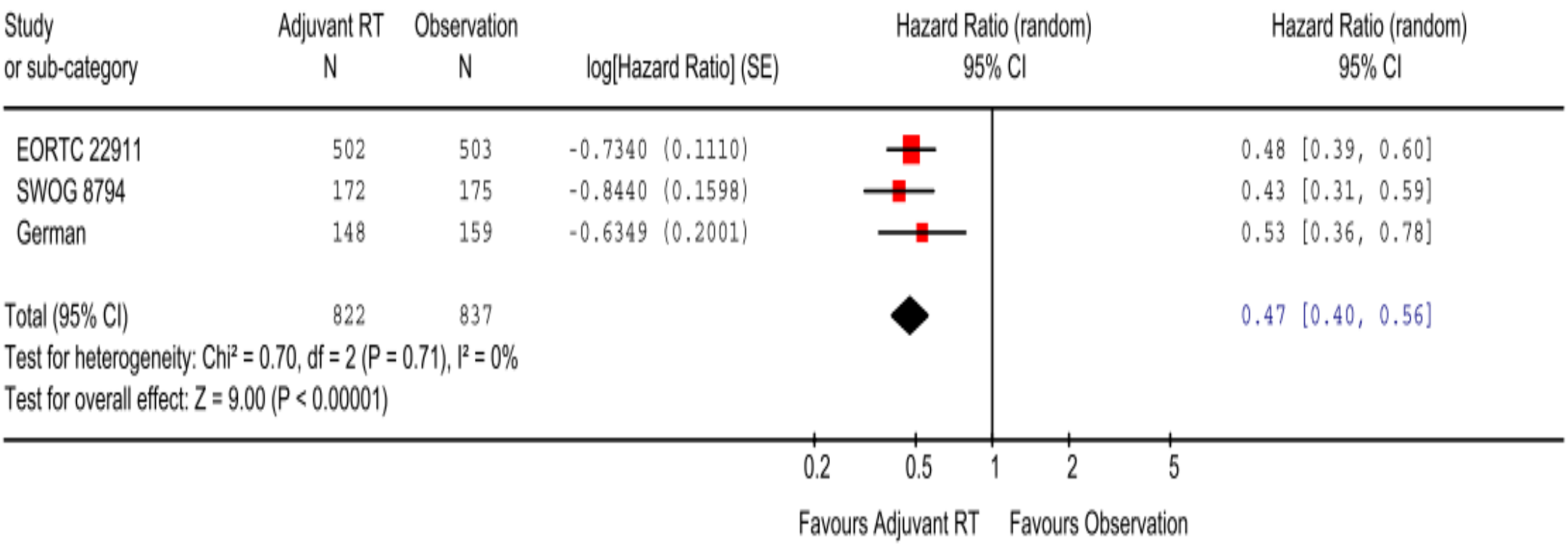


Fig. 2. Meta-analysis of biochemical progression using a random effects model. Hazard ratios (95% CI) are shown on a logarithmic scale.

Morgan et al, Radiother Oncol. 2008 Jul;88(1):1-9

What are the evidences in the postoperative setting PC?

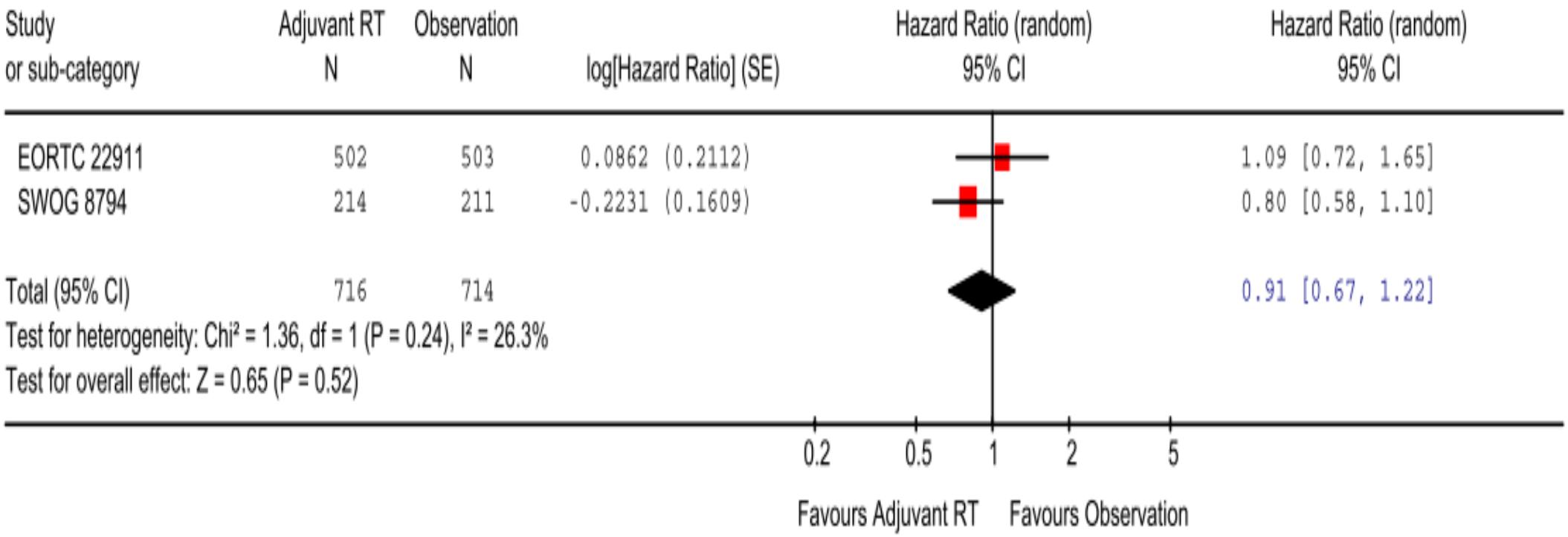
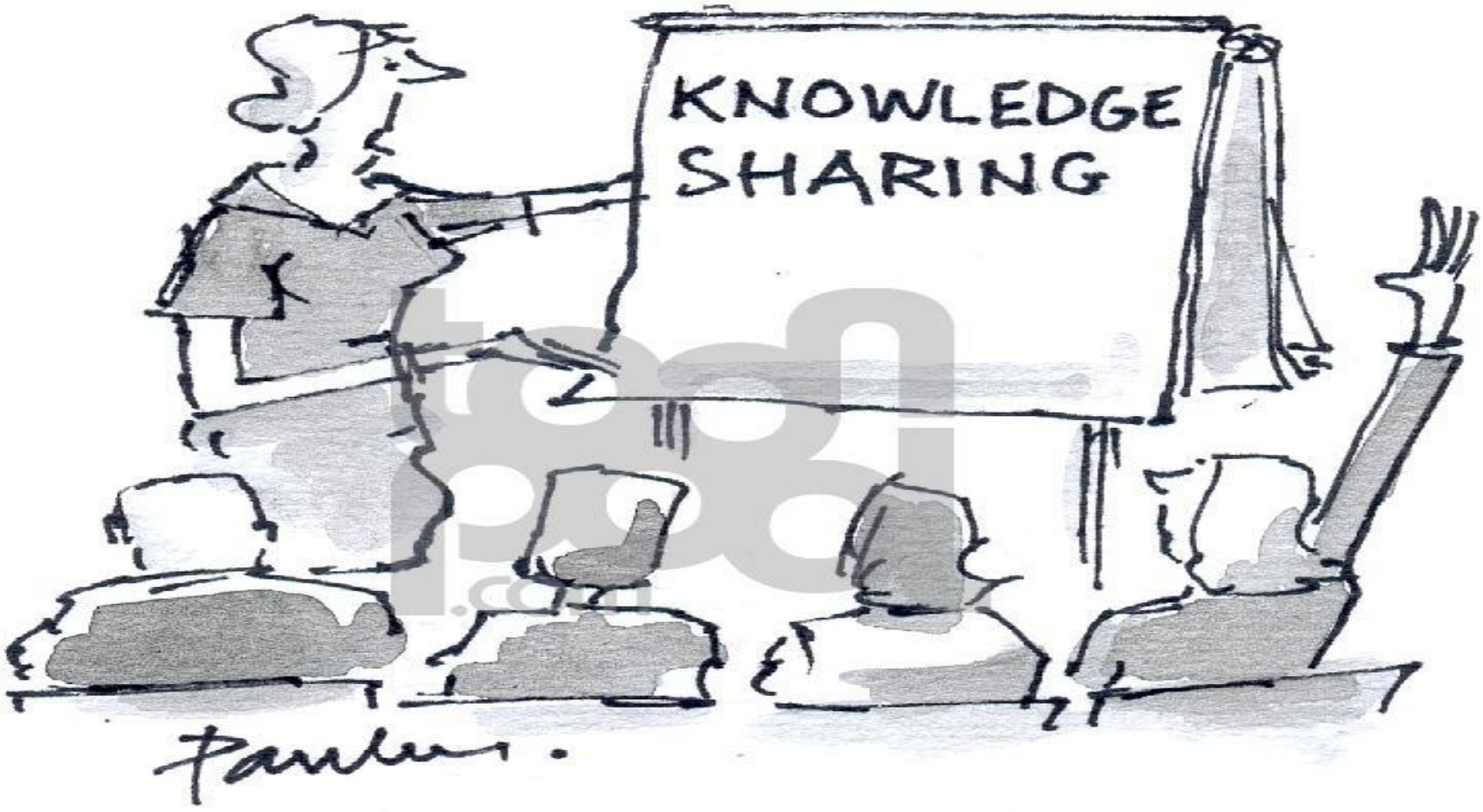


Fig. 1. Meta-analysis of overall mortality using a random effects model. Hazard ratios (95% CI) are shown on a logarithmic scale.

Morgan et al, Radiother Oncol. 2008 Jul;88(1):1-9

What are the evidences in the postoperative setting PC?



The 5 W and 1 H of EBM

What ….is the role of RT in the postop setting?

Why should we continue to discuss about ART?

When …

Which…

Where …

How …

A cast of shadow on adjuvant radiotherapy for prostate cancer: A critical review based on a methodological perspective

- SWOG and EORTC trial: only few patients presented a PSA dosage

- Only the German trial delivered really ART, as 1/3 of the patients of the other 2 studies with a dosage of PSA presented an elevated value of PSA…it is SRT!

- Impact of ADT in the observational arms…

[1]Arcangeli S et al. Crit Rev Oncol Hematol. 2016 Jan;97:322-7

Why should we continue to discuss about ART?

- These trials typically represent a paradigm of the time delay-related limitations[1]

- Indeed, only 20% of the patients potentially candidate to ART really receive it[2]

- Introduction of the PSA dosage and of the concept of early salvage RT (SRT)

[1]Arcangeli S et al. Crit Rev Oncol Hematol. 2016 Jan;97:322-7
[2]Hoffman Ke et al, J Urol. 2011; 185 (1): 116–120

The 5 W and 1 H of EBM

What ….is the role of RT in the postop setting?

Why should we continue to discuss about ART?

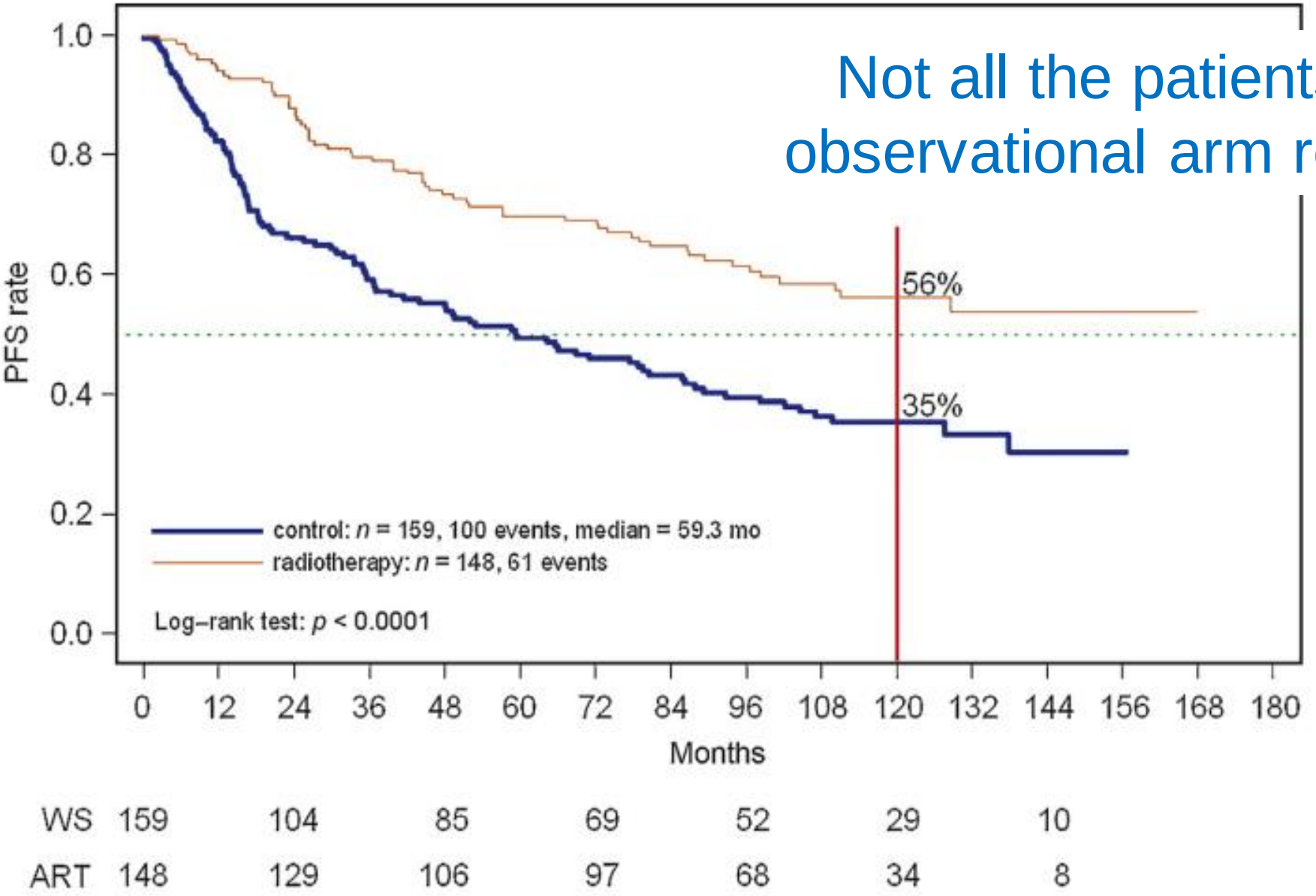
When ..the best timing for postop RT...

Which…

Where …

How …

The emerging concept of early salvage RT (ESRT)



Not all the patients in the observational arm relapsed!!

When…the best timing for postop RT

Early Salvage Radiotherapy Following Radical Prostatectomy

David Pfister[a,], Michel Bolla[b], Alberto Briganti[c], Peter Carroll[d], Cesare Cozzarini[e], Steven Joniau[f], Hein van Poppel[f], Mack Roach[g], Andrew Stephenson[h], Thomas Wiegel[i], Michael J. Zelefsky[j]*

EUROPEAN UROLOGY 65 (2014) 1034–1043

Early Salvage Radiotherapy Following Radical Prostatectomy

EUROPEAN UROLOGY 65 (2014) 1034–1043

Table 4 – Oncologic outcome

First author	No. of patients	PSA pre-RT, ng/ml, (range)	Follow-up (range)	Fraction bRFS at specific time points	Nodal involvement
Bernard [23]	69	0.32 (0.1–0.49)	8 yr (0.6–15)	5 yr: 79.8%	pN0
Terai [29]	21 of 37	<0.15	31.9 mo (34.3–69.8)	5 yr: 80%	N0
Liauw [24]	34	0.27 (0.05–0.5)	72.4 mo (5.2–136.3)	5 yr: 71%	pN0
Goenka [25]	143	<0.5	60 mo (4–221)	5 yr: 48%	pN0
Briganti [4]	390	<0.5 <0.3	40.6 mo	2 yr: 92.8% 5 yr: 81.8%	pN0
Stephenson [26]	181	0.4 (0.3–0.4)	33 mo (15–56)	6 yr: 48% 5 yr: 61% 3 yr: 69%	pN0
Ost [11]	48	0.3 (0.1–0.5)	53 mo (18–132)	5 yr: 77.1%	pN0/cN0

PSA = prostate-specific antigen; RT = radiation therapy; bRFS = biochemical recurrence-free survival.

Early Salvage Radiotherapy Following Radical Prostatectomy

EUROPEAN UROLOGY 65 (2014) 1034–1043

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PSA = prostate-specific antigen; RT = radiation therapy; bRFS = biochemical recurrence-free survival.

Adjuvant and Salvage Radiotherapy after Radical Prostatectomy in Prostate Cancer Patients

Table 4 – Selected retrospective studies comparing adjuvant and salvage radiotherapy (RT) in prostate cancer patients

	Patients (*N*)	Patient characteristics	Pre-sRT PSA (median)	Technique	Concomitant ADT	Dose (median)	Study period	Follow-up (median)	Outcomes
Ost et al [30]	104 aRT vs 134 sRT	GS >3 + 4: 28 vs 28% SVI: 25.8 vs 24.7% PSM: 23.6 vs 33.7%	>0.5 ng/ml in 57% of pts	IMRT to the prostate bed and seminal vesicles	46% vs 37%	74 Gy vs 76 Gy	1999–2009	36 mo	• 3-yr PFS: 95 vs 87% for aRT vs sRT ($p = 0.08$) • 3-yr BCR-free survival: 90 vs 65% for aRT vs sRT ($p = 0.002$)
Budiharto et al [25]	130 aRT vs 89 sRT	GS 8–10: 7.7 vs 14.6% PSM: 35.4 vs 58.4%	0.30 ng/ml	3D-CRT to the prostate bed and seminal vesicles	No	60 Gy vs 66 Gy	NA	103 mo vs 121 mo	• aRT improved PFS
D'Amico et al [26]	65 aRT vs 49 sRT with PSADT <10 mo vs 46 sRT with PSADT ≥10 mo	GS 8–10: 31 vs 10 vs 28% PSM: 97 vs 53 vs 59% SVI: 32 vs 22 vs 20%	NA	3D-CRT to the prostate bed and seminal vesicles	NA	64 Gy vs 66.6 Gy	1989–2008	7.7 yr	• sRT with PSADT <10 mo increased risk of OM • No differences between aRT and sRT with PSADT ≥10 mo in OM
Jereczek-Fossa et al [28]	258 aRT vs 173 sRT	SVI: 26.7 vs 15% PSM: 60.5 vs 33.5%	0.78 ng/ml	The 3D six-field and 3D-ART techniques were used in 25.1% and 74.9% of pts	35% vs 41%	70 Gy	1996–2006	32 mo vs 30 mo	• PFS significantly longer in pts treated with aRT (79.8 vs 60.5% at 4 yr; $p < 0.001$)

aRT better

aRT better

aRT +/- better

aRT better

Adjuvant and Salvage Radiotherapy after Radical Prostatectomy in Prostate Cancer Patients

aRT better

aRT better

No difference

Mishra et al [29]	102 aRT vs 74 sRT	GS 8–10: 25.7 vs 29.5% SVI: 31.1 vs 30.4% PSM: 81.1 vs 76.8%	0.6 ng/ml	3D-CRT and IMRT to the bed of the prostate and seminal vesicles	14.9% vs 26.8%	66 Gy vs 66.6 Gy	1990–2009	103 mo	• 10-yr BCR-free survival: 73 vs 41% for aRT and sRT ($p < 0.001$) • 10-yr CR-free survival: 98.6 vs. 80.9% for aRT and sRT ($p = 0.003$)
Detti et al [27]	203 aRT vs 104 sRT	GS 8–10: 40.4 vs 51% SVI: 89.2 vs 77.9% PSM: 49.8 vs 23.1%	1.73 ng/ml[a]	3D-CRT to the prostate bed and seminal vesicles	14.8% vs 26.0%	66.2 Gy vs 66.8 Gy[a]	1995–2010	4.9 yr	• 20.7 vs 31.7% pts experienced BCR in the aRT vs sRT groups ($p = 0.03$)
Fossati et al [43]	243 aRT vs 267 observation ± sRT	GS 8–10: 27 vs 27%	0.2 ng/ml	Conventional nonconformal treatment or 3D-CRT to the bed of the prostate bed and seminal vesicles	No	60 Gy vs 67 Gy	1996–2009	94 mo	• 8-yr CR-free survival: 92 vs 91% for aRT vs sRT ($p = 0.9$) • 8-yr OS: 89 vs 92% ($p = 0.9$)

ADT = androgen deprivation therapy; aRT = adjuvant radiotherapy; GS = Gleason score; IMRT = intensity-modulated radiotherapy; NA = not applicable; OM = overall mortality; PFS = progression-free survival; PSA = prostate specific antigen; PSADT = prostate specific antigen doubling time; PSM = positive surgical margins; pts = patients; sRT = salvage radiotherapy; SVI = seminal vesicle invasion; 3D-CRT = three-dimensional conformal radiation therapy.

[a] Mean.

Adjuvant and Salvage Radiotherapy after Radical Prostatectomy in Prostate Cancer Patients

Table 4 – Selected retrospective studies comparing adjuvant and salvage radiotherapy (RT) in prostate cancer patients

	Patients (*N*)	Patient characteristics	Pre-sRT PSA (median)	Technique	Concomitant ADT	Dose (median)	Study period	Follow-up (median)	Outcomes
Ost et al [30]	104 aRT vs 134 sRT	GS >3 + 4: 28 vs 28% SVI: 25.8 vs 24.7% PSM: 23.6 vs 33.7%	>0.5 ng/ml in 57% of pts	IMRT to the prostate bed and seminal vesicles	46% vs 37%	74 Gy vs 76 Gy	1999–2009	36 mo	• 3-yr PFS: 95 vs 87% for aRT vs sRT ($p = 0.08$) • 3-yr BCR-free survival: 90 vs 65% for aRT vs sRT ($p = 0.002$)
Budiharto et al [25]	130 aRT vs 89 sRT	GS 8–10: 7.7 vs 14.6% PSM: 35.4 vs 58.4%	0.30 ng/ml	3D-CRT to the prostate bed and seminal vesicles	No	60 Gy vs 66 Gy	NA	103 mo vs 121 mo	• aRT improved PFS
D'Amico et al [26]	65 aRT vs 49 sRT with PSADT <10 mo vs 46 sRT with PSADT ≥10 mo	GS 8–10: 31 vs 10 vs 28% PSM: 97 vs 53 vs 59% SVI: 32 vs 22 vs 20%	NA	3D-CRT to the prostate bed and seminal vesicles	NA	64 Gy vs 66.6 Gy	1989–2008	7.7 yr	• sRT with PSADT <10 mo increased risk of OM • No differences between aRT and sRT with PSADT ≥10 mo in OM
Jereczek-Fossa et al [28]	258 aRT vs 173 sRT	SVI: 26.7 vs 15% PSM: 60.5 vs 33.5%	0.78 ng/ml	The 3D six-field and 3D-ART techniques were used in 25.1% and 74.9% of pts	35% vs 41%	70 Gy	1996–2006	32 mo vs 30 mo	• PFS significantly longer in pts treated with aRT (79.8 vs 60.5% at 4 yr; $p < 0.001$)

aRT better

aRT better

aRT +/- better

aRT better

Adjuvant and Salvage Radiotherapy after Radical Prostatectomy in Prostate Cancer Patients

aRT better

aRT better

No difference

Mishra et al [29]	102 aRT vs 74 sRT	GS 8–10: 25.7 vs 29.5% SVI: 31.1 vs 30.4% PSM: 81.1 vs 76.8%	0.6 ng/ml	3D-CRT and IMRT to the bed of the prostate and seminal vesicles	14.9% vs 26.8%	66 Gy vs 66.6 Gy	1990–2009	103 mo	• 10-yr BCR-free survival: 73 vs 41% for aRT and sRT ($p < 0.001$) • 10-yr CR-free survival: 98.6 vs. 80.9% for aRT and sRT ($p = 0.003$)
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ADT = androgen deprivation therapy; aRT = adjuvant radiotherapy; GS = Gleason score; IMRT = intensity-modulated radiotherapy; NA = not applicable; OM = overall mortality; PFS = progression-free survival; PSA = prostate specific antigen; PSADT = prostate specific antigen doubling time; PSM = positive surgical margins; pts = patients; sRT = salvage radiotherapy; SVI = seminal vesicle invasion; 3D-CRT = three-dimensional conformal radiation therapy.

[a] Mean.

Early Salvage Radiotherapy Following Radical Prostatectomy

EUROPEAN UROLOGY 65 (2014) 1034–1043

Table 1 – Ongoing prospective trials on salvage radiation therapy (RT), early salvage RT, and adjuvant RT and hormone treatment

Trial	Design	Arms	Pts	Intention	Dosage, Gy	Primary end points	Secondary end points
RADICALS RT	International, multicentre, open-labelled, randomised, controlled	Adjuvant vs Deferred RT (PSA failure)	1150	RT	66 Gy in 33 fractions 52.5 in 20 fractions	Freedom from distant disease PCa mortality	PCa-specific survival Freedom from treatment failure Clinical PFS OS Nonprotocol hormone therapy Treatment toxicity Patient-reported outcomes
RADICALS HD	International, multicentre, open-labelled, randomised, controlled	No hormones, short-term ADT (6 mo) vs long-term ADT (24 mo)	2000	Hormones	66 Gy in 33 fractions	PCa-specific survival	Freedom from distant metastases (any distant metastases or PCa-specific death) Freedom from treatment failure Clinical PFS OS Nonprotocol hormone therapy Treatment toxicity Patient-reported outcomes
GETUG-17	Multicentre, open-labelled, randomised, controlled	Adjuvant RT vs early salvage RT (PSA >0.2 ng/ml)	718	RT and hormones (6 mo)	66 Gy in 33 fractions	PFS (clinical or biochemical)	OS Metastasis-free survival Toxicity QoL Functional results in patients >75 yr of age
RAVES	Multicentre, open-labelled, randomised, controlled	Adjuvant RT vs early salvage RT (PSA >0.2 ng/ml)	470	RT Noninferiority of early salvage RT	64 Gy in 32 fractions	PFS QoL	Toxicity OS PCa-specific survival Time to local failure Time to distant failure Time to ADT
EORTC 22043-30041	Multicentre, open-labelled, randomised, controlled	Adjuvant RT vs early salvage RT (0.1< PSA <0.5 ng/ml) plus ADT	600	RT and hormones	64–74 Gy	bRFS	Toxicity, early/late Clinical PFS OS Distant metastasis-free survival QoL

RADICALS = Radiotherapy and Androgen Deprivation in Combination After Local Surgery; RT = radiation therapy; PSA = prostate-specific antigen; PCa = prostate cancer; PFS = progression-free survival; OS = overall survival; ADT = androgen-deprivation therapy; QoL = quality of life; RAVES = Radiotherapy Adjuvant vs Early Salvage; EORTC = European Organisation for Research and Treatment of Cancer; bRFS = biochemical recurrence-free survival.

Which is the better timing?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Prostate Cancer

aRT

Indications for adjuvant RT include pT3 disease, positive margin(s), Gleason score 8–10, or seminal vesicle involvement. Adjuvant RT is usually given within 1 year after RP and once any operative side effects have improved/ stabilized. Patients with positive surgical margins may benefit the most.

sRT

- Indications for salvage RT include an undetectable PSA that becomes detectable and then increases on 2 subsequent measurements. Treatment is more effective when pre-treatment PSA is low and PSADT is long.

The 5 W and 1 H of EBM

What ….is the role of RT in the postop setting?

Why should we continue to discuss about ART?

When ..the best timing for postop RT...

Which… is the better dose level?

Where …

How …

Which is the better dose level?

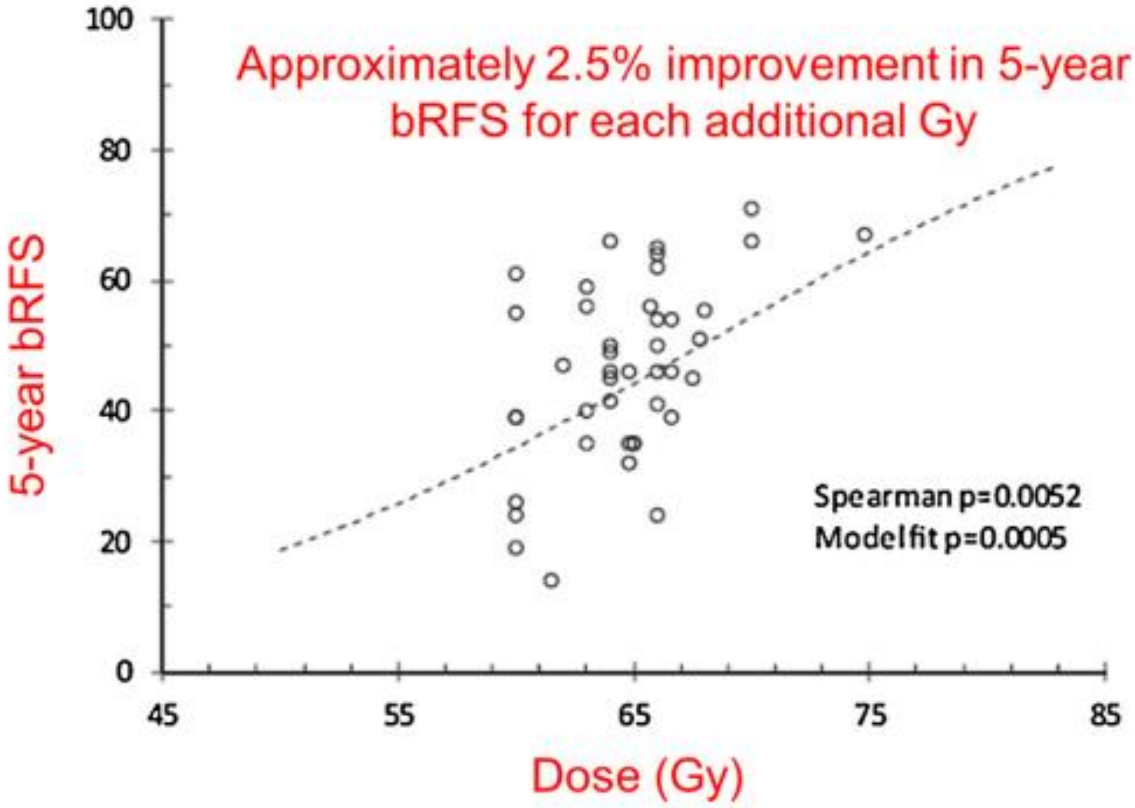


Fig. 1. PSA b-RFS as a function of the delivered dose. Each symbol represents an individual published series of postoperative RT. The data suggest that there is approximately a 2.5% improvement in b-RFS for each additional Gy with postoperative RT.

King CR et al, Int J Radiat Oncol Biol Phys. 2008 May 1;71(1):23-7.

Which is the better dose level?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Prostate Cancer

- The recommended prescribed doses for adjuvant/salvage post-prostatectomy RT are 64–72 Gy in standard fractionation. Biopsy-proven gross recurrence may require higher doses.

King CR et al, Int J Radiat Oncol Biol Phys. 2008 May 1;71(1):23-7.

The 5 W and 1 H of EBM

What ….is the role of RT in the postop setting?

Why should we continue to discuss about ART?

When ..the best timing for postop RT...

Which… is the better dose level?

Where … the volumes of treatment

How …

Evidence based volumes in the postoperative setting

Table 1
Characteristics of eligible trials

Trial descriptors	EORTC 22911	SWOG 8794	German Cancer Society ARO 96-02 and AUO AP 09/95
Adjuvant RT volume	• Initial phase: 50 Gy to ''volume including surgical limits from seminal vesicles to apex with security margin to encompass subclinical disease in peri-prostatic area'' • 10 Gy boost to ''reduced volume circumscribing the previous landmarks of the prostate with a reduced security margin''	Single phase: RT delivered to ''prostatic fossa and paraprostatic tissues''	Prostatic fossa and region of seminal vesicles with 1 cm margin

Morgan et al, Radiother Oncol. 2008 Jul;88(1):1-9

Distribution of prostate nodes: a PET/CT-derived anatomic atlas of prostate cancer patients before and after surgical treatment

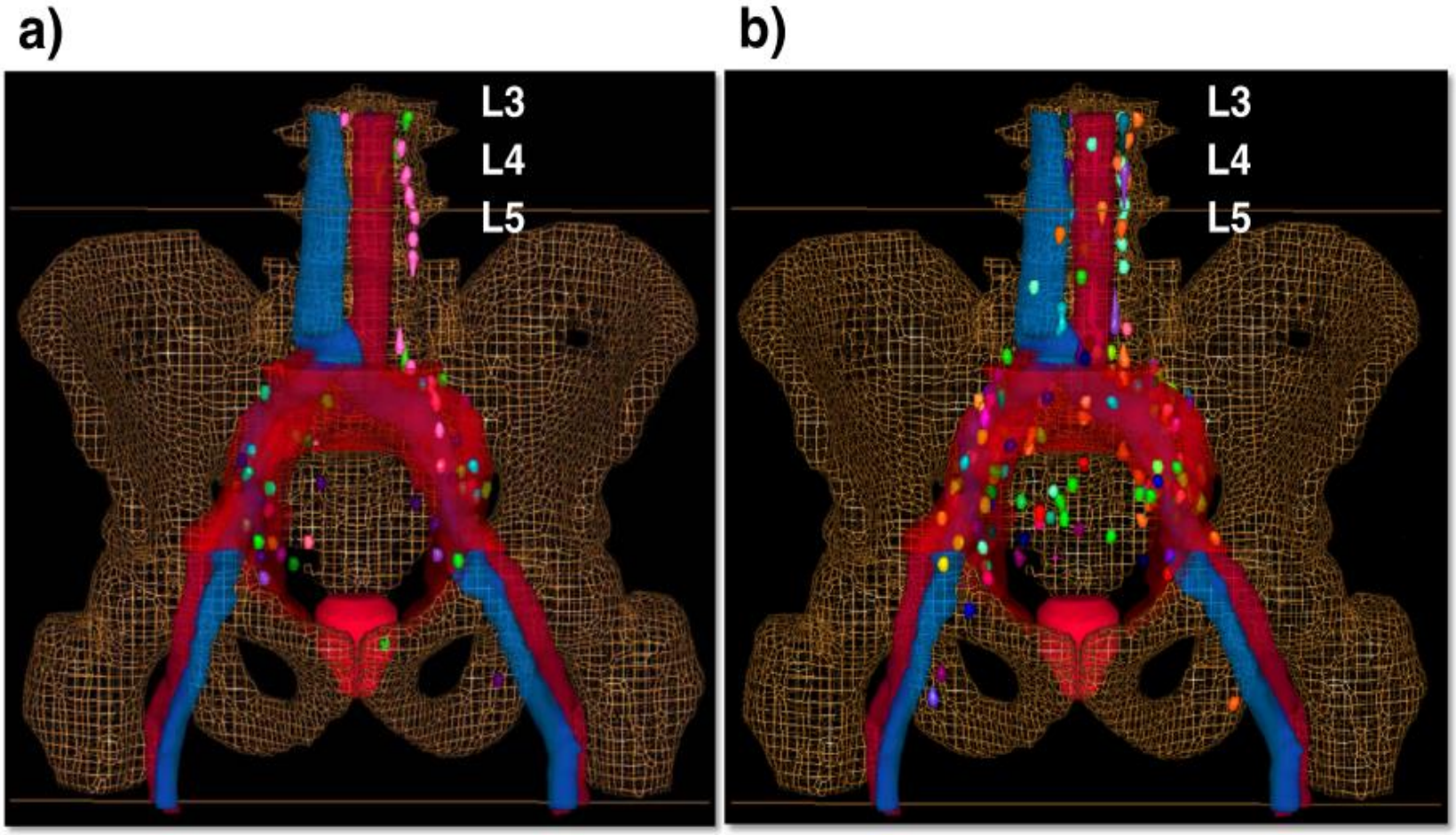


Fig. 1 a Distribution and geographic miss according to RTOG – CTV (*red*) of PET positive lymph nodes in patients with no prior treatment ($n = 32$); **b** Distribution and geographic miss according to RTOG – CTV (*red*) of PET positive lymph nodes in postoperative patients ($n = 87$)

The 5 W and 1 H of EBM

What ….is the role of RT in the postop setting?

Why should we continue to discuss about ART?

When ..the best timing for postop RT...

Which… is the better dose level?

Where … the volumes of treatment

How … to combine with ADT?

How to combine ADT in the postoperative setting?

Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial

Christian Carrie, Ali Hasbini, Guy de Laroche, Pierre Richaud, Stéphane Guerif, Igor Latorzeff, Stéphane Supiot, Mathieu Bosset, Jean-Léon Lagrange, Véronique Beckendorf, François Lesaunier, Bernard Dubray, Jean-Philippe Wagner, Tan Dat N'Guyen, Jean-Philippe Suchaud, Gilles Créhange, Nicolas Barbier, Muriel Habibian, Céline Ferlay, Philippe Fourneret, Alain Ruffion, Sophie Dussart

Carrie et al., Lancet Oncol. 2016 Jun;17(6):747-56.

Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial

	Radiotherapy alone (n=373)	Radiotherapy and goserelin (n=369)
Age (years)	67 (52–85)	67 (49–80)
Gleason score		
<8	332 (89%)	329 (89%)
≥8	41 (11%)	40 (11%)
Pathological tumour stage (TNM 2005)		
pT2a	37 (10%)	29 (8%)
pT2b	76 (20%)	75 (20%)
pT2c	88 (24%)	92 (25%)
pT3a	121 (32%)	127 (34%)
pT3b	50 (13%)	44 (12%)
pT4 bladder neck involvement	0	1 (<1%)
Missing	1 (<1%)	1 (<1%)
Pathological node involvement (TNM 2005)		
pN0	274 (74%)	273 (74%)
pNX	99 (27%)	96 (26%)
Positive surgical margins	196 (53%)	175 (47%)
Seminal vesicle involvement	318 (85%)	312 (85%)
PSA doubling time >6 months	276 (74%)	270 (73%)
ECOG performance status		
0	345 (92%)	329 (89%)
1	13 (4%)	22 (6%)
Missing	15 (4%)	18 (5%)
PSA at baseline randomisation (µg/L), median (IQR)*	0·30 (0·20–0·50)	0·30 (0·20–0·50)
Time between surgery and relapse (months), median (IQR)*	29·99 (19–52)	33·98 (21–53)
Presurgery PSA (µg/L), median (IQR)†	8·10 (6–12)	8·35 (6–12)

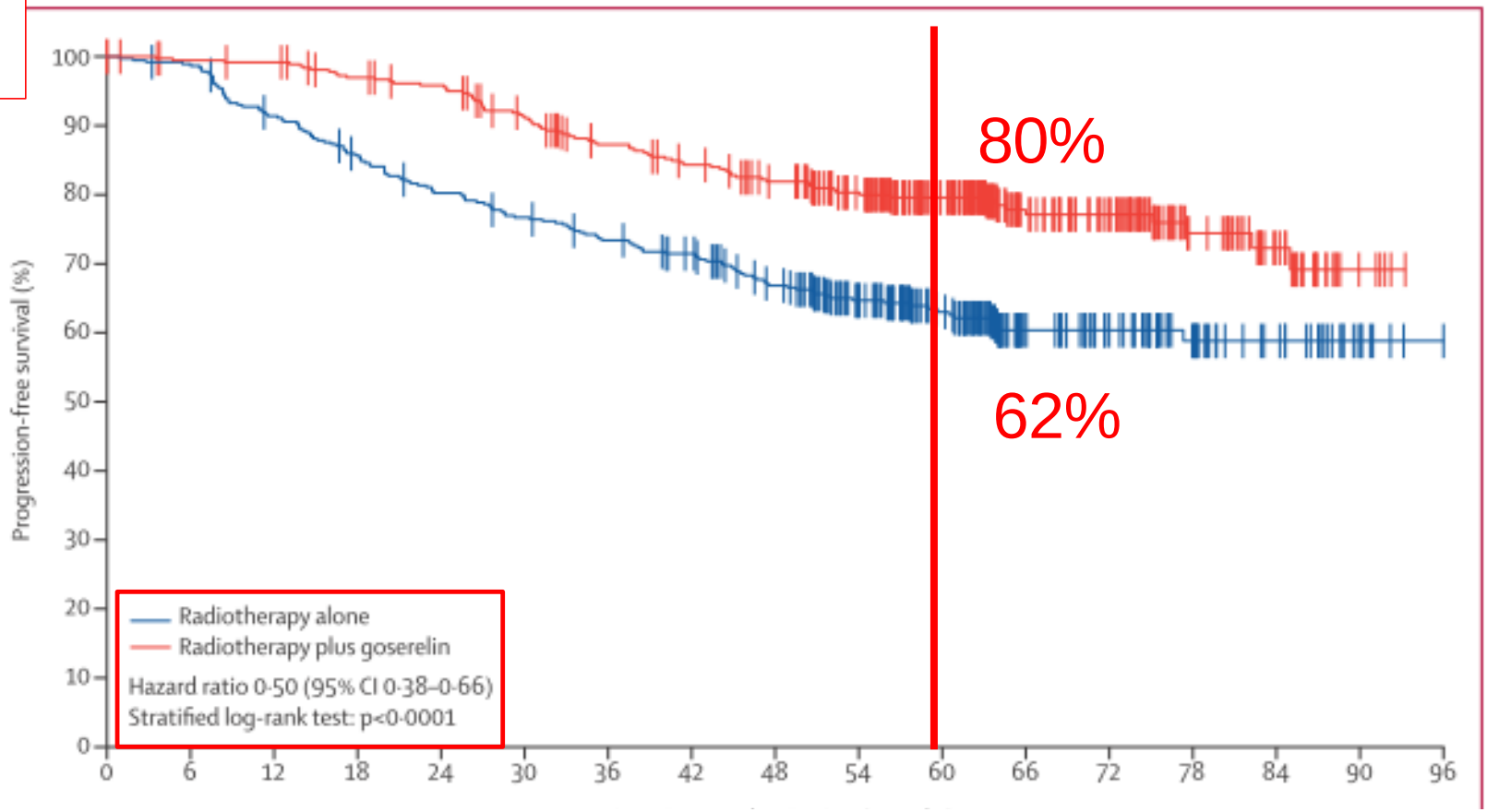
Date are n (%) or median (range) unless otherwise noted. PSA=prostate-specific antigen. ECOG=Eastern Cooperative Oncology Group. TNM=TNM Classification of Malignant Tumours. Percentages might not sum to 100 because of rounding.
*Four missing values. †169 missing values.

Table 1: **Baseline characteristics in the intention-to-treat population**

Carrie et al., Lancet Oncol. 2016 Jun;17(6):747-56.

Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial

Median FUP: 63 months



Carrie et al., Lancet Oncol. 2016 Jun;17(6):747-56.

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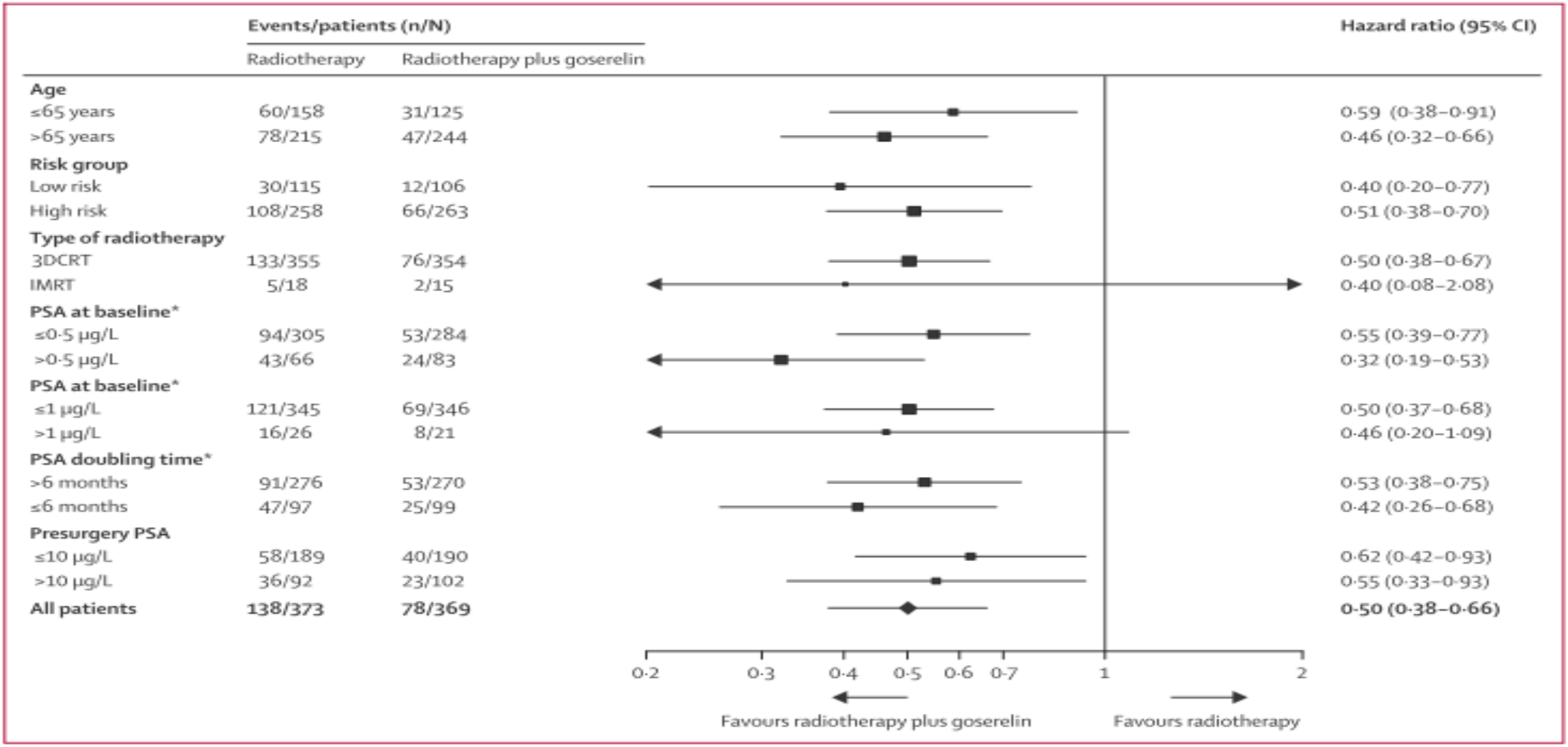
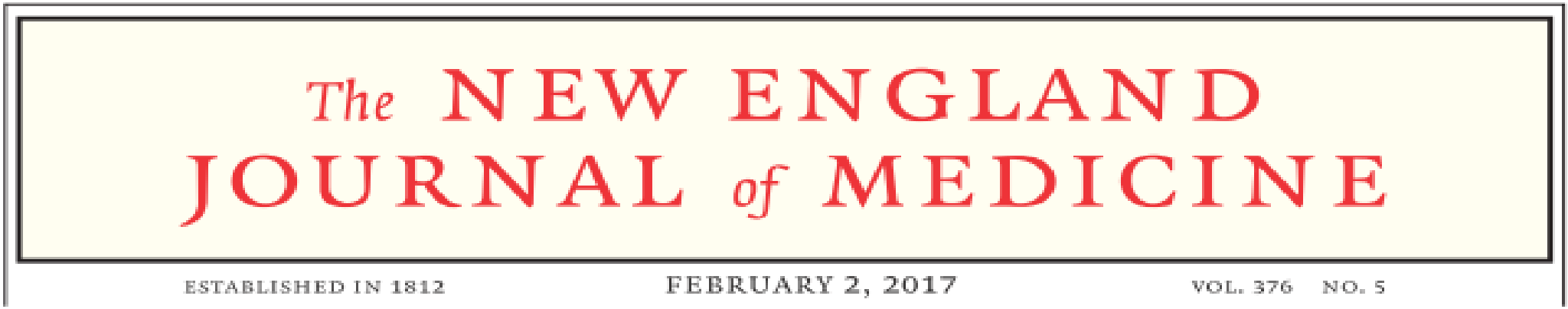


Carrie et al., Lancet Oncol. 2016 Jun;17(6):747-56.

How to combine ADT in the postoperative setting?



Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer

Shipley et al., NEJM 2017: 376; 417-428.

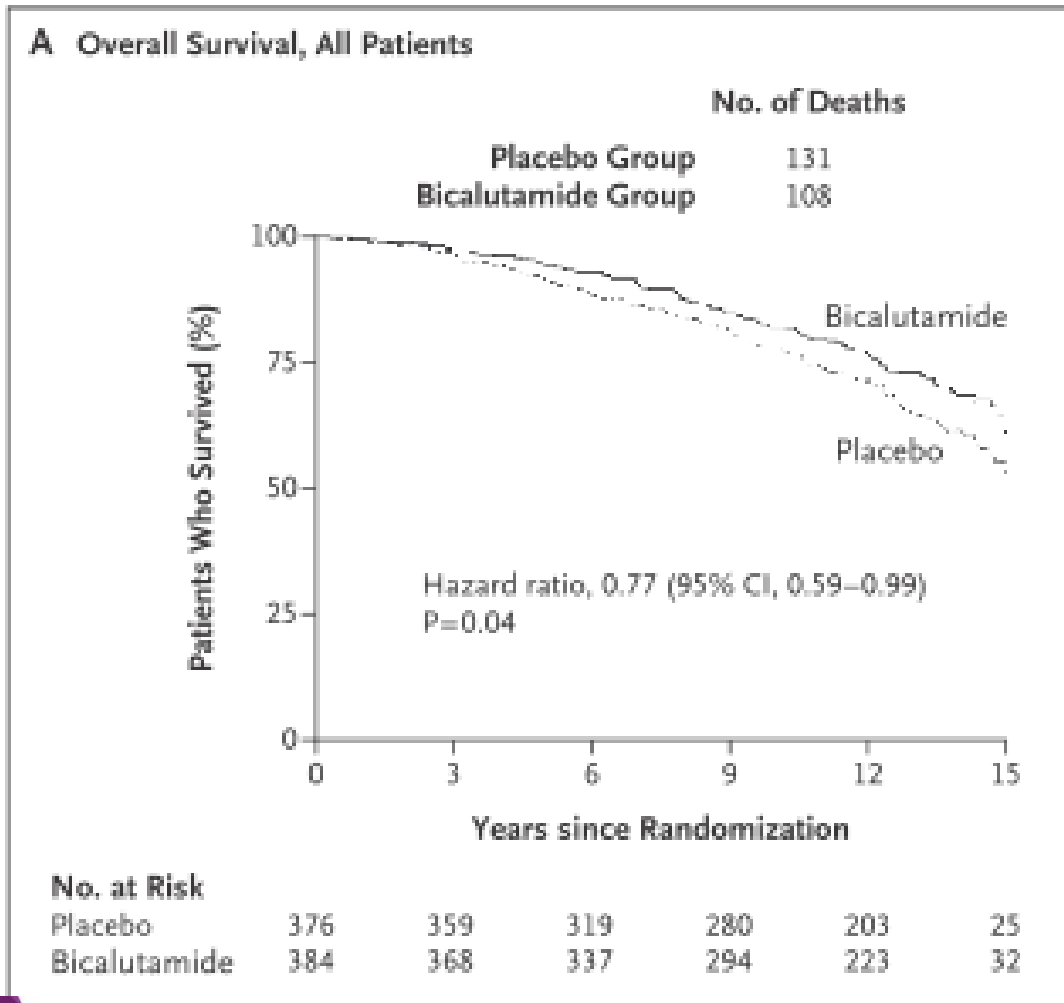
Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer

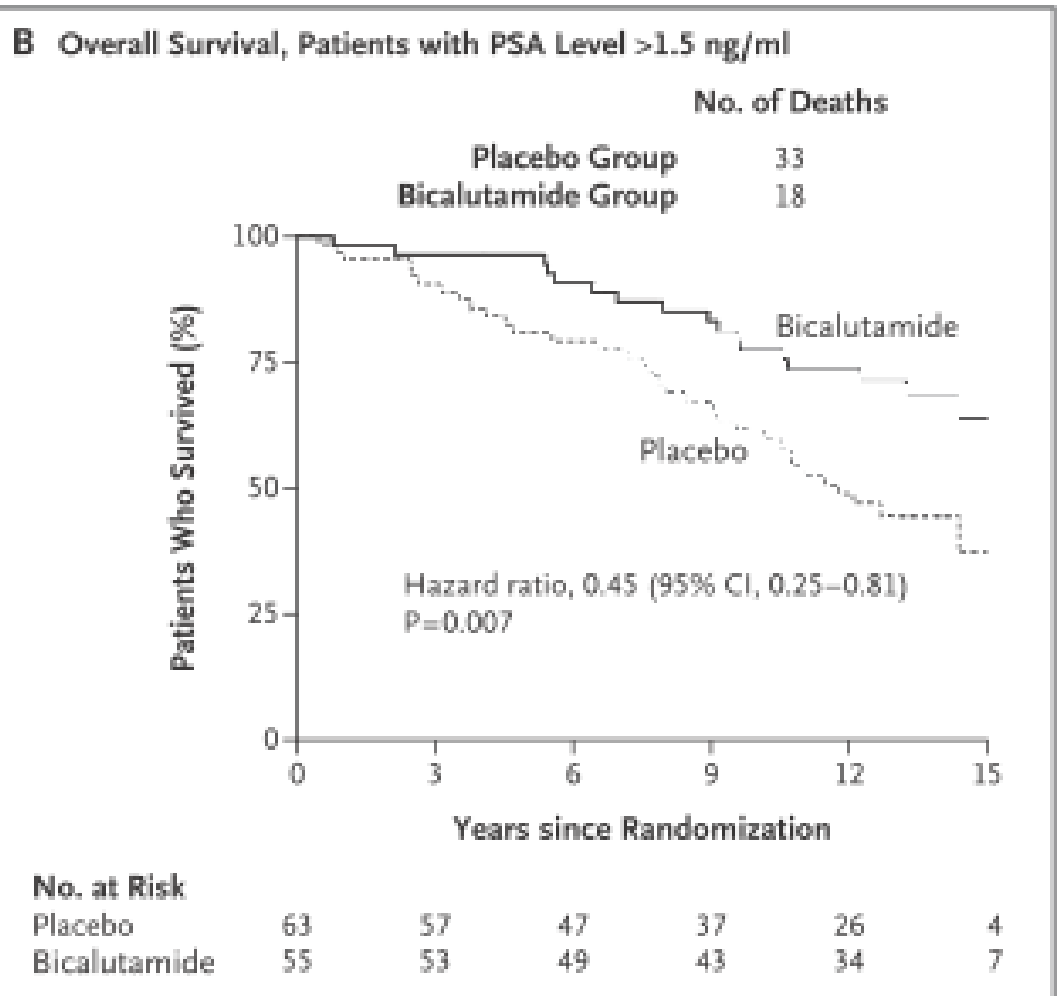
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Bicalutamide Group (N = 384)	Placebo Group (N = 376)	All Patients (N = 760)
Age — no. (%)			
≤49 yr	6 (1.6)	4 (1.1)	10 (1.3)
50–59 yr	93 (24.2)	84 (22.3)	177 (23.3)
60–69 yr	192 (50.0)	194 (51.6)	386 (50.8)
70–79 yr	90 (23.4)	91 (24.2)	181 (23.8)
≥80 yr	3 (0.8)	3 (0.8)	6 (0.8)
Gleason score — no./total no. (%)§			
2–6	111/383 (29.0)	103/375 (27.5)	214/758 (28.2)
7	205/383 (53.5)	208/375 (55.5)	413/758 (54.5)
8–10	67/383 (17.5)	64/375 (17.1)	131/758 (17.3)
T stage — no. (%)¶			
T2	128 (33.3)	120 (31.9)	248 (32.6)
T3	256 (66.7)	256 (68.1)	512 (67.4)
Positive surgical margin — no. (%)			
No	96 (25.0)	95 (25.3)	191 (25.1)
Yes	288 (75.0)	281 (74.7)	569 (74.9)
PSA nadir after surgery — no. (%)			
<0.5 ng/ml	338 (88.0)	332 (88.3)	670 (88.2)
≥0.5 ng/ml	46 (12.0)	44 (11.7)	90 (11.8)
PSA level at trial entry — no. (%)			
<0.7 ng/ml	210 (54.7)	195 (51.9)	405 (53.3)
0.7–1.5 ng/ml	119 (31.0)	118 (31.4)	237 (31.2)
>1.5–4.0 ng/ml	55 (14.3)	63 (16.8)	118 (15.5)

Shipley et al., NEJM 2017: 376; 417-428.

Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer

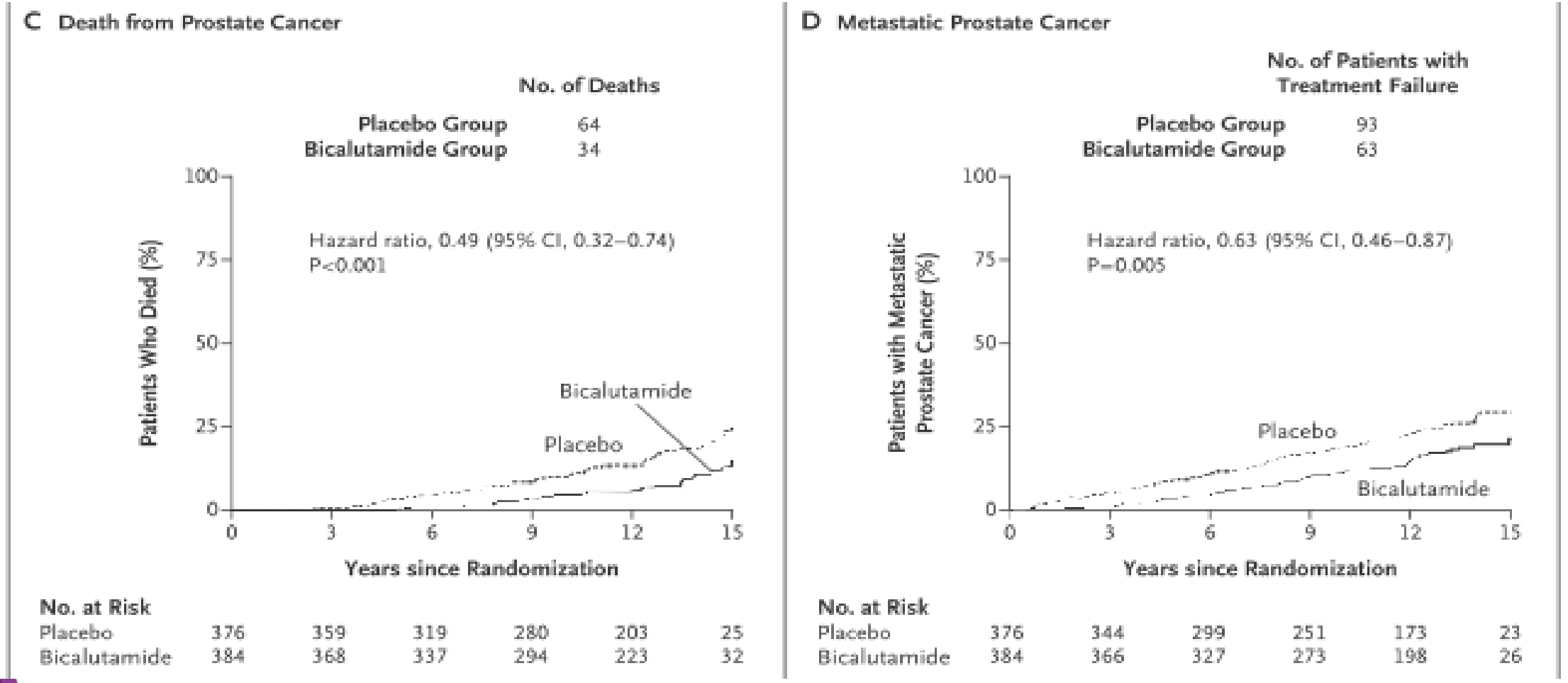




Median FUP: 13 years

Shipley et al., NEJM 2017: 376; 417-428.

Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer



Median FUP: 13 years

Shipley et al., NEJM 2017: 376; 417-428.

Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer

Subgroup	No. of Patients (%)	Bicalutamide Group	Placebo Group	Hazard Ratio (95% CI)	P Value
		12-yr overall survival rate (%)			
Overall	760 (100.0)	76.3	71.3	0.77 (0.59–0.99)	0.04
Gleason score					
2–6	214 (28.2)	79.5	79.2	0.95 (0.57–1.59)	0.84
7	413 (54.5)	78.5	70.9	0.69 (0.49–0.98)	0.04
8–10	131 (17.3)	63.9	58.4	0.76 (0.44–1.30)	0.32
PSA level at trial entry					
<0.7 ng/ml	405 (53.3)	76.8	80.7	1.13 (0.77–1.65)	0.53
0.7–1.5 ng/ml	237 (31.2)	77.0	67.5	0.61 (0.39–0.95)	0.03
>1.5 ng/ml	118 (15.5)	73.5	48.9	0.45 (0.25–0.81)	0.007
Positive surgical margin					
No	191 (25.1)	73.5	72.9	0.87 (0.53–1.41)	0.56
Yes	569 (74.9)	77.3	70.7	0.73 (0.54–0.98)	0.04

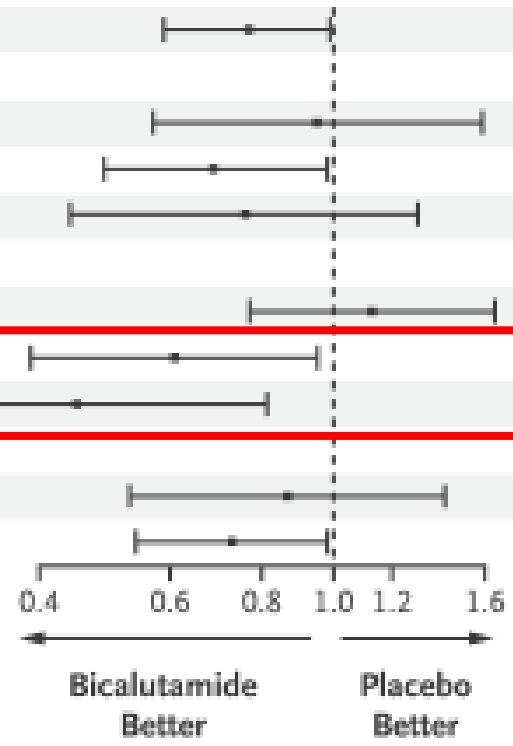


Figure 3. Effect of Antiandrogen Therapy with Bicalutamide on 12-Year Overall Survival.

Median FUP: 13 years

Shipley et al., NEJM 2017: 376; 417-428.

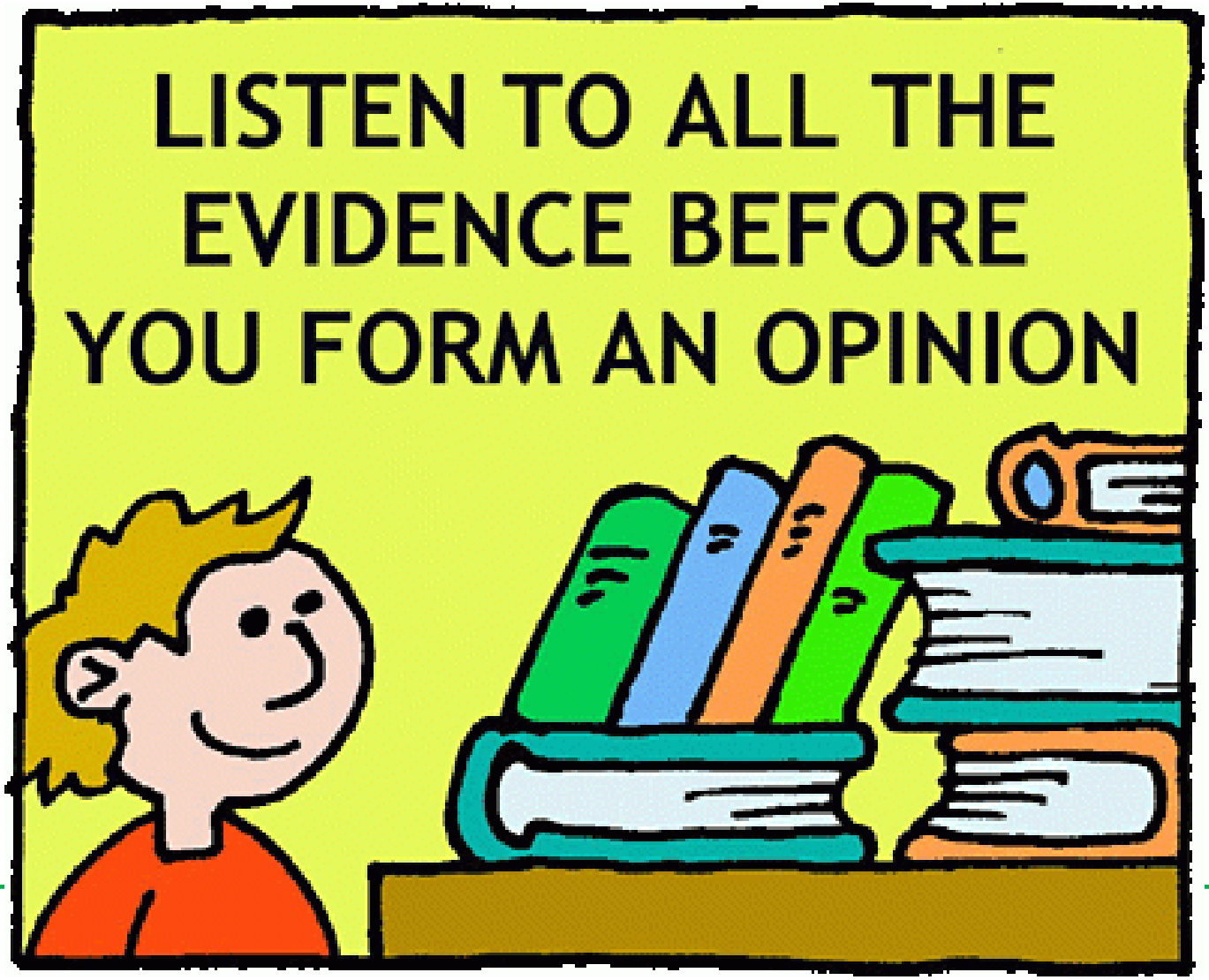
How to combine ADT in the postoperative setting?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017 Prostate Cancer

- Two years instead of 6 months of ADT can be considered in addition to RT based on RTOG 9601 for men with persistent PSA after RP or for PSA levels that exceed 1.0 ng/mL at the time of initiation of salvage therapy. Six months of ADT can be considered coadministered with salvage radiation based on the results of GETUG-16. An LHRH agonist should be used. For 2-year ADT, there is level 1 evidence to support 150 mg bicalutamide daily but an LHRH agonist could be considered as an alternative.

Take home message….



Evidence Based Radiation Oncology: Prostate cancer

THANK YOU FOR YOUR KIND ATTENTION

De Bari Berardino, MD, fESTRO

Radiation Oncology Dpt.
Centre Hospitalier Régional Universitaire «Jean Minjoz»
France

Systematic approach to scientific literature

A few tips for critical reading

Cancéropôle Nord-Ouest

litis

ESTRO European Society for RADIOTHERAPY & ONCOLOGY

UNIVERSITÉ DE ROUEN

CENTRE HENRI BECQUEREL HAUTE-NORMANDIE

“I quote no authors but God and experience”

Andrew Taylor Still

How many papers do you read per week ?

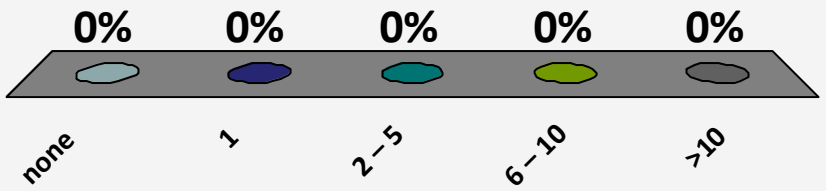
A. none

B. 1

C. 2 – 5

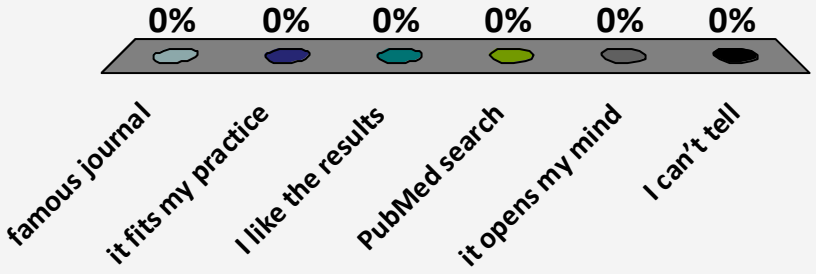
D. 6 – 10

E. >10



How do you select paper(s) to read ?

A. famous journal
B. it fits my practice
C. I like the results
D. PubMed search
E. it opens my mind
F. I can’t tell



Critical reading / writing

- Numerous and intricated criterions
  - medical
  - statistical
  - editorial
- Need for a systematic approach
  - checklist for the busy clinician

The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials

*David Moher, Kenneth F Schulz, Douglas G Altman, for the CONSORT Group**

To comprehend the results of a randomised controlled trial (RCT), readers must understand its design, conduct, analysis, and interpretation. That goal can be achieved only through total transparency from authors. Despite several decades of educational efforts, the reporting of RCTs needs improvement. Investigators and editors developed the original CONSORT

"... (to avoid) biased estimates of treatment effect,

... to judge the reliability or the relevance of the findings"

primary data analysis. Inclusion of these numbers allows the reader to judge whether the authors have done an intention-to-treat analysis. In sum, the CONSORT statement is intended to improve the reporting of an RCT, enabling readers to understand a trial's conduct and to assess the validity of its results.

Moher Lancet 2001

I'll buy it if …

- The question makes sense to me
  - fits to my clinical practice
  - opens my mind
- The data provide a reliable answer
  - study design and conduct
  - quality of data and analysis
- The paper follows the rules
  - the information I need …
  - where I expect to find it

Criteria

- Clinical relevance
- Trial design and conduct
- Data
- Results

Clinical relevance

- a question
- a primary endpoint
- a reference group
- inclusion / non inclusion criteria

(Non-)inclusion criteria

(Non-) inclusion criteria

Simple endpoints

Endpoint	Event
survival	death
tumour control	relapse
complication	complication

Complex endpoints and competitors

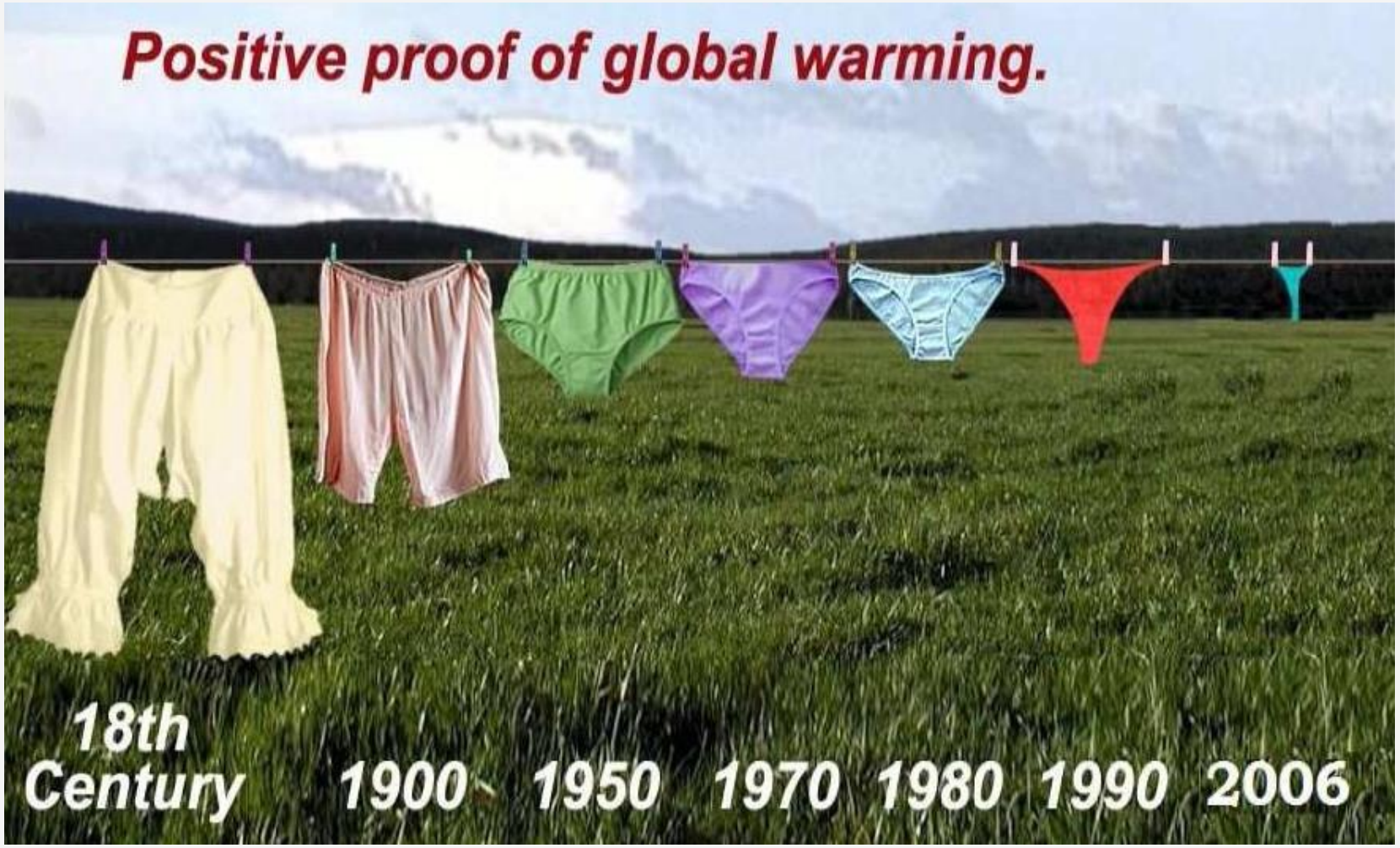
Endpoint	Event(s)	Competitors
cancer specific survival	death of cancer	other causes
disease free survival	relapse or death	…
time to progression	relapse	death
complication	complication	death or relapse
uncomplicated cure	complication or relapse	death

Note: relapse can be local / regional / distant …
or clinical / biological / …

Surrogate endpoint

- Replace the “true” endpoint
  - e.g. overall survival
- by a more “convenient” surrogate
  - easier to measure
  - obtained earlier
- AND reflecting clinical benefit

Surrogate endpoint



Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

BMJ 2003

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

What is already known about this topic

Parachutes are widely used to prevent death and major injury after gravitational challenge

Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury

Studies of free fall do not show 100% mortality

What this study adds

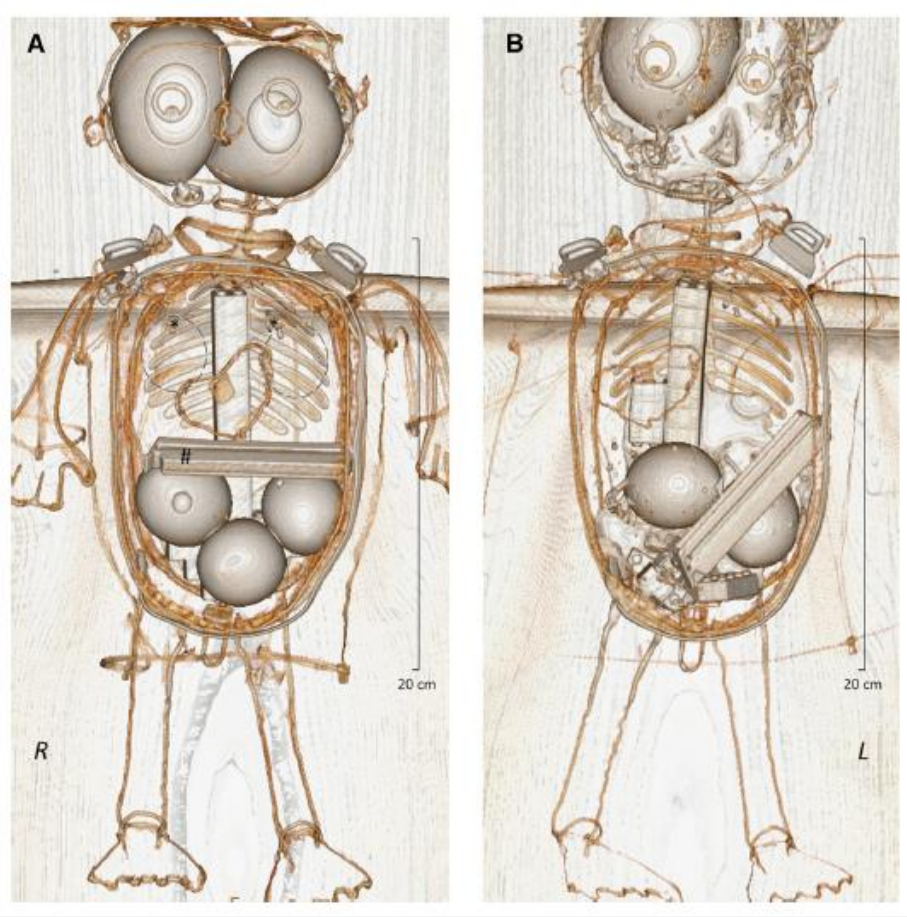
No randomised controlled trials of parachute use have been undertaken

The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect

Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

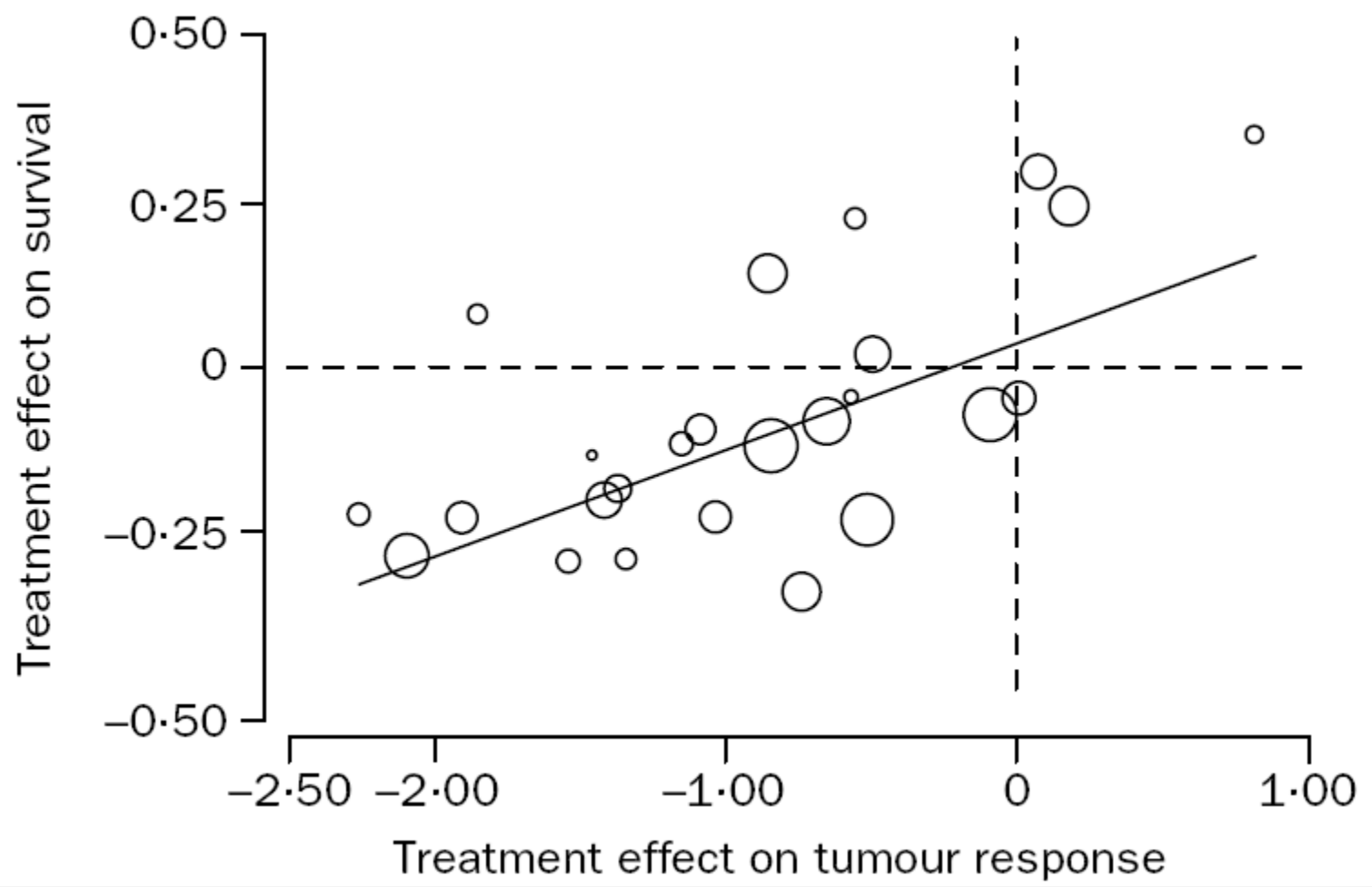
Does usage of a parachute in contrast to free fall prevent major trauma?: a prospective randomised-controlled trial in rag dolls

Patrick Czorlich[1] · Till Burkhardt[1] · Jan Hendrik Buhk[2] · Jakob Matschke[3] · Marc Dreimann[4] · Nils Ole Schmidt[1] · Sven Oliver Eicker[1]



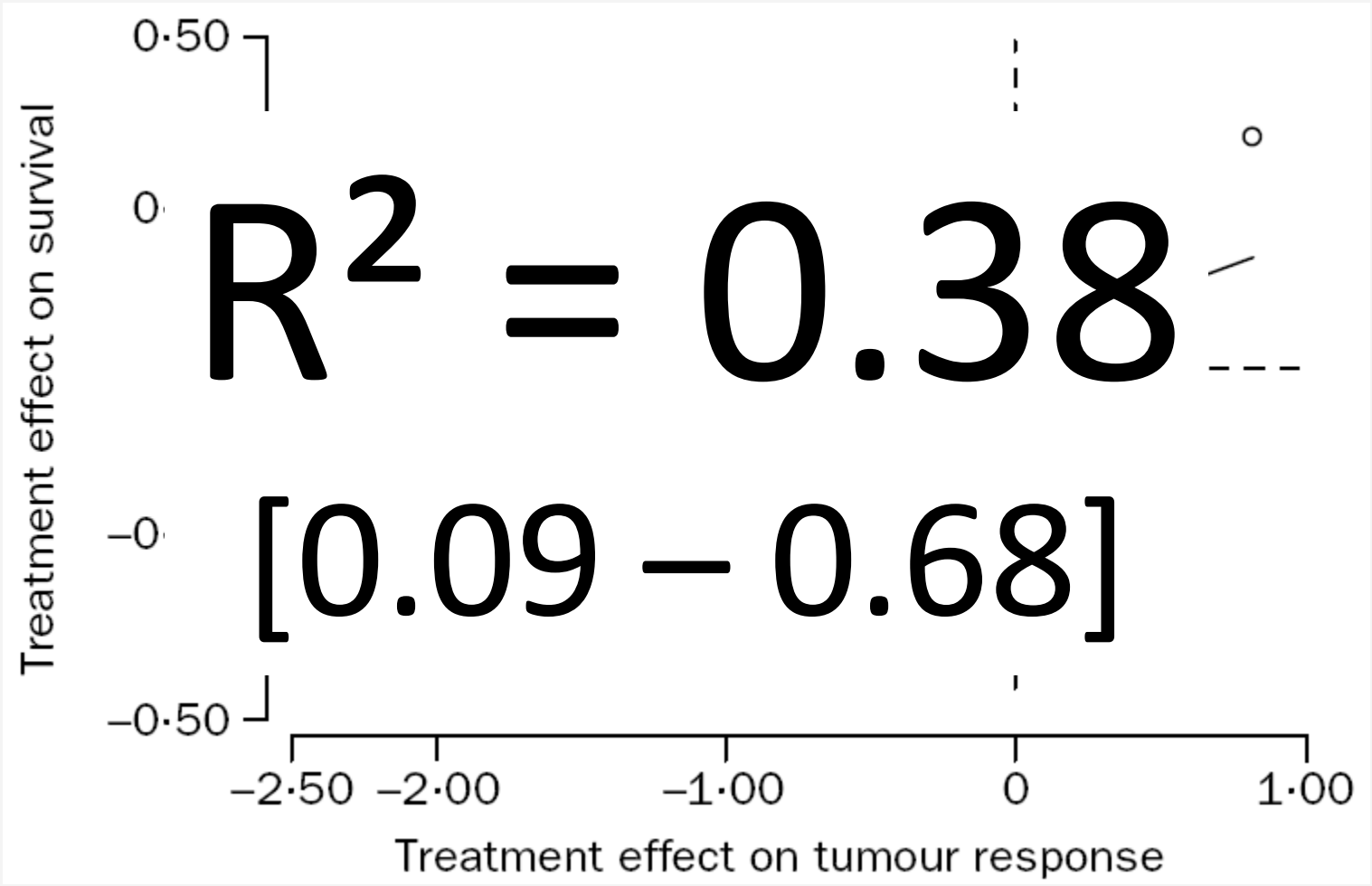
Eur Spine J 2016

Response vs. survival



Buyse Lancet 2000

Response vs. survival



Buyse Lancet 2000

Censored event

- The event has not happened (… yet !)
  - follow-up too short
  - competitive events
  - missing data
- Specific to delayed endpoints
  - late toxicity
- “Time-dependent” statistics
  - i.e. Kaplan-Meier, actuarial, …

Censored events

- Quality of the data
  - follow-up duration in censored patients
  - number / nature of competitive events
  - missing data and cause
- Advantages of overall survival
  - clear-cut endpoint
  - only depends on follow-up duration
  - “statisticians love blood”

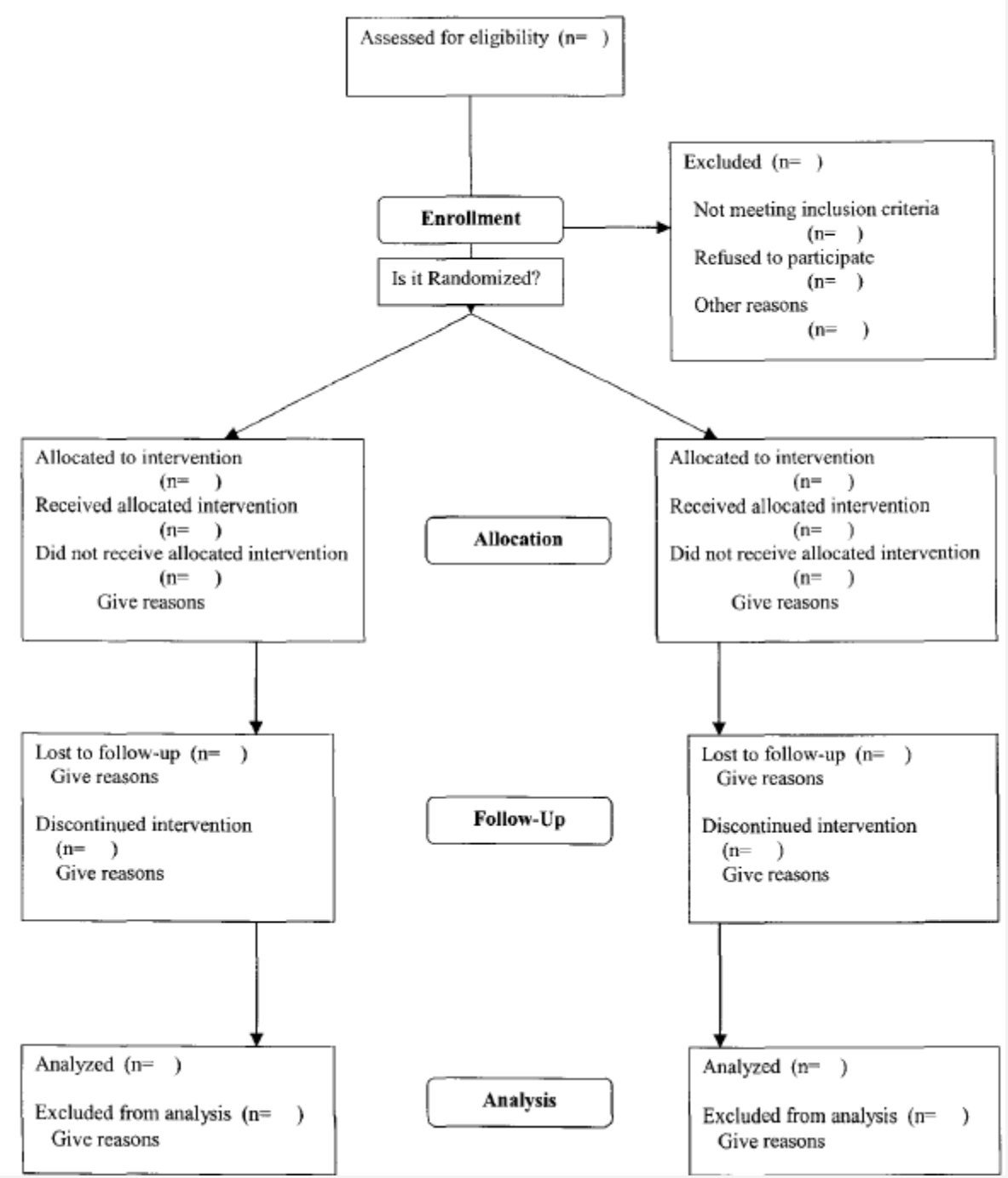
Methodology of trial

- Sample size
  - calculated a priori
- Treatment allocation
  - investigator cannot guess next patient’s group
- Follow-up
  - same modalities in all groups
- Evaluation of effect
  - simple / double / triple blind
  - independent assessment of endpoint

Conduct of trial

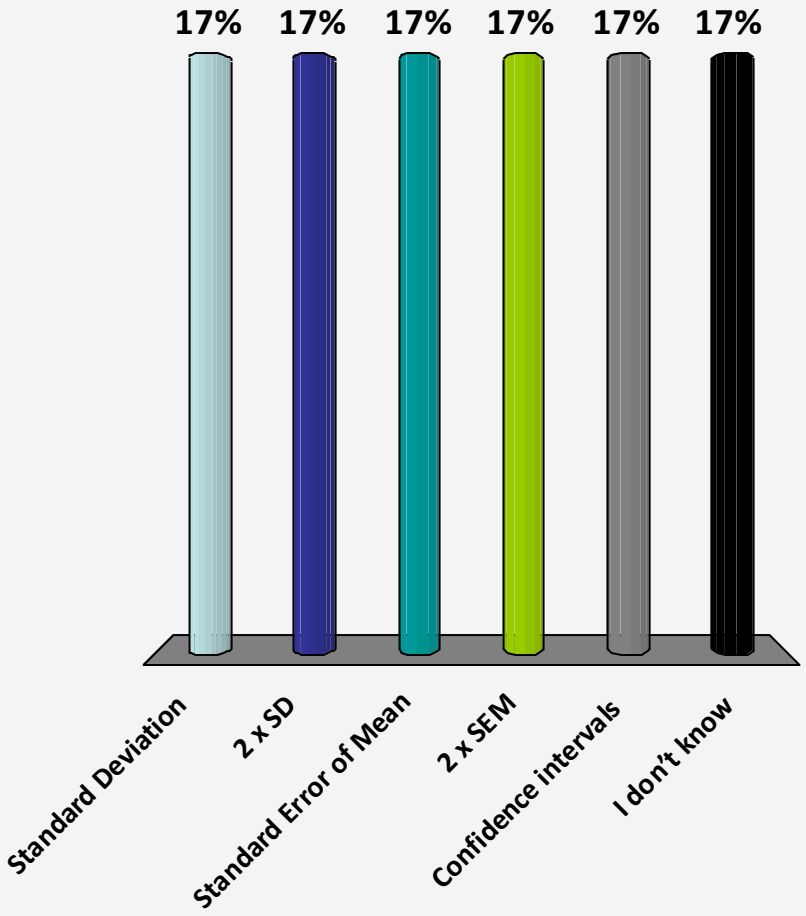
- Duration of inclusion period
- Inclusion of planned number of patients
- Adequate duration of follow-up

Data description



What are the error bars ?

A. Standard Deviation
B. 2 x SD
C. Standard Error of Mean
D. 2 x SEM
E. Confidence intervals
F. I don’t know



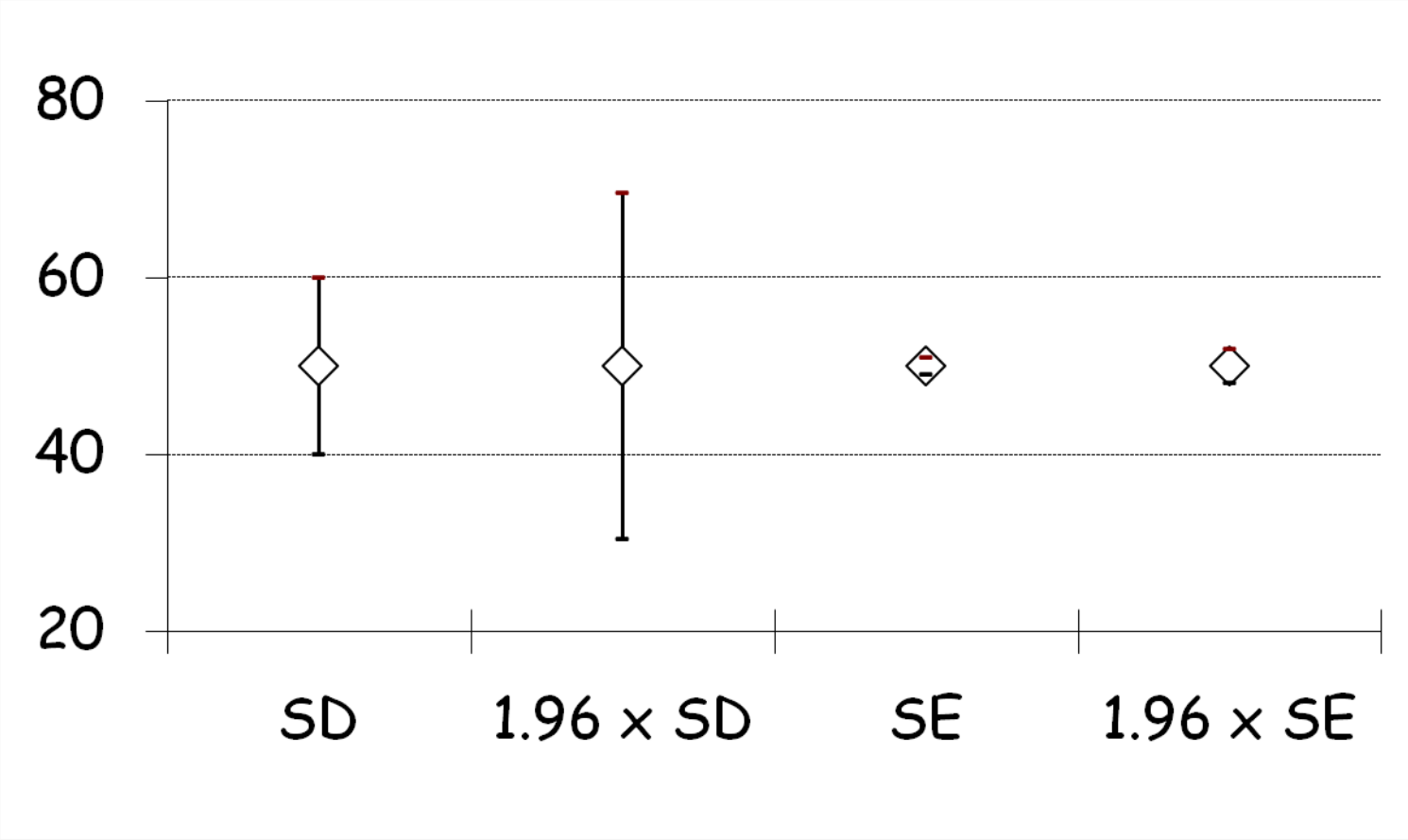
Confidence intervals

- Parameter values estimated on a sample
  - not on whole population
- 95% confidence interval
  - limits around the observed value
  - 95% chance to include result of the same study run with another sample of patients
- Describe the data ++++
  - reliability / precision of estimation

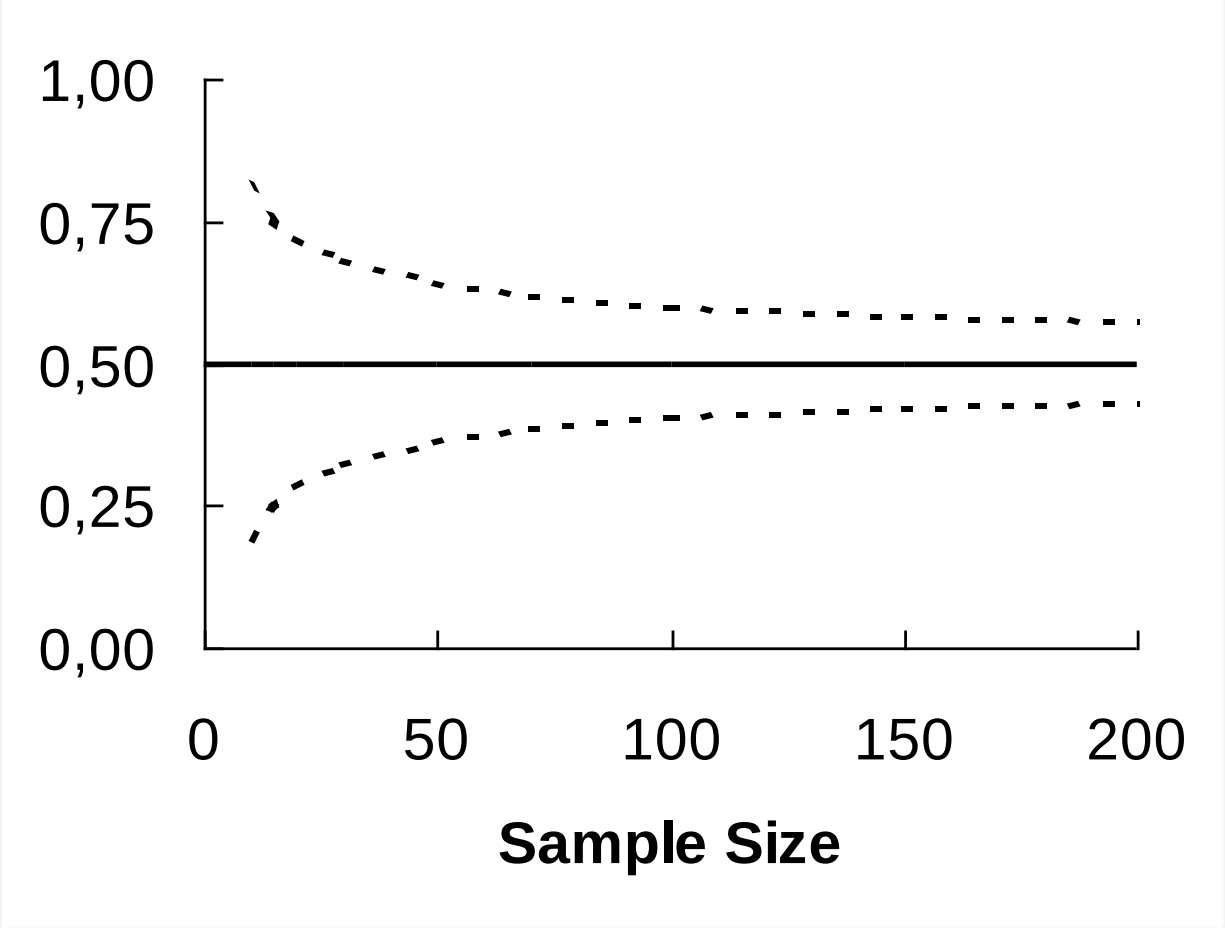
SD or SE ?

- SD = standard deviation = $\sqrt{}$(variance)
  - variance = $\sum_i^n (x_i - m)^2 / (n-1)$
- SE(M) = standard error of the mean
  - SE = $\sqrt{}(s^2/n)$ << SD
- SD or SE ?
  - the author's choice has to be explicit

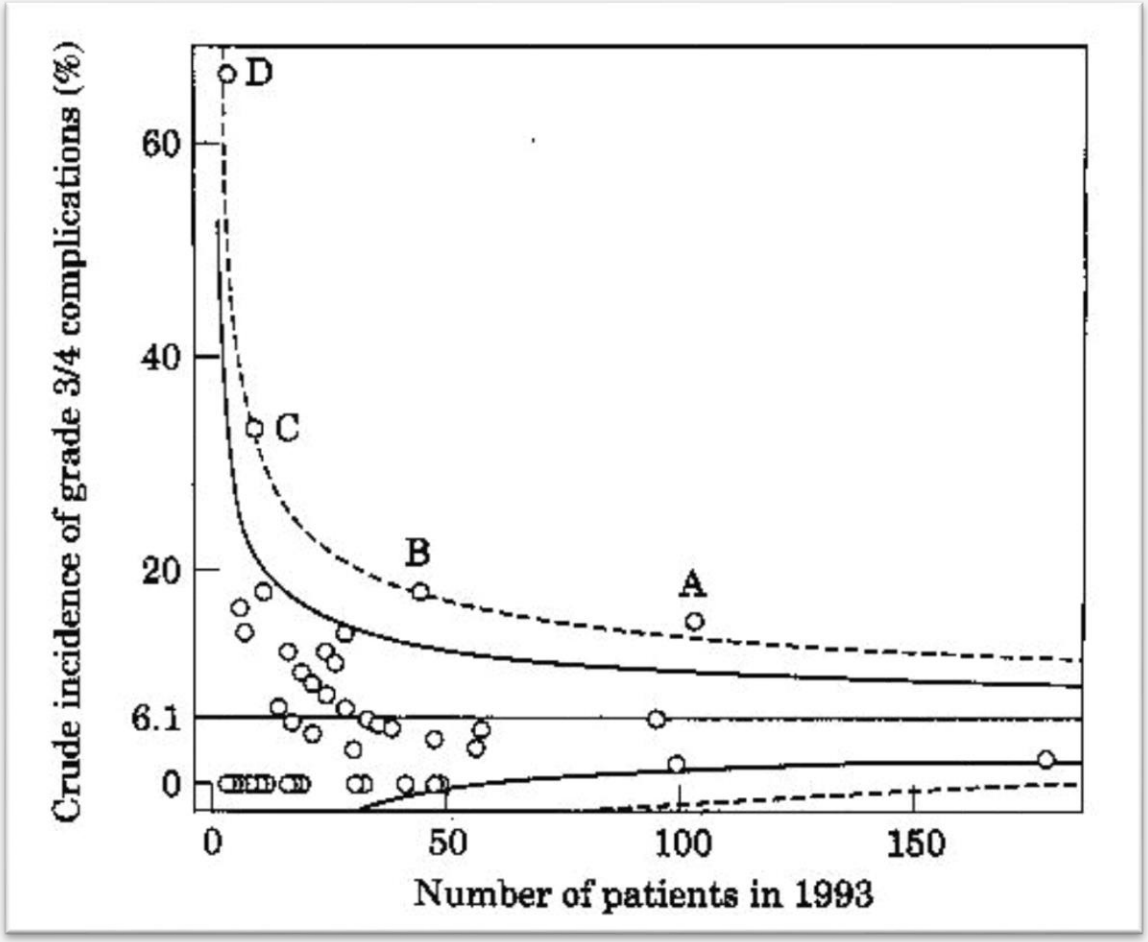
Error bars



The CI only depends on sample size



The CI only depends on sample size



Denton Clin Oncol 2002

Interpretation of results

- Intent-to-treat analysis ++++
  - patients analysed as randomised
  - whatever actual treatment
- Reasonable results of reference group
- Adequate statistics
  - tests appropriate for endpoint (2-tailed)
  - confirmation by multivariate analysis
  - consistency of subgroup analyses

Conclusion according to primary endpoint

Cetuximab Monotherapy and Cetuximab plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer

METHODS

We randomly assigned 329 patients whose disease had progressed during or within three months after treatment with an irinotecan-based regimen to receive either cetuximab and irinotecan (at the same dose and schedule as in a prestudy regimen [218 patients]) or cetuximab monotherapy (111 patients). In cases of disease progression, the addition of irinotecan to cetuximab monotherapy was permitted. The patients were evaluated radiologically for tumor response and were also evaluated for the time to tumor progression, survival, and side effects of treatment.

CONCLUSIONS

Cetuximab has clinically significant activity when given alone or in combination with irinotecan in patients with irinotecan-refractory colorectal cancer.

Flibbertygibbet Famous Journal 2004

Same results in my practice ?

- Multicenter trial
- Sample representative of population
- Clinical / biological plausibility
- Consistency with other trials

Other elements

- Renown of investigators / groups
- Renown of journal
- Potential conflicts of interest
  - independent financing
  - industry-sponsored

Checklist for Evaluation of Phase III Trials

B. Dubray & M. Debled, version 1.0 – September 8, 2003

		Yes	No	???	NA	Notes
Medical interest of trial						
1	A relevant question					
2	An adequate primary endpoint					
3	A standard as reference					
4	Adequate inclusion / non inclusion criteria					
Methodology of trial						
5	Concealment of treatment allocation					
6	Simple / double / triple blind					
7	Same follow-up in all arms					
8	Independant assessment of primary endpoint					
9	A priori calculation of number of patients					
Conduct of trial						
10	"Reasonnable" duration of inclusion period					
11	Inclusion of planned number of patients					
12	Adequate duration of follow-up					
Data description						
13	Balance between arms (pc, FU, ...)					
14	Inclusion errors, withdrawals, lost for FU, ...					
15	Assessment of primary endpoint with CI					
16	Description of protocol violations					
17	Description of toxicities					

Checklist for Evaluation of Phase III Trials

B. Dubray & M. Debled, version 1.0 – September 8, 2003

	Yes	No	???	NA	Notes
Interpretation of results					
18 Intent to treat analysis					
19 Conclusion according to primary endpoint					
20 Adequate statistical test (2-tailed)					
21 Confirmation by multivariate analysis					
22 Concordance of subgroup analyses					
23 Reasonable results of reference arm					
Generalisation of results					
24 Multicenter trial					
25 Trial sample representative of population					
26 Clinical / biological plausibility					
27 Consistency with other trials					
Other elements					
28 Renown of authors / research group					
29 Renown of journal					
30 Indépendant financing of trial					
TOTAL / 30					
Summary	+++	++	+	???	Commentaries
Validity of methodology					
Precision of result					
Exportability of result					
Clinical relevance					
Consequence for my practice					

Conclusion

- Description of the data +++
- Need for a systematic approach
  - reliability and relevance of findings
  - complex issues
- Further readings
  - www.consort-statement.org
  - with links

Research takes time !

Edgeworth U. of Queensland (Australia)

ESTRO School

EVIDENCE BASED RADIATION ONCOLOGY

11-16 June, 2017
Ljubljana, Slovenia

Evidence Based Radiation Oncology in upper gastro-intestinal cancer

Gian Carlo Mattiucci

Università Cattolica - Roma

EBRO
2017

Oesophageal cancer

EBRO 2017

Epidemiology of esophageal cancer

- 6th leading cause of cancer-related mortality
- 8th most common cancer worldwide
- Worldwide >450,000 people are affected
- Overall 5-year survival 15-25%
- Diagnosis at advanced (metastatic) stages
- 30-40% present with resectable disease
- SCC is predominant type; in some western European countries adenocarcinoma exceeds SCC

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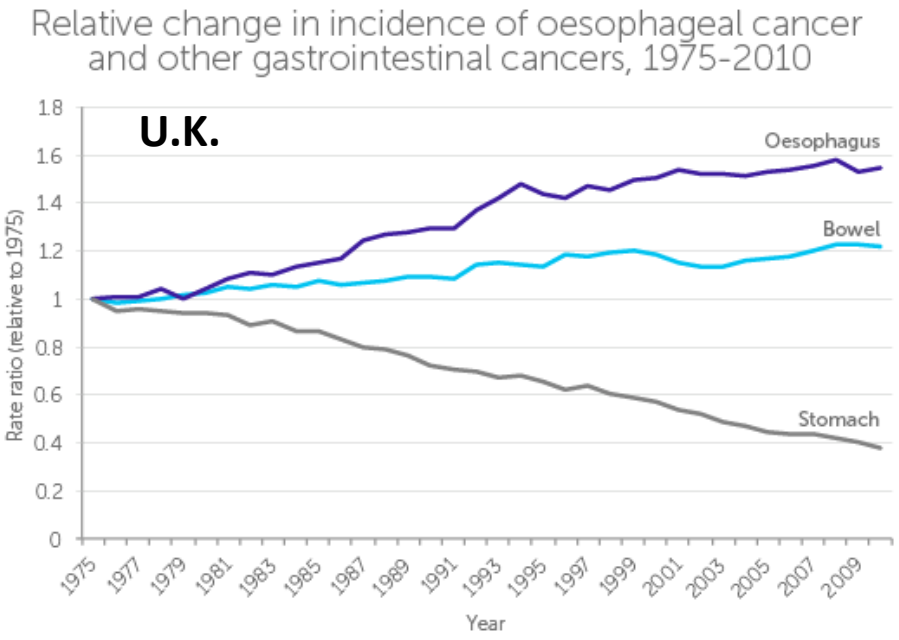
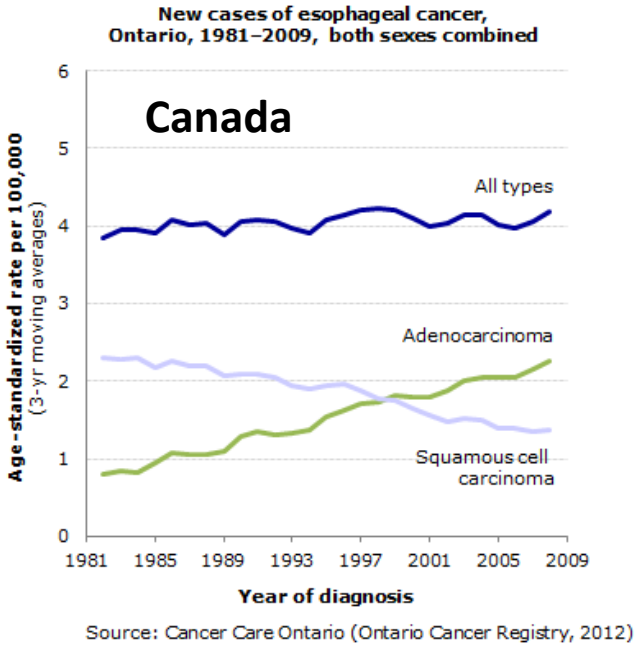
Incidence is increasing





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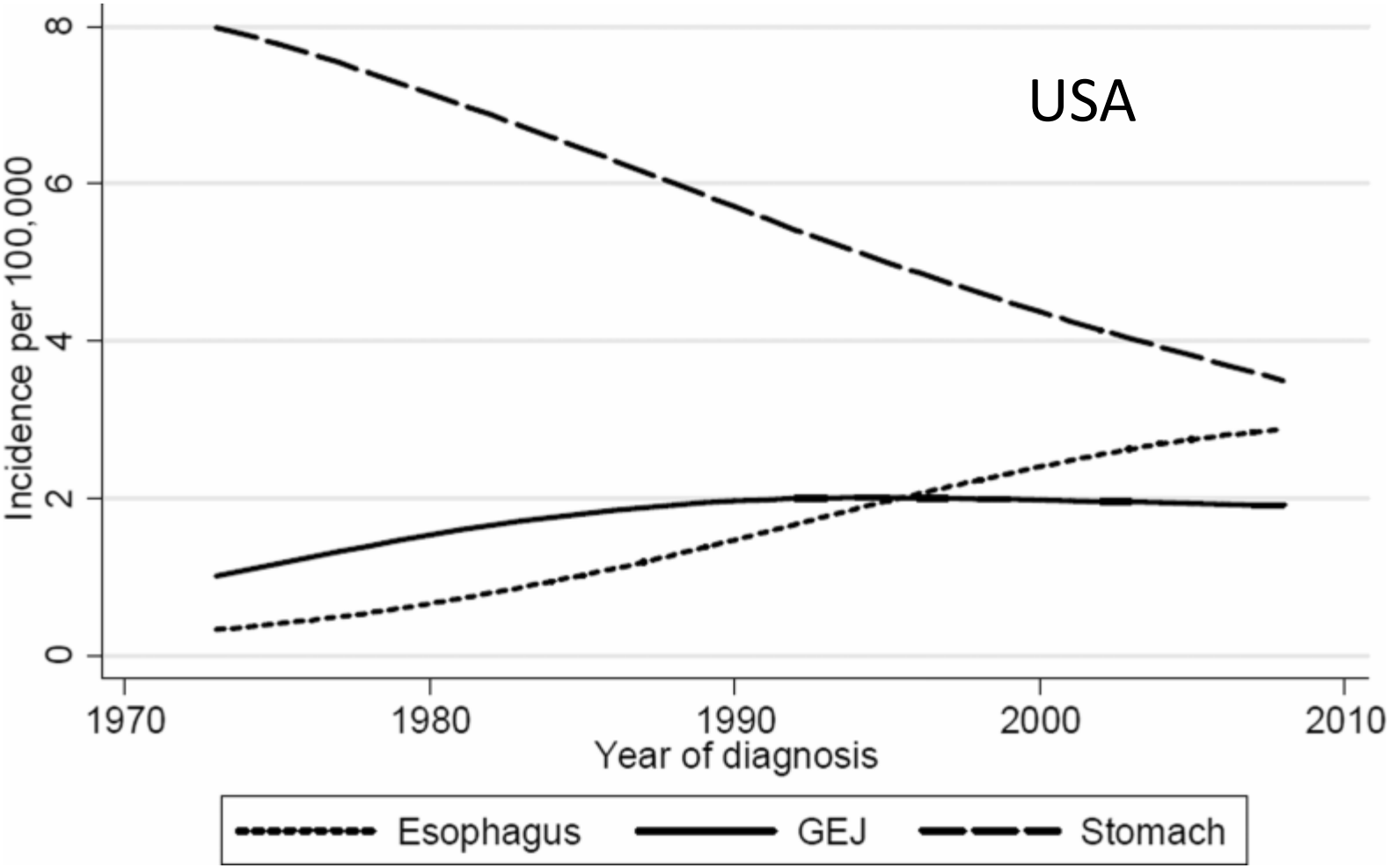
Incidence is increasing



Buas et al, Semin Radiat Oncol 2013

Esophageal cancer: risk factors

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	Squamous cell carcinoma (SCC)	Adenocarcinoma (AC)
Risk factors		
Smoking	Strong link	Linked
Alcohol	Strong link	No link
Oesophageal reflux (GORD)	No link	Strong link
Obesity	No link	Strong link
Disease site	20% upper third 50% middle third 30% lower third	> 90% lower third

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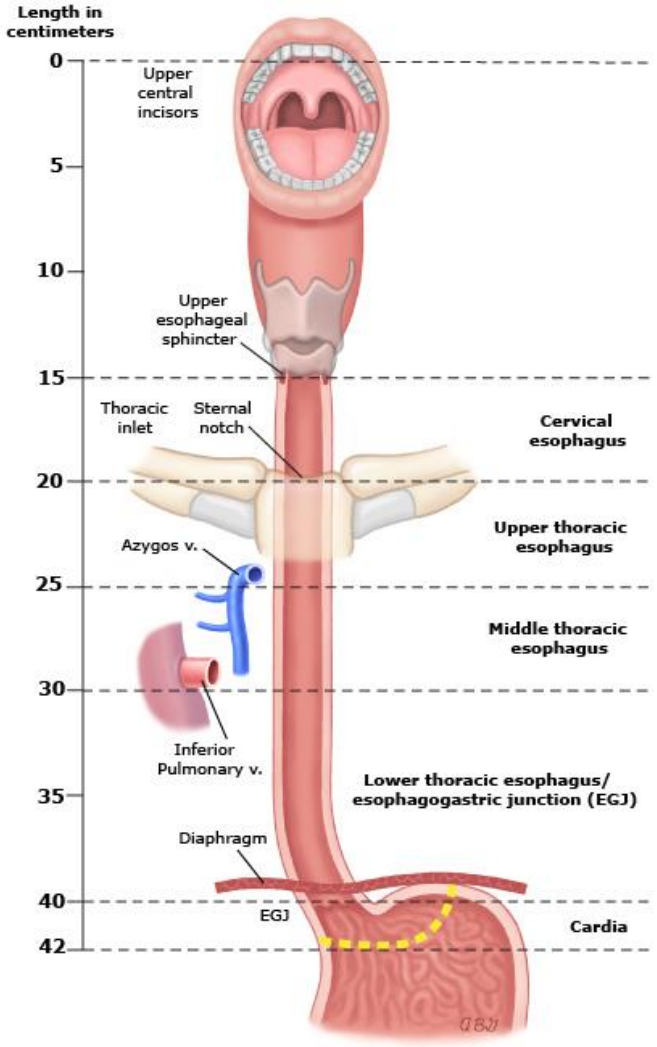
Most in lower part or GEJ



41 %

AJCC: American Joint Committee on Cancer

Rice TW, Kelsen D, Blackstone EH, et al. Esophagus and esophagogastric junction. In: AJCC Cancer Staging Manual, 8th Ed, Amin MB (ed), Springer Science+Business Media, LLC, New York, 2017.

Siewert Classification of GEJ Tumour

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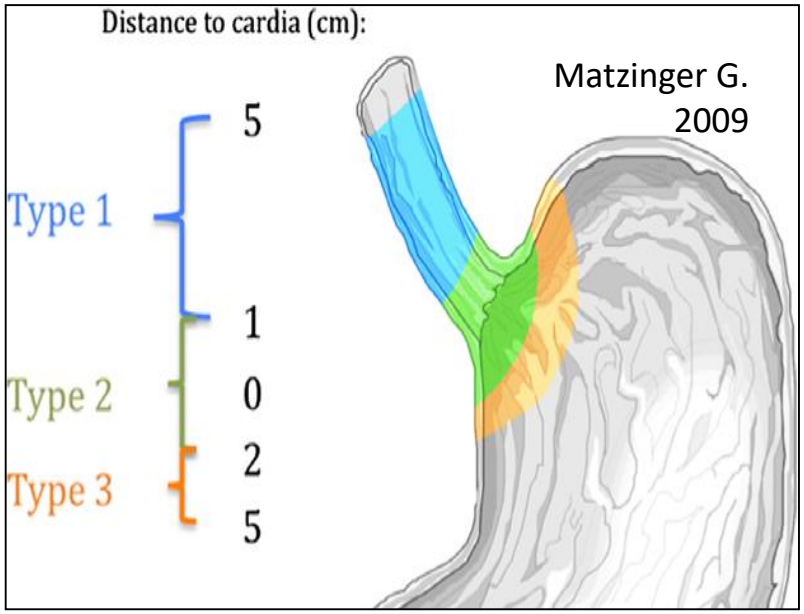
GEJ:"Upper end of the typical longitudinal fold of the gastric mucosa

Based on the relationship between the tumour centre and the GEJ at endoscopy:

- Type I tumours have their tumour centres more than 1 cm above the anatomical GEJ.
- Type II tumours are the true carcinomas of the cardia and have their tumour centres located within 1 cm cranial and 2 cm caudal of the anatomical GEJ.
- Type III tumours have their tumour centre more than 2 cm but not more than 5 cm below the anatomical GEJ.



Siewert JR. B. J. Surg. 1998

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Diagnostic work-up

- Diagnosis – Endoscopic biopsy
- Initial Imaging: CT

- Potentially curable disease:
  - PET/CT – exclude distant spread
  - EUS – Early disease, Proximal/ Distal Extent

Diagnostic work-up

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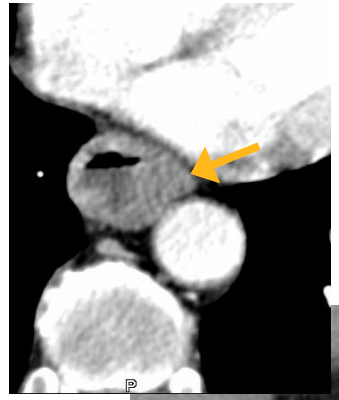
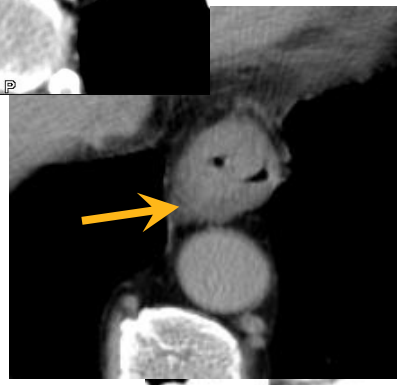
T staging: CT

T stage - based on wall thickness and outline

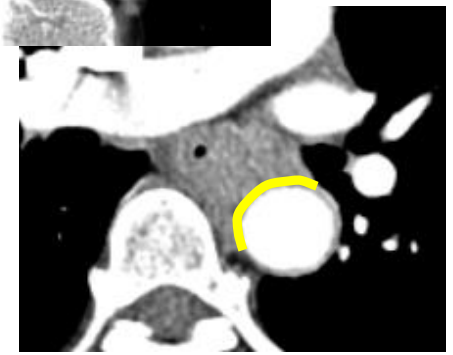
- Limited soft tissue contrast
- Poor for early tumours



pT2



pT3



pT4

T Stage	Wall thickness	Wall Contour
T2	>3mm, <5mm	Smooth
T3	5-15mm	Irregular
T4	>15mm	Contact with adjacent structure

T Staging Accuracy - 74%*

* Davies, A. R., D. A. Deans, et al. (2006). Dis Esophagus **19**(6): 496-503

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Diagnostic work-up

N staging: CT

- CT - high specificity, but low sensitivity
- Based on size criteria (short axis):
  - ≥6mm perigastric
  - ≥ 8mm extra perigastric
  - ≥10mm mediastinum

Accuracy of N staging	
Oesophageal Cancer	68%*
Gastric Cancer	67%†

* Davies, A. R., D. A. Deans, et al. (2006). Dis Esophagus **19**(6): 496-503

†Hur, J., M. S. Park, et al. (2006). J Comput Assist Tomogr **30**(3): 372-7.

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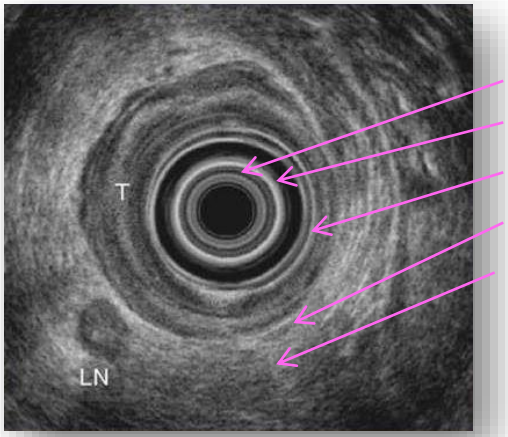
Diagnostic work-up

T and N staging: EUS



1. Superficial mucosa (hyperechoic)
2. Deep mucosa (hypoechoic)
3. Submucosa (hyperechoic)
4. Muscularis propria (hypoechoic)
5. Adventitia (hyperechoic)

- Endoscopic Ultrasound is able to delineate the layers of the oesophageal wall
- More accurate staging of tumours confined within the wall (<T3)
- Accuracy:

T staging 60% N Staging 74%

T1 80% FNA citology can improve accuracy for N

Diagnostic work-up

M staging: PET-CT

Detection of occult metastases

- Initial studies using FDG PET:
  - Metastatic disease detected in 15% patients considered potentially resectable*.
- Prospective trial 187 patients showed confirmed up-staging in 18 (9.5%) patients with unconfirmed metastases‡
- 25/156 (16%) patients up staged to M1b disease on PET-CT§

*Flamen, P., A. Lerut, et al. (2000). J Clin Oncol **18**(18): 3202-10

‡Meyers, B. F., R. J. Downey, et al. (2007). J Thorac Cardiovasc Surg **133**(3): 738-45

§ Purandare, N. C., C. S. Pramesh, et al. (2014). Nucl Med Commun **35**(8): 864-869

Diagnostic work-up

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Meta-analysis of staging tests in oesophageal cancer

Regional node metastases	**EUS**	**CT**	**PET**
Sensitivity (CI)	80% (75-84)	50% (41-60)	57% (43-70)
Specificity (CI)	70% (65-75)	83% (77-89)	85% (76-95)
Distant node metastases	**EUS** (coeliac nodes)	**CT** (abdominal nodes)	
Sensitivity (CI)	85% (72-99)	42% (29-54)	
Specificity (CI)	96% (92-100)	93% (86-100)	
Distant metastases		**CT**	**PET**
Sensitivity (CI)		52% (33-71)	71% (62-79)
Specificity (CI)		91% (86-96)	93% (89-97)

van Vliet et al (2008) Br J Cancer 98:547-57

Esophageal cancer - Treatment options

EBRO 2017

- Surgery alone
- Neoadjuvant chemotherapy with surgical resection
- Neoadjuvant chemoradiotherapy with surgical resection
- Surgery with adjuvant chemotherapy, radiotherapy, or chemoradiotherapy
- Definitive (chemo-) radiotherapy

Treatment options

EBRO 2017

- Surgery alone
- Neoadjuvant chemotherapy with surgical resection
- Neoadjuvant chemoradiotherapy with surgical resection
- Surgery with adjuvant chemotherapy, radiotherapy, or chemoradiotherapy
- Definitive (chemo-) radiotherapy

Treatment options

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Surgery alone

30-40% potentially resectable

5-20% alive at 3-5 years
- pN0 44-57% 5 year survival
- pN1 13-15% 5 year survival

70% fail with distant metastases

A multimodality approach is necessary to improve the poor results of surgery

Treatment options

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- Surgery alone
- Neoadjuvant chemotherapy with surgical resection
- Neoadjuvant chemoradiotherapy with surgical resection
- Surgery with adjuvant chemotherapy, radiotherapy, or chemoradiotherapy
- Definitive (chemo-) radiotherapy

Surgery vs. neoadjuvant chemotherapy + surgery

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	Number of patients	Study treatments	Chemotherapy regimen	Histology	Median survival (months)	Overall survival (%)
Kelsen et al, 1998[91]	440	Surgery vs surgery and chemotherapy	Cisplatin+fluorouracil for three cycles before surgery	204 (46%) SCC, 236 (54%) adenocarinoma	14·9 vs 16·1	(3-year) 26% vs 23%
MRC, 2002[92] and Allum et al, 2009*	802	Surgery vs surgery and chemotherapy	Cisplatin+fluorouracil for two cycles before surgery	247 (31%) SCC, 533 (66%) adenocarcinoma, 24 (3%) undifferentiated or unknown	13·3 vs 16·8	(5-year) 17% vs 23%†
Cunningham et al, 2006[93]	503	Surgery vs surgery and chemotherapy	Epirubicin+cisplatin+ fluorouracil for three cycles before and after surgery	503 (100%) adenocarcinoma (372 [74%] gastric, 131 [26%] oesophageal)	NR	(5-year) 23% vs 36%†

SCC=squamous-cell carcinoma. MRC=Medical Research Council Oesophageal Cancer Working Group. NR=not reported. *Appendix p 7. †Significant difference in favour of the neoadjuvant chemotherapy group.

Table 2: **Results of randomised trials of neoadjuvant chemotherapy**

- Rationale: control early spread of systemic disease
- MAGIC study (Cunningham) may not be generalisable to all esophageal adenocarcinoma (26% EGJ/adeno)
- Meta-analyses favor neoadjuvant chemotherapy over surgery alone

Pennathur et al, Lancet 2013

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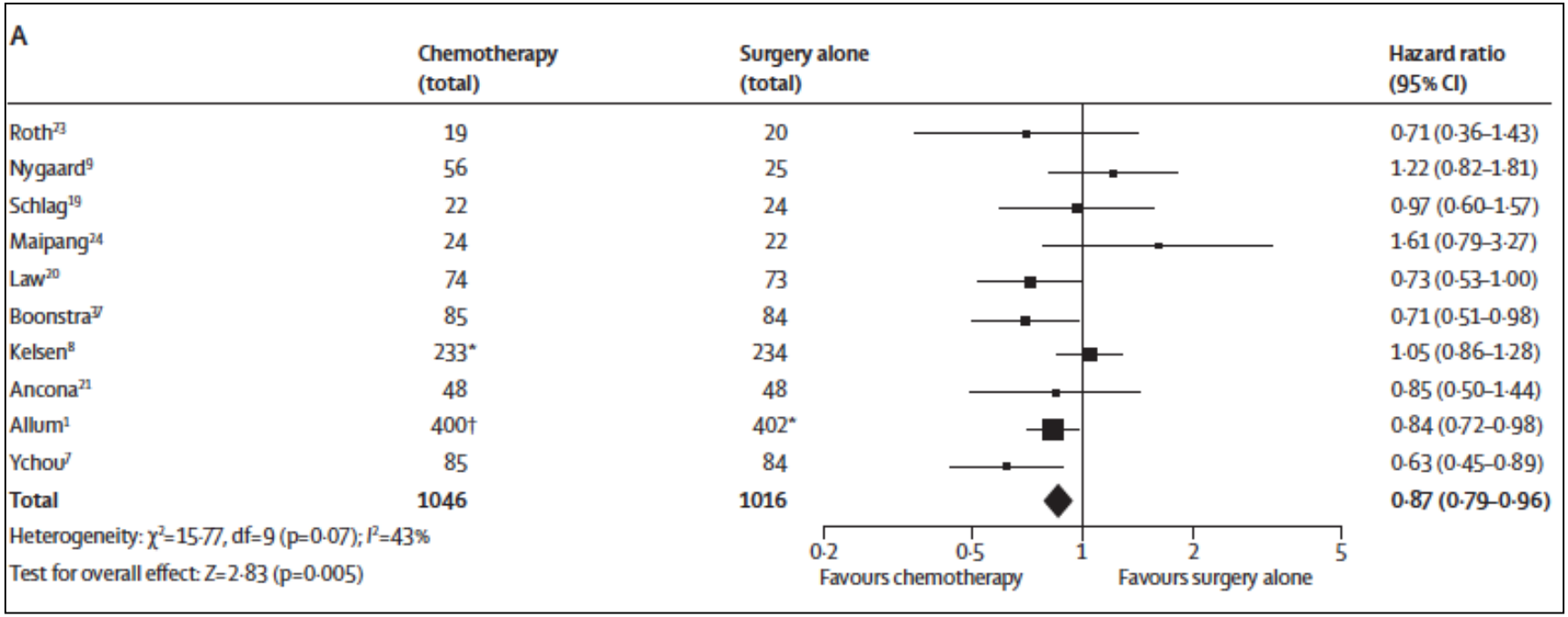
Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis

Katrin M Sjoquist, Bryan H Burmeister, B Mark Smithers, John R Zalcberg, R John Simes, Andrew Barbour, Val Gebski, for the Australasian Gastro-Intestinal Trials Group



A	Chemotherapy (total)	Surgery alone (total)	Hazard ratio (95% CI)
Roth[23]	19	20	0·71 (0·36–1·43)
Nygaard[9]	56	25	1·22 (0·82–1·81)
Schlag[19]	22	24	0·97 (0·60–1·57)
Maipang[24]	24	22	1·61 (0·79–3·27)
Law[20]	74	73	0·73 (0·53–1·00)
Boonstra[37]	85	84	0·71 (0·51–0·98)
Kelsen[8]	233*	234	1·05 (0·86–1·28)
Ancona[21]	48	48	0·85 (0·50–1·44)
Allum[1]	400†	402*	0·84 (0·72–0·98)
Ychou[7]	85	84	0·63 (0·45–0·89)
Total	**1046**	**1016**	**0·87 (0·79–0·96)**

Heterogeneity: χ^2=15·77, df=9 (p=0·07); I^2=43%

Test for overall effect: Z=2·83 (p=0·005)

Sjoquist et al. Lancet Oncol 2011

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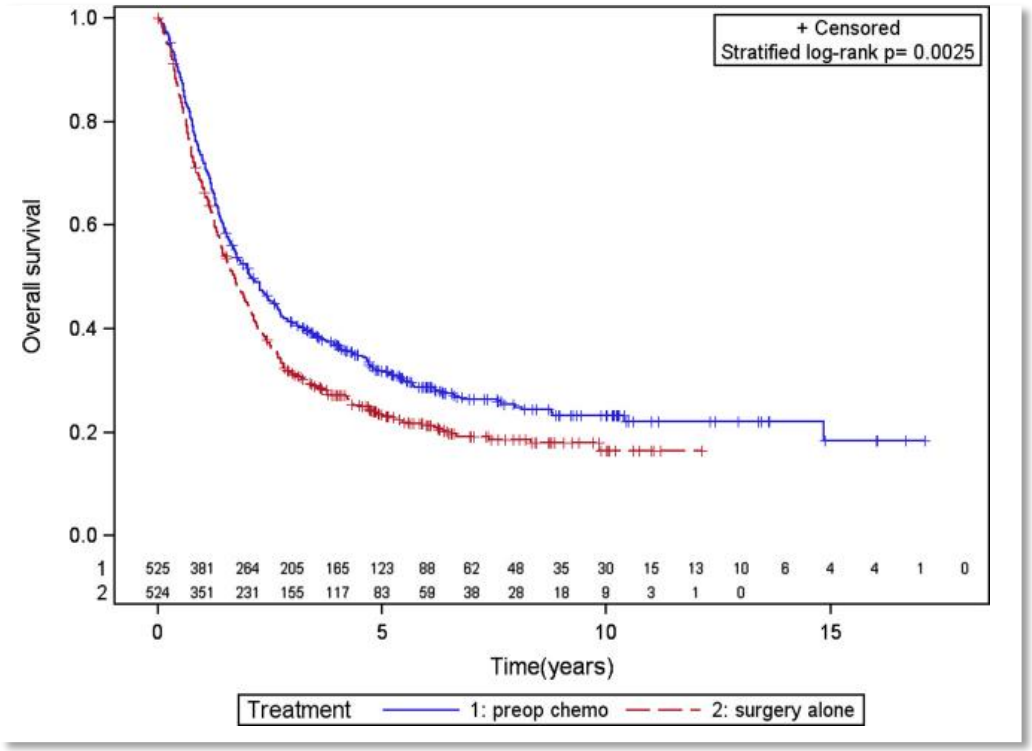
Preoperative chemotherapy vs. primary surgery for gastro-esophageal adenocarcinoma: A systematic review and meta-analysis

14 RCTs

2,422 patients

HR 0.80
(95% CI 0.69-0.93)

P=0.0025



Ronellenfitsch et al. Eur J Cancer 2013

Preoperative chemotherapy vs. primary surgery for gastro-esophageal adenocarcinoma: A systematic review and meta-analysis

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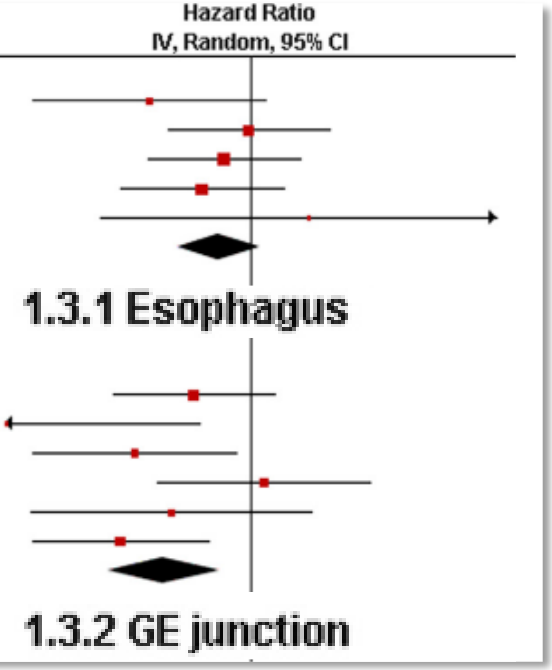
Study or Subgroup	log[Hazard Ratio]	SE	peri-op chemo Total	surgery Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
1.3.1 Esophagus							
Walsh 2002	-0.44078	0.25775	42	32	13.0%	0.64 [0.39, 1.07]	2002
TROG-AGITG 2005	-0.003	0.1806	80	78	26.4%	1.00 [0.70, 1.42]	2005
MAGIC 2006	-0.11078	0.16933	37	36	30.1%	0.90 [0.64, 1.25]	2006
RTOG 8911 2007	-0.20912	0.18046	68	75	26.5%	0.81 [0.57, 1.16]	2007
ACCORD 07 2011	0.25913	0.46317	15	10	4.0%	1.30 [0.52, 3.21]	2011
Subtotal (95% CI)			**242**	**231**	**100.0%**	**0.87 [0.73, 1.05]**	
Heterogeneity: Tau² = 0.00; Chi² = 2.85, df = 4 (P = 0.58); I² = 0%							
Test for overall effect: Z = 1.47 (P = 0.14)							
1.3.2 GE junction							
Wang 2000	-0.24512	0.17991	30	30	23.7%	0.78 [0.55, 1.11]	2000
Walsh 2002	-1.06278	0.42923	16	23	7.0%	0.35 [0.15, 0.80]	2002
MAGIC 2006	-0.50155	0.22661	28	30	18.3%	0.61 [0.39, 0.94]	2006
RTOG 8911 2007	0.06214	0.23608	47	46	17.4%	1.06 [0.67, 1.69]	2007
EORTC 40954 2010	-0.34205	0.31183	37	39	11.8%	0.71 [0.39, 1.31]	2010
ACCORD 07 2011	-0.56469	0.19468	70	74	21.8%	0.57 [0.39, 0.83]	2011
Subtotal (95% CI)			**228**	**242**	**100.0%**	**0.69 [0.54, 0.87]**	
Heterogeneity: Tau² = 0.03; Chi² = 7.78, df = 5 (P = 0.17); I² = 36%							
Test for overall effect: Z = 3.06 (P = 0.002)							



Ronellenfitsch et al. Eur J Cancer 2013

Treatment options

EBRO 2017

- Surgery alone
- Neoadjuvant chemotherapy with surgical resection
- Neoadjuvant chemoradiotherapy with surgical resection
- Surgery with adjuvant chemotherapy, radiotherapy, or chemoradiotherapy
- Definitive (chemo-) radiotherapy

Surgery vs. neoadjuvant chemoradiotherapy + surgery

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	Number of patients	Study treatments	Regimen	Histology	Median survival (months)	Overall survival (%)
Le Prise et al, 1994[94]	86	Surgery vs surgery and CRT	Sequential cisplatin+fluorouracil and RT to 20·0 Gy	86 (100%) SCC	10·0 vs 10·0	(1-year) 47% vs 47%
Walsh et al, 1996[98]	103	Surgery vs surgery and CRT	Concurrent cisplatin+fluorouracil and RT to 40·0 Gy	103 (100%) adenocarcinoma	11·0 vs 16·0	(3-year) 6% vs 32%*
Bosset et al, 1997[95]	282	Surgery vs surgery and CRT	Sequential interrupted cisplatin and RT to 37·0 Gy	282 (100%) SCC	18·6 vs 18·6	(3-year) 34% vs 36%
Urba et al, 2001[96]	100	Surgery vs surgery and CRT	Concurrent cisplatin+fluorouracil +vinblastine and RT to 45·0 Gy	25 (25%) SCC, 75 (75%) adenocarcinoma	17·6 vs 16·9	(3-year) 16% vs 30%
Burmeister et al, 2005[100]	256	Surgery vs surgery and CRT	Concurrent cisplatin+fluorouracil and RT to 35·0 Gy	95 (37%) SCC, 158 (62%) adenocarcinoma, 3 (1%) mixed or other	22·2 vs 19·3	NR
Tepper et al, 2008[99]	56	Surgery vs surgery and CRT	Concurrent cisplatin+fluorouracil and RT to 50·4 Gy	14 (25%) SCC, 42 (75%) adenocarcinoma	21·5 vs 53·8	(5-year) 16% vs 39%*

CRT=chemoradiotherapy. RT=radiotherapy. SCC=squamous-cell carcinoma. NR=not reported. *Significant difference in favour of neoadjuvant chemoradiotherapy.

***Table 3*: Results of randomised trials of neoadjuvant chemoradiotherapy**

- Rationale: downstaging, improve resectability (R0)
- Results not consistent
- CROSS study and meta-analysis show benefit for preoperative CRT

Pennathur et al, Lancet 2013

Neoadjuvant chemoradiation in esophageal cancer: CROSS trial

EBRO 2017

N=363

T1N1M0
or
T2-3N0-1M0

AC (75%)
SCC (23%)

RANDOM

Neo-adjuvant chemoradiotherapy: 41.4 Gy + weekly Carboplatin AUC2 / Paclitaxel 50 mg/m^2
RESECTION

Primary endpoint: Overall survival

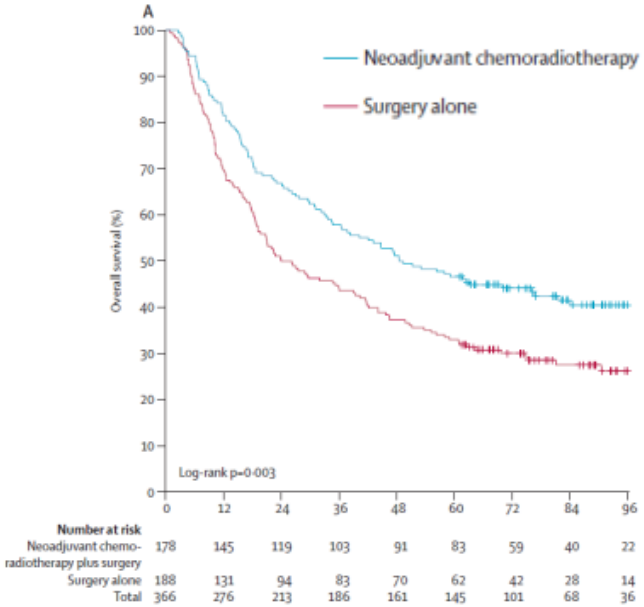
RESECTION

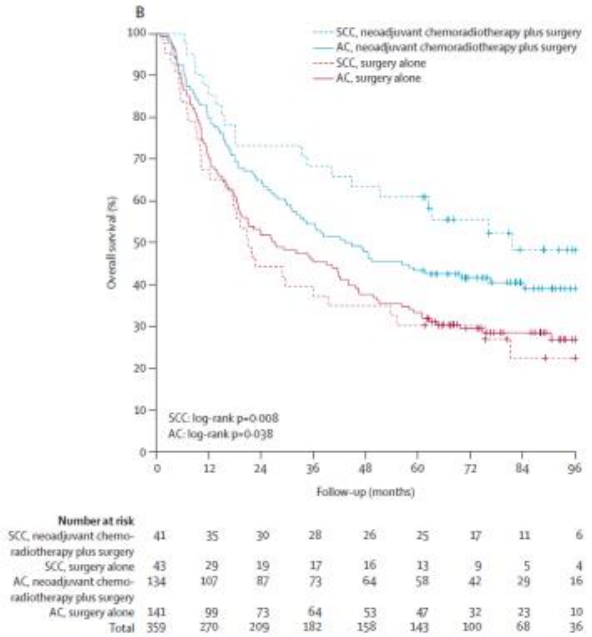
Van Hagen et al. NEJM 2012

Shapiro et al. Lancet Oncol 2015

Neoadjuvant chemoradiation in esophageal cancer: CROSS trial

EBRO 2017





Median follow-up for surviving patients: 84.1 months
(HR 0.68 [95% CI 0.53-0.88]; log-rank p=0.003)

SCC: HR 0.48 [95% CI 0.28-0.83]; log-rank p=0.008
AC: HR 0.73 [95% CI 0.55-0.98]; log-rank p=0.038

Shapiro et al. Lancet Oncol 2015

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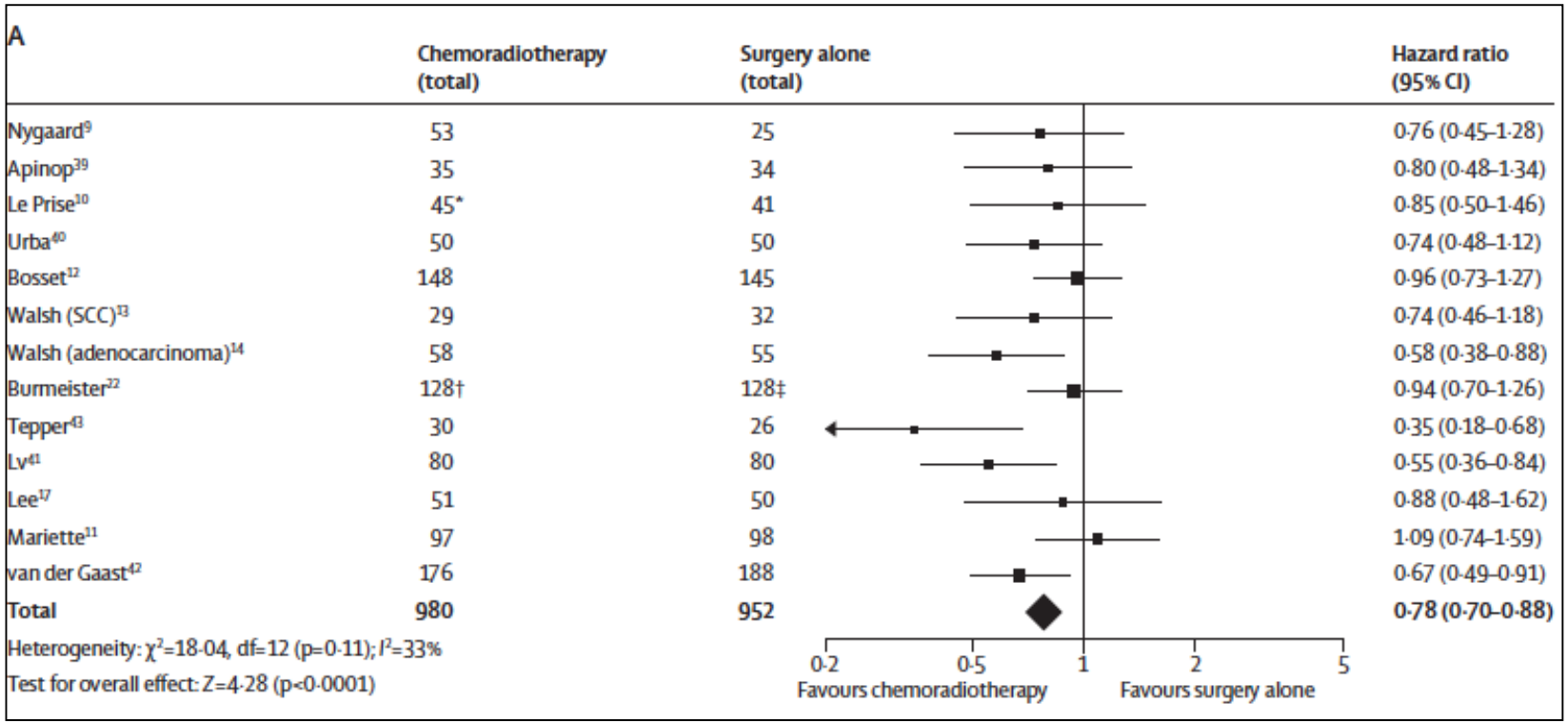
Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis

Katrin M Sjoquist, Bryan H Burmeister, B Mark Smithers, John R Zalcberg, R John Simes, Andrew Barbour, Val Gebski, for the Australasian Gastro-Intestinal Trials Group



A	Chemoradiotherapy (total)	Surgery alone (total)	Hazard ratio (95% CI)
Nygaard[9]	53	25	0·76 (0·45–1·28)
Apinop[39]	35	34	0·80 (0·48–1·34)
Le Prise[10]	45*	41	0·85 (0·50–1·46)
Urba[40]	50	50	0·74 (0·48–1·12)
Bosset[12]	148	145	0·96 (0·73–1·27)
Walsh (SCC)[13]	29	32	0·74 (0·46–1·18)
Walsh (adenocarcinoma)[14]	58	55	0·58 (0·38–0·88)
Burmeister[22]	128†	128‡	0·94 (0·70–1·26)
Tepper[43]	30	26	0·35 (0·18–0·68)
Lv[41]	80	80	0·55 (0·36–0·84)
Lee[17]	51	50	0·88 (0·48–1·62)
Mariette[11]	97	98	1·09 (0·74–1·59)
van der Gaast[42]	176	188	0·67 (0·49–0·91)
Total	**980**	**952**	**0·78 (0·70–0·88)**

Heterogeneity: χ^2=18·04, df=12 (p=0·11); I^2=33%
Test for overall effect: Z=4·28 (p<0·0001)

Sjoquist et al. Lancet Oncol 2011

Esophageal cancer: Neo-adjuvant Chemoradiotherapy or Chemotherapy?

EBRO 2017

N=126

T3-4 N0-1 M0

AC GEJ

R A N D O M

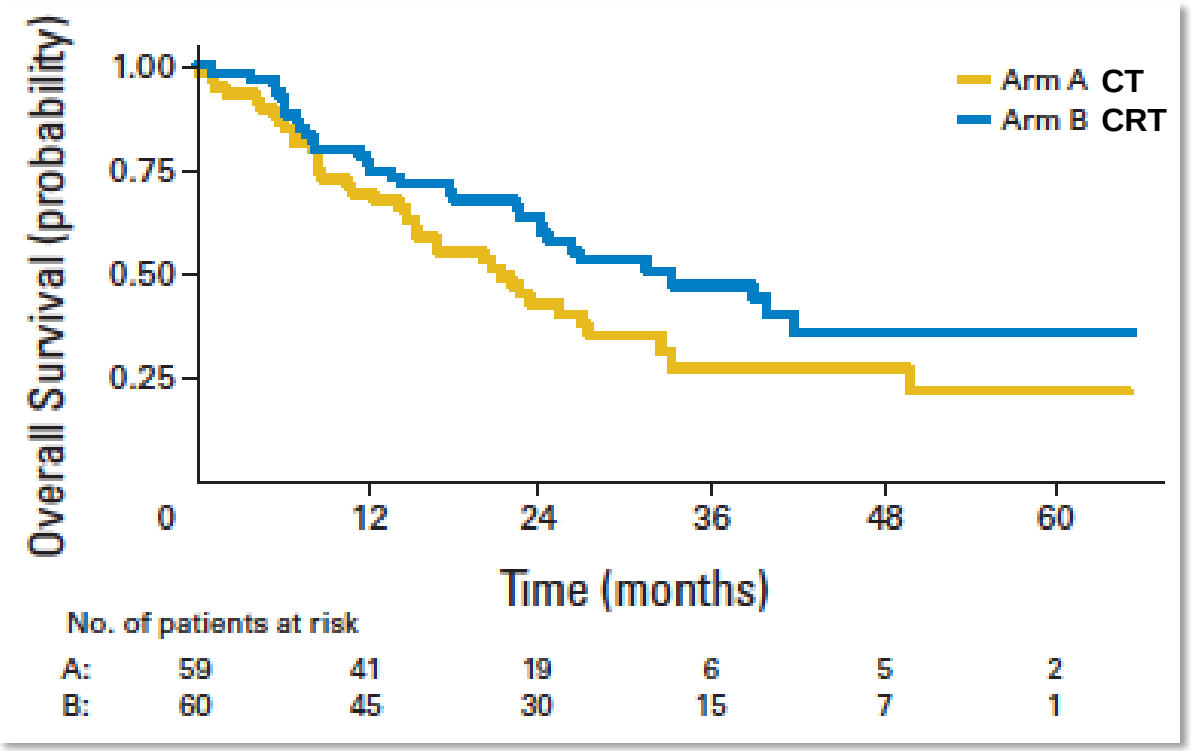
Neo-adjuvant chemoradiotherapy: PLF x2 + 30 Gy + Cisplatin 50 mg/m^2 d1,8 + etop 80 mg/m^2 d3-5
RESECTION

Primary endpoint: 3-year overall survival

Neo-adjuvant chemotherapy (PLF):
Cisplatin 50 mg/m^2 bi-wk + 5FU 2 g/m^2 wk x2.5
RESECTION

Stahl et al. J Clin Oncol 2009

Esophageal cancer: Neo-adjuvant Chemoradiotherapy or Chemotherapy?



3-year survival: 27.7% (arm A) vs. 47.4% (arm B); p=0.07

Stahl et al. J Clin Oncol 2009

Esophageal cancer: Neo-adjuvant Chemoradiotherapy or Chemotherapy?

EBRO 2017

N=180

T1N1M0
or
T2-3N0-1M0

AC (73%)
SCC (27%)

RANDOM

Neo-adjuvant chemoradiotherapy: 40 Gy +
Cisplatin 100 mg/m^2 d1 + 5FU 750 mg/m^2 d1-5 x3
RESECTION

Primary endpoint:
Pathologic complete response (pCR)

Neo-adjuvant chemotherapy:
Cisplatin 100 mg/m^2 d1 + 5FU 750 mg/m^2 d1-5 x3
RESECTION

Klevebro et al. Ann Oncol 2016

EBRO 2017

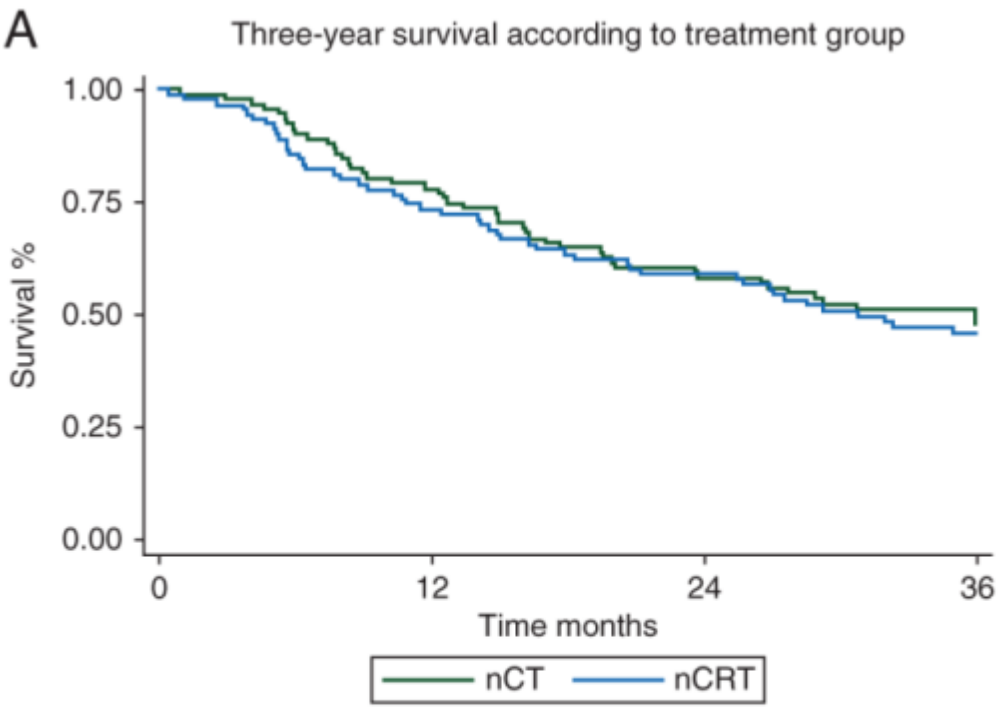
Esophageal cancer: Neo-adjuvant Chemoradiotherapy or Chemotherapy?

	Neo-adjuvant Chemoradiotherapy	Neo-adjuvant Chemotherapy	p-value
pCR	28%	9%	0.002
N+	35%	65%	0.001
R0	87%	74%	0.04

Klevebro et al. Ann Oncol 2016

Esophageal cancer: Neo-adjuvant Chemoradiotherapy or Chemotherapy?

EBRO 2017



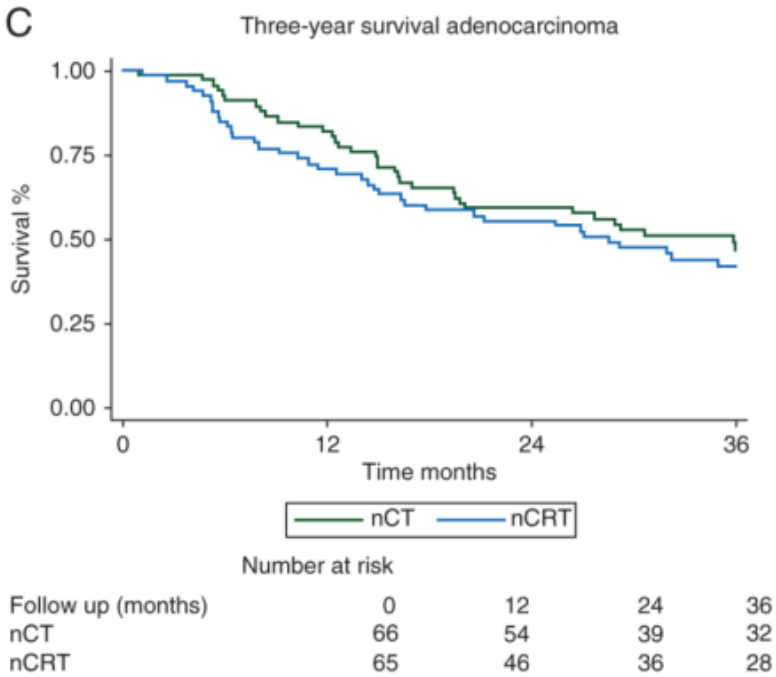
Number at risk

Follow up (months)	0	12	24	36
nCT	91	71	53	45
nCRT	90	66	53	42

Klevebro et al. Ann Oncol 2016

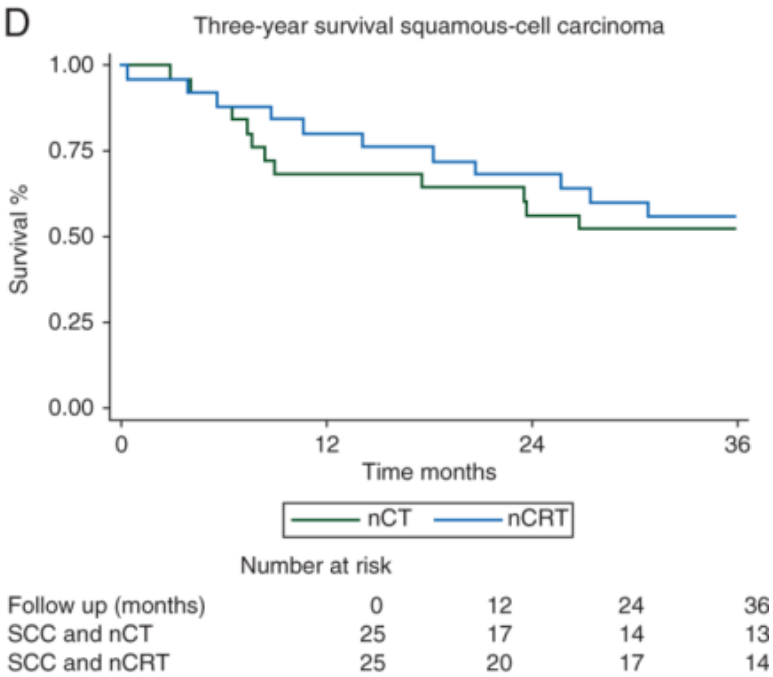
Esophageal cancer: Neo-adjuvant Chemoradiotherapy or Chemotherapy?

EBRO 2017



Number at risk

Follow up (months)	0	12	24	36
nCT	66	54	39	32
nCRT	65	46	36	28



Number at risk

Follow up (months)	0	12	24	36
SCC and nCT	25	17	14	13
SCC and nCRT	25	20	17	14

Conclusion: The addition of radiotherapy to neoadjuvant chemotherapy results in higher histological complete response rate, higher R0 resection rate, and a lower frequency of lymph-node metastases, without significantly affecting survival.

Klevebro et al. Ann Oncol 2016

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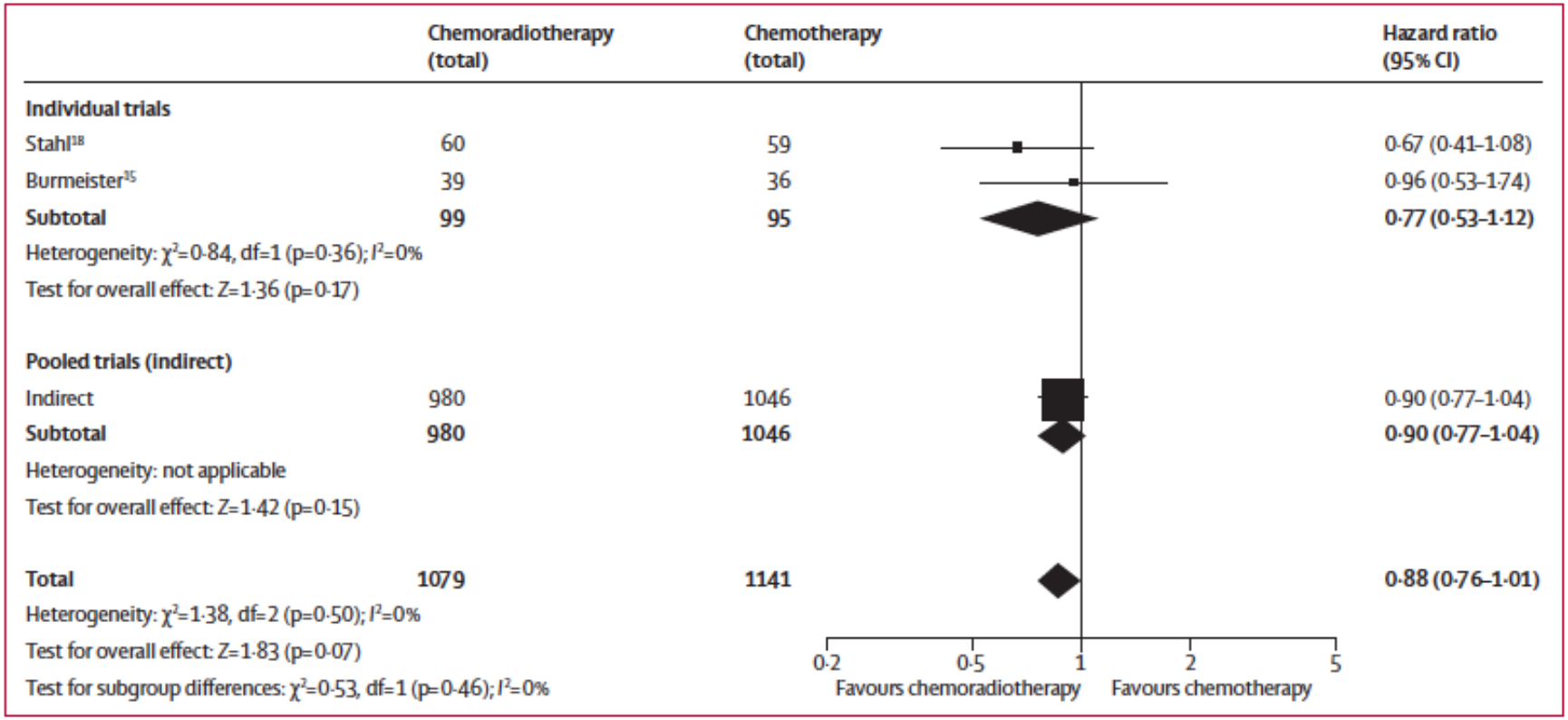
Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis

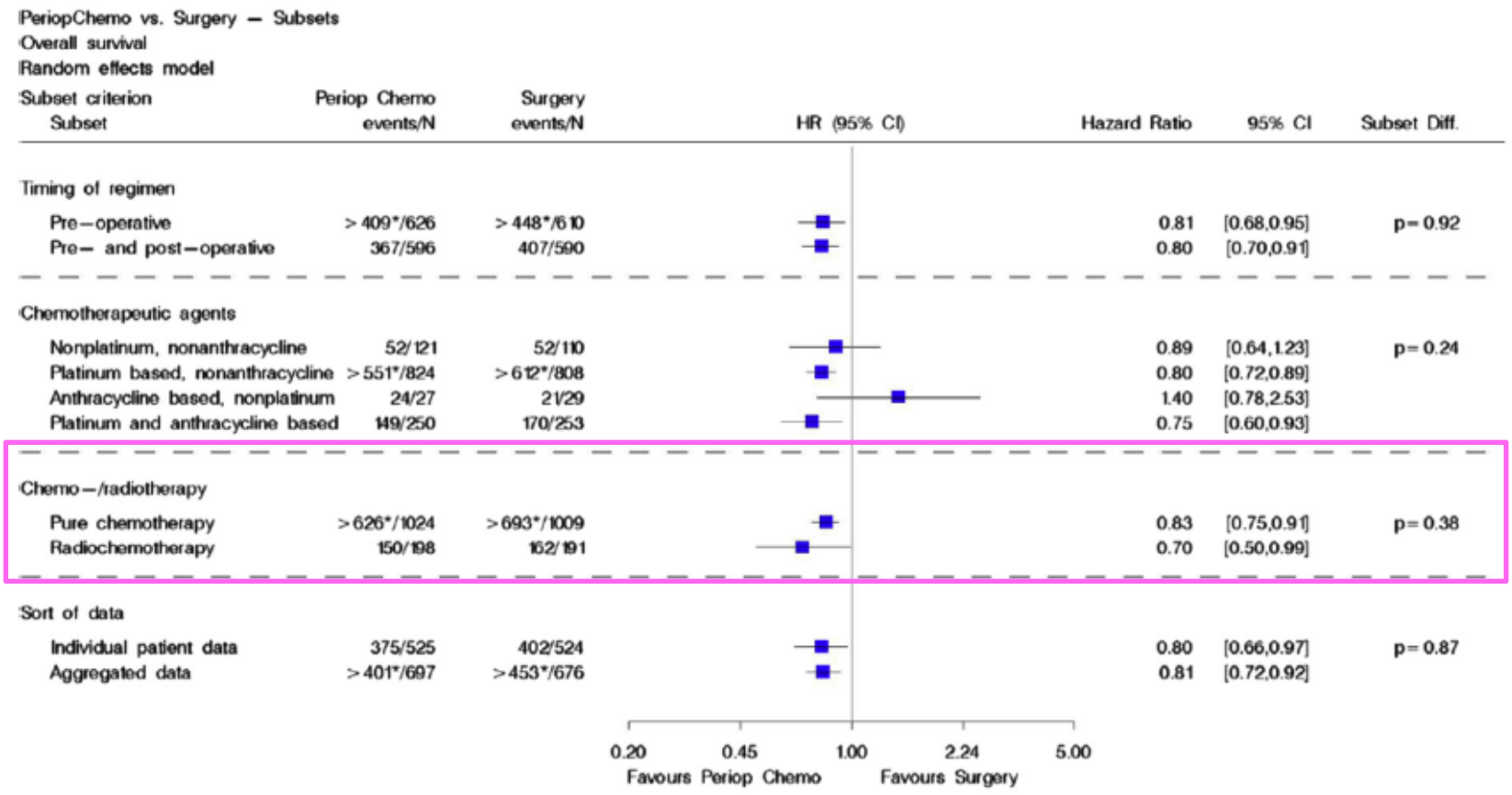
Katrin M Sjoquist, Bryan H Burmeister, B Mark Smithers, John R Zalcberg, R John Simes, Andrew Barbour, Val Gebski, for the Australasian Gastro-Intestinal Trials Group



Sjoquist et al. Lancet Oncol 2011

EBRO 2017

Preoperative chemotherapy vs. primary surgery for gastro-esophageal adenocarcinoma: A systematic review and meta-analysis



Ronellenfitsch et al. Eur J Cancer 2013

Treatment options

EBRO 2017

- Surgery alone
- Neoadjuvant chemotherapy with surgical resection
- Neoadjuvant chemoradiotherapy with surgical resection
- Surgery with adjuvant chemotherapy, radiotherapy, or chemoradiotherapy
- Definitive (chemo-) radiotherapy

Surgery vs. surgery + adjuvant chemotherapy, radiotherapy, CRT

EBRO 2017

	Number of patients	Study treatments	Regimen	Histology	Median survival (months)	Overall survival (%)
Macdonald et al, 2001[106]	556	Surgery vs surgery and adjuvant CRT	Sequential and concurrent CRT with fluorouracil	556 (100%) adenocarcinoma (445 [80%] stomach, 111 [20%] gastro-oesophageal junction)	27 vs 36	(3-year) 41% vs 50%*
Ando et al, 2003[105]	242	Surgery vs surgery and adjuvant chemotherapy	Fluorouracil+ cisplatin	242 (100%) SCC	NR	(5-year) 52% vs 61%†
Armanios et al, 2004[103]‡	55	Surgery and adjuvant chemotherapy	Cisplatin+ paclitaxel	55 (100%) adenocarcinoma	31·2	(3-year) 42%
Xiao et al, 2003§	495	Surgery vs surgery and adjuvant RT	50·0–60·0 Gy in 25–30 fractions	495 (100%) SCC	NR	(5-year) 31·7% vs 41·3%
Ténière et al, 1991§	221	Surgery vs surgery and adjuvant RT	45·0–55·0 Gy	221 (100%) SCC	18 vs 18	(5-year) 17·6% vs 18·6%
Fok et al, 1993§	130	Surgery vs surgery and adjuvant RT	49·0–52·5 Gy in 14 fractions	104 (80%) SCC, 26 (20%) adenocarcinoma	15·2 vs 8·7¶	NR
Zieren et al, 1995§	68	Surgery vs surgery and adjuvant RT	Up to 30·6 Gy	68 (100%) SCC	NR	(3-year) 20% vs 22%

CRT=chemoradiotherapy. RT=radiotherapy. SCC=squamous-cell carcinoma. NR=not reported. *Difference significant for overall survival. †Although overall survival did not differ (p=0·13), disease-free surival was improved with adjuvant chemotherapy (45% vs 55%, p=0·037). ‡Phase 2 non-randomised, non-controlled trial. §Appendix pp 7–8. ¶Difference significant for median survival.

Table 4: **Results of trials of adjuvant chemotherapy, radiotherapy, and chemoradiotherapy**

Pennathur et al, Lancet 2013

- Rationale: may be beneficial for specific subgroups (node-positive disease; positive margins)
- No consistent benefits

Post-operative Radiotherapy

EBRO 2017

N=495

Radically resected Stage II-III SCC

1986-1997

RANDOM

Observation

N=275

Primary endpoint: Survival

Radiotherapy (50-60 Gy)

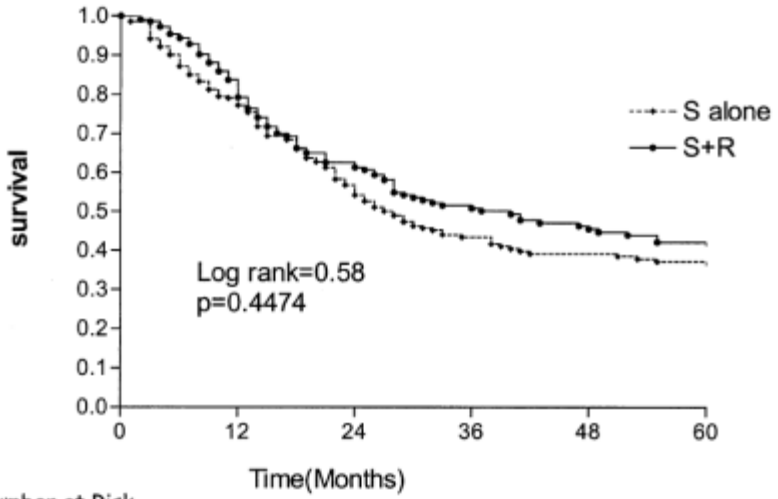
N=220

Xiao et al. Ann Thorac Surg 2003

Post-operative Radiotherapy

EBRO 2017

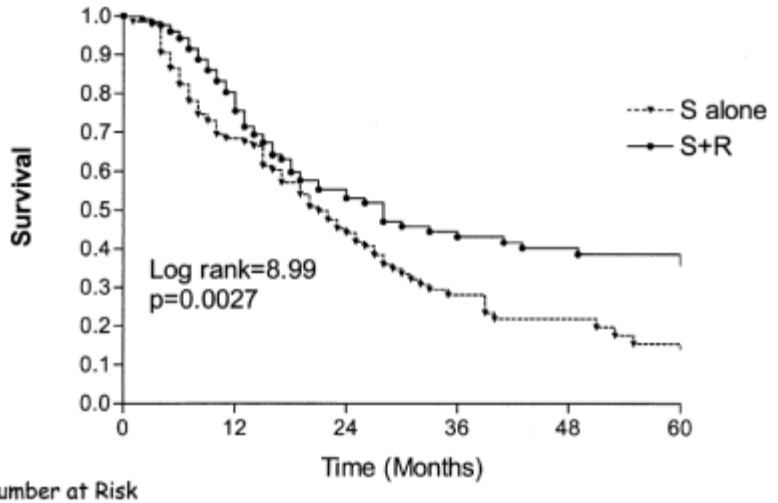
All stages



Number at Risk

S alone	275	180	114	74	58	54
S+R	220	143	99	72	58	45

Stage III



Number at Risk

S alone	143	69	39	15	9	6
S+R	129	78	47	32	24	10

Table 2. Cause of Failure as Related to Treatment

	S (n = 243)		S+R (n = 191)			
	n	%	n	%	χ^2	*p*
Intrathoracic lymph node metastasis	63	25.0	31	16.2	5.925	0.015
Anastomotic recurrence	14	5.8	1	0.5	8.793	0.003
Supraclavicular lymph node metastasis	38	13.2	6	3.1	13.439	0.000
Intraabdominal metastasis	24	9.9	14	7.3	0.868	0.351
Hematogenous metastasis	44	18.1	45	23.6	1.951	0.162

S = surgery alone; S+R = surgery plus radiotherapy.

Xiao et al. Ann Thorac Surg 2003

Treatment options

EBRO 2017

- Surgery alone
- Neoadjuvant chemotherapy with surgical resection
- Neoadjuvant chemoradiotherapy with surgical resection
- Surgery with adjuvant chemotherapy, radiotherapy, or chemoradiotherapy
- Definitive (chemo-) radiotherapy

Definitive chemoradiotherapy vs. radiotherapy in locally advanced esophageal cancer

RTOG 85-01

Local Advanced thoracic esophagus SCC and AD

RANDOM

Radiotherapy N=62

(64 Gy)

Primary endpoint: Survival

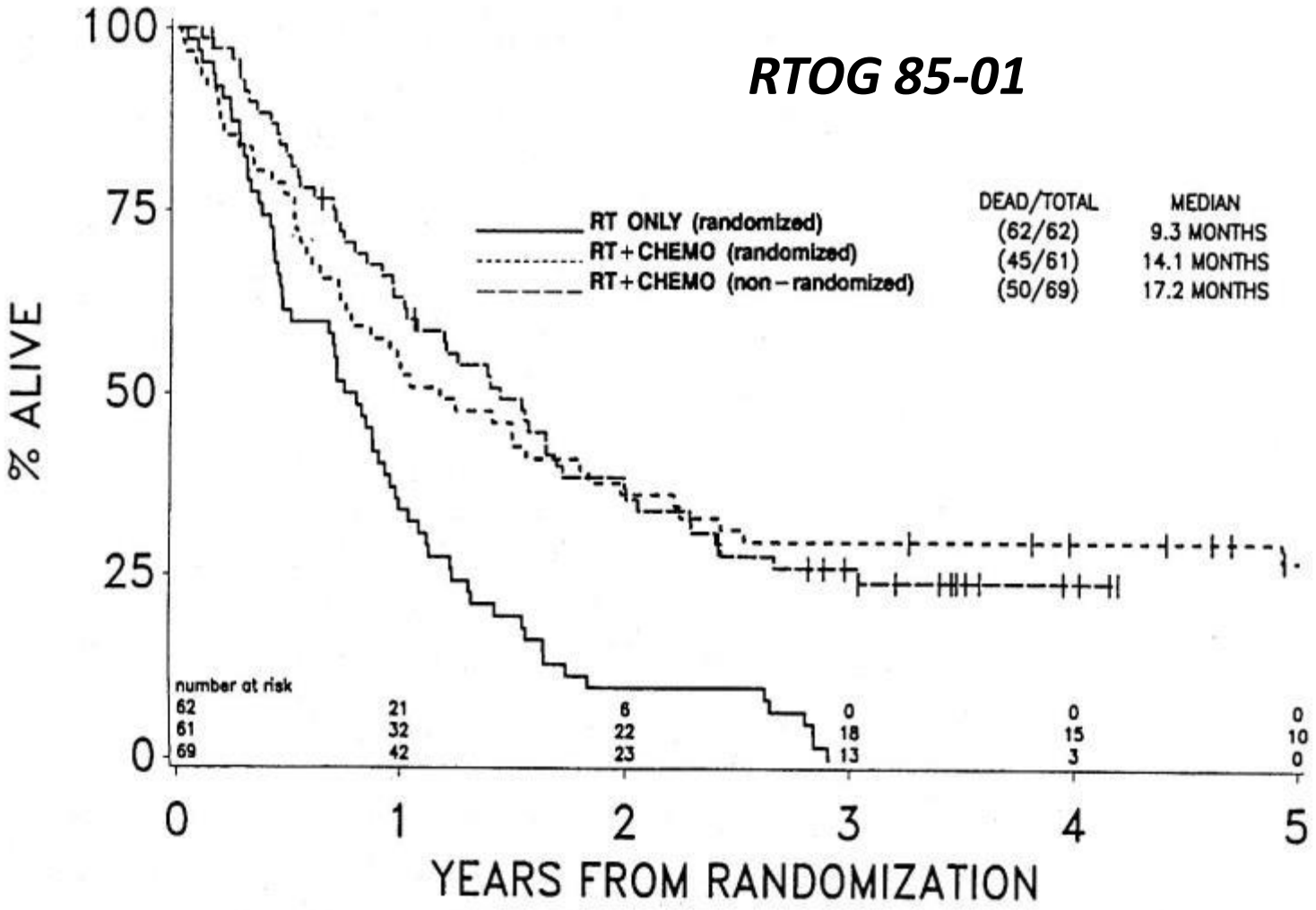
Chemoradiation N=61

(50 Gy + 2x cisplatin/5FU ➔ 2x cisplatin/5FU)

Al-Sarraf et al. J Clin Oncol 1997

Definitive chemoradiotherapy vs. radiotherapy in locally advanced esophageal cancer

EBRO 2017



Al-Sarraf et al. J Clin Oncol 1997

Definitive chemoradiotherapy in locally advanced esophageal cancer

RTOG 94-05

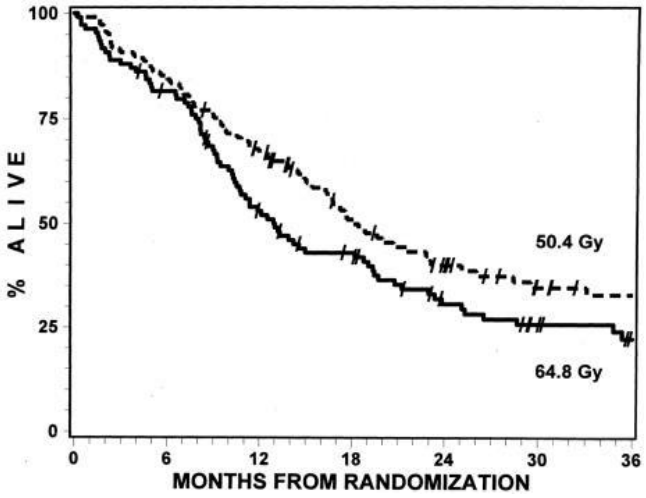
T1-T4,
N0-N1
M0
SCC and AD

RANDOM

Chemoradiotherapy (standard RT dose)
(50.4 Gy + cisplatin/5FU) **N= 109**

Primary endpoint: Survival

Chemoradiotherapy (high RT dose)
(64.8 Gy + cisplatin/5FU) **N= 109**



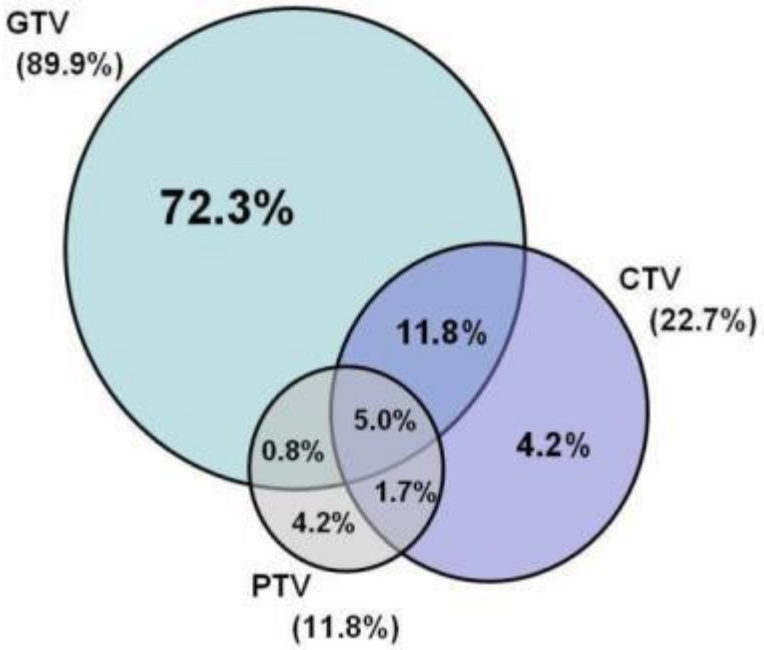
higher radiation dose does not improve outcome

Minsky et al. J Clin Oncol 2002

Failure patterns in patients with esophageal cancer treated with definitive chemoradiation

EBRO 2017

- 239 patients dCRT
  - 87% T3/T4
  - 50.4Gy/28 fr + 5FU
- Median FU 52.6 months
  - 50% (n=119) local failure
  - 48% (n=114) distant failure
  - 31% (n= 74) NED
- Local failure (n=119)
  - 90% GTV failure(107/119)
  - 23% CTV failure (27/119)
  - 12% PTV failure (14/119)



Welsh, Cancer 2012

Failure patterns in patients with esophageal cancer treated with definitive chemoradiation

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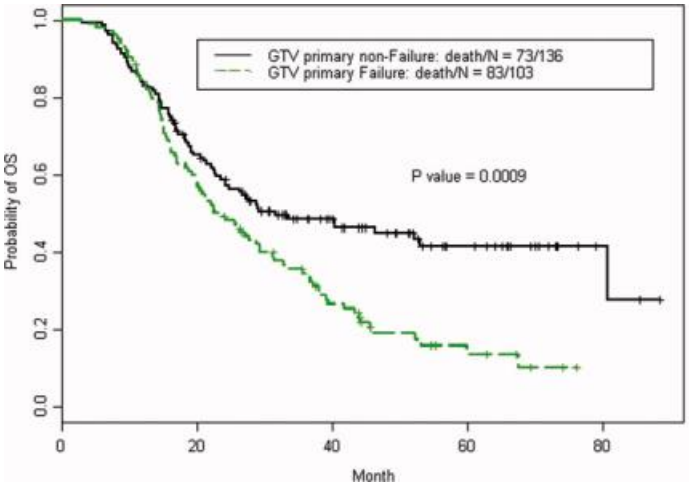
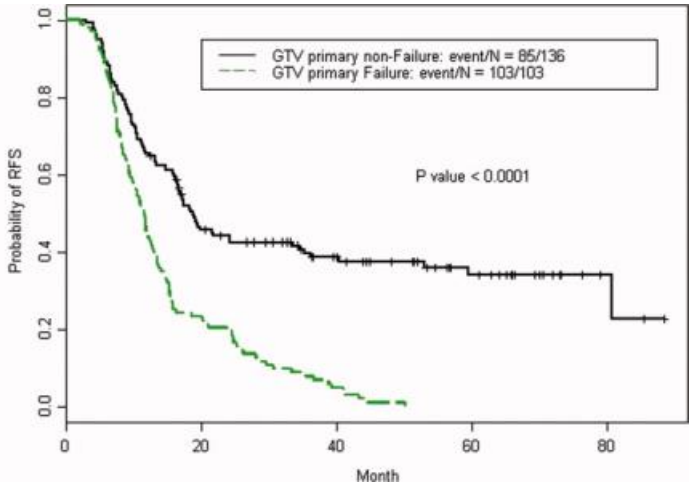




Welsh, Cancer 2012

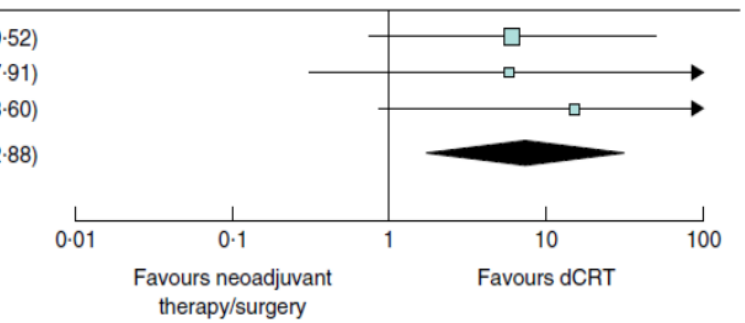
Definitive chemoradiotherapy vs. neoadjuvant chemoradiotherapy or surgery in locally advanced esophageal cancer

EBRO 2017

Meta-analysis in operable SCC

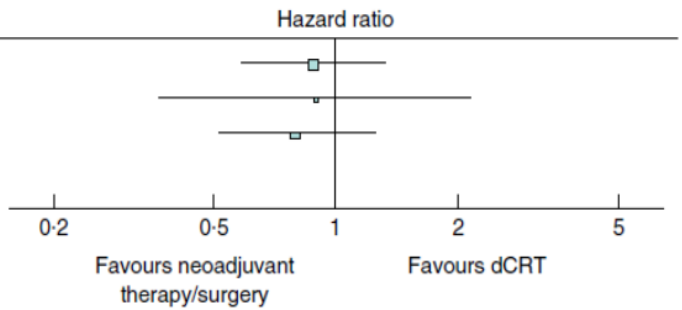
Reference	Mortality rate: Neoadjuvant therapy/surgery	Mortality rate: dCRT	Weight (%)	Hazard ratio
Bedenne *et al.*[3]	6 of 129	1 of 130	48·5	6·05 (0·74, 49·52)
Chiu *et al.*[31]	3 of 44	0 of 36	25·0	5·76 (0·31, 107·91)
Stahl *et al.*[4]	7 of 86	0 of 86	26·5	15·00 (0·87, 258·60)
Total	16 of 259	1 of 252	100·0	7·60 (1·76, 32·88)

Heterogeneity: $\tau^2 = 0{\cdot}00$, $\chi^2 = 0{\cdot}31$, 2 d.f., $P = 0{\cdot}856$, $I^2 = 0\%$



30 day mortality

Reference	Treatments	Hazard ratio
Bedenne *et al.*[3]	Neoadjuvant CRT + surgery *versus* dCRT	0·88 (0·59, 1·31)
Chiu *et al.*[31]	Surgery *versus* dCRT	0·89 (0·37, 2·17)
Stahl *et al.*[4]	Neoadjuvant chemotherapy/CRT + surgery *versus* dCRT	0·83 (0·54, 1·23)



Overall Survival

Kranzfelder et al. Br J Surg 2011

Conclusions

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- Incidence of esophageal cancer is increasing
- Prognosis is poor due to advanced stages at diagnosis
- Treatment is challenging and requires multidisciplinary approach
- Largest gain is obtained in neo-adjuvant setting (CRT>CT?)

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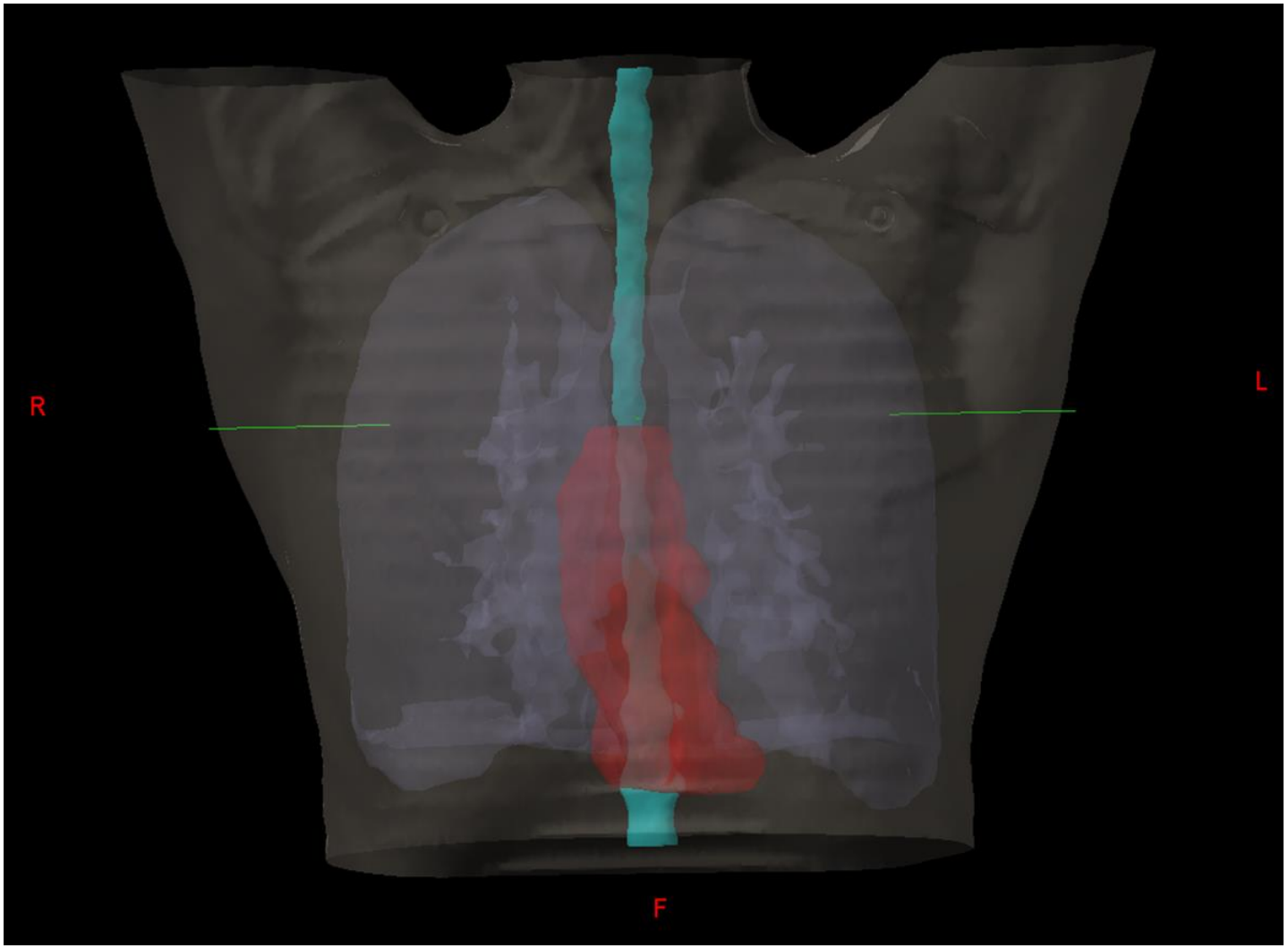
Radiotherapy treatment planning



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2017

Radiotherapy considerations

- Defining GTV
- Marginis from GTV to CTV
- Defining elective nodal CTV
- Organ motion and ITV

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2017

Radiotherapy considerations

- Defining GTV
- Marginis from GTV to CTV
- Defining elective nodal CTV
- Organ motion and ITV

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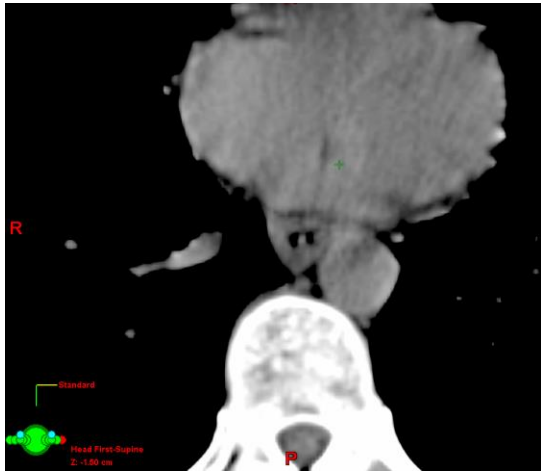
Defining GTV



Problems

- Translating EUS findings to planning CT
- Differentiating tumour from normal oesophagus
- Differentiating tumour from other pathology

Possible solution

- Endoscopic placement of clips
- Integrating staging imaging and CT planning

Defining GTV

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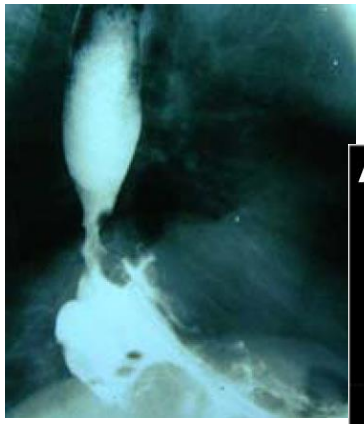
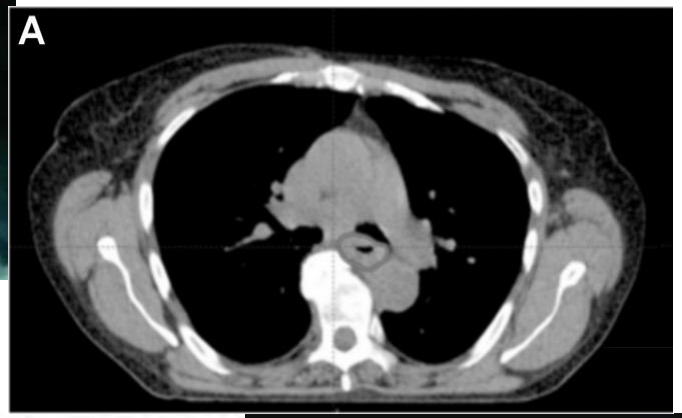
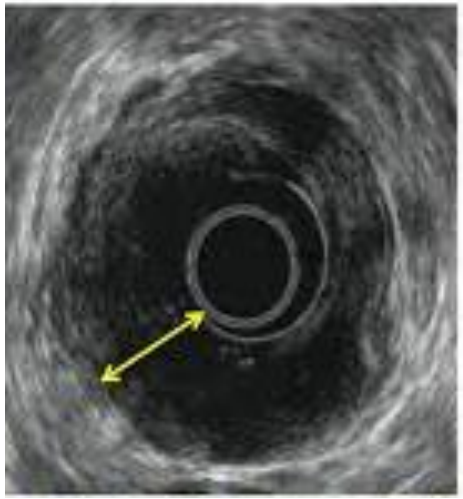
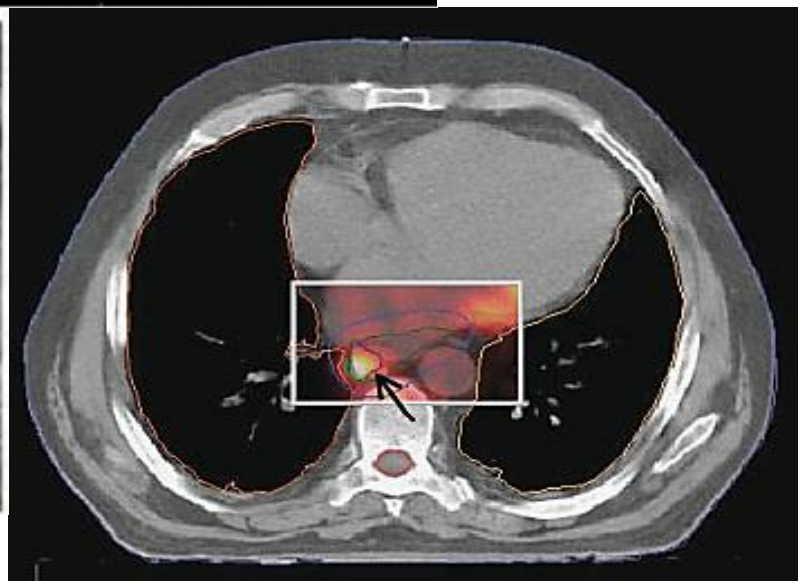




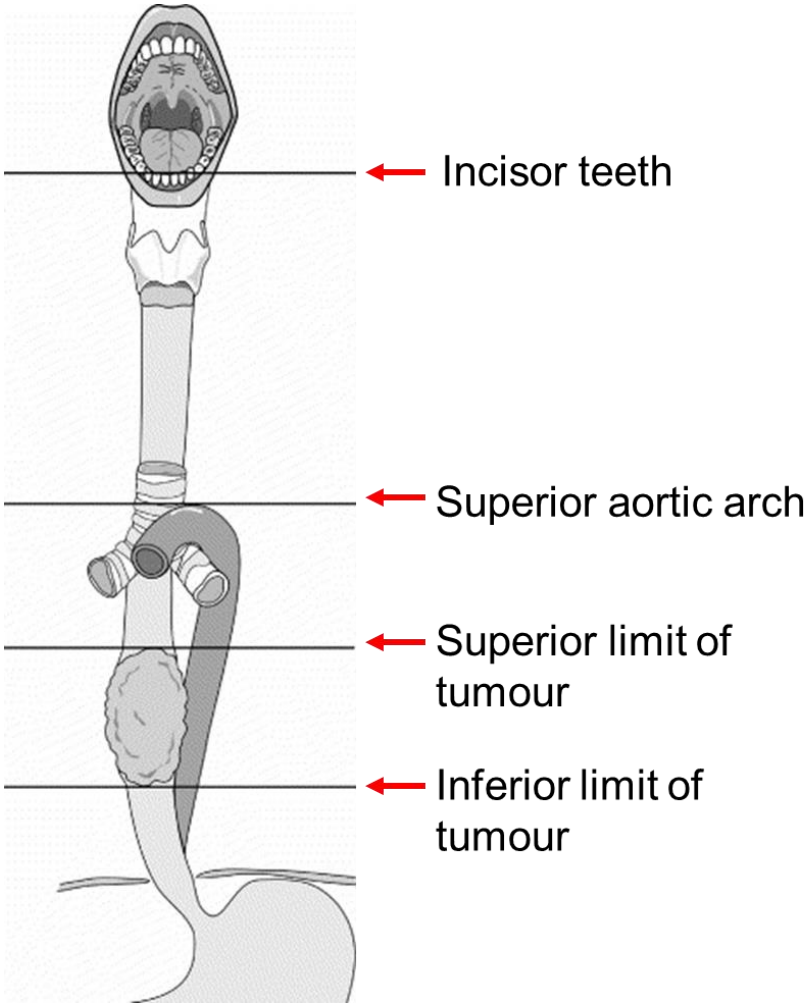
- Barium swallow
- CT-Scan
- Endoscopy
- EUS
- PET - CT





Defining GTV: EUS in treatment planning

EBRO 2017



11 cases

GTV^{CT} mean = 5.95 cm

GTV^{EUS} mean = 6.91 cm

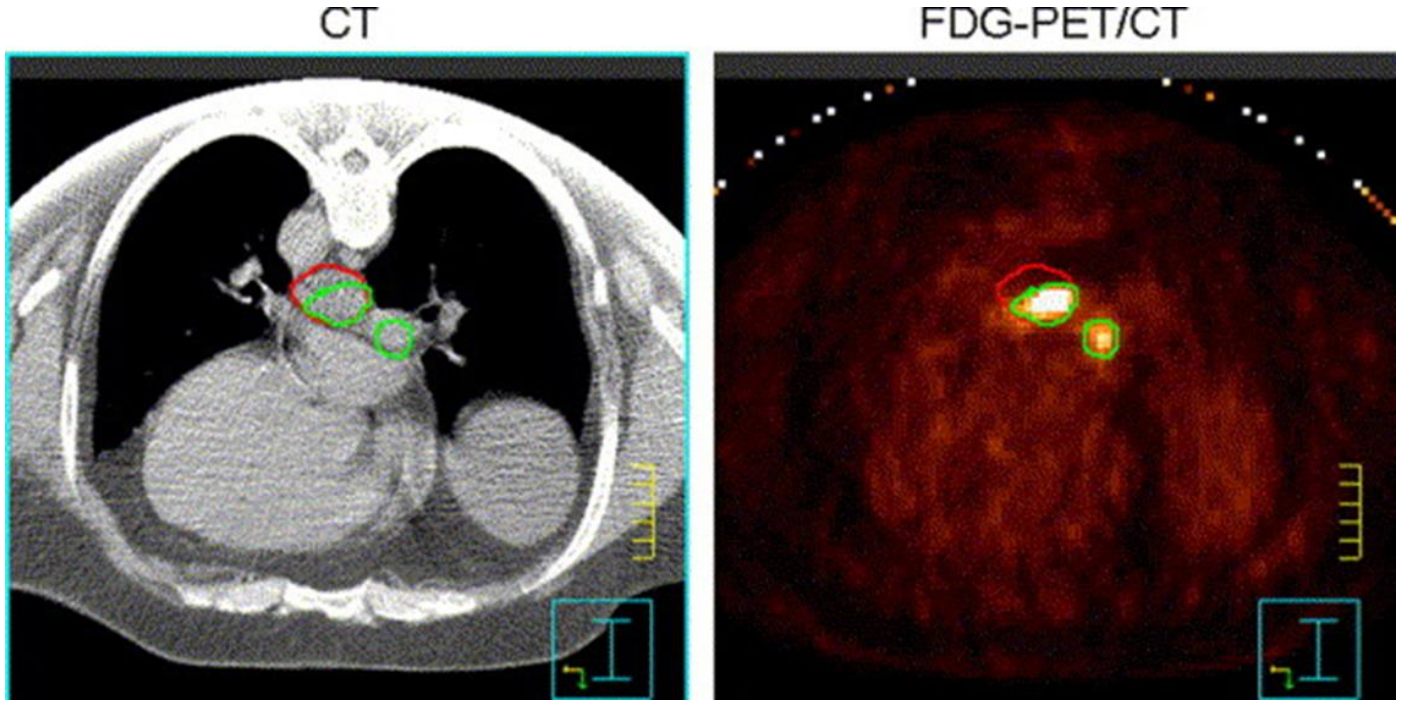
Variation in position:

Superior limit -25 to +75 mm

Inferior limit – 55 to + 15 mm

Thomas et al Radiother. Oncol. 2004

Defining GTV:
PET-CT in treatment planning



GTV defined by PET is smaller than by CT alone in 10/16

Gondi et al IJROBP 2007

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Defining GTV:
PET-CT in treatment planning

- PET is more accurate for nodal assessment
- Distant lymph nodes and distant metastasis

- PET can improve the RT planning
  - PET shows the longitudinal extent better than CT
  - PET may be the only way to visualize the lower border of the tumor in case of tight stenosis

•*Duong Eur J Nucl Med Imaging 2006*
•*Van Westreneen JCO 2004*

Radiotherapy considerations

- Defining GTV
- Marginis from GTV to CTV
- Defining elective nodal CTV
- Organ motion and ITV

Lymphatic drainage

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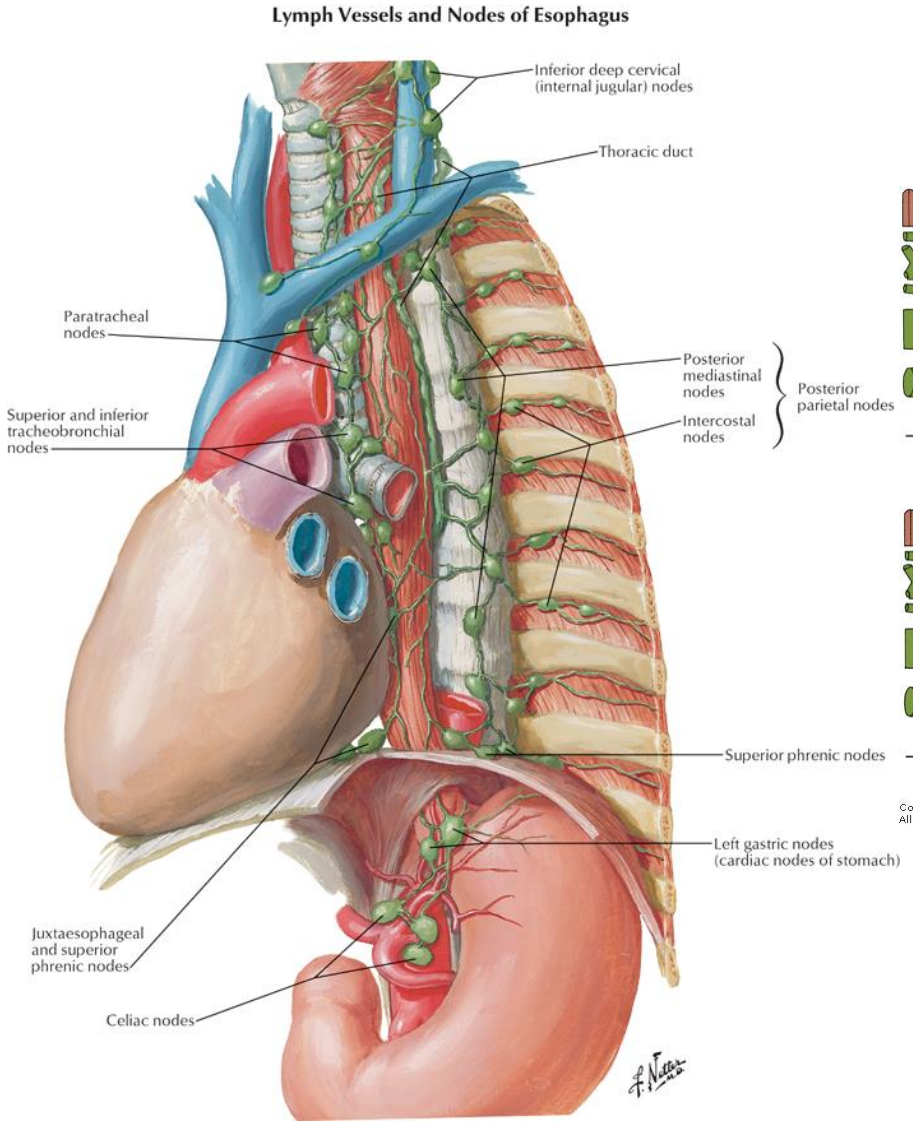

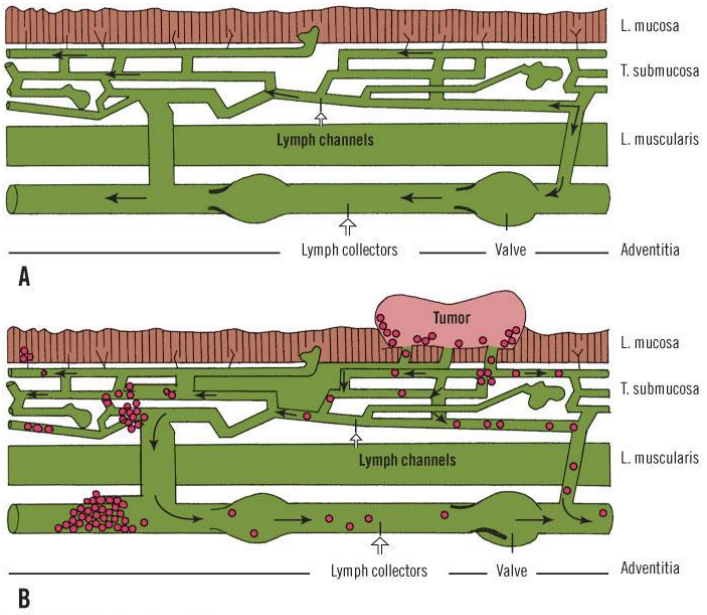

Radiotherapy considerations

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- Defining GTV
- Marginis from GTV to CTV
- Defining elective nodal CTV
- Organ motion and ITV

Marginis from GTV to CTV

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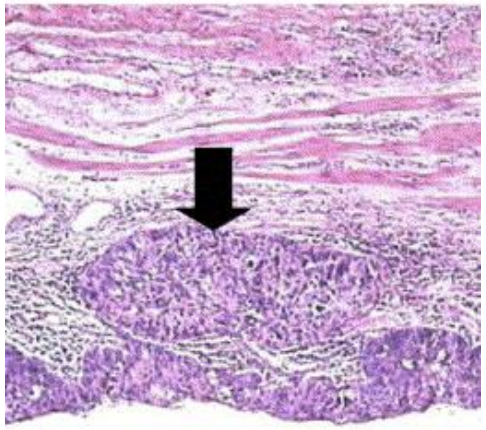
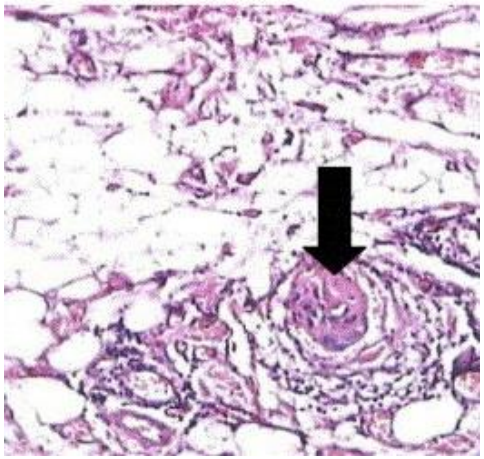
Evidence from pathological specimens

- Intraepithelial spread
- Subepithelial spread
  - Intramural (muscularis) extension and metastasis
  - Lymphovascular space invasion
- Multifocal disease, skip lesions





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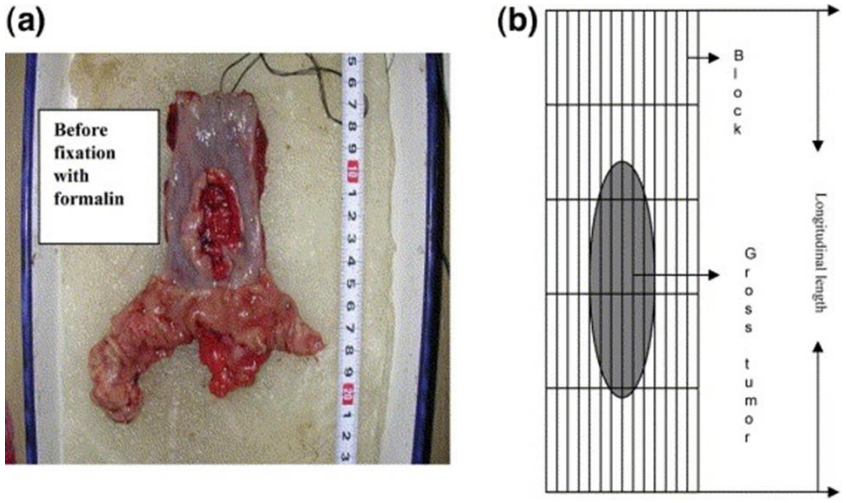
Marginis from GTV to CTV

On surgical specimens: n= 34 SCC/32ADK

Microscopic spread from gross tumour:

Oesophagus and GEJ (proximal) spread – 94% cases < 30 mm

GEJ distal spread – 94% cases < 50 mm



Gao S et al., IJROBP 2007

Marginis from GTV to CTV

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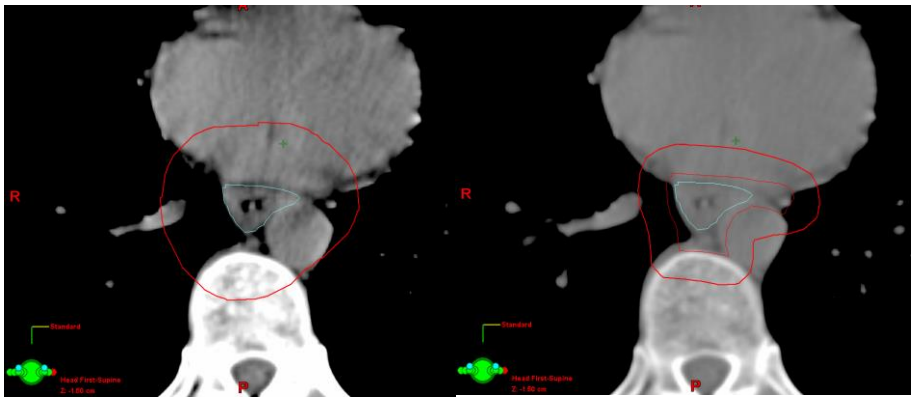
Margins generally applied

CTV: GTV + 3 to 5 cm craniocaudally

+1 to 2 cm circumferentially

+ positive nodes



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Radiotherapy considerations

- Defining GTV
- Marginis from GTV to CTV
- Defining elective nodal CTV
- Organ motion and ITV

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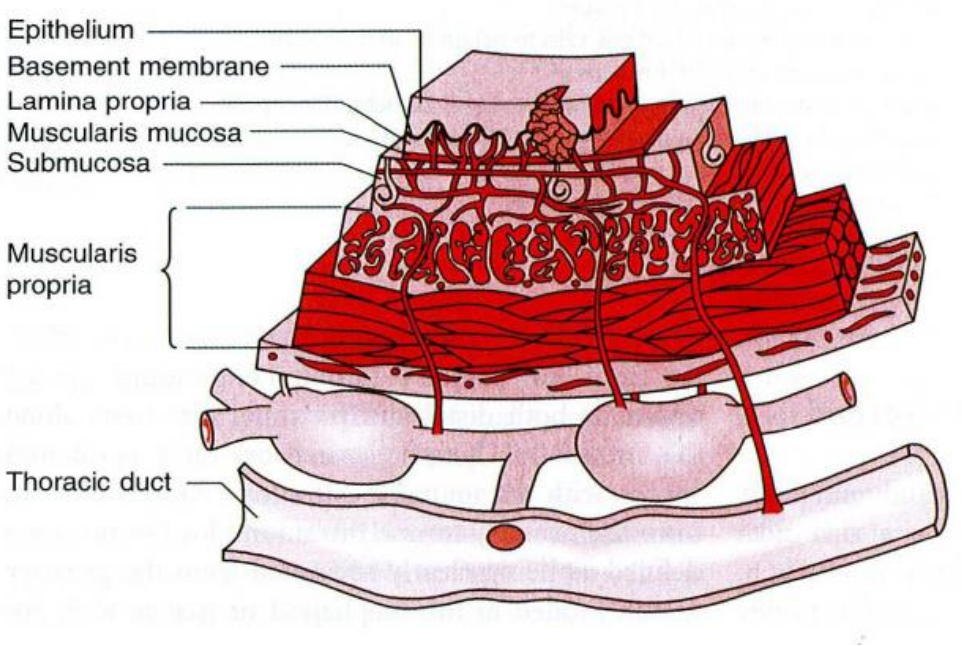
Defining elective nodal CTV

- Tis 0%
- T1b 31-56%
- T2 58-78%
- T3 83-100%



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Defining elective nodal CTV

TABLE 3. Rate of LNM to Different Regions According to the Location of the Primary Tumor

Location	Cervical	Um	Mm	Lm	Abdominal
Ut	12/82 (14.6)	24/82 (29.3)	7/82 (8.5)	8/82 (9.8)	6/82 (7.3)
Mt	55/1266 (4.3)	63/1266 (5.0)	417/1266 (32.9)	32/1266 (2.5)	189/1266 (14.9)
Lt	11/545 (2.0)	12/545 (2.2)	84/545 (15.4)	208/545 (38.1)	150/545 (27.5)
Total	78/1893 (4.1)	99/1893 (5.2)	508/1893 (26.8)	248/1893 (13.1)	345/1893 (18.2)

LNM, lymph node metastasis; Ut, upper thoracic; Mt, middle thoracic; Lt, lower thoracic; Um, upper mediastinal; Mm, middle mediastinal; Lm, lower mediastinal.

LNM distribution according to location of T

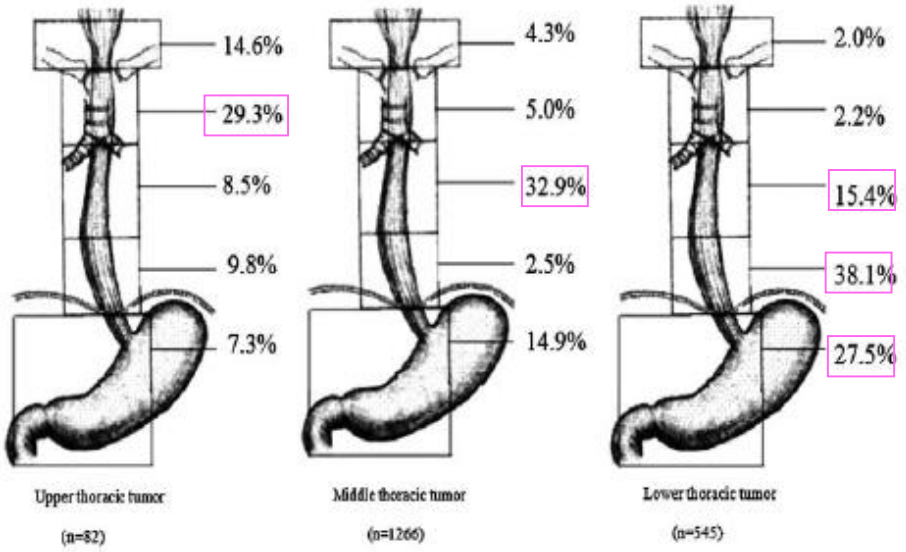

FIGURE 1. Rate of LNM in different regions according to the location of the primary tumor. LNM, lymph node metastasis.

J Thorac Oncol. 2013;8: 359-365

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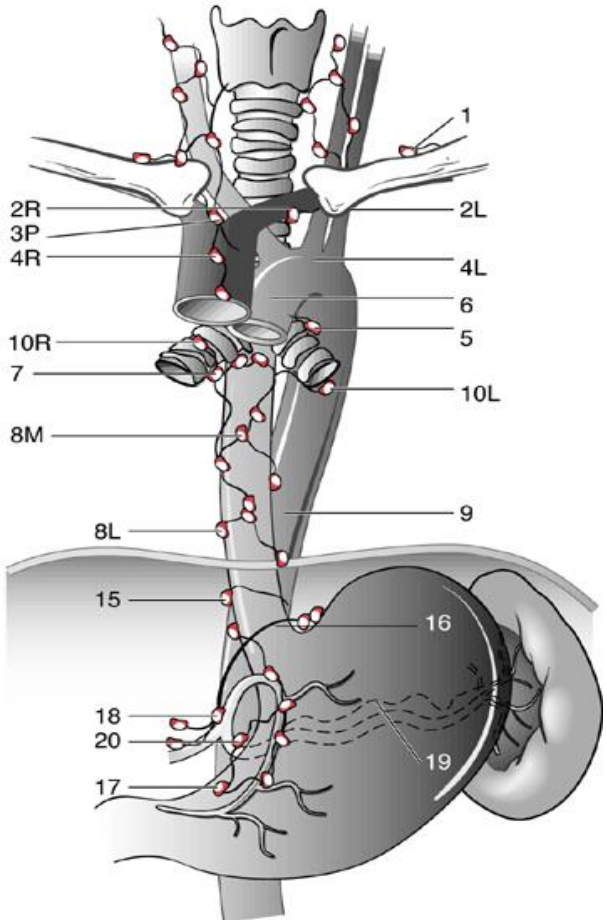
Defining elective nodal CTV



1	Supraclavicular nodes
2R	Right upper paratracheal nodes
2L	Left upper paratracheal nodes
3P	Posterior mediastinal nodes
4R	Right lower paratracheal nodes
4L	Left lower paratracheal nodes
5	Aortopulmonary nodes
6	Anterior mediastinal nodes
7	Subcarinal nodes
8M	Middle paraesophageal lymph nodes
8L	Lower paraesophageal lymph nodes
9	Pulmonary ligament nodes
10R	Right tracheobronchial nodes
10L	Left tracheobronchial nodes
15	Diaphragmatic nodes
16	Paracardial nodes
17	Left gastric nodes
18	Common hepatic nodes
19	Splenic nodes
20	Celiac nodes

RTOG Staging system

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Defining elective nodal CTV

Levels	Cervical	Upper	Middle	Lower	ADC Distal	Siewert I	Siewert II
1	×	×					
2R/2L	×	×	×				
3P	×	×					
4R/4L	×	×					
5		×	×				
6	Anterior Mediastinal						
7		×	×				
8M			×				
8L			×	×	×	×	×
9			×	×			
10R/10L			×				
15				×	×	×	×
16				×	×	×	×
17			×	×	×	×	×
18	Common Hepatic						
19	Splenic						
20			×	×	×	×	×

RTOG recommandations

RTOG recommendations

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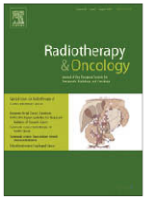
Defining elective nodal CTV

Radiotherapy and Oncology 92 (2009) 164–175

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Guidelines

EORTC-ROG expert opinion: Radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach

Oscar Matzinger[a,b,*], Erich Gerber[c], Zvi Bernstein[d], Philippe Maingon[e], Karin Haustermans[f], Jean François Bosset[g], Akos Gulyban[a], Philip Poortmans[h], Laurence Collette[a], Abraham Kuten[d]

[a] *EORTC Headquarters, Brussels, Belgium*
[b] *CHU Vaudois, Department of Radiation Oncology, Lausanne, Switzerland*
[c] *Radiation Oncologist, Vienna, Austria*
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[h] *Dr. Bernard Verbeeten Institute, Department of Radiation Oncology, Tilburg, The Netherlands*

Defining elective nodal CTV

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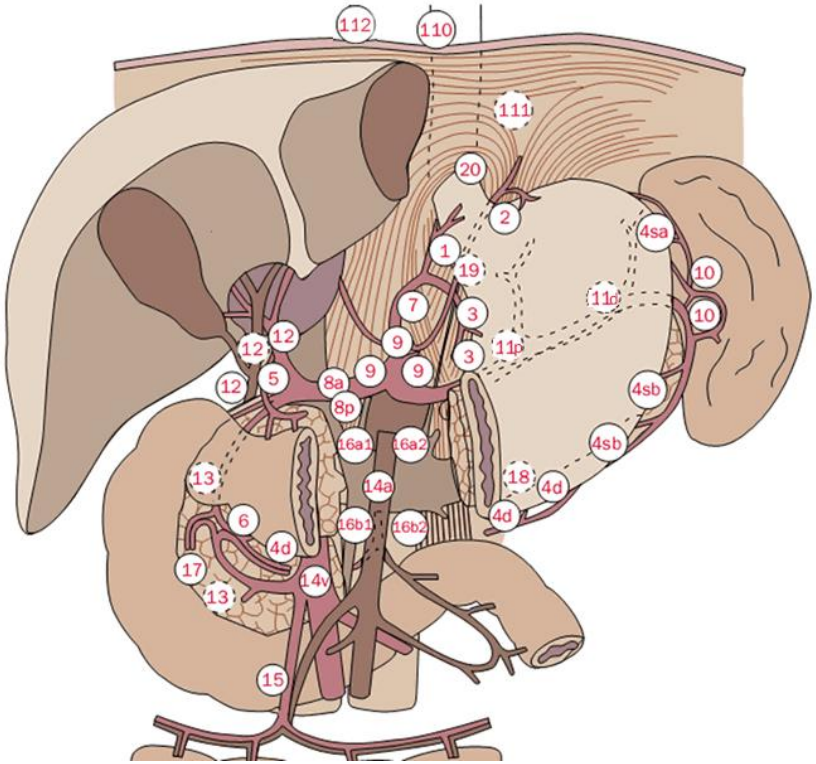
No. 1	Right paracardial LN
No. 2	Left paracardial LN
No. 3	LN along the lesser curvature
No. 4sa	LN along the short gastric vessels
No. 4sb	LN along the left gastroepiploic vessels
No. 4d	LN along the right gastroepiploic vessels
No. 5	Suprapyloric LN
No. 6	Infrapyloric LN
No. 7	LN along the left gastric artery
No. 8a	LN along the common hepatic artery (Anterosuperior group)
No. 8p	LN along the common hepatic artery (Posterior group)
No. 9	LN around the celiac artery
No. 10	LN at the splenic hilum
No. 11p	LN along the proximal splenic artery
No. 11d	LN along the distal splenic artery
No. 12a	LN in the hepatoduodenal ligament (along the hepatic artery)
No. 12b	LN in the hepatoduodenal ligament (along the bile duct)
No. 12p	LN in the hepatoduodenal ligament (behind the portal vein)
No. 13	LN on the posterior surface of the pancreatic head
No. 14v	LN along the superior mesenteric vein
No. 14a	LN along the superior mesenteric artery
No. 15	LN along the middle colic vessels
No. 16a1	LN in the aortic hiatus
No. 16a2	LN around the abdominal aorta (from the upper margin of the celiac trunk to the lower margin of the left renal vein)
No. 16b1	LN around the abdominal aorta (from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery)
No. 16b2	LN around the abdominal aorta (from the upper margin of the inferior mesenteric artery to the aortic bifurcation)
No. 17	LN on the anterior surface of the pancreatic head
No. 18	LN along the inferior margin of the pancreas
No. 19	Infradiaphragmatic LN
No. 20	LN in the esophageal hiatus of the diaphragm
No. 110	Paraesophageal LN in the lower thorax
No. 111	Supradiaphragmatic LN
No. 112	Posterior mediastinal LN



The classification of the lymph node stations of the stomach and the perigastric region according to the JGCA

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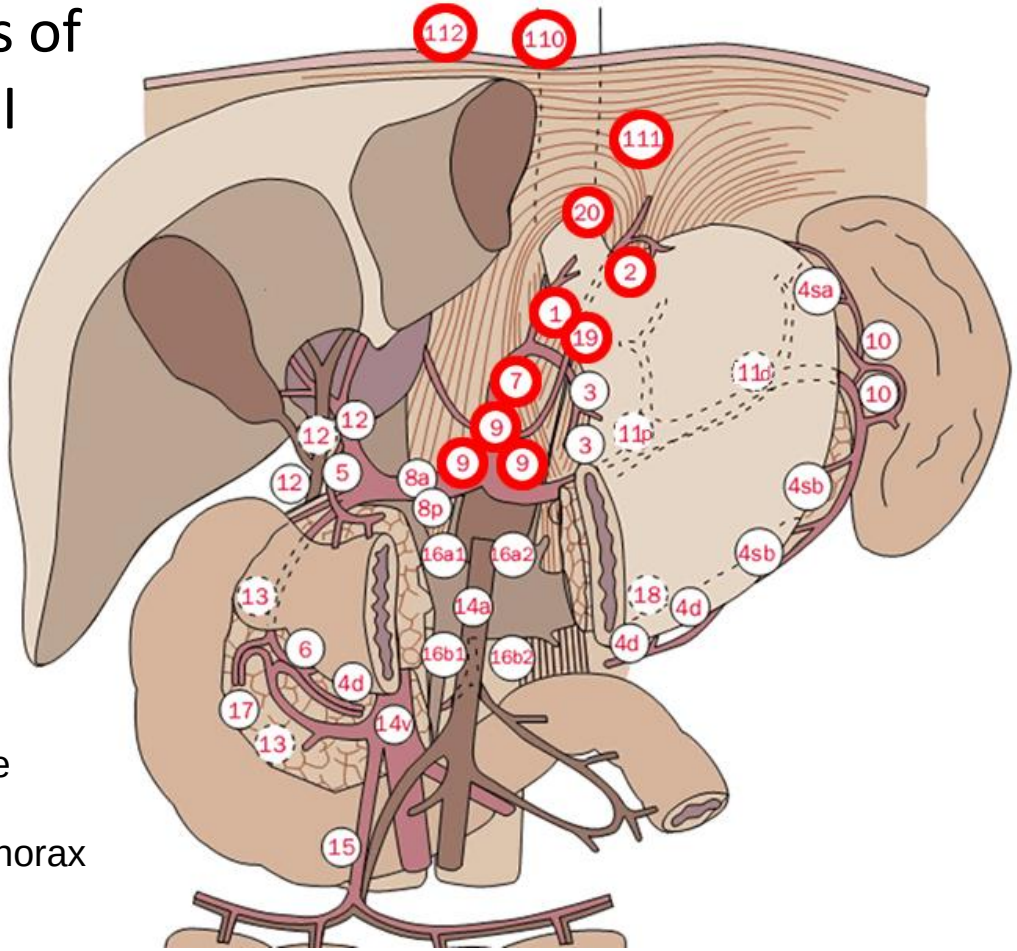
Defining elective nodal CTV

Lymph node stations of GEJ tumors: Type I



1 Right paracardial LN
2 Left paracardial LN
7 LN along the left gastric artery
9 LN around the celiac artery
19 Infradiaphragmatic LN
20 LN in the oesophageal hiatus of the diaphragm
110 Paraoesophageal LN in the lower thorax
111 Supradiaphragmatic LN
112 Posterior mediastinal LN

Defining elective nodal CTV

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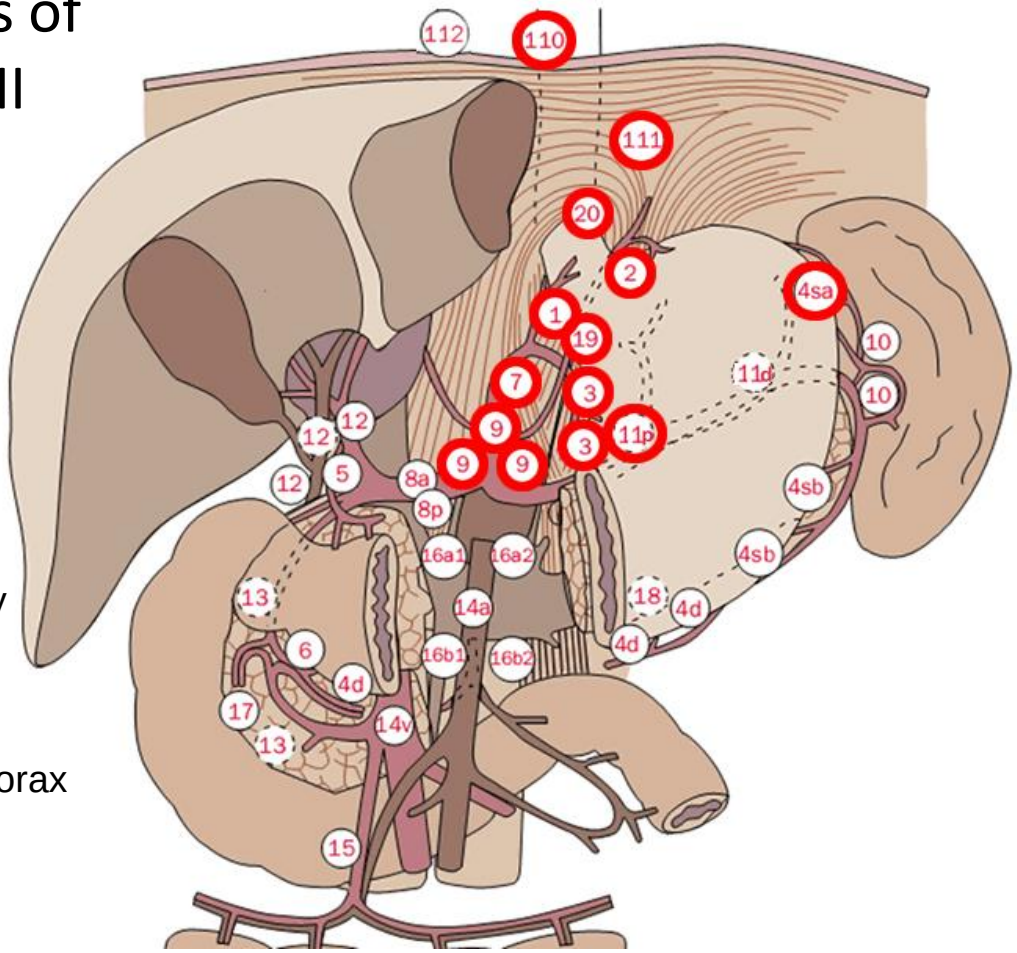
Lymph node stations of GEJ tumors: Type II

1 Right paracardial LN
2 Left paracardial LN
3 LN along the lesser curvature
4sa LN along the short gastric vessels
7 LN along the left gastric artery
9 LN around the celiac artery
11p LN along the proximal splenic artery
19 Infradiaphragmatic LN
20 LN in the oesophageal hiatus of the diaphragm
110 Paraoesophageal LN in the lower thorax
111 Supradiaphragmatic LN



Defining elective nodal CTV

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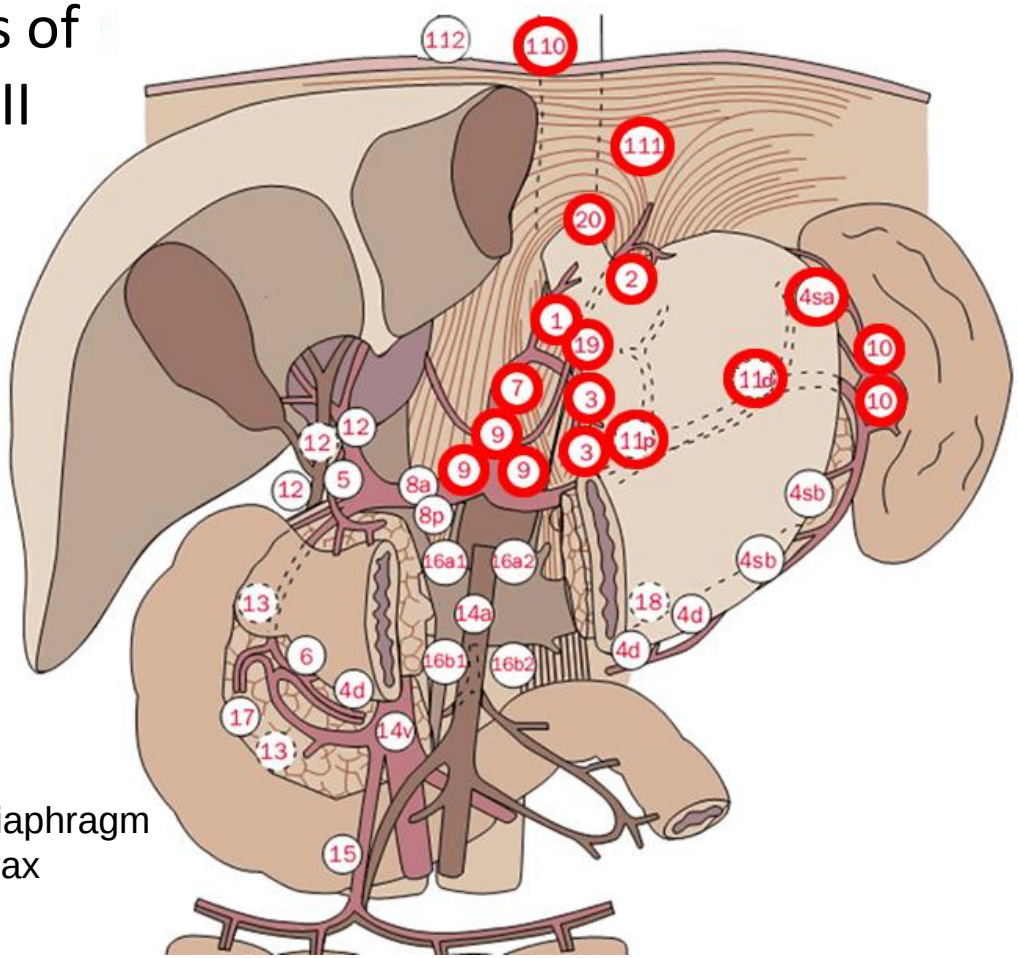
Lymph node stations of GEJ tumors: Type III



1 Right paracardial LN
2 Left paracardial LN
3 LN along the lesser curvature
4sa LN along the short gastric vessels
7 LN along the left gastric artery
9 LN around the celiac artery
10 LN at the splenic hilum
11p LN along the proximal splenic artery
11d LN along the distal splenic artery
19 Infradiaphragmatic LN
20 LN in the oesophageal hiatus of the diaphragm
110 Paraoesophageal LN in the lower thorax
111 Supradiaphragmatic LN

Defining elective nodal CTV

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Other consensus atlas from US

Clinical Investigation

Expert Consensus Contouring Guidelines for Intensity Modulated Radiation Therapy in Esophageal and Gastroesophageal Junction Cancer

Abraham J. Wu, MD,* Walter R. Bosch, DSc,† Daniel T. Chang, MD,‡ Theodore S. Hong, MD,§ Salma K. Jabbour, MD,‖ Lawrence R. Kleinberg, MD,¶ Harvey J. Mamon, MD, PhD,# Charles R. Thomas Jr, MD,** and Karyn A. Goodman, MD*

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Received Nov 16, 2014, and in revised form Mar 24, 2015. Accepted for publication Mar 26, 2015.

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Radiotherapy considerations

- Defining GTV
- Marginis from GTV to CTV
- Defining elective nodal CTV
- Organ motion and ITV

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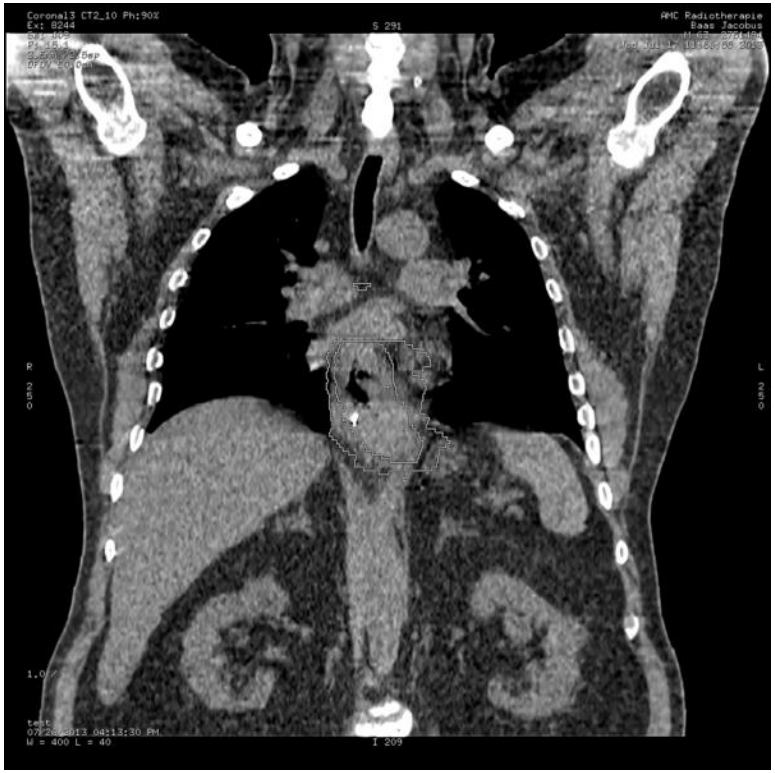
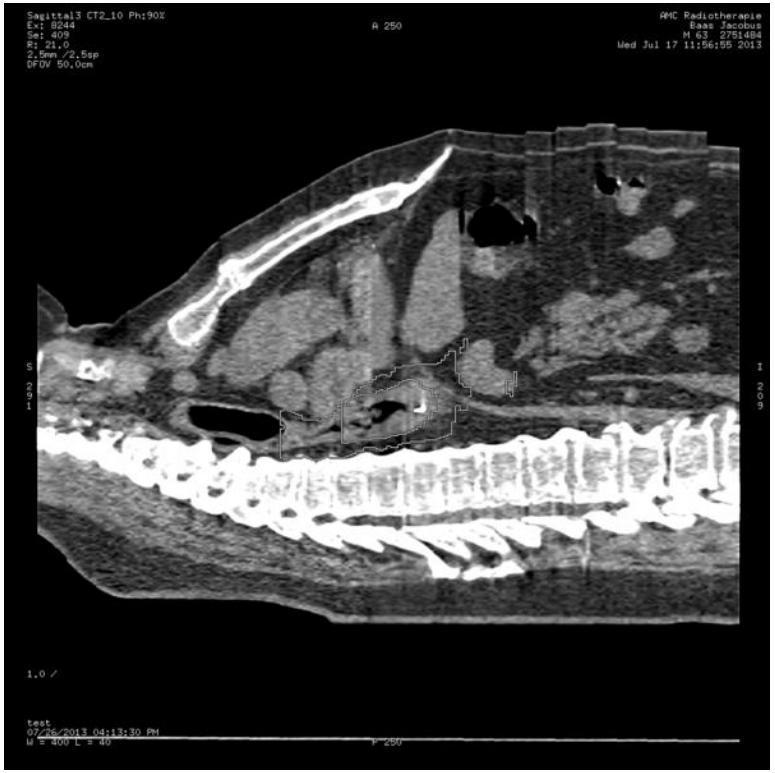
Organ motion and PTV

Is esophagus a mobile organ?





Organ motion and PTV

Effect of breathing on oesophagus

	Thoracic part	Abdominal part
Yaremko 2008	8 mm	10 mm
Welch 1982	4 mm	6 mm
Dieleman 2007	7 mm	9 mm

Organ motion and PTV

CTV-ITV margins proximal and middle- esophageal tumors

- APPA: 7-8 mm
- Lateral: 5-7 mm
- Craniocaudal: 10 mm

CTV-ITV margins lower- esophageal and EGJ tumors

- 4D-CT recommended for personalized ITV

Wei Wang Onco Targ Ther 2016

Radiotherapy technique

"Treatment of esophageal cancer is a great challenge for every radiotherapy oncologist"

- Large volumes
- Dose range 40 -60 Gy
- Concurrent chemotherapy
- Normal tissue tollerance dose

Radiotherapy technique

EBRO 2017

Normal tissue tollerance dose

Table 2 Summary of Dosimetric Parameters for Clinical Toxicity

Organ	Emami[2] TD 5/5	Emami[2] TD 50/5	Endpoints	Dosimetric Parameters	Endpoints
Brainstem	1/3: 60 Gy 2/3: 53 3/3: 50	1/3: - 2/3: - 3/3: 65 Gy	Necrosis, infarction	V60 <0.9 mL	<5% grade≥1 toxicity
Spinal cord	5 cm: 50 Gy 10 cm: 50 20 cm: 47	5 cm: 70 Gy 10 cm: 70 20 cm: -	Myelitis, necrosis	max <50 Gy	<5% grade≥3 toxicity
Cervical spinal cord	—	—	—	EUD <52 Gy, max. <55 Gy	<5% grade≥3 toxicity
Parotid	1/3: - 2/3: 32 Gy 3/3: 32	1/3: - 2/3: 46 Gy 3/3: 46	Xerostomia	Mean dose <26 Gy	Late grade 2 xerostomia resulting from >75% functional loss
Lung	1/3: 45 Gy 2/3: 30 3/3: 17.5	1/3: 65 Gy 2/3: 40 3/3: 24.5	Pneumonitis	V13<40% V20<25-30% V30<10-15% MLD<10-20 Gy	Late grade 2 in <10-20% Late grade 3 in <5-10%
Heart	1/3: 60 Gy 2/3: 45 3/3: 40	1/3: 70 Gy 2/3: 55 3/3: 50	Pericarditis	V33 <60%, V38 <33% V42 <20%	5% excess cardiac mortality
Esophagus	1/3: 60 Gy 2/3: 58 3/3: 55	1/3: 72 Gy 2/3: 70 3/3: 68	Clinical stricture/ perforation	V50 and S50 <30%	5% risk of late toxicity
Rectum	1/3: 60 Gy 2/3: 60 3/3: 60	1/3: 80 Gy 2/3: 80 3/3: 80	Proctitis, necrosis, fistula, stenosis	V70-80 ≤15 cc V70≤20-25%	Late grade 2 in <5-10%
Liver	1/3: 50 Gy 2/3: 35 3/3: 30	1/3: 55 Gy 2/3: 45 3/3: 40	Liver failure	1/3: 40-80 Gy 2/3: 30-50 3/3: 25-35	Late grade 3-4 liver toxicity <5%
Kidney	1/3: 50 Gy 2/3: 30 3/3: 23	1/3: - 2/3: 40 Gy 3/3: 28	Clinical nephritis	median dose <17.5 Gy	anemia, azotemia, hypertension and edema

Milano MT, Semin Radiat Oncol 2007:17;131-40

Radiotherapy technique

EBRO 2017

OAR: Spinal cord

- Spinal cord injury rare but extremely debilitating

  paralysis, sensory, deficits, pain, and bowel/bladder incontinence

- Schultheiss review:

  risk of myelopathy to be 0.2% at 50 Gy and 5% at 59.3 Gy

- Similar conclusions published by QUANTEC

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Spinal cord	Partial organ	3D-CRT	Myelopathy	Dmax = 50	0.2	Including full cord cross-section
	Partial organ	3D-CRT	Myelopathy	Dmax = 60	6	
	Partial organ	3D-CRT	Myelopathy	Dmax = 69	50	

Schultheiss TE, Kun LE, Ang KK, et al. Radiation response of the central nervous system. Int J Radiat Oncol Biol Phys 1995;31:1093–1112.

Radiotherapy technique

EBRO 2017

OAR: Heart

Most relevant cardiac toxicities

- Clinical pericarditis
- Long-term cardiac mortality

QUANTEC:

Organ	Endpoint	Rate (%)	Dose-volume parameter	D_{max} (Gy)	D_{mean} (Gy)
Heart	Pericarditis	<15	V30 <46%		<26
	Long-term cardiac mortality	<1	V25 <10%		

Radiotherapy technique

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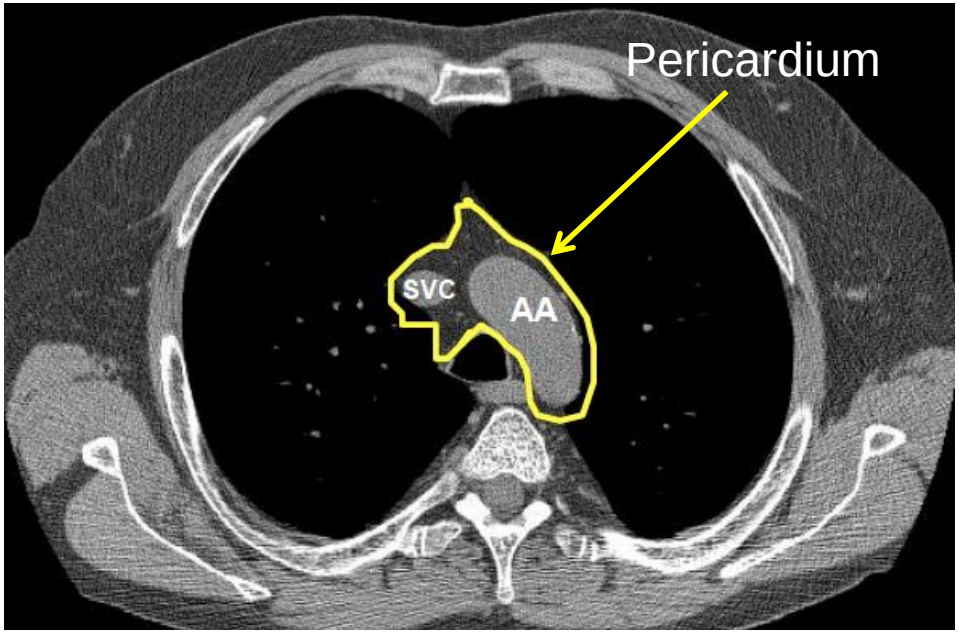
OAR: Heart



Pericardium	The structure of pericardium includes pericardial fatty tissue, part of great vessels, normal recesses, pericardial effusion (if applicable) and heart chambers. Pericardium starts at one slice above the top of aortic arch, ends at the last slice of heart apex at diaphragm. Pericardium includes the heart.

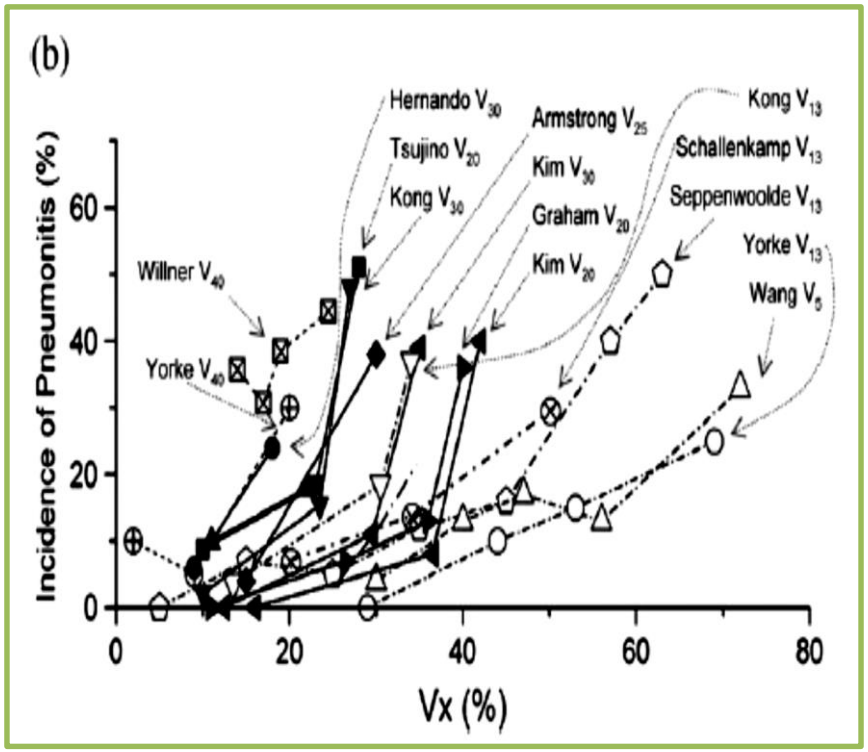
RTOG 1106 OAR Atlas

Radiotherapy technique

OAR: Lung

QUANTEC reviews >70 articles: mean lung doses & Vx parameters

- no clear threshold dose
- 20% risk of pneumonitis for a **mean lung dose** of 20 Gy
- **V20** most useful parameter



Marks L. IJROBP 2010

Radiotherapy technique

EBRO 2017

OAR: Lung

QUANTEC:

Organ	Endpoint	Rate (%)	Dose-volume parameter	D_{max} (Gy)	D_{mean} (Gy)
Lung	Symptomatic pneumonitis	5	V5 <42%, V20 <22%		7
		10	V20 <31%		13
		20	V20 <40%		20
		30			24
		40			27

NCCN Guidelines

- Spinal cord — Dmax = 45Gy
- Heart — 1/3 < 40Gy, ALARA left ventricule
- Lungs — D max normal lung (2 cm outside PTV) < 40 Gy
  V 20 Gy < 25%;
  V5 Gy < 50 %

Radiotherapy technique

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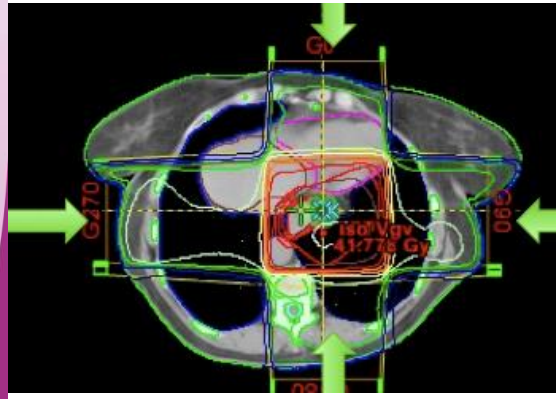
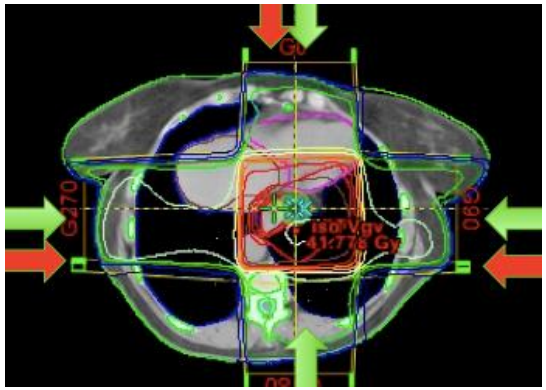
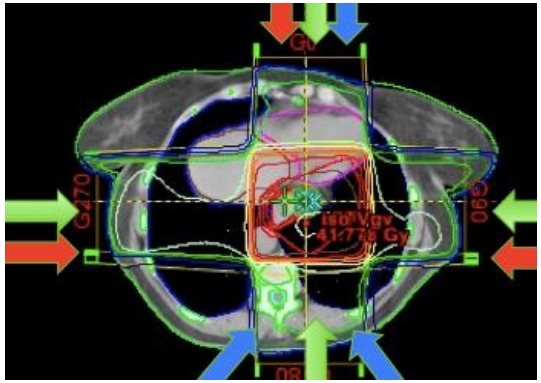
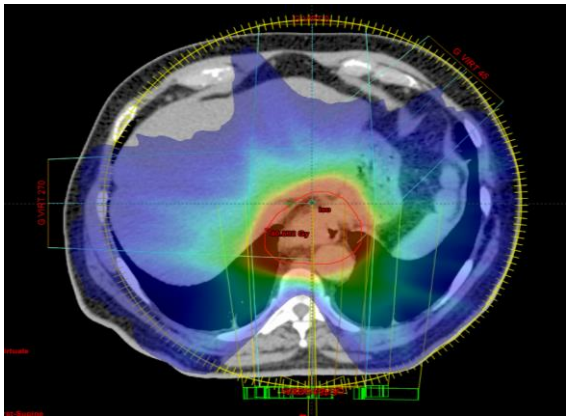
3D-CRT or IMRT/VMAT







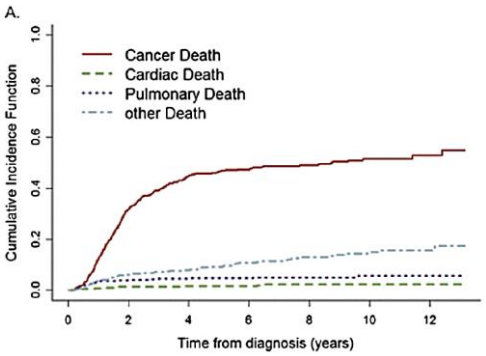


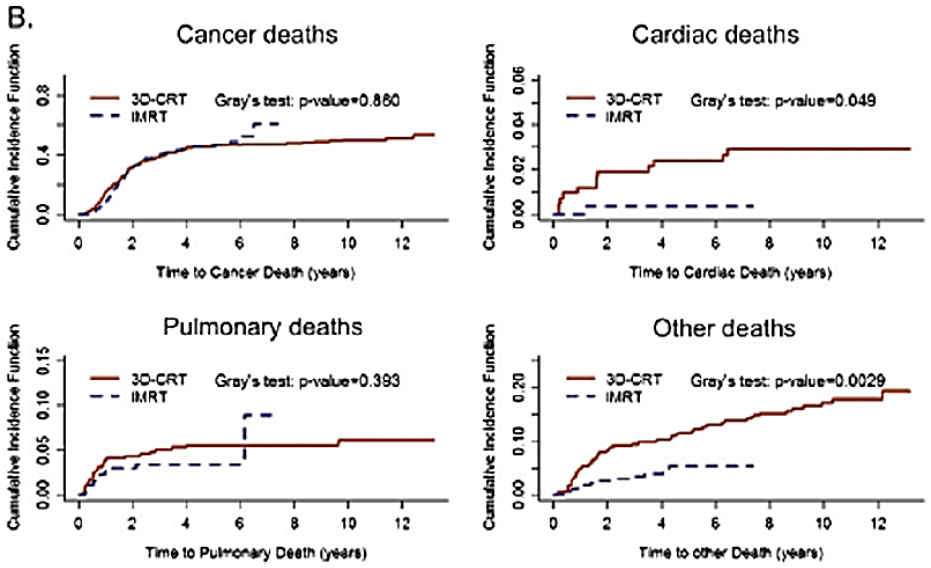
Radiotherapy technique

EBRO 2017

3D-CRT or IMRT/VMAT

Propensity score-based comparison of long-term outcomes with 3-dimensional conformal radiotherapy vs intensity-modulated radiotherapy for esophageal cancer.





Conclusions—Overall survival, locoregional control, and non-cancer related deaths were significantly better for IMRT compared to 3DCRT. Although these results need confirmation, IMRT should be considered for the treatment of esophageal cancer.

Int J Radiat Oncol Biol Phys. 2012 Dec 1;84(5):1078-85.

Radiotherapy technique

EBRO 2017

3D-CRT or IMRT/VMAT

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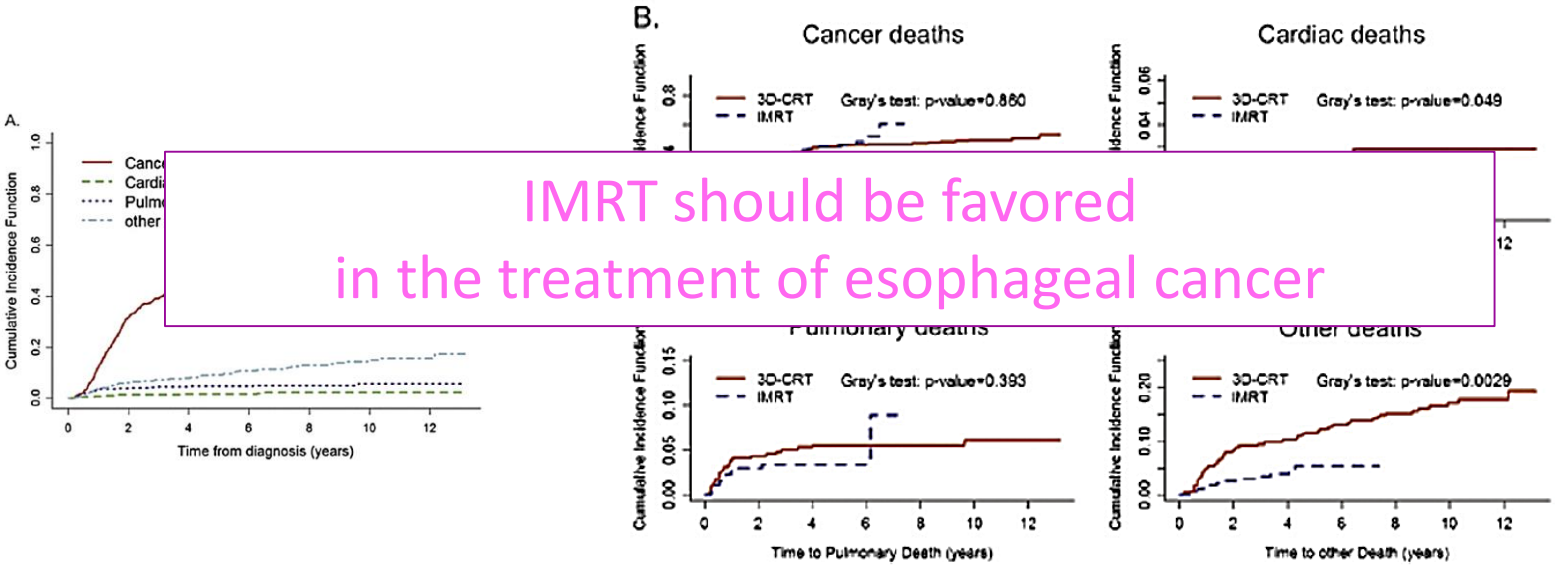


IMRT should be favored
in the treatment of esophageal cancer

Conclusions—Overall survival, locoregional control, and non-cancer related deaths were significantly better for IMRT compared to 3DCRT. Although these results need confirmation, IMRT should be considered for the treatment of esophageal cancer.

Int J Radiat Oncol Biol Phys. 2012 Dec 1;84(5):1078-85.

Radiotherapy technique

EBRO 2017

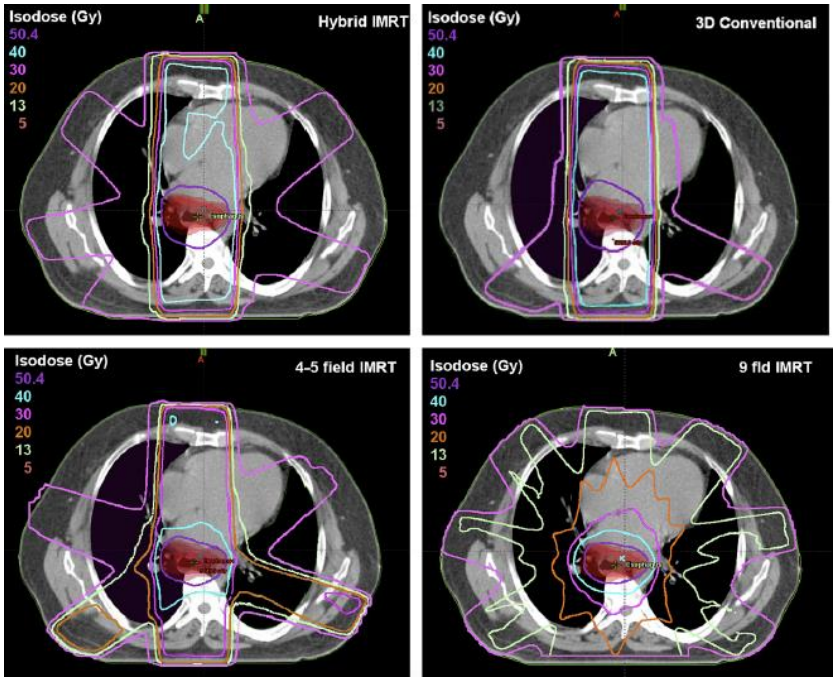
Meeting lung constrains sometime is difficult also with IMRT or VMAT

HYBRID IMRT FOR TREATMENT OF CANCERS OF THE LUNG AND ESOPHAGUS

CHARLES S. MAYO, PH.D.,* MARCIA M. URIE, PH.D.,*† THOMAS J. FITZGERALD, M.D.,*†
LINDA DING, PH.D.,* YUAN CHYUAN LO, PH.D.,* AND MADELEINE BOGDANOV, CMD.*

* University of Massachusetts Medical School, Department of Radiation Oncology, Worcester, MA;
† Quality Assurance Review Center, Providence, RI

Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 5, pp. 1408–1418, 2008



Hybrid plan compared to IMRT reduces low-medium dose to total and controlateral lung.

Largest reductions were for controlateral V5, V13 andV20 respectively -16%, 20% e 7%

Int J Radiat Oncol Biol Phys. 2012 Dec 1;84(5):1078-85.

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Gastric cancer

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Gastric cancer

- 5th most common cancer worldwide (988600)
- 3rd leading cause of cancer death (737400)
- 8% of all cancers
- Wide geographical variation

  high incidence Japan, Asia, Eastern Europe

  declining incidence - Western Europe, USA
- Marginal improvement in survival in last 2 decades (Overall survival 23% in 1990s vs.15% in 1970s)

Gastric cancer

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Depth of invasion	5 year survival (%)	Number of nodes involved	5 year survival (%)
Mucosa (Tis)	93	0	81
Submucosa (T1)	90	1-3	63
Muscle (T2)	77	4-6	11-37
Subserosa (T3)	60	7+	7
Serosa (T4a)	40		
Adjacent structures (T4b)	9		

Gastric cancer

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Patterns of failure after “curative” resection

	Incidence (%) in patient group		
Pattern of failure	Clinical	Reoperation	Autopsy
Locoregional*	38	64	80-93
Peritoneal seedling	23	39	30-50
Localised		18	
Diffuse		21	
Distant metastases	52	21	49

* Gastric bed / anastomosis / lymph nodes

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Gastric cancer - Treatment options

- Adjuvant therapies
- Neo-Adjuvants therapies

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Gastric cancer – adjuvant therapy

Radiation therapy alone

- Limited data
- No impact on survival, reduced local recurrence

Chemotherapy alone

- Historically over 30 (mostly small) randomised trials
- Meta-analyses suggest small benefit (HR ? 0.8)
- Recent positive studies:
  - ACTS-GC trial (oral TS-1)

    Sasako M *et al* (2011) J Clin Oncol 29:4387-4393
  - CLASSIC trial (capecitabine+oxaliplatin)

    Bang YJ *et al* (2012) Lancet 379:315-321

Concurrent chemo-radiation therapy

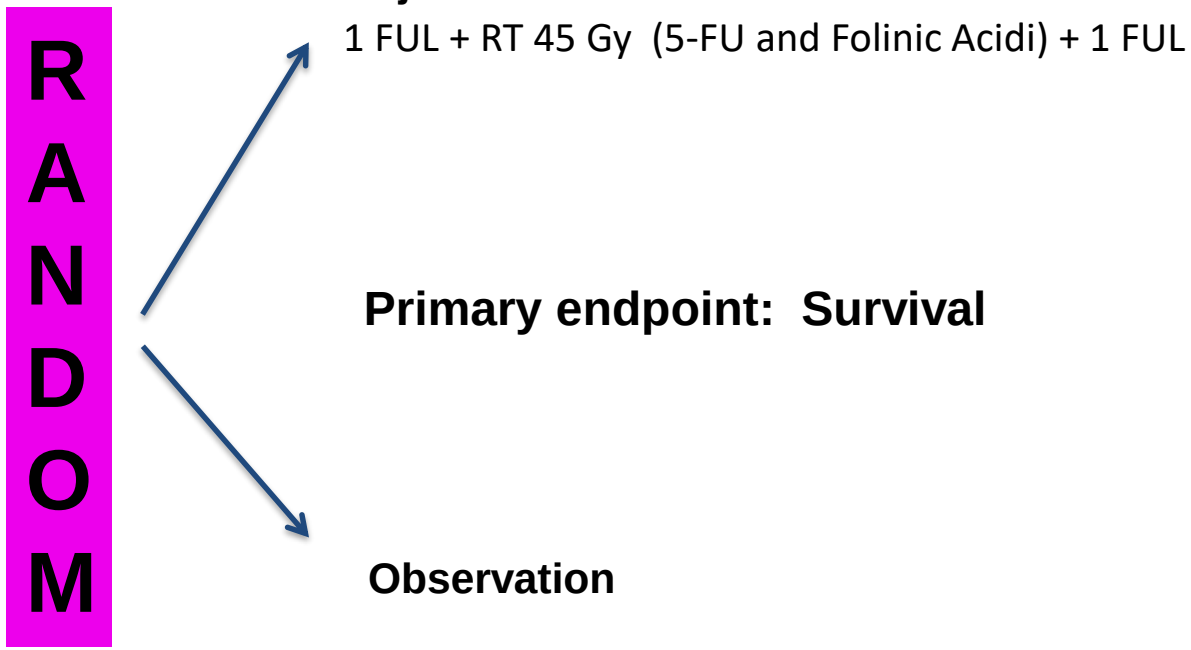
- No benefit in small randomized trials in 1970-80s
- Gastric Surgical Adjuvant Trial INT 0116 (Macdonald *et al* 2001)

Gastric cancer adjuvant chemoradiation

EBRO 2017

INT 0116

N 559
Stage I-IV-M0
R0 resection
D2 recommended



Macdonald JS et al (2001) NEJM 345:725-30
Updated: Smalley SR et al (2012) J Clin Oncol 30:2327-2333

Gastric cancer adjuvant chemoradiation

EBRO 2017

INT 0116

- 65% completed chemotherapy & chemo-radiation
- 4/282 treatment-related deaths (chemo-RT)
- No late toxicity reported in survivors

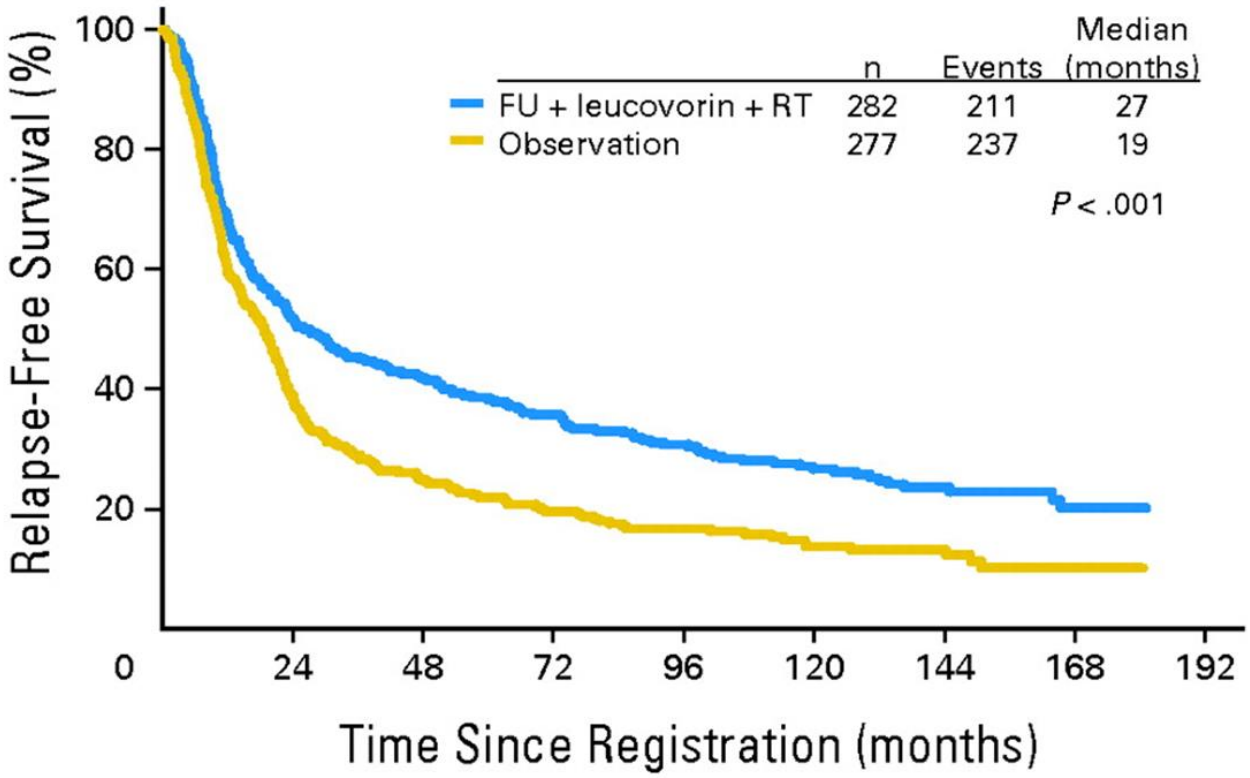
Macdonald JS et al (2001) NEJM 345:725-30
Updated: Smalley SR et al (2012) J Clin Oncol 30:2327-2333

Gastric cancer adjuvant chemoradiation

EBRO 2017

INT 0116

Relapse-free survival by intention-to-treat



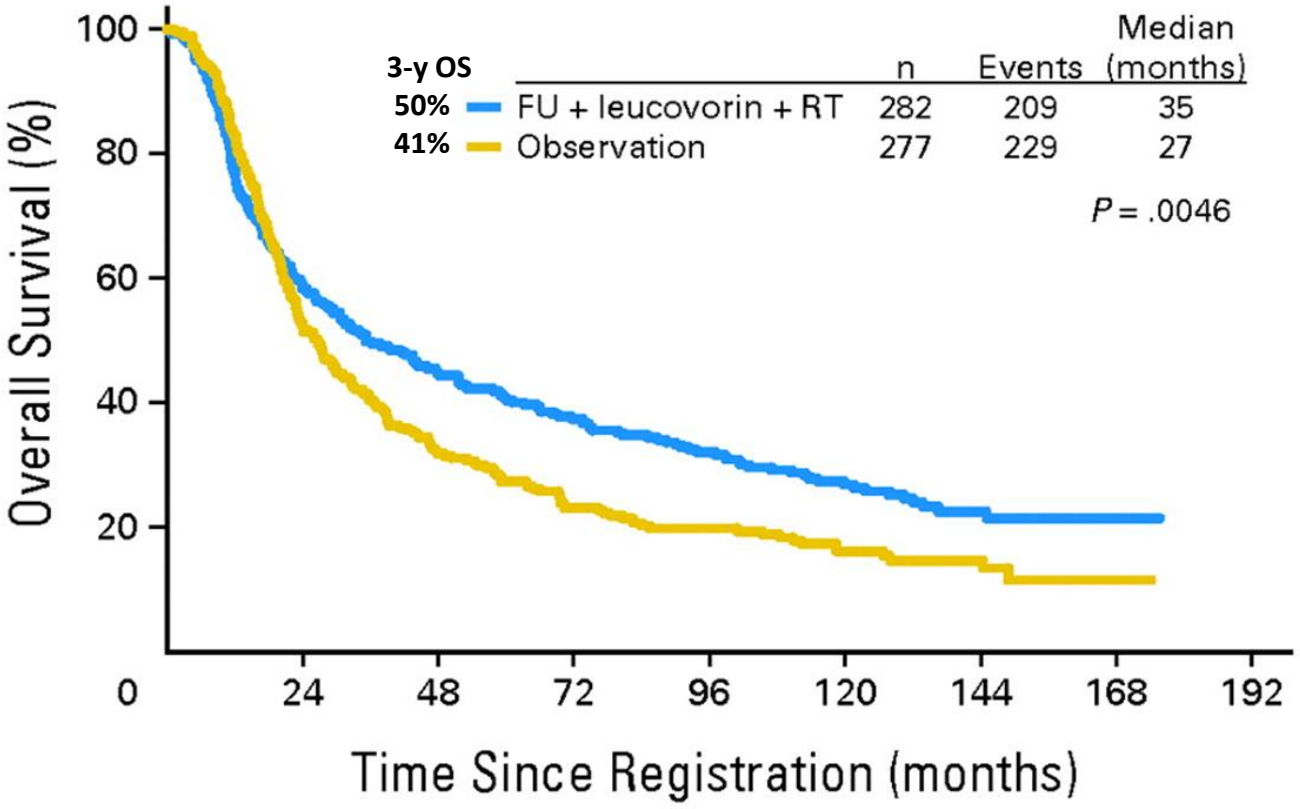
Smalley SR et al (2012) J Clin Oncol 30:2327-2333

Gastric cancer adjuvant chemoradiation

EBRO 2017

INT 0116

Overall survival by intention-to-treat



Smalley SR et al (2012) J Clin Oncol 30:2327-2333

Gastric cancer adjuvant chemoradiation

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INT 0116 Patterns of failure

Table 2.

Patterns of Failure by Arm

Relapse Status	Radiochemotherapy		Control(surgery alone)		Total	
	No.	%	No.	%	No.	%
No relapse*	135	48	67	24	202	36
Relapse*	147	52	210	76	357	64
Sites of relapse (% of those randomly assigned)*						
Local	7	2	21	8	28	5
Regional	62	22	109	39	171	31
Distant	46	16	49	18	95	17
Unknown site	32	11	31	11	63	11
Total	282		277		559	

- ↵* Indicates statistically significant comparisons. $P < .001$ for relapse *v* no relapse (χ^2); $P = .012$ for sites of relapse (among those with sites reported, χ^2 test for trend).

Smalley SR et al (2012) J Clin Oncol 30:2327-2333

Gastric cancer adjuvant chemoradiation

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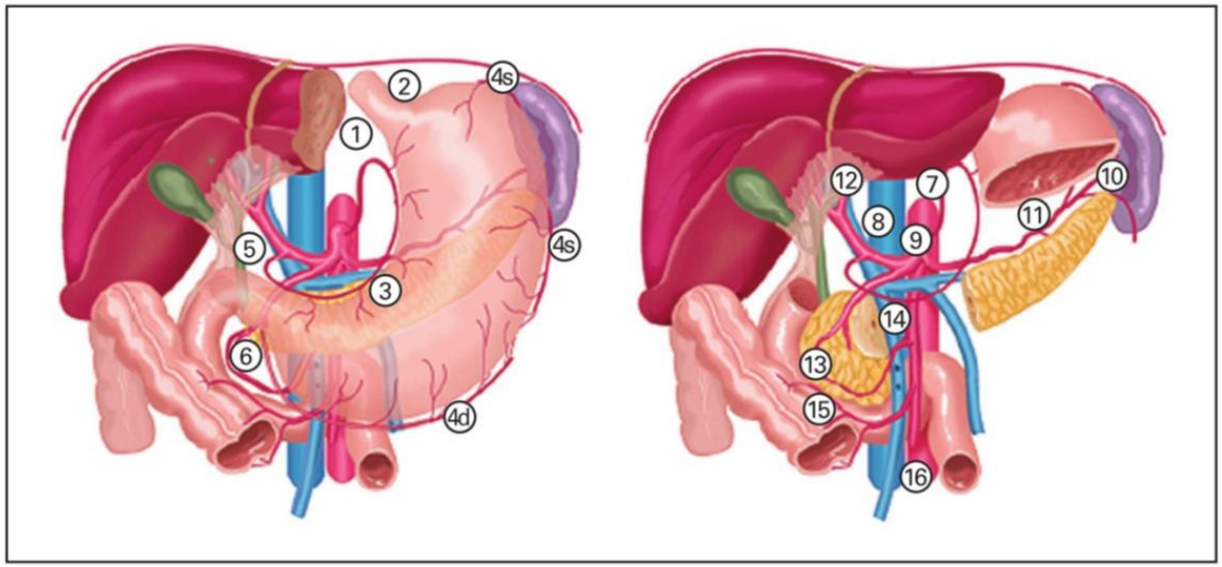
INT 0116

but

- D2 dissection recommended (done in 10%)
  - 54% D0 dissection, 36% D1, 10% D2

D2 or not D2?



Lymph node stations as defined by the Japanese Research Society for Gastric Cancer. The Maruyama Computer Program calculates the likelihood of disease (percentage) for each of these 16 lymph node stations.

From: Dikken JL et al (2010) J Clin Oncol 28:2430-2436

Gastric cancer adjuvant chemoradiation

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D2 or not D2?

Extended versus limited lymph nodes dissection technique for adenocarcinoma of the stomach (Review)

McCulloch P, Nita ME, Kazi H, Gama-Rodrigues J

THE COCHRANE COLLABORATION®

Gastric cancer adjuvant chemoradiation

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D2 or not D2?

Analysis 1.1. Comparison 1 RCTS, Outcome 1 5 Year Survival D2 vs D1 Randomised.

Review: Extended versus limited lymph nodes dissection technique for adenocarcinoma of the stomach

Comparison: 1 RCTS

Outcome: 1 5 Year Survival D2 vs D1 Randomised

Study or subgroup	Limited n/N	Extended n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bonenkamp 1995	171/380	156/331		66.2 %	0.92 [0.68, 1.23]
Cuschieri 1996	66/200	70/200		33.8 %	0.91 [0.60, 1.38]
Total (95% CI)	**580**	**531**		**100.0 %**	**0.92 [0.72, 1.17]**

Total events: 237 (Limited), 226 (Extended)
Heterogeneity: $Chi^2 = 0.00$, $df = 1$ ($P = 0.99$); $I^2 = 0.0\%$
Test for overall effect: $Z = 0.71$ ($P = 0.48$)

No survival benefit for D2 dissection

0.1 0.2 0.5 1 2 5 10
Favours treatment | Favours control

Analysis 1.4. Comparison 1 RCTS, Outcome 4 Operative Mortality.

Review: Extended versus limited lymph nodes dissection technique for adenocarcinoma of the stomach

Comparison: 1 RCTS

Outcome: 4 Operative Mortality

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bonenkamp 1995	32/331	15/380		52.9 %	2.60 [1.38, 4.90]
Cuschieri 1996	26/192	13/192		47.1 %	2.16 [1.07, 4.34]

But modern Japanese trials consistently show ~ 1% post-operative mortality for ≥ D2 surgery

Gastric cancer adjuvant chemoradiation

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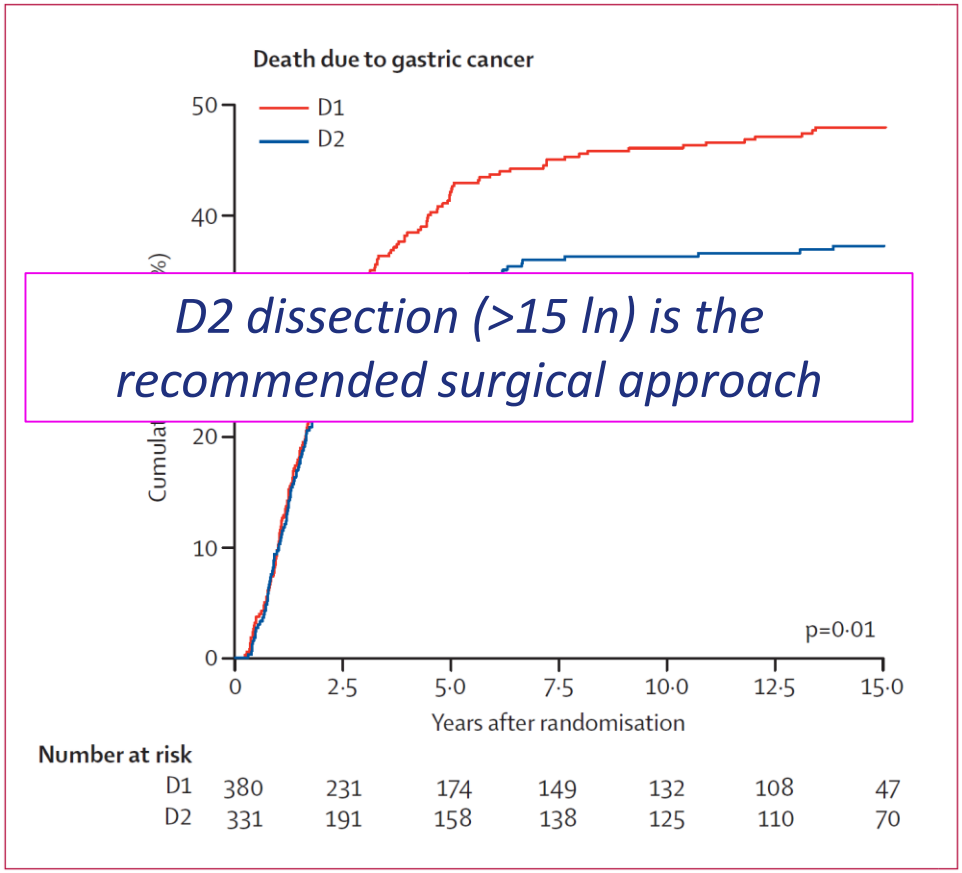
Surgical treatment of gastric cancer
15 years follow-up results D1-D2 study



D2 dissection (>15 ln) is the recommended surgical approach

Songun et al. Lancet Oncol 2010

Gastric cancer adjuvant chemoradiation

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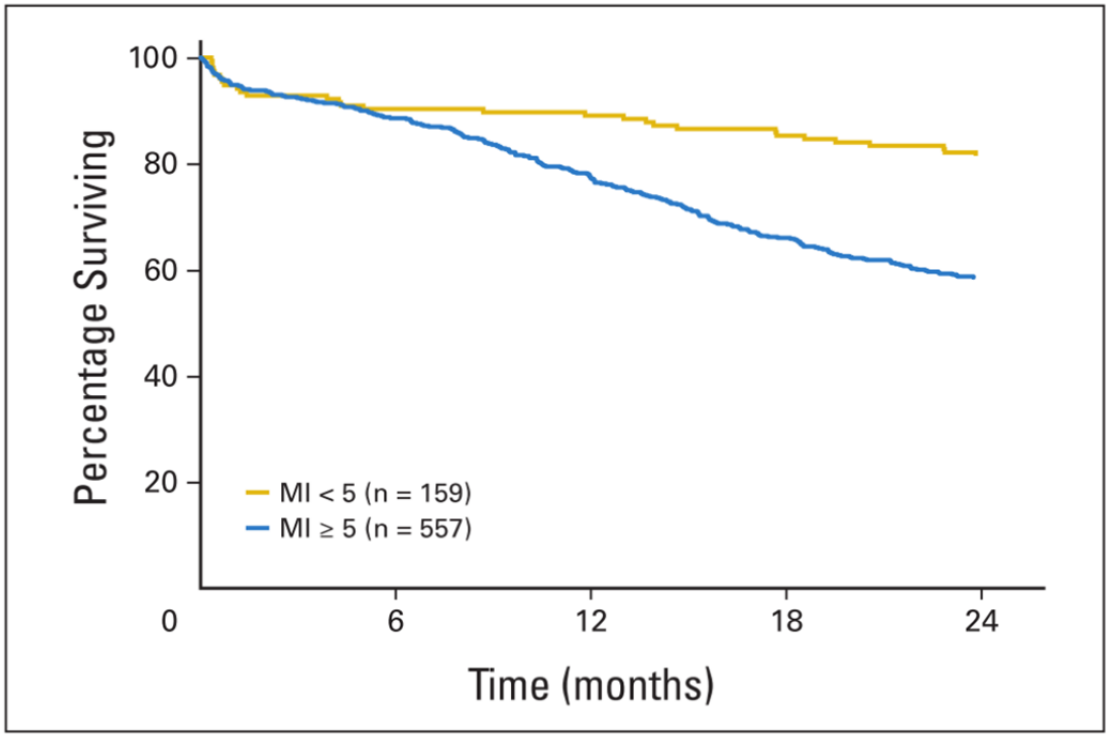
Maruyama Index of un-resected disease is a strong independent predictor of survival



Kaplan-Meier survival curves for Maruyama Index (MI) less than 5 and MI ≥ 5: pooled data from all 716 patients in which the MI was calculated. $P < .001$.

From: Dikken JL et al (2010) J Clin Oncol 28:2430-2436

Gastric cancer adjuvant chemoradiation

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INT 0116 Was the surgery sub-optimal?

Maruyama Index of analysis of INT 0116-eligible patients
suggests surgical under-treatment

See Hundahl SA et al (2002) Ann Surg Oncol 9:278-286

Gastric cancer adjuvant chemoradiation

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If D2 is the standard
What is the role of postoperative chemo-RT on recurrence patterns in gastric cancer?

Results controvrsial

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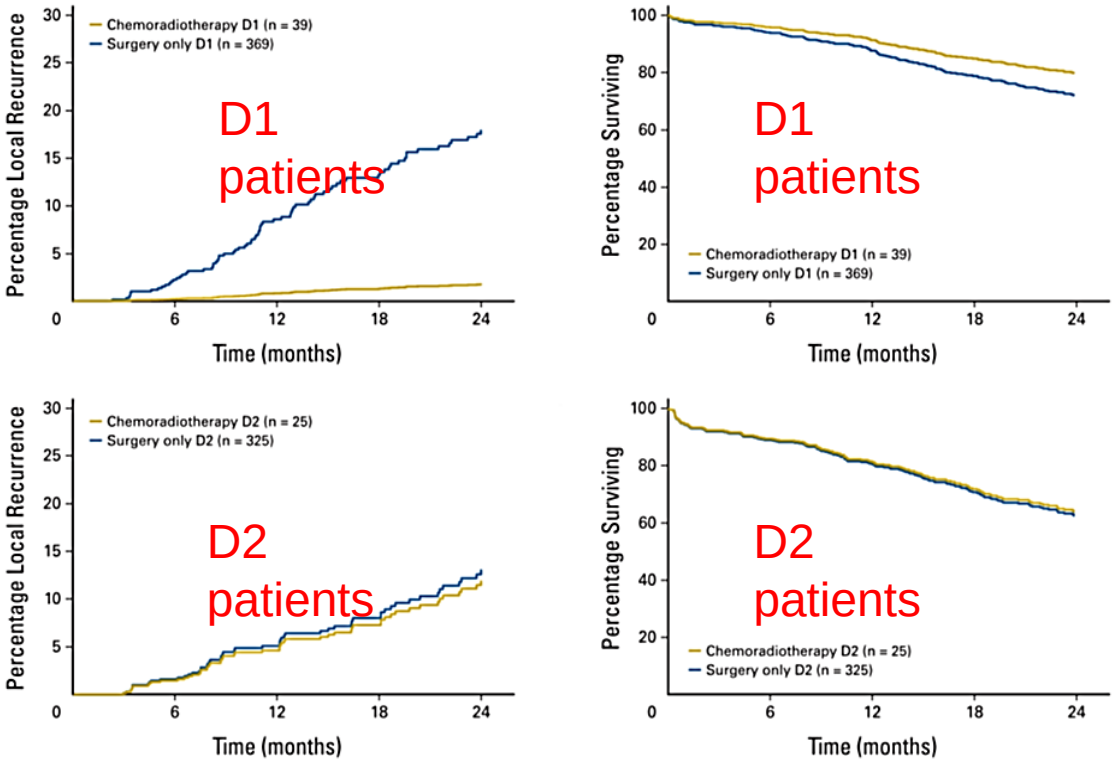
Gastric cancer adjuvant chemoradiation

Retrospective comparison of patients treated in phase I/II post-op CRT trials vs. Dutch surgical trial D1 and D2 patients



Dikken JL et al (2010) J Clin Oncol 28:2430-2436

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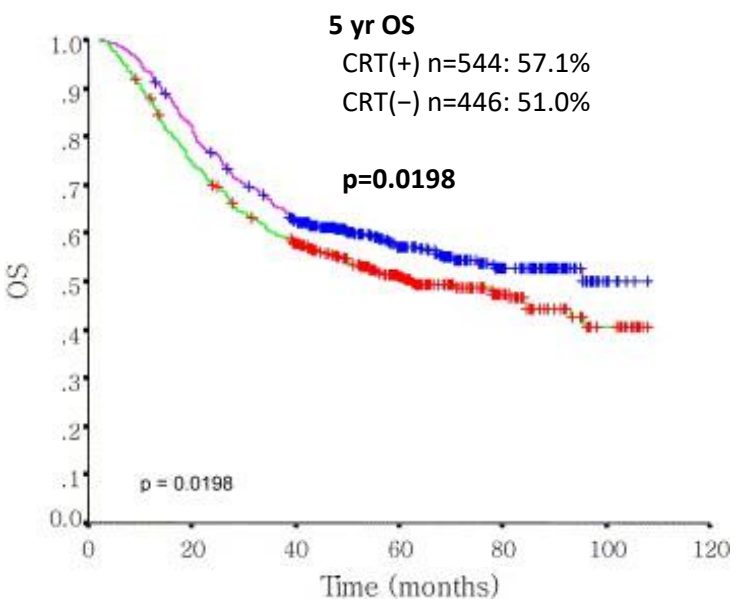
Gastric cancer adjuvant chemoradiation

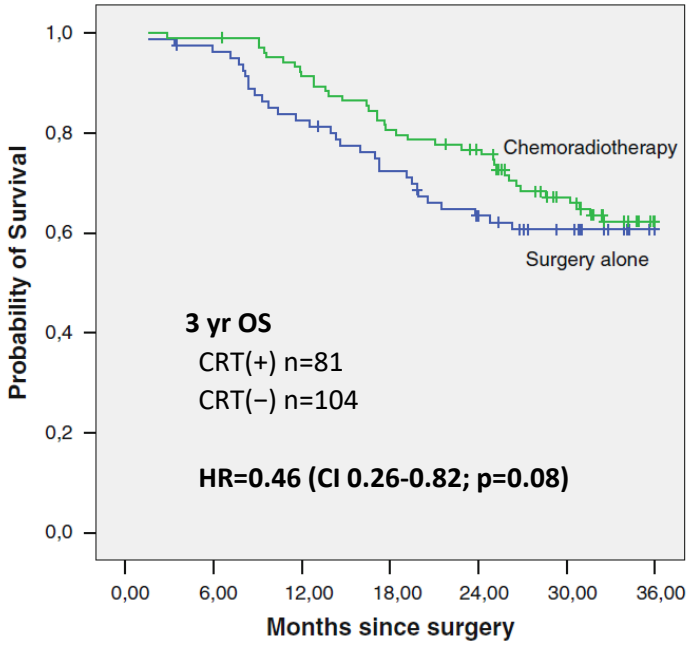
Adjuvant chemoradiotherapy in D2-resected gastric cancer patients: retrospective studies

Eastern countries



Kim et al. IJROBP 2005

Western countries



Jácome et al. Gastric Cancer 2013

Gastric cancer adjuvant chemoradiation

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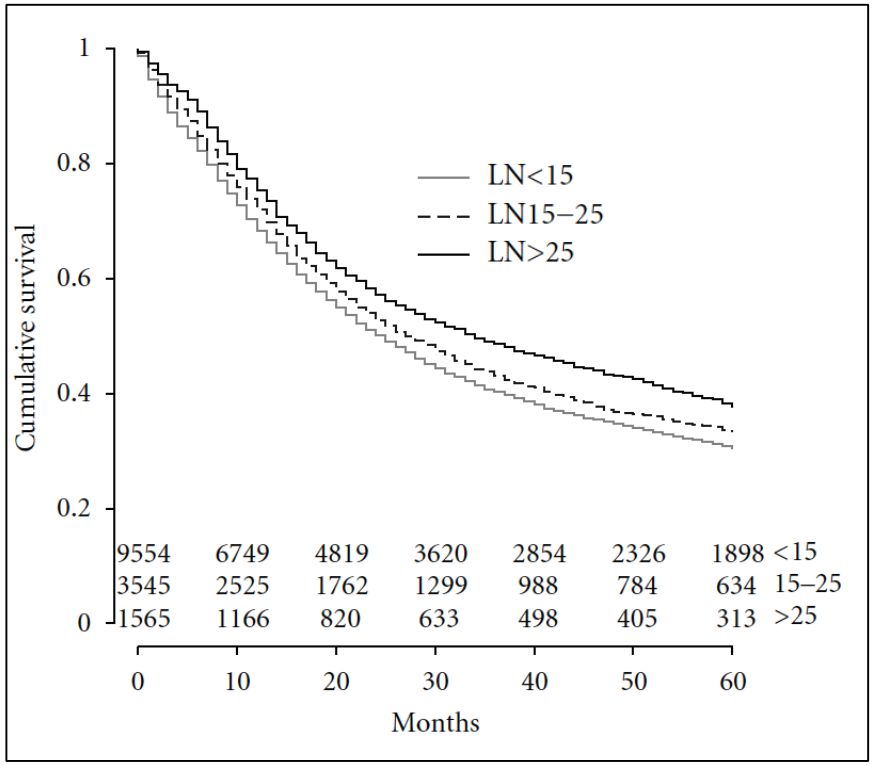
SEER registry: Survival benefit of adjuvant chemoradiotherapy following gastrectomy persists after extended lymphadenectomy



Variable	HR	*P* value
No XRT	1.00	<0.001
Adjuvant XRT	0.67	
Age		
≤60	1.00	<0.001
>60	1.49	
Gender		
Male	1.00	<0.001
Female	0.88	
Race		
White	1.00	
Black	1.06	0.075
Other	0.77	<0.001
Lymph nodes		
LN <15 : >25	0.65	<0.001
LN 15–26 : >25	0.84	<0.001
Stage		
IA	1.00	
IB	1.689	0.004
II	3.08	<0.001
IIIA	4.44	<0.001
IIIB	6.02	0.003
IV (M0)	7.14	<0.001

Snyder et al. Int J Surg Oncol 2012

Gastric cancer adjuvant chemoradiation

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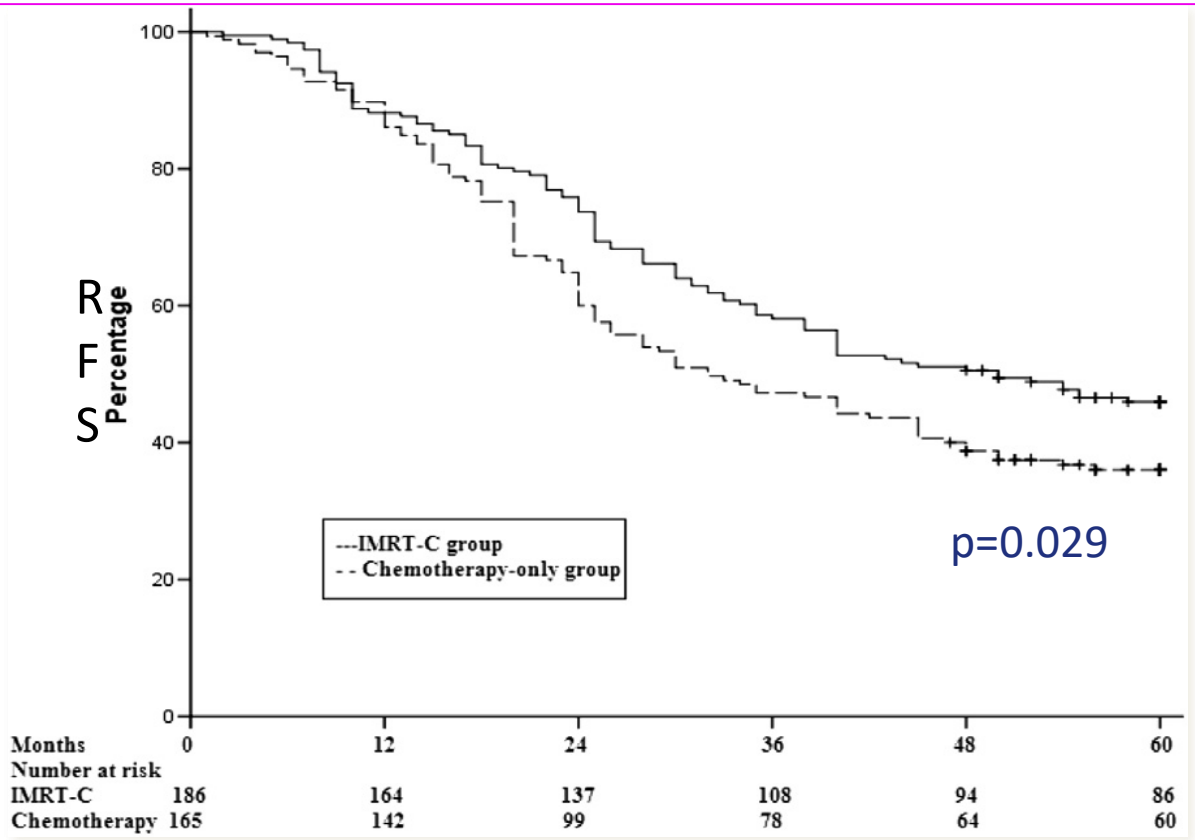
Randomized study comparing IMRT-CRT vs. chemotherapy after D2 resection

Benefit in Recurrence Free Survival not in overall survival



Zhu et al., Radiother Oncol 2012

Gastric cancer adjuvant chemoradiation

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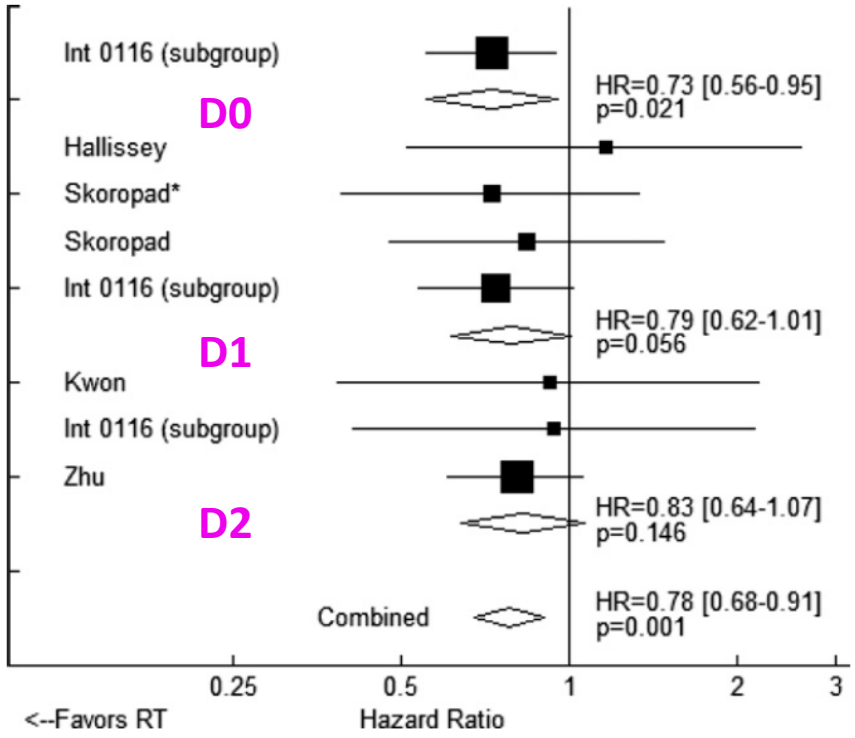
A meta-analysis (n=2811)

No benifit on Overall Survivial in D2 subgroup



Ohri et al. IJROBP 2013

Gastric cancer adjuvant chemoradiation

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ARTIST Trial

N 458
stage Ib-III
R0 resection
D2 node dissection

R A N D O M

Adjuvant chemotherapy

XP (cisplatin (60 mg/m2 d1)+ capecitabine (1000mg/m2 BD d1-14) 3-weekly x 6

Primary endpoint:
Disease free survival

Adjuvant chemoradiation

XP x 2 → XP-RT (45 Gy 25# capecitabine 825mg/m2 BD) → XP x 2

Lee et al. J Clin Oncol 2012; Park et al. J Clin Oncol 2015

Gastric cancer adjuvant chemoradiation

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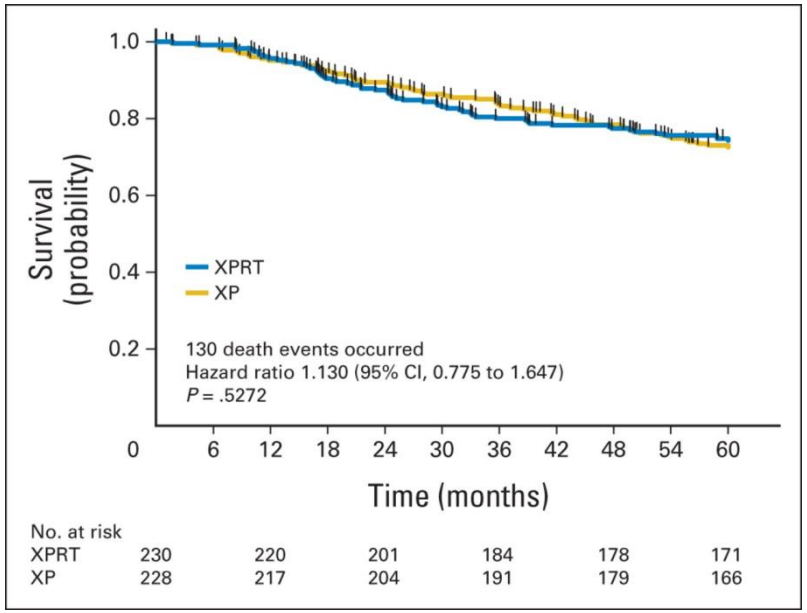

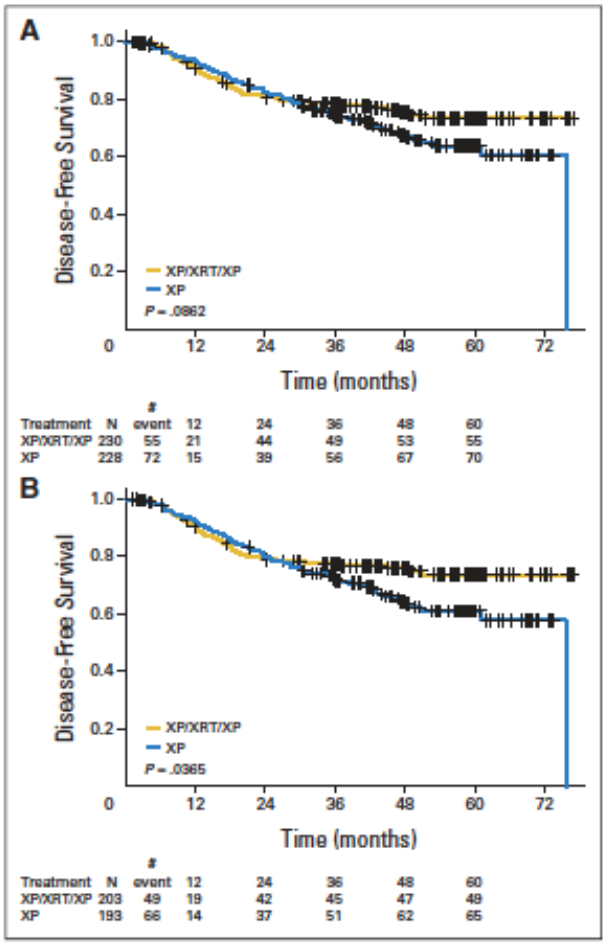

Fig 2. Disease-free survival in (A) all patients and (B) lymph node–positive patients. XP, capecitabine plus cisplatin; XRT, radiotherapy with capecitabine.

Lee et al. J Clin Oncol 2012; Park et al. J Clin Oncol 2015

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Gastric cancer –neo-adjuvant therapies

Neoadjuvant chemotherapy

Neoadjuvant chemoradiation

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Gastric cancer –neo-adjuvant therapies

Neoadjuvant chemotherapy

- MRC MAGIC trial
- Several ongoing randomised trial

Gastric cancer –neo-adjuvant chemotherapy

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MRC MAGIC Trial

Perioperative chemotherapy + surgery vs. surgery alone

Chemotherapy: Epirubicin + cisplatin + PVI 5-FU
3-weekly x 3 pre-operative and x 3 post-operative

Operation performed*	Chemotherapy - surgery	Surgery
Esophagogastrectomy	58/219 (26.5)	52/238 (21.8)
D1 distal resection	19/219 (8.7)	30/238 (12.6)
D1 total resection	20/219 (9.1)	20/238 (8.4)
D2 distal resection	32/219 (14.6)	24/238 (10.1)
D2 total resection	61/219 (27.9)	72/238 (30.3)
Nonresectional surgery	29/219 (13.2)	40/238 (16.8)
Unknown	10/229 (4.4)	6/244 (2.5)

Cunningham D et al (2006) N Eng J Med 355:11-20

Gastric cancer –neo-adjuvant chemotherapy

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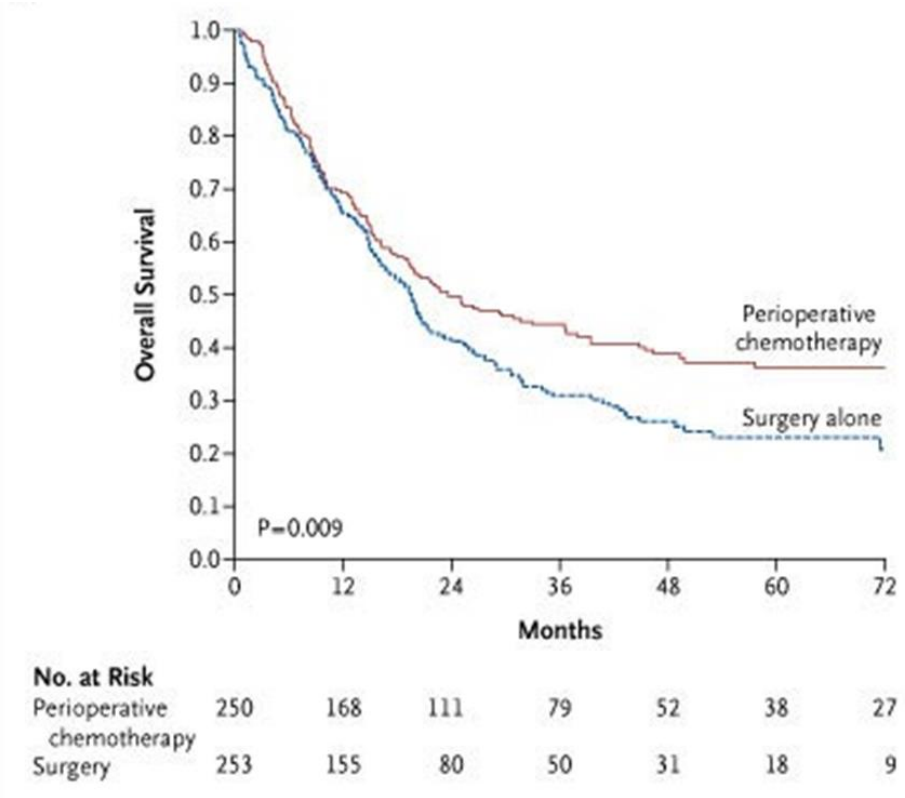
MRC MAGIC Trial



Cunningham D et al (2006) N Eng J Med 355:11-20

Gastric cancer –neo-adjuvant therapies

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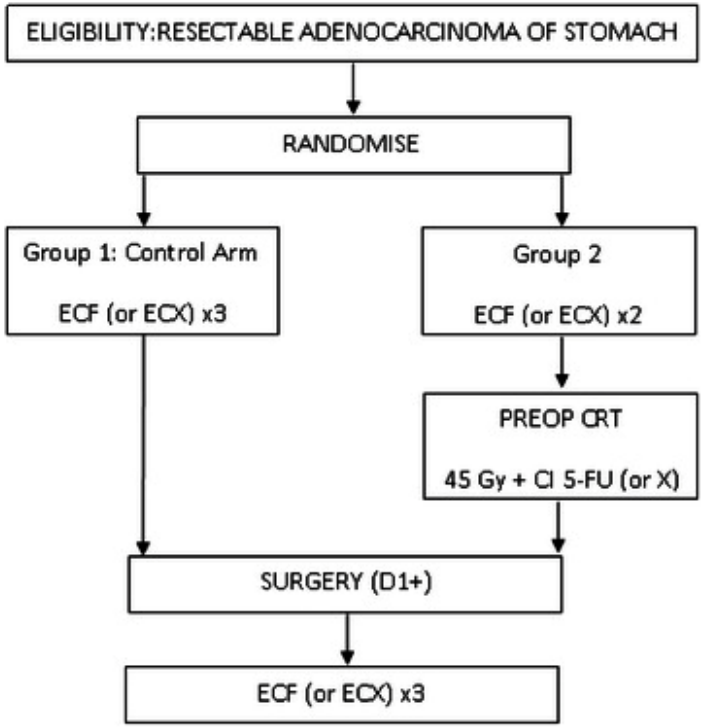
Neoadjuvant chemoradiation

- Limited phase II data
- TOPGEAR ongoing Trial



BMC Cancer. 2015 Jul 21;15:532..

Conclusions

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- The role of radiationtherapy is still not clear
- Adjuvant radiochemotherapy only in selected patients (D1 nodal dissection or N+ patients)
- Neoadjuvant radiochemotherapy only in clinical trials

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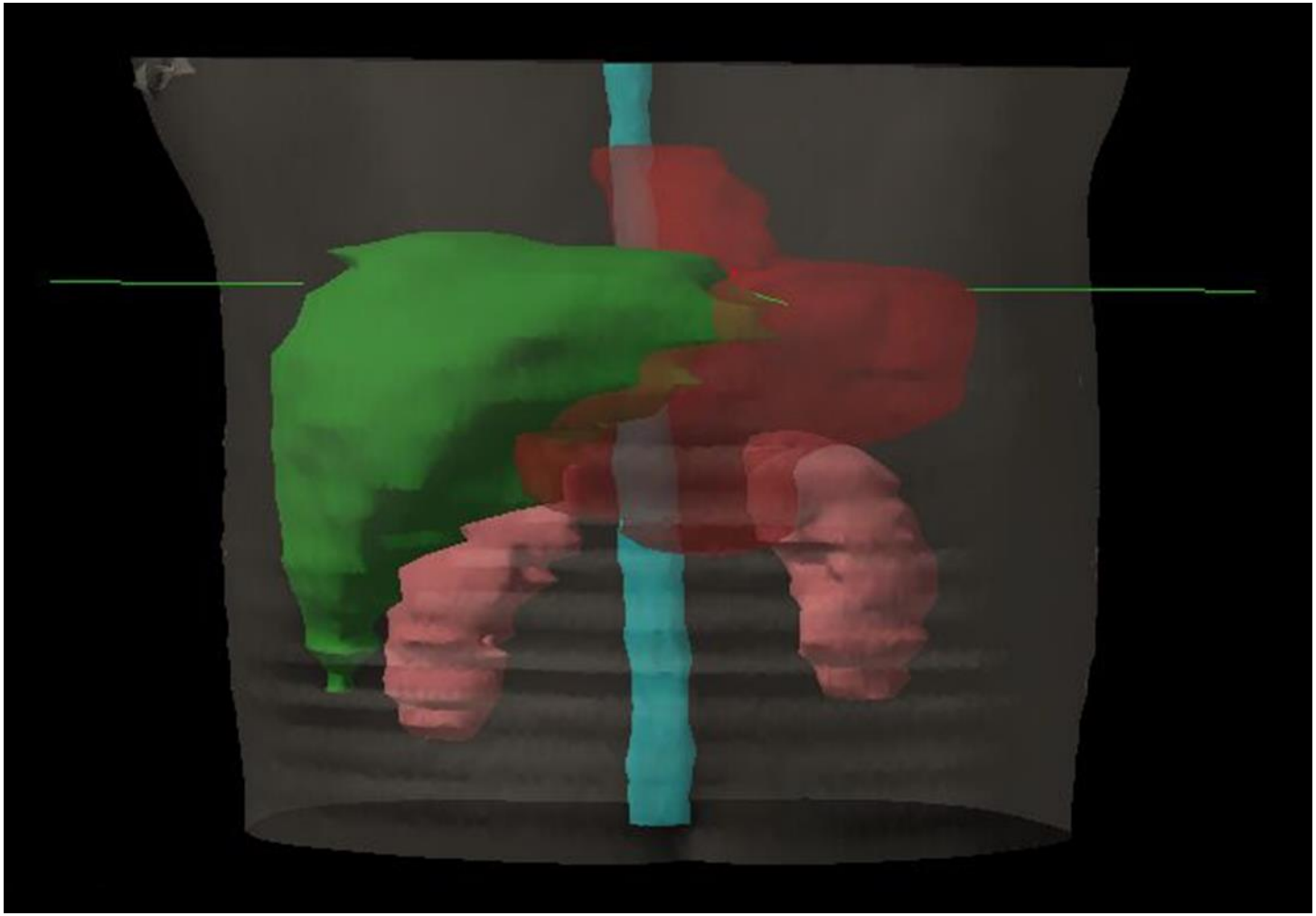
Gastric cancer – radiotherapy planning



Gastric cancer – radiotherapy planning

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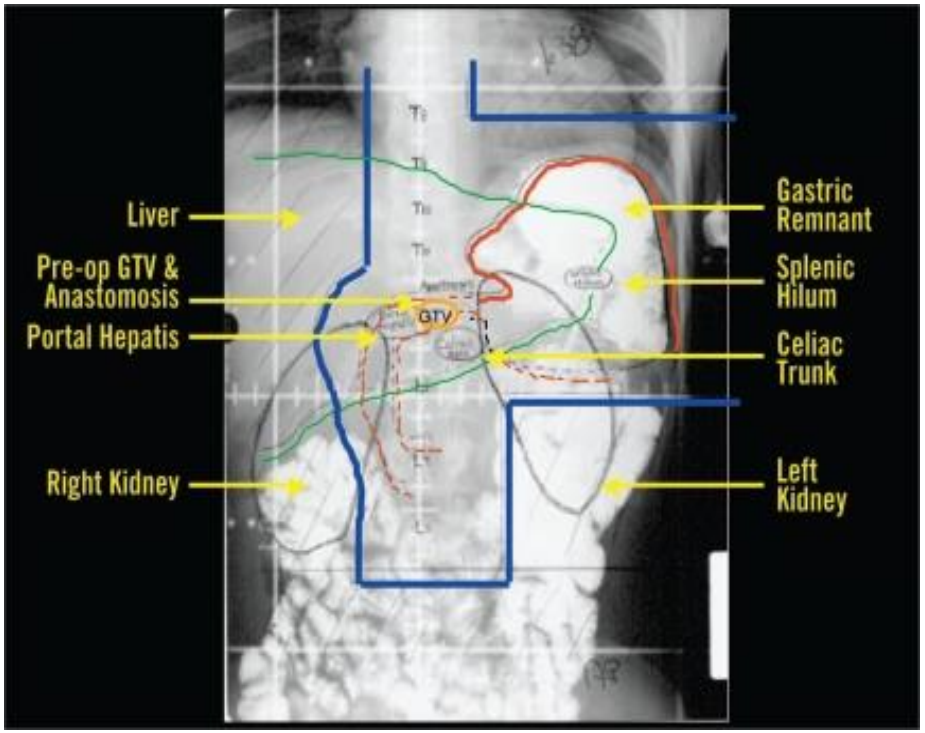
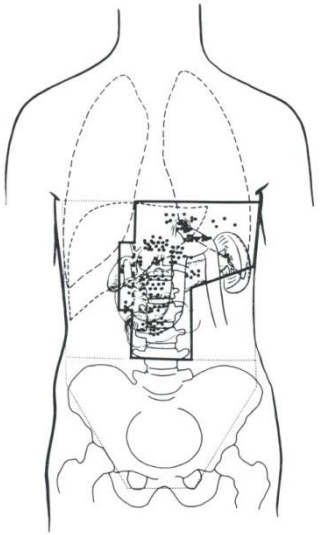
Radiotherapy-technique according to the SWOG protocol (2001)





Gastric cancer – radiotherapy planning

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Gastric Surgical Adjuvant Radiotherapy Consensus Report: Rationale and Treatment Implementation
Smalley S *et al* (2002) IJROPB 52:283-293

Careful attention to nutrition

Tumour bed defined by pre-operative imaging

Include all regional lymph nodes

Include at least 2 cm beyond resection margins

Include left hemidiaphragm for T3 lesions

Gastric cancer – radiotherapy planning

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Gastric Surgical Adjuvant Radiotherapy Consensus Report: Rationale and Treatment Implementation
Smalley S *et al* (2002) IJROPB 52:283-293

Equivalent of at least 3/4 of one kidney spared
30 Gy to < 60% of liver
40 Gy to < 30% of heart
45 Gy spinal cord maximum
AP-PA fields the most practical arrangement
Limit lateral field contribution to < 20 Gy

Gastric cancer – radiotherapy planning

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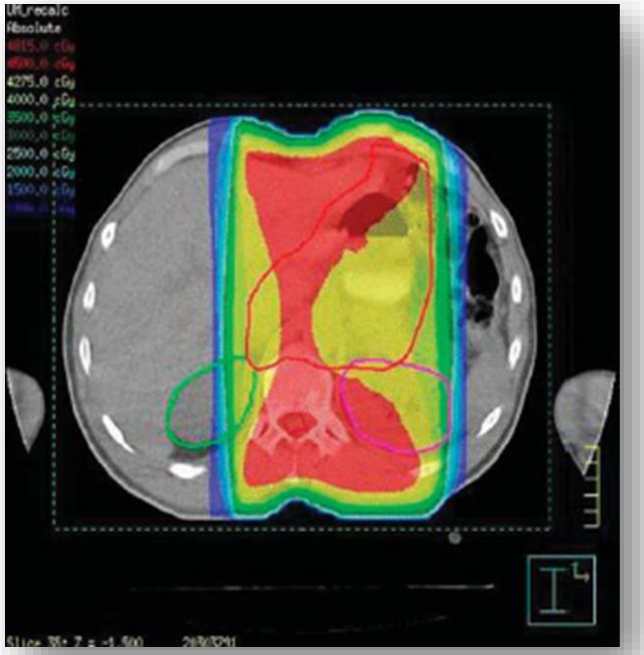
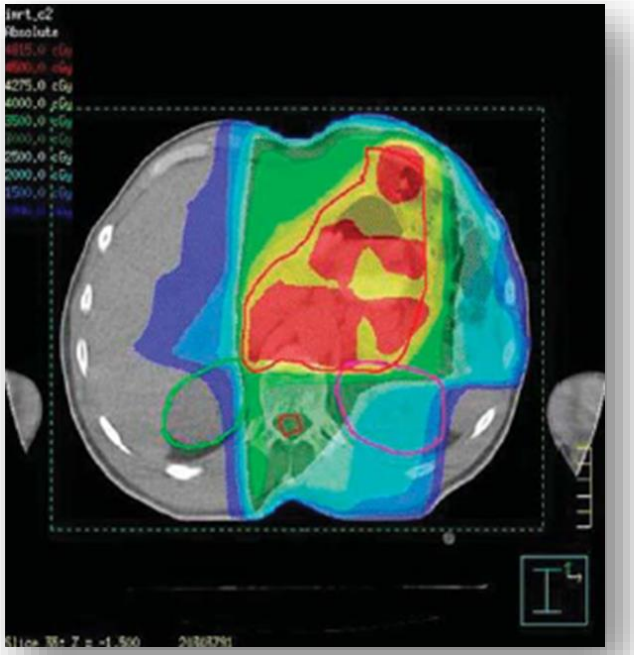
INT 0116: Can we improve the radiotherapy?

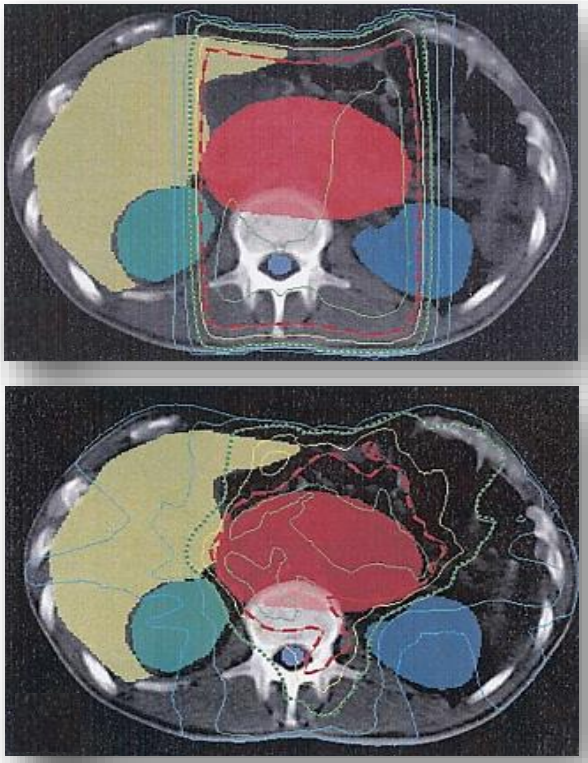


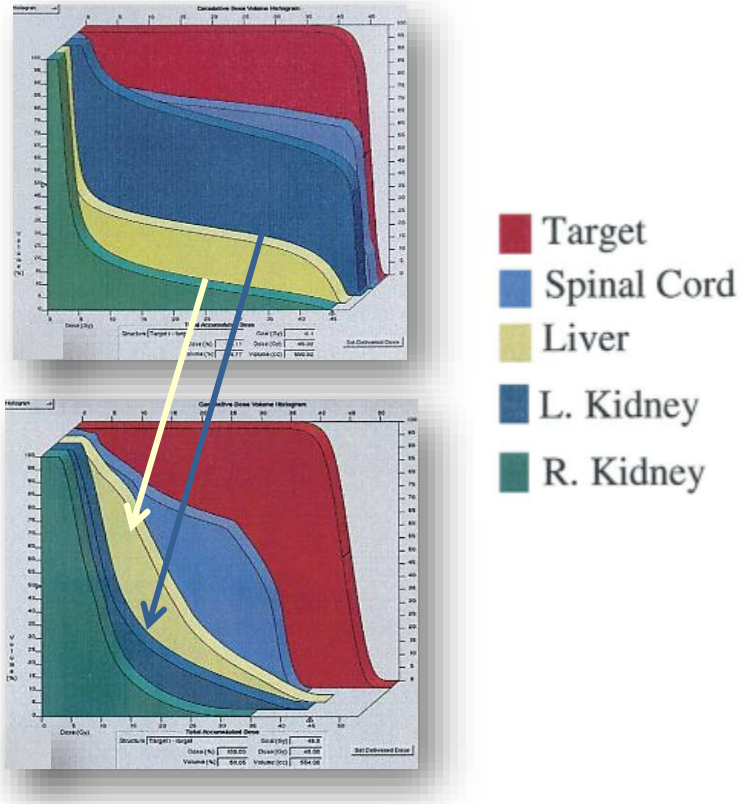


Gastric cancer – radiotherapy planning

EBRO 2017

INT 0116: Can we improve the radiotherapy?



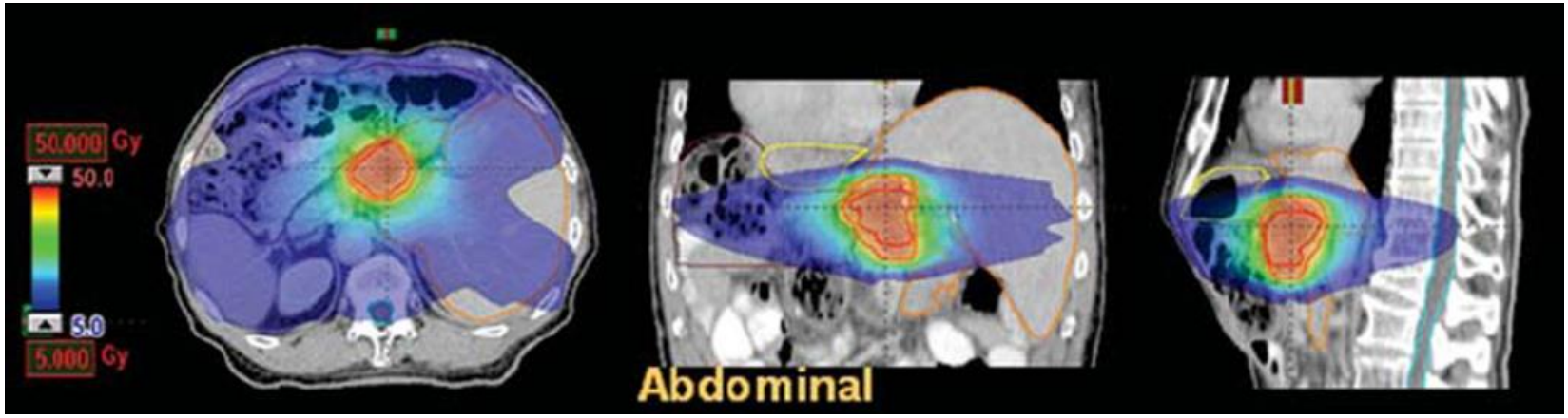


Wieland P et al (2004) IJROBP 59:1236-1244

Gastric cancer – radiotherapy planning

EBRO 2017

INT 0116: Can we improve the radiotherapy?



…..but……

PHYSICS CONTRIBUTION

LIMITED ADVANTAGES OF INTENSITY-MODULATED RADIOTHERAPY OVER 3D CONFORMAL RADIATION THERAPY IN THE ADJUVANT MANAGEMENT OF GASTRIC CANCER

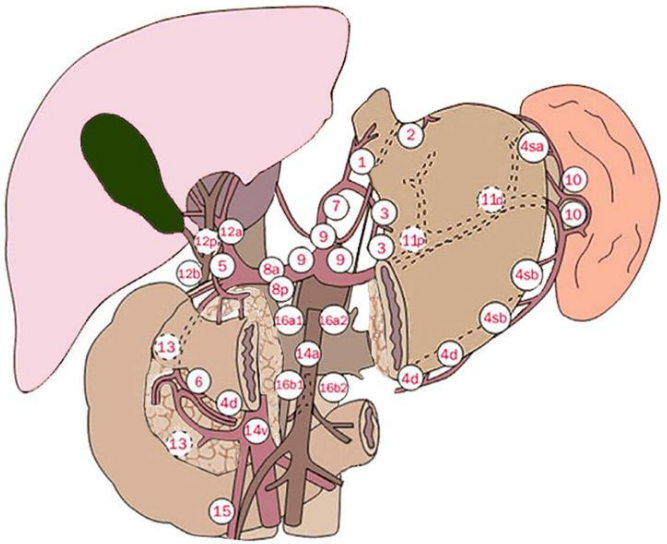
Alani S et al (2009) Int J Radiat Oncol Biol Phys 74: 562-566

Gastric cancer – radiotherapy planning

EBRO 2017

and nodes……

Pattern of lymph node metastases and its implication in radiotherapeutic clinical target volume delineation of regional lymph nodes in gastric cancer

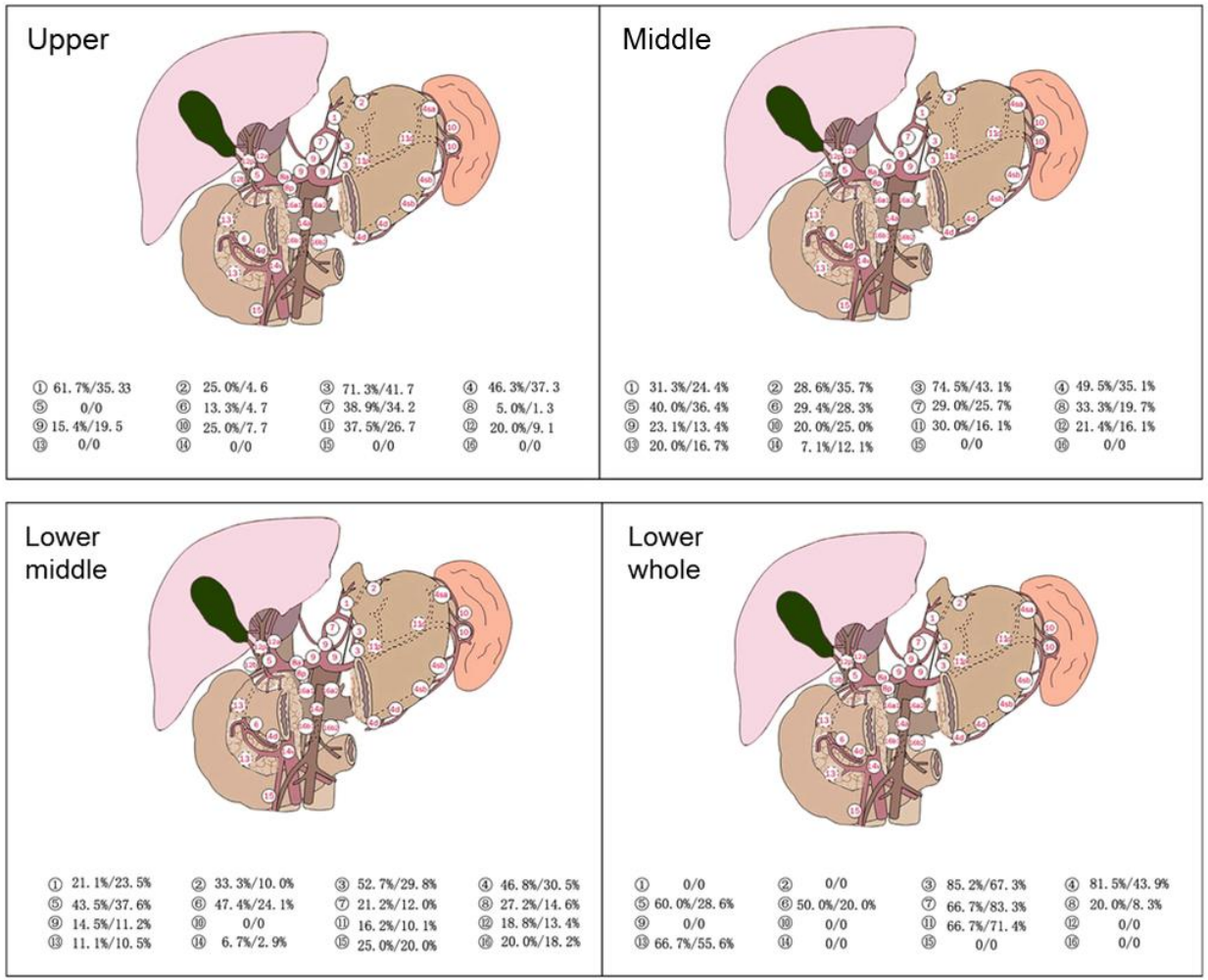


① 41.4%/31.8%	② 25.0%/12.7%	③ 61.8%/36.8%	④ 48.8%/32.3%
⑤ 39.7%/34.8%	⑥ 38.5%/21.8%	⑦ 26.3%/18.0%	⑧ 26.6%/14.1%
⑨ 16.2%/12.5%	⑩ 15.8%/9.7%	⑪ 24.1%/15.8%	⑫ 19.0%/13.5%
⑬ 17.2%/18.2%	⑭ 9.3%/5.0%	⑮ 17.7%/15.0%	⑯ 11.1%/9.5%

Yi Y et al (2010) Radiother Oncol 96:223-230

Gastric cancer – radiotherapy planning

EBRO 2017



Yi Y et al (2010) Radiother Oncol 96:223-230

Gastric cancer – radiotherapy planning

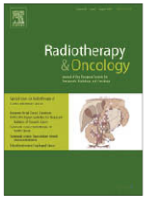
EBRO 2017

Radiotherapy and Oncology 92 (2009) 164–175

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Guidelines

EORTC-ROG expert opinion: Radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach

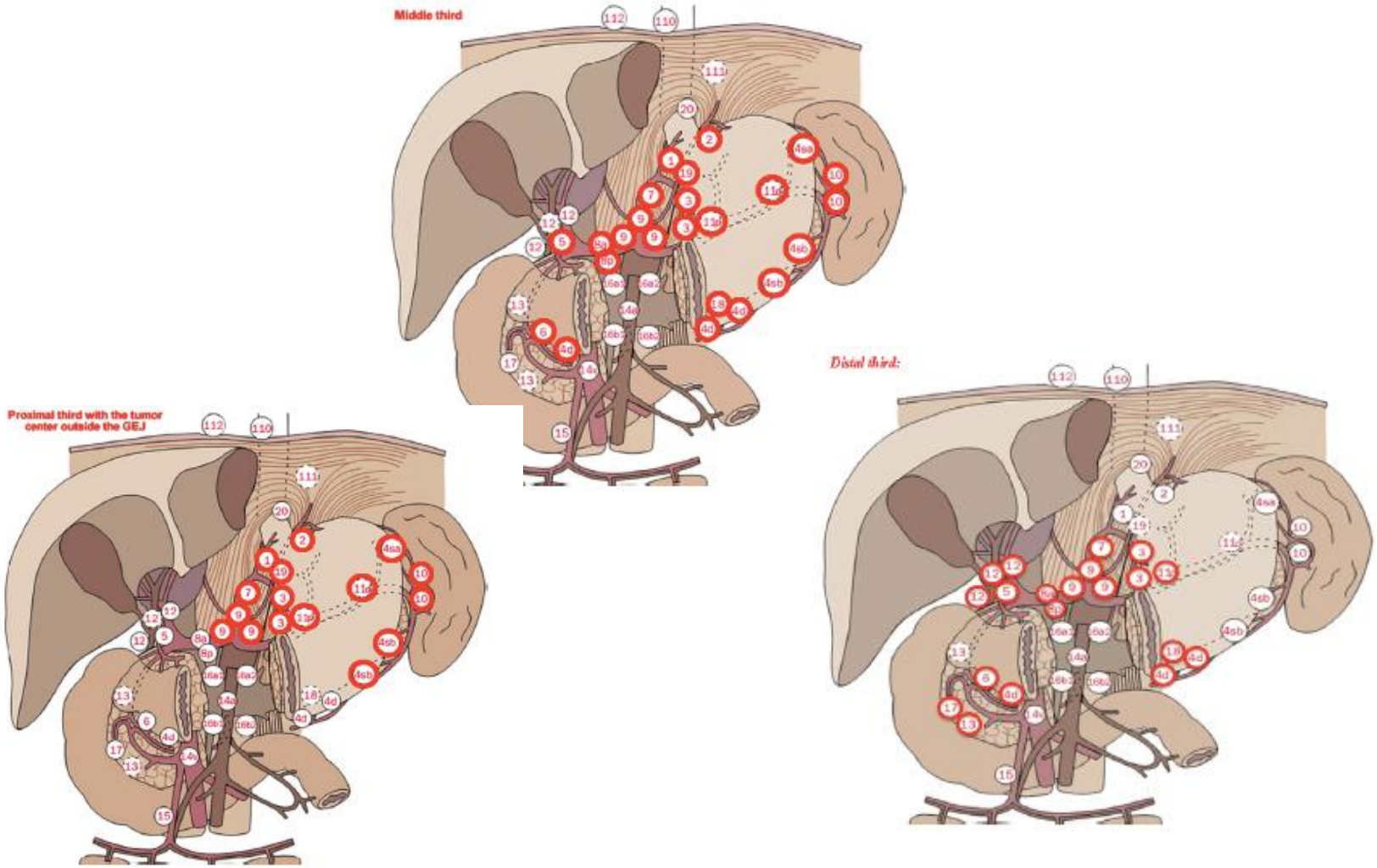
Oscar Matzinger [a,b,*], Erich Gerber [c], Zvi Bernstein [d], Philippe Maingon [e], Karin Haustermans [f], Jean François Bosset [g], Akos Gulyban [a], Philip Poortmans [h], Laurence Collette [a], Abraham Kuten [d]

[a] EORTC Headquarters, Brussels, Belgium
[b] CHU Vaudois, Department of Radiation Oncology, Lausanne, Switzerland
[c] Radiation Oncologist, Vienna, Austria
[d] Rambam Health Care Campus, Oncology Department, Haifa, Israel
[e] Centre Georges-Francois Leclerc, Department of Radiation Oncology, Dijon, France
[f] U.Z. Gasthuisberg, Department of Radiation Oncology, Leuven, Belgium
[g] CHR de Besancon, Department of Radiation Oncology, Besancon, France
[h] Dr. Bernard Verbeeten Institute, Department of Radiation Oncology, Tilburg, The Netherlands

Matzinger O et al (2009) Radiother Oncol 92: 164-175

EBRO
2017

Gastric cancer – radiotherapy planning



Matzinger O et al (2009) Radiother Oncol 92: 164-175

Gastric cancer – radiotherapy planning

Critical structures and dose constraints

EBRO 2017

Table 2 Summary of Dosimetric Parameters for Clinical Toxicity

Organ	Emami[2] TD 5/5	Emami[2] TD 50/5	Endpoints	Dosimetric Parameters	Endpoints
Brainstem	1/3: 60 Gy 2/3: 53 3/3: 50	1/3: - 2/3: - 3/3: 65 Gy	Necrosis, infarction	V60 <0.9 mL	<5% grade≥1 toxicity
Spinal cord	5 cm: 50 Gy 10 cm: 50 20 cm: 47	5 cm: 70 Gy 10 cm: 70 20 cm: -	Myelitis, necrosis	max <50 Gy	<5% grade≥3 toxicity
Cervical spinal cord	—	—	—	EUD <52 Gy, max. <55 Gy	<5% grade≥3 toxicity
Parotid	1/3: - 2/3: 32 Gy 3/3: 32	1/3: - 2/3: 46 Gy 3/3: 46	Xerostomia	Mean dose <26 Gy	Late grade 2 xerostomia resulting from >75% functional loss
Lung	1/3: 45 Gy 2/3: 30 3/3: 17.5	1/3: 65 Gy 2/3: 40 3/3: 24.5	Pneumonitis	V13<40% V20<25-30% V30<10-15% MLD<10-20 Gy	Late grade 2 in <10-20% Late grade 3 in <5-10%
Heart	1/3: 60 Gy 2/3: 45 3/3: 40	1/3: 70 Gy 2/3: 55 3/3: 50	Pericarditis	V33 <60%, V38 <33% V42 <20%	5% excess cardiac mortality
Esophagus	1/3: 60 Gy 2/3: 58 3/3: 55	1/3: 72 Gy 2/3: 70 3/3: 68	Clinical stricture/ perforation	V50 and S50 <30%	5% risk of late toxicity
Rectum	1/3: 60 Gy 2/3: 60 3/3: 60	1/3: 80 Gy 2/3: 80 3/3: 80	Proctitis, necrosis, fistula, stenosis	V70-80 ≤15 cc V70≤20-25%	Late grade 2 in <5-10%
Liver	1/3: 50 Gy 2/3: 35 3/3: 30	1/3: 55 Gy 2/3: 45 3/3: 40	Liver failure	1/3: 40-80 Gy 2/3: 30-50 3/3: 25-35	Late grade 3-4 liver toxicity <5%
Kidney	1/3: 50 Gy 2/3: 30 3/3: 23	1/3: - 2/3: 40 Gy 3/3: 28	Clinical nephritis	median dose <17.5 Gy	anemia, azotemia, hypertension and edema

Milano MT, Semin Radiat Oncol 2007:17;131-40

Gastric cancer – radiotherapy planning

EBRO 2017

Critical structures and dose constraints

Kidneys:	Mean dose <18Gy V20 <32% V28 < 20%	Renal impairement <5%
Liver:	Mean dose ≤ 30 Gy	RIDL <5%

From QUANTEC

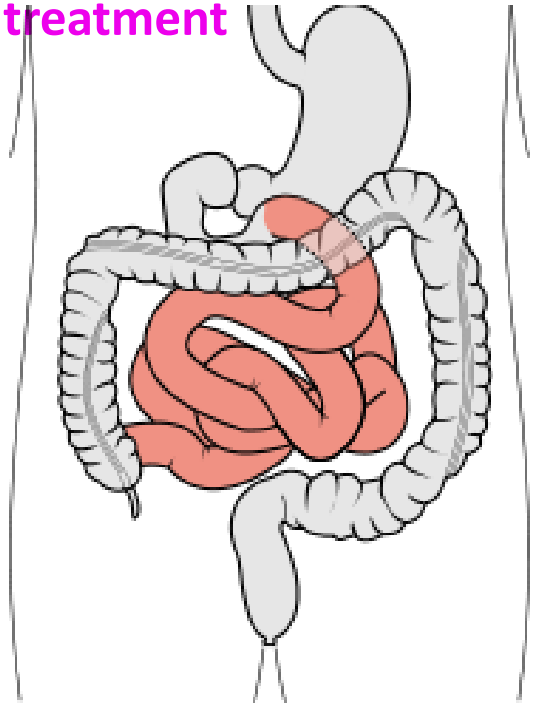
Gastric cancer – radiotherapy planning

EBRO 2017

Critical structures and dose constraints

Small bowel Acute Toxicity

Onset: 2nd week of treatment → 15-20 days after treatment



Symptoms:

- Abdominal pain (cramps)
- Diarrhea
- Nausea
- Lack of appetite
- Weight loss

Andreyev HJ. Clin Oncol.2007 Ruiz-Tovar. J,Clin Transl Oncol 2009

EBRO 2017

Gastric cancer – radiotherapy planning

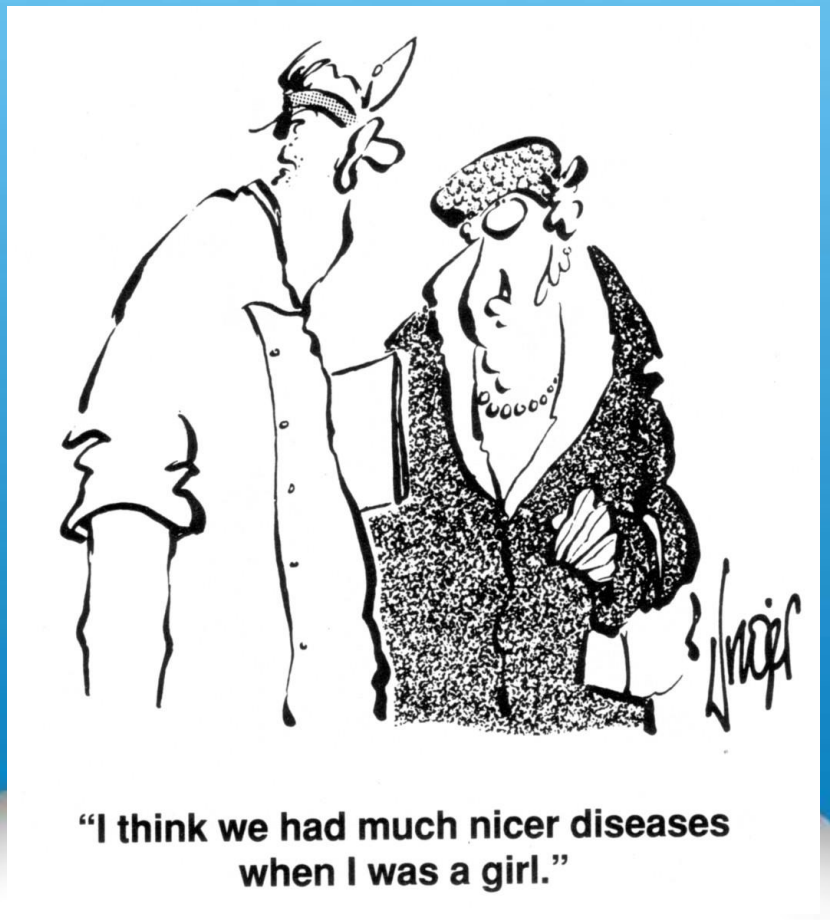
Critical structures and dose constraints

Small bowel Toxicity

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)* (*Continued*)

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Small bowel	Individual small bowel loops	3D-CRT	Grade ≥ 3 acute toxicity§	V15 <120 cc	<10	Volume based on segmentation of the individual loops of bowel, not the entire potential peritoneal space
	Entire potential space within peritoneal cavity	3D-CRT	Grade ≥ 3 acute toxicity§	V45 <195 cc	<10	Volume based on the entire potential space within the peritoneal cavity

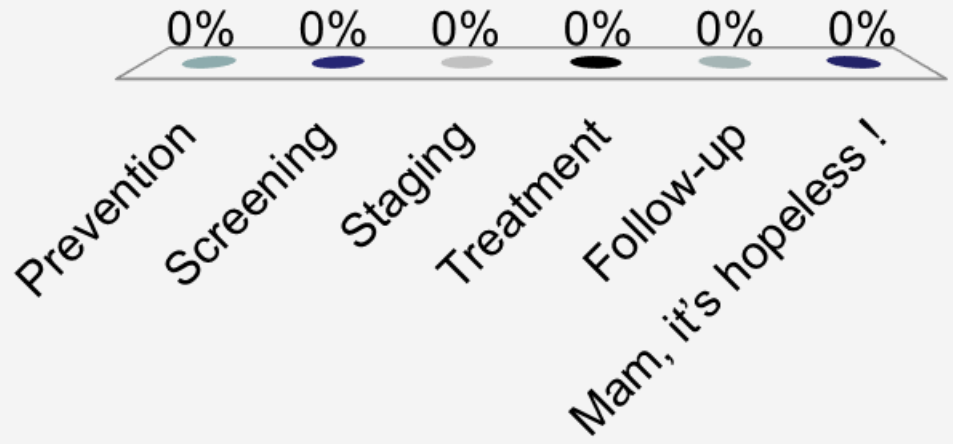
Non small cell lung cancer



"I think we had much nicer diseases when I was a girl."

To reduce lung cancer mortality, what do you recommend ?

A. Prevention
B. Screening
C. Staging
D. Treatment
E. Follow-up
F. Sir, it's hopeless !



Facts …

- > 1 million new cases per year worldwide
  - 75 - 80 % non small cell cancers
- Leading cause of cancer death in the world
  - overall survival @ 5 years ~10%
- 80 – 90 % caused by smoking
  - prevention more cost-effective than treatment

34 439 male UK doctors

- Persistent smokers
  - died 10 years younger than non-smokers
  - 50% killed by tobacco-induced diseases
  - 25% killed before age 70
- Life duration over study period
  - increased in non-smokers
  - stable in persistent smokers

Doll BMJ 2004

The Effects of a Smoking Cessation Intervention on 14.5-Year Mortality

A Randomized Clinical Trial

% smokers @ 5yr	intervention	usual care	p
none	22	5	
intermittent	29	23	<.001
permanent	49	71	

- 5887 patients with asymptomatic airway obstruction
  - intervention + inhaled bronchodilator
  - intervention + inhaled placebo
  - usual care

Anthonisen Ann Intern Med 2005

The Effects of a Smoking Cessation Intervention on 14.5-Year Mortality

A Randomized Clinical Trial

% smokers @ 5yr	intervention	usual care	p

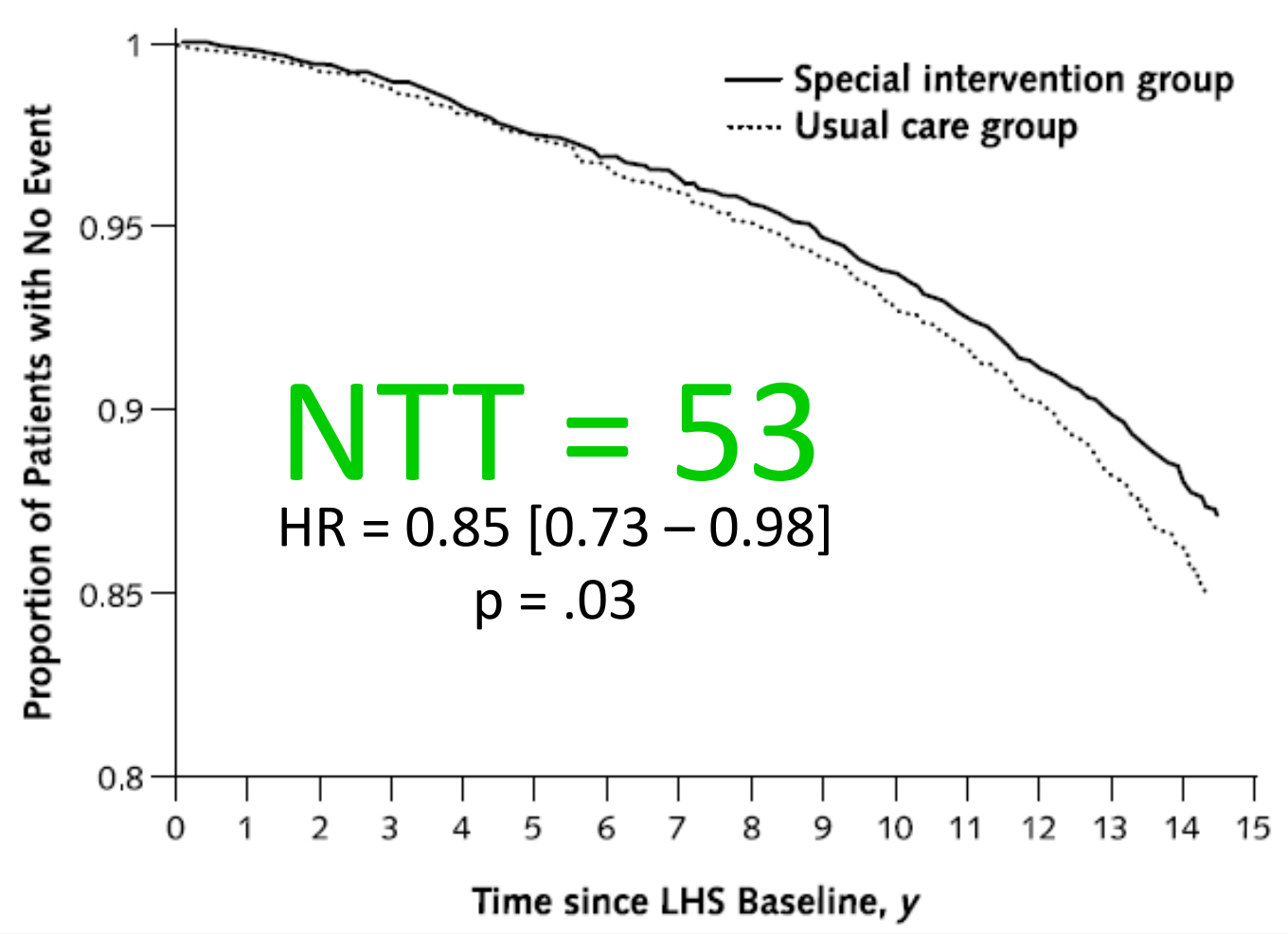
NTT = 100/17 = 6

- 5887 patients with asymptomatic airway obstruction
  - intervention + inhaled bronchodilator
  - intervention + inhaled placebo
  - usual care

Anthonisen Ann Intern Med 2005

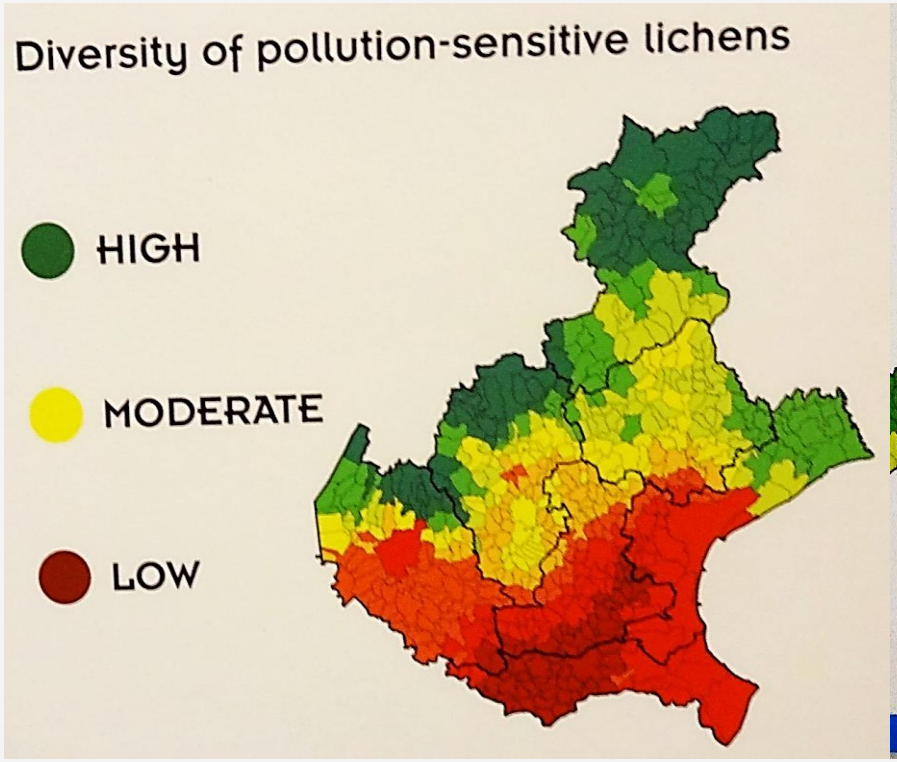
The Effects of a Smoking Cessation Intervention on 14.5-Year Mortality

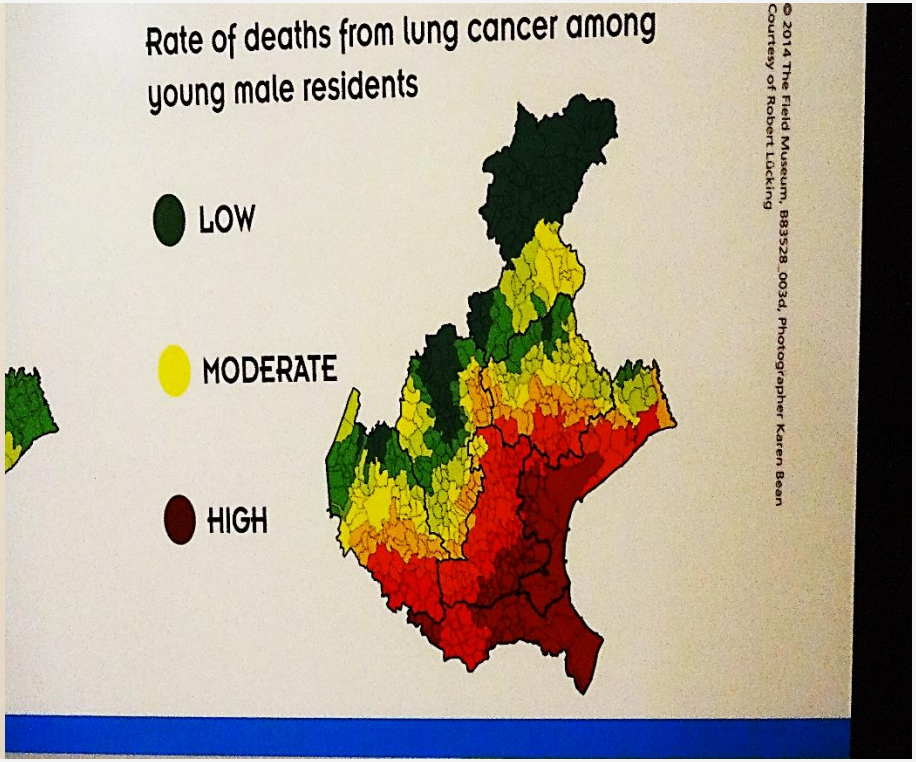
A Randomized Clinical Trial



Anthonisen Ann Intern Med 2005

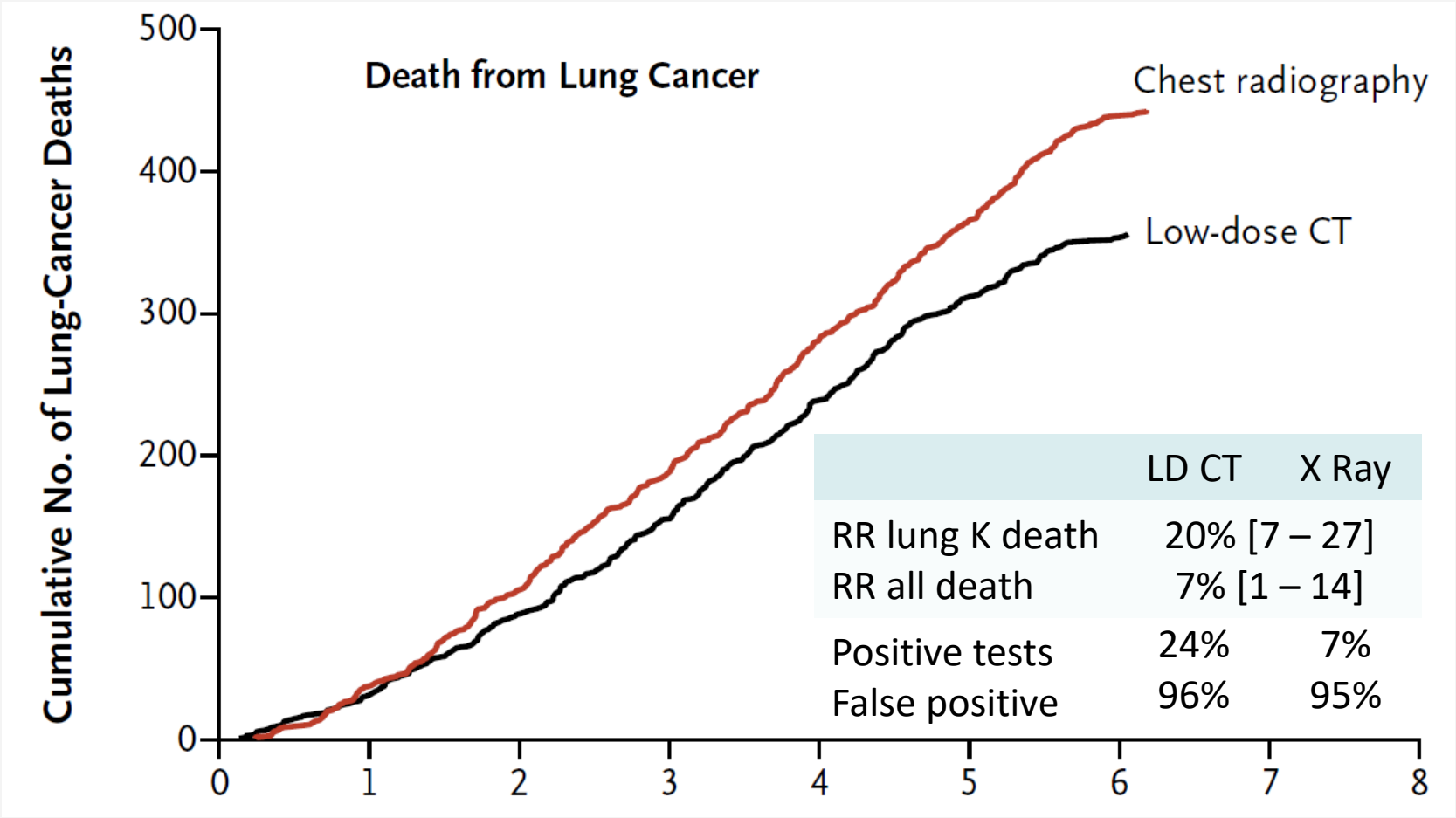
Prevention & environment





Anonymous, Lichen Exhibit, Field Museum Chicago 2016

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening



National Lung Screening Trial Research Team NEJM 2011

Conclusion (1)

- Prevention is effective
- Smoking cessation is effective
  - even when only a minority quits
- Screening still under investigation
  - target population
  - process

IASLC Lung Cancer Staging Project

RPA on 12 428 NSCLC treated 1990-2000

weight loss, comorbidities not included

Group	Stage	PS	Age	Survival (med)
I	IA-IIA	any	any	53 months
II	IIB-IIIA	0-1	any	16 months
III	IIB-IIIA	2	any	8 months
	IIIB-IV	0	any	
	IIIB-IV	1	<81	
IV	IIB-IIIA	3-4	any	3 months
	IIIB-IV	2-4	any	
	IIIB-IV	1	>80	

Sculier J Thorac Oncol 2008

Clinical staging is not reliable

	pN0	pN1	pN2	pN3	Total
cN0	47	18	16	1	82
cN1	10	16	12	0	38
cN2	10	12	28	0	50
Total	67	46	56	1	170

Correctly classified = 91/170 = 54%

Depierre JCO 2002

Better staging with FDG PET-CT

	Sensitivity	Specificity
Primary		
PET-CT	80-90%	40-80%
Mediastinum		
CT	60%	80%
PET-CT	80%	90%
mediastinoscopy	78%	100%

De Ruysscher R&O 2012

Better staging, better treatment

	No PET	PET	p
Thoracotomy	78/96 (81%)	60/92 (65%)	
curative	39 (41%)	41 (44%)	
futile	39 (41%)	19 (21%)	0.003
Relapse/death <1yr	19	10	

51% [32–80] reduction in risk
of futile thoracotomy

PLUS trial, van Tinteren Lancet 2002

Better staging, better treatment

	No PET	PET	p
Th			
			03
Relapse/death <1yr	19	10	

Number To Image:

5 to avoid 1 futile thoracotomy

11 to avoid 1 relapse/death <1yr

51% [32–80] reduction in risk
of futile thoracotomy

PLUS trial, van Tinteren Lancet 2002

Better staging, better treatment

	CT alone	PET-CT
Radical RT	146 / 158 (92%)	118 / 152 (72%)
OS @ 2 yrs	39%	47%

Overall survival	HR [95% CI]
PET vs. CT	0.8 [0.6 – 1]
IIIB vs. IIIA	1.4 [1.1 – 1.9]
ECOG	1.7 [1.3 – 2.6]

OCOG, Ung ASCO 2011 (abstract 7018)

Better staging, better treatment

	CT alone	PET-CT
Radical RT	146 / 158 (92%)	118 / 152 (72%)
OS		
PET vs. CT		[illegible]
IIIB vs. IIIA	1.4 [1.1 – 1.9]	
ECOG	1.7 [1.3 – 2.6]	

Number To Image:

5 to avoid 1 futile irradiation

13 to avoid 1 death

OCOG, Ung ASCO 2011 (abstract 7018)

Isn’t it stage migration ?

Stage	Overall survival @ 2 years			
	‘98 - ’99	2002 - 2003		
	no PET	all	no PET	PET (48%)
I	72	71	64	76
II	56	59	57	69
IIIA	30	33	26	39
IIIB	19	21	14	32
IV	8	11	7	19
?	34	35	30	41

Dinan SEER JCO 2012

Conclusion (2)

- Prognostic factors stronger than treatment
  - weight loss (50% at diagnosis)
  - performance status (40% at diagnosis)
  - TN stage (PET)
- Better staging, better treatment
  - high incidence of metastasis at diagnosis
  - role of PET/CT
- Co-existent diseases
  - tobacco

European Organisation for Research and Treatment of Cancer Recommendations for Planning and Delivery of High-Dose, High-Precision Radiotherapy for Lung Cancer

Level of recommendation	Quality of evidence		
	A (high)	B (moderate)	C (low)
1 (strong)	applies for most patients, in most circumstances without reservation		may change with new evidence
2 (weak)	best action depends on patients, circumstances, and societal values		other alternatives may be equally reasonable

De Ruysscher JCO 2010

Stereotactic Body Radiotherapy

Well tolerated by elderly and frail patients	1B
Poor pulmonary function is not a contraindication	1B
May be safely administered after pneumonectomy	1C
Can be safely delivered without rigid immobilization	1B
Doses per fraction ≥18 Gy should not be given to centrally located tumours	1C
Lower doses per fraction adapted to OAR may be safe for centrally located tumours	1C

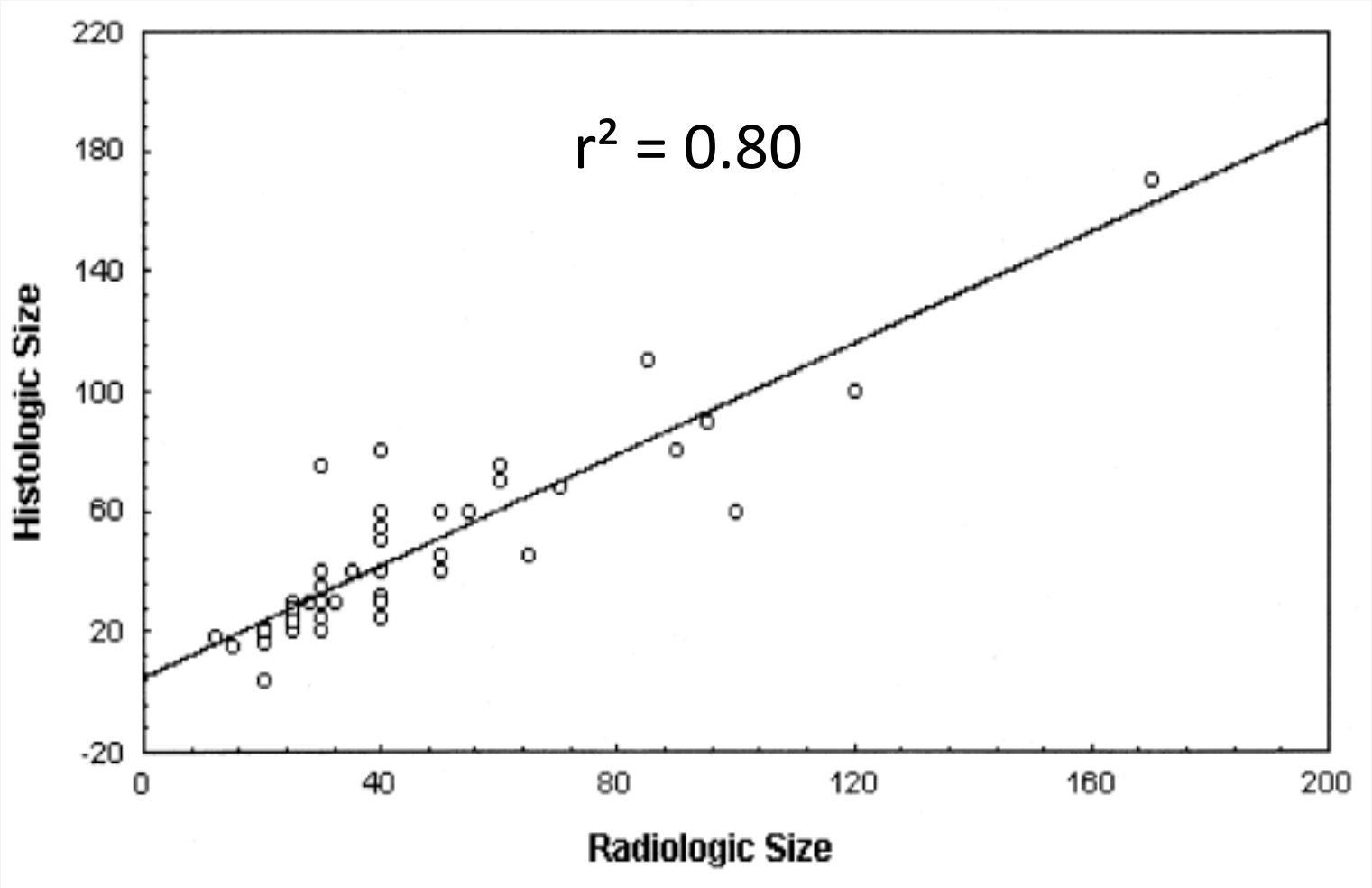
De Ruysscher EORTC JCO 2010

Radical external radiotherapy

A stable and reproducible position during imaging and treatment is essential • arms above head • stable arm support	1B
Planning CT scan extends from cricoid cartilage to L2	1B
Slice thickness of 2-3 mm for delineation and DRR	1B
IV contrast can improve delineation of centrally located primary tumors and lymph nodes	1C
4D-CT scan is strongly preferred	1B

De Ruysscher EORTC JCO 2010

Delineating GTV_T on CT



Giraud IJROBP 2000

Do you delineate primary tumour on FDG-PET ?

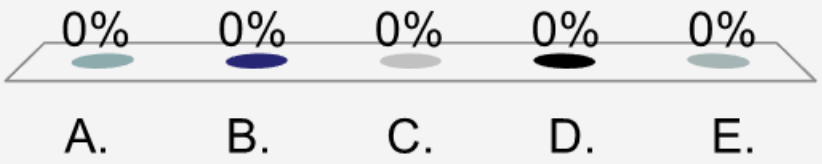
A. No

B. Yes, no registration on CT

C. Yes, with registration on CT

D. Yes, PET in RT position

E. No access to PET



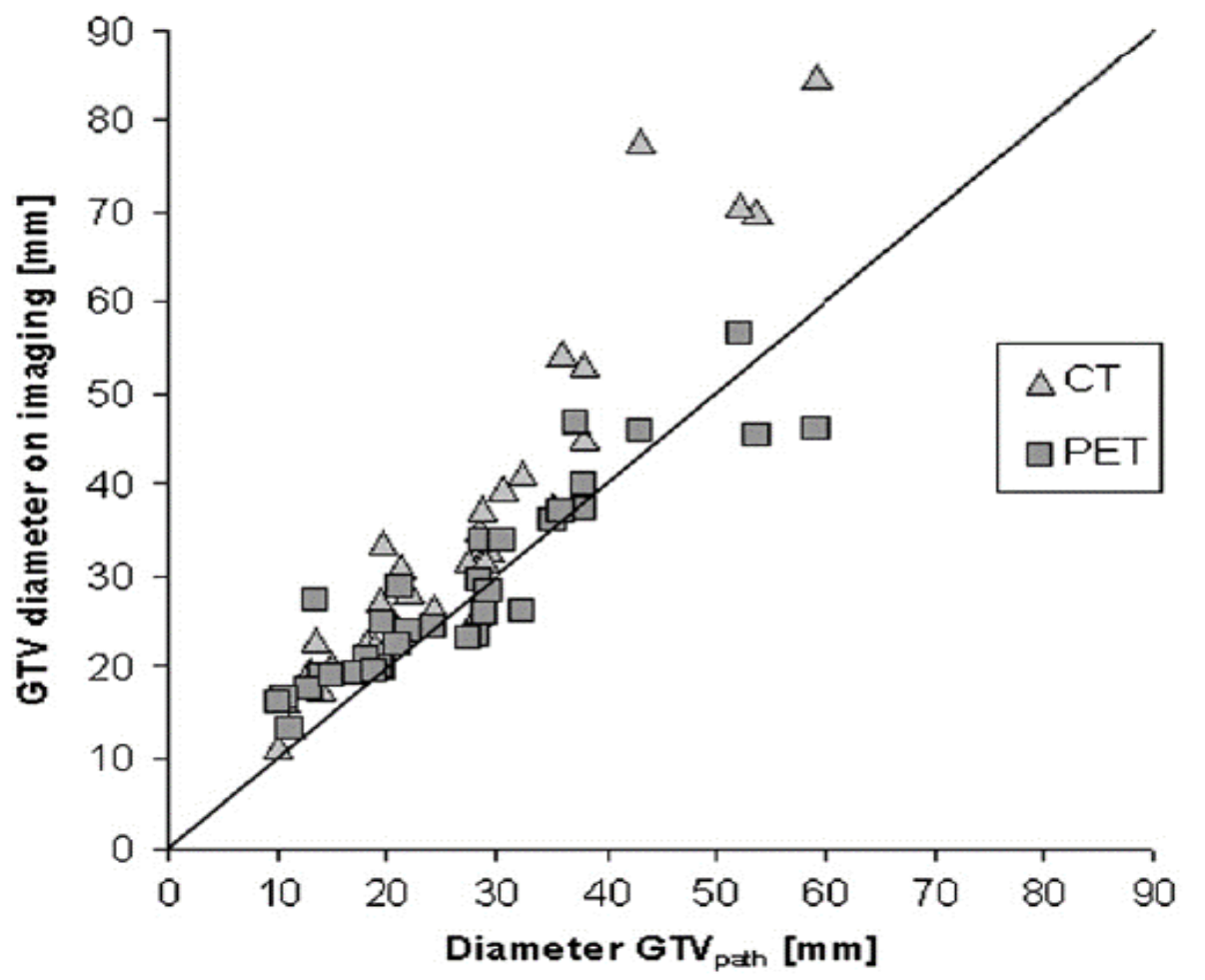
PET/CT for RT planning

PET/CT is recommended for target volume definition	1B
Strictly standardized protocols with nuclear medicine	2B
Should be acquired in radiotherapy position	1B
Should be registered with CT using rigid methods	1B

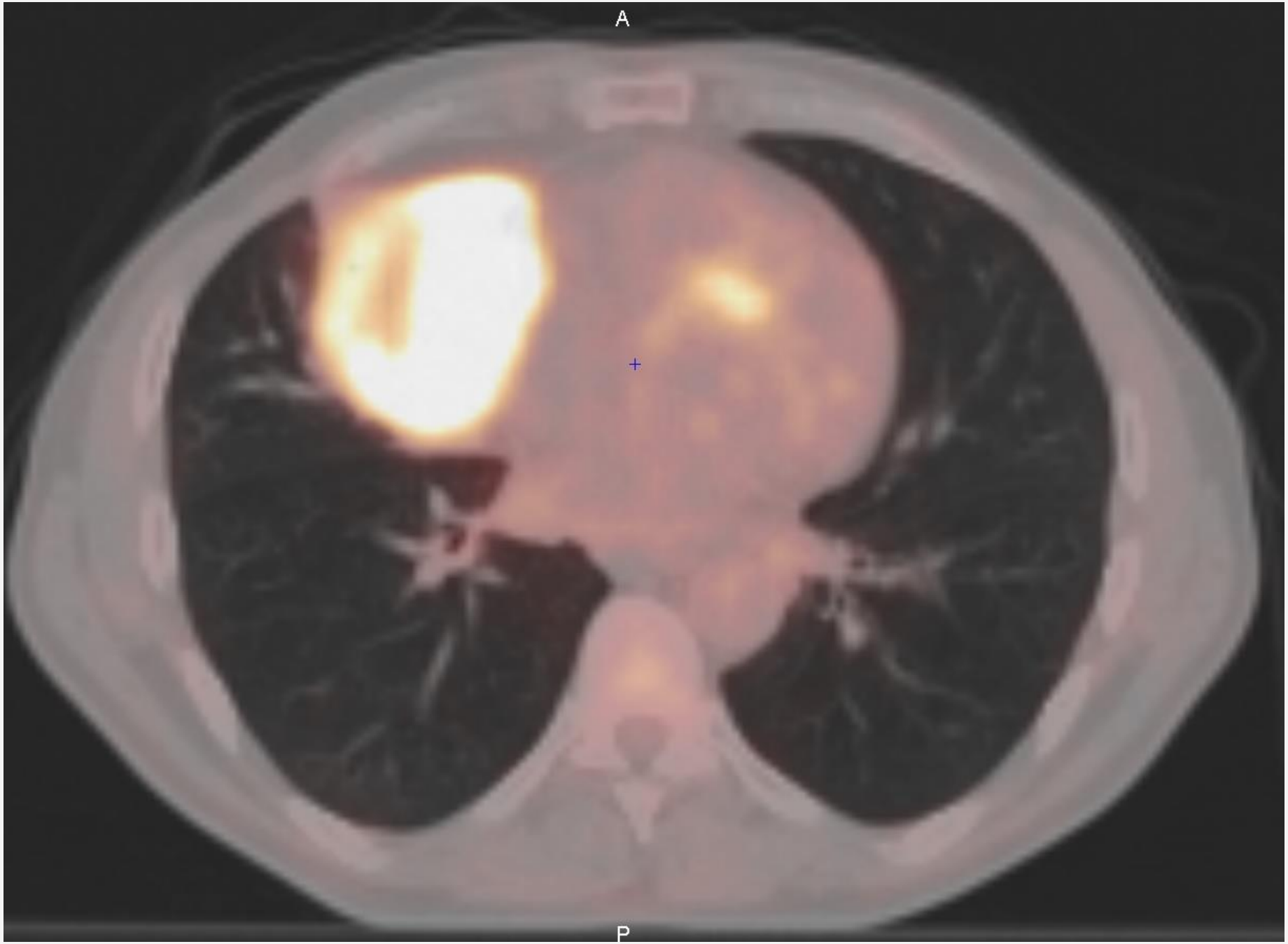
Remark : any automated task (registration, delineation) should be supervised

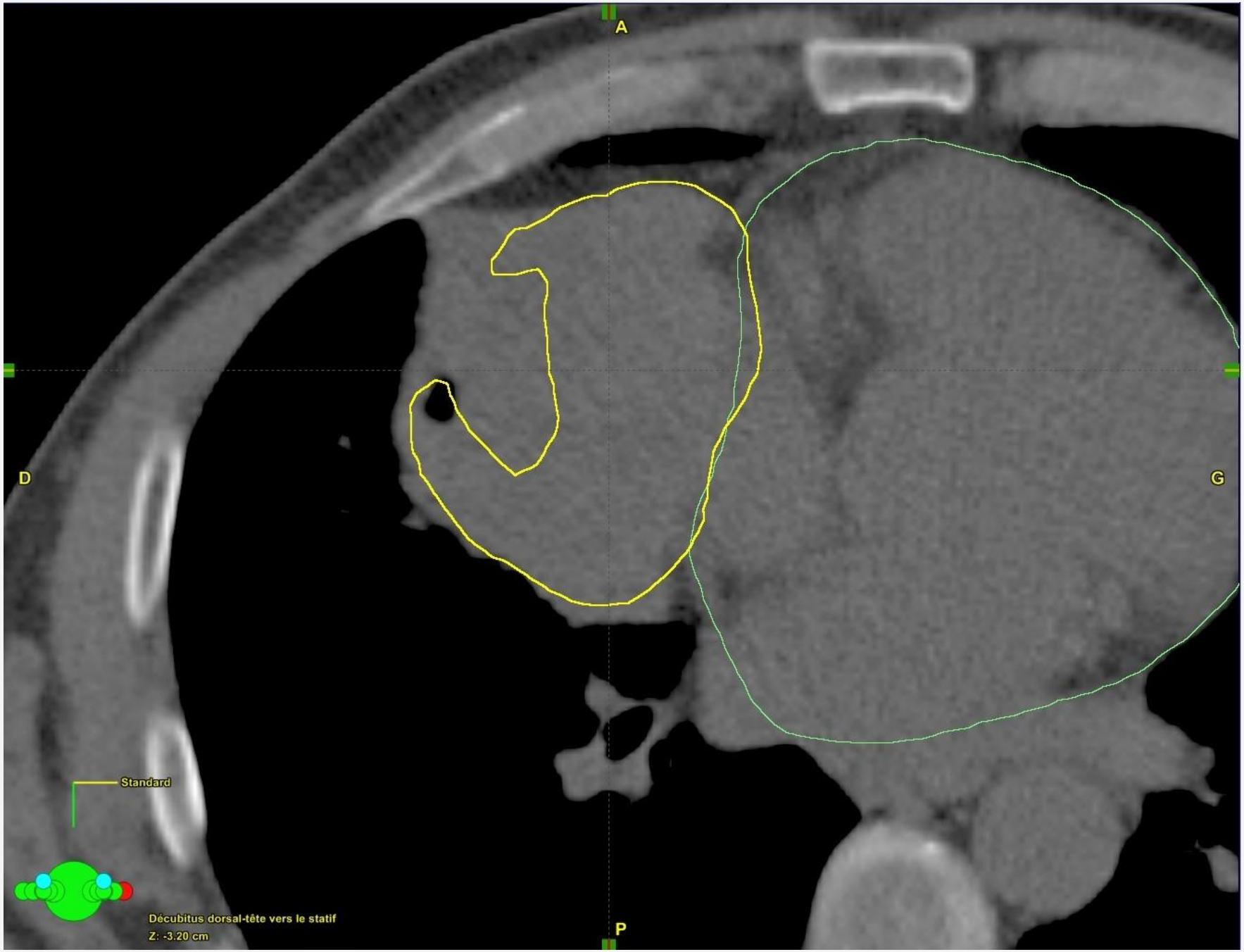
De Ruysscher EORTC JCO 2010

Delineating GTV_T on PET/CT



van Loon IJROBP 2012


A
P


A
D
G
P
Standard
Décubitus dorsal-tête vers le statif
Z: -3.20 cm

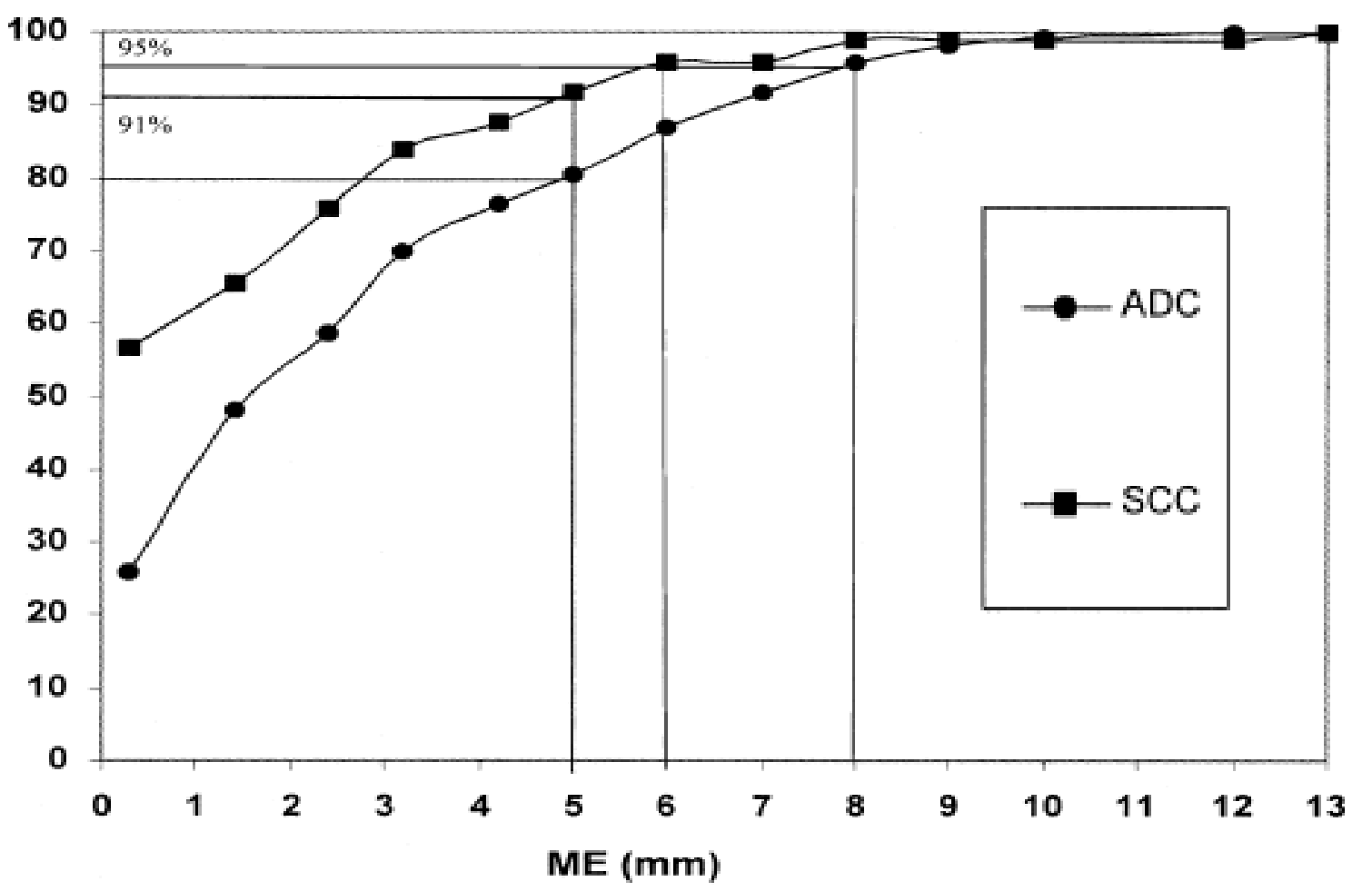
Margins for CTV_T

A fixed 5-mm CTV margin may be used	2B
Adjustment according to histology may be done	2B
Adjustment according to normal tissues (bones, vessels, …) may be appropriate	2B

Remark : any automated task (registration, delineation) should be supervised

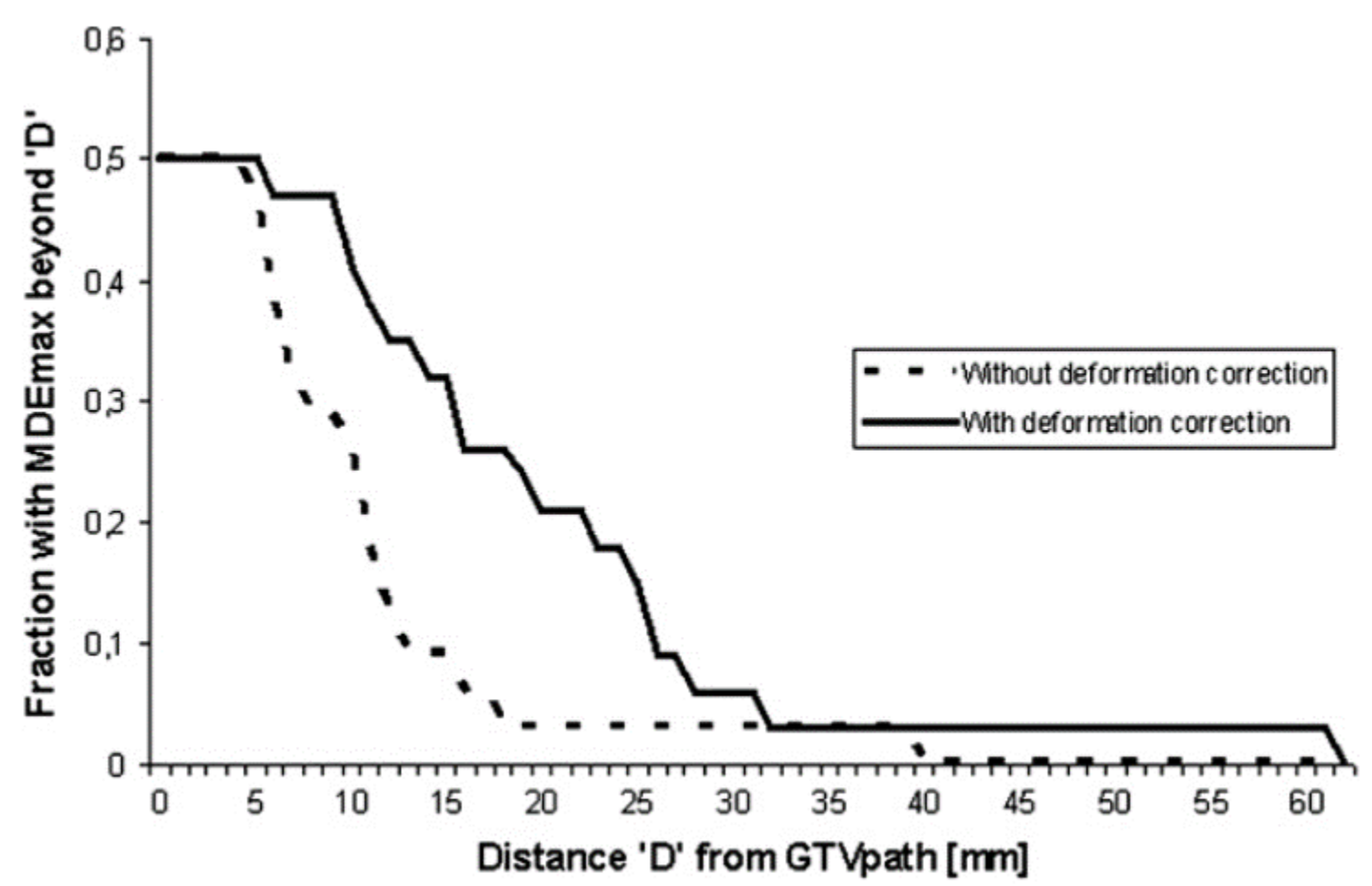
De Ruysscher EORTC JCO 2010

Margins for CTV_T



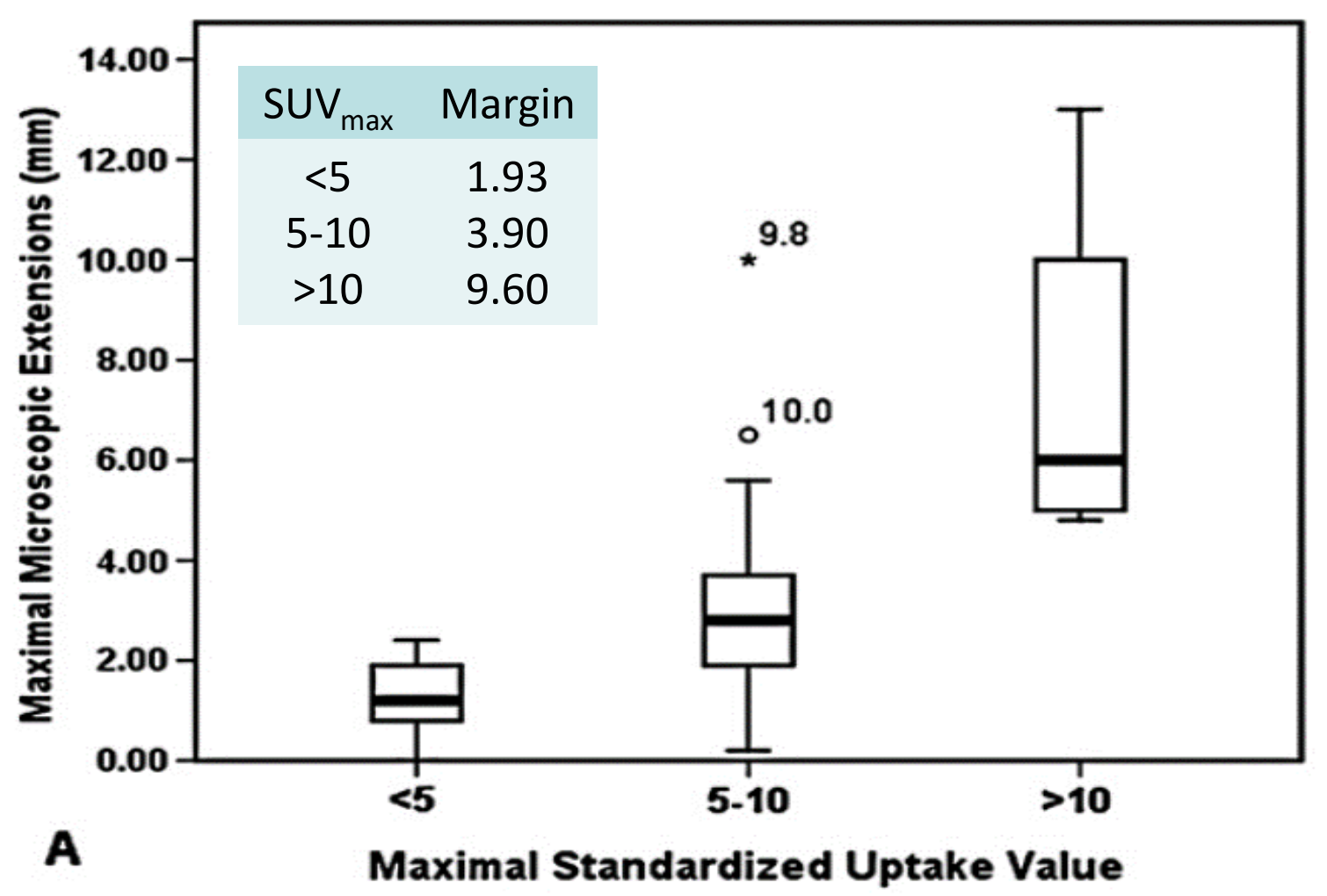
Giraud IJROBP 2000

Margins for CTV vs. pathology



van Loon IJROBP 2012

Delineating CTV_T on PET/CT



Meng IJROBP 2012

Mediastinal irradiation ?

A. never
B. if N+
C. always
D. don‘t know

Mediastinal irradiation

Selective nodal irradiation is recommended •CT : short axial diameter ≥1 cm •FDG uptake before chemotherapy •endoscopy, US FNA, mediastinoscopy, …	1B
Elective irradiation is not recommended	1B

De Ruysscher EORTC JCO 2010

Elective nodal (ENI) versus involved-field irradiation (IFI)

N = 200	Elective nodal (60-64 Gy)	Involved field (68-74 Gy)	p
Local control @ 5yrs	36 %	51 %	.03
node-only failure	4 %	7 %	.35
IF failure	55 %	38 %	.02
Pneumonitis	29%	17%	.04
OS @ 2 yrs	26 %	39 %	.2
@ 5 yrs	18 %	25 %	

- ✓ Inoperable stage III, no PET, ∅ ≤ 6 cm, SC -, pleura –
- ✓ IK ≥ 80, weight loss < 10 %
- ✓ 4 – 6 cycles DDP-based CT concomitantly

Yuan AJCO 2007

Elective nodal (ENI) versus involved-field irradiation (IFI)

N = 200	Elective nodal (60-64 Gy)	Involved field (68-74 Gy)	p
Lo	36 %	51 %	03
			35
			02
Pr			04
OS			
@ 5 yrs	18 %	25 %	.2

Number To IFI

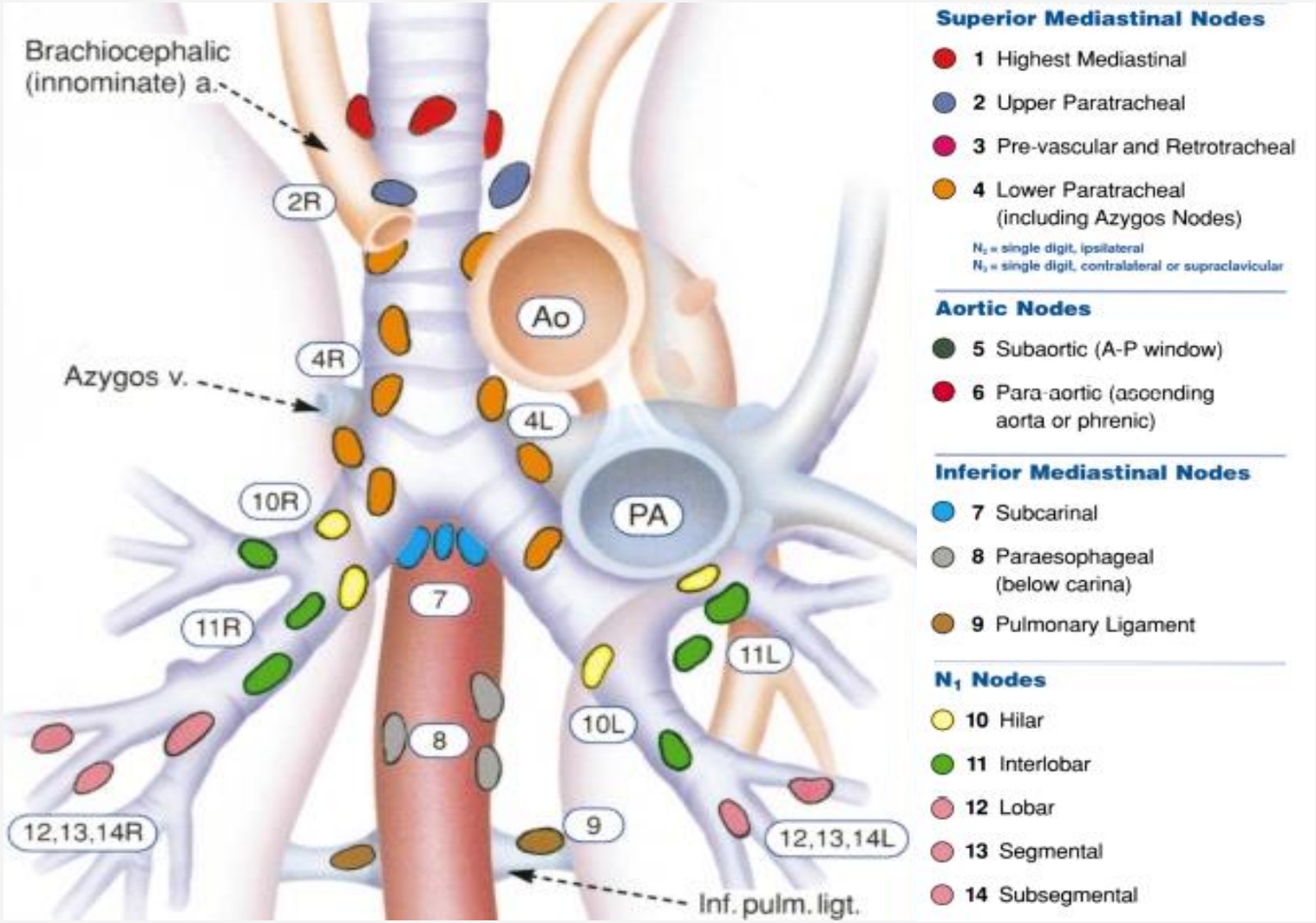
8 to avoid 1 pneumonitis

9 to avoid 1 local failure @ 5 years

- ✓ Inoperable stage III, no PET, ∅ ≤ 6 cm, SC -, pleura –
- ✓ IK ≥ 80, weight loss < 10 %
- ✓ 4 – 6 cycles DDP-based CT concomitantly

Yuan AJCO 2007

Mediastinal nodes



Mountain Chest 1997

How good is the test ?

	Sensitivity TP/(TP+FN)	Specificity TN/(FP+TN)	LR+ TP/FP	LR- FN/TN
CT	60 %	80 %	3 : 1	1 : 2
FDG-PET				
all stages	80 %	90 %	8 : 1	1 : 5
enlarged nodes	90 %	70 %	3 : 1	1 : 7
normal nodes	70 %	94 %	11 : 1	1 : 3
Mediastinoscopy				
all stages	78 %	100 %	∞	1 : 5
enlarged nodes	82 %	100 %	∞	1 : 6
normal nodes	42 %	100 %	∞	1 : 2

De Ruysscher R&O 2012

LLL tumour, 4R PET+ : Probability of actual involvement ?

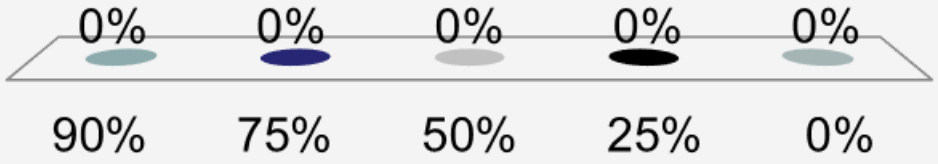
A. 90%

B. 75%

✓ C. 50%

D. 25%

E. 0%



LLL tumour, 7 PET- : Probability of no involvement ?

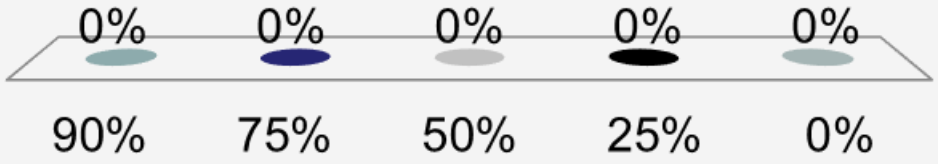
✔ A. 90%

B. 75%

C. 50%

D. 25%

E. 0%



LLL tumour, left hilum PET- : Probability of no involvement ?

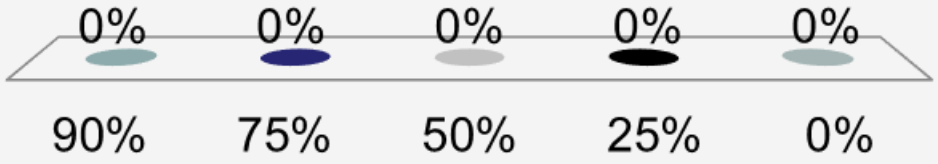
A. 90%

✓ B. 75%

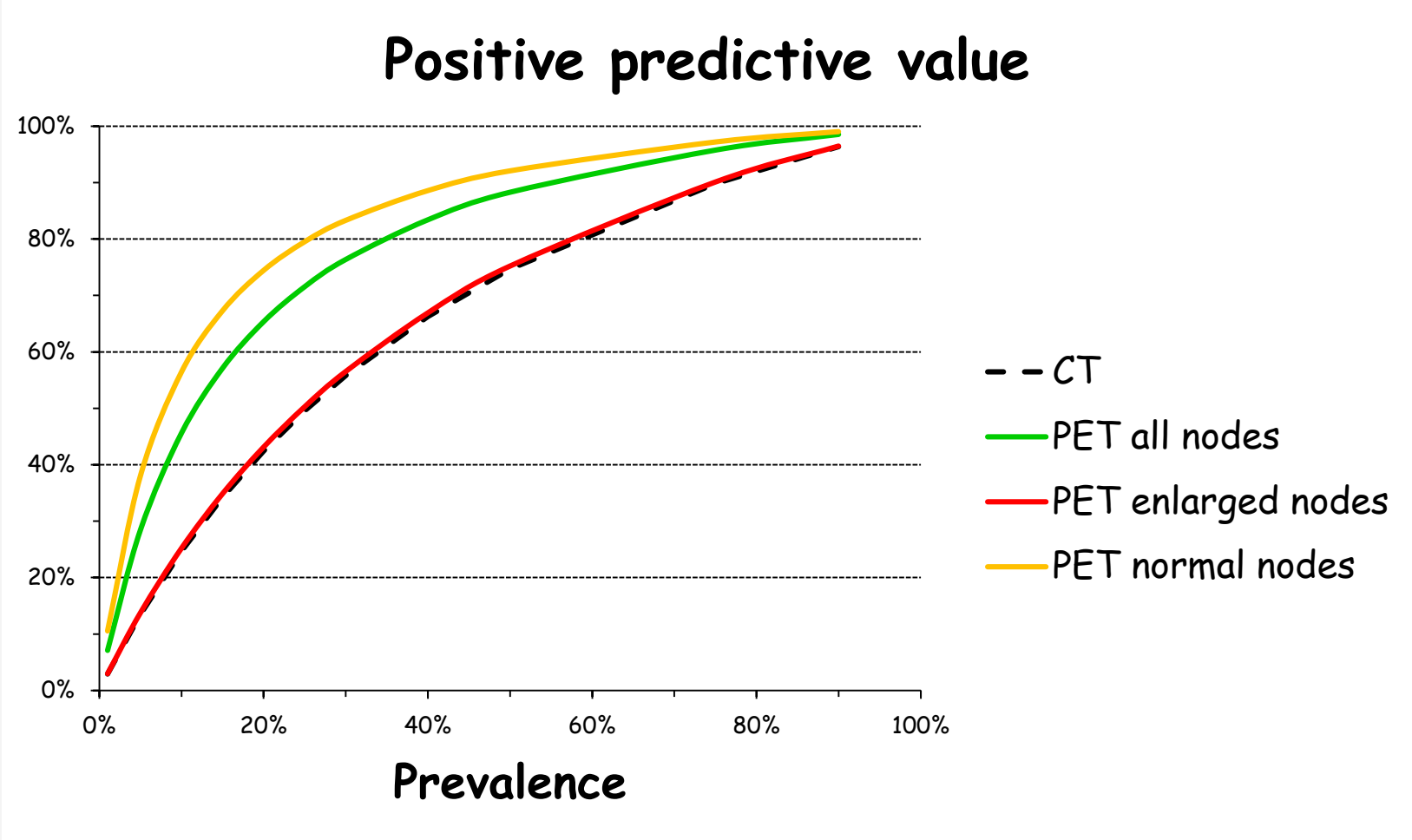
C. 50%

D. 25%

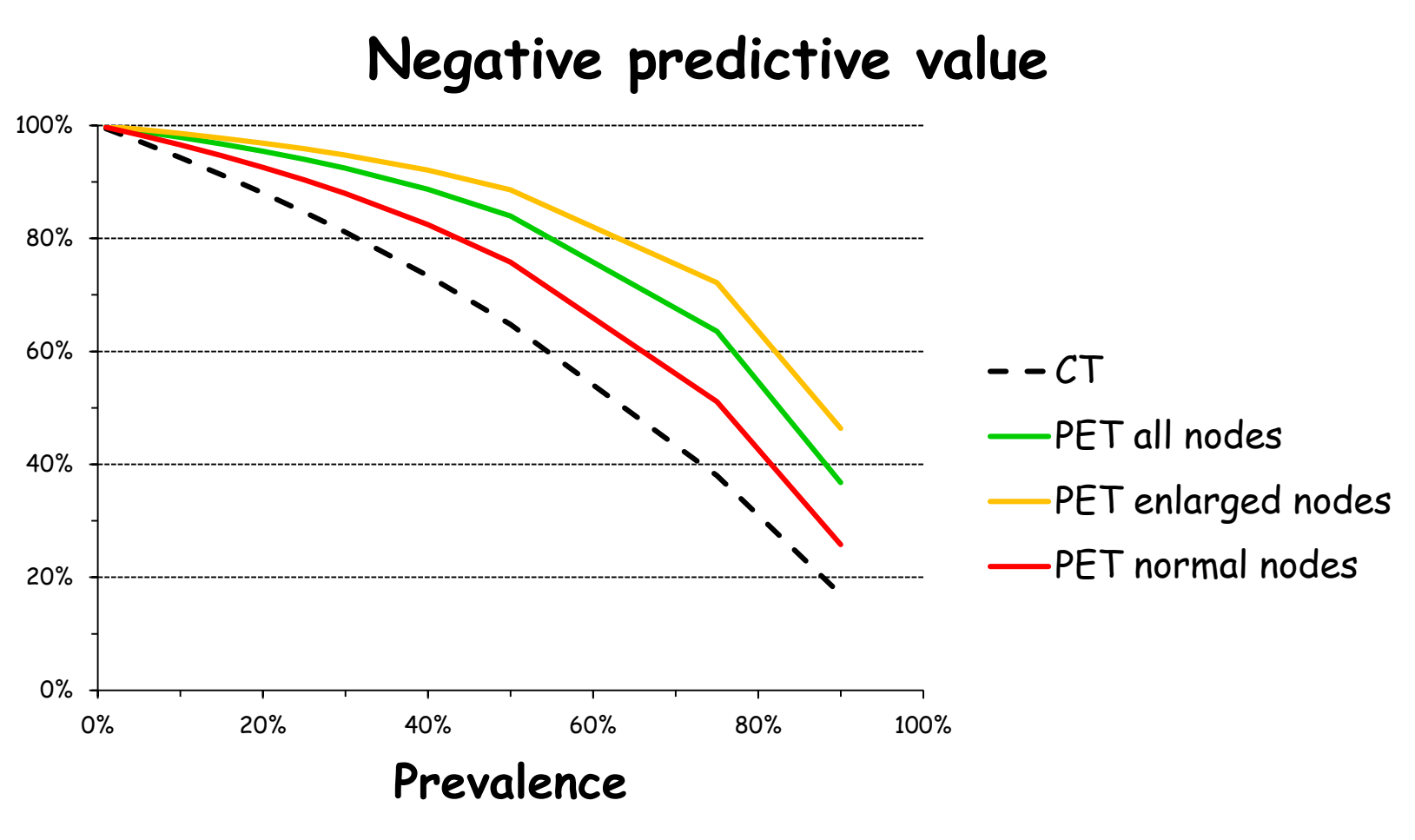
E. 0%



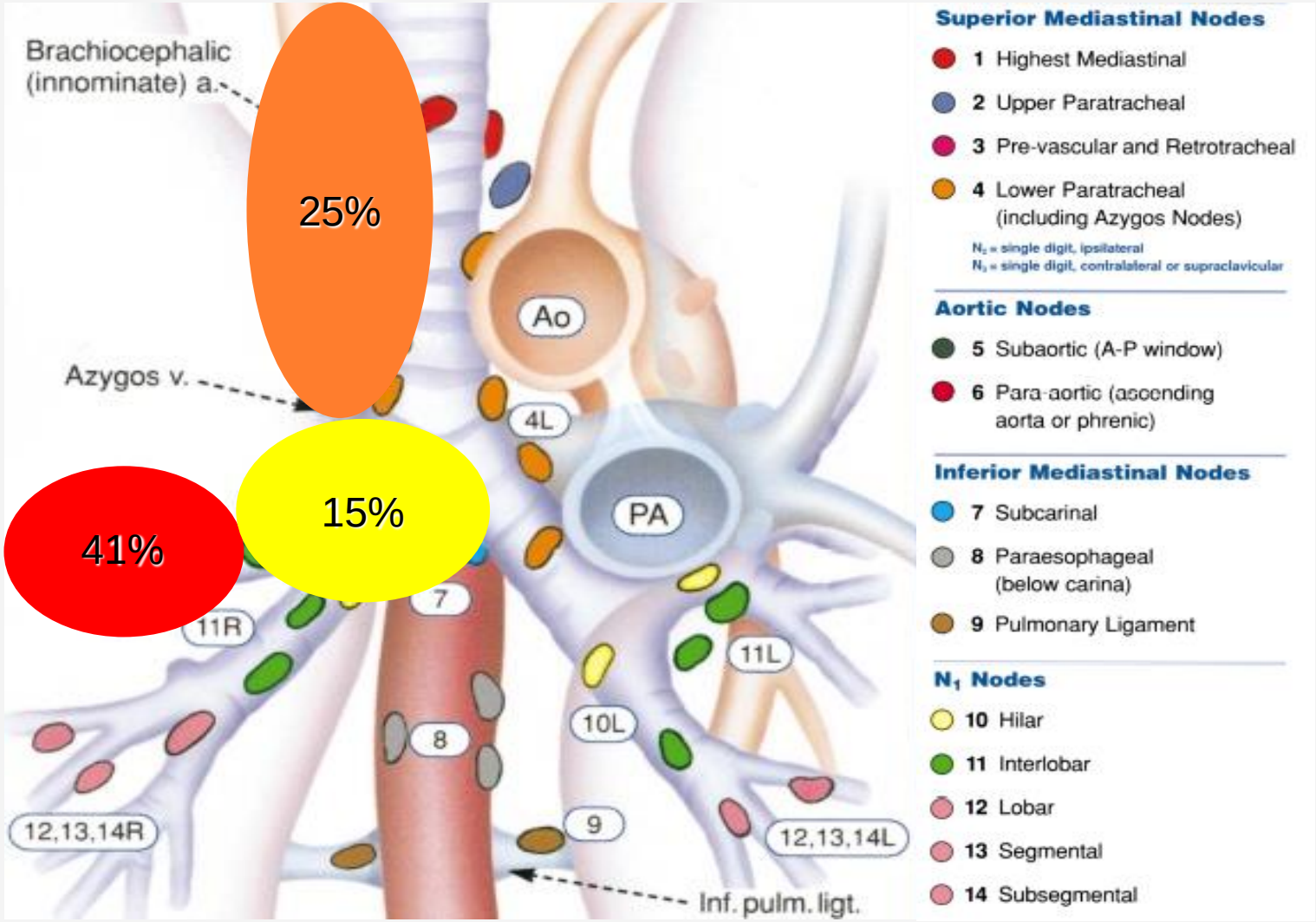
How good is your diagnosis ?



How good is your diagnosis ?

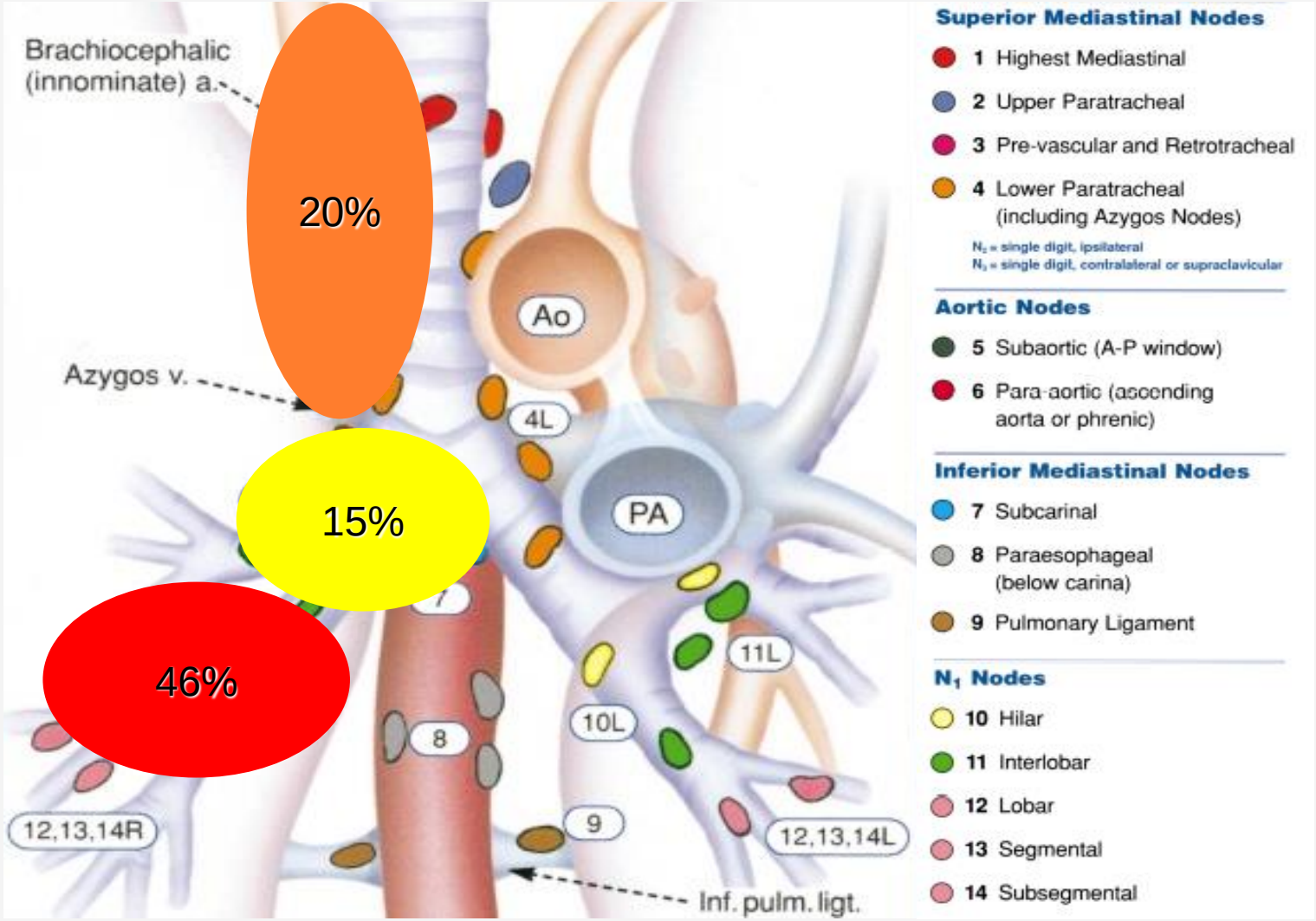


Right upper lobe tumour



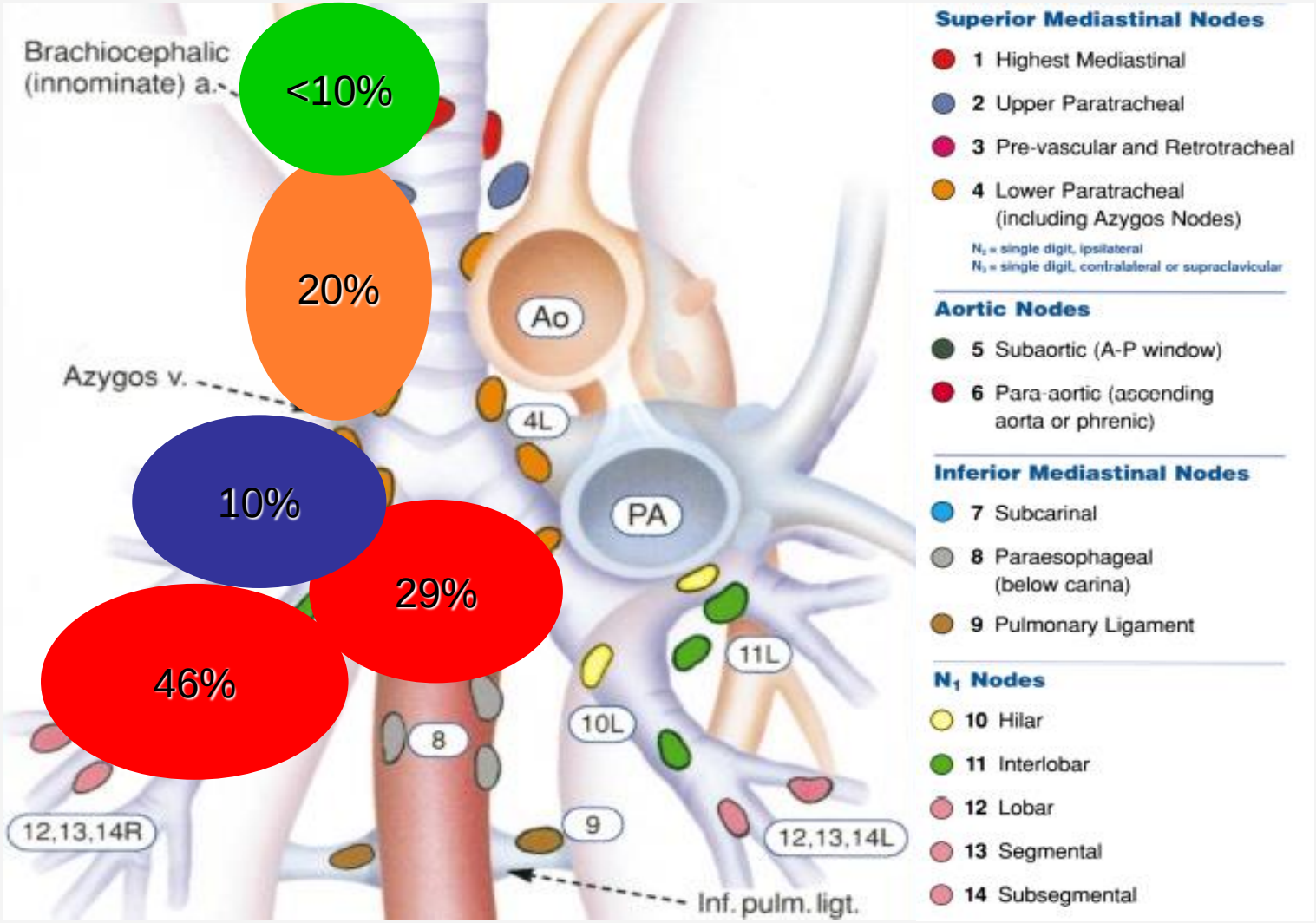
Review in Giraud IJROBP 2006

Right medial lobe tumour



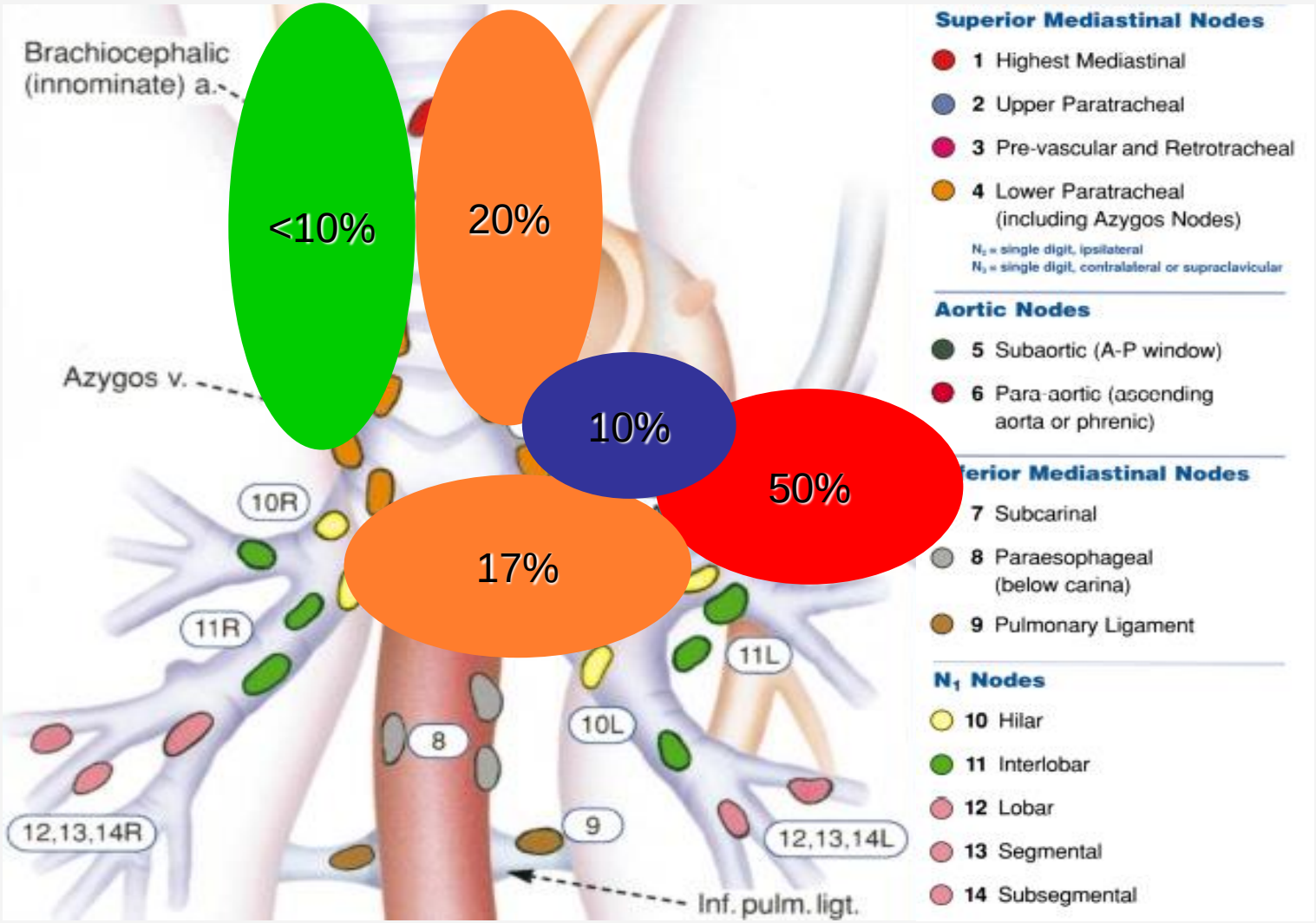
Review in Giraud IJROBP 2006

Right lower lobe tumour



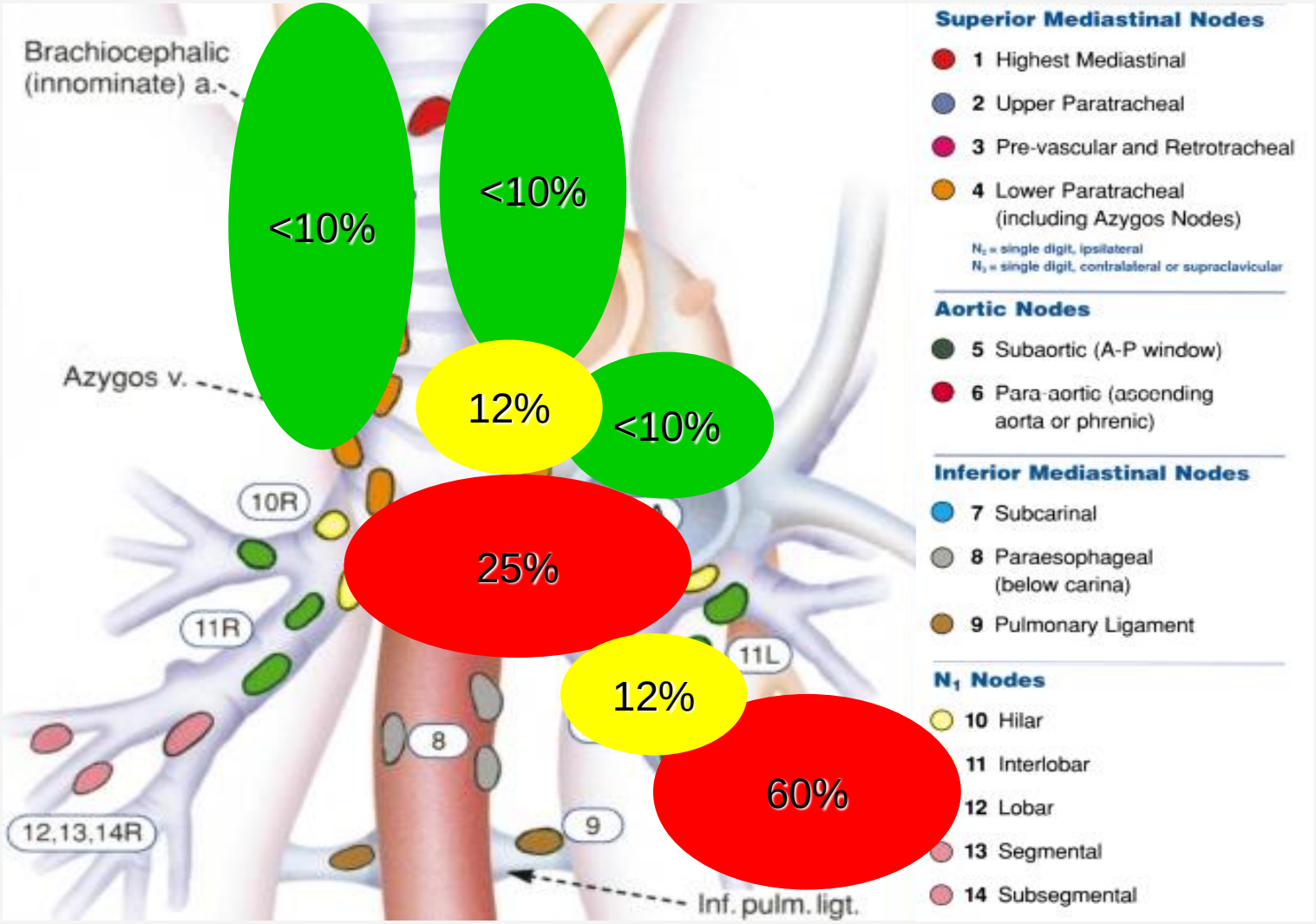
Review in Giraud IJROBP 2006

Left upper lobe tumour



Review in Giraud IJROBP 2006

Left lower lobe tumour



Review in Giraud IJROBP 2006

How good is your diagnosis ?

	P(N+) = 10 %			P(N+) = 50 %			P(N+) = 90 %		
	PET+	PET-	Total	PET+	PET-	Total	PET+	PET-	Total
N+	8	2	10						
N-	9	81	90						
Total	**17**	**83**	**100**						

	P(N+)	10 %	50 %	90 %
Se	TP / TP + FN	80 %		
Sp	TN / TN + FP	90 %		
PPV	TP / TP + FP	47 %		
NPV	TN / TN + FN	98 %		

How good is your diagnosis ?

	P(N+) = 10 %			**P(N+) = 50 %**			**P(N+) = 90 %**		
	PET+	PET-	Total	PET+	PET-	Total	PET+	PET-	Total
N+	8	2	10	40	10	50			
N-	9	81	90	5	45	50			
Total	**17**	**83**	**100**	**45**	**55**	**100**			

	P(N+)	**10 %**	**50 %**	**90 %**
Se	TP / TP + FN	80 %	80 %	
Sp	TN / TN + FP	90 %	90 %	
PPV	TP / TP + FP	47 %	89 %	
NPV	TN / TN + FN	98 %	82 %	

How good is your diagnosis ?

	P(N+) = 10 %			P(N+) = 50 %			P(N+) = 90 %		
	PET+	PET-	Total	PET+	PET-	Total	PET+	PET-	Total
N+	8	2	10	40	10	50	72	18	90
N-	9	81	90	5	45	50	1	9	10
Total	**17**	**83**	**100**	**45**	**55**	**100**	**73**	**27**	**100**

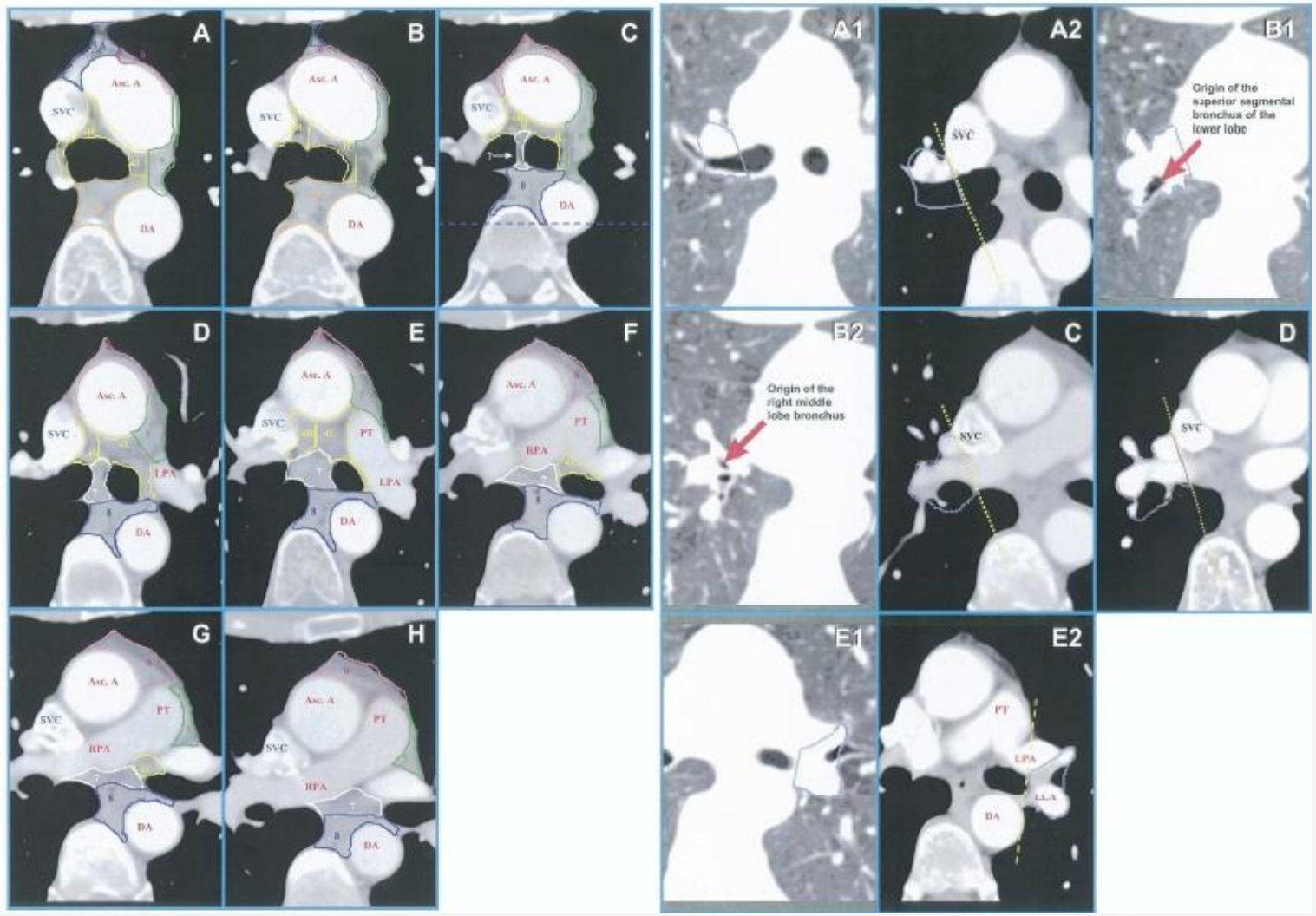
	P(N+)	10 %	50 %	90 %
Se	TP / TP + FN	80 %	80 %	80 %
Sp	TN / TN + FP	90 %	90 %	90 %
PPV	TP / TP + FP	47 %	89 %	99 %
NPV	TN / TN + FN	98 %	82 %	33 %

Doses to electively NOT irradiated nodes

Nodal region	Failure / total N0	Median dose [range]
SC ipsilateral	8 / 473	0 [0 – 70]
SC contralateral	9 / 515	0 [0 – 70]
Sup. med. ipsilateral	2 / 415	22 [0 – 84]
Sup. med. contralateral	3 / 502	6 [0 – 84]
Inf. med. ipsilateral	8 / 270	60 [0 – 84]
Inf. med. contralateral	8 / 454	21 [0 – 84]
Subcarinal	4 / 350	46 [0 – 84]

Rosenzweig JCO 2007

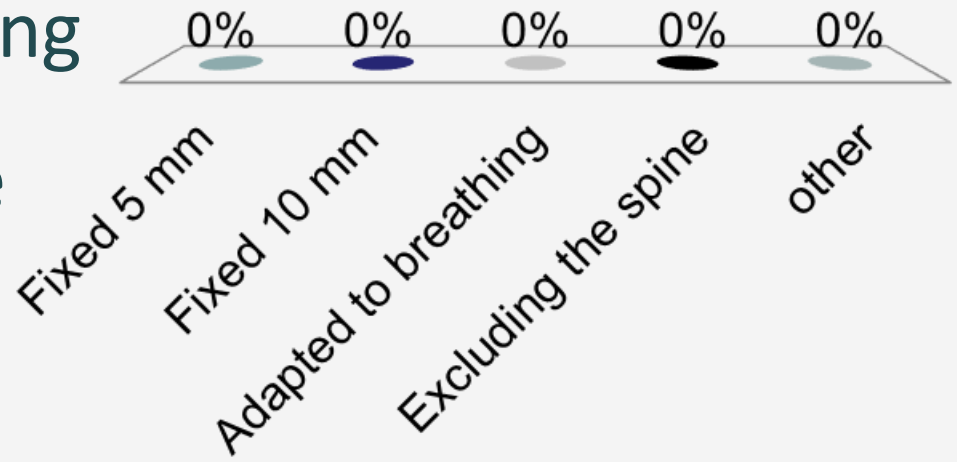
Delineate CTV_N according to anatomy



Chapet IJROBP 2005

Your margins from CTV to PTV ?

A. Fixed 5 mm
B. Fixed 10 mm
C. Adapted to breathing
D. Excluding the spine
E. other



Margins for PTV

- Ideally, measure random and systematic error
  - calculate margins so that ≥99 % of CTV receives ≥95 % of prescribed dose

Adjustment of the PTV is not permitted	1C
Dose prescription and reporting follow ICRU standards	1B

“Old-fashion” RT	“High-precision” RT
Blocks = GTV + 2 cm	CTV = GTV + 5-8 mm PTV = CTV + mobility + planning + setup Blocks = PTV + PENUMBRA

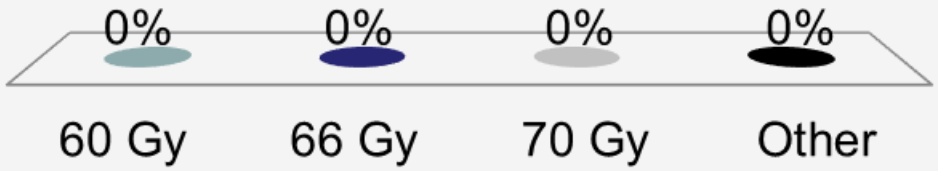
Your total dose (2Gy/f) ?

A. 60 Gy

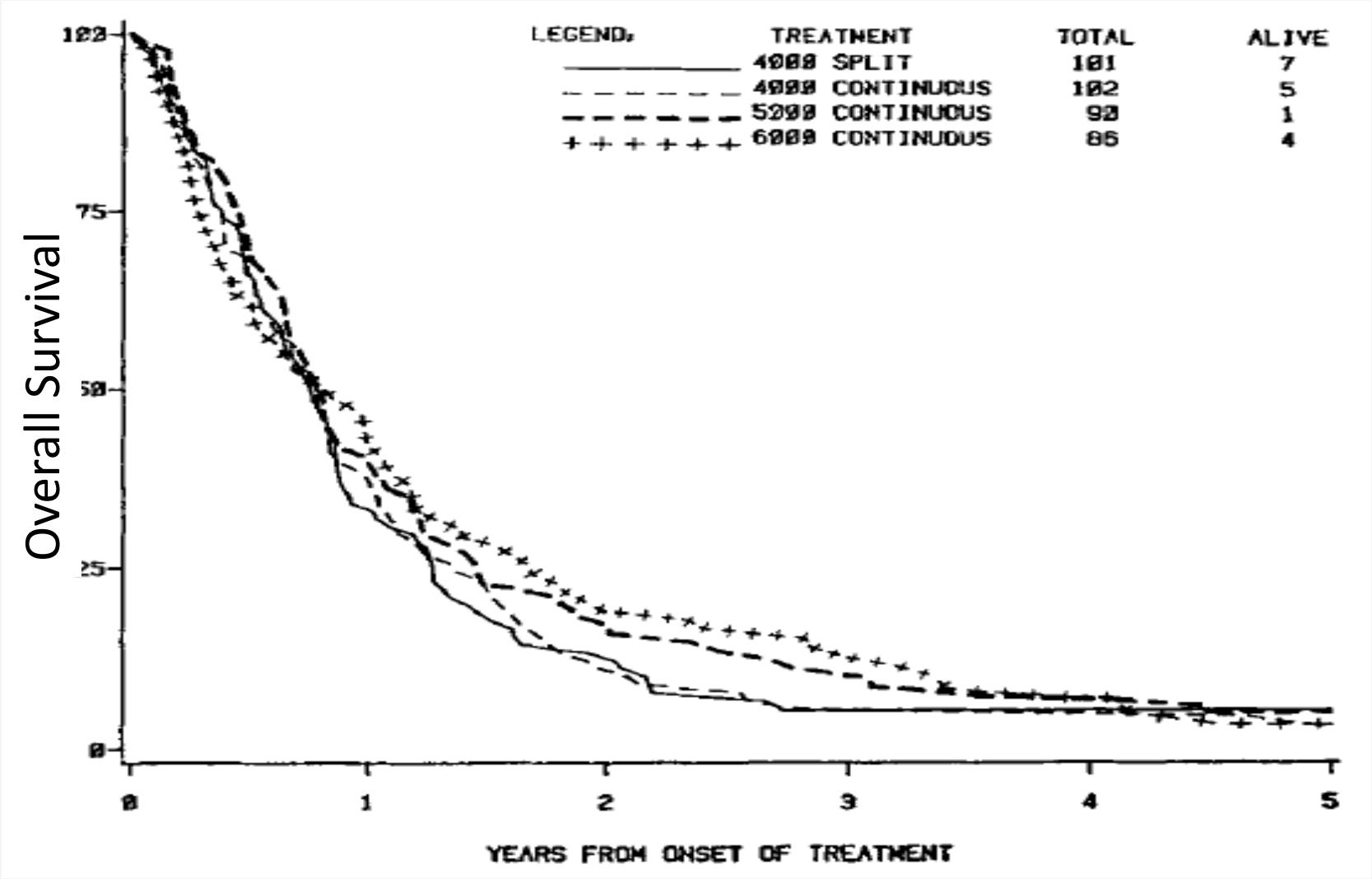
B. 66 Gy

C. 70 Gy

D. Other

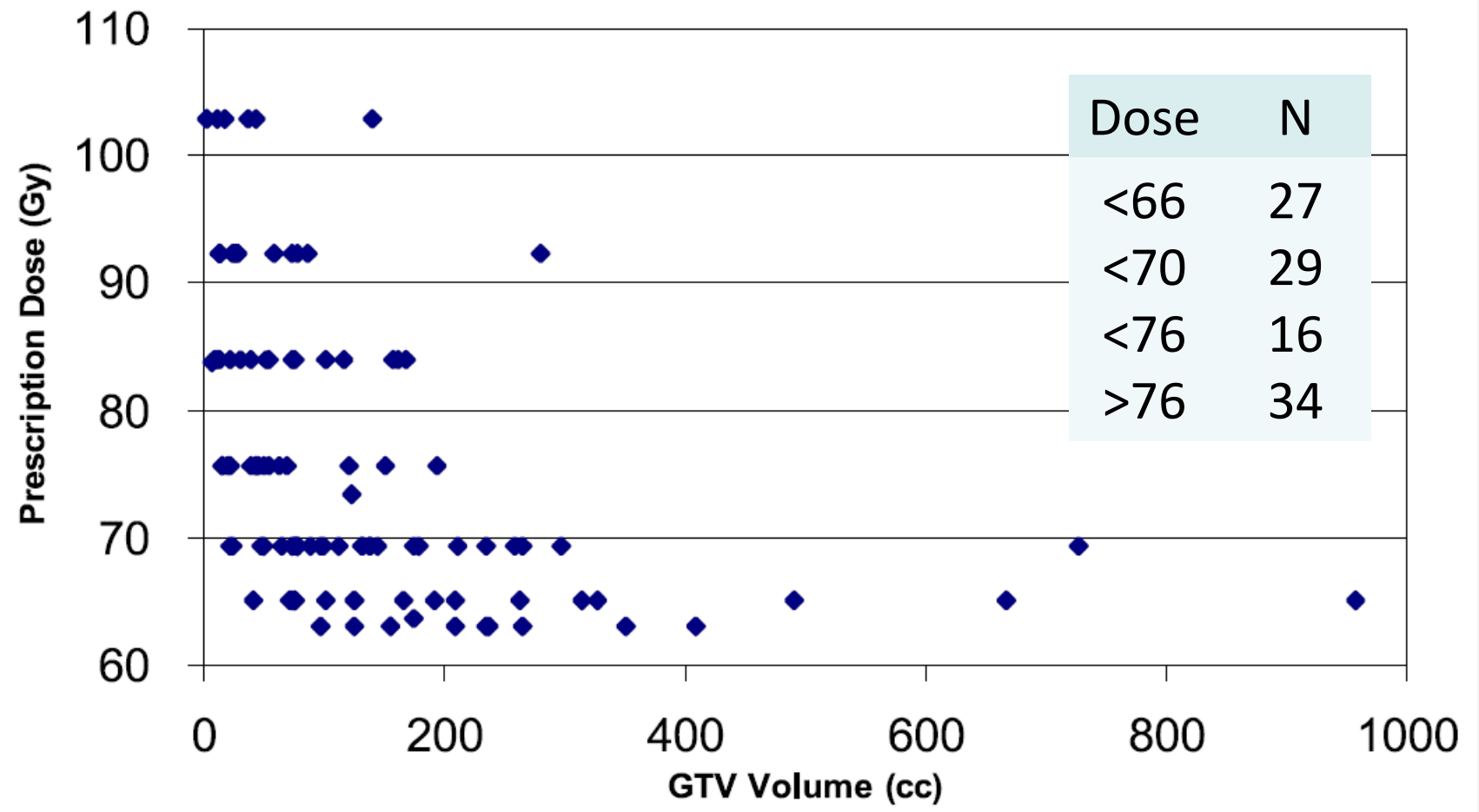


Total dose



Perez RTOG 73-01 Cancer 1987

Doses decreased with larger GTVs



Kong IJROBP 2005

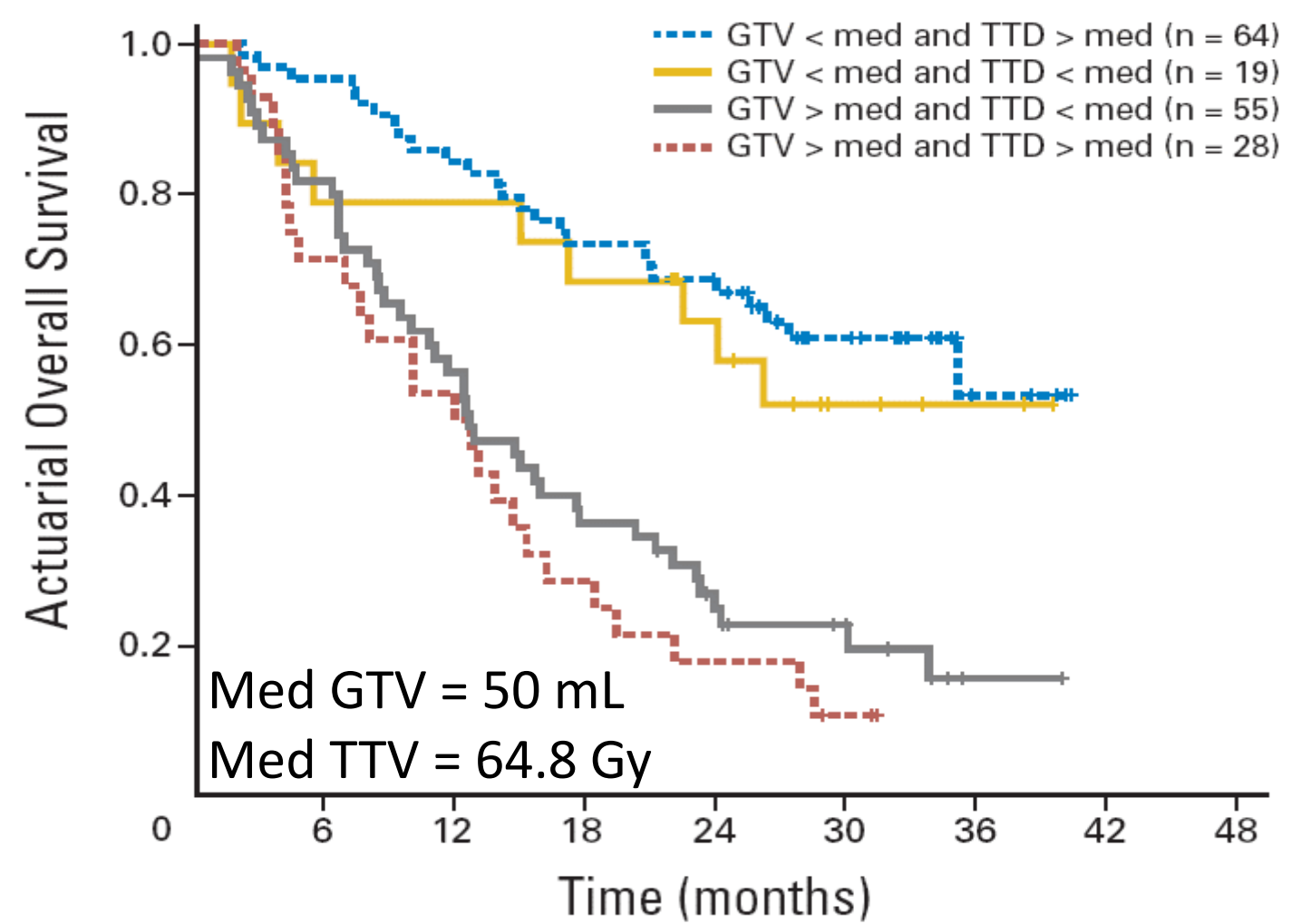
Doses decreased with larger GTVs

Stage	N	GTV (mL)	TTD (Gy)	MLD (Gy)
I	48	11 [59]	79 [10]	9 [4]
II	16	52 [63]	71 [10]	14 [9]
IIIA	35	65 [77]	61 [8]	15 [4]
IIIB	64	73 [296]	61 [9]	17 [4]

Figures are means and [SD]

van Baardwijk JCO 2010

Is it dose or volume ?



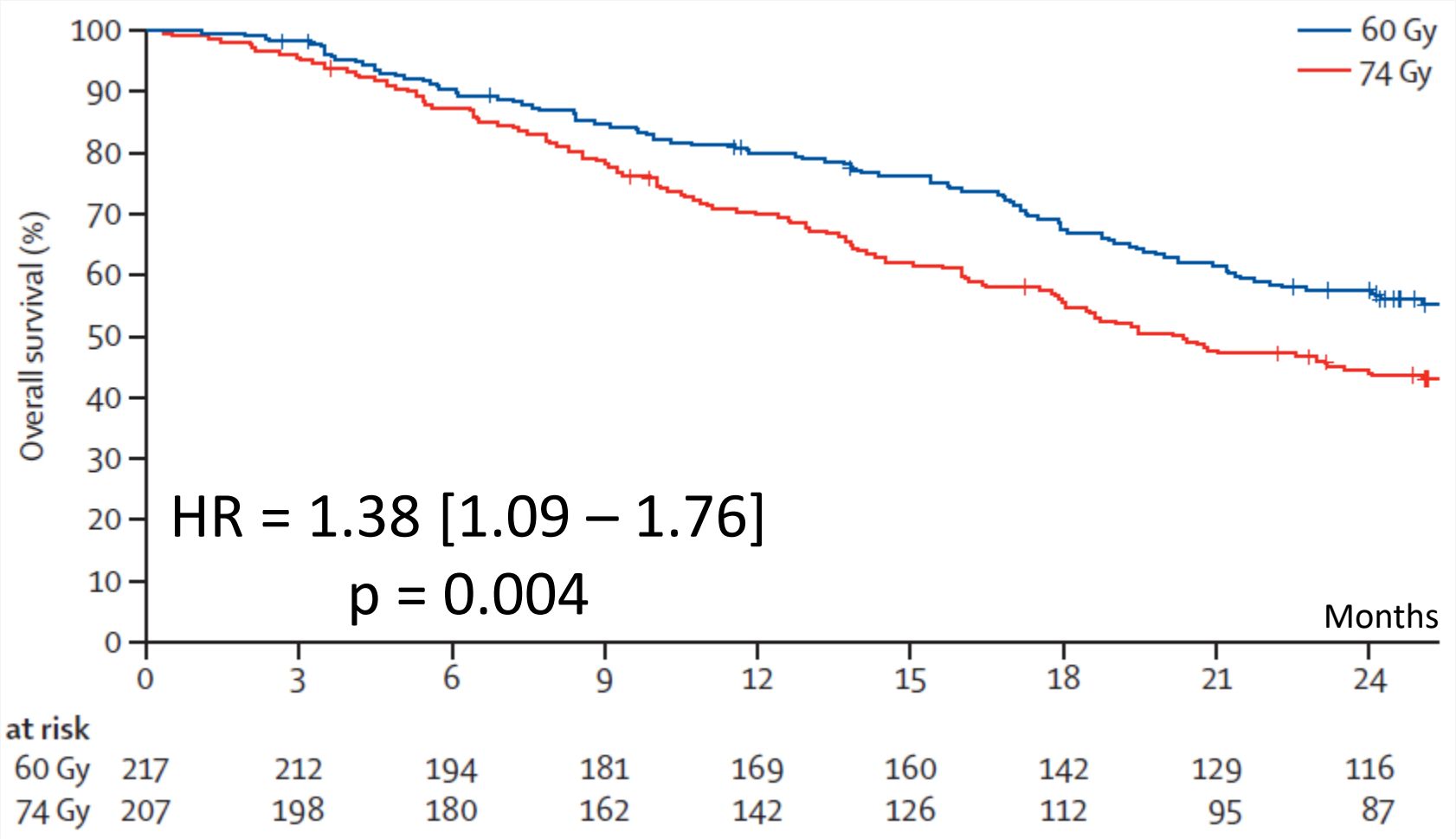
van Baardwijk JCO 2010

RTOG 0617

	Arm	Treatment	Consolidation
R	A	CTRT 60Gy	CT
A N	B	CTRT 74Gy	CT
D O	C	CTRT 60Gy + Cetux	CT + Cetux
M	D	CTRT 74Gy + Cetux	CT + Cetux

Bradley Lancet Oncology 2015

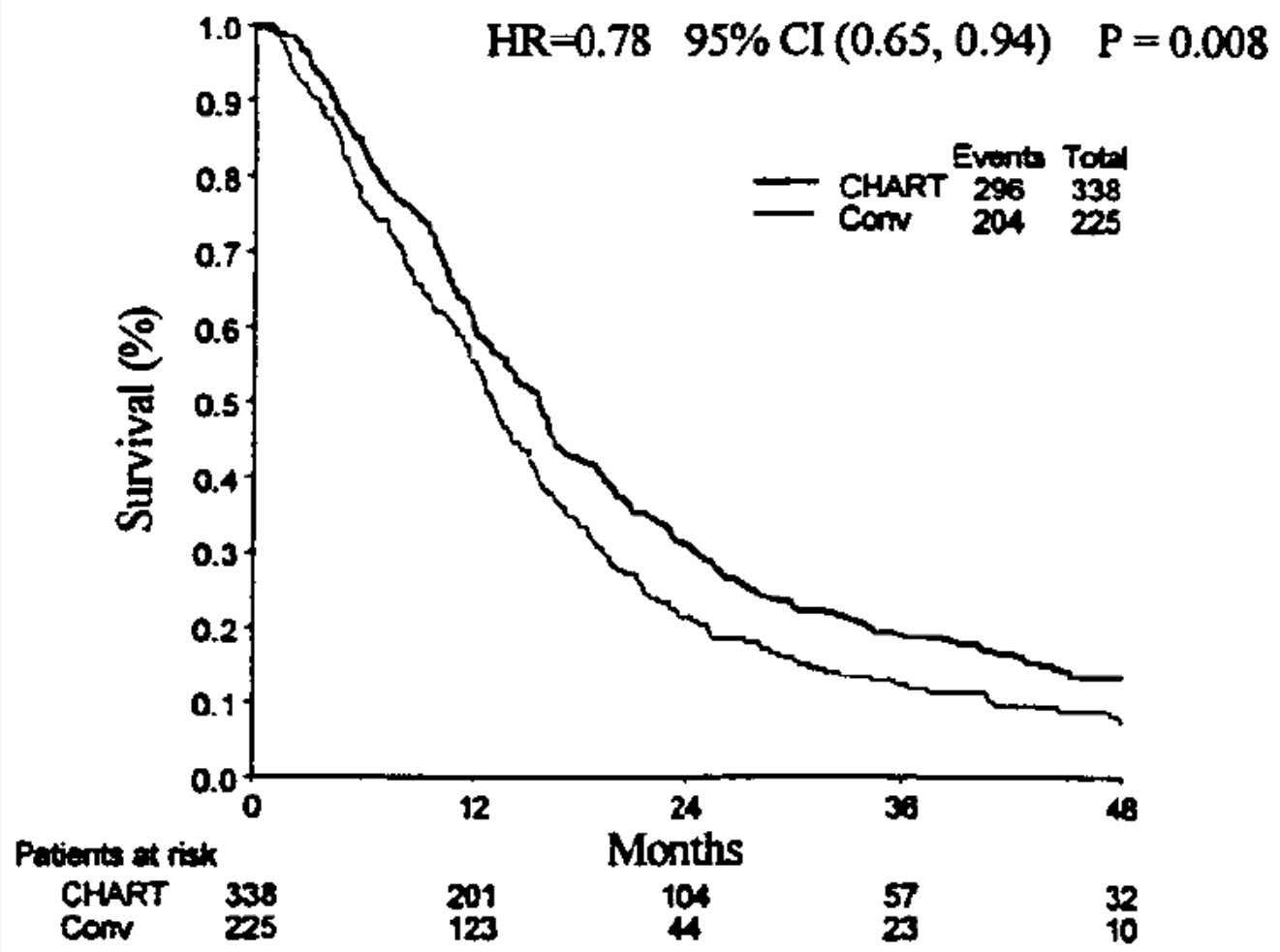
RTOG 0617: RT dose



Bradley Lancet Oncology 2015

Accelerated radiotherapy : CHART

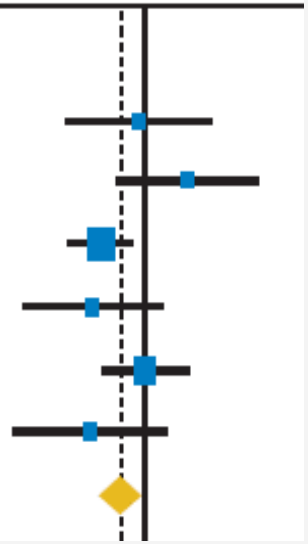
54 Gy / 1.5 Gy tid / 12 days



Saunders R&O 1999

Accelerated radiotherapy

Category / Trial	No. Deaths / No. Entered Exp. RT	Conv. RT	O-E	Variance	HR
Very accelerated RT					
PMCI 88C091	48/48	52/53	-0.8	24.3	
PMCI 88C091 CT	51/51	56/56	6.0	25.6	
CHART	316/338	217/225	-29.4	120.7	
ECOG 2597	51/60	55/59	-7.4	25.8	
CHARTWEL	132/150	132/150	0.2	65.8	
CHARTWEL CT	40/53	47/53	-6.4	21.2	
Subtotal	638/700	559/596	-37.8	283.4	



HR = 0.88 [0.78 to 0.98]

Absolute benefit : 3.8% at 3 yrs, 2.5% at 5 years

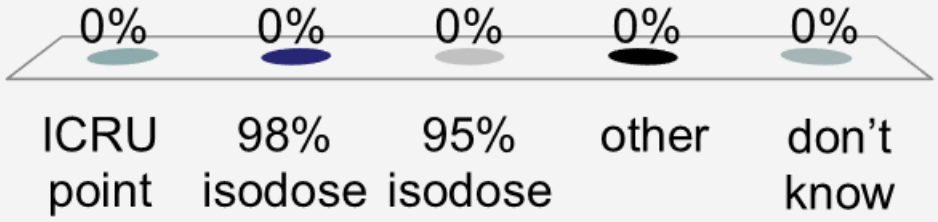
Mauguen JCO 2012

Conclusion (3)

- Total dose, conventional fractionation
  - 2D : no proof for doses > 60 Gy
  - 3D : ~~≥ 66 Gy if proper QA~~
  - 3D : no proof for doses > 60 Gy
- Acceleration may be useful
  - do not split treatment !

Where do you prescribe dose ?

A. ICRU point
B. 98% isodose
C. 95% isodose
D. other
E. don’t know

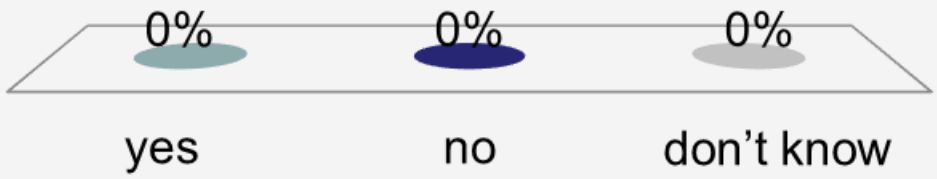


Do you correct for heterogeneities ?

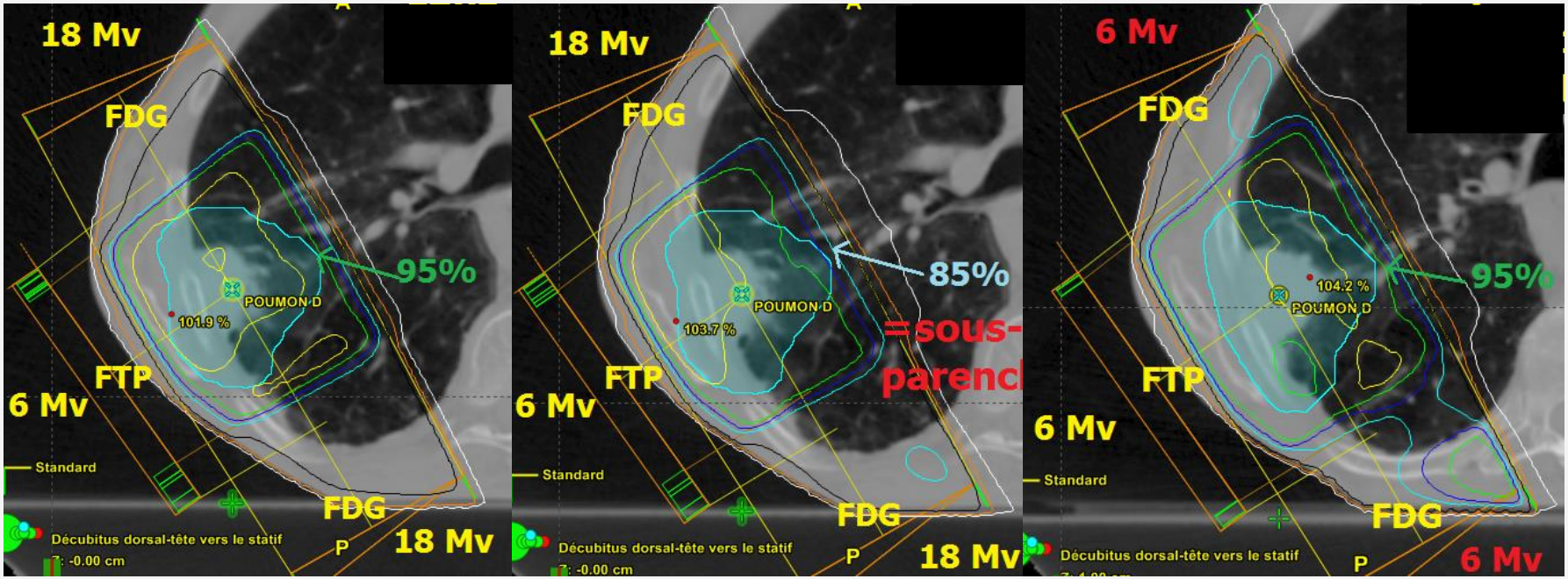
A. yes

B. no

C. don’t know



Correction for heterogeneities



No correction

Same MUs
with correction

Replanning
with correction

Courtesy C. Cabanel & D. Voisard

Correction for heterogeneities

- Dose to ICRU point = -2.3% [-9 – 4]
  - no correction vs same MUs with correction

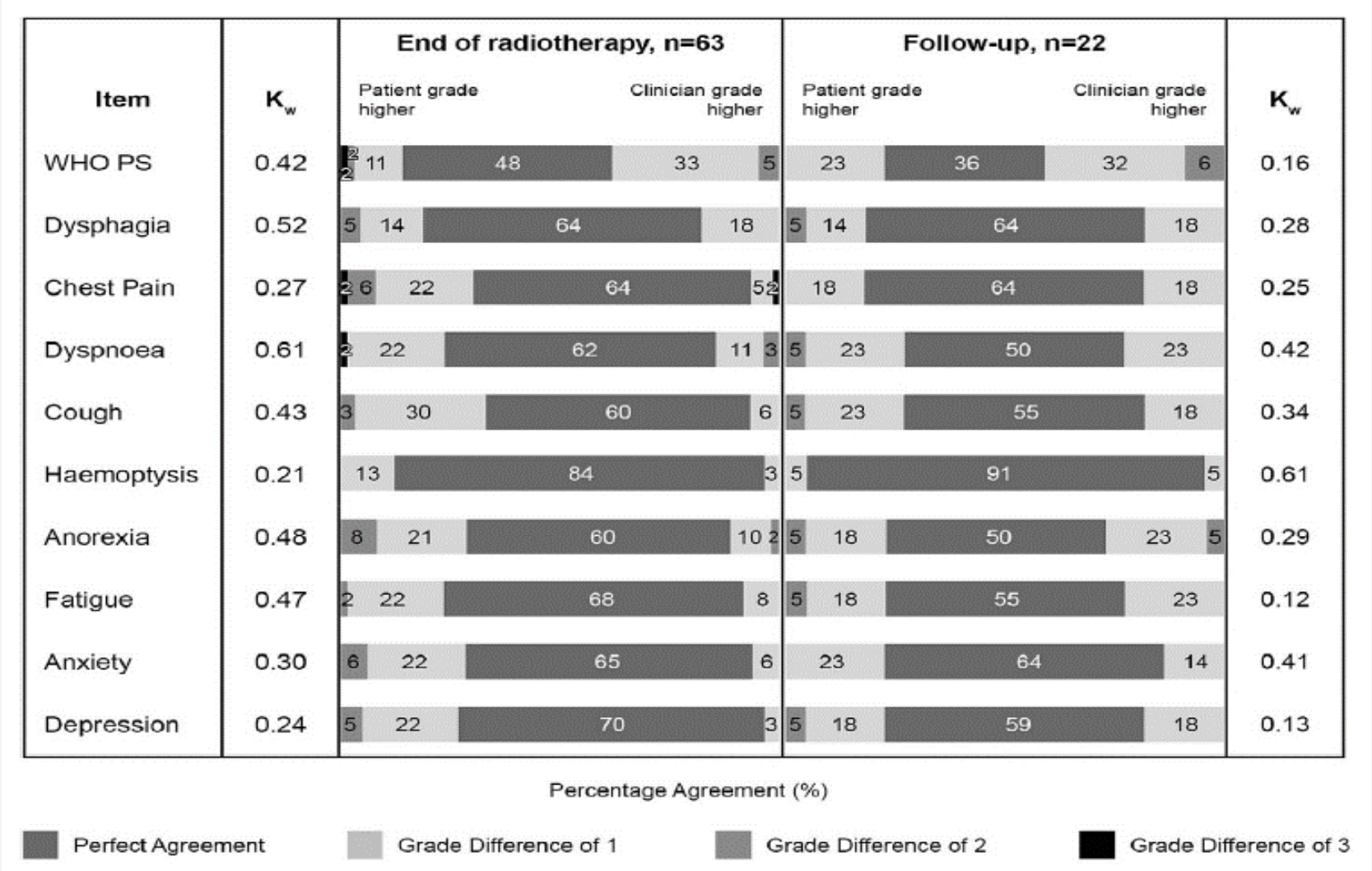
Organs at risk	No correction	Replan with correction	Delta (%)
lung (MLD)	14.4 [7.0 – 21.7]	14.8 [7.5 – 22.2]	4 [-18 – 27]
chord (Dmax)	32.0 [2.2 – 61.7]	30.7 [-1.5 – 63]	-6 [-29 – 16]
heart (V35)	9 [-9 – 28]	10 [-8 – 29]	13 [-33 – 58]

Courtesy C. Cabanel & D. Voisard

Organs at risk

- Lungs
- Spinal cord
- Oesophagus
- Heart
- Skin

Who should score for tolerance ?



Christodoulou R&O 2014

“Predictors” for pneumonitis

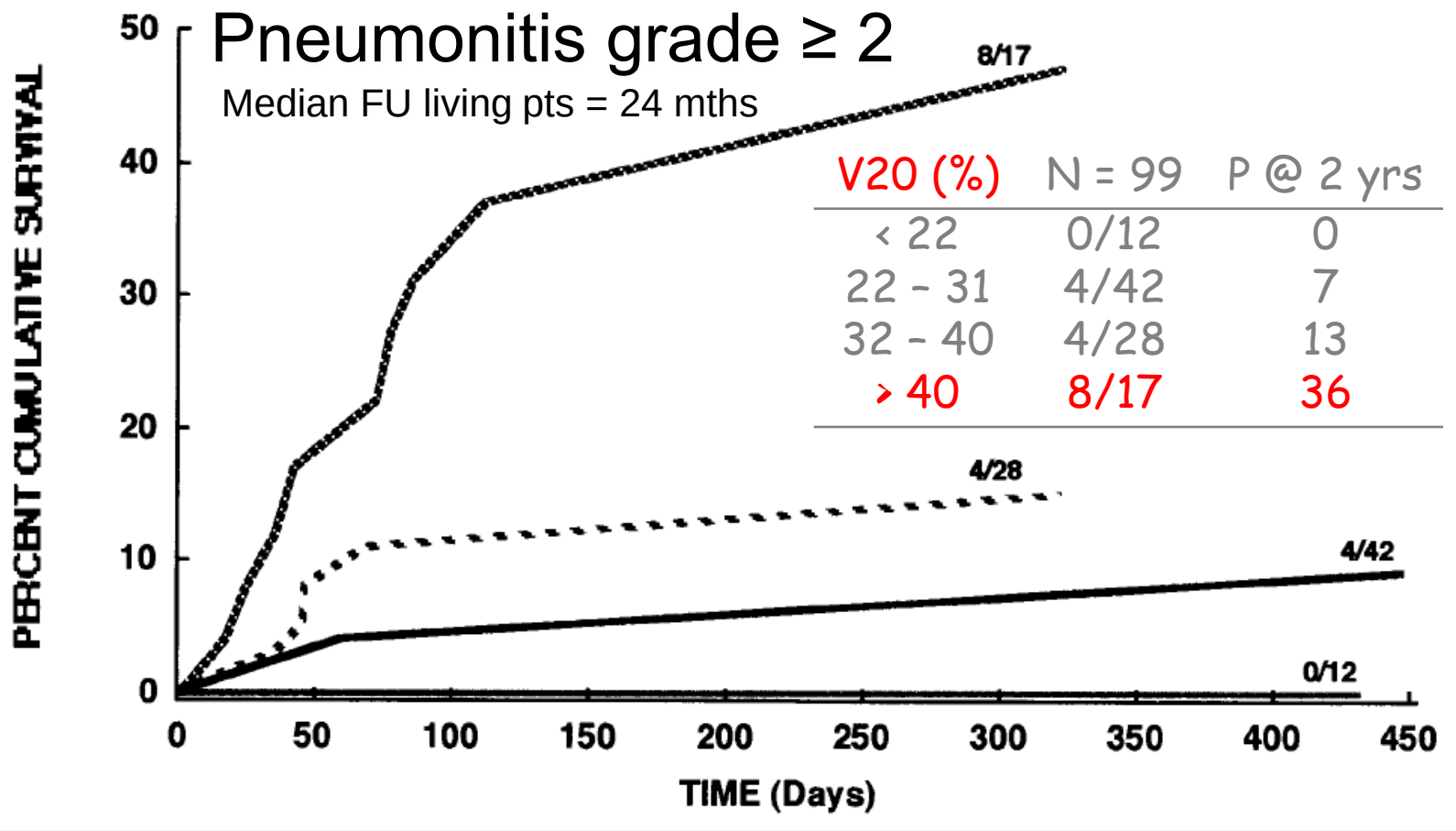
- Radiotherapy
  - total / fractional dose
  - DVH, NTCP
- Tumour location
- Other treatments, incl. chemo
- Patient’s tolerance
  - performance status
  - pulmonary function
  - comorbidity

DVH-derived parameters

- Vdose
  - volume of lung receiving dose > threshold
- Mean Lung Dose (MLD)
  - average dose in total lung volume
- NTCP
  - Normal Tissue Complication Probability
- Quiz : definition of total lung volume ?
  - exclude GTV ? ... CTV ? ... PTV ?

Risk of pneumonitis

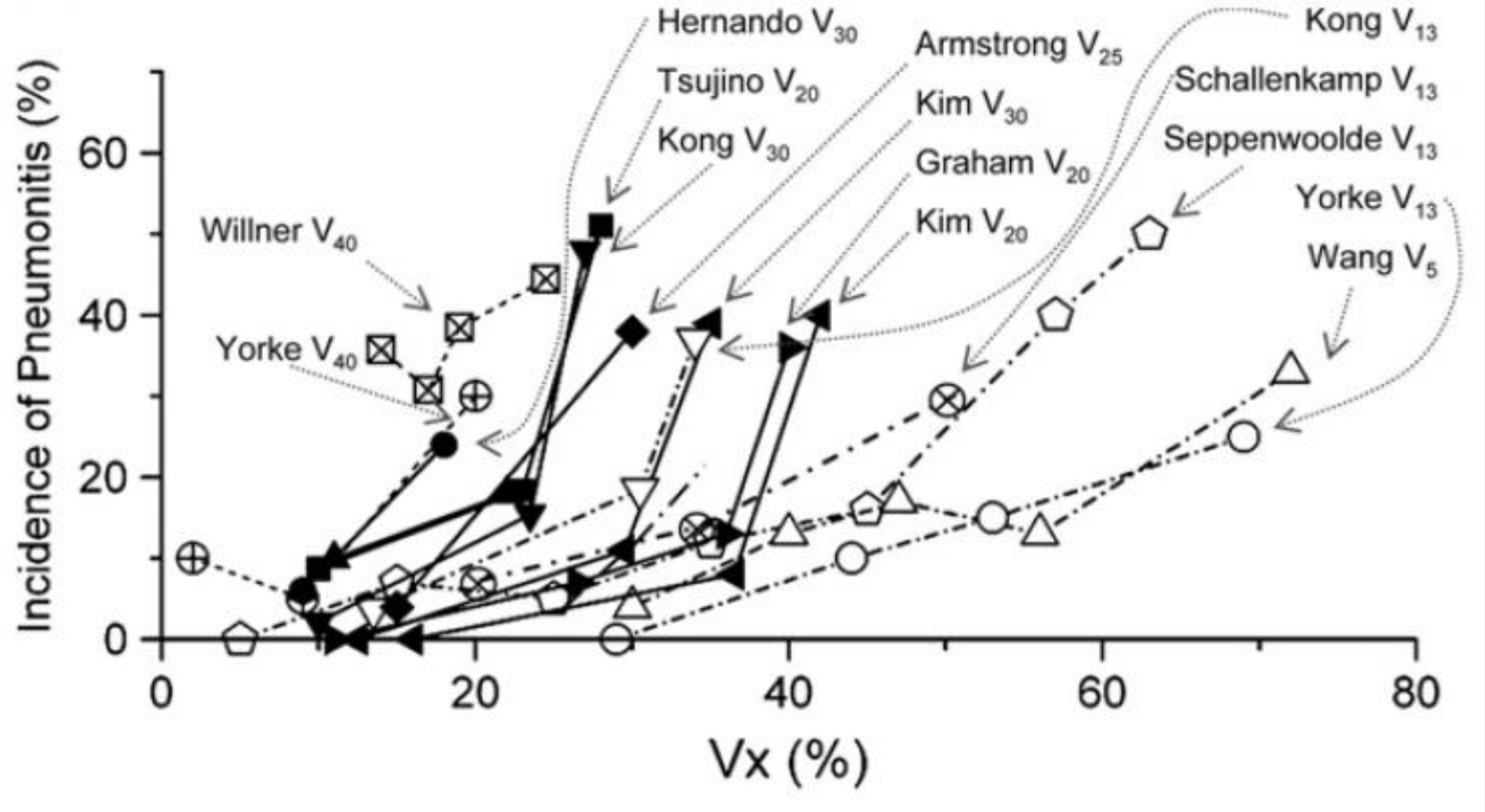
- V20 : % of total lung volume minus PTV -



V20 (%)	N = 99	P @ 2 yrs
< 22	0/12	0
22 - 31	4/42	7
32 - 40	4/28	13
> 40	8/17	36

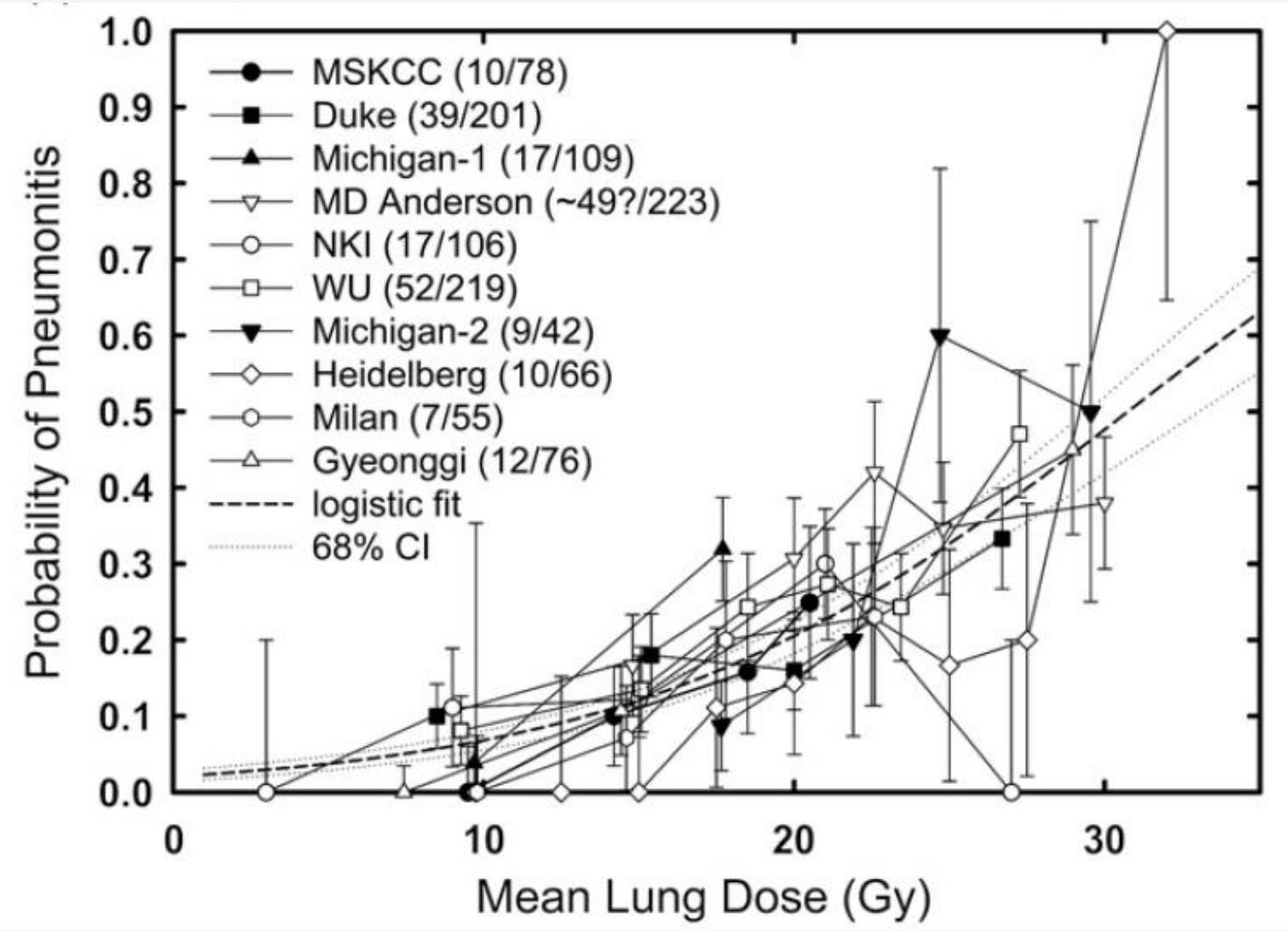
Graham IJROBP 1999

Risk of pneumonitis : Vdose



Marks IJROBP 2010

Risk of pneumonitis : MLD



Marks IJROBP 2010

Mean Lung Dose

Reference	N	MLD (Gy)	Accuracy
Oetzel 1995	66	> 22.5	0.65
Kwa 1998	400	> 16	0.56
Graham 1999	99	> 20	0.61
Hernando 2001	201	> 20	0.55

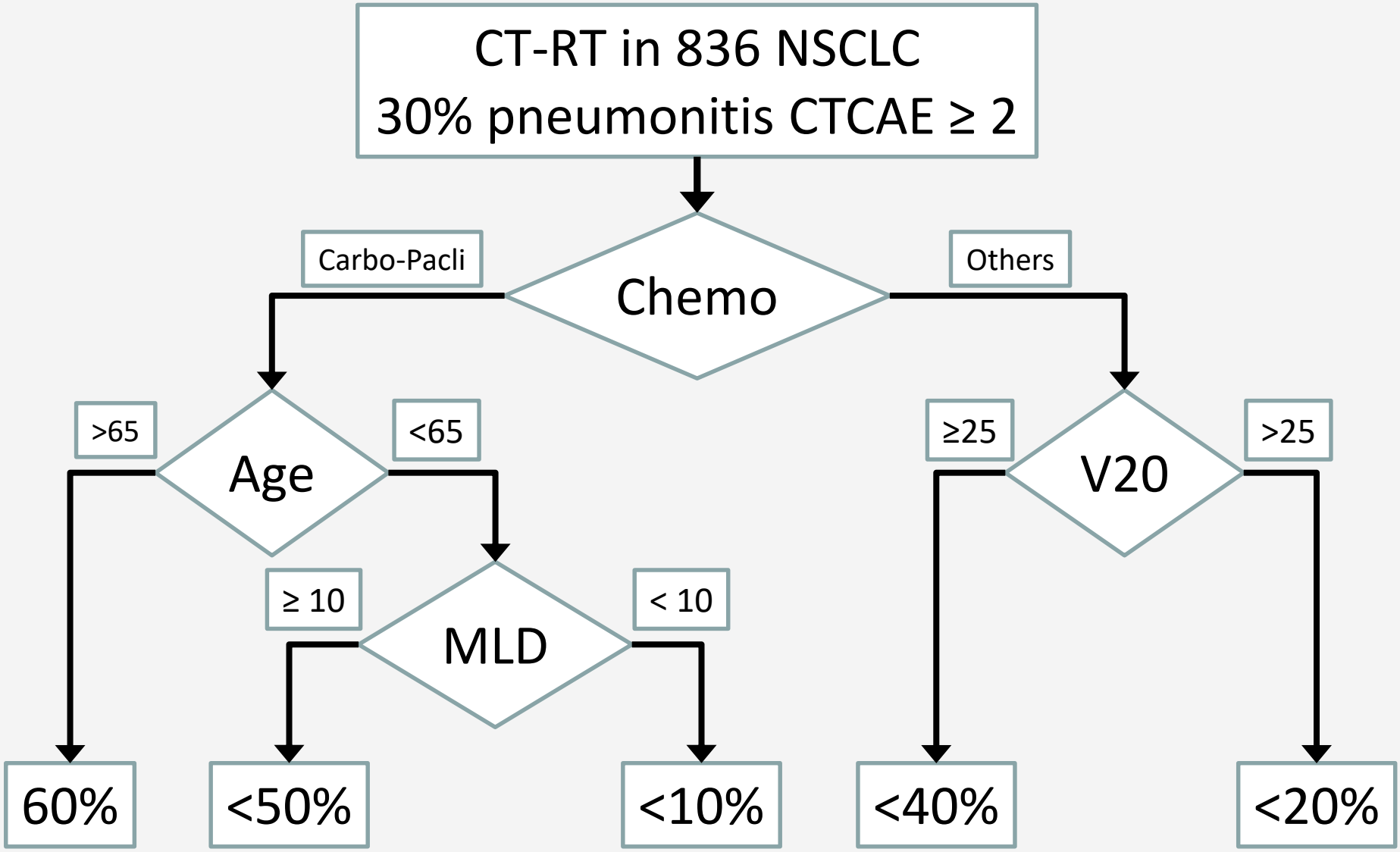
Rodrigues R&O 2004

Lung constraints

V20 ≤ 35%-37%	1B
MLD ≤ 20-23 Gy	1B
Dose to central bronchi ≤ 80 Gy if concurrent CT-RT	1B
Advanced dose calculation algorithms (type B) are recommended	1A
Doses and dose distributions calculated with type A versus type B algorithms cannot be compared	1A
Dose prescriptions and reporting follow ICRU standards	1B

De Ruysscher EORTC JCO 2010

Lung constraints

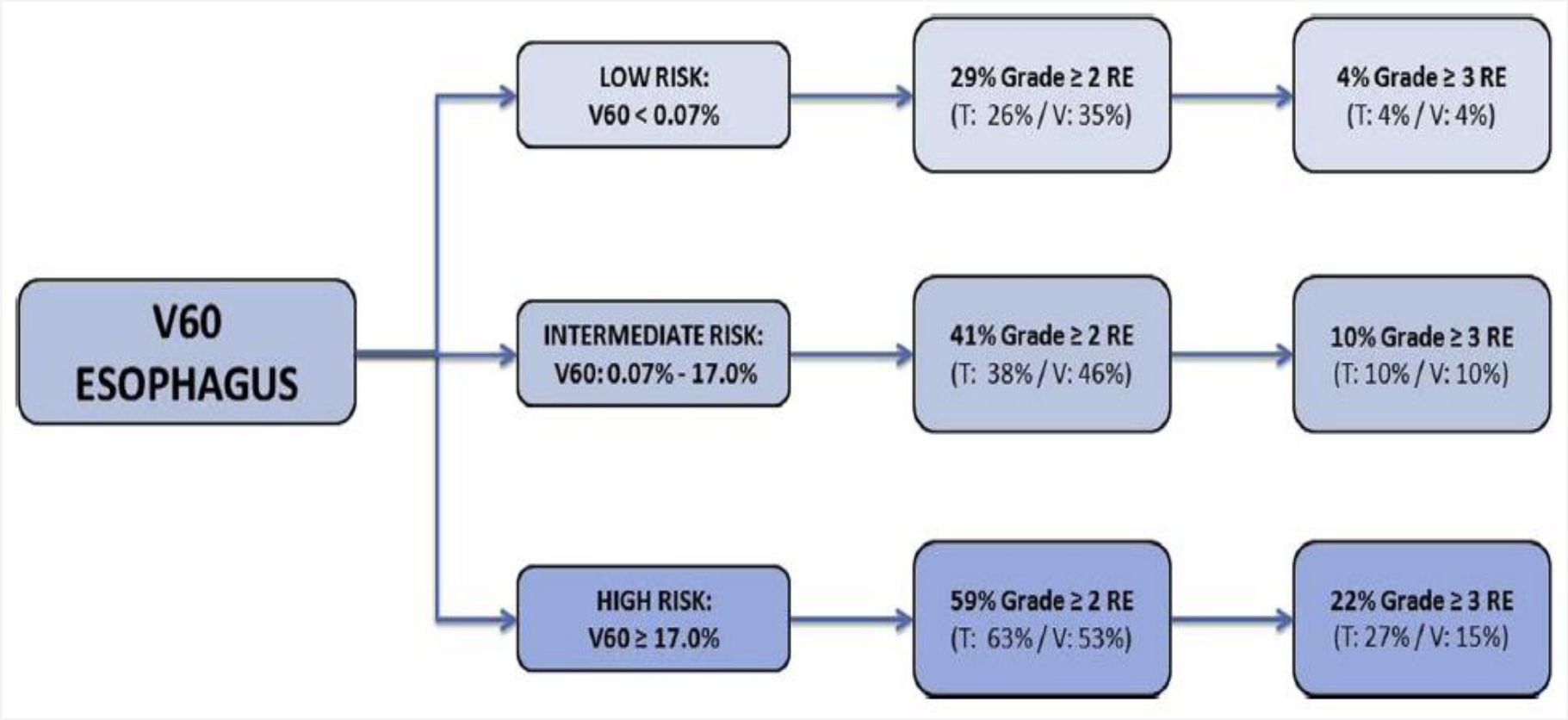


Palma IJROBP 2013

Other OARs

- Spinal cord
  - Dmax < 45 Gy (54 Gy ??)
- Oesophagus
  - length receiving > 45 Gy
  - V50, V55 (< 20 %), MOD (< 22 Gy), Dmax
- Heart and pericardium
  - insufficient data ?

Oesophagitis



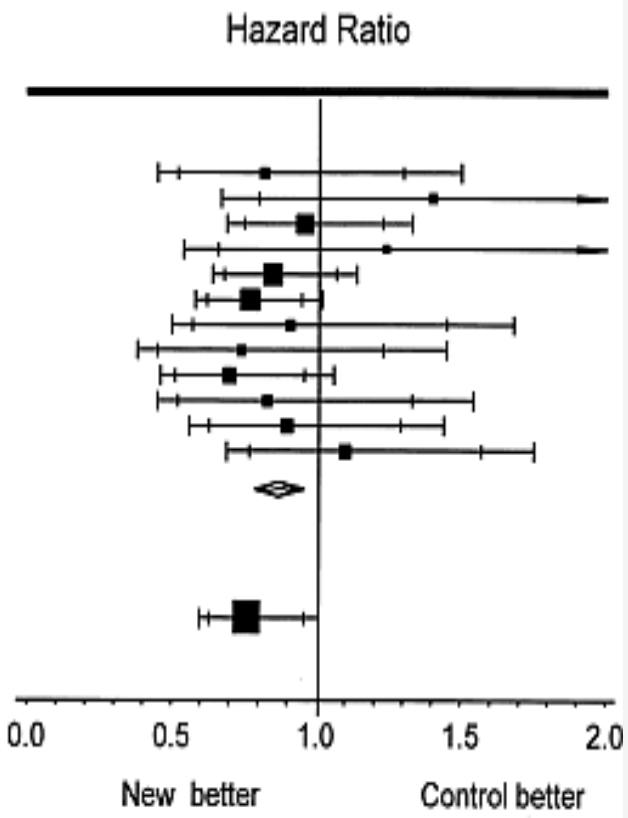
Palma IJROBP 2013

Conclusion (4)

- OARs : a complex issue ...
- Clinical benefits of technical improvements ?
  - likely, but not evidence-based
- Many uncertainties
  - need for guidelines
  - enter clinical trials (best !)
- Quiz : how do you compromise ...
  - between OARs ?
  - between OARs and tumour ?

Add chemotherapy to RT

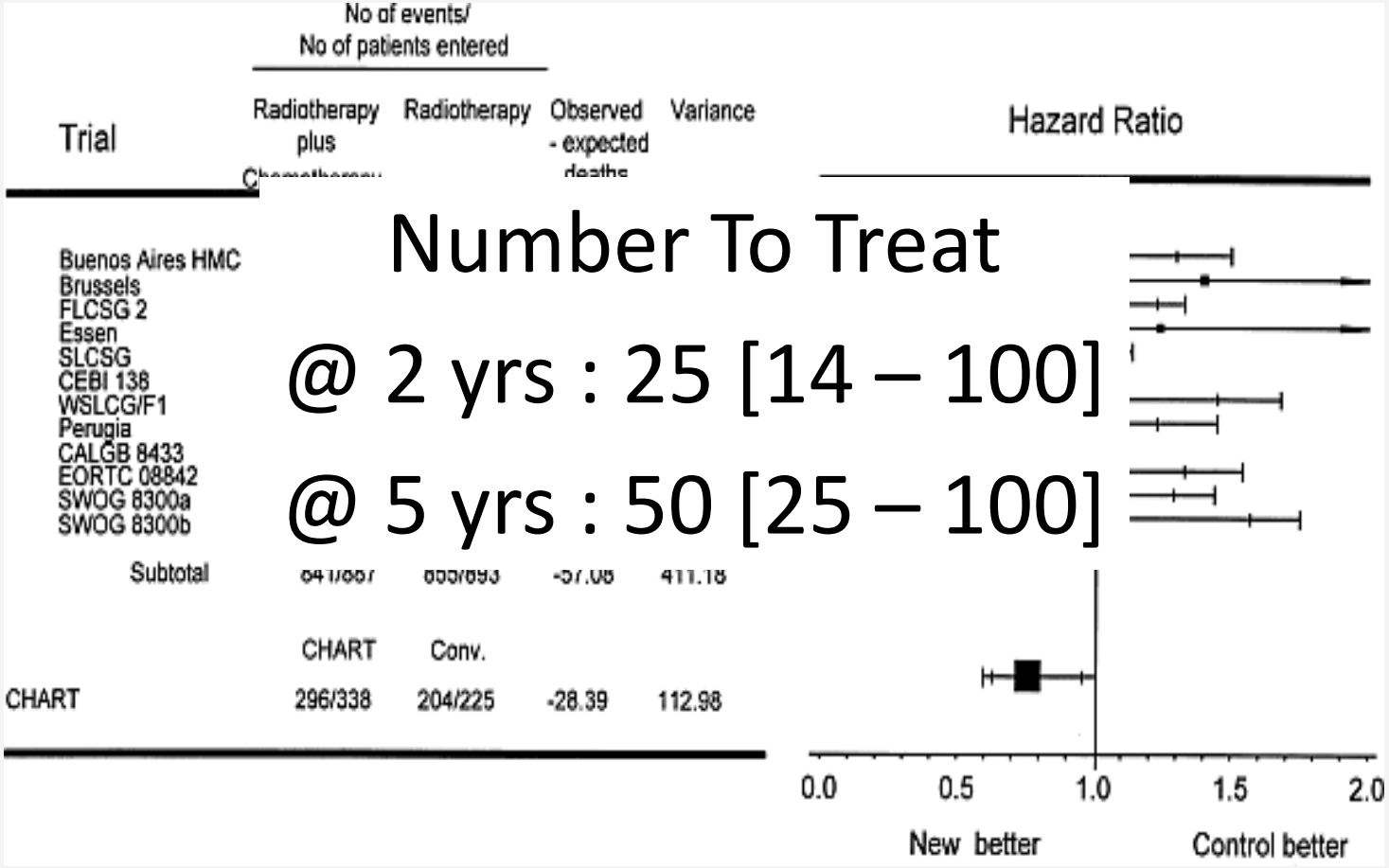
Trial	No of events/ No of patients entered: Radiotherapy plus Chemotherapy	Radiotherapy	Observed - expected deaths	Variance
Buenos Aires HMC	43/43	35/38	-3.57	18.26
Brussels	25/31	29/34	4.18	12.31
FLCSG 2	124/125	126/127	-2.49	62.14
Essen	21/22	22/26	2.09	9.80
SLCSG	159/163	161/164	-12.39	77.92
CEBI 138	166/176	173/177	-21.95	82.68
WSLCG/F1	37/40	35/39	-1.61	17.82
Perugia	32/33	32/33	-4.45	14.84
CALGB 8433	73/89	80/91	-13.39	37.13
EORTC 08842	36/38	37/37	-3.23	17.70
SWOG 8300a	62/64	62/64	-3.07	30.19
SWOG 8300b	63/63	63/63	2.81	30.38
Subtotal	841/887	855/893	-57.08	411.18
	CHART	Conv.		
CHART	296/338	204/225	-28.39	112.98



HR = 0.87 [0.79 – 0.96]

Saunders R&O 1999

Add chemotherapy to RT



Number To Treat

@ 2 yrs : 25 [14 – 100]

@ 5 yrs : 50 [25 – 100]

HR = 0.87 [0.79 – 0.96]

Saunders R&O 1999

RT versus concomitant CTRT

- Trials
  - 12 eligible (1921 patients)
  - 9 included (1764 patients, 1657 deaths)
- Overall survival
  - HR = 0.89 [0.81 – 0.98]
  - +4% @ 2 years, +2.2% @ 5 years
  - NTT : 25 @ 2 years, 45 @ 5 years
- Event free survival
  - HR = 0.84 [0.74 – 0.96]
  - +6% @ 2 years, +3.5% @ 5 years

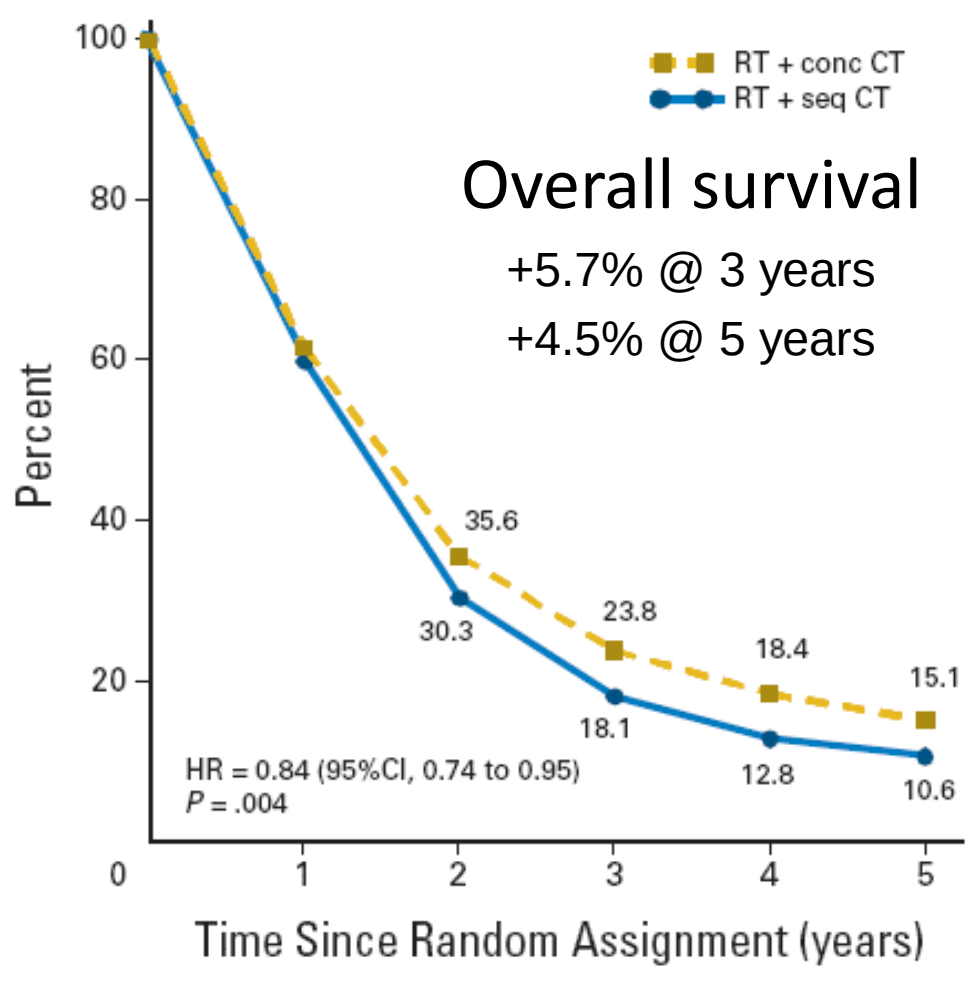
Auperin Ann Oncol 2006

RT versus concomitant CTRT

Characteristic	RT+CT N=959[‡]	RT alone N=805[‡]
Male	752 (78%)	630 (78%)
Median age (range) in years[£]	61 (36–83)	61 (31–82)
≤60 years	433 (45%)	371 (46%)
61–70 years	435 (46%)	357 (44%)
≥71 years	88 (9%)	76 (9%)
Performance status[†]		
0	427 (45%)	346 (43%)
1	476 (50%)	425 (53%)
2–3	54 (6%)	33 (4%)
Weight loss>5%*	229/740 (31%)	165/585 (28%)
Squamous carcinoma[$]	439/784 (56%)	392/675 (58%)
Stage[#]		
I	30 (3%)	28 (4%)
II	22 (2%)	18 (2%)
IIIa	548 (60%)	449 (58%)
IIIb	301 (33%)	273 (35%)
IV	8 (1%)	3 (0%)

Auperin Ann Oncol 2006

Sequential versus concomitant CTRT



Auperin JCO 2010

Sequential versus concomitant CTRT

Toxicity	HR [95% CI]	p
Oesophagitis gr. 3-4	4.9 [3.1 – 7.8]	< 0.001
Pneumonitis gr. 3-4	0.69 [0.42 – 1.12]	0.13
Blood	Not assessable	
Late lung	Not assessable	

	Sequential CTRT	Concomitant CTRT
No RT	10%	4%

Auperin JCO 2010

Conclusion (5)

Sequential / concurrent CTRT can be safely administered if •WHO performance status 0-1 •no major comorbidity •age ≤ 70-75 years	1A
Only cisplatin, carboplatin, etoposide, paclitaxel, docetaxel, and vinorelbine can be safely combined with concurrent radiotherapy	1A
Dose to central bronchi ≤ 80 Gy if concurrent CT-RT	1B

De Ruysscher EORTC JCO 2010

Conclusion (5bis)

- Concomitant CRT is standard (level 1)
  - platinum-based doublet
- CT added to RT increases acute toxicity (level 1)
  - no applicable to unfit patients
- Survival benefit is relatively small (level 1)
- What about new drugs ?????

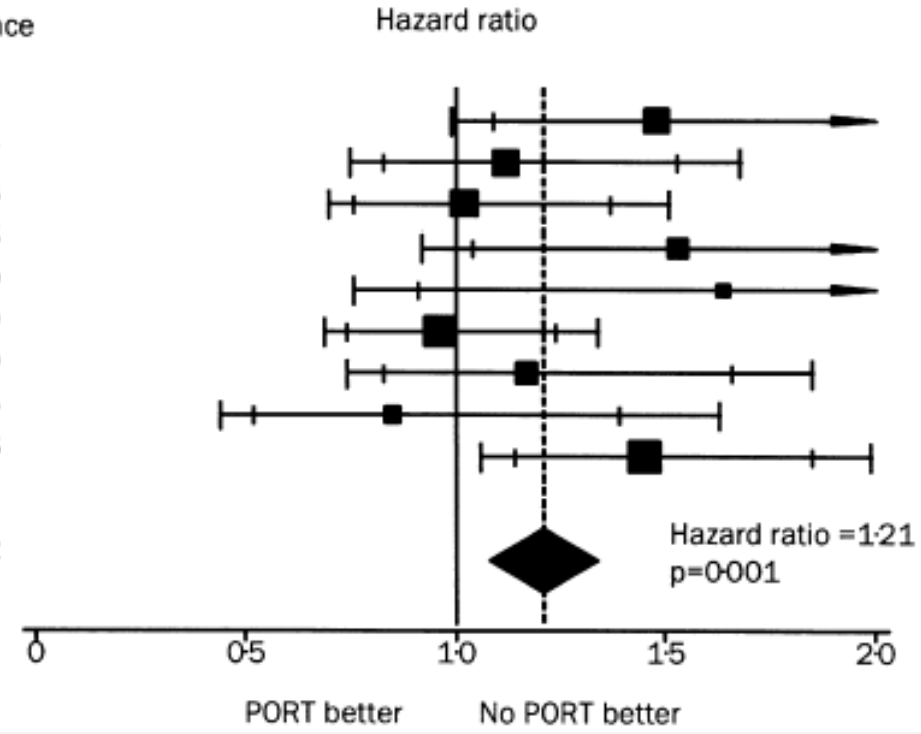
Conclusion (6)

- Pre-operative chemotherapy
  - survival benefit ...
  - RT = surgery if response to CT
- Pre-operative chemo-radiotherapy
  - surgery improves local control, not survival ...
  - but no evidence for pre-operative CT-RT
- Comments
  - high incidence of metastases
  - how do you plan RT after induction CT ?

Post-operative radiotherapy

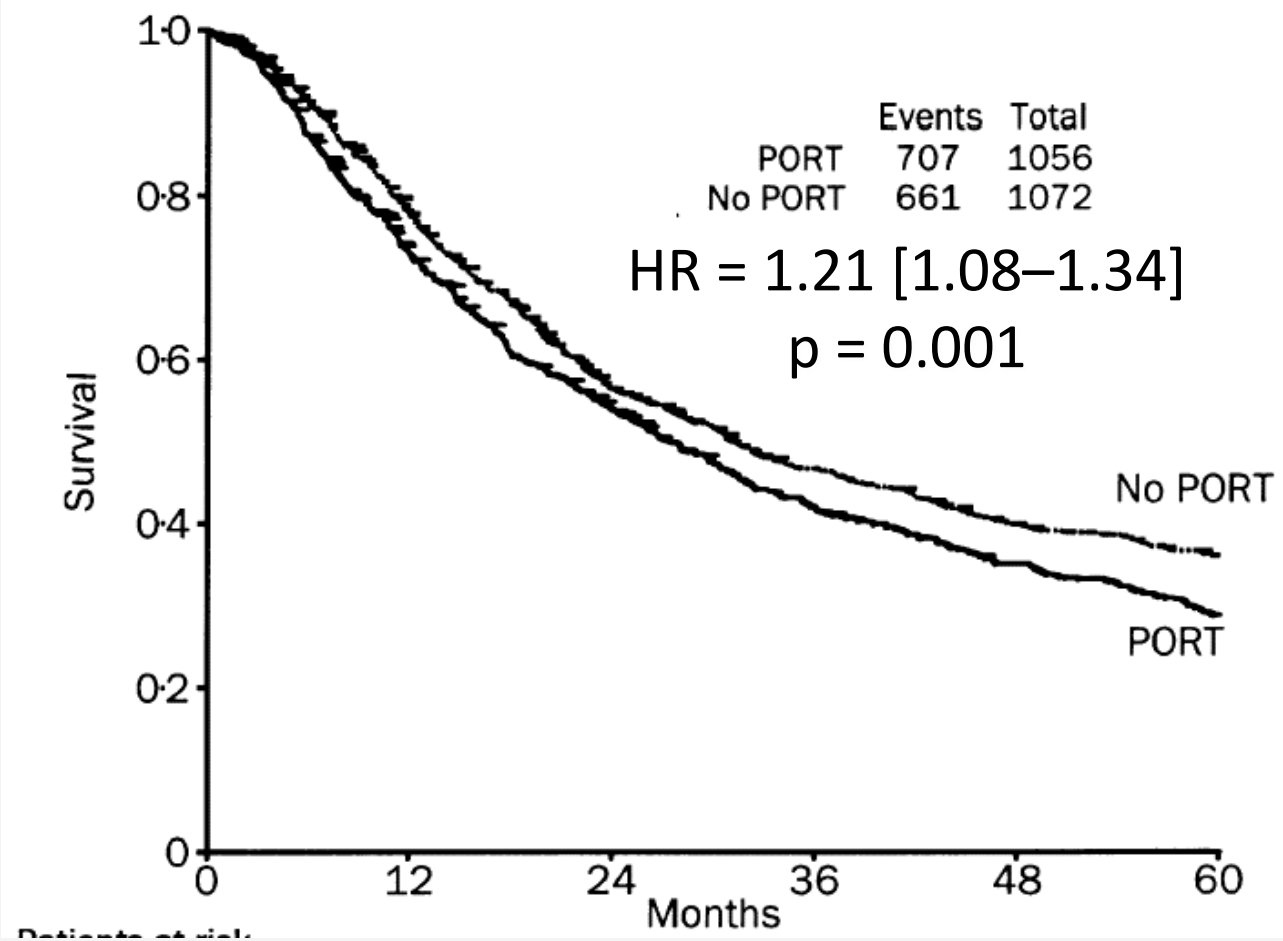
9 trials, 2128 patients

Trial	Number of events/ number entered PORT	No PORT	O-E	Variance
Belgium (10)	88/98	80/104	16·04	40·67
LCSG 773 (11)	84/110	81/120	4·77	41·02
CAMS (12)	83/153	100/164	1·07	44·88
Lille (13)	59/81	45/82	10·87	25·66
EORTC 08861	26/52	20/54	5·53	11·20
MRC LU11 (14)	116/154	123/154	-2·48	59·39
GETCB 04CB86	69/99	59/90	4·95	31·59
Slovenia (15)	30/35	33/39	-2·56	15·63
GETCB 05CB88	152/274	120/265	25·13	67·08
Total	707/1056	661/1072	63·32	337·12



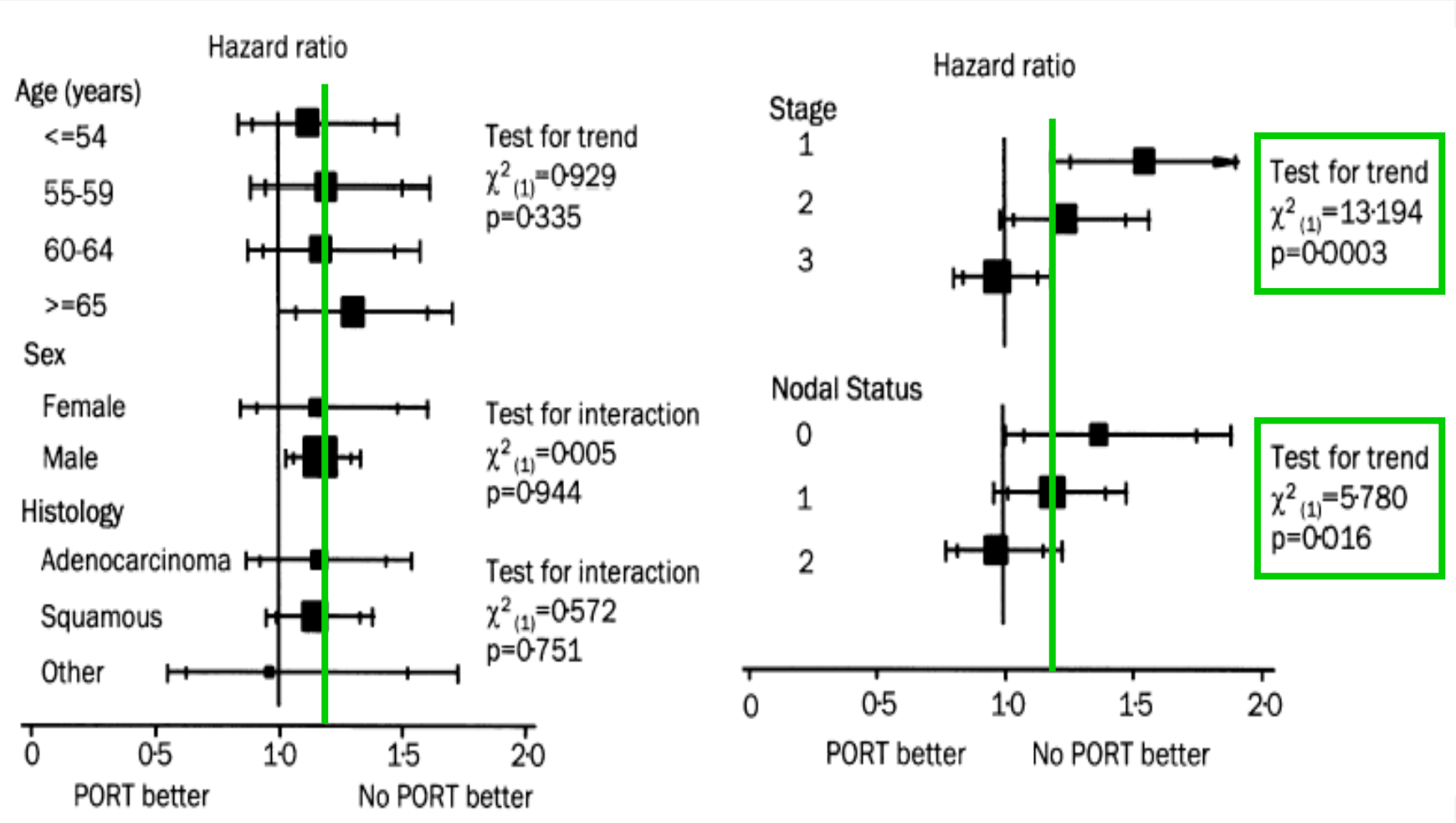
PORT Meta-analysis Lancet 1998

Post-operative radiotherapy



PORT Meta-analysis Lancet 1998

Post-operative radiotherapy



PORT Meta-analysis Lancet 1998

Commentary

- Poor data description
  - surgery technique
  - site of relapses
  - causes of death
- Obsolete radiotherapy
  - too large target volumes
  - total and fractional dose
  - no planning CT

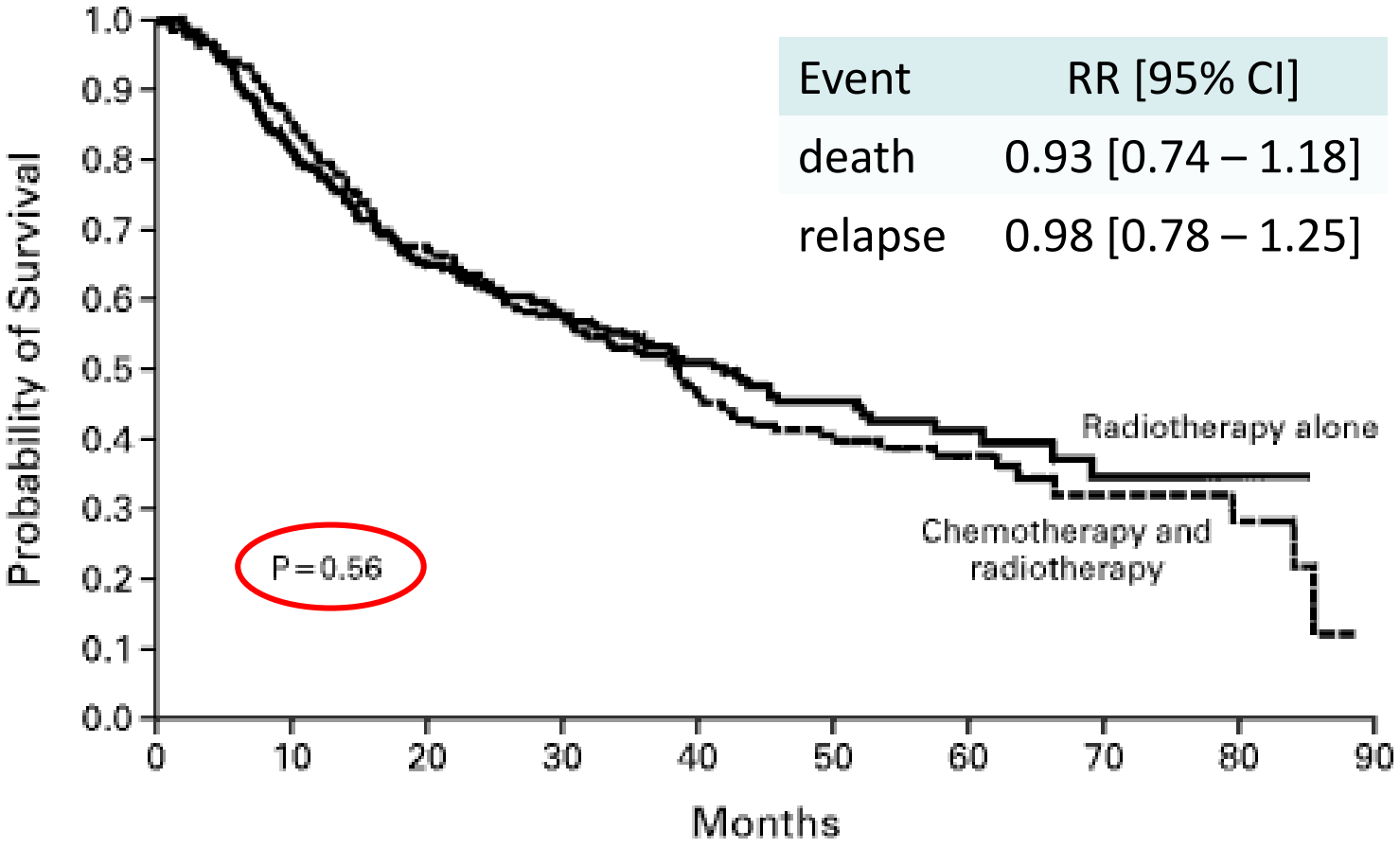
Loco-regional control after surgery

Study	Stage	N pts	Total dose / *Fraction size*	LRR (%)	p
Van Houtte	T1-3N0	104	_	10.9%	NS
		98	60/*2* Gy	1.2%	
LCSG	II-III SCC	120	_	41%	0.001
		110	50.4/*1.8*	3%	
GETCB Dautzenberg	I-II-III	355	_	28%	NS
		373	60/*2 to 2.5*	22%	
Mayer¤	I-II-III	72	_	20%*	<0.01
		83	50-56/*2*	7%*	
Trodella¤	T-2N0	53	_	23%	0.019
		51	50.4/*1.8*	2.2%	
Feng	II-III	182		33.2%	0.01
		183	60/2	12.7%	

Lung–ART trial (ongoing)

- To include 700 patients pTx pN2 R0
- Planning CT mandatory
  - description of target volumes ++++
- 54 Gy to ICRU point
  - photons ≥ 6 MV
  - 1 fraction / day, 5 fractions / week
  - ≥ 3 fields treated daily
  - (no IMRT)

Post-operative CTRT



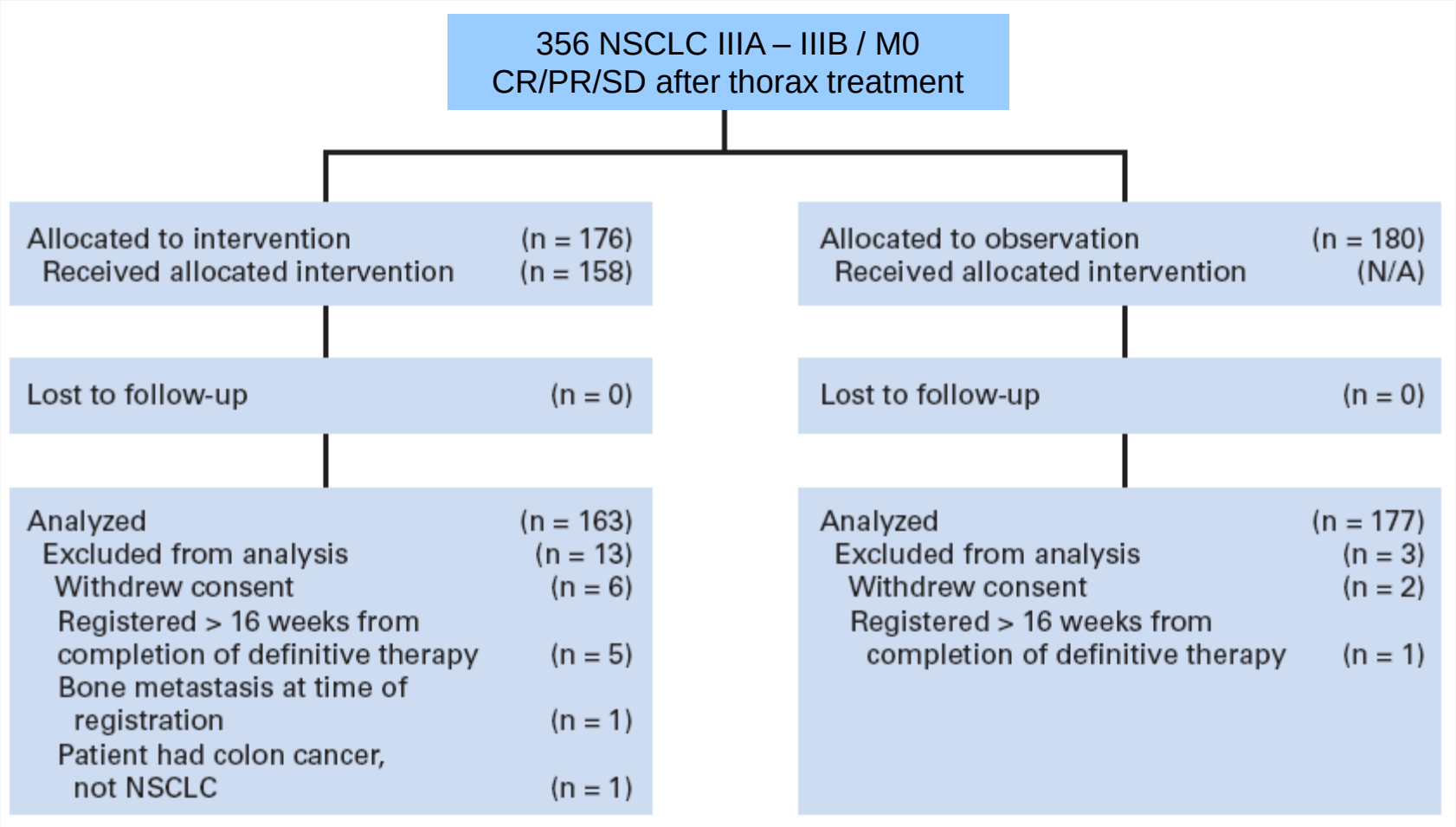
Event	RR [95% CI]
death	0.93 [0.74 – 1.18]
relapse	0.98 [0.78 – 1.25]

Keller INT 0115 NEJM 2000

Conclusion (7)

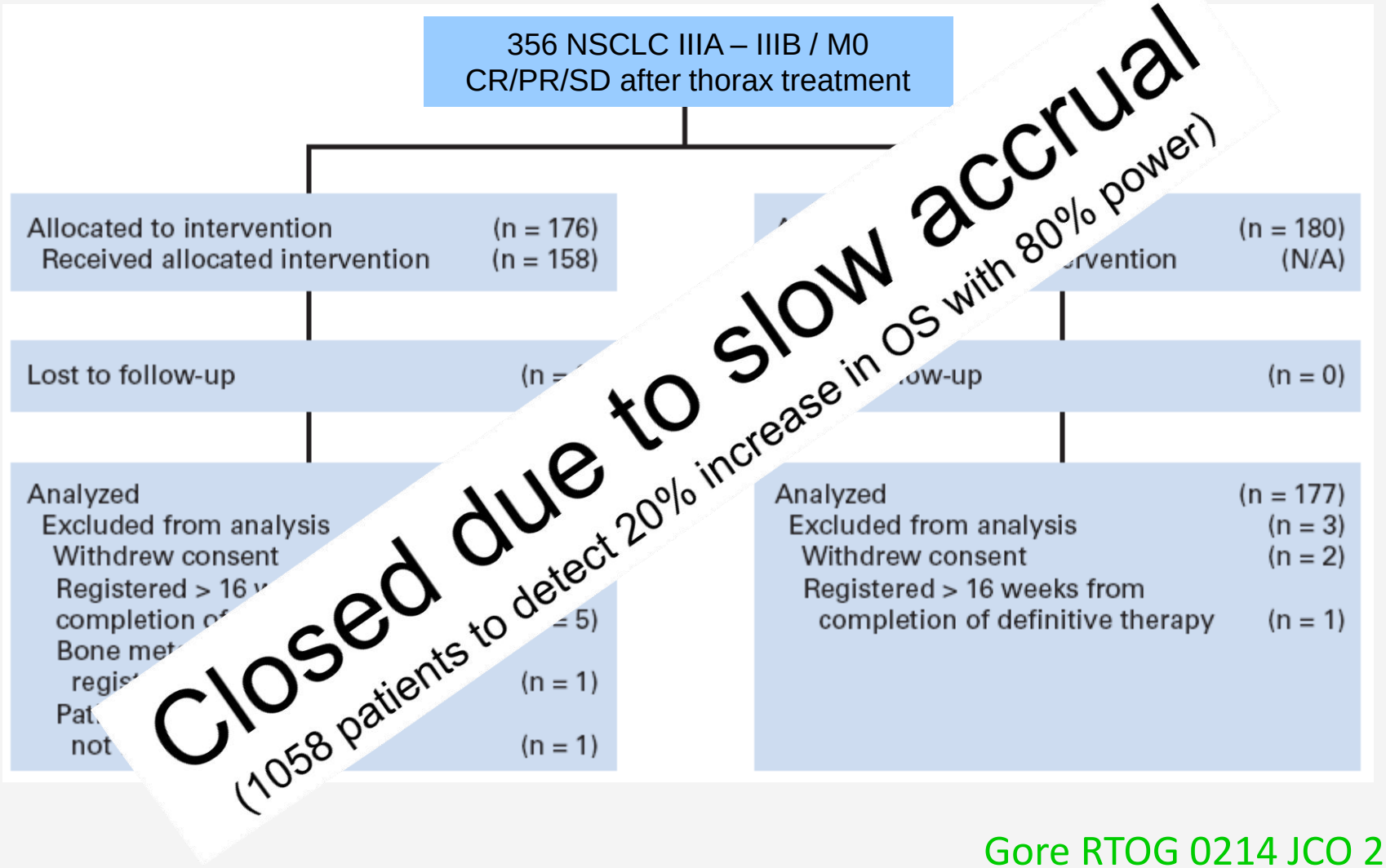
- Post-operative CT
  - improves survival (level 1)
- Post-operative RT
  - decreases survival (level 1)
- Post-operative RT-CT
  - no benefit (level 2)

Prophylactic cranial RT in NSCLC



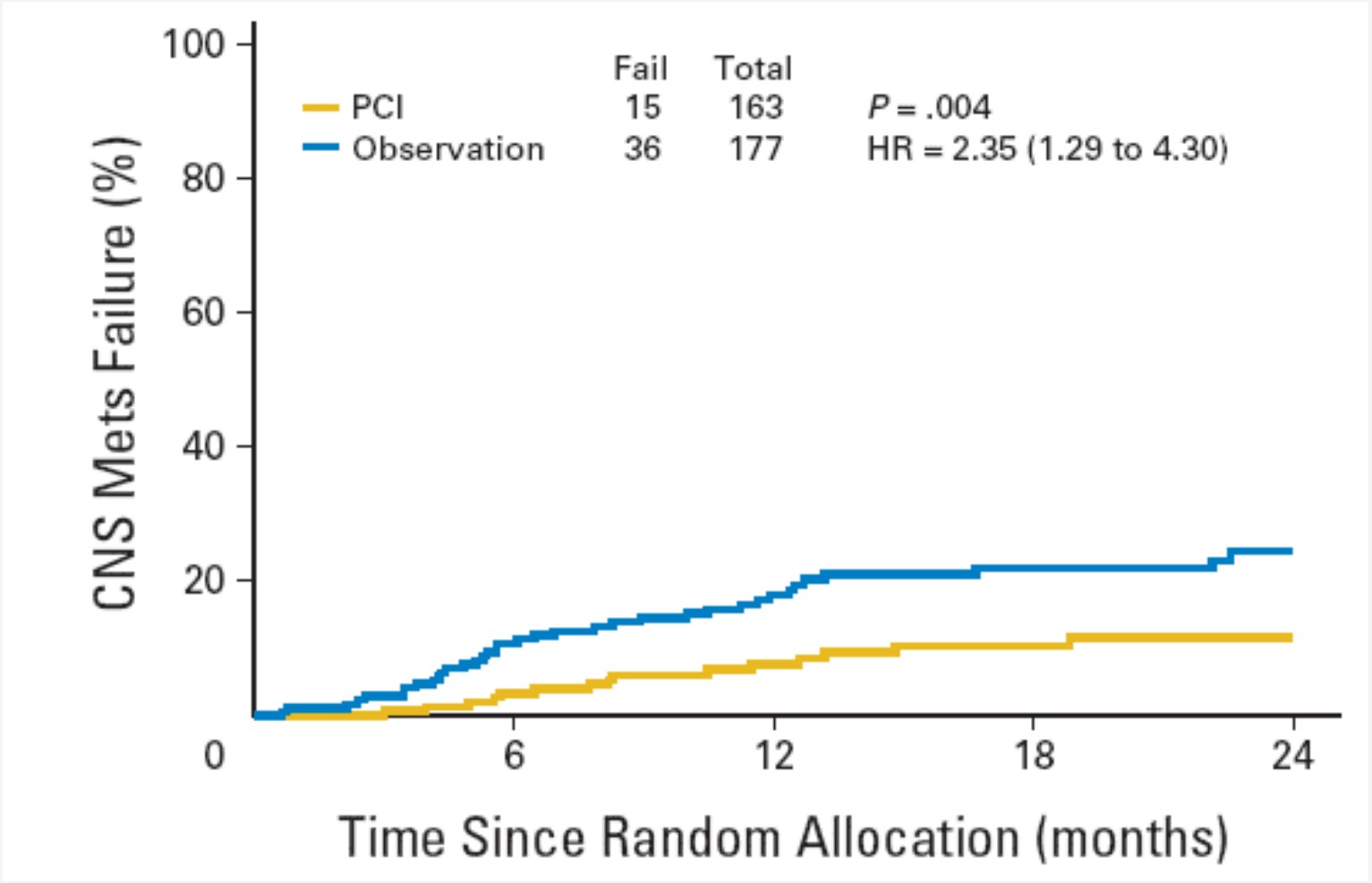
Gore RTOG 0214 JCO 2011

Prophylactic cranial RT in NSCLC



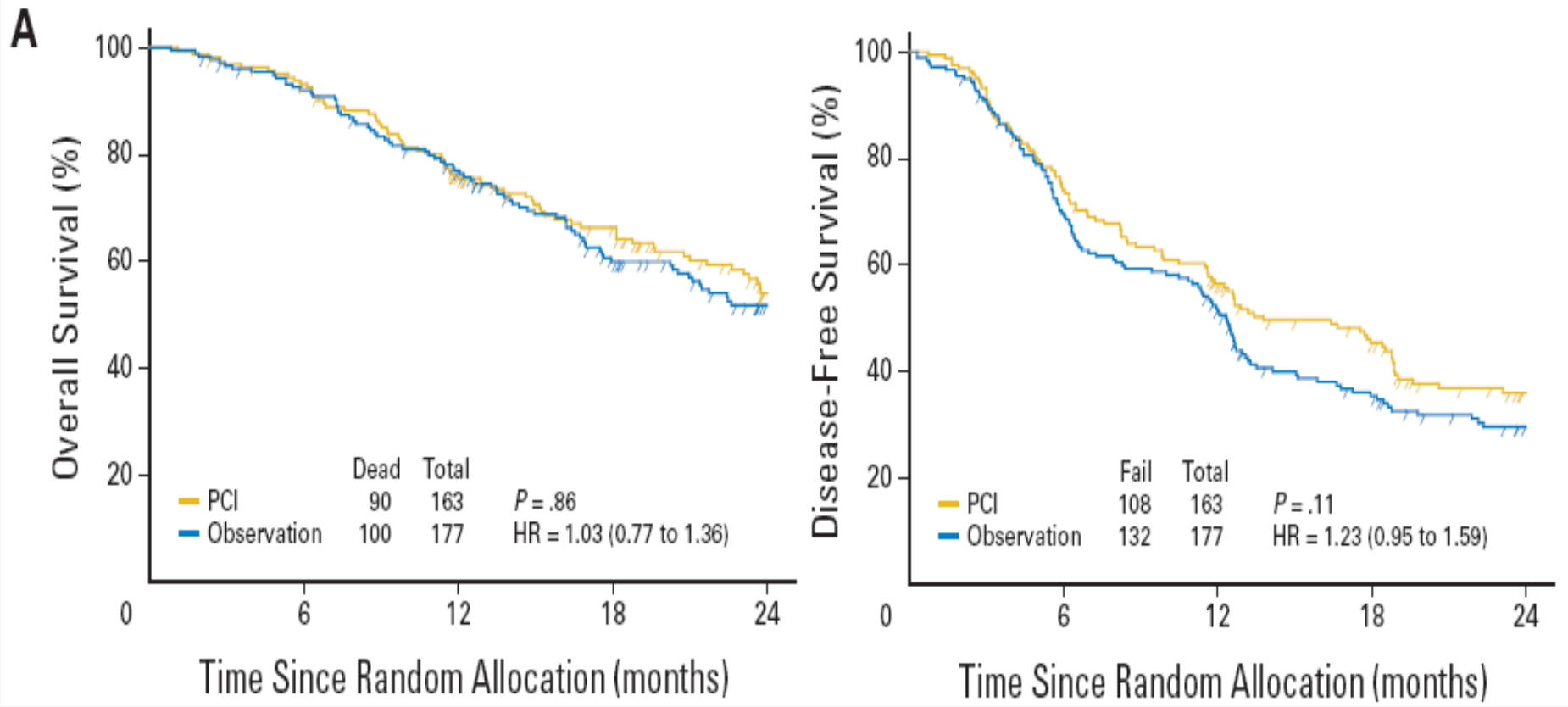
Gore RTOG 0214 JCO 2011

Prophylactic cranial RT in NSCLC



Gore RTOG 0214 JCO 2011

Prophylactic cranial RT in NSCLC



Gore RTOG 0214 JCO 2011

Prophylactic cranial RT in NSCLC

	PCI n = 87	Observation N = 88	p
Symptomatic BM	4 (5%)	25 (28%)	$<10^{-5}$
Median OS (mths)	24.2	21.9	0.052

Groen NVALT11 ASCO 2017 (#8502)

Conclusion (8)

- PCI in NSCLCC
  - lower risk of secondary BM (level 1)
  - no change in OS (early closure)

Small Cell Lung Cancer

Limited disease

- Can be included in a *tolerable* radiation “field”
  - tumour in hemi-thorax
  - mediastinum
  - ipsilateral supra-clavicular nodes
- No (malignant) pleural effusion
- No metastasis

IASLC Lung Cancer Staging Project

RPA on 6 609 SCLC treated 1990-2000

weight loss, comorbidities not included

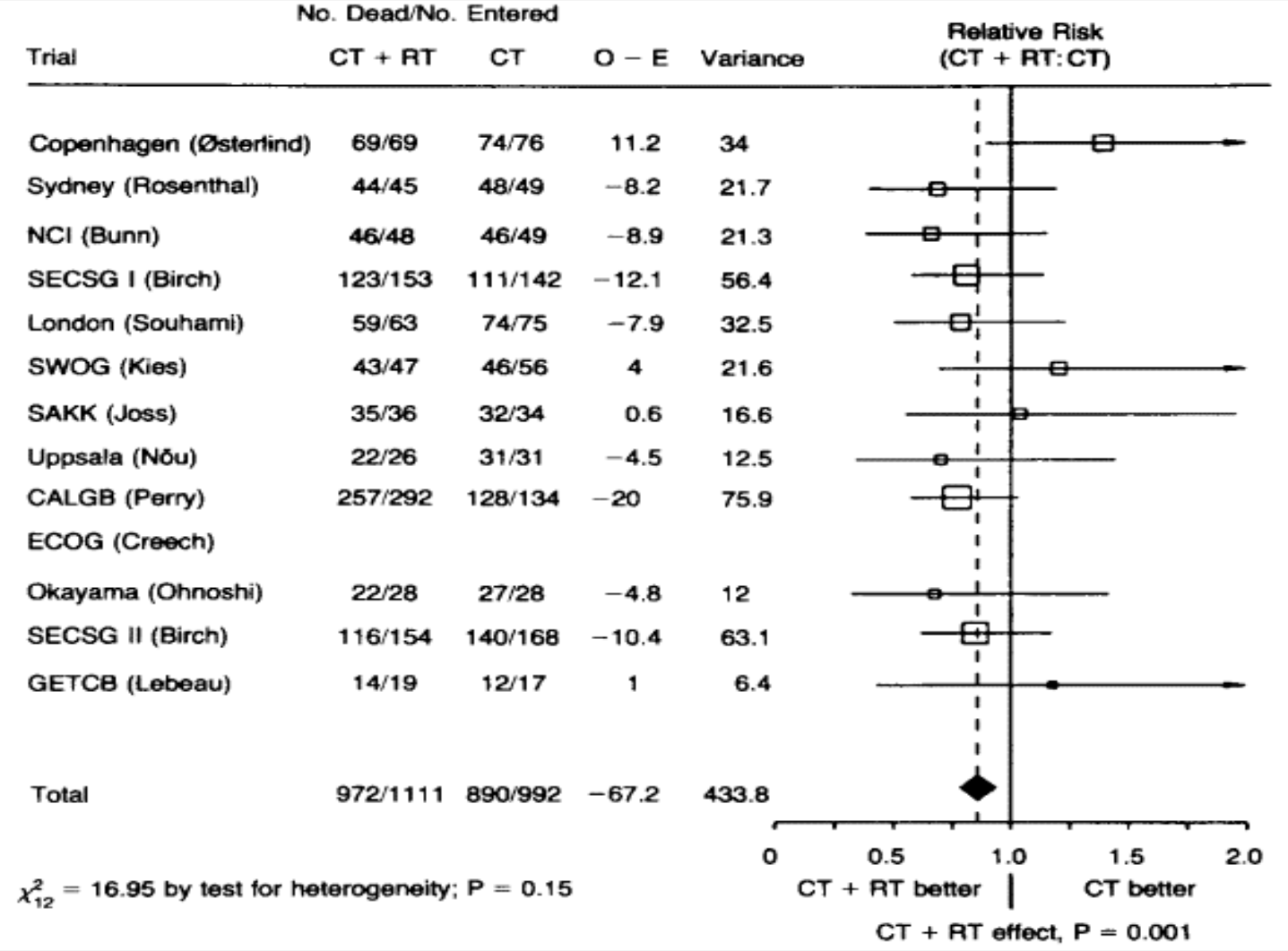
Group	Gender	Disease	PS	Age	Survival (med)
I		localized	0	<60	17 months
		localized	1-2	<65	
II		localized	1-2	≥65	12 months
	F	extended	0	<65	
III	F	extended	0	≥65	10 months
	M	extended	0		
		extended	1	<70	
IV		localized	3-4		6 months
		extended	1	≥70	
		extended	2-4		

Sculier J Thorac Oncol 2008

Treatment options

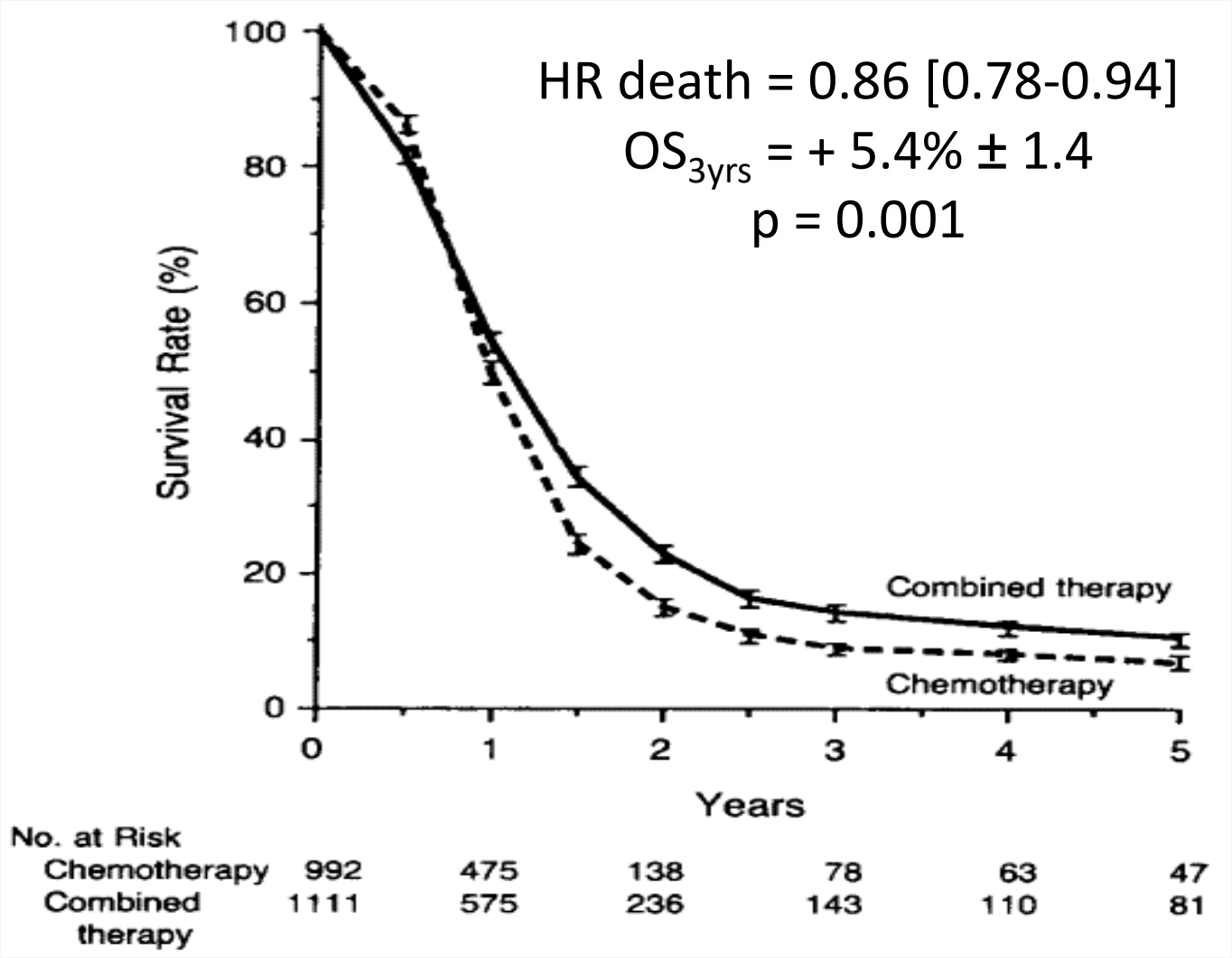
- Surgery alone is NOT an option
- Concurrent chemotherapy and radiation
  - standard treatment
- Prophylactic cranial irradiation
  - if complete / good response
  - 24 – 25 Gy in 10 fractions

Limited SCLC: CT vs CT+RT



Pignon NEJM 1992

Limited SCLC: CT vs CT+RT



Pignon NEJM 1992

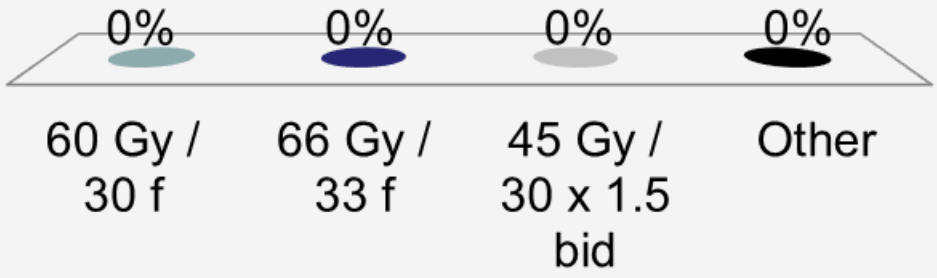
What is your total dose ?

A. 60 Gy / 30 f

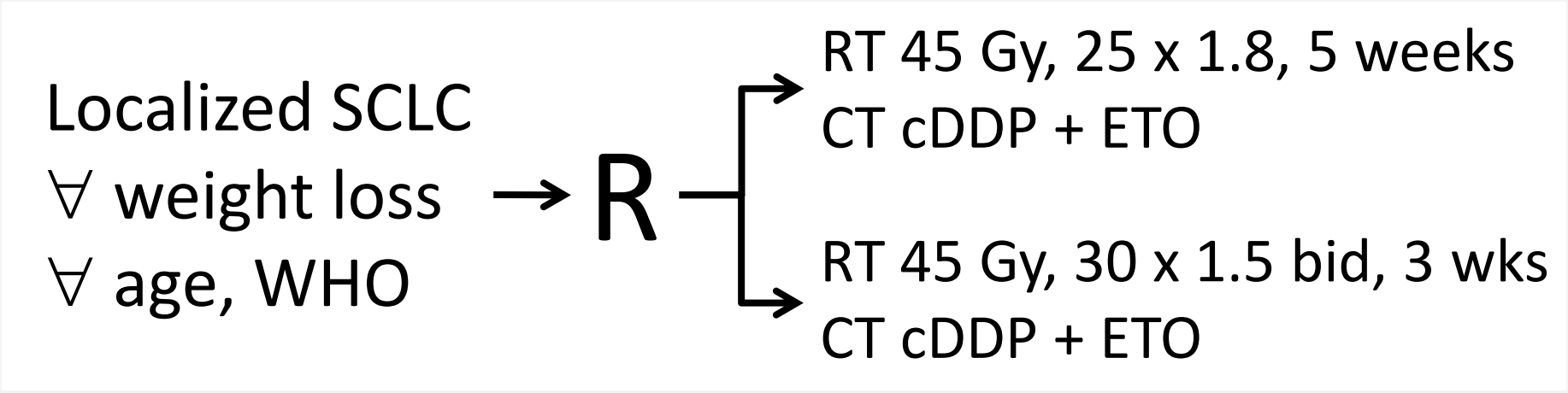
B. 66 Gy / 33 f

C. 45 Gy / 30 x 1.5 bid

D. Other



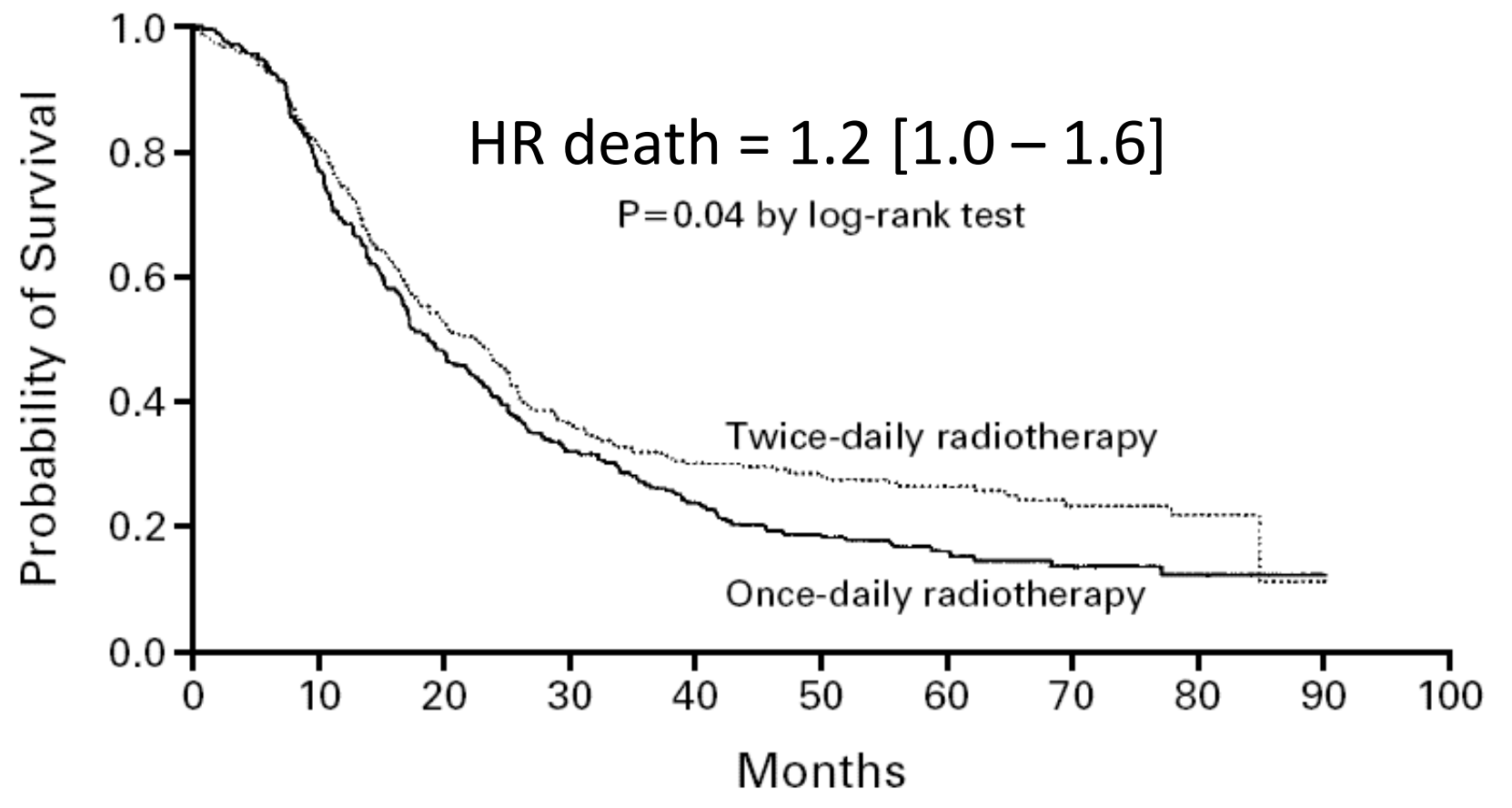
Dose / fractionation of RT



N = 206 / 211

Turrisi ECOG NEJM 1999

Dose / fractionation of RT



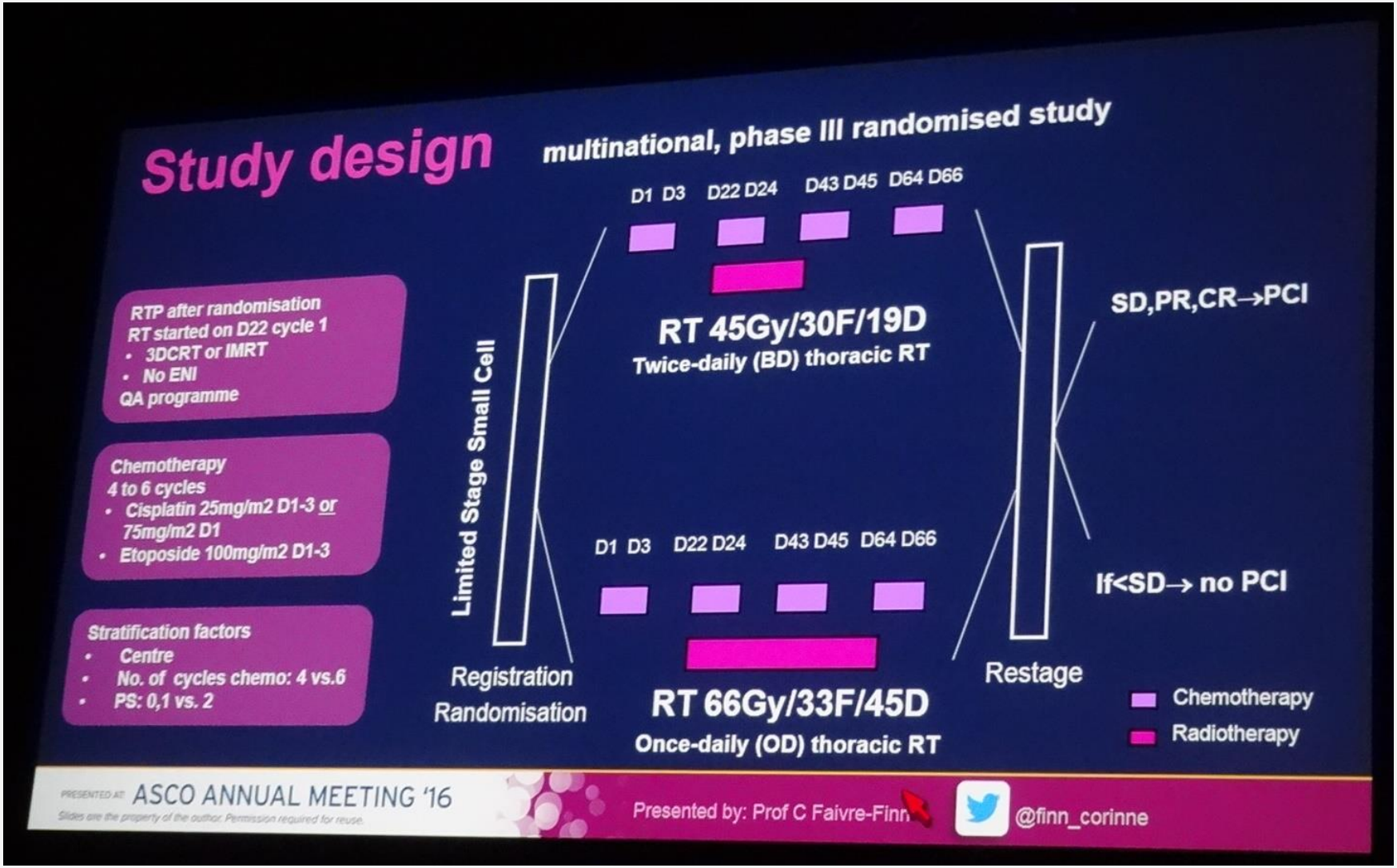
Turrisi ECOG NEJM 1999

Current phase III clinical trials addressing the role of dose and fractionation in SCLC

- CONVERT (N=532)
  - 45 Gy/30fx BID
  - 66 Gy/33fx OD
- CALGB 30610 (N=712)
  - 45 Gy/30fx BID
  - 70 Gy/35fx OD
  - 61.2 Gy/34fx OD→BID

Dziadziusko ESTRO 2008

CONVERT


Study design
multinational, phase III randomised study
RTP after randomisation
RT started on D22 cycle 1
• 3DCRT or IMRT
• No ENI
QA programme
Chemotherapy
4 to 6 cycles
• Cisplatin 25mg/m2 D1-3 or 75mg/m2 D1
• Etoposide 100mg/m2 D1-3
Stratification factors
• Centre
• No. of cycles chemo: 4 vs.6
• PS: 0,1 vs. 2
Limited Stage Small Cell
Registration
Randomisation
D1 D3 D22 D24 D43 D45 D64 D66
RT 45Gy/30F/19D
Twice-daily (BD) thoracic RT
D1 D3 D22 D24 D43 D45 D64 D66
RT 66Gy/33F/45D
Once-daily (OD) thoracic RT
Restage
SD,PR,CR→PCI
If<SD→ no PCI
Chemotherapy
Radiotherapy
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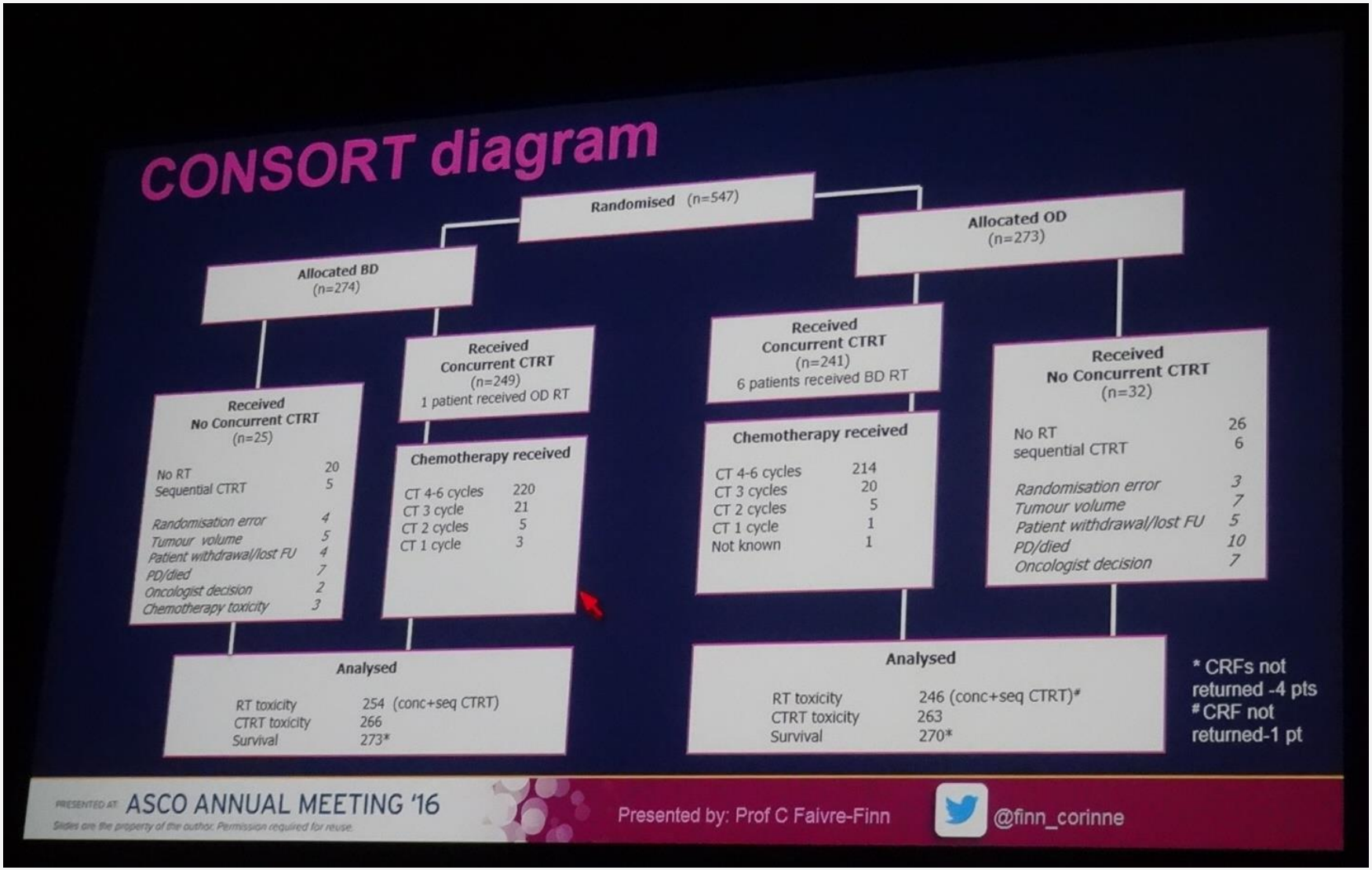
@finn_corinne

CONVERT


CONSORT diagram
Randomised (n=547)
Allocated BD (n=274)
Allocated OD (n=273)
Received No Concurrent CTRT (n=25)
No RT 20
Sequential CTRT 5
Randomisation error 4
Tumour volume 5
Patient withdrawal/lost FU 4
PD/died 7
Oncologist decision 2
Chemotherapy toxicity 3
Received Concurrent CTRT (n=249)
1 patient received OD RT
Chemotherapy received
CT 4-6 cycles 220
CT 3 cycle 21
CT 2 cycles 5
CT 1 cycle 3
Received Concurrent CTRT (n=241)
6 patients received BD RT
Chemotherapy received
CT 4-6 cycles 214
CT 3 cycles 20
CT 2 cycles 5
CT 1 cycle 1
Not known 1
Received No Concurrent CTRT (n=32)
No RT 26
sequential CTRT 6
Randomisation error 3
Tumour volume 7
Patient withdrawal/lost FU 5
PD/died 10
Oncologist decision 7
Analysed
RT toxicity 254 (conc+seq CTRT)
CTRT toxicity 266
Survival 273*
Analysed
RT toxicity 246 (conc+seq CTRT)#
CTRT toxicity 263
Survival 270*
* CRFs not returned -4 pts
# CRF not returned-1 pt
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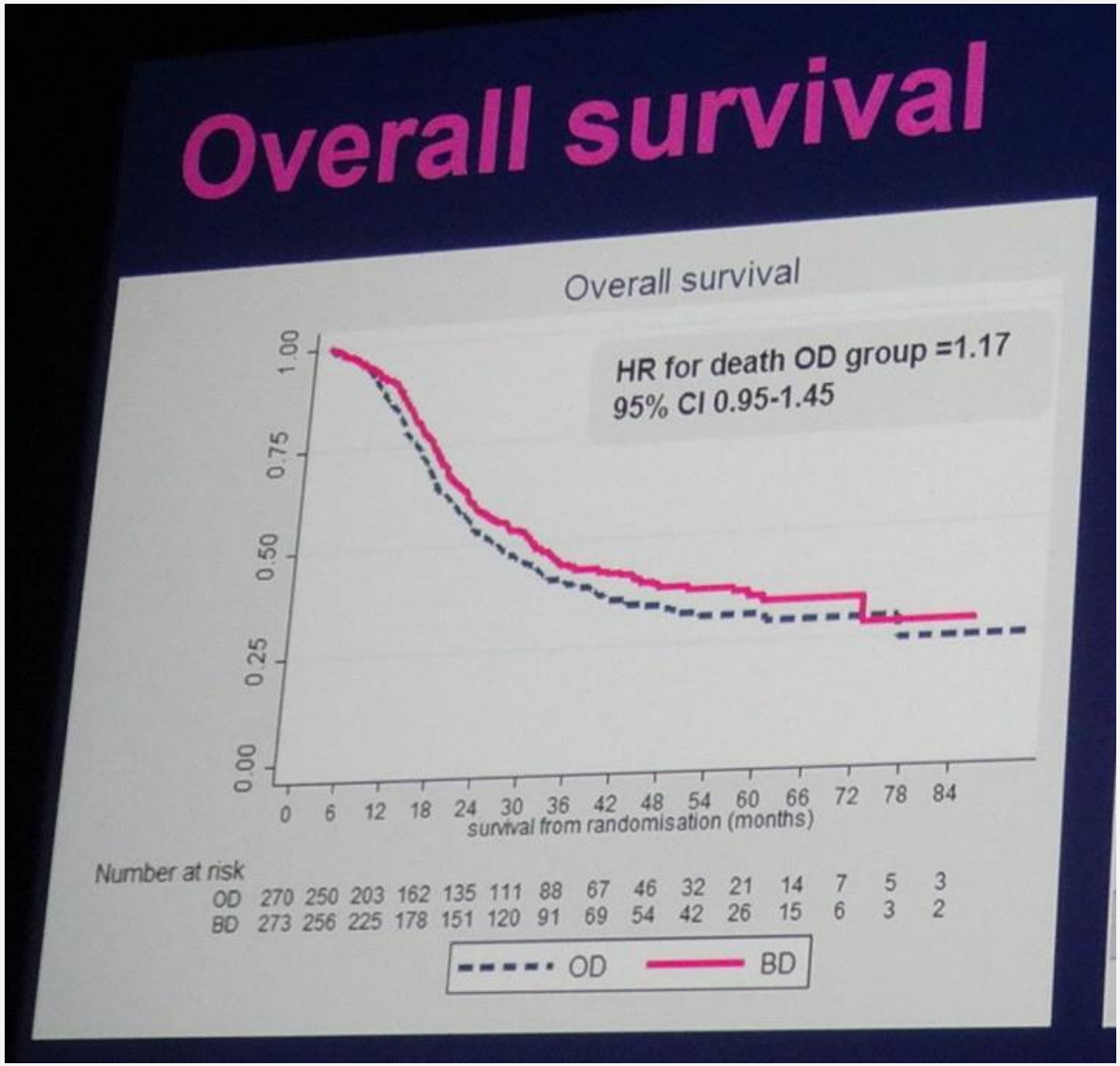
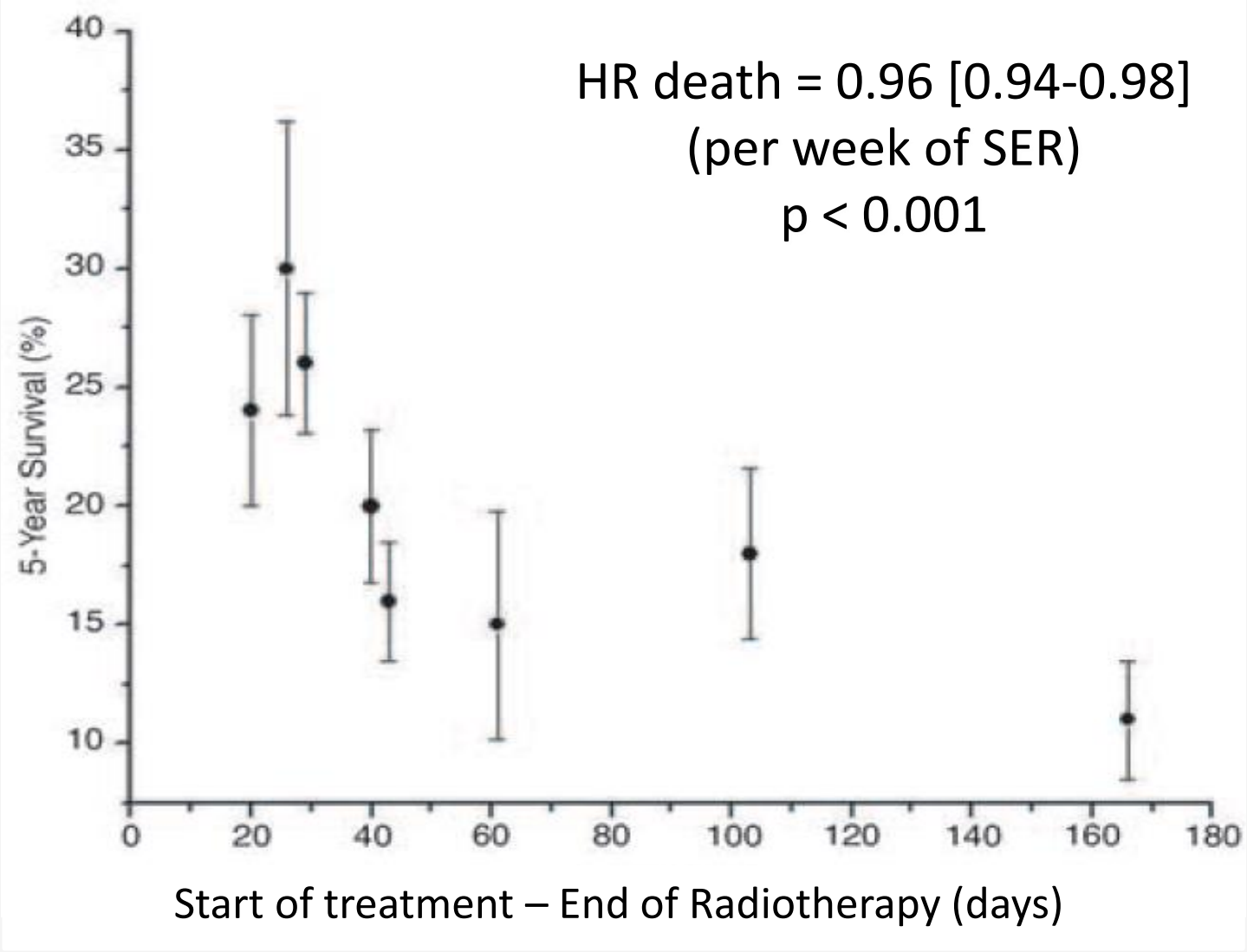
@finn_corinne

CONVERT


Overall survival
Overall survival
HR for death OD group =1.17
95% CI 0.95-1.45
1.00
0.75
0.50
0.25
0.00
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84
survival from randomisation (months)
Number at risk
OD 270 250 203 162 135 111 88 67 46 32 21 14 7 5 3
BD 273 256 225 178 151 120 91 69 54 42 26 15 6 3 2
OD
BD

Timing of treatment



De Ruysscher JCO 2006

Selective nodal irradiation

	CT staged	PET staged
N patients	27	60
OS (med, mths) PFS (med, mths)	21 [15 – 27] 16 [7 – 26]	19 [17 – 21] 14 [12 – 16]
Isolated N failure	3 11% [2 – 29]	2 3% [1 – 11]
gr. 3 oesophagitis	30% [14 – 50]	12% [6 – 22]

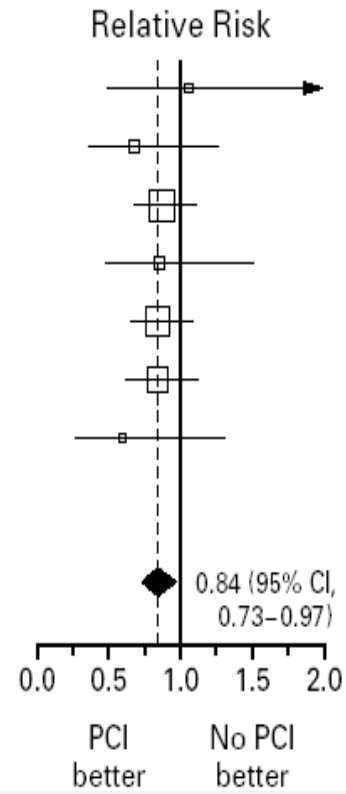
De Ruysscher R&O 2006 / van Loon IJROBP 2010

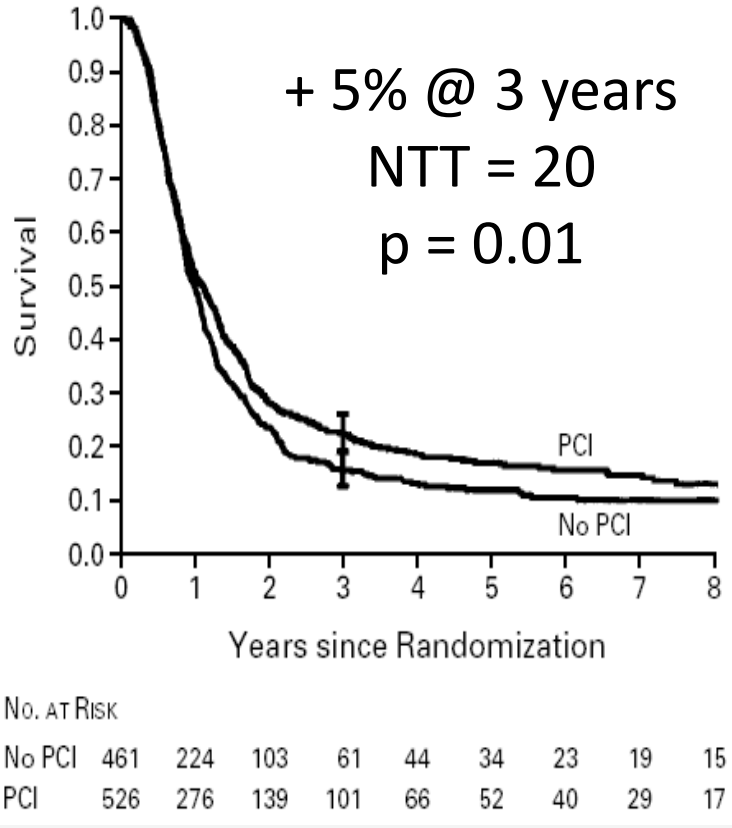
PCI in limited SCLC

- overall survival -

Study	No. of Events/No. Enrolled		O−E	Variance
	PCI	no PCI		
UMCC	14/15	13/14	0.4	6.7
Okayama	21/23	21/23	−3.8	10.1
PCI-85	133/149	135/151	−8.9	66.5
Danish−NCI	24/28	24/27	−1.8	11.8
UKCCCR−EORTC	154/194	106/120	−10.1	60.3
PCI-88	80/100	94/111	−7.6	43.1
ECOG−RTOG	14/17	13/15	−3.2	6.1
Total	440/526	406/461	−35.0	204.4

Test for heterogeneity: $\chi^2_6 = 1.62$, P = 0.95





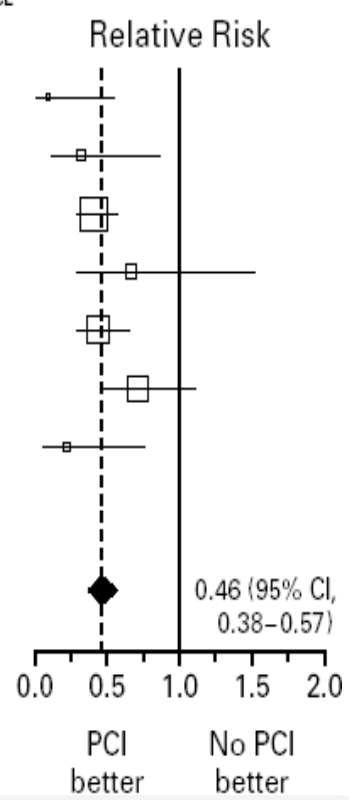
Auperin NEJM 1999

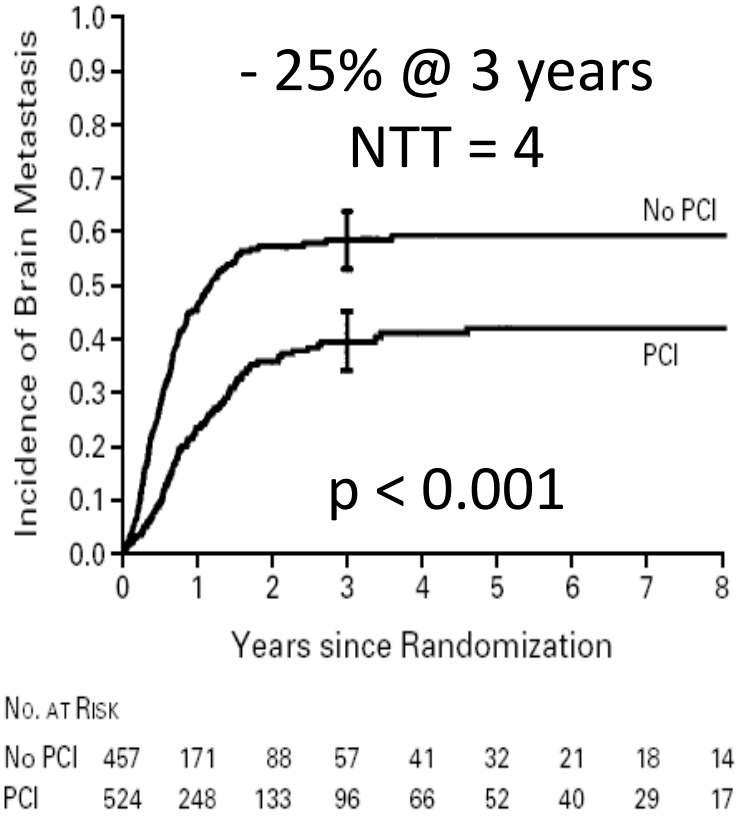
PCI in limited SCLC

- brain metastasis -

Study	No. of Events/No. Enrolled		O−E	Variance
	PCI	no PCI		
UMCC	0/14	5/12	−2.9	1.2
Okayama	5/23	11/23	−4.4	3.8
PCI-85	46/149	87/151	−28.7	32.5
Danish−NCI	10/27	13/25	−2.3	5.7
UKCCCR−EORTC	46/194	54/120	−18.7	22.8
PCI-88	32/100	44/111	−6.4	18.9
ECOG−RTOG	4/17	8/15	−3.9	2.6
Total	143/524	222/457	−67.2	87.6

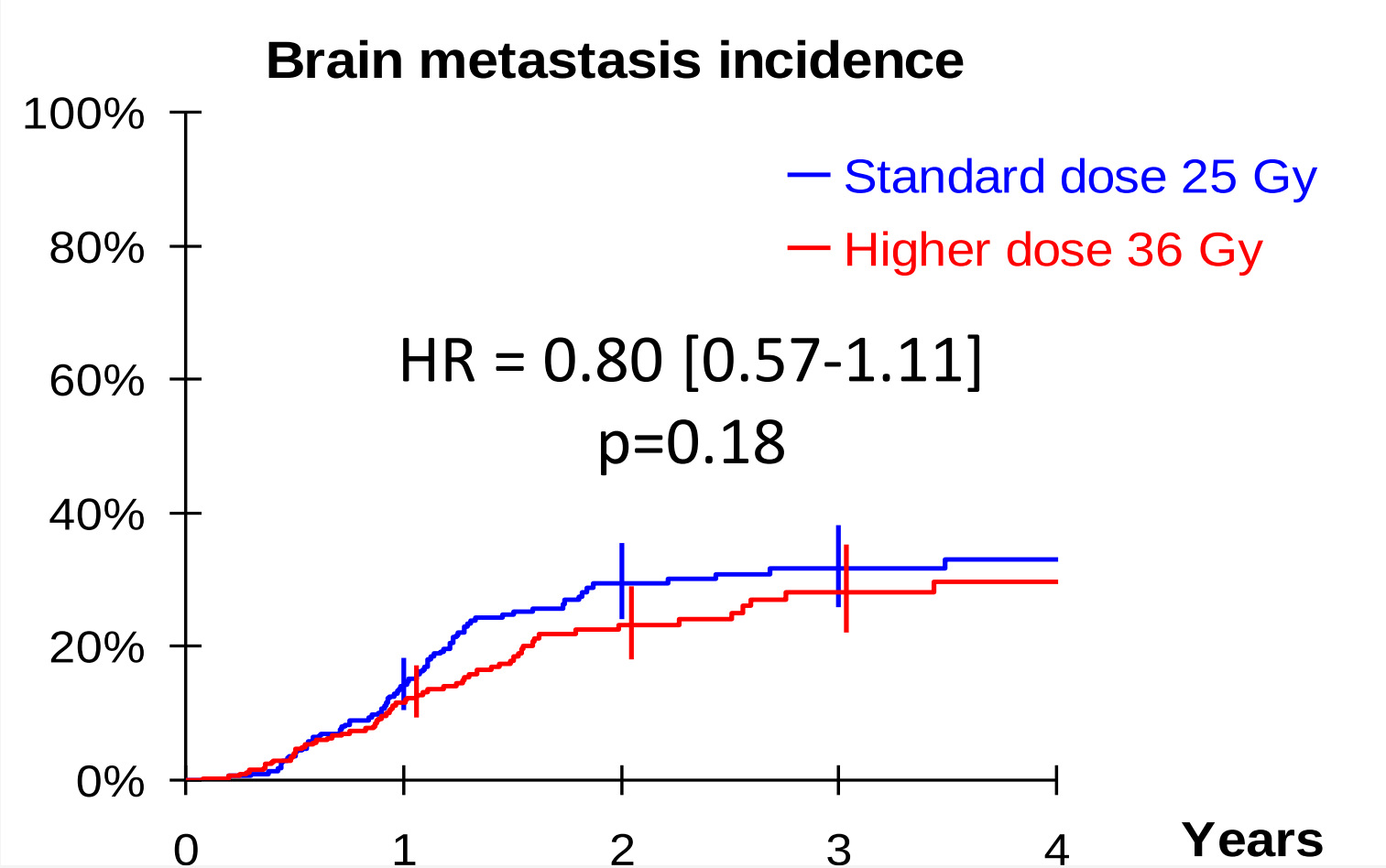
Test for heterogeneity: $\chi^2_6 = 9.71$, P=0.14





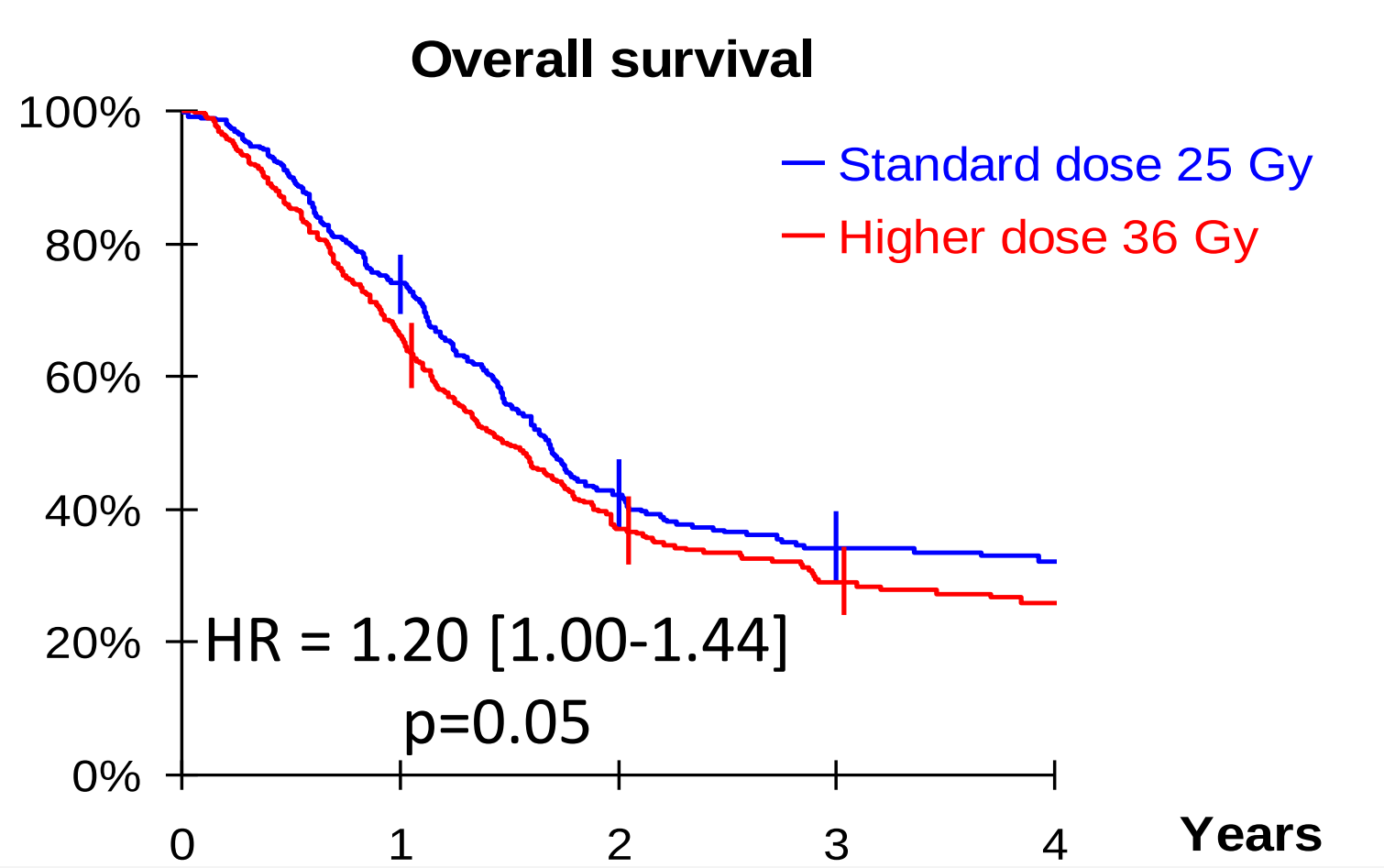
Auperin NEJM 1999

EULINT PCI 99



Le Pechoux Lancet Oncol 2009

EULINT PCI 99



Le Pechoux Lancet Oncol 2009

Limited SCLC summary

- An intensive chemo-radiation package
  - 1rst. day of any treatment
  - last day of radiation
- Thoracic irradiation
  - as soon as possible
  - improves overall survival
  - omit ENI only if FDG-PET pre-chemo
- Prophylactic cranial irradiation
  - improves overall survival
  - 25 Gy / 10 fractions

PCI in extensive SCLC

	PCI N =143	Control N = 143	HR	NTT	p
Symptomatic brain mets	15 % [8 – 21]	40 % [32 – 49]	0.27 [0.16 – 0.44]	4	<0.0001
OS 1 yr	27 % [19 – 36]	13 % [8 – 20]	0.68 [0.59 – 0.88]	7	0.003

- ✓ Extensive SCLC, 18 - 75 yrs., WHO 0 – 2, 2001 – 2006
- ✓ Response to chemotherapy
- ✓ Radiotherapy within 4 – 6 weeks after chemotherapy
- ✓ 20/8, 20/10, 24/12, 30/10, 30/12

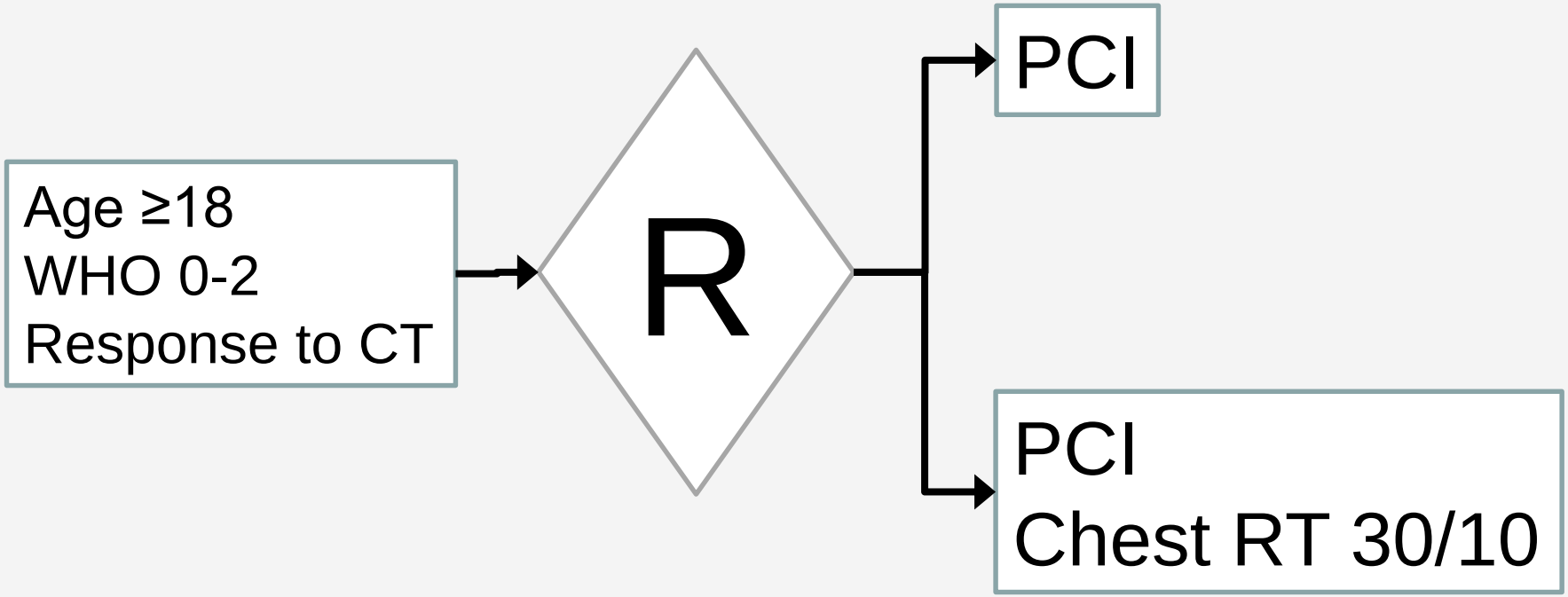
Slotman NEJM 2007

PCI in extensive SCLC

Quality-of-Life Score	Assessment Time	Prophylactic Cranial Irradiation	Control	P Value†
Primary end points				
Global health status	0–9 mo‡			0.10
Role functioning	0–9 mo‡			0.17
Cognitive functioning	0–9 mo‡			0.07
Emotional functioning	0–9 mo‡			0.18
Fatigue	6 wk	43.2±2.56	29.3±2.47	<0.001
	3 mo	53.6±3.03	38.5±3.24	<0.001
Hair loss	6 wk	36.5±3.96	11.7±3.73	<0.001
Exploratory results				
Appetite loss	6 wk	28.9±3.25	10.6±3.06	<0.001
	3 mo	43.9±3.87	14.8±4.18	<0.001
Nausea and vomiting	6 wk	15.0±1.73	5.3±1.64	<0.001
	3 mo	26.9±2.92	8.2±3.15	<0.001
Leg weakness	6 wk	25.2±2.71	11.8±2.48	<0.001
	3 mo	32.2±3.62	16.0±3.93	0.003

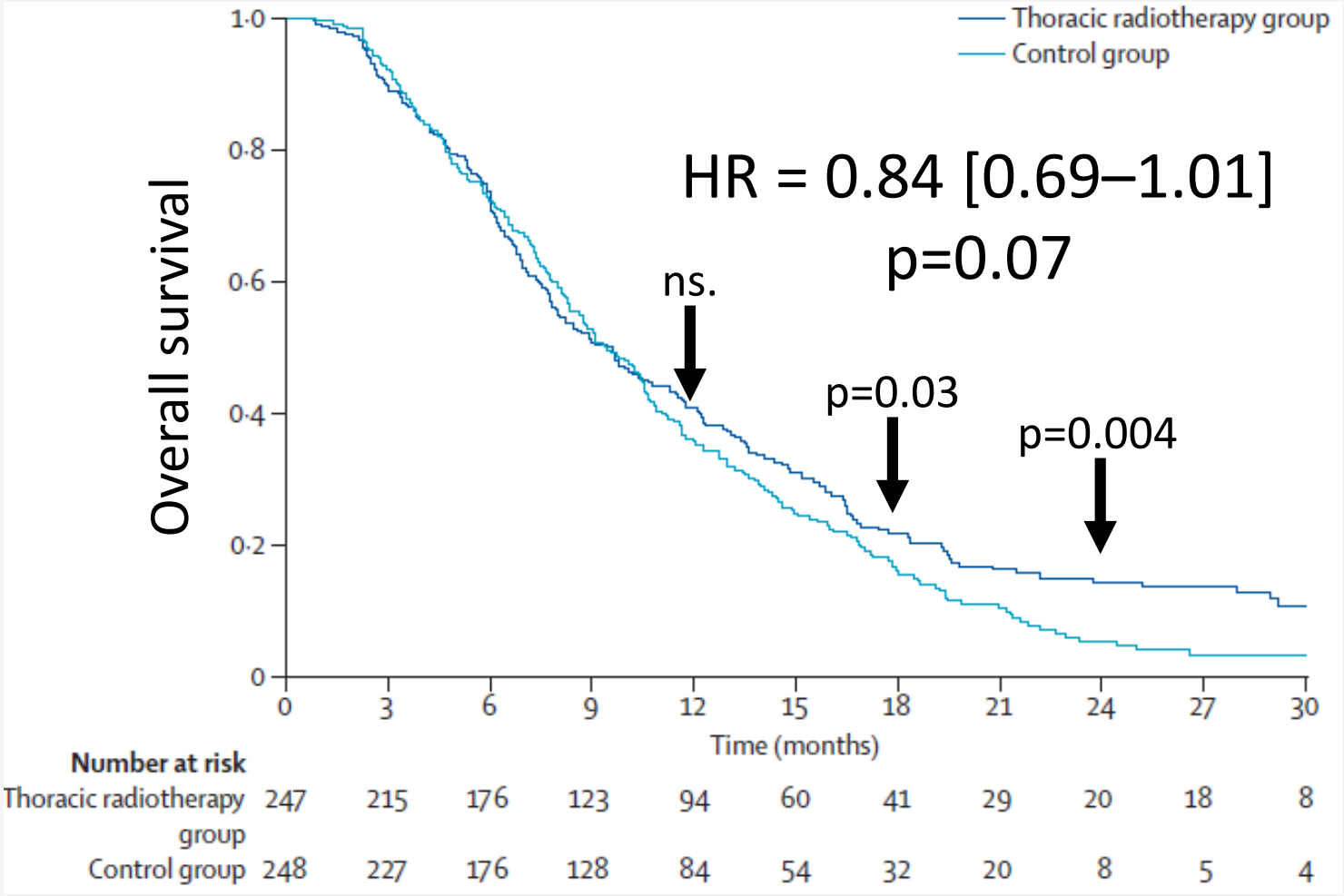
Slotman NEJM 2007

Thoracic RT in extensive SCLC



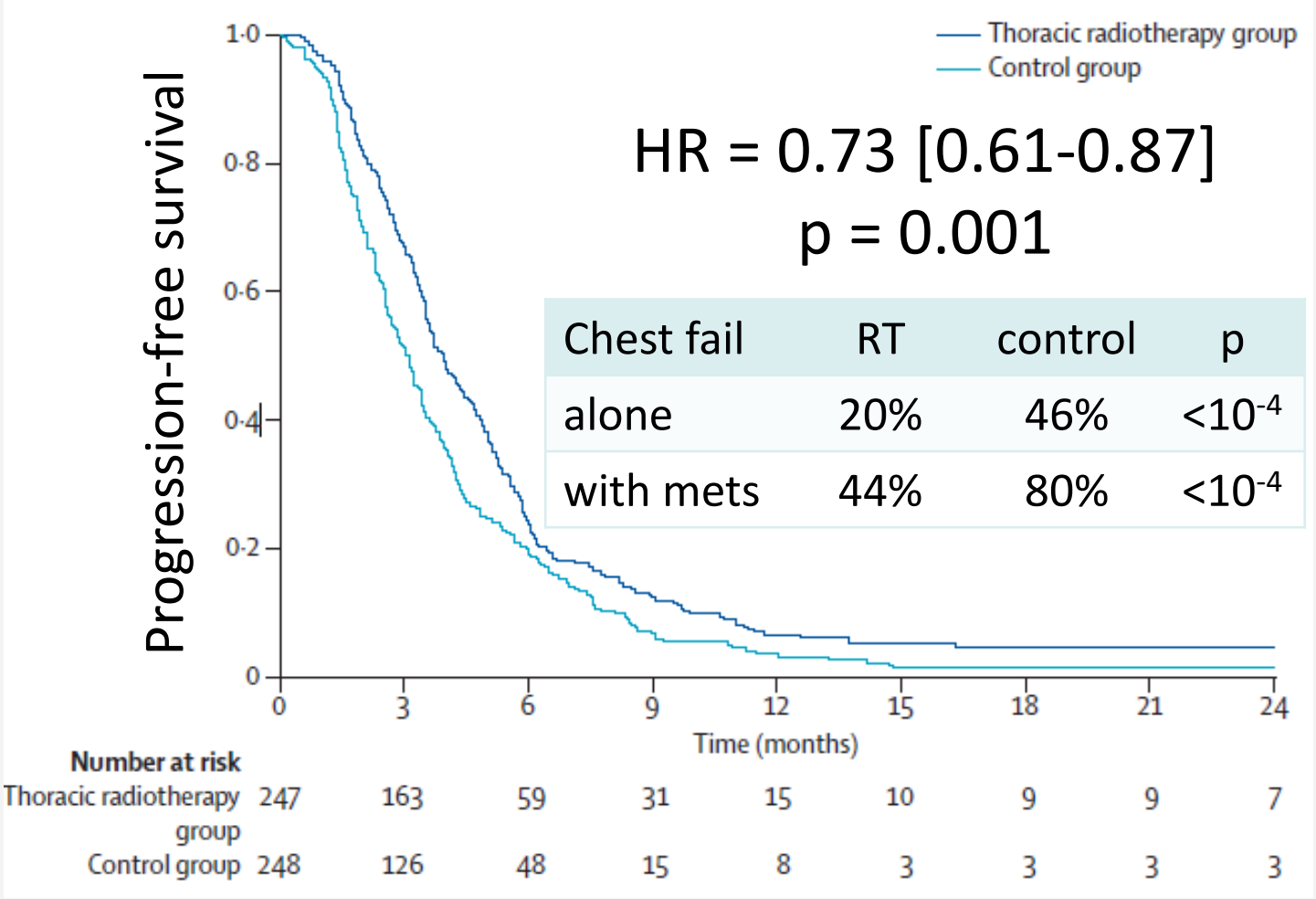
Slotman NEJM 2014

Thoracic RT in extensive SCLC



Slotman NEJM 2014

Thoracic RT in extensive SCLC



HR = 0.73 [0.61-0.87]

p = 0.001

Chest fail	RT	control	p
alone	20%	46%	$<10^{-4}$
with mets	44%	80%	$<10^{-4}$

Slotman NEJM 2014

Extensive SCLC summary

- Prophylactic cranial irradiation
  - improves overall survival
  - reduces brain metastases
- Thoracic irradiation
  - improves chest control
  - may improve overall survival
  - 30 Gy in 10 fractions

Follow-up


Cancéropôle
Nord-Ouest


litis

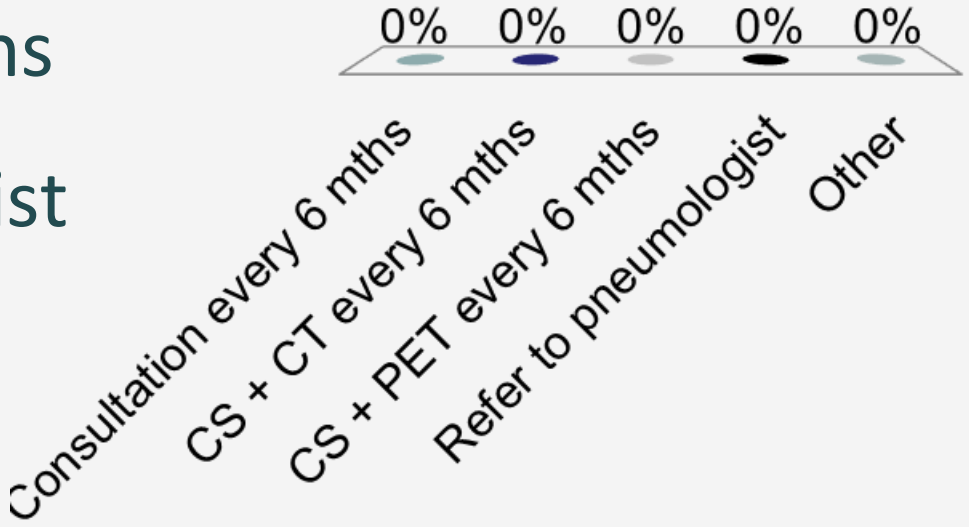

ESTRO
European SocieTy for
RADIOTHERAPY
& ONCOLOGY


UNIVERSITÉ
DE ROUEN

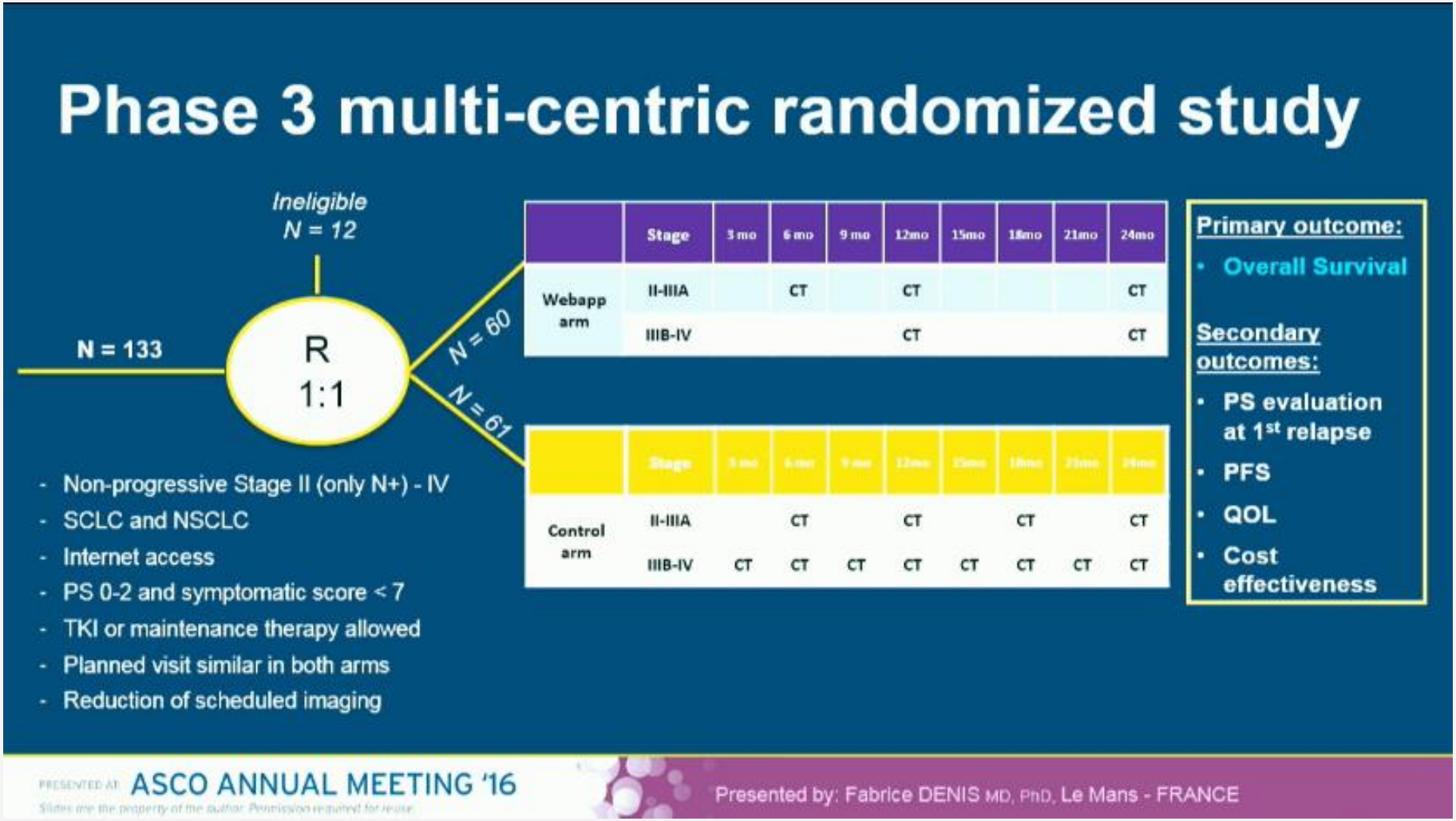

CENTRE HENRI
BECQUEREL
HAUTE-NORMANDIE

How do you follow your patients ?

A. Consultation every 6 mths
B. CS + CT every 6 mths
C. CS + PET every 6 mths
D. Refer to pneumologist
E. Other

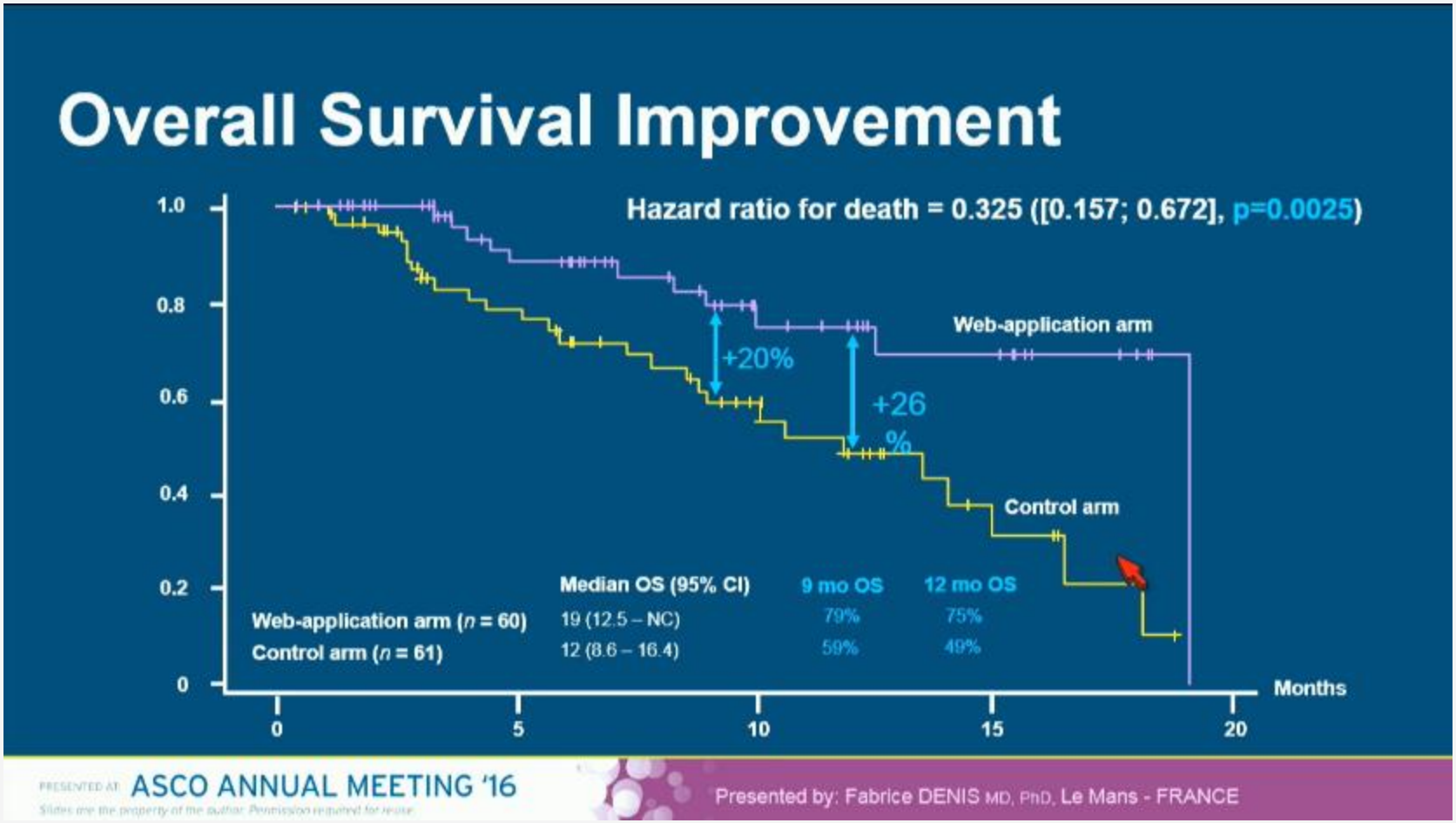


Electronic follow-up



Denis JNCI 2017

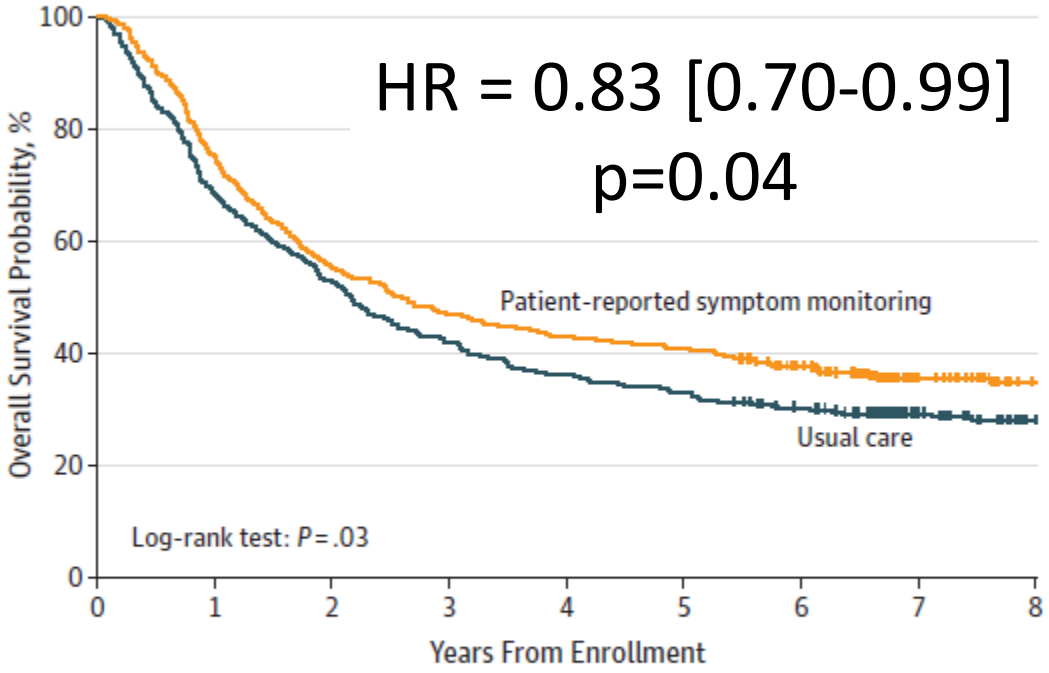
Electronic follow-up



Denis JNCI 2017

Electronic follow-up

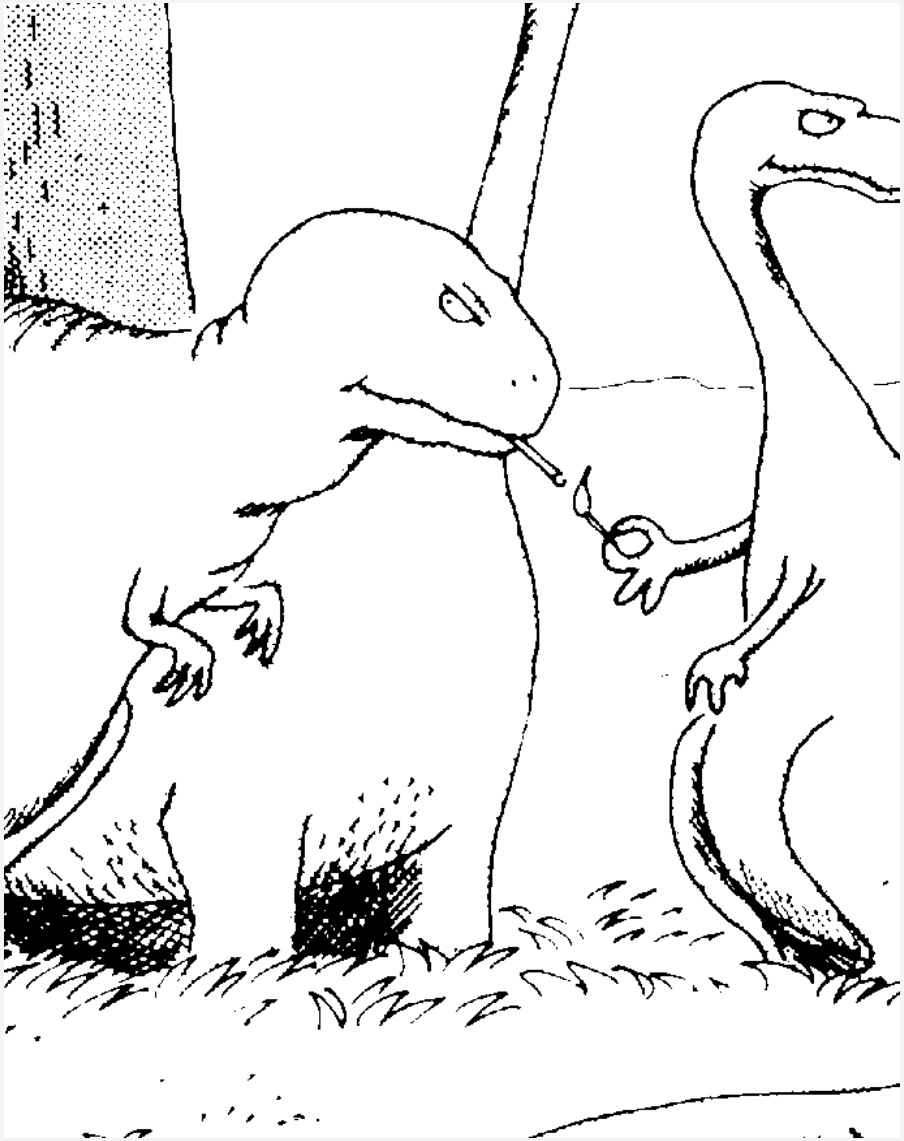
Figure. Overall Survival Among Patients With Metastatic Cancer Assigned to Electronic Patient-Reported Symptom Monitoring During Routine Chemotherapy vs Usual Care



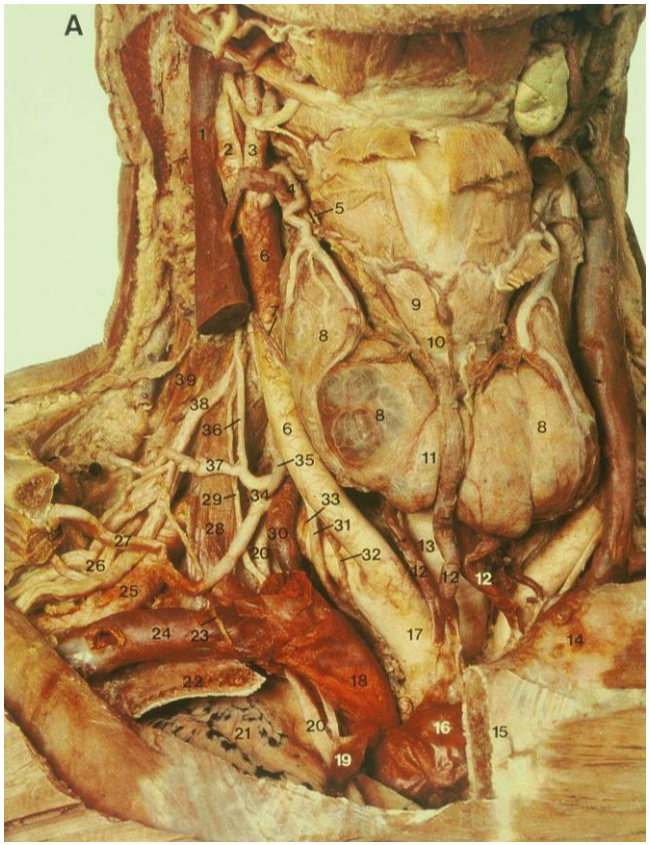
No. at risk									
Patient-reported symptom monitoring	441	331	244	207	190	181	148	65	33
Usual care	325	223	171	137	118	107	89	50	27

Basch JAMA 2017

The reason dinosaurs became extinct



Head and neck cancer



Hans Kaanders

Radboud University Nijmegen Medical Centre

The Netherlands

Head and neck cancer

Main subsites:

- Oral cancer
- Oropharynx cancer
- Larynx cancer
- Hypopharynx cancer
- Nasopharynx carcinoma

Issues:

- Epidemiology
- Etiology
- Diagnostic work-up
- Treatment
  Radiotherapy (technique, dose fractionation, combined modality)
- New developments

Head and neck cancer: diagnostic workup

Medical history

general (well-being, weight loss)

dietary assessment

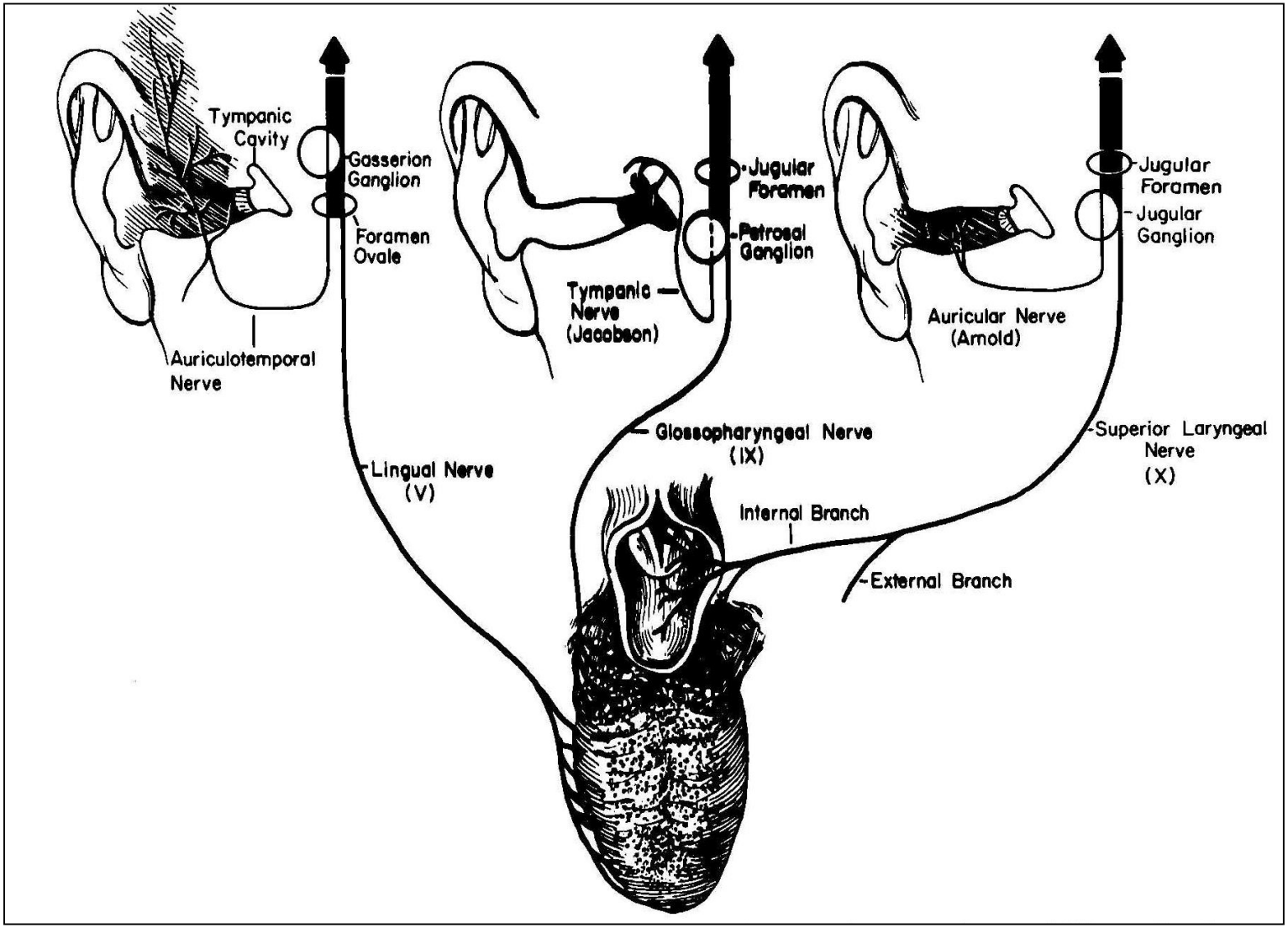
co-morbidity

initial symptom

site-specific symptoms, e.g.

- otalgia
- trismus
- nerve palsies

} indicative for deep invasion


Tympanic Cavity
Gasserion Ganglion
Foramen Ovale
Auriculotemporal Nerve
Jugular Foramen
Petrosal Ganglion
Tympanic Nerve (Jacobson)
Jugular Foramen
Jugular Ganglion
Auricular Nerve (Arnold)
Glossopharyngeal Nerve (IX)
Lingual Nerve (V)
Superior Laryngeal Nerve (X)
Internal Branch
External Branch

Head and neck cancer: diagnostic workup

Physical examination

- Inspection + palpation of upper aero-digestive tract
- Inspection + palpation of neck

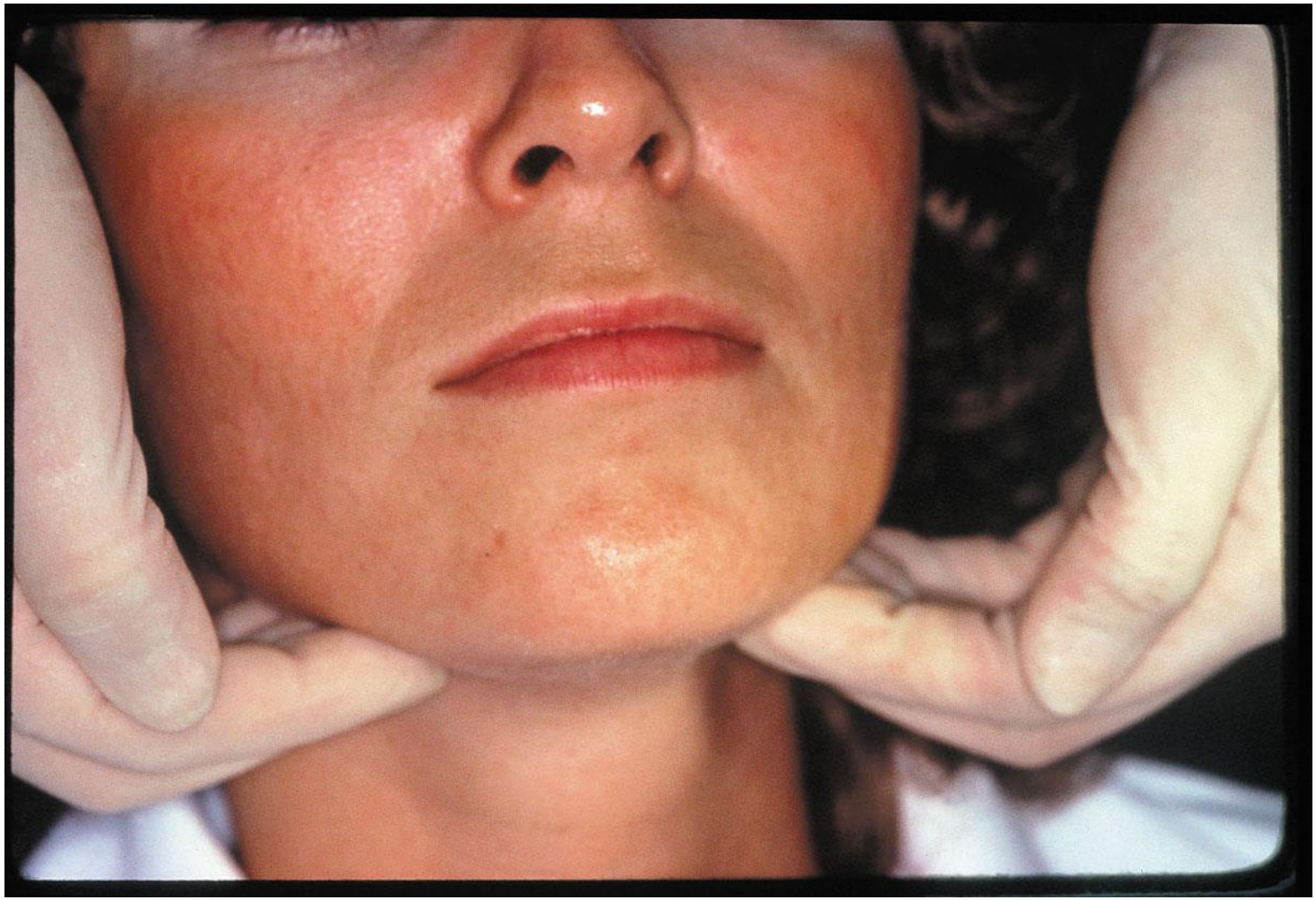
} Diagram/photograph!

- Additional for specific sites:
  - cranial nerve function (nasopharynx, parotid gland)
  - bimanual palpation (floor of mouth, level I nodes)
  - tongue mobility (base of tongue)
- Dental status
- General condition
- Weight

Examination under anesthesia

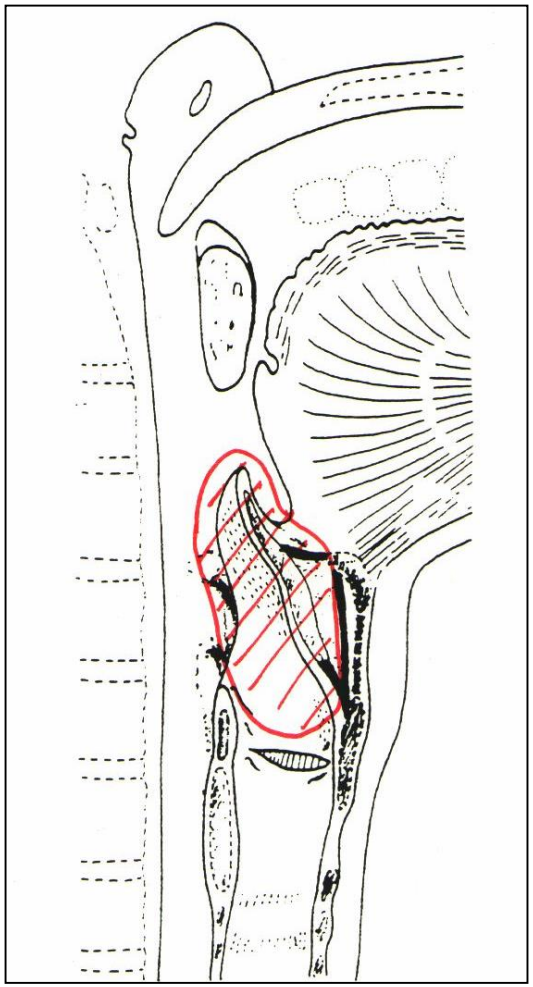
Palpation of level Ib nodes

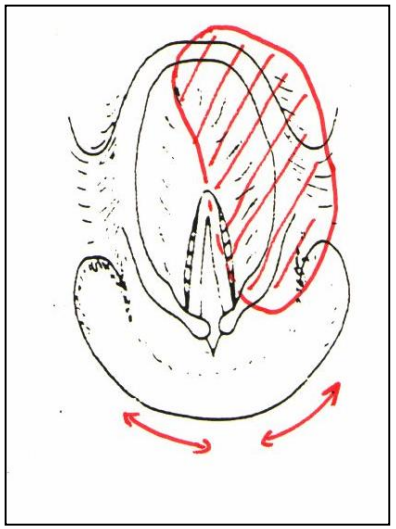
wrong…



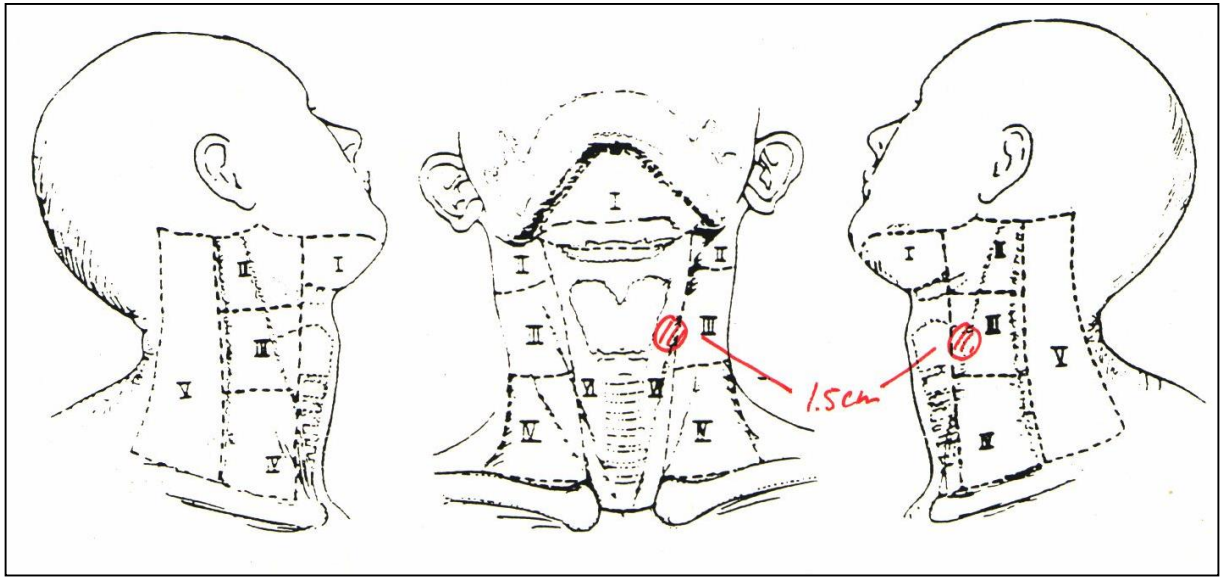
Palpation of level Ib nodes

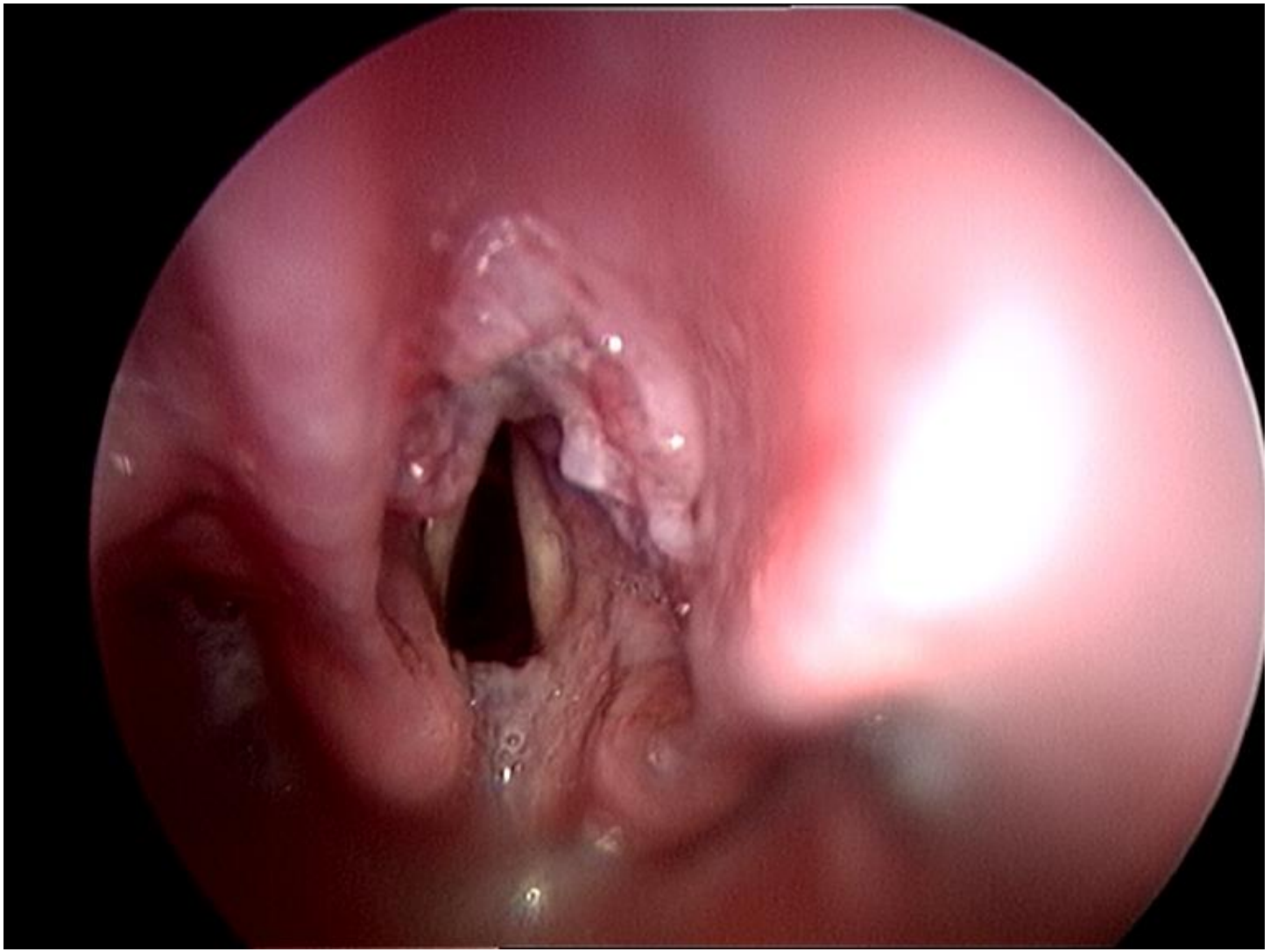
correct





T3N1M0
supraglottic carcinoma



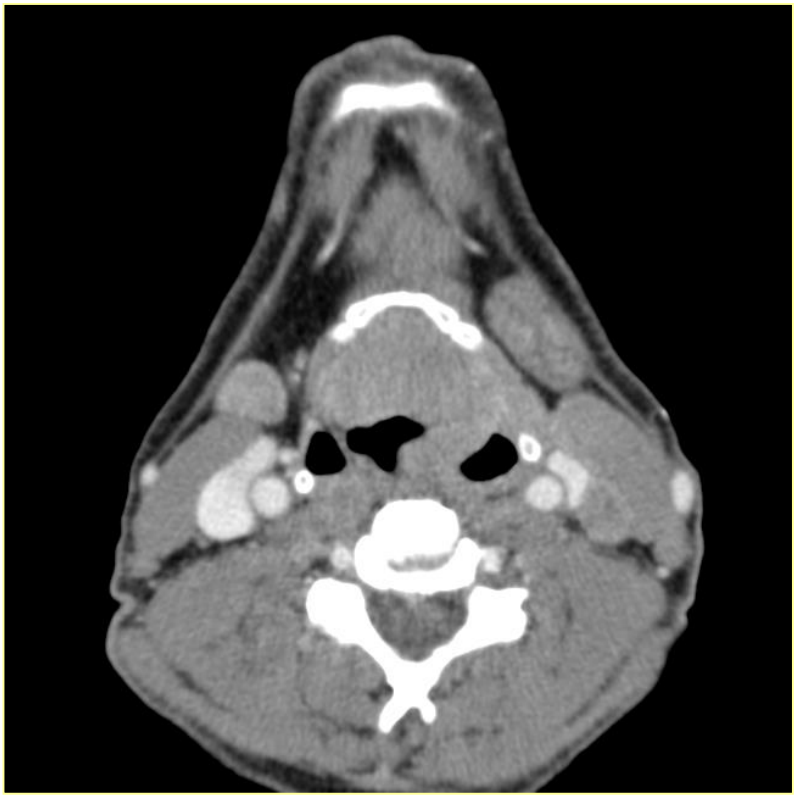


Head and neck cancer: diagnostic workup

Diagnostic imaging

Clinical “blind spots”

- parapharyngeal space
- retropharyngeal nodes
- deep muscles of tongue and floor of mouth
- pterygoid muscle compartment
- paranasal sinuses, retromaxillar area
- pre- and paravertebral areas
- pre-epiglottic space
- bone/cartilage
- base of skull
- thoracic inlet/upper mediastinum



MRI or CT

Ultrasound + cytology (neck nodes)

Chest X-ray, chest CT (extensive nodal disease, supraclavicular nodes)

PET?

Head and neck cancer: short case 1

Man, 57 yrs in good general condition is referred to your multidisciplinary H&N team because of sore throat.

•Referring physician observed tumor in left tonsillar area and biopsy showed squamous cell carcinoma.

•Patient comes into your office and first thing you notice on him after starting talking is that he has trismus……

How do you stage the tumor?

A. T1
B. T2
C. T3
D. T4

Head and neck cancer: short case 1

Man, 57 yrs in good general condition is referred to your multidisciplinary H&N team because of sore throat.

•Referring physician observed tumor in left tonsillar area and biopsy showed squamous cell carcinoma.

•Patient comes into your office and first thing you notice on him after starting talking is that he has trismus……

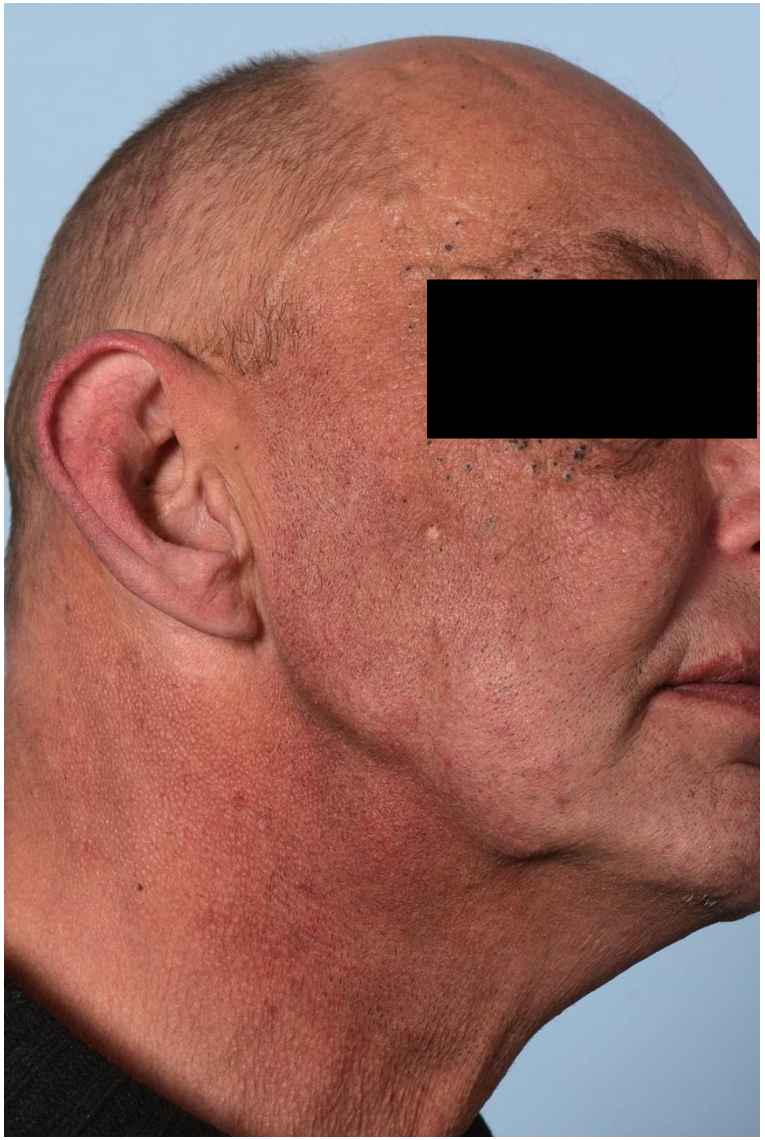
What treatment do you recommend?

A. Surgery + or – postop radiotherapy
B. Radiotherapy
C. Radiotherapy + cetuximab
D. Chemoradiation

Head and neck cancer: short case 2

Man, 64 yrs noticed a right submandibular neck mass.

Physical exam reveals right submandibular mass, firm, mobile, 2,5 cm.



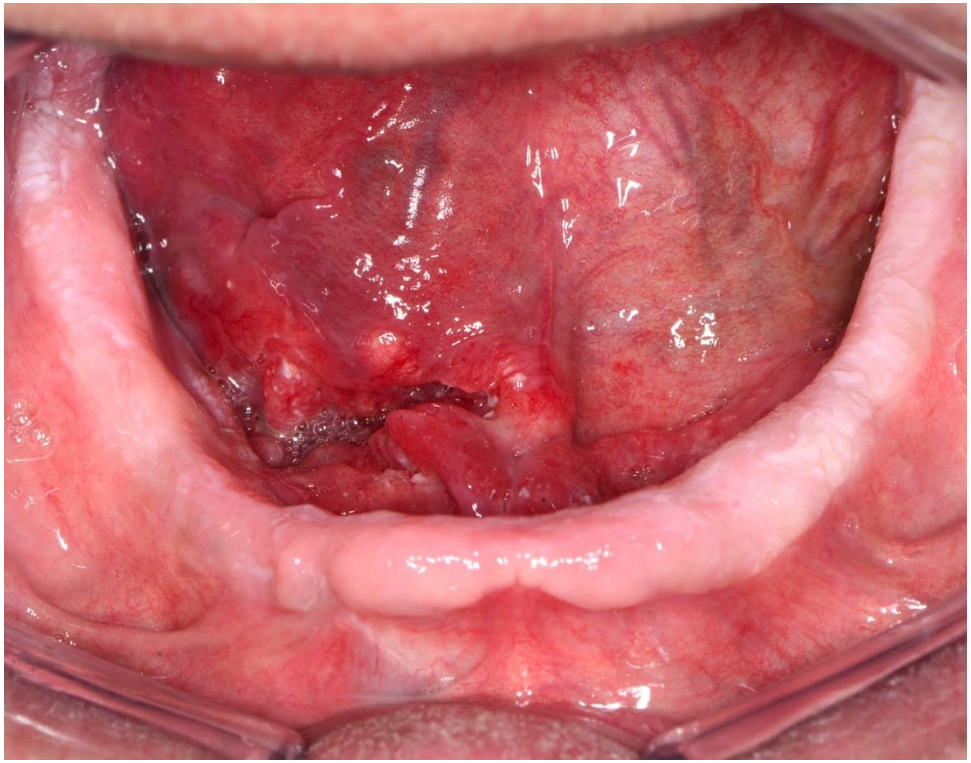
Head and neck cancer: short case 2

Man, 64 yrs noticed a right submandibular neck mass.

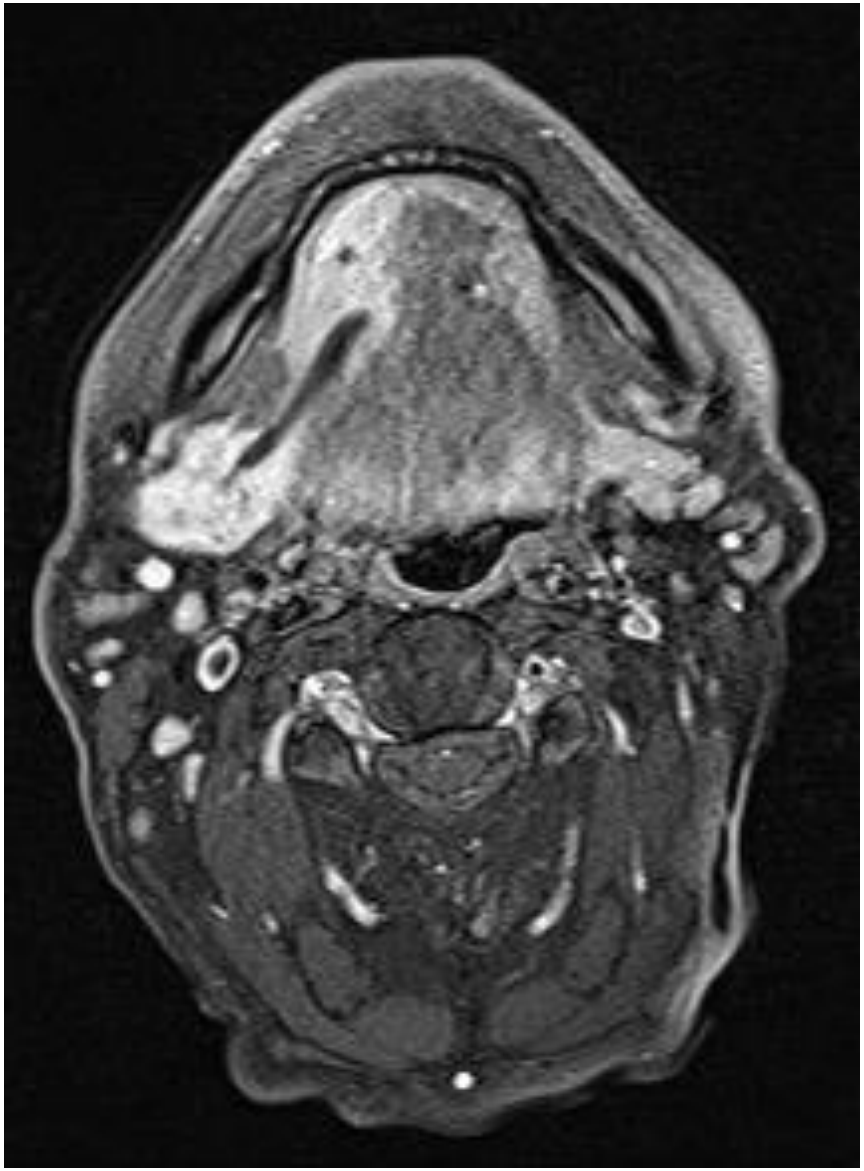
Physical exam reveals right submandibular mass, firm, mobile, 2,5 cm.

Intra-orally there is an ulcerating tumor in the anterior floor of mouth on the right side with extension over midline. Largest dimension 3 cm

Biopsy of the intra-oral lesion shows squamous cell carcinoma.

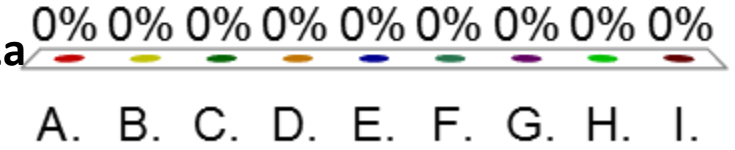


Head and neck cancer: short case 2



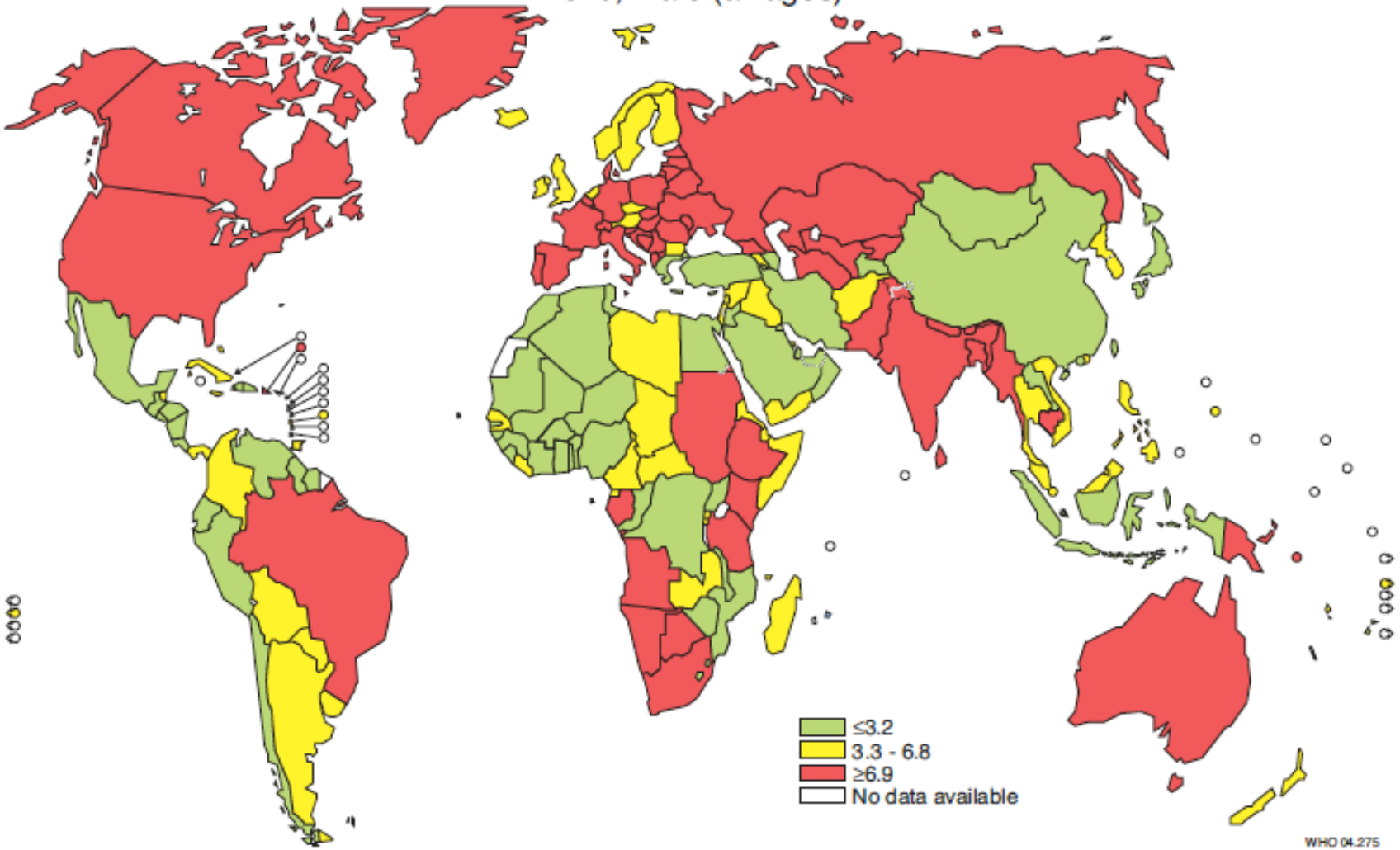
How do you stage this tumor?

A. **T1N0**
B. **T1N1**
C. **T2N0**
D. **T2N1**
E. **T2N2a**
F. **T3N0**
G. **T3N1**
H. **T3N2a**
I.



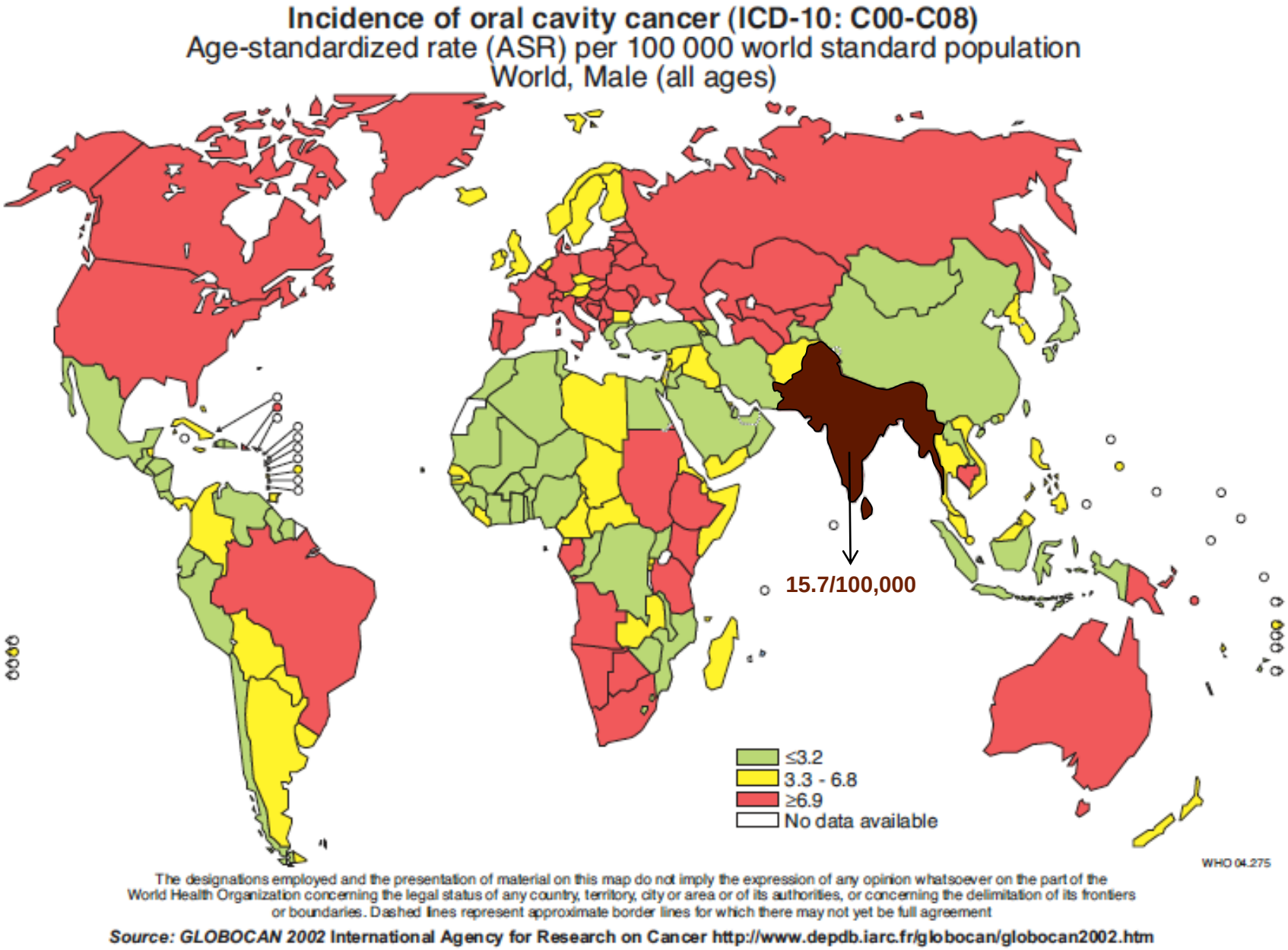
ORAL CANCER

Incidence of oral cavity cancer (ICD-10: C00-C08)
Age-standardized rate (ASR) per 100 000 world standard population
World, Male (all ages)



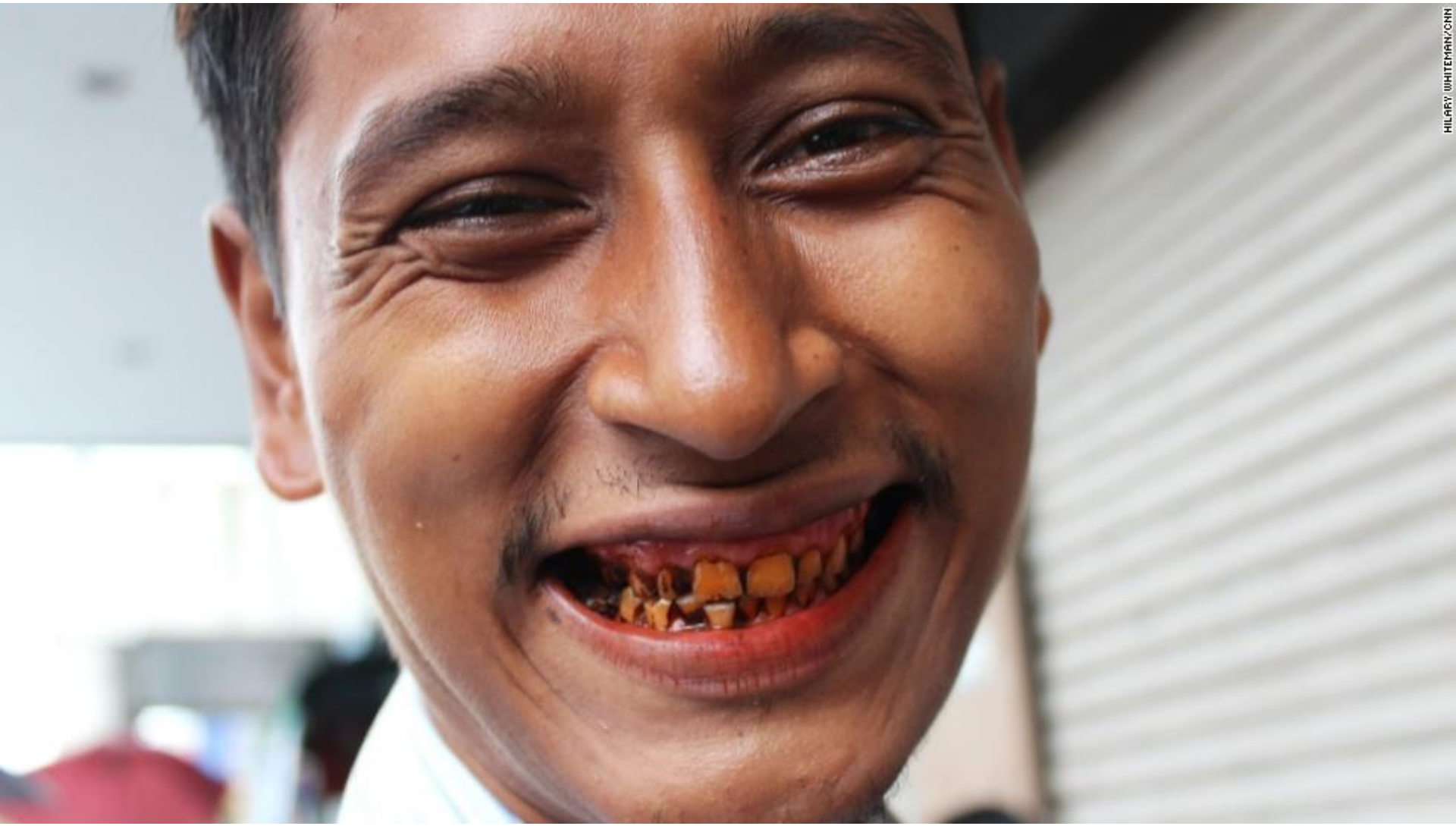
The designations employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dashed lines represent approximate border lines for which there may not yet be full agreement

Source: GLOBOCAN 2002 **International Agency for Research on Cancer http://www.depdb.iarc.fr/globocan/globocan2002.htm**


Incidence of oral cavity cancer (ICD-10: C00-C08)
Age-standardized rate (ASR) per 100 000 world standard population
World, Male (all ages)
15.7/100,000
≤3.2
3.3 - 6.8
≥6.9
No data available
WHO 04.275
The designations employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dashed lines represent approximate border lines for which there may not yet be full agreement
Source: GLOBOCAN 2002 International Agency for Research on Cancer http://www.depdb.iarc.fr/globocan/globocan2002.htm

Betel quid

600 million frequent users



Relative risk if used with tobacco and alcohol: ~ 120

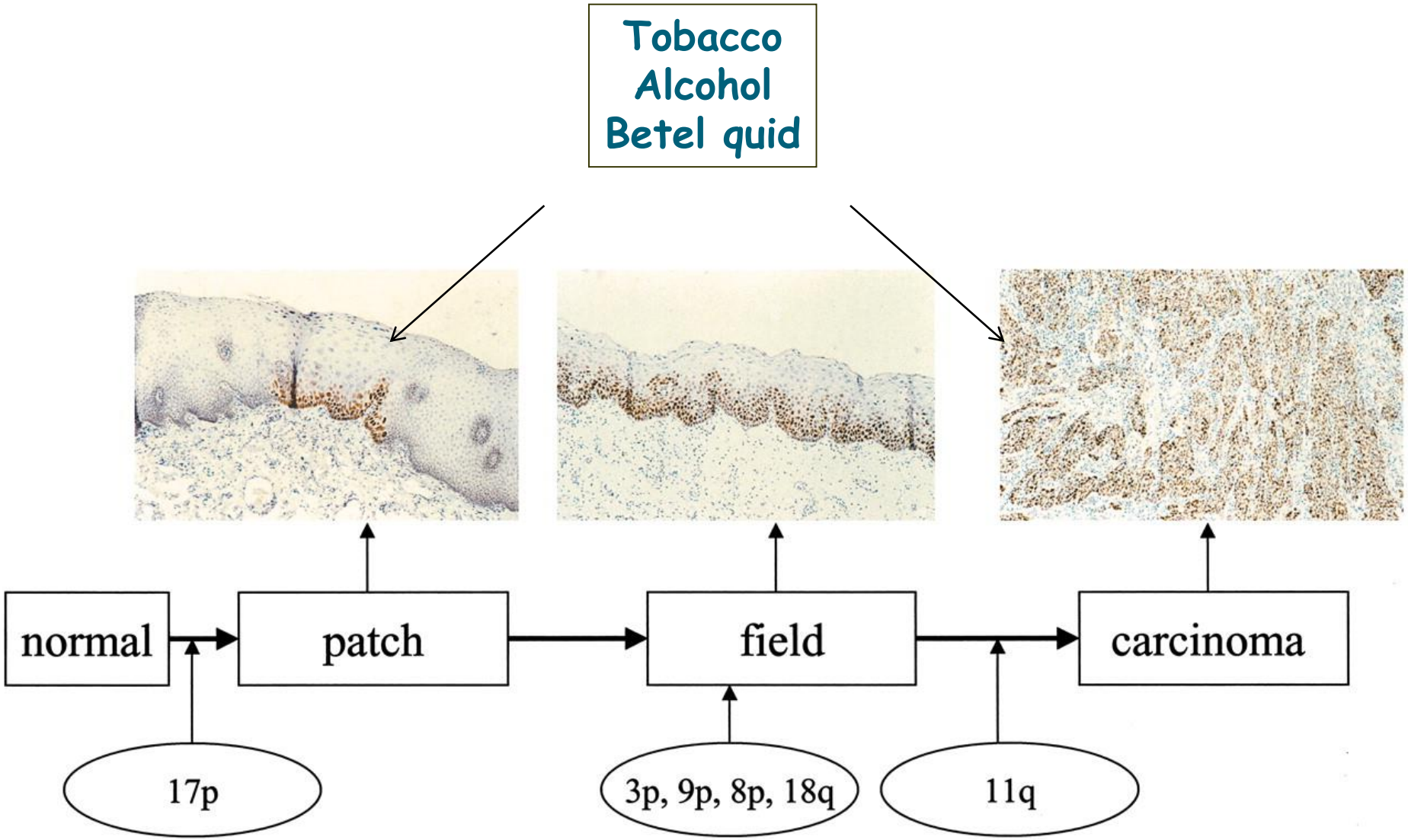
Head and neck cancer: etiologic factors

- Tobacco use (smoking, chewing)
- Alcohol abuse

Other factors:

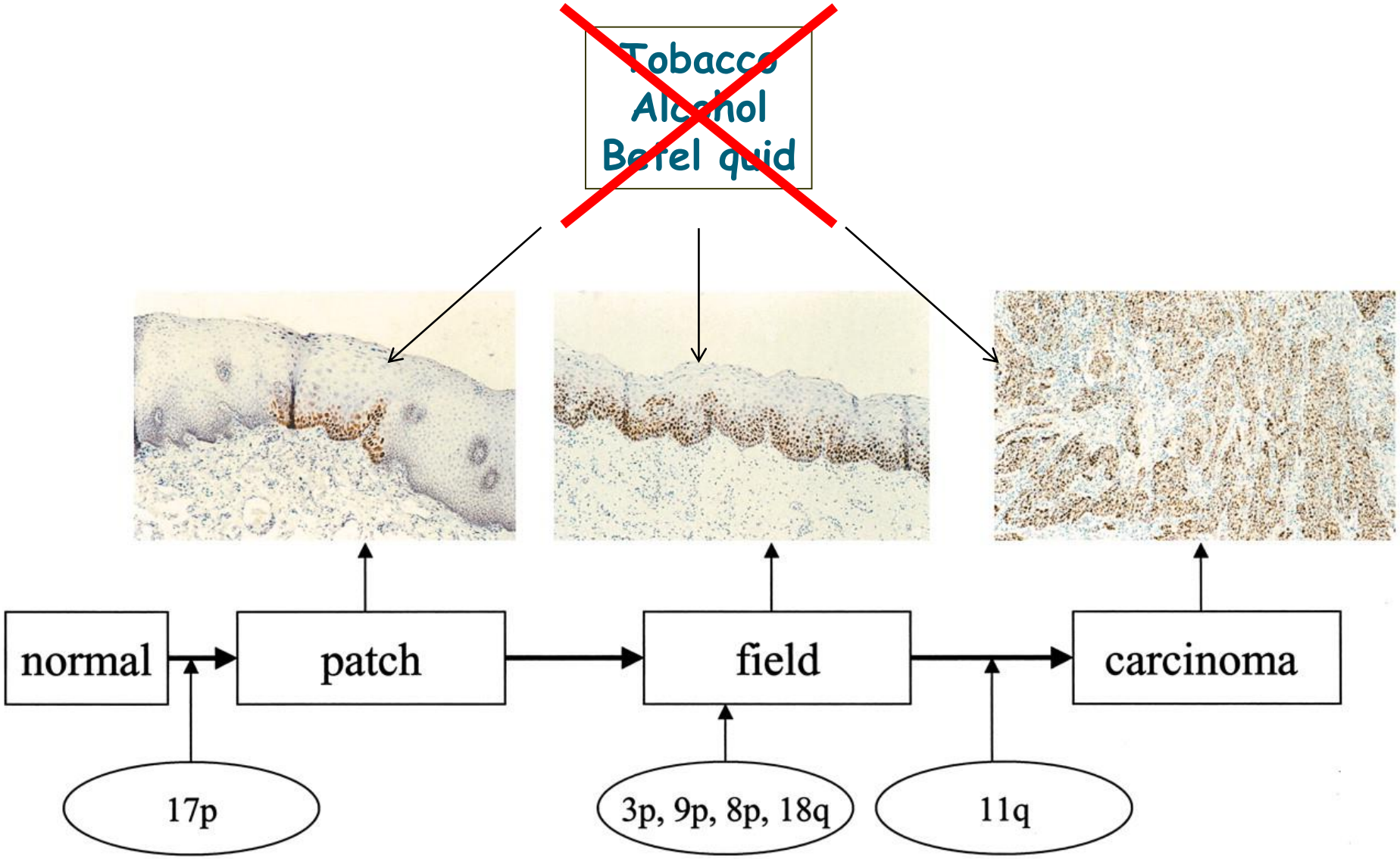
- Oral cancer: betel quid, poor oral hygiene
- Nasal cavity and paranasal sinus cancers: wood dust, leather dust
- Nasopharynx carcinoma: EBV associated, salted fish consumption, genetic factors?
- Oropharynx carcinoma: HPV associated
- Hypopharynx carcinoma: vitamin C and iron deficiency (Plummer-Vinson syndrome)
- Salivary gland tumors: ionizing radiation, asbestos, certain metals

A genetic progression model of oral carcinogenesis



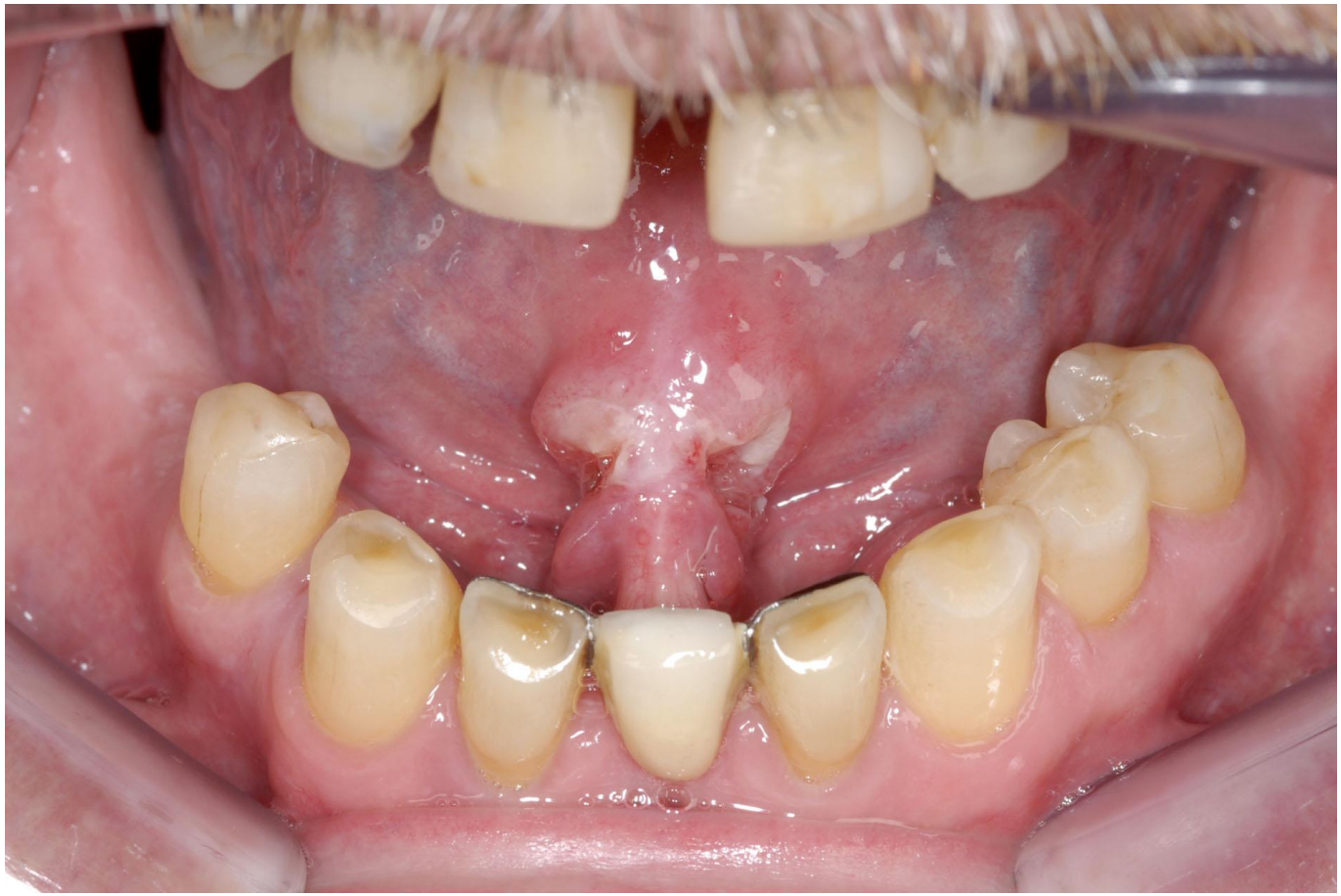
Braakhuis et al. Cancer Res 2003

Best strategy to reduce mortality of oral (head and neck) cancer is prevention!



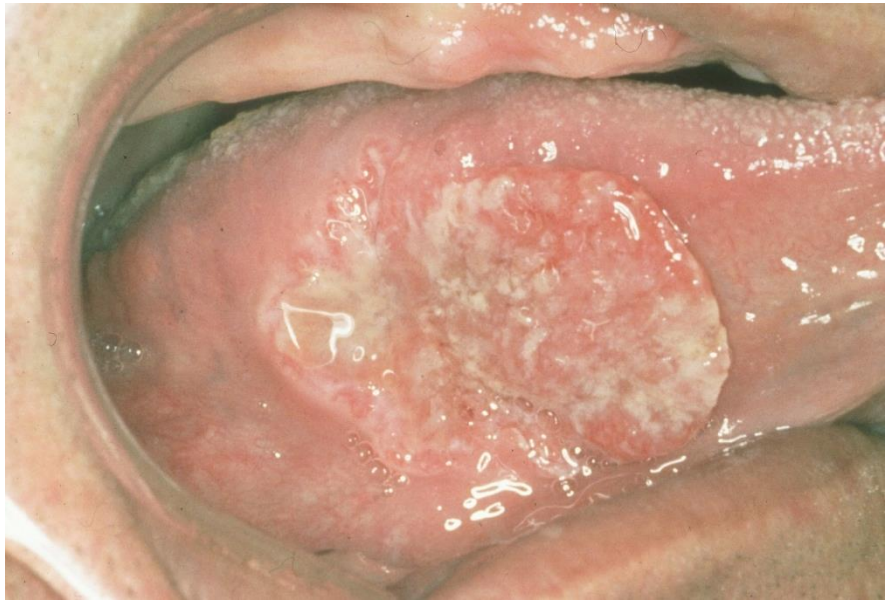
Braakhuis et al. Cancer Res 2003

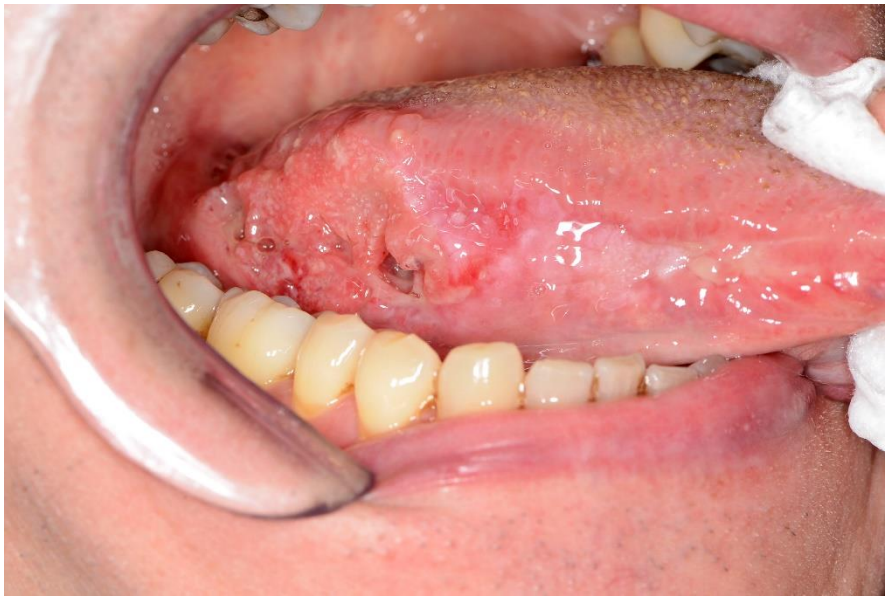
Floor of mouth cancer T1



T1: ≤ 2 cm

Oral tongue cancer T2





T2: 2 - 4 cm

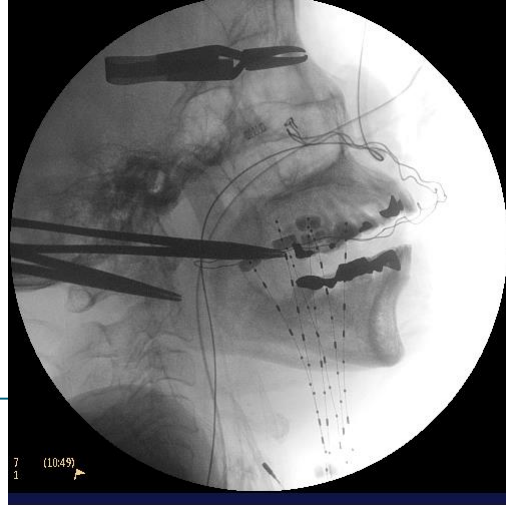
Surgery for early (T1-T2) oral cancer

Selection of literature data

Study	N	Local control		
		Radiotherapy	Surgery (+ or – RT)	
Akine ‘91	244	90%	84%	
Rodgers ’93	95	78%	82%	(abs. rates)
Fein ‘94	102	75%	76%	
Hicks ‘97	43		84%	(abs. rate)
Wolfensberger ‘01	105		89%	(abs. rate)
Magge ‘03	153		85%	(abs. rate)
Overall		75-90%	76-89%	

Radiotherapy for oral tongue cancer

Better local control with greater component of dose delivered by brachytherapy



Study	Stage	Local control	
Mendenhall ’89	T2	brachy + EBRT < 30 Gy	brachy + EBRT ≥ 30 Gy
		75%	40%
Wendt ’90	T1-2	brachy + EBRT < 40 Gy	brachy + EBRT ≥ 40 Gy
		92%	65%
Pernot ‘94	T2	brachy alone	brachy + EBRT
		90%	50%

Brachytherapy for oral tongue cancer

Selection of literature data

Study	N	Local control T1	Local control T2	
Decroix ’81	382	86%	78%	
Volterrani ’87	180	84%	71%	(abs. rates)
Wendt ’90	103	81%	67%	
Mazeron ’90	121	86%	84%	(abs. rates)
Lefebvre ’90	299	98%	89%	
Pernot ‘94	448	93%	65%	
Overall		81-98%	65-89%	

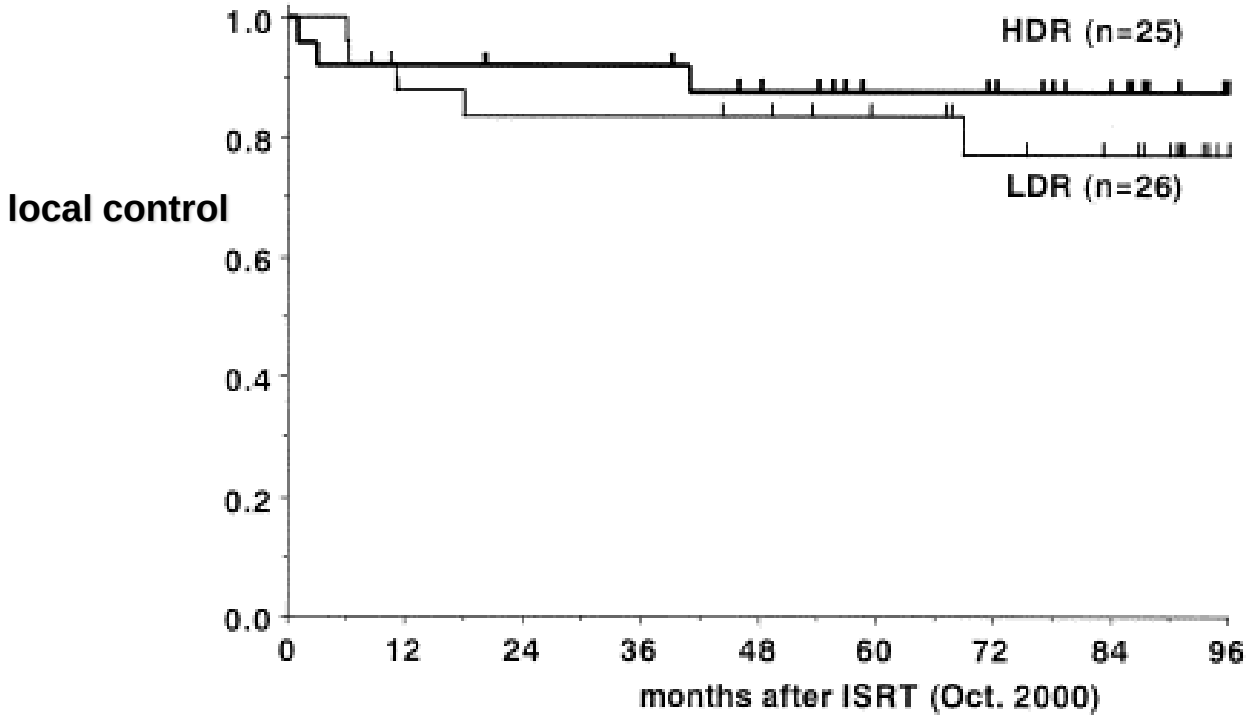
Brachytherapy for floor of mouth cancer

Selection of literature data

Study	N	Local control T1	Local control T2	
Fitzpatrick ‘82	377	83%	65%	(abs. rates)
Aygun ’84	116	78%	75%	(abs. rates)
Mazeron ’90	117	93%	71%	(abs. rates)
Pernot ’95	207	97%	72%	
Matsumoto ’96	90	89%	70%	(abs. rates)
Marsiglia ’02	160	93%	88%	(abs. rates)
Overall		78-97%	65-88%	

Brachytherapy for T1-T2 oral cancer

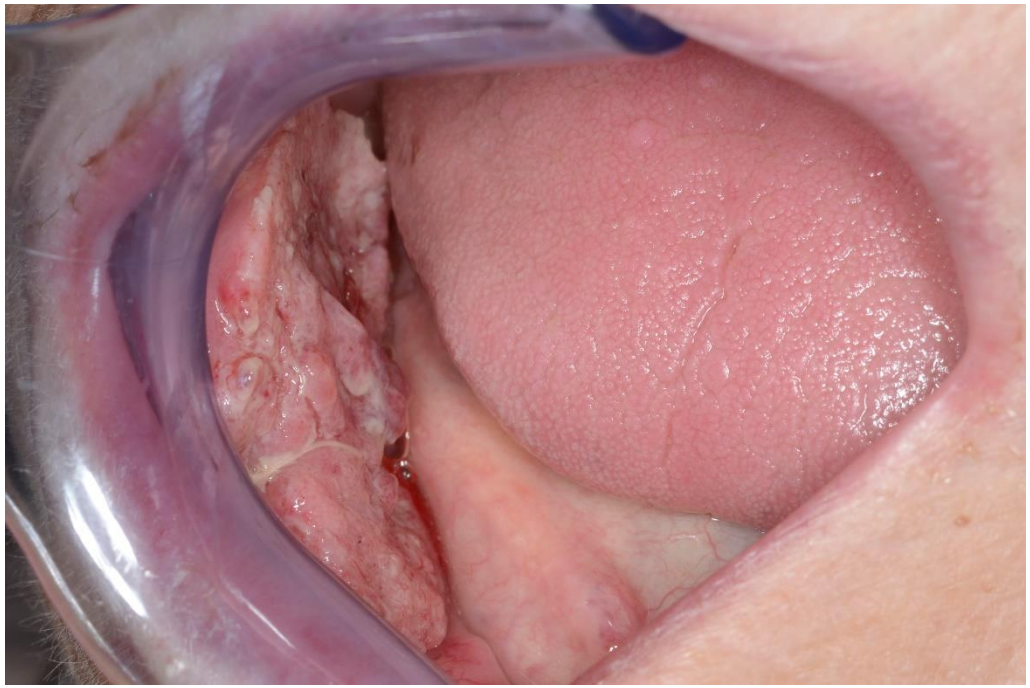
LDR vs HDR (randomized trial)

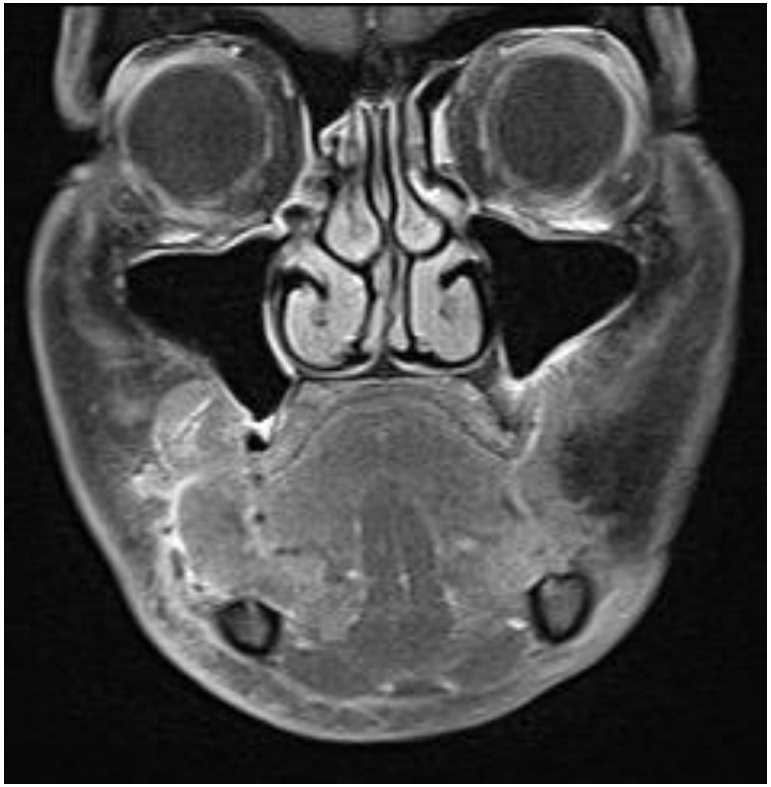


But: 24% regional recurrences!!

Inoue et al. IJROBP 2001

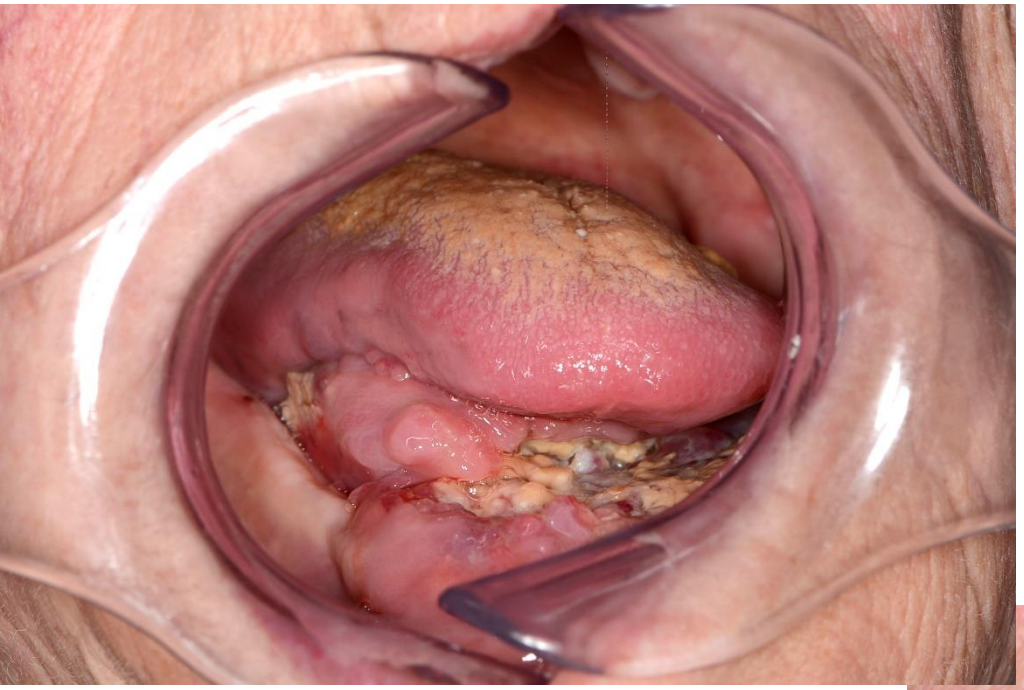
Carcinoma of buccal mucosa T3





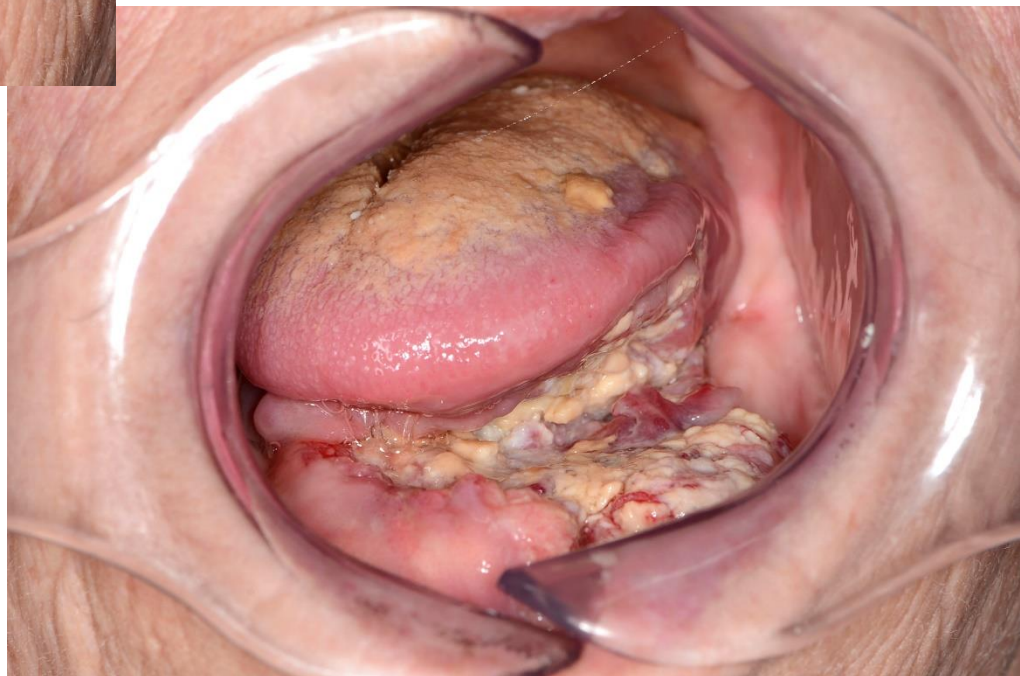
T3: > 4 cm

Floor of mouth / tongue cancer T4aN2c

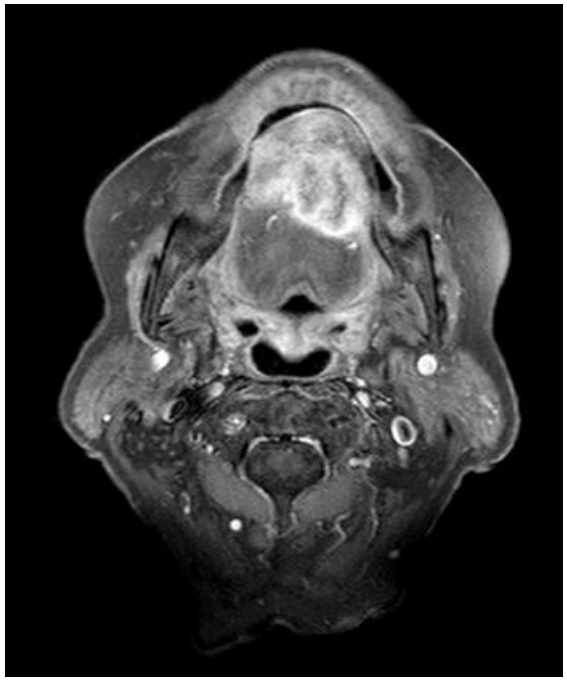
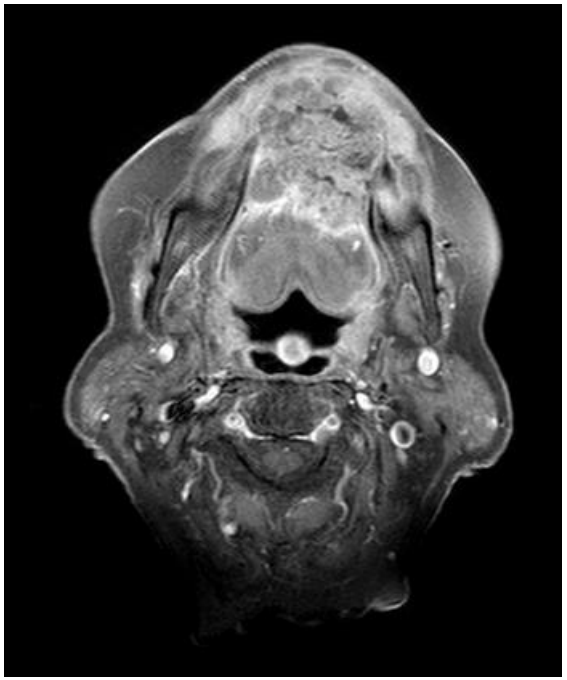
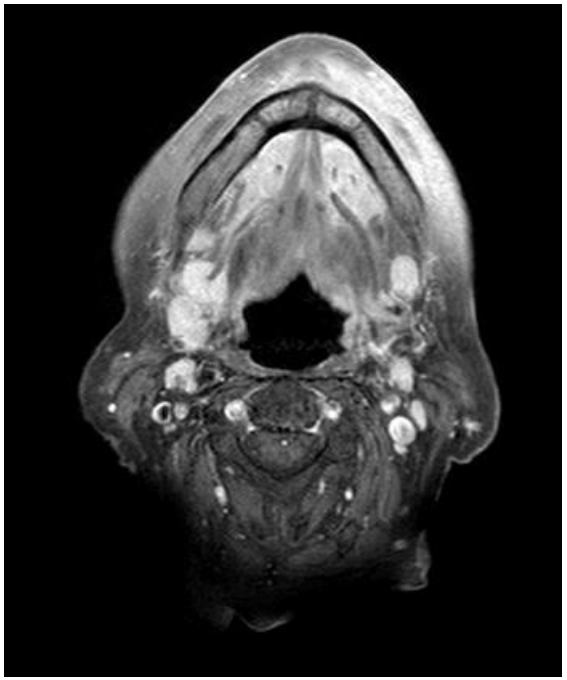


T4a: invasion of
- cortical bone
- deep muscles of tongue
- maxillary sinus
- skin of face

T4b: invasion of
- masticator space
- pterygoid plates
- skull base
- encasement int. carotid artery

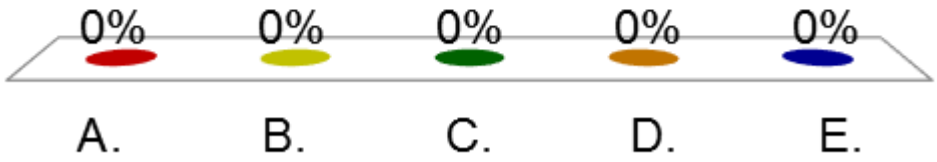


Floor of mouth / tongue cancer T4aN2c - MRI

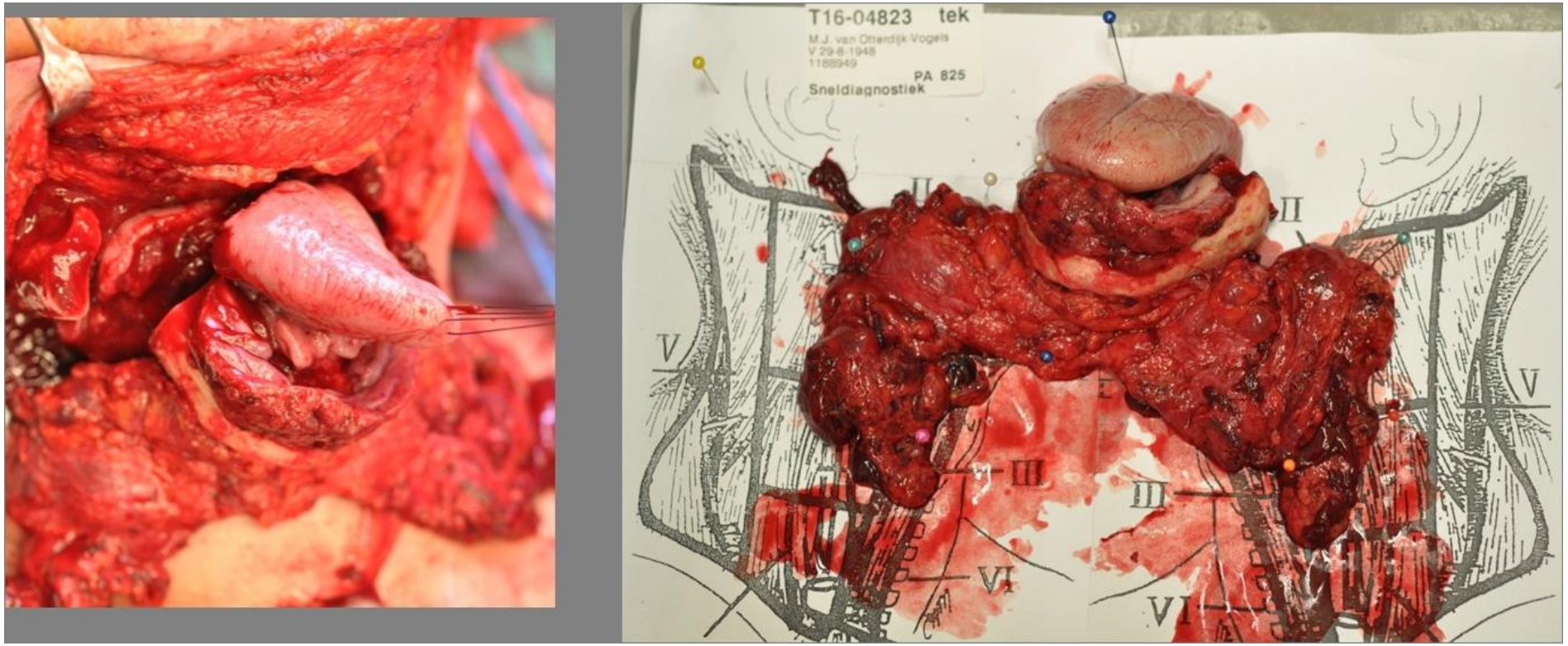




Oral cancer cT4aN2cM0
-
How would you treat this patient?

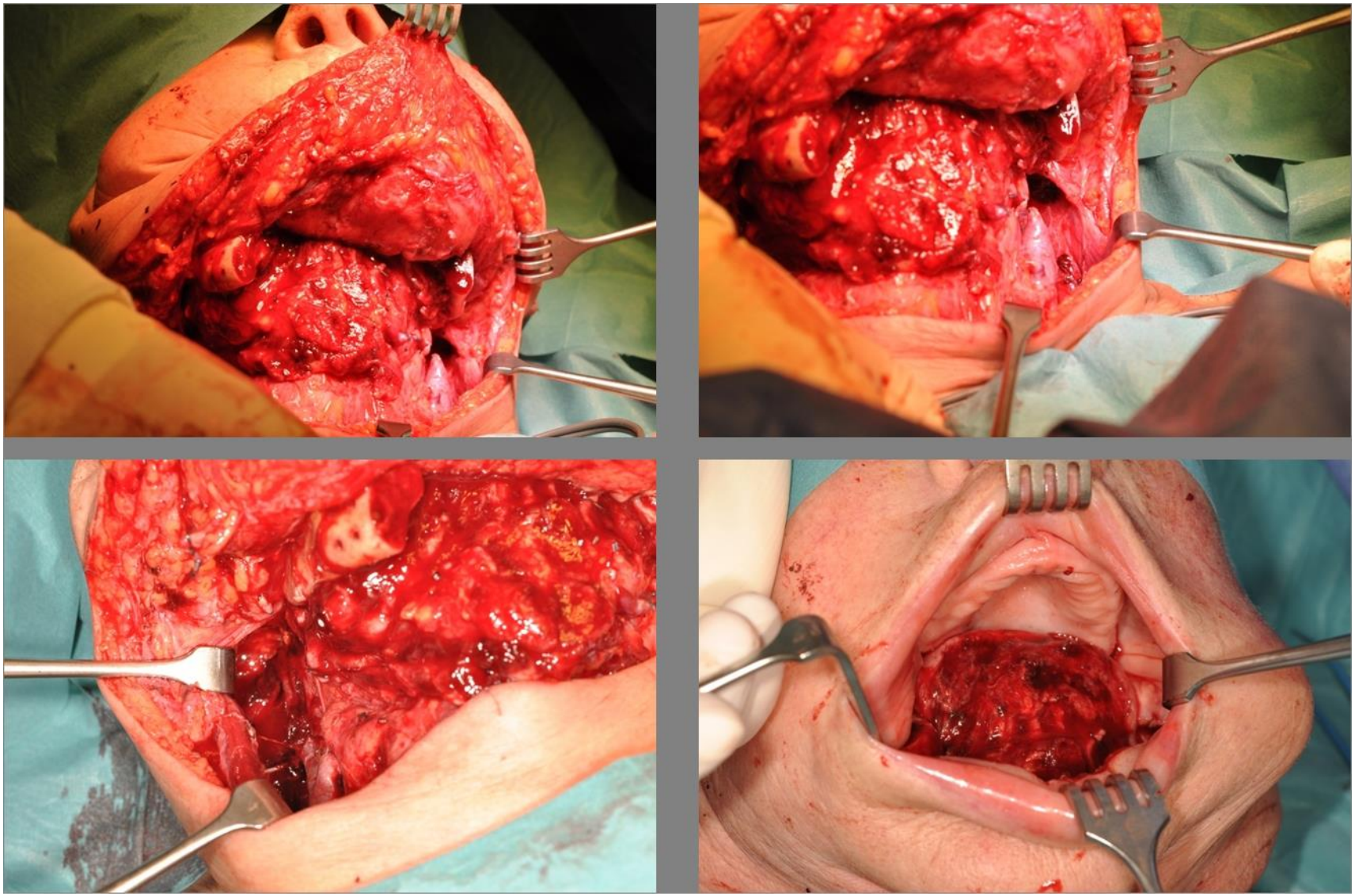
A. **Surgery and postoperative radiotherapy**
B. **Chemoradiation**
C. **Neoadjuvant chemotherapy followed by chemoradiation**
D. **Radiotherapy + cetuximab**
E. **Palliative care**



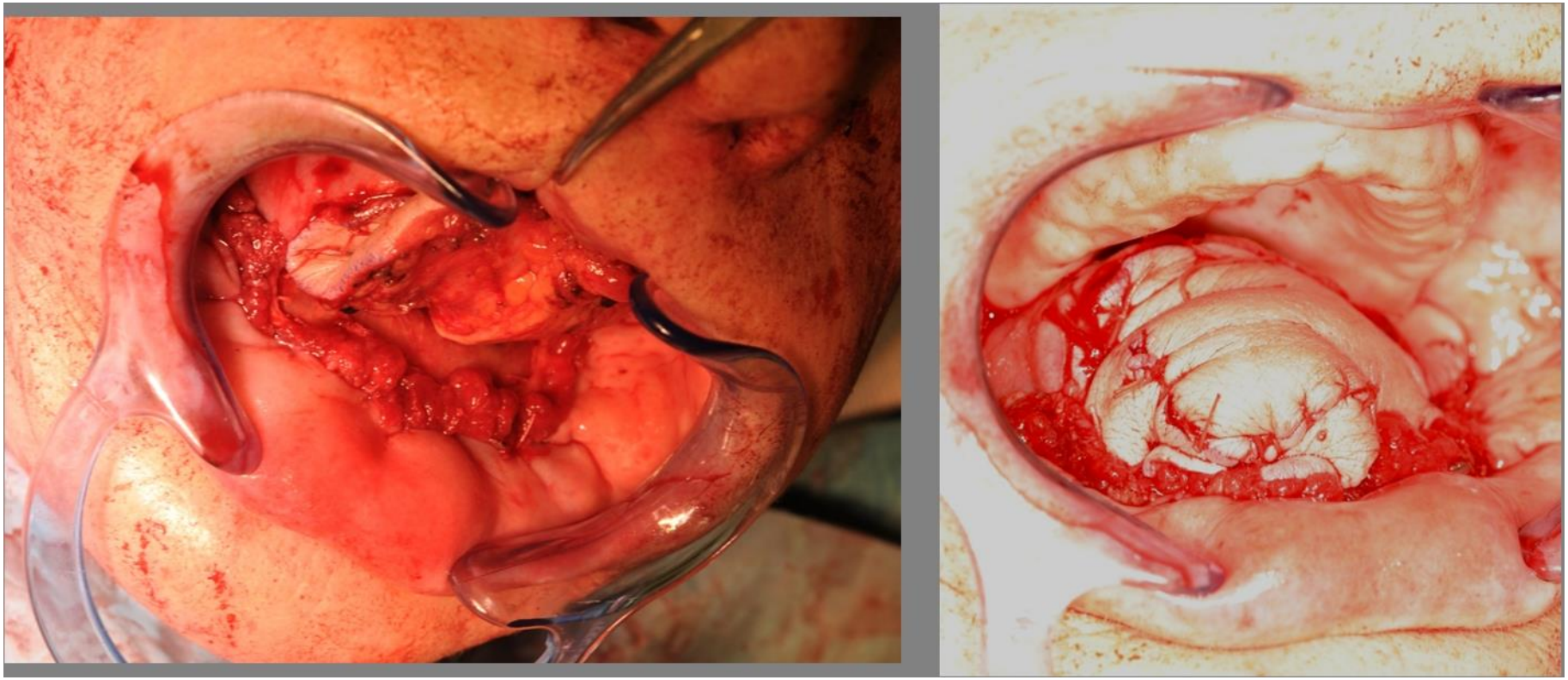
Oral cancer T4aN2c - surgery



Oral cancer T4aN2c - surgery



Oral cancer T4aN2c - reconstruction



Oral cancer T4aN2c – postoperative RT

Pathology:

Well differentiated squamous cell carcinoma

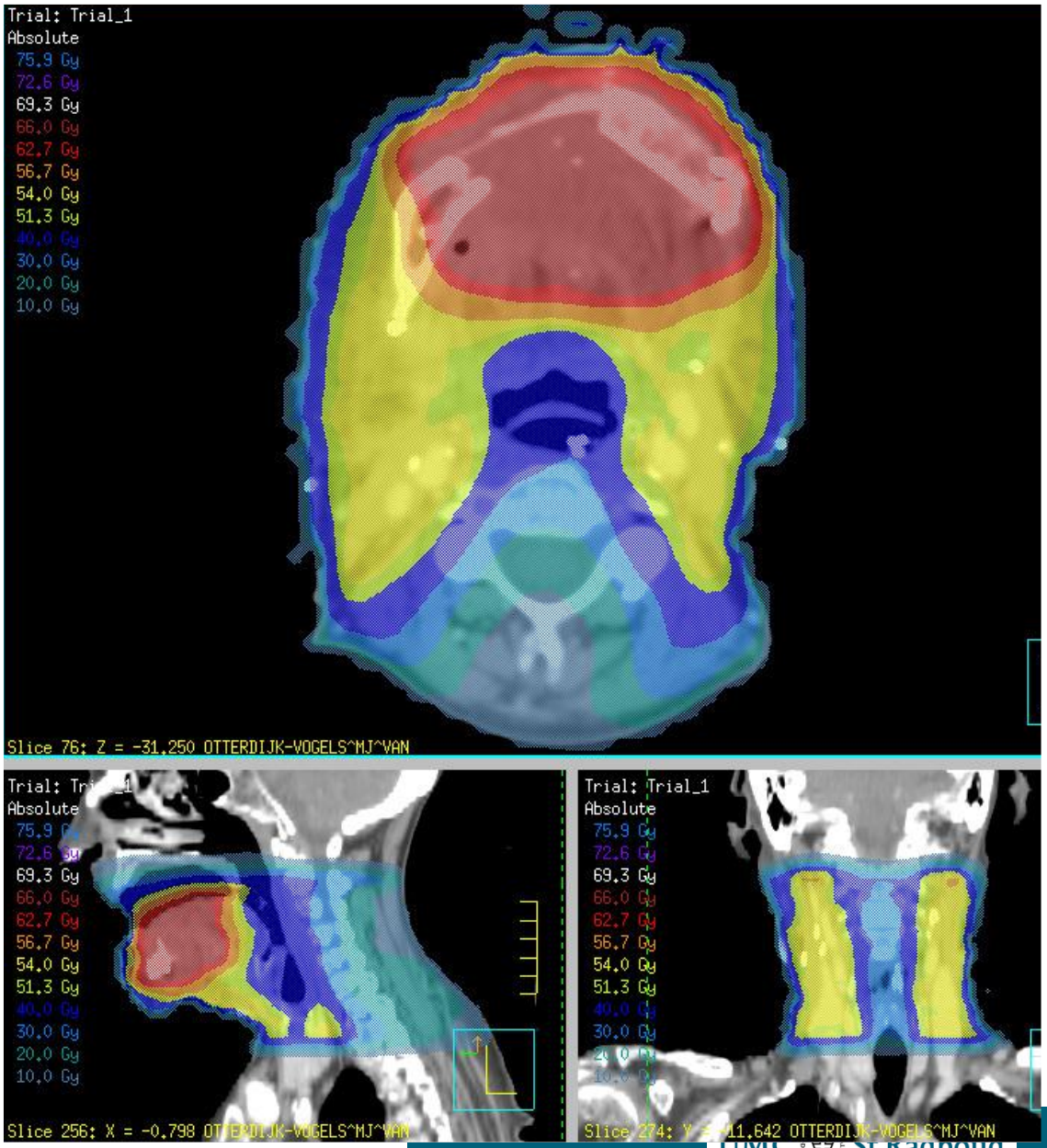
Invasion of mandibula

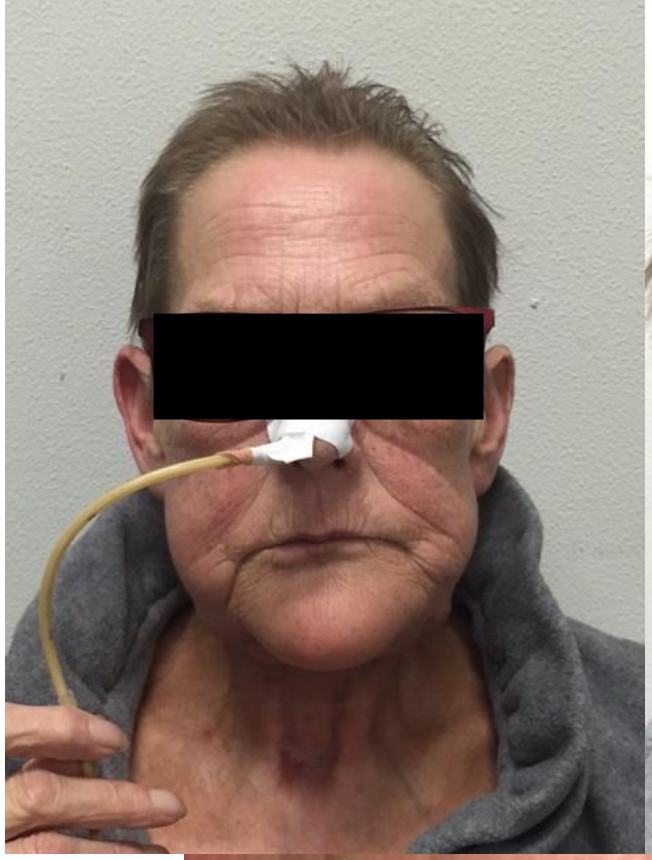
Closest margin 0,1 mm (ventral towards lip)

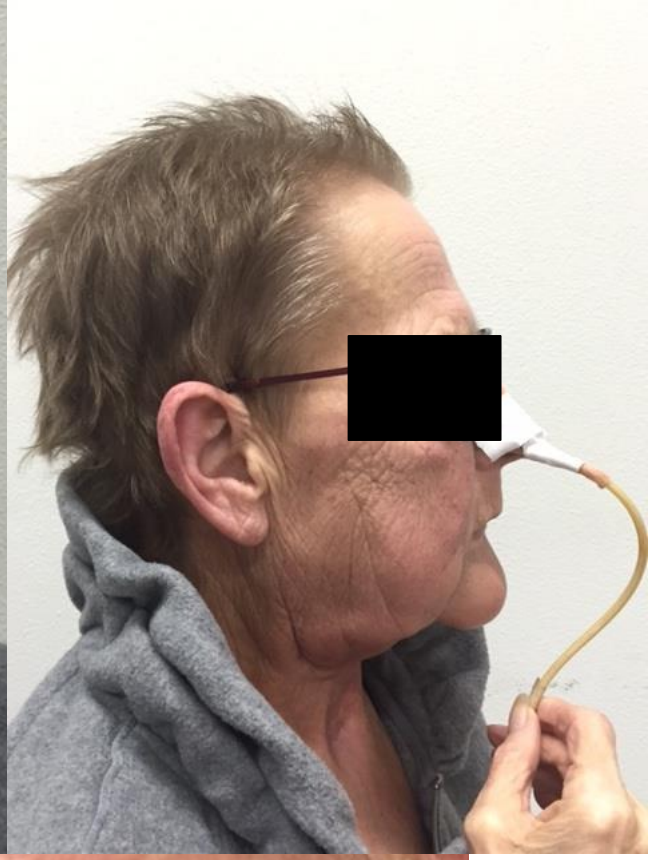
Dorsal margin 3 mm

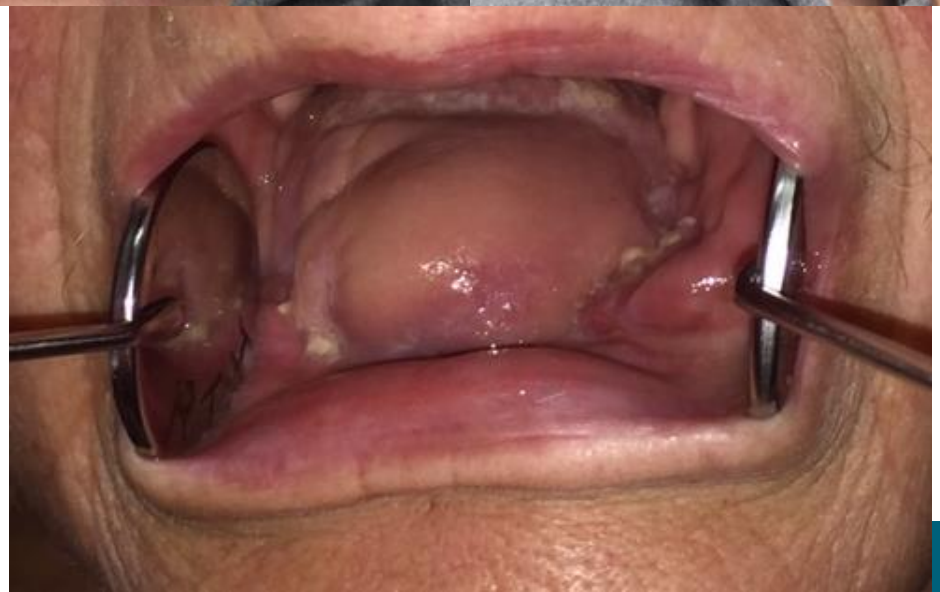
Other margins > 5mm

All lymph nodes negative

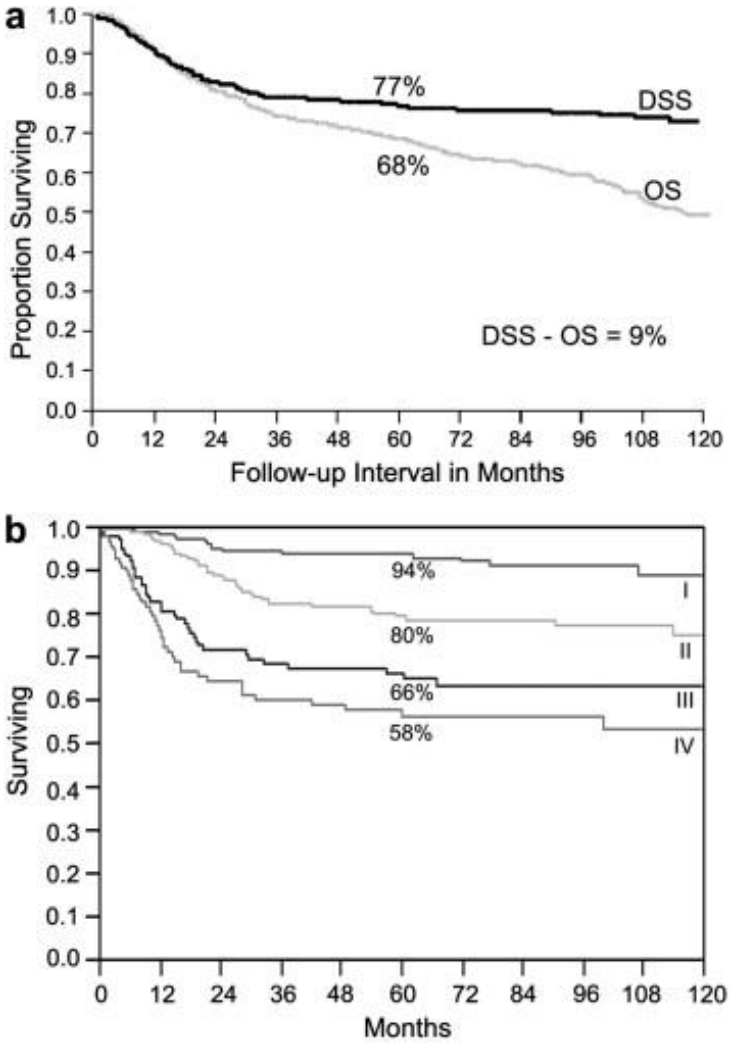








Surgery for oral cancer (N = 595)



Shah et al. Oral Oncol 2009

Treatment of early (T1-T2) oral cancer

- Comparable results with surgery and radiotherapy.
- Choice of treatment - relevant factors:
  - functional outcome
  - long term sequelae
  - competence and skills of H&N team
- Brachytherapy is an integral part of radiotherapy for oral cancer (expertise required!).
- Complication risk of brachytherapy increases with total dose and implanted volume.

Treatment of T3-T4 oral cancer

- Surgery with or without postoperative (chemo)radiation.
- If not resectable or patient inoperable: (chemo)radiation.

Indications for postoperative radiotherapy

- Positive or close resection margins
- Nodal metastases with extracapsular spread
- Multiple nodal (levels) metastases
- Bone- or cartilage invasion
- Invasion of soft tissues of the neck
- Vascular invasion
- Perineural spread
- Tumor volume
- Tumor spillage
- Histology

Postoperative radiotherapy for head and neck cancer: dose?

2-year actuarial control at primary site

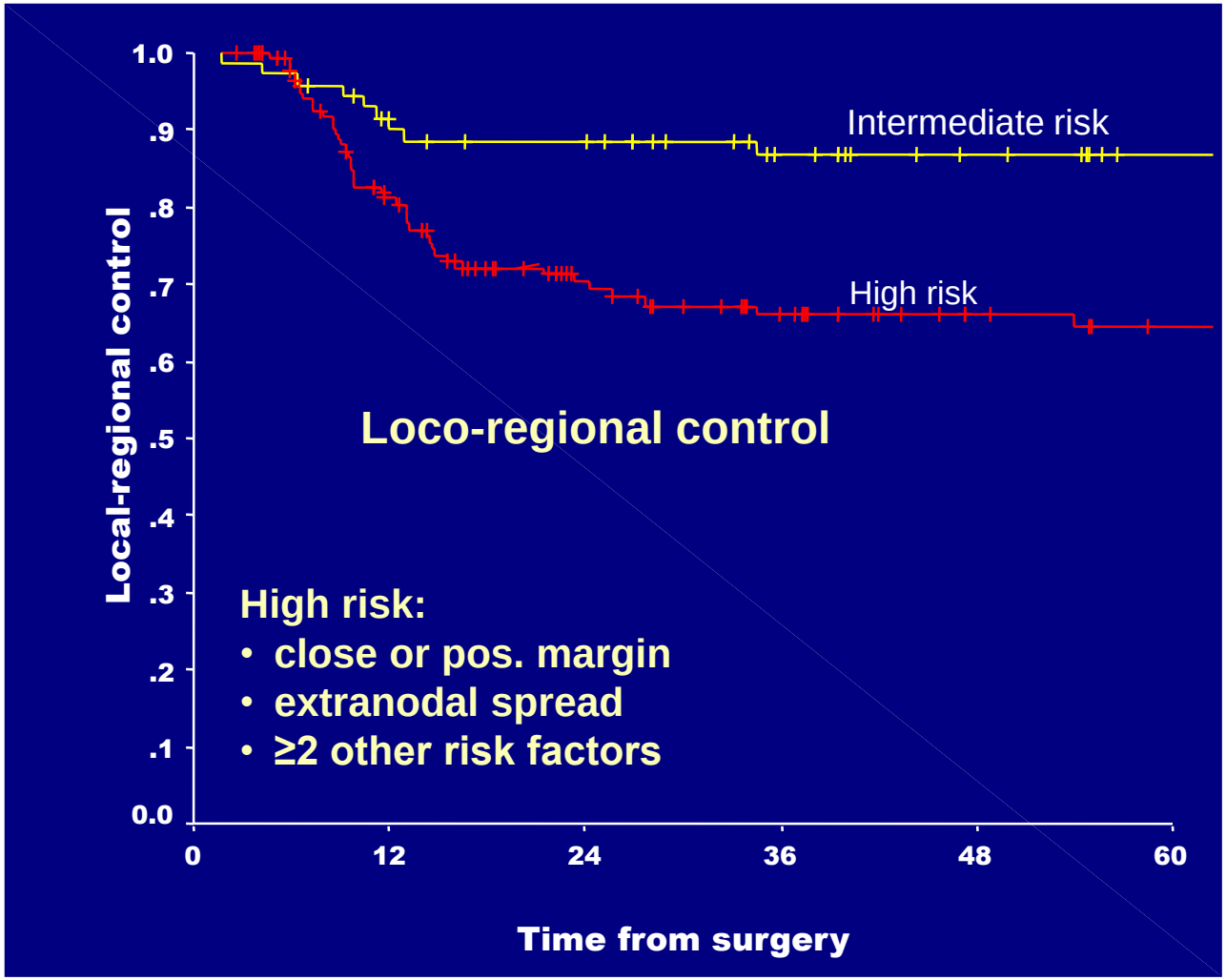
Risk	Dose (Gy)	Control rate (%)
Lower	54.0	63
	57.6	92
	63.0	89
Higher	63.0	89
	68.4	81

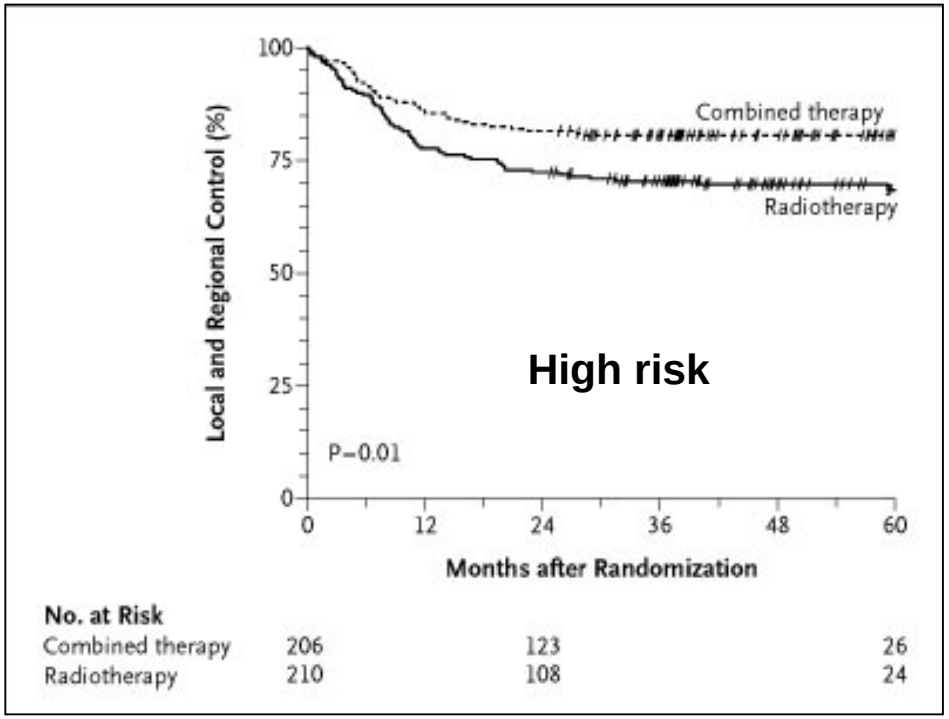
2-year actuarial control in the neck

Risk	Dose (Gy)	Control rate (%)
Lower	54.0	89
	57.6	86
	63.0	89
Higher	63.0	84
	68.4	77

Peters IJROBP, 1993

Risk grouping in postoperative radiotherapy for oral cancer (217 patients)

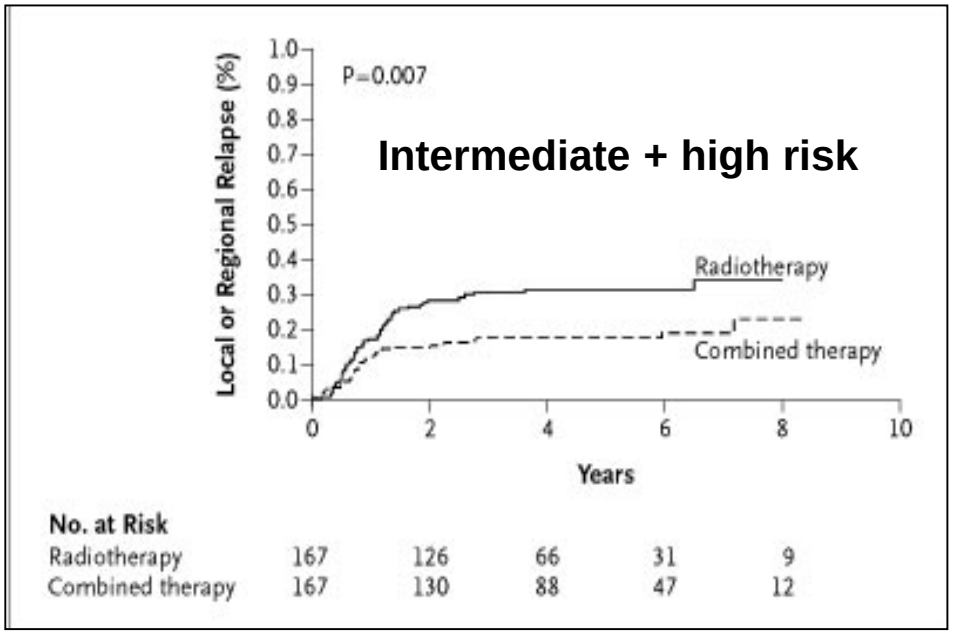




Cooper et al. (RTOG)
NEJM, 2004

↑ 10%

Concomitant radiotherapy + chemotherapy

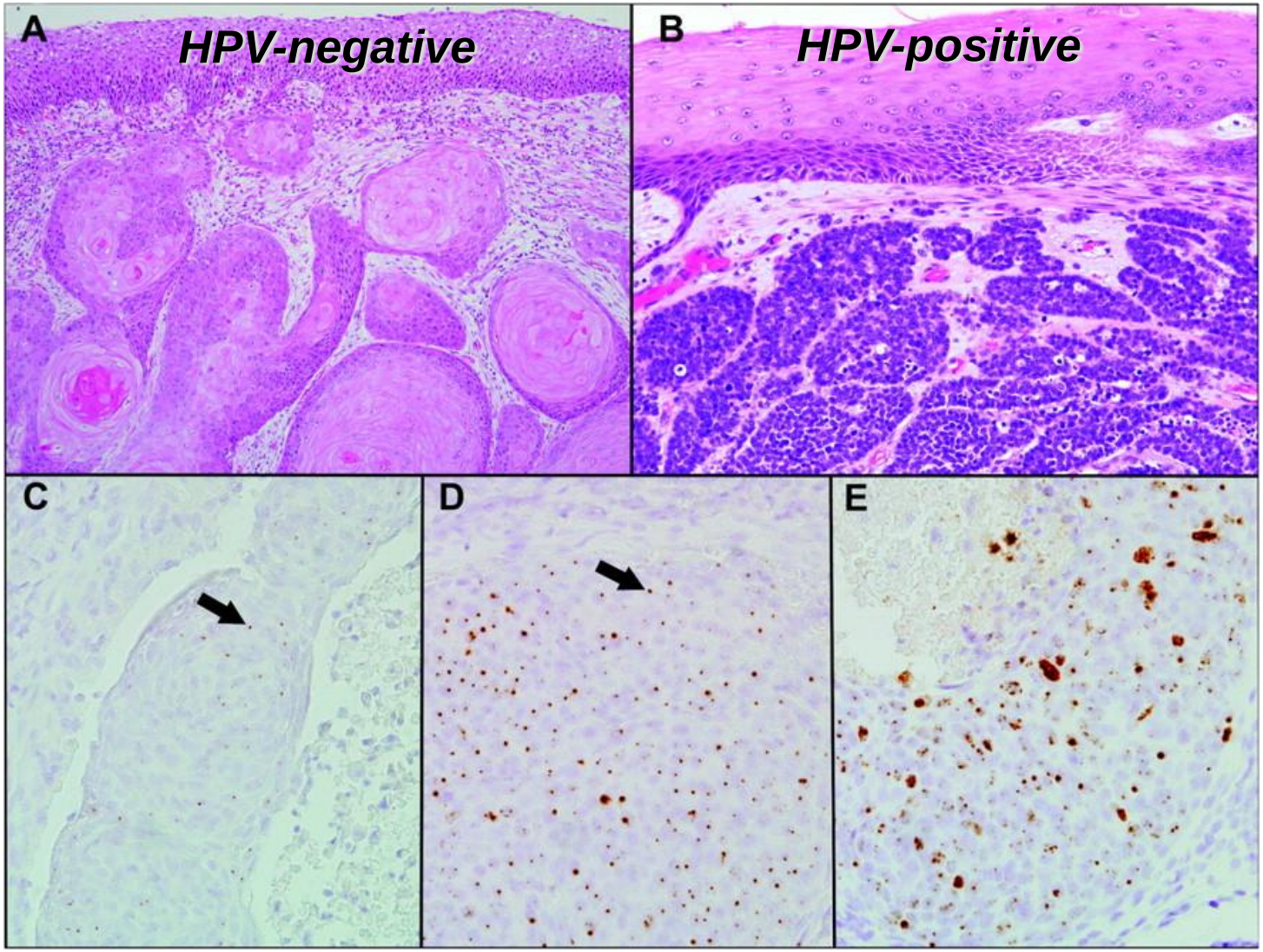


↓ 13%

Bernier et al. (EORTC)
NEJM, 2004

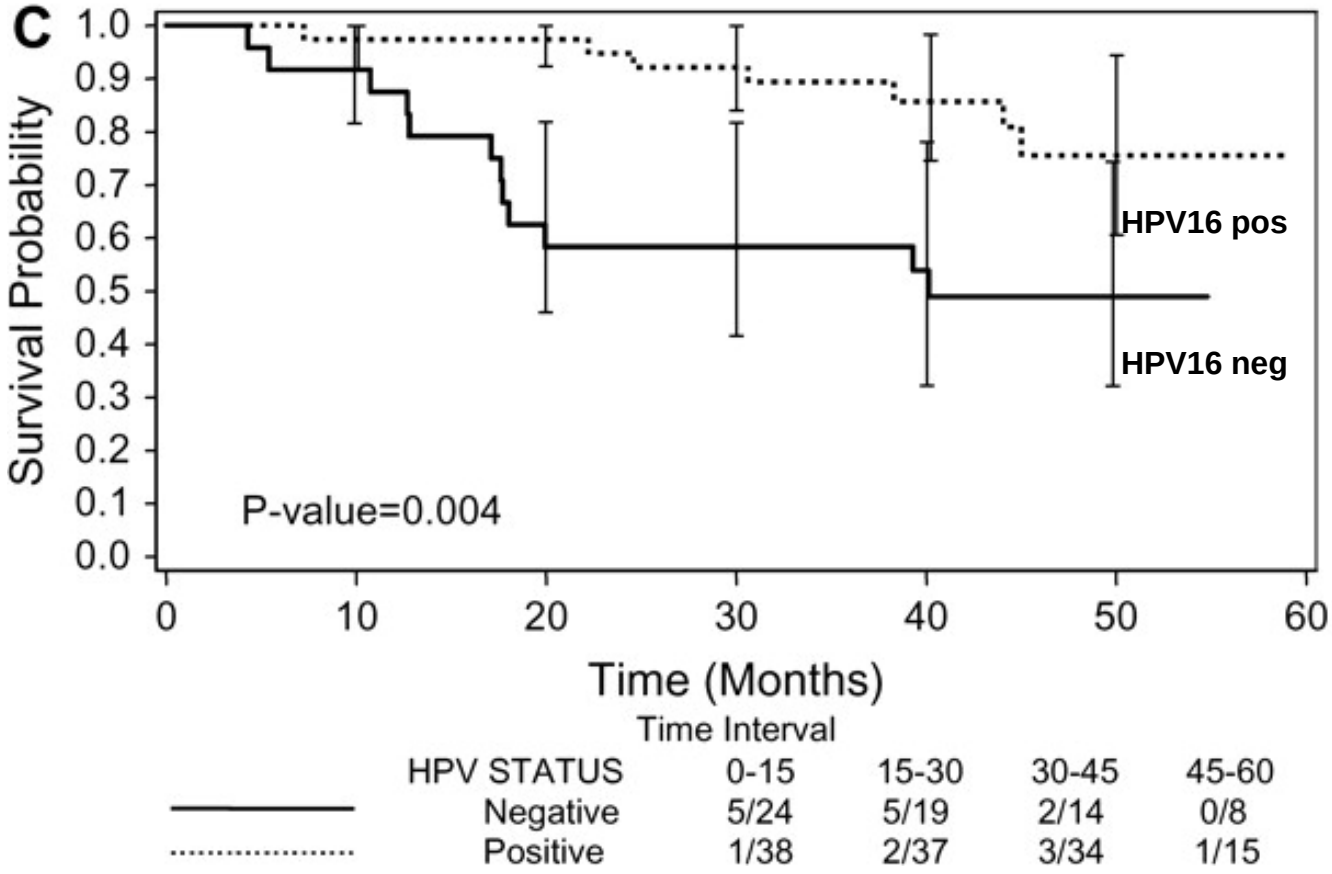
OROPHARYNGEAL CANCER

Histopathology (basaloid features) and ISH signal of HPV16 positivity



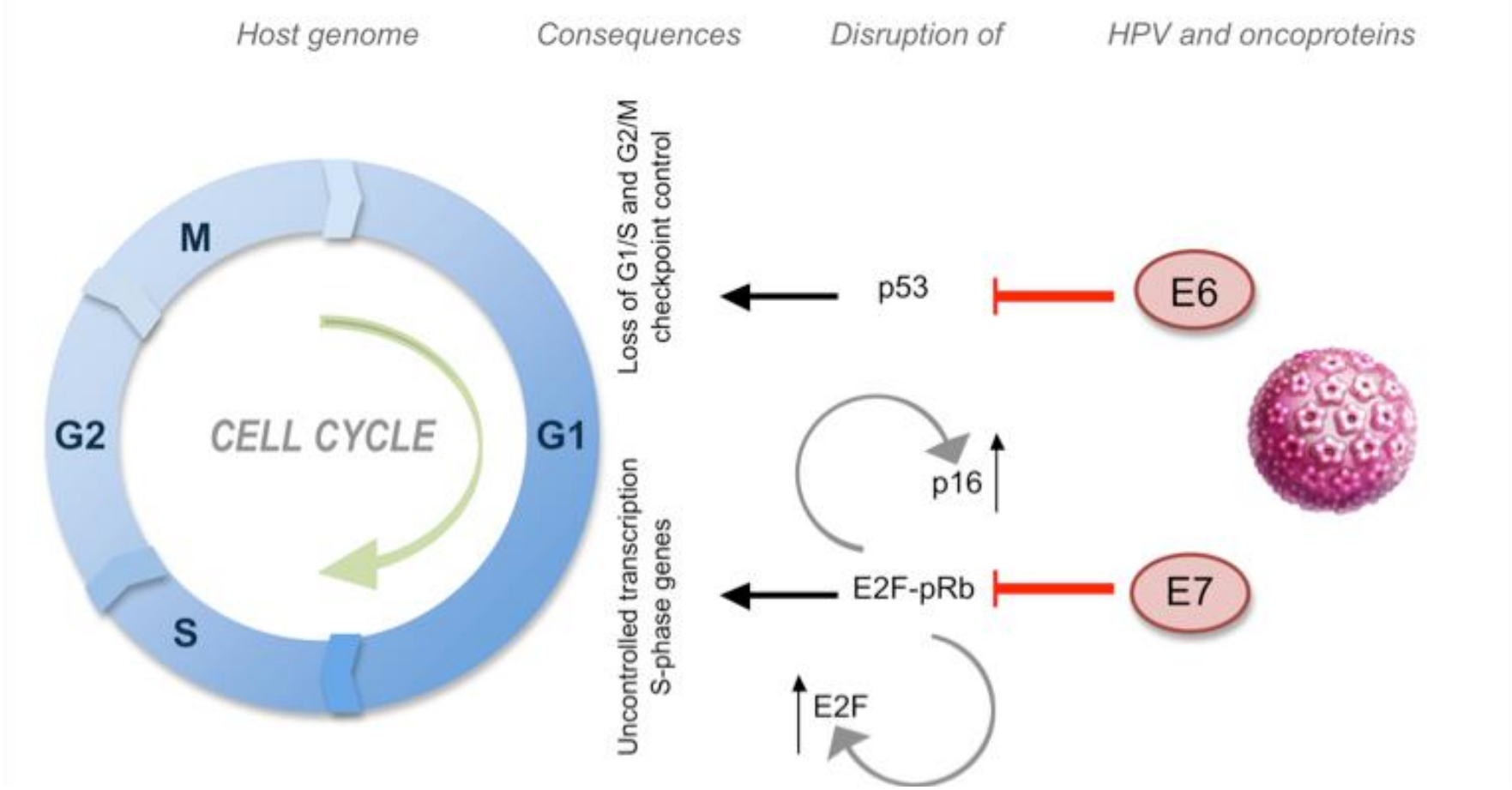
Fakhry et al. J Natl Cancer Inst 2008

Survival by HPV16 status (oropharynxca)

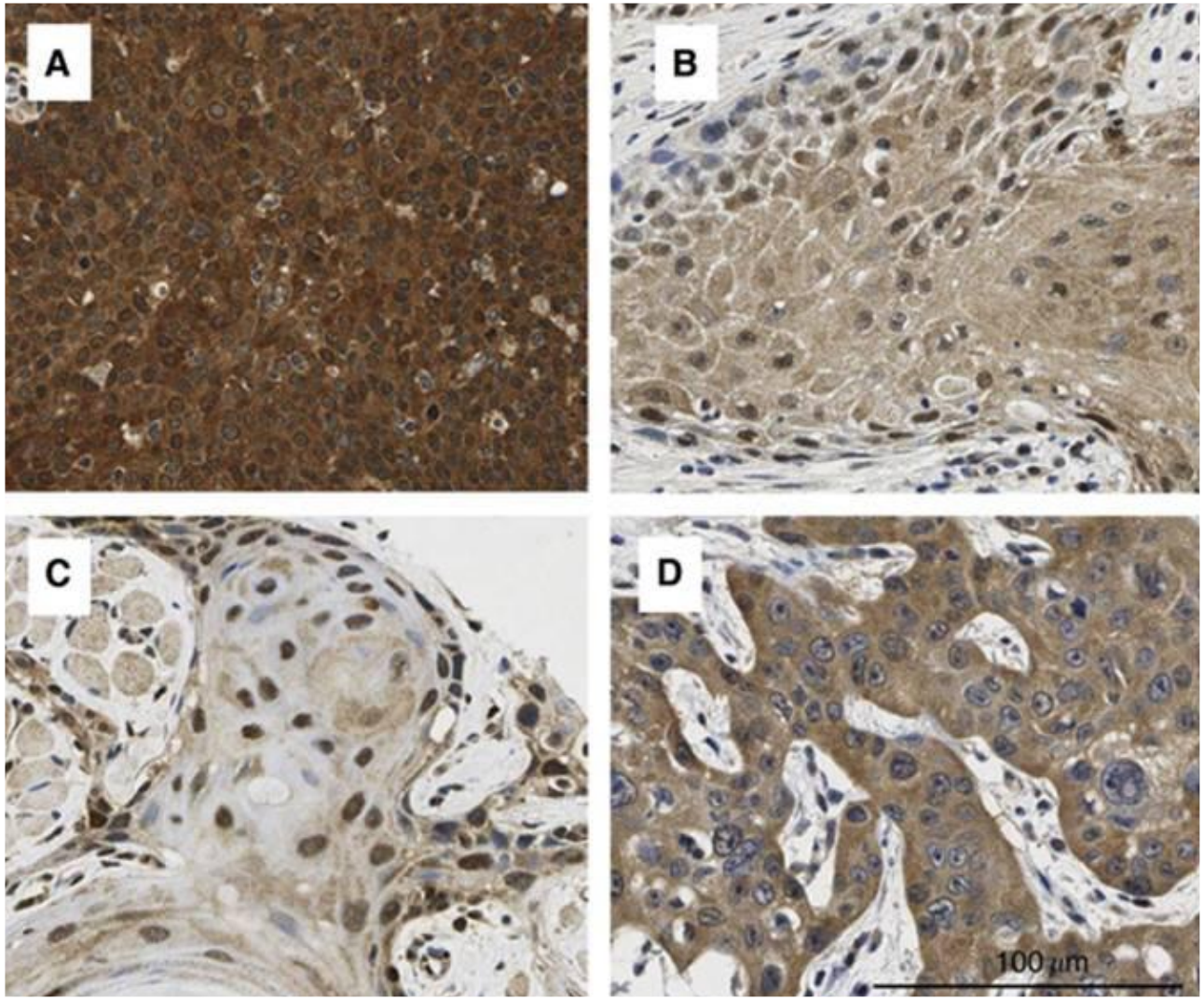


Fakhry et al. J Natl Cancer Inst 2008

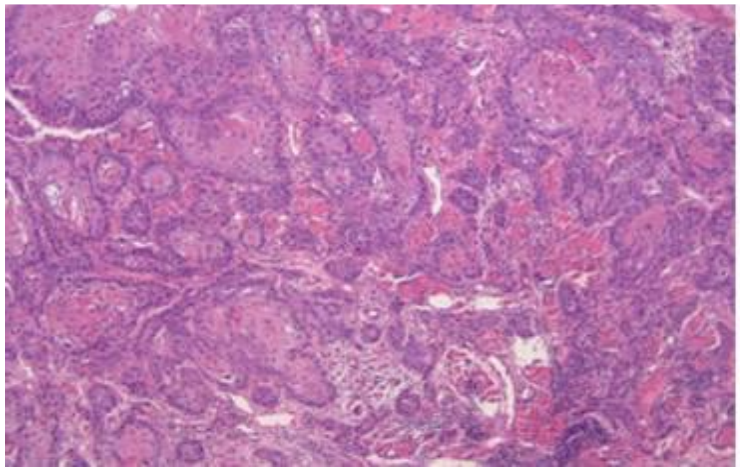
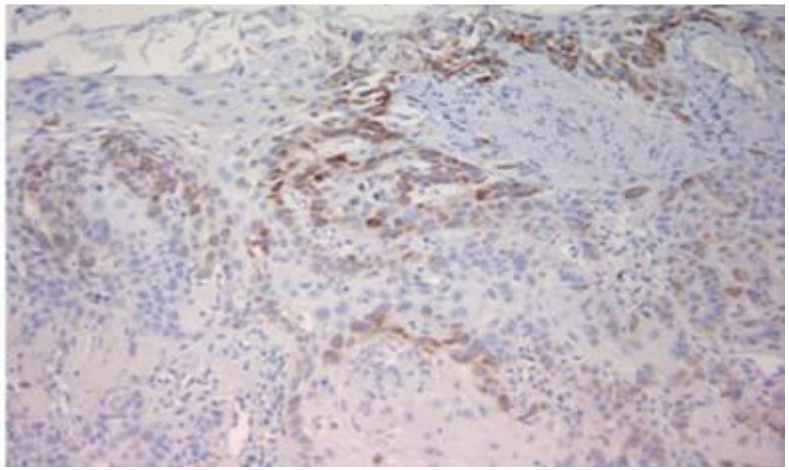
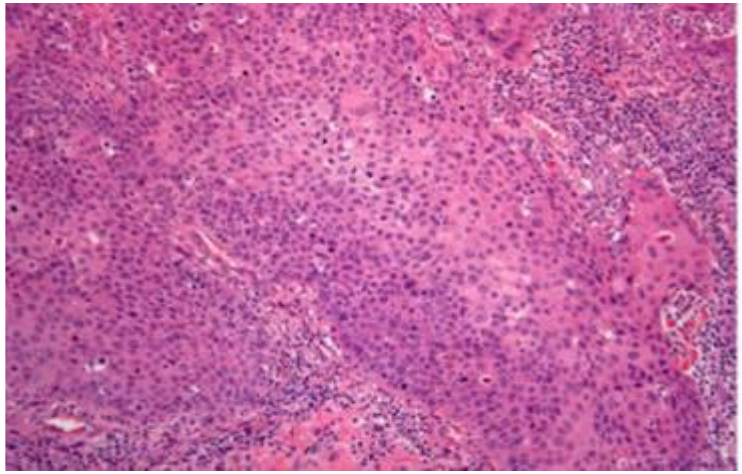
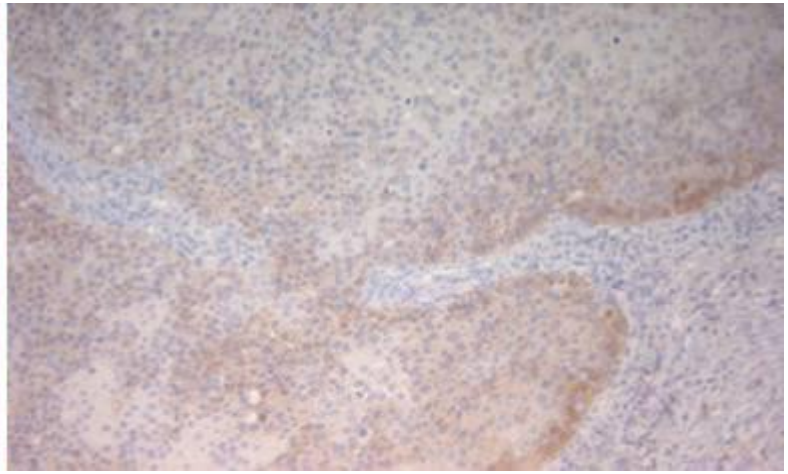
HPV E6 and E7 oncoproteins disrupt p53 and pRb pathways with upregulation of p16



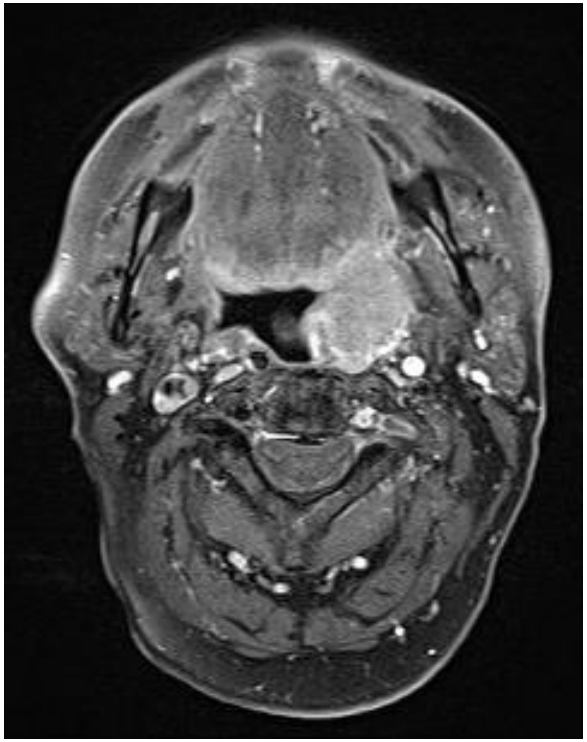
P16 expression in oropharynx carcinoma

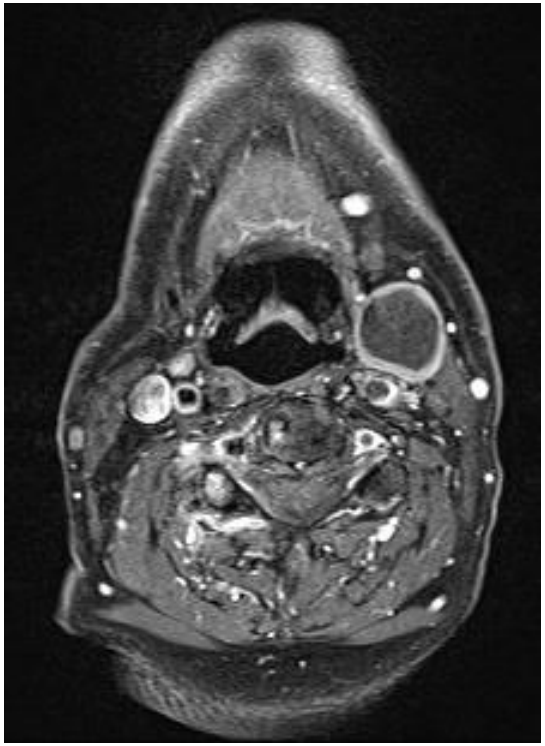


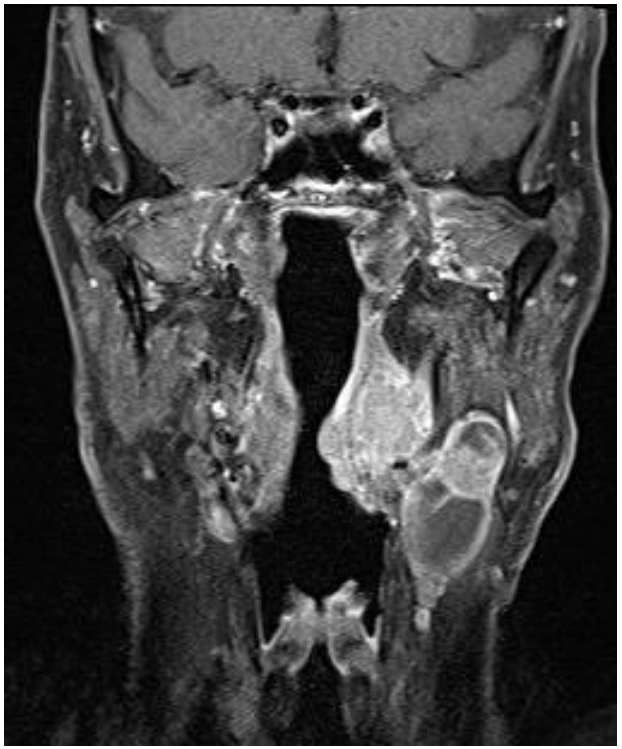
P16 expression in oropharynx carcinoma

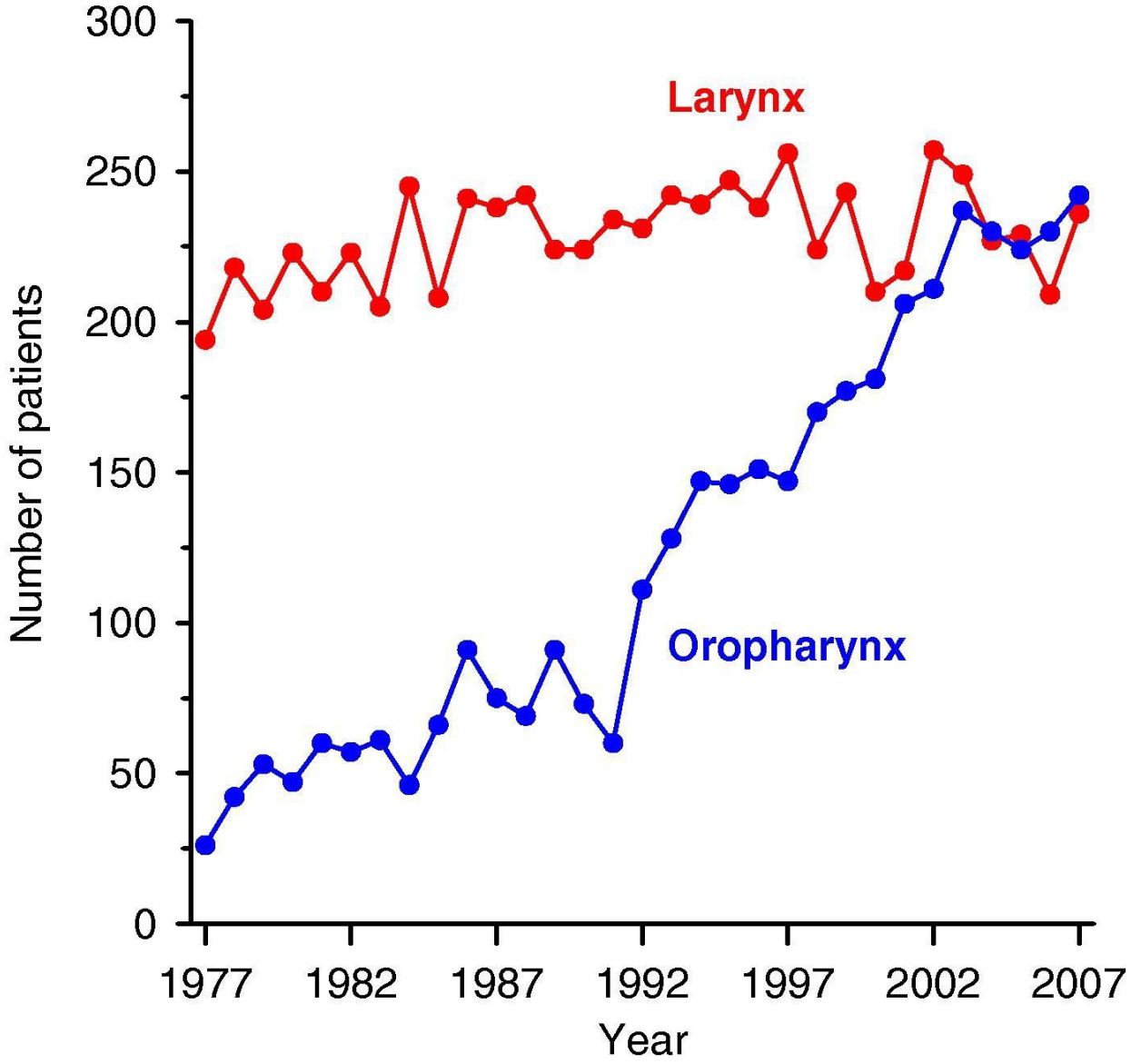
HPV-associated oropharynx carcinoma





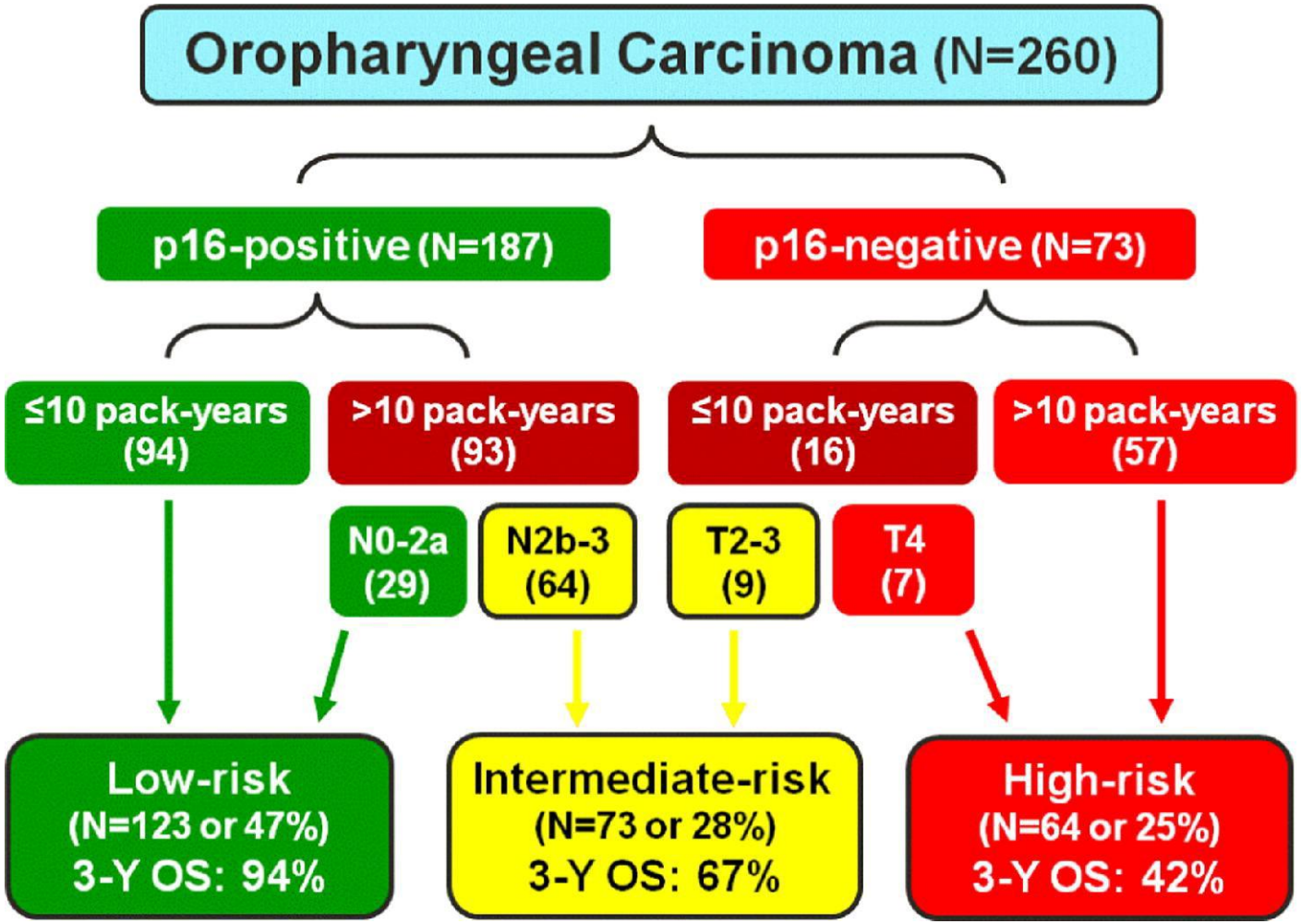


Incidence of laryngeal and oropharyngeal cancers in Denmark



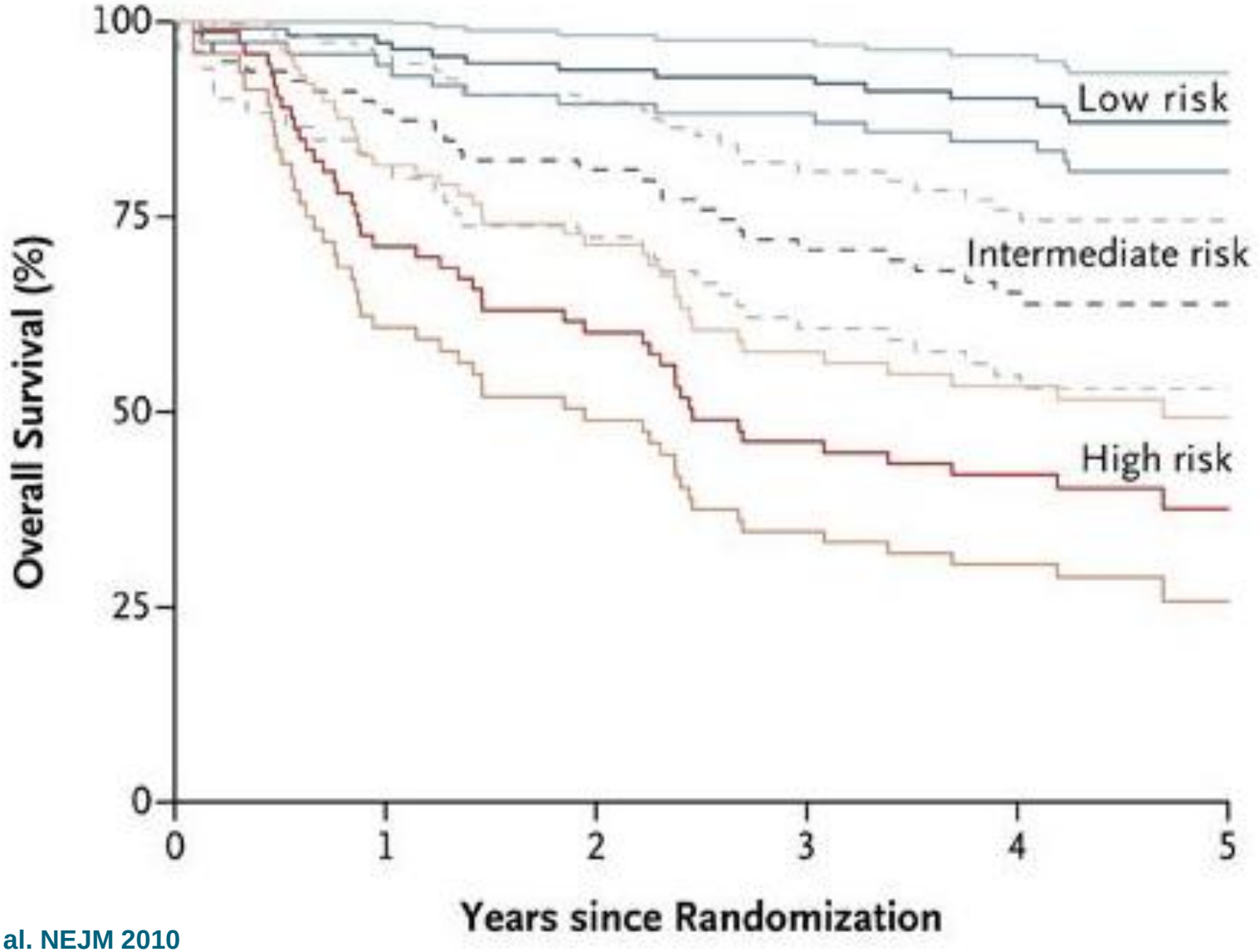
Lassen et al. R&O 2010

HPV16 status, smoking and TN-stage: risk factors for death of oropharynxca (RTOG 0129)



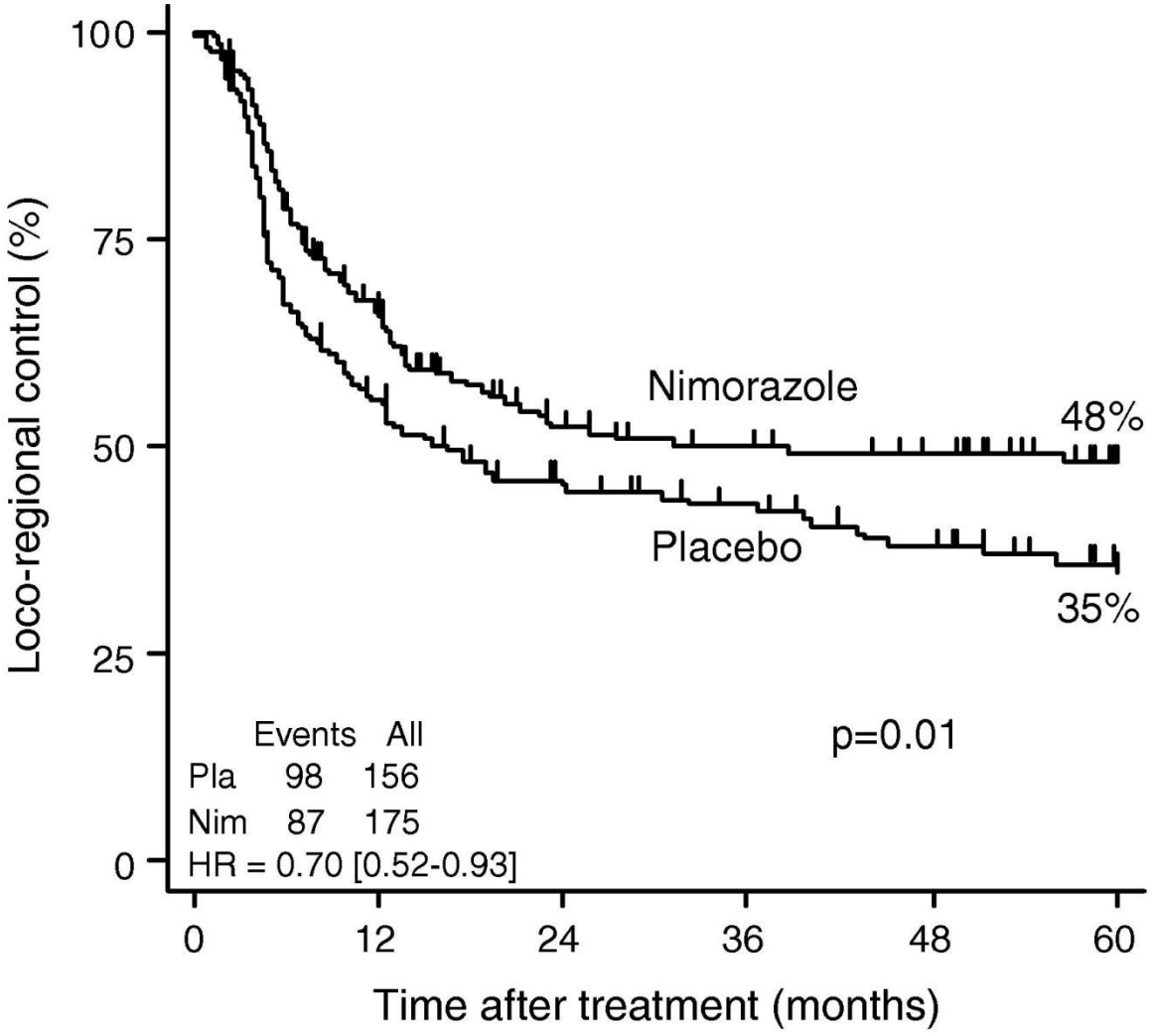
Ang et al. NEJM 2010

HPV16 status, smoking and TN-stage: risk factors for death of oropharynxca (RTOG 0129)



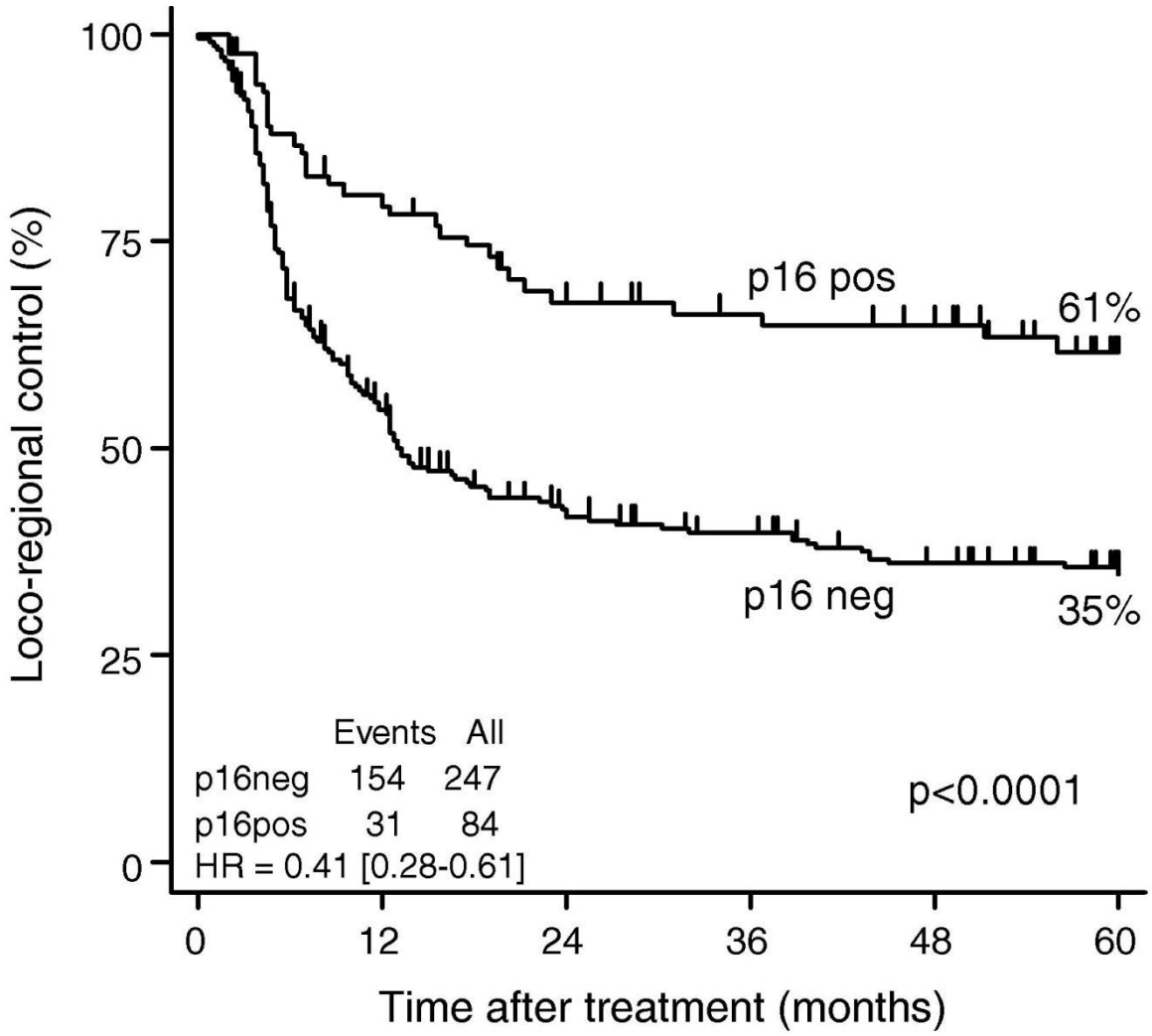
Ang et al. NEJM 2010

DAHANCA-5 study



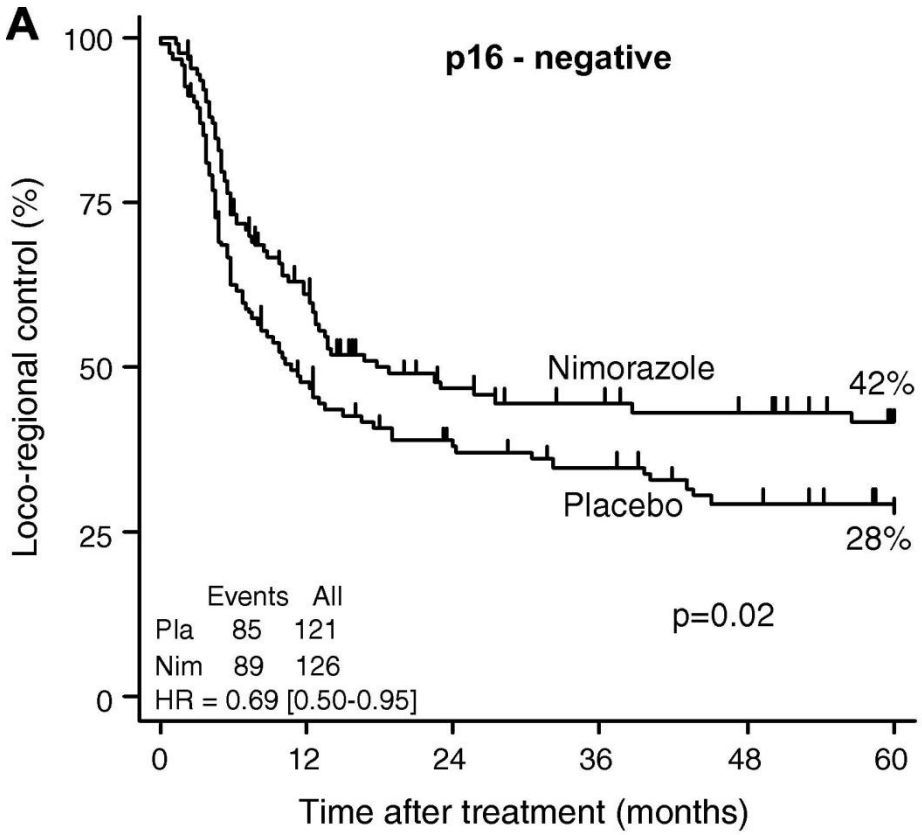
Lassen et al. R&O 2010

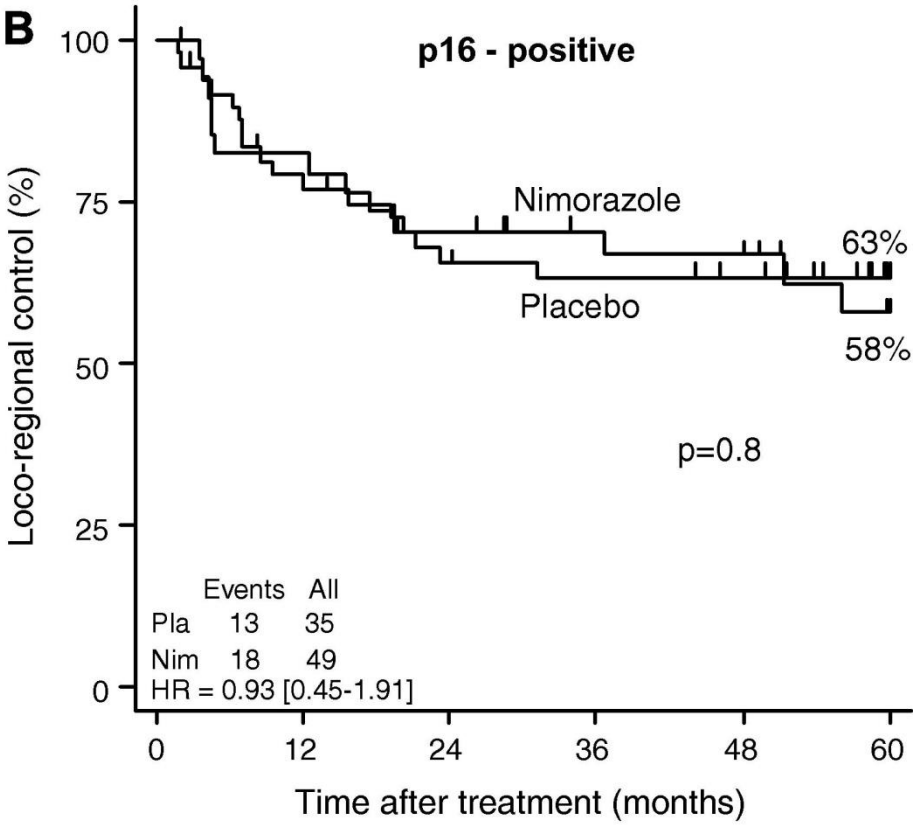
DAHANCA-5 study, locoregional control by p16 status



Lassen et al. R&O 2010

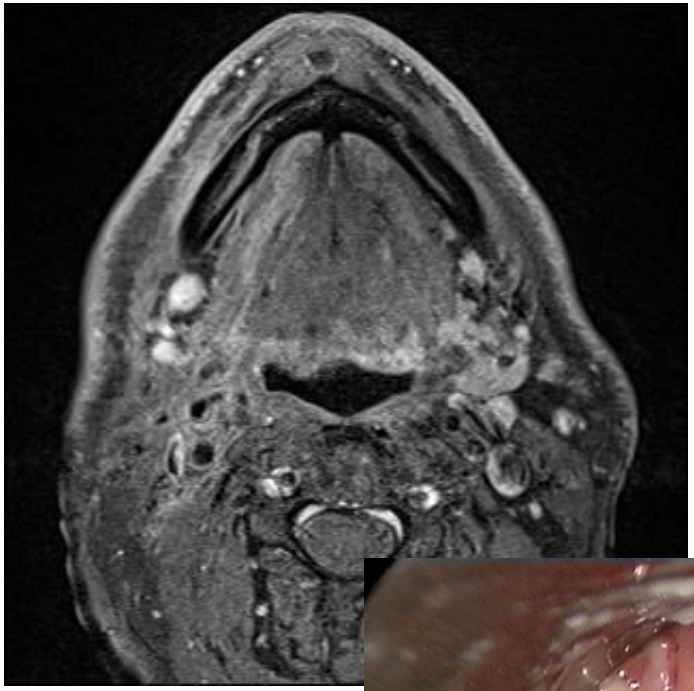
DAHANCA-5 study, locoregional control by p16 status and effect of hypoxic sensitization

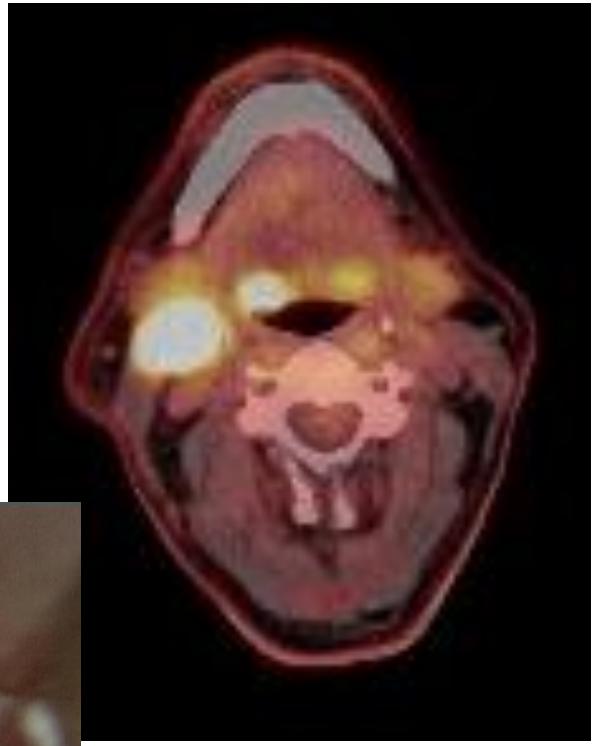


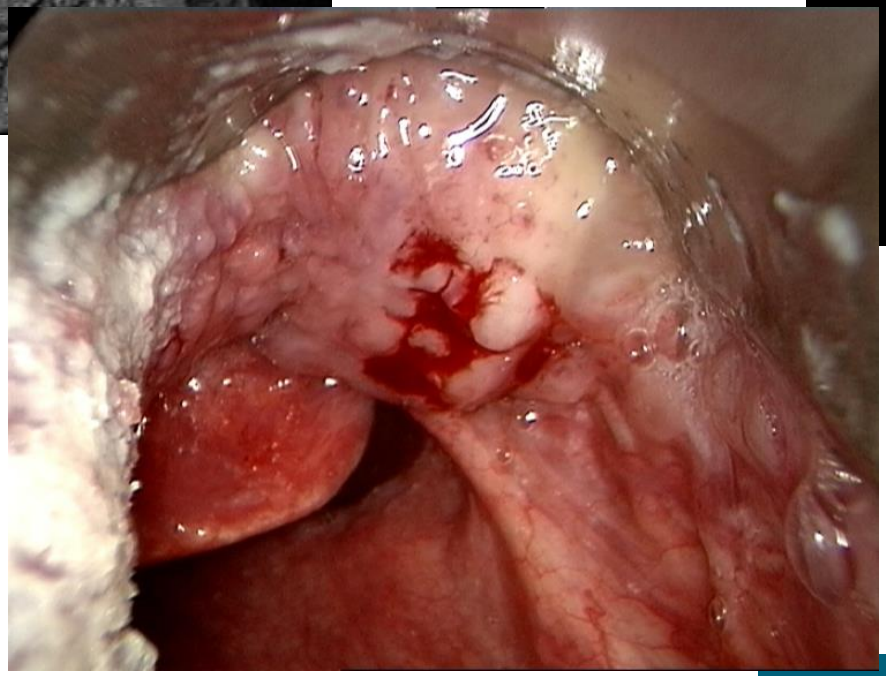


Lassen et al. R&O 2010

Base of tongue cancer T1

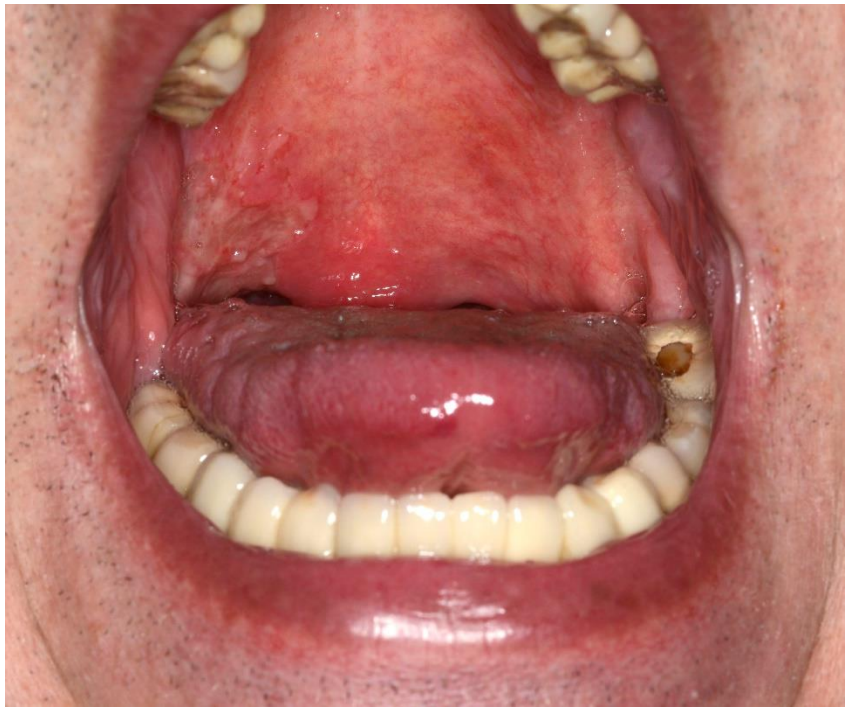


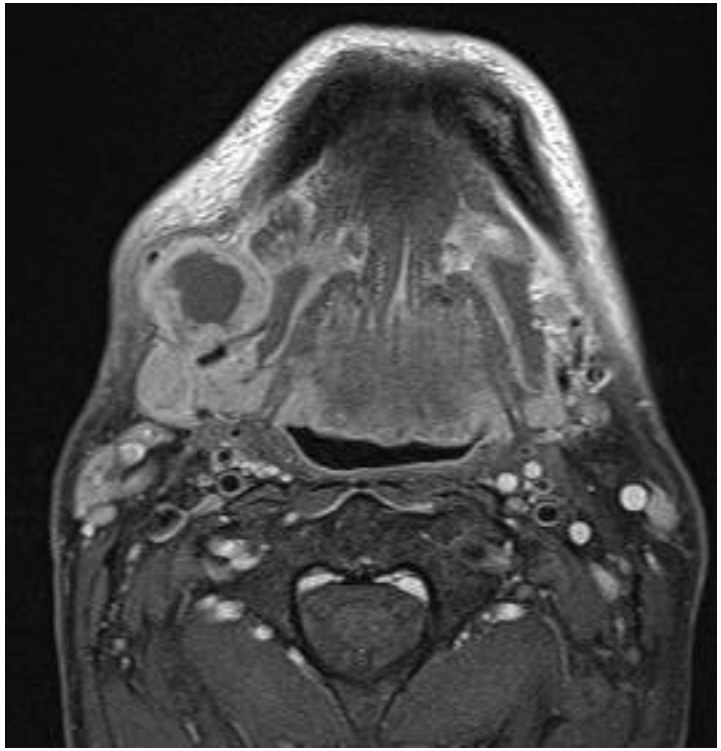




T1: ≤ 2 cm

Carcinoma soft palate T2





T2: 2 - 4 cm

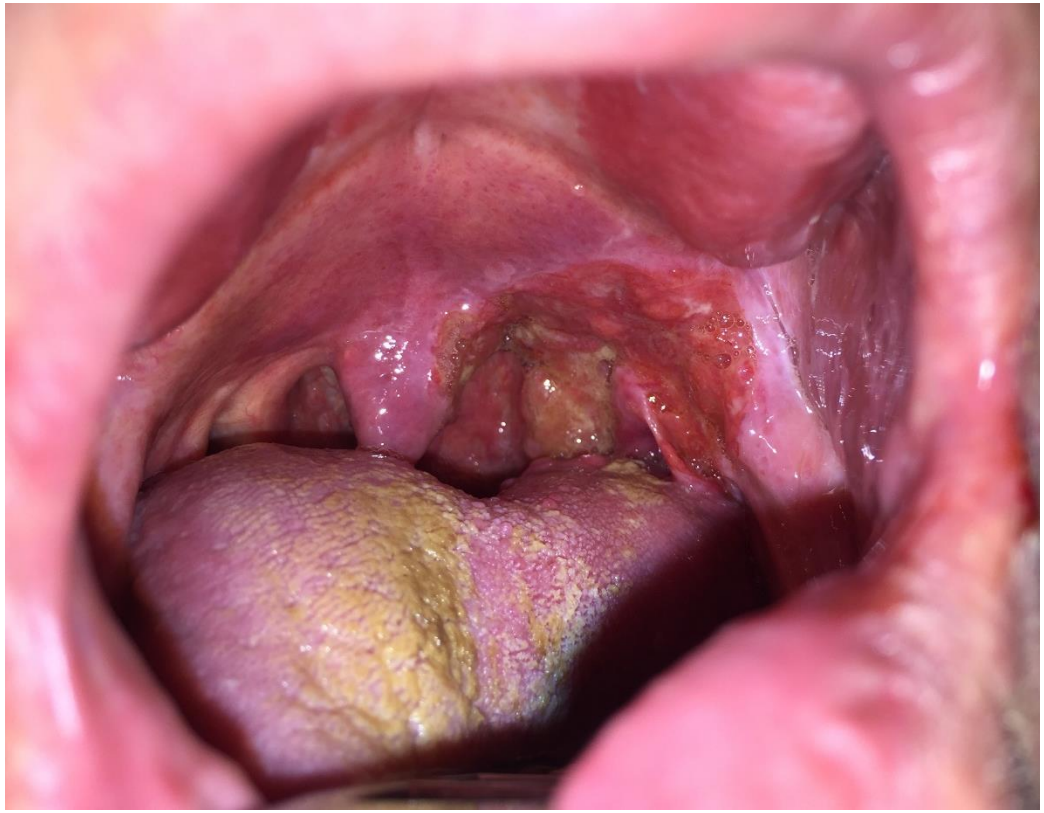
Carcinoma soft palate (case)

Man, 65 yrs with pain left side throat and otalgia since 6 weeks.
Normal intake, no weight loss.
No significant comorbidity.
Smoking 70 PY, alcohol 25-30 U/wk.

Physical exam reveals tumor soft palate (L) involving uvula, ant/post faucial pillar, retromolar trigone, tonsillar area.
Base of tongue and posterior pharyngeal wall uninvolved.

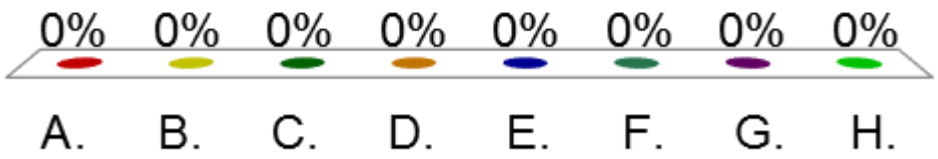
Palpable lymph node 2 cm level II left.

Biopsy shows moderately differentiated squamous cell carcinoma.



Carcinoma soft palate (case)
-
What imaging do you order for assessment of loco-regional extensions?

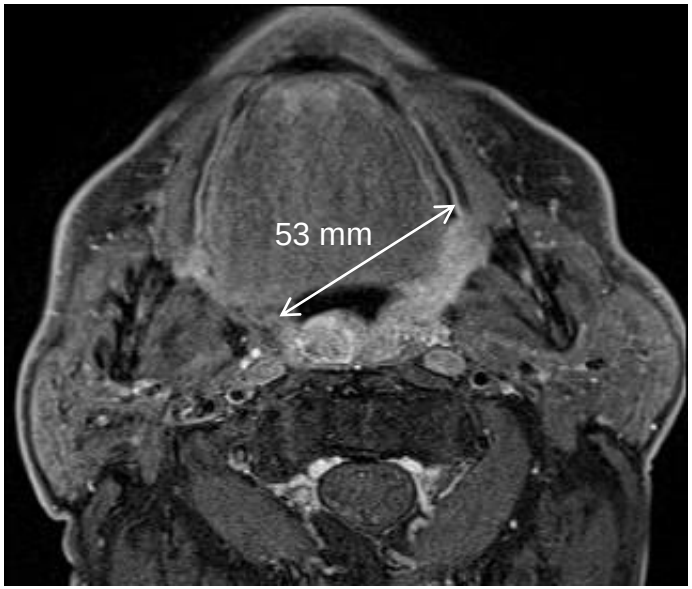
A. CT
B. MRI
C. PET
D. Ultrasound neck (US)
E. CT + MRI
F. MRI + PET
G. MRI + US
H. MRI + PET + US



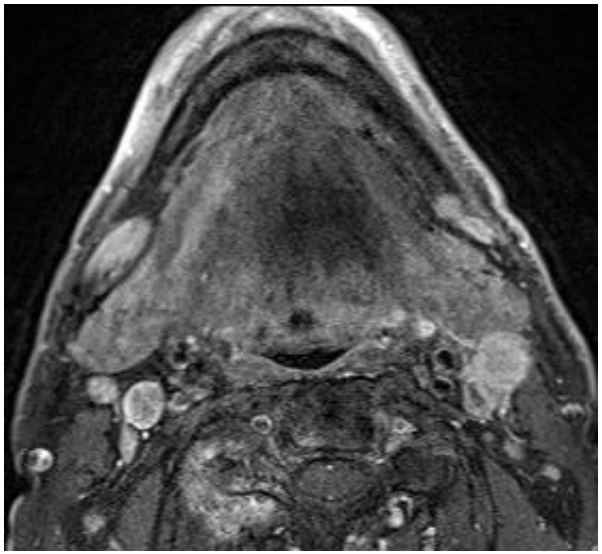
Carcinoma soft palate (case)

MRI:

tumor soft palate (L) involving uvula, ant faucial pillar, retromolar trigone, tonsillar area.

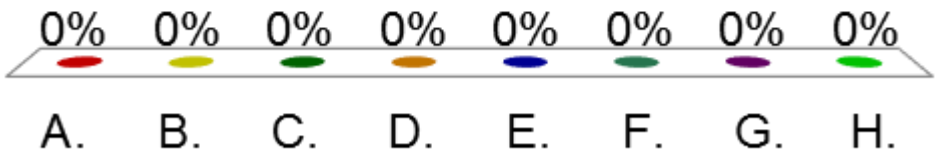


Neck: bilateral retropharyngeal lymph nodes; enlarged lymph nodes level Ib and II (L+R).



Carcinoma soft palate (case)
-
How do you stage this tumor?

A. T2N1
B. T2N2b
C. T2N2c
D. T3N1
E. T3N2b
F. T3N2c
G. T4N2b
H. T4N2c



Carcinoma soft palate (case)

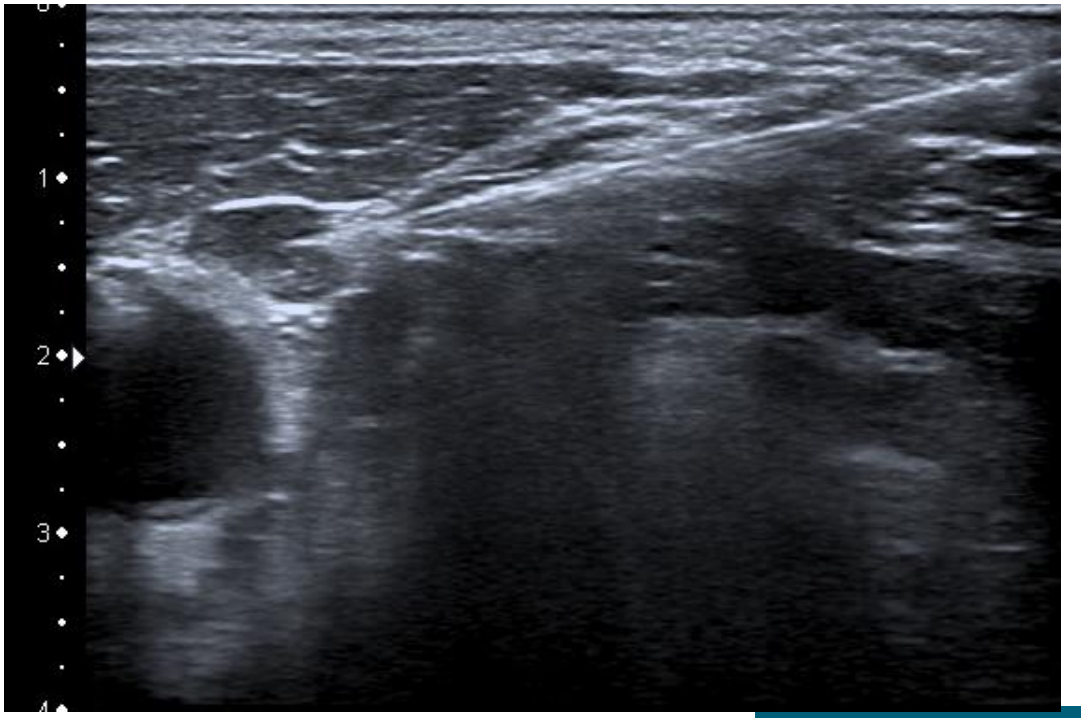
US + cytology:

level Ib (R): lymphoid cells, reactive.

level II (R): lymphoid cells, reactive.

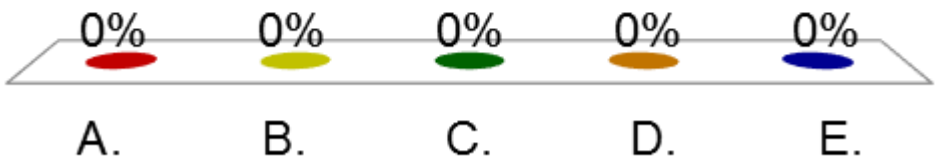
level Ib (L): few cells, not malignant.

Level II (L): squamous cell carcinoma.



Carcinoma soft palate (case)
-
What imaging do you order for assessment of distant metastases?

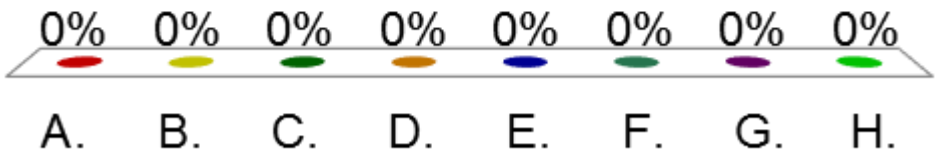
A. Chest X-ray
B. CT chest
C. CT chest + abdomen
D. PET-scan
E. CT chest/abdomen + PET-scan



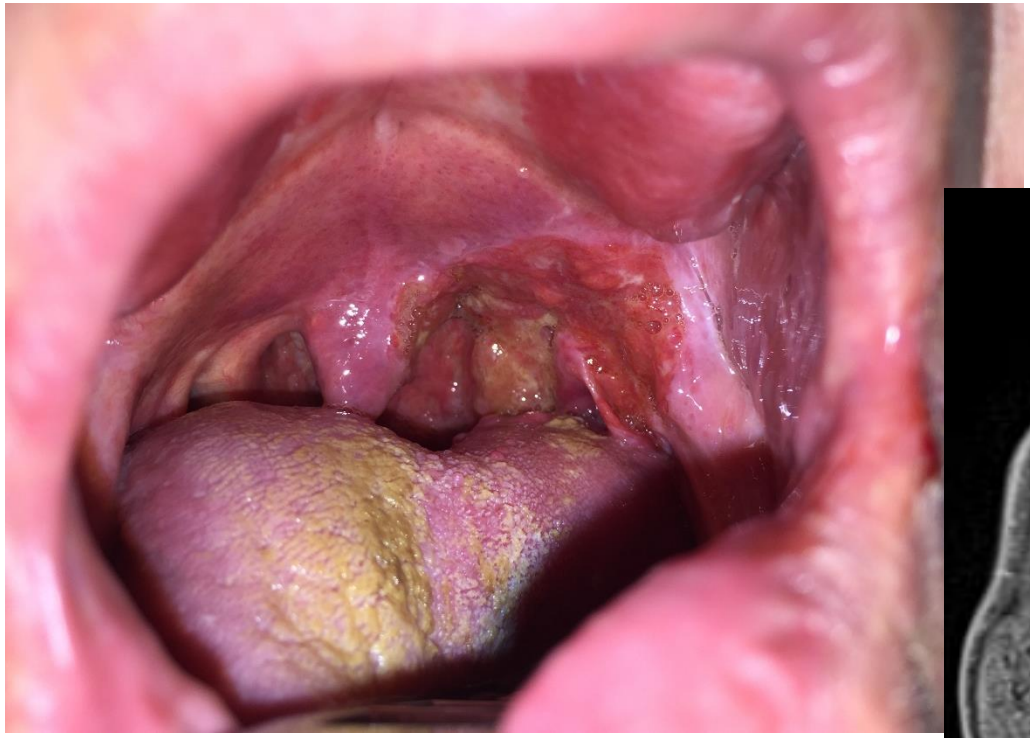
Carcinoma soft palate (case)
-
Chest X-ray negative

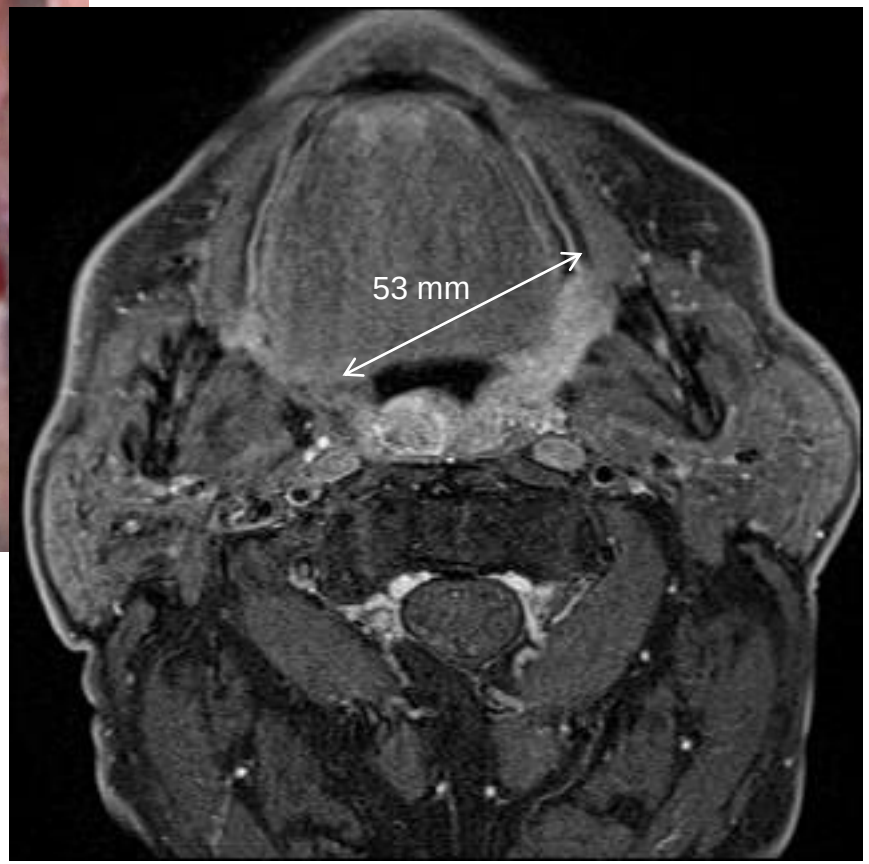
How do you stage this tumor?

A. T2N1M0
B. T2N2bM0
C. T2N2cM0
D. T3N1M0
E. T3N2bM0
F. T3N2cM0
G. T4N2bM0
H. T4N2cM0



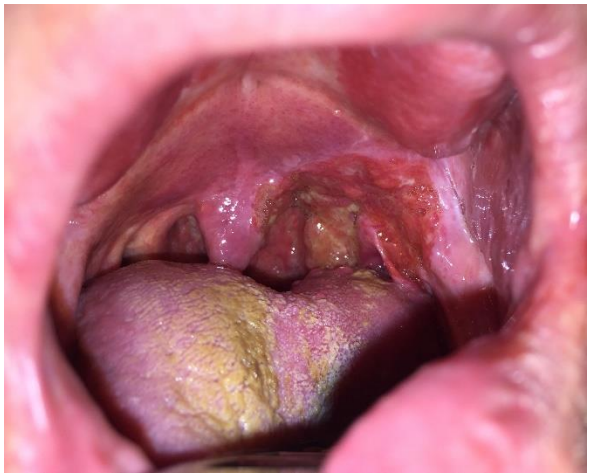
Carcinoma soft palate: T3N2cM0

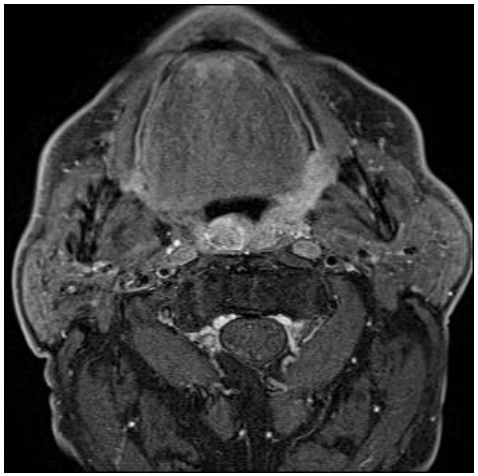




T3: > 4 cm
or extension to lingual surface epiglottis

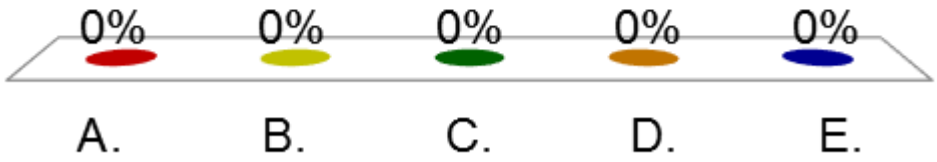
Carcinoma soft palate: T3N2cM0





What treatment do you recommend?

A. Surgery + or – postop radiotherapy
B. Radiotherapy
C. Radiotherapy + cetuximab
D. Chemoradiation
E. Chemoradiation + cetuximab



Patient consented to be randomized in EORTC 1219:

Accelerated radiotherapy + cisplatin

with or without nimorazole

Primary tumor + metastatic nodes: 70 Gy in 35 fr, 6x/wk

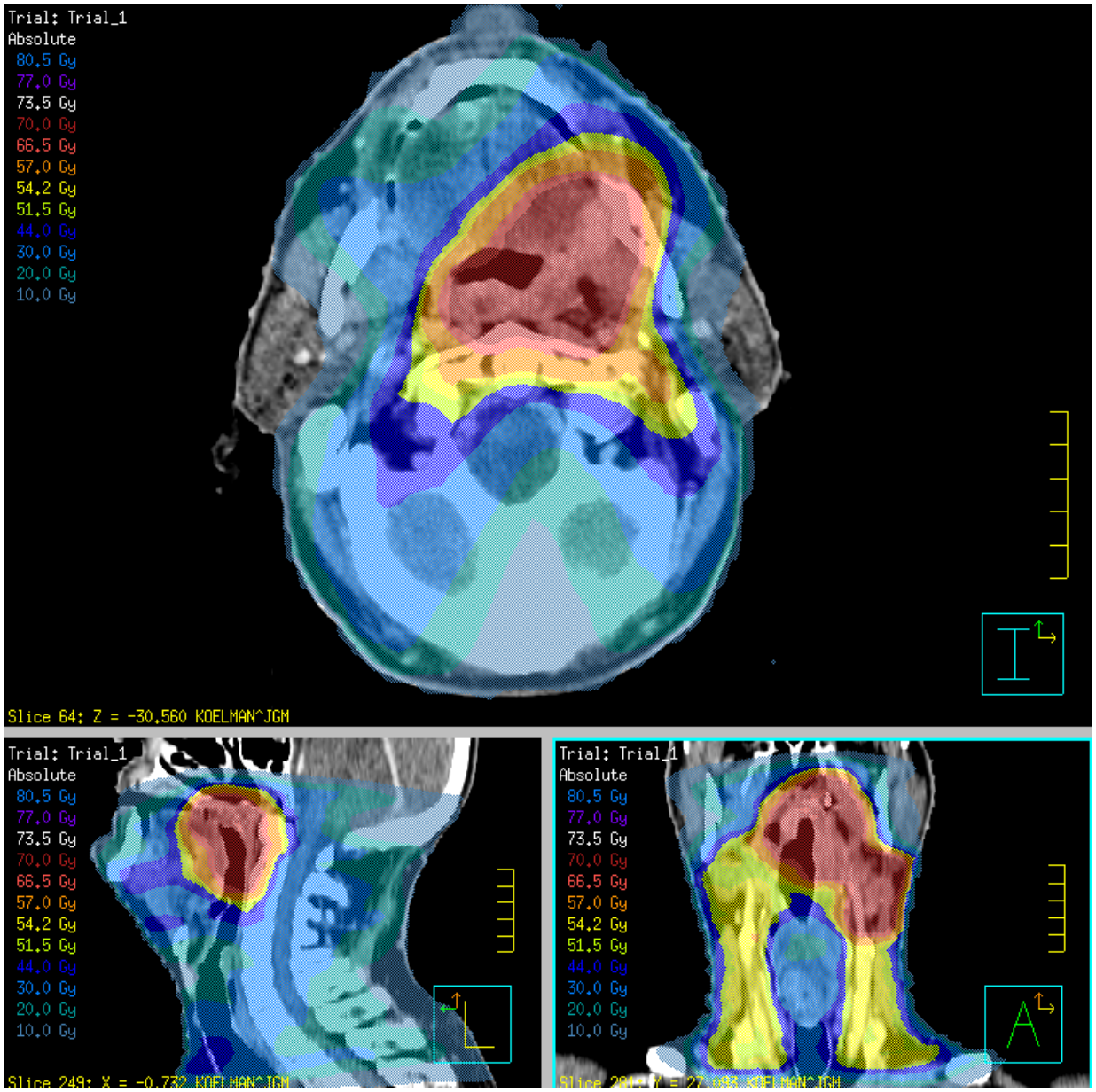
Neck (L), levels Ib-II-III-IV-V, retrostyloid and RP: 54.25 Gy

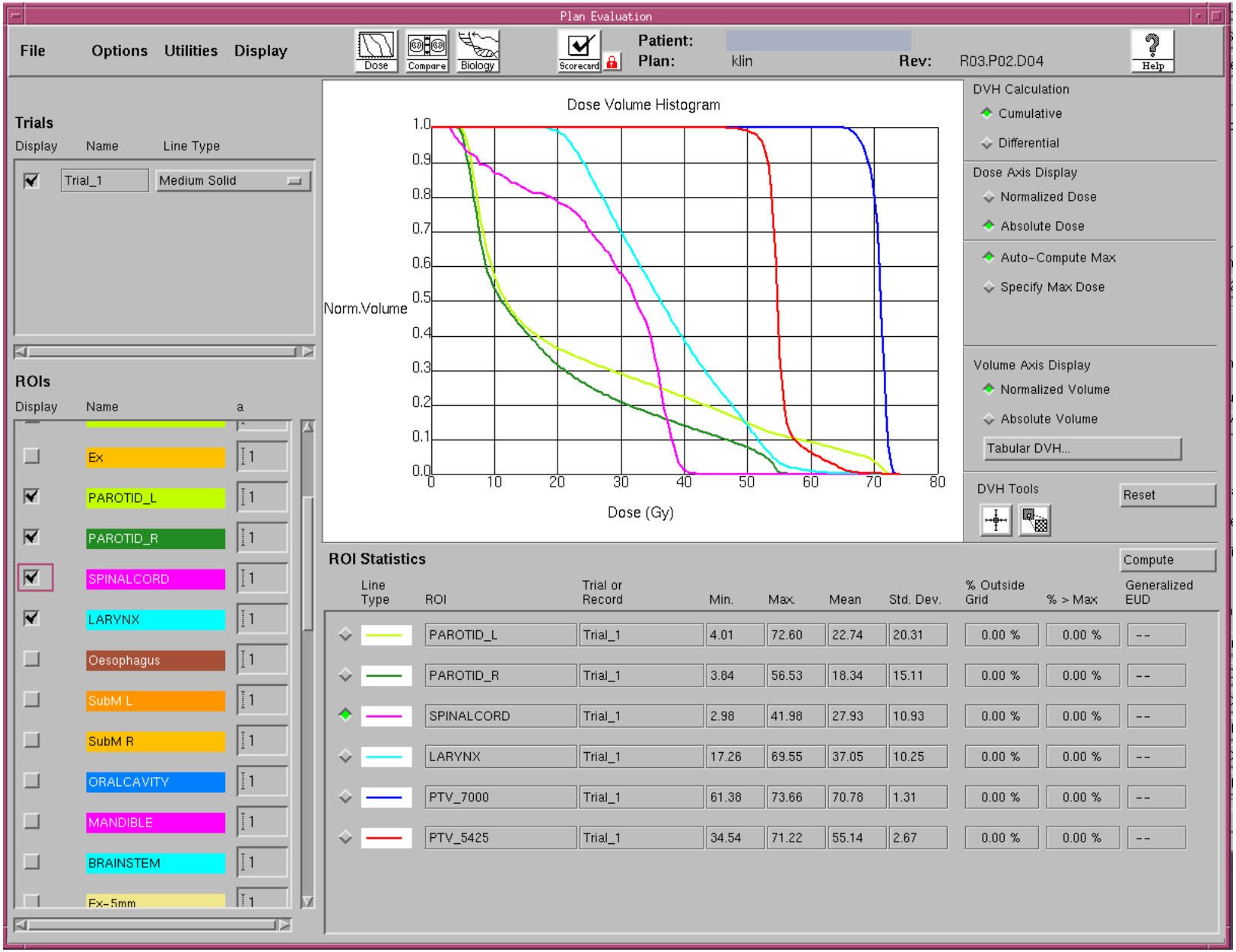
Neck (R), levels II-III-IV and RP: 54.25 Gy

VMAT-SIB technique

Cisplatin weekly 40 mg/m^2

Nimorazole or placebo


Trial: Trial_1
Absolute
80.5 Gy
77.0 Gy
73.5 Gy
70.0 Gy
66.5 Gy
57.0 Gy
54.2 Gy
51.5 Gy
44.0 Gy
30.0 Gy
20.0 Gy
10.0 Gy
Slice 64: Z = -30.560 KOELMAN^JGM
Trial: Trial_1
Absolute
80.5 Gy
77.0 Gy
73.5 Gy
70.0 Gy
66.5 Gy
57.0 Gy
54.2 Gy
51.5 Gy
44.0 Gy
30.0 Gy
20.0 Gy
10.0 Gy
Trial: Trial_1
Absolute
80.5 Gy
77.0 Gy
73.5 Gy
70.0 Gy
66.5 Gy
57.0 Gy
54.2 Gy
51.5 Gy
44.0 Gy
30.0 Gy
20.0 Gy
10.0 Gy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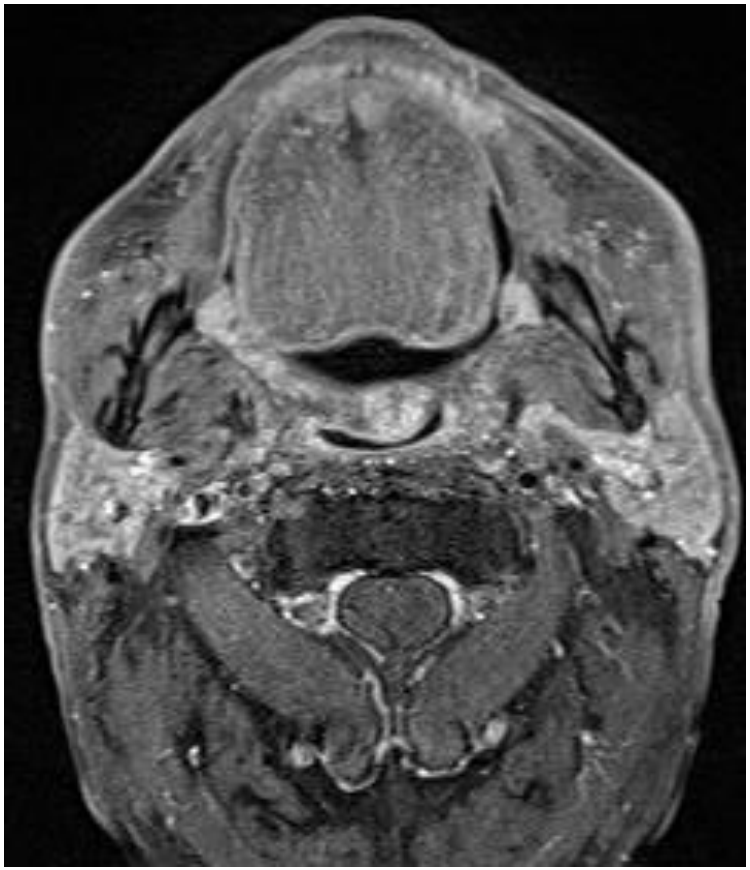
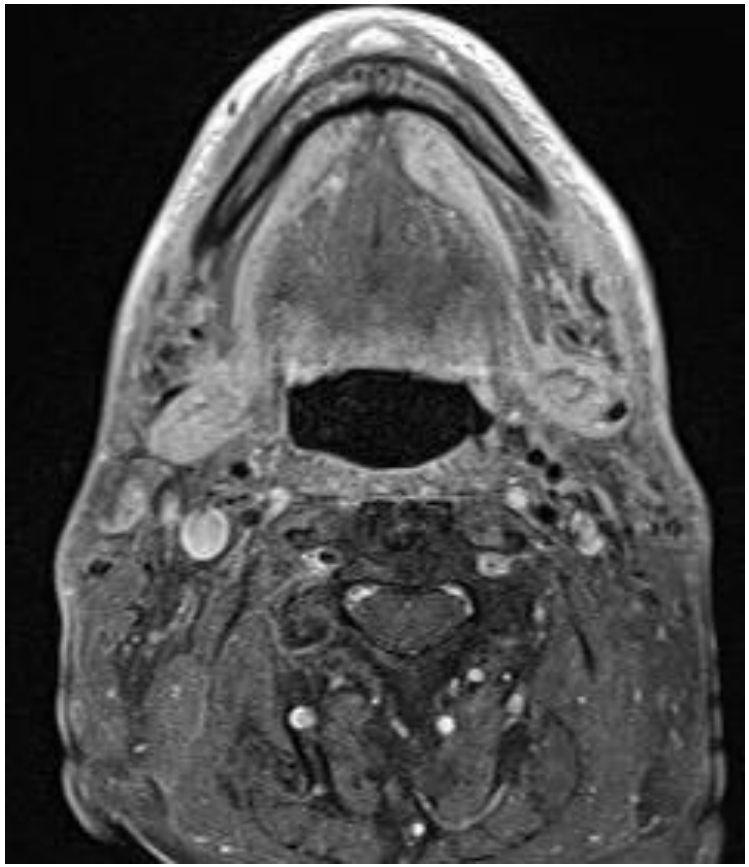
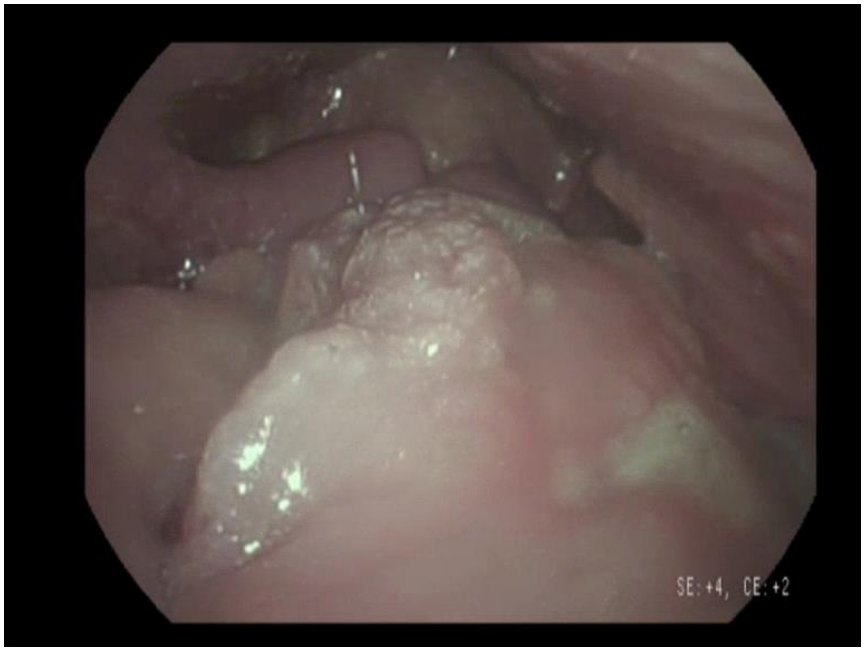
SPINALCORD
LARYNX
Oesophagus
SubM L
SubM R
ORALCAVITY
MANDIBLE
BRAINSTEM
Ex-5mm
Dose Volume Histogram
Norm.Volume
Dose (Gy)
DVH Calculation
Cumulative
Differential
Dose Axis Display
Normalized Dose
Absolute Dose
Auto-Compute Max
Specify Max Dose
Volume Axis Display
Normalized Volume
Absolute Volume
Tabular DVH...
DVH Tools
Reset
ROI Statistics
Compute
Line Type
ROI
Trial or Record
Min.
Max.
Mean
Std. Dev.
% Outside Grid
% > Max
Generalized EUD
PAROTID_L Trial_1 4.01 72.60 22.74 20.31 0.00 % 0.00 % --
PAROTID_R Trial_1 3.84 56.53 18.34 15.11 0.00 % 0.00 % --
SPINALCORD Trial_1 2.98 41.98 27.93 10.93 0.00 % 0.00 % --
LARYNX Trial_1 17.26 69.55 37.05 10.25 0.00 % 0.00 % --
PTV_7000 Trial_1 61.38 73.66 70.78 1.31 0.00 % 0.00 % --
PTV_5425 Trial_1 34.54 71.22 55.14 2.67 0.00 % 0.00 % --

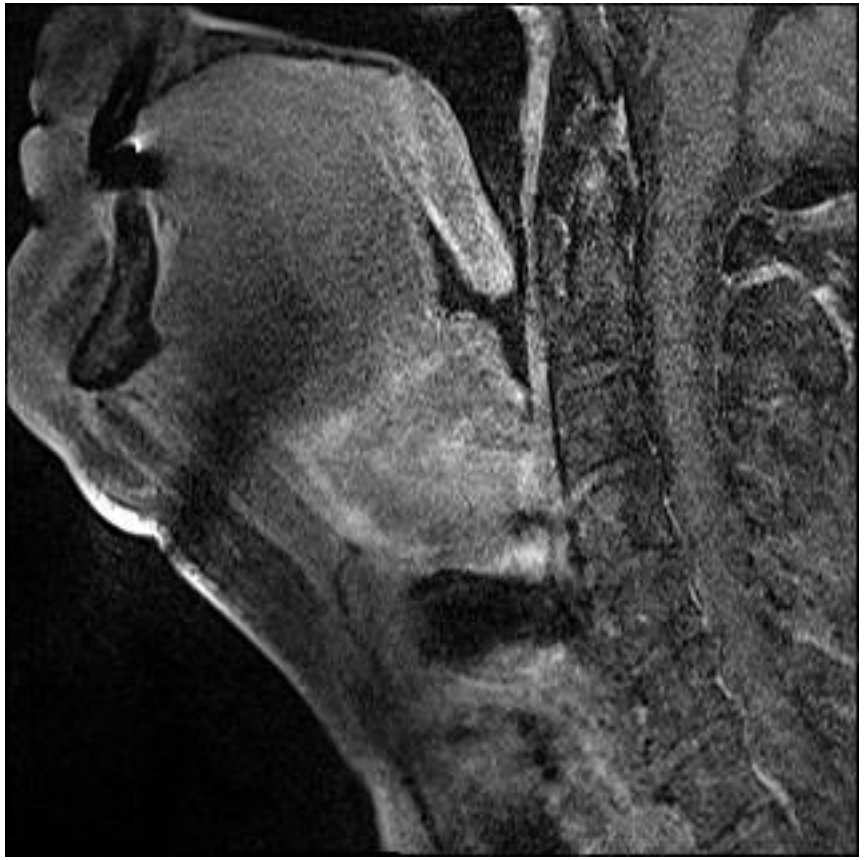
Three months after completion of treatment





Carcinoma base of tongue T4a





T4a: invades
- **larynx,**
- **deep muscles of tongue**
- **medial pterygoid**
- **hard palate**
- **mandible**

Oropharynx cancer

Radiotherapy or surgery?

no randomized trials

Oropharynx cancer: Surgery, Radiation Therapy or Both?

A survey of treatment results from North American Institutions

Parsons et al. Cancer, June 1, 2002

Surgery

with or without adjuvant radiotherapy

Radiotherapy

alone or followed by neck dissection

Oropharynx cancer: Surgery, Radiation Therapy or Both?

Parsons et al. Cancer, June 1, 2002

51 reported series

1970 - 2000

± 6400 patients across USA and Canada

Endpoints:

- **Local control**
- **Loco-regional control**
- **5-Year absolute or cause specific survival**
- **Severe or fatal treatment complications**

Oropharynx cancer: Surgery, Radiation Therapy or Both?

Parsons et al. Cancer, June 1, 2002

Base of Tongue carcinoma

Treatment	No. of patients	Stage IV	loco-regional control
Surgery	370	42%	60%
Radiotherapy	370	66%	69%
			5-yr survival
Surgery	500	31%	49%
Radiotherapy	473	62%	52%

Oropharynx cancer: Surgery, Radiation Therapy or Both?

Parsons et al. Cancer, June 1, 2002

Tosillar carcinoma

Treatment	No. of patients	Stage IV	loco-regional control
Surgery	281	31%	65%
Radiotherapy	858	52%	69%
			5-yr survival
Surgery	321	44%	47%
Radiotherapy	2276	49%	43%

Oropharynx cancer: Surgery, Radiation Therapy or Both?

Parsons et al. Cancer, June 1, 2002

Complications

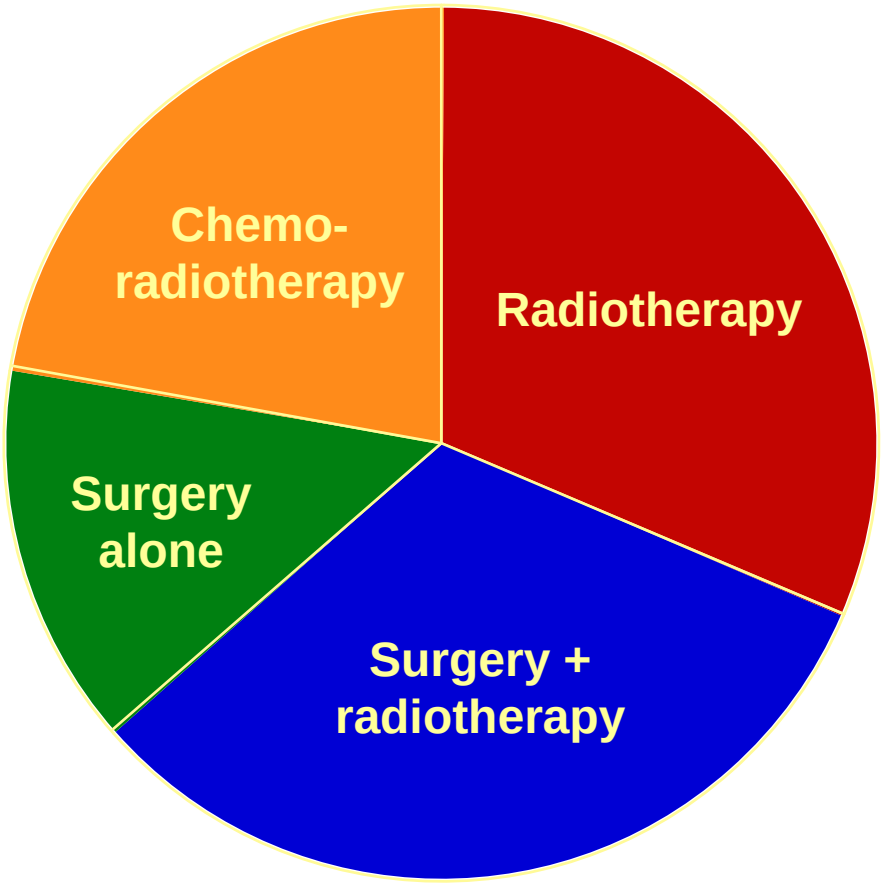
Tonsillar carcinoma

Treatment	No. of patients	Complications	
		Severe	Fatal
Surgery	616	23%	3.2%
Radiotherapy	2308	6%	0.8%

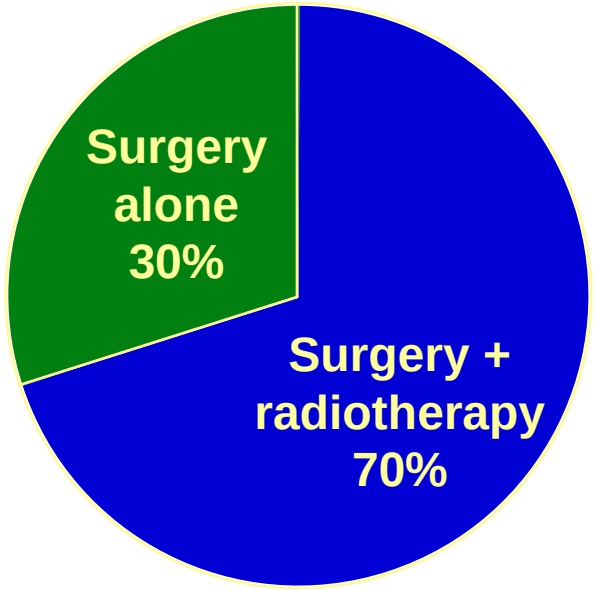
Base of tongue carcinoma

Treatment	No. of patients	Complications	
		Severe	Fatal
Surgery	407	32%	3.5%
Radiotherapy	842	3.8%	0.4%

Treatment of oropharynx cancer at UMC Nijmegen: 1986-2001 (388 patients)



All patients



Patients treated with primary surgery

Articles

LANCET 2000

Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data

*J P Pignon, J Bourhis, C Domenge, L Designé, on behalf of the MACH-NC Collaborative Group**

65 trials

10,850 patients

individual patient data

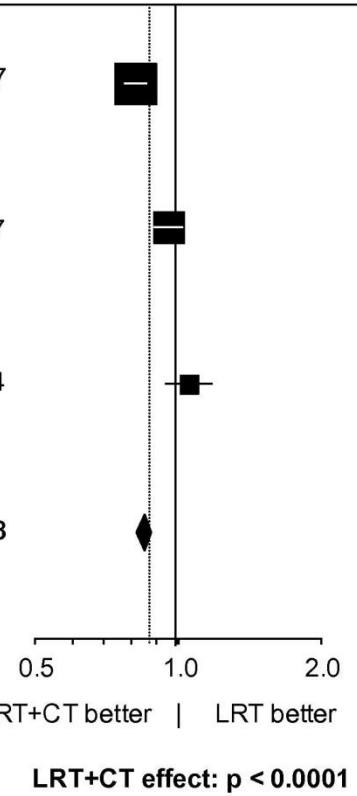
Meta-analysis of locoregional treatment with and without chemotherapy: update

93 trials

17,346 patients

(a) Hazard ratio of death.

Timing	No. Deaths / No. Entered LRT+CT	LRT	O-E	Variance	Hazard Ratio	HR [95% CI]
Concomitant	3171/4824	3389/4791	-326.4	1587.7		0.81 [0.78;0.86]
Induction	1877/2740	1813/2571	-40.0	900.7		0.96 [0.90;1.02]
Adjuvant	631/1244	661/1323	17.9	317.4		1.06 [0.95;1.18]
Total	**5679/8808**	**5863/8685**	**-348.5**	**2805.8**		**0.88 [0.85;0.92]**



Test for heterogeneity: $\chi^2_{107} = 179.8$ $p < 0.0001$

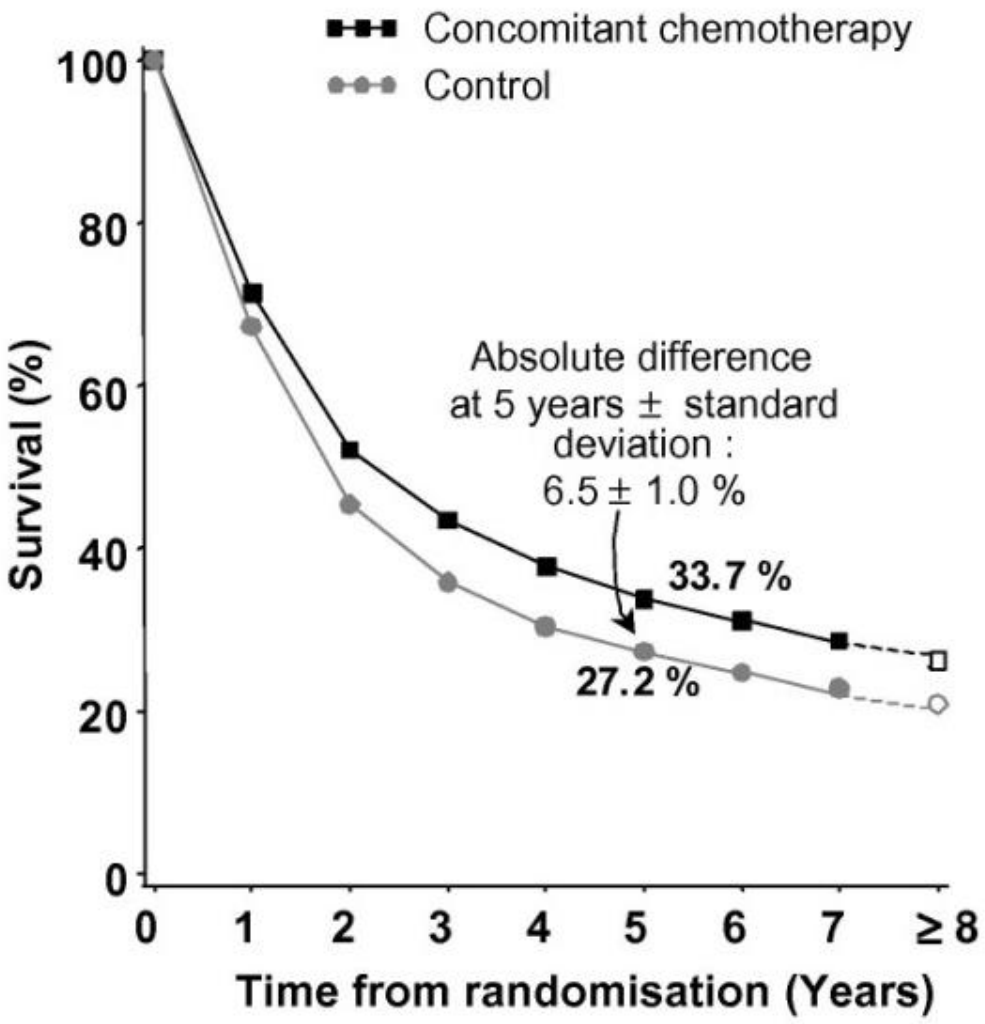
Test for interaction: $\chi^2_2 = 26.60$ $p < 0.0001$

$I^2 = 41\%$

LRT+CT effect: p < 0.0001

Pignon et al. R&O 2009

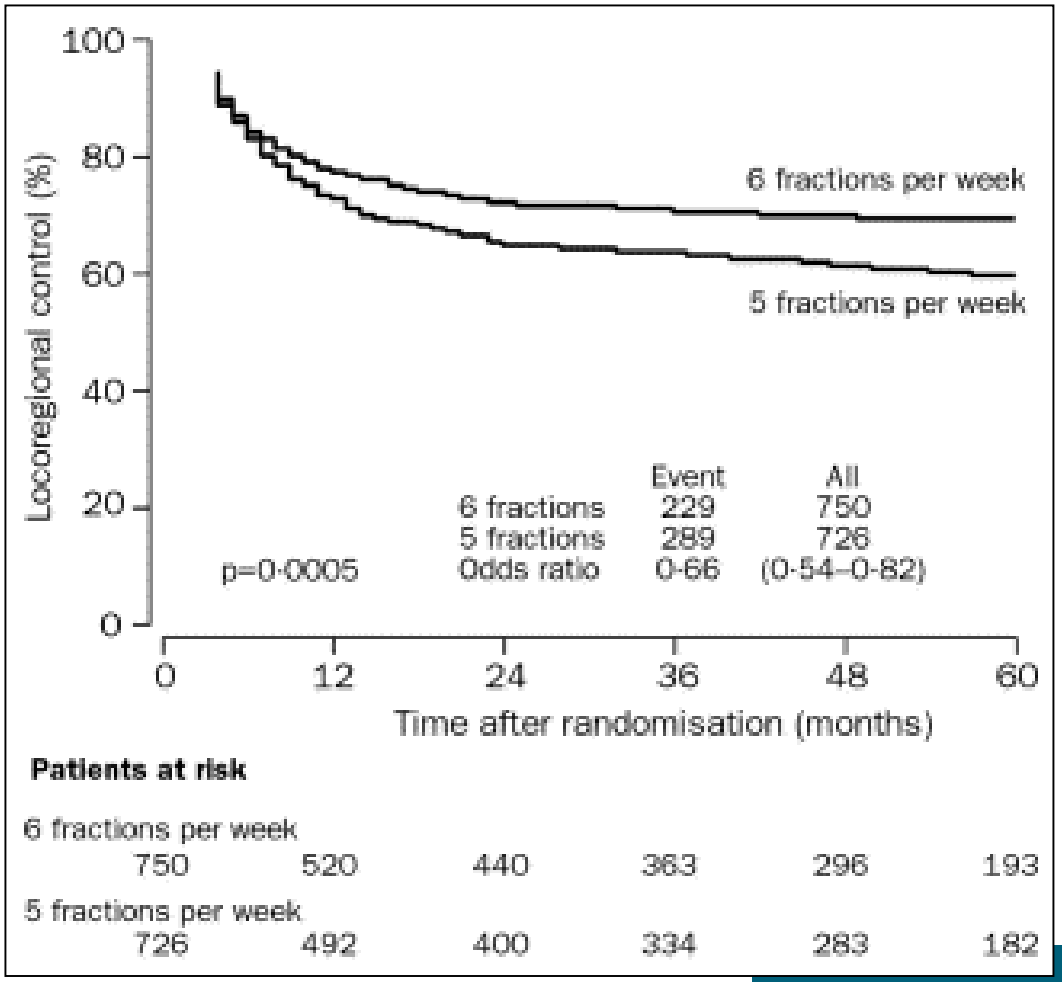
Survival gain with concomitant chemotherapy 6.5%



Pignon et al. R&O 2009

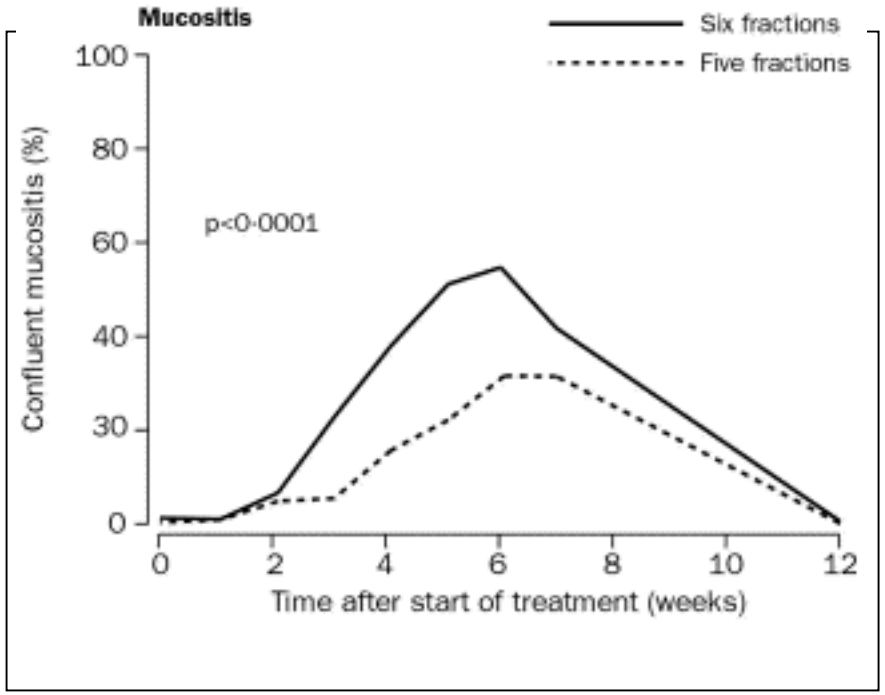
DAHANCA 6-7, loco-regional control

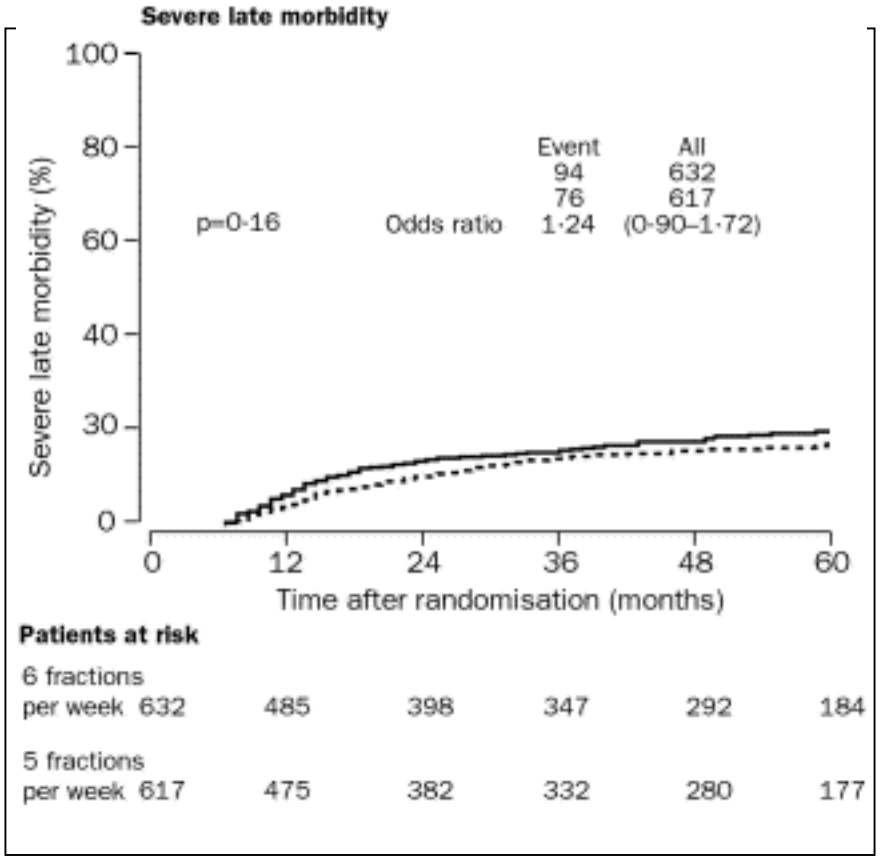
66 Gy - 33 fx - 5.5 wks ⟷ control: 66 Gy - 33 fx - 6.5 wks



Overgaard, Lancet 2003

DAHANCA 6-7, acute and late morbidity





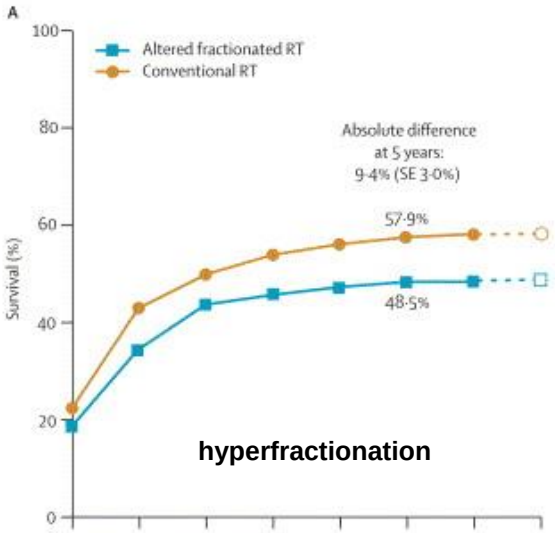
Overgaard, Lancet 2003

Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis

Bourhis et al. Lancet 2006; 368: 843-854

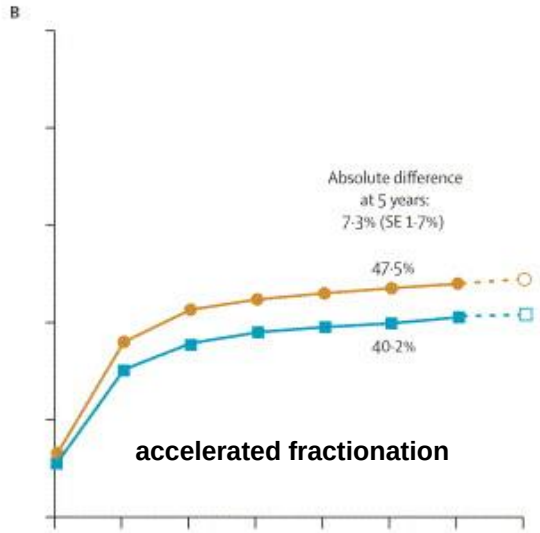
- **Fifteen trials with 6515 patients included**
- **Mainly oropharynx and larynx tumors**
- **74% of patients had stage III-IV disease**
- **Three categories:**
  - **hyperfractionated**
  - **accelerated**
  - **accelerated with total dose reduction**
- **Data were collected for individual patients.**

Locoregional recurrence



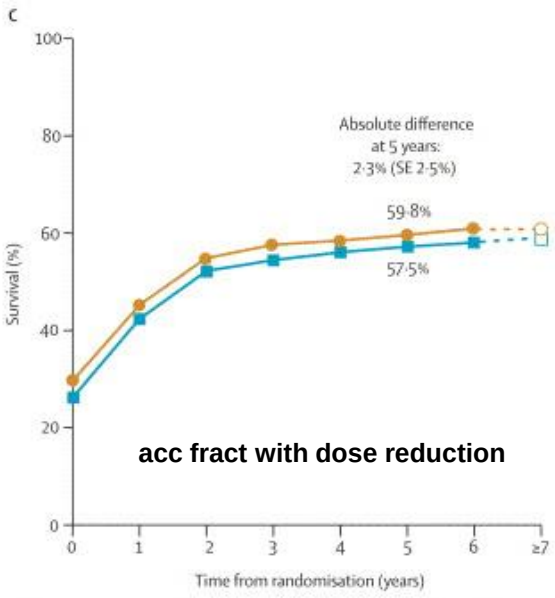
hyperfractionation

Death/person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	331/1313	30/483	2/261
Altered fractionated RT	288/1453	20/652	2/400

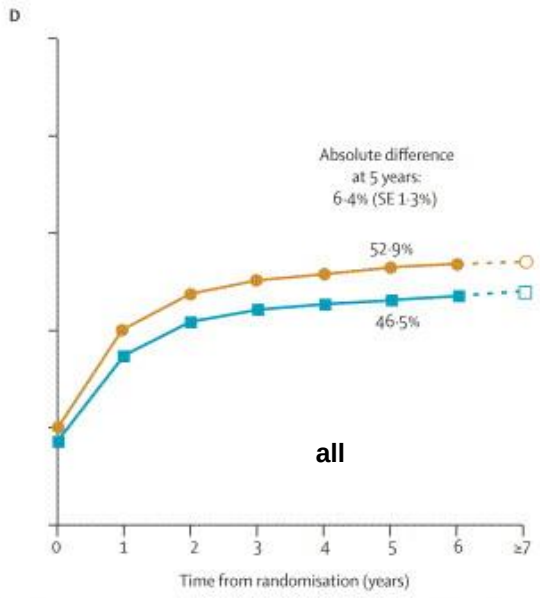


accelerated fractionation

Death/person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	786/4127	57/1916	13/824
Altered fractionated RT	645/4357	54/2153	13/937



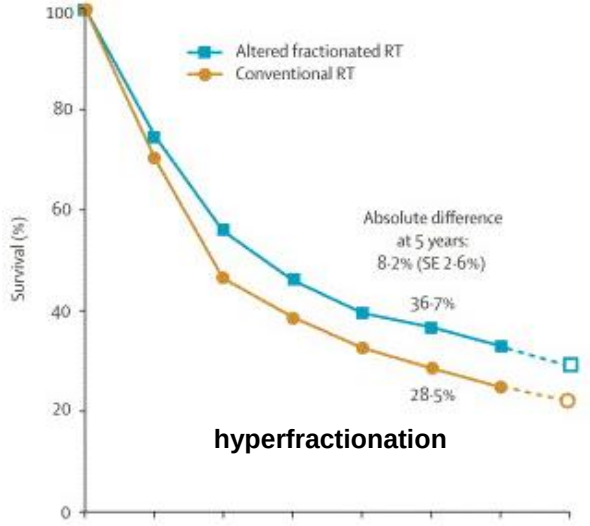
acc fract with dose reduction



all

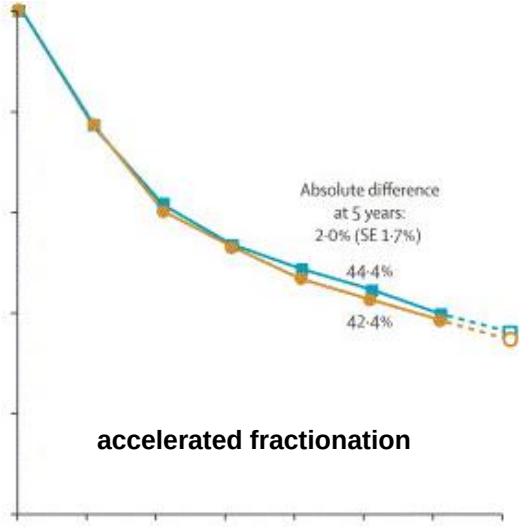
Bourhis 2006

Overall survival



hyperfractionation

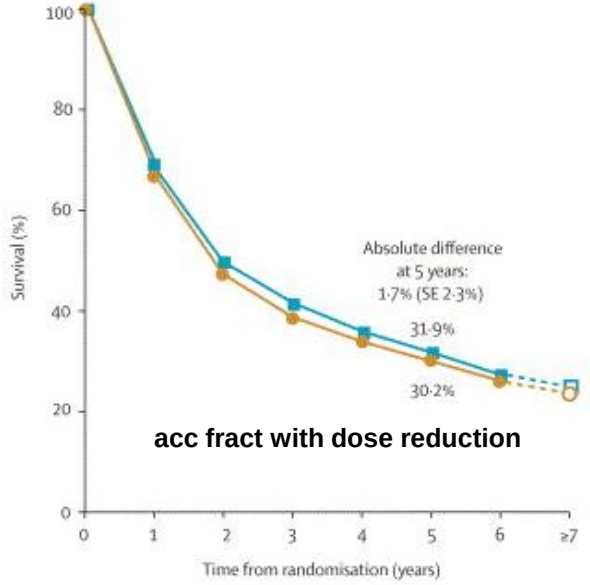
Death/person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	356/929	106/638	45/339
Altered fractionated RT	290/1019	124/818	56/492



accelerated fractionation

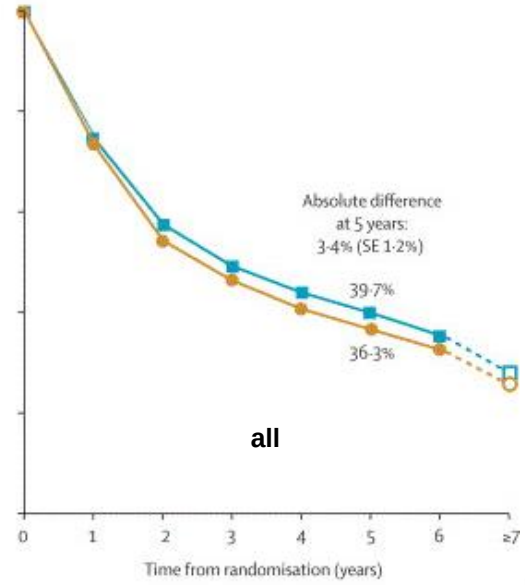
Death/person years by period	Years 0–2	Years 3–5	Years ≥6
Conventional RT	746/2918	283/2365	99/982
Altered fractionated RT	734/2977	284/2545	112/1079

C



acc fract with dose reduction

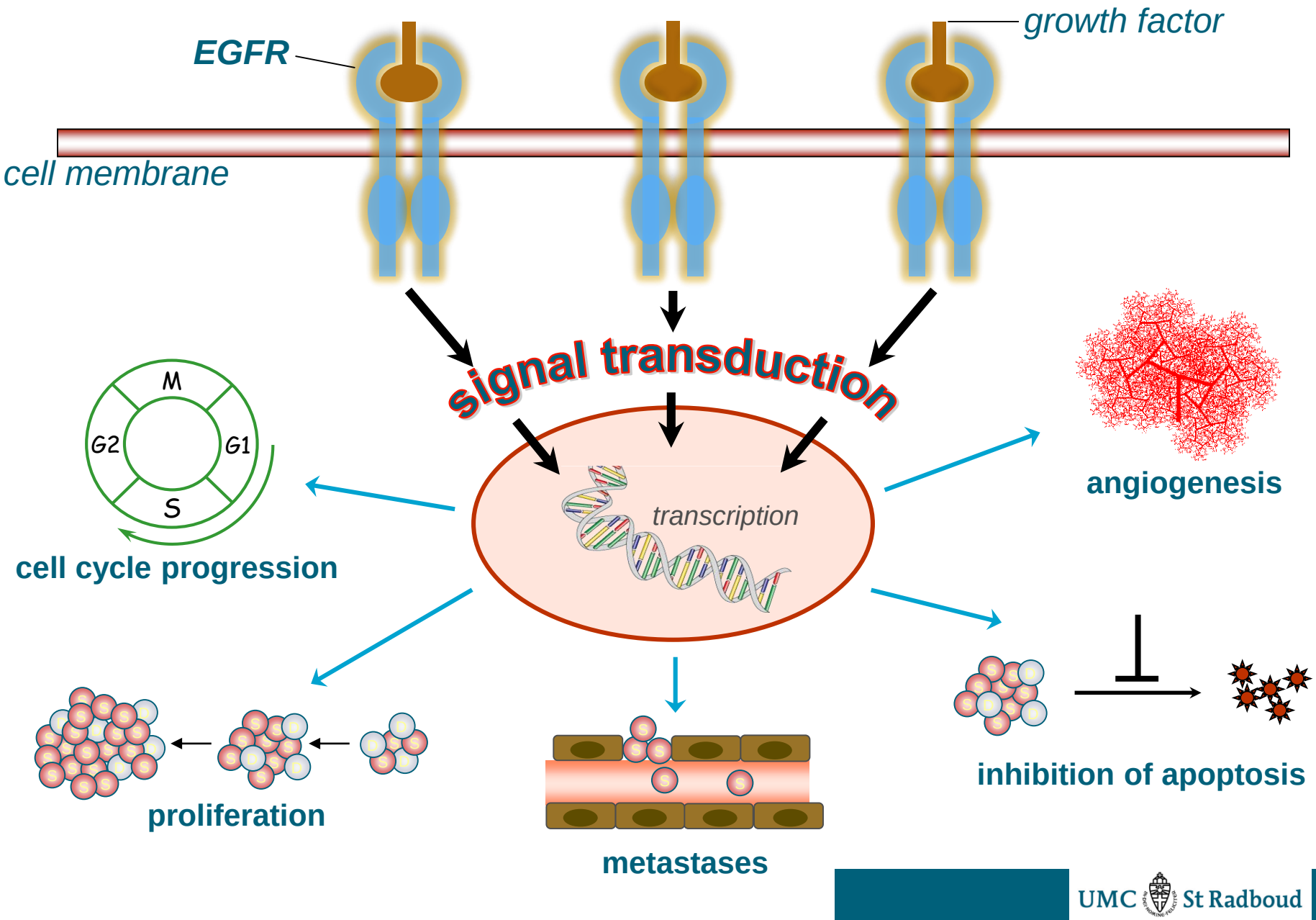
D

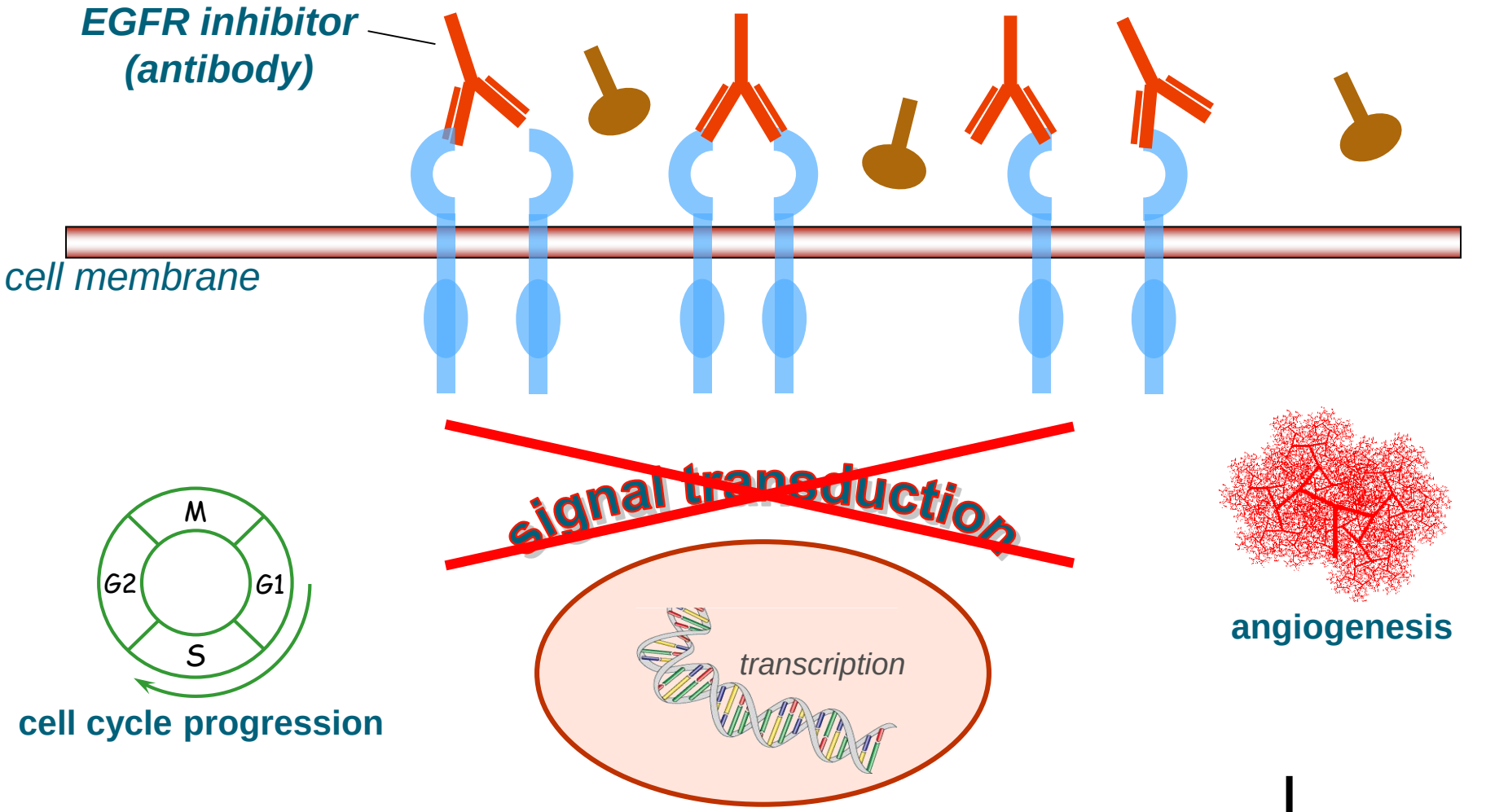


all

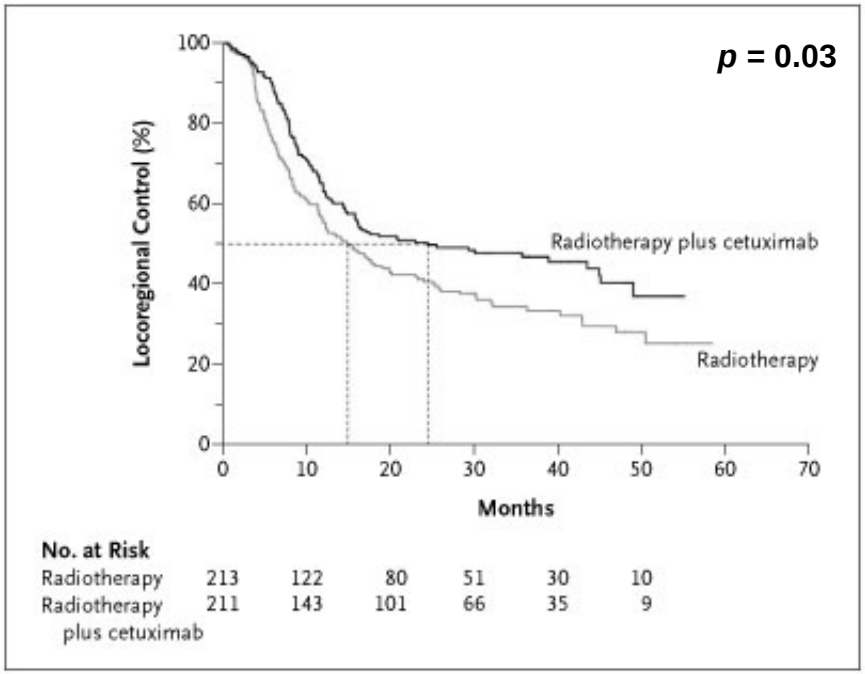
Bourhis 2006

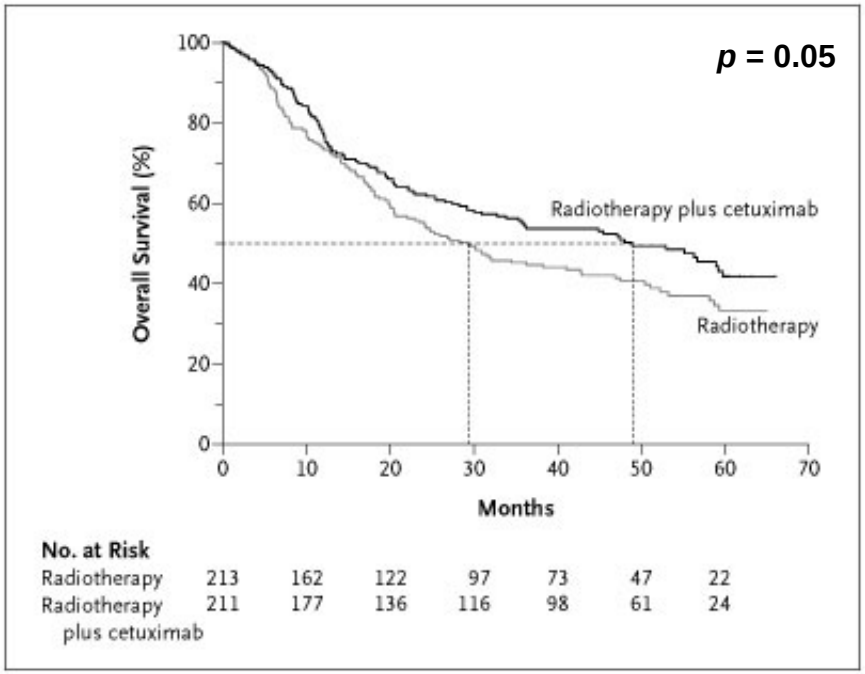
Epidermal growth factor receptor (EGFR)




EGFR inhibitor
(antibody)
cell membrane
signal transduction
transcription
M
G2
G1
S
cell cycle progression
angiogenesis
proliferation
metastases
inhibition of apoptosis

Radiotherapy combined with EGFR inhibitor randomized phase III trial





Bonner et al. NEJM, 2006

Radiotherapy combined with EGFR inhibitor randomized phase III trial

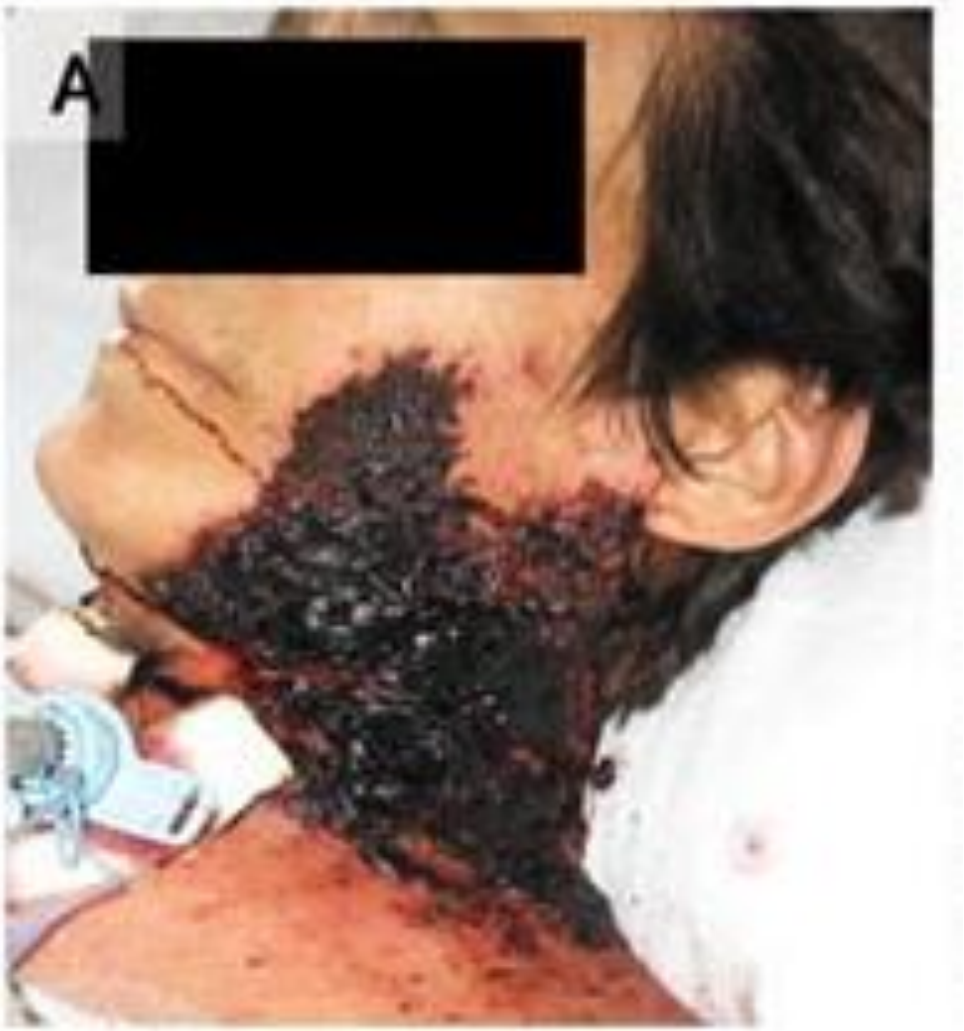
Acute toxic effects (WHO criteria)

	RT alone	RT + cetuximab	*p* - value
Mucositis (grade 3-5)	52%	56%	N.S.
Skin rash (all grades)	10%	87%	< 0.001
Radiation dermatitis (grade 3-5)	18%	23%	N.S.
Weight loss (all grades)	72%	84%	0.005
Nausea (all grades)	37%	49%	0.02
Fever (all grades)	13%	26%	0.001
Anemia (all grades)	13%	3%	< 0.001

Late toxicity: no difference

Bonner et al. NEJM, 2006

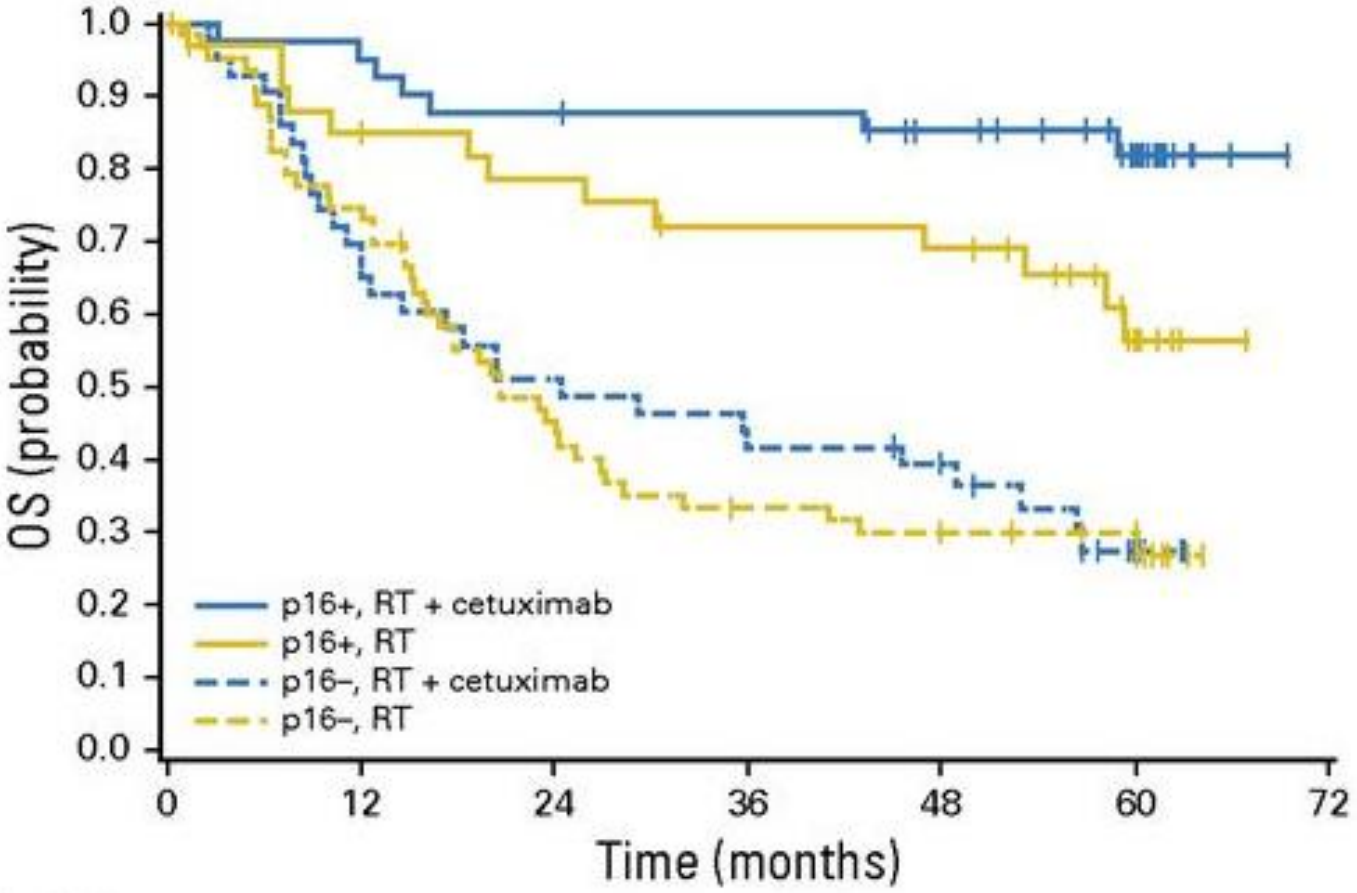
Severe cutaneous reaction during radiation therapy with concurrent cetuximab



Budach et al. NEJM, 2007

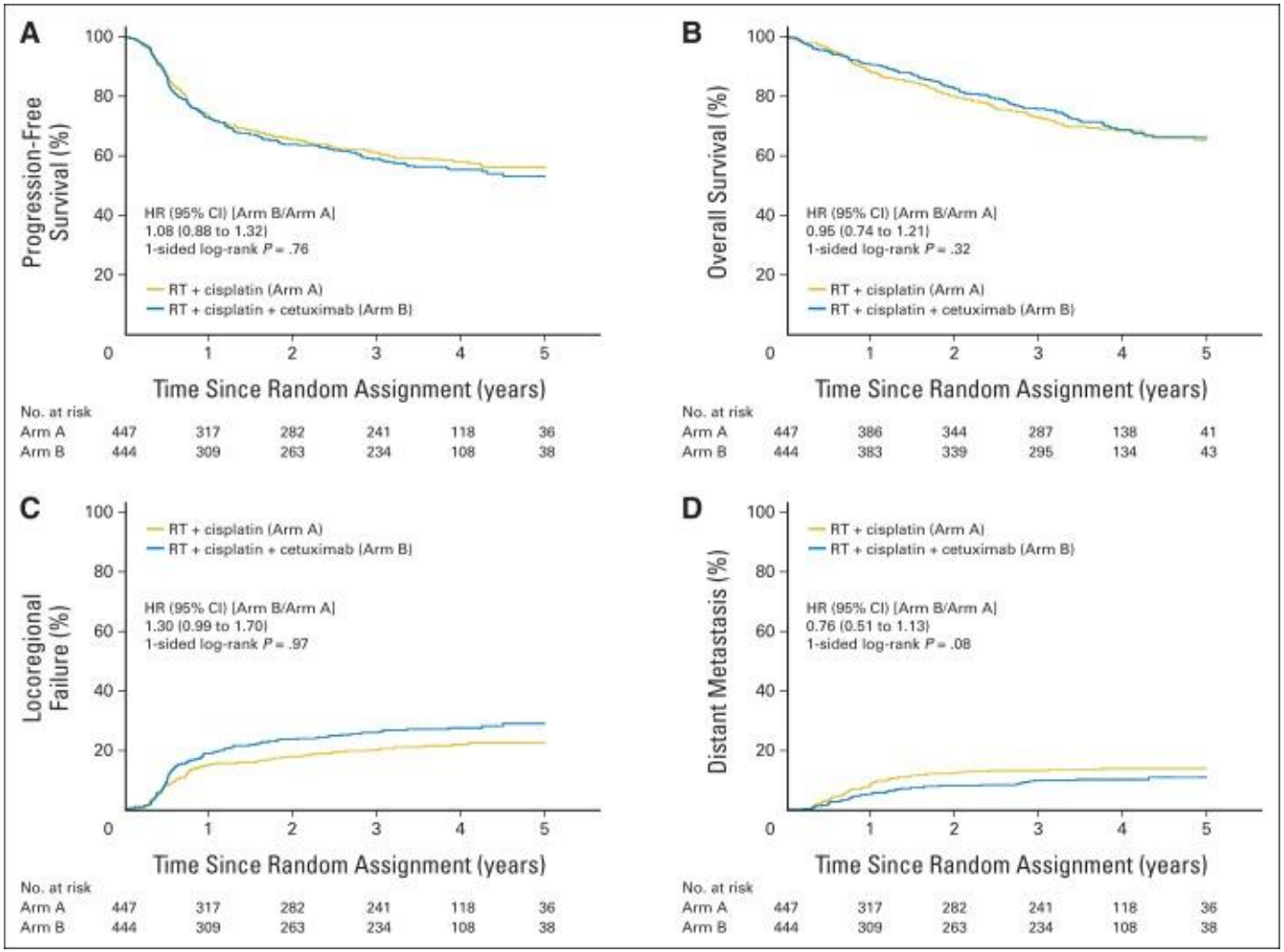
Radiotherapy combined with EGFR inhibitor randomized phase III trial

Association HPV-status with outcome



Rosenthal al. JCO, 2016

Chemoradiotherapy combined with EGFR inhibitor randomized phase III trial

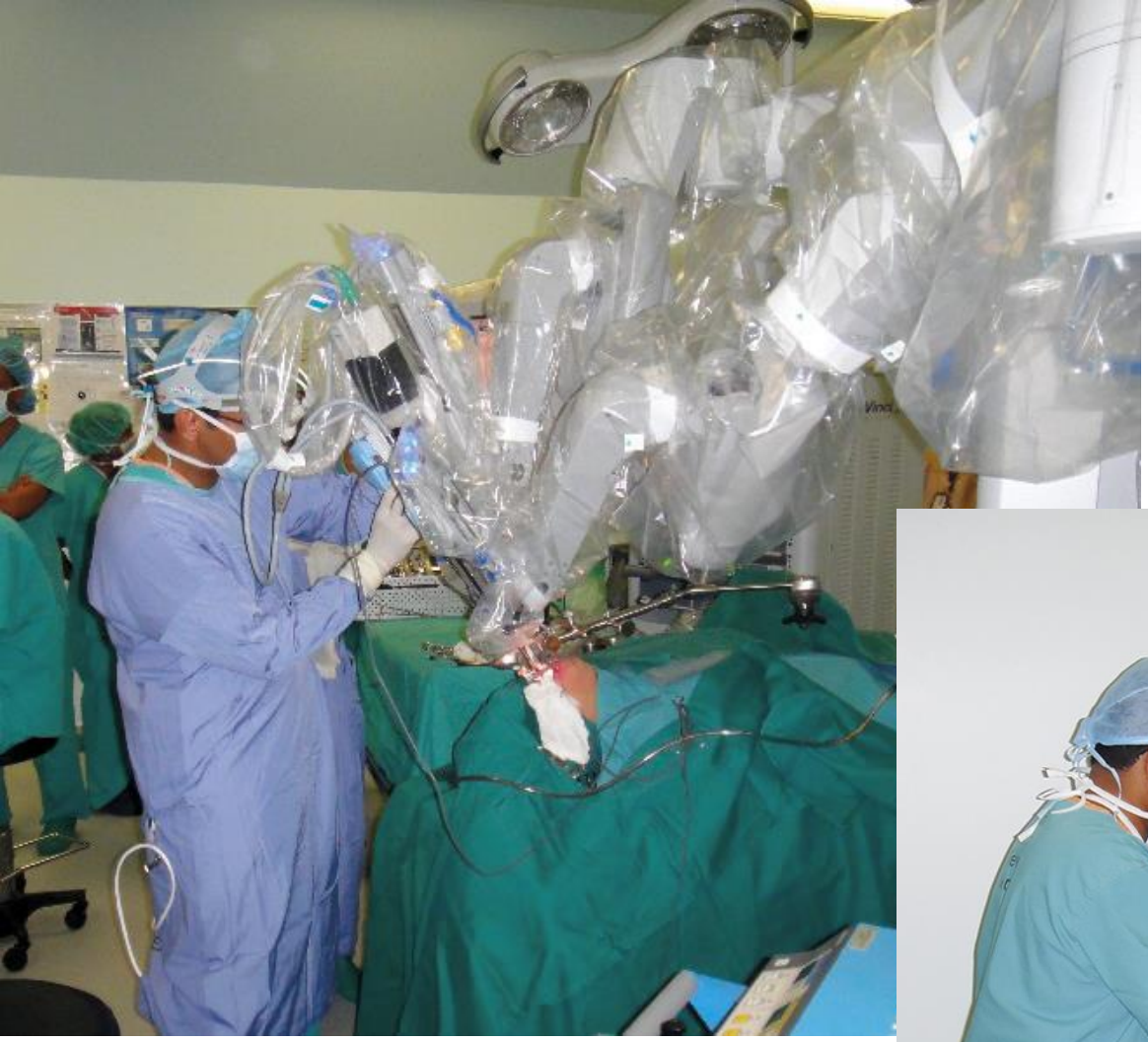


Ang et al. JCO, 2014

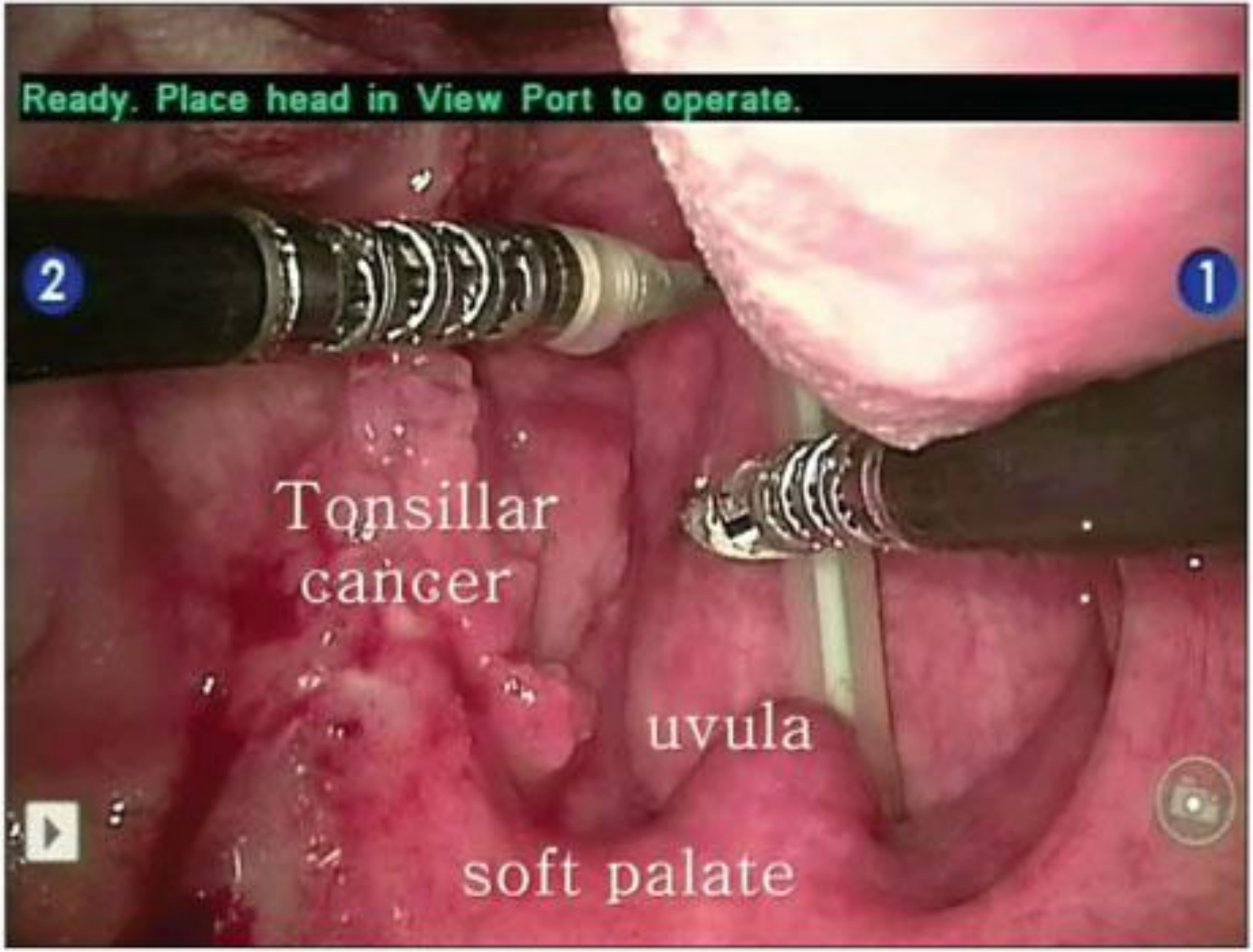
Do you use cetuximab as (part of) treatment for H&N patients?

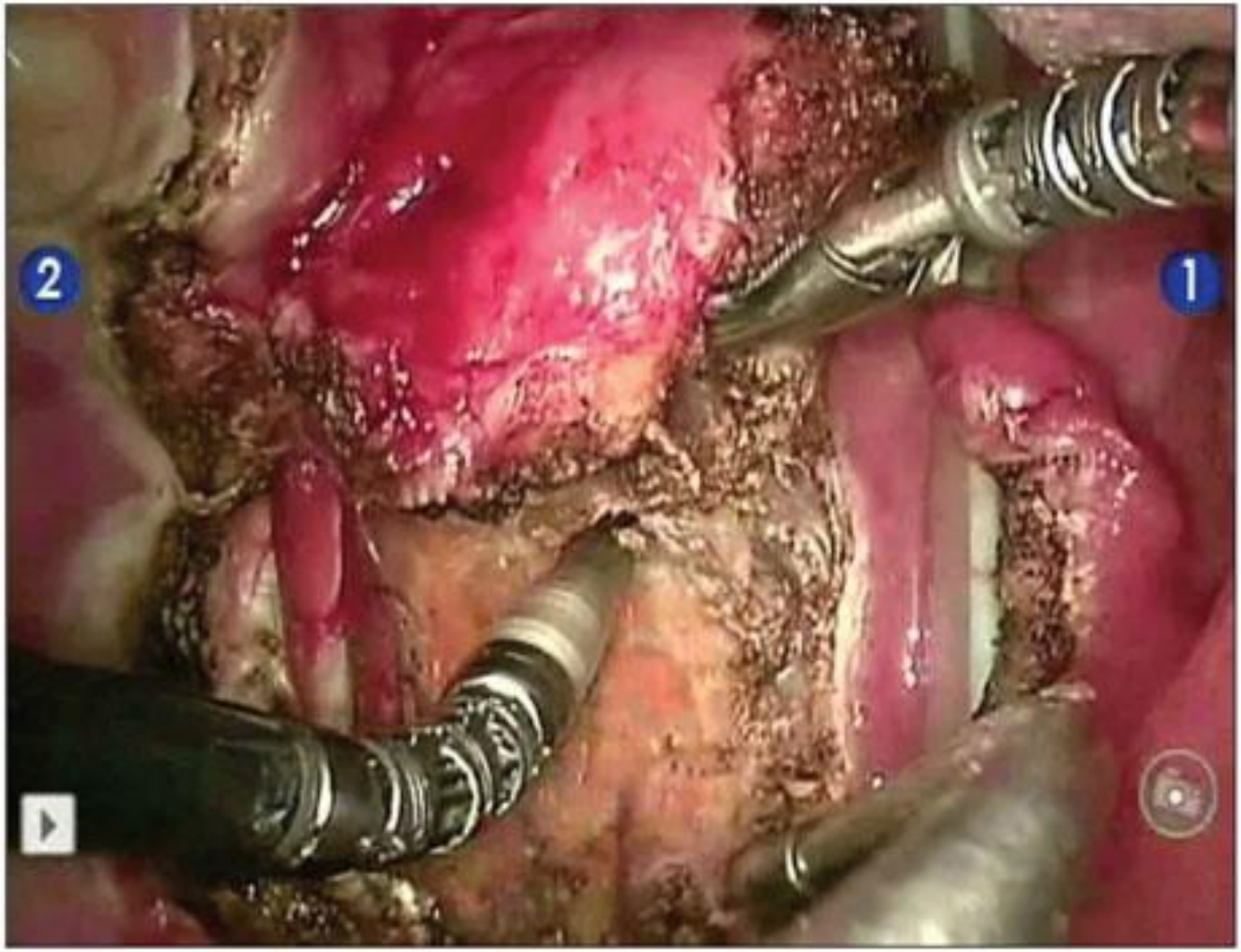
A. No
B. Yes, incidentally
C. Yes, for patients not fit for cisplatin
D. Only in the palliative setting

The new fashion:
“transoral robotic surgery (TORS)“




da Vinci S
SURGICAL SYSTEM

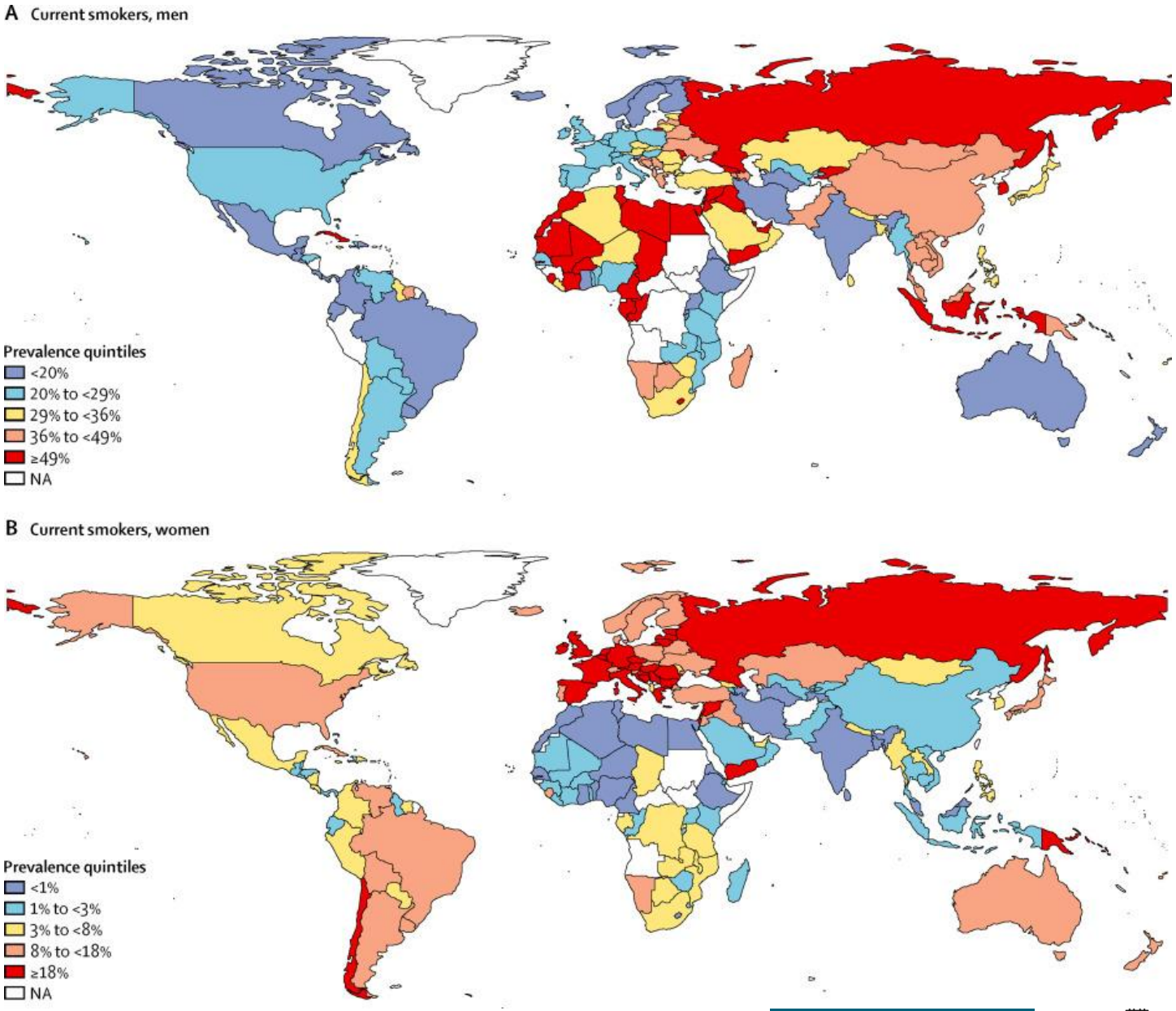

Ready. Place head in View Port to operate.
2
1
Tonsillar cancer
uvula
soft palate


2
1


Ready. Place head in View Port to operate.
2
1
Internal carotid artery

CARCINOMA OF THE LARYNX

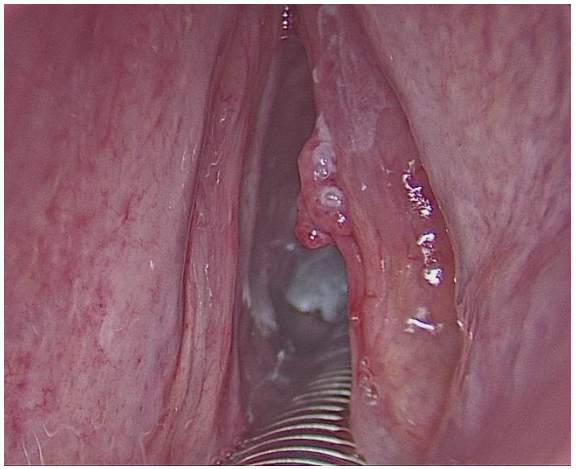
Estimated prevalence of current tobacco smoking in 2010

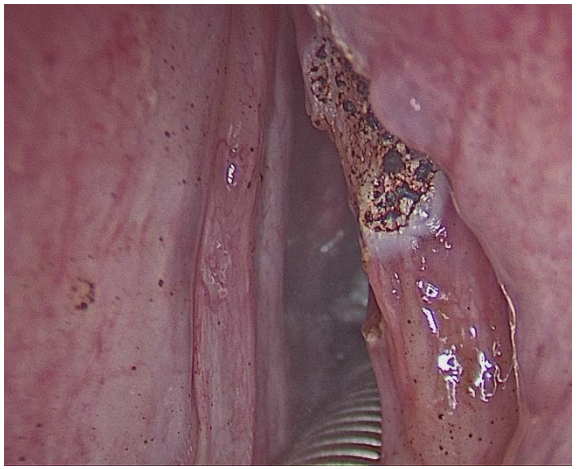


The Lancet 2015 385, 966-976

Larynx cancer T1

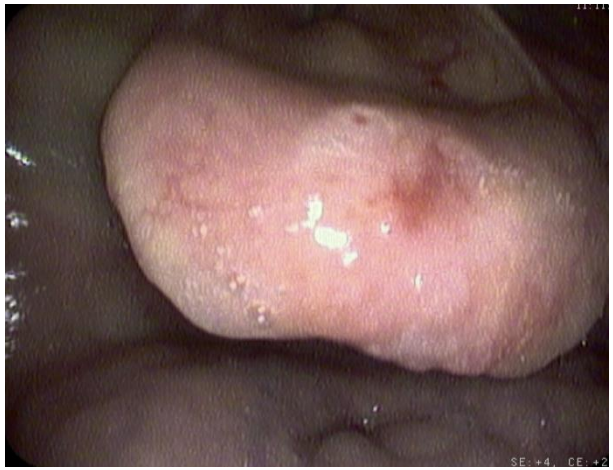
glottic

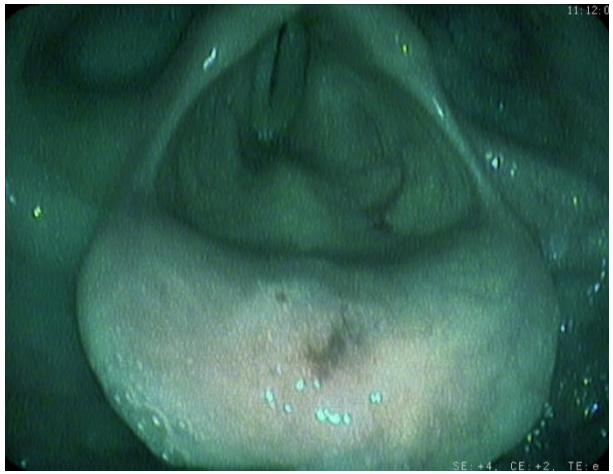




T1: limited to vocal cords with normal mobility

supraglottic

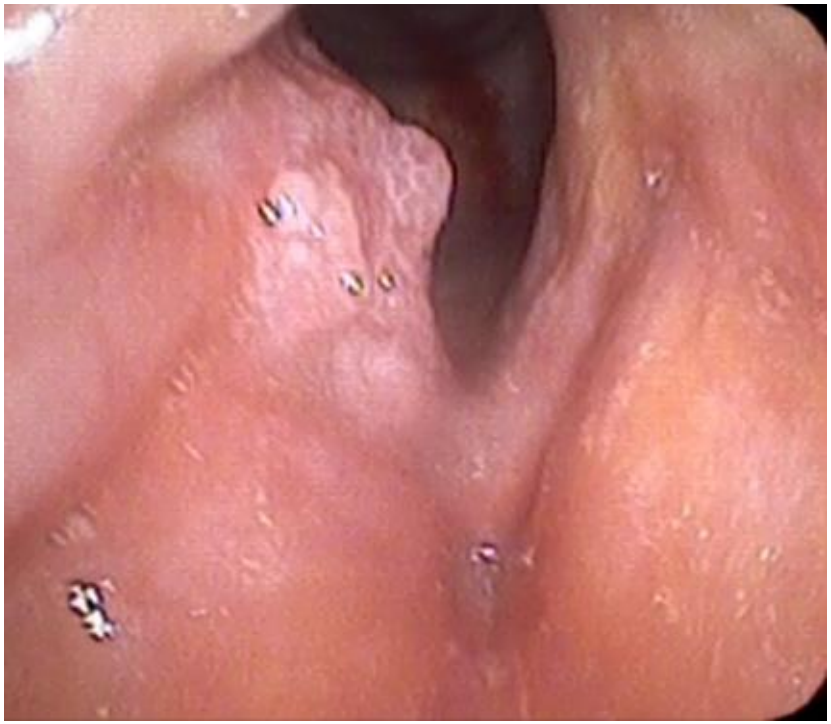




T1: limited to one subsite with normal mobility

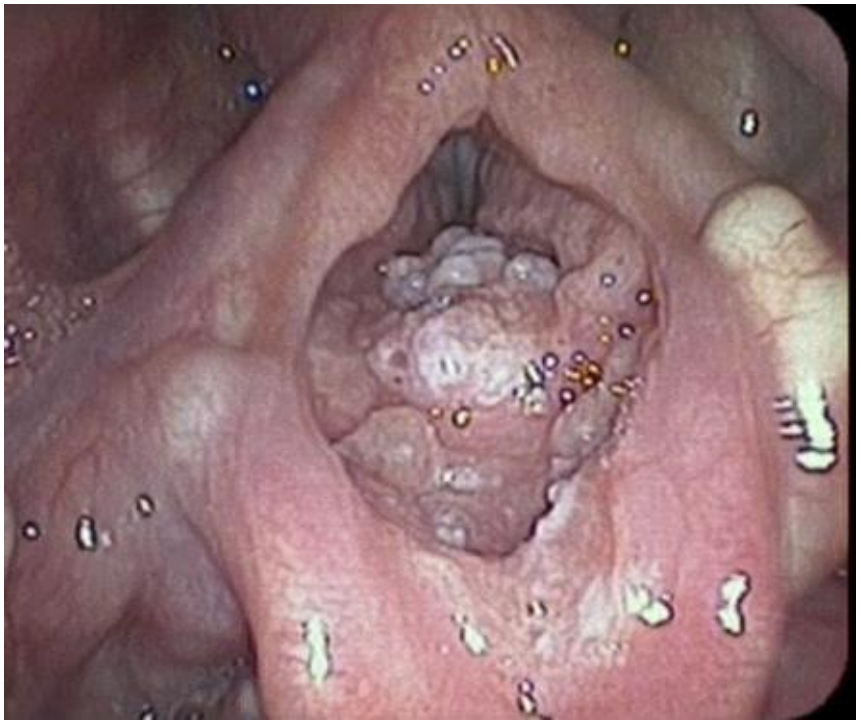
Larynx cancer T2

glottic



T2: supra- and/or subglottic extension and/or impaired mobility

supraglottic

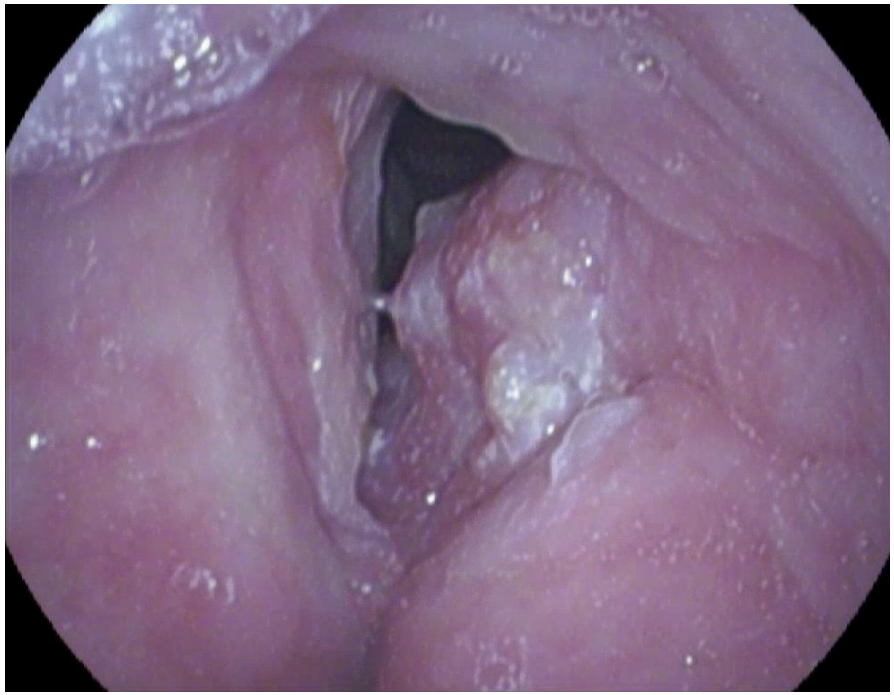


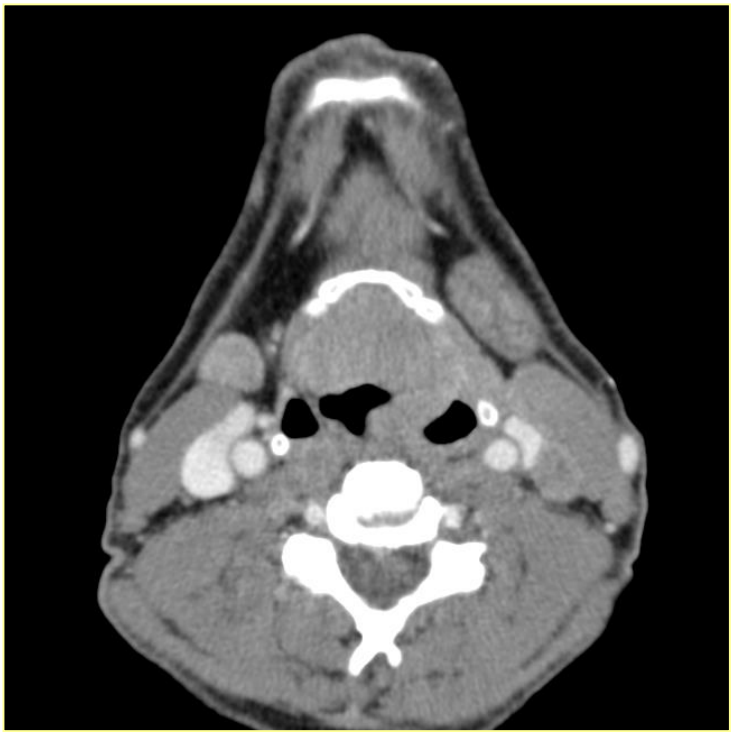
T2: more than one subsite without fixation

Larynx cancer T3

glottic

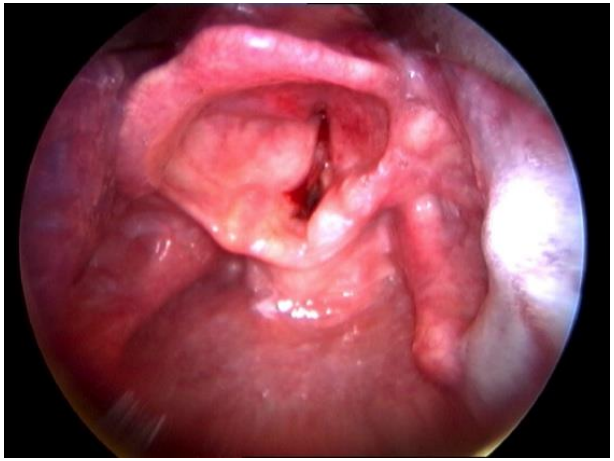
supraglottic

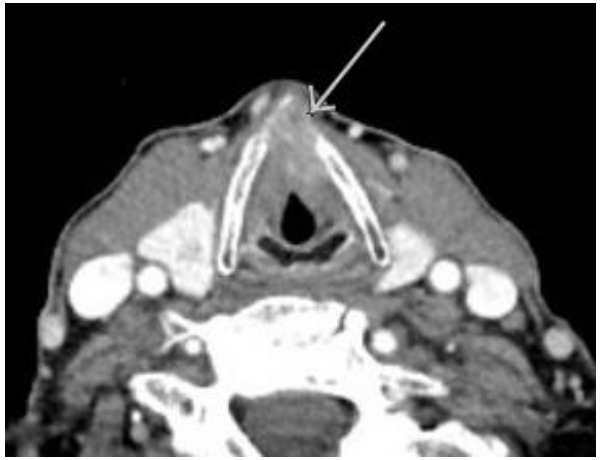


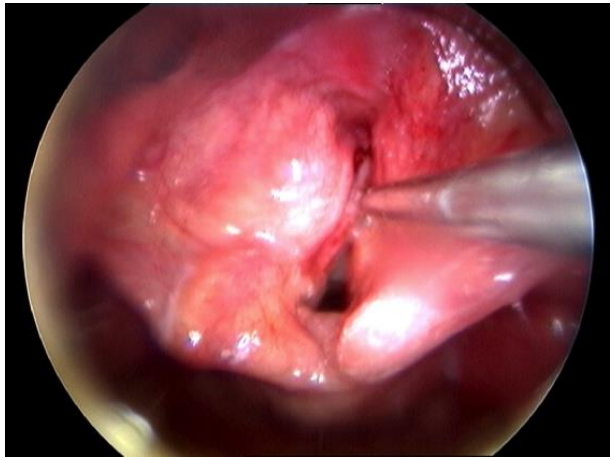


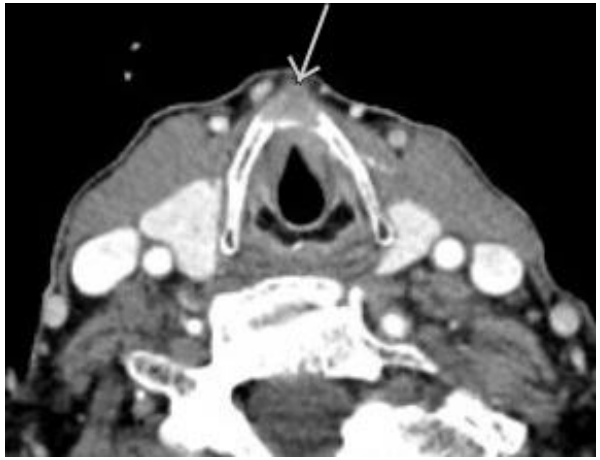
Limited to larynx with vocal cord fixation and/or invades postcricoid area, pre-epiglottic space, paraglottic space or inner cortex of thyroid cartilage

Larynx cancer T4

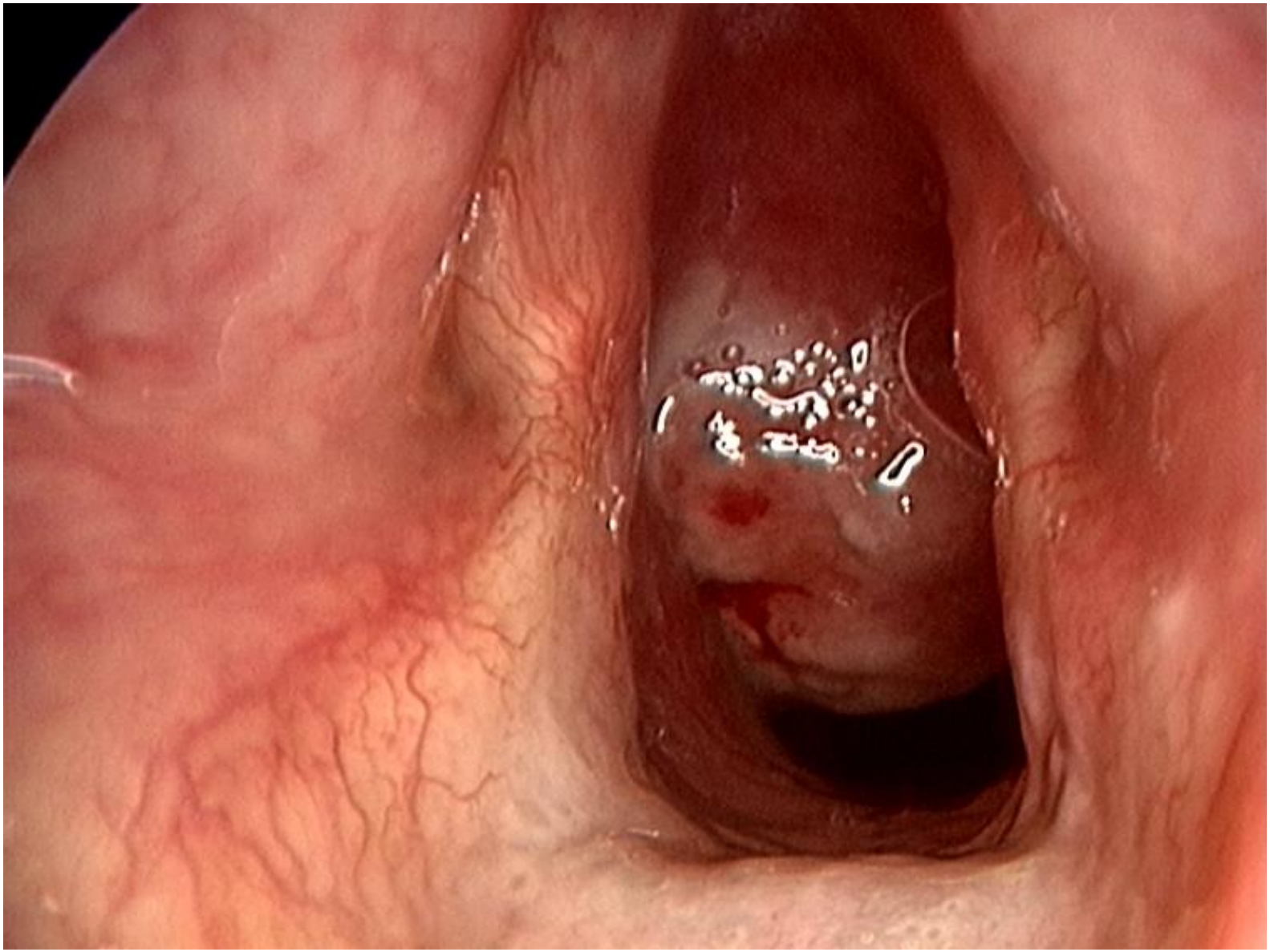








Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx



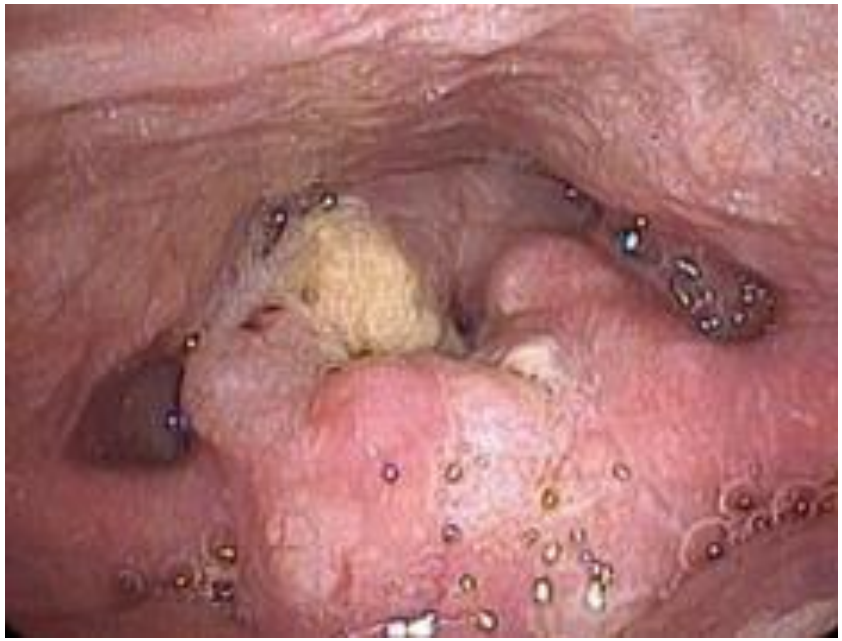
Larynx carcinoma (case)

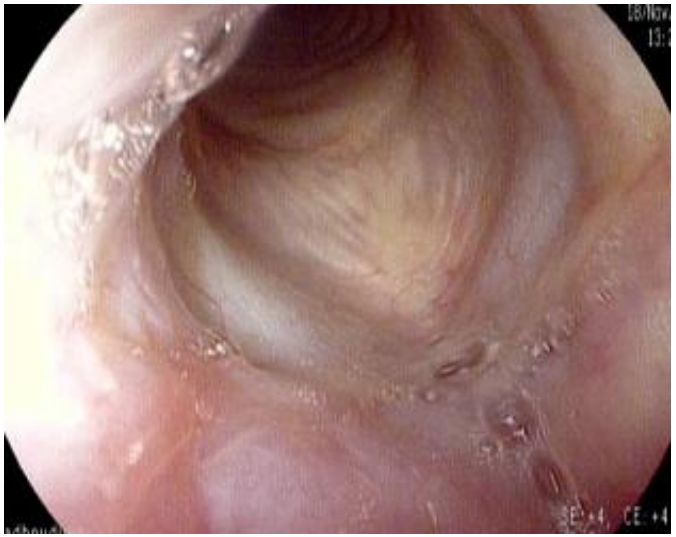
Man, 66 yrs with voice change (“hot potatoe”) and dysphagia since 3-4 months.
Normal intake, no weight loss.
No comorbidity.
Smoking 44 PY, alcohol no.

Physical exam reveals supraglottic tumor with deformation of epiglottis, involvement of bilateral a-e folds and limited invasion false cords.
Bilateral pyriform sinus and vocal cords uninvolved and normal mobility.

Palpable lymph nodes level II-III right and level II left.

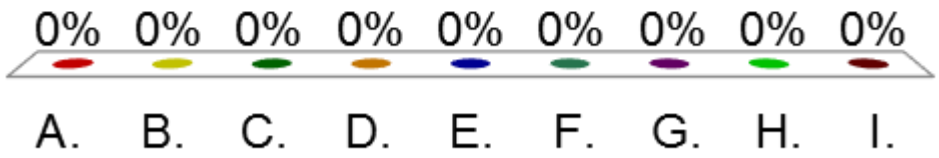
Biopsy shows squamous cell carcinoma.



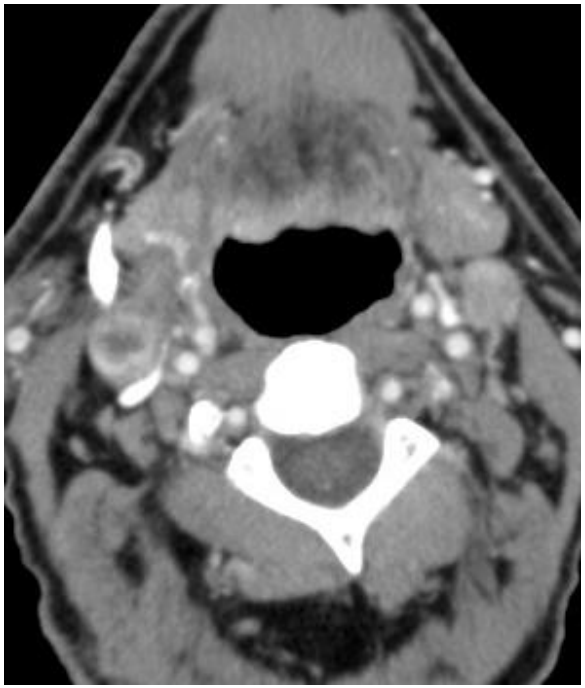


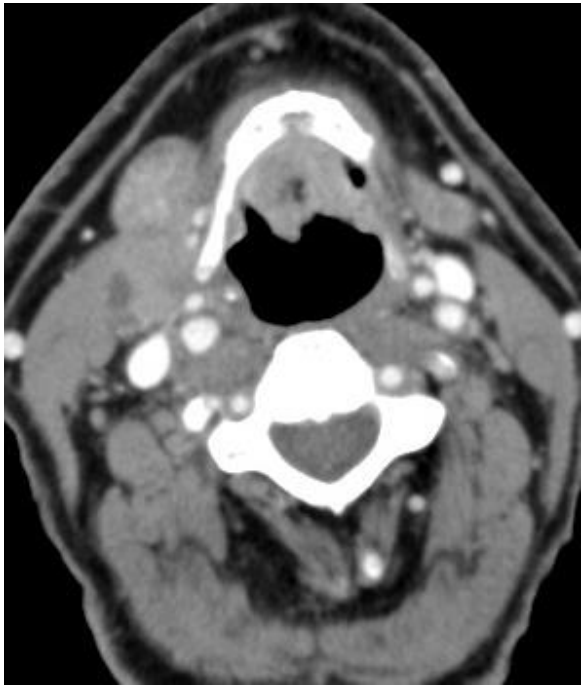
Larynx carcinoma (case)
-
What imaging do you order for assessment of loco-regional extensions?

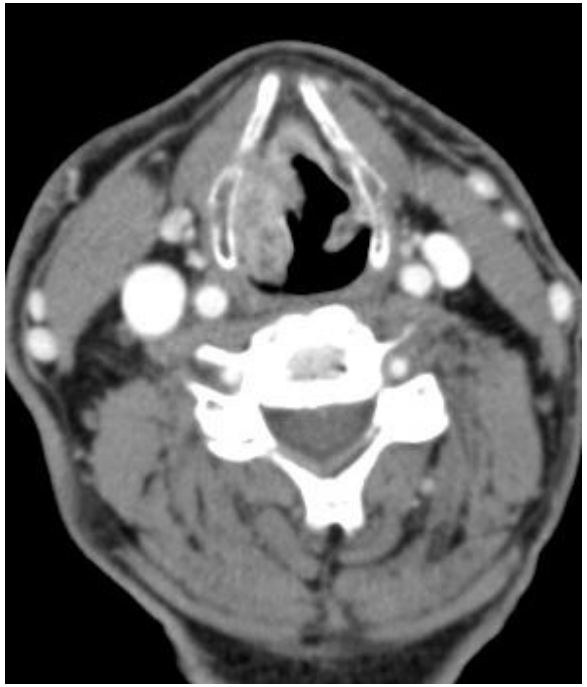
A. CT
B. MRI
C. CT + MRI
D. CT + US
E. CT + PET
F. MRI + PET
G. MRI + US
H. CT + US + PET
I. MRI + US + PET

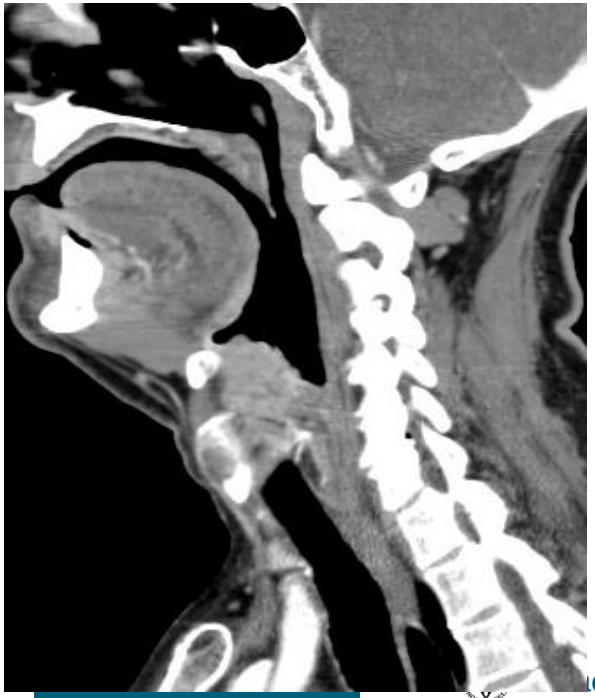


Stage?



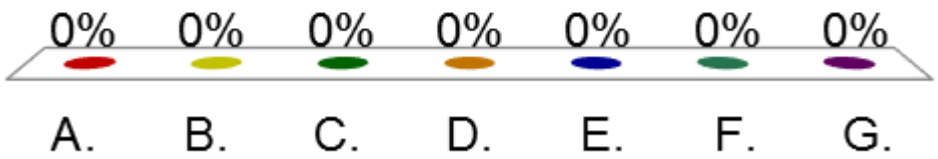






Carcinoma larynx (case)
-
How do you stage this tumor?

A. T1N1
B. T1N2c
C. T2N1
D. T2N2b
E. T2N2c
F. T3N2b
G. T3N2c

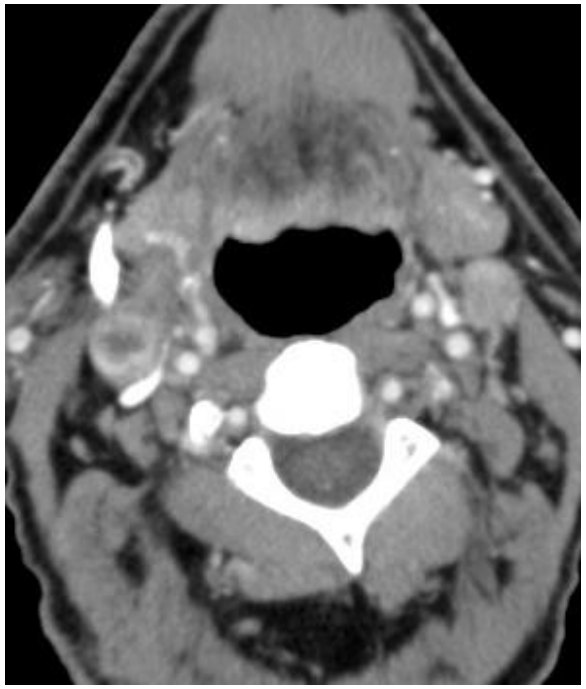


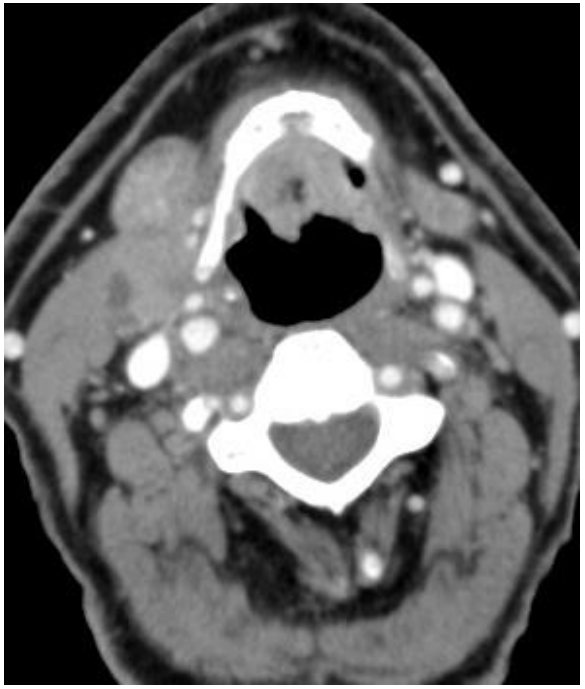
US + cytology:

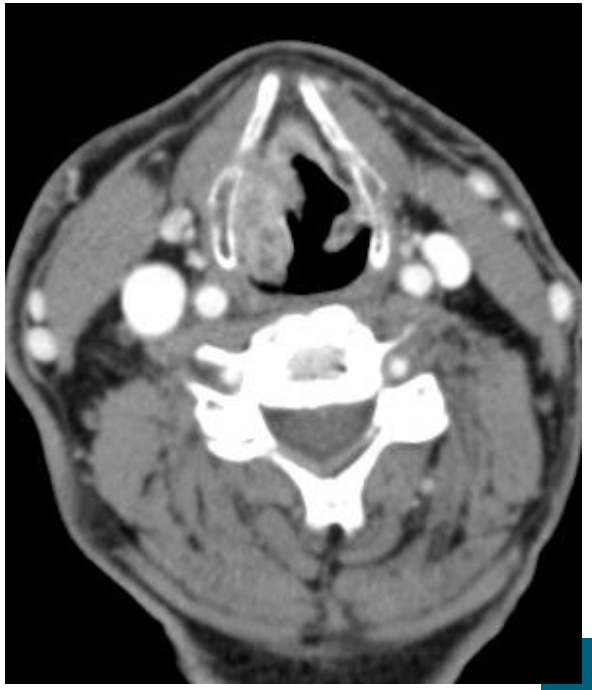
Level II left:
squamous cells with severe atypia

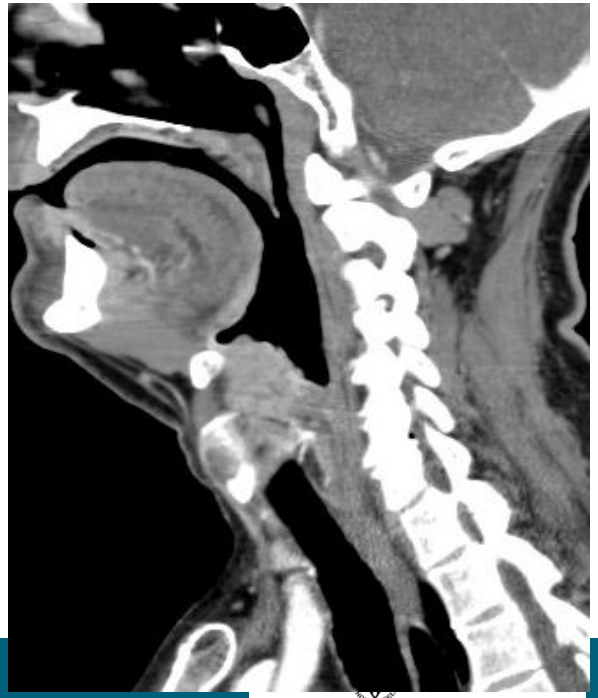
Level II right:
few cells, no malignancy

CT chest: normal



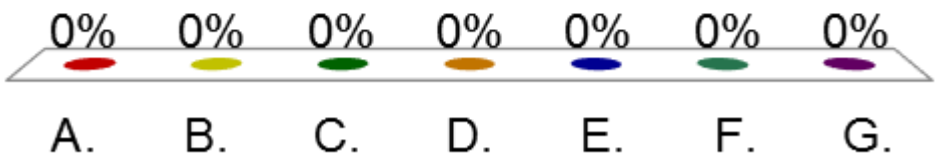




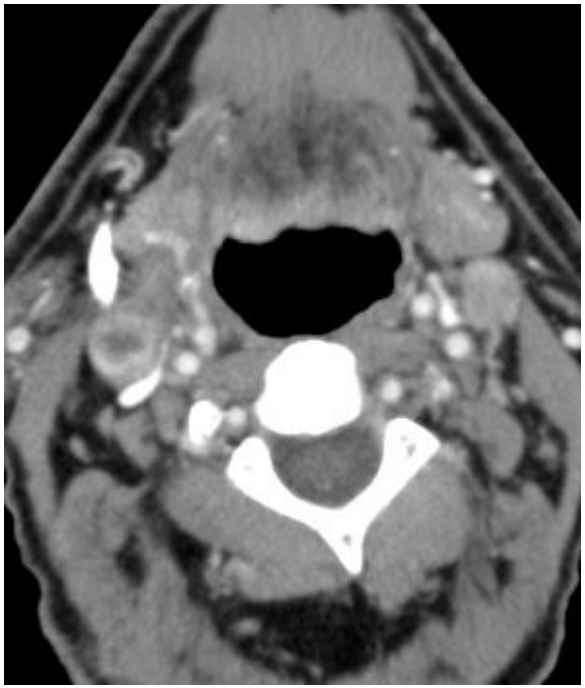
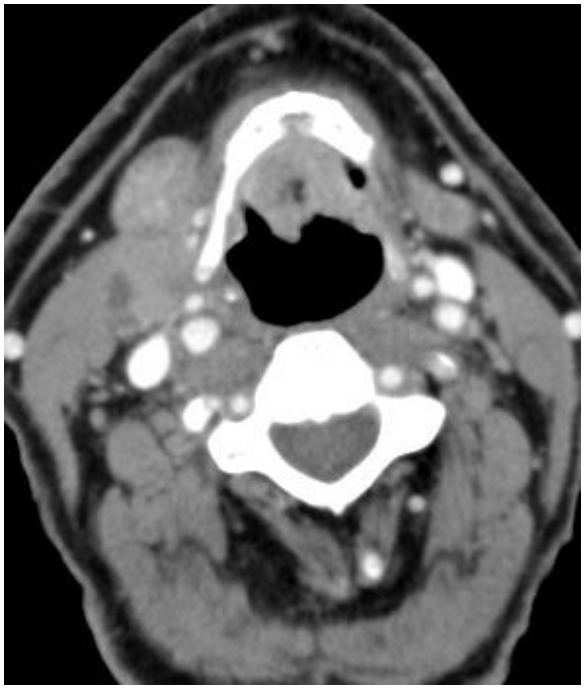
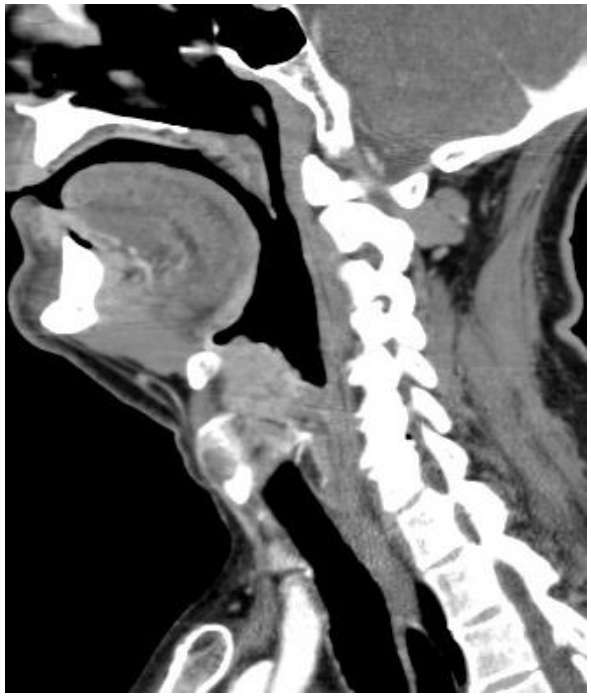


Carcinoma larynx (case)
-
How do you stage this tumor?

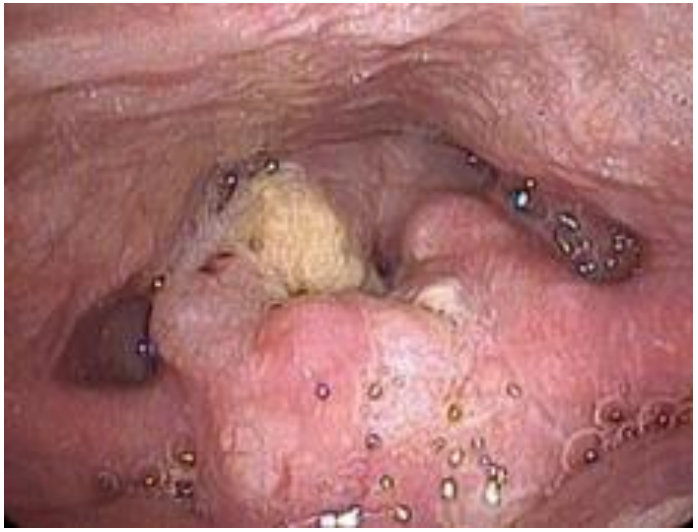
A. T1N1M0
B. T1N2cM0
C. T2N1M0
D. T2N2bM0
E. T2N2cM0
F. T3N2bM0
G. T3N2cM0

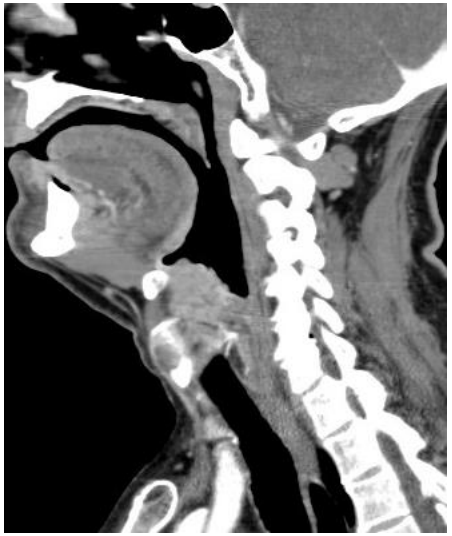


Larynx carcinoma: T3N2cM0

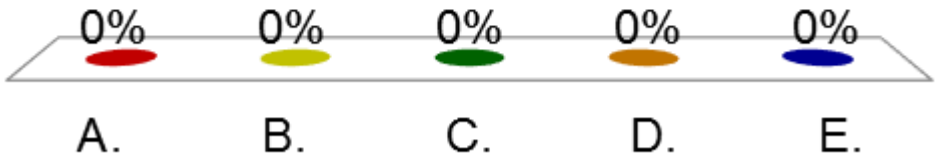
Larynx carcinoma: T3N2cM0





What treatment do you recommend?

A. Partial laryngectomy
B. Laser surgery
C. Radiotherapy
D. Radiotherapy + cetuximab
E. Chemoradiation

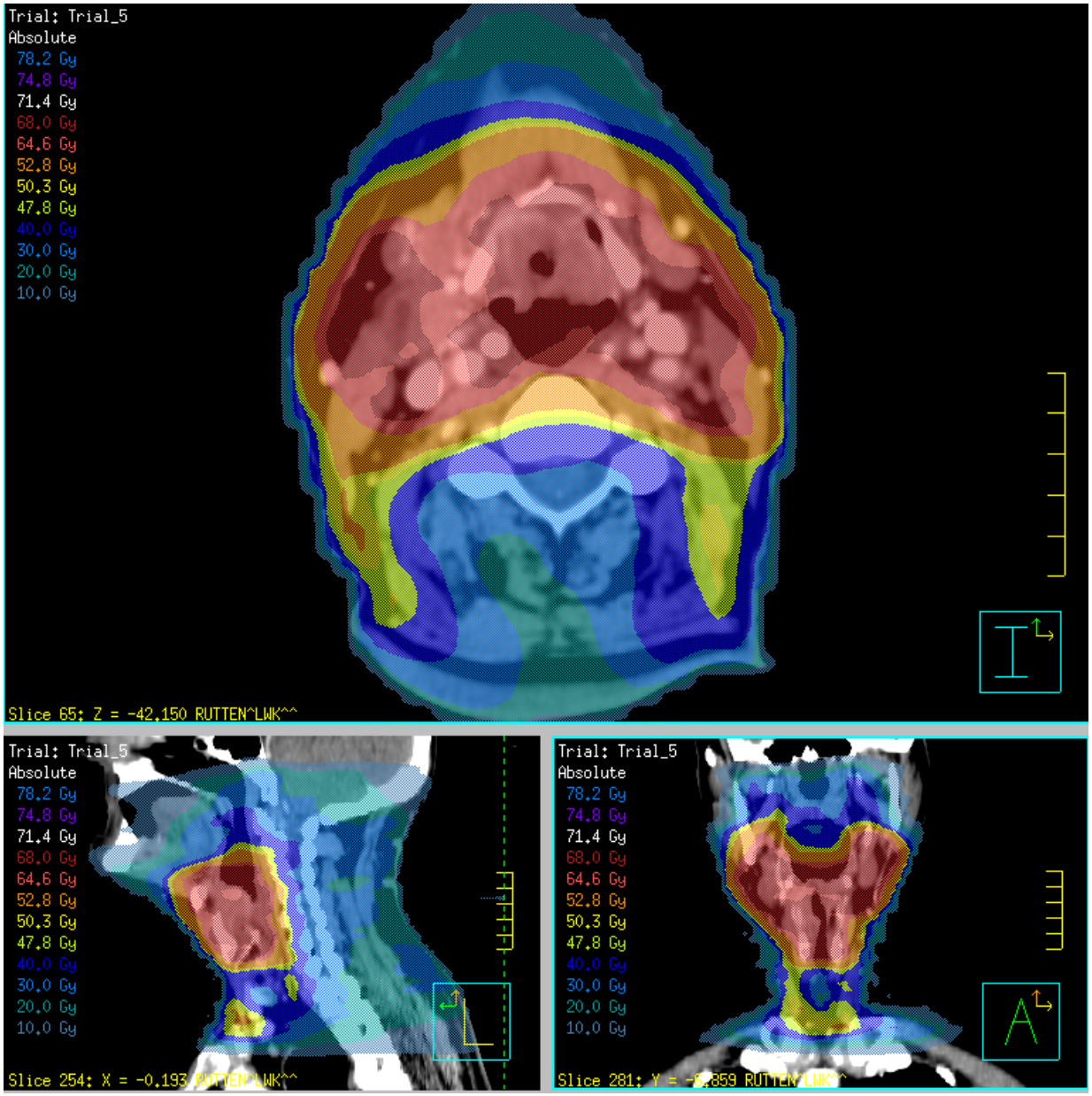


Patient was offered accelerated radiotherapy

Primary tumor + metastatic nodes: 68 Gy in 34 fr, 6x/wk

Neck (L + R), levels II-III-IV-V and retrostyloid: 50.3 Gy

VMAT-SIB technique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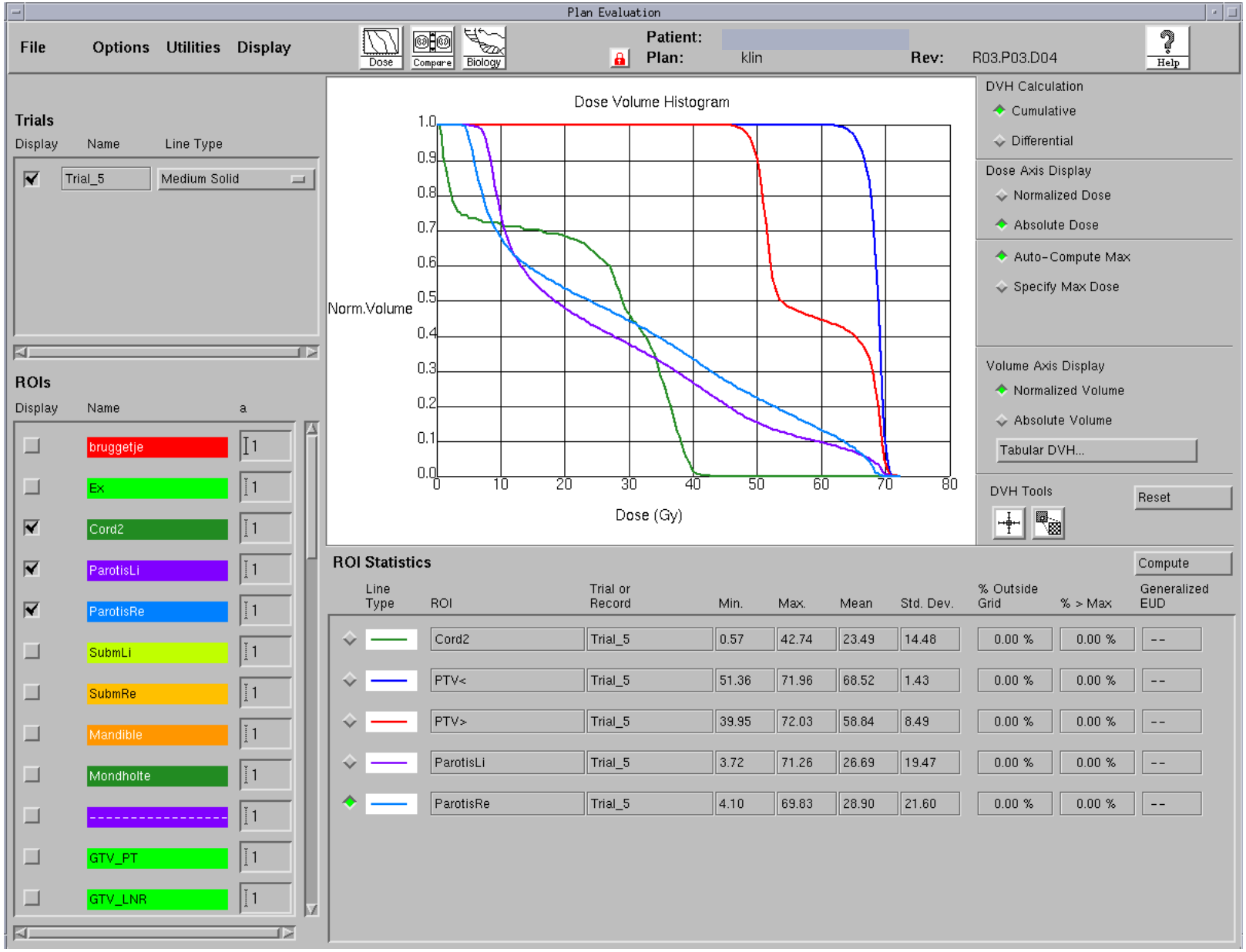
Absolute
78.2 Gy
74.8 Gy
71.4 Gy
68.0 Gy
64.6 Gy
52.8 Gy
50.3 Gy
47.8 Gy
40.0 Gy
30.0 Gy
20.0 Gy
10.0 Gy
Slice 65: Z = -42,150 RUTTEN^LWK^^
Trial: Trial_5
Absolute
78.2 Gy
74.8 Gy
71.4 Gy
68.0 Gy
64.6 Gy
52.8 Gy
50.3 Gy
47.8 Gy
40.0 Gy
30.0 Gy
20.0 Gy
10.0 Gy
Slice 254: X = -0,193 RUTTEN^LWK^^
Trial: Trial_5
Absolute
78.2 Gy
74.8 Gy
71.4 Gy
68.0 Gy
64.6 Gy
52.8 Gy
50.3 Gy
47.8 Gy
40.0 Gy
30.0 Gy
20.0 Gy
10.0 Gy
Slice 281: Y = -3,859 RUTTEN^LWK^^


Plan Evaluation
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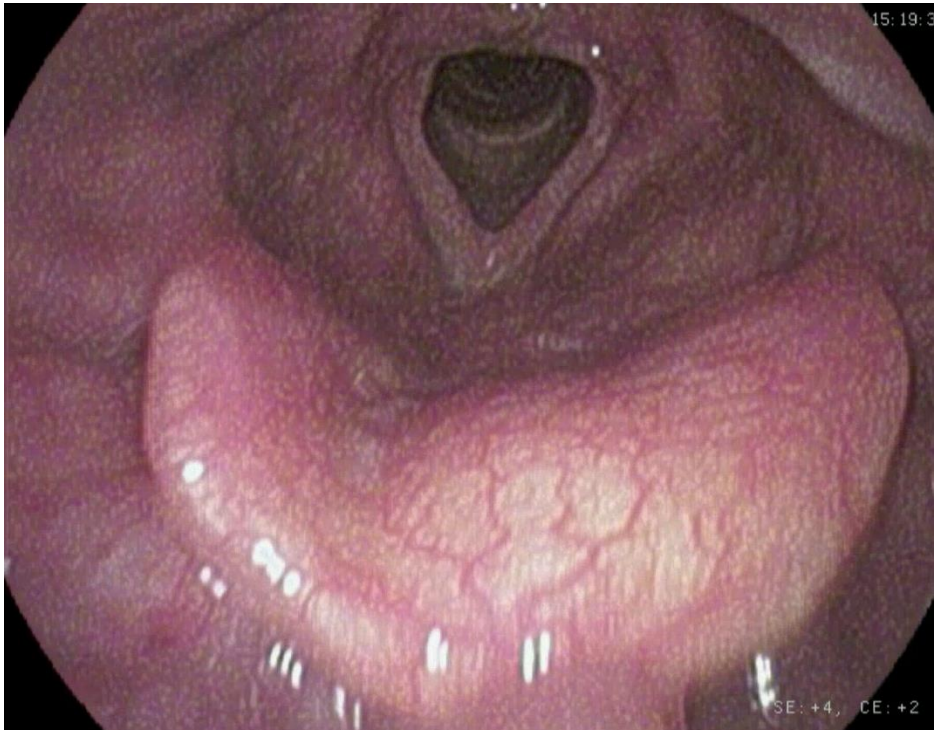
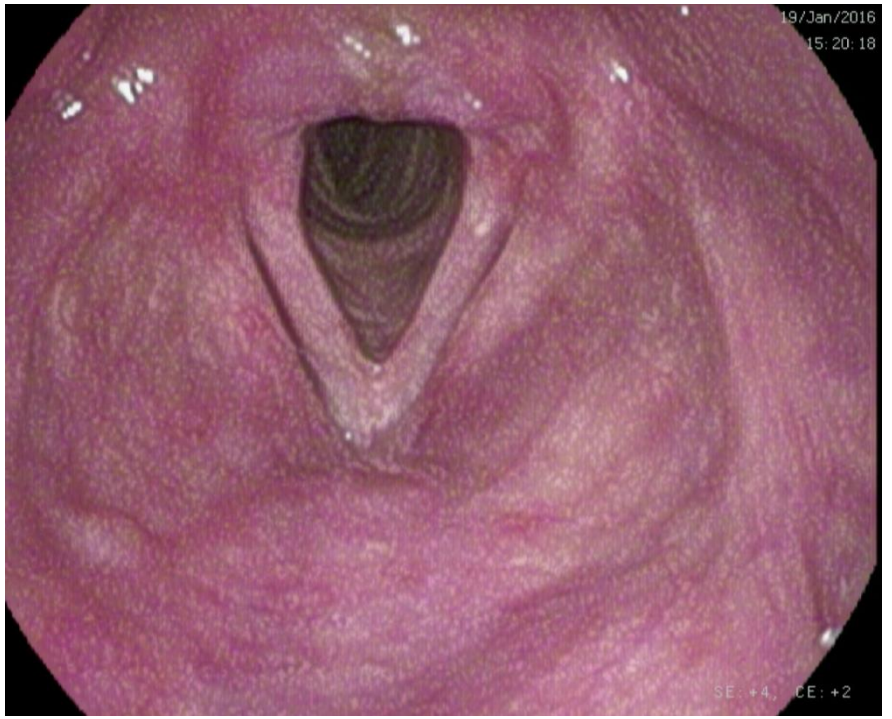
Cord2
ParotisLi
ParotisRe
SubmLi
SubmRe
Mandible
Mondholte
GTV_PT
GTV_LNR
Dose Volume Histogram
Norm.Volume
Dose (Gy)
DVH Calculation
Cumulative
Differential
Dose Axis Display
Normalized Dose
Absolute Dose
Auto-Compute Max
Specify Max Dose
Volume Axis Display
Normalized Volume
Absolute Volume
Tabular DVH...
DVH Tools
Reset
ROI Statistics
Compute
Line Type
ROI
Trial or Record
Min.
Max.
Mean
Std. Dev.
% Outside Grid
% > Max
Generalized EUD
Cord2 Trial_5 0.57 42.74 23.49 14.48 0.00 % 0.00 % --
PTV< Trial_5 51.36 71.96 68.52 1.43 0.00 % 0.00 % --
PTV> Trial_5 39.95 72.03 58.84 8.49 0.00 % 0.00 % --
ParotisLi Trial_5 3.72 71.26 26.69 19.47 0.00 % 0.00 % --
ParotisRe Trial_5 4.10 69.83 28.90 21.60 0.00 % 0.00 % --

One year after completion of treatment





ELSEVIER

Radiotherapy and Oncology 63 (2002) 299–307

RADIOTHERAPY & ONCOLOGY
JOURNAL OF THE EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

www.elsevier.com/locate/radonline

Carcinoma of the larynx: the Dutch national guideline for diagnostics, treatment, supportive care and rehabilitation

- **A function preserving treatment should be the first choice for every patient with a larynx carcinoma.**
- **Surgery is used only if the expected functional outcome is poor or for large tumor volumes or for patients with severe stridor while adequate endoscopic debulking is not possible.**

American Society of Clinical Oncology Clinical Practice Guideline for the use of Larynx-Preservation Strategies in the Treatment of Laryngeal Cancer

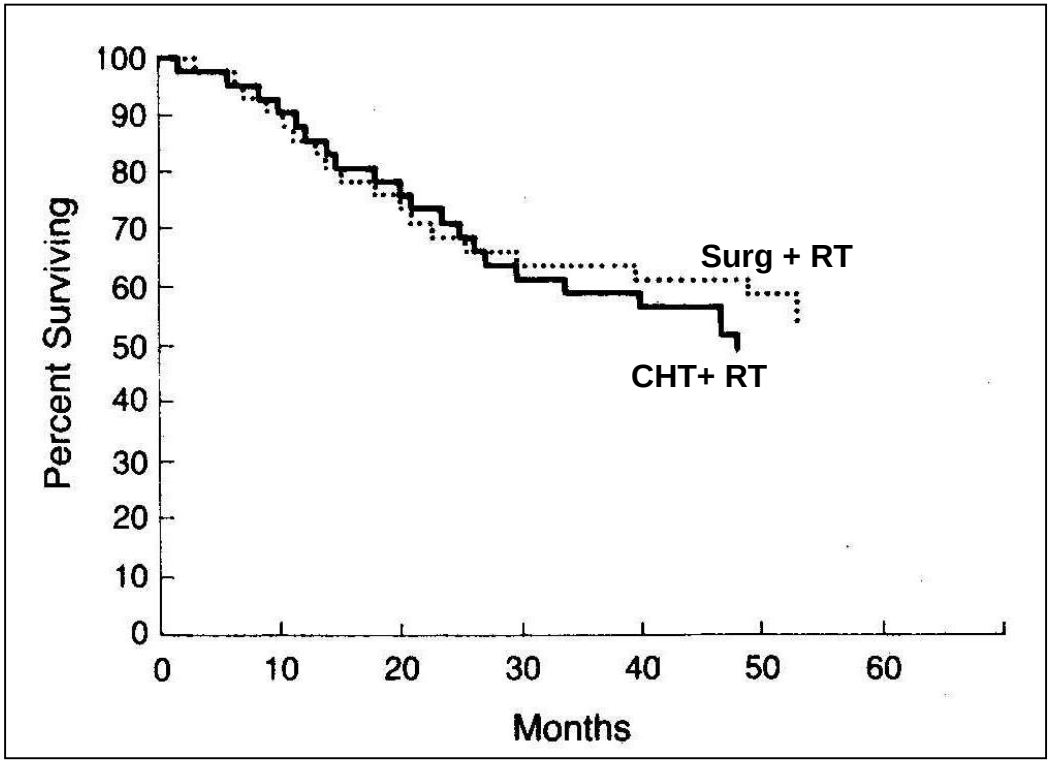
Journal of Clinical Oncology 24:3693-3704, 2006

- **Evidence supports the use of larynx-preservation approaches for appropriately selected patients.**
- **For most patients with T3 or T4 disease without tumor invasion through cartilage into soft tissues, a larynx-preservation approach is an appropriate, standard treatment option.....**

Larynx preservation therapy is recommended for advanced larynx carcinoma:
-
What is the cost in terms of 5-year survival ?

A. 0%
B. 5%
C. 10%
D. 20%

VA study: laryngectomy + RT vs. neoadjuvant CHT + RT



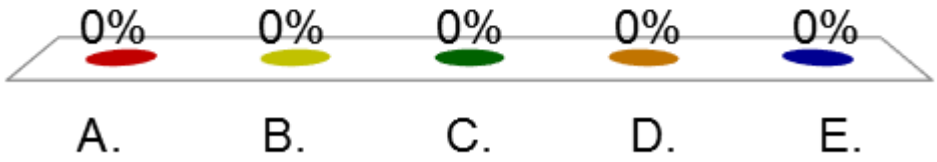
Distribution by T-stage:

T1,2	9%
T3	65%
T4	26%

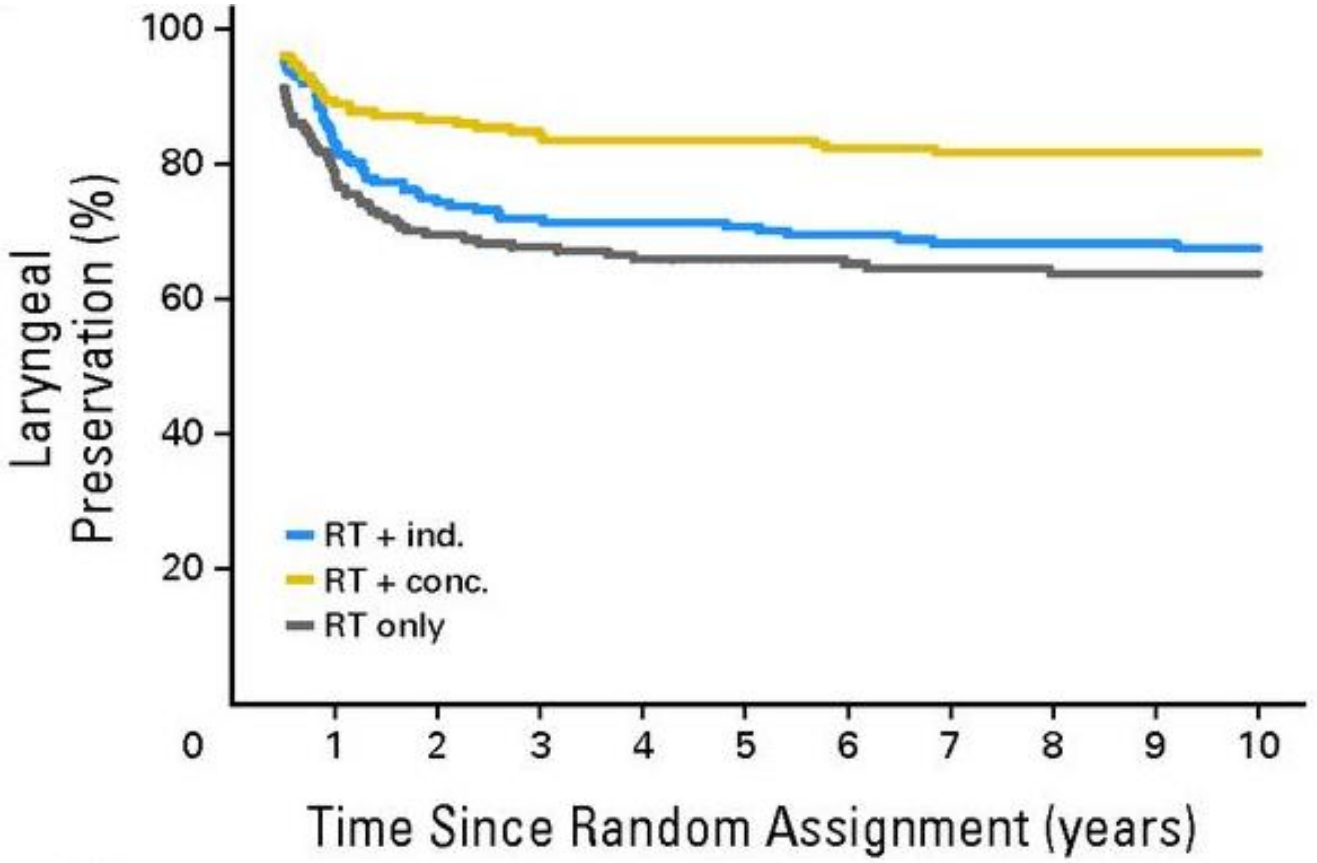
VA. NEJM, 1991

Larynx preservation therapy is recommended for advanced (T2-T4) larynx carcinoma:
-
What is the larynx preservation rate after chemoradiation ?

A. 40 - 50%
B. 50 - 60%
C. 60 - 70%
D. 70 - 80%
E. > 80%



Larynx preservation: larynx carcinoma

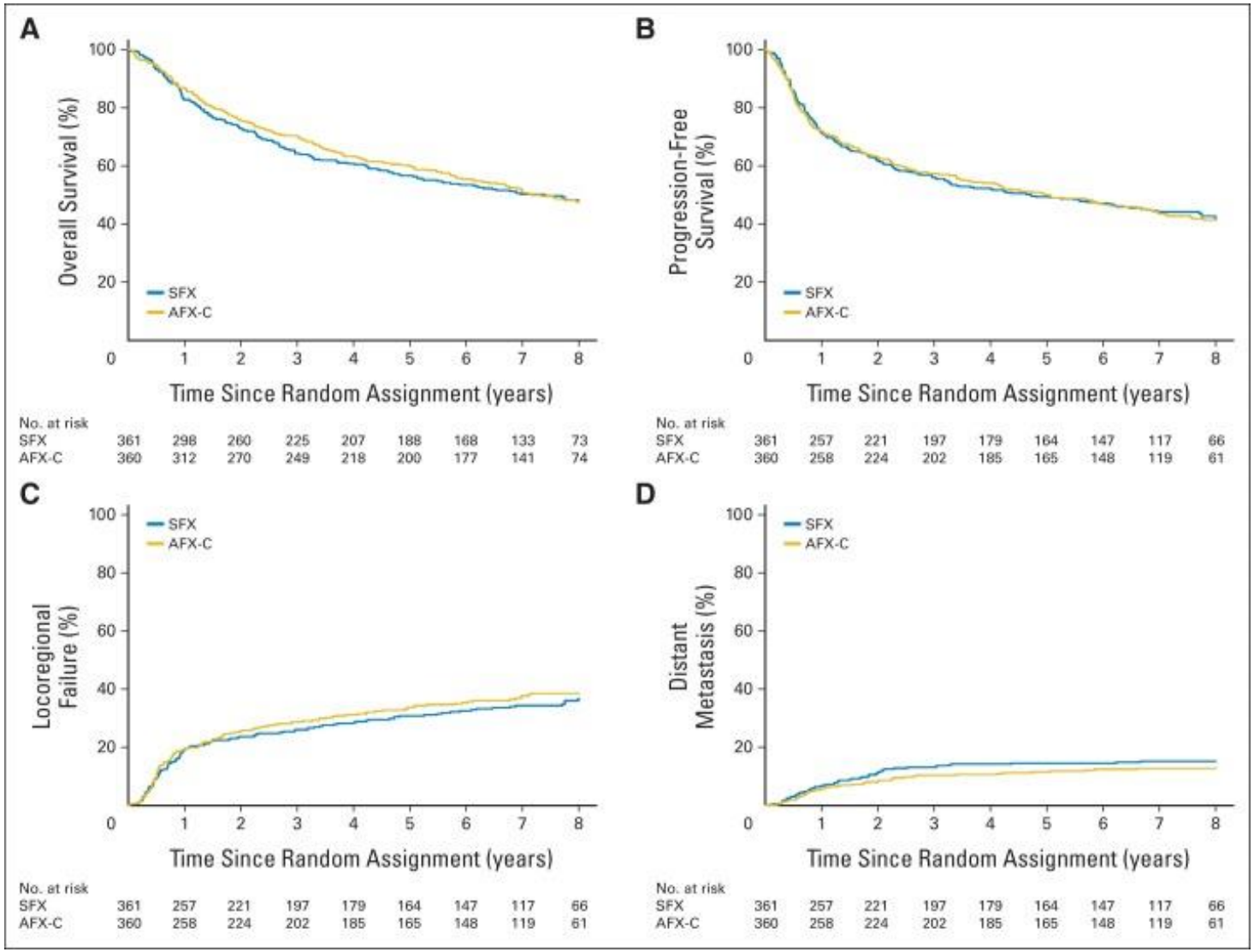


5-yr-overall survival:

Radiotherapy with concurrent cisplatin	**54%**
Radiotherapy with neoadjuvant chemotherapy	**58%**
Conventional radiotherapy alone	**55%**

Forastiere et al. NEJM, 2003; JCO, 2013

Accelerated vs conventionally fractionated chemoradiation



Nguyen-Tan et al. J. Clin. Oncol. 2014

ARCON for T2-4 squamous cell carcinoma of the larynx

Randomization
345 pts

174 → **Accelerated Radiotherapy**

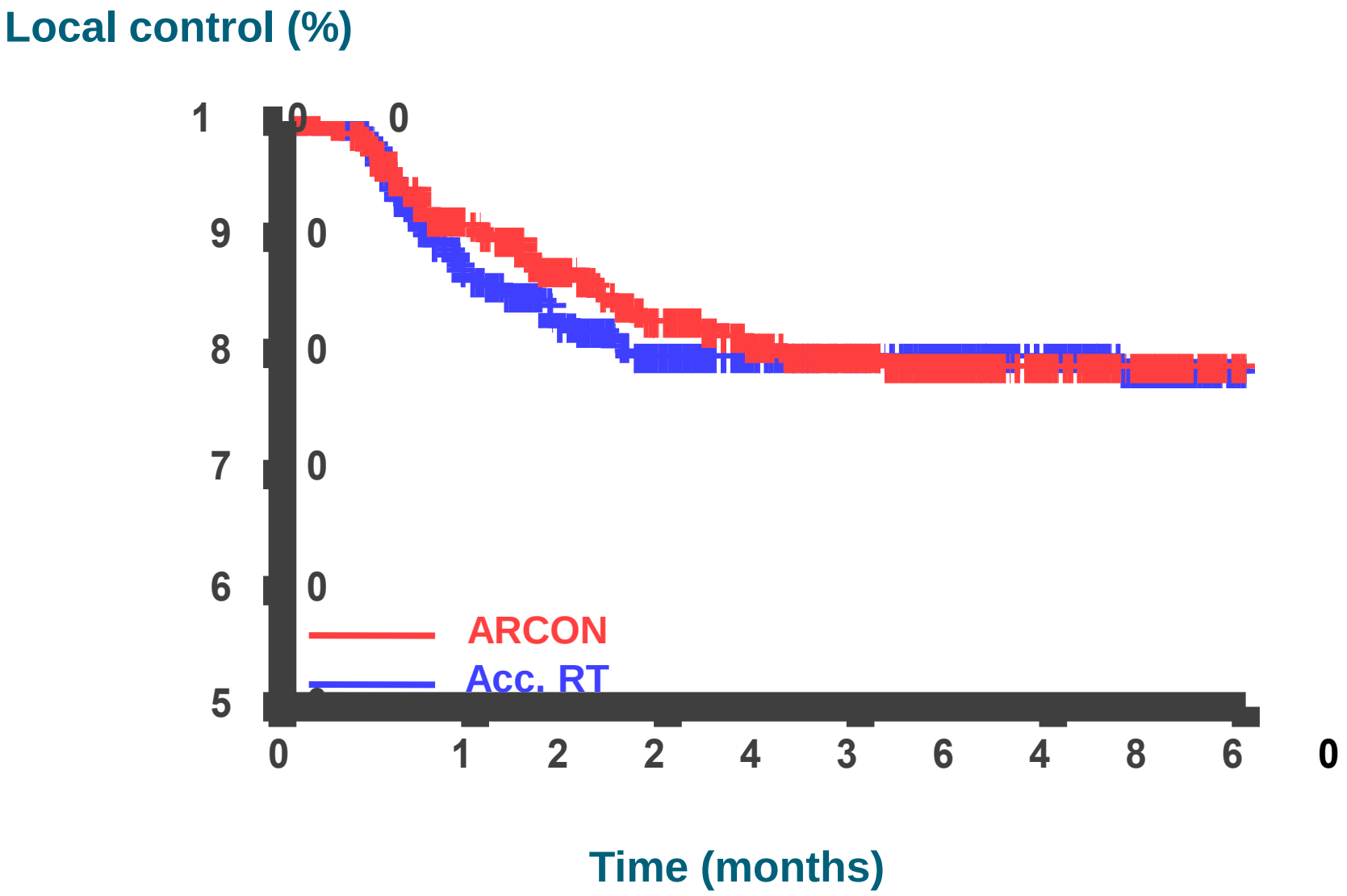
171 → **Accelerated Radiotherapy + carbogen and nicotinamide**

Fractionation schedule:

	primary	metastatic nodes
Acc. RT	68 Gy	68 Gy
ARCON	64 Gy*	68 Gy

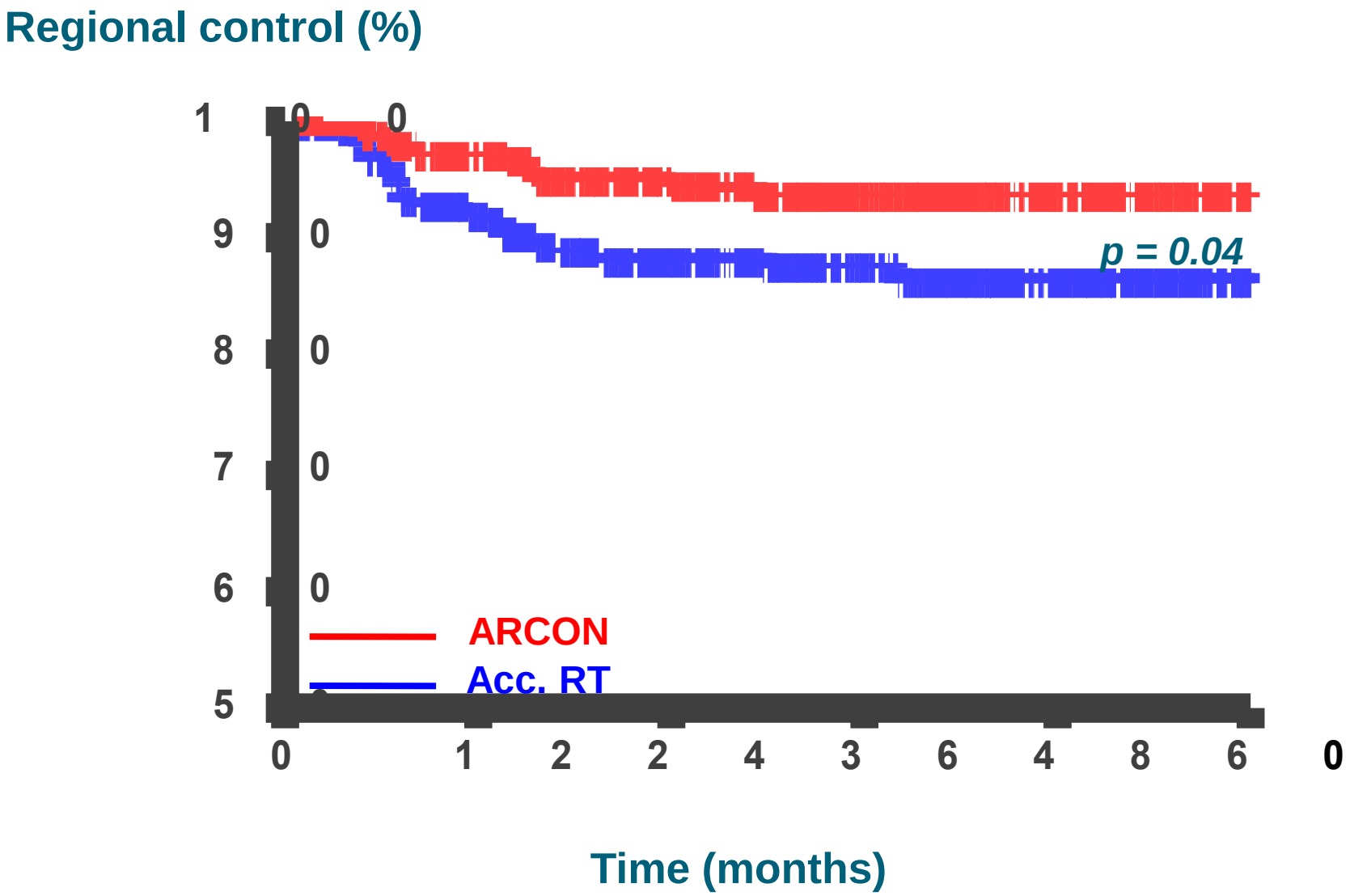
*Aim: improve tumor control with equal toxicity between arms!

ARCON for larynx carcinoma, local control



Janssens et al. JCO 2012

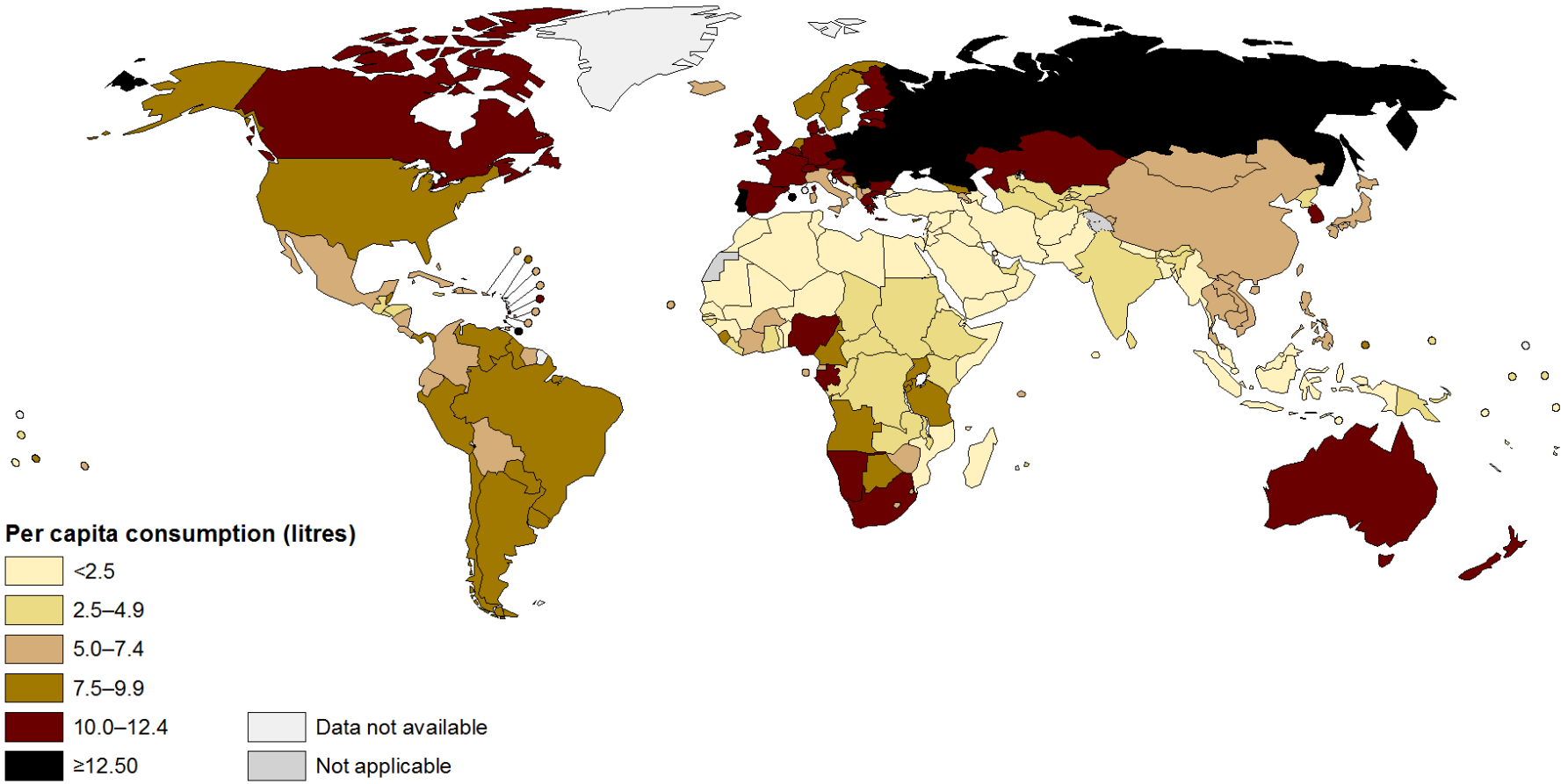
ARCON for larynx carcinoma, regional control



Janssens et al. JCO 2012

CARCINOMA OF THE HYPOPHARYNX

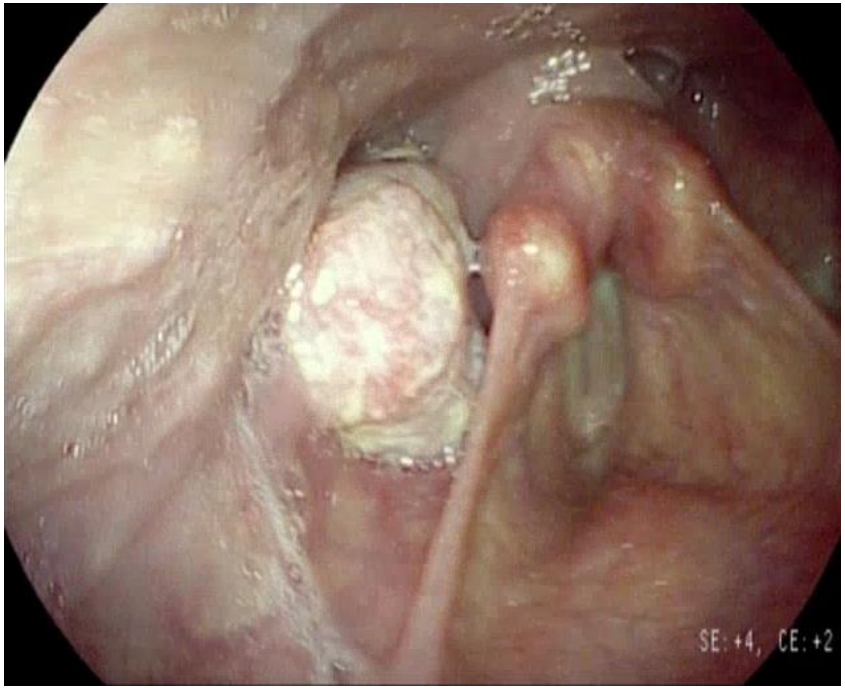
Total alcohol per capita (15+ years) consumption, in litres of pure alcohol, 2010

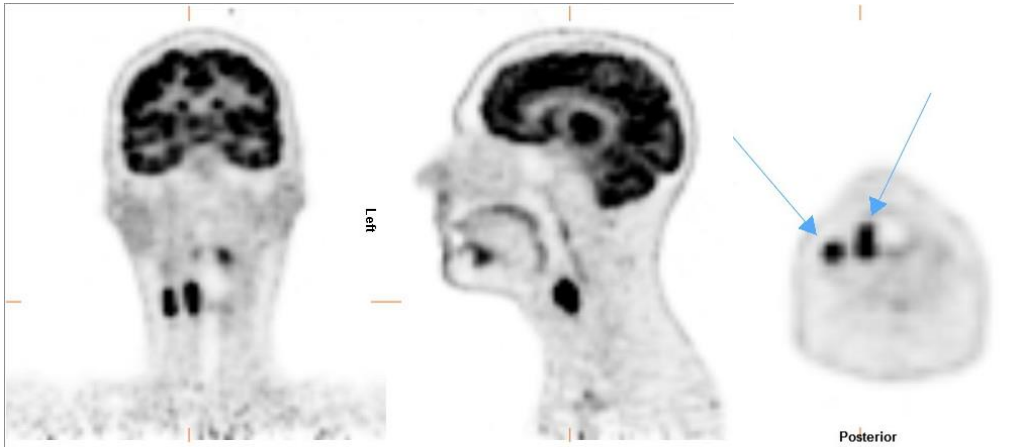


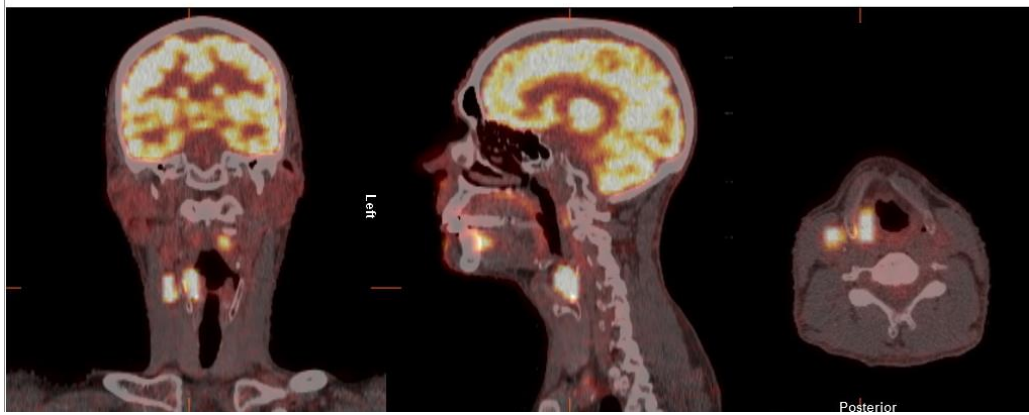
Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

World Health Organization

Hypopharynx cancer T1

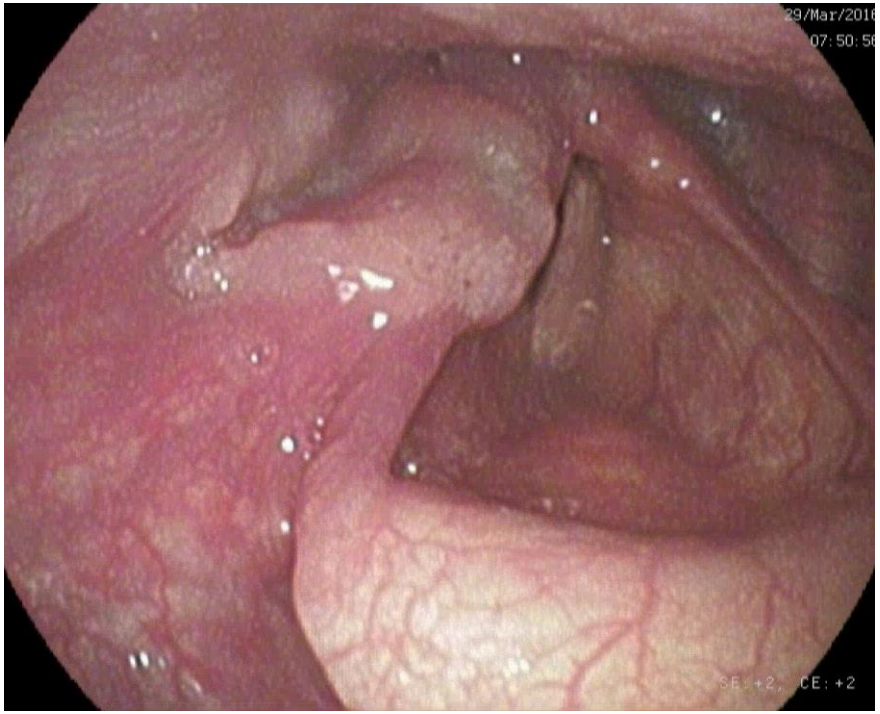


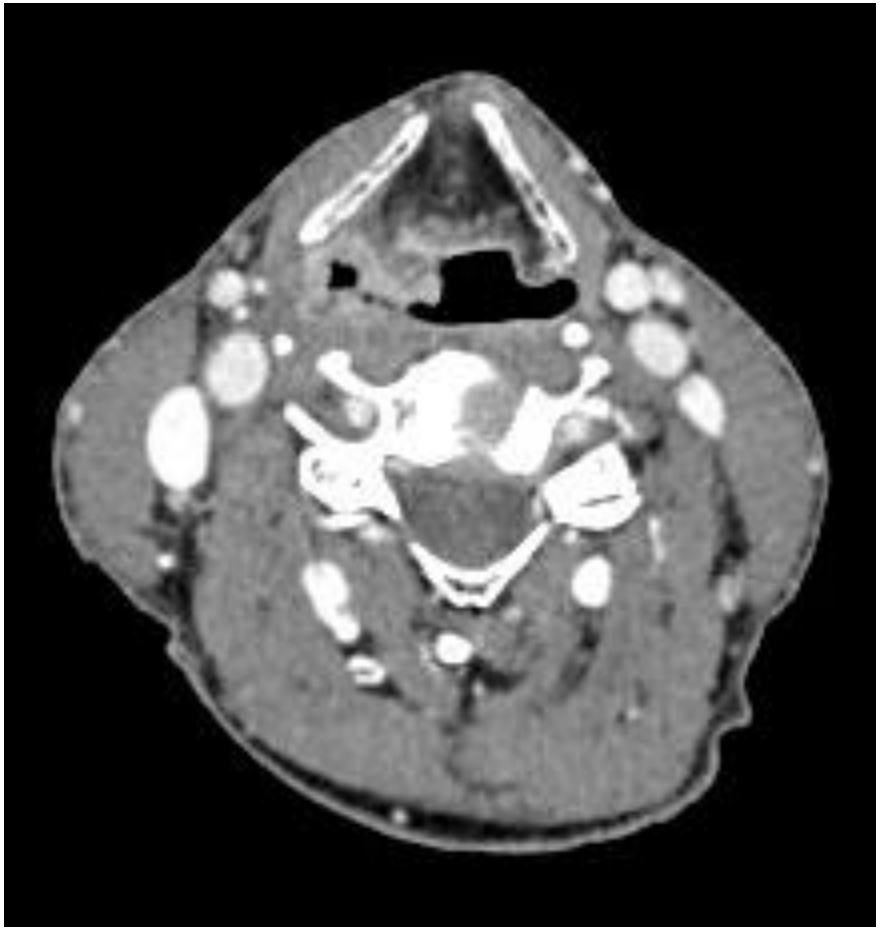




T1: ≤ 2 cm, one subsite

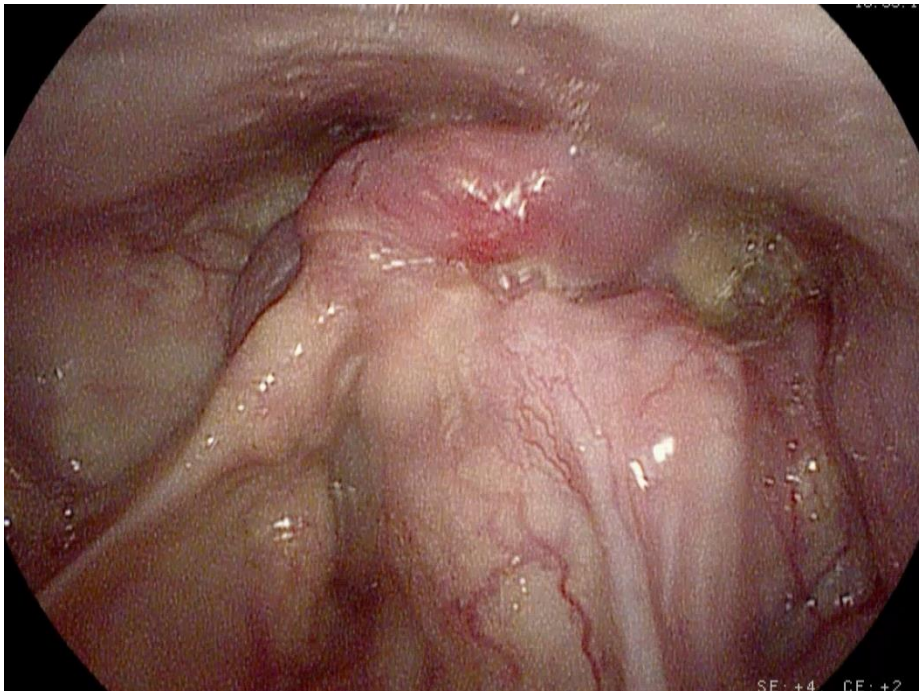
Hypopharynx cancer T2

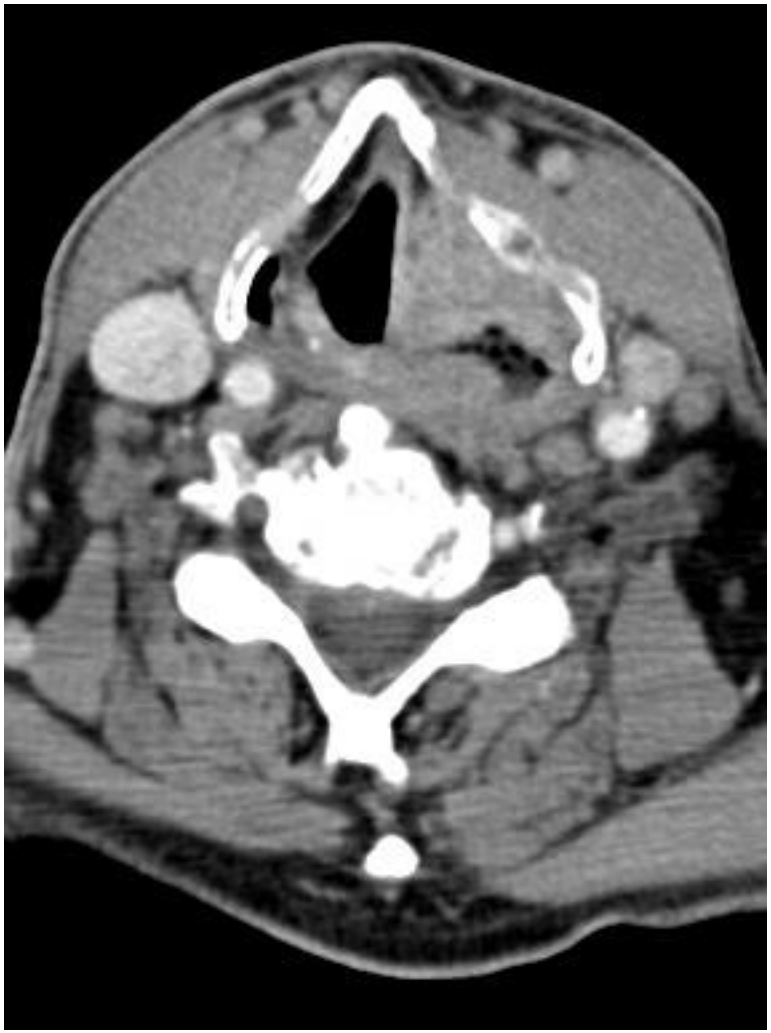




T2: 2-4 cm, > 1 subsite

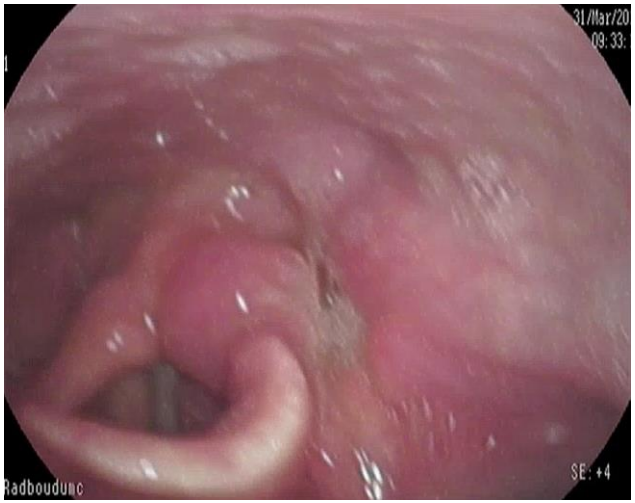
Hypopharynx cancer T3



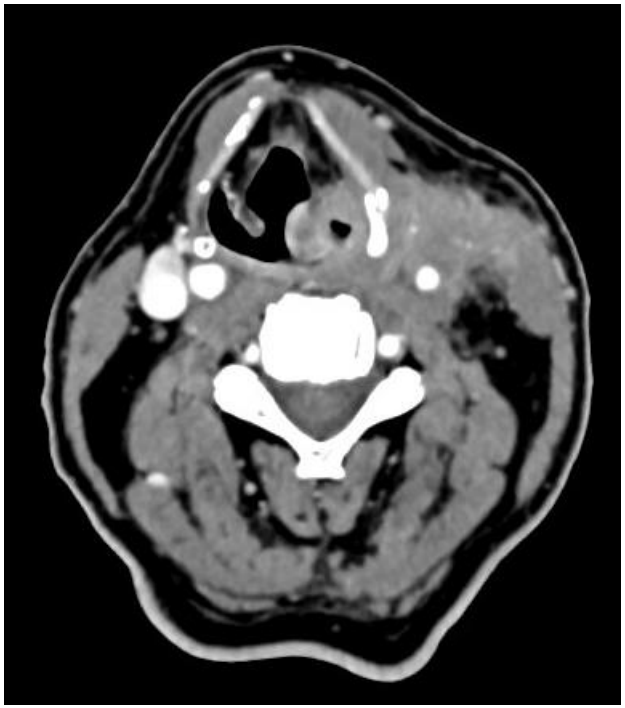


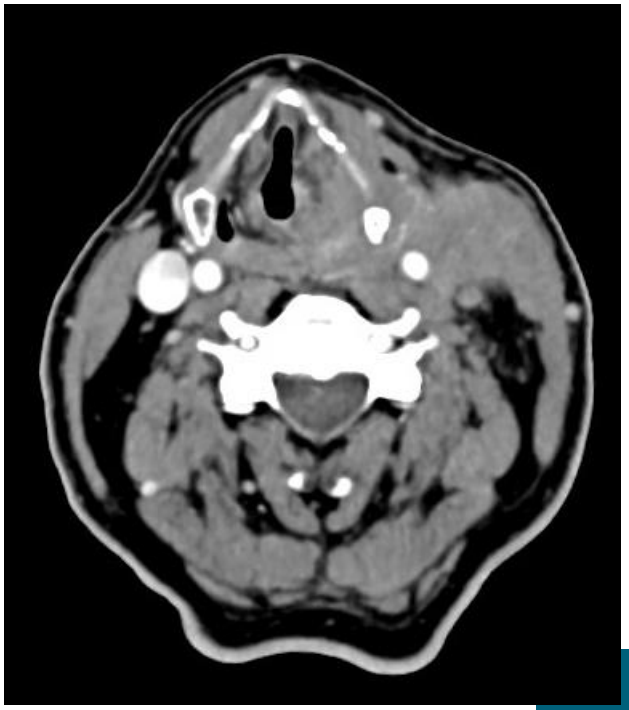
T3: >4 cm,
fixation hemilarynx or
extension esophagus

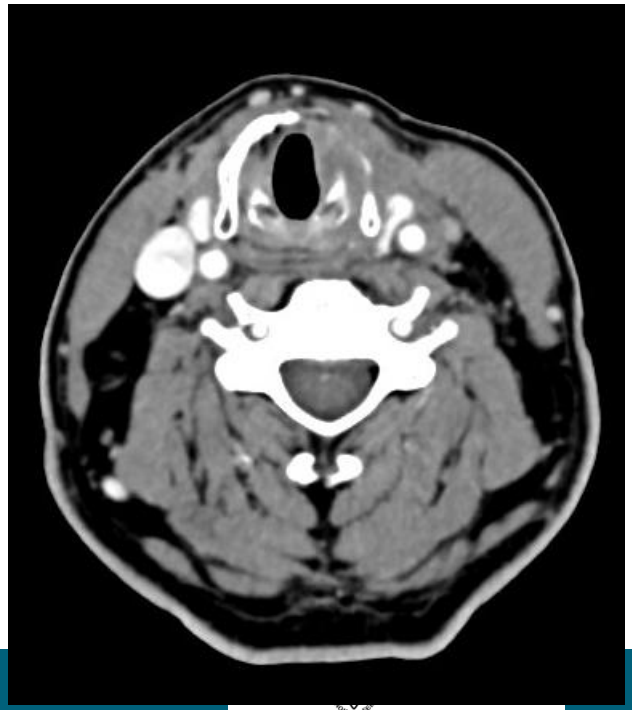
Hypopharynx cancer T4



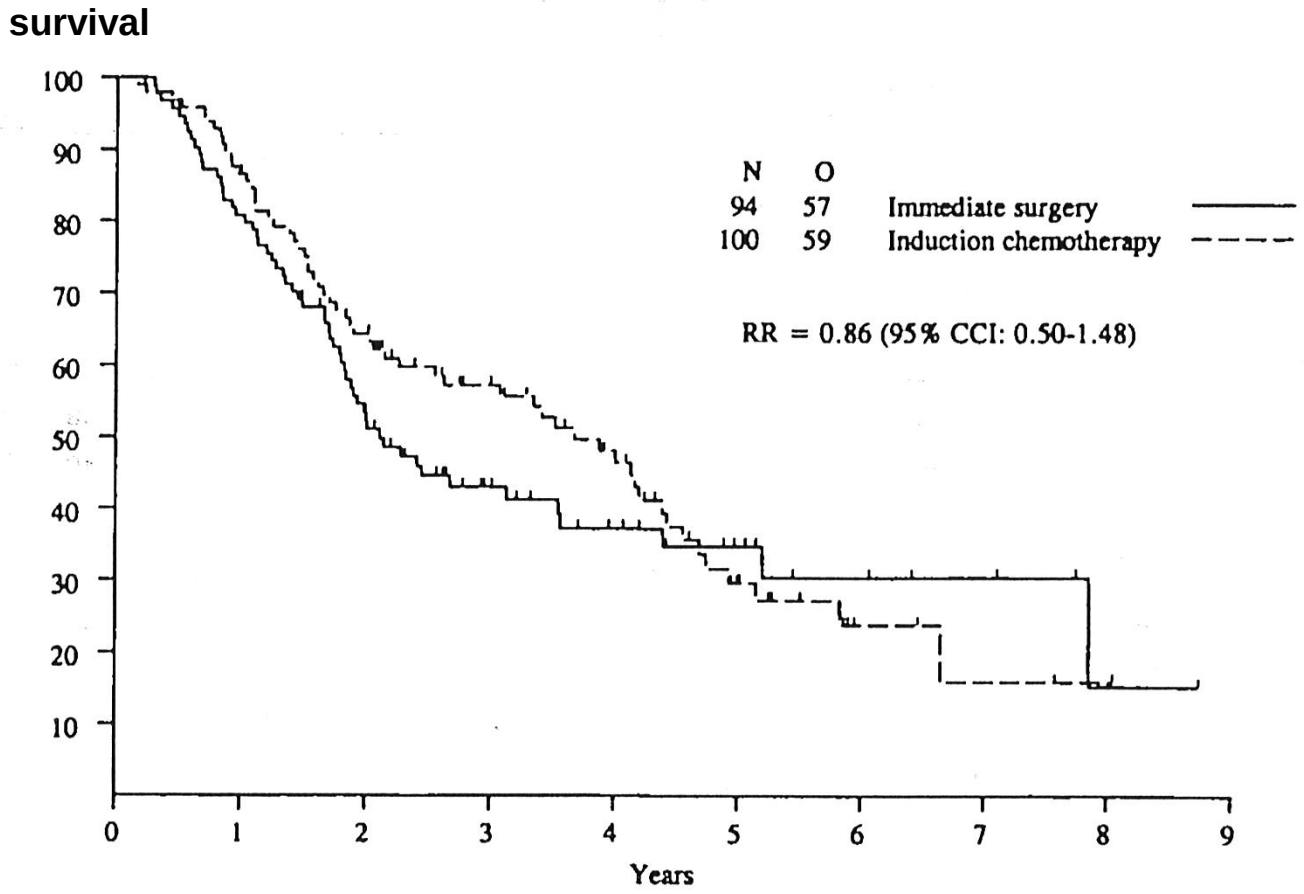
T4a: invades laryngeal cartilage, hyoid bone, thyroid gland, esophagus, soft tissues







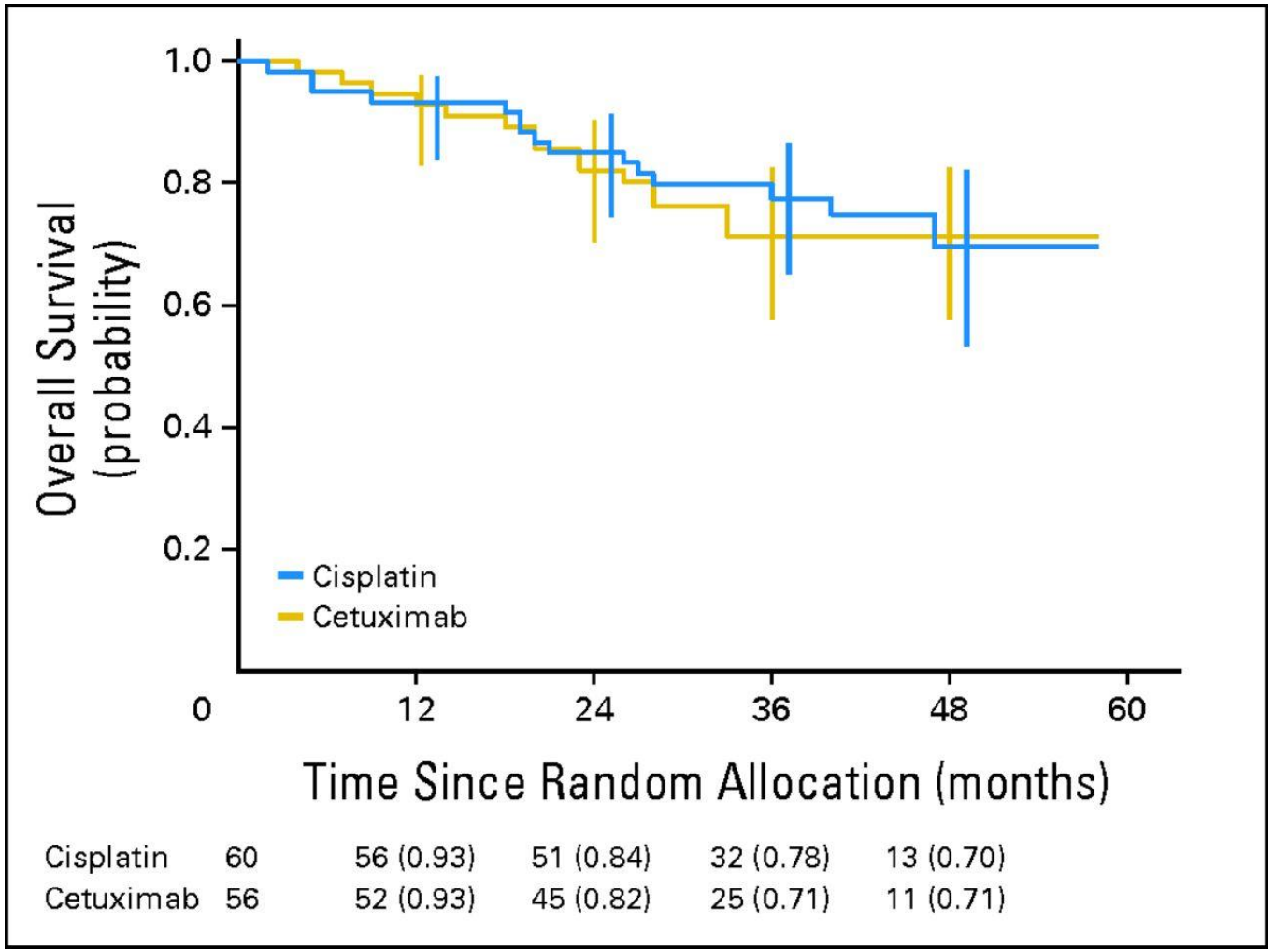
Larynx preservation in pyriform sinus cancer: surgery + postop RT vs induction CHT + RT



Lefebvre et al., JNCI 1996

Induction chemotherapy followed by chemoradiotherapy or bioradiotherapy for larynx preservation

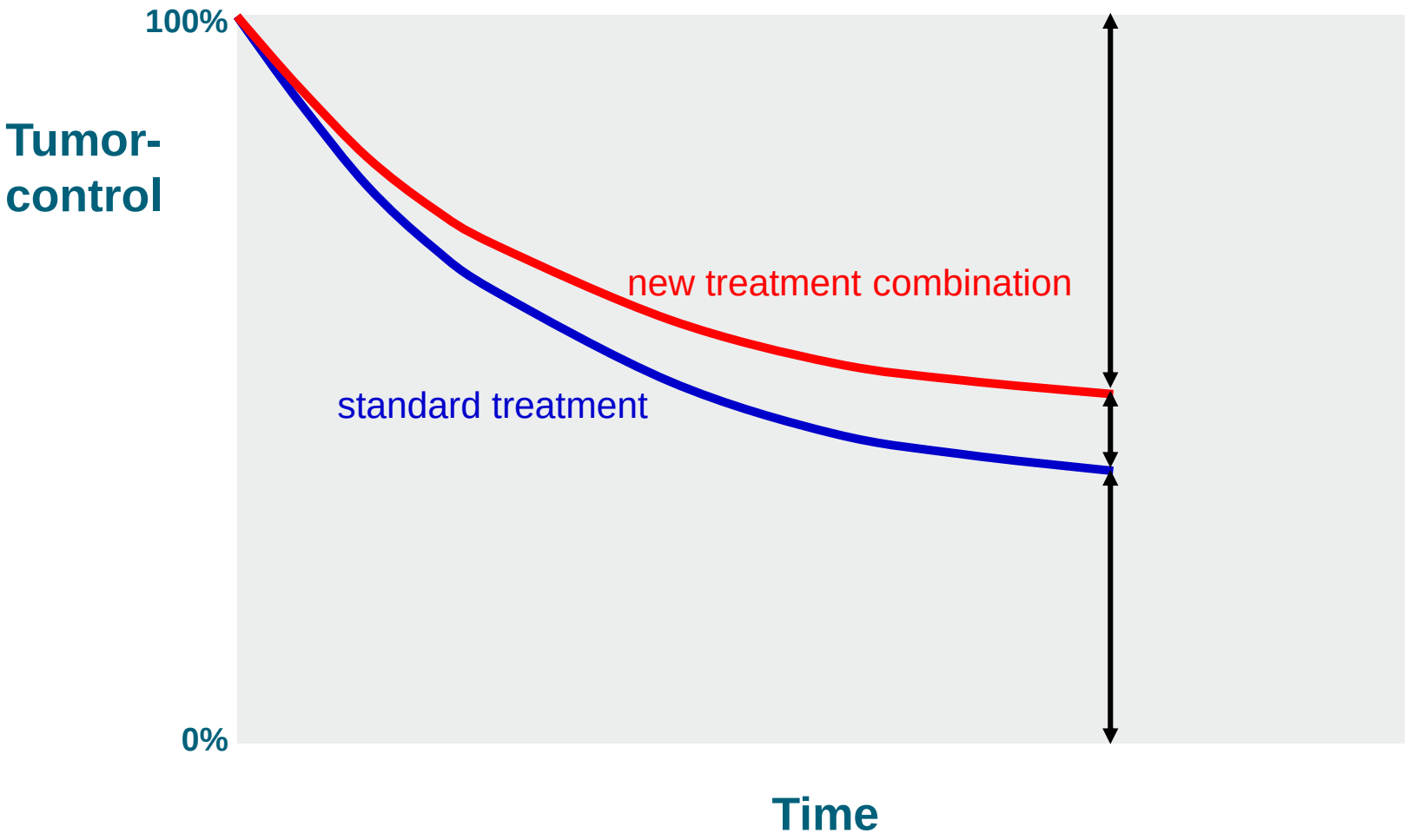
TREMPLIN trial – survival of responders (> 50% volume reduction)



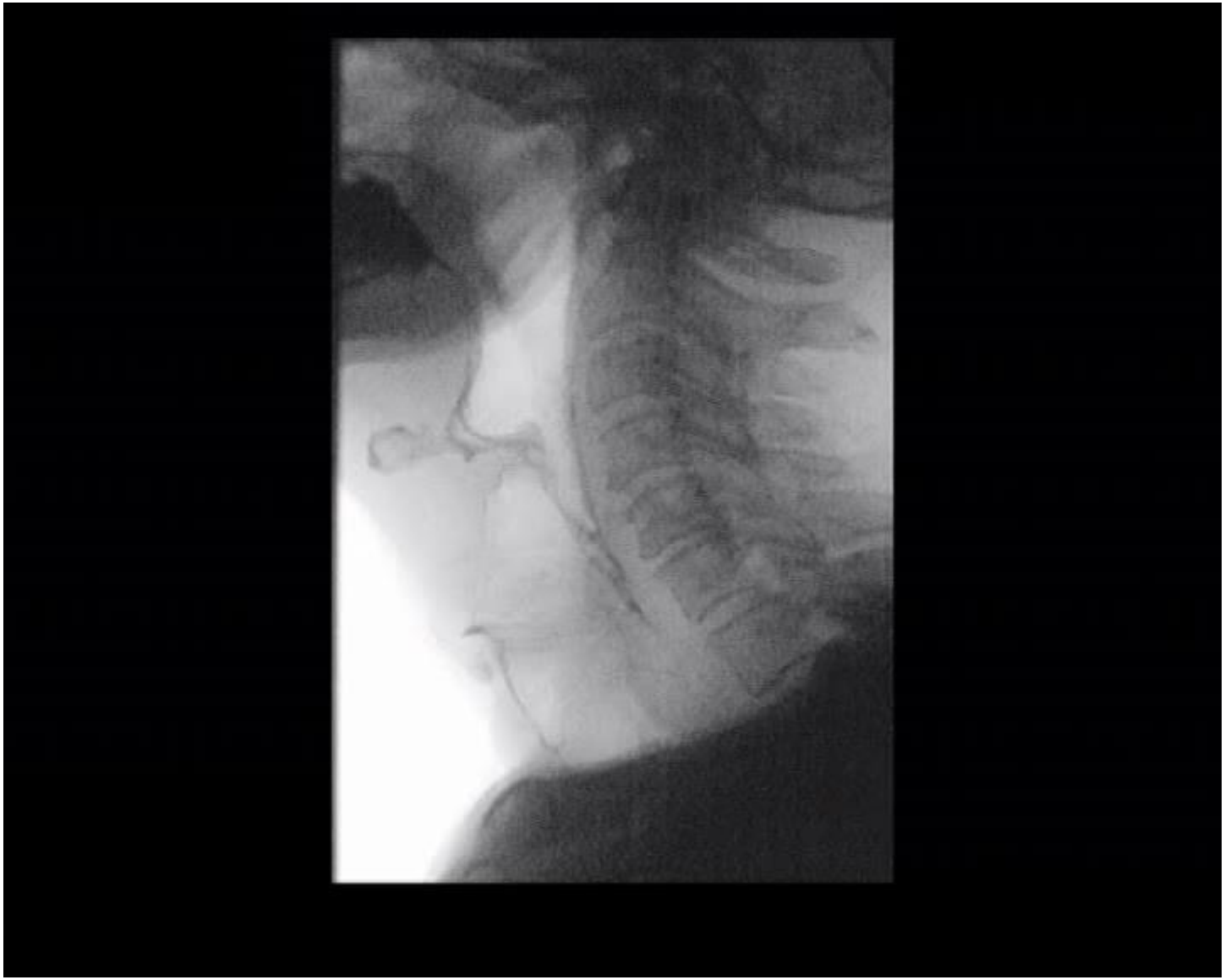
Lefebvre et al., JCO 2013

TOXICITY

New treatment combinations, who profits?



Swallowing act after chemoradiation for larynx carcinoma



Reporting of late morbidity: deficiencies

- *Early reports: insufficient length of follow-up*
- *Incomplete reporting*
- *Pooled data for multiple toxicity items*
- *Crude rates*
- *Clinician graded toxicity vs. patient reported outcomes*
- *Differences in scoring/reporting between studies*

Randomized trials testing new strategies for curative treatment of head and neck cancer

Published between 2000 and 2008 in:

- N Engl J Med
- Lancet
- Lancet Oncol
- J Clin Oncol
- Int J Radiat Oncol Biol Phys
- Radiother Oncol

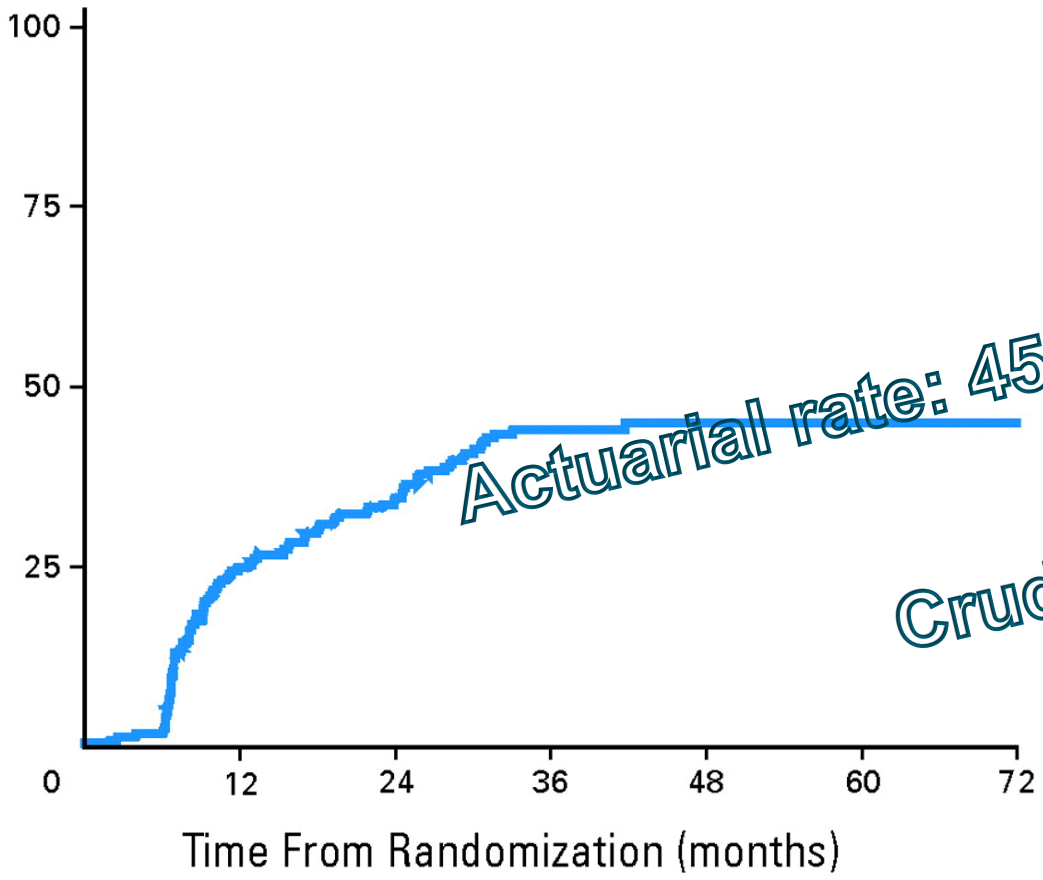
46 studies

→ 31/46 reported late morbidity

→ 20/46 systematic and detailed

→ 10/46 by actuarial method

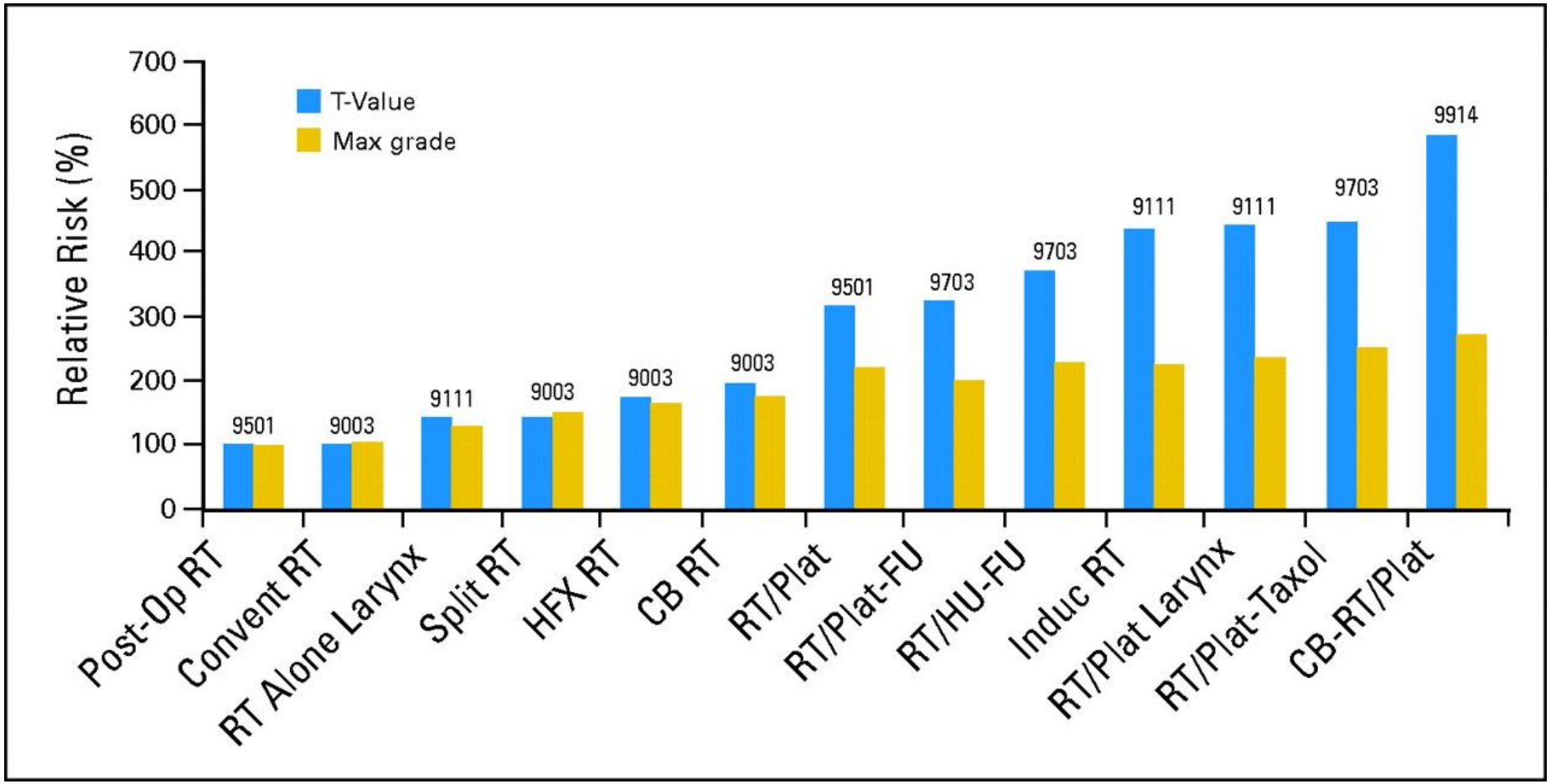
Severe late toxicity (≥ gr 3) after concurrent chemoradiation in RTOG studies 91-11, 97-03 and 99-14.



Patients at risk	230	174	143	81	36	17	11

Machtay et al. J Clin Oncol 2008

A new method for summarizing toxicity scores: “TAME”



Acute toxicity relative risk values (T) vs. relative max-grade values for 13 H&N treatment groups from RTOG trials

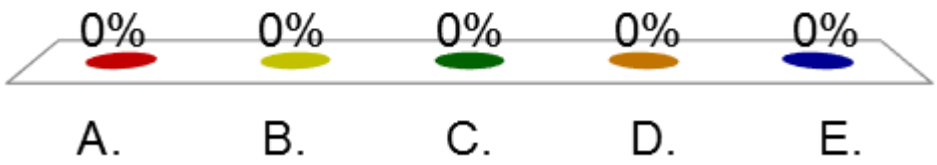
Trotti et al. Lancet Oncol 2007

For a multicenter randomized trial in H&N cancer:

-

What is the average accrual per center per year?

A. < 5
B. 5 - 10
C. 10 - 15
D. 15 - 20
E. > 20

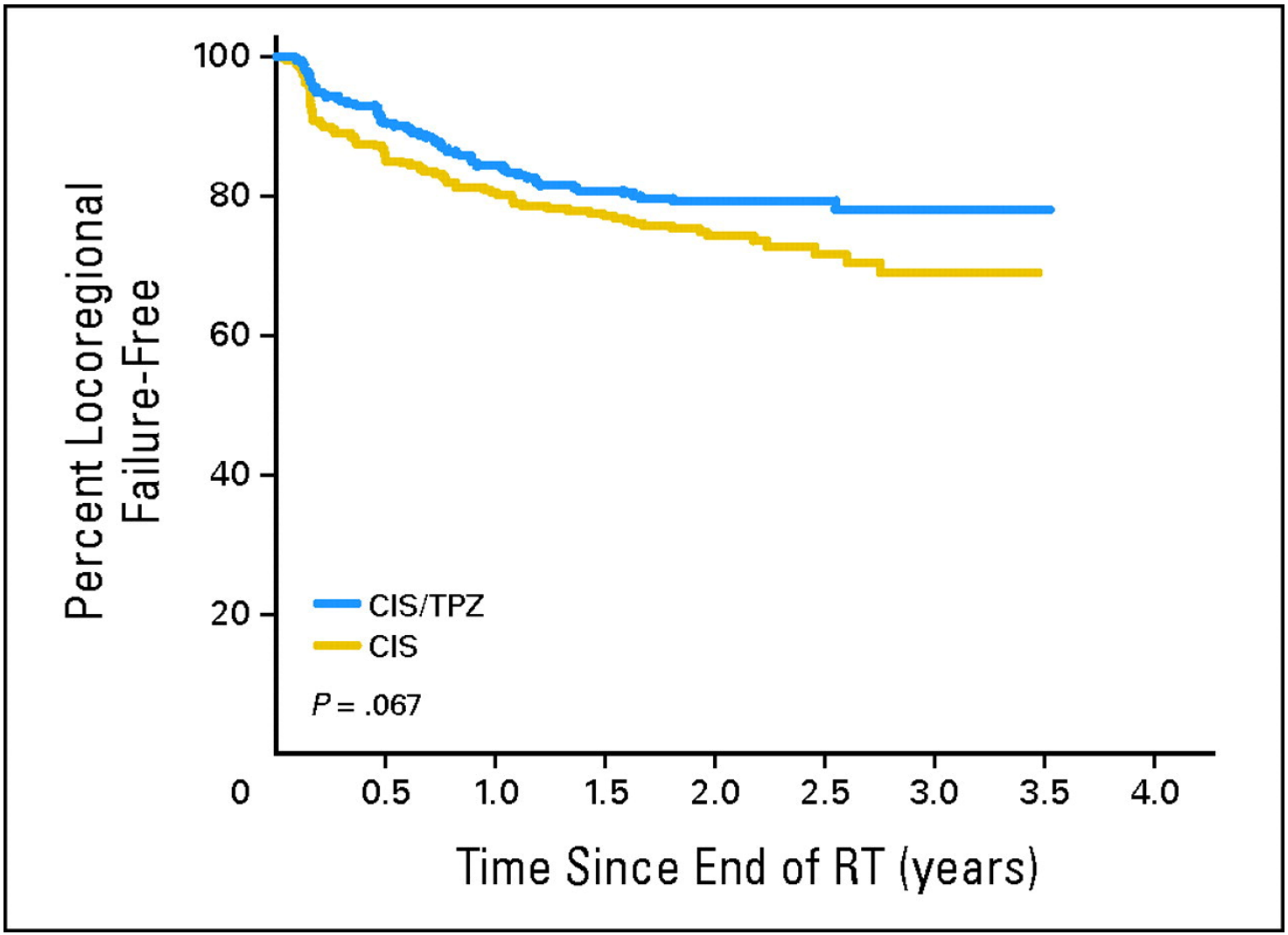


Most influencial studies H&N cancer 2000-2006

Study	No. study-arms	No. patients	No. centers	Duration (years)	No. patients in experimental arm per center per year
Fu, Int J Rad Oncol Biol Phys 2000 **fractionation**	4	1113	45	6	**3,1**
Overgaard, Lancet 2003 **fractionation**	2	1476	6	8	**15,4**
Forastiere, N Engl J Med 2003 radiotherapy ± **chemotherapy**	3	547	> 100	8	**< 0,5**
Bernier, N Engl J Med 2004 surgery+ radiotherapy ± **chemotherapy**	2	334	23	7	**1,0**
Cooper, N Engl J Med 2004 surgery+ radiotherapy ± **chemotherapy**	2	459	> 100	5	**< 0,5**
Bonner, N Engl J Med 2006 radiotherapy ± **cetuximab**	2	424	73	3	**0,9**

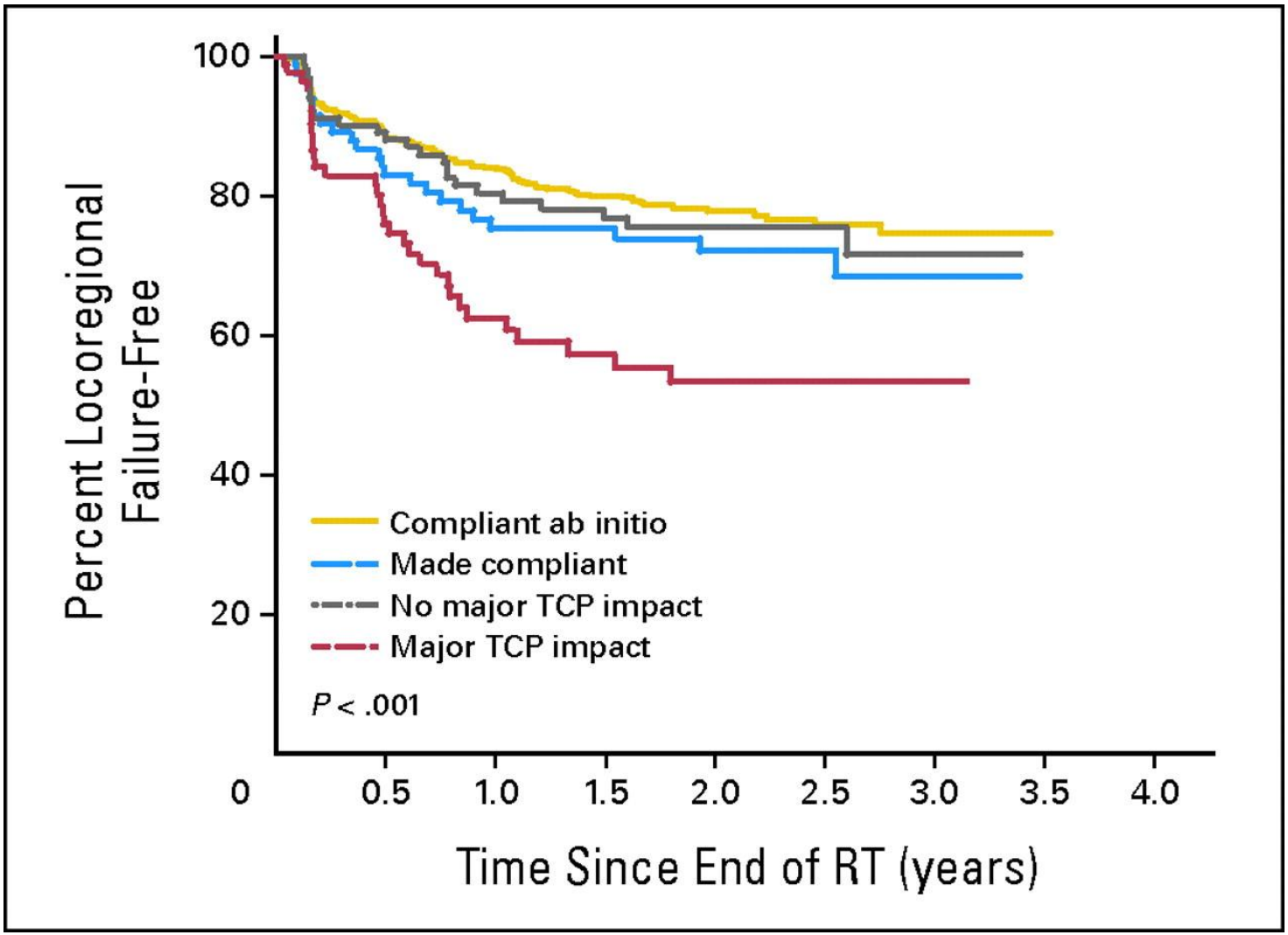
RADIOTHERAPY PREPARATION AND PLANNING

TROG 02.02: chemoradiation + or - tirapazamine



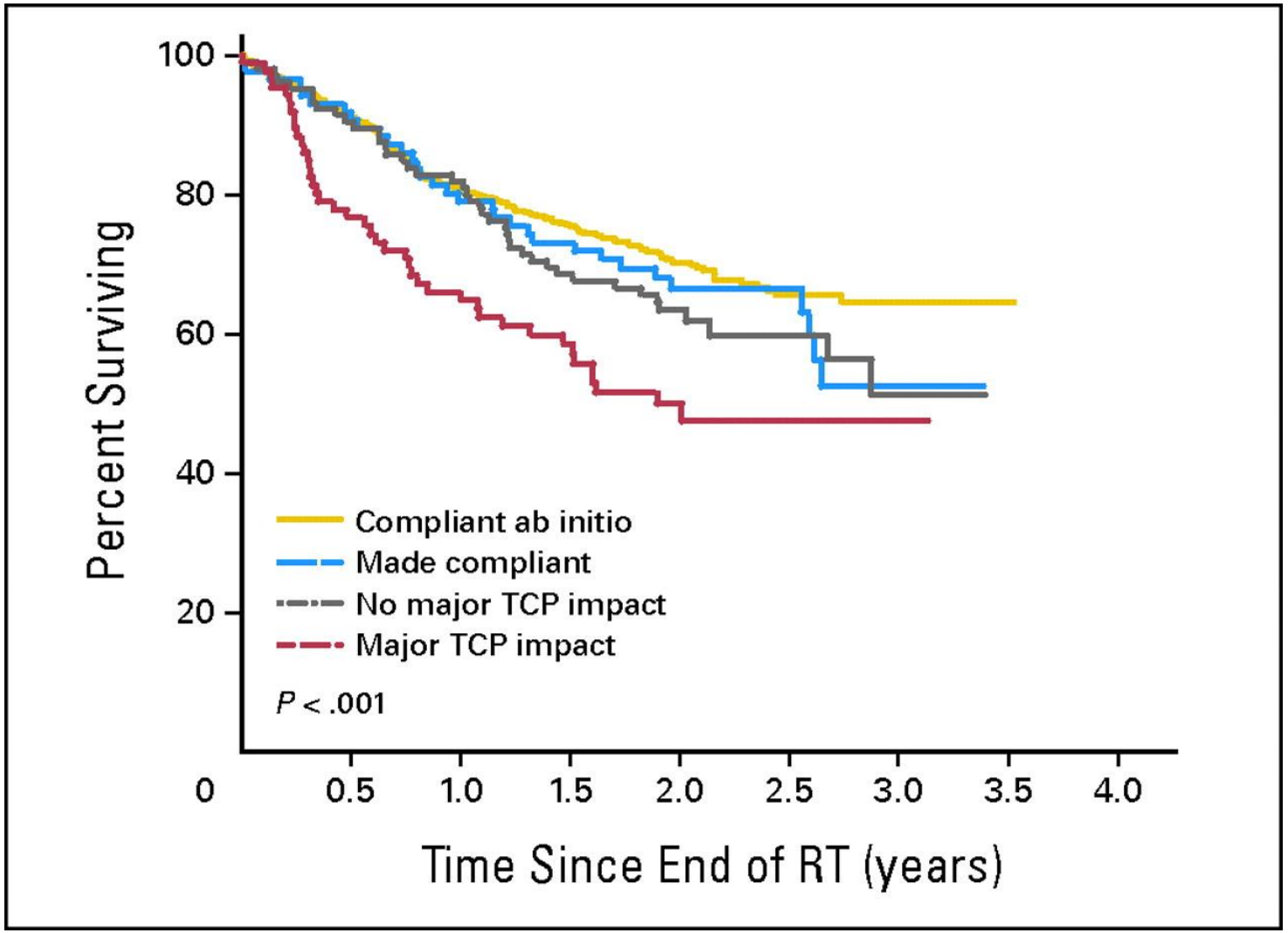
Peters et al. J Clin Oncol 2010

Quality of radiotherapy planning and delivery matters (loco-regional control)



Peters et al. J Clin Oncol 2010

Quality of radiotherapy planning and delivery matters (survival)



Peters et al. J Clin Oncol 2010

Target volume definition

GTV: ***Gross tumor volume:***

Use all information available from clinical examination and imaging (physician drawing target volume must have examined the patient!)

CTV: ***GTV + potential routes of subclinical spread***

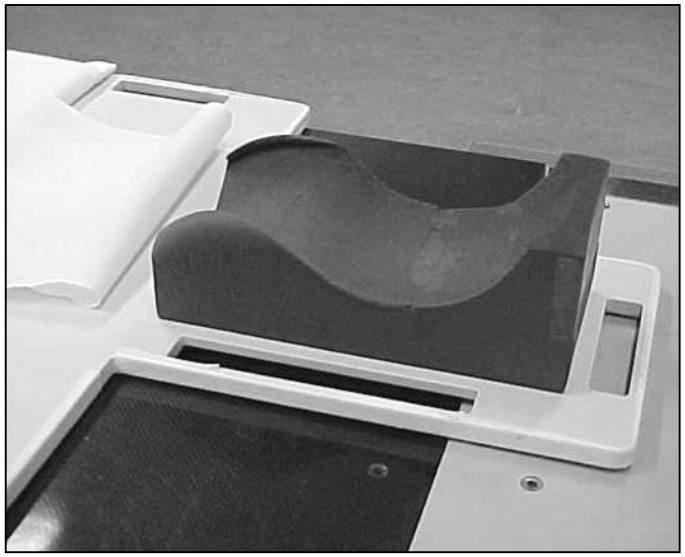
GTV - CTV margins: ***fixed margins generally don't work***

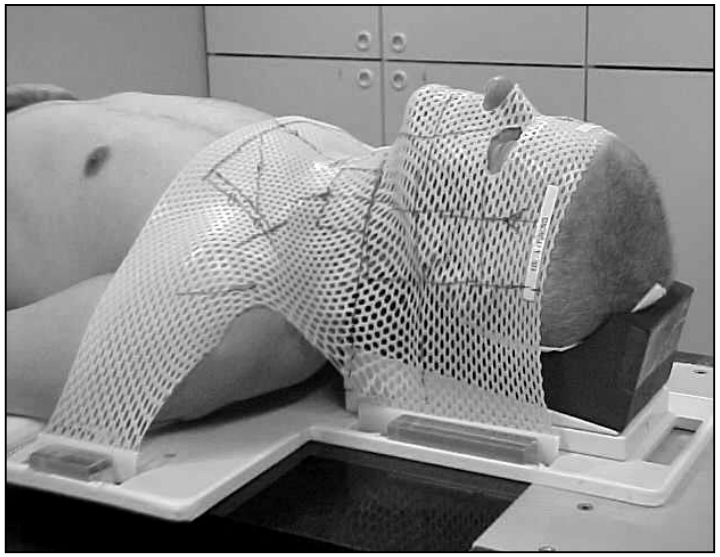
- Soft tissues: generous margins (1-1.5 cm)
- Bone, cartilage, air cavities: tighter margins
- Known routes of spread:
  Nasopharynx: cavernous sinus
- Neck nodes: 0.5 cm; if extranodal growth ≥ 1.0 cm

PTV: ***CTV - PTV margins:***

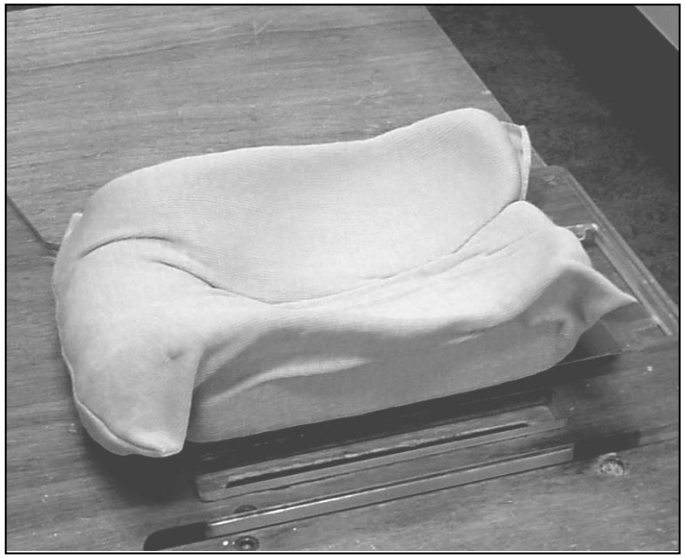
- 5 mm is generally adequate
- Can be reduced to 2-3 mm with customized positioning and immobilization devices and DPI/CBCT-based correction protocols. To 1-2 mm with robust fixation and CBCT online.

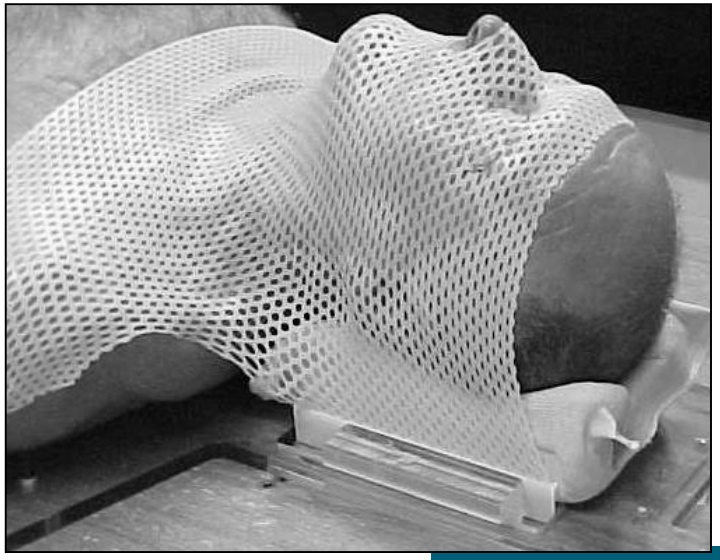
Head support and immobilization mask





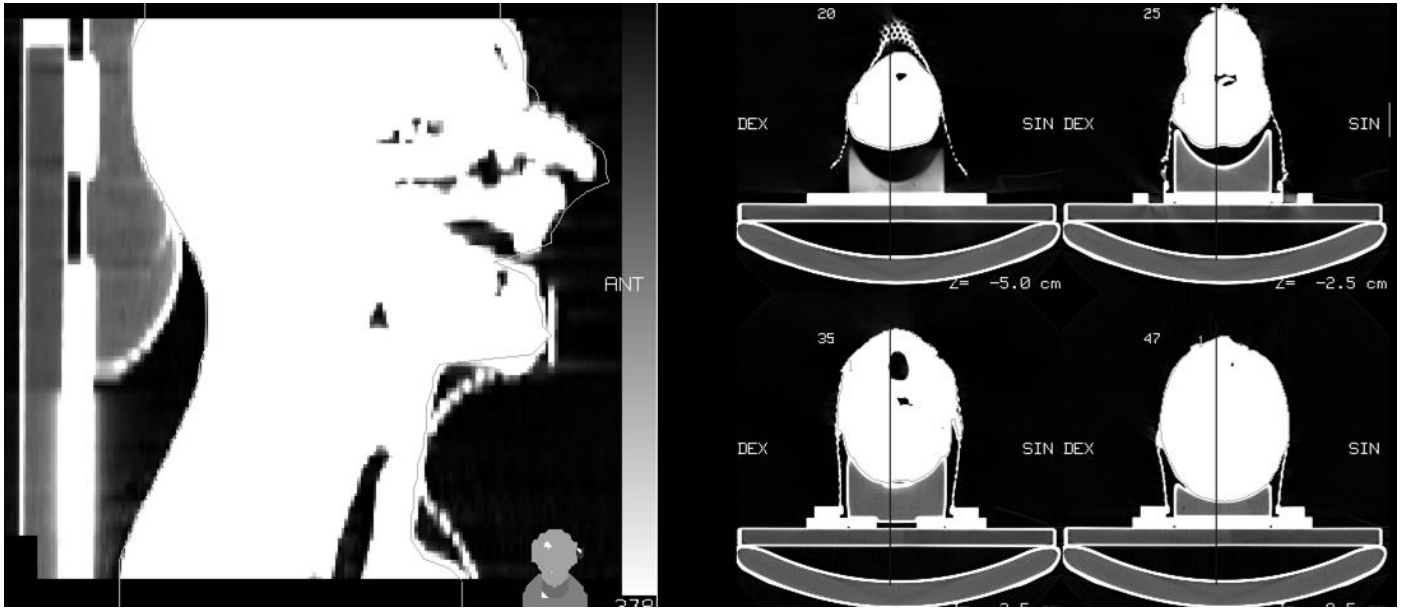
standard



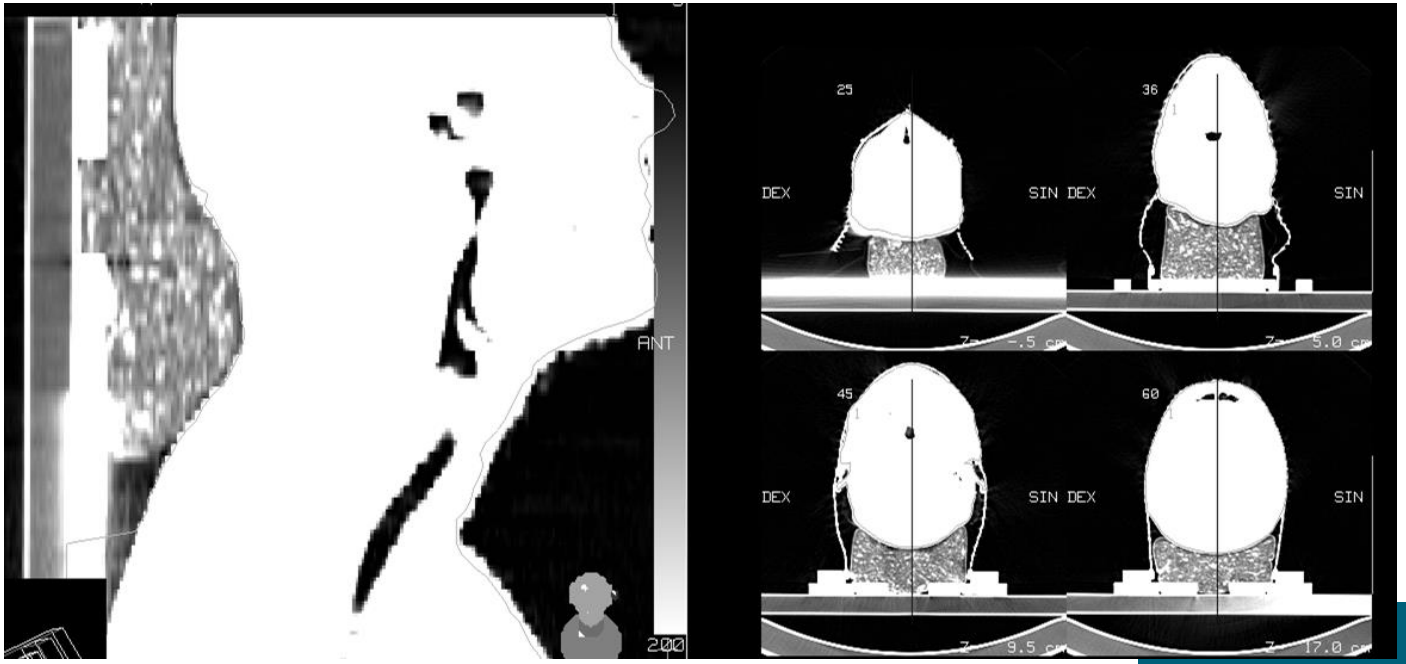


customized

Head support and immobilization mask



standard



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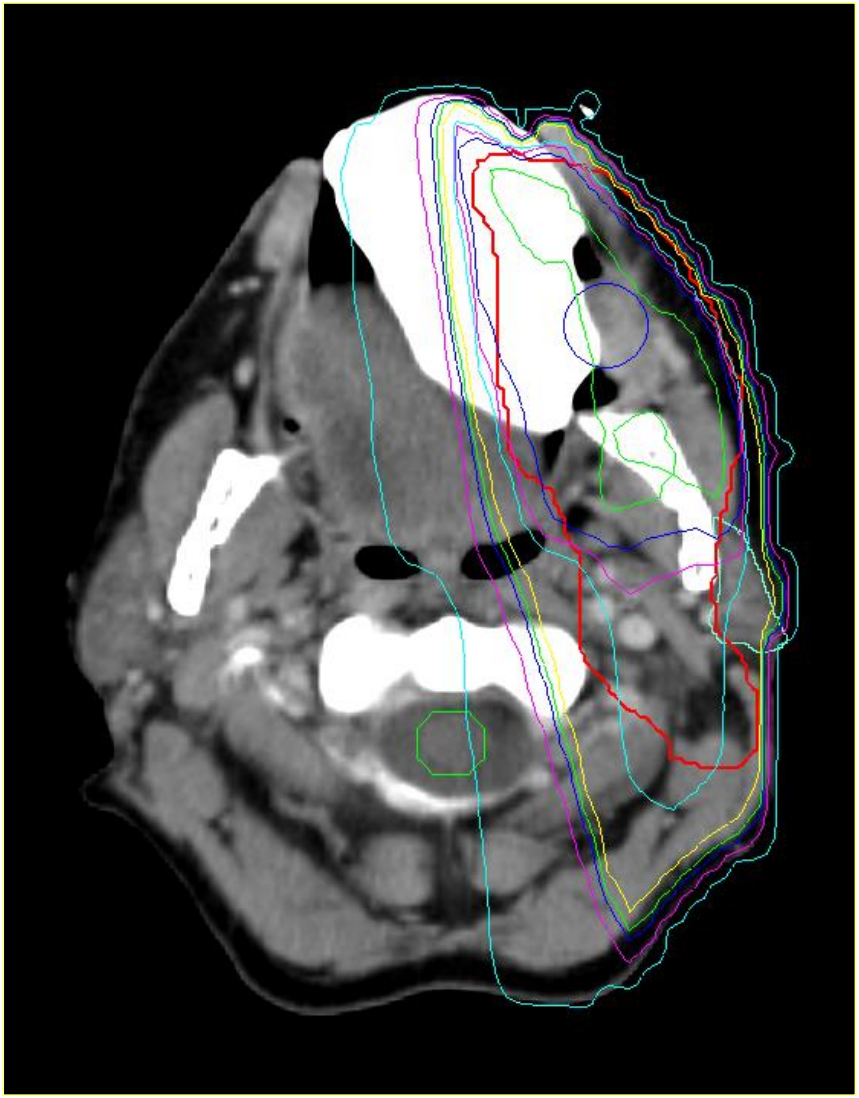
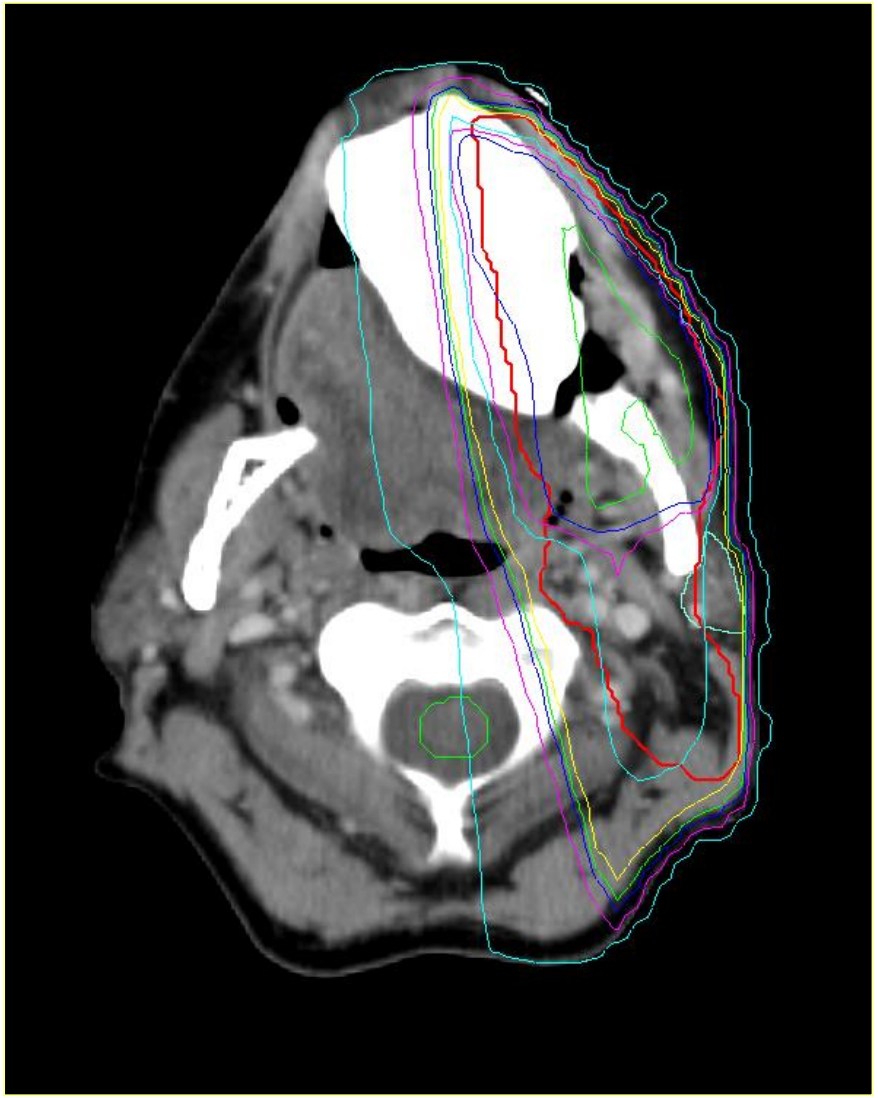
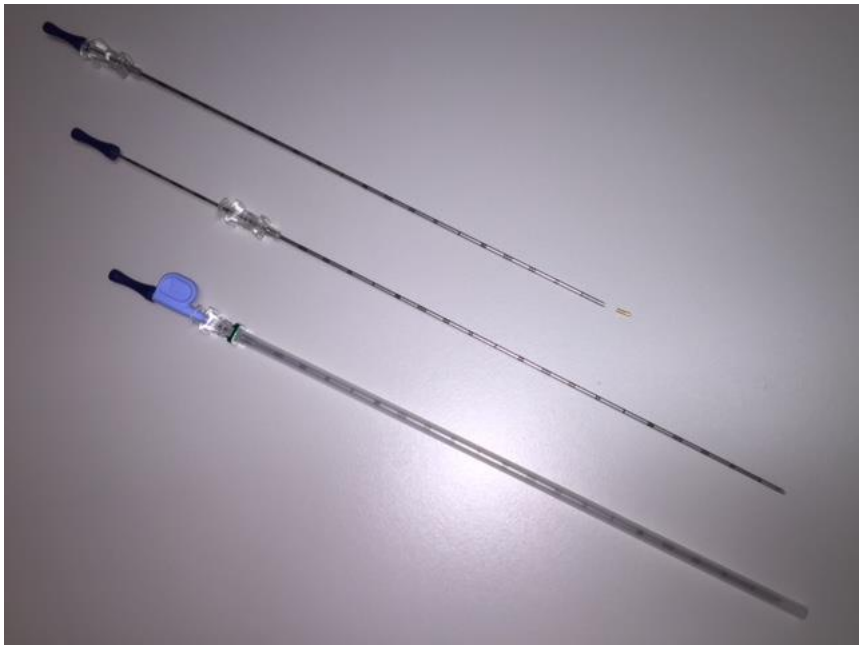
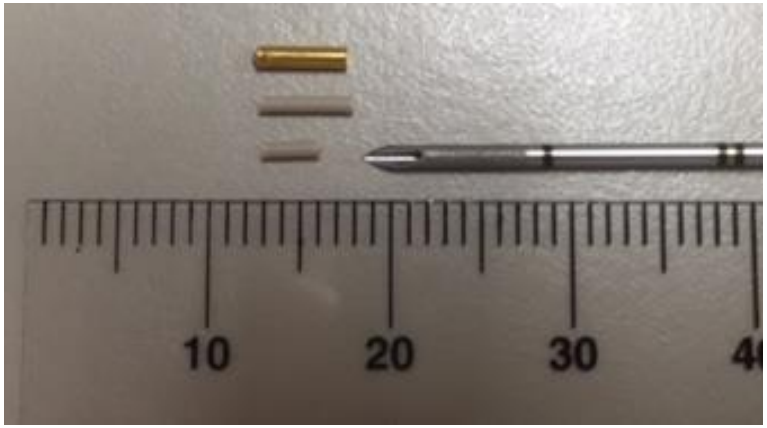
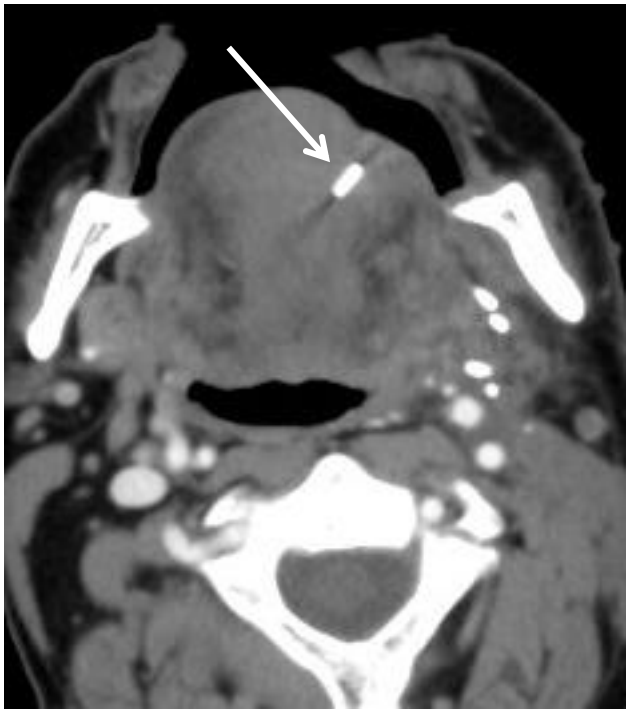




Fiducial markers

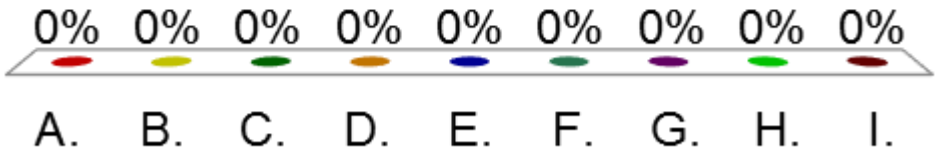






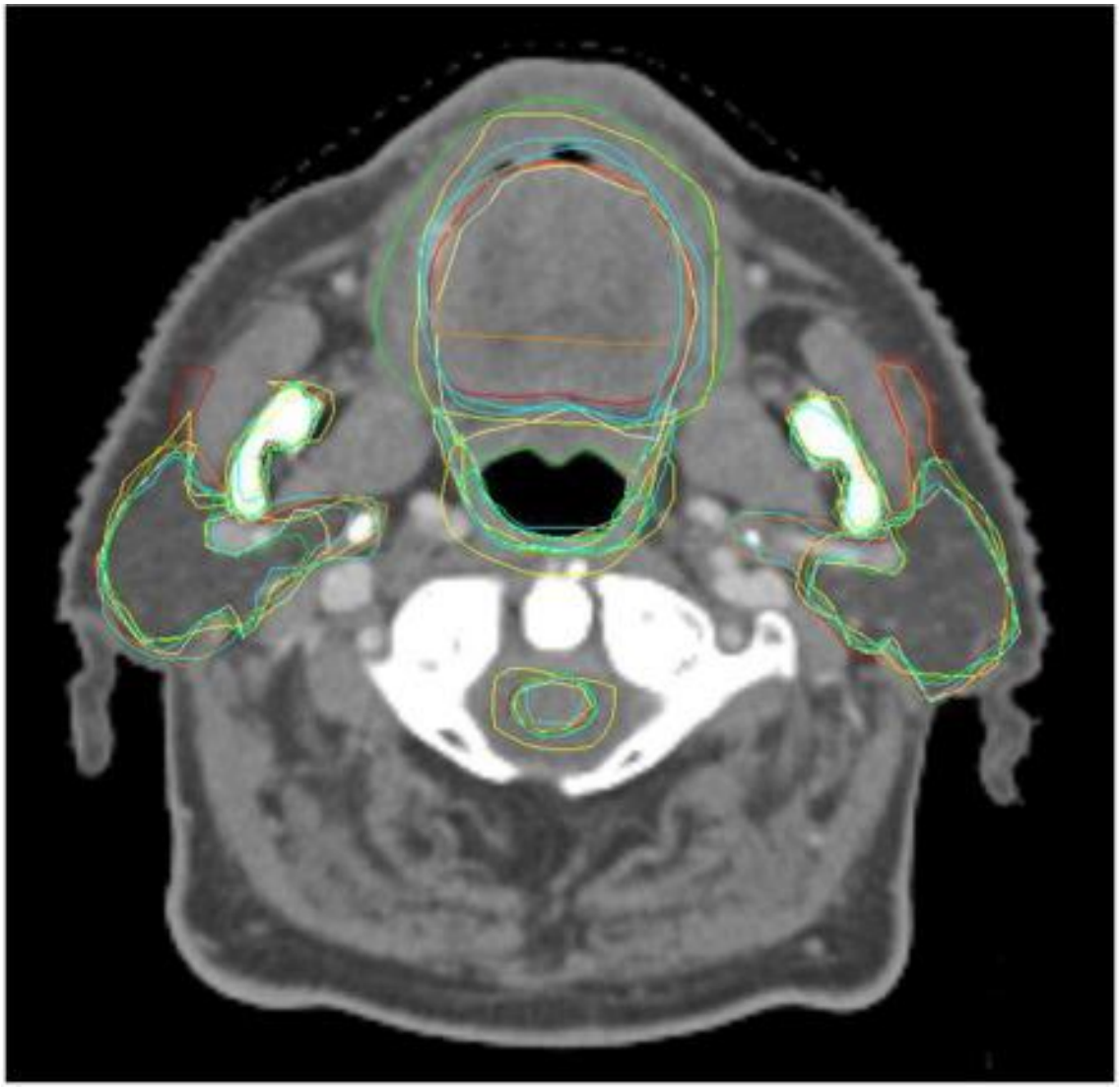
Which normal structures do you attempt to spare with IMRT routinely?

A. none
B. parotids
C. submandibular glands
D. larynx
E. pharyngeal constrictor muscles
F. B+C
G. B+D
H. B+C+D
I. all



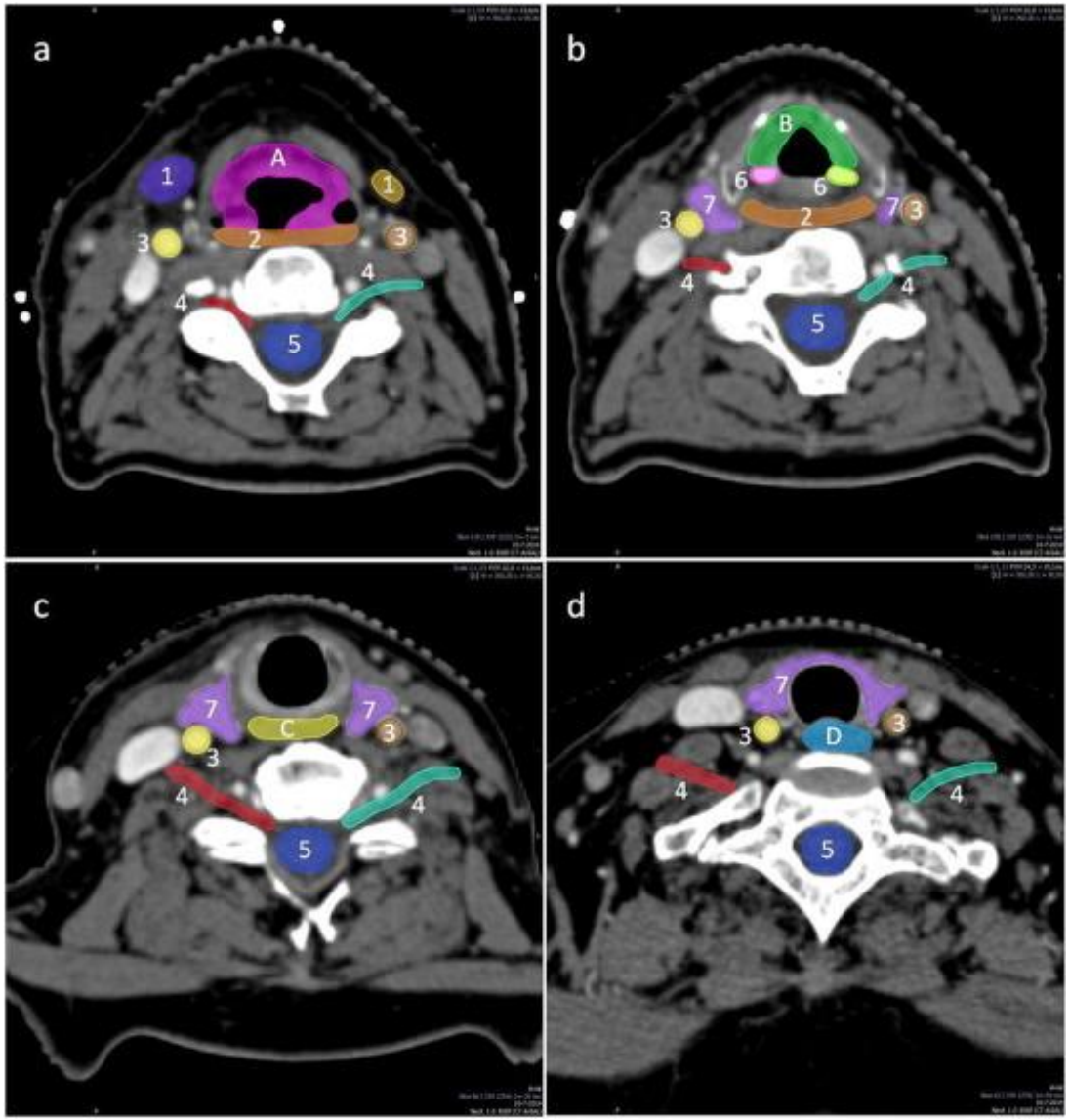
Delineation variation

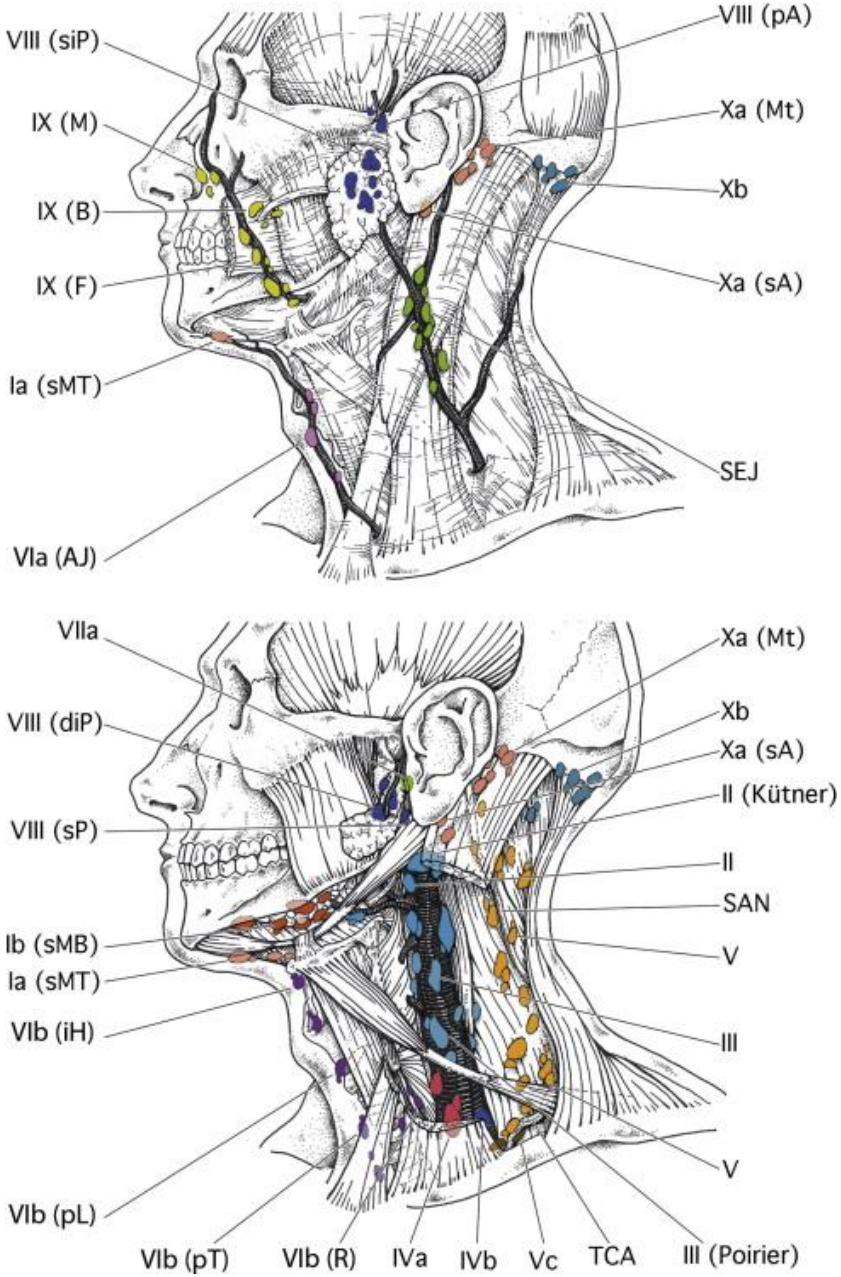
Brouwer et al. Radiother. Oncol. 2015;117:83-90



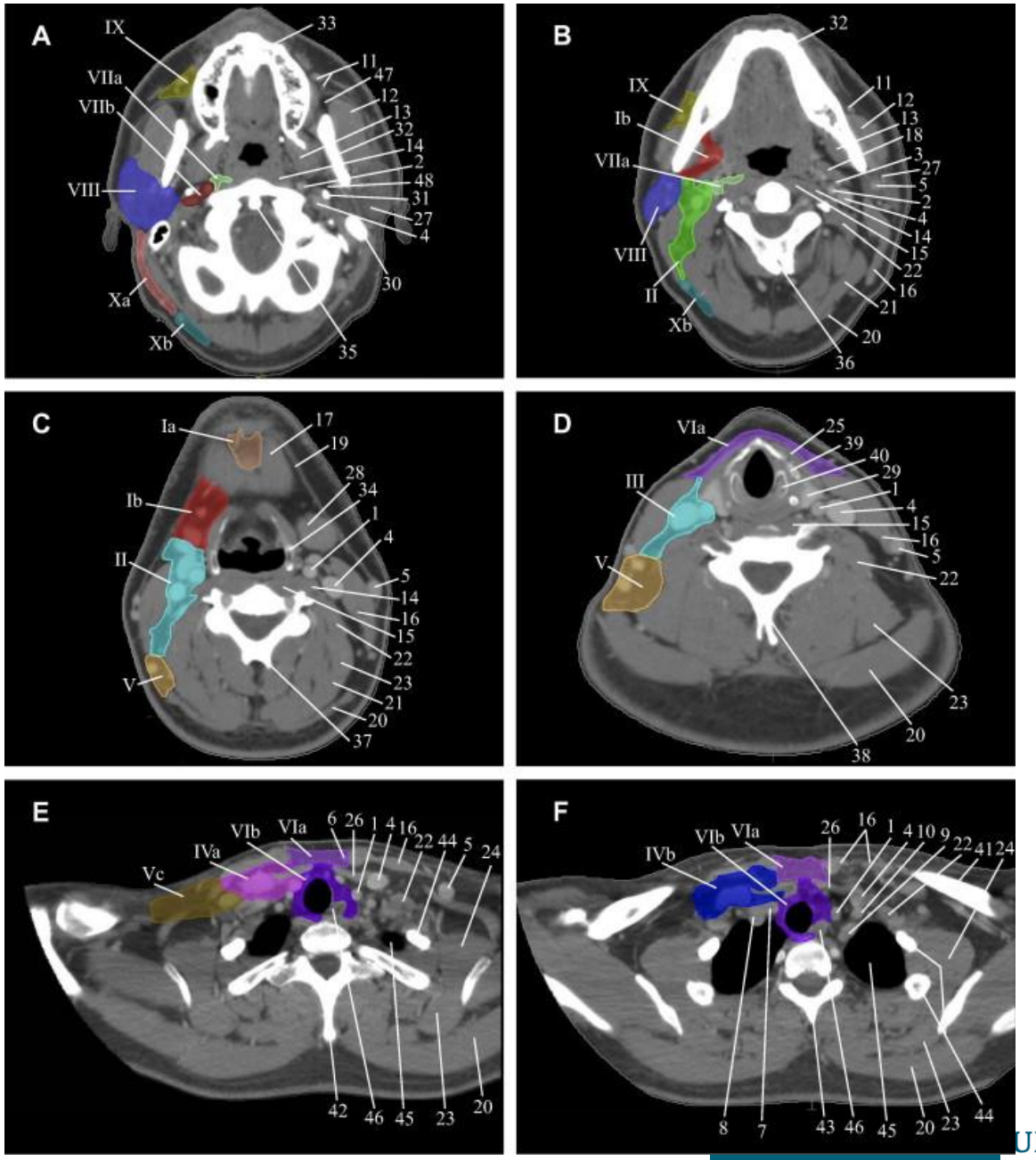
Delineation guidelines

Brouwer et al. Radiother. Oncol. 2015;117:83-90



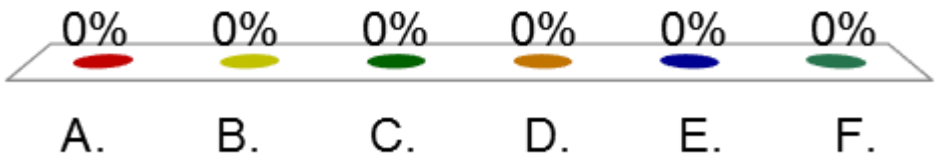

VIII (siP)
IX (M)
IX (B)
IX (F)
Ia (sMT)
VIa (AJ)
VIII (pA)
Xa (Mt)
Xb
Xa (sA)
SEJ
VIIa
VIII (diP)
VIII (sP)
Ib (sMB)
Ia (sMT)
VIb (iH)
VIb (pL)
VIb (pT)
VIb (R)
IVa
IVb
Vc
TCA
III (Poirier)
Xa (Mt)
Xb
Xa (sA)
II (Kütner)
II
SAN
V
III
V

Gregoire et al. Radiother. Oncol. 2014;110:172-181



Which radiotherapy technique do you use for the majority of your H&N patients?

A. 2D conventional
B. 3D conformal
C. IMRT
D. VMAT/Rapid Arc
E. Tomotherapy
F. Protons



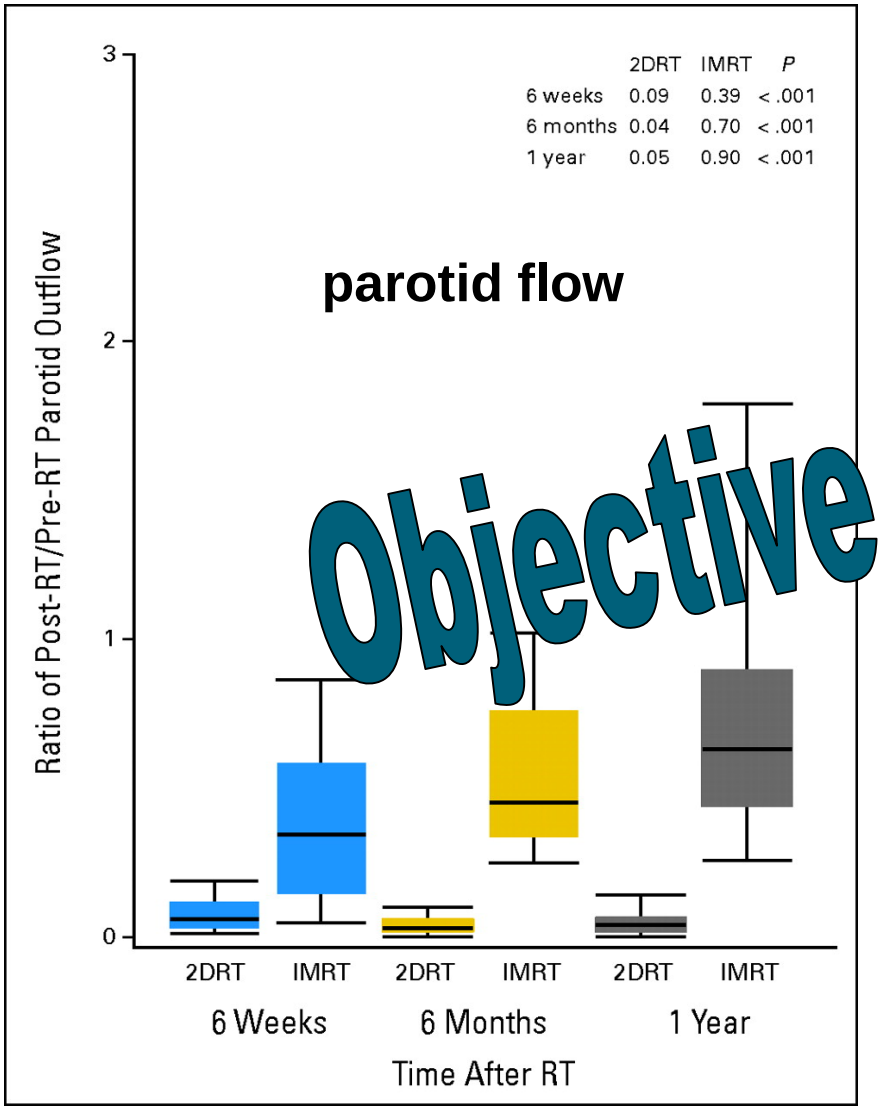
A randomized trial of IMRT vs 2-D radiotherapy in nasopharyngeal carcinoma (n=60)

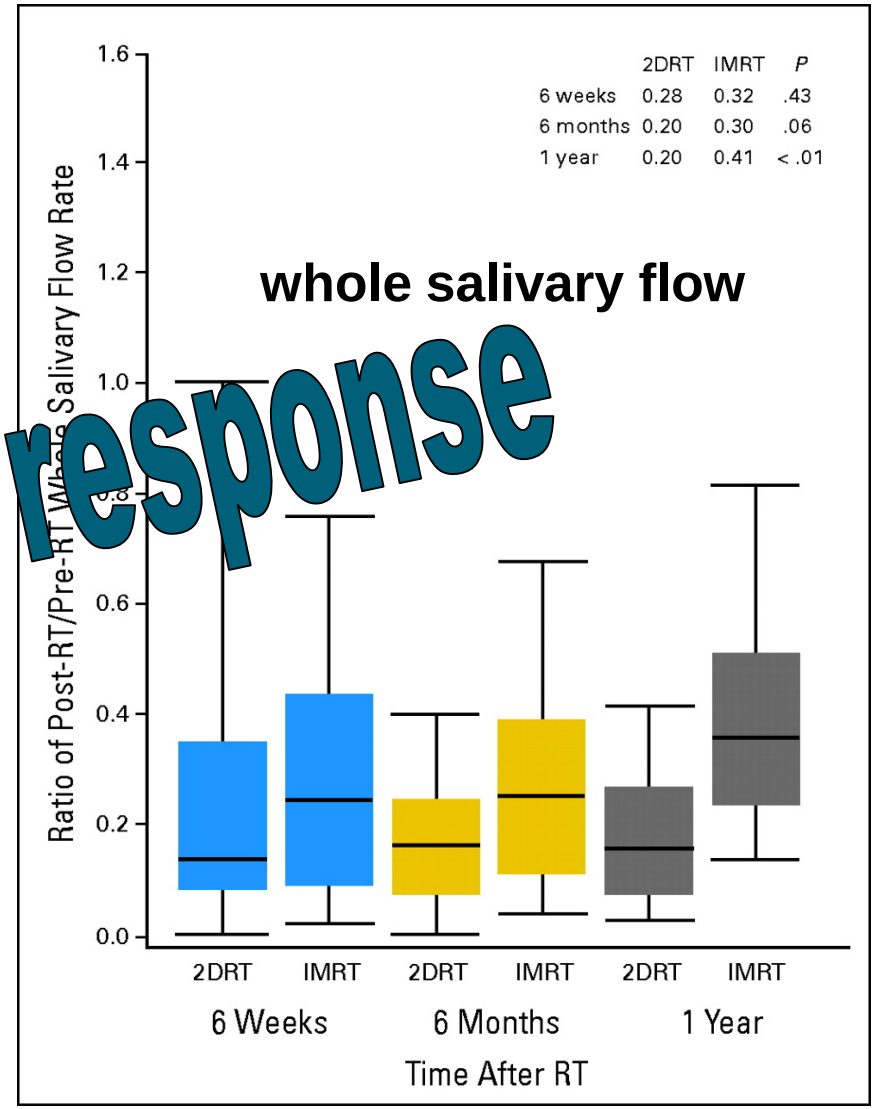
Observer rated

Kam 2007

UMC St Radboud

A randomized trial of IMRT vs 2-D radiotherapy in nasopharyngeal carcinoma (n=60)

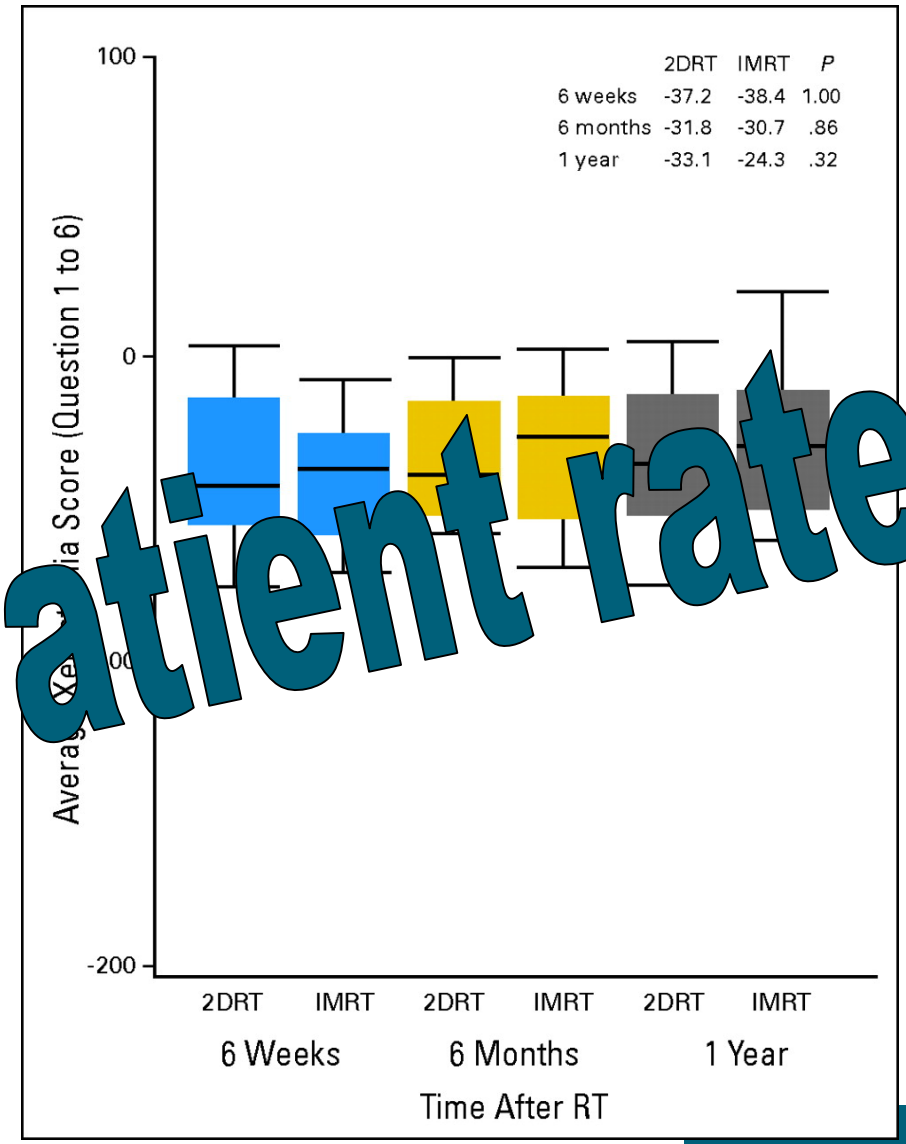




Objective response

Kam 2007

A randomized trial of IMRT vs 2-D radiotherapy in nasopharyngeal carcinoma (n=60)



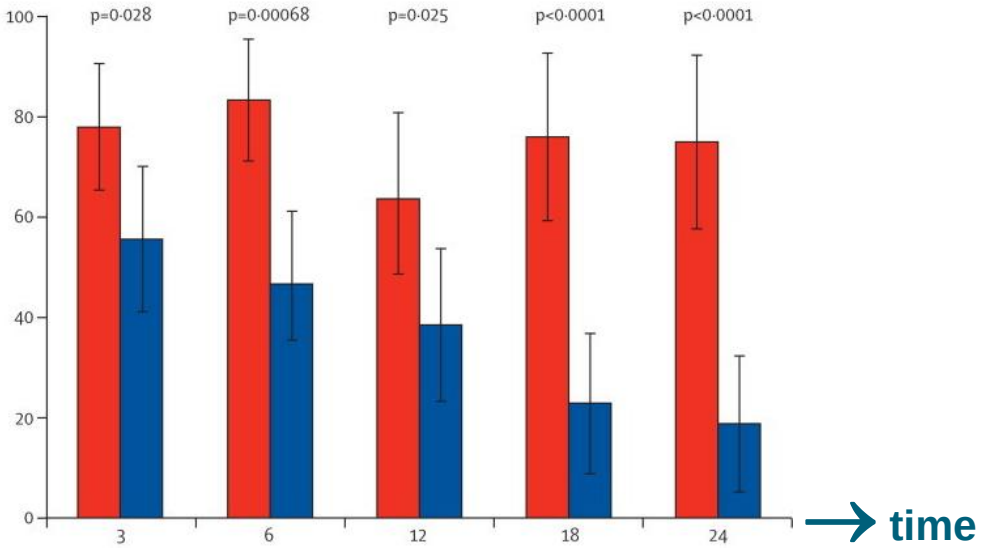
Patient rated

A third randomized trial of IMRT vs 3-D radiotherapy in head and neck cancer (n=94) - PARSPORT

Percentage of patients with ≥ grade 2 xerostomia

conventional

IMRT

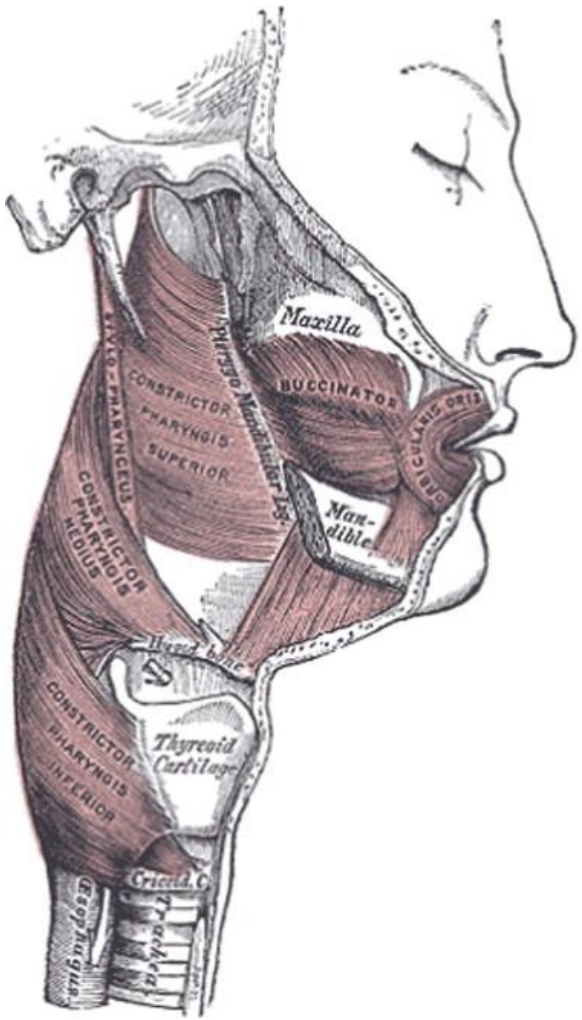


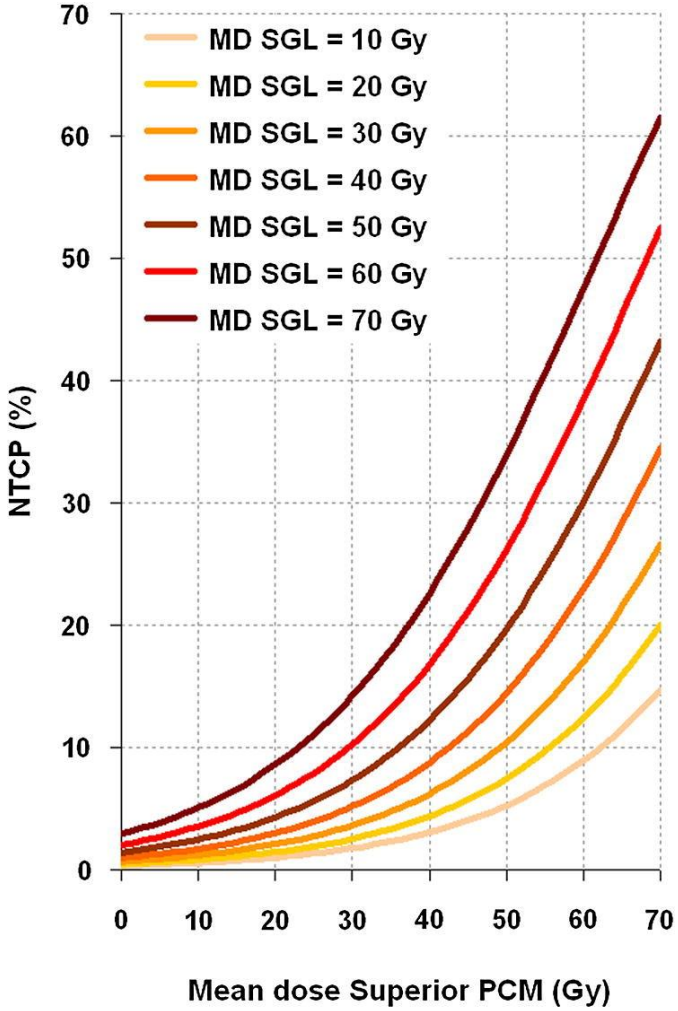
	Conventional radiotherapy		IMRT	
	No measurable salivary flow* (n=25)	Measurable salivary flow (n=0)	No measurable salivary flow (n=18)	Measurable salivary flow (n=16)
Subjective xerostomia better than grade 2	6 (24%)	0	10 (56%)	12 (75%)
Subjective xerostomia grade 2 or worse	19 (76%)	0	8 (44%)	4 (25%)

Nutting 2011

Dysphagia and dose to swallowing structures: dose-effect relationships

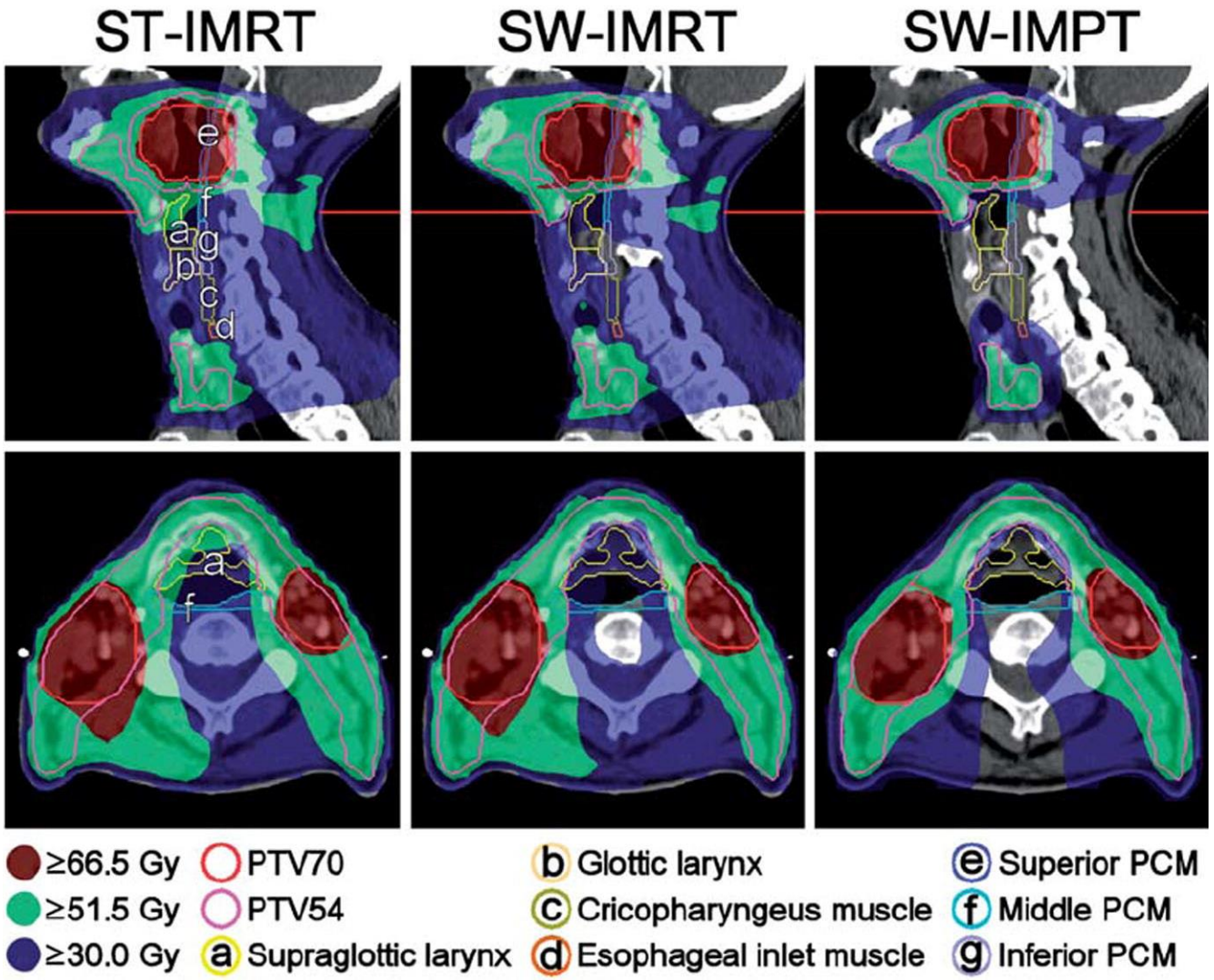
Christianen et al. Radiother. Oncol. 2012;105:107-114





Sparing of swallowing structures: comparing IMRT with photons and protons

van der Laan et al. Acta. Oncol. 2013;52:561-569



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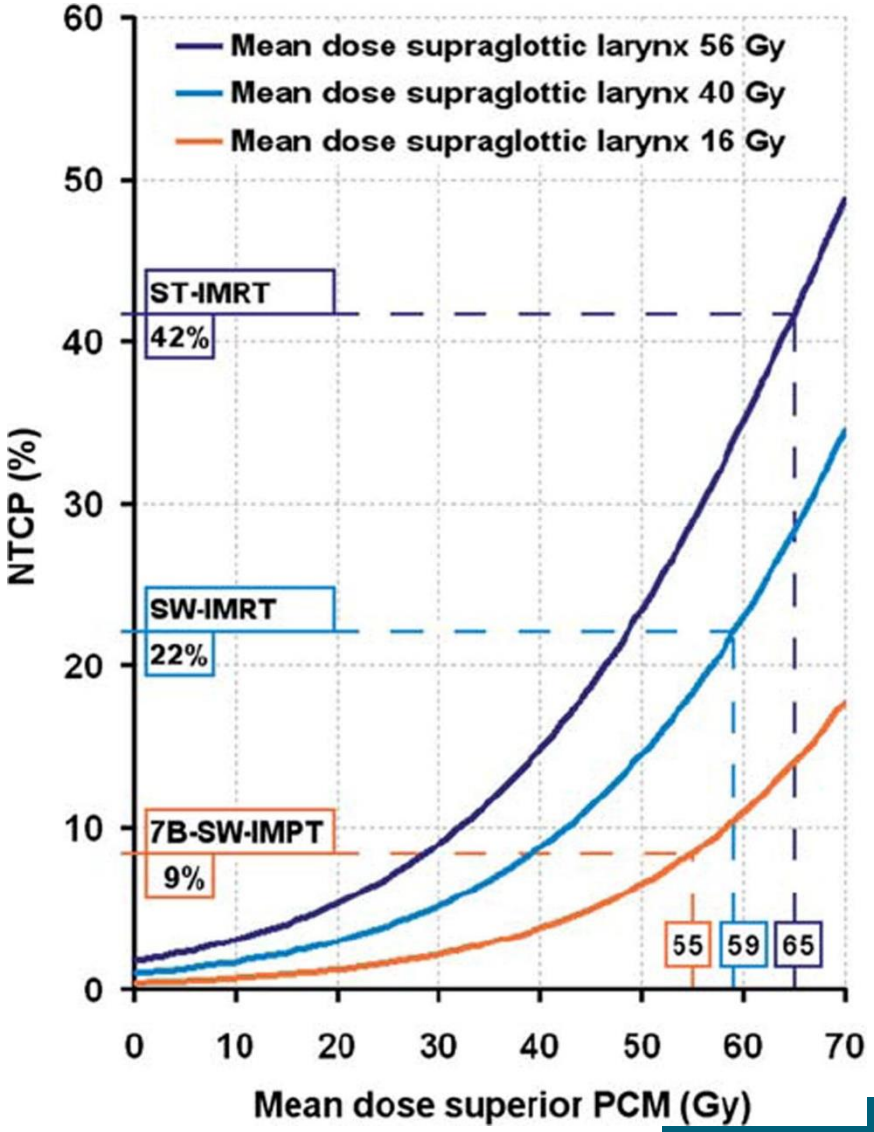
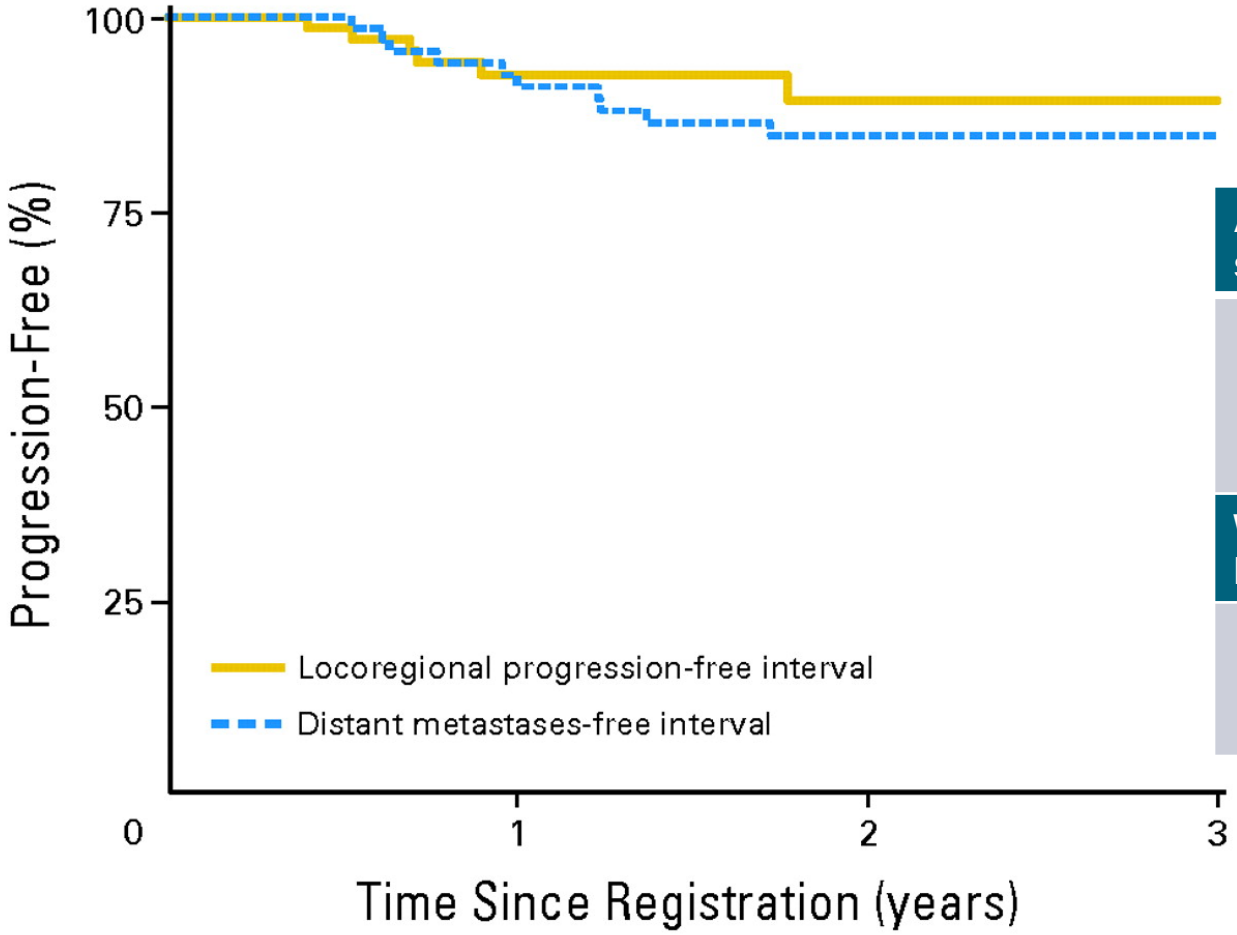


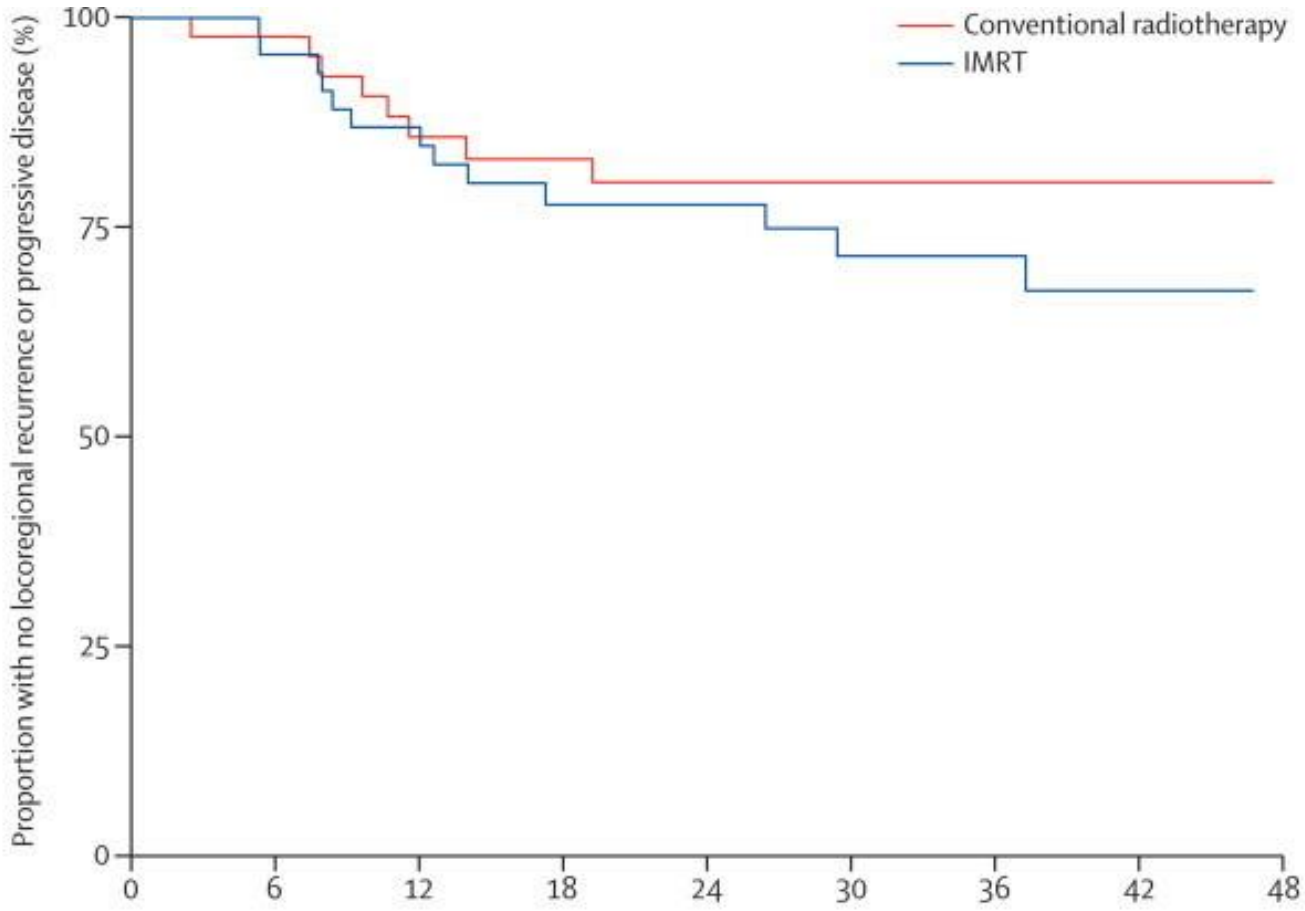
High tumor control rates with IMRT for nasopharyngeal cancer (RTOG 0255, 68 pts)



AJCC stage	No. patients
I	9
II	19
III	21
IV	19
WHO histology	
I	6
II	24
II	37

Lee 2009

A randomized trial of IMRT vs 3-D radiotherapy in head and neck cancer (n=94) - PARSPORT

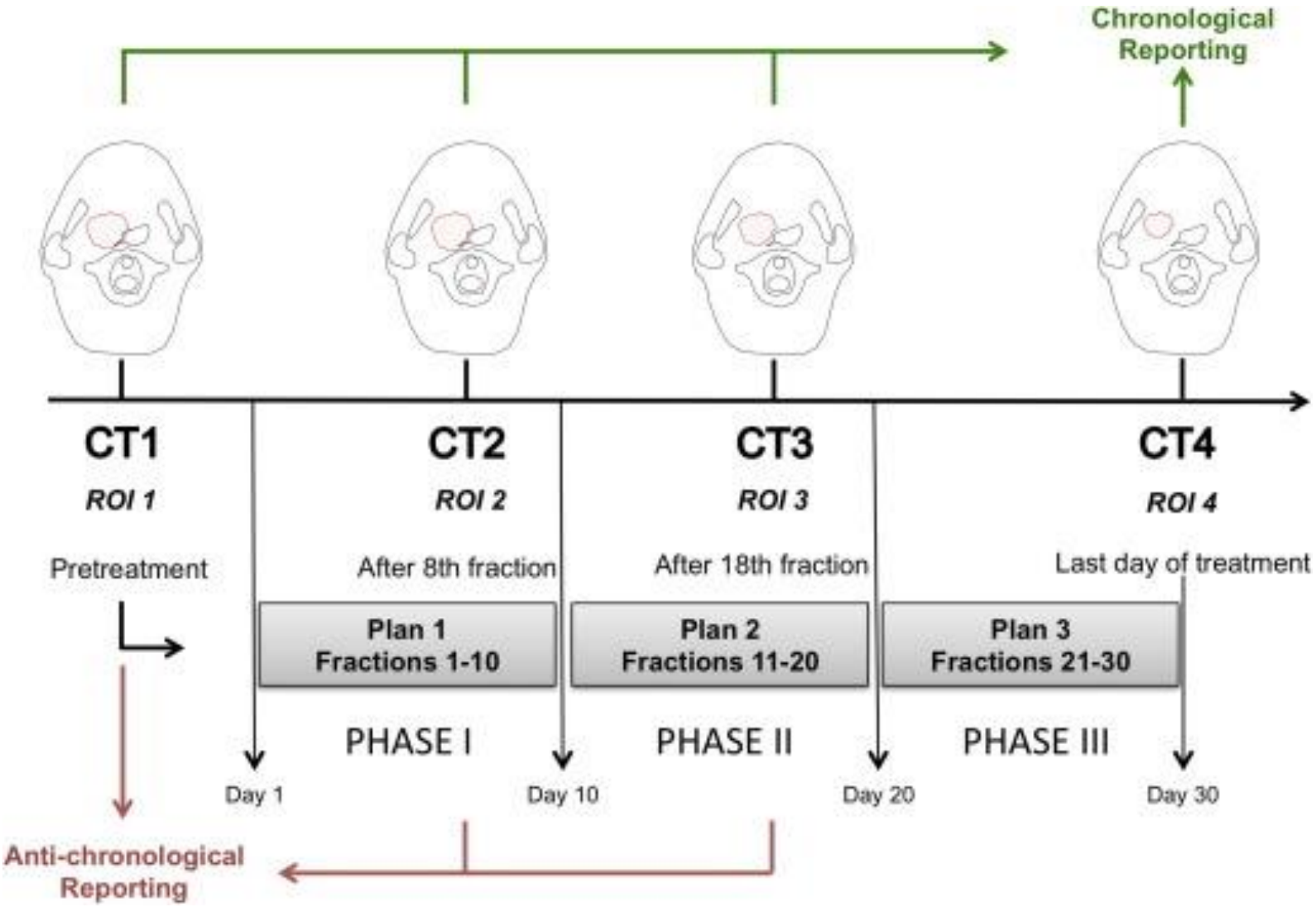


Number of events/at risk									
Conventional radiotherapy	0/47	1/42	5/34	1/30	1/29	0/23	0/19	0/15	0/8
IMRT	0/47	2/44	4/39	4/31	0/28	2/22	0/18	1/15	0/11

Nutting 2011

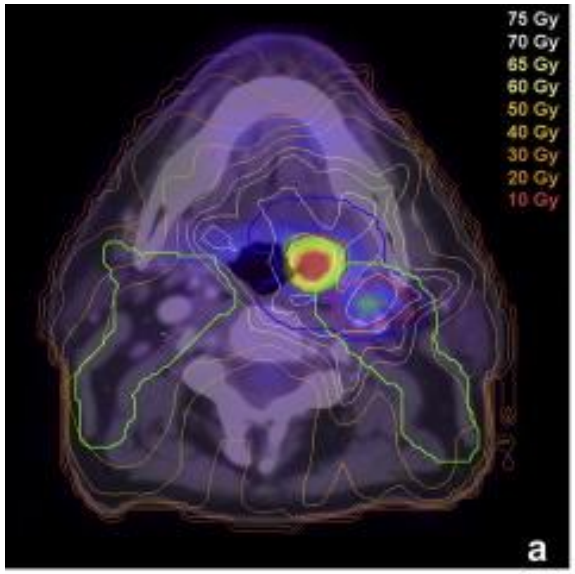
Adaptive radiotherapy

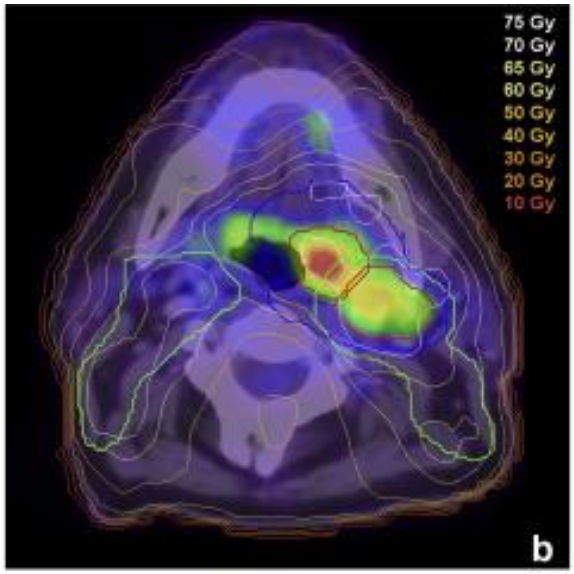
Berwouts et al. Radiother. Oncol. 2013;107:310-316

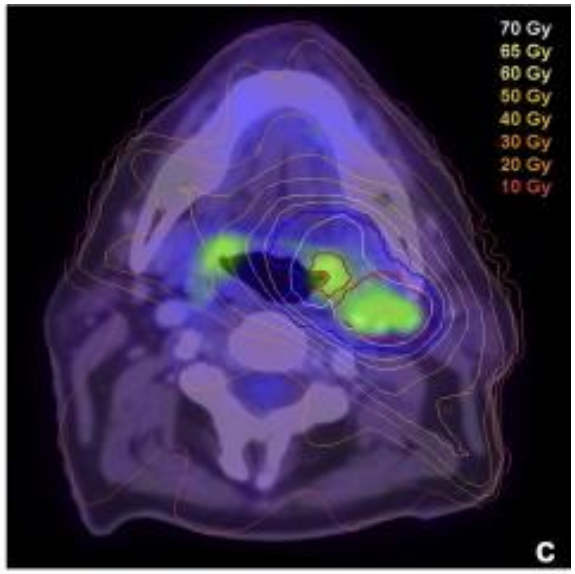


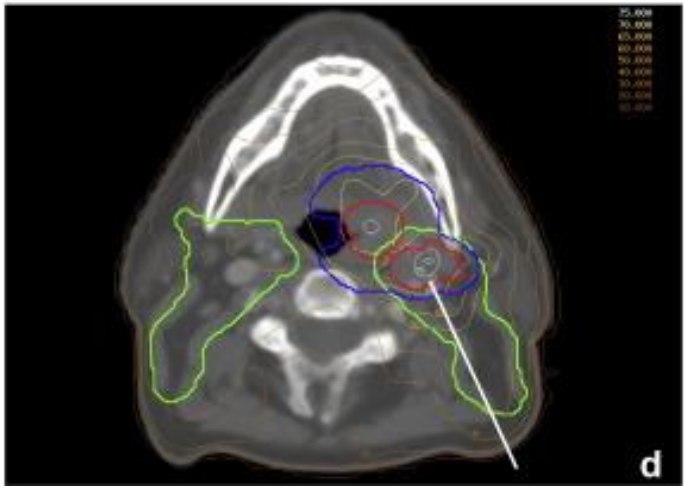
Adaptive radiotherapy

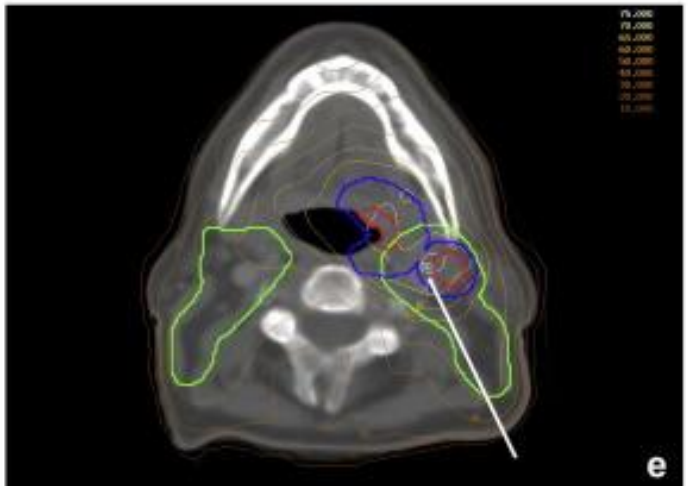
Berwouts et al. Radiother. Oncol. 2013;107:310-316





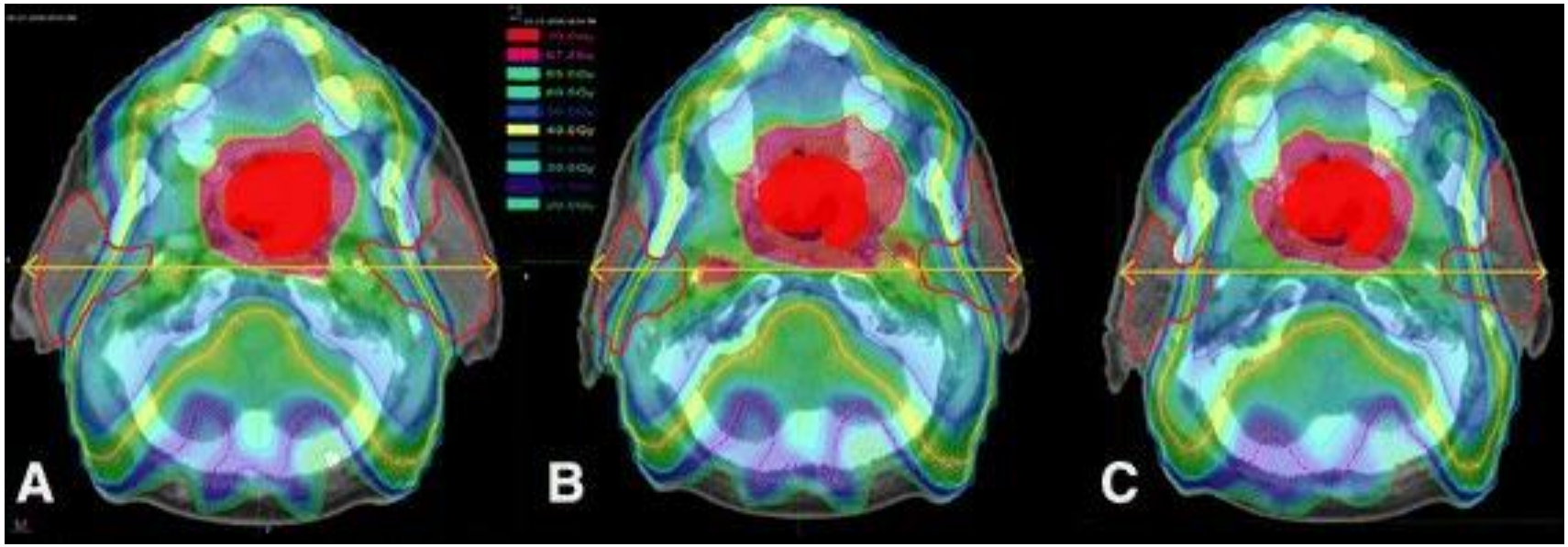


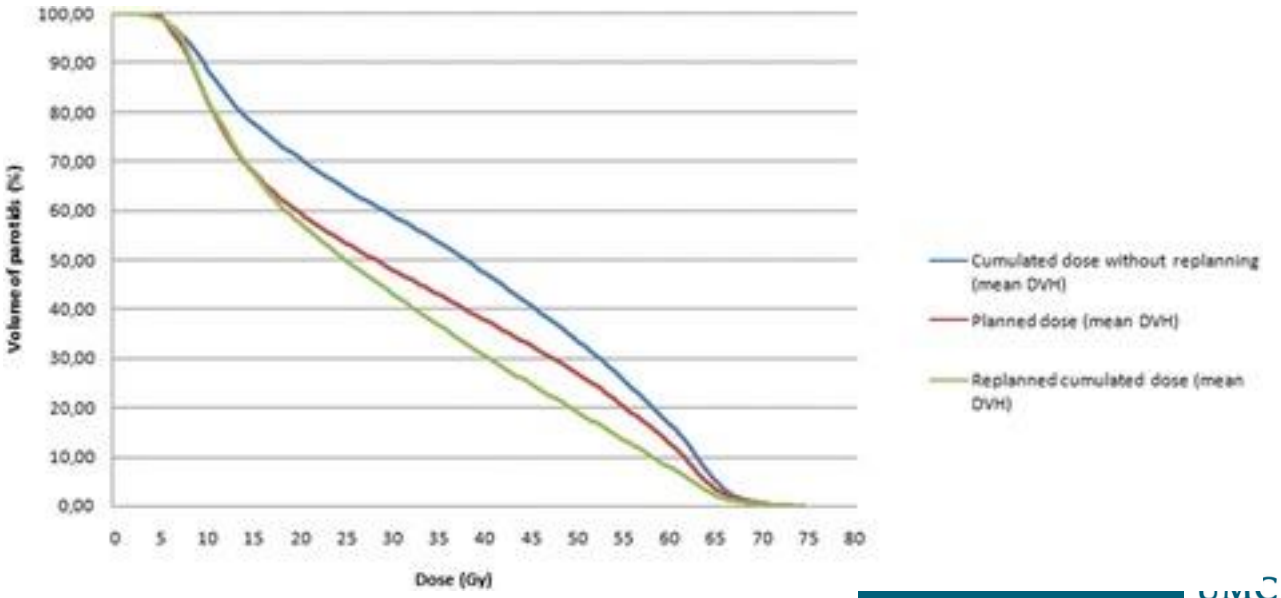




Adaptive radiotherapy for volume changes parotids

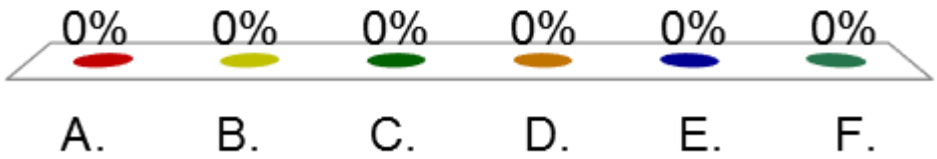
Castelli et al. Radiat. Oncol. 2015





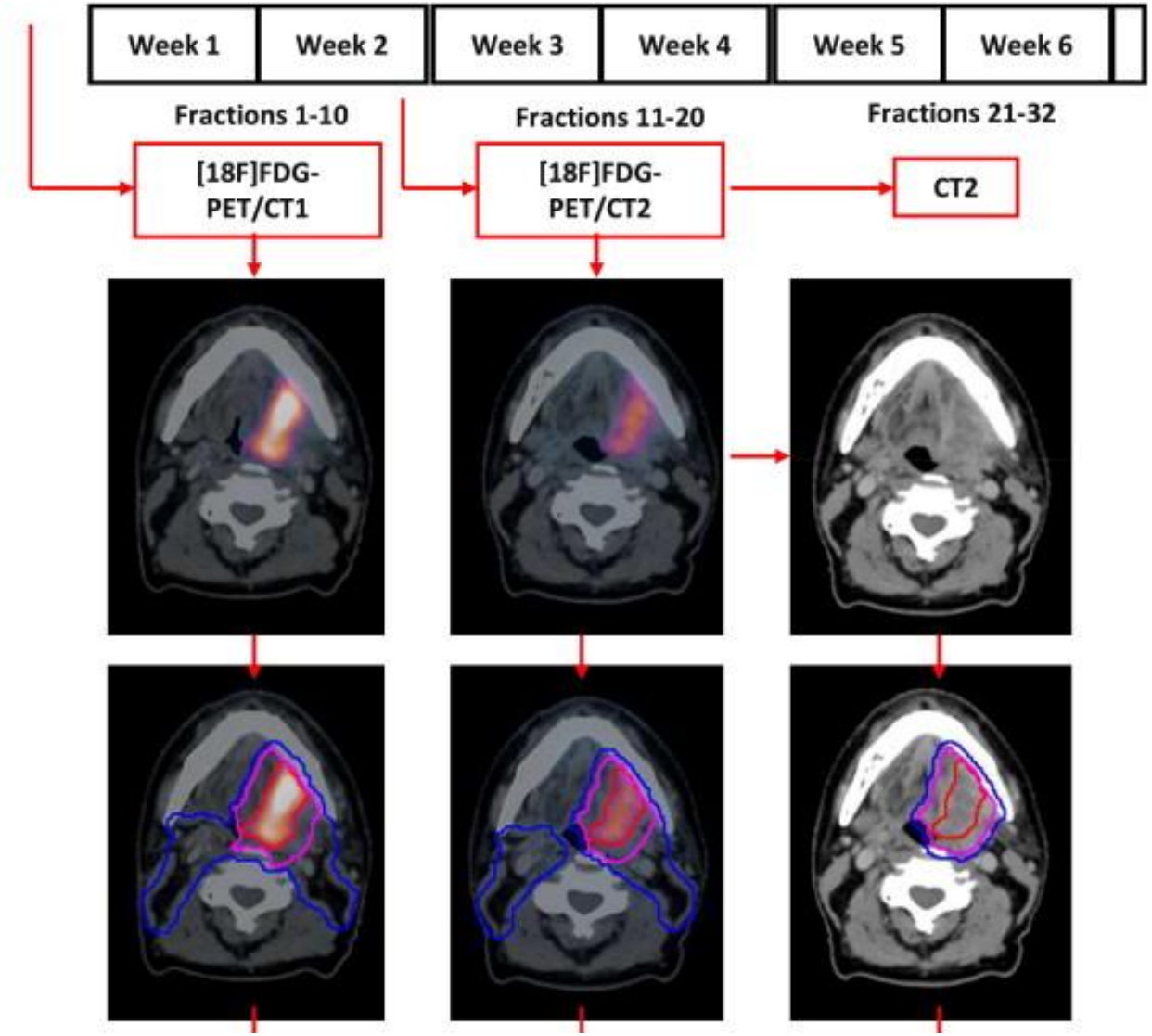
Do you use adaptive radiotherapy routinely for your H&N patients?

A. No
B. Yes, for changes in normal structures
C. Yes, for changes in tumor volume
D. Yes, for both
E. Yes, for changes in tumor biology, based on functional imaging
F. Yes, for B, C and E



Adaptive dose painting and dose escalation

Duprez et al. Int. J. Radiat. Oncol. Biol. Phys. 2011;80:1045-1055



Adaptive dose painting and dose escalation

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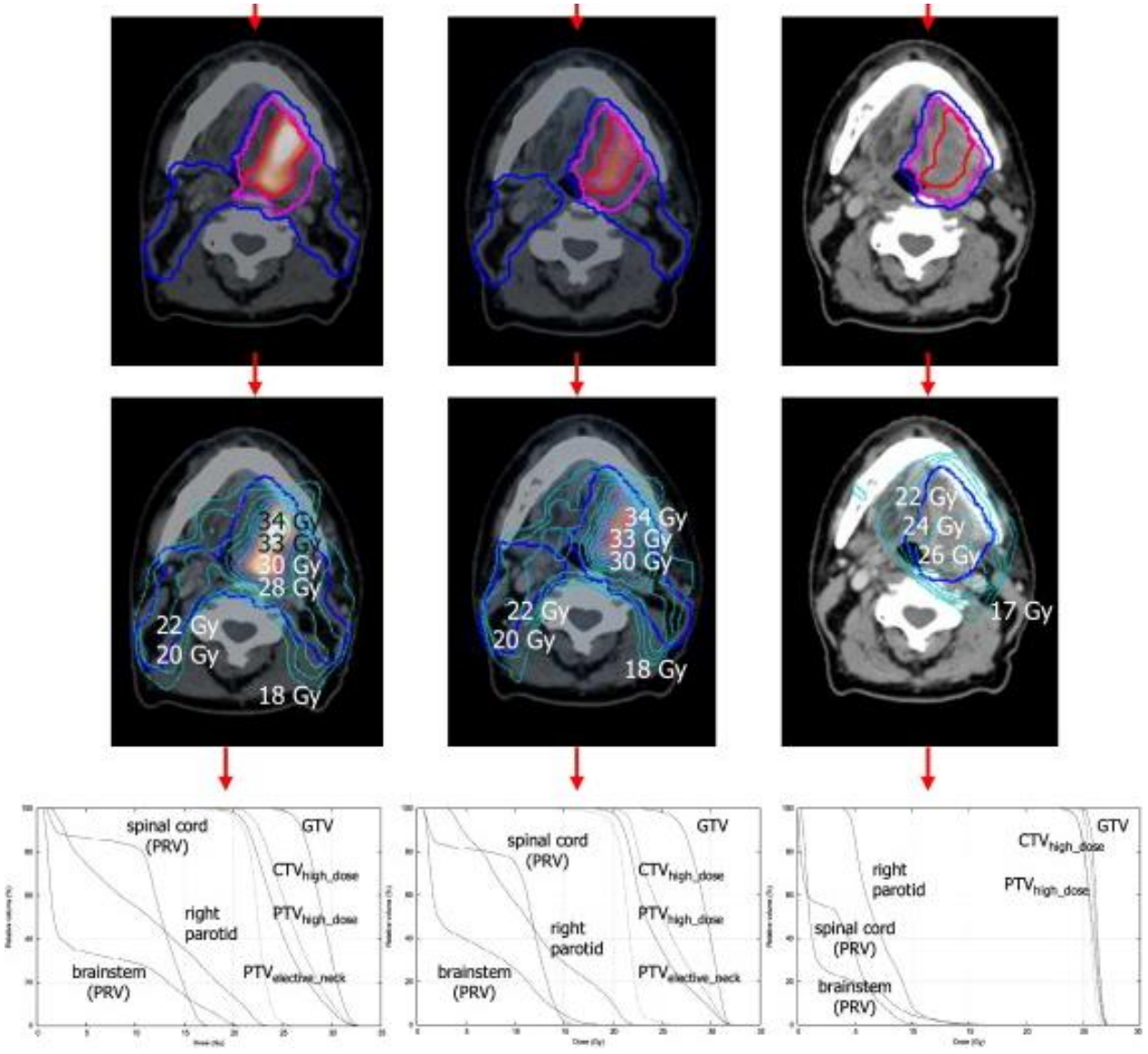

Evidenced-based Radiation Oncology

Breast cancer
Part I

Epidemiology, Genetics and Tumours characteristics

Youlia M. Kirova, MD,
Head of Breast Cancer Research and Treatment
in the Department of Radiation Oncology

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ESTRO School

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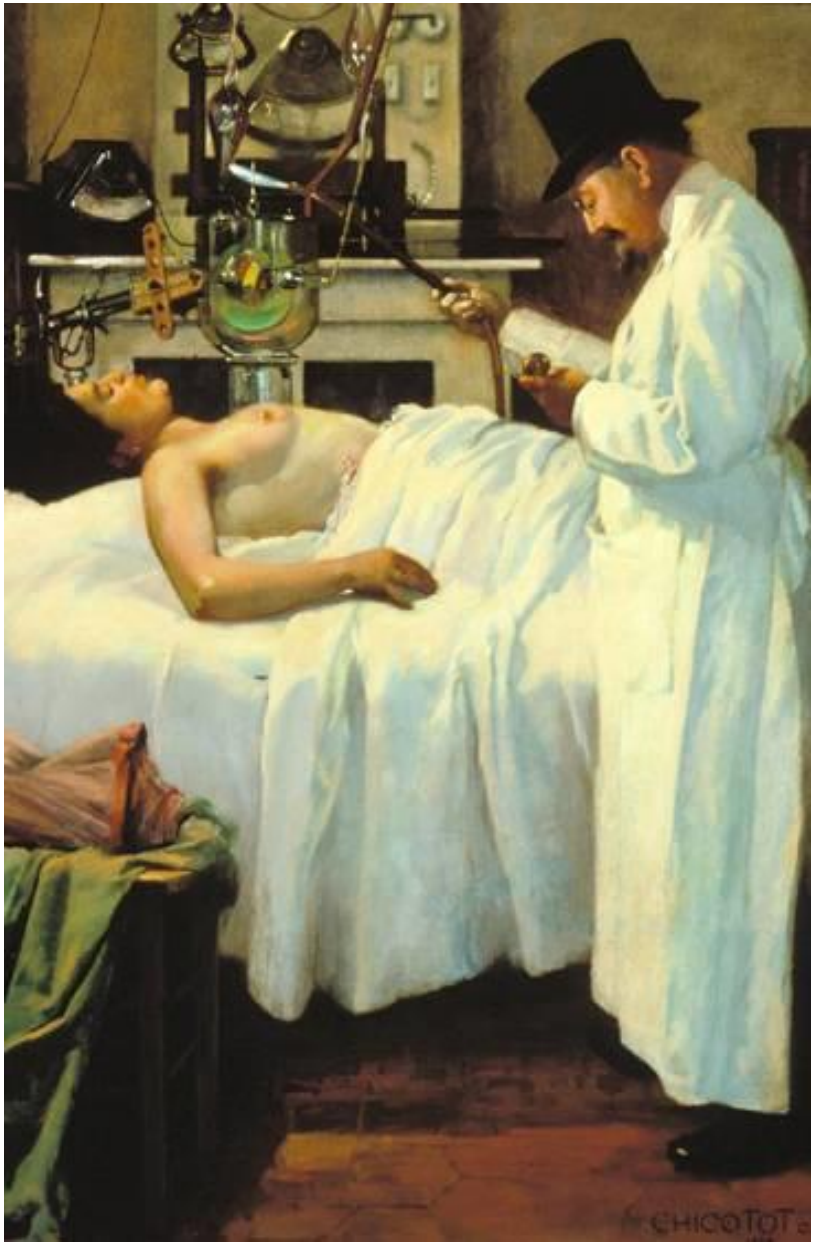

DISCLOSURES

- **I am radiation oncologist**

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Breast cancer and the Radiation Oncologist

- Prevention and genetic testing
- Early detection
- Effective treatment of pre-malignant lesions
- Effective local-regional therapy
- Effective adjuvant systemic therapy
- Treatment of locally advanced and metastatic disease

….but consider the impact of your treatment

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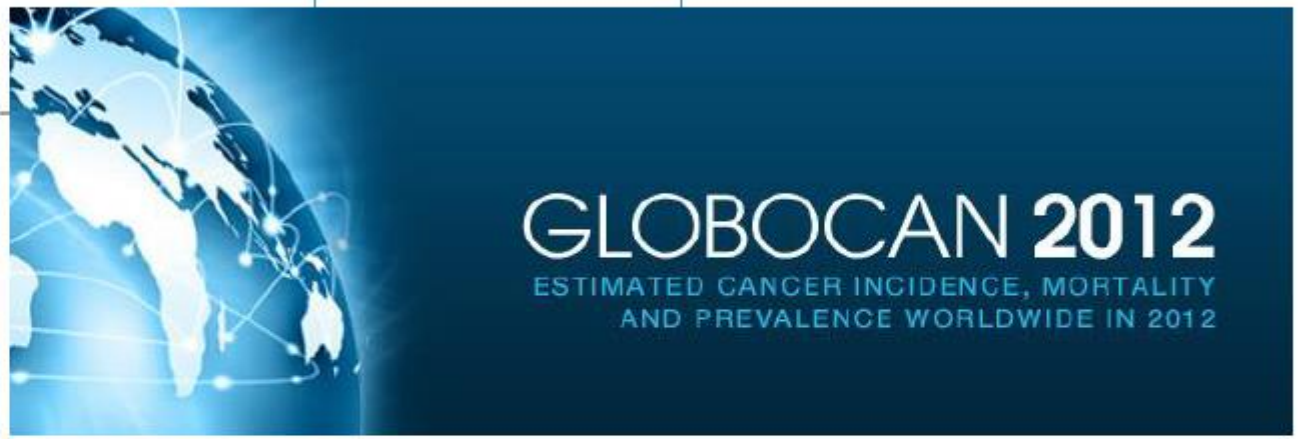
International Agency for Research on Cancer

World Health Organization

GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012

QUICK LINKS

- Population Fact Sheets
- Cancer Fact Sheets
- Simple Maps
- Predictions
- FAQ



You are here: **Home**

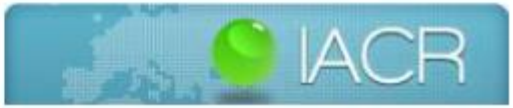
THE GLOBOCAN PROJECT

Welcome to the **GLOBOCAN** project. The aim of the project is to provide contemporary estimates of the incidence of, mortality and prevalence from major types of cancer, at national level, for 184 countries of the world. The GLOBOCAN estimates are presented for **2012**, separately for each sex. 1-, 3- and 5-year prevalence data are available for the adult population only (ages 15 and over). Please note that:

1. These estimates are based on the most recent data available at IARC and on information publically available on the Internet, but more recent figures may be available directly from local sources.
2. Because the sources of data are continuously improving in quality and extent, estimates may not be truly comparable overtime and **care should be taken when comparing these estimates with those published earlier**. The observed differences may be the

Cancer Mondial

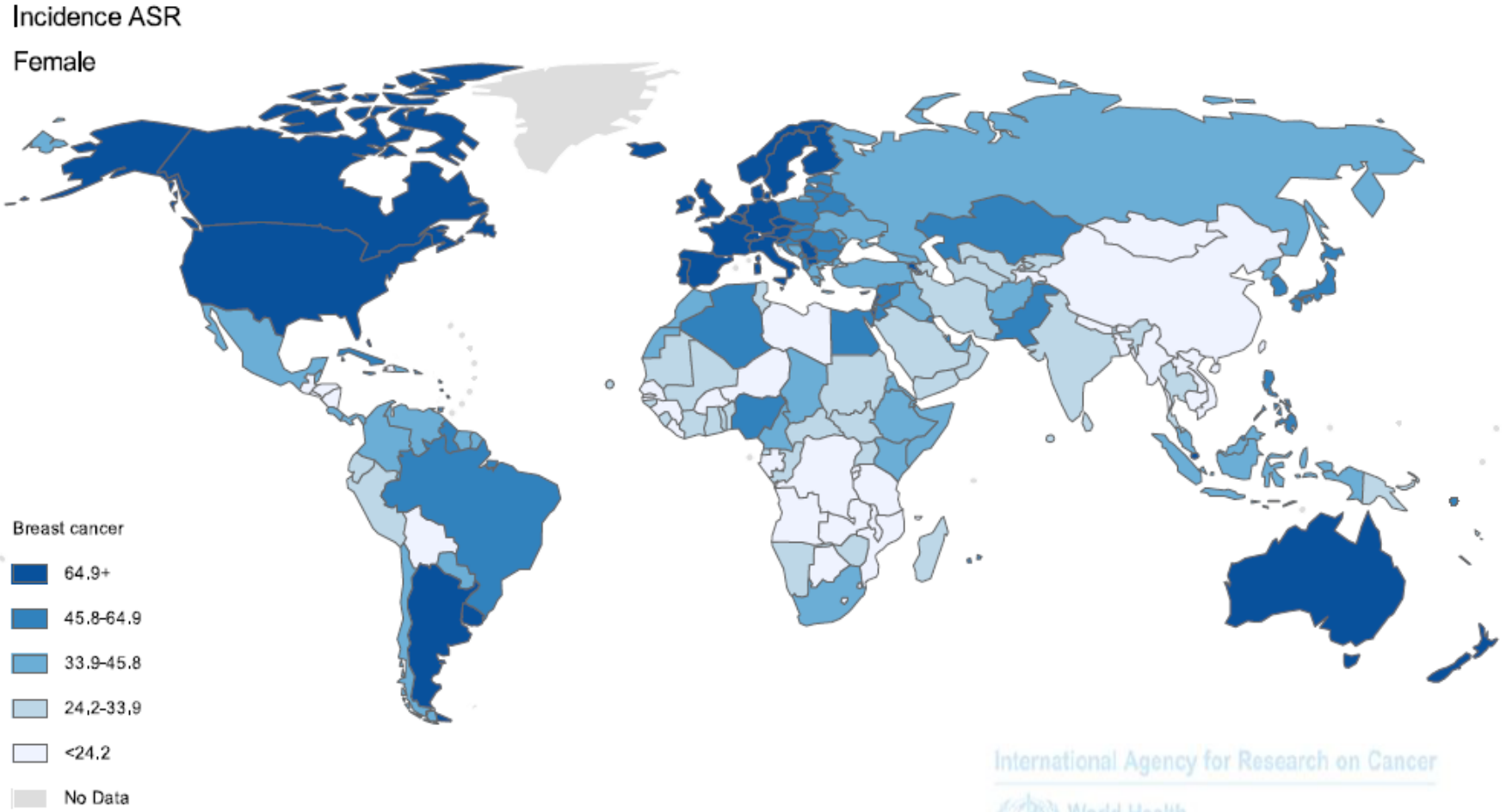
CI5



IACR

http://globocan.iarc.fr/Default.aspx

Incidence of female breast cancer, 2012 (nationwide estimates)



Source: GLOBOCAN 2012 (IARC)

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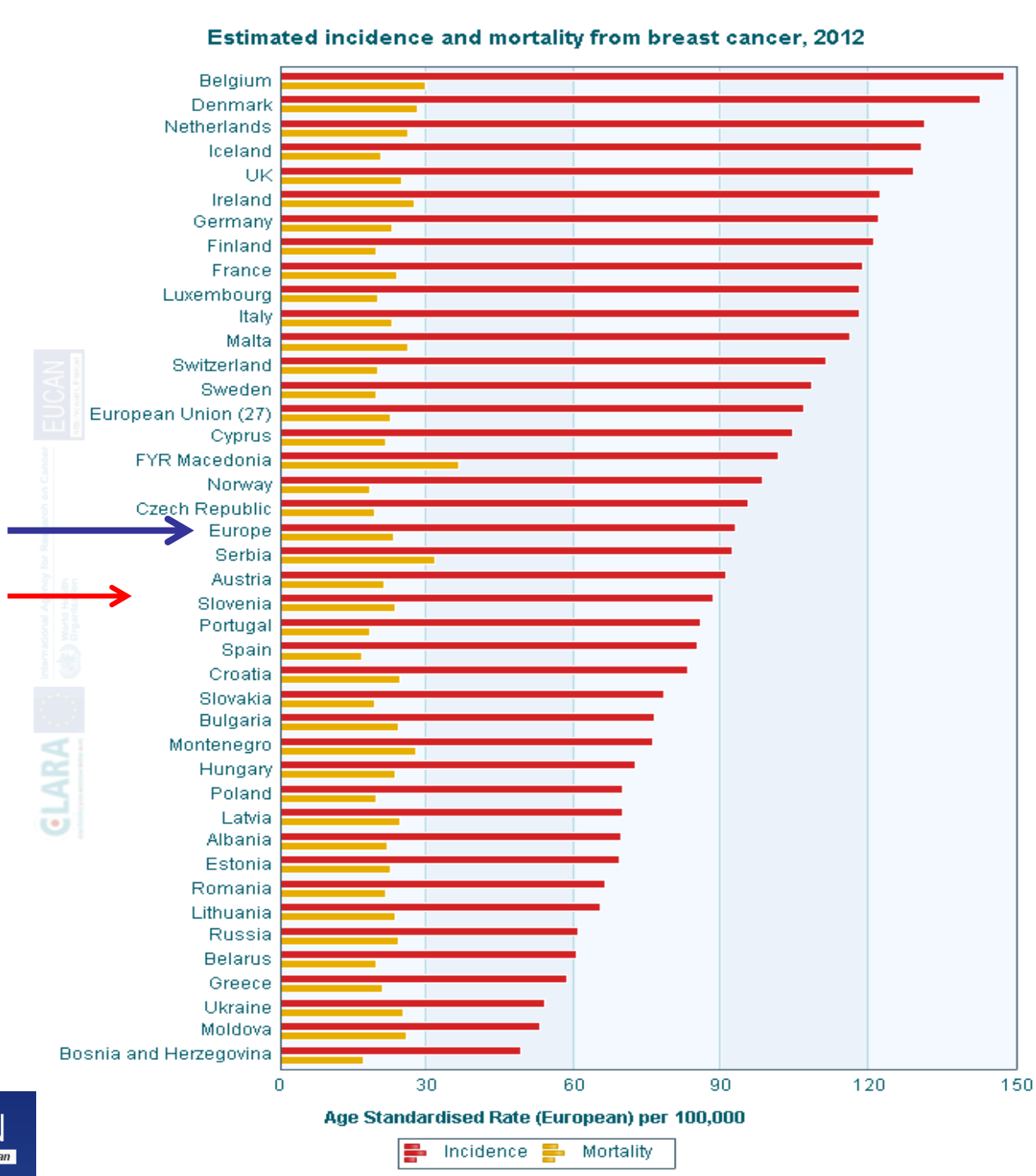
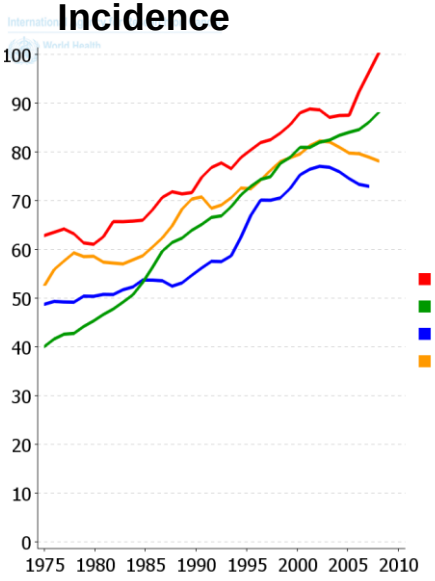


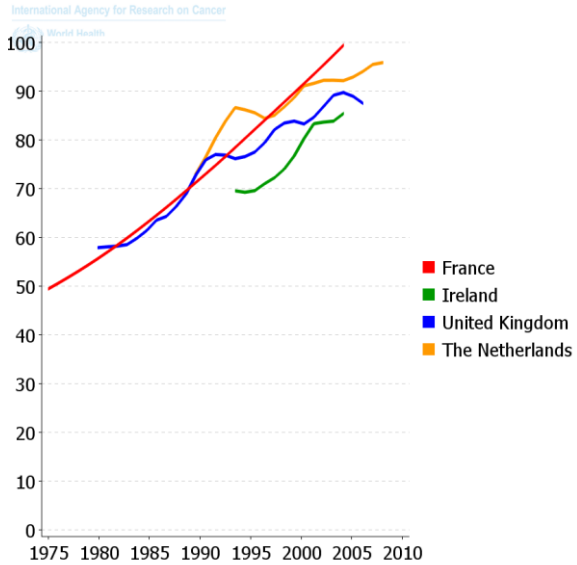
International Agency for Research on Cancer
World Health Organization

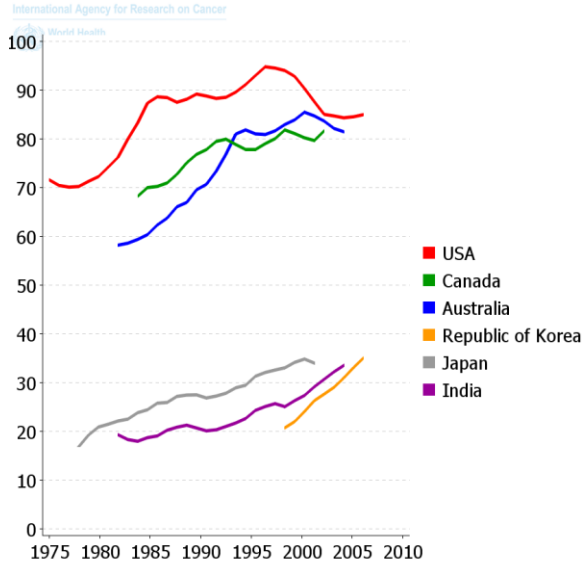
EUCAN
http://eco.iarc.fr/eucan

Comparison of trends in incidence and mortality of female breast cancer, 1975-2010, in selected countries

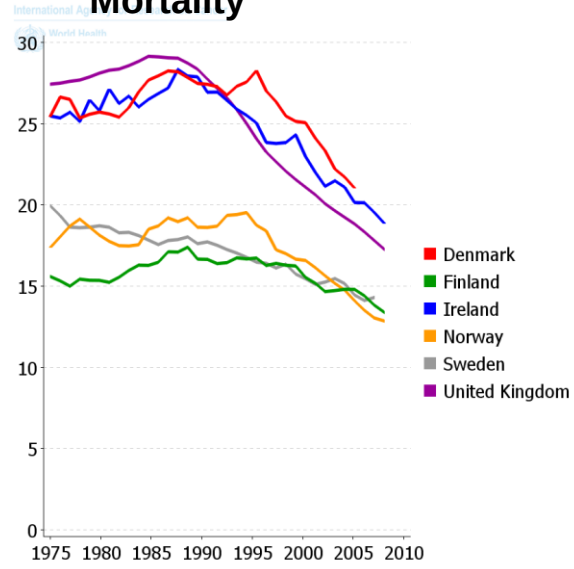
Incidence

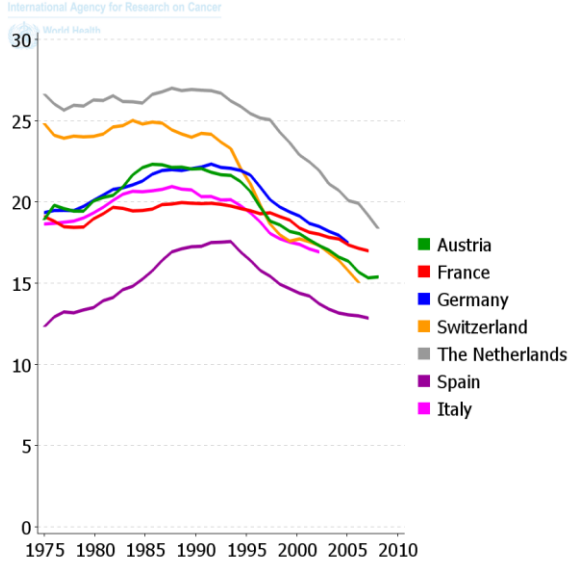


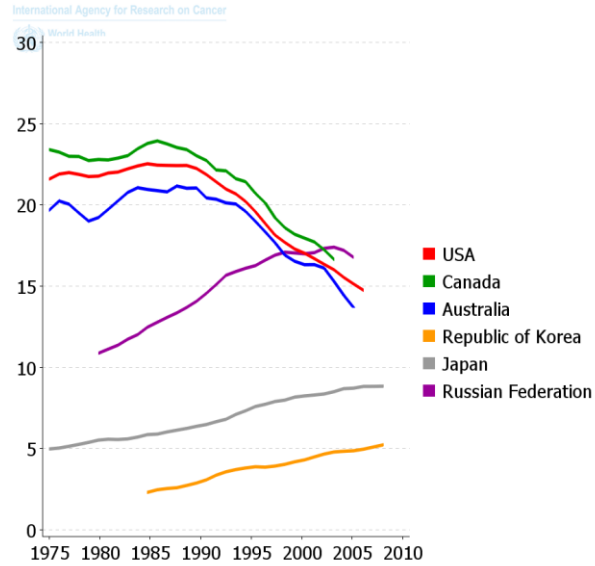




Mortality







Rates shown are age-standardised rate per 100,000 using the standard world population

Source: *Globocan, 2008*

Prognostic factors for recurrence

•**Tumour and patient factors:**

Family history with or without BRCA1/2 mutation

Age

- Tumour size and stage
- Vascular Invasion
- Surgical positive margin
- Young age

•Treatment related

- Radiotherapy
- Adjuvant systemic therapy

But also related to biological sub-type

Risk factors for breast cancer

-BRCA 1 and BRCA 2 Mutations

-Life style

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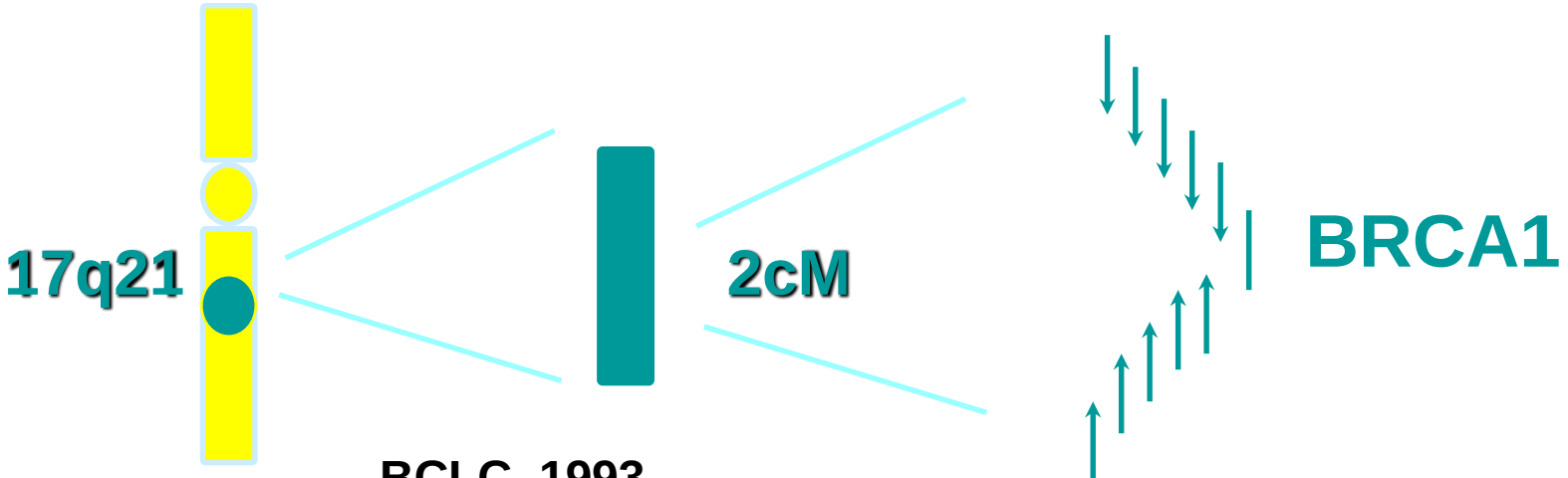
Lifestyle factors which might be modified to reduce breast cancer incidence in the UK

Factor	% of breast cancers attributable to lifestyle risk factor that might be modified
Alcohol	6
Overweight and obesity	9
Physical exercise	3
Post-menopausal hormones	3
Ionizing radiation	1
Occupation	5
Reproduction (breast-feeding)	3
Total	**27**

This is the theoretical maximum amount. Realistically, not all this could be achieved.

So lifestyle changes can only make a modest contribution to reduction in breast cancer..

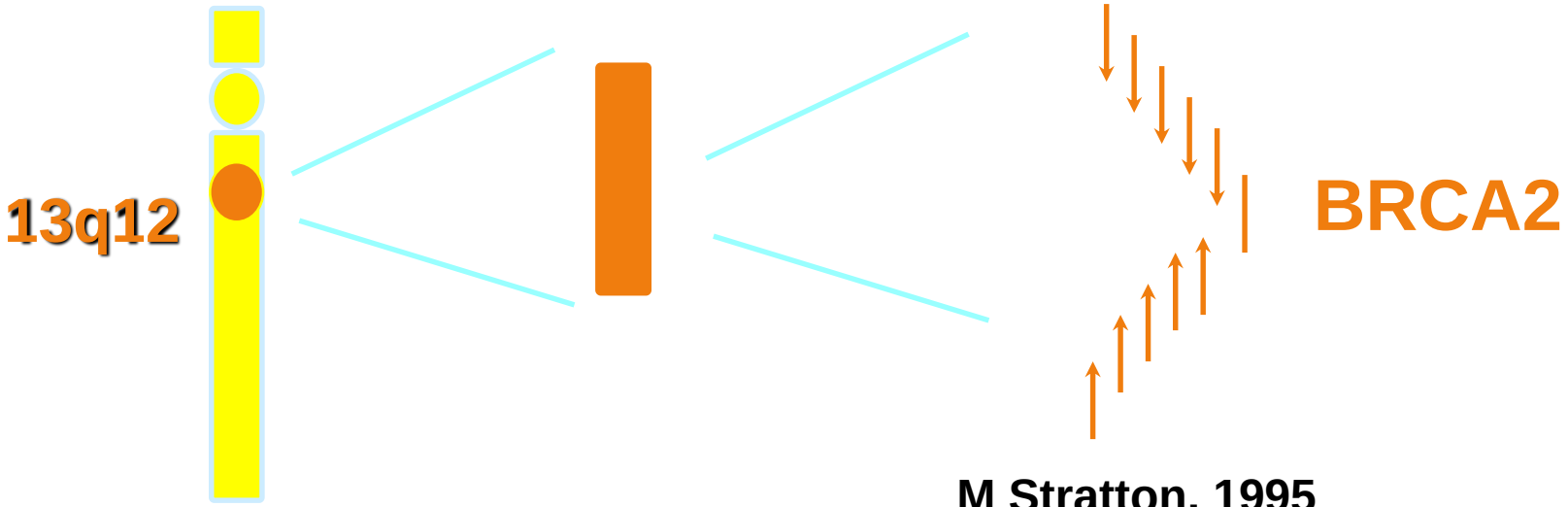
Parkin et al Br J Cancer 2011;105(S2):S77-S81



MC King, 1990

BCLC, 1993
Breast Cancer Linkage Consortium

M Skolnick, 1994
Myriad Genetics



BCLC, M Stratton, 1994

M Stratton, 1995

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BRCA gene products are involved in:

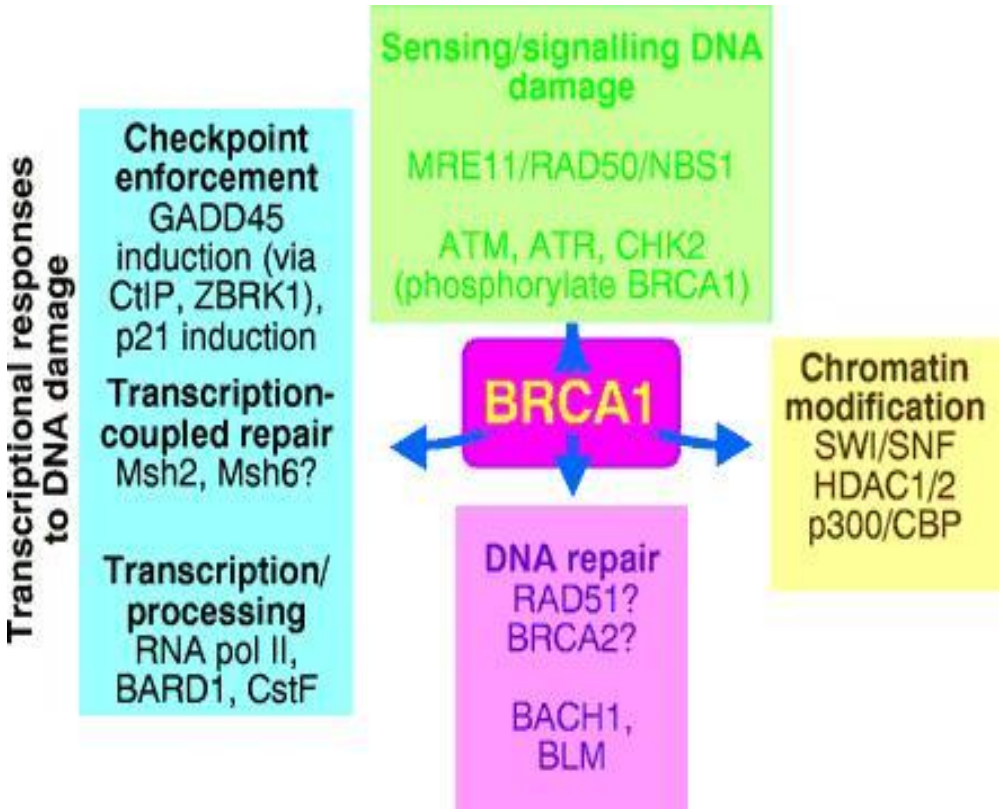
Double-strand break repair mechanisms

Cell-cycle checkpoints control

Regulation of apoptosis

"Caretakers" genes

Involved in the maintenance of genome integrity and stability



Protein partners of BRCA1 in DNA damage responses. There is accumulating evidence that BRCA1 performs multiple functions in the cellular response to DNA damage through its interactions with different protein partners. The list of BRCA1-interacting proteins indicated here is not exhaustive but illustrates points made in the text (*Image Permit Pending* Venkitaraman,2001).

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BRCA1 and radiation sensitivity

Enhanced radiosensitivity of cell lines lacking functional BRCA1 protein (murine embryonic Brca1 $^{-/-}$ cell lines, human Brca1 $^{-/-}$ tumors)

Enhanced sensitivity to doxorubicin and to irradiation of "conditional knock-out" murine Brca1-/- cell lines

BRCA mutations

- **Major risk factor of breast cancer: up to 80% cumulative risk at age 70**
- **5 % of all women with breast cancer**
- **Up to 10% in young women < 35**
- **Also risk factor of ovarian cancer (BRCA1 and BRCA2), prostate, pancreas (BRCA2)**

Family history: the highest breast cancer risk factor

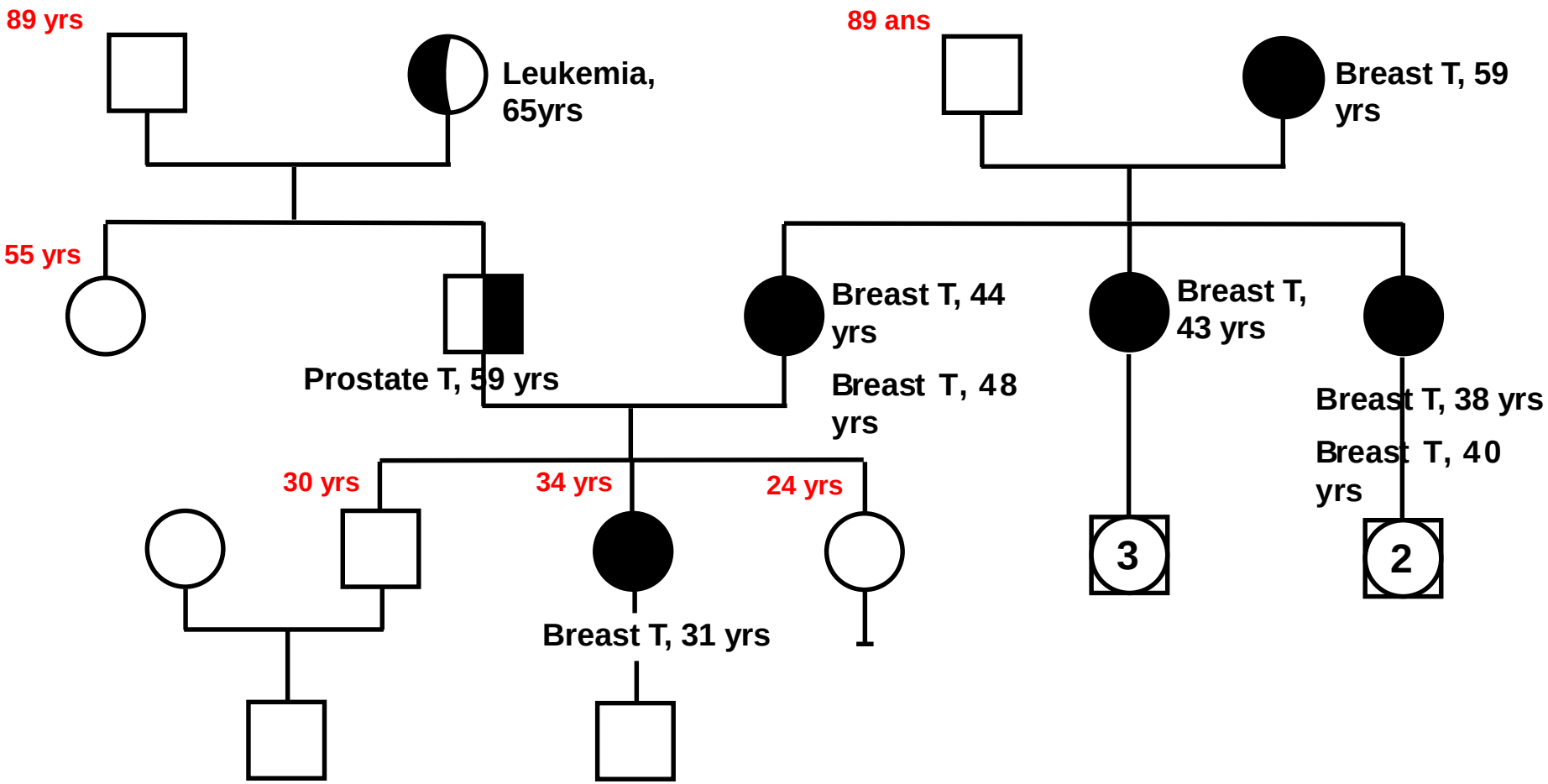
Relative risk according to the number of affected first degree relatives

Oxford meta-analysis
52 studies – 58 209 cases; 101 986 controls

Nb of affected first degree relatives	Relative risk
None (reference)	*1.00*
One affected	1.80 (CI: 1.70 – 1.91)
Two affected	2.93 (CI: 2.37 – 3.63)
Three affected	3.90 (CI: 2.03 – 7.49)

Lancet, 358: 1389, 2000

A breast cancer family with a dominant pattern



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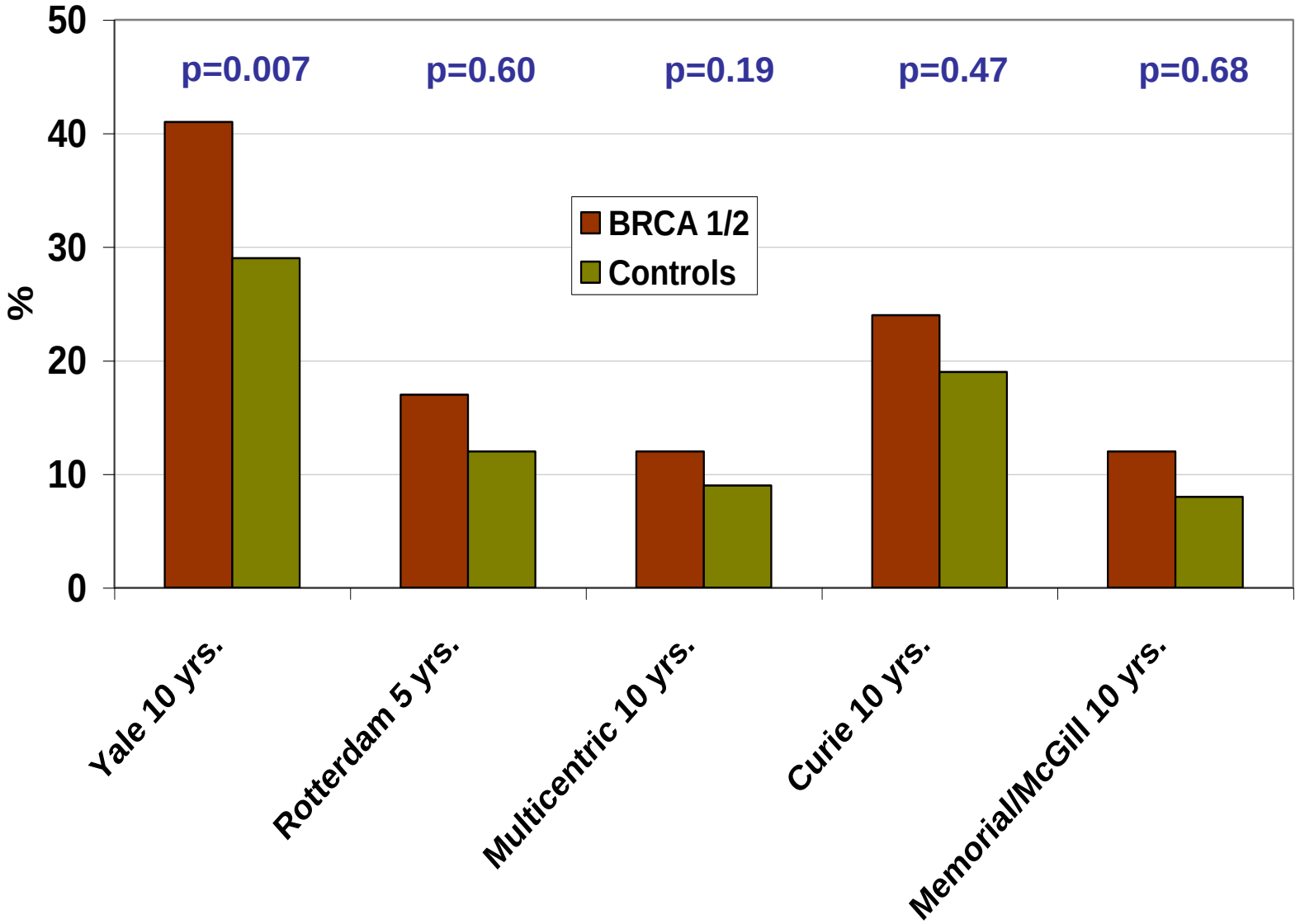
BRCA mutations

BRCA1 and BRCA2 **germline mutations are associated with a high risk of breast cancer, which may preclude breast-conserving treatments in carriers.**

Breast-conserving surgery and radiotherapy in *BRCA* mutation carriers

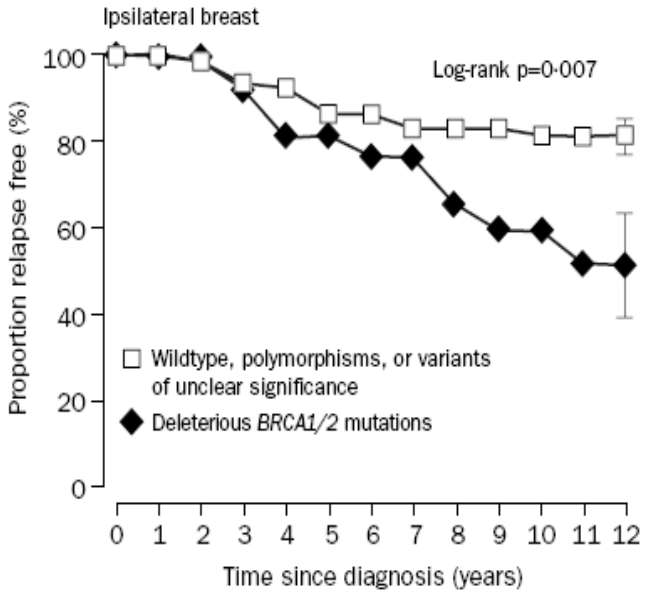
- **Retrospective, non-matched studies**
- **Retrospective, matched studies**
- **Prospective studies**

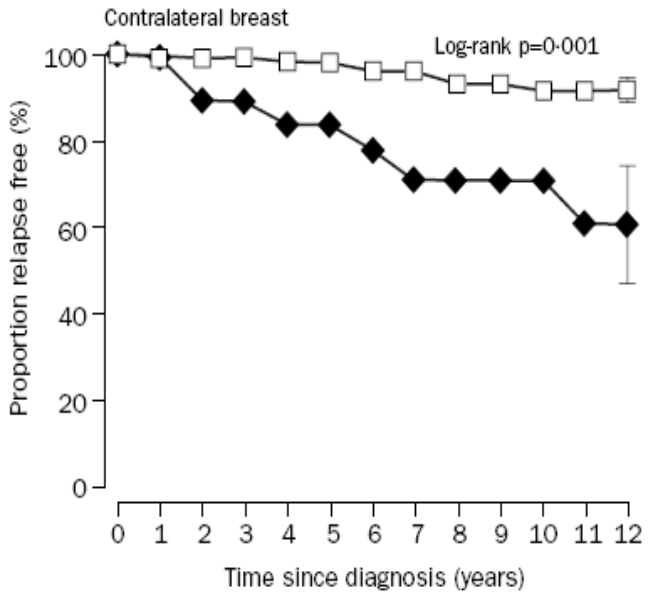
Ipsilateral breast recurrences



Results of BCT with radiotherapy in *BRCA* carriers. Retrospective study comparing *BRCA* mutation carriers vs. non carriers

	Period of study	Selection criteria	Median f/u (yrs.)	No. *BRCA* 1/2	No. Non-mutated	% 10-year IPBR		
						Carriers	Non-carriers	*p*
Haffty Lancet 2002	**1975-1998**	**Age < 42 Pts. Alive only**	**12.7**	**22 (15/7)**	**105**	**41**	**29**	***0.007***





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Contralateral Breast Cancer

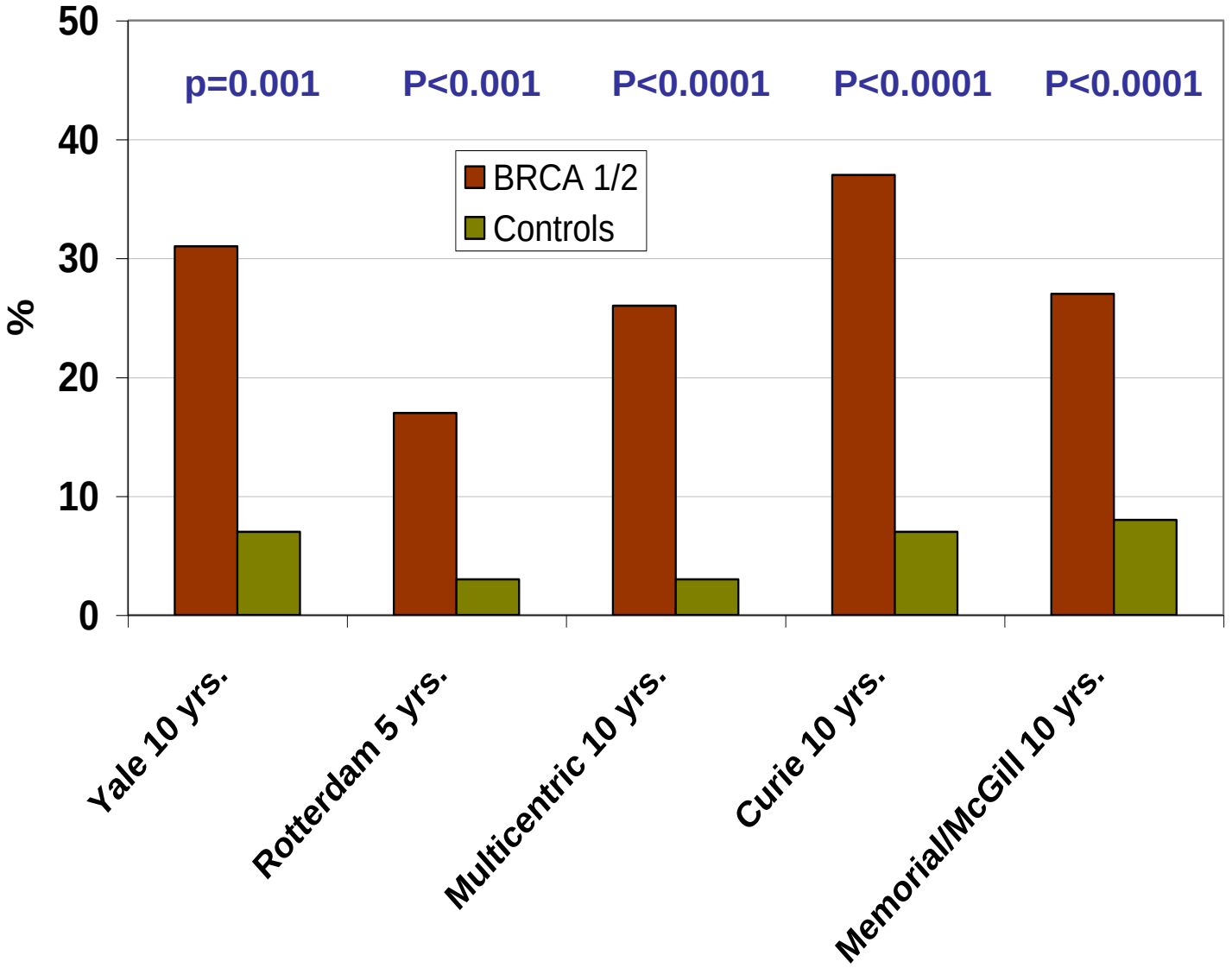

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Table 1: Outcomes of affected BRCA1/2 mutation carriers.

Study	Design	Patients	Followup	IBTR	BCSS	OS
Pierce et al. [40]	1	BCT = 302 Mast. = 353	8.2 to 8.9 years. Data projected to 15 years	BCT = 23.5% Mast. = 5.5%	BCT = 91.7% Mast. = 92.8% $P = 0.85$	BCT = 87.3% Mast. = 89.8% $P = 0.73$
Haffty et al. [22]	2	BRCA = 22 Sporadic = 105	12.7 years	BRCA = 41% Sporadic = 19% $P = 0.007$		
Garcia-Etiene et al. [23]	3	BRCA = 54 Sporadic = 162	4 years. Data projected to 10 years	BRCA = 27% Sporadic = 4% $P = 0.03$		
Pierce et al. [21]	4	BRCA = 160 Sporadic = 445	6.7 to 7.9 years. Data projected to 15 years	BRCA = 24% Sporadic = 17% $P = 0.19$		
Kirova et al. [20]	5	BRCA = 27 Familial = 104 Sporadic = 261	13.4 years	BRCA = 45% Familial = 31% Sporadic = 24% $P = 0.33$		Not significant at 20 years. Actual rates not reported.
Brekelmans et al. [25]	6	BRCA = 326 Familial = 311 Sporadic = 759	4.3 to 5.1 years. Data projected to 10 years	BRCA = 20 to 25% Familial = 6% Sporadic = 5% $P = 0.001$	BRCA = 62 to 68% Familial = 70% Sporadic = 59% $P = 0.17$	BRCA = 50 to 60% Familial = 66% Sporadic = 55% $P = 0.32$
Robson et al. [41]	7	BRCA = 28 Sporadic = 277	10.3 years	BRCA = 22% Sporadic = 7% $P = 0.25$	BRCA = 72% Sporadic = 87% $P = 0.02^*$	BRCA = 66% Sporadic = 81% $P = 0.05^*$
Robson et al. [19]	8	BRCA = 56 Sporadic = 440	9.7 years		BRCA1 = 63% BRCA2 = 86% Sporadic = 86% $P = < 0.0001^{**}$	

Largest series

Longest FU

Croshaw et al, 2011

Loco-Regional Therapy in *BRCA 1/2* Carriers

Collaborative Series

- Analysis of 655 women with *BRCA 1/2* – associated invasive breast cancer treated with BCT or Mastectomy (M)
- All patients had Stage I – III breast cancer
- 302 patients treated with BCS + RT; 353 with M (103 with RT; 241 without RT; 9 unknown)
- Median F/U
  - 8.2 years BCT
  - 8.9 years M

Pierce et al. BCRT, 2010

Patient, tumor and treatment characteristics by surgery type

Characteristic	*Lumpectomy*	*Mastectomy*
Frequency, n	**302**	**353**
Patient age at biopsy, years (p = 0.13)		
Median	**40.5**	**41.9**
Menopausal status at primary (p = 0.003)		
Pre-	**240 (79.5)**	**240 (68.0)**
Post-	**52 (17.2)**	**89 (25.2)**
Peri-	**10 (3.3)**	**24 (6.8)**
BRCA gene mutation (p = 0.01)		
1	**197 (65.2)**	**197 (55.8)**
2	**105 (34.8)**	**156 (44.2)**
Histology (p = 0.07)		
Infiltrating ductal	**258 (85.4)**	**292 (82.7)**
Lobular or Infiltrating ductal & lobular	**10 (3.3)**	**26 (7.4)**
Medullary or other	**34 (11.2)**	**35 (9.9)**
Pathologic T-stage (p = 0.001)		
T0/T1	**214 (70.8)**	**203 (57.5)**
T2	**81 (26.8)**	**125 (35.4)**
T3	**4 (1.3)**	**16 (4.5)**
Estrogen receptor (p = 0.006)		
Positive	**90 (29.8)**	**126 (35.7)**
Negative	**154 (51.0)**	**131 (37.1)**
Unknown	**54 (17.9)**	**93 (26.4)**

Pierce et al. BCRT, 2010

Patient, tumor and treatment characteristics by surgery type

Characteristic	*Lumpectomy*	*Mastectomy*
Final microscopic surgical margins (p = 0.003)		
Positive	**16 (5.3)**	**4 (1.1)**
Negative	**248 (82.1)**	**272 (77.1)**
Unknown	**38 (12.6)**	**73 (20.7)**
Nodal surgery		
Positive lymph nodes removed (p = 0.004)		
0	**210 (71.9)**	**223 (63.4)**
1 – 3	**62 (21.2)**	**76 (21.6)**
4+	**20 (6.9)**	**53 (15.1)**
Radiotherapy		
No	**0**	**241 (68.3)**
Yes	**302 (100)**	**103 (29.2)**
Chemotherapy (p = 0.20)		
No	**82 (27.2)**	**108 (30.6)**
Yes	**219 (72.5)**	**231 (65.4)**
Hormone therapy (p = 0.09)		
No	**202 (66.9)**	**210 (59.5)**
Yes	**90 (29.8)**	**125 (35.4)**
Tamoxifen	**81 (90.0)**	**106 (84.8)**
Other	**9 (10.0)**	**19 (15.2)**
Adjuvant therapy (p = 0. 35)		
Yes	**254 (84.1)**	**287 (81.3)**
No	**48 (15.9)**	**66 (18.7)**
Bilateral oophorectomy (p = 0.28)		
No	**141 (46.7)**	**150 (42.5)**
Yes	**161 (53.3)**	**203 (57.5)**
Prophylactic contralateral mastectomy (p <0.0001)		
No	**256 (84.8)**	**214 (60.6)**
Yes	**44 (14.6)**	**134 (38.0)**

Pierce et al. BCRT, 2010

Significant multivariate hazard ratios for local-component of first failure

Sample/Characteristic	Hazard ratio (95% CI)	p-value
Total sample (N = 655)		
Treatment decision:		
BCT	**4.5 (2.3 – 8.9)**	**<0.0001**
Mastectomy	**1.0**	
BCT sample (N = 302)		
Gene mutation		
BRCA 1	**1.00**	
BRCA 2	**2.9 (1.2 – 7.1)**	**0.019**
Adjuvant chemotherapy		
Yes	**1.0**	
No	**5.4 (2.3 – 13.3)**	**0.0001**
Mastectomy sample (N = 353)		
Histology		
Infiltrating ductal carcinoma (IDC)	**1.0**	
IDC + lobular/Lobular carcinoma	**9.9 (2.1 – 47.1)**	**0.0003**
Medullary/Other	**2.7 (0.4 – 17.3)**	**0.289**

Pierce et al. BCRT, 2010

Analysis of Local Failures (LF)

Median time to failure

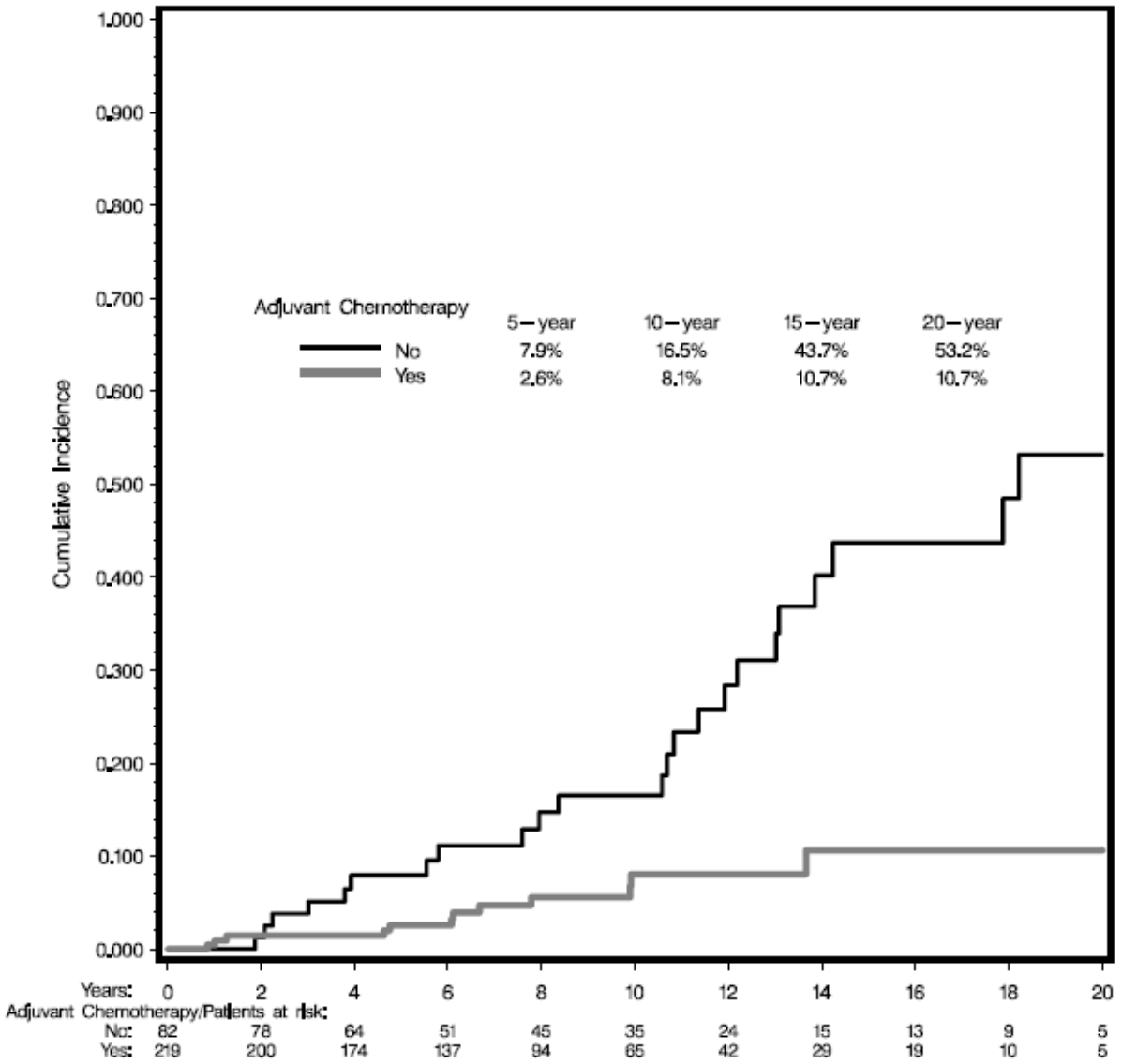
7.8 yrs with BCT

9.4 yrs with M

Among BCT patients with LF, 70% in different quadrant, of different histology, or both

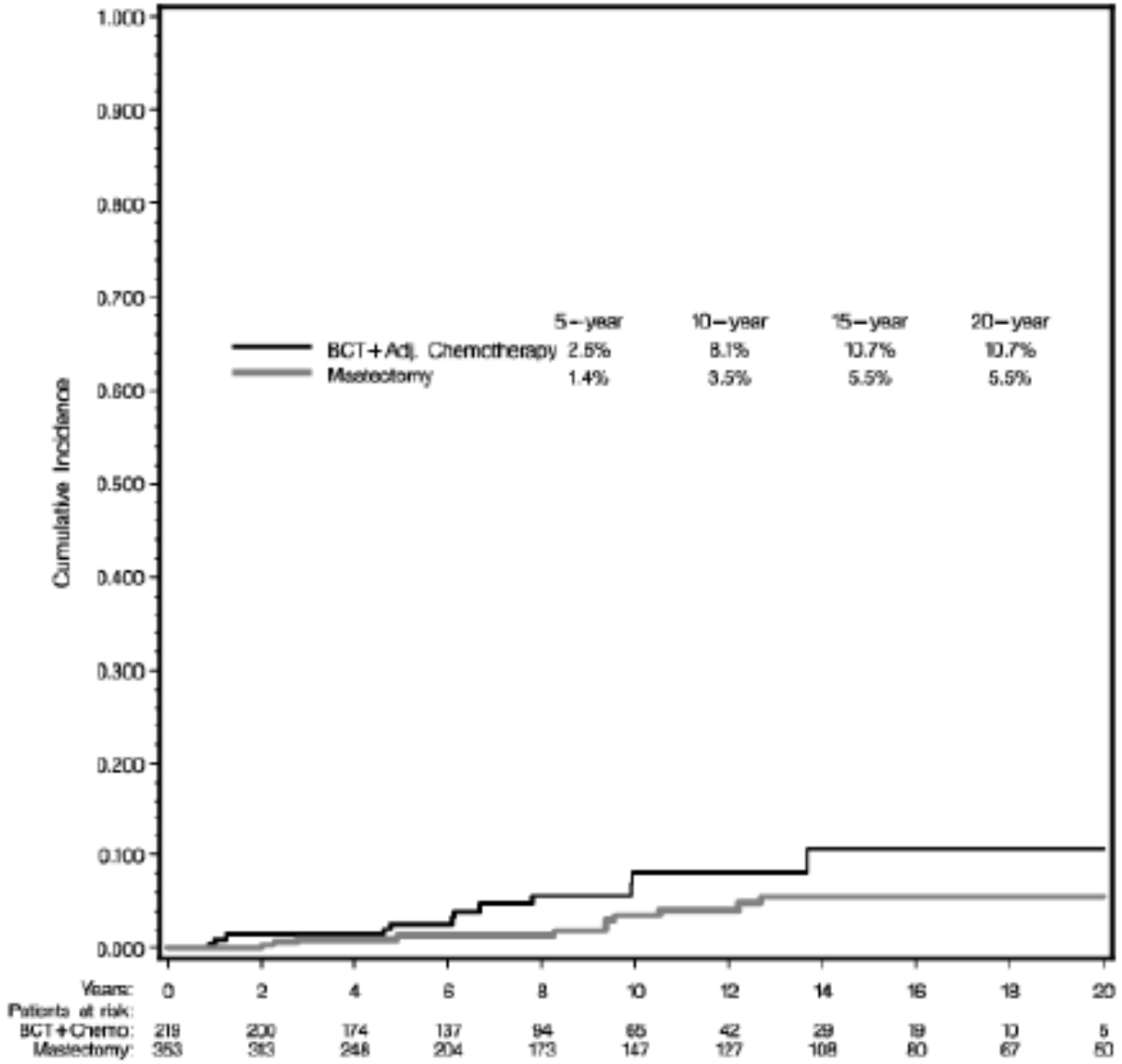
Pierce et al. BCRT, 2010

Cumulative incidence estimates for local component of first failure for patients choosing breast conservation by use of adjuvant chemotherapy



p <0.0001

Local failure among BCT pts receiving chemotherapy vs. M patients



p = 0.082

Local Failure (LF) in BCT Subgroup

Hormonal therapy: Uni-variate analysis suggested trend in reduction of LF with tamoxifen in BRCA2 carriers

BRCA1 p=0.13
BRCA2 p=0.08

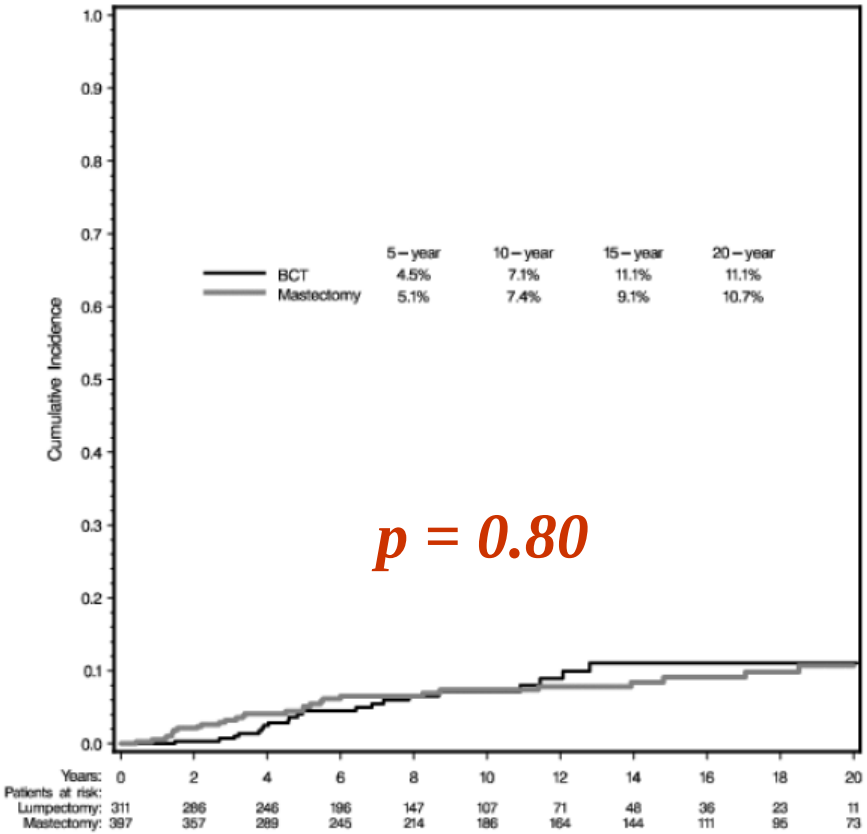
Oophorectomy did not significantly impact LF*

BRCA1 p=0.27
BRCA2 p=0.125

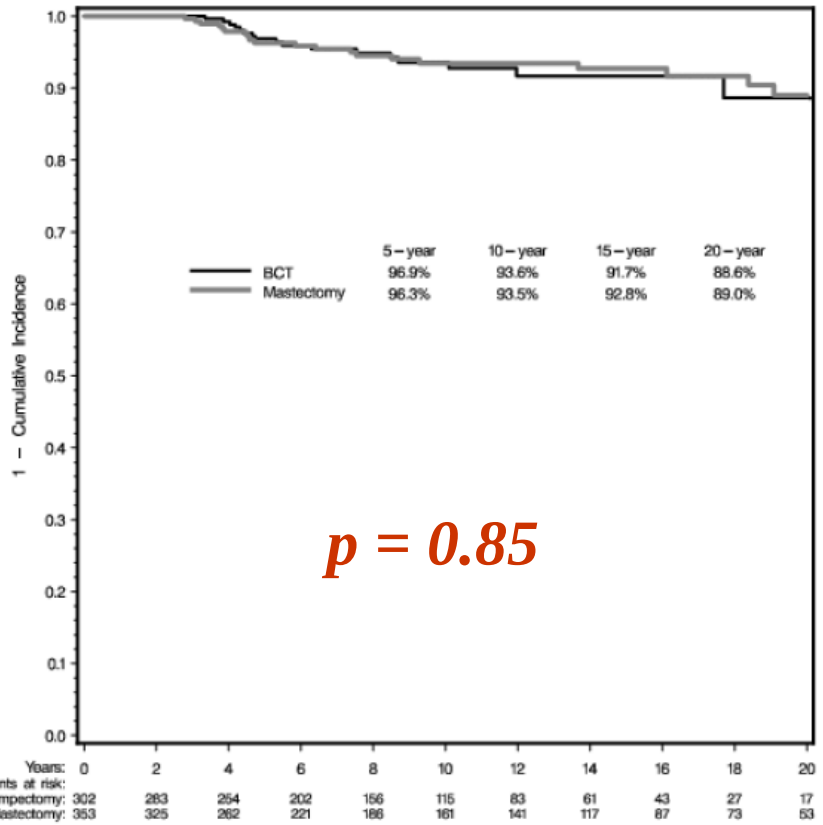
***but 73% received chemotherapy;**

only 16% received no adjuvant therapy.

Pierce et al. BCRT, 2010



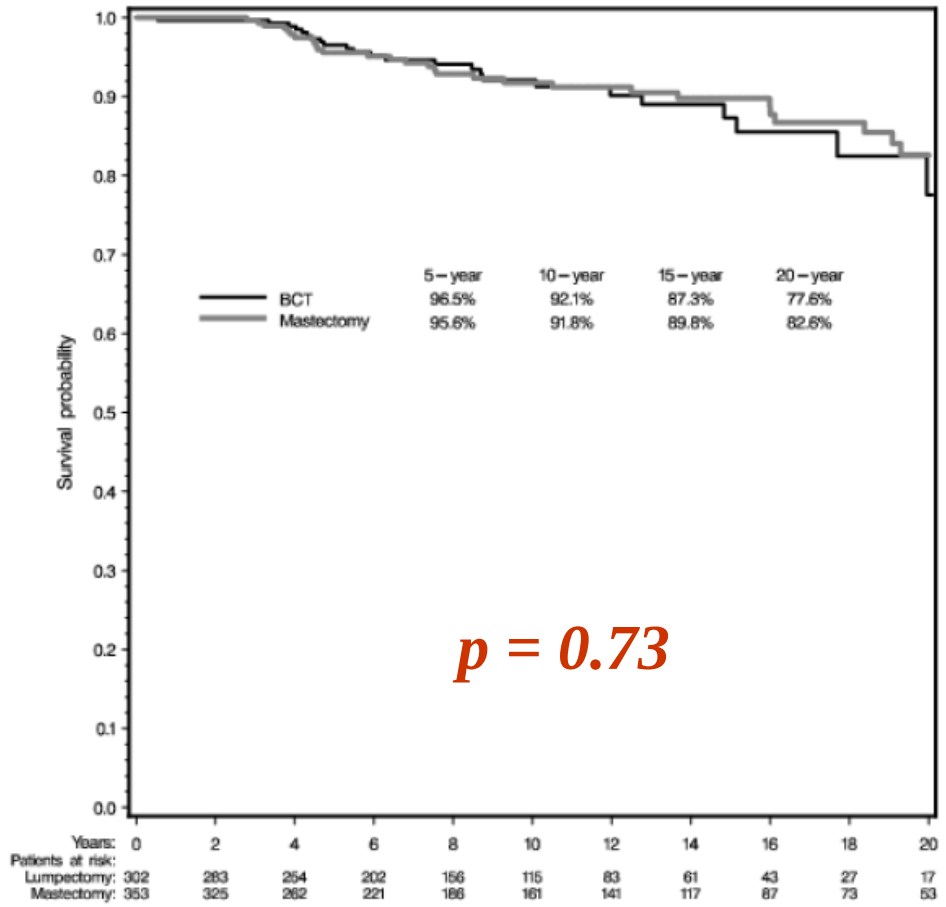
Cumulative incidence estimates for distant component of first failure by choice of primary treatment



Breast cancer-specific survival by choice of primary treatment

Pierce et al. BCRT, 2010

Overall survival by choice of primary treatment



Only factor significant on MVA analysis was development of ovarian cancer. (HR 5.0, p = 0.0001)

Pierce et al. BCRT, 2010

Institut Curie series

Breast Cancer Res Treat
DOI 10.1007/s10549-009-0685-6

CLINICAL TRIAL

Is the breast-conserving treatment with radiotherapy appropriate in *BRCA1/2* mutation carriers? Long-term results and review of the literature

Youlia M. Kirova · Alexia Savignoni · Brigitte Sigal-Zafrani · Anne de La Rochefordiere · Rémy J. Salmon · Pascale This · Bernard Asselain · Dominique Stoppa-Lyonnet · Alain Fourquet

Background and Purpose

- **Because tumors in *BRCA* mutation carriers might be more sensitive to radiation with increased risk of second primaries, we report after long term follow-up whether mutation status influenced the rate of ipsilateral tumors after breast-conserving treatment.**

- **A case-control study was performed**

Patients Selection

- **Retrospective analysis of BC patients treated at the Institut Curie between 1981 and 1999.**

- **Genetic testing was proposed to women who presented one of the following family criteria:**

  - **2 first-degree relatives affected with cancer, with at least one with invasive BC before 41 yrs, or one with ovarian cancer at any age**

  - **At least 3 first- or second-degree relatives from the same lineage affected with invasive breast or ovarian cancer at any age**

Patients and Methods

131 pts with family history (with 136 breast tumors) were tested.

They were matched to 261 control BC pts (with 271 tumors) without family history (sporadic cases), chosen from a population of 9179 pts, treated between 1981 and 1999.

Matching criteria

1. Age at diagnosis
2. Year of treatment
3. Follow-up of controls at least equal to the time-interval between diagnosis and genetic testing in cases.

BRCA status

- BRCA status was unknown in all pts but one at the time of diagnosis and treatment.

- Mutations were found in 20.6% pts with familial history (21.3% tumors)
  - BRCA1: 19 pts (with 21 tumors)
  - BRCA2: 8 pts (with 8 tumors)

Follow-up

- **Median follow-up for all patients 13.4 years**

–Cases (BRCA1/2 mutation carriers):	**13.9 years**	**[3-19.2]**
–Familial cases (Non carriers)	**13.4 years**	**[2.3-22.5]**
–Controls:	**13 years**	**[2.7-24.8]**

Patients characteristics

	BRCA1/2 carriers n= 27	Non carriers (n= 104)	Sporadic cases (n= 261)	p
Median age (yrs) Range	43 [26-60]	43.5 [24-78]	43 [23-79]	0.92
Premenopausal %	85	70	76	0.24
Mean interval btwn diagn.& gen test (mths) Range	39.5 [-17 - 158]	38 [6 - 98]	-	-
Median probability of being a carrier % Range	90 [73 - 98]	50 [6 - 98]		0.002

Clinical tumors characteristics

	BRCA1/2 carriers n = 29	Non carriers n= 107	Sporadic tumors n=271	p
T stage % non palpable T1-2 T3 Tx	 10 90 0 0	 15 80 0 5	 18 78 1 3	0.85
Median tumor size (mm) Range	20 [0-35]	15 [0-35]	20 [0-70]	0.49
N stage [%] N0 N1	 90 10	 84 16	 70 30	0.22

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Pathologic features

	BRCA1/2 carriers n = 29	Non carriers n= 107	Sporadic tumors n=271	p
Pathology % Medullary Others	 11.5 88.5	 1.1 98.9	 0.8 99.2	$< 10^{-4}$
Grade % I, II III	 31 69	 76 24	 81 19	$< 10^{-4}$
ER –ve %	48	28	21	0.018
PR -ve %	48	22	22	0.02
Ax. Node status % pN-ve pN+ve No LN dissection	 73 10 17	 46 19 35	 49 15 36	0.13

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Locoregional treatments

	BRCA1/2 carriers n = 29	Non carriers n= 107	Sporadic tumors n=271	p
Node Dissection %	82	65	64	0.14
Nodes Irradiation %	48	63	60	0.40
Whole breast dose (Gy) Median Range	 52 [45-62]	 52 [43-62]	 52 [45-66]	0.87
Tumor dose (Gy) Median Range	 65 [50-75]	 64 [50-78]	 65 [45-82]	0.75

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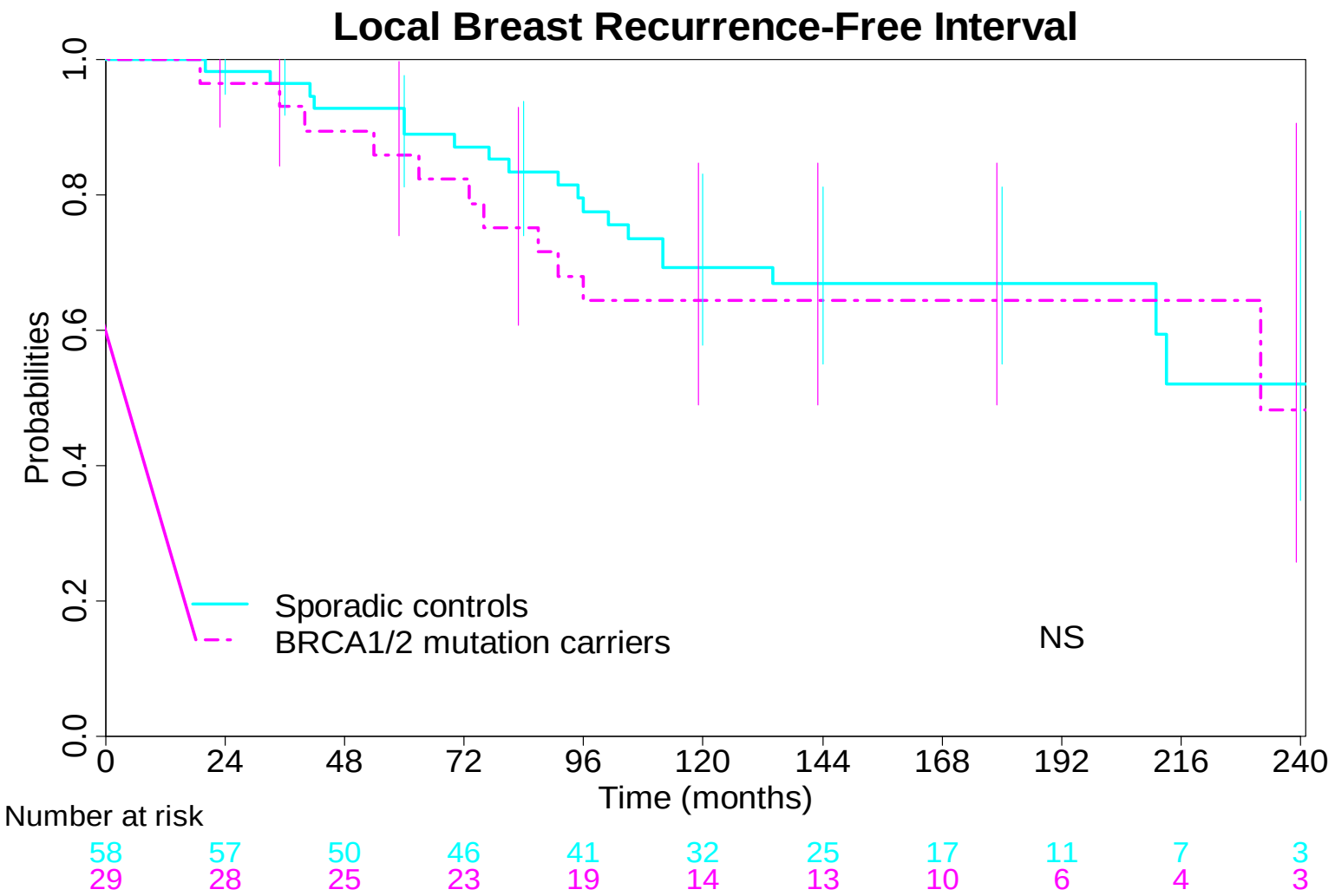
Adjuvant *medical* treatments

	BRCA1/2 carriers n = 29	Non carriers n= 107	Sporadic tumors n=271	p
Chemotherapy %	38	28	25	0.29
Hormone therapy %	7	13	6	0.045



Mutation carriers (n=29) and their controls (n=58)

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Multivariate analysis of breast recurrence risk (Cox's model)

	RR	IC 95%	*p*
Age (for every decreasing year)	**1.05**	**[1.02-1.07]**	$< 10^{-3}$

On multivariate analysis the age was the only significant predictor for the risk to develop ipsilateral breast tumor

BRCA mutation status, lymph node status, hormonal receptor status, and tumour grade were not significant predictors of local recurrence.

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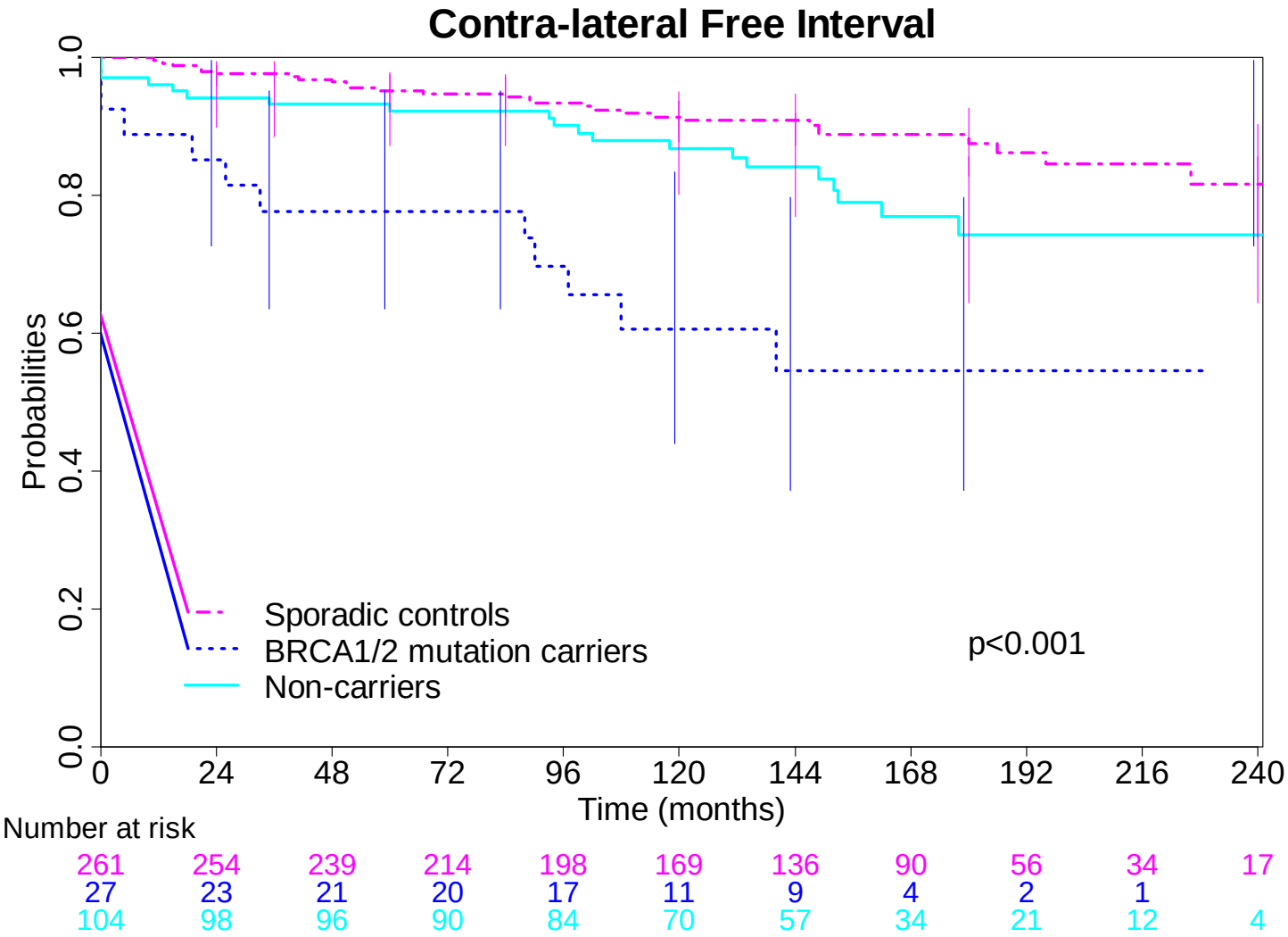

All patients

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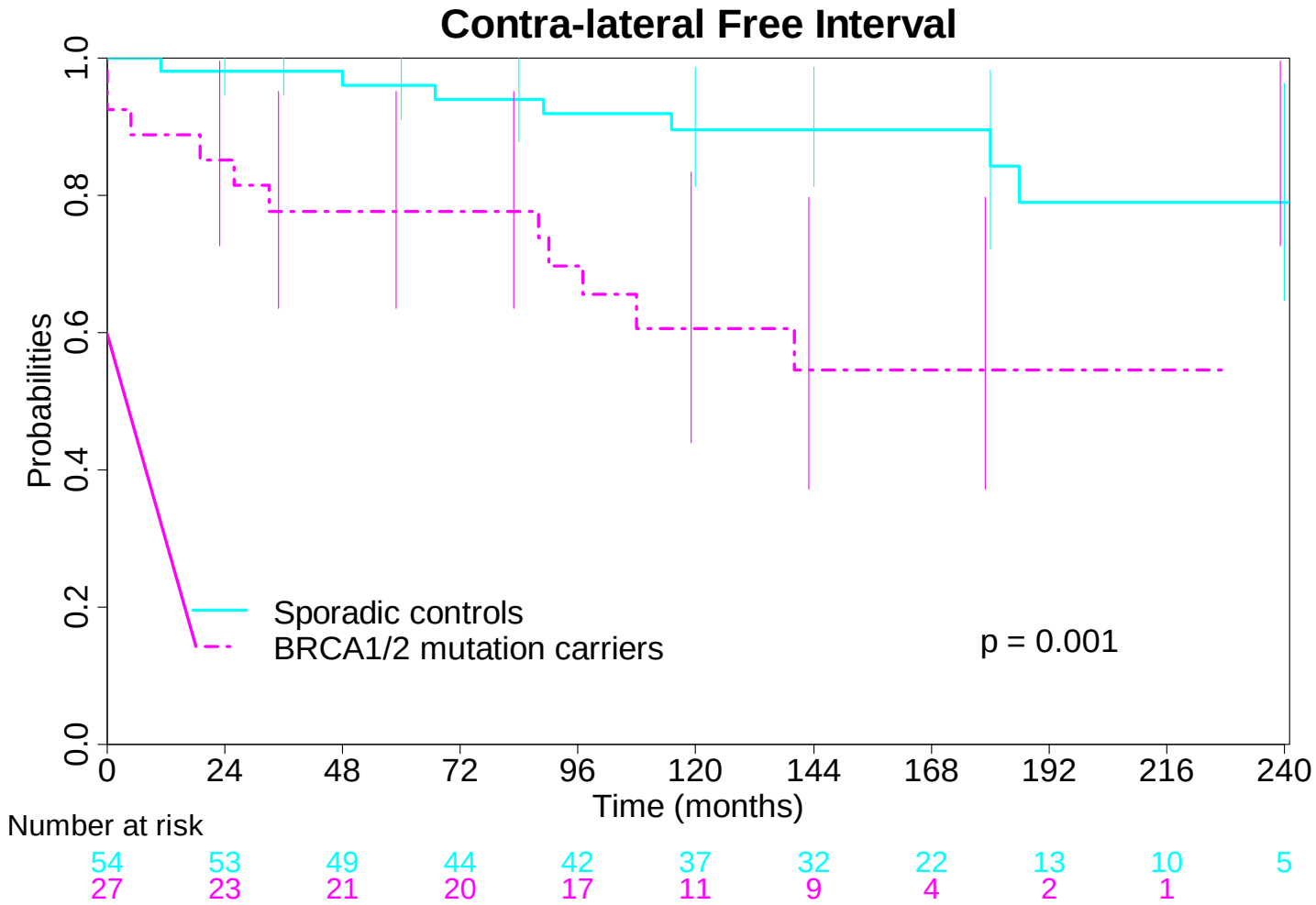

Mutation carriers (n=27) and their controls (n=54)

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Multivariate analysis of CBC (Cox's model)

	RR	IC 95%	*p*
Controls	**1**		
Non carriers	**1.9**	**[1.1-3.2]**	***< 10^{-3}***
***BRCA1/2* mutation carriers**	**5.2**	**[2.6-10.4]**	

On multivariate analysis the BRCA mutation status was the only significant predictor for the risk to develop contralateral cancer ($p<10^{-4}$).

Age, lymph node status, hormonal receptor status, and tumour grade were not significant predictors of local recurrence.

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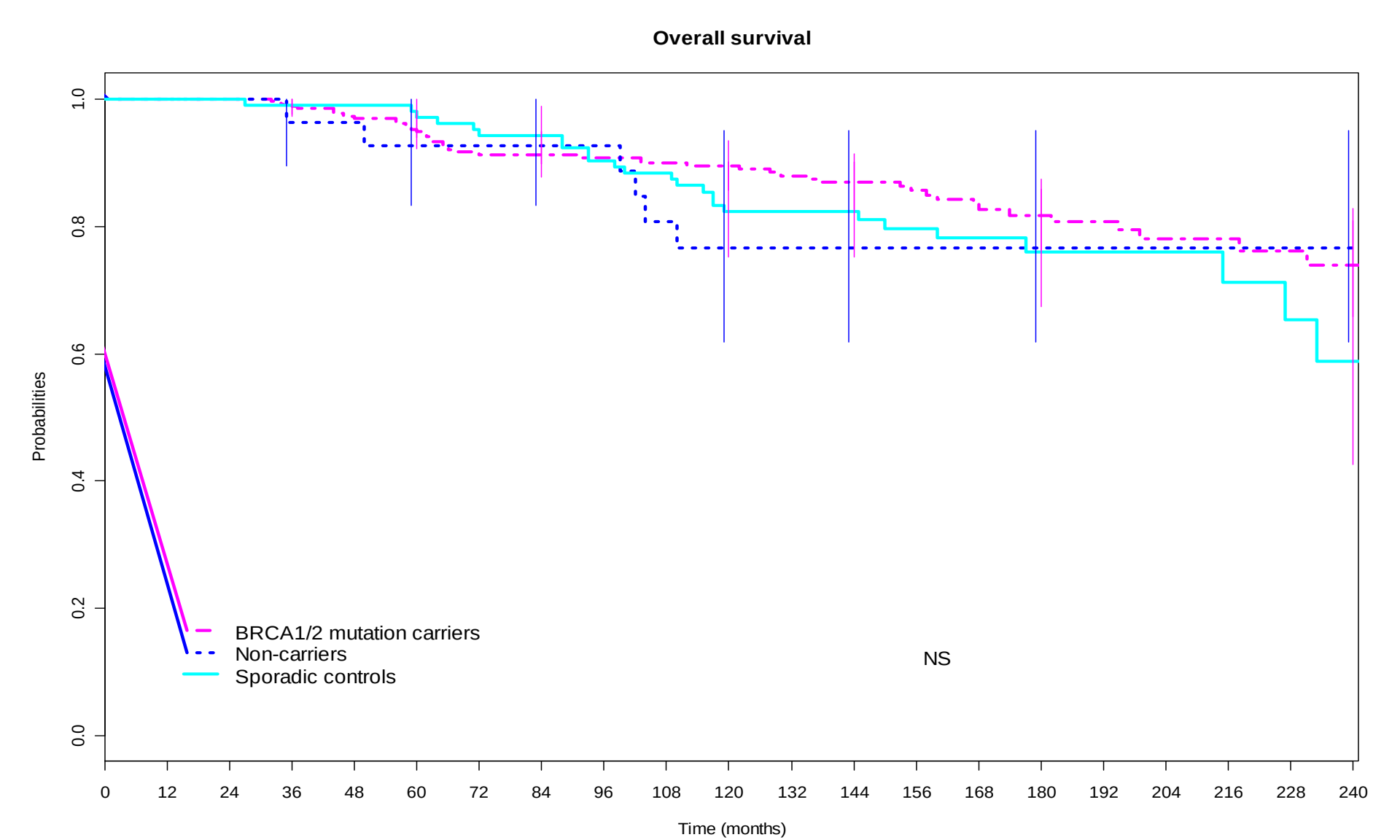

Number at risk

M.C.	261	259	246	224	211	186	153	103	66	42	21
Non M.C.	27	27	26	25	24	19	17	12	8	5	4
S.C.	104	104	103	98	93	78	66	43	28	15	6

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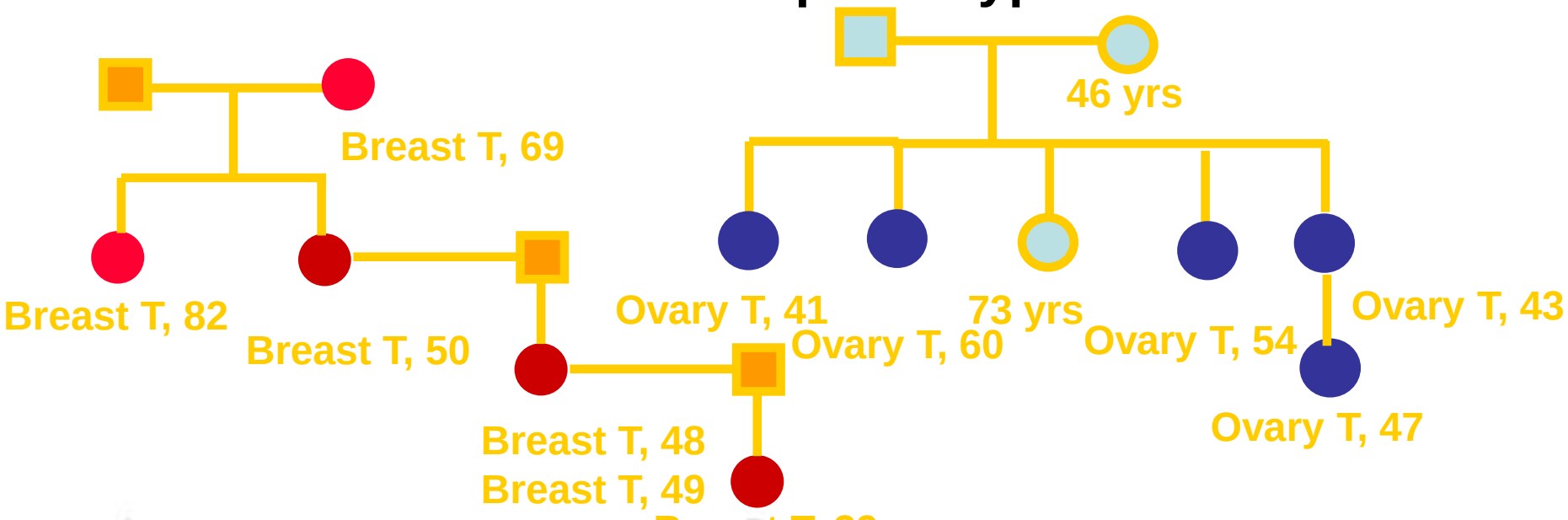
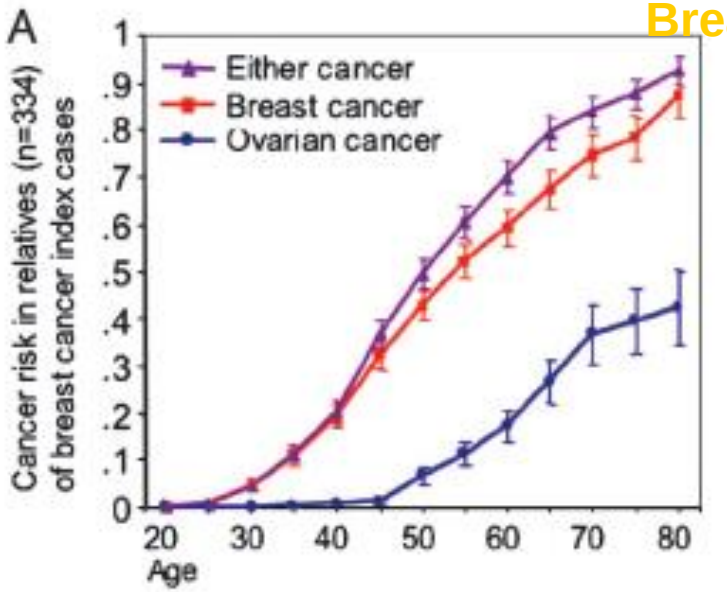
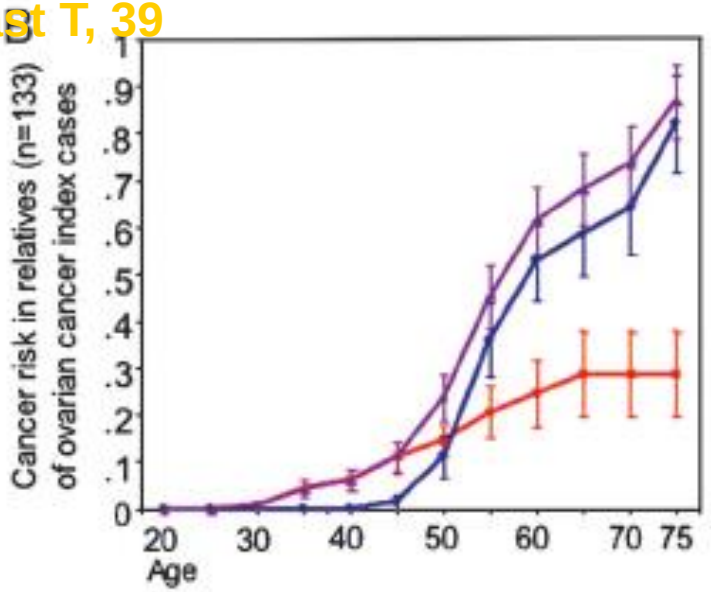
Two families with the same BRCA1 mutation but with a different phenotype







Simchoni et al, 2006

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Main features of the management of women carrying a *BRCA1* or *BRCA2* germline mutation

Annual breast screening with mammography, ultrasonography, and MRI, beginning at age 30

Prophylactic surgery

- **oophorectomy recommended between at age 40 when *BRCA1* mutation and delayed if *BRCA2* mutation**
- **mastectomy is an option which must be discussed at 30 yrs or latter (but not too late)**

Medical prevention (still in clinical trials)

- **Anti-estrogenes such as aromatase inhibitors after menopauses**

Rapid genetic counseling

Wevers et al, BMC Cancer 2011

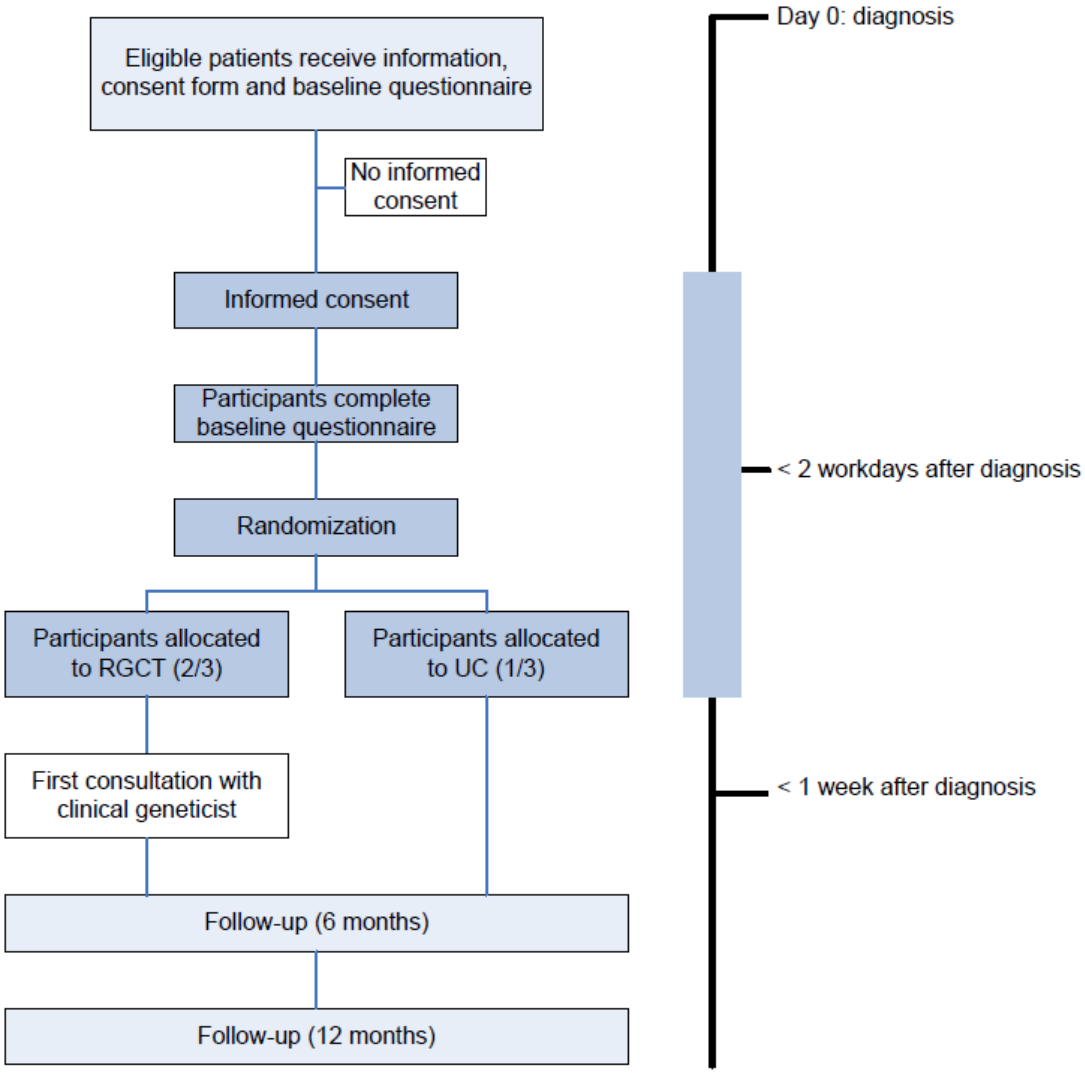

Figure 1 Study flow diagram.

Still running, evaluation of QoL

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Breast Conserving surgery and radiotherapy in *BRCA1* and *BRCA2* mutations carriers

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Prophylactic mastectomy

- **Prophylactic mastectomy has been shown to reduce the risk of breast cancer incidence or recurrence, but there is insufficient data to support an improvement in survival in affected or unaffected carriers**

- **The complexity of the problem demands a multidisciplinary approach within the context of a family cancer clinic.**

- *Menke-Pluymers MB, et al, Ned Tijdschr Geneeskd. 2005*
- *Meijers-Heijboer EJ, et al, Lancet. 2000*

Prophylactic mastectomy

- The resultant lack of knowledge drives and sustains patient anxiety, sometimes prompting them to select mastectomy in hopes of a cure while sacrificing cosmesis, body image, and perhaps sexuality
- *Kiebert GM, et al, J Clin Oncol. 1991*
- *Schover LR.CA Cancer Journal for Clinicians. 1991*

- *BRCA1/2* mutation carriers who underwent prophylactic mastectomy reported a less favorable body image, while 70% of them reported changes in their sexual relationships.
- *Van Oostrom I, et al. Long-term psychological impact of carrying a BRCA1/2 mutation and prophylactic surgery: a 5-year follow-up study. Journal of Clinical Oncology.2003*

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Prospective Study of Breast Cancer Incidence in Women With a *BRCA1* or *BRCA2* Mutation Under Surveillance With and Without Magnetic Resonance Imaging

Ellen Warner, Kimberley Hill, Petrina Causer, Donald Plewes, Roberta Jong, Martin Yaffe, William D. Foulkes, Parviz Ghadirian, Henry Lynch, Fergus Couch, John Wong, Frances Wright, Ping Sun, and Steven A. Narod

J Clin Oncol 29.

- Prospective multicentric study
- 1275 BRCA1/2 women
- 445 women with MRI screening
- 830 women with mammography only
- Mean follow up 3.2 yrs

Warner et al., 2011

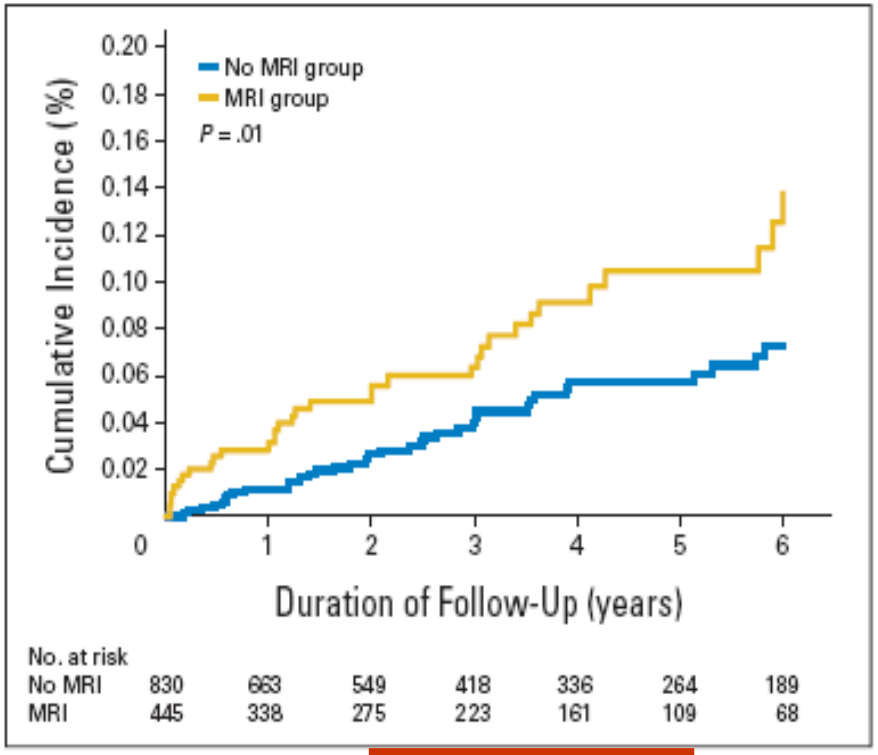

Fig 2. Cumulative incidence of early-stage (stages 0 to I) breast cancer in magnetic resonance imaging (MRI) –screened cohort and comparison group (competing risk model).

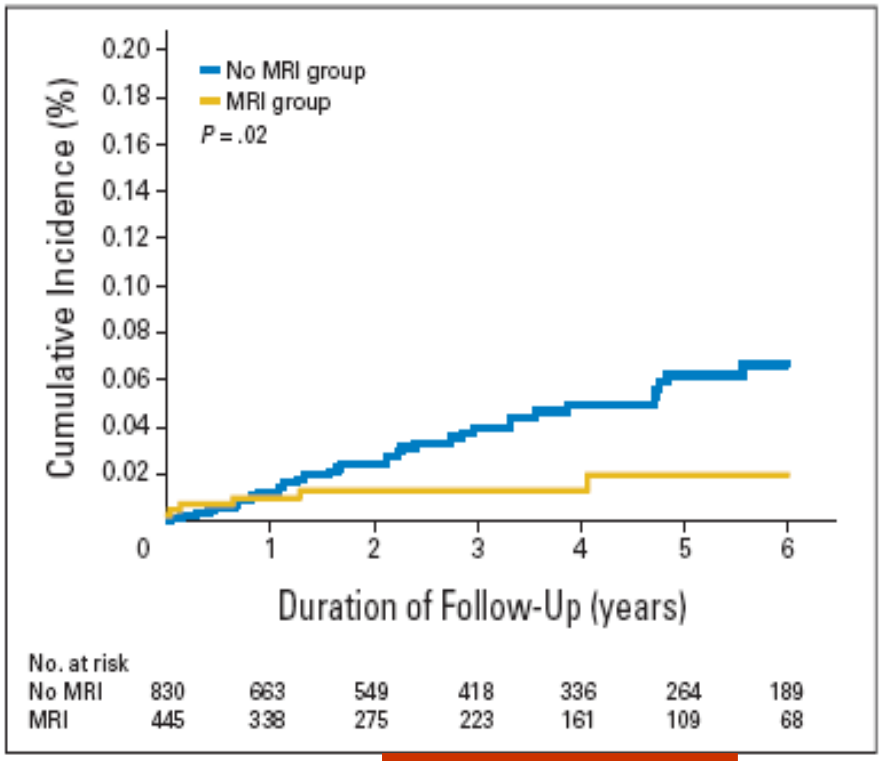

Fig 3. Cumulative incidence of stages II to IV breast cancer in magnetic resonance imaging (MRI) –screened cohort and comparison group (competing risk model).

Among 31 invasive cancers in the MRI group, 1 interval diagnosis
Among 77 invasive cancers in the control group, 38 interval diagnoses (p <0.001)

Warner et al., 2011

Association of risk reducing surgery in *BRCA1* or *BRCA2* mutation carriers with cancer risk and mortality

Domchek et al. JAMA, 2010

Prospective, multicenter cohort study of 2482 women *BRCA1/2* mutation carriers ascertained between 1974 and 2008 and followed up until December 2009

Control group with no prophylactic mastectomy underwent mammography and MRI surveillance (until 50 yrs in the UK).

Mean follow up: 4 yrs

Domchek et al, 2010

Protective effect of mastectomy on the risk of breast cancer

	BRCA1 Oophorectomy N = 617	*BRCA2* Oophorectomy N = 342	*BRCA1* No Oophorectomy N = 415	*BRCA2* No Oophorectomy N = 245
Mastectomy Breast T	116 0	56 0	43 0	32 0
No mastectomy Breast T	501 44 (8.8%)	286 20 (7%)	372 43 (10.4%)	213 15 (7%)

Domchek et al, 2010

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Protective effect of oophorectomy on the breast cancer risk

	BRCA1 No previous breast T N = 869	*BRCA2* No previous breast T N = 501	*BRCA1* Previous breast T N = 397	*BRCA2* Previous breast T N =250
Oophorectomy Breast T	236 32 (13.6%)	100 7 (7.0%)	138 19 (13.8%)	70 4 (5.7%)
No oophorectomy Breast T	633 129 (20.4%)	401 94 (23.4%)	259 46 (17.8%)	180 14 (7.8%)

Domchek et al, 2010

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Fourquet A et al. Familial breast cancer: clinical response to induction chemotherapy or radiotherapy related to *BRCA1/2* mutations status. Am J Clin Oncol 2009

- **The BRCA1 and BRCA2 genes were screened for germline mutation in a retrospective cohort of 90 pts (with 93 tumors) with a family history of breast and/or ovarian cancer, treated with induction anthracycline-containing chemotherapy and/or radiotherapy.**

- Median tumor size was 40 mm.

- Clinical responses and breast preservation rates were correlated to BRCA1/2 mutation status, and to other clinical and pathologic factors.

- A complete clinical response was achieved in 15/39 (46%) BRCA1/2-mutated tumors and in 7/54 (17%) nonmutated tumors (P = 0.008). Complete or major clinical response rate was observed in 55 of the 74 tumors treated with induction chemotherapy (74.3%).

Fourquet A et al. Familial breast cancer: clinical response to induction chemotherapy or radiotherapy related to *BRCA1/2* mutations status. Am J Clin Oncol 2009,(continued)

- The overall complete or major clinical response rate in the tumors treated with induction radiotherapy was 68% (13/19 tumors).

- Following induction treatment by either chemotherapy or radiotherapy, more breast-conserving treatments could be performed in mutation carriers than in noncarriers: the rates of breast preservation were 82% in BRCA1/2-mutated tumors and 63% in nonmutated tumors, respectively (P = 0.045).

- ***BRCA mutation was the sole predictor of breast conservation. This suggests that impaired repair mechanisms related to the BRCA1/2 mutations increased the chemosensitivity and radiosensitivity of large breast cancers.***

Standard Histological Morphology Subtypes

- Ductal :
  - invasive,
  - in situ
- Lobular
  - invasive,
  - in situ
- *Tubular*
- *Mucinous*
- *Medullary*
- *Mixed*
- *Spindle cell*

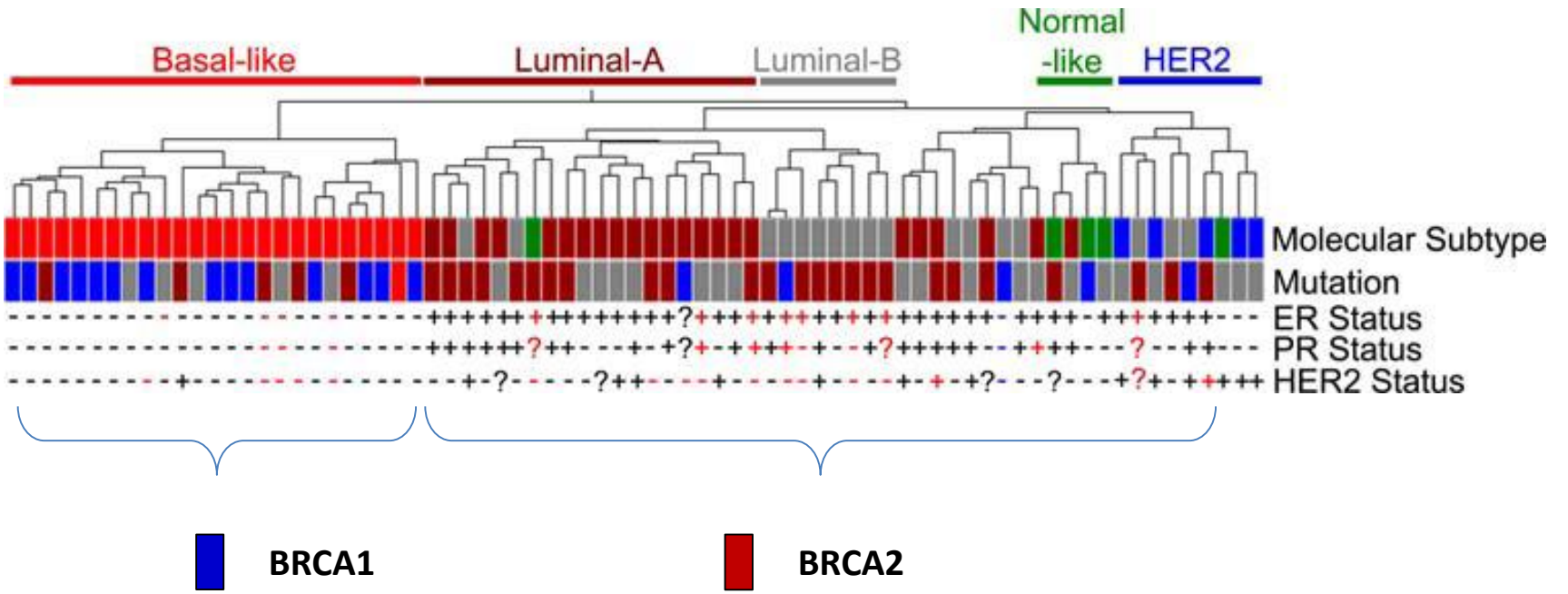
Estrogen Receptors

Progesteron receptors

HER 2

- ***Proliferation:***
  - ***histoligical grade, mitotic index, Ki 67***

BRCA1 and *BRCA2* Tumors Characteristics: transcriptome/phenotype



Waddell et al, BCRT, 2009

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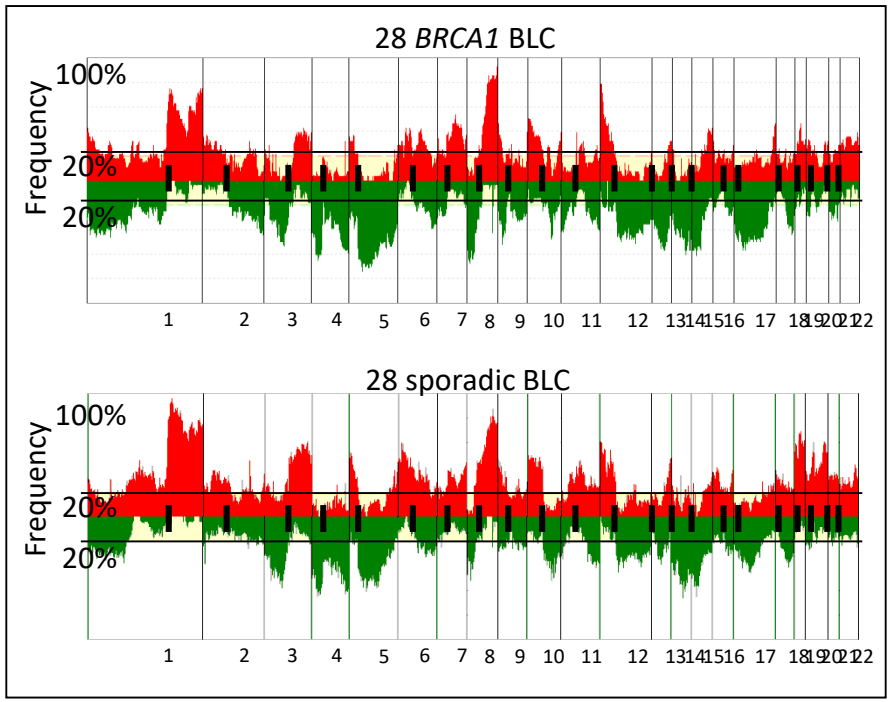
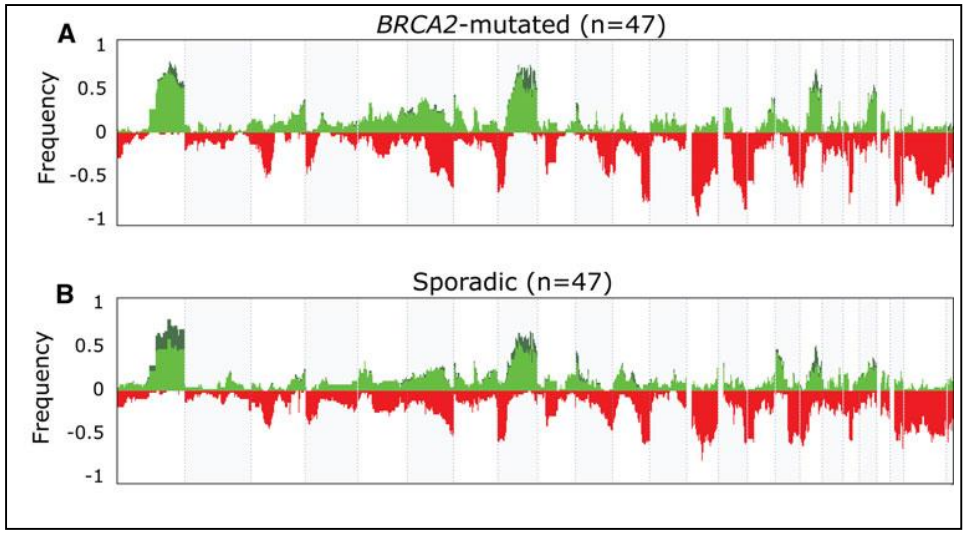
BRCA1 and *BRCA2* Tumors Characteristics: Genome





Tirkkonen et al, Cancer Research, 1997
Van Beers et al, Cancer Research, 2005
Jönsson et al, Cancer Research 2005
Stefansson et al, BCR, 2009
Waddell et al, BCRT, 2009
Manie, Stern, unpublished data

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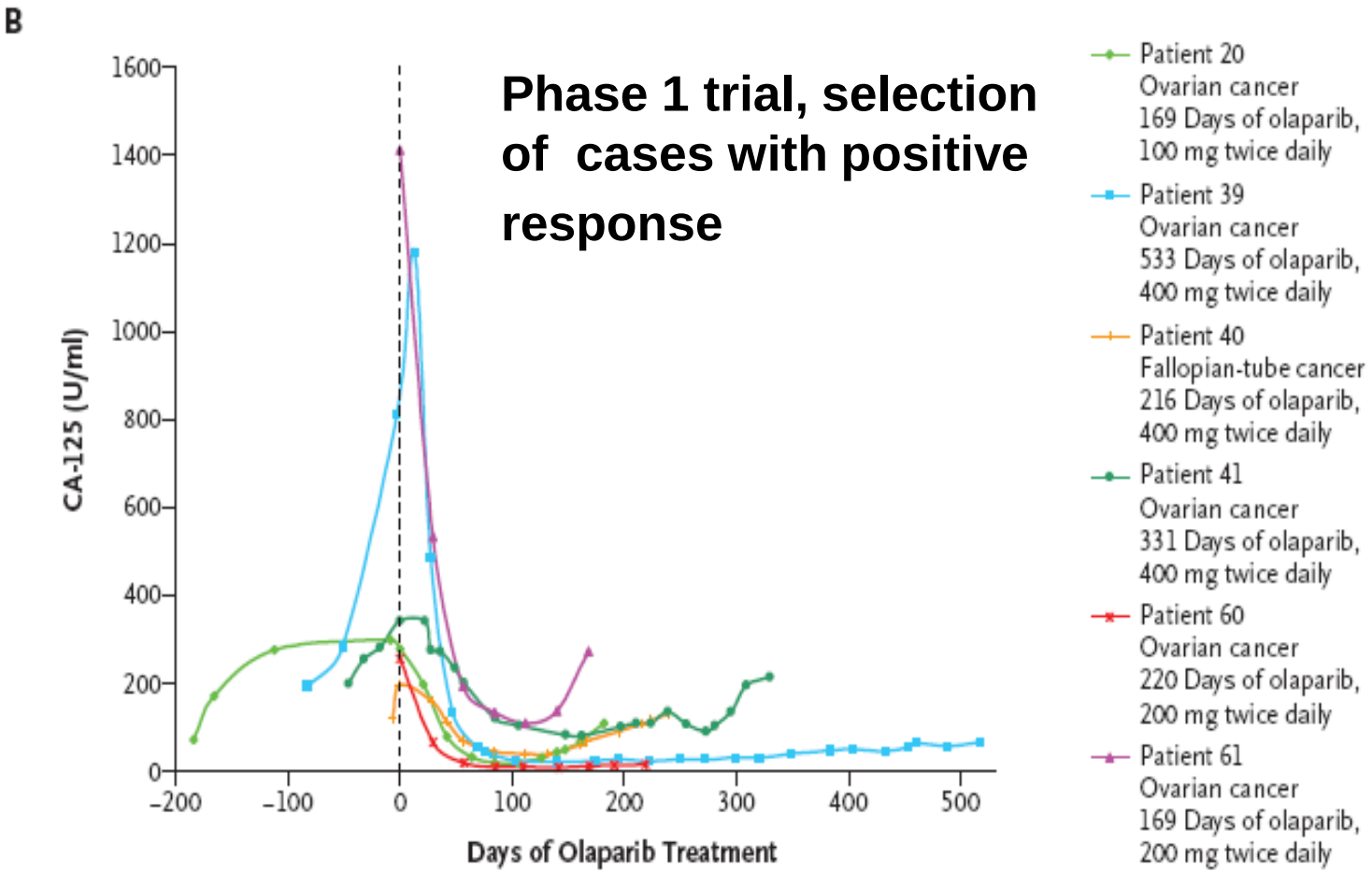
Inhibition of Poly(ADP-ribose) polymerase in tumors from *BRCA1/2* mutation carriers



Fong et al, NEJM, 2009

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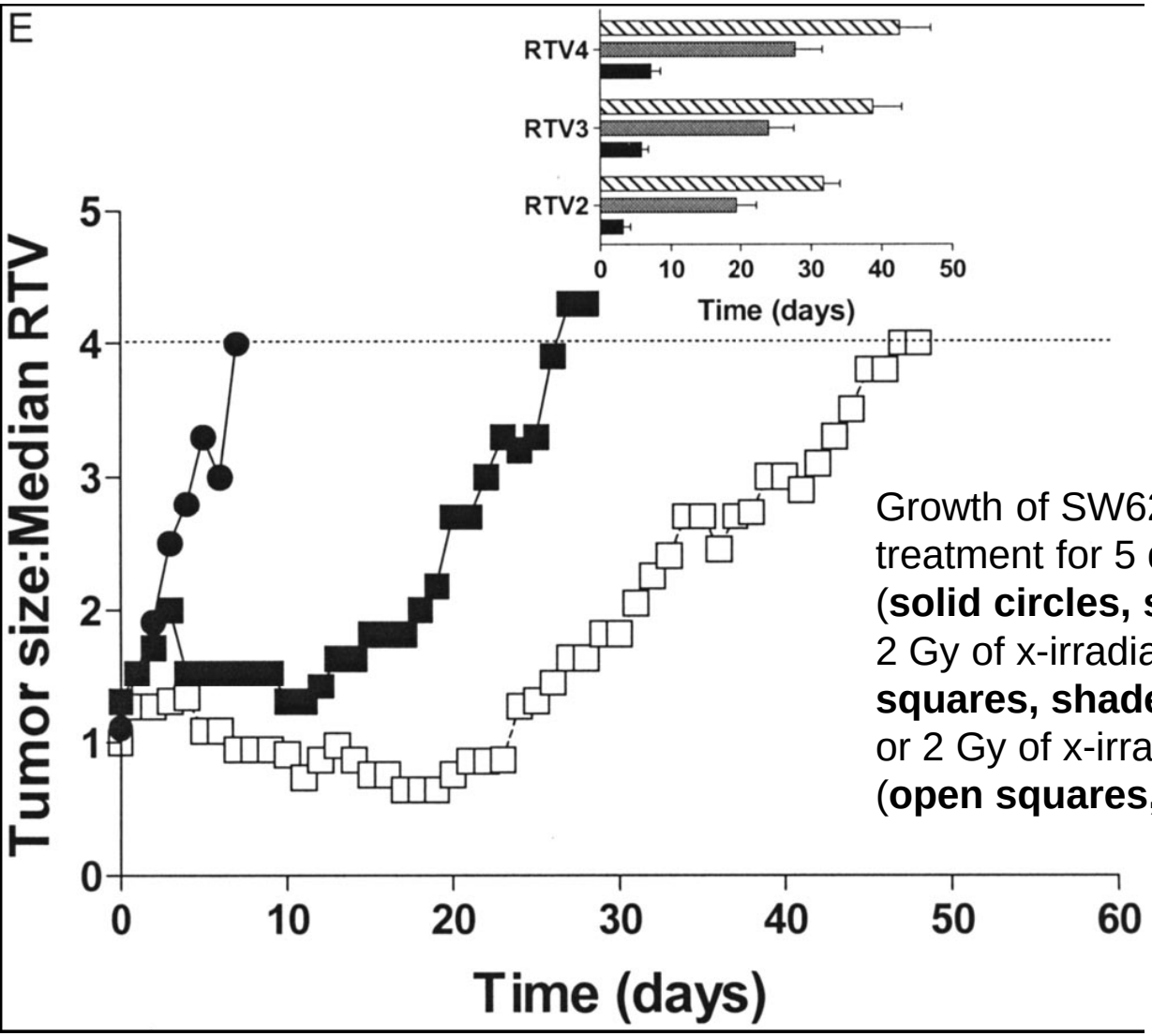

Growth of SW620 tumor xenografts after daily treatment for 5 days with vehicle control alone (**solid circles, solid bars**),
2 Gy of x-irradiation (IR) vehicle (**solid squares, shaded bars**),
or 2 Gy of x-irradiation AG14361 at 15 mg/kg (**open squares, hatched bars**).

Calabrese et al., JNCI 2004

PARP inhibitors combined with radiation will also increase the formation of DSBs and increase cell killing, particularly in a background of reduced levels of DSB repair proteins.

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Phase I studies currently running:

Differences, similarities	NKI/AVL	Inst Curie
Pat population	Metast breastca, also ER pos	Mets and loc adv breast ca, TN
Dose esc schedule	50, 100, 200, 300	50, 100, 150,200, 300
RT dose	46.69/23 fr, 14.49Gy SIB	50 Gy, 16 Gy boost sequ
Additional treatment	no surgery	Surgery in some cases
Translational res	HRD, par assay	HRD, ctDNA, parp1 IHS
Tite CRM	DLT period 12 weeks	DLT period 12 weeks
Late tox	Evaluated in the protocol	Evaluated in the protocol
Pat with bolus on skin/WEM	Separate groups in protocol	Depends

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Conclusions

Most studies suggest there is no increased risk of breast recurrence in *BRCA 1/2* carriers at 10 years and longer follow-up

Age is the strongest predictor of local recurrence

Added benefit from tamoxifen and / or oophorectomy

Added benefit from chemotherapy

New targeted treatments could change the prognosis of these cancers

But:

- All studies carry methodological biases: selection criteria, non-matched comparisons, longevity (Neyman) biases

- Very few data on long follow-up (> 10 year)

- High risk of CBC

Treatment decisions have to take into account:

- Whether the patient is a known *BRCA* carrier or not
- Her family history
- Her choice

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Breast Cancer:

How do clinical trials impact on practice of radiotherapy in breast cancer?

Youlia Kirova, M.D.,
Department of Radiation Oncology

Evidenced Based Radiation Oncology

Introduction

- Several large phase III clinical trials conducted over the years have set up the scene for breast cancer irradiation
- To evaluate their impact of practice
  - Main trials, and metaanalyses
  - National guidelines

Material

- Trials and metaanalyses
- Guidelines
  - NCCN (USA) 2016
  - INCa (France) 2015
  - REMAGUS (Institut Curie & Institut Gustave Roussy) 2017

Trials

1. Postmastectomy Radiotherapy
2. Mastectomy vs Breast-conserving treatment with RT
3. Whole-breast irradiation after breast-conserving surgery
    - Invasive cancer
    - DCIS
4. Fractionation trials
5. Toxicity

Trials

1. **Postmastectomy Radiotherapy**
2. **Mastectomy vs Breast-conserving treatment with RT**
3. **Whole-breast irradiation after breast-conserving surgery**
    - **Invasive cancer**
    - **DCIS**
4. **Fractionation trials**
5. **Toxicity**

Trials: Postmastectomy Radiotherapy

“Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials”

- ***Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)***
- **Lancet 2014; 383:2127-35**

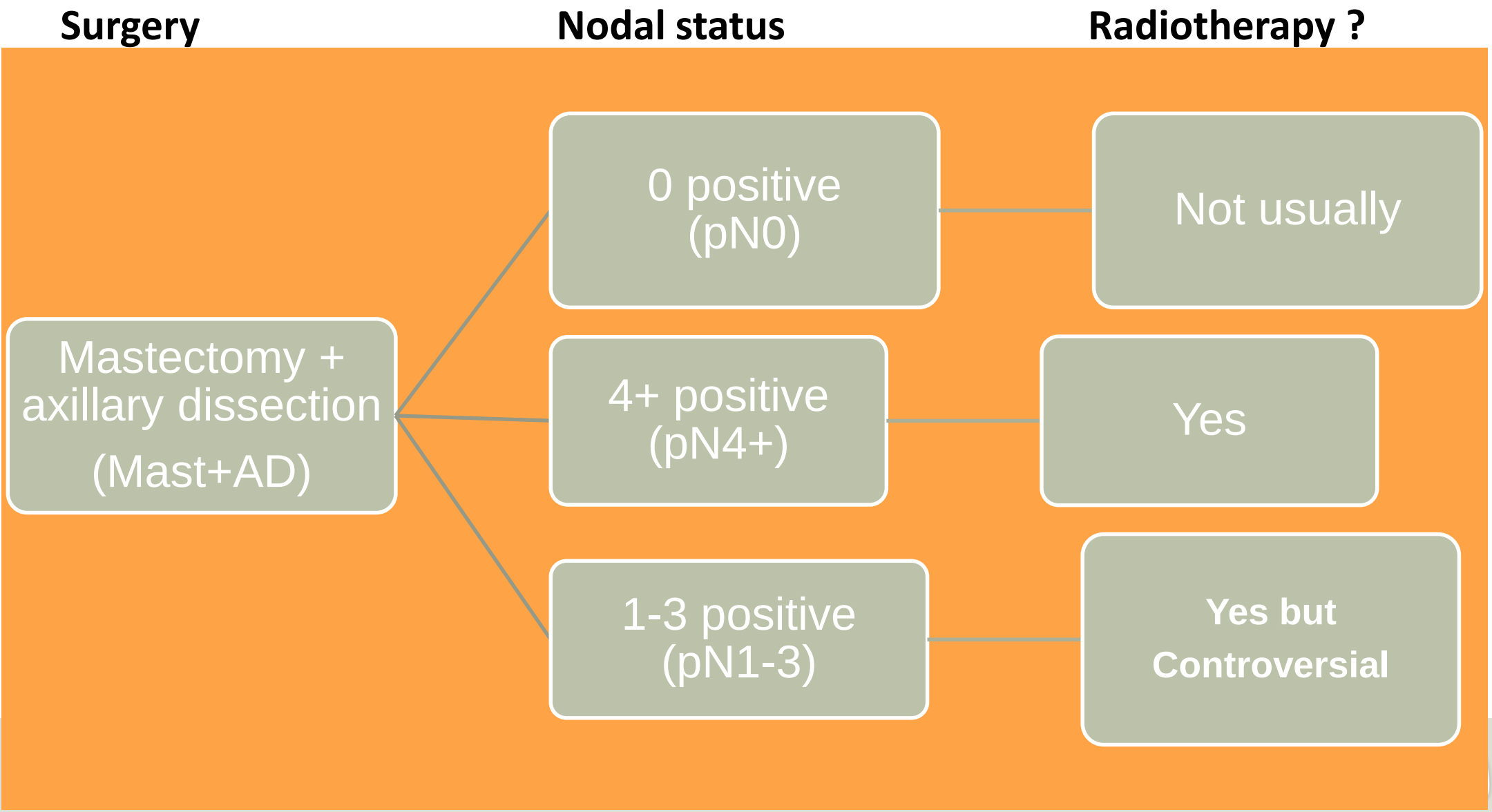
Individual patient data

- **Criteria:**
  - **Randomised trials of radiotherapy (RT) versus same surgery but no RT**
  - **Started before 2000**
  - **Mastectomy and axillary dissection to at least level II**
  - **RT to include chest wall**

- **Found:**
  - **3786 women in 14 trials (started 1964 to 1982)**
  - **43 000 years of follow-up to 2009 (median 9.0 years)**
  - **RT to axillary, internal mammary and supraclavicular nodes**

EBCTCG, Lancet 2014

Current Guidelines

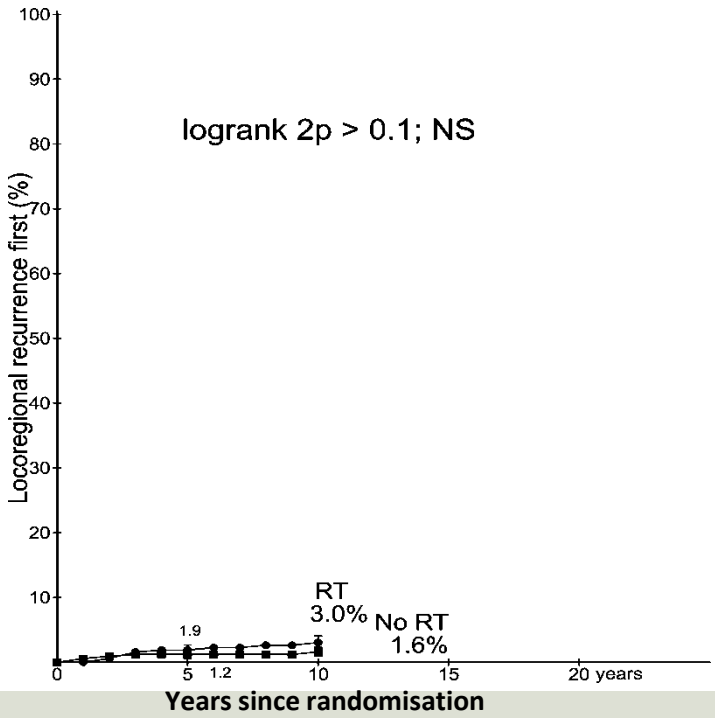


Trials of radiotherapy after mastectomy and axillary dissection

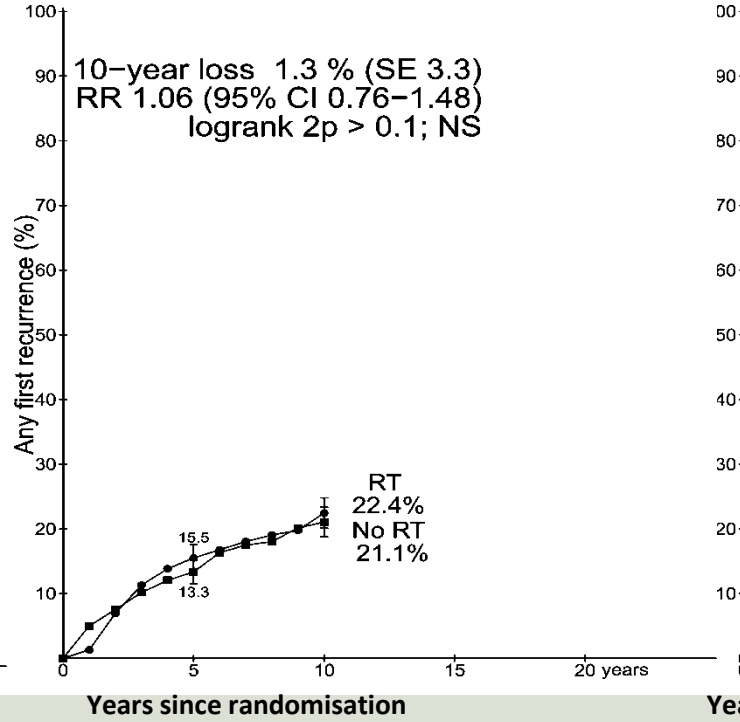
700 pN0 women

RT: No significant benefit

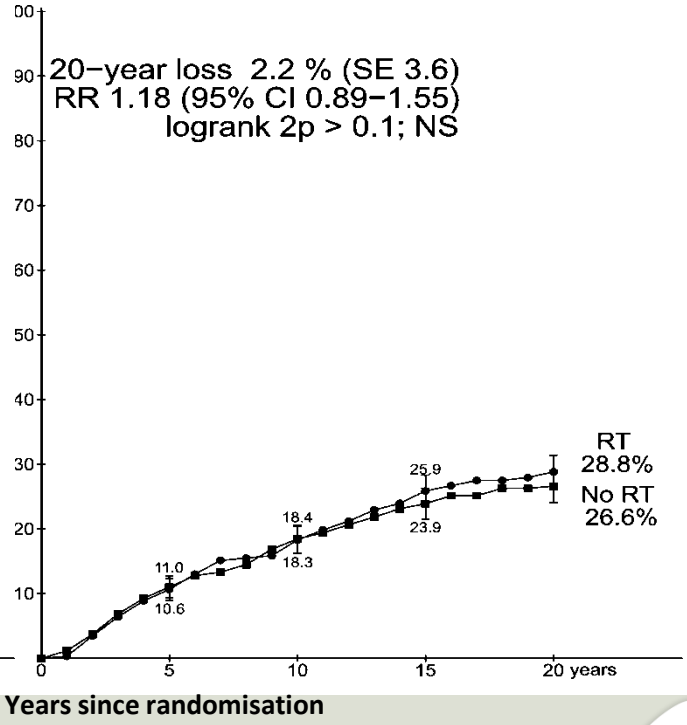
Locoregional recurrence first



Any first recurrence



Breast cancer mortality



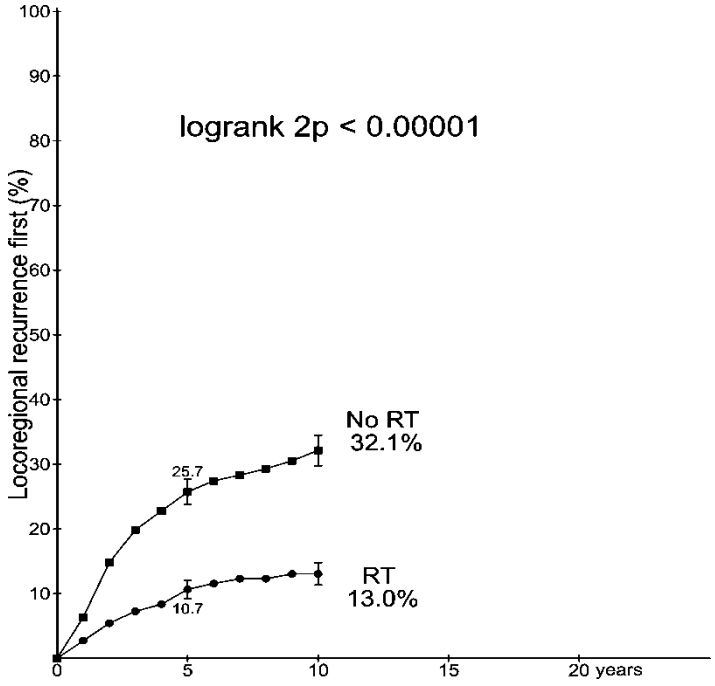
EBCTCG, Lancet 2014

Trials of radiotherapy after mastectomy and axillary dissection

1772 pN4+ women

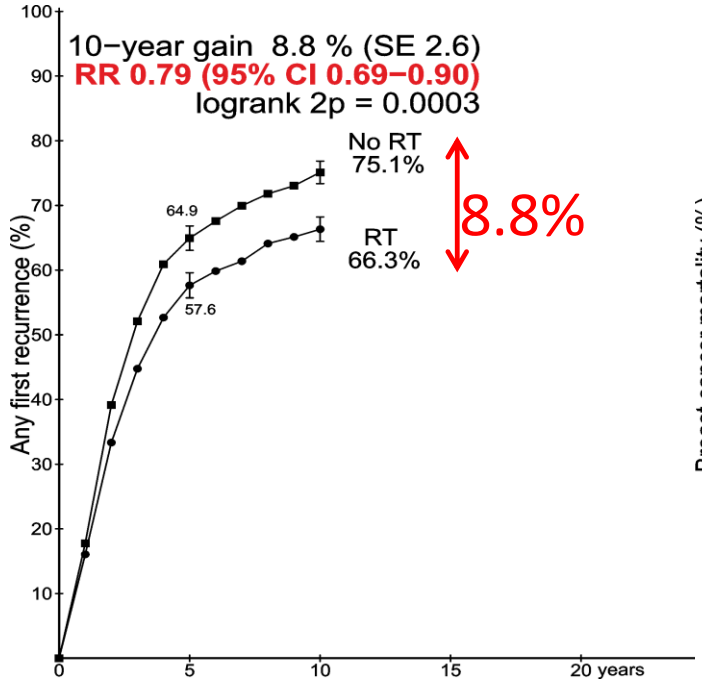
RT: Significant benefit

Locoregional recurrence first



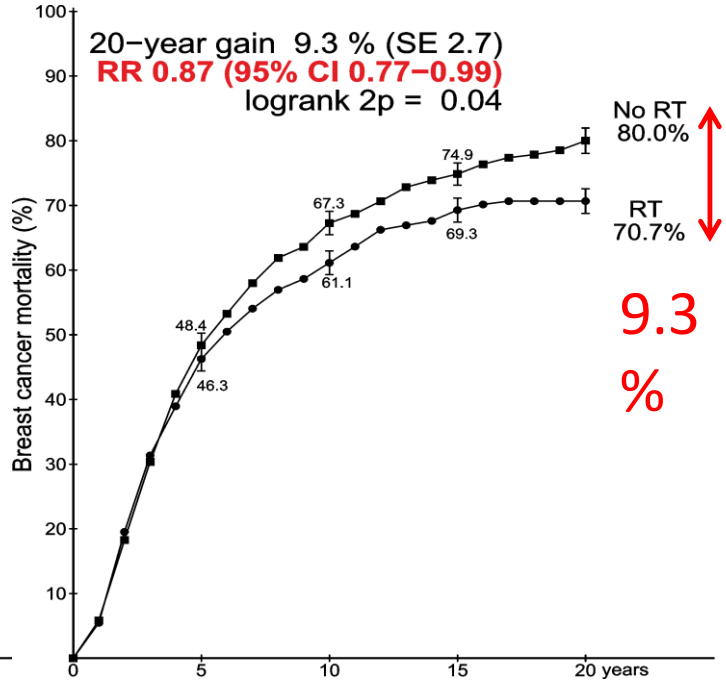
Years since randomisation

Any first recurrence



Years since randomisation

Breast cancer mortality



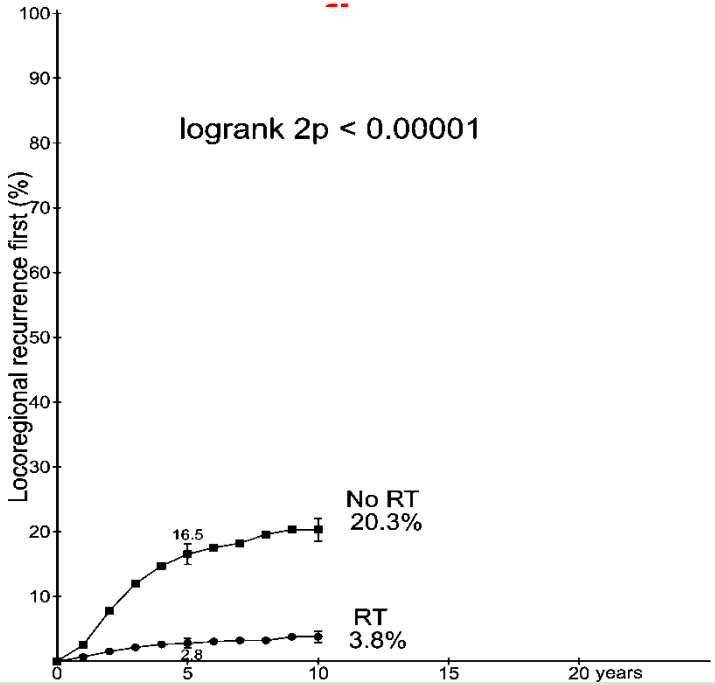
Years since randomisation

Trials of radiotherapy after mastectomy and axillary dissection

1314 pN1-3 women

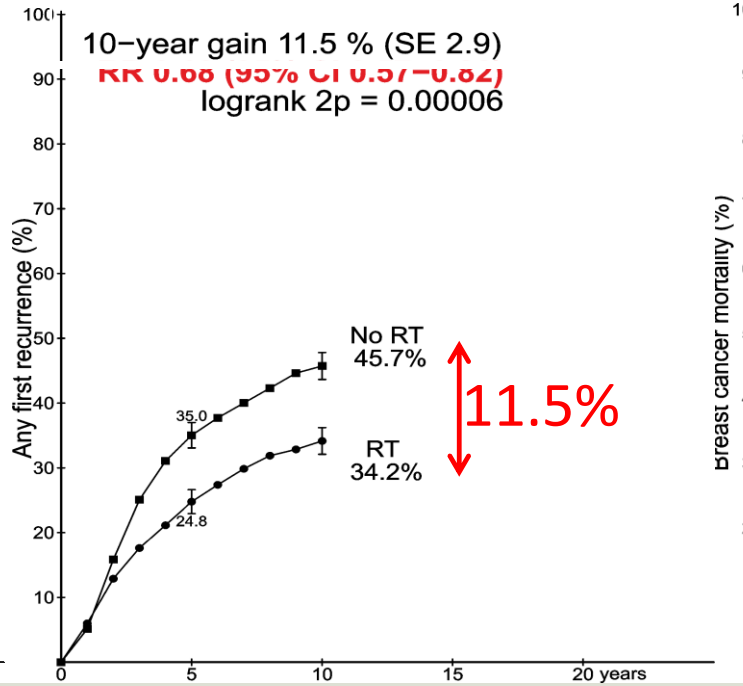
RT: Significant benefit

Locoregional recurrence



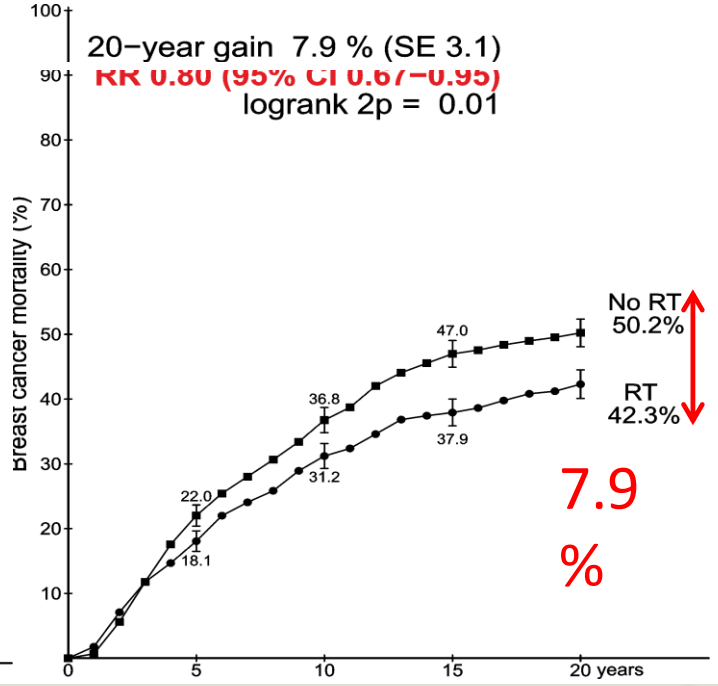
Years since randomisation

Any first recurrence



Years since randomisation

Breast cancer mortality



Years since randomisation

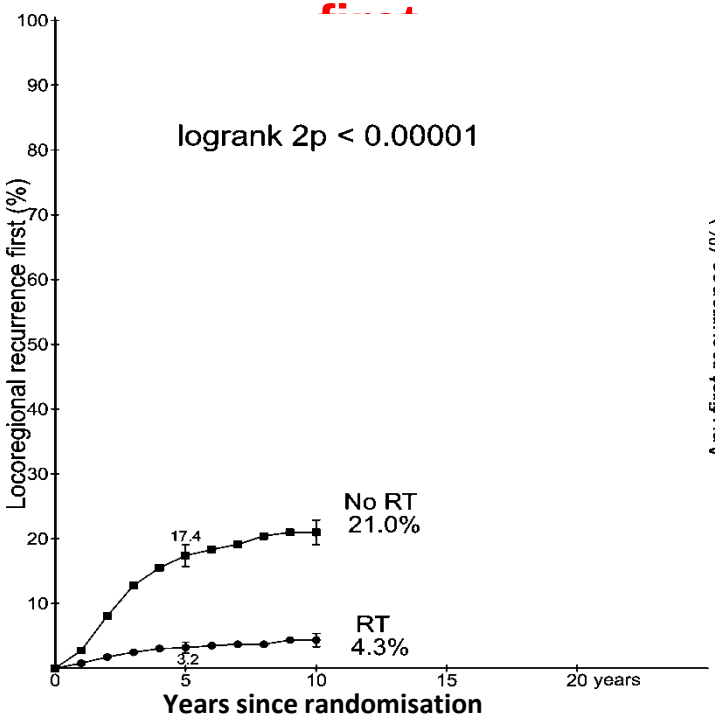
EBCTCG, Lancet 2014

Trials of radiotherapy after mastectomy and axillary dissection

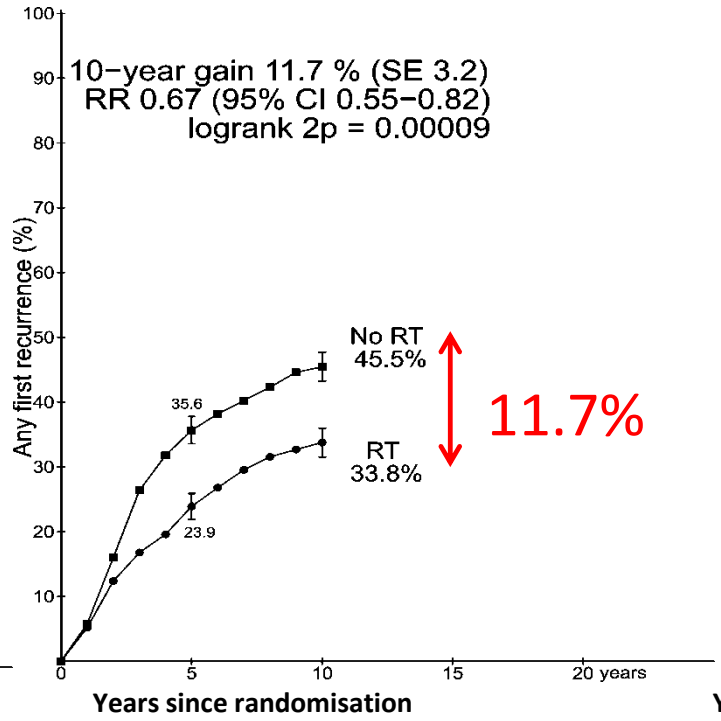
1133 pN1-3 women in trials with systemic therapy

RT: Significant benefit

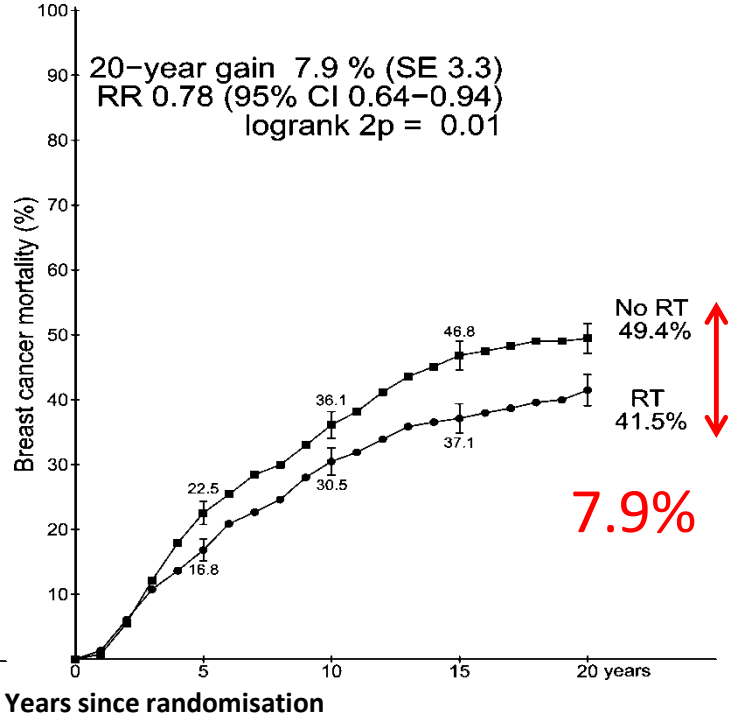
Locoregional recurrence first



Any first recurrence



Breast cancer mortality

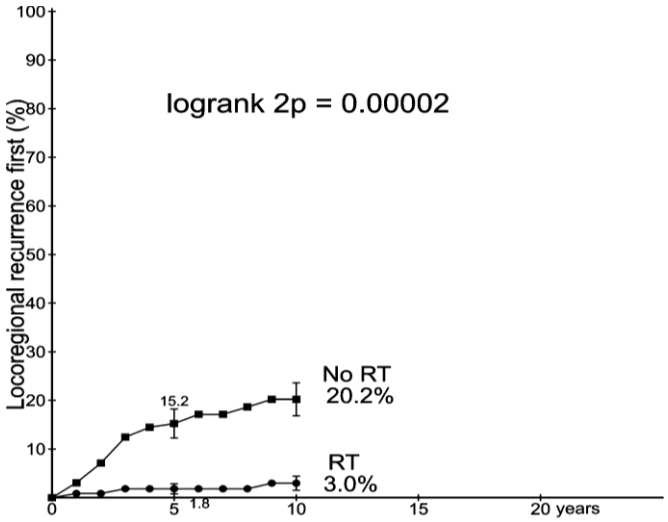


EBCTCG, Lancet 2014

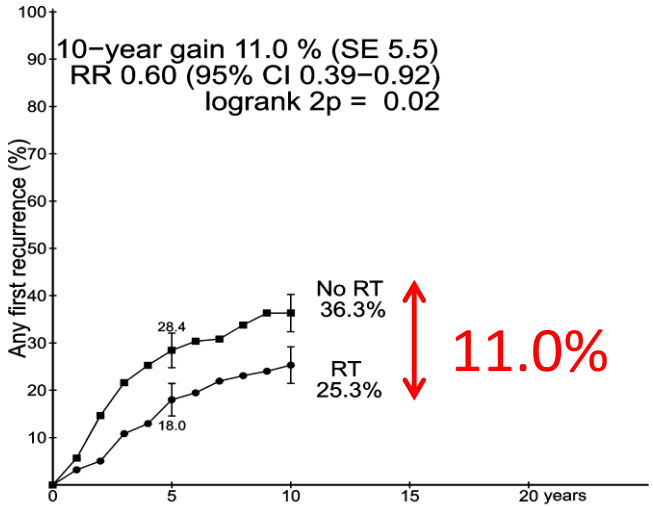
Trials of radiotherapy after mastectomy and axillary dissection

318 women with Mast+AD, systemic therapy and 1 positive node

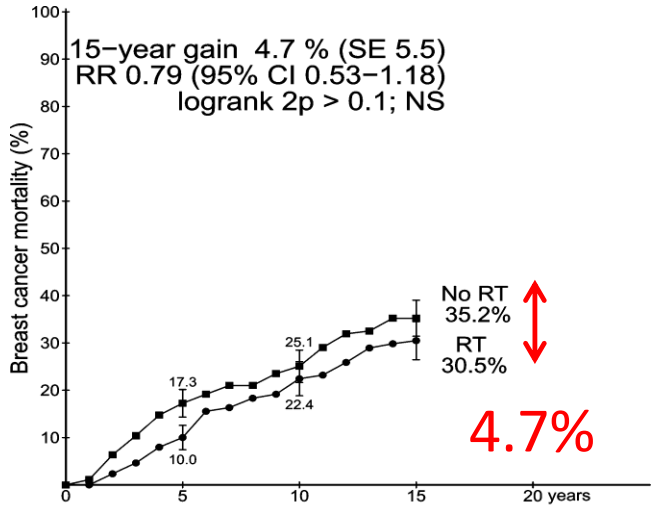
Locoregional recurrence first



Any first recurrence



Breast cancer mortality



EBCTCG, Lancet 2014

Conclusions: radiotherapy after mastectomy and axillary dissection

- In these trials, for pN1-3 women, **RT gave significant benefit**
  - Absolute reductions
    - 10-year recurrence: 11.5 % (34.2% vs. 45.7 %)
    - 20-year breast cancer mortality: 7.9% (42.3 % vs. 50.2 %)
  - Proportional reductions
    - Recurrence: 32 % (SE 8)
    - Breast cancer mortality: 20 % (SE 8)

- For women today, RT
  - Absolute reductions likely to be smaller
  - Proportional benefits at least as big

EBCTCG, Lancet 2014

Conclusion 1

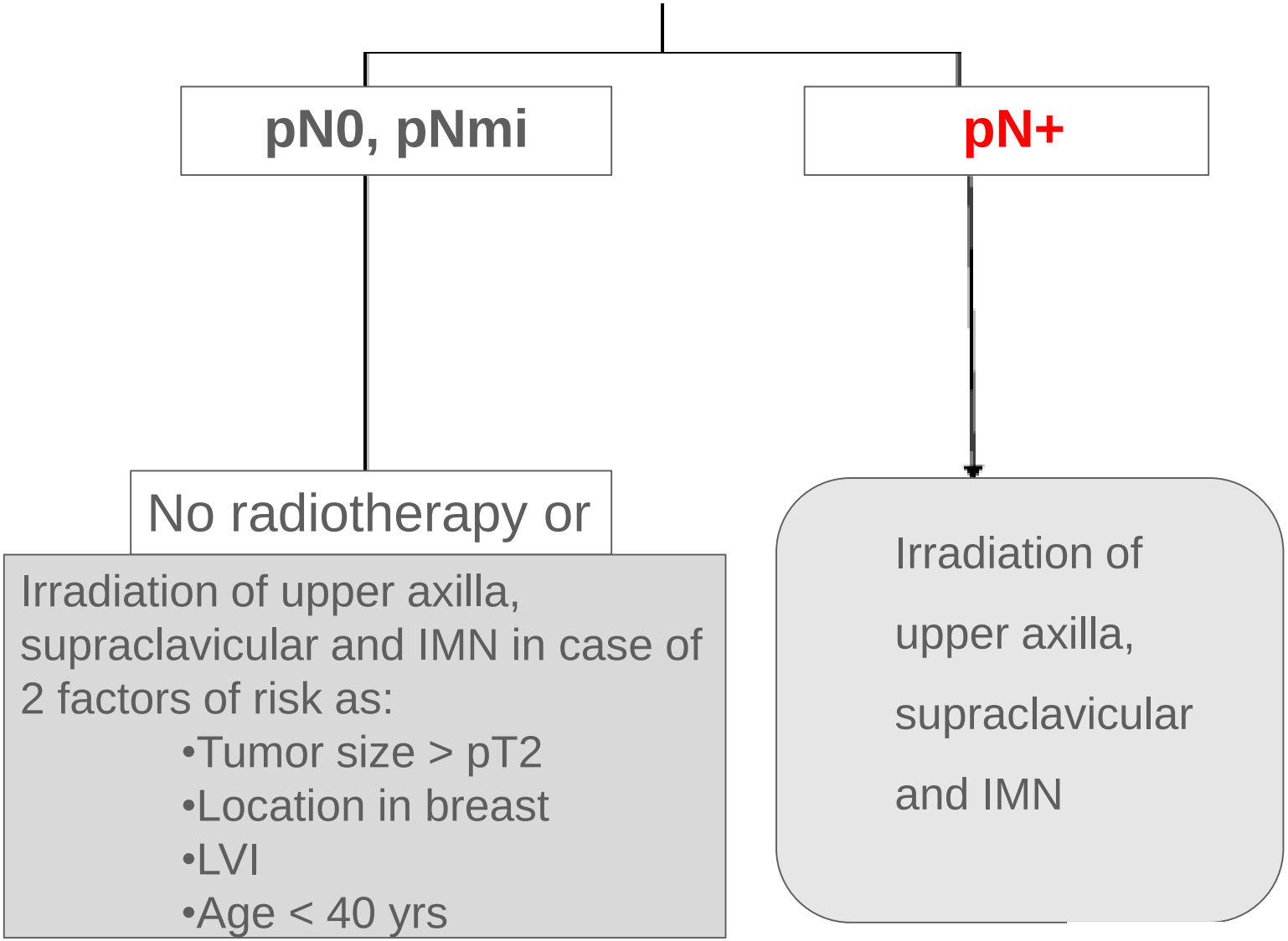
- A 70% locoregional risk reduction was achieved by PMRT, mostly during the first five years of follow-up
- In node positive cancer, PMRT significantly reduced mortality: this effect became apparent after 5 years

PMRT. NCCN guidelines

	Chest wall	Supra/Infra clavicular nodes	IMN
pN > 3	√	√	***
pN1-3	***	***	***
pN0 and pT> 5 cm or margins pos.	**	**	***
pN0 and pT< 5 cm and margins close (<1mm)	**	-	-
pN0 and pT<5 cm and margins free	-	-	-

√: recommended
***: strongly consider
**: consider

Therefore: Guidelines for LN irradiation



Trials

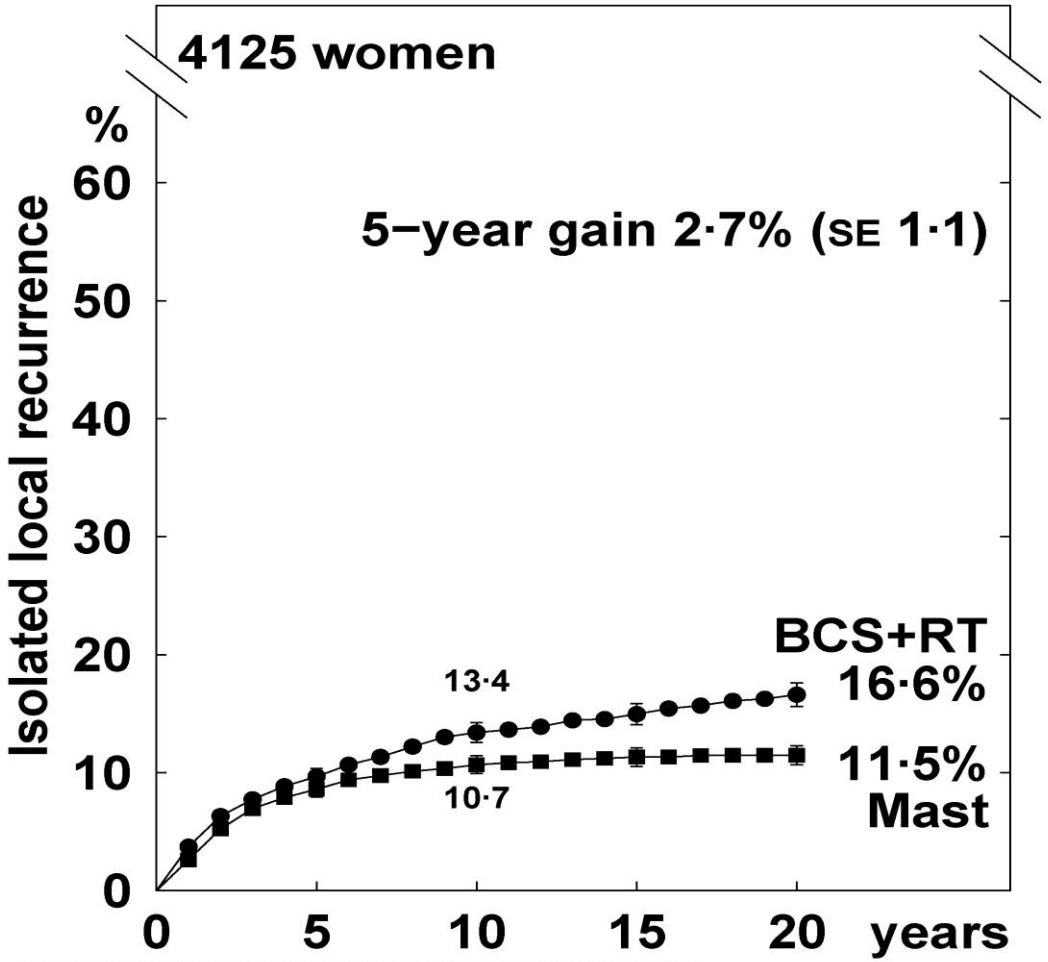
1. Postmastectomy Radiotherapy
2. **Mastectomy vs Breast-conserving treatment with RT**
3. Whole-breast irradiation after breast-conserving surgery
    - Invasive cancer
    - DCIS
4. Fractionation trials
5. Toxicity

Breast-conserving surgery and WBRT vs. Mastectomy

- 1972-1986
- 7 trials
- 4125 women

EBCTCG *Lancet*, 2005 and update 2006

Mastectomy vs BCS + RT, both with AC
ISOLATED LOCAL RECURRENCE

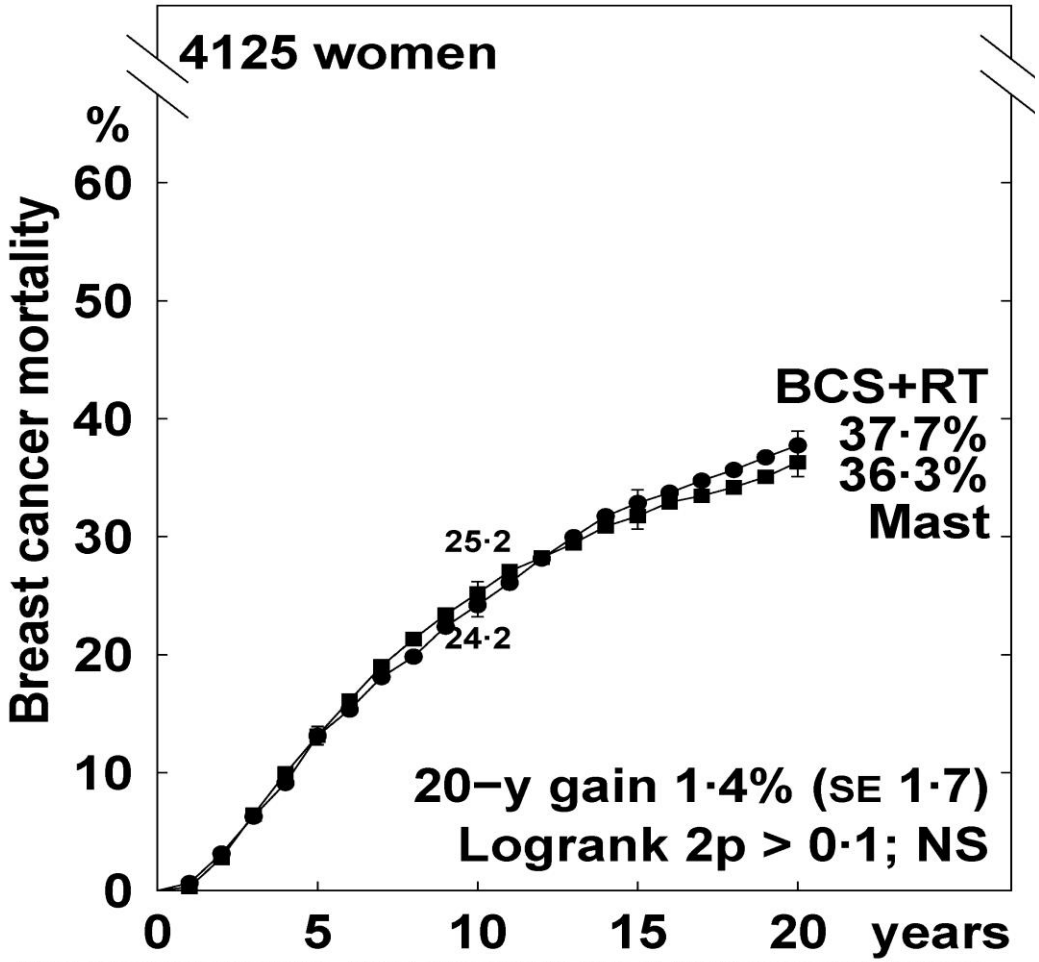


Isolated local recurrence rates (% / year) and logrank analyses

	Years 0 – 9	Years 10 – 19	Year 20+
Mast	1·29 (187 / 14524)	0·10 (8 / 7731)	0·0(0/1163)
BCS+RT	1·60 (234 / 14626)	0·37 (29 / 7736)	0·43 (5 / 1157)
Rate ratio, from (O−E) / V	0·80 SE 0·09 −22·6 / 101·1	0·32 SE 0·20 −10·4 / 9·2	0·14 SE 0·45 −1·9 / 1·0

10:30:08 7 September 2006 Overview: BC, ICE: 4
Not for publication or citation (plot #: PM_SRT_0002156)

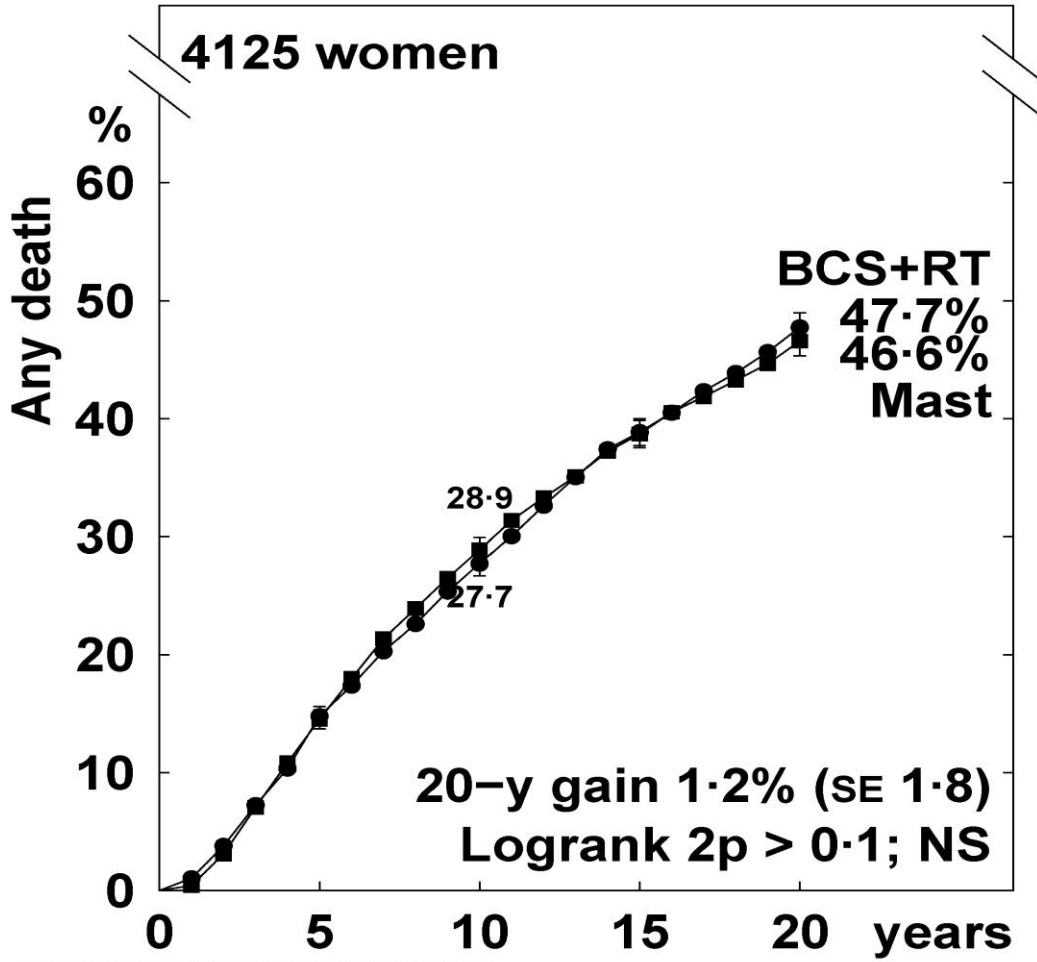
Mastectomy vs BCS + RT, both with AC
BREAST CANCER MORTALITY



After−recurrence or possible−breast−cancer death rates (% / year) and logrank analyses

	Years 0 − 9	Years 10 − 19	Year 20+
Mast	2·84 (479 / 16842)	1·64 (154 / 9386)	1·15 (17 / 1473)
BCS+RT	2·77 (483 / 17437)	2·09 (209 / 10010)	1·99 (32 / 1612)
Rate ratio, from	1·05 SE 0·07	0·80 SE 0·10	0·63 SE 0·24
(O−E) / V	10·7 / 227·9	−19·2 / 85·8	−5·3 / 11·5

Mastectomy vs BCS + RT, both with AC
ANY DEATH



Death rates (% / year) and logrank analyses

	Years 0 − 9	Years 10 − 19	Year 20+
Mast	3·33 (561 / 16842)	2·90 (272 / 9386)	2·85 (42 / 1473)
BCS+RT	3·22 (562 / 17437)	3·25 (325 / 10010)	3·97 (64 / 1612)
Rate ratio, from	1·05 SE 0·06	0·88 SE 0·08	0·68 SE 0·17
(O−E) / V	12·3 / 267·5	−17·8 / 142·6	−9·7 / 25·0

Conclusions 2

- The long-term rate of local recurrence was higher following breast-conserving treatment than after mastectomy
- But long-term rates of specific and overall mortality were not increased

Trials

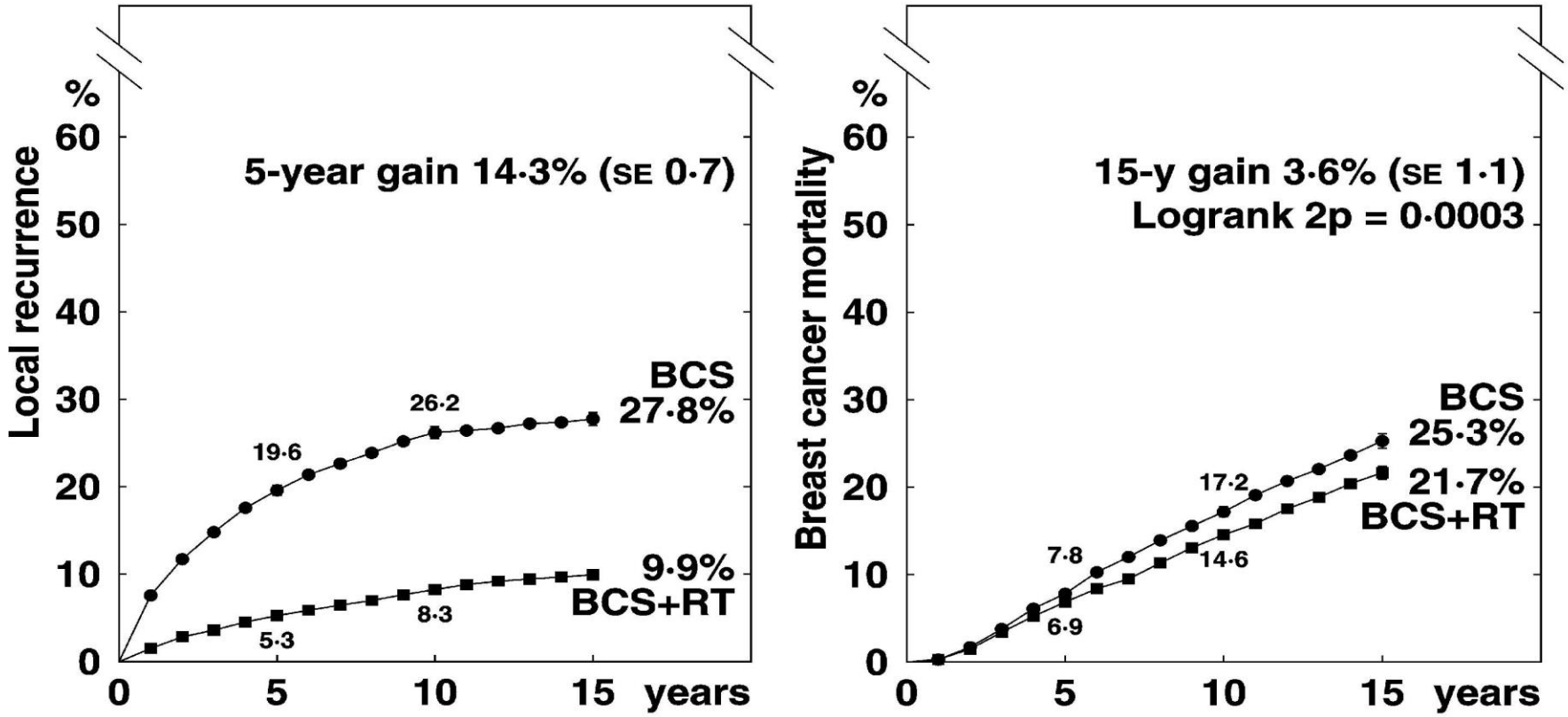
1. Postmastectomy Radiotherapy
2. Mastectomy vs Breast-conserving treatment with RT
3. **Whole-breast irradiation after breast-conserving surgery**
    - **Invasive cancer**
    - DCIS
4. Fractionation trials
5. Toxicity

EBCTCG Overview

- 17 trials
- 1976-1999
- 10801 women
- Median f/u: 9.5 years
- 25% with > 10 year F/U

EBCTCG *Lancet* 2005 et *Lancet* 2011

Trials of BCS ± RT: 15-year risks
10,906 women randomised in 17 trials

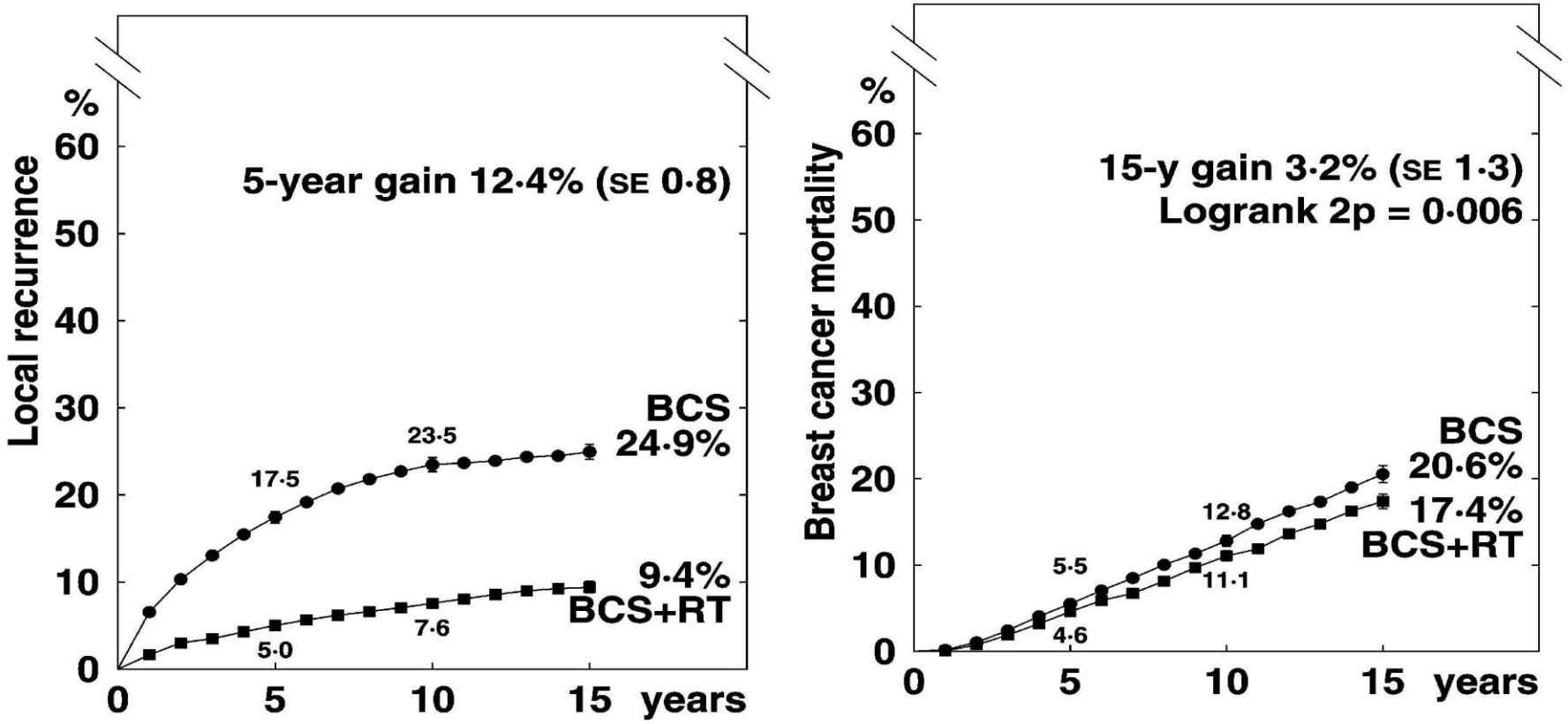


For every four local recurrences avoided by year 5
about one breast cancer death avoided by year 15

Preliminary results: subject to revision

Darby S *SABCS*, 2009

pN0 in trials of BCS ± RT: 15-year risks
7334 women



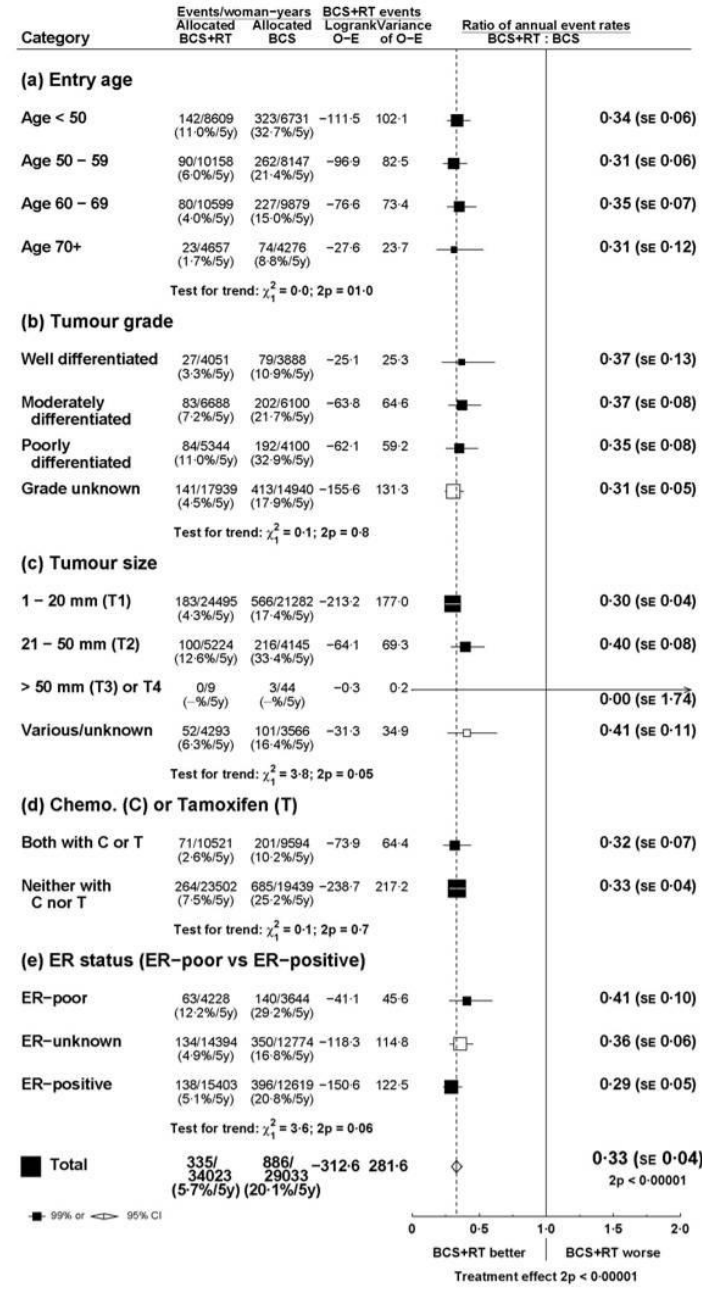
For every four local recurrences avoided by year 5
about one breast cancer death avoided by year 15

Preliminary results: subject to revision

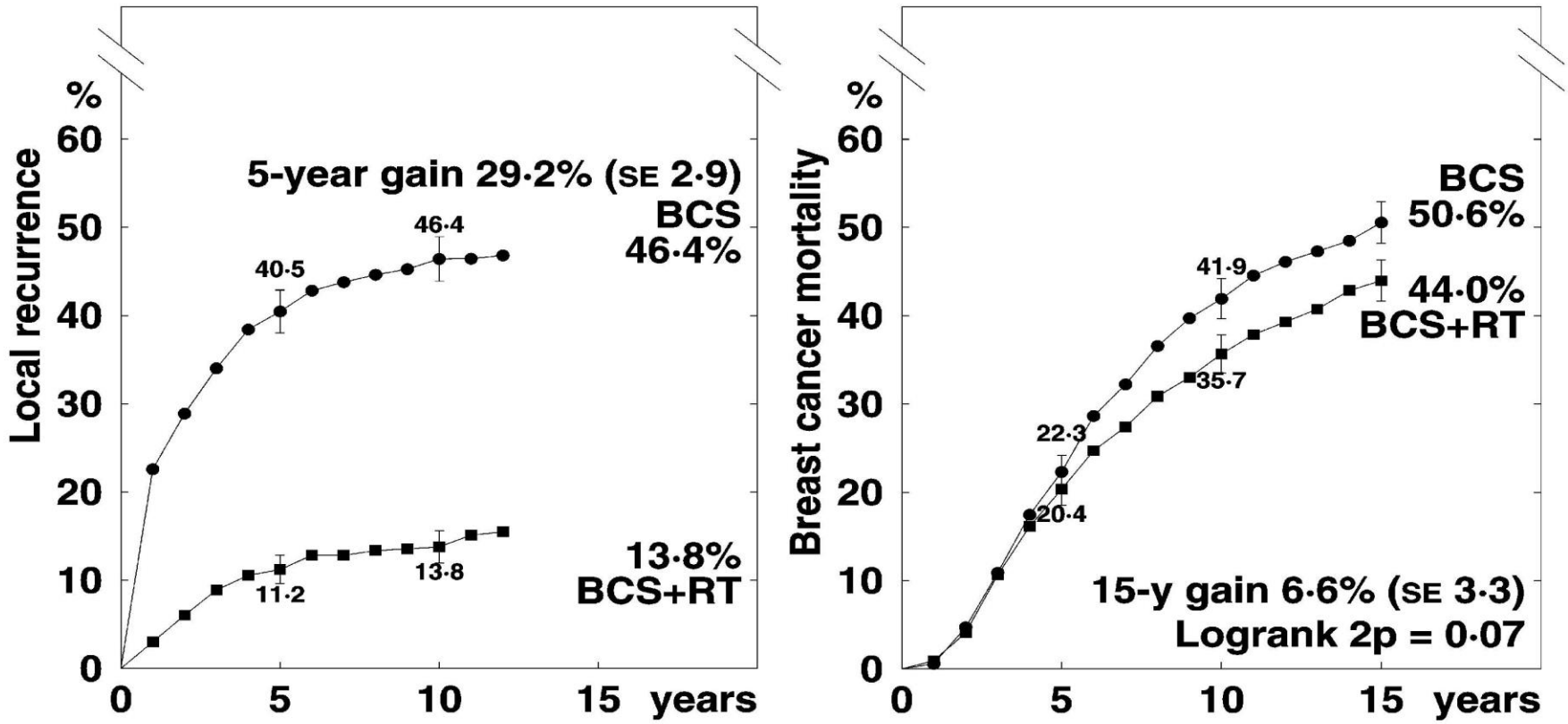
Darby S *SABCS*, 2009

EBCTCG
pN0
2006

N0/N−: BCS ± RT
ISOLATED LOCAL RECURRENCE



pN+ in trials of BCS ± RT: 15-year risks
1111 women



For every four local recurrences avoided by year 5
about one breast cancer death avoided by year 15

Preliminary results: subject to revision

Darby S *SABCS*, 2009

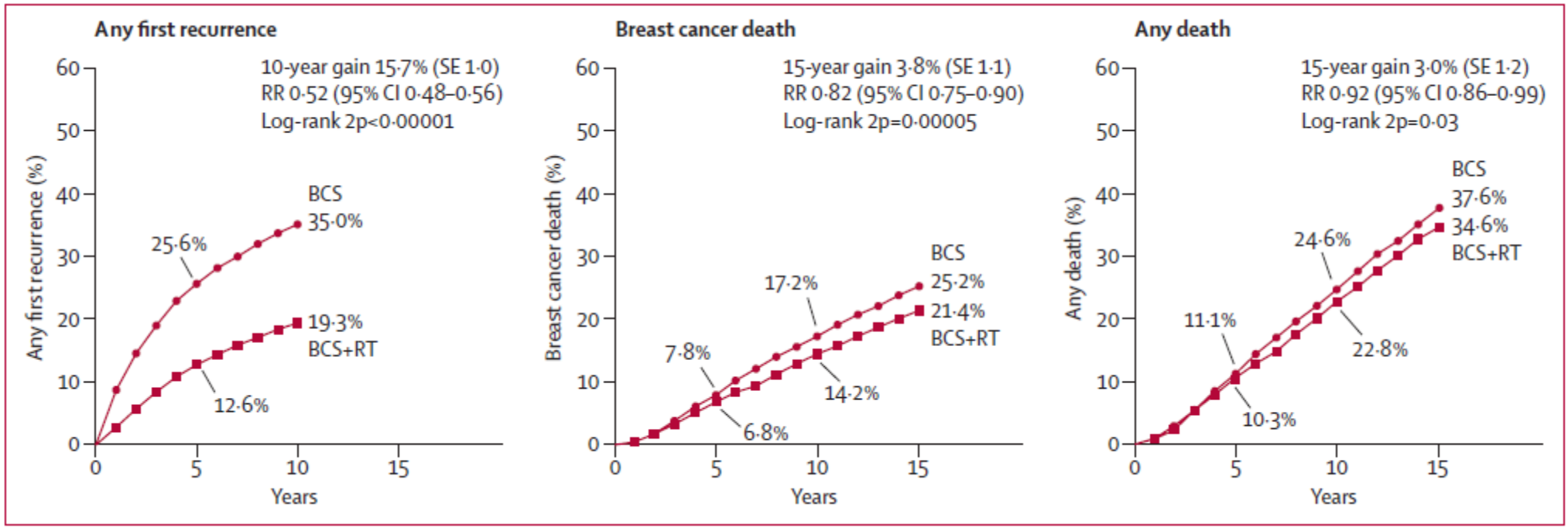
Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

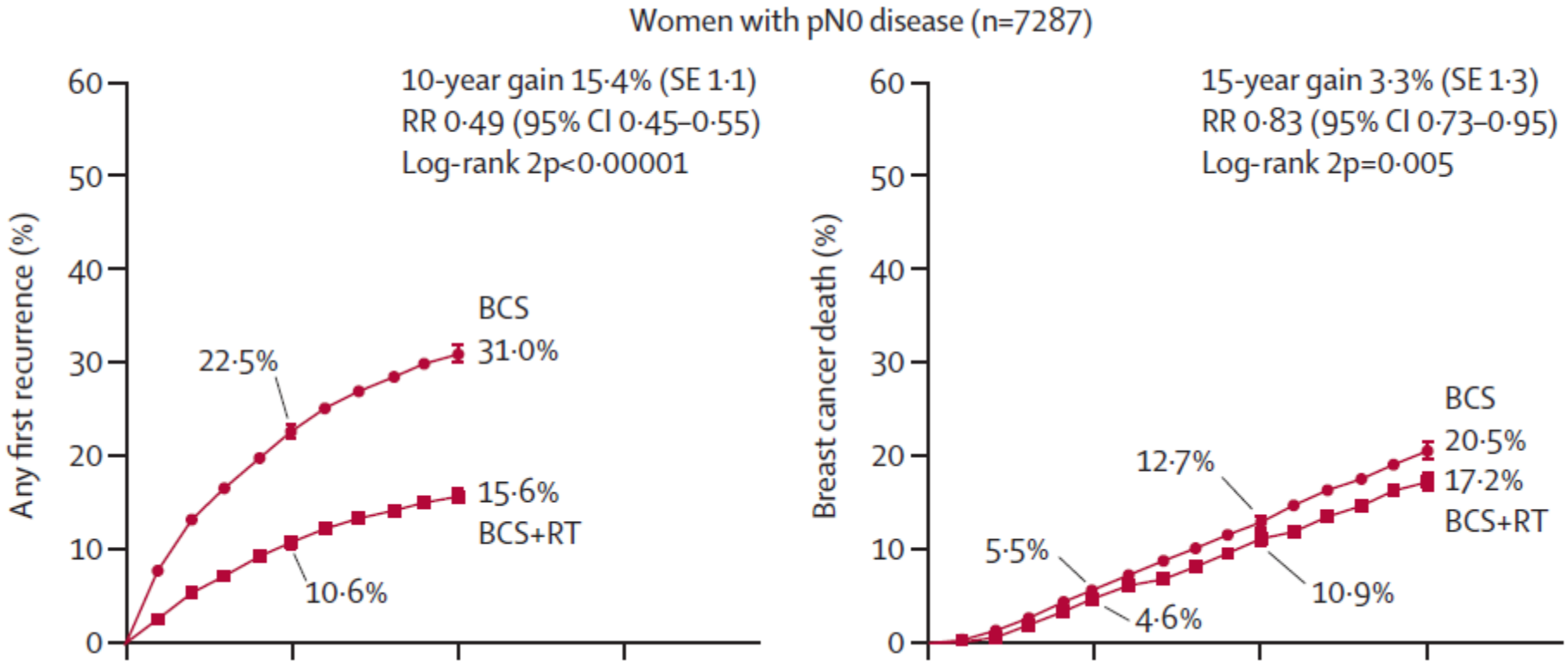
Recurrence: breast, nodes, metastasis, or contralateral breast cancer *as first event*

***Lancet*, 2011; 378:771-84**

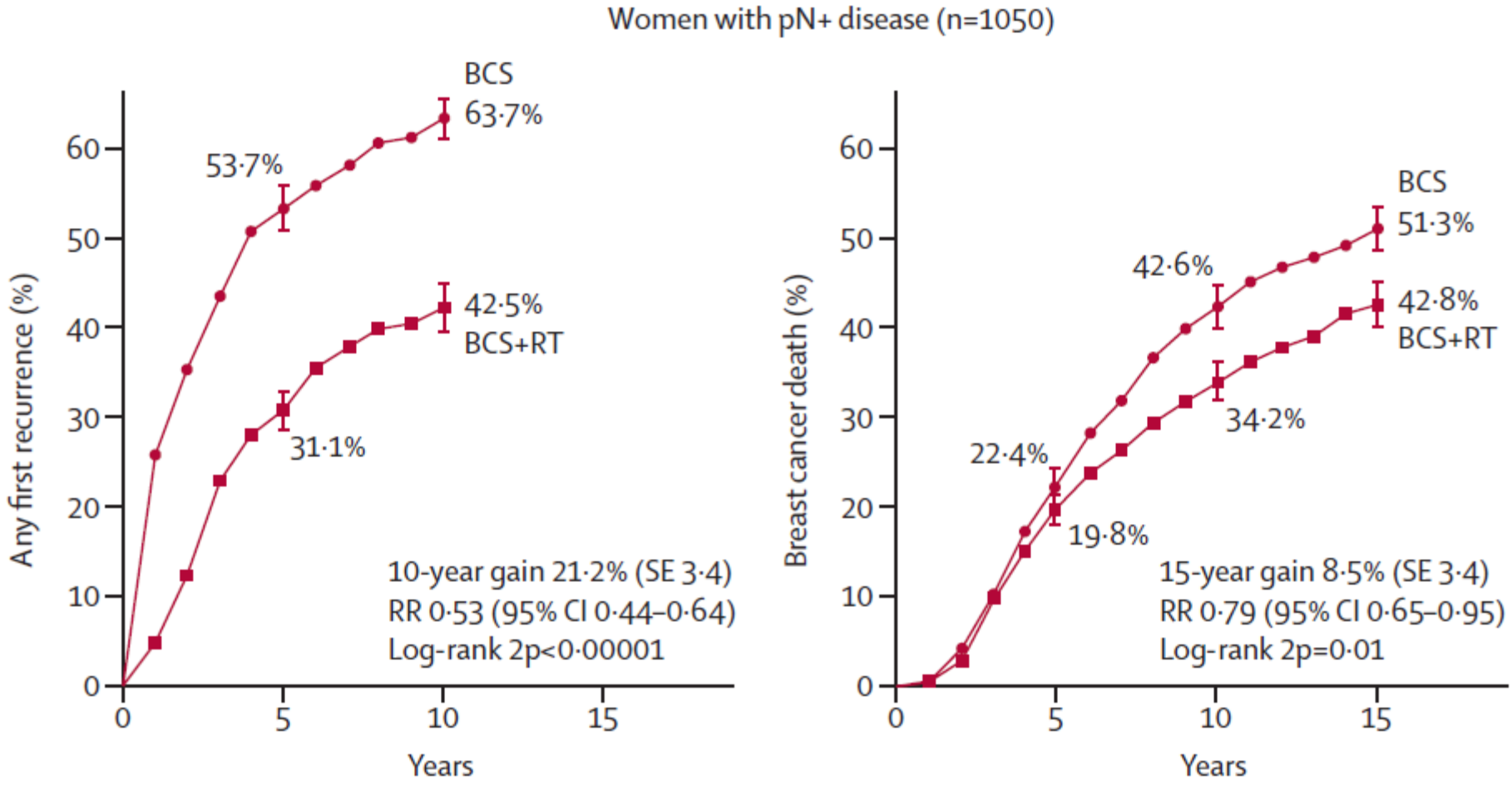
EBCTCG


Any first recurrence
10-year gain 15·7% (SE 1·0)
RR 0·52 (95% CI 0·48–0·56)
Log-rank 2p<0·00001
BCS
35·0%
25·6%
19·3%
BCS+RT
12·6%
Any first recurrence (%)
Years
Breast cancer death
15-year gain 3·8% (SE 1·1)
RR 0·82 (95% CI 0·75–0·90)
Log-rank 2p=0·00005
BCS
25·2%
17·2%
21·4%
BCS+RT
7·8%
14·2%
6·8%
Breast cancer death (%)
Years
Any death
15-year gain 3·0% (SE 1·2)
RR 0·92 (95% CI 0·86–0·99)
Log-rank 2p=0·03
BCS
37·6%
24·6%
34·6%
BCS+RT
11·1%
22·8%
10·3%
Any death (%)
Years

EBCTCG. pN0. 7287 ptes



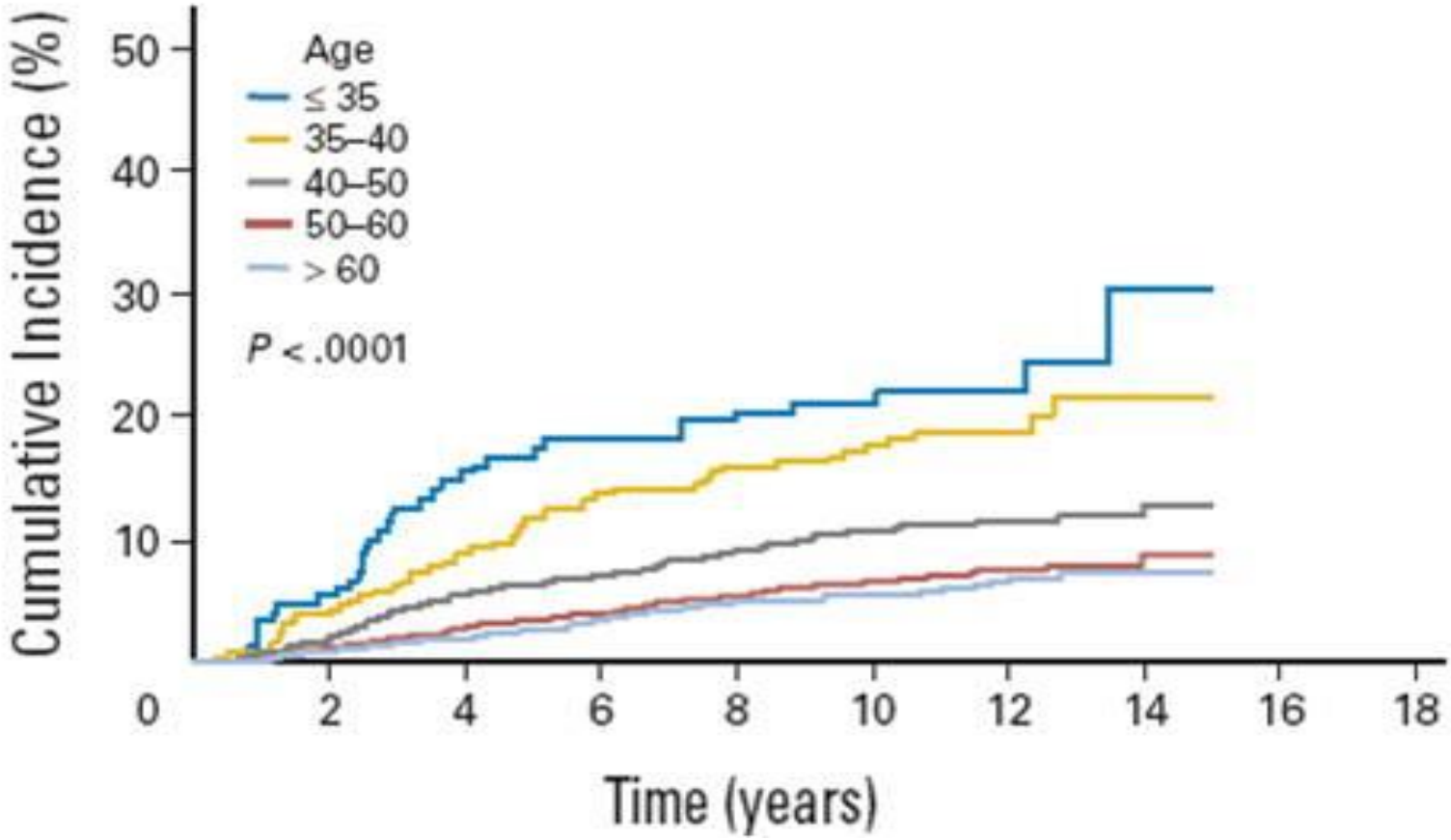
EBCTCG. pN+. 1050 ptes



Conclusions 3

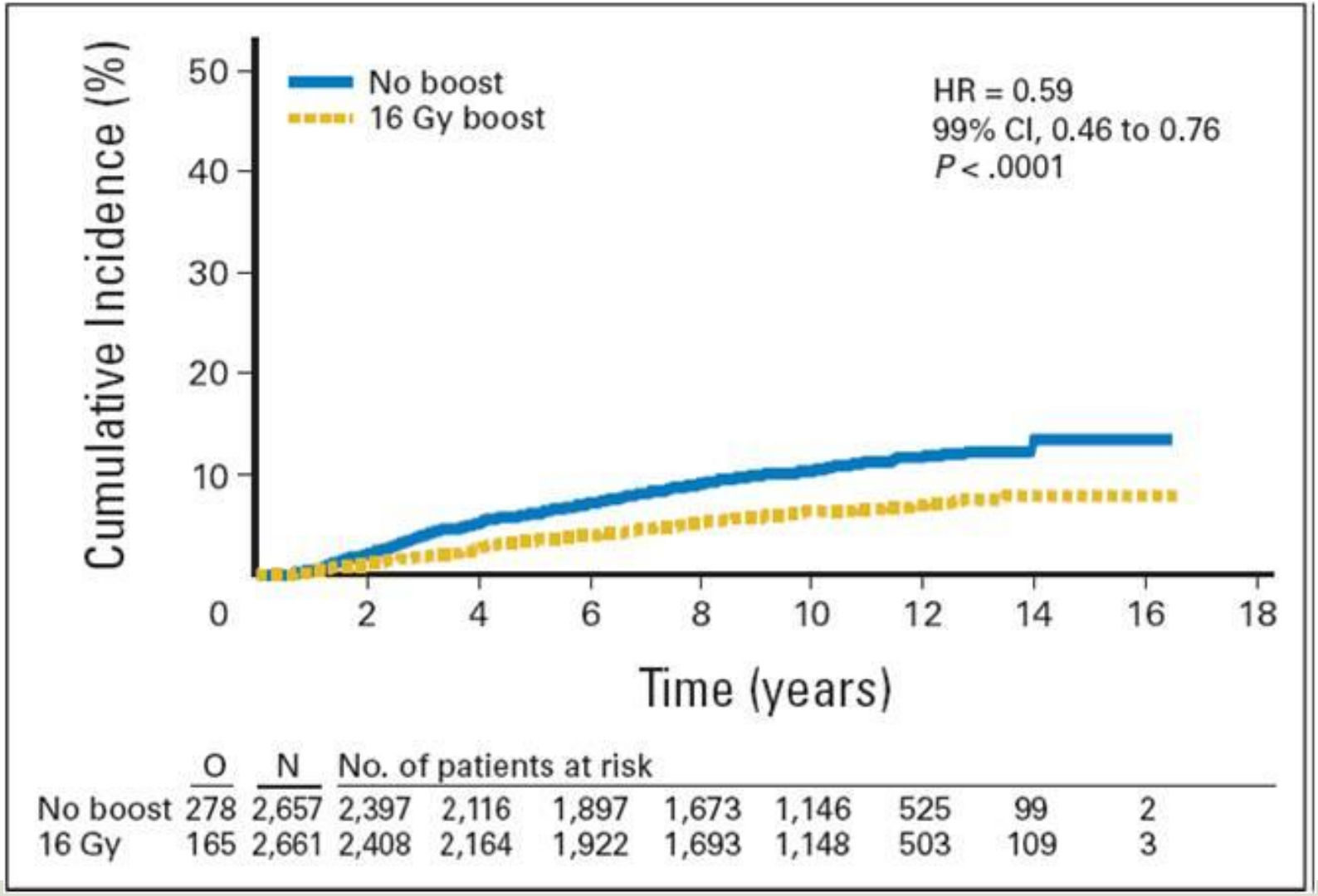
- Following breast-conserving surgery, the rate of loccoregional recurrence was reduced by 70% with radiotherapy.
- The rate of any recurrence (LRR, metastasis, CBC) as first event was reduced by 42 % with RT.
- Locoregional radiotherapy was associated with an 18% decrease in breast cancer mortality, after 5 years.
- The effects of radiotherapy were proportional, independent, from known risk factors: the higher the risk following surgery, the higher the benefit from RT.

EORTC. Local recurrences in relation to age
5319 ptes. Median F/U: 10.2 years



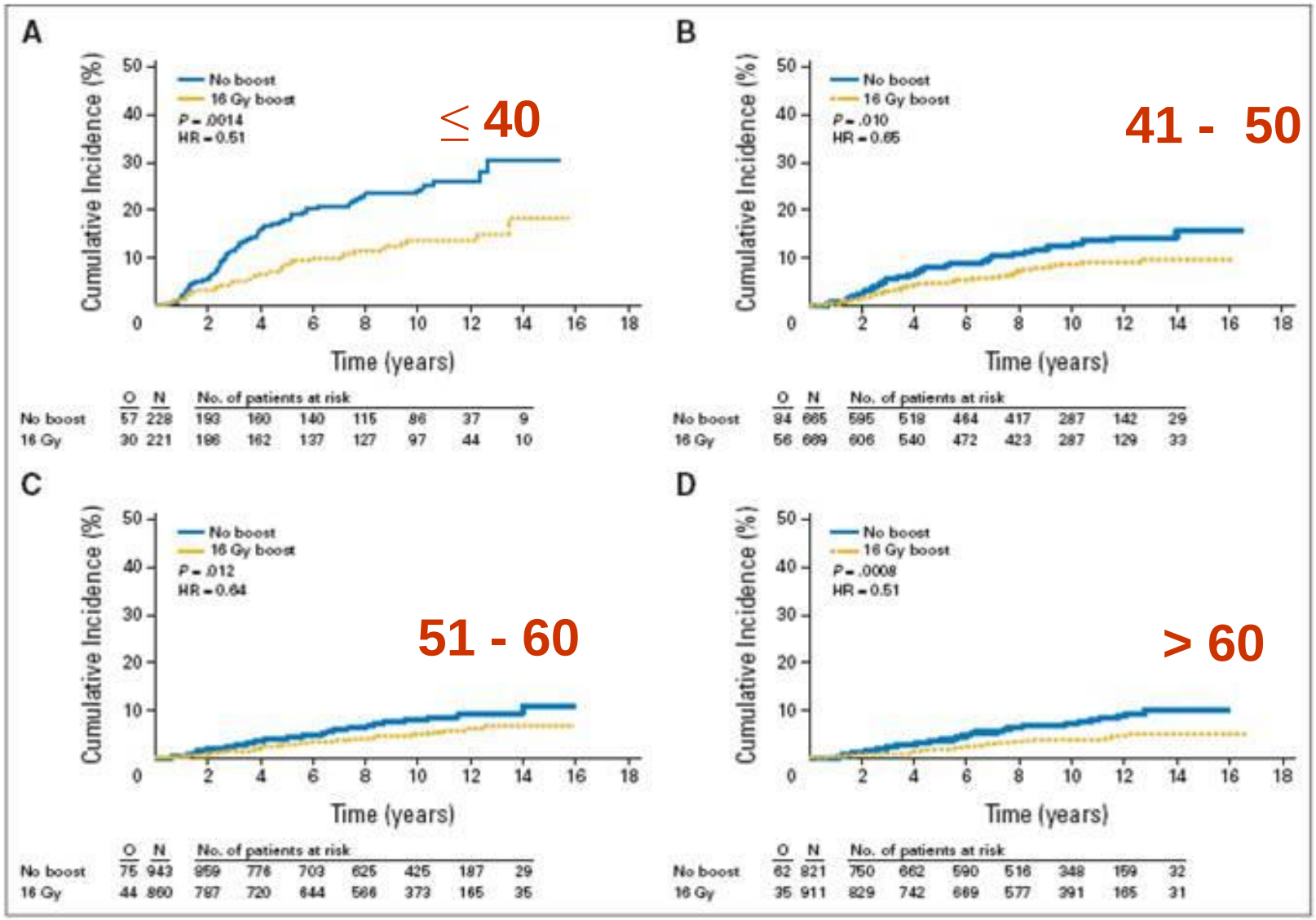
Bartelink H et al. *J Clin Oncol*, 2007

EORTC Boost Trial. 10-year results
Breast recurrences. First event



	O	N	No. of patients at risk							
No boost	278	2,657	2,397	2,116	1,897	1,673	1,146	525	99	2
16 Gy	165	2,661	2,408	2,164	1,922	1,693	1,148	503	109	3

EORTC. Local recurrences per age groups and treatment

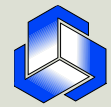


Bartelink H et al. *J Clin Oncol*, 2007

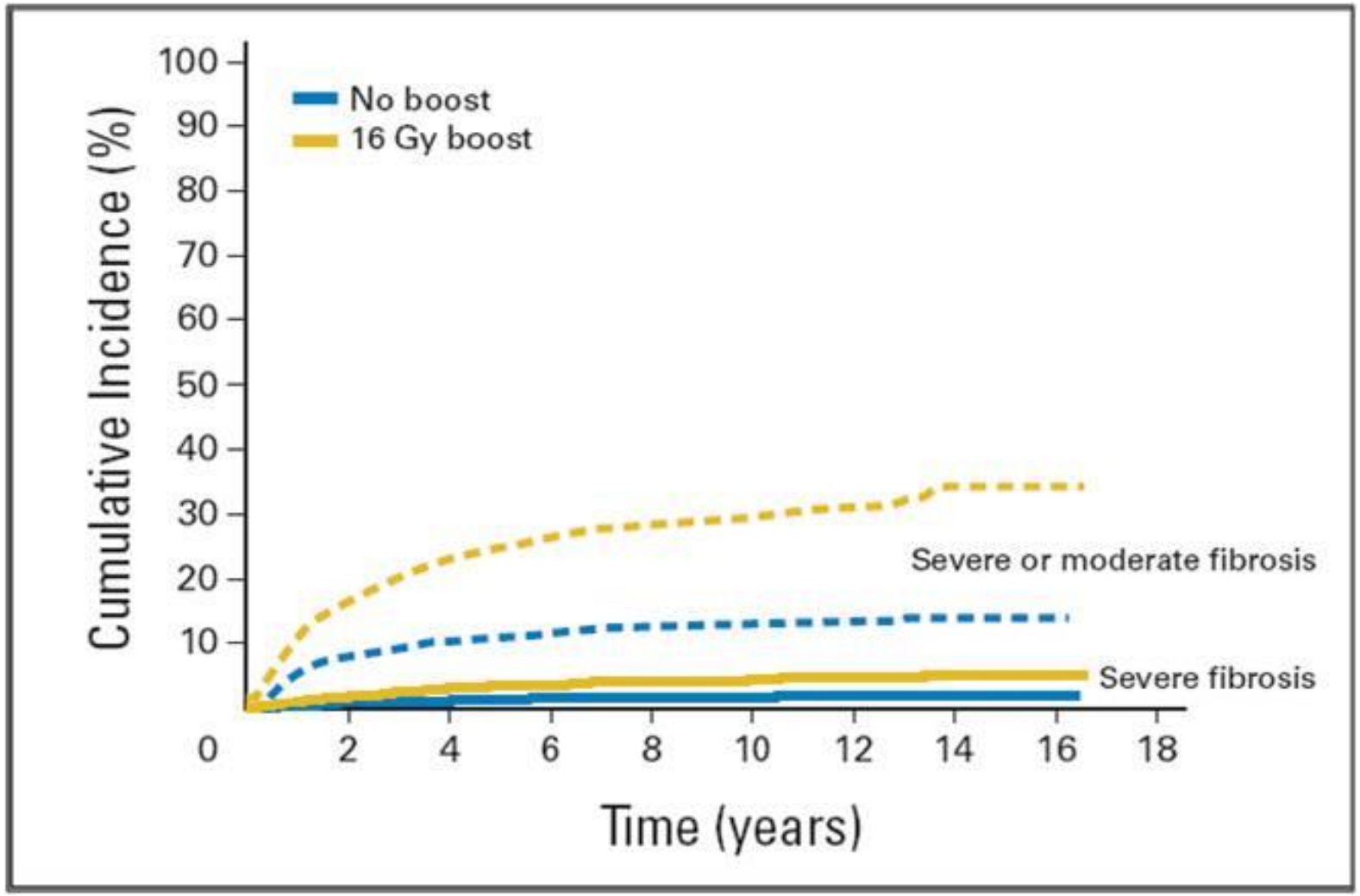
EORTC Boost Trial

Age (years)	% 10-year IBTR as first event	
	50 Gy	50 Gy + 16 Gy
≤ 40	23.9	13.5
41-50	12.5	8.7
51-60	7.8	4.9
>60	7.3	3.8

Bartelink H et al. *J Clin Oncol*, 2007



EORTC Boost Trial. 10-year results
Fibrosis



Breast-conserving surgery. NCCN guidelines

	Whole Breast	Tumor bed (Boost)	Supra/Infra clavicular nodes	IMN
pN > 3	√	±	√	***
pN1-3	√	±	***	***
pN0	√	±	-	-

√: recommended
*****: strongly consider**
****: consider**

NCI France. Guidelines

- Following breast-conserving surgery and whole-breast irradiation to 50 Gy, a 16 Gy boost to the tumor bed is recommended

- Omission of a boost can be considered in women older than 70 years (60 years in REMAGUS Guidelines)

Why radiothérapy to regional lymph nodes (LN)?

EBCTCG´s conclusions

PMRT to pN+ patients:
- LRR ↓ Any first rec ↓ BC mortality ↓

PMRT to pN+ patients is effective
- systemic therapy
- 1 pos node
- pN1-3 nodes
- pN4+ nodes

RT after BCS to pN+ disease
- Any first rec ↓ BC mortality ↓

No consensus on RT to pN1-3

- Old data
- Outdated surgical techniques
- Outdated systemic therapy
- Today´s patients do much better

But we have new data on modern treated patients

MA 20

- 2000-2007
- 1832 pts
- Breast-conserving surgery + Whole Breast Irradiation
- Randomisation

Breast RT **50 Gy/25f**

vs. Breast RT & nodes **45 Gy/25f**

IMN

Supra and infraclavicular ± inferior axilla

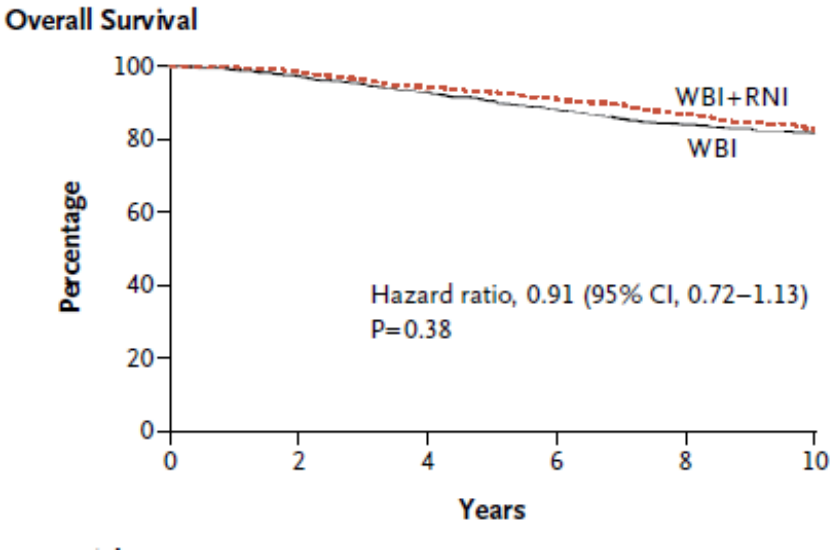
Whelan T et al. N Engl J Med, 2015

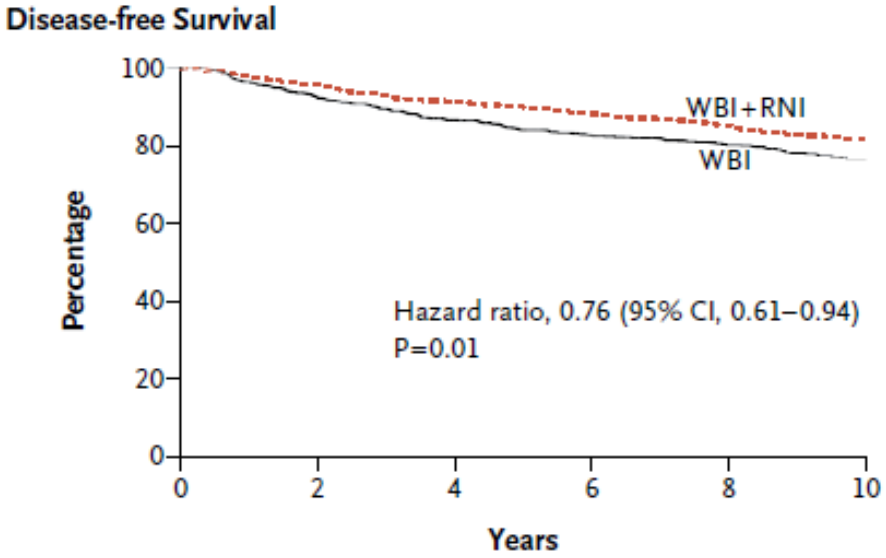
Baseline Characteristics (*Whelan et al, NEJM 2015)*

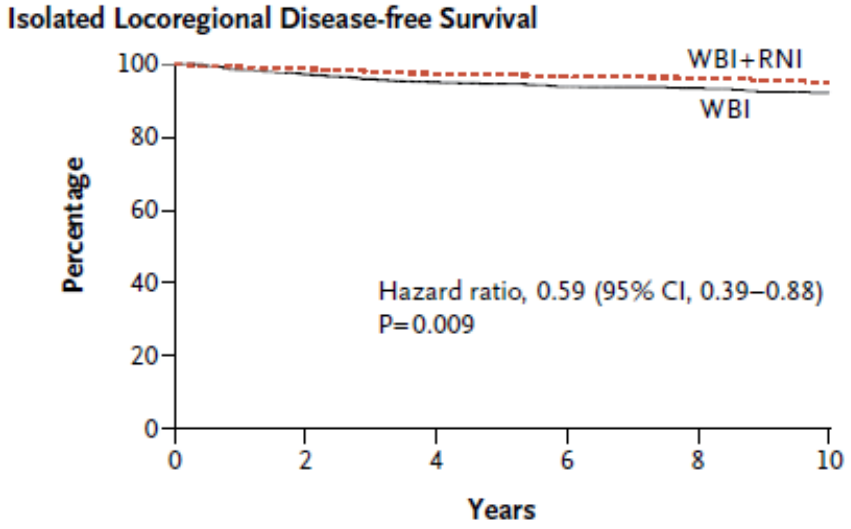
	WBI N=916	WBI+RNI N=916
Age *(mean)*	53	54
Axillary nodes removed *(mean)*	12	12
Node Negative	10%	10%
Node Positive (1-3)	85%	85%
Tumor size > 2cm	45%	50%
Grade III	42%	43%
ER Negative	26%	25%
Adjuvant chemotherapy	91%	91%
Adjuvant endocrine therapy	77%	77%
Boost irradiation	35%	32%

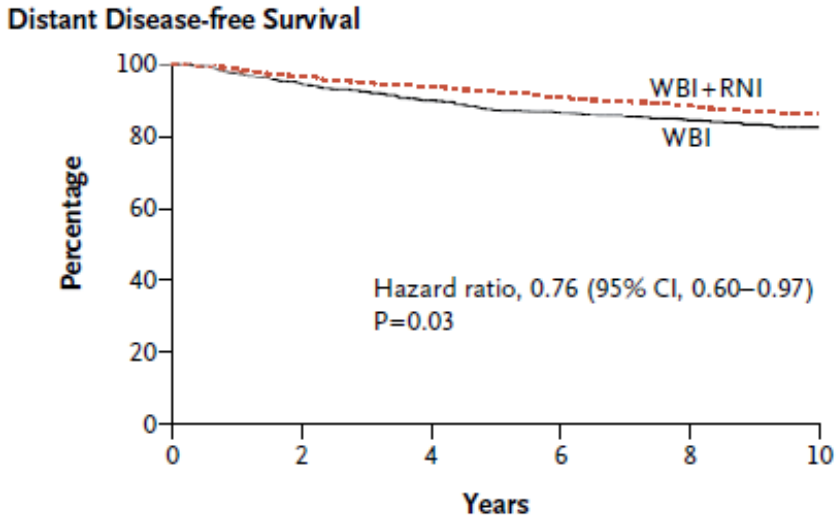
Median follow-up of 62 months

MA 20. Survivals. Median F/U: 9.5 yrs









Whelan T et al. *N Engl J Med*, 2015

MA 20. Results Median follow-up: 9.5 years

Table 2. Disease Recurrence or Death.

Event	WBI (N=916)	WBI+RNI (N=916)
	no. of patients with event (%)	
Isolated locoregional recurrence	62 (6.8)	39 (4.3)
Local (in breast) only	38 (4.1)	33 (3.6)
Regional only	23 (2.5)*	5 (0.5)†
Local and regional	1 (0.1)*	1 (0.1)†
Distant recurrence	151 (16.5)	118 (12.9)
First or concurrent with locoregional recurrence	118 (12.9)	100 (10.9)
After locoregional recurrence	33 (3.6)	18 (2.0)
Any recurrence or contralateral breast cancer	195 (21.3)	154 (16.8)
Any recurrence	175 (19.1)	134 (14.6)
Contralateral breast cancer	20 (2.2)	20 (2.2)
Death	168 (18.3)	155 (16.9)
Breast cancer	113 (12.3)	93 (10.2)
Other cancer	26 (2.8)	32 (3.5)
Cardiovascular cause	11 (1.2)	11 (1.2)
Other cause	12 (1.3)	8 (0.9)
Unknown	6 (0.7)	11 (1.2)

Whelan T et al. *N Engl J Med*, 2015

EORTC 22922/10925

- 1996-2004
- 4004 patients
- Breast-conserving surgery (76%) or Mastectomy
- Randomisation
  - Breast/CW RT 50 Gy/25f
  - vs Breast/CW + IM-MS RT

Poortmans P. et al. *N Engl J Med*, 2015

EORTC RT Trial. Patients distribution

	No IM-MS (N=2002)	IM-MS (N=2002)
Median age (yrs.)	54	54
	%	%
Breast-conserving surgery	76.1	76.2
pT1	60.1	60.2
pN0	44.5	44.4
pN+ 1-3	43.3	42.9
pN+ > 3	12.2	12.6
ER+ve	73	74
Chemotherapy	55.1	54.6
Endocrine treatment	60	59.6

Poortmans P. et al. *N Engl J Med,* 2015

EORTC

Table 2. Events in the Intention-to-Treat Population.

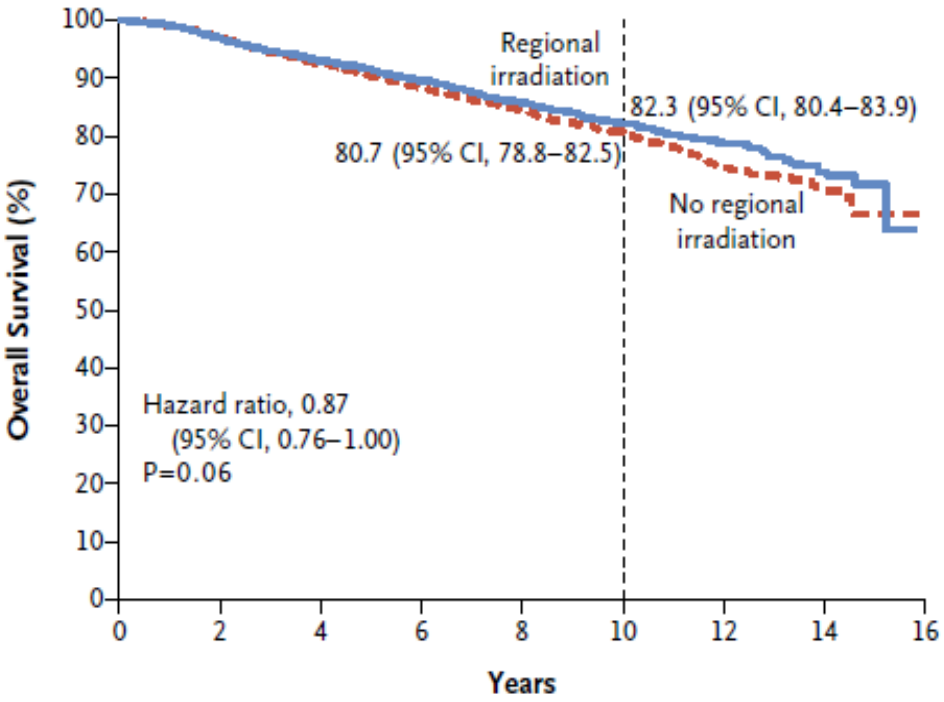
Event	Control Group (N = 2002)	Nodal-Irradiation Group (N = 2002)	Total (N=4004)
		no. of patients (%)	
Recurrence			
Local	107 (5.3)	112 (5.6)	219 (5.5)
Regional*	85 (4.2)	54 (2.7)	139 (3.5)
Axillary	38 (1.9)	27 (1.3)	65 (1.6)
Medial supraclavicular	41 (2.0)	30 (1.5)	71 (1.8)
Internal mammary	16 (0.8)	4 (0.2)	20 (0.5)
Distant disease	392 (19.6)	319 (15.9)	711 (17.8)
Second cancer			
Any	222 (11.1)	191 (9.5)	413 (10.3)
Ipsilateral or contralateral breast cancer	105 (5.2)	97 (4.8)	202 (5.0)

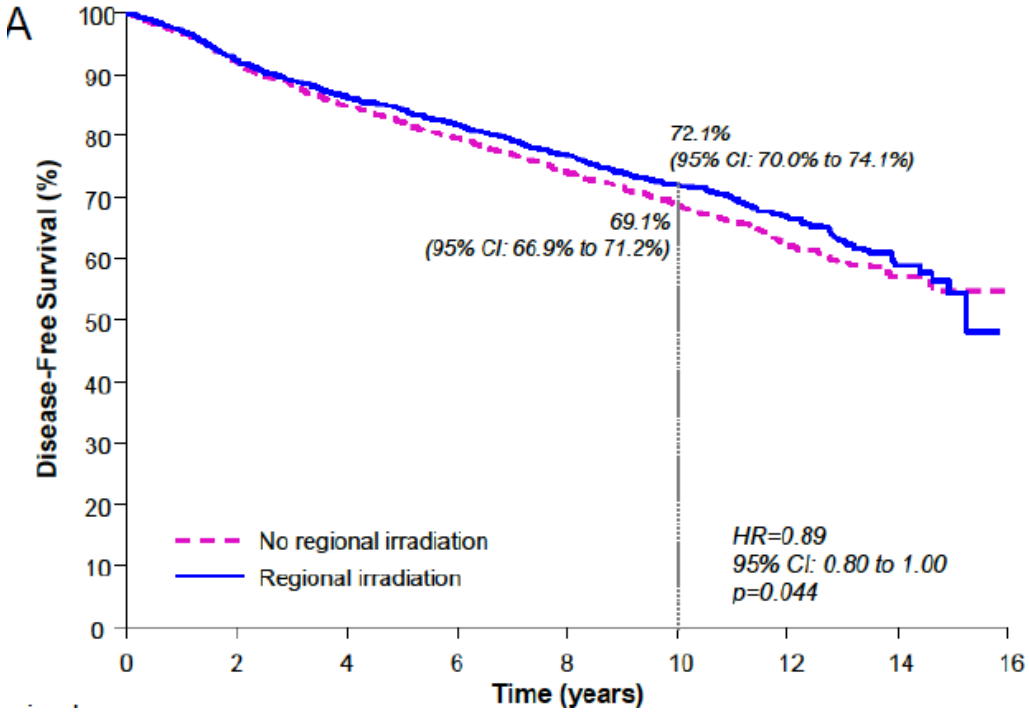
* Multiple locations of regional recurrence may have been observed.

Cardiac toxicity 6.5% in LN irradiation group, NS

Poortmans P. et al. *N Engl J Med*, 2015

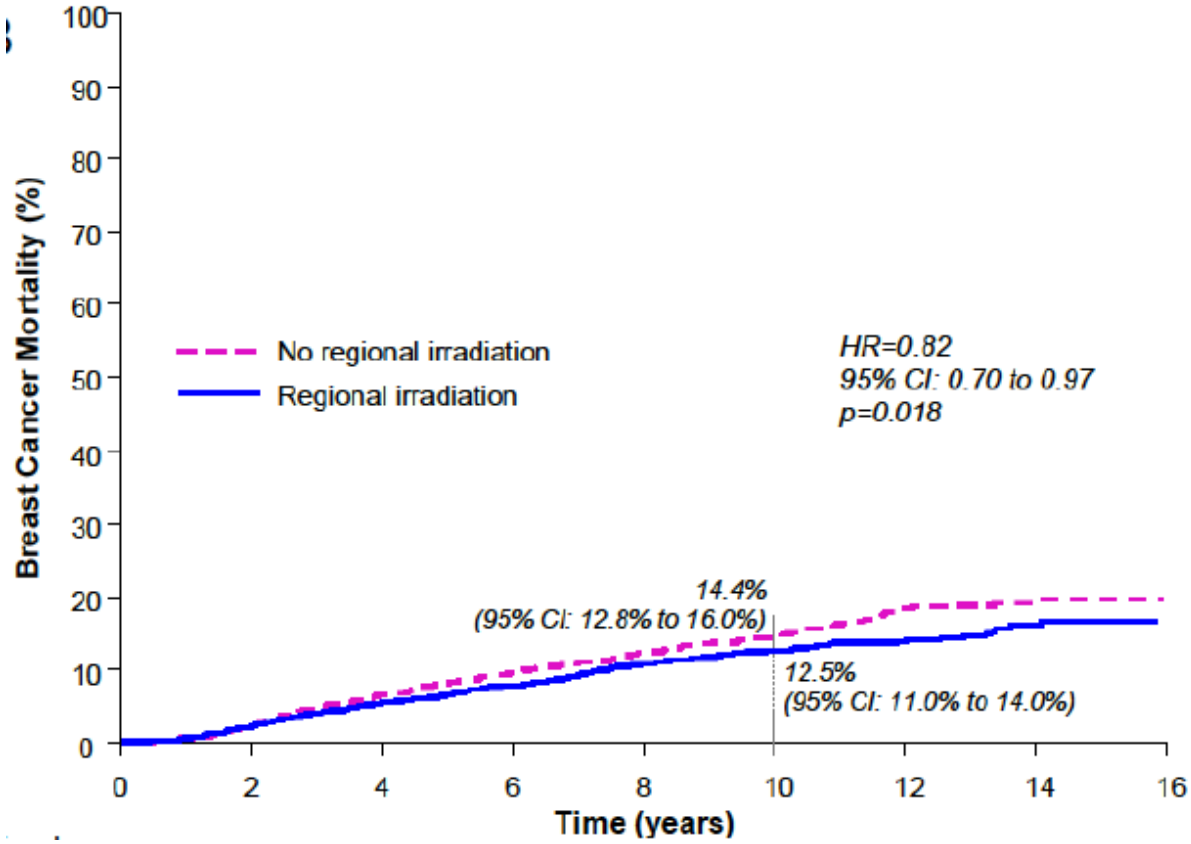
EORTC RT Trial: OS, DFS





Poortmans P. et al. *N Engl J Med*, 2015

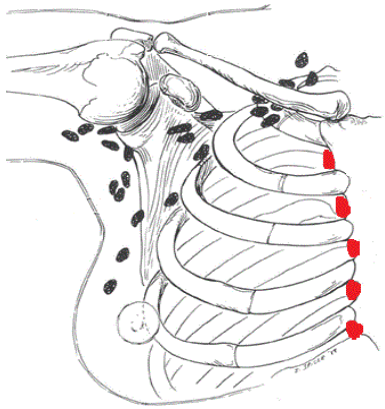
EORTC RT Trial: BC mortality



Poortmans P. et al. *N Engl J Med*, 2015

Regional treatment: DBCG-IMN trial

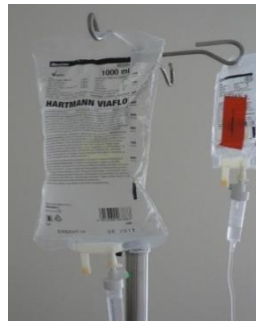
Internal mammary nodes (IMN)
Known reservoir for occult metastases
No consensus on adjuvant radiotherapy

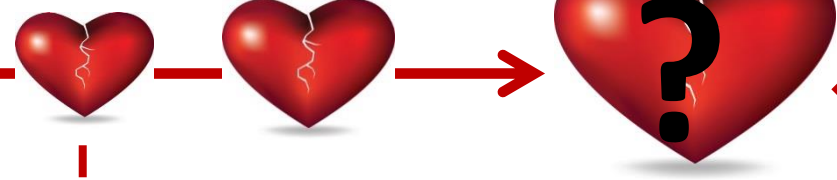


DK: 1980's
IMN RT for all N+ breast cancer patients

1990's
Increased awareness on RT-induced heart disease

2000
Anthracyclines





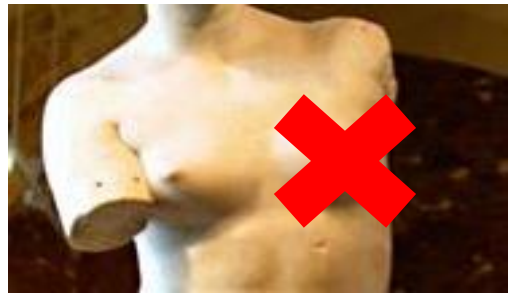
No evidence for effect of IMN-RT

2003

Right side
+ IMN RT

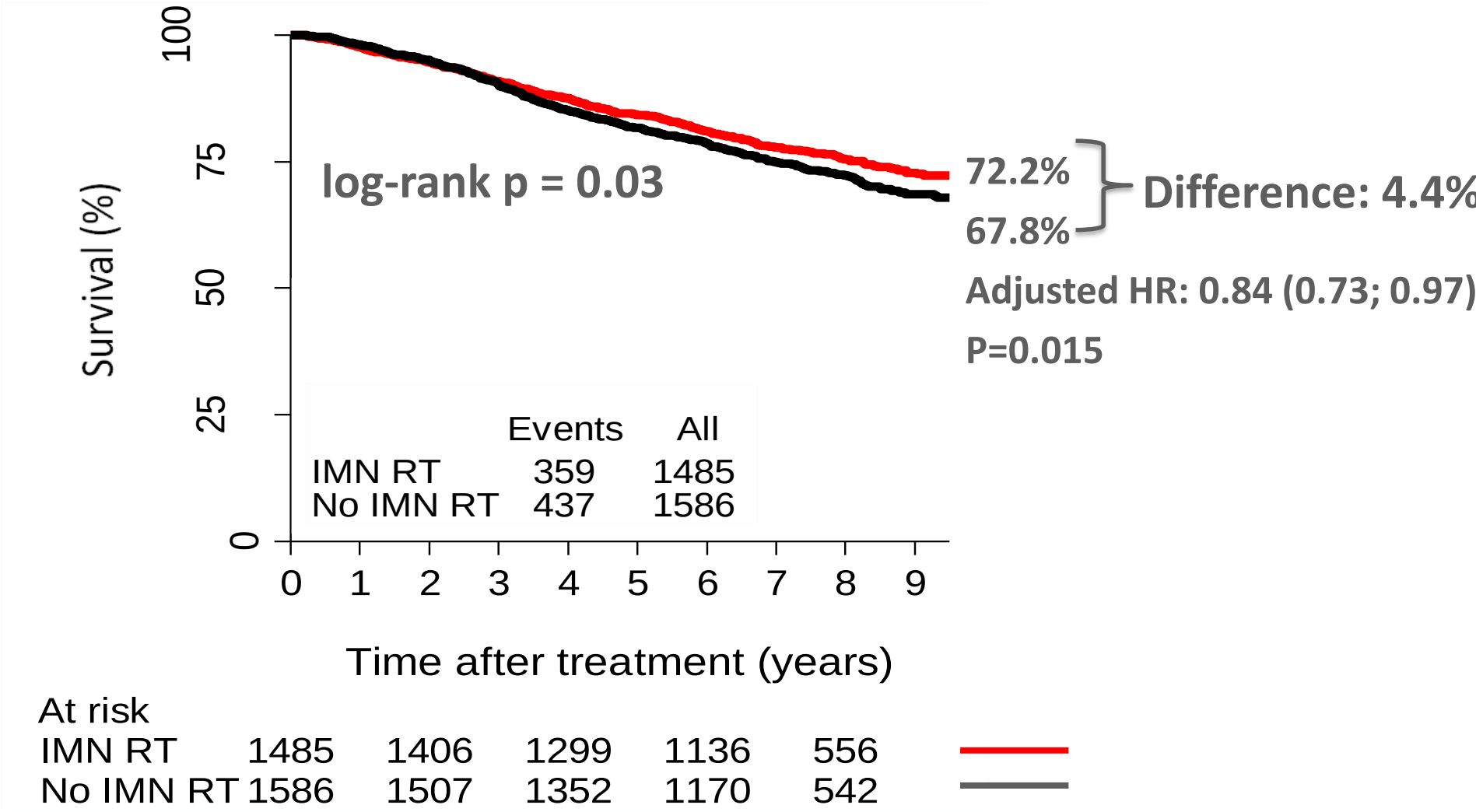
Left side
No IMN-RT

Left side heart dose high



Thorsen LBJ, et al. J Clin Oncol. 2016 Feb 1;34(4):314-20, courtesy Dr Offersen.

Danish study: Overall Survival, n=3376, left vs right, no IMN vs IMN RT, *Lise B J Thorsen et al, JClinOncol 2016,*

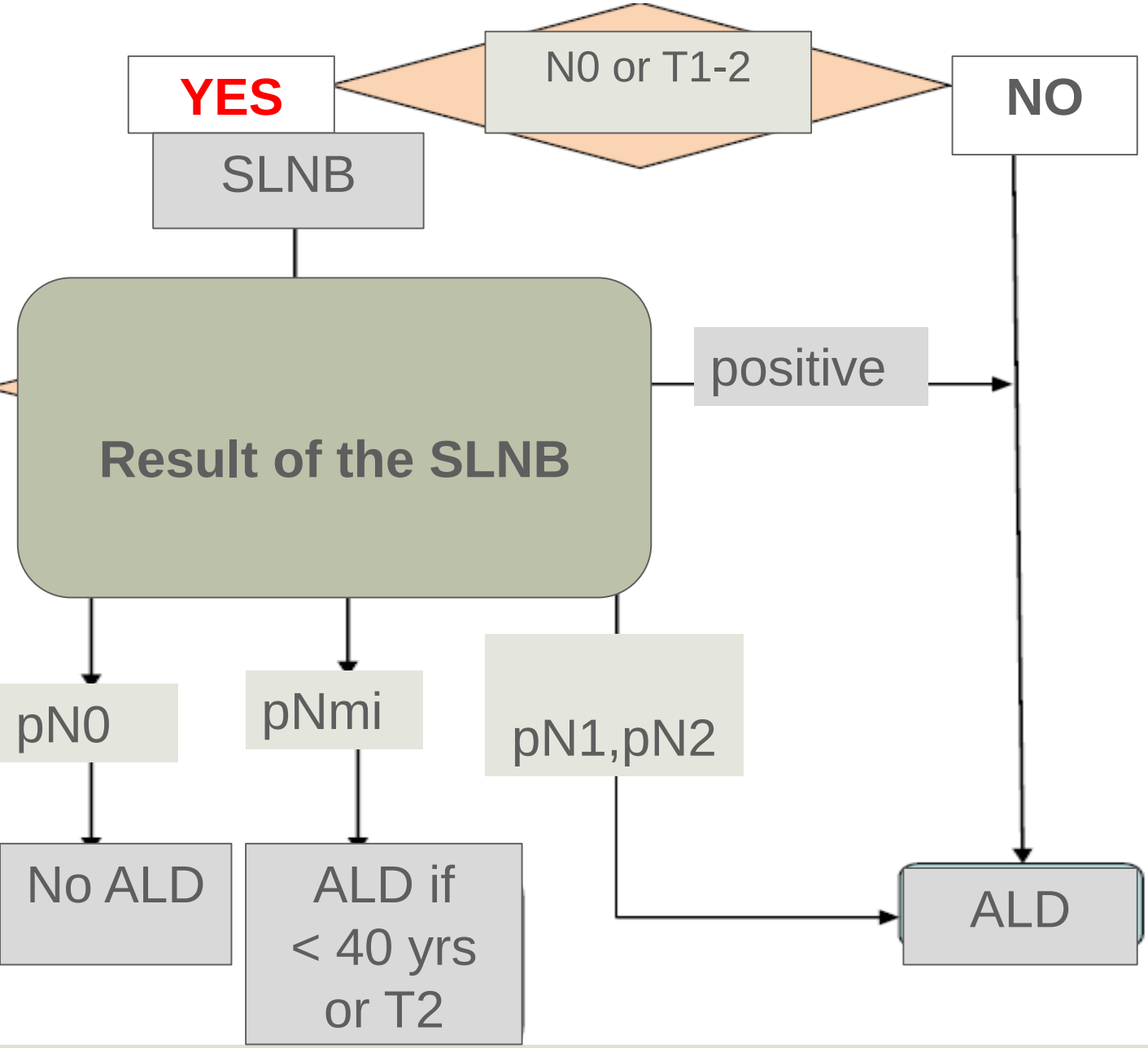


CIRRO

DBCG

Aarhus University Hospital

Therefore: Guidelines for LN Surgery



SUMMARY SURGERY

SLNB is the standard of care for patients with invasive breast cancer who undergo primary surgery

The role of the axillary staging is declining for systemic treatment decisions

AD is indicated in clinically N+ disease

SLNB after PST is reliable in cN0 patients

SUMMARY RADIOTHERAPY

-Regional lymph node radiotherapy to stage II and III breast cancer patients applied in an everyday treatment setting

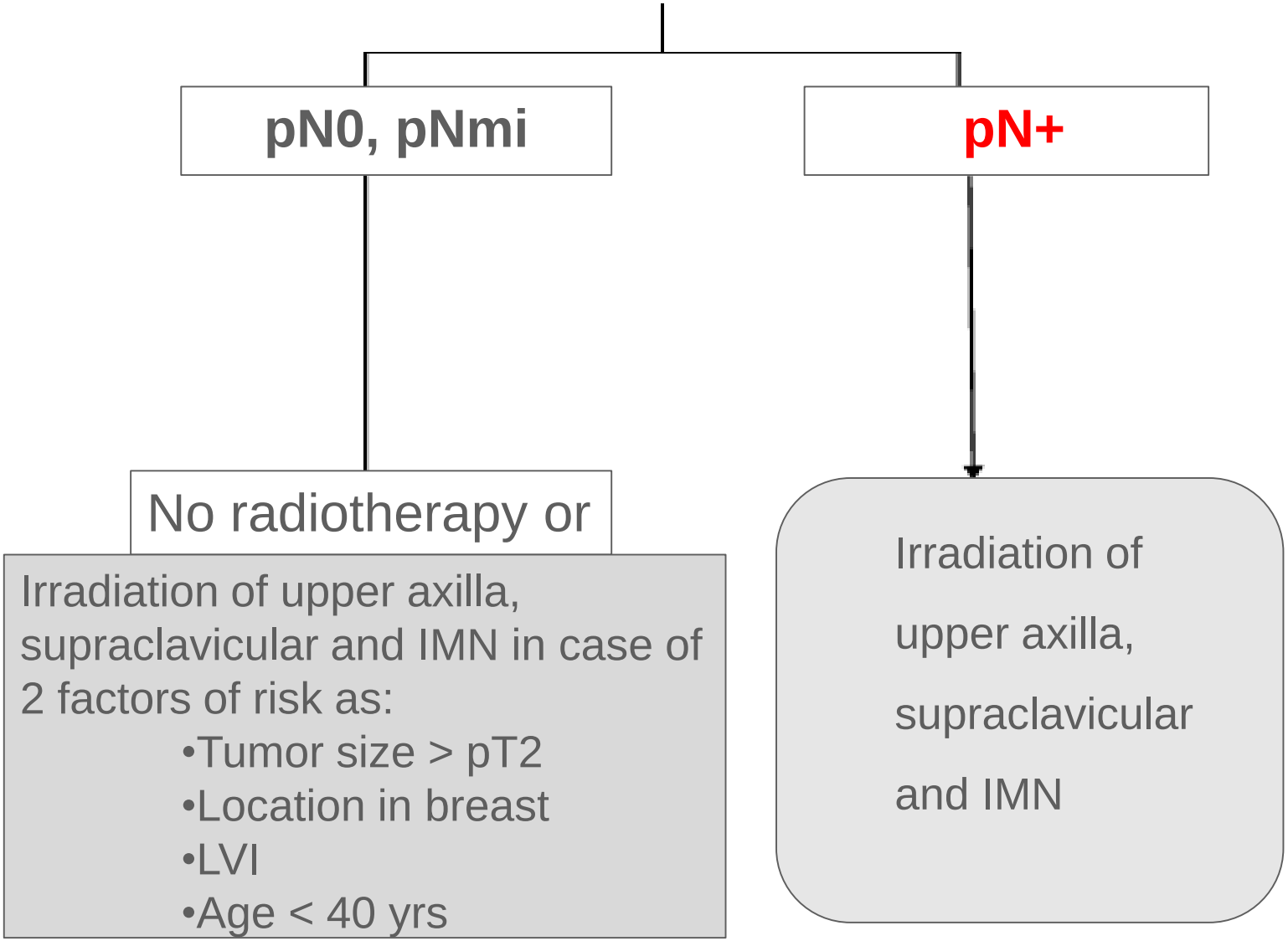
-Improved overall survival

-Decreased incidence of metastatic disease

-Decreased incidence of breast cancer death

-RT is an apropiate tool to replace AD to ensure regional control in N+ patients

Therefore: Guidelines for LN irradiation



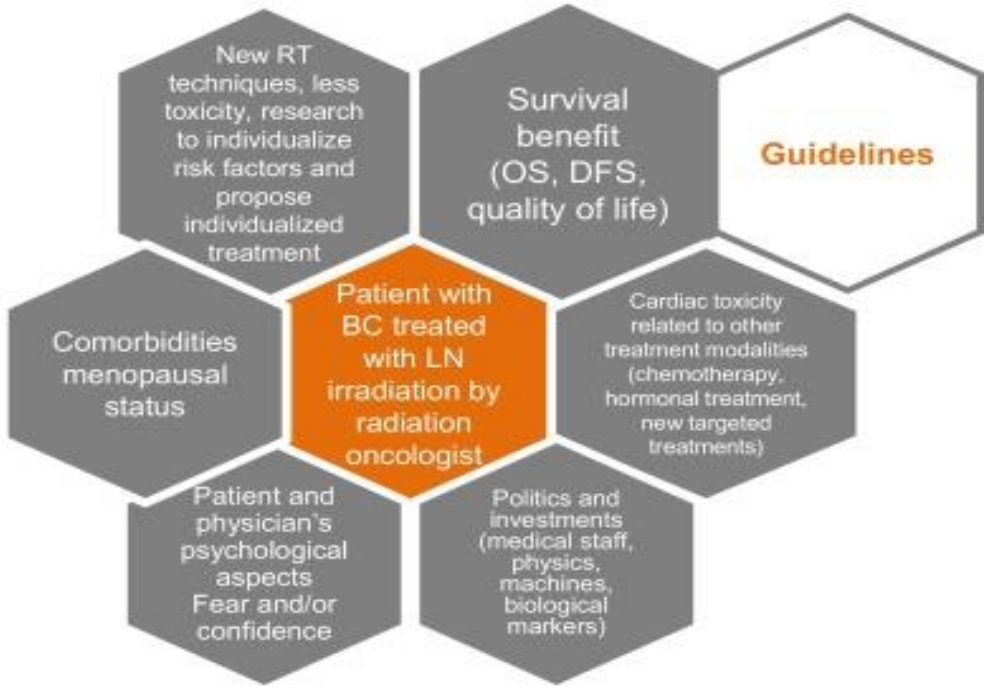


Fig. 1. Consideration of irradiation of regional lymph nodes in the complex breast cancer treatment. RT: radiation therapy; OS: overall survival; DFS: disease-free survival; BC: breast cancer; LN: lymph node.

Y.M. Kirova, J.-Y. Chen

Breast cancer: Is radiotherapy of internal mammary nodes the "state of the art" or "reheating the cold dish"? About a discussion, review of the literature and own opinion

Cancer/Radiothérapie, Volume 21, Issue 3, 2017, 226–227

http://dx.doi.org/10.1016/j.canrad.2016.12.002

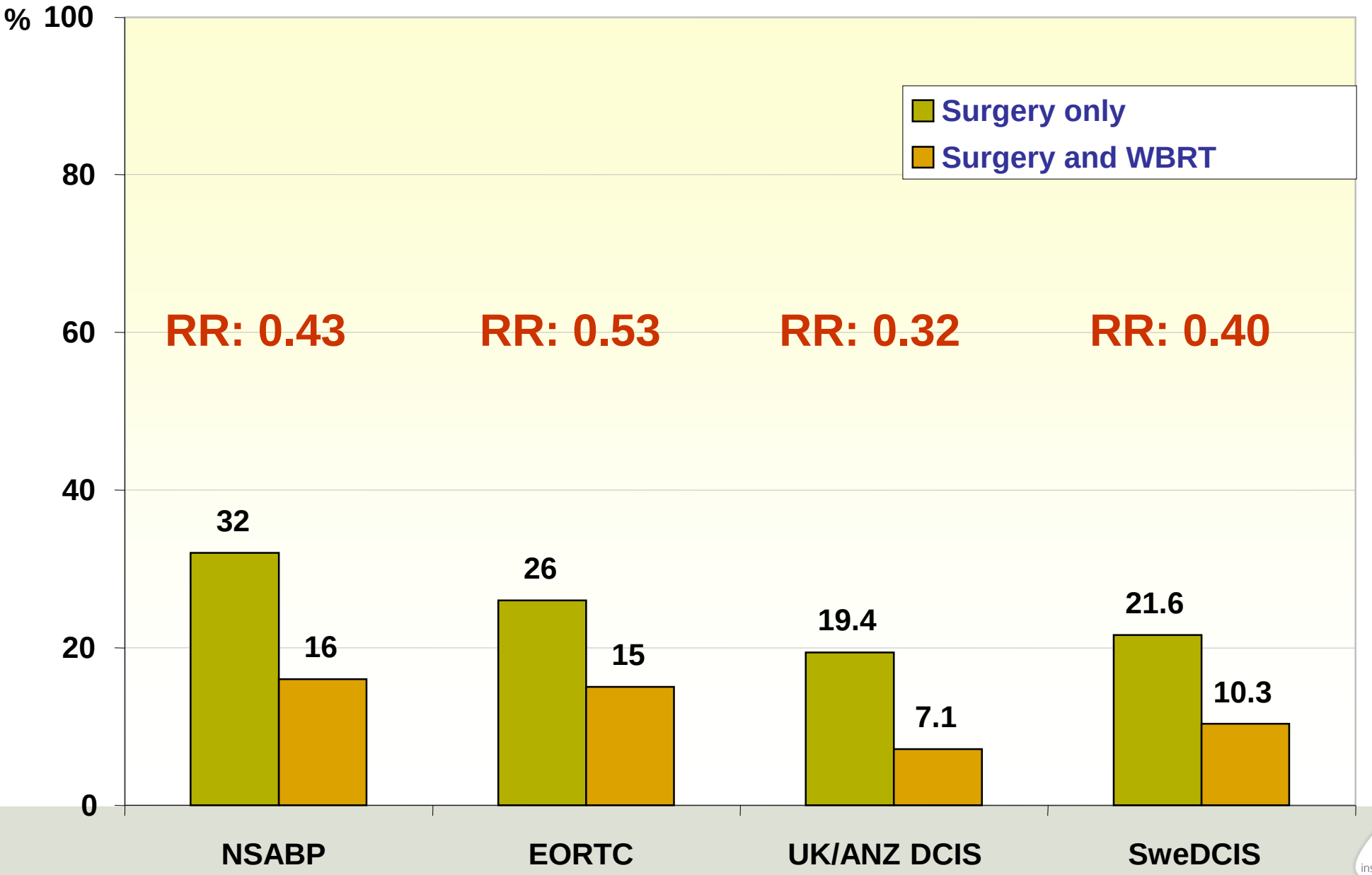
Trials

1. Postmastectomy Radiotherapy
2. Mastectomy vs Breast-conserving treatment with RT
3. **Whole-breast irradiation after breast-conserving surgery**
    - Invasive cancer
    - **DCIS**
4. Fractionation trials
5. Toxicity

Can radiotherapy be omitted in patients with DCIS who underwent breast-conserving surgery?

- Large retrospective studies
- Five trials
- Meta-analysis

10-year local recurrence rates



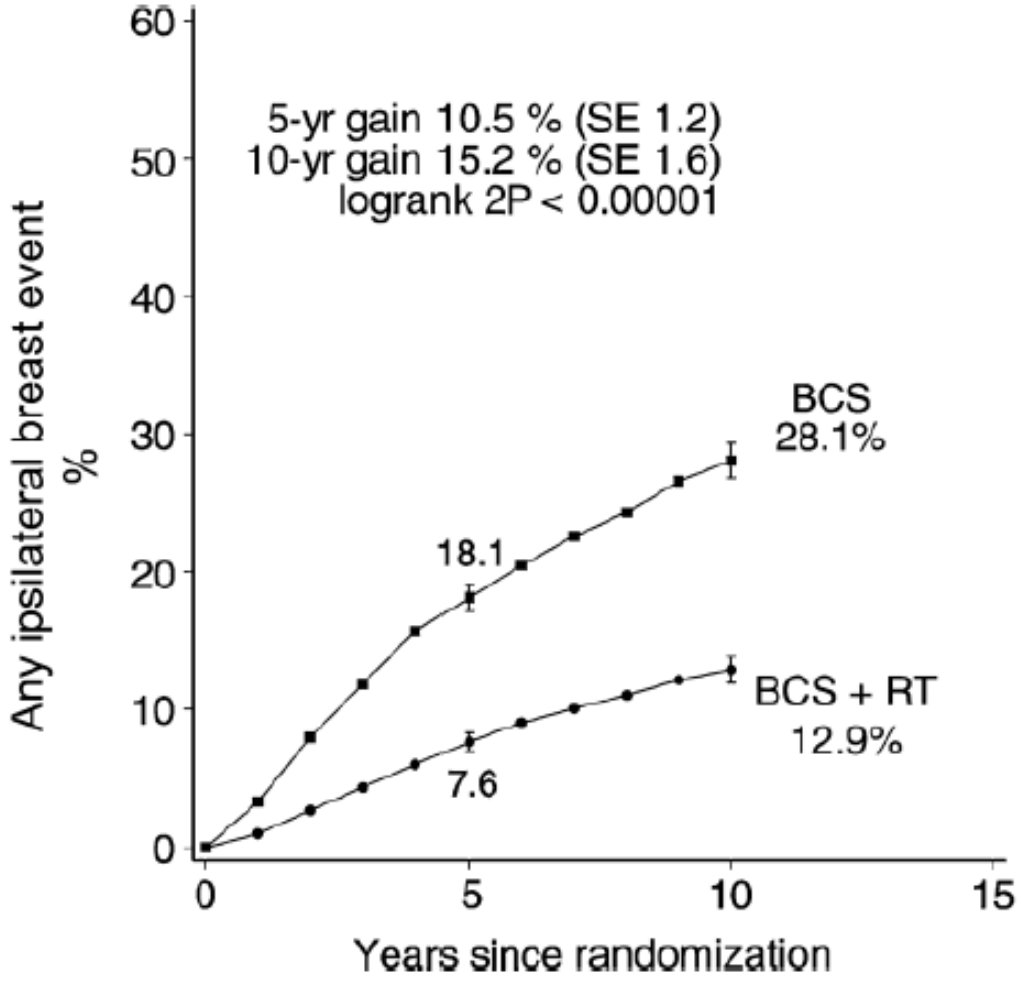
Overview EBCTCG

- Ductal Carcinoma In Situ
- Breast-conserving surgery
- WBRT 50 Gy vs none
- 4 trials
- 1985-2000

EBCTCG *J Natl Cancer Inst Monogr*, 2010

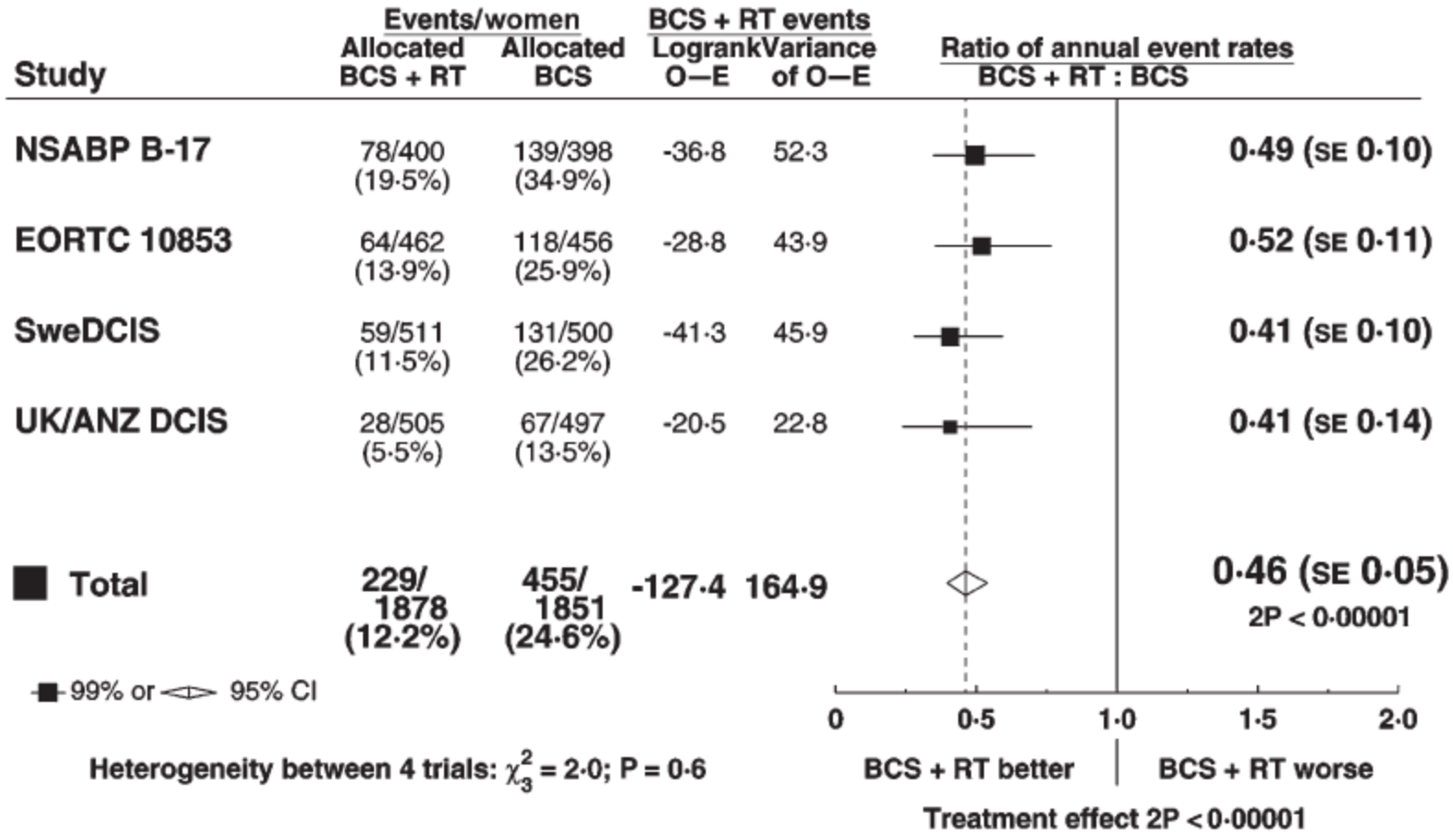
Overview DCIS

- 3729 patients
- Median F/U: 8.9 years
- RR= 0.46



EBCTCG *J Natl Cancer Inst Monogr*, 2010

EBCTCG. DCIS Trials



VOLUME 33 · NUMBER 7 · MARCH 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

RTOG 9804: A Prospective Randomized Trial for Good-Risk Ductal Carcinoma In Situ Comparing Radiotherapy With Observation

Beryl McCormick, Kathryn Winter, Clifford Hudis, Henry Mark Kuerer, Eileen Rakovitch, Barbara L. Smith, Nour Sneige, Jennifer Moughan, Amit Shah, Isabelle Germain, Alan C. Hartford, Afshin Rashtian, Eleanor M. Walker, Albert Yuen, Eric A. Strom, Jeannette L. Wilcox, Laura A. Vallow, William Small Jr, Anthony T. Pu, Kevin Kerlin, and Julia White

RTOG 9804: Primary Objective: In the defined good-risk DCIS group following lumpectomy to negative margins, assess the role of whole breast irradiation ± tamoxifen compared to observation ± tamoxifen, in decreasing or delaying the appearance of local failure, both invasive and *in situ.*

RTOG 9804

Low-risk DCIS

-No symptoms: either mammographic finding or incidental finding in otherwise benign bx

-ONLY low or intermediate grade anywhere

-Size (defined on mammogram if possible) ≤ 2.5 cm

-Margin width ≥ 3 mm

-Stratified by age (+/- 50), size (≤1 cm, >1 cm), margin width (3-9 mm, >1 cm, negative re-excision)

McCormick et al., JCO, 2015

RTOG 9804

Stratify

Age
1. < 50
2. ≥ 50

Final Path Margins
1. Negative (re-excision)
2. 3-9 mm
3. ≥ 10 mm

Mammographic/Pathologic Size of Primary
1. ≤ 1 cm
2. > 1 cm to ≤ 2.5 cm

Nuclei Grade
1. Low
2. Intermediate

Tamoxifen Use
1. No
2. Yes

Randomize

Arm 1
Observation with or without tamoxifen 20 mg per day for 5 years

Arm 2
Radiation therapy* to the whole breast, with or without tamoxifen 20 mg per day for 5 years

McCormick et al., JCO 2015

RTOG 9804

From 1999 to 2006 a total of 636 patients were included.

Radiotherapy:

50 Gy at 2 Gy per fraction x 25 or

50.4 Gy at 1.8 Gy per fraction x 28 or

42.5 Gy at 2.65 Gy per fraction x 16

No Boost

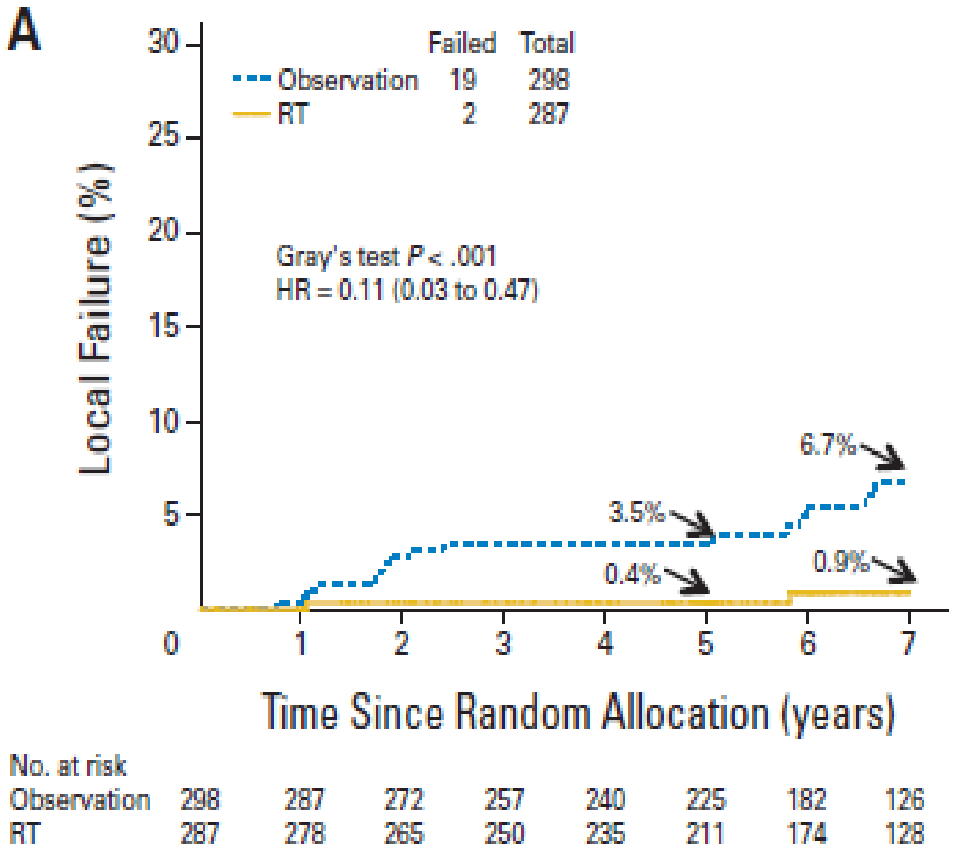
RTOG 9804

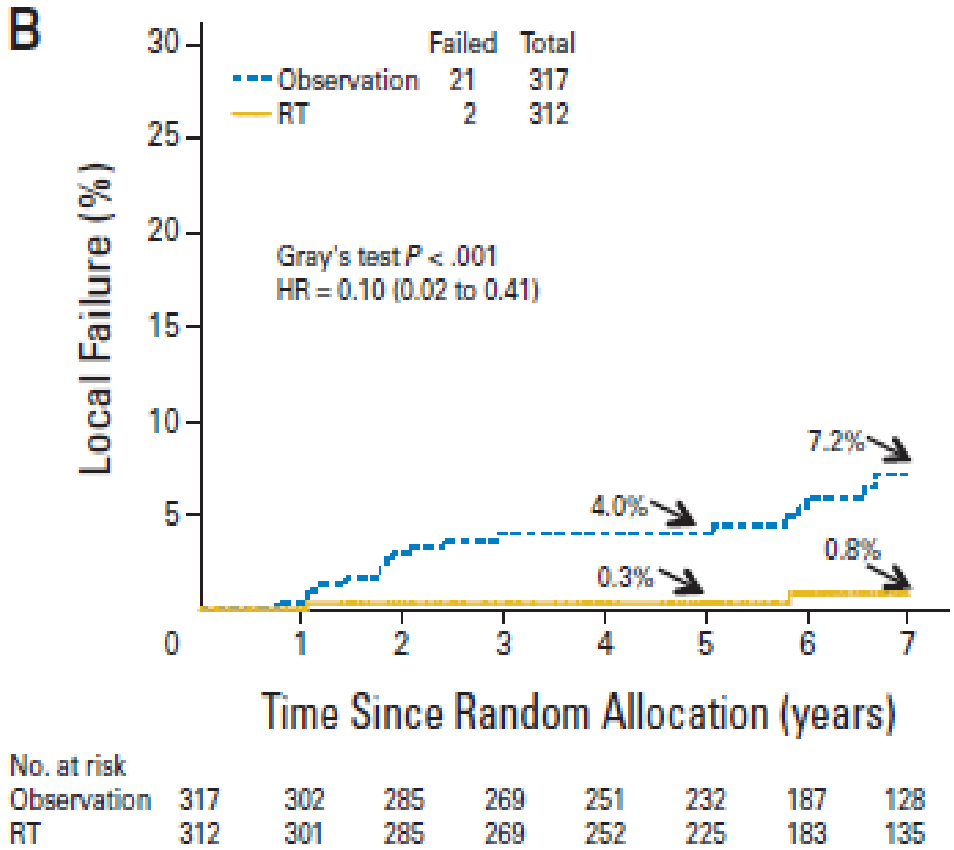
Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	Observation ± Tamoxifen (n = 298)		Radiotherapy ± Tamoxifen (n = 287)	
	No. of Patients	%	No. of Patients	%
Age, years				
< 50	61	20.5	54	18.8
≥ 50	237	79.5	233	81.2
Final microscopic margins, mm				
≥ 3-9	106	35.6	104	36.2
≥ 10	48	16.1	45	15.7
Negative by negative re-excision	144	48.3	138	48.1
Mammographic size of primary tumor, cm				
≤ 1	217	72.8	207	72.1
> 1	81	27.2	80	27.9
Nuclear grade				
1	131	44.0	121	42.2
2	167	56.0	166	57.8
Tumor location				
Left breast	148	49.7	142	49.5
Right breast	150	50.3	145	50.5
Intention to use tamoxifen				
No	91	30.5	90	31.4
Yes	207	69.5	197	68.6

McCormick et al., JCO 2015

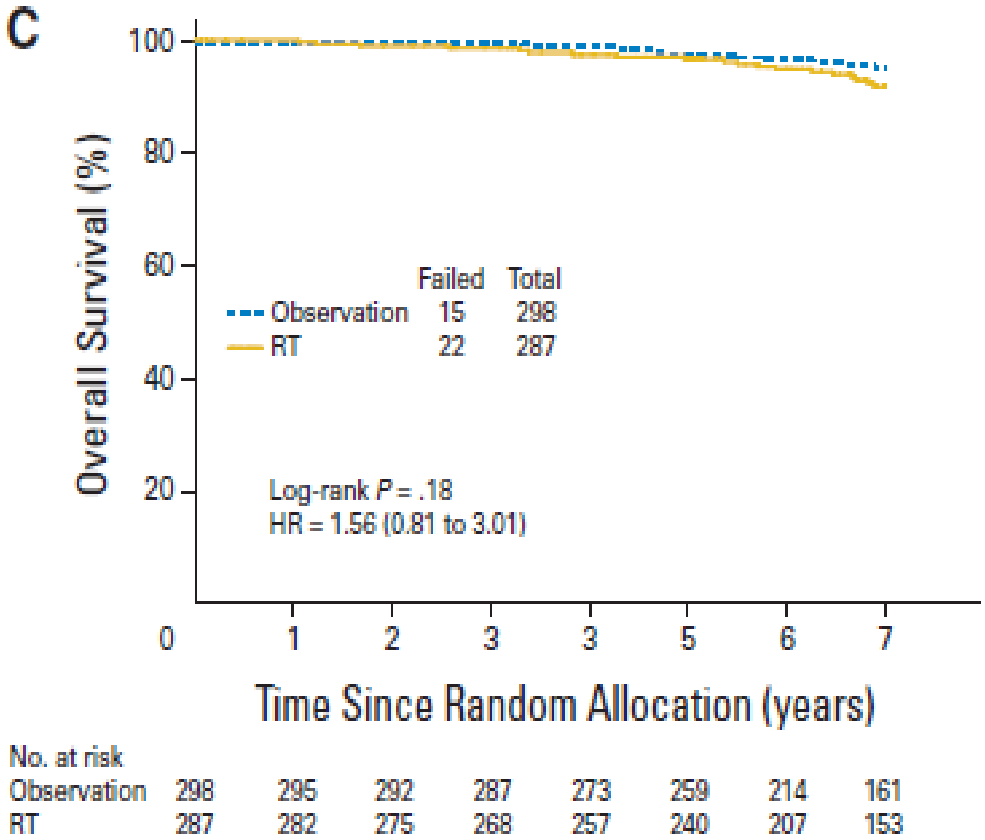
RTOG 9804: Results, local failure

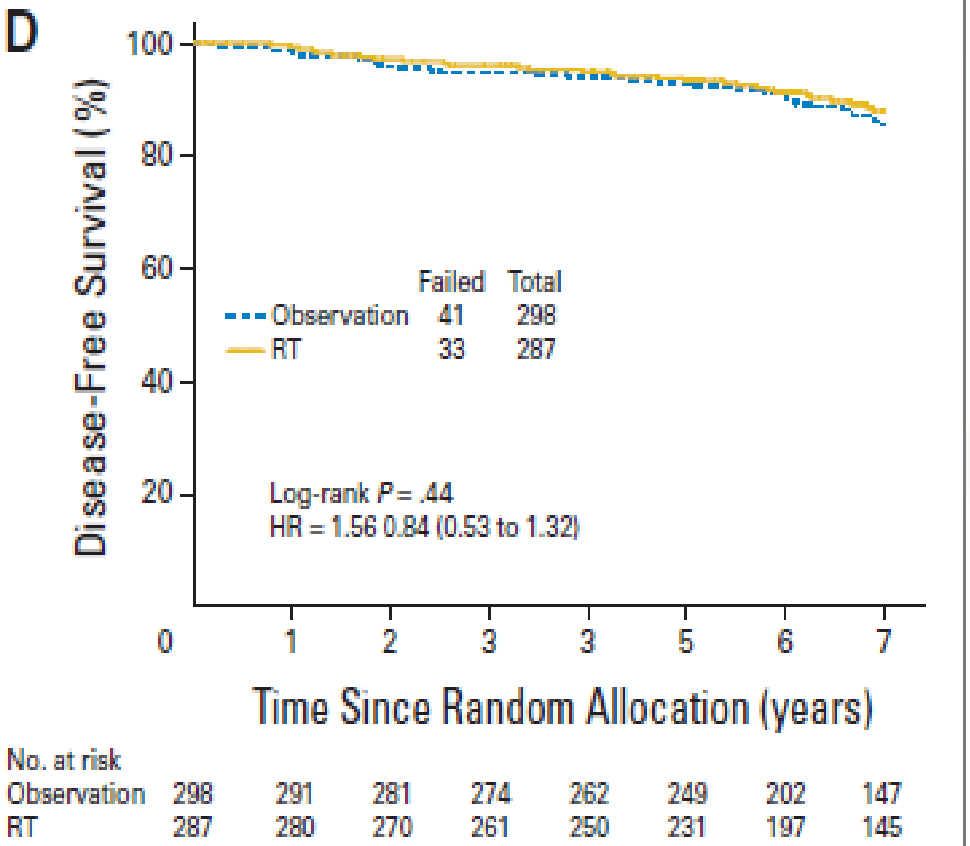




McCormick et al., JCO 2015

RTOG 9804: Results, Overall Survival





McCormick et al., JCO 2015

RTOG 9804: Results, Conclusions

In conclusion, the RTOG 9804 trial in DCIS successfully identified a subset of women with good-risk DCIS based on standard pathology features including nuclear grade, size, and margin width. Although the addition of RT significantly decreased the LF rate for the patients accrued to this study, the full clinical implications of these results will require further follow-up, given the historic patterns of LF over 10 to 15 years from diagnosis of good-risk DCIS.

McCormick et al., JCO 2015

Conclusions

Following breast-conserving surgery of DCIS, WBRT reduces the rate of breast recurrence by 50-60%

The effect is proportional

No subgroups were identified where radiotherapy could be omitted

NCCN Guidelines

Lumpectomy and WBRT

or Total Mastectomy

or Lumpectomy alone

Radiotherapy reduces local recurrence risk by 50%, but no differences in survival

DCIS: the role of boost

How to increase the efficacy of radiation therapy?

The role of boost to the tumor bed.

Radiation Boost for Ductal Carcinoma In Situ (DCIS) After Whole Breast Radiation Therapy (WBRT) Improves Local Control: Collaborative Analysis of Patients Treated at Ten Academic Institutions,

Moran MS, Zhao Y, Ma S, Kirova YM, et al, JAMA Oncol, 2017

Purpose:

To estimate the benefit of the DCIS boost

Calculate sample size needed to show this difference

To assess the independent effects of the DCIS-boost on ipsilateral breast tumor recurrence (IBTR) in a large DCIS cohort

Radiation Boost for Ductal Carcinoma In Situ (DCIS) After Whole Breast Radiation Therapy (WBRT) Improves Local Control

Methods and patients:

Inclusion Criteria:

Centers with existing DCIS databases
Pure DCIS (no micro-invasion)
Treated with WBRT (no APBI)
Minimum 5 years follow-up
LR relative to clinical pathologic parameters
No brachytherapy boost (photon/electron only)

Parameters collected:

Grade, Size,Age
RT boost no boost

Margin status
Comedo necrosis
ER status & Tamoxifen

Moran et al, JAMA Oncol, 2017

Radiation Boost for Ductal Carcinoma In Situ (DCIS) After Whole Breast Radiation Therapy (WBRT) Improves Local Control:

Collaborative Analysis of Patients Treated at Ten Academic Institutions,

Participating institutions/P.I. :

- British Columbia
- Dana Farber
- Institut Curie
- M.D. Anderson
- UMDNJ
- U. Montreal
- University Pennsylvania
- McGill University
- William Beaumont
- Yale University

Radiation Boost for Ductal Carcinoma In Situ (DCIS) After Whole Breast Radiation Therapy (WBRT) Improves Local Control

Moran MS, et al, JAMA Oncol, 2017

Results: Median f/u time =9 years

- Total n= 4131 patients Median age 56 years
  - No boost = 1470 (35.6%)
  - Boost = 2661 (64.4%)
- Margin+ (ink on tumor) =4.1% (n=168)
- Grade II/III component: 68% (n=2817)
- ER Status: Known 37% (n= 1538)

Exceeded sample size estimation by 39%

Characteristics	Total	No Boost N (%)	Boost N (%)	Chi-squared p value
Number of patients	4131	1470 (35.6)	2661(64.4)	
Age (median)	56.1	56.2	56.0	NS
Standard Deviation	10.9	10.7	11.0	
Age (years)				0.1245
<50	1301(31.5)	441(30)	860 (32.3)	
≥50	2830(68.5)	1029 (70)	1801(67.7)	
DCIS Grade				0.4846
I	694(16.8)	250(17)	444(16.7)	
II /III	2817(68.2)	975(66.3)	1842(69.2)	
Unknown	620(15)	245(16.7)	375(14.1)	
Tumor size				0.0808
≤1.0cm	1659(40.2)	608(41.4)	1051(39.5)	
>1.0cm	1680(40.7)	665(45.2)	1015(38.1)	
unknown	792(19.2)	197(13.4)	595(22.4)	
Margin status				<0.001
(Positive-0mm)	168(4.1)	44(3.0)	124(4.7)	
(Negative>0mm)	3611(87.4)	1285(87.4)	2326(87.4)	
Unknown	352(8.5)	141(9.6)	211(7.9)	
Comedo necrosis				0.0266
Absent	1066(25.8)	262(17.8)	804(30.2)	
Present	1301(31.5)	270(18.4)	1031(38.7)	
Unknown	1764(42.7)	938(63.8)	826(31)	
Estrogen receptor status				0.0429
negative	296(7.2)	85(5.8)	211(7.9)	
positive	1242(30.1)	287(19.5)	955(35.9)	
unknown	2593(62.8)	1098(74.7)	1495(56.2)	

Radiation Boost for Ductal Carcinoma In Situ (DCIS) After Whole Breast Radiation Therapy (WBRT) Improves Local Control

Results:

Outcome entire cohort,

n=4131

- 253 IBTR events (6.1%)
- 118 invasive events (47%)
- 135 DCIS events (53%)

Years	Boost % (95% CI)	No-boost % (95% CI)	p=0.0389
5	97.1% (0.96-0.98)	96.3% (0.95-0.97)	
10	94.1% (0.93-0.95)	92.5% (0.91-0.94)	
15	91.6% (0.90-0.93)	88.0% (0.85-0.91)	

IBTR-free survival:

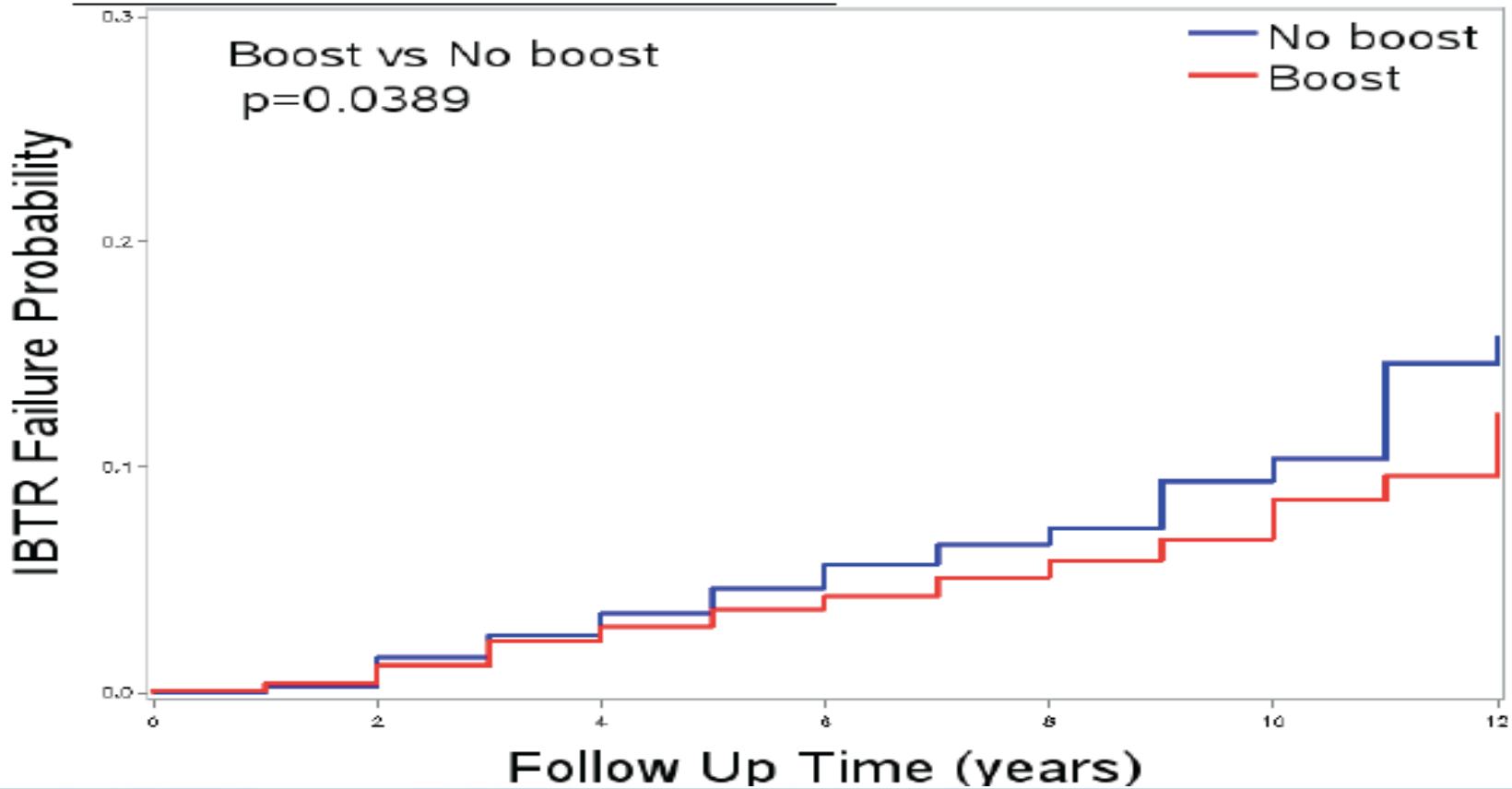
- 96.8% at 5 years
- 93.6% at 10 years
- 90.4% at 15 years

Moran et al, JAMA Oncol, 2017

Radiation Boost for Ductal Carcinoma In Situ (DCIS) After Whole Breast Radiation Therapy (WBRT) Improves Local Control

Results: n=4131

Figure 1. Boost vs. no Boost in All Patients:



Moran et al, JAMA Oncol, 2017

Radiation Boost for Ductal Carcinoma In Situ (DCIS) After Whole Breast Radiation Therapy (WBRT) Improves Local Control; *Moran et al, JAMA Oncol, 2017*

Results: *Univariate Analysis Boost vs. No Boost*

		HR	P-value
Boost	no	1.0	-
	yes	0.728	0.013
Grade	I	1.0	-
	II/III	1.631	0.019
Comedo	no	1.0	-
	yes	1.324	0.081
Tamoxifen	no	1.0	-
	yes	0.518	<0.001
Margin	neg	1.0	-
	+/unk	2.345	<0.001
Age	<50	1.0	-
	≥50	0.54	<0.001
Age	<60	1.0	-
	≥60	0.61	<0.001
Age	<70	1.0	-
	≥70	0.57	0.023

Radiation Boost for Ductal Carcinoma In Situ (DCIS) After Whole Breast Radiation Therapy (WBRT) Improves Local Control: *Moran MS, et al, JAMA Oncol, 2017*

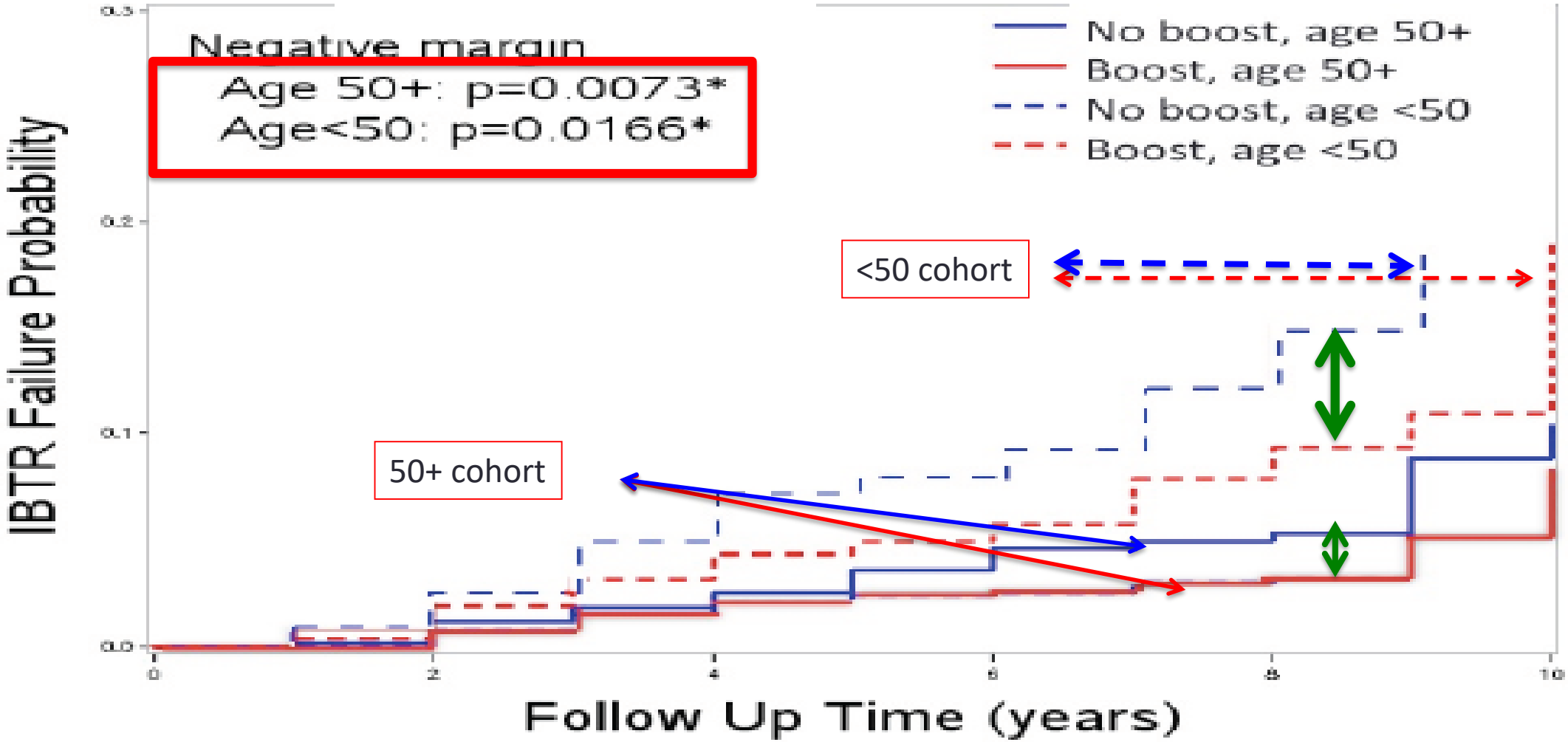
Results: *Multivariate Analysis Boost vs. No Boost*

Characteristics		HR	P-value
Boost	no	1.0	-
	yes	0.69(0.53-0.91)	<0.010
Grade	I	1.0	-
	II/III	1.62 (1.06-2.47)	0.020
Comedo	no	1.0	-
	yes	1.13 (0.81-1.57)	0.470
Tamoxifen	no	1.0	-
	yes	0.60 (0.42-0.95)	0.030
Margin	neg	1.0	-
	positive	1.79(1.05-3.05)	0.030
Age	<50	1.0	-
	≥50	0.57 (0.45-0.74)	0.010

LR ratio: interaction between age and boost: p-value 0.463 (NS)

Radiation Boost for Ductal Carcinoma In Situ (DCIS) After Whole Breast Radiation Therapy (WBRT) Improves Local Control, *Moran MS, et al, JAMA Oncol 2017*

Boost Stratified by Age (<50 vs. 50+)



Radiation Boost for Ductal Carcinoma In Situ (DCIS) After Whole Breast Radiation Therapy (WBRT) Improves Local Control,

Conclusions:

These findings suggest that the DCIS-boost results in a small, statistically significant benefit in decreasing long-term IBTR of similar magnitude to boost for invasive cancers

- This benefit appears to be independent of:
  - Tamoxifen use
  - Definition of negative margins

- Similar to anticipated benefits seen in magnitude and age trends as with invasive cancers

DCIS treatment decisions are complex; Tailor to:

- Clinical-pathologic features & tumor biology
- Patient preferences
- Anticipated longevity

These data support the use of a boost in DCIS

A boost should be considered for DCIS for patients undergoing WBRT, with life expectancies 10-15+ years

Moran MS, et al, JAMA Oncol 2017

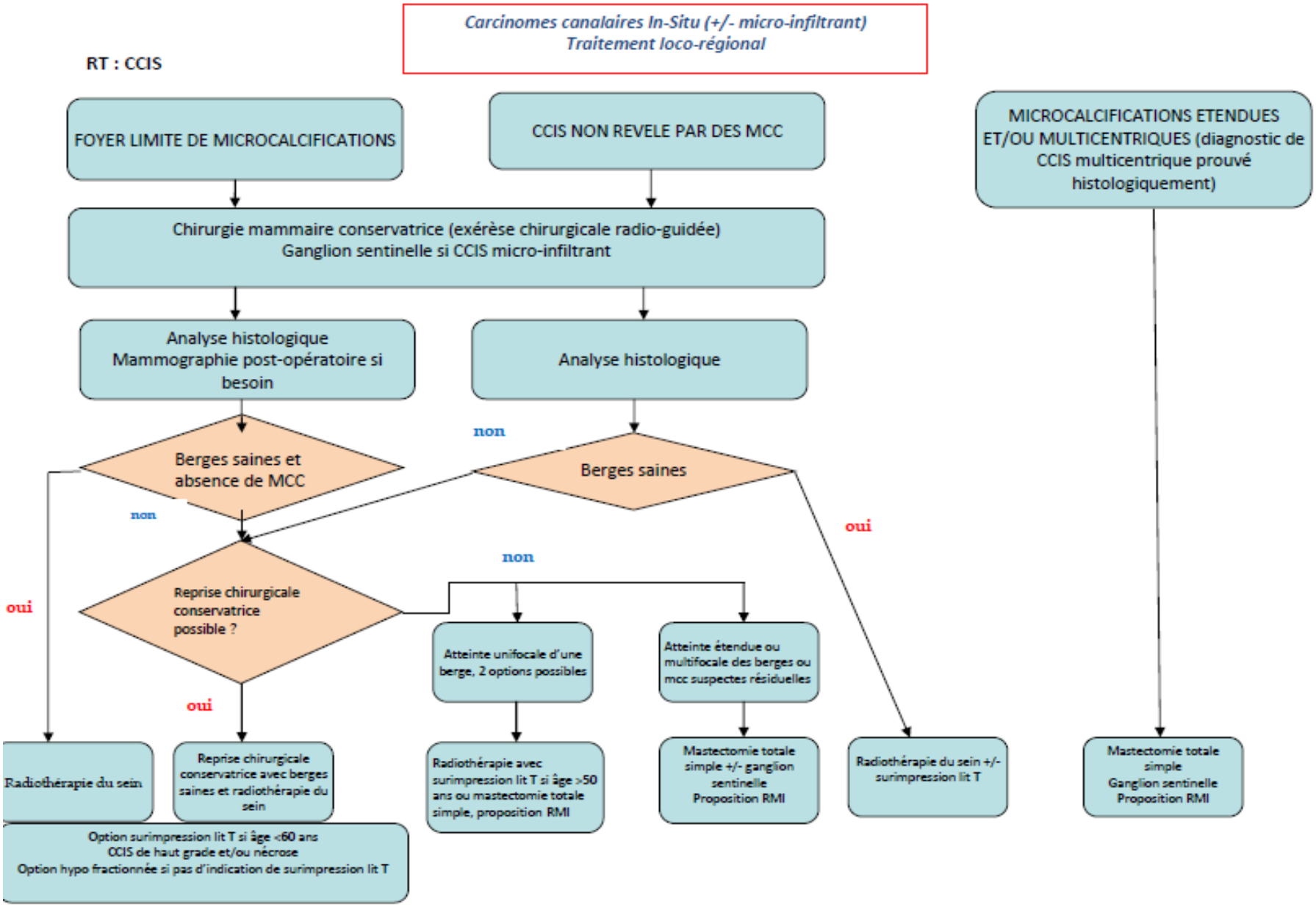
Conclusions 4

- Following breast-conserving surgery of DCIS, WBRT reduces the rate of breast recurrence by 50-60%
- The effect is proportional
- No subgroups were identified where radiotherapy could be omitted
- The DCIS-boost results in a small, statistically significant benefit in decreasing long-term IBTR of similar magnitude to boost for invasive cancers

DCIS. NCCN Guidelines

- Lumpectomy and WBRT
- or Total Mastectomy
- or Lumpectomy alone

Radiotherapy reduces local recurrence risk by 50%, but no differences in survival



Trials

1. Postmastectomy Radiotherapy
2. Mastectomy vs Breast-conserving treatment with RT
3. Whole-breast irradiation after breast-conserving surgery
    - Invasive cancer
    - DCIS
4. **Fractionation trials**
5. Toxicity

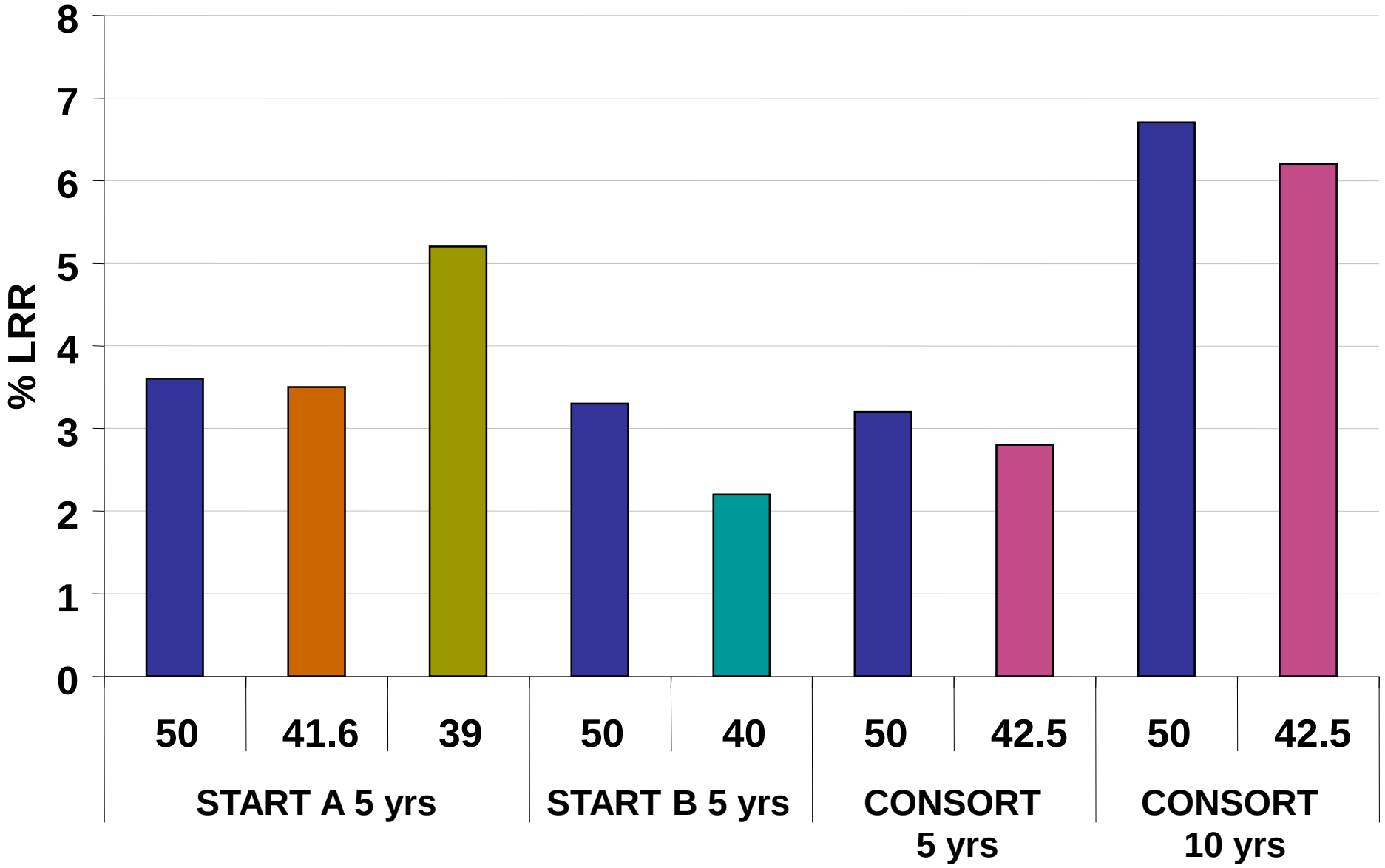
Hypofractionation trials

- Canada
- UK

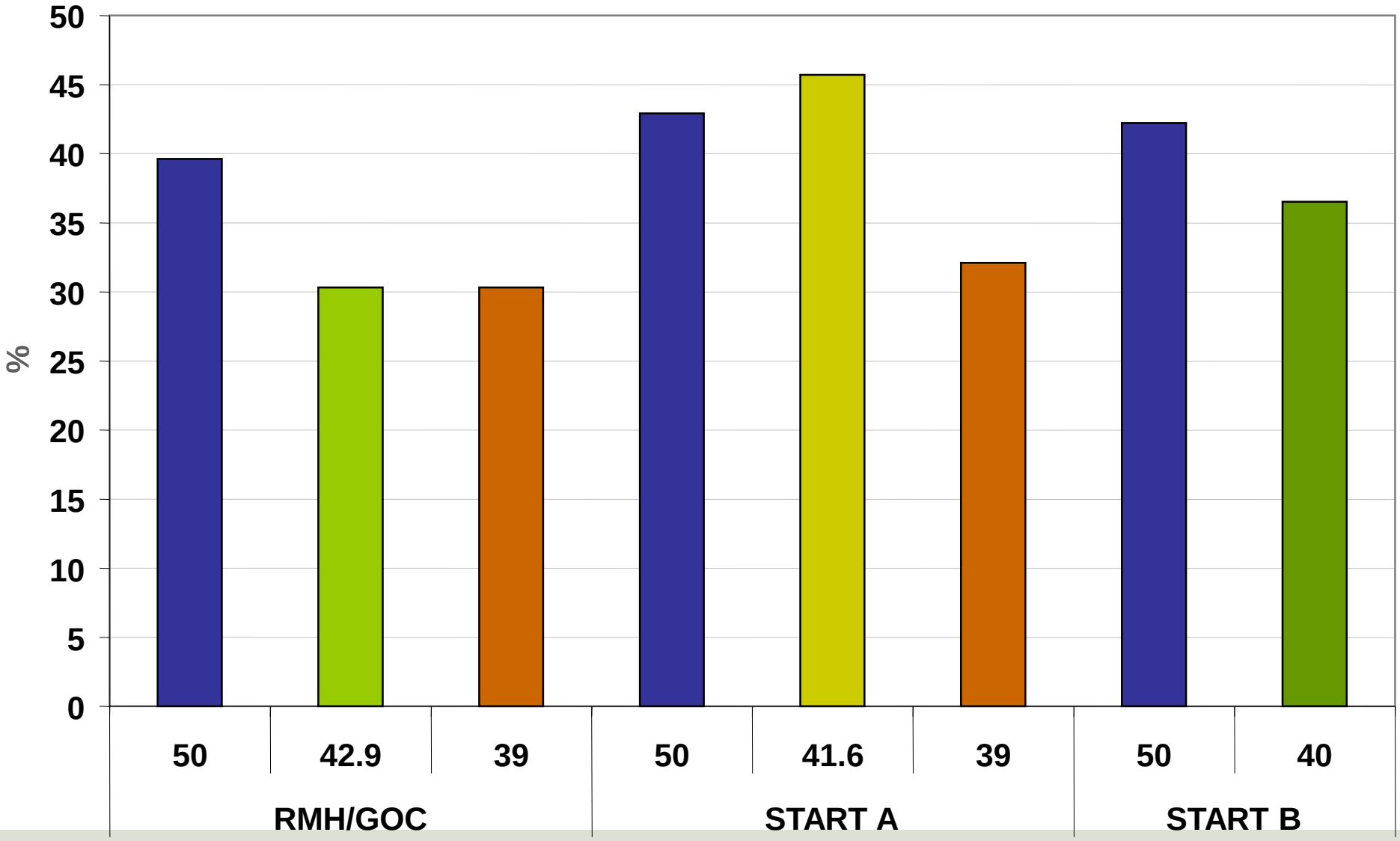
Irradiation schemes

Protocole	Dose (Gy)	No. fractions	Dose / fraction	No. weeks
Standard	50	25	2	5
RMH/GOC	42.9	13	3.3	5
START A	41.6	13	3.2	5
CONSORT	42.5	16	2.66	3
START B	40	15	2.67	3

Local recurrences



Toxicity


50
45
40
35
30
25
20
15
10
5
0
%
50
42.9
39
50
41.6
39
50
40
RMH/GOC
START A
START B

Local control: are HF schemes applicable in all patients?

1. Chest wall irradiation after mastectomy:
   - Subgroup of the START trials
   - Insufficient statistical power

2. Lymph nods irradiation
   - Idem

HF and Boost

- No boost delivered in the CONSORT trial

- Only some patients had a boost in the UK trials, *with a conventional 2 Gy per fraction regimen*

HF in high recurrence risk tumors?

- Young women
- High grade, high proliferation
- Basal-like or HER2+

NCCN

- The breast should receive a dose of 45-50 Gy at 1.8 – 2 Gy per fraction, or 42.5 Gy at 2.66 Gy per fraction.

NCI France

- Hypofractionation should be considered if all criteria are present:
  - Age > 50 years
  - pT1-2, pN0,
  - Grade I-II
  - HR +ve tumors
  - Free margins

NCI France

- HF is not recommended if either one is present
  - Adjuvant chemotherapy
  - Mastectomy
  - Lymph nodes irradiation
  - Grade III
  - Lymphovascular involvement

NCI France

- No recommendation for a boost
- Recommended fractionation regimen:
  - 42.5 Gy/16 fractions in 3 weeks
  - 41.6 Gy/13 fractions in 5 weeks
  - 40 Gy/15 fractions in 3 weeks
- Special care is advised to limit heart and lungs dose, and to ensure an homogeneous dose coverage of the breast

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Review, 2010

Pushing the limits of hypofractionation for adjuvant whole breast radiotherapy

John Yarnold [a,*], Joanne Haviland [b]

[a] Section of Radiotherapy, Institute of Cancer Research and Royal Marsden Hospital, Sutton, UK
[b] Clinical Trials and Statistics Unit, (ICR-CTSU), Institute of Cancer Research, Sutton, UK

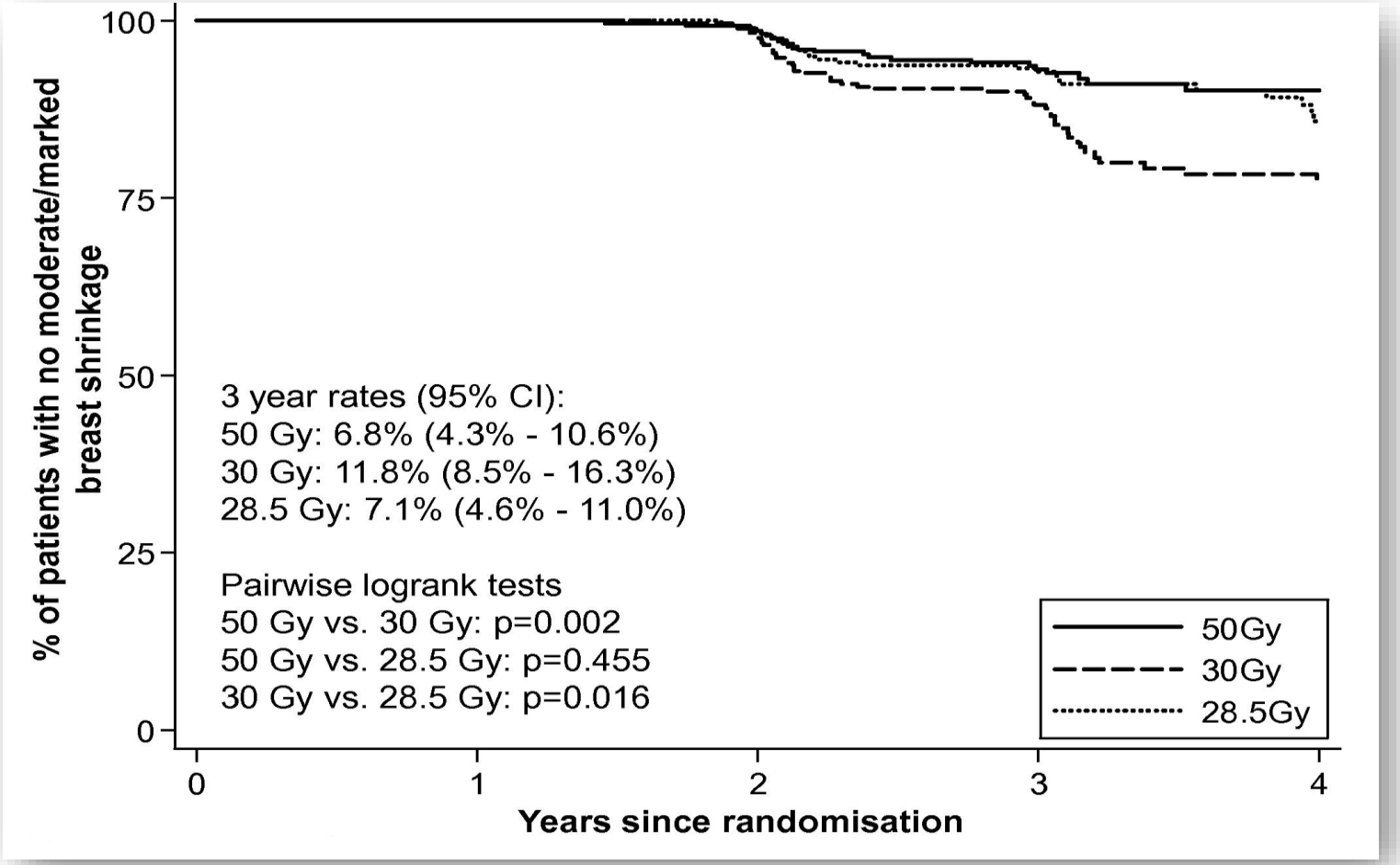
Table 2
Schema of the UK FAST trial testing two dose levels of a 5-fraction regimen delivered as one fraction per week versus 50 Gy in 25 fractions over 5 weeks to the whole breast after local tumour excision of early breast cancer.

Group	Total dose (Gy)	Fraction size (Gy)	Number of fractions	Fractions per week
Control	50.0	2.0	25	5
Test 1[a]	30.0	6.0	5	1
Test 2[b]	28.5	5.7	5	1

[a] Iso-effective with Control if $\alpha/\beta = 4.0$ Gy.
[b] Iso-effective with Control if $\alpha/\beta = 3.0$ Gy.

UK FAST Trial

Physician-assessed moderate/marked breast shrinkage



Fast Trialists Group (2011) Radiother Oncol 100: 93-100

More extreme whole breast hypofractionation?

Centre Antoine-Lacassagne — Courdi
A *et al* (2006) Radiother Oncol 79:156-161

- 115 patients median age 83
- 32.5Gy in 5 x 6.5Gy once-weekly with 6.5Gy boost
- Good local control, grade 3 fibrosis in 6% (95%CI 1.7-9.5)

Institut Curie Breast Cancer Study Group — Kirova Y
et al (2009) Int J Radiat Oncol Biol Phys 75:76-81

- 50 patients ≥ 70 years old
- 32.5Gy in 5 x 6.5Gy once-weekly, no boost
- Compared to 317 patients treated 50Gy in 25#
- Equivalent control, no toxicity data

UK FAST Trial — Fast
Trialists Group (2011) Radiother Oncol 100:93-100

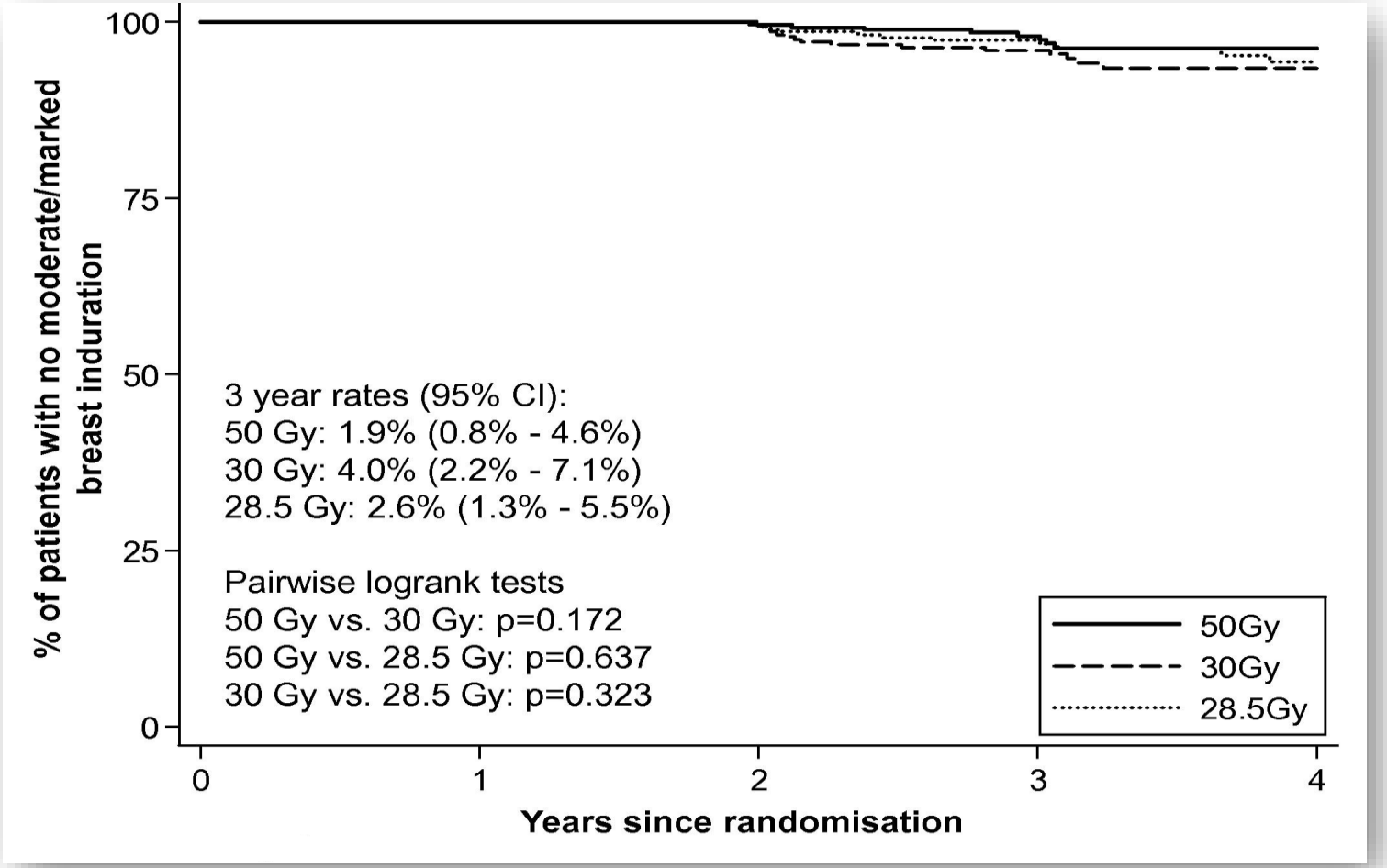
- Multicentre randomised trial 2004-2007, 915 patients
- 50Gy 25 # vs. 28.5Gy 5 x 5.7Gy once weekly vs. 30Gy x 6Gy once weekly
- First report at median follow-up 3 years

Courtesy Chris Cottrill

institutCurie

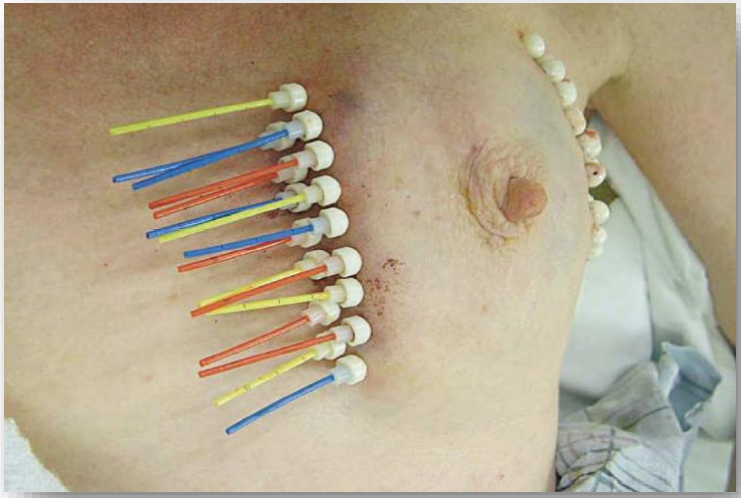
UK FAST Trial

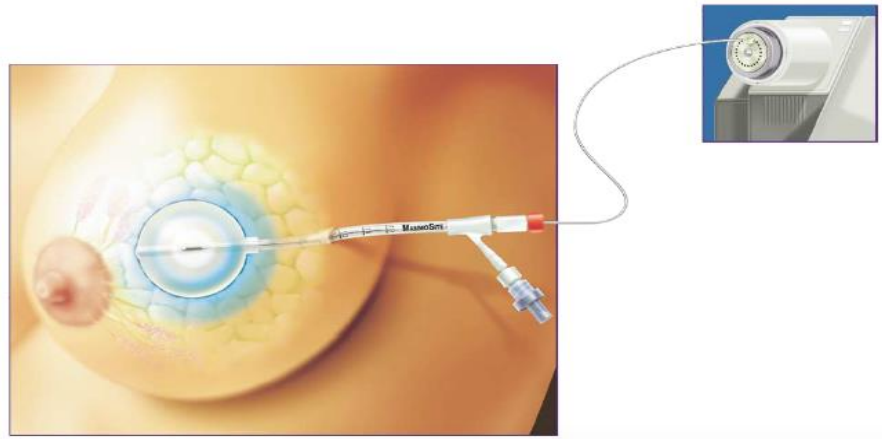
Physician-assessed moderate/marked breast induration

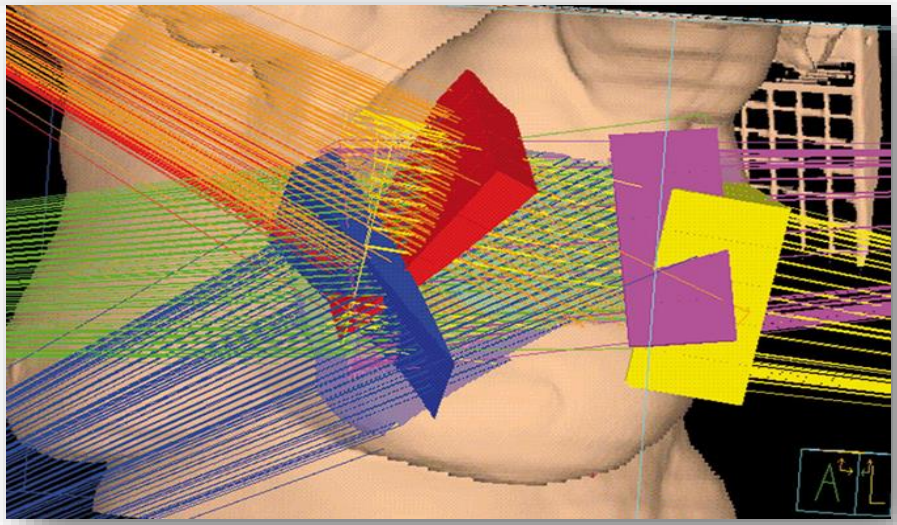


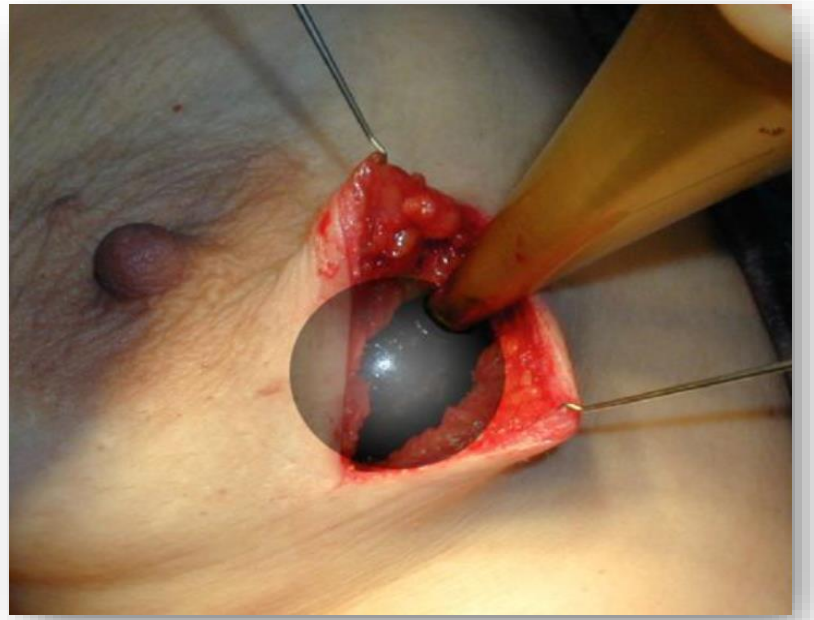
Fast Trialists Group (2011) Radiother Oncol 100: 93-100

Partial breast irradiation-techniques and studies









For selected population of patients

ESTRO
European Society for Therapeutic Radiology and Oncology

institutCurie
Ensemble, prenons le cancer de vitesse.

GEC-ESTRO multicatheter brachytherapy APBI trial

Multicentre randomised non-inferiority trial

Age ≥ 40 with DCIS (VNPI < 8) or invasive ≤ 3 cm (pT2a)

Margin ≥ 2mm (ductal Ca) or ≥ 5mm (DCIS or lobular Ca)

pN0 or pNmi with no lymphatic or vascular invasion

Wide local excision and axillary dissection or SNB

Strnad V *et al* (2016) Lancet 387:229-238

Courtesy Chris Cottrill

GEC-ESTRO APBI trial: Treatment protocols

Control arm: Whole breast RT 50Gy +10 Gy boost

APBI CTV = tumour bed and 20 mm beyond DCIS or Ca

Pre-implant and post-implant CT mandatory

100% of dose to ≥ 90% of target and skin dose < 70%

HDR: 8 x 4Gy (BID) or 7 x 4.3Gy (BID)

Pulsed-dose-rate 50Gy / 0.6-0.8Gy x 1 per hour / 24h/day

Strnad V *et al* (2016) Lancet 387:229-238

Courtesy Chris Cottrill

GEC-ESTRO APBI trial: Patient characteristics

1328 randomised from 2004 to 2009

Median age 62; Median follow-up 6.6 years

95% invasive carcinoma; 86% pT1

APBI n = 633: 119 PDR 451 HDR 8# 59 HDR 7#

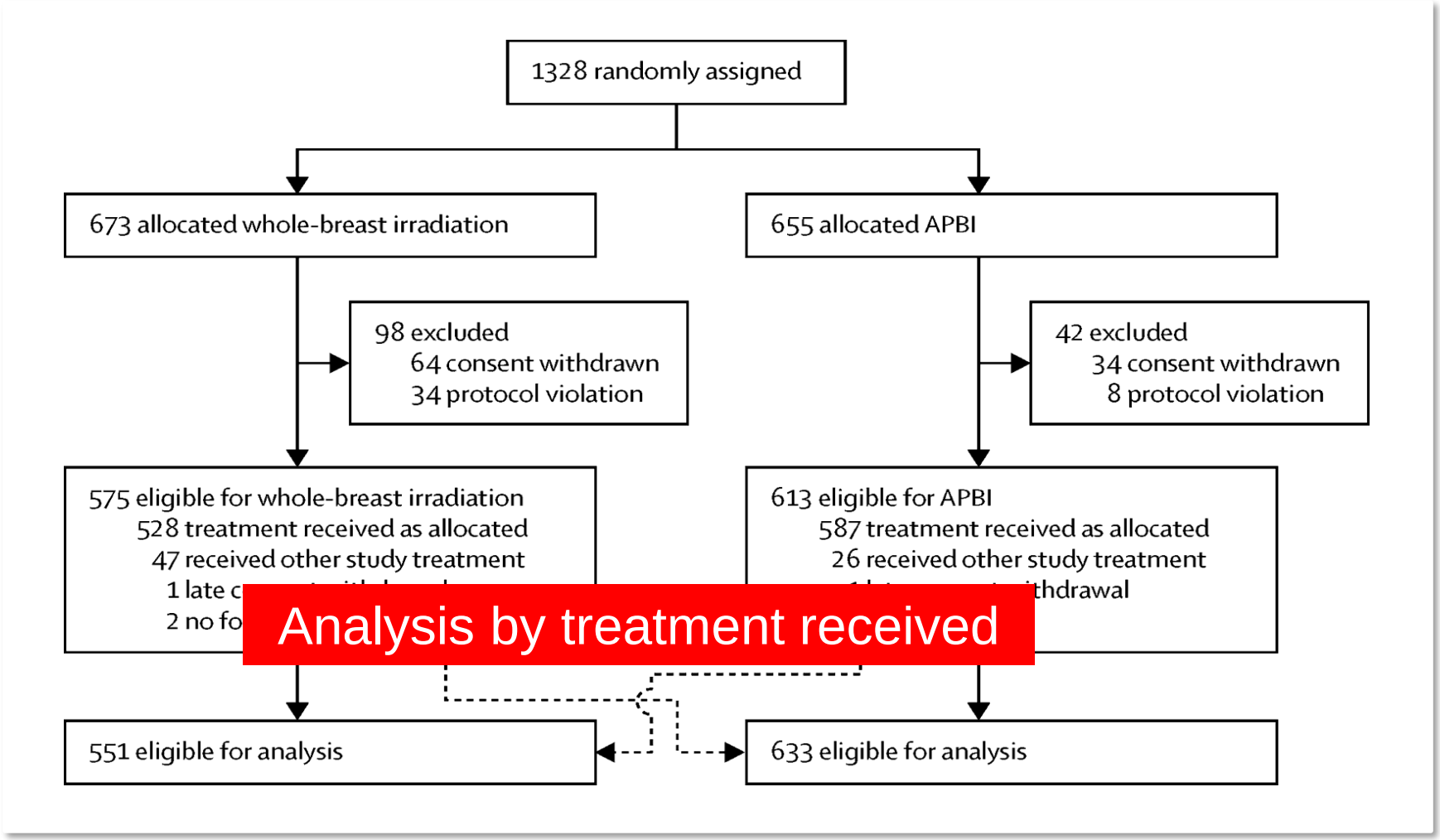
90% G1-G2 75% ductal NST 92% ER+

87% adjuvant endocrine therapy 11% chemotherapy

Strnad V *et al* (2016) Lancet 387:229-238

Courtesy Chris Cottrill

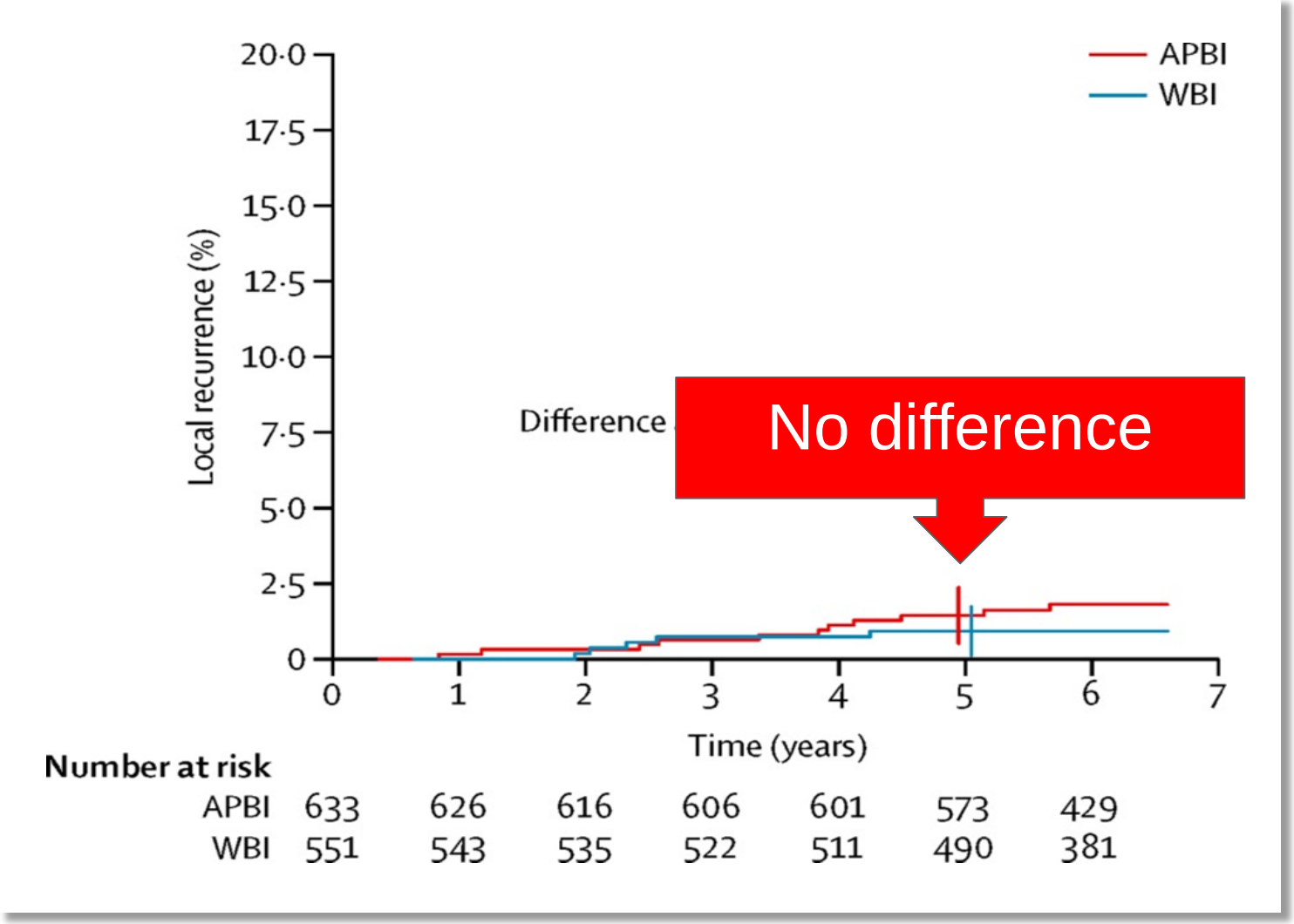
GEC-ESTRO multicatheter brachytherapy APBI trial



Strnad V *et al* (2016) Lancet 387:229-238

Courtesy Chris Cottrill

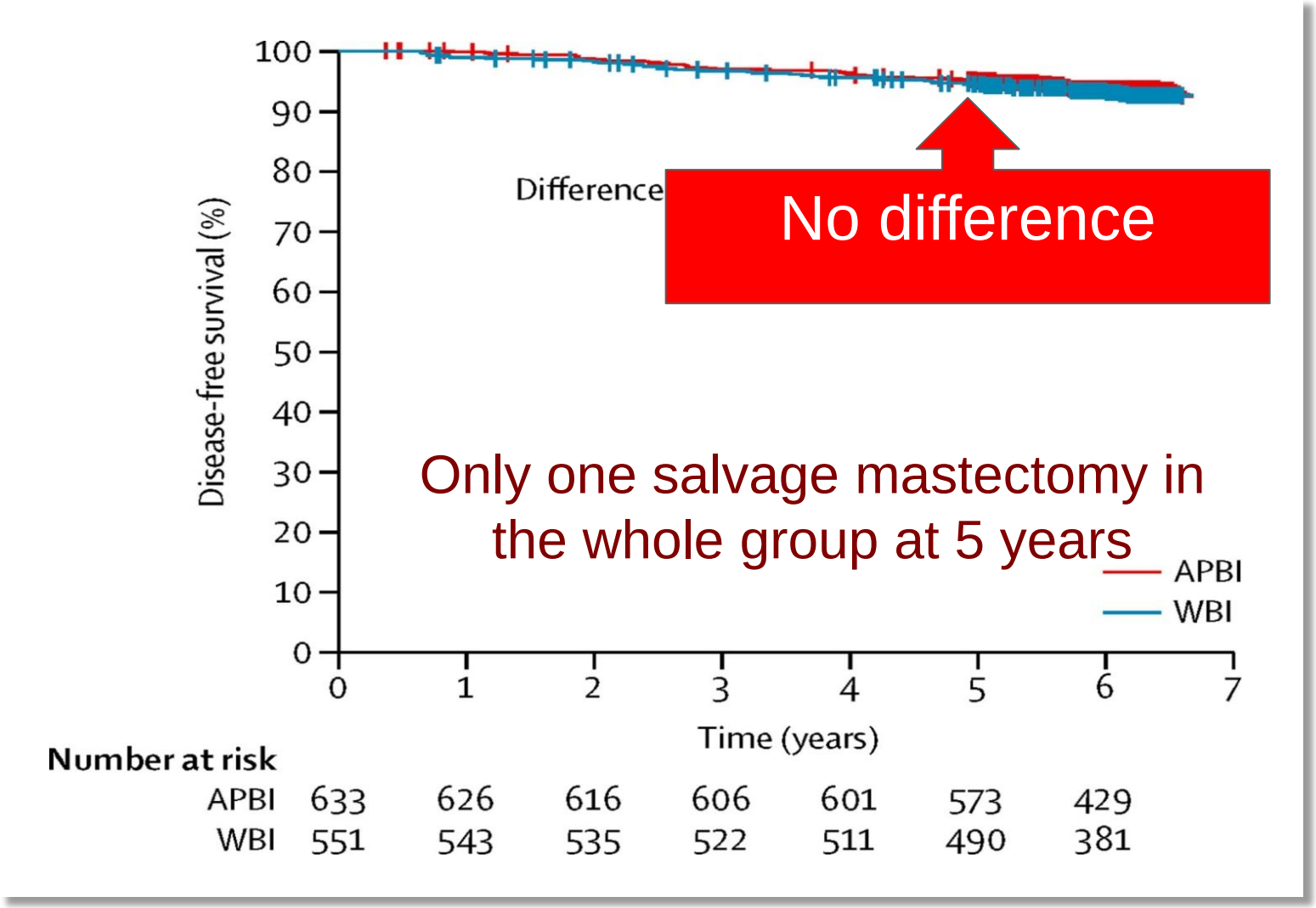
GEC-ESTRO: Ipsilateral breast tumour recurrence



Strnad V *et al* (2016) Lancet 387:229-238

Courtesy Chris Cottrill

GEC-ESTRO: Disease-free survival



Strnad V *et al* (2016) Lancet 387:229-238

Courtesy Chris Cottrill

GEC-ESTRO APBI: Toxicity at 5 years

	APBI	WBI
Grade 2-3 late skin	3.23%	5.66% (ns)
Grade 2-3 subcutaneous fibrosis	7.59%	6.33% (ns)
Grade 2-3 breast pain	1.14%	3.17% (p = 0.04)
No grade 4 side effects at 5 years		
Detailed analysis of late side-effects to be published seperately		

Strnad V *et al* (2016) Lancet 387:229-238

Courtesy Chris Cottrill

Trials

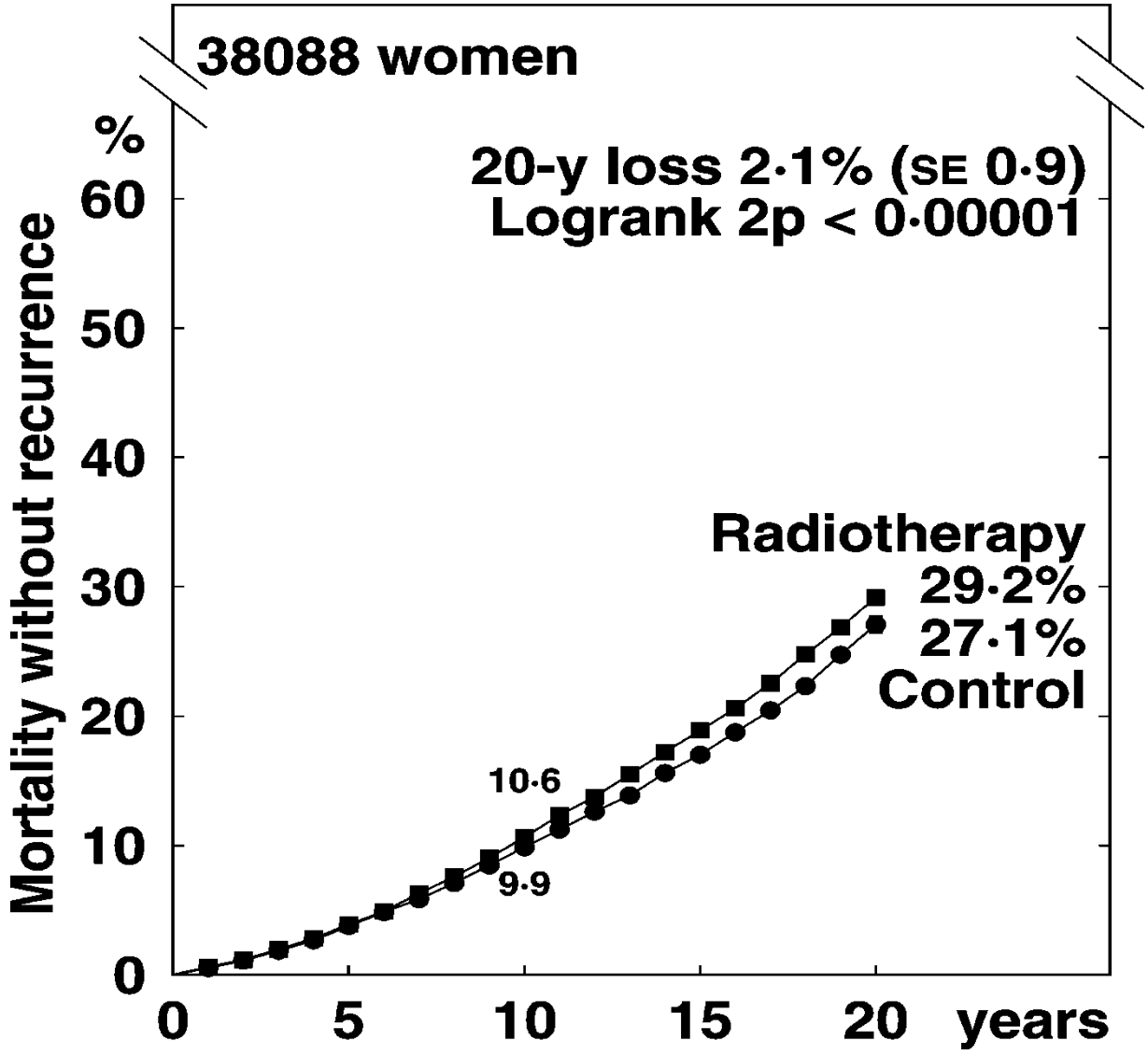
1. Postmastectomy Radiotherapy
2. Mastectomy vs Breast-conserving treatment with RT
3. Whole-breast irradiation after breast-conserving surgery
    - Invasive cancer
    - DCIS
4. Fractionation trials
5. Toxicity

EBCTCG. Second cancers 29 587 womenRT vs no RT

	Total events	Excess events	Ratio of rates (se)[a]	2p
Contralateral breast cancer[b]	1316	122.4	1.22 (0.06)	0.0005
Cancer of other site[c]	1534	139.2	1.22 (0.06)	0.0002
Lung cancer	255	57.0	1.60 (0.16)	0.0002
Oesophagus cancer	32	10.0	1.89 (0.50)	0.08
Leukaemia	59	15.0	1.71 (0.36)	0.04
Soft-tissue sarcoma	26	10.8	2.34 (0.62)	0.03
Other specified sites	1020	31.6	1.07 (0.07)	NS

[a] Ratio of annual event rates irradiated vs unirradiated
[b] Contralateral breast cancer as the first or only site of recurrence.
[c] Other than breast or non-melanoma skin cancer.

Mortality rates without breast recurrence

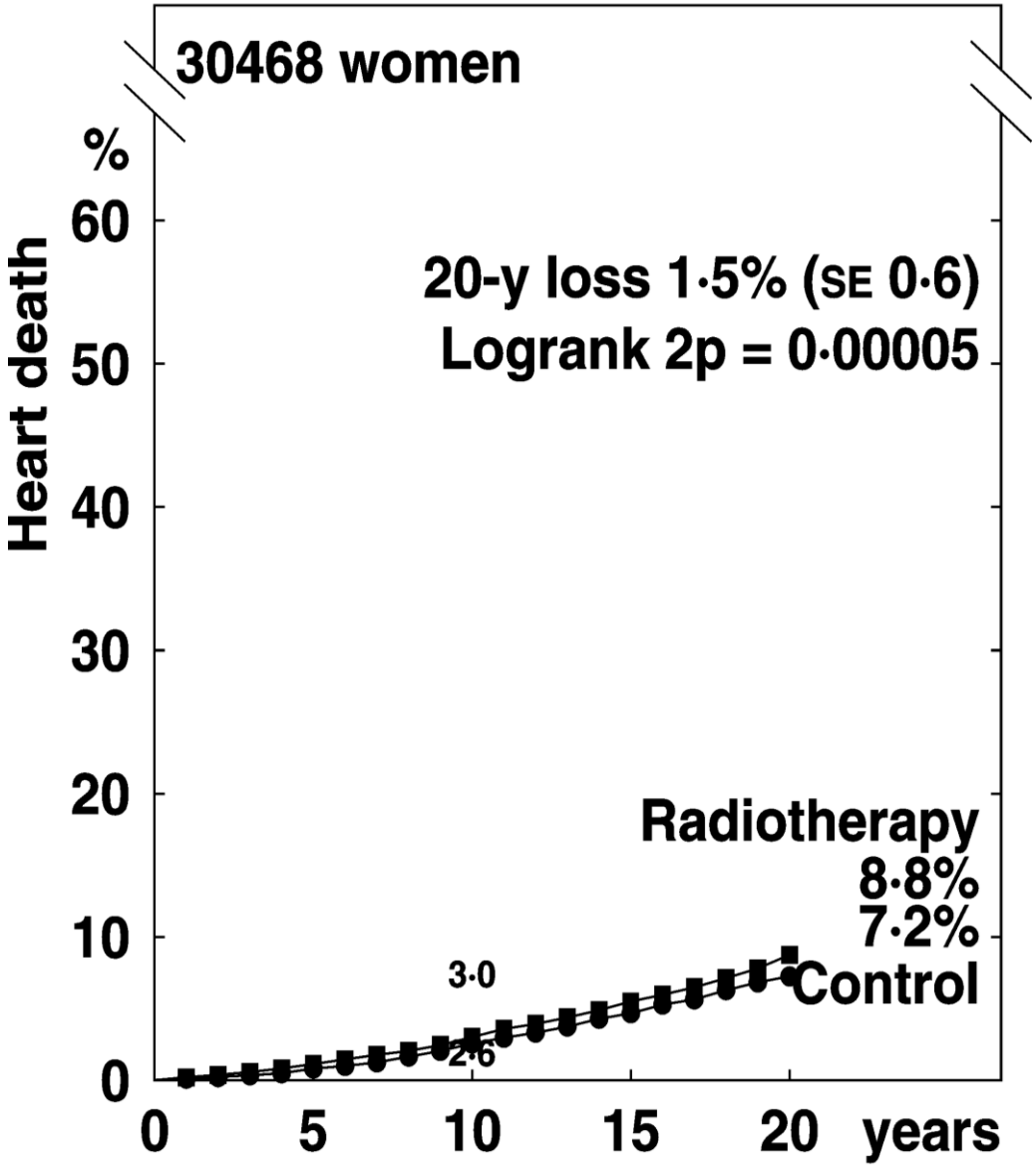


EBCTCG *Lancet*, 2005 and *2006 update*

EBCTCG. Non-breast cancer mortality
25 500 women in 52 RT trials

	Total Events	Excess with RT	Ratio of rates RT/not	2p
Circulatory disease	**1617**	**150**	**1.23 (0.06)**	**0.00009**
Heart disease	1207	128	1.26 (0.07)	0.0001
Stroke	352	4	1.05 (0.11)	0.6
Pulmonary embolism	58	14	1.68 (0.36)	0.06
Other specified cause	**1647**	**50**	**1.07 (0.05)**	**0.2**
Unknown cause	**2444**	**122**	**1.11 (0.04)**	**0.01**
Total non-breast-cancer deaths	**5708**	**322**	**1.13 (0.03)**	**<0.00001**

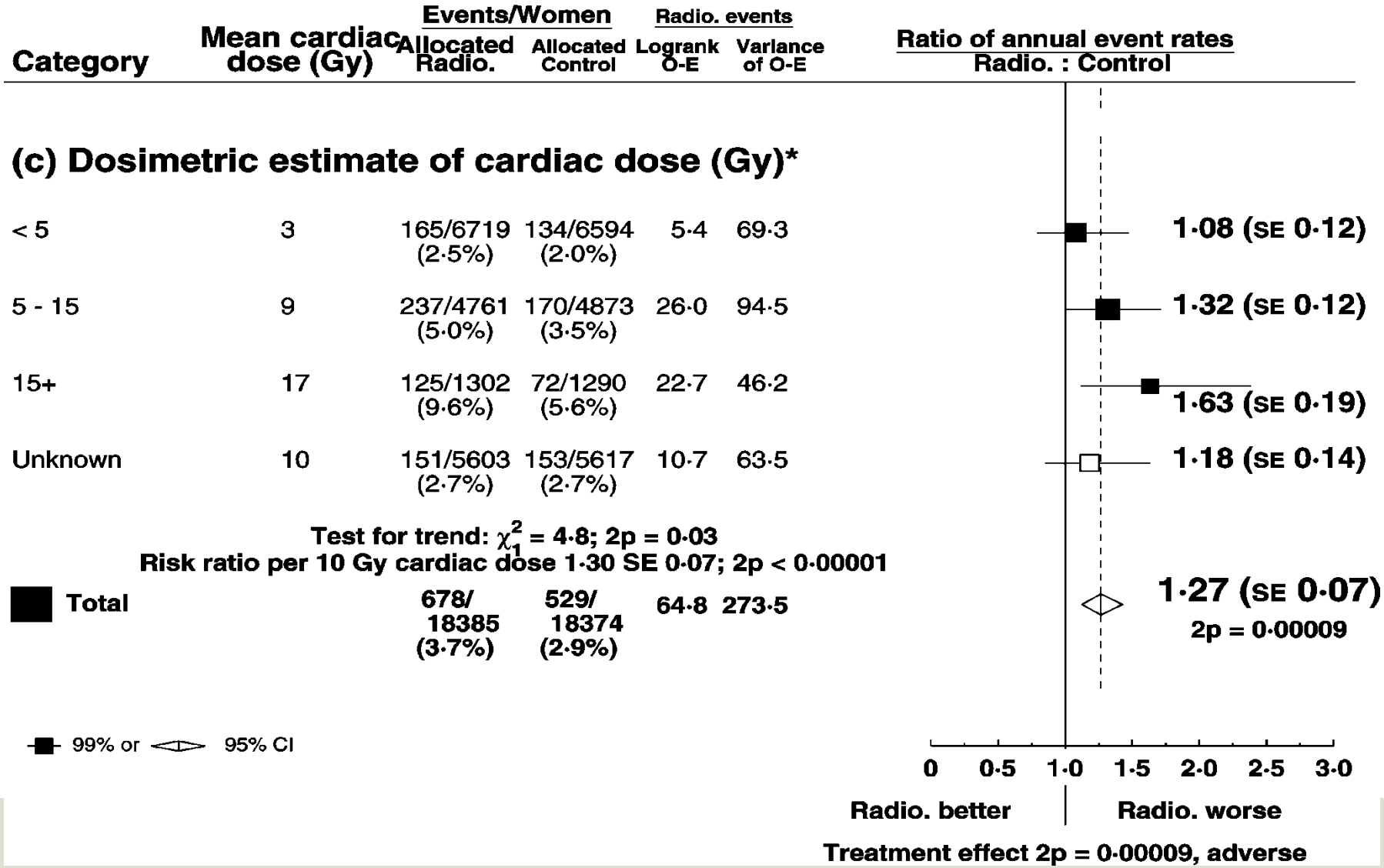
Heart disease mortality



Heart disease death rates (% / year) and logrank analyses

	Years 0 - 9	Years 10 - 19	Year 20+
Radiotherapy	0·28 (280 / 100847)	0·58 (248 / 42890)	0·93 (141 / 15205)
Control	0·23 (204 / 89408)	0·47 (175 / 37137)	0·67 (98 / 14555)
Rate ratio, from	1·24 SE 0·10	1·20 SE 0·11	1·55 SE 0·17
(O-E) / V	25·2 / 118·4	18·5 / 99·6	23·1 / 53·0

Retrospective evaluation of mortality in relation to cardiac dose

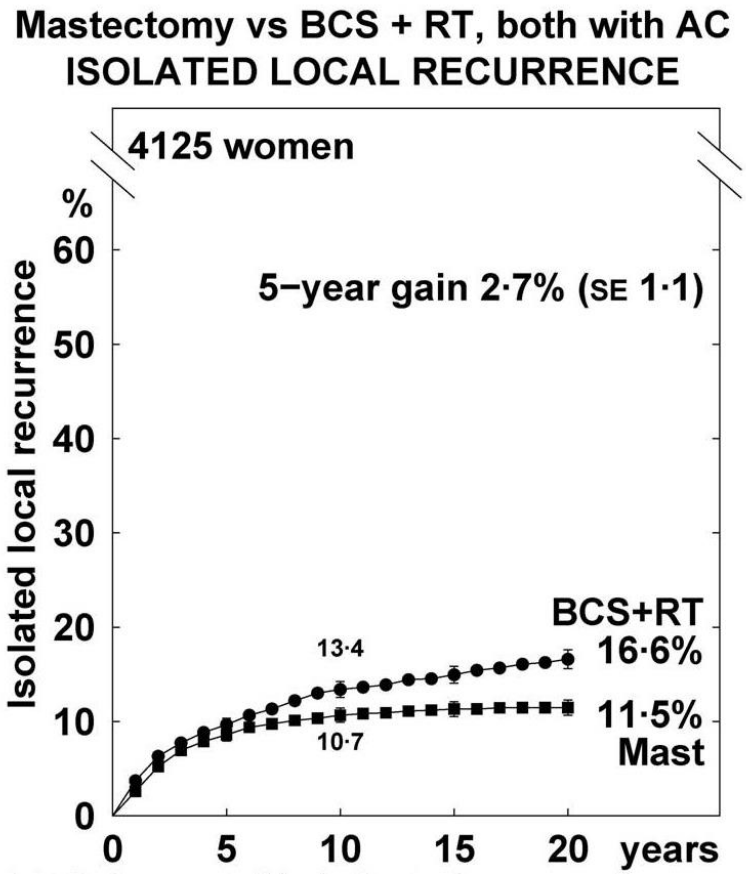


Conclusions

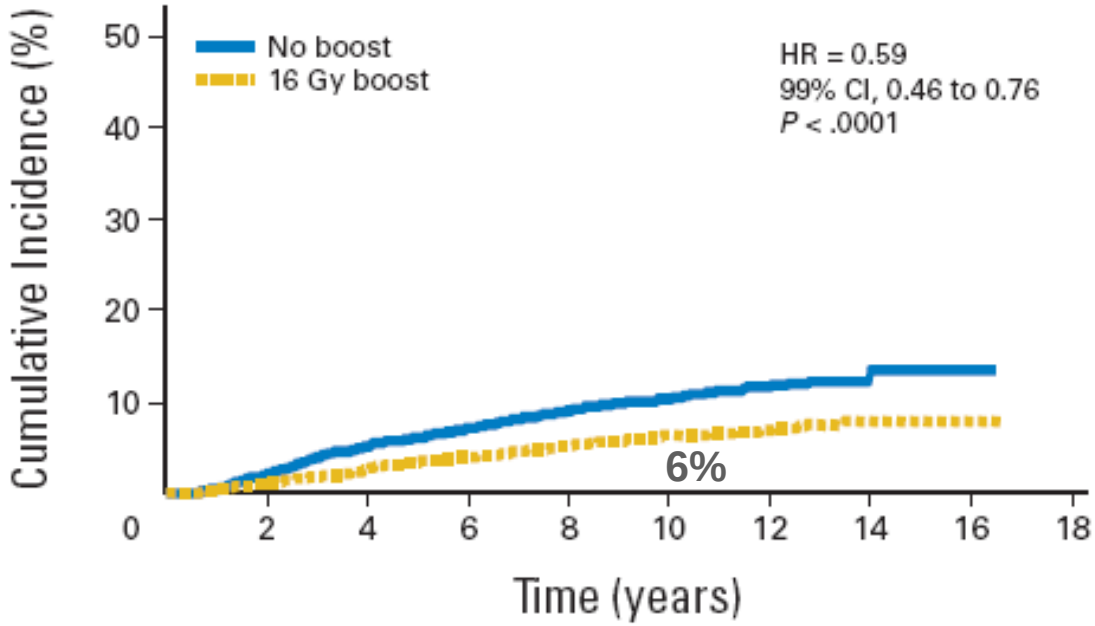
- Clinical trials of radiotherapy over the past 40 years have significantly impacted the clinical practice by
  - Allowing a large number of women to preserve their breast
  - Demonstrating the relationship between local control and survival
  - Stimulating the improvement in RT delivery, thus reducing its potential toxicity
- They have contributed to continuously decrease the rate of recurrence of breast cancer

Locoregional rates following BCT were reduced by 50% over a decade...

EBCTCG. 1972-1986



EORTC. 1989-1996
BCS + RT
5318 women



Thank you for your attention

Questions and discussion of a case

For forgotten questions: youlia.kirova@curie.fr

EORTC - 10041

The future of cancer therapy

BIG - 3-04

Breast International Group

And also about systemic treatment

MINDACT

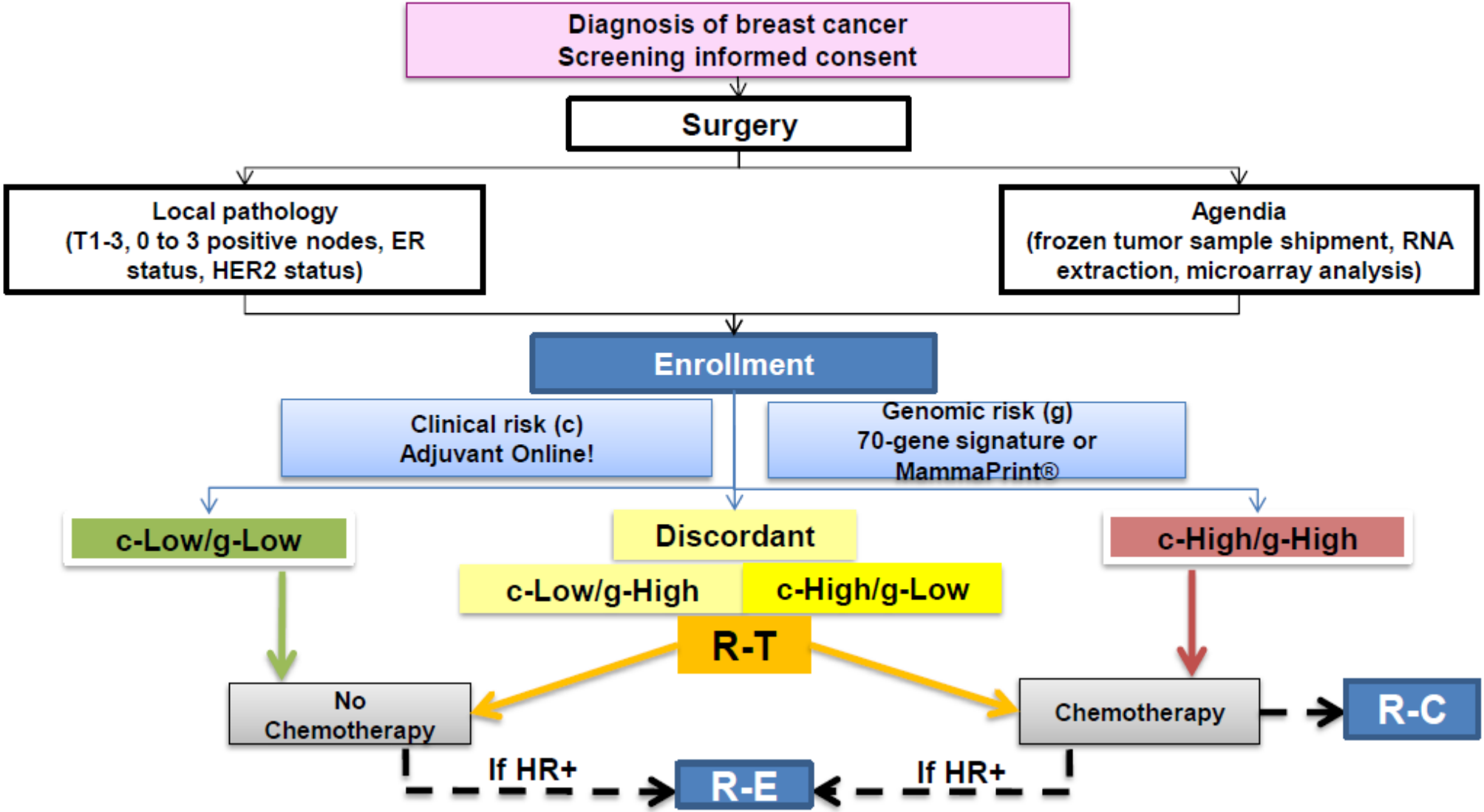
« Microarray for node negative disease may avoid chemotherapy »

Primary analysis of the EORTC 10041/ BIG 3-04 MINDACT study: A prospective, randomized study evaluating the clinical utility of the 70-gene signature (MammaPrint®) combined with common clinical-pathological criteria for selection of patients for adjuvant chemotherapy in breast cancer with 0 to 3 positive nodes

Martine Piccart, Emiel Rutgers, Laura van' t Veer, Leen Slaets, Suzette Delaloge, Giuseppe Viale, Jean Yves Pierga, Peter Vuylsteke, Etienne Brain, Suzan Vrijaldenhoven, Peter Neijenhuis, Bruno Coudert, Tineke Smilde, Miguel Gil, Alastair Thompson, Isabel T. Rubio, Rodolfo Passalaqua, Erika Matos, Urlike Nitz, Mauro Delorenzi, Geraldine Thomas, Theodora Goulioti, Carolyn Straehle, Konstantinos Tryfonidis, Jan Bogaerts & Fatima Cardoso

On behalf of the European Commission supported TRANSBIG consortium and MINDACT investigators

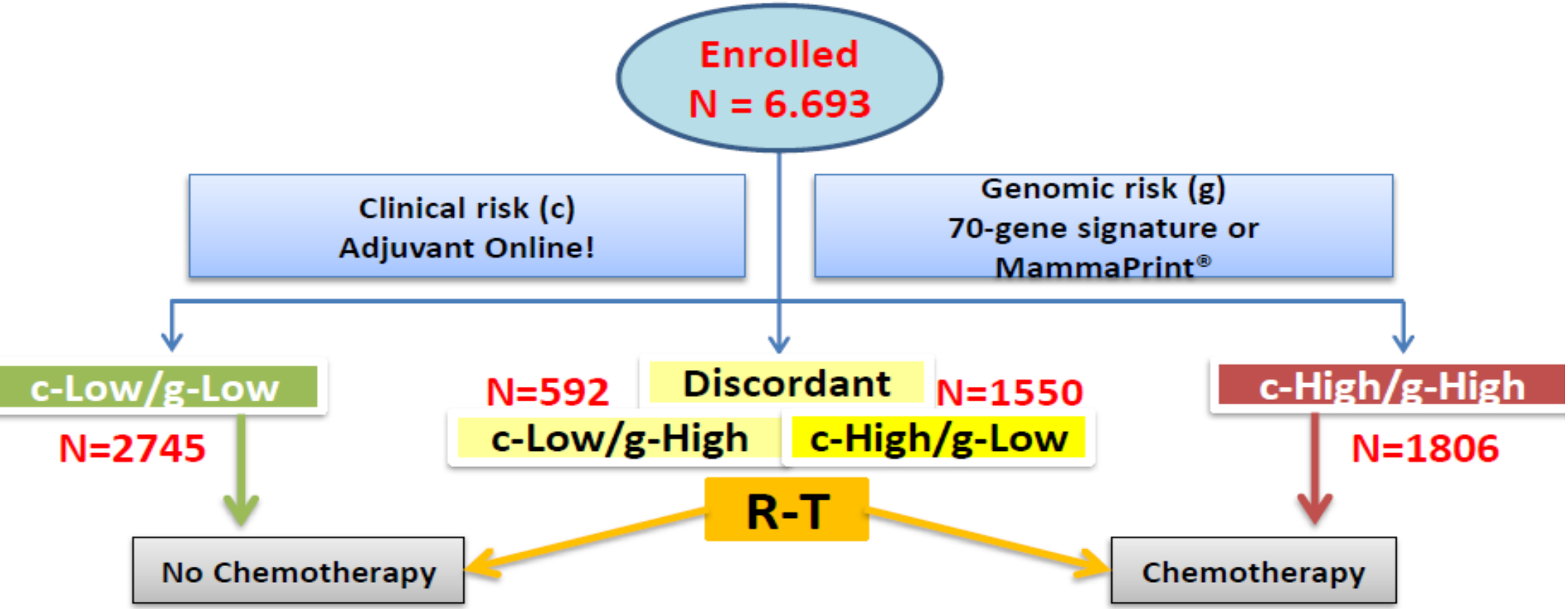
The MINDACT study design



Presented by M. Picart, AACR 2016

2007-2011

The MINDACT study: Patient enrollment



Presented by M. Picart, AACR 2016

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Ensemble, prenons le cancer de vitesse.

2007-2011
MINDACT

Primary test

Primary endpoint: Distant metastasis free survival (DMFS) at 5 years

Null hypothesis: 5-year DMFS rate in PT population = 92%

Alpha: 2.5% (1-sided)

Power: 80% when true 5-year DMFS rate=95%

Primary test:

95% 2-sided Confidence interval (CI) for the 5-year DMFS rate will be compared to 92%

Presented by M. Picart, AACR 2016

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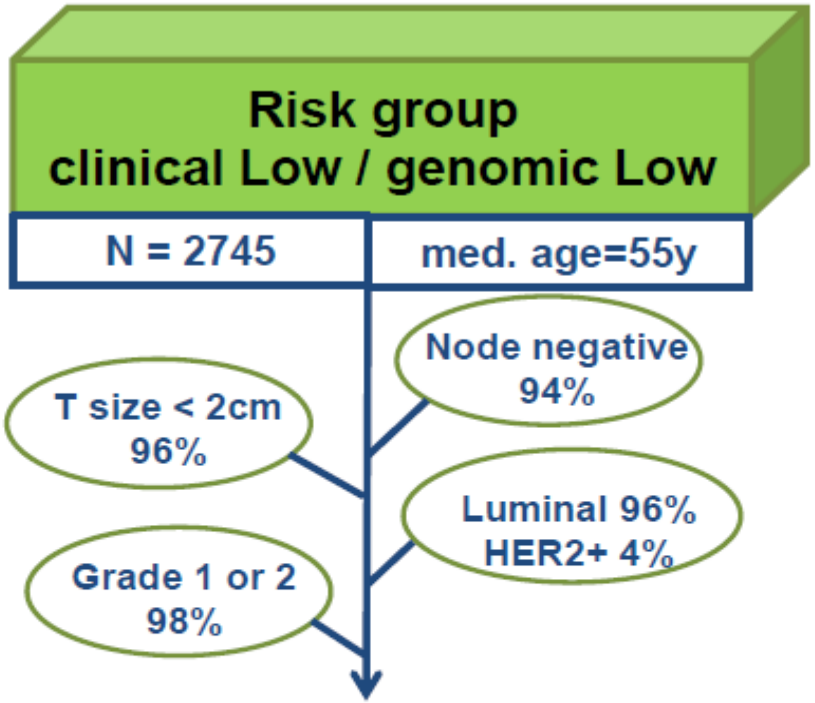
Ensemble, prenons le cancer de vitesse.

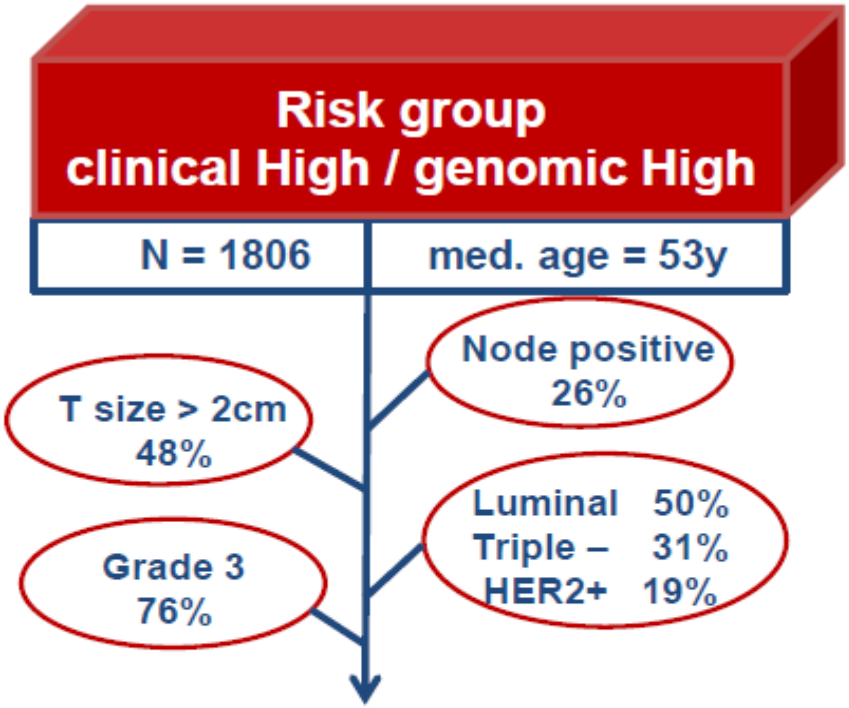
MINDACT



Assigned:
NO CHEMOTHERAPY

Compliance = 99%

(Received Endocrine therapy: 79%)



Assigned:
CHEMOTHERAPY

Compliance = 96%

(Received Endocrine therapy: 59%
Received trastuzumab: 15%)

Presented by M. Picart, AACR 2016

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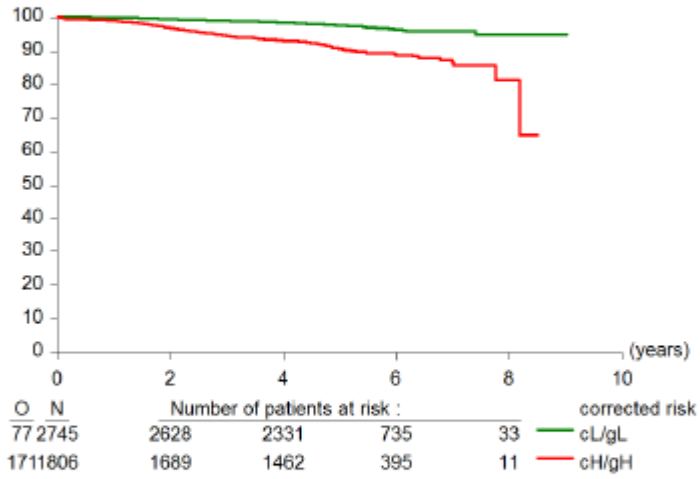
Ensemble, prenons le cancer de vitesse.

MINDACT

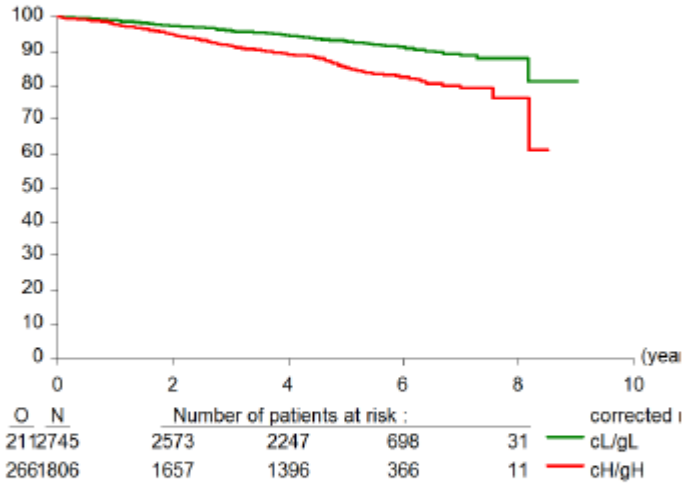
at 5y median follow-up

A) CONCORDANT RISK GROUPS (using corrected risk)

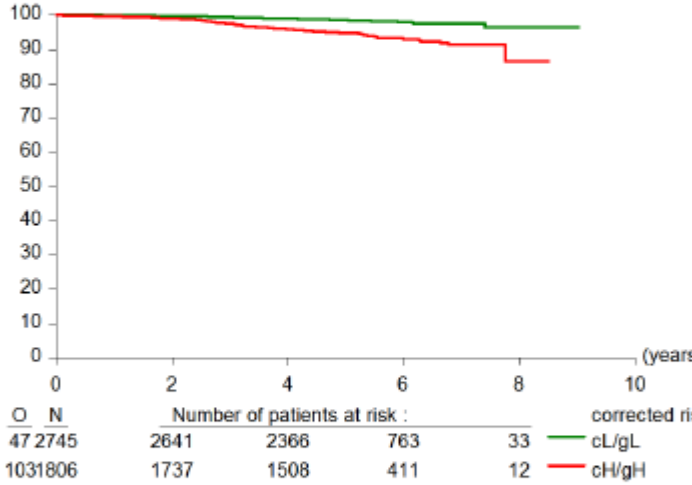
DMFS



DFS



OS



	% at 5y (95% CI)	% at 5y	% at 5y
cL/gL	**97.6** (96.9 – 98.1)	**92.8** (91.7 – 93.7)	**98.4** (97.8 – 98.9)
cH/gH	**90.6** (89.0 – 92.0)	**85.3** (83.4 – 87.0)	**94.7** (93.4 – 95.7)

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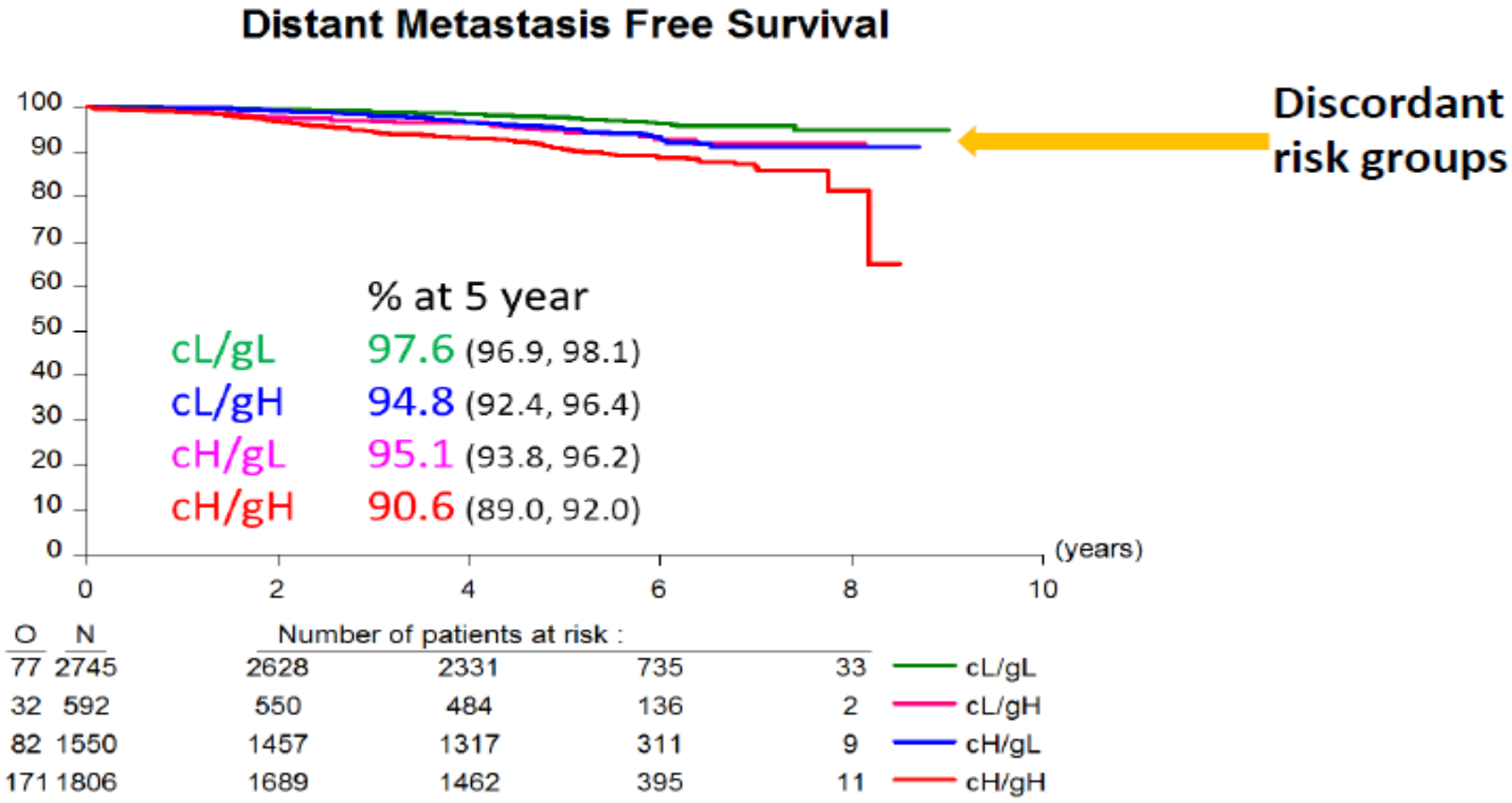
MINDACT

at 5y median follow-up
DMFS IN ALL 4 RISK GROUPS



Presented by M. Picart, AACR 2016

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MINDACT-CONCLUSIONS

- Mindact results provide level 1A evidence of the clinical utility of MammaPrint® for assessing the lack of a clinically relevant chemotherapy benefit in the clinically high risk (c-High) population.
- c-High/g-Low patients, including 48% Node positive, had a 5-year DMFS rate in excess of 94%, whether randomized to adjuvant CT or no CT.
- In the entire MINDACT population, the trial confirmed the hypothesis that the « genomic » strategy leads to a 14% reduction in CT prescription versus the « clinical » strategy.
- Among the c-High risk patients, the clinical use of MammaPrint® is associated with a 46% reduction in chemotherapy prescription.

Presented by M. Picart, AACR 2016

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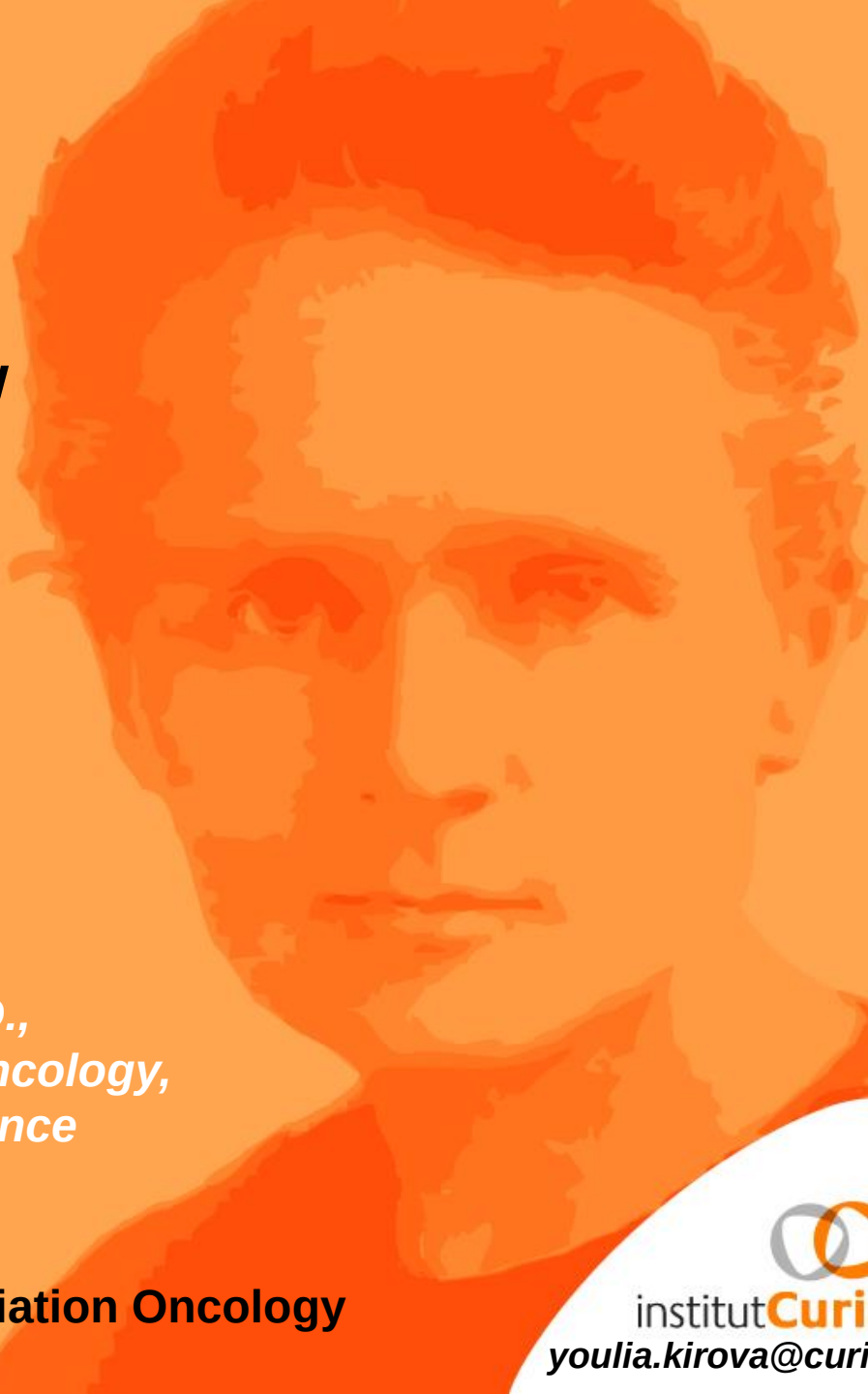
2017
ESTRO SCHOOL
LIVE COURSE

Multidisciplinary Management of Breast Cancer

10-13 September 2017
Dublin, Ireland

Target Volume delineation: chest wall, breast, boost, PBI, lymph nodes and OAR or how to increase the efficacy and decrease the toxicity: practical challenges in radiation oncology



Youlia M. Kirova, M.D.,
Department of Radiation Oncology,
Institit Curie, Paris, France

ESTRO School

Evidence Based Radiation Oncology

institutCurie

youlia.kirova@curie.fr

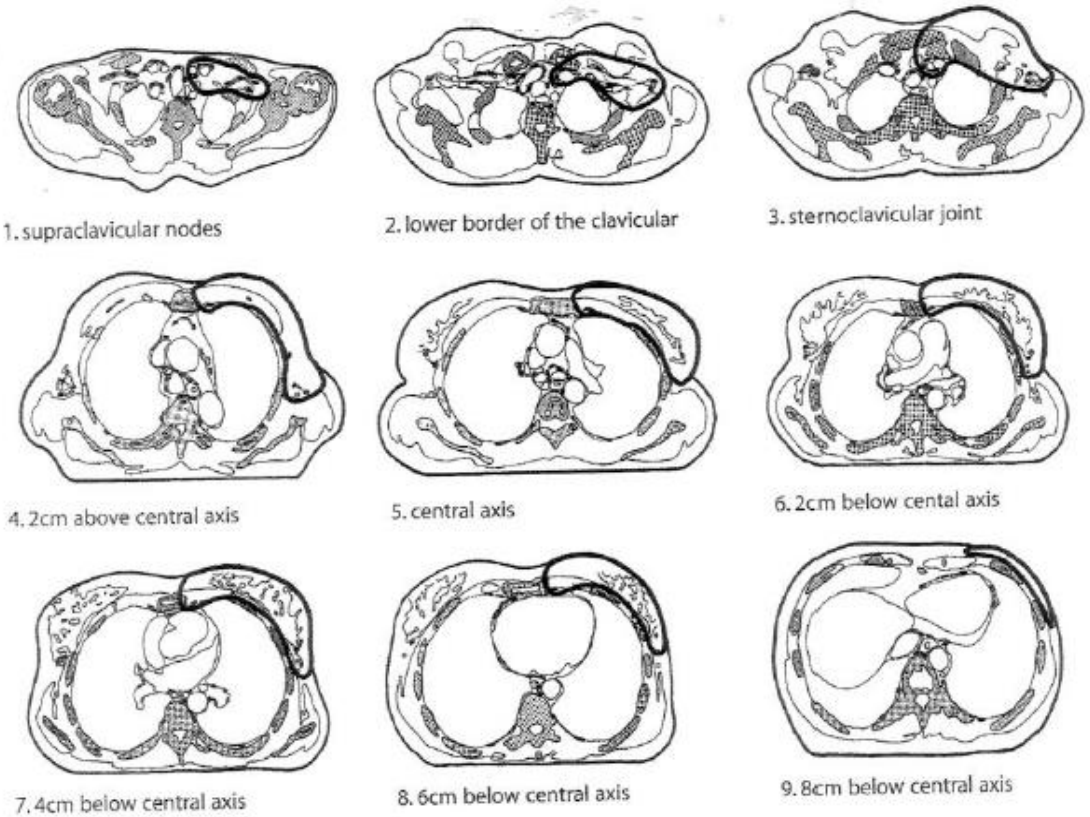
Delineation or why we need guidelines?

Literature: different sources

Target Volume Selection and Delineation in Breast Cancer Conformal Radiotherapy

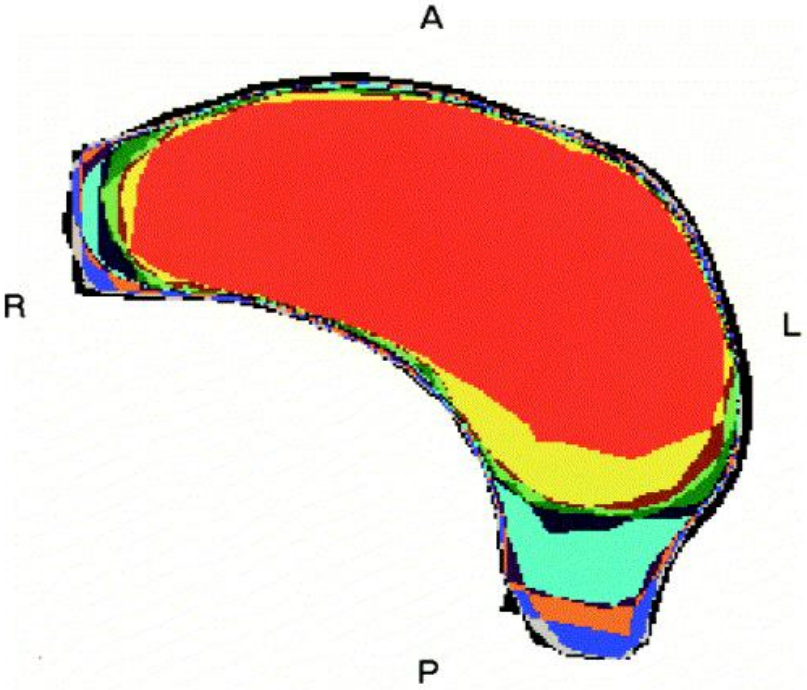
I. C. Kiricuta

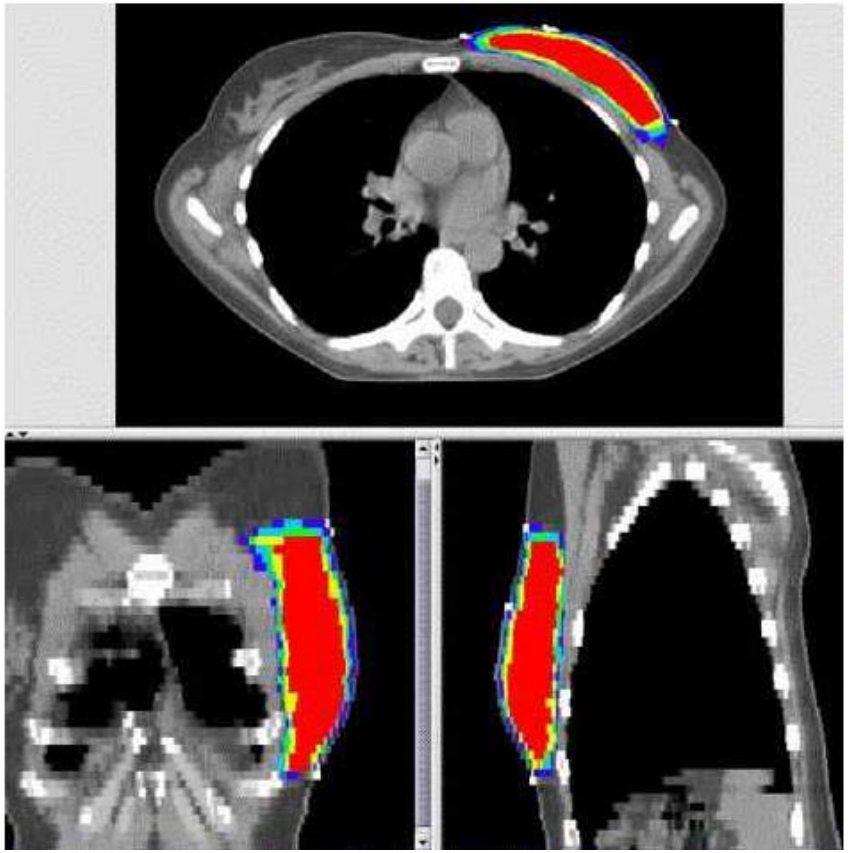
b



But: Large interobserver variation, especially at cranial, posterior and medial borders- CT scan

Struikmans et al, R&O 2005





Hurkmans et al, IJROBP 2001

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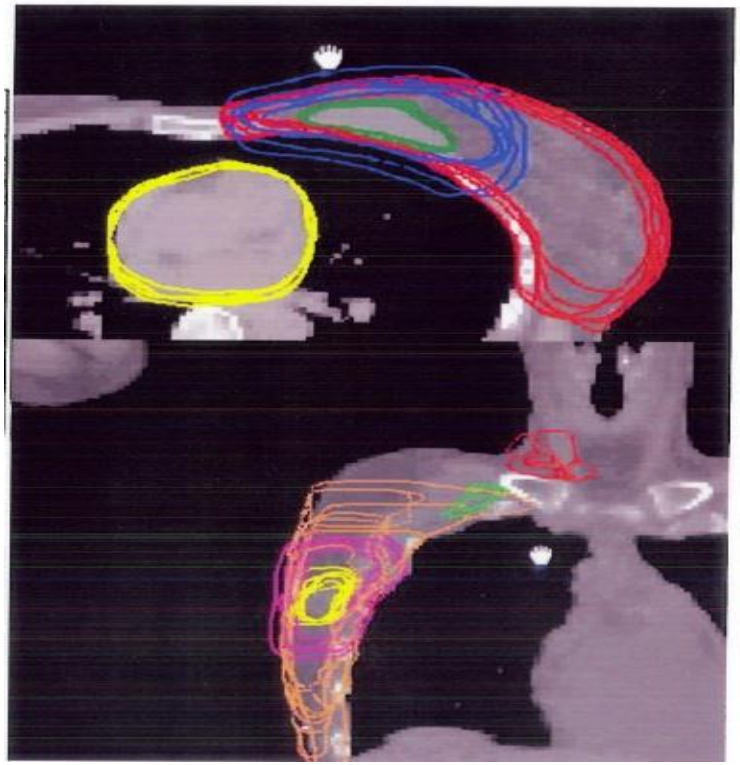
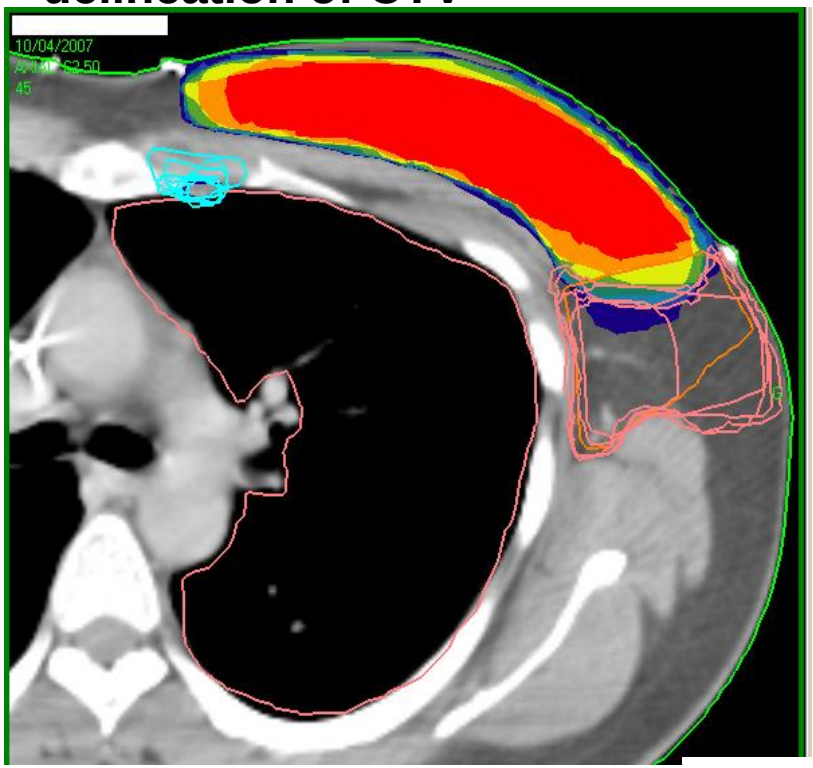
Two studies showed the large individual variations between different radiation oncologists in the delineation of treatment volumes

- **Li et al. ASTRO 2007: different institutions in USA**

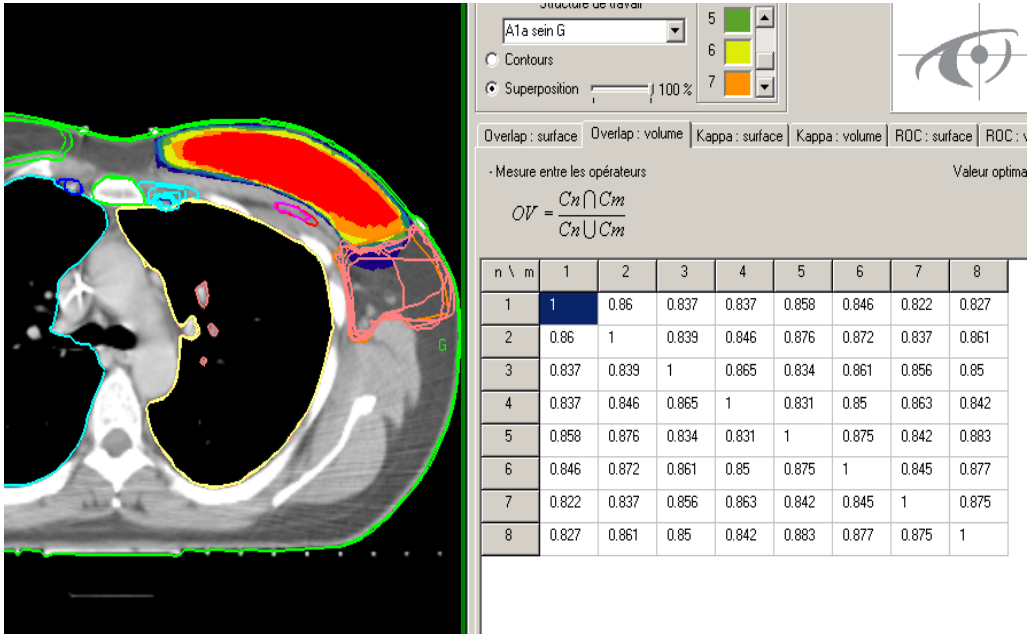


- **Castro Pena, Kirova et al. RSNA 2007: 11 persons from the same Department: delineation of CTV**

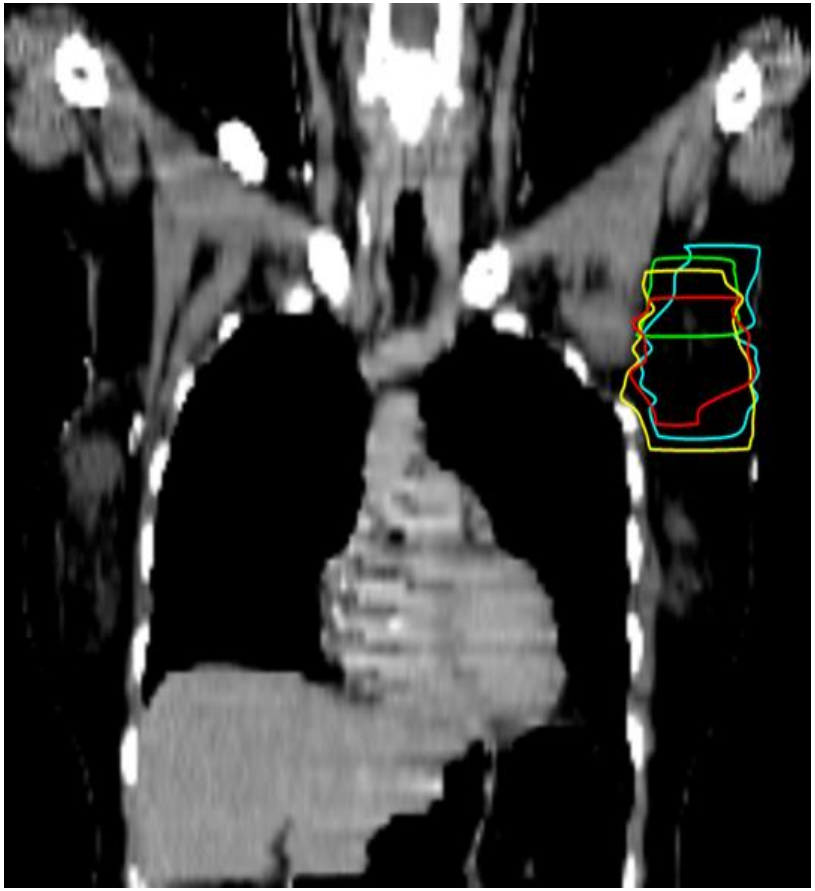


Both authors concluded that major differences in anatomical and radiological delineation for BC RT were observed between the various physicians.

Castro Pena, et al. RSNA 2007: 11 radiation oncologists : delineation of LN areas: after training



n \ m	1	2	3	4	5	6	7	8
1	1	0.86	0.837	0.837	0.858	0.846	0.822	0.827
2	0.86	1	0.839	0.846	0.876	0.872	0.837	0.861
3	0.837	0.839	1	0.865	0.834	0.861	0.856	0.85
4	0.837	0.846	0.865	1	0.831	0.85	0.863	0.842
5	0.858	0.876	0.834	0.831	1	0.875	0.842	0.883
6	0.846	0.872	0.861	0.85	0.875	1	0.845	0.877
7	0.822	0.837	0.856	0.863	0.842	0.845	1	0.875
8	0.827	0.861	0.85	0.842	0.883	0.877	0.875	1



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Int. J. Radiation Oncology Biol. Phys., Vol. 73, No. 3, pp. 944–951, 2009

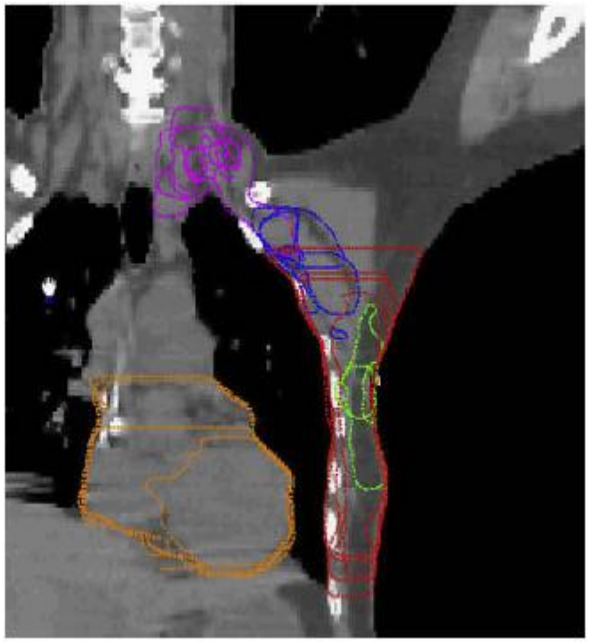
0360-3016/09/$–see front matter

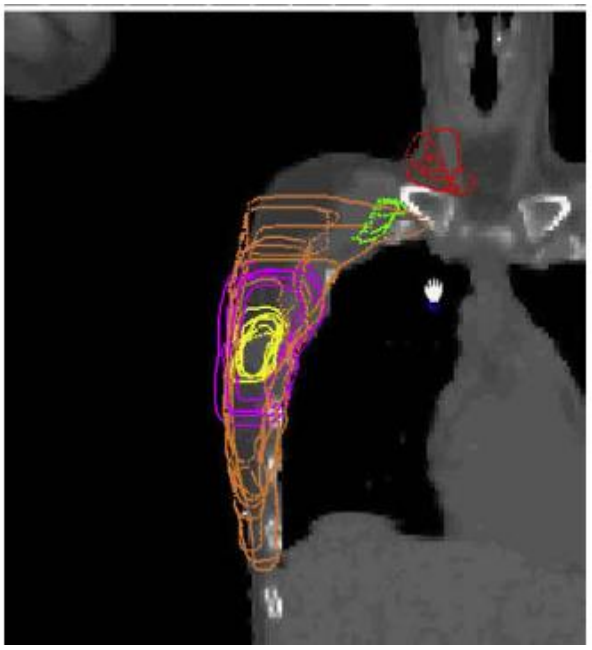
doi:10.1016/j.ijrobp.2008.10.034

PHYSICS CONTRIBUTION

VARIABILITY OF TARGET AND NORMAL STRUCTURE DELINEATION FOR BREAST CANCER RADIOTHERAPY: AN RTOG MULTI-INSTITUTIONAL AND MULTIOBSERVER STUDY

X. Allen Li, Ph.D.,* An Tai, Ph.D.,* Douglas W. Arthur, M.D.,† Thomas A. Buchholz, M.D.,‡ Shannon Macdonald, M.D.,§ Lawrence B. Marks, M.D.,¶ Jean M. Moran, Ph.D.,‖ Lori J. Pierce, M.D.,‖ Rachel Rabinovitch, M.D.,** Alphonse Taghian, M.D., Ph.D.,§ Frank Vicini, M.D.,†† Wendy Woodward, M.D., Ph.D.,‡ and Julia R. White, M.D.*





The British Journal of Radiology, 82 (2009), 595–599

Anatomical, clinical and radiological delineation of target volumes in breast cancer radiotherapy planning: individual variability, questions and answers

P CASTRO PENA, MD, Y M KIROVA, MD, F CAMPANA, MD, R DENDALE, MD, M A BOLLET, MD, N FOURNIER-BIDOZ, PhD and A FOURQUET, MD

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 73, No. 3, pp. 944–951, 2009

0360-3016/09/$–see front matter

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X. ALLEN LI, PH.D.,* AN TAI, PH.D.,* DOUGLAS W. ARTHUR, M.D.,† THOMAS A. BUCHHOLZ, M.D.,‡ SHANNON MACDONALD, M.D.,§ LAWRENCE B. MARKS, M.D.,¶ JEAN M. MORAN, PH.D.,‖ LORI J. PIERCE, M.D.,‖ RACHEL RABINOVITCH, M.D.,** ALPHONSE TAGHIAN, M.D., PH.D.,§ FRANK VICINI, M.D.,†† WENDY WOODWARD, M.D., PH.D.,‡ AND JULIA R. WHITE, M.D.*

Rafael Martinez-Monge, MD
Patrick S. Fernandes, MD
Nilendu Gupta, PhD
Reinhard Gahbauer, MD

1999

Cross-sectional Nodal Atlas: A Tool for the Definition of Clinical Target Volumes in

Index terms:
Computed tomography
three-dimensional, 9
99.92
Lymphatic system, 99.1
Special reports
Treatment planning, 99

Radiology 1999; 211:8

Abbreviations:
CTV = clinical target vo
GTV = gross tumor volu
3D = three-dimensiona

[1] From the Division of Ra
ogy, the Arthur G. James C
Ohio State University, 30

Chika N. Madu, BS
Douglas J. Quint, MD
Daniel P. Normolle, PhD
Robin B. Marsh, CMD
Edwin Y. Wang, MD
Lori J. Pierce, MD

2001

Definition of the Supraclavicular and Infraclavicular Nodes: Implications for

Index terms:
Breast neoplasms, 0
Breast neoplasms, t
radiology, 00.12
Lymphatic system,
997.92
Lymphatic system, t
radiology, 997.33
Treatment planning

ELSEVIER

2004

Radiotherapy and Oncology 71 (2004) 287–295

RADIOTHERAPY & ONCOLOGY

www.elsevier.com/locate/radonline

Loco-regional conformal radiotherapy of the breast: delineation of the regional lymph node clinical target volumes in treatment position

Ivessa M. Dijkema[a,*], Pieter Hofman[a], Cornelis P.J. Raaijmakers[a], Jan J. Lagendijk[a],

Radiotherapy and Oncology 79 (2006) 310–315
www.thegreenjournal.com

2006

Breast treatment planning

CT-scan based localization of the internal mammary chain and supra clavicular nodes for breast cancer radiation therapy planning☆

Youlia M. Kirova[a,*], Vincent Servois[b], François Campana[a], Remi De
Marc A. Bollet[a], Fatima Laki[c], Nathalie Fournier-Bidoz[a], Alain Fou

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Radiotherapy and Oncology 84 (2007) 335–347
www.thegreenjournal.com

2007

Educational review

Anatomical bases for the radiological delineation of lymph node areas. Upper limbs, chest and abdomen

Benoit Lengelé[a], Catherine Nyssen-behets[a], Pierre Scalliet[b,*]

2009

The British Journal of Radiology, 82 (2009), 595–599

Anatomical, clinical and radiological delineation of target volumes in breast cancer radiotherapy planning: individual variability, questions and answers

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2010

The British Journal of Radiology, 83 (2010), 683–686

Simplified rules for everyday delineation of lymph node areas for breast cancer radiotherapy

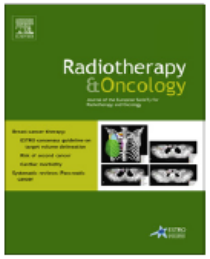
[1]Y M KIROVA, MD, [1]P CASTRO PENA, MD, [1]R DENDALE, MD, [2]V SERVOIS, MD, [1]M A BOLLET, MD, [1]N FOURNIER-BIDOZ, PhD, [1]F CAMPANA, MD and [1]A FOURQUET, MD

Radiotherapy and Oncology 114 (2015) 3–10

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



ESTRO consensus guidelines

ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer

Birgitte V. Offersen [a,*], Liesbeth J. Boersma [b], Carine Kirkove [c], Sandra Hol [d], Marianne C. Aznar [e], Albert Biete Sola [f], Youlia M. Kirova [g], Jean-Philippe Pignol [h], Vincent Remouchamps [i], Karolien Verhoeven [j], Caroline Weltens [j], Meritxell Arenas [k], Dorota Gabrys [l], Neil Kopek [m], Mechthild Krause [n], Dan Lundstedt [o], Tanja Marinko [p], Angel Montero [q], John Yarnold [r], Philip Poortmans [s]

[a] *Department of Oncology, Aarhus University Hospital, Denmark;* [b] *Department of Radiation Oncology, Maastricht University Medical Centre – GROW (MAASTRO), The Netherlands* [c] *Department of Radiation Oncology, Catholic University of Louvain, Belgium;* [d] *Department of Radiation Oncology, Institute Verbeeten, Tilburg, The Netherlands;* [e] *Department of Oncology, Rigshospitalet, Copenhagen, Denmark;* [f] *Department of Radiation Oncology, Hospital Clinic i Provincial, Barcelona, Spain;* [g] *Department of Radiation Oncology, Institut Curie, Paris, France;* [h] *Department of Radiation Oncology, Erasmus University Medical Center, Rotterdam, The Netherlands;* [i] *Department of Radiation Oncology, Clinique Sainte Elisabeth (AMPR), Namur;* [j] *Department of Radiation Oncology, University Hospitals Leuven, KU Leuven, Belgium;* [k] *Department of Radiation Oncology, Hospital Universitari Sant Joan, Reus, Spain;* [l] *Department of Radiation Oncology, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice, Poland;* [m] *Department of Oncology, Division of Radiation Oncology, McGill University, Montréal, Canada;* [n] *German Cancer Consortium (DKTK) Dresden and German Cancer Research Center (DKFZ) Heidelberg, Dept. of Radiation Oncology and OncoRay, University Hospital Carl Gustav Carus, Technische Universität Dresden and Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany;* [o] *Department of Oncology, Sahlgrenska Universitetssjukhuset, Gothenborg, Sweden;* [p] *Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia;* [q] *Department of Radiation Oncology, Centro Integral Oncológico Clara Campal, Hospital Universitario Sanchinarro, Madrid, Spain;* [r] *Division of Radiotherapy and Imaging, Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, UK;* [s] *Department of Radiation Oncology, Radboud university medical centre, The Netherlands*

Radiotherapy and Oncology 114 (2015) 3–10

Contents lists available at ScienceDirect

Radiotherapy and Oncology 118 (2016) 205–208

Contents lists available at ScienceDirect

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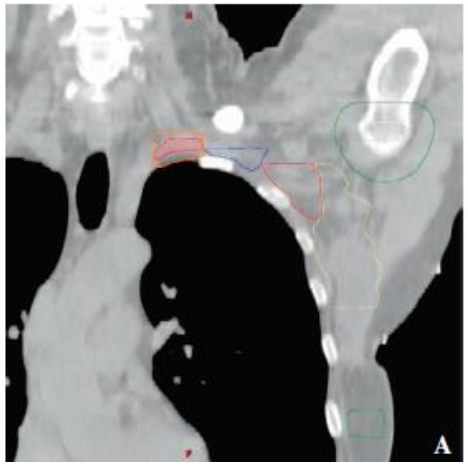
journal homepage: www.thegreenjournal.com

ESTRO breast cancer consensus guidelines

ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer, version 1.1 ☆



To the Editor,

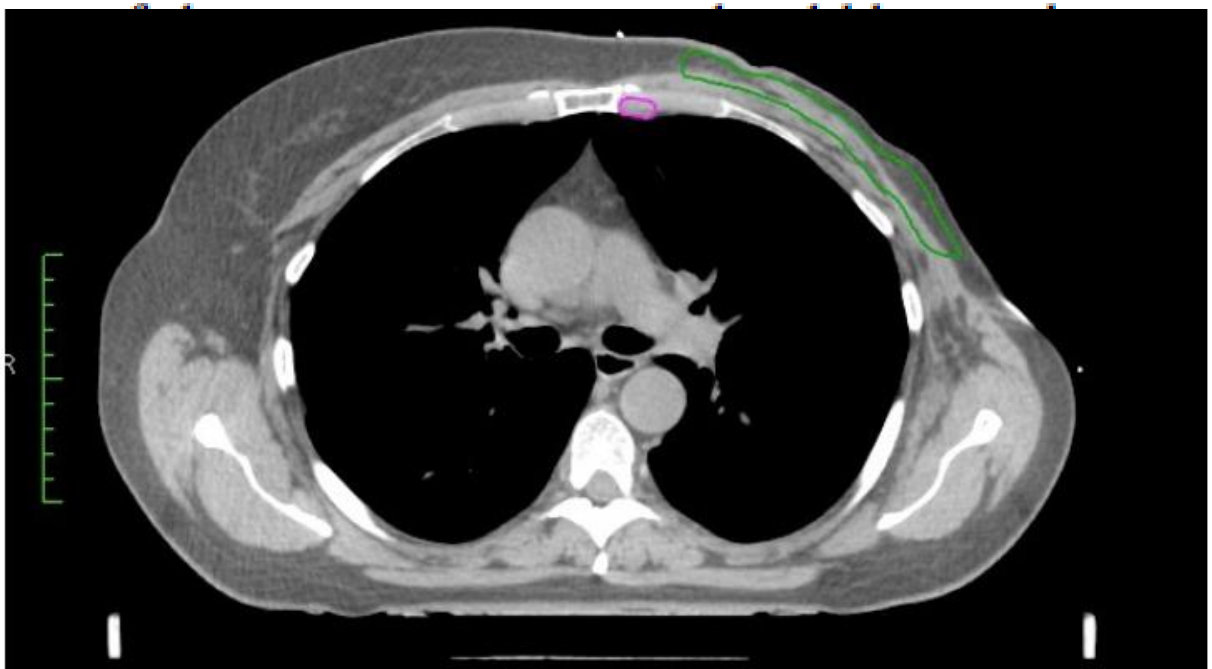
One year ago we presented the ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer [1]. We hereby present an update following the need for modification of the caudal part of CTVn_L4 and the lateral border of CTVn_IMN in the published pdf-files. Also, as a consequence of frequent questions, we provide more information regarding the lateral border of the CTVp_breast and for dose planning in relation to the humeral joint.

CHEST WALL AFTER MASTECTOMY

Delineation of the thoracic wall

CTVp_thoracic wall

In mastectomy patients, radio-opaque wires should be positioned around the –imaginary – original site of the breast and also corresponding to the mastectomy scar. While the position of the contra-lateral breast can be helpful for this if both arms are symmetrically elevated, in general the surface of the CTVp_thoracic wall is reduced by the surgical procedure following the pulling on adjacent skin and subcutaneous tissue to close the defect after removal of the breast. Therefore, careful palpation of the thoracic wall while positioning the radio-opaque markers

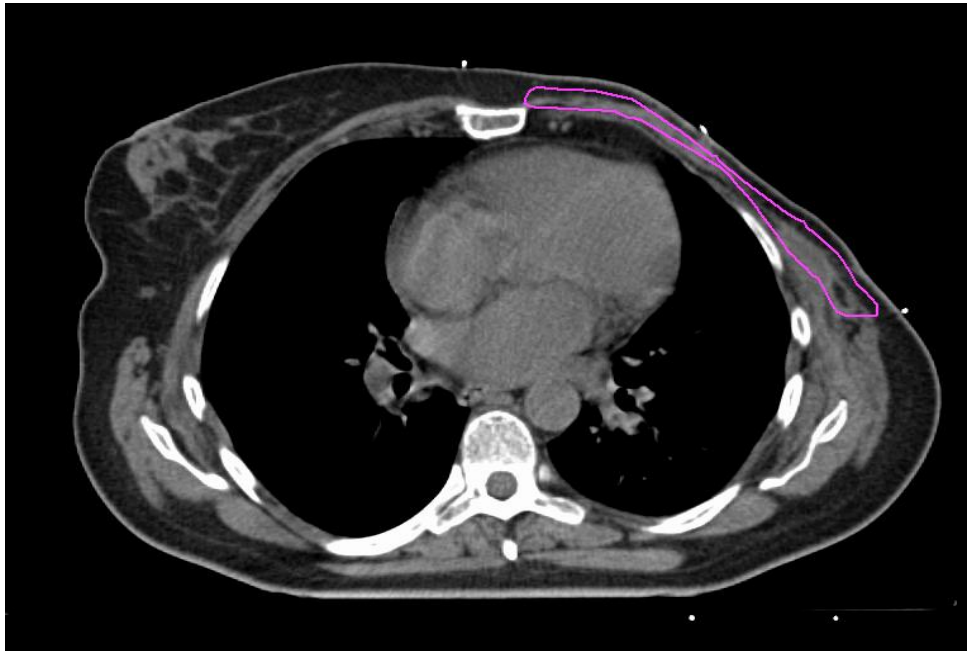


ESTRO Consensus, Radiother Oncol, 2015

ESTRO School

Delineation of the thoracic wall

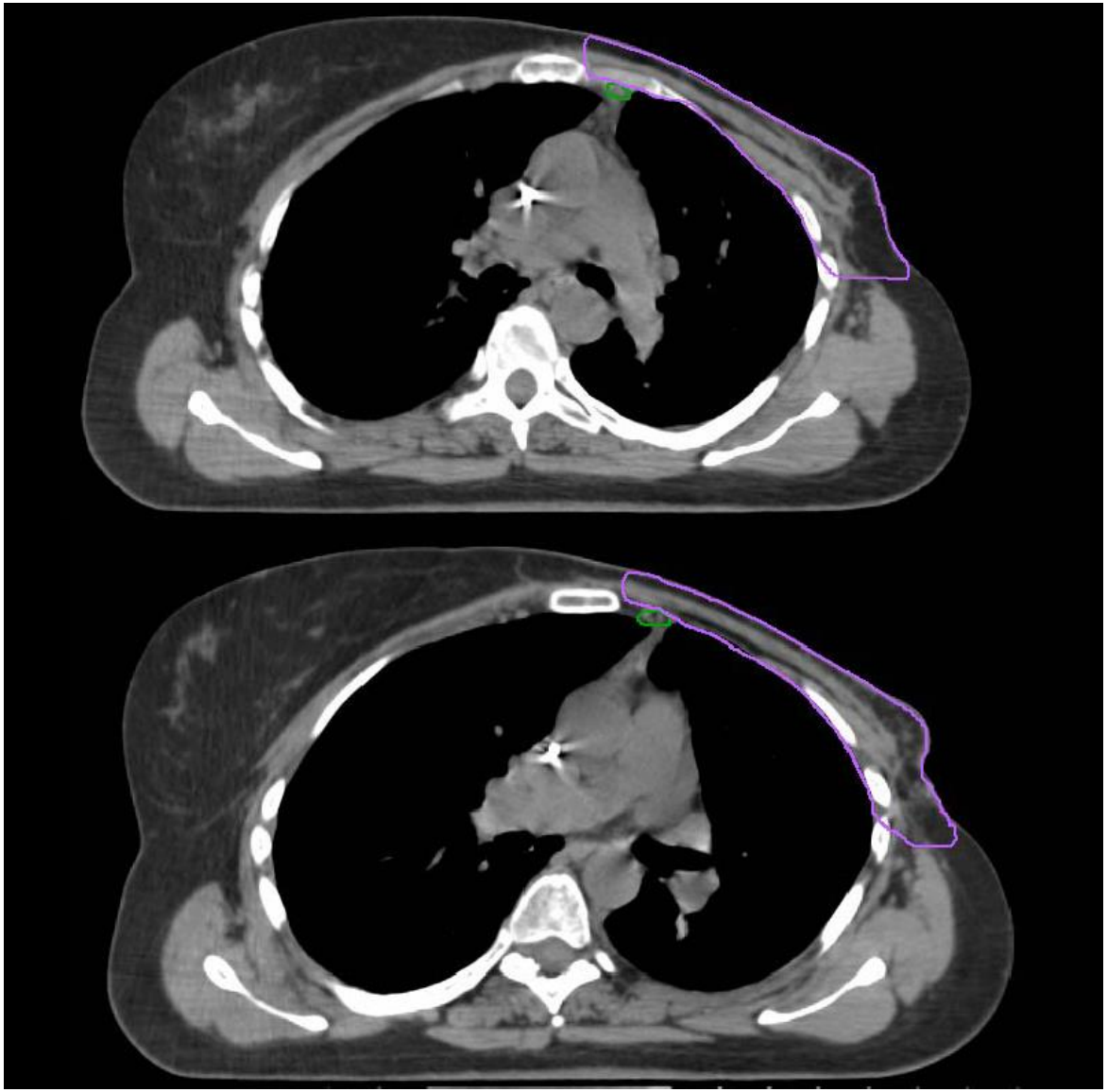
- **All borders of the CTV thoracic wall are usually considered to be identical to the CTV breast.**
- **In case of an extremely thin thoracic wall, omission of the first 5 mm beneath the skin may result in no CTV at all.**
- **In that case, do extend the CTV into the skin, and consequently use bolus.**



ESTRO Consensus, Radiother Oncol, 2015

ESTRO School

Delineation of the thoracic wall: RTOG



Discussion:

Always include skin and/or thoracic wall in CTV ?

Ref: BreastCancer Atlas RTOG

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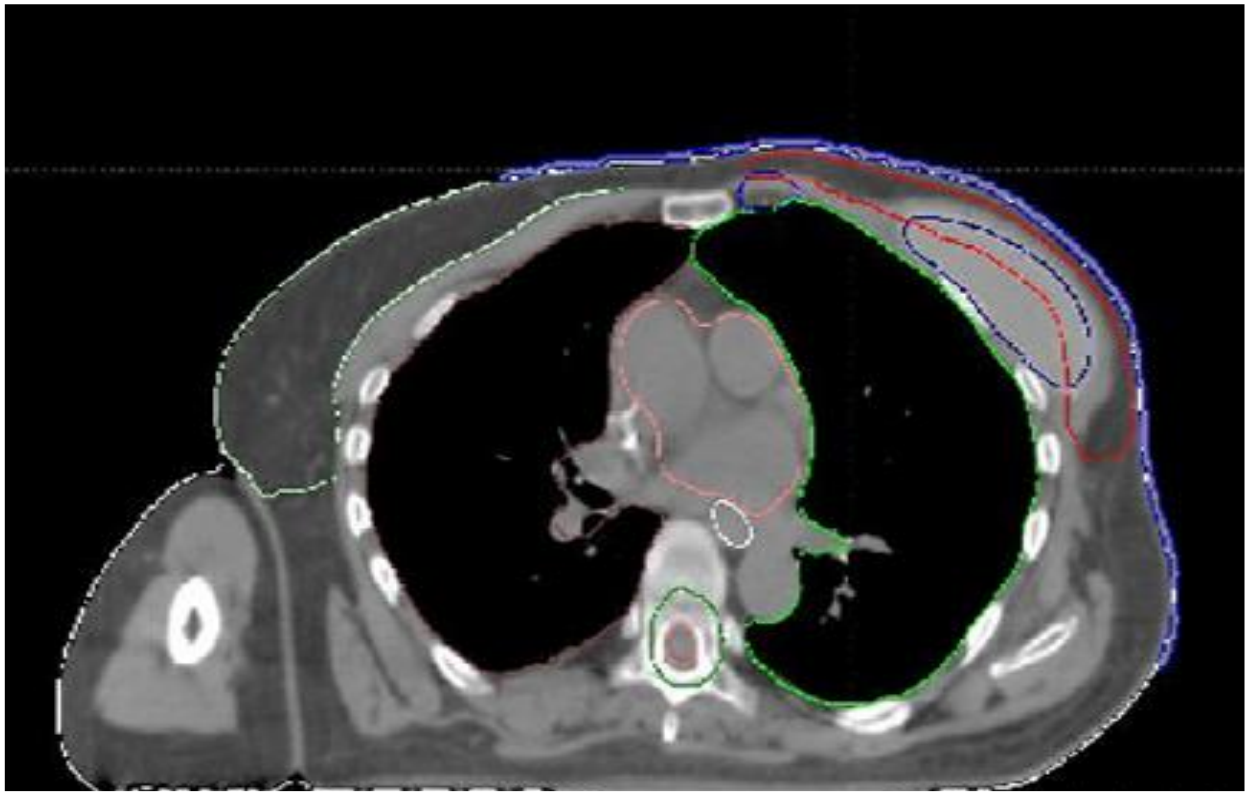
Immediate breast reconstruction

The clinical target volume (CTV) was defined as the biologic entity that included the remaining breast tissue at risk of microscopic disease (CTV1),



The volume between skin and implant, the pectoral muscle must be included

Massabeau et al., Med Dosim 2012

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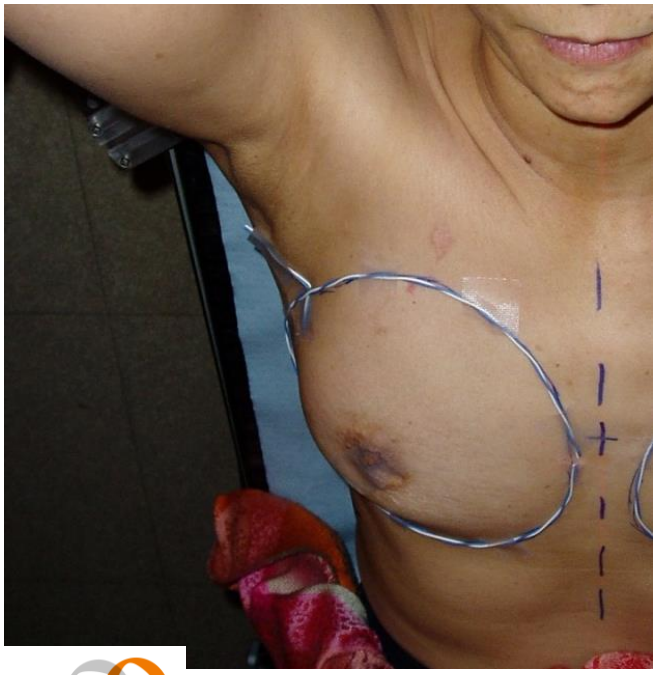
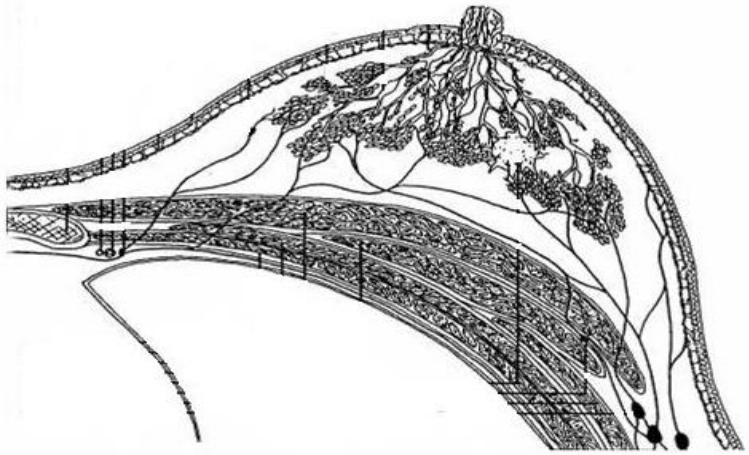
Breast

Delineation of the CTV breast using CT:
CTV breast = “whole glandular breast tissue”

This target volume includes the total glandular breast tissue, whose borders are often not clearly visible. To facilitate delineation, radio-opaque markers may be placed around the breast for CT-scanning, keeping in mind that these markers do not necessarily represent the true borders of the CTVp_breast.



ESTRO Consensus, Radiother Oncol, 2015



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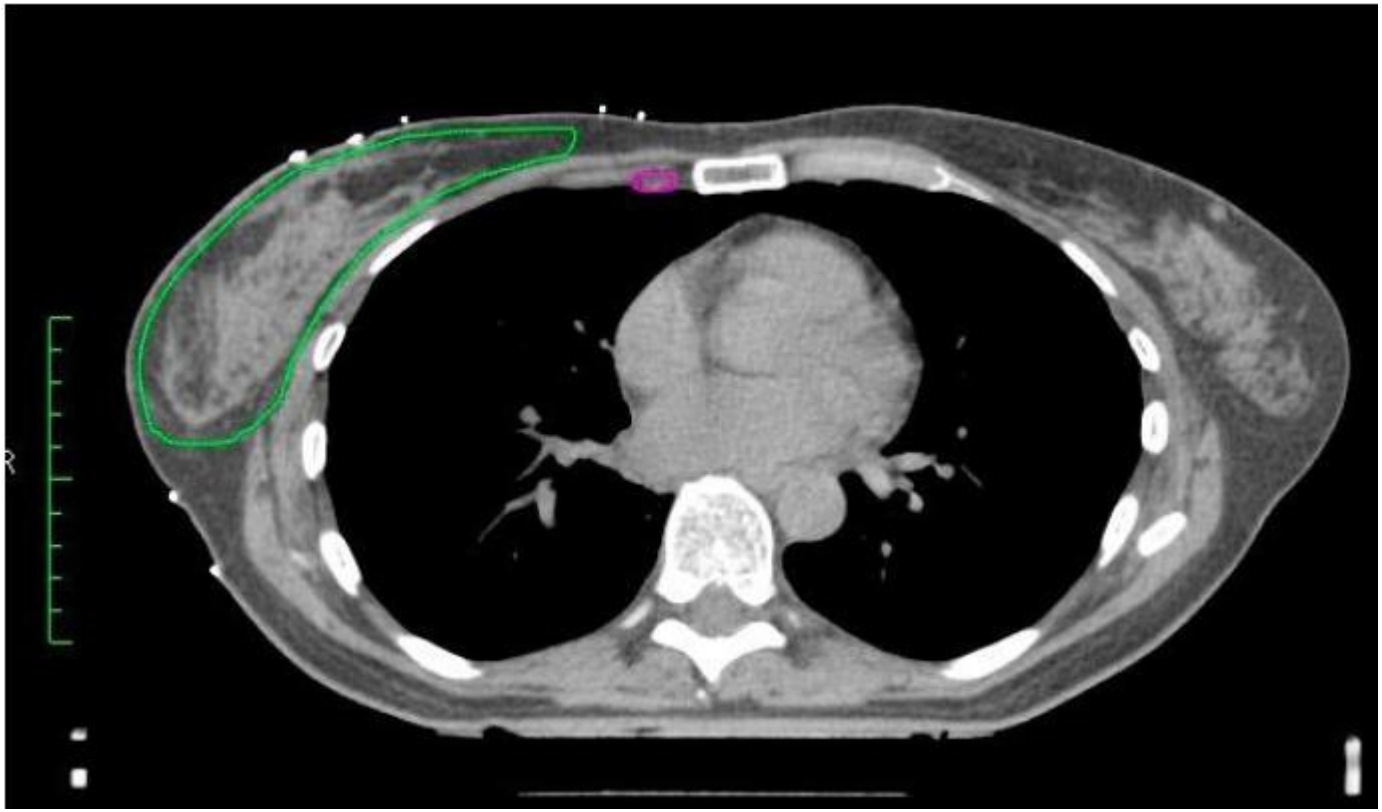
Breast



Between Pectoral Muscle and 5 mm below the skin (dosimetric considerations), within the space outlined by skin markers, that showed the limits of the palpable breast tissue.

ESTRO Consensus, Radiother Oncol, 2015

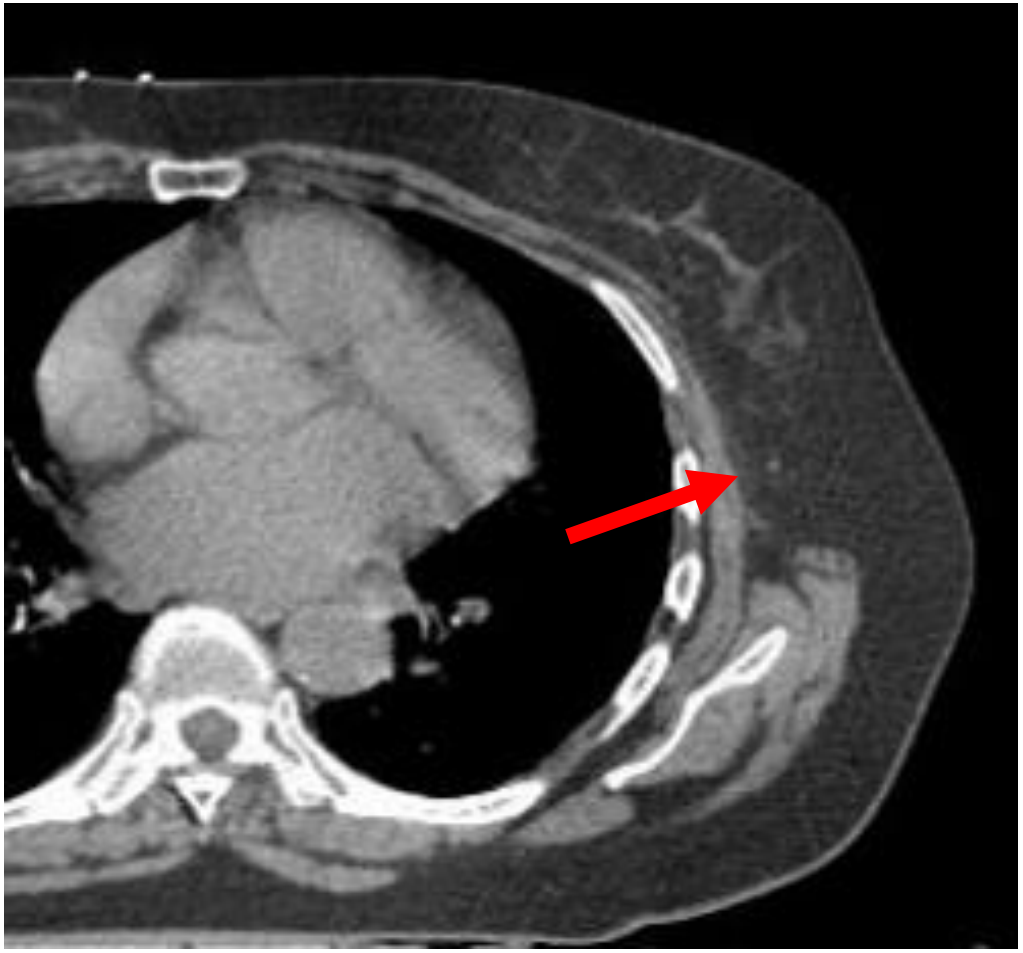
Helpful: Vessels

Medial:
<ipsilateral edge of the sternum

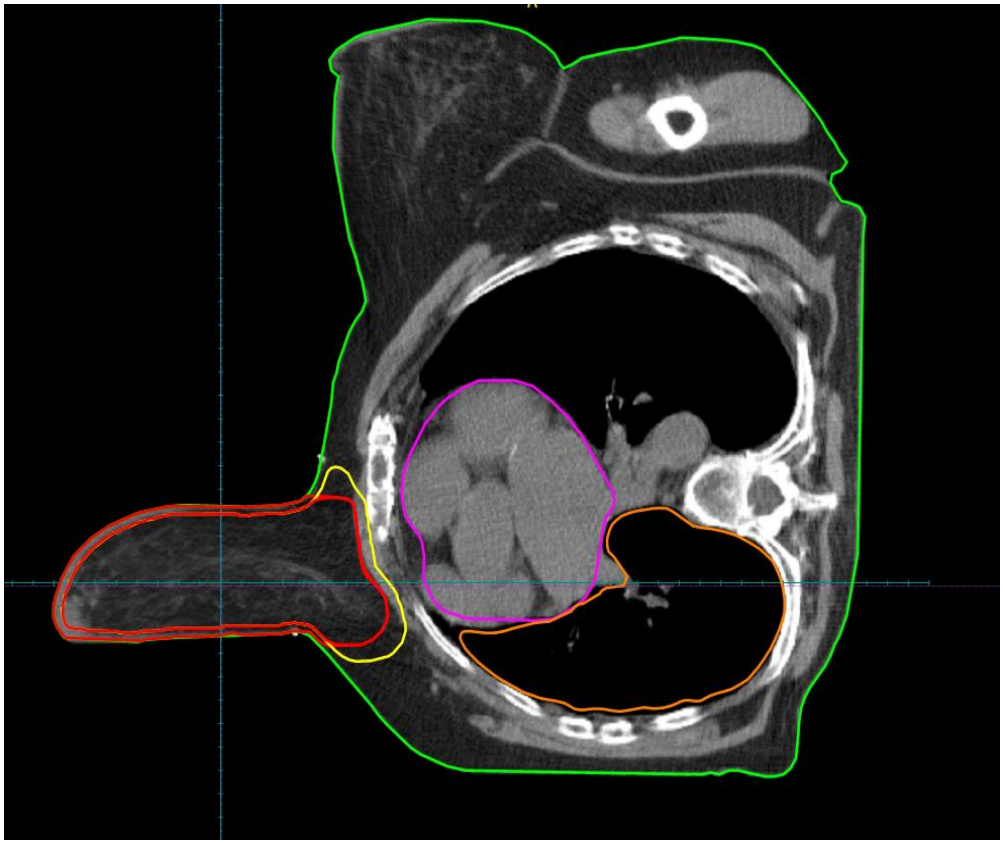
< vessels: rami mammarii (from thoracica int)

Lateral:
< lateral side of the visible breast contour

< vessel: thoracica lateralis



Breast: Delineation in lateral position



Courtesy Dr Castro Pena

BOOST VOLUME

Breast Boost: Are We Missing the Target?

A Dosimetric Comparison of Two Boost Techniques

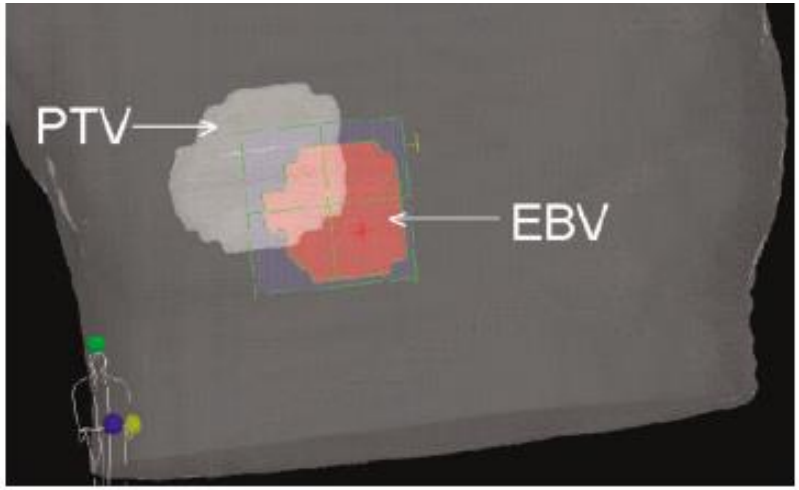
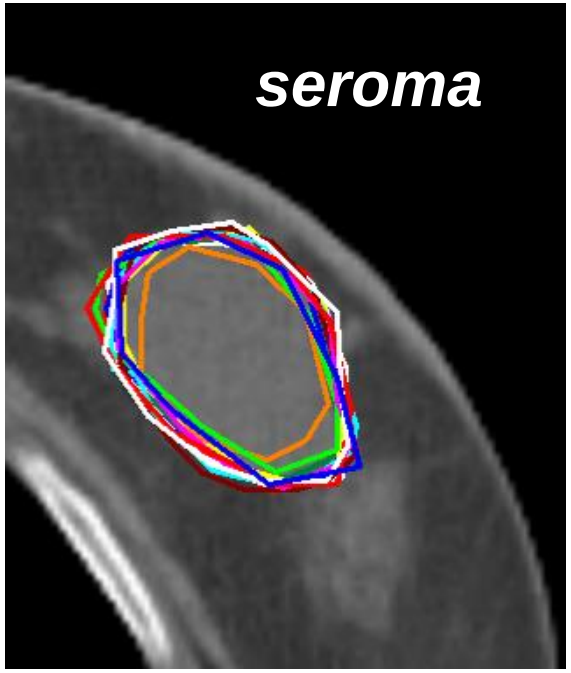


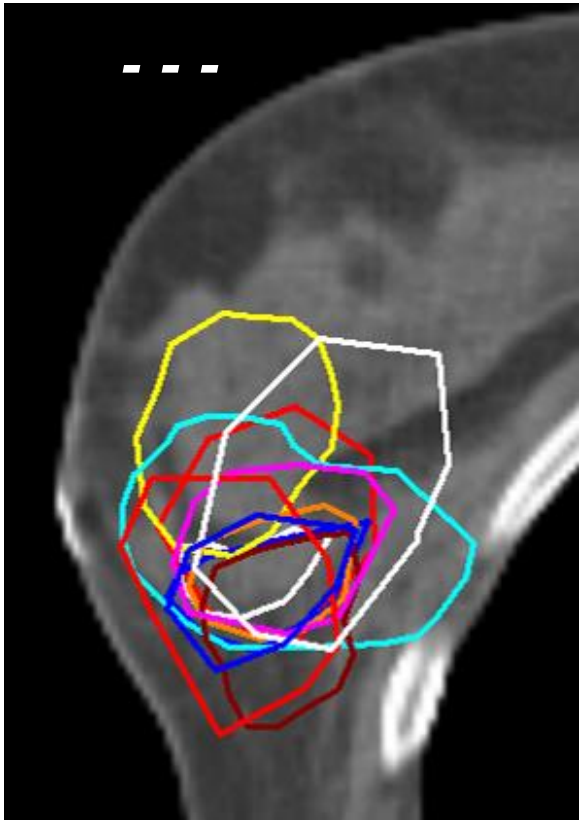
FIGURE 2. Minimal overlap of the two volumes was noted in the plans based on this patient, resulting in significant underdosing of the tumor bed and unnecessary irradiation of the normal breast tissue. PTV: planning target volume; EBV: electron boost volume.

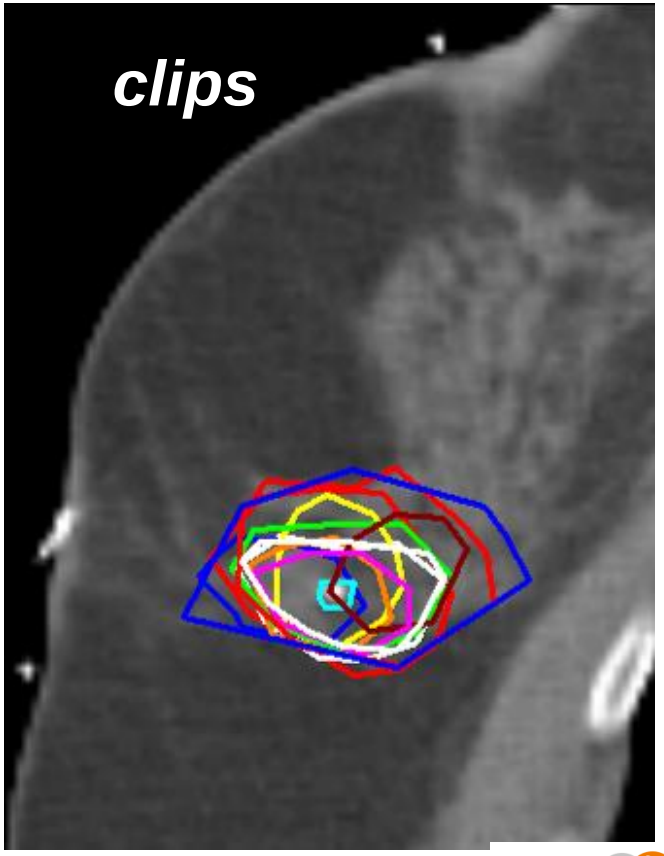
Benda et al.; Cancer, 2003

CONCLUSIONS. Clinical delineation of the tumor bed not only carries a significant risk of missing the target, but unnecessarily treats breast tissue that may otherwise be spared. Better delineation of the tumor bed, which optimizes coverage of the target volume and spares normal breast tissue, has the potential to improve both local control and cosmetic outcome. The authors recommend the use of surgical clips to delineate the target volume, followed by CT-based treatment planning, accounting for not only microscopic disease, but also organ motion and daily setup error. *Cancer* 2003;97:905–9.

Volume delineation: variations

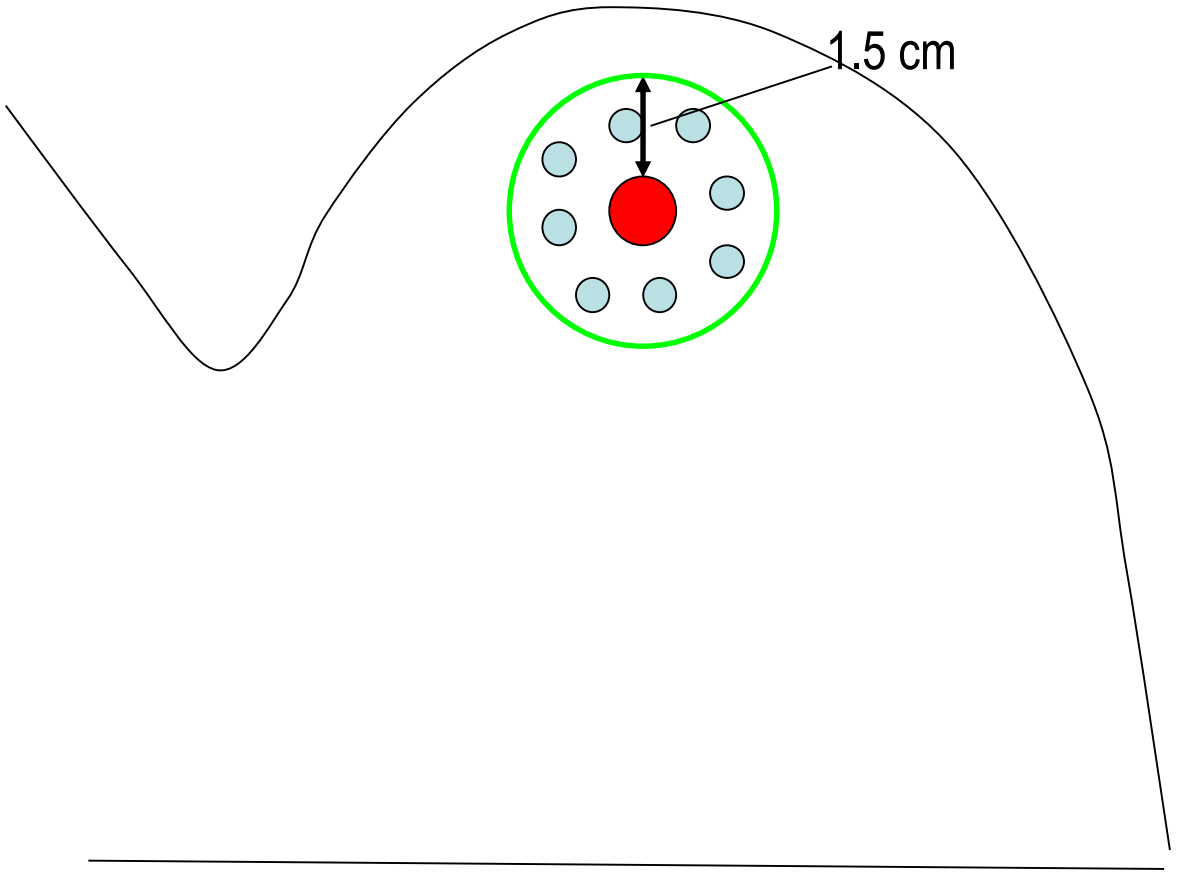






Von Mourik et al., 2008.

Target volume delineation: boost



Tumor=GTV

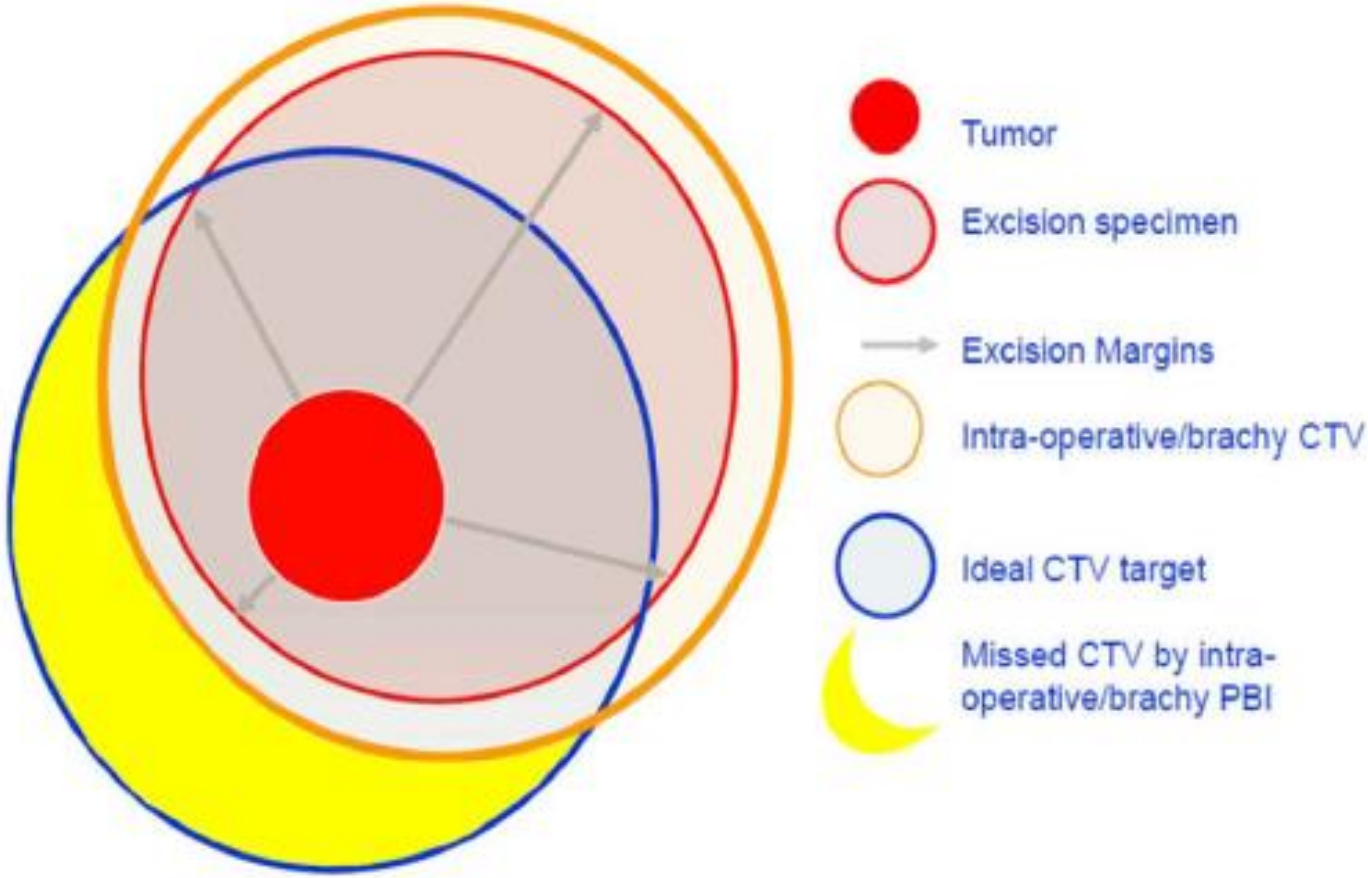
Micr. extension

Region with microscopic extension, within 1.5 cm of primary tumor

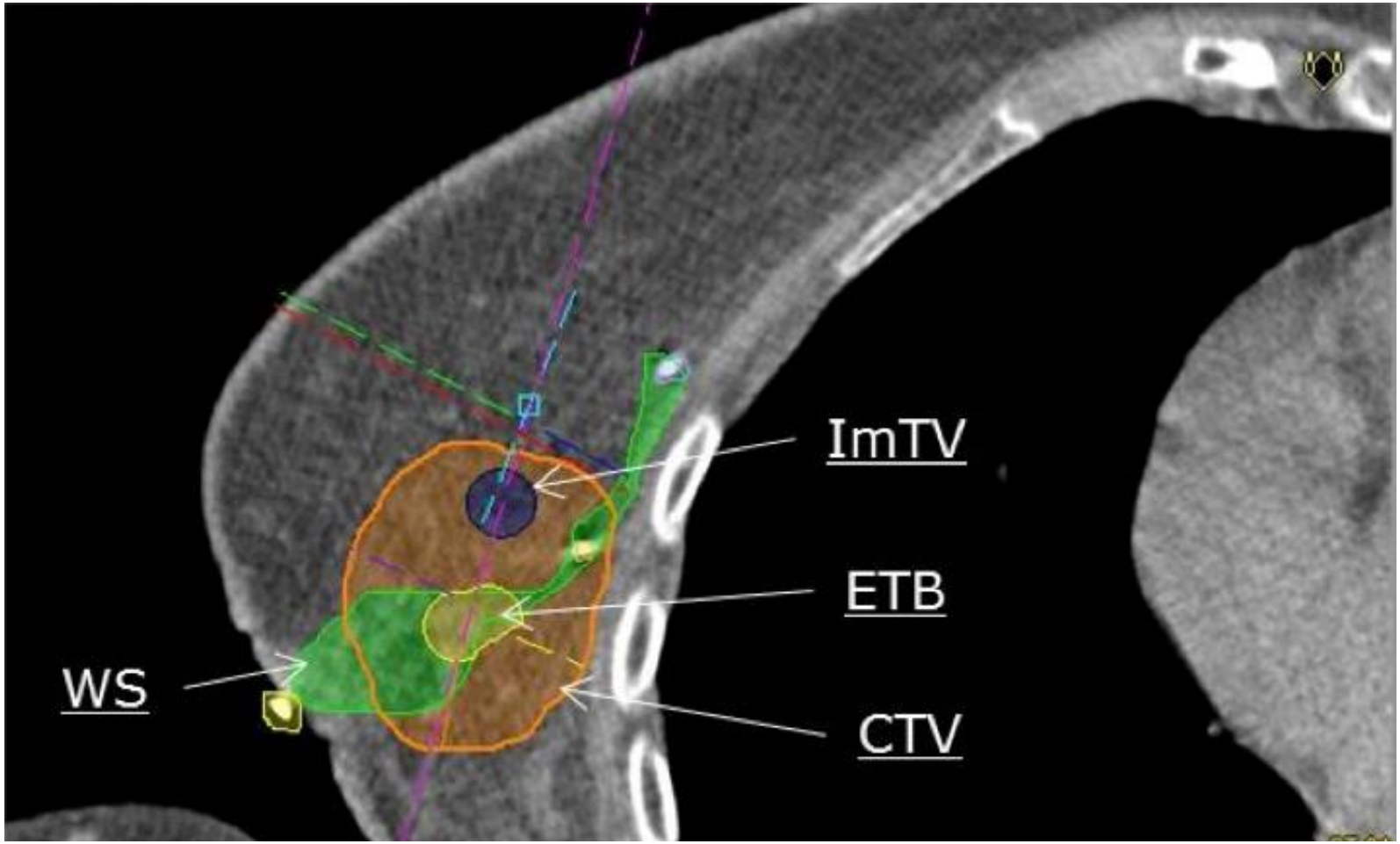
Boersma et al. Radiother Oncol. 2012

Primary tumour bed

✓Mind local tumour extension!



Bartelink H et al, Radiother Oncol 2012

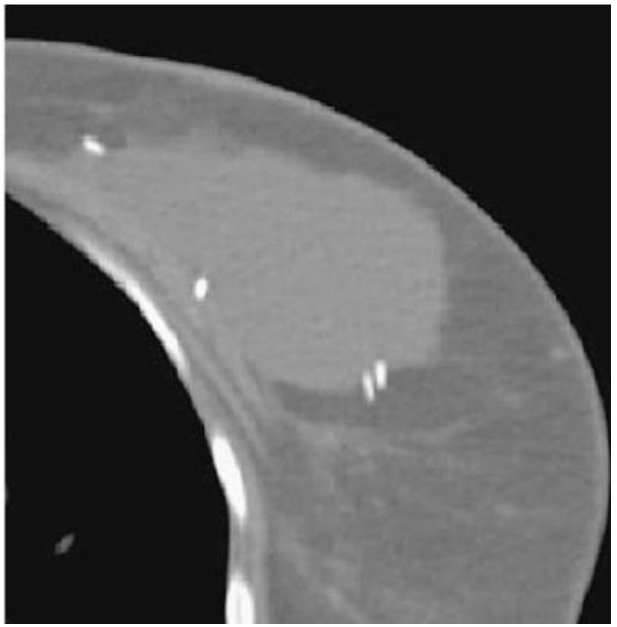


WS:	Whole surgical Scar	ImTV:	Imaging related Target Volume
ETB:	Estimated Tumour Bed	CTV:	Clinical Target Volume

Strnad V et al, GEC-ESTRO guidelines, 2016

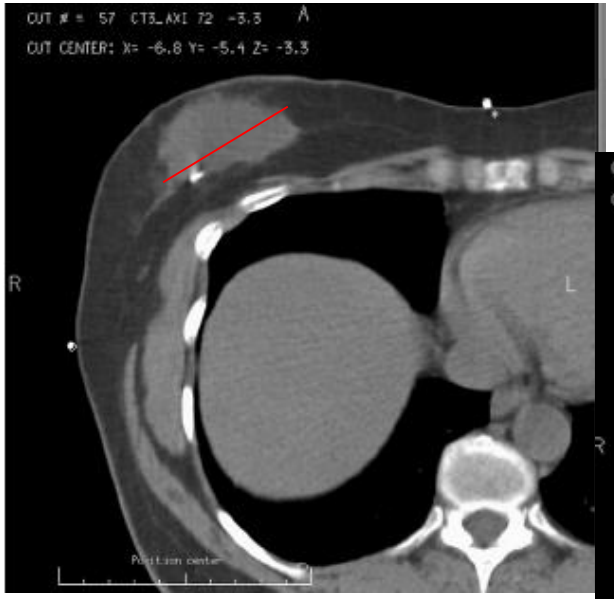
Placement of clips using a strict protocol

- **UK-protocol:**
  - **6 x 2 clips**
  - **At 4 points: medial, lateral, superior & inferior, at the level of the tumor.**
  - **In the center of the deep margin, usually at the fascia, and superficially, beneath the skin.**

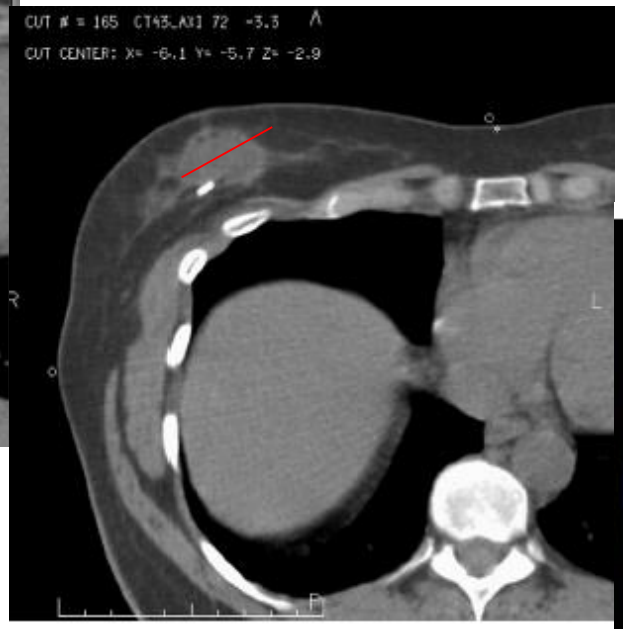


Coles et al, EJSO 2008

Shape and size of the cavity change with time after surgery



Before RT



WBRT 40 Gy

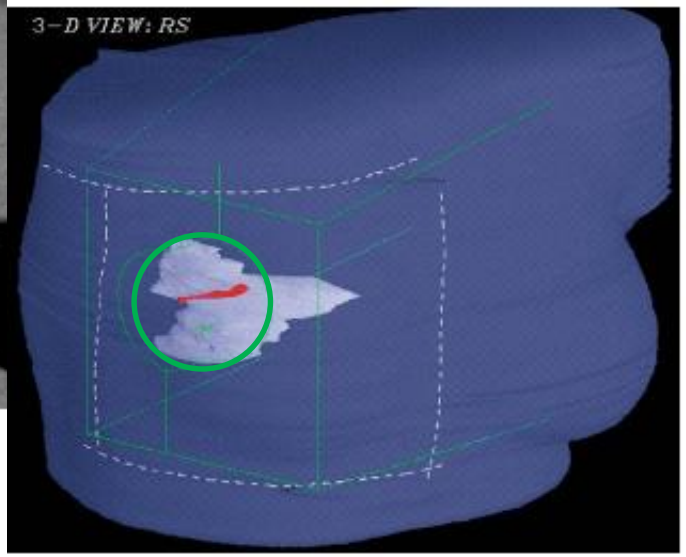


Fig. 5. Digitally reconstructed radiograph depicting the scar (red), excision cavity (light blue), and scar-based hypothetical field border (green oval). In this case, the excision cavity extends far beyond an electron boost field based on the surgical scar.

Oh et al, IJROBP 2006

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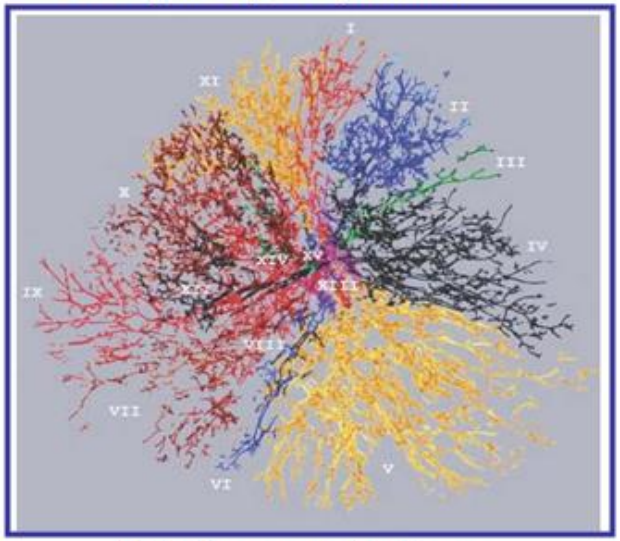
BOOST VOLUME

Institut Curie procedure

Arbre galactophorique en 3D



10 à 16 canaux principaux

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ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 2, pp. 494–500, 2008

0360-3016/08/$–see front matter

doi:10.1016/j.ijrobp.2007.12.059

CLINICAL INVESTIGATION **Breast**

HOW TO BOOST THE BREAST TUMOR BED? A MULTIDISCIPLINARY APPROACH IN EIGHT STEPS

Youlia M. Kirova, M.D.,* Nathalie Fournier-Bidoz, Ph.D.,* Vincent Servois, M.D.,† Fatima Laki, M.D.,‡ Guillaume A. Pollet, M.D.,‡ Remy Salmon, M.D.,‡ Alexandra Thomas,* Rémi Dendale, M.D.,* Marc A. Bollet, M.D.,* François Campana, M.D.,* and Alain Fourquet, M.D.*

2008

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 78, No. 5, pp. 1352–1355, 2010

0360-3016/$–see front matter

doi:10.1016/j.ijrobp.2009.10.049

CLINICAL INVESTIGATION **Breast**

IMPROVING THE DEFINITION OF TUMOR BED BOOST WITH THE USE OF SURGICAL CLIPS AND IMAGE REGISTRATION IN BREAST CANCER PATIENTS

Youlia M. Kirova, M.D.,* Pablo Castro Pena, M.D.,* Tarek Hijal, M.D.,* Nathalie Fournier-Bidoz, Ph.D.,* Fatima Laki, M.D.,† Brigitte Sigal-Zafrani, M.D.,‡ Rémi Dendale, M.D.,* Marc A. Bollet, M.D.,* Francois Campana, M.D.,* and Alain Fourquet, M.D.*

2010

Institut Curie procedure
Illustrated by clinical case T1N0 breast cancer

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8 steps, multidisciplinary

Table 1. Tumor bed localization and treatment workflow

Step	Actors	Time
1. Patient selection and patient agreement	Surgeon Radiation oncologist	
2. Preoperative CT scan	Radiologist Radiation oncologist RT technologists	Week −1
3. Surgery	Surgeon	Week 0
4. Postoperative CT scan	Radiologist Radiation oncologist RT technologists	Week +4
5. Pre- to postoperative CT registration	Dosimetrist	Week +4
6. Volume delineation	Radiation oncologist	Week +4.5–5
7. Treatment volume definition	Radiation oncologist	Week +4.5–5
8. Treatment planning	Dosimetrist Physicist Radiation oncologist	Week +5.5–6

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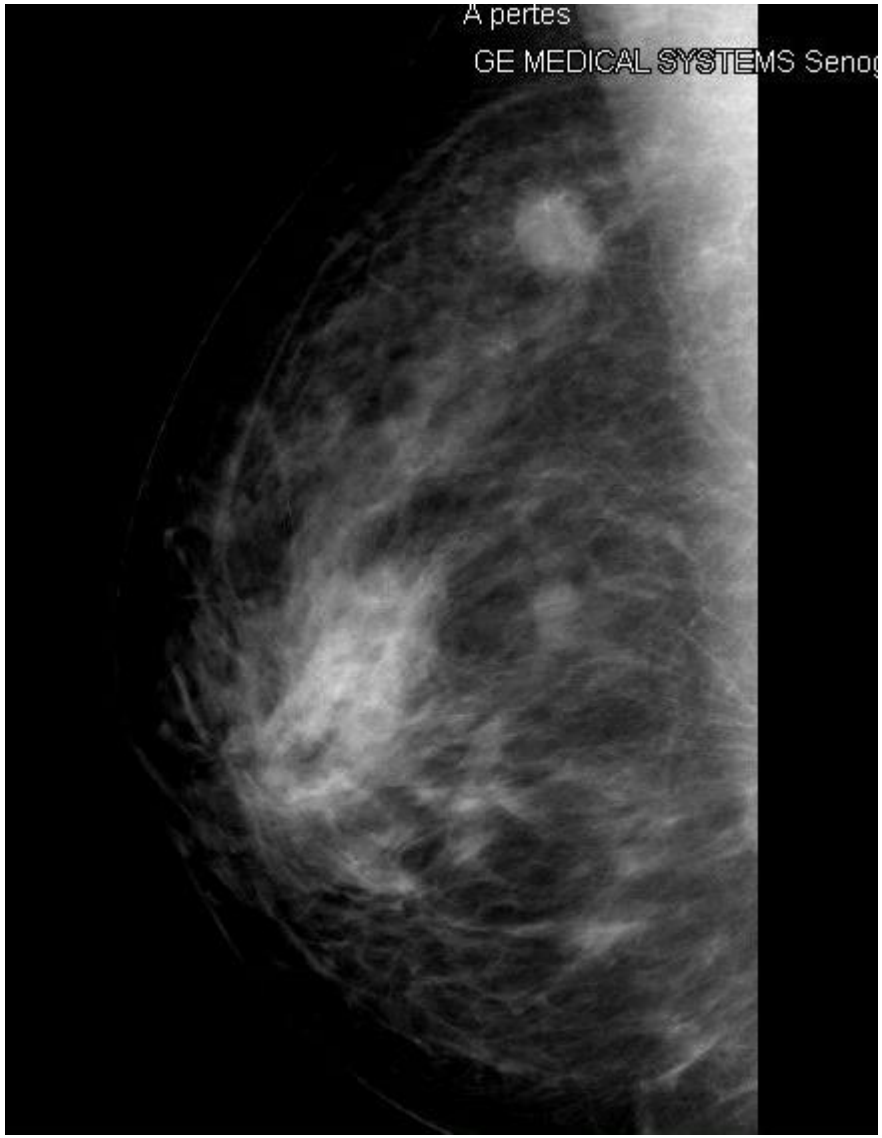


CASE

Step 1: Patient's selection

Mammography: 15 mm opacity in female patient, 46 years old,

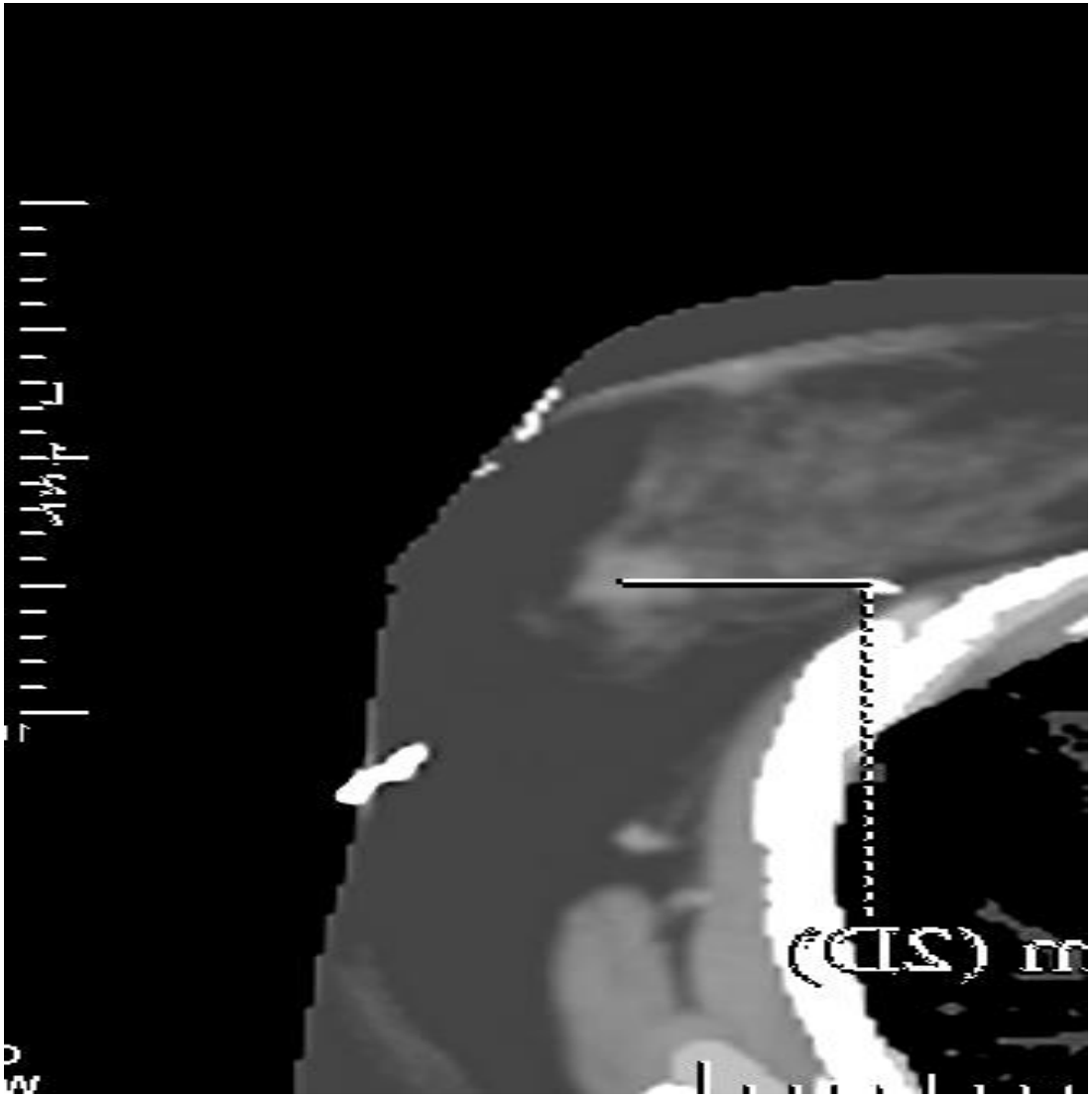
Biopsy: IDC grade I, RE+RP+HER2-, Ki 67 5%

Stage?

Your treatment proposal?

Type of Surgery, RT, systemique treatment?

Step 2 - CT in treatment position before the surgery



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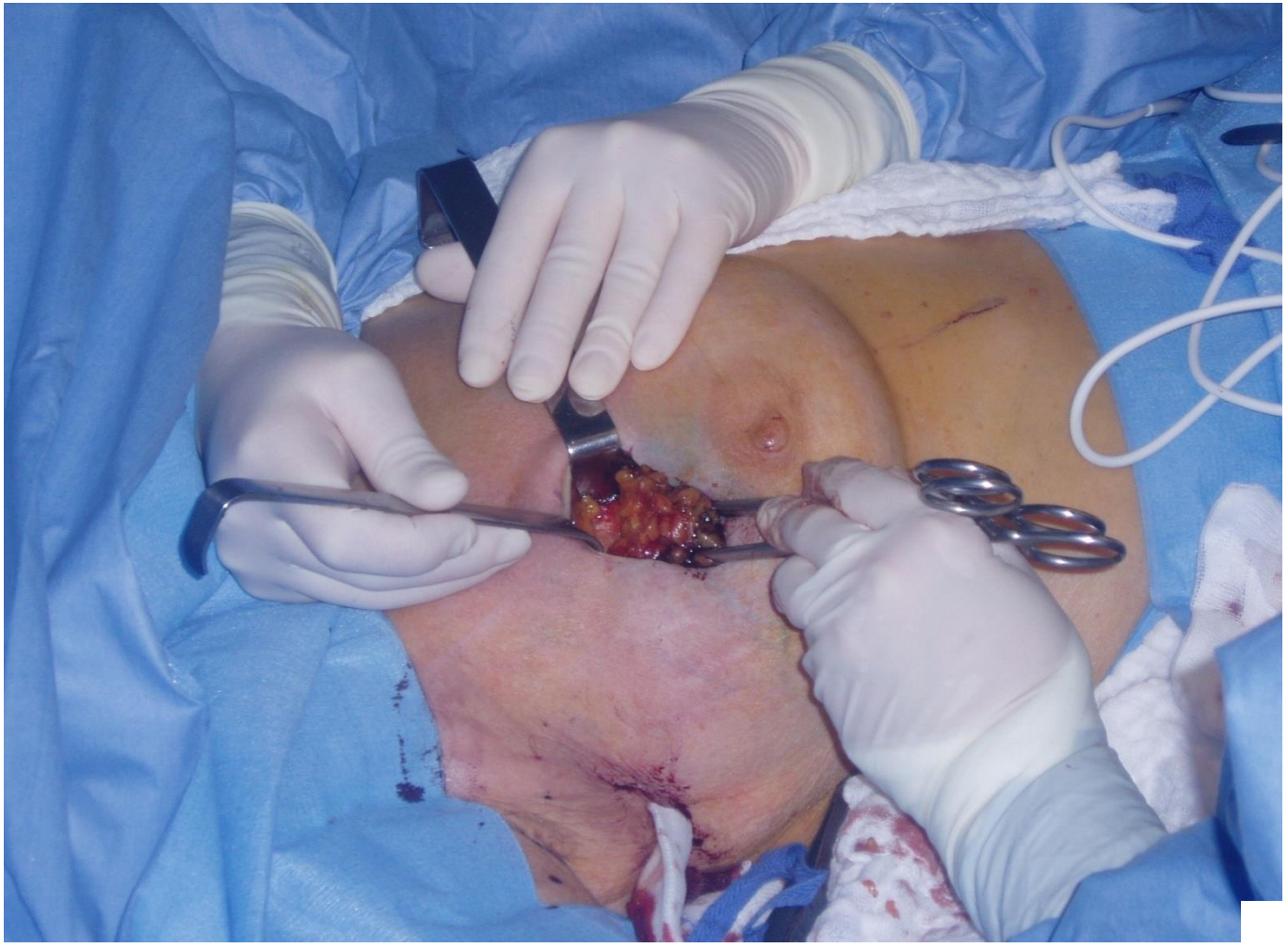
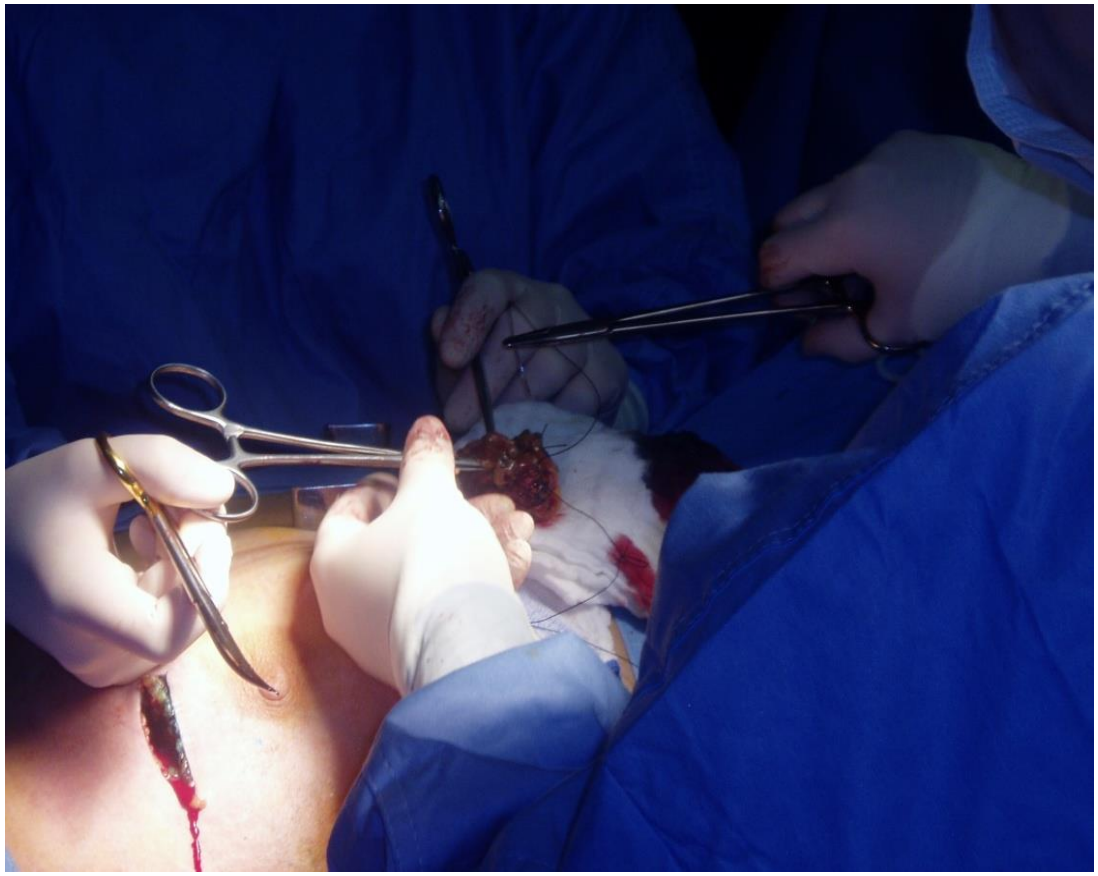
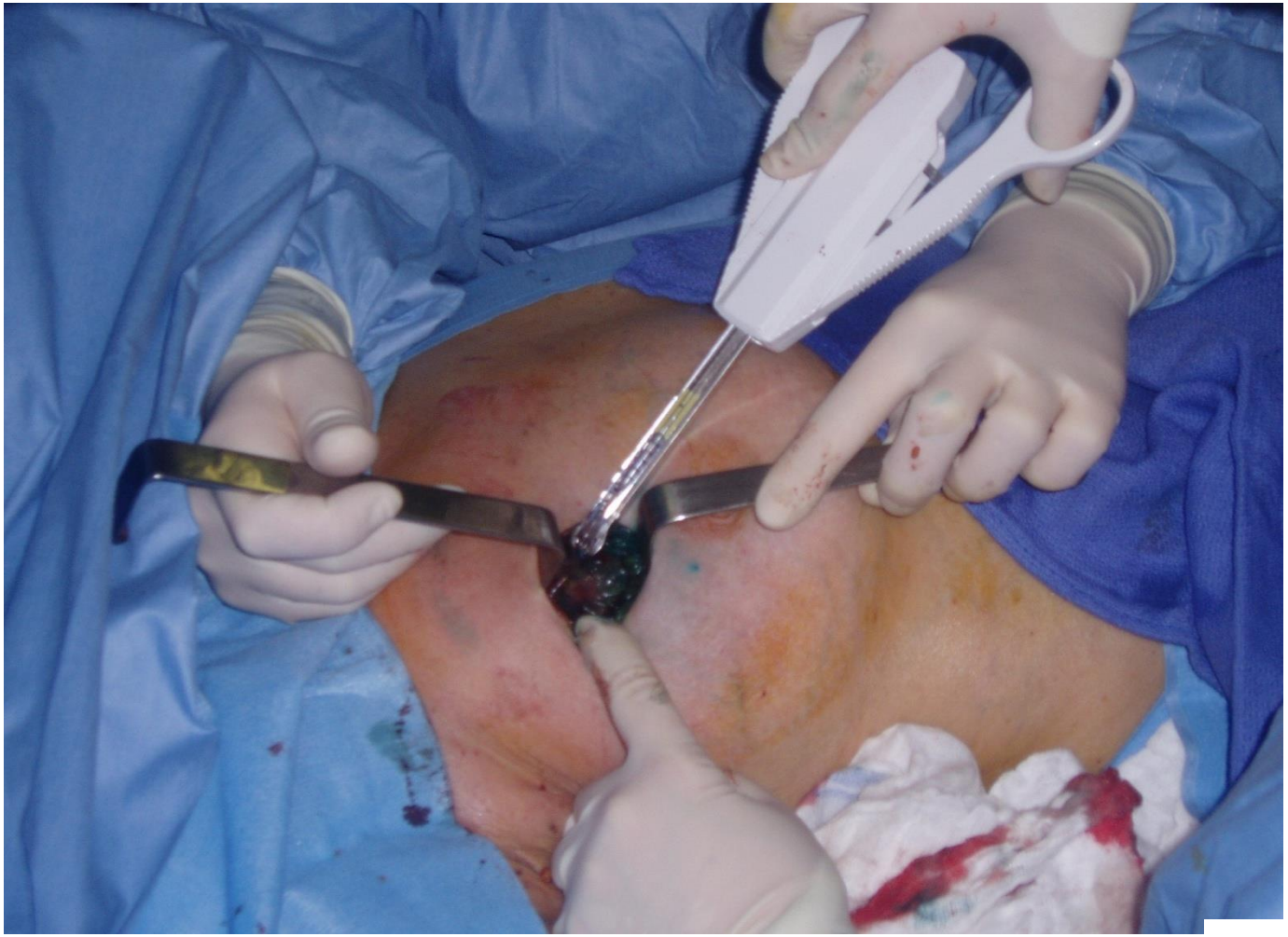
Step 3- Surgery: Tumorectomy - SLN

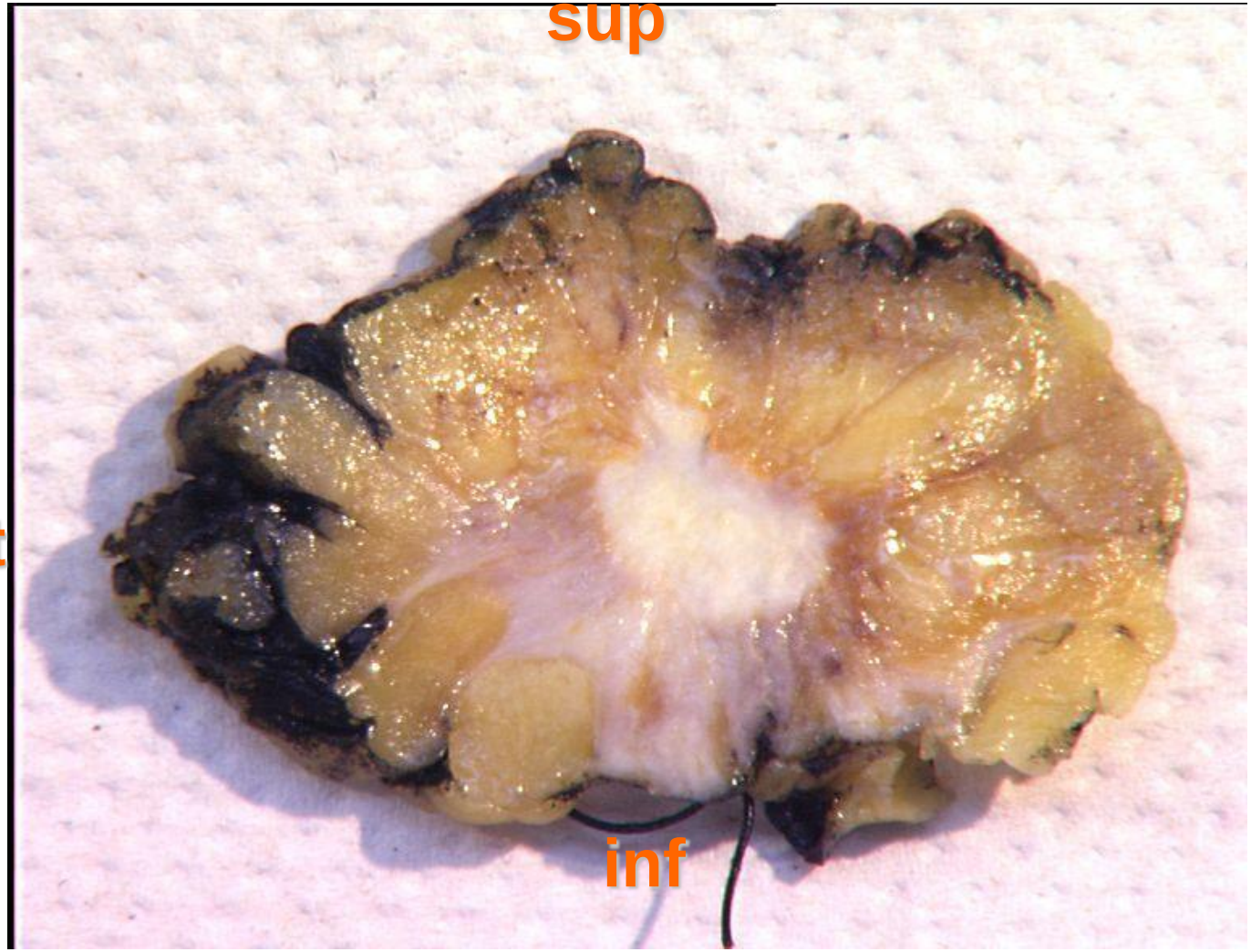


Step 3- Surgery: orientation of the surgical specimen and measurements



Step 3- Surgery: clips with respect of previously discussed protocol

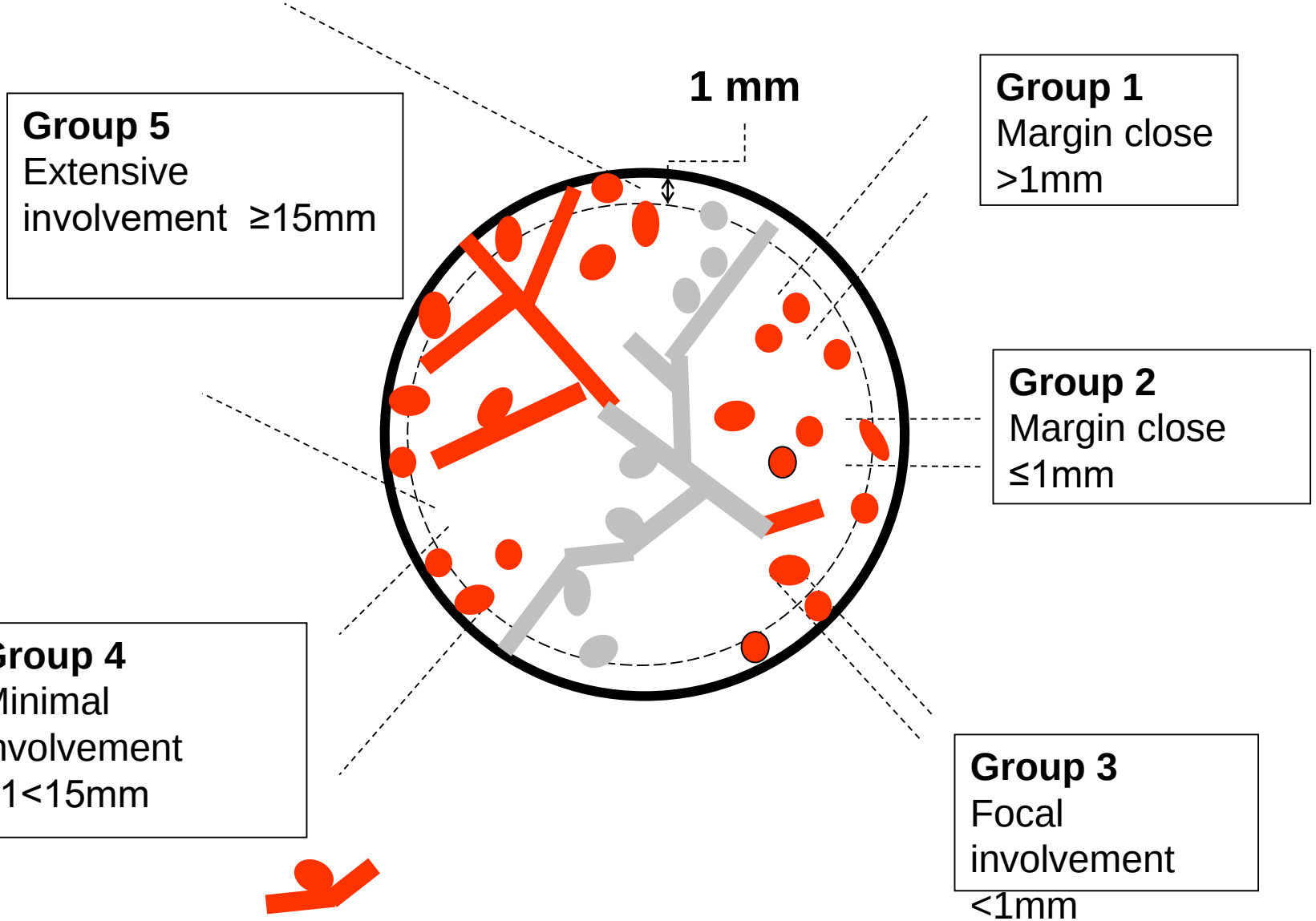




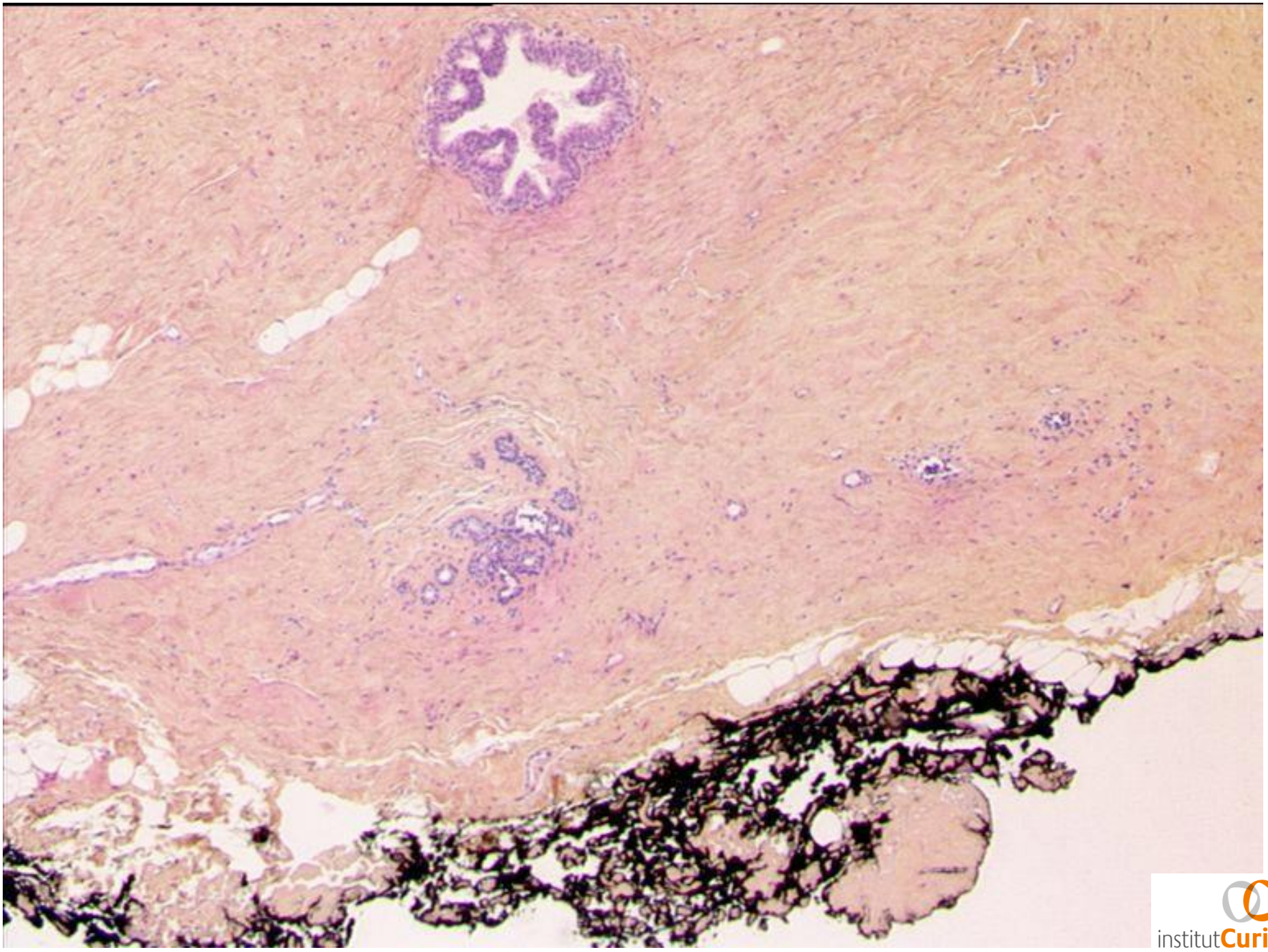
The report of your pathologist is extremely important part of the definition of the boost volume +++

Courtesy Dr Sigal

DCIS: Margins width and focality



Sigal-Zafrani et al. *Mod Pathol*, 2004



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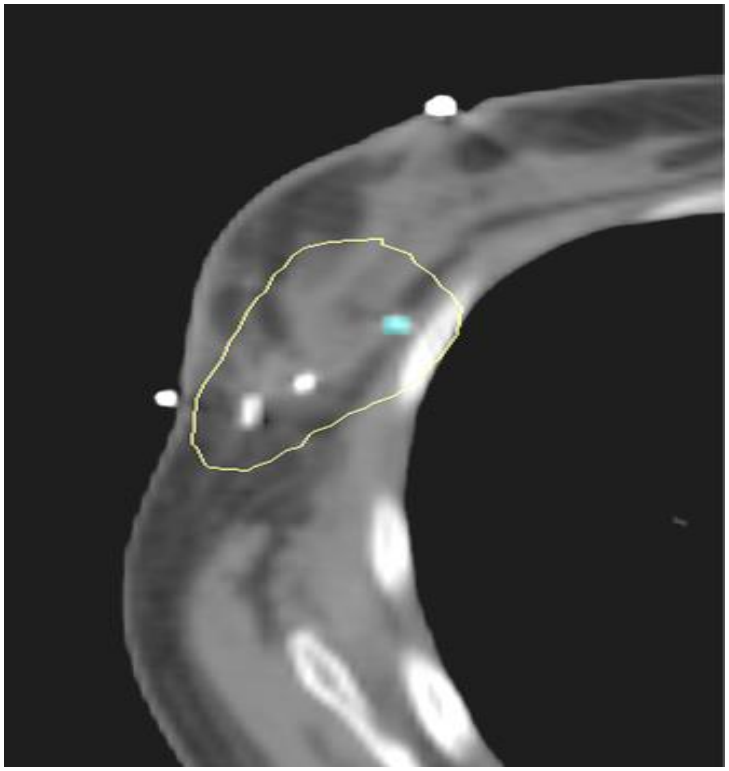
Ensemble, prenons le cancer de vitesse.

Step 4- Post op CT Scan in treatment position 4-5 wks after surgery



Clips' position

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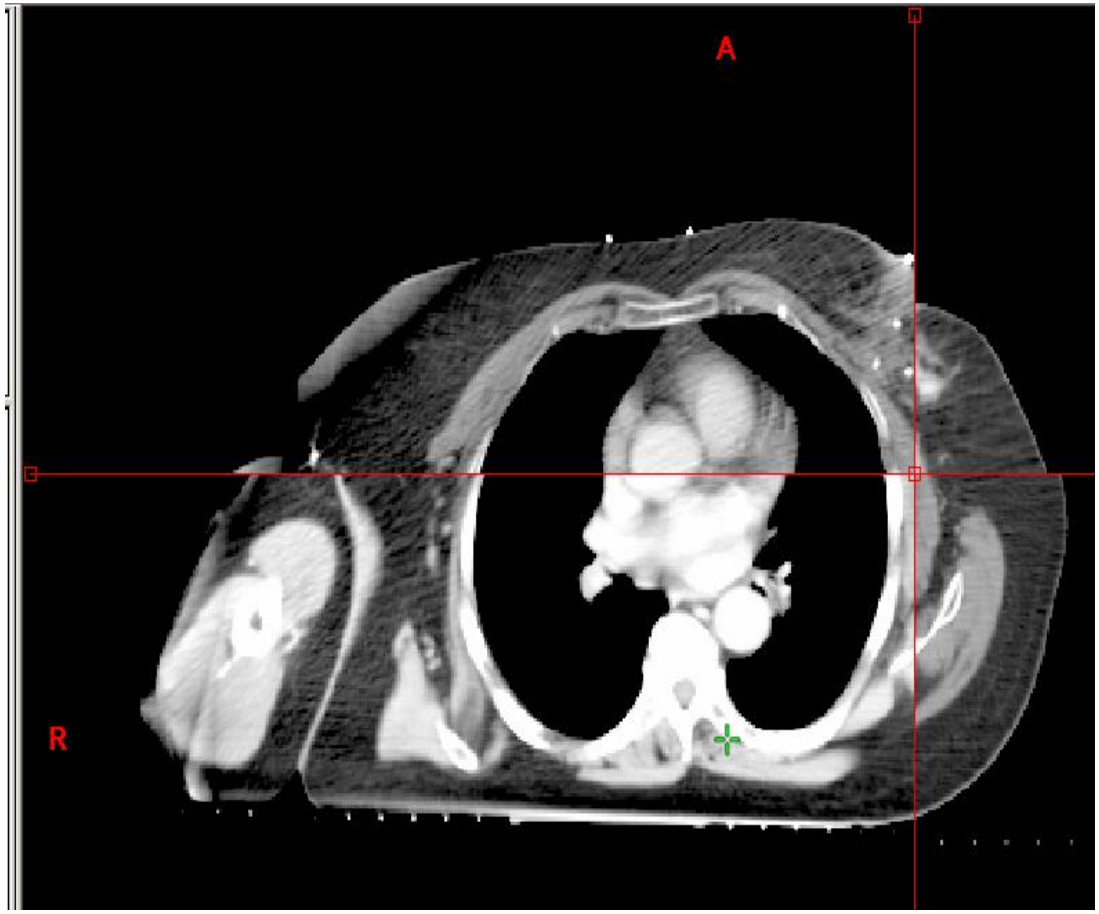
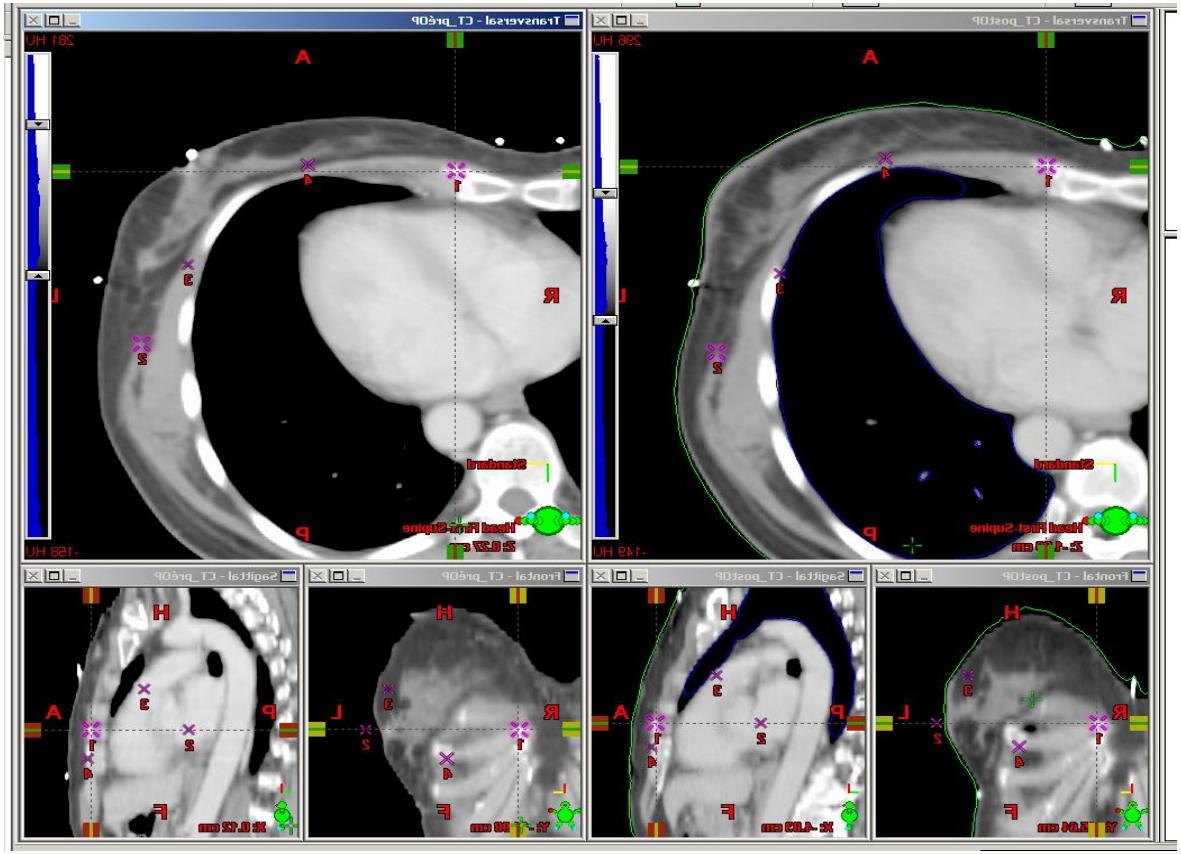
5. Images registration



Edema

Step 5 Pre- and post-operative image registration



Rigid or elastic registration

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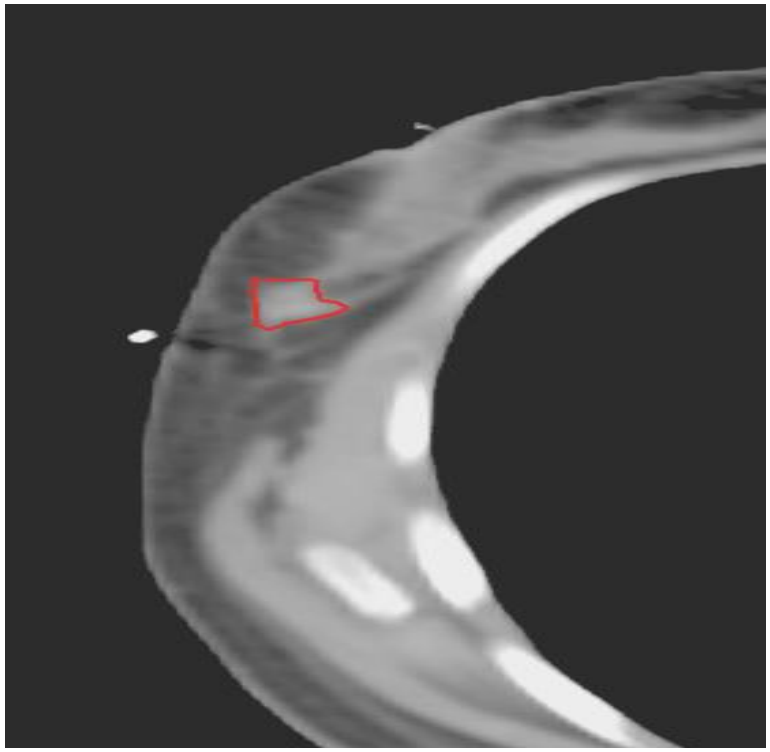
Step 6- Delineation of the tumeur (GTV) on the pre op. CT scan



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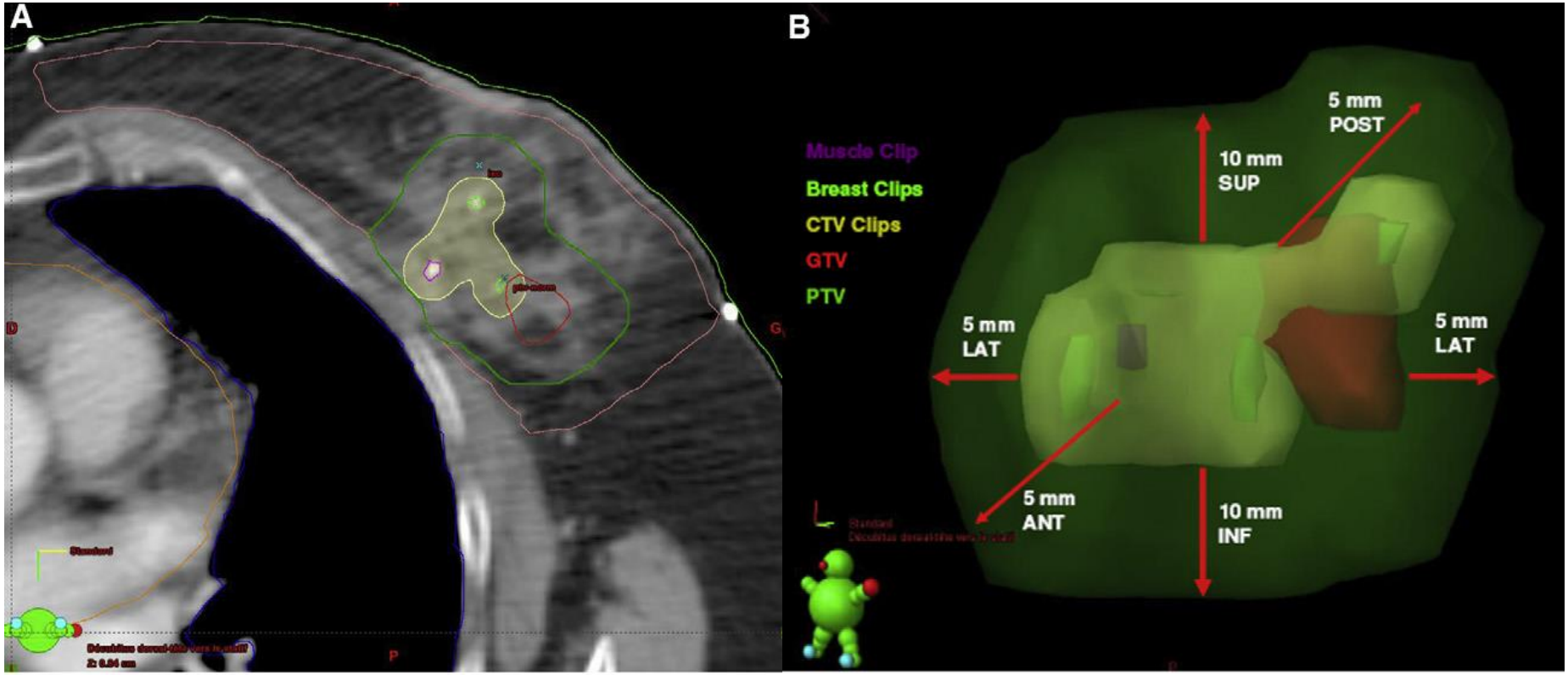
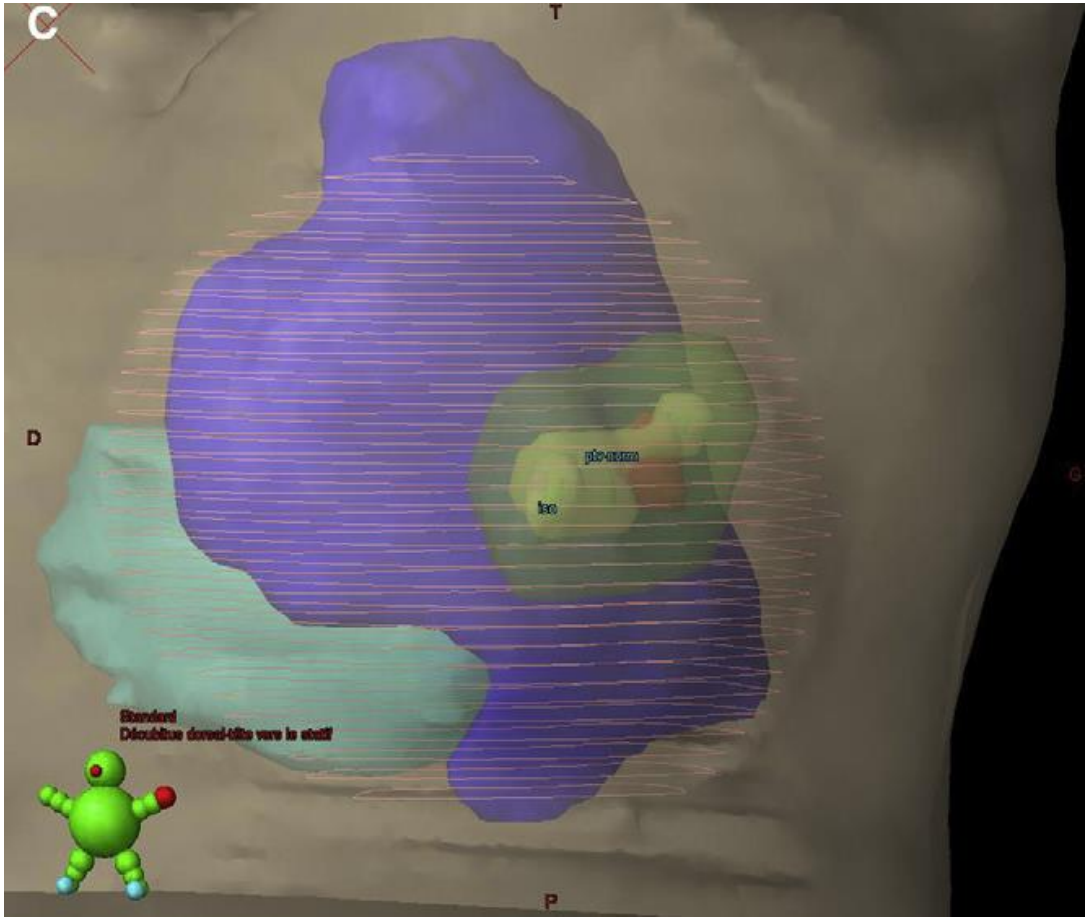
Step 6 - Delineation of the clips CTV and definition of PTV



Kirova et al, IJROBP 2010

3D treatment volumes definition after pre and post operative CT scan in treatment position



Kirova et al, IJROBP, 2008, 2010

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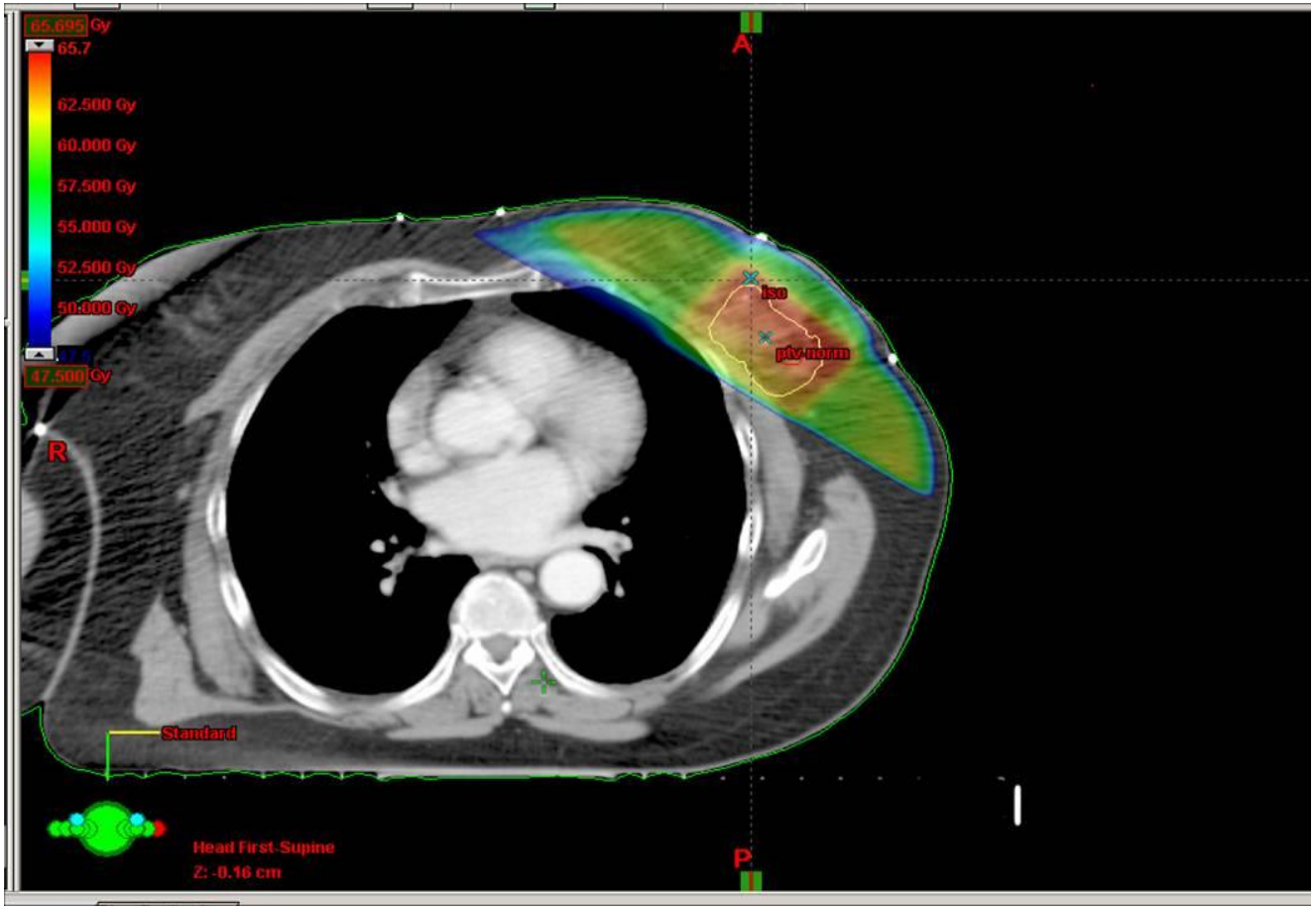
Step 8- Dosimetric work (simplified IMRT) and treatment



Treated by surgery pT1c, pN0 M0, RT to breast and boost,
Followed by TAMOXIFENE

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Practical use of the procedure

Reducing interobserver variation of boost-CTV delineation in breast conserving radiation therapy using a pre-operative CT and delineation guidelines ☆

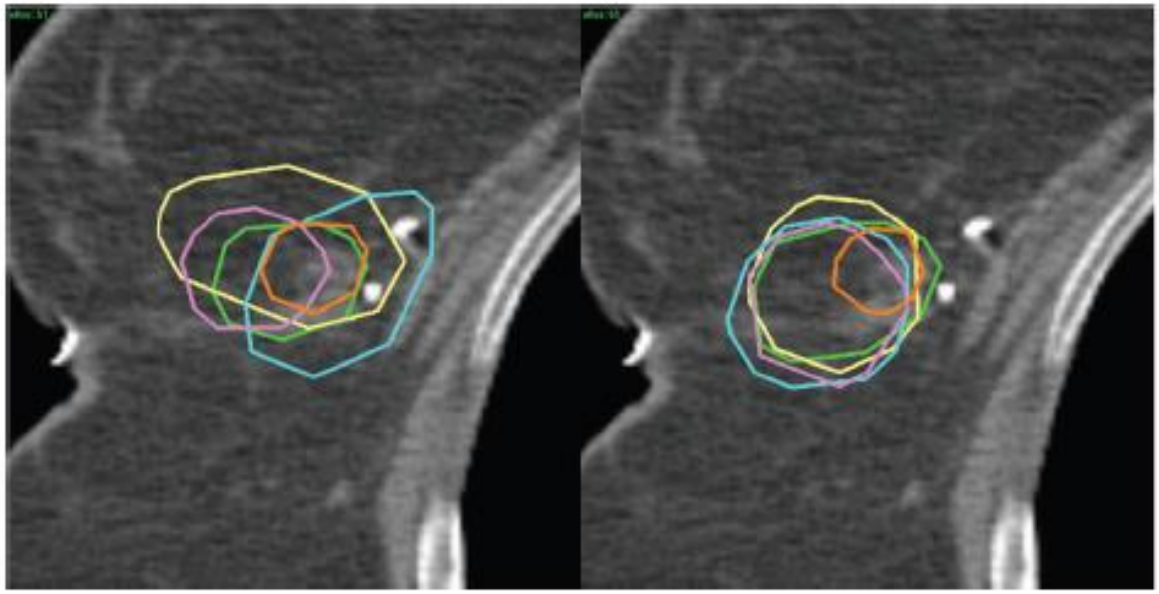
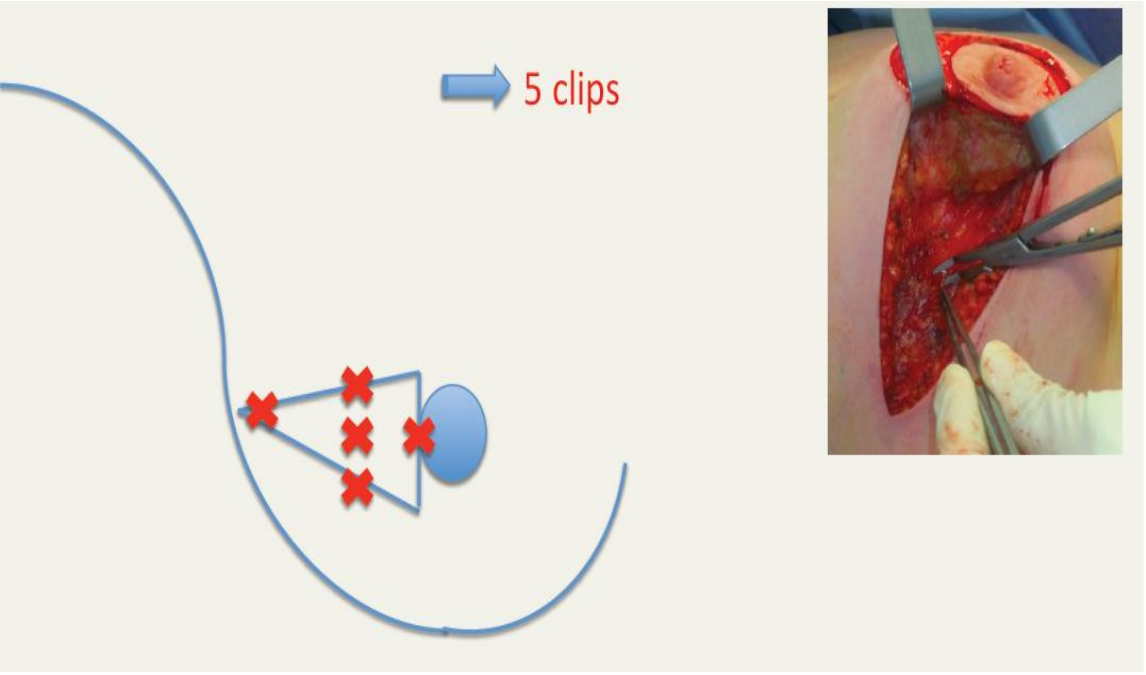
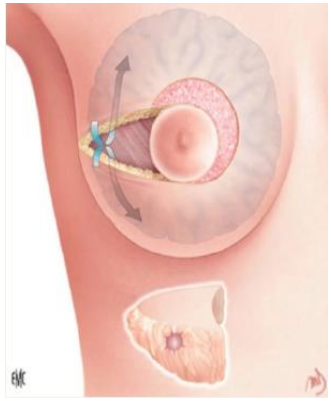


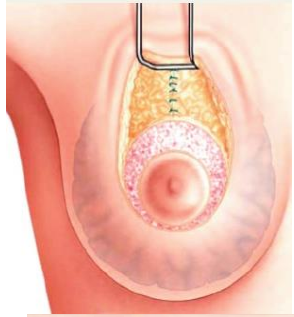
Fig. 1. Example showing the boost-CTV-1 delineations (left) and boost-CTV-2 delineations (right) for a case with GTV consensus and no tumour free margins known. A considerable decrease in interobserver variation can be seen.

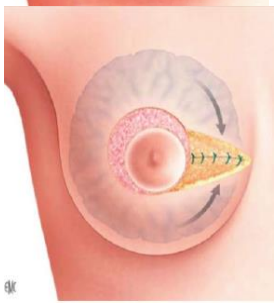
Boersma et al, Radiother Oncol 2012

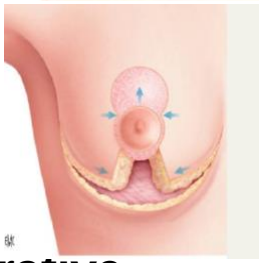
Boost after oncoplastic surgery: specific recommandations











The use of more than 3 clips associated with pre- to post-operative CT image registration allows better definition of the PTV boost volume after oncoplastic surgical procedure and decrease the risk of recurrence and complications.

The multidisciplinary approach with close collaboration between surgeons, pathologists and radiation oncologists is needed

Furet et al, EJSO, 2014

institutCurie
Ensemble, prenons le cancer de vitesse.

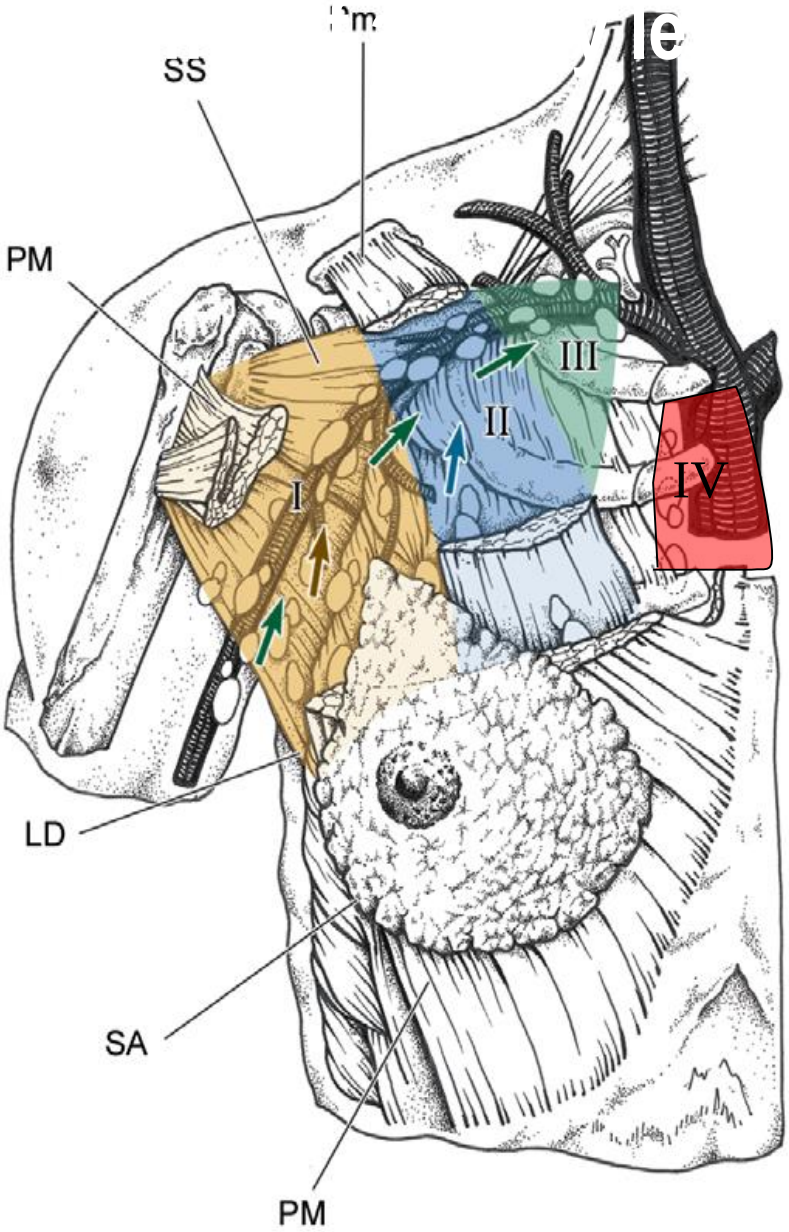
Conclusions Boost

The definition of the tumor bed boost volume is still challenge for different teams and multidisciplinary approach with collaboration of radiation oncologist, surgeon, radiologist, pathologist is recommended as well as written protocols for the clips placement.

This will contribute to substantially reduce long-term toxicity and preserve the cosmesis.

To improve the definition of tumor bed volume, all available methods as the pre- and postoperative image registration, placement of clips protocols, margins information, as well as the post operative deformation have to be used.

Pm: pectoralis minor



Level I

Level II

Level III

Level IV

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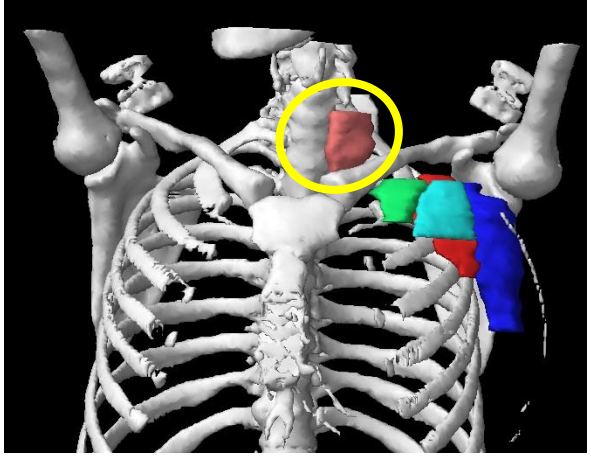

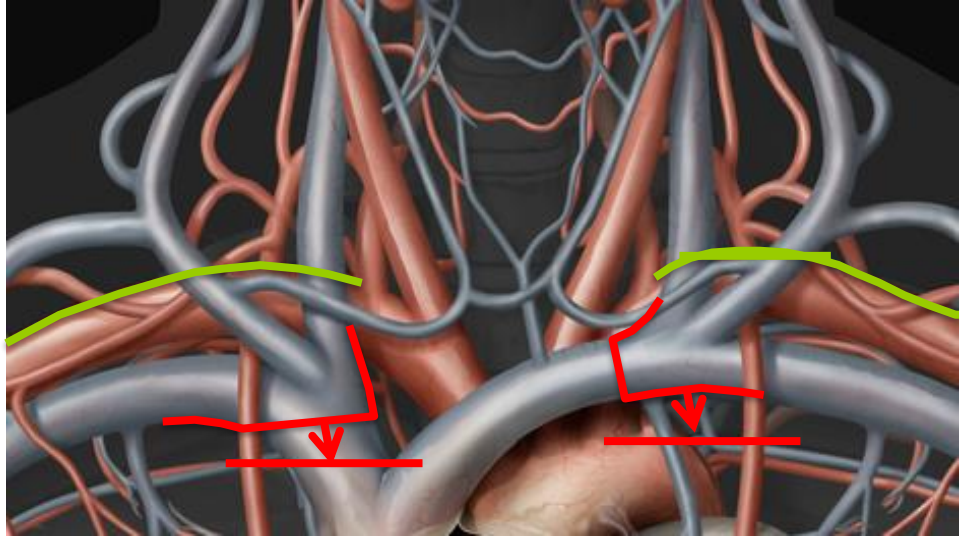

Supraclavicular LN area, CTVn_L4:

- ✓ Superior border: upper limit of subclavian artery
- ✓ Caudal border: 5mm caudal from junction of subclavian and internal jugular veins
- ✓ Ventral border: sternocleidomastoideus muscle, clavicle
- ✓ Dorsal border: Pleura
- ✓ Medial border: including the jugular vein without margin; excluding the thyroid gland and the common carotid artery
- ✓ Lateral border: includes the anterior scalene muscle, and connects to medial border CTVn L3

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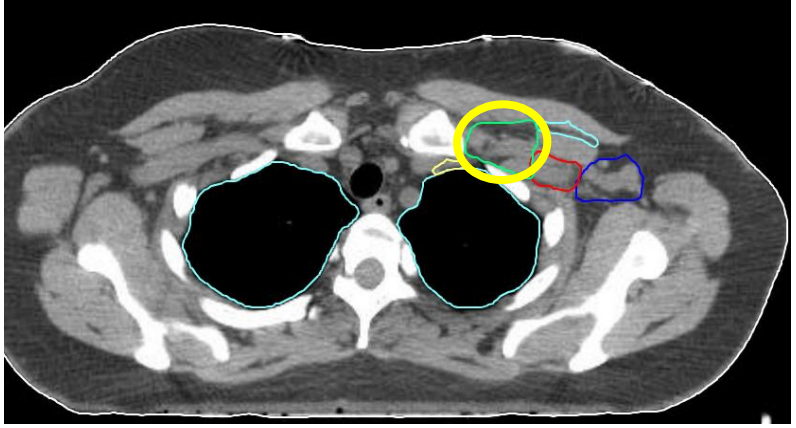
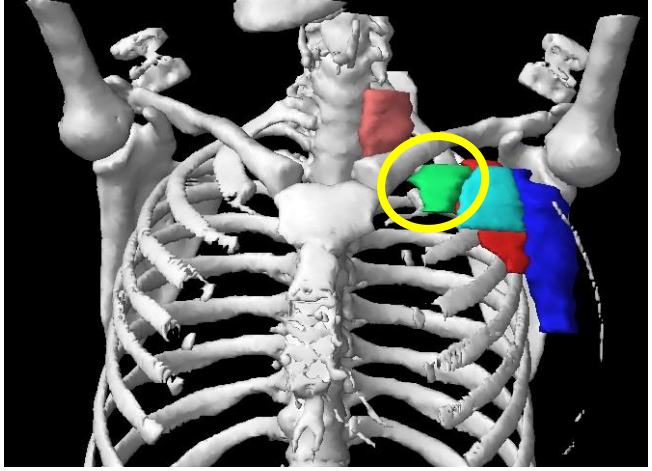
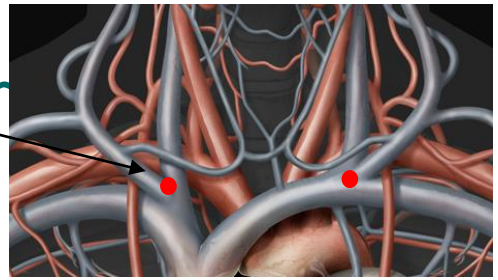




Axilla level 3 (infraclavicular) – CTVn_L3:

- ✓ Cranial border: 5 mm cranial of the subclavian vein. More medially it is the clavicle
- ✓ Caudal border: 5 mm below the subclavian vein
- ✓ Lateral border: medial side of the pectoralis minor muscle
- ✓ Medial border: junction of subclavian and jugular vein
- ✓ Ventral border: pectoralis major muscle
- ✓ Dorsal border: up to 5mm post. of subclavian/axillary vein



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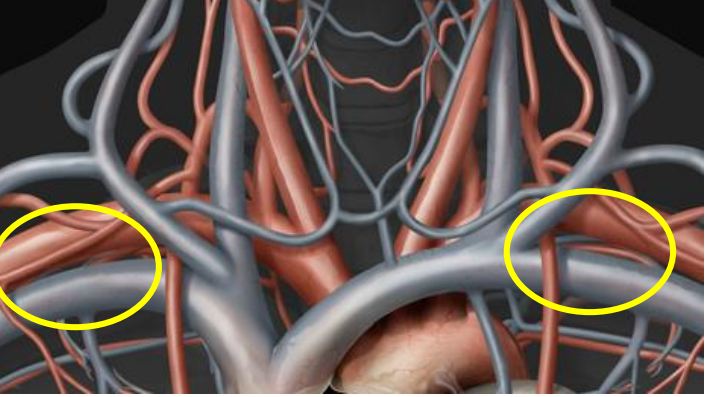
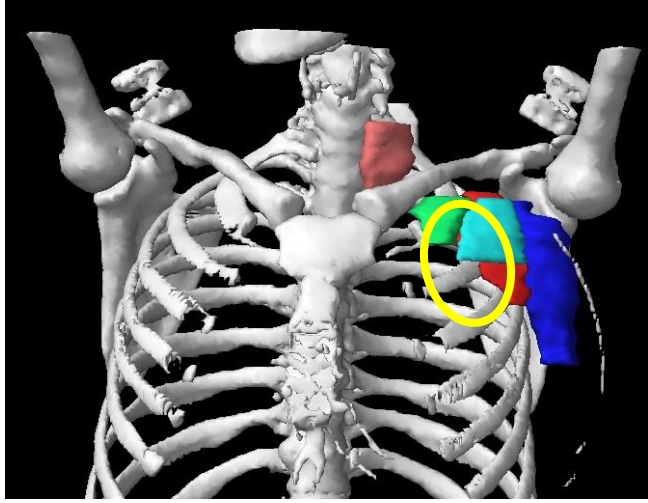
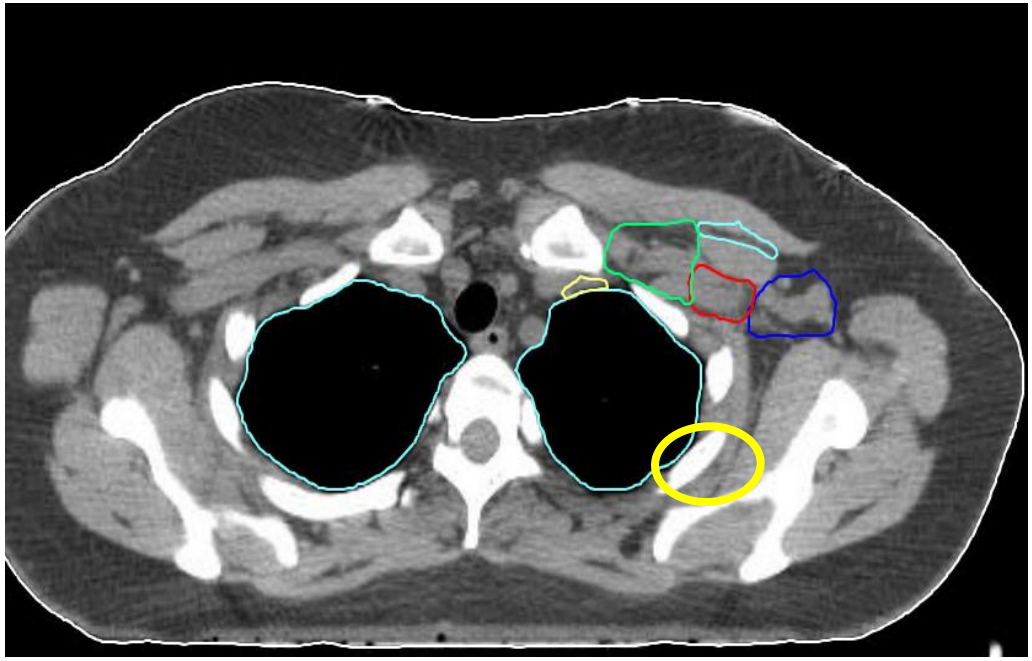




Axilla level 2 – CTVn_L2

- ✓ In between levels 1 and 3
- ✓ Dorsal of minor pectoral muscle
- ✓ Cranial/Dorsal: 5 mm around axillary vein
- ✓ Caudal: dorsal of minor pectoral muscle



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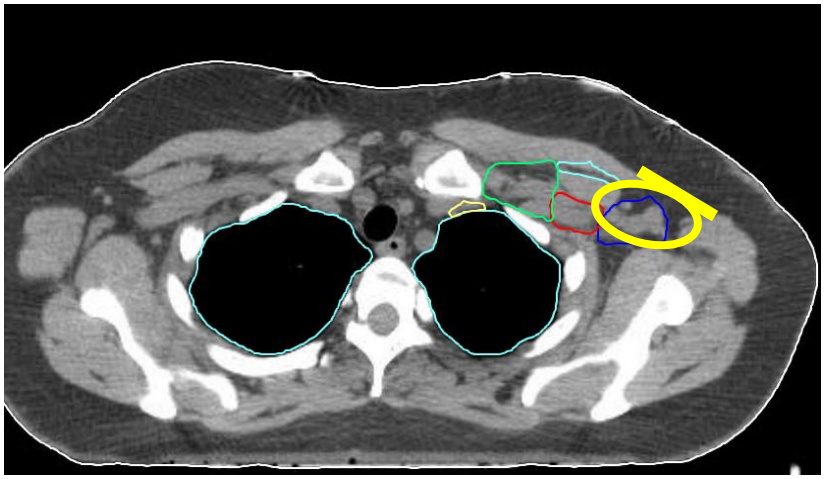

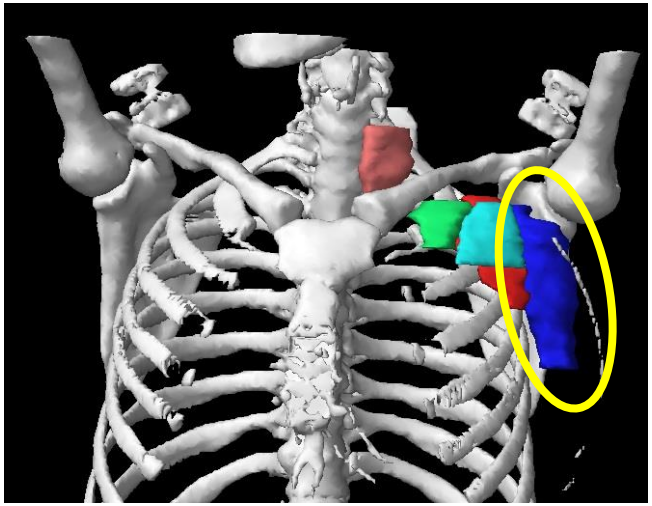

Axilla level 1- CTVn_L1:

- ✓ General: use surgical effects to guide
- ✓ Cranio-medial: lateral limit of level 2/ interpectoral nodes
- ✓ Cranio-lateral: up to 1 cm below and following edge of caput humeri, OR where axillary vein crosses the minor pectoral muscle; 5mm around axillary vein
- ✓ Caudal border: between the level of ribs 4 – 5
- ✓ Lateral border: up to superficial part of muscles **(line)**
- ✓ Medial border: level 2 and thoracic wall
- ✓ Ventral border: pectoralis major & minor muscles
- ✓ Dorsal border: up to the posterior blood vessels

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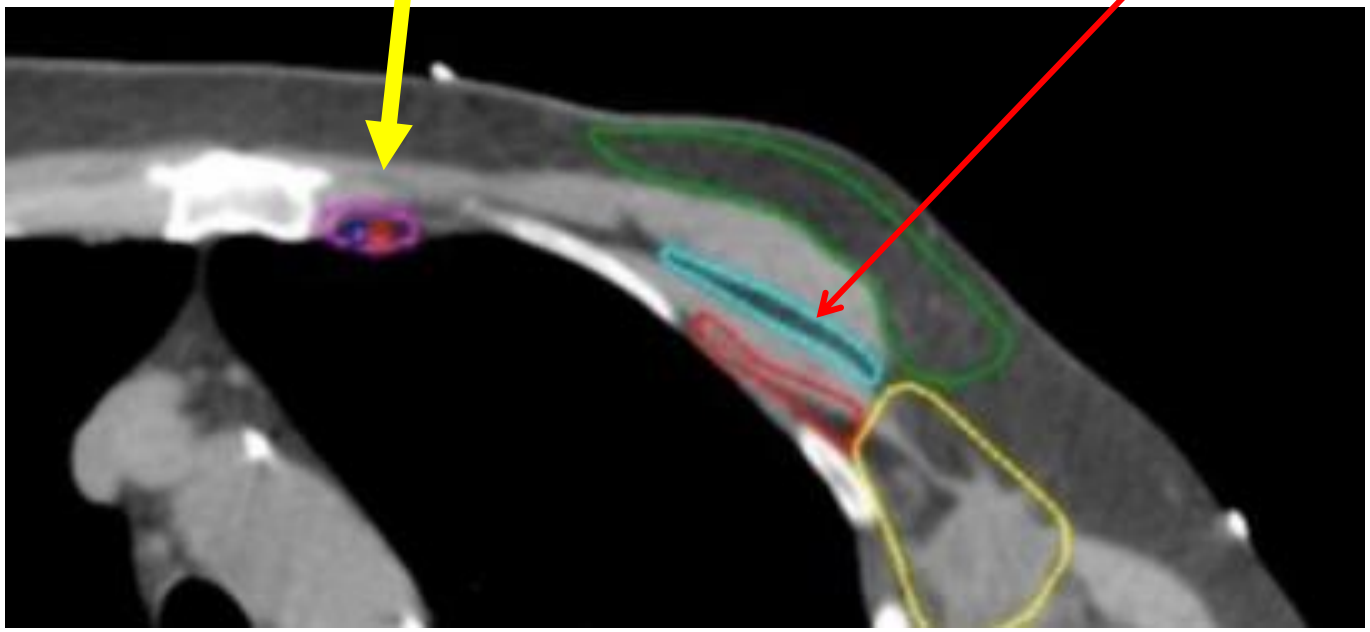
CTV of internal mammary lymph node area

- ✓ Cranial: junction of subclavian and internal jugular veins → *L4*
- ✓ Caudal: superior side of the 4th rib
- ✓ Ventral: anterior limit of the vascular area
- ✓ Medial: 5 mm medial of vessels; edge of the sternal bone
- ✓ Dorsal: pleura
- ✓ Lateral: 5 mm lateral of vessels

Intrapectoral LN=Rotter



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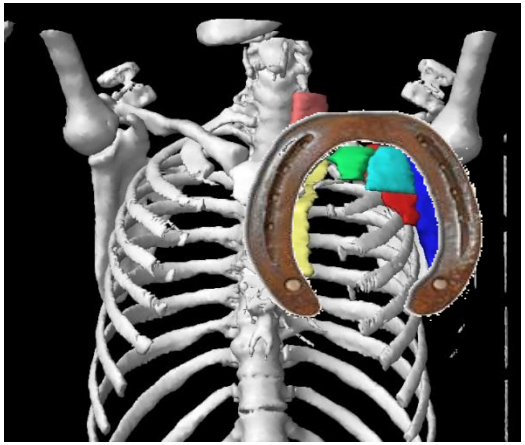
Conclusions for LN volumes

- General rule for LN areas: veins+ 5mm margin in surrounding fatty tissue.
- IV contrast ➔ facilitates ➔
- for learning but not required.
- Normal anatomy atlas = more than helpful.
- Coronal views: very helpful as well !
- Lymph node regions should all interconnect.
- Some discussion points left:
  - Are we ready to leave a gap between PTVs of primary tumor and LN areas ?



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Recent comments on RTOG atlases (& probably also valid for ESTRO atlas):

- In case of massive involvement supraclavicular nodes: nodes extend beyond CTVn_L4 → should atlas be adapted ? (*Brown et al, IJRBOP 2015; Jing et al IJRBOP 2015)*
- To cover 95% of lymph nodes at cranial and anterior borders of level 1, CTVn_L1 should be increased considerably: i.e. take into account nodal involvement seen before surgery/ chemotherapy *(Gentile et al, IJRBOP 2015).*
- *NB: ESTRO guidelines are meant for elective irradiation of early stage breast cancer; i.e. in case of clinically overt pathological nodes: individualise target volume delineation !*

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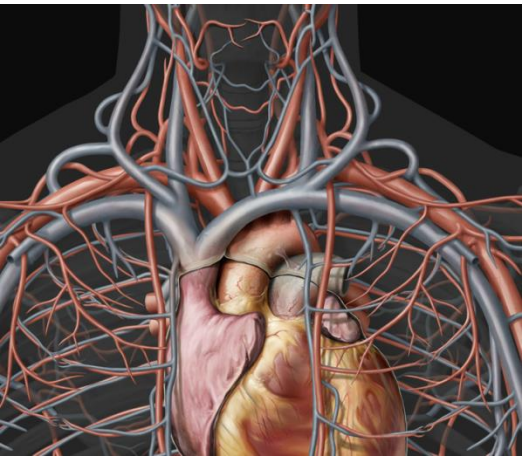
General considerations

- We don’t have clinical reason to increase field size compared to the old standard fields.

  ➔ mind resulting field size/including OAR!

  ➔a margin of 5 mm from CTV to PTV should be sufficient (if adequate fixation as well as a carefully designed IGRT procedure are used)



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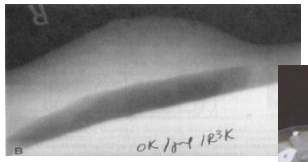
Technological developments should aim at:

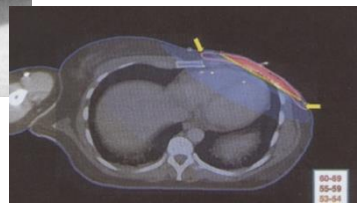
1. More precisely defining target volumes, with the help of imaging
2. Ensuring an optimal, homogeneous coverage of target volumes
3. Avoiding or limiting unnecessary irradiation of organs at risk
4. Ensuring a precise day-to-day set-up reproducibility

Emergence of new techniques in breast cancer RT

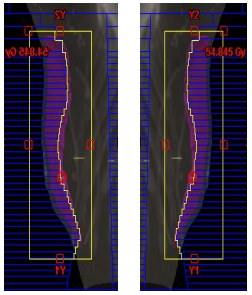
2D RT



3D RT



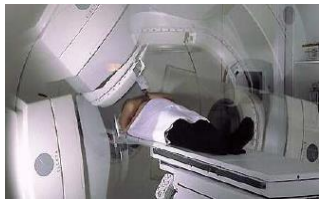
Simplified IMRT with forward planning



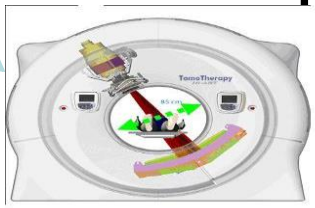
IMRT with inverse planning

IMRT

VMAT



Tomotherapy



Increasing complexity

1990

2013

Clinical relevance and patients benefit?

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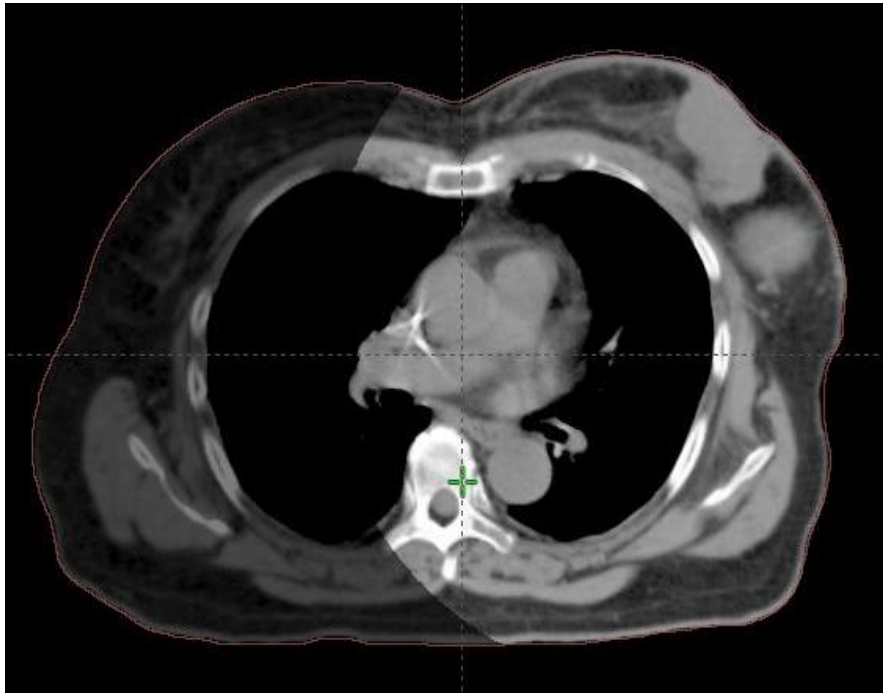
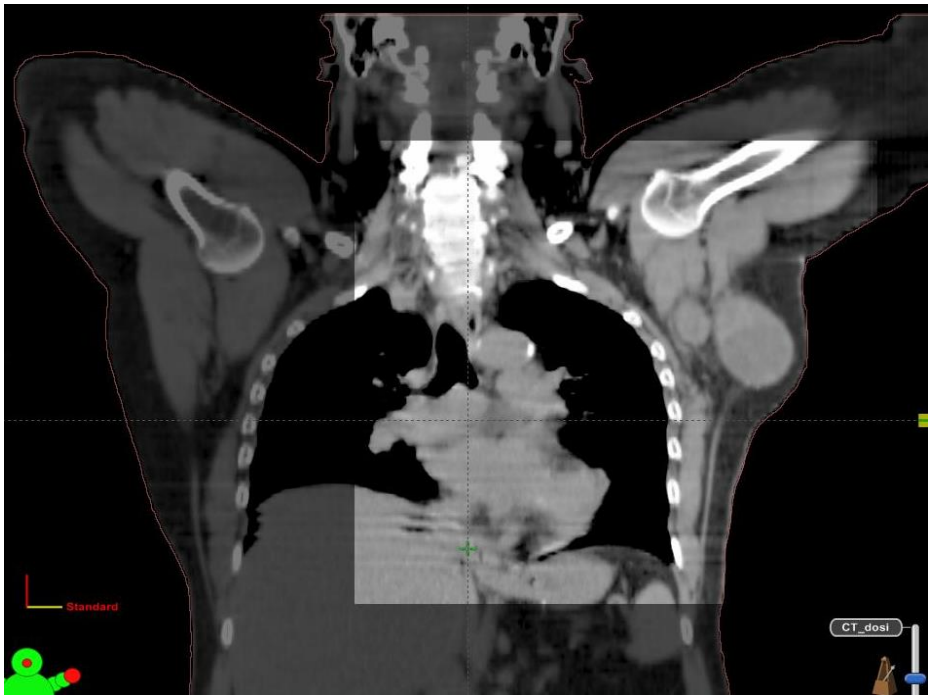
Breast irradiation: challenges
First: homogeneity

Case and question

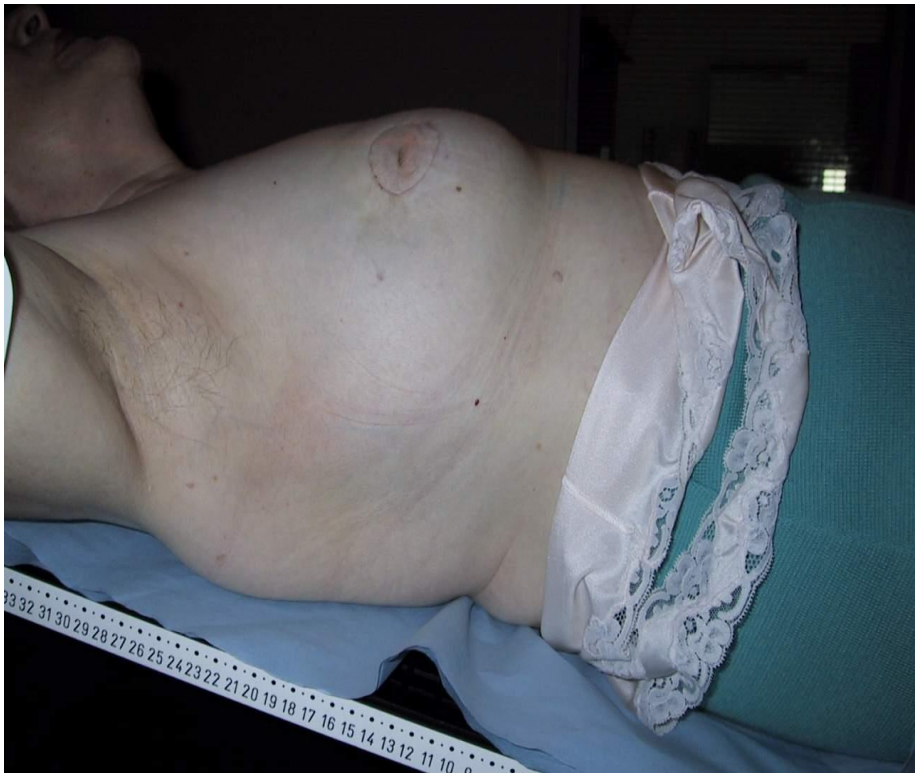
How you will this T4N3 patient?

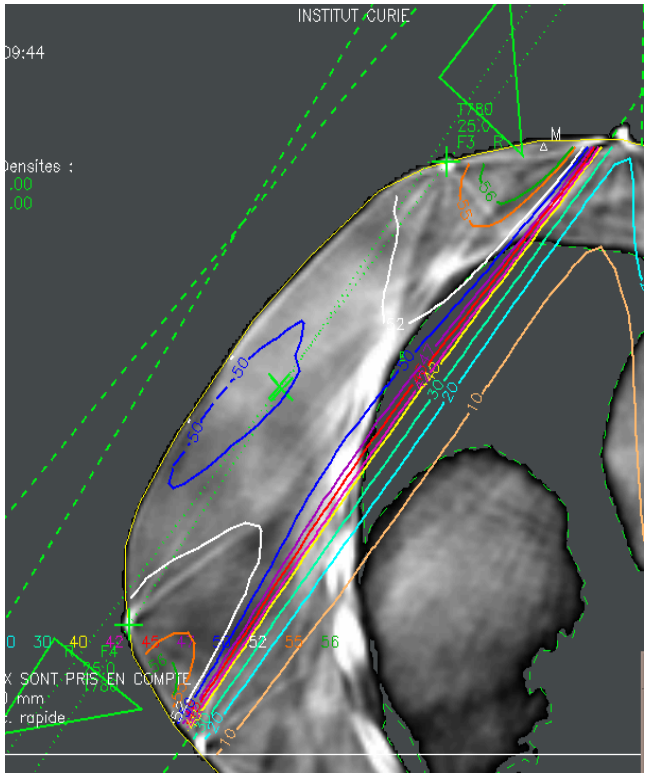
- After non response to chemotherapy, patient adressed for preoperative radiotherapy?





Heterogeneity of dose distribution





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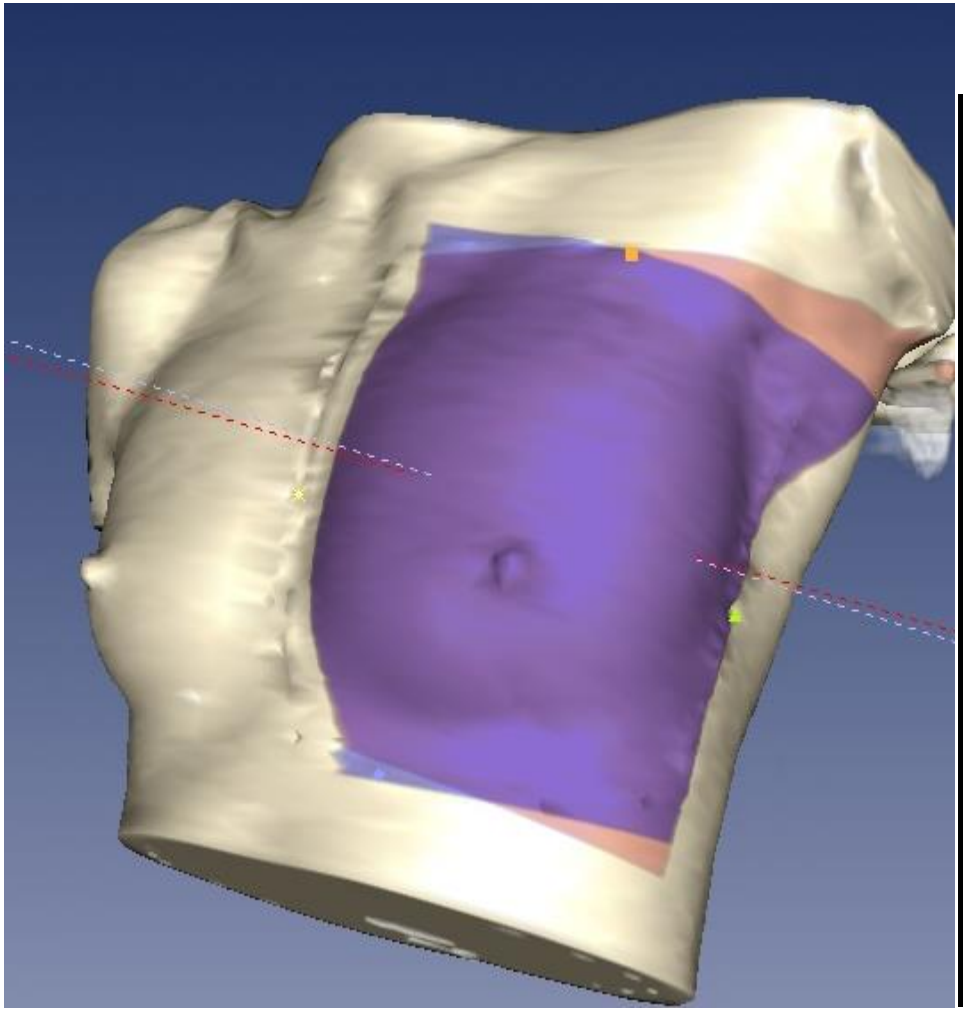
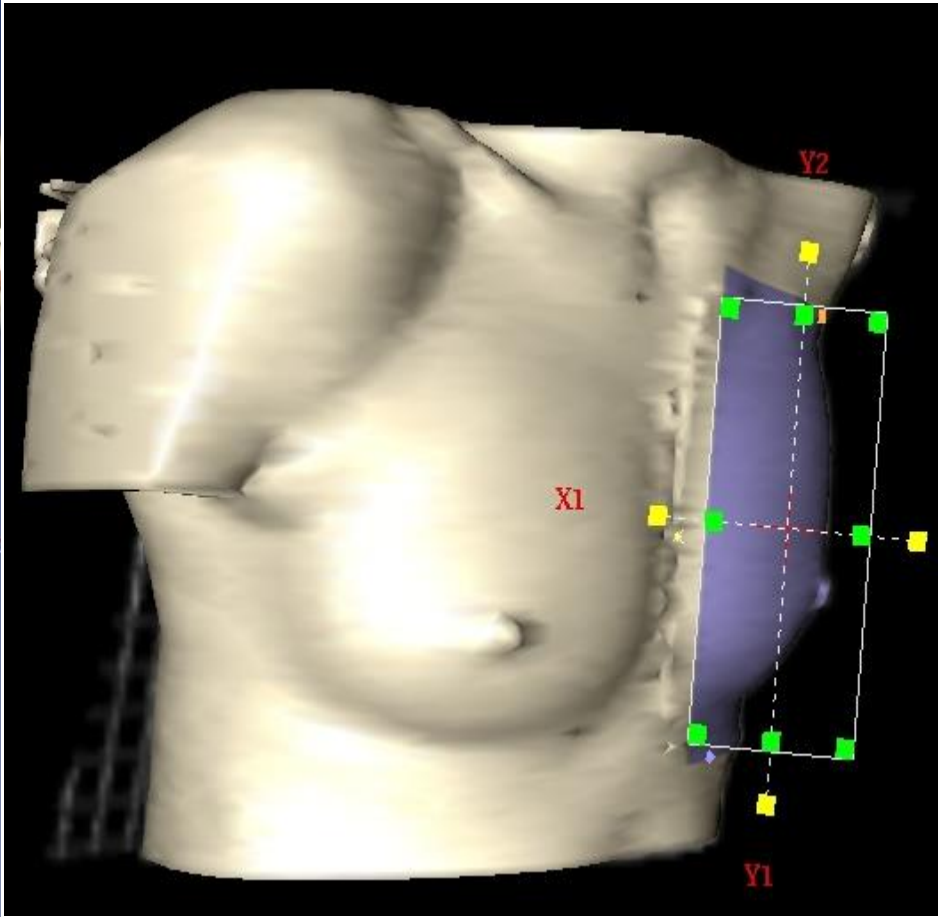
Compensation of dose heterogeneity

- 3D CT planning
- Standard tangential opposed beam irradiation with wedge filters
- Electronic compensation, intensity modulation and rotational techniques
- Alternative treatment positions

Virtual simulation





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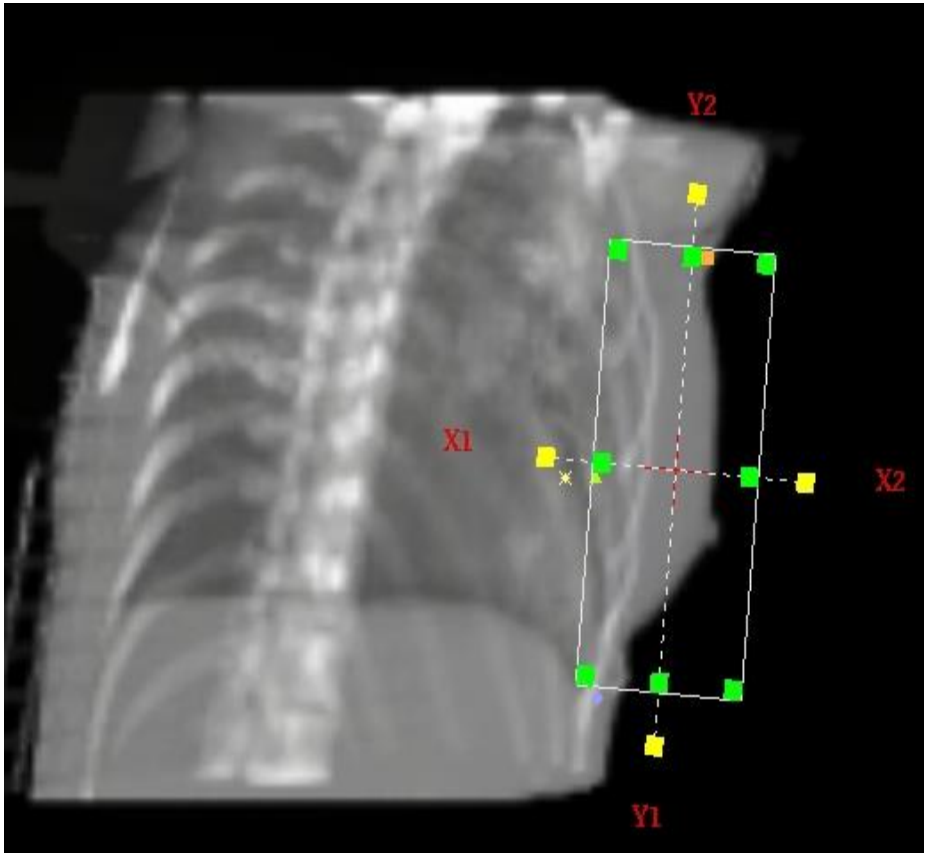
Digital reconstructed radiography. DRR



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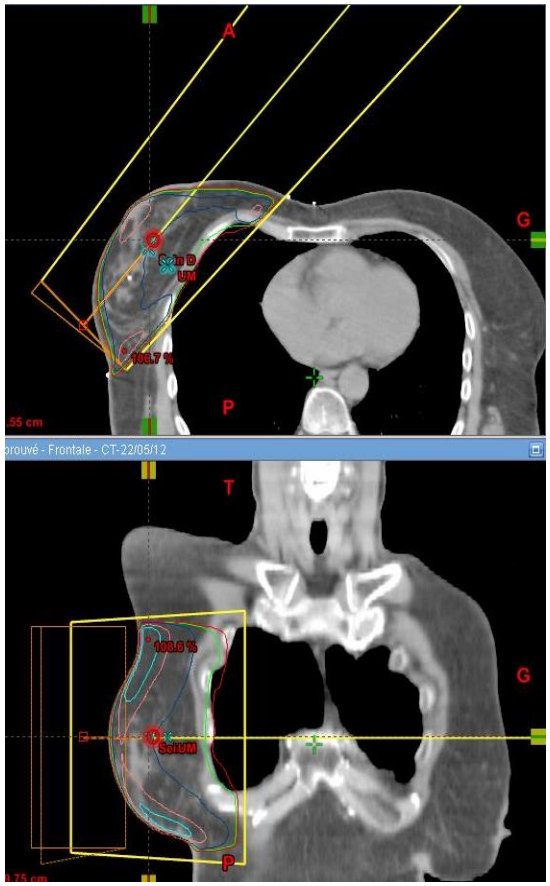
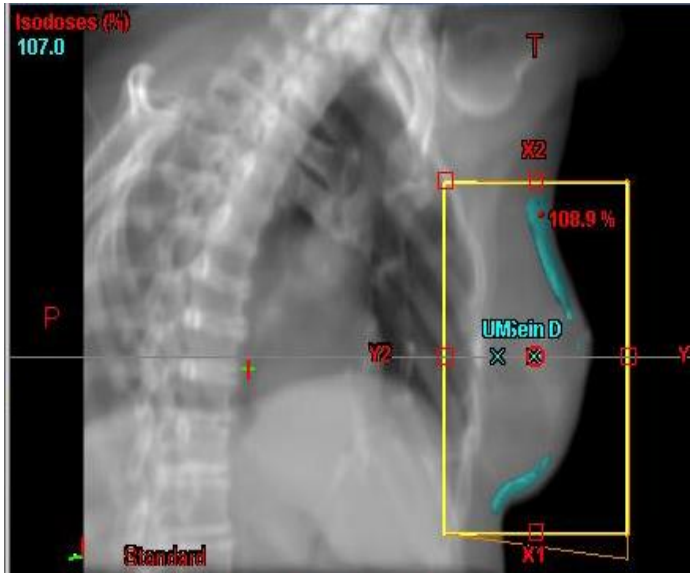
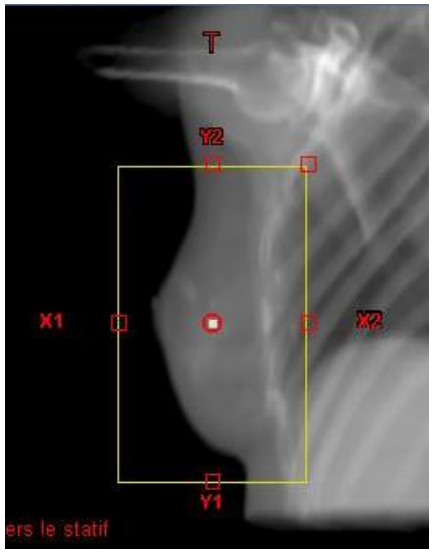
Simplified IMRT with a field-in-field technique

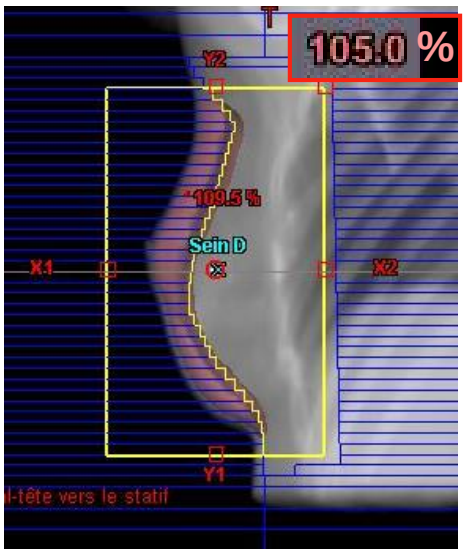


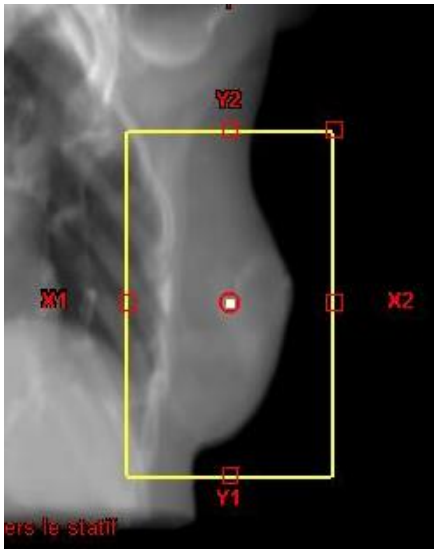


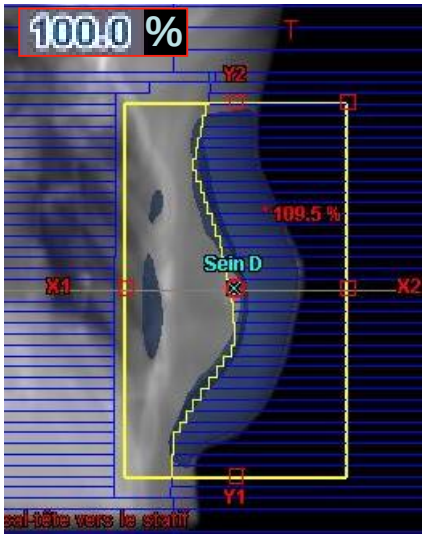
Fournier-Bidoz et al. *Medical Dosimetry*, 2012

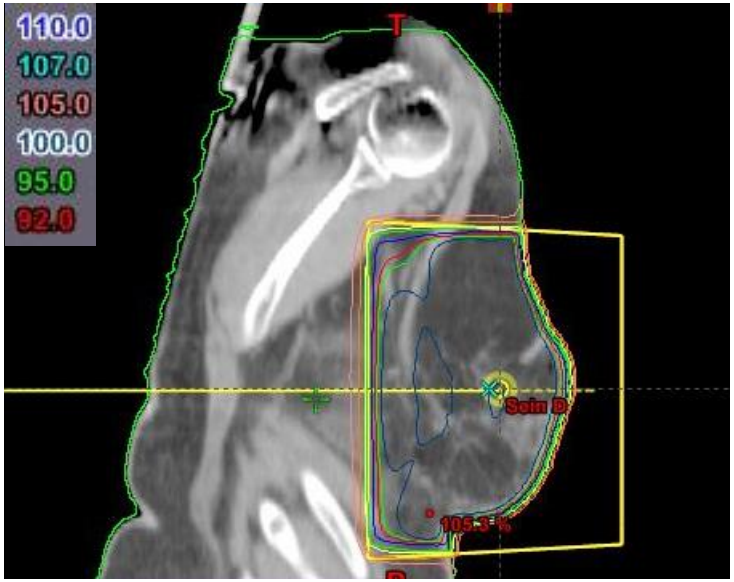
Field in field technique











Fournier-Bidoz et al. *Medical Dosimetry*, 2012

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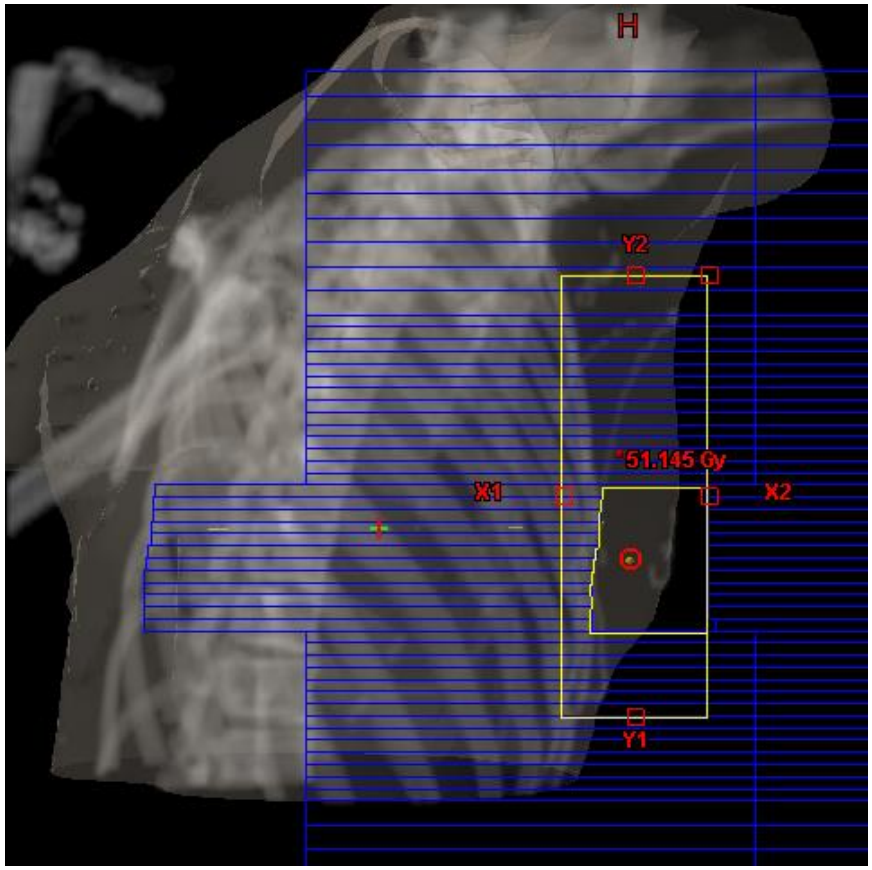
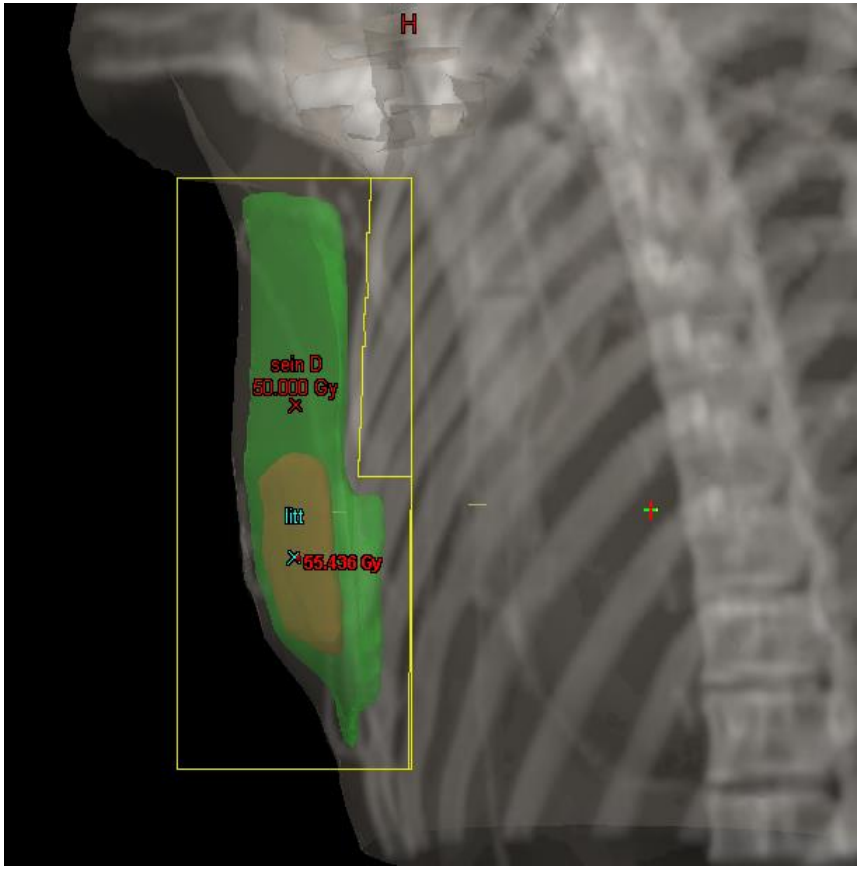
Simultaneous integrated boost





Fournier-Bidoz et al. *Medical Dosimetry*, 2012

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Randomized Trial of IMRT vs. Standard Wedge for Breast Irradiation

- 358 patients
- 50 Gy/25 fractions ± boost 16 Gy/8

	Standard wedge	IMRT	p
Moist desquamation (all)	48%	31%	0.002
Moist desquamation (IMF)	43%	26%	0.001

Pignol et al. *Int J Radiation Oncology Biol Phys*, 2006

Randomized Trial of IMRT vs. Standard RT in early breast cancer

- 306 patients
- 50 Gy/25 fractions ± boost 11 Gy/5

	Standard	IMRT	p
> 20% of breast >105% of dose	15%	1%	0.005
Worsen in breast appearance	58%	40%	0.008
Central breast fibrosis	32%	21%	0.02

Donovan et al. *Radiother Oncol*, 2007

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Simplified IMRT vs Standard 2D

- **1145 pts**
- **Standard tangents**
- **Randomisation if ≥ 2 cm^3 received > 107%**
  - **Standard vs**
  - **Forward planned simplified IMRT**
- **At 2 years**
  - **More telangectasia in 2D**
  - **Impaired cosmesis in poor post surgical results**

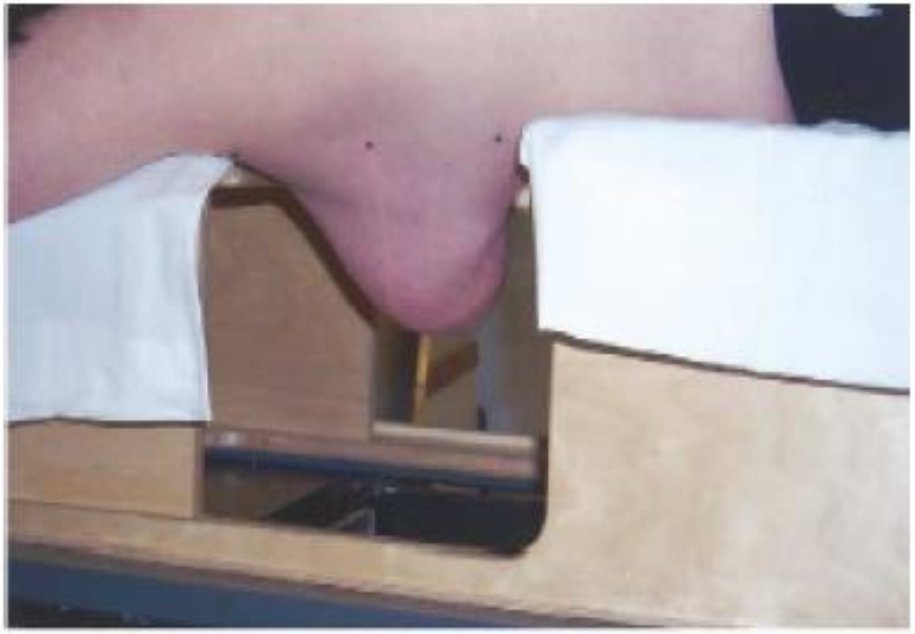
Barnett et al. *Int J Radiation Oncol Biol Phys*, 2011

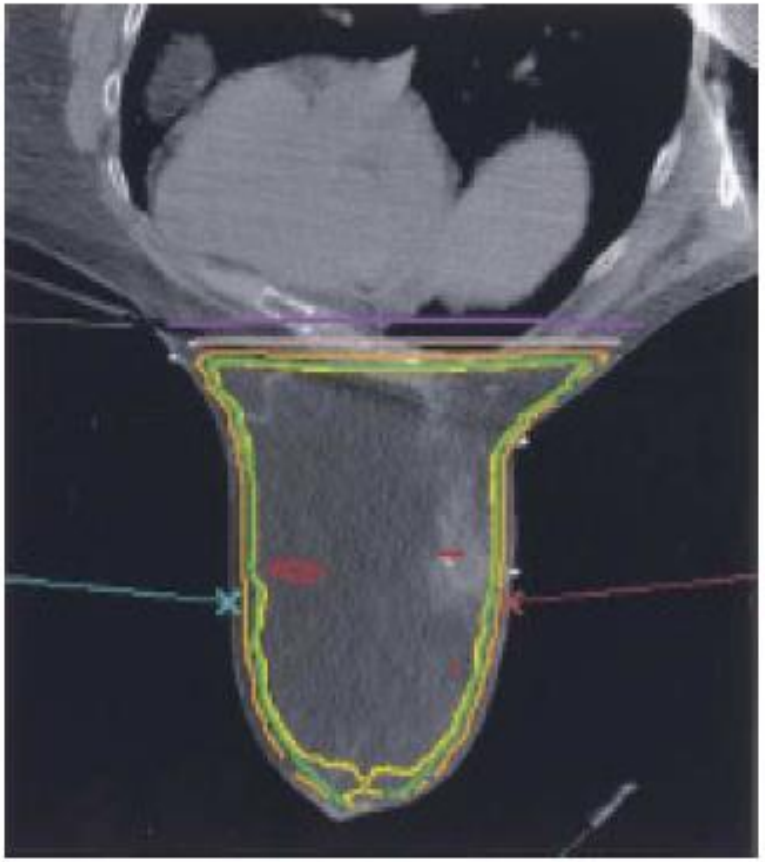
Breast irradiation in difficult situations or alternative techniques to obtain better dose distribution and reduce the doses to OAR

- Patients with large and pendulous breasts
- Bilateral breast irradiation
- Pectus excavatum

Alternative techniques

Prone

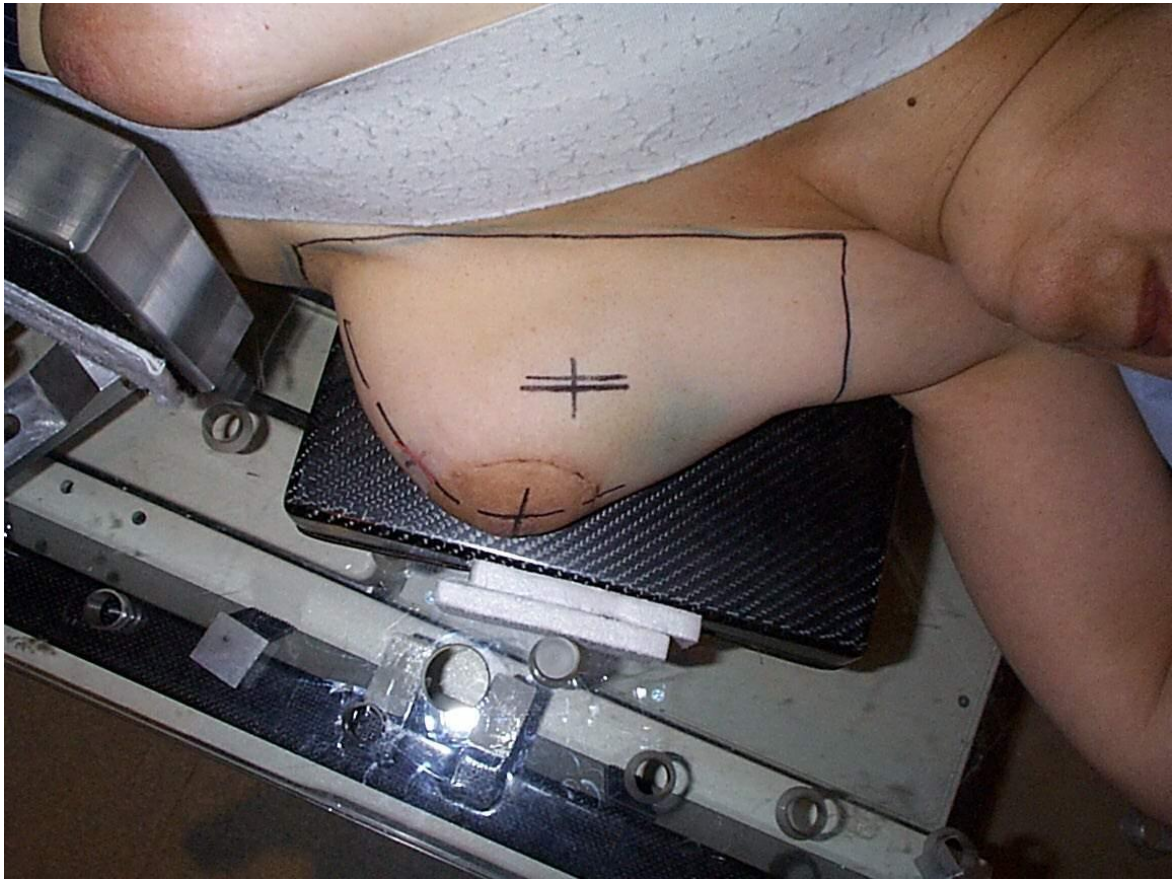




Memorial Sloan-Kettering, New York

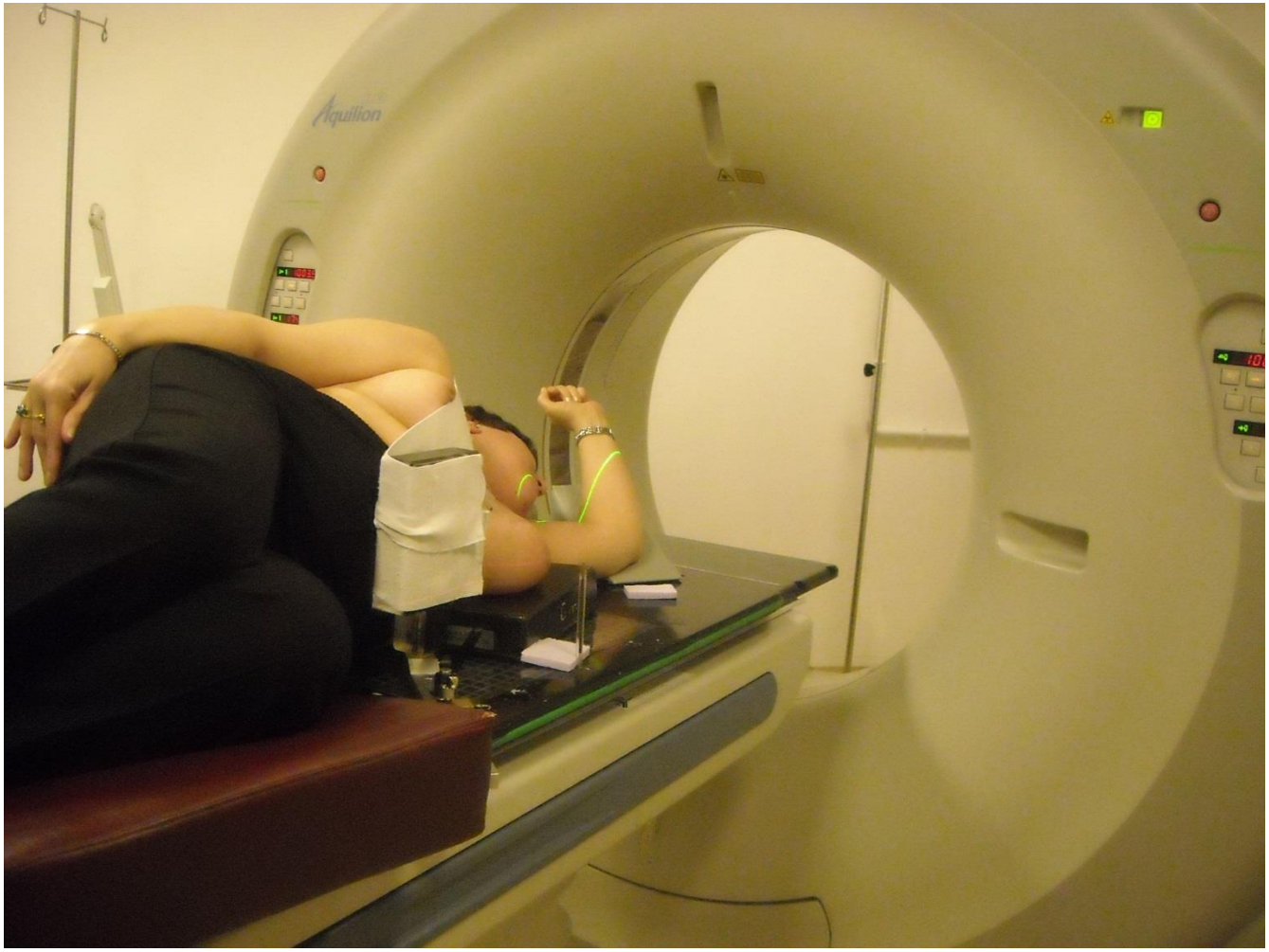
Goodman et al *Int J Radiation Oncology Biol Phys* 2004

Lateral decubitus

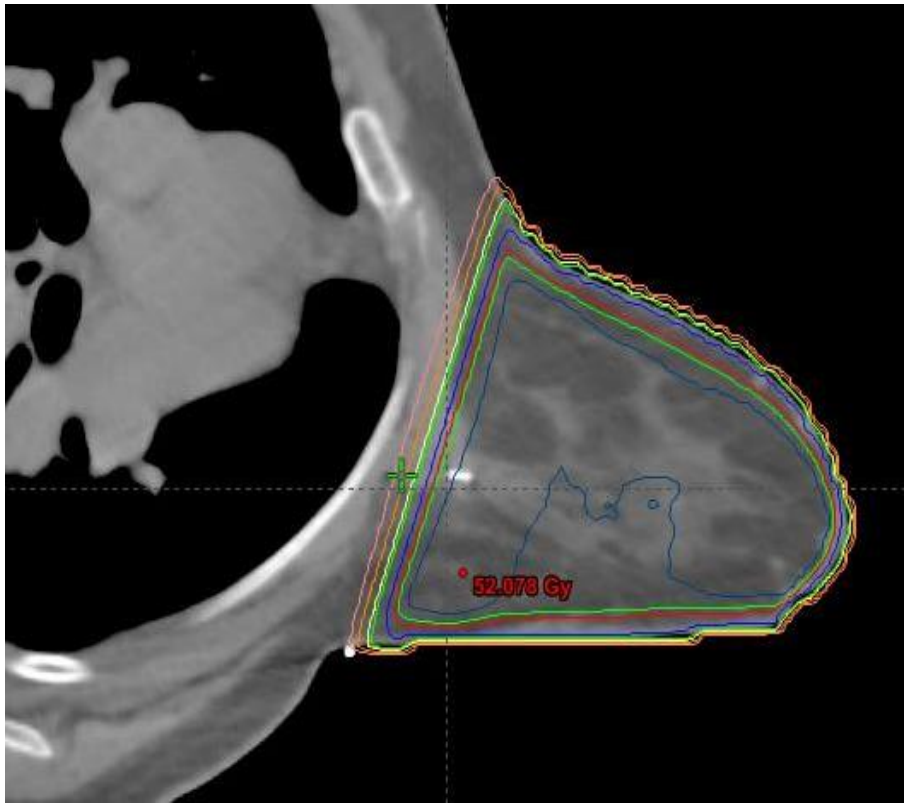


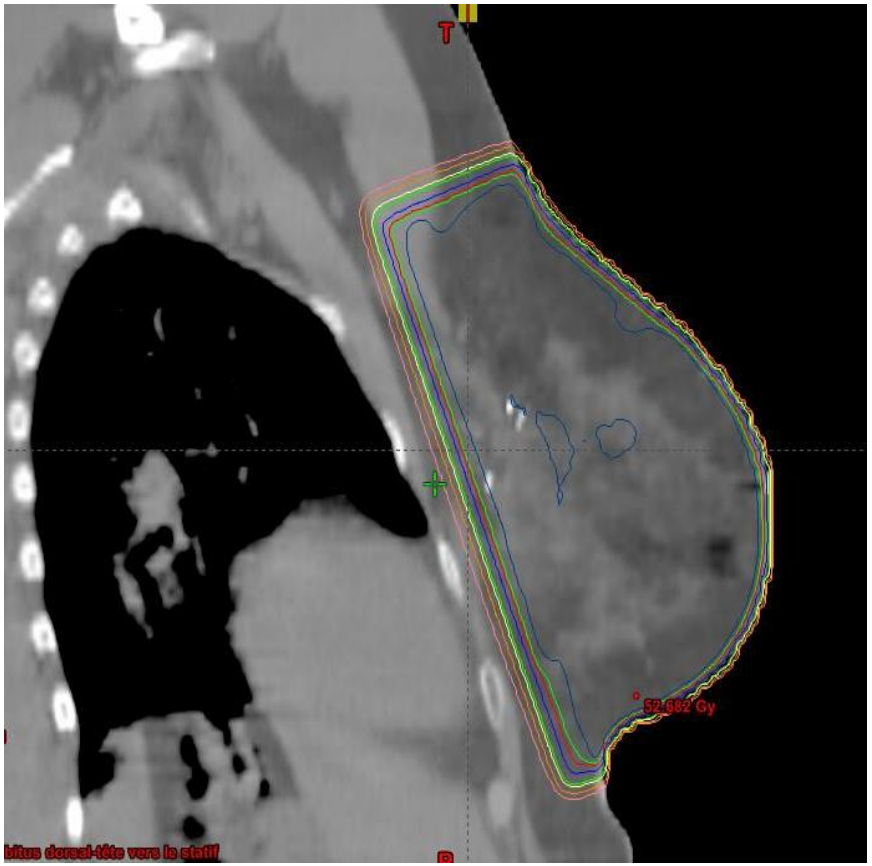
Kirova et al, Radiother Oncol 2013

Large Bore CT-Scan



Dosimetry. Whole breast





50 Gy

47.5 Gy

25 Gy

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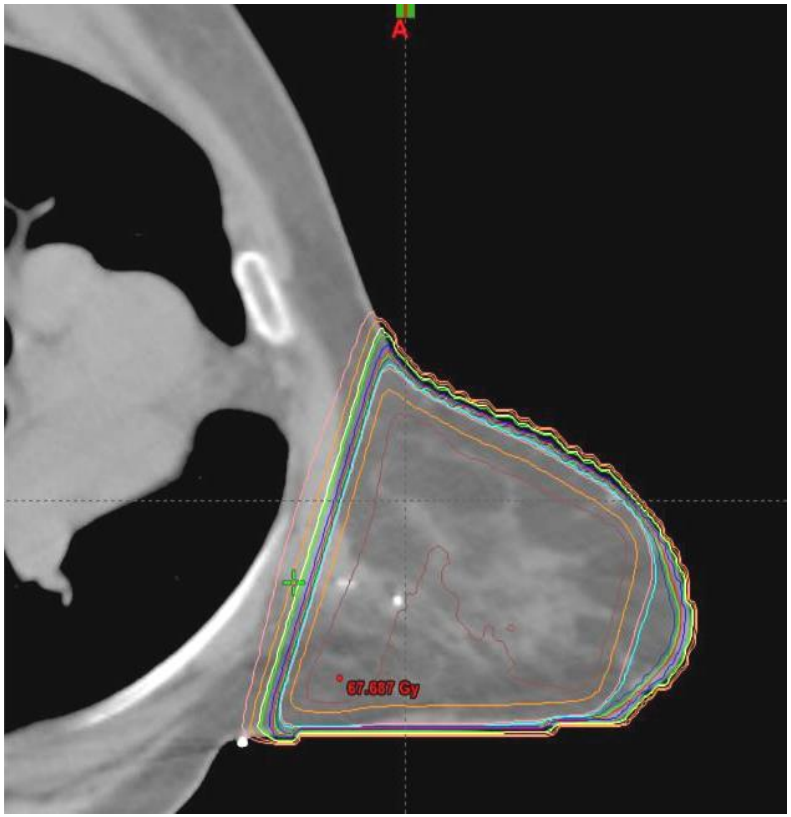
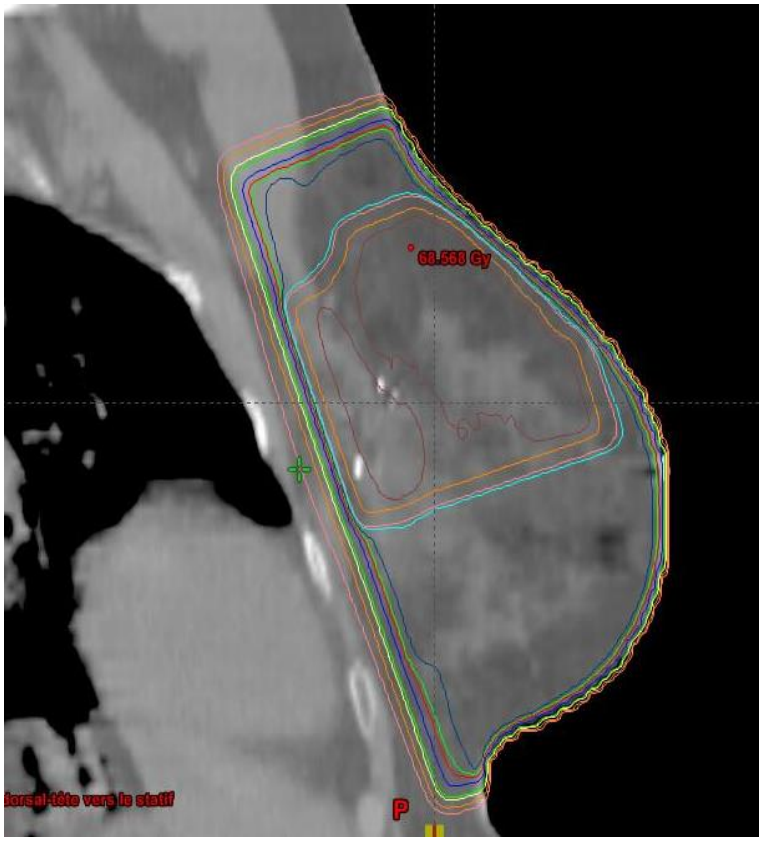
Ensemble, prenons le cancer de vitesse.

Breast 50 Gy + boost 16 Gy





66 Gy
62.7 Gy
53.5 Gy
50 Gy
47.5 Gy
25 Gy

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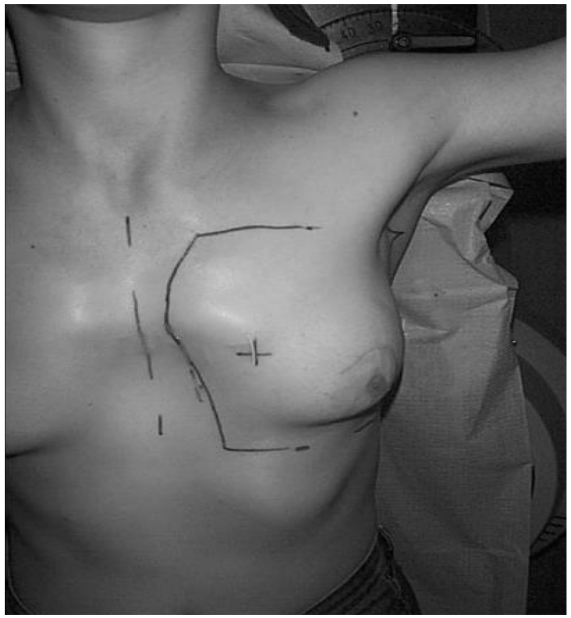
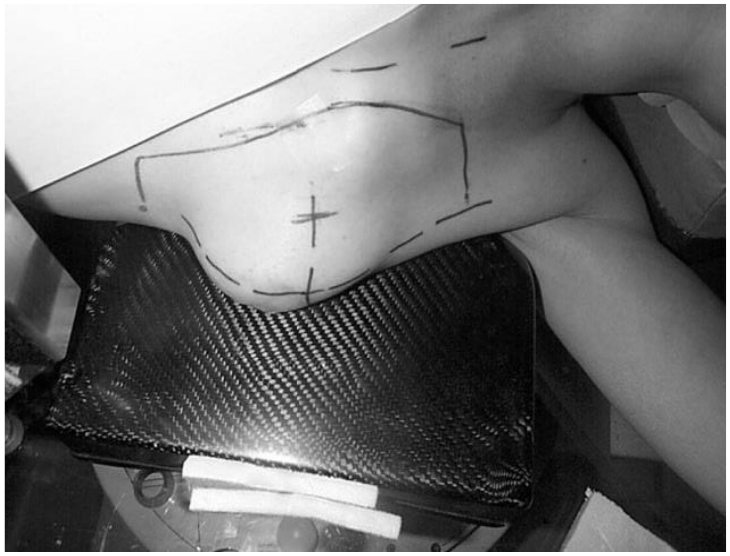
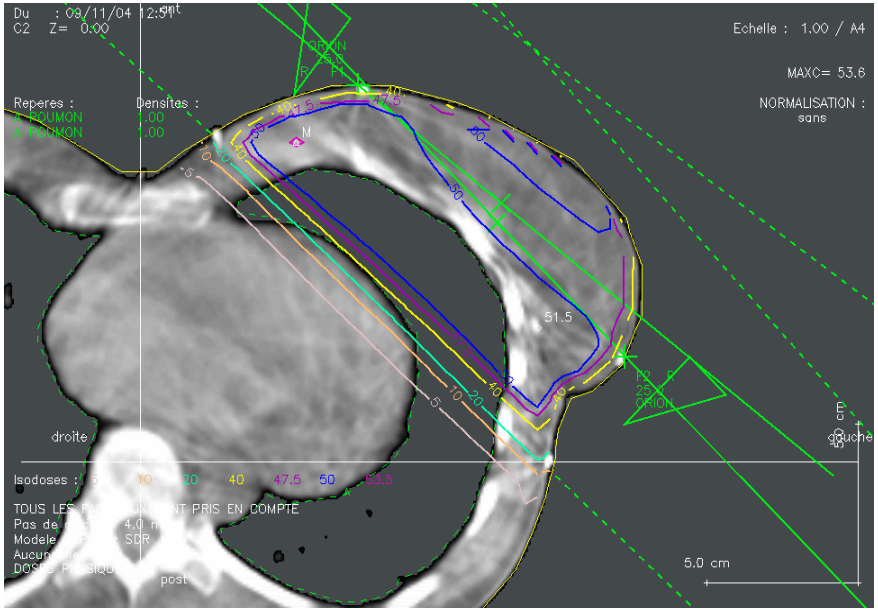
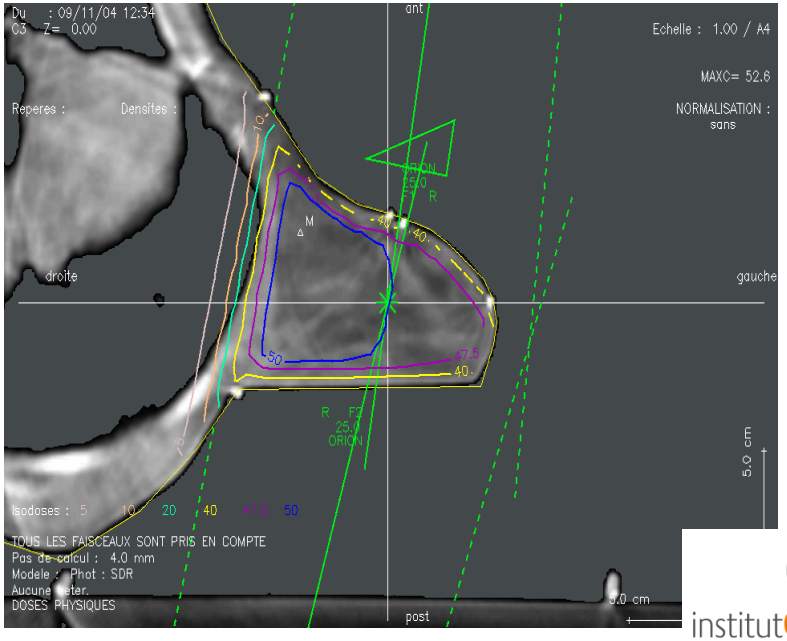
Pectus excavatum

Bollet et al, BJR









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Ensemble, prenons le cancer de vitesse.

HOW TO REDUCE the side effects and obrain the optimal dose couverage ?

The place of IMRT in the BC RT

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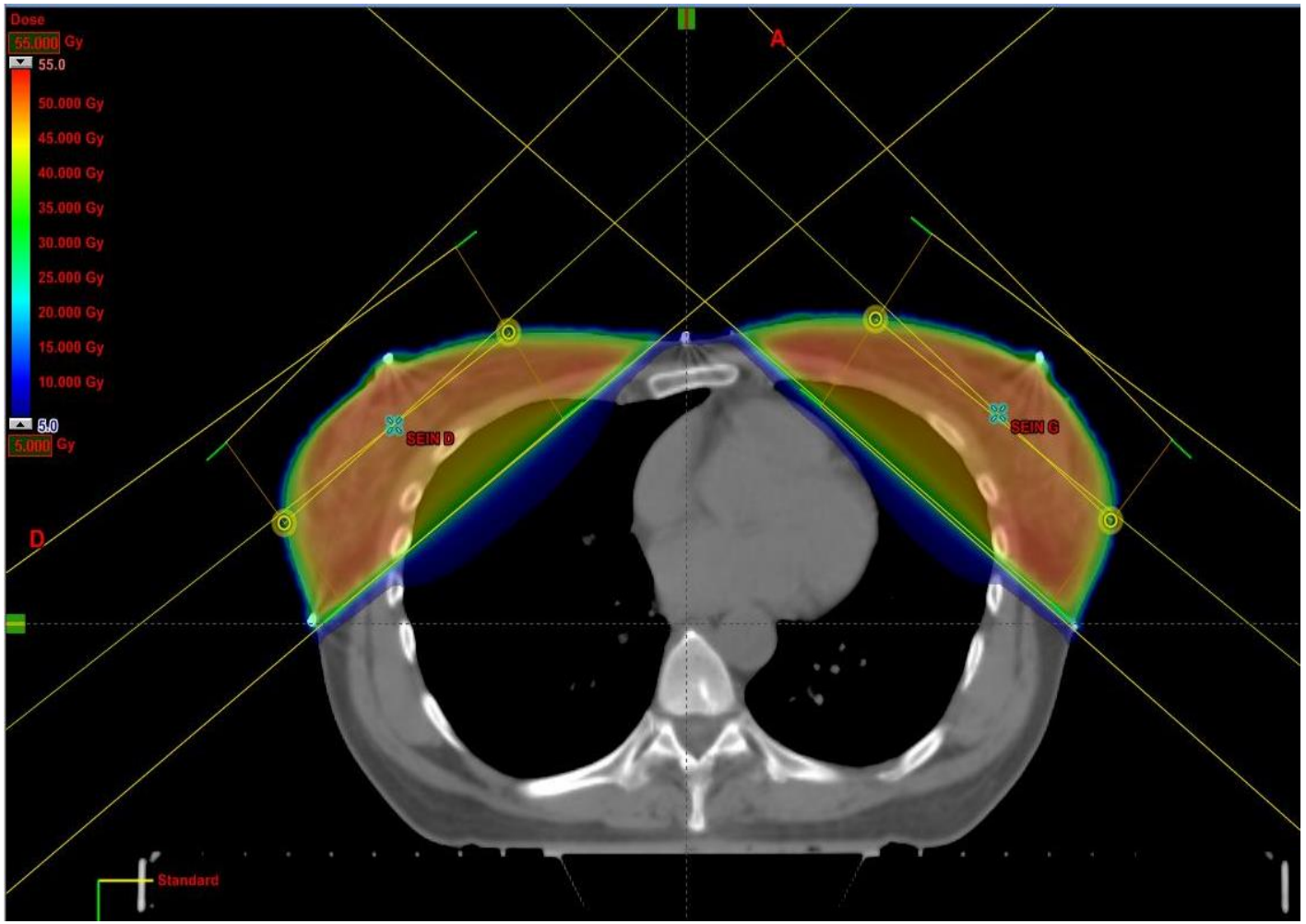
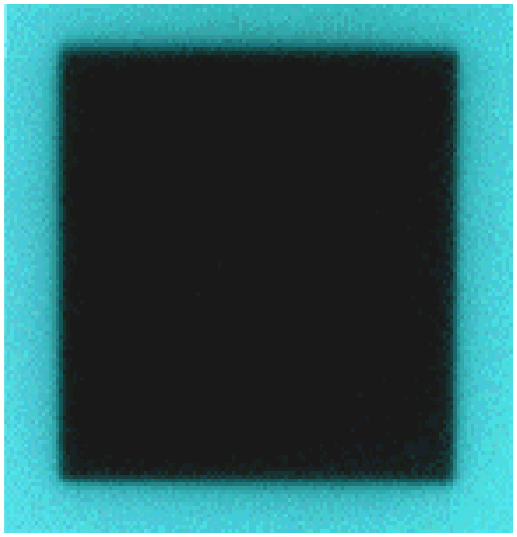
Bilateral BC.
3D tangents with field-in-field



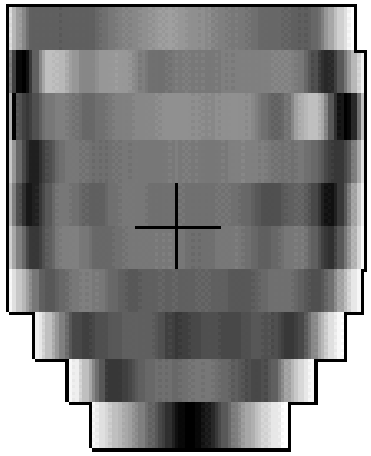
F in F dosimetry

IMRT

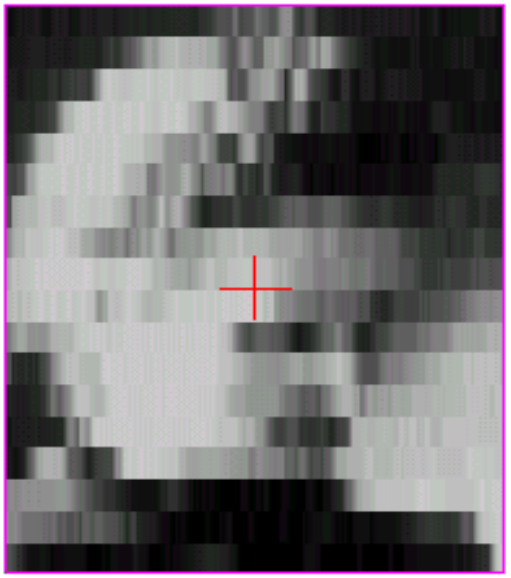
Champ classique



Champ modulé

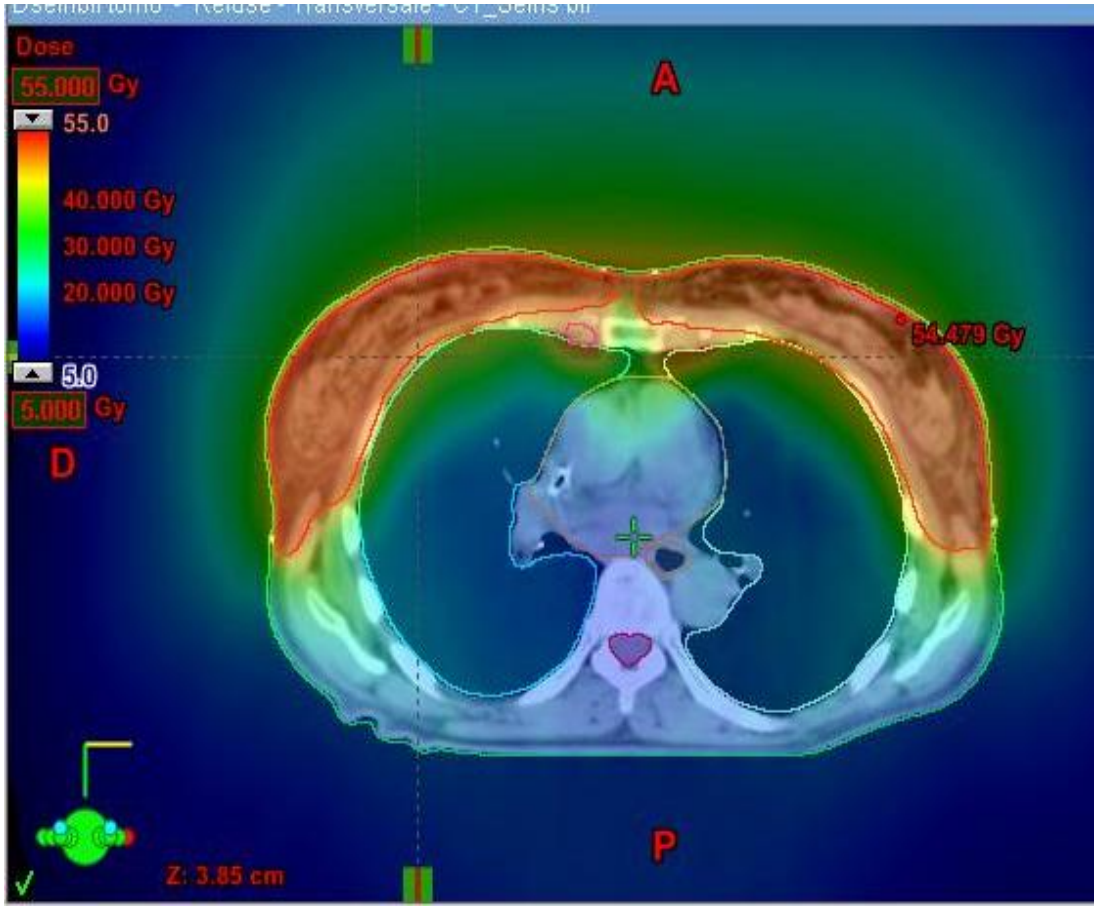


IMRT
Varian
80 ML



IMRT
Varian
120 ML

Bilateral breast RT. Helicoïdal tomotherapy



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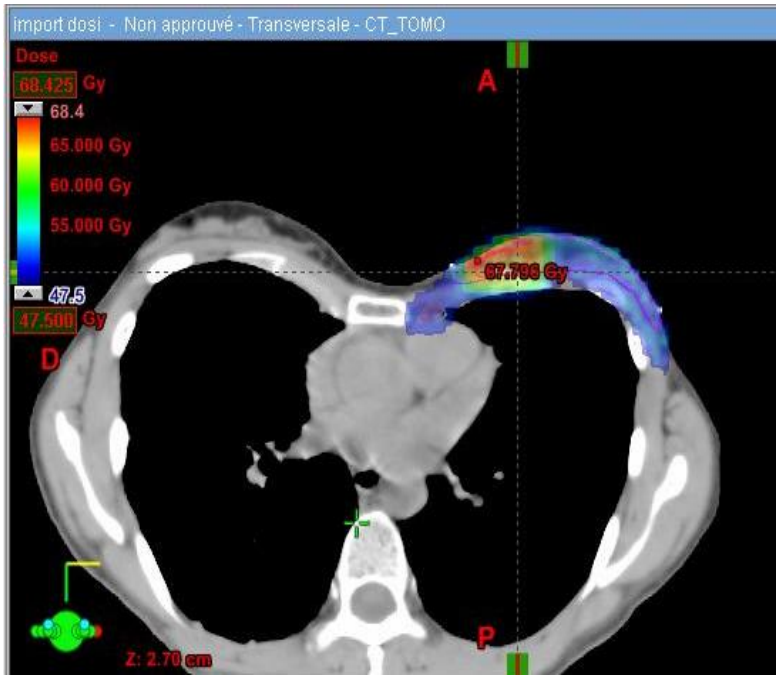
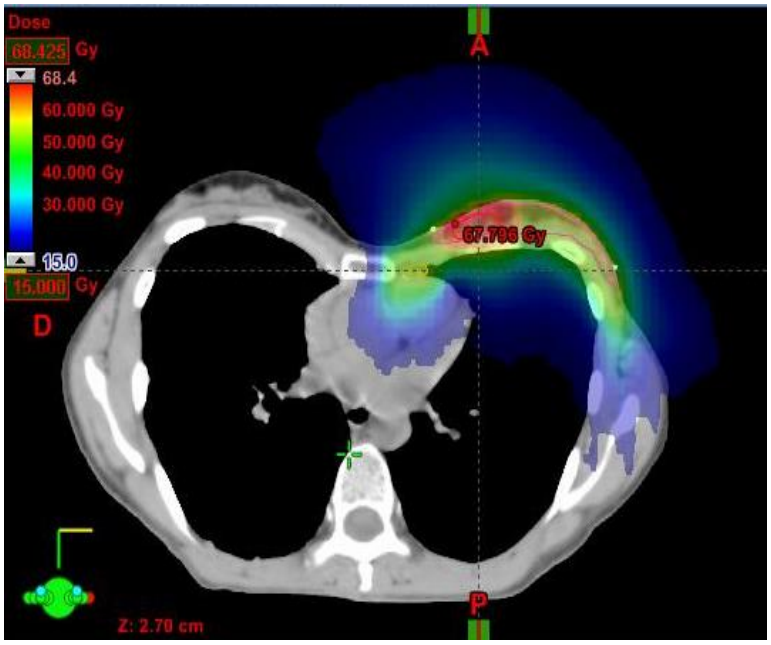
Ensemble, prenons le cancer de vitesse.

Pectus excavatum. Tomotherapy



95% isodose



30% isodose

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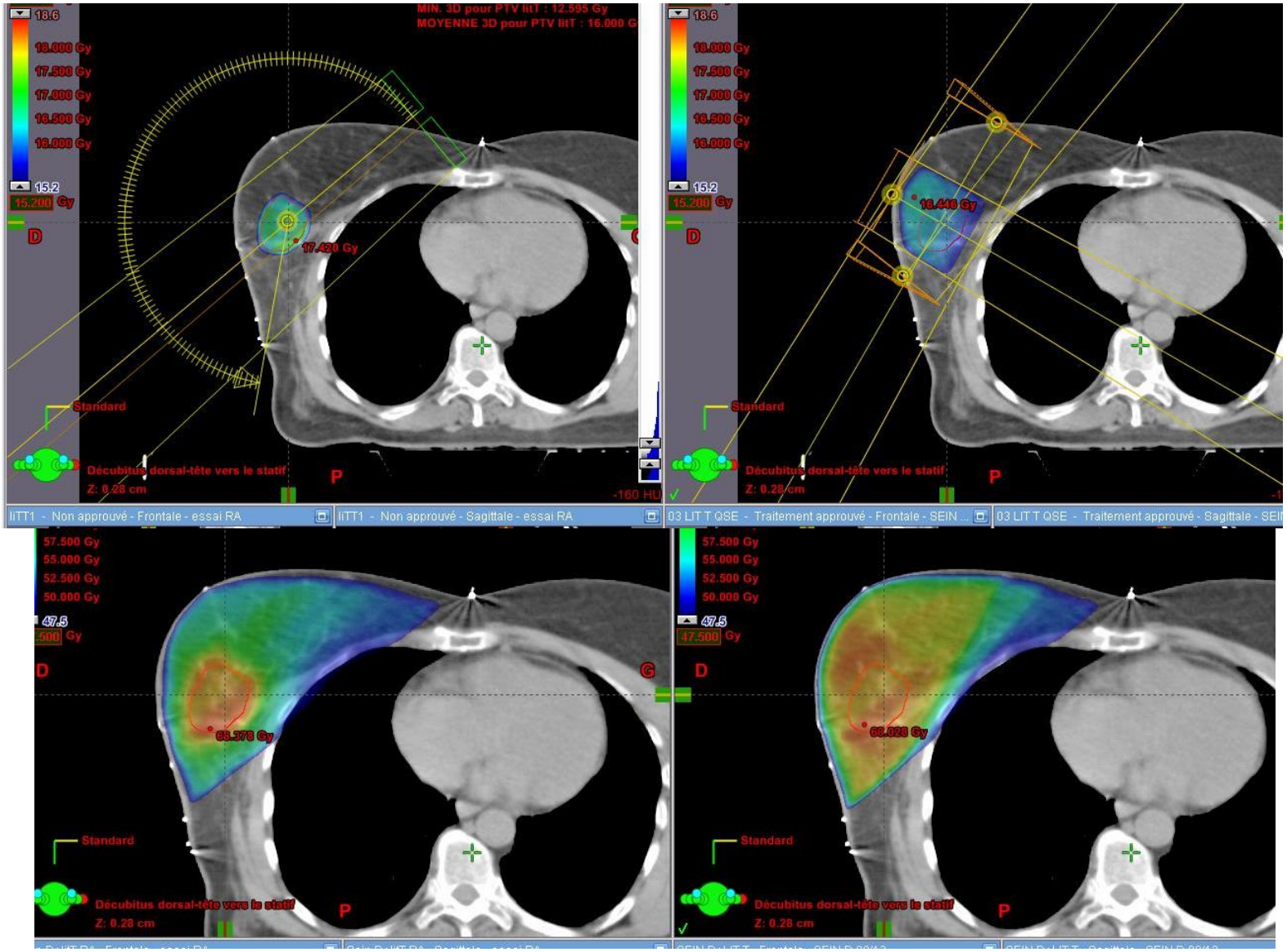
Boost. 3D vs VMAT



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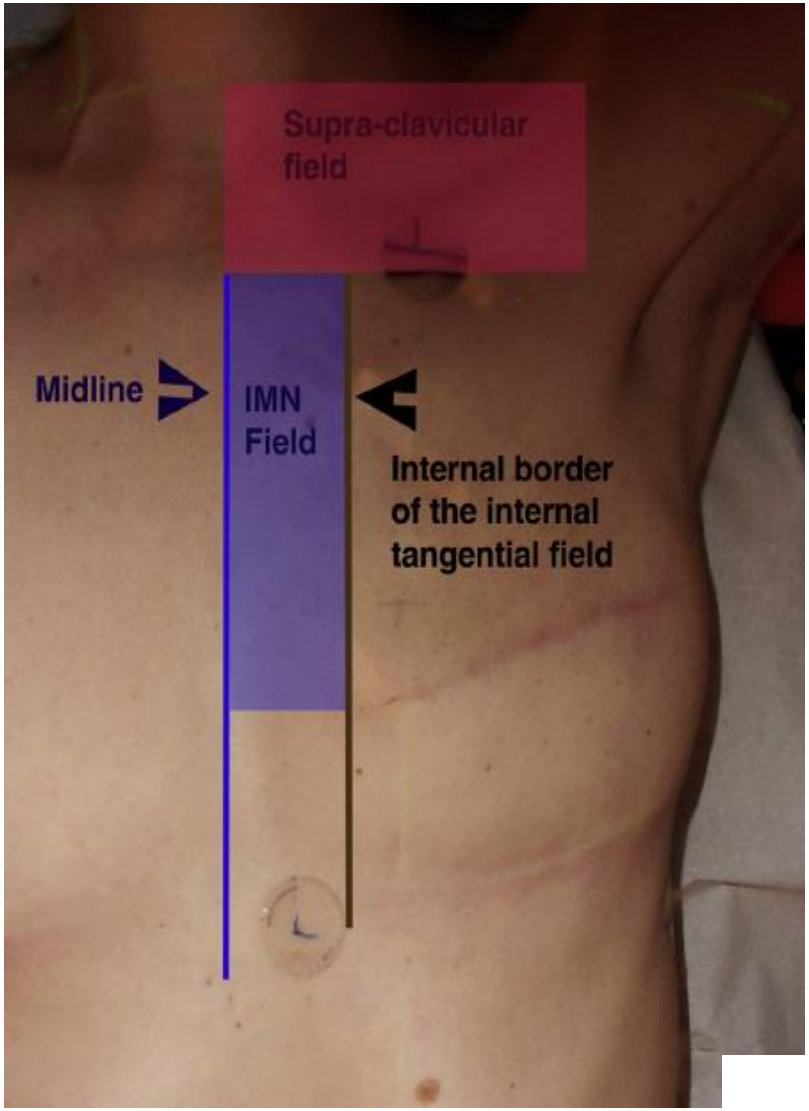
Ensemble, prenons le cancer de vitesse.

OAR and
Lymph nodes irradiation

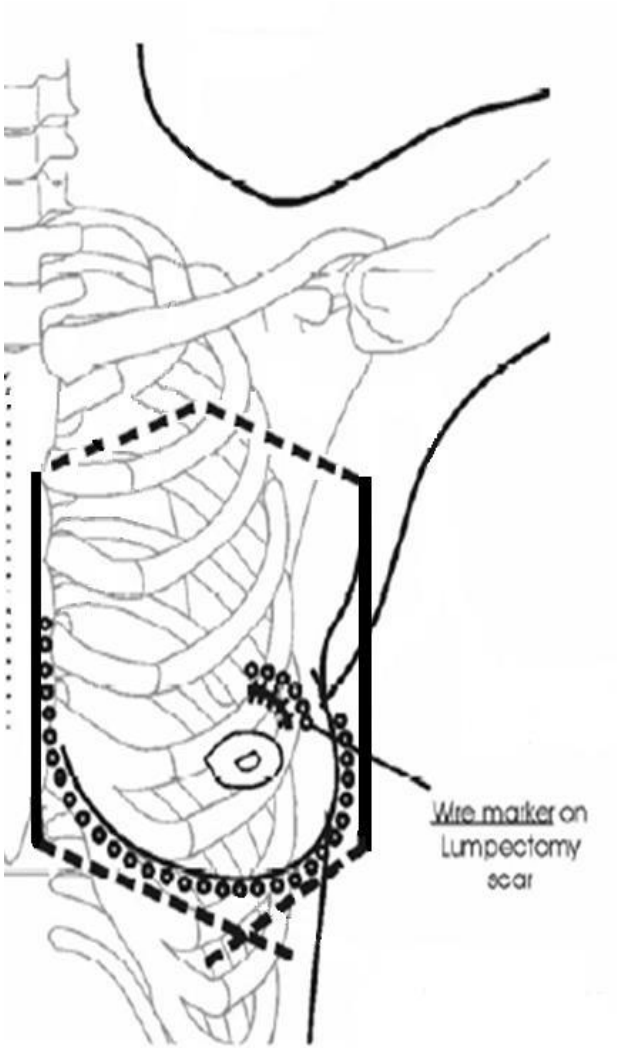
French IMN Trial

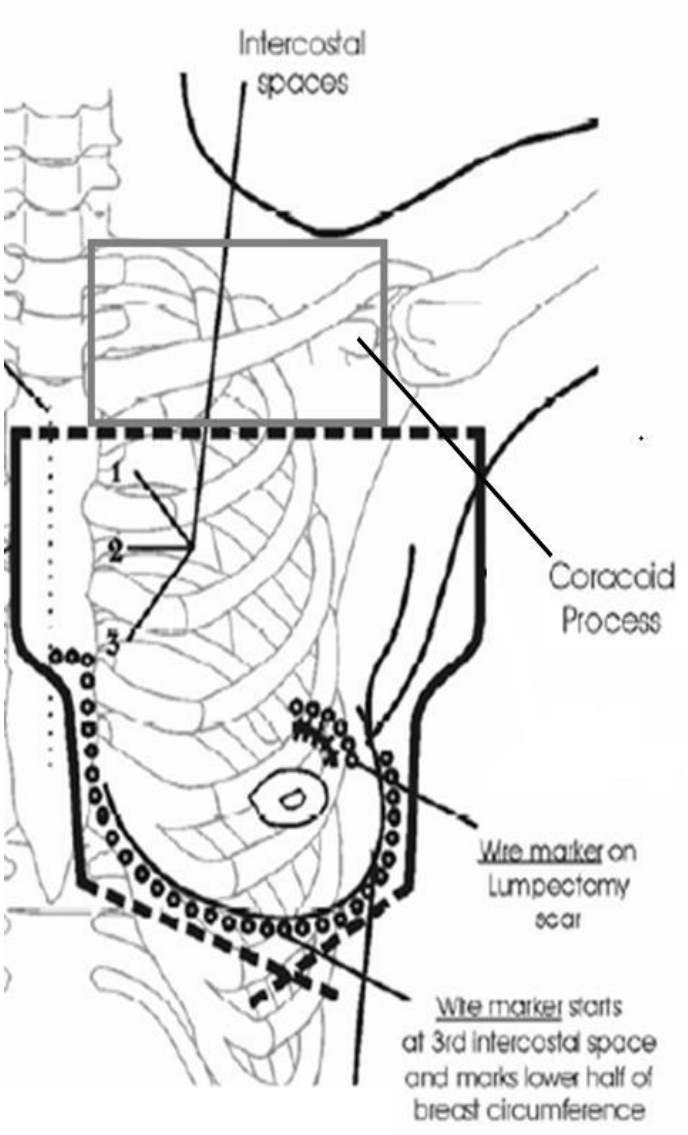
- **First five intercostal spaces**
- **Photons/electrons 1/3-2/3**
- **45 Gy/18f of 2.5 Gy, 4f. p/wk**



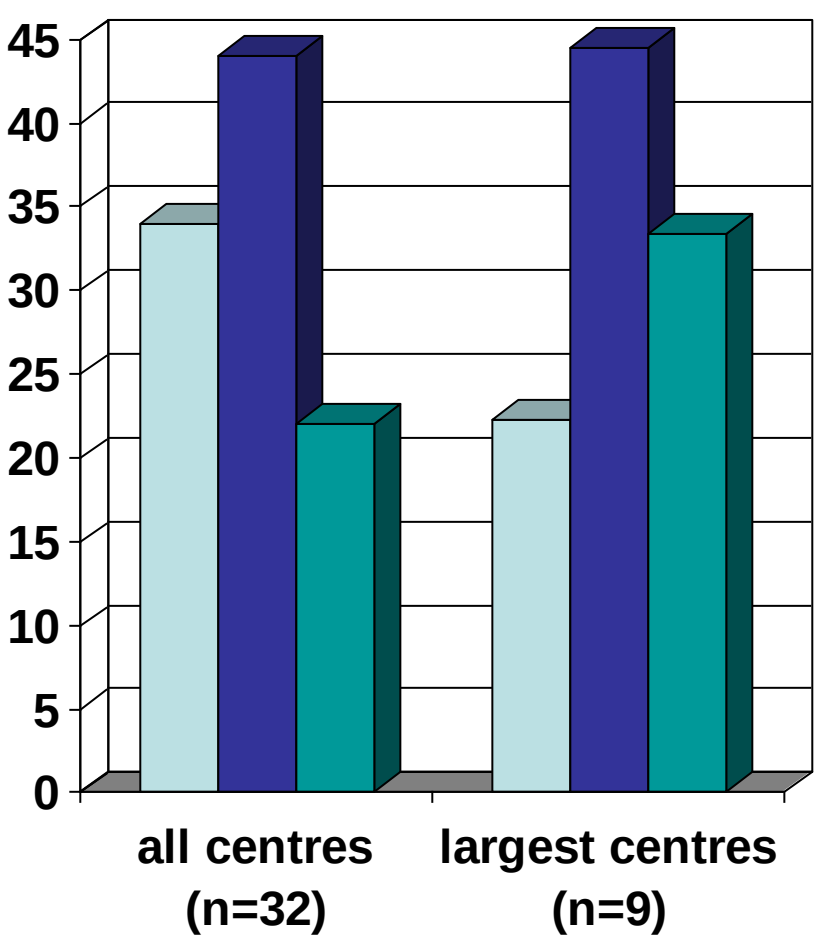
Hennequin C et al. *Int J Radiation Oncology Biol Phys* 2013

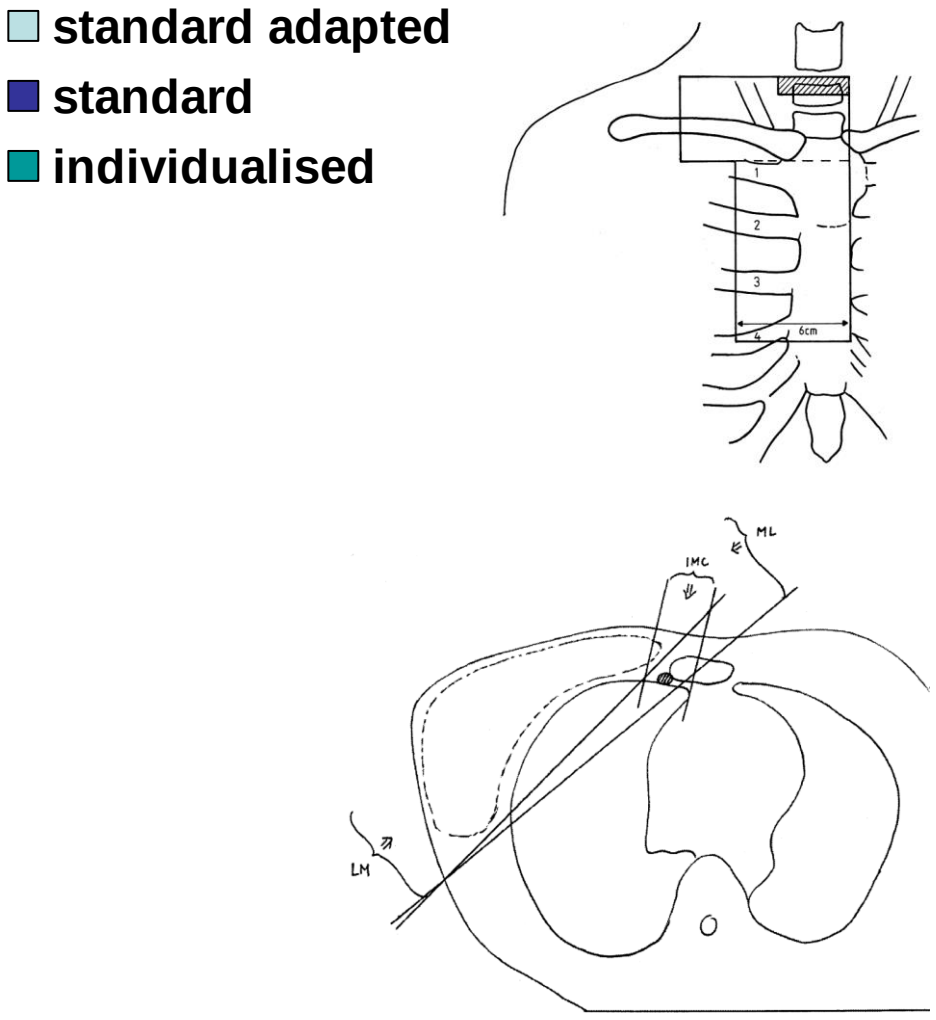
MA 20





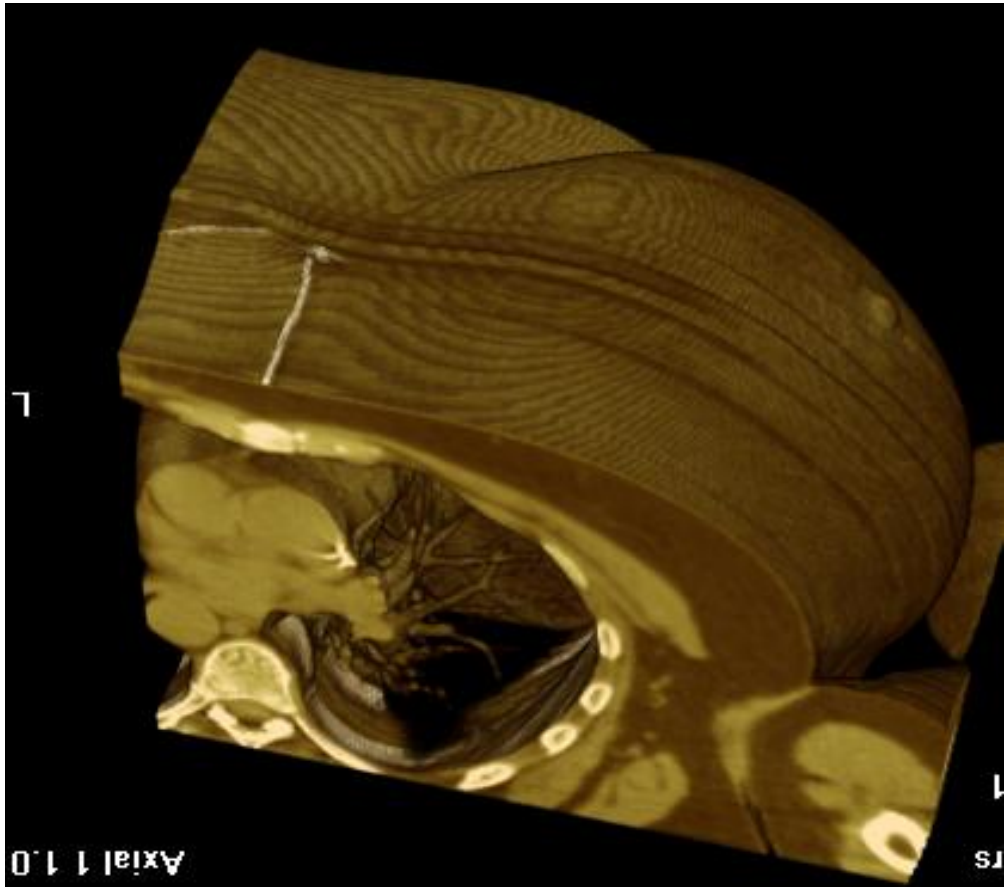
Whelan T et al. *ASCO* 2011





Lievens Y et al. R&O 2001;60:257-265.

OAR: from 2D to 3D



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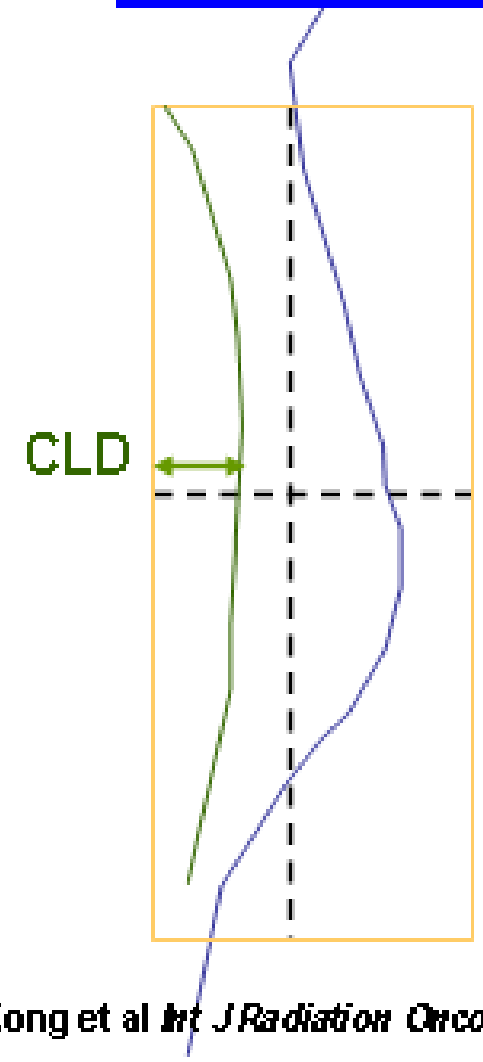
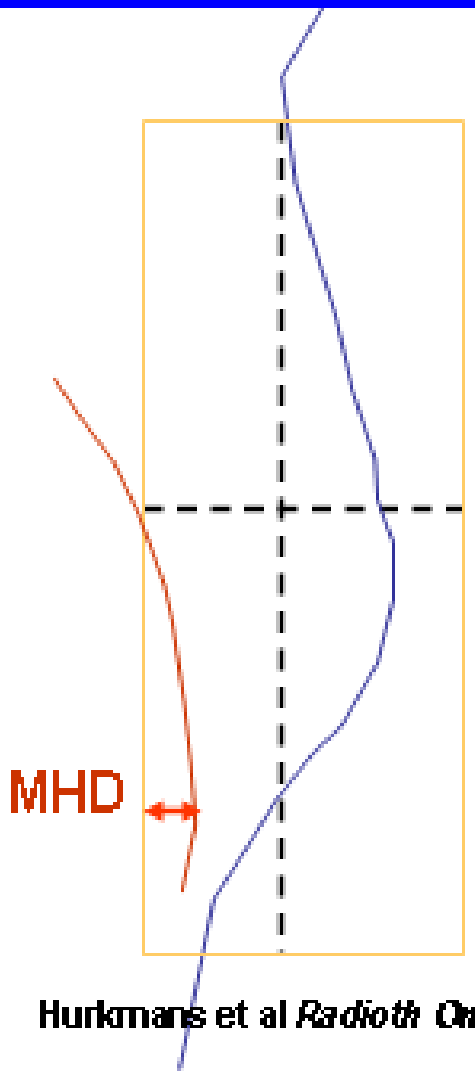
CLD and MHD are related to lung and heart complication probability



Kong et al *Int J Radiation Oncology Biol Phys* 2002



Hurkmans et al *Radioth Oncol* 2002

Is this 3D conformal definition of OAR?

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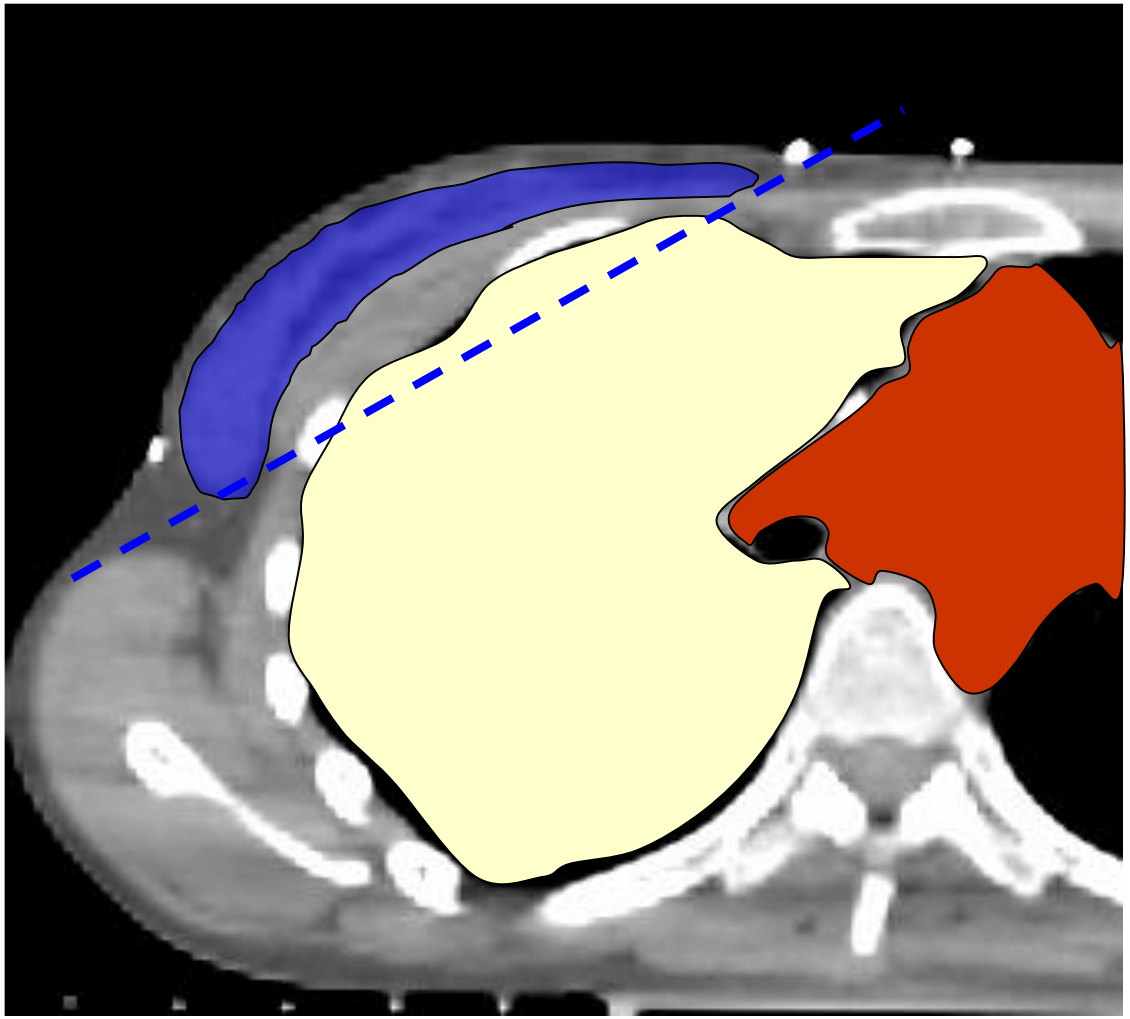
Comparison 2D vs. 3D
Volumes modification using CT scan and delineation



Lungs

Heart

CTV

+1cm → PTV

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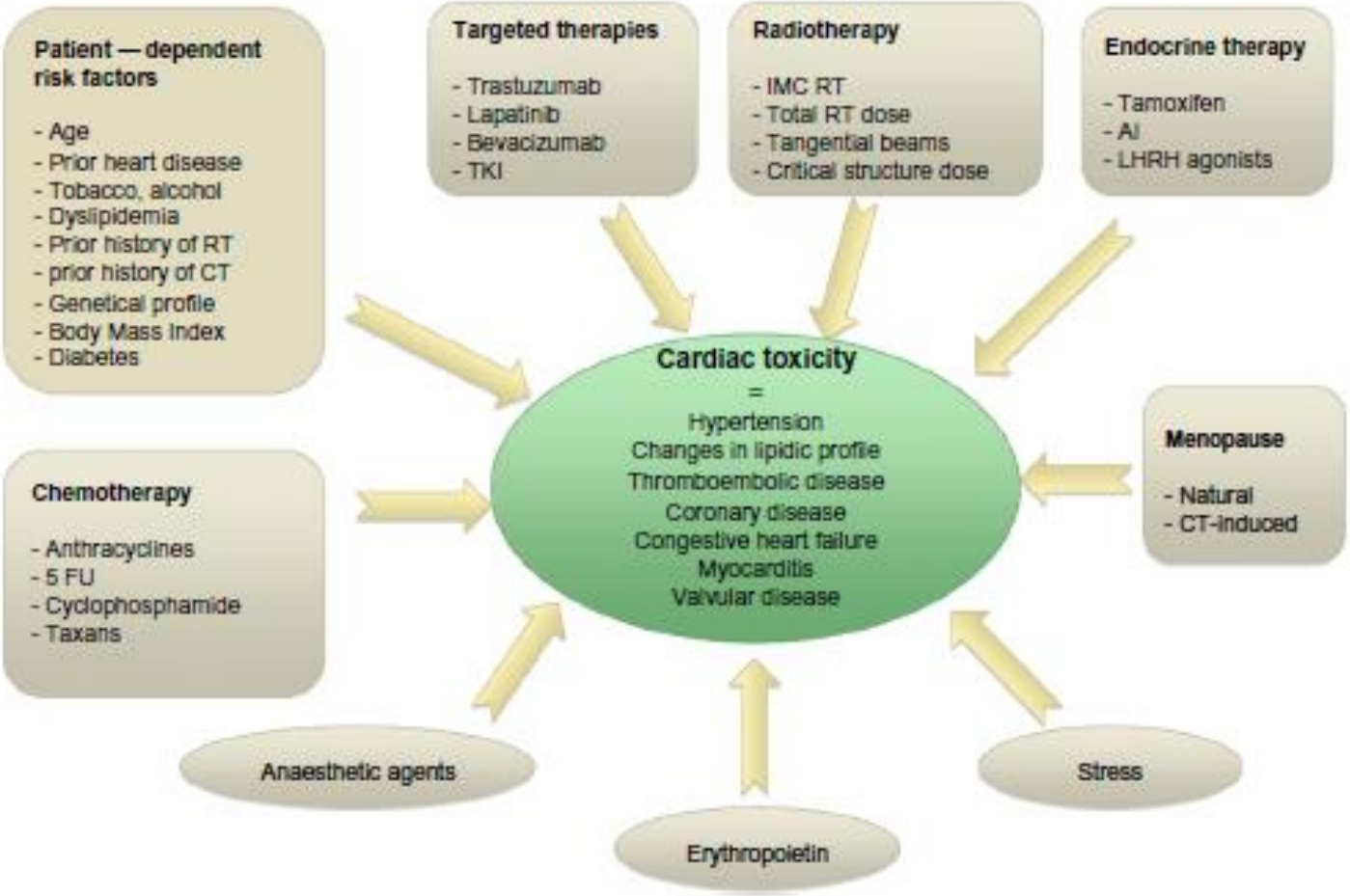
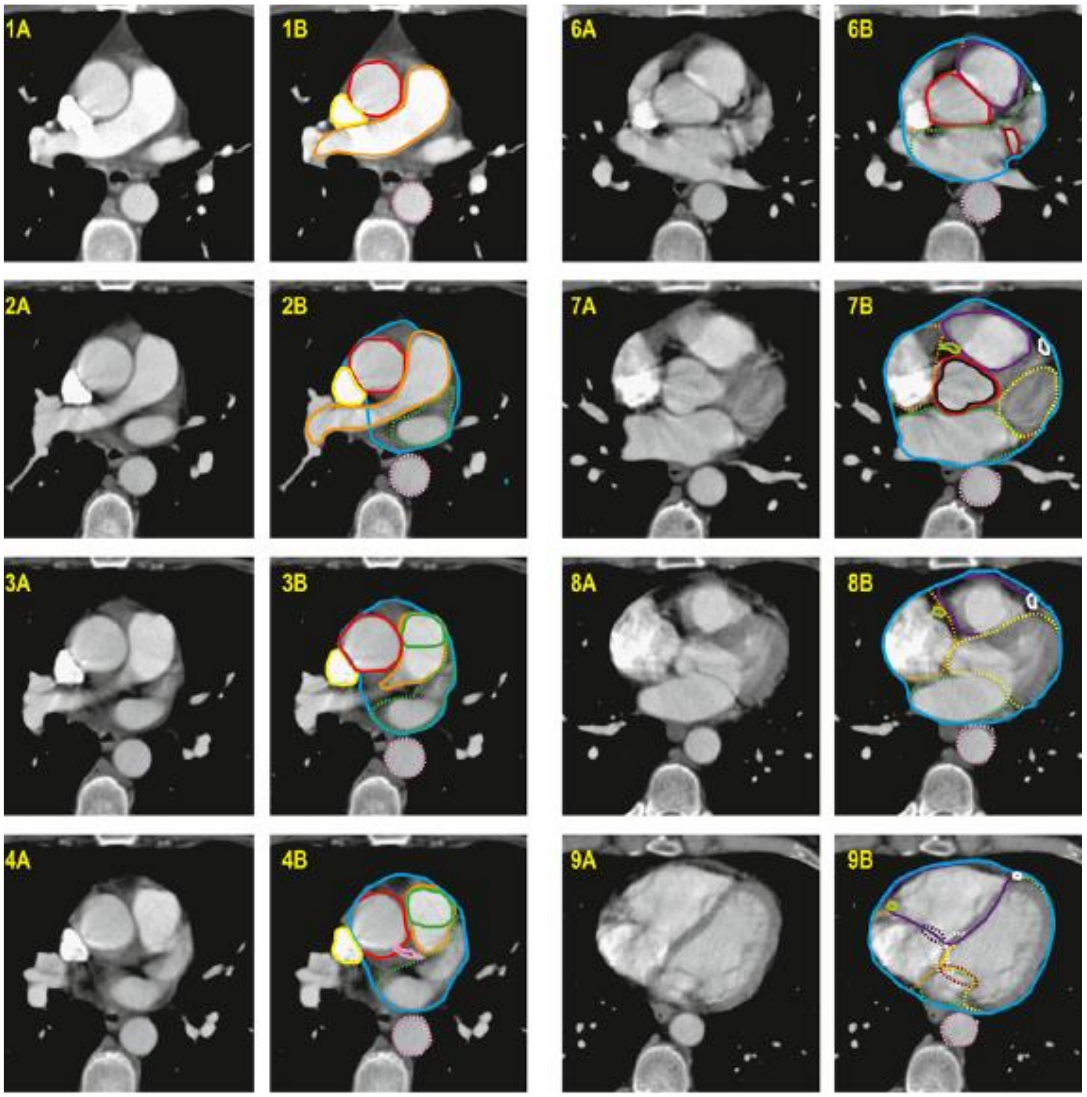


Fig. 1. List of factors that may potentially lead to cardiac hazard in breast cancer patients.

Please cite this article in press as: Chargari C et al. Cardiac toxicity in breast cancer patients: From a fractional point of view to a global assessment. *Cancer Treat Rev* (2010), doi:10.1016/j.ctrv.2010.08.007

Heart atlas, Feng et al, IJROBP, 2010

precisions are needed for the everyday practice, but useful tool



ESTRO
European Society for Therapeutic Radiology and Oncology

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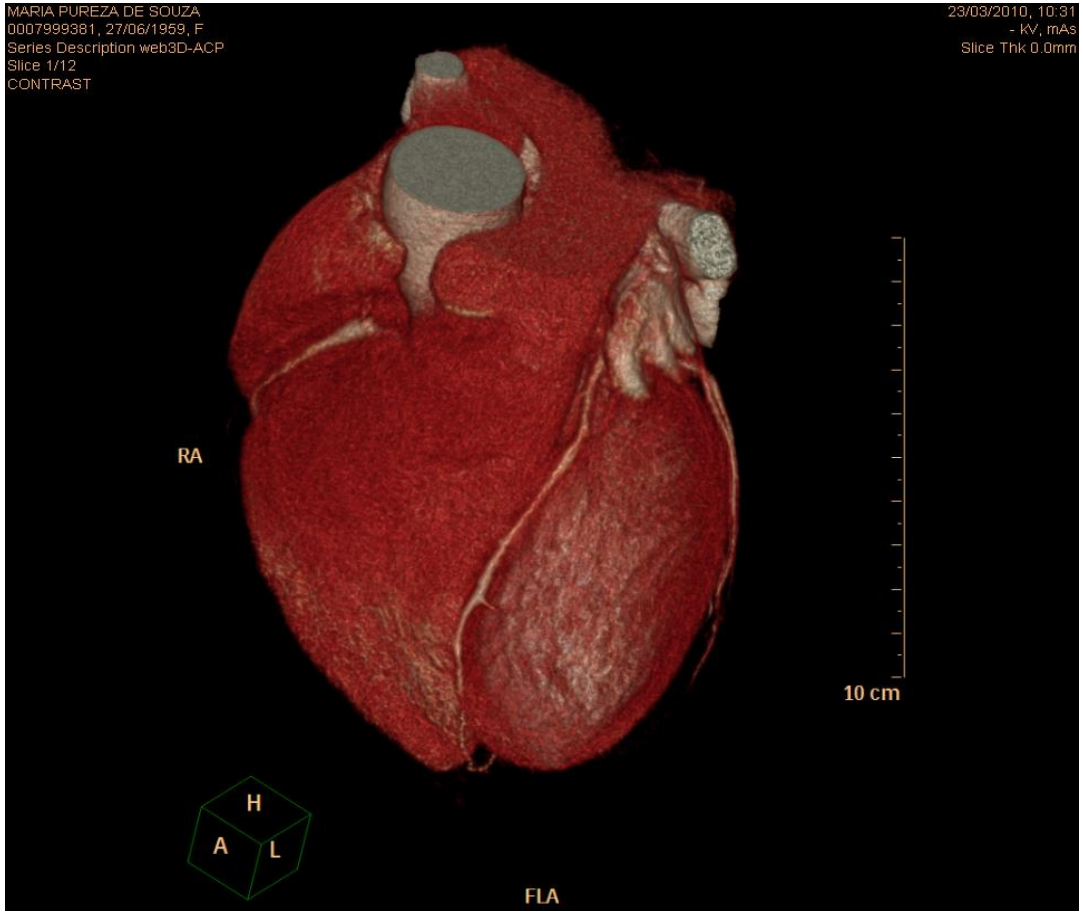
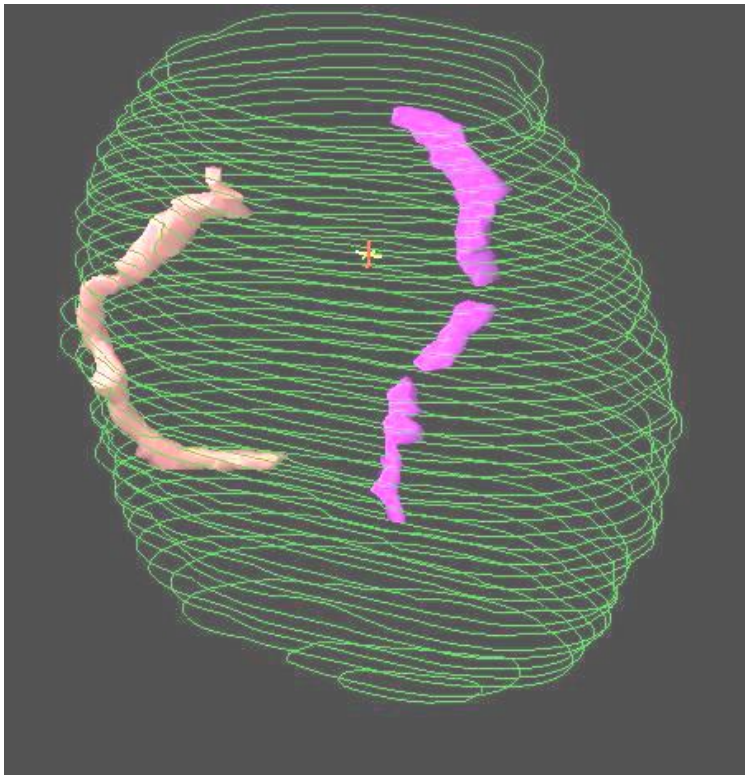
Ensemble, prenons le cancer de vitesse.

➢Images Univ Hospital of Rio de Janeiro

➢Cardiac gating during ’administration of 70 ml de contrast solution (Henetix 350mg/ml-Guerbet) - 5 ml/sec





Kirova, de Almeida, The Breast 2011

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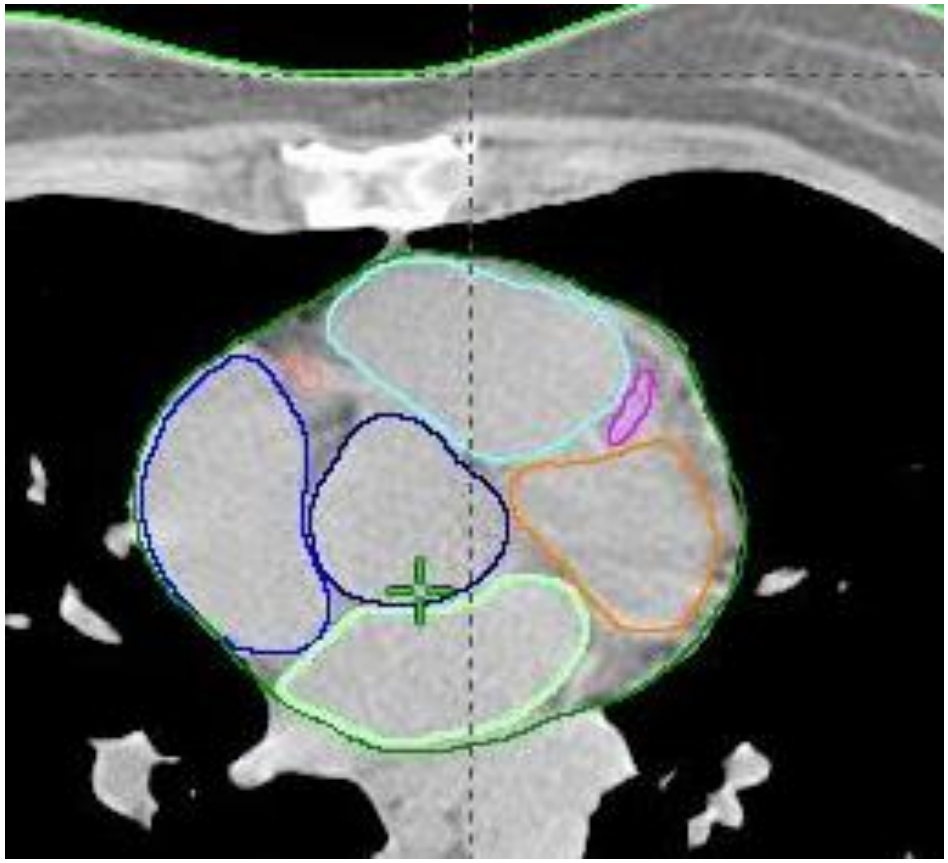
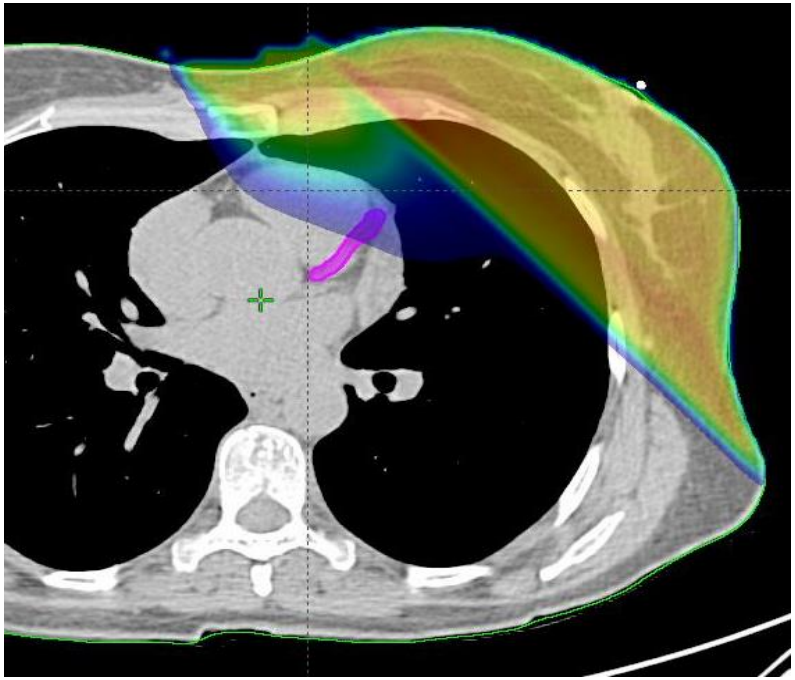


➢Cardiac gating during 'administration of 70 ml de contrast solution (Henetix 350mg/ml-Guerbet) - 5 ml/sec

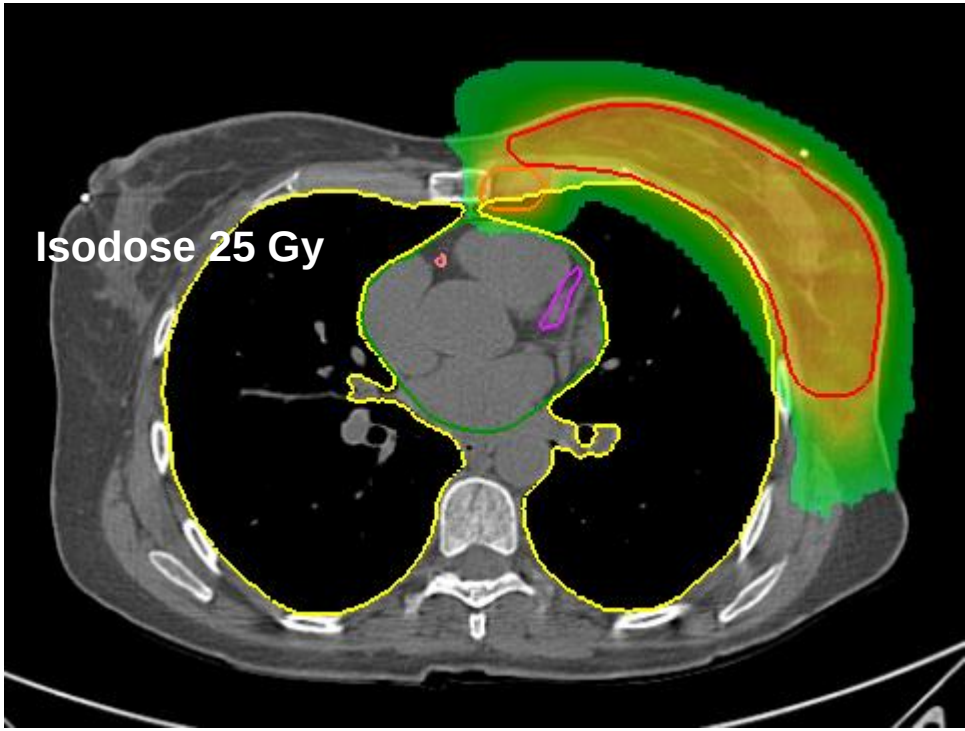
de Almeida, et al, Cancer Radiother 2012

Breast and LN irradiation

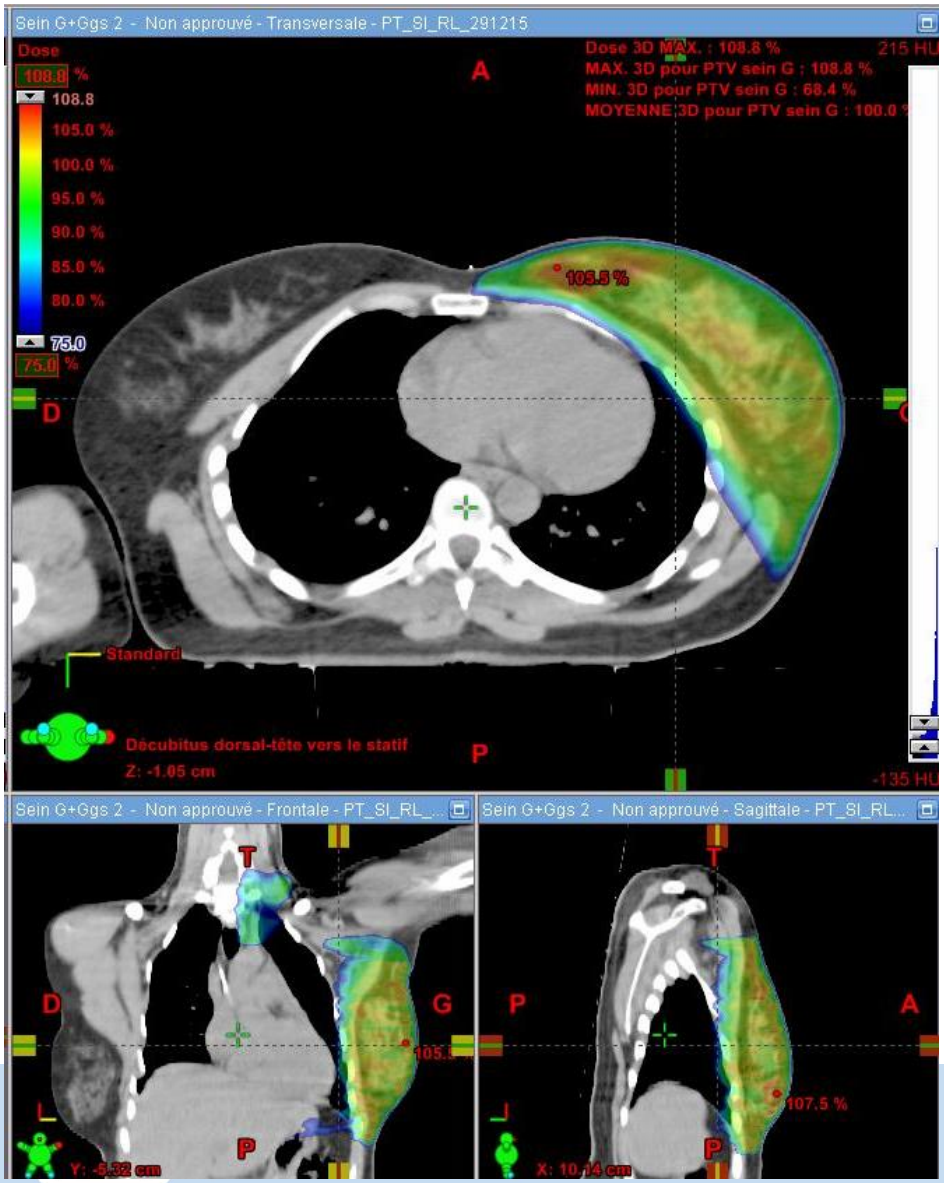


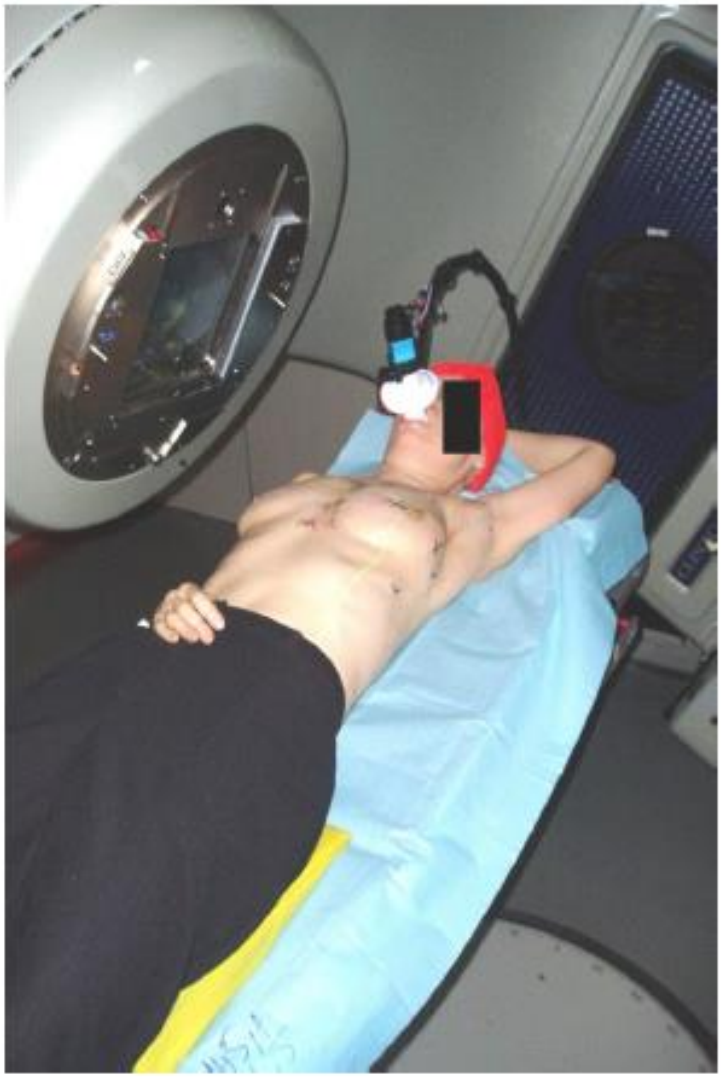
Electrons and photons

Tomotherapy



De Almeida, Fournier-Bidoz et al. *Cancer Radiother*, 2011


Sein G+Ggs 2 - Non approuvé - Transversale - PT_SI_RL_291215
Dose
108.8 %
108.8
105.0 %
100.0 %
95.0 %
90.0 %
85.0 %
80.0 %
75.0
75.0 %
Dose 3D MAX. : 108.8 %
MAX. 3D pour PTV sein G : 108.8 %
MIN. 3D pour PTV sein G : 68.4 %
MOYENNE 3D pour PTV sein G : 100.0 %
A
D
P
103.5 %
Standard
Décubitus dorsal-tête vers le statif
Z: -1.05 cm
Sein G+Ggs 2 - Non approuvé - Frontale - PT_SI_RL_...
T
D
G
L
P
Y: -5.32 cm
Sein G+Ggs 2 - Non approuvé - Sagittale - PT_SI_RL...
T
P
A
L
P
107.5 %
X: 10.14 cm



After mastectomy

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 69, No. 4, pp. 1139–1144, 2007

0360-3016/07/$–see front matter

doi:10.1016/j.ijrobp.2007.05.007

POSTMASTECTOMY ELECTRON BEAM CHEST WALL IRRADIATION IN WOMEN WITH BREAST CANCER: A CLINICAL STEP TOWARD CONFORMAL ELECTRON THERAPY

YOULIA M. KIROVA, M.D., FRANCOIS CAMPANA, M.D., NATHALIE FOURNIER-BIDOZ, PH.D., ANNE STILHART, REMI DENDALE, M.D., MARC A. BOLLET, M.D., AND ALAIN FOURQUET, M.D.

Department of Radiation Oncology, Institut Curie, Paris, France

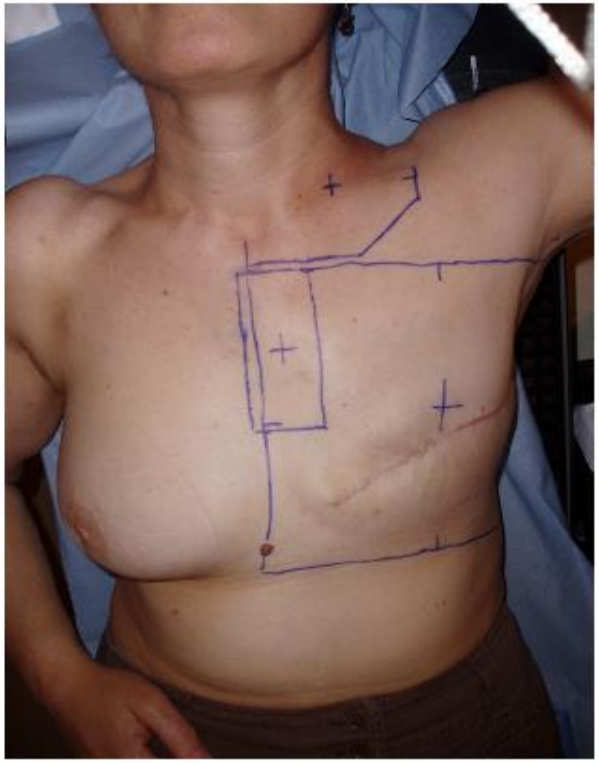


Fig. 3. Postmastectomy fields for new technique: chest wall (electrons), internal mammary chain (electrons and photon boost), and supraclavicular nodes (photons).

slice; and the maximal depth of the 40-Gy isodose in the ipsilateral

Prospective clinical study

The data of all patients treated with the new technique were prospectively recorded, and early toxicity was assessed weekly according to the Radiation Therapy Oncology Group classification (9). The Radiation Therapy Oncology Group grades were as follows: Grade 0, no skin reaction; Grade 1, follicular, faint, or dull erythema, epilation, dry desquamation, and decreased sweating; Grade 2, tender or bright erythema, patchy moist desquamation, and moderate edema; Grade 3, confluent, moist desquamation other than skin

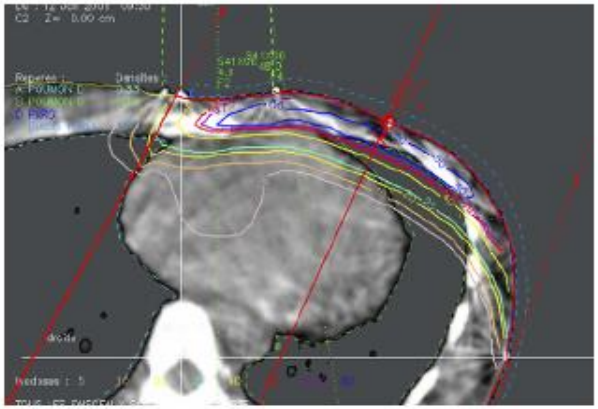
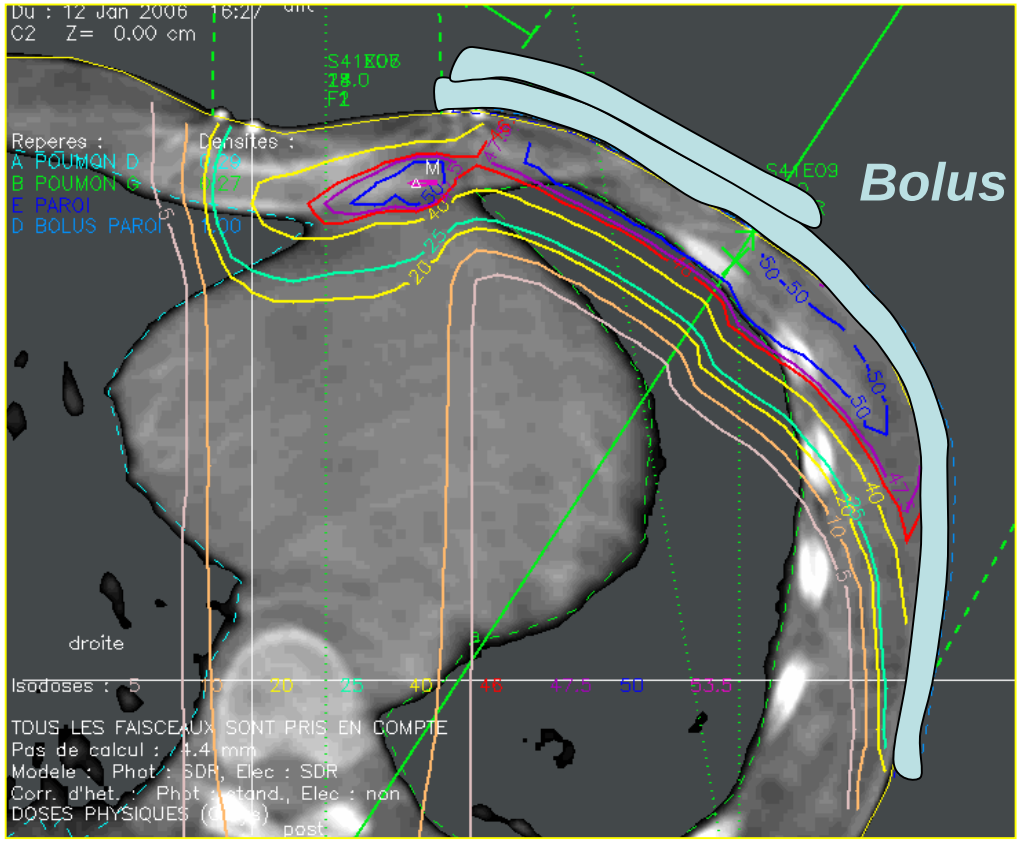


Fig. 4. Dose distribution for 50-Gy prescribed dose using new technique.

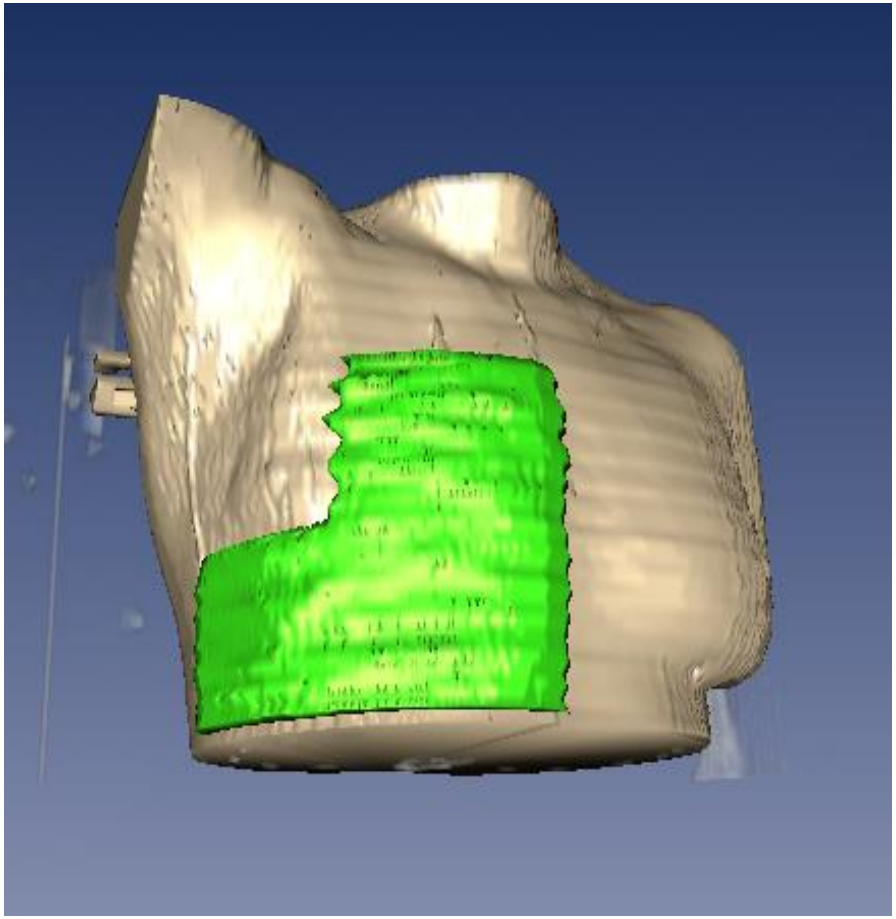
New technique, solutions in case of problems



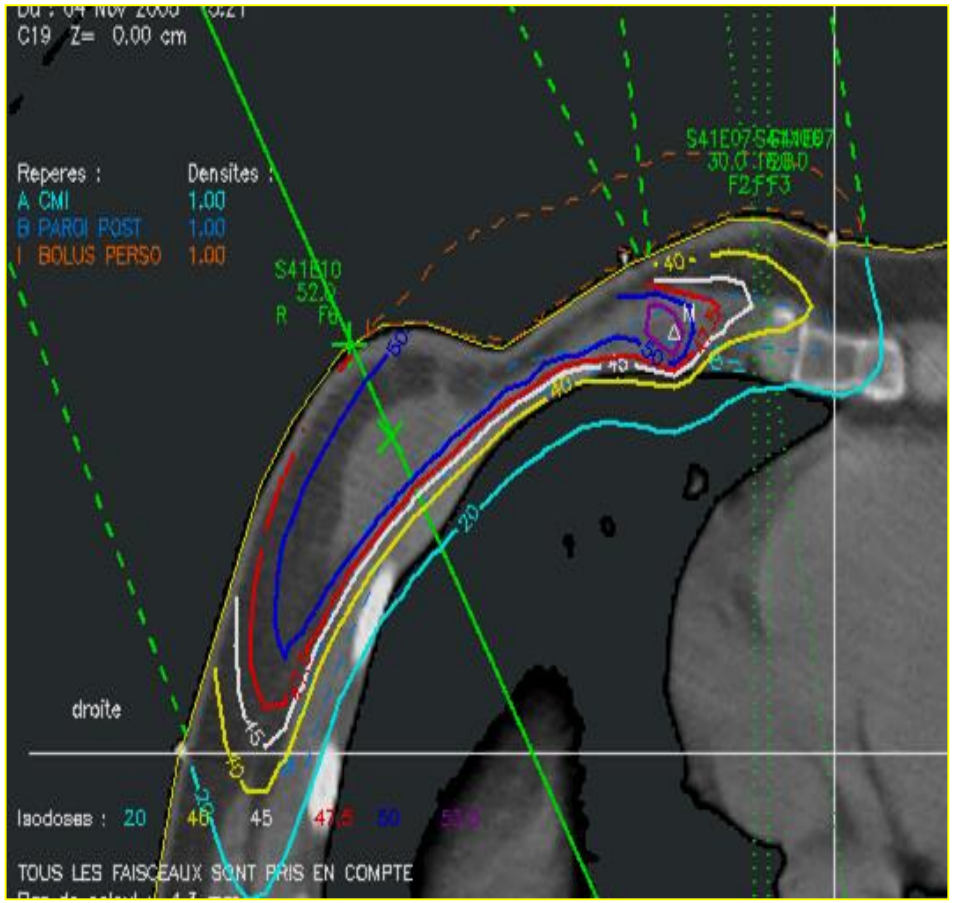
- **When the reference isodose (47.5 Gy) enters into the ipsilateral lung, a second layer of bolus of 0.5 cm is placed (prepared by the dosimetrist).**

- **When two layers of bolus are needed to protect the lung, a beam's eye view showing the projection of the bolus layers limits helps for bolus confection.**

Future directions



3 D individual bolus



Dose distribution using 3D bolus

Immediate breast reconstruction when postmastectomy radiotherapy is indicated should be done with caution

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Ensemble, prenons le cancer de vitesse.

Capsular contracture following IBR with implant and RT

	IBR No.	IBR + RT No.	RT Protocol	CC %		Re-operation	Med. F/U
				no RT	with RT	%	(mths)
Marseilles 2003	69	47	50Gy/25f	0	17	11	25
New York 2004	143	68	50Gy/25f	40	68	1.2	34
Stockholm 2006	107	24	46Gy/23	15	42	15	60
London 2006	136	44	50Gy/25f	14	39	9	48
Bristol 2008	53	18	50gy/25f	11	39	22.2	33
Cambridge 2009	120	42	40Gy/15f	0	19	19.5	50

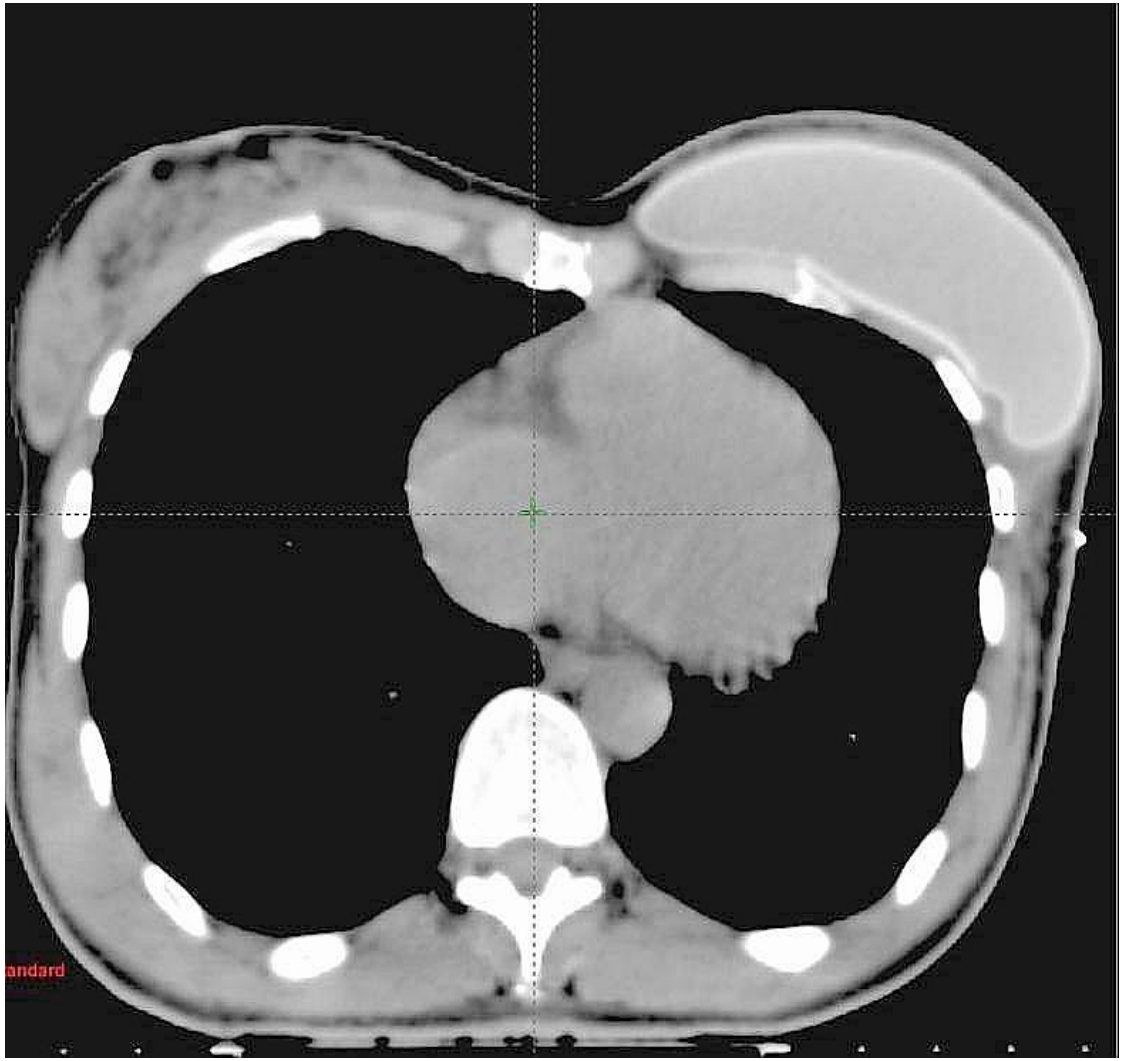
Autologous tissue reconstruction vs implant, followed by irradiation

	Implant	Autologous graft	Median F/U	Complications	Reoperation
	No	No	mths.	%	%
Philadelphia, 2004	44	26	28	TRAM:0 Implant:5	2 (implants)
Boston, 2002	18	30	32	TRAM:12 Implant:53	TRAM:8 Implant:42
Long Island, 2008	69	23	38	ATR:9 Implant:55	ATR:0 Implant:19

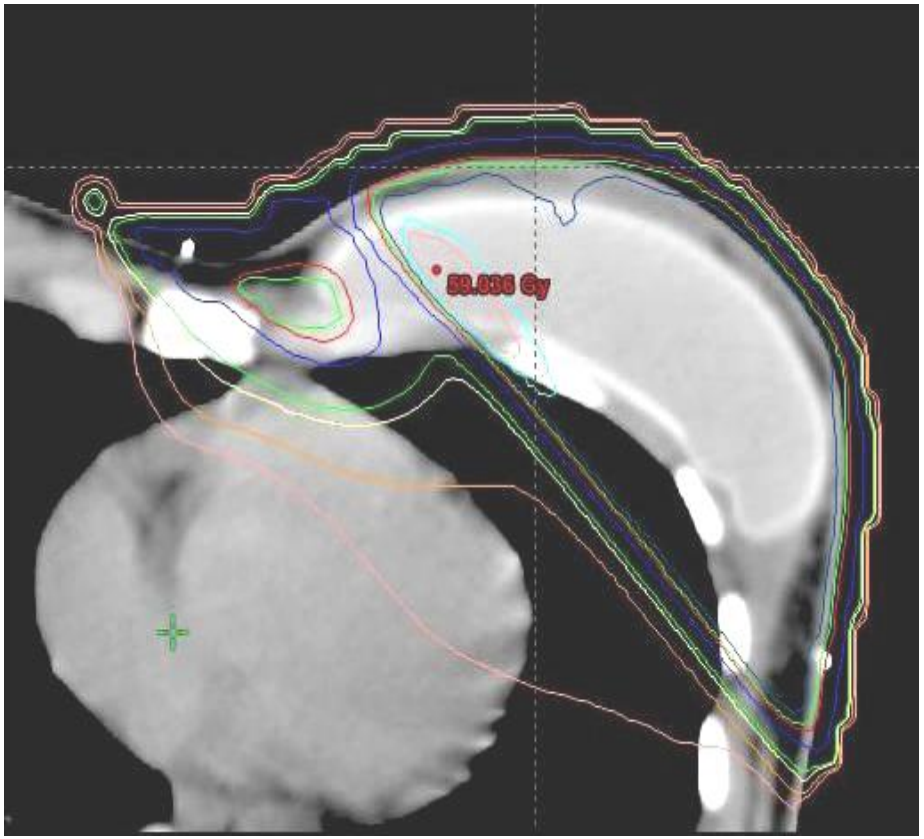
Postmastectomy irradiation with immediate breast reconstruction is often a technical problem

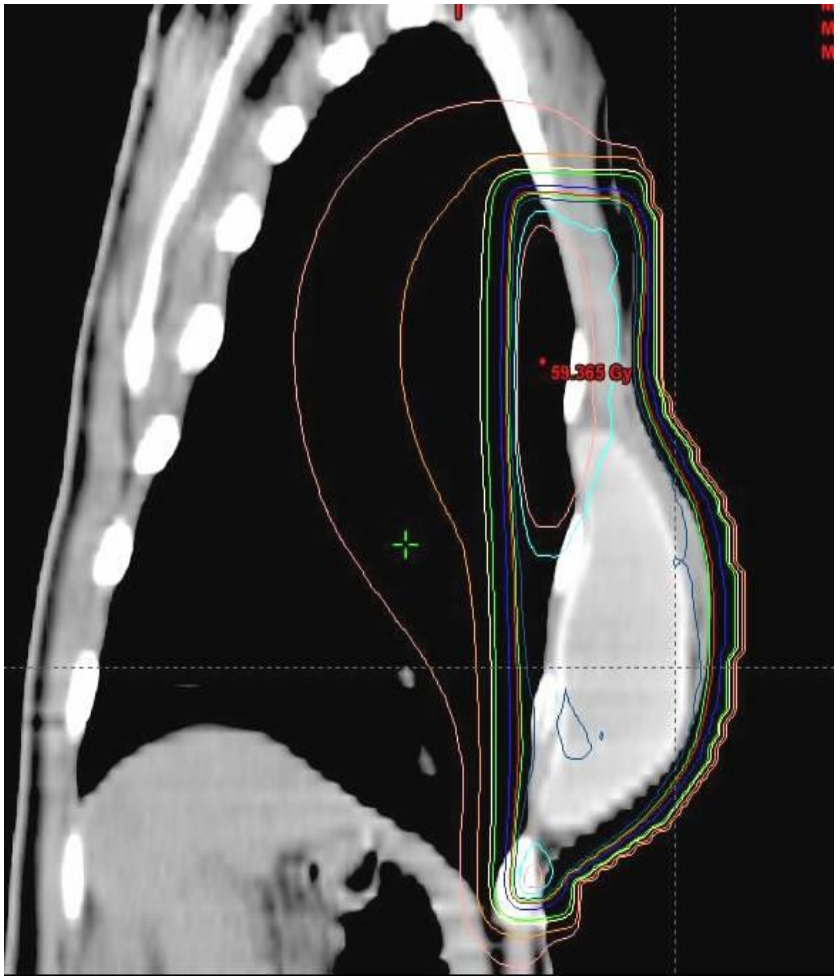
- **Chest wall coverage and heterogeneities**
- **Combination with regional nodes irradiation**
- **Lung and heart avoidance**
- **Delay in initiation of radiotherapy**

Left breast. IBR with retropectoral implant

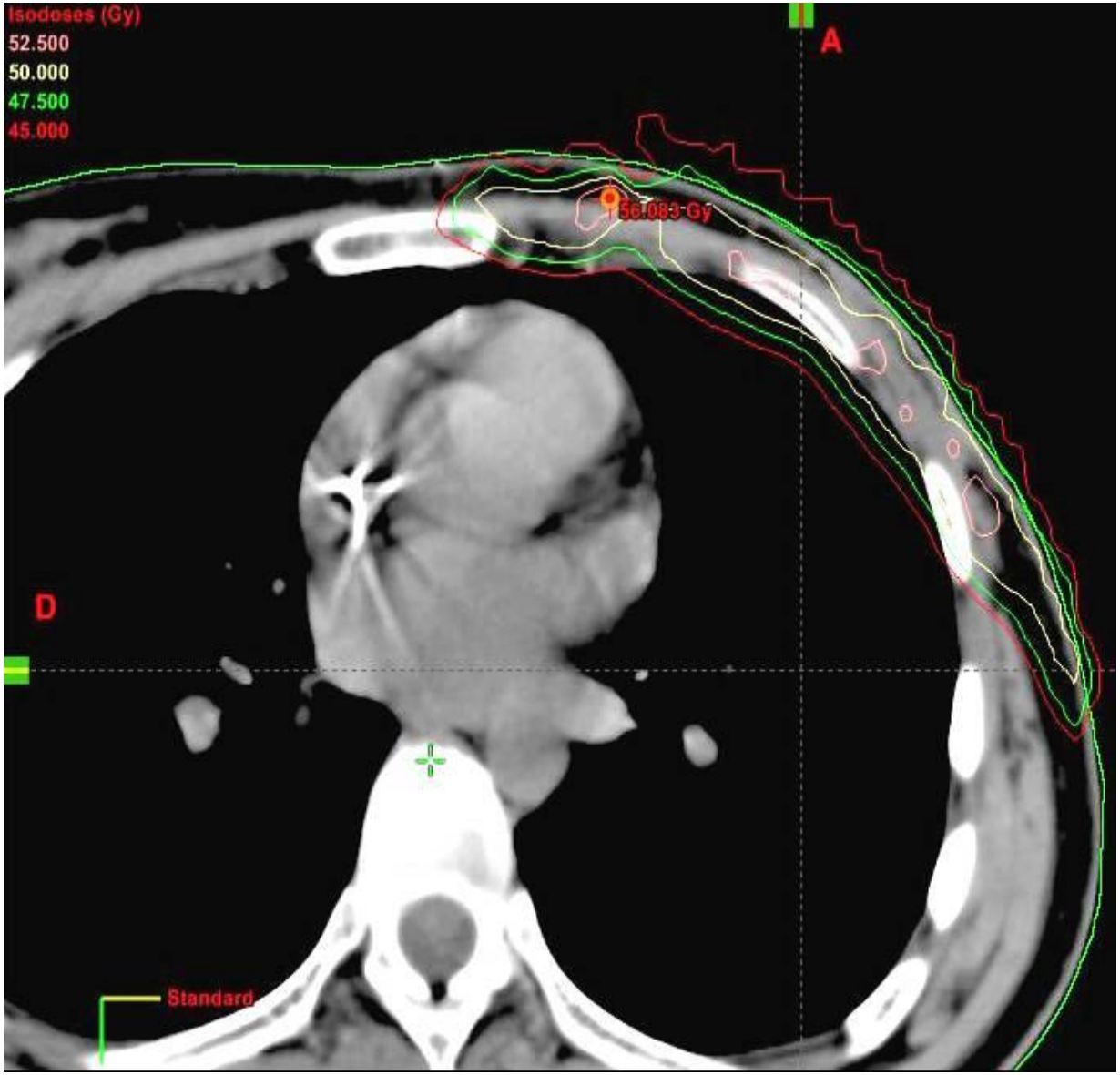


Dosimetry of chest wall and IMN irradiations

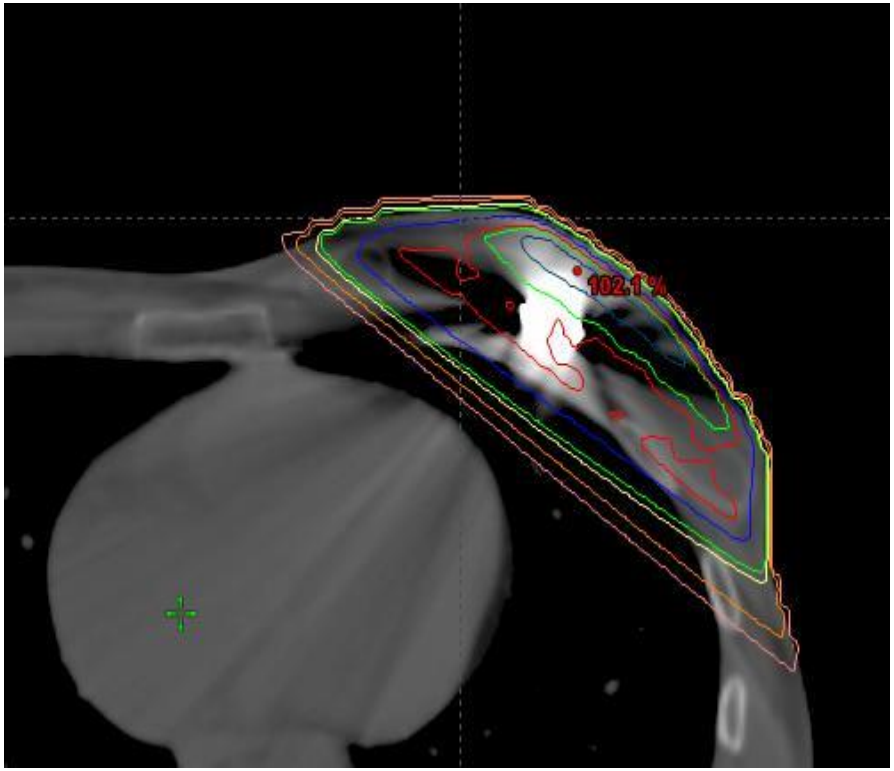


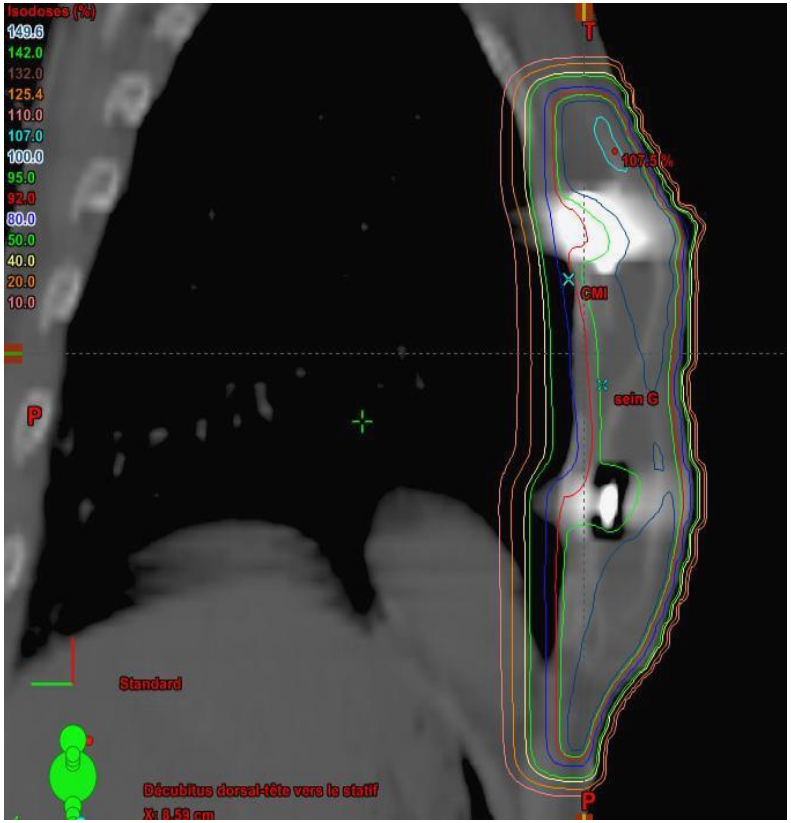


Chest wall and IMN irradiation without IBR



Breast irradiation with a temporary breast expander





Impact of immediate autologous graft on irradiation delivery
Motwani et al. *Int J Radiation Oncology Biol Phys*, 2006

- **112 patients treated with modified radical mastectomy and immediate breast reconstruction with autologous graft (TRAM in 96%)**

- **106 patients with modified radical mastectomy without IBR**

- **Dosimetric comparisons**

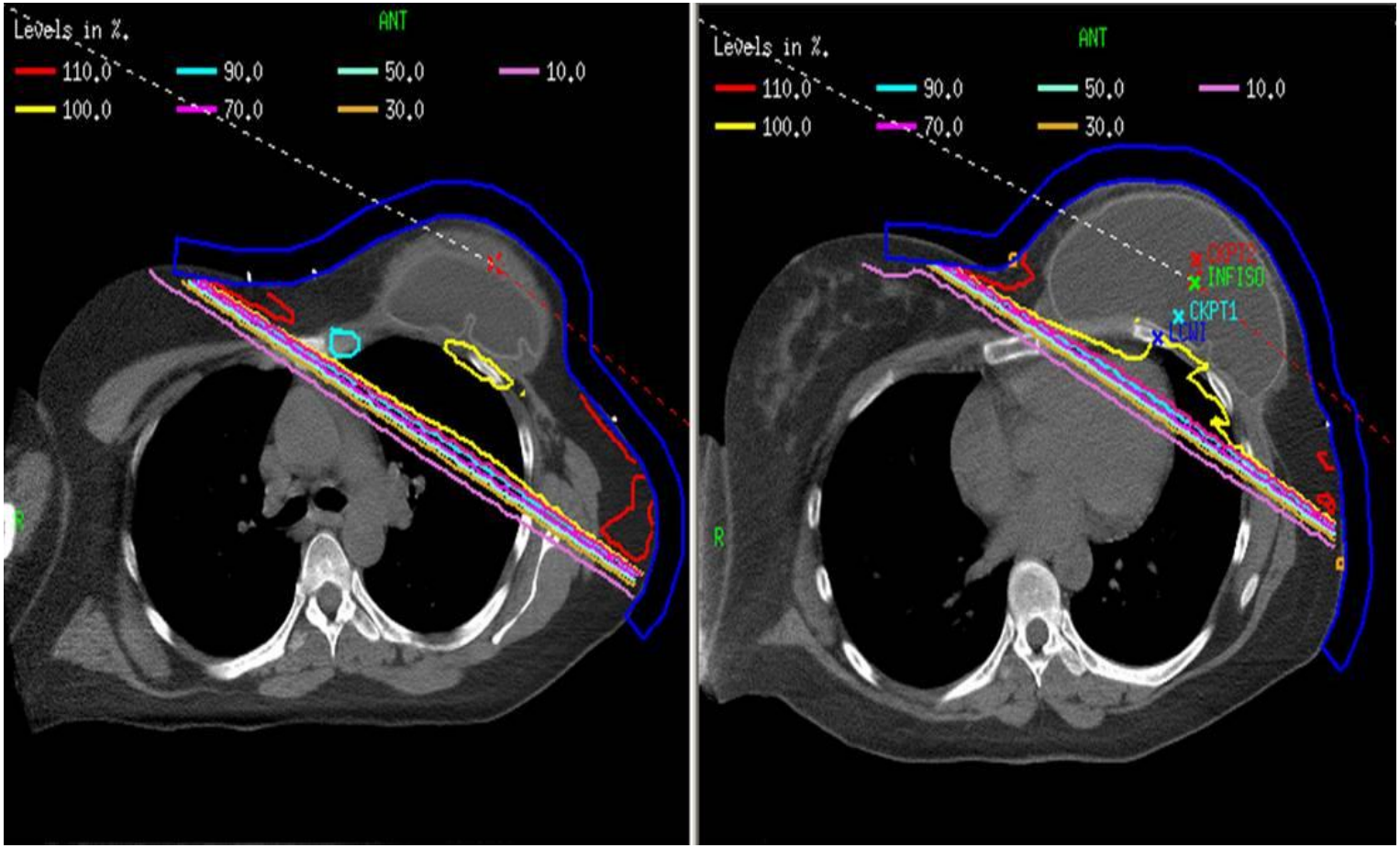
Impact of IBR on radiation delivery from Motwani et al. *Int J Radiat Oncol Biol Phys*, 2006

	% optimal dosimetry		
	without reconstruction	with reconstruction	
	n=112	n=106	*p*
Chest wall coverage	100	78	*< 0.0001*
Treatment of IMC	93	45	*< 0.0001*
Lung irradiation	97	83	*< 0.0015*
Heart protection	92	85	*0.14*

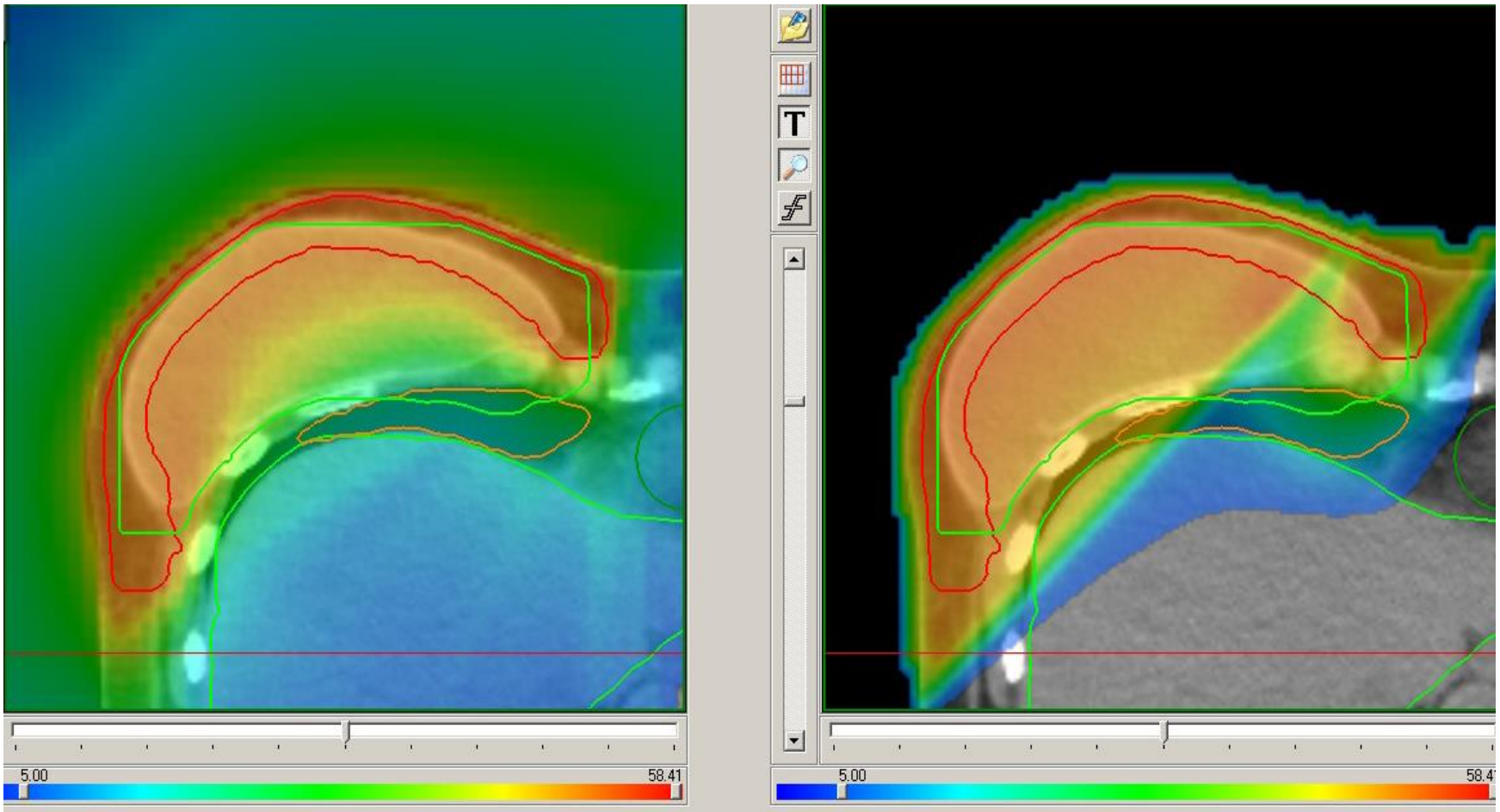
Would new radiotherapy techniques help?

- Intensity modulation radiotherapy (IMRT)
- IMRT with helicoïdal tomotherapy, rotational arctherapy, etc.

Post-Mastectomy IMRT and breast reconstruction
Koutcher L et al. ASTRO 2007

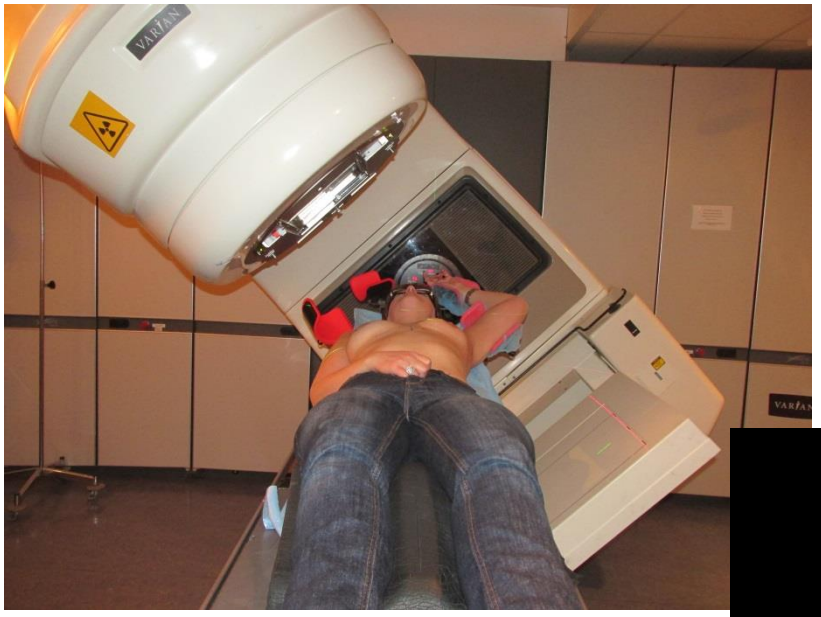


Place of IMRT: TOMO VS 3D

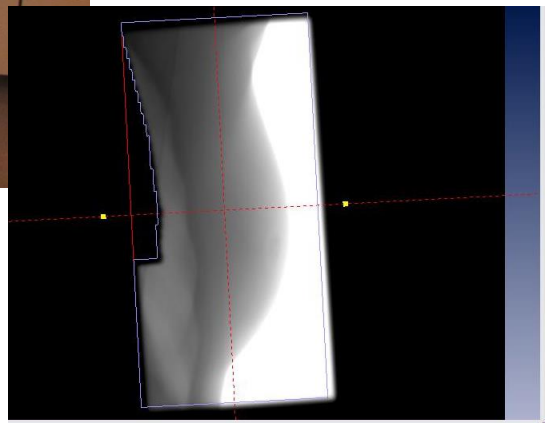


Massabeau et al, ESTRO 2011

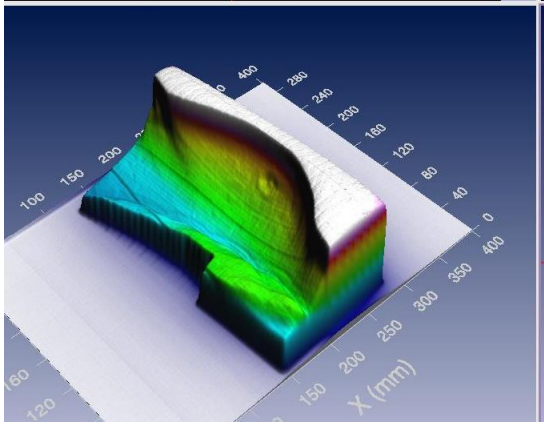
institutCurie
Ensemble, prenons le cancer de vitesse

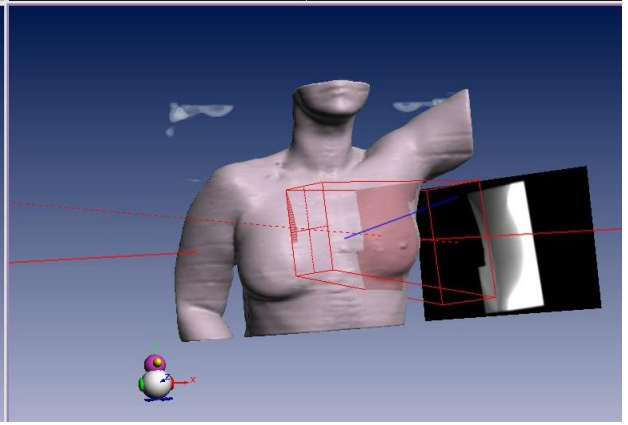


Don’t forget: In vivo dosimetry and quality controls



Transit dosimetry





François P et al. *Phys Med*, 2011

Conclusions 1

- Women with breast cancer present with a wide variety of clinical situations and anatomical differences
- Technical improvements allow to individualize the delivery of irradiation, with the aim of increasing its efficacy and limiting its toxicity

Conclusions 2

- Breast cancers represent a significant part of patients in a radiation oncology department (30-40 % of patients)

- A large majority of patients with preserved breast can be adequately treated with simplified IMRT field-in field techniques

Conclusions 3

- At present, full IMRT and rotational techniques (VMAT, Tomotherapy) should be used in difficult cases only, where adequate coverage of the target volumes cannot be achieved with conventional techniques, or organs at risk may receive unacceptable high doses.

Conclusions 4

These technical developments have drawbacks which could preclude their expected benefits.

- Increased costs
- Increased time for treatment planning
- Increased complexity which may impair security

Conclusions 5

- Not all patients need highly sophisticated treatment
- Training and expertise are mandatory
- Clinical expertise and judgement are essential

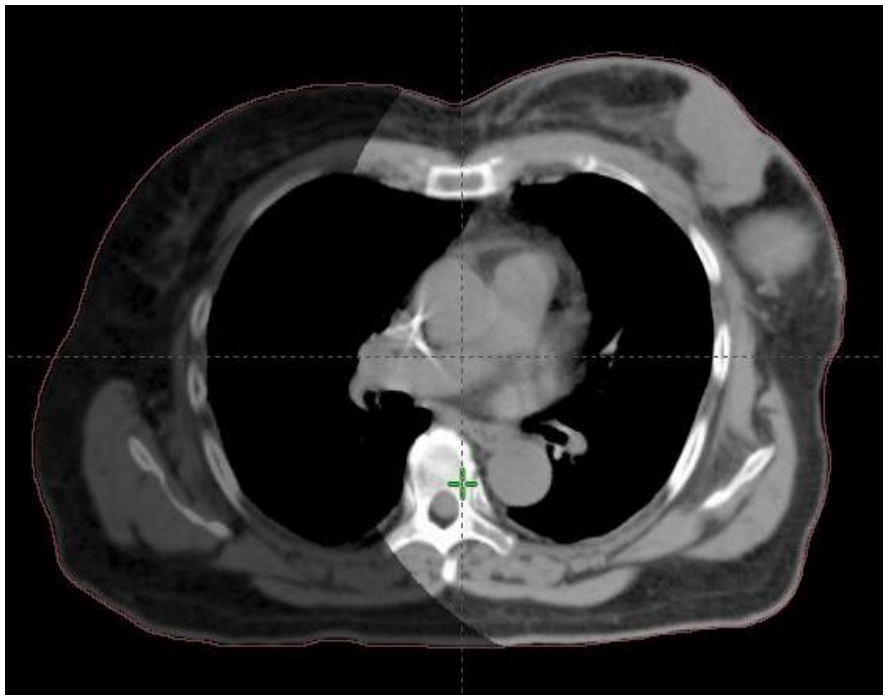
Conclusions 6

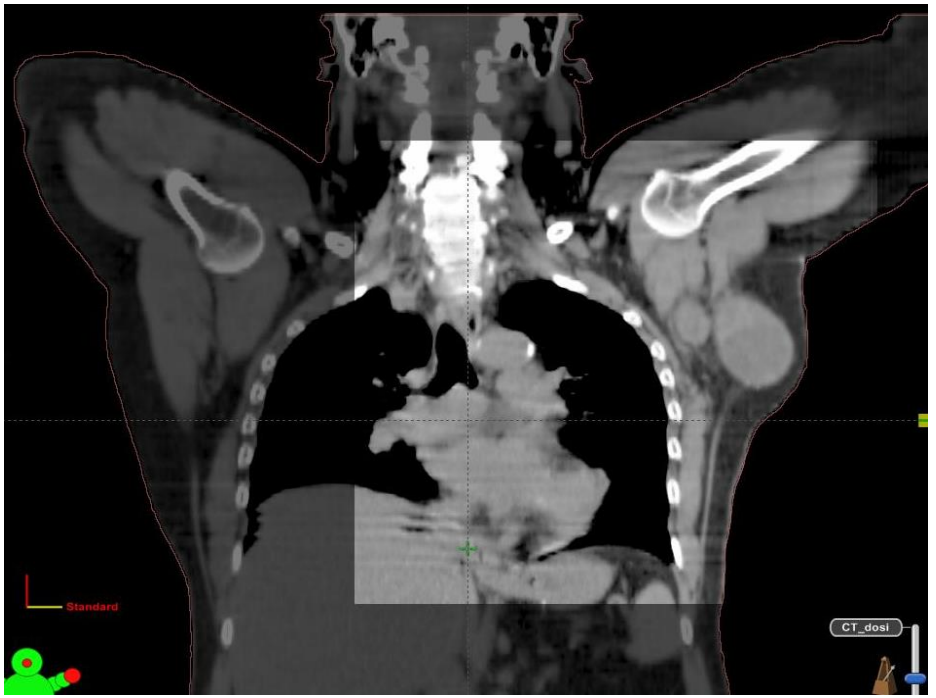
- Experience with immediate breast reconstruction + RT = limited.
- IBR has a negative impact on target coverage and dose homogeneity
- New treatment modalities could be an interesting option in case of bilateral implant irradiation as Intensity modulation radiotherapy (IMRT), IMRT with helicoïdal tomotherapy, rotational arc therapy, etc.

- …There is also for selected patients…

How you will this T4N3 patient?

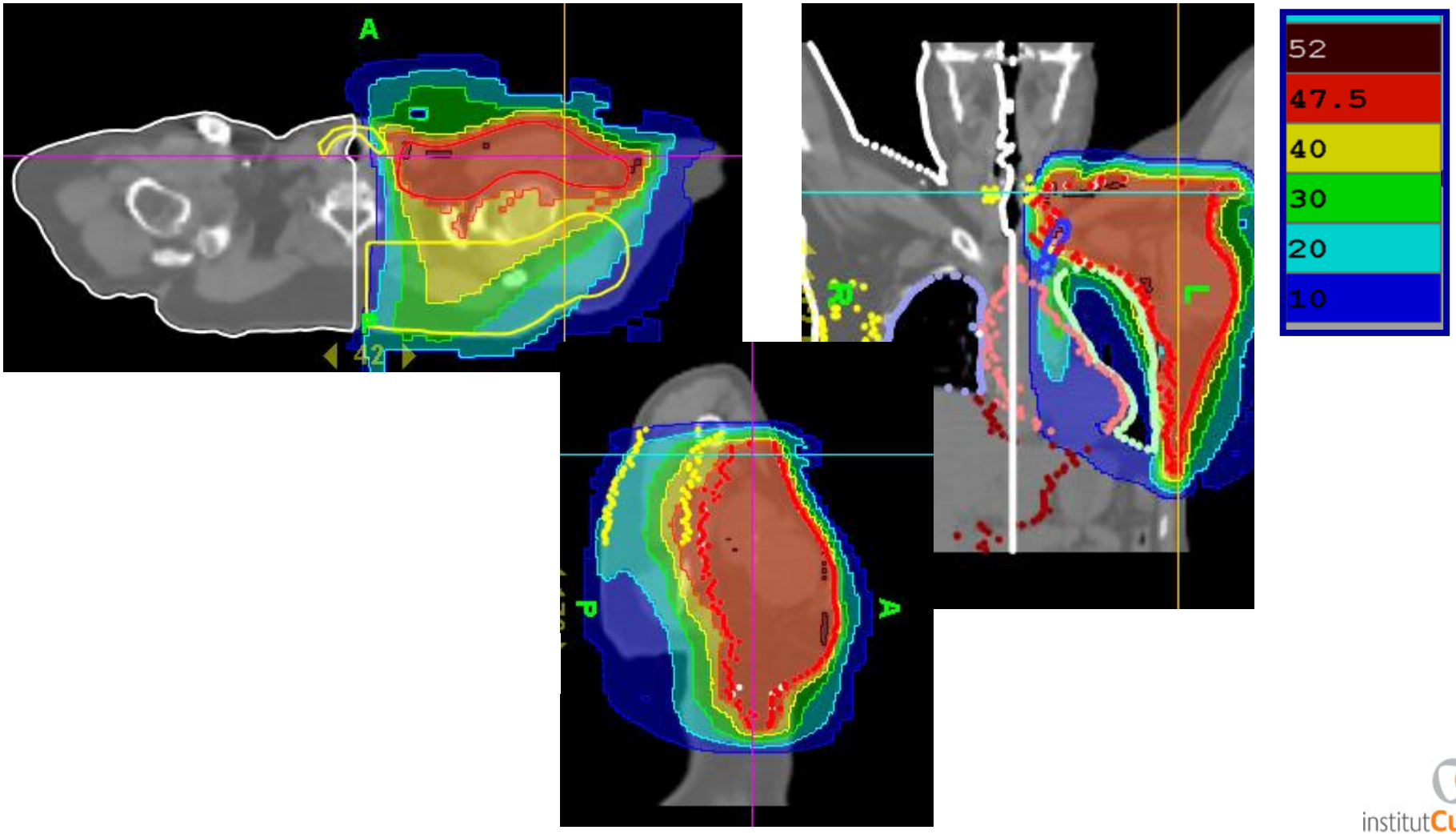
- After non response to chemotherapy, patient adressed for preoperative radiotherapy?





Inverse planning avec la Tomothérapie

- Evaluation du plan dosimétrique



Thank you for your attention

Special acknowledgements to:

L. Boersma

ESTRO School

and all my team:

A. Fourquet, N. Fournier-Bidoz,

D. Peurien, F. Laki,

R. Dendale, V. Servois

institutCurie
Ensemble, prenons le cancer de vitesse.

2017
ESTRO SCHOOL
LIVE COURSE

Multidisciplinary Management of Breast Cancer

10-13 September 2017
Dublin, Ireland

CANCER RESEARCH UK

Imperial College Healthcare NHS
NHS Trust

EBRO: Palliative RT

Ljubljana 2017

Dr. Matt Williams FRCR PhD

(Thanks to Yvette vdL)

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Imperial College London

BTRC

Outline

- Thinking about palliation & prognosis
- Palliative RT
- Evidence-base in specific areas of palliative RT

Palliation

- What are we trying to achieve with palliative radiotherapy ?

Palliation

- Multiple aims
- Different aims in different patients
- Different aims over times
- Different between doctors

Example Symptomatic Brain Metastases of SCLC

	Europe	USA
Extend Life	23 %	48 %
Relieve Symptoms	87 %	96 %
Prevent Symptoms	39 %	80 %
Give Hope	20 %	44 %

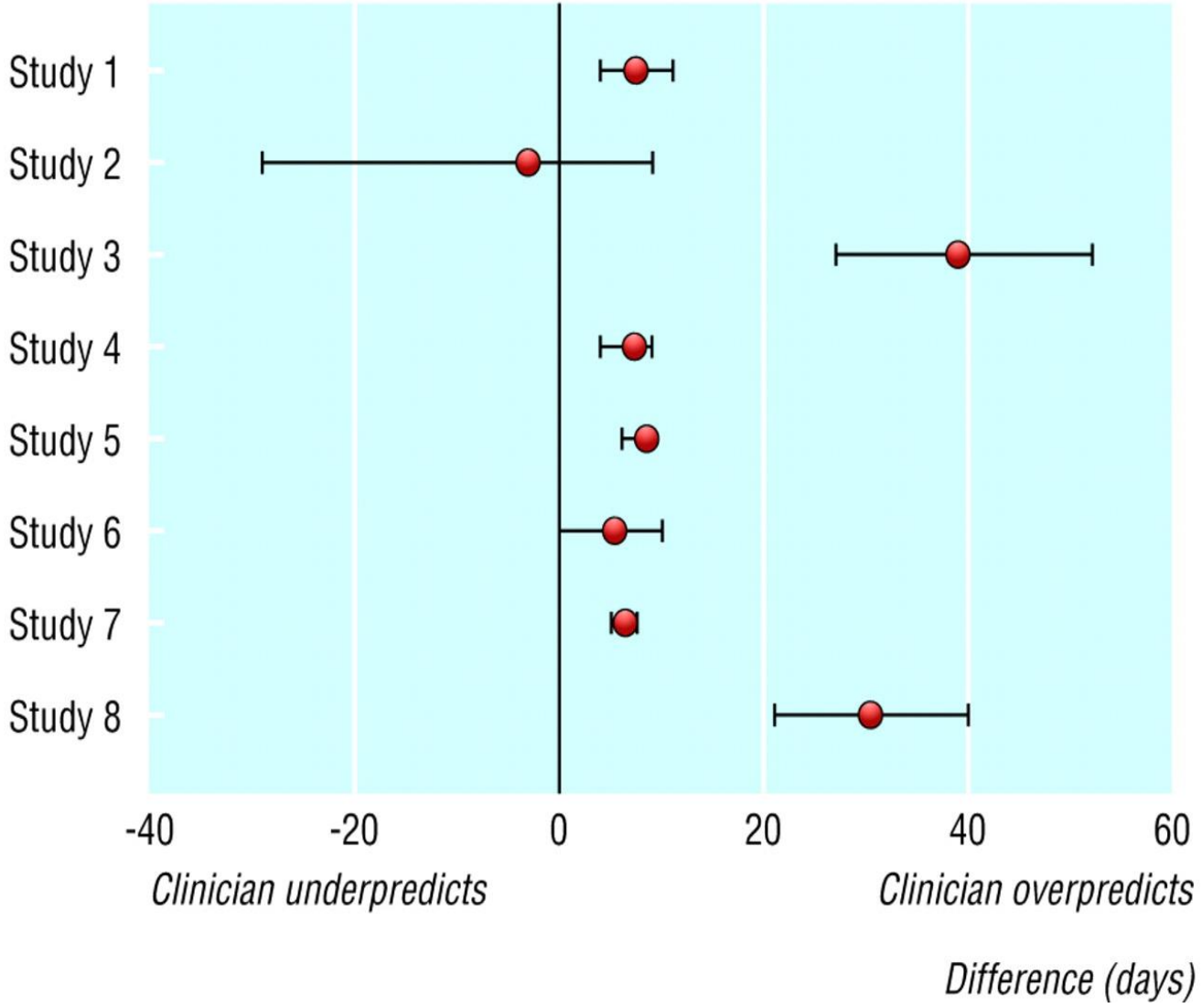
Maher et al, RedJ 1992

Prognosis

- Tailoring ideal palliative care requires understanding prognosis
- How good are we at predicting prognosis ?

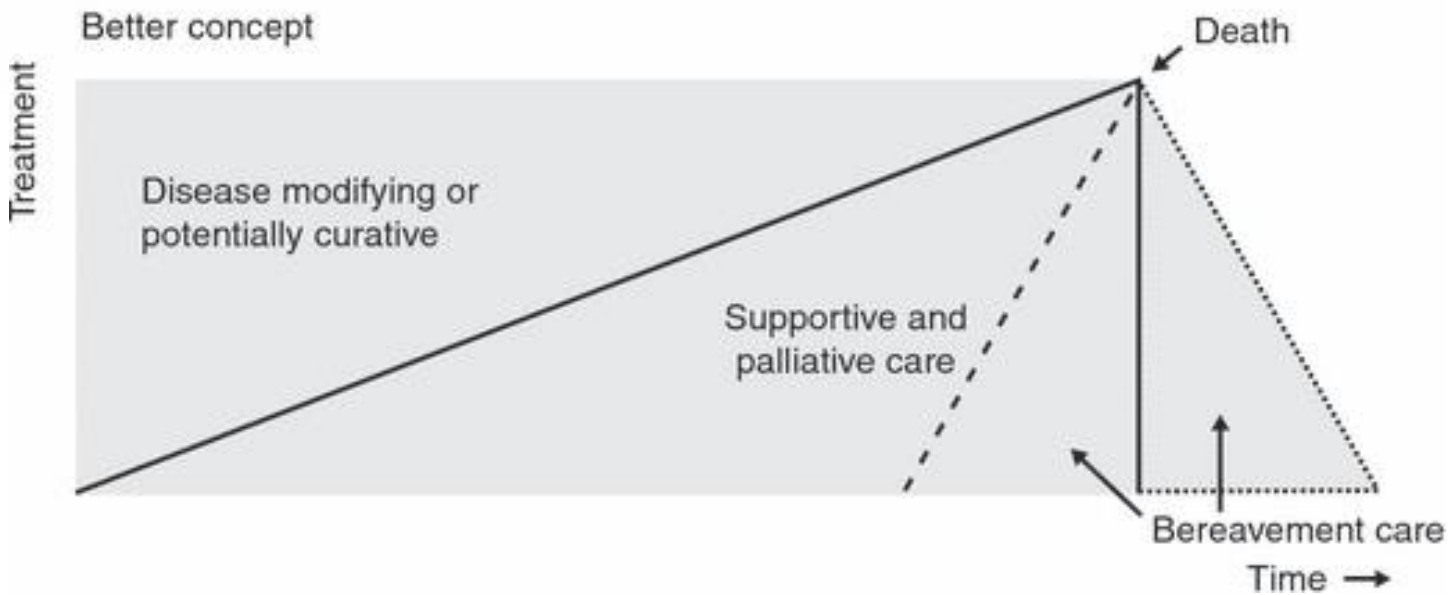
Prognosis

- Clinicians are not very good
- Doctors are worse than nurses



Glare BMJ 2003

Aims of palliation



Lynn & Adamason 2003

Expected Prognosis

- What is the expected survival in patients who receive palliative radiotherapy for:

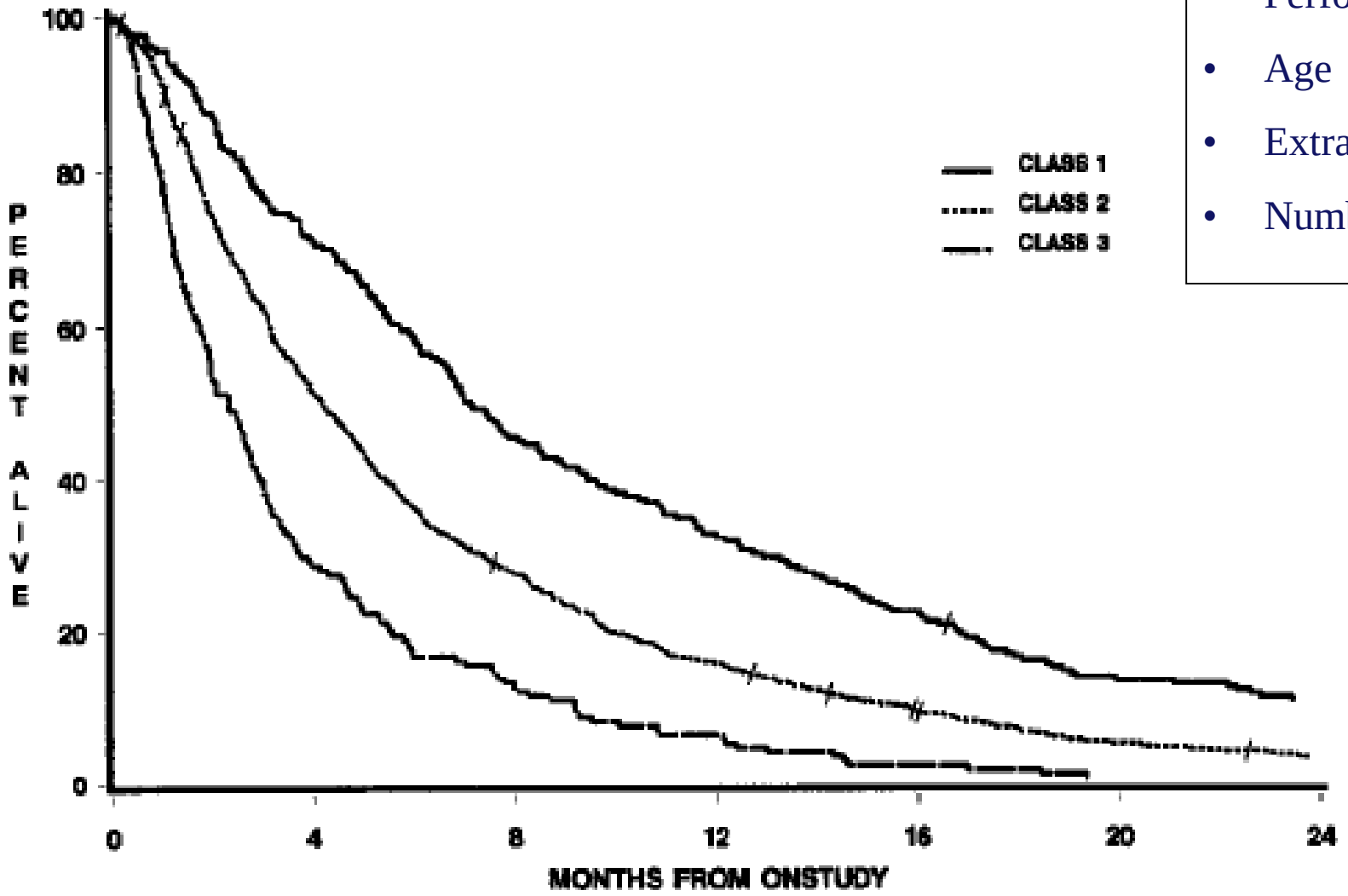
- Breast cancer with bone mets
- Brain mets (lung cancer)
- Oesophageal cancer (primary)

Beware of trials

GPA (Brain mets)

4000 pts

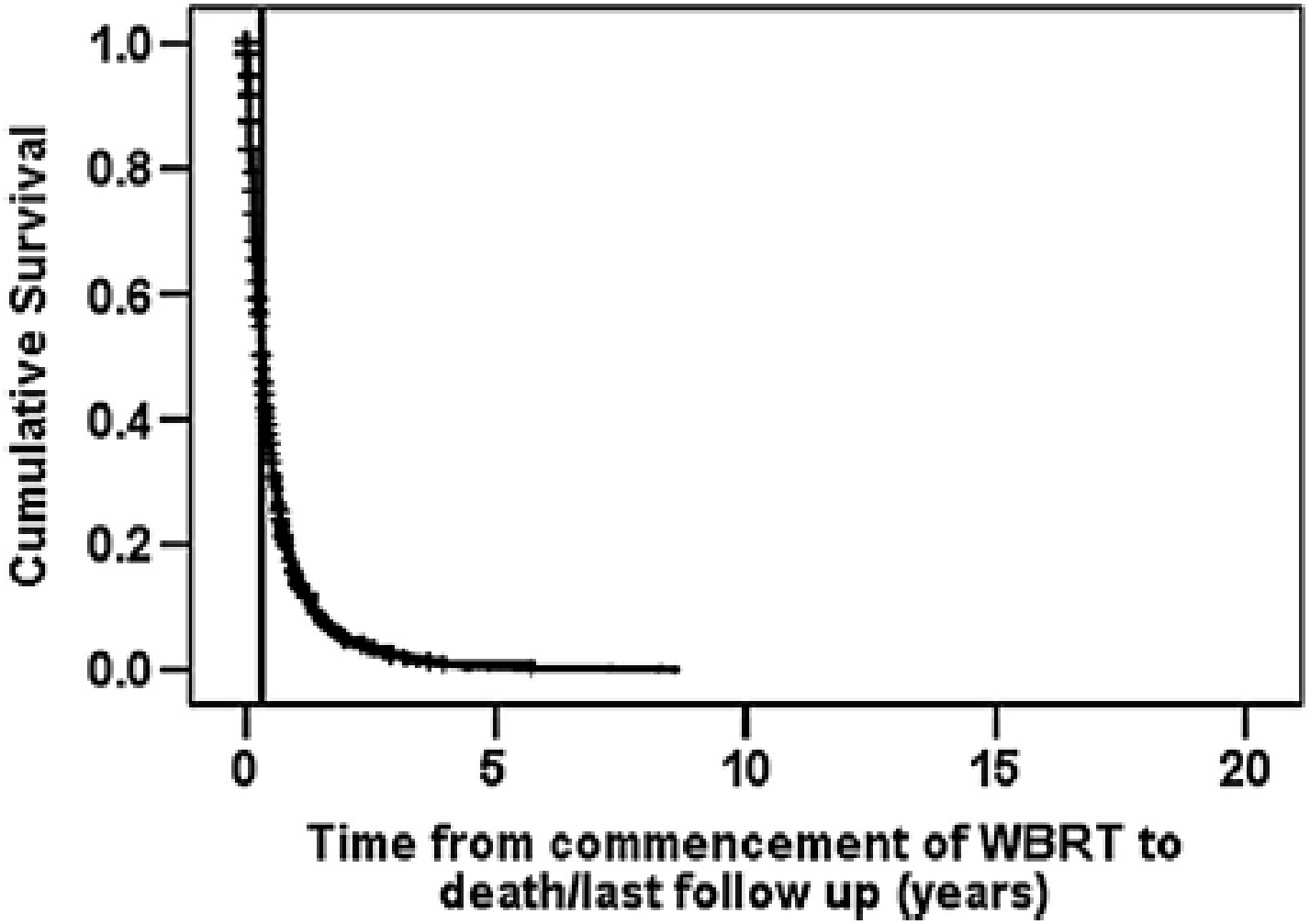
- Performance
- Age
- Extracranial mets
- Number of brain mets



Beware of trials

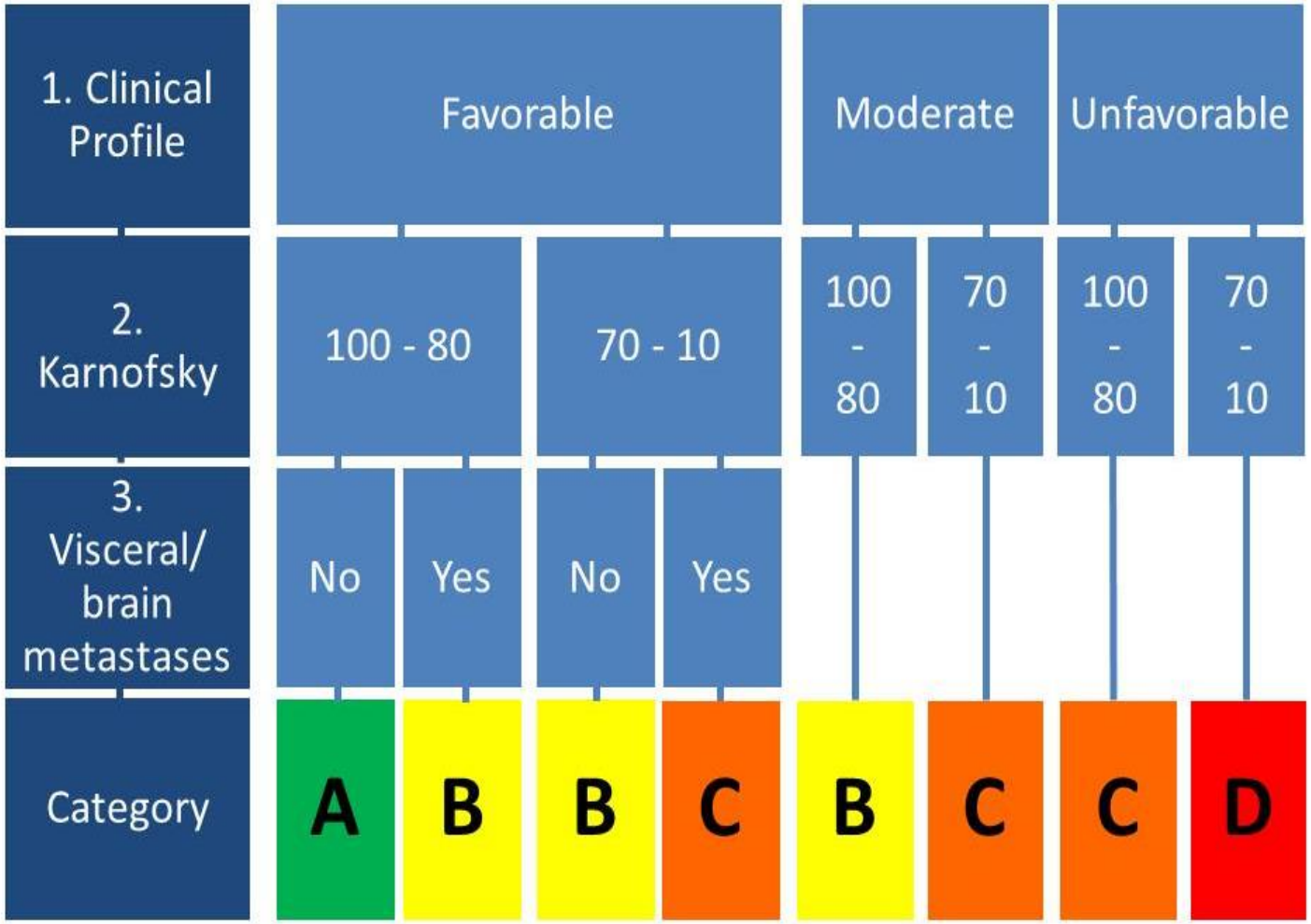
Brain mets (Routine care)

- N= 3459, three centers (n= 709 Dutch)
- Risk factors
  - Older age
  - Short time between diagnosis and brain mets
  - Primary tumor
- Median OS 4 months
- 25% died < 8 weeks

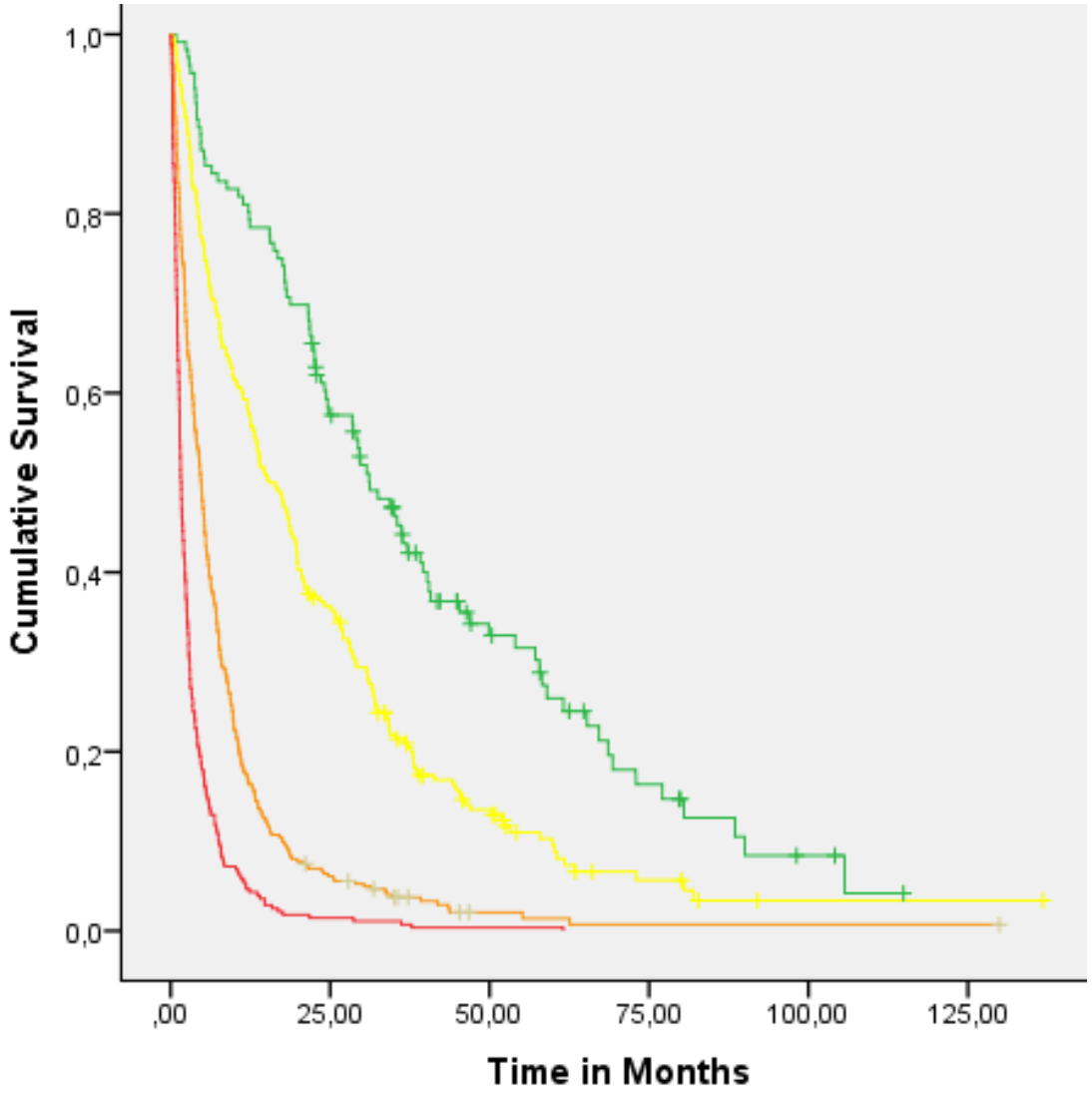


Windsor et al, Clin Oncol 2013

Formal prognostic tools can help

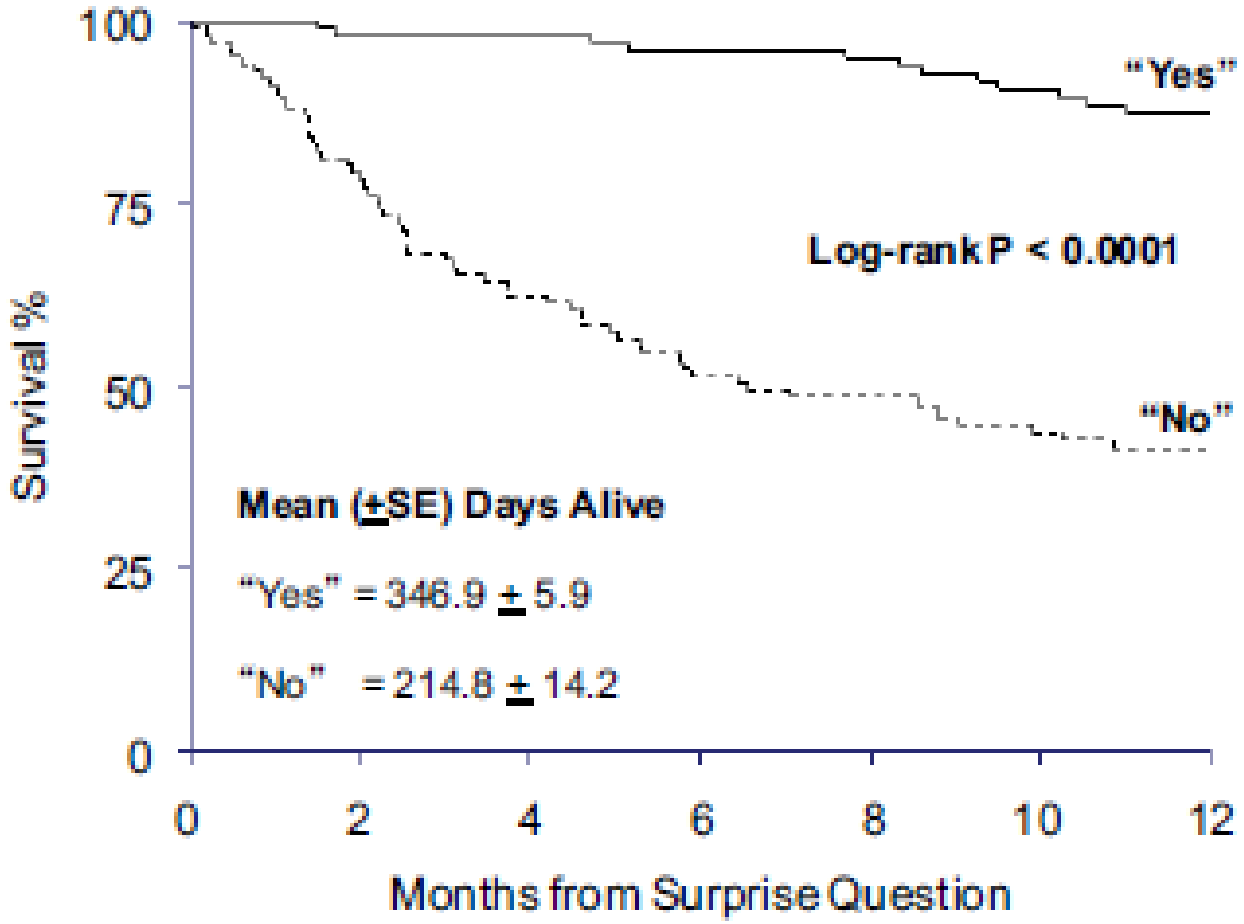


Formal prognostic tools can help



Would I be surprised ?

- Would I be surprised if my patient died in the next year ?



Survival Intervals

- Median * 0.25: 90%
- Median* 0.5: 75%
- Median * 2: 25%
- Median * 3: 10%

- “Worst, Some, Many, Most”
- 50% die between 75% and 25%

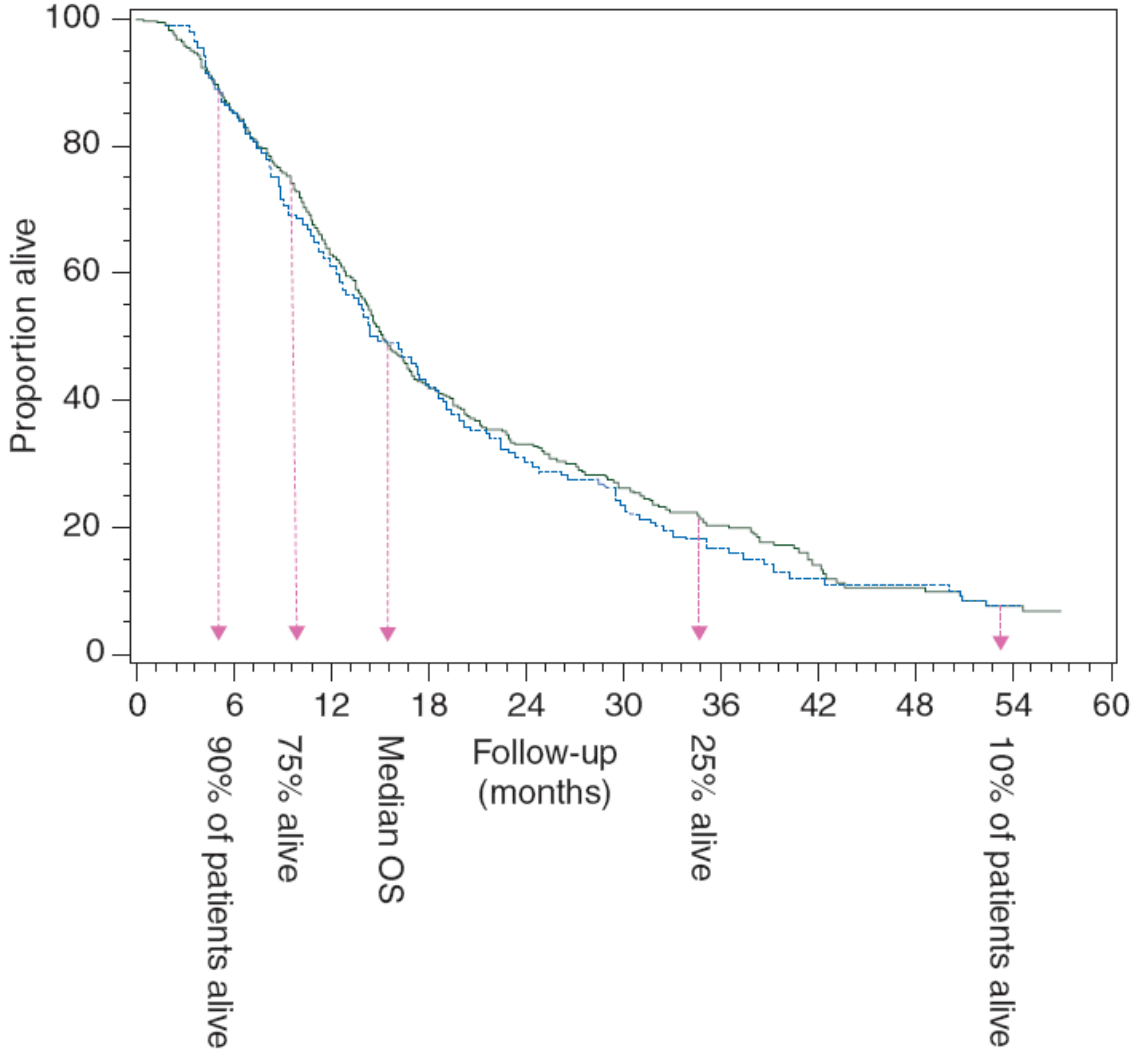


Figure 1. Measuring the time to different levels of survival from published survival curves.

Kiely, JCO 2011
Williams, AnnOnc 2014

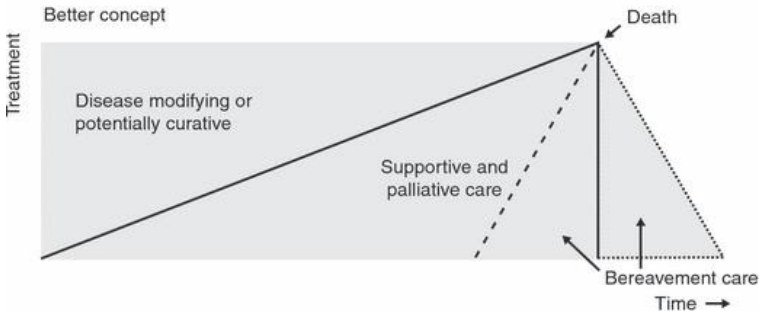
Prognosis

?

Role of radiotherapy in palliation

- Palliative RT can (should) run alongside other palliative measures
- Is it effective?
- Safe?
- Cost-effective?
- Tolerable?

- Palliative RT as a palliative intervention
  not an RT technique



Effectiveness of palliative RT

Condition	*Rates of symptom improvement*
Metastatic bone pain	
Partial relief	70%–94%
Complete relief	28%–80%
Hemoptysis	72%–86%
Chest pain (lung cancer)	59%–86%
Dyspnea (lung cancer)	41%–66%
Cough (lung cancer)	48%–66%
Dysphagia	61%–65%
Superior vena cava obstruction	60%–90%
Brain metastases	50%–70%
Spinal cord compression	64%–73%

Samant & Tucker Curr Onc 2006

Effectiveness of palliative RT

Condition	*NNT*
Painful bone metastases	
Partial relief	1.25
Complete relief	2.5
Hemoptysis	1.25
Chest pain (lung cancer)	1.43
Superior vena cava syndrome	1.3
Brain metastases	1.67
Spinal cord compression	1.5

Effectiveness of palliative RT

Condition	*NNT*
Painful bone metastases	
Partial relief	1.25
Complete relief	2.5
Hemoptysis	1.25
Chest pain (lung cancer)	1.43
Superior vena cava syndrome	1.3
Brain metastases	1.67
Spinal cord compression	1.5

- Some of these are over estimates
- Some are wrong
- But the “pooled” NNT for palliative RT remains good

Comparative NNT

Costs of palliative RT

- Different treatment modalities
  - Hillner et al — JCO 2000
    - *Oral pamidronate US$ 775 per month*
    - *Prevent SRE US$ 3940 chemo vs $ 9390 hormonal*
  - Swedish Council — Acta Oncol 1996
    - *RT US$ 2000 per patient*
  - Ferrel et al — J.Pain Sympt.Man 1994
    - *Oral analgesics US$ 1000 per patient / month*
    - *Parenteral US$ 4000*
  - Macklis et al — Am.J.Clin.Onc 1998
    - *RT US$ 1200-2500 vs narcotics $9000 – 36000*
  - Stevens et al — Austral.Rad. 1997
    - *RT costs per month survival AUS$ 105*

What drives the cost of palliative RT

- Case: man with hormone refractory prostate cancer
  1. Pain medication
  2. Chemotherapy (trial on mitoxantrone + prednison)
  3. Radiotherapy
     - SF 1 x 8 Gy, MF 10 x 3 Gy
     - Retreatments included

- For each treatment -> based on literature data
  - Model entering -> transition probabilities
  - Costs calculations
  - Utilities calculations

Konski RedJ 2004

Costs of palliative RT

Treatment	Cost ($)	Incremental cost ($)	Effectiveness (QALM)	Incremental effectiveness (QALM)	Incremental cost-effectiveness ($/QALY)
Pain medication	11 700		5.75		
Single fraction radiotherapy	11 900	200	6.1	0.35	6857
Multiple fraction radiotherapy	13 200	1500	6.25	0.5	36 000
Chemotherapy	15 300	3600	4.93	−0.82	–

QALM, quality-adjusted life per month; QALY, quality-adjusted life year.

Costs of RT

		8 Gy × 1 ($n=80$)		4 Gy × 6 ($n=86$)	*P* value*
Costs of radiotherapy		2438		3311	<0.001
Initial treatment		1838		2448	–
Re-treatments ≤12 weeks	18%	466	5%	159	0.01
Time, travel, out of pocket	10 h	134	25 h	704	<0.001
Other medical costs		2072		3114	0.18
Hospitalisation	28%	914	41%	2160	0.08
Systemic therapy	61%	373	59%	247	0.19
Consultations	6.3	302	6.4	248	0.42
Pain medication		79		56	0.19
Other medication		322		247	0.51
Home nursing care	5 h	81	9 h	156	0.22
Other non-medical costs		190		28	0.44
Time, travel	8 h	94		130	0.35
Out of pocket		127		64	0.19
Domestic help	42 h	438	43 h	482	0.65
(Un)paid labour	56 h	−468	77 h	−647	0.26
Medical costs		**4376**		**5720**	0.09
Societal costs		**4700**		**6453**	0.06

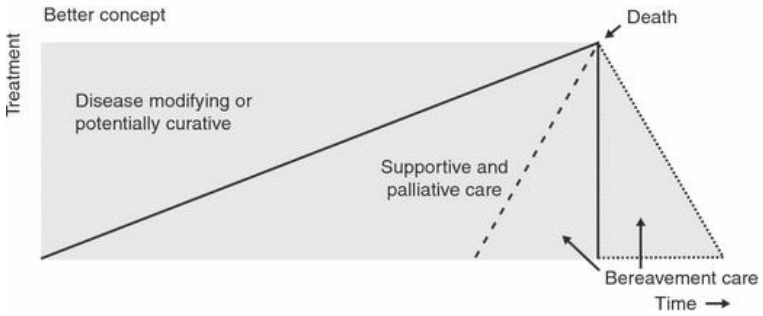
Konski RedJ 2004

Message

- Palliative RT is an effective palliative measure
- It is cost effective
- Costs are driven by a variety of measures
  - RT Treatment
  - Other medical costs
  - Travel, time, care costs
- Costs to patient (ambulance, stretcher, etc.) can be great, and non-monetary

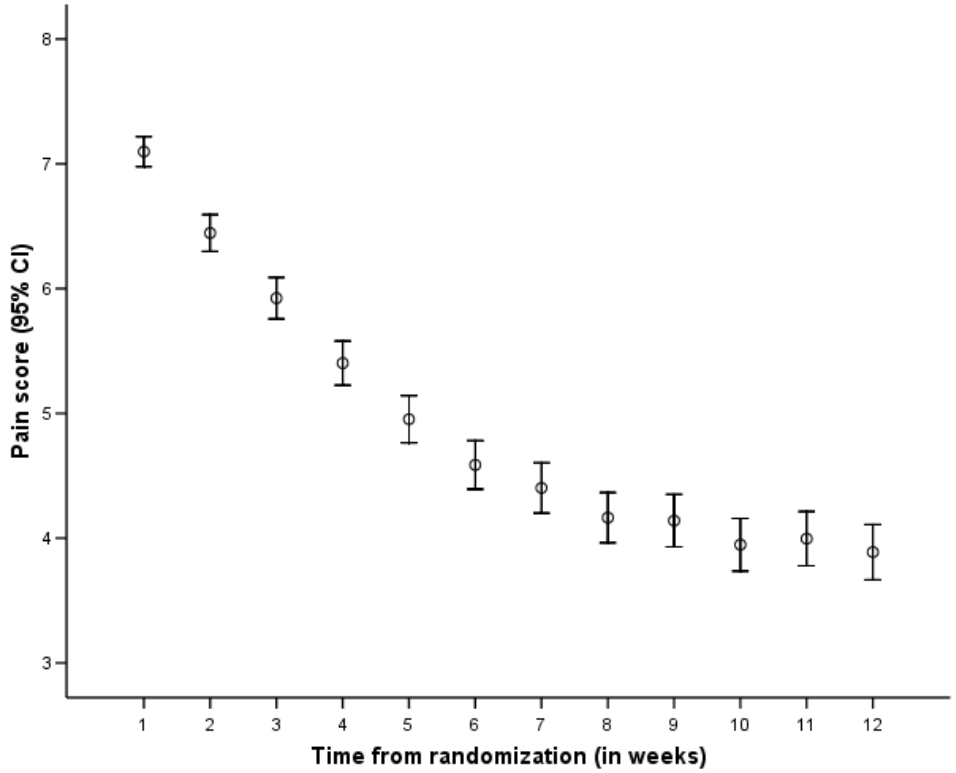
Specific clinical situations for Pall RT

- Bone mets
  - Retreatment
- MSCC
- Lung cancer
- Brain Mets



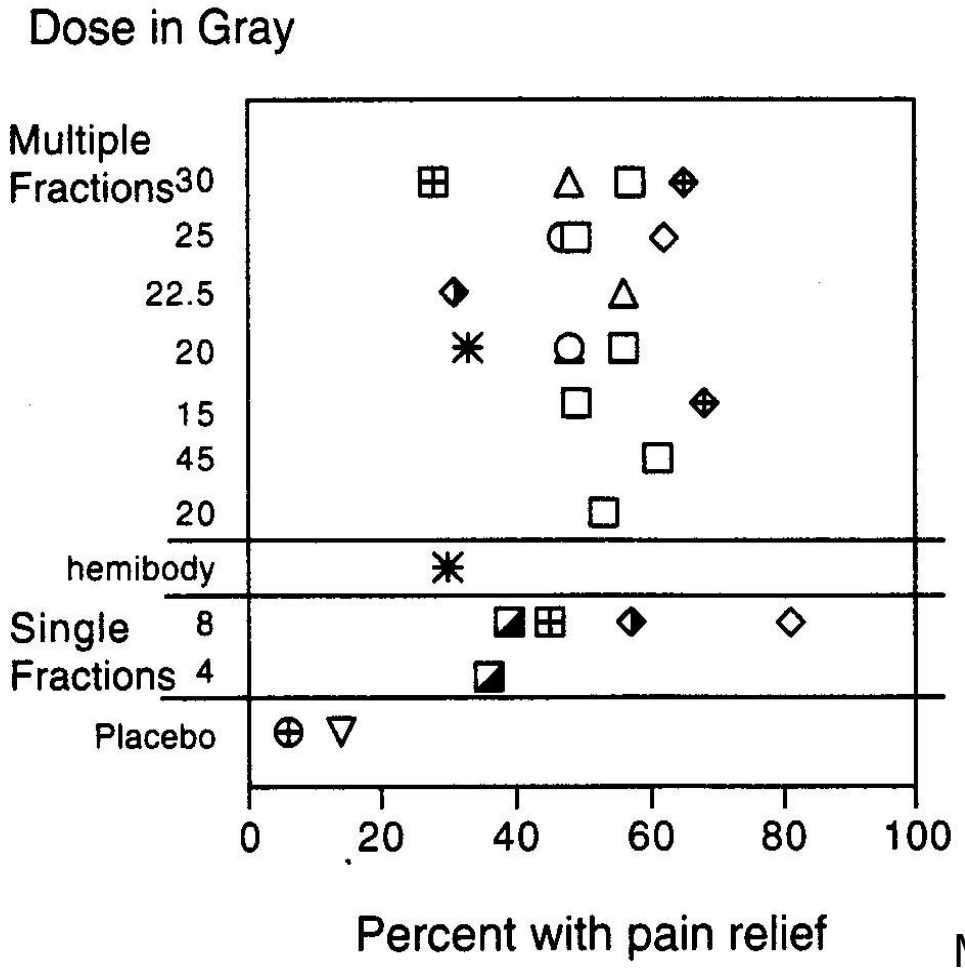
PallRT is an effective treatment for bone mets

- 75% of patients get significant pain relief within 3 weeks



PallRT is an effective treatment for bone mets

- Multiple fractions no better than single fraction

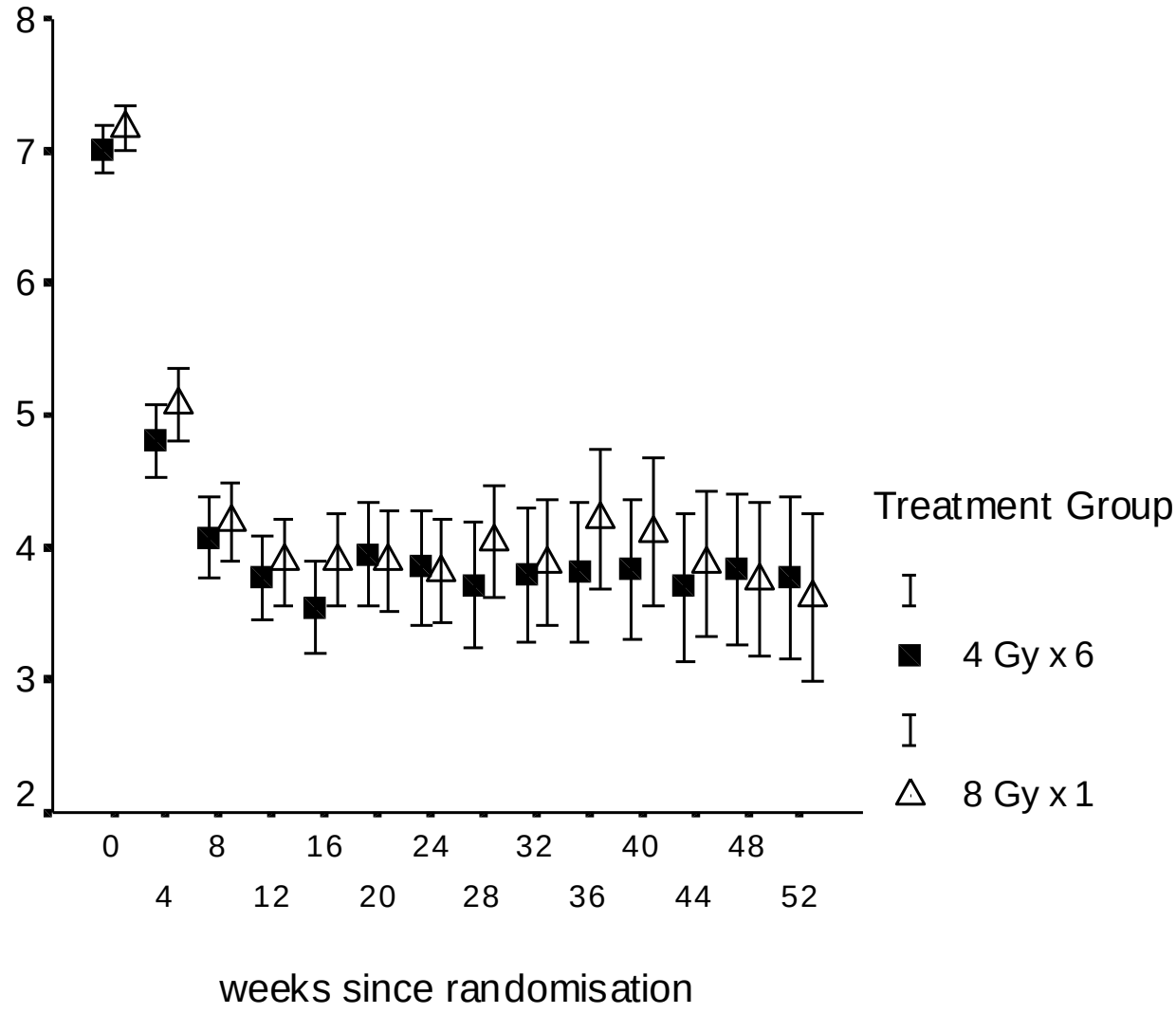


McQuay 1997

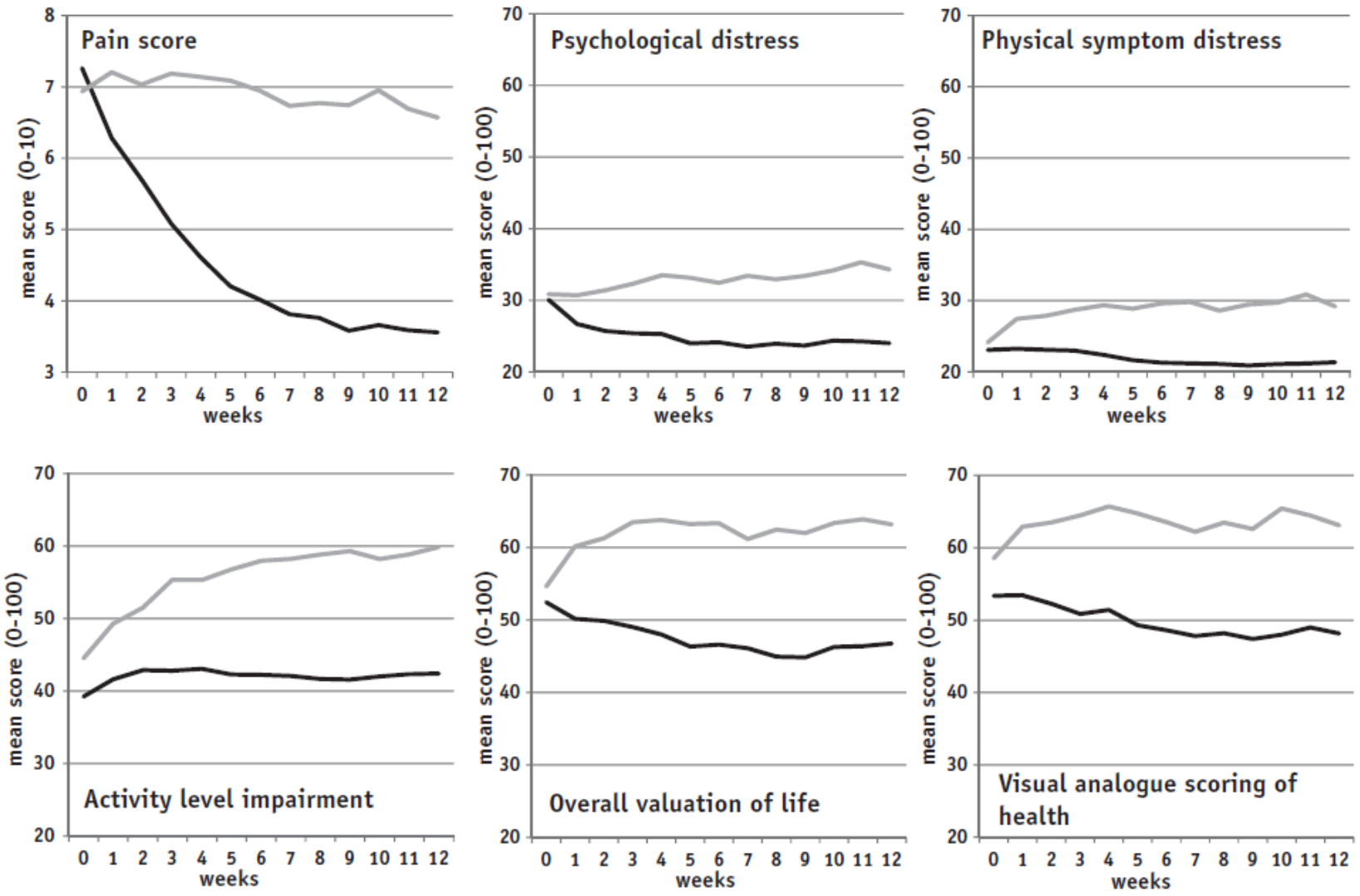
PallRT is an effective treatment for bone mets

- Single fraction offer durable response
- (N = 320 lived longer than 1 year; no benefit from multi #)
- No difference between tumours subgroups
- Elderly

- 4Gy is worse than 8Gy



Responding pts have improved QoL



Nesthoff et al. IJROBP 2015

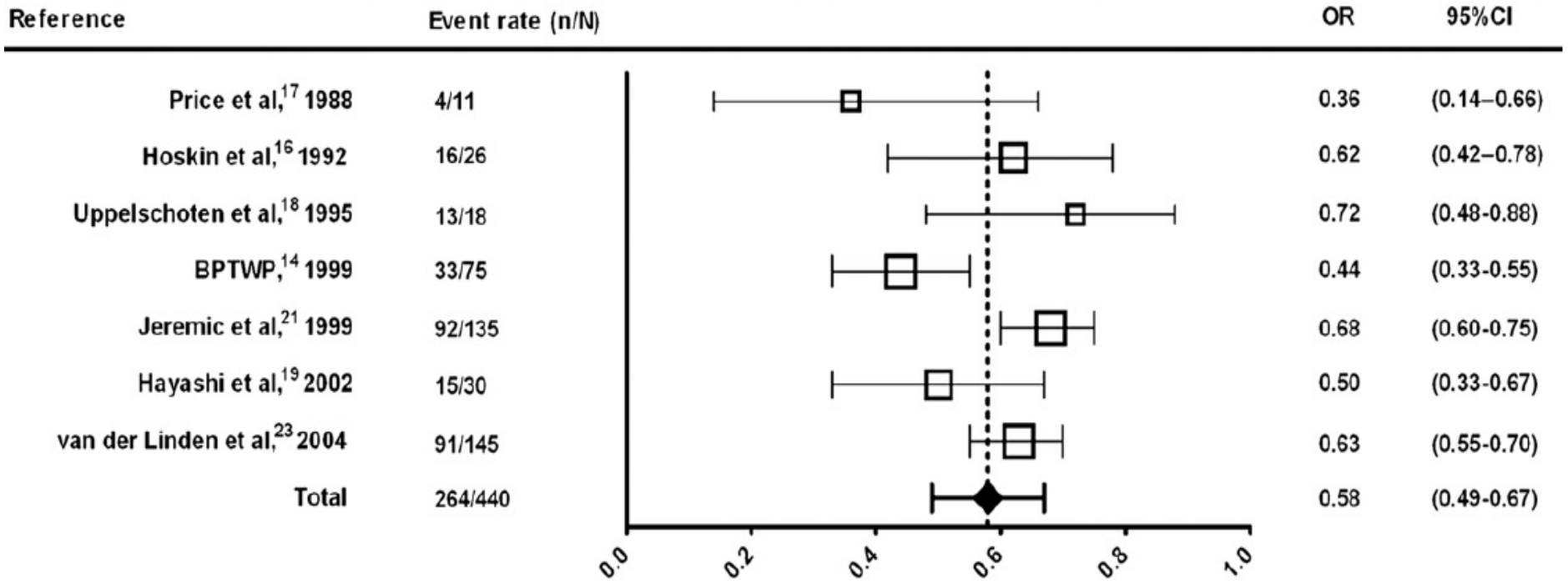
Recurrent pain

- ~50% of patients experience recurrent pain
  - 50% of patients died by 7 months

- Are those who have single fraction more likely to have retreatment
  - In some trials, yes
  - But pain scores no different
  - -> Probably clinicians more willing to prescribe second course if first was single fraction

Bone met retreatment

- Retreatment is possible
- Effective (~60% RR) - non randomsied
- Safe



RCT on retreatment

Two-month Response	Intention to Treat Analysis		Per-Protocol Analysis	
	8 Gy Single Fraction (N = 425)	*20 Gy Multiple Fractions (N = 425)*	*8 Gy Single Fraction (N = 258)*	*20 Gy Multiple Fractions (N = 263)*
Complete Response	36 (8%)	32 (8%)	35 (14%)	31 (12%)
Partial Response	83 (20%)	104 (24%)	82 (32%)	104 (40%)
Overall Response	**119 (28%)**	**136 (32%)**	**117 (45%)**	**135 (51%)**
Inevaluable	162 (36%)	160 (36%)	0	0
Not Defined	92 (22%)	90 (21%)	91 (35%)	90 (34%)
No Change	7 (2%)	7 (2%)	7 (3%)	7 (3%)
Pain Progression	45 (11%)	32 (8%)	43 (17%)	31 (12%)

Chow Lancet Onc 2014

Bone mets

?

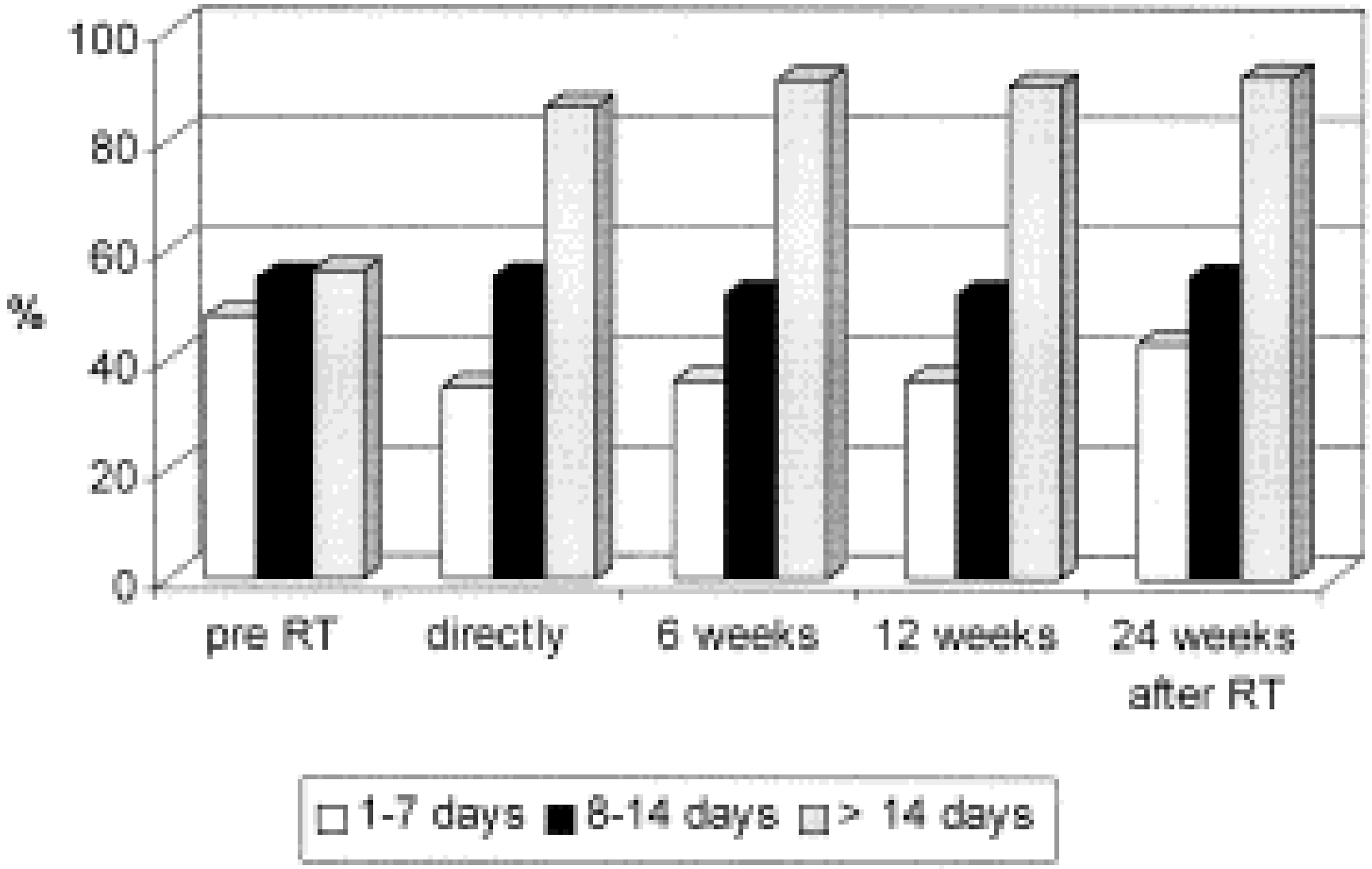
Metastatic Spinal Cord Compression

- Traditionally 20Gy/5#; 30/10 or similar
- Modestly successful

Motor and sphincter function before and after treatment according to radiotherapy regimen.

	8 Gy × 2 short-course No. of patients (%)	8 Gy single-dose No. of patients (%)	Total No. of patients (%)
Motor function			
1. Walking pretreatment	101 (67)	98 (64)	199 (65)
Walking	91 (90)	86 (88)	177 (89)
Not walking	10 (10)	12 (12)	22 (11)
2. Not walking pretreatment	49 (33)	55 (36)	104 (35)
Ambulation regained	13 (26)	9 (16)	22 (21)
Not walking	36 (74)	46 (84)	82 (79)
Total of responders	104 (69)	95 (62) p = N.S.	199 (66)

MSCC time to onset



MSCC Surgery

- Surgery may be beneficial
- No apparent benefit from laminectomy
- Patchell paper (!)
- Also consider stability (SINS)

	LE+RT ($n = 24$)	RT ($n = 48$)	p value
Ambulatory following treatment	33%	50%	0.41
Regaining ambulatory status	15%	19%	0.97
Treatment effect on motor function			
Improvement	13%	13%	0.15
No change	46%	65%	
Deterioration	42%	23%	
Local control of MSCC			
At 6 months	89%	92%	0.60
At 12 months	71%	92%	
Survival			
At 6 months	38%	44%	0.67
At 12 months	27%	14%	

Rades JCO 2010

MSCC dose/ fractionation

Motor and sphincter function before and after treatment according to radiotherapy regimen.

	8 Gy × 2 short-course No. of patients (%)	8 Gy single-dose No. of patients (%)	Total No. of patients (%)
Motor function			
1. Walking pretreatment	101 (67)	98 (64)	199 (65)
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Total of responders	104 (69)	95 (62) p = N.S.	199 (66)

Maranzano GreenJ 2009

SCORAD III

- ASCO 2017
- 688 pts; MSCC (single level)
- 8Gy/1# vs. 20Gy/5#
- 11% non-inferiority AS 1-2 @ 8 weeks
- 73% male; Median age 70
- Single field

- No difference in AS or OS (median ~12 weeks)

MSCC

?

Lung cancer

- Stage IV lung cancer pts often have significant symptoms

- 69 pts 3Gy/#
- Upto 30 Gy
- AP fields

Table 4. Pretreatment symptoms

Symptom or functioning scale	% of patients	Mean score in all patients (SD)
Symptoms		
Fatigue	94	54.4 (26.8)
Cough	89	51.3 (28.9)
Dyspnea	88	46.3 (30.8)
Pain	86	42.3 (32.4)
Appetite loss	71	47.7 (36.9)
Pain chest wall	62	34.9 (33.6)
Insomnia	57	35.4 (36.7)
Hemoptysis	46	21.5 (26.6)
Pain arm/shoulder	43	28.2 (36.9)
Nausea and vomiting	34	13.8 (26.3)
Constipation	31	17.4 (31.2)
Dysphagia	25	14.4 (27.6)
Functioning scales and global quality of life		
Physical functioning	—	43.6 (32.9)
Role functioning	—	50.0 (37.5)
Emotional functioning	—	56.7 (23.8)
Cognitive functioning	—	73.1 (27.0)
Social functioning	—	69.7 (34.0)
Global QoL	—	40.1 (22.3)

Langendijk, RedJ 2000

Palliative RT is effective

Table 5. Response classification for general and respiratory symptoms

		Cough	Hemoptysis	Dyspnea	Pain arm/ shoulder	Chest pain	Fatigue	Appetite loss
Total patients		65	65	65	65	65	65	65
Inadequate follow-up data*		13	18	12	19	18	13	17
Remaining for analysis		52	47	53	46	47	52	48
Improvement	Mild	2/21 (10%)	7/18 (39%)	7/14 (50%)	1/5 (20%)	4/15 (27%)	0/10 (0%)	4/9 (44%)
	Moderate/severe	12/24 (50%)	4/8 (50%)	8/31 (26%)	6/16 (38%)	8/17 (47%)	5/48 (10%)	4/27 (15%)
Control	Mild	8/21 (38%)	5/18 (28%)	7/14 (50%)	2/5 (40%)	5/15 (33%)	4/10 (40%)	1/9 (11%)
Prevention	Nil	3/7 (43%)	20/21 (95%)	3/8 (38%)	17/25 (68%)	11/15 (73%)	2/4 (50%)	7/12 (58%)
Dead without palliation	Nil	1/7 (14%)	0/21 (0%)	1/8 (13%)	1/25 (4%)	0/15 (0%)	0/4 (0%)	0/12 (0%)
	Mild	5/21 (24%)	1/18 (6%)	2/14 (14%)	1/5 (20%)	2/15 (13%)	3/10 (30%)	0/9 (0%)
	Moderate/severe	6/24 (25%)	3/8 (38%)	10/31 (32%)	4/16 (25%)	5/17 (29%)	9/48 (19%)	8/27 (30%)
Response rate		25/52 (48%)	37/47 (79%)	19/53 (36%)	26/46 (57%)	28/47 (60%)	11/52 (21%)	16/48 (33%)

* The number of patients with inadequate follow-up data may differ between scales because of the definition of "inadequate follow-up" (see also Table 2).

More than just physical effects

- In those with an objective response (!)
  - Physical functioning
  - Cognitive, emotional, global QoL all improve

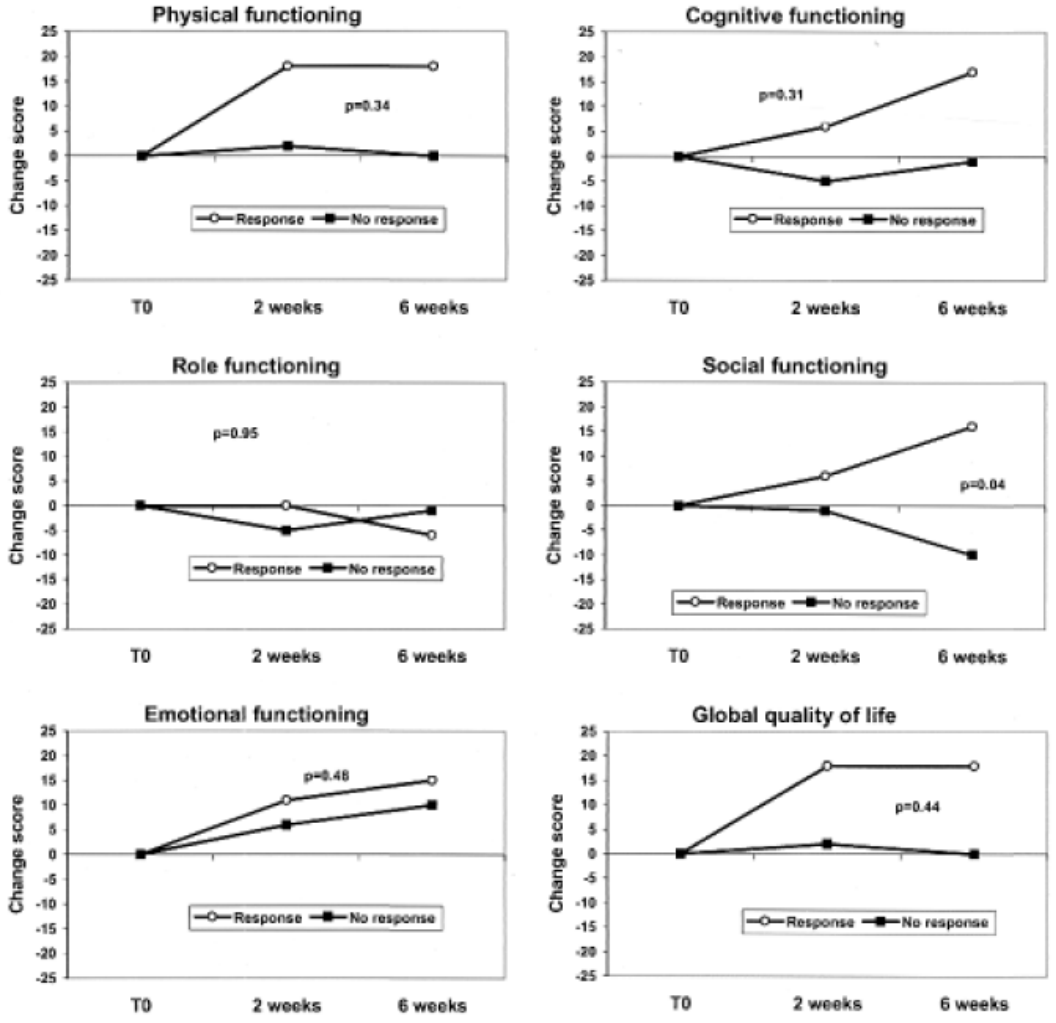


Fig. 2. Change scores for functioning scales and global QoL stratified by objective tumor response.

Early Palliative care

- 151 pts new diagnosis metastatic NSCLC
- Randomised to early palliative care (plus oncology) vs. oncology alone
- QoL at baseline and 12 weeks
  - Survival, use of chemo, documentation of DNAR wishes

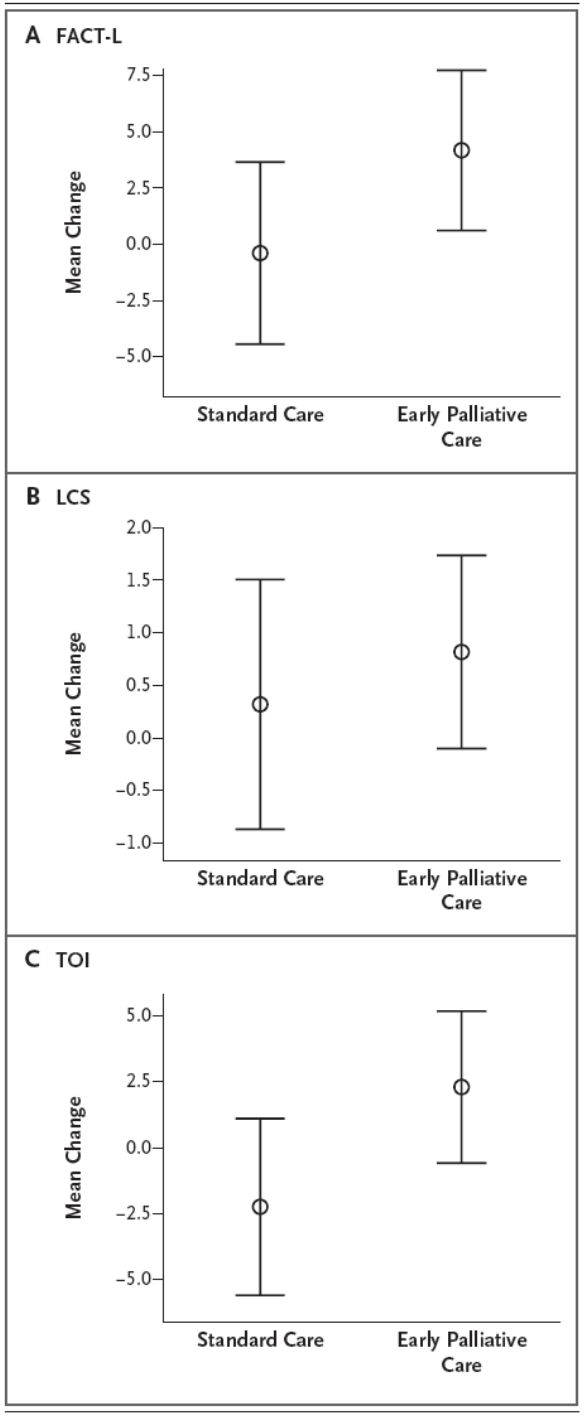
ORIGINAL ARTICLE

Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alona Muzikansky, M.A., Emily R. Gallagher, R.N., Sonal Admane, M.B., B.S., M.P.H., Vicki A. Jackson, M.D., M.P.H., Constance M. Dahlin, A.P.N., Craig D. Blinderman, M.D., Juliet Jacobsen, M.D., William F. Pirl, M.D., M.P.H., J. Andrew Billings, M.D., and Thomas J. Lynch, M.D.

Outcomes

- QoL better

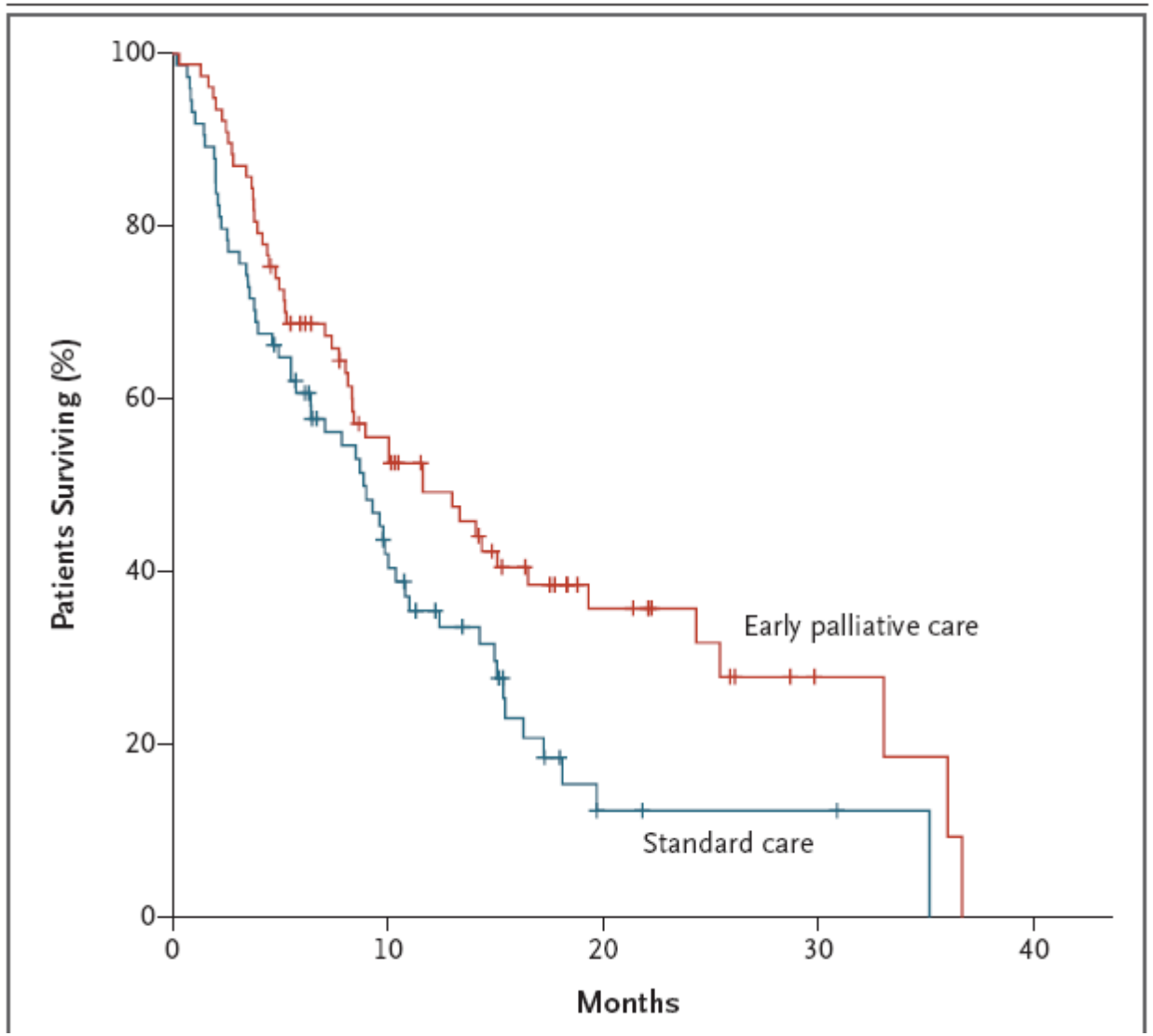


Survival better

- 8.9 vs. 11.6 months
- Persists on multivariate analysis

- Single centre
- In USA

- Other studies NOT shown OS benefit



Temel, NEJM, 2010

Palliative RT lung dose & fractionation

- Poor PS:
  - 1 fraction (10Gy) as good as 2 fraction (17Gy/ 2#; 1 week apart)
  - PS 2 – 4; Main symptoms from primary
  - Max 200 cm^2 field
  - Median OS 3.5 vs 4 months

- Better PS:
  - 13 fraction (39Gy/ 13#) vs. 2 fraction (17Gy/ 2#)
  - Locally advanced, non-metastatic
  - 7 vs. 9 months OS

Bleehan, BJC, 1992
Macbeth, ClinOnc1996

Lung

?

Brain metastases

- Other half neuro-oncology talks
- Talking about poor PS, large disease, extensive ECD

- Is WBRT effective for palliation?

The effects of WBRT

- Lots of retrospective studies

- 75 pts. WBRT 20Gy/5#
  - Median OS 85 days (2.5 months)
  - At 1 month, 19% patients had improved symptoms
  - 4 pts had improved PS

  - 84% had improvement with steroids
    - No relationship between oedema and steroids
    - No relationship to steroid response and RT response

Bezjak, EJC, 2002

FEBRUARY, 1971

THE MANAGEMENT OF METASTASES TO THE BRAIN BY IRRADIATION AND CORTICOSTEROIDS*

By JOHN HORTON, M.B., CH.B.,† DONALD H. BAXTER, M.D.,‡ KENNETH B. OLSON, M.D.,†
and THE EASTERN COOPERATIVE ONCOLOGY GROUP§
ALBANY, NEW YORK

- Prednisolone 40mg +/ RT
- 40 Gy (4 000 rads) over 4 weeks
- Cobalt
- Assessed PS and median OS as outcome

Horton, AJR, 1971

The results indicate that a combination of irradiation and prednisone offers only a slight advantage over prednisone alone. This hardly justifies the expense, work and inconvenience to the patient and his family of a 4 week course of irradiation taking up about a third of his final days.

Quartz trial

- Non-inferiority Phase 3 RCT
- NSCLC brain mets
- Primary outcome QUALYs (survival and EQ-5D)
  - Non-inferior if no less than 7 QUALY days
- BSC + steroids vs BSC + steroids + RT (20Gy/5#)
- 538 pts 72 centres

Quartz patients

- Originally intended to be > 1000 pts
- Slow recruitment
- Reduced target to 530
- One-sided tests

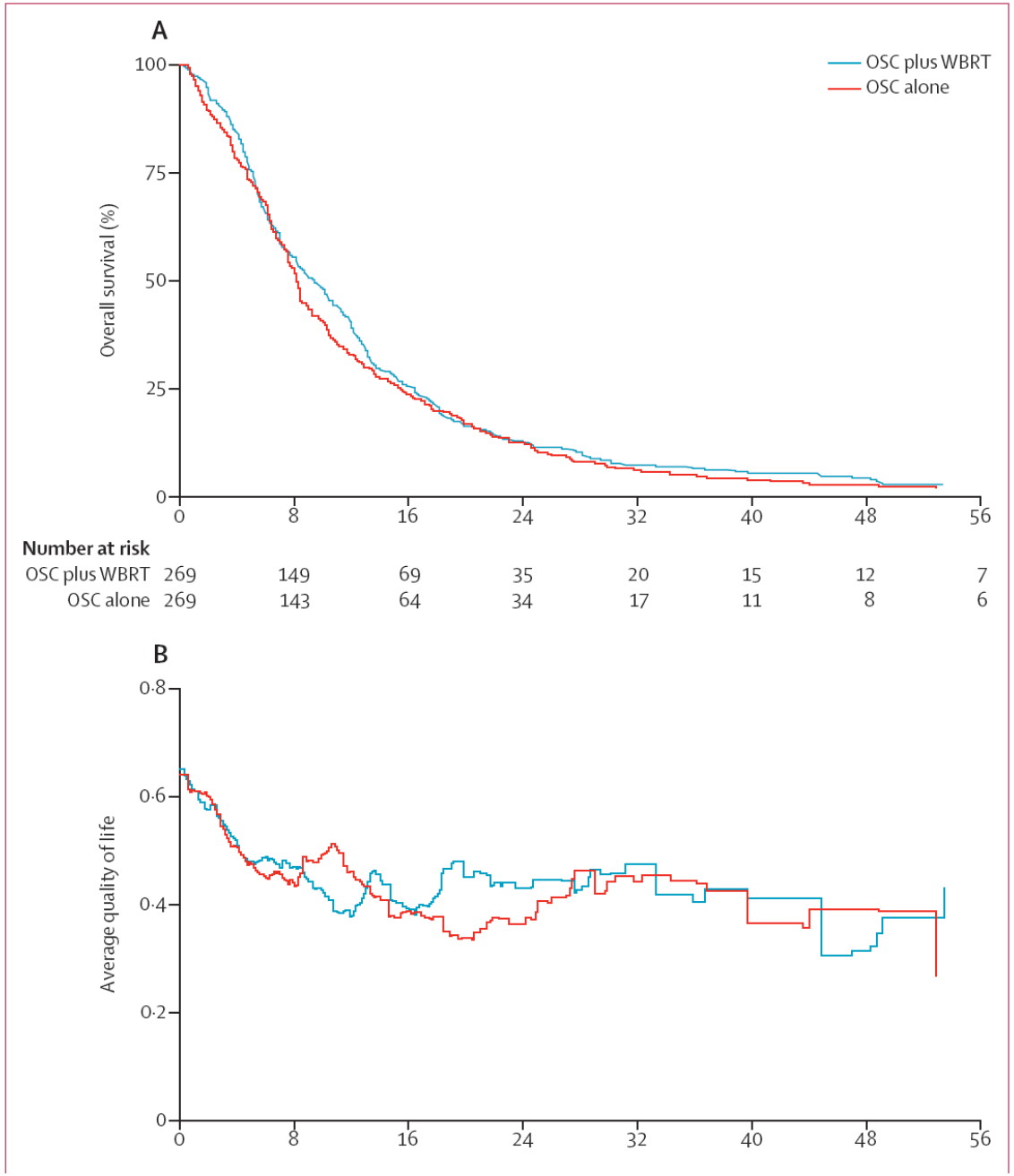
- Took 7 years to recruit
- Released interim data in 2013 (151 pts)

- 98% on steroids

	OSC plus WBRT (n=269)	OSC alone (n=269)
(Continued from previous column)		
GPA prognostic class		
3·5–4·0	5 (2%)	2 (1%)
2·5–3·0	39 (15%)	40 (15%)
1·5–2·0	109 (41%)	104 (39%)
0·0–1·0	111 (42%)	123 (46%)
Data unavailable	5	0

Quartz results

- Median OS 9.2 weeks
- 84% had response to steroids
- No change in steroid use
- -4.7 QUALY days for avoiding WBRT



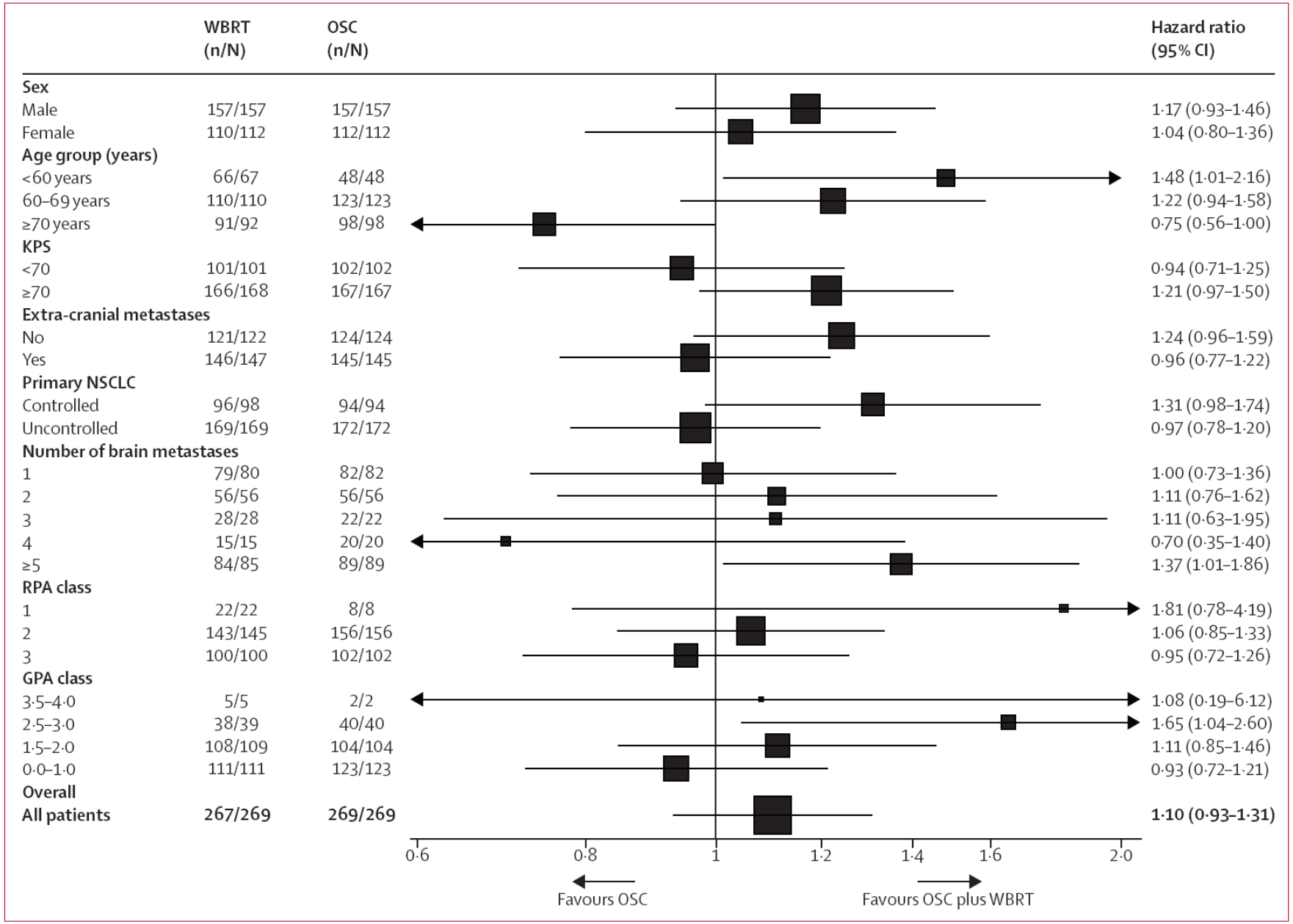


***Figure 3*: Forest plot of overall survival by patient characteristics**

All hazard ratios are obtained from Cox proportional hazard models with adjustment for randomised group only. KPS=Karnofsky Performance Status. NSCLC=non-small cell lung cancer. RPA=recursive partitioning analysis. GPA=graded prognostic assessment. WBRT=whole brain radiotherapy. OSC=optimal supportive care.

Quartz message

- WBRT is not effective in patients with NSCLC and poor prognosis
  - Survival, QoL, Steroids
  - Steroids ARE effective
- However….
  - Not apply to ALL NSCLC pts
- Recruitment difficult
  - Interim results
- 1971….. 2016

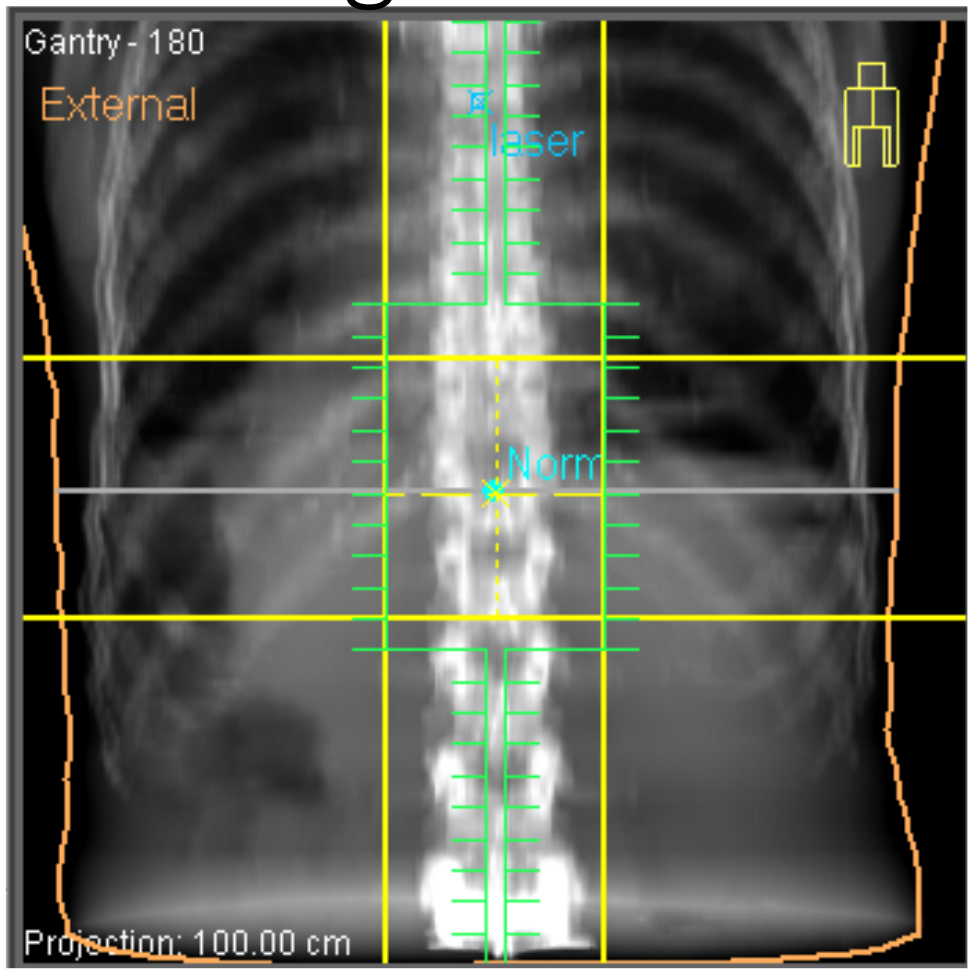
Brain Mets

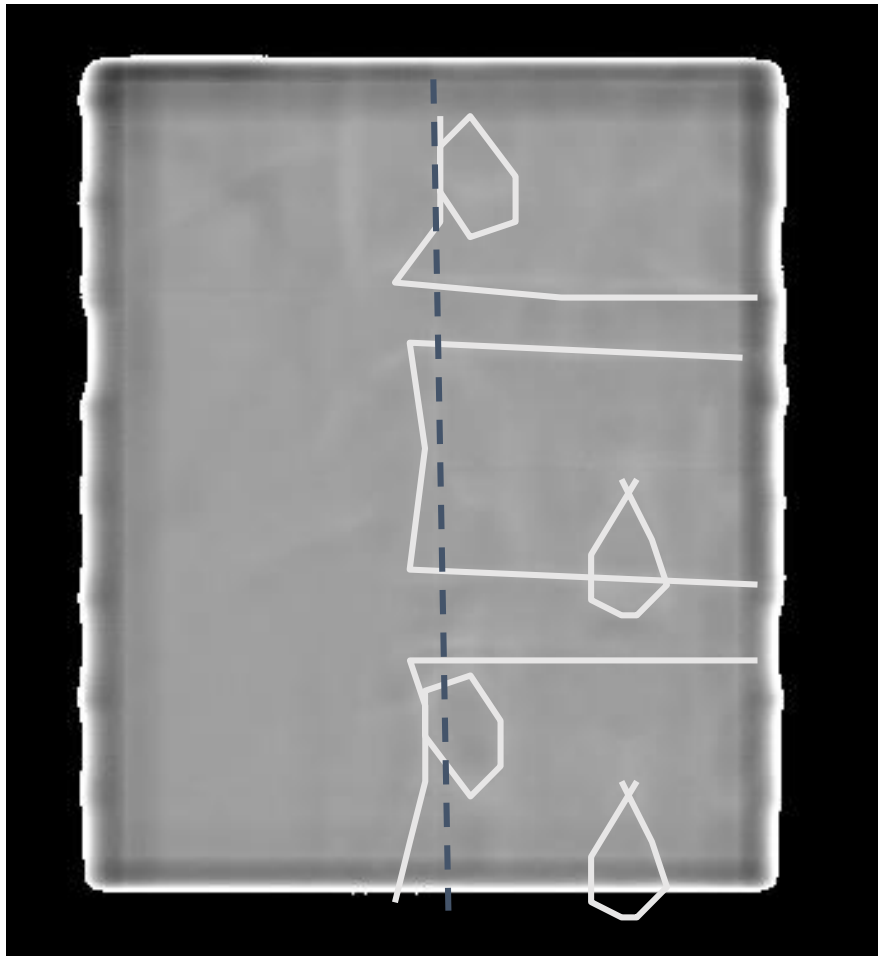
?

Palliative RT is still RT

- Need to consider set-up

Shift during treatment -> position verification





Lateral shift 2 cm

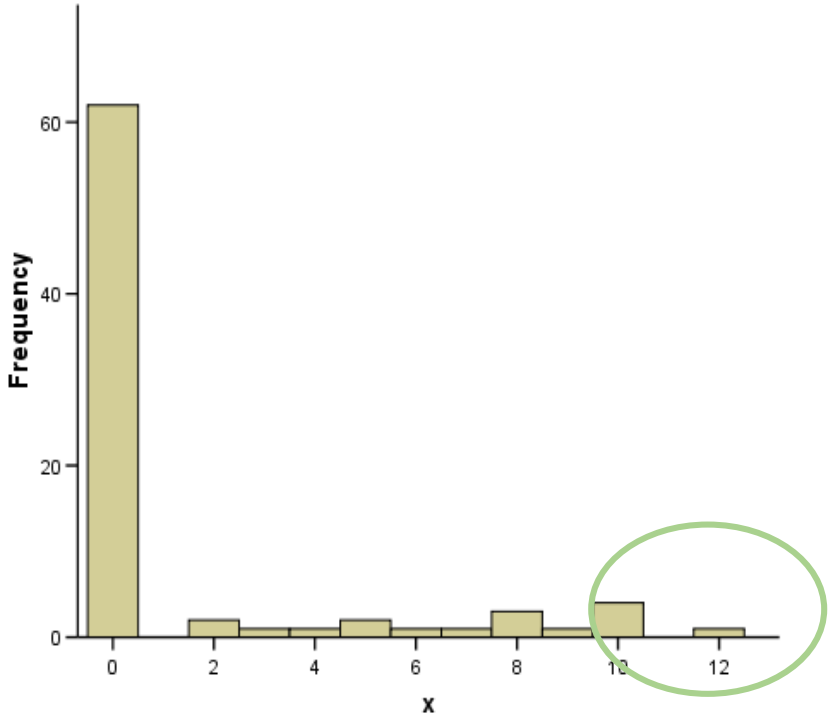
Set up errors

	Patient A	Patient B	Patient C
distress	relaxed	nervous	nervous
performance	good	good	poor
physical complaints	no pain	no pain	highly symptomatic
set up error	1 mm	3 mm	5mm

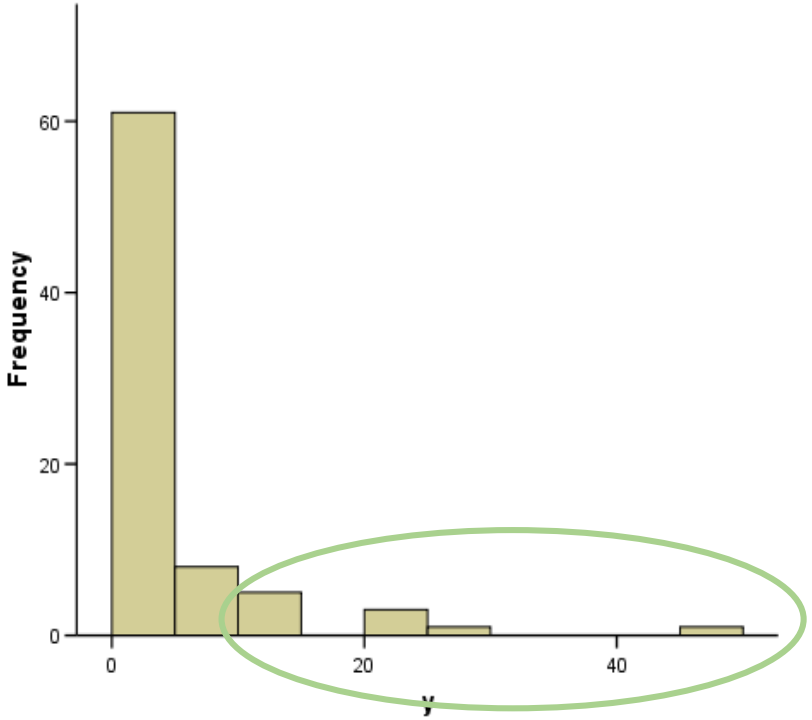
O. Morin, EPI workshop Leuven 2010

Errors ≥ 10mm in 14%

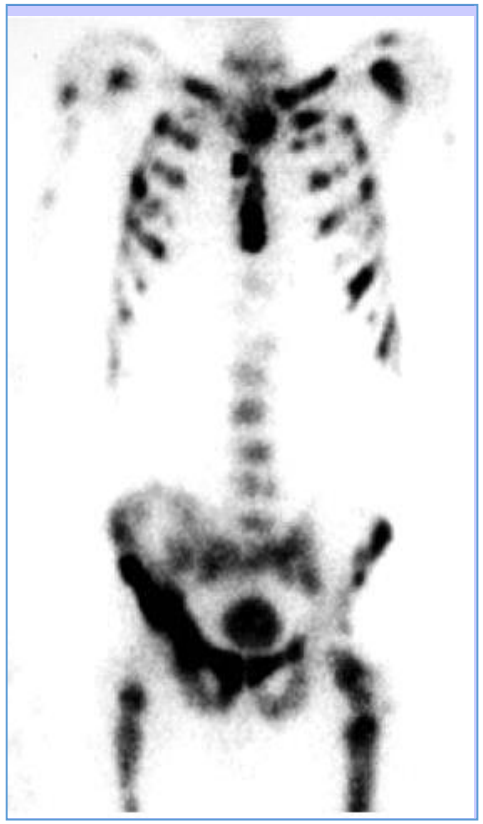
X-axis; lateral shift



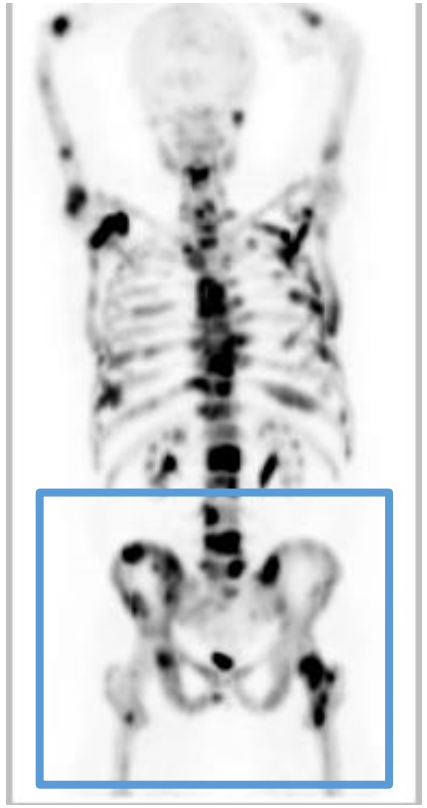
Y-axis; longitudinal shift



Patients with diffuse pain from e.g. prostate cancer



Strontium^{89}



Hemibody

Now also consider ^{223}Ra

Palliative care

Every patient who faces a life-threatening incurable disease.

1. *What do you know of your illness and how far advanced it is?*
2. *What are your fears and uncertainties regarding your future?*
3. *What are your goals and priorities in life?*
4. *What are you willing to give up or not , and what will you accept?*
5. *What makes a day a good day for you?*

Summary

- Many cancer patients die
- Many treatments are ineffective, and expensive, and time-consuming
  - More expensive, less effective nearer the end of life

- Palliative RT is effective and cost-effective
- Short dose/# schedules

- Chose who NOT to treat
- Integrate palliative RT within palliative care

Evidence in Palliative RT

- Good data for bone mets
  - Still slow to change practice
- Reasonable data for other sites
  - Although lung data was pre-chemotherapy era
- It is possible to run RCTs in palliative RT….. But not easy
  - “Toxicity” of single fraction
  - Reimbursement
  - Slow progress (1971 – 2016)

Believe what people do, not say

- Lots of interest in hypofractionated RT
- People still often use multi-fraction
- SCORAD and QUARTZ both found it difficult to recruit

Fish Finger for MP

Project home | Updates 0 | Comments 3 | Supporters 98 | Contact project

Let's make Fish Finger vs. Tim Farron for MP for Westmorland and Lonsdale in June's General Election a reality. #VoteFishFinger

£1,341 raised of £500 target 100 %

98 supporters **26** days left

Support us

This project will only be funded if at least £500 is pledged by 8:21pm 16th May 2017

Project by Mr Fish Finger for MP

Share or follow

Kendal, Cumbria Community

99% of twitters users said they would prefer a Fishfinger to Tim Farron

- 23 686
- 309 votes

Don’t always believe what people say

- Audit local practice
  - Most audits show low rates of single-fraction RT

- What proportion of patients with bone mets are treated as a single fraction ?
- How long do people live after WBRT ?

Presenting and publishing scientific data

A few tips to convince

Bernard Dubray

How many papers have you written ?

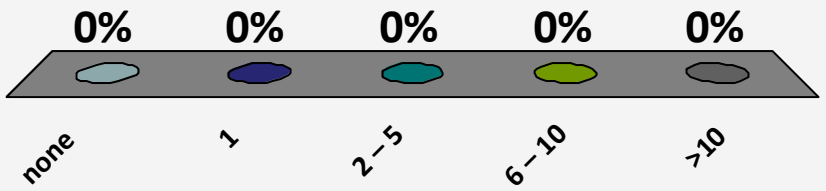
A. none

B. 1

C. 2 – 5

D. 6 – 10

E. >10



How many times have you presented scientific data ?

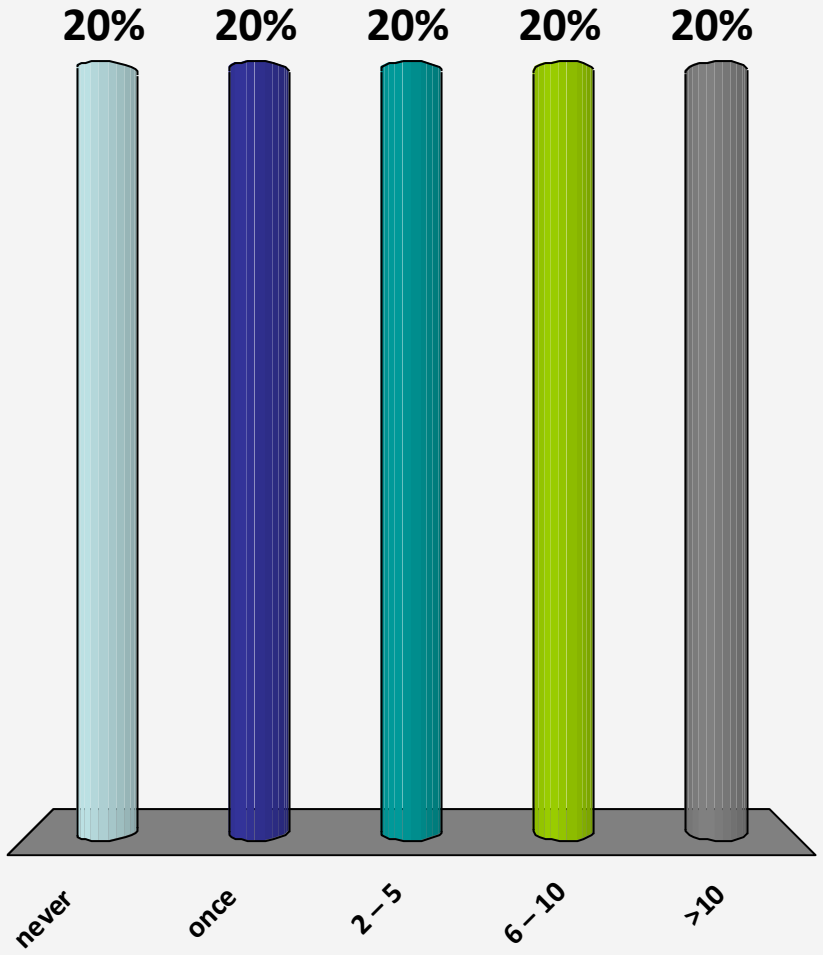
A. never

B. once

C. 2 – 5

D. 6 – 10

E. >10



Presenting and publishing

- Numerous issues
  - medicine /science
  - statistics
  - format and rules
  - communication skills
- Objectives
  - author: “my stuff is worth your money !”
  - audience: “do I really want to buy that ?”

I'll buy it if …

- The question makes sense to me
  - fits to my clinical practice
  - opens my mind
- The data provide a reliable answer
  - study design and conduct
  - quality of data and analysis
- The presentation / paper follows the rules
  - the information I need …
  - where I expect to find it

I'll sell it if …

- The question makes sense to them
  - what is my message ?
- The data provide a reliable answer
  - study design and conduct
  - quality of data and analysis
- The presentation / paper follows the rules
  - the information they need …
  - where they expect to find it

Getting ready

- What is my message ?
- What is the audience ?
- What are the rules ?

A good title

- Informative
- Short (< 12 words)
- Matching the content
- Attractive (reasonably …)

Which paper would you read first ?

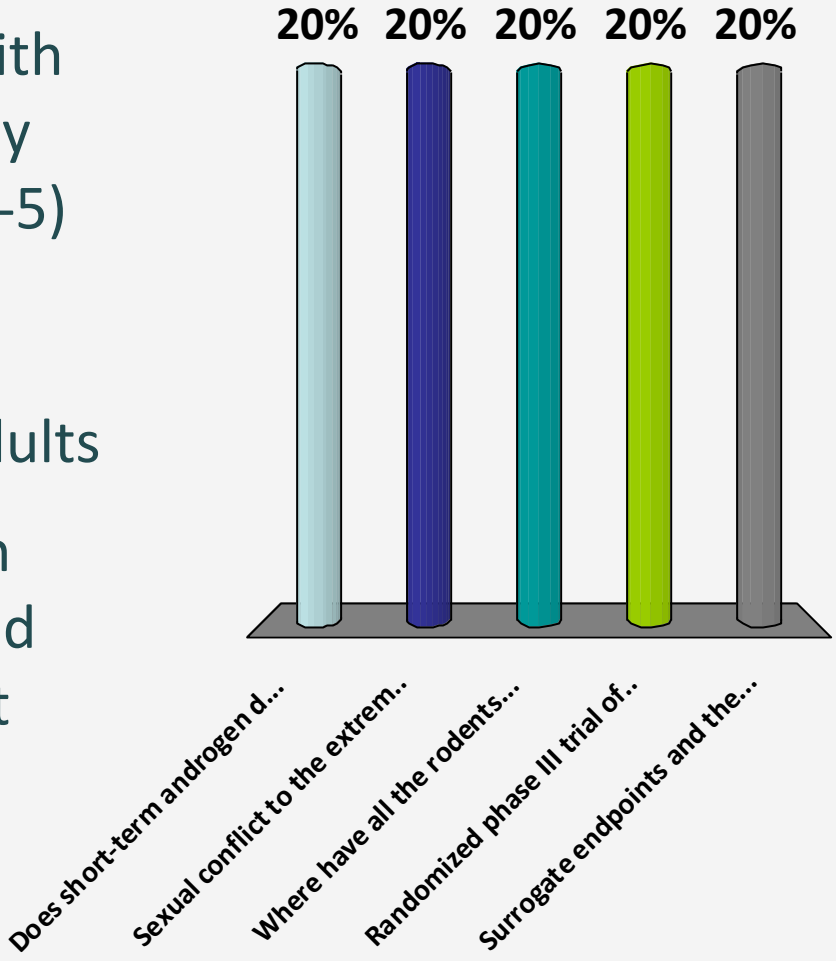
A. Ceritinib versus CT in patients with *ALK*-rearranged NSCLC previously given CT and crizotinib (ASCEND-5)

B. Sexual conflict to the extreme

C. Toilet reading habits in Israeli adults

D. Uromycitisis Poisoning Results in Lower Urinary Tract Infection and Acute Renal Failure: Case Report

E. The conceptual penis as a social construct



THE LANCET
Oncology

Available online 9 June 2017
In Press, Corrected Proof — Note to users

Articles

Ceritinib versus chemotherapy in patients with *ALK*-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial

Dr Alice T Shaw, MD[a], Tae Min Kim, MD[b], Prof Lucio Crinò, MD[c], Cesare Gridelli, MD[d], Katsuyuki Kiura, MD[e], Geoffrey Liu, MD[f], Prof Silvia Novello, MD[g], Alessandra Bearz, MD[h], Oliver Gautschi, MD[i],
Show more

https://doi.org/10.1016/S1470-2045(17)30339-X

Sexual Conflict to the Extreme:

Traumatic Insemination in Bed Bugs

Margie Pfiester, Philip G. Koehler, and Roberto M. Pereira

American Entomologist 2009

Neurogastroenterol Motil (2009) **21**, 291–295 doi: 10.1111/j.1365-2982.

Toilet reading habits in Israeli adults

O. GOLDSTEIN,*,[1] Y. SHAHAM,†,[1] T. NAFTALI,‡ F. KONIKOFF,‡ A. LAVY* & R. SHAOUL†

*Department of Gastroenterology, Bnai Zion Medical Center, Faculty of Medicine, Technion, Haifa, Israel
†Department of Pediatrics, Bnai Zion Medical Center, Faculty of Medicine, Technion, Haifa, Israel
‡Department of Gastroenterology, Meir Hospital, Kfar Saba, Tel Aviv University Sackler School of Medicine, Israel

- Toilet reading is a common habit in the Israeli population
- Toilet reading is correlated with a longer time spent in the toilet and seems to be a benign habit.

MedCrave
Step into the World of Research

Urology & Nephrology Open Access Journal

Uromycitisis Poisoning Results in Lower Urinary Tract Infection and Acute Renal Failure: Case Report

Abstract

Uromycitisis is a rare but serious condition that affects over 2,000 mostly adult men and women in the United States each year. Described simply, it is caused by prolonged failure to evacuate the contents of the bladder and can result in a serious infection of the lower urinary tract known as "uromycitisis poisoning," which, if untreated, can cause acute renal failure and has an associated high mortality. Because people with uromycitisis often cannot hold in their urine and feel they must-and, at times, actually must-urinate in inappropriate places, sometimes running afoul of local public sanitation ordinances, they can feel great personal shame and place themselves in legal jeopardy, through no fault of their own. We report the case of a 37-year-old male who suffers from uromycitisis, was prevented from urinating in public, was admitted to the emergency room with uromycitisis poisoning, was misdiagnosed, and was referred to our institution for treatment.

Case Report

Volume 4 Issue 3 - 2017

Martin van Nostrand[1]*, Jay Riemenschneider[1] and Leonard Nicodemo[2]

[1]Department of Interventional Urology, Arthur Vandelay Urological Research Institute, USA

[2]Department of Psychology, Weill Cornell Medical College, USA

***Corresponding author:** Martin van Nostrand, Arthur Vandelay Urological Research Institute, 129 W 81st Street, New York, NY 10024, USA, Email: martinvannostrand1949@gmail.com

Received: March 22, 2017 | **Published:** March 31, 2017

MedCrave
Step into the World of Research

Urology & Nephrology Open Access Journal

Uromycitisis Poisoning Re… …ower Urinary Tract Infection and Acute… … Case Report

Abstract

Uromycitisis is a rare but serious co… men and women in the United St… by prolonged failure to evacuat… serious infection of the lows… which, if untreated, can caus… mortality. Because people with… …ine and feel they must-and, at times, a… …places, sometimes running afoul of local publ… …eel great personal shame and place themselves in… …ault of their own. We report the case of a 37-year-old m… …mycitisis, was prevented from urinating in public, was adm… …gency room with uromycitisis poisoning, was misdiagnosed, and… …d to our institution for treatment.

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Received: March 22, 2017 | **Published:** March 31, 2017

Lindsay & Boyle, *Cogent Social Sciences* (2017), 3: 1330439
https://doi.org/10.1080/23311886.2017.1330439

cogent social sciences

SOCIOLOGY | RESEARCH ARTICLE

The conceptual penis as a social construct

Jamie Lindsay[1]* and Peter Boyle[1]

Abstract: Anatomical penises may exist, but as pre-operative transgendered women also have anatomical penises, the penis *vis-à-vis* maleness is an incoherent construct. We argue that the conceptual penis is better understood not as an anatomical organ but as a social construct isomorphic to performative toxic masculinity. Through detailed poststructuralist discursive criticism and the example of climate change, this paper will challenge the prevailing and damaging social trope that penises are best understood as the male sexual organ and reassign it a more fitting role as a type of masculine performance.

Subjects: Gender Studies - Soc Sci; Postmodernism of Cultural Theory; Feminism

Keywords: penis; feminism; *machismo braggadocio*; masculinity; climate change

Received: 17 April 2017
Accepted: 11 May 2017

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Reviewing editor:
Jamie Halsall, University of Huddersfield, UK

Additional information is available at the end of the article

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SOCIOLOGY | RESEARCH ART

The conceptual p… …nstruct

Jamie Lindsay[1]* and Pete…

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Reviewing editor:
Jamie Halsall, …
Huddersfie…

Additiona…
the end of t…

Introduction

- Short
  - informative
- Summarizing
  - background
  - question
  - aim of study
- Adapted to audience

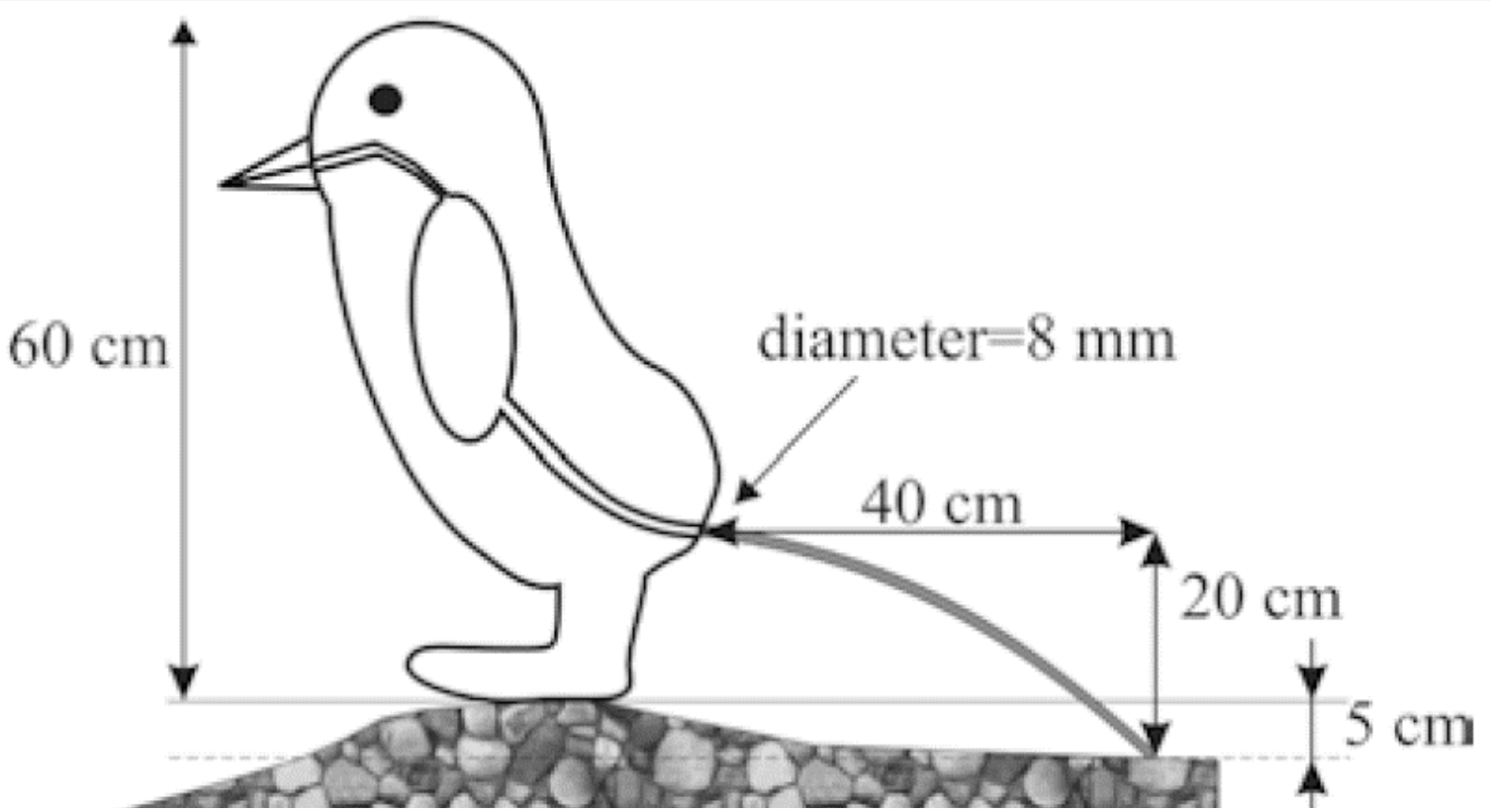
Materials and methods

- Description
  - selection, diagnosis, treatment, …
  - study flow (diagram)
  - randomisation
  - statistics (sample size)
  - QA & QC
  - ethics & funding
- Message
  - quality of the data
  - relevant to the question

Results

- Describe as announced in M&Ms
  - conduct of trial
  - demographics
  - endpoints and analyses
- No discussion
- Message
  - quality of the data

Use graphics !



Victor Benno Meyer-Rochow · Jozsef Gal

Pressures produced when penguins pooh—calculations on avian defaecation

Polar Biol (2003) 27: 56–58

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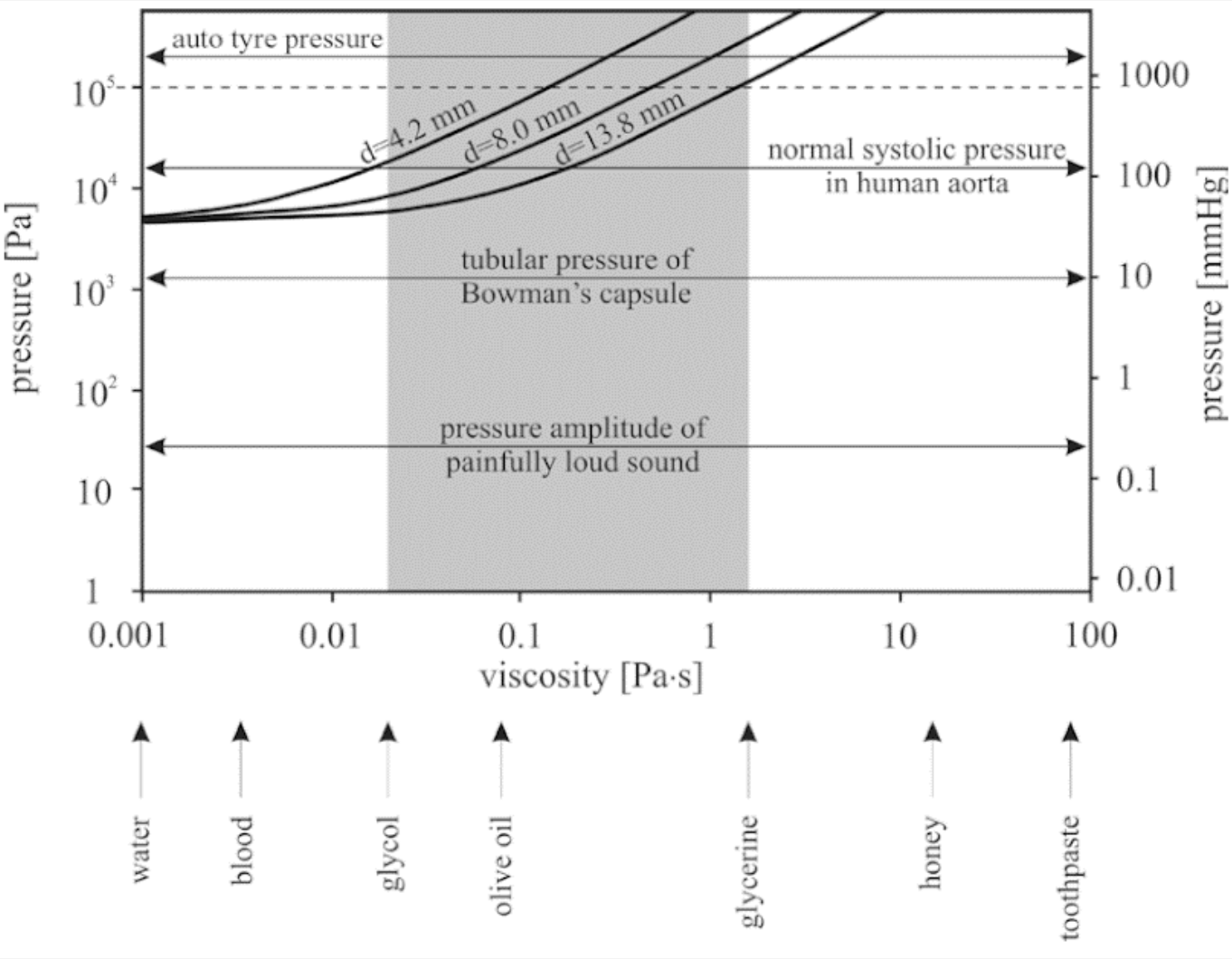
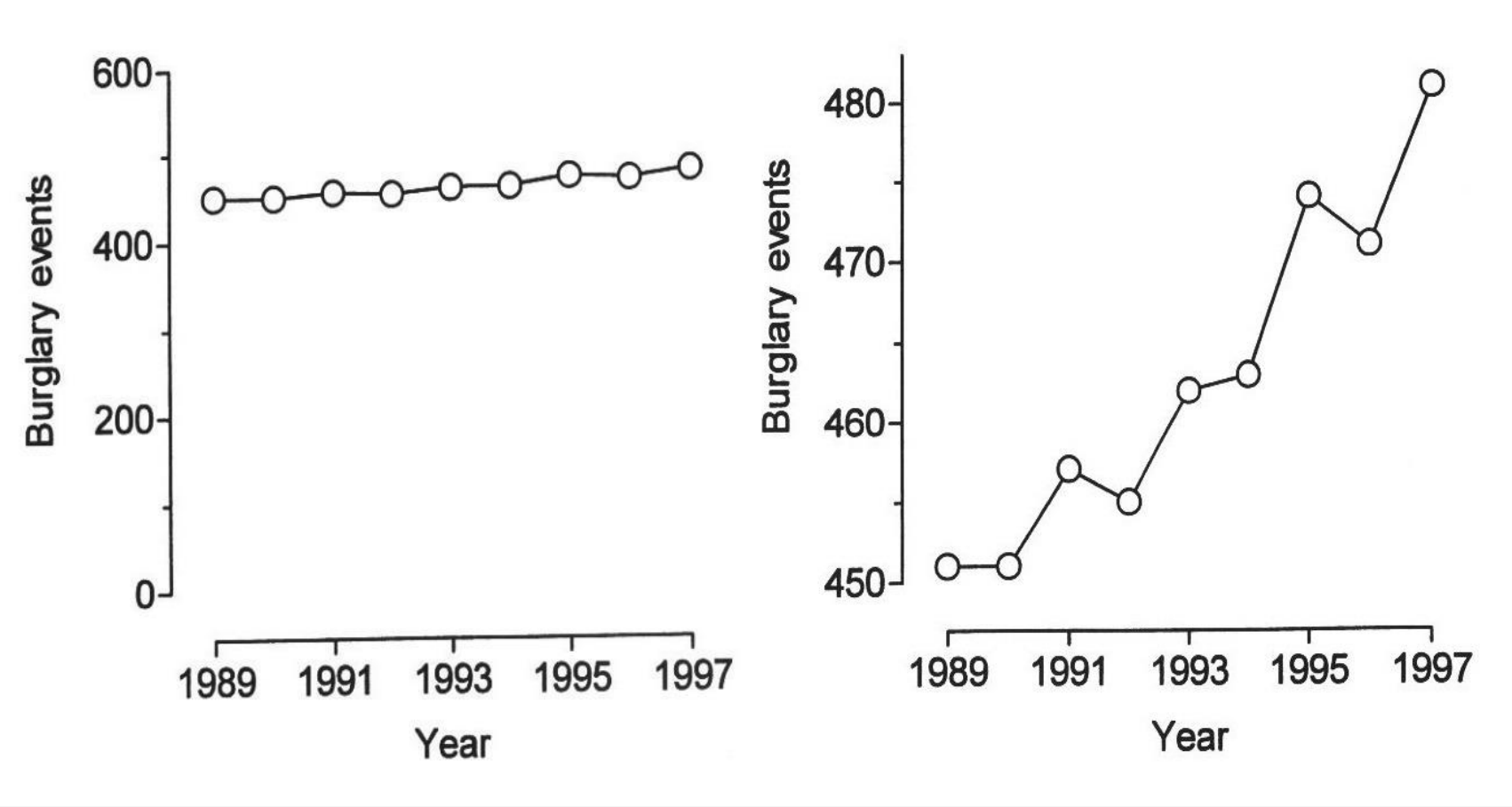


Fig. 2 Rectal pressure (in Pa along *left* and mmHg along *right* ordinate) in relation to viscosity (*abscissa*) and three cloacal apertures (4.2 mm = rockhopper, 8.0 mm = Adélie, and 13.8 mm = gentoo penguin). The viscosity of penguin faeces lies between glycol and olive oil. For comparison, known viscosities of other substances are given along the *abscissa*

Is crime on the sharp rise ?



Courtesy H.-P. Beck-Bornhold

Costinib reduces mortality rate

1- by 20.3%

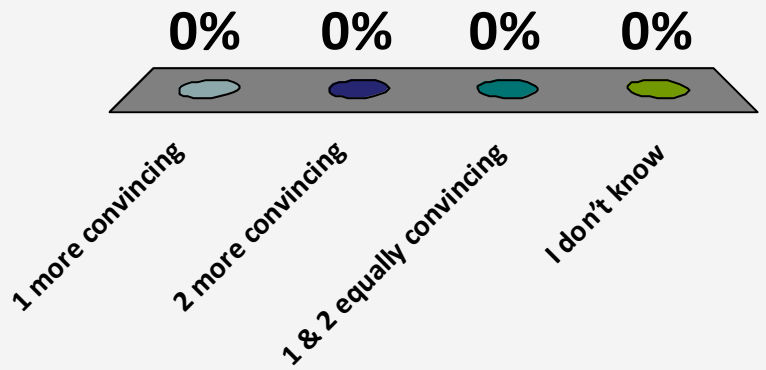
2- from 7.8% to 6.3%

A. 1 more convincing

B. 2 more convincing

C. 1 & 2 equally convincing

D. don't know



Rephrazed from Forrow Am J Med 1992

Costinib reduces mortality rate

1- by 20.3% (relative)

2- from 7.8% to 6.3% (absolute)

	235 MDs	p
1 = 2	127 (54%)	
1 > 2	97 (41%)	$<10^{-4}$
1 < 2	11 (5%)	

Forrow Am J Med 1992

Discussion

- Short
- Major findings
  - don’t repeat results …
- Comparison with others
- Limitations and strong points
  - « Whether a bird chooses the direction into which it decides to expel its faeces, and what role the wind plays in this, remain unknown. »

References

- Relevant
- As few as possible
- Up-to-date
- Not read, not quoted !

Abstract / summary

- Short
- Informative
- Consistent with content

Consistency …

- Discussion
  - “These data do not show accelerated proliferation … but they agree with the hypothesis that accelerated proliferation occurs and is important in determining outcome”
- Abstract
  - “These data support the hypothesis that proliferation (possibly accelerated) of tumor clonogens during treatment influences the outcome”
- Title
  - “New Evidence for Accelerated Proliferation from …”

Famous RadOnc, Cancer 1992

Oral presentation

- Be adequately dressed
- Arrive ahead of time
  - load and check your slides
  - microphone, buttons, pointer
- Switch off your mobile
- Speak to the audience
  - loudly and slowly
  - don’t read

Oral presentation

- Plan to be too short
  - 1 minute per slide
- Short introduction / conclusion
  - summary prepared in advance
- Be ready to skip slides
  - don’t forget the message !
- Be pleased with questions
  - short answers
  - let’s meet at the bar !

Legible slides

- Sharp, few colours
- Prefer graphics
- Fill the projection field (2:3)
- Use horizontal lettering
  - title: max. 6 words
  - no more than 7 lines of 7 words
  - no sentence

Jokes … ?

Paris Orly airport 2016

Jokes … ?

- Adapt to the audience
- Stimulate attention
- What is your message ?


Don’t forget collaborators

Before submitting / presenting …

- Check everything once again
  - instructions
  - proofreading
  - consistency

Conclusion

- Follow the rules
- Description of the data +++
- Be an active audience
  - ask questions, please !

Good research takes time !

Edgeworth U. of Queensland (Australia)

Good research takes time !

Let’s not spoil it
with poor communication !