ESTRO course on IMRT and other conformal techniques
3-7 April 2016, London – United Kingdom

Sunday 03 April

8.30 – 8.45 Introduction to the course - *Marco Schwarz*

8.45 - Group B: Going to UCLH London

9.30 – 10.00 Demo 1: Plan verification using 2D and 3D methods - V*asilis Rompokos/ Narinder Lalli*

10.00 – 10.30 Demo 2: Imaging and Positional Verification with 6DOF corrections - *Chris Stacey/Maria Kilkenny*

10.30 – 11.00 Coffee break

11.00-11.30 Demo 3: Multimodality Image Registration for Volume Delineation - *Turmi Patel/Peter Lac*

11.30 – 12.00 Demo 4: Immobilisation Strategies for Sarcoma and Paediatric - *David Marsh/Kristina Quingua*

Group A : Lectures at the Hotel
Chair: *Frank Lohr*

9.15 – 9.30 Opening and welcome - *Dr Yen Chang*

9.30 – 10.00 Cancer and the current status of IMRT and UCLH - *Dr Yen Chang*

10.00 – 10.30 Coffee break

10.30 – 10.55 Treatment Image review+ adaptive strategies for H&N and Lung
RTT perspective - *Syed Moinuddin*

10.55 - 11.20 Treatment Image review+ adaptive strategies for H&N and Lung
Physics perspective - *Dr Rachel Bodey*

11.20 – 11.50 IMRT for Paediatrics - *Dr Jenny Gains*

11:50 – 12:20 IMRT for Sarcoma - *Dr Franel LeGrange*

12.30 - 13.30 Lunch

13.30 - Group A Going to UCLH London

14.00 – 14.30 Demo 1: Plan verification using 2D and 3D methods - V*asilis Rompokos, Narinder Lalli*

14.30 – 15.00 Demo 2: Imaging and Positional Verification with 6DOF corrections - *Chris Stacey/Maria Kilkenny*

15.00 – 15.30 Coffee break

15.30-16.00 Demo 3: Multimodality Image Registration for Volume Delineation - *Turmi Patel/Peter Lac*

16.00 – 16.30 Demo 4: Immobilisation Strategies for Sarcoma and Paediatric - *David Marsh/Kristina Quingua*

Group B - Lectures at the hotel:

Chair: *Matthias Soehn*

14.00 – 14.30 Opening and welcome - *Dr Yen Chang*

14.30 – 15.00 Cancer and the current status of IMRT and UCLH - *Dr Yen Chang*

15.00 – 15.30 Coffee break

15.30 – 15.55 Treatment Image review+ adaptive strategies for H&N and Lung
RTT perspective - *Syed Moinuddin*

15.55 - 16.20 Treatment Image review+ adaptive strategies for H&N and Lung
Physics perspective - *Dr Rachel Bodey*

16.20 – 16.50 IMRT for Paediatrics - *Dr Jenny Gains*

16:50 – 17:20 IMRT for Sarcoma - *Dr Beatrice Seddon*

Monday 04 April

Chair: *Giovanna Gagliardi*

9.00 - 9.30 Rational of IMRT. A clinician's point of view - *Frank Lohr*

9.30 - 10.15 IMRT delivery techniques – *Marco Schwarz*

10.15 - 10.45 Coffee Break

10.45 - 11.30 Dosimetry issues in IMRT – *Koen Tournel*

11.30 - 12.00 TPS commissioning – *M. Schwarz*

12.00 – 12.45 Potential and limitations of rotational IMRT – *Koen Tournel*

12.45 - 14.00 Lunch

Chair: *Koen Tournel*

14.00 - 14.45 Highly conformal techniques in early stage lung cancer: indications, techniques, normal tissue constraints, results – *Andrea Filippi*

14.45 - 15.30 IMRT in breast and risk of secondary cancer after IMRT – *Frank Lohr*

15.30 - 16.00 Coffee break

16.00 - 16.45 Highly conformal techniques in advanced stage lung cancer: indications, techniques, normal tissue constraints, results – *Andrea Filippi*

16.45 – 17.30 IMRT in GI and gynecology - Dr Gemma Eminowicz

Tuesday 05 April

Chair: *Marco Schwarz*

9.00 - 9.45 IMRT optimization: algorithms and cost functions – *Matthias Soehn*

9.45 – 10.30 Modeling adverse effects after 3DCRT and IMRT– *Eva Onjukka*

10.30 - 11.00 Coffee break

11.00 -11.45 Review of Dose-volume relationships I: H&N - *Giovanna Gagliardi*

11.45 - 12.30 IMRT in Head and neck – *Frank Lohr*

12.30 - 14.00 Lunch

14.00 - 15.30

Group A:
Clinical case discussion 1 (14.00-14.45)

Clinical session 1: Andrea Filippi, Koen Tournel (Room Trinity) - Lymphoma
Clinical session 2: Heather Payne, Matthias Soehn (Room Somerville) - Prostate
Clinical session 3: Frank Lohr, Giovanna Gagliardi (Room Merton) – H&N

Clinical case discussion 2 (14.50-15.30)

Clinical session 1: Heather Payne, Matthias Soehn (Room Trinity) - Prostate
Clinical session 2: Frank Lohr, Giovanna Gagliardi (Room Somerville) – H&N
Clinical session 3: Andrea Filippi, Koen Tournel (Room Merton) – Lymphoma

Group B: Vendor session (**Room Oxford**)

Chair of the session: *Marco Schwarz*

15.30 - 16.00 Coffee break

16.00 – 16.45

Group A:
Clinical case discussion 3

Clinical session 1: *Frank Lohr, Giovanna Gagliardi (**Room Trinity**) - Lymphoma*
Clinical session 2: *Andrea Filippi, Koen Tournel (**Room Somerville**) - Prostate*
Clinical session 3: *Heather Payne, Matthias Soehn (**Room Merton**) – H&N*

Group B: free

Wednesday 06 April

Chair: *Frank Lohr*

9.00 - 09.45 'Patient specific' QA – *Eva Onjukka*

9.45 - 10.30 Impact of geometrical uncertainties on IMRT dose distributions – *Koen Tournel*

10.30 - 11.00 Coffee break

11.00 - 11.45 Review of Dose-volume relationships II: Pelvis – *Giovanna Gagliardi*

11.45 – 12.30 IMRT of prostate cancer – *Heather Payne*

12.30-14.00 Lunch

14.00-15.30

Group B:
Clinical case discussion 1 (14.00-14.45)

Clinical session 1: Andrea Filippi, Koen Tournel (Room Trinity) - Lymphoma
Clinical session 2: Heather Payne, Matthias Soehn (Room Somerville) - Prostate
Clinical session 3: Frank Lohr, Giovanna Gagliardi (Room Merton) – H&N

Clinical case discussion 2 (14.50-15.30)

Clinical session 1: Heather Payne, Matthias Soehn (Room Trinity) - Prostate
Clinical session 2: Frank Lohr, Giovanna Gagliardi (Room Somerville) – H&N
Clinical session 3: Andrea Filippi, Koen Tournel (Room Merton) – Lymphoma

Group A: Vendor session (**Room Oxford**)
Chair of the session: *Marco Schwarz*

15.30-16.00 Coffee break

16.00 – 16.45
Group B:

Clinical case discussion 3

Clinical session 1: Frank Lohr, Giovanna Gagliardi (Room Trinity) – H&N
Clinical session 2: Andrea Filippi, Koen Tournel (Room Somerville) - Lymphoma
Clinical session 3: Heather Payne, Matthias Soehn (Room Merton) – Prostate

Group A: free

Thursday 07 April

Chair: *Andrea Filippi*

9.00 - 9.45 Practical IMRT planning and ‘biological optimization’ – *Marco Schwarz*

9.45 – 10.30 Dose calculations in static and rotational IMRT - *Matthias Soehn*

10.30-11.00 Coffee break

11.00 - 11.45 Image-guidance & Adaptive: concept and approaches – *Matthias Soehn*

11.45 - 12.30 Image-guidance & Adaptive: Clinical applications – *Frank Lohr*

12.30 -13.00 Final discussion and closing of the course

Cancer, IMRT and UCLH

Dr Yen-Ching Chang

Consultant in Clinical Oncology

Clinical Lead for Radiotherapy

University College London Hospitals NHS Foundation Trust

University College Hospital site


University College Hospital


Macmillan Cancer Centre


Elizabeth Garrett Anderson Wing (maternity)


Hospital for Tropical Diseases


Institute of Sport, Exercise and Health


University College Hospital at Westmoreland Street


Royal National Throat, Nose and Ear Hospital


Royal London Hospital for Integrated Medicine


National Hospital for Neurology and Neurosurgery


Eastman Dental Hospital

Number of staff
8,000+

Number of beds
1,093

Turnover
£934 million

What we do

Patients seen per year
1,000,000+

Outpatients
1,010,950

Inpatients
170,000

Visits to our Emergency Department


131,000

Babies born


6,734

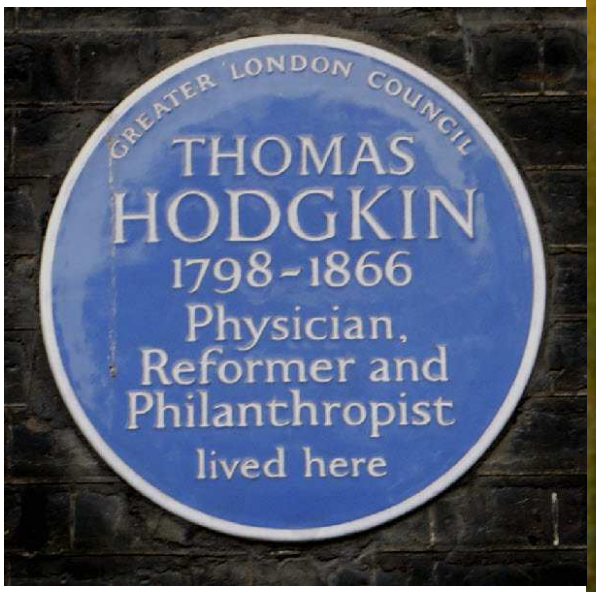
Clinical trials and studies

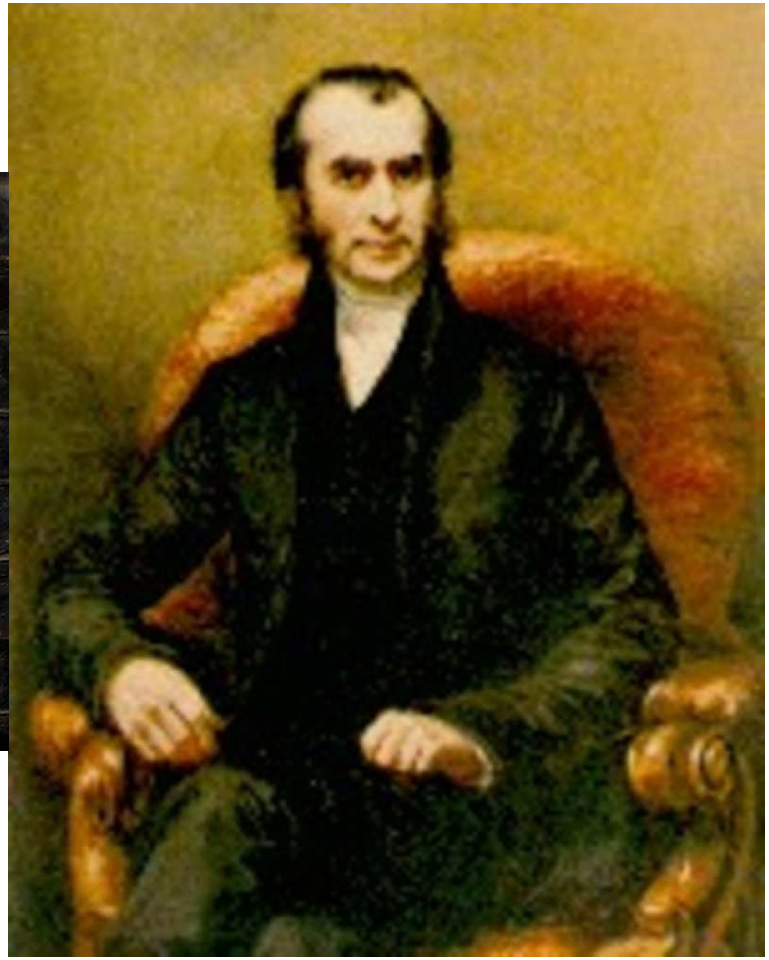

1,200+

Patients recruited for research studies in a typical year

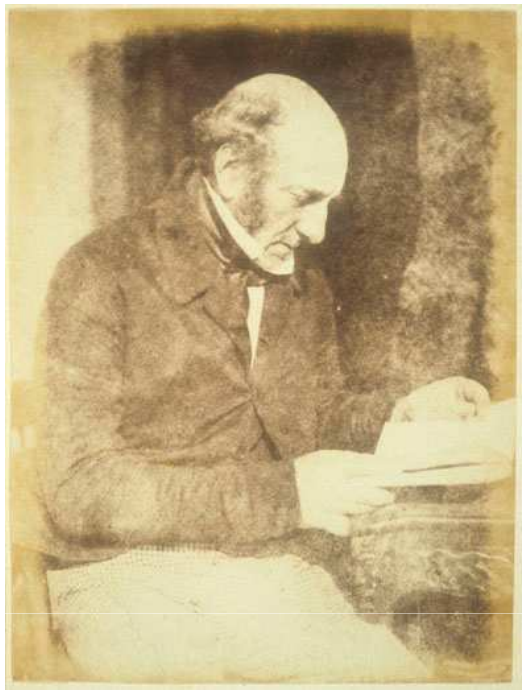

12,000

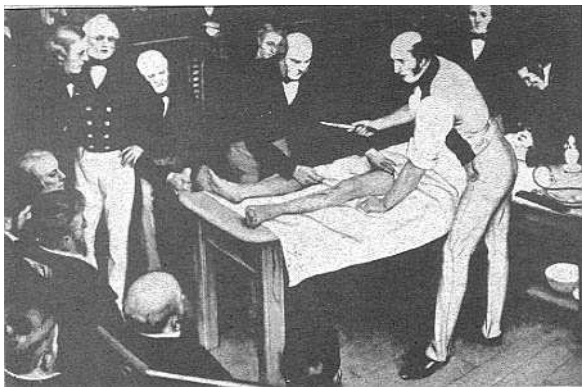
University College Hospital


GREATER LONDON COUNCIL
THOMAS
HODGKIN
1798-1866
Physician,
Reformer and
Philanthropist
lived here



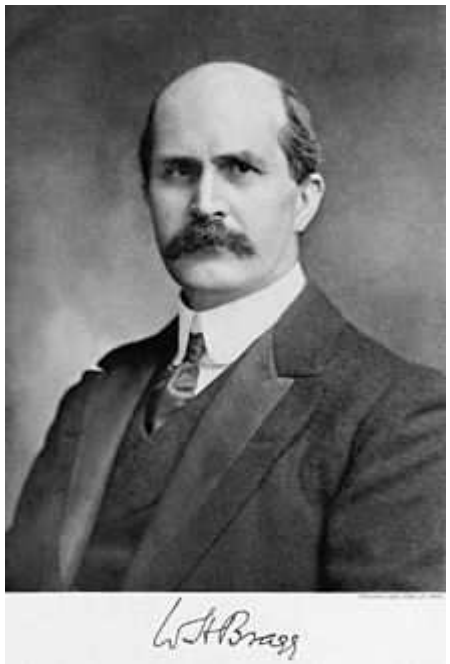
Robert Liston

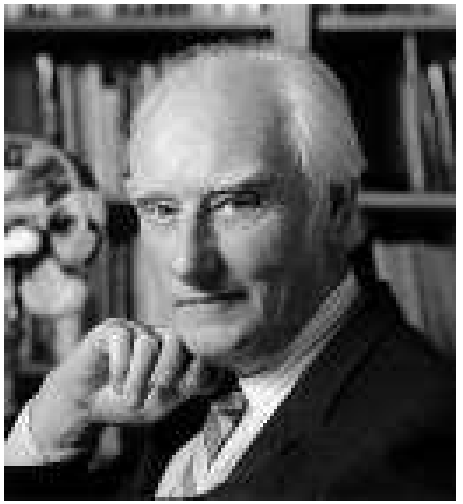




Cancer at UCLH

University College London

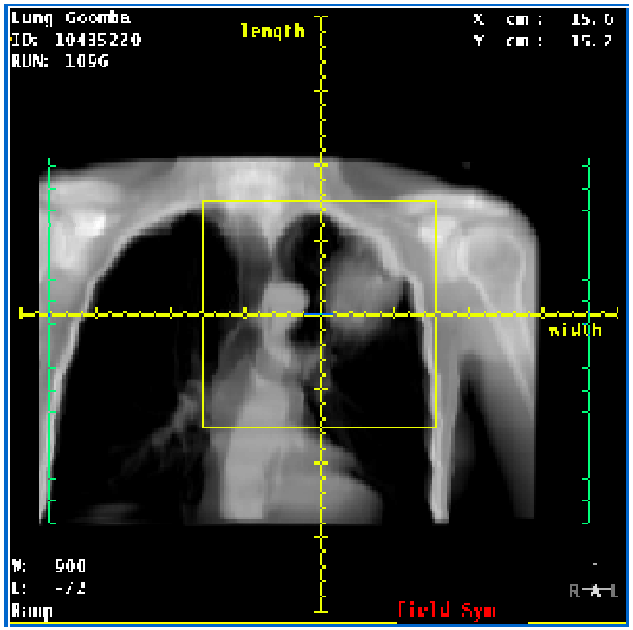




Cancer at UCLH

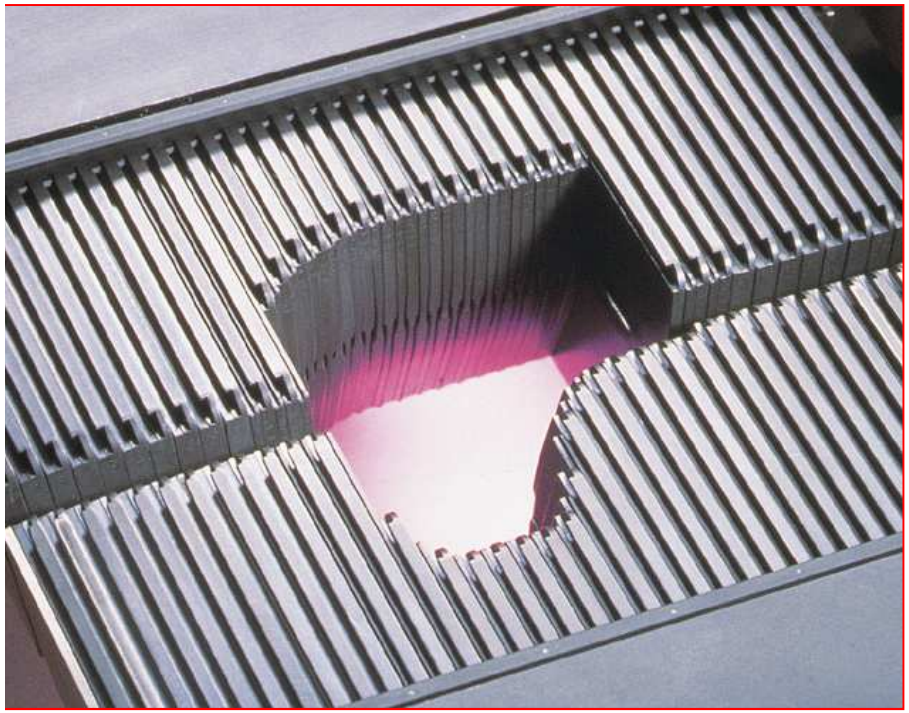
2005 Inpatients and Radiotherapy

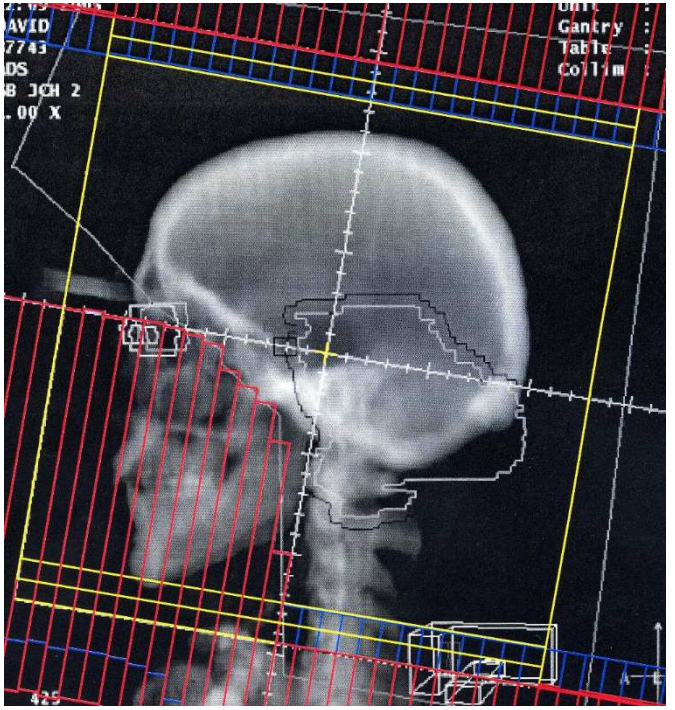
Conventional simulation



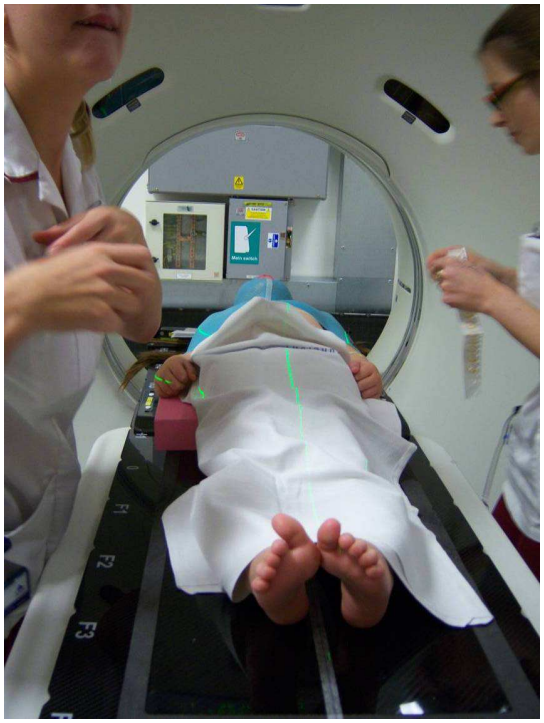
Lead Blocks

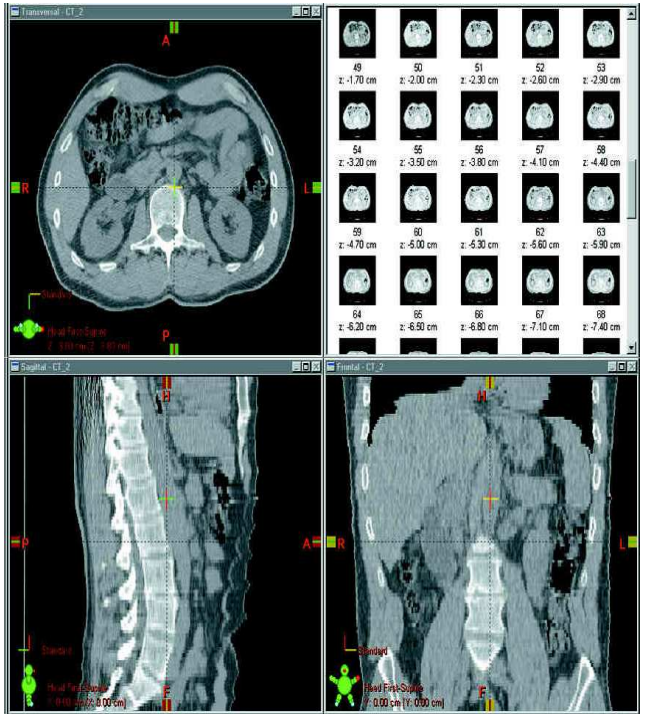
MLC



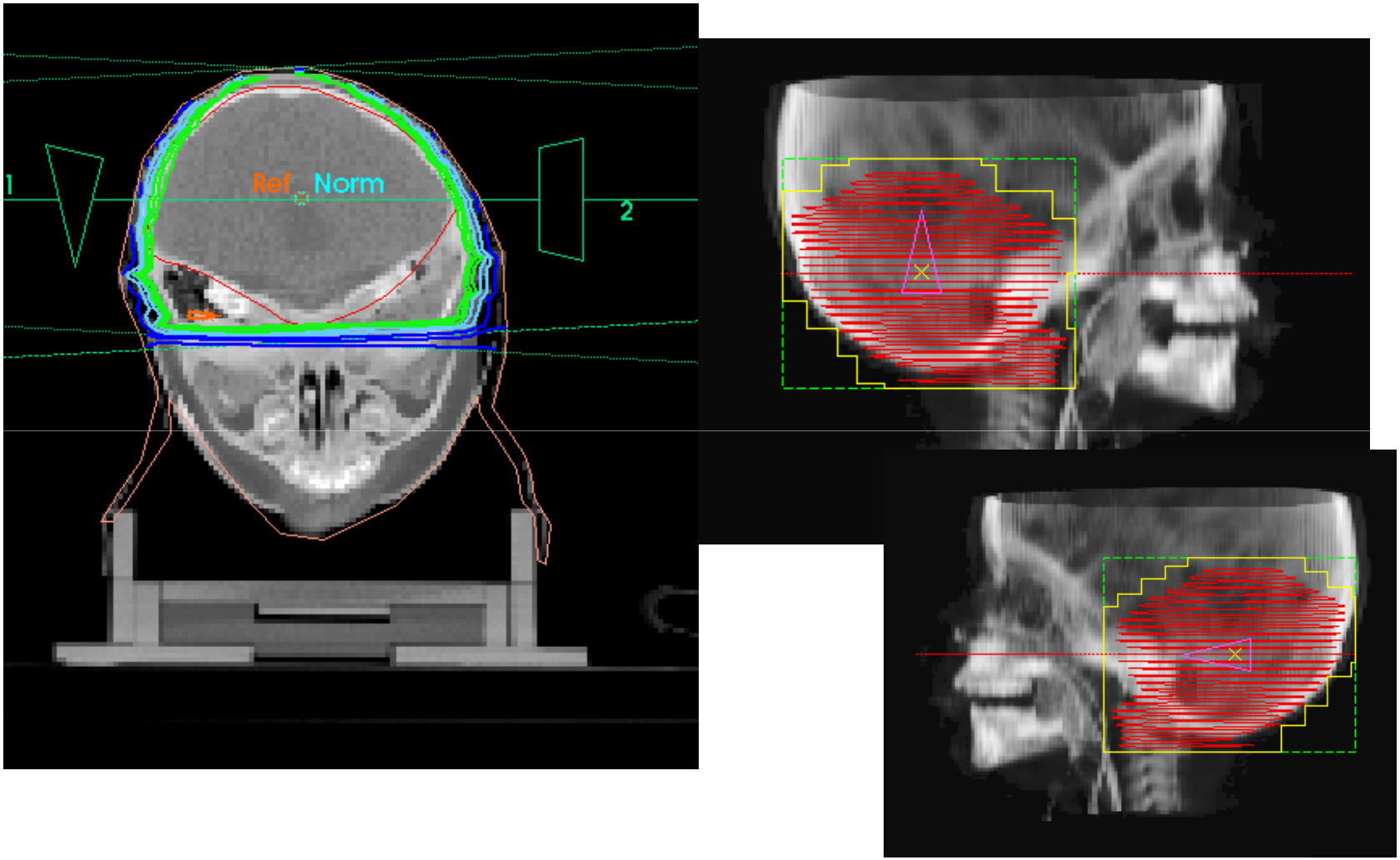


Computerised Tomography

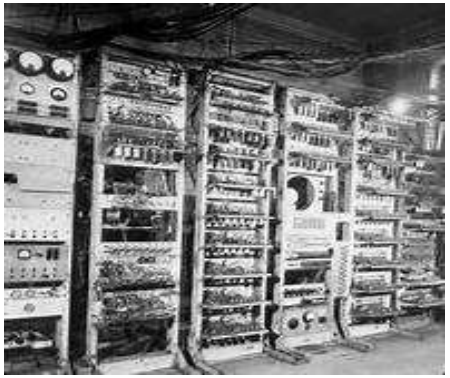




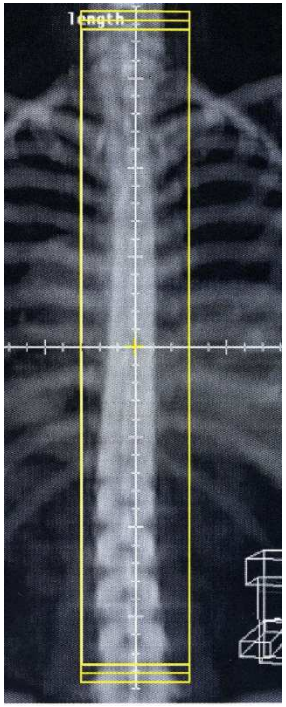
Conventional Planning

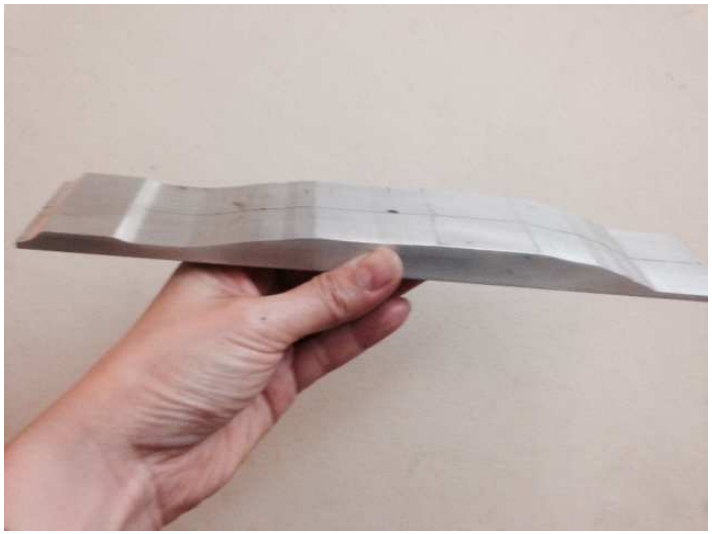


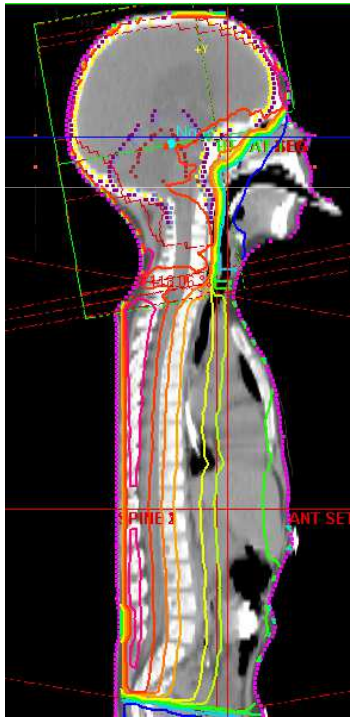
Computer Revolution



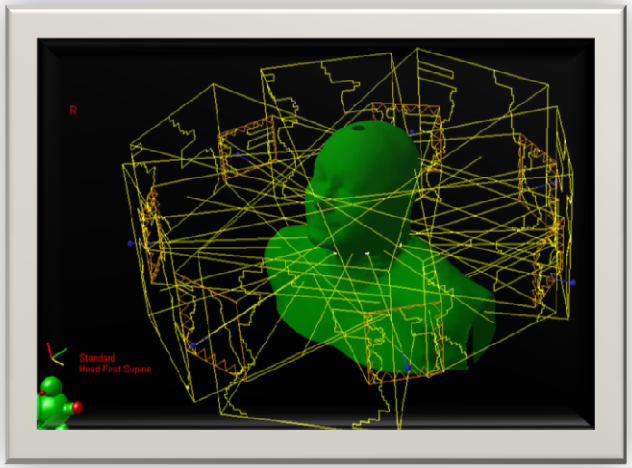
Field in Field Techniques

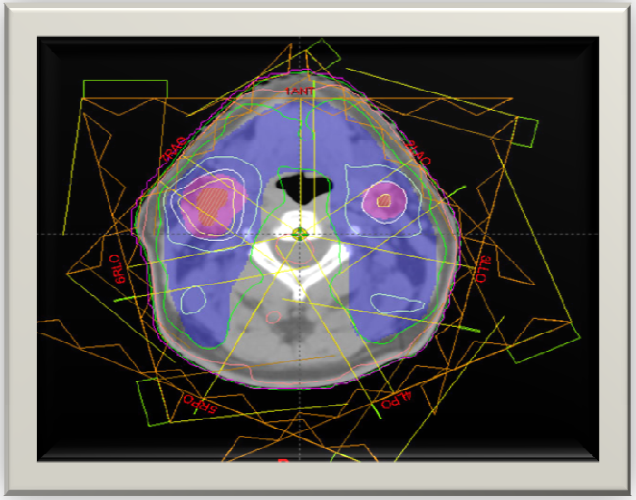


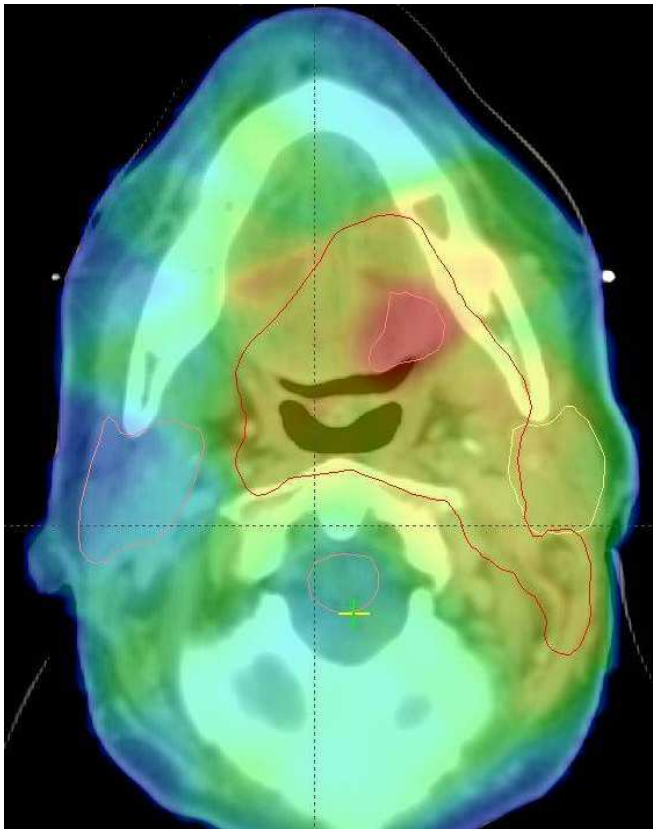




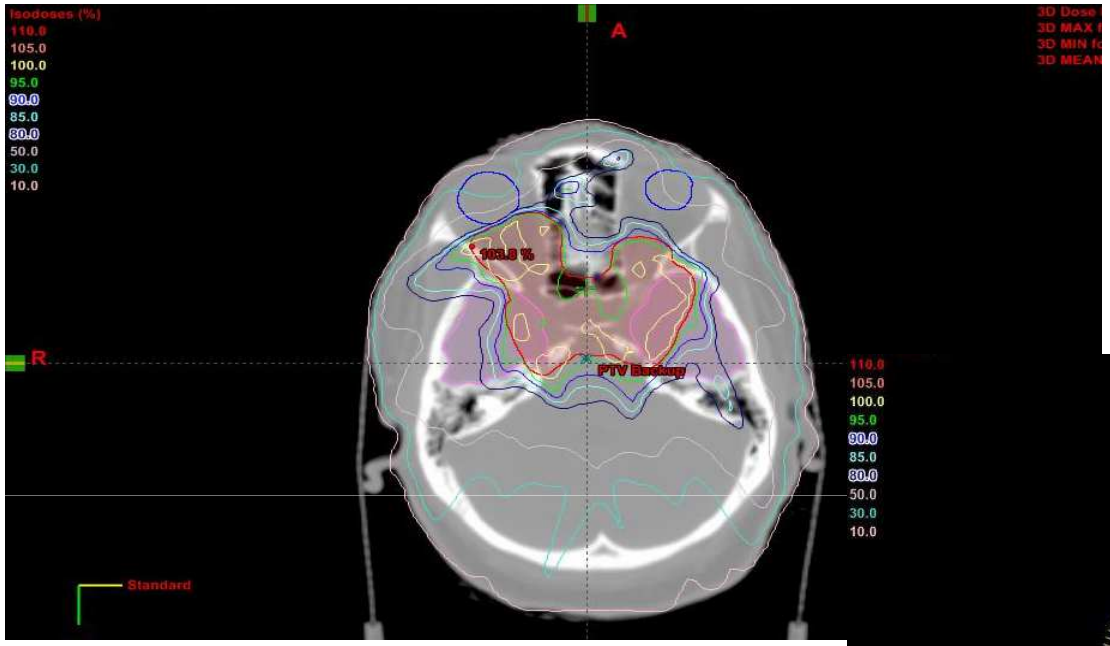
Fixed field IMRT

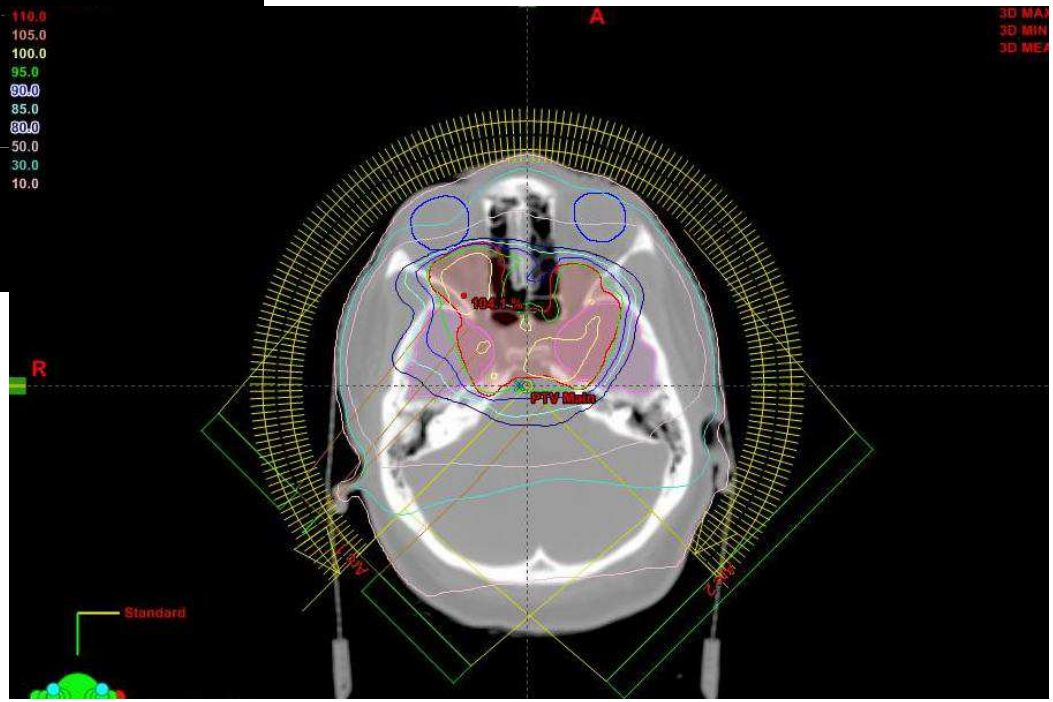




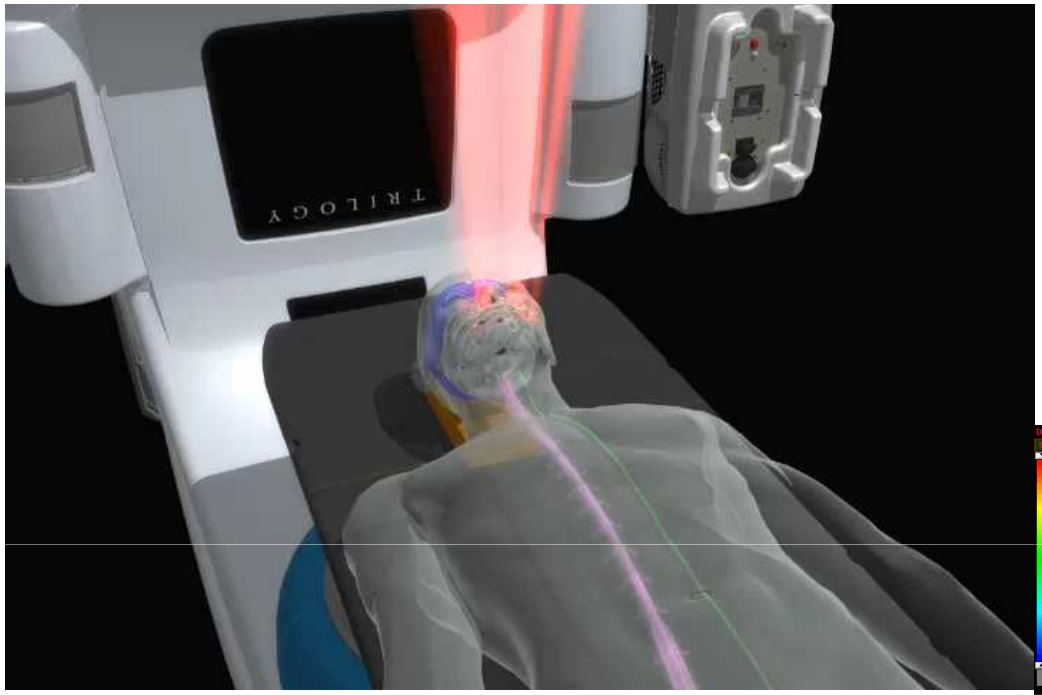


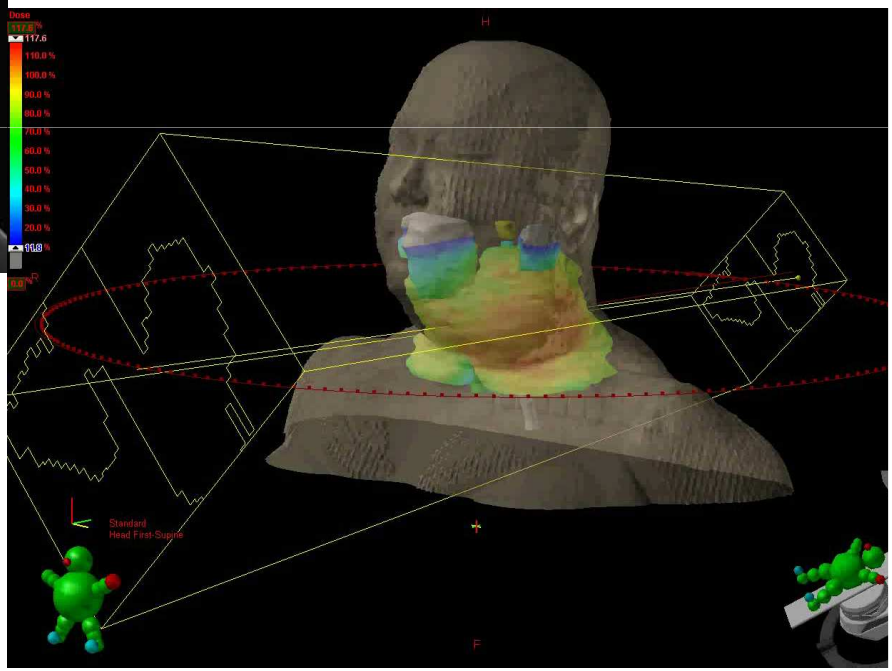
IMRT


Isodoses (%)
110.0
105.0
100.0
95.0
90.0
85.0
80.0
50.0
30.0
10.0
A
R
PTV Boost
Standard

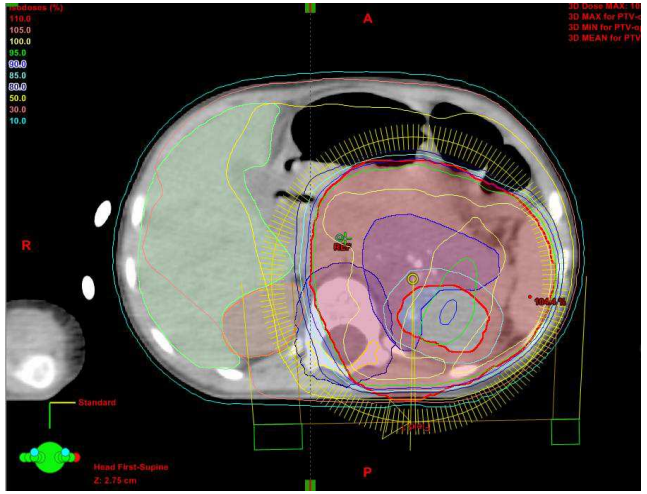

A
R
PTV Main
Standard

Arc Therapy

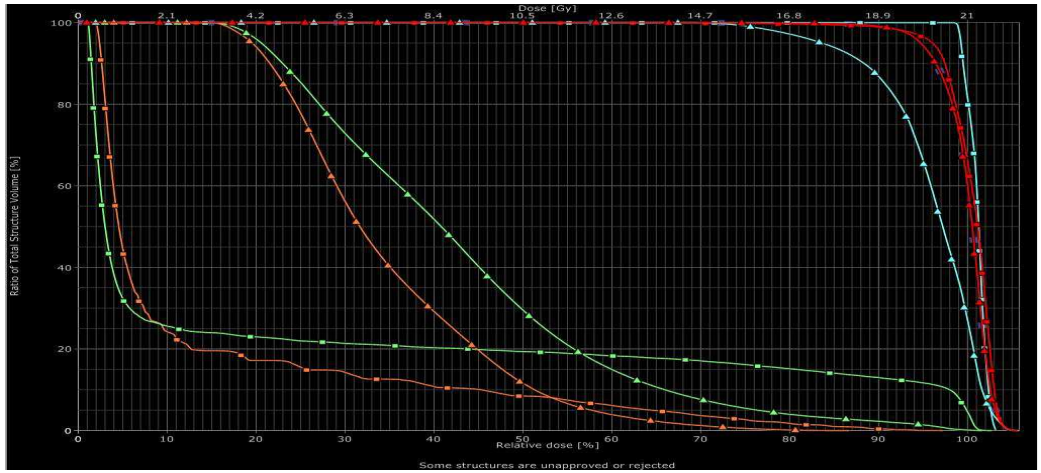

TRILOGY

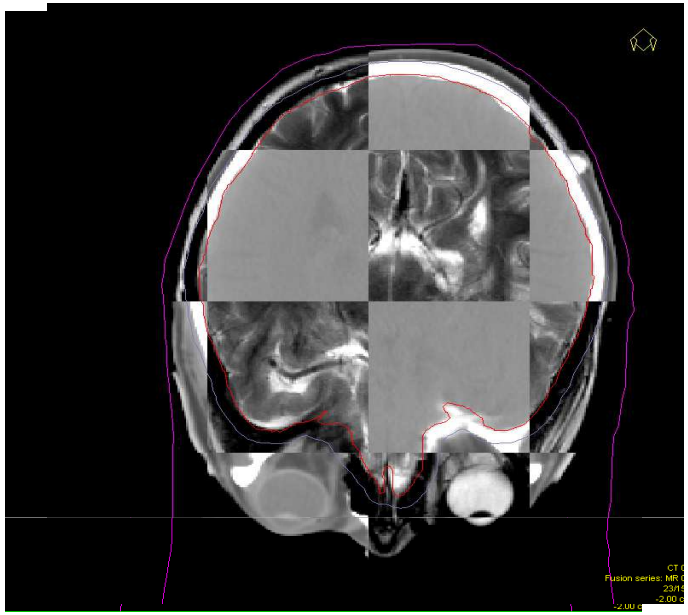

Dose
117.6
110.0 %
100.0 %
90.0 %
80.0 %
70.0 %
60.0 %
50.0 %
40.0 %
30.0 %
20.0 %
11.8
H
F
Standard
Head First-Supine

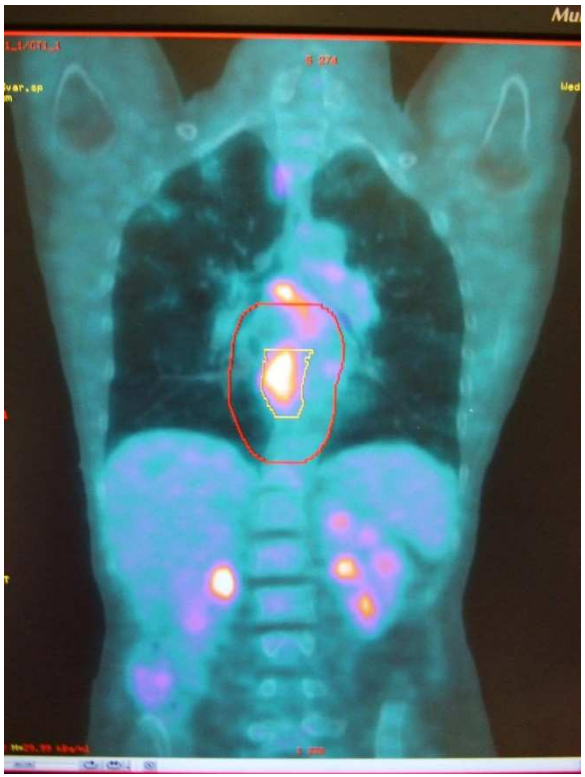
Plan comparison – Conventional versus RapidArc



PTV=red
Liver=green
L Kidney=blue
R Kidney=orange

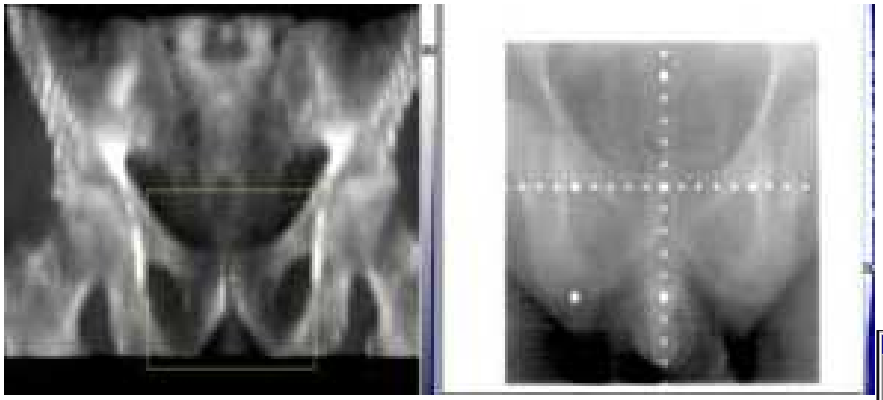


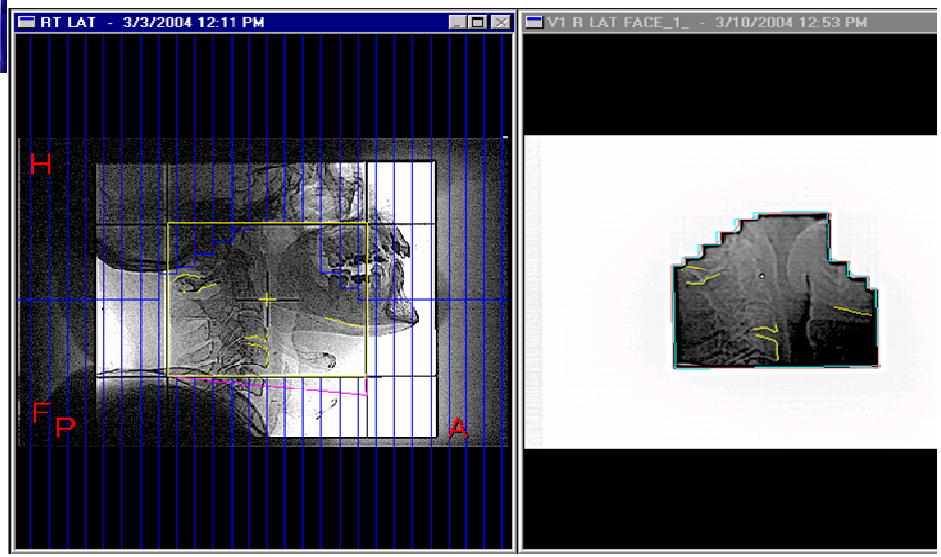




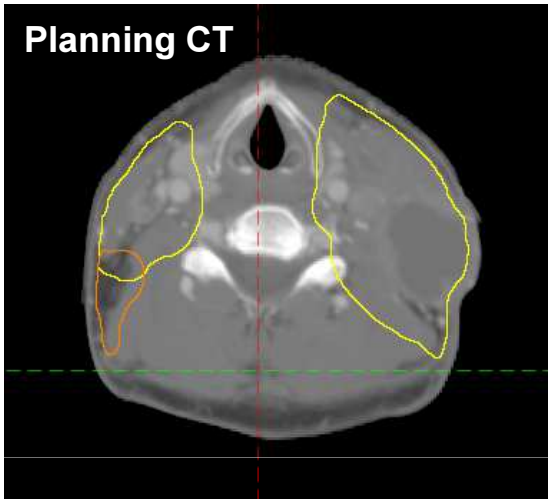
CT PET
Upper GI
Lung
Rectum

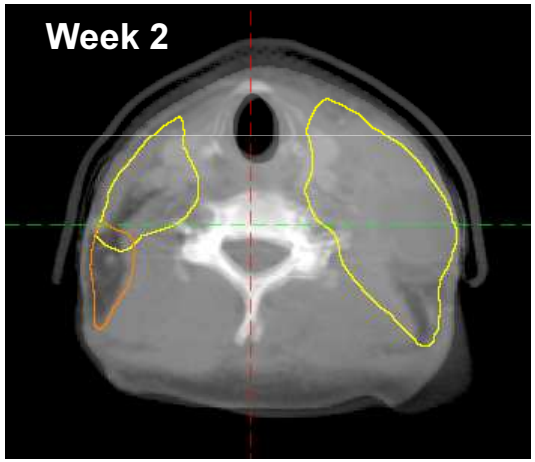
Treatment verification

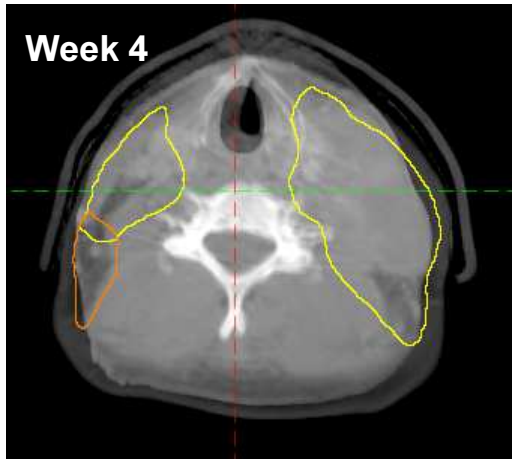




Cone Beam CT

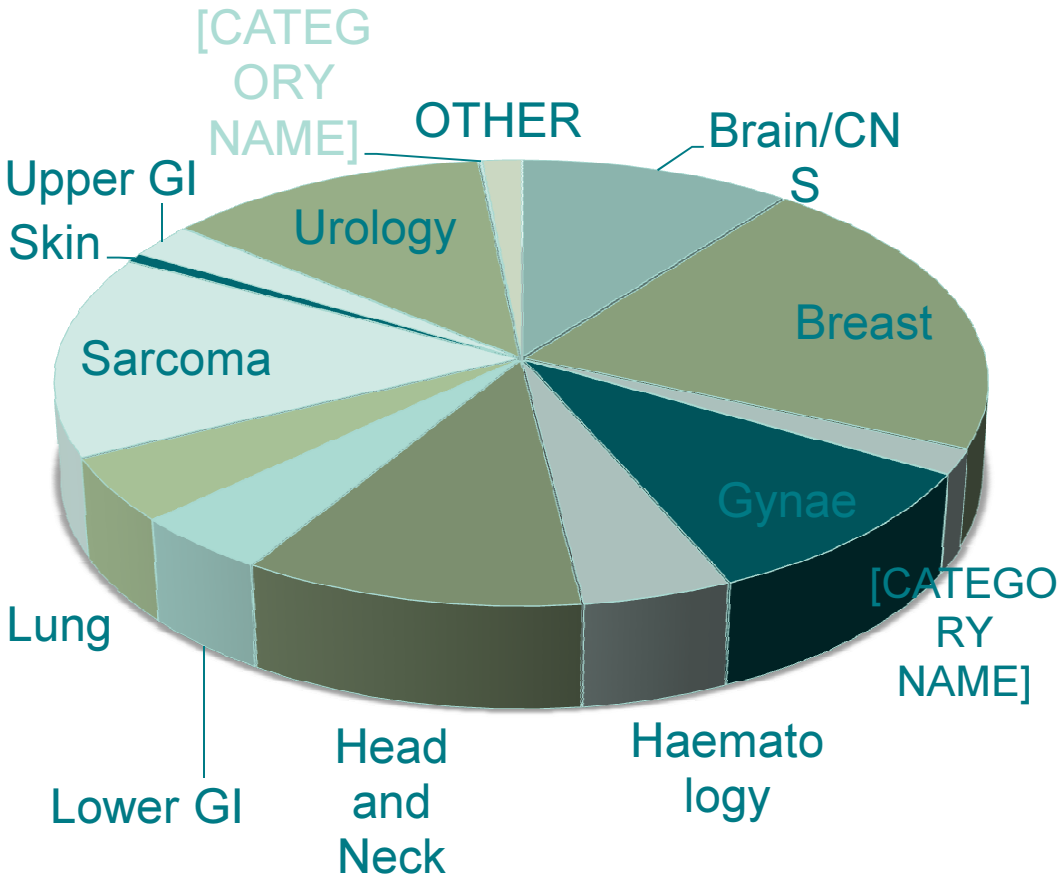






Radiotherapy at UCLH

- **Radiotherapy:** UCLH -a national leader in complex and highly-technical RT 55% IMRT/VMAT
- **Brain/whole CNS cancers:** NHNN is the largest neurosurgical centre in Europe
- **Paediatric cancers:** The UCLH/GOS centre = 3rd largest paediatric centre in the world
- **Sarcomas:** UCLH/RNOH provide one of Europe's largest sarcoma services
- **Head & Neck cancers:** UCLH leads in use of IMRT for head & neck - third largest caseload of any UK centre
- **Proton Beam Therapy:** UCLH has been designated by DH to be one of the first two PBT centres for UK National Service. UCLPartners already sees 1 in 6 of all patients in England eligible for PBT, and 1 in 4 of all eligible children



Radiotherapy at UCLH – Treatment Planning

- 1 dedicated GE CT Sim
- Eclipse
  - IMRT/RapidArc
- Oncentra Masterplan Workstations
  - External Beam Planning
  - Brachytherapy Planning
- ARIA Oncology Management system

Radiotherapy at UCLH – Treatment Equipment

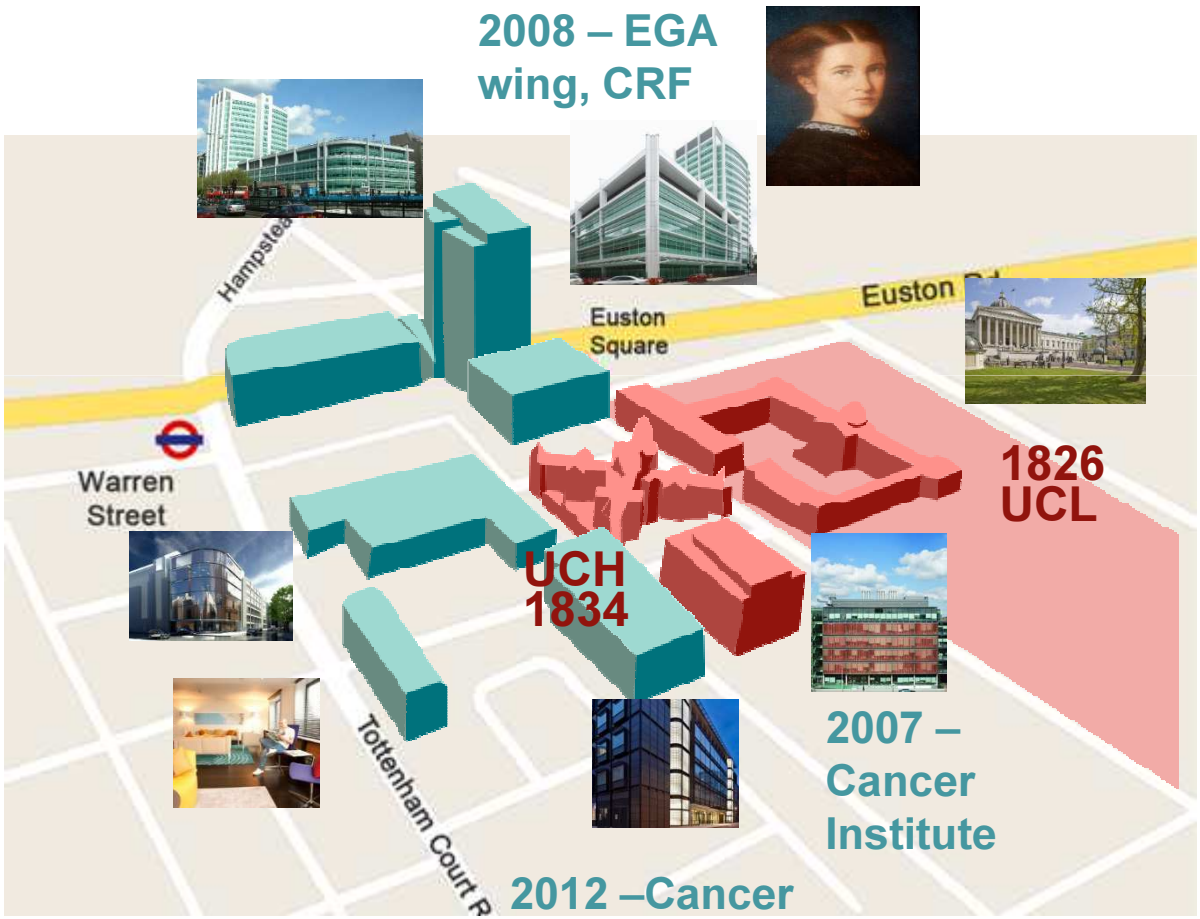
- 1x TrueBeam STx Linac
- 4x matched Varian Linacs
  - 120 Millennium MLC
  - 3x On Board Imaging
  - 3x RapidArc
  - Respiratory Gating
- Brachytherapy
  - MicroSelectron HDR Unit
  - Gynae; Prostate; Head and Neck; Oesophagus/Bronchus; Paeds and Adult Sarcoma

- Radionuclide Therapy
- Gamma Knife at NHNN

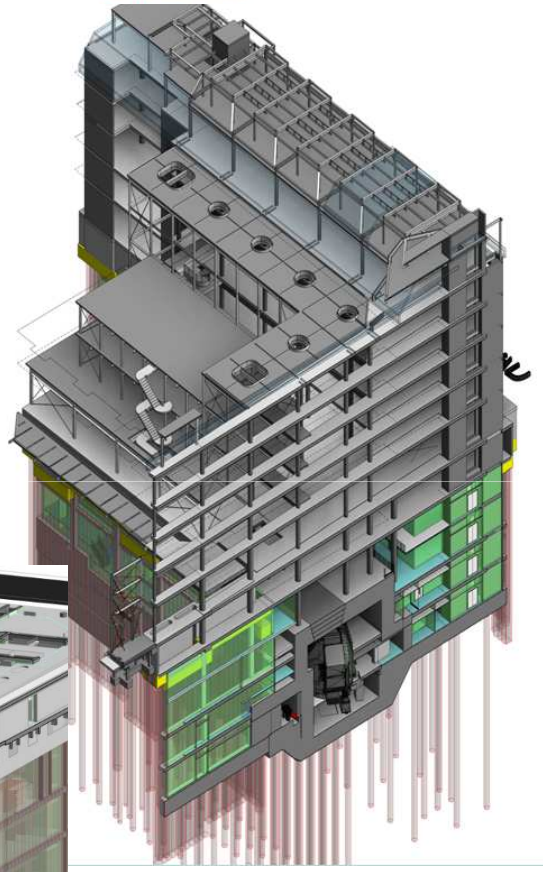
Cancer at UCLH

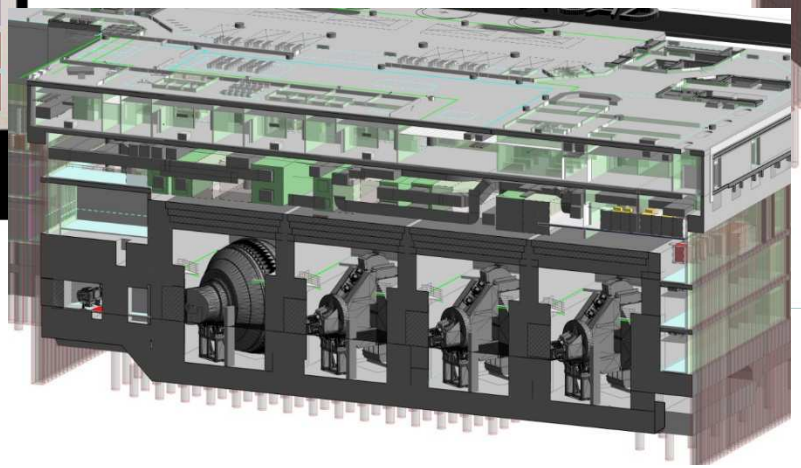
2005
Inpatients
and
Radiotherapy

2018 –
Proton Beam
Therapy and
beds



Proton Beam Therapy





Any Questions?

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Treatment Image Review + Adaptive Strategies for H&N and Lung- an RTT perspective

ESTRO IMRT School 03/04/16

Syed Ali Moinuddin
Lead Research and Development Radiographer, UCLH

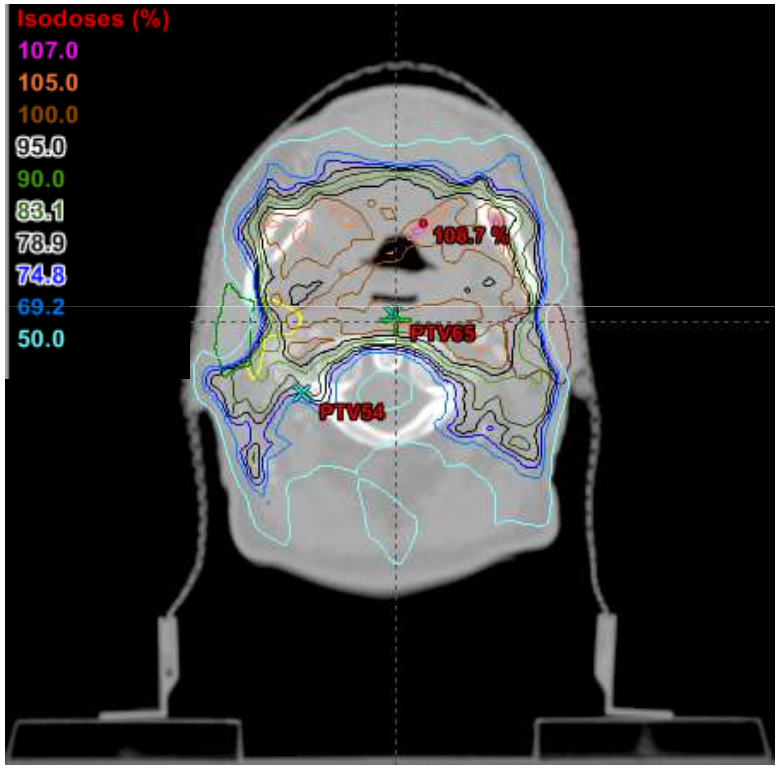
Overview

- Introduction
- Head and Neck
    - Immobilisation, CT scanning and Linac verification protocol
    - Clinical examples
- Lung
    - Immobilisation, CT scanning and Linac verification protocol
    - Clinical Examples

Introduction

The key aim of radiotherapy is to deliver a lethal dose to the tumour whilst limiting the dose (toxicity) to surrounding normal tissues.

Intensity Modulated Radiotherapy (IMRT) offers a method of delivering a much more conformal treatment with substantially lower normal tissue toxicity allowing the possibility of dose escalation to improve local control.



Introduction

However:

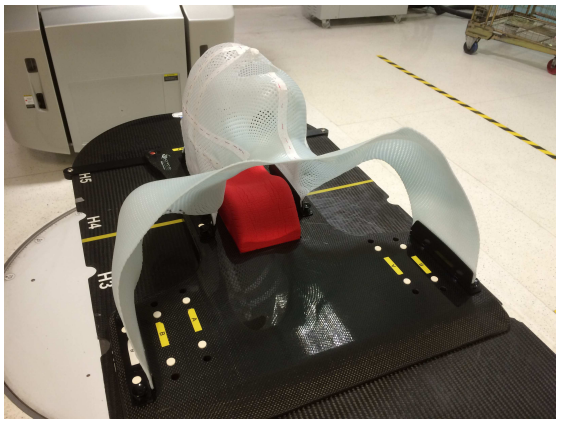
This steep dose gradient is greatly influenced/affected by:

- Variations in patient set-up
- Changes in overall patient separation/weight loss
- Changes in tumour volume size and position
- Changes in size and position of Organ at Risk (OAR) volumes.

Management of this patient cohort requires:

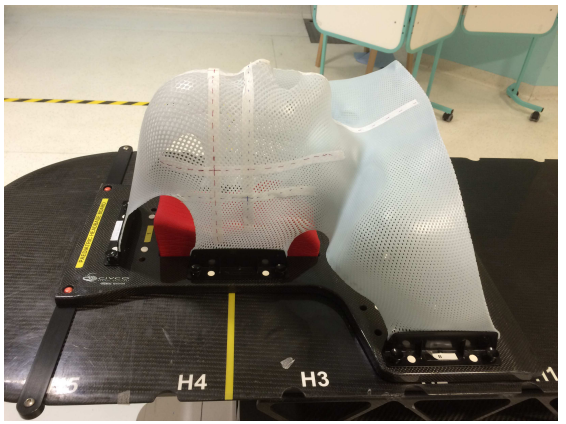
- Effective immobilisation
- Image guidance
- Comprehensive nutritional management

Head and Neck



- First UCH IMRT patient APRIL 2006

- All H/N patients
- Supine with head on foam headrest
- Arms by side
- Head and shoulders immobilised by 5 point thermoplastic shell



- 2.5mm CT scan with iv contrast

Head and Neck (current)

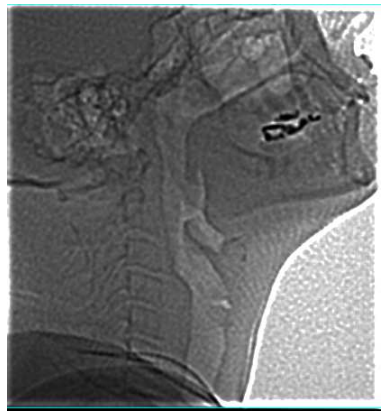
- Imaging protocol

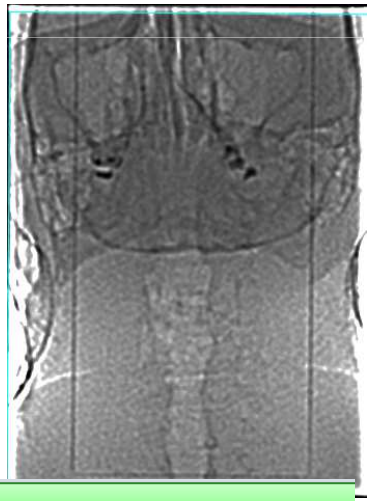
- Online daily orthogonal kV imaging with ‘shift to zero’ protocol (3mm)
- Matching to bone (systematic adjustment after #1-3)

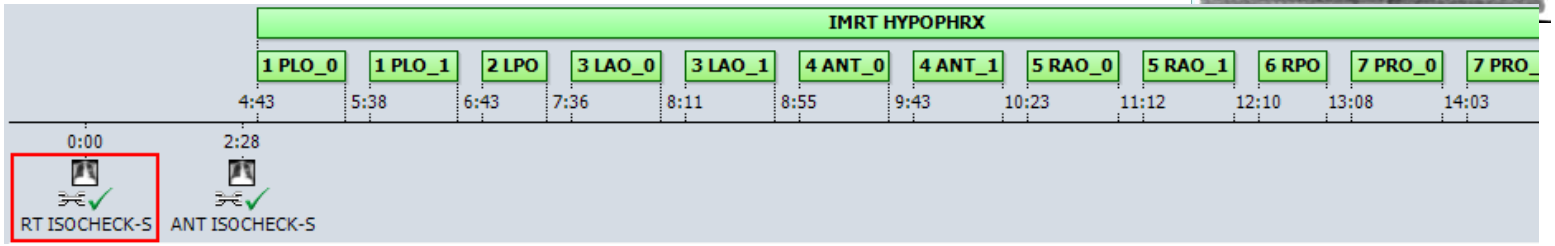
- Additional weekly offline CBCT for PTV coverage and OAR avoidance.

Head and Neck (historical!)

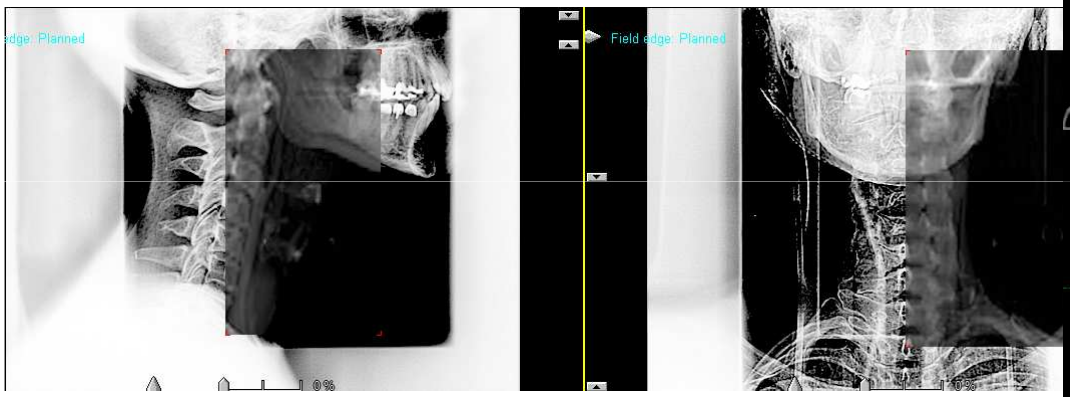
- Imaging protocol
- Orthogonal MV imaging #1-3 and weekly
- No CBCT

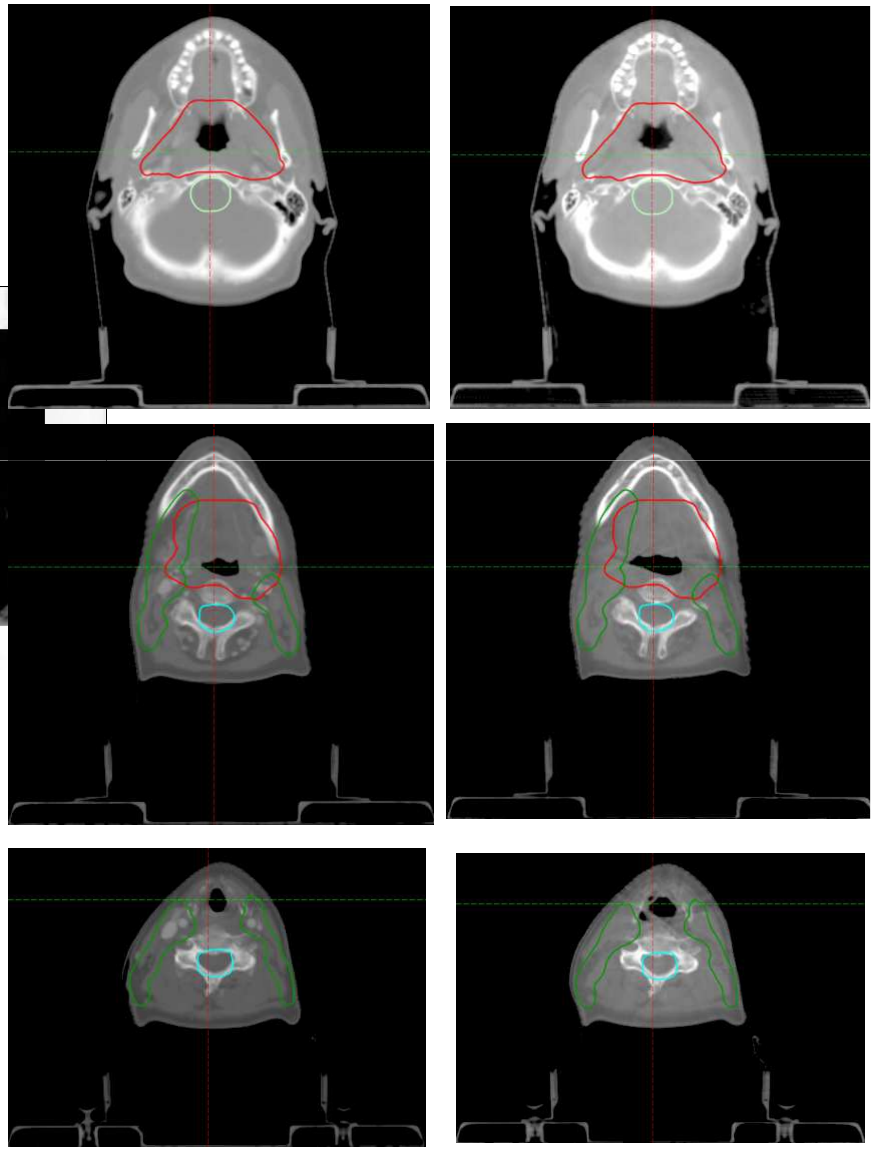


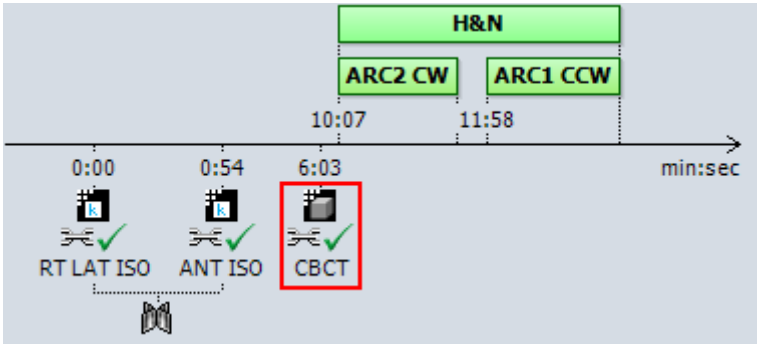




Head and Neck







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Head and Neck

Issues:

Weight loss

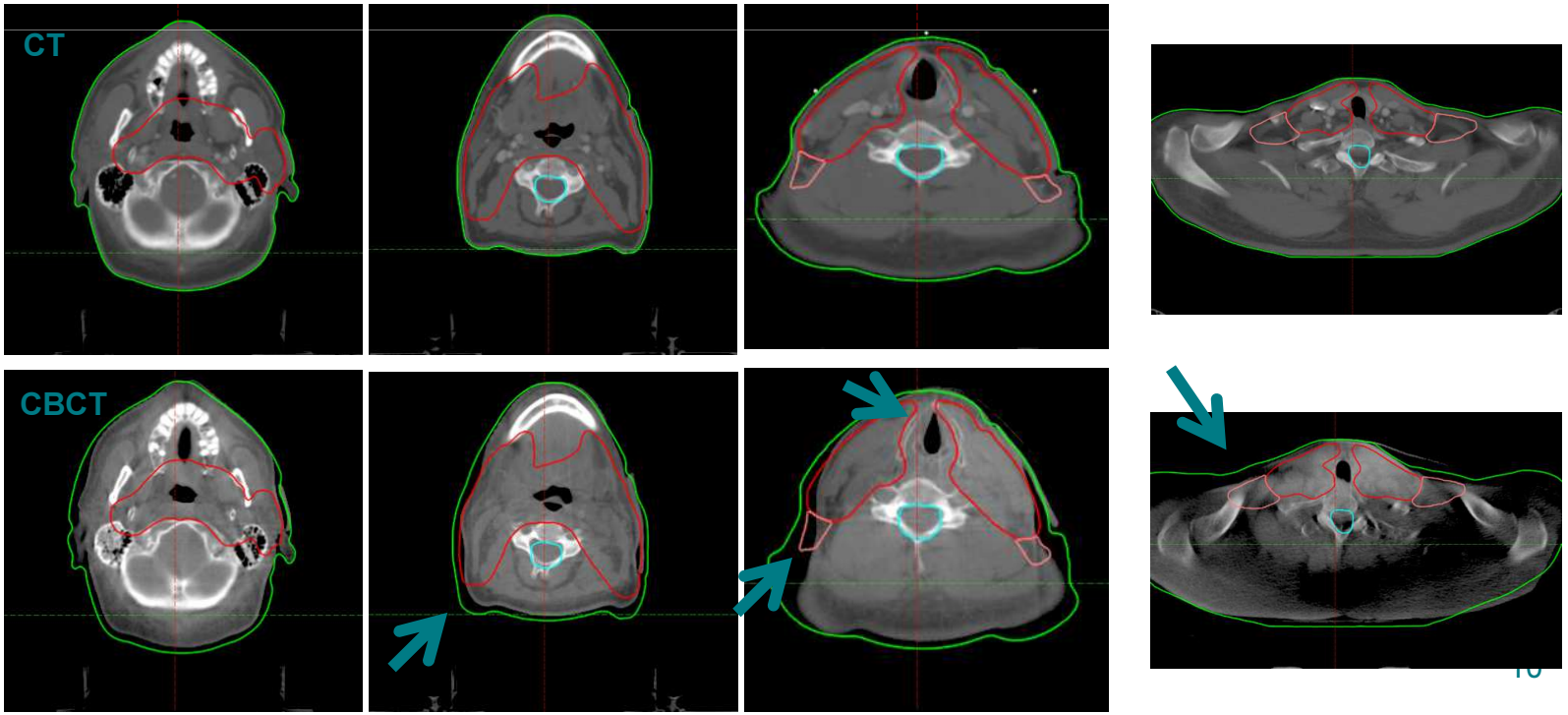
Bone positional changes

Soft tissue changes

Head and Neck

Issues:

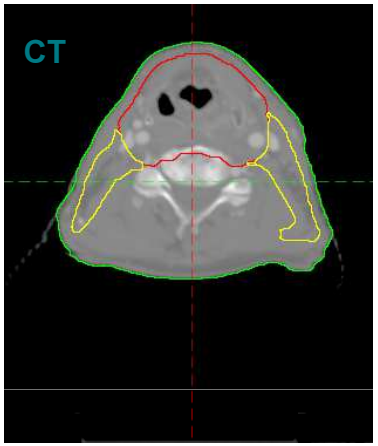
Weight loss (Non compliance)

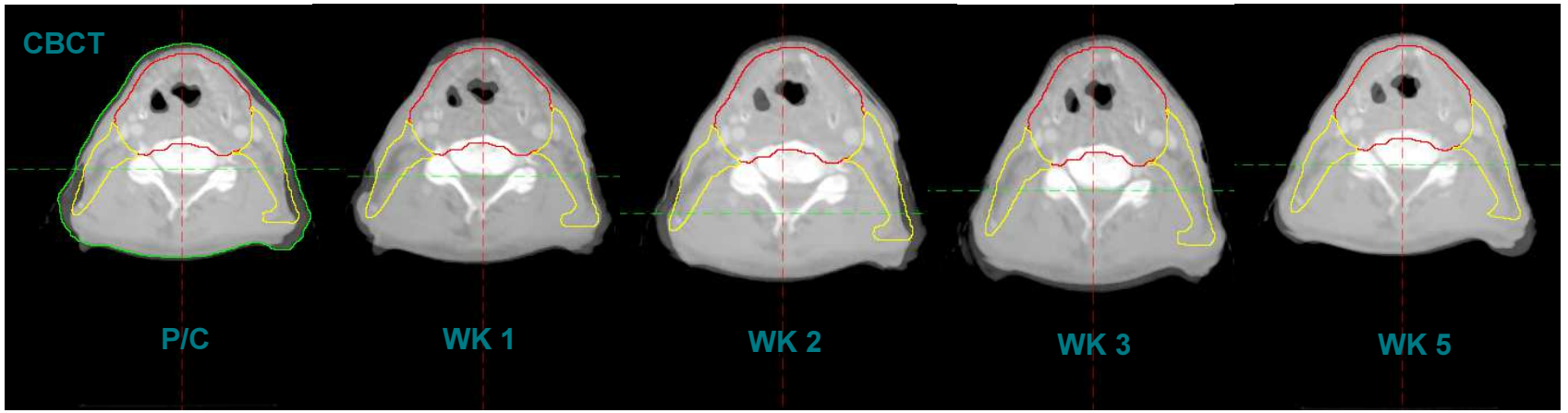


Head and Neck

Issues:

Weight loss (Compliance)





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Head and Neck

Issues:

Weight loss

- Prophylactic use of PEG
- Introduction of H/N radiographer role to improve patient experience
- Introduction of twice weekly dietetic clinic

Head and Neck

Issues:

Bone positional changes

Corrected by:

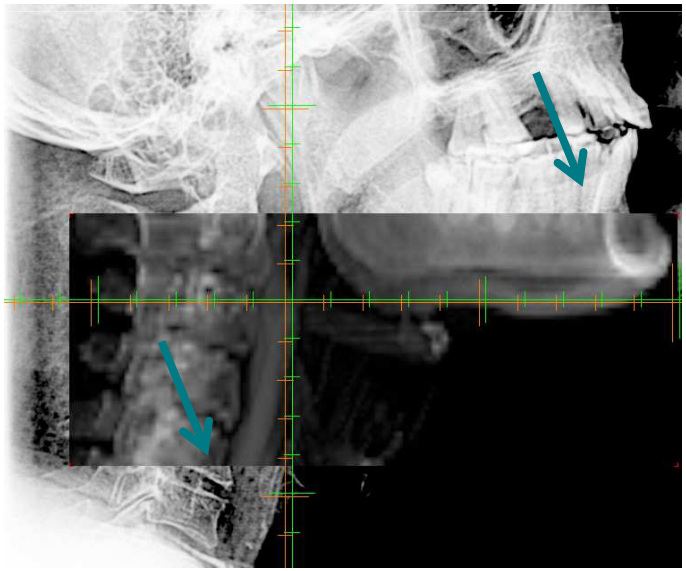
Intervention and repeat imaging
Addition of Dalzafoam
Reduction of height of the foam headrest

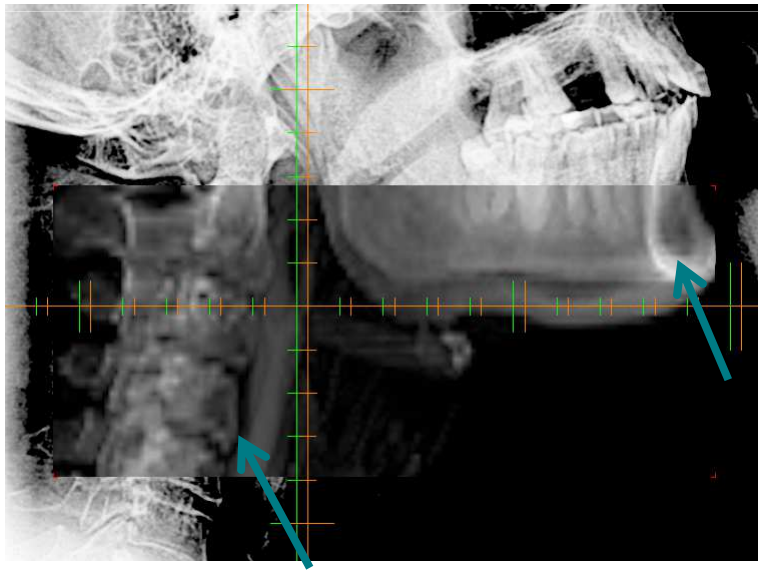
Preferential bone match to part of the cord closest to the high dose volume

Head and Neck

Issues:

Bone positional changes



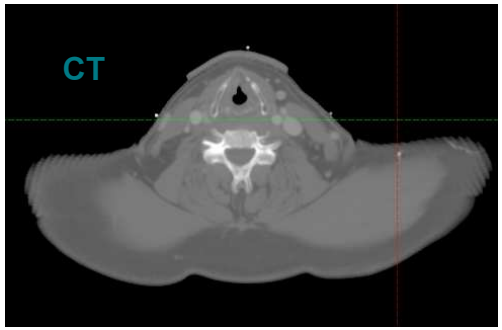


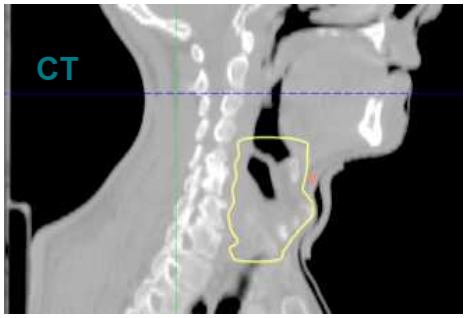
Head and Neck

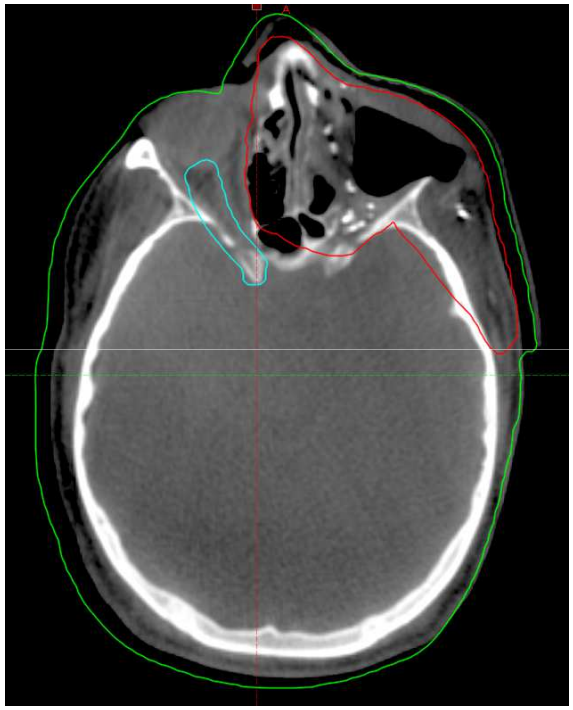
Issues:

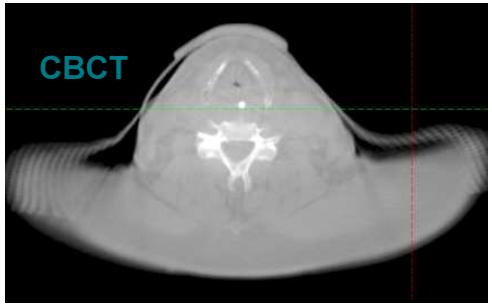
Soft tissue changes

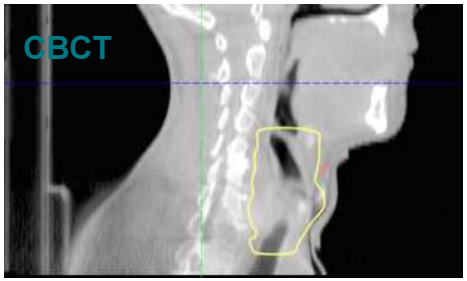
Head and Neck











Occluded airway. May require steroids, surgical intervention or surveillance

CBCT Larynx CTV systematically in a different position.

Weight loss resulting in inadequate immobilisation and roll. NB R ON outside PRV

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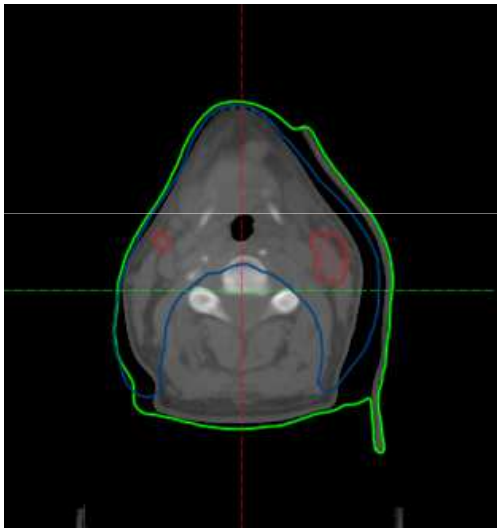
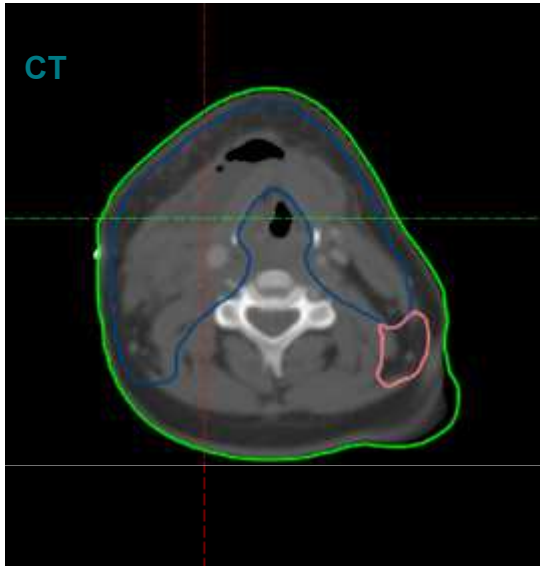
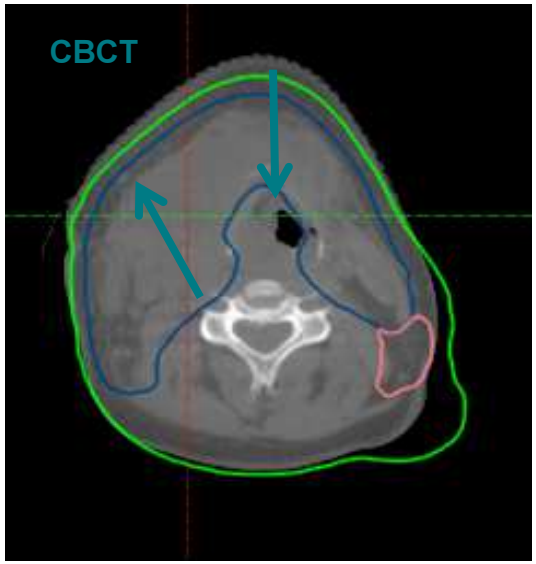
Head and Neck



Weight loss resulting separation change, increase in air gap between patient and bolus and movement of nodal volume





Tumour volume increasing resulting in airway displacement

Head and Neck

Dependent on….. MDT discussion

- Patient compliance
- Random or systematic difference
- Original plan assessment
- How many fractions left!
- Resource availability

Lung

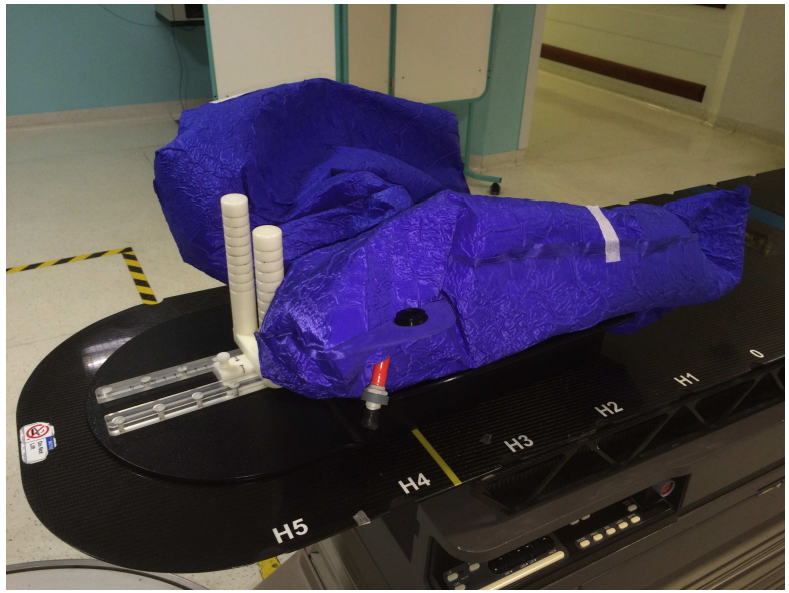
- First UCH lung IMRT patient 2012
- Lung SABR from 2013

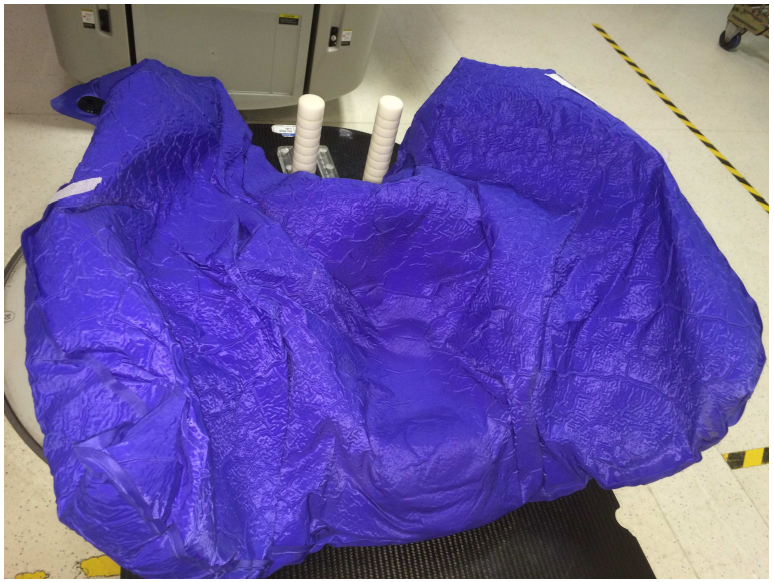
- Selected non SABR cases close to cord or brachial plexus
- Supine with arms up on a Wing Board. Arms supported by Vac Bag

- All patients have a 4d CT with contrast and coached breathing.

- Target delineation on the MIP and dosimetry on AVE-IP

Lung





Lung

- Imaging protocol (non-SABR)

- Online daily orthogonal kV imaging with ‘shift to zero’ protocol (5mm)
- Matching to bone (systematic adjustment after #1-3)

- Additional weekly offline CBCT for PTV coverage and OAR avoidance. Initial radiographer review with weekly clinical update.

Lung

- Imaging protocol (SABR)
- Online daily CBCT imaging with ‘shift to zero’ protocol (5mm)
- Matching to ITV
- Additional post treatment CBCT for PTV coverage and OAR avoidance.
- (Initial cohort also had post ‘shift to zero’ CBCT to assess effect of couch travel on coverage-not necessary!)

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Lung

Issues:

Weight loss

Bone positional changes

Tumour volume changes: position and size

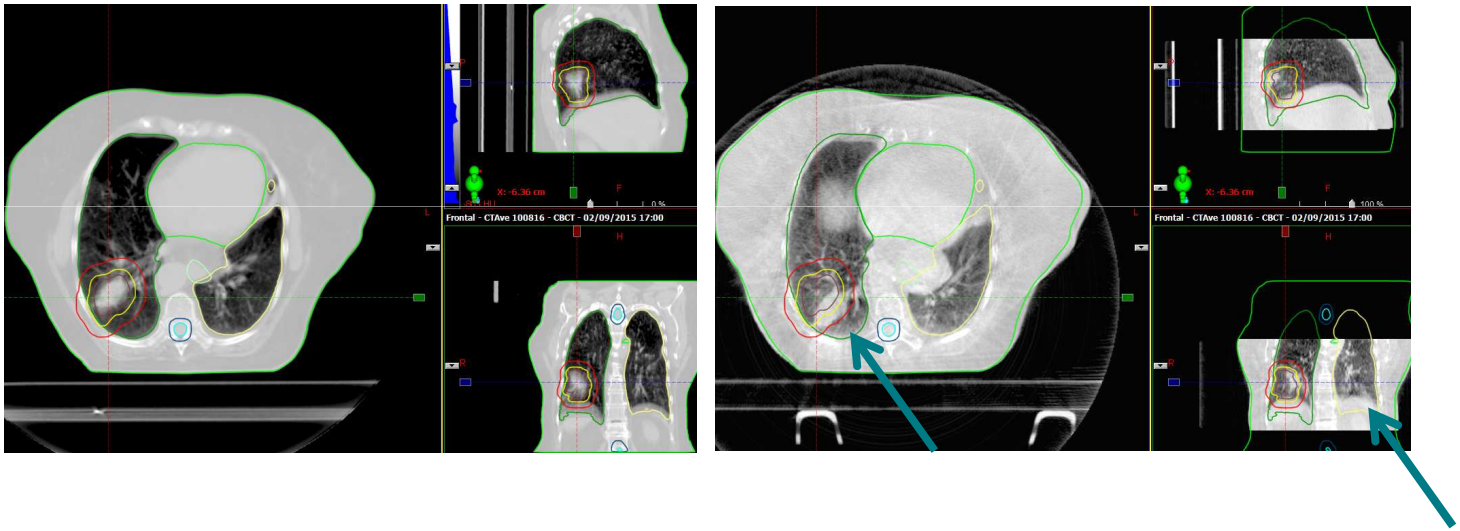
Lung deflation/Re-inflation

Infection (+/-)

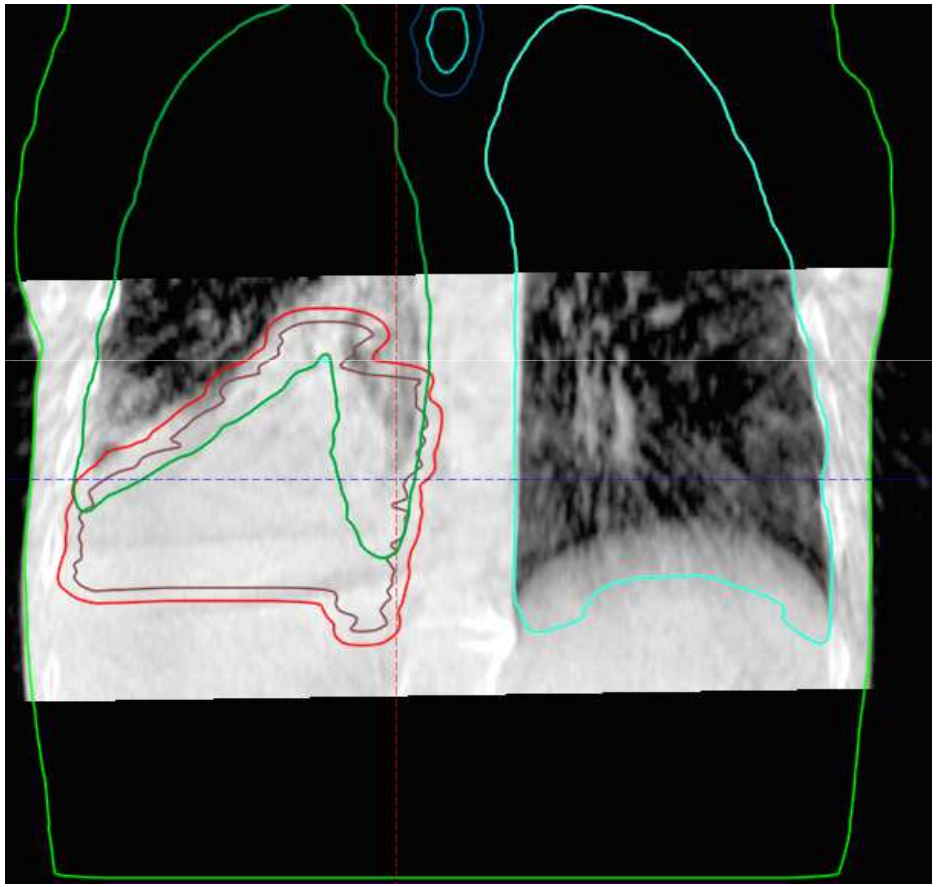
Imaging Limitations (Varian)

- kV-low dose, bone anatomy
- Maximum length is 20cm
- CBCT-not low dose, soft tissue
- Maximum length is 16cm
- Image quality
- Data acquired in 1 minute so motion artefact-4d CBCT coming soon!

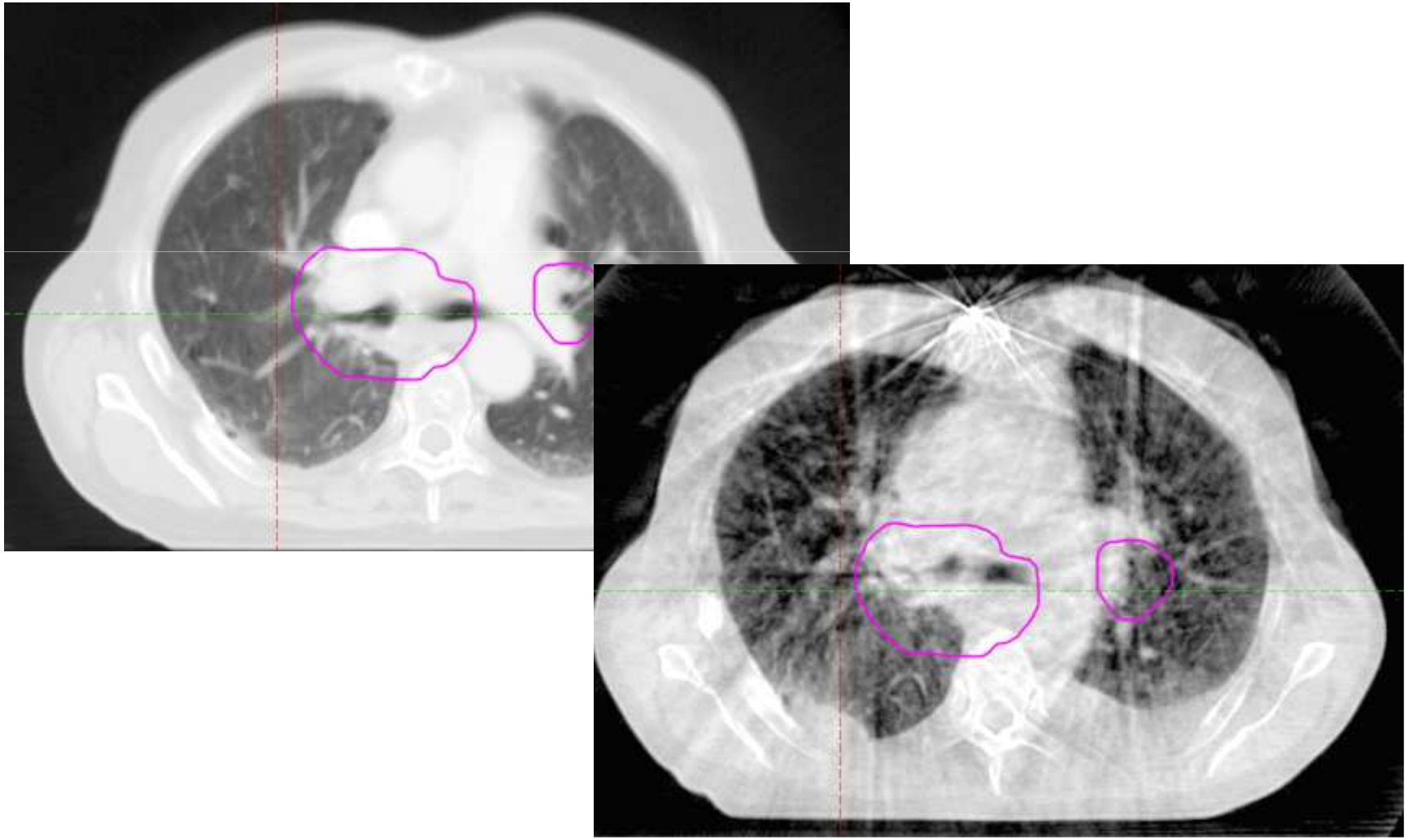
Clinical Cases- non SABR Lung



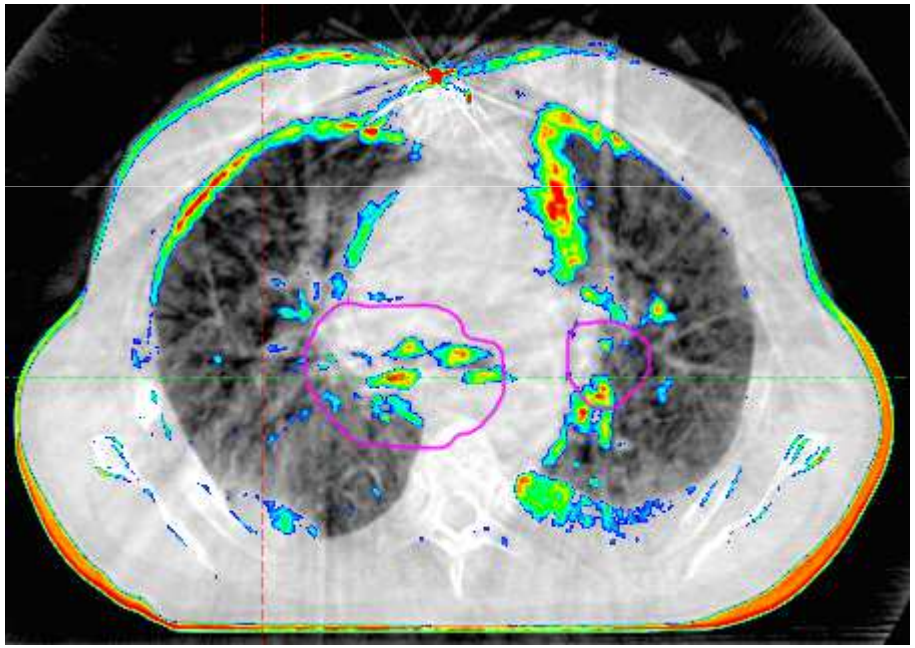
Clinical case: non-SABR

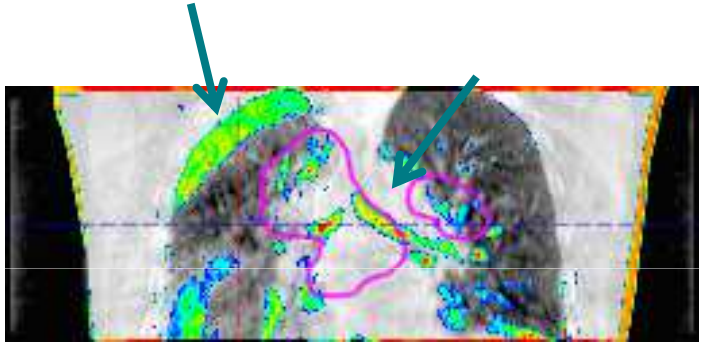


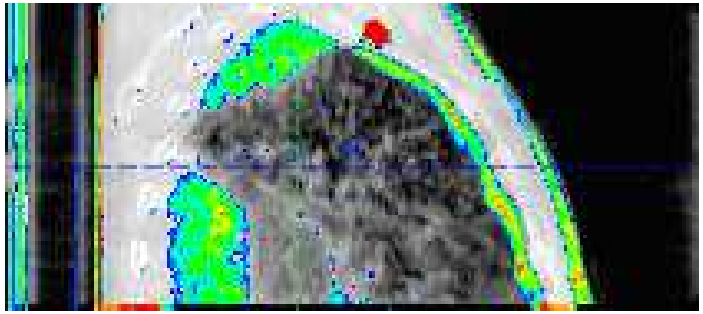
Clinical Cases- non SABR



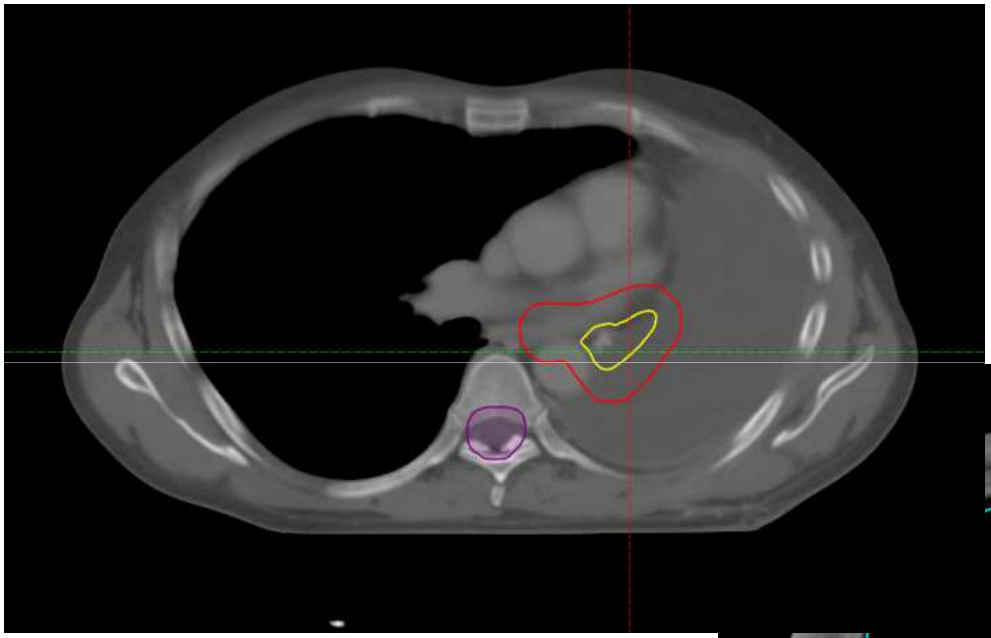
Clinical case: non-SABR

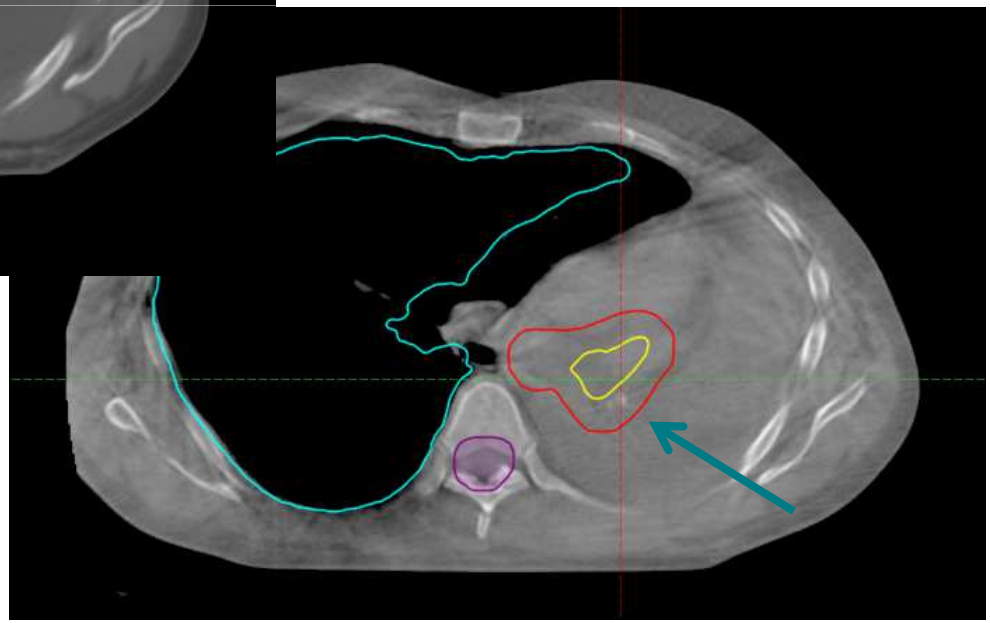






Clinical case: non-SABR

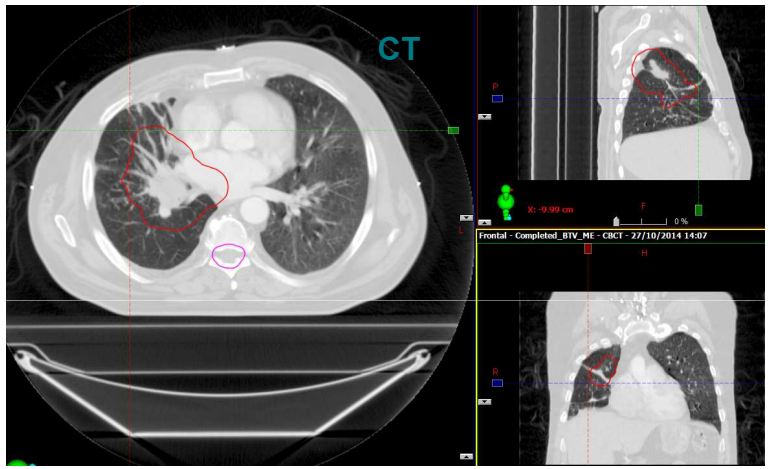


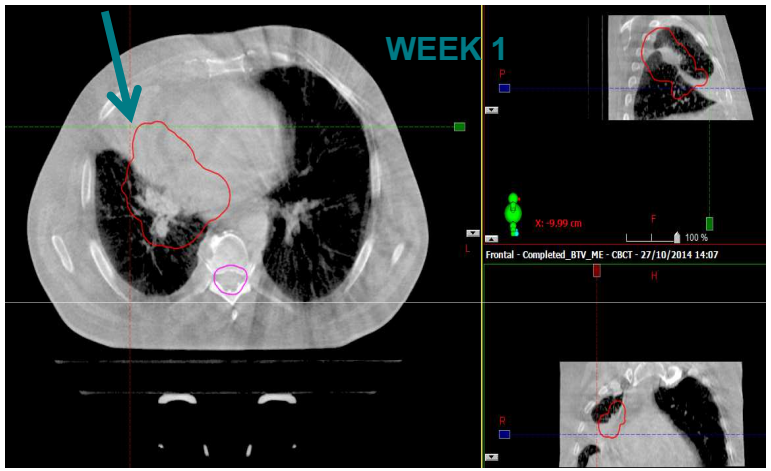


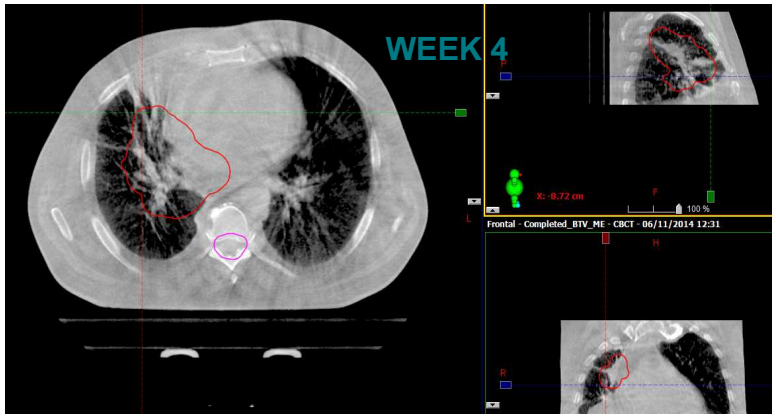
Pt has one functioning lung

kV shows good bone set up
CBCT show RT lung re-inflation
CBCT shows movement of heart etc. to left
NB calcification
Action: Re-plan!

Clinical case: non-SABR





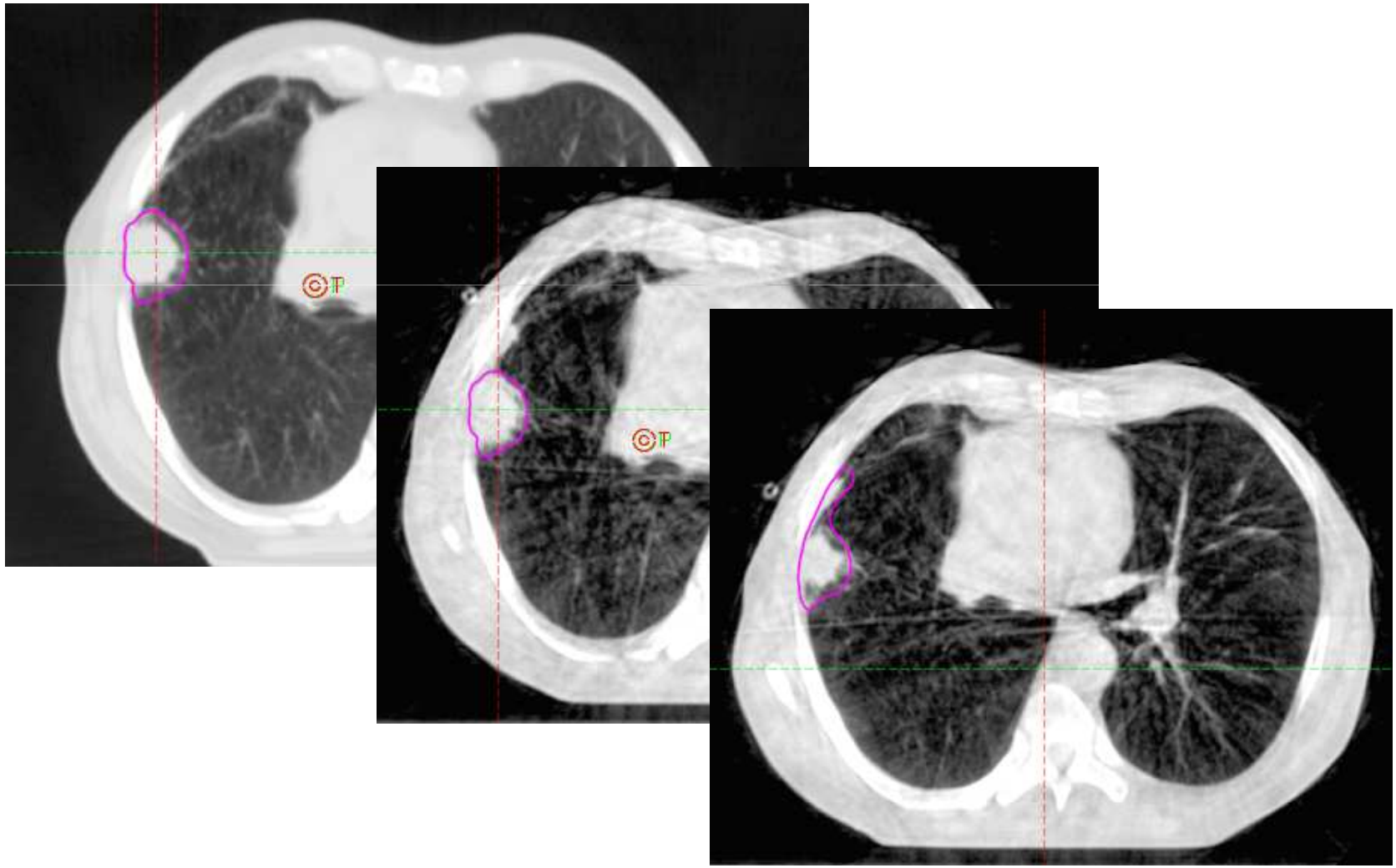


CBCT WK1 shows reduced lung volume and increased anterior density-coverage tight posteriorly

CBCT frequency changed to x2 weekly

CBCT week 4 shows resolution of change-no re-plan required

Clinical Cases-SABR lung



Summary

- CBCT is a useful imaging tool
- Highlights anatomical changes
- Does not tell you about dosimetric impact
- Density changes can have a greater impact in lung than other anatomical sites.
- Useful paper Kwint et al, (2014)

Thank you

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University College London Hospitals NHS
NHS Foundation Trust

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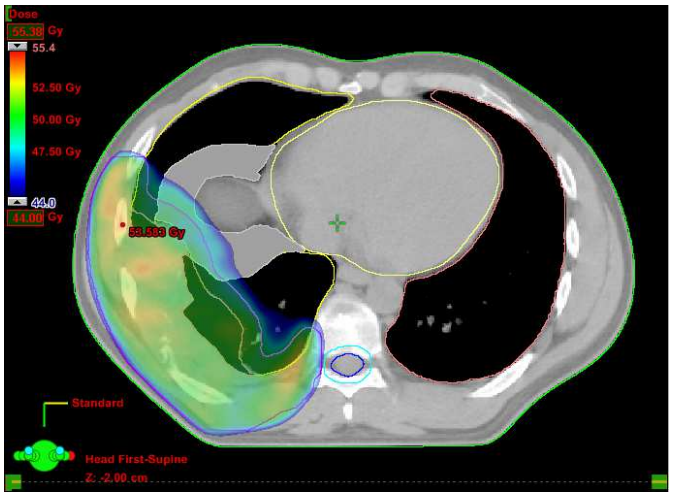
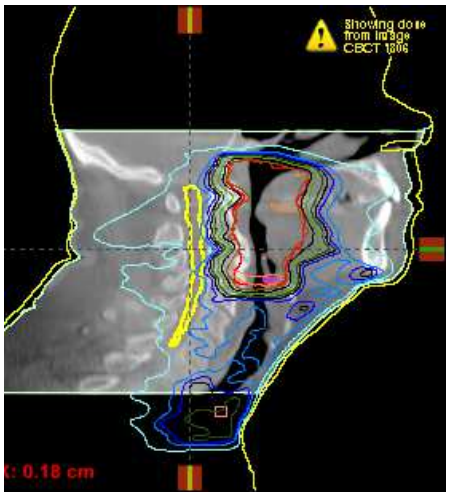
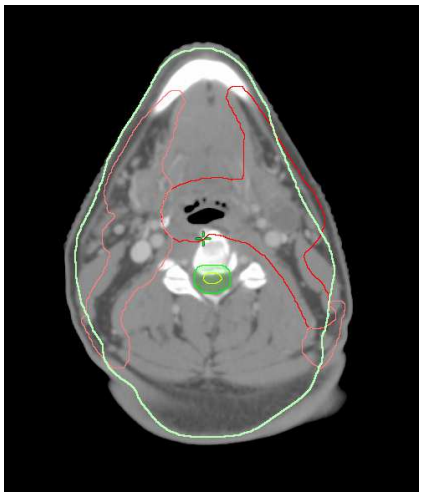
Adaptive strategies for head & neck and lung: Physics perspective

ESTRO IMRT course, London April 2016

Rachel Bodey
Principal Physicist for Treatment Planning, UCLH





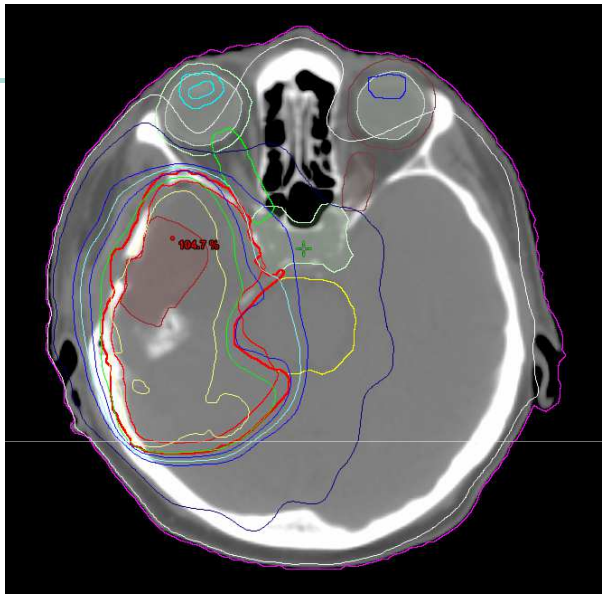


Impact of anatomical/positional changes

- Increased used of image guidance → increased information about current anatomy & position vs. plan.
- Image comparison allows us to make subjective judgements about e.g:
  - consistency of setup
  - effectiveness of immobilisation
  - external shape changes
  - internal anatomical changes

- What we REALLY want to know is impact on dose delivered.
- At what point are changes clinically significant? When is action required?

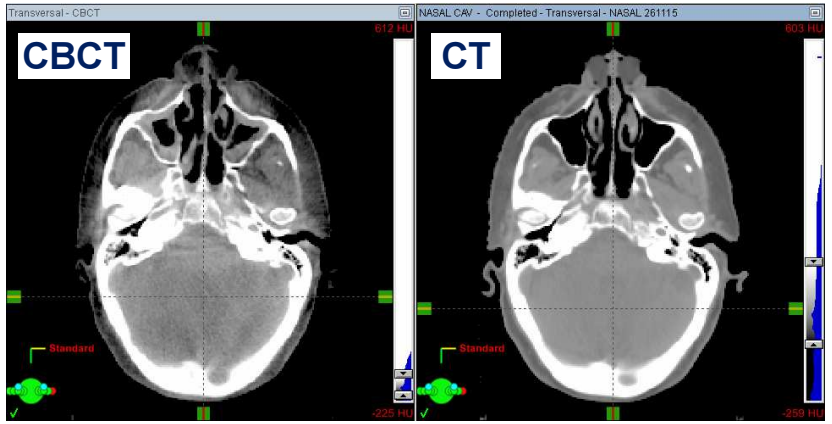
Considerations for IMRT



- Typically characterised by:
  - highly conformal dose distributions;
  - steep dose gradients at edge of PTV and OAR;
  - dose concavities to spare OAR;
  - multiple dose levels;
  - dose escalation.
- Potential advantages, but associated risks.
- A small positional change can translate to a large dosimetric difference – risk of underdosing PTV, or overdosing OAR.
- Assessing impact of changes may be less intuitive compared with conformal techniques.

Adaptive radiotherapy

- Ongoing monitoring of position and anatomy during treatment, comparison with initial conditions.
- Strategy for design or modification of treatment to accommodate changes.
- Patient-specific, image driven.
- Desirable to base decisions on dosimetric impact of changes.
- Can we use CBCT to calculate dose actually delivered, compared with that planned?
- Assess current suitability of treatment plan.



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CBCT for dose calculation

- Direct use of CBCT for dose calculation can be challenging.

Review articles:

- Cone beam computed tomography: The challenges and strategies in its application for dose accumulation.

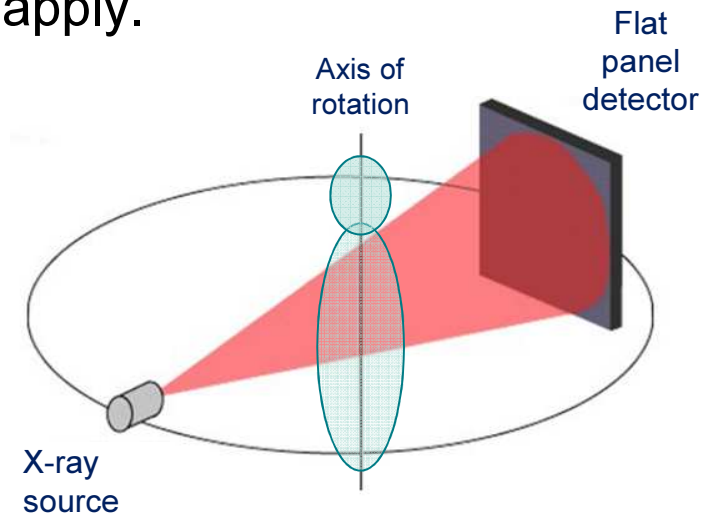
  V Kong, A Marshall, H Chan, J Med Imag Radiat Sci; March 2016; 47(1): 92–97.

- Applications of linac-mounted kilovoltage cone-beam computed tomography in modern radiation therapy: a review.

  K Srinivasan, M Mohammadi, J Shepherd; Pol J Radiol. 2014; 79: 181–193.

CBCT for dose calculation

- Volumetric imaging, scatter from whole object contributes.
- Fewer projections; less raw data.
- Poor SNR cf. fan beam CT.
- HU numbers less reliable – dependent on imaging parameters, size of object, presence of inhomogeneities, artefacts. Calibration curve may not apply.
- Large uncertainties can result from using CBCT HU for dose calculation.
- Motion artefact (gantry rotation time).
- Limited image length.

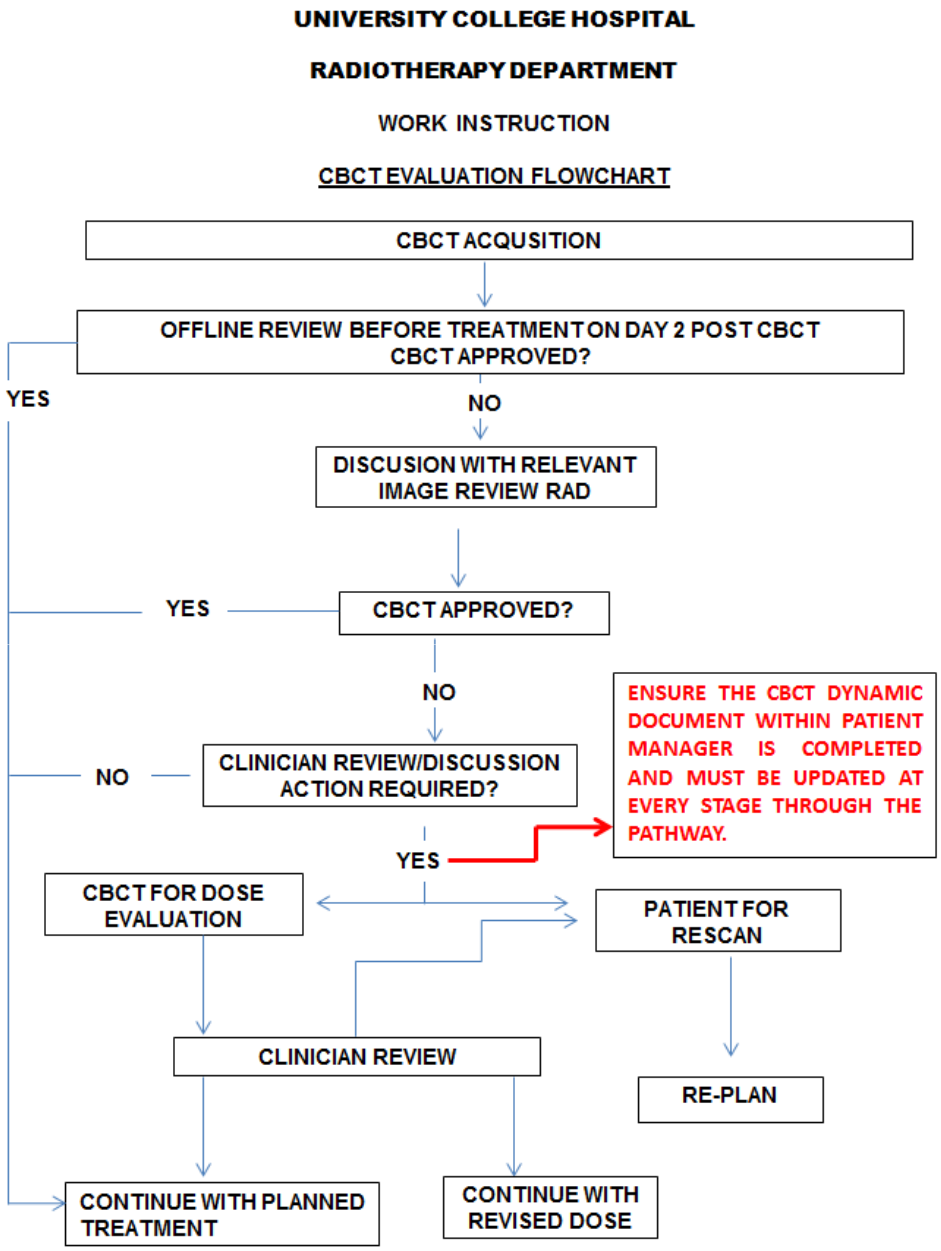


UCLH strategy

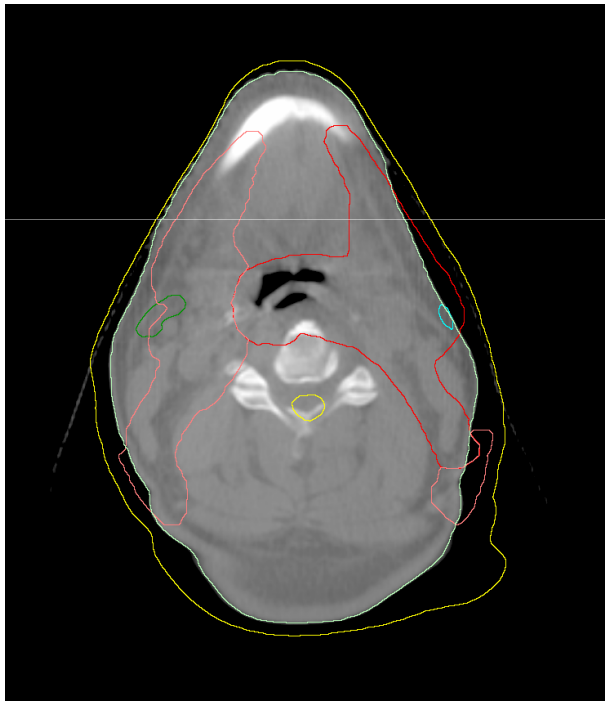
- Developed a process for CBCT based dosimetric review.
- Use CBCT to modify CT – override HU numbers in CT.
  - Head and Neck IMRT – assess impact of weight loss (or gain) though modifications to external contour.
  - Lung - override internal density changes if external shape and positioning is good.
  - Limited ability to quantify impact of positional changes or shifting internal anatomy.
- Primary aim – assess need for rescan, replan, or revised dose, if:
  - OAR tolerances likely to be exceeded.
  - PTV coverage not achieved.
  - Uncertainty is excessive.

UCLH strategy

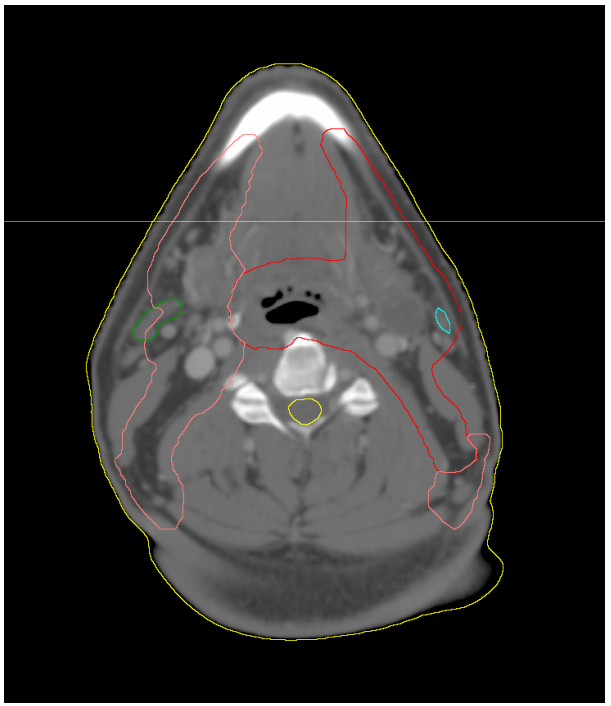
- Flow chart – defines timescales for review and action.
- Responsibilities and requirement for staff group input – radiographers, clinicians, dosimetrists/physicists.
- Multi-disciplinary approach.



Example – head & neck weight loss

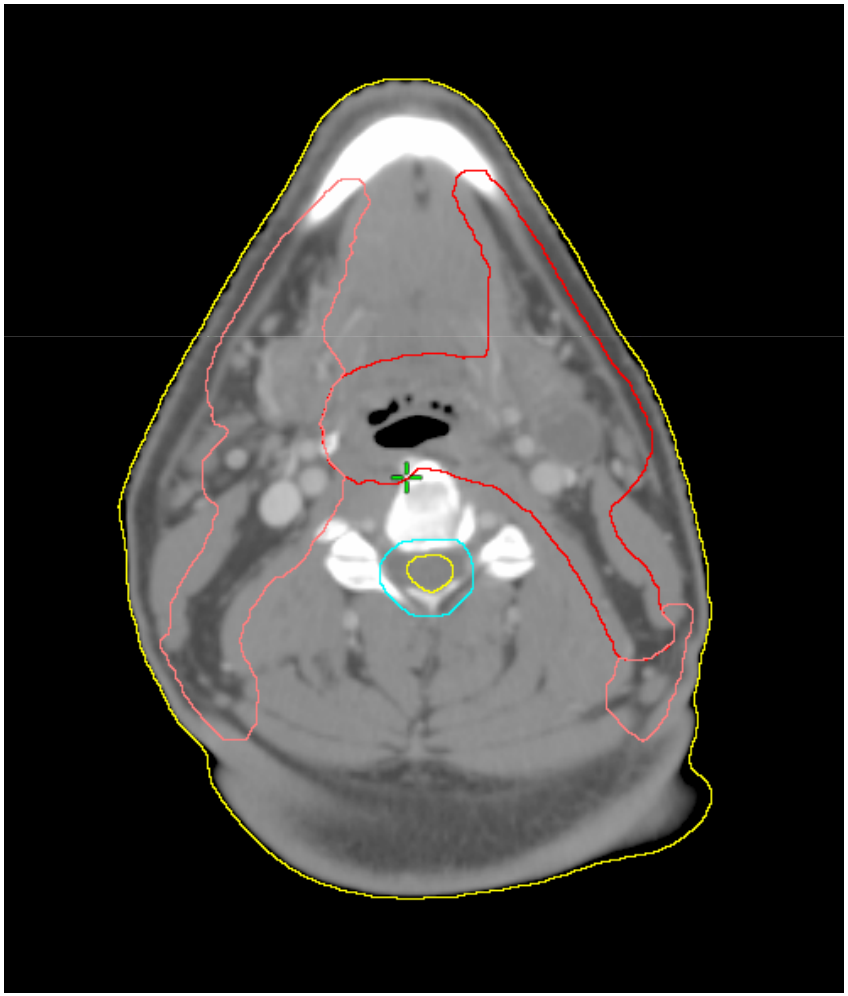


CBCT + original structures

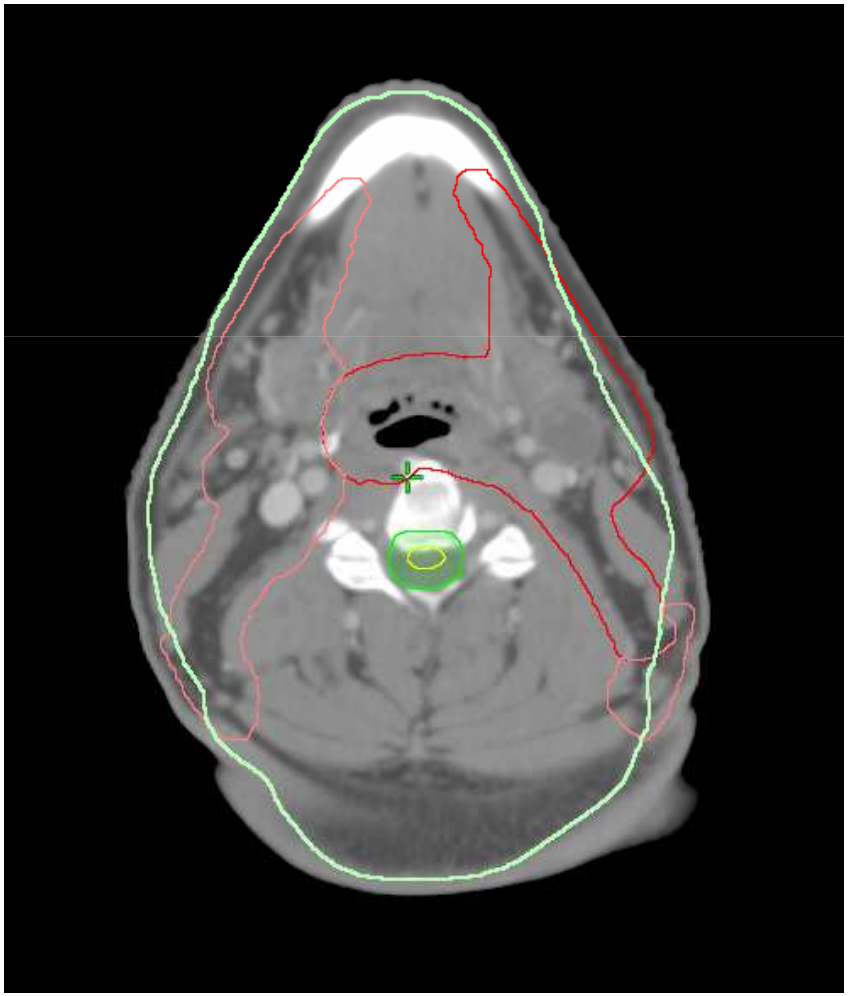


Original CT + structures

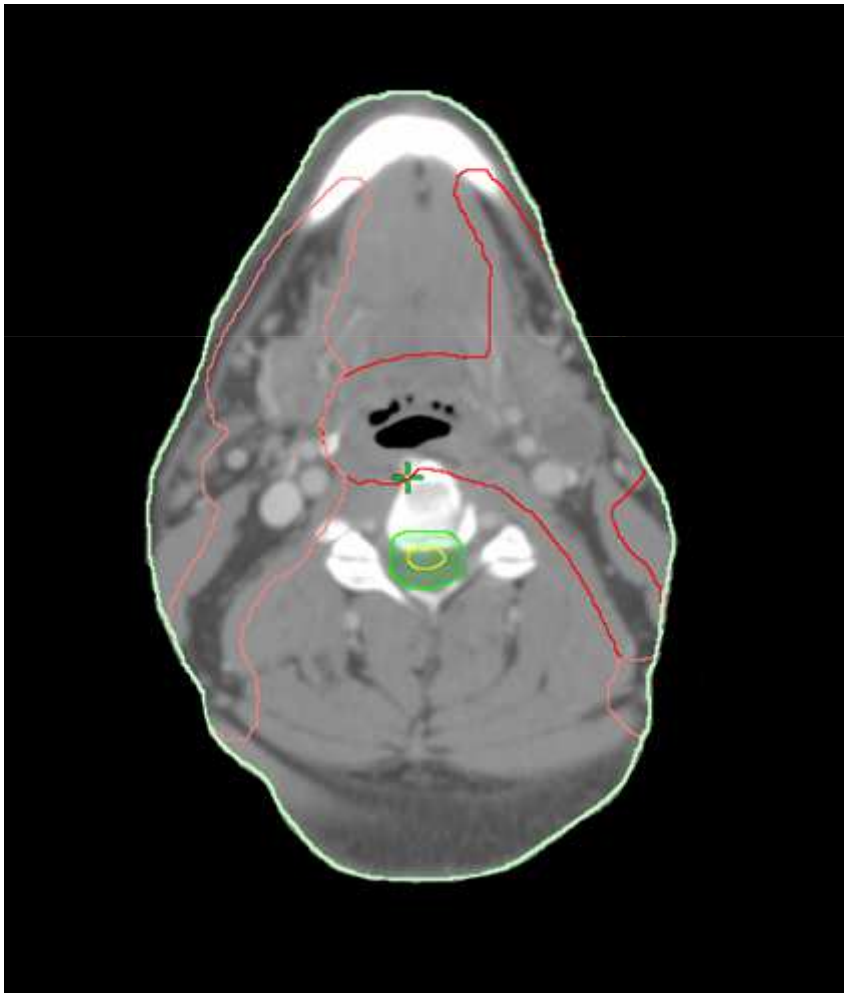
Example – head & neck weight loss



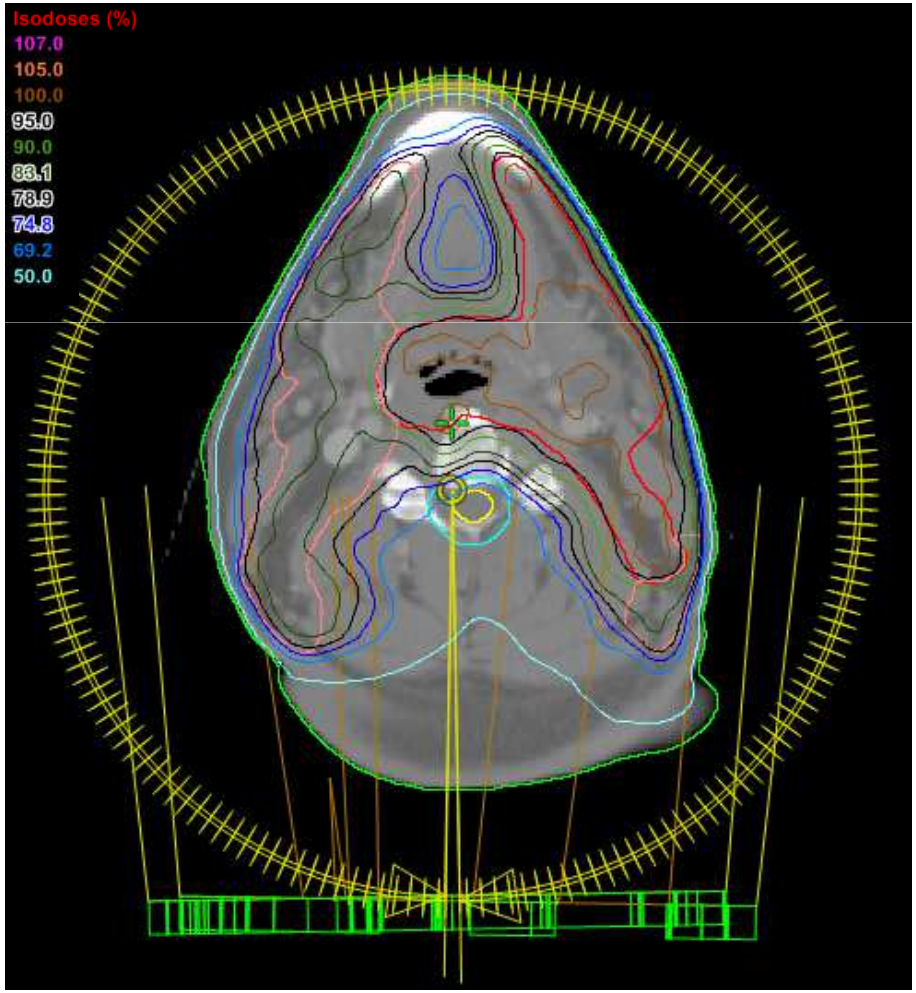
Example – head & neck weight loss



Example – head & neck weight loss



Example – head & neck weight loss



- Original plan on CT
- VMAT
- 2 full arcs
- 65Gy / 54Gy 30#

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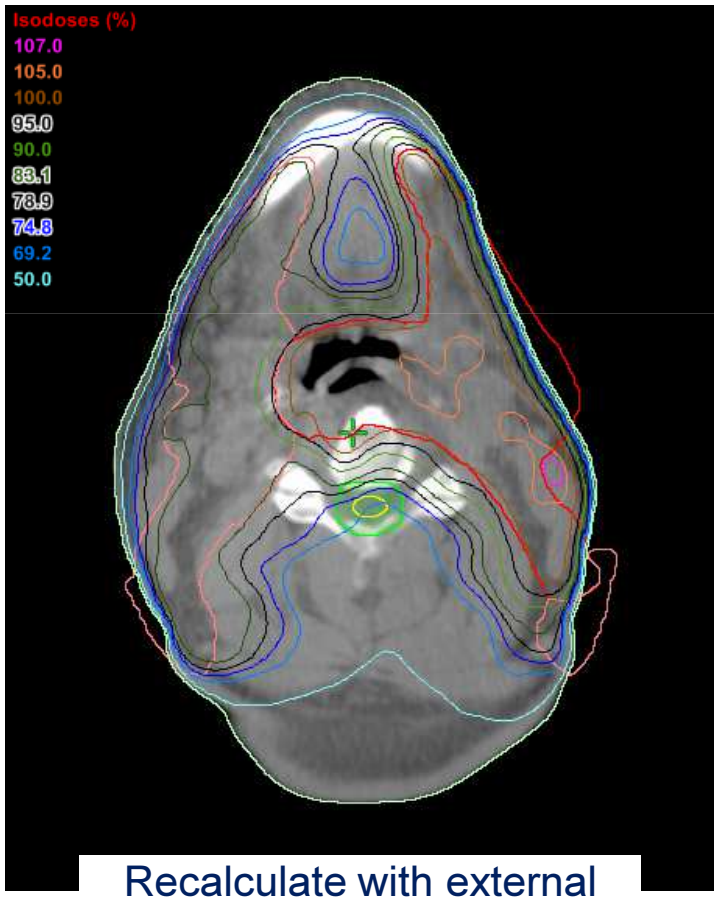
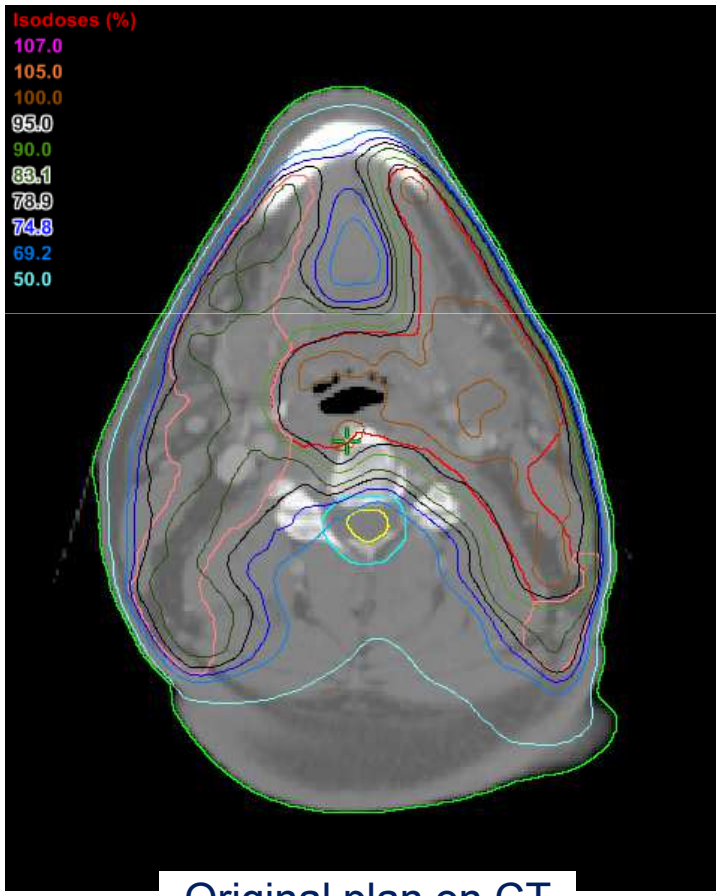
Example – head & neck weight loss



Recalculate with external contour modified to CBCT



Original plan on CT

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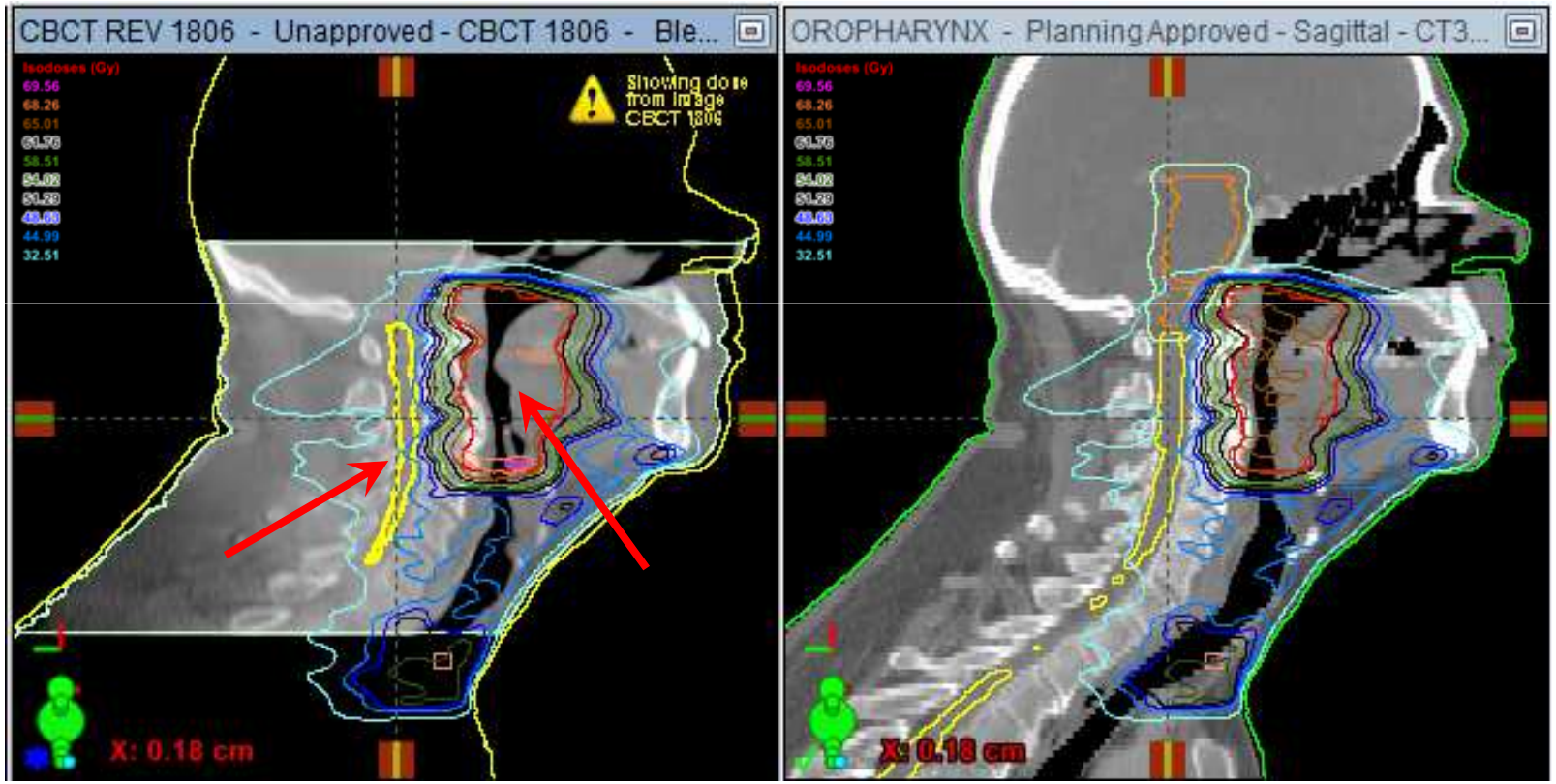
Example – head & neck weight loss

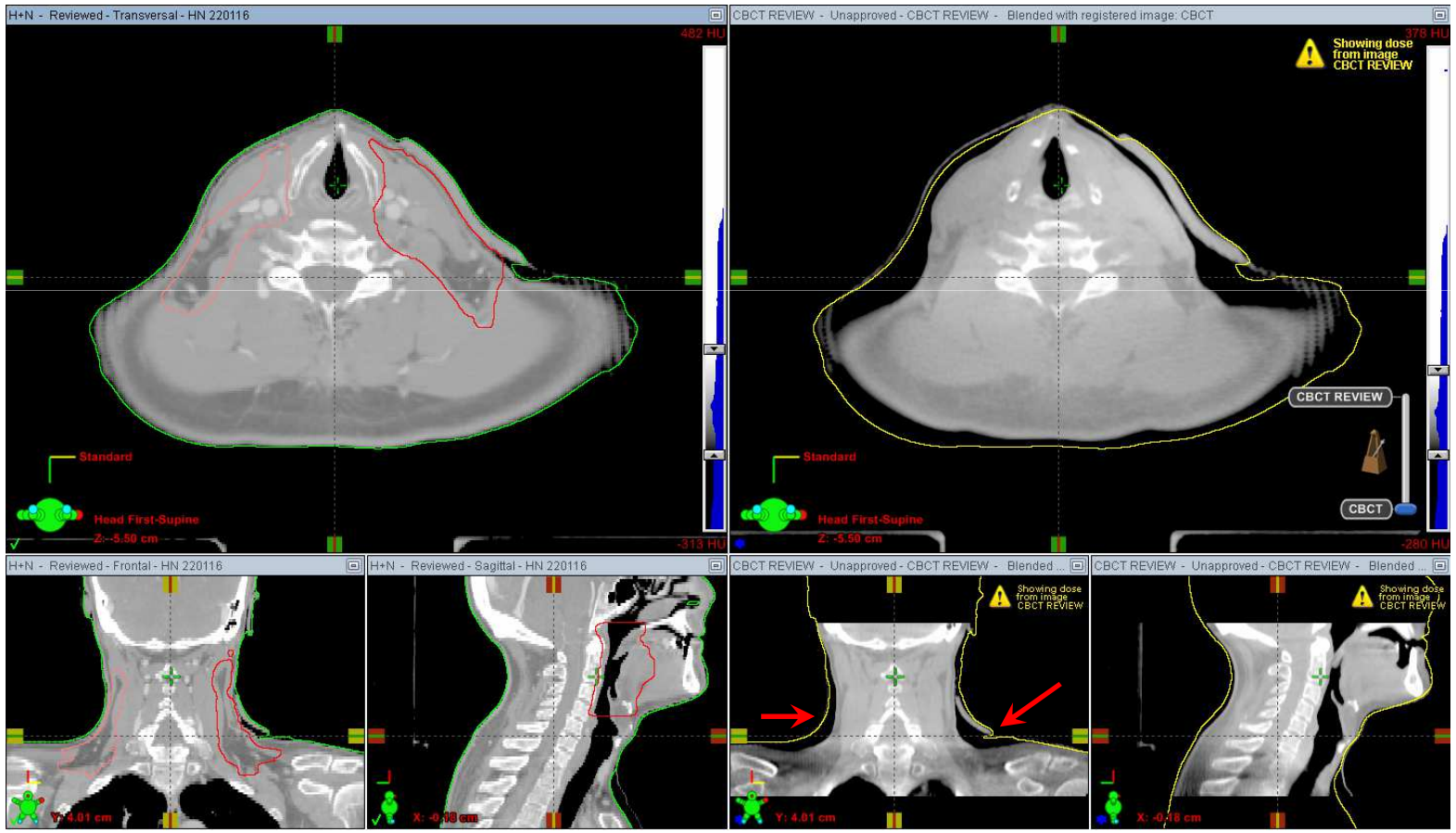


Recalculate with external contour modified to CBCT

Original plan on CT

ucln

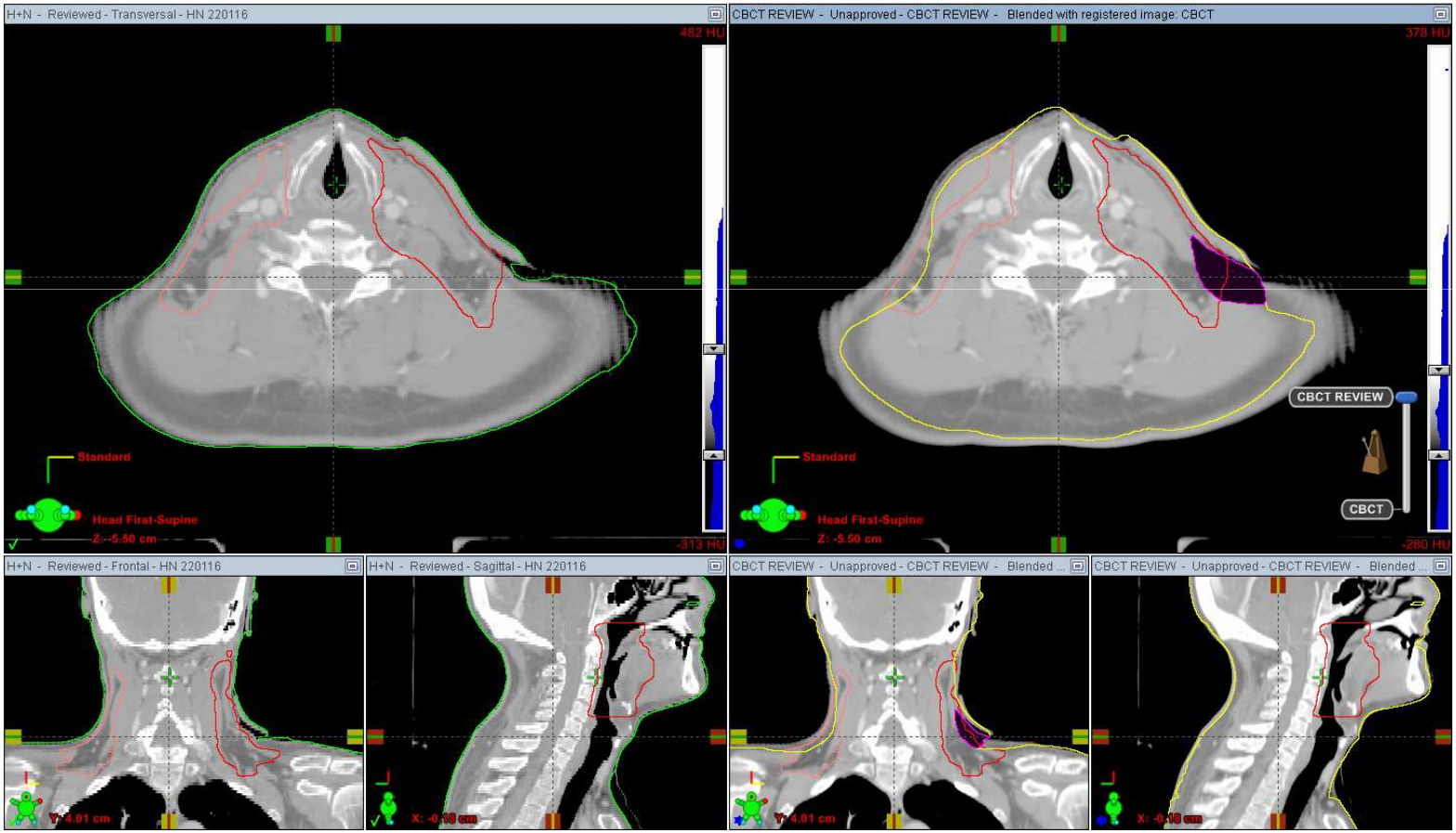
Head & neck example 2



Original CT + structures

CBCT + original external contour

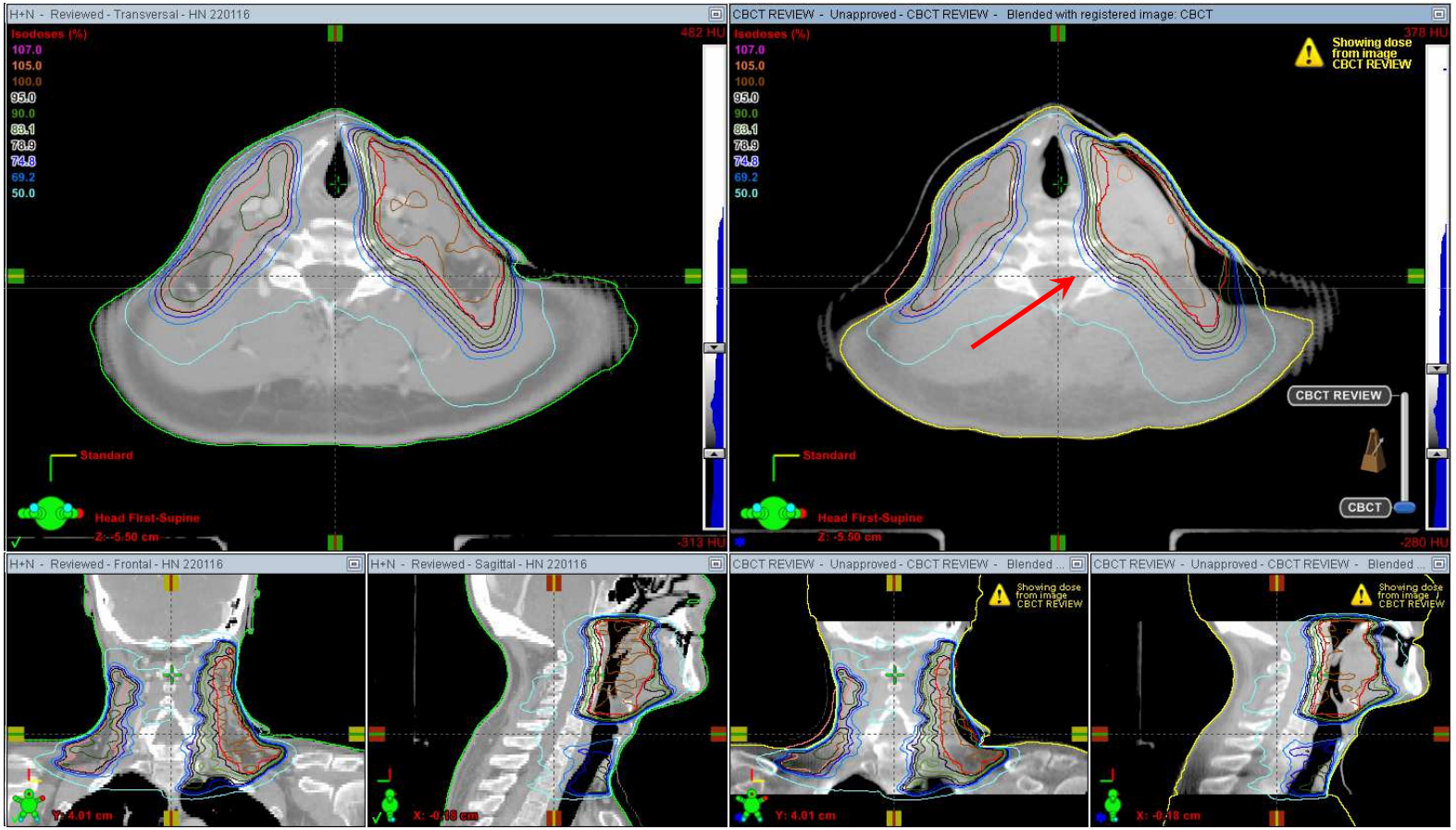
Head & neck example 2



Original CT + structures

Original CT + CBCT external contour

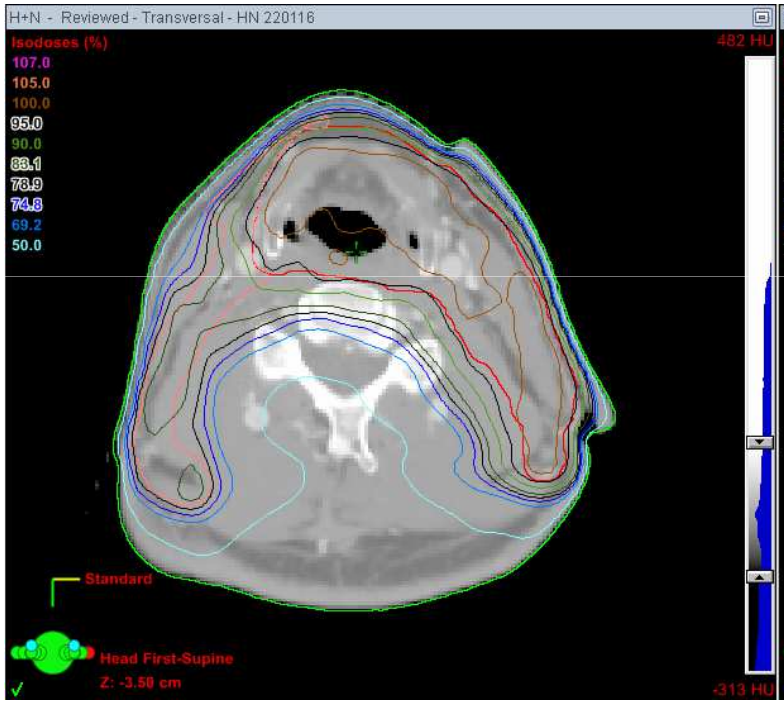
Head & neck example 2



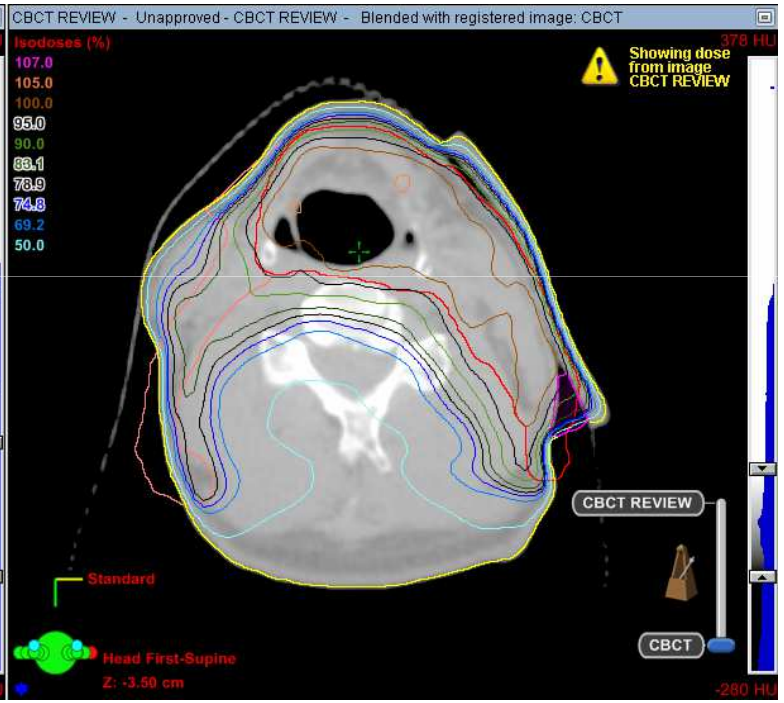
Original CT + plan

Dose recalculated on modified CT (overlaid on CBCT)

Head & neck example 2

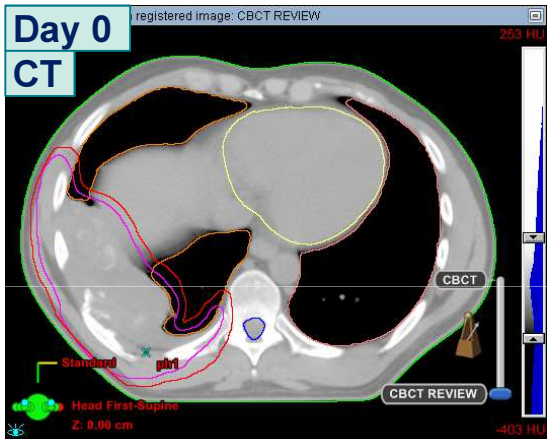


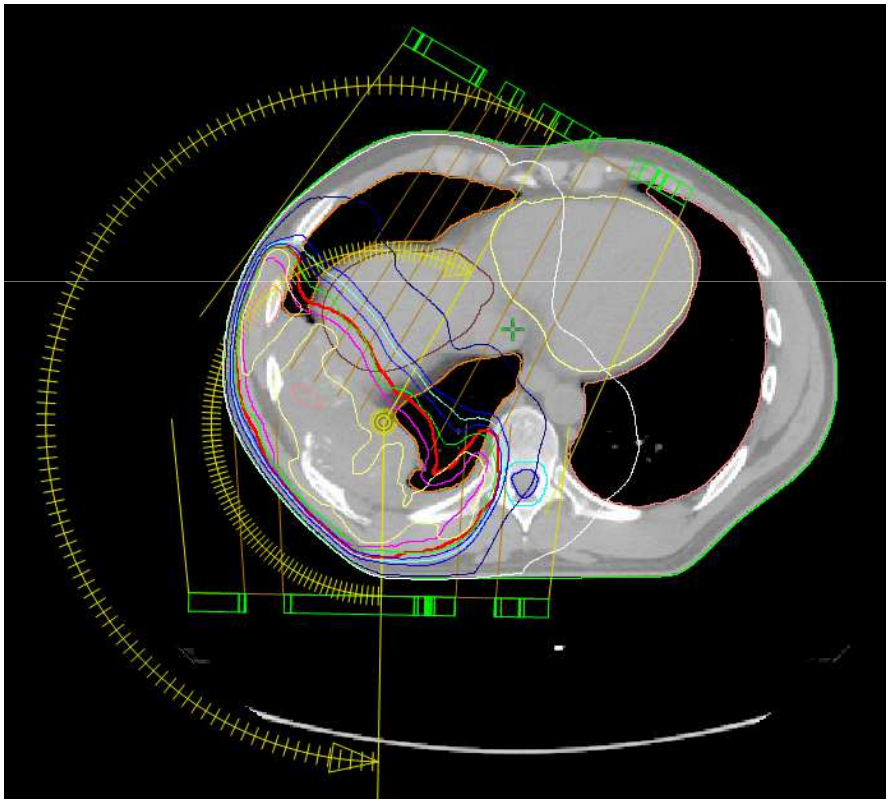
Original CT + plan



Dose recalculated on modified CT (overlaid on CBCT)

Example – lung density changes





- Ewings sarcoma
- VMAT
- 2 partial arcs
- 50.4Gy 28#

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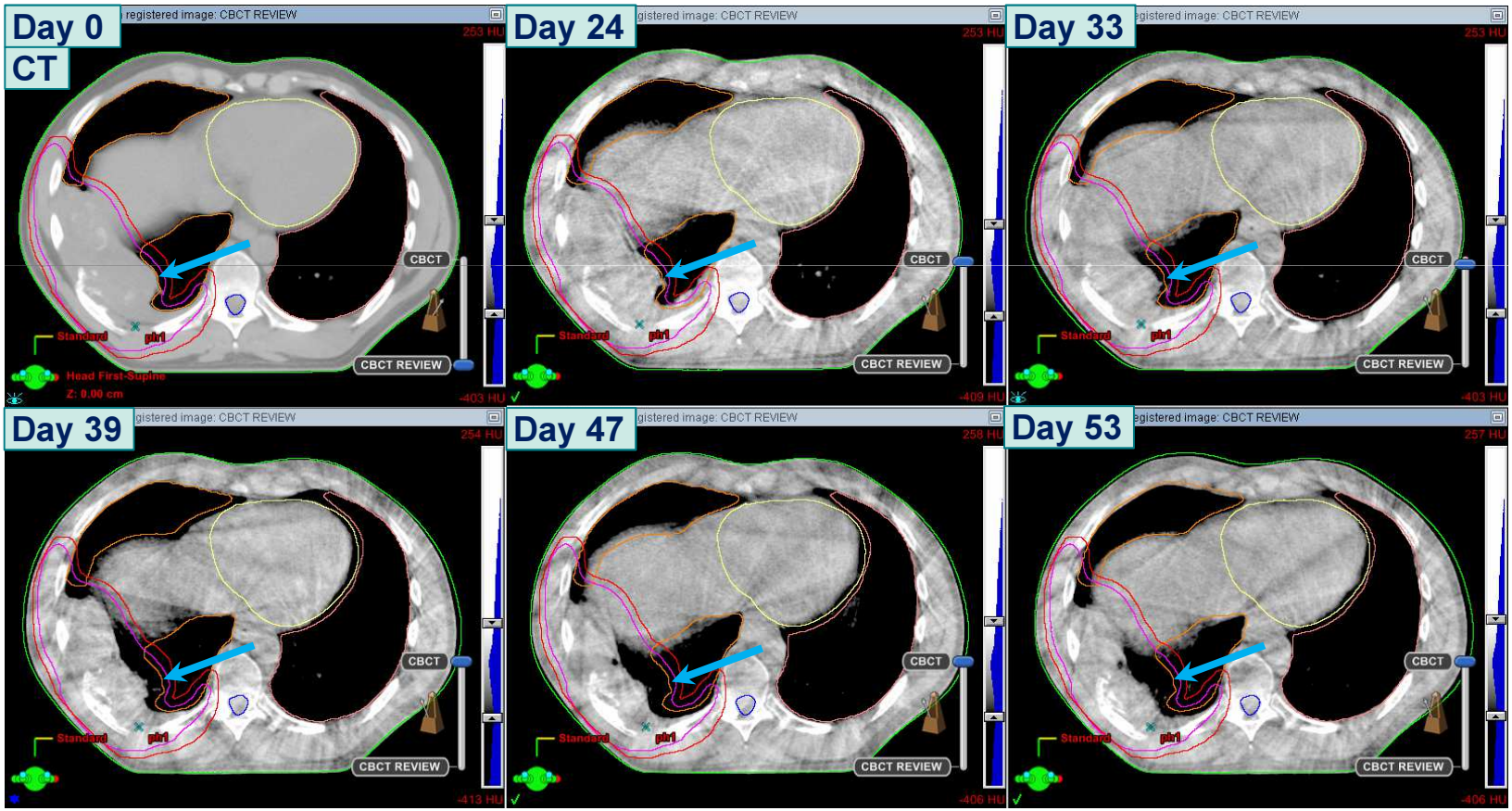
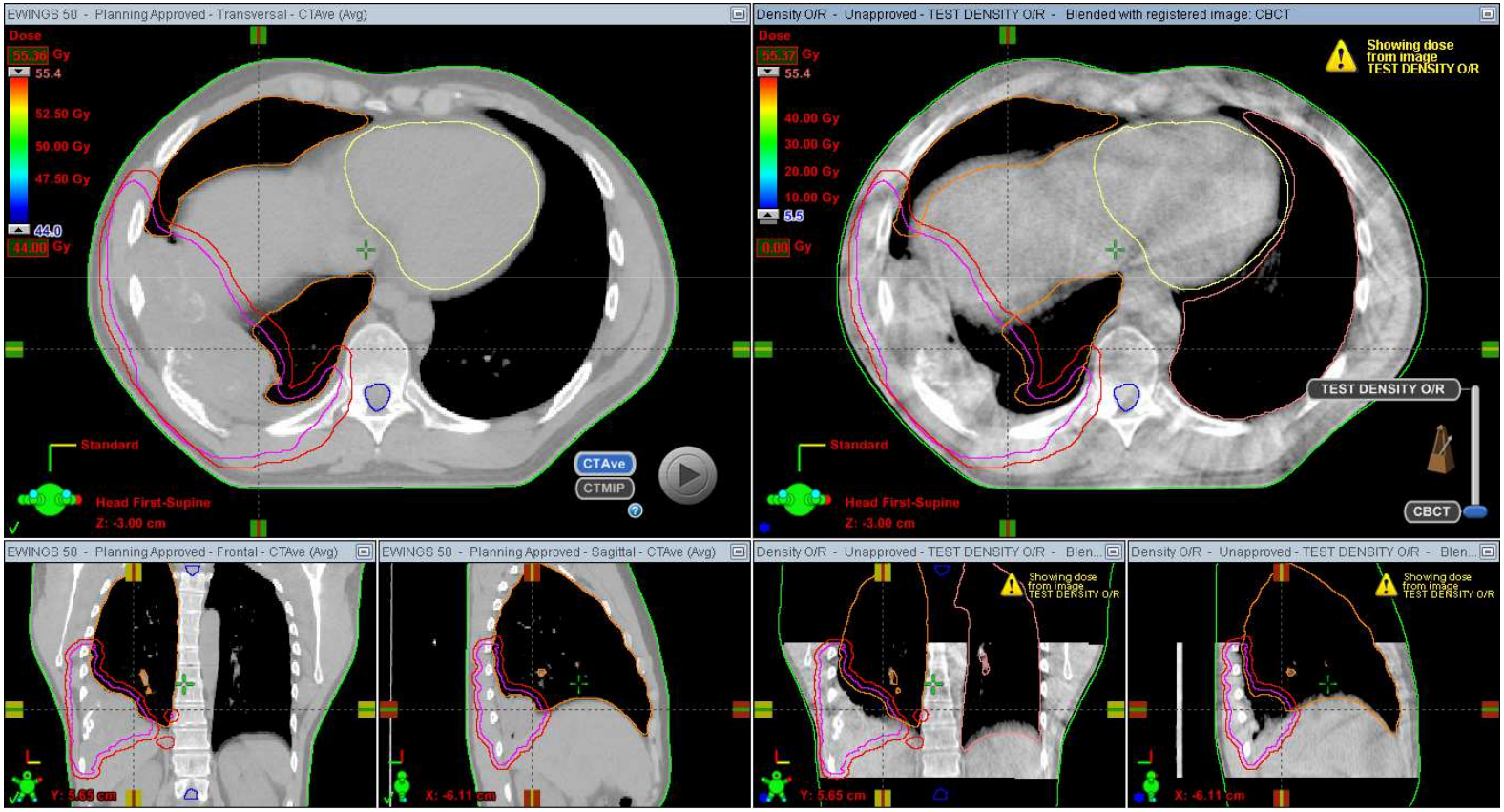
Example – lung density changes



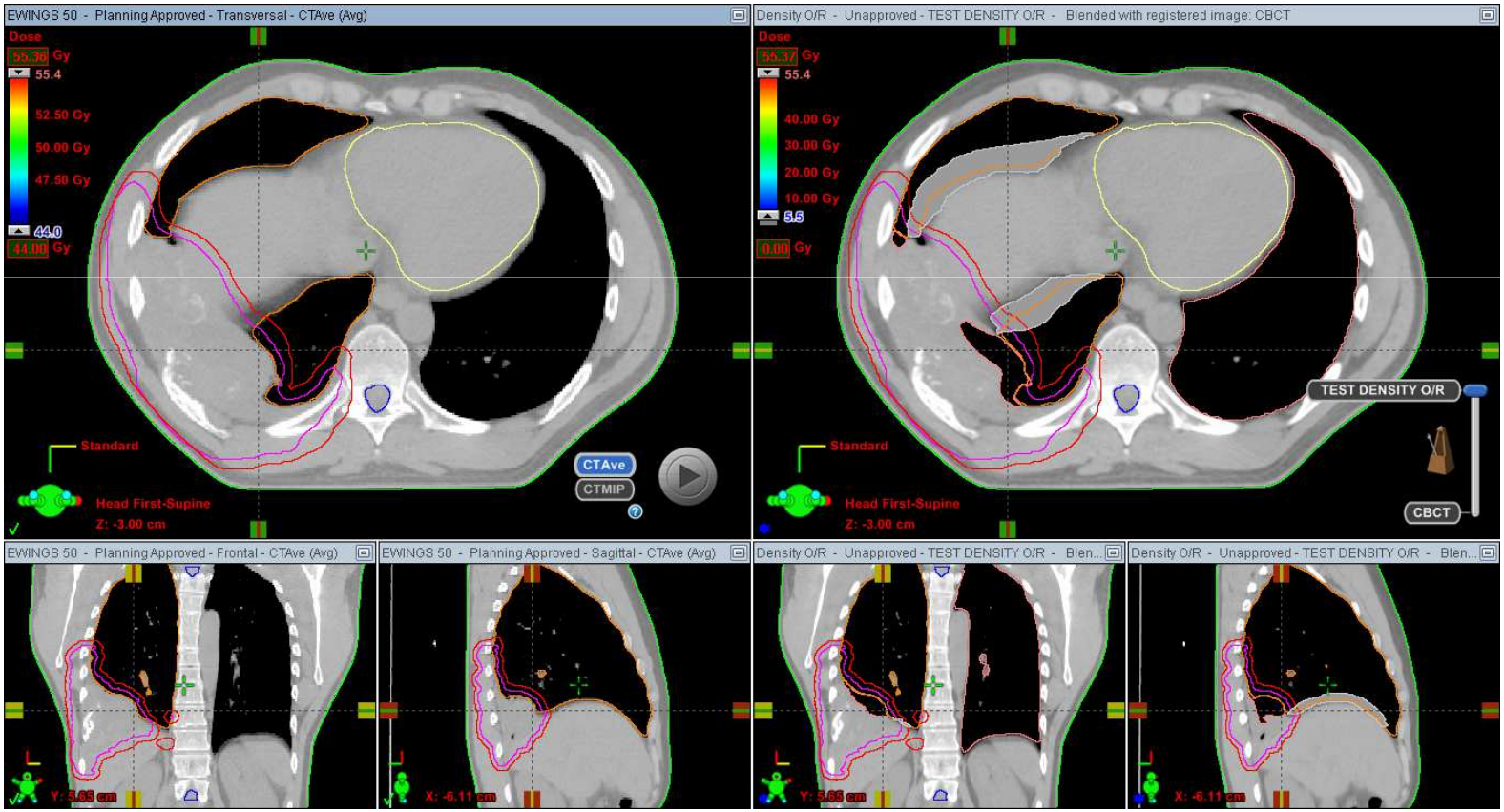
Example – lung density changes



CT day 0

CBCT day 47

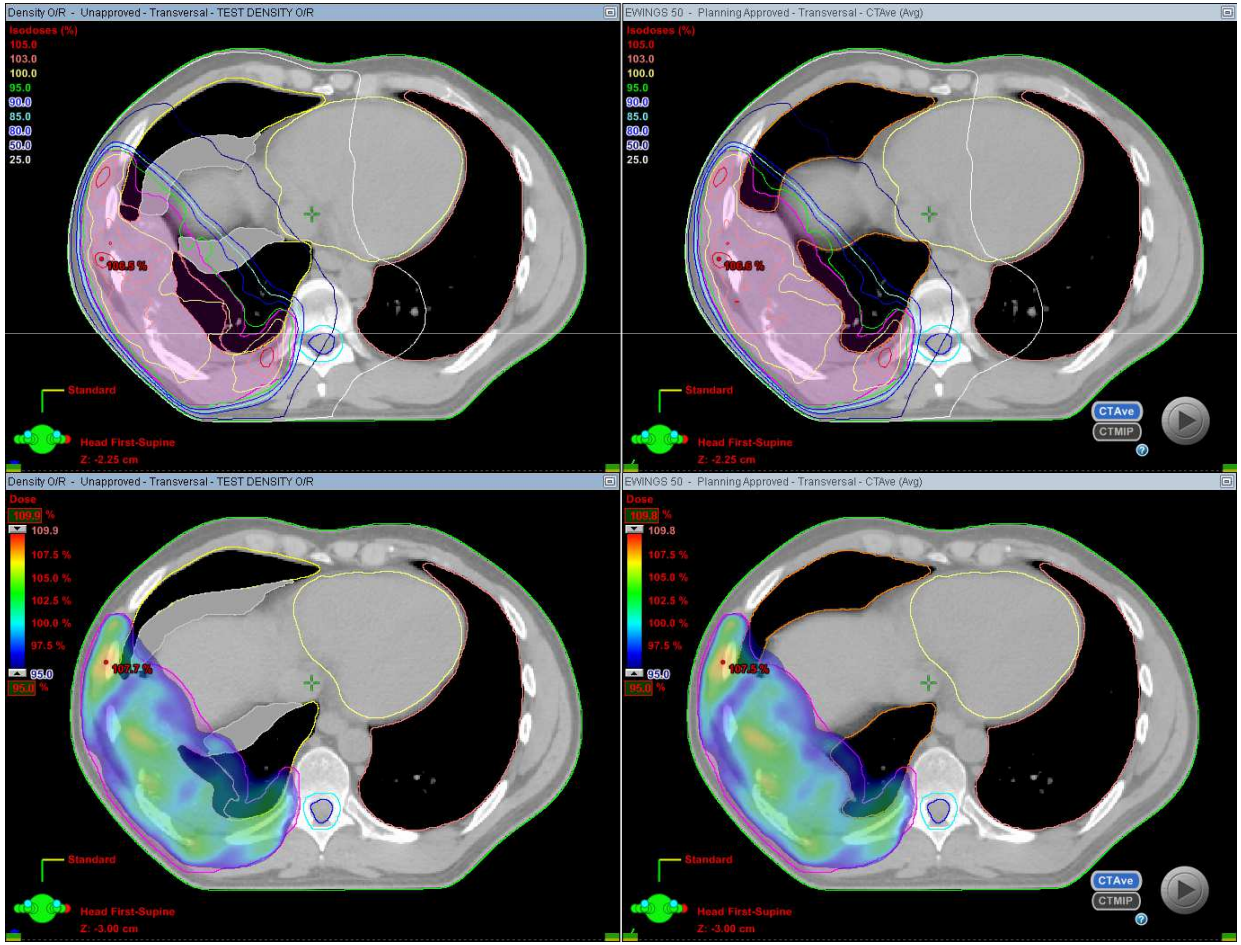
Modified CT – lung density changes



CT day 0

CT – density override to CBCT

Modified CT – lung density changes



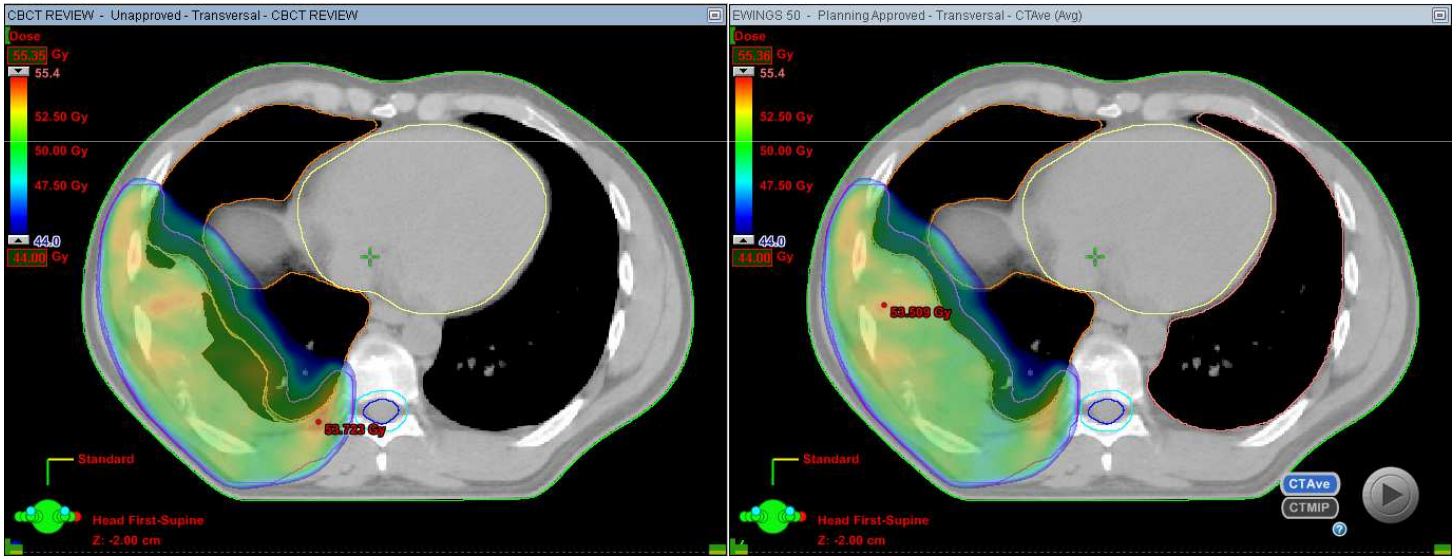
Recalculate with density override

Original plan

Colourwash:
95% dose

Modified CT – lung density changes

Colourwash: 44Gy



Recalculate with density override

Original plan

Adaptive RT - practical considerations

- Imaging dose - may limit imaging frequency.
- Limited quality/information of CBCT image.
- One image is only a snapshot – how representative is the assessment?
- Time is required to respond to changes:
  - Time for image review and assessment;
  - Availability of clinician;
  - Time for rescan, recontour, replan, review, plan QA.
- Take into account time through treatment course when assessing dosimetric impact.
- Dose accumulation?

Advances

- Improved imaging technology.
- Improved reconstruction algorithms.
  - Improved image quality, reduced imaging dose?
- Ability to stitch multiple images – increase imaged length.
- 4D-CBCT – reduce motion artefacts, capture respiratory motion.
- Deformable registration.
- Automatic contouring.

Conclusions

- UCLH – process established for on-treatment image review and simple dosimetric assessment of anatomical changes.
- Scope for adaptation governed by quality/quantity of imaging information and planning pathway constraints.
- Ongoing areas of research and development may lead to improved image information, streamlined processes - increased ability to adapt.

University College London Hospitals NHS
NHS Foundation Trust

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Intensity Modulated Radiotherapy for Paediatrics

Dr Jenny Gains

ESTRO teaching course on IMRT, London

3rd April 2016

Background

- Cancer in children is rare

- Between 1,500 and 1,700 children under the age of 16 years develop cancer or leukaemia in the UK *(Cancer Research UK Cancerstats: Childhood Cancer – Great Britain and UK)*

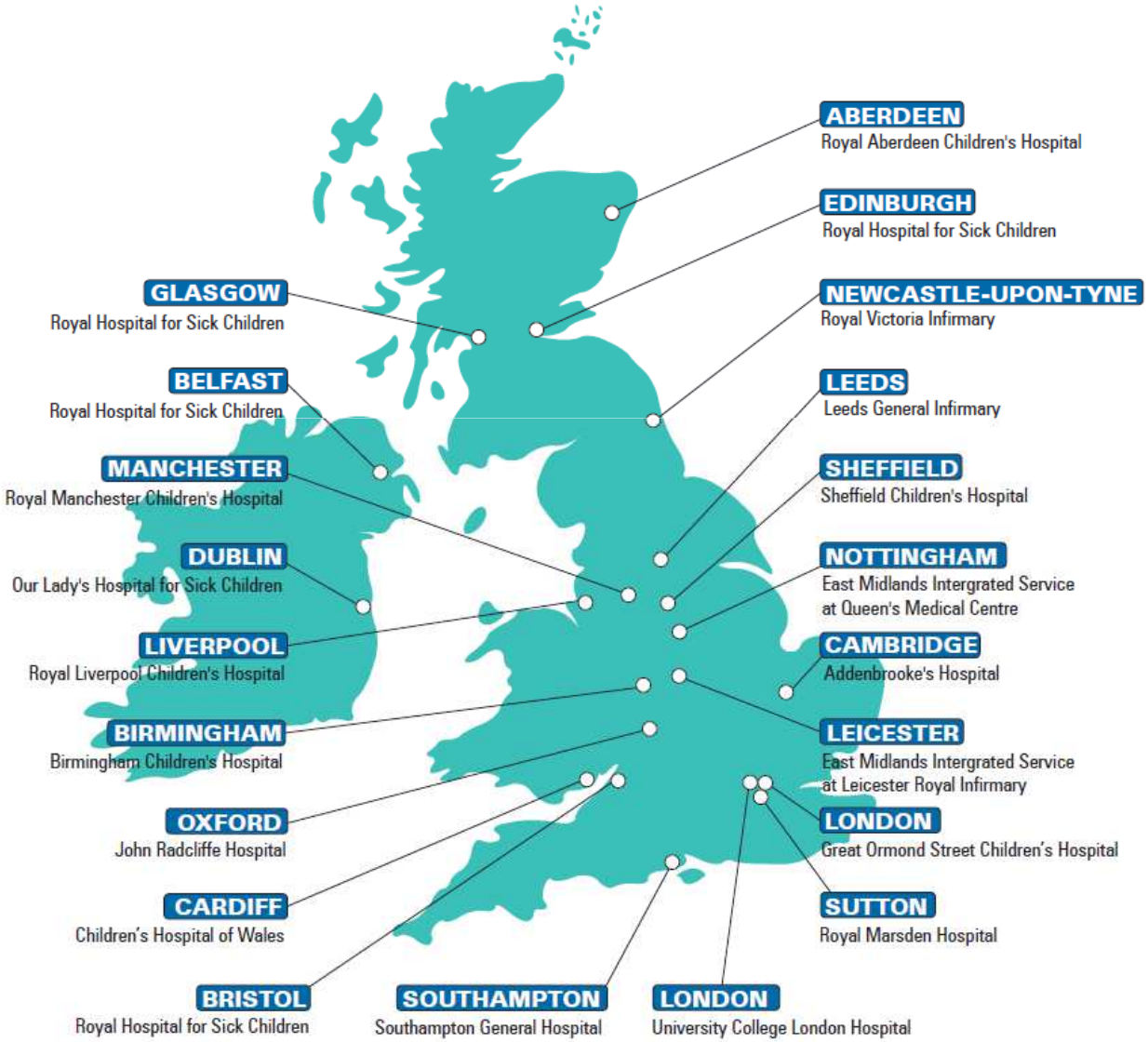
- Wide range of tumour types and anatomical sites

- Patient care is complex

Background

- Radiotherapy is a component of treatment for many children and teenagers
- Radiotherapy should only be given in specialist centres
- Specialist multidisciplinary team
- Management of acute and late effects

CHILDREN'S CANCER CENTRES



Paediatric Radiotherapy at 18 Centres: UK and Ireland

UCLH serves GOS and UCLH and more specialist services for the whole UK

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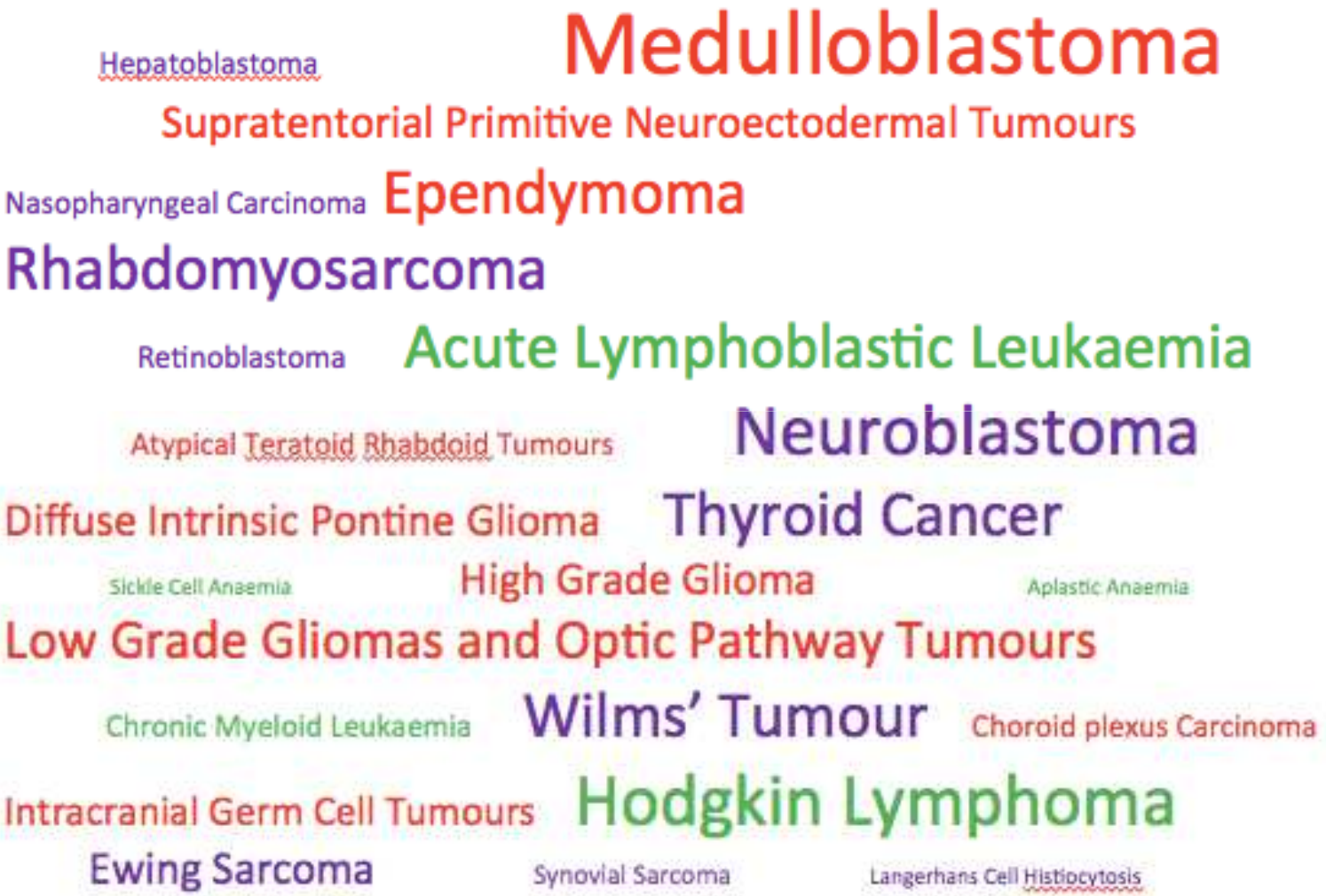
Medulloblastoma
Hepatoblastoma
Supratentorial Primitive Neuroectodermal Tumours
Nasopharyngeal Carcinoma
Ependymoma
Rhabdomyosarcoma
Retinoblastoma
Acute Lymphoblastic Leukaemia
Neuroblastoma
Atypical Teratoid Rhabdoid Tumours
Diffuse Intrinsic Pontine Glioma
Thyroid Cancer
Sickle Cell Anaemia
High Grade Glioma
Aplastic Anaemia
Low Grade Gliomas and Optic Pathway Tumours
Chronic Myeloid Leukaemia
Wilms' Tumour
Choroid plexus Carcinoma
Intracranial Germ Cell Tumours
Hodgkin Lymphoma
Ewing Sarcoma
Synovial Sarcoma
Langerhans Cell Histiocytosis

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Paediatric Radiotherapy

Improving Efficacy

Reducing Late Effects

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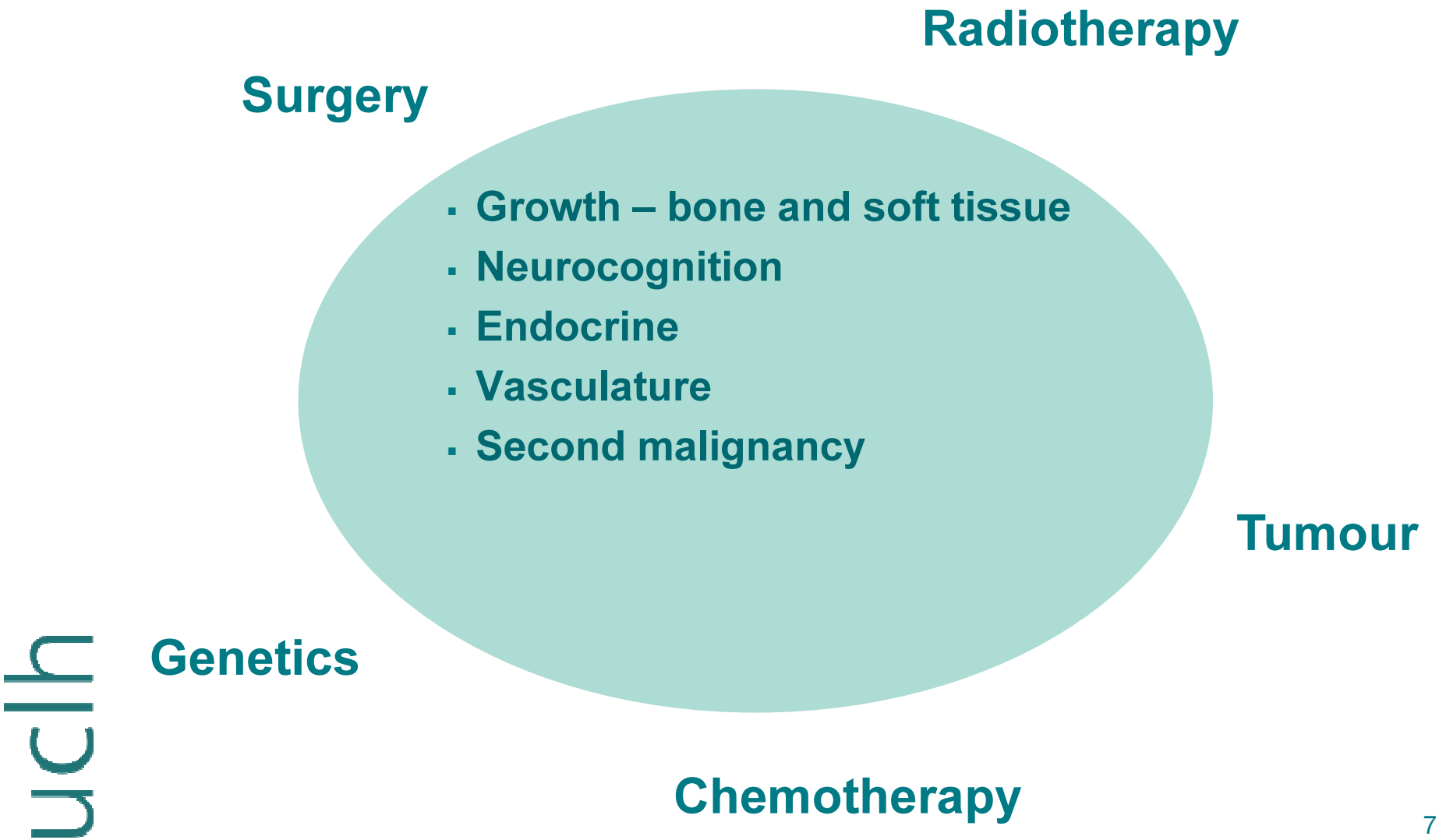
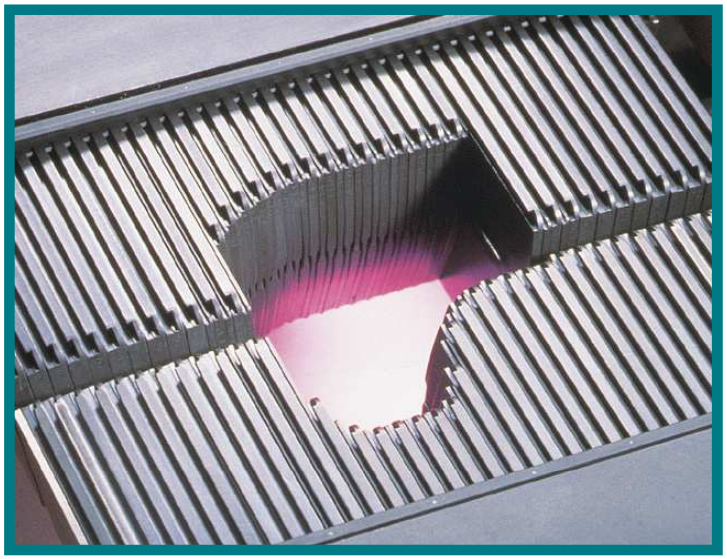
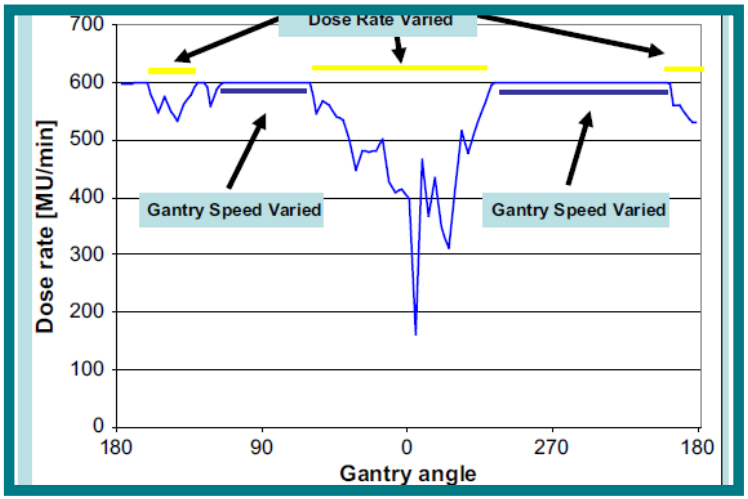
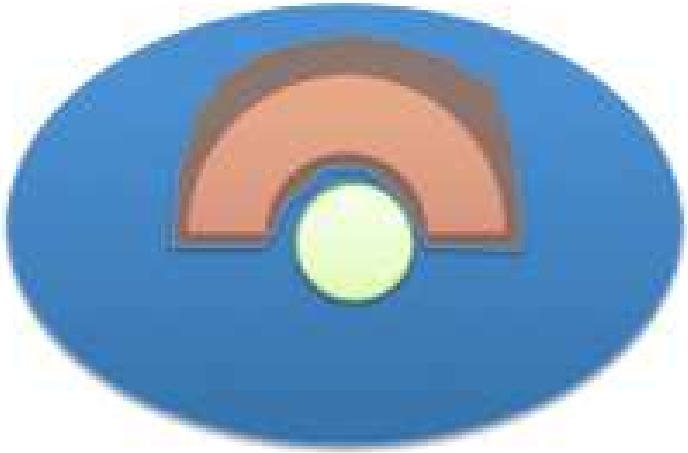

Radiotherapy
Surgery
Growth – bone and soft tissue
Neurocognition
Endocrine
Vasculature
Second malignancy
Tumour
Genetics
Chemotherapy

IMRT




Dose Rate Varied
Gantry Speed Varied
Gantry Speed Varied
Dose rate [MU/min]
700
600
500
400
300
200
100
0
180
90
0
270
180
Gantry angle



IMRT

- Treatment planning studies 3D conformal radiotherapy v's IMRT clearly demonstrate the improved conformality of high dose area with IMRT
- Better PTV homogeneity
- Potential dose escalation and reduction in toxicity
- Widely adopted in the adult setting
- More reservation in paediatric population
- Lack of prospective evaluation in terms of clinical studies , determining better outcomes and long term toxicity

Paediatric IMRT

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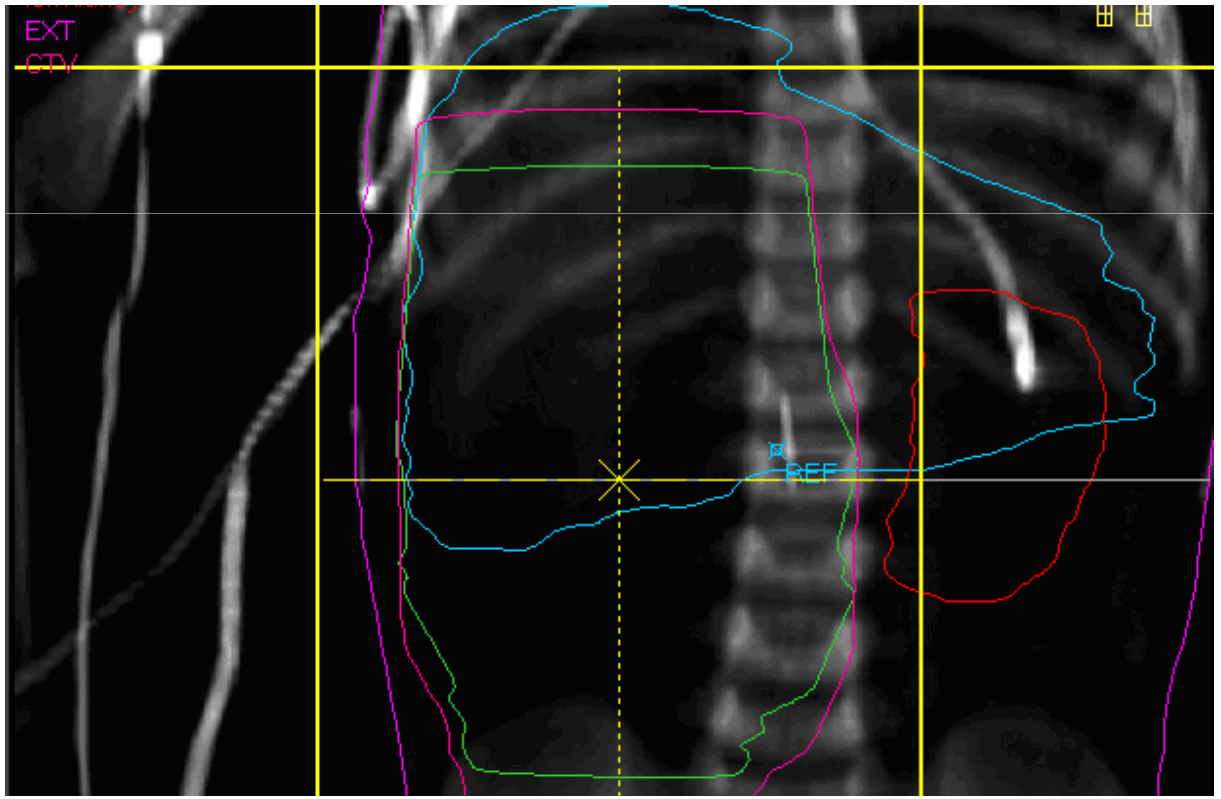
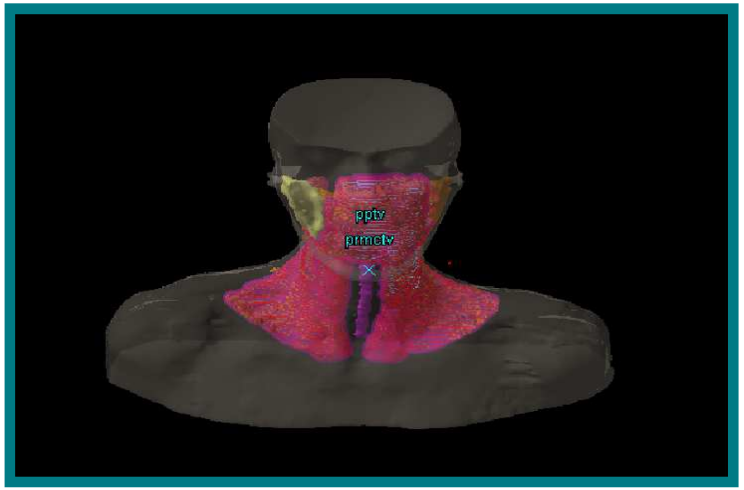
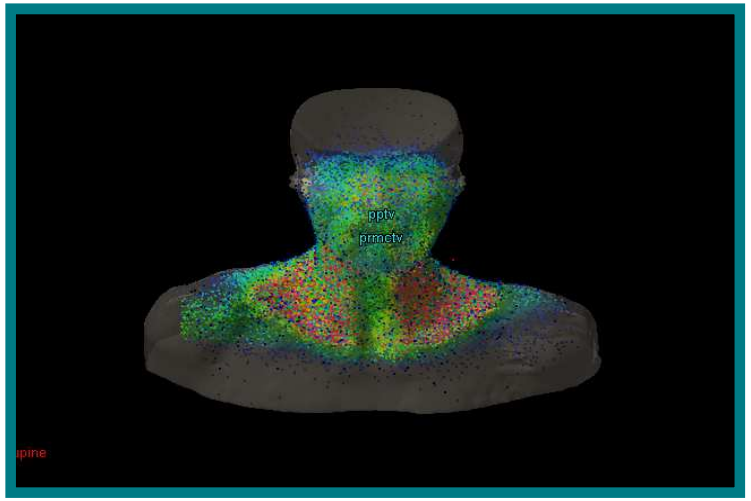
- Improved Target Volume Coverage
- OAR sparing
- Second malignancy
- Effects on growth

Effects on growth



Second Malignancies



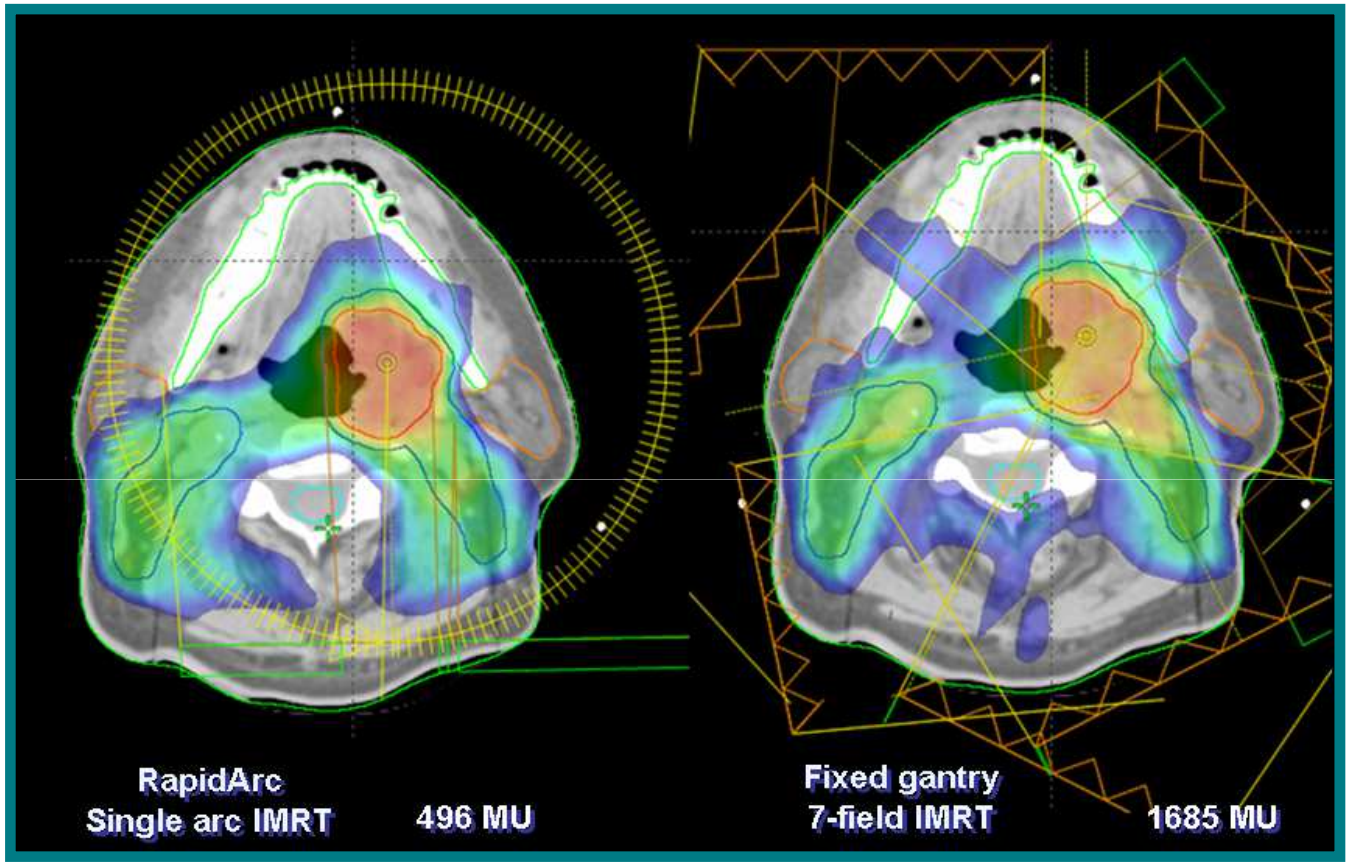


- *Hall et al.* (*IJROBP 2003*) IMRT may increase second malignancy rate from 1% to 1.75%
- Higher MU's, increased leakage resulting in increase body dose, larger volume of normal tissue receiving a lower dose
- But, most second malignancies seen in the moderate or high dose volume

Paediatrics

- More sensitive to RT induced cancers
- Scattered radiation in small body
- Genetic susceptibility

IMRT technique



- Shorter Treatment Times
- Less MU
- ? Less second malignancy
- ? Better conformality

Preparation

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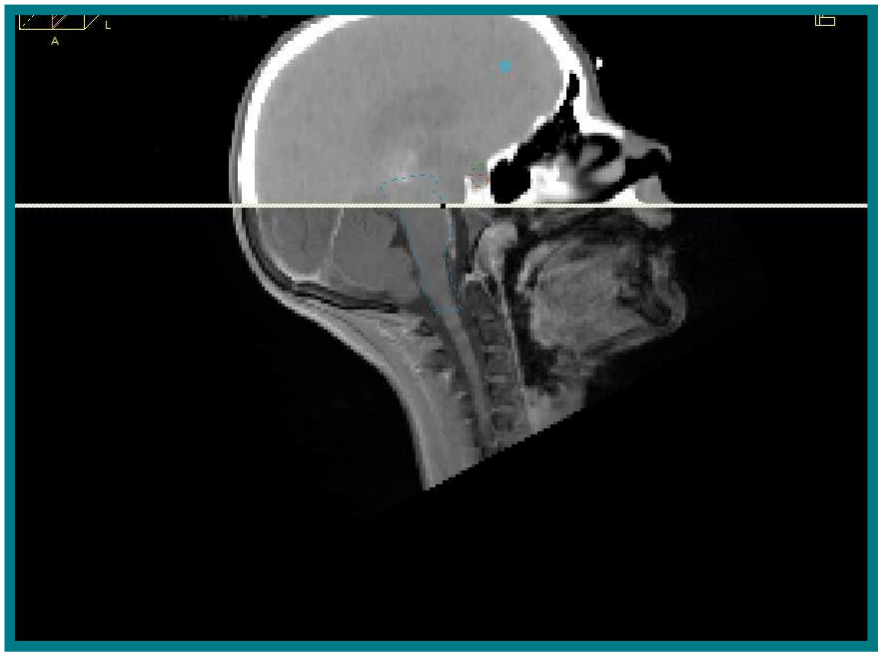
Image Fusion



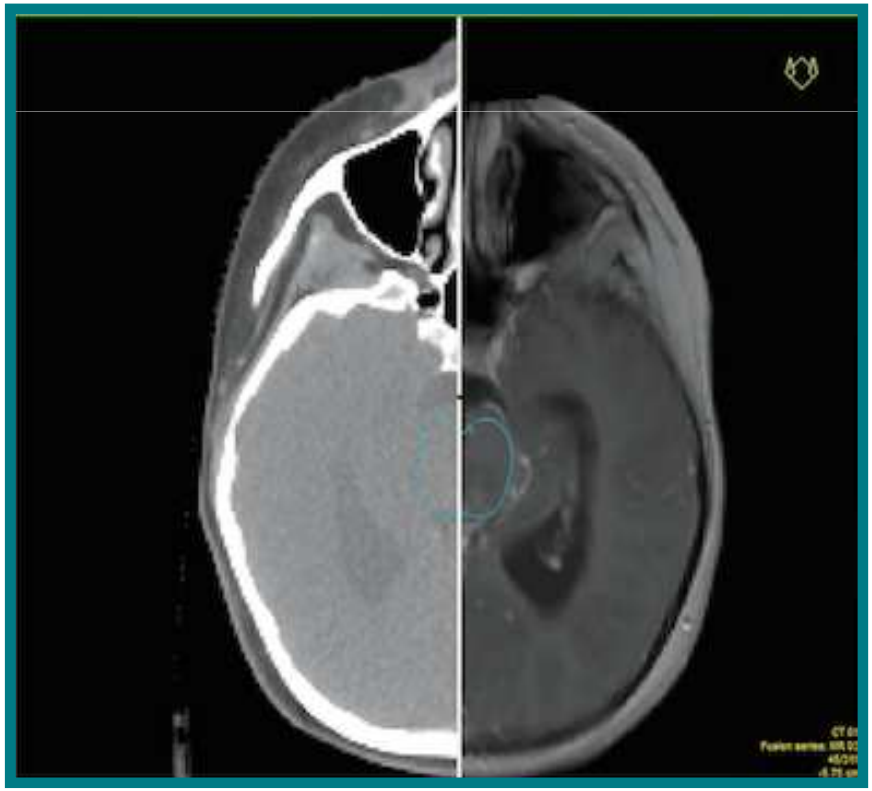


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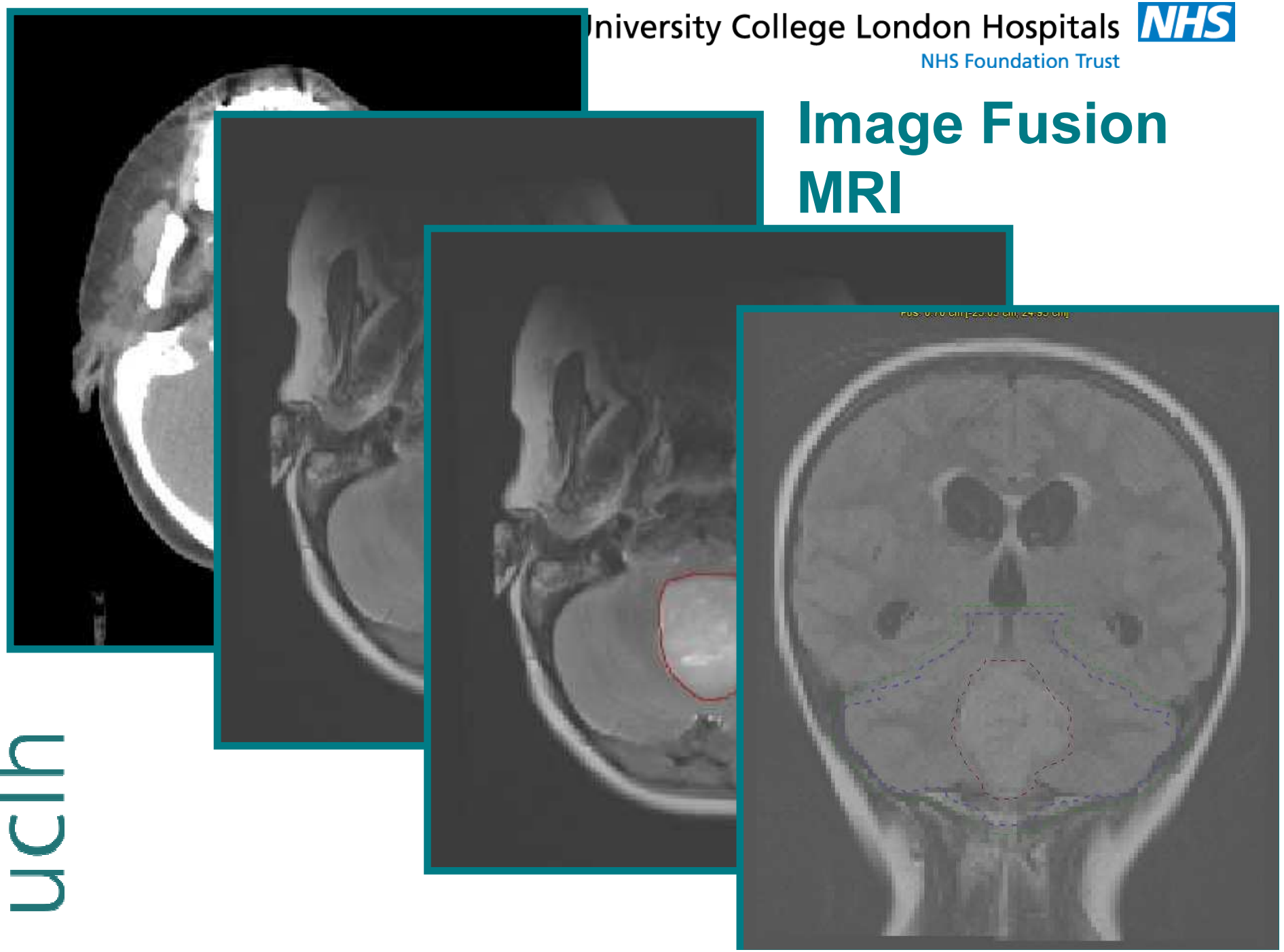
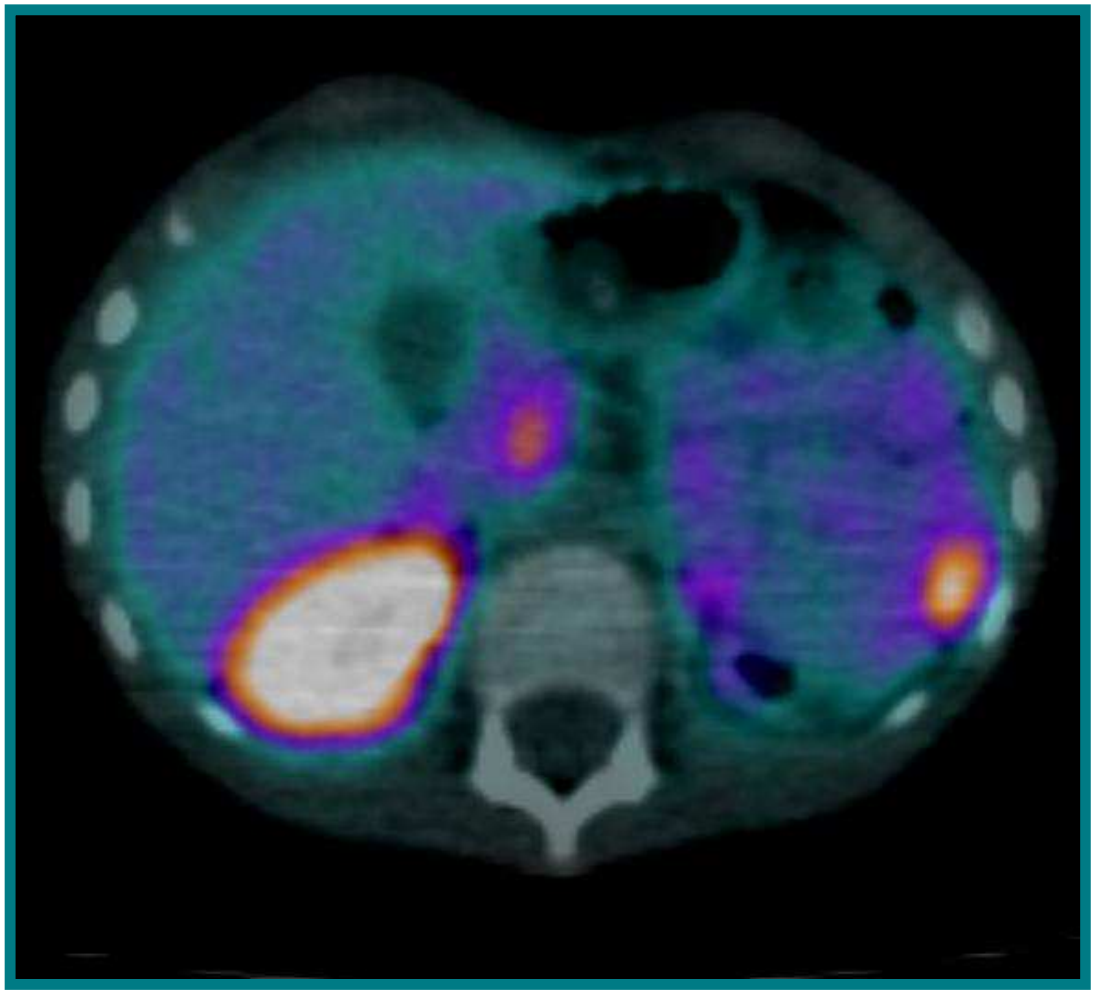
Image Fusion MRI

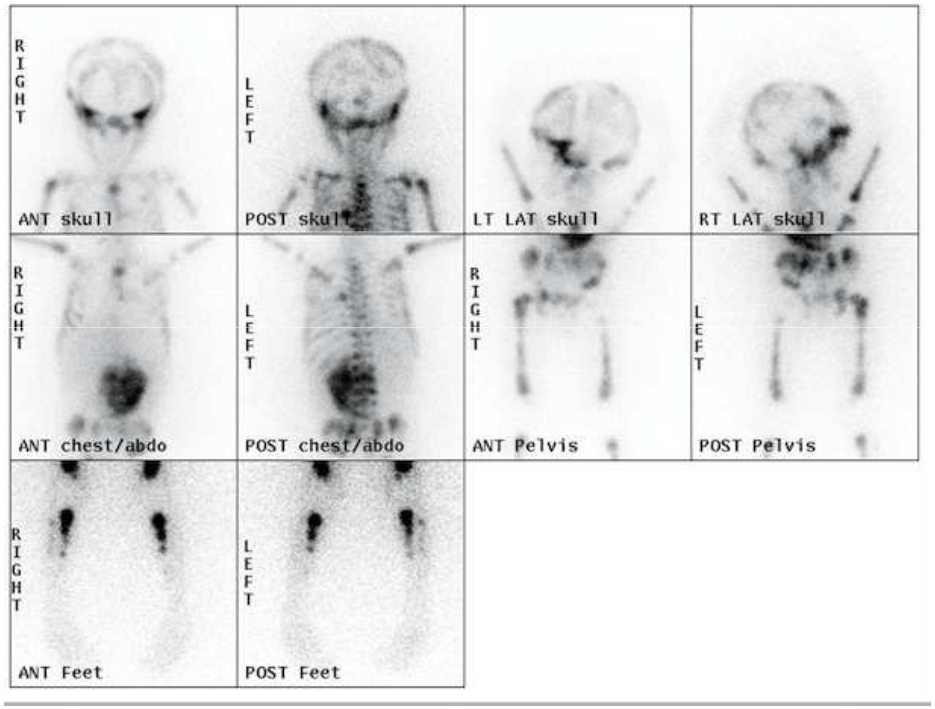


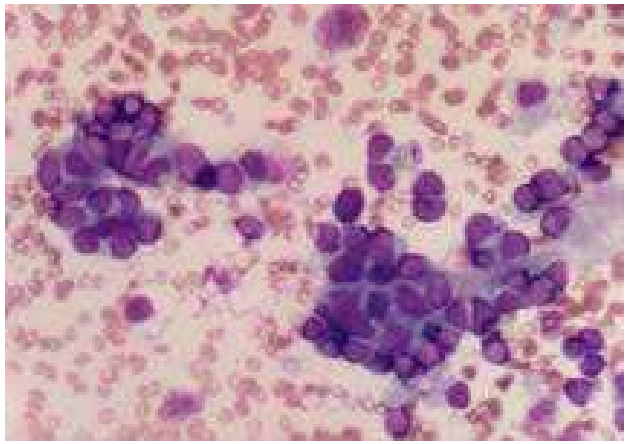
uclh

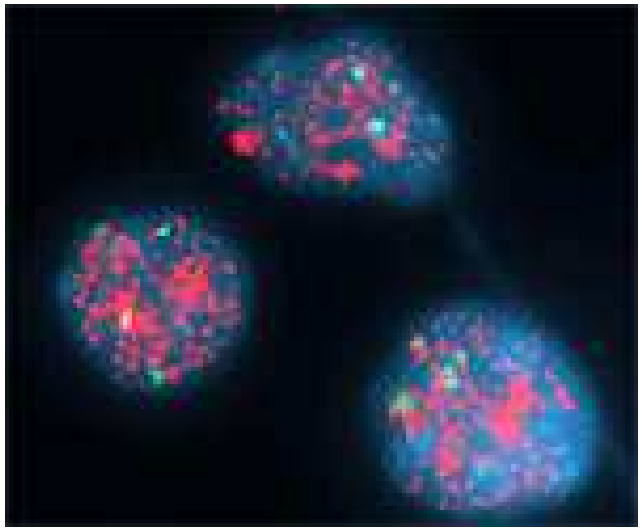
Image Fusion
PET/CT



Neuroblastoma







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Neuroblastoma

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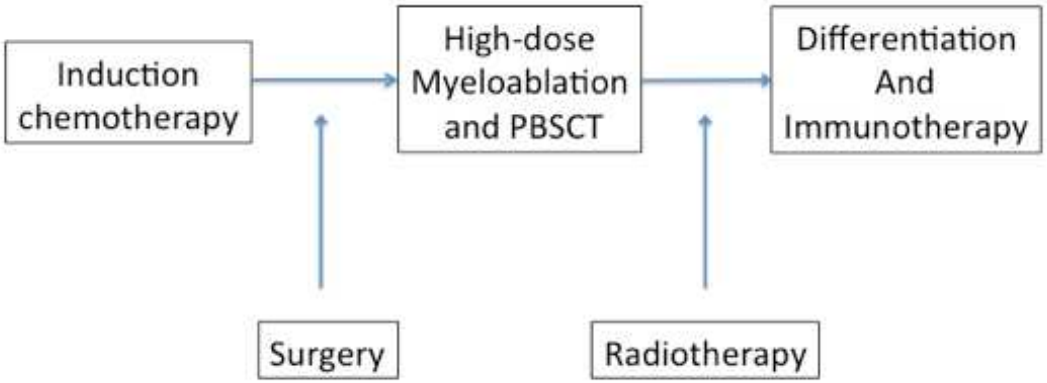
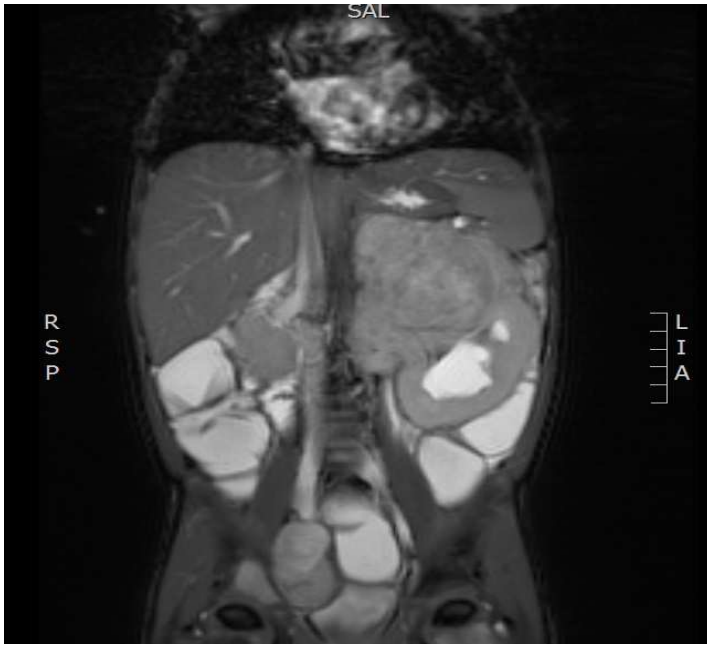
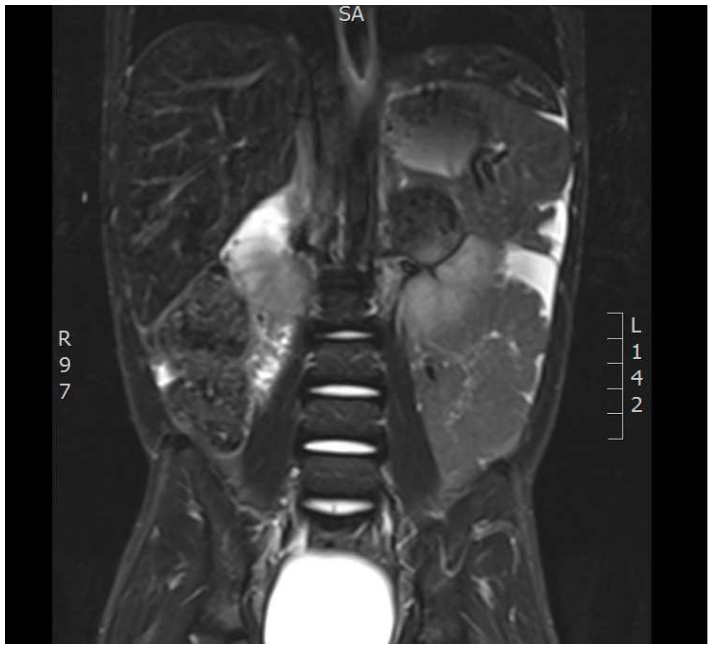
NHS Foundation Trust

SIOPEN R-NET







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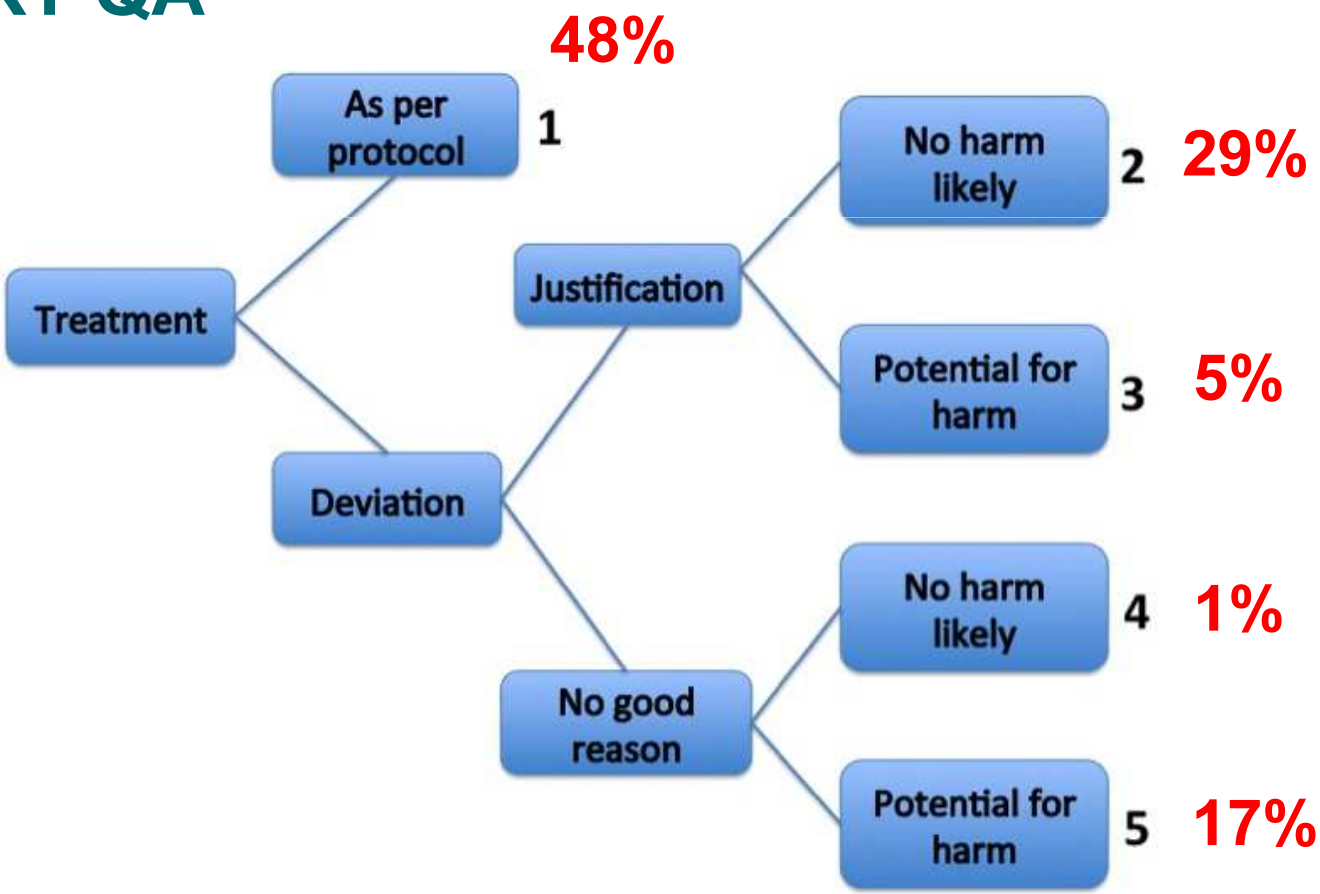
Int J Radiat Oncol Biol Phys. 2013 Jan 1;85(1):170-4. doi: 10.1016/j.ijrobp.2012.05.004. Epub 2012 Jun 30.

Results of a quality assurance review of external beam radiation therapy in the International Society of Paediatric Oncology (Europe) Neuroblastoma Group's High-risk Neuroblastoma Trial: a SIOPEN study.

Gaze MN[1], Boterberg T, Dieckmann K, Hörmann M, Gains JE, Sullivan KP, Ladenstein R.

SIOPEN RT QA



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Future Oncol. 2013 Mar;9(3):439-49. doi: 10.2217/fon.12.199.

Intensity-modulated arc therapy to improve radiation dose delivery in the treatment of abdominal neuroblastoma.

Gains JE[1], Stacey C, Rosenberg I, Mandeville HC, Chang YC, D'Souza D, Moroz V, Wheatley K, Gaze MN.

Retrospective Planning Study

- To assess whether RapidArc™ (Varian Medical Systems), an IMAT technique could improve the number of patients where the full protocol dose could be delivered compared to conventional radiotherapy.

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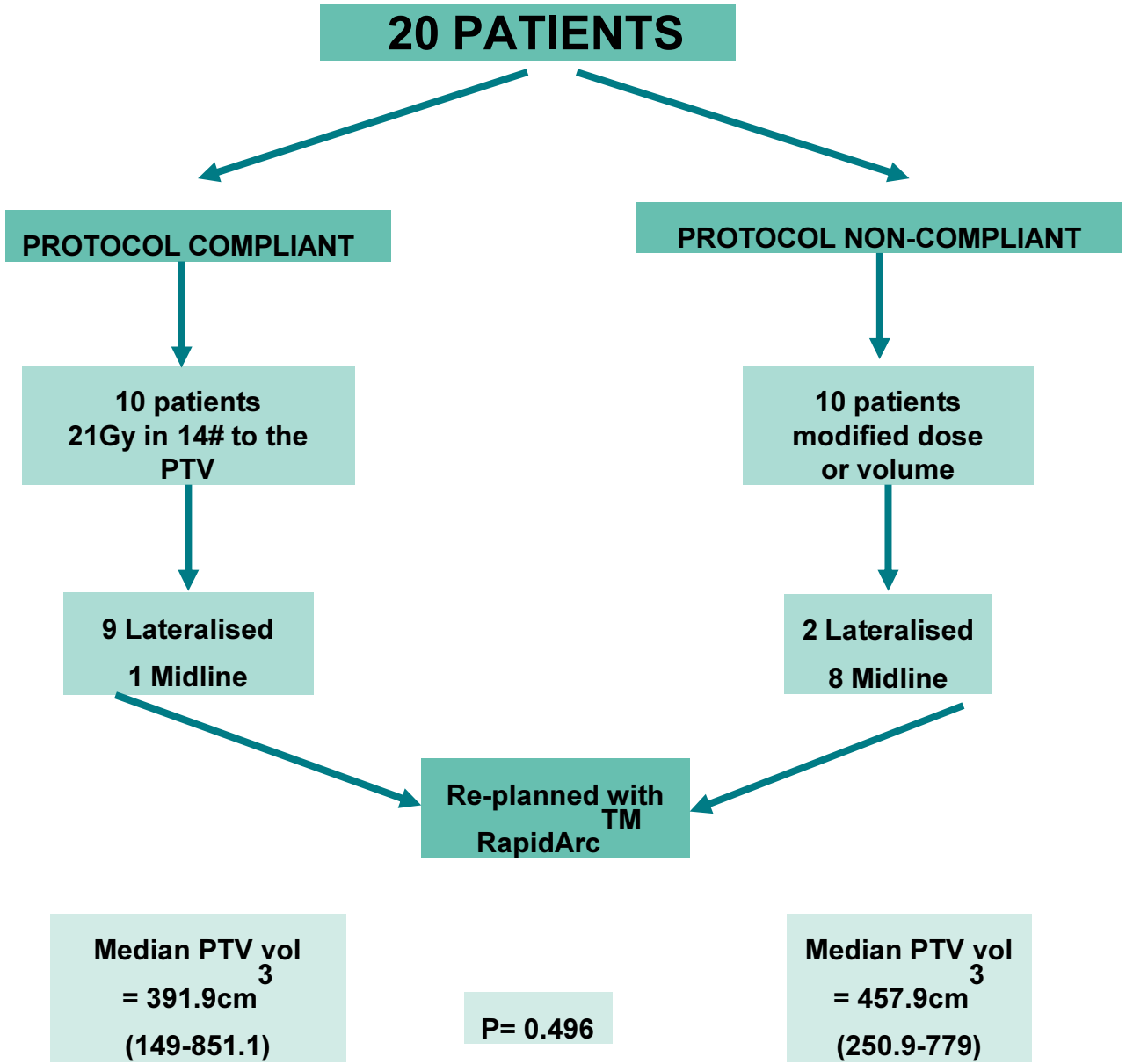
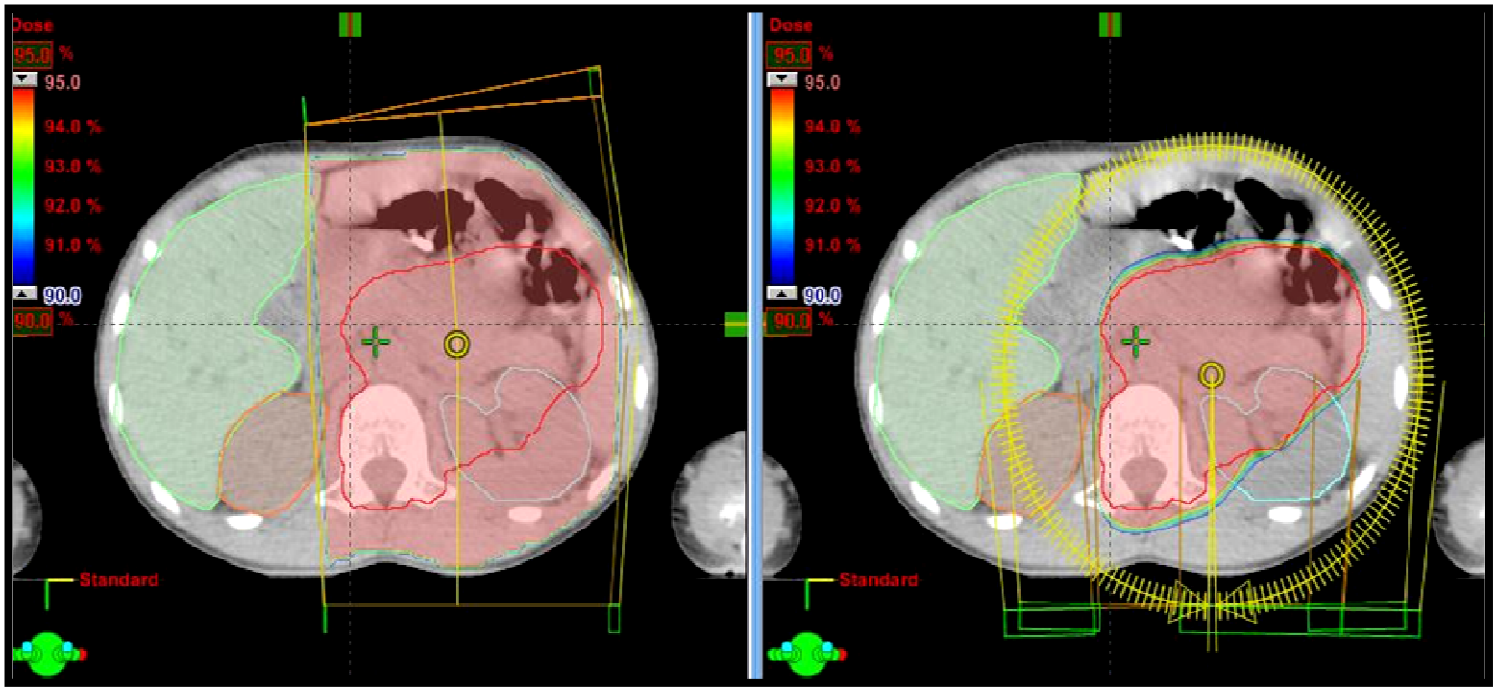
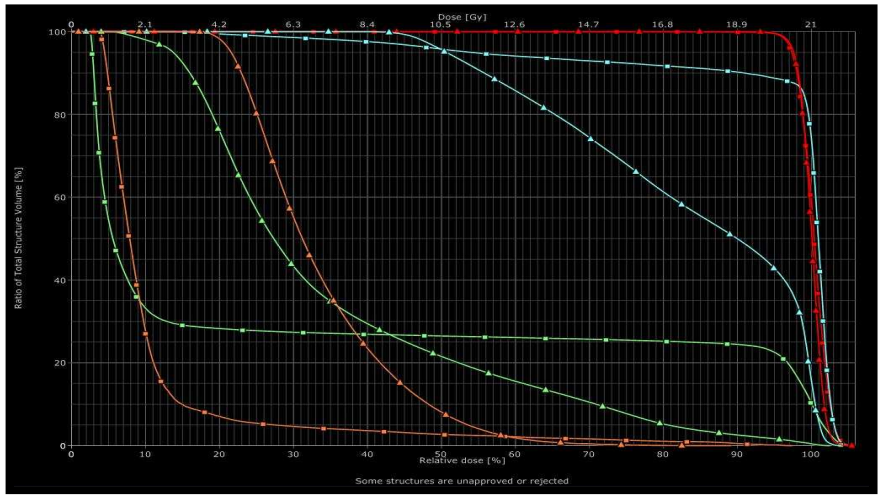

20 PATIENTS
PROTOCOL COMPLIANT
PROTOCOL NON-COMPLIANT
10 patients
21Gy in 14# to the
PTV
10 patients
modified dose
or volume
9 Lateralised
1 Midline
2 Lateralised
8 Midline
Re-planned with
RapidArc™
Median PTV vol
= 391.9cm3
(149-851.1)
P= 0.496
Median PTV vol
= 457.9cm3
(250.9-779)

PTV Coverage

	Conventional	RapidArc™	
Median $D_{2\%}$	21.8Gy (15Gy-22.4Gy)	21.8Gy (21.5Gy-22.5Gy)	P=0.723
Median $D_{98\%}$	15Gy (0.8Gy-20.3Gy)	19.9Gy (12.2Gy-20.5Gy)	P=<0.001
Conformity Index	1.75 (0.9-2.7)	1.1 (0.97-1.2)	P=<0.001
Homogeneity Index	0.33 (0.07-1.01)	0.09 (0.05-0.48)	P=<0.001



21Gy in 14# **21Gy in 14#**



□ **Conventional**

Δ **RapidArc**

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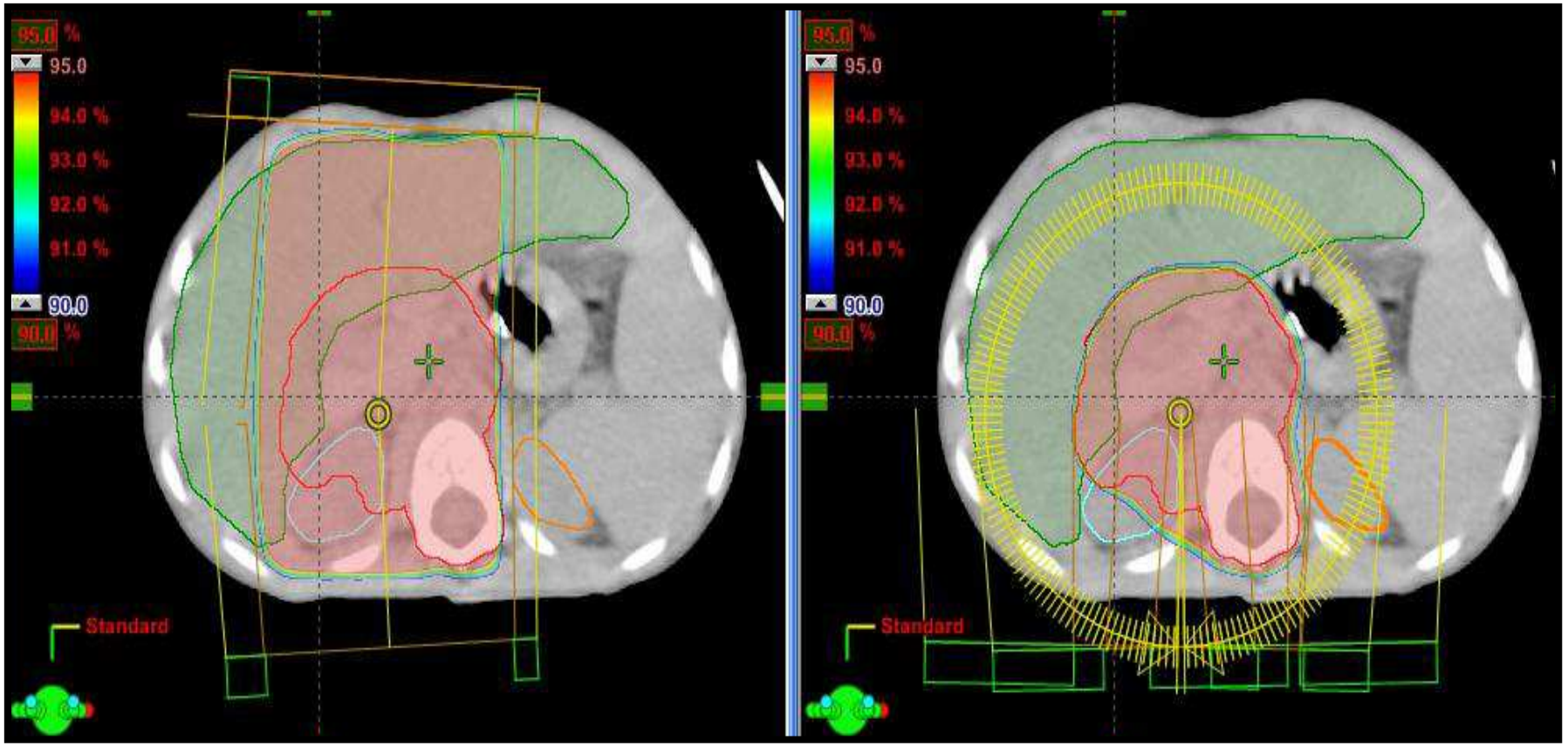

21 Gy in 14#

21 Gy in 14#

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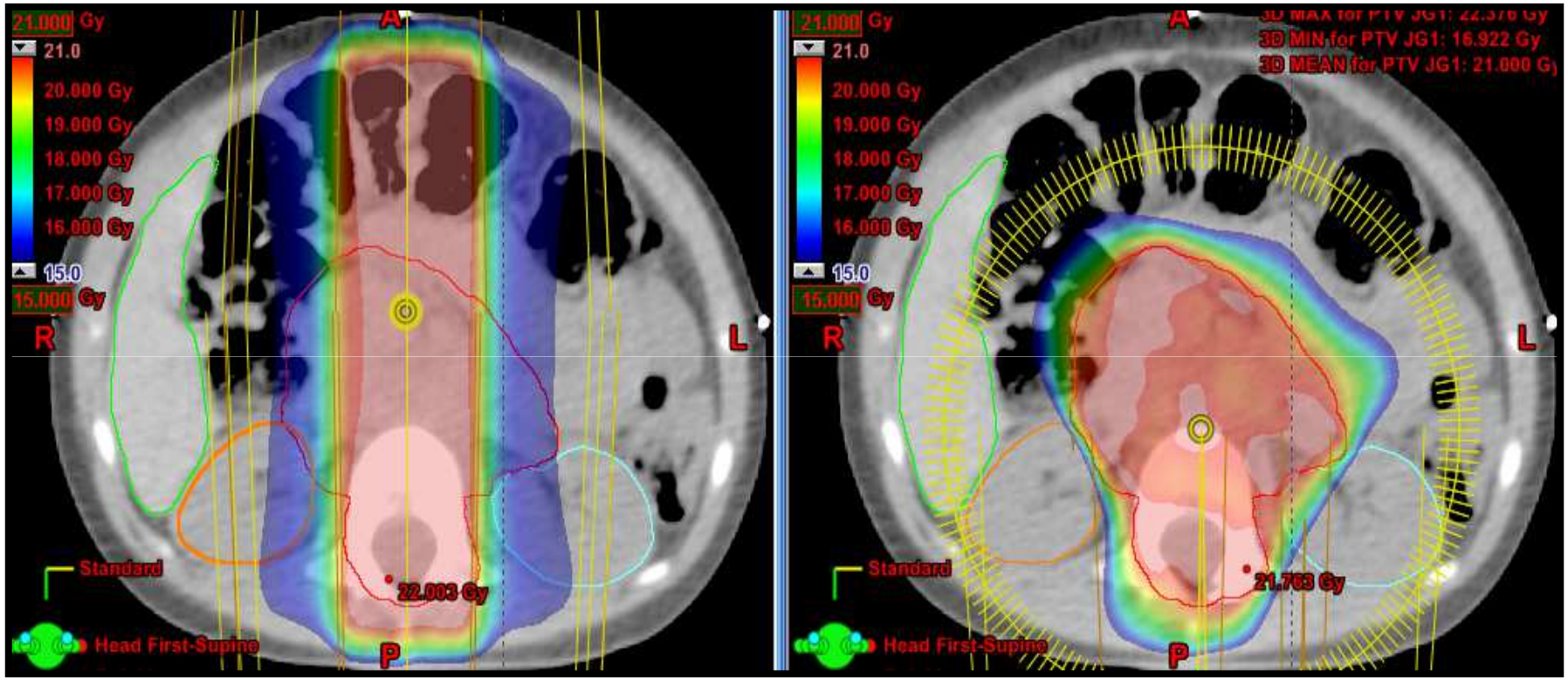
Protocol Non-compliant Group



Phase 1 15Gy in 10#
Phase 2 6Gy in 4#

21Gy in 14#

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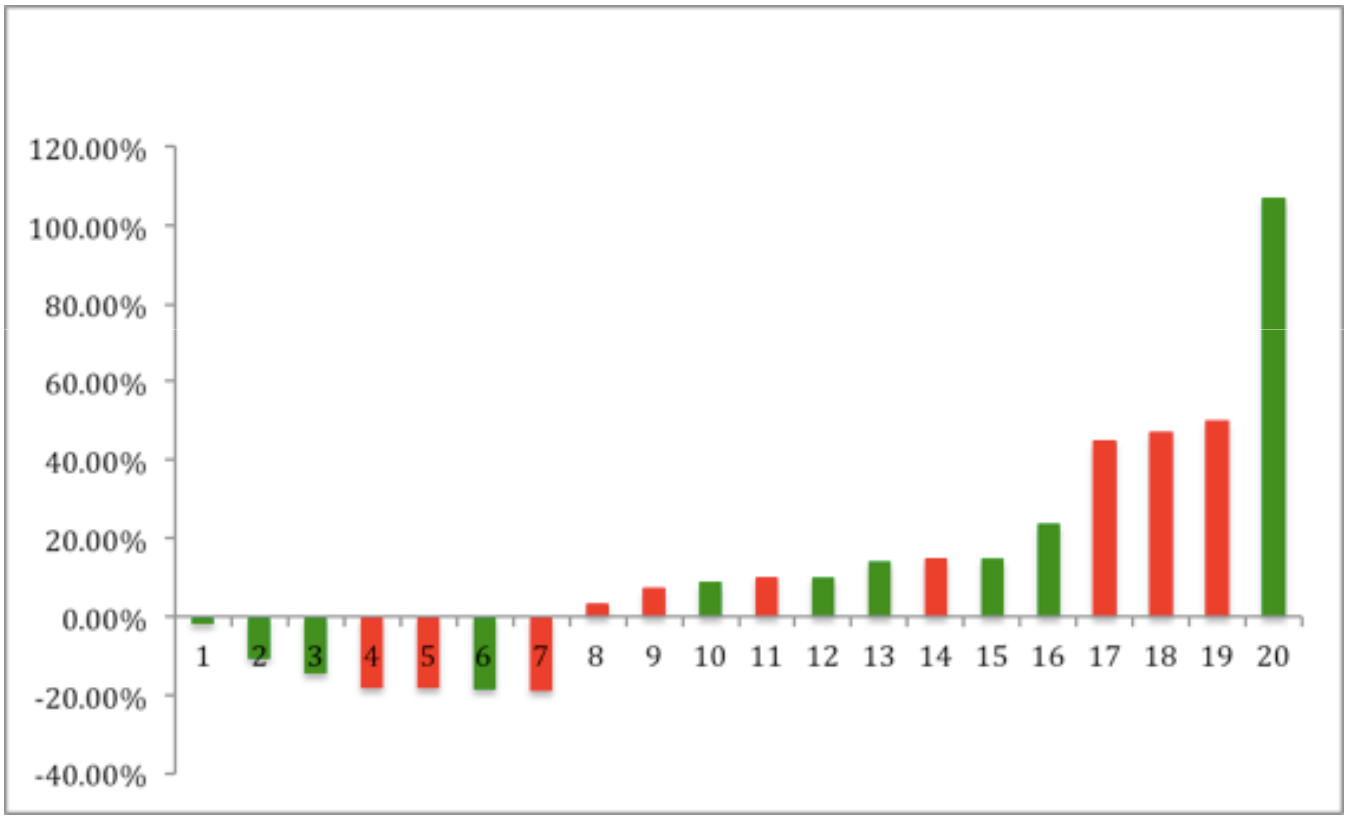
Non-PTV Integral Dose



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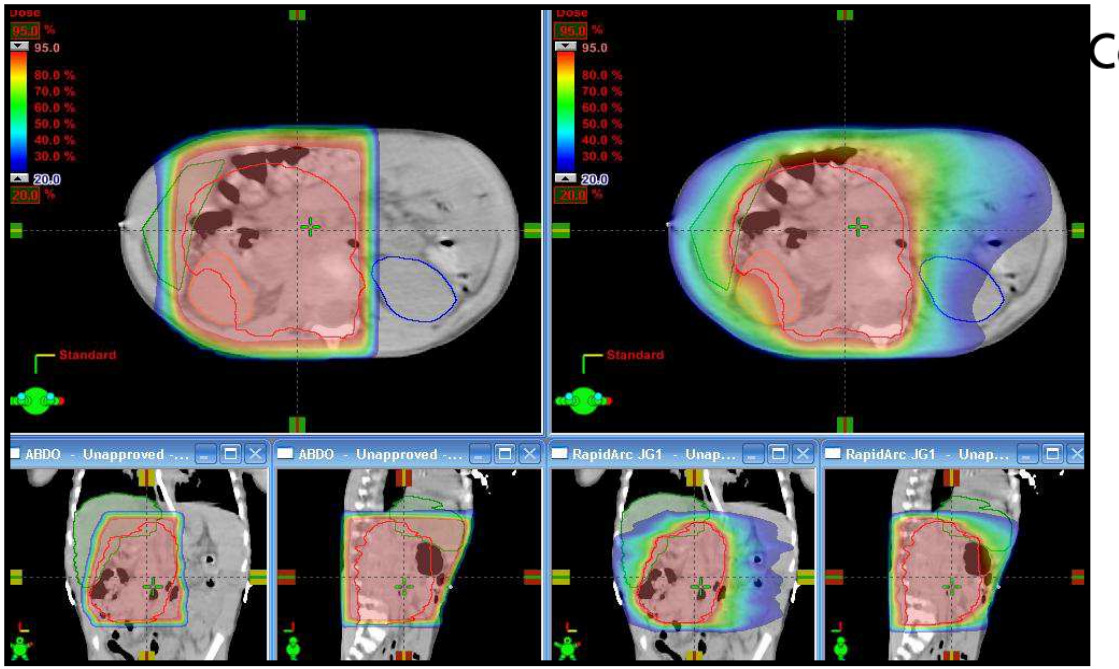
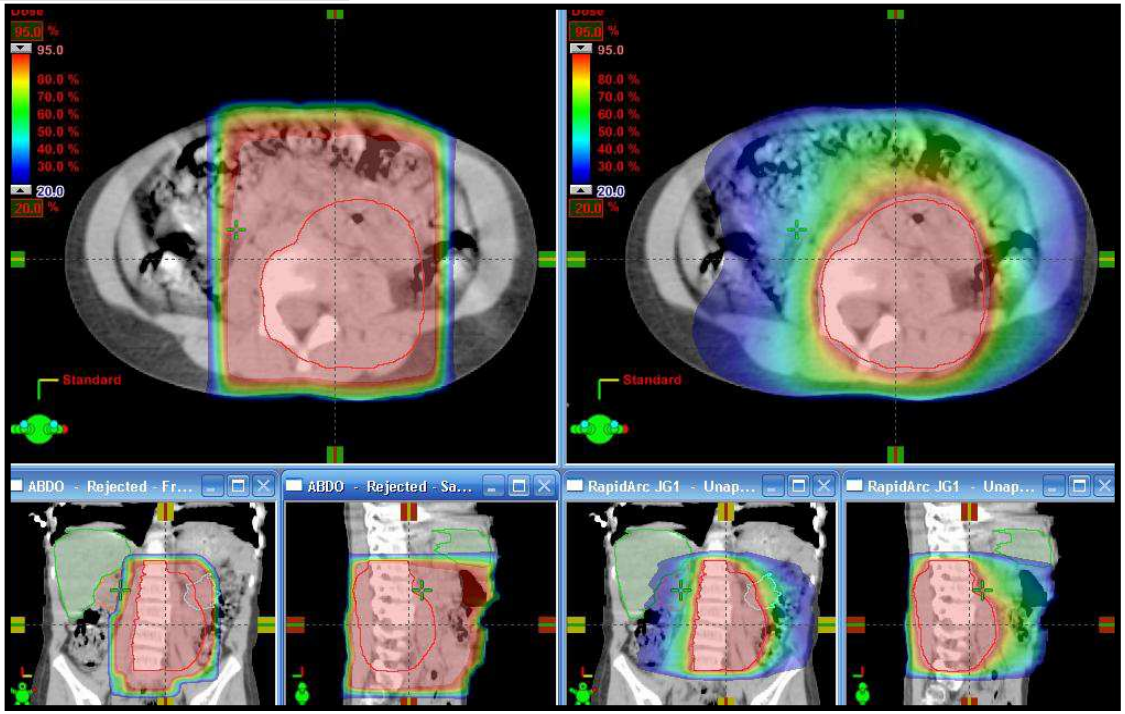


Increased NPID

Reduced NPID



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Conclusions

- RapidArc™ gave improved dose distributions and conformity to the PTV

Main Advantages

- Midline tumours where conventional radiotherapy cannot deliver the dose within normal tissue tolerance
- Right sided tumours

Conclusions

- Long term risks of IMRT in paediatric setting are not quantified
- An inability to deliver dose to the PTV in high-risk neuroblastoma could impact on local control and possibly survival
- Dose escalation to gross residual disease unlikely to be possible with conventional techniques
- Essential that we prospectively evaluate new radiotherapy techniques in the paediatric group

IMAT
neuroblastoma

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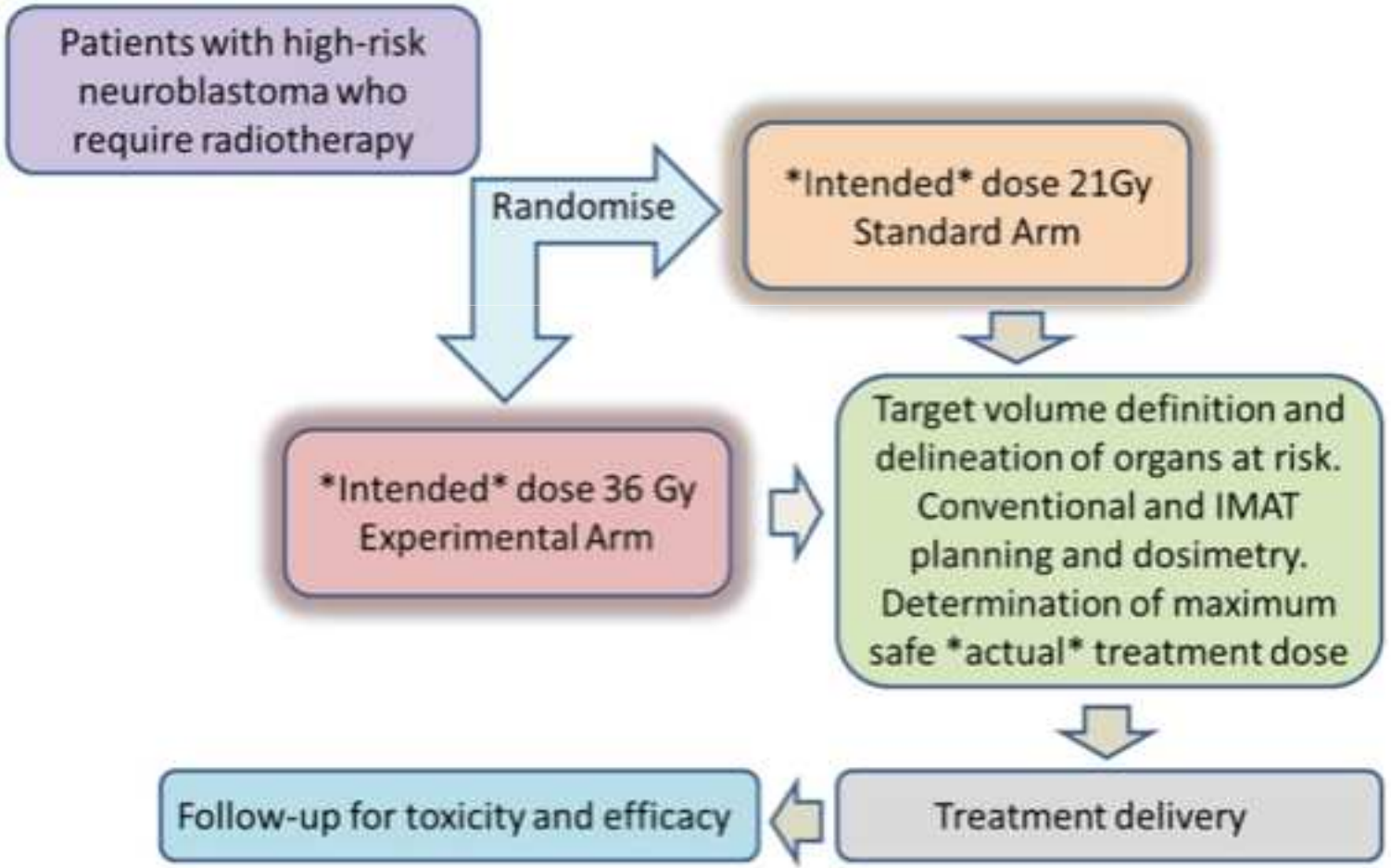

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Other Clinical Scenarios

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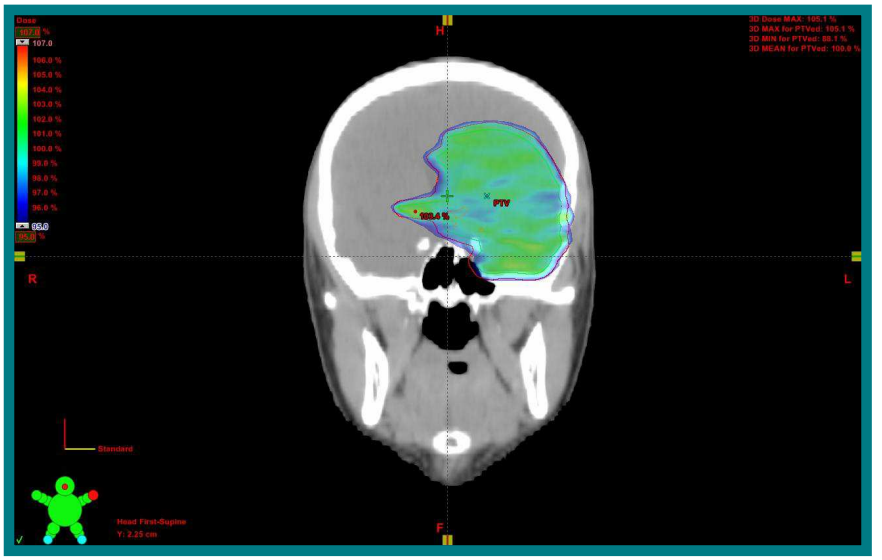
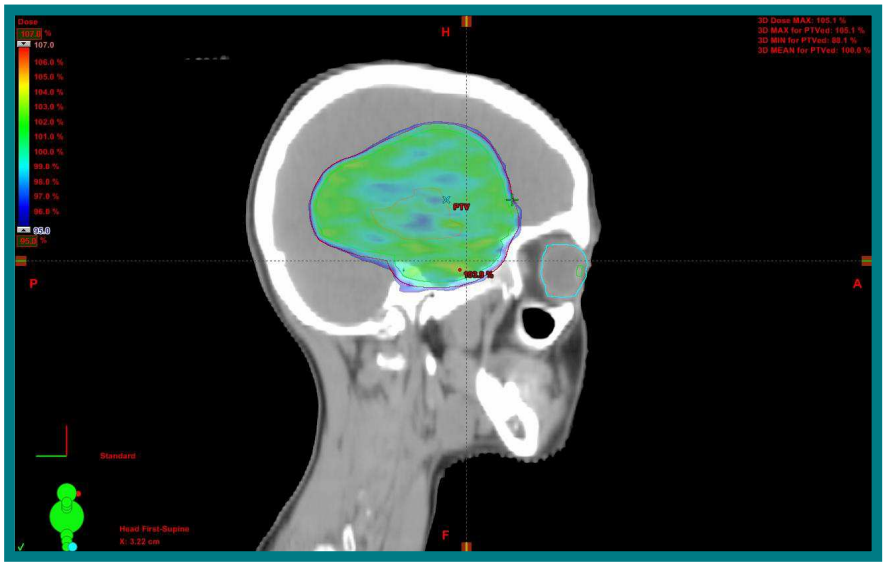
Supratentorial Brain Tumours





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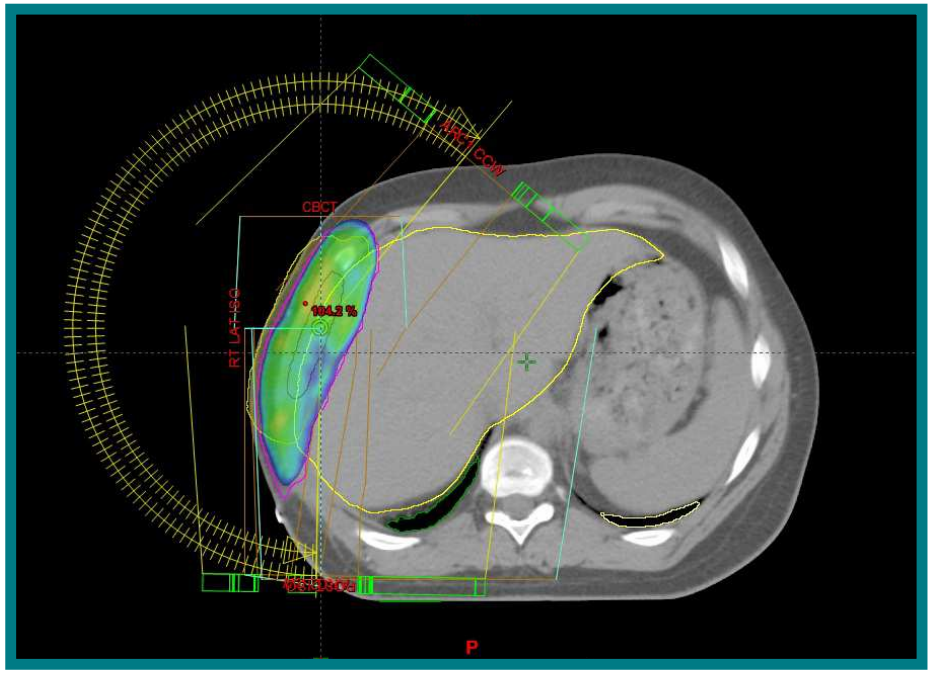
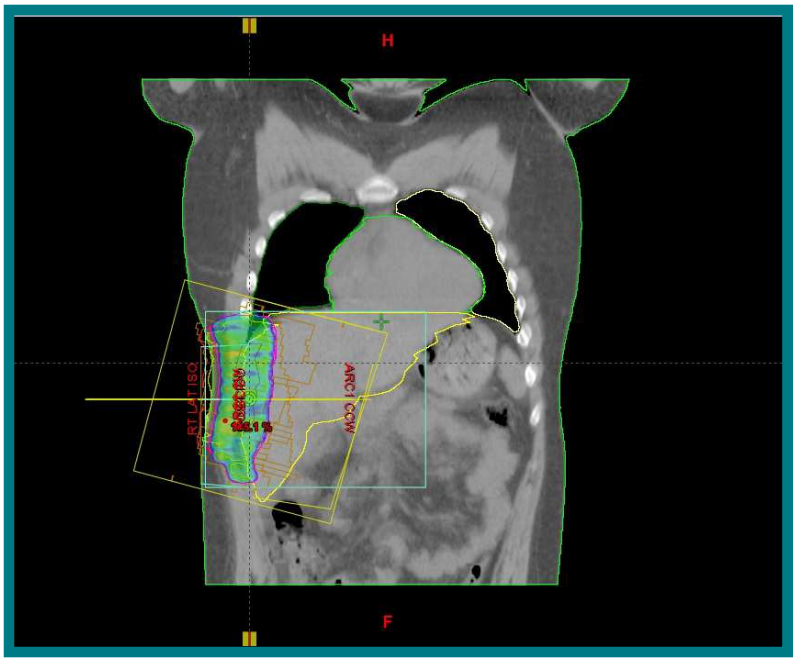
Chest Wall Ewing's Sarcoma





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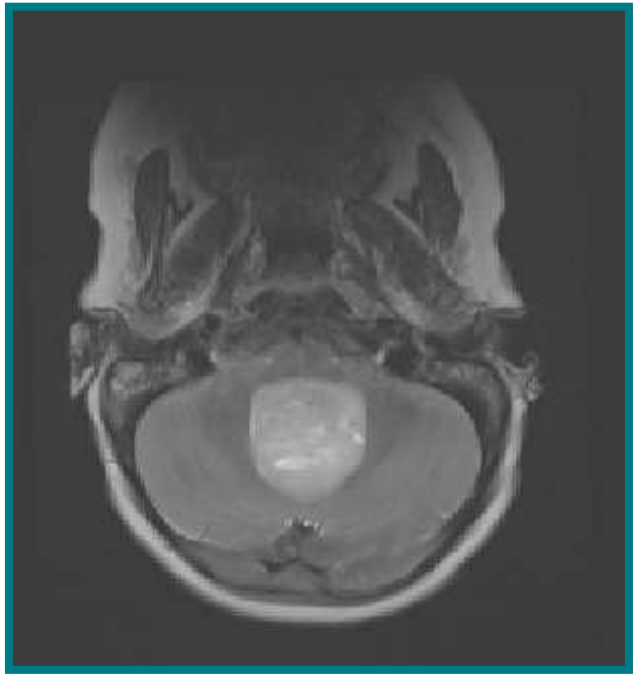
Medulloblastoma



Int J Radiat Oncol Biol Phys. 2002 Mar 1;52(3):599-605.

Intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity.

Huang E[1], Teh BS, Strother DR, Davis QG, Chiu JK, Lu HH, Carpenter LS, Mai WY, Chintagumpala MM, South M, Grant WH 3rd, Butler EB, Woo SY.

- IMRT V Conventional
- Grade 3 or 4 hearing loss
- 13% IMRT v 64% Conventional (p <0.14)

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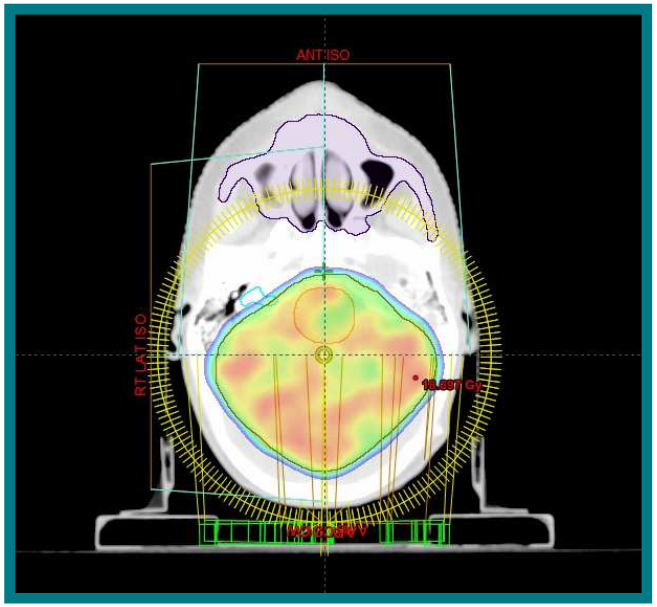
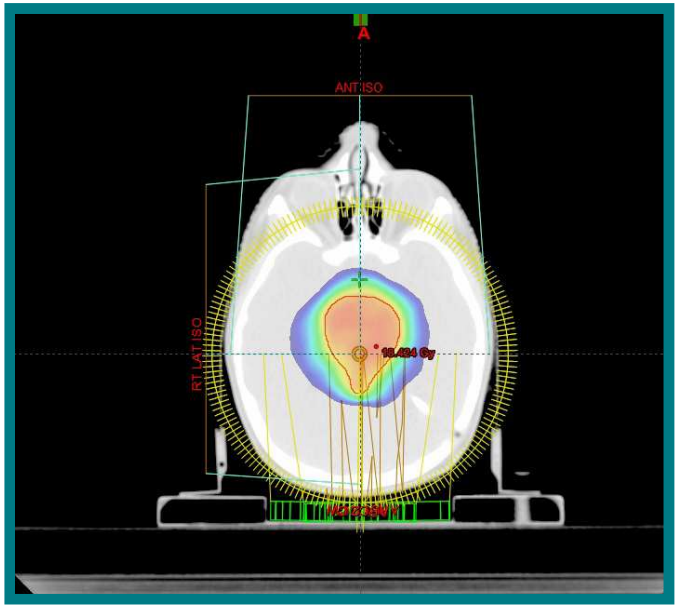
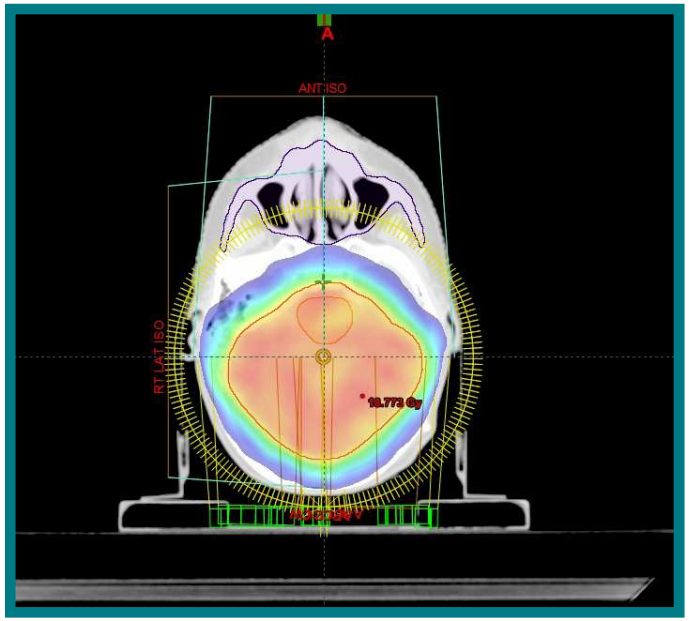
Medulloblastoma - Post Fossa Boost







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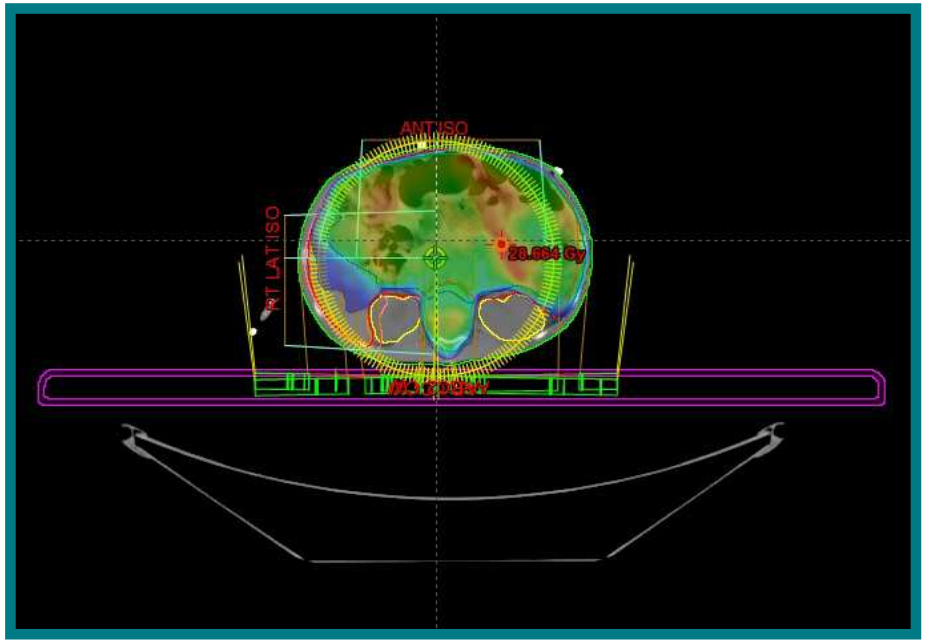
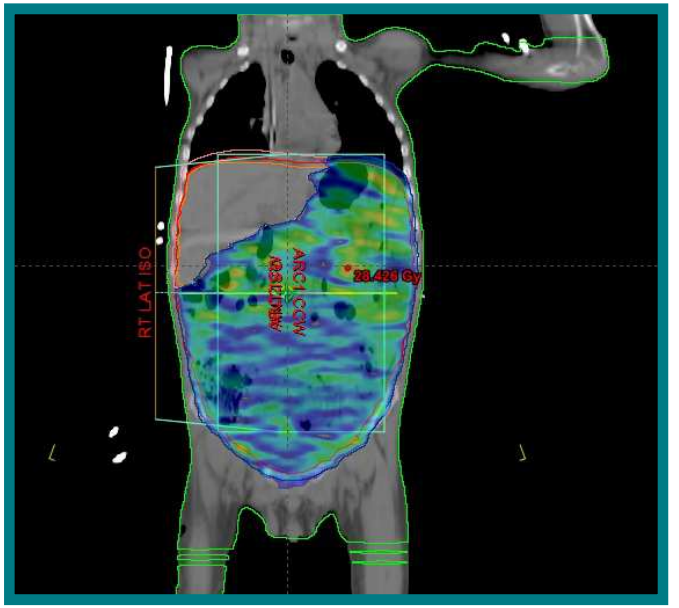
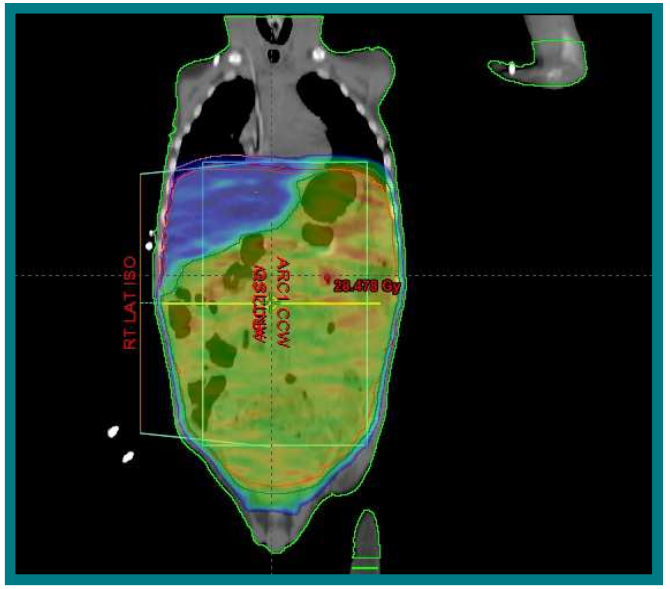
Desmoplastic small round cell tumour







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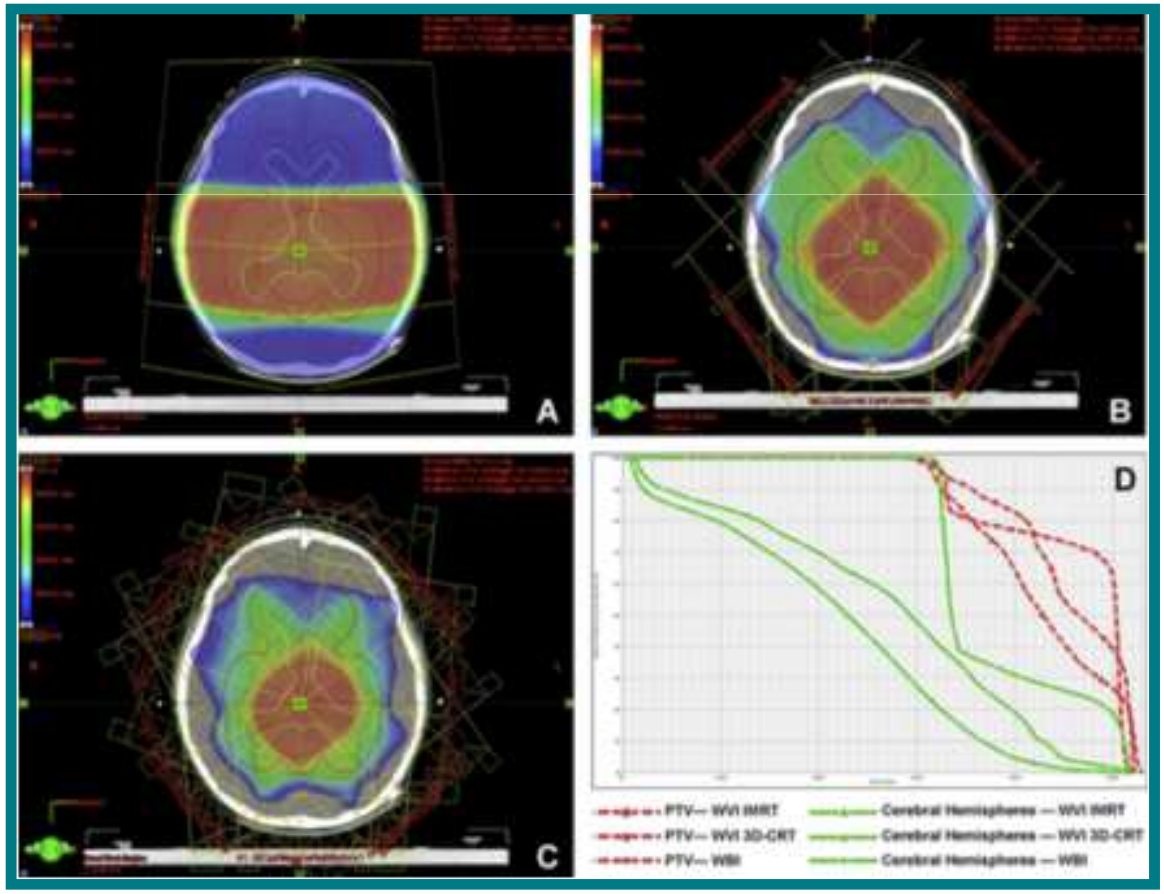
Intracranial Germ Cell Tumours

Int J Radiat Oncol Biol Phys. 2010 Feb 1;76(2):608-14. doi: 10.1016/j.ijrobp.2009.06.028. Epub 2009 Oct 30.

Intensity-modulated and 3D-conformal radiotherapy for whole-ventricular irradiation as compared with conventional whole-brain irradiation in the management of localized central nervous system germ cell tumors.

Chen MJ[1], Santos Ada S, Sakuraba RK, Lopes CP, Gonçalves VD, Weltman E, Ferrigno R, Cruz JC.



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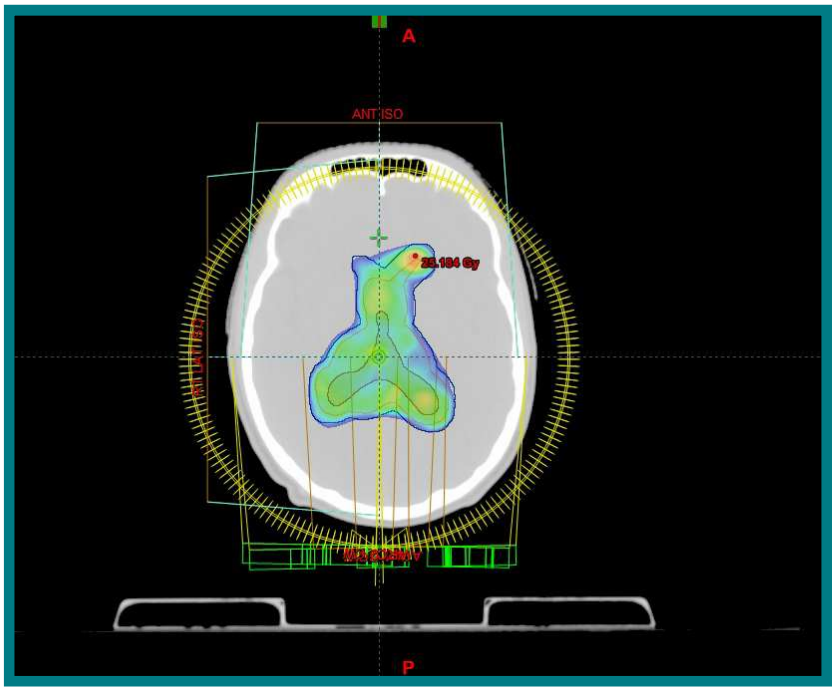
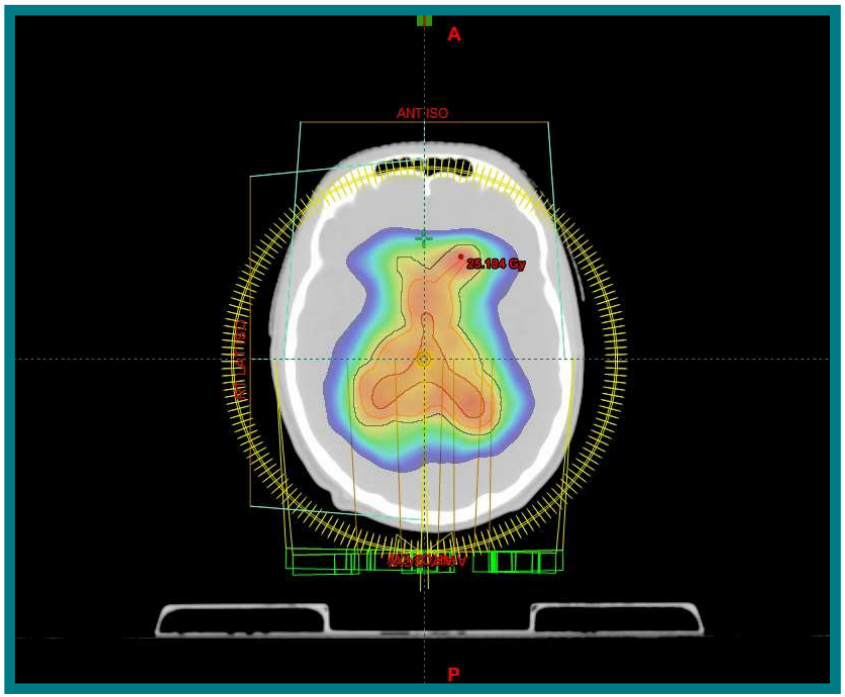
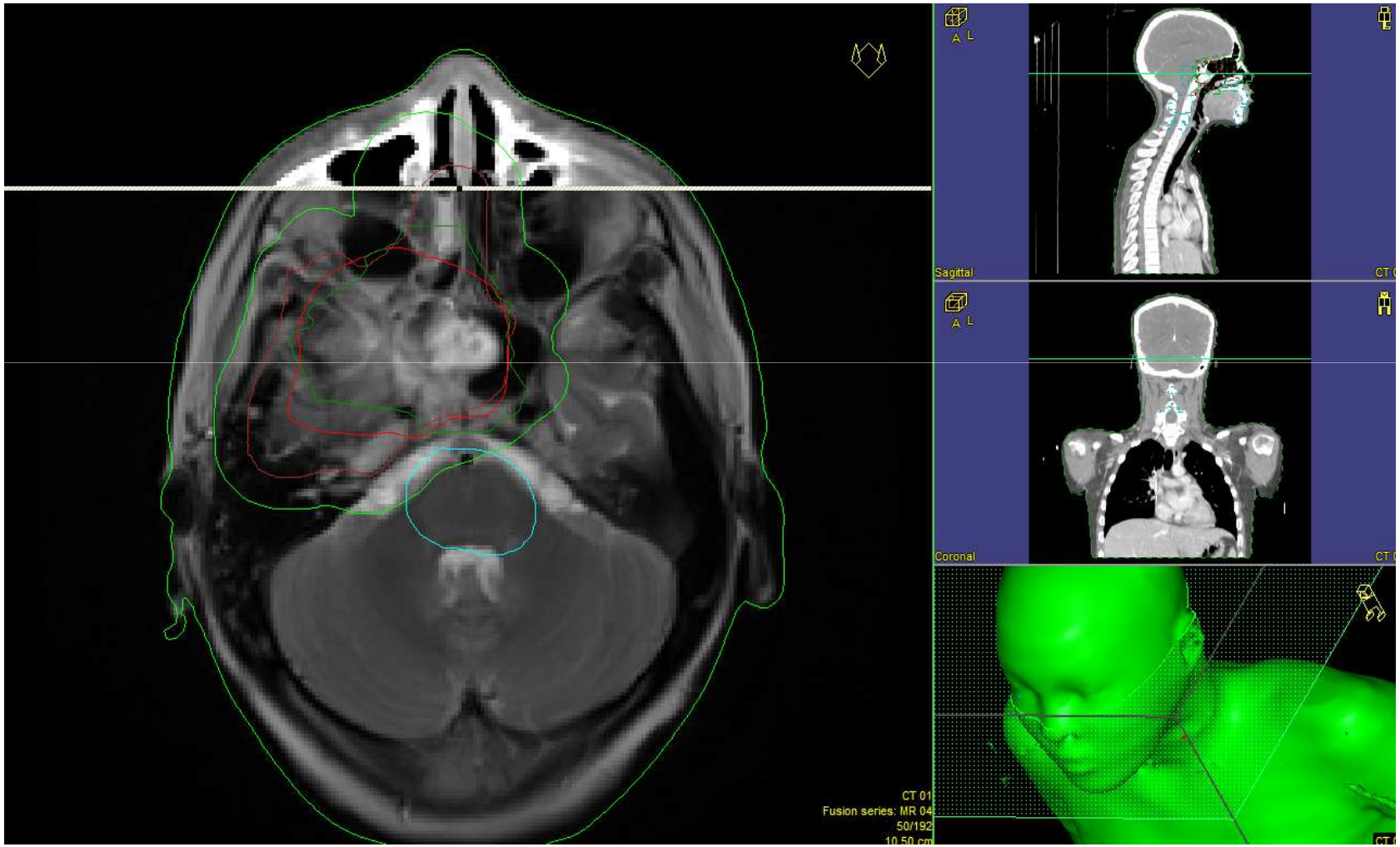
Whole Ventricular Radiotherapy

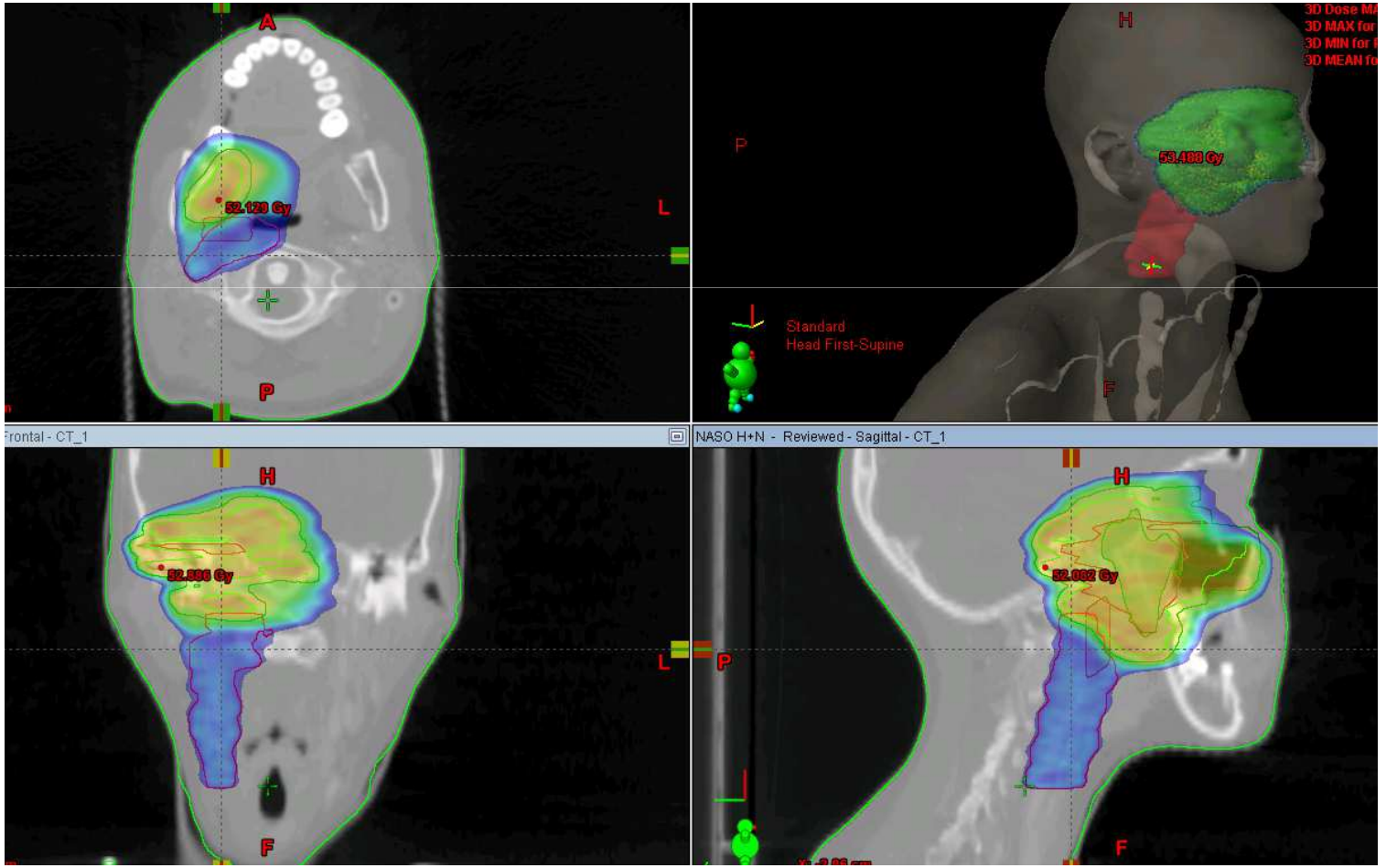


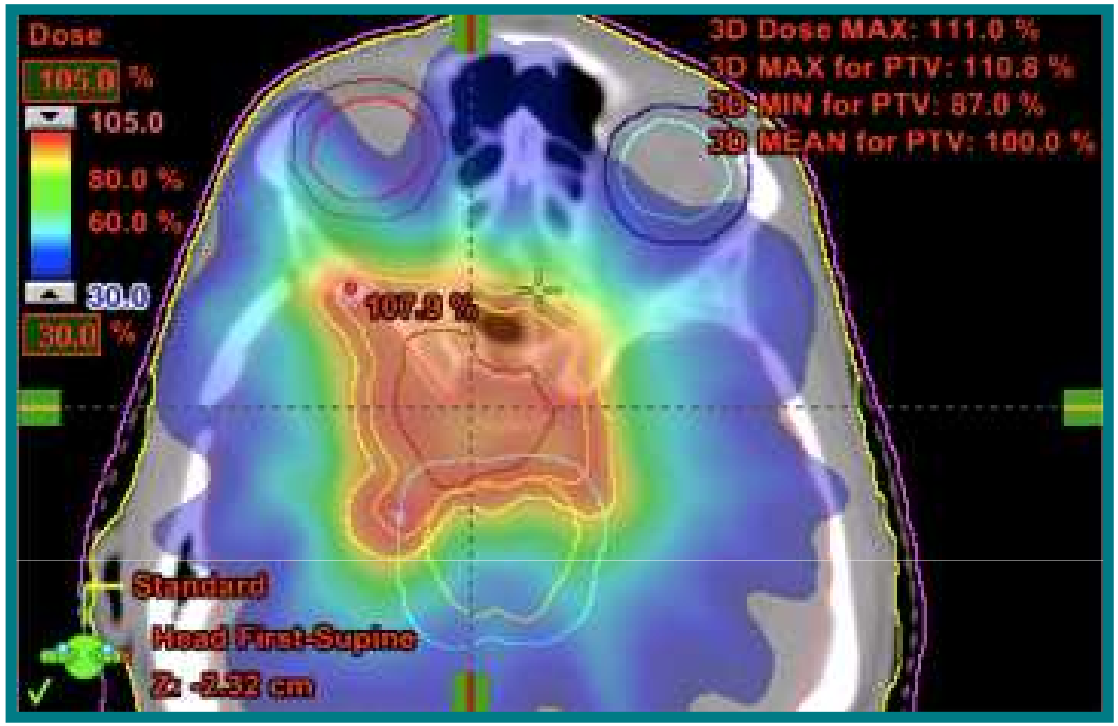


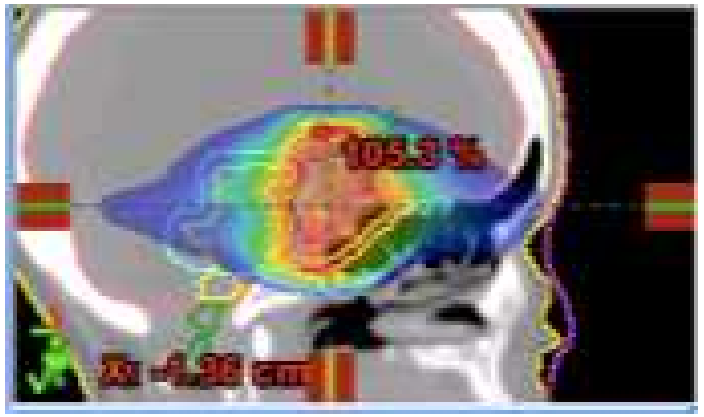
Parameningeal Rhabdomyosarcoma

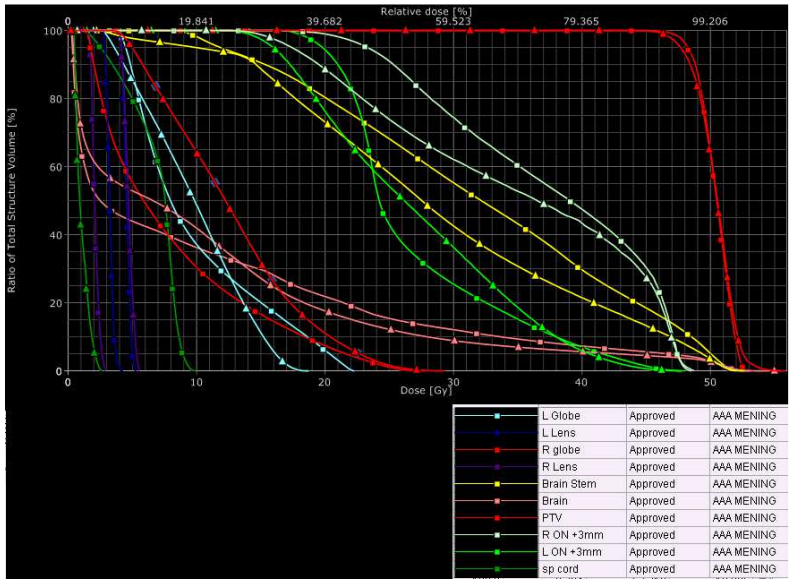


Parameningeal Rhabdomyosarcoma




Dose
105.0 %
105.0
80.0 %
60.0 %
30.0
30.0 %
3D Dose MAX: 111.0 %
3D MAX for PTV: 110.8 %
3D MIN for PTV: 87.0 %
3D MEAN for PTV: 100.0 %
107.8 %
Standard
Head First-Supine
Z: -8.32 cm


105.3 %


Relative dose [%]
0
19.841
39.682
59.523
79.365
99.206
Ratio of Total Structure Volume [%]
100
80
60
40
20
0
0
10
20
30
40
50
Dose [Gy]
L Globe Approved AAA MENING
L Lens Approved AAA MENING
R globe Approved AAA MENING
R Lens Approved AAA MENING
Brain Stem Approved AAA MENING
Brain Approved AAA MENING
PTV Approved AAA MENING
R ON +3mm Approved AAA MENING
L ON +3mm Approved AAA MENING
sp cord Approved AAA MENING

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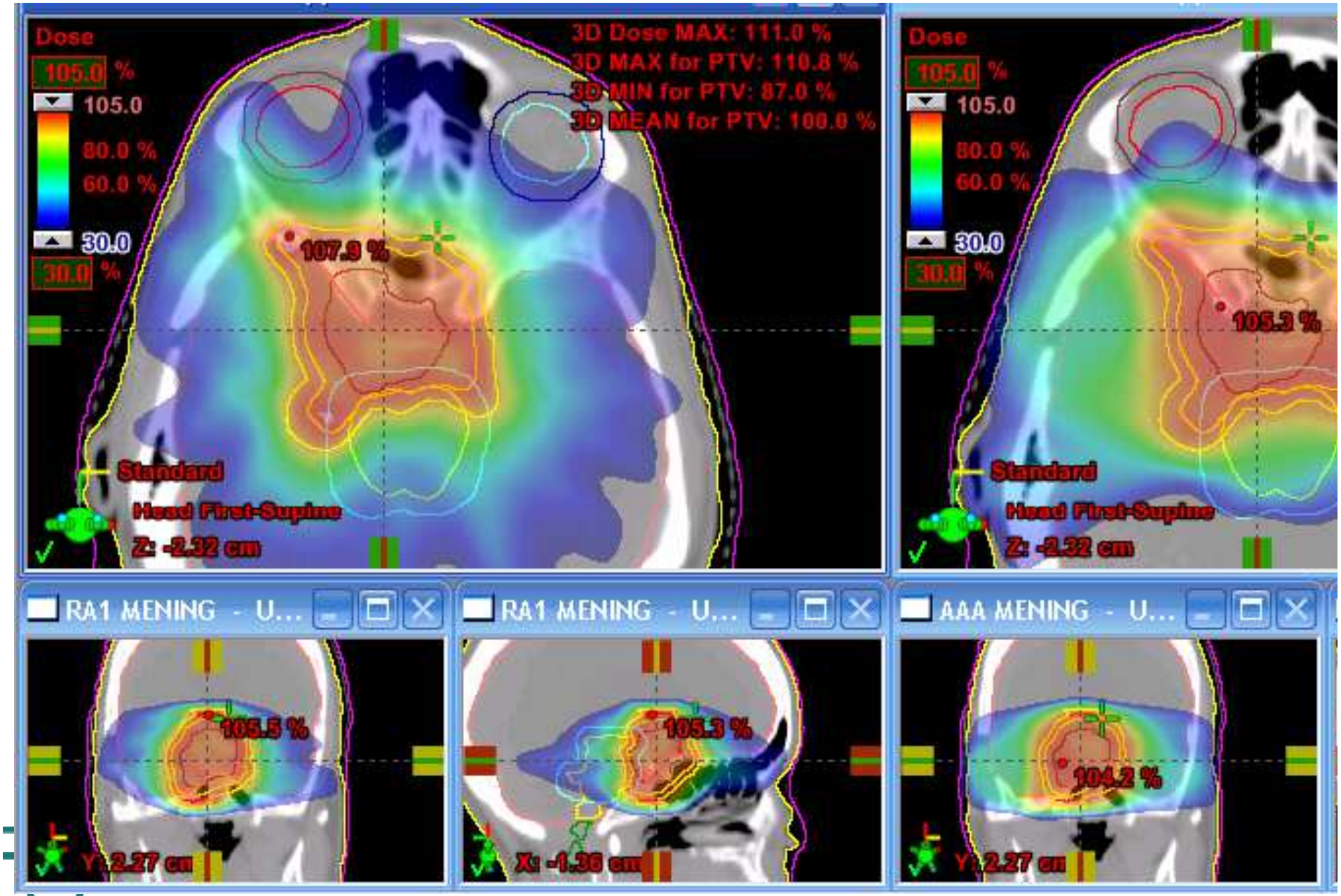
Summary

- IMRT has an important role in improving dose distributions and reducing doses to OAR in paediatric patients
- Need to consider effects on growing tissues and balance the risks and benefits
- Studies with short follow up have not confirmed a rise in second malignancies
- Needs prospective evaluation and long term follow up

Thank you for listening


Dose
105.0 %
105.0
80.0 %
60.0 %
30.0
30.0 %
3D Dose MAX: 111.0 %
3D MAX for PTV: 110.8 %
3D MIN for PTV: 87.0 %
3D MEAN for PTV: 100.0 %
107.9 %
Standard
Head First-Supine
Z: -2.32 cm
Dose
105.0 %
105.0
80.0 %
60.0 %
30.0
30.0 %
105.3 %
Standard
Head First-Supine
Z: -2.32 cm
RA1 MENING - U...
105.5 %
Y: 2.27 cm
RA1 MENING - U...
105.3 %
X: -1.36 cm
AAA MENING - U...
104.2 %
Y: 2.27 cm

the london
sarcoma service

University College London Hospitals
NHS Foundation Trust

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Intensity modulated radiotherapy in sarcoma

Dr Beatrice Seddon
Dr Franel le Grange
Sarcoma Unit, University College Hospital

3rd April 2016 ESTRO teaching course on IMRT, London

Radiotherapy in sarcoma

Soft tissue sarcoma

- Most commonly in limbs
- Standard management is surgery ± (neo)adjuvant RT
- Local control of primary tumour >80%
- Acute effects: wound healing
- Long term side effects: impact on limb function

Radiotherapy in sarcoma

Ewing Sarcoma

- Standard management with chemotherapy
- Local management: surgery/surgery + RT/ RT alone
- Young patients, need to minimise late effects of RT

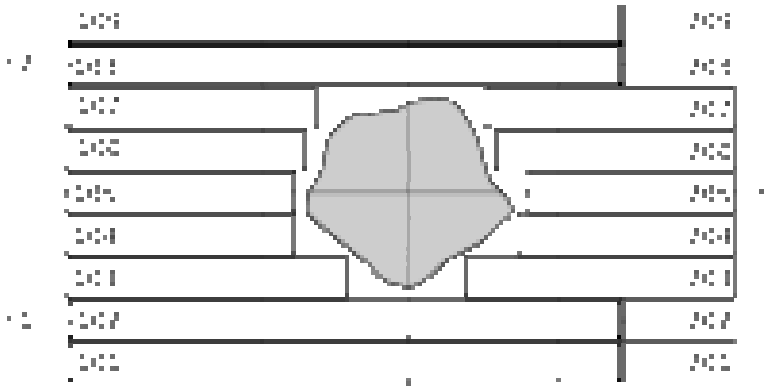
Other primary bone sarcomas/ chordoma

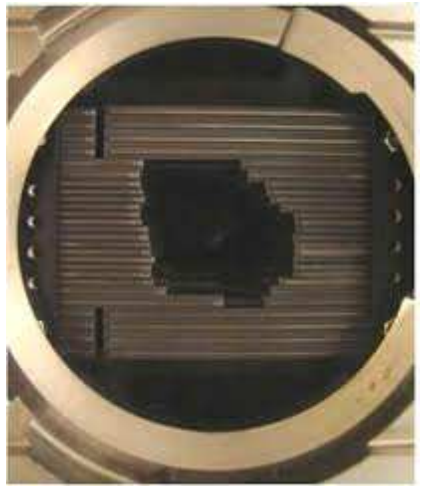
- Curative management is surgery ± chemotherapy
- Not radiosensitive, requires high doses to achieve local control

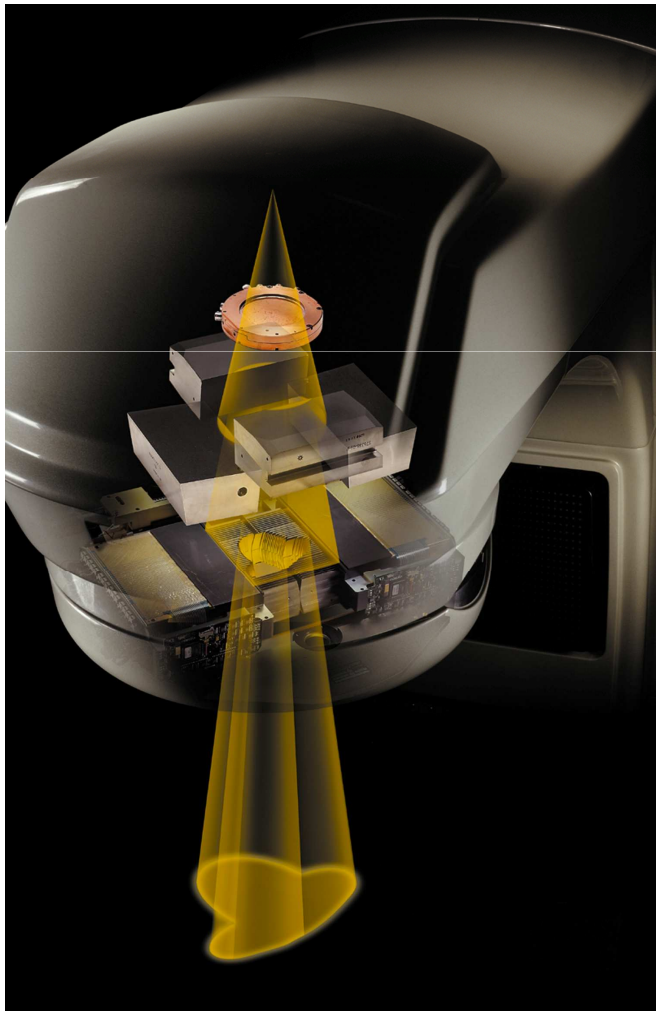
Radiotherapy in sarcoma

- Until recently standard technique was with 3D conformal radiotherapy
- Uses static beams which are shaped to conform to the tumour volume
- Results in:
  - Un-necessary treatment of large volumes of normal tissue
  - Dose inhomogeneity and hot spots in normal tissues
  - With potential consequences on toxicity and function

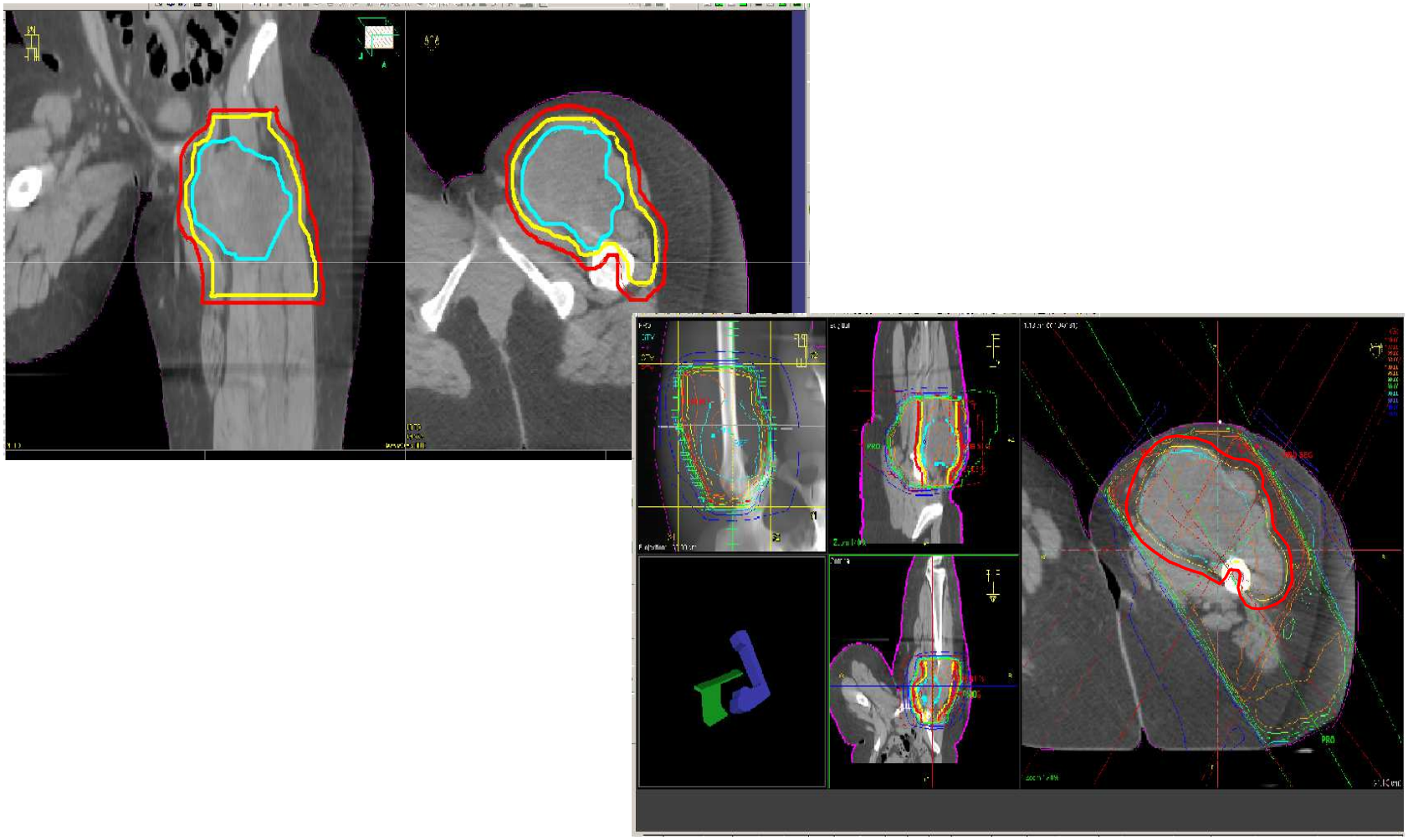
3D conformal radiotherapy



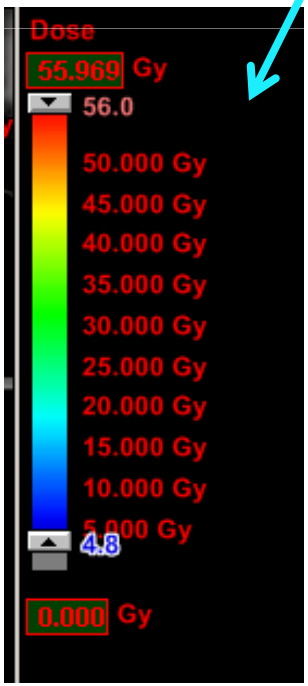




Current standard: 3D conformal radiotherapy



3D conformal radiotherapy

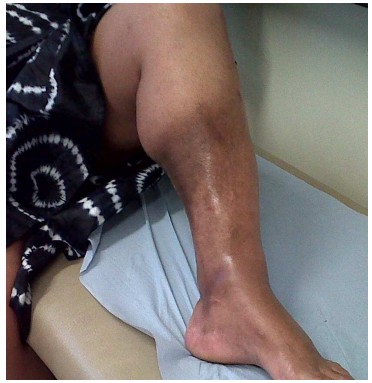


Late toxicity after 3D conformal radiotherapy

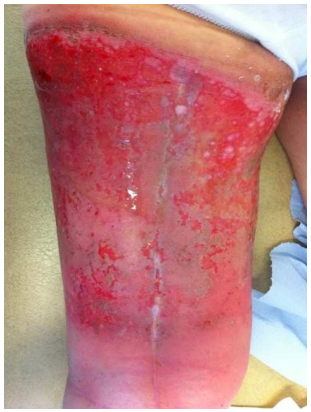
- Late toxicity and limb function are related to treatment volumes and RT dose
  - Soft tissue fibrosis
  - Lymphoedema
  - Bone fractures, joint stiffness
- Rates of ≥grade 2 fibrosis in 48.2% with post-operative RT

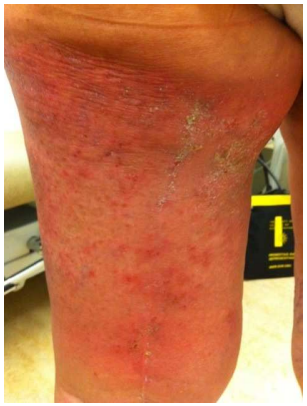
Davis et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiotherapy and Oncology 2005, 75:48–53.

- Negative impact on function



50 Gy/25# pre-op





66 Gy/33# post-op

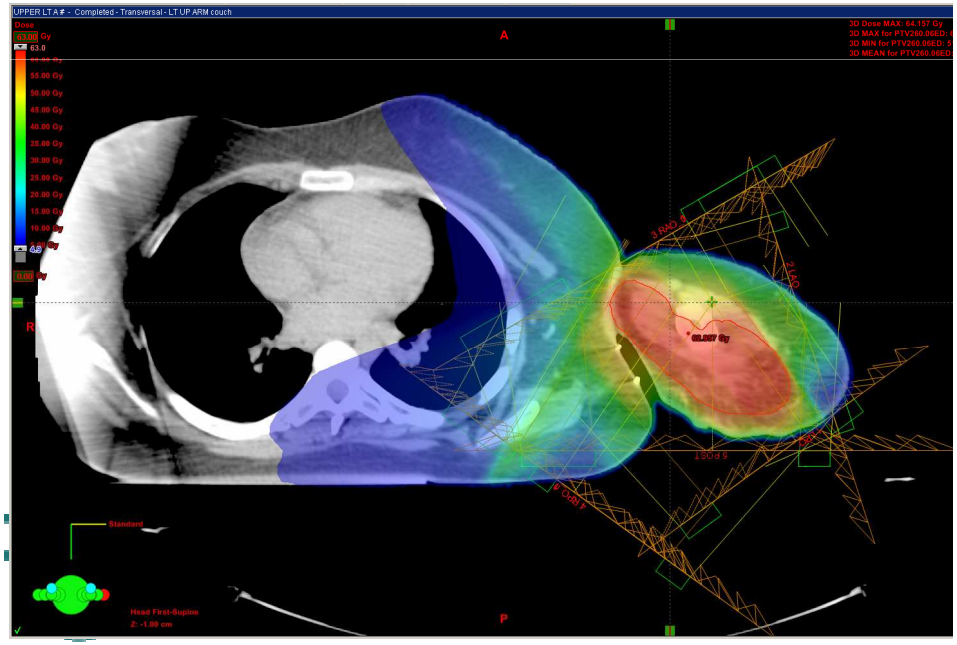
Intensity modulated radiotherapy

- Offers the opportunity to:
  - Conform better to the planning target volume (PTV)
  - Treat with greater homogeneity within PTV
  - Vary dose within PTV (‘dose painting’ concept)

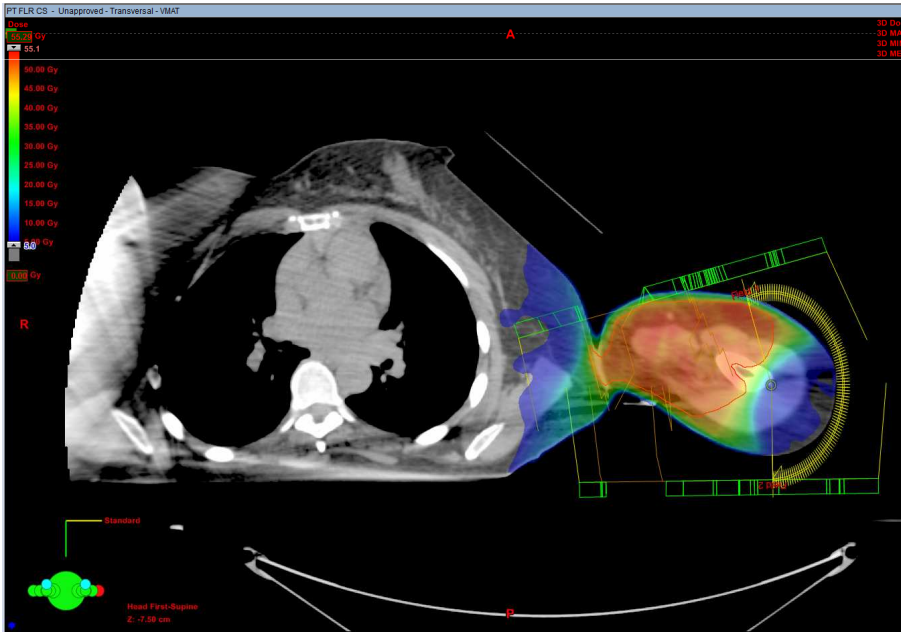
  - Spare normal tissues – soft tissues and bone
  - Allow dose escalation, improved local control, survival
  - Reduce hot spots in normal tissues
  - Reduce normal tissue acute and late toxicity
  - Improve long term function

Intensity modulated radiotherapy delivery

Multiple fixed static beam angles 'step and shoot'



Volumetric modulated arc therapy (RapidArc®), TomoTherapy®



IMRT opportunities in sarcoma

- To spare normal tissues and improve functional outcomes in limb sarcomas
- To achieve better tumour coverage in difficult locations:
  - Paraspinal tumours
  - Pelvic tumours
  - Ribs tumours
  - Head and neck tumours
  - Retroperitoneal tumours
- To deliver higher doses than normally achievable for inoperable tumours:
  - Osteosarcoma, spindle cell sarcoma of bone
  - Chondrosarcoma
  - Chordoma

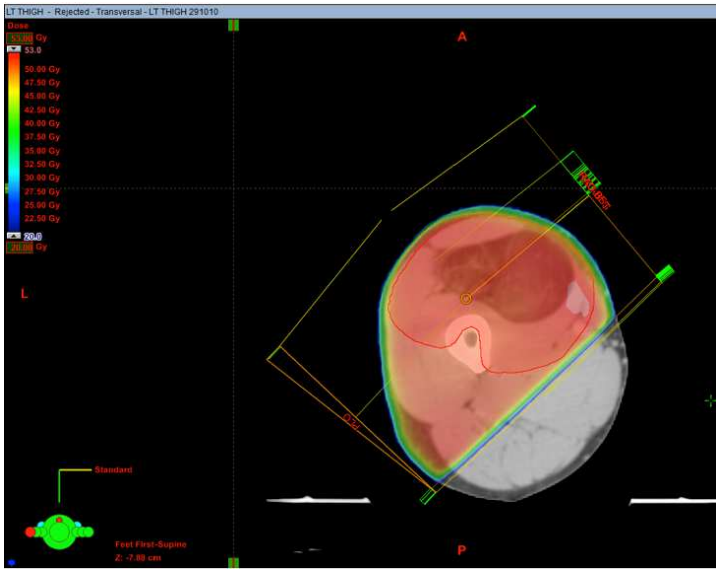
IMRT in soft tissue sarcoma

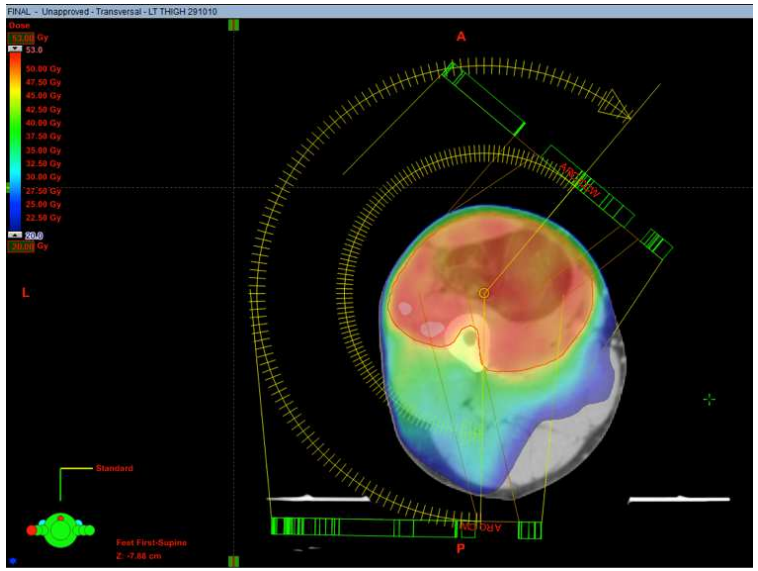
IMRT planning study: Limb soft tissue sarcoma
Example cases

Dosimetric advantage for IMRT vs 3D-CRT:

- Reduction of volume of normal tissues receiving moderate or high doses of radiotherapy
- Sparing of normal tissues, e.g. femur

3DCRT





VMAT IMRT

Anterior thigh, 50Gy in 25#

Le Grange, Stacey, Seddon, UCLH 2014

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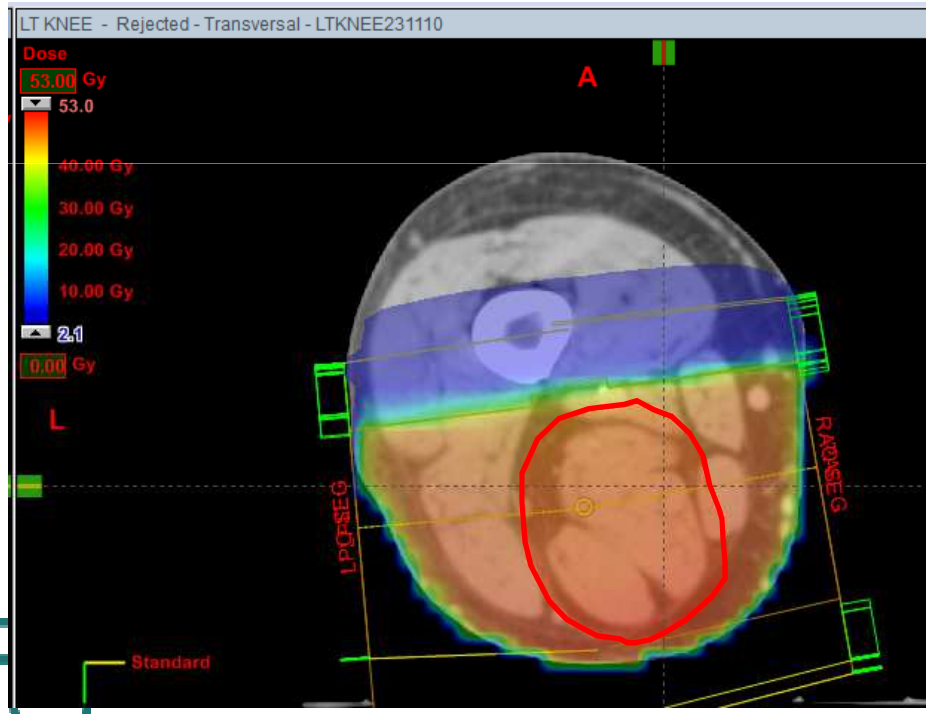
Calf: 50Gy in 25#

3DCRT



VMAT

Shin: 60Gy in 30#

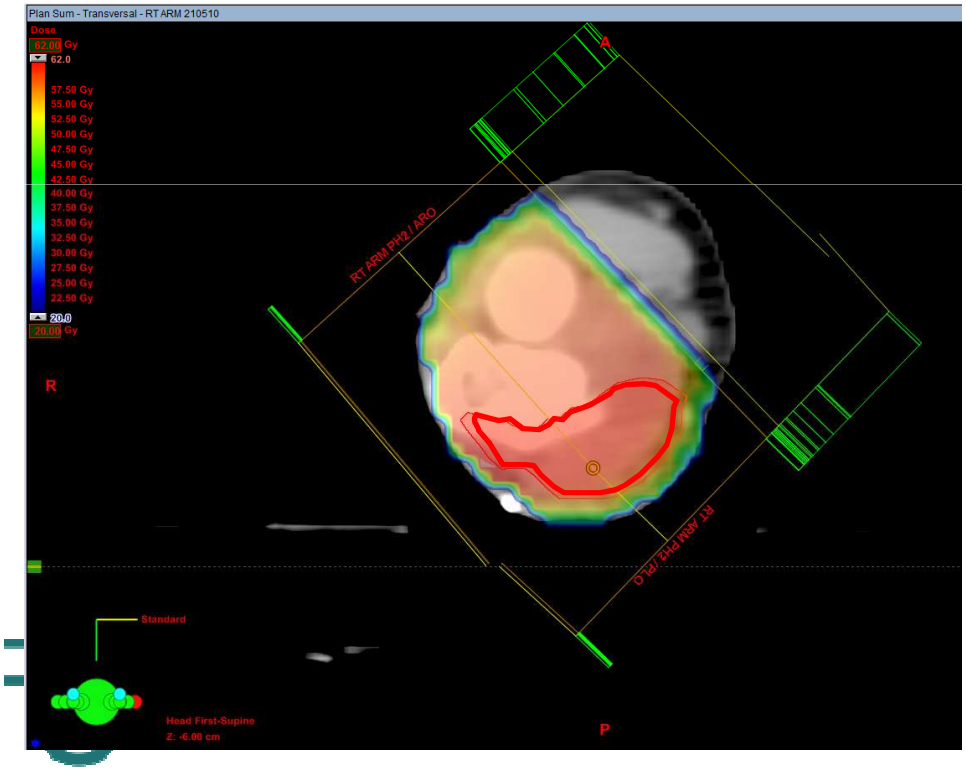
3DCRT

VMAT

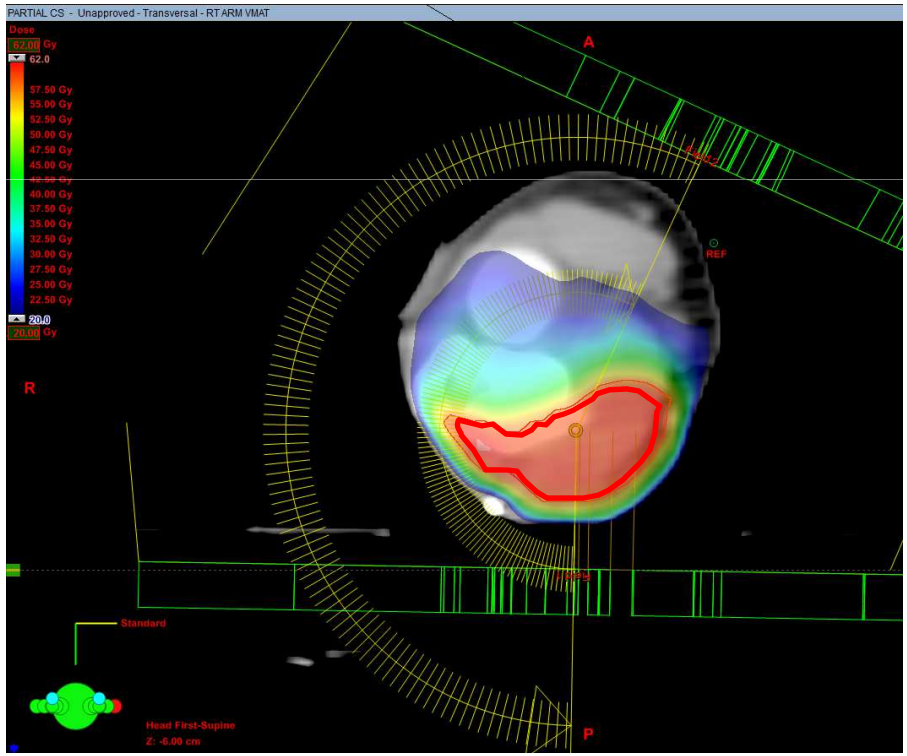
Le Grange, Stacey, Seddon, UCLH 2014

Upper arm: 60Gy in 30#

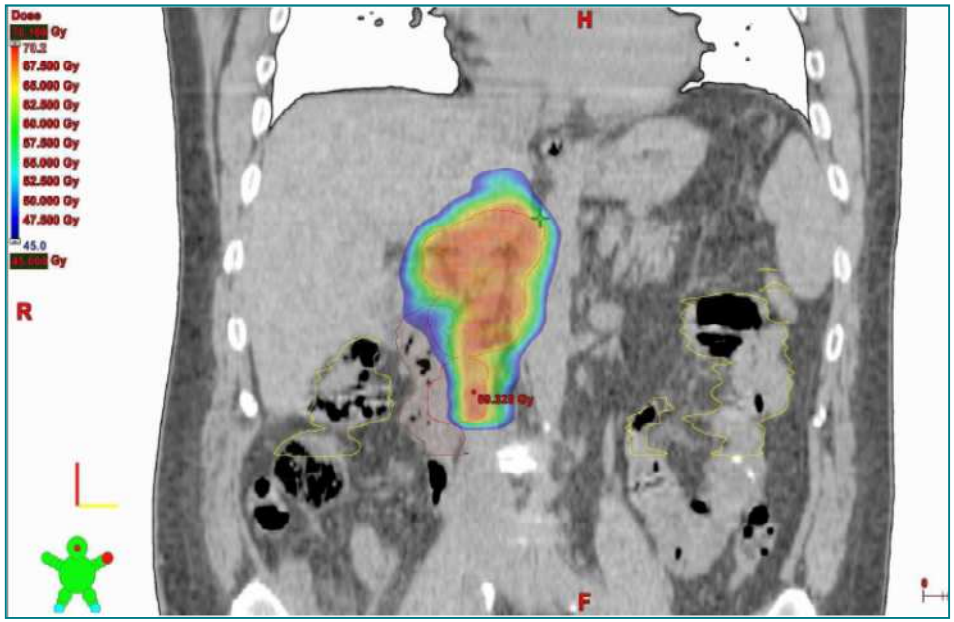
3DCRT

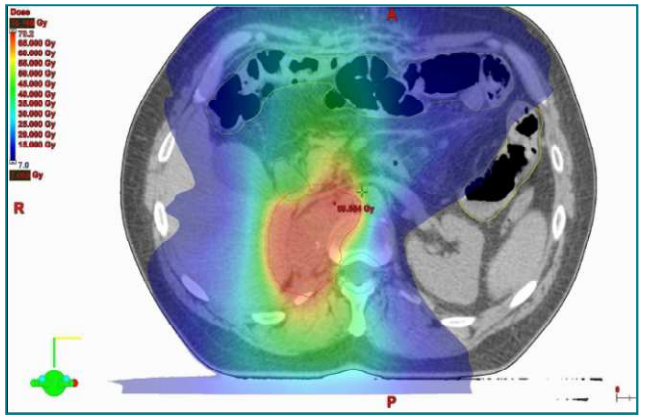


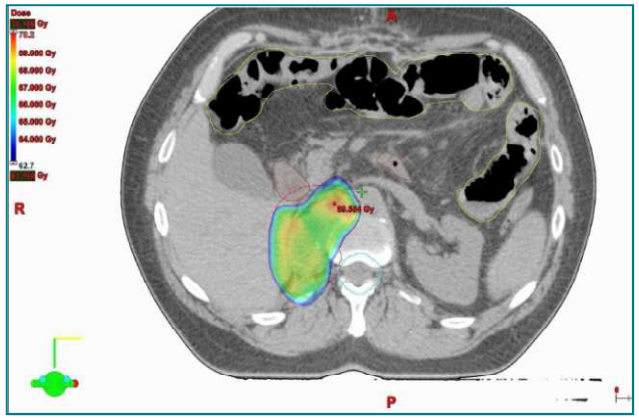
VMAT



Soft tissue sarcoma at other sites
Retroperitoneal sarcoma: 66Gy in 33#



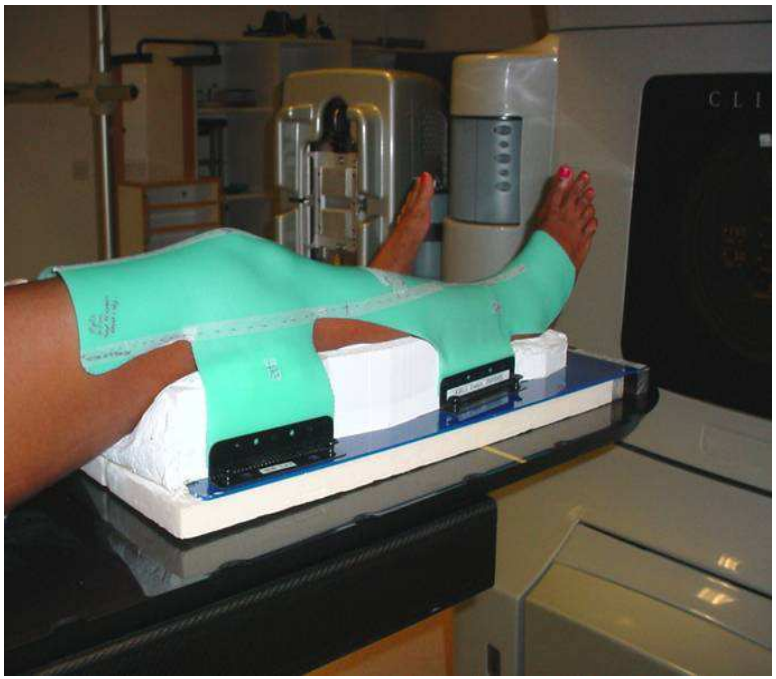




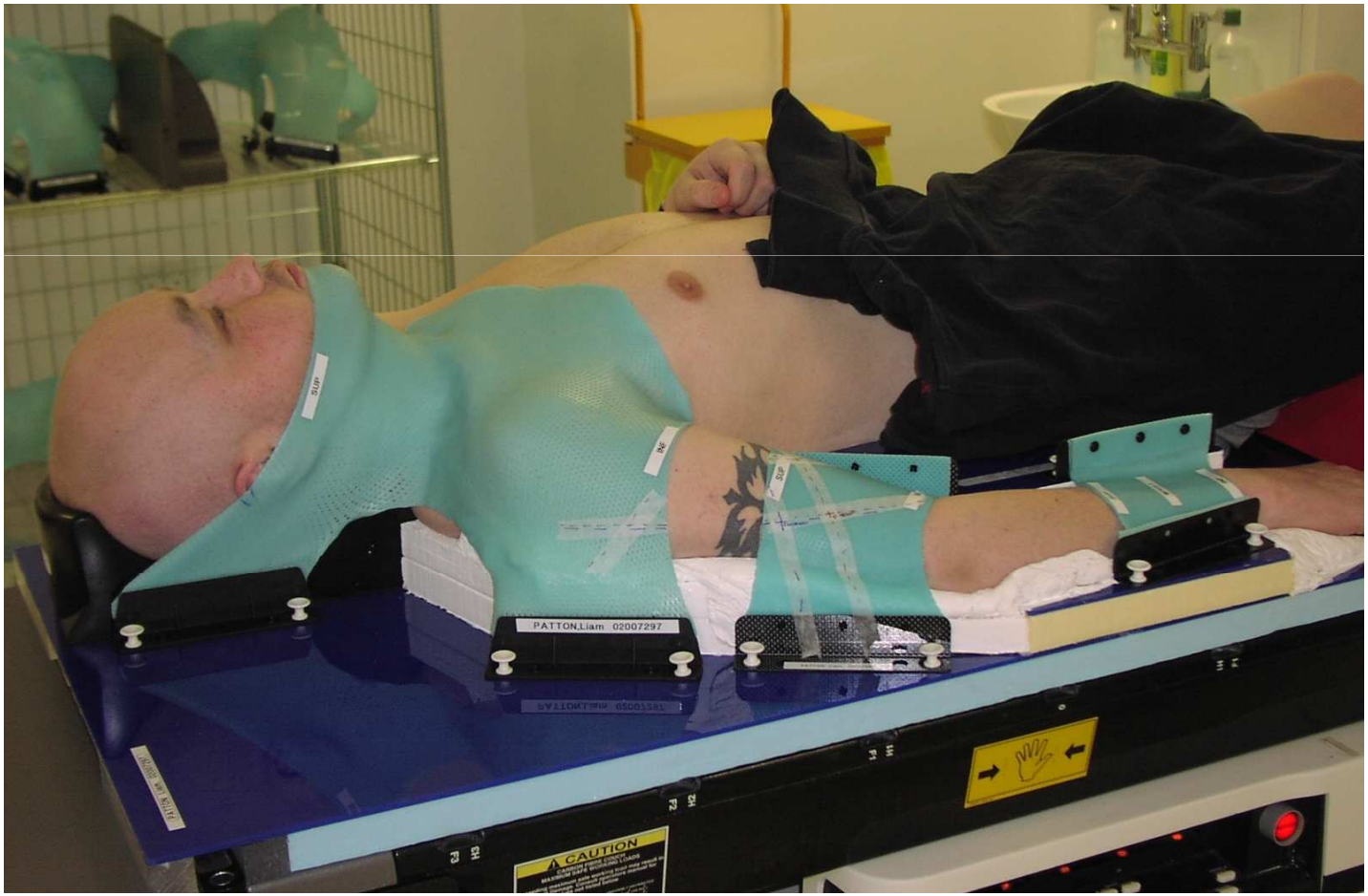
Immobilisation for limb sarcomas

- Reduce day to day variation in patient position (potential source of error)
- Impression of limb with patient in the optimum treatment position:
  - Customised foam mould fixed to baseboard
  - sheet of thermoplastic (Orfit) moulded around limb, clipped to baseboard
  - Baseboard is indexed and fixed onto the treatment couch

Immobilisation of lower limb



Immobilisation of upper limb



Evidence for using IMRT in soft tissue sarcomas

- Increasing use in soft tissue sarcomas
- Adoption by stealth
- Perceived superiority of IMRT
- Limited resource in some countries
- Little published, mostly retrospective data, in limb sarcomas

IMRT Retrospective evidence: 1

Local Control Comparison of Adjuvant Brachytherapy to Intensity-Modulated Radiotherapy in Primary High-Grade Sarcoma of the Extremity

Kaled M. Alektiar, MD[1]; Murray F. Brennan, MD[2]; and Samuel Singer, MD[2]

BACKGROUND: Based on results of a prospective randomized trial, brachytherapy (BRT) had been the preferred form of adjuvant radiotherapy for patients with high-grade extremity soft tissue sarcoma (STS) at our institution. In recent years, intensity-modulated radiotherapy IMRT had been increasingly used. This study compared local control by IMRT versus by BRT in primary-extremity STS. **METHODS:** Between January 1995 and December 2006, 134 adult patients with high-grade primary nonmetastatic STS of the extremity were treated at this institution with limb-sparing surgery and adjuvant radiotherapy (RT). Low-dose-rate BRT was given to 71 patients between January 1995 and November 2003 to a median dose of 45 Gray (Gy). IMRT was given between February 2002 and December 2006: preoperatively to 10 (50 Gy) and postoperatively to 53 (median, 63 Gy). Median follow-up was 46 months. **RESULTS:** Treatment groups were comparable in terms of gender, age, site, depth, histology (malignant fibrous histiocytoma vs other), and use of adjuvant chemotherapy. More IMRT patients had positive/close margins (<1 mm), large tumors (>10 cm), and bone or nerve stripping/resection ($P = 0.006$, 0.005, 0.02, and 0.002, respectively). Median follow-up was 46 months for IMRT and 47 months for BRT. Five-year local control was 92% (95% confidence interval [CI], 85-100) for IMRT versus 81% (95% CI, 71-90) for BRT, $P = 0.04$. On multivariate analysis, IMRT was the only predictor of improved local control, $P = 0.04$. **CONCLUSIONS:** Local control with IMRT was significantly better than BRT despite higher rates of adverse features for IMRT in this nonrandomized comparison. IMRT should be further examined as the treatment of choice for primary high-grade extremity sarcoma. *Cancer* 2011;117:3229–34. © *2011 American Cancer Society.*

KEYWORDS: IMRT, brachytherapy, sarcoma, extremity.

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IMRT Retrospective evidence: 1

- Retrospective comparison of 134 IMRT patients with 71 brachytherapy (BRT) patients
- 5 year local control 92% for IMRT vs 81% with BRT
- 'IMRT should be further examined as the treatment of choice for extremity sarcoma'
- But no toxicity data published

Alektiar et al, Cancer 2011; 117:3229-34

IMRT Retrospective evidence: 2

Comparison of Local Recurrence With Conventional and Intensity-Modulated Radiation Therapy for Primary Soft-Tissue Sarcomas of the Extremity

Michael R. Folkert, Samuel Singer, Murray F. Brennan, Deborah Kuk, Li-Xuan Qin, Wendy K. Kobayashi, Aimee M. Crago, and Kaled M. Alektiar

A B S T R A C T

Purpose
The use of intensity-modulated radiation therapy (IMRT) in the treatment of soft tissue sarcoı (STS) of the extremity is increasing, but no large-scale direct comparison has been report between conventional external-beam radiation therapy (EBRT) and IMRT.

Methods
Between January 1996 and December 2010, 319 consecutive adult patients with prim nonmetastatic extremity STS were treated with limb-sparing surgery and adjuvant radiothera (RT) at a single institution. Conventional EBRT was used in 154 patients and IMRT in 165 w similar dosing schedules. Median follow-up time for the cohort was 58 months.

Results
Treatment groups were comparable in terms of tumor location, histology, tumor size, depth, a use of chemotherapy. Patients treated with IMRT were older ($P = .08$), had more high-gra lesions ($P = .05$), close (< 1 mm) or positive margins ($P = .04$), preoperative radiation ($P < .00$ and nerve manipulation ($P = .04$). Median follow-up was 90 months for patients treated w conventional EBRT and 42 months for patients treated with IMRT. On multivariable analy adjusting for patient age and tumor size, IMRT retained significance as an independent predic of reduced LR (hazard ratio = 0.46; 95% CI, 0.24 to 0.89; $P = .02$).

Conclusion
Despite a preponderance of higher-risk features (especially close/positive margin) in the IM group, IMRT was associated with significantly reduced local recurrence compared with conv tional EBRT for primary STS of the extremity.

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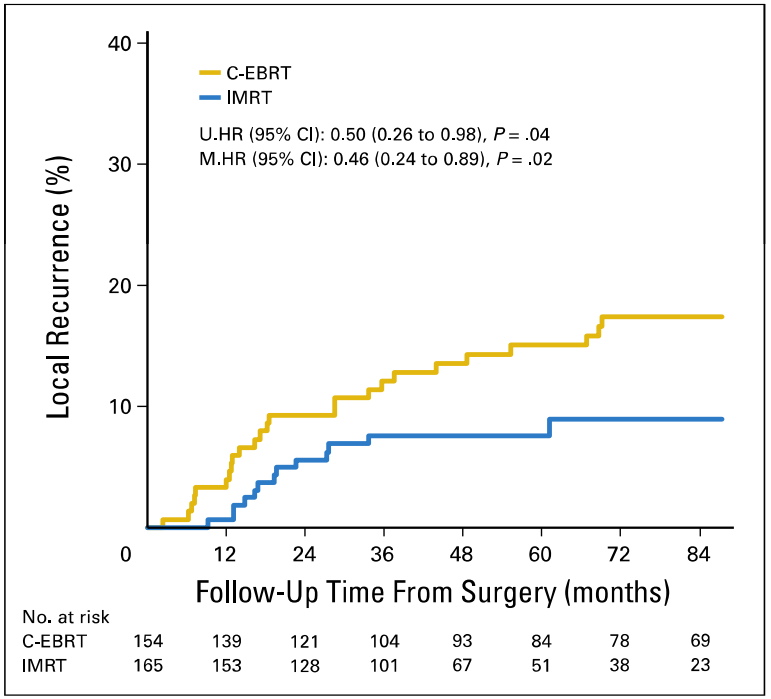
IMRT Retrospective evidence: 2

- 165 IMRT vs 154 3D-CRT patients
- Median time to local recurrence 18 months
- 5 year local recurrence rates:
  - IMRT 7.6%
  - 3D-CRT 15.1% p=0.05
- Acute grade 2 skin reaction less with IMRT (48.7% vs 31.5%)
- Chronic ≥ grade 2 toxicity

(fractures, joint stiffness, oedema) no difference



Folkert MR et al. Comparison of Local Recurrence With Conventional and Intensity-Modulated Radiation Therapy for Primary Soft-Tissue Sarcomas of the Extremity. J Clin Oncol 2014, 32:3236-3241

IMRT prospective clinical trials: 1

Phase 2 Study of Preoperative Image-Guided Intensity-Modulated Radiation Therapy to Reduce Wound and Combined Modality Morbidities in Lower Extremity Soft Tissue Sarcoma

Brian O'Sullivan, MD[1,2]; Anthony M. Griffin, MSc[3]; Colleen I. Dickie, MSc[1]; Michael B. Sharpe, PhD[1,2]; Peter W. M. Chung, MD[1,2]; Charles N. Catton, MD[1,2]; Peter C. Ferguson, MD[2,3]; Jay S. Wunder, MD[2,3]; Benjamin M. Deheshi, MD[2,3]; Lawrence M. White, MD[2,4]; Rita A. Kandel, MD[2,5]; David A. Jaffray, PhD[1,2]; and Robert S. Bell, MD[2,3]

BACKGROUND: This study sought to determine if preoperative image-guided intensity-modulated radiotherapy (IG-IMRT) can reduce morbidity, including wound complications, by minimizing dose to uninvolved tissues in adults with lower extremity soft tissue sarcoma. **METHODS:** The primary endpoint was the development of an acute wound complication (WC). IG-IMRT was used to conform volumes to avoid normal tissues (skin flaps for wound closure, bone, or other uninvolved soft tissues). From July 2005 to June 2009, 70 adults were enrolled; 59 were evaluable for the primary endpoint. Median tumor size was 9.5 cm; 55 tumors (93%) were high-grade and 58 (98%) were deep to fascia. **RESULTS:** Eighteen (30.5%) patients developed WCs. This was not statistically significantly different from the result of the National Cancer Institute of Canada SR2 trial ($P = .2$); however, primary closure technique was possible more often (55 of 59 patients [93.2%] versus 50 of 70 patients [71.4%]; $P = .002$), and secondary operations for WCs were somewhat reduced (6 of 18 patients [33%] versus 13 of 30 patients [43%]; $P = .55$). Moderate edema, skin, subcutaneous, and joint toxicity was present in 6 (11.1%), 1 (1.9%), 5 (9.3%), and 3 (5.6%) patients, respectively, but there were no bone fractures. Four local recurrences (6.8%, none near the flaps) occurred with median follow-up of 49 months. **CONCLUSIONS:** The 30.5% incidence of WCs was numerically lower than the 43% risk derived from the National Cancer Institute of Canada SR2 trial, but did not reach statistical significance. Preoperative IG-IMRT significantly diminished the need for tissue transfer. RT chronic morbidities and the need for subsequent secondary operations for WCs were lowered, although not significantly, whereas good limb function was maintained. ***Cancer* 2013;119:1878–84.** © *2013 American Cancer Society.*

KEYWORDS: sarcoma, image-guided radiotherapy, intensity-modulated radiotherapy, preoperative radiotherapy, phase 2 study.

IMRT prospective clinical trials: 1

- Phase II study to determine if preoperative IMRT is effective in minimizing the dose to skin and subcutaneous tissues used to close the resection site and reduce the risk of wound complications (PMH, Toronto)(1)
- Dose was reduced to the anticipated surgical flaps by using IMRT planning
- Primary endpoint: acute wound healing within 120 days
- Secondary endpoints: limb oedema and fibrosis, bone fracture, limb function, overall patient function
- 70 patients 2005 – 9
- Median 9.5cm, 93% G3, 98% deep to fascia

(1) O'Sullivan B, Griffin AM, Dickie CI, et al. Phase 2 study of preoperative image-guided intensity-modulated radiation therapy to reduce wound and combined modality morbidities in lower extremity soft tissue sarcoma. *Cancer* 2013; **119**(10): 1878-84.

IMRT prospective clinical trials: 1

- Wound complications in 30.5% (vs 43% in SR2 study) (p=0.2, NS)(1)
- Commonest sites: buttock, adductor and posterior compartments of thigh
- Reduced need for tissue transfer for closure
- Reduced second surgery for wound complications 33% vs 43% (SR2)
- Trend for increased dose to flap and increased volume of flap receiving 50Gy in patients with wound complications
- Negative result thought to be due to compromising of flap sparing in order to ensure adequate PTV coverage
- Grade 2+ fibrosis at 2 years 9.3% vs 31.5% (SR2)
- Moderate joint stiffness 5.4% vs 17.8% (SR2)

(1) O'Sullivan B, Griffin AM, Dickie CI, et al. Phase 2 study of preoperative image-guided intensity-modulated radiation therapy to reduce wound and combined modality morbidities in lower extremity soft tissue sarcoma. *Cancer* 2013; **119**(10): 1878-84.

IMRT prospective clinical trials: 2

Wang et al Journal of Clinical Oncology 2015 Jul 10;33(20):2231-8. doi: 10.1200/JCO.2014.58.5828. Epub 2015 Feb 9.

IMRT prospective clinical trials 2

- Preoperative IGRT 50Gy in 25 fractions prior to surgery
- IGRT used in order to reduce target volumes
- Primary endpoint: 15% absolute improvement in rate of grade ≥2 radiation morbidity (subcutaneous tissue fibrosis, joint stiffness, oedema) at 2 years, from 37% to 22%
- 79 patients (2008 – 2010)
- Could receive IMRT (74.7%) or 3DCRT (25.3%)
- Results:
  - 5/74 (7%) local recurrences (all in field)
  - 57 patients assessed for late toxicity – 10.5% experienced at least one grade ≥2 toxicity (vs 37% in SR2 trial) $p<0.001$
- Conclusion: The significant reduction in late toxicities, and absence of marginal recurrences suggest that the reduced volumes used were appropriate

Wang et al Journal of Clinical Oncology 2015 Jul 10;33(20):2231-8. doi: 10.1200/JCO.2014.58.5828. Epub 2015 Feb 9.

IMRT prospective clinical trials: 3

IMRiS: Intensity Modulated Radiotherapy in Sarcoma

- UK wide multi-centre trial opened in March 2016
- Prospective phase II cohort study
- Questions:
  - How should IMRT be incorporated into current practice?
  - What is the incidence of toxicity related to IMRT?
  - Does IMRT improve function and quality of life?
- Three cohorts:
  - Cohort 1: limb soft tissue sarcoma
  - Cohort 2: Ewing's sarcoma pelvis and spine
  - Cohort 3: Primary non-Ewing's sarcomas of pelvis and spine (osteosarcoma, chondrosarcoma, chordoma, spindle cell sarcoma of bone)

IMRiS: Intensity Modulated Radiotherapy in Sarcoma

- Cohort 1: Limb soft tissue sarcoma (110 patients)
  - Does use of IMRT reduce late toxicity?
  - Primary endpoint: rate of grade 2+ late soft tissue fibrosis at 2 years following radiotherapy (aim to reduce from 30% to 20%)
  - Secondary endpoints: acute and late toxicity, patient reported limb function and quality of life, wound complications, time to local recurrence

IMRiS: Intensity Modulated Radiotherapy in Sarcoma

- Cohorts 2 and 3: Pelvic/spinal bone sarcomas (33 patients)
  - Does the use of IMRT enable achievement of a radiotherapy treatment plan that delivers the optimal dose while keeping within normal tissue tolerances?
  - Primary endpoint: The proportion of patients where the recommended optimal radiotherapy dose can be achieved with IMRT
    - Cohort 2 (Ewing's): Increase proportion of patients receiving 95% of optimal dose from 70% to 90%
    - Cohort 3 (non-Ewing's): Increase proportion of patients receiving 95% of optimal dose from 0% to 50%
  - Secondary endpoints: Toxicity, response, quality of life, time to local recurrence/disease progression, survival

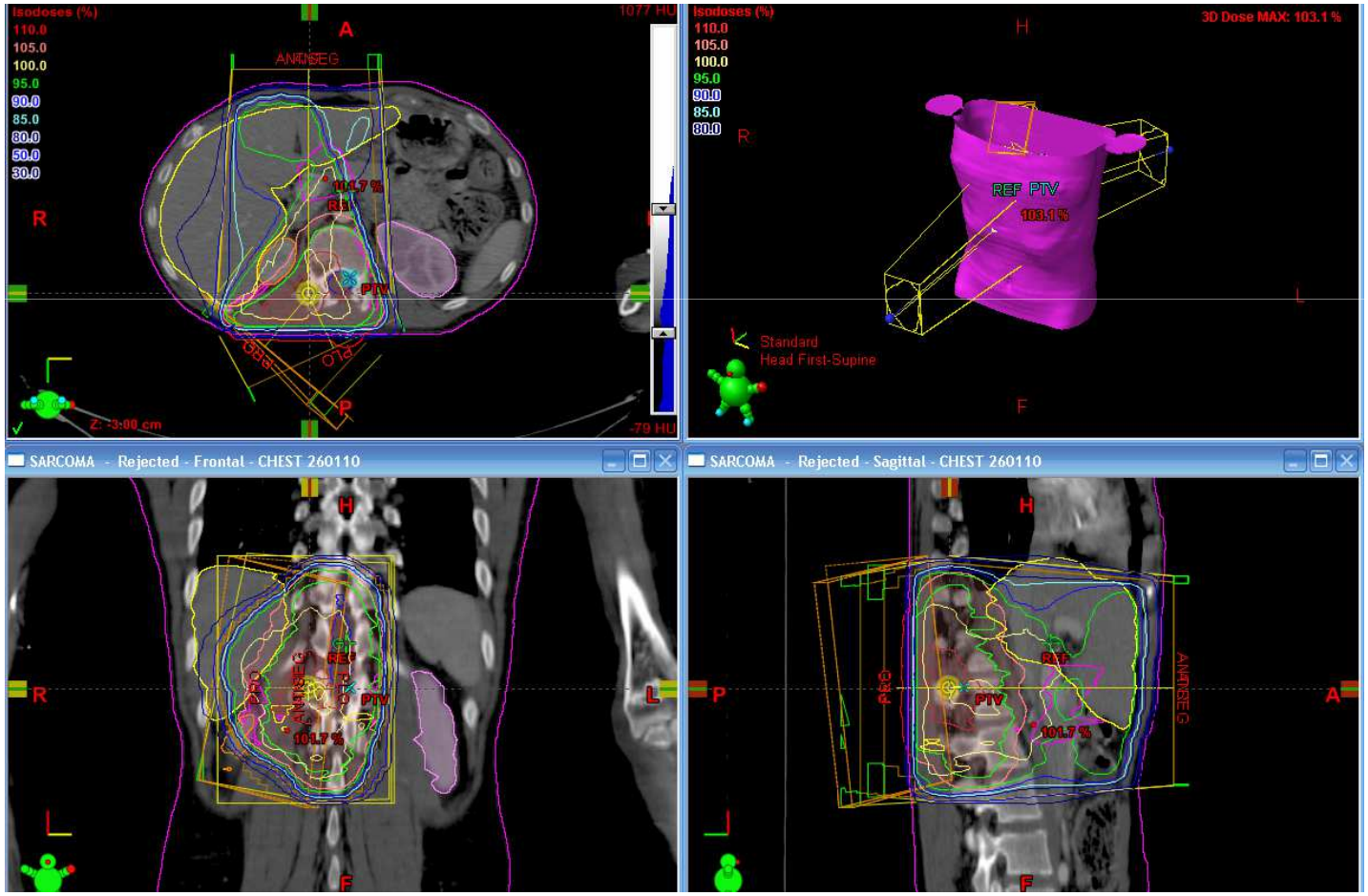
IMRT in bone sarcomas

IMRT in Ewing's Sarcoma

- IMRT shown to be superior to 3D-CRT in two small planning studies (5 patients)
- IMRT used in 43% of cases of a series of 33 spinal and pelvic tumours [1]
- Retrospective review at UCH of 24 cases of Ewing's sarcoma of pelvis/spine treated with 3D-CRT showed that the optimal radiotherapy dose could only be safely achieved in 70% (unpublished data)
- Increasing use of PBRT means that further data on IMRT unlikely

[1]La TH et al. Radiation therapy for Ewing's sarcoma: Results from Memorial Sloan Kettering in the modern era. Int J Rad Oncol Biol Phys, 2006:64:544-550.

Ewing's sarcoma T12 spine: 49.5Gy in 33#



Comparative planning study: IMRT vs PBT in pelvic Ewing Sarcoma

- Question: can PBT spare normal tissues (in particular uterus and ovaries) better than IMRT?
- Patients
  - 10 female patients (median age 20)
  - Ewing sarcoma of pelvic bones
- Dose: 54Gy in 30#
- Technique
  - VMAT
  - Intensity modulated PBT (pencil beam scattering)

Comparative planning study: IMRT vs PBT in pelvic Ewing Sarcoma

- **VMAT**
  - Good bowel, rectum and bladder sparing
  - Femoral head within tolerance
  - Spare one ovary to mean dose 4.3Gy
  - Uterus mean dose <10Gy in 80% of cases
  - Low dose bath

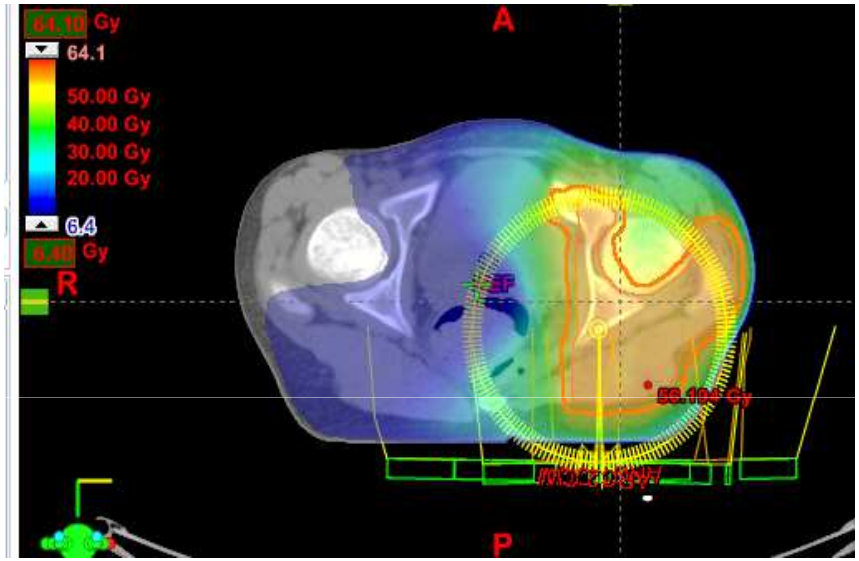
- **IMPT**
  - Superior sparing of:
    - Femoral head
    - Ovaries
    - Uterus
    - No low dose bath but high entry dose

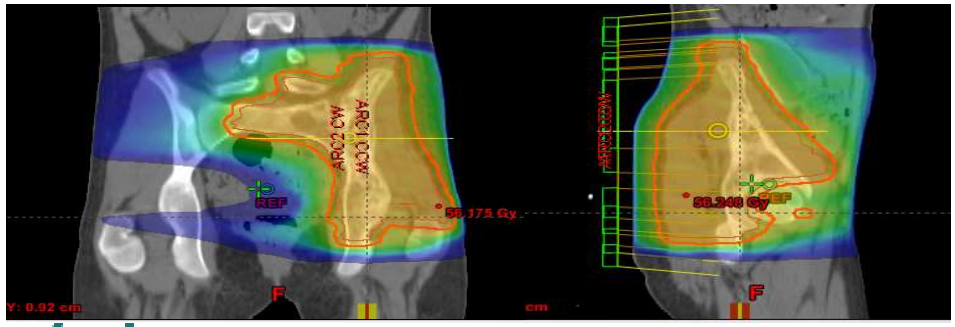
the london
sarcoma service

University College London Hospitals NHS
NHS Foundation Trust

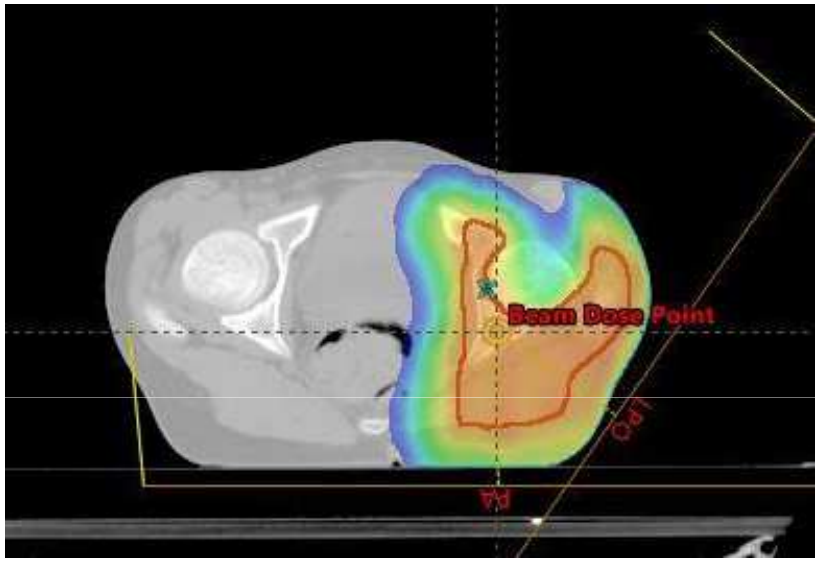
Case 1: Iliac bone

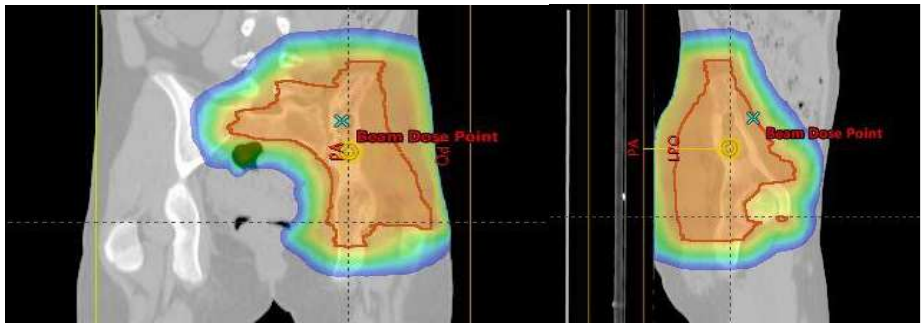
VMAT





IMPT

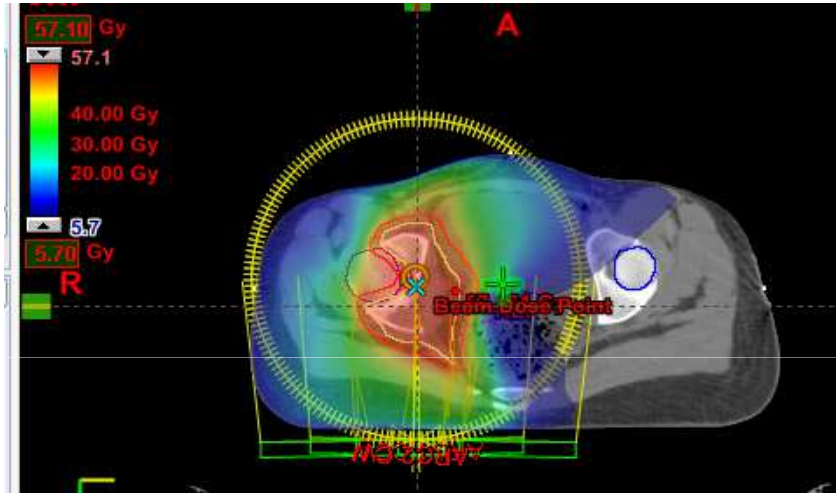


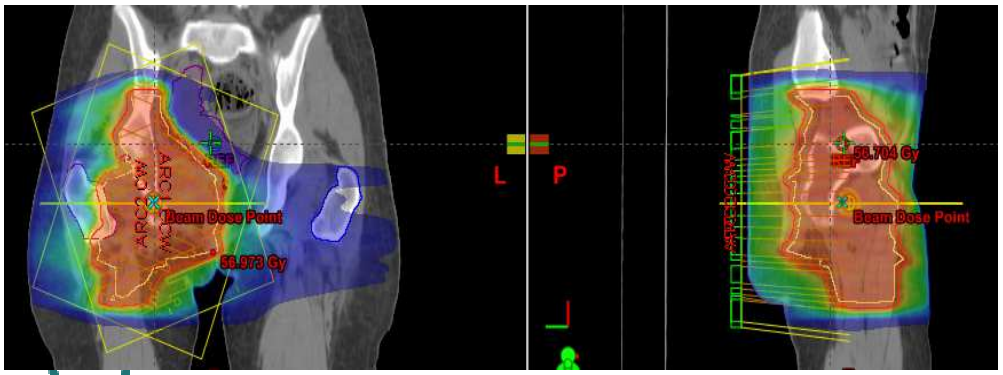


Le Grange, Amos, Bodey, Seddon, UCLH 2015

Case 2: ischium

VMAT





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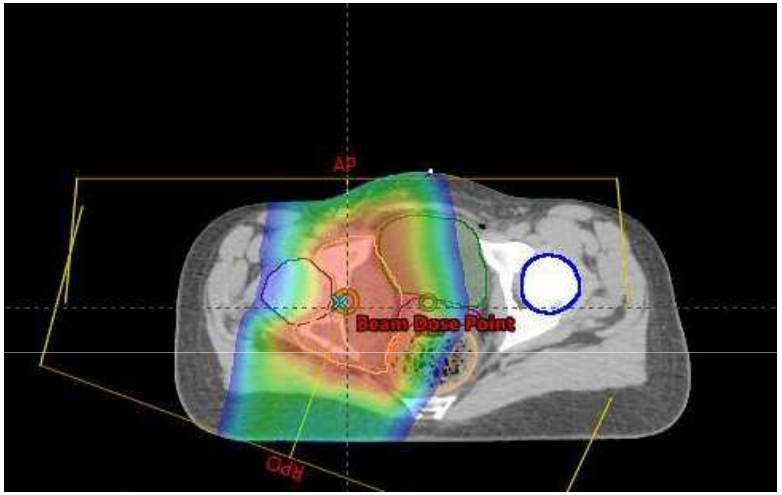
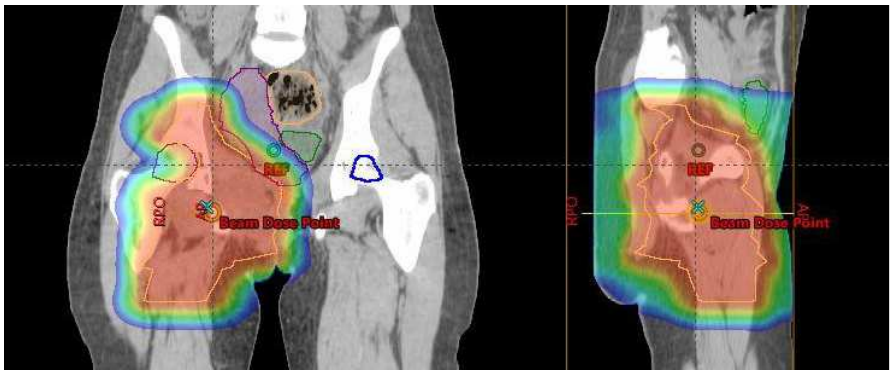
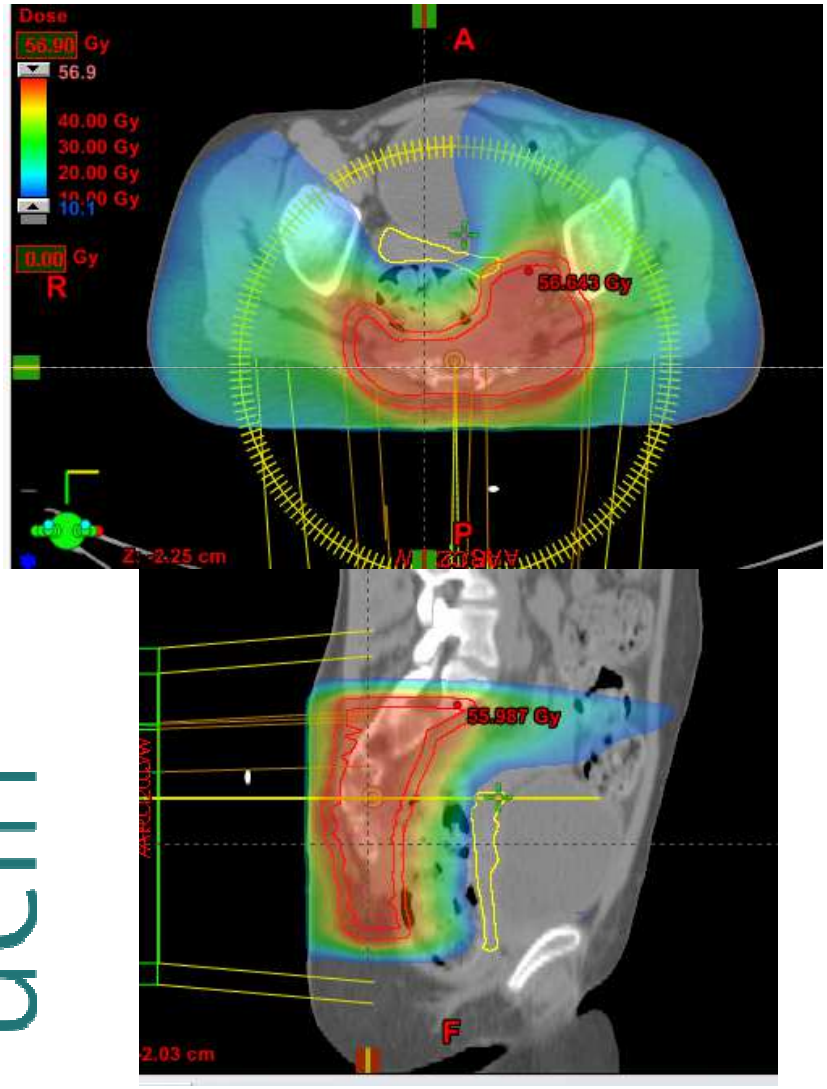




Le Grange, Amos, Bodey, Seddon, UCLH 2015

Case 4: sacrum – uterus sparing

VMAT



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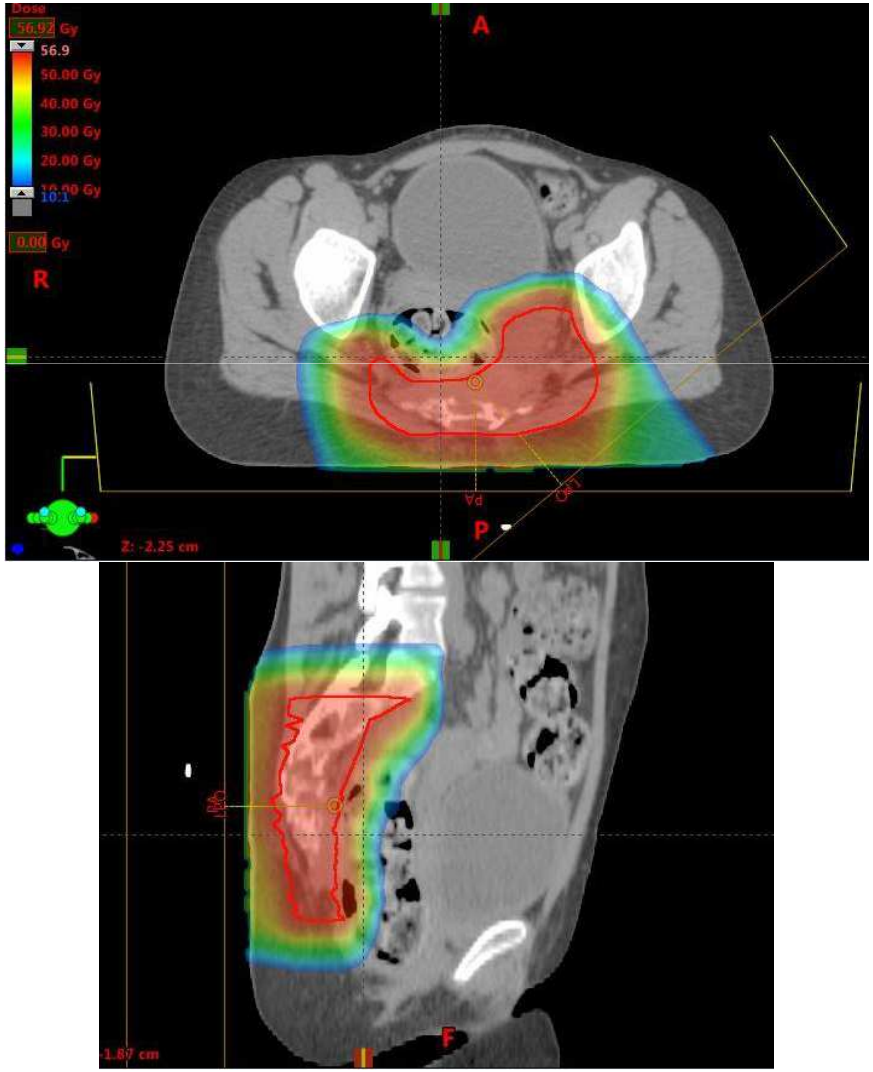


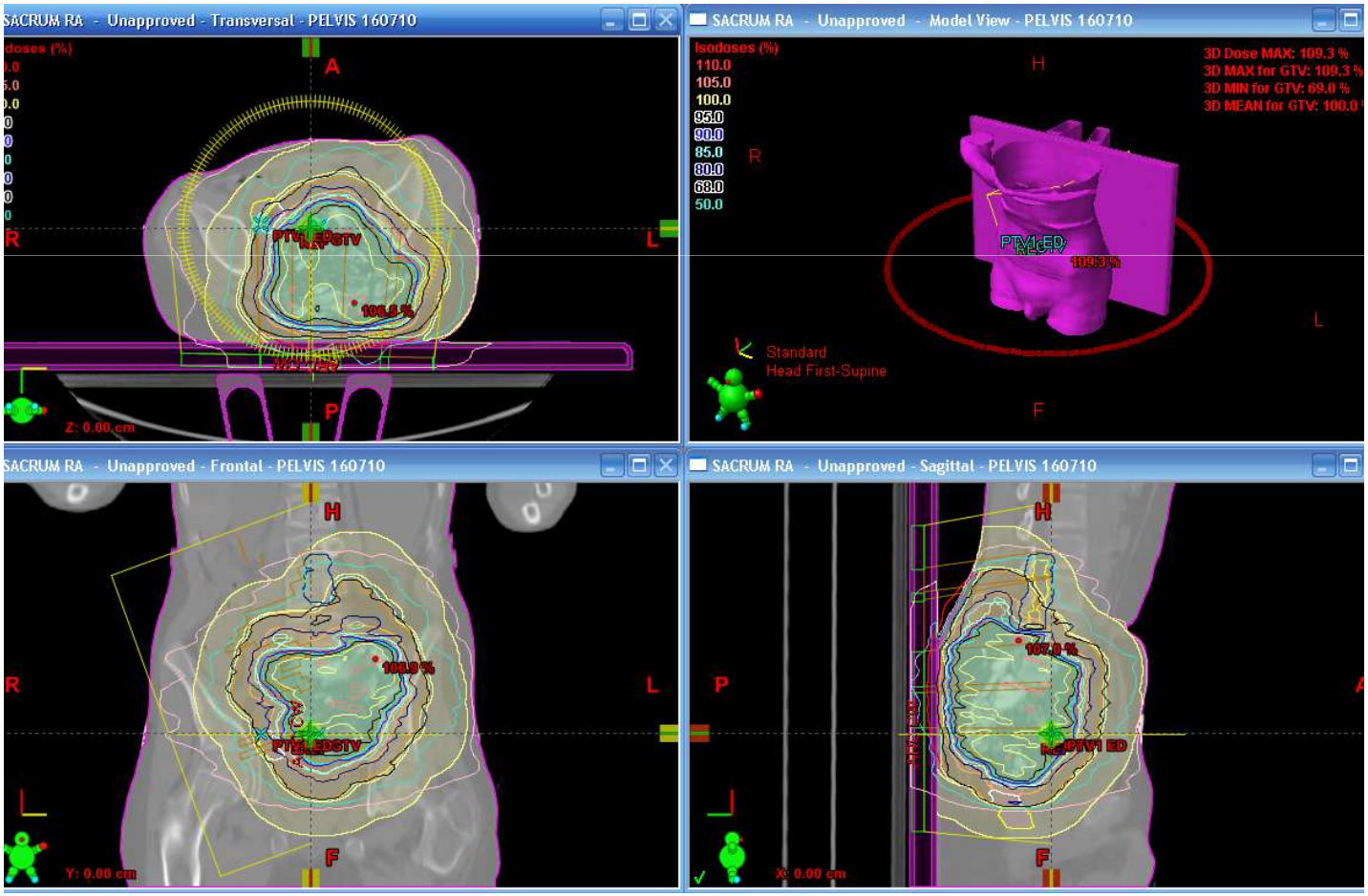
uclh

IMRT in other bone sarcomas and chordoma

- More radio-resistant tumours
- High doses of radiotherapy required ≥ 66 – 70+Gy
- Local control rates for RT alone around 40% at 5 years (protons +/- photons) [1]
- Increasingly, move towards using protons +/- photons, or carbon ions
- Inoperable tumours not approved for PBT in UK

[1] Delaney T et al. Radiotherapy for local control of osteosarcoma. Int J Rad Oncol Biol Phys. 61:492 – 498, 2005

Osteosarcoma pelvis: PTV1 50Gy in 28#, PTV2 70Gy in 28#



Conclusions

- IMRT offers opportunities across different sarcomas:
  - Soft tissue sarcomas – improved conformality to PTV, reduced dose to normal tissues, sparing of normal structures (e.g. bone), improved late toxicity?
  - Bone sarcomas:
    - Delivery of optimal dose to PTV with normal tissue sparing (Ewing's sarcoma)
    - Dose escalation for more radioresistant tumours (primary bone sarcomas, chondrosarcoma, chordoma)
    - PBT/carbon ions will offer advantage for some patients, but not easily accessible to all, so IMRT remains important

Thank you

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Modena
Policlinico

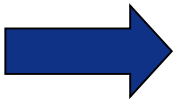
IMRT - a physician‘s view

(As if physician‘s, physicists and RTs should have different views of the world…..)

One's own experience has the advantage of absolute certainty - *Schopenhauer*

No man's knowledge (here) can go beyond his own experience - *Locke*

Stupid is as stupid does - *Gump*



Some VERY SUBJECTIVE COMMENTARIES!!

Disclosure

Research and Training Agreement, Expert Testimony and Travel Grants with Elekta/IBA/C-Rad

Board Member of C-Rad

Stock holdings Imuc

Drivers of IMRT

Thing‘s weren‘t perfect prior to IMRT

Need to avoid Toxicity

Conveniece / Economical Factors / Simplification of established paradigms

Evolution of Technology / IGRT / Online Adaptation

Chronification of Disease/Oligometastases

Expanding Indications for SBRT (e.g. Prostate with the need for dose shaping)

Potentially a new Paradigm in Combination with Immunotherapy

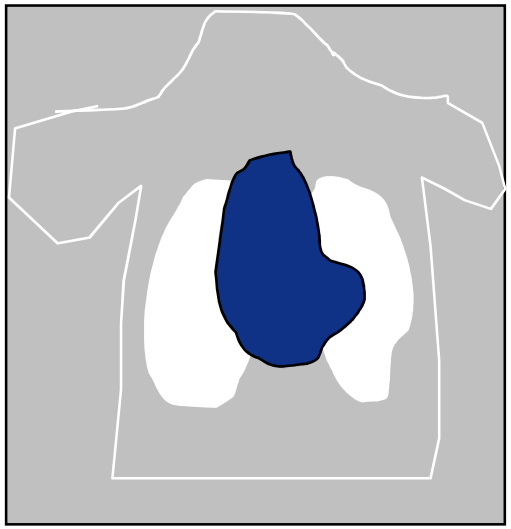
Technical Basis

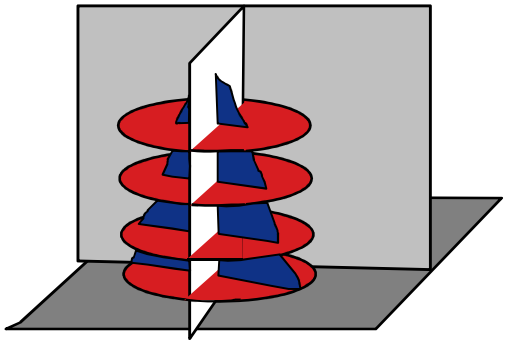
Radiotherapy Treatment Planning

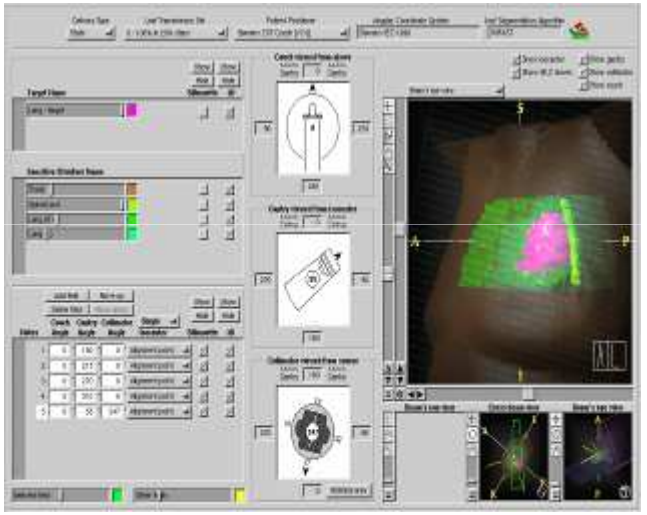
Simulator

2-D

3-D

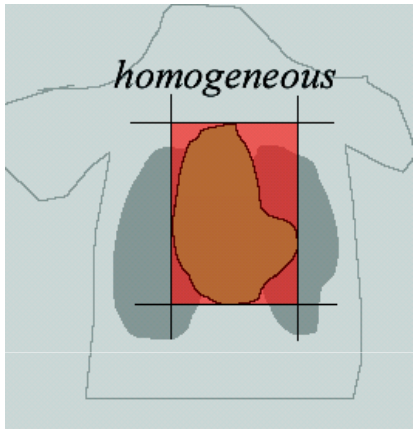


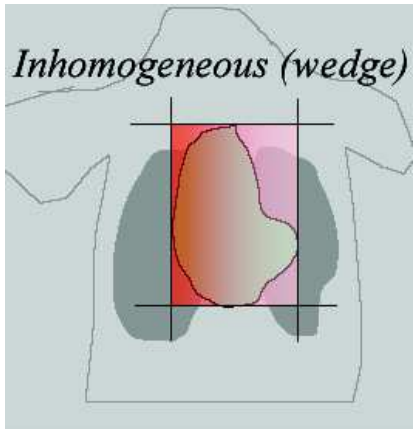




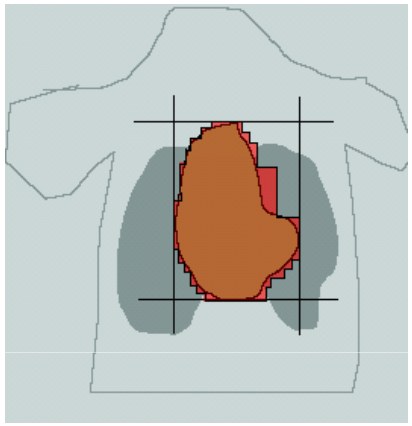
Treatment Delivery

Conventional

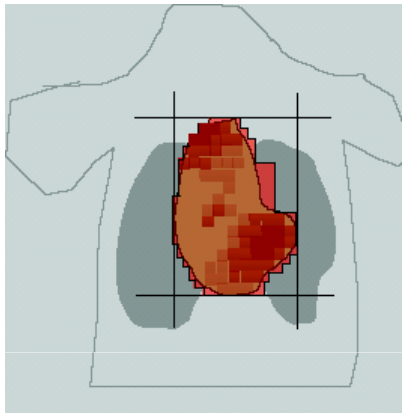




Conformal



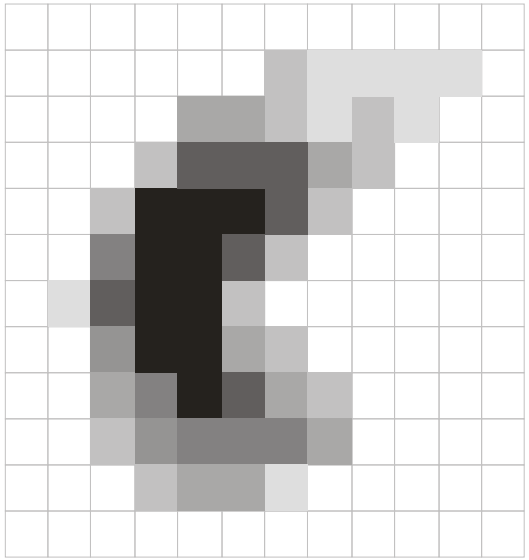
IMRT

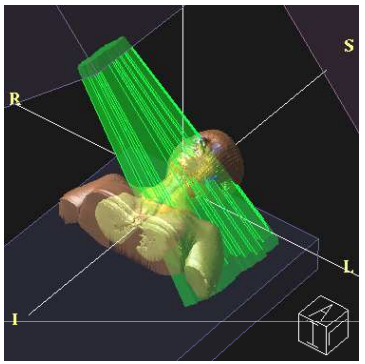


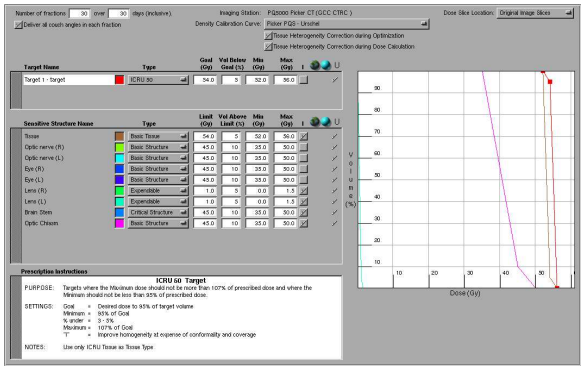
Inverse Planning

Inverse Planning (IP)

User enters port/arc layout, and treatment objectives, computer optimizes beam modulation







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Requirements

1. IMRT-Capable Delivery System
2. Inverse Planning System
3. Record & Verify / Console Module
4. QA Protocols
5. Training / On-Site Consultations

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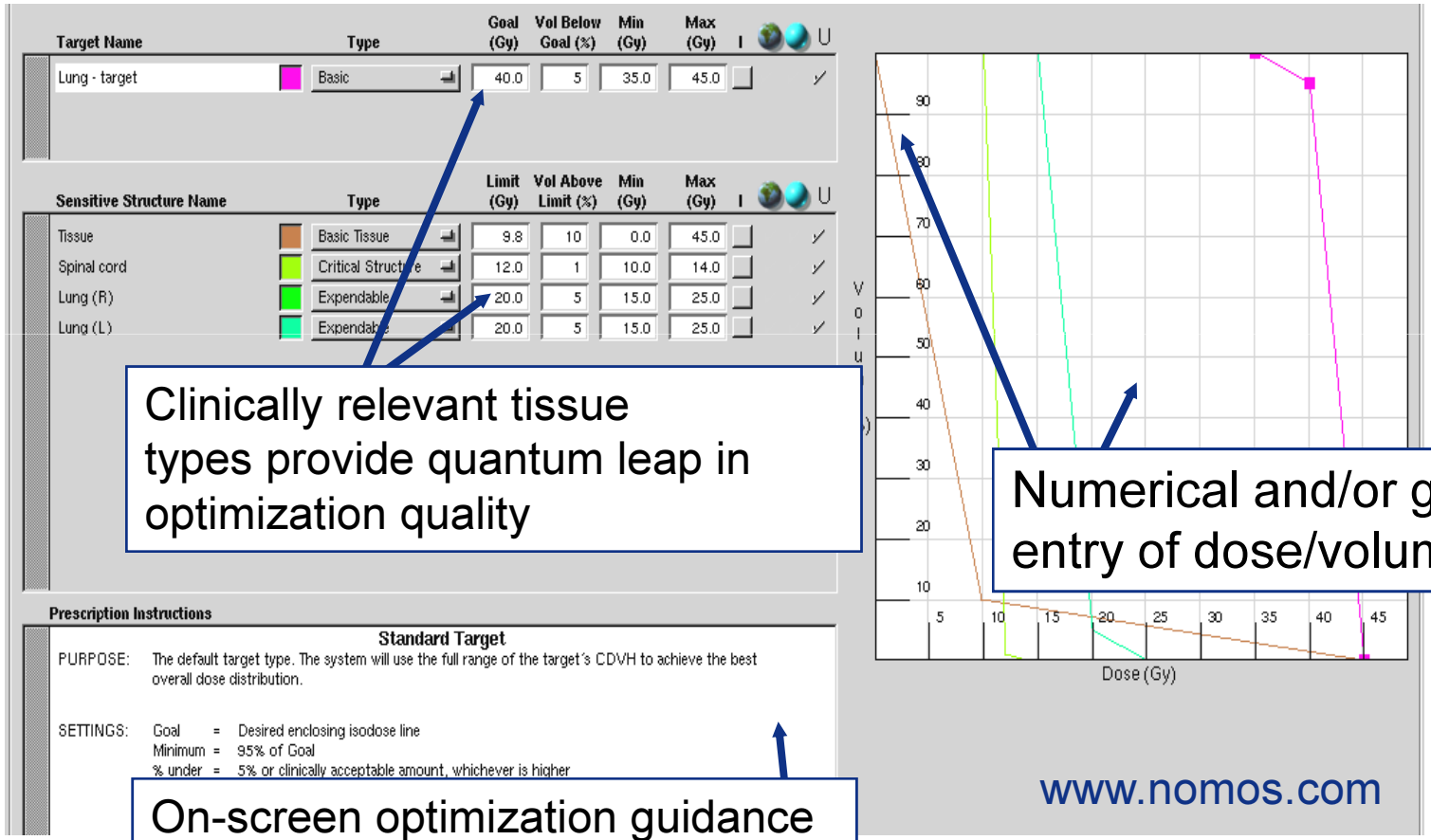
Prescription

The Key to Inverse Planning is a prescription tool that easily and efficiently captures the physician's most critical clinical judgements



Everything works fine up to here

But:

How much time you spend everyday planning?

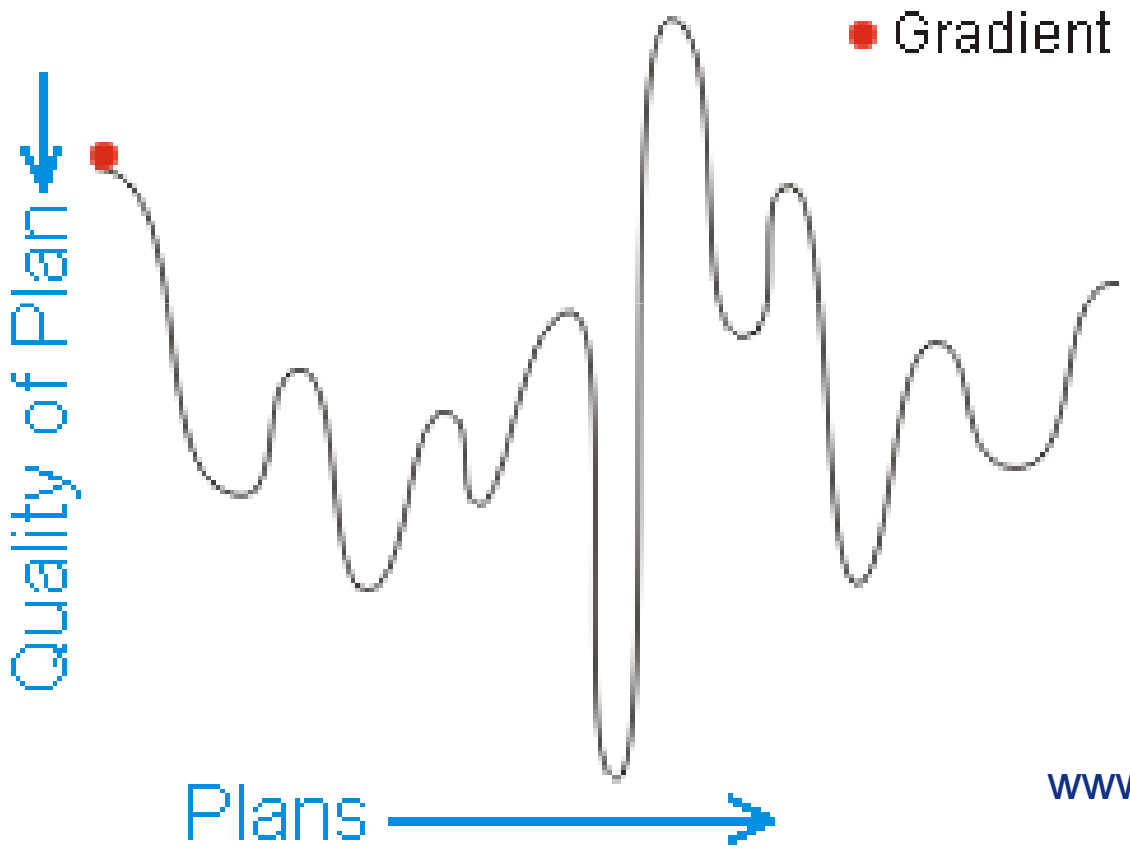
How many of you are using autoplanning?

Optimization

A “cost function” trades off different portions of the CDVH curves in order to arrive at a composite “**Optimal Result**”

Optimization Strategies

Gradient vs. Stochastic



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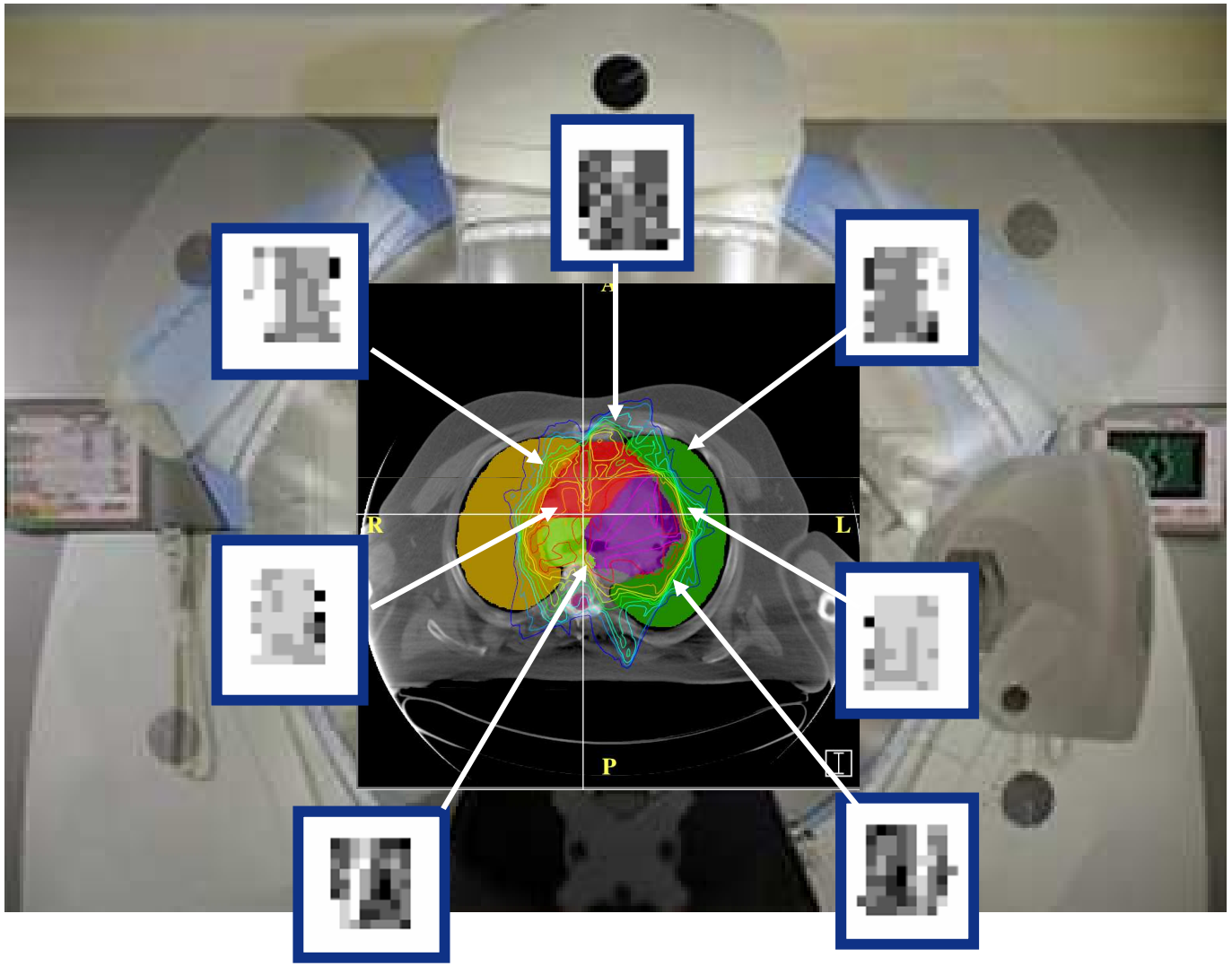
IMRT-Capable Delivery System



Basic treatment techniques

K. Bratengeier

In: Kiricuta, Definition of Target Volumes, 2001

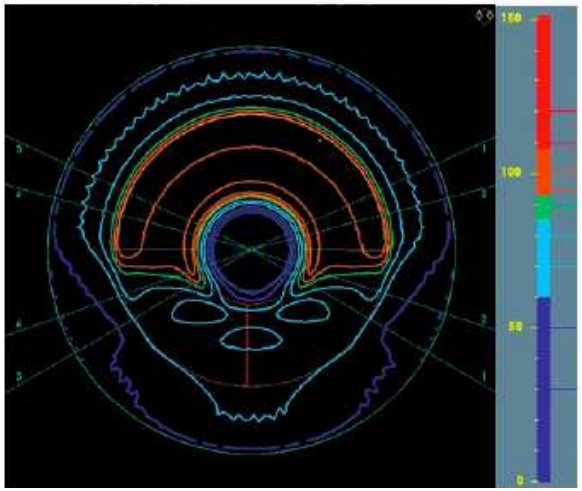
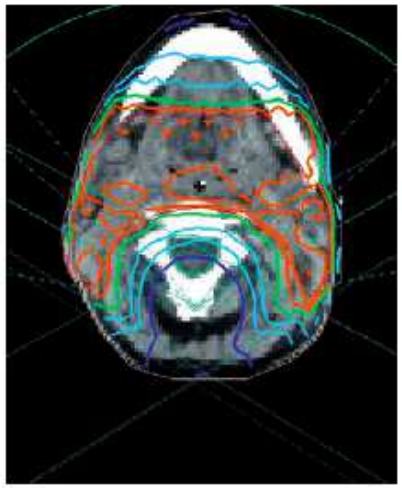
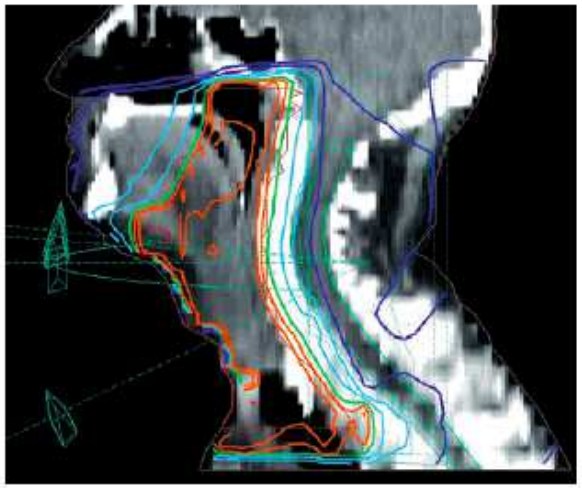


Figure 8. *Two-step IMAT in the case of a patient with Hypopharynx-Carcinoma. Left: transversal plane. Right: sagittal plane; 30%, 50%, 70%, 80%, 90% and 95% isodoses are shown in the same colors as labelled in figure 7.*





2 “Slices” Treated per Rotation

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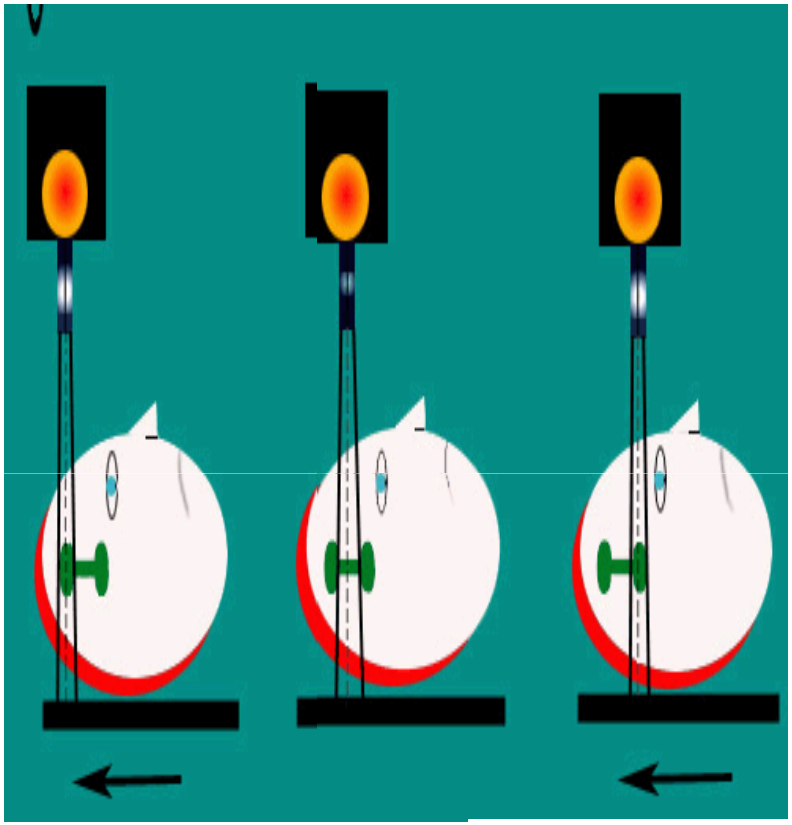


Couch Indexing

Ok, everything is almost perfect up to this point

But:

How much time you spend everyday contouring?

How many of you are using autocontouring?

Clinical Application of IMRT

Most important indications and treatment philosophy

1. **Head and Neck Cancer**
   CNS

   Paranasal Sinus Tumors / Integrated Boost
   (Better Tumor coverage and shortening of overall treatment time)

   NPC and other ENT Tumors
   (Parotid sparing when possible, better tumor coverage for NPC)

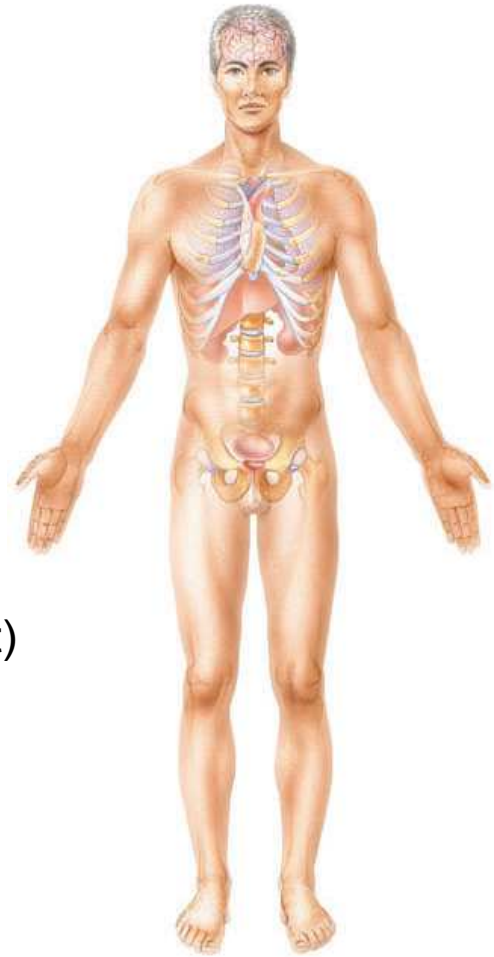
2. **Prostate / Integrated boost**
   (Potentially hypofractionation)

3. **Gastric cancer**
   (Better kidney sparing while treating the whole of the target)

4. **Breast Cancer**

5. **Lung Cancer**

6. **Metastases**



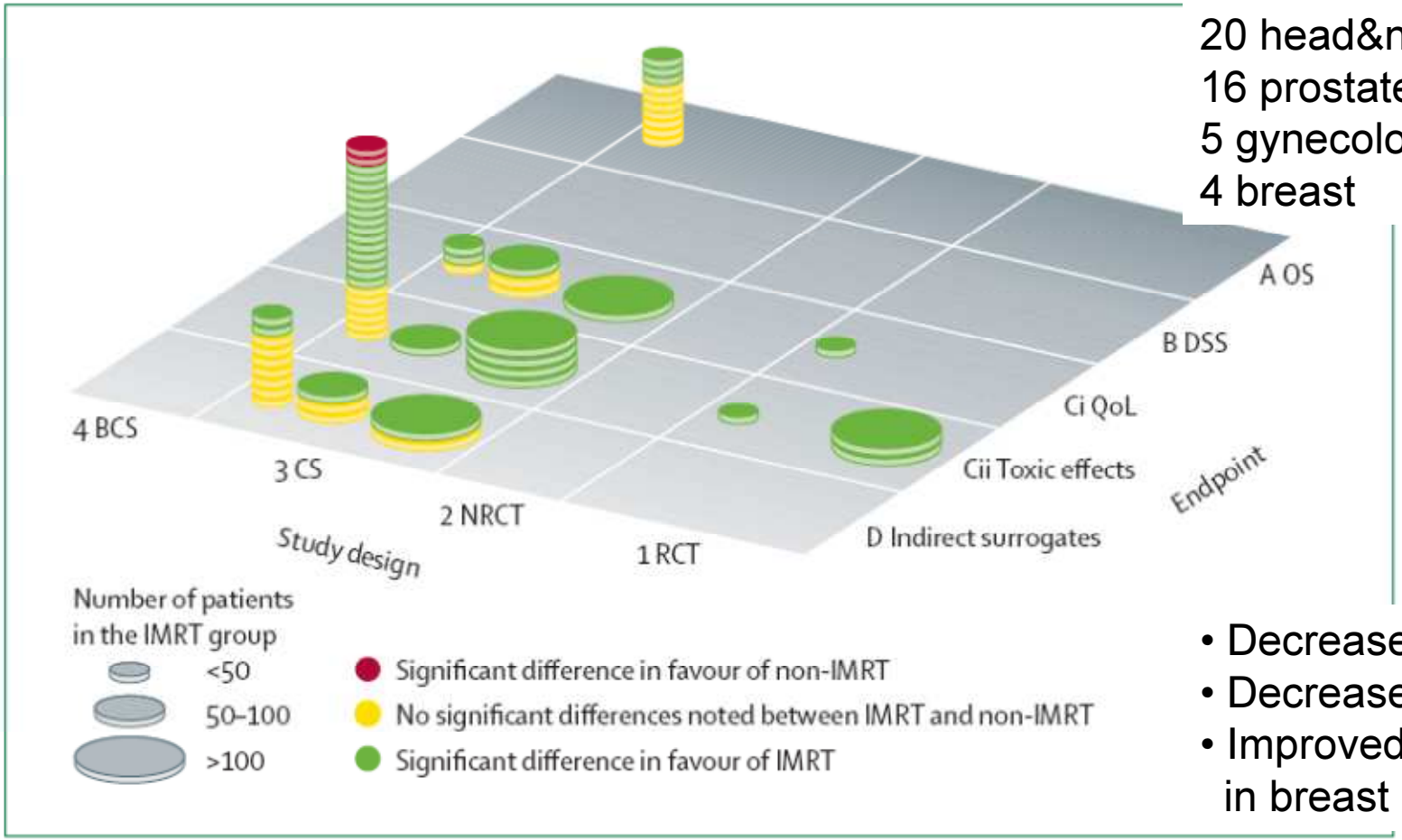
Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies

Liv Veldeman, Indira Madani, Frank Hulstaert, Gert De Meerleer, Marc Mareel, Wilfried De Neve

Lancet Oncol 2008; 9: 367–375

56 studies/reports

20 head&neck	3 lung
16 prostate	5 GI
5 gynecological	3 CNS
4 breast	



- Decreased xerostomia
- Decreased rectal toxicity
- Improved cosmesis in breast cancer

Figure 3: **Evaluation tool for relevance of clinical statements reported in 56 studies of IMRT**
BCS=best case series. CS=case series. NRCT=non-randomised controlled trial. RCT=randomised controlled trial. OS=overall survival. DSS=disease-specific survival. QoL=quality of life.

IMRT clinical outcome

Factors influencing the rational use of IMRT for head-and-neck cancer

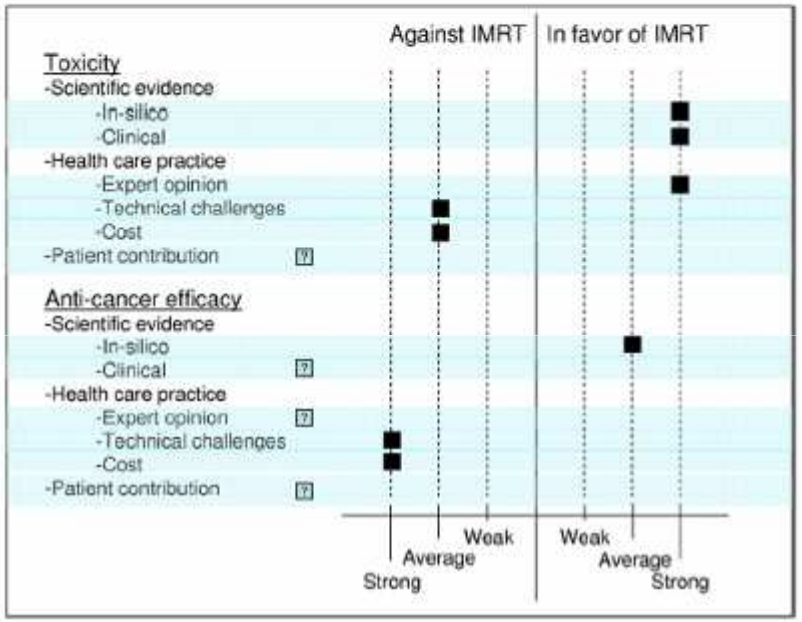


Figure 1 Factors in favor or against IMRT are represented by a rectangle on the right or on the left of the vertical solid line, respectively. A question mark inside a rectangle indicates too much uncertainty for using the factor in the graph.

Factors influencing the rational use of IMRT for whole breast irradiation

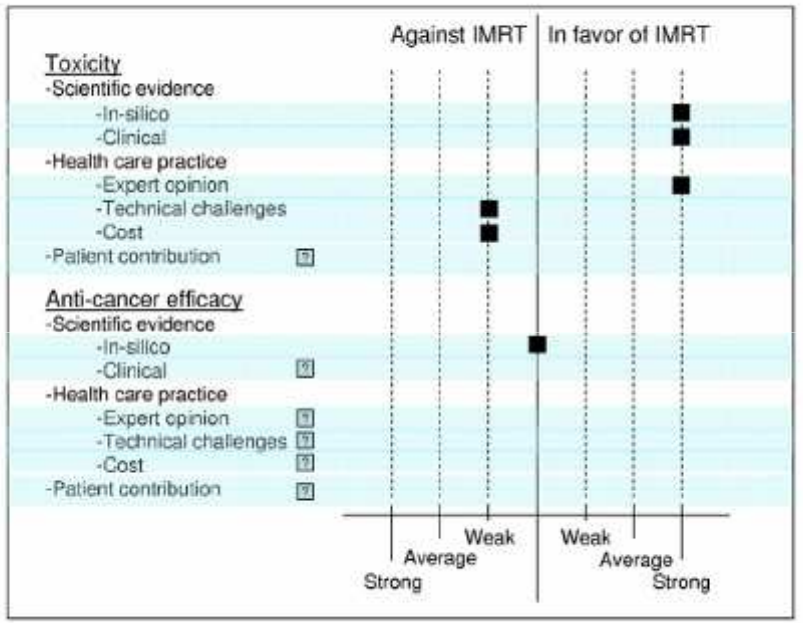
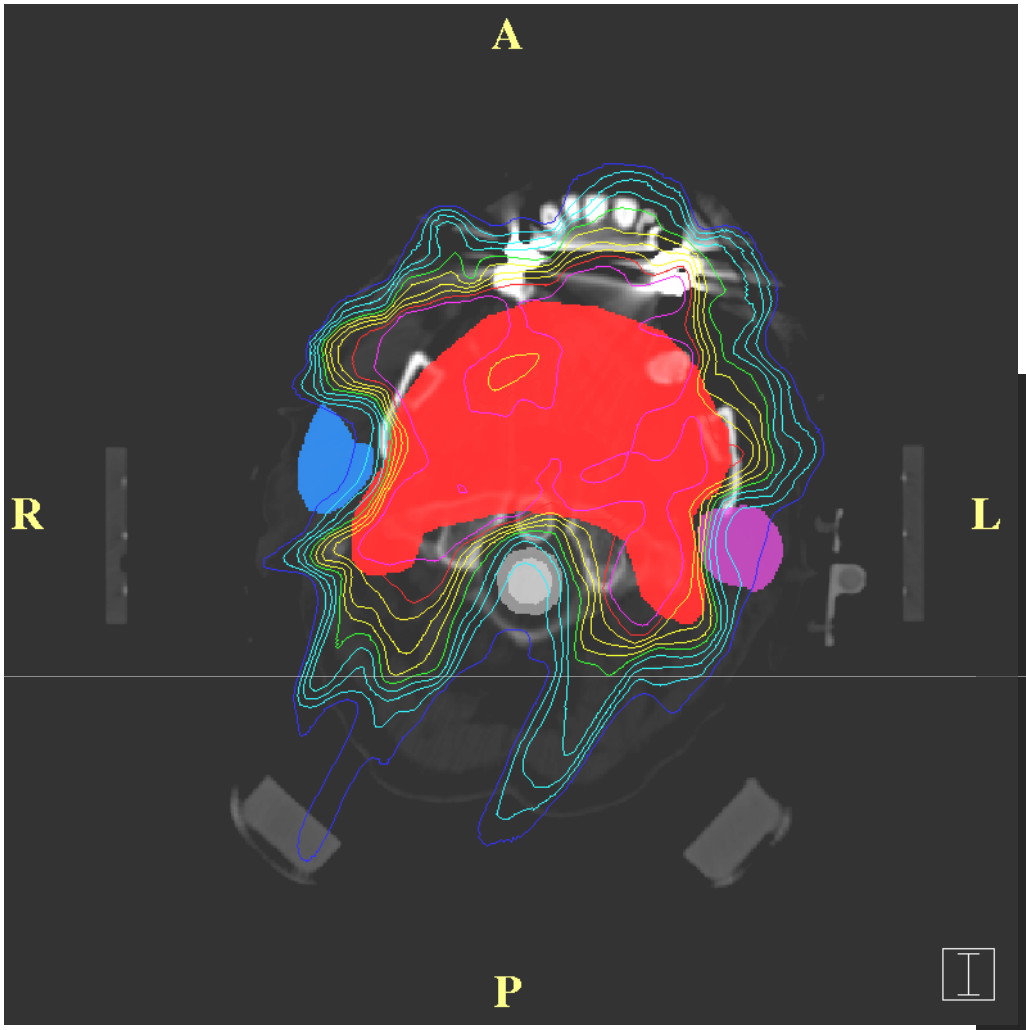


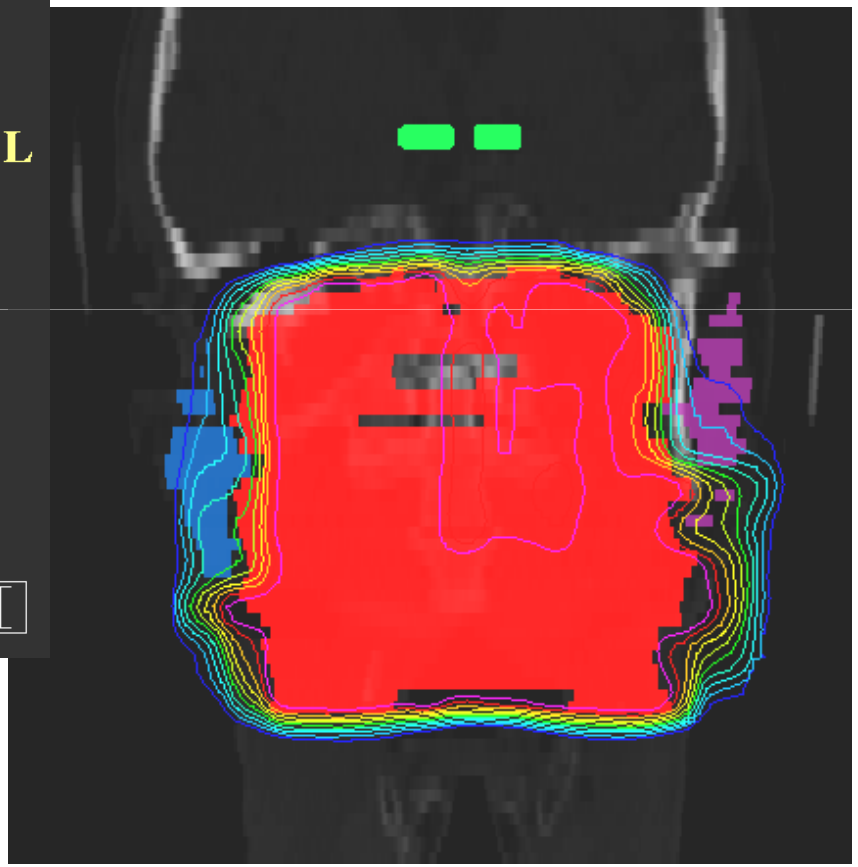
Figure 2 Factors in favor or against IMRT are represented by a rectangle on the right or on the left of the vertical solid line, respectively. A question mark inside a rectangle indicates too much uncertainty for using the factor in the graph.

De Neve et al. Sem Rad Onc, 2012

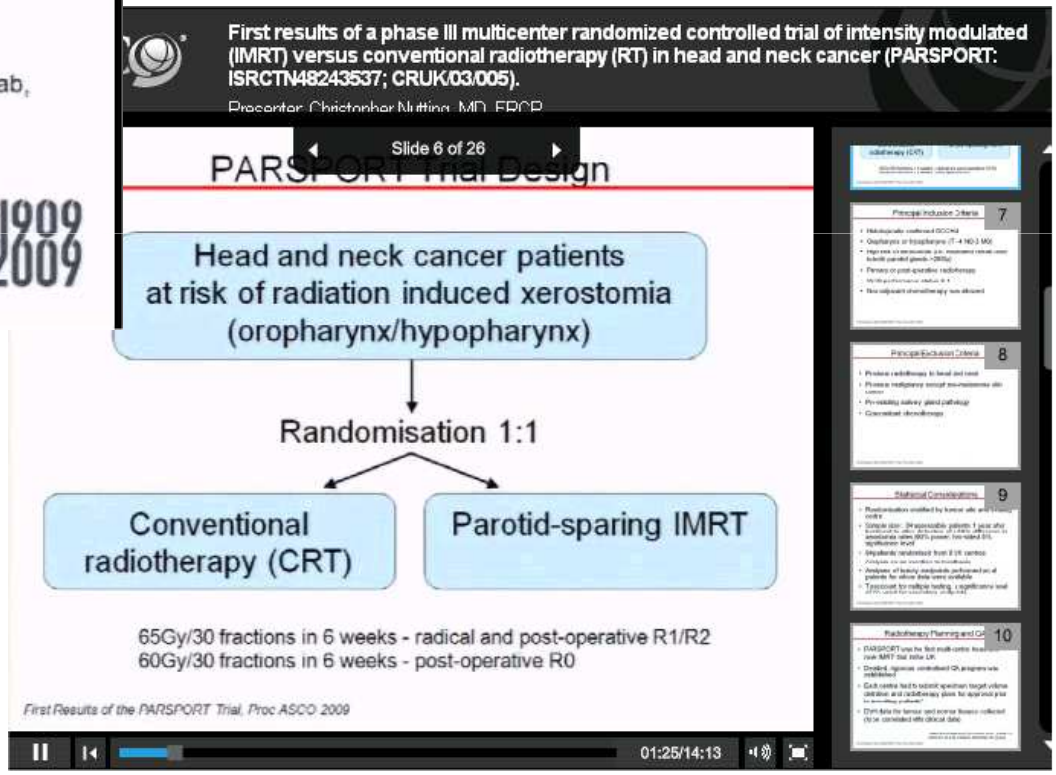
Avoiding unnecessary toxicity

Oropharnynx (Tongue) T3N0 Bilateral Parotid Sparing






First results of a phase III multicenter randomized controlled trial
(IMRT) versus conventional radiotherapy (RT) in head and neck
ISRCTN48243537; CRUK/03/005).
Slide 1 of 26
PARSPORT
First Results of a Phase III Multi-Centre Randomised Controlled Trial of Intensity Modulated vs Conventional Radiotherapy in Head and Neck Cancer: PARSPORT (CRUK/03/005)
C. Nutting, R. A'Hern, M. S. Rogers, M. A. Sydenham, F. Adab, K. Harrington, S. Jefferies, C. Scrase, B. K. Yap, E. Hall, on behalf of the PARSPORT Trial Management Group
CANCER RESEARCH UK
ICR
The institute
1909
2009


First results of a phase III multicenter randomized controlled trial of intensity modulated (IMRT) versus conventional radiotherapy (RT) in head and neck cancer (PARSPORT: ISRCTN48243537; CRUK/03/005).
Slide 6 of 26
PARSPORT Trial Design
Head and neck cancer patients at risk of radiation induced xerostomia (oropharynx/hypopharynx)
Randomisation 1:1
Conventional radiotherapy (CRT)
Parotid-sparing IMRT
65Gy/30 fractions in 6 weeks - radical and post-operative R1/R2
60Gy/30 fractions in 6 weeks - post-operative R0
First Results of the PARSPORT Trial, Proc ASCO 2009
01:25/14:13

IMRT is evil….is it? The SEER-Database suggests…

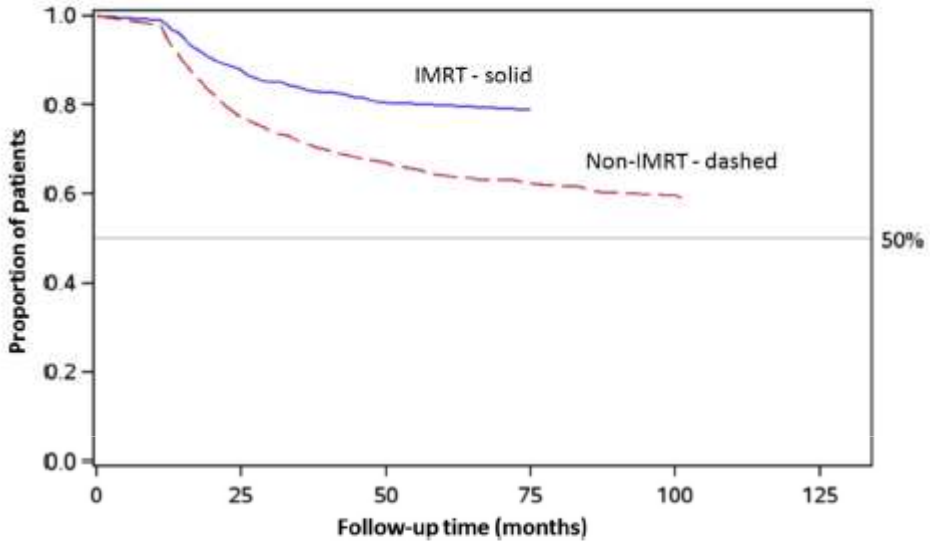
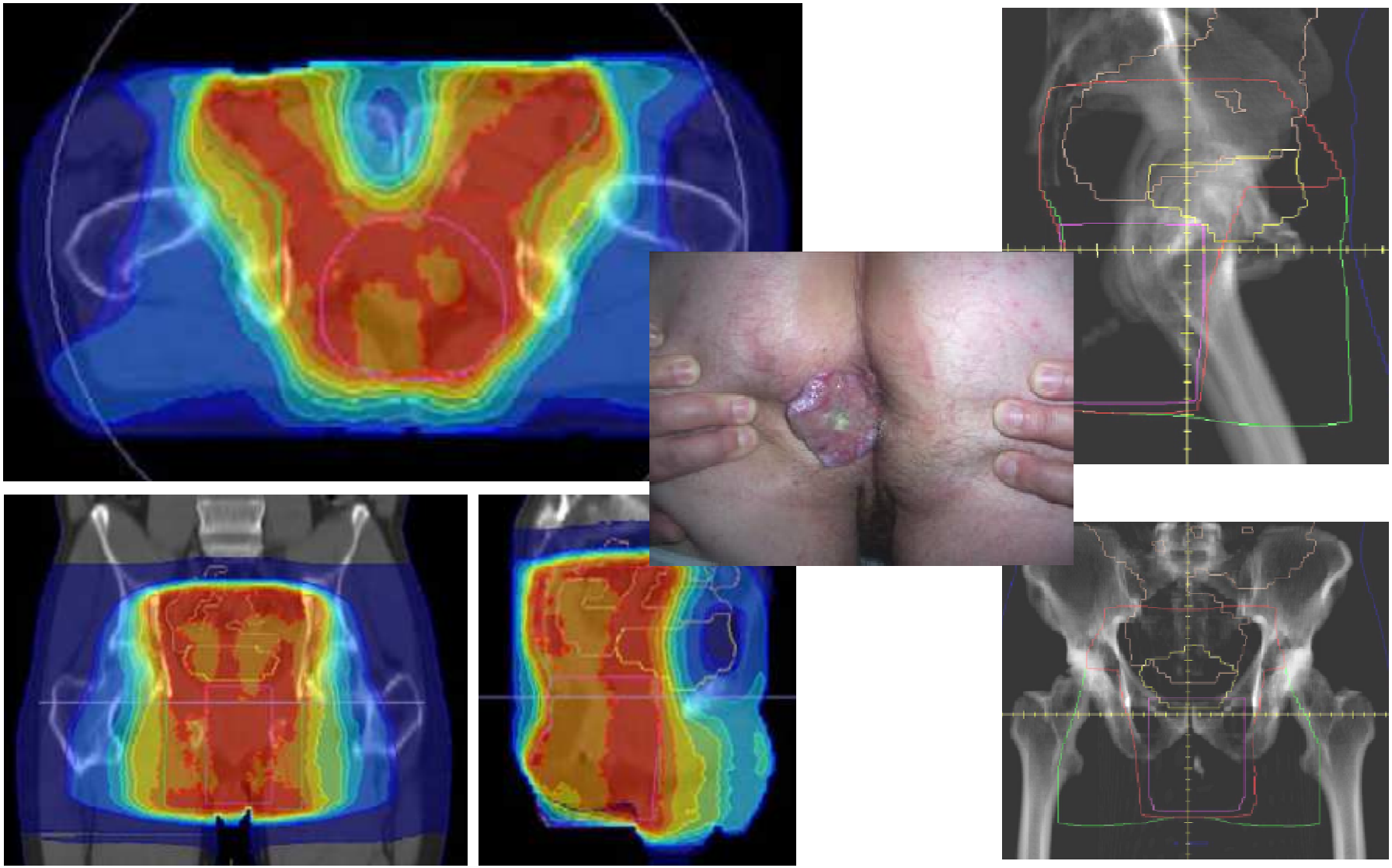


Figure 1. Impact of intensity-modulated radiation therapy (IMRT) on cause-specific survival. Kaplan-Meier curve depicting the cause-specific survival with time for patients treated with IMRT (dashed) compared to those treated with non-IMRT (solid).

Beadle et al., Cancer, 2014

Lohr, Mai, in:
Wannenmacher, Strahlentherapie, 2013



Caveat: Marginal misses and high doses to large volumes

Tata Memorial Randomized Trial

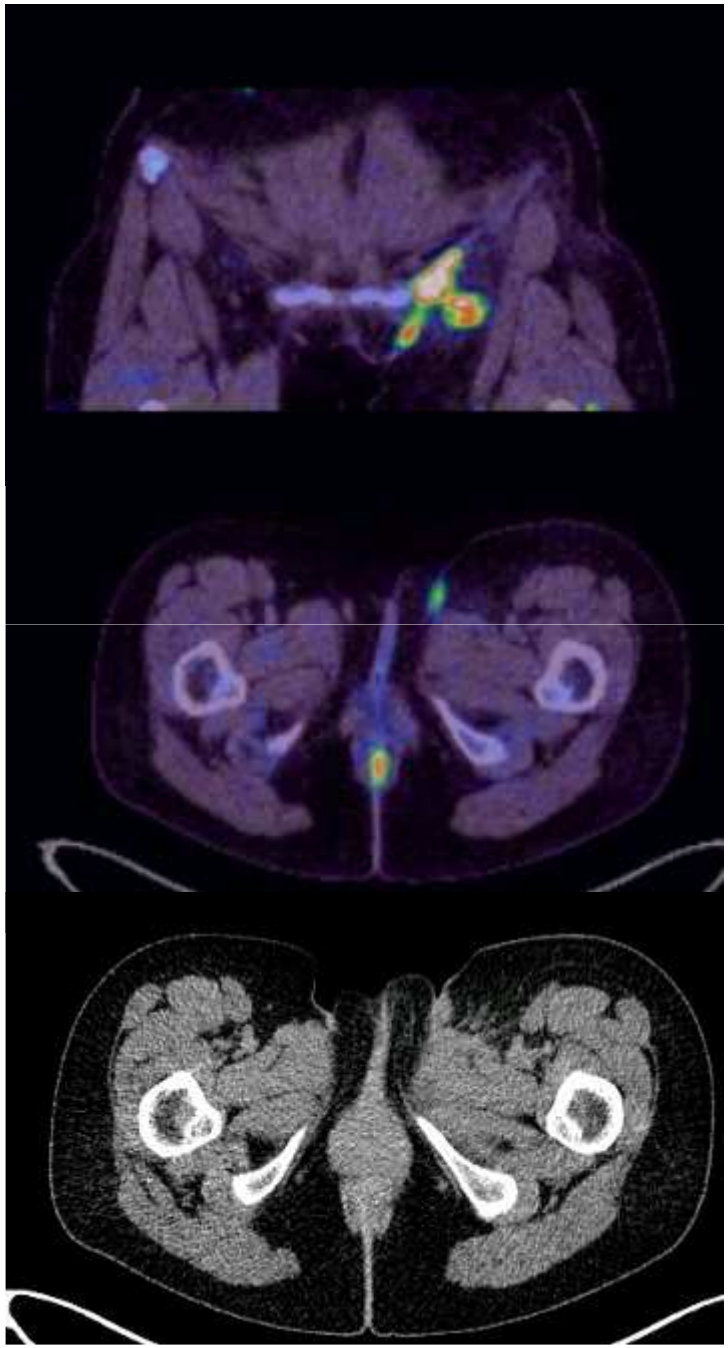
Rathod et al.,
Oral Oncol, 2013

Caveat:

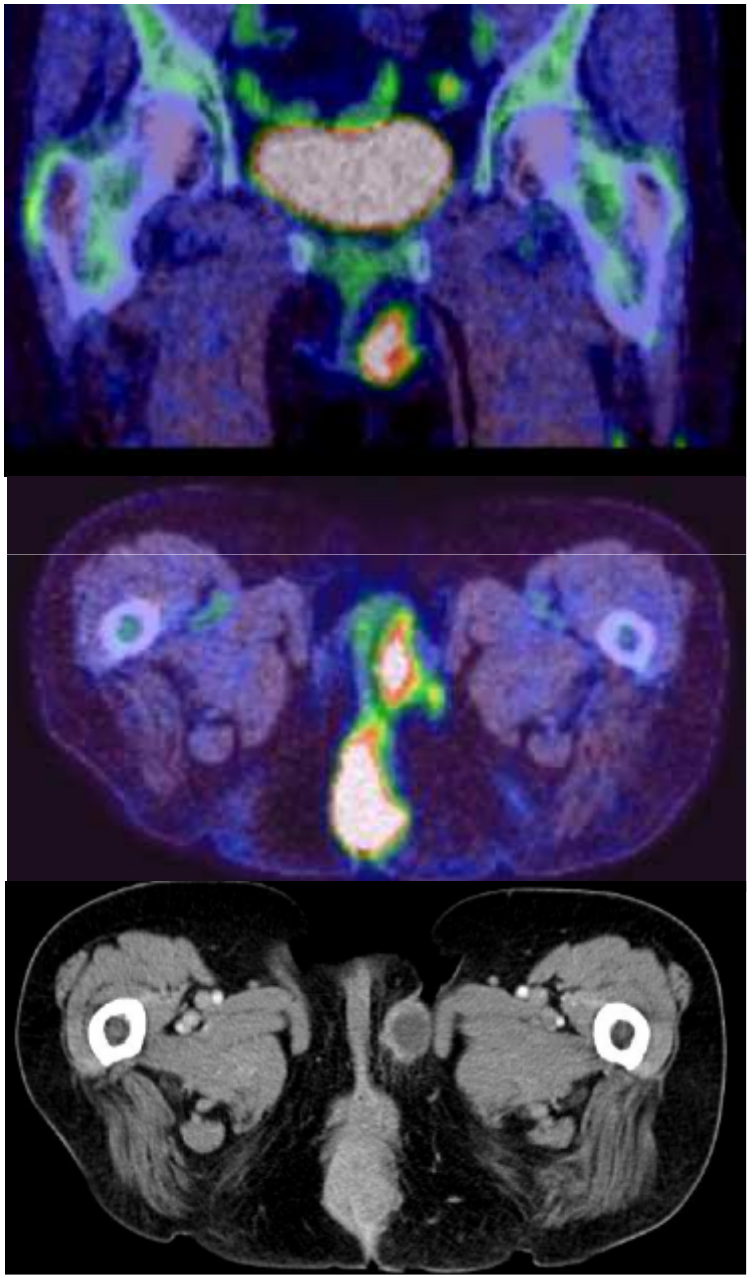
At a median followup of 40 months (inter-quartile range 26-50 months):

The 3-year estimates of loco-regional control with 95% confidence intervals (95%CI) were
88.2%** (75.4–100%) for **3D-CRT
80.5%** (66.1–94.9%) for **IMRT
(p = 0.45).

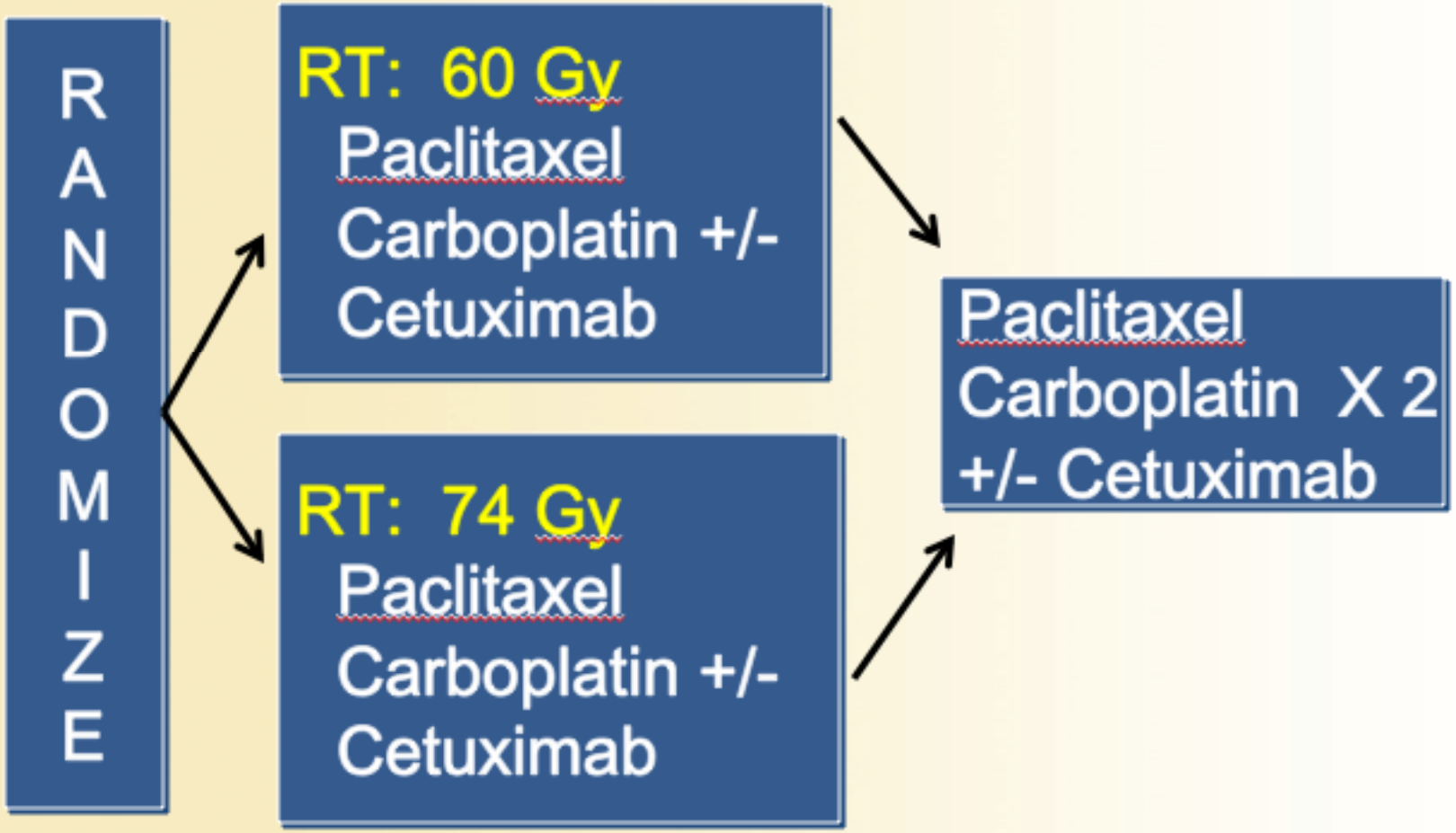
Pitfalls



Koeck et al., Radiation Oncology, 2016



RTOG 0617, NCCTG N0628,CALGB 30609
Conventional vs. High Dose RT



Now comes the strange part…..

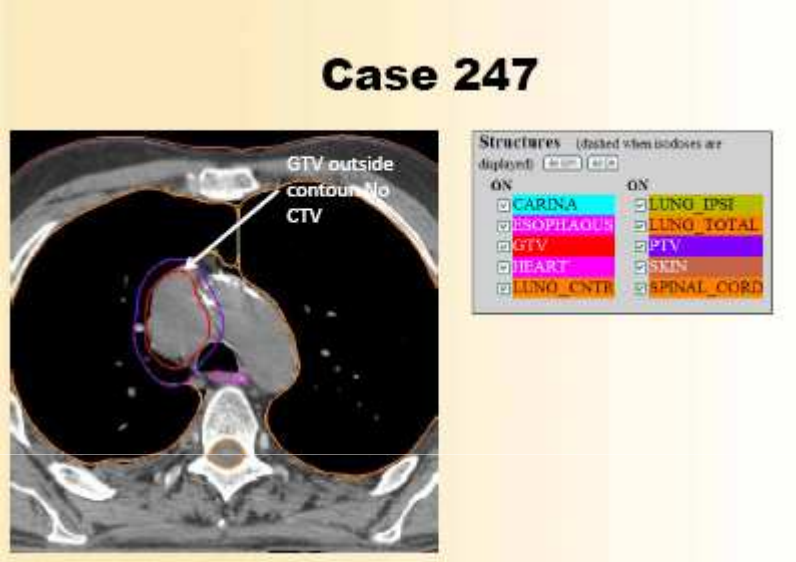
„**Local failure rates** at 18 months were

25.1% vs 34.3% for SD and HD patients,

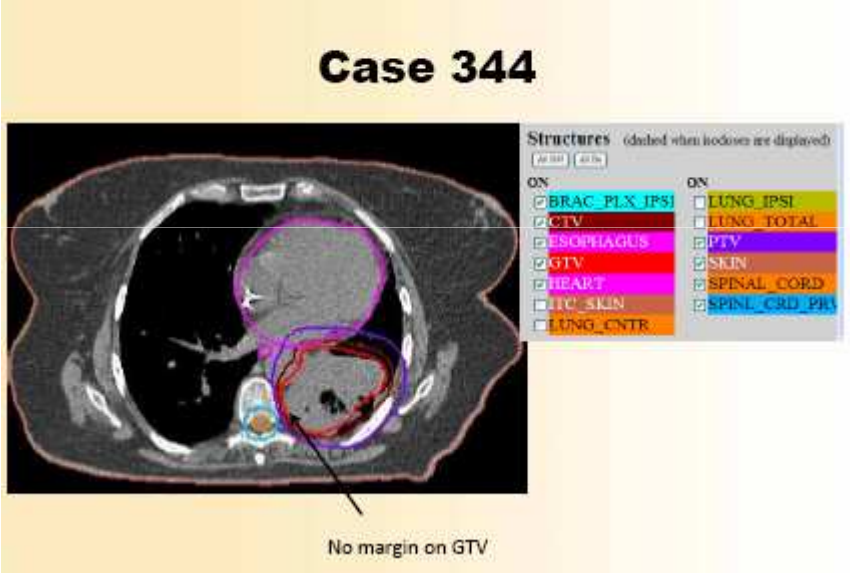
respectively(p=0.03). Local-regional and distant failures at 18 months were 35.3% vs 44%(p=0.04) and 42.4% vs 47.8%(p=0.16) for SD and HD arms, respectively. Factors predictive of less favorable OS on multivariate analysis were higher radiation dose, higher esophagitis/dysphagia grade, greater gross tumor volume, and heart volume >5 Gy“

Bradley et al., ASCO, 2013

Target Delineation



Bradley, 2014



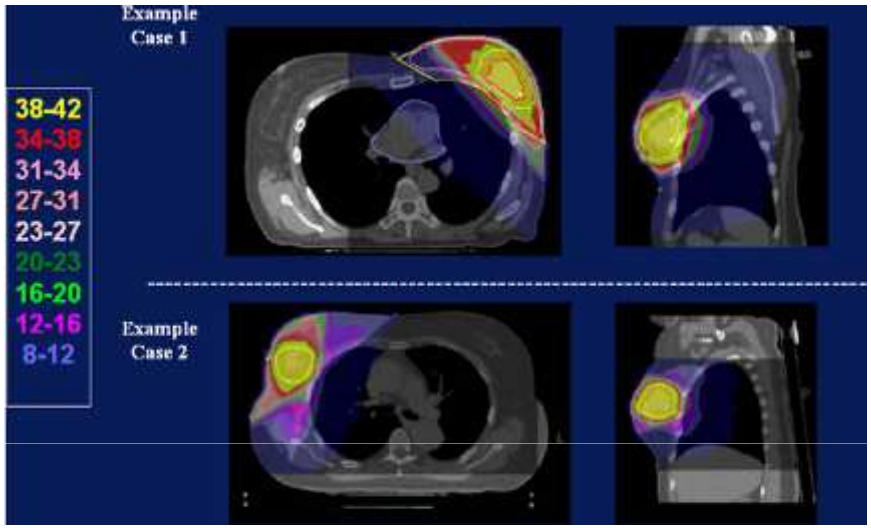
http://thoracicsymposium.org/MeetingProgram/documents/GSIXBradley.pdf

The good news, however……

In this trial, IMRT was apparently clearly better than 3D and Lung V5 did not correlate with toxicity (V20 did, which is logical, since it marks a threshold dose…..as does V45 for heart)

This was a sneak preview to ASTRO 2015.
It is free. Donations are nevertheless accepted.
Beer above 8% Alkohol preferred currency!

Hypofractionation/SIB-> Watch the Volume



Jagsi et al., IJROBP, 2009

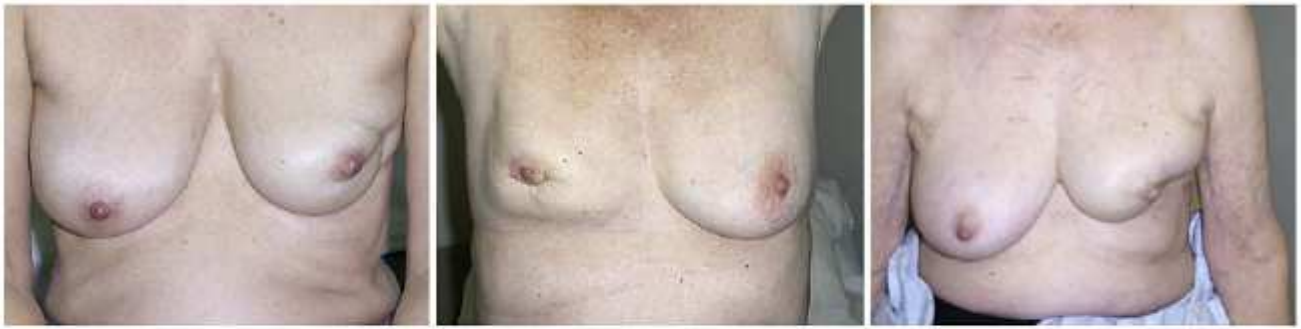
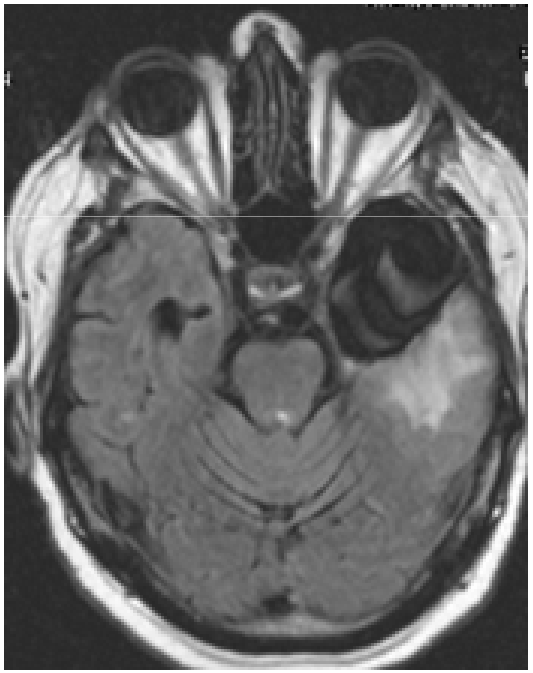
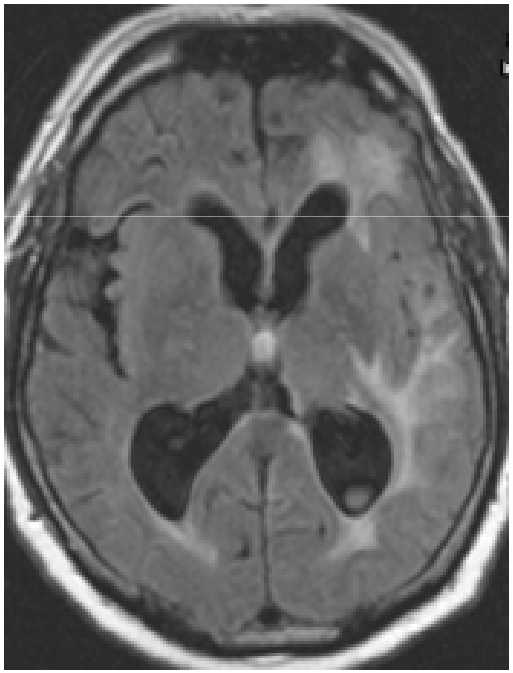


Fig. 3. Visible impairment in cosmesis observed in 3 patients deemed to have unacceptable cosmesis after treatment.

Brain tumor cells are interdispersed with normal cells
The Brain is the central human organ. Severe damage here alters the personality….and thus effectively kills the patient alive





There is good news on the secondary tumor front:

Randomized Data: PORTEC etc.

Wiltink et al., JCO, 2015

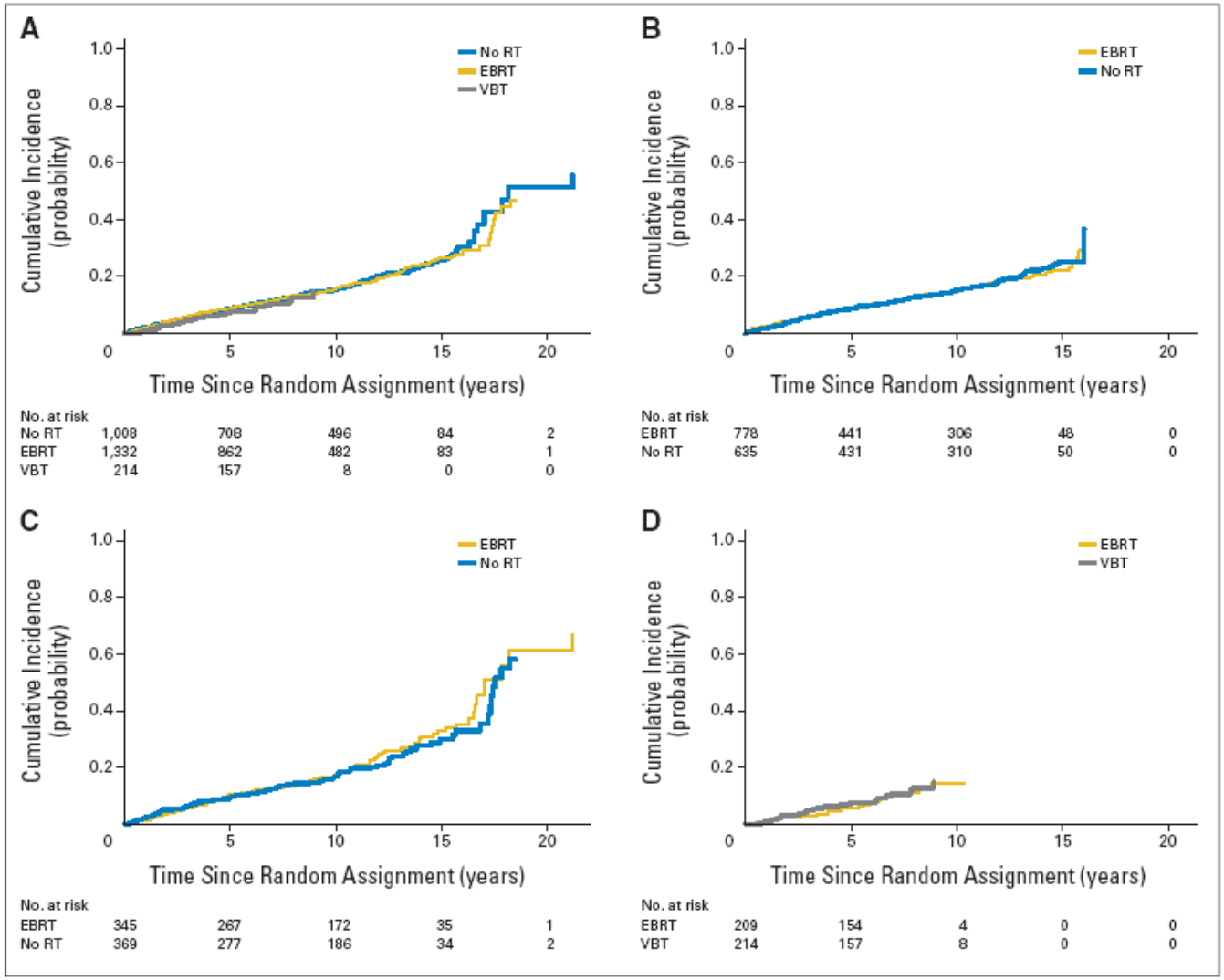
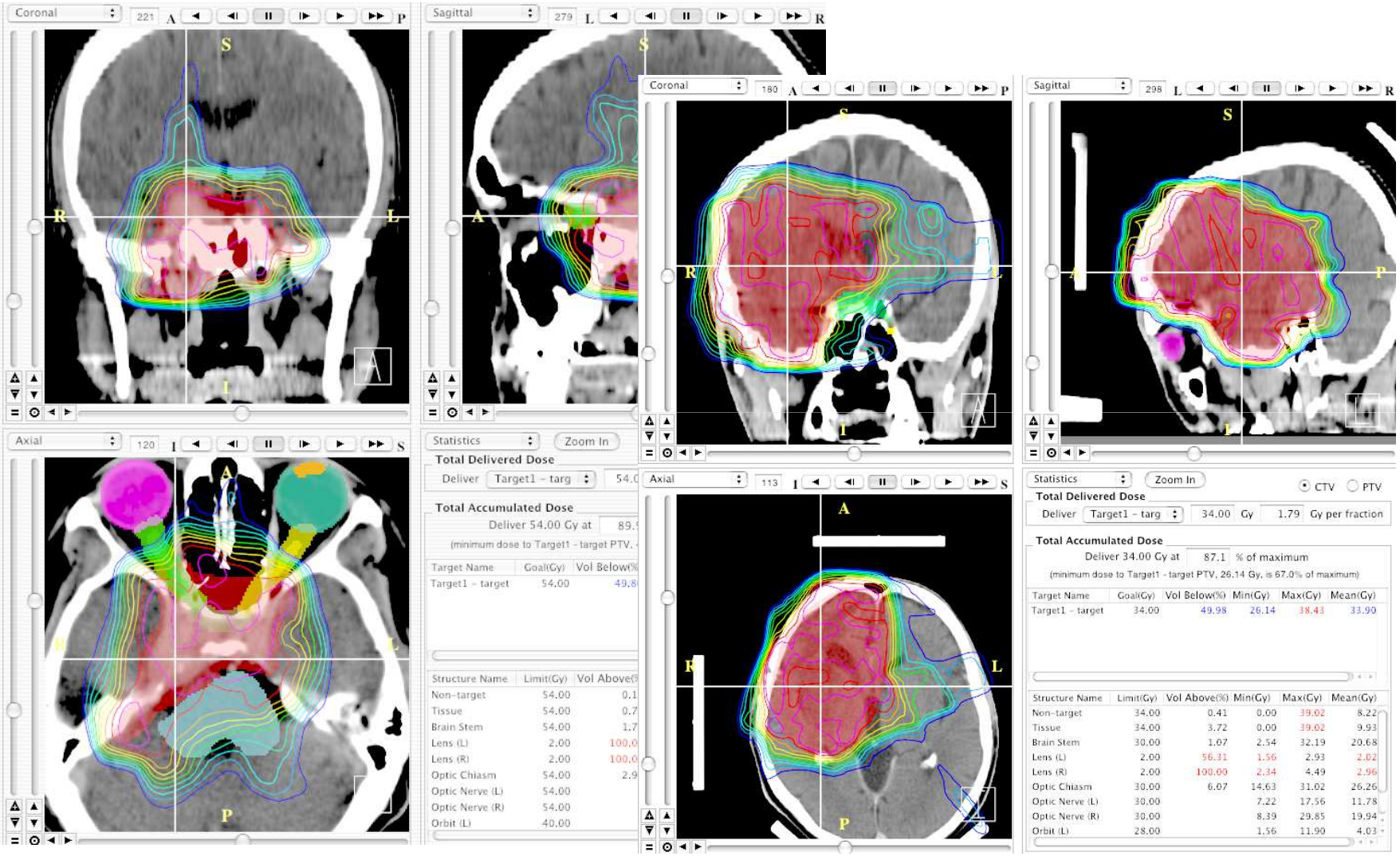


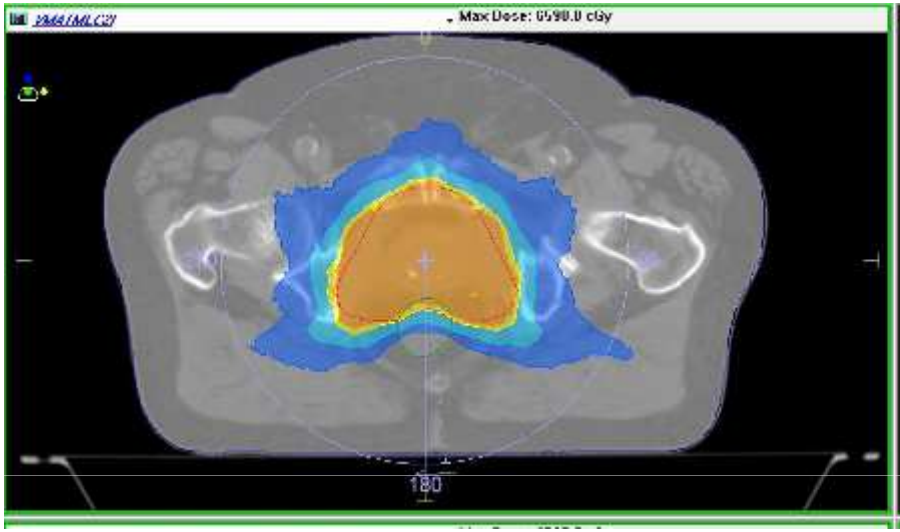
Fig 2. Cumulative probability of developing second cancer in (A) all, (B) TME (Total Mesorectal Excision), (C) PORTEC-1 (Post Operative Radiation Therapy in Endometrial Carcinoma 1), and (D) PORTEC-2 trials. NOTE. Because only four patients were included in no-RT group in the PORTEC-2 trial, these patients are not represented in panel D. EBRT, external-beam radiotherapy; RT, radiotherapy; VBT, vaginal brachytherapy.

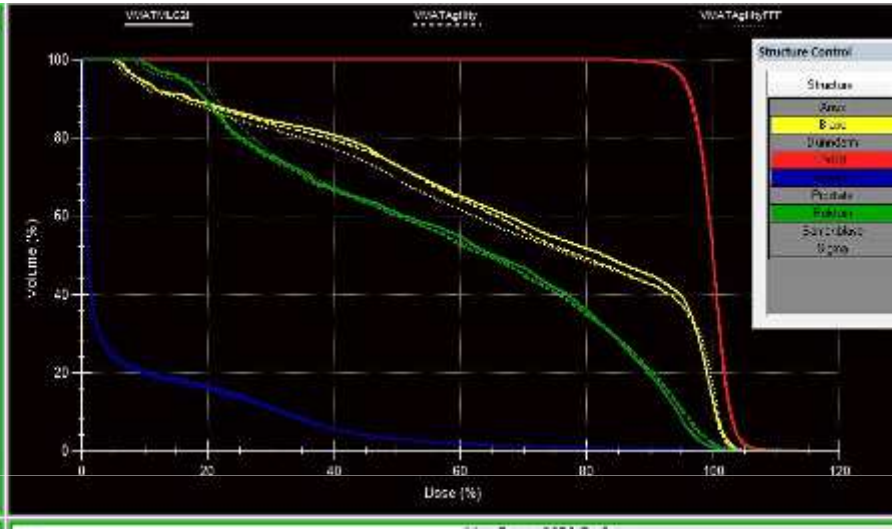
Convenience and Optimization of existing Paradigms

Head and Neck

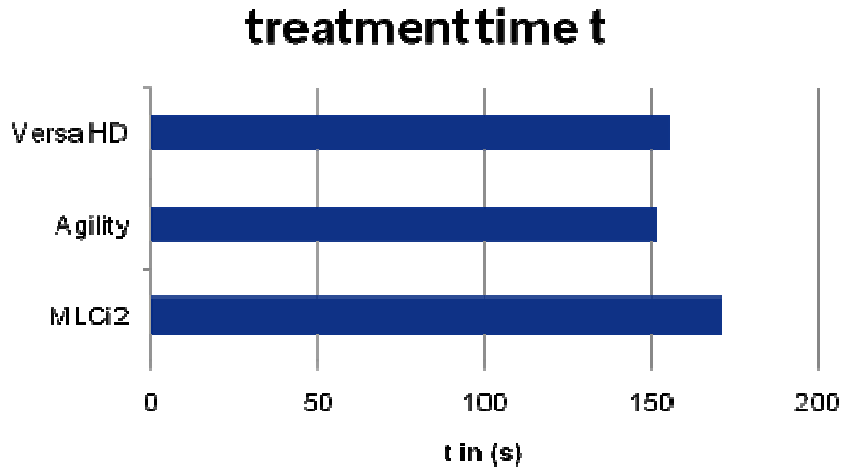


Prostate – low degree of modulation, D= (30 × 2) Gy, 2 VMAT arcs

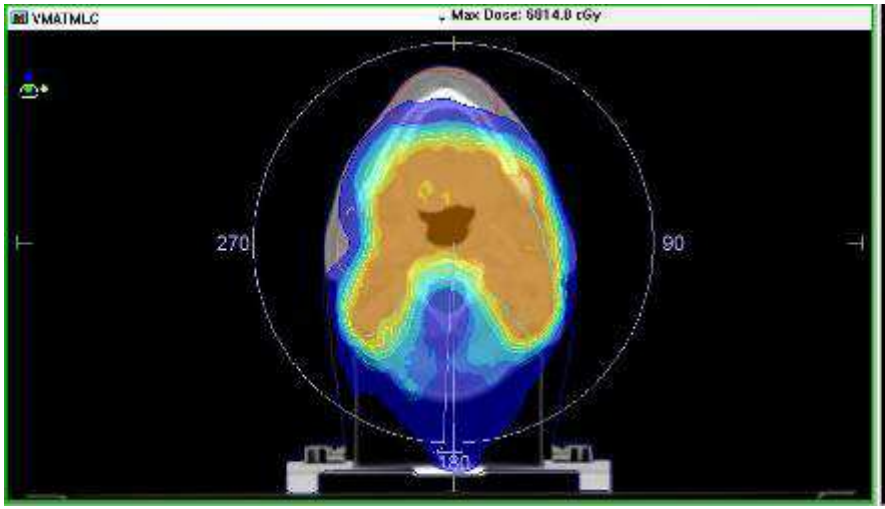


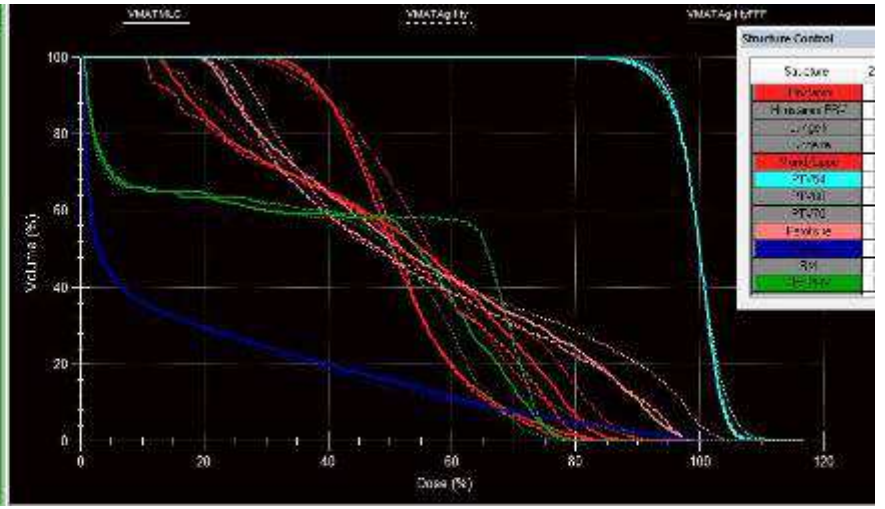


PROSTATE	MLCi2 Monaco 3.3	Agility Monaco 3.3	Versa HD Monaco 3.3
Homogenity index	1.09	1.09	1.09
OAR Rectum, mean dose	35.8Gy	35.6	35.96 Gy
OAR Bladder, mean dose	42.3 Gy	41.7	40.95 Gy
beam-on time per fraction	171 s	152 sec	156 s
number of MU's delivered	789	762	915

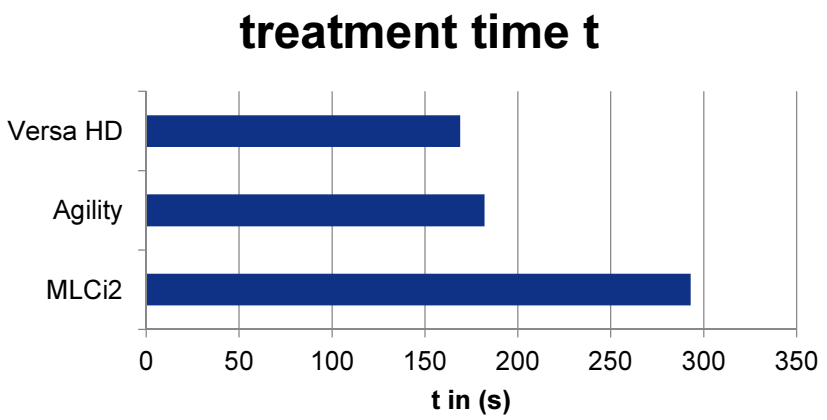


Head & Neck - high degree of modulation, D= (30 × 1.8) Gy, 2 VMAT arcs

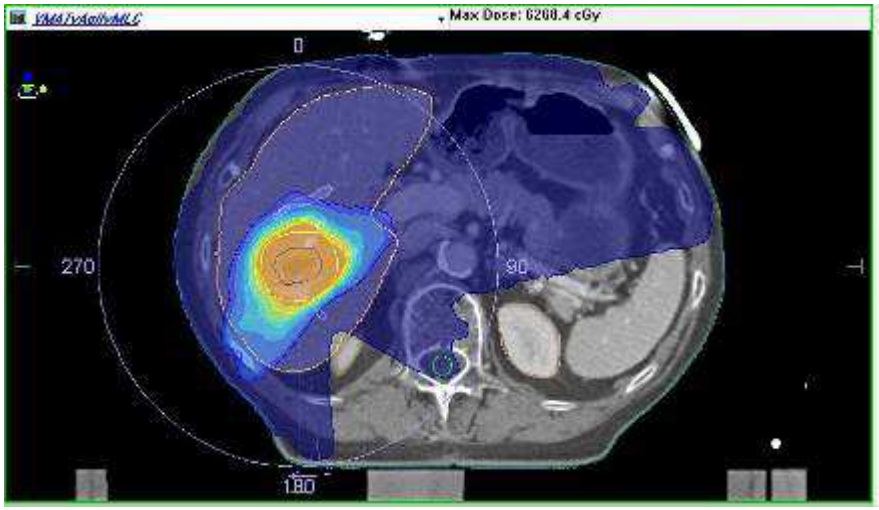


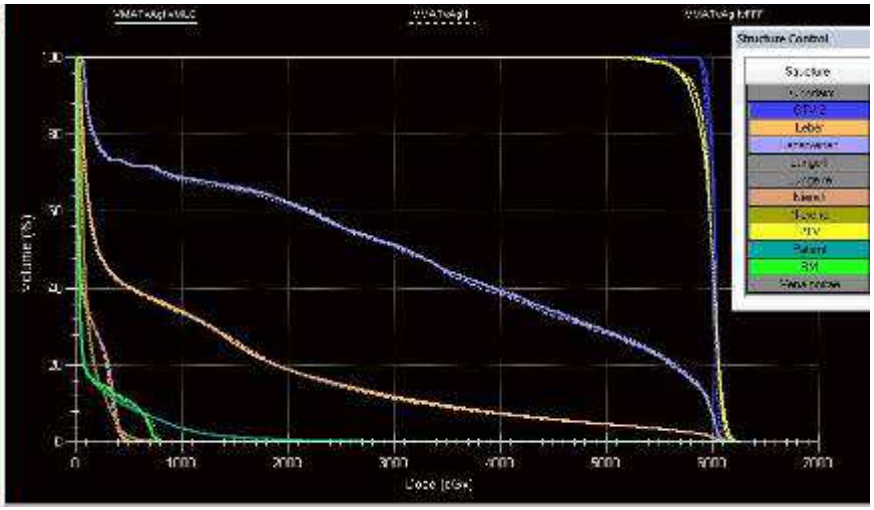


Head and neck	MLCi2 Monaco 3.3	Agility Monaco 3.3	Versa HD Monaco 3.3
Homogeneity Index	1.12	1.14	1.13
OAR Parotis, mean dose	29.79 Gy	28.86 Gy	30.91 Gy
OAR Spinal Cord, max dose	44.33 Gy	42.40 Gy	44.62 Gy
OAR Lips, Mean dose	27.99 Gy	28.01 Gy	30.82 Gy
OAR Brain stem, mean dose	28.32 Gy	26.94 Gy	29.46 Gy
beam-on time per fraction	293 s	182 s	169 s
number of MU's delivered	635	633	1123

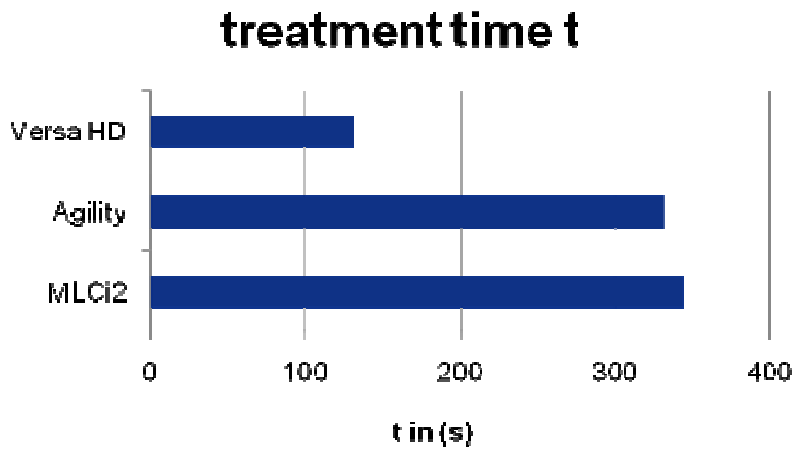


Liver – intermediate degree of modulation, D= (5 × 12) Gy, 2 VMAT arcs

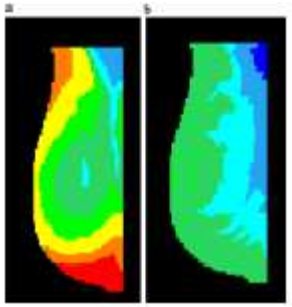




LIVER	MLCi2 Monaco 3.3	Agility Monaco 3.3	Versa HD Monaco 3.3
Homogeneity index	1.07	1.06	1.06
OAR Liver, mean dose	10.57 Gy	10.46 Gy	10.44 Gy
OAR Kidney, max dose	8.63 Gy	8.15 Gy	8.13 Gy
OAR Spinal Cord, max dose	7.82 Gy	7.91 Gy	8.20 Gy
beam-on time per fraction	345 s	331 s	132 s
number of MU's delivered	2494	2710	2733



Clinical Results with Tangential IMRT



2 Randomized trials, several retrospective analyses

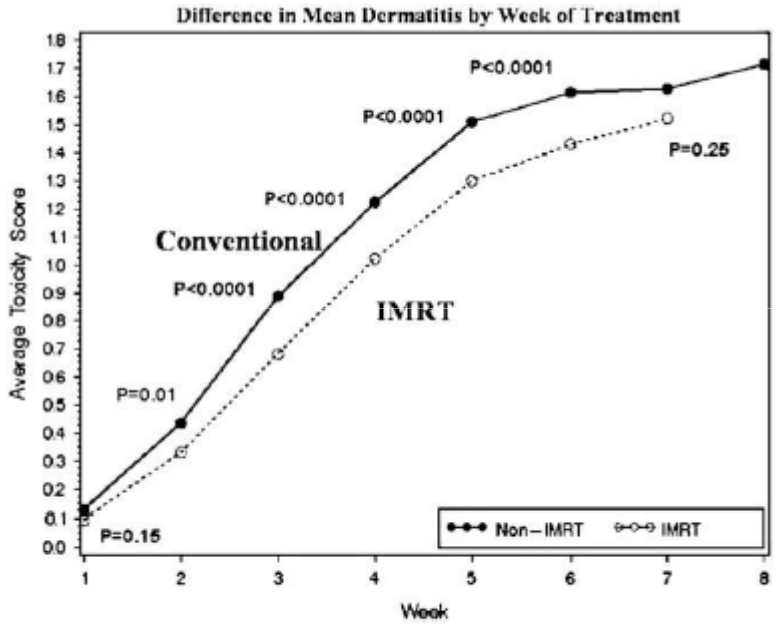


Fig. 1. Mean frequency of dermatitis by week of treatment during radiation therapy for patients treated with conventional radiation therapy (n = 405) and intensity-modulated radiation therapy (IMRT; n = 399).

Freedman et al., IJROBP, 2009

Score (change)	Standard (2D) Number (%)	IMRT (3D) Number (%)
Photographic score at year 1		
None	84 (64.1)	92 (74.2)
Mild	37 (28.2)	26 (21.0)
Marked	10 (7.6)	6 (4.8)
Total	131	124
Photographic score at year 2		
None	73 (56.6)	84 (65.1)
Mild	49 (38.0)	39 (30.2)
Marked	7 (5.4)	6 (4.7)
Total	129	129
Photographic score at year 5		
None	51 (41.8)	71 (60.2)
Mild	54 (44.3)	35 (29.7)
Marked	17 (13.9)	12 (10.2)
Total	122	118

Donovan et al., R&O, 2007
Pignol et al., JCO, 2008

Scatter Reduction with tangential IMRT

Table 2: Dose to various organs for various breast radiotherapy techniques.

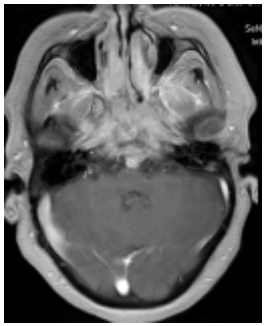
Technique	PBSI	HDR (catheters)	Wedge	IMRT	3D-CRT
Treated Breast	90 Gy	34 Gy	50 Gy	50 Gy	38.5 Gy
Contralateral Breast	2.2 mSv	230 mSv	1695 mSv	206 mSv	140 mSv
Spleen	44 mSv	1171 mSv	2300 mSv	810 mSv	130 mSv
Ipsilateral lung	790 mSv	2471 mSv	582 mSv	121 mSv	80 mSv
Heart (LAD)	0.7 Gy	3.6 Gy	2.7 Gy	1.1 Gy	0.7 Gy

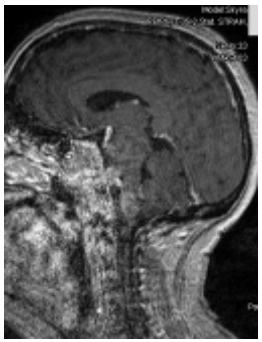
Pignol et al., 2011

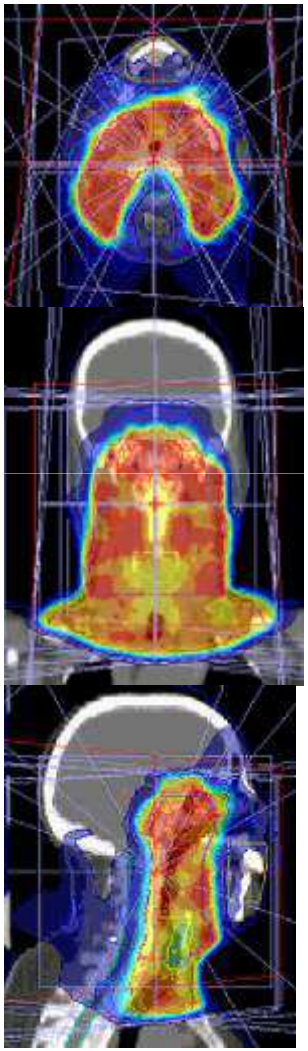
NPC

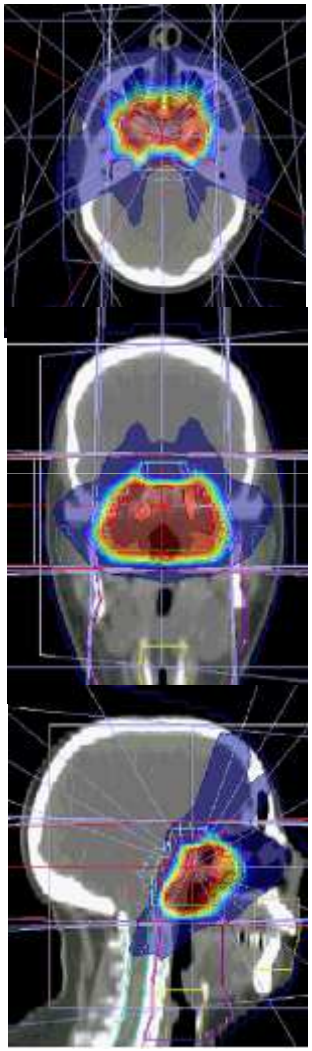
Treatment Sequence

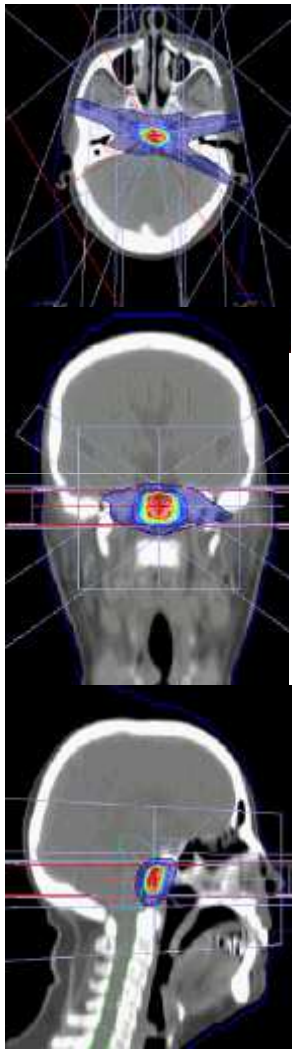
before



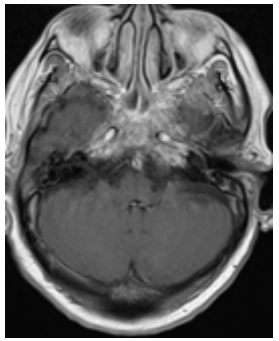


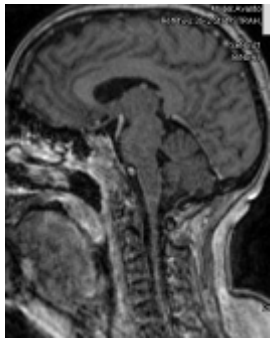






after

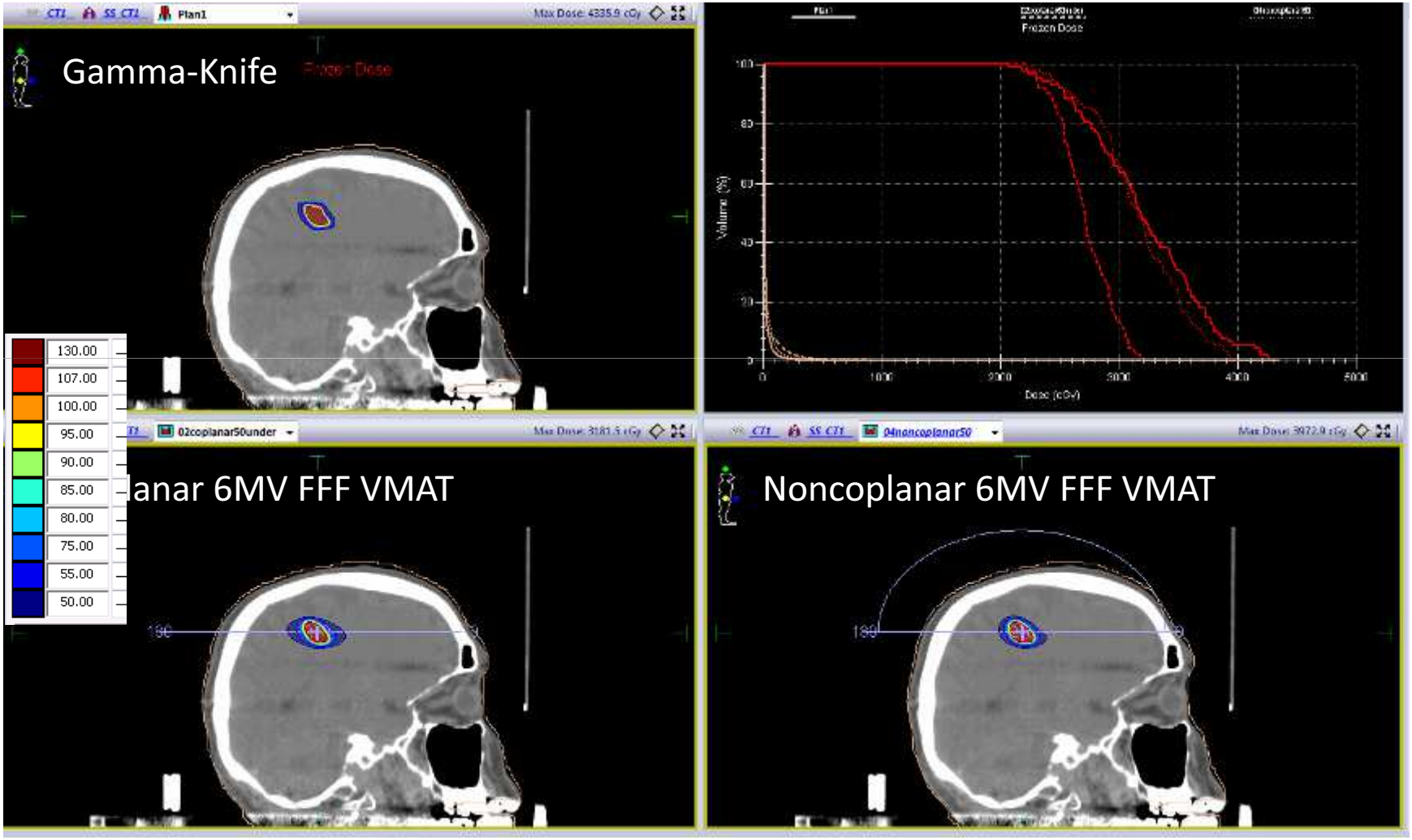




IMRT allows SRS with relatively large leaf sizes
and facilitates multi-lesion treatments with one isocenter

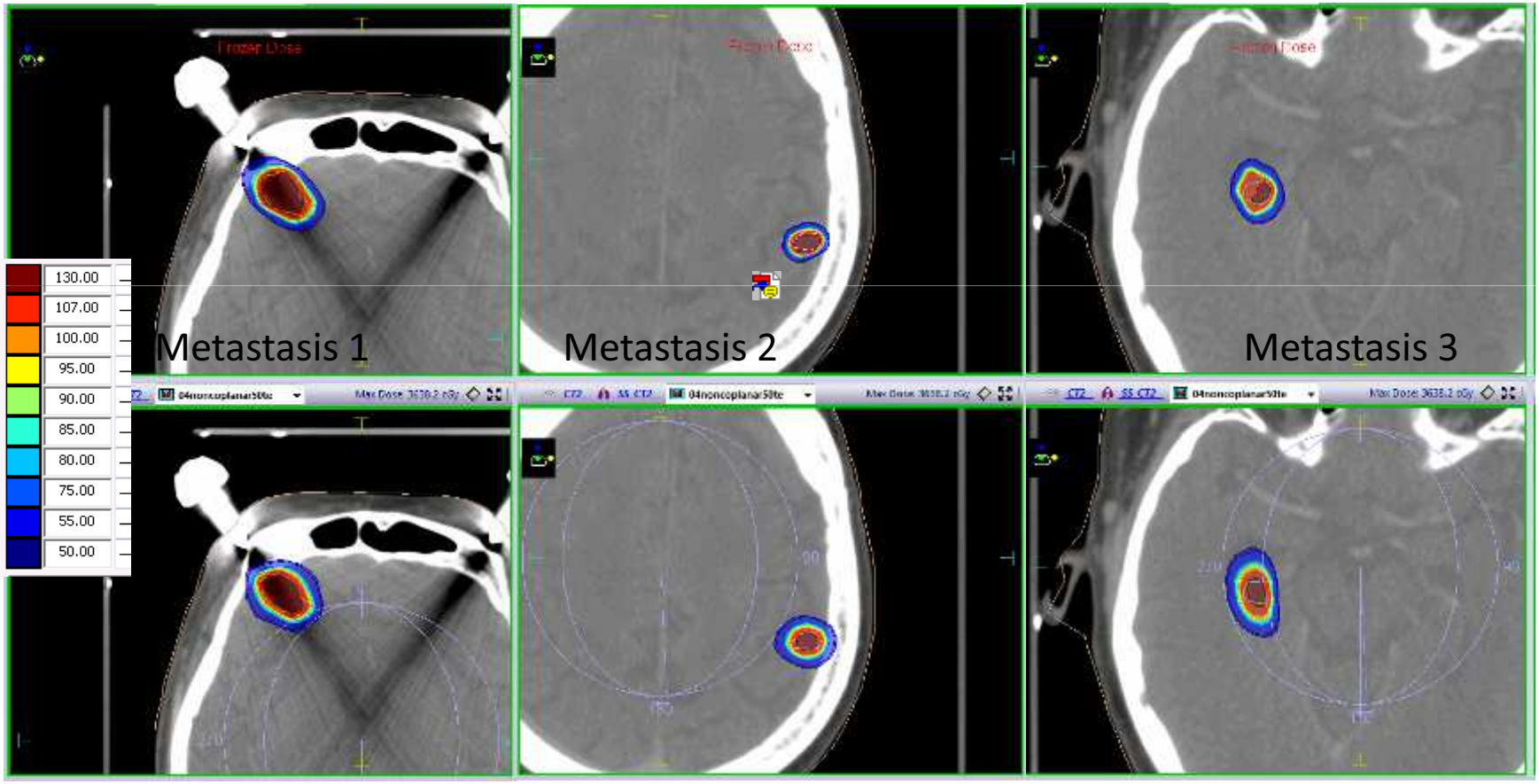
Courtesy L Jahnke, M. Polednik, F. Stieler

Inhomogenous dose sagittal



Transversal inhomogenous

Gammaknife



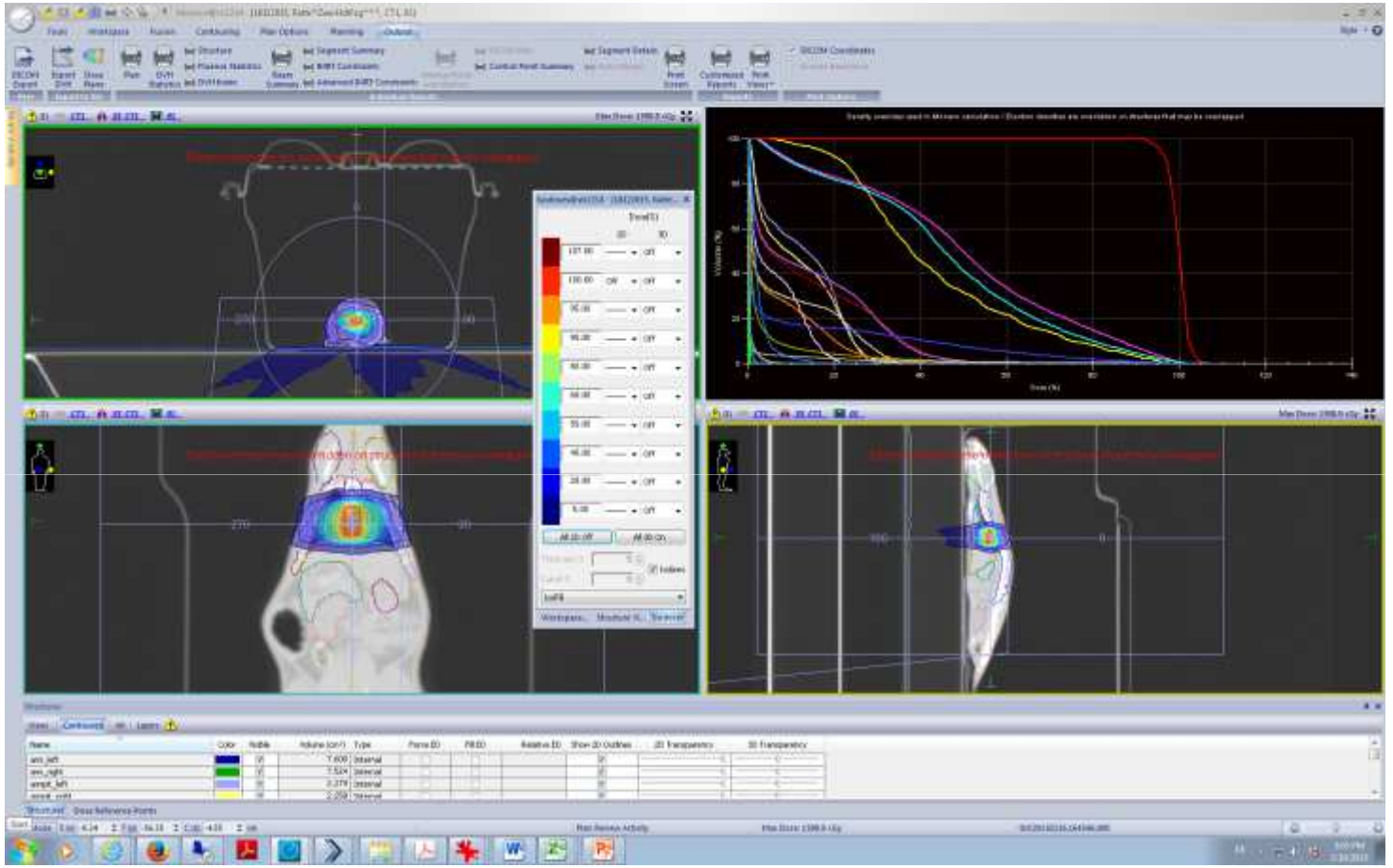
Noncoplanar VERSA HD 6MV FFF VMAT

Treatment Times

All Plans shown can be treated in
<10 min beam on time

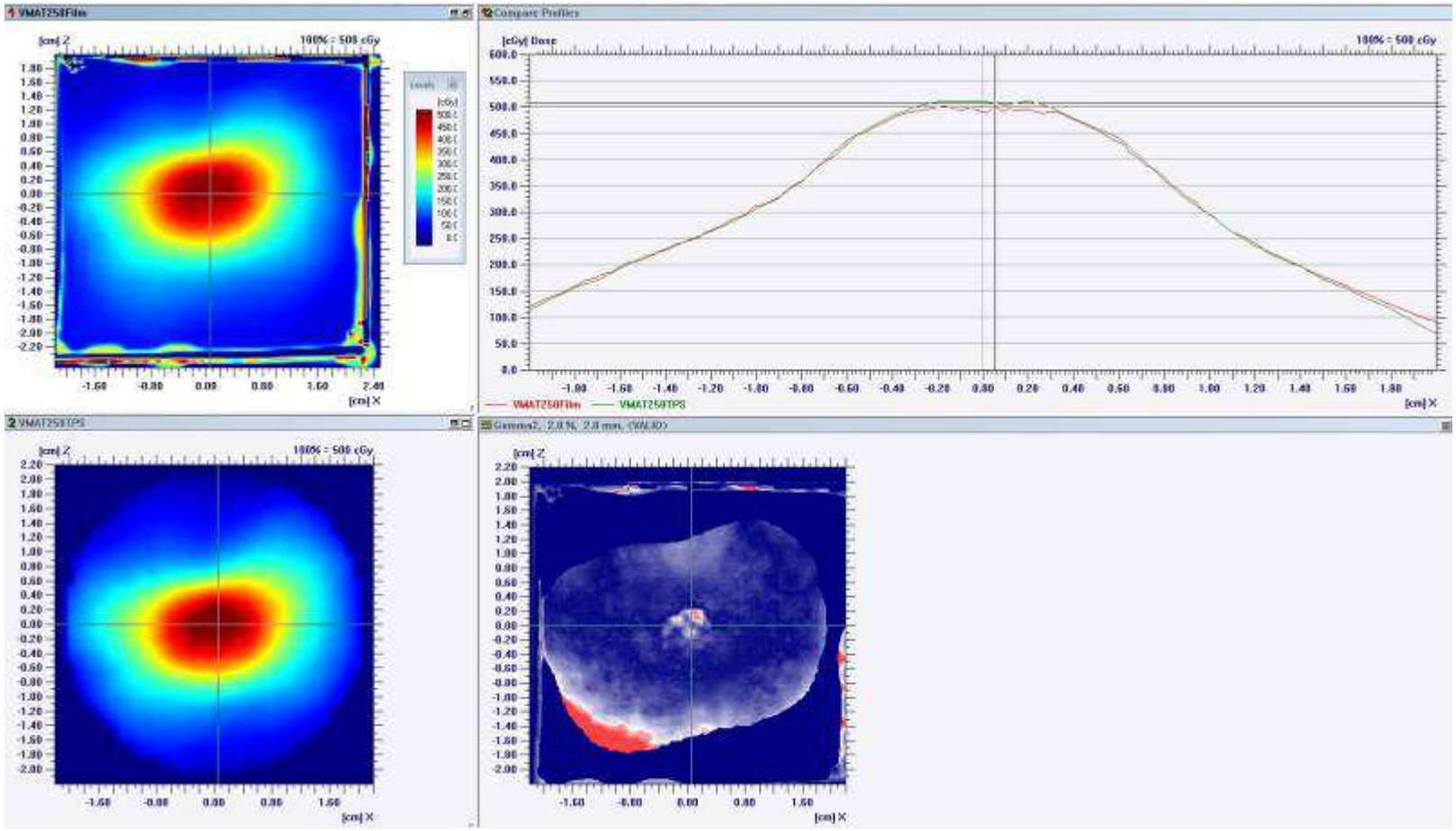
<15 min treatment time
(plus ~4-5 in time for CBCT/positioning)

A very special patient



Courtesy J. Fleckenstein

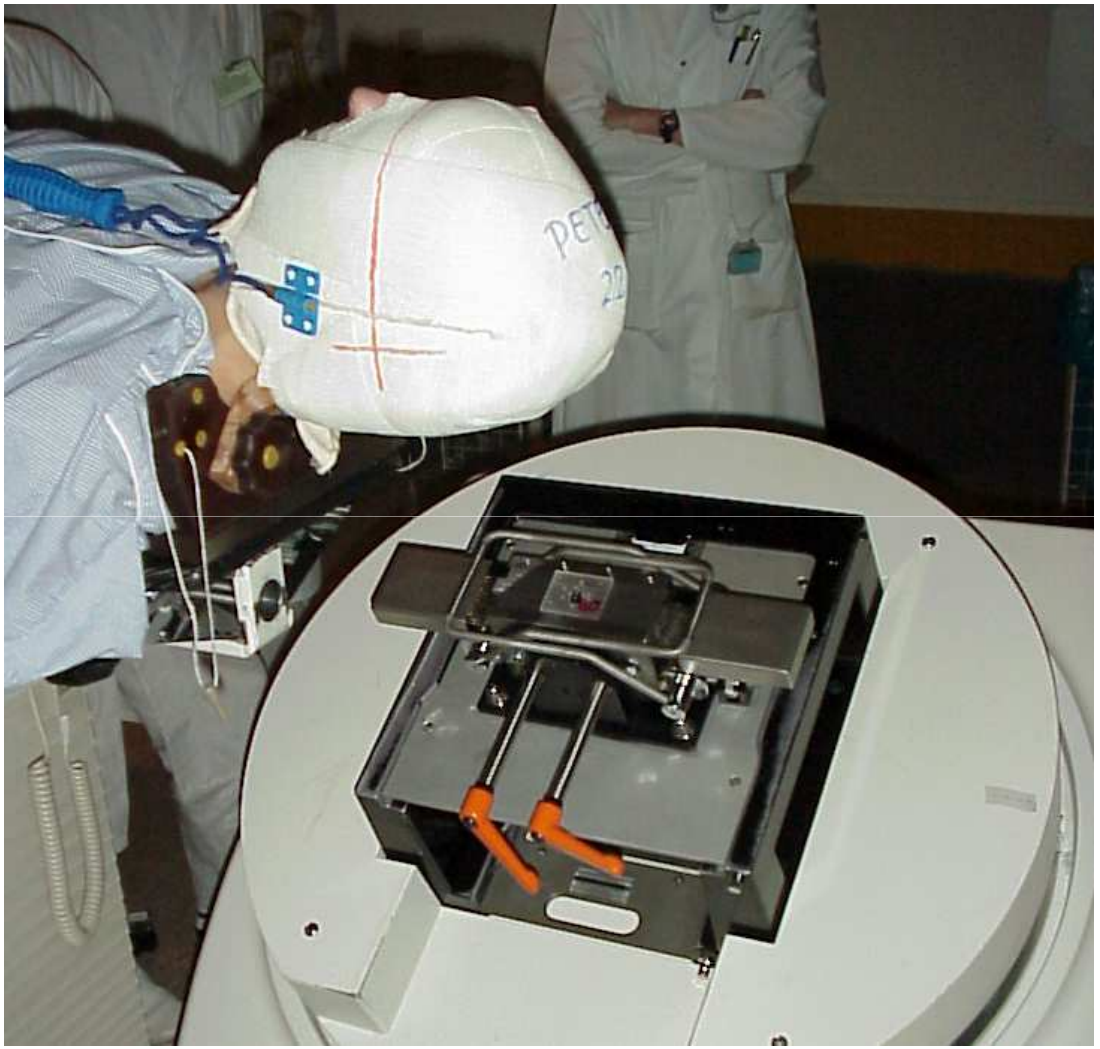
Quality assurance with Gafchromic EBT3 films



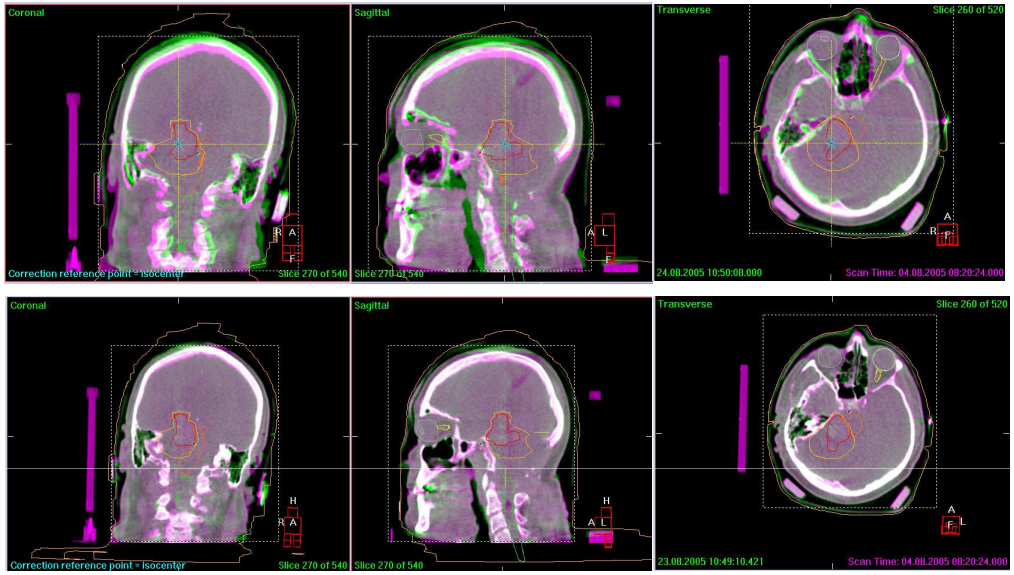
Courtesy J. Fleckenstein

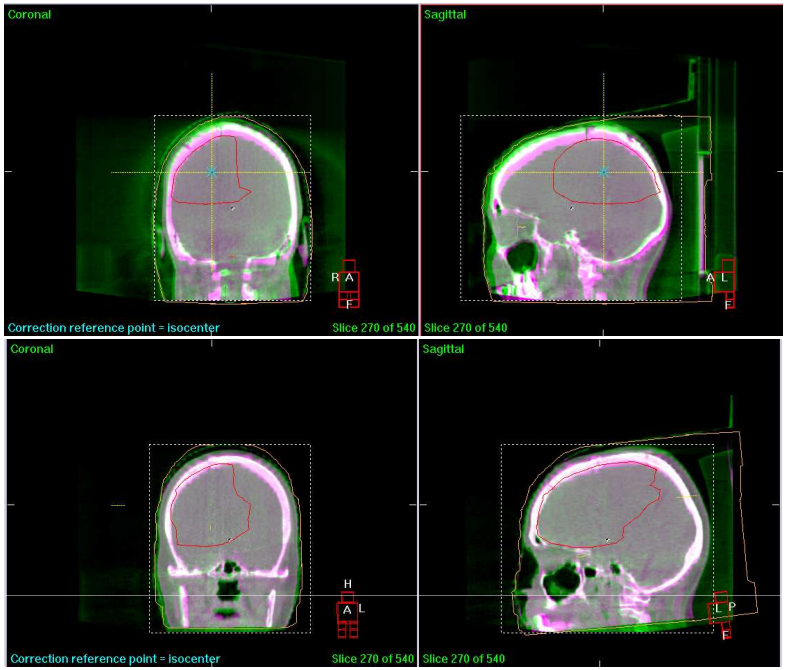
IGRT / Online-adaptation

Target / Organ Motion



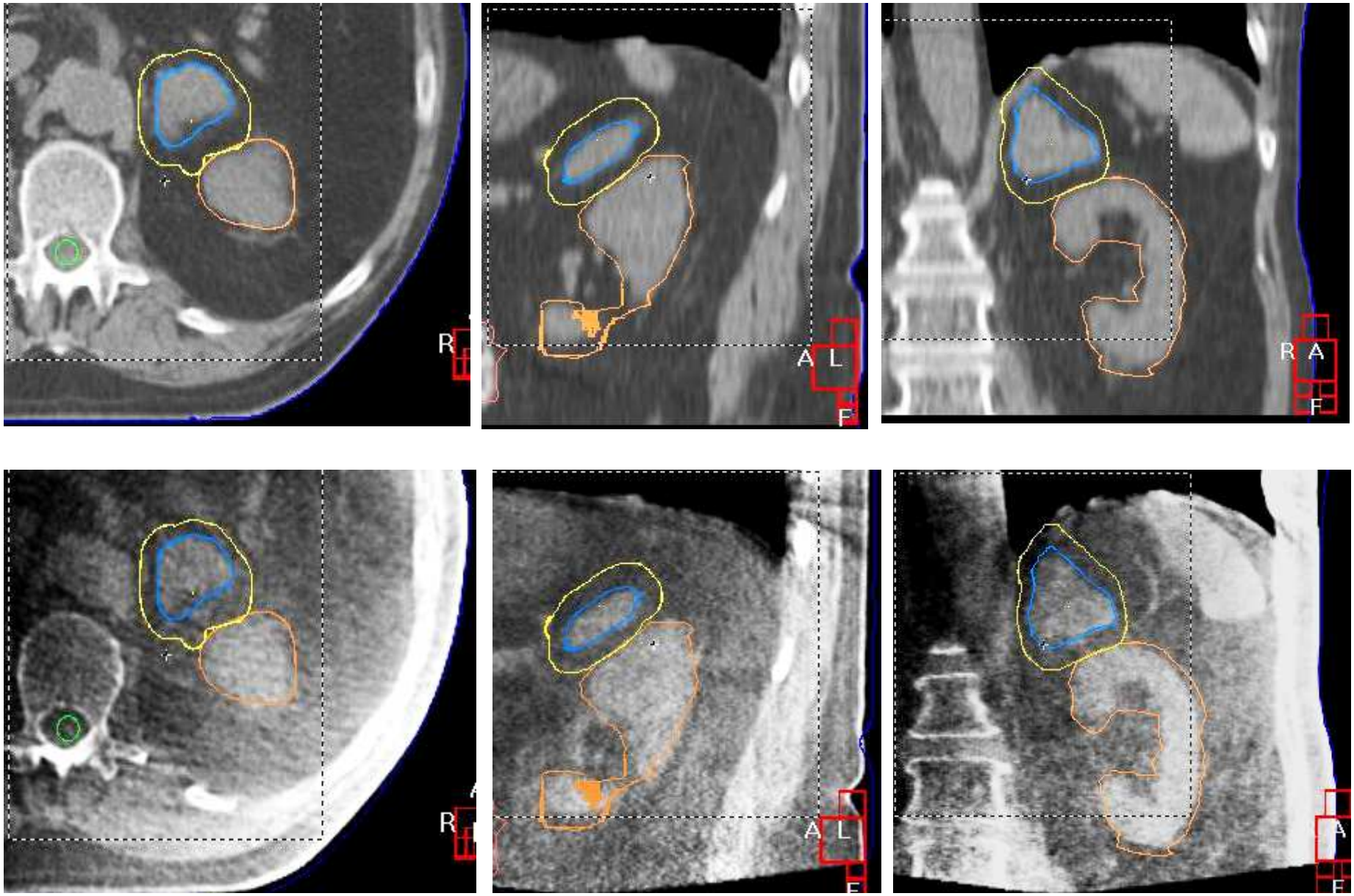
J. Boda-Heggemann, IJROBP, 2006





	Translation (MV±SD, cm)				Rotation (degrees)		
	x	y	z	**Vector (cm)**	x	y	z
Delta-Cast™ (Intracranial)	0.039±0.175	0.083±0.232	0.005±0.174	**0.312±0.152**	0.073±1.018	0.13±1.653	-0.25±0.0881
Thermoplastic masks (intracranial)	-0.02±0.227	0.23±0.233	-0.154±0.277	**0.472±0.174**	-1.47±1.75	-0.13±1.921	-0.06±2.18
Delta-Cast™ (neck)	-0.158±0.207	0.225±0.241	0.179±0.479	**0.586±0.294**	1.027±3.527	1.013±2.556	1.257±3.008
Thermoplastic masks (neck)	0.205±0.298	0.407±0.516	0.142±0.393	**0.726±0.445**	-0.2±2.31	-1.3±2.69	-1.09±2.02

Table 1. Results with the example of automatic bony registration


R
A
L
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R
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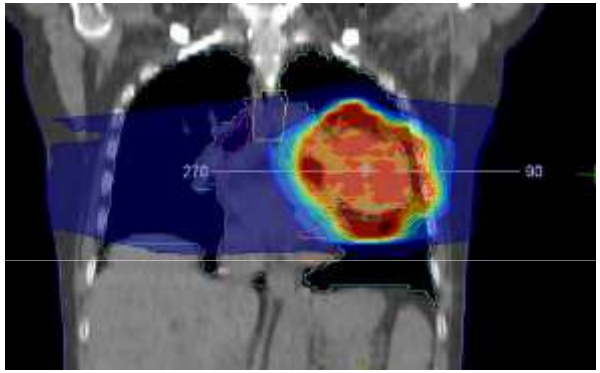
F

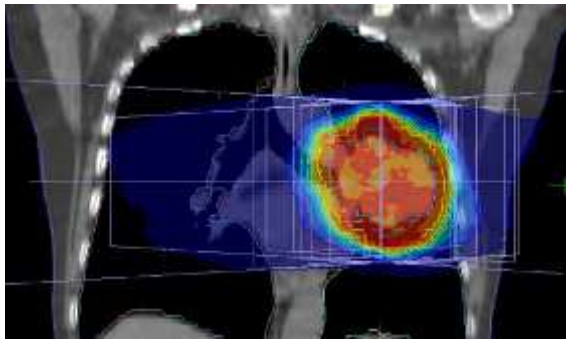
Possible (partial) remedy: IMRT/VMAT in computer-controlled deep-inspiration breath hold

Midventilation CT

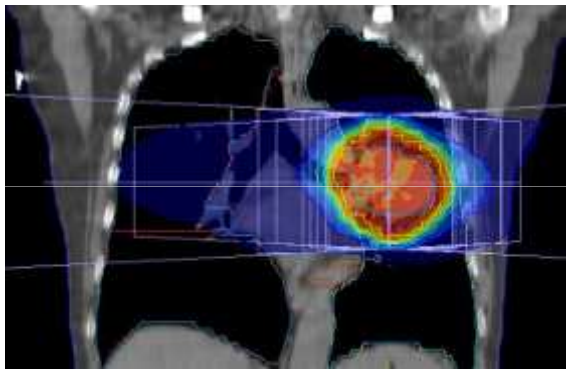


1.12.2011

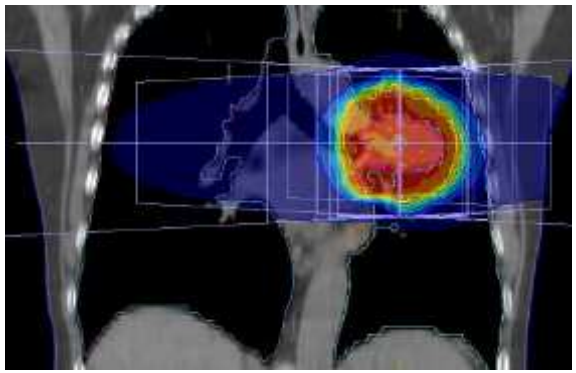
CC-controlled DIB, ART-Sequence



5.12.2011

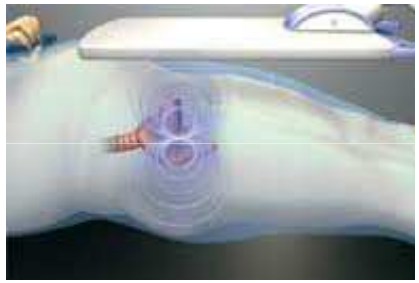


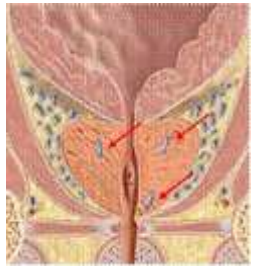
27.12.2011



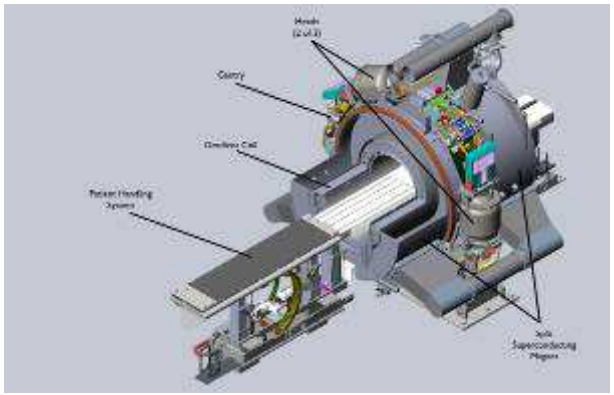
10.01.2012

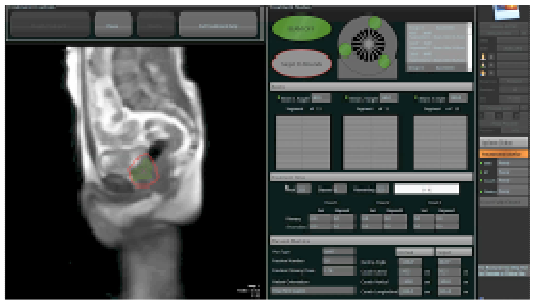
Volumetric imaging - online during a treatment fraction



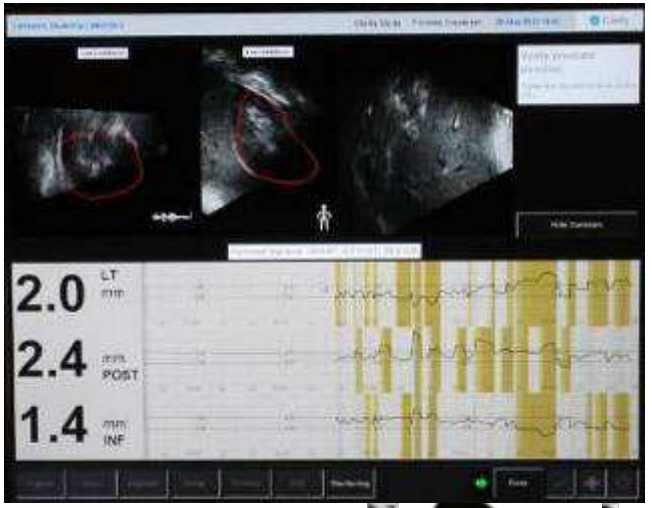


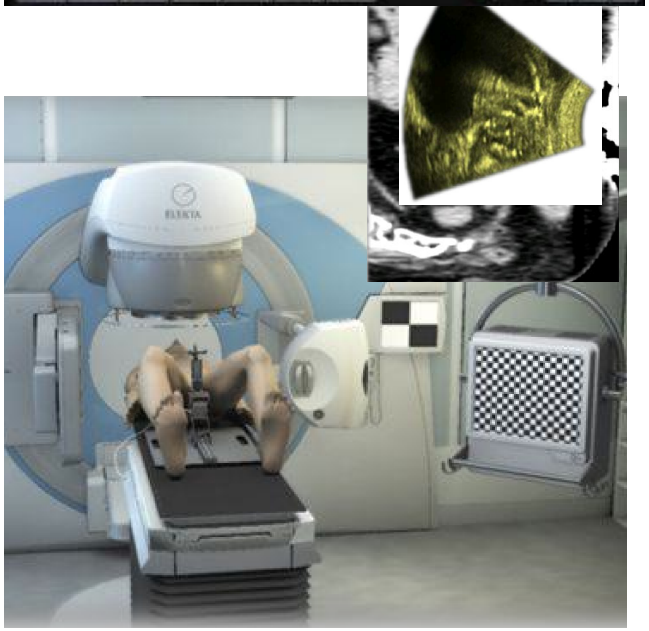
Beacon transponder





MR-IGRT





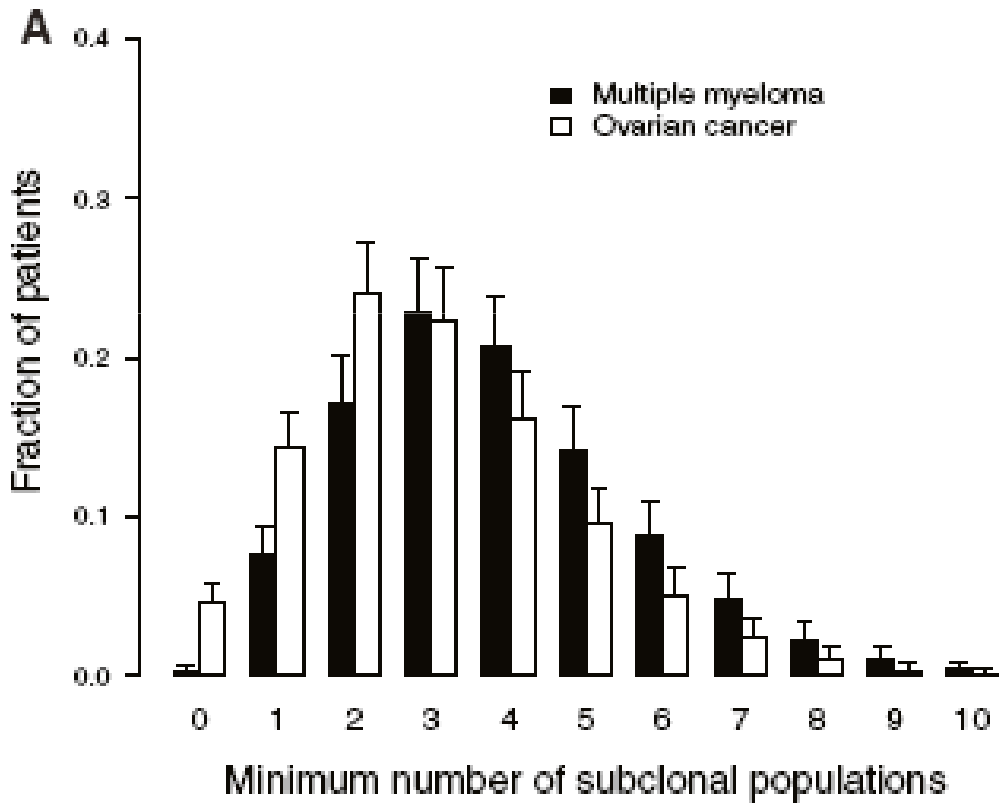
Ultraschall (Clarity, Elekta)

The good thing that comes out of these machines:

Ultrafast treatment planning for the rest of us!!!

New methods for detection of subclinical metastases
a) in general ->Liquid Biopsy

Polyclonality is always a problem with any (vaccination) strategy:



Lohr, Cancer Cell, 2014

New methods for detection of subclinical metastases
b) providing topical information at high resolution->MRI

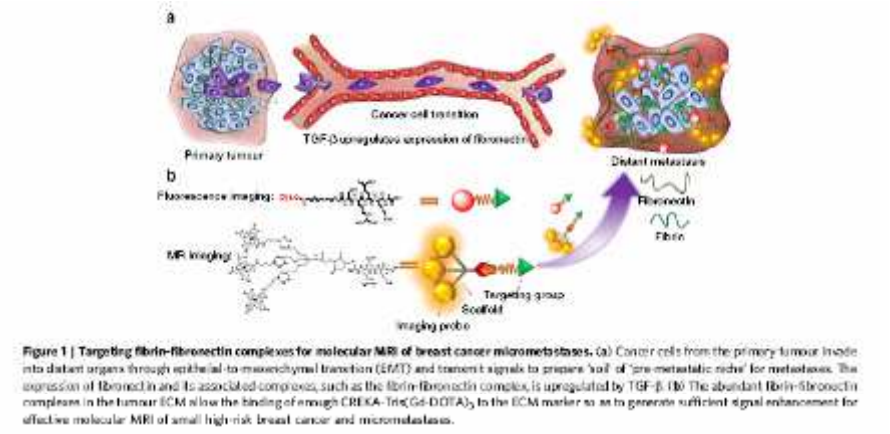
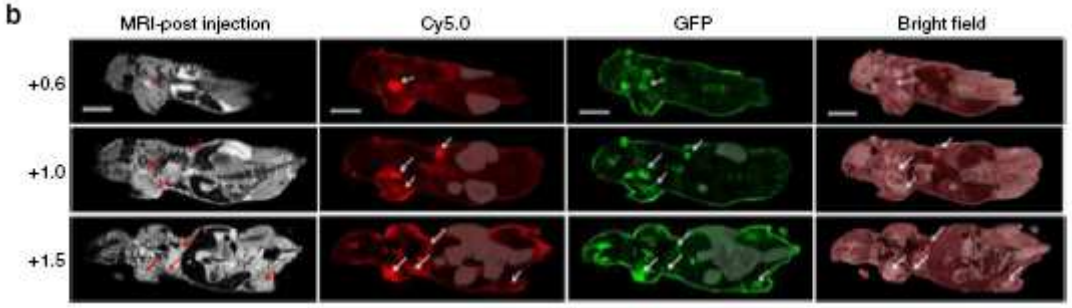


Figure 1 | Targeting fibrin-fibronectin complexes for molecular MRI of breast cancer micrometastases. (a) Cancer cells from the primary tumour invade into distant organs through epithelial-to-mesenchymal transition (EMT) and transmit signals to prepare 'soil' of 'pre-metastatic niche' for metastases. The expression of fibronectin and its associated complexes, such as the fibrin-fibronectin complex, is upregulated by TGF-β. (b) The abundant fibrin-fibronectin complexes in the tumour ECM allow the binding of enough CREKA-Tris(Gd-DOTA)$_3$ to the ECM marker so as to generate sufficient signal enhancement for effective molecular MRI of small high-risk breast cancer and micrometastases.

Zhou et al., Nature Comm, 2015



MRI with a lymph-node-specifi c contrast agent as an alternative to CT scan and lymph-node dissection in patients with prostate cancer: a prospective multicohort study

Roel A M Heesakkers, Anke M Hövels, Gerrit J Jager, Harrie C M van den Bosch, J Alfred Witjes, Hein P J Raat, Johan L Severens, Eddy M M Adang, Christina Hulsbergen van der Kaa, Jurgen J Fütterer, Jelle Barentsz

9/2008

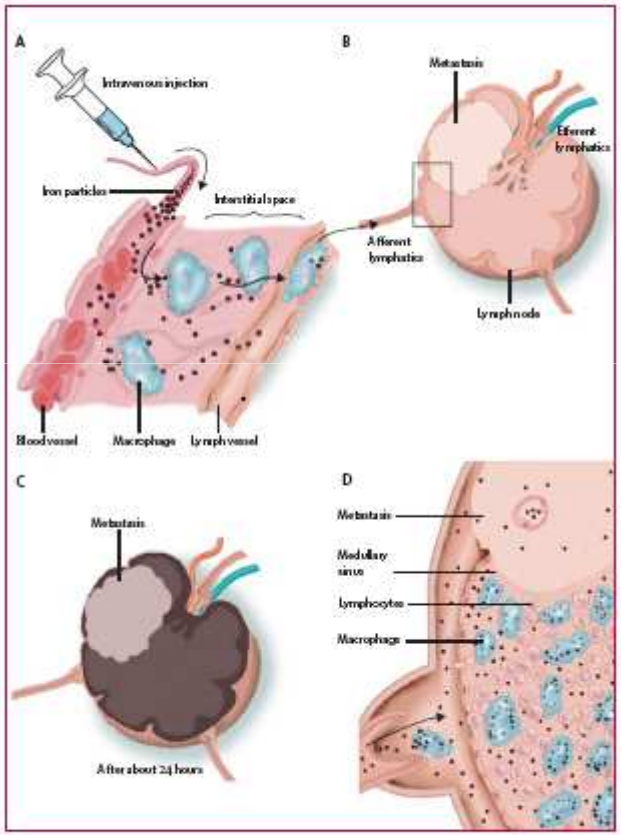
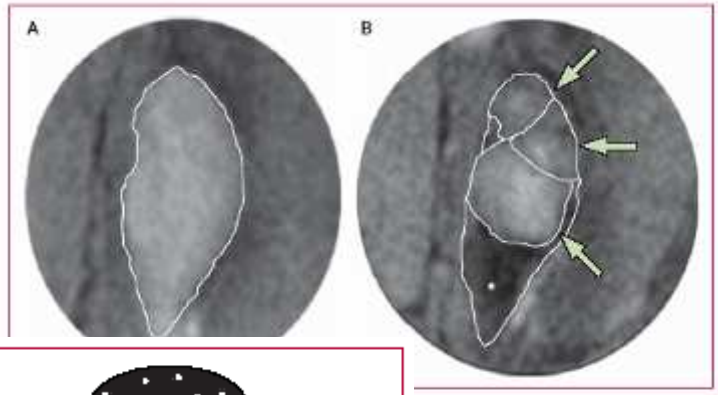


Figure 1: Mechanism of ferumoxtran-10
(A) Infused iron-particles slowly extravasate from the vascular to the interstitial space and are internalised by macrophages. (B) and (C) Iron-loaded macrophages are transported to lymph nodes via lymphatic vessels and accumulate in normal-sized lymph node tissue. These iron-loaded macrophages cause low signal intensity on T2*-weighted MR image. Box in B shows area depicted in D. (D) Disturbances of lymph flow or nodal architecture by metastases leads to less macrophages, depicted at MR imaging by higher signal intensity.



mage with partial metastatic lymph node before annot be discriminated. (B) MRL image, shows (arrows). Histopathology showed low signal

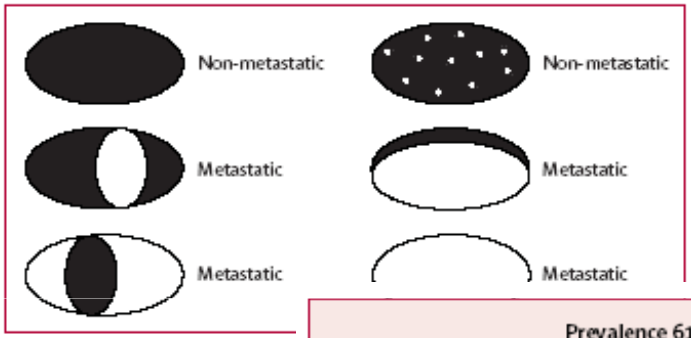


Figure 3: Classification of lymph r
echo images

	Prevalence 61/375 (16%)	
	MDCT	MRL
Sensitivity (%) (95% CI)	21/61 (34) (23–48)	50/61 (82) (70–90)
Specificity (%) (95% CI)	303/314 (97) (94–98)	291/314 (93) (89–95)
PPV (%) (95% CI)	21/32 (66) (47–81)	50/73 (69) (56–79)
NPV (%) (95% CI)	303/343 (88) (84–91)	291/302 (96) (93–98)
Post-test probability of	40/343 (12)	11/302 (4)

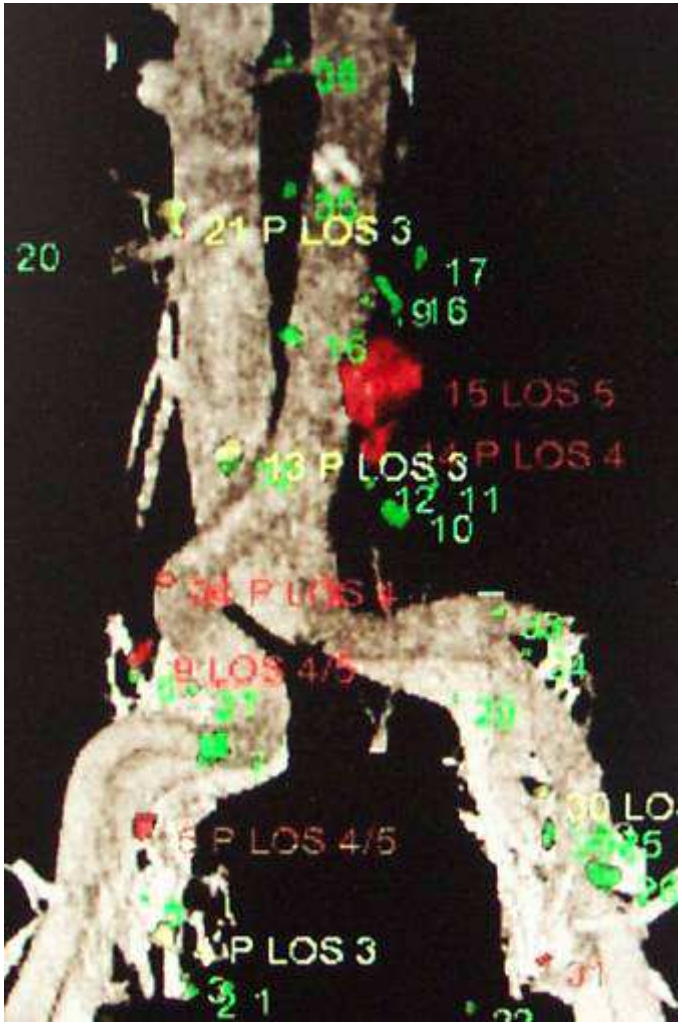
	Three experienced hospitals	Seven less experienced hospitals
Patients with MRL results, n	295	80
Sensitivity, n (%) (95% CI)	46/51 (90) (78–96)	4/10 (40) (14–73)
Specificity, n (%) (95% CI)	229/244 (94) (90–96)	62/70 (89) (78–96)
PPV, n (%) (95% CI)	46/61 (75) (62–85)	4/12 (33) (11–65)
NPV, n (%) (95% CI)	229/234 (98) (95–99)	62/68 (91) (81–96)
Post-test probability of false-negative finding (%)	5/234 (2)	6/68 (9)

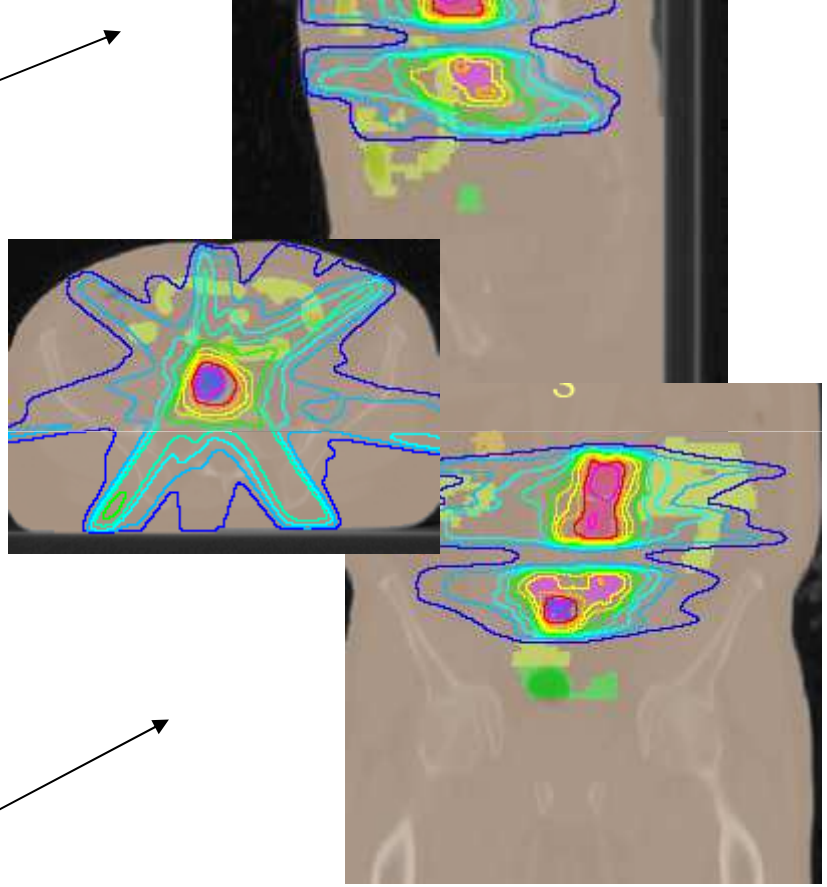
Table 3: Results of MRL in experienced and less-experienced participating hospitals

MRI with a lymph-node-specifi c contrast agent as an alternative to CT scan and lymph-node dissection in patients with prostate cancer: a prospective multicohort study

Roel A M Heesakkers, Anke M Hövels, Gerrit J Jager, Harrie C M van den Bosch, J Alfred Witjes, Hein P J Raat, Johan L Severens, Eddy M M Adang, Christina Hulsbergen van der Kaa, Jurgen J Fütterer, Jelle Barentsz

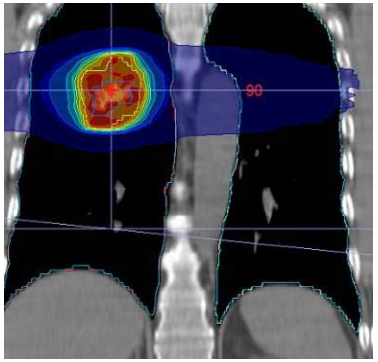
9/2008



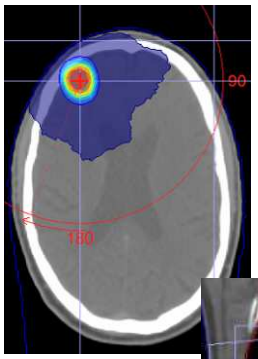


Oligometastases/Multitargets

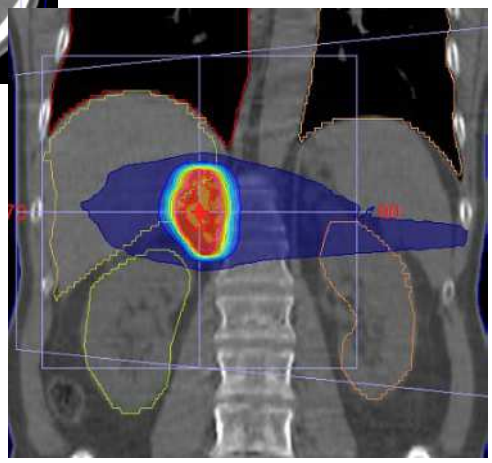
Oligomets – all lesions on one device

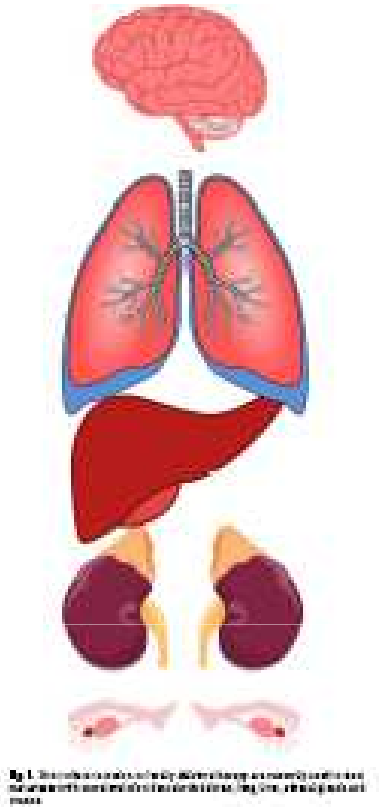


Primary Lung Cancer (60/5Gy)
after GR to Chemo 10/14



Brain Met Relapse
after WBRT 11/14



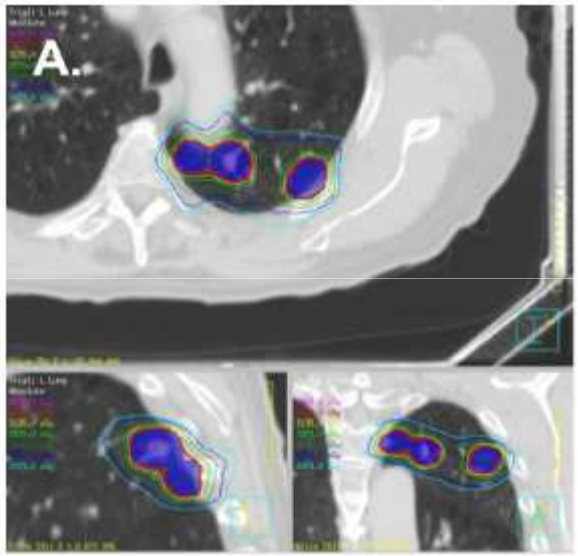


Westover, Lung Cancer, 2015

Suprarenal Met 10/5Gy 7/2015

New treatment possibilities in metastatic patients
Multiple lesions with one setup

Gupta, Webmedcentral, 2011

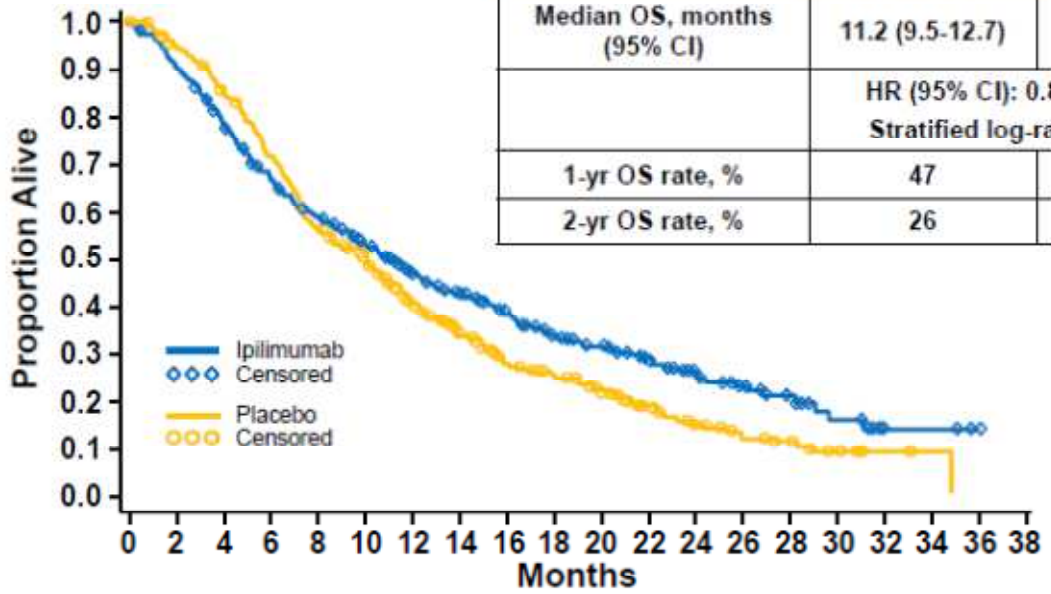


There is initial clinical proof but further data are needed
There is a strong clinical push in some indications such as Ewing‘s sarcoma

Immuntherapie

Overall Survival: ITT Population

	Ipilimumab (n=399)	Placebo (n=400)
Median OS, months (95% CI)	11.2 (9.5-12.7)	10.0 (8.3-11.0)
	HR (95% CI): 0.85 (0.72-1.00) Stratified log-rank P=0.0530	
1-yr OS rate, %	47	40
2-yr OS rate, %	26	15



Patients at Risk

Ipilimumab	399	362	306	260	228	195	155	131	106	85	69	52	37	24	15	9	4	3	1	0
Placebo	400	376	332	281	222	184	138	106	77	65	47	36	26	16	12	6	2	1	0	0

CP-Inhibitor combinations

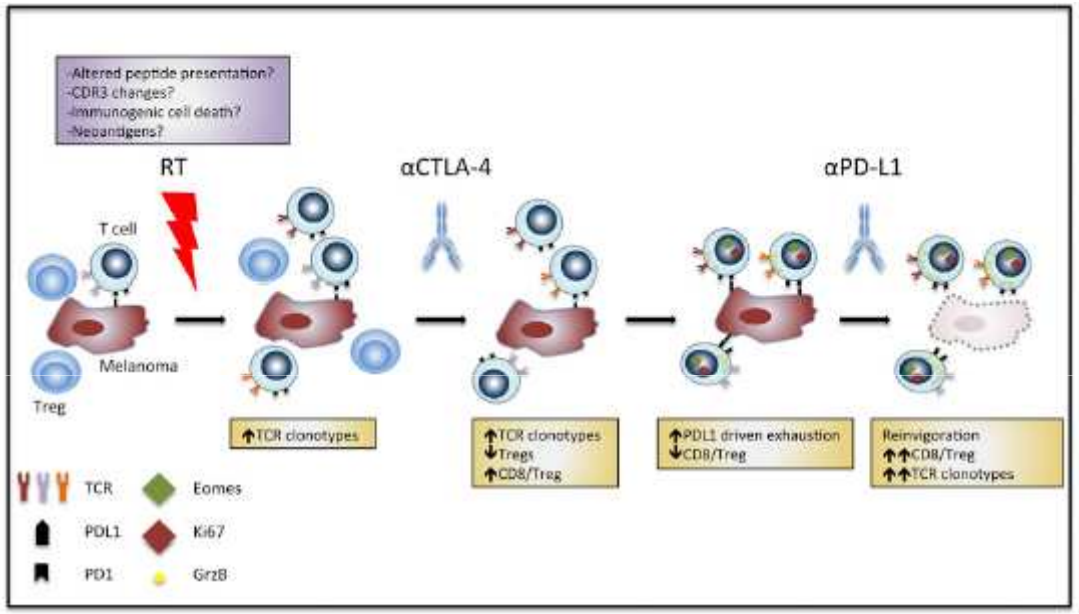


Figure 1. Schematic Model for Non-redundant Mechanisms of RT/Anti-CTLA-4/Anti-PD-L1 Therapy to Combat Immune Resistance in Melanoma
Adapted from Victor et al. (2015) Extended Data Figure 6.

Ngiow, Cancer Cell, 2015

RT Fraction Size

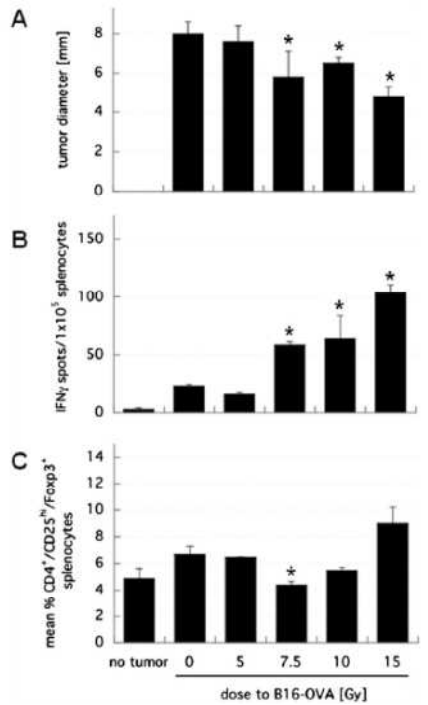


Fig. 1. Radiation dose-dependently increases tumor control and tumor-specific IFNγ$^+$ splenocytes and alters splenic regulatory T cells (Tregs). Mice were implanted with 0.8×10^6 B16-OVA cells subcutaneously in the leg and treated 10 days later with various doses of radiation. Tumor size and splenic responses were measured 7 days after treatment. (A) Tumor size as mean diameter in millimeters (2 dimension) of $n = 4-16 \pm$ standard error of the mean s.e.m. (B) Splenocytes were mixed *ex vivo* with EG7.OVA cells, and the number of IFNγ-producing cells was determined by enzyme-linked immunospot assay. Data are mean number of spots per 10^5 splenocytes of $n = 3-16 \pm$ s.e.m. (C) Splenocytes were stained for CD4, CD25, and Foxp3 and enumerated by flow cytometry. Data are mean CD4+, CD25+, and Foxp3+ Tregs as fraction of CD4+ splenocytes of $n = 1-11 \pm$ s.e.m. $*p < 0.05$ compared with 0 Gy.

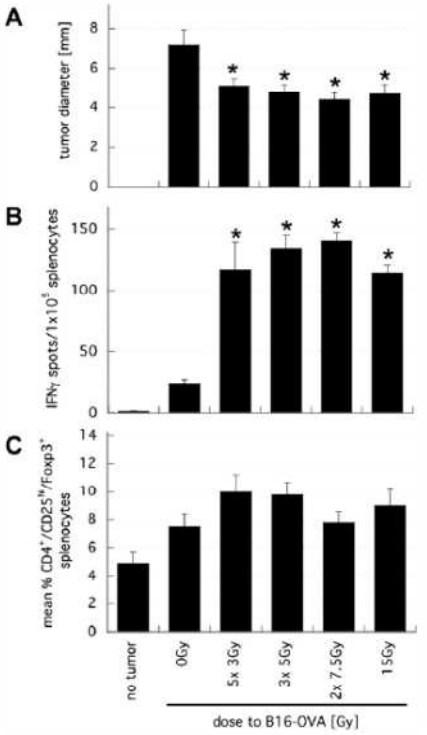


Fig. 2. Fractionated radiation affects tumor control and tumor-specific IFNγ$^+$ splenocytes and alters splenic regulatory T cells (Tregs). Mice bearing B16-OVA tumors 4 mm in size were given fractionated radiation in 6 hour intervals of a total dose of 15 Gy and left for 7 days to recover. (A) Tumor size as mean diameter of $n = 12 \pm$ standard error of the mean s.e.m. (B) Mean number of IFNγ-enzyme-linked immunospots per 10^5 splenocytes of $n = 3-6 \pm$ s.e.m. in response to EG7.OVA *ex vivo* restimulation. (C) Mean percent of splenic CD4$^+$CD25$^+$Foxp3$^+$ Tregs as analyzed by Fluorescent Activated Cell Sorting FACS of $n = 8-12 \pm$ s.e.m. $*p < 0.05$ compared with 0 Gy.

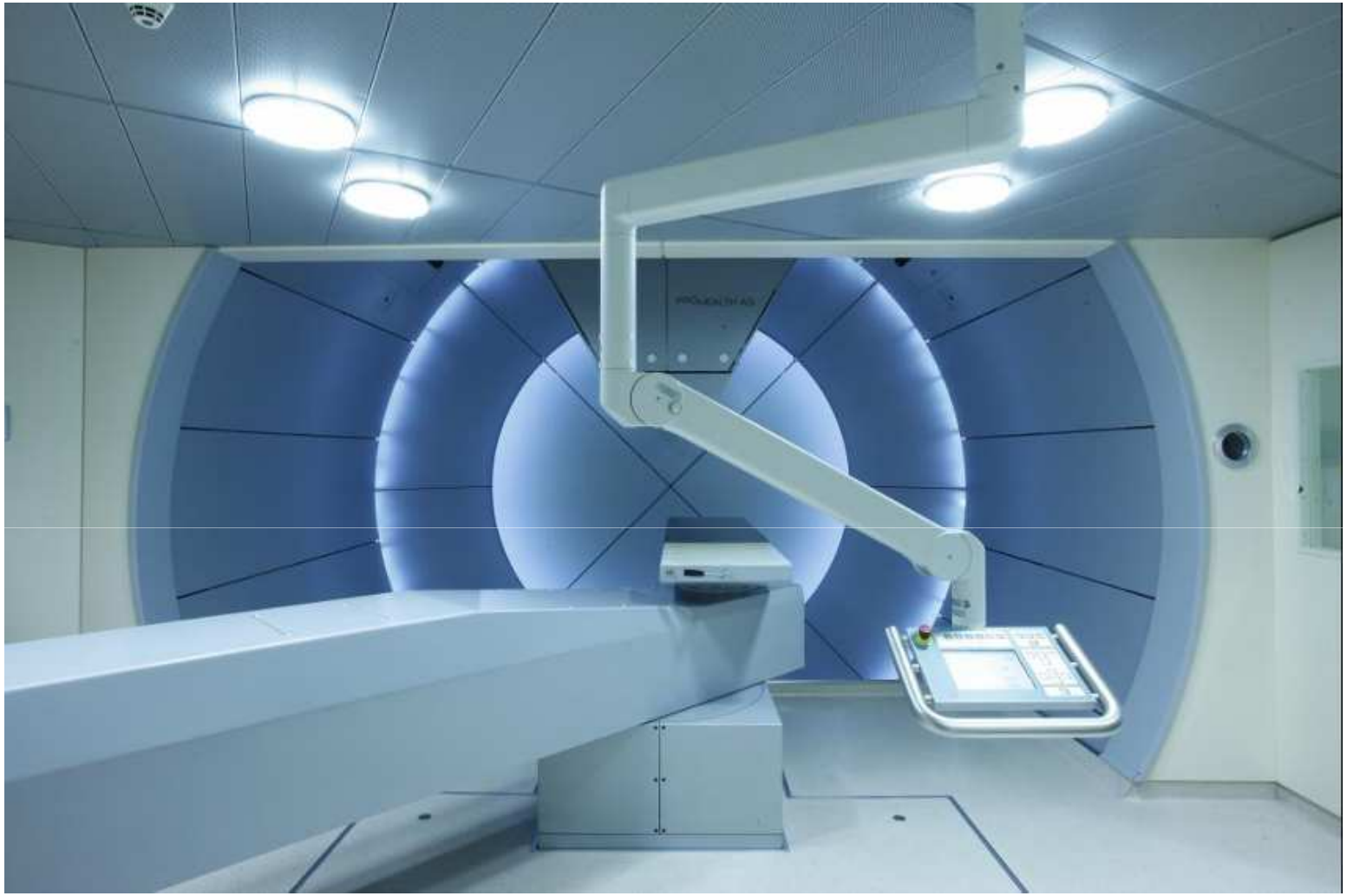
Schaue/McBride, IJROBP,2011

…..and keeping in mind this….

„Nivolumab versus Everolimus in advanced renal cell carcinoma“

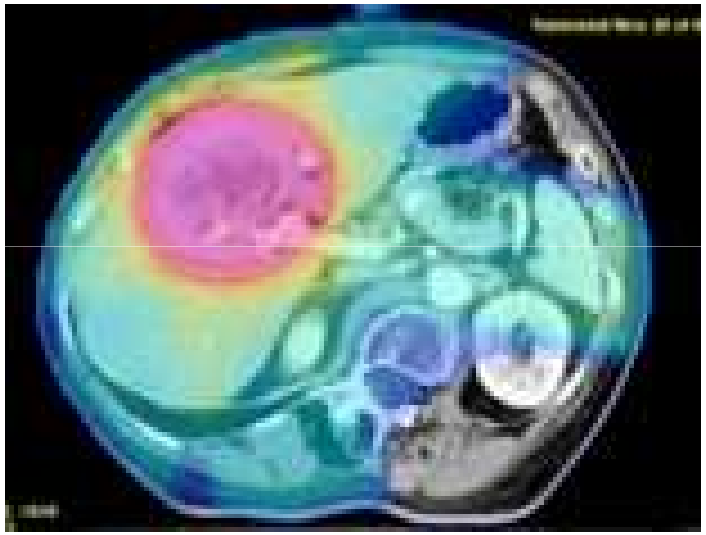
Motzer et al., NEJM, published online a few days ago

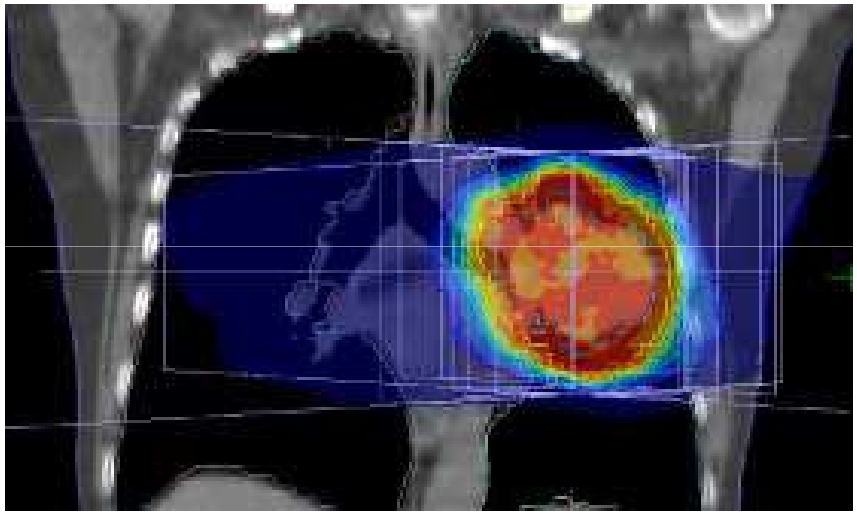
And finally: Is there anything left for……



?

Rationale for Particles in Radiosurgery





Large Liver and Lung Lesions

Drivers of IMRT

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Modena
Policlinico

Thing‘s weren‘t perfect prior to IMRT

Need to avoid Toxicity

Evolution of Technology / IGRT / Online Adaptation

Chronification of Disease/Oligometastases

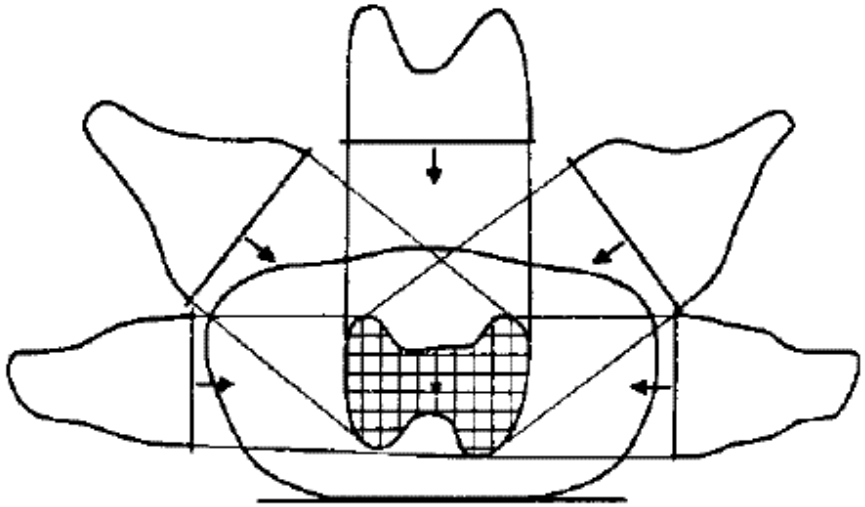
Conveniece / Economical Factors / Simplification of established paradigms

Expanding Indications for SBRT (e.g. Prostate with the need for dose shaping)

Potentially a new Paradigm in Combination with Immunotherapy

Centro di Protonterapia
Azienda Provinciale per i Servizi Sanitari
Trento, Italy

IMRT dose delivery methods



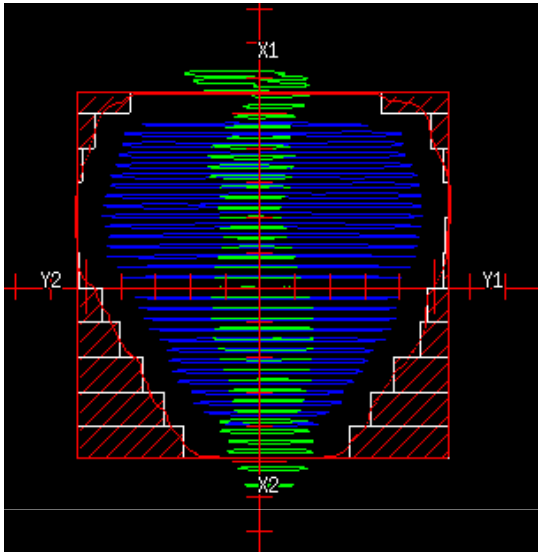
Marco Schwarz

marco.schwarz@apss.tn.it

Disclosure

My department has a contract with Philips Medical Systems concerning alpha and beta testing of treatment planning software for proton therapy with pencil beam scanning.

Why did we end up with IMRT?

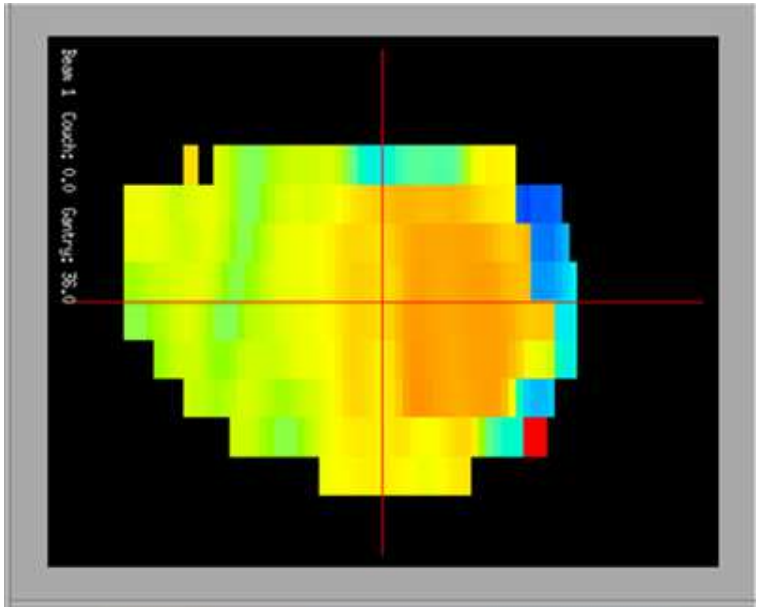


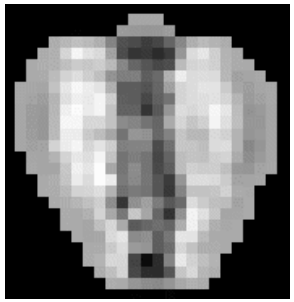
What we were calling ‘3D conformal RT’ was often not that conformal.

With photons, achieving dose modulation with the falloff along the beam direction is hopeless

No technology, however fancy, will change that.

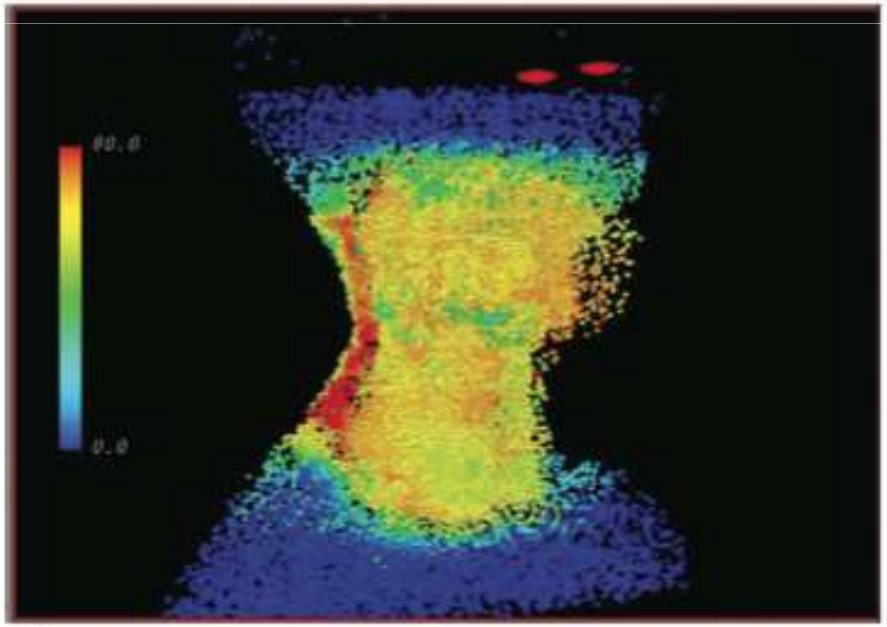
We are therefore left with modulating particles fluence in the cross plane, hence IMRT.

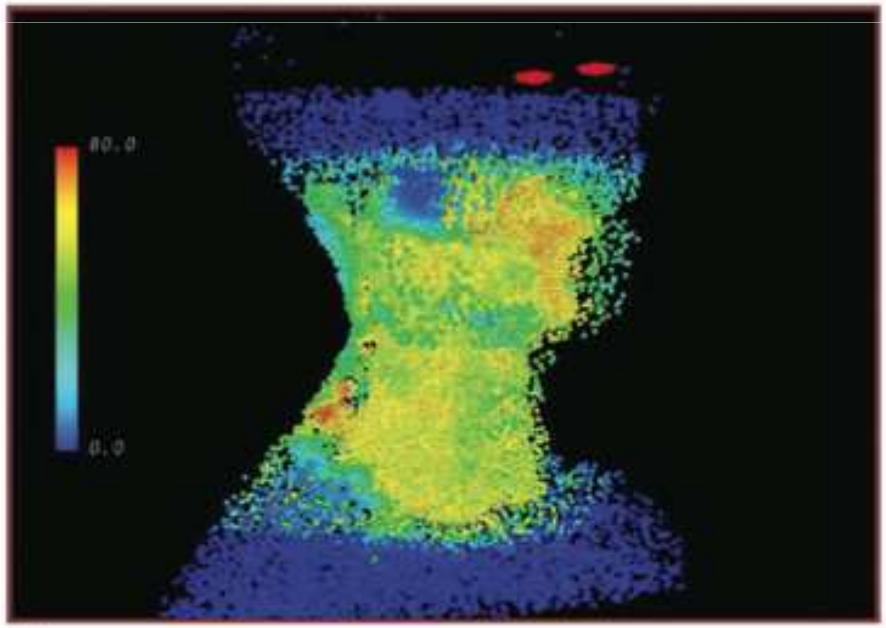




How can we modulated particle fluence?

In principle, by controlling the beam intensity at the level of the single beam elements (‘bixel’/’beamlet’)

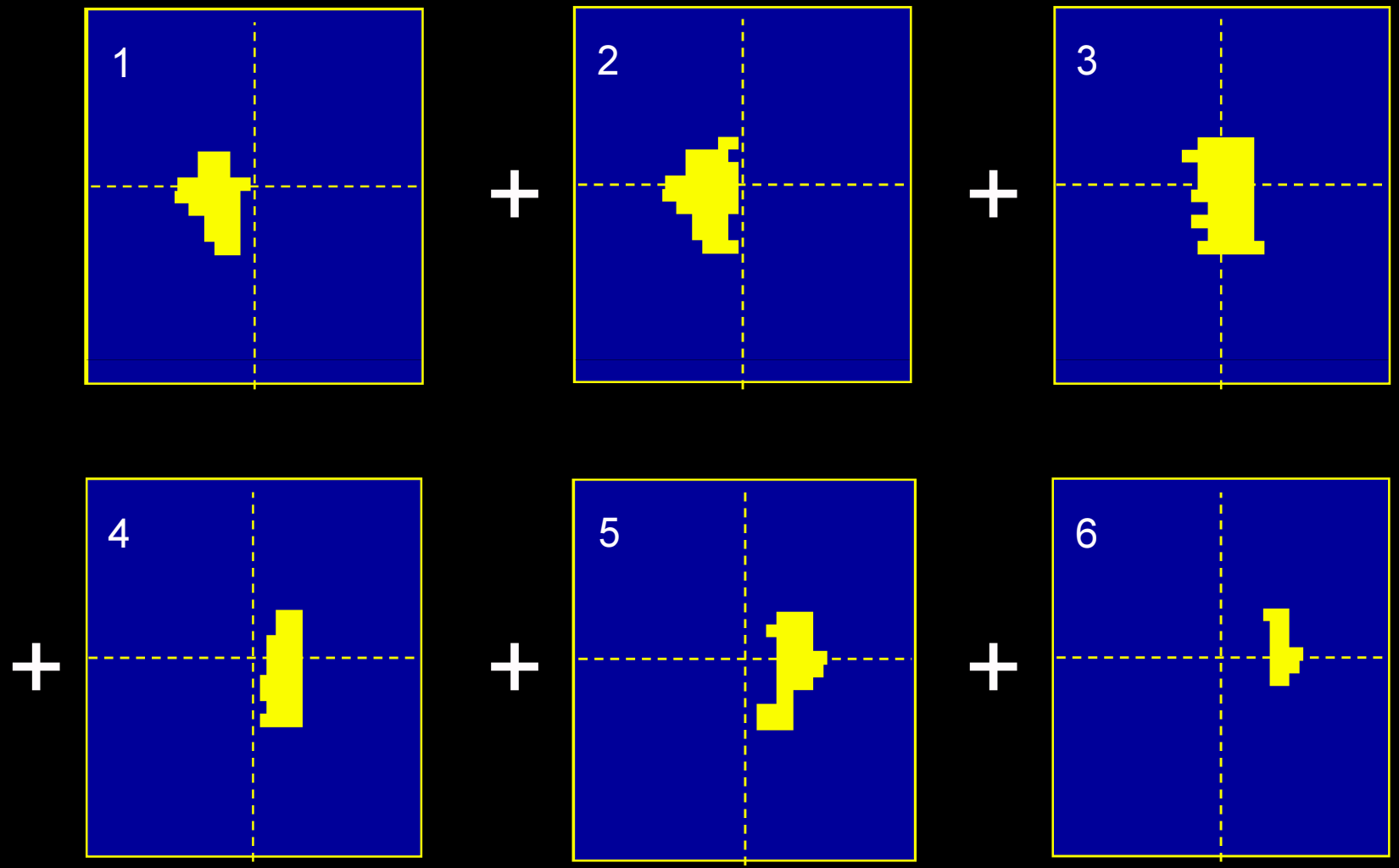




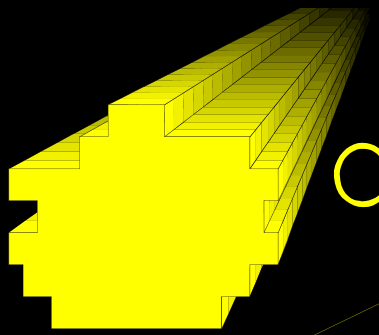
Principle and terminology

Calculated fluence map, bixels, intensity levels

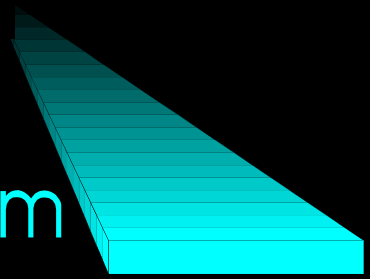
Subfields (or segments)



Intensity modulation with MLC



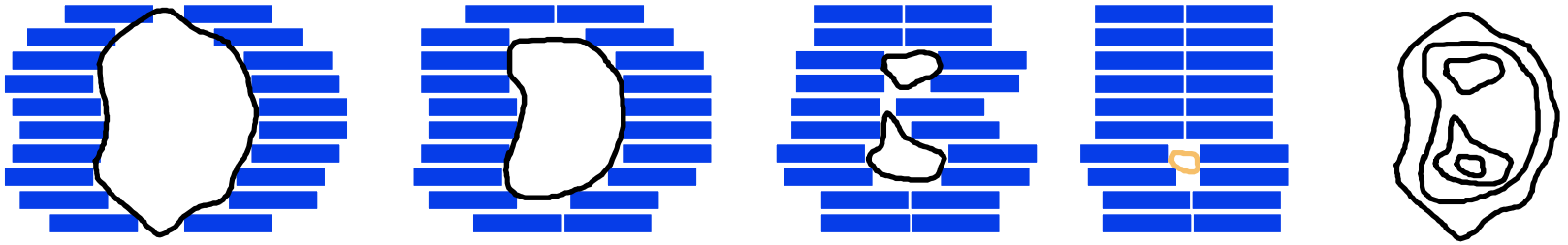
Cone Beam



Fan Beam

- Static Fields
  - MLM
    - dynamic
    - multiple subfields
- Arc Treatment
  - IMAT
- Spiral Treatment
  - Tomotherapy
- Multiple Rotations
  - Peacock/ NOMOS Mimic

‘Close-in’ technique



A-Leaves B-Leaves

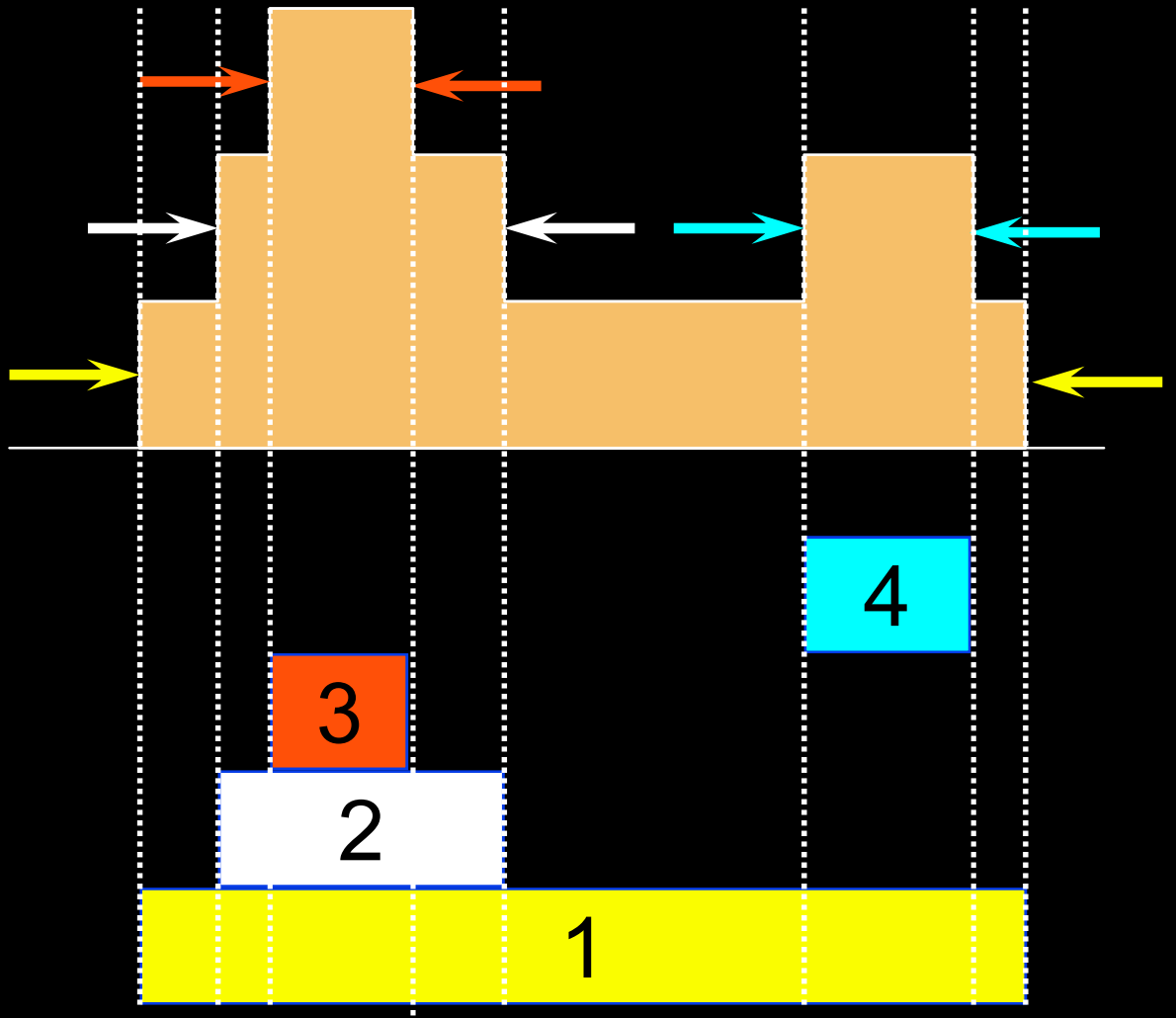
‘Sweep’ technique

A-Leaves B-Leaves

Close-in vs. sweep ≠ static vs. dynamic

“Close-in” technique

IM-Profile:

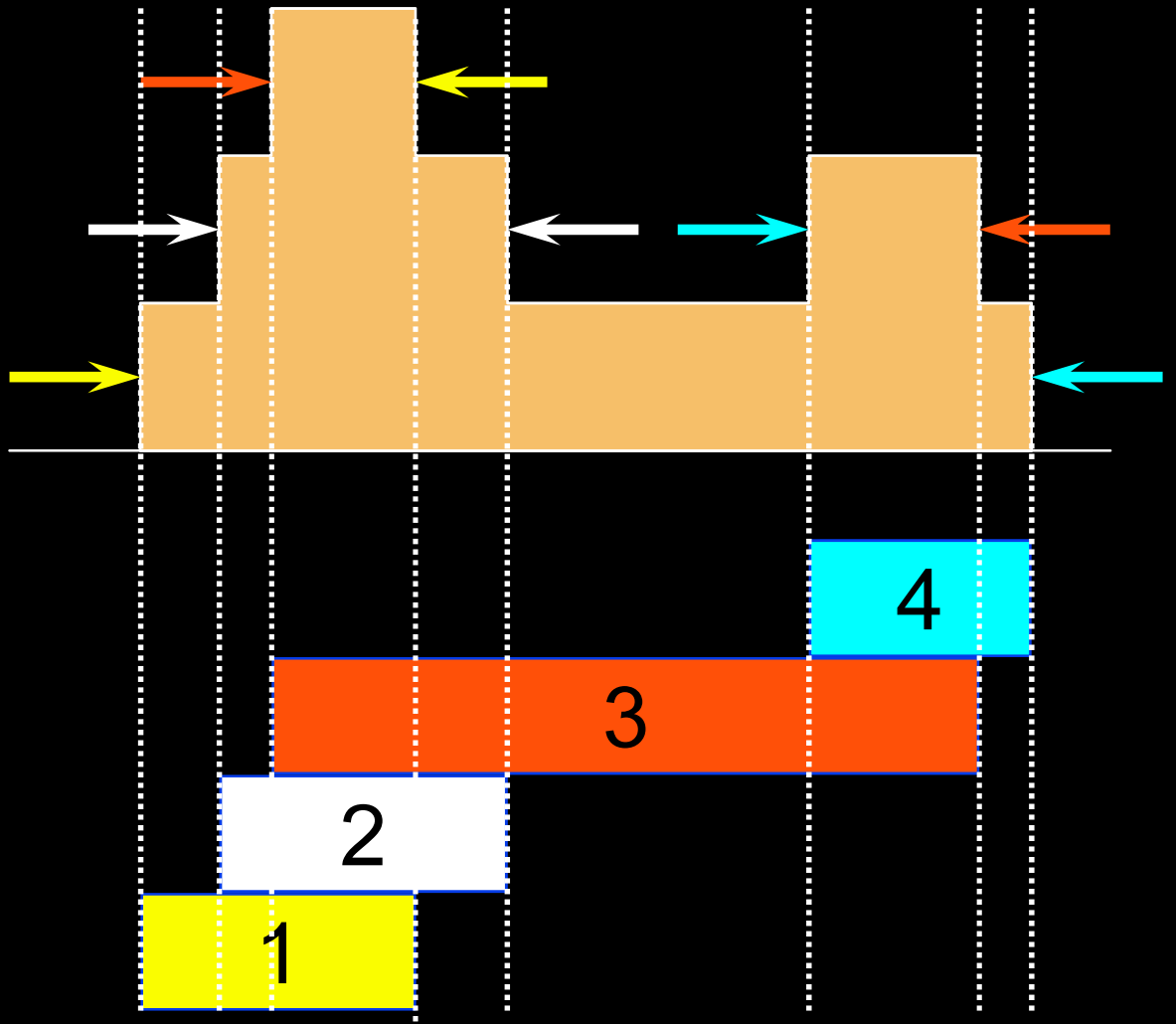


Trajectory:

“Sweep” technique

IM-Profile:

Trajectory:



Pro's and Con's

Pro static delivery

- Simpler extension of 3D-CRT techniques
- Somewhat more intuitive
- Somewhat easier to control the level of complexity

Pro dynamic delivery

- Generally faster
- Better suited for highly complex profiles
- Enables rotational therapy, dynamic tracking

Sequencing & Optimization: The “reducing levels” technique (Xia, Verhey)

Desired fluence map

1	6	7	3
1	4	4	2
2	0	5	7
3	2	6	3

The “reducing levels” technique (Xia, Verhey)

Bixel values 4 or higher

1	6	7	3
1	4	4	2
2	0	5	7
3	2	6	3

The “reducing levels” technique (Xia, Verhey)

Treat with 4 units

1	6	7	3
1	4	4	2
2	0	5	7
3	2	6	3

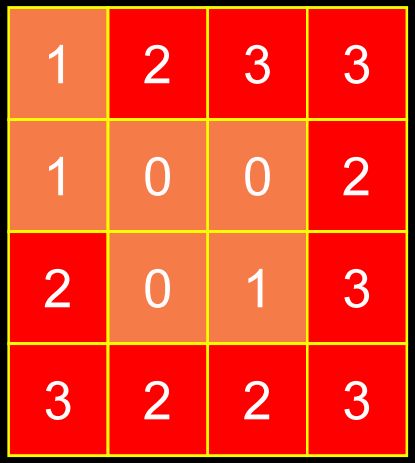
The “reducing levels” technique (Xia, Verhey)

Remainder

1	2	3	3
1	0	0	2
2	0	1	3
3	2	2	3

The “reducing levels” technique (Xia, Verhey)

Bixel values 2 or higher



The “reducing levels” technique (Xia, Verhey)

Treat with 2 units

1	2	3	3
1	0	0	2
2	0	1	3
3	2	2	3

The “reducing levels” technique (Xia, Verhey)

Remainder

1	0	1	1
1	0	0	2
0	0	1	3
1	0	0	1

The “reducing levels” technique (Xia, Verhey)

Bixel values 2 or higher

1	0	1	1
1	0	0	2
0	0	1	3
1	0	0	1

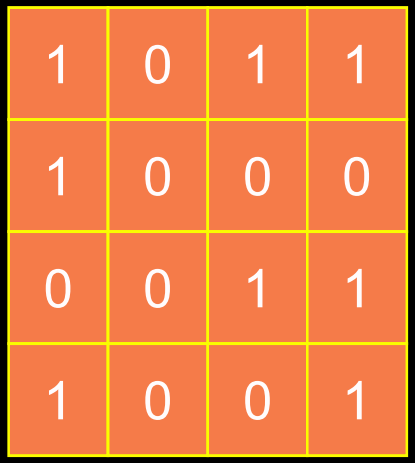
The “reducing levels” technique (Xia, Verhey)

Treat with 2 units

1	0	1	1
1	0	0	2
0	0	1	3
1	0	0	1

The “reducing levels” technique (Xia, Verhey)

Remainder



The “reducing levels” technique (Xia, Verhey)

Treat with 1 unit

1	0	1	1
1	0	0	0
0	0	1	1
1	0	0	1

The “reducing levels” technique (Xia, Verhey)

Treat with 1 unit

0	0	1	1
0	0	0	0
0	0	1	1
0	0	0	1

Delivered MUs

Affected by quality of sequencing algorithms

Tradeoff between quality of treatment and delivery efficiency

Significant issues with old-style MLCs

In the past 7-10 years the optimization of deliverable segments (available for years in research TPS platforms) became increasingly popular, allowing more efficient planning and delivery approaches

IMRT-relevant features of MLCs

1 Geometric Design

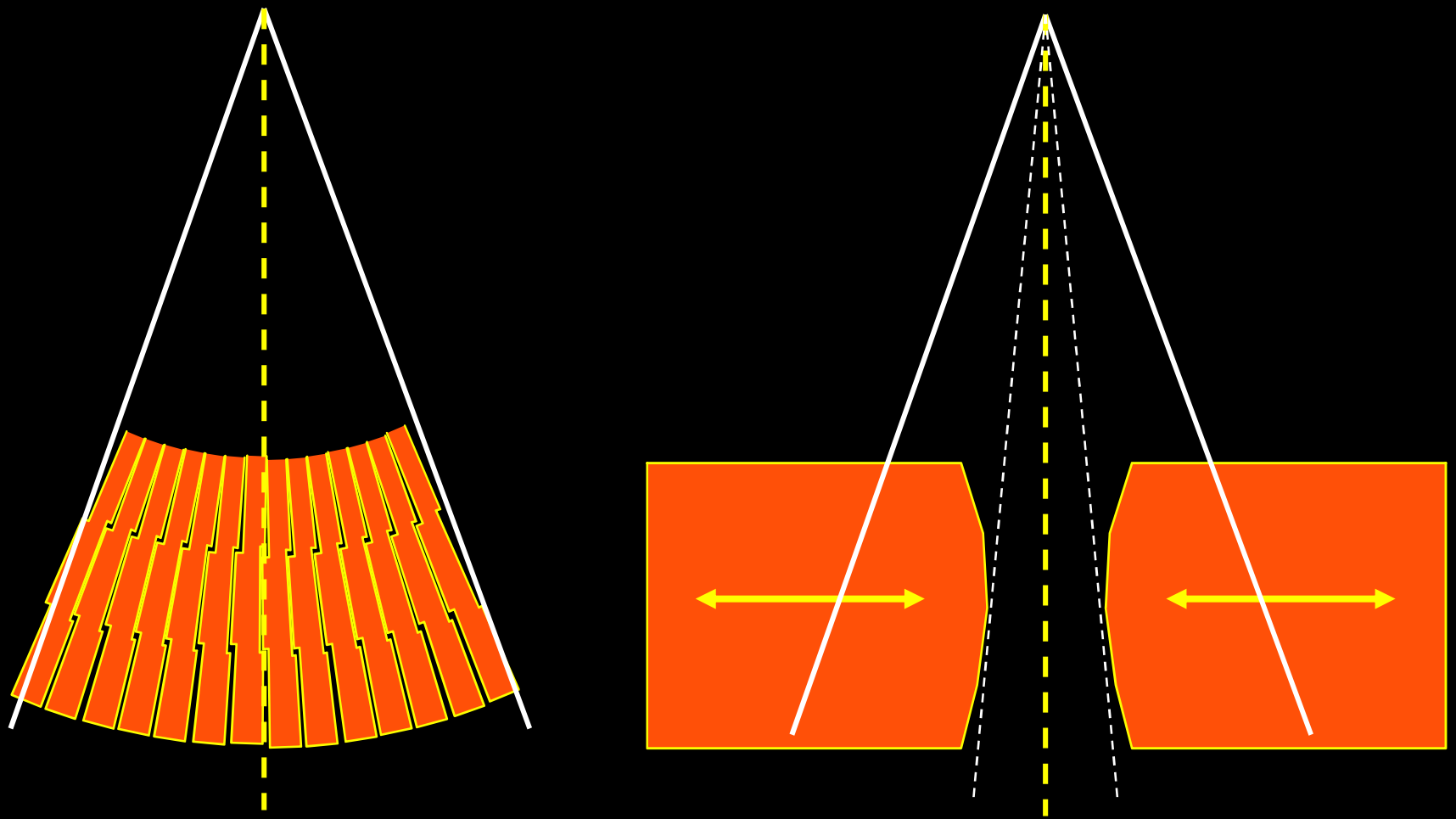
2 Tongue & Groove Construction

3 Collision Protection

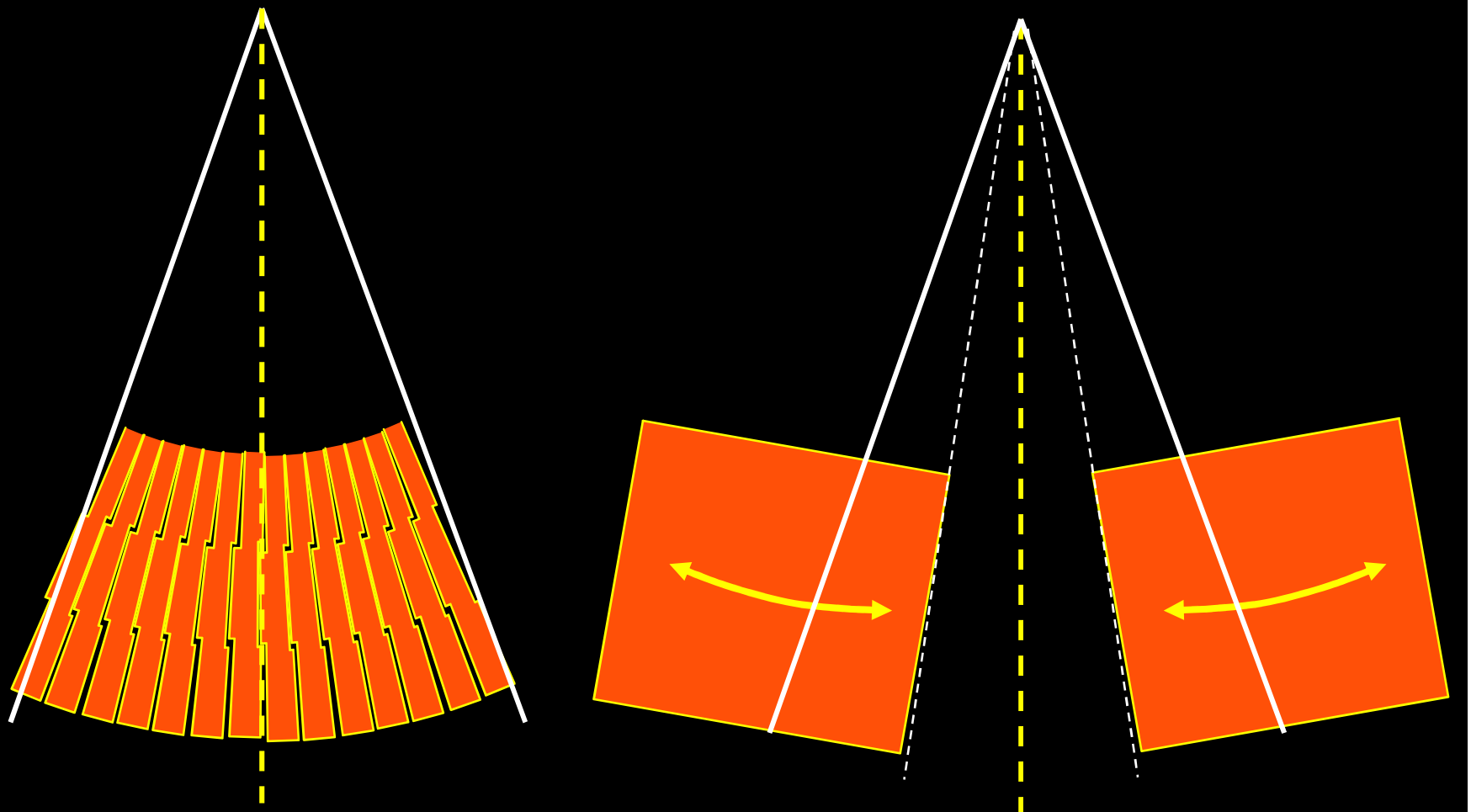
4 Leaf Transmission & Interleaf Leakage

5 MLC tip shape

Geometric design: single focused



Geometric design: double focused



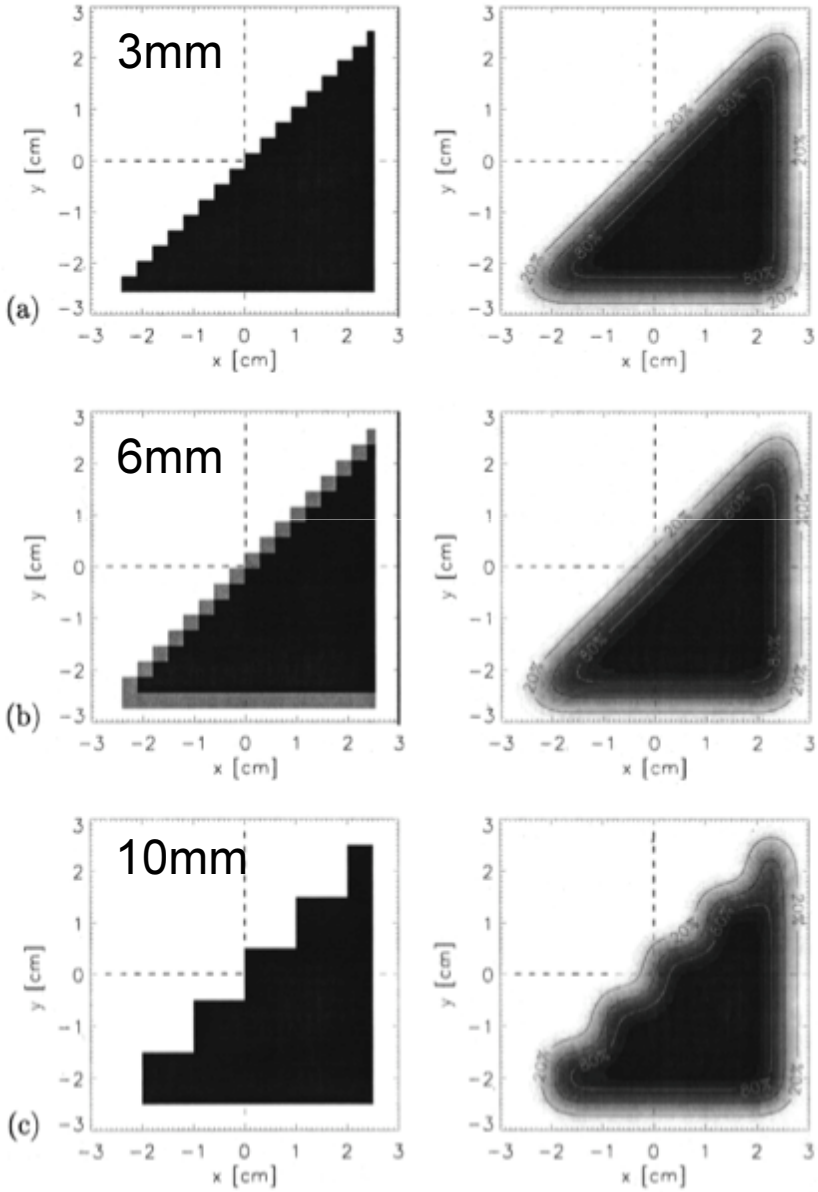
Saves about 0.5 mm penumbra
Light field and radiation field coincide
Leaves can be closed in the field

What is the optimum leaf width ?

1.5 - 2 mm ideally
(from sampling theory)

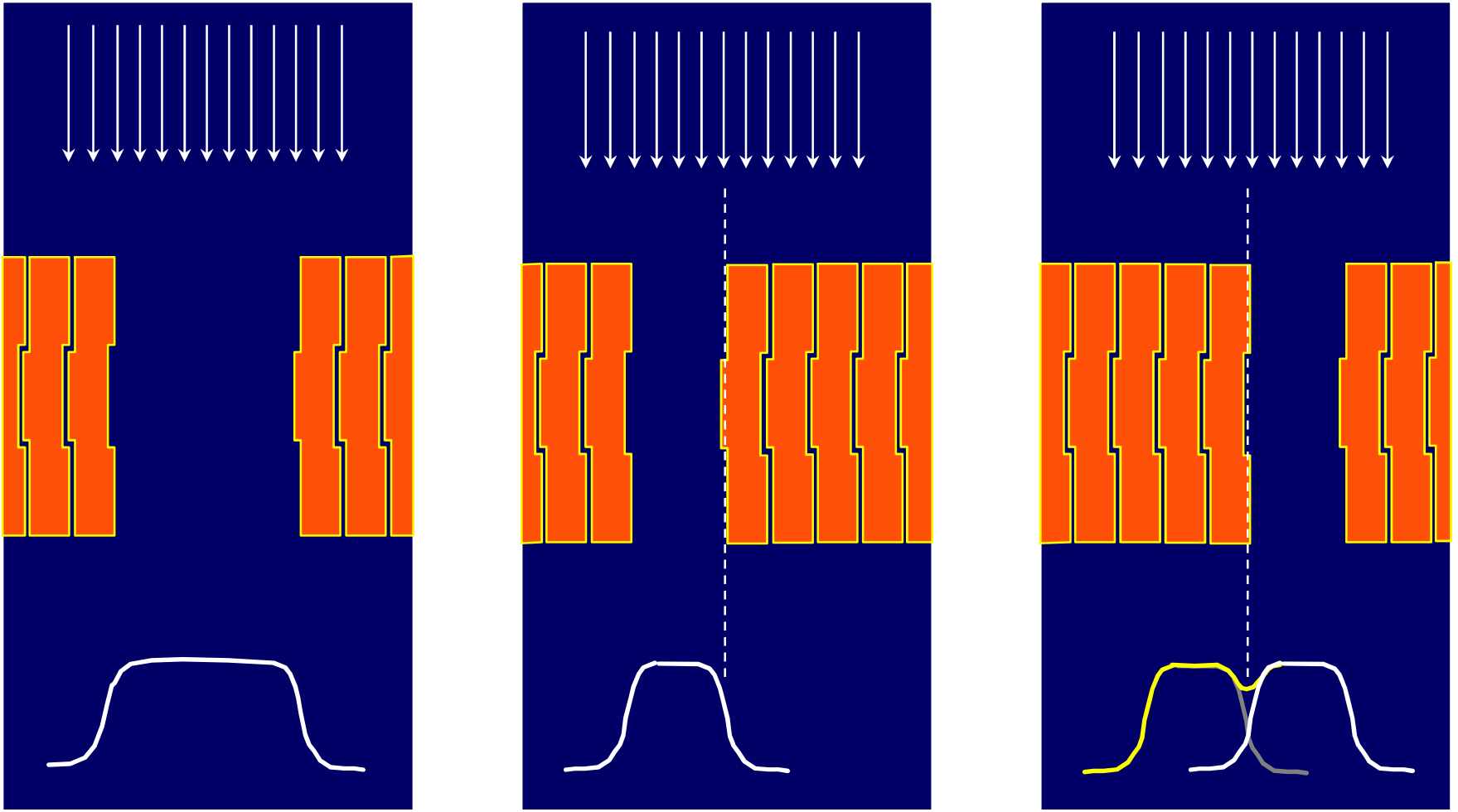
3 - 4 mm realistically

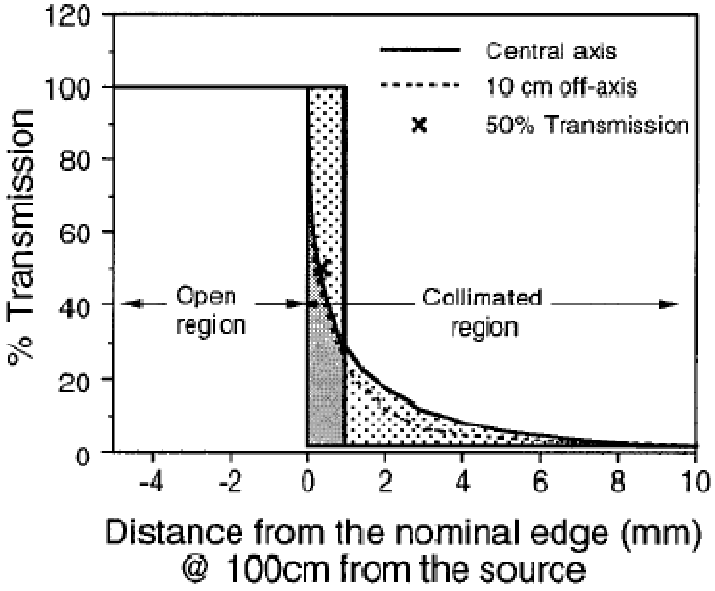
5 mm pragmatic solution for
'general purpose' MLC



Bortfeld, Med. Phys. 2000

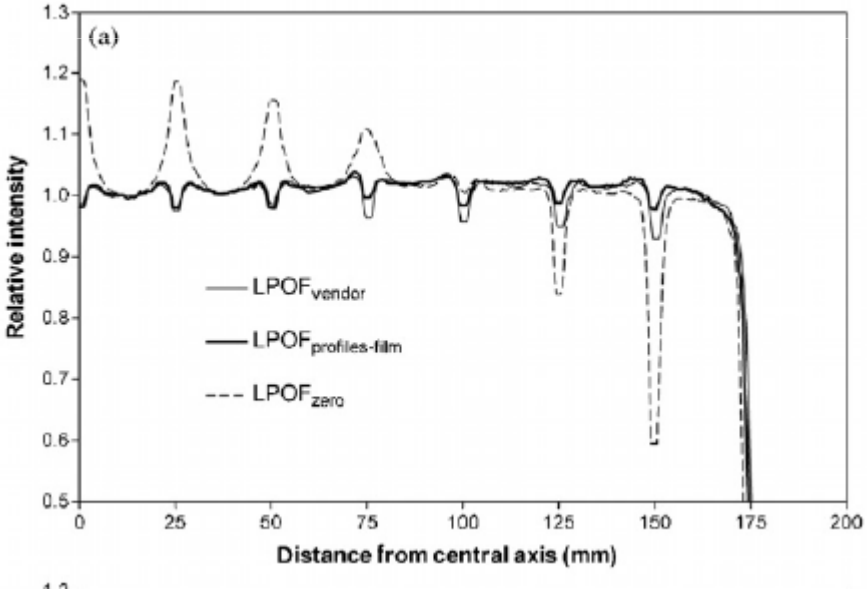
Tongue & groove effect





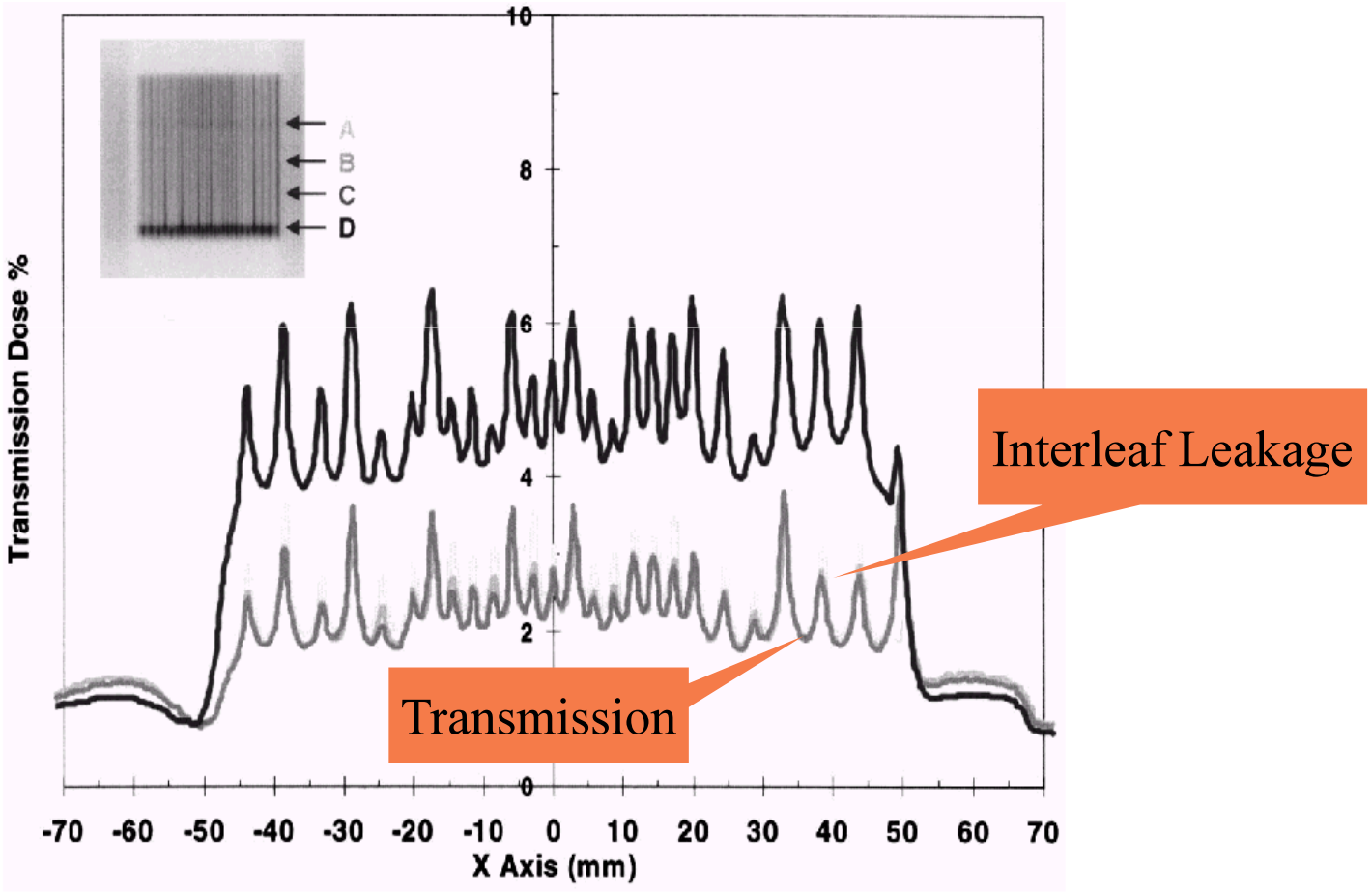
Dosimetric leaf separation

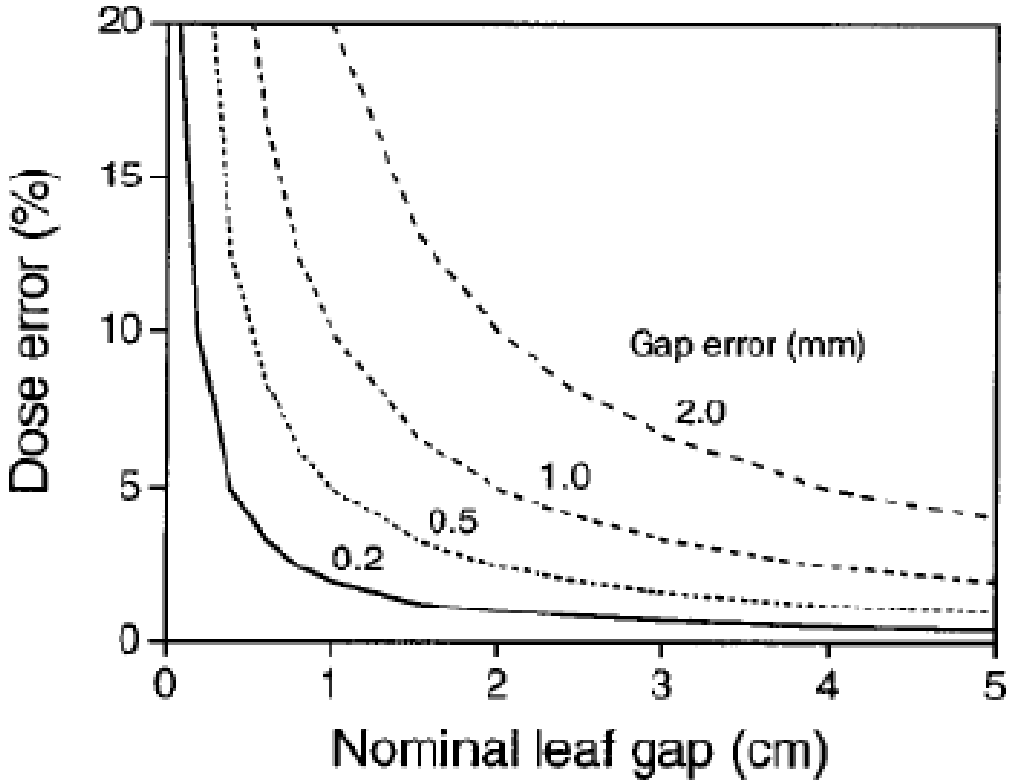
Need to correct
for the MLC rounded tip



Vial et al, PMB '06

Leaf transmission and interleaf leakage



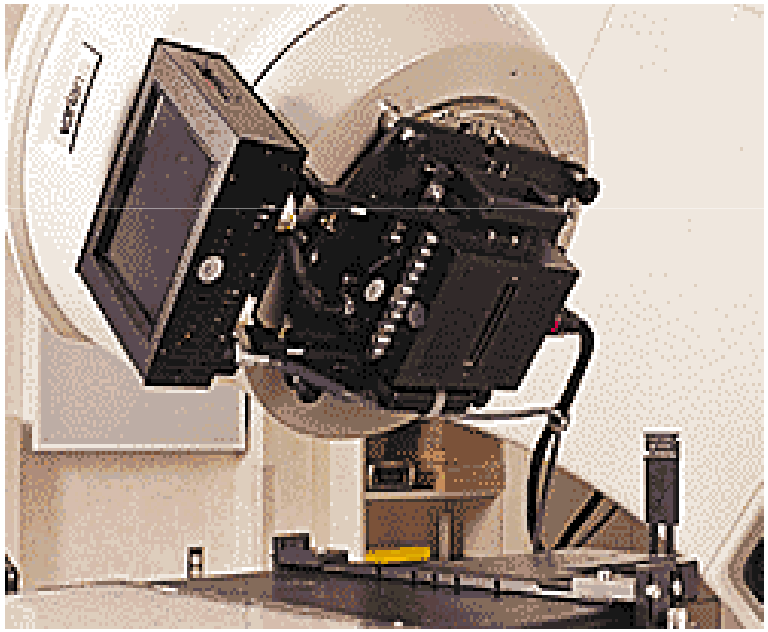


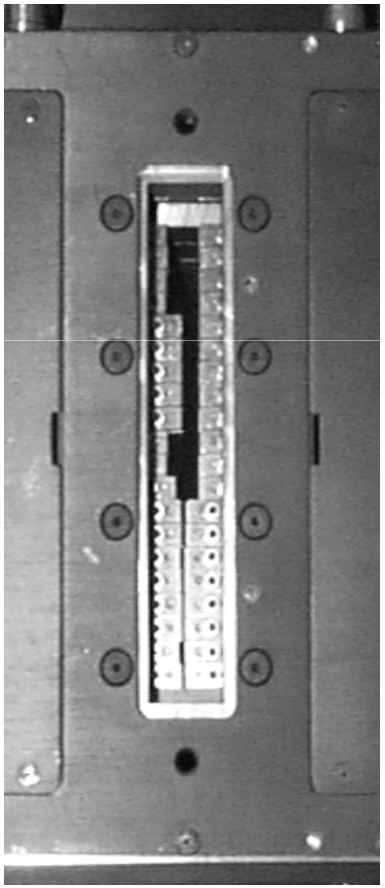
LoSasso et al, MedPhys '98

Tight(er) leaf position accuracy criteria, in particular for DMLC

MLCs through the years

‘serial tomotherapy’ mimic system





Elekta MLCi2

Number of Leaf Pairs: 40

Field Size: 40 cm x 40 cm

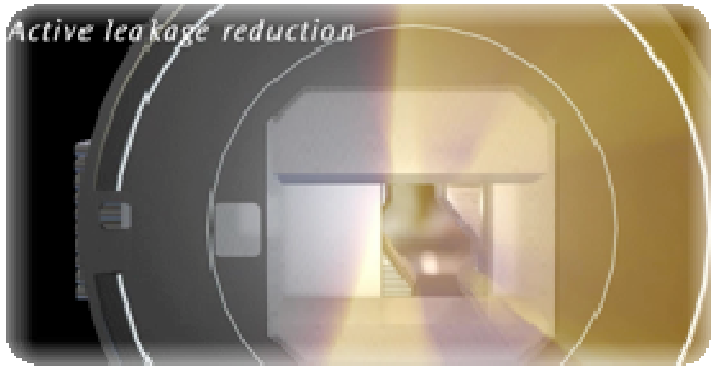
Maximum Overtravel: 12.5 cm

Leaf Width at Isocenter: 1 cm

Maximum Leaf Speed: 2 cm/s

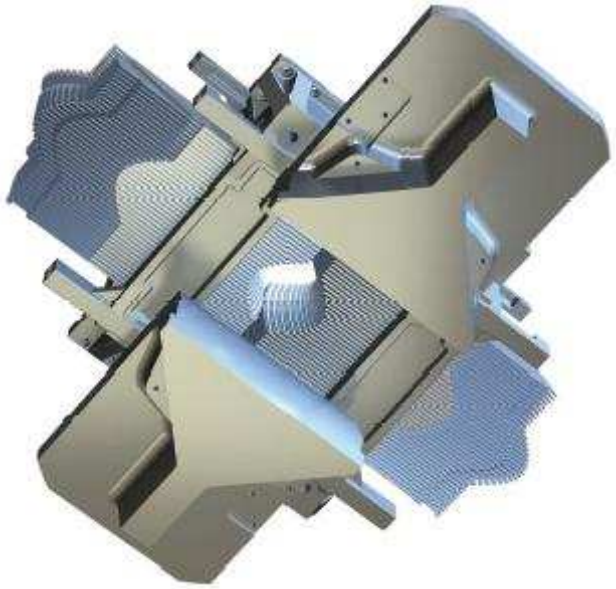
Clearance to Isocenter: 45 cm

Replaces Upper Jaw Pair
(+ Backup Jaws)



Elekta Agility

Number of Leaf Pairs: 80
Field Size: 40 cm x 40 cm
Maximum Overtravel: 15 cm
Leaf Width at Isocenter: 0.5 cm
Leaf Transmission: < 0.5%
Maximum Leaf Speed: 6.5 cm/s
Clearance to Isocenter: 45 cm
Replaces Upper Jaw Pair



Leaves	35mm/s
Dynamic Leaf Guides	30mm/s
Diaphragms	90mm/s

Elekta Beam Modulator

Number of Leaf Pairs: 40

Field Size: 21 cm x 16 cm

Maximum Overtravel: 10.5 cm

Leaf Width at Isocenter: 0.4 cm

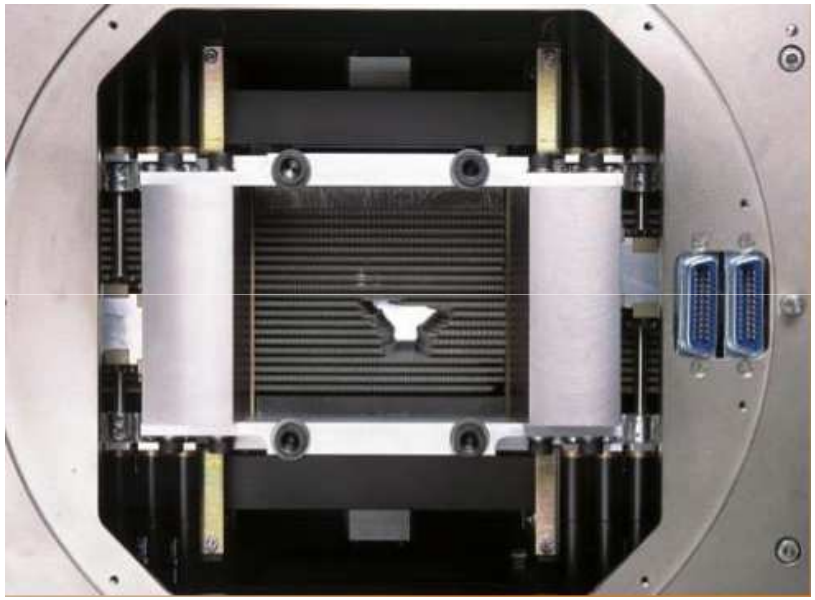
Leaf Transmission: < 1% @ 6MV

Maximum Leaf Speed: 2.2 cm/s

Clearance to Isocenter: 45 cm

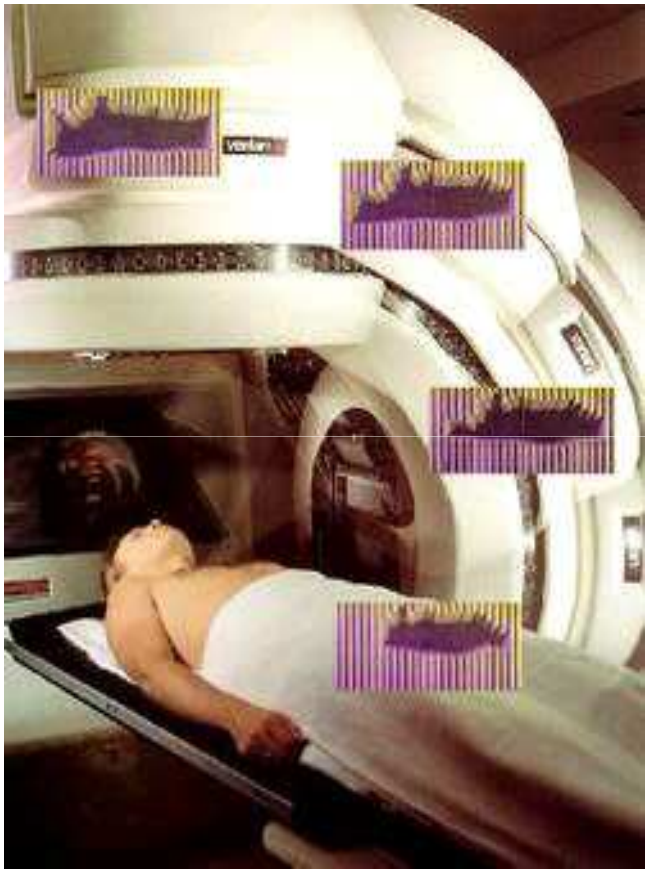
Fixed jaws

Leaves interdigitation allowed



Varian MLCs - 1

Number of Leaf Pairs: 40 or 60
Field Size: 40 cm x 40 cm
Maximum Overtravel: 16 cm
Maximum Leaf Separation: 14.5 cm
Leaf Width at Isocenter: 1 cm
  or 0.5 cm
Leaf Transmission: < 1.5-2%
Maximum Leaf Speed: 1.5 cm/sec
Clearance to Isocenter: 41.5 cm



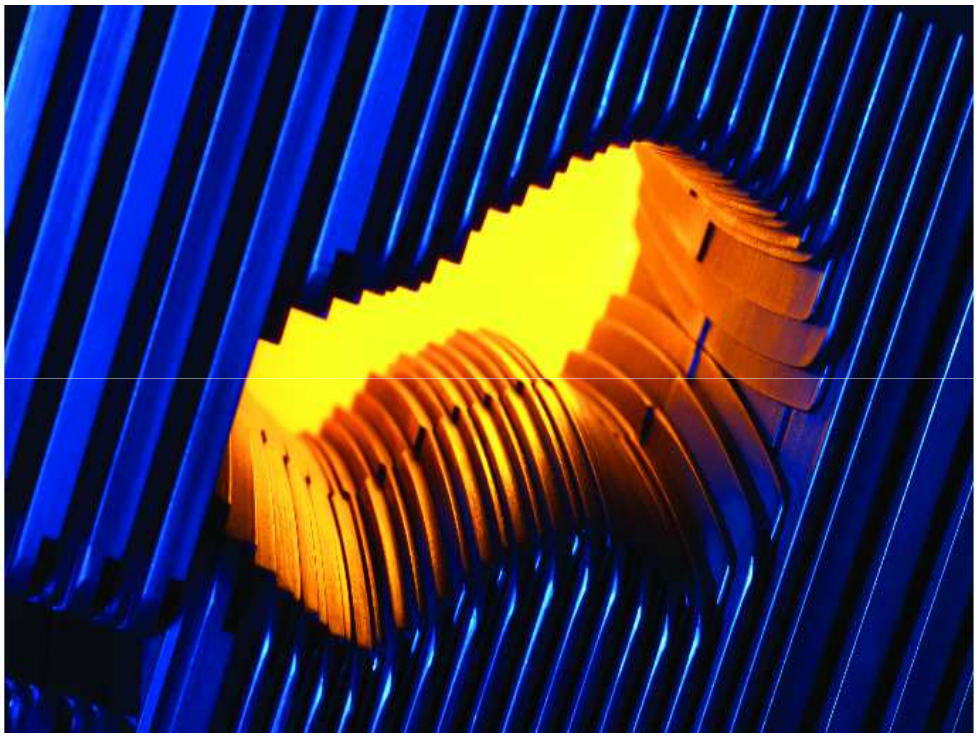
VARIAN MLCs -2

HD 120

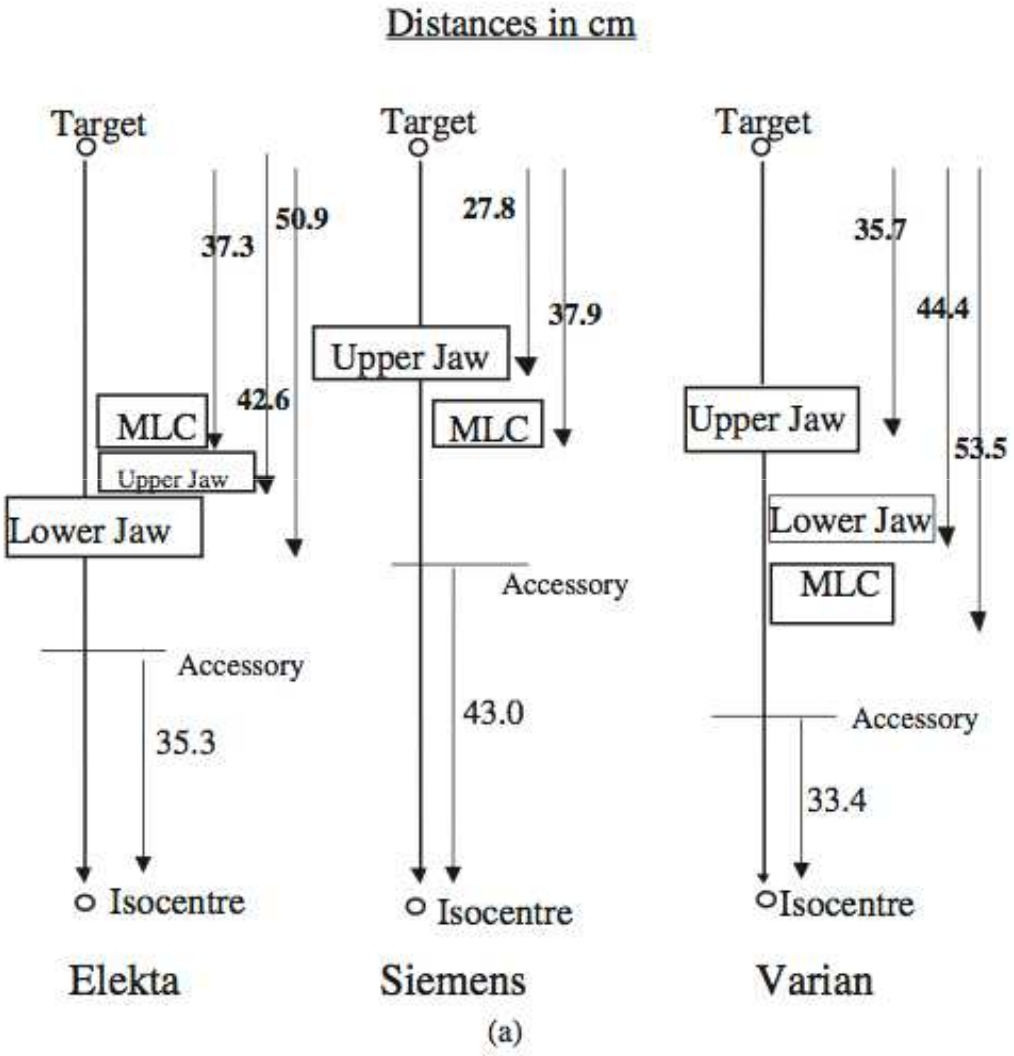
32 central LP 2.5 mm leaf width

28 outer LP 5.0 mm leaf width

Attenuation:1%



Collimation geometry

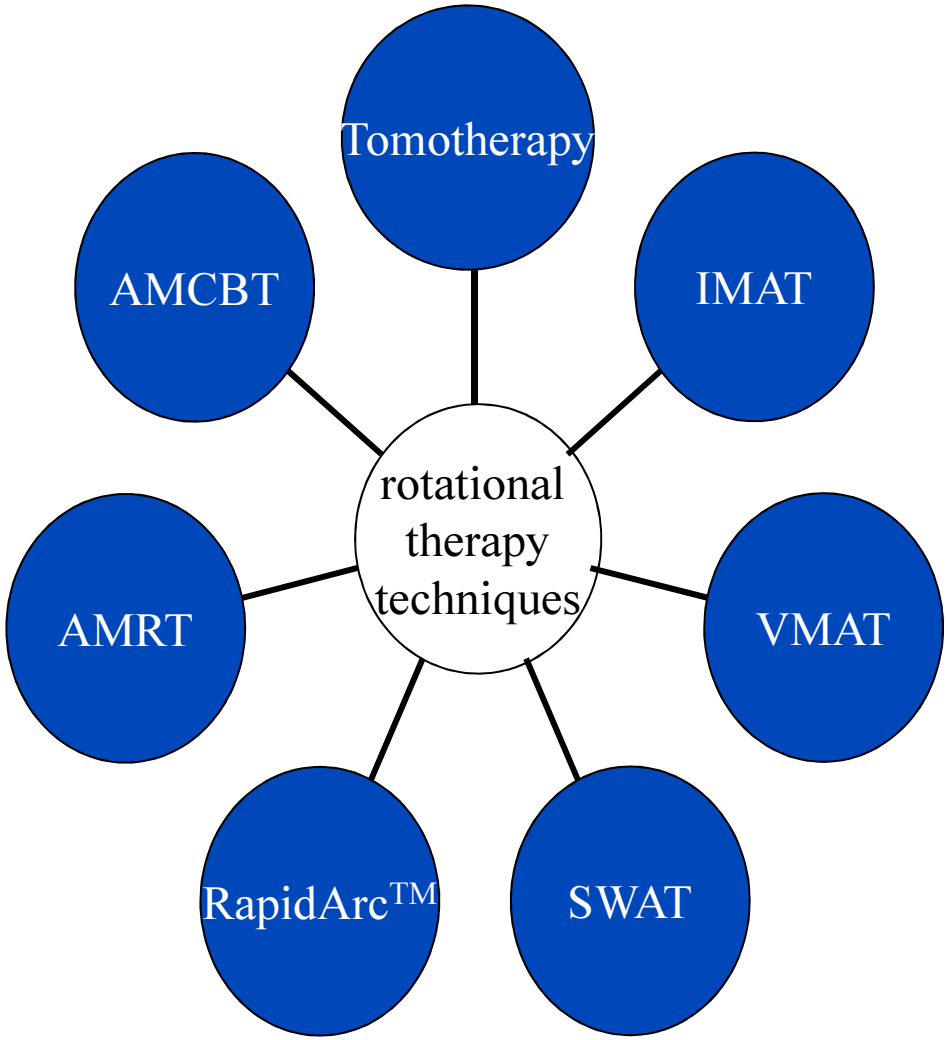


Huq et al.
PMB 47 N159-N170
2002

Add-on MLCs

Company	Brain-LAB m3	Radionics	Siemens** (MRC) µ-MLC	Siemens (MRC) Moduleaf	3D Line	Direx AccuLeaf
# Leaf pairs	26	31	40	40		36
Field size (cm^2)	10 x 10	10 x 12	7.3 x 6.4	12 x 10		11 x 10
Overcenter travel (cm)	5	No data	1.4	5.5		3,3
Leaf width (mm)	3.0 – 5.5	4.0	1.6	2.5		3,1-4,6
Leaf trans-mission (%)	< 4	< 2	< 1	< 1		< 2
Maximum speed (cm/s)	1.5	2.5	1.5	3		1.5
Clearance to isocenter (cm)	31	35	30	30		?
Total weight (kg)	31	35	38	39.7		31
Geometric design	Single focused	Single focused	Parallel	Single focused		Two sets of leaf pairs at 90°

Dynamic rotational treatment techniques



Dynamic rotation therapy

In dynamic rotation therapy the following parameters can be varied during dose delivery:

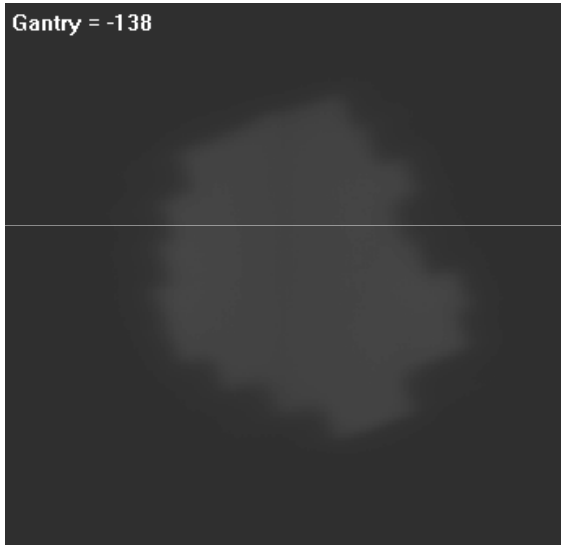
MLC leaf position

Dose rate

Gantry velocity

Collimator angle

Table angle

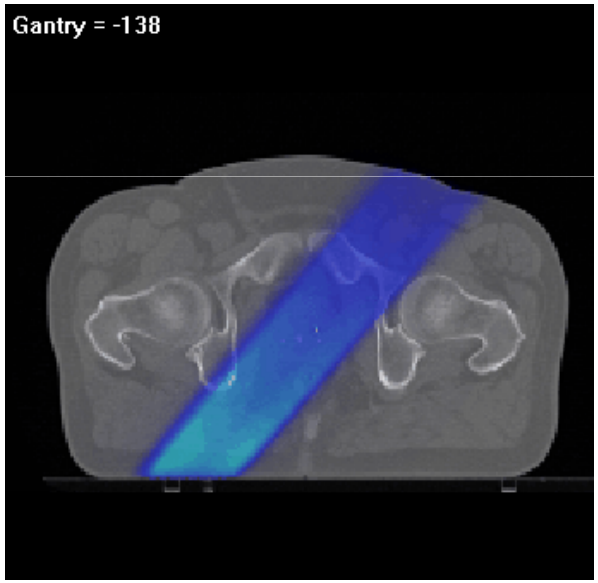


B. Mijnheer (NKI)

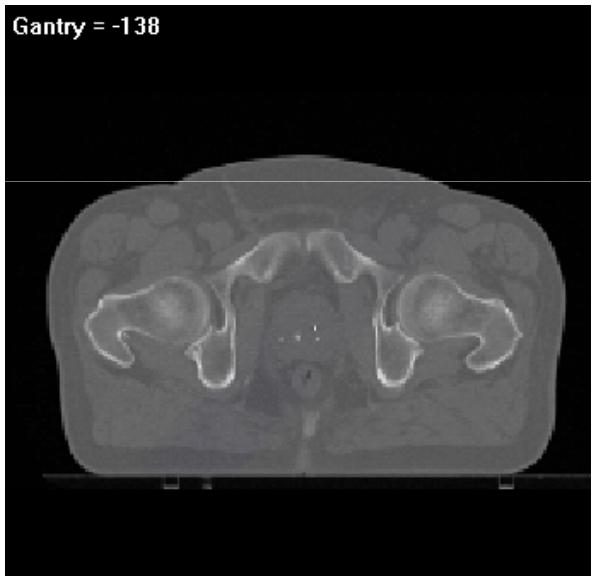
VMAT in action

Shape and MU for a single gantry angle

Field dose



Cumulative dose



Courtesy B. Mijnheer

Differences among techniques

Treatment machine (tomotherapy $\Rightarrow$ fan beams
conventional linac $\Rightarrow$ cone beam)

Delivery parameters (variable dose rate, variable gantry speed, …)

Number of arcs (single arc – multiple arcs)

Optimization concept (algorithm, DAO, …)

...

See lecture on comparing rotational techniques

See review in Yu PMB 2011 for treatment delivery

See review in Unkelbach Med Phys 2015 for plan optimization

Single Arc techniques

(Very) fast delivery in single rotation of the gantry

During gantry rotation the dose is delivered while varying

- MLC leave positions and
- **dose rate** and/or
- gantry rotation speed

Different optimization/sequencing algorithms

- Sweeping window arc therapy (SWAT)
- Arc-modulated cone beam threapy (AMCBT)
- Volumetric-modulated arc therapy (VMAT)
- RapidArc™
- Arc-modulated radiation therapy (AMRT)

Quite some discussions on the subject

Phys. Med. Biol. 54 (2009) N9–N20

NOTE

Single-Arc IMRT?

Thomas Bortfeld[1,3] and Steve Webb[2]

[1] Massachusetts General Hospital and Harvard Medical S
Oncology, 30 Fruit St, Boston, MA 02114, USA
[2] Joint Department of Physics, Institute of Cancer Resear
Trust, Downs Road, Sutton, Surrey, SM2 5PT, UK

Phys. Med. Biol. 54 (2009) L31–L34 doi:10.1088/0031-9155/54/8/L01

LETTER TO THE EDITOR

Comments on 'Single-Arc IMRT?'*

W F A R Verbakel[1], S Senan, F J Lagerwaard, J P Cuijpers and B J Slotman

Phys. Med. Biol. 54 (2009) L35–L36 doi:10.1088/0031-9155/54/8/L02

LETTER TO THE EDITOR

Reply to 'Comments on 'Single-Arc IMRT?''

Thomas Bortfeld[1] and Steve Webb[2]

Phys. Med. Biol. 54 (2009) L37–L41 doi:10.1088/0031-9155/54/8/L03

LETTER TO THE EDITOR

Letter to the Editor on 'Single-Arc IMRT?'*

Karl Otto

Phys. Med. Biol. 54 (2009) L43–L44 doi:10.1088/0031-9155/54/8/L04

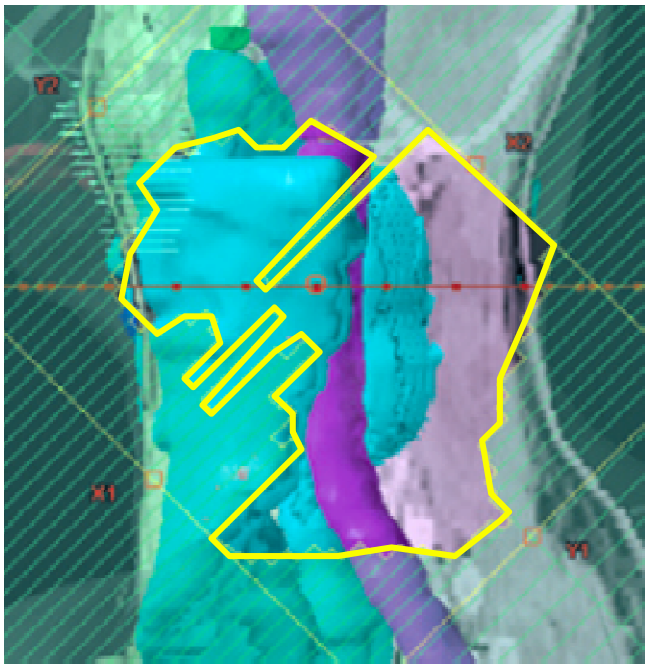
LETTER TO THE EDITOR

Reply to 'Letter to the Editor on 'Single-Arc IMRT?''

Thomas Bortfeld[1] and Steve Webb[2]

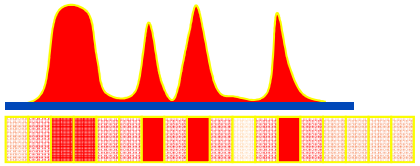
Not all rotational techniques are created equal

Single arc

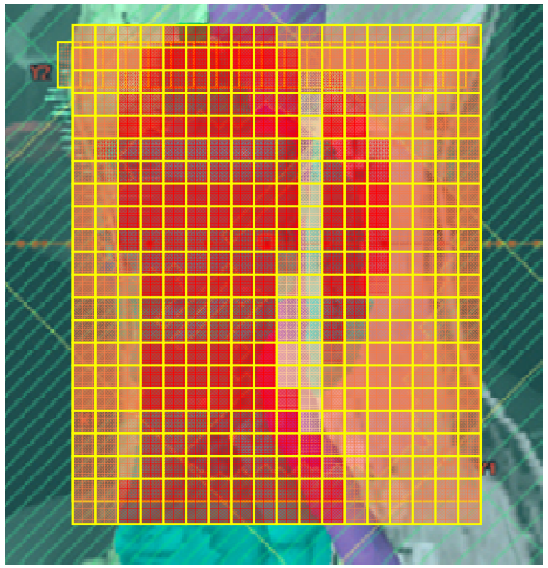


Little or no modulation for the individual gantry angle

Tomo



Modulated beam projection



One projection each rotation for this angle

Multiple modulated beam projections

Static field IMRT vs arc techniques

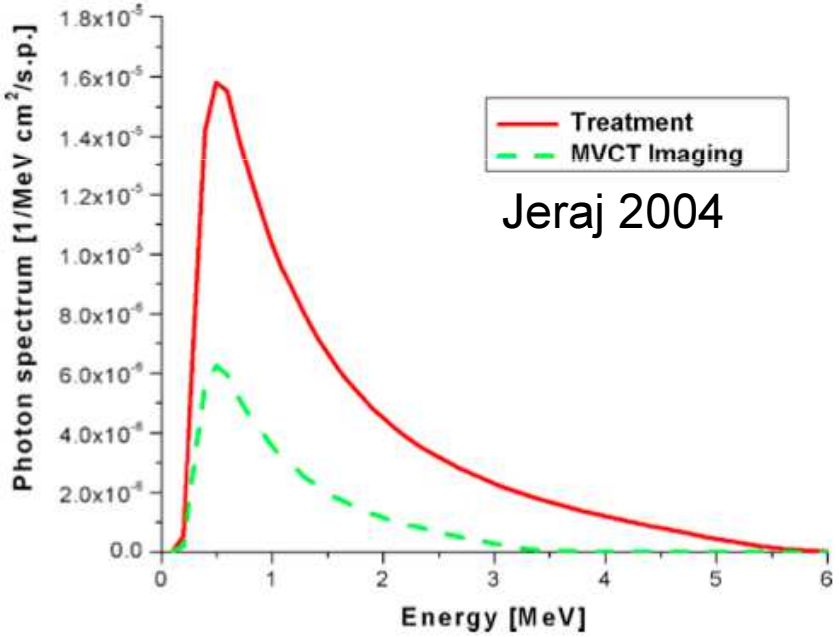
After the initial quite strong claims on (and heated discussions about) (linac-based) arc techniques, we are getting close to an objective assessment of the (dis)advantages of each techniques.

Is the focus on improved delivery efficiency (as opposed to quality of the dose distributions) an indication that we reached the limits of dose modulation with photons?

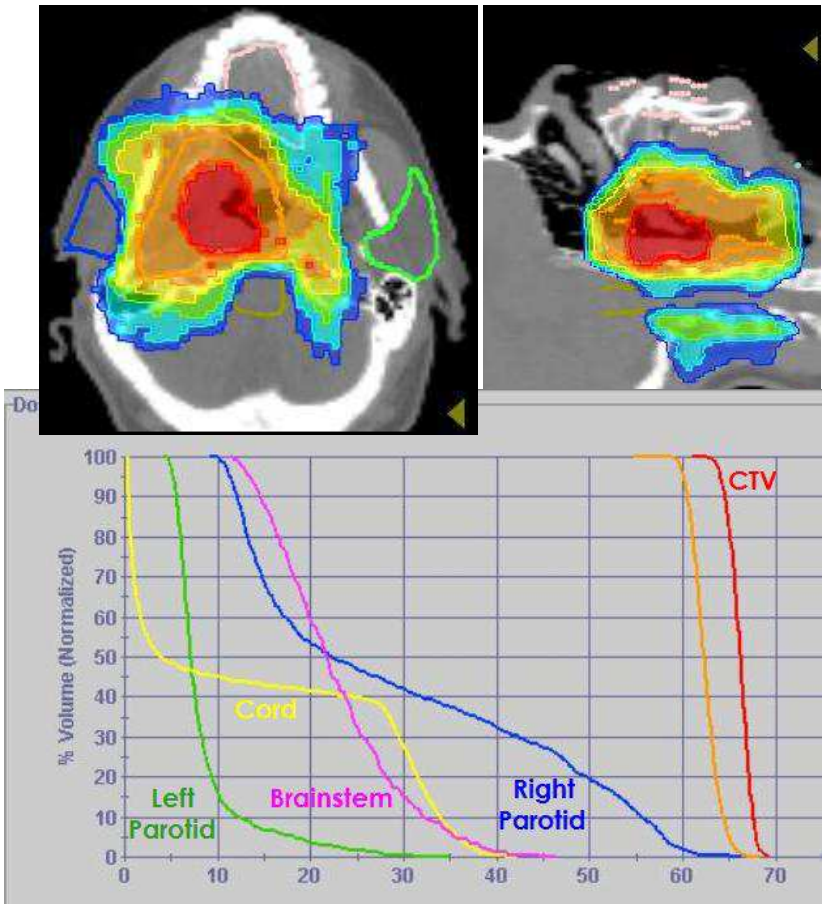
Dedicated IMRT/IGRT devices

TomoTherapy HI -ART System

85 cm Aperture
40 cm Image FOV



HT dose delivery system



6mm binary MLC over a large field (40cm)

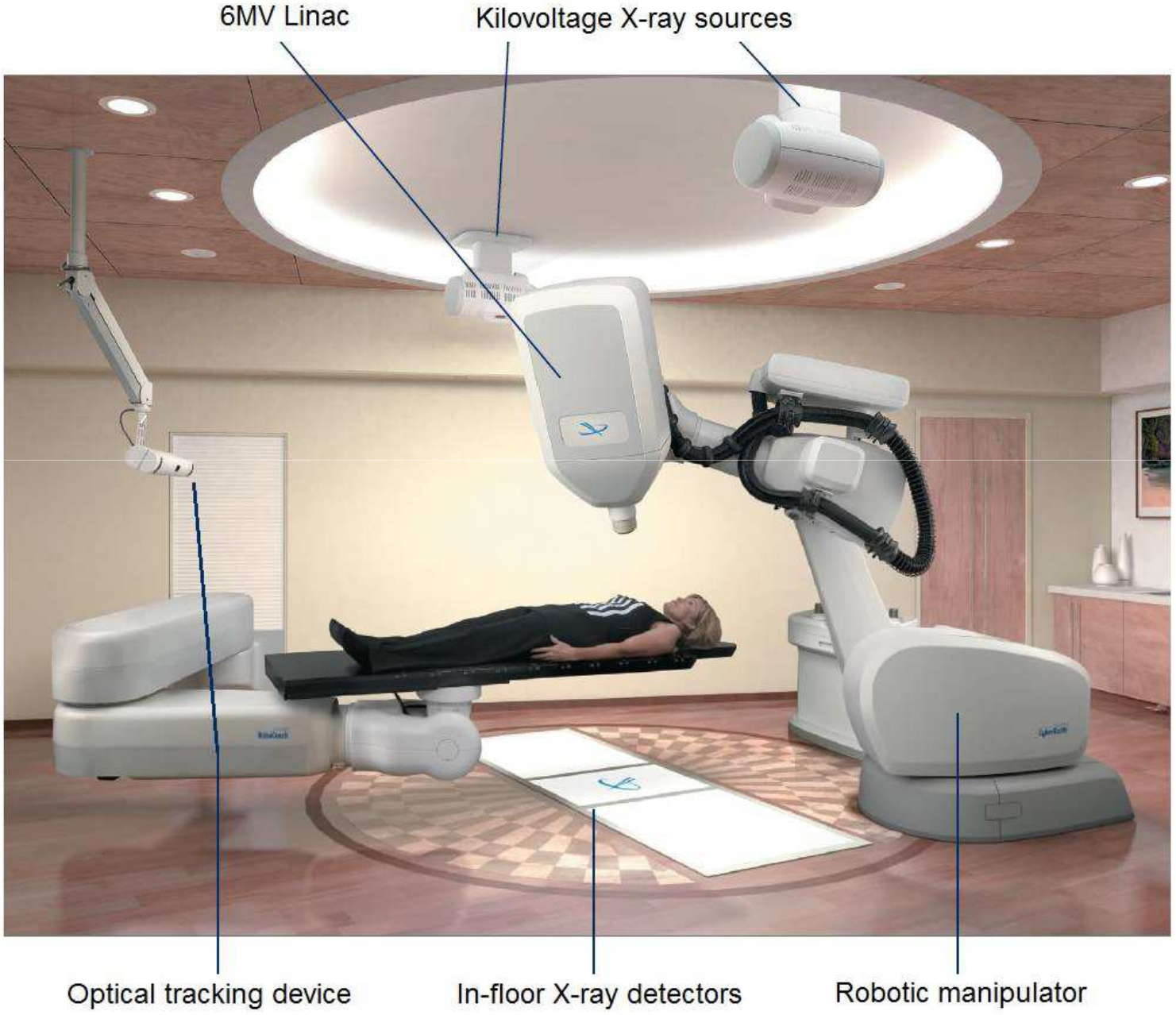
No flattening filter

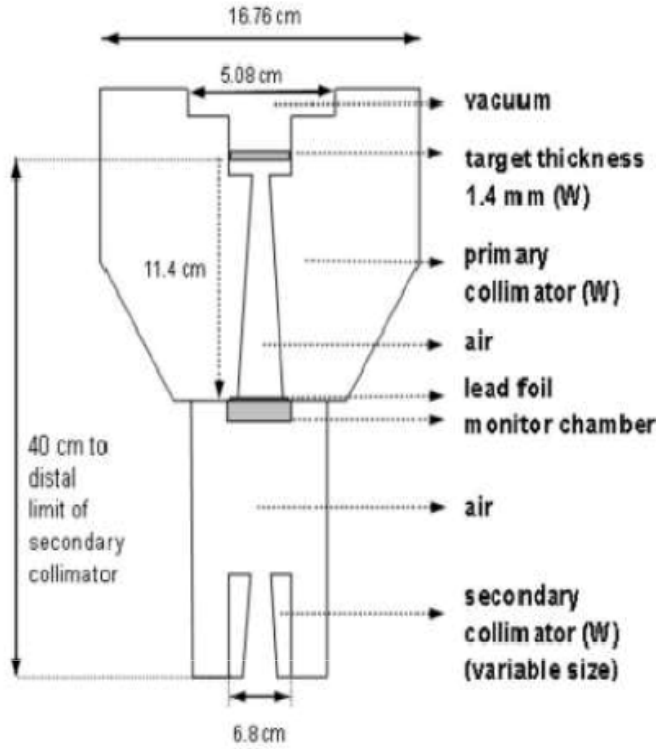
10 cm leaf thickness
Designed for delivery of IMRT (i.e. low transmission)

Degrees of freedom in planning and delivery:

Field width
Pitch
Modulation factor

Cyberknife


6MV Linac
Kilovoltage X-ray sources
Optical tracking device
In-floor X-ray detectors
Robotic manipulator



Robotic arm

6 degrees of freedom

About 120 positions around the patient

12 beam directions per position → 1440 possible beam entrances

Declared position accuracy < 0.12 mm

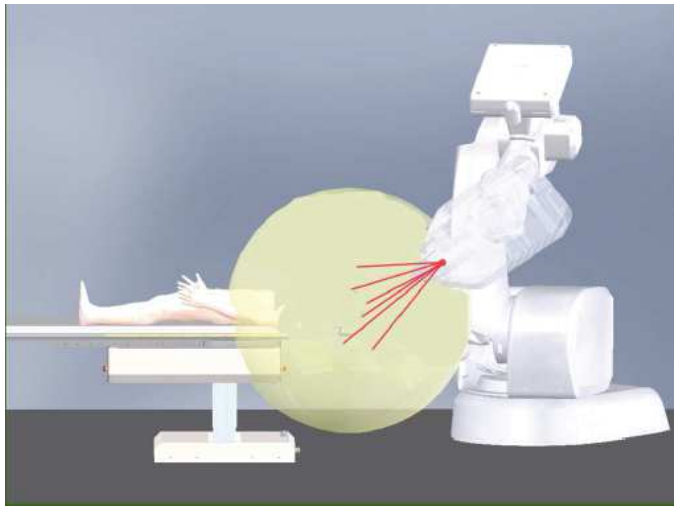
LINAC

About 160 kg

6 MV X-rays

Dose rate up to 800 MU/min

No flattening filter



Collimating systems

12 fixed circular collimators (5 to 60 mm)

IRIS – Variable aperture collimator

Its use is currently restricted to a set of 12 sizes corresponding to the sizes of the set of 12 fixed collimators, (5 to 60 mm)

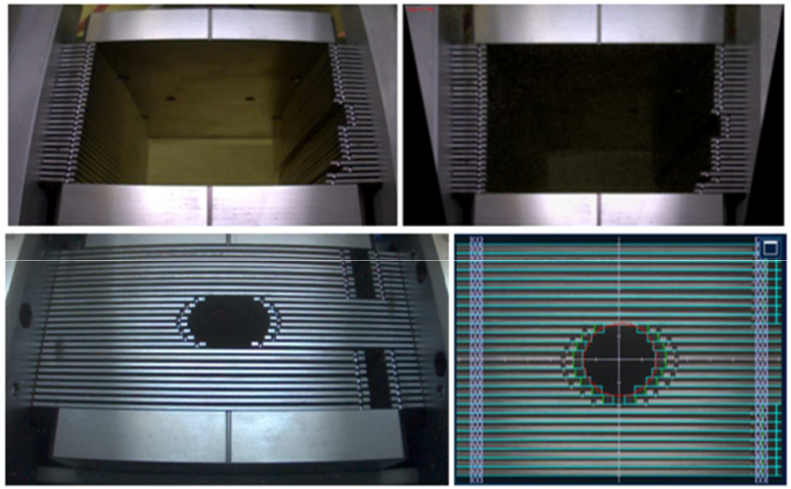
INCISE – MLC

INCISE™ MULTILEAF COLLIMATOR SPECIFICATION *As defined by IEC 60976*

Beam Targeting	Non-Isocentric, Non-Coplanar Beam Targeting
Maximum Field Size	Nominal: 120 mm (leaf motion direction) x 100 mm at 800 mm SAD
Number of Leaves	41 leaf pairs
Leaf Thickness	2.5 mm at 800 mm SAD
Leaf Tilt	Leaves tilted 0.5°
Leaf Tip Design	3-Sided
Leaf Height	90 mm
Leaf Material	Tungsten
Distal Plane of Leaves to Linac Source Distance	400 mm
Leaf Positioning Accuracy	0.5 mm at 800 mm SAD
Mechanical Accuracy	0.25 mm
Leaf Positioning Reproducibility	0.4 mm at 800 mm SAD
Mechanical Reproducibility	0.2 mm
Leaf Over-Travel	100%
Leaf Inter-Digitation	Full Leaf Inter-Digitation
Transmission Includes intra-leaf, inter-leaf and leaf tip transmission	<0.3% Average (<0.5% Maximum)
Weight	48 kg (~105 lbs)

INCISE□ 2 – MLC

Number of leaves	52
Leaf width (at 800 mm SAD)	3.85 mm
Maximum treatment field size (at 800 mm SAD)	115 mm × 100 mm
Leaf height	90 mm
Leaf tip design	Three flat, focussed edges
Leaf side design	Flat, focussed
Interdigitation	Yes, no restrictions
MLC assembly weight	54 kg
Source to collimator distance (lower side of leaves)	400 mm
MLC assembly physical envelope	375 mm tall × 572 mm wide × 295 mm deep
Maximum leaf speed (at 800 mm SAD)	25 mm s^{-1}
Maximum leaf over-travel (at 800 mm SAD)	60 mm



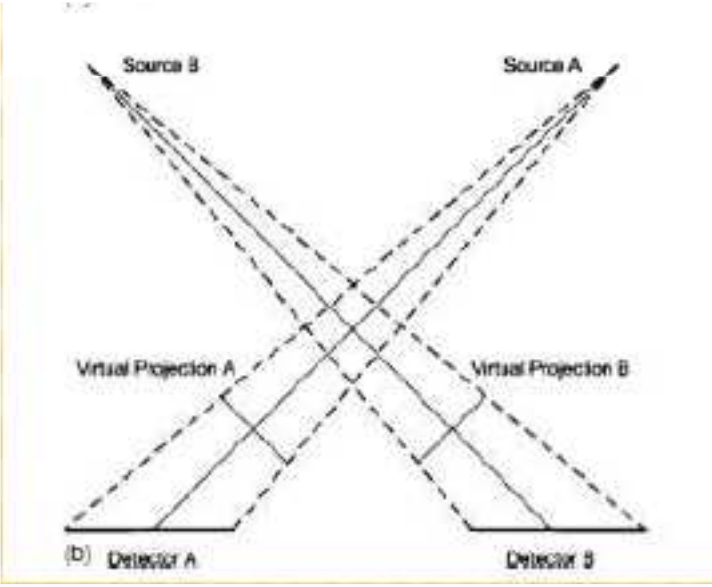
The design and physical characterization of a multileaf collimator for robotic radiosurgery, G. Asmerom et al., Biomed. Phys. Eng. Express 2 (2016) 017003

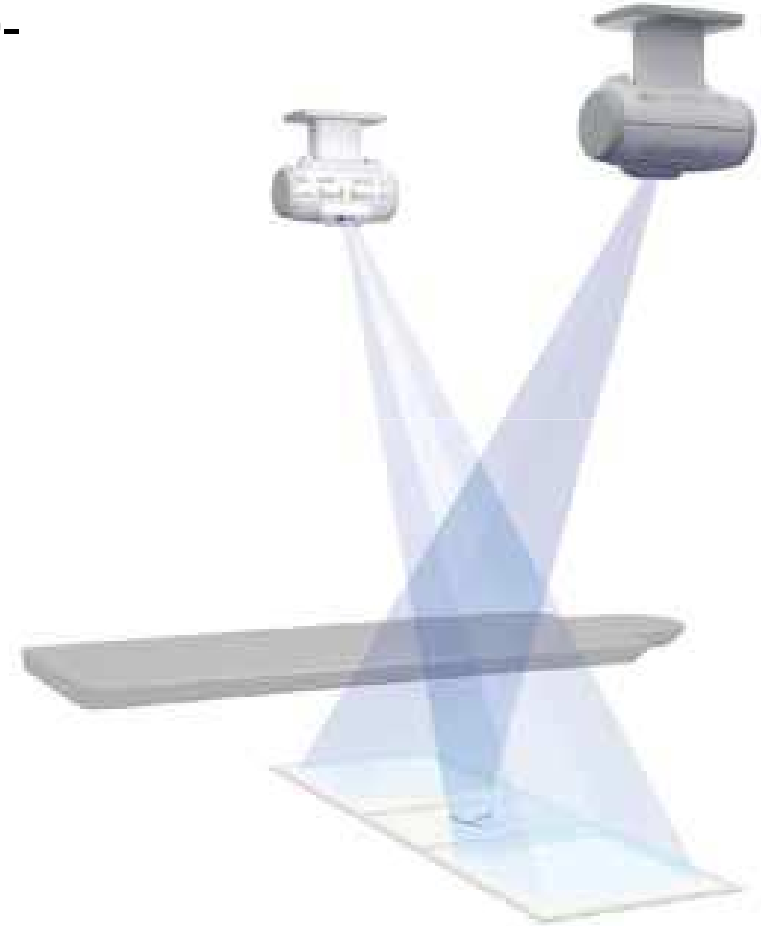
doi:10.1088/2057-1976/2/1/017003

Imaging System

kV X-rays sources on the ceiling (100-150 kV)

Two amorphous silicon flat panels (1024x1024) on the floor





General purpose vs dedicated devices

Advantages of dedicated devices should be weighted vs

Impossibility of decoupling TPS, imaging & delivery system (and Oncology Information Systems?)

- Highly ‘integrated’ devices designed to work on their own, simple needs (e.g. summing plans) may not have a simple solution

Operational issues

- multiple planning, delivery and imaging systems in the department
- Availability may not be as good as for linac. (What are you going to do in case of treatment failures?)

Conclusions

IMRT delivery systems did significantly develop in the past 10+ years.

Users have multiple (reasonable and reliable) solutions available.

Abundance of options may be a problem if it's not combined with a clear understanding of why a given machine/performace is useful (or needed).

Be careful not to get lost in the supermarket of RT hardware.

ESTRO School

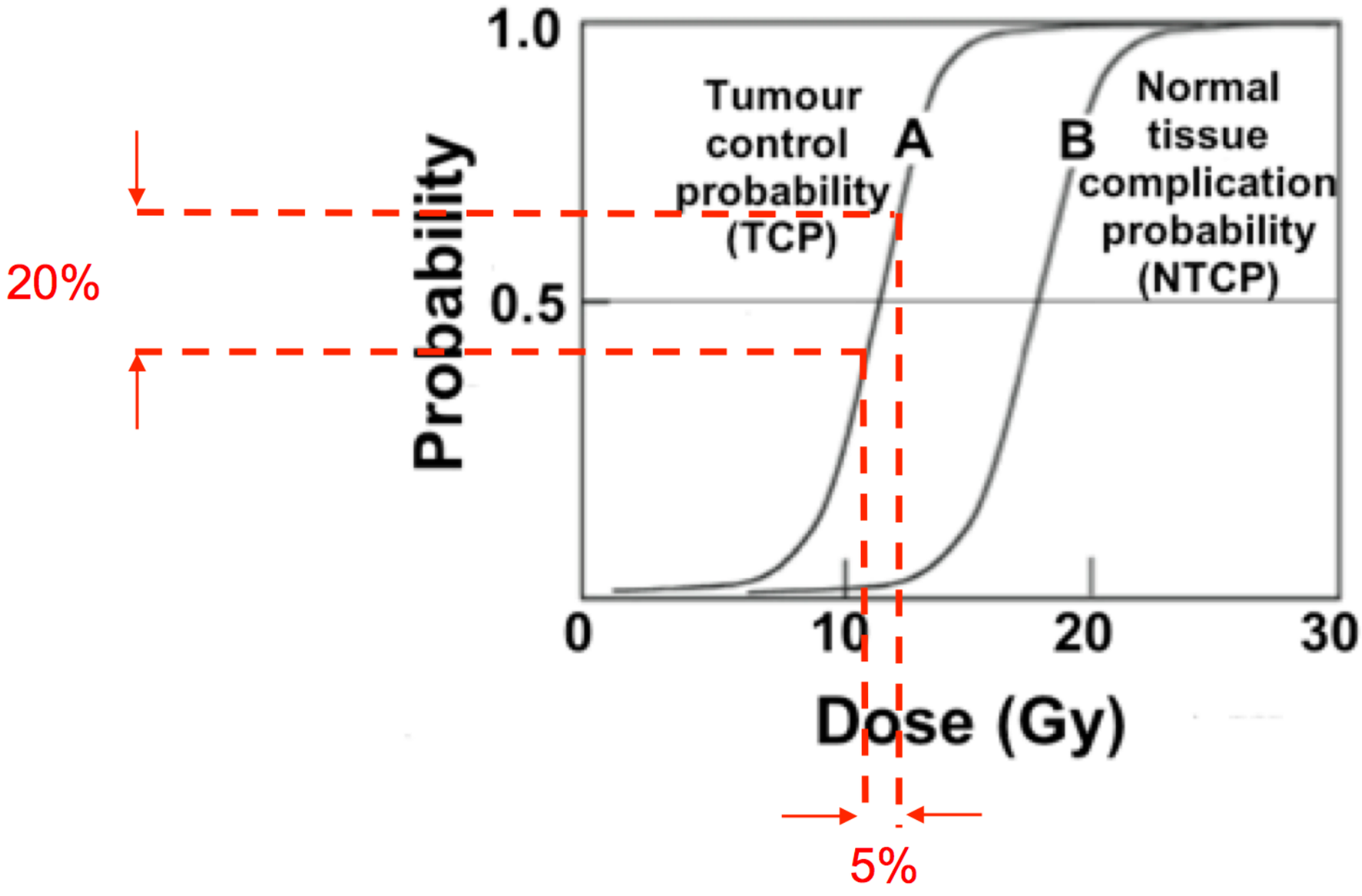
WWW.ESTRO.ORG/SCHOOL

Dosimetry issues in IMRT

Koen Tournel - Physicist
Radiotherapy Department UZ Brussel

ESTRO School

The Big Picture



A 5% dose error can lead to a 20% difference in NTCP/TCP

Back to basics...

Table 3
Dose intercomparison under reference conditions: X-ray beams

Study	Year	Visiting team protocol	*n*		M	SD	Δ
Scandinavia [6]	1982	NACP	50	PAT[a]	1.017	0.023	0.100
Europe [4]	1986	NACP	16	PAT	1.024	0.033	0.140
			16	COR[b]	1.013	0.022	0.090
The Netherlands [13]	1987	NCS	40	PAT	1.008	0.020	0.100
USA [1]	1991	AAPM	740	COR	1.008	0.019	0.140
UK [11]	1992	HPA	100	PAT	1.003	0.015	0.100
Belgium	1992	NCS	21	PAT	1.006	0.023	0.080
(this work)			21	COR	1.011	0.014	0.055

[a]PAT, 'Patient' value (see text).
[b]COR, 'Corrected' value (see text).

- Phew, this seems to be OK...
- IMRT 2.0, however, compares to this as driving a F1 car to talking a walk

Hoornaert et al., Radiother Oncol, 1993

What's the baseline?

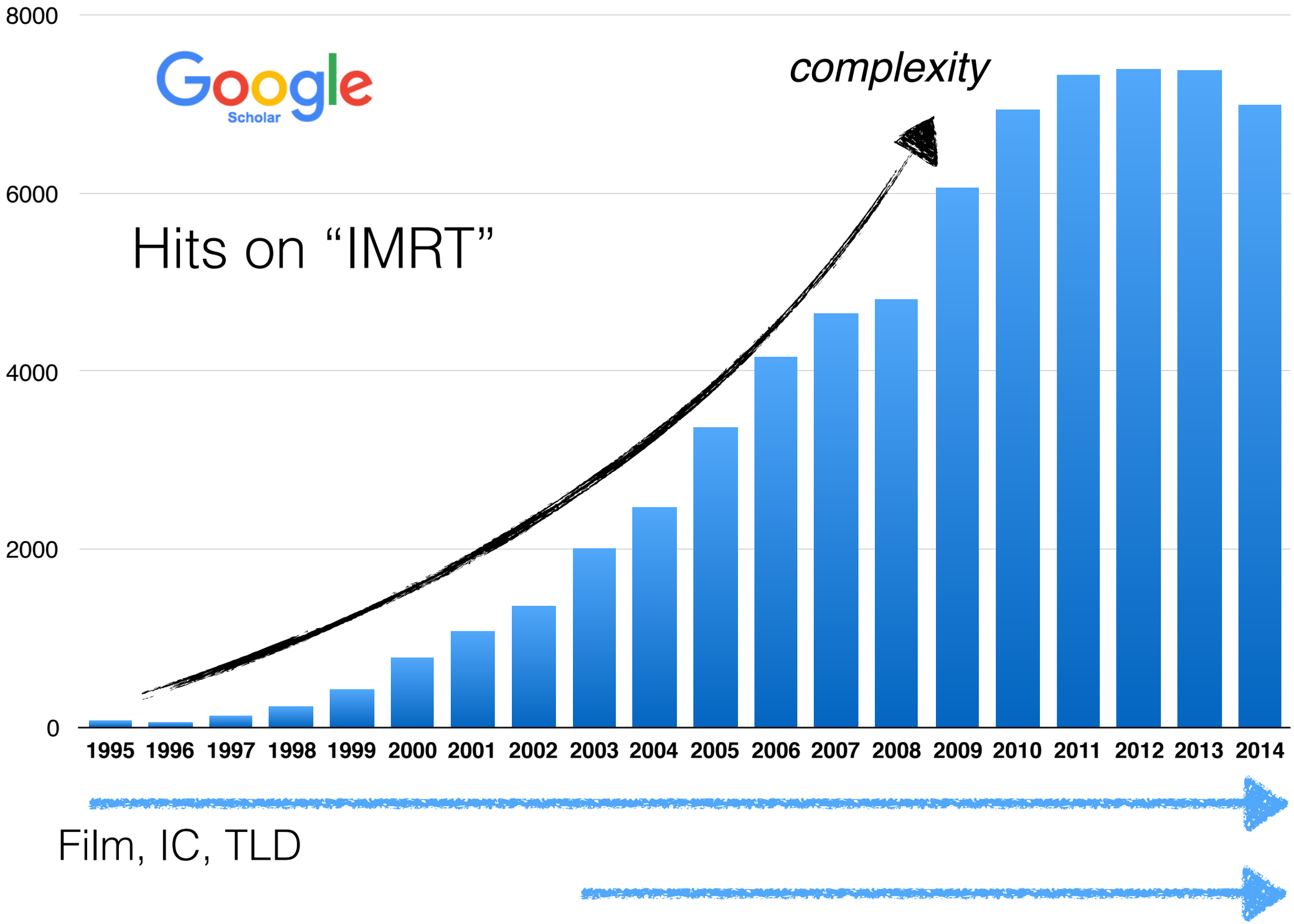
There has been a marked improvement in radiation dosimetry over the past three decades, and the RPC has been monitoring it through its auditing tools. Between 1970 and 1980, the compliance rate (±3%) for beam calibration increased from approximately 70% to 90%. Improvement since then has been gradual, with compliance now near 98%, for both photons and electron beam calibrations.

So we're doing well...on the basic dosimetry front that is...

Radiological Physics Center, Houston

Ibbott et al. : Challenges in credentialing institutions and participants in advanced technology multi-institutional clinical trials (Int. J. Radiation Oncology Biol. Phys. ,Vol. 71, No. 1

But what about IMRT?


Google Scholar
complexity
Hits on “IMRT”
8000
6000
4000
2000
0
1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
Film, IC, TLD
Arrays, dose rec.

IMRT

- Increasing complexity
- Sold as "plug and play" by vendors
- Clinical implementation under pressure of medical -and especially- management staff
- Clinical implementation not that straightforward : In the US 30% failed to deliver IMRT

With the **complexity of therapy increasing**, discrepancies in other components of the treatment are more prevalent. Over the past four years, at approximately **45%** of the institutions reviewed by an on-site review, the RPC found at least one clinical situation where patients could be at risk to receive a dose more than **5% different** from that intended.

Ibbott et al. : Challenges in credentialing institutions and participants in advanced technology multi-institutional clinical trials (Int. J. Radiation Oncology Biol. Phys. , Vol. 71, No. 1

What do audits tell us?

RPC phantom results

Site	Institutions	Irradiations	Tolerance	Pass rate
H&N	472	631	7%/4mm	75
Pelvic	108	130	7%/4mm	82
Lung	67	77	5%/5mm	71
Liver	15	18	7%/4mm	50

Ibbott, G. et al, update 2013

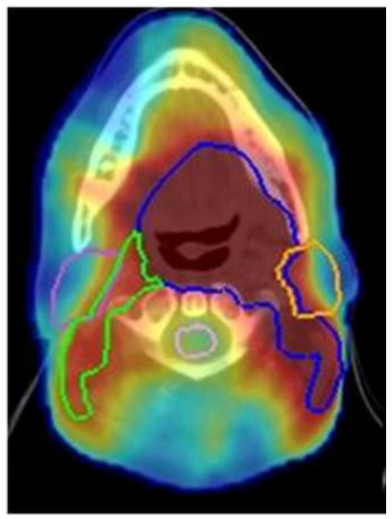
Dosimetry audit for a multi-centre IMRT head and neck trial

Catharine H. Clark [a,c,*], Vibeke Nordmark Hansen [c], Hannah Chantler [d], Craig Edwards [e], Hayley V. James [f], Gareth Webster [g], Elizabeth A. Miles [b], M. Teresa Guerrero Urbano [b], Shree A. Bhide [b], A. Margaret Bidmead [a], Christoper M. Nutting [*b], On behalf of the PARSPORT Trial Management Group [1]

Centre	Treatment planning system	Linac	Delivery technique	Dose point detector	Phantom for dose point and dose distribution*	Dose distribution verification	Plane for dose distribution
1	Eclipse 6.1.67	Varian 2100C	Dynamic	0.015 cc IC	Cylindrical PX (25d × 25l) Cuboidal SW (30 × 30 × 15)	EDR2	2 Coronal
2	Pinnacle 6.2b	Elekta SL series	Step and shoot	0.6 cc IC	Cuboidal SW (30 × 30 × 20)	EDR2/GC	2 Coronal
3	Eclipse 7.1.67	Varian 2300EX	Dynamic	0.015 cc IC	Cuboidal PX (15 × 15 × 10) Cuboidal SW (40 × 40 × 15)	XV or Diode array	Each field
4	Pinnacle 6.2	Elekta Precise	Step and shoot	0.125 cc IC	H&N PX (30x15x15or45) Cuboidal SW (15 × 15 × 10)	EDR2/GC	1 coronal
5	Xio 4.2	Siemens Primus, Oncor	Step and shoot	0.125 cc IC	In house SW (24 × 29 × 20) Cubic SW (20 × 20 × 20)	EDR2	Each field & 1 coronal
6	Eclipse 6.5	Varian 2100CD	Dynamic	IC array	IC array (40 × 40 × 5)	IC array	Each field

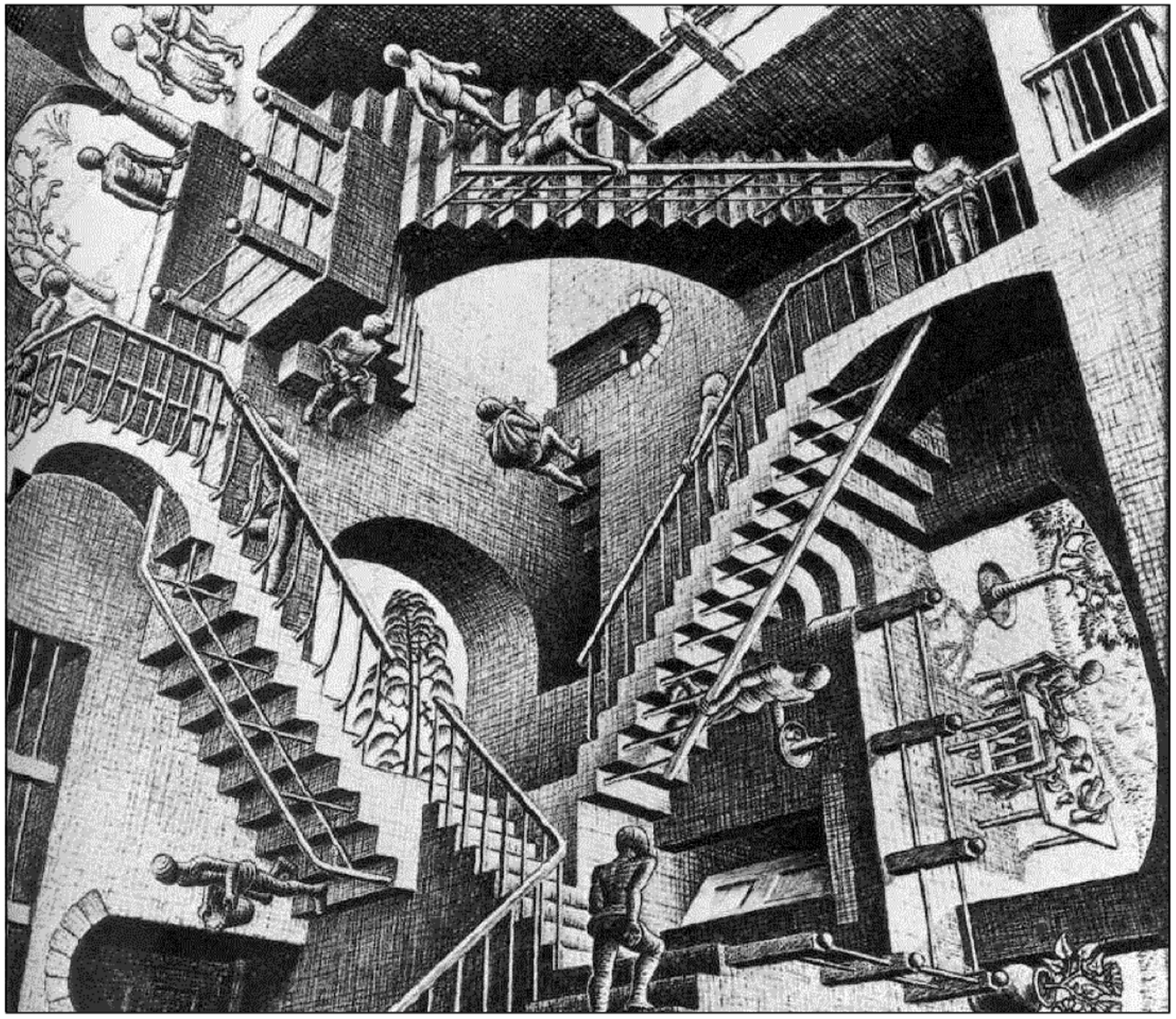
Results from the individual and combined field film tests. (Thresholds applied are 10% for individual beams and 20% for combined beams.)

Gamma parameters%/mm	2/2	3/2	3/3	4/3	4/4	5/3	5/4	5/5
% Individual films passing (/31)	48% (15)	84% (26)	94% (29)	100% (31)	100% (31)	–	–	–
Mean	90.9	95.0	97.7	98.7	99.4	–	–	–
% Combined films passing (/12)	–	–	67% (8)	75% (9)	83% (10)	92% (11)	92% (11)	100% (12)
Mean	–	–	94.9	97.4	98.2	98.7	99.1	99.4

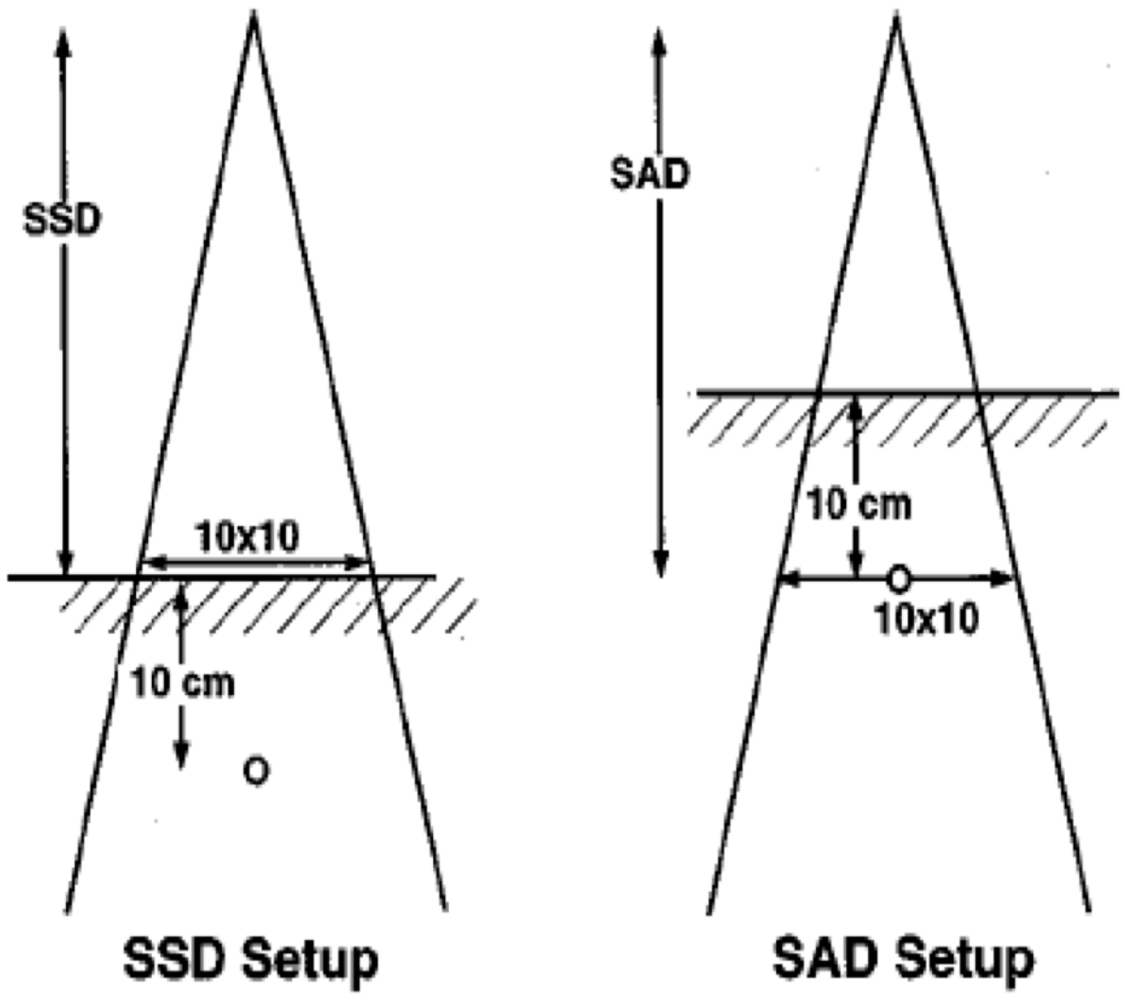


Dose Measurement

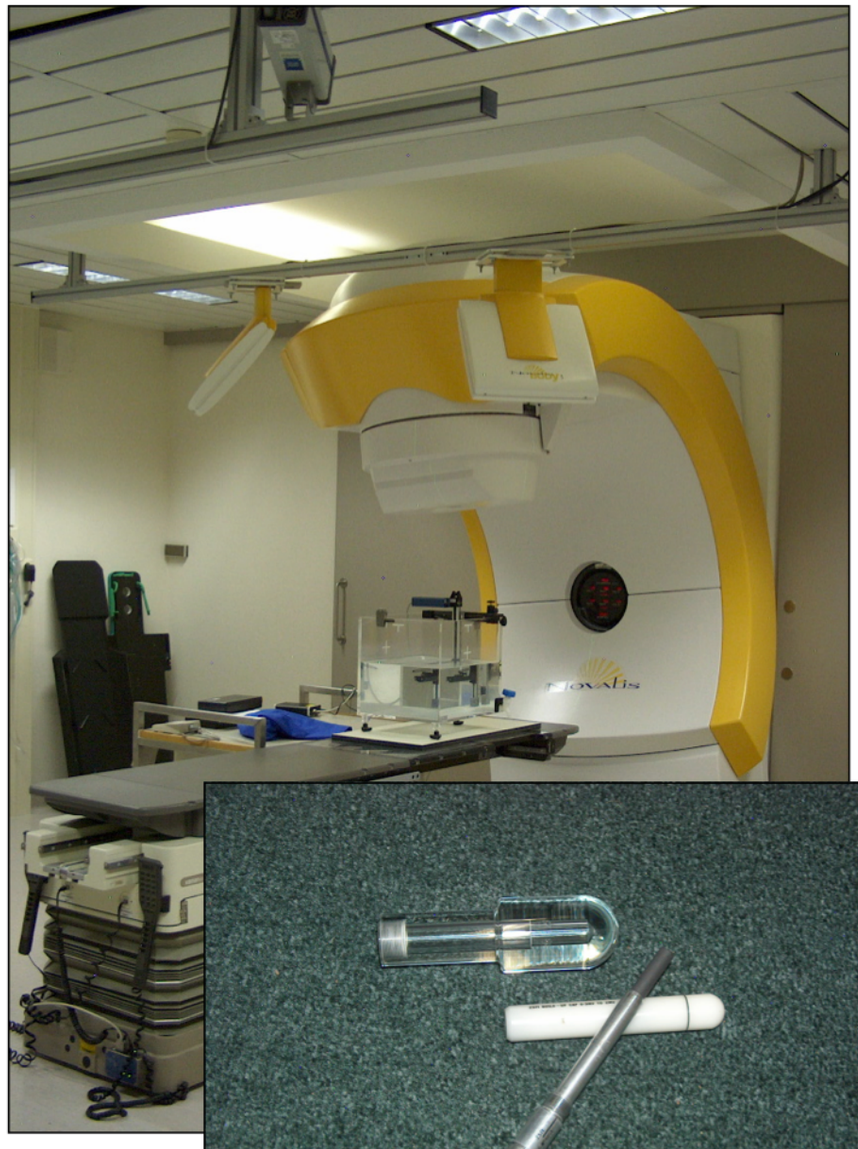
- Let's start with the concept of "Absolute Dose" in IMRT



“Reference conditions”

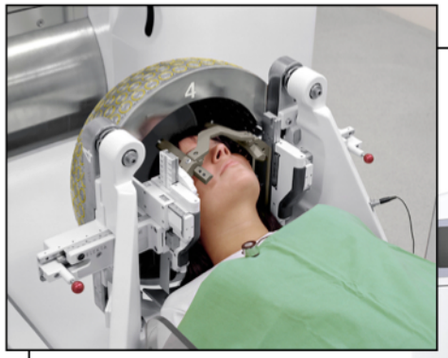


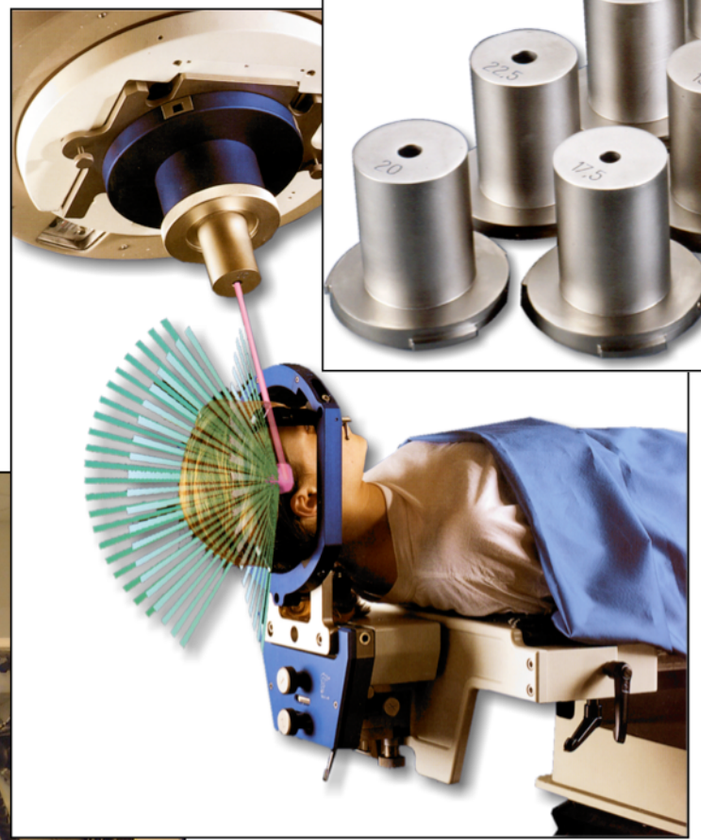
SSD Setup SAD Setup

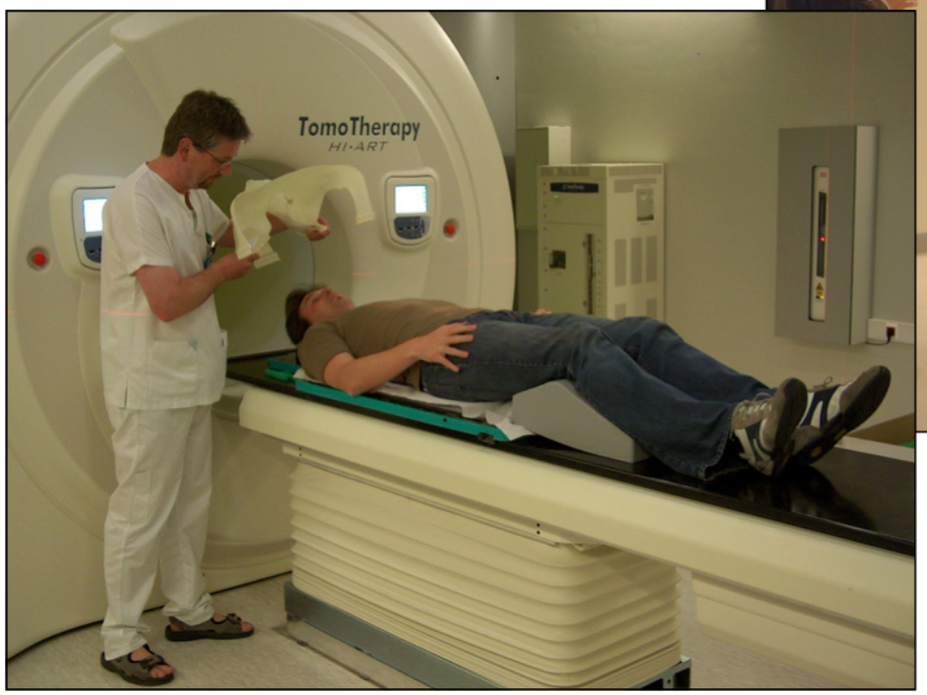


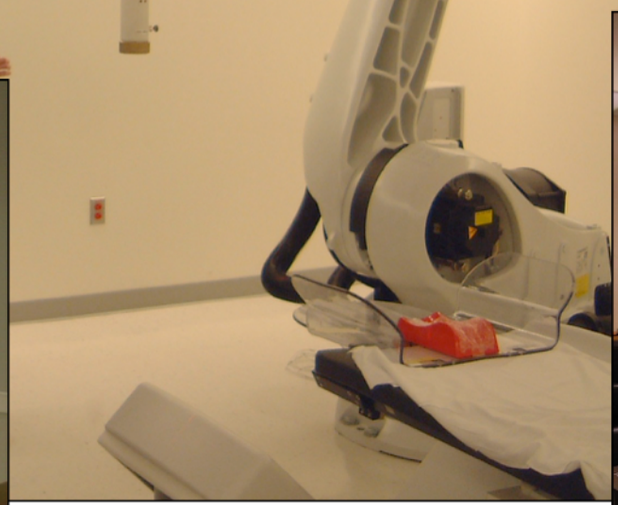
$$D_w^Q = Mk_Q N_{D,w}^{^{60}Co} \left(Gy\right)$$

Non-reference Conditions









Non-reference conditions

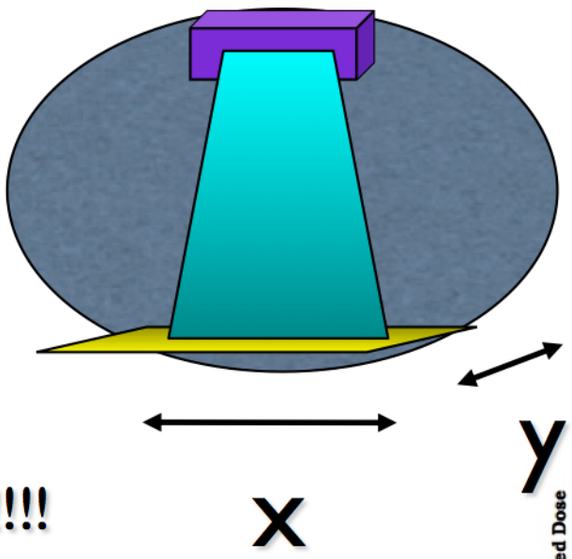
- Sudden fashion of using "flattening free" beams (tomotherapy, Varian, CK)

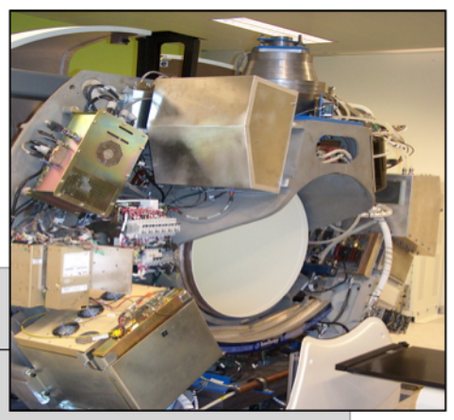
  - High dose rate to speed up dose delivery (compensating for motion, delivering hypofractionation in conventional time slots)
  - Why bother with flattening filters as we are going to use IMRT anyway (e.g. tomotherapy), moreover it makes beam modeling easier as the scatter component is reduced

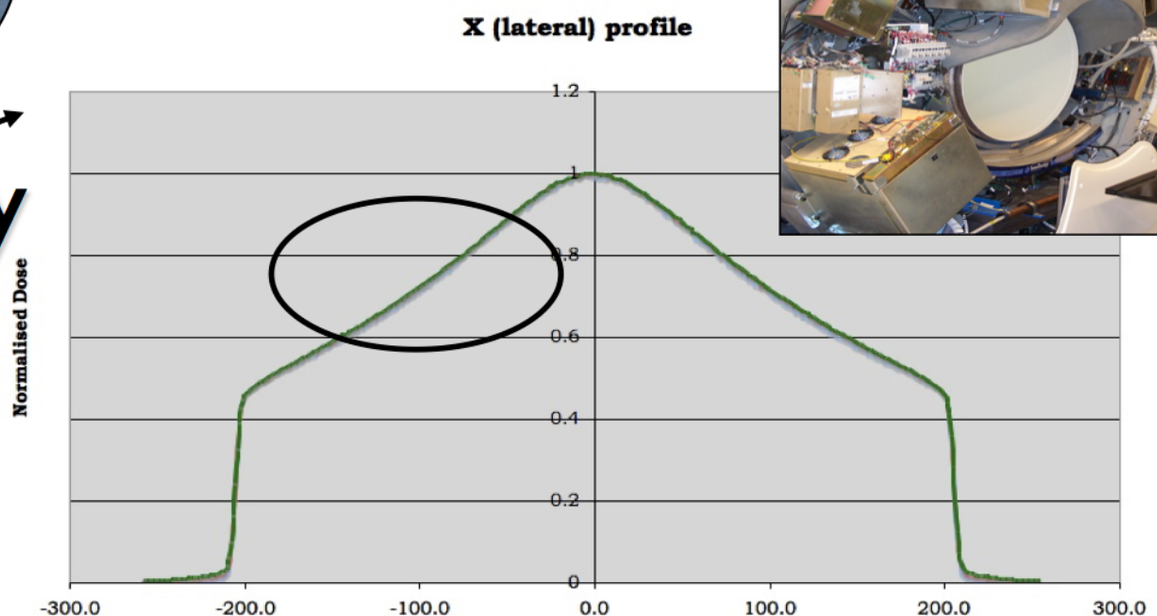
"40cm" x (1.0,2.5,5.0)cm

SSD 85cm

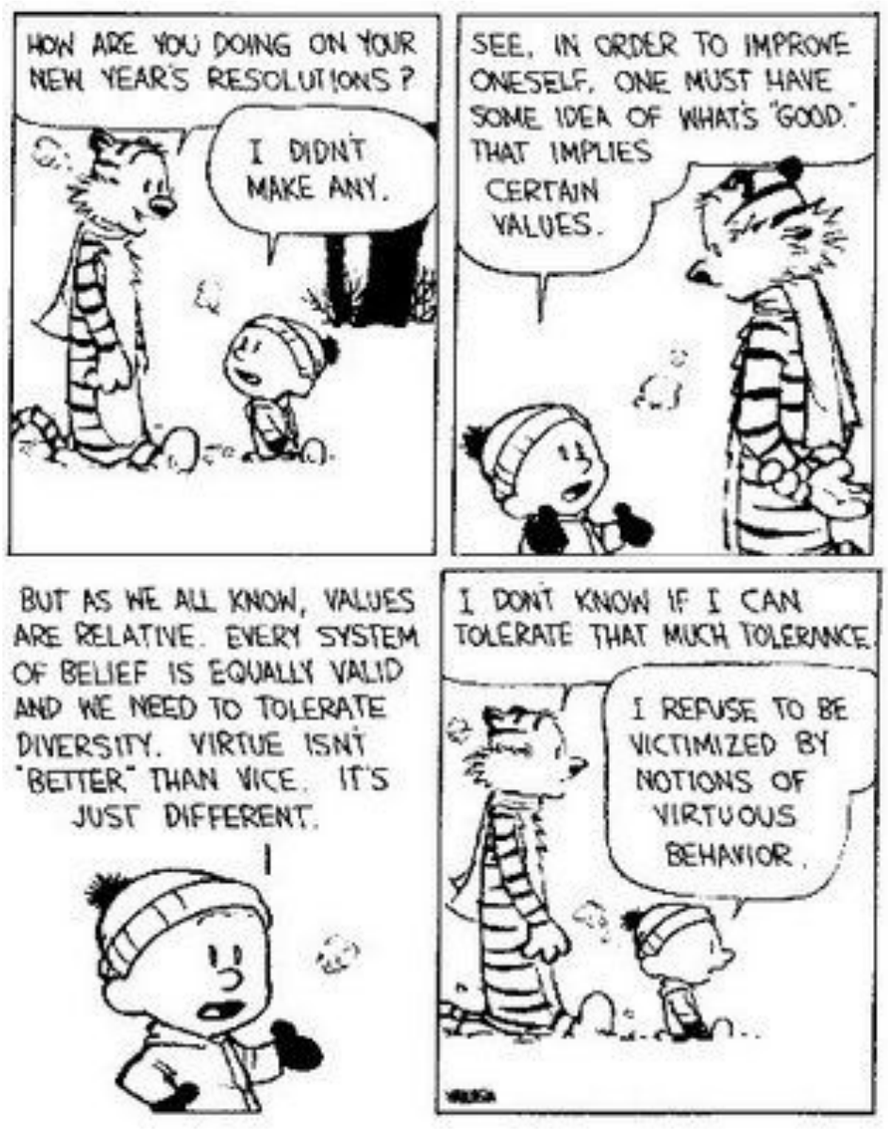
NO FLATTENING FILTER!!!!







So, what is exactly the problem?



"A relativity problem"

Conversion from ionisation to absorbed dose to water based on cavity theory and using the currently available perturbation factors used in dosimetry protocols is not accurate

“Traceability”

So, what is exactly the problem?

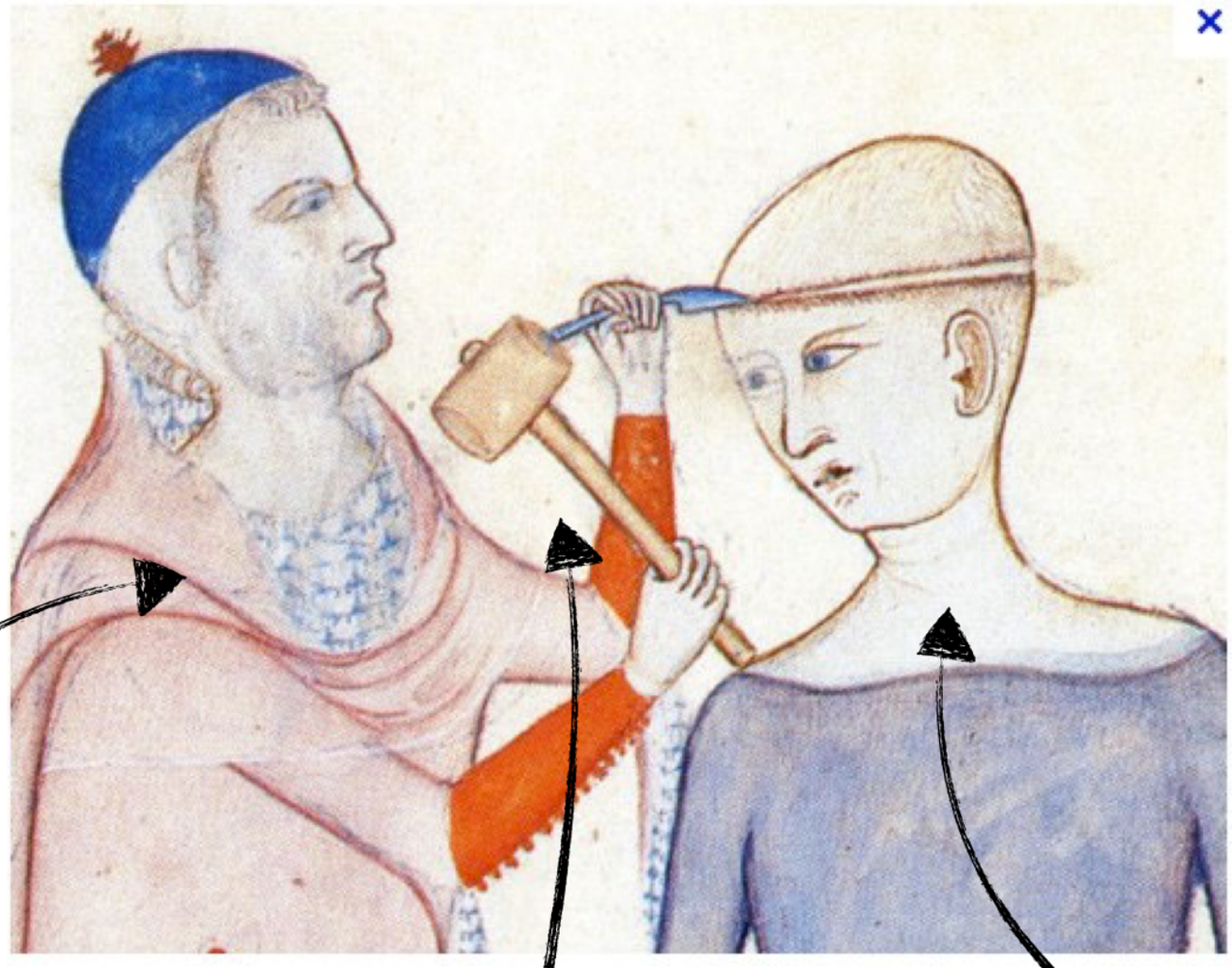
- Codes of Practice (CoP) in clinical dosimetry are undermined by the new developments in treatment delivery
  - Users have to decide by themselves how to perform clinical dosimetry. (***a highly uncomfortable situation***)
- Ionisation Chambers (IC) have traditionally been the "backbone" of radiotherapy dosimetry
  - However, they are not suitable/designed for many situations
    - High dose gradients
    - Time-dose variance
    - Non-uniform beams

So what exactly is the problem?

It is not possible to establish reference conditions on some machines

IMRT treatments for “normal” size targets are “composites” of fields in which “normal” CoPs do not apply.

So what exactly is the problem?



Physicist

CoP

Poor
IMRT-Treatment

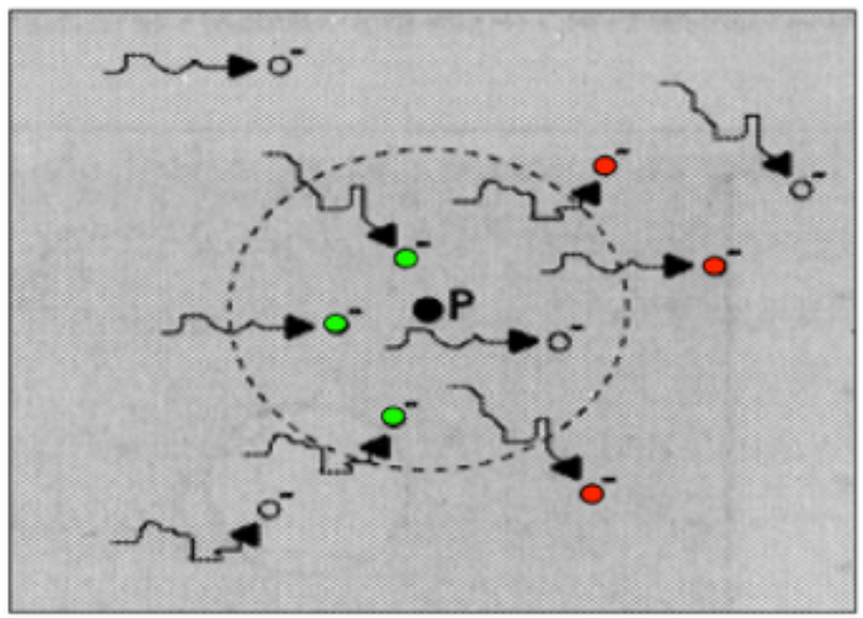
Let’s dig a bit deeper….

- IMRT Treatments are composite treatments of several small field segments*
- We need careful characterisations of these segments
- And that’s where small field dosimetry comes into the picture

*Let’ s assume that neither gantry or collimator is rotating, it’s hard enough as it is…

What is a small field?

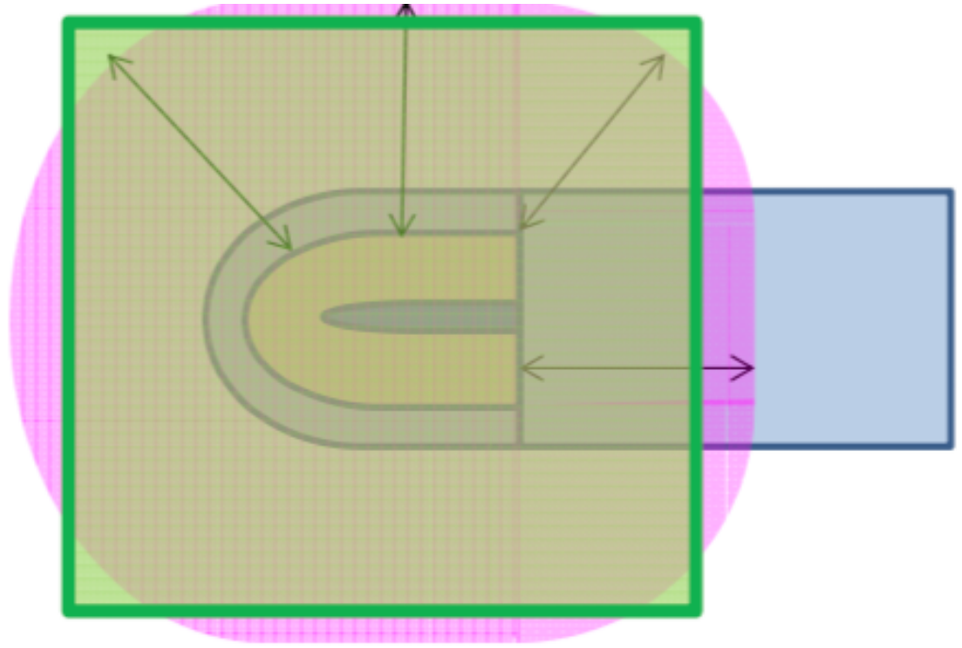
1. Loss of lateral equilibrium
2. Source Occlusion
3. Detector Size



What is a small field? (1)

“Small field conditions” exist when one of the edges of the sensitive volume of the detector is less than the lateral charged particle equilibrium range away from the edge of the field

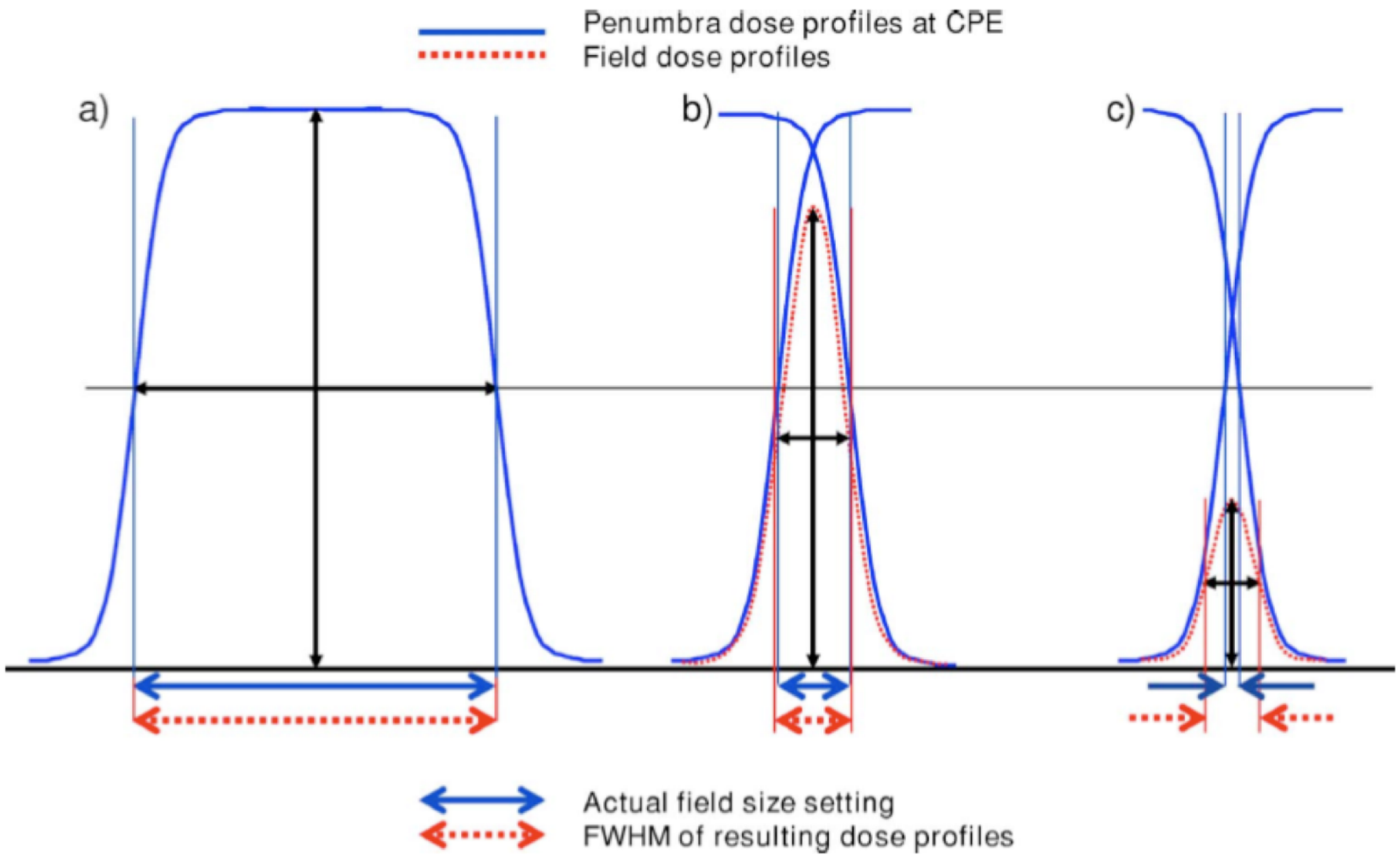
$$r_{LCPE}\ (\text{in cm}) = 5.973 \bullet TPR_{20,10} - 2.688$$



Li et al. (1995) med. Pays court. H.Palmans

“Small field”

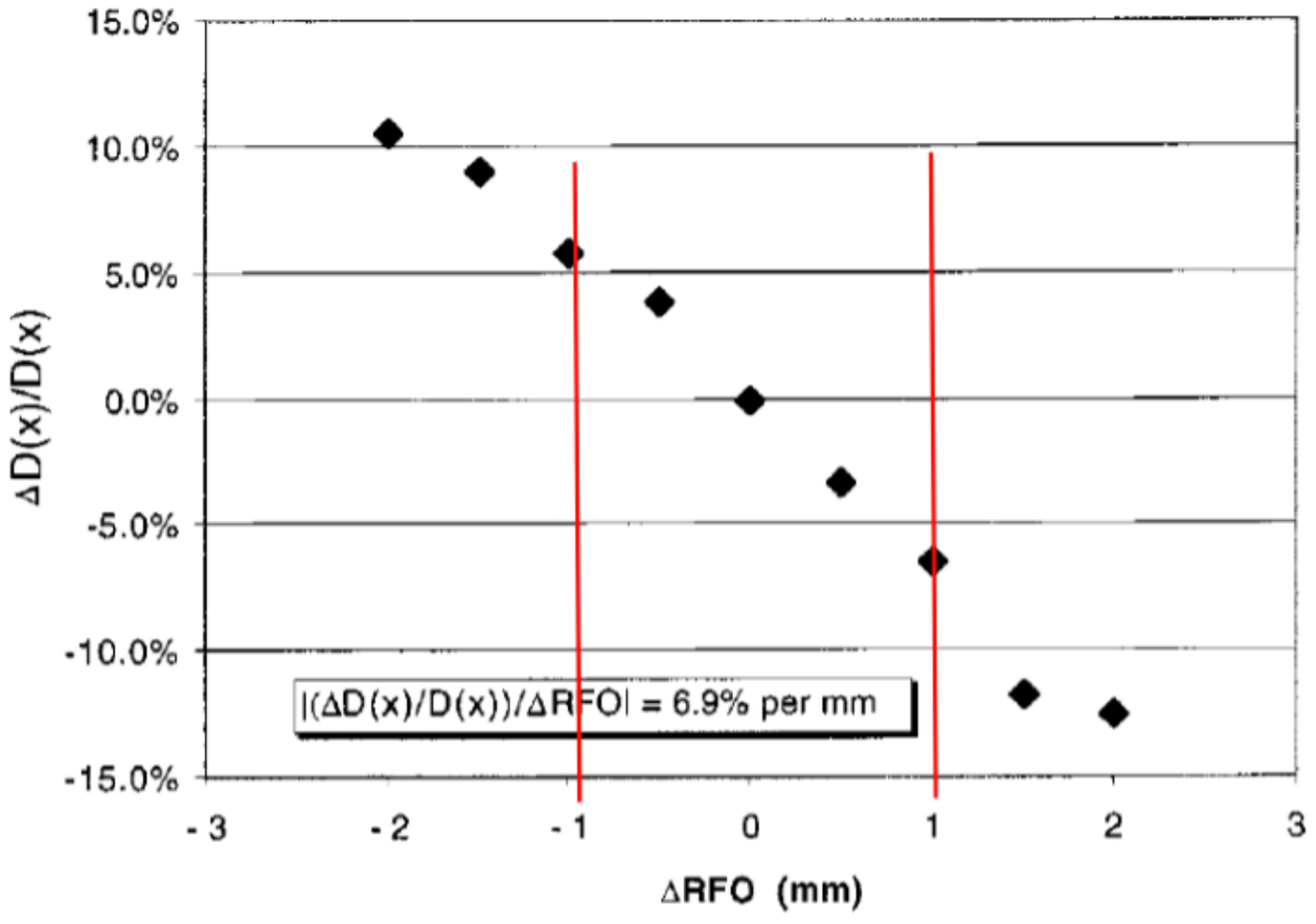
“ Beam Broadening Effect”
field size definition?



FS of same order or smaller as charged particle diffusion distance: (b) and (c).

Das et al, Medical Physics, Vol. 35, No. 1, January 2008

Field size def. vs. machine precision

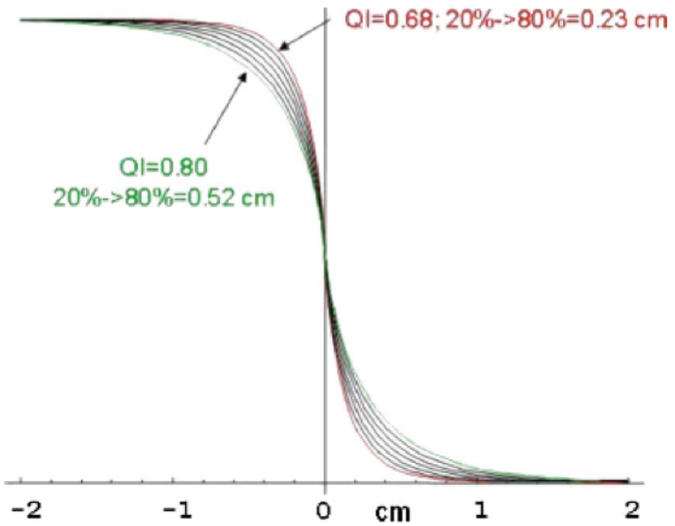


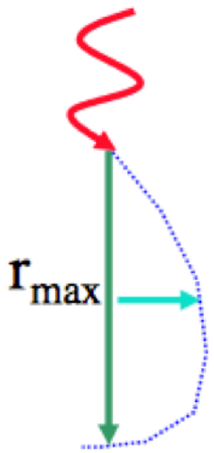
RFO: Radiation and light field offset at SAD for an MLC [mm]

Kung and Chen (2000), Med Phys 27(7): 1617-22

Electron range for CPE

- Forward range : dmax
- lateral range (ideal spot sizes)
  - equal to penumbra, depends on energy

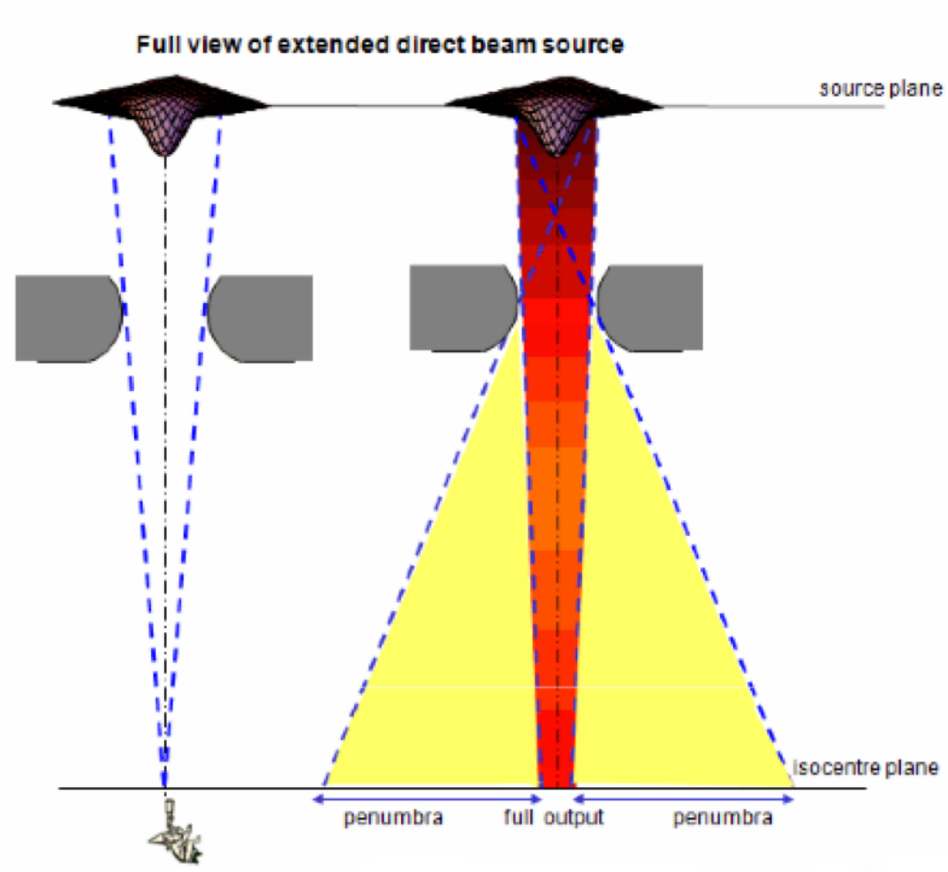


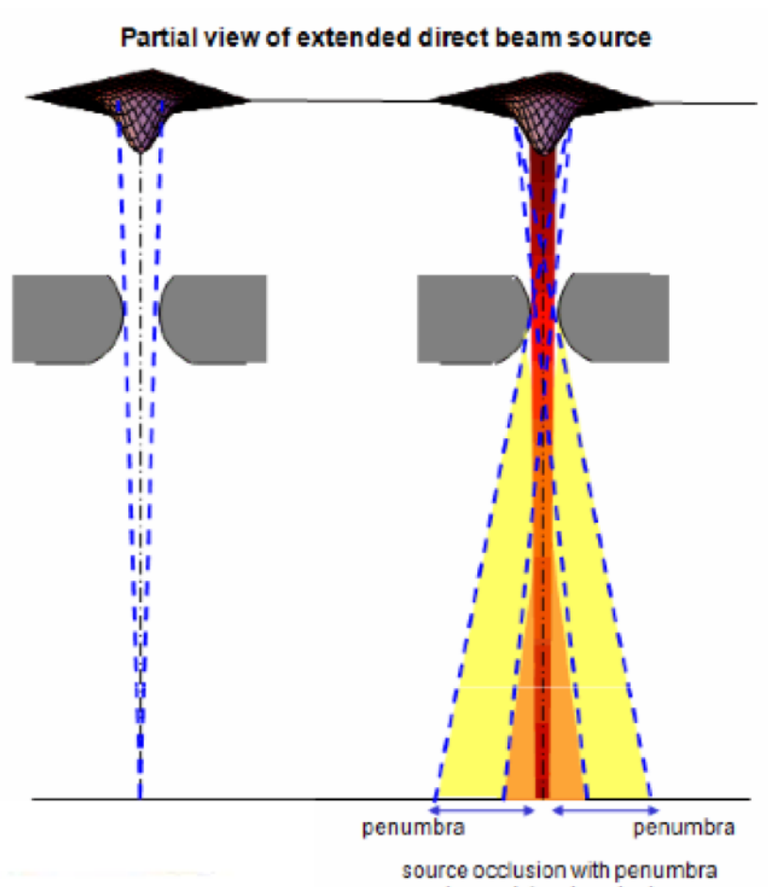


  - For decreasing field sizes the lateral scatter influences the dose in the center of the field
- Field size needed for CPE depends on lateral range

Small Field (2)

“Source Occlusion”

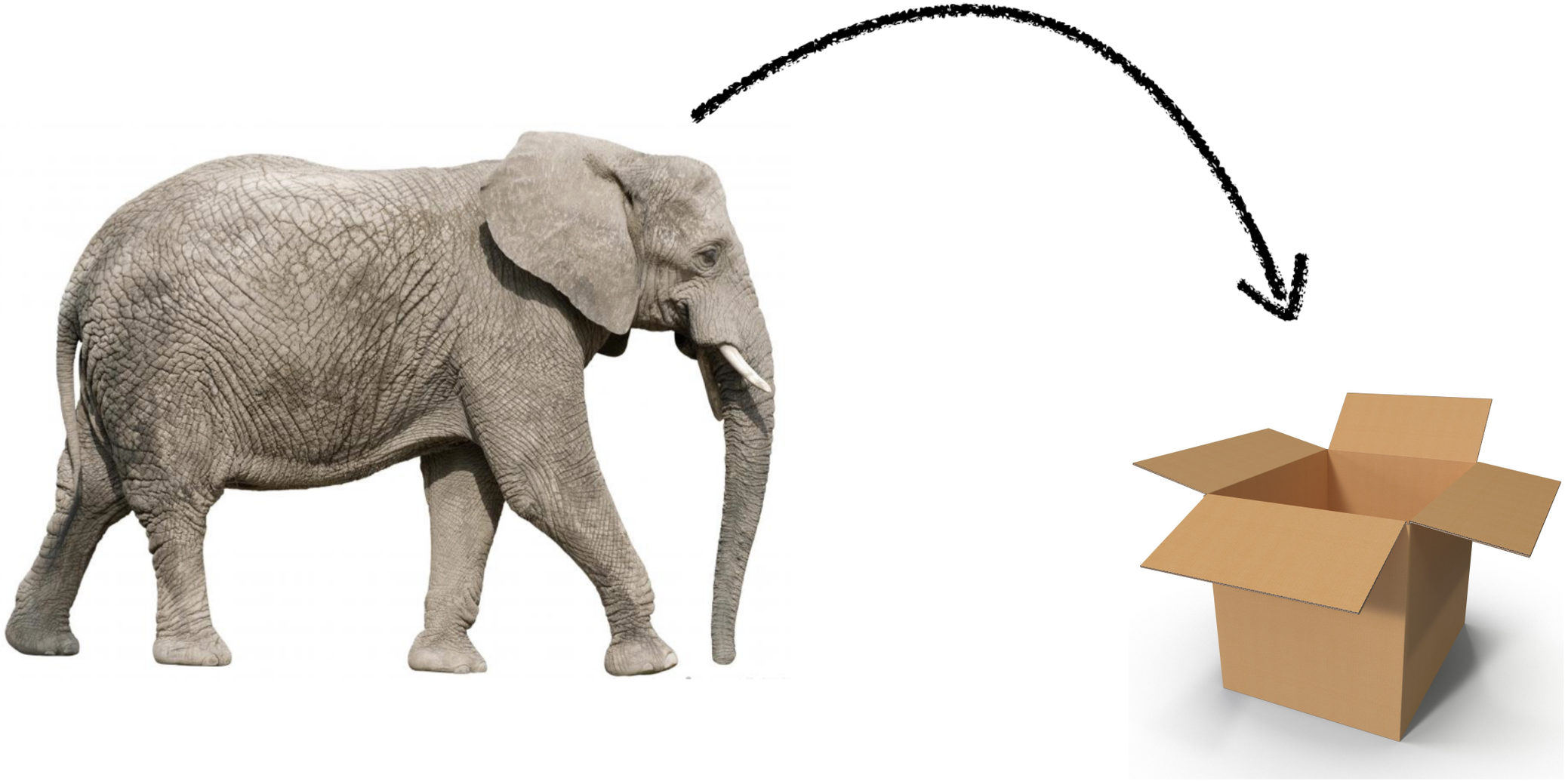




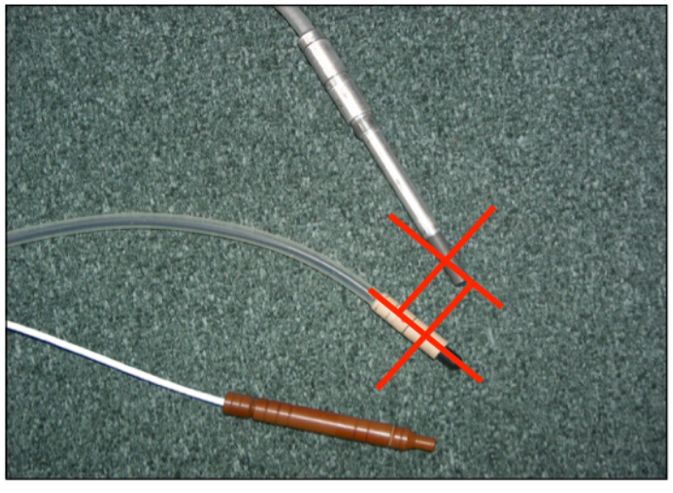
Entire Beam source not visible

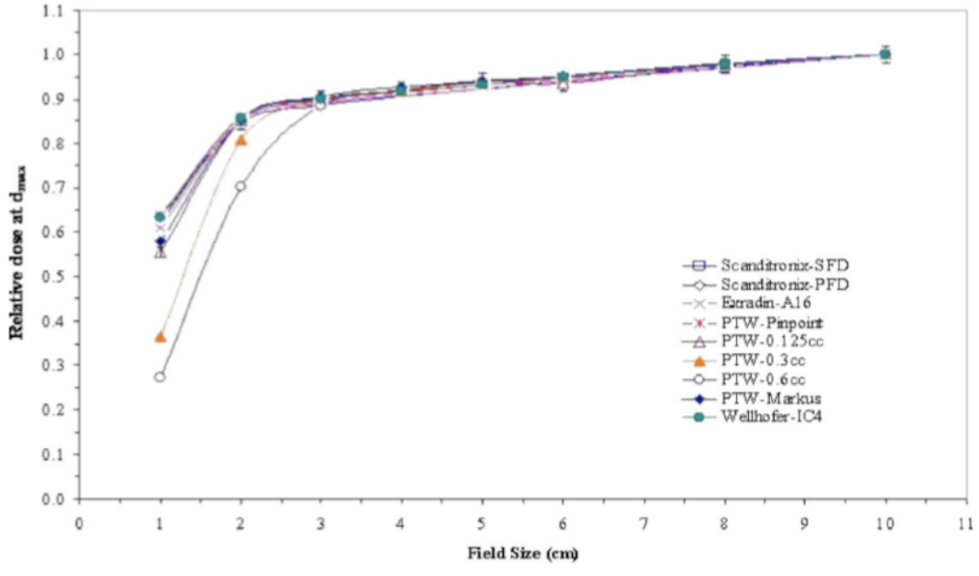
Aspradakis et al

How to measure dose in small fields?



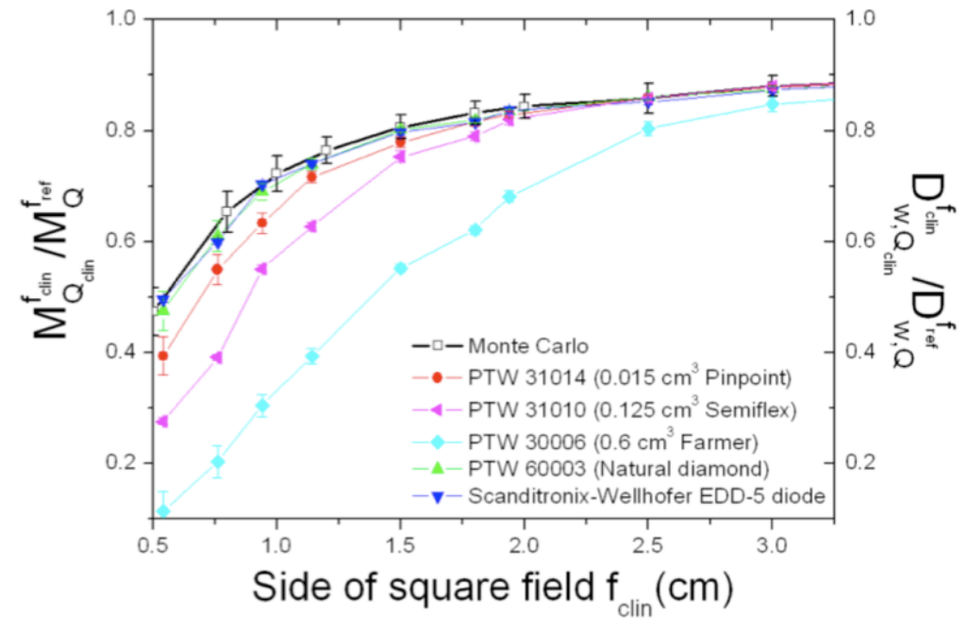
Use the correct chamber?





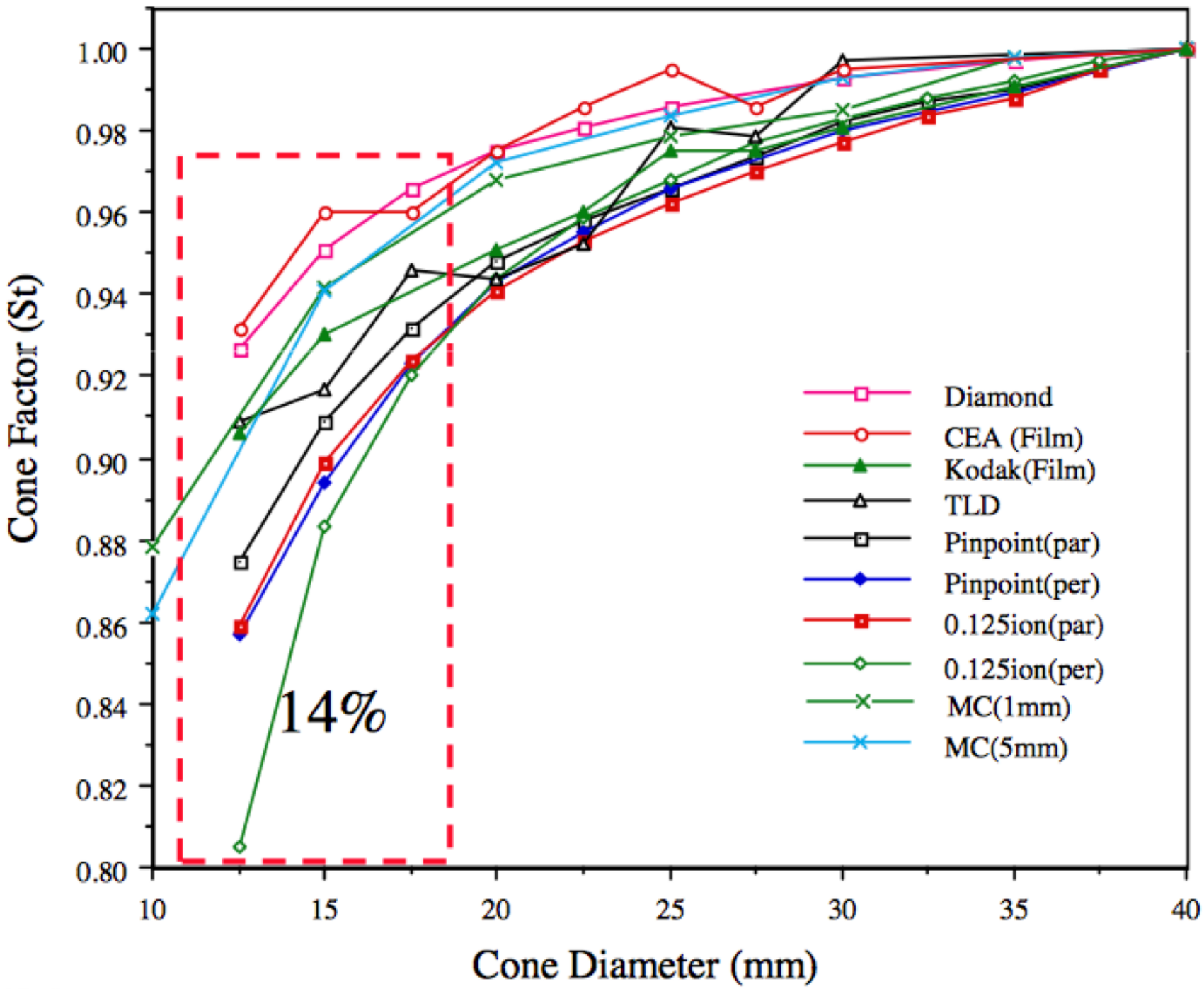
- Availability of detectors:
  - Standard chamber ($\approx 10^{-1}$ cm^3): the active volume of a standard Farmer-type IC is on average 0.6 cm^3.
  - Mini chamber ($\approx 10^{-2}$ cm^3): on average 0.05 cm^3.
  - Micro chamber ($\approx 10^{-3}$ cm^3): on average 0.007 cm^3 ideally suited for high gradient dose regions and for small field dosimetry.
- Each detector has limitations that need to be addressed!!!!!

Das IJ, *et al.*, Med Phys, 2008



Sanchez-Doblado F. *et al.*, 2007

SRS dosimetry



Das et al, J Radiosurgery, 3, 177-186, 2000

Chamber size : volume effect in FFF beams

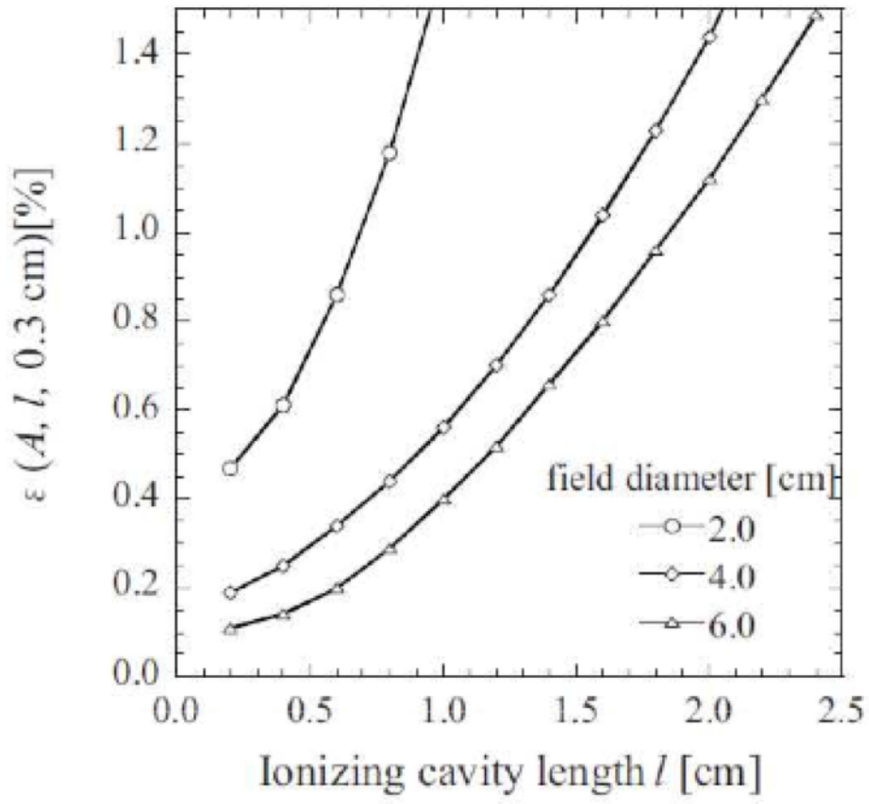


FIG. 2. The error of dosimeter reading $\varepsilon(A,l,0.3\text{ cm})$ (%) as a function of cavity length l of ionization chamber and field A. The cavity radius r is calculated in 0.3 cm, and these values are for a SCD of 80 cm at a depth of 10 cm in water.

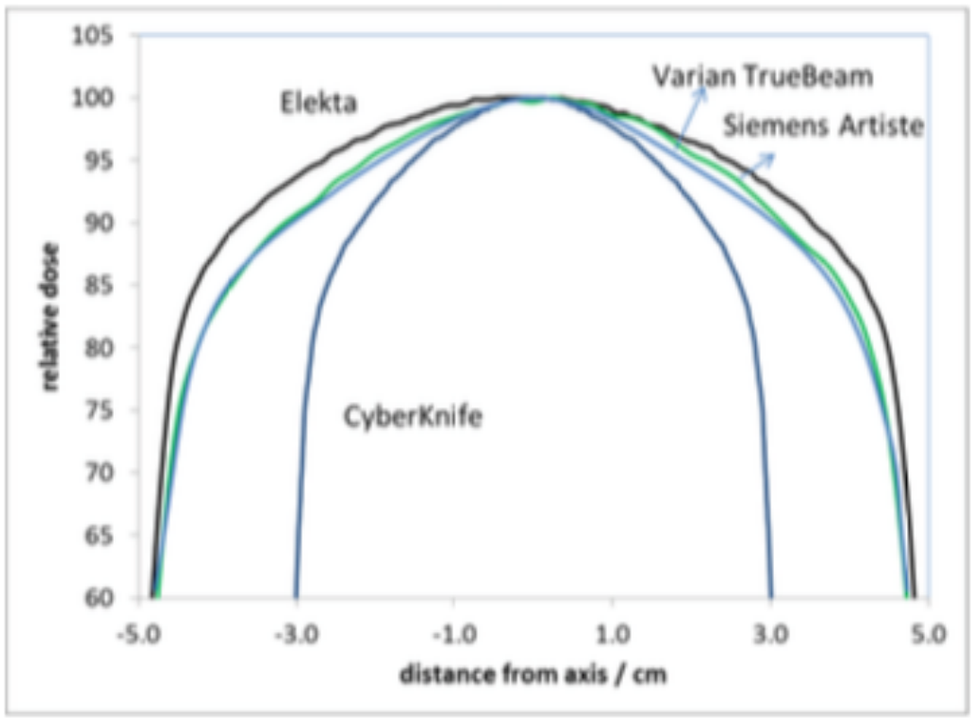
Kawachi *el al* (2008), Med Phys 35 (10)

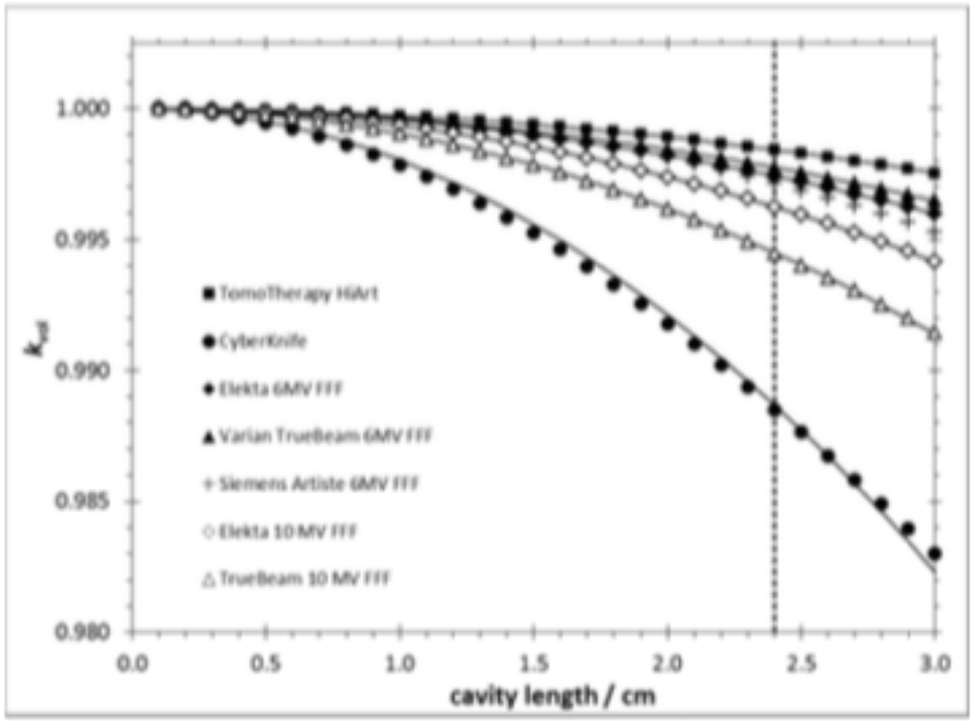
$$\varepsilon(A,l,r)=\frac{100\int_{-l/2}^{l/2}\int_{-r}^{r}|\mathrm{OAR}(A,x,y)-1|\,\mathrm{d}x\mathrm{d}y}{\int_{-l/2}^{l/2}\int_{-r}^{r}\mathrm{d}r\mathrm{d}y}$$

OAR(x,y) is the off axis distribution of field A in orthogonal directions x and y

Using a 24mm cavity results in 1.5% dose underestimation for a 6cm field on CK

Volume effect in FFF beams





Court. of H. Palmans

AUTORITÉ DE SÛRETÉ NUCLÉAIRE

DIVISION DE BORDEAUX

RÉPUBLIQUE FRANÇAISE

Bordeaux, le 29 mai 2007

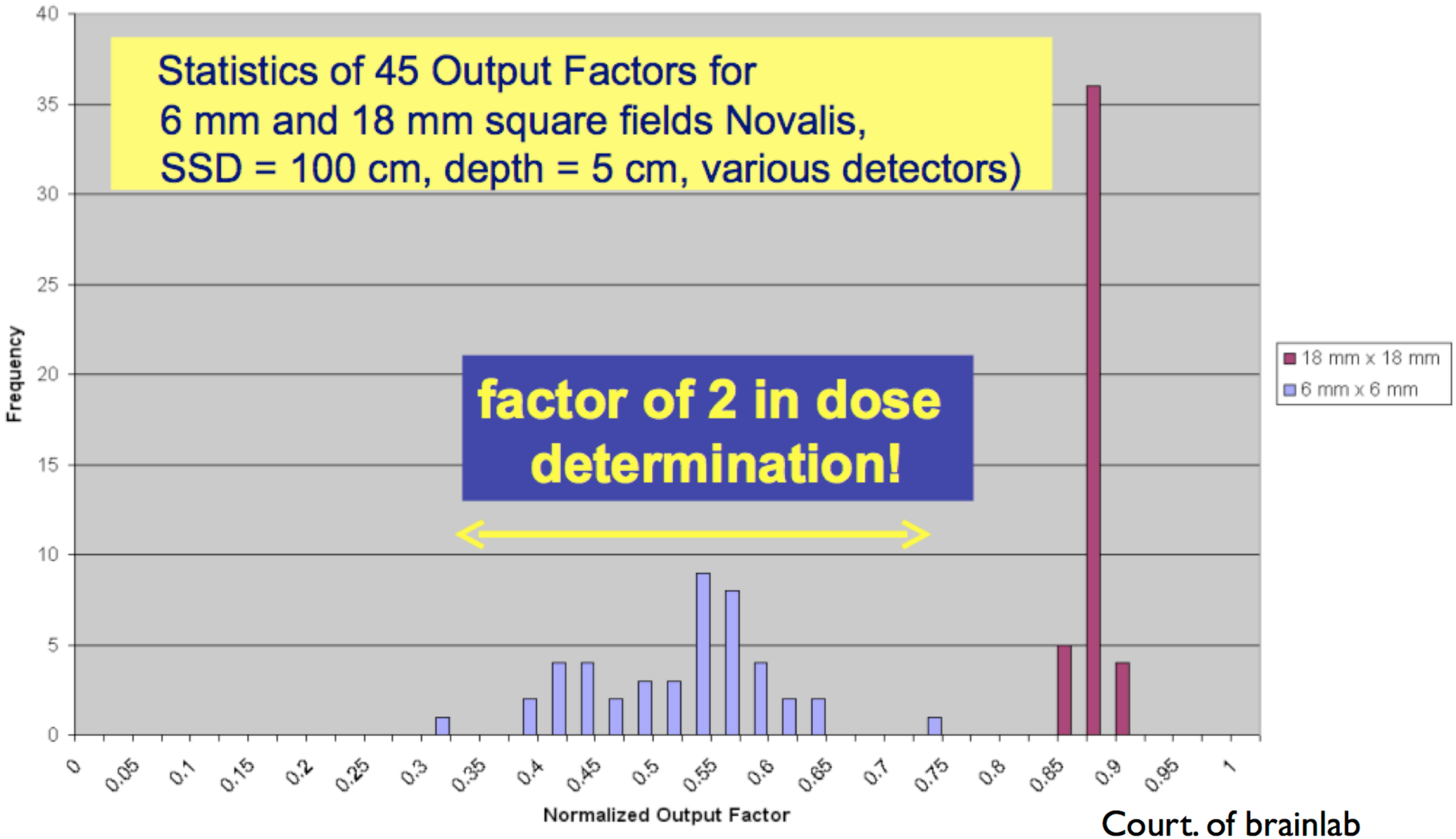
http://www.asn.fr/sites/default/files/files/Toulouse_ASN_report1.pdf?nocache=1225460993.4

REPORT

concerning the radiotherapy incident at the university hospital centre (CHU) in Toulouse – Rangueil Hospital

Although the origin of the event is clearly identified (use of a measuring device which was inappropriate for calibrating microbeams), the underlying causes remain to be determined; this, however, was not the main goal of the inspection. The letter following the inspection therefore asks the CHU to analyse the organisational and human factors, especially human resources, work load, skills and training.

and even using the “correct” chamber...



Court. of brainlab

Let's get even more basic : standard dosimetry protocols

Reference dosimetry

$$D_{water} = M\left[\left(\frac{\overline{W}}{e}\right)\frac{1}{m_{gass}}\right]\left[\left(\frac{\overline{S}}{\rho}\right)_{air}^{water} p_{corr}\right]$$

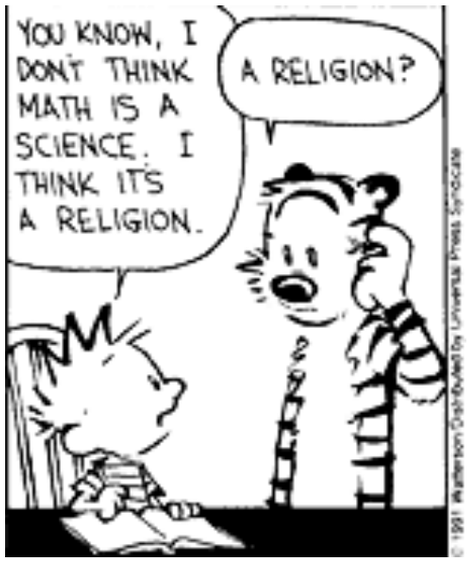
Correcting from water to air

Correcting for the fact the chamber is not perfect and does not disturb the medium

$$p_{corr} = p_{wall}\, p_{cell}\, p_{repl}$$

$$D_{\text{water},Q} = M_{\text{water},Q}\, N_{D_w,Q_o}\, k_{Q,Q_o}$$

Kq= quality index



$$k_{Q,Q_0} = \frac{\left(\frac{W_{air}}{e}\right)_Q \left[\left(\frac{\overline{S}}{\rho}\right)_{air}^{water}\right]_Q p_Q}{\left(\frac{W_{air}}{e}\right)_{Q_0} \left[\left(\frac{\overline{S}}{\rho}\right)_{air}^{water}\right]_{Q_0} p_{Q_0}}$$

Kq= quality index

$$k_{Q,Q_0} = \frac{\left(\frac{W_{air}}{e}\right)_Q \left[\left(\frac{\overline{S}}{\rho}\right)^{water}_{air}\right]_Q p_Q}{\left(\frac{W_{air}}{e}\right)_{Q_0} \left[\left(\frac{\overline{S}}{\rho}\right)^{water}_{air}\right]_{Q_0} p_{Q_0}}$$

Kq= quality index

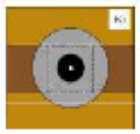
$$k_{Q,Q_0} = \frac{\left(\frac{W_{air}}{e}\right)_Q \left[\left(\frac{\bar{S}}{\rho}\right)^{water}_{air}\right]_Q p_Q}{\left(\frac{W_{air}}{e}\right)_{Q_0} \left[\left(\frac{\bar{S}}{\rho}\right)^{water}_{air}\right]_{Q_0} p_{Q_0}}$$

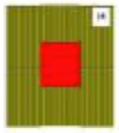
In small fields; the spectrum changes, how is this affecting this term?

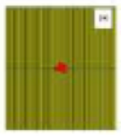
Spenser-Attix Stopping power ratios (central axis, d=5cm)


100 mm×100 mm


Beam ∅ 10 mm


Beam ∅ 3mm


100 mm×100 mm


20 mm×20 mm irregular on axis


20 mm×20 mm irregular off axis

6 MV beams	Beam quality ($TPR_{20,10}$)	$s_{w,air}$ Andreo (1994)[a]	$s_{w,air}$ This work	$s_{w,air}$ Ratio this work/ Andreo	$s_{PMMA,air}$ Andreo (1994)[a]	$s_{PMMA,air}$ This work	$s_{PMMA,air}$ Ratio this work/ Andreo
Elekta SL-18 radiosurgery							
10×10 cm^2	0.690	1.1187	1.1188	1.000	1.0853	1.0856	1.000
1.0 cm diameter			1.1155	0.997		1.0819	0.997
0.3 cm diameter			1.1153	0.997		1.0817	0.997
Siemens Primus MLC							
10×10 cm^2	0.677	1.1213	1.1221	1.001	1.0880	1.0892	1.001
2×2 cm^2 irregular on-axis			1.1203	0.999		1.0870	0.999
2×2 cm^2 irregular 8 cm off-axis			1.1250	1.003		1.0922	1.004
MLC transmission			1.1300	1.008			
IMRT beam (10×10 cm^2 approx)			1.1201	0.999			

[a] These are the values in the IAEA TRS-398 code of practice (Andreo *et al* 2000).

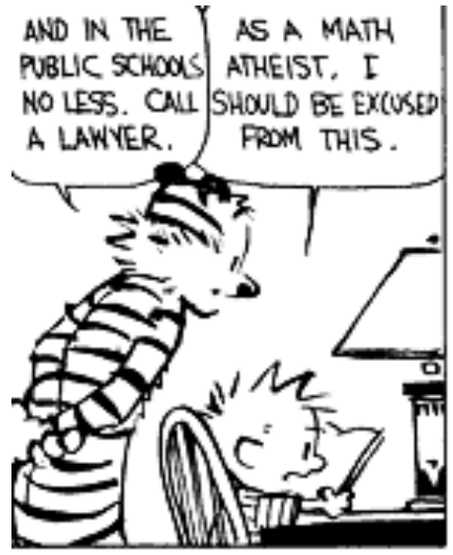
0.3%

0.5%

< 0.2%

Sanchez-Doblado et al (2003), PMB 48: 2081

Kq= quality index, for differences between calibration beam quality and clinical beam quality



$$k_{Q,Q_0} = \frac{\left(\frac{W_{air}}{e}\right)_Q \left[\left(\frac{\bar{S}}{\rho}\right)_{air}^{water}\right]_Q}{\left(\frac{W_{air}}{e}\right)_{Q_0} \left[\left(\frac{\bar{S}}{\rho}\right)_{air}^{water}\right]_{Q_0}} \; p_Q \; p_{Q_0}$$

What is the perturbation of the chamber on our medium

(What does the elephant do to the interior of our box)

Perturbation factors

TABLE IV. Wall correction factors, replacement correction factors, and calculated k_Q of cylindrical ion chambers for a Cyberknife system and a linear accelerator.

$$p_{det} \approx p_{wall}\, p_{repl}$$

	P_{wall}		P_{repl}		k_Q	
Chamber type	Linac	Cyberknife	Linac	Cyberknife	Linac	Cyberknife
PTW 31002 flexible	1.0005	1.0004	0.9905	0.9893	0.9914	0.9887
PTW 30001 Farmer	1.0007	1.0006	0.9895	0.9881	0.9913	0.9885
PTW 30002 Farmer	0.9947	0.9945	0.9895	0.9881	0.9949	0.9921
PTW 30004 Farmer	0.9947	0.9945	0.9895	0.9881	0.9959	0.9930
PTW 30013 Farmer	1.0004	1.0003	0.9895	0.9881	0.9916	0.9889
Exradin A 12 Farmer	0.9915	0.9914	0.9895	0.9881	0.9984	0.9957

±0.3%

TABLE I. Physical characteristics of cylindrical ion chambers.

		Cavity dimensions		Wall			
Chamber type	Cavity volume (cm^3)	Length (mm)	Radius (mm)	Material	Thickness (g/cm^2)	Central electrode material	Waterproof
PTW 31002 flexible	0.13	6.5	2.8	PMMA	0.078	Aluminum	Y
PTW 30001 Farmer	0.6	23.0	3.1	PMMA	0.045	Aluminum	N
PTW 30002 Farmer	0.6	23.0	3.1	Carbon	0.079	Carbon	N
PTW 30004 Farmer	0.6	23.0	3.1	Carbon	0.079	Aluminum	N
PTW 30013 Farmer	0.6	23.0	3.1	PMMA	0.057	Aluminum	Y
Exradin A 12 Farmer	0.65	24.2	3.1	C-552	0.088	C-552	Y

Araki (2006), Med Phys 33(8)

Perturbation Factors

Cyberknife 8mmx8mm

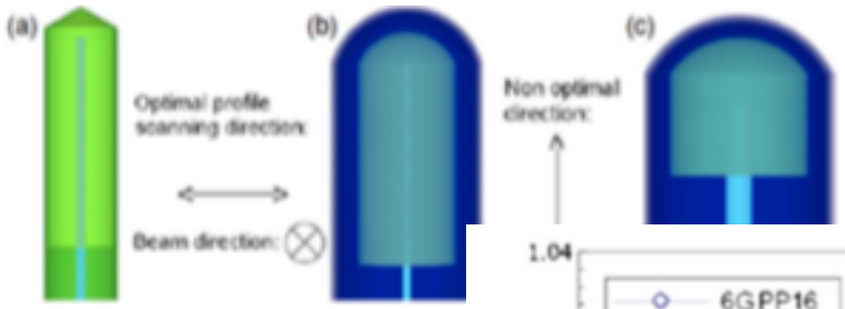
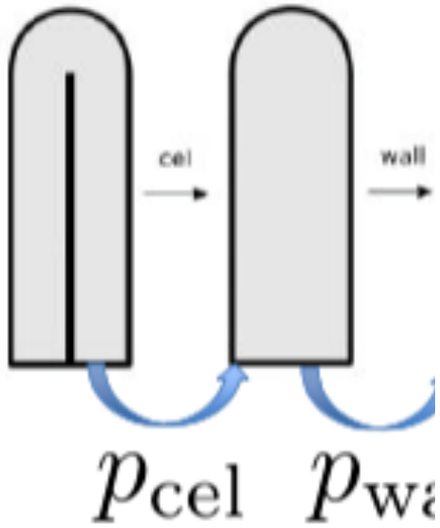
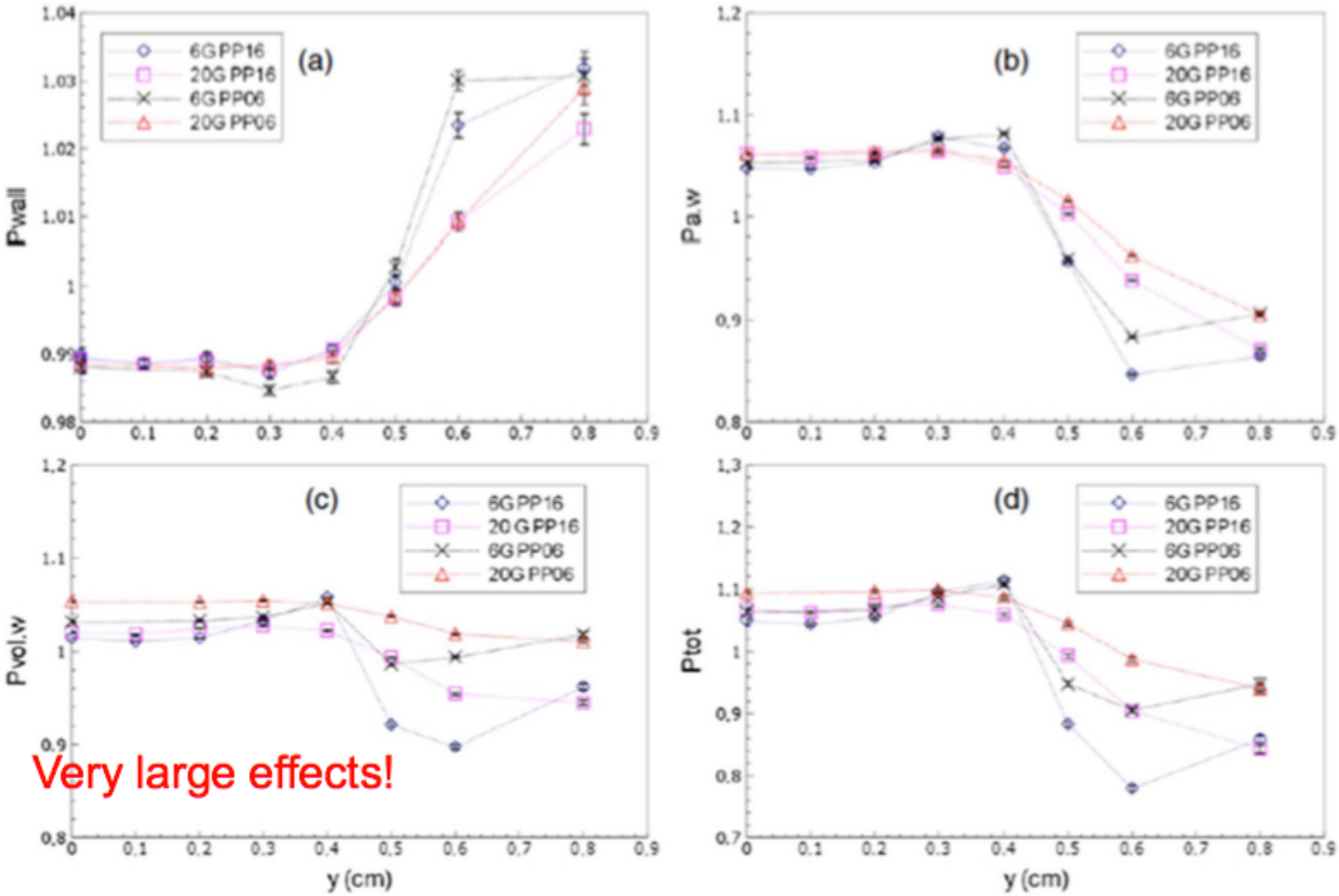


Figure 2. Geometrical models of (a) NE257 (images are not on the same scale).





F.Crop et al, PMD 2009

So…

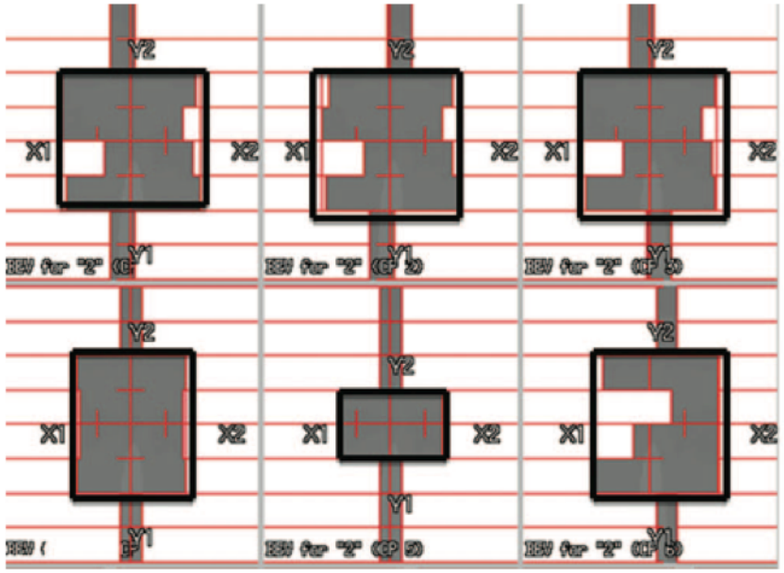
- We've got a lot of small effects, which of course all add up to a larger uncertainty
- All these effects will be present in OF measurements, profiles, PDD-curves,…
  - …and will be higher for low density materials (TPS)
  - dose2medium vs. dose2water?
- Certainty on factors is growing thanks to MC calculations.
- Measurements on larger SSD

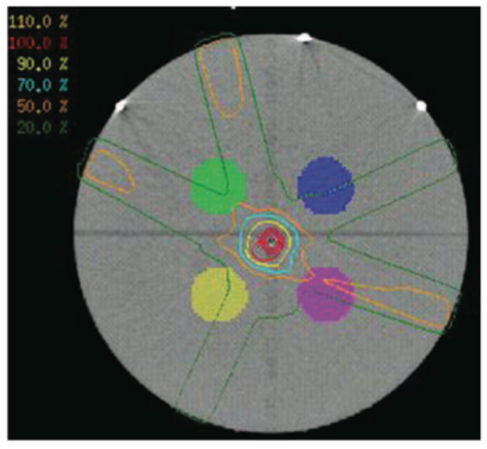
Effect of variation in output factors in TPS

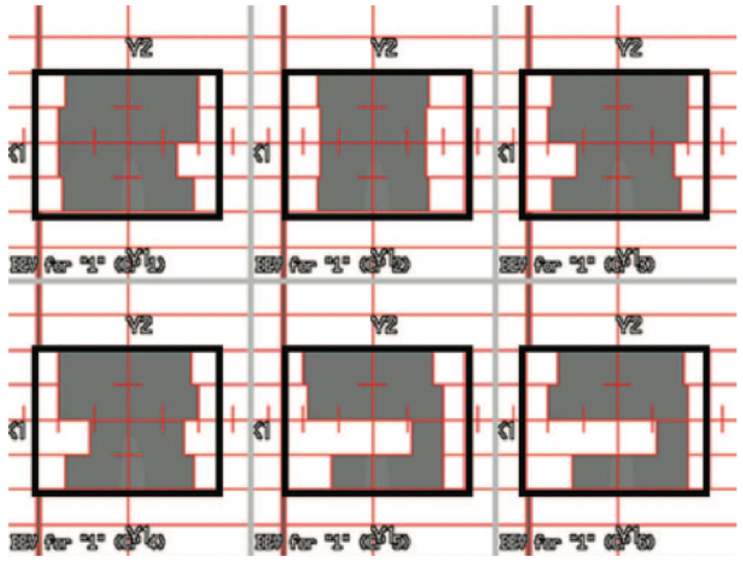
Elekta

"Identical" MLC
Identical plan and TPS

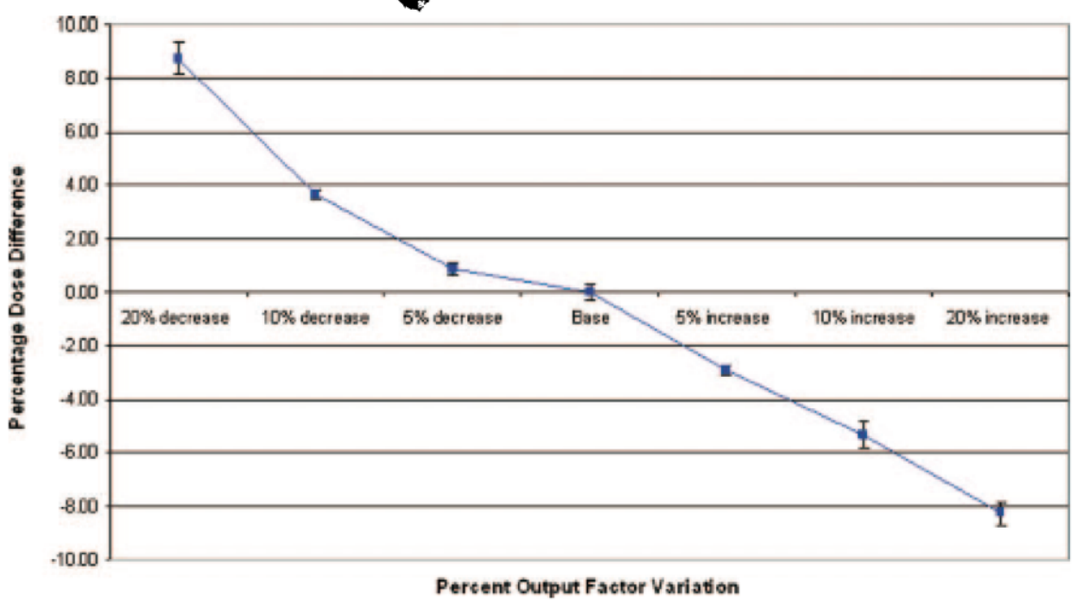
Varian

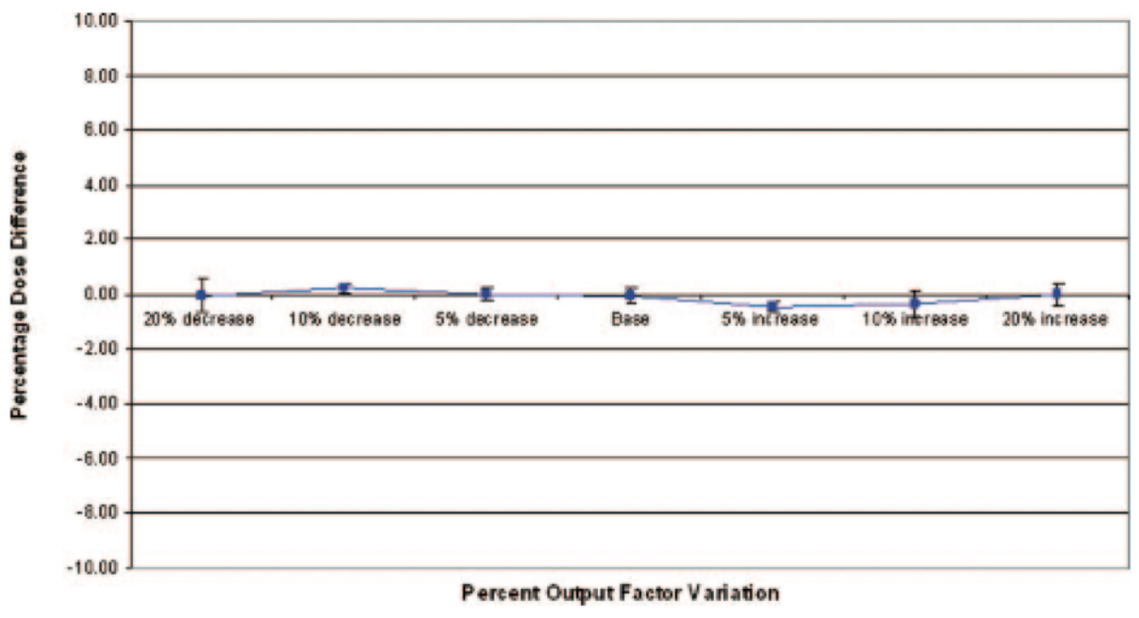






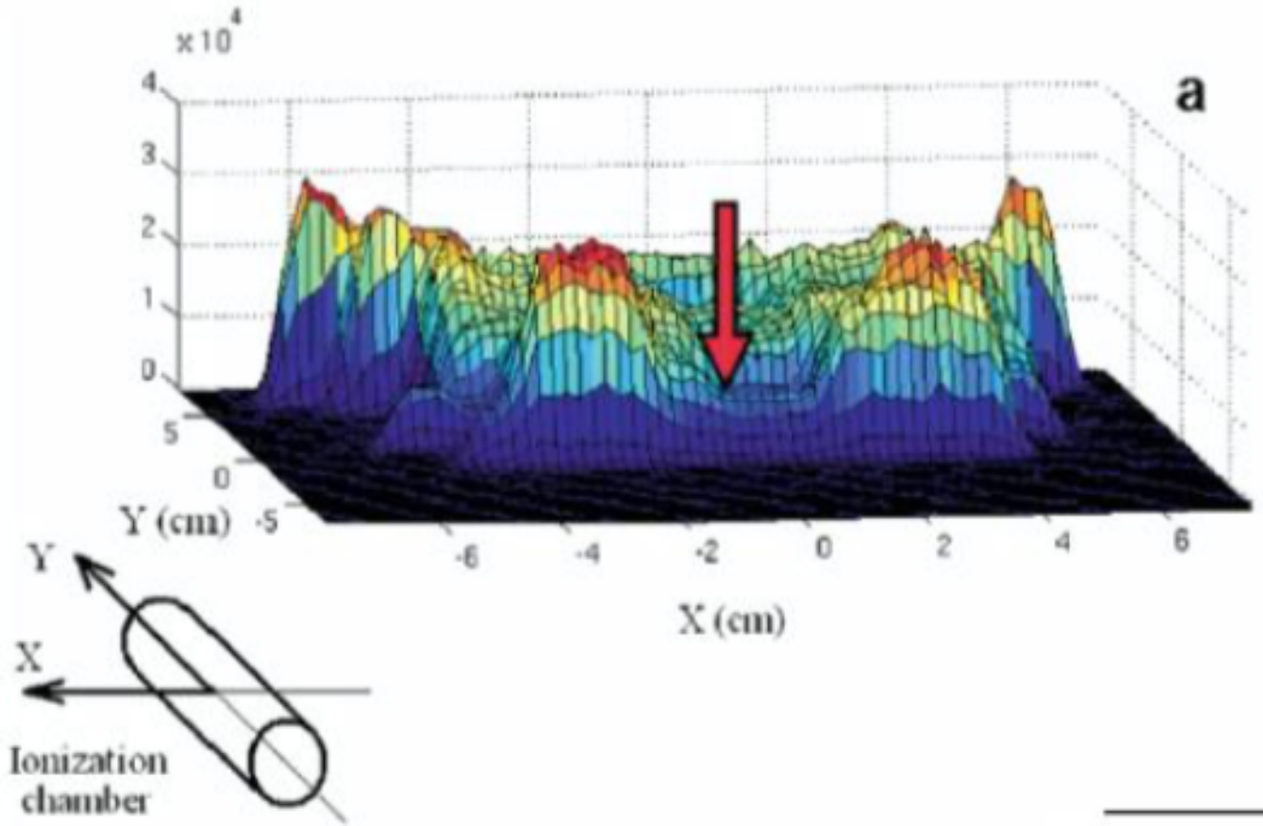
Introduction of errors in OF between up to 20%

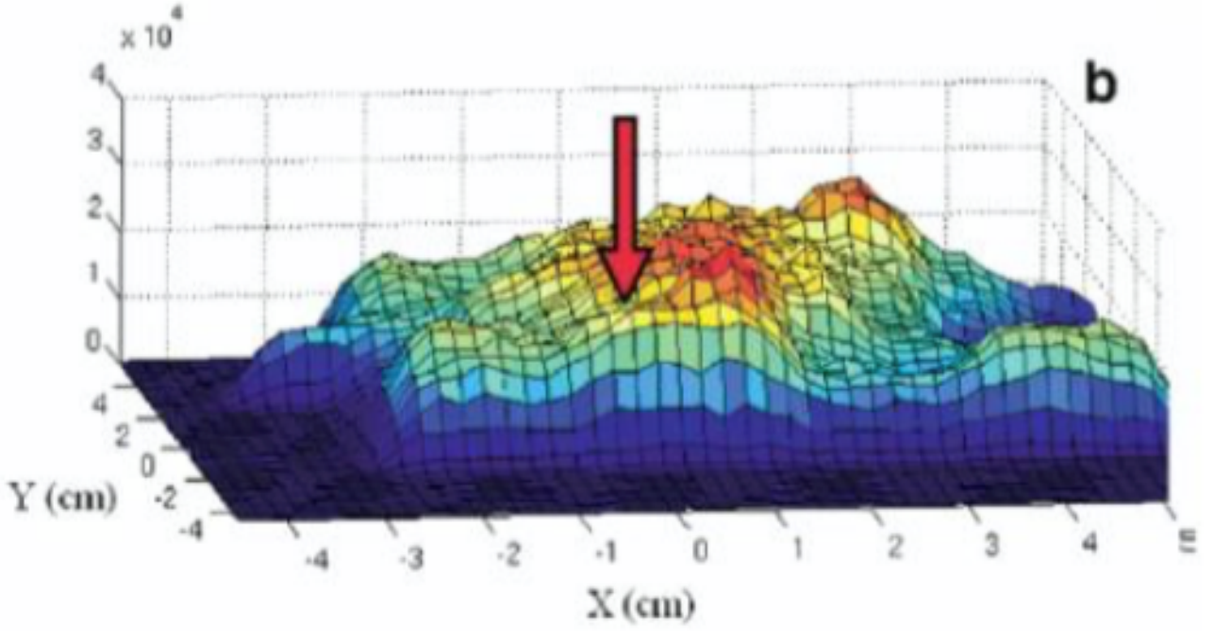


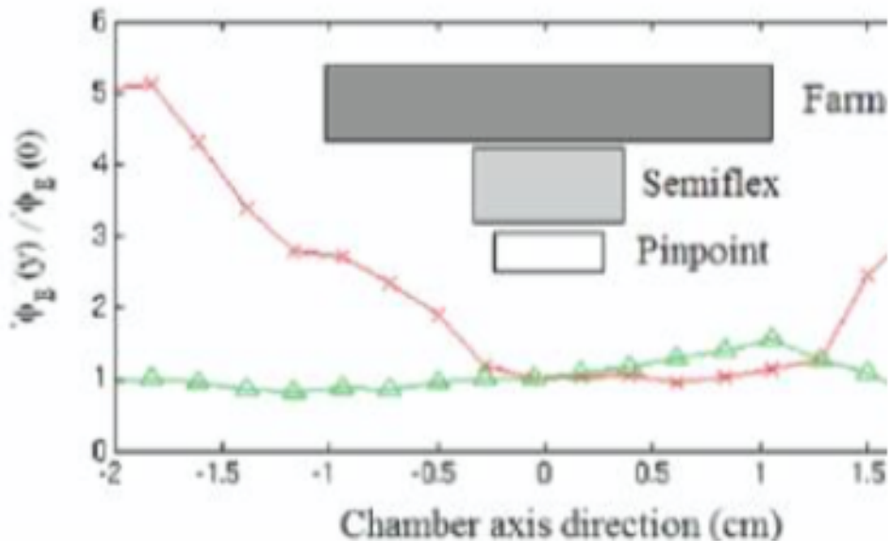


Azimi et al, Medical Physics, Vol. 39, No. 8, August 2012

IMRT







Incident	Pinpoint	Semiflex	Farmer
0°	0.95	0.93	0.75
72°	1.02	1.01	0.99
144°	1.02	1.04	1.03
216°	1.00	1.02	1.02
288°	0.99	1.00	0.97

court. R. Capote

Non-standard fields

- For IMRT:

- Even if the dose in the measurement area is large and homogeneous, generated by many beamlets, DON'T use large chambers to measure dose.

Reference dosimetry in small fields

- Use of mini or micro (air filled) IC
  - ….that fits in the field
- Perturbation factors not known in many cases (effect worse for low densities)
- Leakage, cable and polarity effects?
- Use of diamond-detectors, diodes

What do we do when reference conditions cannot be achieved?

Small & non-standard field

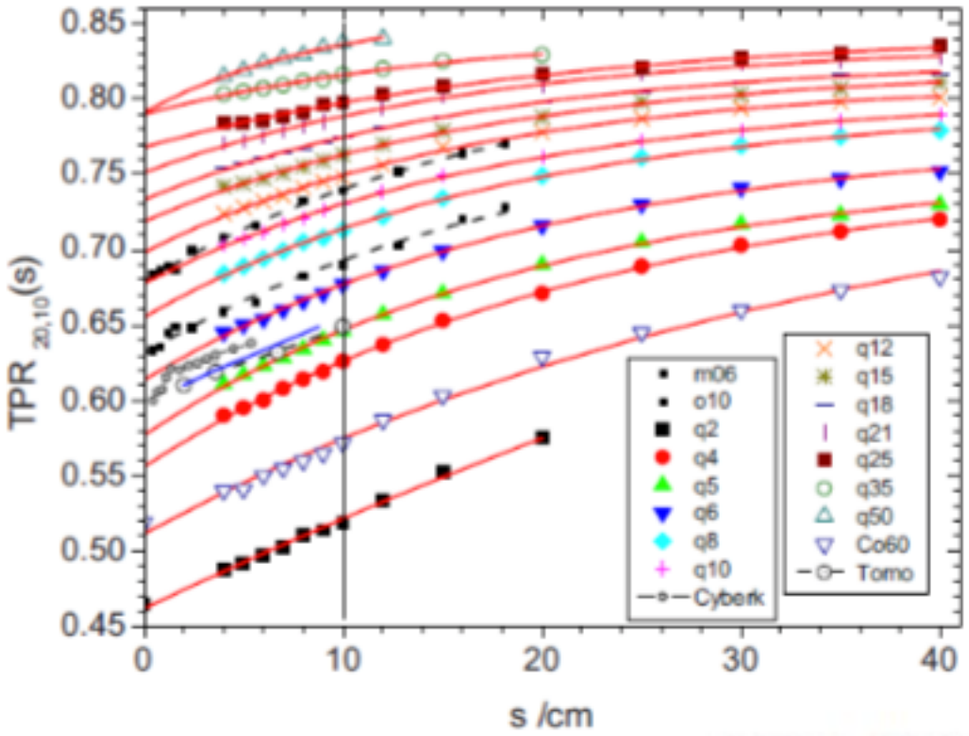
➔A proposal for a new formalism by the IAEA

- 2 routes
- Both routes require the extension of the concept of reference field to incorporate small and non-standard fields, as well as modified reference conditions such as phantom shape and material

Small and non-standard field dosimetry

- Alternative procedures to determine beam quality
- The new IAEA/AAPM formalism (aka “alfonso formalism”)

Alternative procedures to determine beam quality



Data from BJR Suppl 25

$$Q = \frac{\mathrm{TPR}_{20,10}(s) - b_1 - A_1(1 - e^{-s/t})}{b_2 + A_2(1 - e^{-s/t})}.$$

TABLE I. Parameters for Eq. (3) valid for $0.62 < Q < 0.8$.

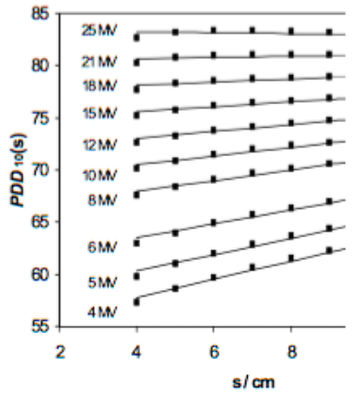
b_1	-0.208 ± 0.022	A_1	$+0.625 \pm 0.036$	t	$+19.5 \pm 2$ cm
b_2	$+1.213 \pm 0.030$	A_2	-0.679 ± 0.050		

Sauer et al, med phys (2009)

Alternative procedures to determine beam quality

e.g. for $PDD_{10X}(10) = \%dd(10)_X$

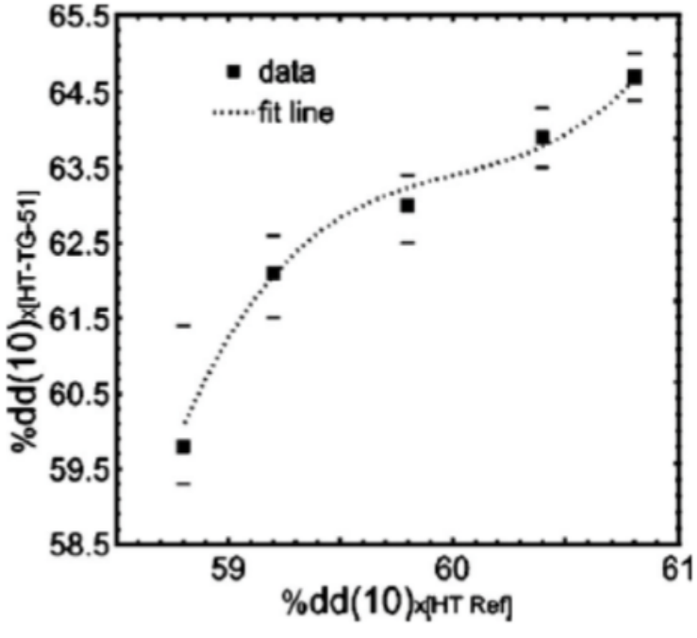
$$PDD_{10}(10) = \frac{PDD_{10}(s) + c_1 \cdot \left(e^{\frac{10-s}{t}} - 1 \right)}{1 + c_2 \cdot \left(e^{\frac{10-s}{t}} - 1 \right)}$$



$$PDD_{10x}(10) = \begin{cases} PDD_{10}(10), & PDD_{10}(10) < 75.0 \\ 1.267 \cdot PDD_{10}(10) - 20.0, & PDD_{10}(10) \geq 75.0 \end{cases} \quad \text{(TG-51)}$$

Palmans et al, med phys (2012)

Beam quality specifier for Tomotherapy



AAPM TG-148 (Langen et al. 2010 Med Phys 37:4817-53): "$dd(10)_{x[HT\text{-}ref]}$"

IAEA/AAPM formalism

- Route 1
  - Small static field dosimetry for machines that cannot establish a conventional reference field
  - Introducing the intermediate machine-specific-reference field (msr)
- Route 2
  - Composite field dosimetry
  - Introducing msr and plan-class-specific reference field (pcsr)
  - The pcsr is a field that should be as close to a class of clinical plans as possible, while generating a homogeneous dose region “much” larger than the sensitive volume of the detector

Machine-specific-reference

- Reference calibration, reference field, f_{ref}

$$D_{w,Q_{msr}}^{f_{msr}} = M_{Q_{msr}}^{f_{msr}} \cdot N_{D,w,Q_0} \cdot k_{Q,Q_0} \cdot k_{Q_{msr},Q}^{f_{msr},f_{ref}}$$

$$k_{Q_{msr},Q}^{f_{msr},f_{ref}} = \frac{D_{w,Q_{msr}}^{f_{msr}} \Big/ M_{Q_{msr}}^{f_{msr}}}{D_{w,Q}^{f_{ref}} \Big/ M_{Q}^{f_{ref}}}$$

- Is a factor which corrects for the differences between the conditions of field size, geometry, phantom material, and beam quality of the conventional reference field, f_{ref}, and the machine-specific-reference field f_{msr}.

- This factor accounts for the difference between the responses of an ionisation chamber in the fields f_{ref} and f_{msr}.

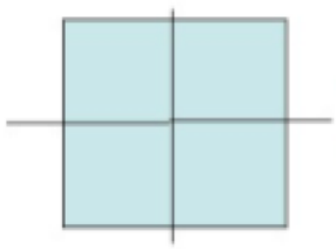
Machine-specific-reference field

1

REFERENCE DOSIMETRY

$$D_{w,Q_{msr}}^{f_{msr}} = M_{Q_{msr}}^{f_{msr}} \; N_{D,w,Q_0} \; k_{Q,Q_0} \; k_{Q_{msr},Q}^{f_{msr},f_{ref}}$$

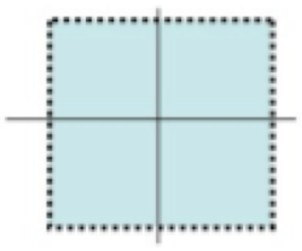
Broad beam reference field f_{ref}



$k_{Q_{msr},Q}^{f_{msr},f_{ref}}$

$N_{D,w,Q_0} \; k_{Q,Q_0}$

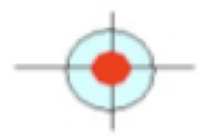
Hypothetical reference field f_{ref}



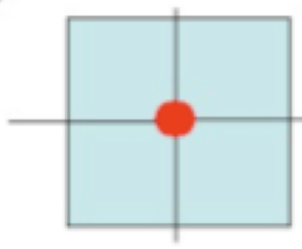
$k_{Q_{msr},Q}^{f_{msr},f_{ref}}$

● ≡ Ionization chamber

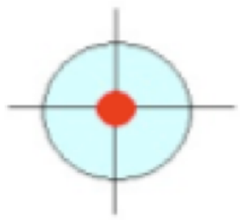
Machine specific reference field f_{msr}



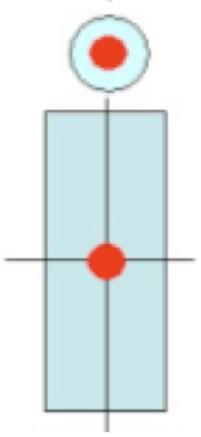
Radiosurgical collimators
∅ as low as 1.8cm



BrainLAB
micro MLC
10cm x 10cm



CyberKnife
∅ 6.0 cm



GammaKnife
∅ 1.6/1.8 cm

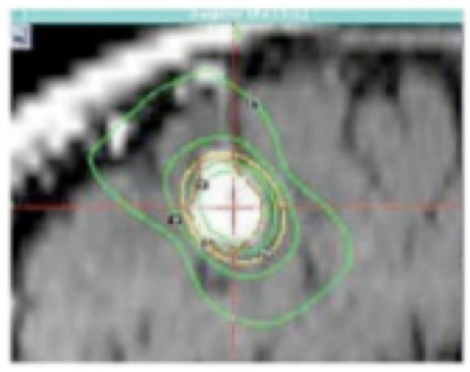
TomoTherapy
5cm x 20cm

RELATIVE DOSIMETRY

$$D_{w,Q_{clin}}^{f_{clin}} = D_{w,Q_{msr}}^{f_{msr}} \; \Omega_{Q_{clin},Q_{msr}}^{f_{clin},f_{msr}}$$

$\Omega_{Q_{clin},Q_{msr}}^{f_{clin},f_{msr}}$

Clinical f_{clin}



e.g. a GammaKnife clinical plan

Plan-class-specific-reference field

- Reference calibration, reference field, f_{pcsr}

$$D_{w,Q_{pcsr}}^{f_{pcsr}} = M_{Q_{pcsr}}^{f_{pcsr}} \cdot N_{D,w,Q_0} \cdot k_{Q,Q_0} \cdot k_{Q_{pcsr},Q}^{f_{pcsr},f_{ref}}$$

or

$$D_{w,Q_{pcsr}}^{f_{pcsr}} = M_{Q_{pcsr}}^{f_{pcsr}} \cdot N_{D,w,Q_0} \cdot k_{Q,Q_0} \cdot k_{Q_{msr},Q}^{f_{msr},f_{ref}} \cdot k_{Q_{pcsr},Q_{msr}}^{f_{pcsr},f_{msr}}$$

$k_{Q_{msr},Q}^{f_{msr},f_{ref}}$

- This factor will generally be close to unity under the condition that the addition and geometrical matching of the composite fields in the homogeneous phantom compensates for the loss of CPE in the penumbra of individual fields.
- Ideally it would be obtained by direct calibration of the IC against a primary standard or another dosimeter such as alanine, or alternatively, Monte Carlo.

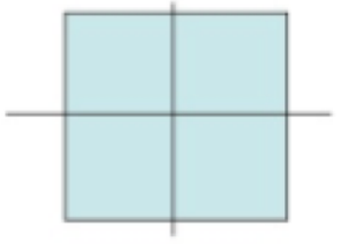
Plan-class-specific-reference field

2

REFERENCE DOSIMETRY

$$D_{w,Q_{pcsr}}^{f_{pcsr}} = M_{Q_{pcsr}}^{f_{pcsr}} \; N_{D,w,Q_0} \; k_{Q,Q_0} \; k_{Q_{pcsr},Q}^{f_{pcsr},f_{ref}}$$

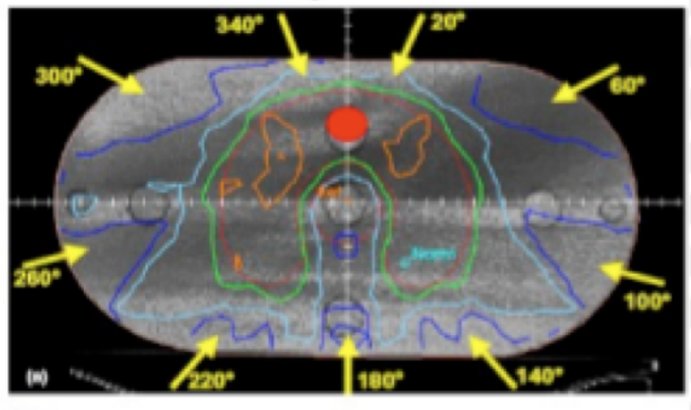
Broad beam reference field f_{ref}



N_{D,w,Q_0} k_{Q,Q_0}

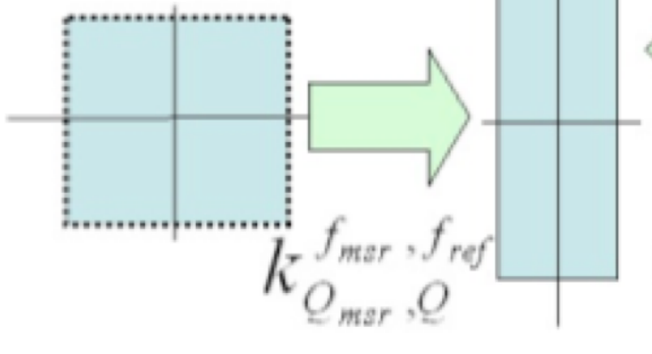
$k_{Q_{pcsr},Q}^{f_{pcsr},f_{ref}}$ (e.g. IMRT Linac)

Plan-class specific reference field f_{pcsr}



e.g. 9-field prostate *pcsr*

Hypothetical reference field



$k_{Q_{msr},Q}^{f_{msr},f_{ref}}$

f_{msr}

$k_{Q_{pcsr},Q_{msr}}^{f_{pcsr},f_{msr}}$

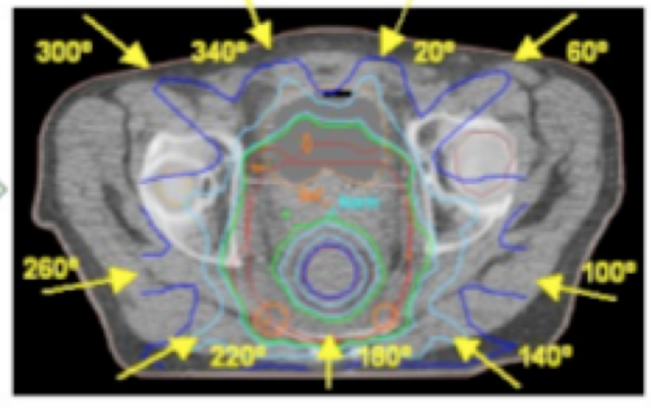
(e.g. **TomoTherapy** 5cm x 20cm)

RELATIVE DOSIMETRY

$$D_{w,Q_{clin}}^{f_{clin}} = D_{w,Q_{pcsr}}^{f_{pcsr}} \; \Omega_{Q_{clin},Q_{pcsr}}^{f_{clin},f_{pcsr}}$$

$\Omega_{Q_{clin},Q_{pcsr}}^{f_{clin},f_{pcsr}}$

Clinical f_{clin}



e.g. 9-field prostate clinical plan

● ≡ Ionization chamber

Small and composite fields

- In both cases, small and composite fields, it can be seen that the formalism stays close to the one of conventional COPs in the sense that a calibration of a reference field is performed followed by the application of output factors or an equivalent type of factors for clinical fields.

- The main difference being the extension of the concept of reference field.

- In line with this approach, it might be possible that a standards laboratory is able to provide a direct calibration coefficient , $N_{D,w,Q_{msr}}^{f_{msr}}$, for an IC in the machine-specific-reference field.

- NCS report on Tomotherapy : 1 Kq, incorporating pcsr, msr and regular kq

Don’t worry...let’s get practical

Practical Example

Helical Tomotherapy

6MV
Non-Flat "coned" field
max field size = 5x40cm^2

Practical Example

Use the msr-method on a 10x5 field

$$D_{w,Q_{msr}}^{f_{msr}} = M_{Q_{msr}}^{f_{msr}} \cdot N_{D,w,Q_0} \cdot k_{Q,Q_0} \cdot k_{Q_{msr},Q}^{f_{msr},f_{ref}}$$

Static output is correctly characterized

Clinical treatment is not static

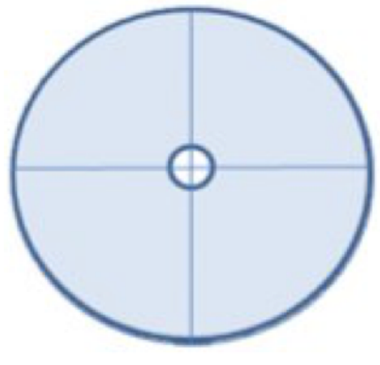
Practical Example

Use the msr-method on a nonmodulated rotational field

$$D_{w,Q_{msr}}^{f_{msr}} = M_{Q_{msr}}^{f_{msr}} \cdot N_{D,w,Q_0} \cdot k_{Q,Q_0} \cdot k_{Q_{msr},Q}^{f_{msr},f_{ref}}$$

Rotational output is correctly characterized

Clinical treatment is modulated



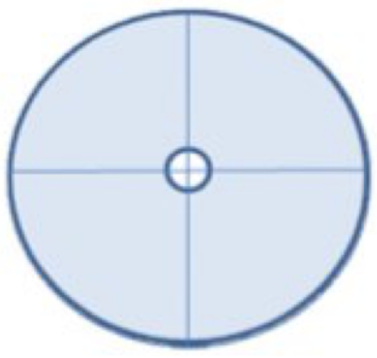
Practical Example

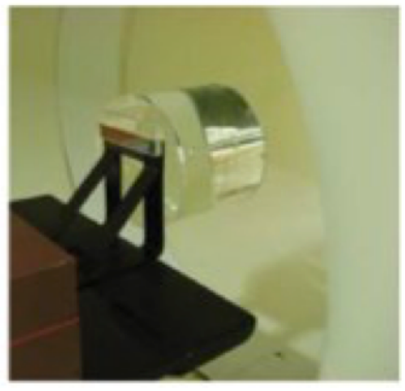
Use the pcsr-method on a modulated rotational field

$$D^{f_{pcsr}}_{w,Q_{pcsr}} = M^{f_{pcsr}}_{Q_{pcsr}} . N_{D,w,Q_0} . k_{Q,Q_0} . k^{f_{msr},f_{ref}}_{Q_{msr},Q} . k^{f_{pcsr},f_{msr}}_{Q_{pcsr},Q_{msr}}$$

Rotational output is correctly characterized

TomoDirect ?





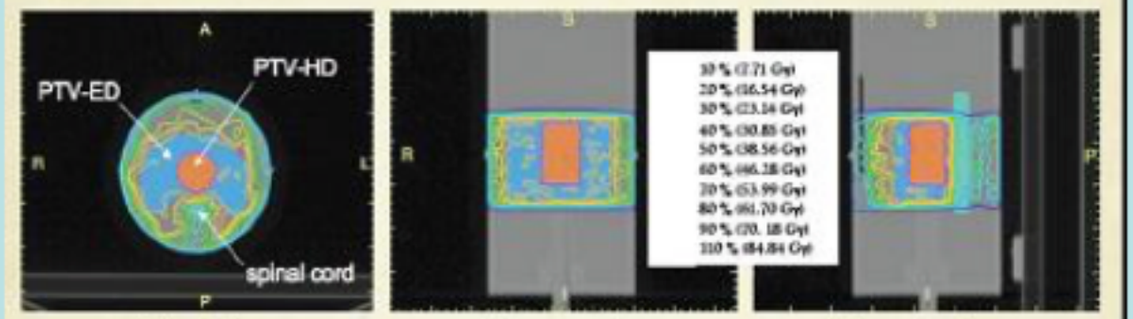
Results

		Deventer (NL) Dose rate (Gy/min)	Ratio meas/TG148	Lille (F) Dose rate (Gy/min)	Ratio meas/TG148	Antwerp (B) Dose rate (Gy/min)	Ratio meas/TG148	UCL (B) Dose rate (Gy/min)	Ratio meas/TG148
Static msr	TG-148	6.303	—	6.261	—	6.168	—	6.220	—
Test 'A'	local prot.	6.345	1.007	6.260	1.000	—	—	6.215	0.992
	Alanine	6.280	0.996	6.265	1.001	6.178	0.998	6.217	0.999
Rot. msr	TG-148	6.313	—	6.250	—	6.159	—	6.298	—
Test 'B'	local prot.	6.355	1.007	6.260	1.002	—	—	6.309	1.002
	Alanine	6.350	1.006	6.325	1.012	6.157	0.996	6.284	0.998
pcsrf/5 cm	TG-148	1.998	—	2.027	—	1.993	—	—	—
Test 'C'	local prot.	2.009	1.006	2.023	0.998	—	—	—	—
	Alanine	1.990	0.996	2.010	0.992	1.981	0.994	—	—
pcsrf/2.5 cm	TG-148	2.000	—	—	—	1.993	—	2.017	—
Test "C'"	local prot.	2.002	1.001	—	—	—	—	2.016	1.000
	Alanine	2.003	1.002	—	—	1.987	0.997	2.014	0.999

De Ost et al, med.phys.38(11)

Checked with alanine and Monte Carlo

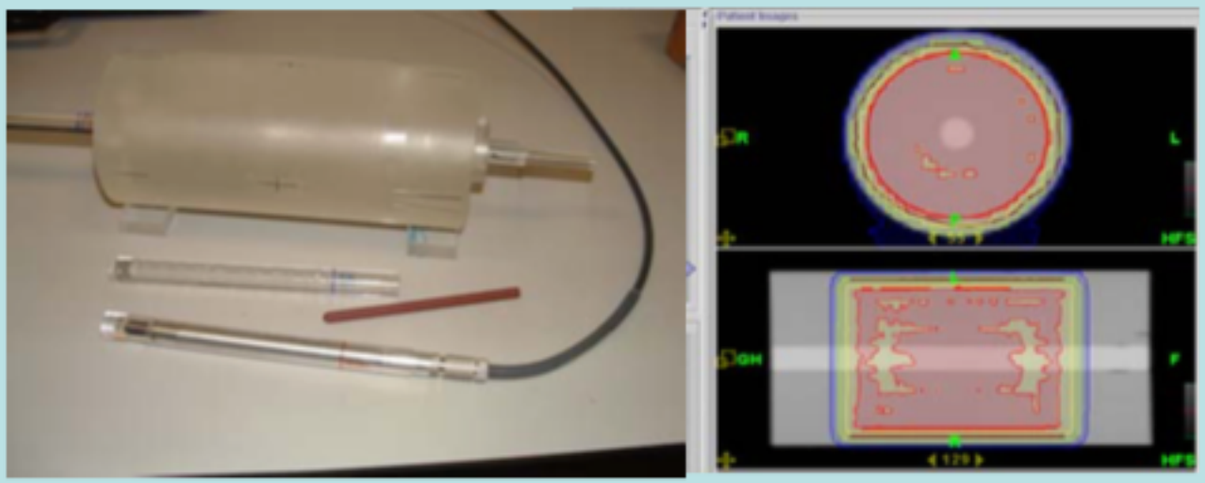
Dynamic IMRT H&N – Chung et al. 2010 Med. Phys. 37:2404-13



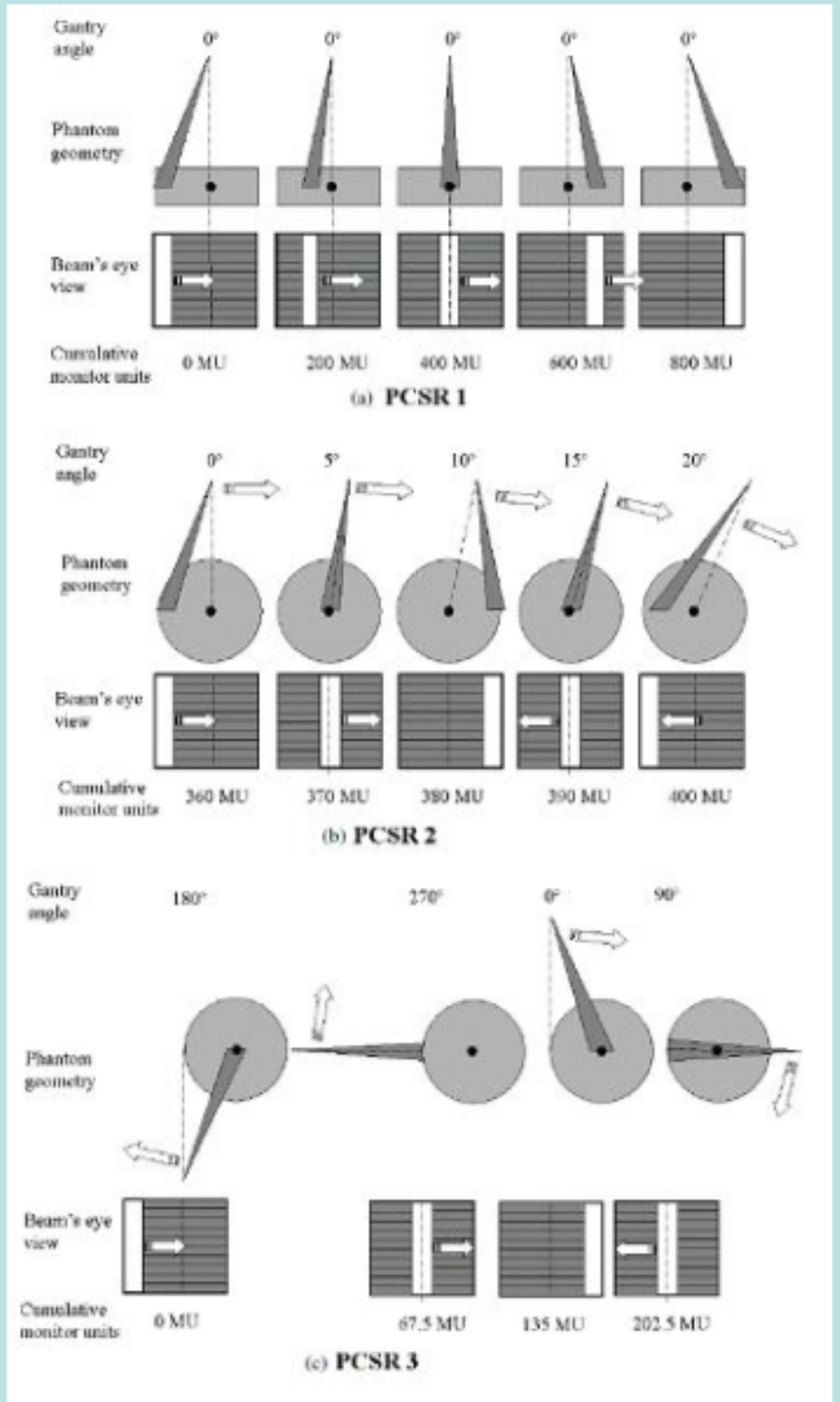
(a) axial (b) coronal (c) sagittal

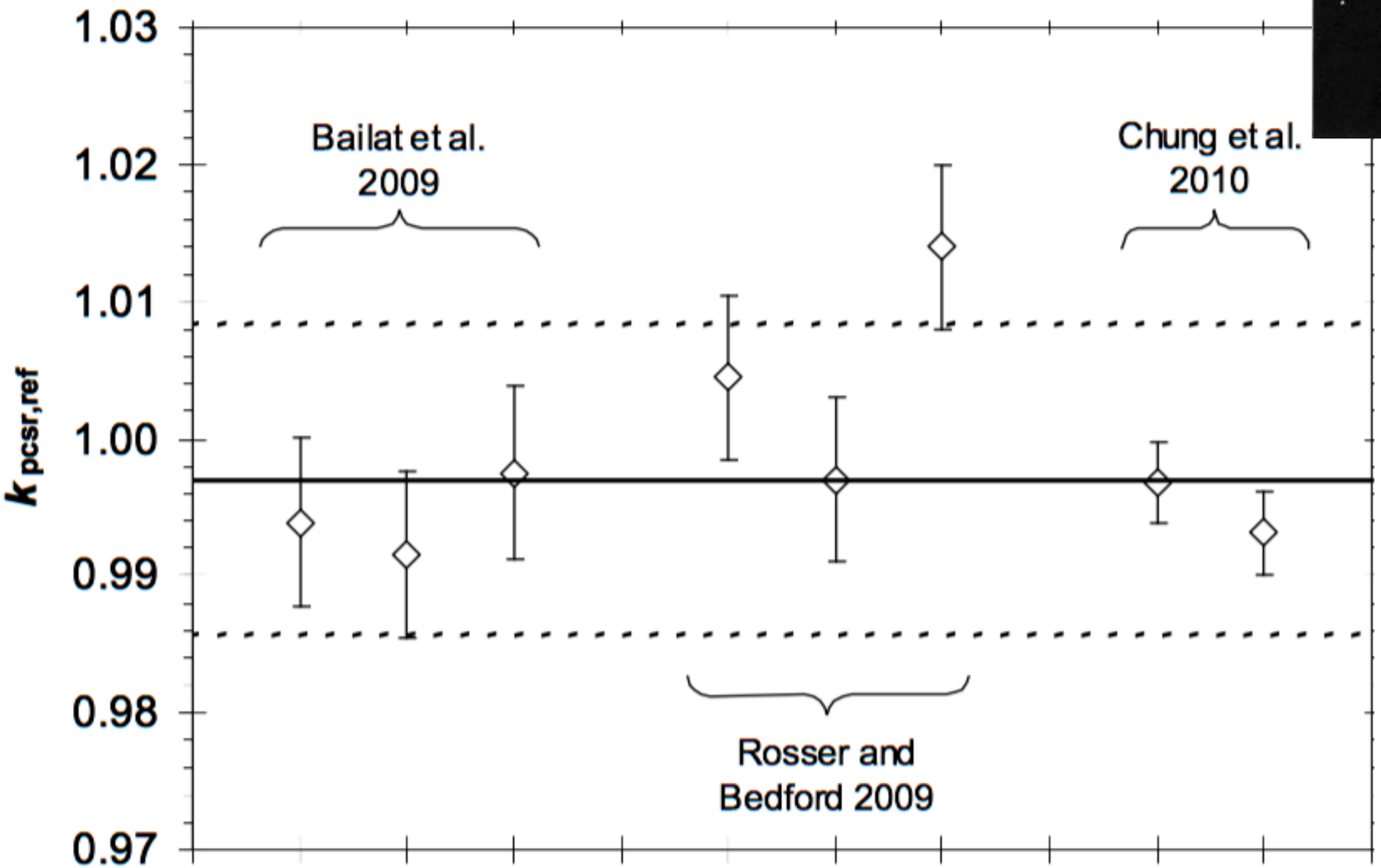
- Radiation: a 6 MV photon beam from a Varian® Clinac™ 6 EX linear accelerator

TomoTherapy – Bailat et al. 2009 Med. Phys. 36:3891-3896



VMAT – Rosser and Bedford 2009 Phys. Med. Biol. 54:7045-7061





court. Palmans

Conclusion

- The concept of 2 intermediate calibration fields is introduced:
  - A static *machine-specific-reference field* for those modalities that cannot establish conventional reference conditions
  - A *plan-class-specific-reference field* closer to the patient-specific clinical fields.
- The main challenge will be the definition of a suitable *pcsr* field.
- Technology is evolving very fast...here today, gone tomorrow.
- Dosimetry has to catch up all the time
- When new techniques/new formalisms are not there yet....an independent check should always be found

Take home message

(physicists)

- Because of increasing complexity, depending on experience and "gut-feeling" is not enough.
- A good understanding of all small parameters affecting IMRT-dosimetry is a must

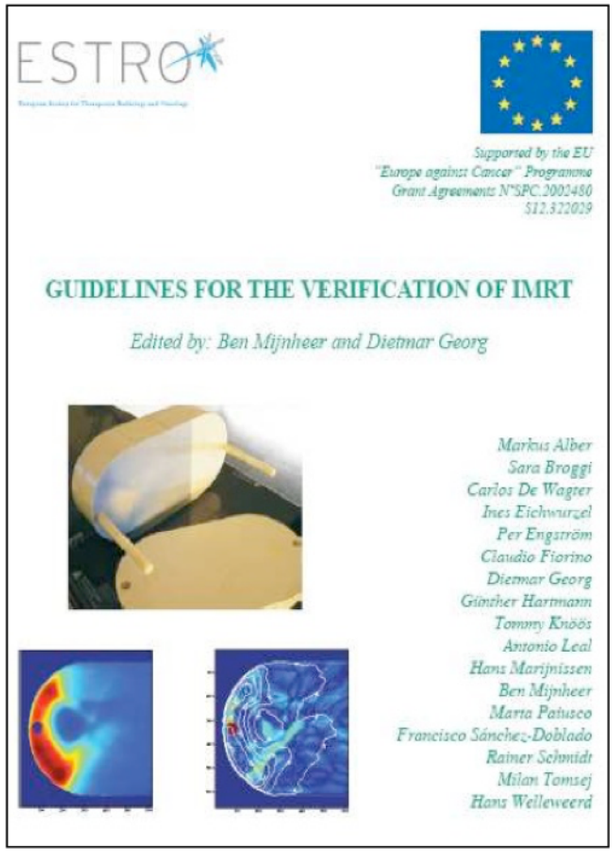
- CoPs are not straightforward applicable, traceability is a necessity.
- External audits can be a very good idea.

Take home message for physicians

- IMRT is not, has not been and will not be plug-and-play, whatever the monkey in the suit told you

- It is not a case of "quickly doing some measurements".
- After commissioning the fun is just starting : loads and loads of non-plug-and-play-patient QA which will keep your physics team busy and frustrated

Take home message, cont'd



Physicist driving the black box

Physician going to the golf court

IMRT treatment

Azienda Provinciale per i Servizi Sanitari
Trento, Italy

TPS commissioning

Marco Schwarz
Marco.schwarz@apss.tn.it

Overview

Generalities

Commissioning of the TPS

- General approach
- MLC/small fields/dose profiles
- Dose calculation during optimisation
- Accuracy criteria

Four steps to define, baseline and monitor the performances of radiotherapy equipment.

1. *Technical specifications*
2. *Acceptance tests*
3. *Commissioning*
4. *(Equipment) QA*

1/4

Define/agree upon the specifications, i.e. the performance requirements that the equipment must/should fulfill

- ✓ *'The MLC must have a positional accuracy of less than x mm'*
- ✓ *'The beam output should be stable within y%'*
- ✓ *'Calculated output factors should be within x% for fields not smaller than y'*
- ✓ *…*

Perform Acceptance (with the vendor), i.e. a series of test to demonstrate that the system complies with the specs.

(*E.g. Comparison between calculation and measurement of OF for 5 field sizes)*

IF the tests are successful

you pay for the equipment, which becomes yours.

ELSE

you ask for the problems to be fixed

N.B. No specs means no meaningful acceptance tests !!

How did you TPS acceptance tests look like?

3/4

Perform Commissioning(on your own), i.e. a series of tests that fully characterize the system before clinical use.

(*E.g. Comparison between calculation and measurement of OF for 25 field sizes)*

In general commissioning tests are a superset of the acceptance tests.

Thorough commissioning provides baseline data for **equipment** QA.

Perform equipment QA, i.e. a series of periodic tests to assess system performances over time.

(*E.g. Every day, MLC positioning accuracy is tested on five out of the 25 field shapes used in commissioning are tested.*

Check integrity of beam data in the TPS)

Commissioning data are the (initial) baseline to judge the system performances

Question: what does it mean to perform QA on a software?

Where does 'patient specific QA' fits into this scheme?

It is an additional QA element, if it is **really** patient specific.

Hardware and software are just a part of the treatment chain. The bottom line is the dose in the patient.

It may be a useful redundant check, in particular in the early phases of clinical implementation.

It is a way to compensate for incomplete/unsatisfactory commissioning.

Commissioning of TPS

Penumbra modeling

OF for small fields

Commissioning of the TPS

Heterogeneity corrections

MLC modeling

Modeling of off-axis fields

How to consider all variables in the acceptability criteria ?

Analytic approach

Find and achieve for each variable the value that will ensure the acceptability of all treatment plans.

This was the approach in CRT

ESTRO Booklets on QA for NON-IMRT beams

	Region	Homogenous, simple geometry	Complex geometry	More complex geometries
δ_1	*Central beam axis data* – high dose, low dose gradient	2%	3%	4%
δ_2*	*Build-up region of central axis beam, penumbra region of the profiles* - high dose, high dose gradient	2 mm or 10%	3 mm or 15%	3 mm or 15%
δ_3	*Outside central beam axis region* - high dose, low dose gradient	3%	3%	4%
δ_4**	*Outside beam edges* – low dose, low dose gradient	3%-3mm	4%-4mm	5%-5mm
RW_{50} ***	*Radiological width* – high dose, high dose gradient.	2 mm or 1%	2 mm or 1%	2 mm or 1%
δ_{50-90}	*Beam fringe* – high dose, high dose gradient	2 mm	3 mm	3 mm

"*… the emphasis on QA of IMRT is shifted from acceptance testing and commissioning of a TPS to patient-specific QA. However, also for patient-specific QA no guidelines are available.*"

ESTRO Booklet 9
"Guidelines on the verification of IMRT"

First, what you can NOT commission/QA

1. **The optimisation algorithm**

   How good/bad is in minimizing the cost function?

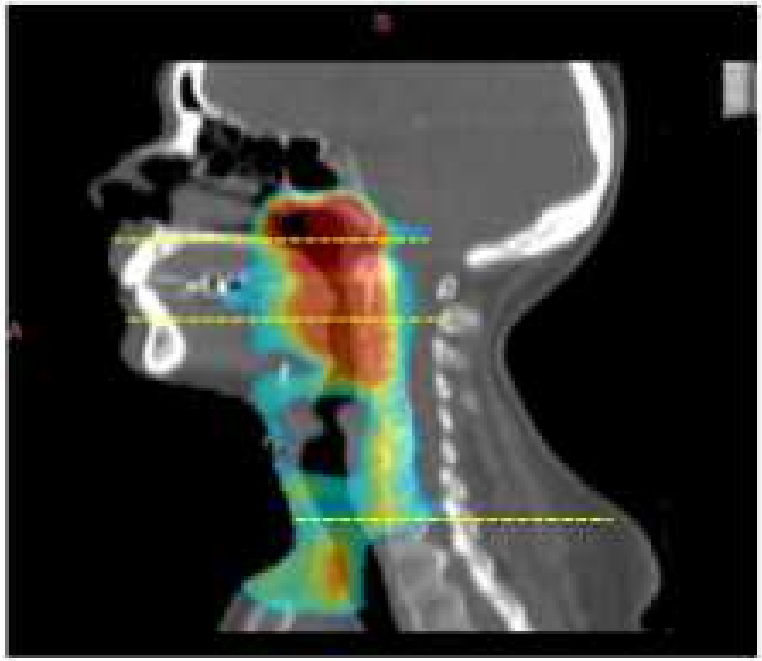
   (Unlikely to affect plan quality)

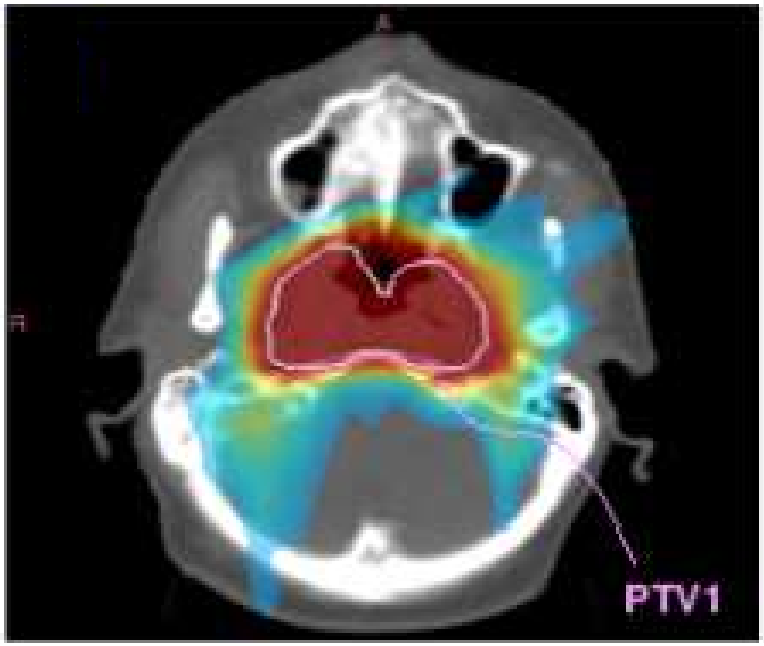
2. **The dose calculation algorithm used in fluence optimization**

   How can I check that the solution space is properly described by the TPS ?

   (Potentially affecting plan quality if there is no optimization after segmentation)

IMRT planning &
Dose calculation



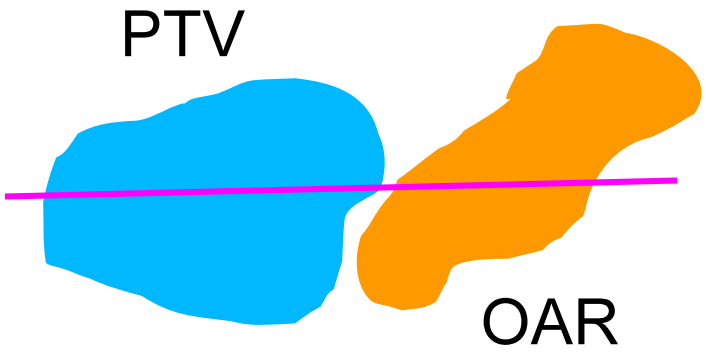


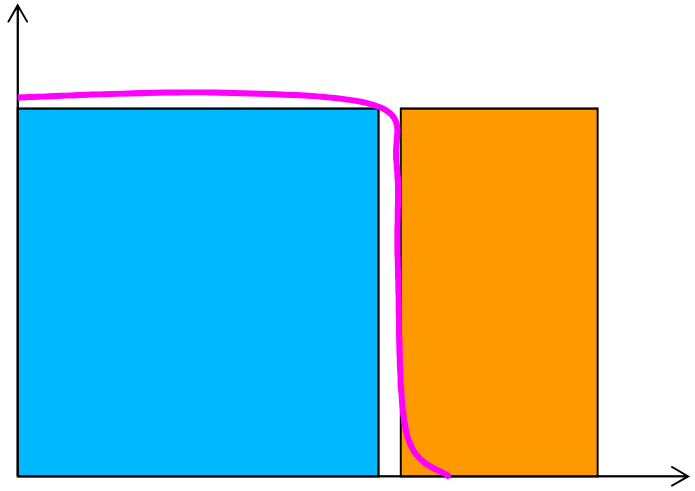
IMRT → Highly automated planning procedure

The solution is found within the solution space, which is shaped by

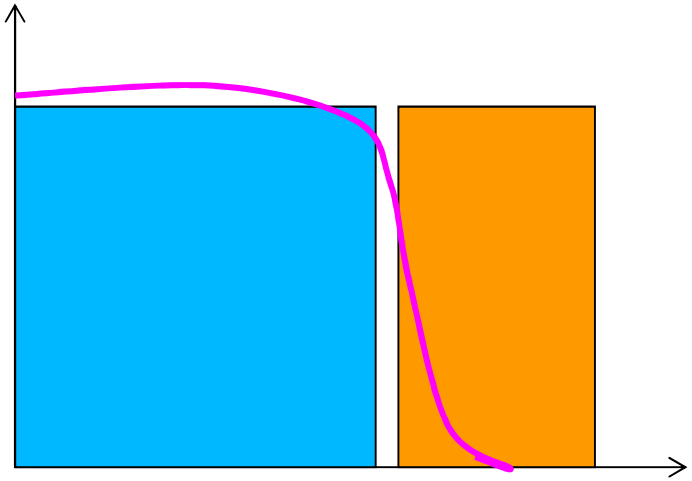
- ✓ Patient anatomy (geometry)
- ✓ The optimisation problem (cost function)
- ✓ The dose calculation

By defining the cost function in a dose range where calculation errors exist a bias is introduced in the optimisation problem



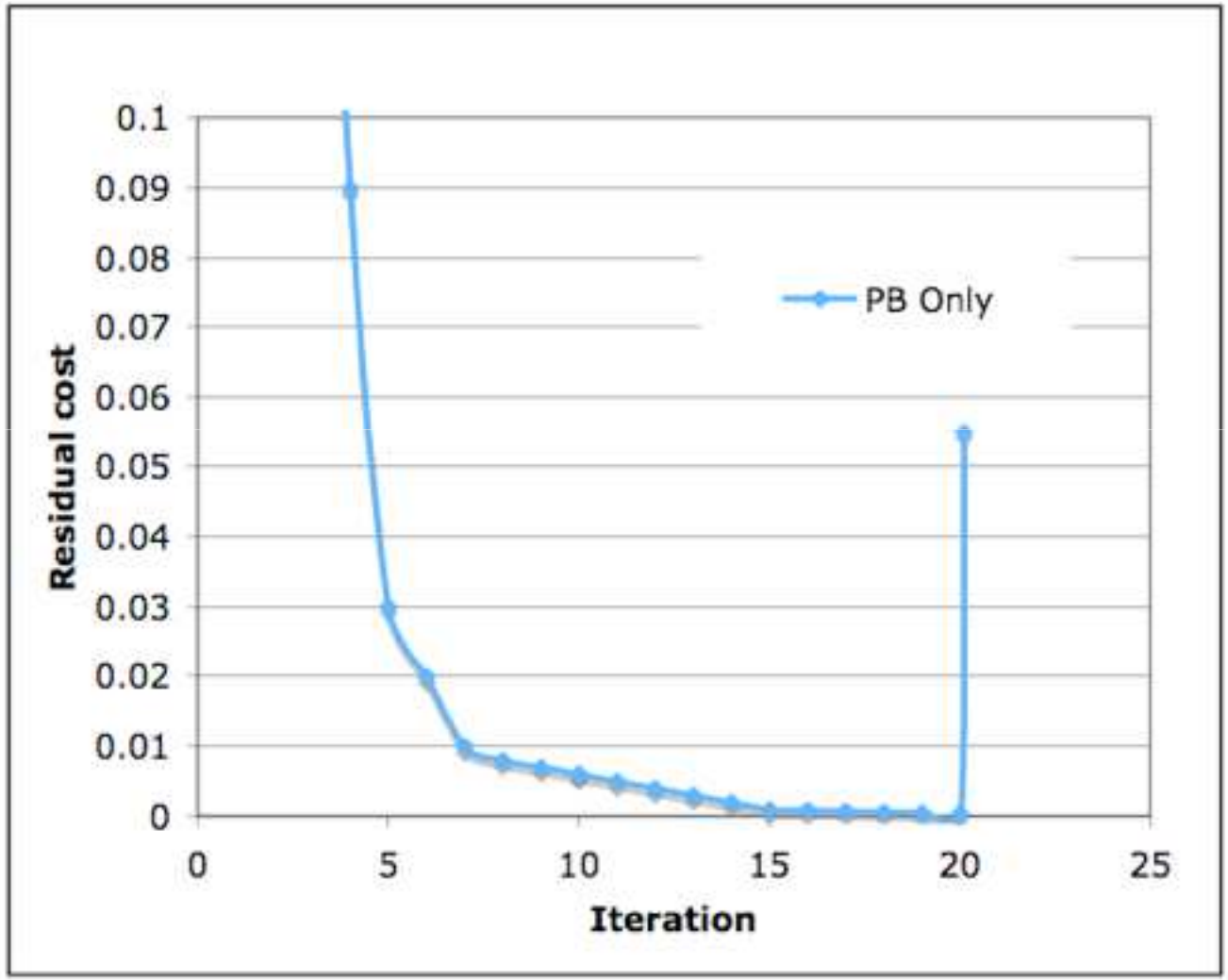


Ideal penumbra
Target coverage +
OAR sparing +



Real penumbra
Target coverage -
OAR sparing -

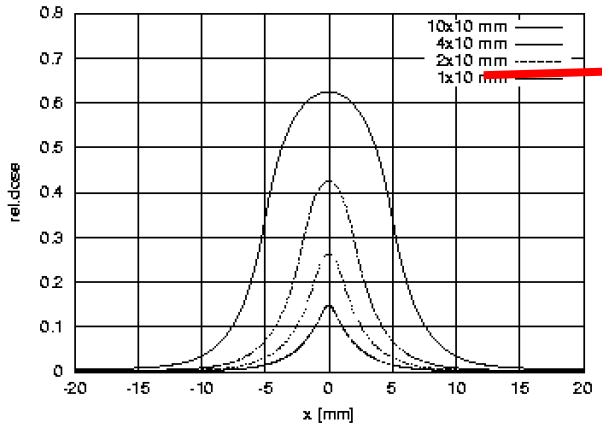
*Dose calc accuracy **during** optimisation*

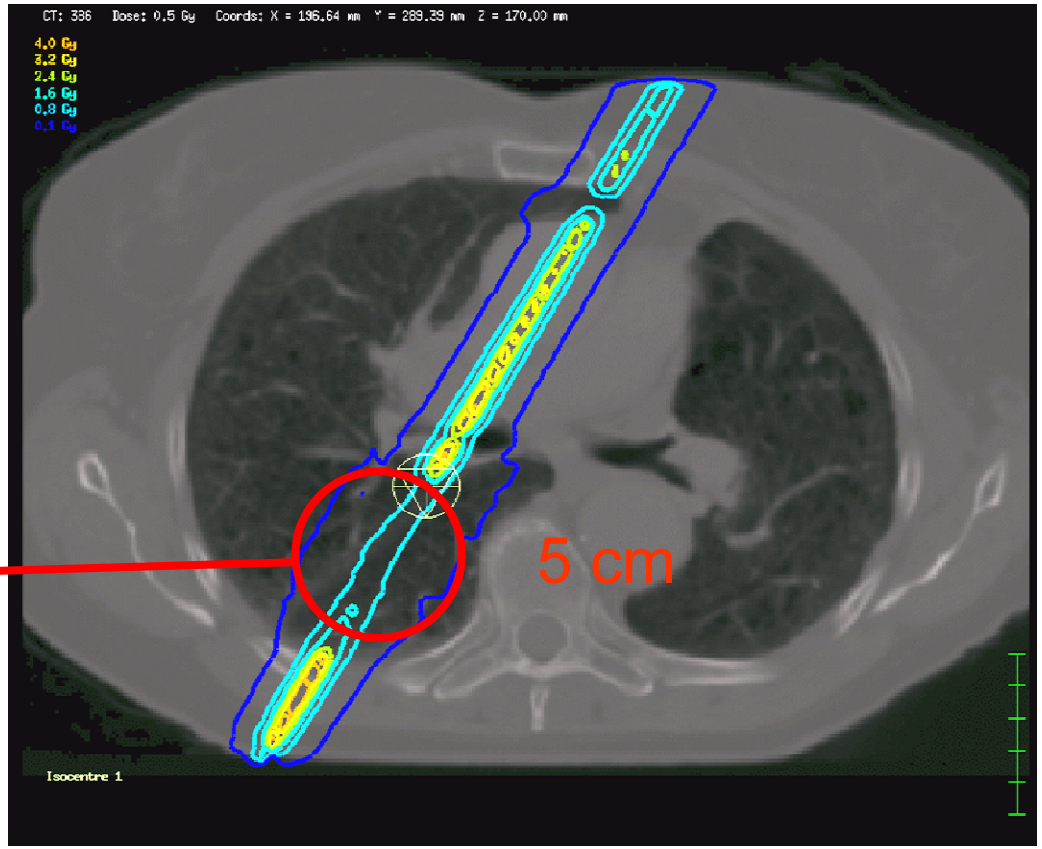


Accurate dose computation during the optimisation

full 3D-density correction for beamlets

wide penumbra

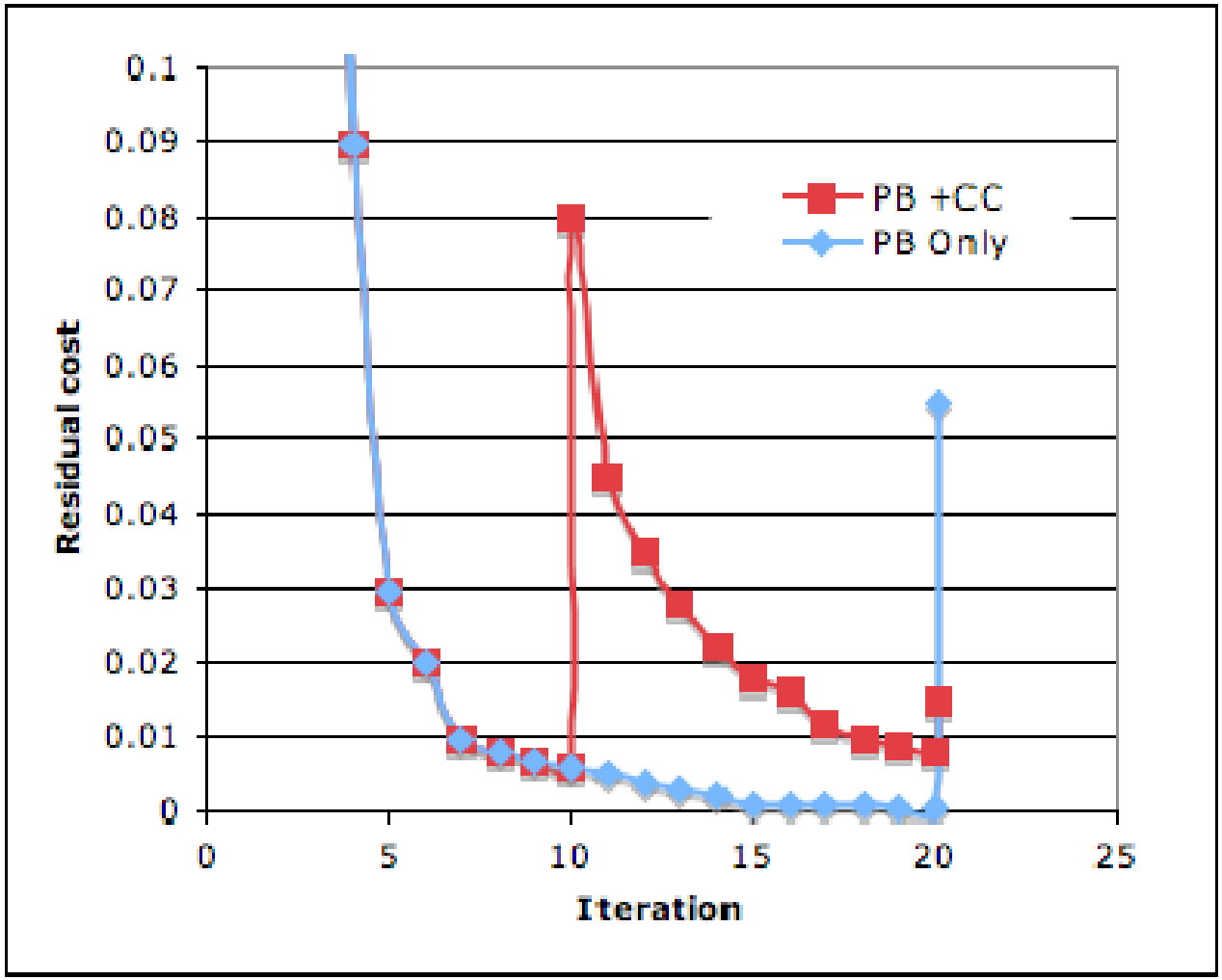




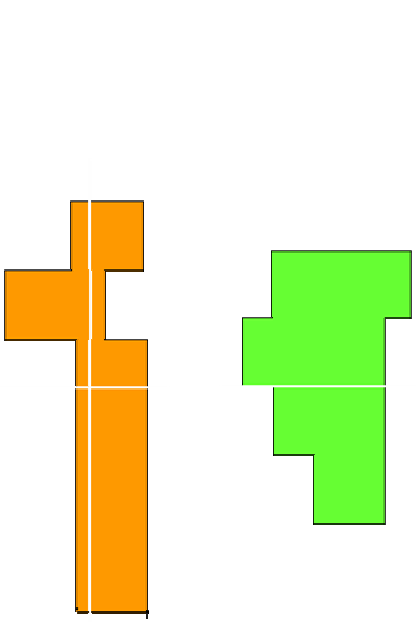
4 mm x 2 mm beamlet, 15 MV

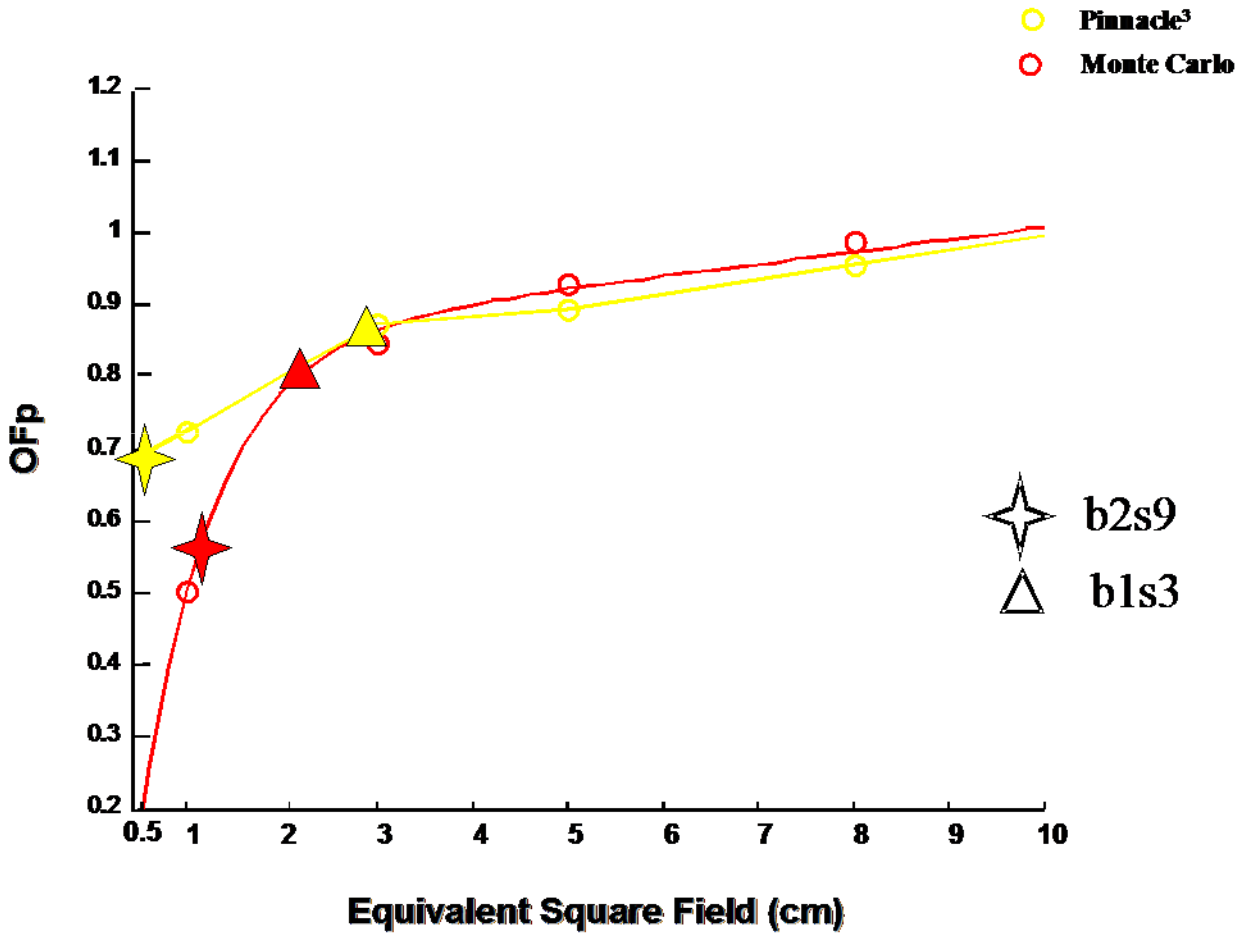
Courtesy M. Alber

Combining different algorithms in the optimisation

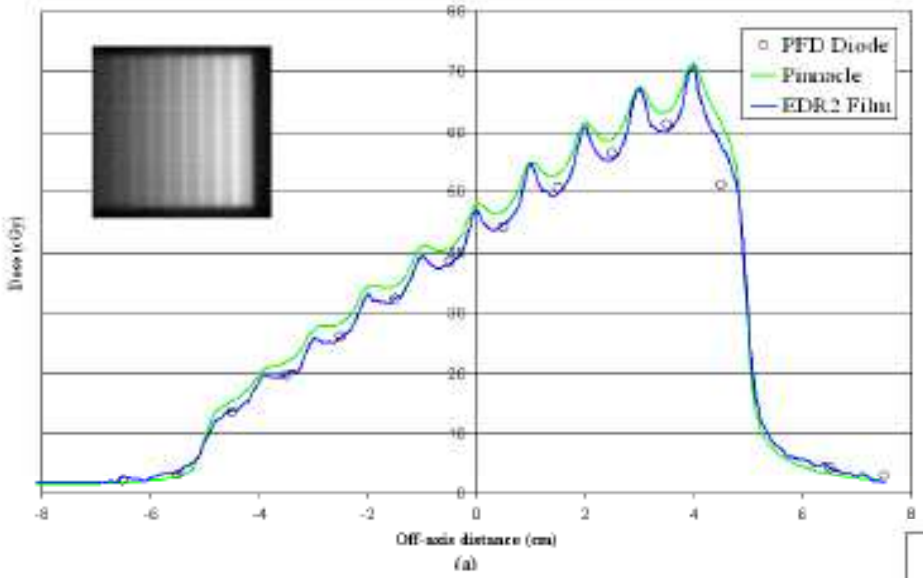


1. Modelling/measuring OF for small and/or elongated fields



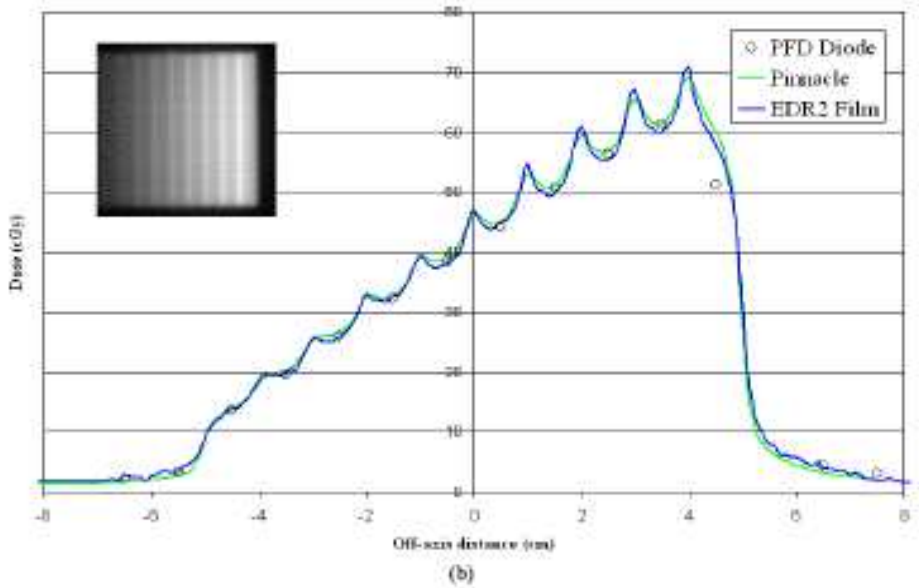


2. MLC modelling



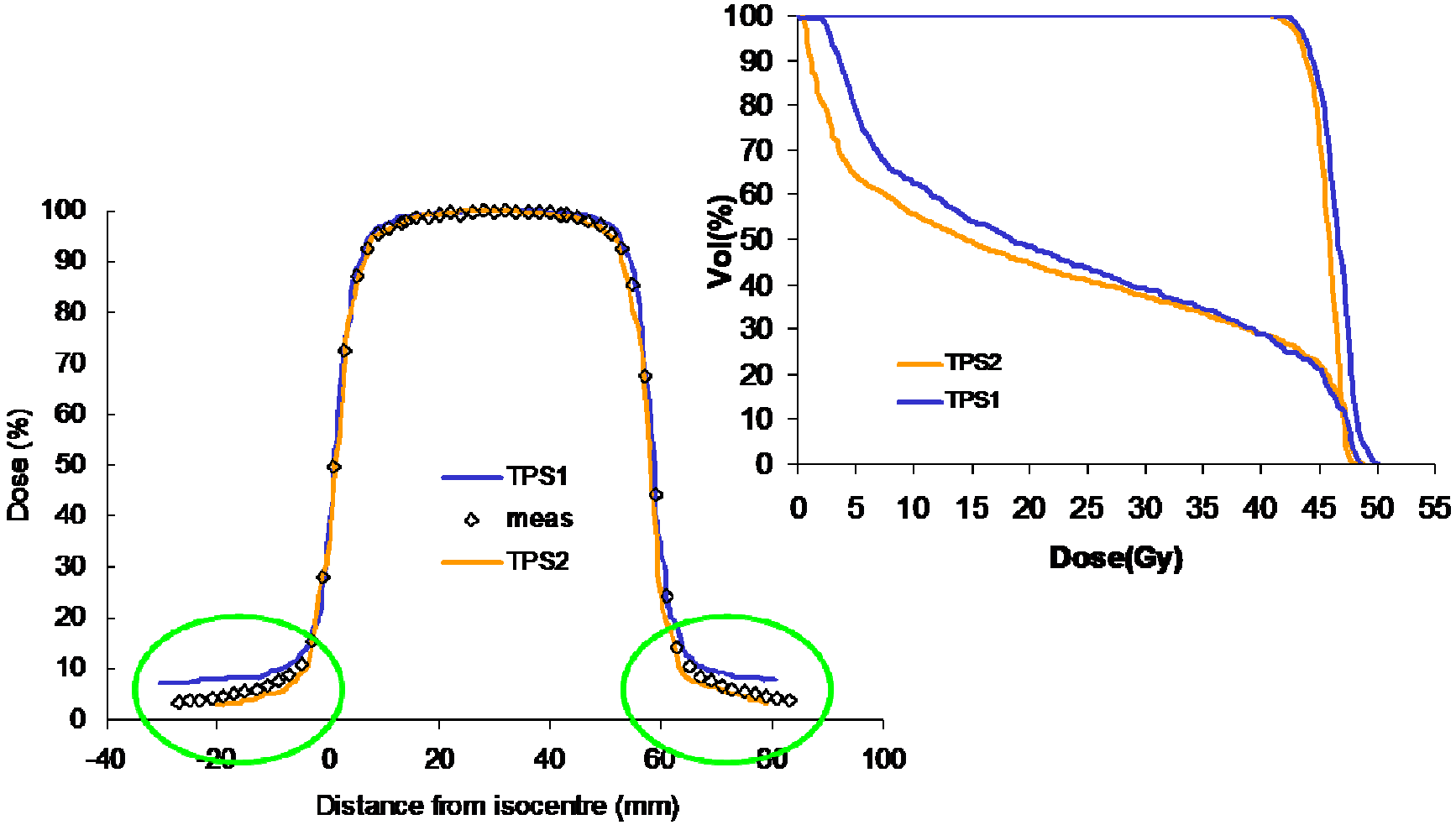
MLC attenuation: 0.023

MLC attenuation: 0.018

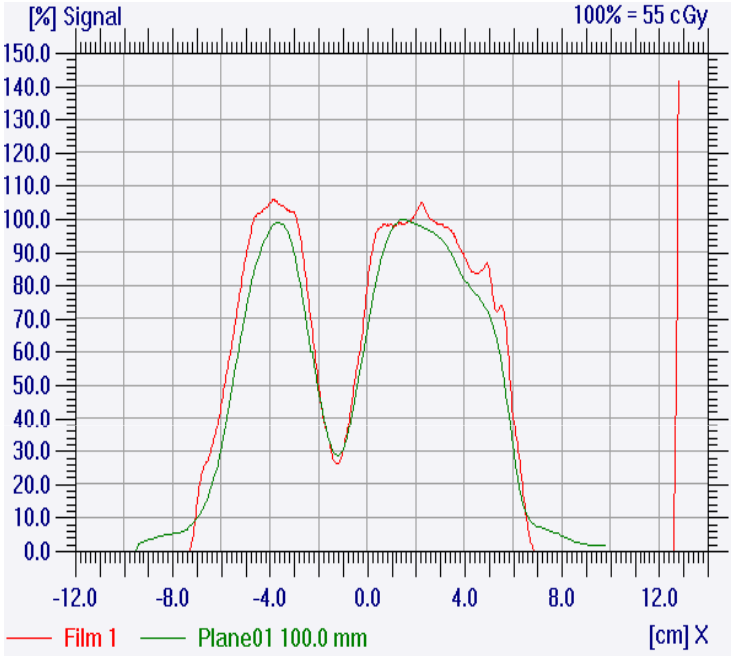


Cadman, JACMP 2005

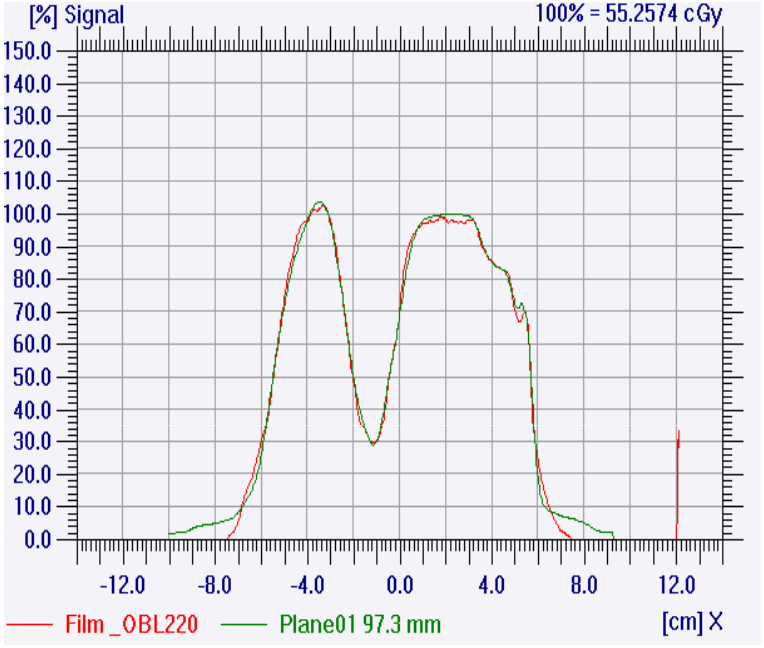
3. Beam 'tails' modeling



4. Sensitivity of beam model w.r.t. detector type



TPS characterized with IC measurements



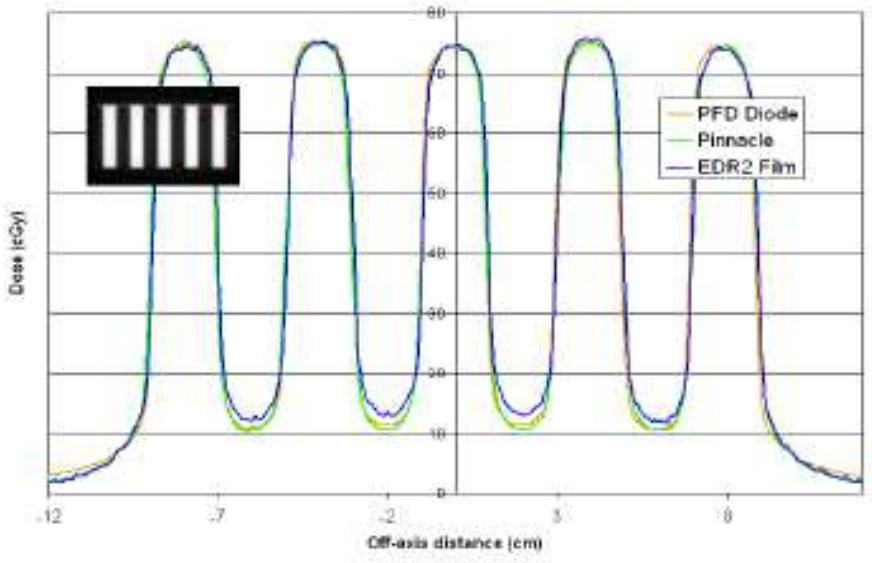
TPS characterized with diode measurements

Measurements vs. calculations
1D dose profiles

Mostly used in the commissioning phase, to

- Model/verify the profiles of small/off axis fields
- Test the capability of the MLC/TPS to generate/calculate highly modulated dose profiles

The agreement can be evaluated with the classical dose-difference and DTA parameters



Measurements vs. calculations
2-D dose distributions

Typically used for TPS commissioning and patient pre-treatment verification

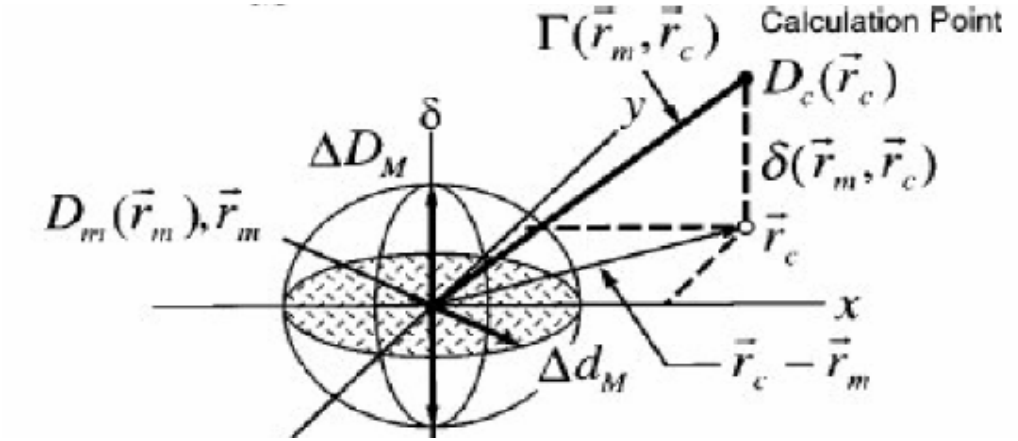
- Applied per-field or on the total dose distribution
- Combined with absolute dose point measurements
- Film dosimetry or 2-D matrix of detectors are the standard tools to obtain them

The issue is how to summarize the results available comparing (stacks of) 2-D dose distributions

Gamma function

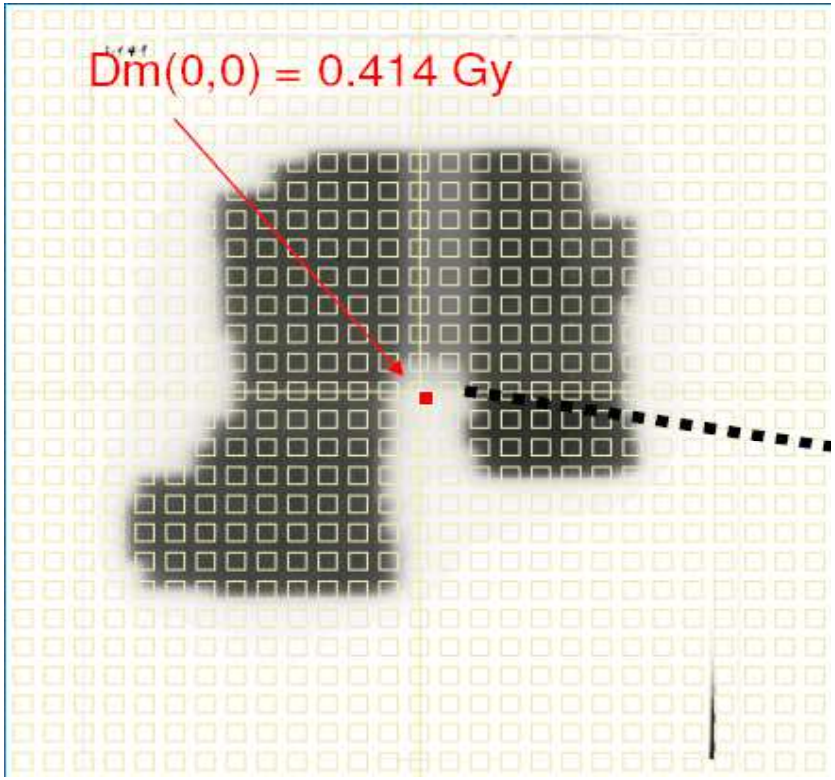
Combination of dose difference and distance to agreement (DTA), in order to apply it to both high and low dose gradient regions

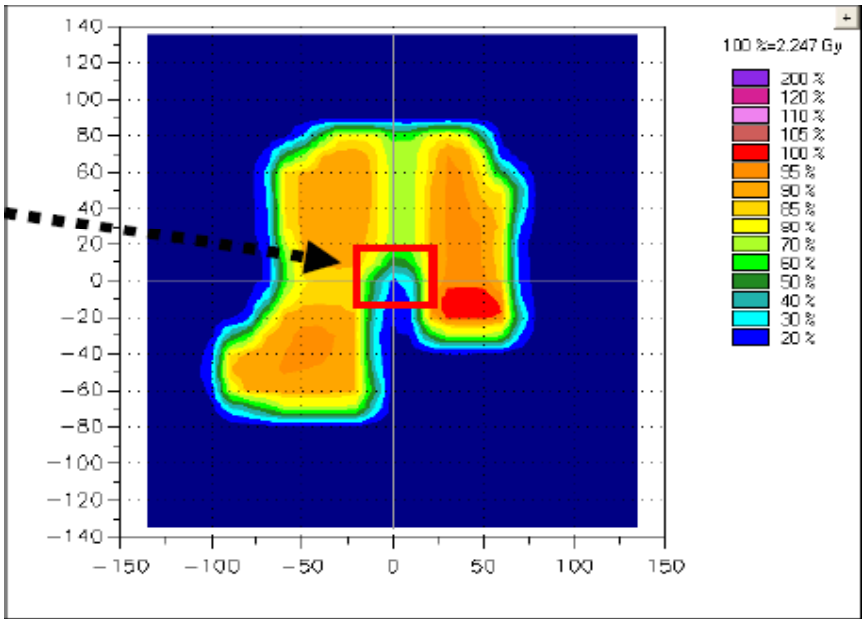
$$\Gamma(\mathbf{r}_m, \mathbf{r}_c) = \sqrt{\frac{r^2(\mathbf{r}_m, \mathbf{r}_c)}{\Delta d_M^2} + \frac{\delta^2(\mathbf{r}_m, \mathbf{r}_c)}{\Delta D_M^2}},$$



Low et al, Med Phys 1998

In practice





Measurement

Calculation

TPS	-3	-2	-1	0	1	2	3
3	0.47	0.461	0.45	0.446	0.439	0.441	0.44
2	0.415	0.405	0.394	0.39	0.385	0.387	0.388
1	0.362	0.353	0.34	0.336	0.331	0.334	0.334
0	0.306	0.297	0.285	**0.281**	0.278	0.28	0.28
-1	0.258	0.25	0.239	0.235	0.232	0.235	0.234
-2	0.23	0.221	0.212	0.208	0.205	0.209	0.208
-3	0.206	0.197	0.189	0.186	0.183	0.186	0.185

Dmeas = 0.4 Gy Tolerances: Dose = 3% DTA = 3mm

$$\Gamma_{r_m, r_c} = \sqrt{\left(\frac{D_{calc} - 0.4}{0.012}\right)^2 + \left(\frac{\|r_{calc} - r_{meas}\|}{3}\right)^2}$$

Gamma Matrix

	-3	-2	-1	0	1	2	3
3	4.73	3.97	3.08	2.76	2.27	2.48	2.53
2	1.20	1.19	1.77	2.04	2.45	2.37	2.41
1	4.32	4.97	5.98	6.29	6.70	6.48	6.53
0	8.75	9.44	10.39	10.71	10.96	10.81	10.84
-1	12.60	13.23	14.10	14.42	14.66	14.43	14.53
-2	14.86	15.57	16.28	16.60	16.84	16.53	16.63
-3	16.81	17.51	18.15	18.38	18.63	18.40	18.49

Here is the gamma

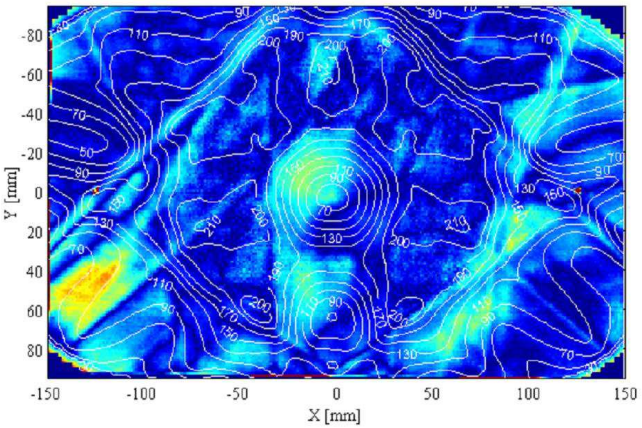
Be careful with noisy data !

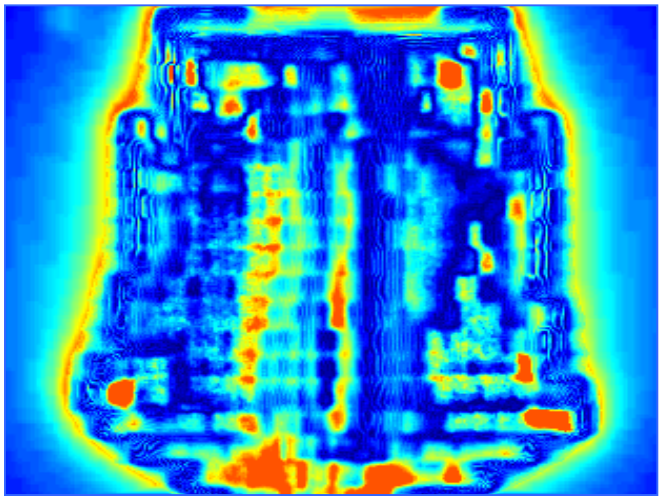
Gamma as an error detection system

Should be evaluated in terms of

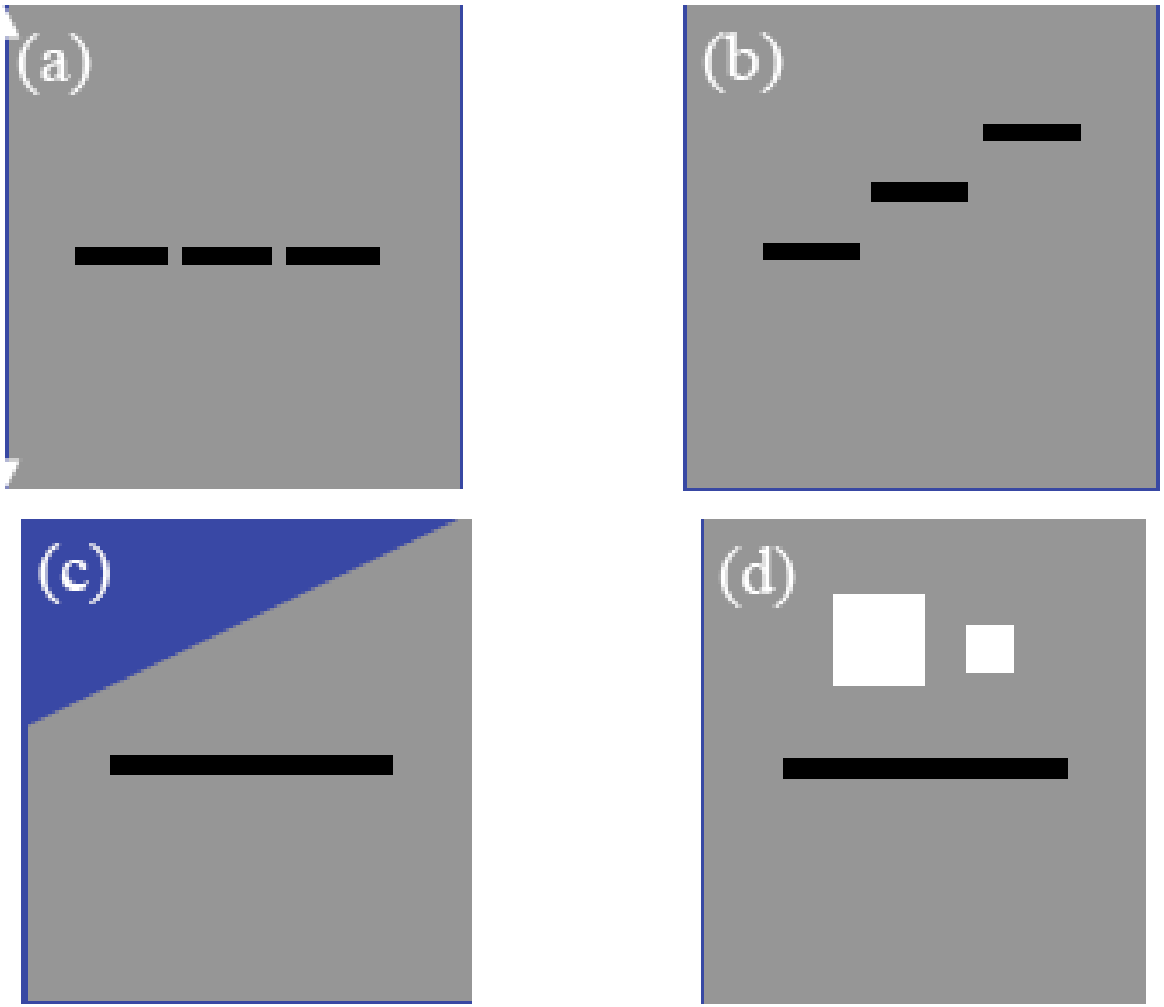
- *Sensitivity*
- *Specificity*
- *Correlation with clinical indices*
- *Ease of use*
- *Does it help problem solving?*

What is good for QA not necessarily is good for commissioning





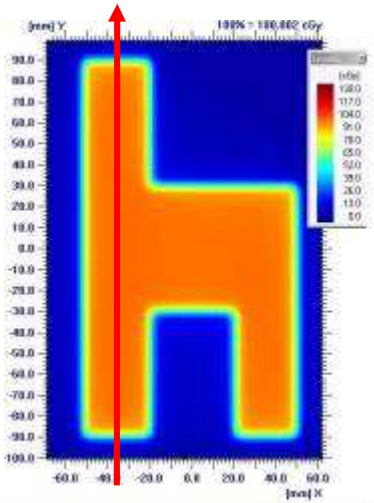
Apply (and verify) 'test case' fluences

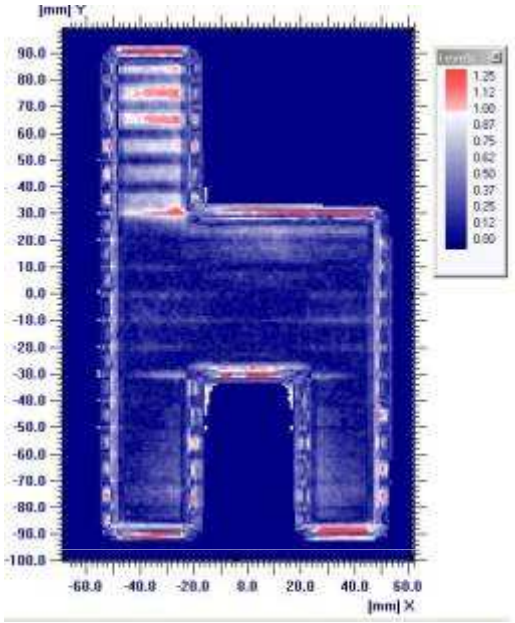


Van Esch, R&O 2002

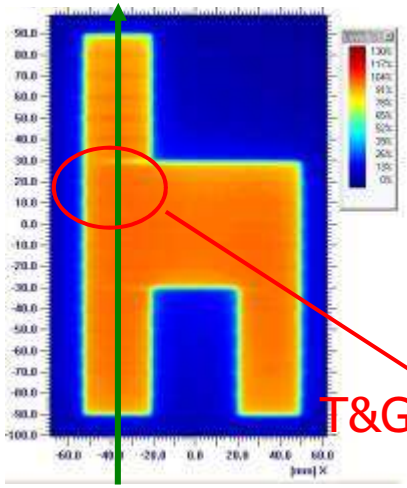
Example - Chair Test

TPS

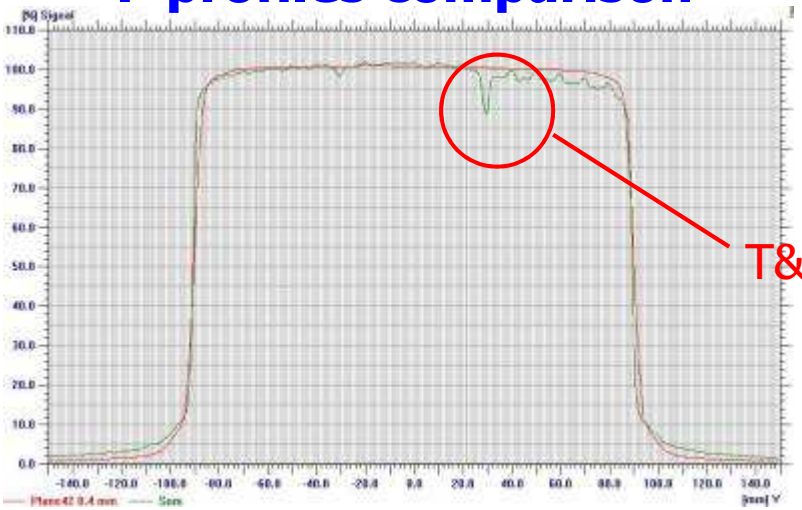




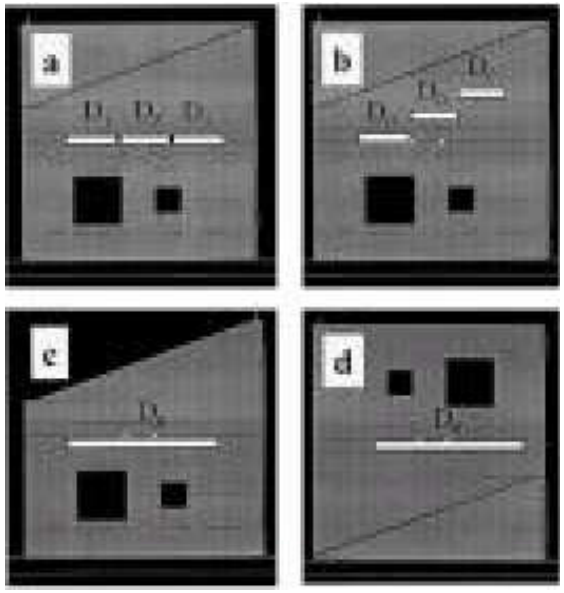
Measurement

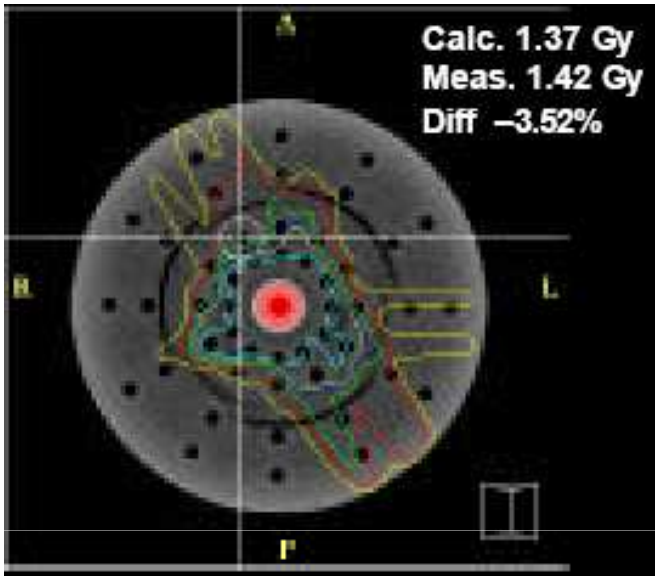


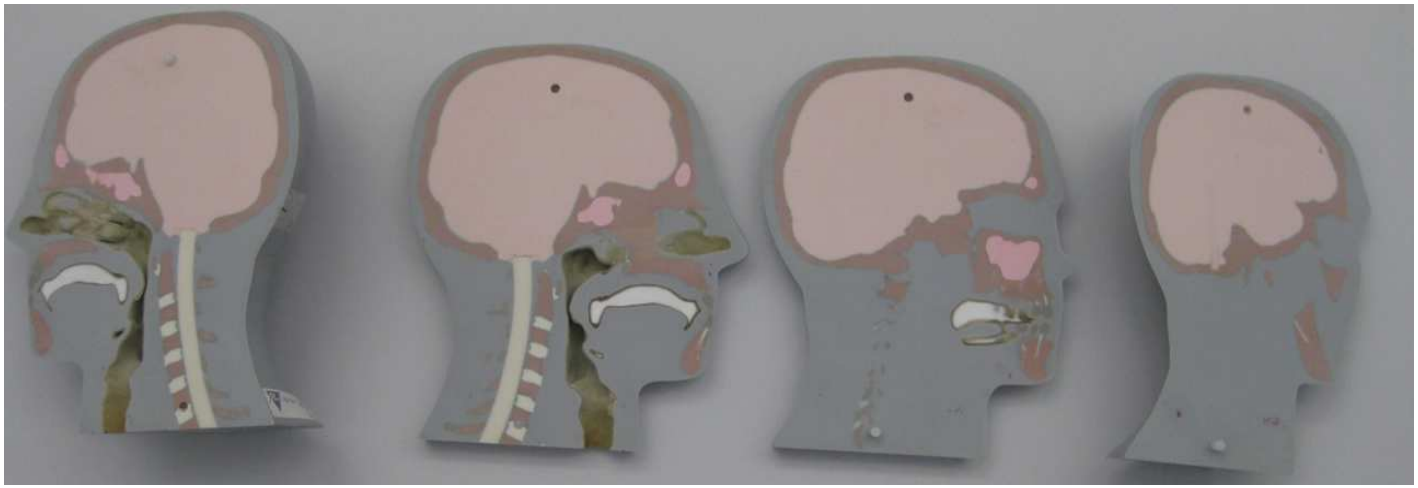
Y-profiles comparison



Dedicated phantoms







Plastic vs realistic patient representations

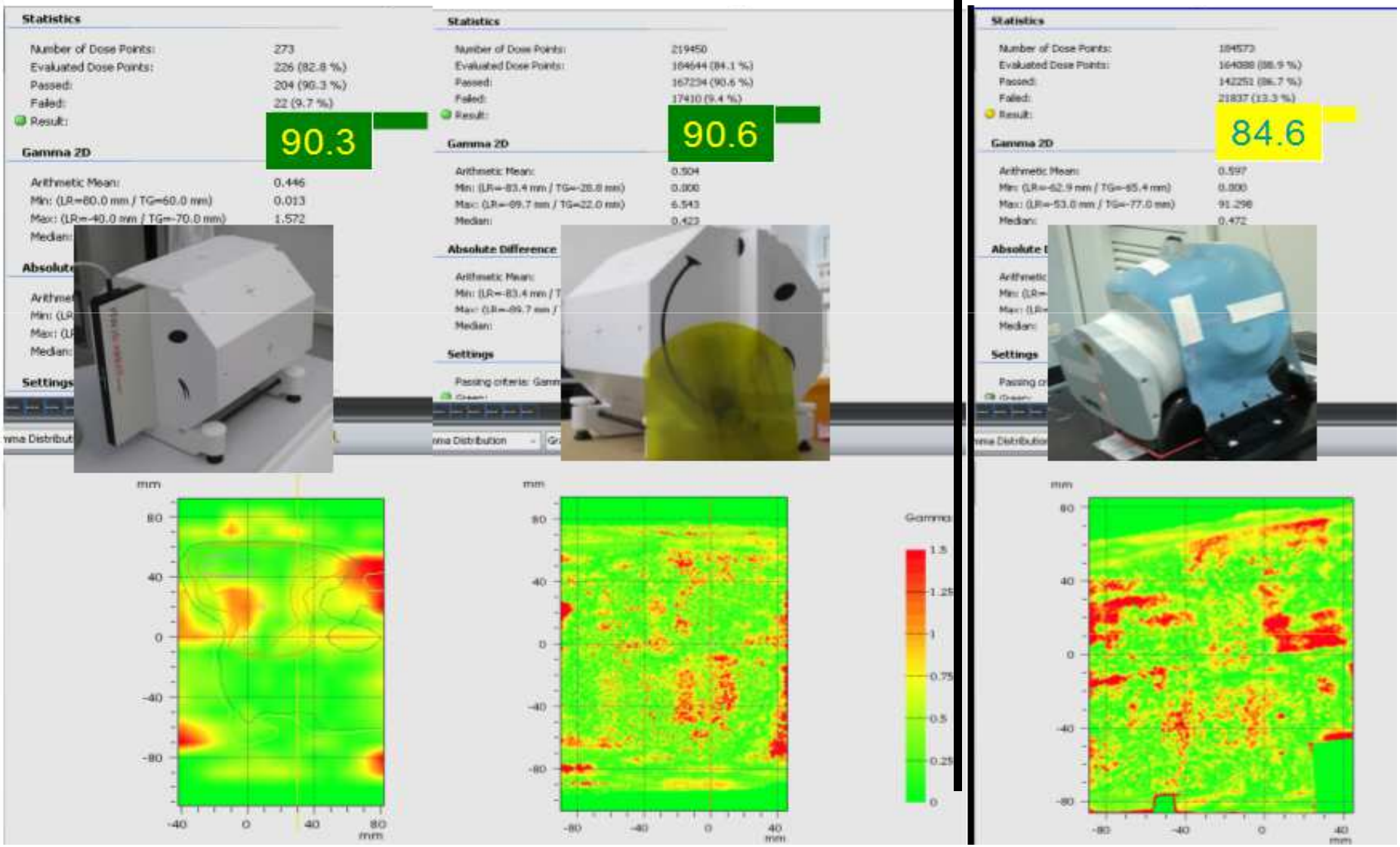
Homogeneous

Octavius 2D array

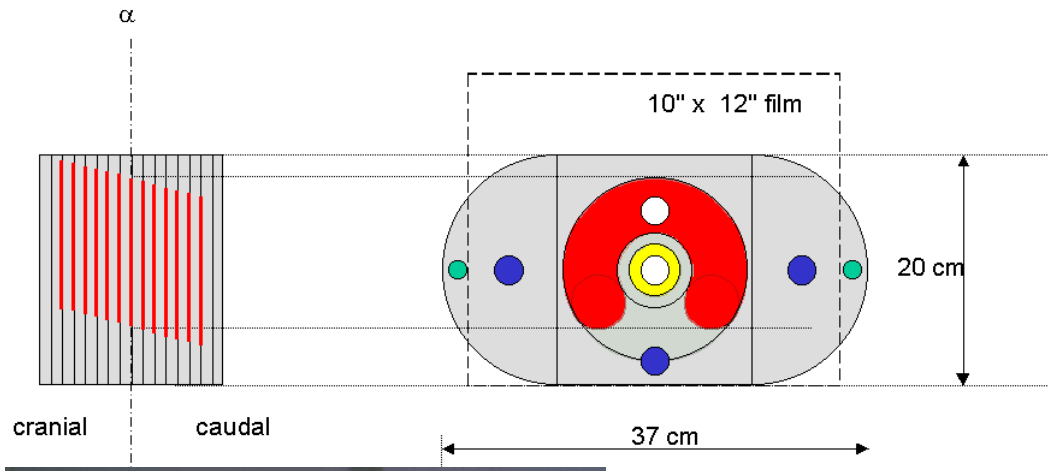
Octavius gafchromic

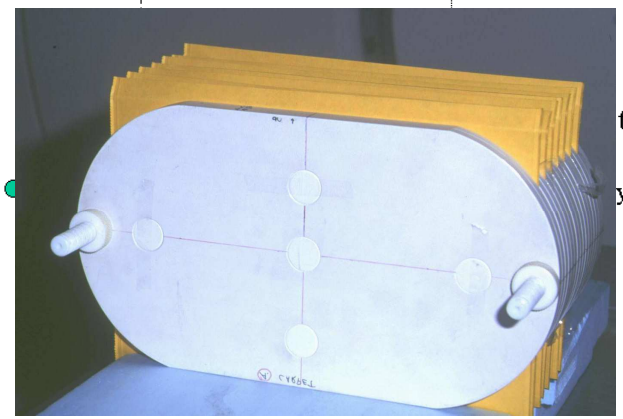
Heterogeneous

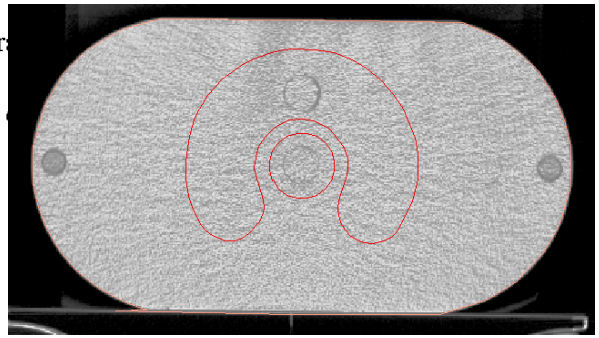
Charlie gafchromic



External audits in IMRT commissioning/verification

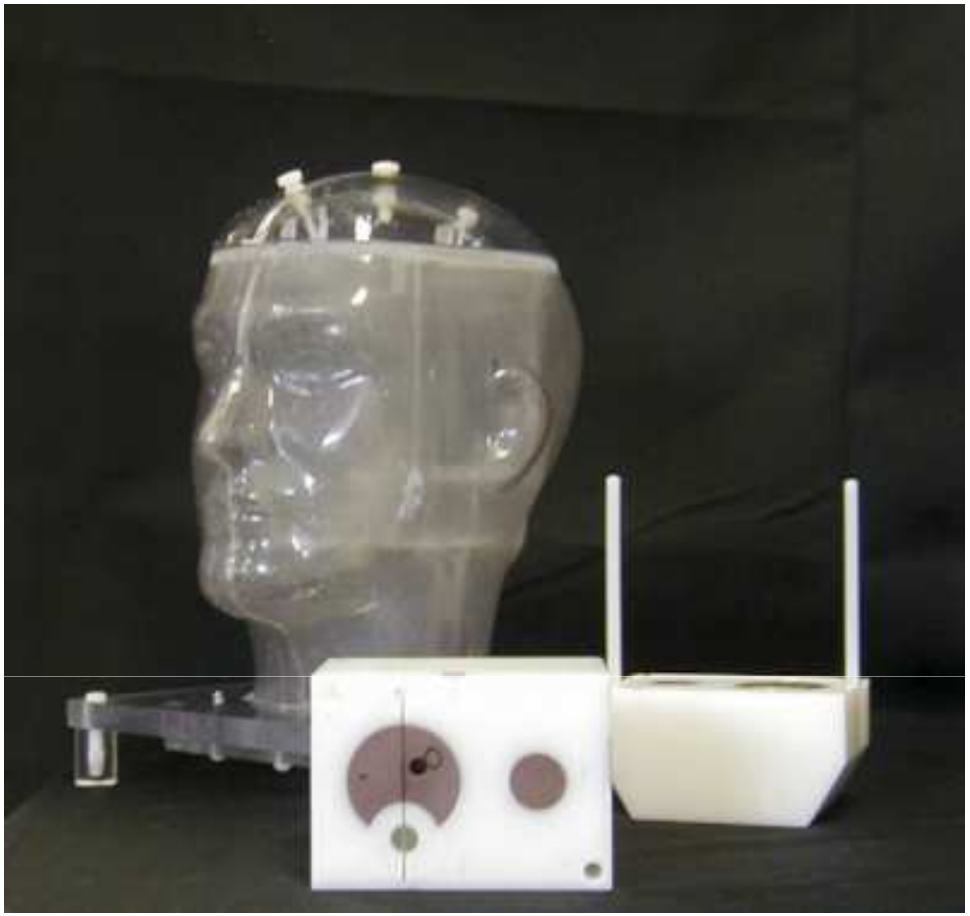






Be sure to solve treatment planning problems representative of **your** clinical practice !

Gillis et al, R&O 2005



RPC experience - US

Acceptance criteria: 7% and 4mm

Ibbott IJROBP 2008

Table 1. Institution passing rates with the Radiological Physics Center phantoms

Phantom	Head and neck	Prostate	Thorax	Liver
Irradiations	250	64	24	4
Pass	179	55	17	3
Fail	71	9	7	1
Year introduced	2001	2004	2004	2005

Conclusions

IMRT is about 15 years old. You can learn from other people successes and mistakes.

Specs, Acceptance, Commissioning and QA should be approached as elements of an *unicum*.

IMRT on a large scale implies effective and fast QA, which implies satisfactory TPS commissioning.

General Guidelines

ESTRO Booklet 9, *Guidelines for the verification of IMRT*,

http://www.estro-education.org/publications/Documents/Booklet9_Physics.pdf

IPEM Project 527, *Guidance for the Clinical Implementation of Intensity Modulated Radiation Therapy,* IPEM 2008.

Galvin JM et al, *Implementing IMRT in clinical practice ...*, Int. J. Radiat. Oncol. Biol. Phys. 58, 1616–1634, 2004.

Ezzell GA et al, *Guidance document on delivery, treatment planning ...*, Med Phys. 30 2089–2115, 2003.

ESTRO School

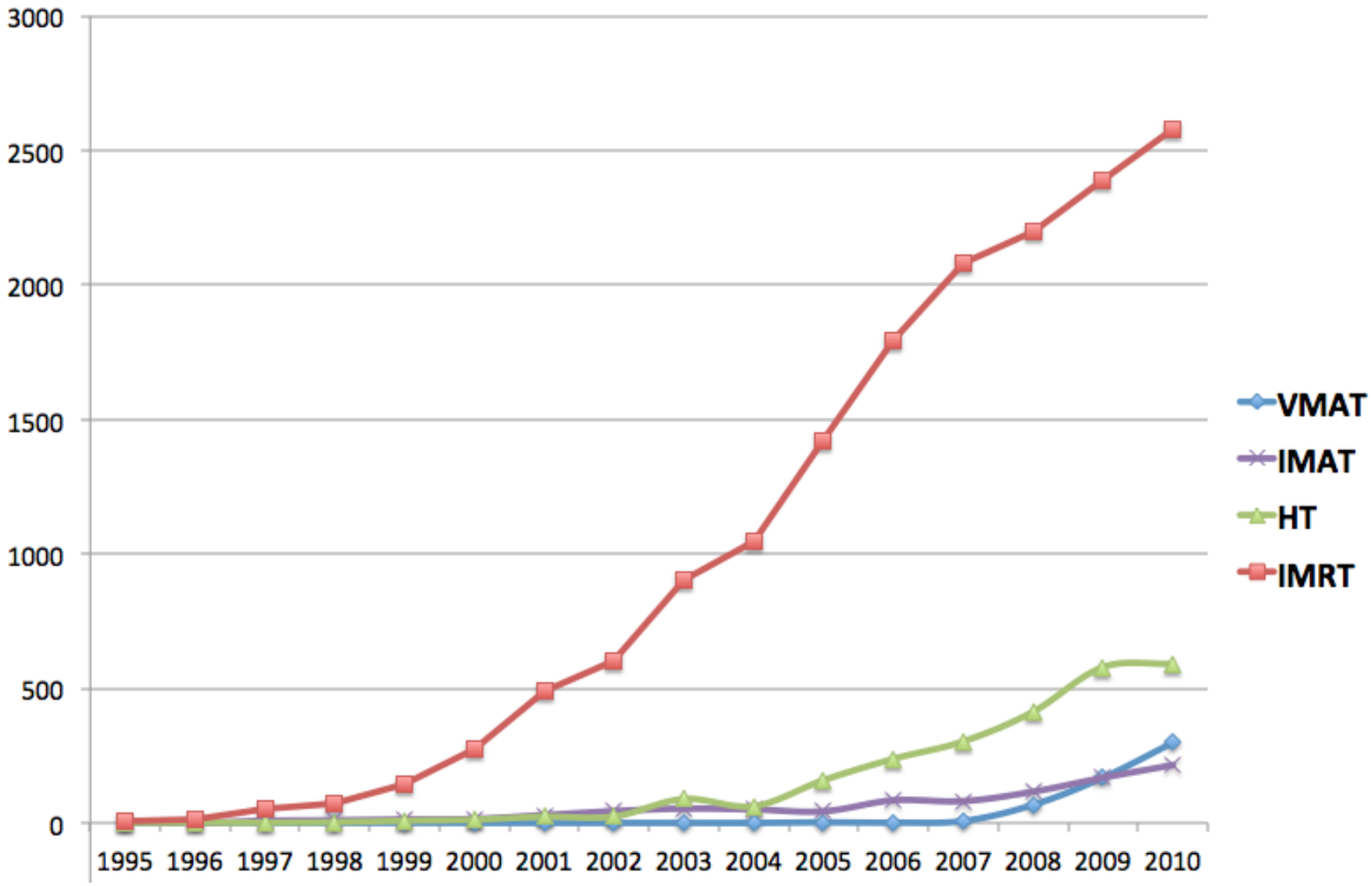
WWW.ESTRO.ORG/SCHOOL

Rotational Therapy

Koen Tournel - Physicist
Radiotherapy Department UZ Brussel

ESTRO School

Evolution of interest



Hits raise last year:

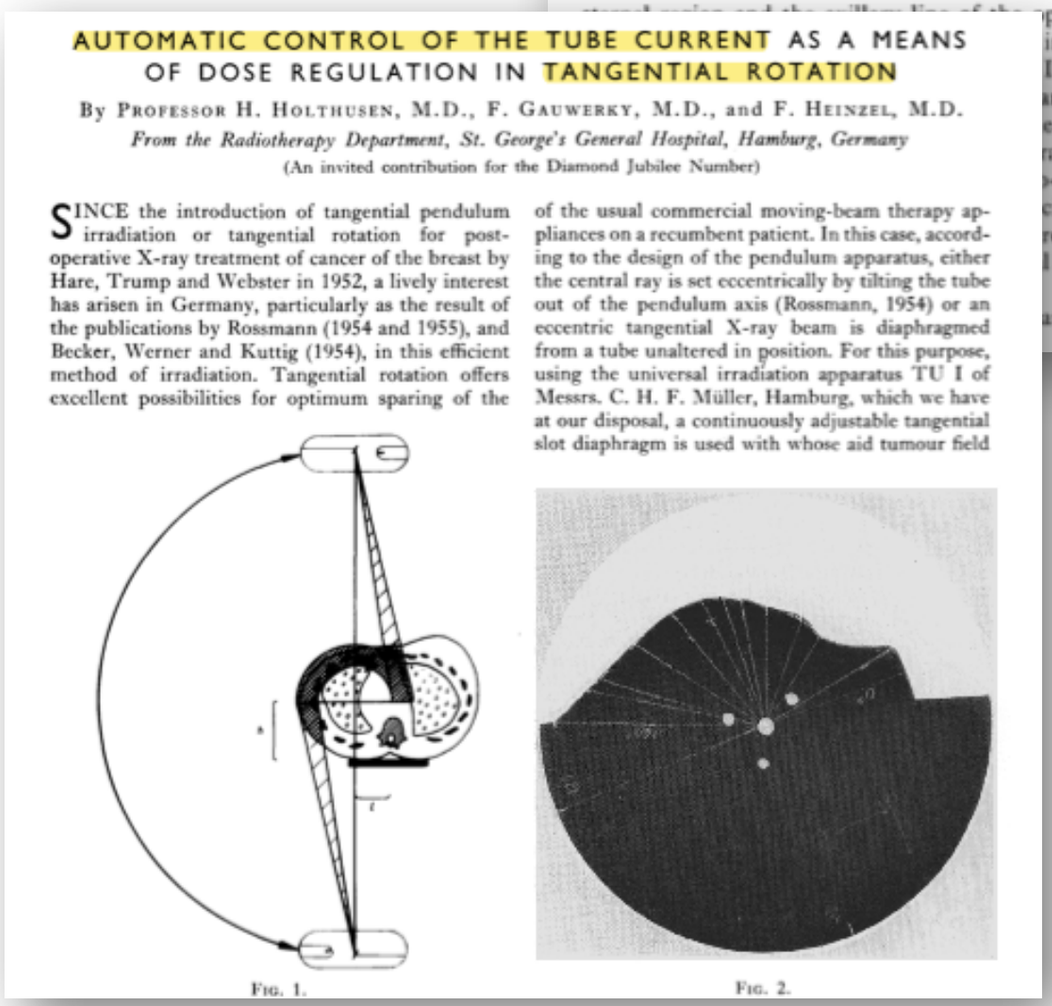
7.9% for IMRT (1982)
(last 3 years 7.1%)

28% for IMAT (1995)
(last 3 years 26.9%)

2.2% for HT (1995)
(last 3 years 17.8%)

77% for VMAT (2005)
(last 3 years 58.0%)

Nothing new (1956)…



AUTOMATIC CONTROL OF THE TUBE CURRENT AS A MEANS OF DOSE REGULATION IN TANGENTIAL ROTATION

By Professor H. Holthusen, M.D., F. Gauwerky, M.D., and F. Heinzel, M.D.

From the Radiotherapy Department, St. George's General Hospital, Hamburg, Germany

(An invited contribution for the Diamond Jubilee Number)

SINCE the introduction of tangential pendulum irradiation or tangential rotation for post-operative X-ray treatment of cancer of the breast by Hare, Trump and Webster in 1952, a lively interest has arisen in Germany, particularly as the result of the publications by Rossmann (1954 and 1955), and Becker, Werner and Kuttig (1954), in this efficient method of irradiation. Tangential rotation offers excellent possibilities for optimum sparing of the

of the usual commercial moving-beam therapy appliances on a recumbent patient. In this case, according to the design of the pendulum apparatus, either the central ray is set eccentrically by tilting the tube out of the pendulum axis (Rossmann, 1954) or an eccentric tangential X-ray beam is diaphragmed from a tube unaltered in position. For this purpose, using the universal irradiation apparatus TU I of Messrs. C. H. F. Müller, Hamburg, which we have at our disposal, a continuously adjustable tangential slot diaphragm is used with whose aid tumour field

Fig. 1.

Fig. 2.

May 1956

Automatic Control of the Tube Current as a Means of Dose Regulation in Tangential Rotation

…perated …irradia- …It must …angle of …e direct …adiated …-lateral …circum- …rotation …l phan- …in the …art near

Of the two possibilities available in principle to carry out the desired compensation, namely variable speed of the X-ray tube movement during irradiation on the one hand and variation of dose output on the other, the latter was chosen since a regulation of the tube current in accordance with a predetermined scheme could be achieved with less constructional difficulties. Thus the tube current will have to be reduced in the higher dosed skin areas, and increased in the positions of the tube in which the surface areas are lower dosed. For this purpose, distribution schemes for the tube current

British Journal of Radiology, **1956**

"Rotational RT has been around for some time, even longer than IMRT …"

Nothing new…

- "A logical extension of multiple beam therapy is to use 1 beam, have it directed towards the tumour, and cause the machine to rotate about an axis through the tumour, or keep the machine fixed and rotate the patient about this axis …"
- When the radiotherapist was limited to the use of 250 kV X-rays, it was very difficult to get enough radiation into an internal tumour … As a result many workers developed rotation techniques …"

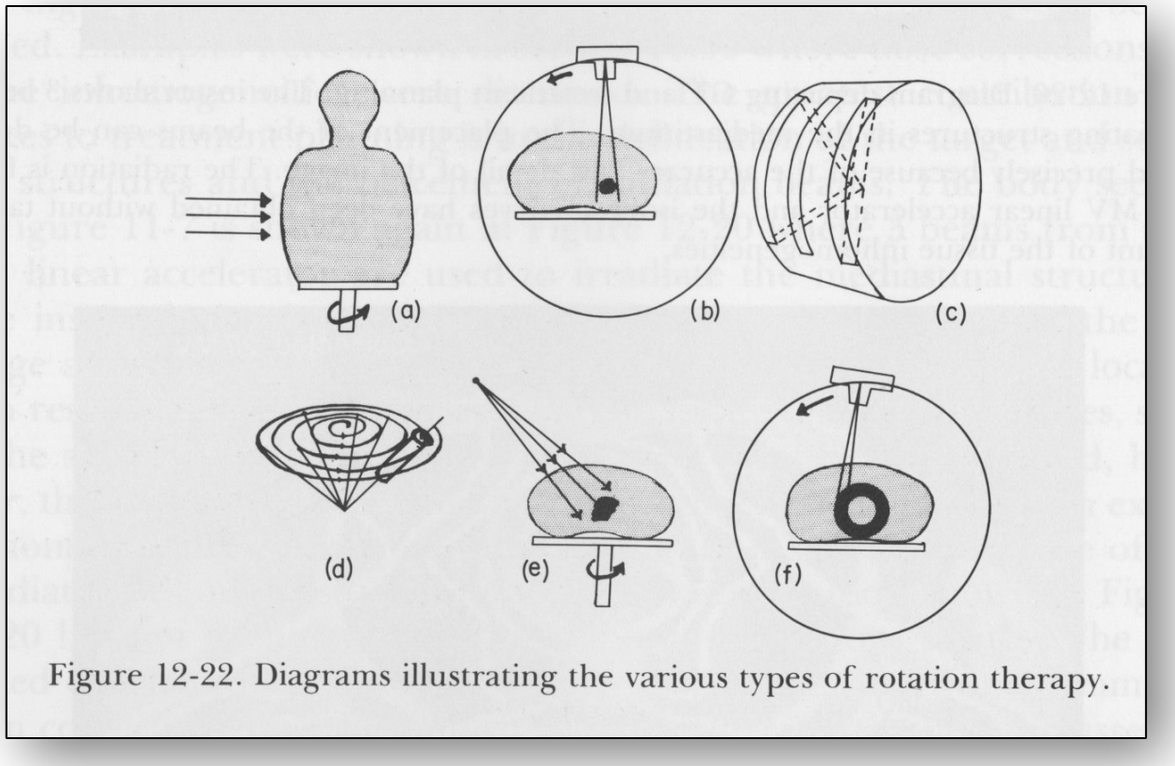
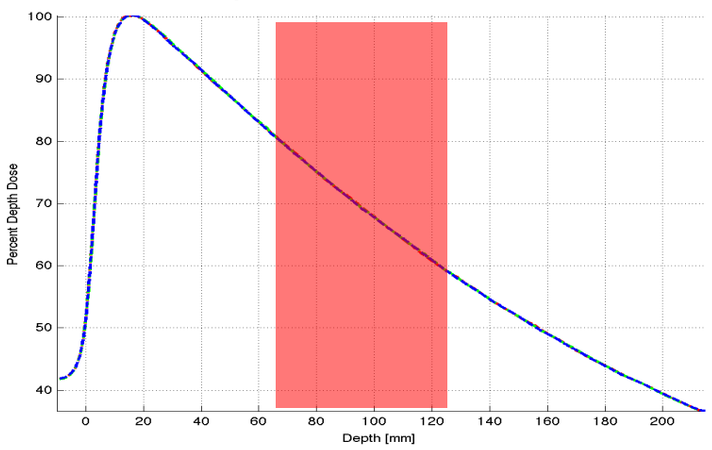


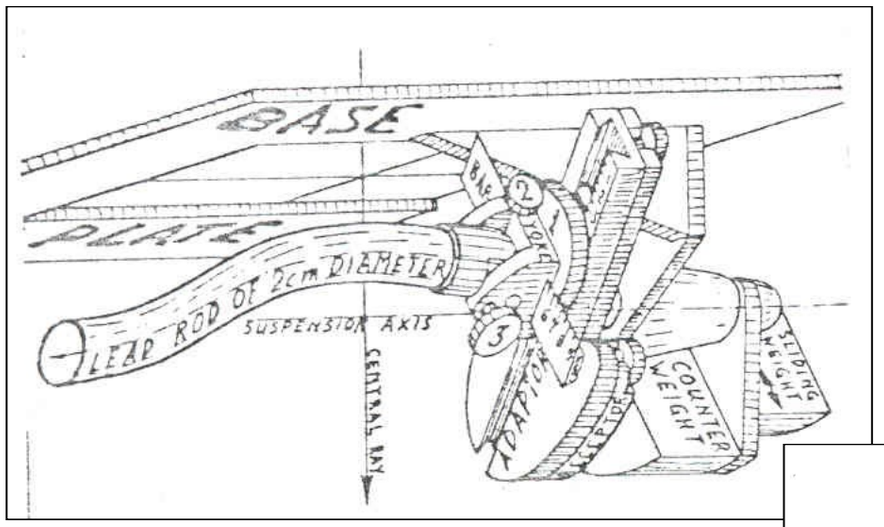
Figure 12-22. Diagrams illustrating the various types of rotation therapy.

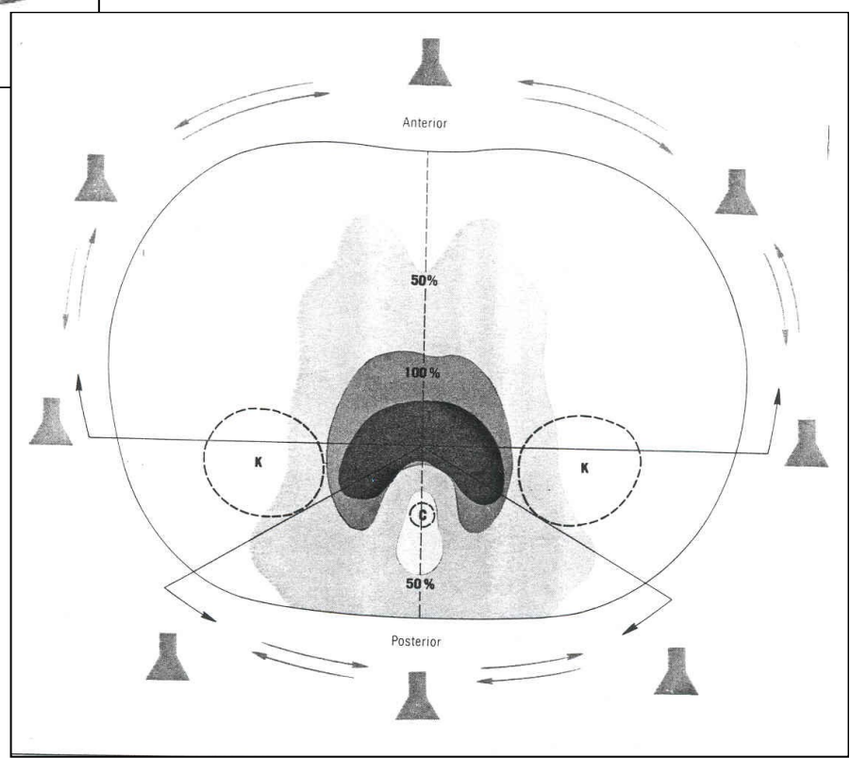
PDD, 6MV photon

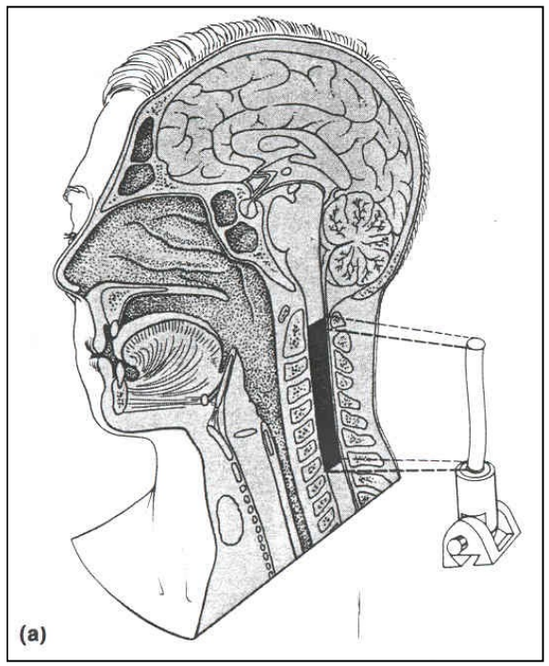


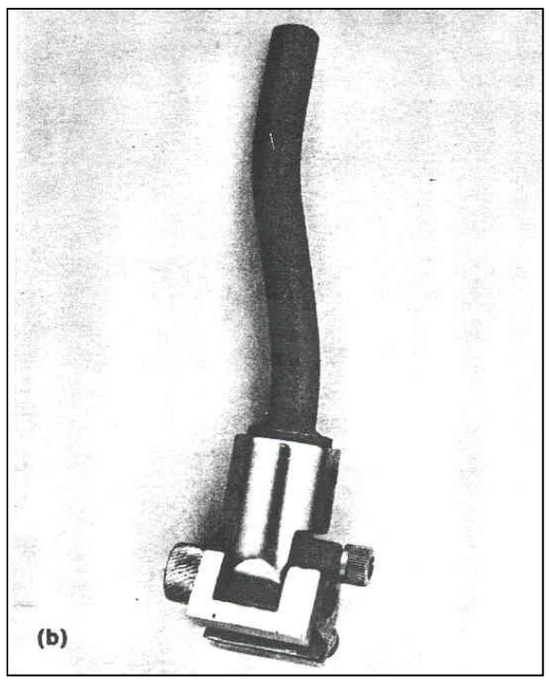
Nothing new…(1966)

"Shielding spinal cord during arc therapy"







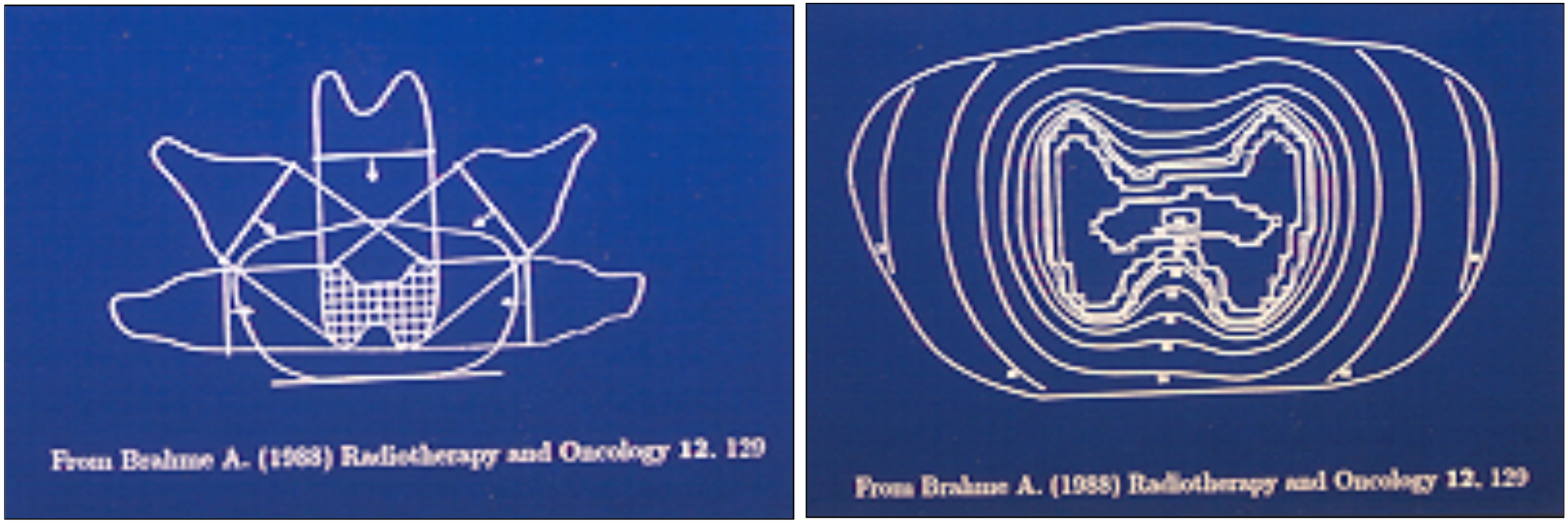


"Creative solutions for OAR sparing in arc therapy"

Proimos et al, 1966

Nothing new : 1982

Brahme's Seminal Paper on IMRT



"In 1982, Anders Brahme first showed that multiple intensity modulated fields of radiation would lead to more conformal dose distributions that would spare normal tissue."

Nothing new : 1993-2004

Tomotherapy: A new concept for the delivery of dynamic conformal radiotherapy

T. Rock Mackie
Department of Medical Physics and Human Oncology, University of Wisconsin, Madison, Wisconsin

Timothy Holmes and Stuart Swerdloff
Department of Medical Physics, University of Wisconsin, Madison, W

Paul Reckwerdt and Joseph O. Deasy
Department of Medical Physics and Human Oncology, University of

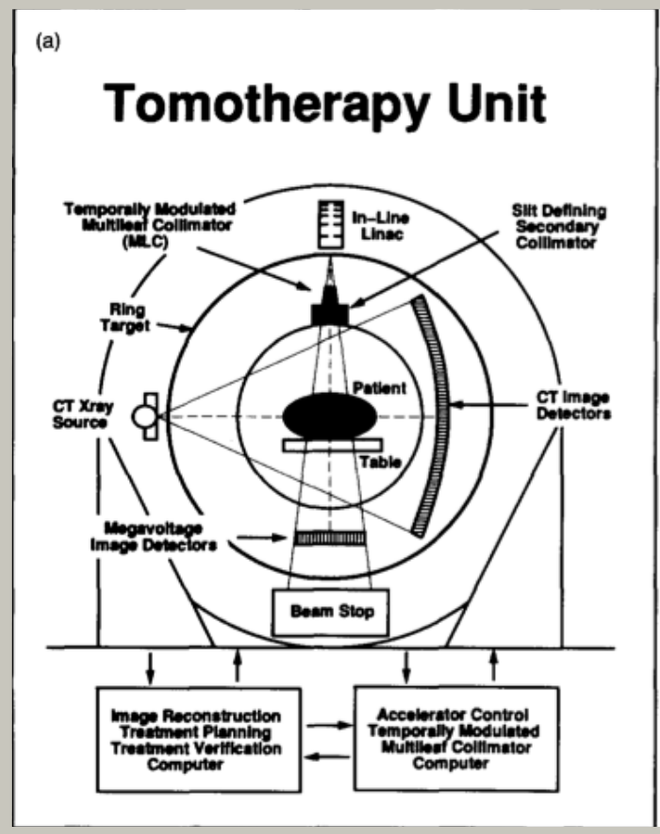
James Yang
Department of Medical Physics, University of Wisconsin, Madison, W

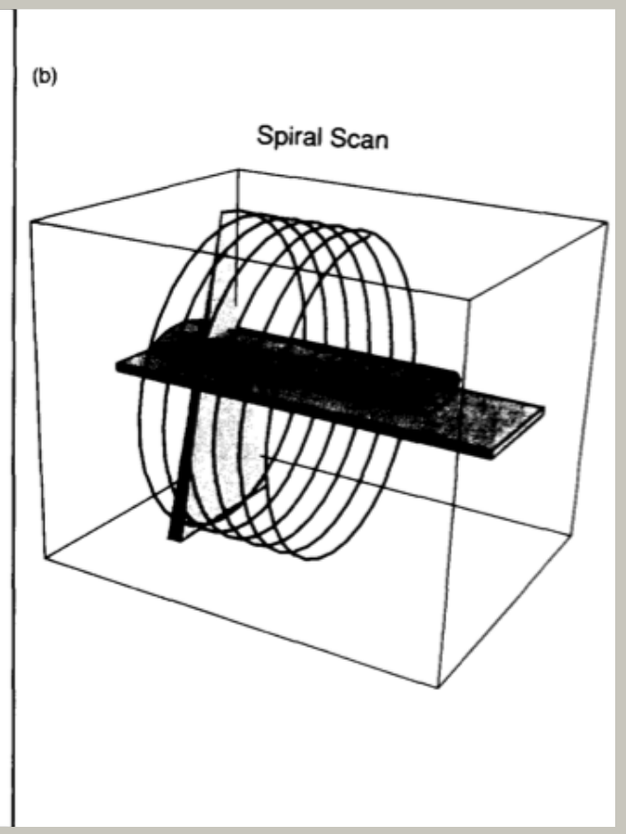
Bhudatt Paliwal
Department of Medical Physics and Human Oncology, University of

Timothy Kinsella
Department of Human Oncology, University of Wisconsin, Madison,

(Received 20 July 1992; accepted for publication 14 June 199

Tomotherapy, literally "slice therapy," is a proposal for the d
intensity-modulated strips of radiation. The proposed method
another radiation-emitting device, which would be mounted on
The patient would move through the bore of the gantry simu
The intensity modulation would be performed by temporally
leaves that open and close across the slit opening. At any gi
closed, covering a portion of the slit, (2) open, allowing rad
between these states. This method would result in the deliver
Overall treatment times should be comparable with contempor
ring gantry would make it convenient to mount a narrow mult
system for beam verification and a CT scanner on the treatm
could become a powerful tool for treatment planning, conformal treatment, and verification using tomographic images. The physical properties of this treatment delivery are evaluated and the fundamental design specifications are justified.





Nothing new…1995

- Cedric Yu's paper in PMB 1995 and patent
- Using multiple superimposed arcs in IMAT

United States Patent [19]
Yu

[11] **Patent Number: 5,818,902**
[45] **Date of Patent: Oct. 6, 1998**

[54] **INTENSITY MODULATED ARC THERAPY WITH DYNAMIC MULTI-LEAF COLLIMATION**

[75] Inventor: **Cedric X. Yu**, Bloomfield Hills, Mich.

[73] Assignee: **Elekta AB**, Stockholm, Sweden

[21] Appl. No.: **609,457**

[22] Filed: **Mar. 1, 1996**

[51] **Int. Cl.**[6] **A61N 5/10**
[52] **U.S. Cl.** **378/65**; 378/151
[58] **Field of Search** 378/65, 147, 150, 378/151, 152; 250/492.3, 505.1

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,160,847	11/1992	Leavitt et al.	378/65 X
5,351,280	9/1994	Swerdloff et al. .	
5,394,452	2/1995	Swerdloff et al. .	
5,418,827	5/1995	Deasy et al. .	
5,442,675	8/1995	Swerdloff et al. .	
5,555,283	9/1996	Shiu et al.	378/65 X
5,596,619	1/1997	Carol	378/65

OTHER PUBLICATIONS

McGraw–Hill Encyclopedia of Science & Technology, 6th Edition, vol. 13, pp. 110, 112, and 126–129 (1987).
McGraw–Hill Encyclopedia of Science & Technology, 6th Edition, vol. 15, pp. 154 and 155 (1987).
McGraw–Hill Encyclopedia of Science & Technology, 6th Edition, vol. 2, p. 506 (1987).
McGraw–Hill Encyclopedia of Science & Technology, 6th Edition, vol. 10, pp. 568–571 (1987).
McGraw–Hill Encyclopedia of Science & Technology, 6th Edition, vol. 13, pp. 413 and 414 (1987).
McGraw–Hill Encyclopedia of Science & Technology, 6th Edition, vol. 15, pp. 138 and 139 (1987).
McGraw–Hill Encyclopedia of Science & Technology, 6th Edition, vol. 4, pp. 292–293 (1987).
McGraw–Hill Encyclopedia of Science & Technology, 6th Edition, vol. 18, pp. 28 and 29 (1987).

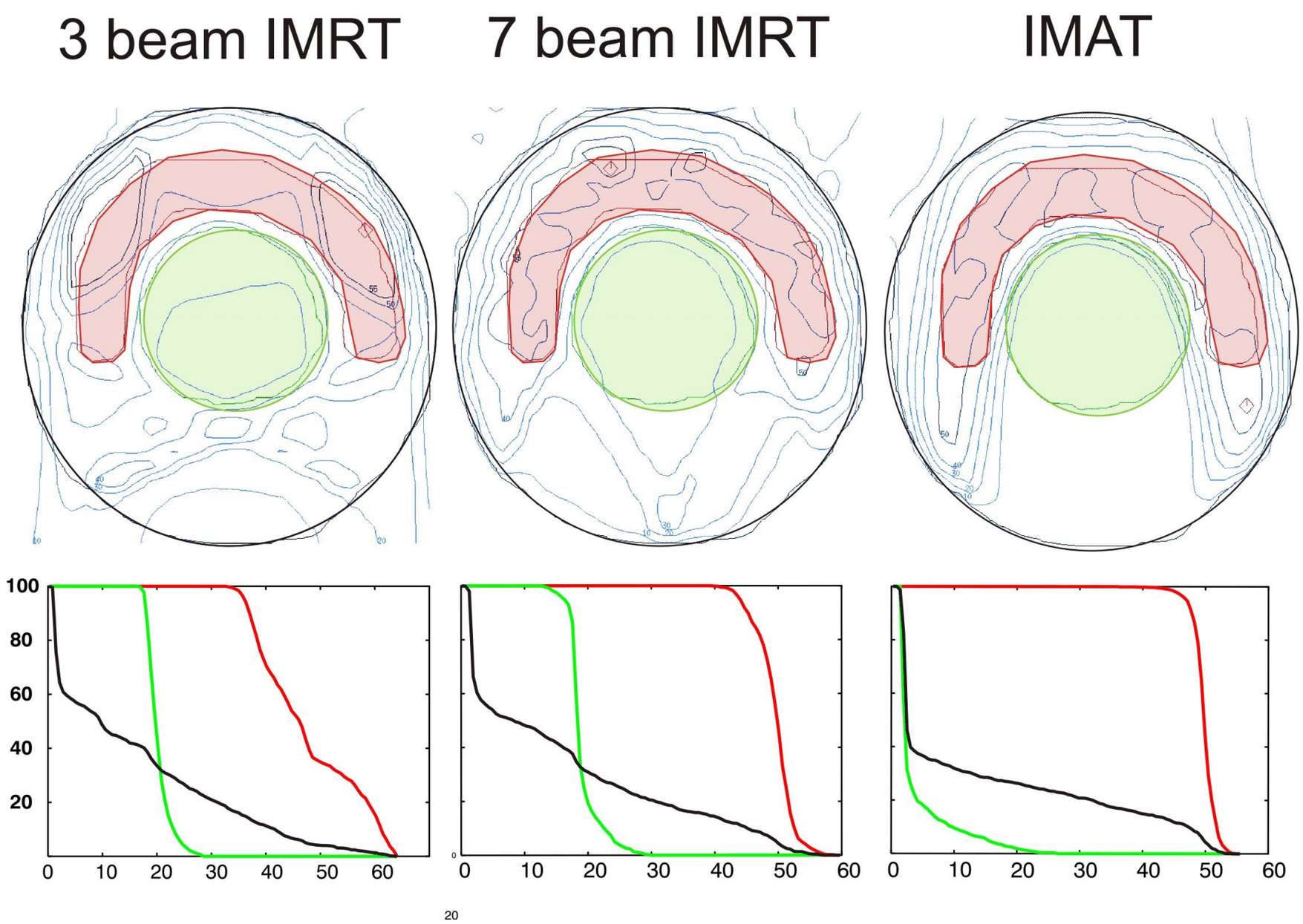
Primary Examiner—David P. Porta
Attorney, Agent, or Firm—Jack D. Slobod; Dwight H. Renfrew

[57] **ABSTRACT**

A method and apparatus for delivering optimized treatment plans to deliver relatively high doses of ionizing radiation to target tissues while minimizing dose to the surrounding healthy tissues. The present invention utilizes continuous gantry motion in which field shape, which is conformed with a multi-leaf collimator, changes during gantry rotation. Using multiple superimposing arcs, arbitrary two-dimensional beam intensity distribution at different beam angles can be delivered, giving arbitrary dose distribution in the patient to maximize the therapeutic ratio.

25 Claims, 9 Drawing Sheets

Gent experience…



De meerleer et al

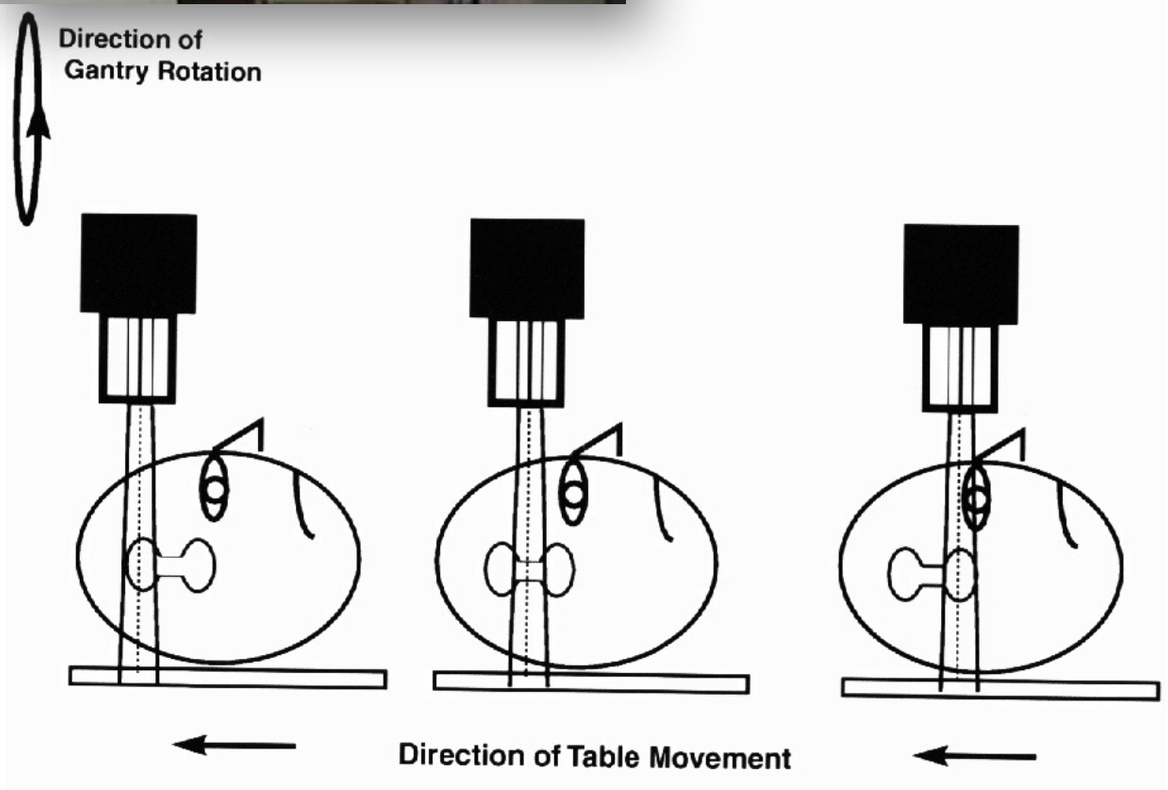
Nothing new…1998

"First commercial solutions but not a hit yet …"

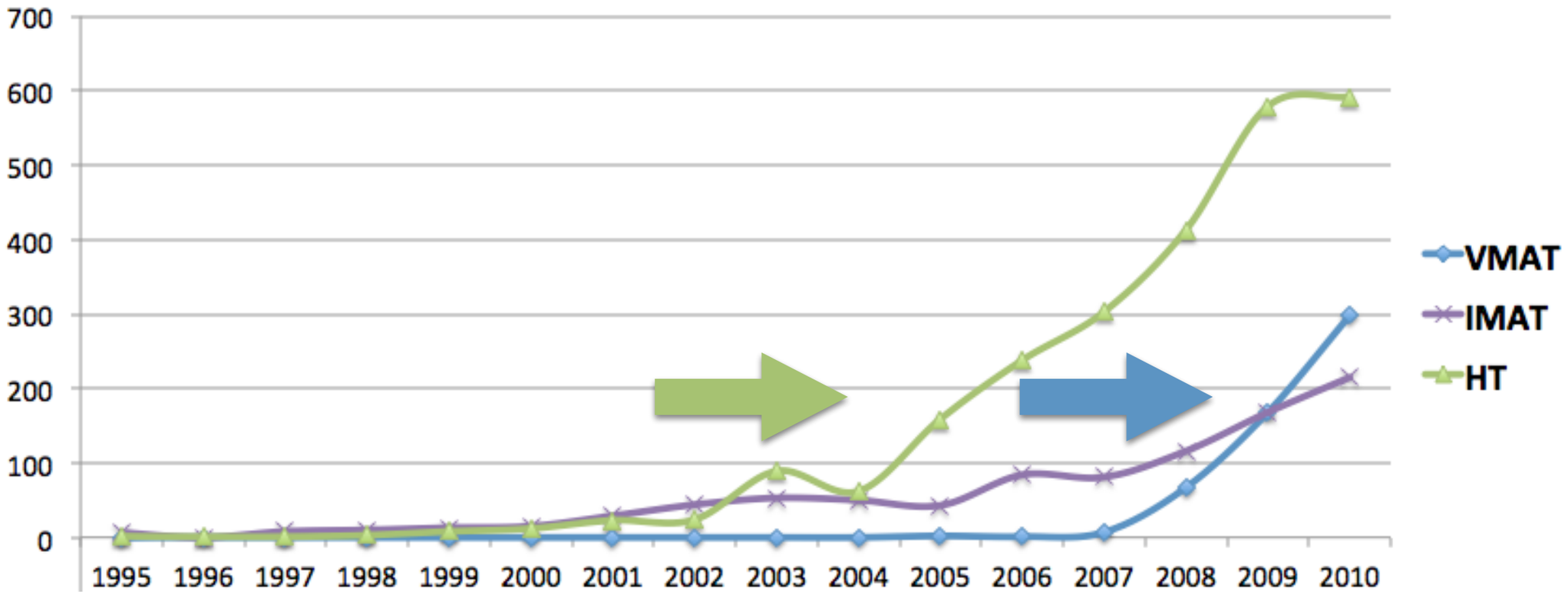
Low et al. 1998

*"A **commercial** **serial tomotherapy** intensity-modulated radiation therapy (IMRT) treatment planning (**Peacock, NOMOS** Corp., Sewickley, PA) and delivery system is in clinical use. The dose distributions are highly conformal, with large dose gradients often surrounding critical structures, and require accurate localization and dose delivery. Accelerator and patient-specific quality assurance (QA) procedures have been developed that address the localization, normalization, and delivery of the IMRT dose distributions."*

Nomos Peacock Add-on system



It took some time to get popular



Hits raise last year:

7.9% for IMRT (1982)
(last 3 years 7.1%)

2.2% for HT (1995)
(last 3 years 17.8%)

28% for IMAT (1995)
(last 3 years 26.9%)

77% for VMAT (2005)
(last 3 years 58.0%)

Issues with early solutions

- Computer treatment planning systems (TPS), inverse planning approaches and optimizer algorithms were in their early days

- Dependence on another new technology at that time, the multi-leaf collimator (MLC), which was initially designed to replace cerobend blocks

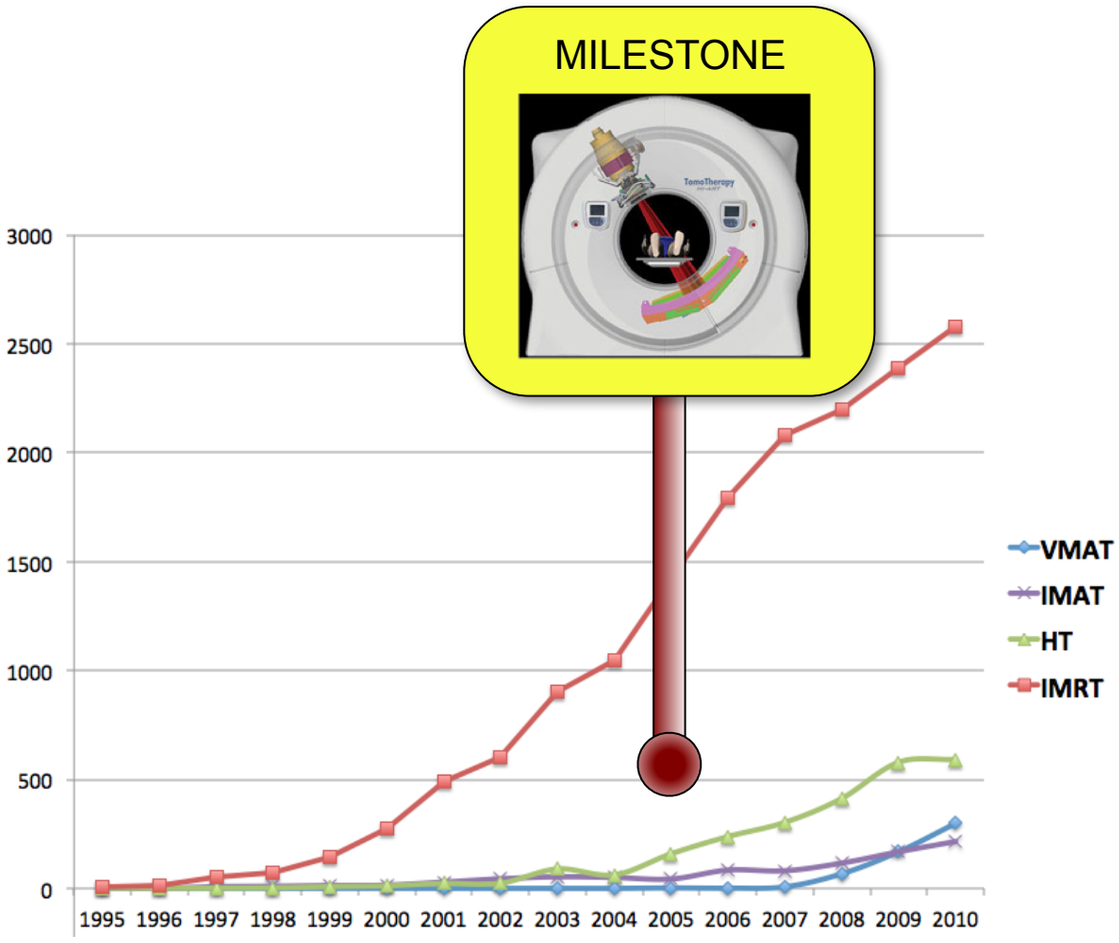
"A handful of research oriented centers developed their own **custom build solution of rotational therapy solutions** (IMAT, …)."

-William Beaumont Hospital group, USA, C. Yu et al.

-UZ Gent, Belgium, De Neve et al.

-…

An industry incentive…



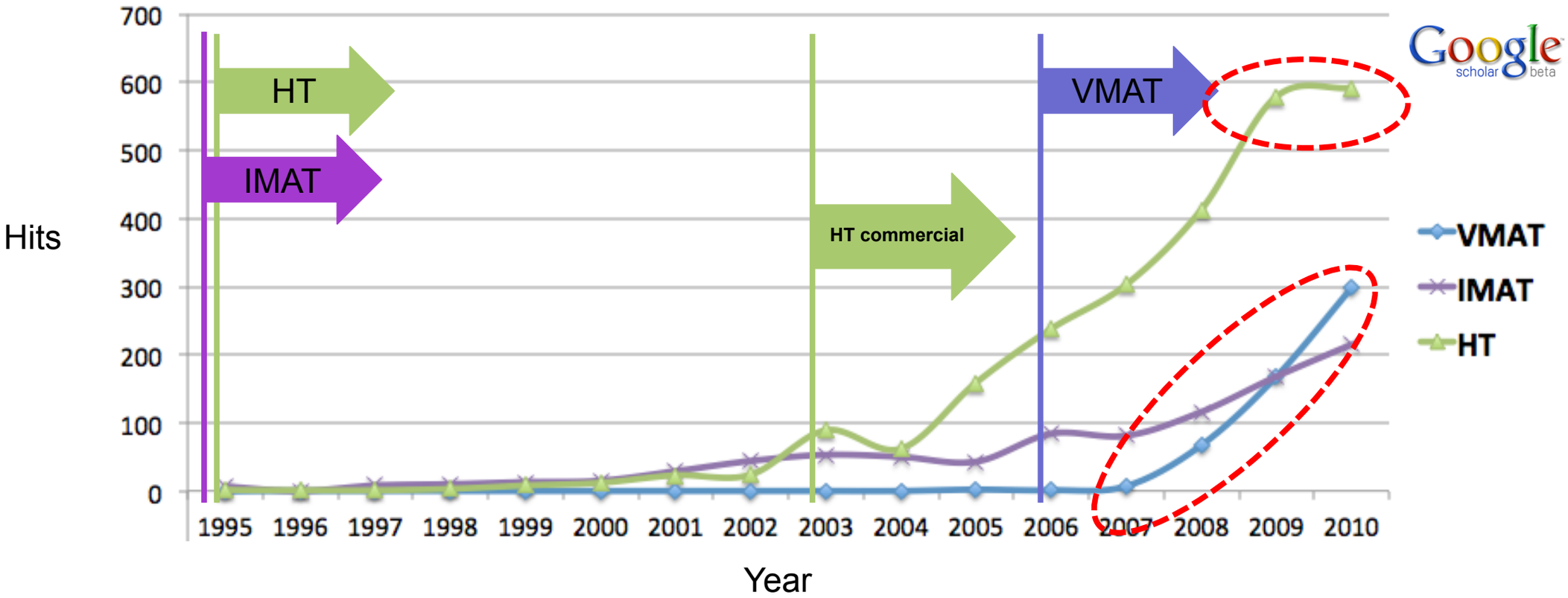
Introduction of the Tomotherapy Hi-Art system for helical tomotherapy:

"Not an add-on solution any more like serial tomo, but a new concept on a dedicated device"

"Brought rotational IMRT to a next level …"

"A new competitor in a very competitive market with only a few players"

An industry incentive



Marketing machine is not afraid to use words like
-”true REVOLUTION …”
-”MAJOR advance …”
-”DRAMATIC improvement … “

But behind the screens the R&D got a lot of resources as well to at least approximate the promises made by marketing …

The field today….

Volumetric Modulated Arc Therapy

ELEKTA with VMAT™

="cone beam delivery"

VARIAN medical systems with RapidArc

Helical Tomotherapy

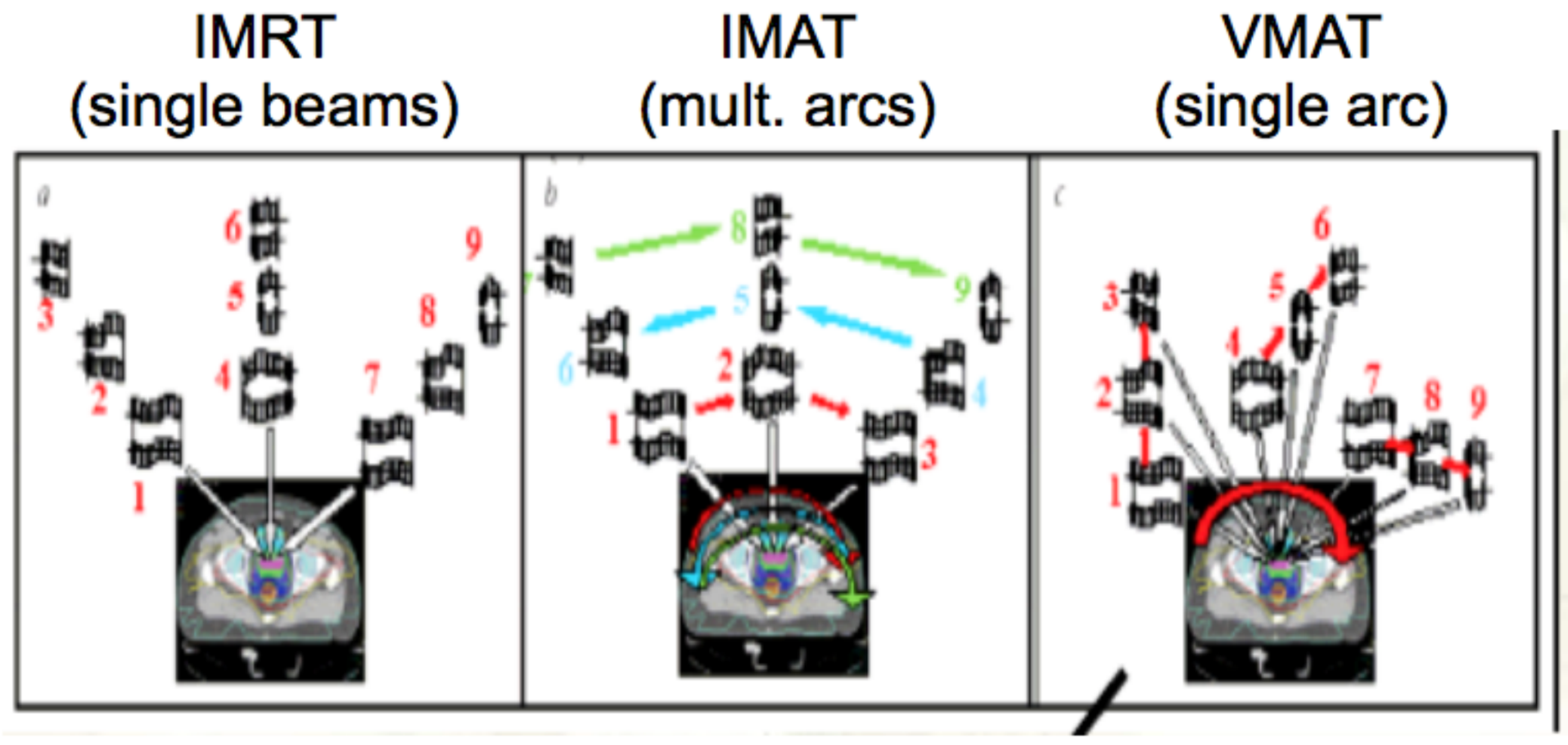
TomoTherapy INCORPORATED

ACCURAY

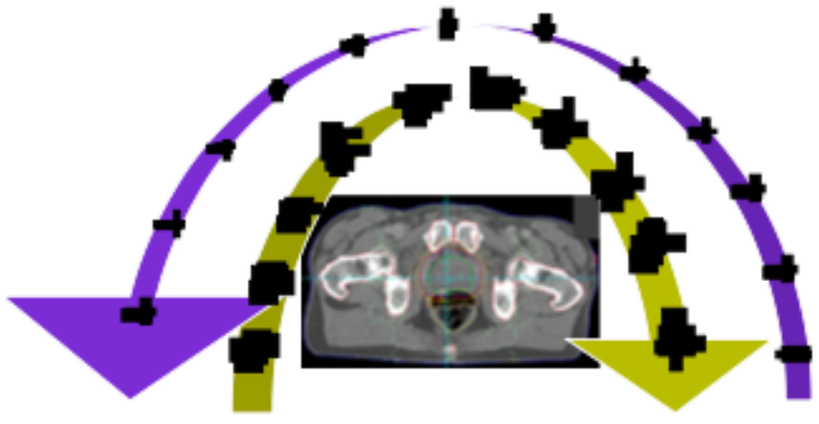
="fan beam delivery"

Static IMRT

Different names/interpretations

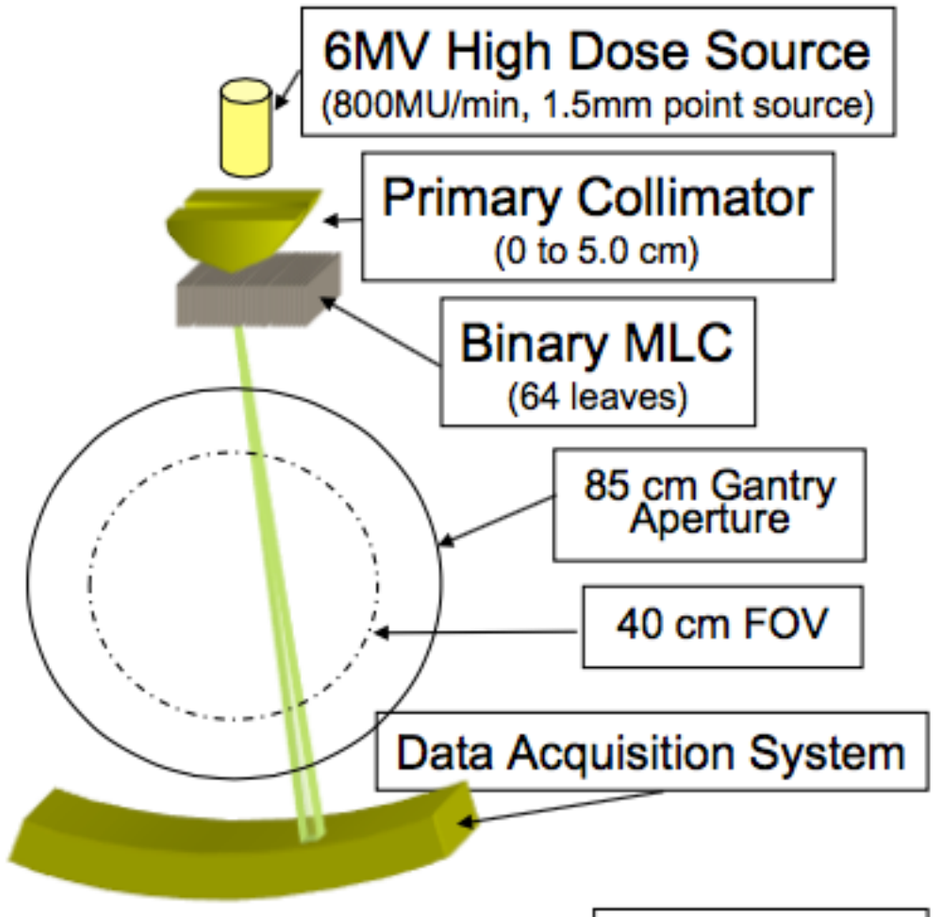


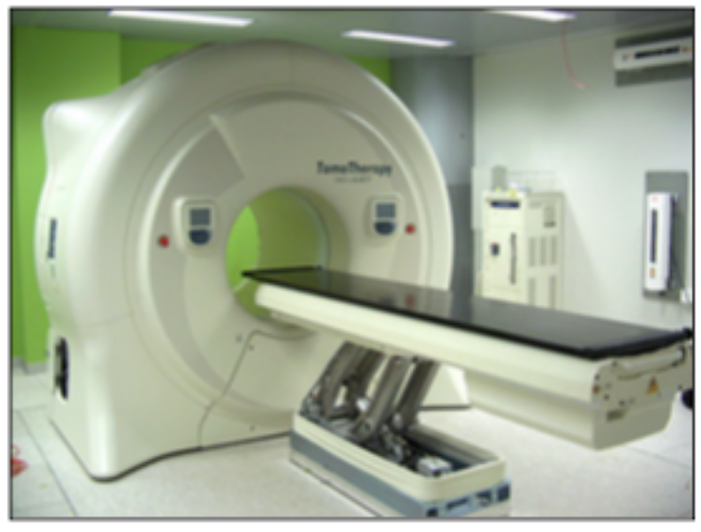
VMAT / RapidArc /

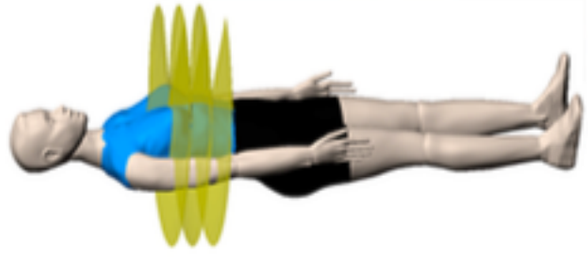


- 1 or more rotations
- Modulation by gantryspeed/doserate/ MLC

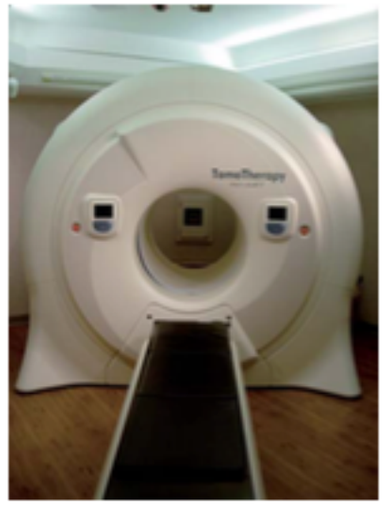
Helical Tomotherapy (Linac meets CT)







Helical Tomotherapy



- Helical Treatment
- Field of 40cmx(5, 2.5 of 1)cm
- Modulation by
  - 64 leaf-binary MLC
  - Pitch (around 0.3)
  - Modulation factor (average/max leaf open time)

“hot” a couple of years ago

- Is cone beam delivery better than helical fan-beam delivery
- Is arc therapy “better” than static beam IMRT
- Should all IMRT be rotational?

Still relevant

The battle was taking place on two fronts….

Practical : “Planning comparison studies between VMAT and HT and other IMRT solutions

Theoretical : Trying to prove differences between the various dose delivery techniques based on intrinsic/theoretical capabilities of the technique

Planning studies

- Can be described as a pragmatic approach to show what we can do with actual clinical cases
- Only valid for specific implementations of different techniques
- prone to bias
  - you are comparing optimisers, not techniques
  - you are comparing planners, not plans (pareto-optimal?)
  - The link to biology was almost never made…
- General conclusion : I’m not a big fan

VMAT (single arc) vs. IMRT (9 Fields)

- Palma et al 2008 (prostate)
- Cozzi et al 2008 (gynec)
- Fogliata et al (brain)

Simple cases (not a lot of modulation) :VMAT at least as good as IMRT
VMAT : treatment time and MU reduction

Thanks to Sara Broggi

VMAT (single arc) vs. VMAT (Mult arc)

- Wu et al (2009) : spinal
- Guckenberger (2009), prostate and H&N
- Vanetti et al (2009), H&N
- Clivio et al (anal canal)
- Verbakel et al (2009), H&N
- Tang et al (2010), H&N, Brain, Lung, Prostate
- Yoo et al (2010), big prostate (incl nodes)

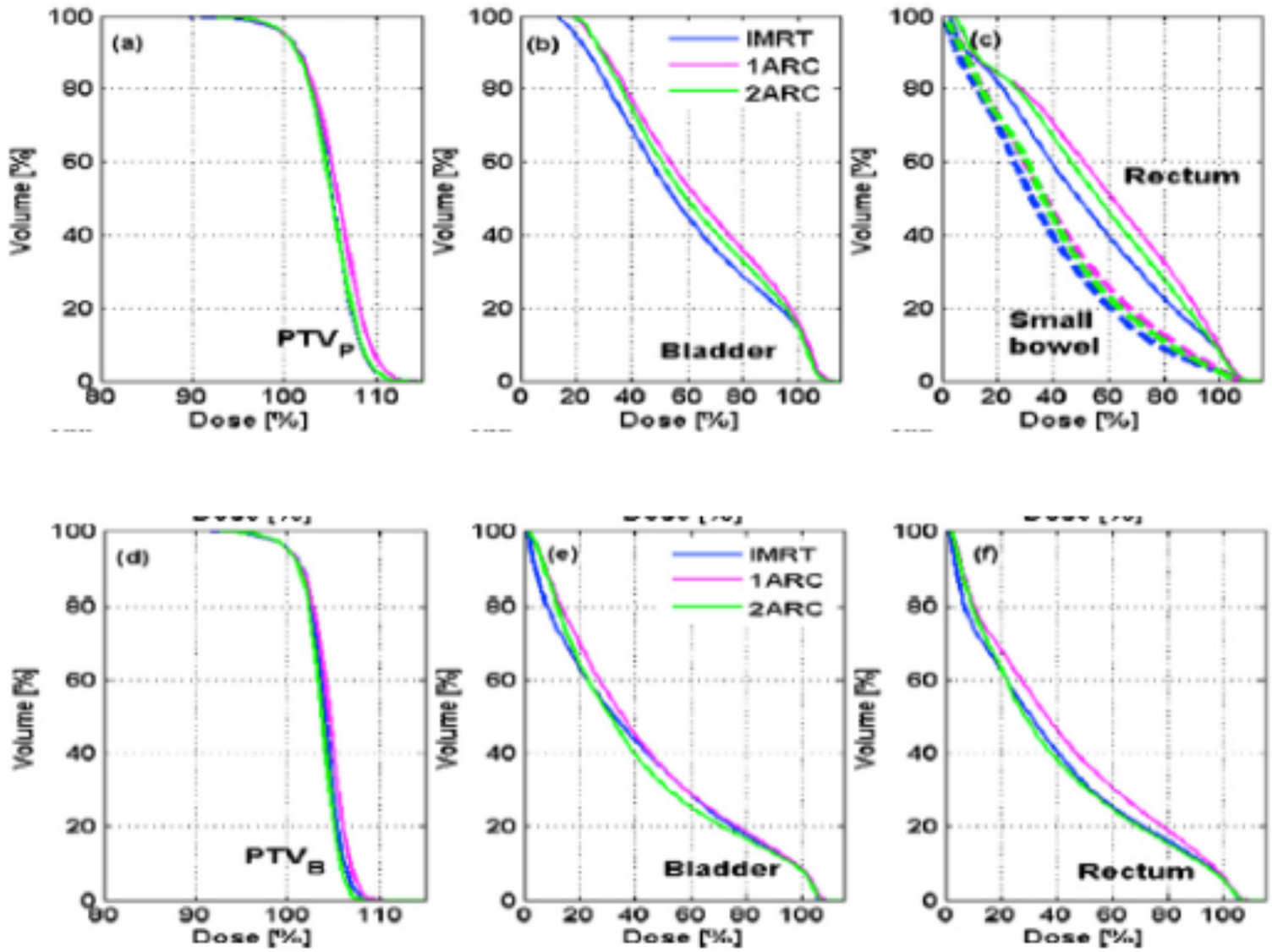
In complex cases single arc has inferior result aot IMRT
Multiple arcs can rise the quality of the treatment plan, especially in the homogeneity of the PTV.
Multiple arcs stay in a timeframe < IMRT

Thanks to Sara Broggi

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, pp. 935–942, 2010

RADIOTHERAPY TREATMENT PLANS WITH RAPIDARC FOR PROSTATE CANCER INVOLVING SEMINAL VESICLES AND LYMPH NODES

SUA YOO, PH.D., Q. JACKIE WU, PH.D., W. ROBERT LEE, M.D., M.S., M.ED., AND FANG-FANG YIN, PH.D.



PTVp + SV + LN
46.8Gy

PTVboost (P+SV)
75.6Gy

VMAT/IMAT vs. HT

- Cao et al (2007) : prostate, brain, H&N
- Iori et al (2008), prostate
- Ulrich et al (2009): Prostate, anal canal, H&N
- Clivio et al (anal canal)
- Fogliata et al (2008) : brain
- Fogliata et al (2009) : pediatric

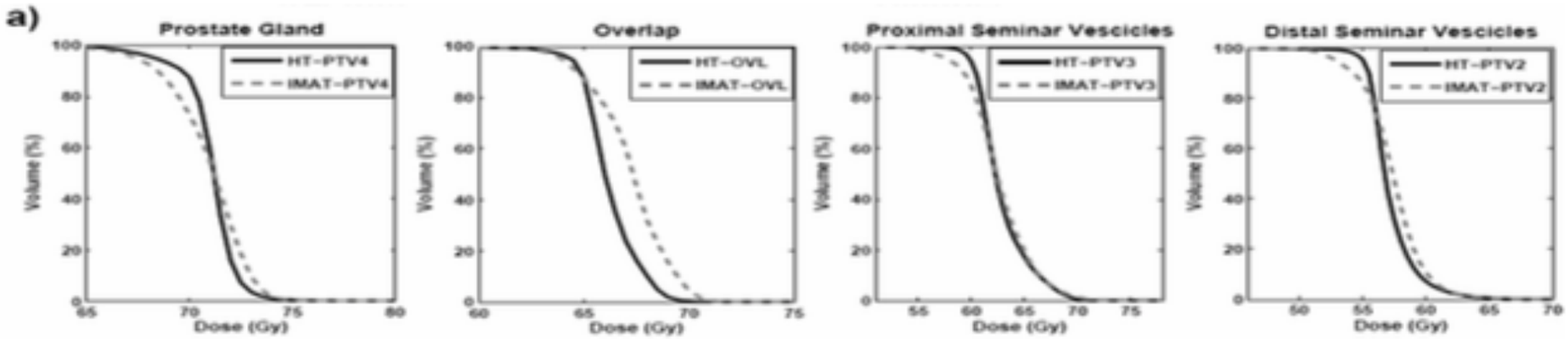
In simple cases VMAT and HT comparable results
In complex cases higher plan quality for HT
Treatment times higher for HT
VMAT : lower integral dose
HT : Gradient in CC direction inferior

Thanks to Sara Broggi

Radiotherapy and Oncology 88 (2008) 34–45

Dose–volume and biological-model based comparison between helical tomotherapy and (inverse-planned) IMAT for prostate tumours

Mauro Iori[a,*], Giovanni Mauro Cattaneo[b], Elisabetta Cagni[a], Claudio Fiorino[b], Gianni Borasi[a], Calandrino Riccardo[b], Cinzia Iotti[c], Ferruccio Fazio[d], Alan E. Nahum[e]

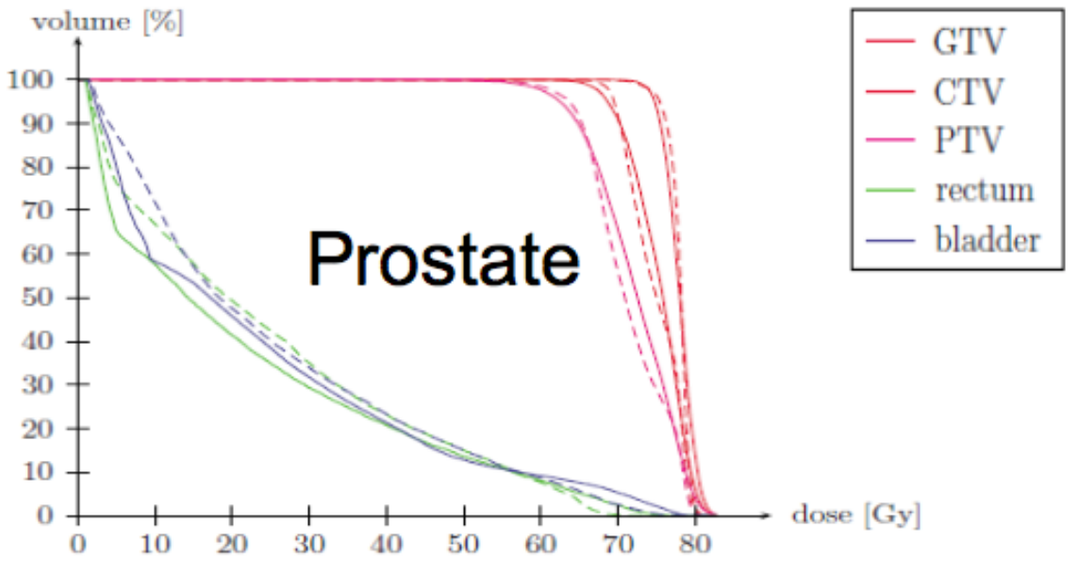


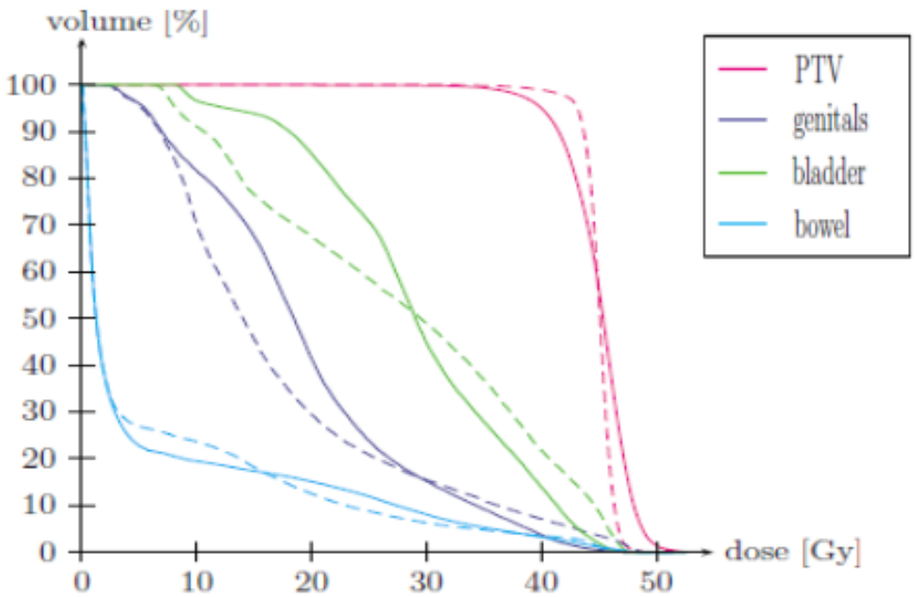
HT : More homogeneous target coverage
comparable results for OAR
HT : gradient in CC direction

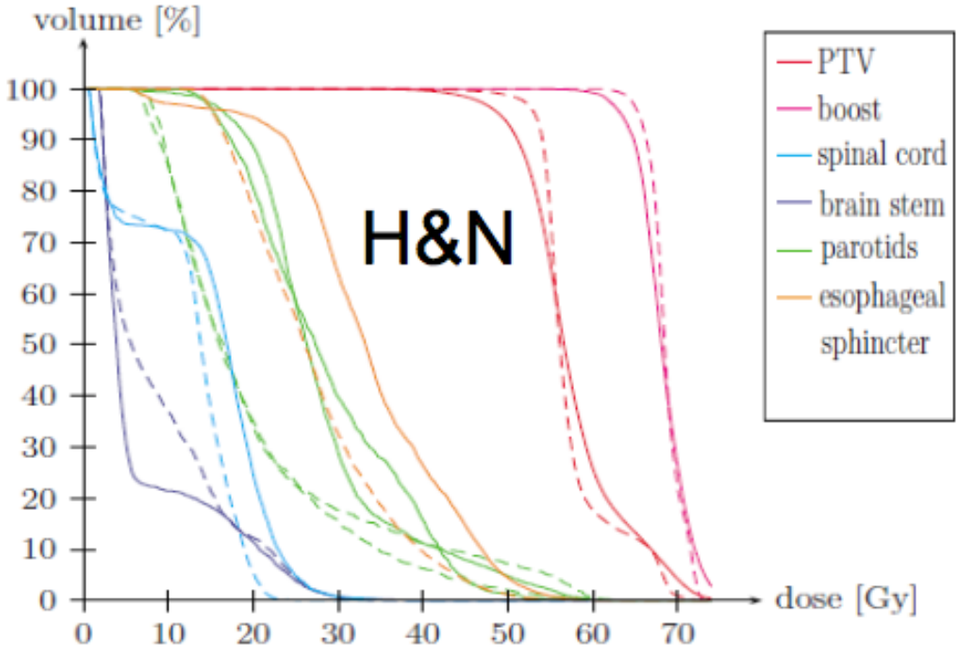
Comparison of arc-modulated cone beam therapy and helical tomotherapy for three different types of cancer

Silke Ulrich[a)]

Medical Physics, Vol. 36, No. 10, October 2009



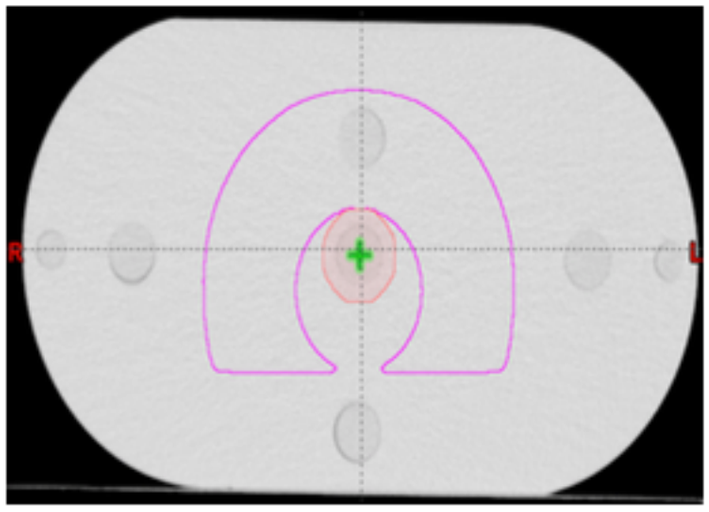




dashed = HT

Phantom “Stress-Test”

Horse-shoe PTV
Single OAR



Metrics:

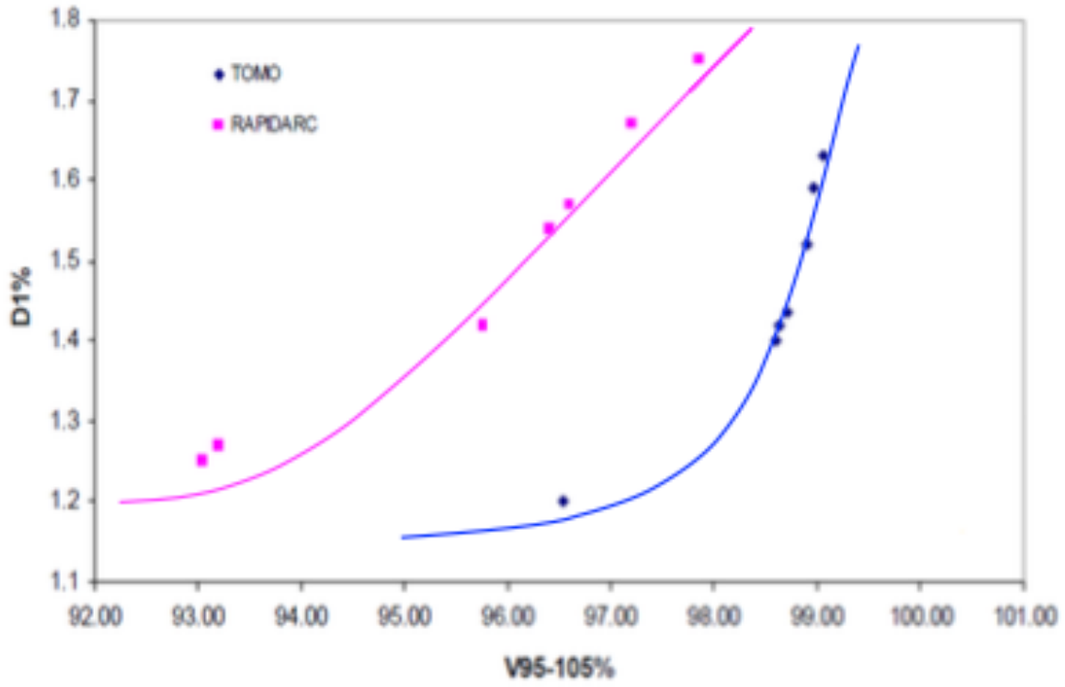
D1% (max dose) OAR
PTV Homogeneity (V105-V95)

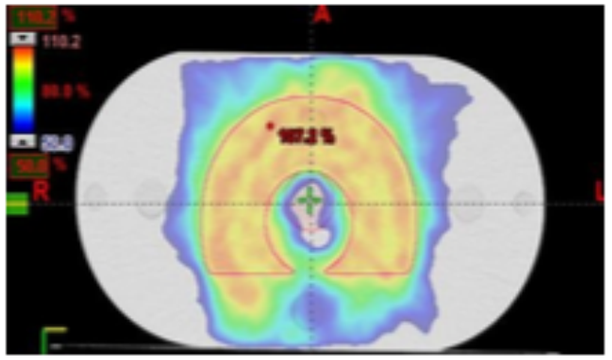
HT :

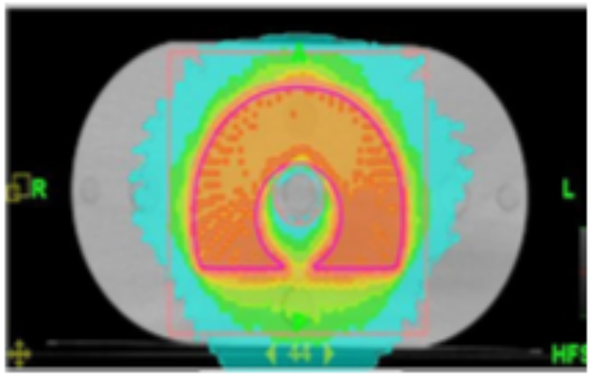
2.5cm field,pitch 0.287, MF 4

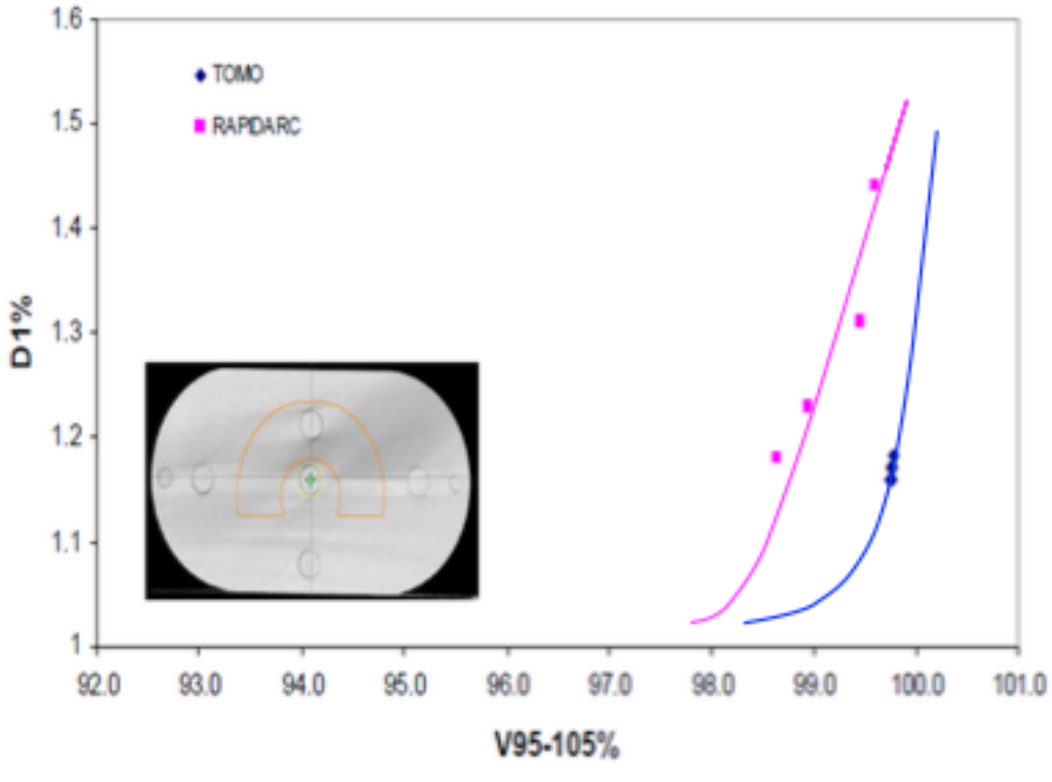
VMAT:

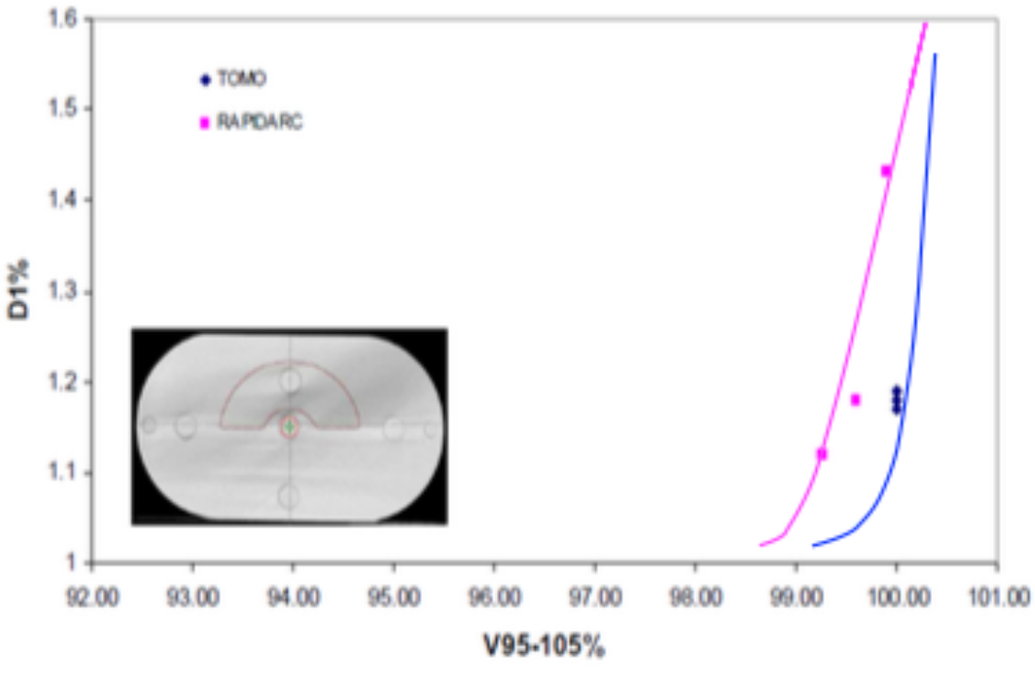
Rapidarc 2 rotations, collimator 45 degreed


TOMO
RAPIDARC
D1%
V95-105%
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
92.00
93.00
94.00
95.00
96.00
97.00
98.00
99.00
100.00
101.00






TOMO
RAPIDARC
D1%
V95-105%
1.6
1.5
1.4
1.3
1.2
1.1
1
92.0
93.0
94.0
95.0
96.0
97.0
98.0
99.0
100.0
101.0


TOMO
RAPIDARC
D1%
V95-105%
1.6
1.5
1.4
1.3
1.2
1.1
1
92.00
93.00
94.00
95.00
96.00
97.00
98.00
99.00
100.00
101.00

Comments

- Planningstudies are plenty, all say the same, but most don't say a lot...
- Yes, HT can achieve better target coverage and nicer sparing
  - with an inferior CC gradient
  - and a longer treatment time
- The question is : is it clinically relevant for this patient, and all my patients?
- Most studies have been catched up by upgrades
  - HT : reduction of CC gradient by "dynamic jaws"
  - reduction of treatment time by use of 5cm field and increased rotation speed.

Comparison approaches IMRT/VMAT/HT

Theoretical discussion:

"Trying to prove differences between the various dose delivery techniques based on intrinsic/theoretical capabilities of the technique."

-Independent of the maturity of currently available solutions in the clinic.
-Possibility of a general conclusion ?!

However …

-A universal theoretical framework to make this comparison for VMAT is lacking
-Not considering some practical/implementation specific issues which do count in practice

Bortfeld&Webb, Verbakel et al., Otto et al., …

Theoretical comparisons IMRT/HT/VMAT

Dose delivery technique degrees of freedom for intensity modulation

Comparing S-IMRT with Rotational IMRT:

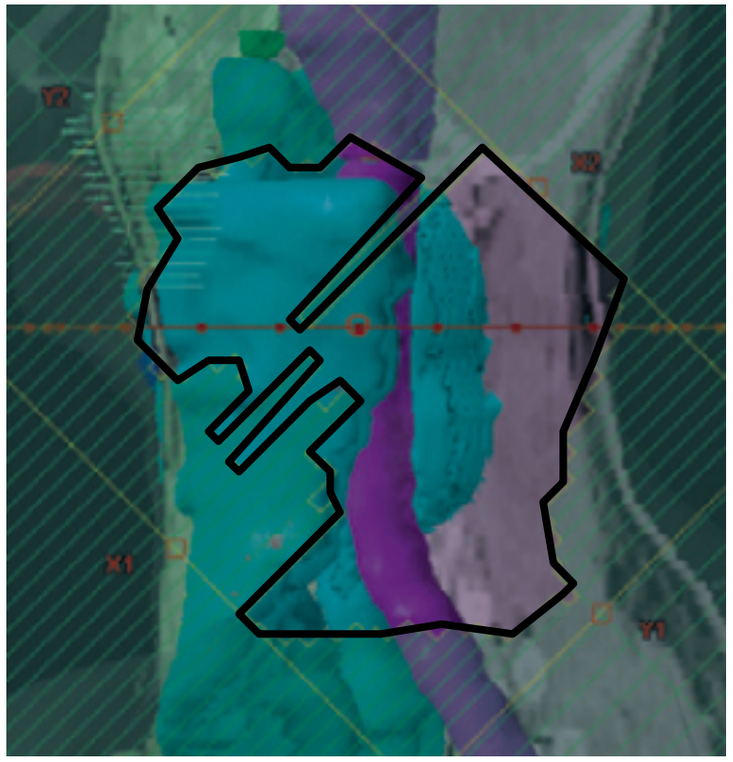
#Contributing beamlets from different gantry angle (VMAT,HT > S-IMRT)

versus

#Modulation in one individual beamlet (S-IMRT > VMAT,HT)

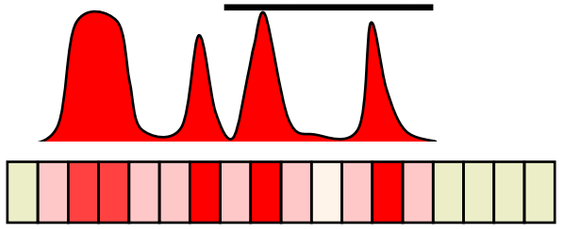
Theoretical comparisons IMRT/HT/VMAT

Single-Arc

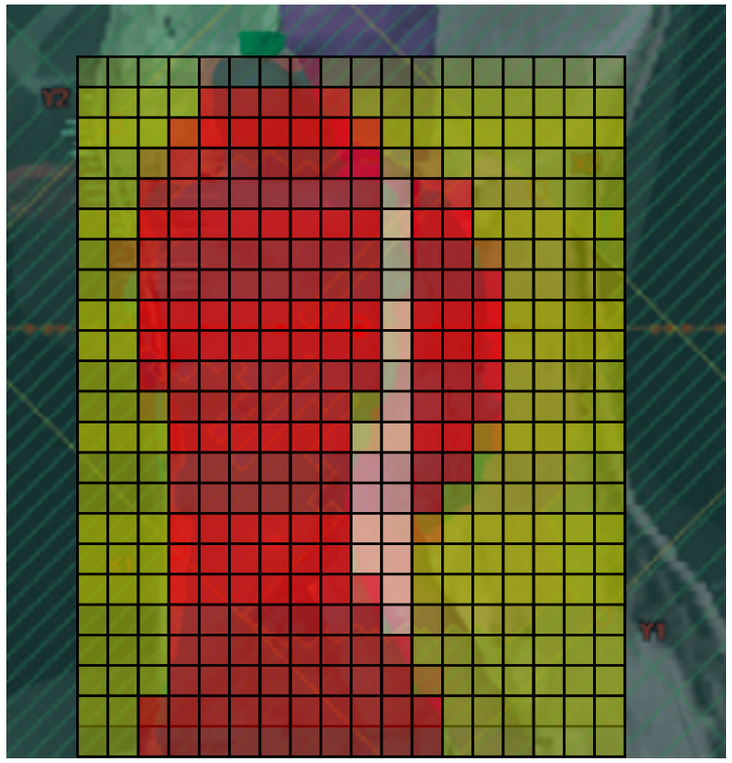


One “<u>un</u>”-modulated beam “segment” at each **single** angle

Tomo



Modulated beam projection

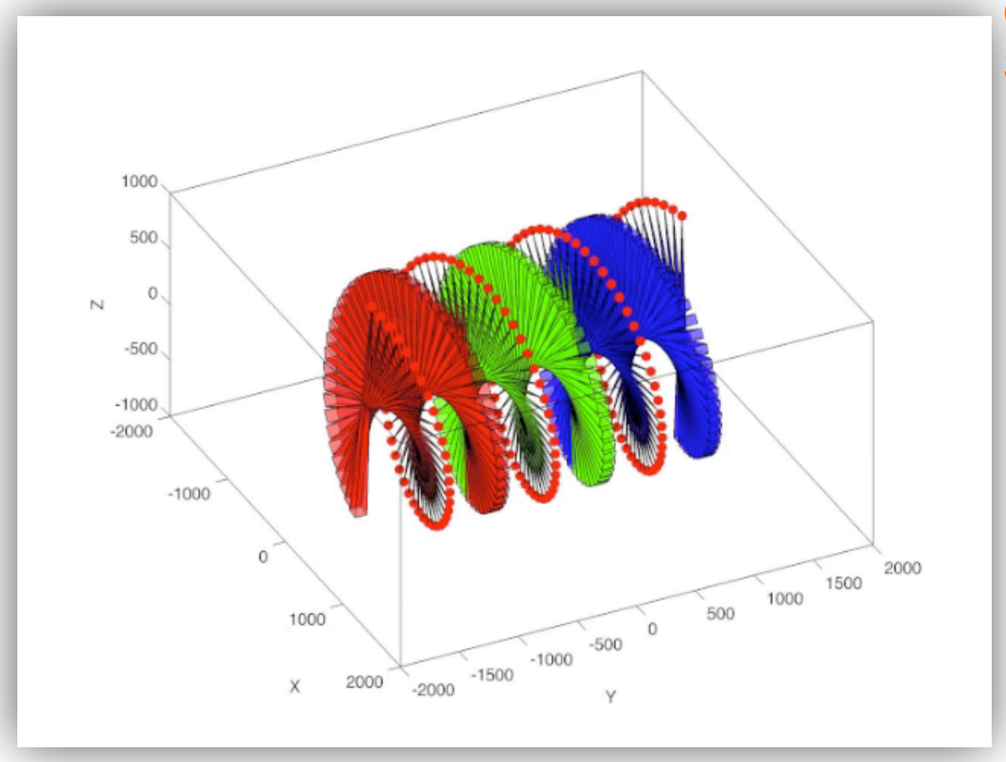


One projection each rotation for this angle

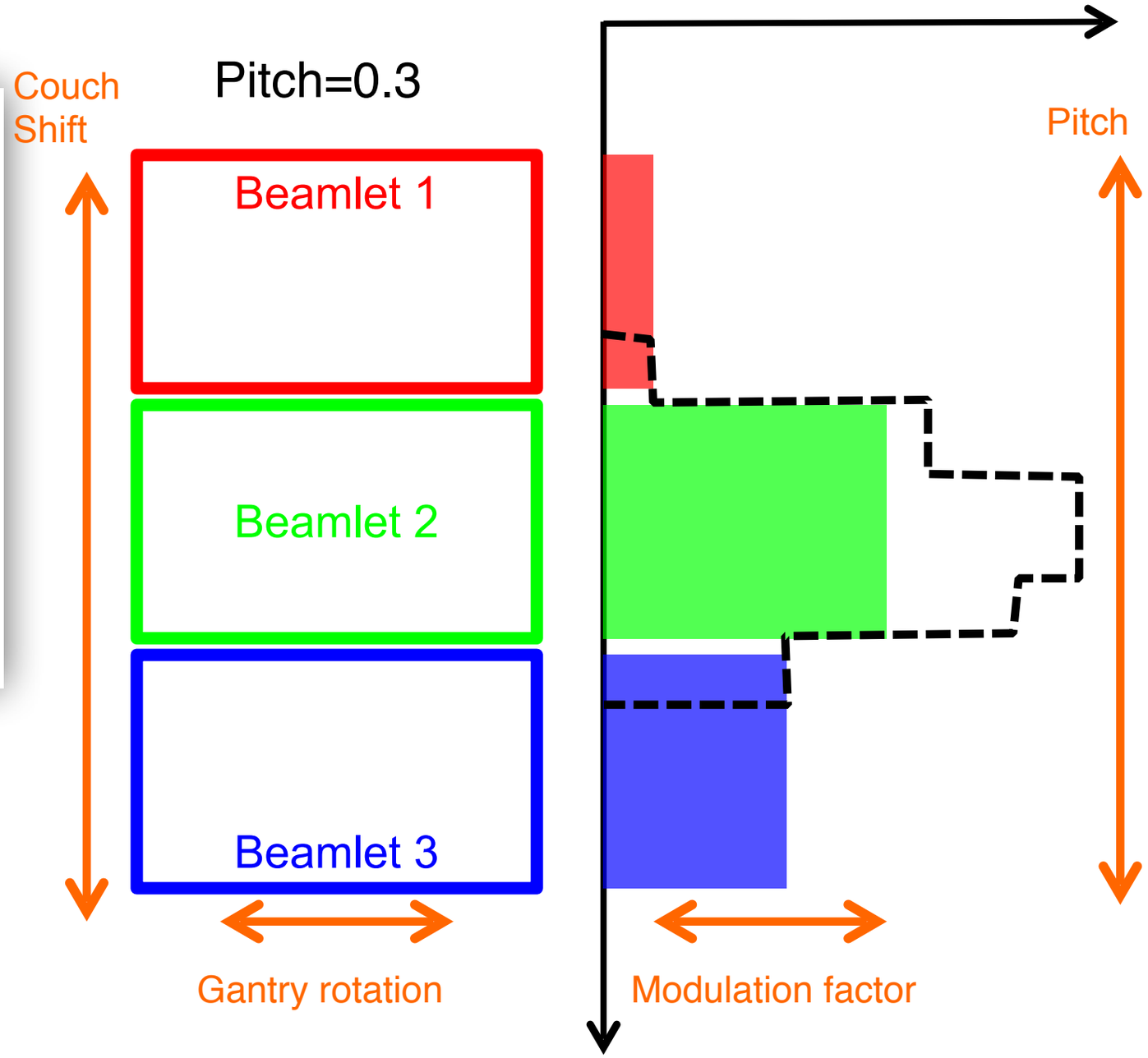
Many <u>modulated</u> beam projections at each angle

Intensity modulation and interconnectivity: HT

The amount of modulation is determined by the pitch, modulation factor and field size

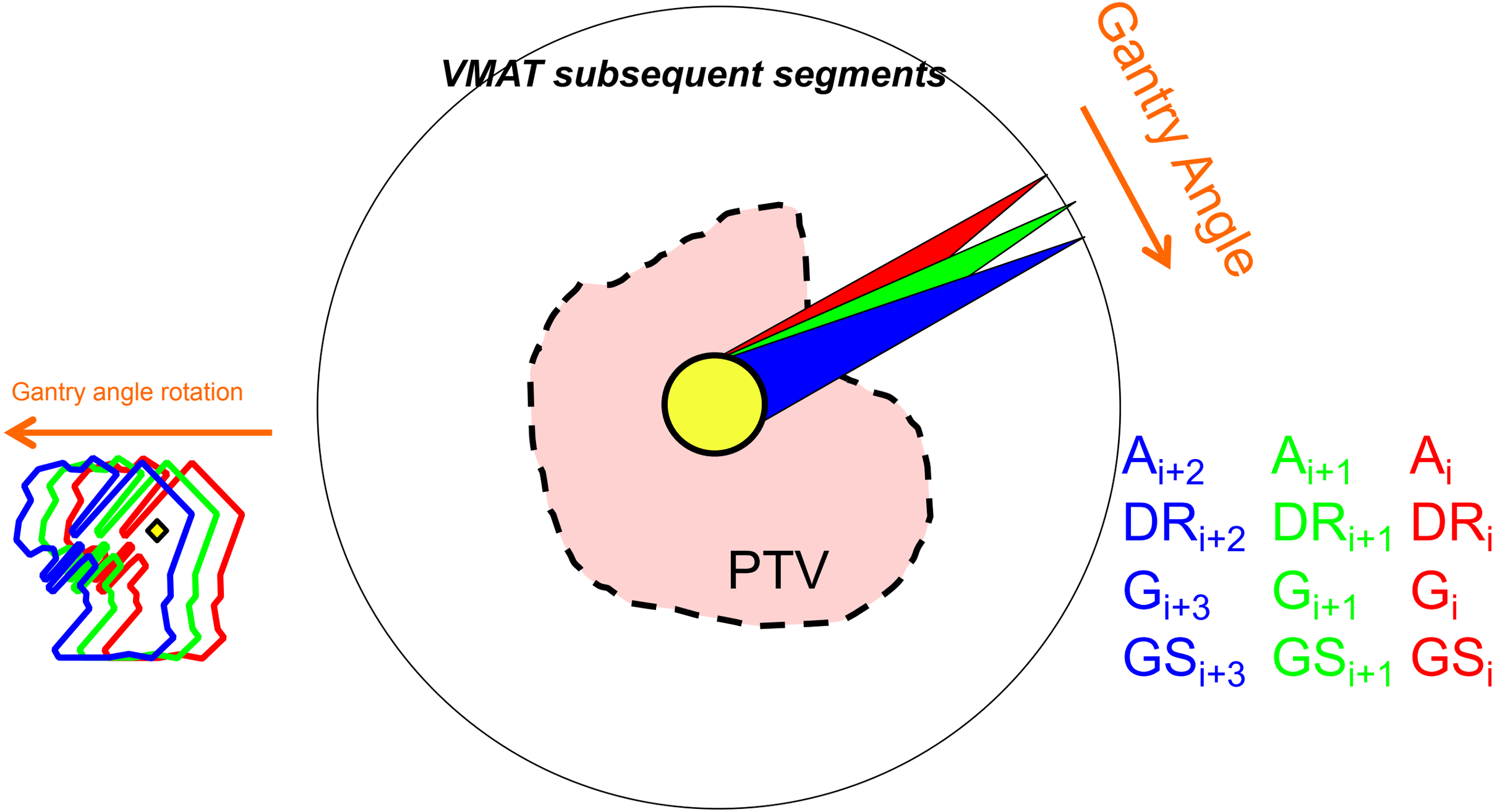


“Each individual beamlet can be intensity modulated changing **leaf opening time.**”



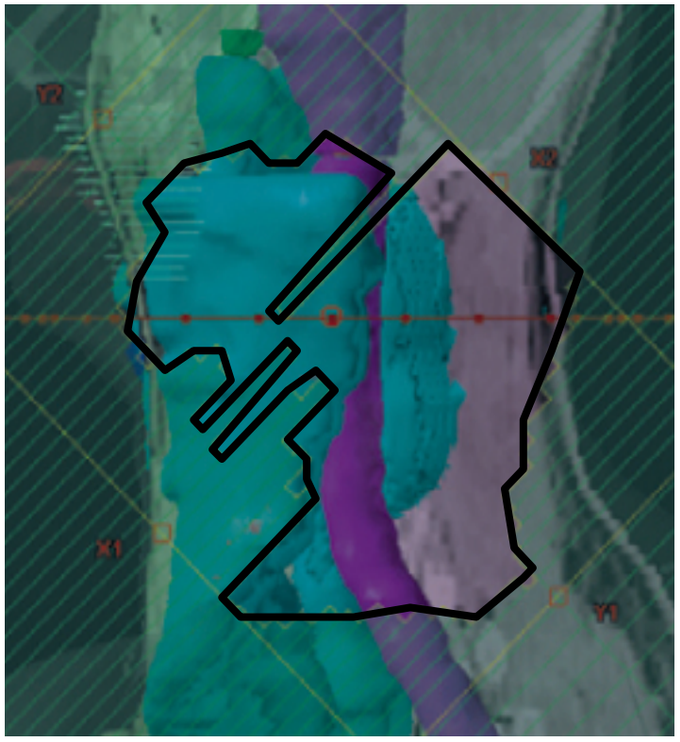
Intensity modulation and interconnectivity: VMAT

Contribution of dose to a small subvolume of the target volume from a small angle



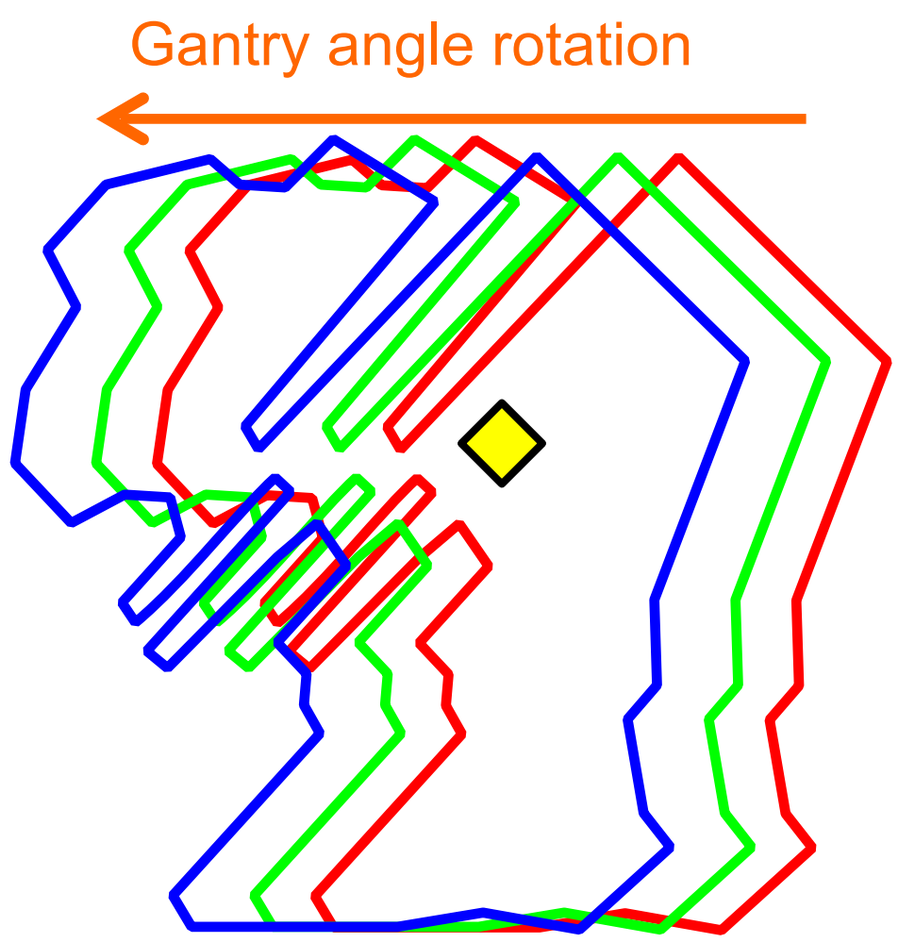
Intensity modulation and interconnectivity: VMAT

Segment Interconnectivity

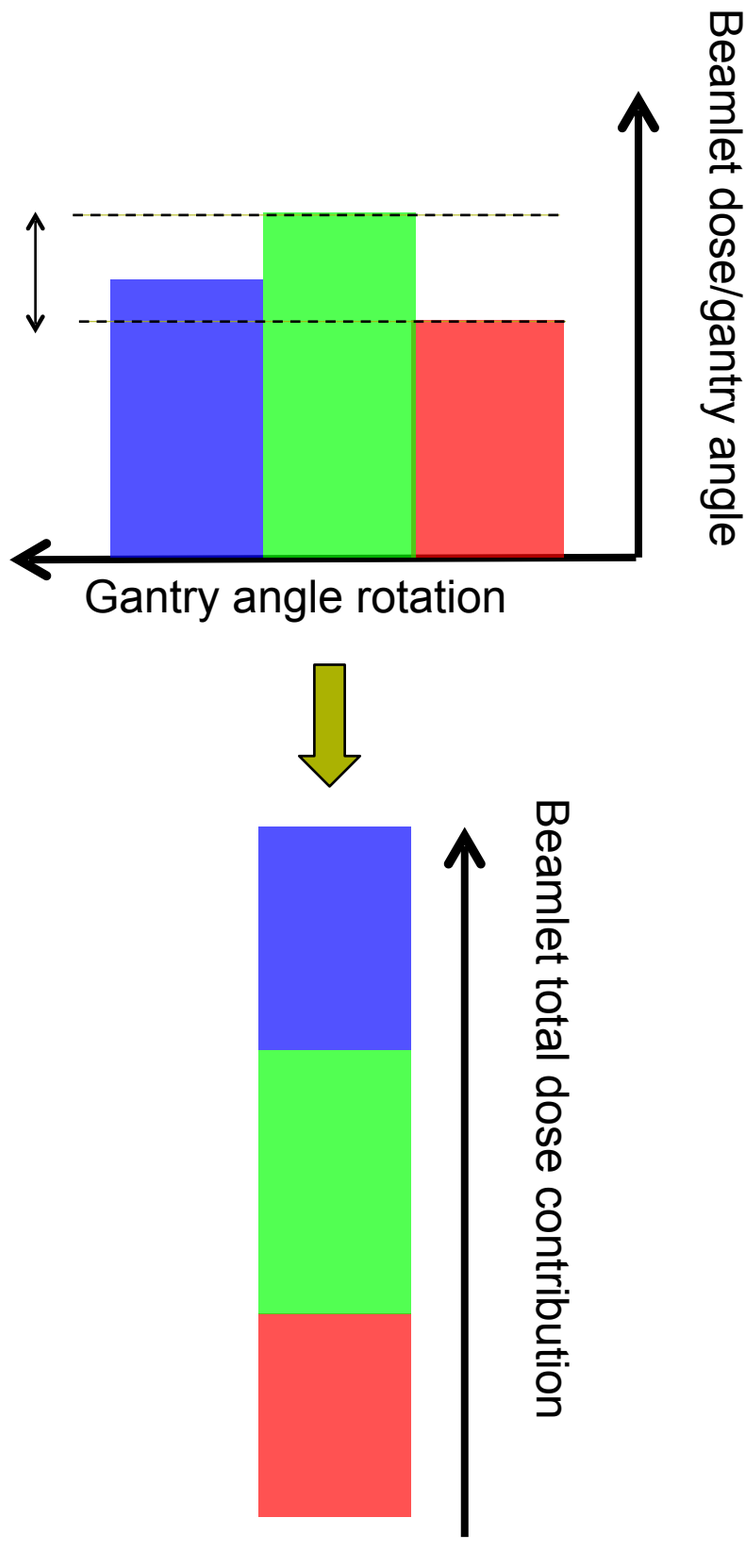


"**<u>Limited amount of change</u> allowed between subsequent segments** due to technical limitations (more than for HT)"

"Smooth changes"

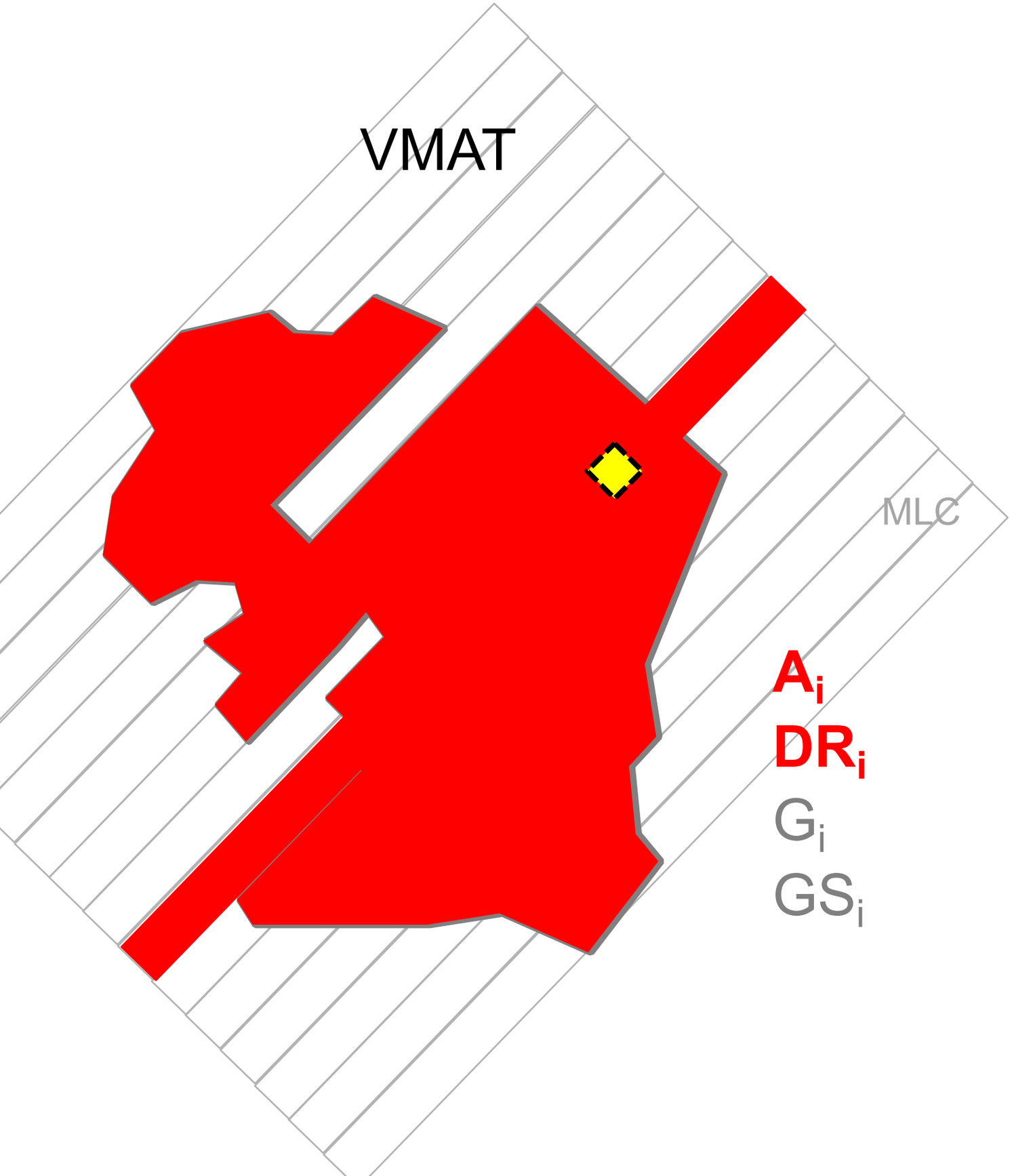


A_{i+2} A_{i+1} A_i
DR_{i+2} DR_{i+1} DR_i
G_{i+3} G_{i+1} G_i
GS_{i+3} GS_{i+1} GS_i



Intensity modulation and interdependency

VMAT



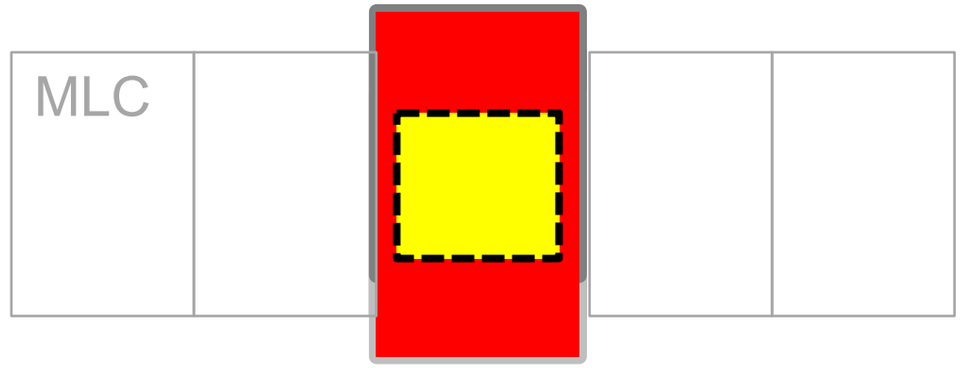
A_i

DR_i

G_i

GS_i

Helical Tomotherapy



"**Interdependency** with other subvolumes of the target far away covered by aperture"

"VMAT > HT"

Theoretical comparisons IMRT/HT/VMAT

To give an impression on how such a theoretical discussion goes …

IOP PUBLISHING — PHYSICS IN MEDICINE AND BIOLOGY
Phys. Med. Biol. 54 (2009) N9–N20 — doi:10.1088/0031-9155/54/1/N02

NOTE

Single-Arc IMRT?

Thomas Bortfeld[1,3] **and Steve Webb**[2]

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Abstract

The idea of delivering intensity-modulated radiation therapy (IMRT) with a multileaf collimator in a continuous dynamic mode during a single rotation of the gantry has recently gained momentum both in research and industry. In this note we investigate the potential of this Single-Arc IMRT technique at a conceptual level. We consider the original theoretical example case from Brahme *et al* that got the field of IMRT started. Using analytical methods, we derive deliverable intensity 'landscapes' for Single-Arc as well as standard IMRT and Tomotherapy. We find that Tomotherapy provides the greatest flexibility in shaping intensity landscapes and that it allows one to deliver IMRT in a way that comes close to the ideal case in the transverse plane. Single-Arc and standard IMRT make compromises in different areas. Only in relatively simple cases that do not require substantial intensity modulation will Single-Arc be dosimetrically comparable to Tomotherapy. Compared with standard IMRT, Single-Arc could be dosimetrically superior in certain cases if one is willing to accept the spreading of low dose values over large volumes of normal tissue. In terms of treatment planning, Single-Arc poses a more challenging optimization problem than Tomotherapy or standard IMRT. We conclude that Single-Arc holds potential as an efficient IMRT technique especially for relatively simple cases. In very complex cases, Single-Arc may unduly compromise the quality of the dose distribution, if one tries to keep the treatment time below 2 min or so. As with all IMRT techniques, it is important to explore the tradeoff between plan quality and the efficiency of its delivery carefully for each individual case.

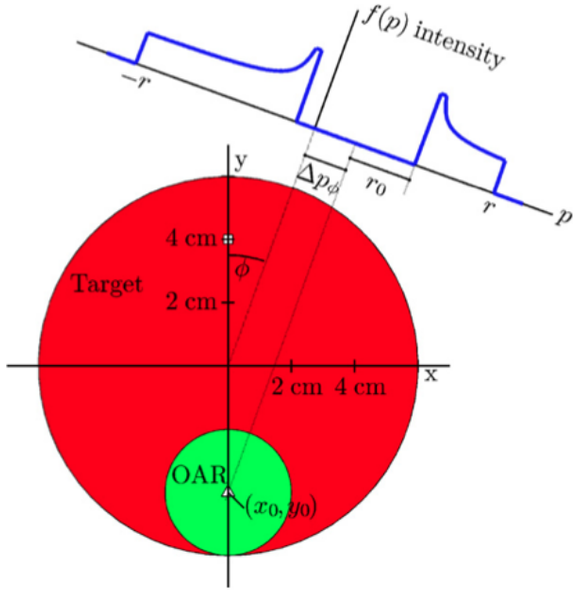
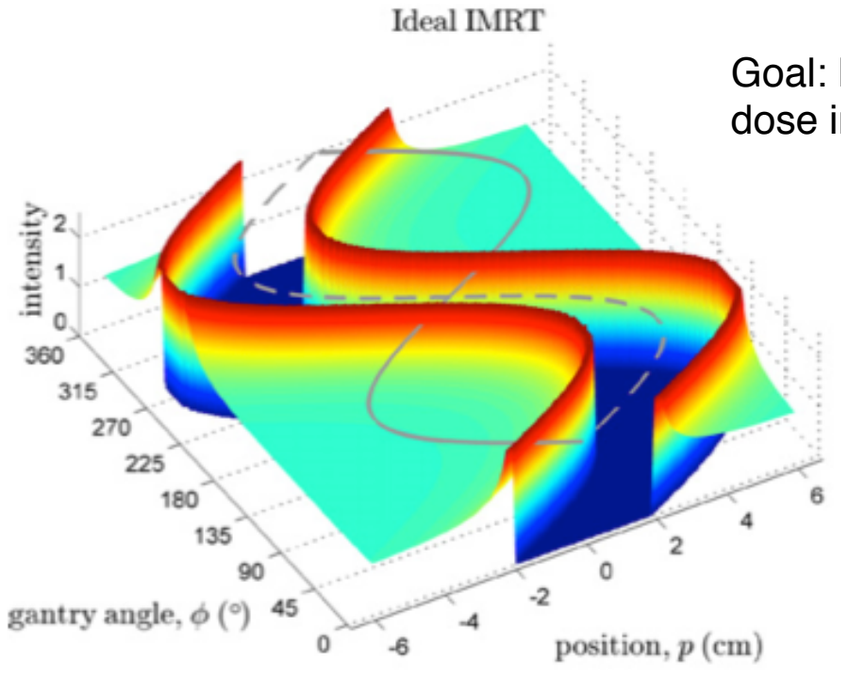


Figure 1. The archetypical IMRT example case where the target volume (red) wraps around an organ at risk (OAR) (Brahme *et al* 1982). This case requires substantial intensity modulation. Simply 'blocking' dose from reaching the OAR does not yield the desired uniform dose coverage of the target volume. One intensity profile from a gantry angle of $\phi = 20°$ is shown.

"Required ideal intensity modulation can be derived theoretically for this artificial situation"

"One AXIAL slice"

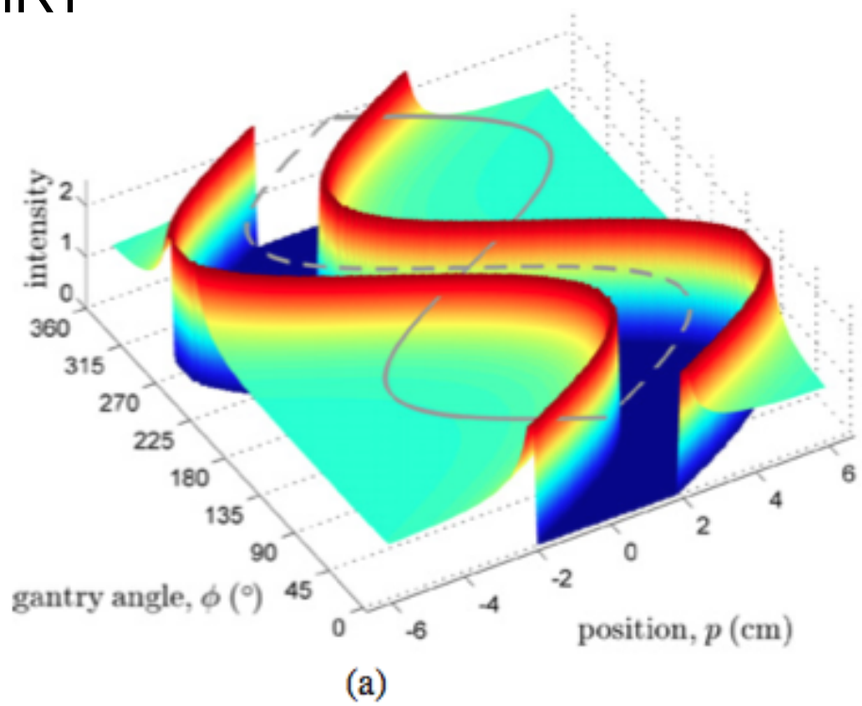


Goal: homogeneous dose in PTV

Bortfeld and Webb, Brahme et al.

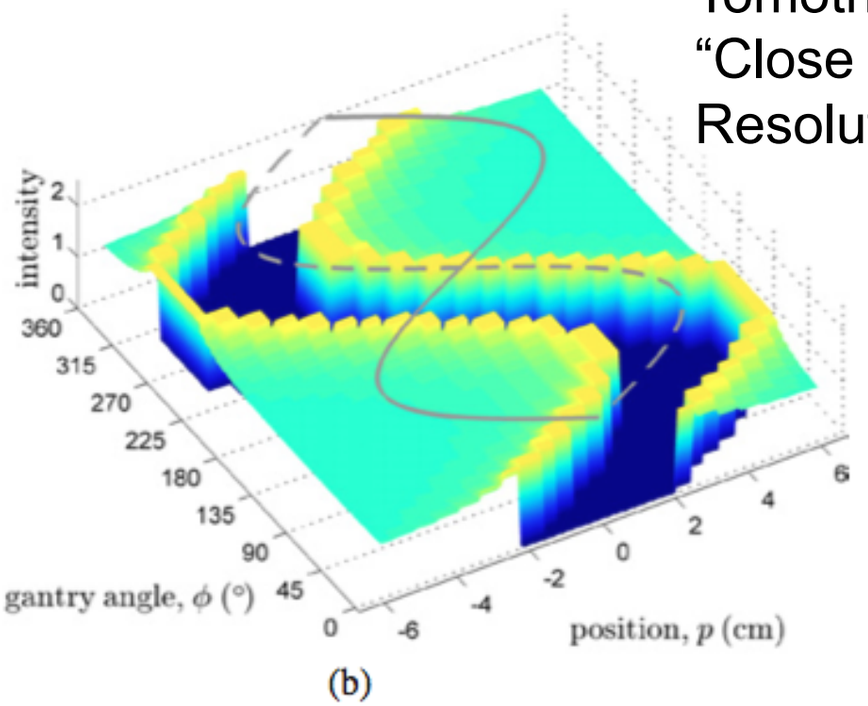
Theoretical comparisons IMRT/HT/VMAT

Ideal IMRT



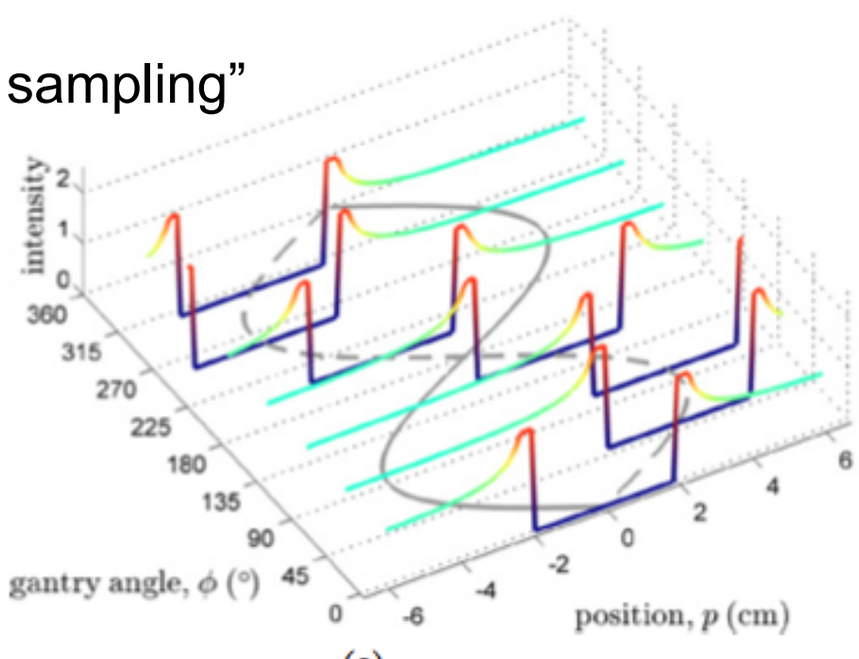
(a)

Tomotherapy
“Close but limitations in Resolution”



(b)

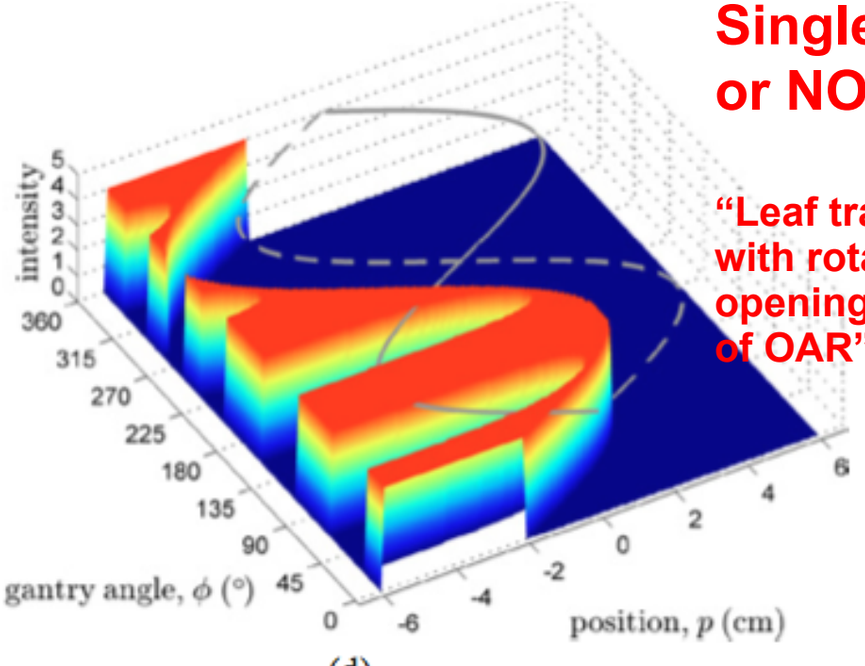
S-IMRT
“Coarse sampling”



(c)

Single Arc IMRT or NOT?

“Leaf tracks inline with rotation direction, opening leafs on one side of OAR”



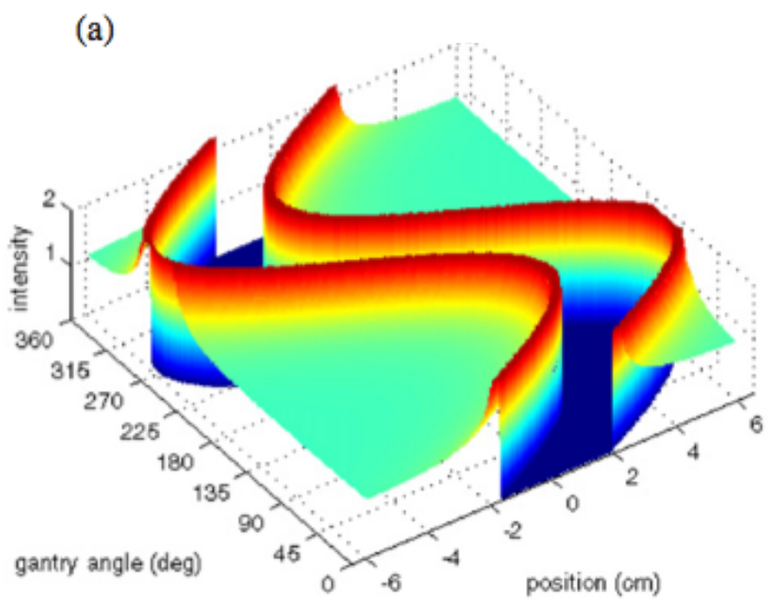
(d)

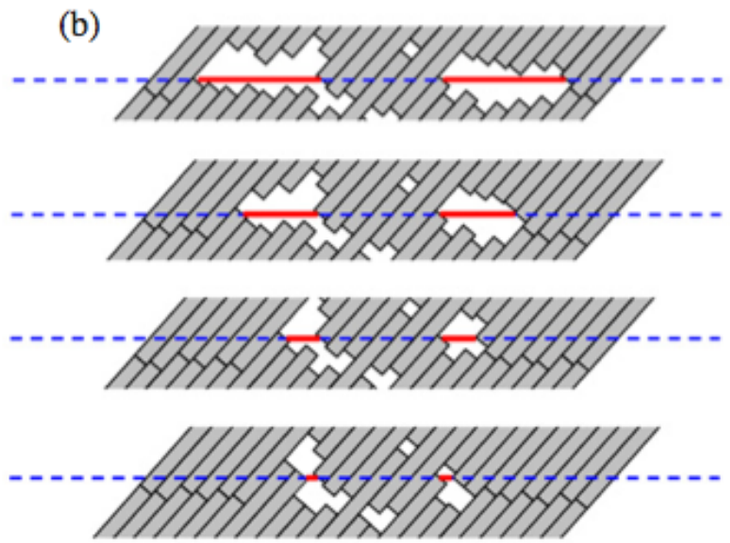
Bortfeld and Webb

Theoretical comparisons IMRT/HT/VMAT

Reply by Otto et al.

Ideal IMRT



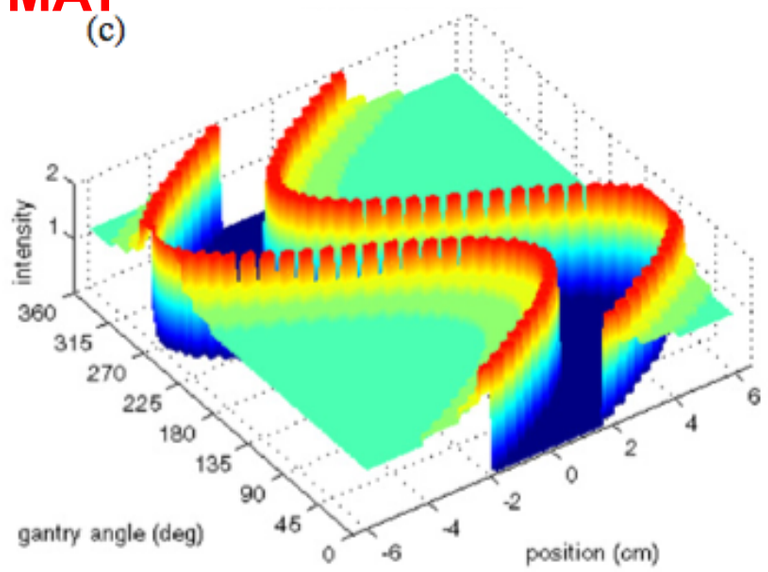


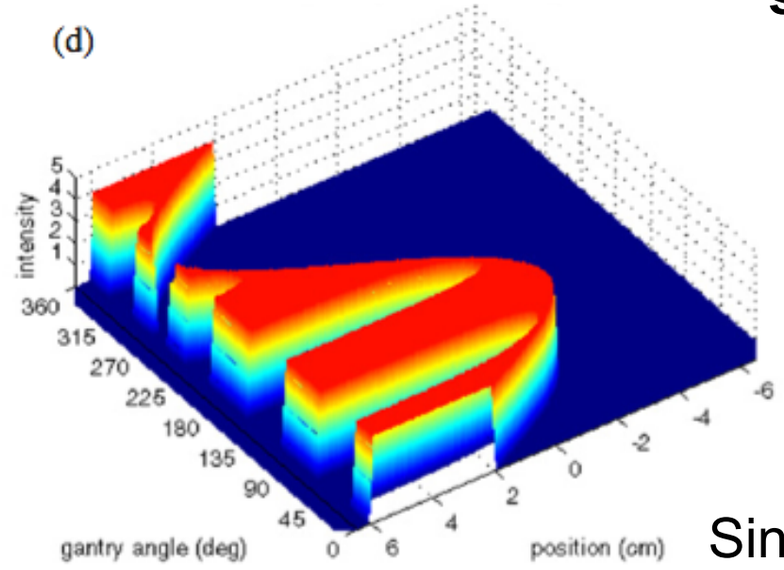
Possibility of exposure on both sides of the OAR in one aperture!

What is the precise definition of a VMAT technique?

“Extend discussion to more than one axial slice?”

RapidArc VMAT





Single Arc IMRT
By Bortfeld&Webb

“Integration over small gantry angle range (360°/51)”

Otto el al. in reply to Bortfeld and Webb

Theoretical comparisons IMRT/HT/VMAT

Moving toward a general conclusion?

IOP PUBLISHING PHYSICS IN MEDICINE AND BIOLOGY

Phys. Med. Biol. **54** (2009) 4345–4360 doi:10.1088/0031-9155/54/14/001

Some considerations concerning volume-modulated arc therapy: a stepping stone towards a general theory

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Published 23 June 2009
Online at stacks.iop.org/PMB/54/4345

Webb&McQuaid:

"No universal theory of VMAT is known in the sense that there is no theory that can predict precisely the performance of a VMAT delivery in terms of the free parameters available (variable gantry speed, variable fluence-delivery rate, set of MLC shapes, MLC orientation, number of arcs, coplanarity versus non-coplanarity, etc). This is in stark contrast to the situation with several other IMRT delivery techniques where such theoretical analyses are known. In this paper we do not provide such a theory; the material presented is a stepping stone on the path towards this."

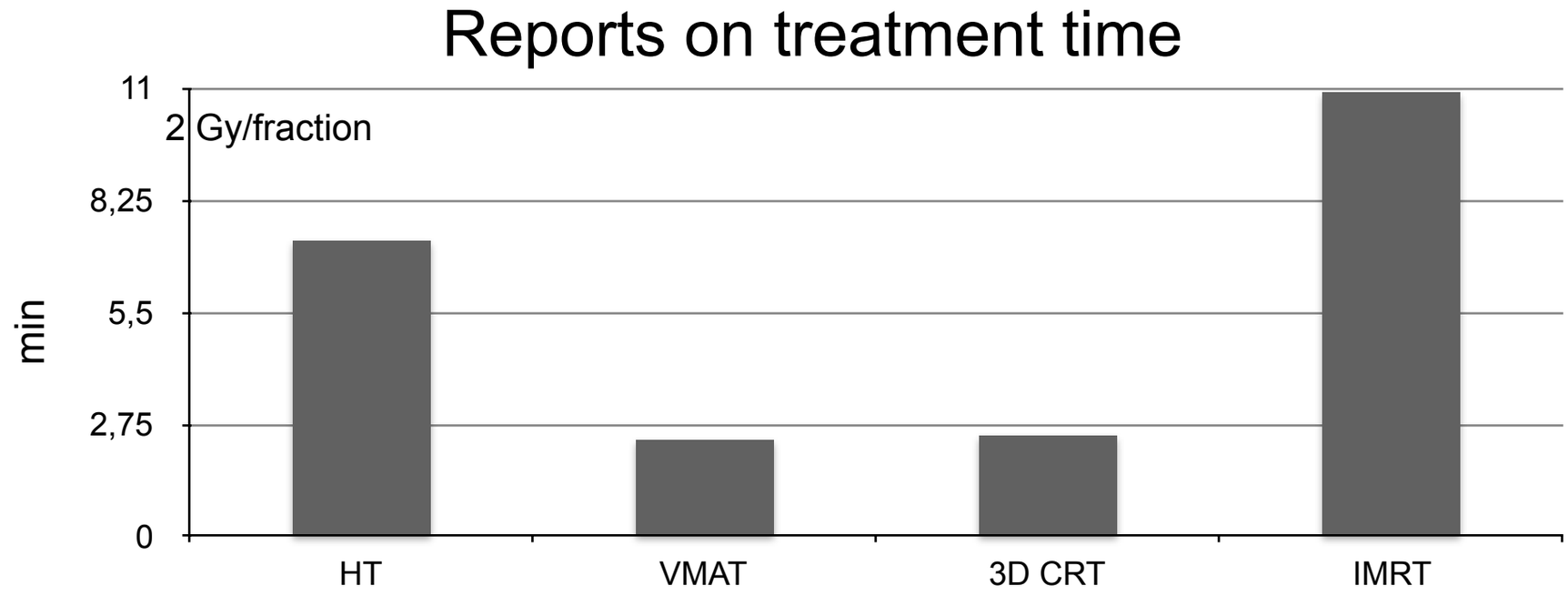
So…

In certain cases HT can be used as some kind of modulation “benchmark” for rotational therapy.

This does not mean it is clinically relevant to use it!

If not modulation, what could be another mode for comparison?

Treatment delivery times



Palma et al

Table 2
Representative treatment times with volumetric modulated arc therapy (VMAT) techniques and tomotherapy. Treatment times may not be directly comparable across studies due to variation in plan complexity. 3D-CRT: 3D-conformal radiotherapy; IMRT: intensity-modulated radiation therapy; * excludes time for patient setup or imaging.

Treatment site	Authors	Dose per fraction	Modalities reported	Treatment times* in minutes (mean or range, unless specified)
Conventionally fractionated treatments				
Several sites	Bauman et al.[21]	Various	Tomotherapy	6 [median]
	Bijdekerke et al.[18]	Various	Tomotherapy	11
	Sterzing et al.[58]	Various	Tomotherapy	10.7
Several sites – Pediatric	Fogliata et al.[36]	Various	Tomotherapy	4.9
			RapidArc	2.1
Lung	Bedford et al.[34]	Not specified	VMAT (Elekta)	1.7
			3D-CRT	2.5
Nasopharynx	Lee et al.[24]	1.8 Gy	Tomotherapy	8
			IMRT	14
Naso-, oro-, hypopharynx	Verbakel et al.[31]	2 Gy	RapidArc	1.3–3
			IMRT	8–12
Prostate	Cozzarini et al.[59]	Up to 2.65 Gy	Tomotherapy	4–6
	Shaffer et al.[60]	Up to 2.4 Gy	VMAT (RapidArc predecessor)	3.7
			IMRT	9.6
Hypofractionated stereotactic treatments				
Lung	Verbakel et al.[33]	7.5–18 Gy	RapidArc	4.5–11
			3D-CRT	11–13
	Hodge et al.[61]	12 Gy	Tomotherapy	22
Vestibular Schwannomas	Lagerwaard et al.[62]	12.5 Gy	RapidArc	4–5
Liver and lung	Subgroup of Sterzing et al.[58]	Not specified	Tomotherapy	46
Liver, lung and spine	Fuss et al.[63]	5–20 Gy	Tomotherapy (helical and serial)	22–48

The vocabulary of “Treatment Times”

Different “Times”:

- Treatment slots: reserved time on the machine, time from the patient entering the bunker, until leaving the bunker

- Total treatment time: time from the first MV photon hitting the patient until the last photon, includes gantry rotation without beam

- Beam-on time: time the therapeutic MV beam is actually on

- Dose accumulation pattern: the way a tissue volume is accumulating dose from primary beam during treatment

Reports on treatment times

Verbakel et al. :

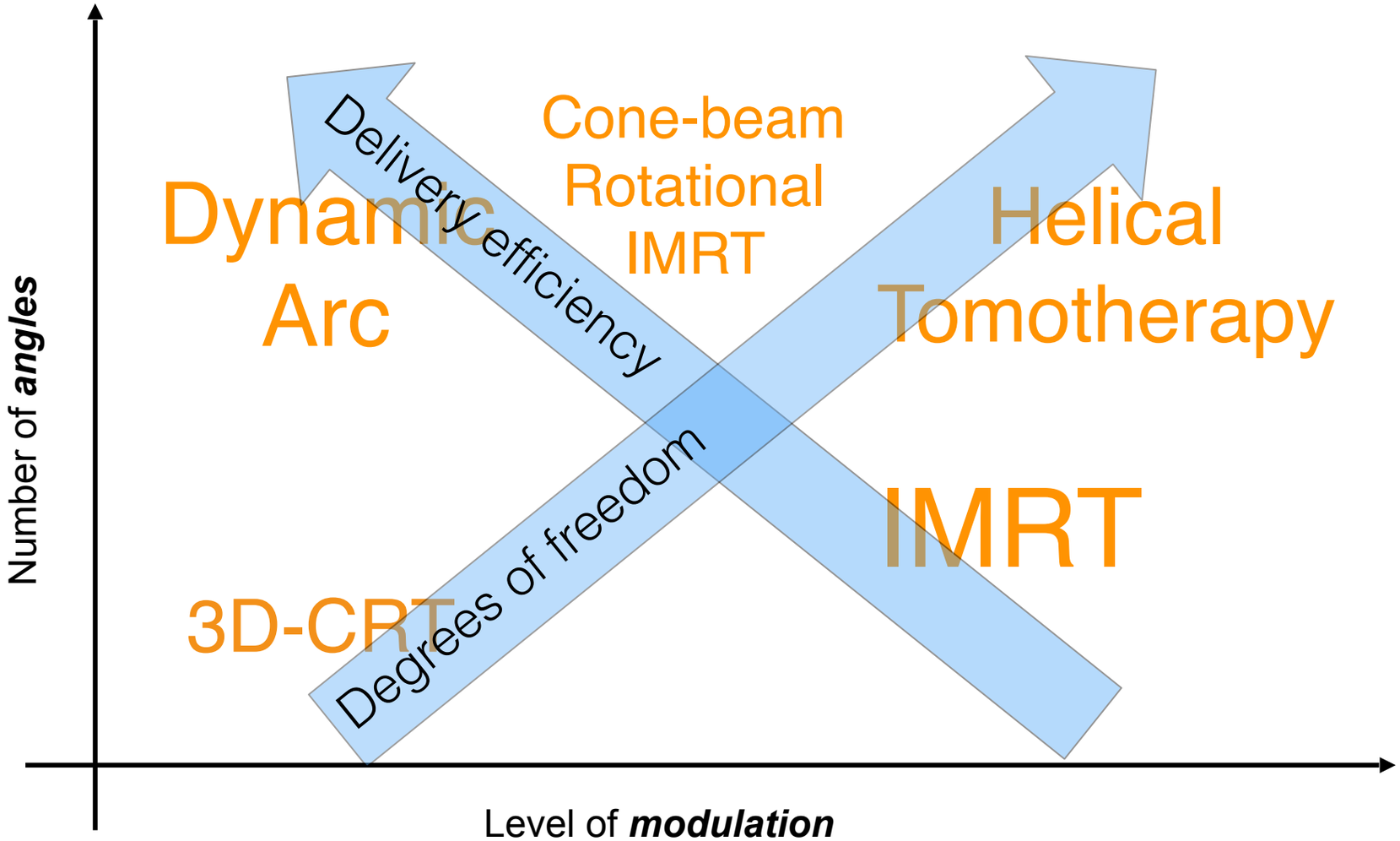
"Delivery times for standard IMRT using sliding window are much longer than for RapidArc for reasons which include the fact that

(1) no radiation is delivered during gantry rotation between fields,

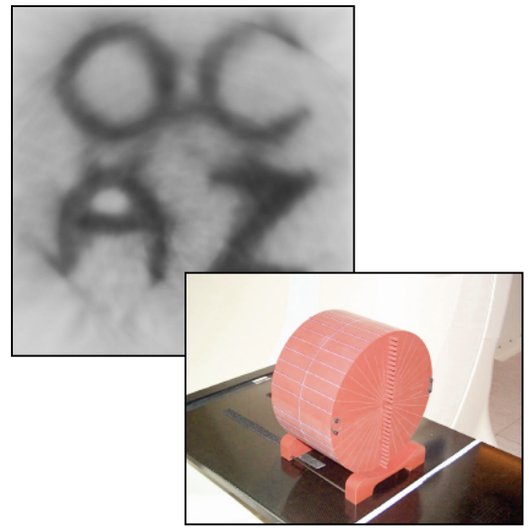
(2) multiple carriage groups are needed for large PTVs and

(3) time required for each field as complex fluence distributions require small leaf openings."

Treatment times : the trade-off



Axial slice



Tomotherapy

Verellen et al.

"High number of beam angles with moderate modulation seems to be more efficient in terms of delivery time on the current generation of treatment units"

Treatment times

➔ Conventional 3D CRT treatments usually take no more than a few minutes

- Low number of treatment beams

➔ IMRT delivery times range usually from 3 to 15 minutes BUT depending on:

- Machine type
- Delivery method (SMLC, DMLC, IMAT, VMAT, …)
- Amount of IMRT beams/segments
- Tumor complexity (Volume, surrounding OAR, …)
- Fraction size (hypofractionation schemes)

treatment times can increase to as long as 20 to 40 minutes

➔ Why are short treatment times preferable?

➔ Can Rotational IMRT techniques bring down the treatment times?

Treatment delivery time

Impact of treatment duration on:

➔ Hospital logistics, Economical aspect

➔ IGRT and intra-fraction motion

➔ Radiobiological efficiency loss

➔ ~~Secondary Cancers~~

cfr. Frank/Andrea

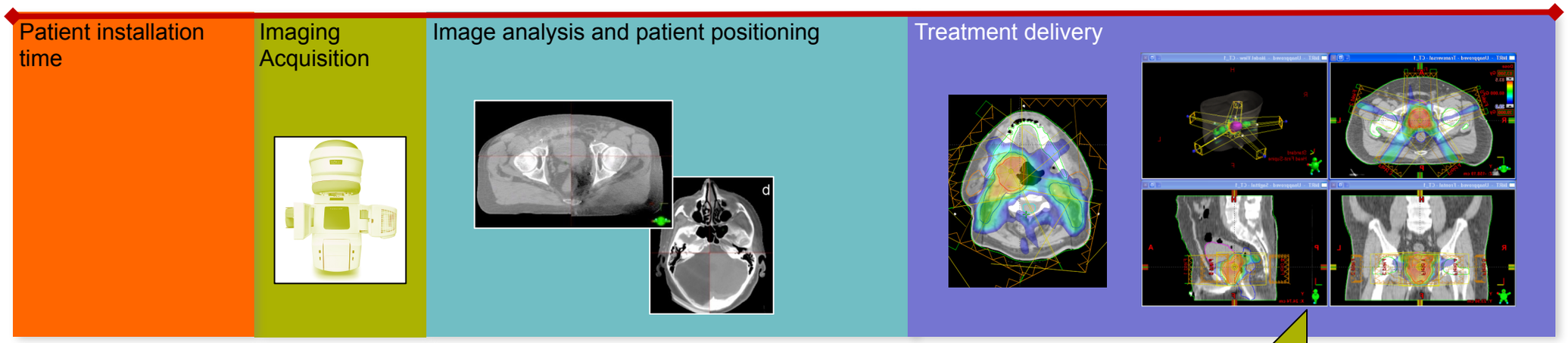
Treatment times : Delivery efficiency

Cozzi et al. :

"Faster treatments could have a clinical impact on single patients in terms of comfort on couch, immobility and minimisation of internal organ's displacement (e.g. bladder or rectum filling changes over time). This could increase the daily treatment quality and allows also more time for imaging procedures within standard time slots. In addition, faster treatments have an impact on the system throughput allowing the possibility to treat more patients per day, and to eventually reduce waiting list for selected groups of patients."

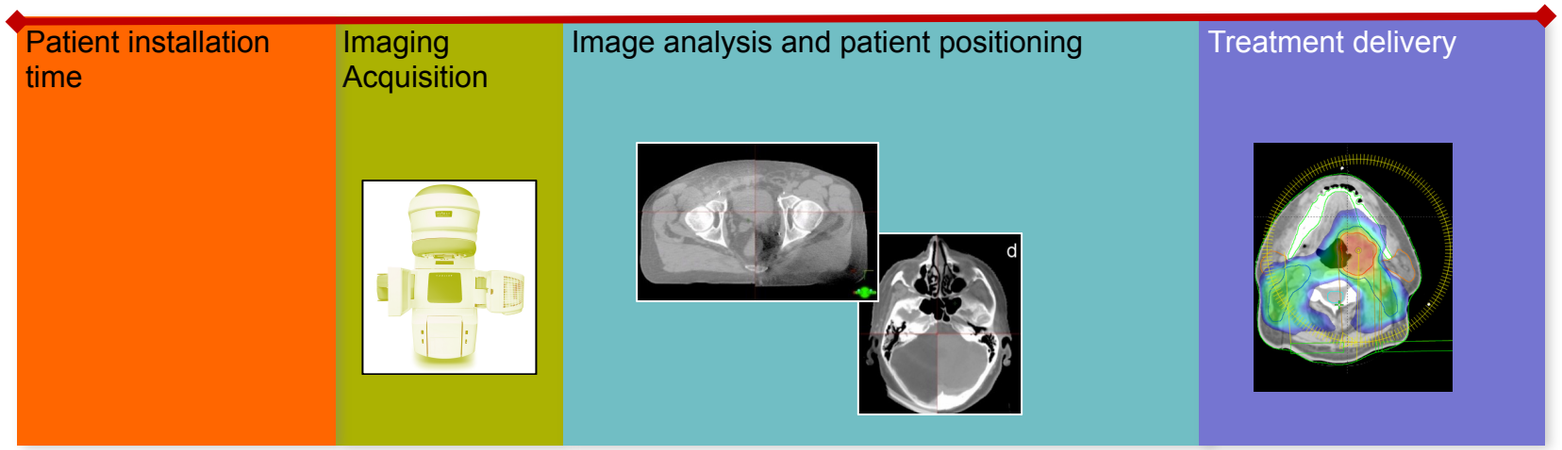
Delivery efficiency : treatment times and hospital logistics

Static Gantry IMRT workflow



20% reduction

VMAT/RA workflow



IMPORTANT:
"More efficient dose delivery **is NOT** more time for imaging and adaptation!"

Treatment delivery time

Impact of treatment duration on:

➔ Hospital logistics, Economical aspect

➔ IGRT and intra-fraction motion

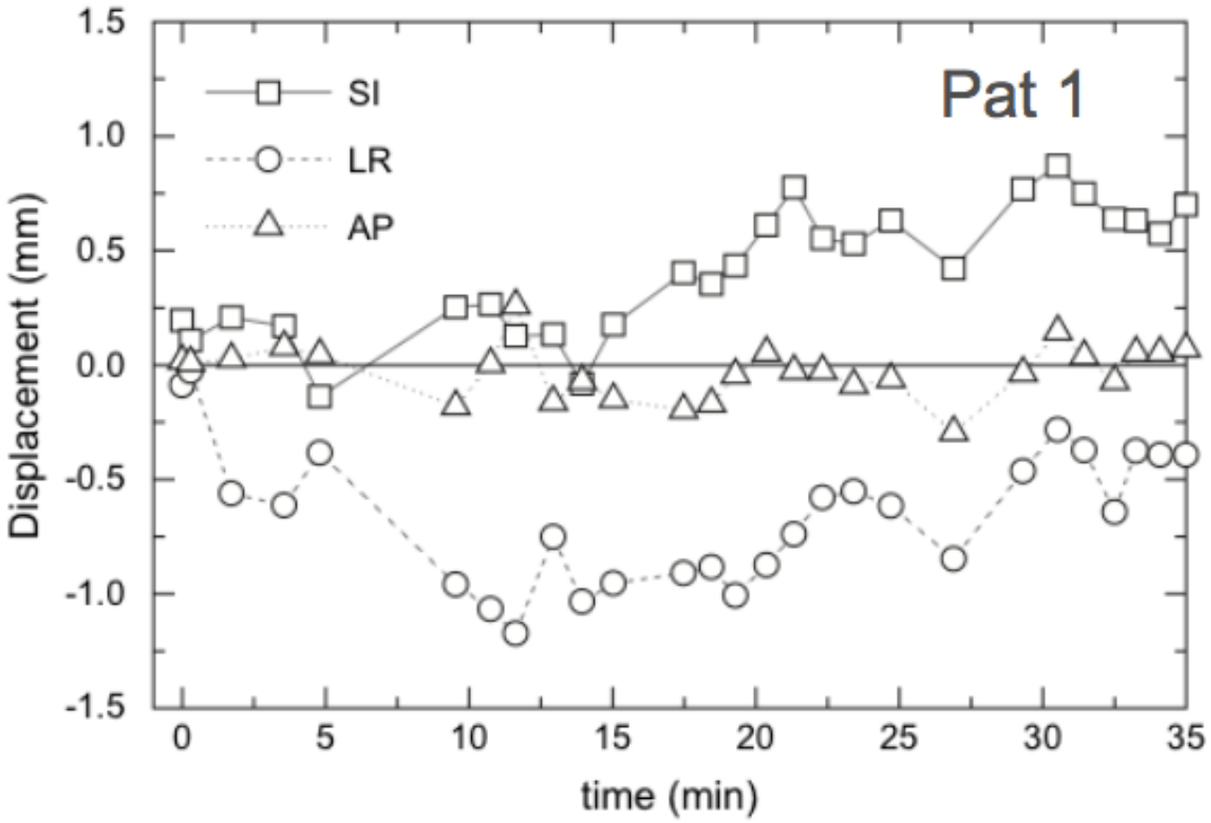
➔ Radiobiological efficiency loss

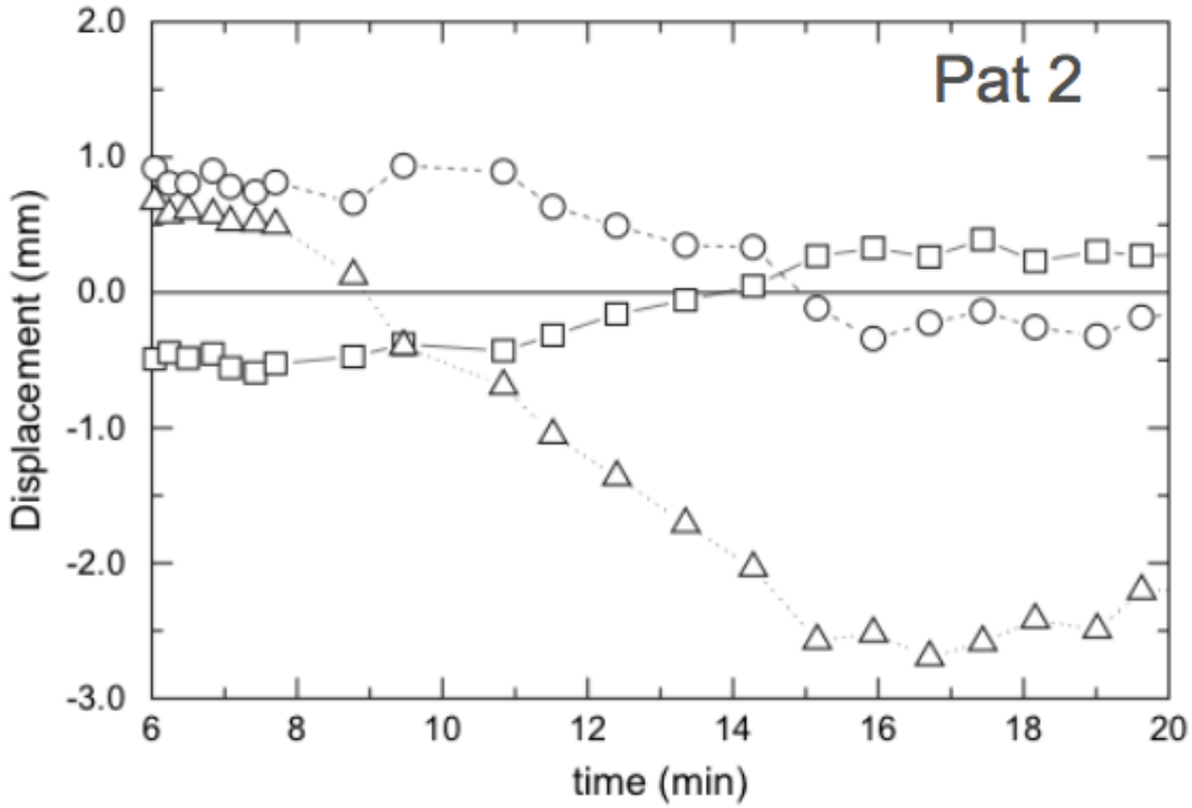
➔ ~~Secondary Cancers~~

cfr. Frank/Andrea

Treatment time : intrafractional movement

Extracranial spine patients, immobilized in vacuum bag,
Position recorded with stereoscopic X-ray system:





Conclusions: Despite the applied immobilization devices, patients drift away from their initial position during a treatment fraction. These drifts are in general small if compared with conventional treatment margins, but will **significantly contribute to the margin for high-precision radiation treatments with treatment times of 15 min or longer.**

Hoogeman et al

Treatment delivery times : susceptibility to intra-fraction motion

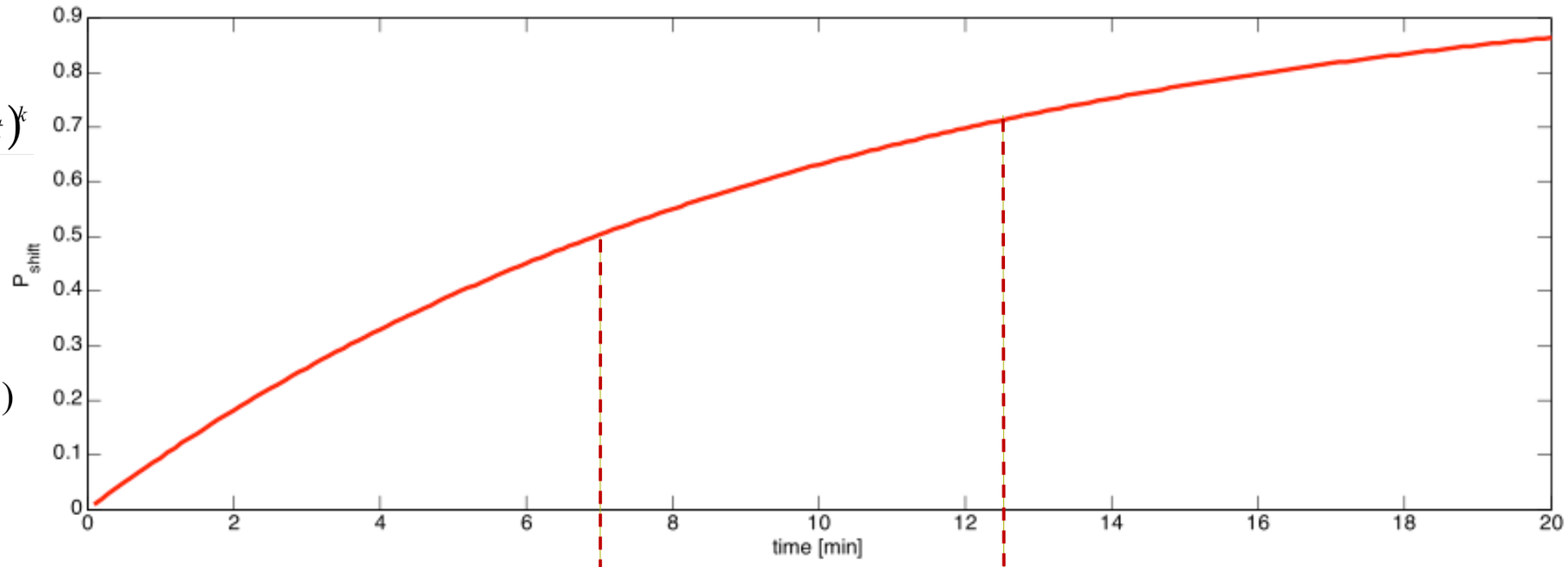
Geometric instability in the pelvic region (prostate, rectal cancer treatment)

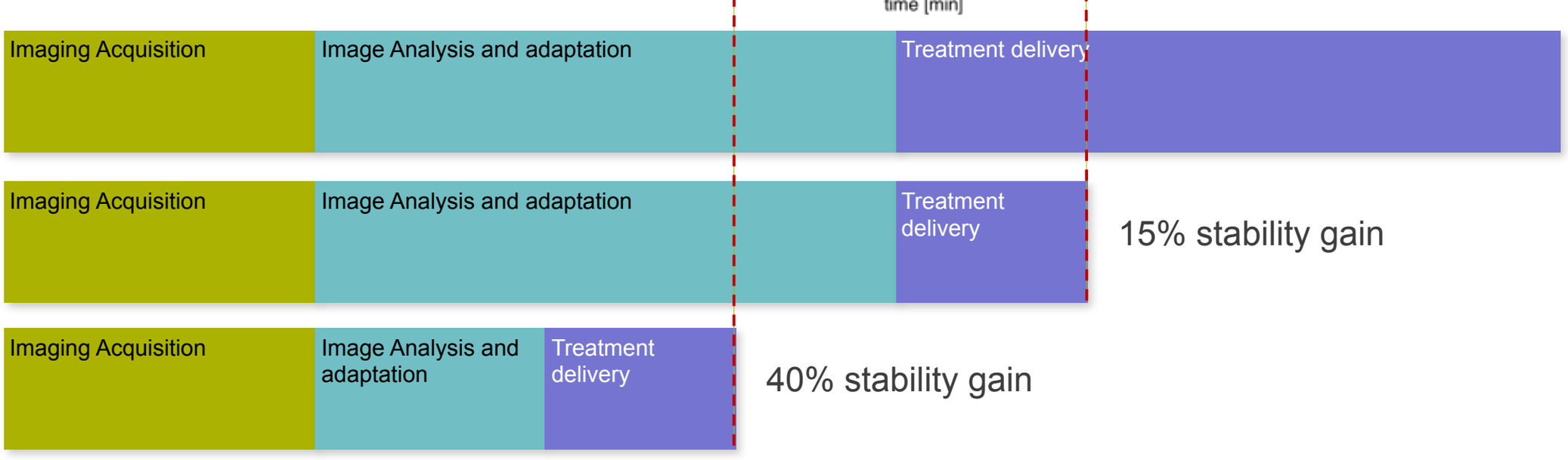
Poisson Model:

$$f(k,\lambda t) = \frac{e^{-\lambda t}(\lambda t)^k}{k!}$$

$$\lambda = 0.1/\min^{*}$$

$$P_{shift} = 1 - f(0,\lambda t)$$





Ghilezan et al.

*Ghilezan et al. IJROBP (62) 406-417, 2005: Probability of prostate shift > 3mm with filled rectum is 10% in 1min

Treatment delivery time

Impact of treatment duration on:

➔ Hospital logistics, Economical aspect

➔ IGRT and intra-fraction motion

➔ Radiobiological efficiency loss

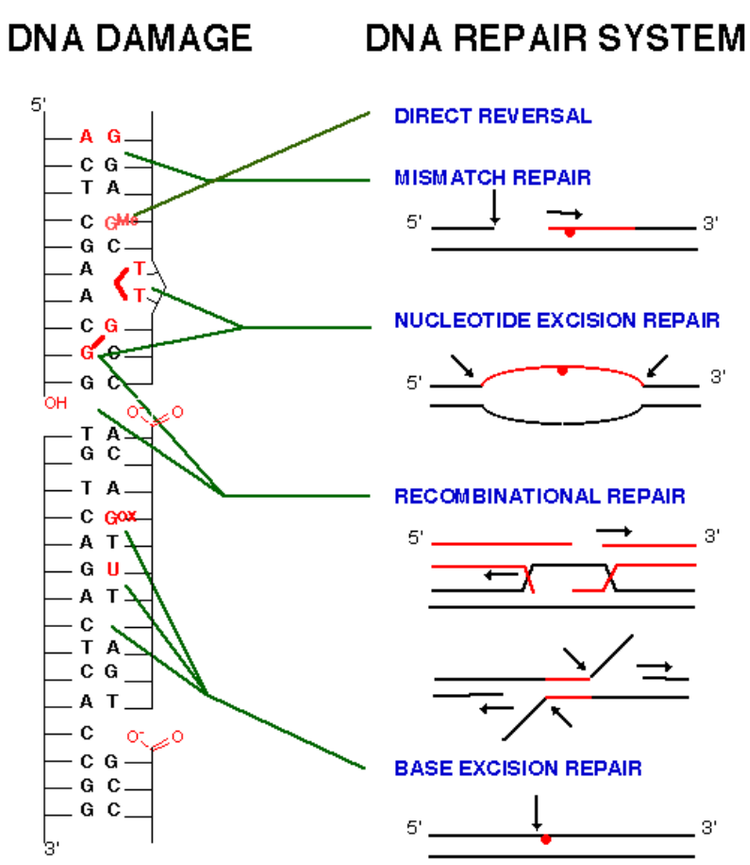
➔ ~~Secondary Cancers~~

cfr. Frank/Andrea

Biological efficiency loss

Verbakel et al. :

"… a reduction in fraction delivery time—from 17 min to a minute —may increase the effectiveness of a given dose by up to 20%, depending on the tumour type."



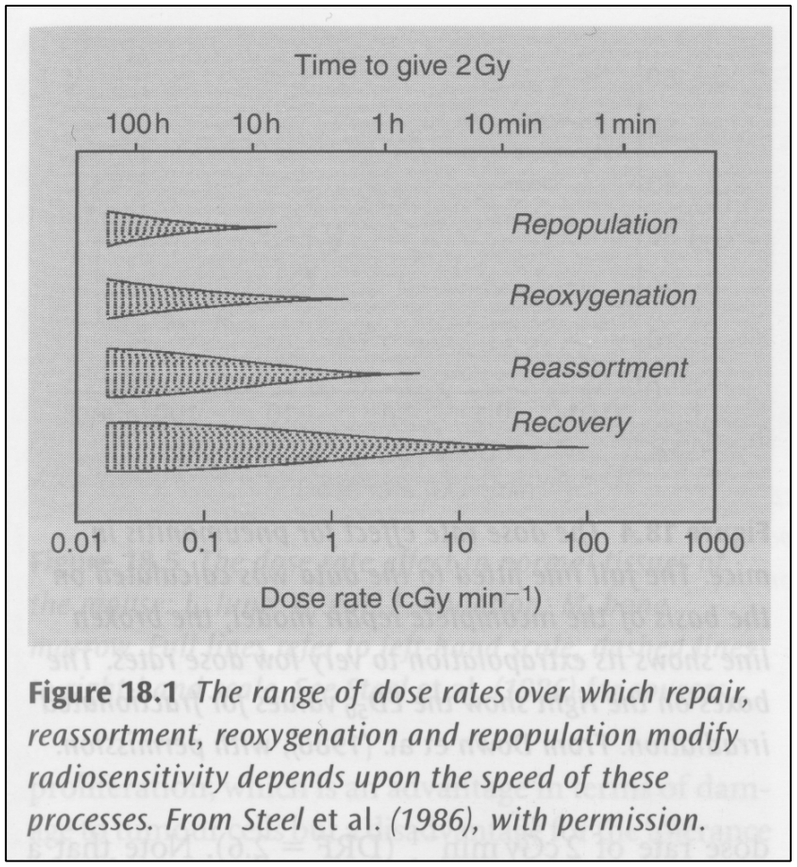


Figure 18.1 *The range of dose rates over which repair, reassortment, reoxygenation and repopulation modify radiosensitivity depends upon the speed of these processes. From Steel* et al. *(1986), with permission.*

Verbakel et al., Steel et al.

Biological efficiency loss

Different “Times”:

- Treatment slots: time from the patient entering the bunker, until leaving the bunker
- Total treatment time: time from the first MV photon hitting the patient until the last photon, includes gantry rotation without beam
- Beam-on time: time the beam is actually on

- Dose accumulation pattern: the way a tissue volume is accumulating dose from primary beam during treatment

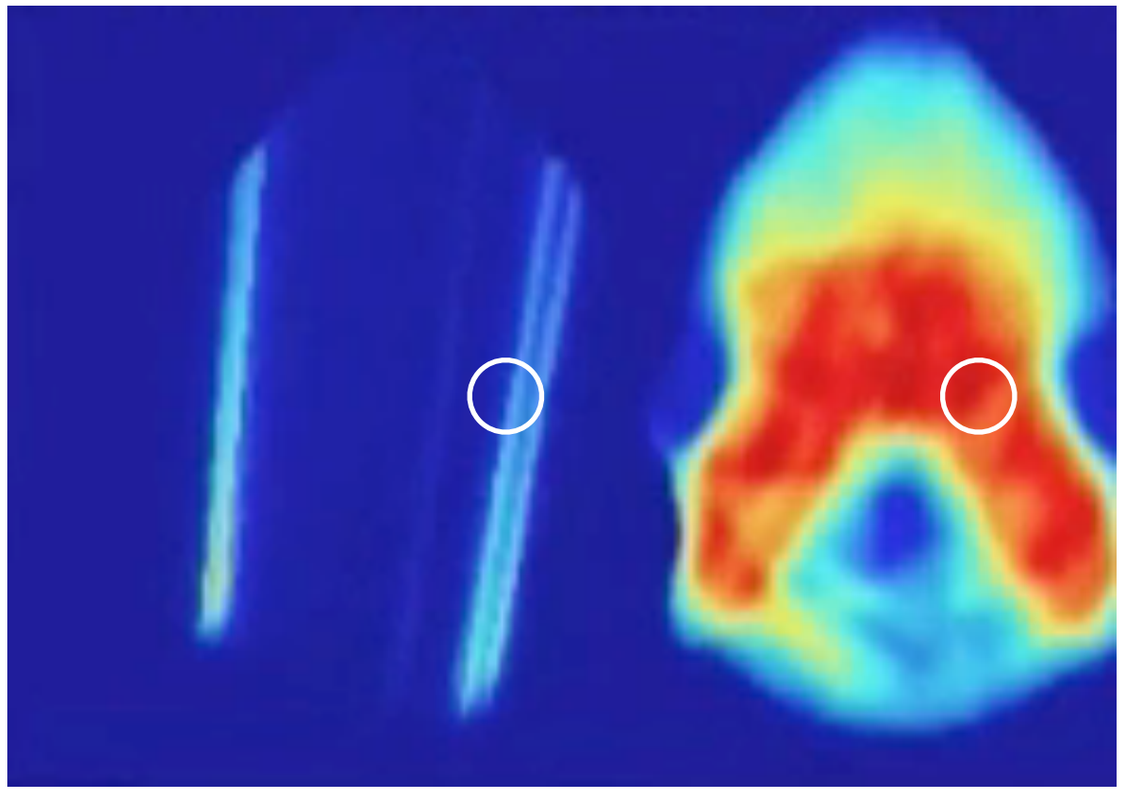
Biological efficiency loss and dose accumulation pattern

Shaikh et al. :

> *"Several studies have pointed out that some of the IMRT 'treatment times' are considerably longer than the average 2–5 min for a conventional treatment, which raise concerns about the **loss of biological effectiveness**. It is well established that protraction of dose over a **longer duration reduces cell kill** because prolonged treatments provide cells with an **opportunity to repair DNA damage**.*
> *Modeling studies suggest that a **significant loss of biological effectiveness** can be expected if the fraction delivery time is **longer than 15–30 min**."*

Cell kill ⟷ Dose accumulation pattern

Dose Accumulation pattern VMAT

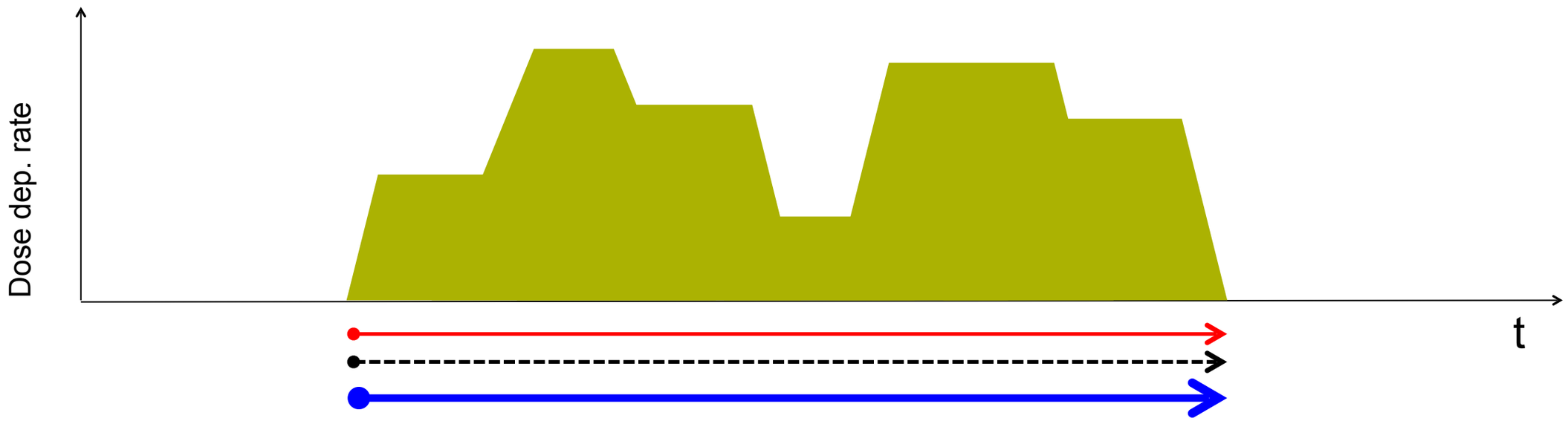


Target subvolume

Beam on

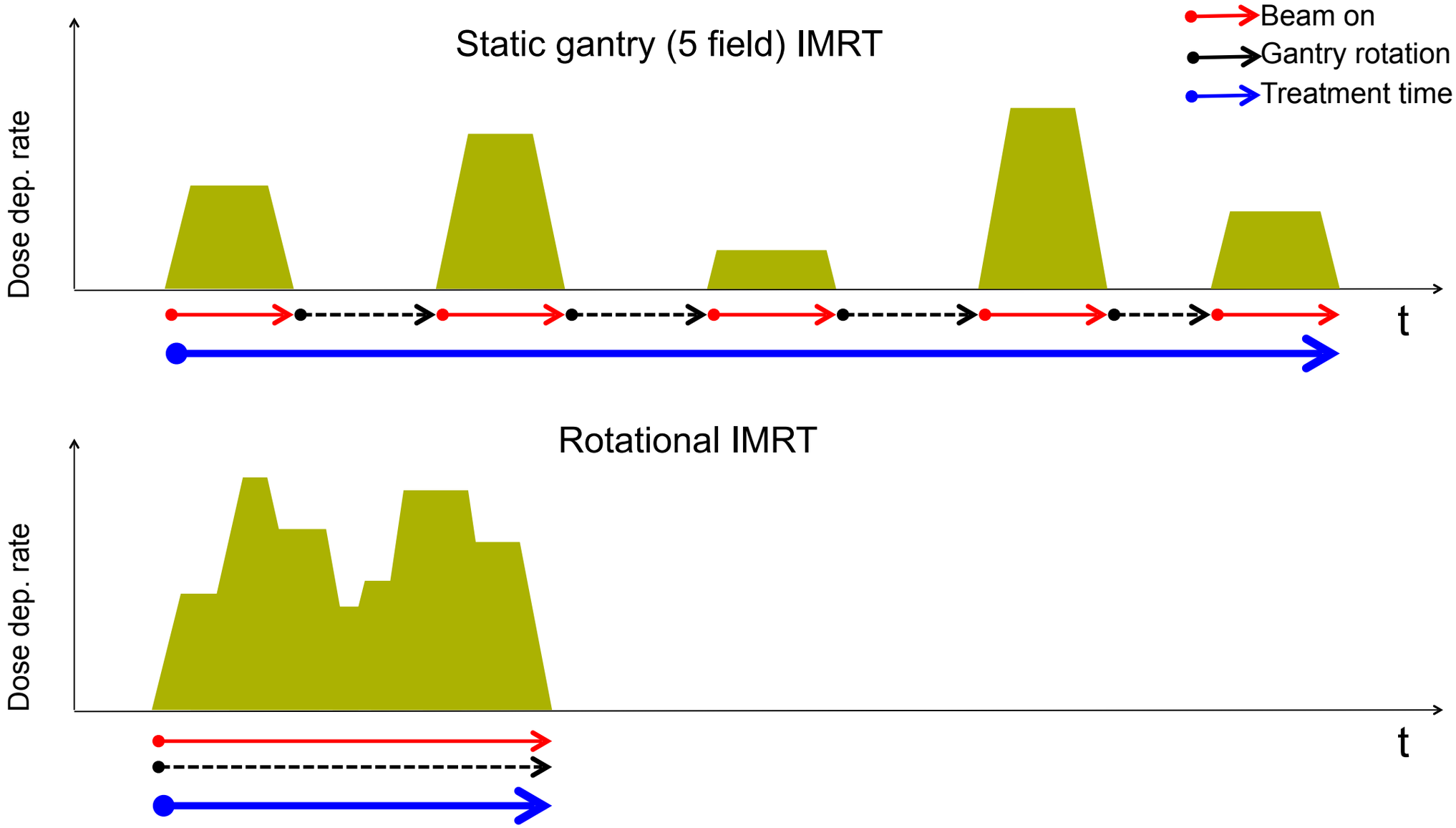
Gantry rotation

Treatment time



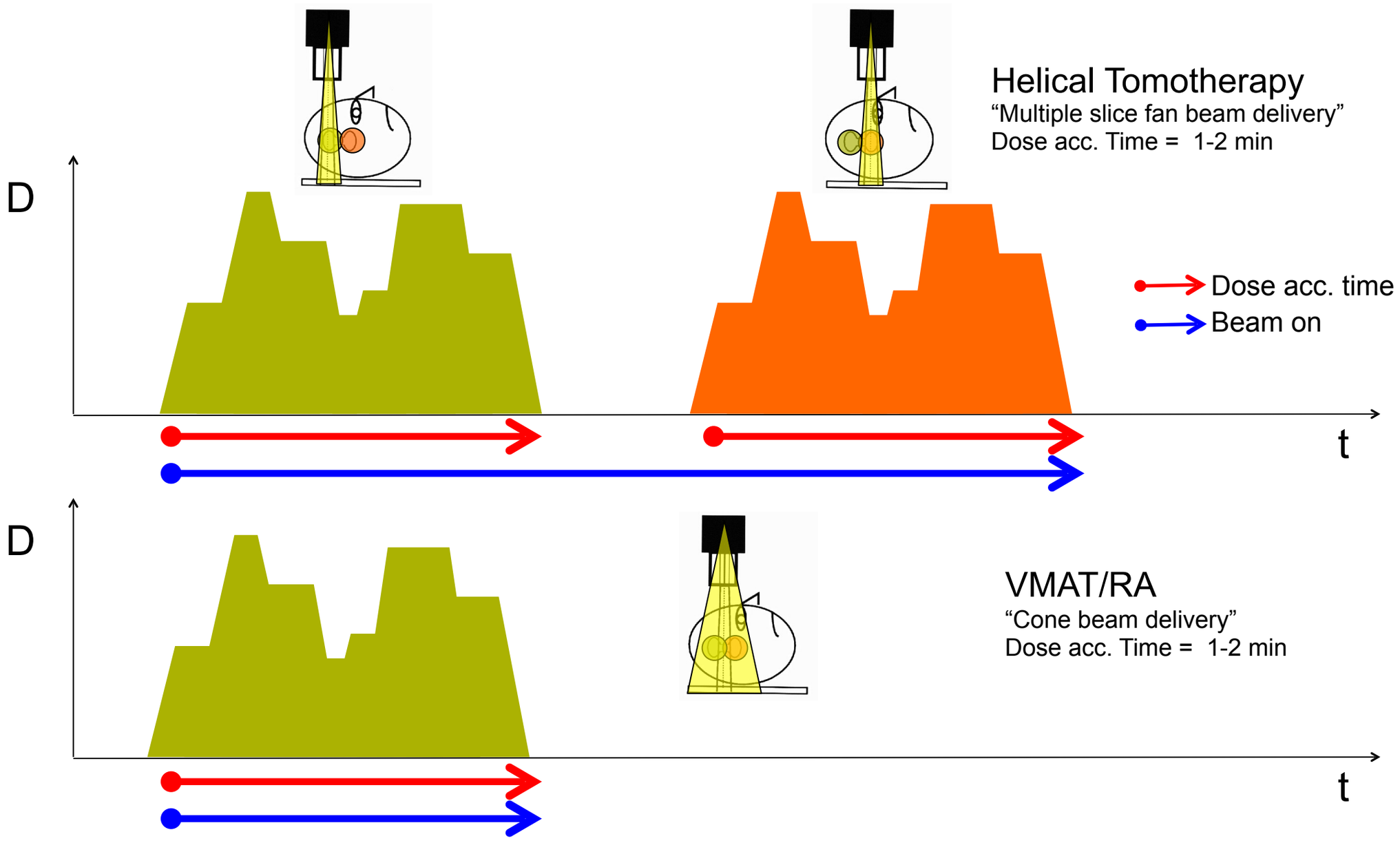
Dose Accumulation patterns

Fraction dose deposition to a target subvolume:

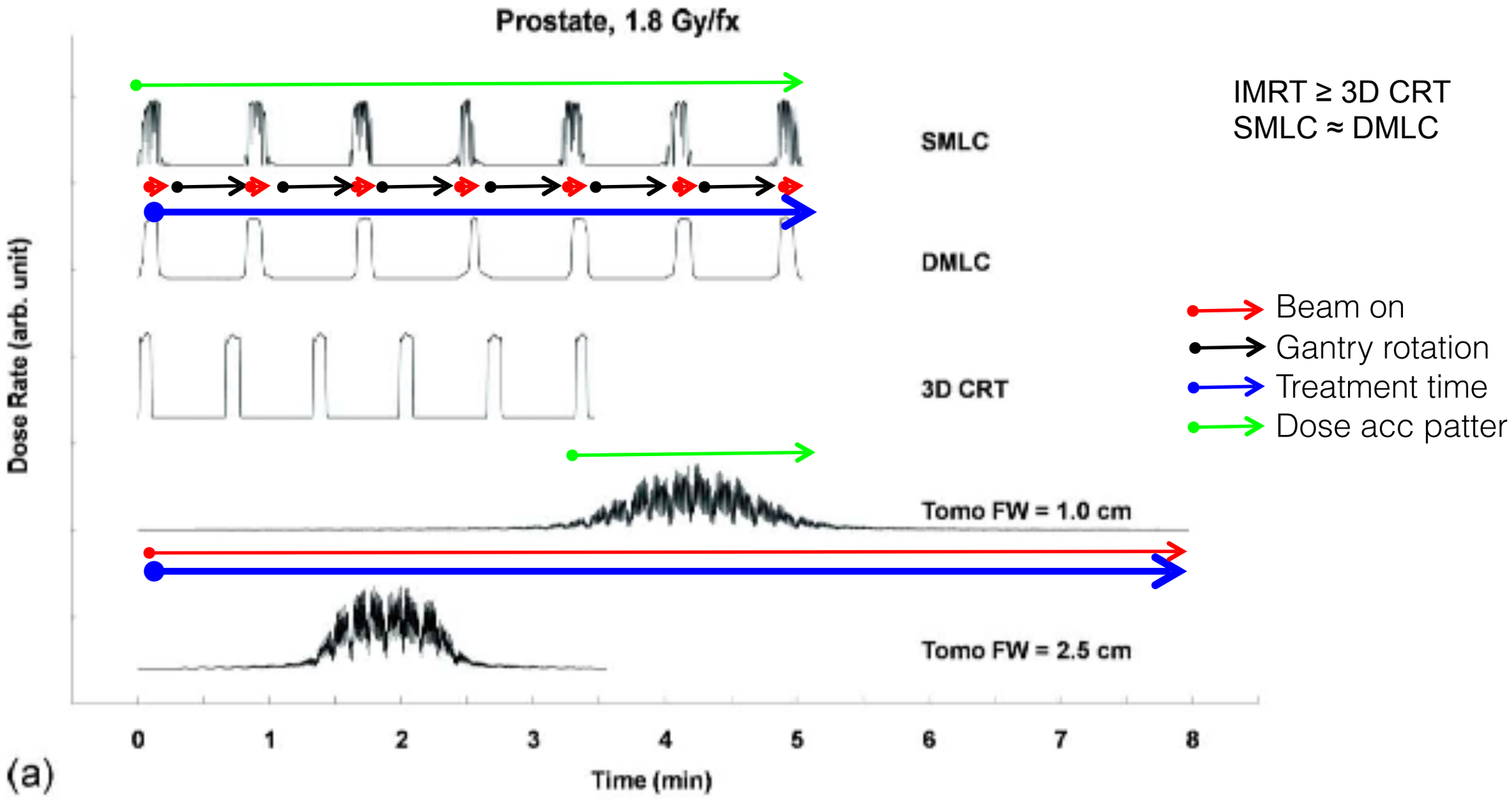


Dose Accumulation patterns

Fraction dose deposition to one target subvolume:



Ionization chamber measurement of the dose accumulation in one single point/subvolume during treatment delivery:

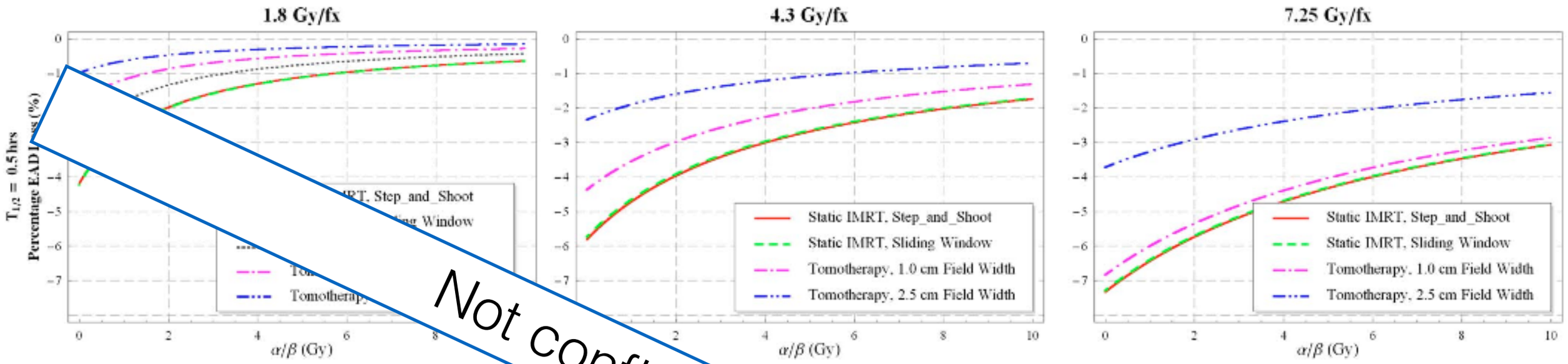


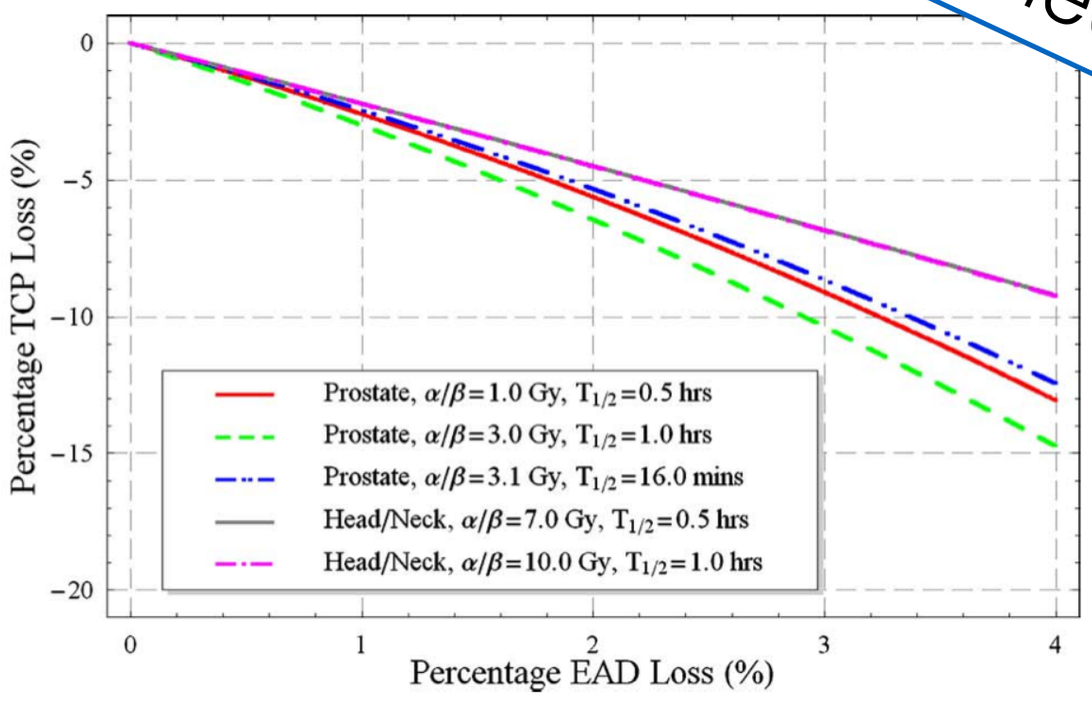
IMRT ≥ 3D CRT
SMLC ≈ DMLC

Beam on
Gantry rotation
Treatment time
Dose acc patter

Shaikh et al. 2010

Biological model results





Not confirmed by clinical data

SMLC and DMLC IMRT delivery, for both
prost neck, the expected additional loss in
BED is abo ed to 3D CRT, which
corresponds to a –3% reduction in TCP.
For tomotherapy, the p ss is smaller in
comparison to 3D CRT; hen expect a TCP
increase of the order of 2%–3%. T ned
differences are due to the dose accumu

Shaikh et al. 2010

Shaikh et al. :

“Our analysis finds that helical tomotherapy treatments are generally superior to SMLC and DMLC treatment plans in this aspect due to the relatively rapid dose accumulation seen by a given target volume element.”

“… Newer rotational delivery techniques such as VMAT, which are capable of total treatment delivery times shorter than any of the techniques studied here, should be expected to result in similar biological effects to those from helical tomotherapy as presented here.”

“If the relationships between treatment time and biological effectiveness were accurately known for clinical situations, one could modify the prescription dose to compensate. Unfortunately, these relationships are not completely understood and depend on factors that are not accurately known (i.e., α / β ratios and repair half-times, etc.)

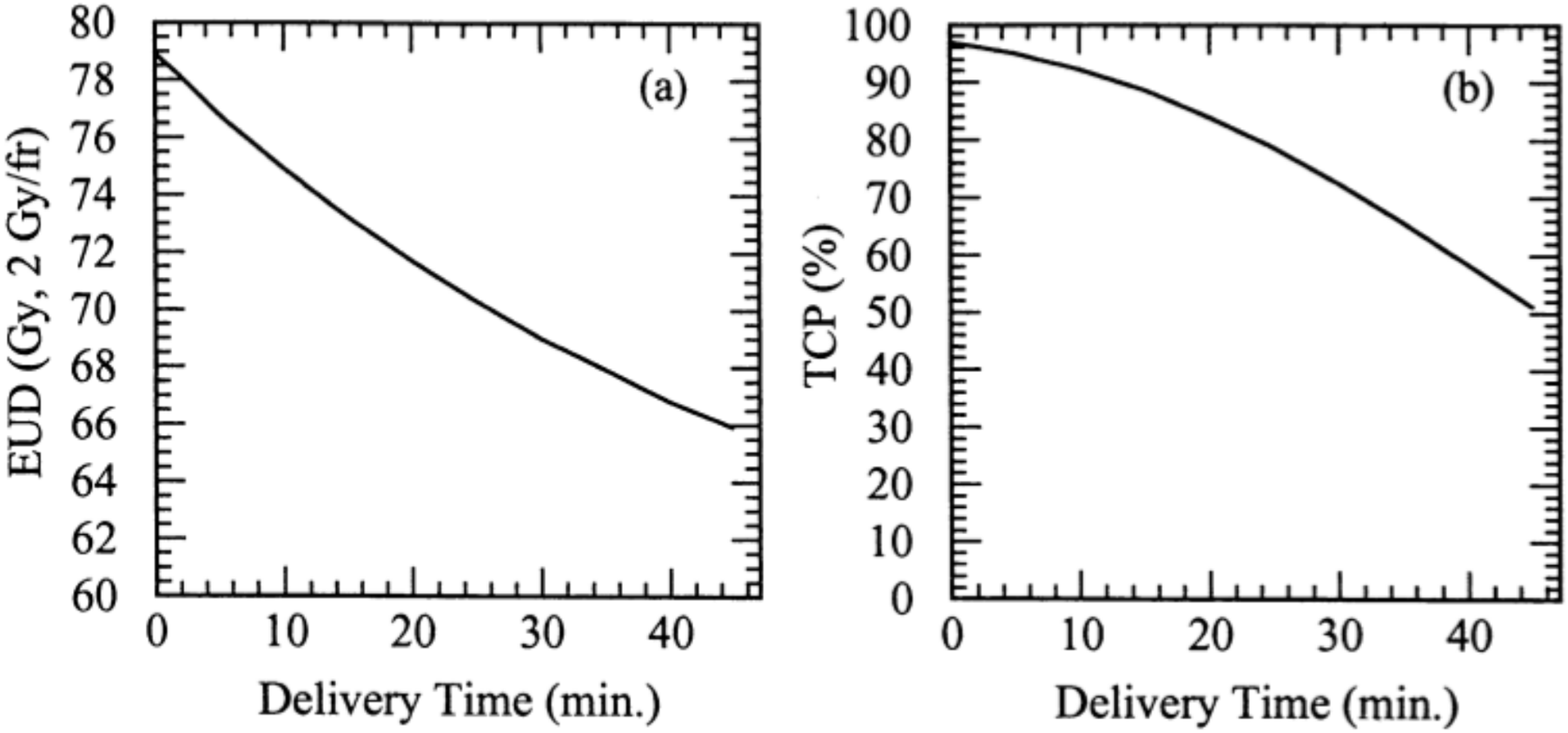


Fig. 5. (a) Equivalent uniform dose (EUD) and (b) tumor control probability (TCP) for an intermediate-risk patient group as a function of IMRT fraction delivery time for prostate cancer. The prescription dose is 81 Gy in 1.8 Gy fractions. Except where explicitly noted otherwise, the following LQ parameters were used in this study: $\alpha = 0.15\ \mathrm{Gy}^{-1}$, $\alpha/\beta = 3.1$ Gy, $T_r = 16$ min, and clonogen number $K = 3.0 \times 10^6$ (18).

Wang et al

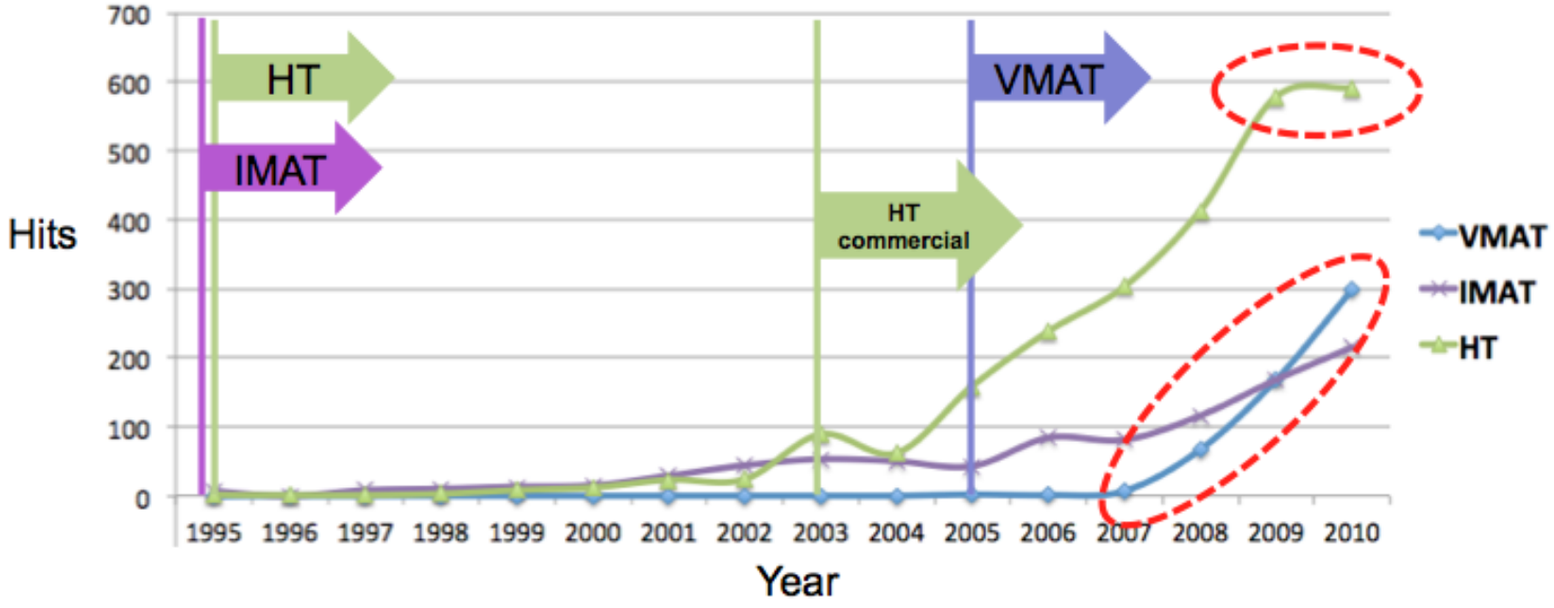
Biological efficiency loss and dose accumulation pattern

Shaikh et al. :

"Our analysis finds that helical **tomotherapy treatments are generally superior to SMLC and DMLC** treatment plans in this aspect due to the relatively **rapid dose accumulation** seen by a given target volume element."

"… Newer rotational delivery techniques such as **VMAT**, which are capable of total treatment delivery times **shorter than any of the techniques studied here**, should be expected to result in **similar biological effects to those from helical tomotherapy** as presented here."

"If the **relationships between treatment time and biological effectiveness** were accurately known for clinical situations, one could modify the prescription dose to compensate. Unfortunately, these relationships **are not completely understood and depend on factors that are not accurately known** (i.e., α / β ratios and repair half-times, etc.)



"Yes, commercial interest of some companies have boosted rotational therapy especially the HT, VMAT, RapidArc competition."

-For technical innovation on equipment level companies are an enabling partner having the required resources for engineering and manufacturing.

-Important is that we, radiation therapy professionals and users of this technology, remain cautious and critical toward newly introduced equipment and techniques. This way the commercial drive is controlled/restrained with a feedback loop and can be used to our and our patients advantage.

Should all IMRT be VMAT? or HT? or static IMRT?

- VMAT produces highly conformal dose distributions … like the other IMRT and HT. However, general superiority over other solutions has not been proven.
- After a period of extreme discussion on all fronts the dust has settled down and every department should make a choice according to needs, resources and indications.
- Reduction of treatment time may be "strongest" argument in making a difference between VMAT and the other solutions: more economical, intra-fraction motion, patient comfort, hypofractionation, … and if it would come with reduced biological efficiency loss that's even better.
- Both HT and VMAT have been upgraded and optimized since the era of the big discussion...

Examples

- HT
    - Dynamic jaws, limiting CC gradient
    - Speed and reliability updates
    - No biological optimization
    - ask you to learn to speak “tomo”
- VMAT
    - faster MLCs (6cm/s), probably no more need for ultra-small leaves
    - Higher doserates
    - In-treatment verification possible
    - TPS are getting better/faster/have biological optimization

Final conclusions

- Rotational therapy has gone mainstream.
- This has not made it the answer to life the universe and everything
- This has not made it any easier to implement, plan or QA
- In hospital economics, this time and effort should also be incorporated
- In planning:
  - Know your machine's limitations
  - Know and understand your optimizer and dose calculation
  - Don't treat it like a coffee machine
- Don't be afraid, be vigilant

Highly conformal techniques in early stage lung cancer: indications, techniques, normal tissue constraints, results

Andrea Riccardo Filippi, MD

Department of Oncology

University of Torino, Italy

andreariccardo.filippi@unito.it

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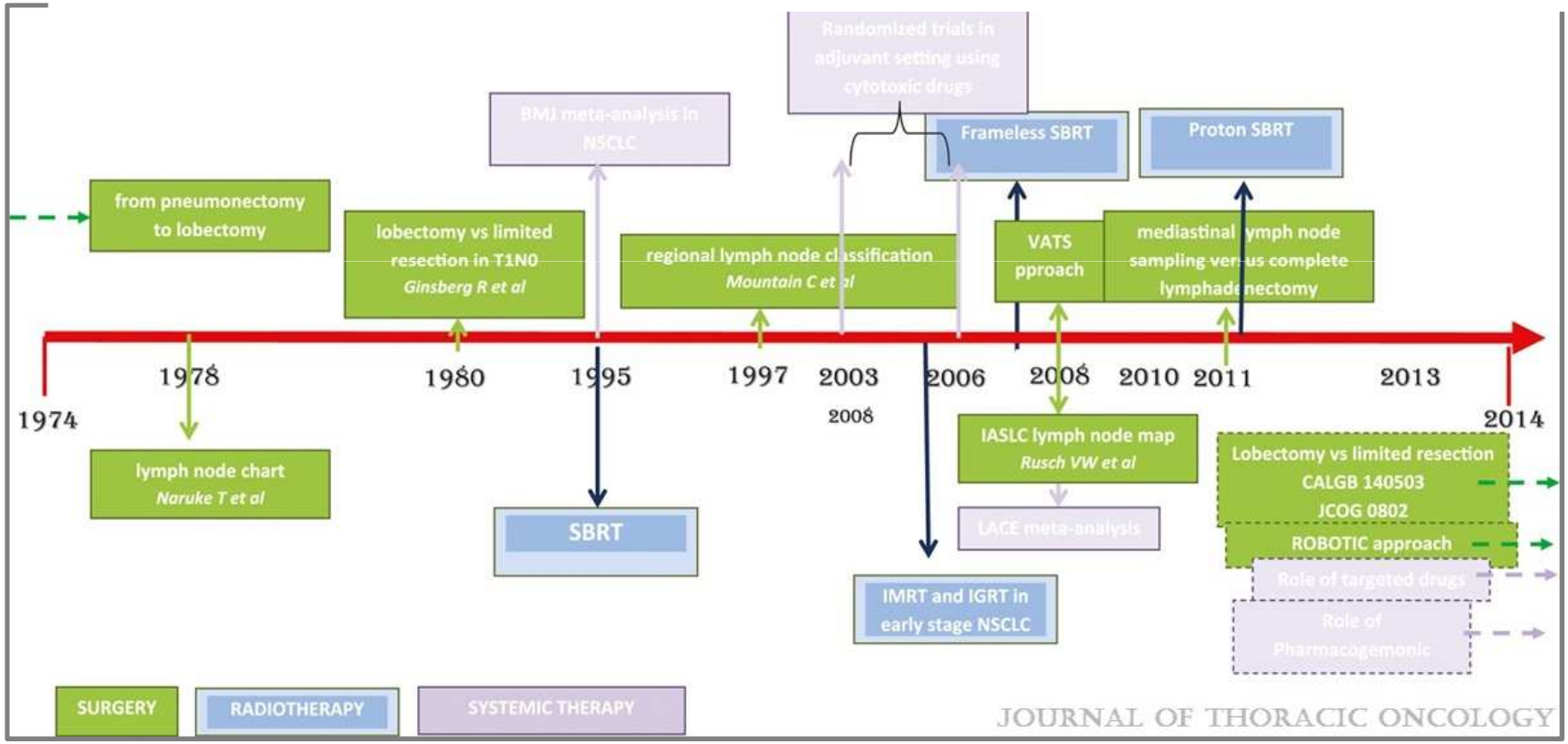
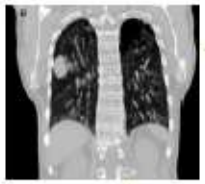
Early-Stage Lung Cancer: 40s Anniversary

Novello, Silvia; Asamura, Hisao; Bazan, Jose; Carbone, David; Goldstraw, Peter; Grunenwald, Dominique; Ricardi, Umberto; Vansteenkiste, Johan

Journal of Thoracic Oncology. 9(10):1434-1442, October 2014

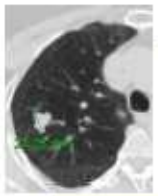


Features of Lung SABR



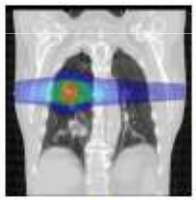
Accounting for Motion

- 4D Planning



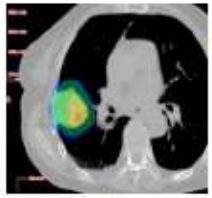
Small tumour volumes

- Small margins



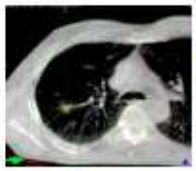
Many Beam Directions

- 7-11 Beams / Arc Therapy



Steep dose gradients

- Inhomogeneous target dose



Accurate Targeting

- CBCT pre-RT

High dose per fraction

- Short total treatment duration

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SBRT or SABR

tə'meɪtoʊ

tə'mɑːtoʊ

From DA Palma, ASTRO 2014

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SABR for peripheral lung tumors

- ESMO Clinical Practice Guidelines 2013: SABR is the non surgical treatment of choice (dose to a biologically equivalent tumor dose $\geq$ 100 Gy)

- NCCN guidelines (version 3.2014): non surgical treatment of choice

SABR for Stage I NSCLC: phase II studies

DISCOVERY MEDICINE

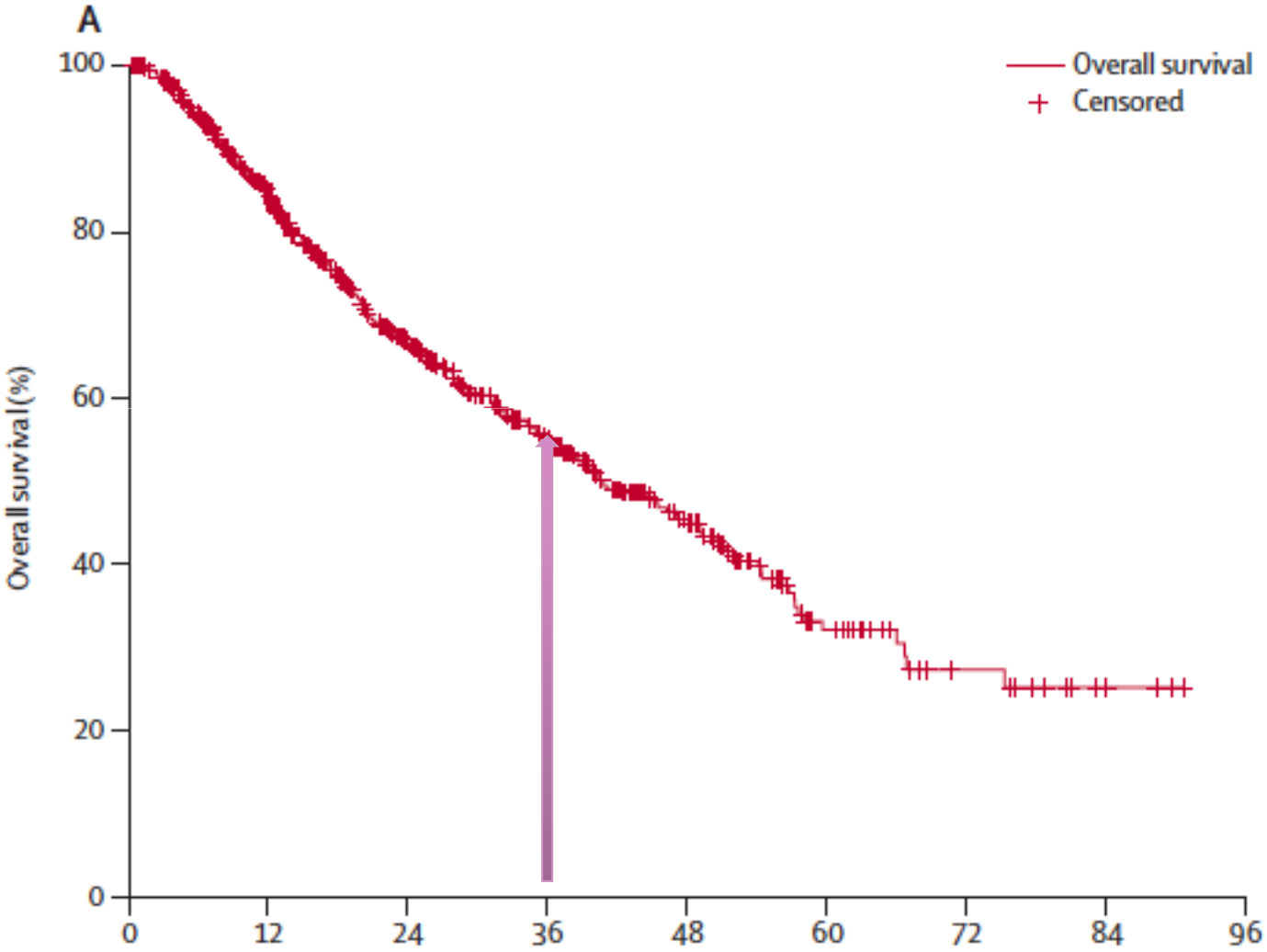
Table 1. Summary of Results of Recently Reported Prospective Trials of SBRT for Stage I NSCLC

Author (Year)	Type/Stage	No. of Patients	Dose	Median Follow-up	Outcomes
Fakiris (Fakiris et al., 2009)	Phase II/Medically inoperable T1-2N0M0 NSCLC	70	T1: 20 Gy x 3 T2: 22 Gy x 3	50.2 months	3-year LC: 88.1% 3-year OS: 42.7% 3-year CaSS: 81.7%
Baumann (Baumann et al., 2009)	Phase II/Medically inoperable stage I NSCLC	57	15 Gy x 3 to 67%	35 months	3-year LC: 92% 1-, 2-, and 3-year OS: 86%, 65%, and 60% 1-, 2-, and 3-year CaSS: 93%, 88%, and 88% 3-year PFS: 52%
Koto (Koto et al., 2007)	Phase II/Stage I NSCLC	31	15 Gy x 3 (45 Gy) and 7.5 Gy x 8 (60 Gy)	32 months	3-year LC: 77.9% for T1 and 40% for T2 3-year OS: 71.7% 3-year CSS: 83.5%
Ricardi (Ricardi et al., 2010)	Phase II/Stage I NSCLC	62	15 Gy x 3	28 months	3-year LC: 87.8% 3-year CSS: 72.5% 3-year OS: 57.1%
Timmerman (Timmerman et al., 2010)	RTOG Phase II/ Medically inoperable T1-2N0M0 NSCLC (peripherally located)	55	18 Gy x 3	34.4 months	3-year LC: 97.6% 3-year DFS: 48.3% 3-year OS: 55.8%

Abbreviations: LC, local control; OS, overall survival; CSS, cause-specific survival; CaSS, cancer-specific survival; DFS, disease-free survival.

Loo et al, Discovery Medicine 2011

Mono-institutional largest study, with/without histological diagnosis



676 patients

Median follow-up time: 32.9 months

Senthi et al, Lancet Oncol 2012

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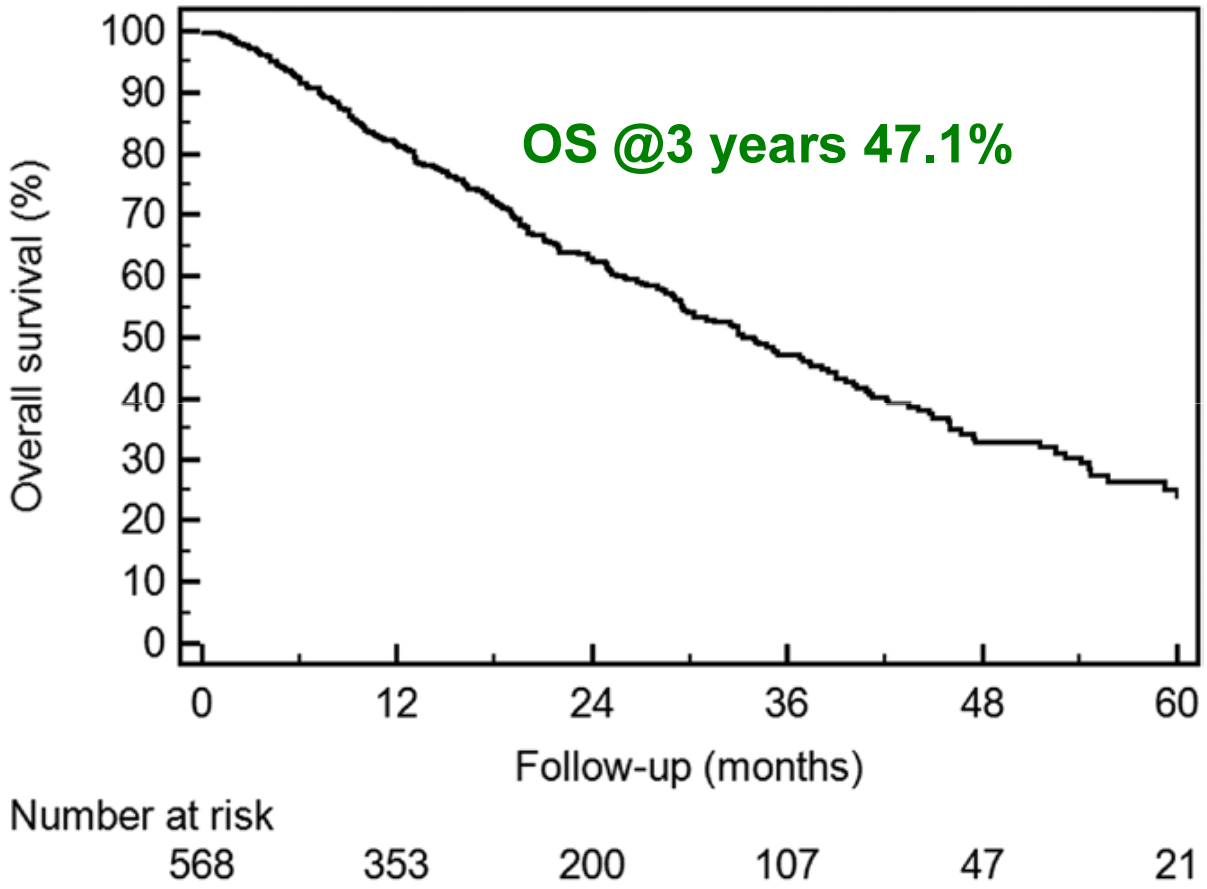
The German Society of Radiation Oncology (DEGRO) Observational Multicentric Study



Guckenberger et al, JTO 2013

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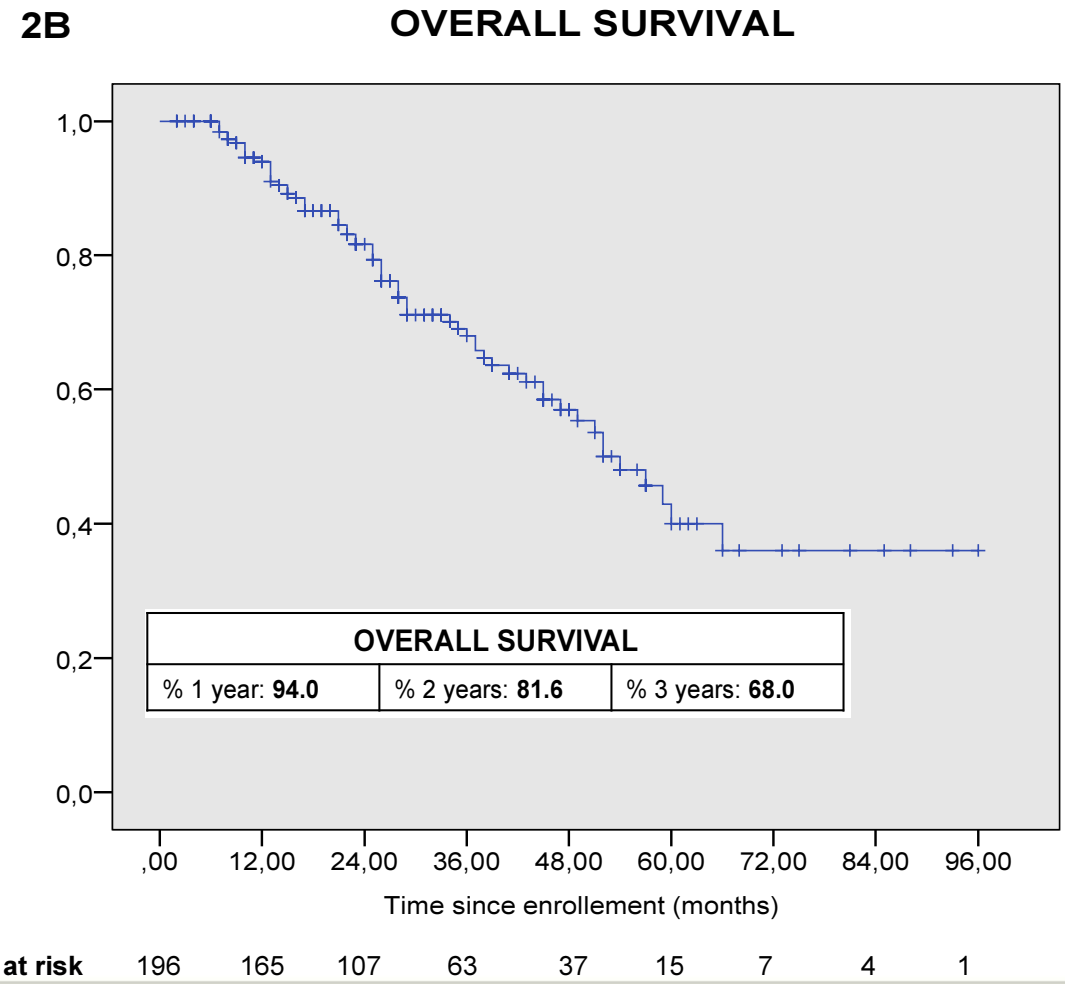
SABR in stage I histologically proven NSCLC: an Italian multicenter observational study



Ricardi et al, Lung Cancer 2014

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Studies demonstrating the variable rates of pathologic confirmation worldwide prior to SABR

Reference	Study type	N° of patients	Region	% biopsy	Overall Survival
Haasbeek	Population registry	1570	Netherlands	72	50% (2 yrs)
Ricardi	Retrospective	196	Italy	100	68% (3 yrs)
Guckenberger	Retrospective	591	Central Europe	85	47% (3 yrs)
Grills	Retrospective	505	United States Canada Netherlands Germany	87-95 72 41 70	48% (3 yrs)
Onishi	Retrospective	2278	Japan	73	91% (2 yrs)
Senthi	Retrospective	676	Amsterdam	35	41 mo (md)
Baumann	Prospective	57	Sweden Denmark Norway	67	60% (3 yrs)
Timmerman	Prospective	55	North America	100	56% (3 yrs)

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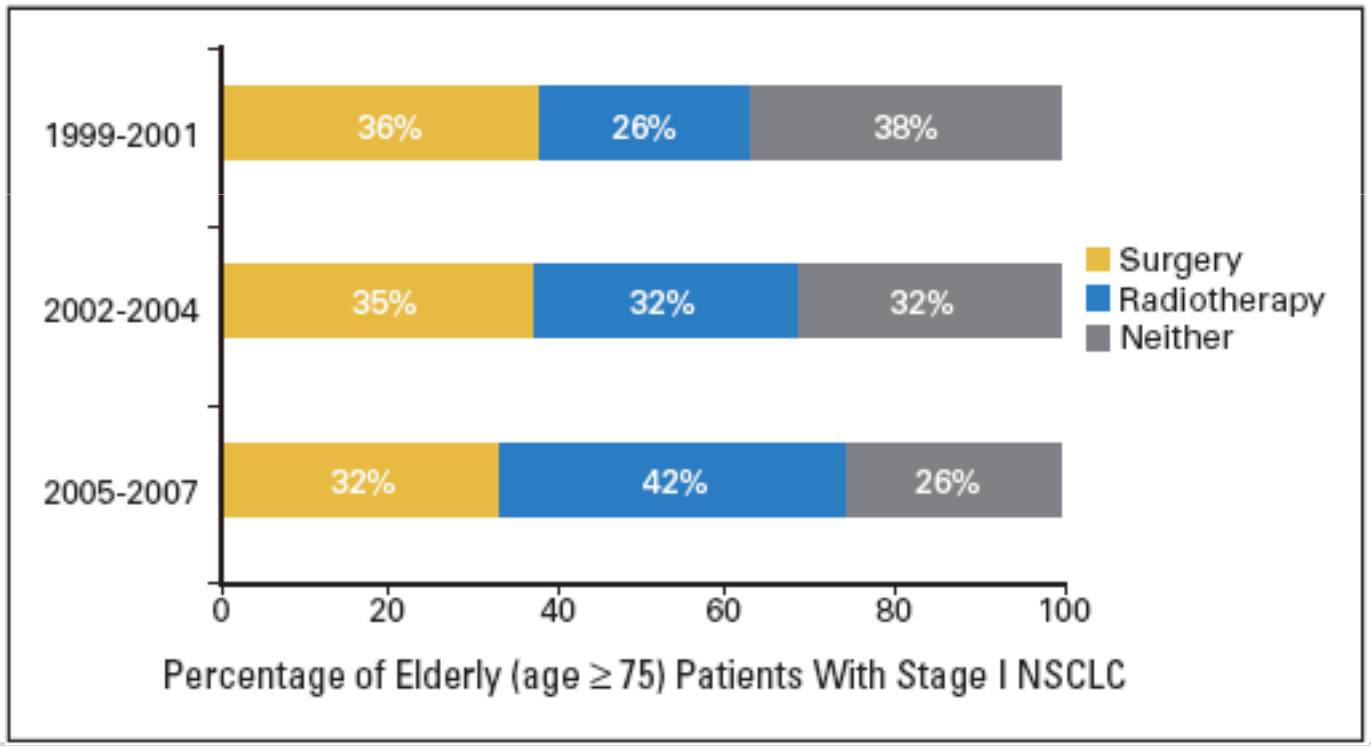
VOLUME 28 · NUMBER 35 · DECEMBER 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Impact of Introducing Stereotactic Lung Radiotherapy for Elderly Patients With Stage I Non–Small-Cell Lung Cancer: A Population-Based Time-Trend Analysis

David Palma, Otto Visser, Frank J. Lagerwaard, Jose Belderbos, Ben J. Slotman, and Suresh Senan



Palma DA et al, 2010

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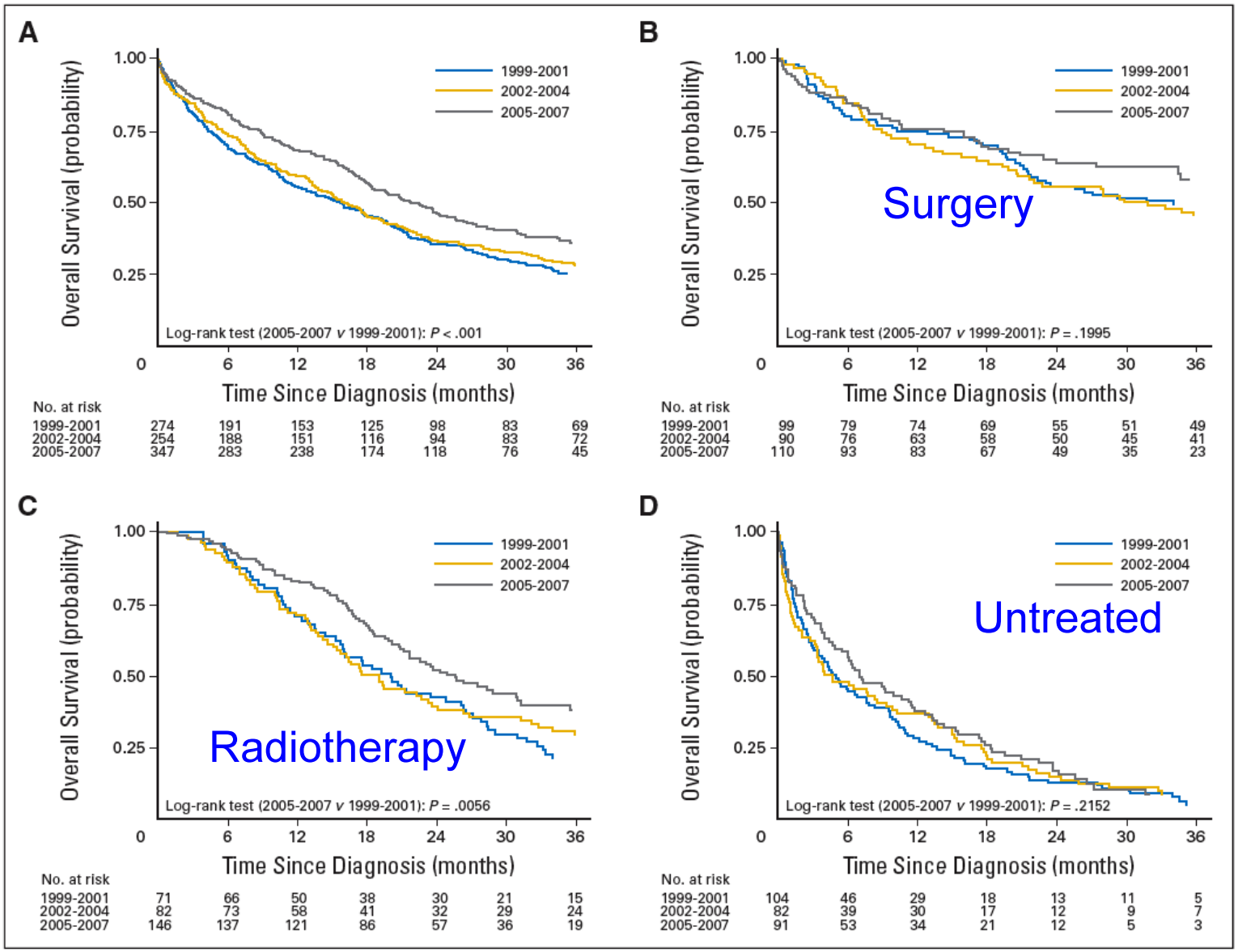

Fig 3. Overall survival for elderly (age ≥ 75 years) patients with stage I non–small-cell lung cancer by time period. (A) All patients; (B) patients treated with surgery; (C) patients treated with radiotherapy; (D) untreated patients.

Palma DA et al, 2010

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Pattern of failure following SBRT

	Local	Regional	Distant
Actuarial 2-year rates	4.9%	7.8%	14.7%
Actuarial 5-year rates	10.5%	12.7%	19.9%

	Median time to event
Local recurrence	14.9 months (95% CI 11.4-18.4)
Regional recurrence	13.1 months (95% CI 7.9-18.3)
Distant recurrence	9.6 months (95% CI 6.8-12.4)
2nd primary tumors	18 months (95% CI 12.5-23.5)

- Stage I-II NSCLC (2003-2011); median follow-up 32.9 months (IQR 14.9 - 50.9);
- 66% of recurrences were distant (DR); isolated DR made up 46% of recurrences

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SABR is well tolerated: toxicity is uncommon

Summary of common toxicity after SBRT for stage I Lung Cancer.

Toxicity	Incidence
Radiation pneumonities	≥G3: 4–8% (12–15% in pulmonary fibrosis)
Chest wall pain	11–15% (2–3% rib fractures)
Skin toxicity	4–6% (<1% skin ulceration)
Brachial plexophaty	Rare
Fatal bleeding	Rare (but 2–3% in centrally located tumours)
Late radiological changes	50–80%

Ricardi, Badellino, Filippi, Lung Cancer 2015

SBRT and severe COPD?

Systematic Review: Eligible patients had to have GOLD III-IV or a predicted postoperative FEV_1 of ≤40%

Table 3. Thirty-day mortality and complications associated with treatment of stage I NSCLC in patients with poor ventilatory function

First author	30-day mortality	Complications
Surgery		
Magdeleinat (26)	8%*	>90% admitted to ICU >45% with complications (pneumonia, air leak, and arrhythmia most common)
Lau (19)	25% after open lobectomy* 7% for open segmentectomy or VATS procedure*	Median hospital stay 8–12 days <10% admitted to ICU
SBRT		
Henderson (27)	0%*	>69% with Grade 1 or 2 toxicity of some kind†
Stephans (28)	0%*	No Grade 3 or higher pneumonitis
Palma (current study)	0%	6 patients (3%) with Grade 3 toxicity

Abbreviations: ICU = intensive care unit; VATS = video-assisted thoracoscopic surgery.
* Denotes values measured from Kaplan-Meier curves.
† 8% Grade 3–4 toxicity with some late deaths related to treatment of central tumors in larger Phase II study, but these rates not specified for subgroup with poor pulmonary function.

Palma D et al, IJROBP 2012

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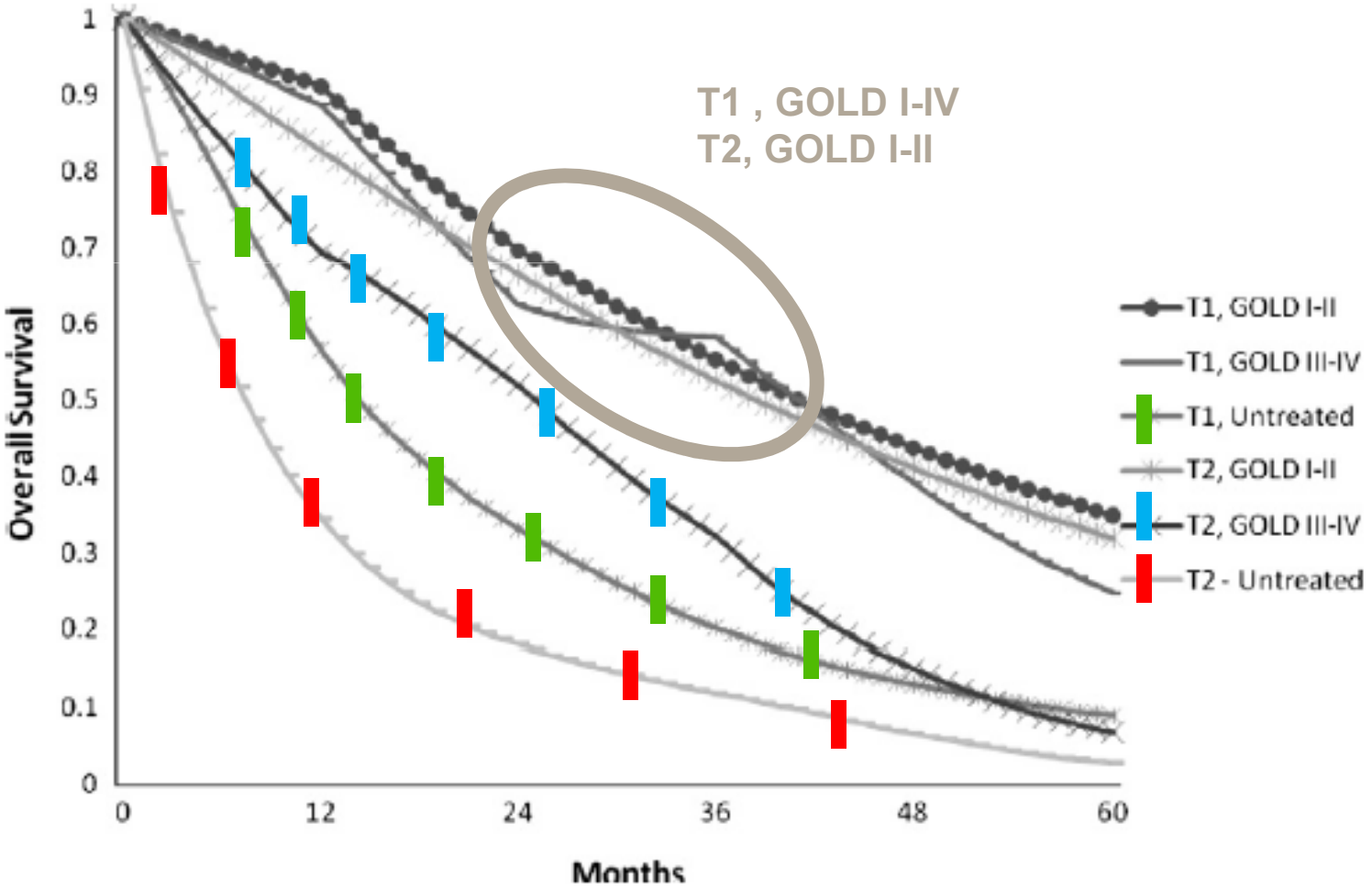
journal homepage: www.thegreenjournal.com

SBRT in lung cancer

Withholding stereotactic radiotherapy in elderly patients with stage I non-small cell lung cancer and co-existing COPD is not justified: Outcomes of a markov model analysis

Alexander V. Louie[a], George Rodrigues[a,b,*], Malek Hannouf[b], Frank Lagerwaard[c], David Palma[a,c], Gregory S. Zaric[b,d], Cornelis Haasbeek[c], Suresh Senan[c]



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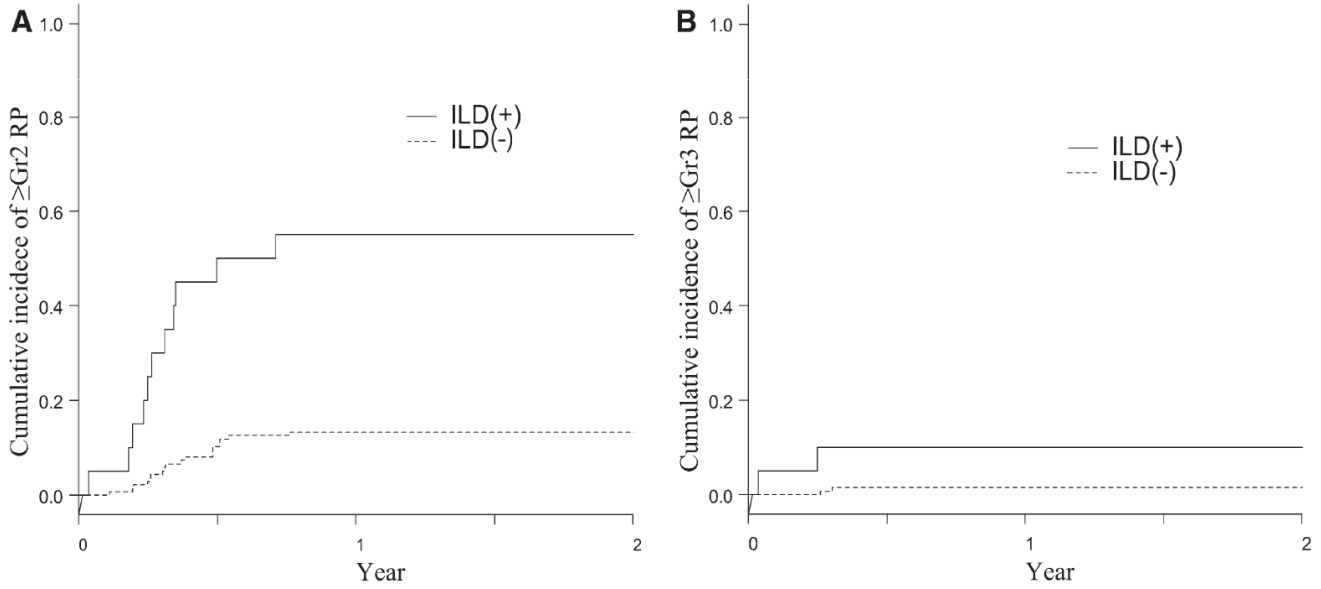
Impact of Pretreatment Interstitial Lung Disease on Radiation Pneumonitis and Survival after Stereotactic Body Radiation Therapy for Lung Cancer

Nami Ueki, MD, Yukinori Matsuo, MD, PhD,* Yosuke Togashi, MD,†‡ Takeshi Kubo, MD,§ Keiko Shibuya, MD, PhD,‖ Yusuke Iizuka, MD,* Takashi Mizowaki, MD, PhD,* Kaori Togashi, MD, PhD,§ Michiaki Mishima, MD, PhD,‡ and Masahiro Hiraoka, MD, PhD**

(*J Thorac Oncol.* 2015;10: 116–125)



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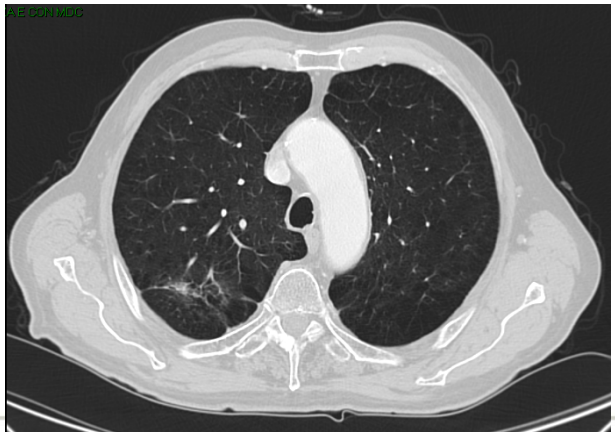
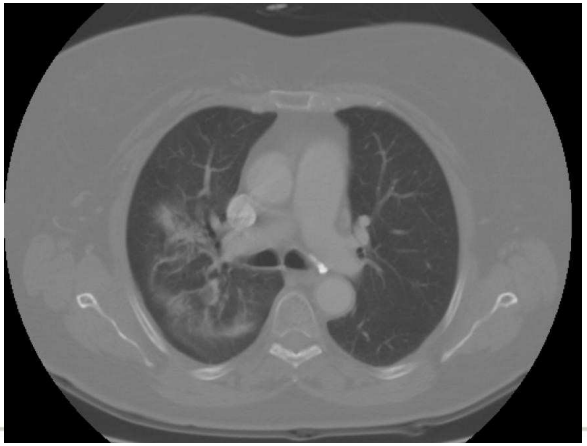
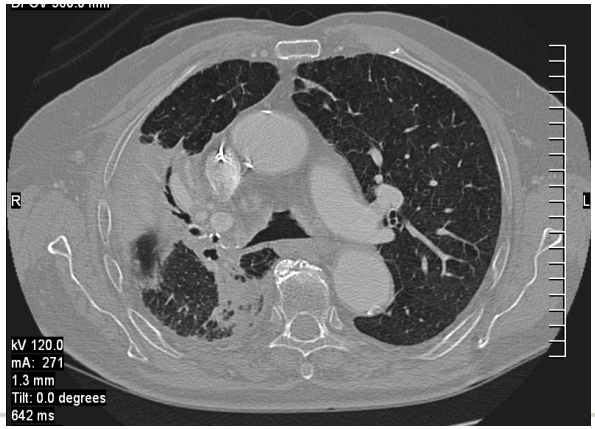
Acute radiological changes after SBRT

Diffuse consolidation (consolidation more than 5 cm in largest dimension)	20-30%
Patchy consolidation (consolidation less than 5 cm in largest dimension)	8-22%
Diffuse ground glass opacities (more than 5 cm of GGO)	4-8%
Patchy ground glass opacities (less than 5 cm of GGO)	10-15%
No evidence of increased density	20-40%







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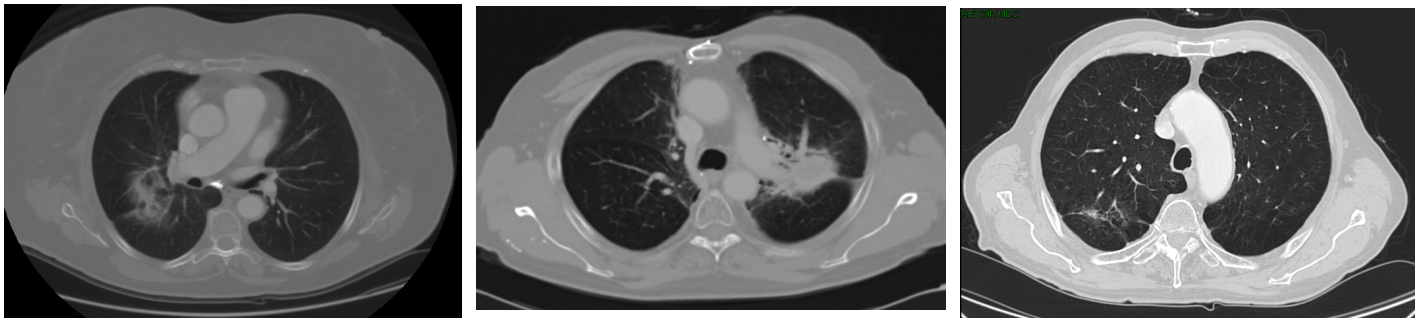
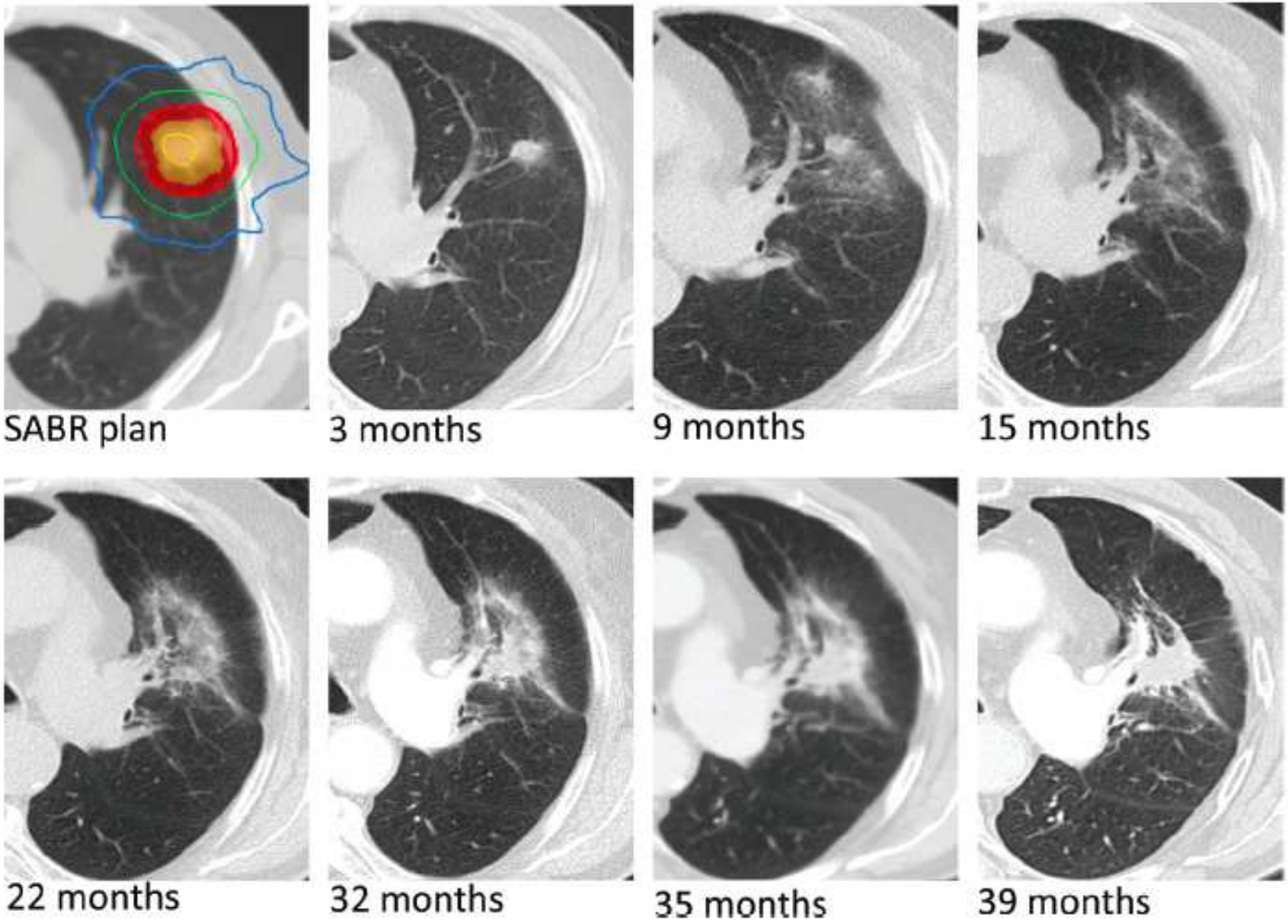
Late radiological changes after SBRT

Radiation fibrosis (later than 6 months)
(Koenig's classification, AJR 2002):

- Modified conventional pattern
- Mass-like pattern
- Scar-like pattern





Operable Patients

CLINICAL INVESTIGATION **Lung**

STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR OPERABLE STAGE I NON–SMALL-CELL LUNG CANCER: CAN SBRT BE COMPARABLE TO SURGERY?

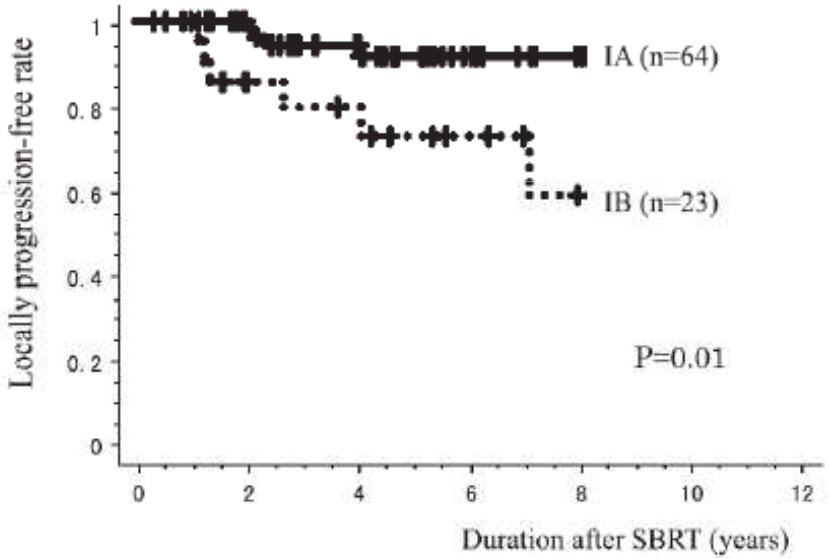


Table 3. Comparison of 5-y overall survival rate between surgical series and SBRT

Clinical stage	United States (1)	Japanese National Cancer Center (2)	Japanese National Survey (3)	SBRT
IA	61	71	77	76
IB	40	44	60	64

Abbreviation: SBRT = stereotactic body radiotherapy.
Values are percentages.

Onishi et al IJROBP 2011

From DA Palma, ASTRO 2014

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Surgery vs. SBRT for stage I NSCLC

Studies comparing surgery and SBRT in stage I NSCLC.

Author (year)	Study design	No. of patients	Surgical procedure	Overall Survival Surgery SBRT
Grills et al. [37]	Retrospective	Surgery = 69 SBRT = 55	Wedge resection	87% 72% 30 mo 30 mo
Crabtree et al. [38]	Propensity-score matching	Unmatched: surgey = 458 SBRT = 151 matched: 112/group	(Bi) lobectomy, 78% sublobar, 19% pneumonectomy, 4%	78% 47% 3-year 3-year 68% 52% 3-year 3-year
Vertstegen [39]	Propensity-score matching	Unmatched: surgey = 86 SBRT = 527 matched: 64/group	VATS, lobectomy	77% 80% 3-year 3-year
Shirvani et al. [40]	SEER population, propensity-score matching	Unmatched: surgery = 8711 SABR = 382 matched: 251/group	Lobectomy 83% Sublobar 17%	Lobectomy vs SBRT, HR 1.01 (SA: 1.16-1.28)
Mokhles et al. [41]	Propensity-score matching	Unmatched: surgery = 96 SBRT = 481 matched: 73/group	VATS, lobectomy	95% 94% 1-year 1-year 80% 53% 3-year 3-year
Chang et al. [42]	Randomized Phase-3 Trial (ROSEL and STARS trials)	Surgery = 27 SBRT = 31	VATS, lobectomy	79% 95% 3-year 3-year

Abbreviations: Non-small-cell lung cancer (NSCLC); Video-assisted thoracoscopic surgery (VATS).

Ricardi, Badellino, Filippi, Lung Cancer 2015

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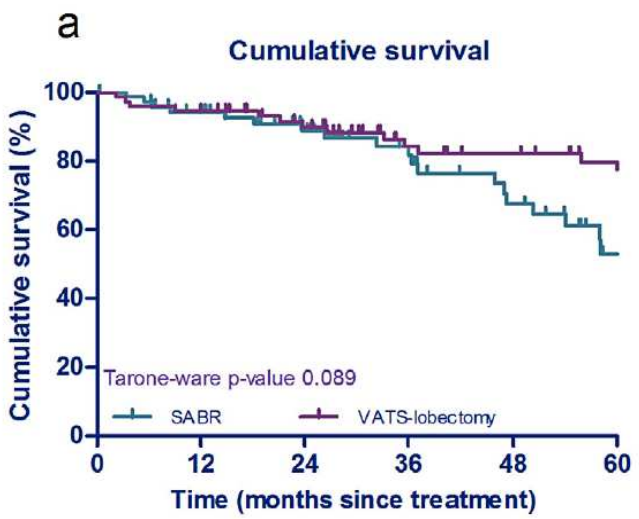
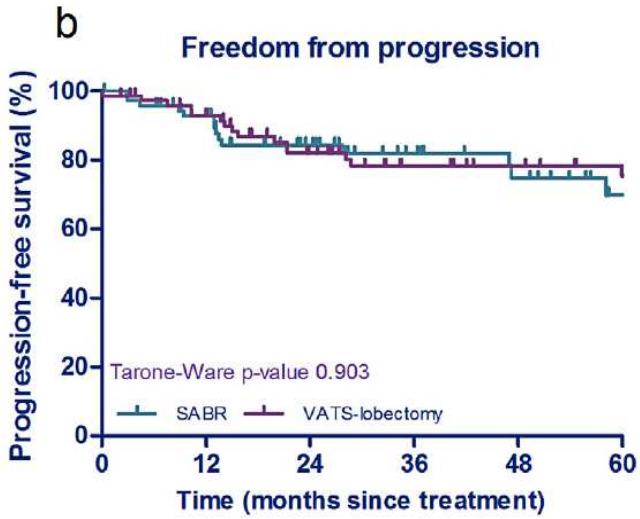
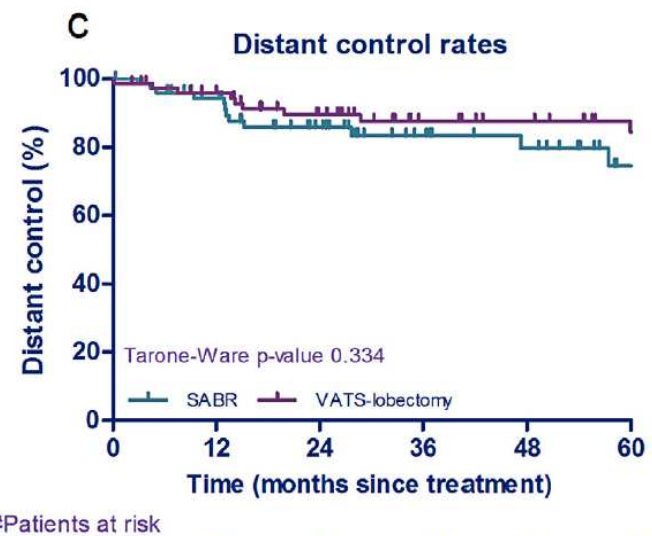


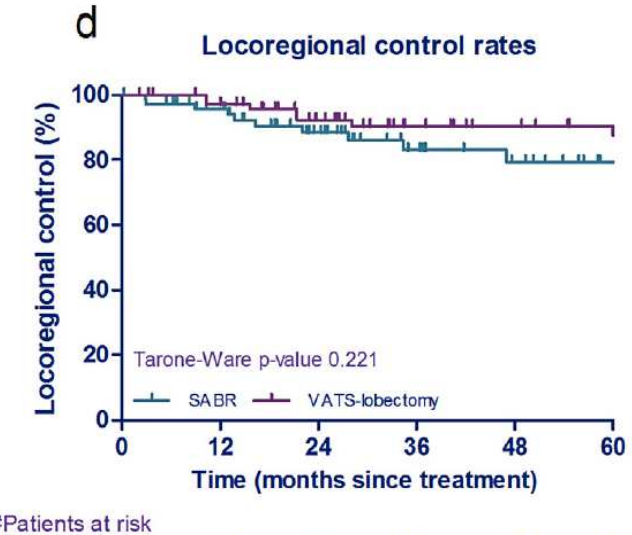
#Patients at risk					
SABR	62	46	34	24	13
VATS-lobectomy	70	58	42	38	32



#Patients at risk					
SABR	61	42	29	22	13
VATS-lobectomy	67	50	38	34	29



#Patients at risk					
SABR	61	42	29	23	13
VATS-lobectomy	66	54	40	36	29



#Patients at risk					
SABR	61	43	28	21	13
VATS-lobectomy	69	54	41	36	32

Mokhles et al, Lung Cancer 2015

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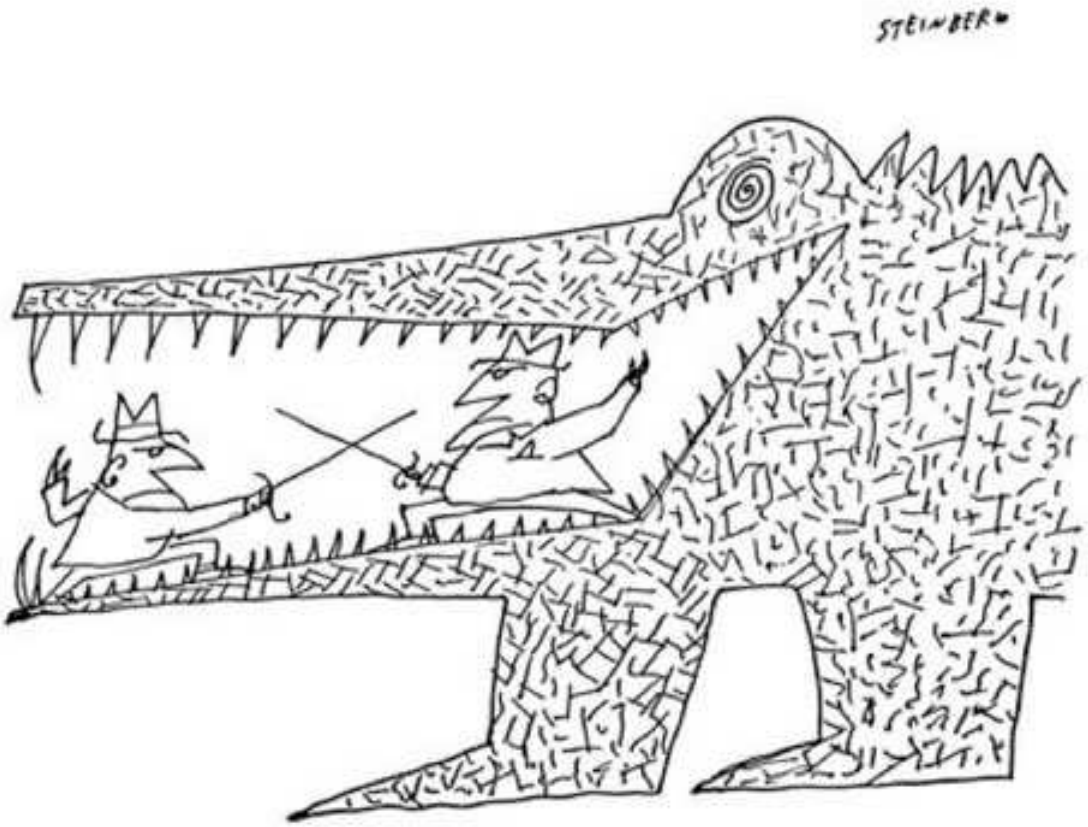
Better outcome for surgery after 3 years:

- optimal lymph node staging: adjuvant therapy
- still some differences between the two groups:
  - matching was done with only a limited number of variables
  - (i.e., staging procedure not included as covariate)
- respiratory failure over time (RILI)
- unable to provide CSS rates

SABR vs SURGERY: randomized trials?



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Trials of surgery versus SABR

Table 1 – Approved Phase III Randomized Trials of Operable Stage I NSCLC Patients (all prematurely terminated due to poor accrual)

Dutch ROSEL trial, NCT00687986, "Randomized Clinical Trial of Stereotactic Radiotherapy or Surgery in Patients with Stage IA Non-Small Cell Lung Cancer who are fit to undergo Primary Resection".

- Sponsored by the The Netherlands Organisation for Health Research and Development.
- Opened at 9 centers
- Opened 2008, Closed 2010
- Enrolled 22 of 960

STARS Trial, NCT00840749, "Randomized Study to Compare CyberKnife to Surgical Resection in Stage I Non-small Cell Lung Cancer"

- Sponsored by Accuray©
- Opened at 15 centers
- Opened 2009, Closed 2013
- Enrolled 36 of 1,030 patients

ACOSOG-Z4099/RTOG-1021, NCT01336894, "A Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) versus Stereotactic Body Radiation Therapy in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)"

- Sponsored by American College of Surgeons
- Opened at 53 centers
- Opened 2011, Closed 2013
- Enrolled 10 of 420 patients

Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials

Joe Y Chang, Suresh Senan*, Marinus A Paul, Reza J Mehran, Alexander V Louie, Peter Balter, Harry J M Groen, Stephen E McRae, Joachim Widder, Lei Feng, Ben E E M van den Borne, Mark F Munsell, Coen Hurkmans, Donald A Berry, Erik van Werkhoven, John J Kresl, Anne-Marie Dingemans, Omar Dawood, Cornelis J A Haasbeek, Larry S Carpenter, Katrien De Jaeger, Ritsuko Komaki, Ben J Slotman, Egbert F Smit†, Jack A Roth†*

Lancet Oncol 2015; 16: 630–37

Published Online
May 14, 2015

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- ✓ **58 patients** were enrolled and randomly assigned in the combined studies
- ✓ **31 SABR and 27 surgery**

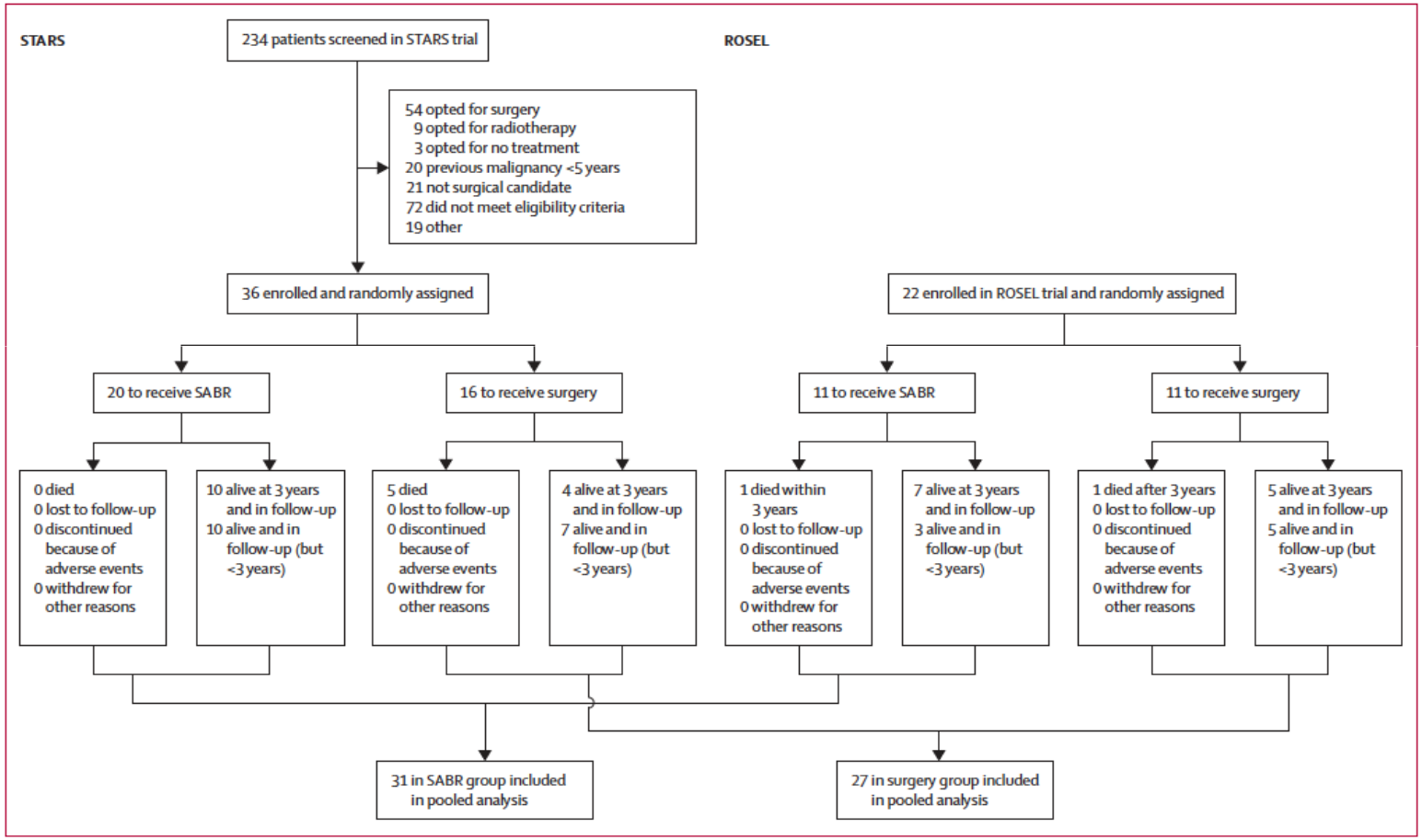

Figure 1: **Study design for STARS and ROSEL trials**
SABR=stereotactic ablative radiotherapy.

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	SABR group (n=31)	Surgery group (n=27)	p value
Sex			0·73
Male	14 (45%)	11 (41%)	
Female	17 (55%)	16 (59%)	
Age (years)			
Mean (SD)	67·3 (9·2)	67·3 (8·2)	--
Median (range)	67·1 (43–82)	66·7 (51–85)	0·69
WHO performance status			0·31
0	21 (68%)	21 (78%)	
1	10 (32%)	5 (19%)	
2	0 (0%)	1 (4%)	
Histology before randomisation			0·62
Adenocarcinoma	16 (52%)	13 (48%)	
Squamous	5 (16%)	7 (26%)	
Other	2 (6%)	1 (4%)	
Unknown	8 (26%)*	6 (22%)*	
Tumour stage			0·41
T1a	16 (52%)	18 (67%)	
T1b	11 (35%)	8 (30%)	
T2a	4 (13%)	1 (4%)	
Tumour site			0·45
Left lower lobe	7 (23%)	4 (15%)	
Left upper lobe	7 (23%)	8 (30%)	
Right lower lobe	5 (16%)	1 (4%)	
Right middle lobe	3 (10%)	2 (7%)	
Right upper lobe	9 (29%)	12 (44%)	
Peripheral			0·66
No	2 (6%)	3 (11%)	
Yes	29 (94%)	24 (89%)	

Data are n (%) unless otherwise stated. SABR=stereotactic ablative radiotherapy. *Histology of six of the 14 tumours of unknown histology was confirmed after surgery in the ROSEL study (three adenocarcinoma, one bronchiolalveolar carcinoma, one squamous-cell carcinoma, and one benign disease); eight tumours in the SABR group had unknown histology in the ROSEL study.

***Table*: Patient characteristics**

- ✓ **Any difference** in age, sex, PS, histology, T stage or tumour location
- ✓ **Median follow up** was 40,2 months in SABR group and 35.4 months in surgery group
- ✓ All stage I NSCLC and were operable for lobectomy with PS 0-2
- ✓ **TC-PET** for staging
- ✓ **20 patients lobectomies,** 5 video-assisted thoracotomy lobectomies, 1 video-assisted thoracotomy biopsy, 1 aborted resection during surgery due to disease progression
- ✓ **STARS:** 16 patients peripherally lesions 54 Gy/3 fr; 4 patients central lesions 50 Gy/4 fr
- ✓ **ROSEL:** 6 patients 54 Gy/3 fr in 5-8 days, 5 patients 60 Gy/5 fr in 10-14 days

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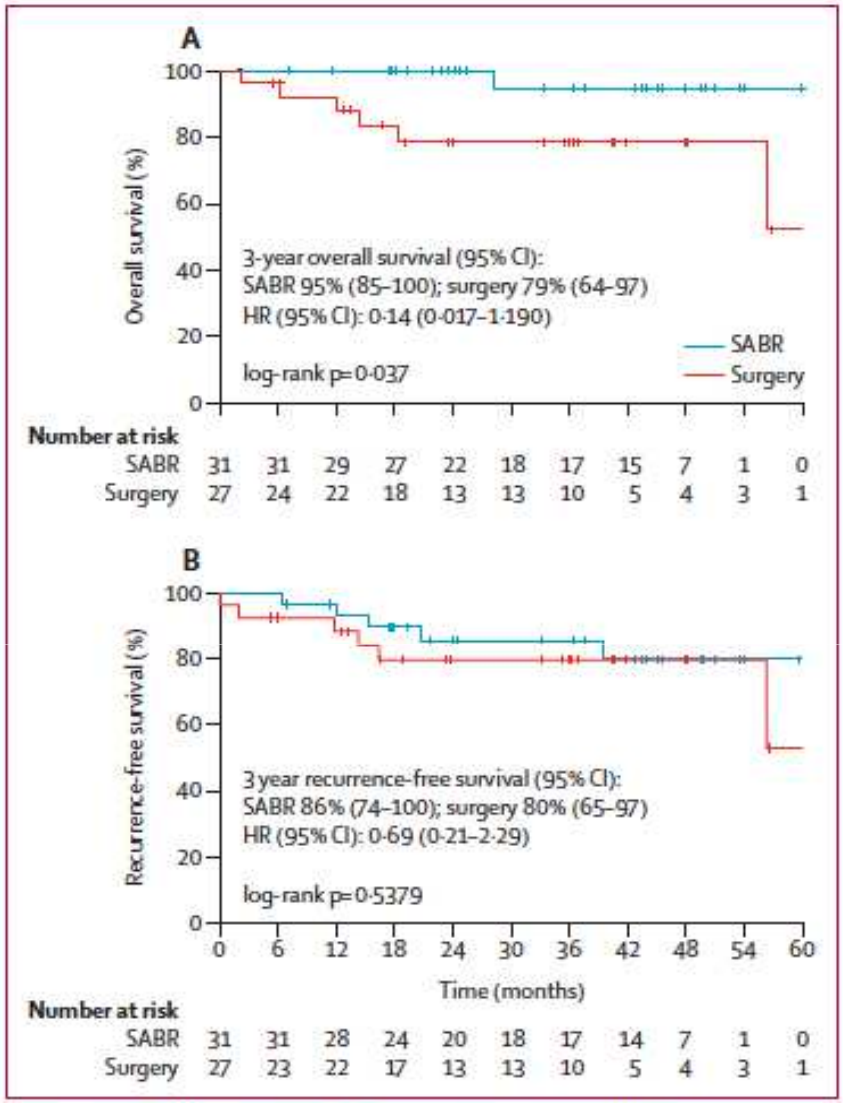

Figure 2: **Overall survival (A) and recurrence-free survival (B)**
One patient died and five had recurrence in the SABR group compared with six and six patients, respectively, in the surgery group. SABR=stereotactic ablative radiotherapy. HR=hazard ratio.

- ✓ **Pooled estimated OS at 1 and 3 years** was **100% and 95% in SABR group; 88% and 79% in surgical group**
- ✓ **Difference in OS** between the two groups was statistically significant
- ✓ This difference in OS is significant in STARS alone but not in ROSEL alone
- ✓ **7 patients died:** 6 in surgery group (2 PD, 1 secondary primary lung cancer, 1 surgical adverse event, 2 comorbidities) and 1 in SABR group (PD)

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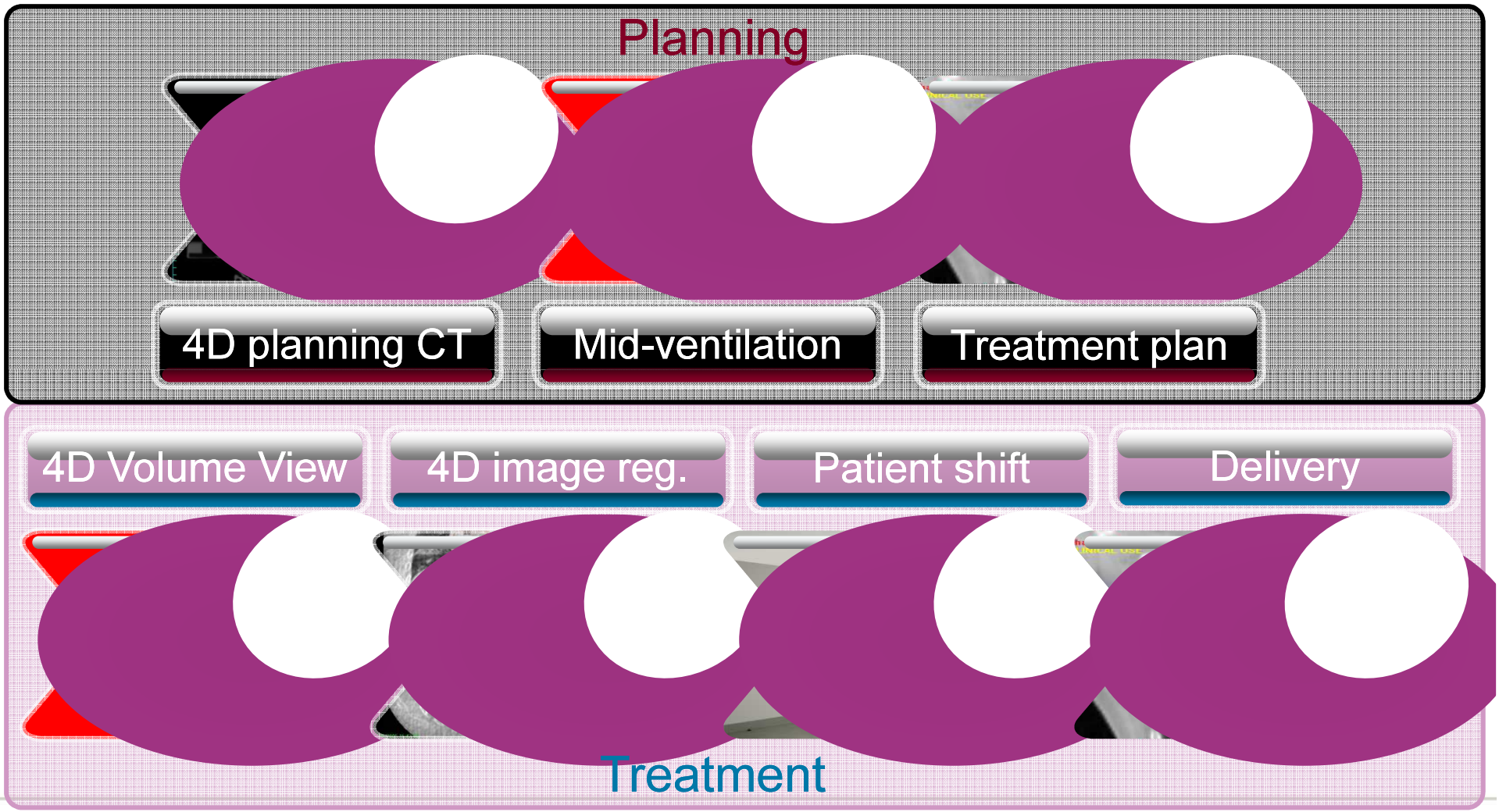
Technical Advances may have an impact on efficacy and toxicity



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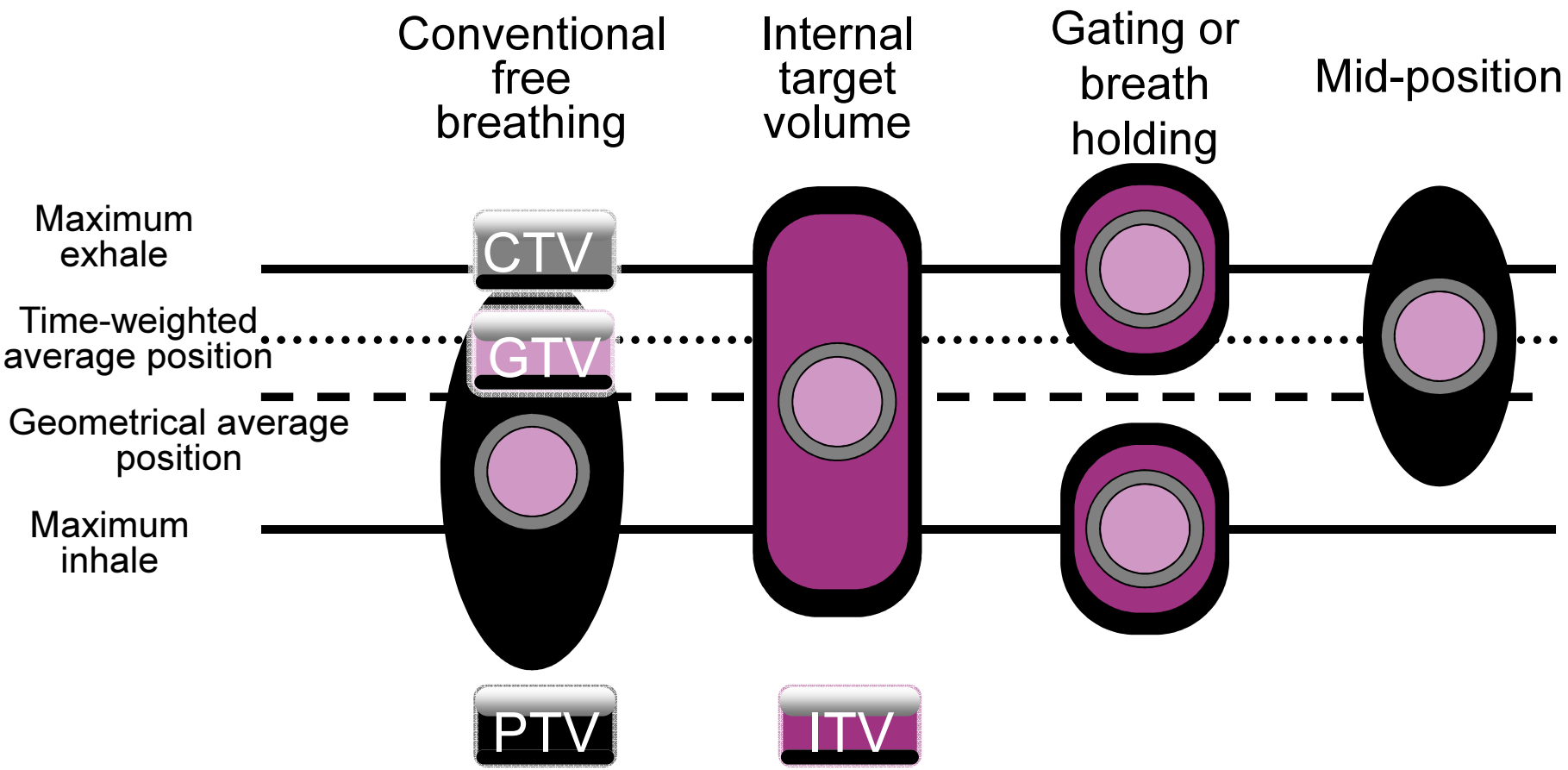
Planning Concepts For Breathing



Wolthaus et al., IJROBP 2008

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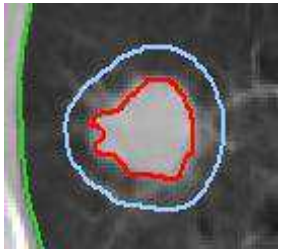
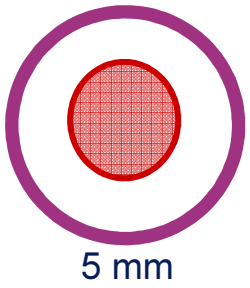
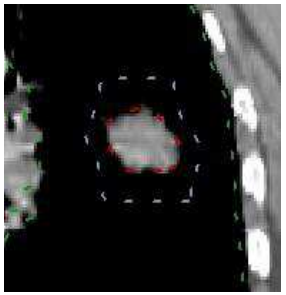
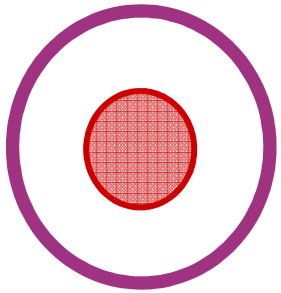
Higher accuracy should translate in less toxicity and better PTV coverage





5 mm

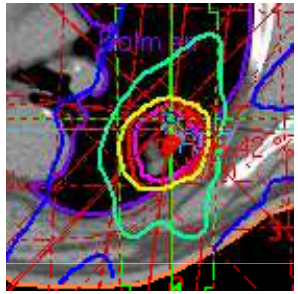


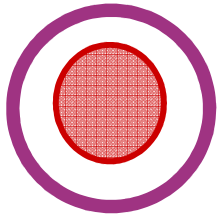


10 mm

GTV=CTV

PTV





3 mm

PTV = ITV + 3-5 mm isotropic

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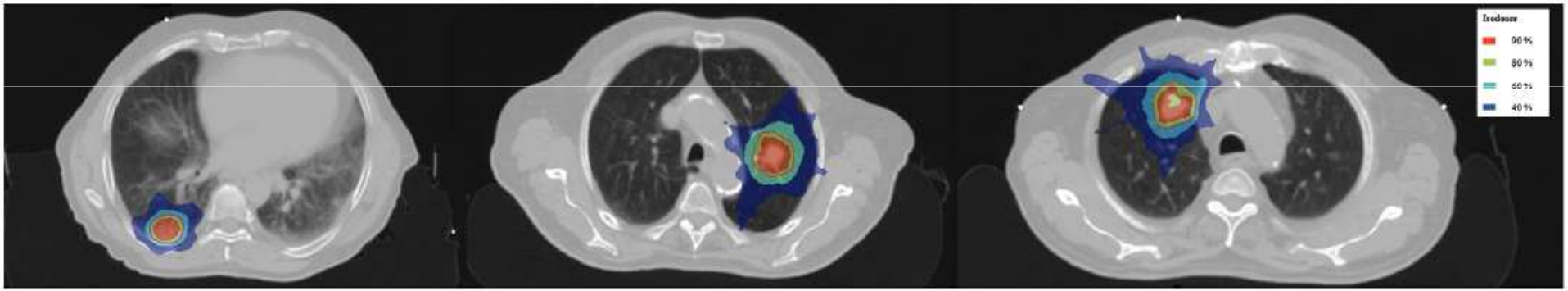
Patients' fixation: frameless SBRT

- non-invasive, dual vacuum activated immobilization and fixation system
- stable immobilization and repeatable positioning by minimizing both voluntary and involuntary patient movement
- patient comfort

SBRT for peripheral and central tumors



Ricardi, Badellino, Filippi, Lung Cancer, 2015

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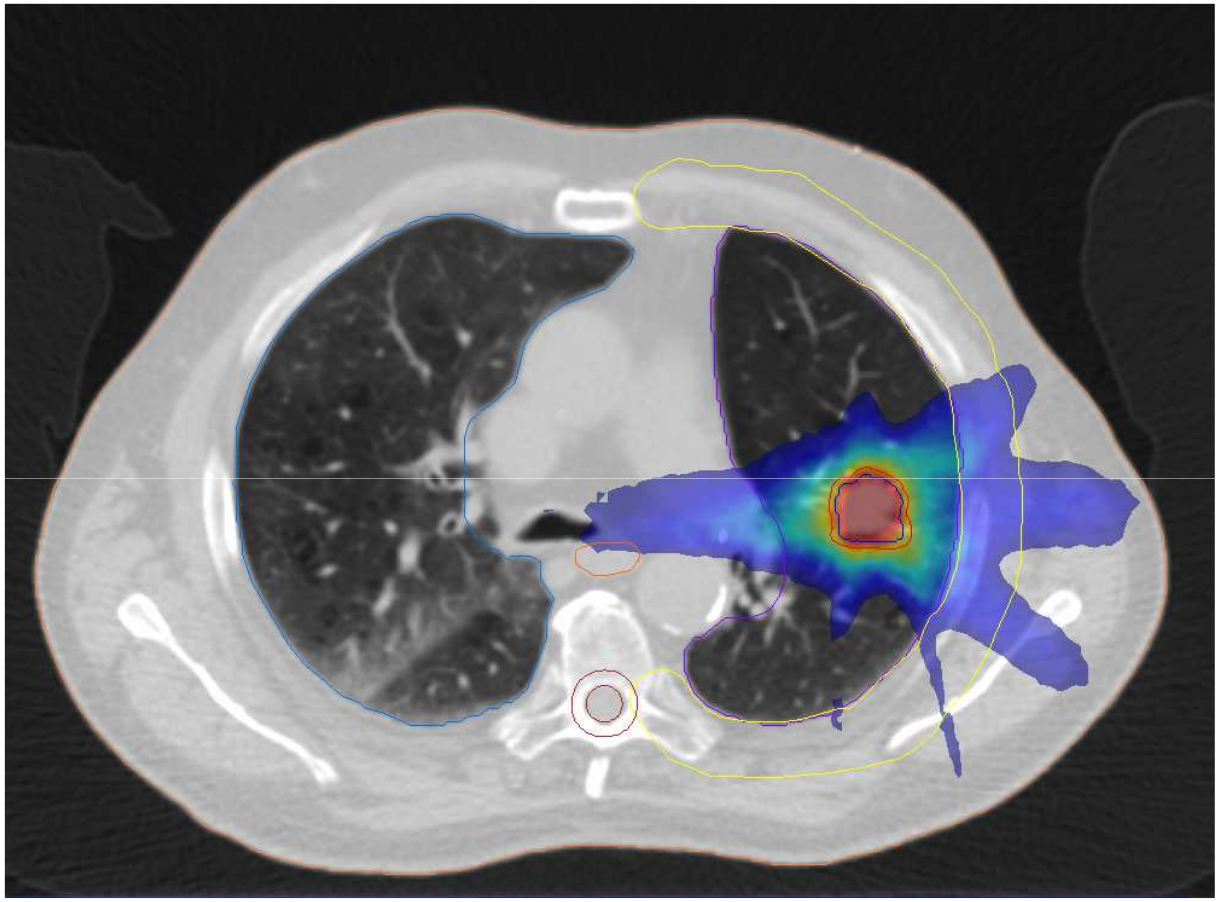
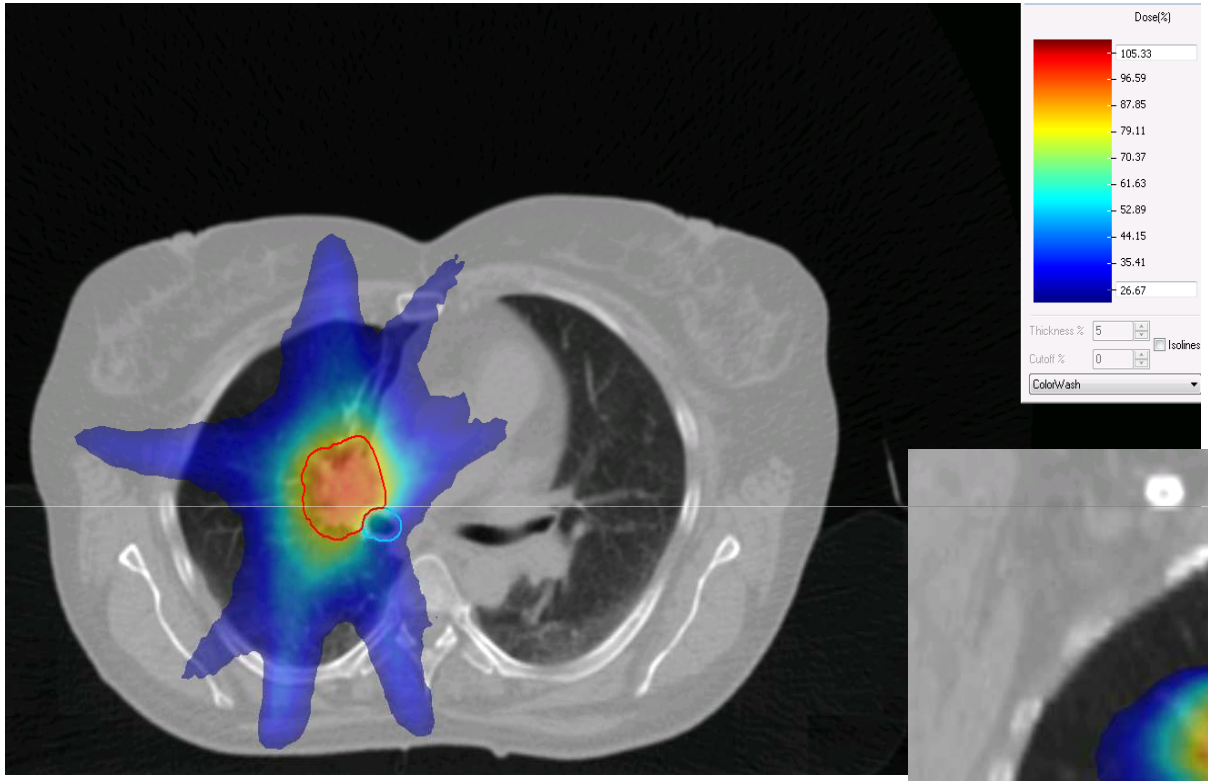
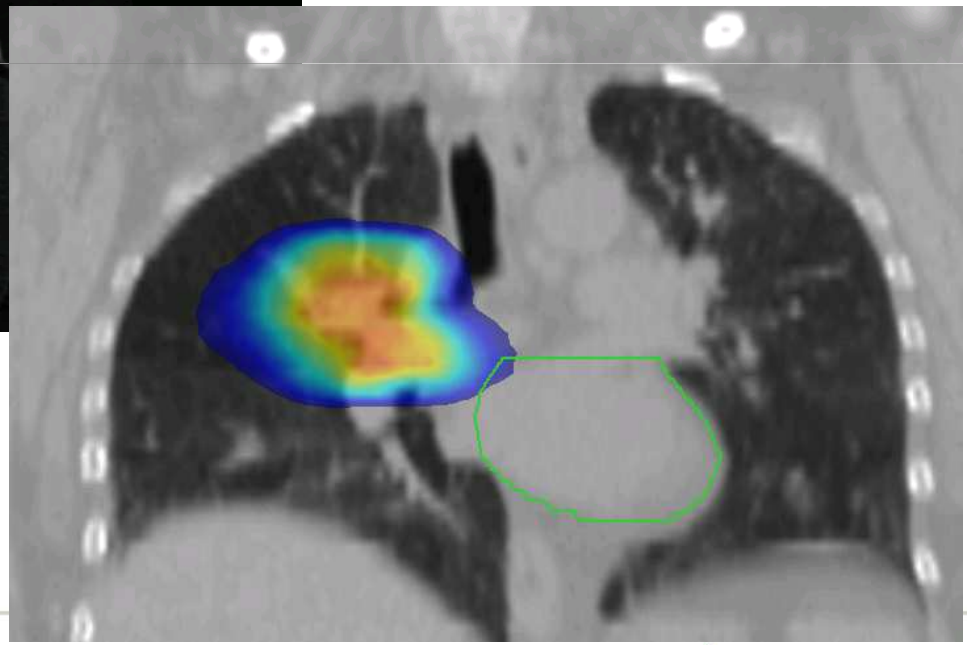
VMAT for early stage lung cancer



DFT 54 Gy/ 18 fx (80% isodose)

VMAT for early stage lung cancer





DFT 60 Gy/ 8 fx (80% isodose)

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Volumetric modulated arc therapy with flattening filter free (FFF) beams for stereotactic body radiation therapy (SBRT) in patients with medically inoperable early stage non small cell lung cancer (NSCLC)

Pierina Navarria [a,*], Anna Maria Ascolese [a], Pietro Mancosu [a], Filippo Alongi [a], Elena Clerici [a], Angelo Tozzi [a], Cristina Iftode [a], Giacomo Reggiori [a], Stefano Tomatis [a], Maurizio Infante [b], Marco Alloisio [b], Alberto Testori [b], Antonella Fogliata [c], Luca Cozzi [c], Emanuela Morenghi [a], Marta Scorsetti [a]

[a] *Radiotherapy and Radiosurgery Department;* [b] *Department of Thoracic Surgery, Humanitas Cancer Center, Istituto Southern Switzerland, IOSI, Bellinzona, Switzerland*

	VMAT		3DCRT		p
	N	(%)	N	(%)	
Total patients	46		86		
Sex					
Female	14	(30)	19	(22)	0.3
Male	32	(70)	67	(78)	
Age (years)					
Median	72.1	(66–83)	75.7	(65–82)	0.03
Range					
Histology					0.5
Unidentified	19	(41)	39	(45)	
Squamous cell carcinoma	6	(59)	10	(55)	
Adenocarcinoma	9		22		
NSCLC NOS	12		15		
Stage (TNM)					0.01
IA					
T1aN0M0	24	(52)	55	(64)	
T1bN0M0	15	(33)	24	(28)	
IB					
T2aN0M0	7	(15)	7	(8)	
Tumor size					
Median tumor diameter	26 mm		21 mm		0.01
Range	(16–36 mm)		(12–38 mm)		

Navarria et al, Radiother Oncol 2013

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	3DCRT	VMAT RA	p
Ipsilateral lung			
V_{5Gy} [%]	31.4 ± 11.9 [6.6–57.8]	25.3 ± 11.8 [6.8–54.0]	0.03
V_{10Gy} [%]	22.6 ± 9.9 [0.0–45.6]	16.4 ± 8.9 [3.8–46.0]	0.007
V_{20Gy} [%]	11.8 ± 7.0 [0.0–26.7]	7.3 ± 4.9 [1.2–26.6]	0.002
MLD [Gy]	7.2 ± 3.0 [0.9–12.6]	4.9 ± 2.4 [1.2–13.3]	<0.001
Contralateral lung			
V_{5Gy} [%]	2.9 ± 4.8 [0.0–18.7]	2.0 ± 3.0 [0.0–11.3]	0.31
V_{10Gy} [%]	0.6 ± 2.5 [0.0–13.3]	0.0 ± 0.2 [0.0–0.9]	0.19
V_{20Gy} [%]	0.1 ± 0.6 [0.0–3.5]	0.0 ± 0.0 [0.0–0.0]	0.31
MLD [Gy]	0.8 ± 0.8 [0.1–3.5]	1.0 ± 0.5 [0.1–2.6]	0.38

Response on CT morphological scan and on functional 18FDG CT–PET imaging.

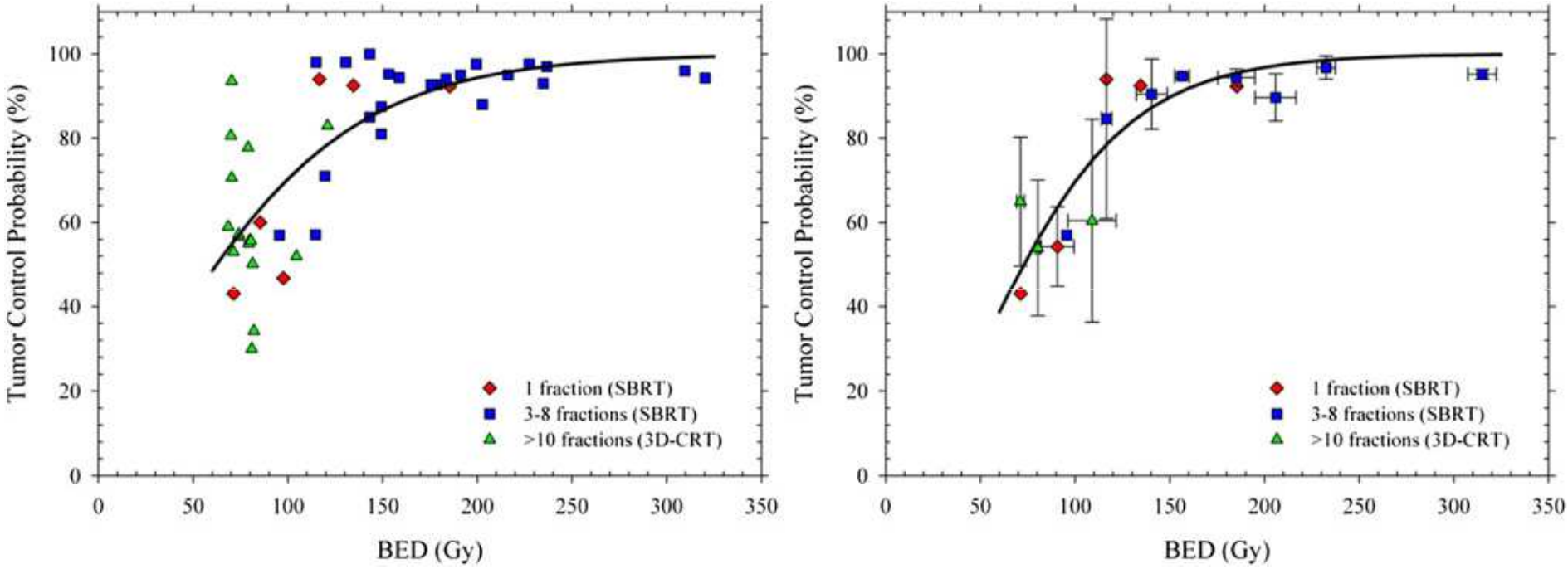
Response	Control at 3 months		Control at 6 months				Control at 12 months			
	CT scan		CT scan		CT–PET		CT scan		CT–PET	
	3DCRT	RA	3DCRT	RA	3DCRT	RA	3DCRT	RA	3DCRT	RA
PD	6 (7%)	0	6 (7%)	0	4 (8%)	0	6 (7%)	0	6 (10%)	0
SD	28 (34%)	6 (15%)	20 (24%)	2 (5%)	3 (6%)	0	16 (20%)	2 (5%)	4 (6.5%)	0
PR	39 (48%)	21 (53%)	41 (50%)	6 (15%)	27 (56%)	3 (11%)	40 (49%)	2 (5%)	33 (53%)	0

PD, progression of disease; SD, stable disease; PR, partial remission; CR, complete remission; RA = volumetric modulated arc therapy with RapidArc; 3DCRT = 3D conformal therapy with conformal arcs.

Navarria et al, Radiother Oncol 2013

Biological Challenges to the 5 Rs for SABR

Crude local control rates (2 years) redrawn from a pooled analysis reported by Mehta et al (3D-CRT and SABR regimens)



Dose Escalation, not “new biology,” can account for the efficacy of stereotactic body radiation therapy with non-small cell lung cancer

Brown et al, IJROBP 2014

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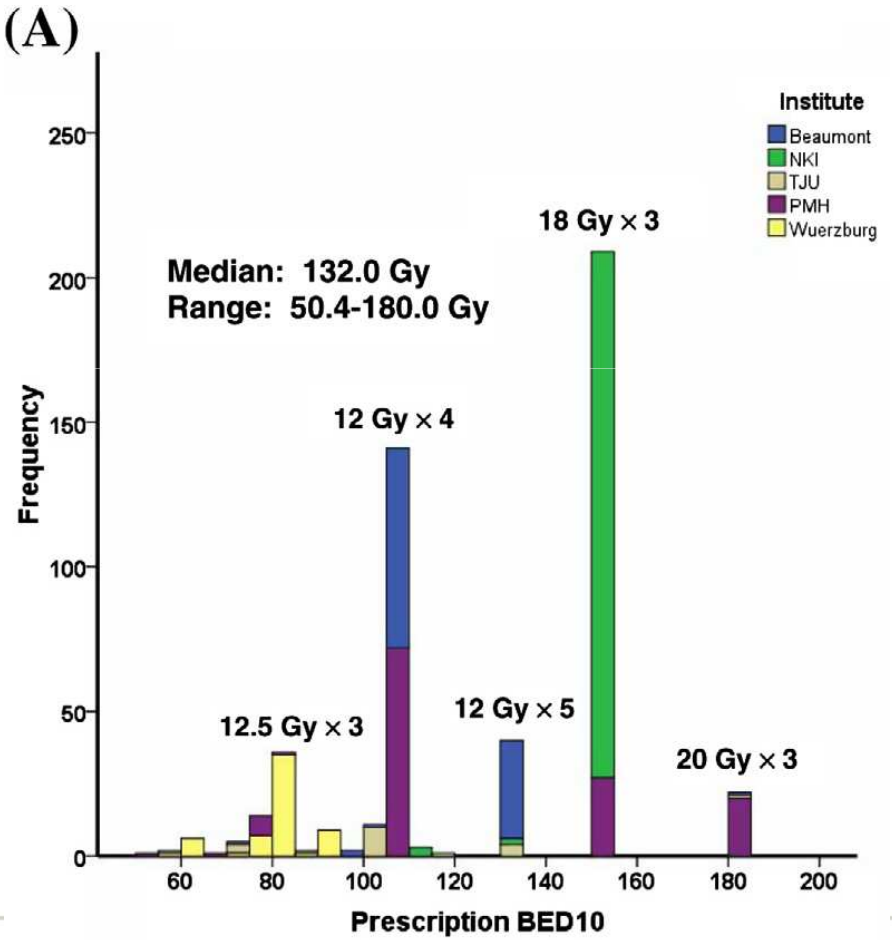
Dose–response relationship with clinical outcome for lung stereotactic body radiotherapy (SBRT) delivered via online image guidance ☆

Larry Kestin [a,*], Inga Grills [b], Matthias Guckenberger [c], Jose Belderbos [d], Andrew J. Hope [e], Maria Werner-Wasik [f], Jan-Jakob Sonke [d], Jean-Pierre Bissonnette [e], Ying Xiao [f], Di Yan [b], on behalf of the Elekta Lung Research Group



- 483 patients T1-2N0 NSCLC
- Five Institutions
- Variety of SBRT fractionations
- On-line IGRT with CBCT

Prescription to PTV edge (10-40% target heterogeneity)

Kestin et al, Radiother Oncol 2014

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ROC curves for factors predicting local control

Parameter	*p*-Value	Optimal cut point	Sensitivity (%)	Specificity (%)	2-Year local control (%)
Prescription BED_{10}	0.001	105.3 Gy	81	50	96 vs. 85
PTV_{mean} BED_{10}	0.02	125.8 Gy	84	57	96 vs. 83
GTV_{mean} BED_{10}	0.02	147.1 Gy	81	52	97 vs. 83
PTV_{max} BED_{10}	0.02	175.3 Gy	68	62	97 vs. 87
GTV_{max} BED_{10}	0.02	175.3 Gy	68	62	97 vs. 88
PTV_{min} BED_{10}	0.03	110.1 Gy	53	77	97 vs. 90
PTV D99 BED_{10}	0.03	92.6 Gy	87	62	95 vs. 83
GTV_{min} BED_{10}	0.04	149.8 Gy	57	72	98 vs. 89
PTV D1 BED_{10}	0.05	163.5 Gy	68	57	96 vs. 87
Treatment duration	0.01	11 days	50	82	96 vs. 86
GTV_{max} dimension	0.05	2.7 cm	65	55	97 vs. 91

Prescription BED_{10} → highest AUC (0.693; $p < 0.001$)
Optimal cut point of 105 Gy (sensitivity of 81% and specificity of 50%)

2-year LR $BED_{10} < 105$ Gy 15%
$BED_{10} > 105$ Gy 4% ($p < 0.001$)

Kestin et al, Radiother Oncol 2014

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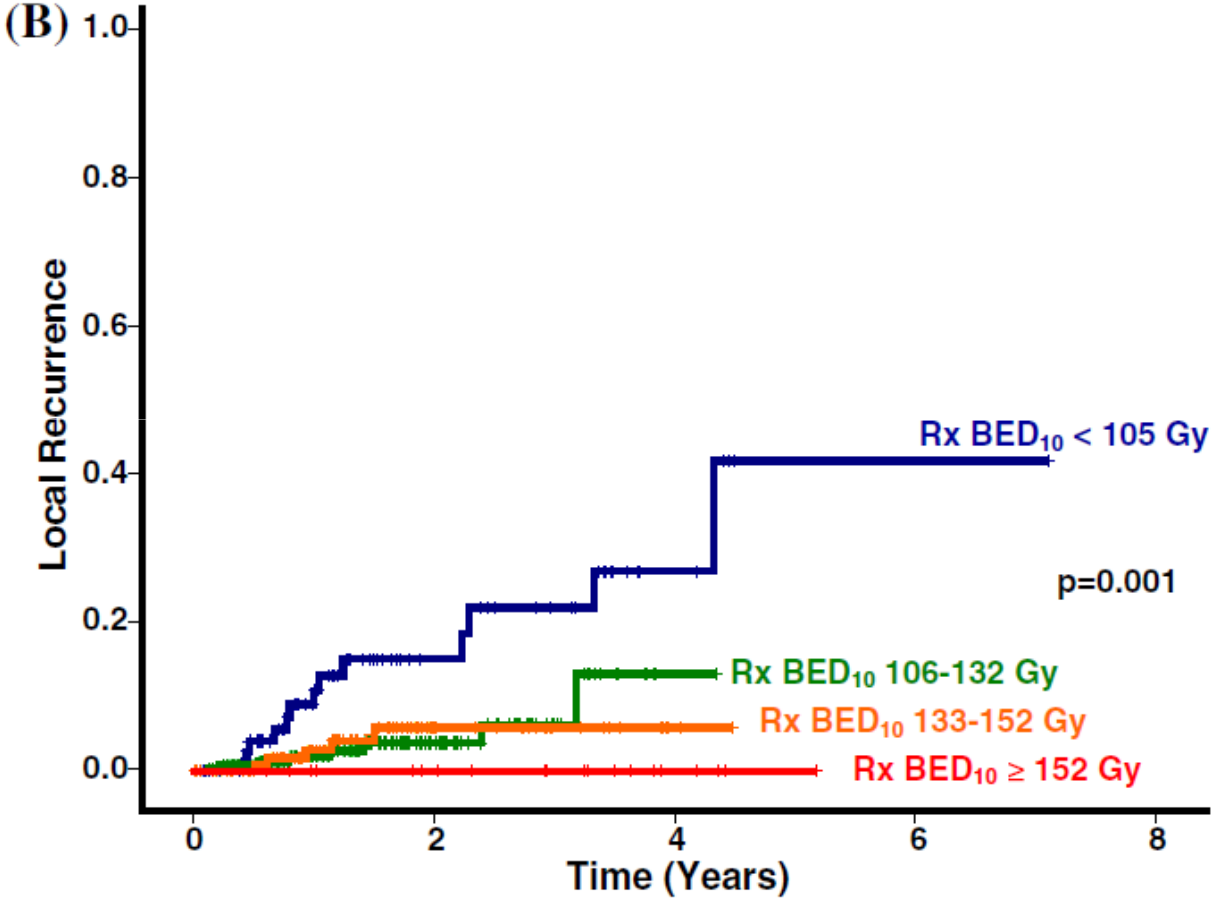
Local recurrence by prescription BED_{10} quartile



2-year LR

15%

6%

4%

0%

Kestin et al, Radiother Oncol 2014

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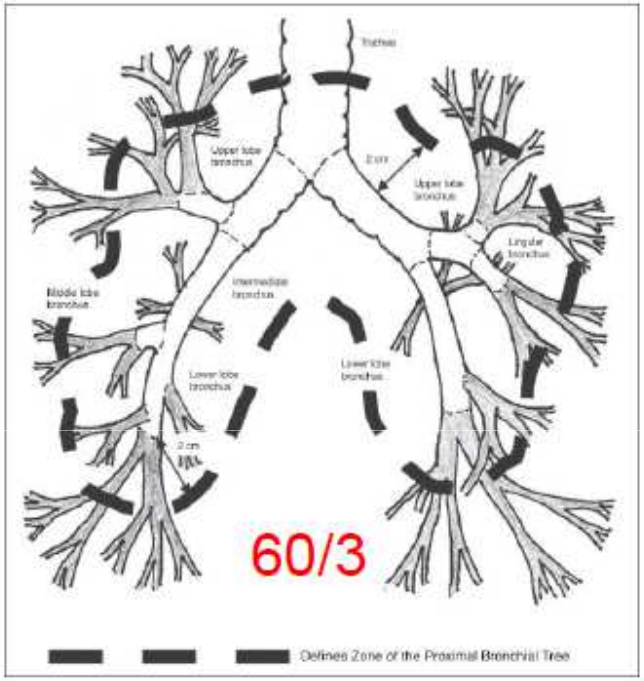
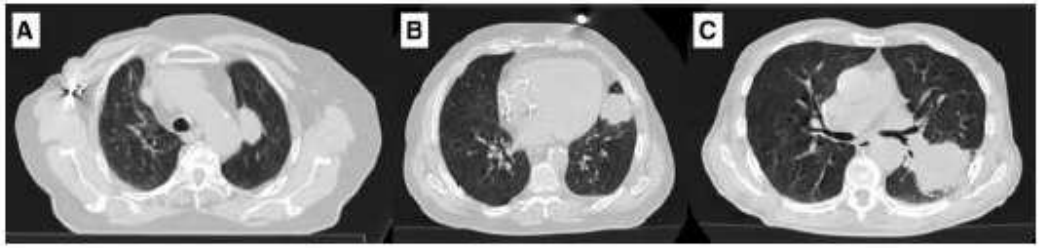
Central Tumors





60/8

- Meta-analysis (Senthi 2012):
  - $BED_{10} \geq 100$ to maximize local control
  - $BED_3 \leq 240$ to keep risk of fatal toxicity to 1%.

TABLE 3. Early and Late Toxicity After SABR in 63 Patients with Central Stage Early-Stage NSCLC (Absolute Patient Numbers)

	Acute Toxicity			Late Toxicity (>3 mo)		
	I	II	III	I	II	III
Dyspnea	5	2	—	3	2	2
Chest wall pain	3	1	1	4	2	1
Fatigue	10	1	—	4	1	—
Coughing	5	—	—	—	—	—
Nausea	3	—	—	—	—	—
Radiation dermatitis	1	1	—	—	1	—
Hemoptysis	1	1	—	—	1	—
Esophagitis	1	—	—	—	—	—
Pleural effusion	—	—	—	—	1	—
Rib fracture	—	—	—	—	—	1
Bronchial stenosis	—	—	—	—	1	—
Total (% of patients)	29 (62)	6 (10)	1 (2)	11 (17)	9 (14)	4 (6)

SABR, stereotactic ablative radiotherapy; NSCLC, non-small cell lung cancer.

From DA Palma, ASTRO 2014

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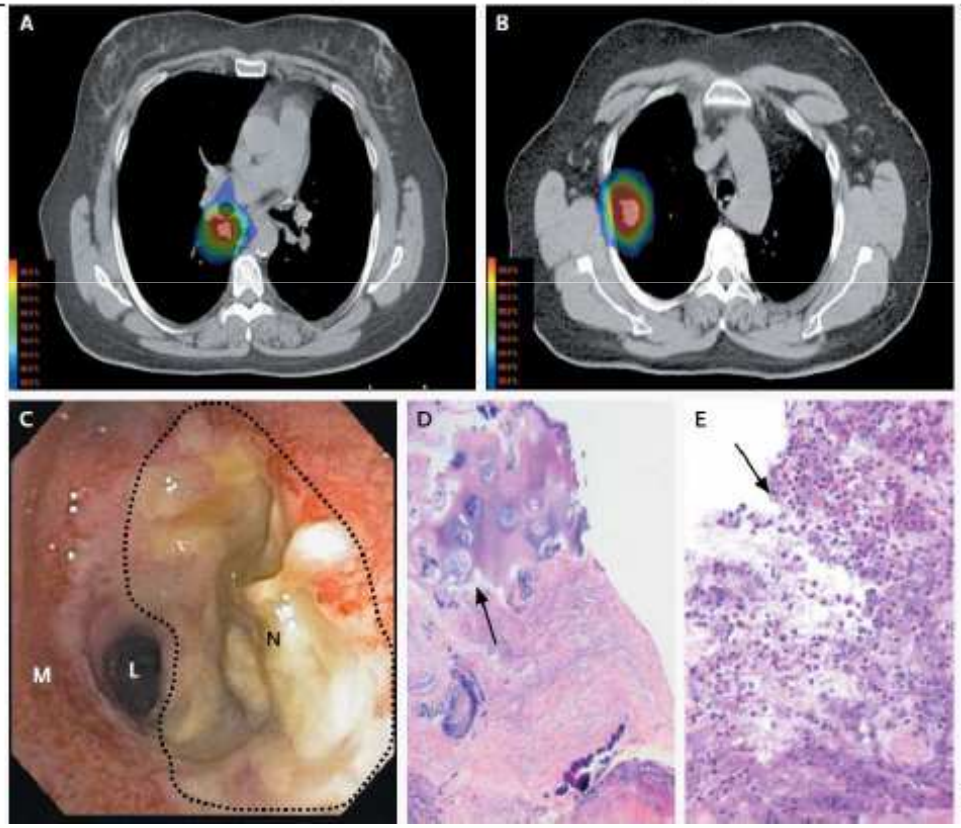
Still need to be cautious

Central-Airway Necrosis after Stereotactic Body-Radiation Therapy



Corradeeti, Haas, Rengan NEJM 2012

From DA Palma, ASTRO 2014

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CONSIDERATION OF DOSE LIMITS FOR ORGANS AT RISK OF THORACIC RADIOTHERAPY: ATLAS FOR LUNG, PROXIMAL BRONCHIAL TREE, ESOPHAGUS, SPINAL CORD, RIBS, AND BRACHIAL PLEXUS

Table 1. Dosimetric limits for thoracic organs at risk

Dose limits for OARs	3D-CRT (RTOG 0617)	3D-CRT (RTOG 0972/CALGB 36050)	SBRT (RTOG 0618, 3 fx)	SBRT (ROSEL European trial, 3 or 5 fx)
Spinal cord (point dose)	Point dose ≤50.5 Gy	Any portion ≤50 Gy	≤18 Gy (6 Gy/fx)	18 Gy (3 fx) 25 Gy (5fx)
Lung	Mean lung dose ≤20 Gy, V_{20} ≤37%	V_{20} ≤35%	V_{20} ≤10%*	V_{20} <5–10%†
Esophagus	Mean dose ≤34 Gy	Not limited	≤27 Gy (9 Gy/fx)	24 Gy (3 fx) 27 Gy (5 fx)
Brachial plexus (point dose)	≤66 Gy	Not limited	≤24 Gy (8 Gy/fx)	24 Gy (3 fx) 27 Gy (5 fx)
Heart‡	≤60, ≤45, ≤40 Gy for 1/3, 2/3, 3/3 of heart	≤60, ≤45, ≤40 Gy for 1/3, 2/3, 3/3 of heart	≤30 Gy (10 Gy/fx)	24 Gy (3 fx) 27 Gy (5 fx)
Trachea, bronchus	Not limited	Not limited	≤30 Gy (10 Gy/fx)	30 Gy (3 fx) 32 Gy (5 fx)
Ribs	Not limited	Not limited	Not limited§	Not limited
Skin	Not limited	Not limited	≤24 Gy (8 Gy/fx)	Not limited

Abbreviations: OARs = organs at risk; 3D-CRT = three-dimensional conformal radiotherapy; RTOG = Radiation Therapy Oncology Group; CALGB = Cancer and Leukemia Group B; SBRT = stereotactic body radiotherapy; ROSEL = *Radiosurgery Or Surgery for Early Lung Cancer*; fx = fraction; V_{20} = percentage of both lungs (without inclusion of gross tumor volume) receiving ≥20 Gy.

* Other constraints limited dose within 2 cm of target.

† V_{20} ≤5% for tumor ≤2 cm, V_{20} ≤5% for tumor 2–5 cm.

Fen-Ming Kong et al, IJROBP 2010

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Normal Tissue Constraints

Tab. 1 Normal tissue constraints according to published major clinical studies. Radiation Therapy Oncology Group (RTOG) protocols can be found on the RTOG website at http://www.rtog.org/ClinicalTrials/ProtocolTable.aspx

Organ at risk	Single fraction (RTOG 0915)	Three fractions (RTOG 0618/1021)	Four fractions (RTOG 0915)	Five fractions (RTOG 0813)	Eight fractions (Haasbeck et al. 2011 [76])
Trachea and large bronchus	D_{max} 20.2 Gy	D_{max} 30 Gy	D_{max} 34.8 Gy 15.6 Gy <4 cc	D_{max} 105%[a] 18 Gy <5 cc[b]	D_{max} 44 Gy
Heart	D_{max} 22 Gy 16 Gy <15 cc	D_{max} 30 Gy	D_{max} 34 Gy 28 Gy <15 cc	D_{max} 105%[a] 32 Gy <15 cc	–
Esophagus	D_{max} 15.4 Gy 11.9 Gy <5 cc	D_{max} 25.2 Gy 17.7 G <5 cc	D_{max} 30 Gy 18.8 Gy <5 cc	D_{max} 105%[a] 27.5 Gy <5 cc[b]	D_{max} 40 Gy
Brachial plexus	D_{max} 17.5 Gy 14 Gy <3 cc	D_{max} 24 Gy 20.4 Gy <3 cc	D_{max} 27,2 Gy 23.6 Gy <3 cc	D_{max} 32 Gy 30 Gy <3 cc	D_{max} 36 Gy
Chest wall	D_{max} 30 Gy 22 Gy <1 cc	30 Gy <30 cc 60 Gy <3 cc [77, 78]	D_{max} 27,2 Gy 32 Gy <1 cc	30 Gy <30 cc 60 Gy <3 cc [77, 78]	–
Spinal cord	D_{max} 14 Gy 10 Gy <0.35 cc	D_{max} 18 Gy (RTOG 0236)	D_{max} 26 Gy 28.8 Gy <0.35 cc	D_{max} 30 Gy 22.5 Gy <0.25 cc	D_{max} 28 Gy

Guckenberger et al, Strahlenther Onkol 2014

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Prognostic factors

TABLE 3. Multivariate Analysis of Factors Influencing OS and FFLP

		OS			FFLP		
Parameter		***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**
Performance status	<80	0.02	1.44	1.05 to 1.97			
Clinical stage	IB	0.007	1.52	1.12 to 2.07	0.08	1.66	0.95 to 2.92
Baseline FEV_1 (%)	Continuous variable	0.07	0.99	0.99 to 1.00			
Biopsy status	No biopsy	0.09	1.49	0.94 to 2.35	0.02	2.53	1.17 to 5.48
Staging FDG-PET	Yes				>0.1		
Histology	SCC				0.03	2.03	1.06 to 3.89
PTV-encompassing dose (Gy BED)	≥106	0.01	0.62	0.43 to 0.90	0.04	0.39	0.16 to 0.93
Dose inhomogeneity (PTV-encompassing dose / maximum dose) (%)	≥ 80				0.06	1.74	0.98 to 3.08
IGRT technology	In-room IGRT				>0.1		
SBRT procedures/institution and year	<9	>0.1			>0.1		

Guckenberger et al, JTO 2013

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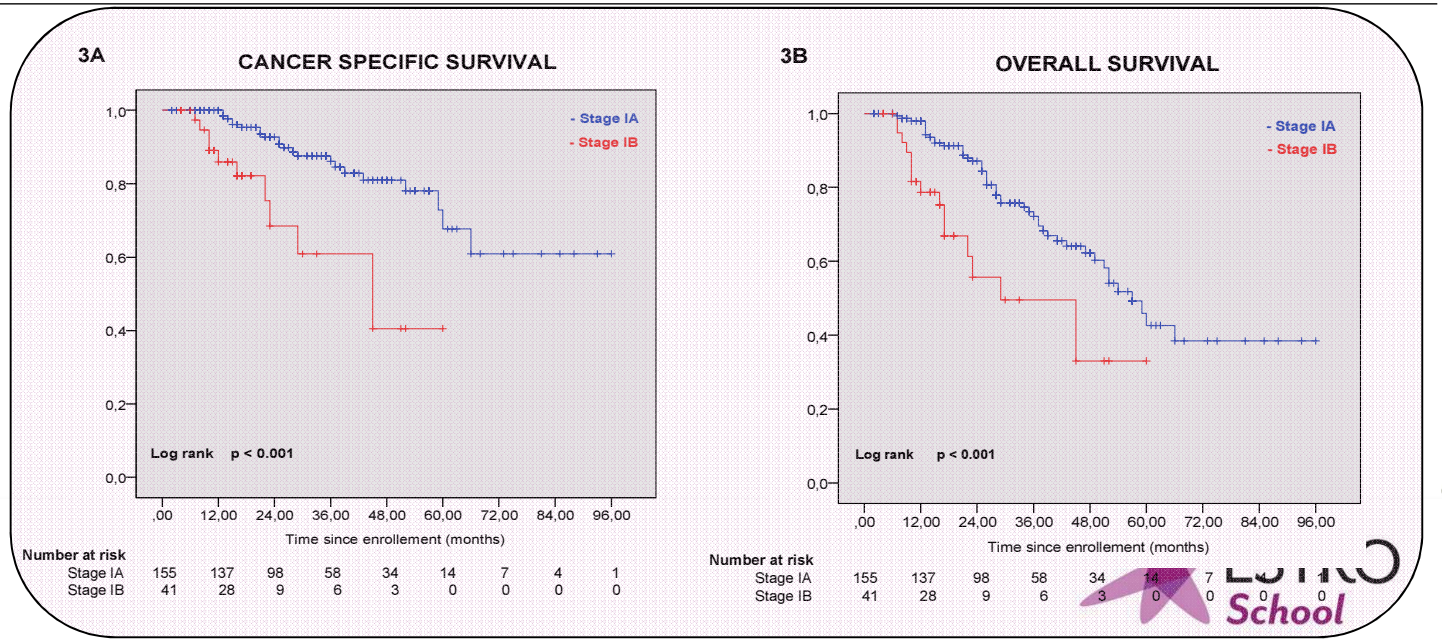
Prognostic factors

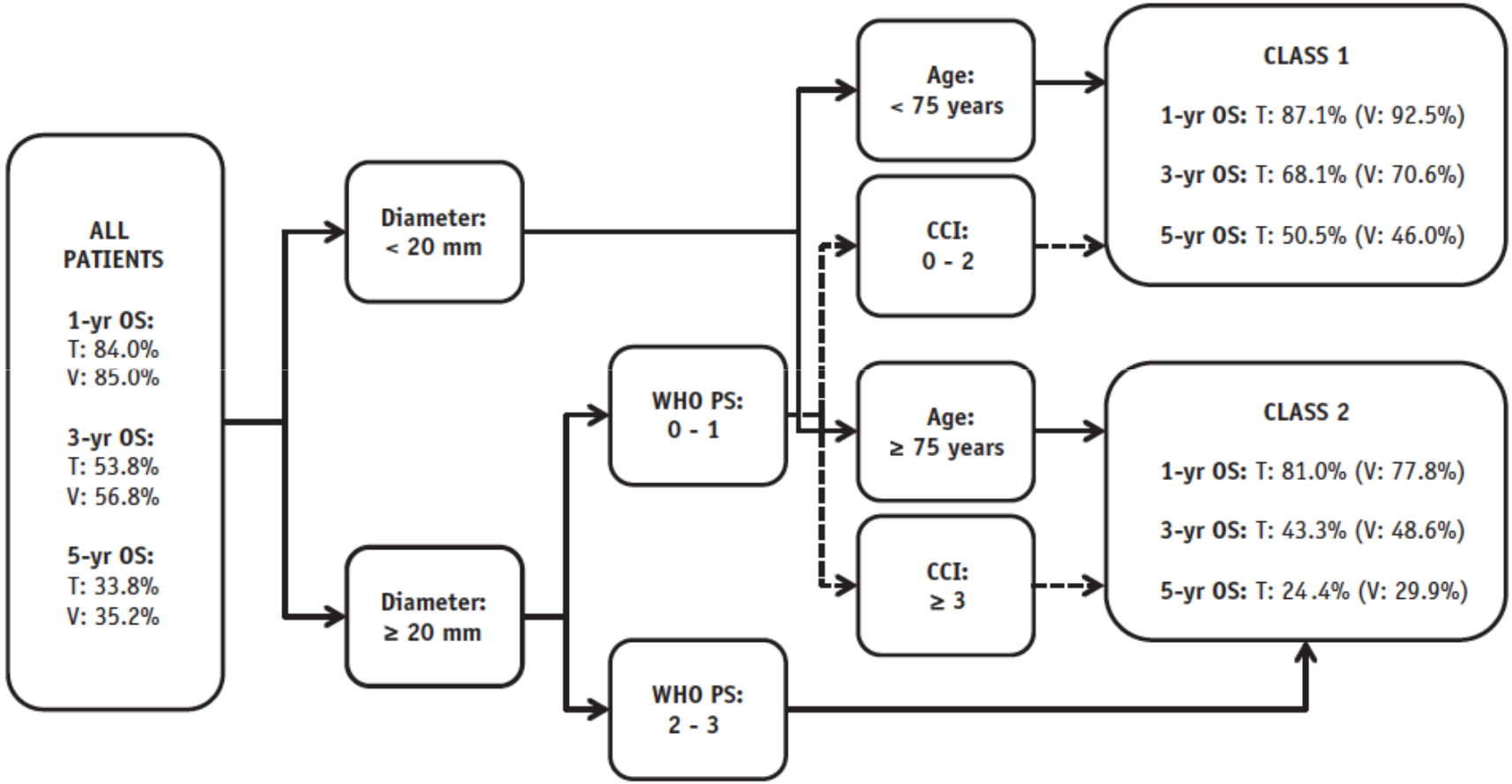
Table 3
Multivariate analysis.

Parameter	LR		DFS		OS		CSS	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Stage								
IB vs IA	0.55 (0.03–10.3)	0.69	3.06 (1.62–5.77)	0.001*	2.46 (1.28–4.74)	0.007*	3.47 (1.50–7.98)	0.003*
GTV volume								
>13 cc vs ≤13 cc	4.4 (0.73–26.7)	0.1	1.04 (0.57–1.88)	0.89	1.04 (0.59–1.82)	0.89	1.37 (0.59–3.16)	0.45
Sex								
Male vs Female	0.5 (0.08–3.2)	0.47	1.05 (0.57–1.92)	0.87	0.94 (0.51–1.74)	0.86	0.79 (0.31–1.98)	0.61
Age								
>75 years vs ≤75 years	0.6 (0.15–2.57)	0.52	1.39 (0.83–2.36)	0.21	1.39 (0.83–2.32)	0.2	1.28 (0.63–2.61)	0.49
Histology								
Adenocarcinoma vs others	2.42 (0.39–14.84)	0.34	1.12 (0.64–1.97)	0.68	1.21 (0.68–2.16)	0.8	1.17 (0.52–2.61)	0.69

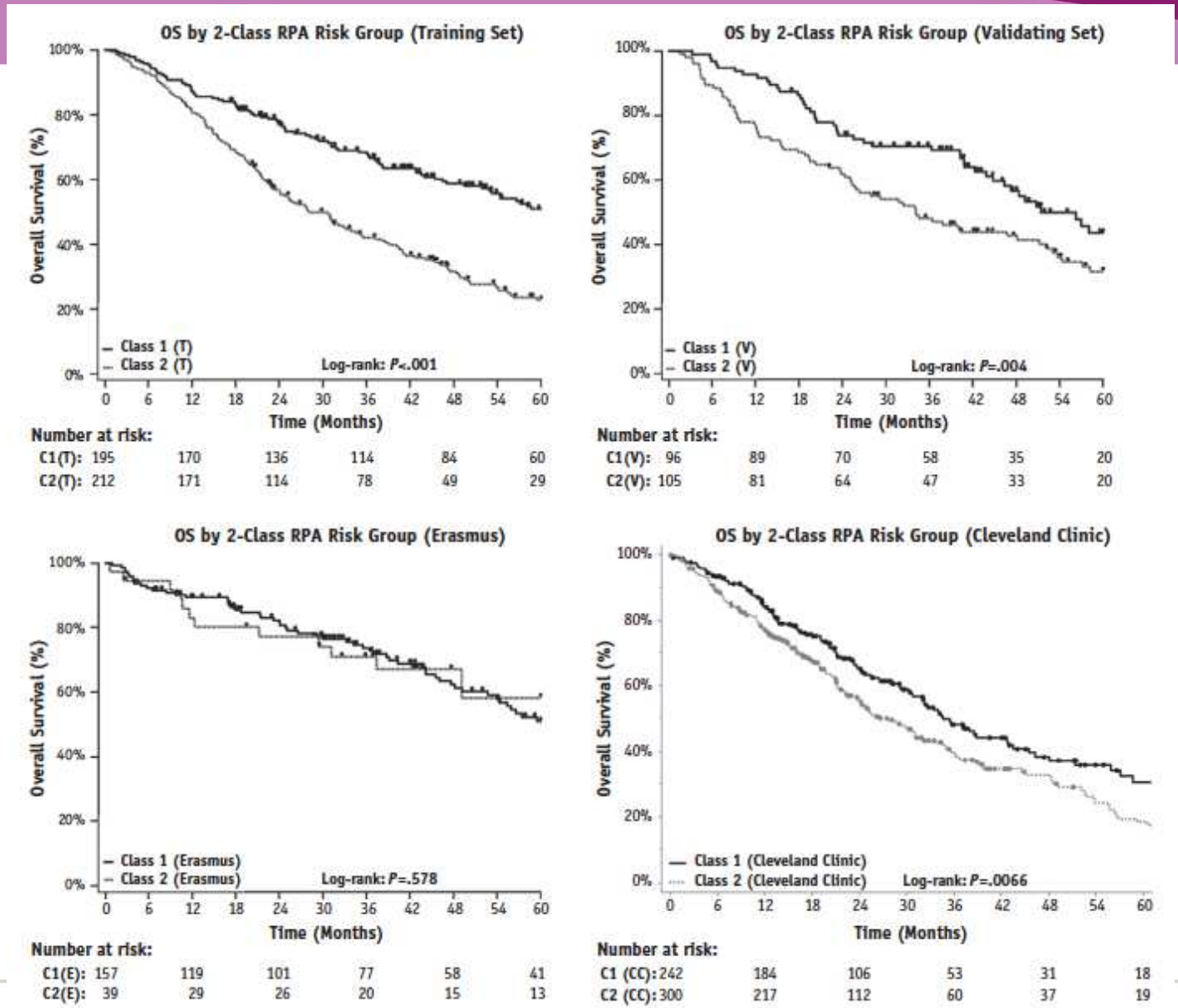


Ricardi et al, Lung Cancer 2014

Prognostic factors: RPA risk groups according to the Amsterdam model



Louie et al, IJROBP 2015



Louie et al, IJROBP 2015

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Toxicity and Quality of Life

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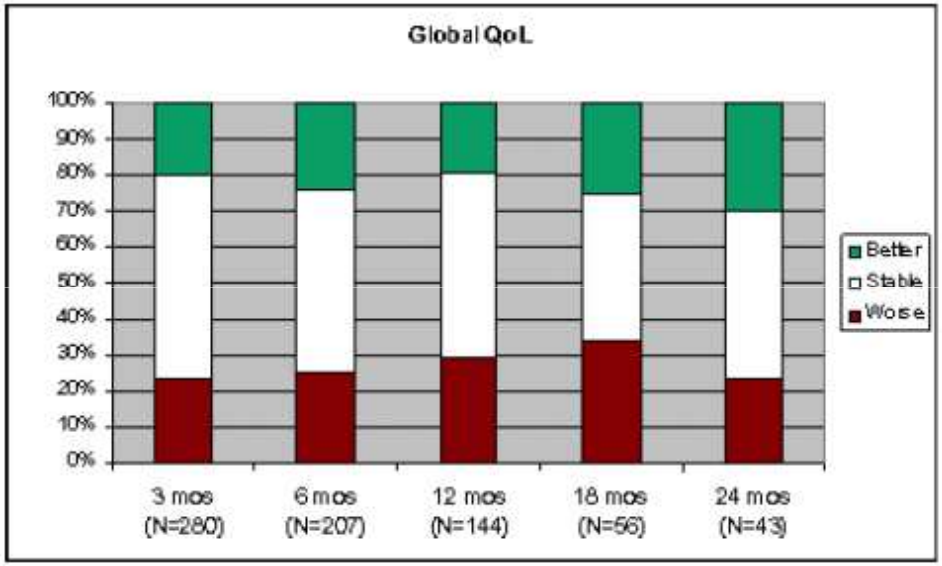
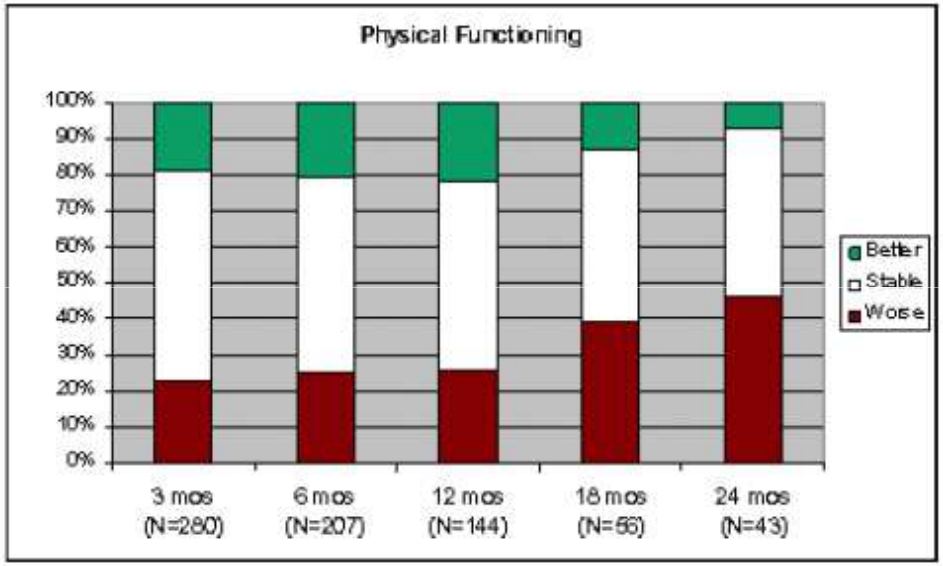
No Clinically Significant Changes in Pulmonary Function Following Stereotactic Body Radiation Therapy for Early-Stage Peripheral Non-Small Cell Lung Cancer: An Analysis of RTOG 0236

- Poor baseline PFT did not predict decreased OS
- FEV1 mean decline 5.8%; DLCO mean decline 6.3% (SS at 6 weeks and 3 months)
- Minimal changes of arterial blood gases and no decline in oxygen saturation

Stanic S et al, IJROBP 2014

Quality of Life – self assessed





Lagerwaard et al, JTO 2012

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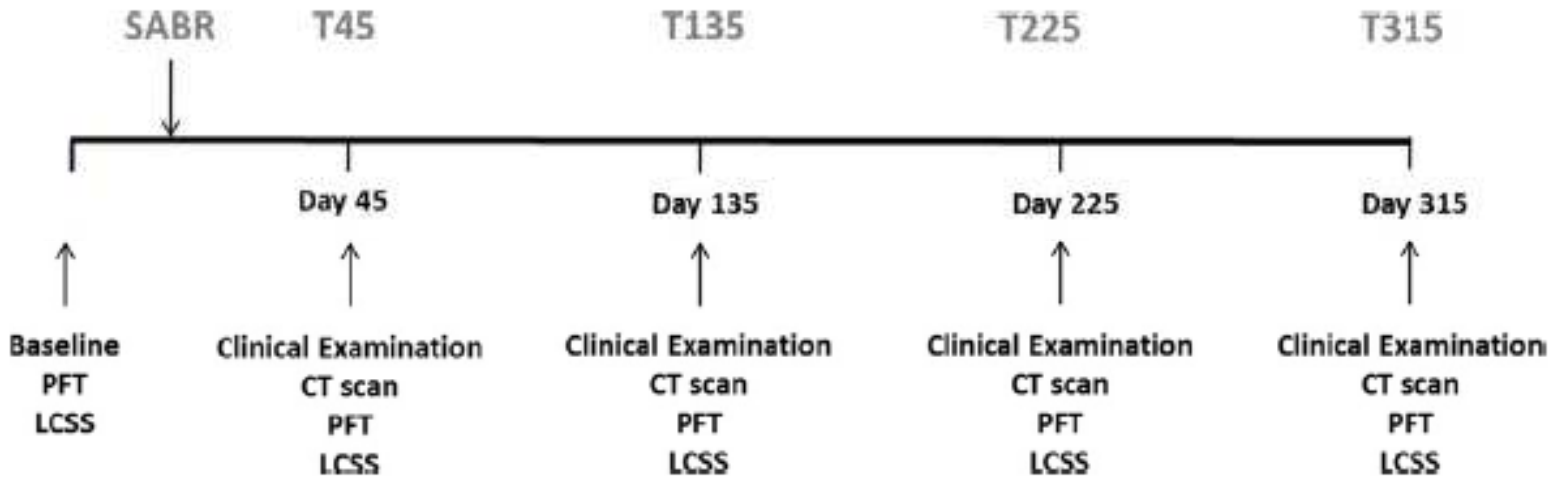
Pulmonary function and quality of life: outline of a prospective study



Pulmonary function and quality of life after VMAT-based stereotactic ablative radiotherapy for early stage inoperable NSCLC: a prospective study

Cinzia Ferrero[a,1], Serena Badellino[b,1], Andrea Riccardo Filippi[b,*], Luana Focaraccio[b], Matteo Giaj Levra[b], Mario Levis[b], Francesco Moretto[b], Roberto Torchio[a], Umberto Ricardi[b], Silvia Novello[b]

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[b] Department of Oncology, University of Torino, Torino, Italy

Age (mean, range)	77 (61–84)
Male	23 (76.7%)
Female	7 (23.3%)
Former smokers	19 (63.3%)
Active smokers	8 (26.7%)
Never smokers	3 (10%)
Performance status (ECOG)	
0	23 (76.7%)
1	6 (20%)
2	1 (3.4%)
AA Charlson CI (mean, range)	6.9 (3–14)
<7	16 (53.3%)
≥7	14 (46.7%)
Stage	
IA	17 (56.7%)
IB	13 (43.3%)
Tumor max diameter, mm (mean, range)	25.5 (12–55)
Histology	
Adenocarcinoma	9 (30%)
Squamous cell carcinoma	8 (26.7%)
NSCLC NOS	4 (13.3%)
Unknown	9 (30%)
Treatment schedules	
45–54 Gy/3 fr	9 (30%)
55 Gy/5 fr	11 (37%)
60 Gy/8 fr	10 (33%)

Lung Cancer, 2015

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Changes in PFTs from baseline at different timepoints

Pulmonary function test	Baseline (n=30)		Days 45 post-SABR			Days 135 post-SABR			Days 225 post-SABR			Days 315 post-SABR		
	N	Raw	n	Raw	Change since baseline	n	Raw	Change since baseline	n	Raw	Change since baseline	n	Raw	Change since Baseline
FEV_1 (liters)	30	1.7 ± 0.5	30	1.7 ± 0.5	−0.01 ± 0.18	28	1.6 ± 0.5	−0.73 ± 0.22	25	1.6 ± 0.5	−0.79 ± 0.23	19	1.5 ± 0.5	−0.19 ± 0.33
FEV_1 (% predicted)	30	75.3 ± 23.1	30	75.5 ± 24.4	−0.49 ± 7.53	28	72.4 ± 25.1	−3.21 ± 9.18	25	72.9 ± 26.3	−3.26 ± 9.49	19	64.3 ± 23.4	−7.57 ± 11.66
FEV_1/SVC	30	61.6 ± 13.3	30	60.0 ± 12.9	−1.12 ± 3.74	28	59.8 ± 13.1	−0.93 ± 4.26	25	59.1 ± 14.2	−0.84 ± 5.68	19	57.1 ± 14.0	−1.85 ± 6.85
FEV_1/SVC (%predicted)	30	82.2 ± 19.1	30	80.3 ± 18.3	−1.41 ± 5.23	28	79.7 ± 18.5	−1.19 ± 6.48	25	78.7 ± 19.9	−0.72 ± 7.33	19	76.1 ± 19.9	−2.14 ± 9.35
SVC (liters)	30	2.9 ± 0.8	30	2.9 ± 0.8	0.06 ± 0.24	28	2.8 ± 0.9	−0.10 ± 0.33	25	2.8 ± 0.7	−0.12 ± 0.34	19	2.7 ± 0.7	−0.26 ± 0.66
SVC (% predicted)	30	92.1 ± 21.8	30	94.5 ± 23.5	1.05 ± 8.45	28	91.2 ± 25.9	−2.56 ± 14.67	25	92.3 ± 23.9	−3.12 ± 10.62	19	84.3 ± 20.8	−7.33 ± 16.88
RV (liters)	30	3.2 ± 1	30	3.0 ± 1	−0.12 ± 0.54	28	3.0 ± 1.0	−0.97 ± 0.54	25	2.8 ± 0.9	−0.34 ± 0.52	19	3.0 ± 1.2	−0.22 ± 0.69
RV (% predicted)	30	130.4 ± 47.0	30	123.6 ± 46.8	−5.02 ± 21.26	28	123.9 ± 49.3	−4.4 ± 21.53	25	117.6 ± 45.4	−14.28 ± 20.39	19	123.3 ± 58.7	−8.94 ± 28.38
TLC (liters)	30	6.0 ± 1.4	30	5.9 ± 1.4	−0.11 ± 0.54	28	5.7 ± 1.5	−0.19 ± 0.61	25	5.6 ± 1.3	−0.46 ± 0.73	19	5.7 ± 1.5	−0.47 ± 0.97
TLC (% predicted)	30	103.2 ± 20.2	30	100.9 ± 20.9	−2.11 ± 8.77	28	99.3 ± 22.5	−3.73 ± 11.09	25	96.9 ± 21.7	−8.46 ± 10.45	19	96.2 ± 25.7	−7.81 ± 14.25
D_LCO (ml/min/mmHg)	30	14.7 ± 4.5	30	13.3 ± 4.4	−1.48 ± 2.36	28	13.5 ± 3.9	−1.50 ± 2.63	25	13.1 ± 3.3	−1.73 ± 3.22	19	11.6 ± 4.6	−3.57 ± 3.55
D_LCO (% predicted)	30	67.0 ± 18.5	30	60.8 ± 18.8	−6.35 ± 11.34	28	62.2 ± 16.4	−6.32 ± 11.56	25	60.6 ± 17.2	−6.84 ± 14.83	19	51.6 ± 17.6	−14.61 ± 14.85
D_LCO/VA (ml/min/mmHg)	30	3.5 ± 1.4	30	3.1 ± 0.9	−0.4 ± 1.23	28	3.2 ± 0.9	−0.41 ± 1.34	25	3.2 ± 0.8	−0.39 ± 15.2	19	2.9 ± 0.8	−0.68 ± 1.43
D_LCO/VA (% predicted)	30	90.2 ± 27.3	30	84.0 ± 26.3	− 5.9 ± 12.45	28	86.5 ± 29.5	− 5.32 ± 14.72	25	85.0 ± 24.3	− 3.92 ± 15.2	19	77.6 ± 23.9	− 10.0 ± 16.33
PaO_2 (mmHg)	30	75.1 ± 8.5	30	73.1 ± 9.7	−1.7 ± 7.89	28	72.7 ± 8.8	−3.11 ± 7.56	25	76.2 ± 6.4	−1.14 ± 7.63	19	74.6 ± 10.3	−1.02 ± 8.83
$PaCo_2$ (mmHg)	30	38.3 ± 4.4	30	37.4 ± 3.7	−0.95 ± 4.05	28	37.7 ± 4.5	−0.48 ± 3.5	25	37.8 ± 3.6	0.32 ± 3.16	19	37.8 ± 4.7	−0.66 ± 5.18

Ferrero, Badellino et al, Lung Cancer 2015

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Logistic regression analysis

Logistic regression model analysis of baseline pulmonary function tests and toxicity.

Pulmonary function test	Any pulmonary toxicity			Grade 2+ pulmonary toxicity			Any late radiological toxicity (Koenig)		
	No. of events/total	OR (95% CI)	*p* Value	No. of events/total	OR (95% CI)	*p* Value	No. of events/total	OR (95% CI)	*p* Value
FEV_1 (liters)	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	16 (0.1–200)	0.26
FEV_1 (%predicted)	16/30	1.5 (0.1–22)	0.75	11/30	3.1 (0.4–21.4)	0.26	7/24	NA-unstable	–
FEV_1/SVC	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	NA-unstable	–
FEV_1/SVC (%predicted)	16/30	0.02 (0–7.7)	0.2	11/30	0.02 (0–7)	0.18	7/24	NA-unstable	–
SVC	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	0.1 (0.003–7.8)	0.34
SVC (%predicted)	16/30	0.1 (0–5)	0.22	11/30	0.1 (0–6.7)	0.21	7/24	NA-unstable	–
RV (liters)	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	NA-unstable	–
RV (%predicted)	16/30	5.04 (0.4–75.2)	0.24	11/30	8.6 (0.5–150.3)	0.14	7/24	NA-unstable	–
TLC (liters)	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	0.7 (0.1–3.6)	0.68
TLC (%predicted)	16/30	0.03 (0–5.5)	0.19	11/30	0.008 (0–2.8)	0.11	7/24	NA-unstable	–
D_LCO (ml/min/mmHg)	16/30	NA-unstable	–	11/30	0.001 (0–6.5)	0.12	7/24	0.9 (0.6–1.2)	0.39
D_LCO (%predicted)	16/30	8.8 (0.6–136)	0.12	11/30	8.8 (0.7–105.4)	0.09	7/24	NA-unstable	–
D_LCO/VA (ml/min/mmHg)	16/30	NA-unstable	–	11/30	NA-unstable	–	7/24	NA-unstable	–
D_LCO/VA (%predicted)	16/30	3.9 (0.3–55)	0.31	11/30	3.7 (0.2–75.2)	0.4	7/24	NA-unstable	–
PaO_2 (mmHg)	16/30	1.0 (0.8–1.3)	0.94	11/30	0.9 (0.5–1.6)	0.72	7/24	1.1 (0.9–1.3)	0.41
$PaCo_2$ (mmHg)	16/30	0.8 (0.1–4.3)	0.75	11/30	0.3 (0.1–1.3)	0.12	7/24	NA-unstable	–

Normal lungs dose-volume distributions by development of any grade clinical lung toxicity.

Parameter	All patients ($n=30$)	Pneumonitis ($n=14$)	No pneumonitis ($n=16$)	OR (95% CI)	*P* value
Ipsilateral lung V_{20Gy} (%)	15.6 ± 5.5	15.1 ± 5.8	16.1 ± 5.4	1.03 (0.91–1.18)	0.61
Ipsilateral lung V_{10Gy} (%)	24.5 ± 6.8	22.9 ± 6.9	26.1 ± 6.5	1.07 (0.96–1.21)	0.22
Ipsilateral lung V_{5Gy} (%)	34.9 ± 8.6	31.7 ± 8.2	38.1 ± 8.0	1.11 (0.99–1.24)	0.058
Ipsilateral mean lung dose (EQD_{2Gy})	11.9 ± 3.5	11.7 ± 3.9	12.1 ± 3.1	1.03 (0.83–1.27)	0.82
Bilateral lung V_{20Gy} (%)	7.8 ± 2.6	7.8 ± 2.8	7.8 ± 2.6	0.99 (0.75–1.32)	0.97
Bilateral lung V_{10Gy} (%)	14.4 ± 5.1	14.6 ± 6.1	14.2 ± 3.9	0.98 (0.85–1.14)	0.84
Bilateral lung V_{5Gy} (%)	24.8 ± 7.4	24.7 ± 8.9	24.8 ± 6.0	1.0 (0.90–1.10)	0.97
Bilateral mean lung dose (EQD_{2Gy})	6.9 ± 1.9	7.0 ± 2.2	6.9 ± 1.6	0.98 (0.66–1.44)	0.91
Absolute lung volume spared from a 5 Gy dose (VS5, in cc)	3088.9 ± 790.3	3157.4 ± 699	3020.4 ± 893.5	1.02 (0.78–1.17)	0.65

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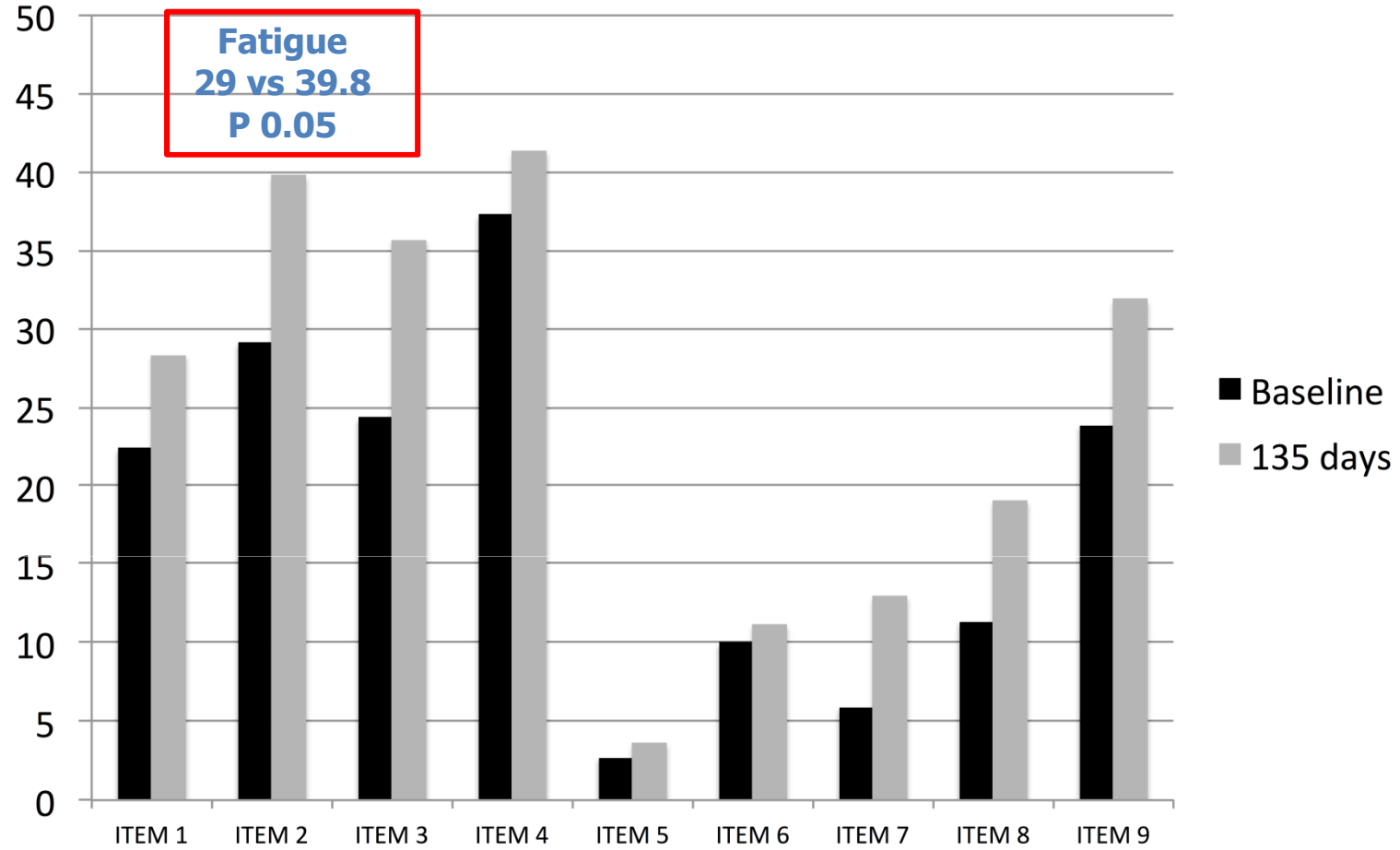

- Lung Cancer Symptom Scale (LCSS)
- Worsening of the item 2 "Fatigue" (mean basal value =29, mean value at T_{135} = 39.8, p = 0.05)

Ferrero C, Badellino S et al, Lung Cancer 2015

ESTRO School

Survivorship following SABR

Second primary lung cancer (SPLC):

- risk of developing a SPLC at a rate of approximately 3% per year (smoking cessation!)

A Brief Report on Outcomes of Stereotactic Ablative Radiotherapy for a Second Primary Lung Cancer: Evidence in Support of Routine CT Surveillance

Gwendolyn H.M.J. Griffioen, MD, Frank J. Lagerwaard, MD, PhD, Cornelis J.A. Haasbeek, MD, PhD, Ben J. Slotman, MD, PhD, and Suresh Senan MRCP, FRCR, PhD

TABLE 1. Patient, Tumor, and Treatment Characteristics (n = 107)

Characteristics	n (%) or Median (Range)
Male gender	73 (68%)
Age at SPLC (years)	72 (50–90)
Treatment interval (months)	48 (6–349)
COPD	85 (79.4%)
Charlson Comorbidity Index	3 (0–10)
WHO Performance Score (PS)	1 (0–3)
Stage initial lung cancer (7th TNM)	
Stage I	67 (62.6%)
Stage II	18 (16.8%)
Stage III	17 (15.9%)
Stage IV	3 (2.8%)
Unknown	2 (1.9%)
Treatment initial lung cancer	
Lobectomy/bilobectomy/trimodality	78 (72.9%)
Pneumonectomy	17 (15.9%)
Wedge/segmentectomy	3 (2.8%)
CRT	7 (6.5%)
Palliative (chemo or RT)	2 (1.9%)

Metachronous second primary lung cancer (SPLC)

J Thor Oncol 2014

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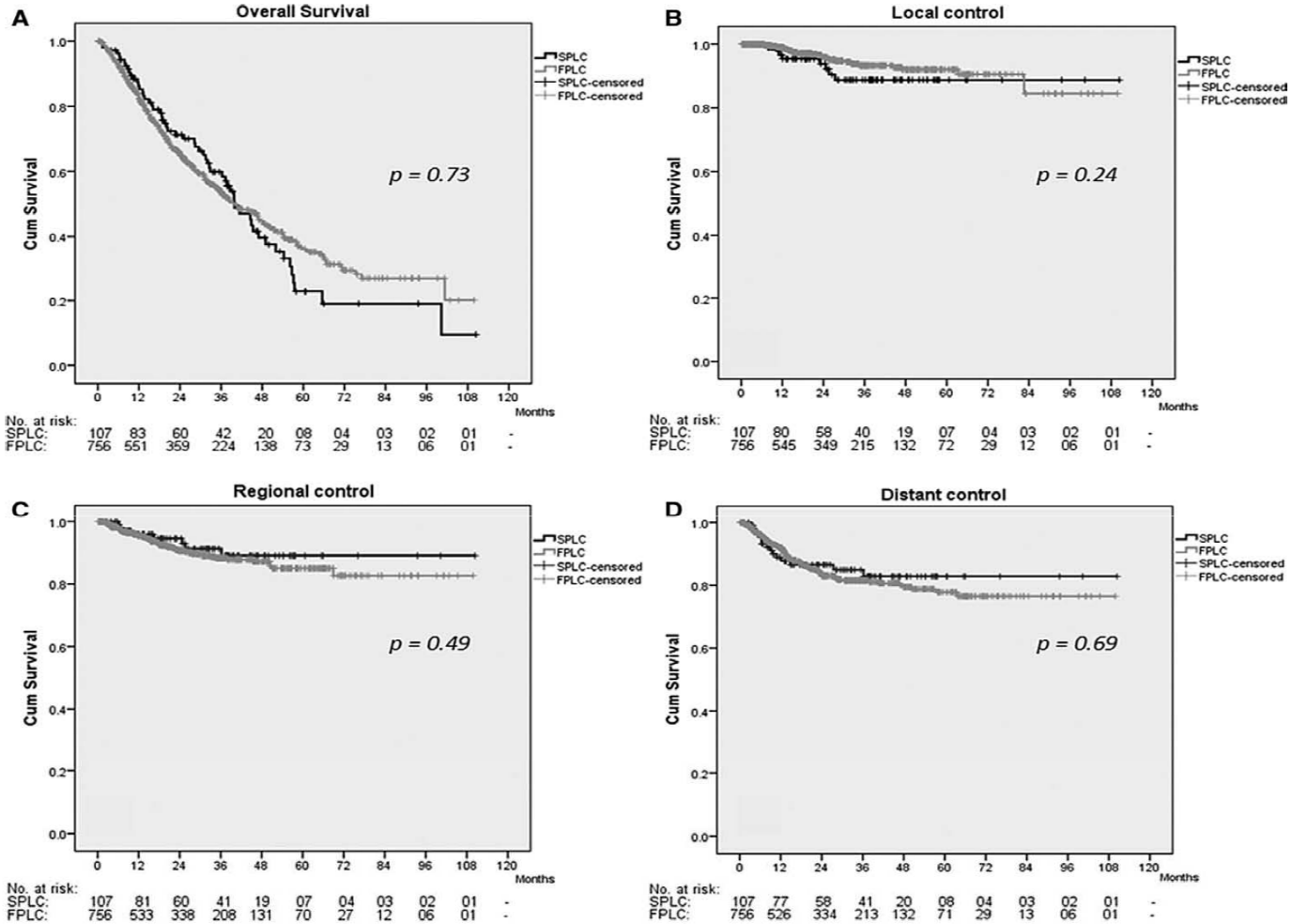

FIGURE 2. Kaplan-Meier curves comparing (*A*) overall survival and (*B*) local, (*C*) regional, and (*D*) distant control rates between patients treated with stereotactic ablative radiotherapy for a "first" primary lung cancer (FPLC; gray line, *n* = 756) and a metachronous second primary lung cancer (SPLC; black line, *n* = 107)

Griffoen et al, J Thor Oncol 2014

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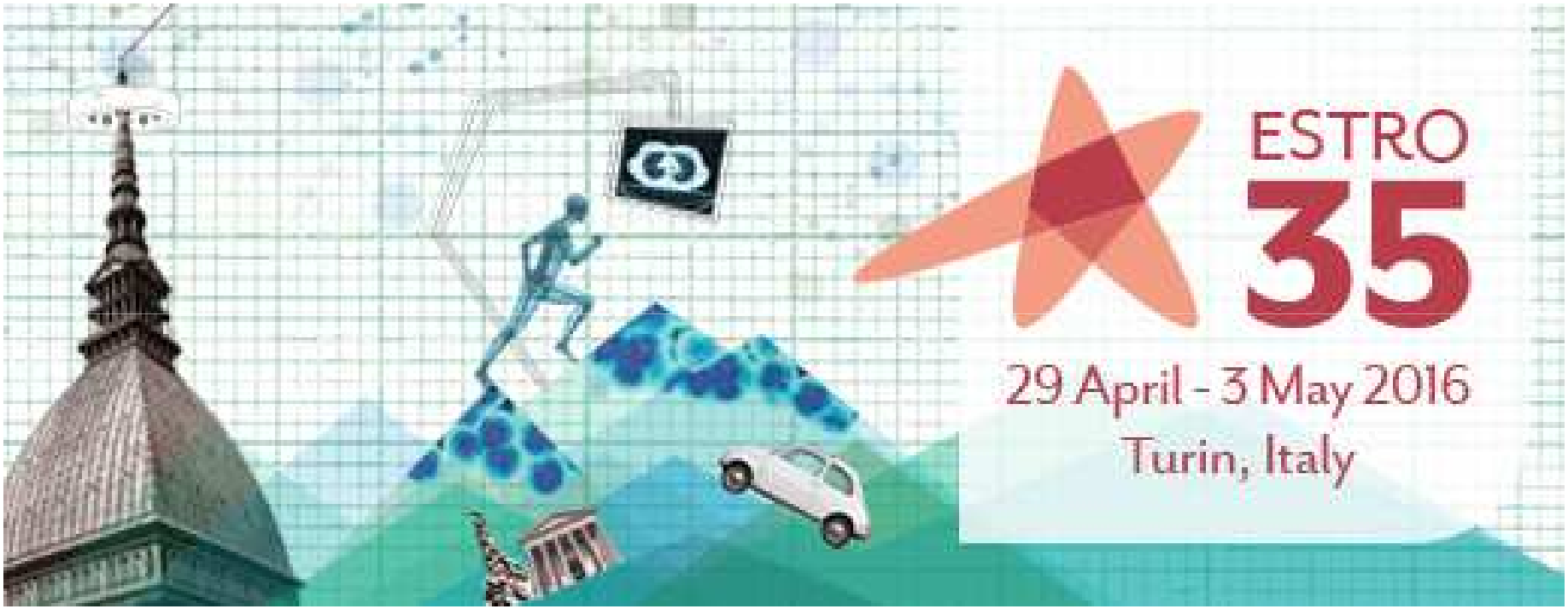
Final Remarks

- SBRT is currently widely accepted as the best alternative to surgery for inoperable early stage lung cancer
- SBRT might be offered also to operable patients
- IGRT-motion management are essential for prescribing high BED: IMRT is an option
- Mature data with long-term follow up are needed to better understand the pattern of relapse across time
- Predictive and prognostic factors are needed to possibly offer to higher risk patients adjuvant therapies



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EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Modena
Policlinico

Breast IMRT
Secondary Tumor Risk

Frank Lohr, M.D.
Policlinico Modena

Disclosure

Research and Training Agreement, Expert Testimony and Travel Grants with Elekta/IBA/C-Rad

Board Member of C-Rad

One's own experience has the advantage of absolute certainty - *Schopenhauer*

No man's knowledge (here) can go beyond his own experience - *Locke*

Stupid is as stupid does - *Gump*

Literature overview plus some VERY SUBJECTIVE COMMENTARIES!!

Clinical Application of IMRT

Most important indications and treatment philosophy

1. **Head and Neck Cancer**
   CNS

   Paranasal Sinus Tumors / Integrated Boost
   (Better Tumor coverage and shortening of overall treatment time)

   NPC and other ENT Tumors
   (Parotid sparing when possible, better tumor coverage for NPC)

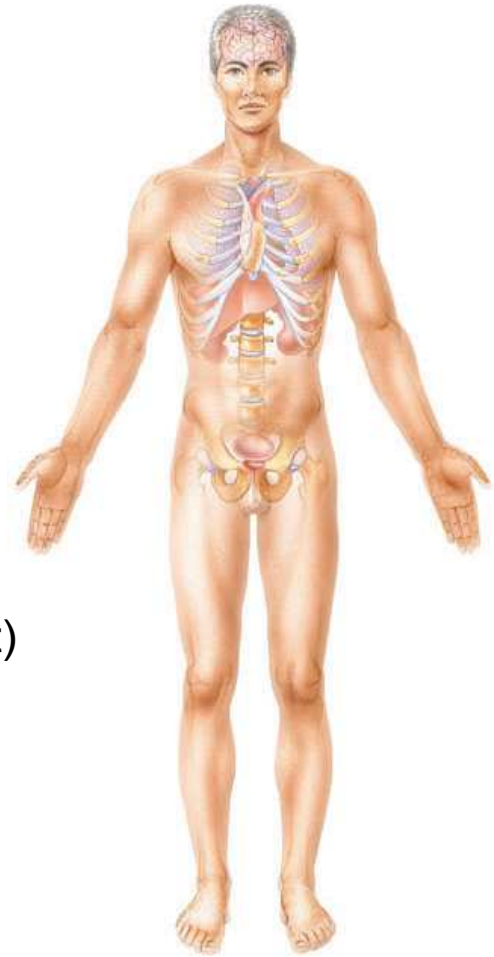
2. **Prostate / Integrated boost**
   (Potentially hypofractionation)

3. **Gastric cancer**
   (Better kidney sparing while treating the whole of the target)

4. **Breast Cancer**

5. **Lung Cancer**

6. **Metastases**



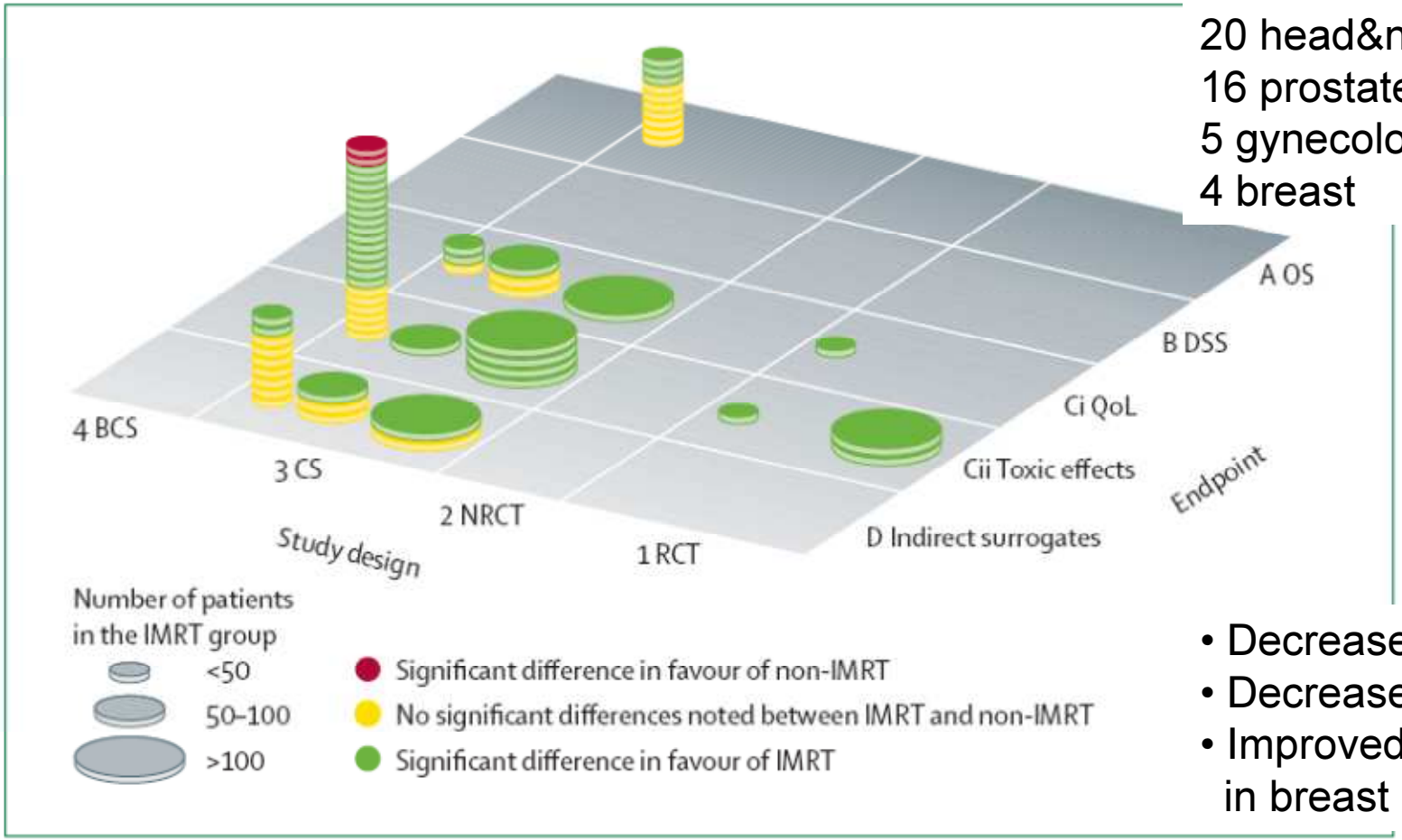
Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies

Liv Veldeman, Indira Madani, Frank Hulstaert, Gert De Meerleer, Marc Mareel, Wilfried De Neve

Lancet Oncol 2008; 9: 367–375

56 studies/reports

20 head&neck	3 lung
16 prostate	5 GI
5 gynecological	3 CNS
4 breast	



- Decreased xerostomia
- Decreased rectal toxicity
- Improved cosmesis in breast cancer

Figure 3: **Evaluation tool for relevance of clinical statements reported in 56 studies of IMRT**
BCS=best case series. CS=case series. NRCT=non-randomised controlled trial. RCT=randomised controlled trial. OS=overall survival. DSS=disease-specific survival. QoL=quality of life.

IMRT clinical outcome

Factors influencing the rational use of IMRT for head-and-neck cancer

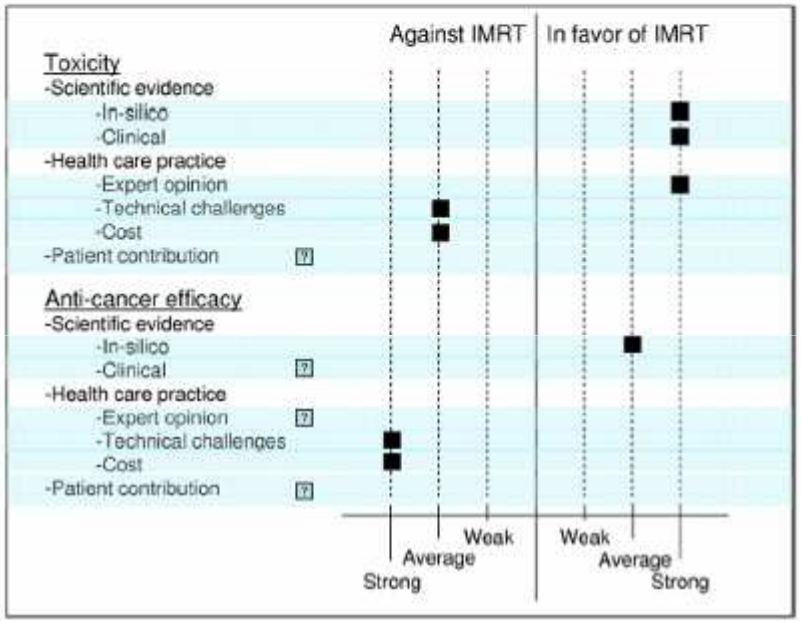


Figure 1 Factors in favor or against IMRT are represented by a rectangle on the right or on the left of the vertical solid line, respectively. A question mark inside a rectangle indicates too much uncertainty for using the factor in the graph.

Factors influencing the rational use of IMRT for whole breast irradiation

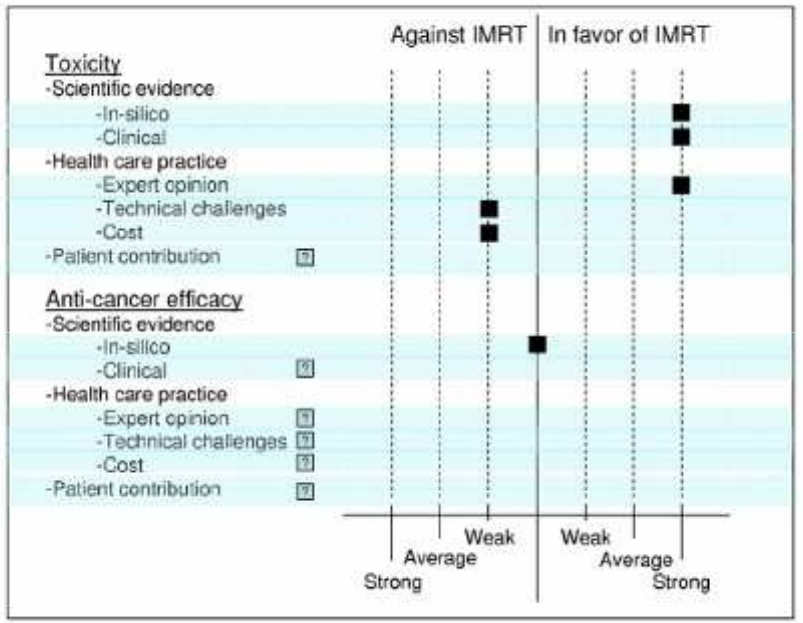


Figure 2 Factors in favor or against IMRT are represented by a rectangle on the right or on the left of the vertical solid line, respectively. A question mark inside a rectangle indicates too much uncertainty for using the factor in the graph.

De Neve et al. Sem Rad Onc, 2012

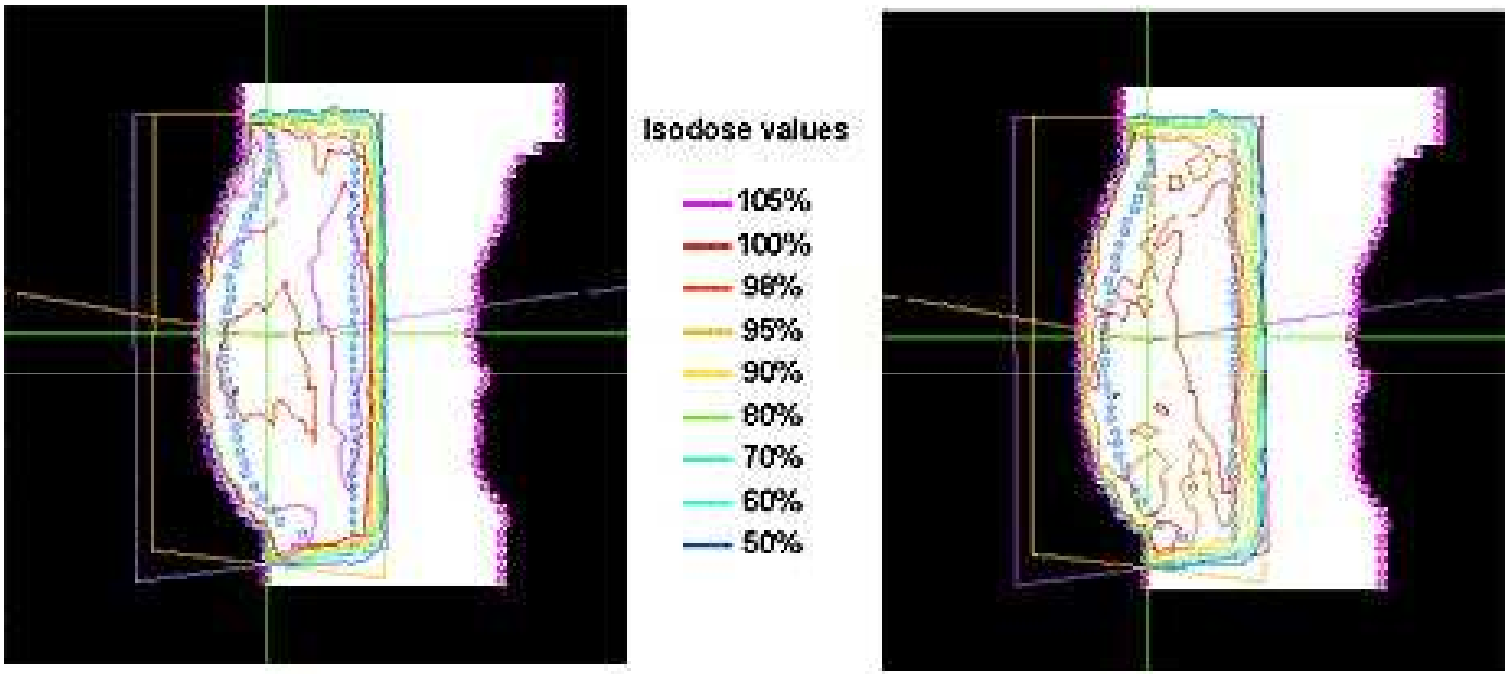
Tumor Localizations

1. Breast Cancer

There are two different paradigms that have to be discussed separately:

1. Tangential IMRT
2. Multi-beam-angle/Multi-field IMRT

1. Improvement of Dose Homogeneit for Tangent Irradiation



Standard wedged treatment

Multiple static MLC fields

http://www.elekta.com/ContentInternational.nsf/pga_Frameset?openpage&url=imrt_for_breast_cancer

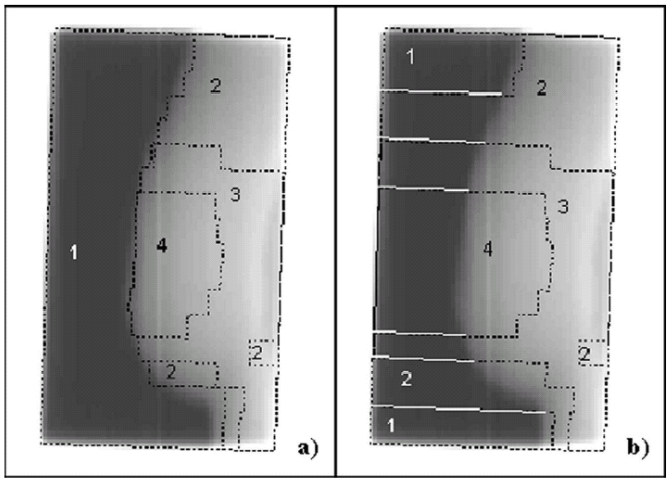
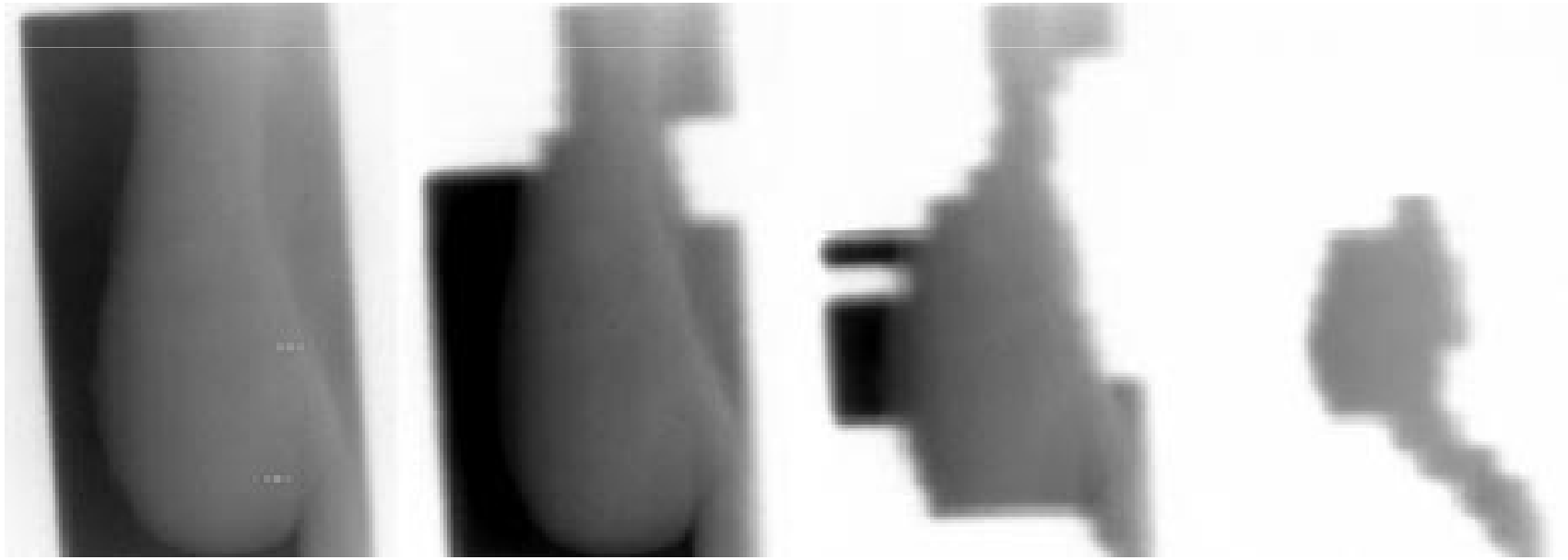


Fig. 2. Superposition of a patient image from the in-house EPID and the four fields to be delivered from this beam direction. A left medial image is shown. In (a) this is overlaid with the fields needed for flash method 1 and in (b) with the fields for flash method 2. The labels inside the images indicate the field numbers.



OPTIMIZING BREAST CANCER TREATMENT EFFICACY WITH INTENSITY-MODULATED RADIOTHERAPY

FRANK A. VICINI, M.D., MICHAEL SHARPE, PH.D., LARRY KESTIN, M.D., ALVARO MARTINEZ, M.D., CHRISTINA K. MITCHELL, R.N., MICHELLE F. WALLACE, R.N., RICHARD MATTER, M.D., AND JOHN WONG, PH.D.

Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, MI

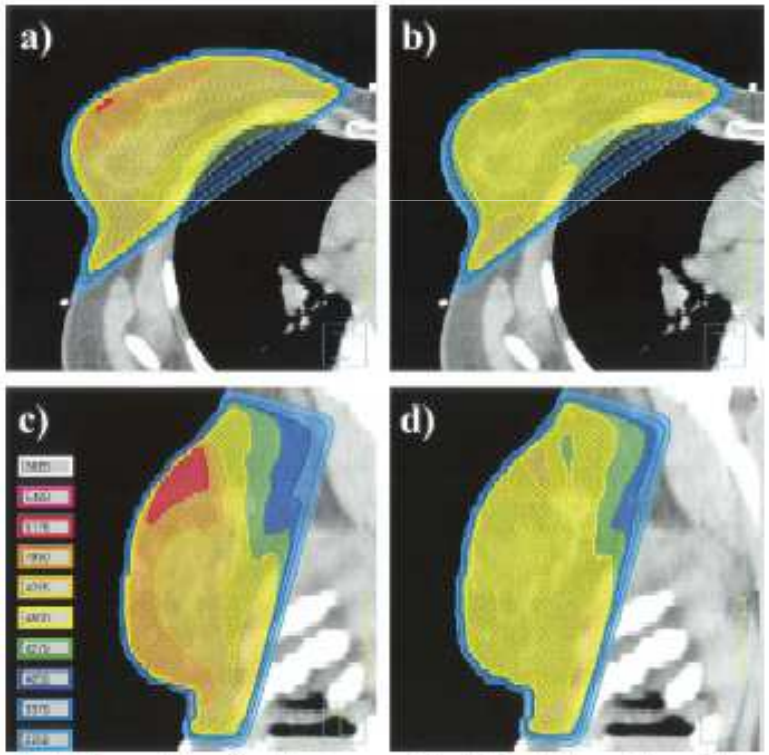


Fig. 1. (a) Transverse CT scan of breast showing uncompensated dose distribution. (b) Transverse CT scan of breast showing IMRT dose distribution. (c) Sagittal CT scan of breast showing uncompensated dose distribution. (d) Sagittal CT scan of breast showing IMRT dose distribution.

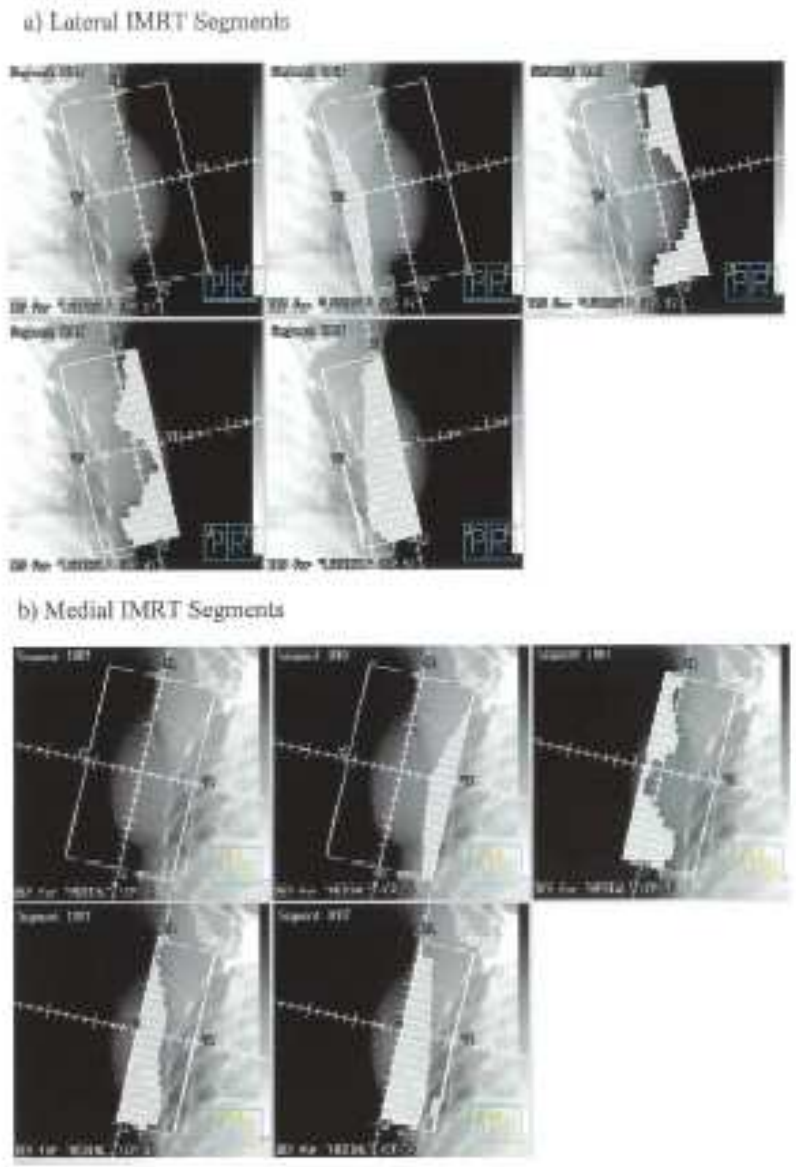
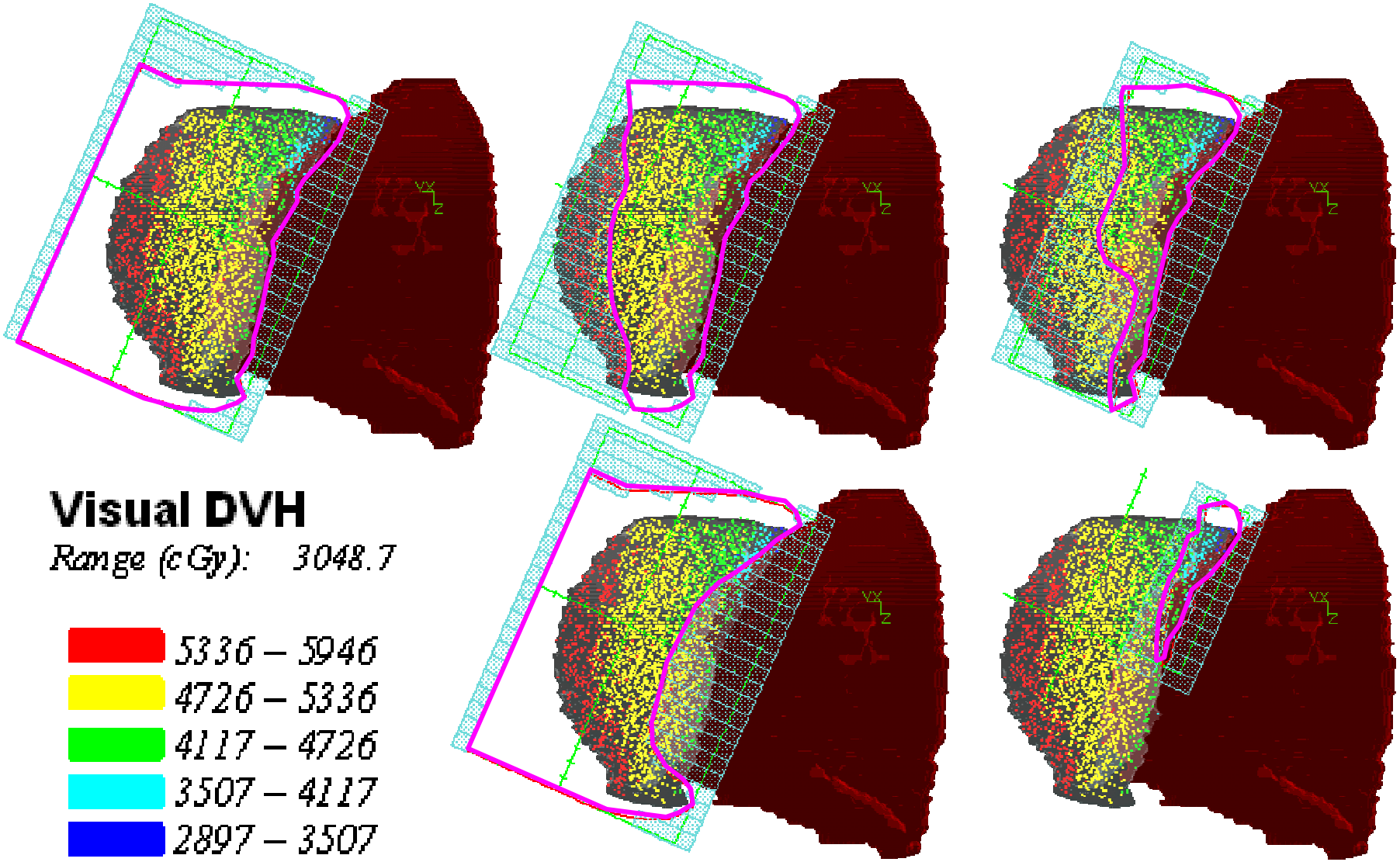


Fig. 2. (a) Lateral sMLC segments used for IMRT dose delivery. (b) Medial sMLC segments used for IMRT dose delivery.

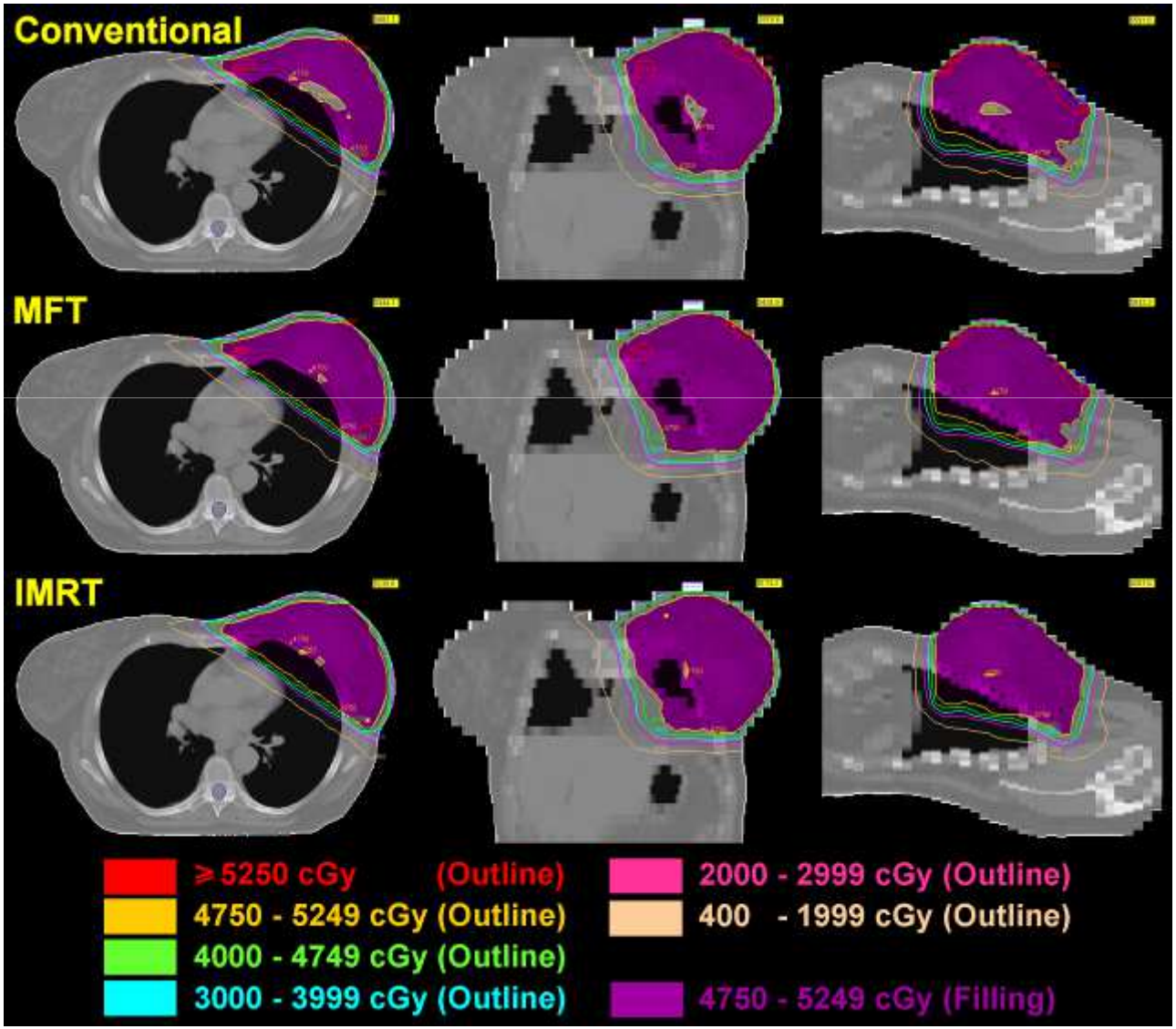
Optimization of Tangent Irradiation

Abo Madyan et al., Strahlentherapie, 2007



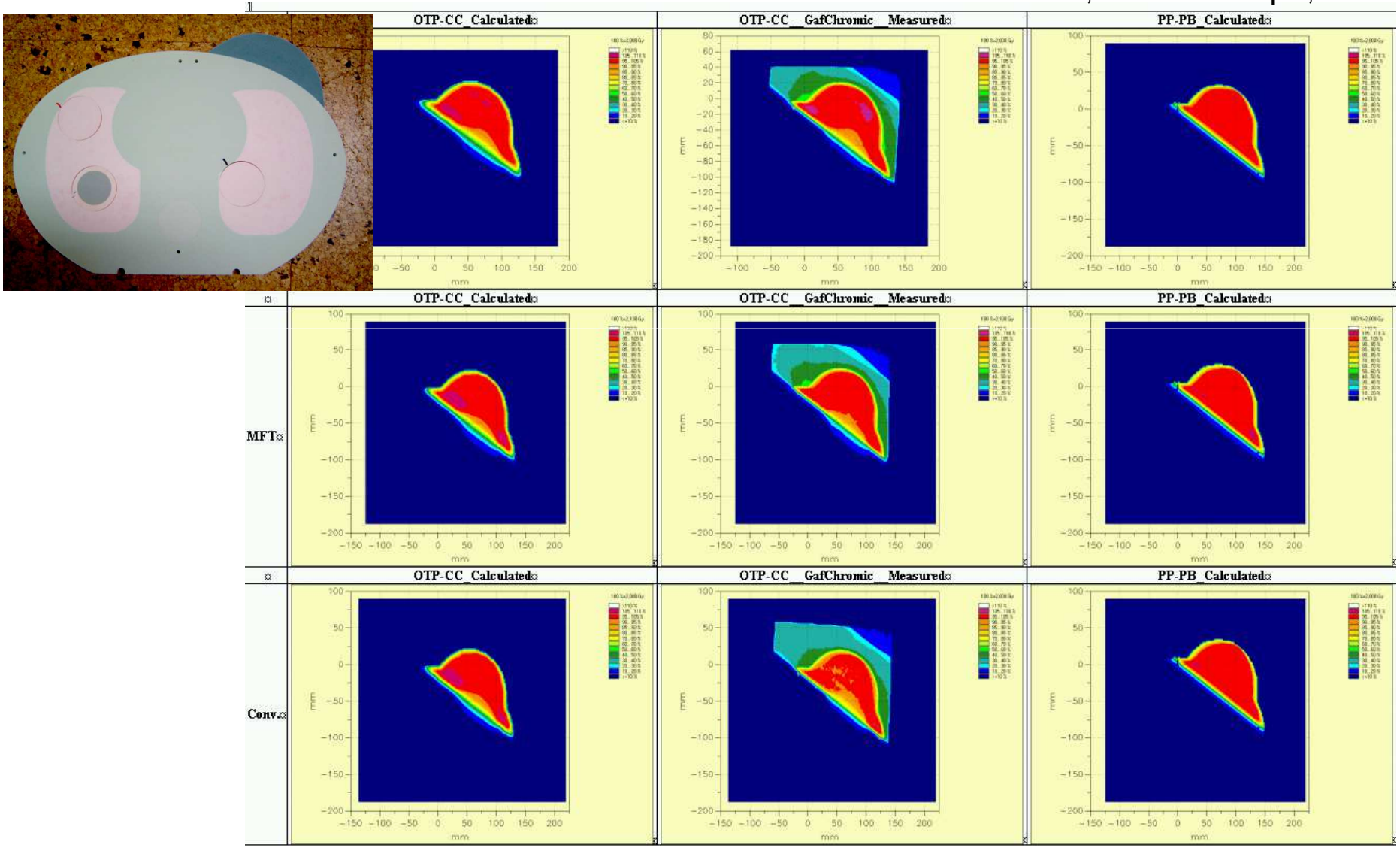
Optimization of Tangent Irradiation

Abo Madyan et al., Strahlentherapie, 2007



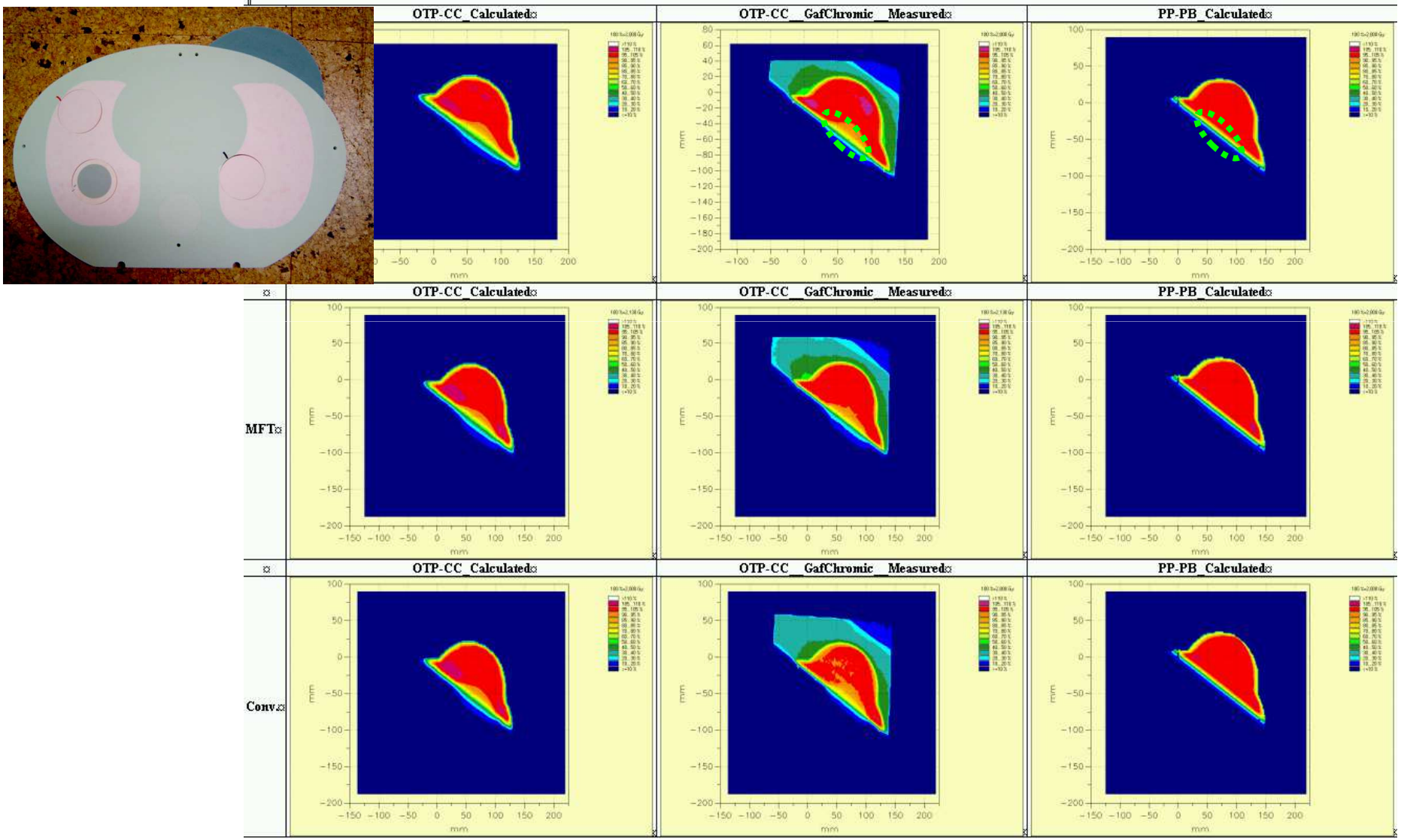
Breast IMRT - Dose Calculation

Polednik et al., Strahlentherapie, 2007



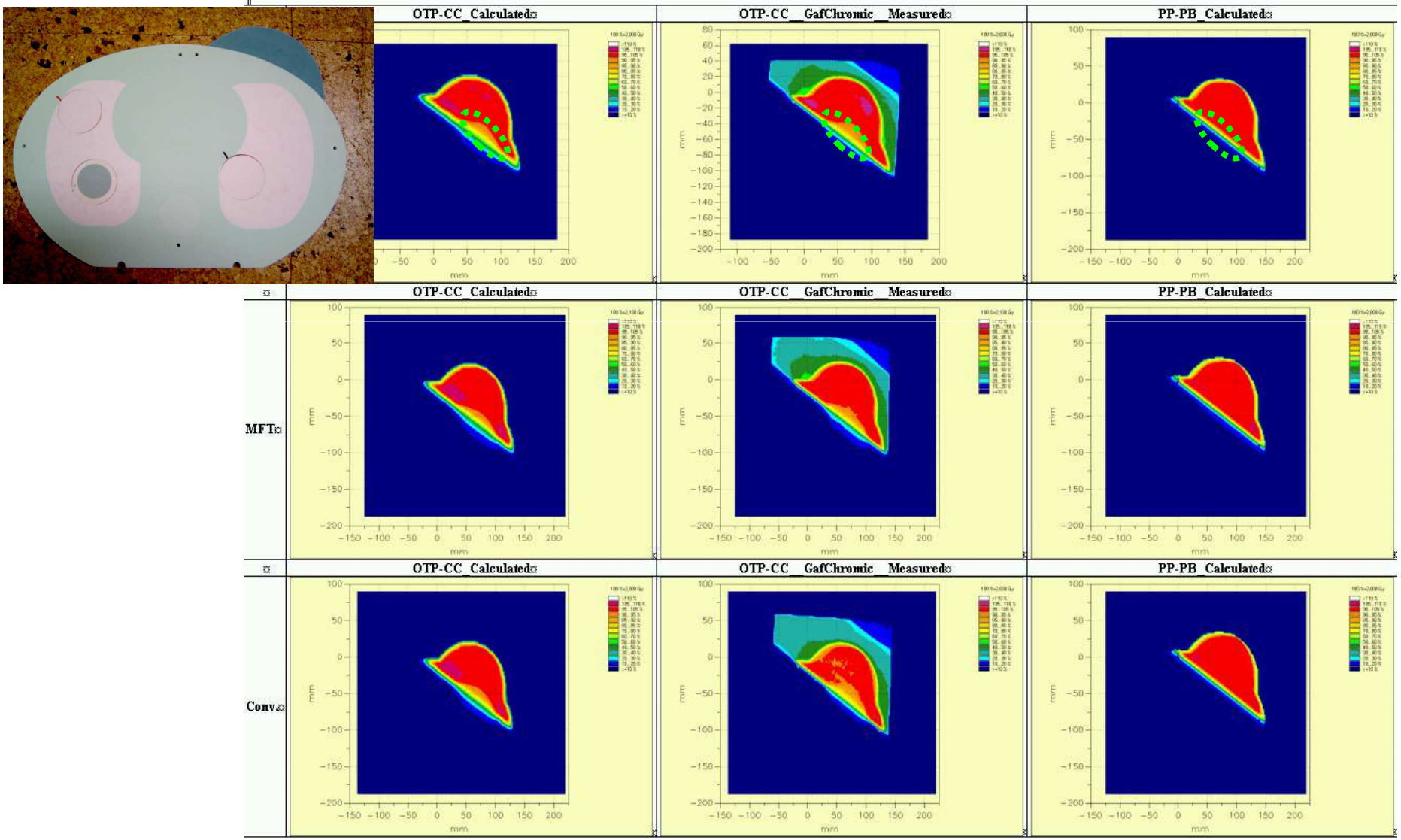
Breast IMRT - Dose Calculation

Polednik et al., Strahlentherapie, 2007

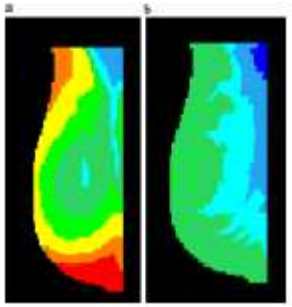


Breast IMRT - Dose Calculation

Polednik et al., Strahlentherapie, 2007



Clinical Results with Tangential IMRT



2 Randomized trials, several retrospective analyses

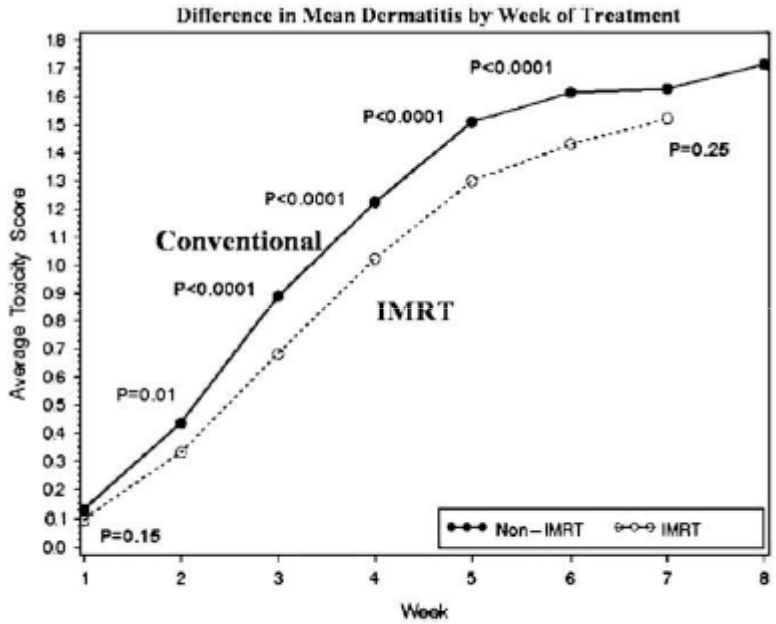


Fig. 1. Mean frequency of dermatitis by week of treatment during radiation therapy for patients treated with conventional radiation therapy (n = 405) and intensity-modulated radiation therapy (IMRT; n = 399).

Freedman et al., IJROBP, 2009

Score (change)	Standard (2D) Number (%)	IMRT (3D) Number (%)
Photographic score at year 1		
None	84 (64.1)	92 (74.2)
Mild	37 (28.2)	26 (21.0)
Marked	10 (7.6)	6 (4.8)
Total	131	124
Photographic score at year 2		
None	73 (56.6)	84 (65.1)
Mild	49 (38.0)	39 (30.2)
Marked	7 (5.4)	6 (4.7)
Total	129	129
Photographic score at year 5		
None	51 (41.8)	71 (60.2)
Mild	54 (44.3)	35 (29.7)
Marked	17 (13.9)	12 (10.2)
Total	122	118

Donovan et al., R&O, 2007
Pignol et al., JCO, 2008

Fox Chase experience, Median F/U 31 mo, 946 women 46 + 16 Gy

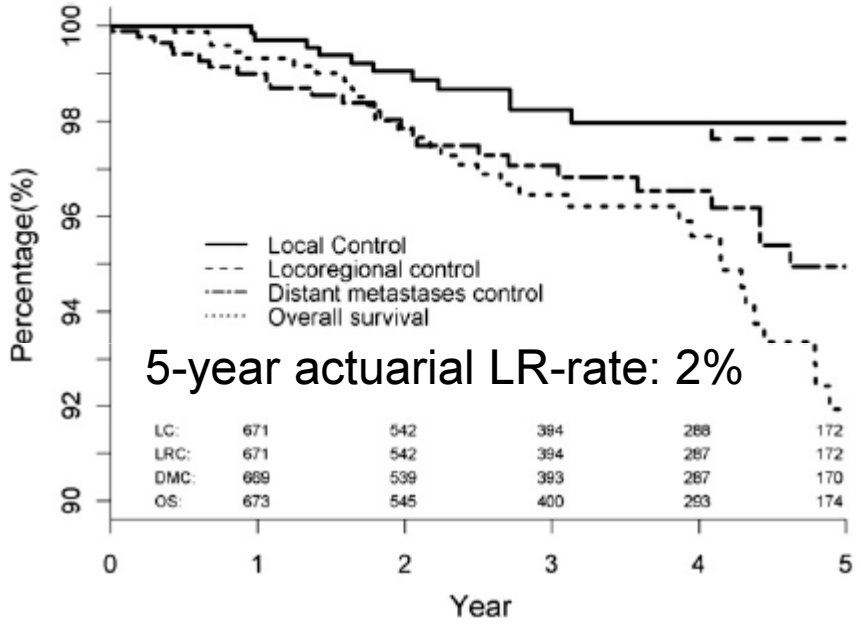


Fig. 1. Actuarial local control, locoregional control, distant metastasis, and overall survival after whole-breast IMRT.

Grading?

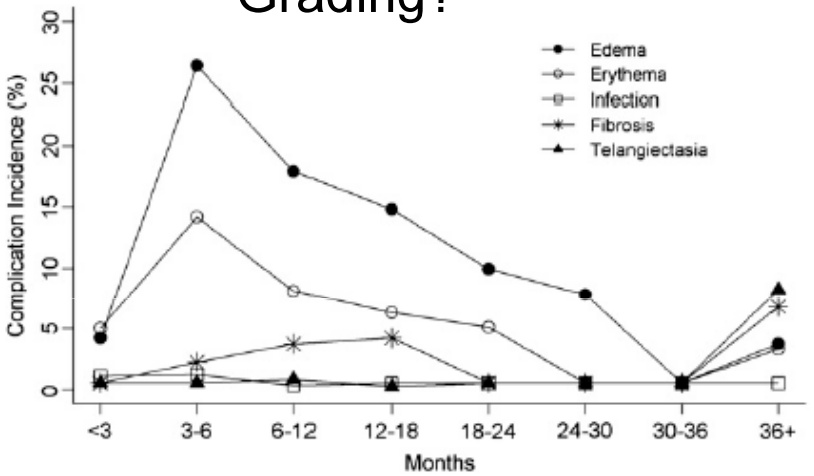


Fig. 2. Treatment-related side effects after whole-breast intensity-modulated radiation therapy (IMRT). Treatment-related effects observed in follow-up after whole breast IMRT, as recorded from the start of breast IMRT.

Keller et al., IJROBP, 2013

Scatter Reduction with tangential IMRT

Table 2: Dose to various organs for various breast radiotherapy techniques.

Technique	PBSI	HDR (catheters)	Wedge	IMRT	3D-CRT
Treated Breast	90 Gy	34 Gy	50 Gy	50 Gy	38.5 Gy
Contralateral Breast	2.2 mSv	230 mSv	1695 mSv	206 mSv	140 mSv
Spleen	44 mSv	1171 mSv	2300 mSv	810 mSv	130 mSv
Ipsilateral lung	790 mSv	2471 mSv	582 mSv	121 mSv	80 mSv
Heart (LAD)	0.7 Gy	3.6 Gy	2.7 Gy	1.1 Gy	0.7 Gy

Pignol et al., 2011

Peripheral dose after 2D, 3D and Tangential IMRT

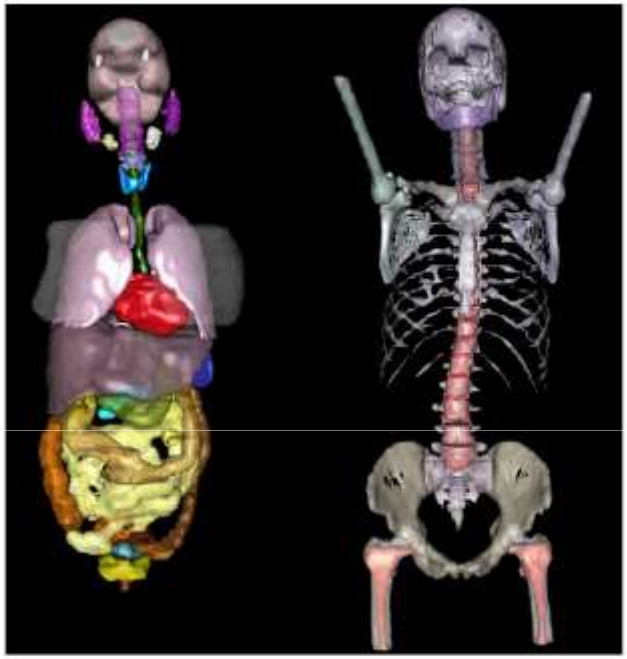


Fig. 1. All delineated organs on the slices of the whole-body CT dataset are represented above in three dimensions.

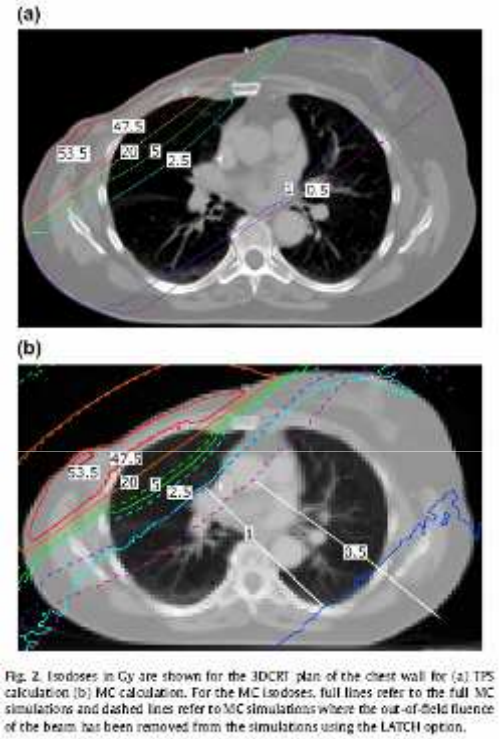
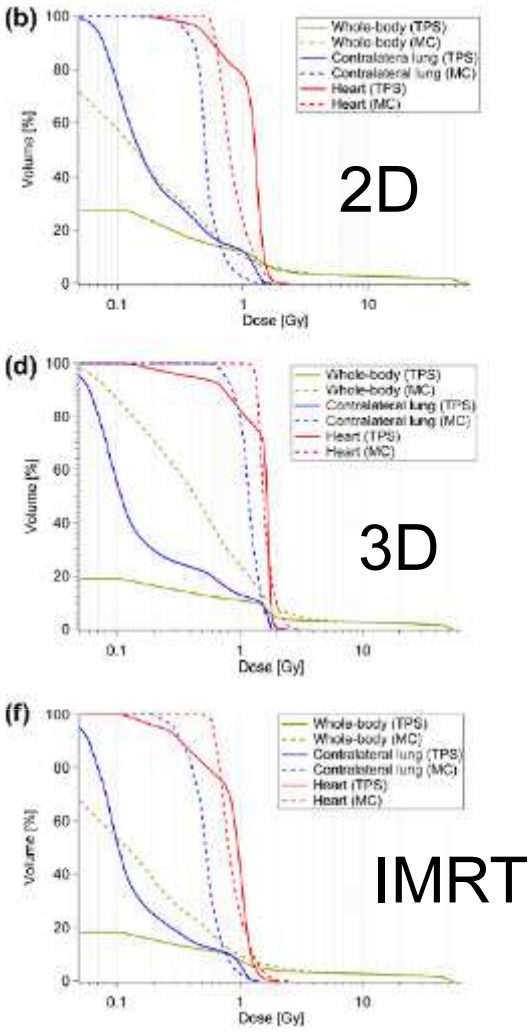


Fig. 2. Isodoses in Gy are shown for the 3DCRT plan of the chest wall for (a) TPS calculation (b) MC calculation. For the MC isodoses, full lines refer to the full MC simulations and dashed lines refer to MC simulations where the out-of-field fluence of the beam has been removed from the simulations using the LATCH option.



"In sharp contrast to popular belief, the IMRT technique investigated here does not increase the out-of-field dose compared to conventional techniques and may offer the most optimal plan."

Joosten et al., R&O, 2013

Tangential (!!!) IMRT vs. DIBH

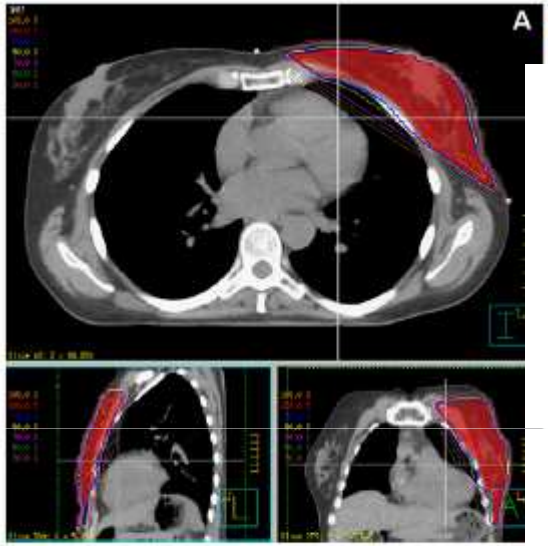
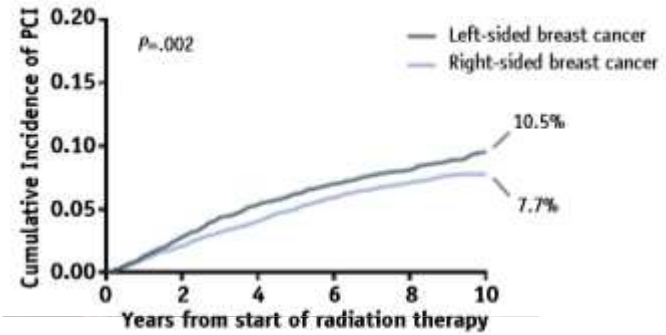
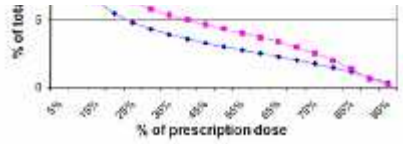


Fig. 1. A representative FB-IMRT isodose plan (A) and 3D-DIBH isodose plan (B
3-dimensional location in the patient. The axial image is obtained at the T7 verte



Number at risk						
Group	0	2	4	6	8	10
Left-sided	7,216	5,921	4,215	2,700	1,364	316
Right-sided	7,115	5,937	4,268	2,743	1,421	315

Fig. 2. Cumulative incidence of percutaneous coronary intervention (PCI) for left- and right-sided breast cancer after radiation therapy for patients with high cardiac risk. The number of patients at risk is shown below. Gray's test of equality was used to evaluate a significant difference between groups.



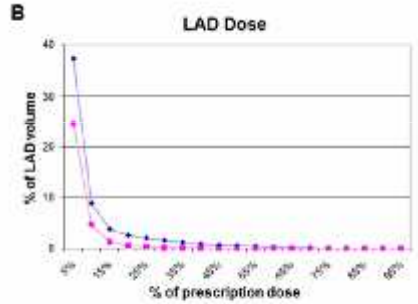
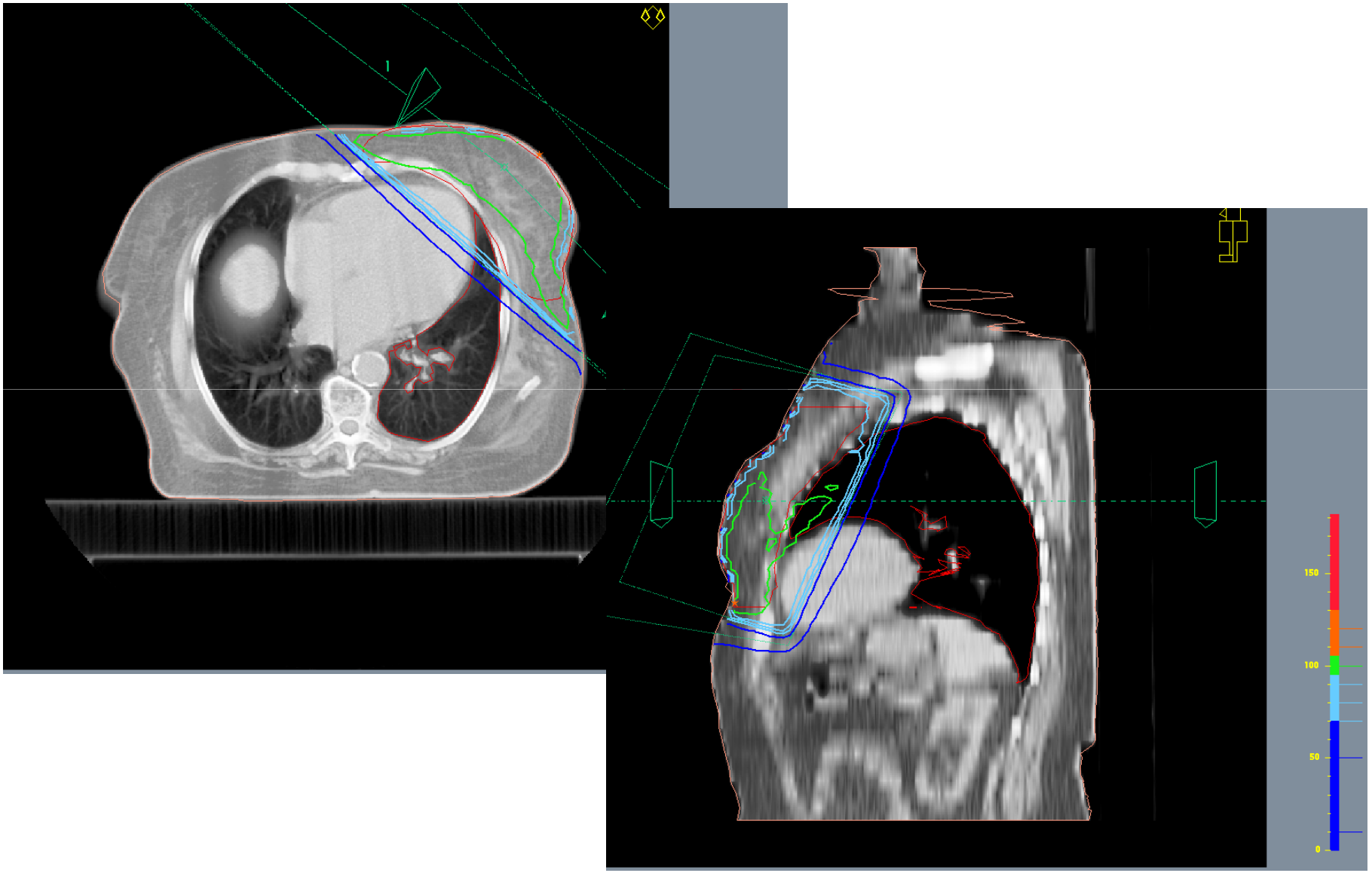


Fig. 2. Graphic comparisons of percent of mean volume of heart (A), LAD (B), total lung (C), and right breast (D) irradiated at different dose levels. Dose levels correspond to the percent of total dose prescribed. In all 4 figures, the blue-diamond line represents the IMRT plan and the pink-square line represents the DIBH plan.

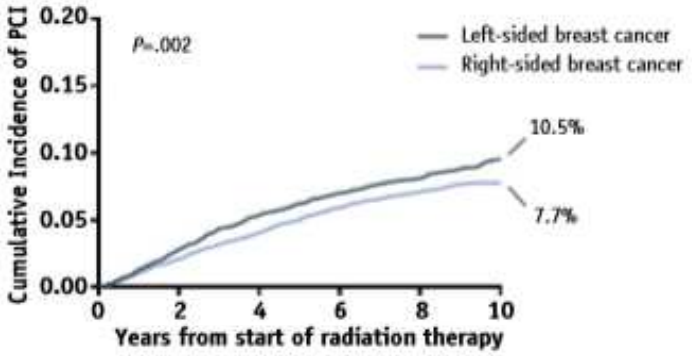
Reardon et al.,
Med Dosim, 2013

2. „Full“, Multifield IMRT for left heart sparing



Is cardiotoxicity still a problem?
In some situations apparently……

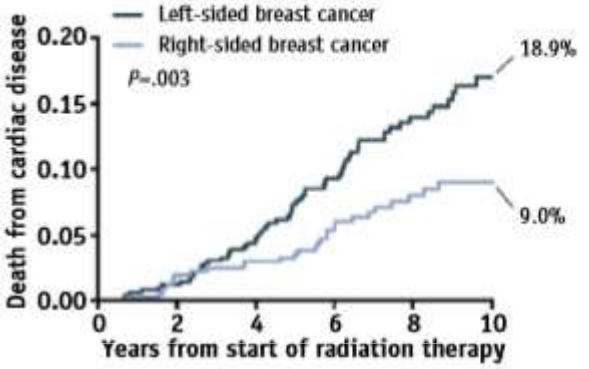
SEER 2000-2009



Number at risk

Group	0	2	4	6	8	10
Left-sided	7,216	5,921	4,215	2,700	1,364	316
Right-sided	7,115	5,937	4,268	2,743	1,421	315

Fig. 2. Cumulative incidence of percutaneous coronary intervention (PCI) for left- and right-sided breast cancer after radiation therapy for patients with high cardiac risk. The number of patients at risk is shown below. Gray's test of equality was used to evaluate a significant difference between groups.



Number at risk

Group	0	2	4	6	8	10
Left-sided	504	482	400	281	165	54
Right-sided	416	398	339	253	142	47

Fig. 3. The incidence of cardiac-associated mortality for left- and right-sided breast cancer patients who received percutaneous coronary intervention (PCI) after radiation therapy (n=920). The number of patients at risk is shown below. Gray's test of equality was used to evaluate a significant difference between groups.

Boero, IJROBP, 2016

Distribution of Coronary Artery Stenosis After Radiation for Breast Cancer

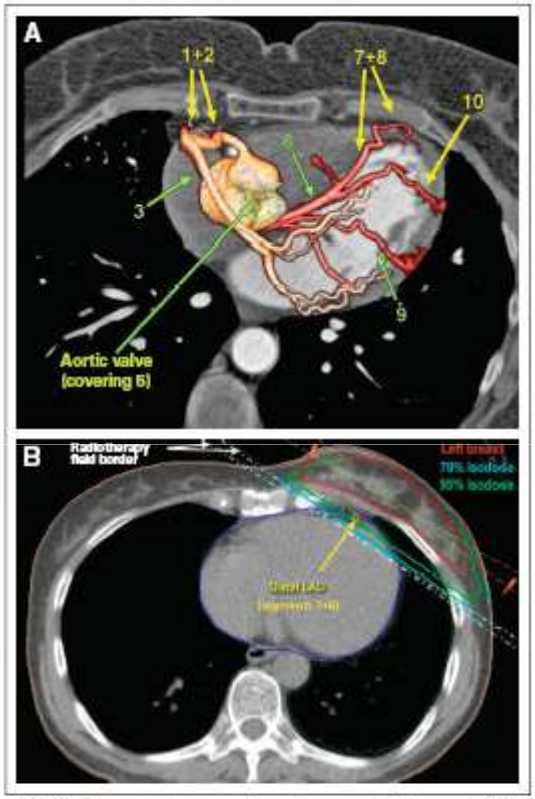


Fig 2. (A) Coronary angiogram superimposed on computed tomography (CT) of heart illustrating anatomy of coronary arteries with branches of right coronary artery (orange) and left circumflex and left anterior descending (LAD) arteries (red); numbered arrows indicate segments. (B) CT dose-planned left tangential breast irradiation showing distal LAD (yellow circle) and radiation fields.

Table 3. ORs From Generalized Linear Mixed Models for Grades of Coronary Artery Stenosis in High- Versus Low-Risk RT or No RT

	Patients With BC					
	All Segments			Hotspot Areas		
Stenosis Grade	LSMEANS Estimate	OR	95% CI	LSMEANS Estimate	OR	95% CI
1-5						
Low-risk RT/no RT	0.18	Ref		0.25	Ref	
High-risk RT	0.27	1.68	1.10 to 2.57	0.39	1.95	1.17 to 2.93
2-5						
Low-risk RT/no RT	0.08	Ref		0.12	Ref	
High-risk RT	0.10	1.25	0.80 to 1.94	0.16	1.33	0.83 to 2.13
3-5						
Low-risk RT/no RT	0.06	Ref		0.07	Ref	
High-risk RT	0.09	1.61	1.00 to 2.59	0.12	1.90	1.11 to 3.24
4-5						
Low-risk RT/no RT	0.04	Ref		0.04	Ref	
High-risk RT	0.08	2.06	1.21 to 3.51	0.08	1.87	1.14 to 3.09

Abbreviations: BC, breast cancer; LSMEANS, least-squares means; OR, odds ratio; Ref, reference; RT, radiotherapy.

Nilsson, JCO, 2012

Supine Breast Movement – intra- and interfraction

Table 5. Combined results for the magnitude of intra-fraction motion in breast cancer patients

Parameter (mm)	Combined results		
	Range of average movement – 1SD	Average movement – 1SD	Range of maximum deviation†
CLD (five articles)[5,7,39,47,49]	0.7–1.8	1.19	1.5–13.1
CBESD (five articles)[5,7,39,47,49]	0.73–2.1	1.26	1.6–14.9
CCD (three articles)[5,47,49]	0.9–3.2	1.82	2.0–25.6

†Fein *et al*.[7] and Kron *et al*.[39] do not report a maximum deviation.
CBESD, central beam edge to skin distance; CCD, cranio-caudal distance; CLD, central lung distance; SD, standard deviation.

Michalski et al., JMIRO, 2013

Table 6. Combined results for the magnitude of inter-fraction motion (random error) in breast cancer patients

Parameter (mm)	Combined results		
	Range of average movement – 1SD	Average movement – 1SD	Range of maximum deviations†
CLD (eight articles)[5,7,39,40,45–47,49]	1.7–4.4	2.21	2.6–11.6
CIW (three articles)[46,47,49]	0.81–2.9	1.9	3.6–18.2
CBESD (six articles)[5,7,39,46,47,49]	0.63–4.4	2.20	3.05–15.6
CCD (five articles)[5,45–47,49]	0.6–4.0	2.6	3.6–22.9
CBD (three articles)[7,39,40]	2.62–3.7	3.18	NA

†Fein *et al*.,[7] Kron *et al*.,[39] Pradier *et al*.[46] and Koseoglu *et al*.[40] do not report a maximum deviation.
CBESD, central beam edge to skin distance; CBD, central breast distance; CCD, cranio-caudal distance; CIW, central irradiated width; CLD, central lung distance; SD, standard deviation.

Invers geplante intensitätsmodulierte Strahlenbehandlung bei einer Patientin mit rechtsseitigem Mammakarzinom und Trichterbrust

Christoph Thilmann[1], Angelika Zabel[1], Sabine Kuhn[1], Rolf Bendl[3], Bernhard Rhein[1], Michael Wannenmacher[2], Jürgen Debus[1, 2]

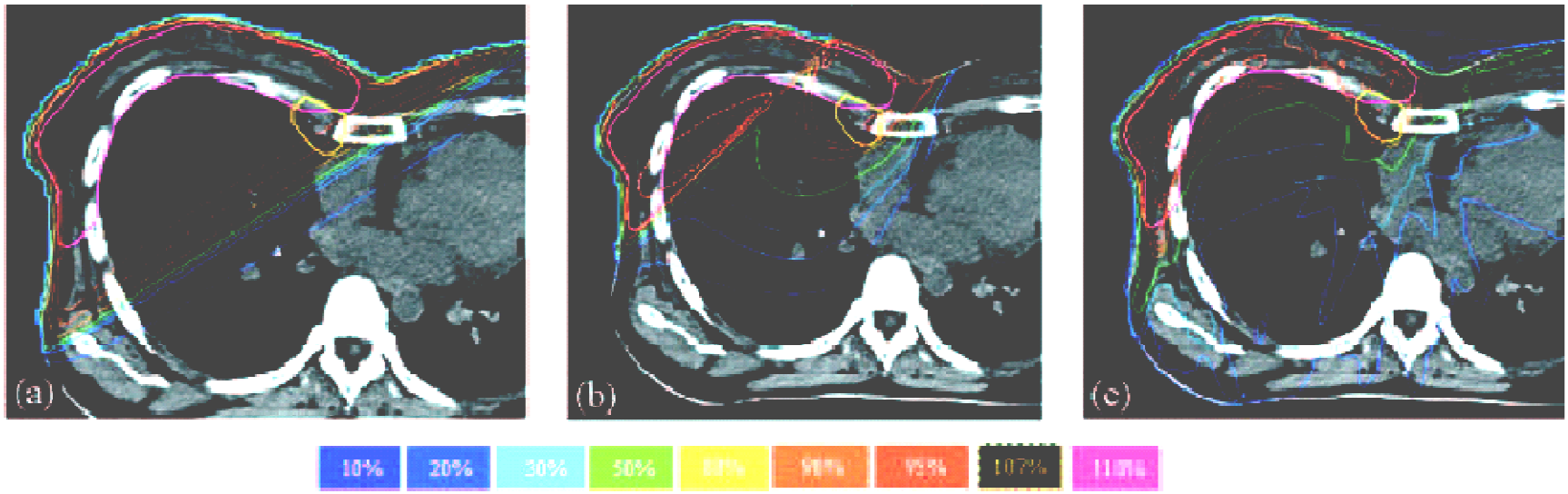
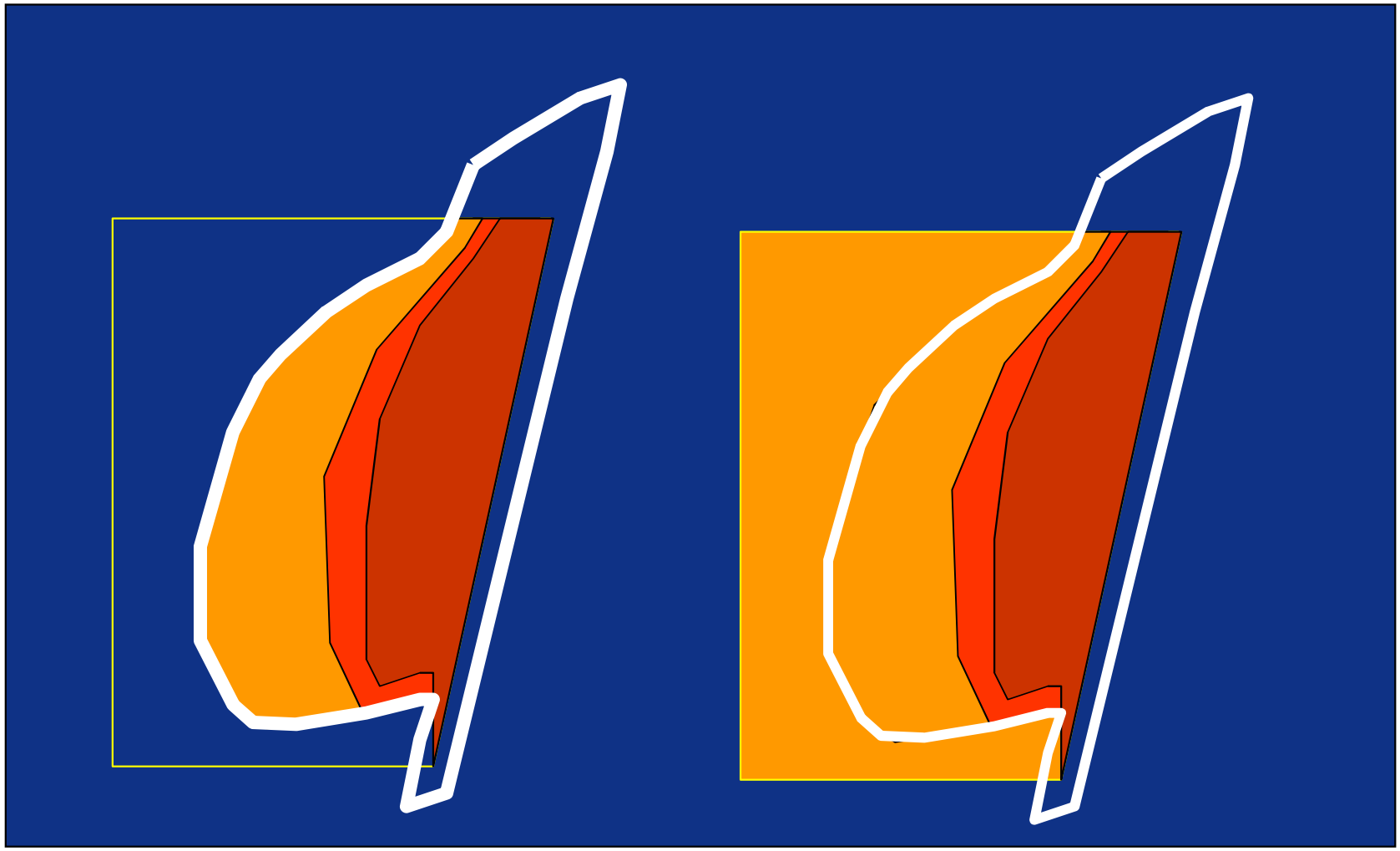
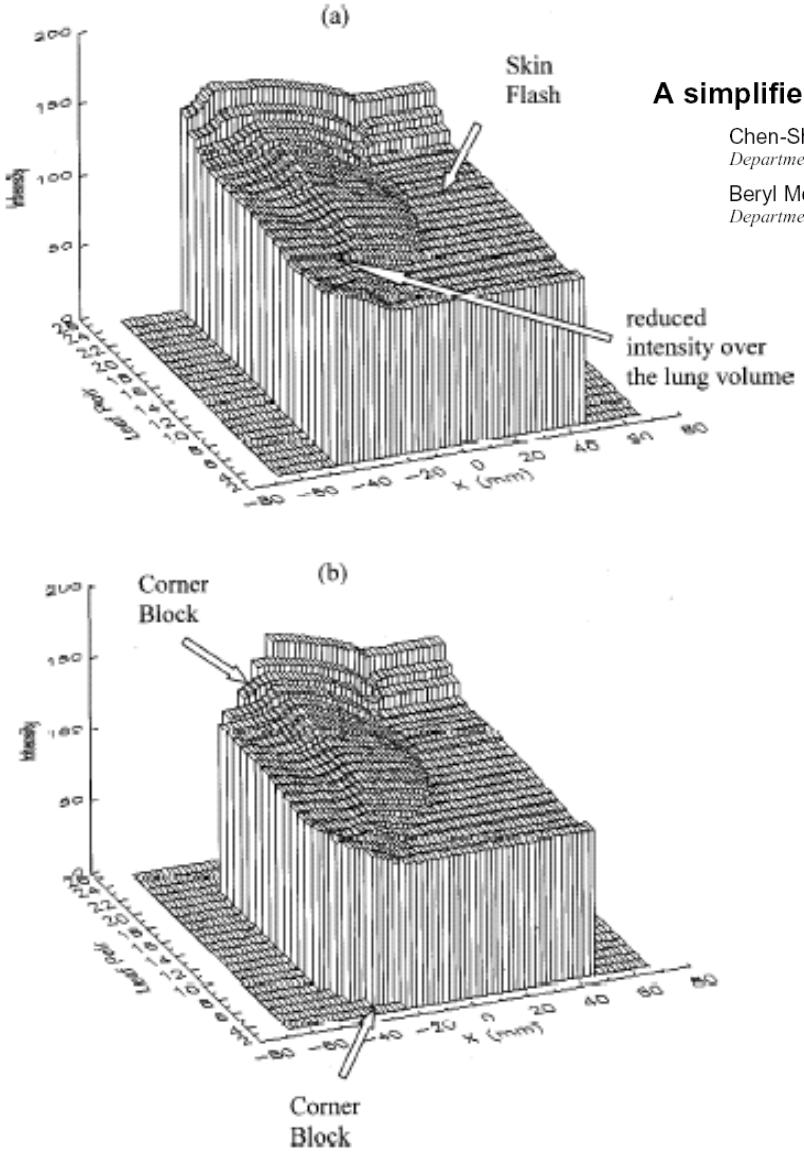


Abbildung 1. Vergleich der Dosisverteilung. a) konventionelle Technik mit tangentialen 6-MV-Keilfilter-Feldern, b) konventionelle Technik mit zusätzlichem 15-MeV-Elektronenfeld, c) IMRT mit zwölf intensitätsmodulierten 6-MV-Photonenfeldern mit sechs Intensitätsstufen (102 Segmente).

Extension of Dose Matrix

to cover „flash“ region





A simplified intensity modulated radiation therapy technique for the breast

Chen-Shou Chui,[a] Linda Hong, and Margie Hunt
Department of Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Beryl McCormick
Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Medical Physics, Vol. 29, No. 4, April 2002

FIG. 2. (a) Intensity distribution for one of the tangential fields. In the skin flash region, the intensity is flat. (b) Corner blocks were used to define the shape of the distribution.

Virtual Bolus

Strahlentherapie
und Onkologie

Originalarbeit

Virtueller Bolus zur inversen Bestrahlungsplanung bei intensitätsmodulierter Radiotherapie des Mammakarzinoms im Rahmen der adjuvanten Therapie

Christoph Thilmann[1], Karl Heinz Grosser[1], Bernhard Rhein[1], Angelika Zabel[1], Michael Wannenmacher[2], Jürgen Debus[1,2]

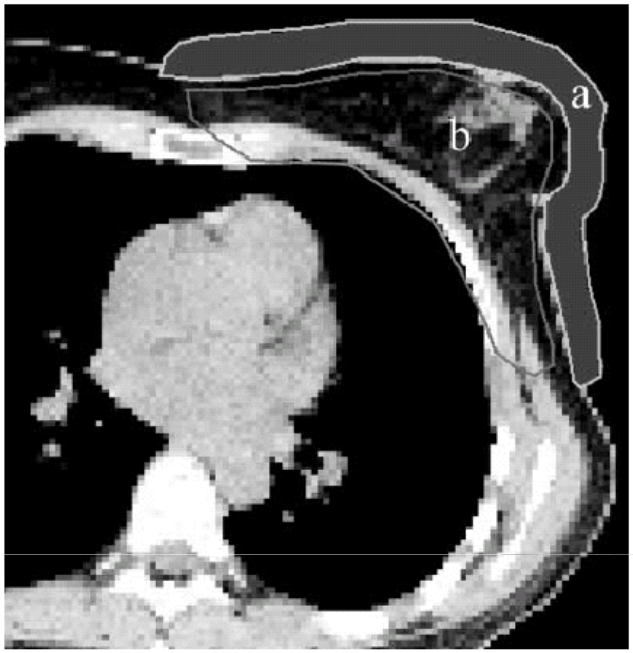


Abbildung 1. Festlegung von Bolus und CTV zur inversen Optimierung: Der Bolus wird nur zur inversen Bestrahlungsplanung verwendet. Die abschließende Dosisberechnung und auch die Bestrahlung erfolgen ohne Bolus: a) Bolus der Dicke von 10 mm (Dichte = –60 HE); b) CTV gemäß EORTC.

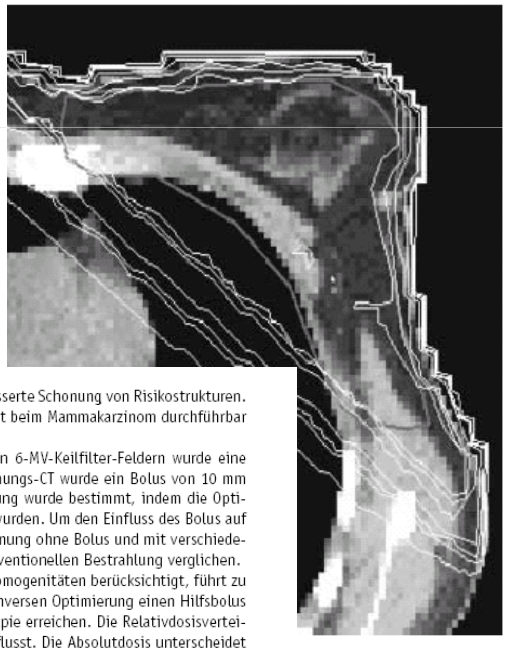
Fragestellung: Die intensitätsmodulierte Strahlenbehandlung (IMRT) verspricht eine verbesserte Schonung von Risikostrukturen. Wir untersuchten, in welcher Form eine inverse Bestrahlungsplanung zur IMRT der Restbrust beim Mammakarzinom durchführbar ist.

Methodik: Neben einer Bestrahlungsplanung in konventioneller Technik mit tangentialen 6-MV-Keilfilter-Feldern wurde eine IMRT-Bestrahlungsplanung mit inverser Planoptimierung (KonRad®) durchgeführt. Im Planungs-CT wurde ein Bolus von 10 mm Dicke und einer Dichte von –60 HE definiert. Der Einfluss des Bolus auf die Planoptimierung wurde bestimmt, indem die Optimierung ohne Bolus, die nachfolgende Dosisberechnung ohne und mit Bolus durchgeführt wurden. Um den Einfluss des Bolus auf die Dosisberechnung zu bestimmen, erfolgte nach Optimierung mit Bolus eine Dosisberechnung ohne Bolus und mit verschiedenen Bolusdicken. Die Planungsergebnisse wurden jeweils mit der Dosisverteilung einer konventionellen Bestrahlung verglichen.

Ergebnisse: Die inverse Planungsoptimierung mit einem Dosisalgorithmus, der Gewebeinhomogenitäten berücksichtigt, führt zu einer erhöhten Hautbelastung. Diese lässt sich reduzieren, indem man ausschließlich zur inversen Optimierung einen Hilfsbolus verwendet. Es lässt sich damit eine Hautschonung entsprechend der konventionellen Therapie erreichen. Die Relativdosisverteilung bleibt von der Verwendung des Bolus bei einer Dicke von 10 mm weitgehend unbeeinflusst. Die Absolutdosis unterscheidet sich bei Dosisberechnung mit und ohne Bolus um 3,4%. Daher muss der Bolus im Sinne eines virtuellen Bolus vor der abschließenden Dosisberechnung wieder entfernt werden.

Schlussfolgerungen: Zur inversen Optimierung einer IMRT der Restbrust ist ein virtueller Bolus erforderlich. Damit ist eine IMRT-Bestrahlung gemäß Konsensus von EORTC, BCCG und EUSOMA (1991) möglich. Insbesondere kann die gleiche Zielvolumendefinition wie bei der konventionellen Therapie verwendet werden. Es sind hiermit IMRT-Techniken in konventioneller Feldgeometrie und in Vielfeldertechnik realisierbar.

Schlüsselwörter: Mammakarzinom · IMRT · Inverse Bestrahlungsplanung



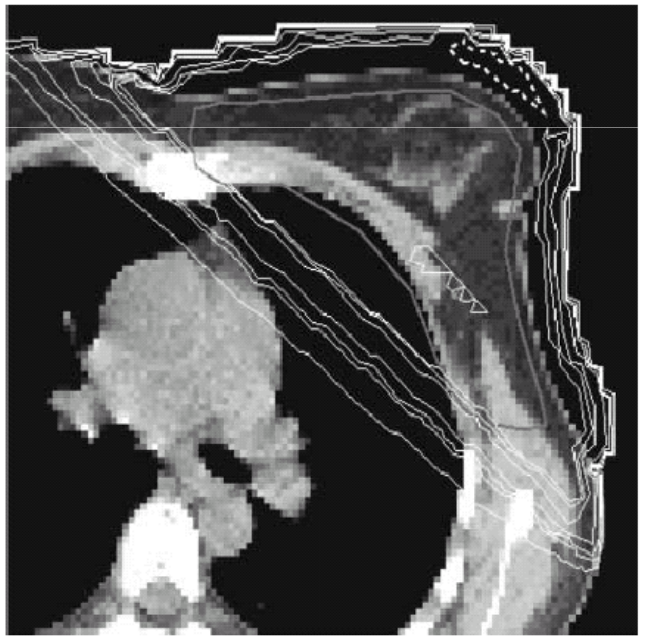
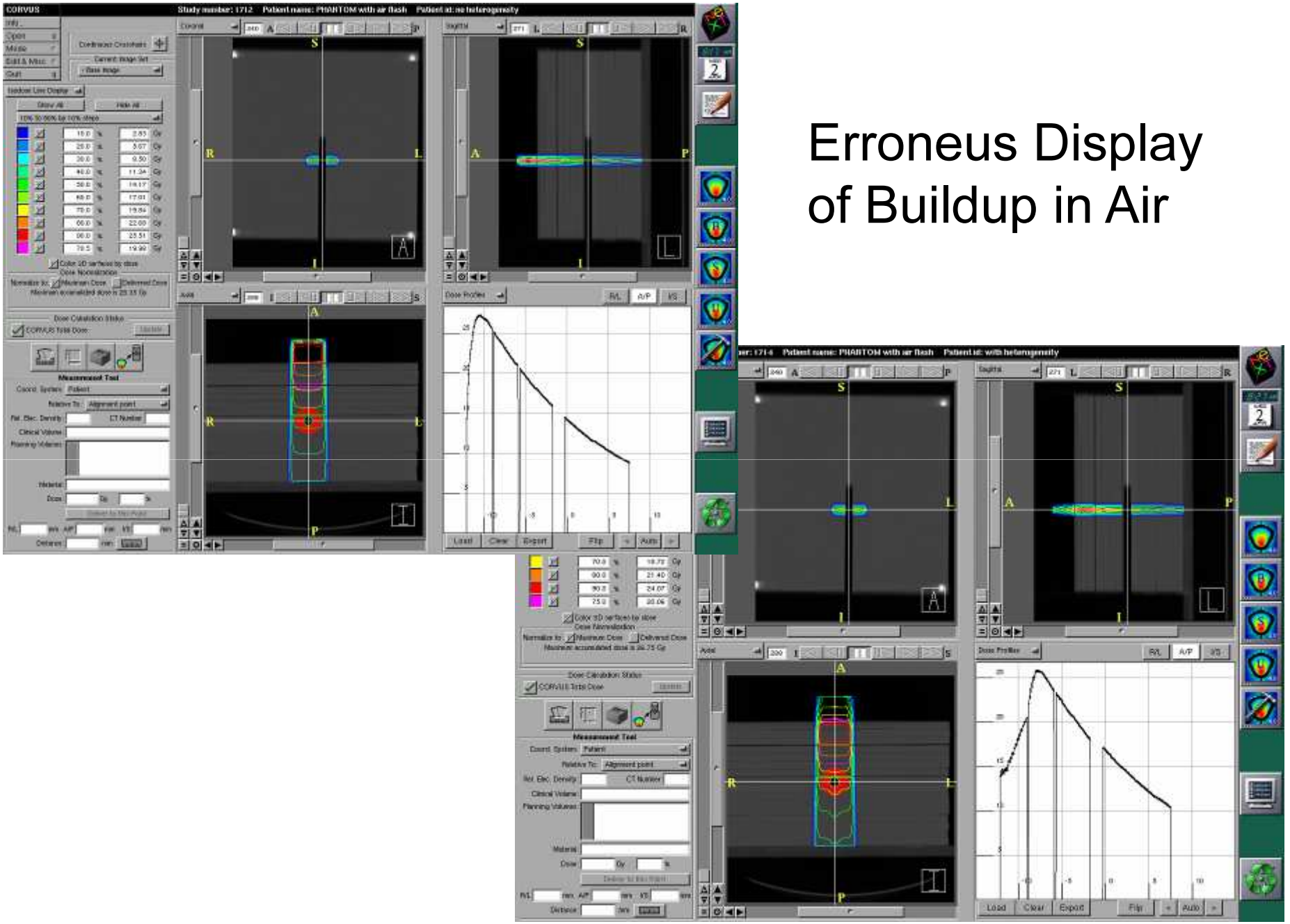
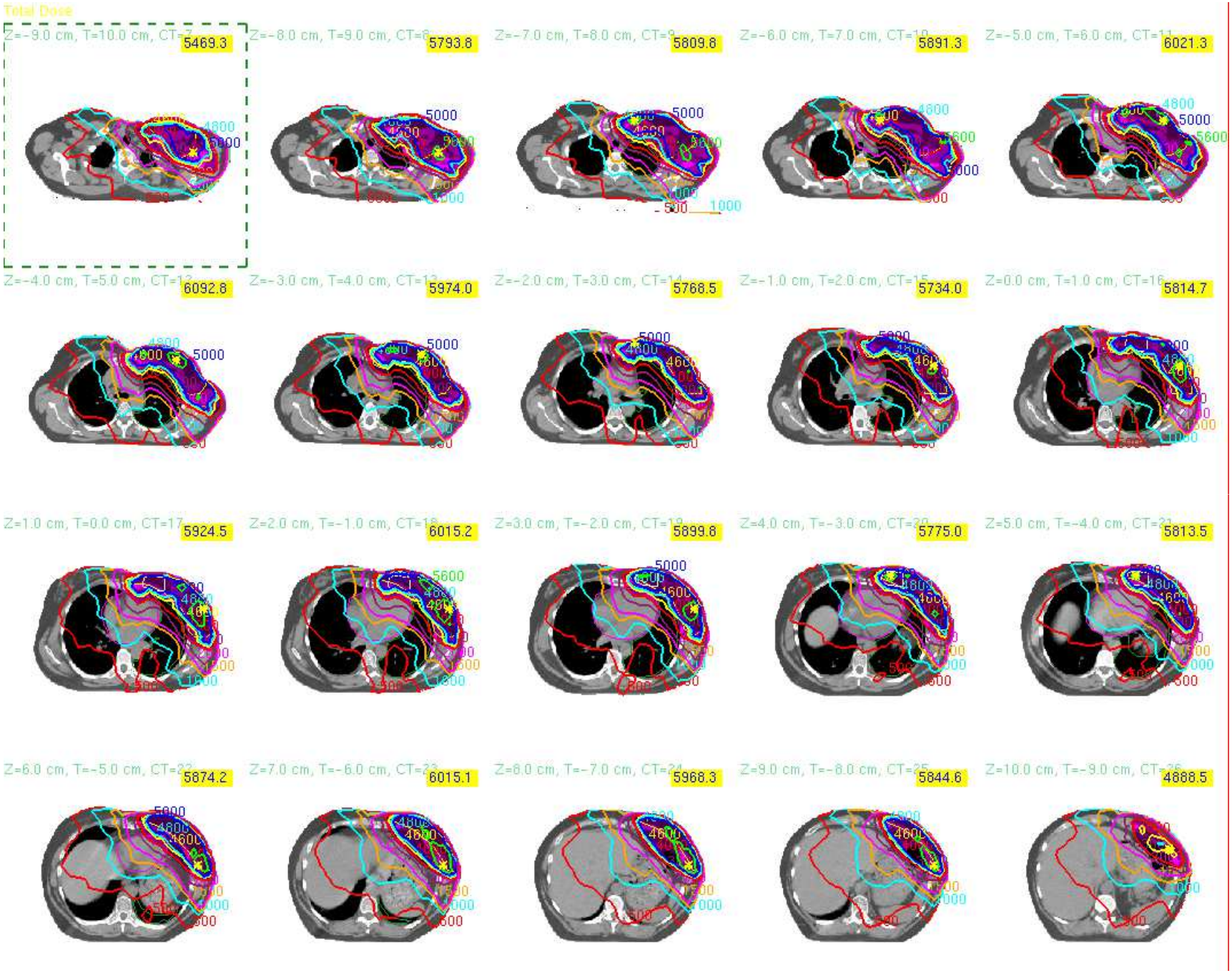


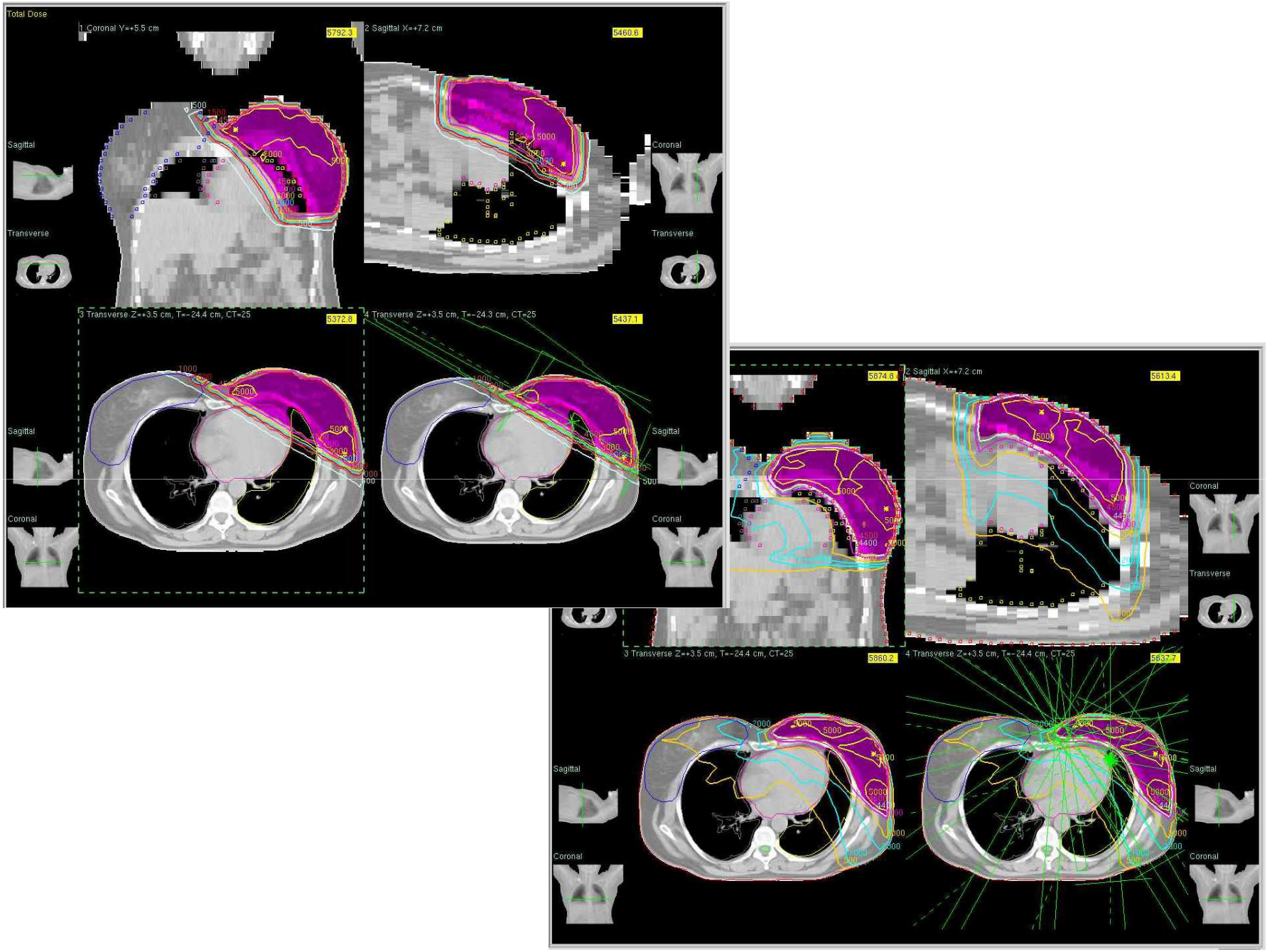
Abbildung 3b – Figure 3b

eilung bei inverser Optimierung ohne Bolus bei IMRT mit zwei tangentialen Feldern: a) inverse Op- inverse Optimierung ohne Bolus, Dosisberechnung mit 10-mm-Bolus. Dargestellte Isodosen: 10%, elt).



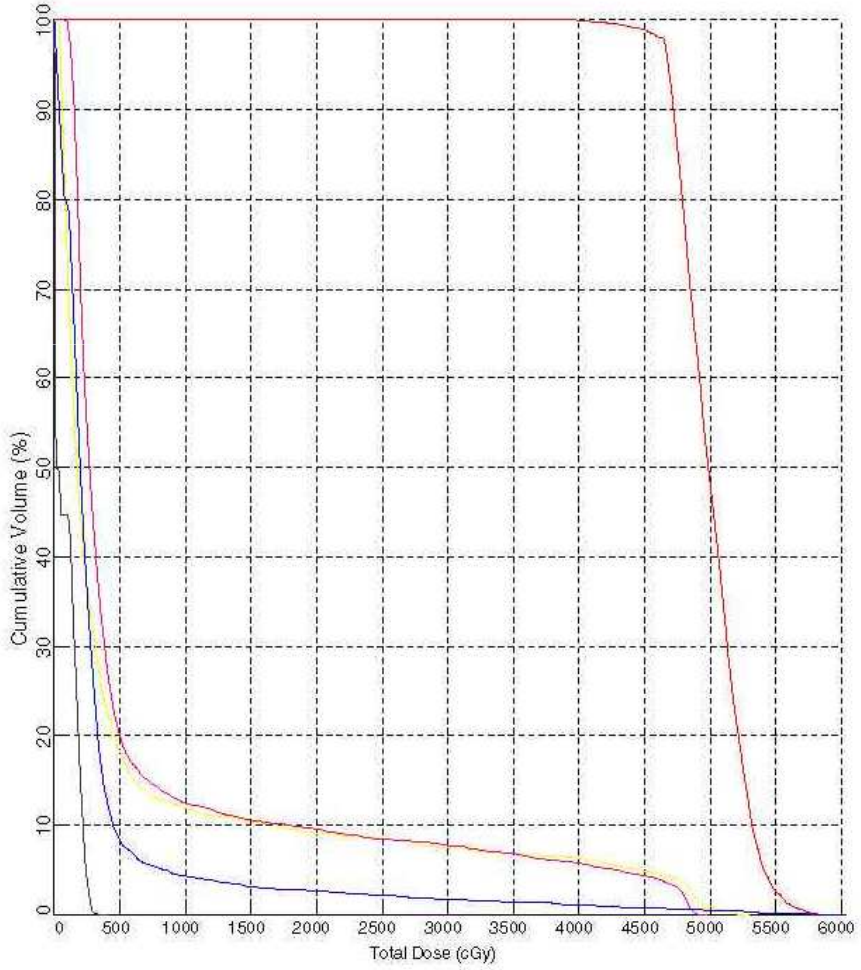
Erroneus Display of Buildup in Air


Total Dose
Z=-9.0 cm, T=10.0 cm, CT=7
5469.3
Z=-8.0 cm, T=9.0 cm, CT=8
5793.8
Z=-7.0 cm, T=8.0 cm, CT=9
5809.8
Z=-6.0 cm, T=7.0 cm, CT=10
5891.3
Z=-5.0 cm, T=6.0 cm, CT=11
6021.3
Z=-4.0 cm, T=5.0 cm, CT=12
6092.8
Z=-3.0 cm, T=4.0 cm, CT=13
5974.0
Z=-2.0 cm, T=3.0 cm, CT=14
5768.5
Z=-1.0 cm, T=2.0 cm, CT=15
5734.0
Z=0.0 cm, T=1.0 cm, CT=16
5814.7
Z=1.0 cm, T=0.0 cm, CT=17
5924.5
Z=2.0 cm, T=-1.0 cm, CT=18
6015.2
Z=3.0 cm, T=-2.0 cm, CT=19
5899.8
Z=4.0 cm, T=-3.0 cm, CT=20
5775.0
Z=5.0 cm, T=-4.0 cm, CT=21
5813.5
Z=6.0 cm, T=-5.0 cm, CT=22
5874.2
Z=7.0 cm, T=-6.0 cm, CT=23
6015.1
Z=8.0 cm, T=-7.0 cm, CT=24
5968.3
Z=9.0 cm, T=-8.0 cm, CT=25
5844.6
Z=10.0 cm, T=-9.0 cm, CT=26
4888.5

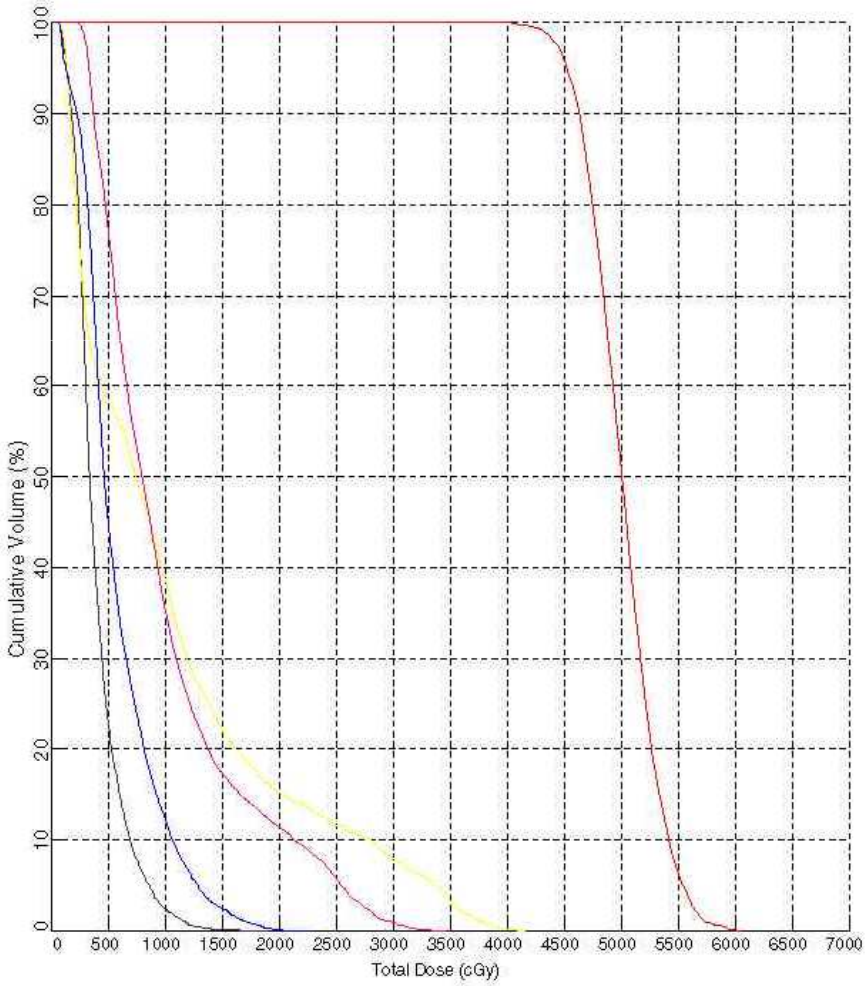

Total Dose
1 Coronal Y=+5.5 cm
5792.3
2 Sagittal X=+7.2 cm
5460.6
Sagittal
Coronal
Transverse
3 Transverse Z=+3.5 cm, T=-24.4 cm, CT=25
5372.8
4 Transverse Z=+3.5 cm, T=-24.3 cm, CT=25
5437.1
5874.8
2 Sagittal X=+7.2 cm
5613.4
3 Transverse Z=+3.5 cm, T=-24.4 cm, CT=25
5860.2
4 Transverse Z=+3.5 cm, T=-24.4 cm, CT=25
5637.7

Breast IMRT reduces Maximum dose to the heart at the expense of higher low dose exposure and a higher dose to the contralateral breast

Key	Structure	Plan	Min Dose(cGy)	Max Dose(cGy)	Mean Dose(cGy)	Total Vol (cc)
	Lunge re	Boggess_breast_study(09)	0	395	83	1065.0
	Lunge li	Boggess_breast_study(09)	26	5242	605	816.4
	Heart	Boggess_breast_study(09)	90	4929	675	564.8
	Lt Breast	Boggess_breast_study(09)	3817	5914	5003	1243.0
	R.Breast	Boggess_breast_study(09)	0	5981	323	1239.9



Key	Structure	Plan	Min Dose(cGy)	Max Dose(cGy)	Mean Dose(cGy)	Total Vol (cc)
	Lunge re	Boggess_breast_study(14)	56	1863	390	1065.0
	Lunge li	Boggess_breast_study(14)	66	4105	1023	816.4
	Heart	Boggess_breast_study(14)	223	3413	991	564.8
	Lt Breast	Boggess_breast_study(14)	3691	6016	5009	1235.6
	R.Breast	Boggess_breast_study(14)	61	2274	563	1239.9



El Haddad/Lohr et al., IJROBP, 2008

Key	Structure	Plan	Min Dose(cGy)	Max Dose(cGy)	Mean Dose(cGy)	Total Vol (cc)
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	R.Breast	Boggess_breast_study(09)	0	5981	323	1239.9
	Lunge re	Boggess_breast_study(14)	56	1863	390	1065.0
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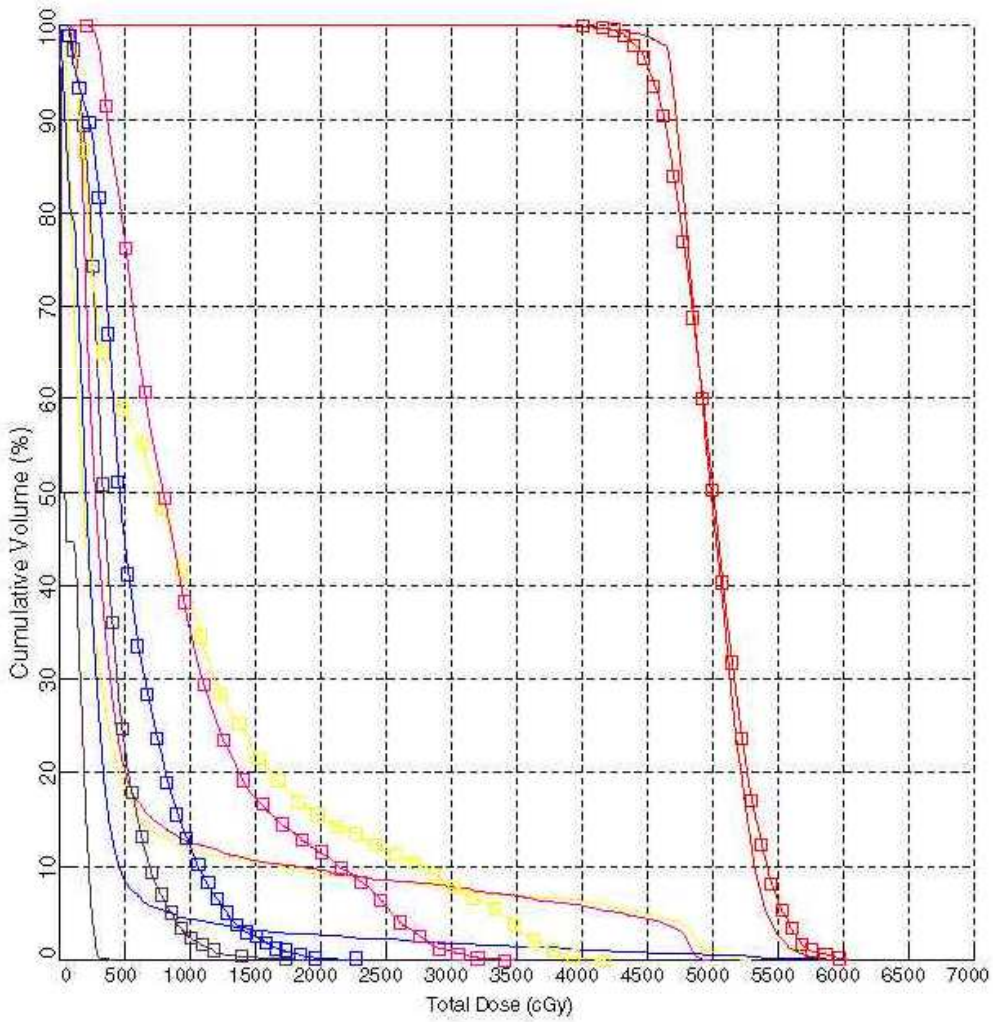
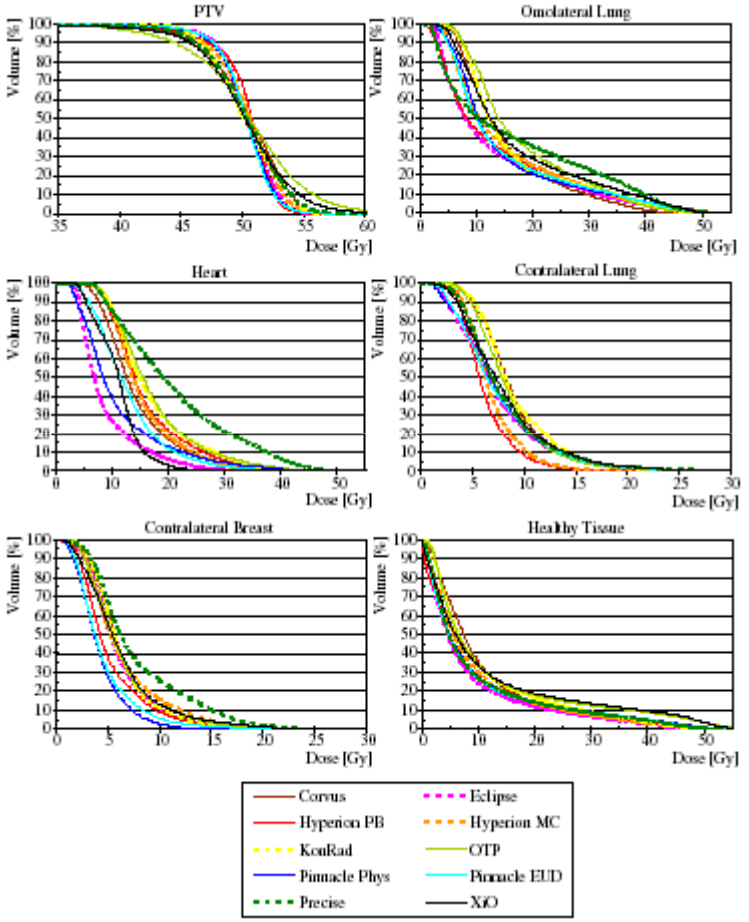
	Lt Breast	Boggess_breast_study(14)	3691	6016	5009	1235.6
	R.Breast	Boggess_breast_study(14)	61	2274	563	1239.9



*"The model-based reduction of the probability for excess therapy-associated cardiac death risk was from **6.03%** for the 3D plans to **0.25%** for the IMRT plans."*

El Haddad/Lohr et al., IJROBP, 2008

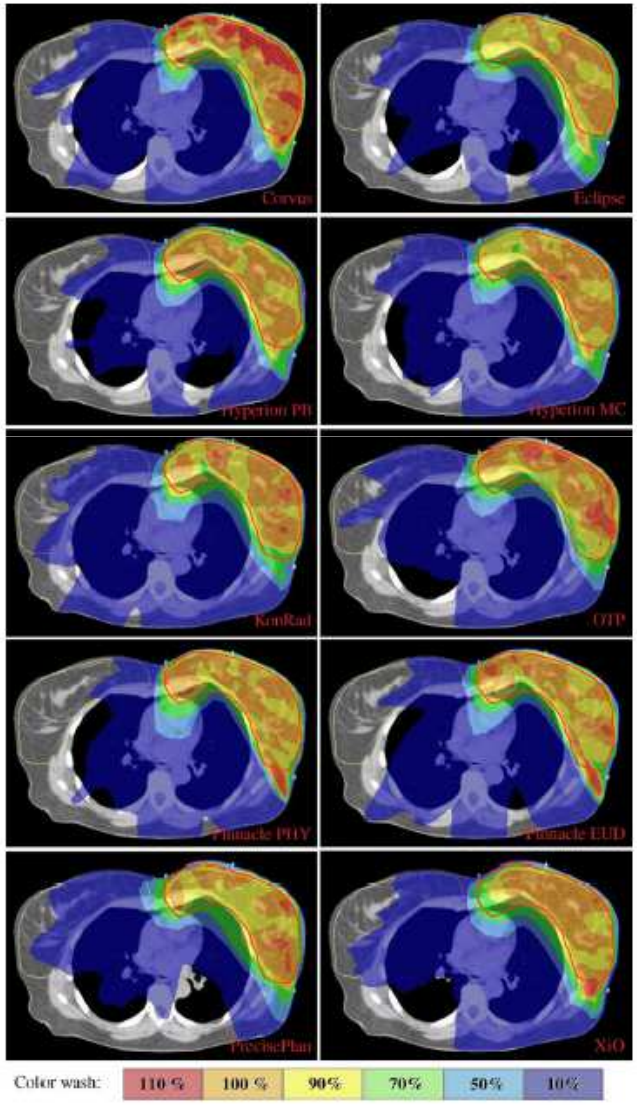
Current status of breast IMRT



IMRT for breast. A planning study

A. Fogliata[a], G. Nicolini[a], M. Alber[b], M. Asell[c], B. Dobler[d], M. El-Haddad[d,h], B. Hårdemark[k], U. Jelen[j], A. Kania[e], M. Larsson[k], F. Lohr[d], T. Munger[f], E. Negri[g], C. Rodrigues[i], L. Cozzi[a,*]

Radiother Oncol, 2005



IMRT vs. VMAT

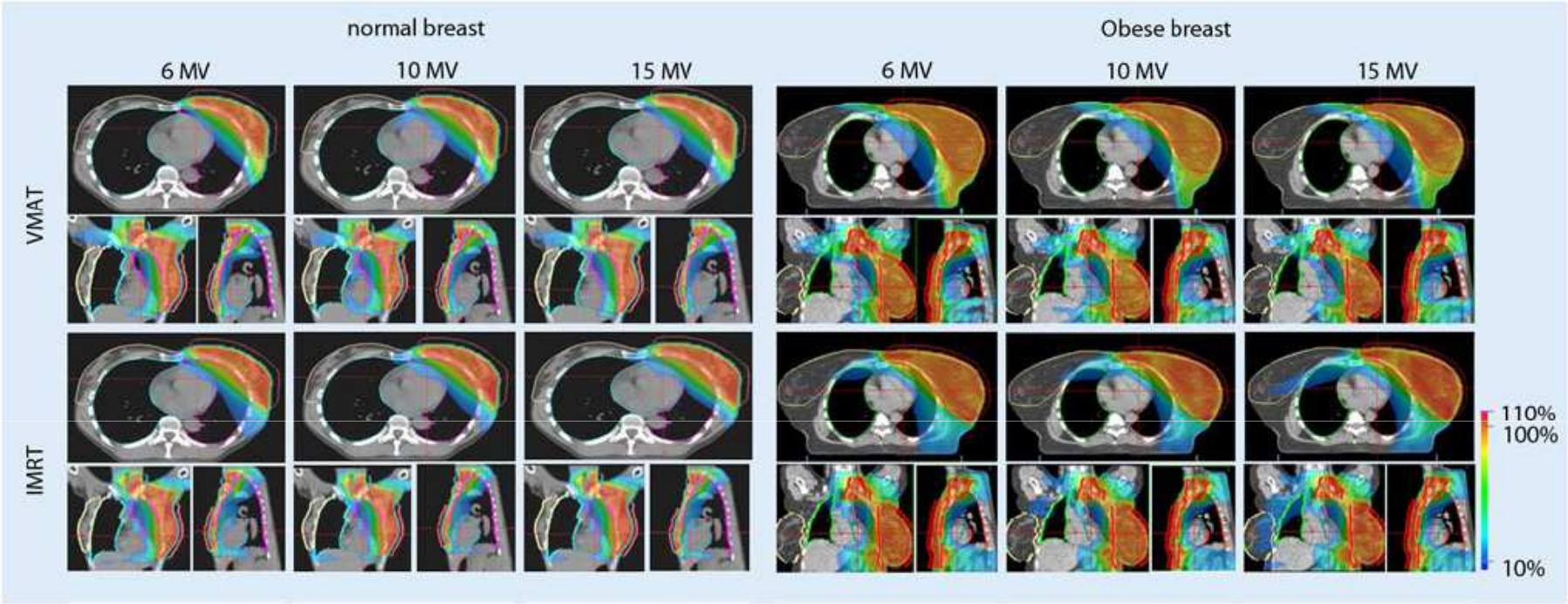


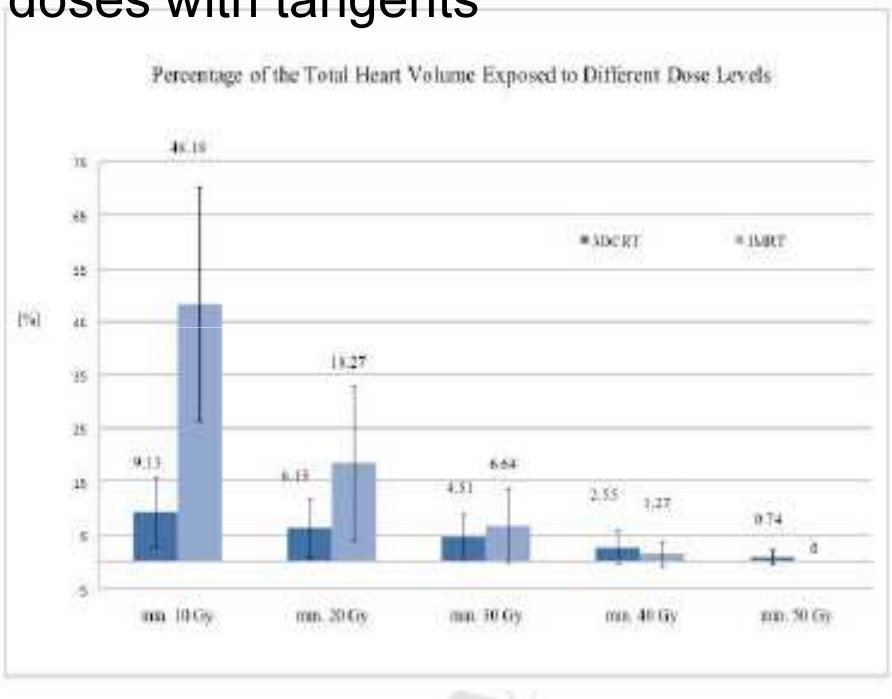
Fig. 2 ▲ Sample isodose distributions in transverse, coronal and sagittal planes (ArtiView™) for VMAT and IMRT plans of a normal (*left*) and an obese (*right*) patient at 6, 10 and 15 MV

Pasler et al., SUON, 2013

First clinical data

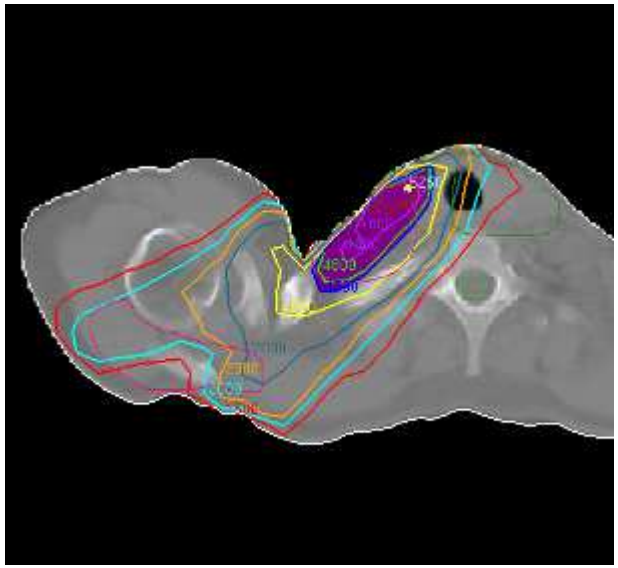
Heggemann et al., IJROBP, 2015

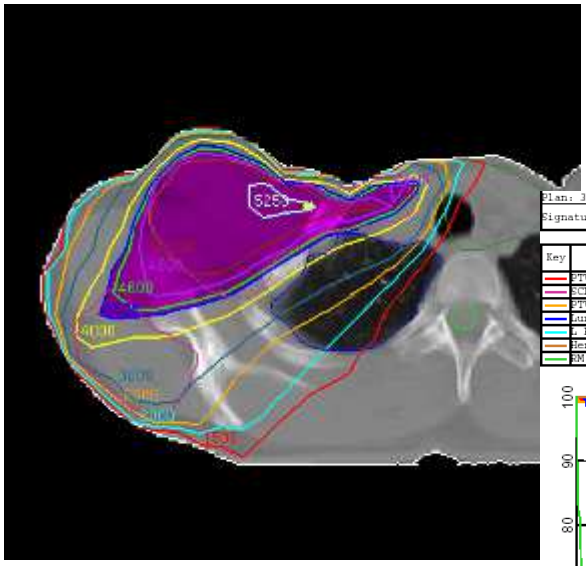
- 3D-CRT in Patients with small heart volumes irradiated with tangents
- IMRT in Patients that would have had large volumes irradiated to high doses with tangents



-Noisy data
-In both groups temporary depression of heart function parameters
-In both groups recovery at 2 years
-No relevatn difference between groups

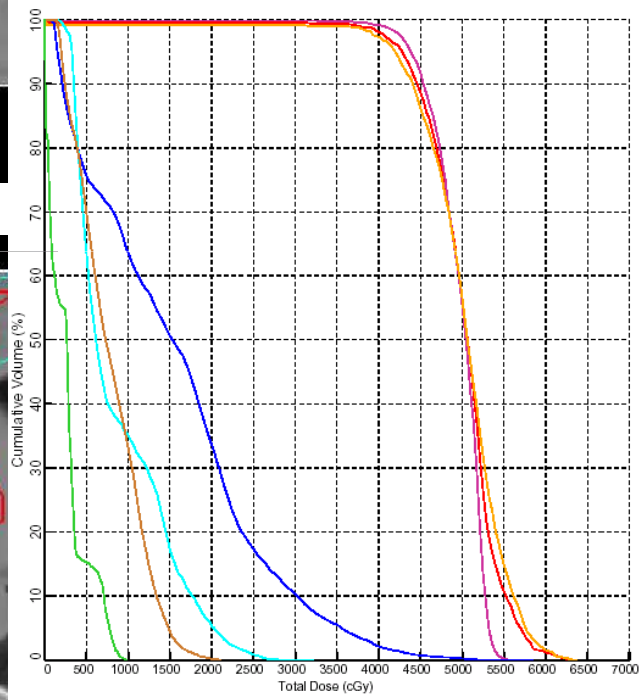
Mean Heart dose is potentially not the best parameter
(ASTRO 2015: in RTOG 0617 V45 was the best predictor…….)

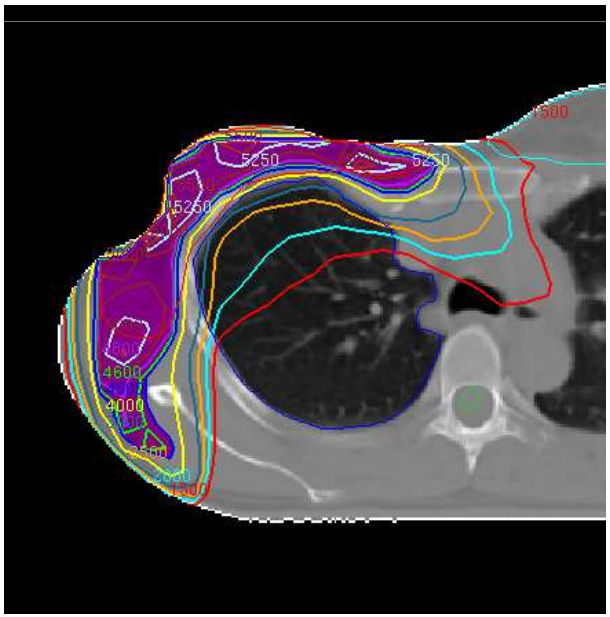


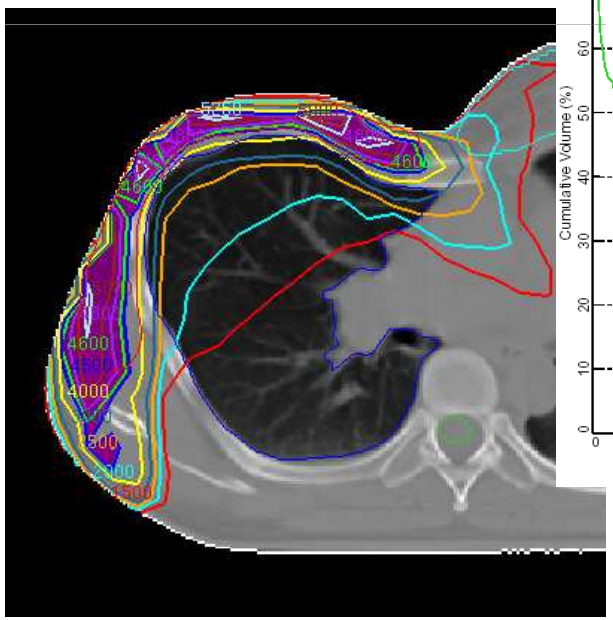


Plan: 37	plan 36 - hot spots out	Plan Date	23-MAY-2006 22:54
Signature	8 Beams - 35 segments - purged for <3 MUs - Flash region added		

Key	Structure	Plan	Min Dose (cGy)	Max Dose (cGy)	Mean Dose (cGy)	Total Vol (cc)
	PTV	Renken Heike(37) Whole PTV	0	6288	5000	774.4
	SCLN	Renken Heike(37) Supraclavicular LNs	0	5545	4962	261.6
	PTV 2	Renken Heike(37) Chest Wall	0	6336	5000	461.1
	Lunge re	Renken Heike(37) Ipsilateral Lung	107	5775	1552	1635.0
	L Breast	Renken Heike(37) Contralateral Breast	0	3186	886	632.5
	Herz	Renken Heike(37)	141	2090	785	409.2
	FM	Renken Heike(37)	0	963	259	60.6

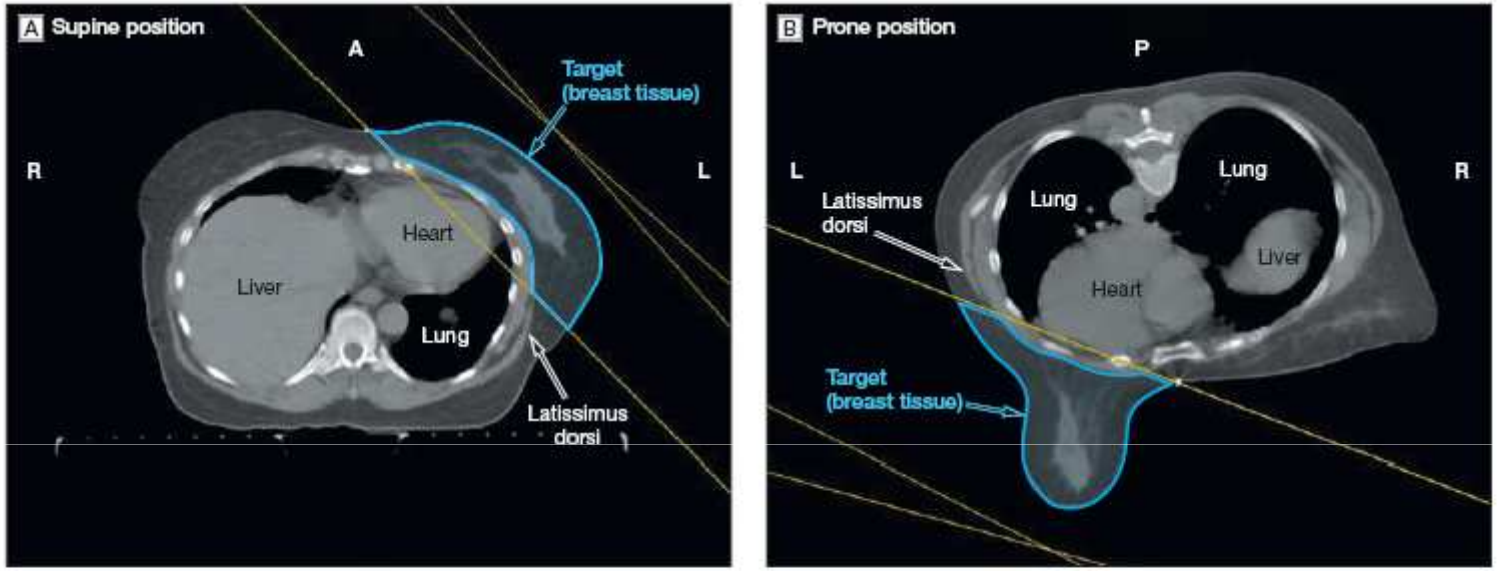






Prone vs. Supine

Formenti et al., JAMA, 2012



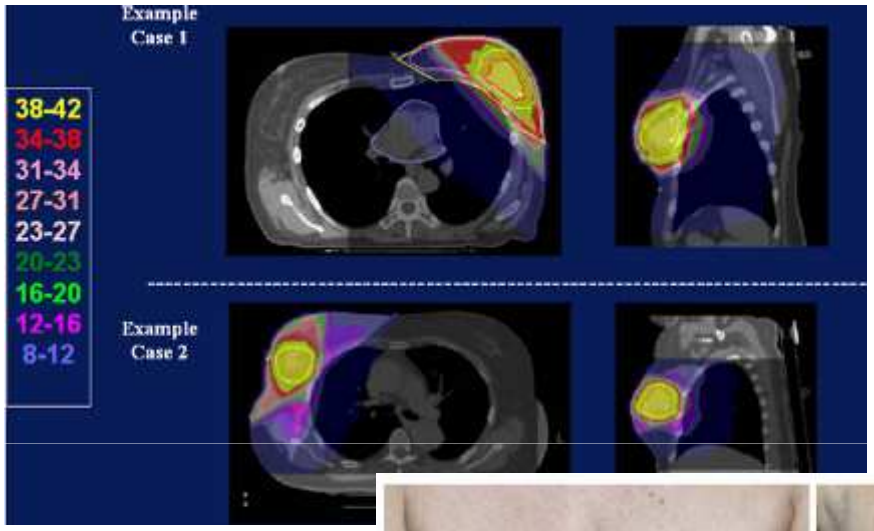
Placing the posterior edge of the fields on a plane connecting the midline to the anterior extent of the latissimus dorsi muscle ensures comparable breast coverage.

Table. Differences in Volumes of Heart and Lung Between Supine and Prone Positions by Breast Volume and Right vs Left Breast Cancer

	Right Breast Cancer[a]				Left Breast Cancer						
		In-Field Lung Volume, Mean (95% CI), cm³				In-Field Lung Volume, Mean (95% CI), cm³			In-Field Heart Volume, Mean (95% CI), cm³		
Breast Volume, cm³	No.	Supine	Prone	Difference of Supine Minus Prone[b]	No.	Supine	Prone	Difference of Supine Minus Prone[b]	Supine	Prone	Change From Supine to Prone[b]
<750	73	122.80 (106.90 to 138.71)	20.91 (15.54 to 26.29)	101.89 (87.05 to 116.73)	78	90.64 (76.80 to (104.47)	17.56 (10.59 to 24.54)	73.07 (60.42 to 85.72)	3.09 (1.56 to 4.61)	2.60 (1.17 to 4.02)	0.49 (−1.62 to 2.60)
750-1500	91	120.71 (105.31 to 136.11)	17.47 (11.19 to 23.74)	103.24 (88.91 to 117.58)	84	110.44 (94.28 to 126.57)	3.65 (1.93 to 5.38)	106.78 (90.75 to 122.82)	10.38 (7.19 to 13.57)	0.57 (0.22 to 0.92)	9.81 (6.60 to 13.02)
>1500	36	120.20 (84.11 to 156.28)	6.66 (0.96 to 12.36)	113.54 (78.58 to 148.49)	38	88.68 (63.63 to 113.73)	1.81 (−1.55 to 5.17)	86.87 (61.50 to 112.23)	16.80 (8.46 to 25.13)	0	16.79 (8.45 to 25.13)
Total	200	121.38 (110.44 to 132.32)	16.78 (13.15 to 20.41)	104.60 (94.26 to 114.95)	200	98.58 (88.77 to 108.39)	8.73 (5.72 to 11.74)	89.85 (80.16 to 99.55)	8.75 (6.53 to 10.97)	1.25 (0.66 to 1.84)	7.50 (5.16 to 9.85)

[a] There was no in-field heart volume in any of the patients with right breast cancer.
[b] The 95% CIs are based on paired *t* statistics.

Hypofractionation/SIB/APBI-> Watch the Volume



Jagsi et al., IJROBP, 2009

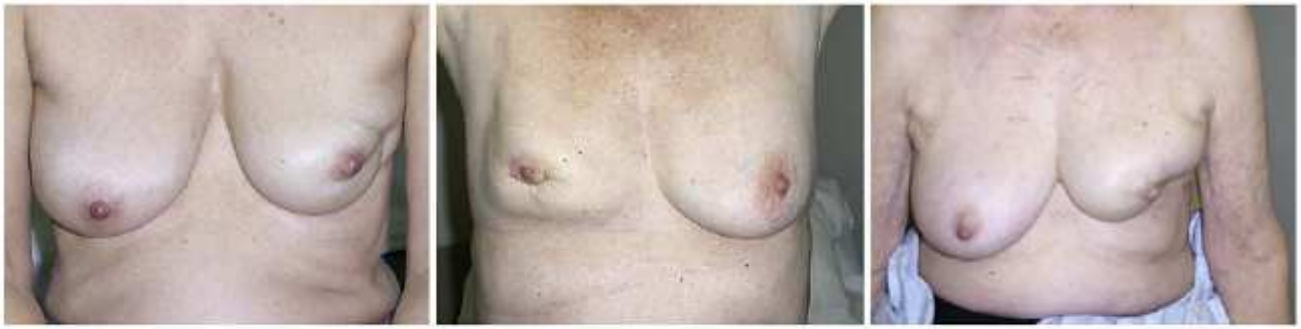


Fig. 3. Visible impairment in cosmesis observed in 3 patients deemed to have unacceptable cosmesis after treatment.

Several Trials with different concepts running (NSABP, IRMA, etc.), results to be expected during the next 2-5 years

SIB Breast – Localization?

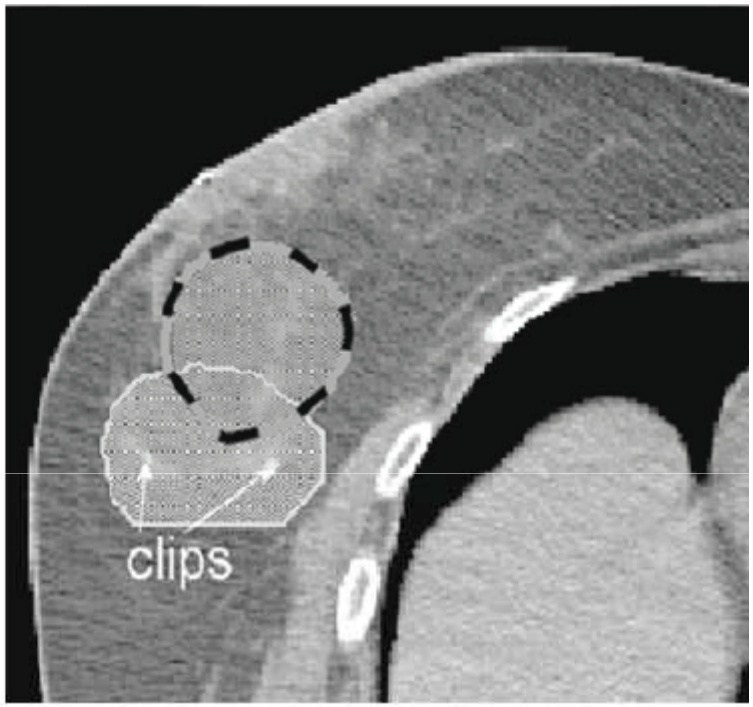
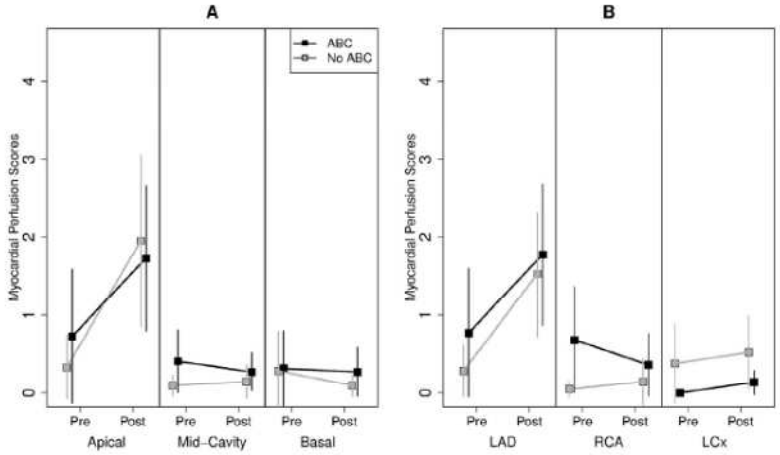


Fig. 2 Examples in two patients (**a** and **b**) of partial breast irradiation. Subclinical doses of the tumor bed PTV marked with clips can be observed, as can be seen from the dose distribution (*black dashed line* corresponding to 40 Gy coverage) and the histograms

Gonzalez Sanchis et al.,
Clin Transl Oncol, 2013

SPECT Analysis of Cardiac Perfusion Changes After Whole-Breast/Chest Wall Radiation Therapy With or Without Active Breathing Coordinator: Results of a Randomized Phase 3 Trial

Similar Perfusion Changes in LAD region w and w/o ABC



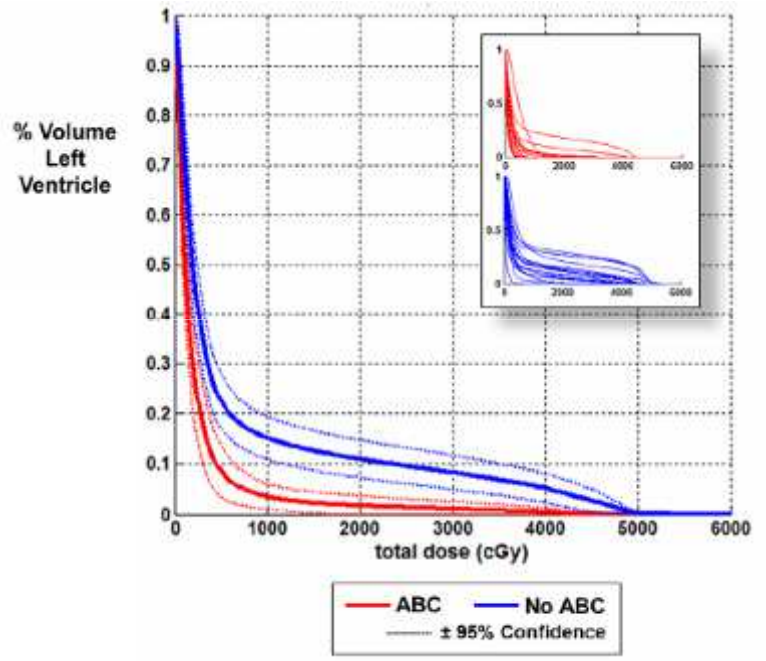
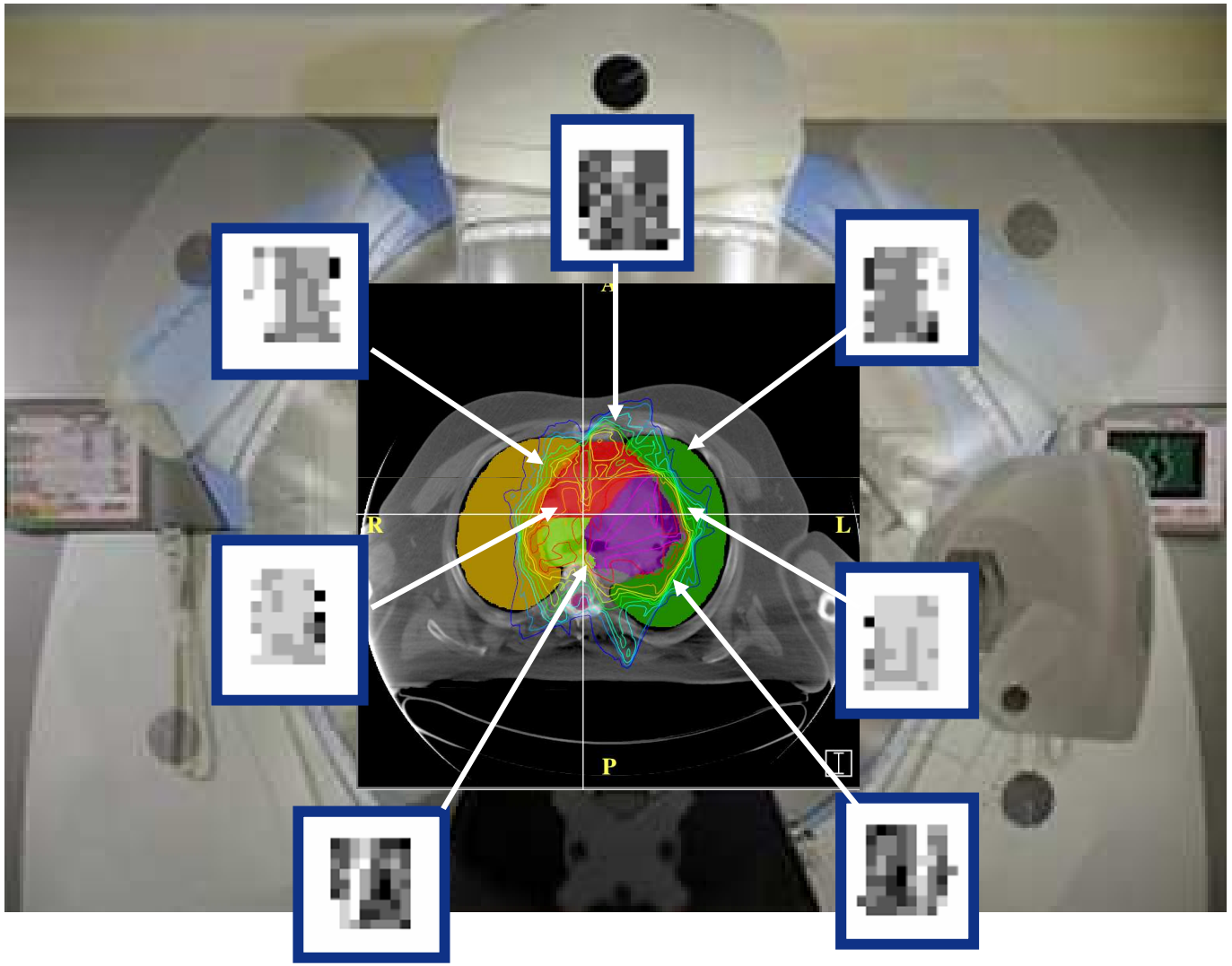


Fig. 2. Change in myocardial perfusion scores are based on quantitative polar mapping using (A) ring segmentation and (B) coronary artery distribution. Squares are estimated means at baseline and follow-up, with vertical lines indicating 95% confidence intervals for means.

Zellars, IJROBP, 2014

Second Malignancies

IMRT-Capable Delivery System



There is nothing new under the sun……1

K. Bratengeier

In: Kiricuta, Definition of Target Volumes, 2001

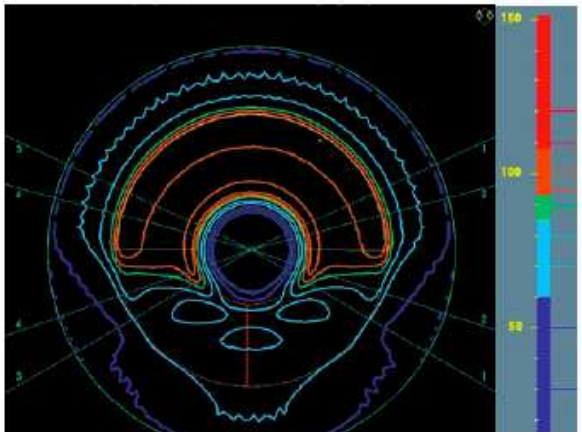
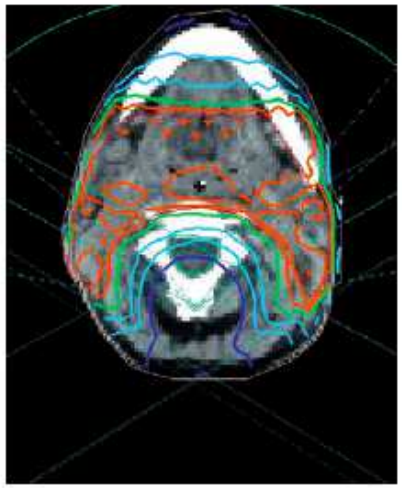
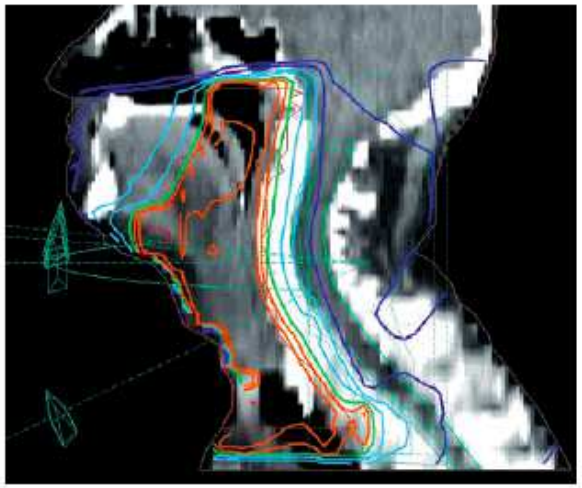


Figure 8. *Two-step IMAT in the case of a patient with Hypopharynx-Carcinoma. Left: transversal plane. Right: sagittal plane; 30%, 50%, 70%, 80%, 90% and 95% isodoses are shown in the same colors as labelled in figure 7.*





There is nothing new under the sun……2

Klaus Welker und Jürgen Richter

Die Geschichte
der Strahlentherapie
an der Robert-Rössle-Klinik
in Berlin-Buch
1950 bis 1984

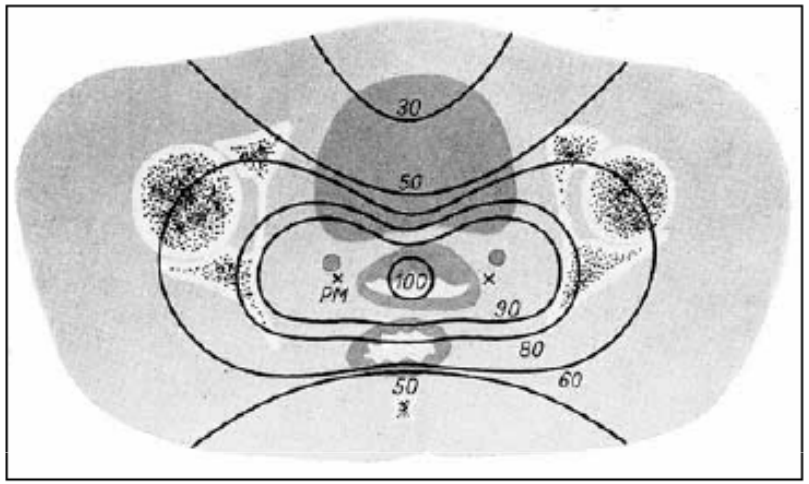


Abb. 2.6.1: Dosisverteilung für eine biaxiale Bewegungsbestrahlung.

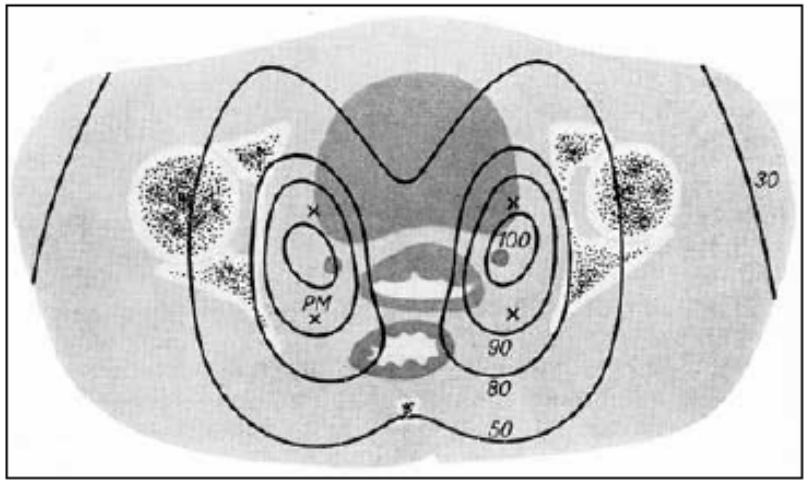


Abb. 2.6.2: Dosisverteilung für eine 4-axiale Bewegungsbestrahlung.

“The most important prerequisite for the development of a second neoplasm is cure of the primary malignancy”

Doerr, Hermann, SUON, 2008

-> Death as confounding factor has to be compensated for in estimates

The effect of fraction time in intensity modulated radiotherapy: theoretical and experimental evaluation of an optimisation problem

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UNEXPECTED CHANGES OF RAT CERVICAL SPINAL CORD TOLERANCE CAUSED BY INHOMOGENEOUS DOSE DISTRIBUTIONS

HENDRIK P. BIJL, M.D.,* PETER VAN LUIJK,† ROB P. COPPES, PH.D.,*‡ JACOBUS M. SCHIPPERS, PH.D.,†1 ANTONIUS W. T. KONINGS, PH.D.,‡ AND ALBERT J. VAN DER KOGEL, PH.D.§

Dental X-Rays and the Risk of Intracranial Meningioma

CANCER March 1, 2004 / Volume 100 / Number 5

A Population-Based Case–Control Study

Effect of low doses of ionising radiation in infancy on cognitive function in adulthood: Swedish population based cohort study

Per Hall, Hans-Olov Adami, Dimitrios Trichopoulos, Nancy L Pedersen, Pagona Lagiou, Anders Ekbom, Martin Ingvar, Marie Lundell, Fredrik Granath

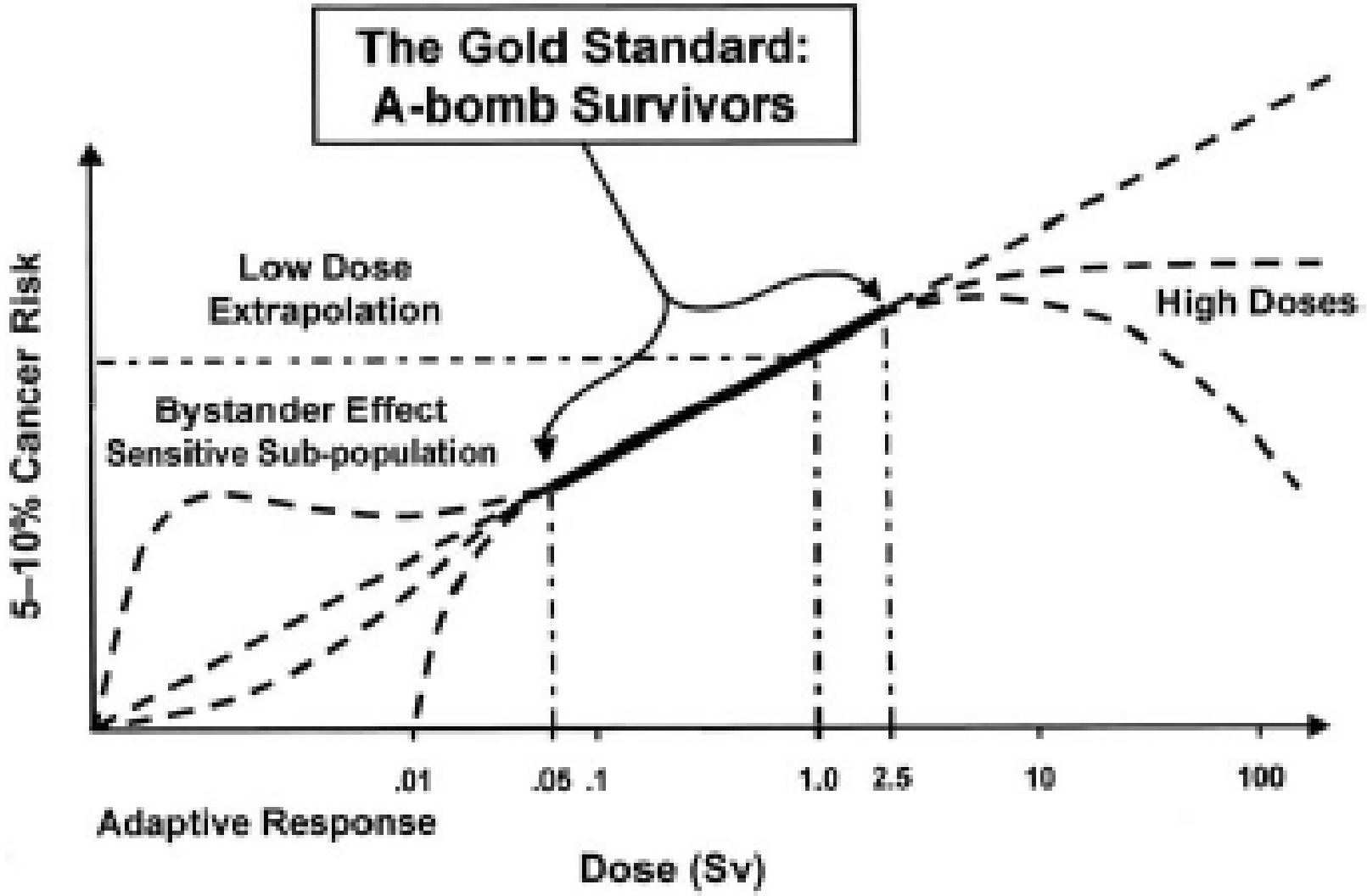
BMJ VOLUME 328 3 JANUARY 2004 bmj.com

Risk estimates for secondary cancer after exposure to ionizing radiation

1. Low dose estimates (0-2 Gy single dose exposure, based on the Atomic Bomb Survivor Study (Life Span Study, LSS), that forms the basis for the Biological Effects of Ionizing Radiation (BEIR VII model)

2. High dose estimates (>2 or >5 Gy, based on clinical follow up data after radiotherapy for benign or malignant disease

Different Aspects of Carcinogenesis - Synopsis



Problems identifying true incidence numbers of secondary cancer after exposure to ionizing radiation

1. Low dose Estimates (LSS):

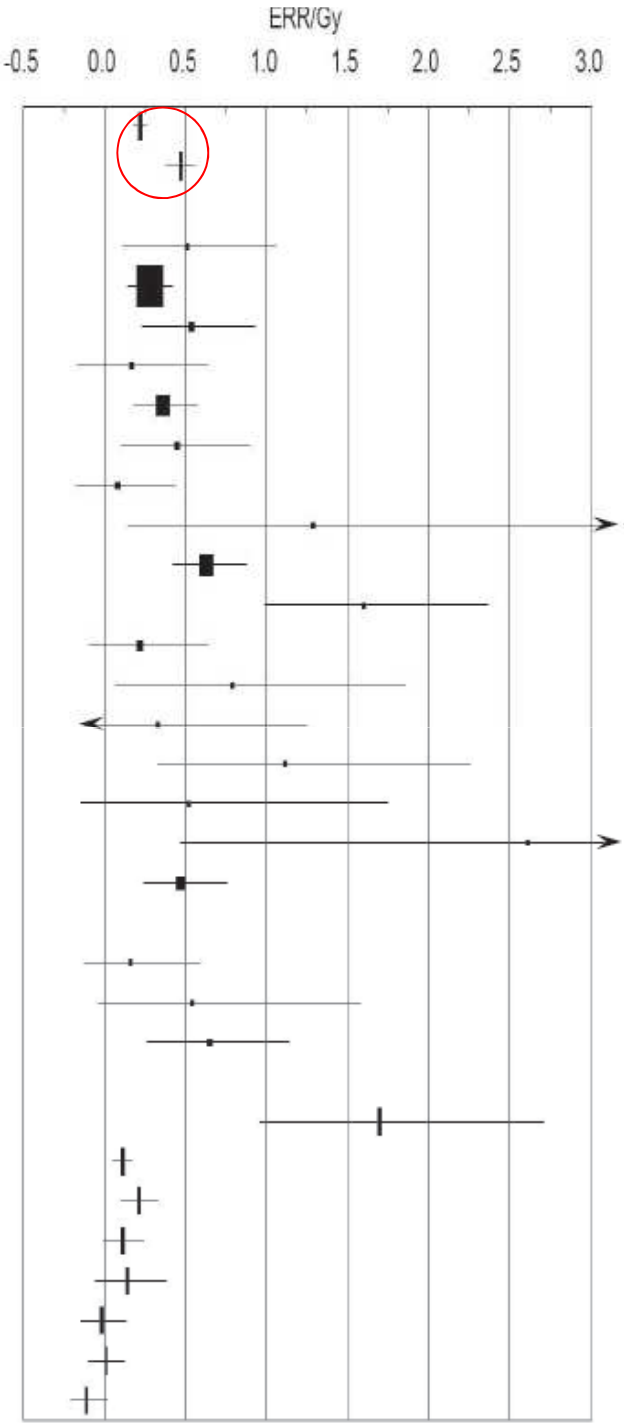
- Low number of events
- Uncertain Dosimetry
- Unclear effects of other toxins
- Difficulties to maintain long follow up
- Very limited dose range (limited by acute lethalty of exposure and explosion force to 0-2 Gy with emphasis on <1 Gy)

2. High dose Estimates (clinical)

- Low number of events
- Combination Therapies
- Information on precise localization and doses at the site of second malignancies hard to obtain (10 year documentation…..)
- Long follow up necessary, hard to obtain without institutional data collection

Low Dose Models

Cause of death	ERR/Gy [a] (95%CI [b])	Cases
All causes	0.22 (0.18, 0.26)	50,620
All solid cancer	0.47 (0.38, 0.56)	10,929
Cancers of Specific sites [c]		
Esophagus	051 (0.11, 1.06)	339
Stomach	0.28 (0.14, 0.42)	3,125
Colon	0.54 (0.23,0.93)	621
Rectum	0.17 (-0.17,0.64)	427
Liver	0.36 (0.18, 0.58)	1,519
Gallbladder	0.45 (0.10, 0.90)	419
Pancreas	0.08 (-0.18, 0.44)	513
Other digestive system	1.29 (0.14, 3.25)	84
Lung	0.63 (0.42, 0.88)	1,558
Breast	1.60 (0.99, 2.37)	324
Uterus	0.22 (-0.09, 0.64)	547
Ovary	0.79 (0.07, 1.86)	157
Prostate	0.33 (NA [e], 1.25)	130
Bladder	1.12 (0.33, 2.26)	183
Kidney parenchyma	0.52 (-0.15, 1.75)	80
Renal pelvis and ureter	2.62 (0.47,7.25)	33
Other solid cancer	0.47 (0.24, 0.76)	864
Lymphoid and hematopoietic malignancies [c, d]		
Malignant lymphoma	0.16 (-0.13,0.59)	284
Multiple myeloma	0.54 (-0.04,1.58)	93
Other neoplasms [c]	0.65 (0.26, 1.14)	518
Non-neoplastic diseases and other causes		
Blood diseases	1.70 (0.96, 2.70)	238
Circulatory diseases	0.11 (0.05, 0.17)	19,054
Respiratory diseases	0.21 (0.10, 0.33)	5,119
Digestive diseases	0.11 (-0.01, 0.24)	3,394
Genitourinary diseases	0.14 (-0.06, 0.38)	1,309
Infectious diseases	-0.02 (-0.15, 0.13)	1,962
Other diseases	0.01 (-0.1, 0.12)	4,847
External causes	-0.11 (-0.21, 0.02)	2,432



LSS, Ozasa, Rad Res, 2012

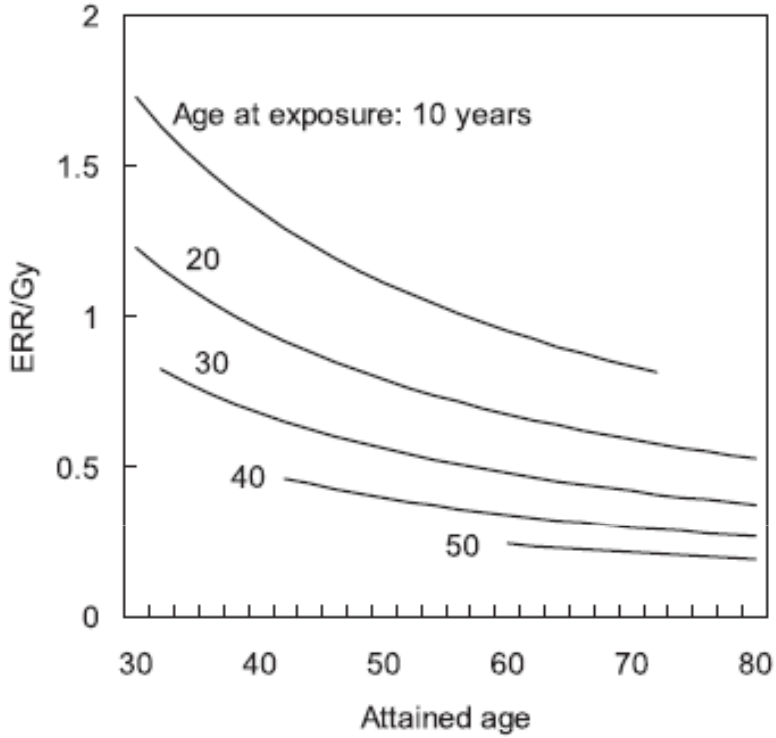


FIG. 2. Modification of the excess relative risk (ERR) for all solid cancer by age at exposure and attained age.

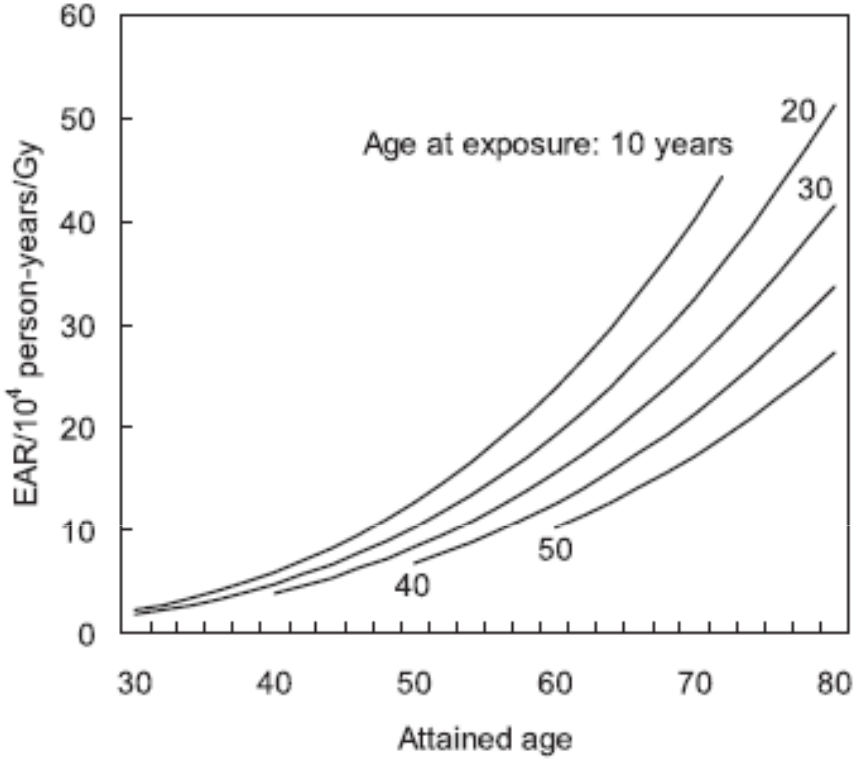


FIG. 3. Modification of the excess absolute risk (EAR) for all solid cancer by age at exposure and attained age.

LSS, Ozasa, Rad Res, 2012

High(er) Dose Exposure

Low Doses are evil…….are they???

Im Feld	46 (51%)
Am Feldrand	20 (22%)
Außerhalb des Feldes	24 (27%)

Tabelle 4. Lokalisation der Zweitmalignome in Beziehung zum Strahlenfeld.

Table 4. Localization of secondary malignancies with respect to the field size.

Gy	n
< 1	14 (16%)
1 – 10	12 (13%)
11 – 20	16 (18%)
21 – 30	8 (9%)
31 – 40	19 (21%)
41 – 50	20 (22%)
> 50	1 (1%)

Tabelle 5. Strahlendosis am Entstehungsort des Zweitmalignoms.

Hochrisikopatienten. Die Patienten mit zusätzlicher Polychemotherapie wiesen insgesamt ein signifikant höheres kumulatives Zweitmalignomrisiko auf als die Patienten mit Radiotherapie allein. Abbildungen 3a und 3b zeigen für das Kollektiv ab 1972 das kumulative Zweitmalignomrisiko selektiert für die typischen Kombinationstherapien (Radiotherapie in Kombination mit MOPP oder ABVD oder MOPP + ABVD) im Vergleich zur Radiotherapie allein, und zwar in Beziehung zur Primärtherapie (Abbildung 3a) und zur gesamten Therapie einschließlich Rezidivtherapie (Abbildung 3b). Die Kombination mit MOPP hatte, für sich betrachtet, bis zu 15 Jahren nach Therapie das geringste Zweitmalignomrisiko, so daß die Anhebung des Zweitmalignomrisikos im Gesamtkollektiv der Patienten mit Polychemotherapie signifikant zu Lasten der Kombinationen mit ABVD bzw. ABVD + MOPP ging (Abbildungen 3a und 3b).

	n		n
Mammakarzinom	14	Schilddrüsenkarzinom	2
Bronchialkarzinom	12	Hirntumor	2
Non-Hodgkin-Lymphome	9	Harnblasenkarzinom	1
Basaliom	8	Chondrosarkom	1
Weichteilsarkom *	7	Hautkarzinom	1
Kolorektales Karzinom	6	Hypopharynxkarzinom	1
Uteruskarzinom	5	Nierenkarzinom	1
Magenkarzinom	5	Parotiskarzinom	1
Seminom	3	Pleurakarzinom	1
AML	3	Vulvakarzinom	1
Pleuramesotheliom	2	Zungenkarzinom	1
Osteosarkom	2	Andere	1

*Malignes Hämangioperizytom; malignes Histiozytom (2); Leiomyosarkom (2); Spindelzellsarkom; malignes Schwannom.

Tabelle 3. Spezifikation der Zweitmalignome (n = 90).

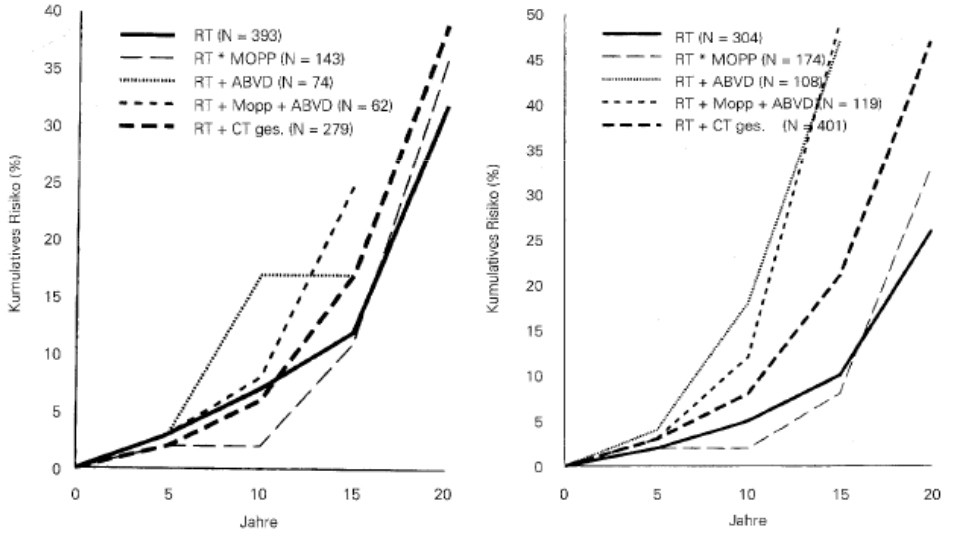


Abbildung 3a – Figure 3a

Abbildung 3b – Figure 3b

Abbildungen 3a und 3b. Morbus Hodgkin. Kumulatives Zweitmalignomrisiko in Beziehung a) zur primären Therapie: Radiotherapie (RT) allein oder in Kombination mit Chemotherapie (CT), hier mit MOPP oder ABVD oder MOPP + ABVD; RT vs. RT + CT (ges.) $p < 0{,}001$. Freiburg 1972 bis 1997, mediane Beobachtungszeit 10,4 Jahre, n = 672. b) Kumulatives Zweitmalignomrisiko in Beziehung zur gesamten Therapie: Radiotherapie (RT) allein oder in Kombination mit Chemotherapie (CT), hier mit MOPP oder ABVD oder MOPP + ABVD; RT vs. RT + CT (ges.) $p < 0{,}001$, RT + MOPP vs. RT + ABVD $p < 0{,}01$, RT + MOPP vs. RT + MOPP + ABVD $p < 0{,}05$. Freiburg 1972 bis 1997, mediane Beobachtungszeit 10,4 Jahre, n = 706.

Slanina et al., Strahlentherapie, 1999

Hodgkin II (GHSG)

Behringer et al., IJROBP, 2004

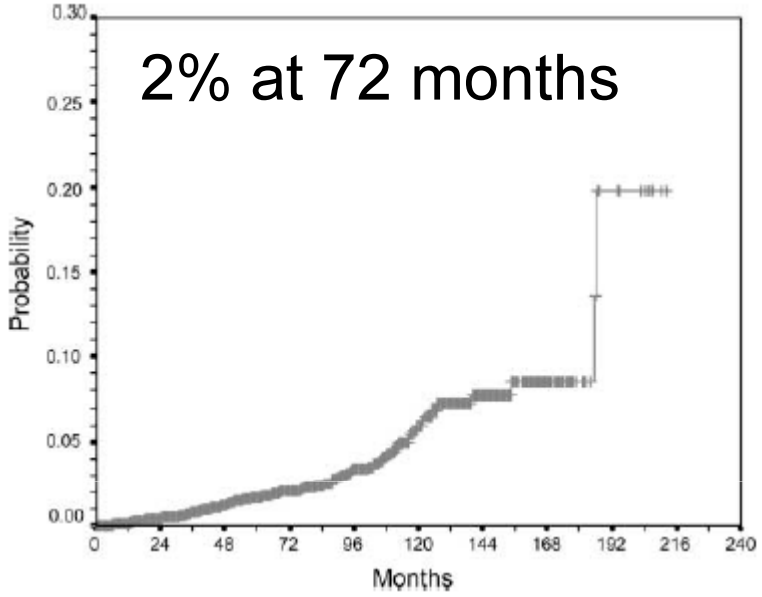


Figure 1. Cumulative risk of solid tumor by time since first treatment.

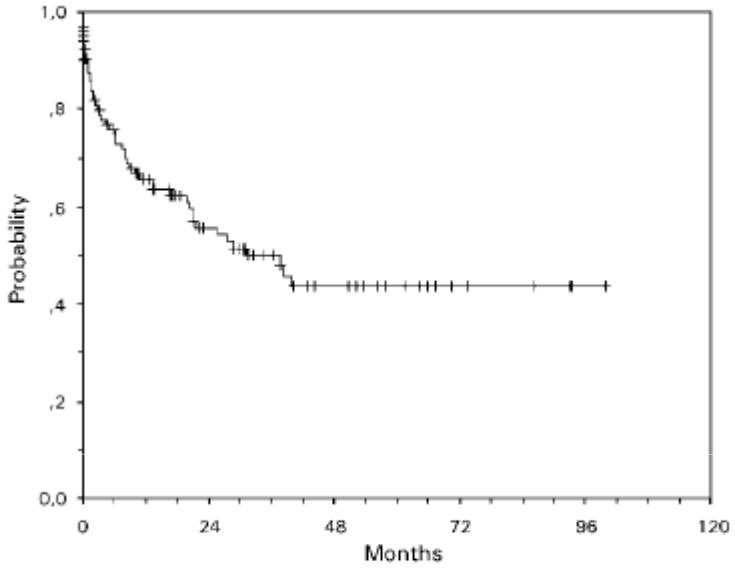


Figure 2. Overall survival from solid tumor.

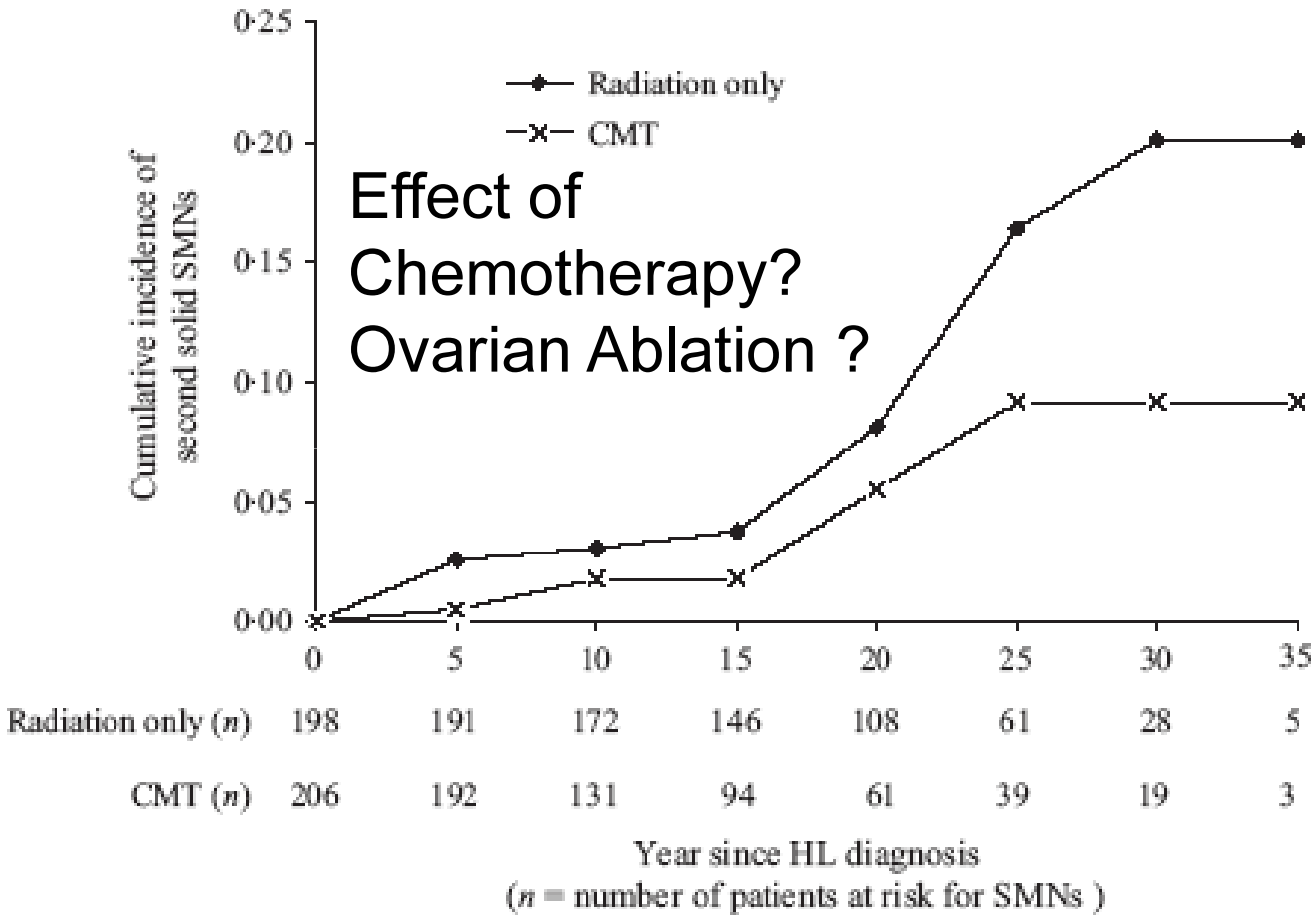
Table 8. Solid tumors within or adjacent to the initial irradiation field

Tumor entity	Location within the initial irradiation field		
	Probable	Not probable	Unknown
Breast	4	3	6
Lung	12	6	12
Thyroid	4	1	0

Uncertainty about SM-Location

Hodgkin III (Yale)

Omer et al., BJH, 2012

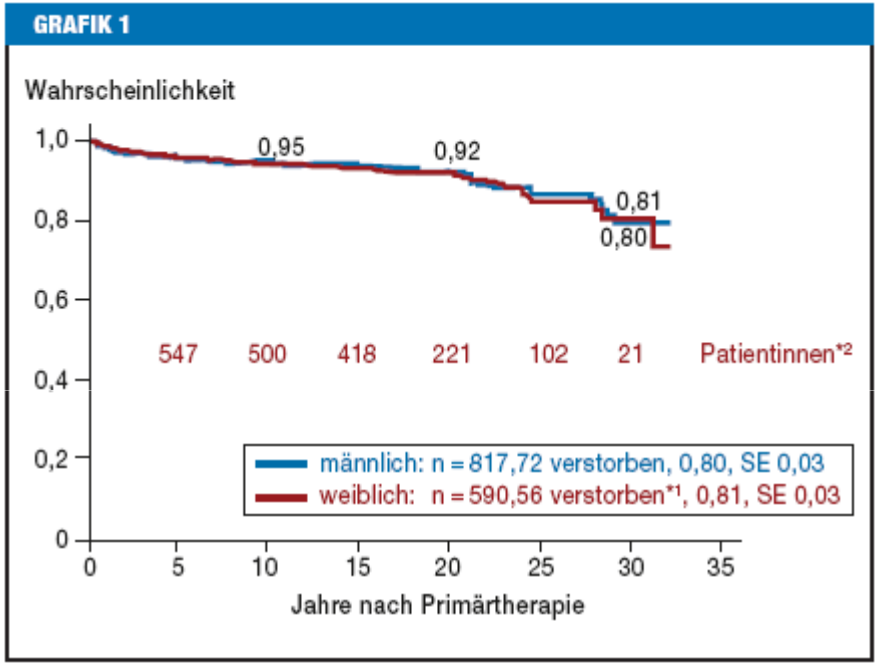


Vast Majority of SMNs in field

CMT Patients received lower doses than RT-only patients (20 vs. 40 Gy)

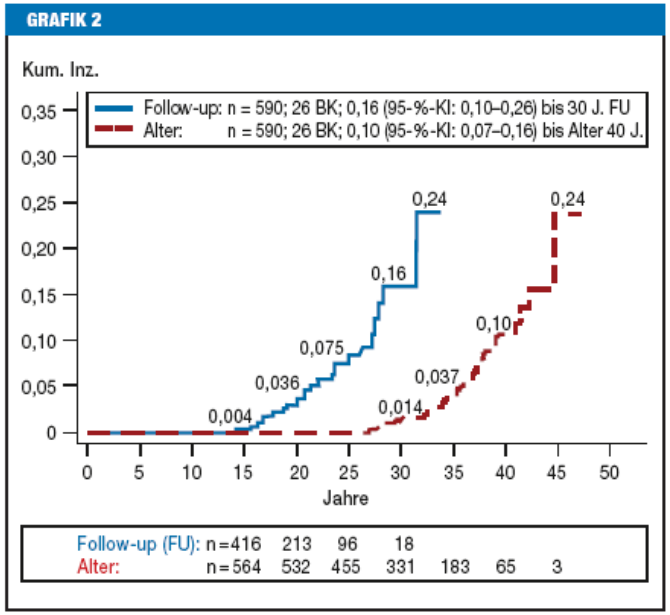
Hodgkin III: Pediatric HD

96% of Secondary Cancers in-field

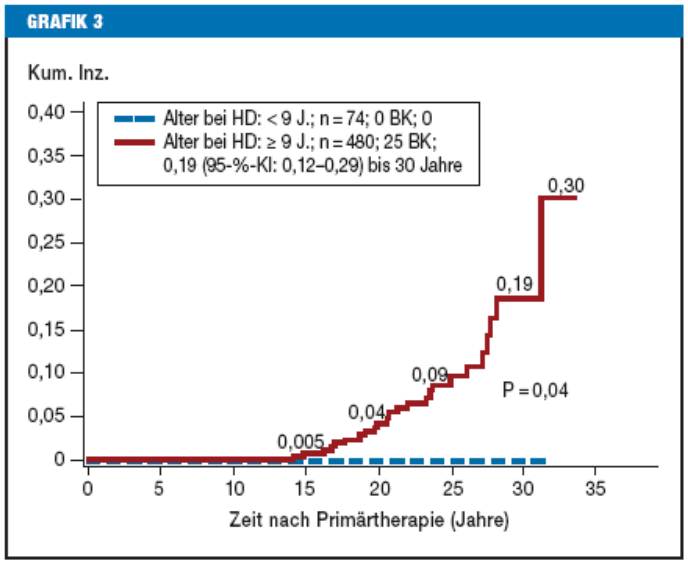


Gesamtüberleben („overall survival" [OS] nach 30 Jahren) in den Morbus-Hodgkin-Therapiestudien HD-78 bis HD-90 bei Jungen und Mädchen (Stand: 1. Juli 2012).
*1 Todesursachen bei den Patientinnen: Hodgkin-Lymphom (n = 18), Post-Splenektomie-Sepsis (n = 7), Sekundärmalignom (n = 15, davon 3 Brustkrebs), Herzerkrankungen (n = 6), sonstige (n = 10, inklusive Unfall, Suizid)
*2 mit dokumentierten Verlaufsinformationen
SE, „standard error"

Schellong, Dt. Ä-Blatt, 2014



Kumulative Inzidenz (Kum. Inz.) für Brustkrebs (BK) in der Gesamtgruppe der Patientinnen aus den pädiatrischen Therapiestudien HD-78 bis HD-90 in Abhängigkeit von der Zeit seit Primärtherapie (blaue Linie), bzw. vom erreichten Lebensalter (rote unterbrochene Linie) mit 95-%-Konfidenzintervall (95-%-KI). Stand: 1. Juli 2012



Kumulative Inzidenz (Kum. Inz.) für Brustkrebs (BK) mit 95-%-Konfidenzintervall (95-%-KI) in der Gruppe der Patientinnen aus den pädiatrischen Therapiestudien HD-78 bis HD-90, die im Brustbereich bestrahlt worden sind. (Stand: 1. Juli 2012)

Hodgkin III: Pediatric HD

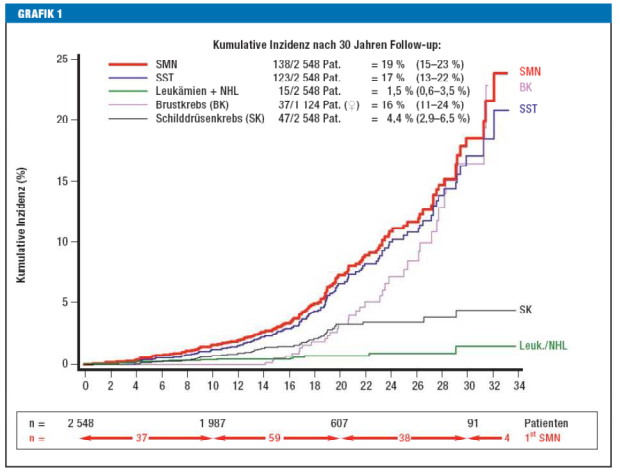
85% of Secondary Cancers in-field
Second Thyroid cancer only in patients with Mediastinal or Neck RT

TABELLE 3

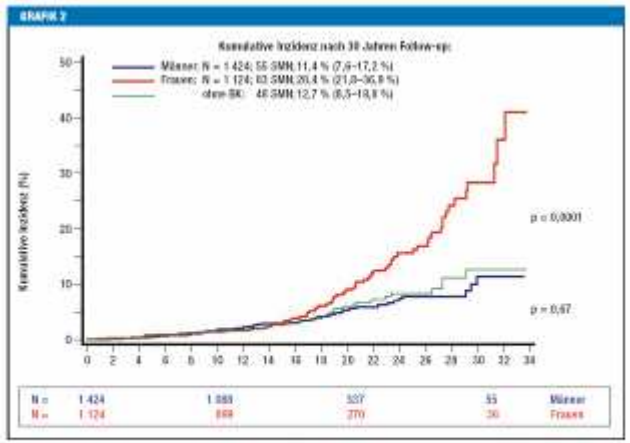
Kumulative Inzidenz von SMN nach Behandlung eines HL in der Kindheit und Jugend

Erstautor (Literaturstelle)	Alter HL-Diagnose (Jahre)	Patienten-rekrutierung (Zeitraum)	Pat. (n)	Medianes Follow-up (Jahre)	Pat. mit SMN (n)	Kumulative Inzidenz (%) nach 20 J.	nach 25 J.	nach 30 J.	SIR	95-%-KI
Sankila (14)	< 21	1943–87	1 641		62*	6,9		18	7,7	5,9–9,9
Wolden (15)	< 21	1960–95	694	12,3	56*	m 9,7			m 10,6	6,6–16,0
						w 16,8			w 15,4	10,6–21,5
Green (16)	< 20	1960–89	182	17,1	28	12,7		26,3	m 9,4	4,1–18,5
									w 10,2	5,6–17,1
Metayer (17)	< 21	1935–94	5 925	10,5	195*	6,5	11,7		7,7	6,6–8,8
Bhatia (18)	< 16	1955–86	1 380	17	212*	10,6		26,3	18,5	15,6–21,7
Constine (19)	< 19	1960–90	930	16,8	102*		19,0		14,2	11,6–17,3
O'Brien (20)	„Kinder"	1970–90	110	20,6	18*	17,0		29,4	22,9	14,2–35
DAL/GPOH	< 18	1978–2002	2 548	14,3	138*	7,0	11,2	18,7	9,1	4,8–10,8

Kumulative Inzidenzen und standardisiertes Inzidenzverhältnis von sekundären malignen Neoplasien nach Behandlung eines Hodgkin-Lymphoms in der Kindheit und Jugend in einigen europäischen und nordamerikanischen Studien.
DAL/GPOH: Die 7 DAL-/GPOH-Studien, die in dieser Publikation analysiert werden.
HL, Hodgkin-Lymphom; m, männlich; n, Anzahl; SIR, standardisiertes Inzidenzverhältnis; SMN, sekundäre maligne Neoplasien; w, weiblich; 95-%-KI, 95-%-Konfidenzintervall; Pat., Patienten; J., Jahre; DAL, Deutsche Arbeitsgemeinschaft für Leukämie-Forschung und -Behandlung im Kindesalter; GPOH, Gesellschaft für Pädiatrische Onkologie und Hämatologie; HD, Hodgkin´s disease
*ohne Basaliome



Kumulative Inzidenzen sekundärer maligner Neoplasien (SMN ohne Basaliome) in den Studien DAL-HD-78 bis GPOH-HD-Intervall. Prozentangaben und 95-%-Konfidenzintervalle für Patienten mit einem Follow-up bis zu 30 Jahren (Stichtag 30. September 2013). Subgruppen: SST (sekundäre solide Tumoren), Leuk. (Leukämien) und NHL (Non-Hodgkin-Lymphome), BK (Brustkrebs) und SK (Schilddrüsenkarzinome). n, Anzahl; 1st SMN, primär aufgetretene sekundäre maligne Neoplasien, also SMN im engeren Sinn; Pat., Patienten; DAL, Deutsche Arbeitsgemeinschaft für Leukämie-Forschung und -Behandlung im Kindesalter; GPOH, Gesellschaft für Pädiatrische Onkologie und Hämatologie; HD, Hodgkin´s disease

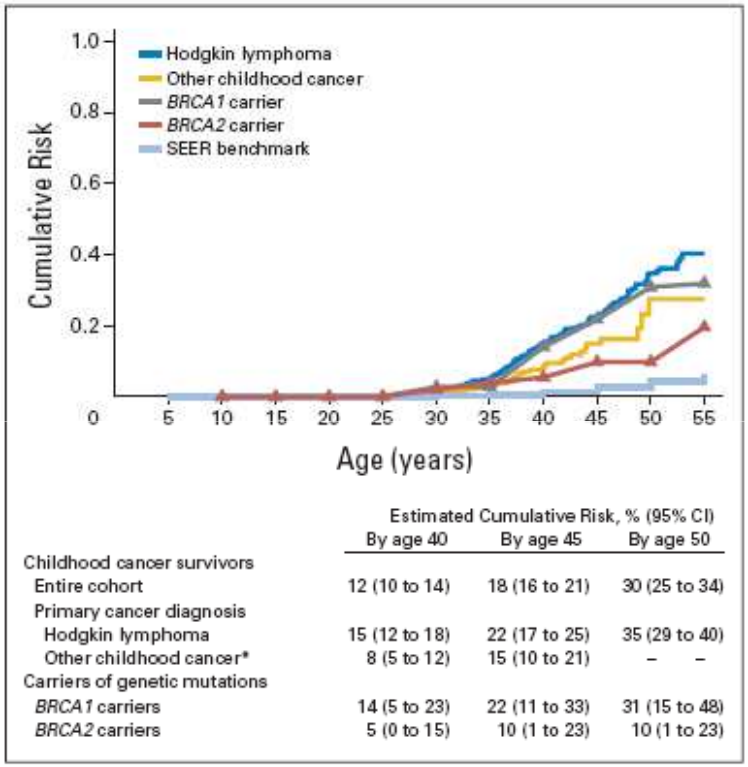


Schellong, Dt. Ä-Blatt, 2015

Hodgkin III: Pediatric HD

Moskowitz, JCO, 2014

Suggestive of Dose and Volume linearity at >10 Gy



	Estimated Cumulative Risk, % (95% CI)		
	By age 40	By age 45	By age 50
Childhood cancer survivors			
Entire cohort	12 (10 to 14)	18 (16 to 21)	30 (25 to 34)
Primary cancer diagnosis			
Hodgkin lymphoma	15 (12 to 18)	22 (17 to 25)	35 (29 to 40)
Other childhood cancer*	8 (5 to 12)	15 (10 to 21)	– –
Carriers of genetic mutations			
BRCA1 carriers	14 (5 to 23)	22 (11 to 33)	31 (15 to 48)
BRCA2 carriers	5 (0 to 15)	10 (1 to 23)	10 (1 to 23)

Fig 2. Cumulative risk of breast cancer. Breast cancer risk among women treated for childhood cancer with chest irradiation contrasted with breast cancer risk in female carriers of *BRCA1* or *BRCA2* deleterious mutations and women in general US population, with a birth-year distribution reflective of CCSS (Childhood Cancer Survivor Study) participants. (*) Insufficient follow-up in this group to provide reliable estimates of cumulative risk of breast cancer by age 50 years.

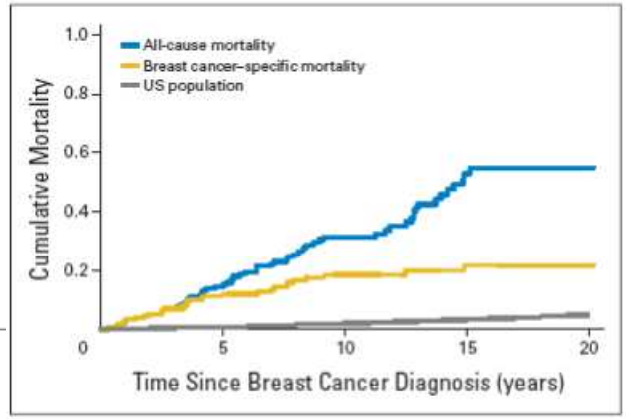


Fig 3. Death after breast cancer among childhood cancer survivors treated with chest irradiation. All-cause and breast cancer–specific mortality after breast cancer after chest radiotherapy for childhood cancer compared with expected mortality, age and year standardized to US population.

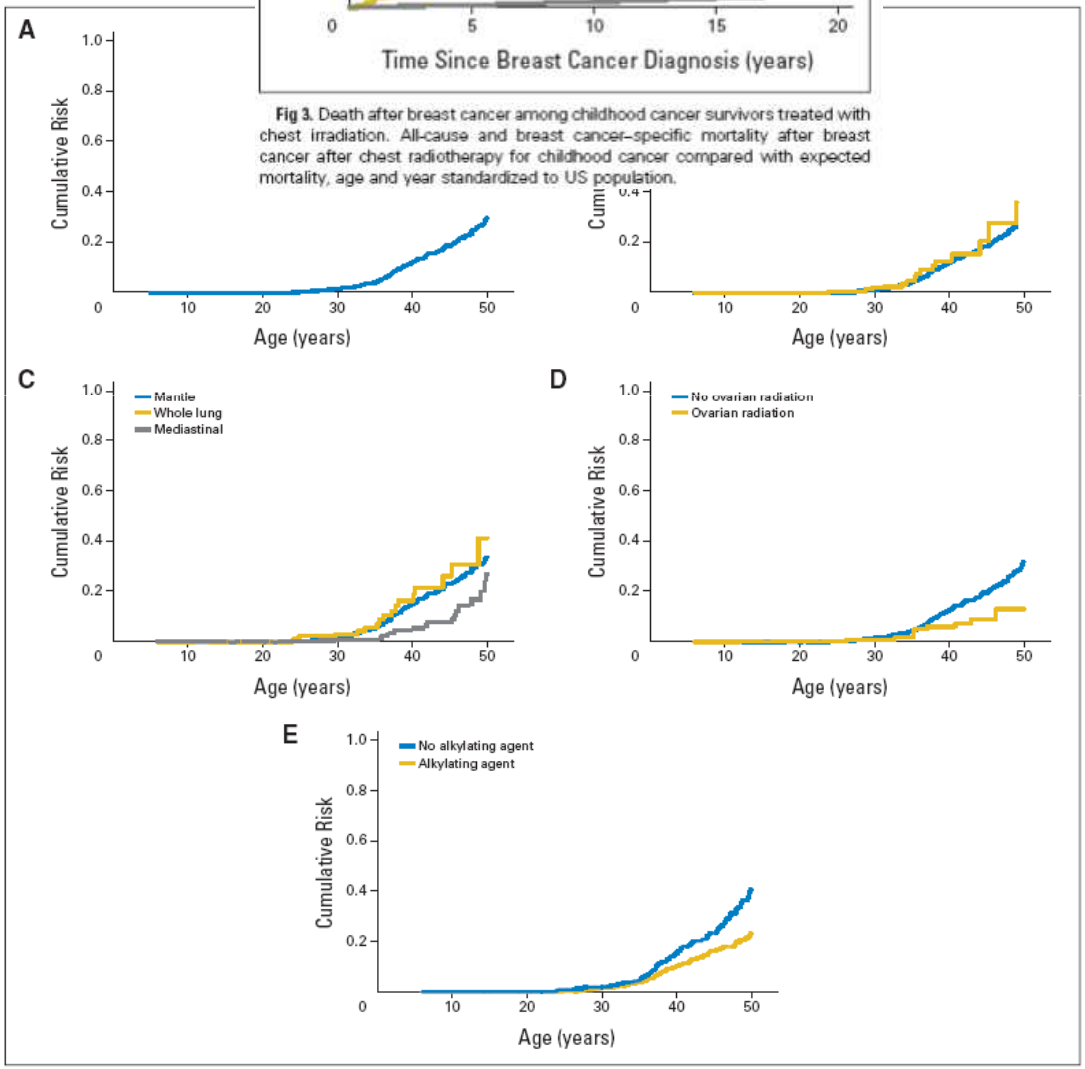


Fig 1. Cumulative risk of breast cancer among women treated for childhood cancer with chest irradiation (A) overall and by childhood cancer therapy: (B) chest radiation dose; (C) chest irradiation field; (D) ovaries in concurrent irradiation field; (E) alkylating agents.

Breast I

Localization???

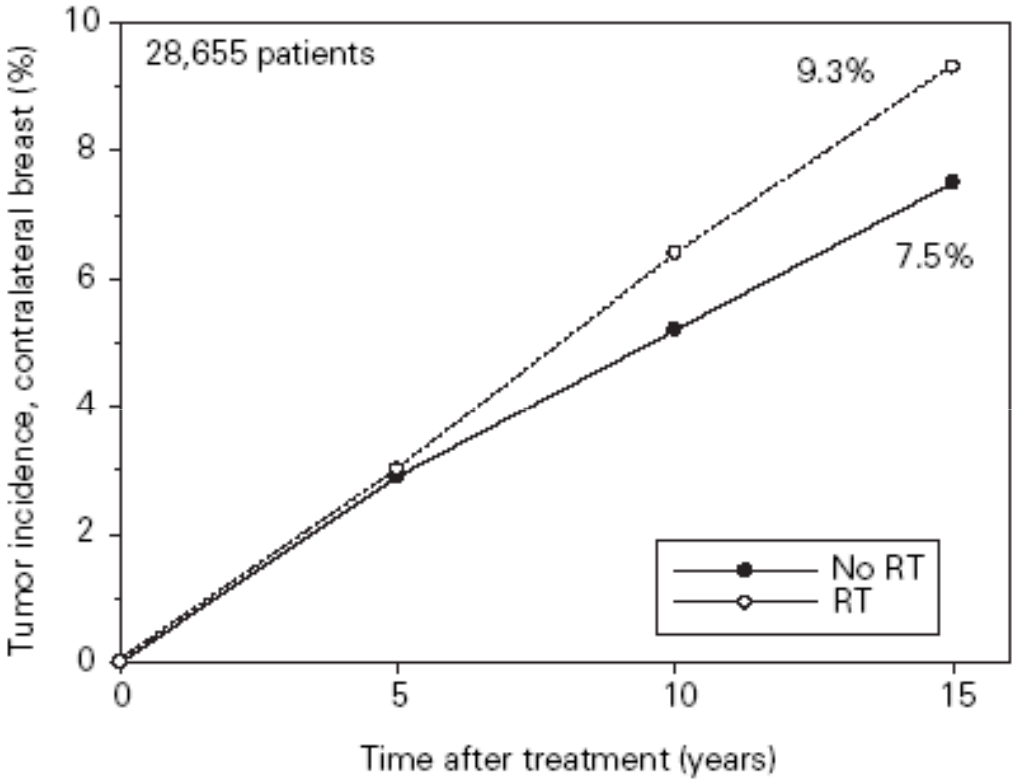


Figure 1. Incidence of contralateral breast cancer. The figure displays the time-to-event for the incidence of tumors in the contralateral breast in patients with breast cancer treated either with surgery alone or with additional irradiation (data from [5], webfigure 7; http://www.ctsu.ox.ac.uk/projects/ebctcg, August 22, 2007).

Doerr, Hermann, SUON, 2008

Breast II – Italian Data (Allegro Project)

„Our initial patient number is very high, but the incidence of a second cancer is relatively low (0.02% of all patients and 0.019% of the patients treated with adjuvant irradiation)“

Minimum F/U: 5 years

Median F/U: not given, but probably around 10 Years

Breast Cancers in High Dose Areas (in-field) excluded

Orecchia et al., Tumori, 2012

Breast III

Breast Cancer Survivors

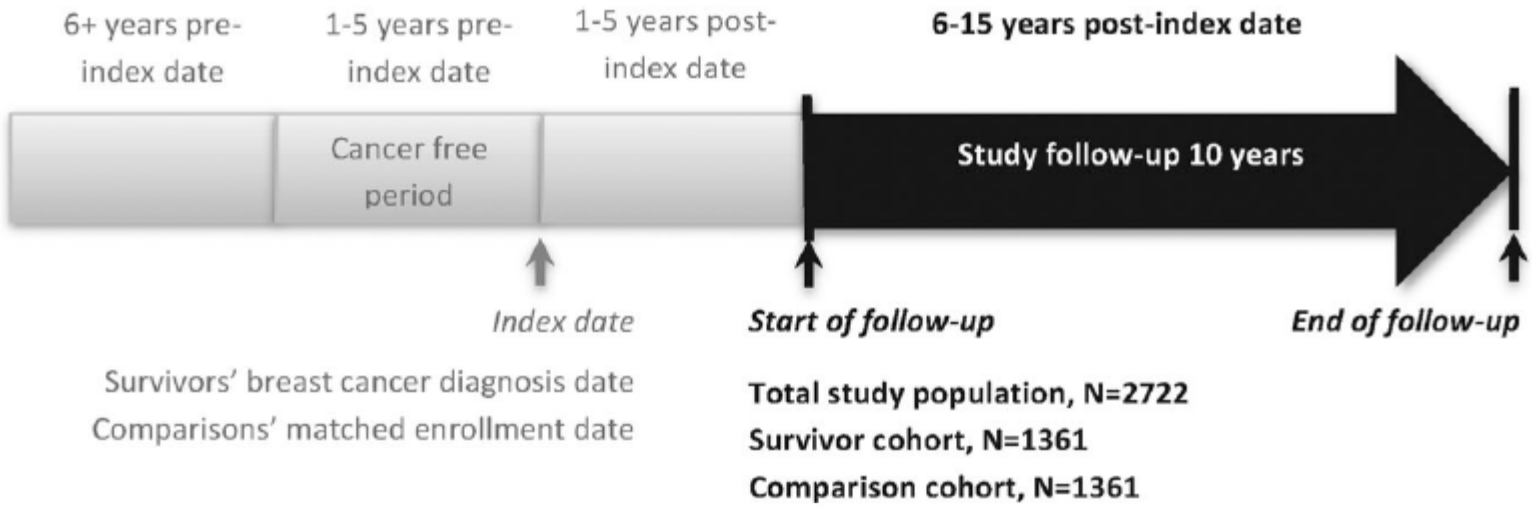


Figure 1. The study timeline is illustrated.

TABLE 3. The Risk of Incident Malignant Cancer in the Survivor Cohort Compared With the Comparison Cohort Adjusted for the Competing Risk of Death Over 10 Years of Follow-Up (6 to 15 Years After the Index Date), N = 2722[a]

	HR_{crude} (95% CI)	$HR_{adjusted}$ (95% CI)[b]
First incident all-cause malignancy	1.16 (0.93-1.46)	1.17 (0.94-1.47)
Type of first incident malignancy		
Breast	1.26 (0.81-1.95)	1.28 (0.83-1.99)
Colorectal	0.66 (0.37-1.19)	0.66 (0.37-1.20)
Gynecologic	2.53 (0.89-7.18)	2.72 (0.96-7.74)
Lymphoma/leukemia	1.33 (0.62-2.84)	1.28 (0.59-2.75)
Lung	1.21 (0.68-2.18)	1.25 (0.69-2.25)
Melanoma	1.01 (0.36-3.32)	0.93 (0.29-2.94)
Other	1.20 (0.77-1.87)	1.19 (0.77-1.86)

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] The index date was either the date of the survivor's diagnosis or the date of the matched comparison woman's enrollment.
[b] Adjusted models included site, age, race, comorbidity, and history of cancer.

The adjusted hazard of developing a first incident malignancy was slightly elevated in survivors in relation to women in the comparison group, but it was not statistically significant (hazard ratio, 1.17; 95% confidence interval, 0.94-1.47)

McClough-Gorr et al., Cancer, 2013

Breast III – DBCG Data (Allegro-Project)

Radiotherapy-associated sites:
HR 1.34 (95% CI 1.11–1.61)
10–14 years after RT: HR 1.55 (95% CI 1.08–2.24)
>15 years after: HR 1.79 (95% CI 1.14–2.81).

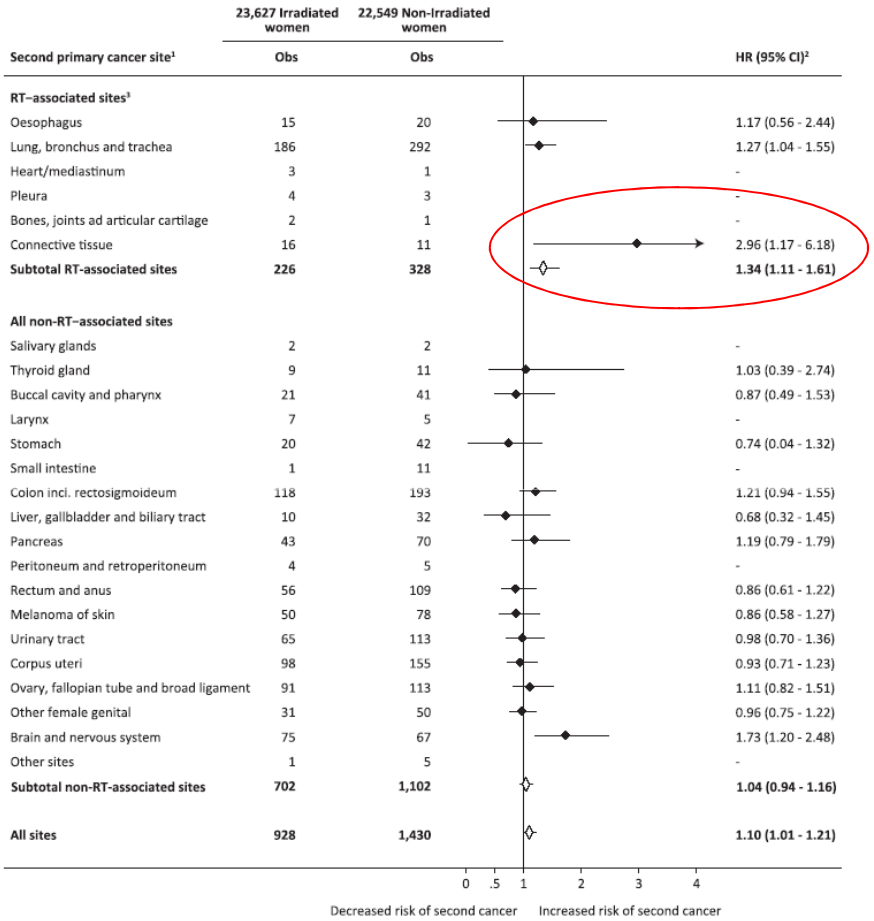
Non-radiotherapy-associated sites:
HR 1.04 (95% CI 0.94–1.1).

The estimated attributable risk related to radiotherapy for the radiotherapy-associated sites translates into one radiation-induced second cancer in every 200 women treated with radiotherapy.

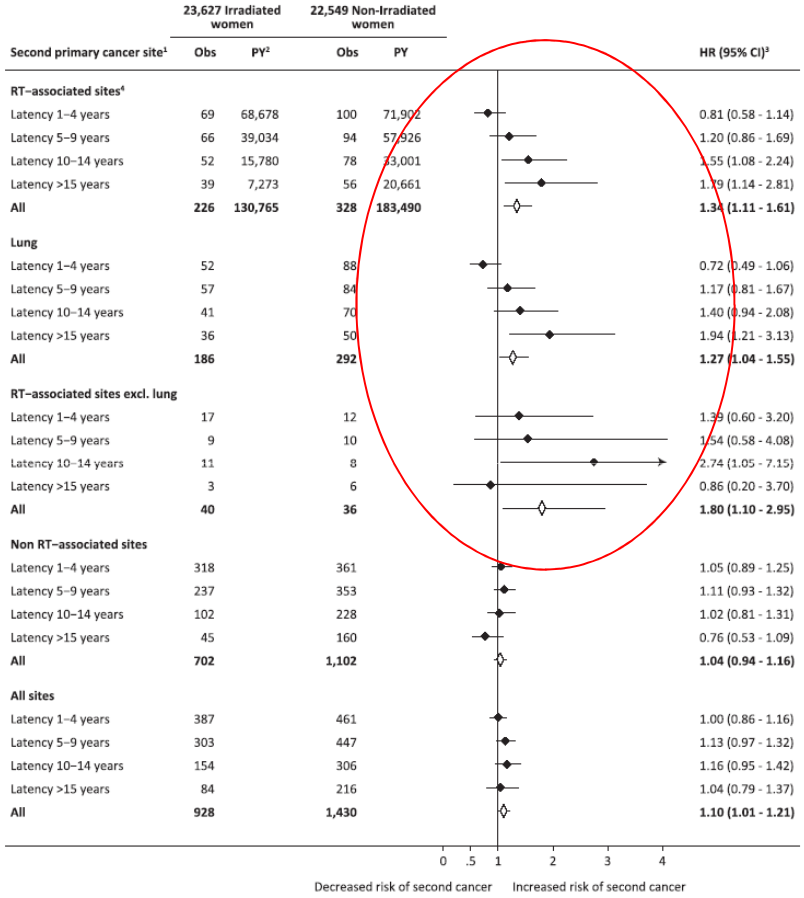
The observed temporal-pattern for the RT-associated sites is consistent with the suggestion that radiation induced solid tumors have a minimum latency of 5–9 years

Granzau et al., R&O, 2013

Breast III – DBCG Data (Allegro-Project)



Second primary cancer site[1]	23,627 Irradiated women Obs	22,549 Non-Irradiated women Obs	HR (95% CI)[2]
RT–associated sites[3]			
Oesophagus	15	20	1.17 (0.56 - 2.44)
Lung, bronchus and trachea	186	292	1.27 (1.04 - 1.55)
Heart/mediastinum	3	1	-
Pleura	4	3	-
Bones, joints ad articular cartilage	2	1	-
Connective tissue	16	11	2.96 (1.17 - 6.18)
Subtotal RT-associated sites	**226**	**328**	**1.34 (1.11 - 1.61)**
All non-RT–associated sites			
Salivary glands	2	2	-
Thyroid gland	9	11	1.03 (0.39 - 2.74)
Buccal cavity and pharynx	21	41	0.87 (0.49 - 1.53)
Larynx	7	5	-
Stomach	20	42	0.74 (0.04 - 1.32)
Small intestine	1	11	-
Colon incl. rectosigmoideum	118	193	1.21 (0.94 - 1.55)
Liver, gallbladder and biliary tract	10	32	0.68 (0.32 - 1.45)
Pancreas	43	70	1.19 (0.79 - 1.79)
Peritoneum and retroperitoneum	4	5	-
Rectum and anus	56	109	0.86 (0.61 - 1.22)
Melanoma of skin	50	78	0.86 (0.58 - 1.27)
Urinary tract	65	113	0.98 (0.70 - 1.36)
Corpus uteri	98	155	0.93 (0.71 - 1.23)
Ovary, fallopian tube and broad ligament	91	113	1.11 (0.82 - 1.51)
Other female genital	31	50	0.96 (0.75 - 1.22)
Brain and nervous system	75	67	1.73 (1.20 - 2.48)
Other sites	1	5	-
Subtotal non-RT-associated sites	**702**	**1,102**	**1.04 (0.94 - 1.16)**
All sites	**928**	**1,430**	**1.10 (1.01 - 1.21)**



Second primary cancer site[1]	23,627 Irradiated women Obs	PY[2]	22,549 Non-Irradiated women Obs	PY	HR (95% CI)[3]
RT–associated sites[4]					
Latency 1–4 years	69	68,678	100	71,902	0.81 (0.58 - 1.14)
Latency 5–9 years	66	39,034	94	57,926	1.20 (0.86 - 1.69)
Latency 10–14 years	52	15,780	78	33,001	1.55 (1.08 - 2.24)
Latency >15 years	39	7,273	56	20,661	1.79 (1.14 - 2.81)
All	**226**	**130,765**	**328**	**183,490**	**1.34 (1.11 - 1.61)**
Lung					
Latency 1–4 years	52		88		0.72 (0.49 - 1.06)
Latency 5–9 years	57		84		1.17 (0.81 - 1.67)
Latency 10–14 years	41		70		1.40 (0.94 - 2.08)
Latency >15 years	36		50		1.94 (1.21 - 3.13)
All	**186**		**292**		**1.27 (1.04 - 1.55)**
RT–associated sites excl. lung					
Latency 1–4 years	17		12		1.39 (0.60 - 3.20)
Latency 5–9 years	9		10		1.54 (0.58 - 4.08)
Latency 10–14 years	11		8		2.74 (1.05 - 7.15)
Latency >15 years	3		6		0.86 (0.20 - 3.70)
All	**40**		**36**		**1.80 (1.10 - 2.95)**
Non RT–associated sites					
Latency 1–4 years	318		361		1.05 (0.89 - 1.25)
Latency 5–9 years	237		353		1.11 (0.93 - 1.32)
Latency 10–14 years	102		228		1.02 (0.81 - 1.31)
Latency >15 years	45		160		0.76 (0.53 - 1.09)
All	**702**		**1,102**		**1.04 (0.94 - 1.16)**
All sites					
Latency 1–4 years	387		461		1.00 (0.86 - 1.16)
Latency 5–9 years	303		447		1.13 (0.97 - 1.32)
Latency 10–14 years	154		306		1.16 (0.95 - 1.42)
Latency >15 years	84		216		1.04 (0.79 - 1.37)
All	**928**		**1,430**		**1.10 (1.01 - 1.21)**

Soft Tissue Sarcoma of thorax and upper arm……

-> High Dose areas……

Granzau et al., R&O, 2013

And most recently……

ELIOT (Veronesi, Lancet Oncol, 2013)
No significant difference in secondary cancers
at median F/U of **5 years**

Uppsala Örebrö (Wickberg, JCO, 2014)
5% (contral. Breast cancer) and 2% (any cancer)
absolute difference after **20 Years**

Prime II (Kunkler et al., SA-Breast Cancer 2013)
No signisficant) difference in secondary cancers
at median F/U of **5 years** (>65Y)

This just in…

Berrington et al
IJROBP, 2013

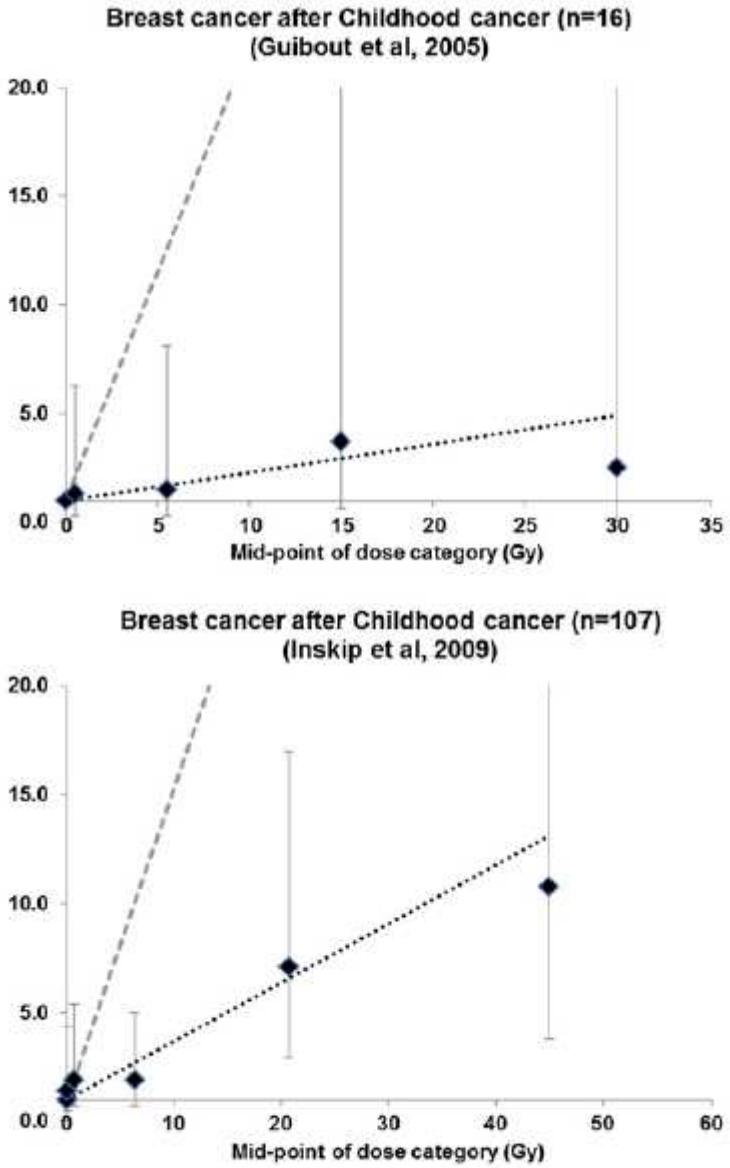
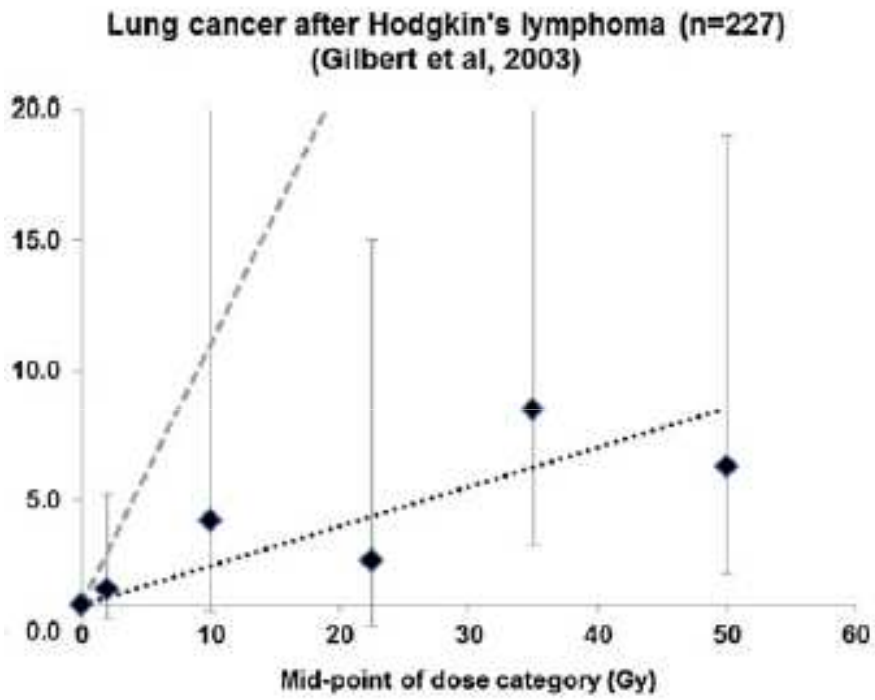


Fig. 1. Relative risk and 95% confidence interval for subsequent breast cancer according to the estimated absorbed radiation dose (Gy). Dotted black line indicates fitted linear dose-response

This just in…….

Overall, there was little evidence that the dose-response curve was nonlinear in the direction of a downturn in risk, even at organ doses of >60 Gy. Thyroid cancer was the only exception, with evidence of a downturn after 20 Gy. **Generally the excess relative risk per Gray, taking account of age and sex, was 5 to 10 times lower than the risk from acute exposures of <2 Gy among the Japanese atomic bomb survivors**.



Berrington et al., IJROBP, 2013

And linear again…and again….

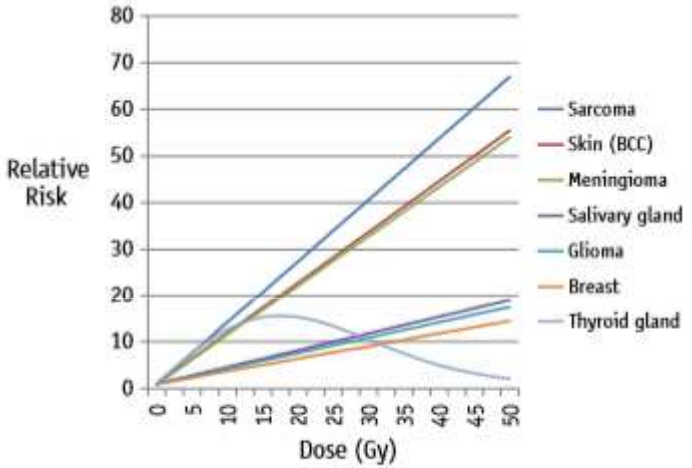


Fig. 1. Fitted radiation dose-response by type of second cancer, based on previously published studies of second sarcoma (16), skin (18), meningioma (10) salivary gland (17), glioma (10), breast (11) and thyroid gland (14). The order of second cancers from top to bottom in the graph is the same as in the key to the right of the panel.

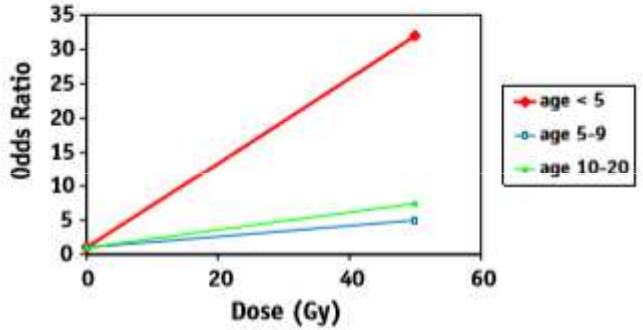


Fig. 2. Risk of glioma after radiation therapy for first cancer, by age at first cancer. Data from Neglia et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2006;98:1528-1537.

Inskip et al., IJROBP, 2016

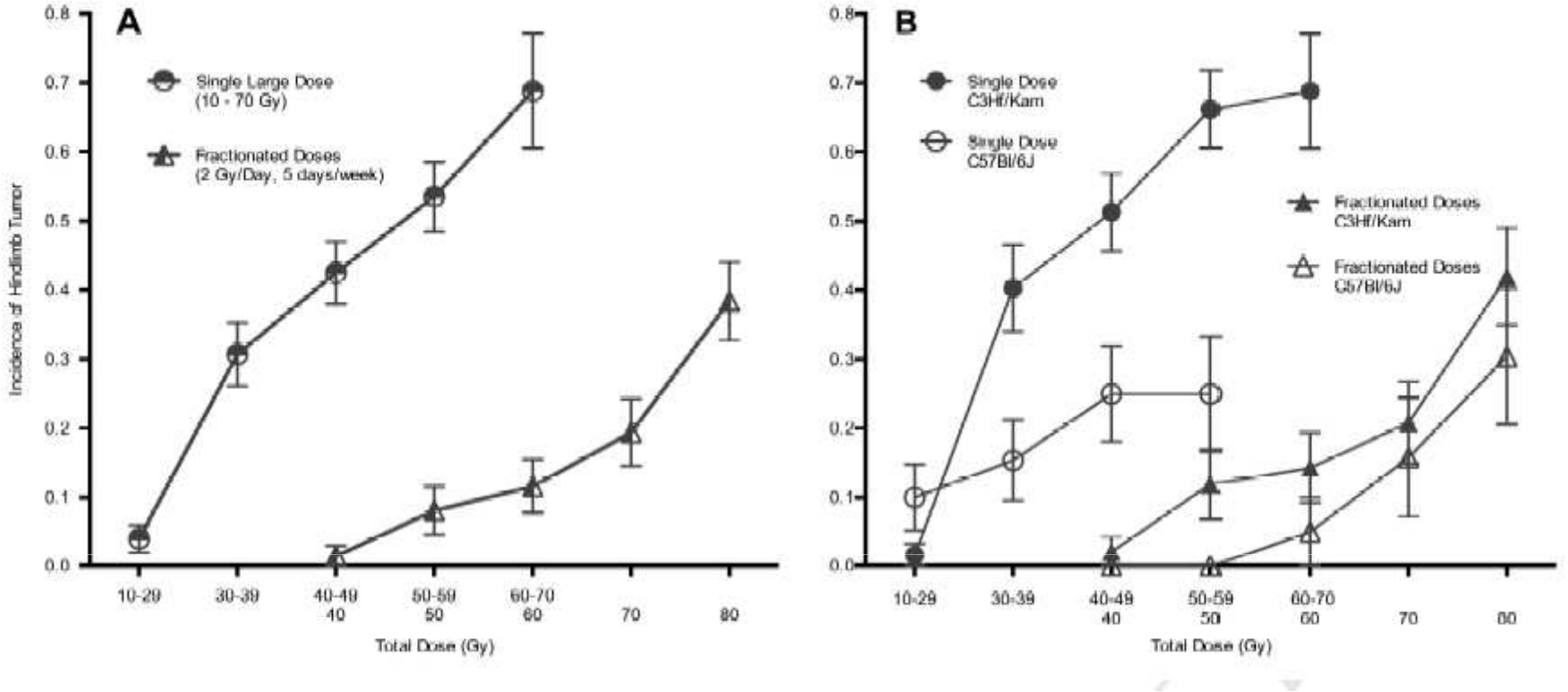


Figure 2. Incidence of hindlimb tumors by radiation dose. (A) Incidences of hindlimb tumors are significantly increased in mice exposed to a single large dose of radiation in comparison to mice exposed to fractionated radiation ($p < 0.001$). (B) Incidences of hindlimb tumors by radiation dose and mouse strain. C3Hf/Kam mice have a significantly higher incidence of hindlimb tumors following single dose exposures than C57BL/6J mice ($p < 0.001$). No significant difference in tumor incidence is observed between C3Hf/Kam and C57BL/6J mice following fractionated exposures. Single doses are grouped as 10-29, 30-39, 40-49, and 50-59 Gy. Fractionated doses were given as 2 Gy/day, 5 days/week for 4 to 8 weeks and are listed as total doses of 40, 50, 60 , 70, and 80 Gy

Edmondson et al., IJROBP, 2015

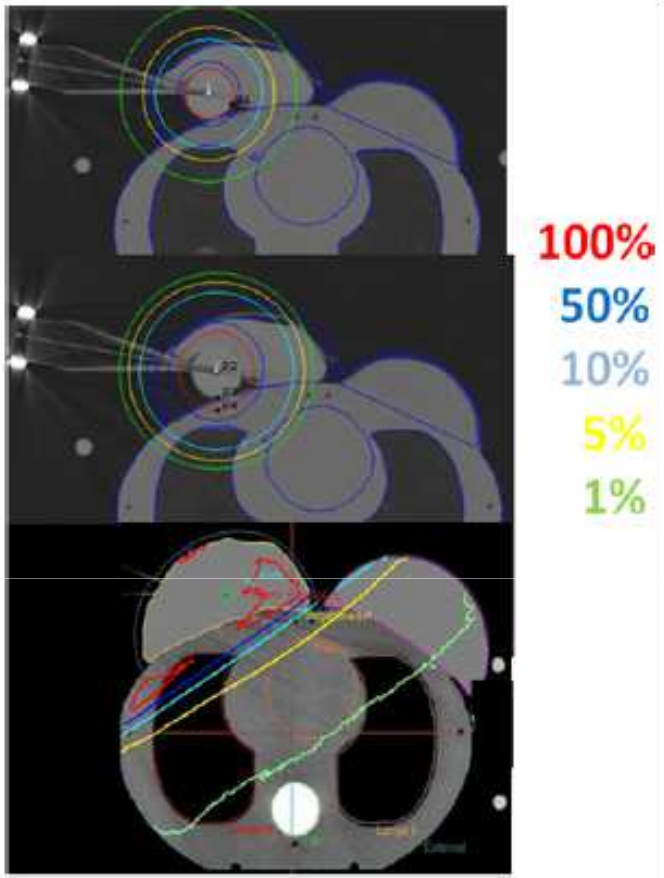


Figure 1 Planning CT of an anthropomorphic phantom with an Intrabeam applicator in the upper outer quadrant of the right breast showing calculated isodoses (1%-100%). (a) IORT (20 Gy at 0 mm, 50 kV). (b) APBI (34 Gy at 10 mm, 50 kV). (c) EBRT (50 Gy, 6 MV).

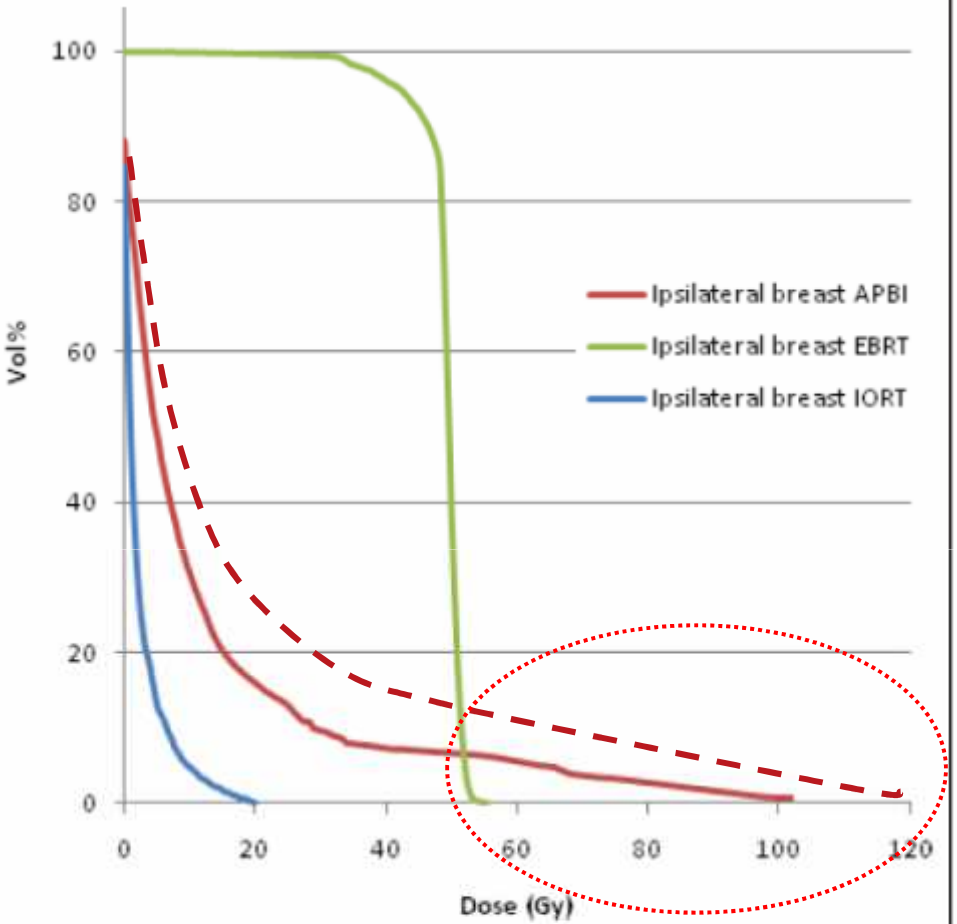


Figure 2 Cumulative DVH for ipsilateral breast for IORT, APBI and EBRT.

Aziz et al., Radiation Oncol, 2011

KV Radiation

[CANCER RESEARCH 49, 229–234, January 1, 1989]

Breast Cancer after Multiple Chest Fluoroscopies: Second Follow-up of Massachusetts Women with Tuberculosis

Zdenek Hrubec,[1] John D. Boice, Jr., Richard R. Monson, and Marvin Rosenstein

Table 1 *Number of women with tuberculosis by follow-up status as of December 31, 1980, and exposure group*

Follow-up status	Exposed (%)	Nonexposed (%)	Total (%)
Alive	653 (62.6)	462 (66.2)	1115 (64.0)
Dead	367 (35.2)	215 (30.8)	582 (33.4)
Lost	24 (2.3)	21 (3.0)	45 (2.6)
Total	1044 (100)	698 (100)	1742 (100)

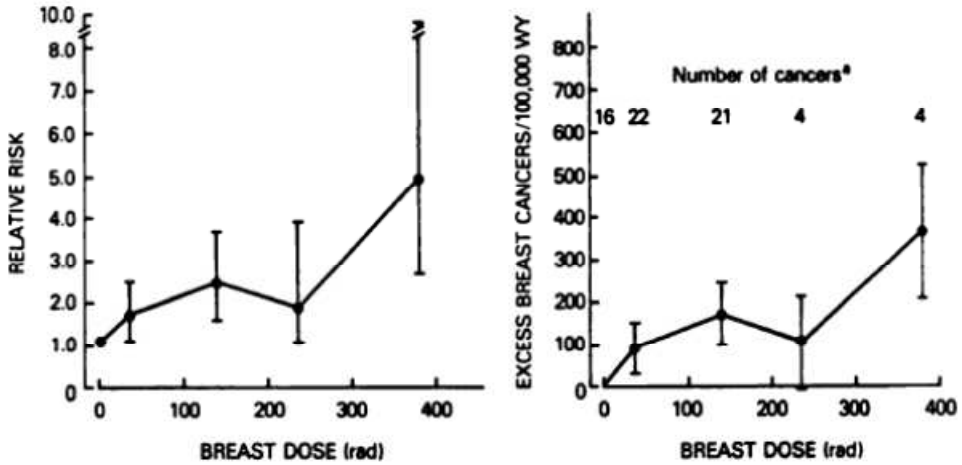


Fig. 1. Relative risk and excess risk of breast cancer and 80% confidence limits among 10-year survivors by absorbed dose to the breast. Nonexposed women as comparison group. [a] See Table 5, footnote *a*.

Randomized Data: PORTEC etc.

Wiltink et al., JCO, 2015

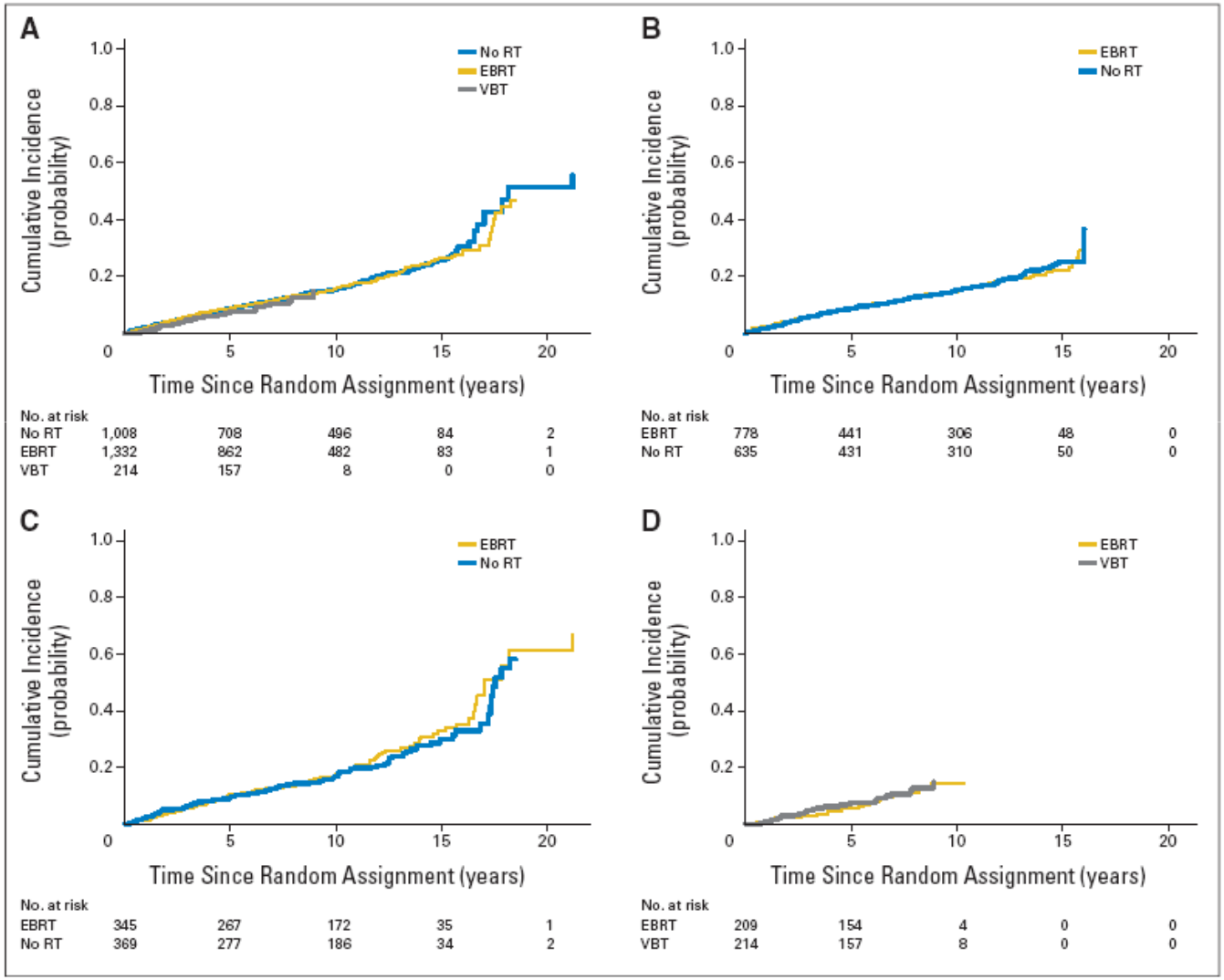


Fig 2. Cumulative probability of developing second cancer in (A) all, (B) TME (Total Mesorectal Excision), (C) PORTEC-1 (Post Operative Radiation Therapy in Endometrial Carcinoma 1), and (D) PORTEC-2 trials. NOTE. Because only four patients were included in no-RT group in the PORTEC-2 trial, these patients are not represented in panel D. EBRT, external-beam radiotherapy; RT, radiotherapy; VBT, vaginal brachytherapy.

“The most important prerequisite for the development of a second neoplasm is cure of the primary malignancy”

Doerr, Hermann, SUON, 2008

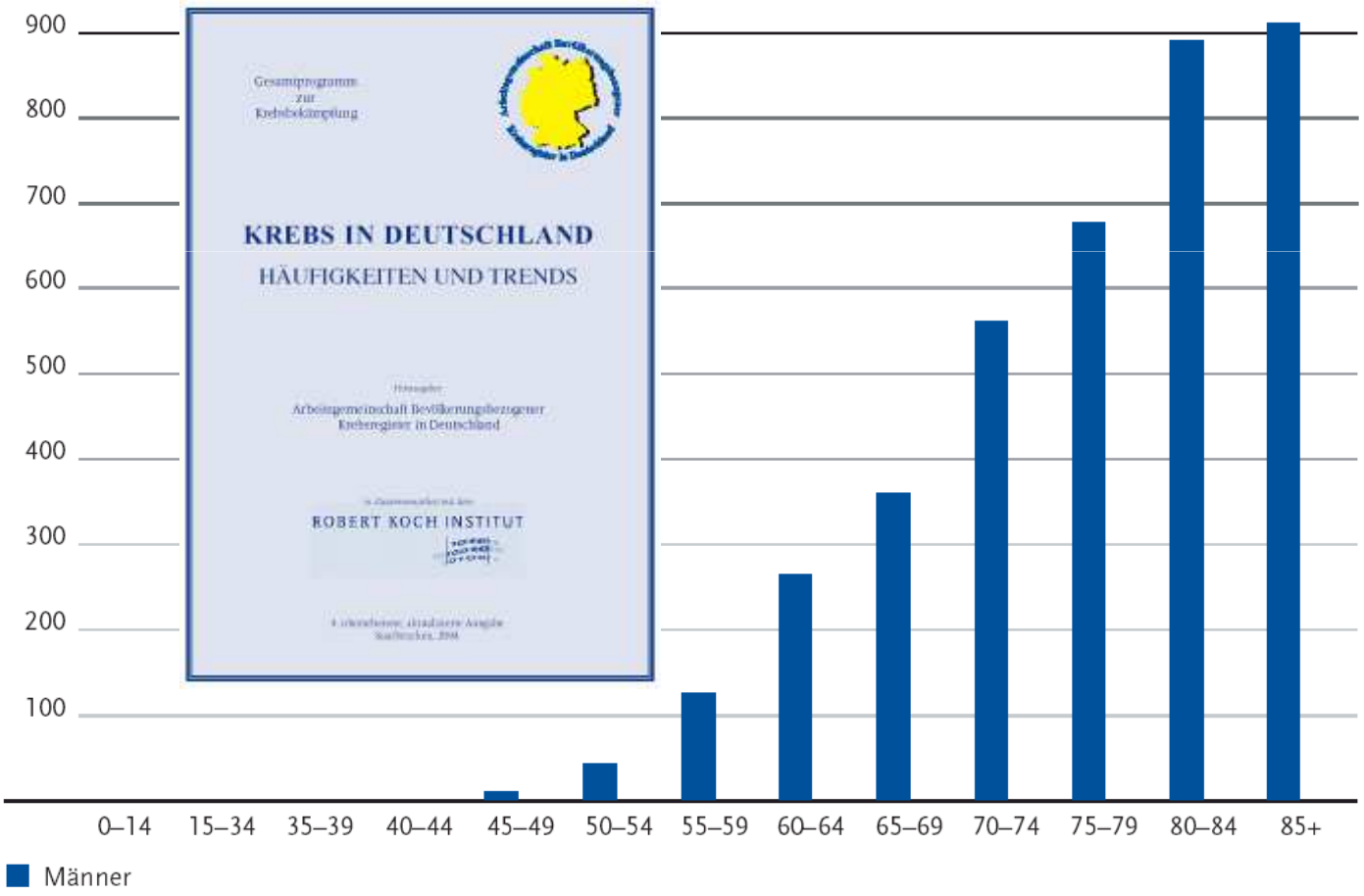
-> Death as confounding factor has to be compensated for in estimates

Secondary Carcinoma

is not a relevant problem for old patients

Prostata **ICD-10 C61**

Schätzung der altersspezifischen Inzidenz in Deutschland 2000
Erkrankungen pro 100.000 in Altersgruppen



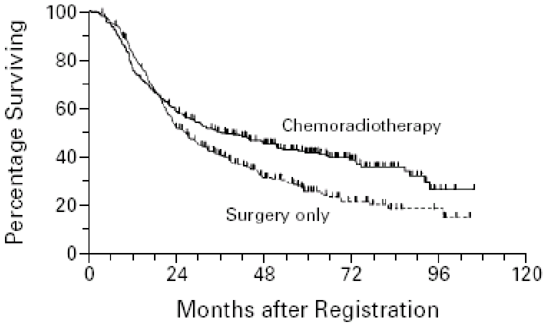


Figure 1. Overall Survival among All Eligible Patients, According to Treatment-Group Assignment.

The median duration of survival was 27 months in the surgery-only group and 36 months in the chemoradiotherapy group. The difference in overall survival was significant (P=0.005 by a two-sided log-rank test). A total of 169 of the 281 patients in the chemoradiotherapy group and 197 of the 275 patients in the surgery-only group died during the follow-up period.

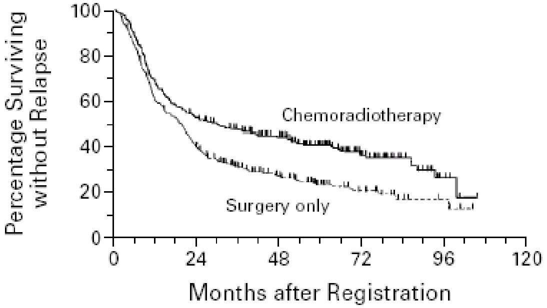


Figure 2. Relapse-free Survival among All Eligible Patients, According to Treatment-Group Assignments.

The median duration of relapse-free survival was 19 months in the surgery-only group and 30 months in the chemoradiotherapy group. This difference in relapse-free survival was significant (P<0.001 by a two-sided log-rank test). A total of 174 of the 281 patients in the chemoradiotherapy group and 206 of the 275 patients in the surgery-only group died or had a relapse during the follow-up period.

CHEMORADIOTHERAPY AFTER SURGERY COMPARED WITH SURGERY ALONE FOR ADENOCARCINOMA OF THE STOMACH OR GASTROESOPHAGEAL JUNCTION

N Engl J Med, Vol. 345, No. 10 · September 6, 2001

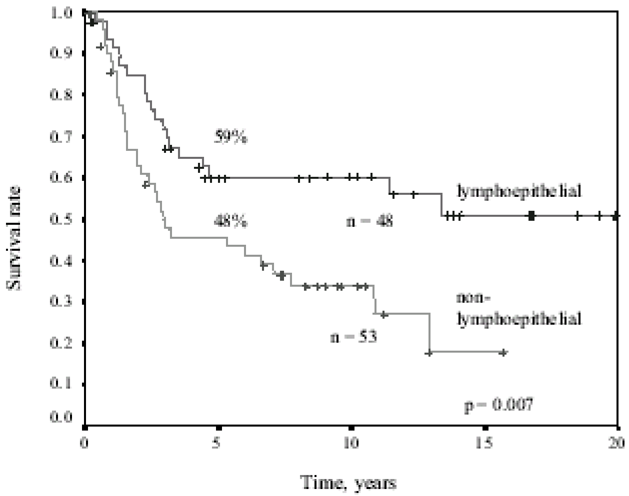


Fig. 1. Overall survival and histology: Upper curve represents 48 patients with lymphoepithelial cancer, lower curve represents 53 patients with other histology (p = 0.007).

Patterns of Failure Following Radiation with and without Chemotherapy in Patients

Onkologie 2003;26:12–18

S. Fuchs, C. Rödel, T. Brunner, H. Iro, G. Niedobitek, R. Sauer, G.G. Grabenbauer

World J. Surg. 27, 849–855, 2003
DOI: 10.1007/s00268-003-7111-8

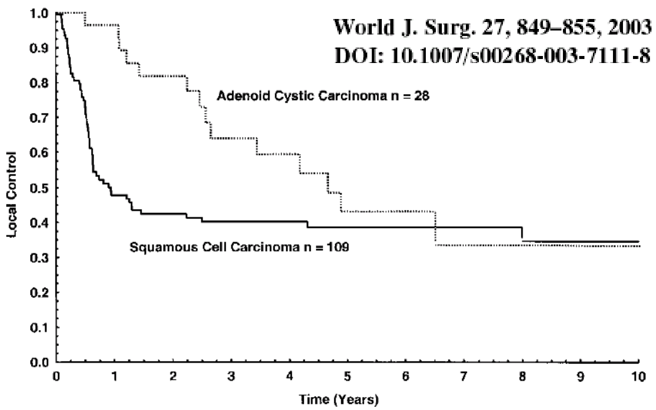


Fig. 2. Actuarial local control of paranasal sinus cancer according to histopathology: adenoid cystic carcinoma, $n = 28$; squamous cell carcinoma, $n = 109$. Data from Waldron et al. [4].

Paranasal Sinus Cancer: Caveats and Controversies

John Waldron, M.D., M.Sc.,[1] Ian Witterick, M.D.[2]

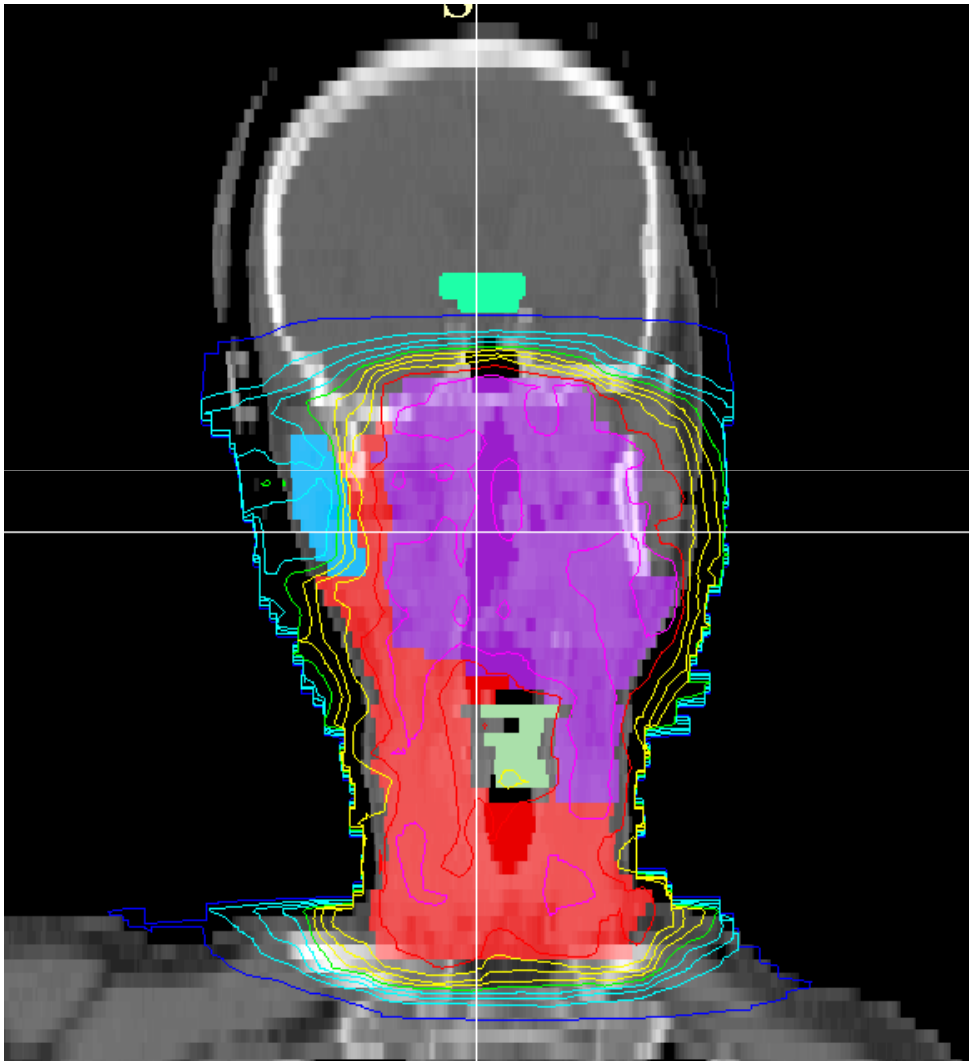
Published Online: May 14, 2003

Secondary Carcinoma

is not a relevant problem when patients with a bad prognosis (such as it is the case with advanced gastric cancer) are treated. Achieving cure is the problem for these patients.

Secondary Tumors: H&N

Risk is not different from 3D if the whole diameter is irradiated



Head and Neck:
Irradiation of (more or less) the whole neck circumference with therapeutic doses (volume very similar to conventional 3D [paradigms changing slowly])
->similar risk for secondary tumors for IMRT and 3D in the Neck area, probably slightly elevated risk outside neck due to elevated MU, increased scatter. High risk for secondary, non RT-induced cancer, though (Lung!!)

Specific Problems with IMRT

Secondary Tumors

Risk assessment of radiation-induced malignancies based on whole-body equivalent dose estimates for IMRT treatment in the head and neck region

Dirk Verellen[a,*], Filip Vanhavere[b]

Radiotherapy and Oncology 53 (1999) 199–203

RADIATION-INDUCED SECOND CANCERS: THE IMPACT OF 3D-CRT AND IMRT

ERIC J. HALL, D.SC.* AND CHENG-SHIE WUU, PH.D.†

Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 1, pp. 83–88, 2003

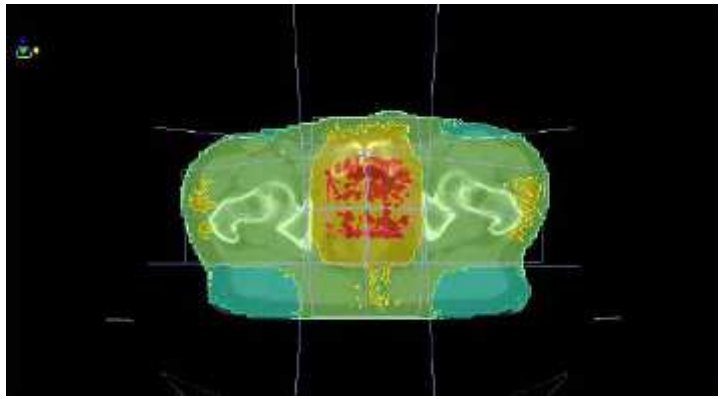
Reasons for a potentially increased incidence of secondary tumors by IMRT

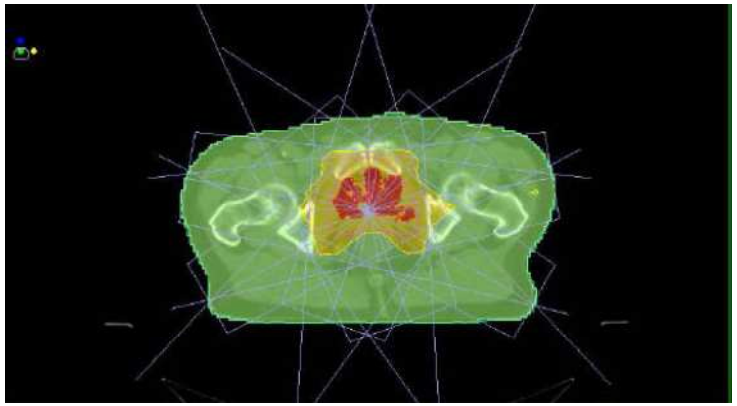
1. Increased biological effectiveness of an elevated total body neutron dose

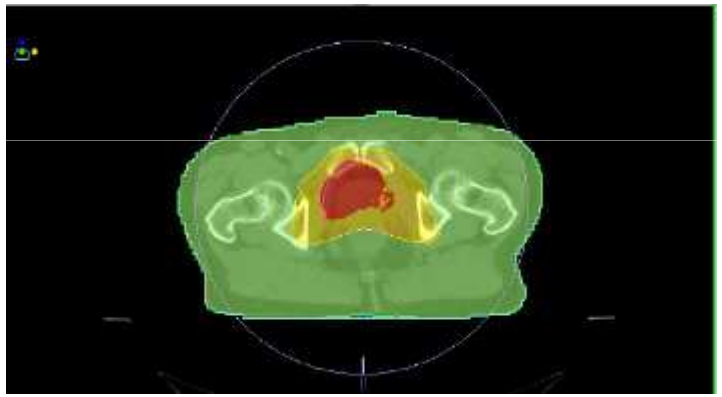
2. When compared to 3D-Conformal RT, IMRT irradiates a more tissue at lower doses

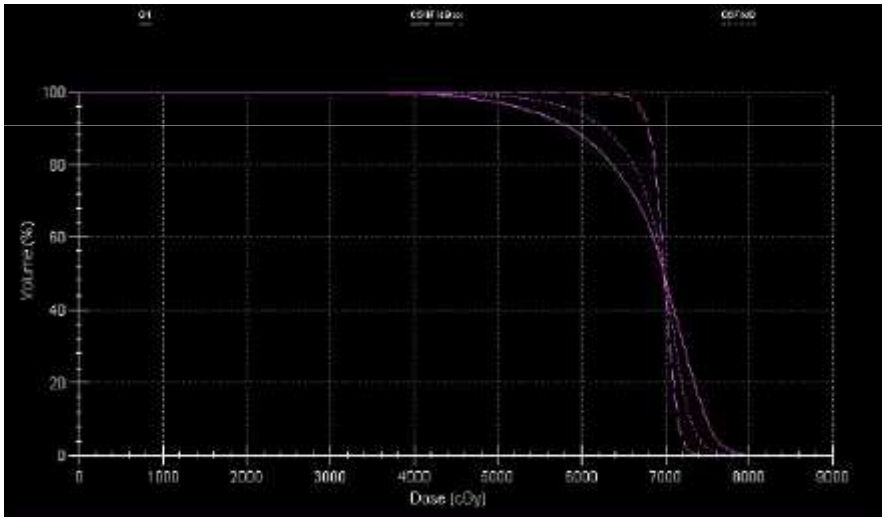
3. Increased scatter dose when dose-escalation is performed

4. Increased leakage radiation because of low MU-efficiency of IMRT









1 Gy (blue), 5 Gy (green), 45 Gy (yellow) and 70 Gy (red)

Prostate IMRT

"The risk of RISPC appears small, in the range of 1 in 220 to 1 in 290 over all durations of follow-up, based on older radiation techniques. Importantly, the risk appears to increase with time, and beyond 5 years, SPCs in the region of the original field may be considered RISPCs. To date there are insufficient clinical data to draw firm conclusions about the impact of more modern RT techniques, although limited evidence is encouraging"

Murray et al. Radiother Oncol, 2014

Secondary Tumors

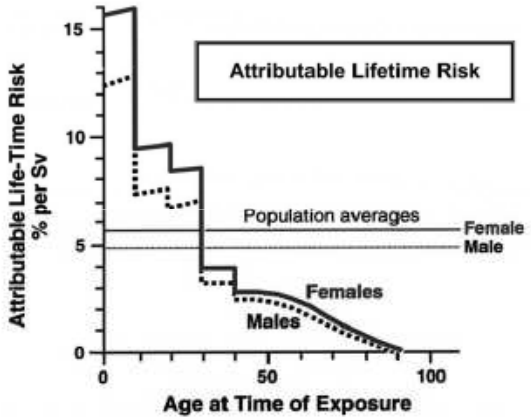


Fig. 6. The attributable lifetime risk from a single small dose of radiation at various ages at the time of exposure. Note the dramatic decrease in radiosensitivity with age. The higher risk for the younger age groups is not expressed until late in life. These estimates are based on a multiplicative model and on a dose and dose-rate effectiveness factor (DDREF) of 2. The figure was adapted from International Commission on Radiological Protection (ICRP) Publication 60 (14).

Same Leakage for Adult RT vs. Pediatric RT — But in Pediatric RT Scatter from the Treatment Volume Is More Significant

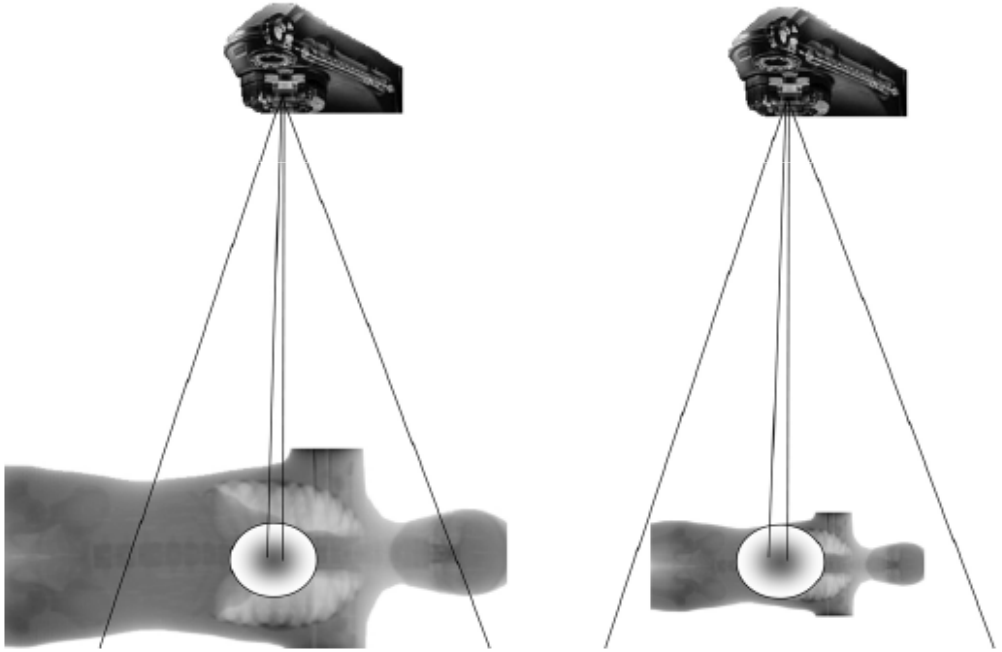


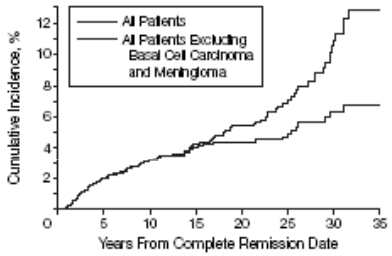
Fig. 7. When a primary tumor is treated with radiotherapy (RT) in a small child, nearby potentially radiogenic organs inevitably receive larger doses of radiation than when a comparable treatment is delivered to an adult, simply because of the closer proximity of organs in a child.

Pediatric Oncology is a problem…but not a disastrous one

The St. Jude Data….Conventional RT Techniques

Median is the line within each box; boxes indicates interquartile ranges and error bars indicate ranges.

Figure 2. Cumulative Incidence of Secondary Neoplasms Occurring in First Complete Remission



No. at Risk	2169	1265	1032	773	511	142
Incidence, % (SE)						
All Patients		1.95 (0.30)	3.14 (0.38)	4.17 (0.46)	5.37 (0.55)	10.85 (1.27)
All Patients Excluding Basal Cell Carcinoma and Meningioma		1.95 (0.30)	3.09 (0.38)	3.99 (0.44)	4.39 (0.48)	6.27 (0.83)

Hijiya, JAMA, 2007

Table 3. Incidence of Secondary Neoplasm in Patients in First Complete Remission Who Were Treated for Acute Lymphoblastic Leukemia in 1962-1998 vs US General Population

Cancer Type/Site	No. of Events		Standardized Incidence Ratio (95% Confidence Interval)*
	Observed	Expected	
All tumors†			
All patients	87	6.4	13.5 (10.9-16.8)
Cranial/craniospinal irradiation	69	5.1	13.6 (10.5-17.1)
No cranial/craniospinal irradiation	18	1.4	13.3 (7.9-21.0)
Myeloid			
All patients	41	0.3	150.9 (98.1-185.4)
Cranial/craniospinal irradiation	27	0.2	138.6 (88.9-196.4)
No cranial/craniospinal irradiation	14	0.1	182.2 (99.5-306.1)
Central nervous system			
All patients	22	0.7	31.8 (19.7-47.6)
Cranial/craniospinal irradiation	21	0.5	45.8 (26.0-64.2)
No cranial/craniospinal irradiation	1	0.2	4.3 (0.1-24.0)
Lymphoma			
All patients	3	1.0	3.0 (0.6-8.8)
Cranial/craniospinal irradiation	2	0.7	2.7 (0.3-9.7)
No cranial/craniospinal irradiation	1	0.3	4.0 (0.1-22.3)
Other solid tumors†			
All patients	21	4.5	4.7 (2.9-7.1)
Cranial/craniospinal irradiation	19	3.7	5.1 (3.1-8.0)
No cranial/craniospinal irradiation	2	0.8	2.5 (0.3-9.0)

*See "Methods" section of the text for details on the calculation of standardized incidence ratios.
†These types of secondary neoplasms in first complete remission were omitted because they are not included or were only recently included in the Surveillance, Epidemiology, and End Results database: myelodysplastic syndrome (n = 7), meningioma (n = 16), and basal cell/squamous cell carcinoma (n = 16). Three malignancies occurring after meningioma or myelodysplastic syndrome were included (2 myeloid leukemias after myelodysplastic syndrome and 1 thyroid carcinoma after meningioma). See text for details.

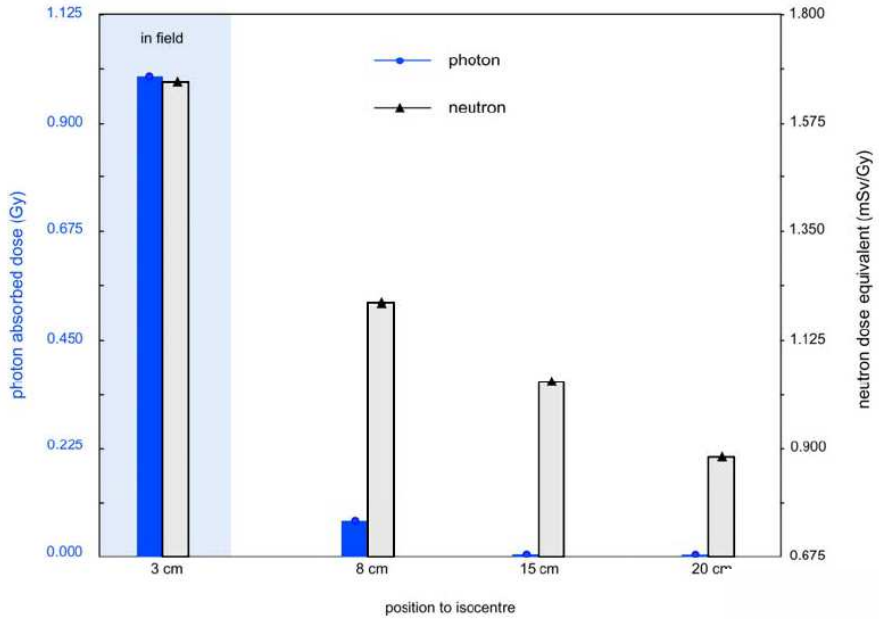


Figure 5. Siemens Mevatron. Integral photon absorbed dose (left-hand scal equivalent (right-hand scale) calculated with MCNP-GN at various positions isocentre.

Phys. Med. Biol. **45** (2000) L55–L61. Printed in the UK PII: S0031-9155(00)15010-9

RAPID COMMUNICATION

Analysis of photoneutron spectra produced in medical accelerators

Carla Ongaro†, Alba Zanini‡, U Nastasi§, José Ródenas‖, Giuseppe Ottaviano† and Claudio Manfredotti†

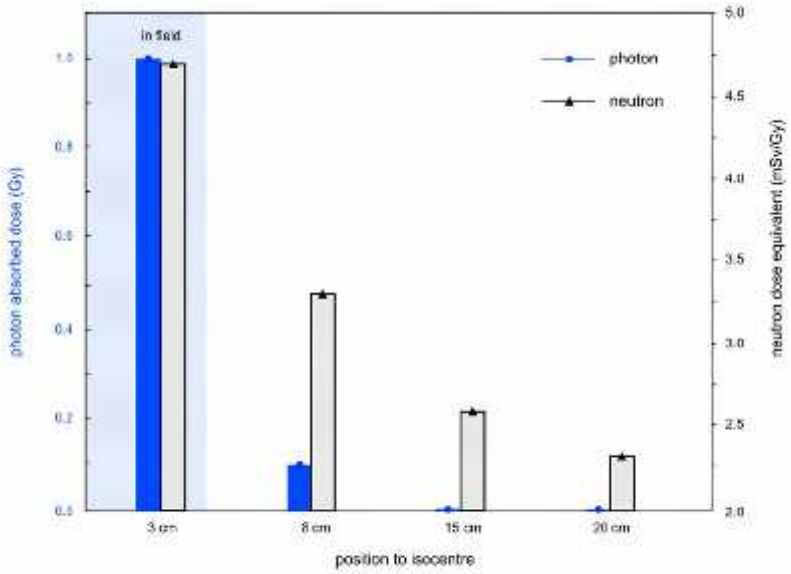


Figure 6. SELEKTA SL20i. Integral photon absorbed dose (left-hand scale) and neutron dose equivalent (right-hand scale) calculated with MCNP-GN at various positions with respect to the isocentre.

But:
Threshold energy for neutron generation is 6-8 MV,
thus relevant only at >10MV

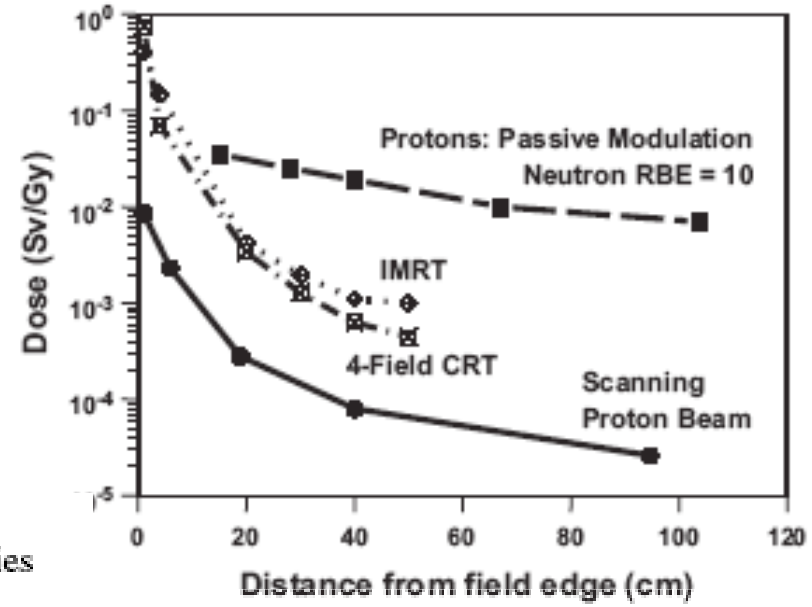


Table 3. Estimated risk of fatal radiation-induced malignancies after RT for prostate cancer (%/Sv)

Hall and Wuu (4)	
Conventional 6 MV	1.5
IMRT 6 MV	3.0
Kry *et al.* (5)	
Conventional 18-MV Varian	1.7
IMRT 6-MV Varian	2.9
Siemens	3.7
IMRT 10-MV Varian	2.1
IMRT 15-MV Varian	3.4
Siemens	4.0
IMRT 18-MV Varian	5.1

Abbreviations: IMRT = intensity-modulated radiation therapy; MV = megavoltage; RT = radiation therapy.

Assessment of radiation-induced second cancer risks in proton therapy and IMRT for organs inside the primary radiation field

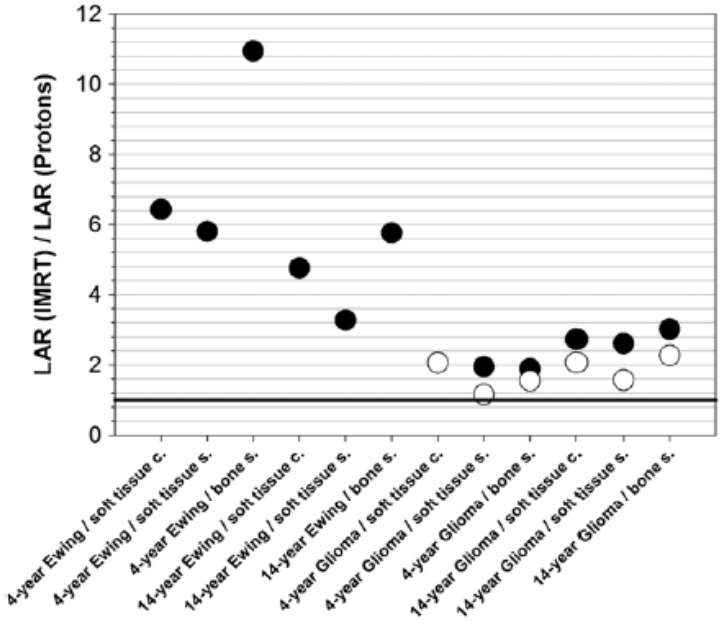


Figure 4. LAR from IMRT versus LAR from proton therapy based on tables 2–5. For the opt glioma cases, the advantage of proton therapy is, on average, slightly lower than the difference integral dose (table 7). For Ewing's sarcoma cases, the advantage of protons is much higher th the integral dose difference. The open circles refer to the four-field proton plans.

Table 6. Total energy deposited (in Joules) in the patient for the treatment plans considered.

	Optic glioma			Ewing's sarcom	
	Protons (three fields)	Protons (four fields)	IMRT	Protons	IMRT
4 year old	10.98	11.64	36.04	24.04	47.70
14 year old	10.73	12.05	29.57	75.48	148.00

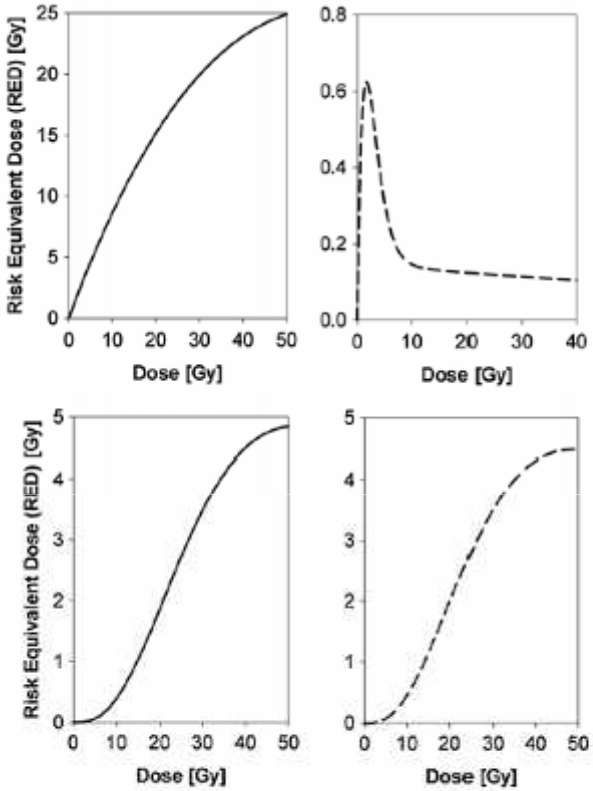


Figure 1. Risk equivalent dose as a function of a point dose (a single voxel). The upper figures show the dose–response for carcinoma (tumor induction for brain/CNS (solid) and bowel (dashed); see table 1) while the lower figures show the dose–response for sarcoma (for soft tissue (solid) and bone (dashed); see parameters in table 1).

Paganetti et al., PMB, 2012

Does this sufficiently reflect reality?

$$\mathrm{OED}_{\mathrm{carcinoma}} = \frac{1}{N}\sum_i \frac{\exp(-\alpha_i' D_i)}{\alpha_i' R}\left(1 - 2R + R^2 \exp\left[\alpha_i' D_i\right] - [1-R]^2 \exp\left[-\frac{\alpha_i' R}{1-R} D_i\right]\right) \quad (1)$$

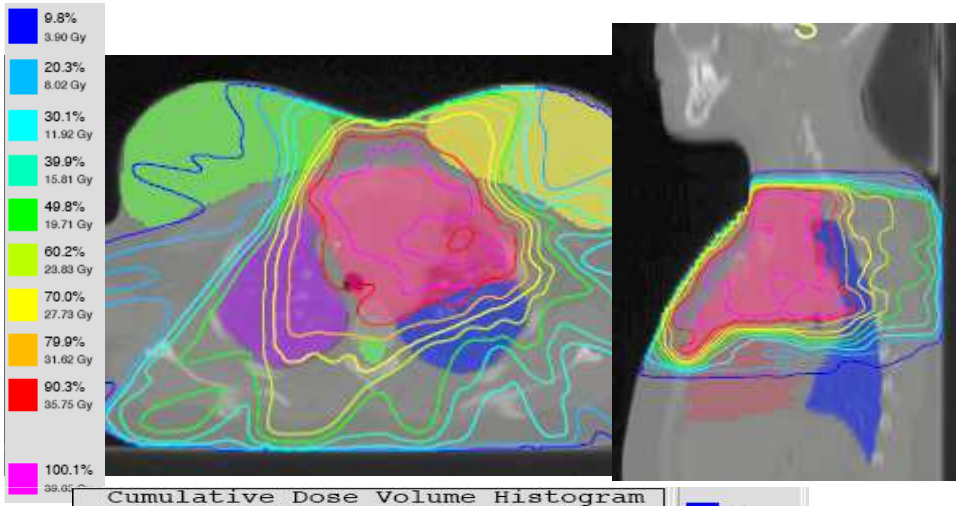
$$\mathrm{OED}_{\mathrm{sarcoma}} = \frac{1}{N}\sum_i \frac{\exp\left(-\alpha_i' D_i\right)}{\alpha_i' R}\left(1 - 2R + R^2 \exp\left[\alpha_i' D_i\right] - \alpha_i' R D_i - [1-R]^2 \exp\left[-\frac{\alpha_i' R}{1-R} D_i\right]\right) \quad (2)$$

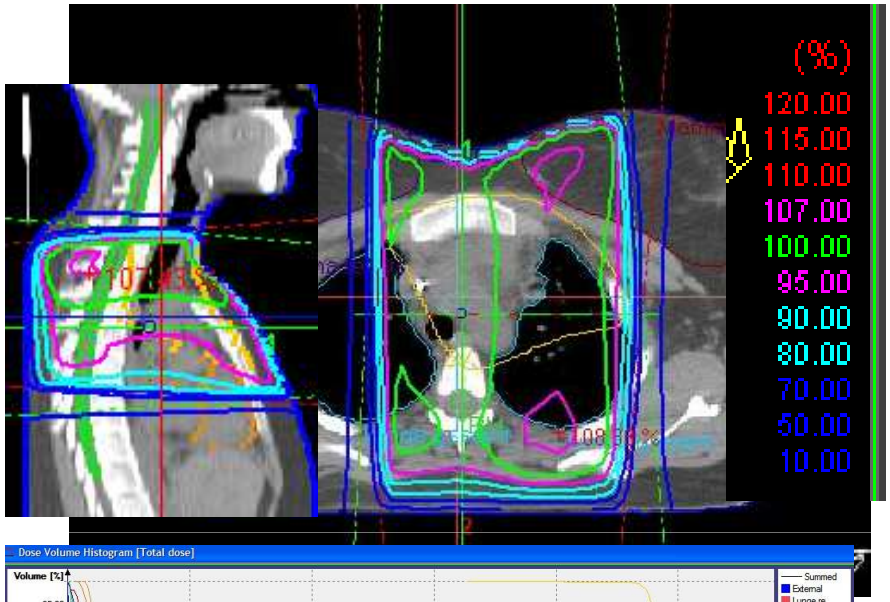
$$\alpha_i' = \alpha + \beta D_i . \frac{d_F}{D}. \quad (3)$$

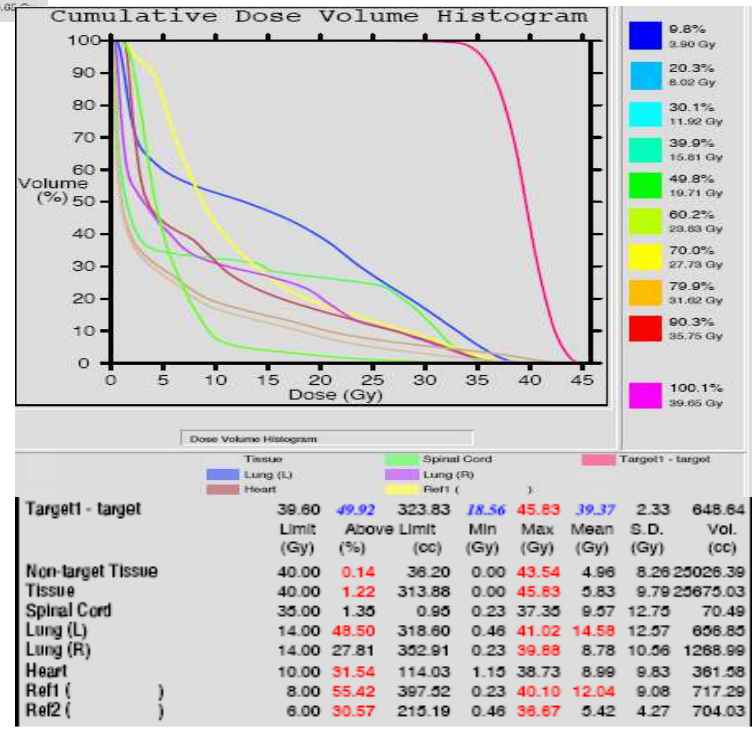
Paganetti et al., PMB, 2012

Mediastinal Tumors: Hodgkin‘s Disease

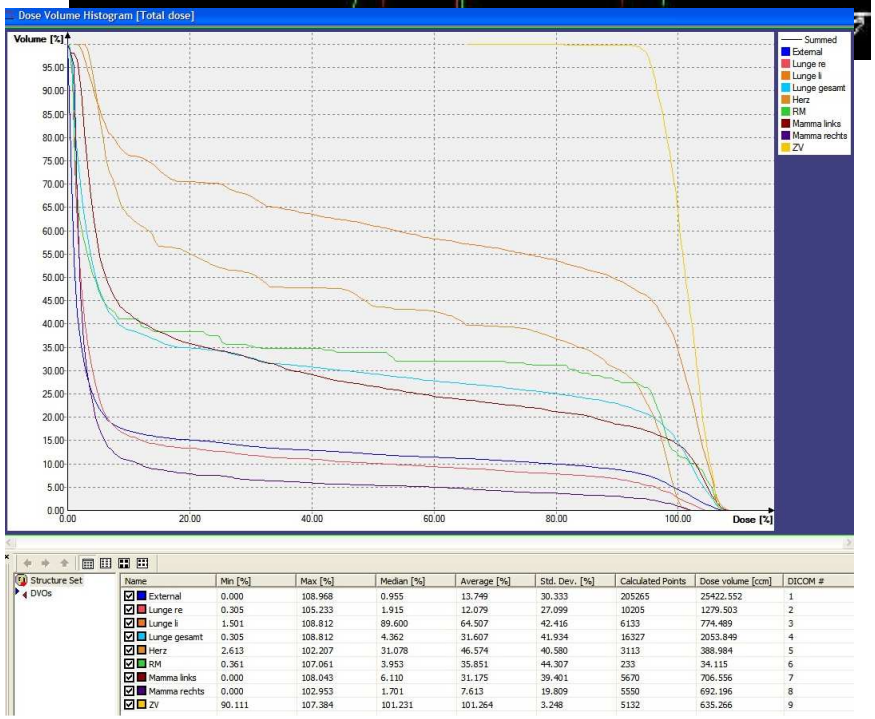
Elevated median but reduced mean breast dose as a result of improved heart protection -> Consequences???







Target1 - target	39.60 Limit (Gy)	49.92 Above Limit (%)	323.83 Limit (cc)	18.56 Min (Gy)	45.83 Max (Gy)	39.37 Mean (Gy)	2.33 S.D. (Gy)	648.64 Vol. (cc)
Non-target Tissue	40.00	0.14	36.20	0.00	43.54	4.96	8.26	25026.39
Tissue	40.00	1.22	313.88	0.00	45.83	5.83	9.79	25675.03
Spinal Cord	35.00	1.35	0.95	0.23	37.35	9.57	12.75	70.49
Lung (L)	14.00	48.50	318.60	0.46	41.02	14.58	12.57	656.85
Lung (R)	14.00	27.81	352.91	0.23	39.88	8.78	10.56	1268.99
Heart	10.00	31.54	114.03	1.15	38.73	8.99	9.83	361.58
Ref1 ( )	8.00	55.42	397.52	0.23	40.10	12.04	9.08	717.29
Ref2 ( )	6.00	30.57	215.19	0.46	36.67	5.42	4.27	704.03

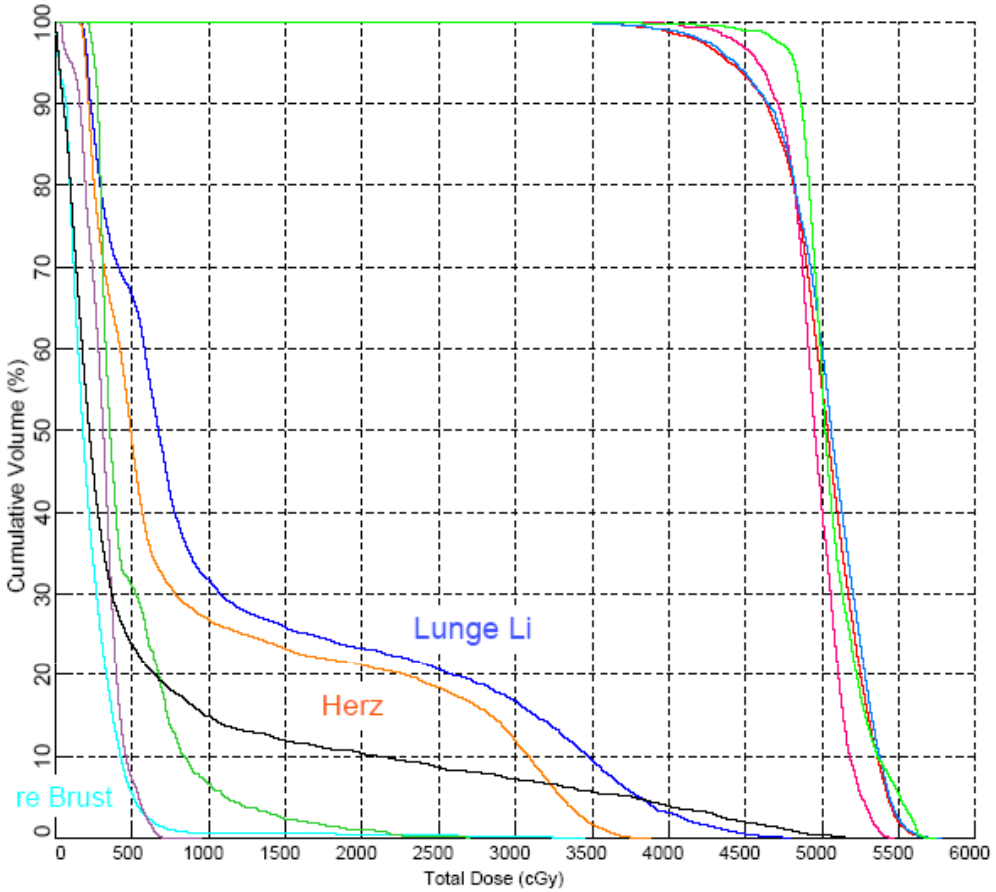


Name	Min [%]	Max [%]	Median [%]	Average [%]	Std. Dev. [%]	Calculated Points	Dose volume [ccm]	DICOM #
External	0.000	108.968	0.955	13.749	30.333	205265	25422.552	1
Lunge re	0.305	105.233	1.915	12.079	27.099	10205	1279.503	2
Lunge li	1.501	108.812	89.600	64.507	42.416	6133	774.489	3
Lunge gesamt	0.305	108.812	4.362	31.607	41.934	16327	2053.849	4
Herz	2.613	102.207	31.078	46.574	40.580	3113	388.984	5
RM	0.361	107.061	3.953	35.851	44.307	233	34.115	6
Mamma links	0.000	108.043	6.110	31.175	39.401	5670	706.556	7
Mamma rechts	0.000	102.953	1.701	7.613	19.809	5550	692.196	8
ZV	90.111	107.384	101.231	101.264	3.248	5132	635.266	9

Problems with Modelling

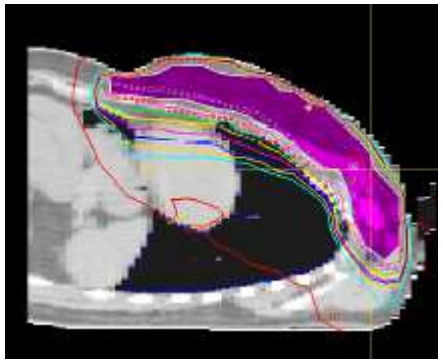
“The mean estimated ERR for breast, lung and thyroid were significantly ($p < 0.01$) lower with INRT than with IFRT planning, regardless of the radiation technique delivery used, assuming a linear dose-risk relationship. An ERR increase was however observed with the non-linear model. With the latter, mean ERR were significantly ($p < 0.01$) increased with IMRT or RA when compared to 3DCRT planning for the breast, lung and thyroid using an IFRT paradigm. After INRT planning, IMRT or RA increased the risk of RIC for lung and thyroid only. “

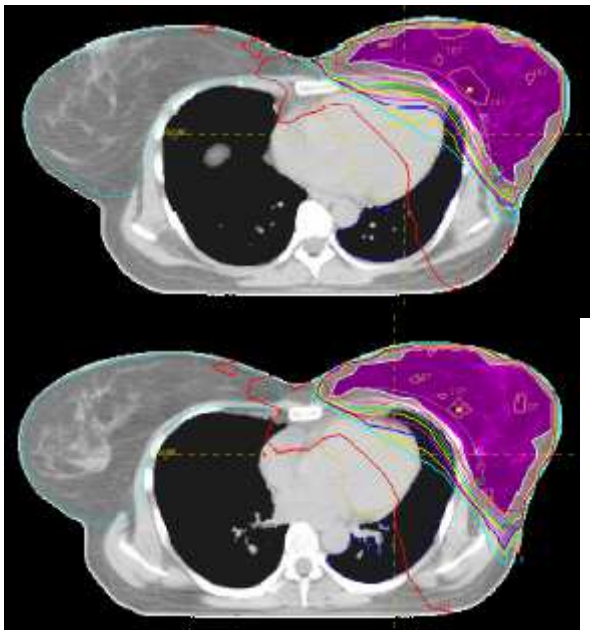
Weber et al., IJROBP, 2011

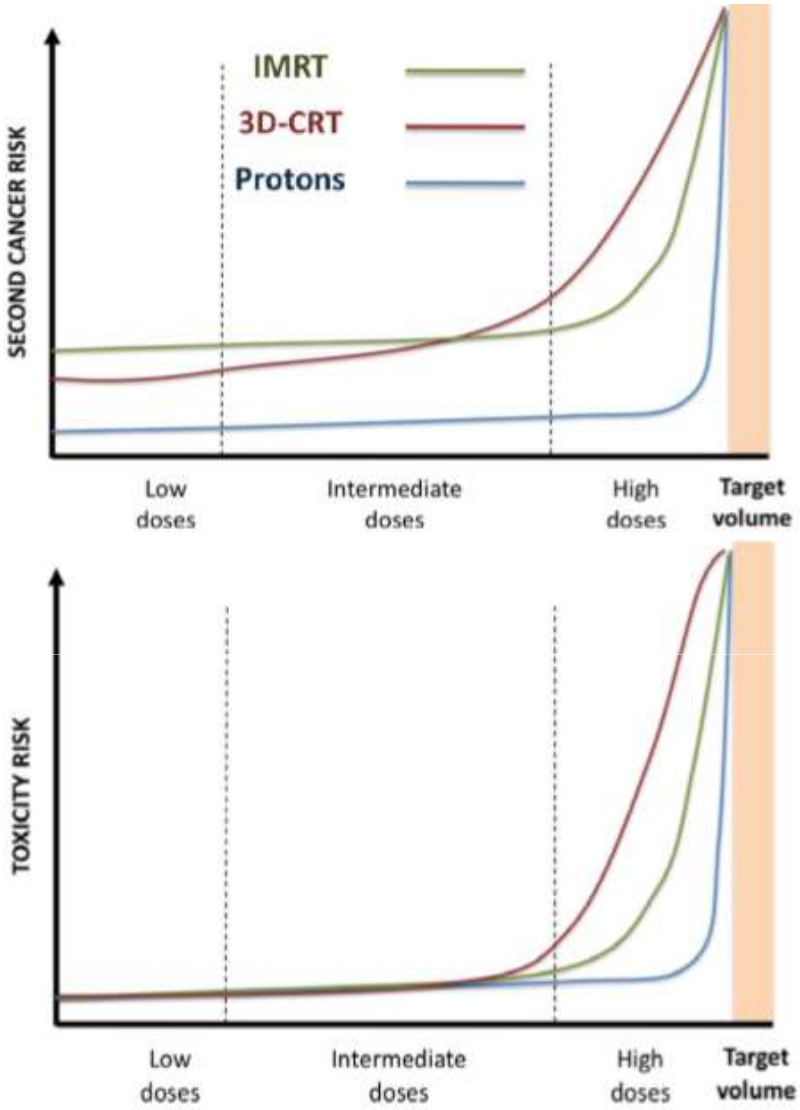


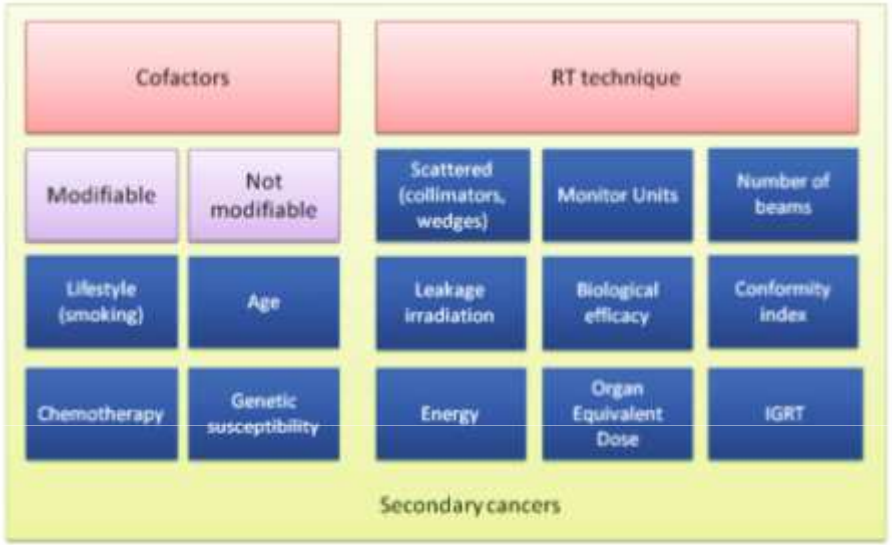
Breast:

Increase of mean and median contralateral breast dose very moderate (from 1.5 to 2.5 Gy) while improved heart protection can be achieved
(Example:
23 Segments - 7 Beams - 362 MUs)









Chargari,
Cancer Metast Review,
2016

Conclusions

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Modena
Policlinico

1. Conventional RT probably goes with a secondary tumor risk of approximately 1% (High- and Low-dose Areas together). The dose/volume effects for secondary tumor risk are currently completely unclear.

2. ***Conservative*** estimates suggest an increase by IMRT to 2%, e.g. the secondary tumor risk doubles when compared to conventional RT.

   But:
   - It is still an overall low number.
   - For most diseases, this is negligible in comparison to the risk of local recurrence.
   - Given the predominantly old age of patients, this is mostly irrelevant anyway
   - New planning systems create efficient plans, so that the number of monitor units decreases dramatically

3. ***Realistic*** estimates suggest a factor of <1.5 between the secondary tumor risk of conventional RT and IMRT.

4. It is not completely improbable, that IMRT *reduces* the risk of secondary tumors

5. Precise knowledge of the dose at SMN origin is necessary to further refine our knowledge (prospective evaluation necessary!!!!)

6. IMRT for children and breast cancer has to be used with caution, weighing benefits against potential risk, but the same holds true for IORT

Where the real danger lurks……

Dental X-Rays and Risk of Meningioma

Elizabeth B. Claus, MD, PhD[1,2]; Lisa Calvocoressi, PhD[1]; Melissa L. Bondy, PhD[3]; Joellen M. Schildkraut, PhD[4]; Joseph L. Wiemels, PhD[5]; and Margaret Wrensch, PhD[5,6]

Cancer, 2012

Variable	Cases, n = 1433 No.	%	Controls, n = 1350 No.	%	OR (95% CI)[b]
Ever had Panorex					
Aged <10 y	22	2.1	5	0.4	4.9 (1.8-13.2)
Ages 10-19 y	91	8	69	6.1	1.5 (1.1-2.1)
Ages 20-49 y	349	30.3	355	31.5	0.9 (0.7-1.1)
Aged ≥50 y	253	29.9	223	27	1.2 (0.9-1.5)
Any age	536	46.7	541	46.7	1.0 (0.8-1.2)
Frequency of Panorex					
Aged <10 y					
Ever	22	2.1	5	0.4	4.9 (1.8-13.2)
Ages 10-19 y					
None	1040	92	1054	93.7	1.0
Less than yearly	74	6.5	63	5.6	1.3 (0.9-1.9)
Yearly or more	17	1.5	6	0.5	3.0 (1.2-7.8)
Ages 20-49 y					
None	803	69.7	773	68.5	1.0
Less than yearly	311	27	341	30.2	0.9 (0.7-1.0)
Yearly or more	38	3.3	14	1.2	2.7 (1.4-5.3)
Aged ≥50 y					
None	592	70.1	603	73	1.0
Less than yearly	214	25.3	209	25.3	1.0 (0.8-1.3)
Yearly or more	39	4.6	14	1.7	3.0 (1.6-5.6)

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Individuals who received therapeutic radiation to the head, neck, face, or chest were not included (114 cases and 60 controls).
[b] Adjusted for age, sex, education, race (white vs nonwhite), and history of head computed tomography.

Table 3. Reported History of Therapeutic Radiation to Head, Neck, Face, or Chest Among Meningioma Cases and Controls

Radiation Treatment For	Cases, n = 1433 No.	%	Controls, n = 1350 No.	%	OR (95% CI)
Cancer	58	4.1	37	2.7	1.5 (1.0-2.2)[a]
Benign tumor	15	1	5	0.4	2.8 (1.0-7.8)[a]
Tonsils/adenoids	5	0.4	0	0	*P* = .0628[b]
Thyroid	9	0.6	2	0.2	*P* = .0660[b]
Acne	10	0.7	6	0.4	*P* = .4565[b]
Ringworm	4	0.4	0	0	*P* = .1253[b]
Ear	3	0.2	1	0.1	*P* = .6254[b]
Other	15	1.1	9	0.7	*P* = .3087[b]
Any	114	8	60	4.4	1.8 (1.3-2.5)[a]

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Adjusted for age, sex, and race (white vs nonwhite).
[b] Fisher exact test (2-sided probability).

Highly conformal techniques in locally advanced lung cancer: indications, techniques, normal tissue constraints, results

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University of Torino, Italy

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The "too much" heterogeneous Stage III

Box 2
Treatment of stage III NSCLC

Standard therapy

Concurrent chemotherapy plus definitive radiotherapy

Induction chemoradiotherapy followed by surgical resection (selected patients with non-bulky mediastinal lymph nodes who do not require pneumonectomy for adequate resection)

Options in poor-risk patients

Sequential chemotherapy followed by radiotherapy

Radiotherapy alone

Pathologic stage III following surgical resection

Adjuvant chemotherapy: platinum-based, 2-drug regimen × 4 cycles

Consider adjuvant radiotherapy after completion of chemotherapy

Gadgeel SM et al, Radiol Clin N Am 50 (2012) 961–974

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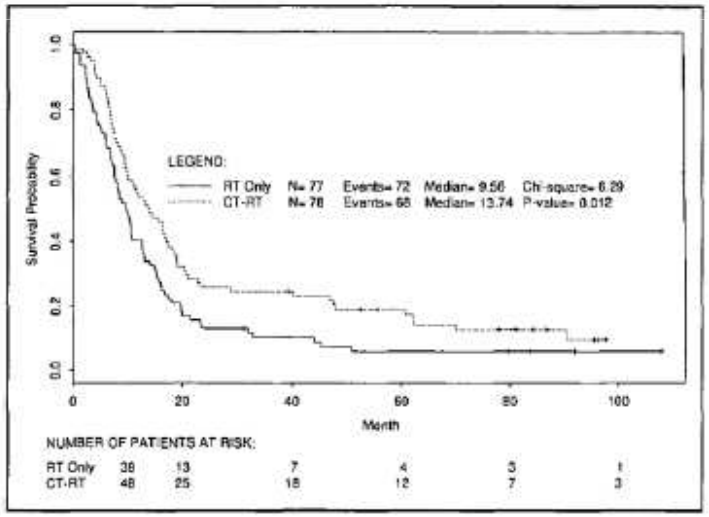
Chemo + RT vs. RT alone

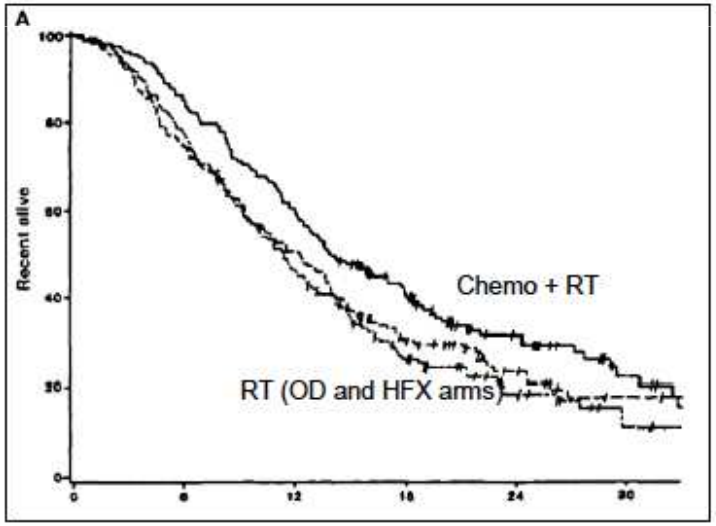
Improved Survival in Stage III Non-Small-Cell Lung Cancer: Seven-Year Follow-up of Cancer and Leukemia Group B (CALGB) 8433 Trial

*Robert O. Dillman, James Herndon, Stephen L. Seagren, Walter L. Eaton, Jr., Mark R. Green**



Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: Preliminary Results of a Phase III Trial in Regionally Advanced, Unresectable Non–Small-Cell Lung Cancer

*William T. Sause, Charles Scott, Samuel Taylor, David Johnson, Robert Livingston, Ritsuko Komaki, Bahman Emami, Walter J. Curran, Roger W. Byhardt, Andrew T. Turrisi, A. Rashid Dar, James D. Cox**



From DA Palma, ASTRO 2014

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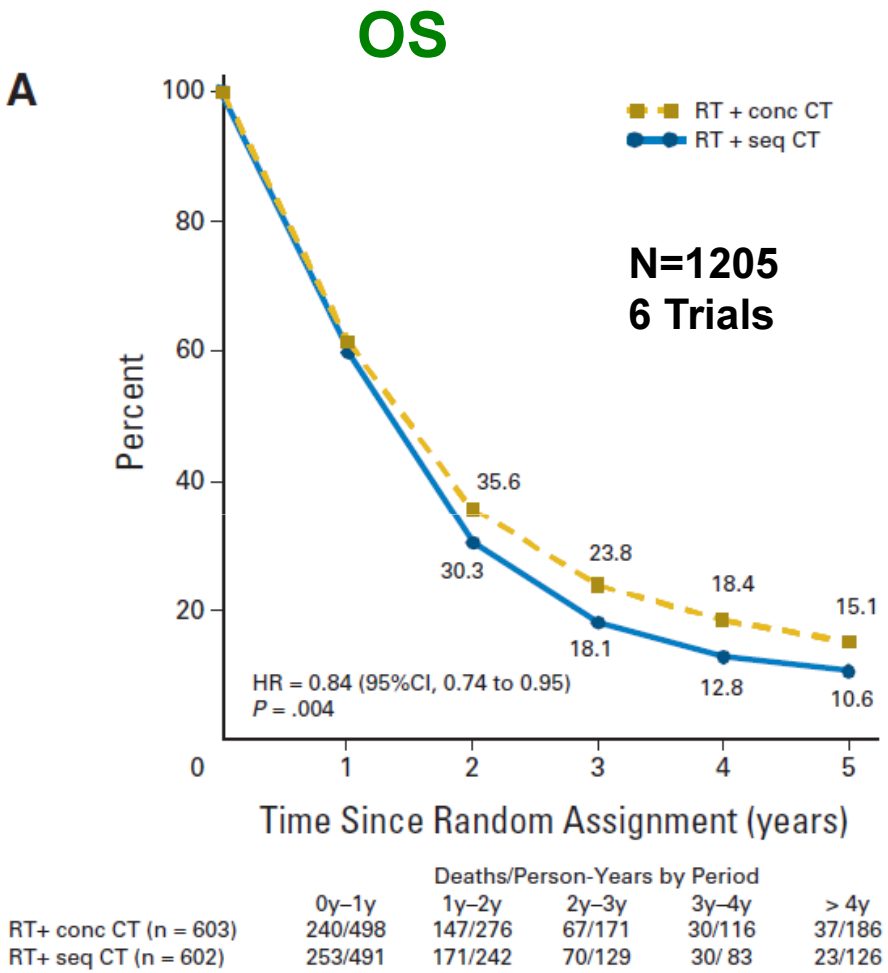
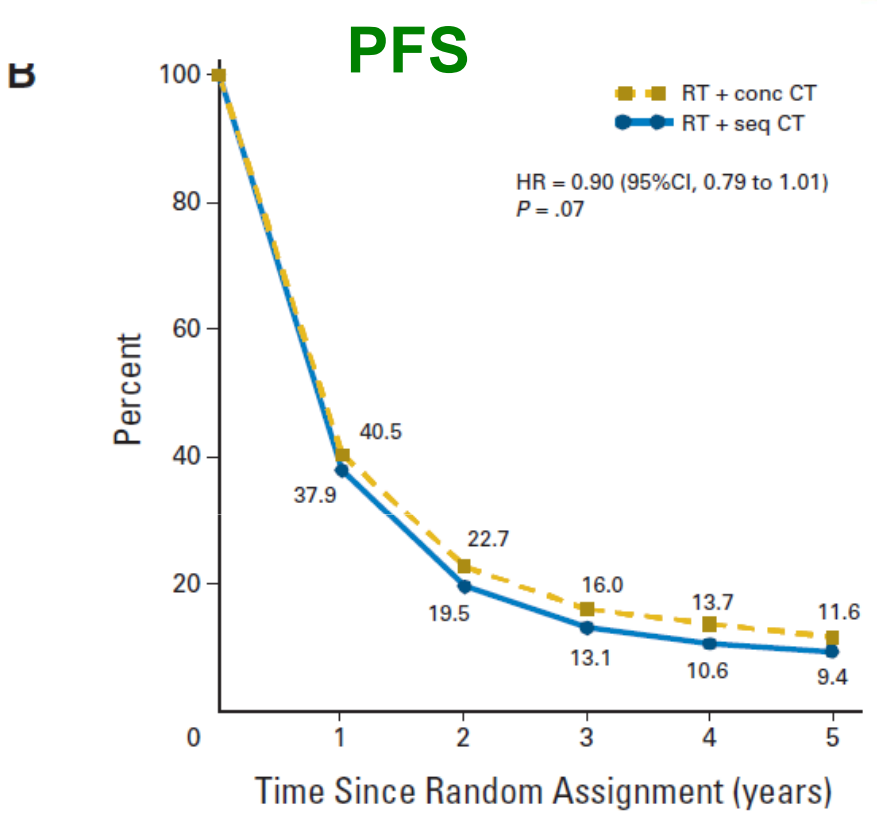
Concurrent vs. Sequential: Meta-analysis



Deaths/Person-Years by Period

	0y–1y	1y–2y	2y–3y	3y–4y	> 4y
RT+ conc CT (n = 603)	240/498	147/276	67/171	30/116	37/186
RT+ seq CT (n = 602)	253/491	171/242	70/129	30/ 83	23/126



Deaths/Person-Years by Period

	0y–1y	1y–2y	2y–3y	3y–4y	> 4y
RT+ conc CT (n = 595)	365/408	98/170	36/104	12/80	21/134
RT+ seq CT (n = 589)	391/399	90/133	33/80	13/58	12/100

Auperin et al, JCO 2010

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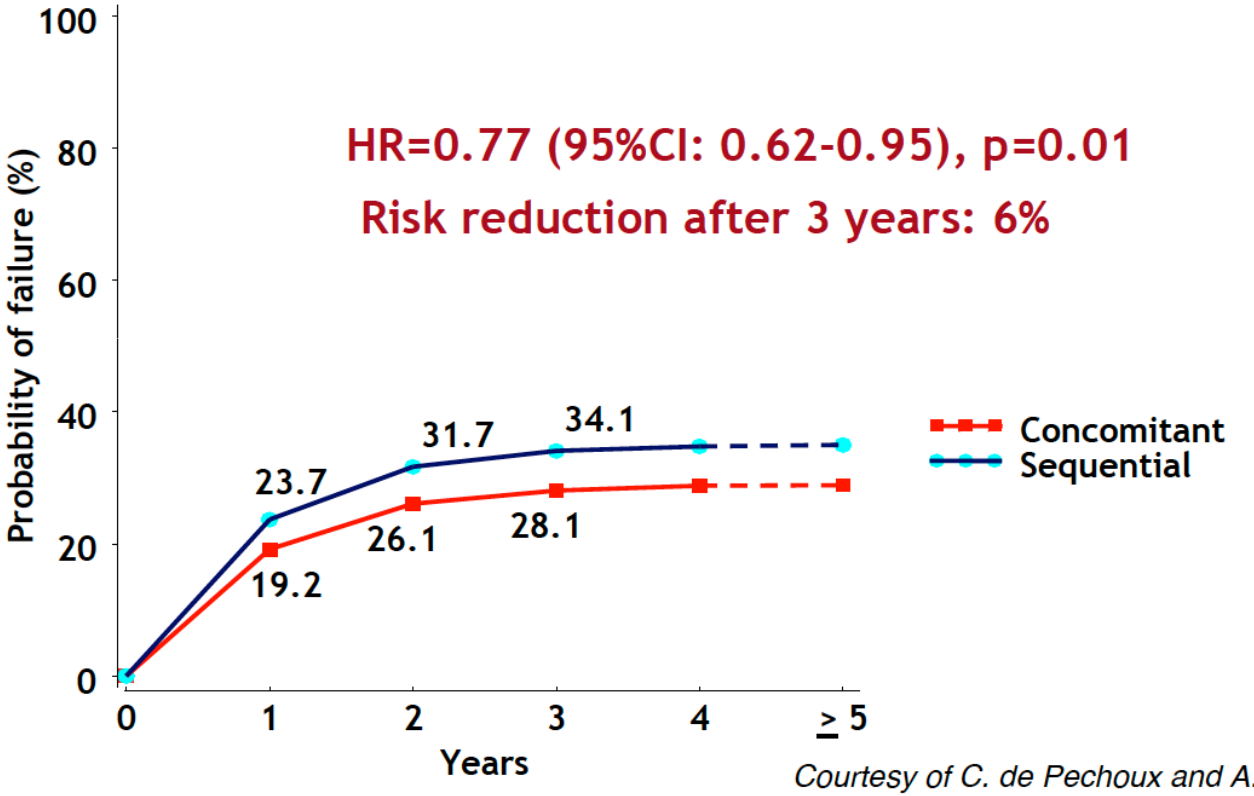
Cumulative risk of locoregional failure



Courtesy of C. de Pechoux and A. Auperin

Optimal Chemotherapy Unknown

VOLUME 33 · NUMBER 6 · FEBRUARY 20 2015

JOURNAL OF CLINICAL ONCOLOGY

E D I T O R I A L

Concurrent Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer: What Is the Best Regimen?

Wilfried Ernst Erich Eberhardt, *West German Cancer Centre; and University Hospital of University Duisburg-Essen, Essen, Germany*

- Most common options in U.S. are carboplatin/paclitaxel and cisplatin/etoposide
- No phase III data to compare these
  - Pneumonitis rates appear higher with carbo/paclitaxel
  - Phase II survival data favors cisplatin/etoposide
- Cis-Vinca alkaloid also reasonable

from DA Palma, ASTRO 2014

A Systematic Review of Carboplatin-Paclitaxel versus Cisplatin-Etoposide Concurrent with Thoracic Radiation for Stage III NSCLC Patients

Conor E. Steuer, Madhusmita Behera, Kristin A. Higgins, Nabil F. Saba, Dong M. Shin, Suchita Pakkala, Rathi N. Pillai, Taofeek K. Owonikoko, Walter J. Curran, Chandra P. Belani, Fadlo R. Khuri, Suresh S. Ramalingam

The Winship Cancer Institute of Emory University (Atlanta)

September 8, 2015

Abstract ID: 600

EMORY | WINSHIP CANCER INSTITUTE

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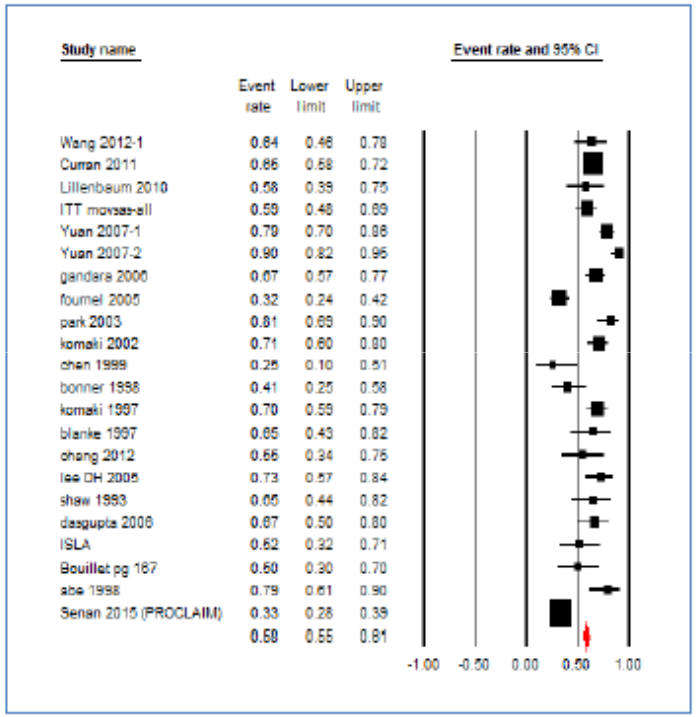
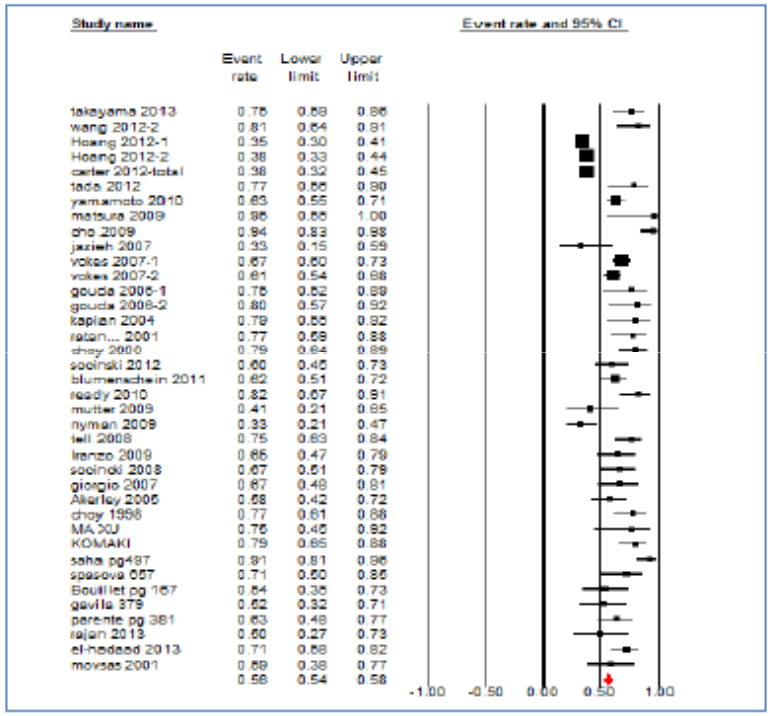
Results: Overall Response Rate





Cisplatin/Etoposide

58% (CI 55%-61%); N=1457

Carboplatin/Paclitaxel

56% (CI 54%- 58%); N=2385 **(p=0.28)**

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Toxicities (Grade 3 and Above)

Toxicity	CE	CP	p-value
Pneumonitis	9%	7%	0.17
Esophagitis	20%	15%	0.18
N/V	20%	9%	**0.018**
Anemia	16%	8%	**0.06**
Thrombocytopenia	14%	6%	**0.001**
Neutropenia	54%	23%	**<0.0001**

IASLC

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

16TH WORLD CONFERENCE ON LUNG CANCER

SEPTEMBER 6-9, 2015 • DENVER, COLORADO, USA

Safety Results of the Consolidation Phase of the Phase III PROCLAIM Trial: Pemetrexed, Cisplatin or Etoposide, Cisplatin plus Thoracic Radiation Therapy followed by Consolidation Cytotoxic Chemotherapy in Locally Advanced Nonsquamous Non-small Cell Lung Cancer

Ramaswamy Govindan

Suresh Senan, Anthony Brade, Johan Vansteenkiste, Françoise Mornex, Helen Ross, Jan Van Meerbeeck, Christophe Hennequin, Nicolas Dickgreber, Yi-long Wu, Jai Prakash Agarwal, Konstantinos Syrigos, Frank Griesinger, Barbara Parente, Mariano Provencio, Anwar M Hossain, Belén San Antonio, Joseph Treat, Andrew G Koustenis, Nadia Chouaki, Everett Vokes

IASLC 40 YEARS

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Selected AEs Possibly Related to Study Treatment by Arm

Consolidation Phase

CTCAE Term*, % of patients	Arm A (N=229) Pem		Arm B (N=202) CE	
	Any Gr	Gr 3–4	Any Gr	Gr 3–4
Patients with ≥1 CTCAE	81.7	29.7	86.1	**50.5**
Hemoglobin	17.0	2.6	19.8	4.5
Neutrophils/granulocytes (ANC/AGC)	21.8	11.8	**43.1**	**37.6**
Platelets	6.1	2.2	**19.3**	5.0
Fatigue	14.4	0.9	13.9	2.0
Febrile neutropenia	3.1	3.1	3.5	3.5
Leukocytes	17.9	8.3	23.3	14.4
Lymphopenia	7.4	3.5	7.4	2.5
Pneumonia (with grade 3/4 neutrophils)	**5.2**	1.7	1.5	0
Radiation-related AEs				
Dysphagia	5.7	1.3	2.5	0.5
Esophagitis	1.3	0	3.5	1.5
Pneumonitis	**11.4**	2.2	4.0	1.0

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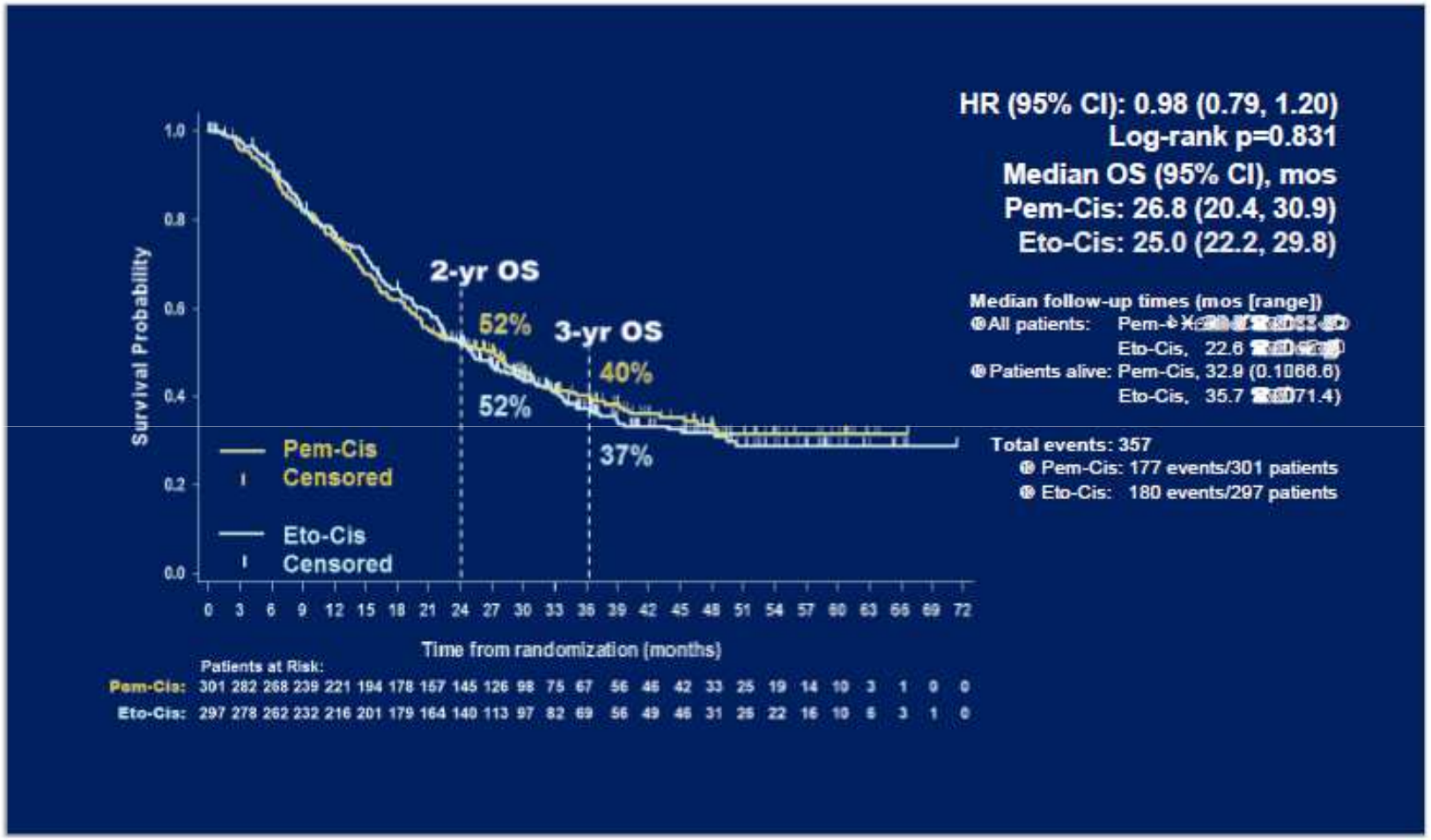
PROCLAIM: Primary Endpoint, OS



Optimal RT Dose – RTOG 0617

Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study

Jeffrey D Bradley, Rebecca Paulus, Ritsuko Komaki, Gregory Masters, George Blumenschein, Steven Schild, Jeffrey Bogart, Chen Hu, Kenneth Forster, Anthony Magliocca, Vivek Kavadi, Yolanda I Garces, Samir Narayan, Puneeth Iyengar, Cliff Robinson, Raymond B Wynn, Christopher Koprowski, Joanne Meng, Jonathan Beitler, Rakesh Gaur, Walter Curran Jr, Hak Choy

RANDOMIZE

	Concurrent Treatment	Consolidation Treatment
	Arm A Concurrent chemotherapy: Carboplatin & Paclitaxel RT to 60 Gy, 5 x per week for 6 weeks	Arm A Consolidation chemotherapy: Carboplatin & Paclitaxel
	Arm B: Closed 6/17/11 Concurrent chemotherapy: Carboplatin & Paclitaxel RT to 74 Gy, 5 x per week for 7.5 weeks	Arm B: Closed 6/17/11 Consolidation chemotherapy: Carboplatin & Paclitaxel
	Arm C Cetuximab Loading Dose: Week 1, Day 1 then Concurrent chemotherapy, Carboplatin & Paclitaxel, and Cetuximab RT to 60 Gy, 5 x per week for 6 weeks	Arm C Consolidation therapy: Cetuximab and Carboplatin & Paclitaxel
	Arm D: Closed 6/17/11 Cetuximab Loading Dose: Week 1, Day 1 then Concurrent chemotherapy, Carboplatin & Paclitaxel, and Cetuximab RT to 74 Gy, 5 x per week for 7.5 weeks	Arm D: Closed 6/17/11 Consolidation therapy: Cetuximab and Carboplatin & Paclitaxel

From DA Palma, ASTRO 2014

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Background for high dose RT with concurrent CT

Phase I and II Trials establishing safety and potential efficacy of 74 Gy delivered using 3D-Conformal Radiation Therapy

Study	Radiation dose (Gy)	Chemotherapy	Median survival time (months)
RTOG 0117	74	Carboplatin/paclitaxel	21.6
NCCTG 0028	74	Carboplatin/paclitaxel	37
North Carolina	74	Carboplatin/paclitaxel	24
Wake Forest	74	Gemcitabine	18
CALGB 30105	74	Carboplatin/paclitaxel	24

RTOG 0617: objectives

To compare the overall survival of patients treated with high-dose versus standard-dose conformal radiation therapy with concurrent chemotherapy.

To compare the overall survival of patients treated with cetuximab versus without cetuximab with concurrent chemoradiotherapy.

RTOG 0617: Trial Design

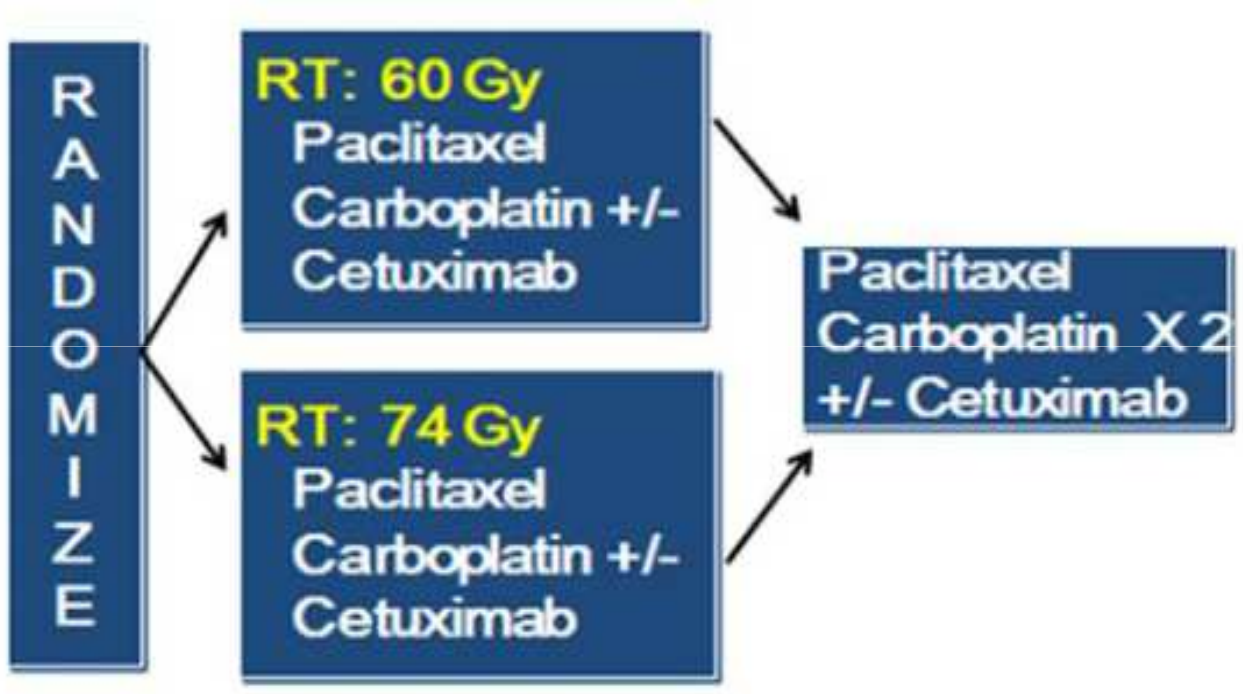
Stratify:

-RT Technique
(IMRT vs 3D)

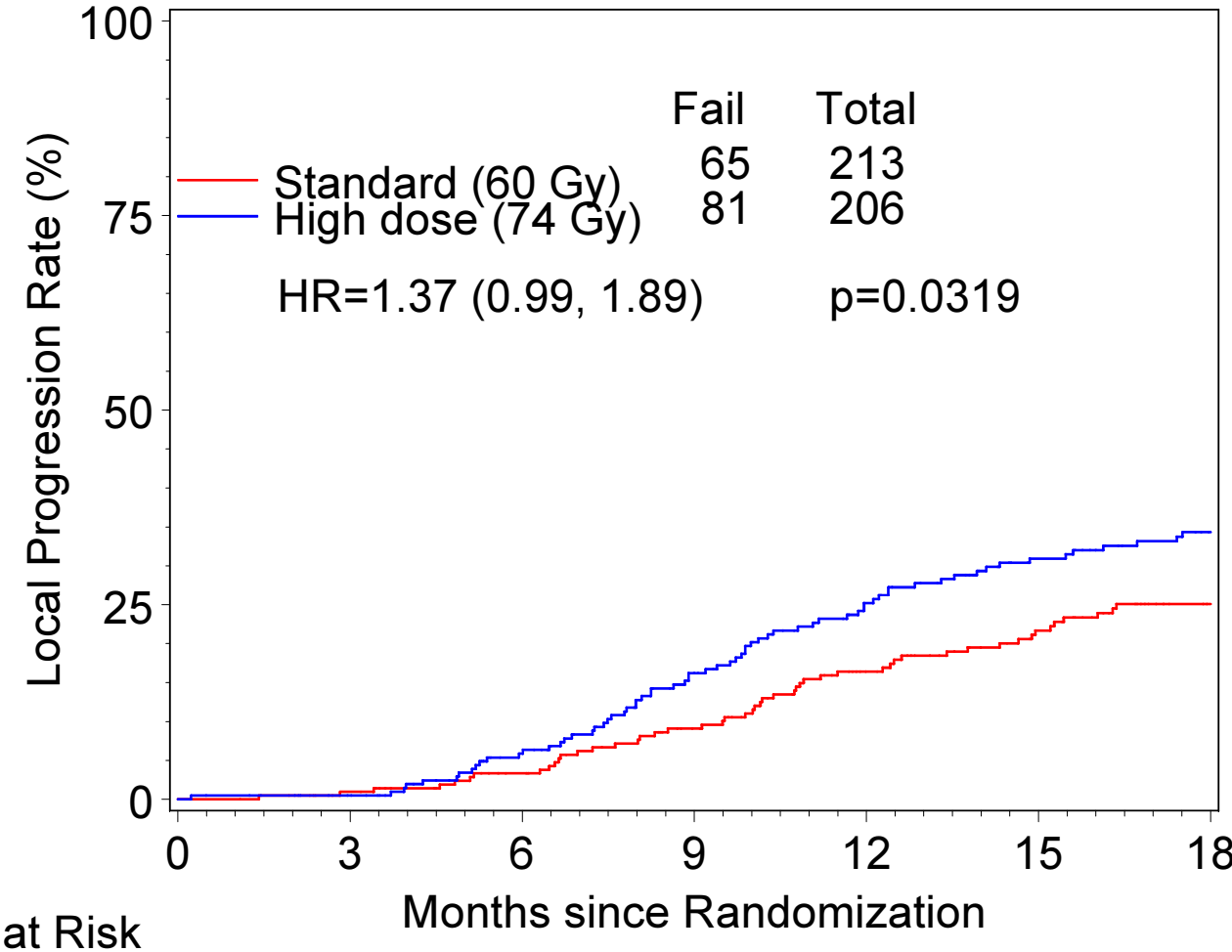
-Perf Status
(0 vs 1)

-Histology
(squam vs other)

-PET staging
(yes vs no)



RTOG 0617: Local Tumor Failure



18-Month Local Progression Rate

34.3%

25.1%

Patients at Risk

Standard	213	205	187	165	137	113	85
High dose	206	197	170	134	105	80	62

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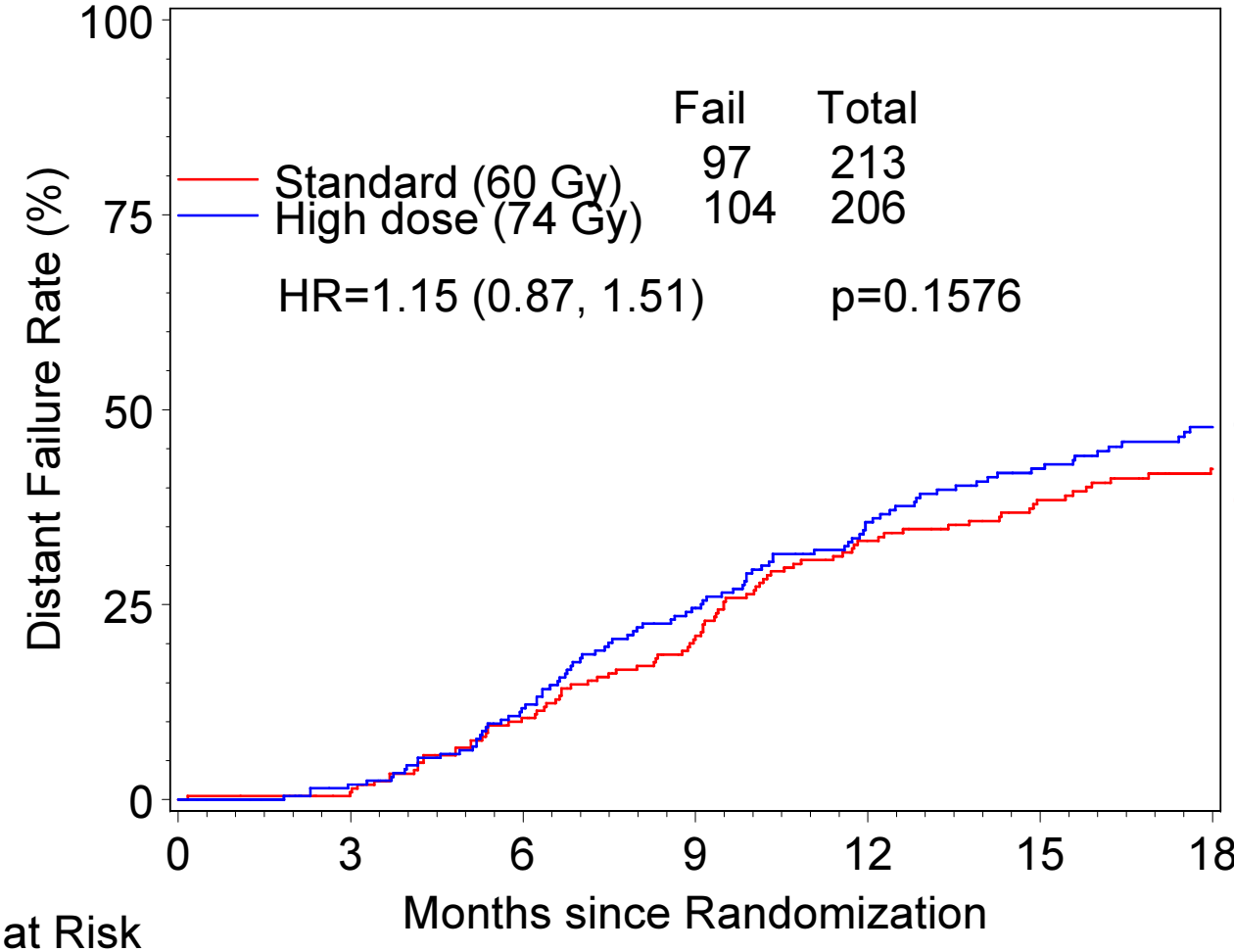
RTOG 0617: Distant Failure



18-Month Failure Rate

47.8%

42.4%

Patients at Risk							
Standard	213	205	175	145	115	94	73
High dose	206	193	161	126	93	73	54

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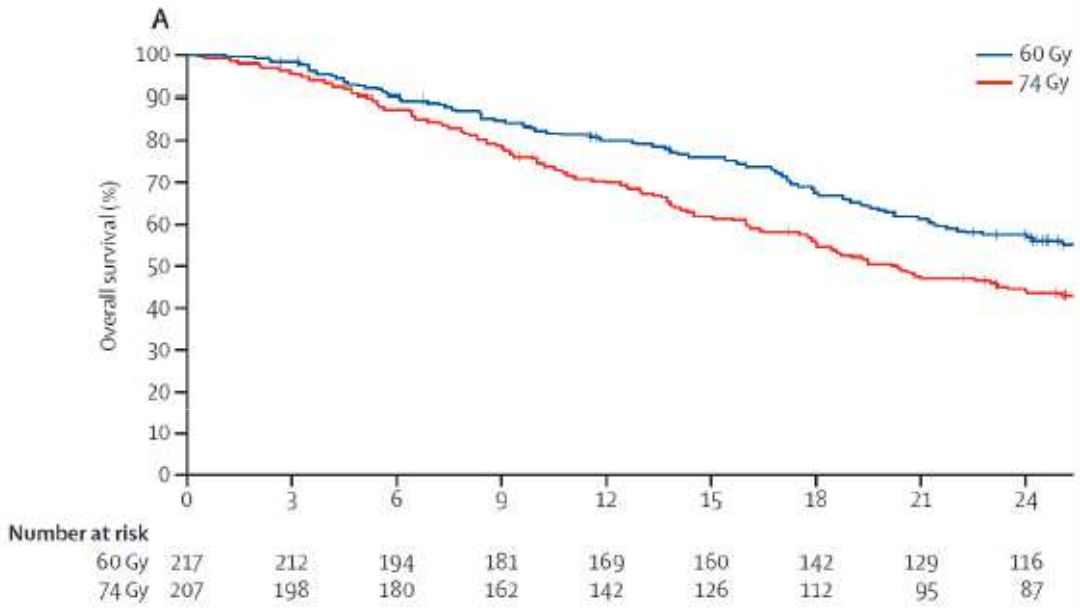
Optimal Dose – RTOG 0617



	60 Gy (n=217)*	74 Gy (n=207)
Overall survival		
Dead	127	140
1 year	80·0% (73·9–84·7)	69·8% (63·1–75·6)
2 year	57·6% (50·6–63·9)	44·6% (37·7–51·3)
Median (months)	28·7 (24·1–36·9)	20·3 (17·7–25·0)
HR	1·38 (1·09–1·76)	..
p value (log-rank, one-sided)	0·004	..
Progression-free survival		
Fail	164	164
1 year	49·2% (42·3–55·6)	41·2% (34·4–47·8)
2 year	29·1% (23·1–35·3)	21·4% (16·1–27·3)
Median (months)	11·8 (10·2–14·3)	9·8 (8·8–11·6)
HR	1·19 (0·95–1·47)	..
p value (log-rank, two-sided)	0·12	..
Local failure		
Fail	77	86
1 year	16·3% (11·4–21·3)	24·8% (18·9–30·7)
2 year	30·7% (24·5–36·9)	38·6% (31·9–45·3)
HR	1·26 (0·93–1·71)	..
p value (Gray, two-sided)	0·13	..

- **Factors predictive of OS**: Radiation dose (60 Gy), maximum esophagitis grade, PTV size, heart V5 and V30

From DA Palma, ASTRO 2014

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RTOG 0617: Dosimetric Data Distribution

	60 Gy (n=203) Mean (Median)	**74 Gy (n=197) Mean (Median)**
GTV Volume (cc)	125 (92)	129 (96)
Heart V5 (%)	47 (46)	46 (46)
Heart V50 (%)	**7 (4)**	**11 (6)**
Lung V20 (%)	29 (29)	31 (32)
Esophagus Dose (Gy)	25 (25)	30 (29)
Esophagus V60 (%)	**15 (13)**	**26 (26)**
Mean Margin CTV to PTV (mm)	8 (7)	8 (7)

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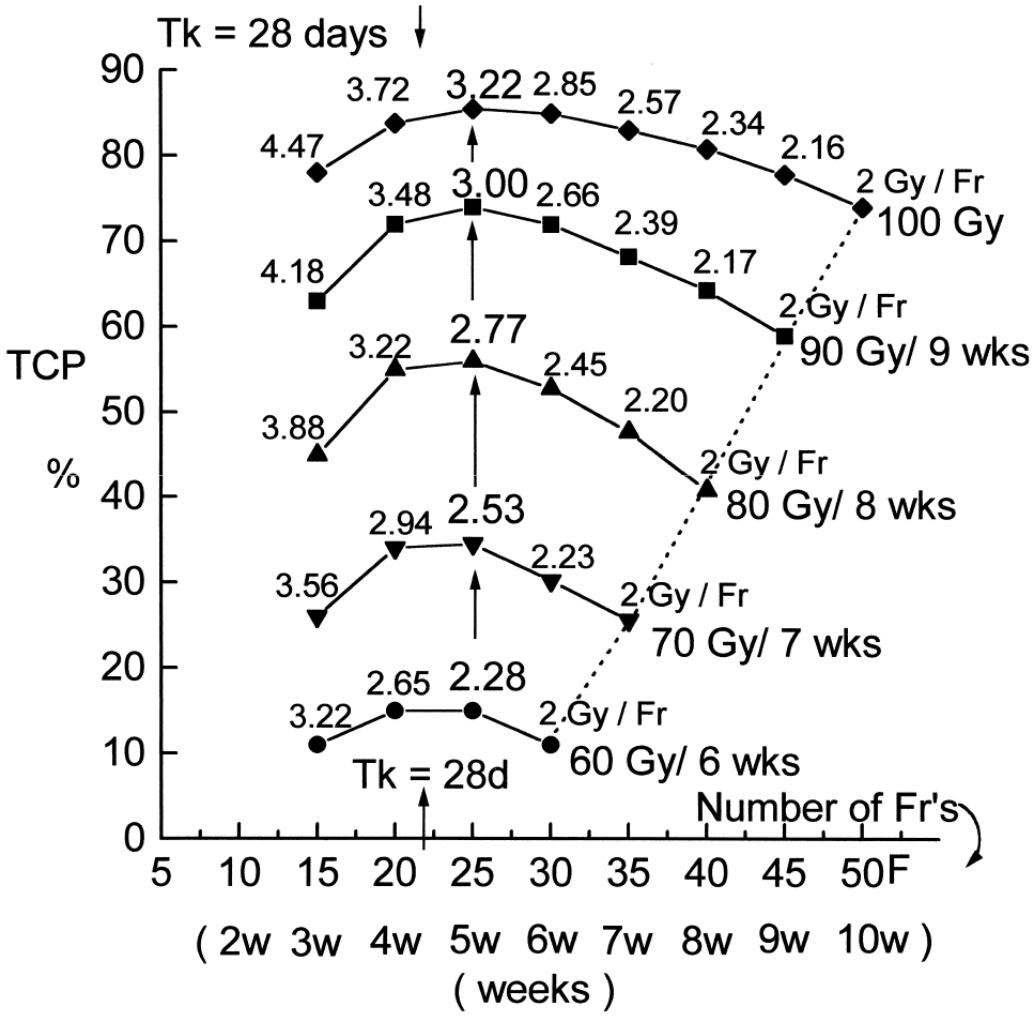
Can “adapted” hypofractionation be applied to lung cancer patients with LA disease through the use of high-tech radiotherapy?

Gain in TCP from shortening overall treatment time to 5 weeks



Fewer and larger fractions calculated to deliver equal late complications also deliver higher biologic dose to tumors

Metha et al, Int J Radiat Oncol Biol Phys 2001

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Dose-Limiting Toxicity After Hypofractionated Dose-Escalated Radiotherapy in Non–Small-Cell Lung Cancer

Donald M. Cannon, Minesh P. Mehta, Jarrod B. Adkison, Deepak Khuntia, Anne M. Traynor, Wolfgang A. Tomé, Richard J. Chappell, Ranjini Tolakanahalli, Pranshu Mohindra, Søren M. Bentzen, and George M. Cannon

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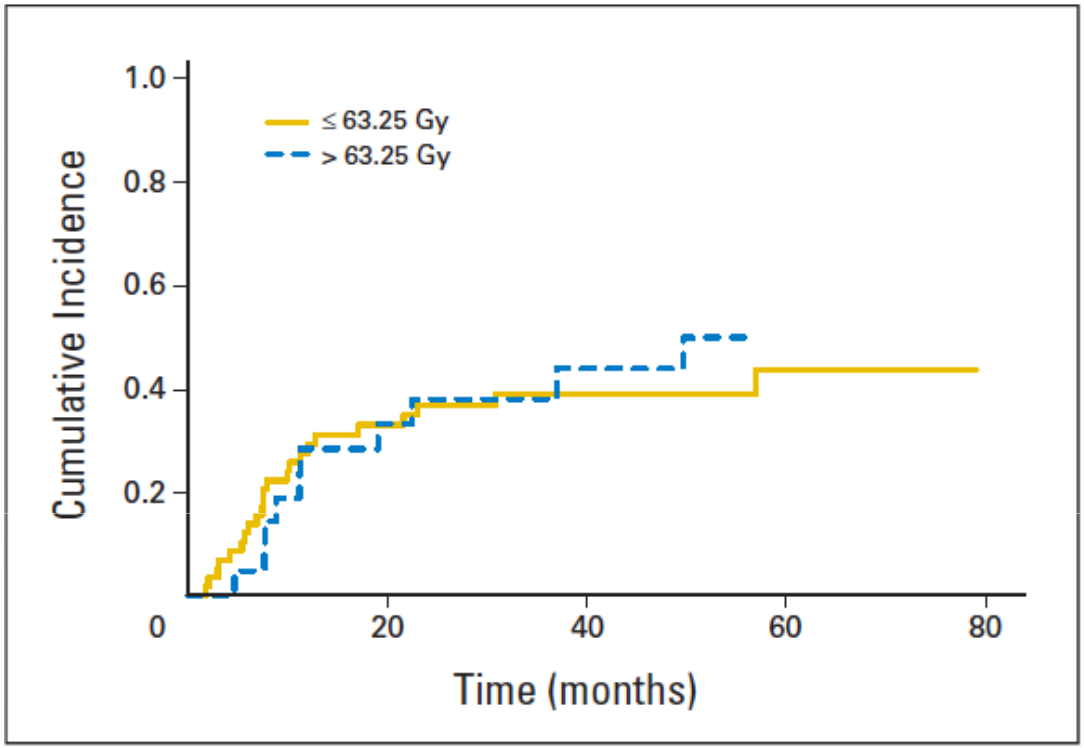
Table 1. Patient and Treatment Characteristics

Characteristic	No. of Patients	%
Total patients	79	100
Age, years		
< 50	6	9
50-69	47	59
≥ 70	26	32
Sex		
Female	33	42
Male	46	58
Stage		
I/II	7	9
IIIA	21	27
IIIB	35	44
IV	10	13
Recurrent	6	8
Histology		
Adenocarcinoma	24	30
Squamous cell carcinoma	26	33
NSCLC, NOS	22	28
Other NSCLC	7	9
Bin assignment, $rNTD_{mean}$		
Pilot (NA)	5	6
1 (0.00-0.119)	6	7
2 (0.12-0.179)	8	10
3 (0.18-0.239)	27	34
4 (0.24-0.309)	29	37
5 (0.31-0.410)	4	5
Performance status		
0	48	61
1	30	38
Not recorded	1	1
Prescribed radiation dose, Gy		
57	47	59
63.25	11	14
69.25	3	4
75	12	16
80.5	4	5
85.5	2	3
Chemotherapy		
Neoadjuvant	17	21
Adjuvant	33	41
Both	3	4
None	25	32
Other*	1	1



Local Failure

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Grade 4-5 toxicity

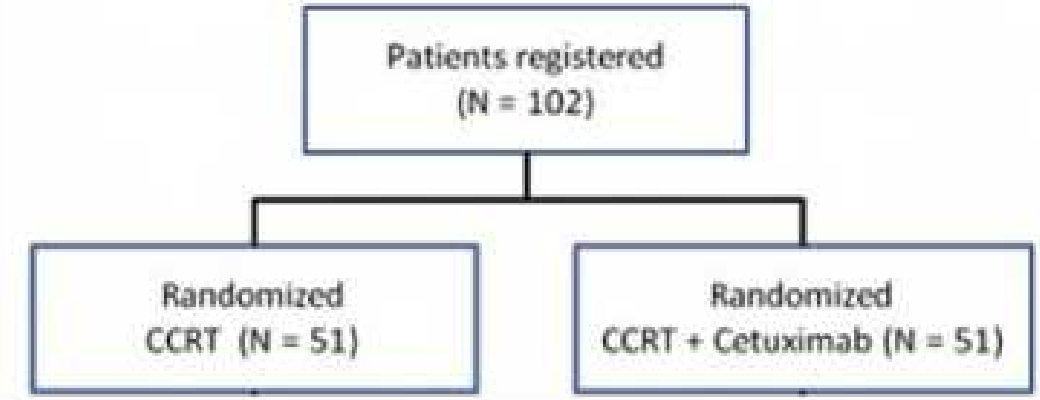
Table 2 Patients With Grade 4-5 Toxicity

Age (years)	Sex	Stage	Bin	Dose (Gy)*	Grade	Interval (months)†	Toxicity
69	M	IIIB	3	63.25	5	1.2	HSV/CMV pneumonitis; history of pre-RT low-dose methotrexate
66	F	IIA	1	85.5	5	55	Fatal hemoptysis
58	M	IIIB	3	75	5	7.9	Fatal hemoptysis
63	M	IIIB	1	75	5	1.6	Lung abscess
62	M	IIIA	3	75	5	8.1	Fatal hemoptysis and abscess
61	F	IV	3	75	4	10.3	Lung abscess, bronchocavitary fistula, tracheoesophageal fistula

Cannon D, JCO 2013

Aim

To investigate 60-month OS in LA-NSCLC patients treated with concurrent chemoradiotherapy +/- cetuximab, using a hypofractionation scheme of 24 x 2.75 Gy



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Raditux trial

- **Randomized multicenter phase II trial**
  - To assess the beneficial effect of cetuximab on concurrent chemoradiotherapy
- **Inclusion criteria**
  - Inclusion between February 2009 and May 2011
  - 102 inoperable stage II & stage III A/B NSCLC patients
  - WHO performance status 0–1
- **Treatment**
  - 24 x 2.75 Gy
  - Daily low-dose cisplatin (6mg/m^2)
  - +/- weekly cetuximab (loading dose 400mg/m^2 followed by a weekly dose of 250 mg/m^2 iv)

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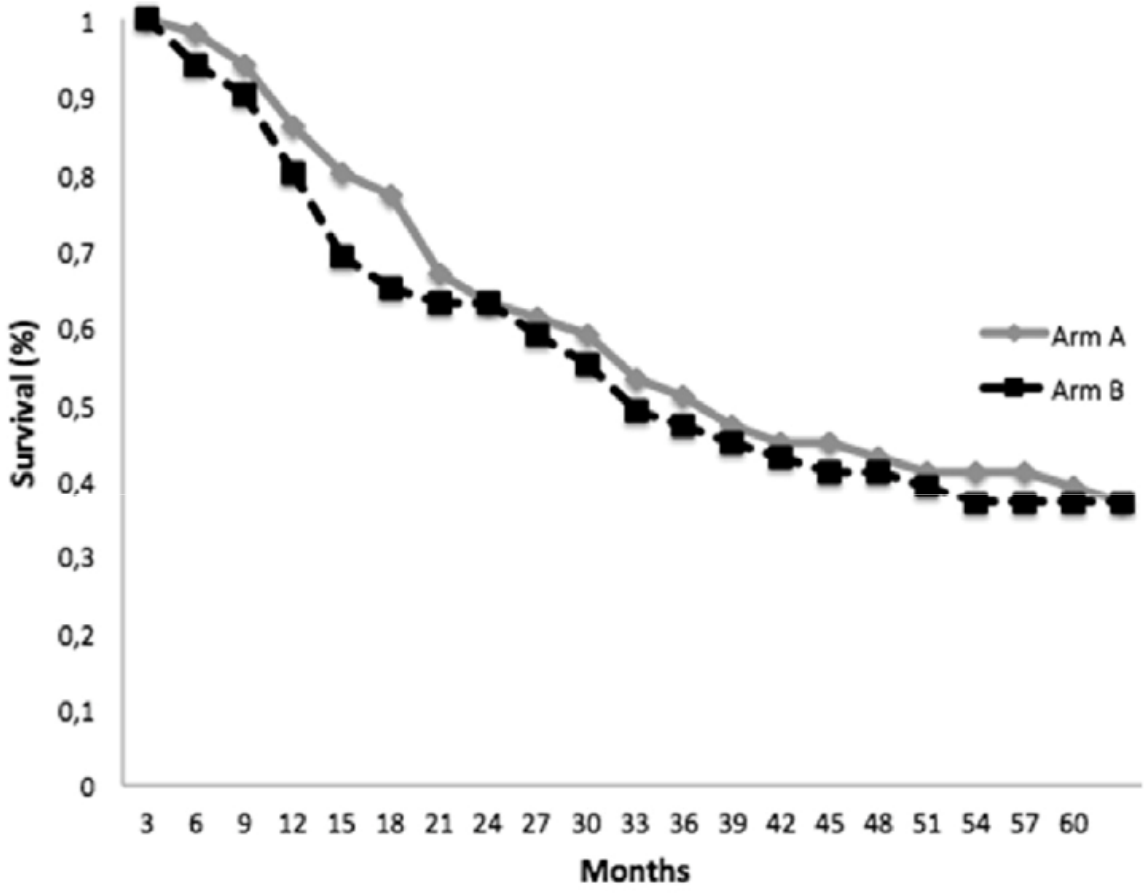
Overall survival rates.

	Total study population	Arm A	Arm B	*P*-value
Total	102 (100%)	51 (50%)	51 (50%)	–
Mortality	65 (63.7%)	32 (62.7%)	33 (65.7%)	0.837
6-month (%)	94 (92.2%)	48 (94.1%)	46 (90.2%)	0.461
1-year (%)	76 (74.5%)	41 (80.4%)	35 (68.6%)	0.173
2-year (%)	61 (59.8%)	31 (60.8%)	30 (58.8%)	0.840
5-year (%)	38 (37.3%)	19 (37.3%)	19 (37.3%)	1.000
Median (months)	31.5 (12.8–52.3)	33.0 (17.0–57.0)	30.0 (11.0–52.0)	0.722

P-values ≤ 0.05 were considered statistically significant.



Arm A	51	50	48	44	41	39	34	32	31	30	27	26	24	23	23	22	21	21	21	20
Arm B	51	48	46	41	35	33	32	32	30	28	25	24	23	22	21	21	20	19	19	19

Overall survival

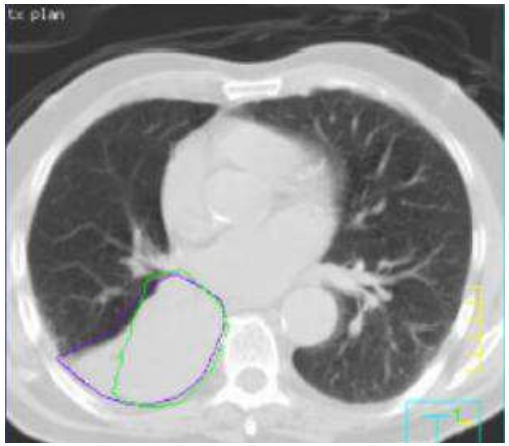
	Raditux trial	RTOG 0617 60 Gy	RTOG 0617 74 Gy
Mortality	64%*	58%[a]	67%[a]
6-month OS (%)	92%	89%	87%
1-year OS (%)	75%	78%	69%
2-year OS (%)	60%	53%	42%
5-year OS (%)	37%	-	-
Median OS (months)	32 months	29 months	20 months

*based on 5-years of follow-up
[a]based on 2-years of follow-up

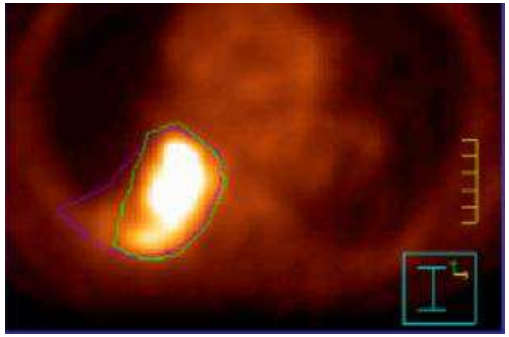
What is the preferred dose-fractionation schedule?

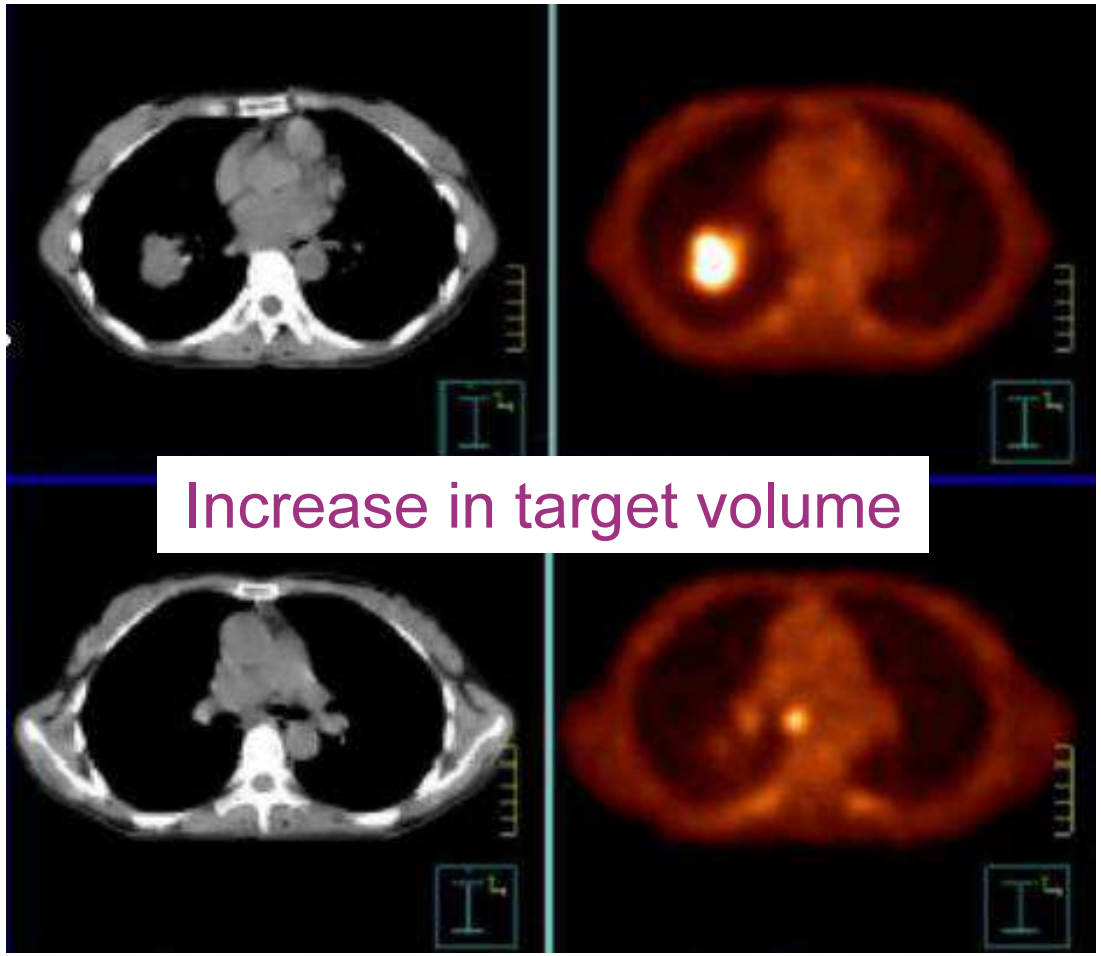
- 60 Gy in 30 fractions is still the standard dose
- A slight hypofractionated regimen (66 Gy/24 fractions, EORTC) may be considered as a valid alternative

GTV delineation: use of CT-PET



Decrease in target volume

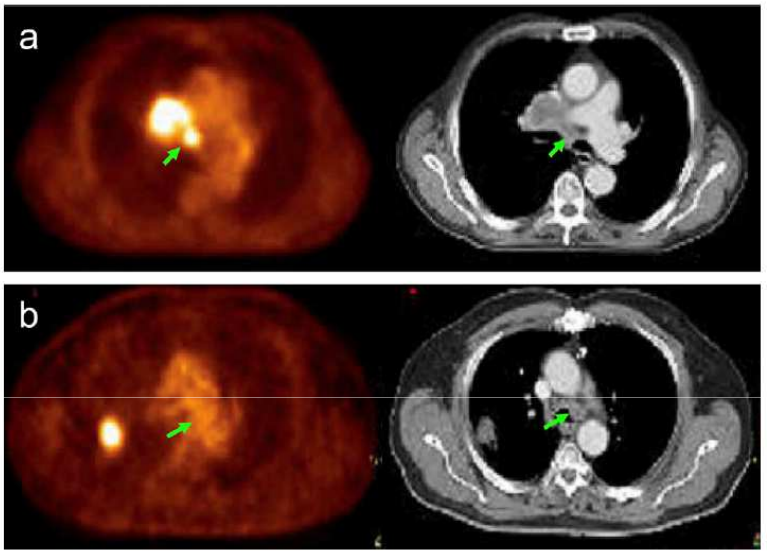




Increase in target volume

PET-guided nodal contouring definitely supports the use of Involved Fields RT

Recurrence	Patients (n)
None	**21 (35)**
Local	**9 (15)**
In field	3 (5.0)
Out of field	4 (6.7)
Both in field and out of field	2 (3.3)
Isolated local	2 (3.3)
Local and distant/nodal	7 (11.7)
Nodal	**20 (33.3)**
In field	8 (13.3)
Out of field	7 (11.7)
Both in field and out of field	5 (8.0)
Isolated nodal	2 (3.3)
Nodal and distant/local	18 (30.0)
Distant	**34 (56.7)**
Isolated distant	19 (31.7)
Distant and local/nodal	15 (25.0)
Isolated brain	9 (15.0)



60 patients included
3% of isolated nodal relapse

Van Loon, De Ruysscher IJROBP 2010

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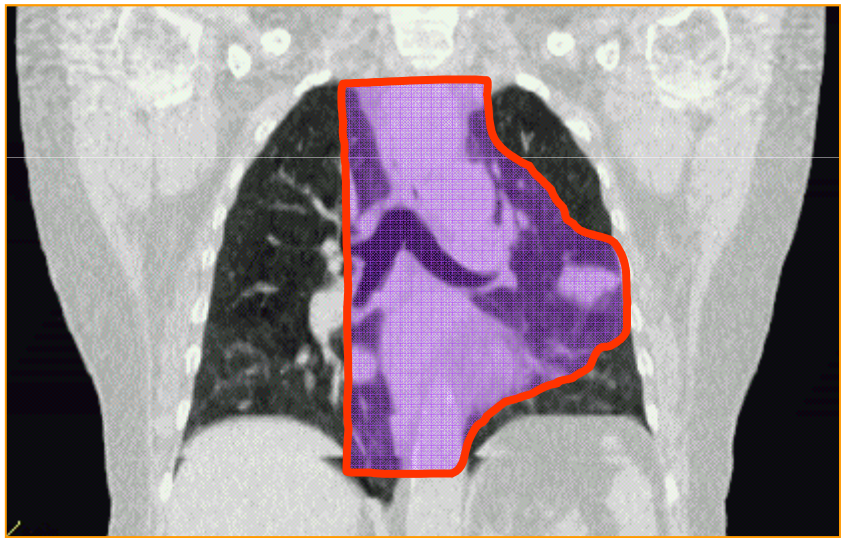
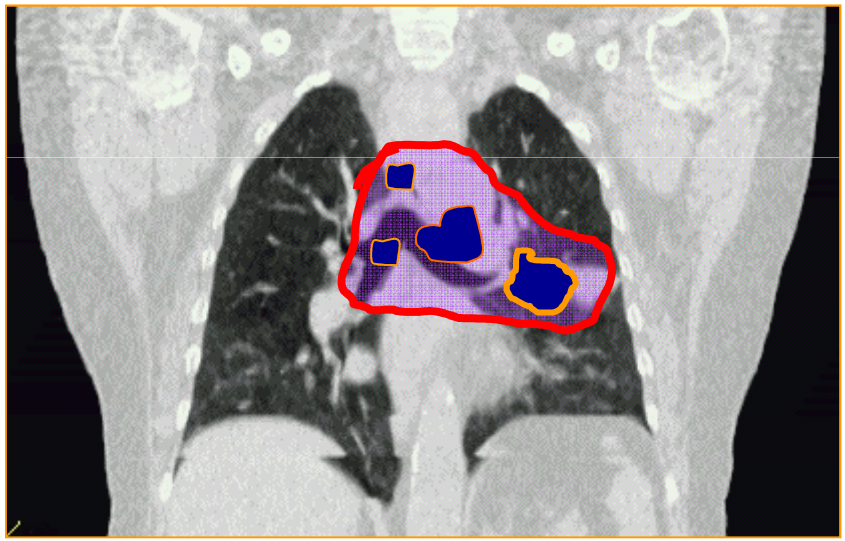
Avoiding ENI

Elective nodal RT



Involved-field RT



RT volumes: EORTC reccomendations

Table 2. EORTC Recommendations for Planning and Delivery of High-Dose, High-Precision Radiotherapy for Lung Cancer (continued)

Variable	Recommendation Grade
CTV	
A fixed, 5-mm CTV margin may be used, although adjustment according to the histology of the primary tumor and the size of the lymph nodes may be done	2B
Adjustment of the CTV according to normal tissues (eg, the bones) may be appropriate	2B
PTV	
Although many viable options to generate the PTV have been described, tumor delineation in the middle or average ventilation position with calculated adequate margin appears to be a feasible and appropriate strategy	1C
Adjustment of the PTV is not permitted, as the PTV takes into account set up errors and breathing motion	1C
PRV	
The use of a PRV margin around critical serial organs should be encouraged	2B

De Ruysscher et al, for EORTC, J Clin Oncol 2010

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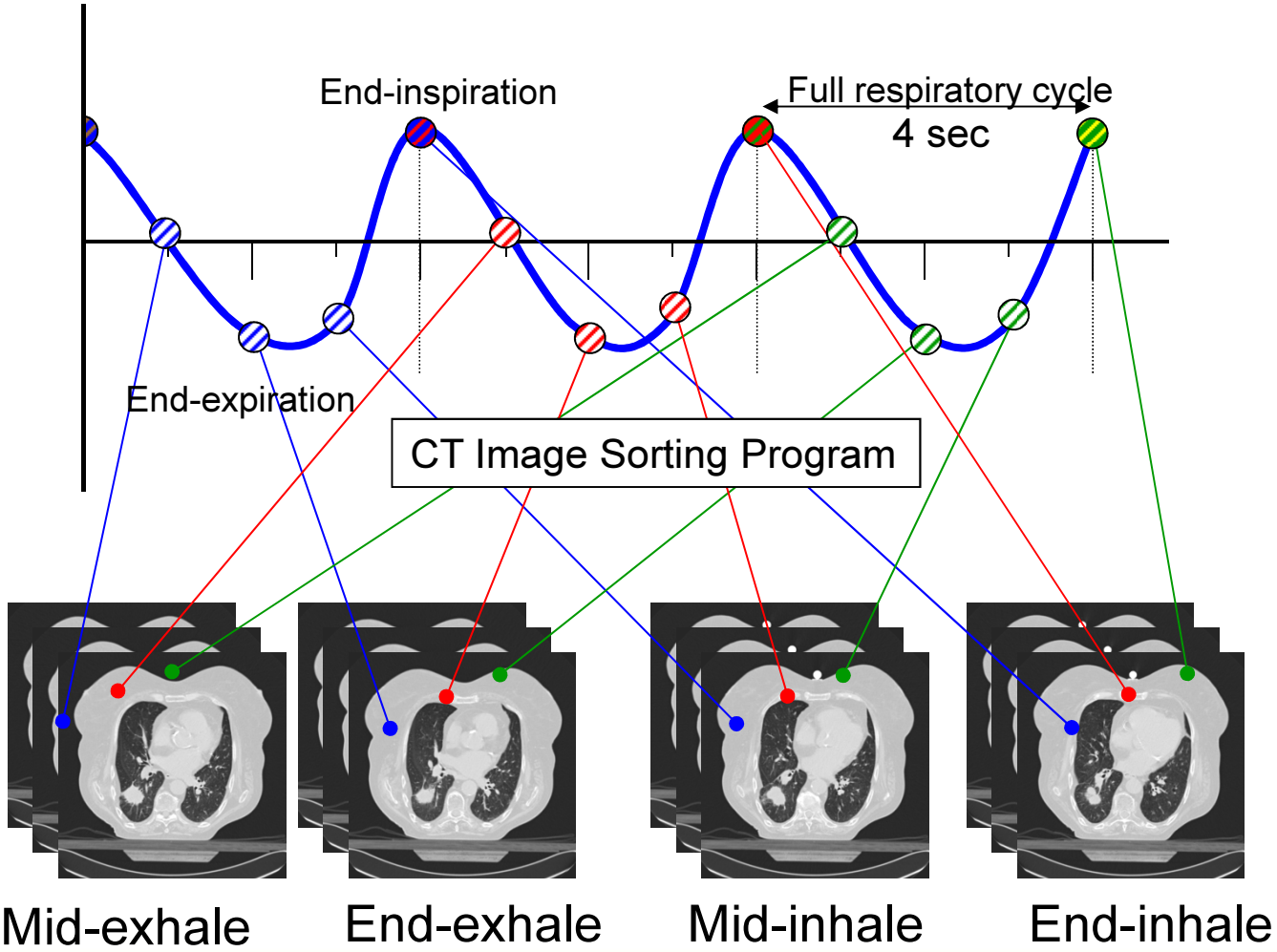
Four dimensions CT (4D-CT)



Up to 20 respiratory 'bins' are obtained

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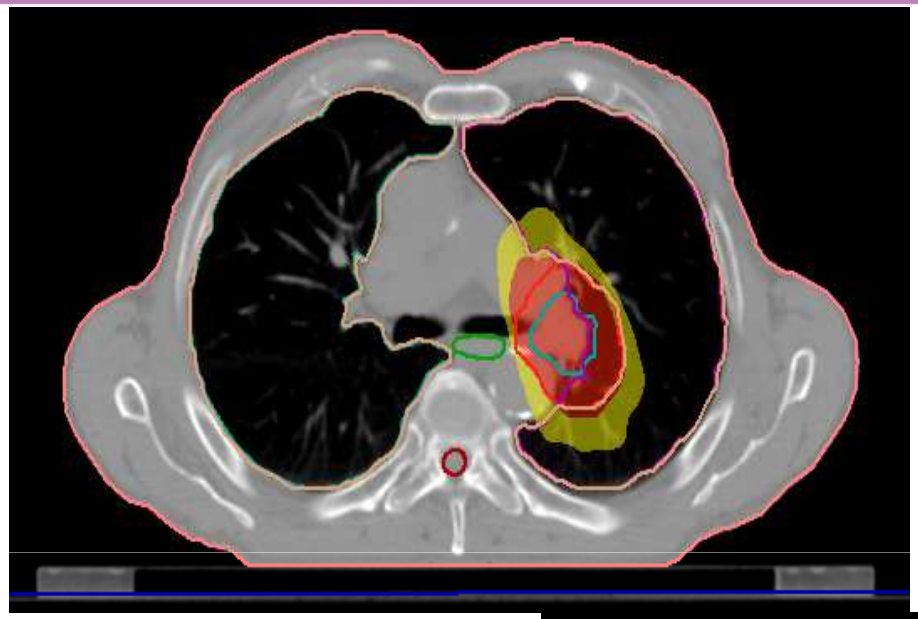
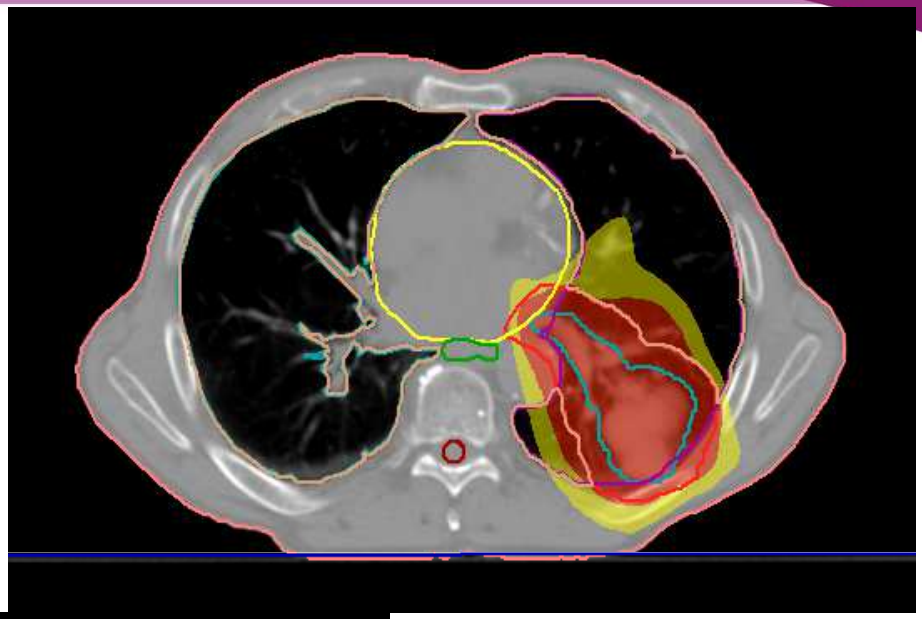
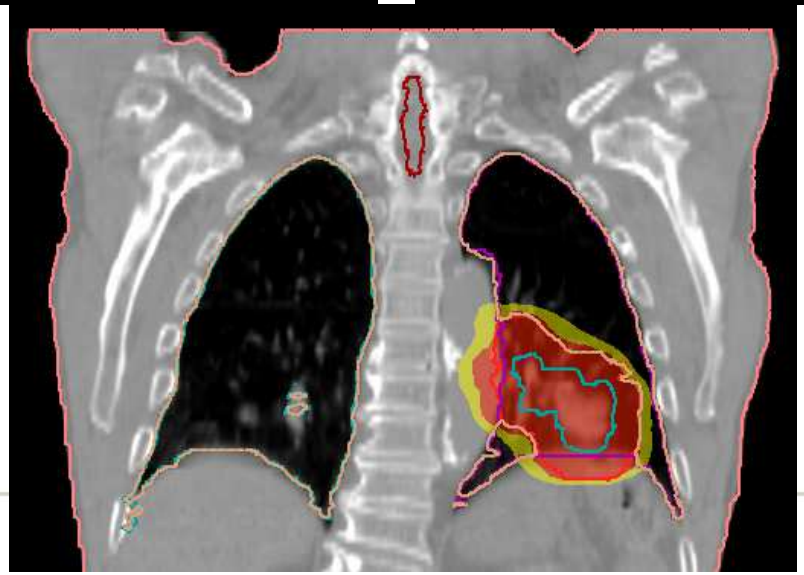
IMRT for locally advanced lung cancer







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3D vs IMRT: PTV

Murshed IJROBP 2004 (sliding window)	41 pts PTV: 623cc (75-1645)	Conformity Index 3D vs IMRT: 1.54 vs 1.41 ($p<0.01$) (IMRT benefit ≈ 21%)
Liu IJROBP 2004 (sliding window)	10 pts PTV: 403 (65-762)	3D IMRT IMRT benefit: CI min 1.33 vs 1.07 20% CI max 4.53 vs 2.09 54% CI med 2.35 vs 1.37 42% p=0.012
Christian IJROBP 2007 (step and shoot)	10 pts PTV 197 (103-271 cc)	PTV90/V20 IMRT benefit ≈ 25% (12-36%); 50% IMRT non planar or 9 fields

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3D vs IMRT: PTV

HOMOGENEITY INDEX by RTOG: Mean Dose/Presc Dose

HI95: D5-D95/dose mean (Palma IJROBP 2008)

Murshed IJROBP 2004	41 pts Stage IIIA-IIIB PTV: 623cc (75-1645) Upper location	Homogeneity Index 3D vs IMRT: 1.16 vs 1.12 ($p<0.01$) (<IMRT ≈ 3%)
Liu IJROBP 2004	10 pts Stage I-IIIB PTV: 403 (65-762)	HI min 1.09 vs 1.06 HI max 1.22 vs 1.23 HI med 1.14 vs 1.15 p=0.813

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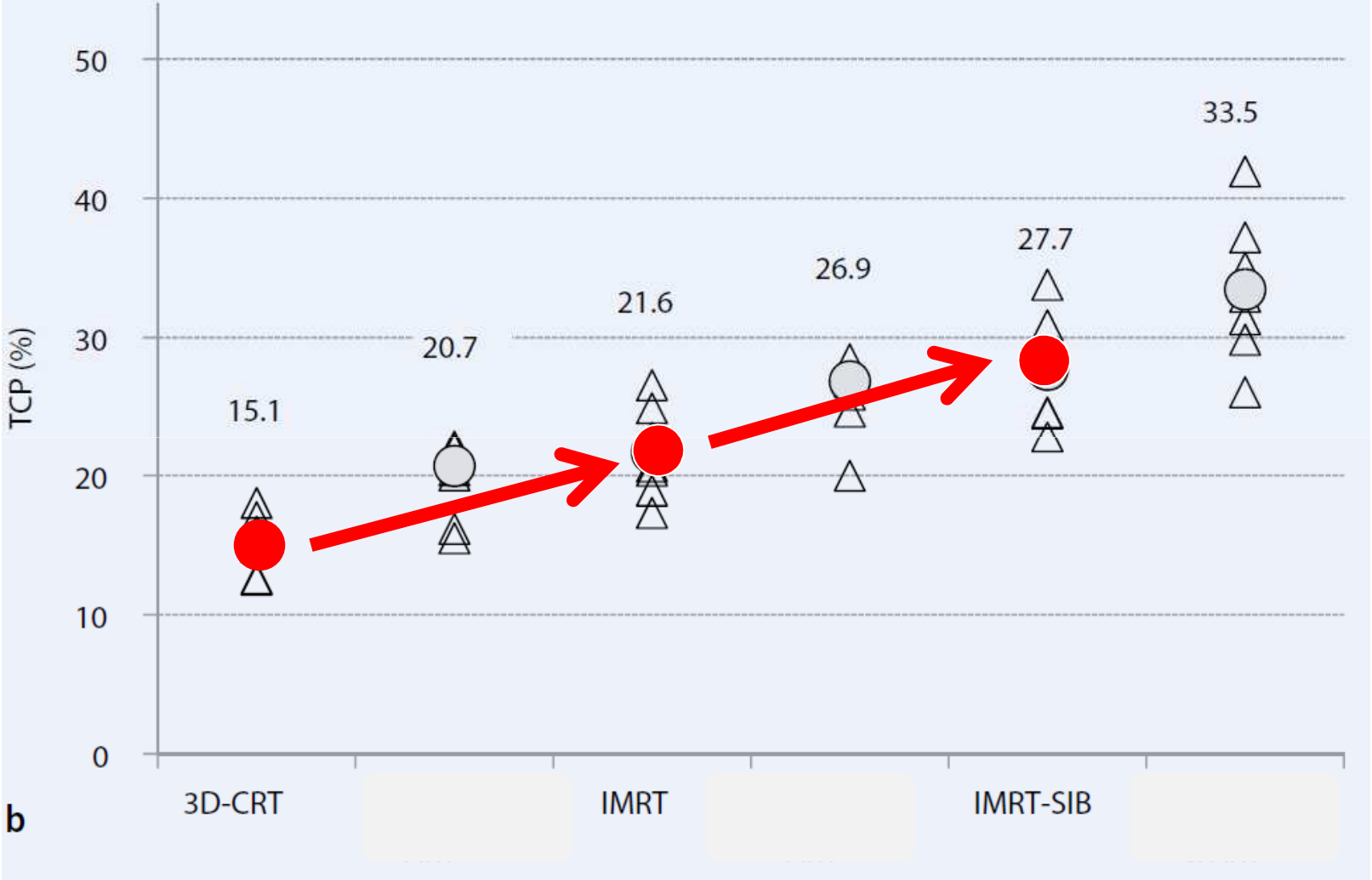
3D vs VMAT-TOMO: PTV

Cattaneo Radiot Oncol 2008	13 pts PTV 215-745cc	PTV95%: 3D vs TOMO 92% vs 97.2% (p<0.01)	Dose distribution: 3D vs TOMO 2.4 vs 1.4 (p<0.01) (TOMO benefit 42%)
Rousseau Cancer Radioth 2012	10 pts PTV 723 (392-885 cc)	Conformity index: 3D 0.55±0.07 vs VMAT 0.89±0.07 (VMAT benefit 60%)	

3D vs IMRT: PTV Dose escalation in the target

Schwartz IJROBP 2005	“Dose heterogeneity is an option to further escalate the dose in the target rather than a price to pay for using IMRT” Dose escalation 3D vs IMRT: 6% vs 17-35%
Grills IJROBP 2003	Dose escalation: IMRT>>25-30%
St Hilare Radiot Oncol 2009	Dose escalation: >78 Gy in 5/7 cases

Tumor Control Probability: 3D vs IMRT-SIB PTV boost



Guckenberger M, Strahl Onkol 2012; 188:894-900

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Remarks on IMRT for LA lung cancer

- IMRT in comparison with 3D dose distribution to the target in locally advanced NSCLC allows to:

1. benefit in conformity index
2. possibility of heterogeneity

3D vs. IMRT: lung DVHs

Murshed IJROBP 2004	41 pts Stage IIIA-IIIB PTV: 623cc (75-1645) Upper location	V5: 52 vs 59 (ns) V10: 45 vs 38 (p<0.01) (IMRT benefit 7-10%) V20: 35 vs 25 (p<0.01) (IMRT benefit 7-10%) MLD 19 vs 17 Gy NTCP: 36 vs 9% (Burman);13 vs 7% (Hyman)
Grills IJROBP 2003	Node - Node +	V20: 25.6 vs 23.6% 36.3 vs 23.6% (IMRT benefit ≈ 15%) MLD: 15.3 vs 15.4 Gy 21.5 vs 15.4
Liu IJROBP 2004	Stage I-IIIB 10 pts	V5: 3D benefit 8% V10: IMRT benefit 1.6% V20: IMRT benefit 8% V30: IMRT benefit 8.9%

3D vs. IMRT: lung DVHs

Rousseau Cancer Radioth 2012	10 pts PTV 723 (392-885 cc)	V5: 13% higher VMAT V20: 24 vs 20 (p<0.01) V30: 20 vs 14 (p<0.01) MLD 14 vs 12.2 Gy		
Cattaneo Radiot Oncol 2008	13 pts PTV: 215-745	Dmean: V5: V10: V15: V20: V30:	20.4 vs 16.8 Gy 67.4 vs 70.4% 56.4 vs 54.2% 43.1 vs 37.4% 33.5 vs 25.8% 27 vs 17.5%	p=0.001 p= 0.61 p=0.694 p=0.013 p= 0.002 p=0.001
Scrimger AMJCO 2003	5 pts PTV 169cc (132-280)	TOMO: Mean lung dose reduction of 31% (10-53%) Mean V20 reduction of 22% (17-37%)		

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Comparative studies on clinical outcomes following either 3D-CRT or IMRT

Comparison	Dose [median] (range)	Total number of patients	Disease stage
YOM 2007: 4DCT + IMRT + chemotherapy	63 Gy [50–72 Gy]	91	Stage I–III (80% stage III)
YOM 2007: 3DCRT* + chemotherapy	63 Gy [50–73]	318	Stage I–III (87% stage III)
LIAO 2010: IMRT + chemotherapy	63 Gy/1.8 Gy/fraction [50.4–76 Gy]	68	Stage II–IV (85% stage III)
LIAO 2010: 3DCRT + chemotherapy	63 Gy/1.8 Gy/fraction [50.4–69.6 Gy]	222	Stage II–IV (90% stage III)

YOM 2007	V20 (median)	Local control (%)		Disease-free survival (%)		Overall survival (%)	
		6 month	12 month	6 month	12 month	6 month	12 month
IMRT + chemotherapy	35% (3–48)	93.5	55.3	66.7	32.1	78.8	57
3DCRT + chemotherapy	38% (8–78) $P < 0.001$	NR	NR	NR	NR	NR	NR

LIAO 2010	V20	Locoregional progression-free rate (%)	Distant metastasis-free rate (%)	Median survival (months)
IMRT + chemotherapy	34.4% (33–36)	NR (estimated as about 78% at 2 years)	NR (estimated as about 48% at 2 years)	16.8
3DCRT + chemotherapy	37% (36–38) $P = 0.0013$	NR (estimated as about 65% at 2 years) $P =$ ns	NR (estimated at about 50% at 2 years) $P =$ ns	10.2 $P = 0.039$

Bezjak A, Clin Oncol 2012; 24: 508-520

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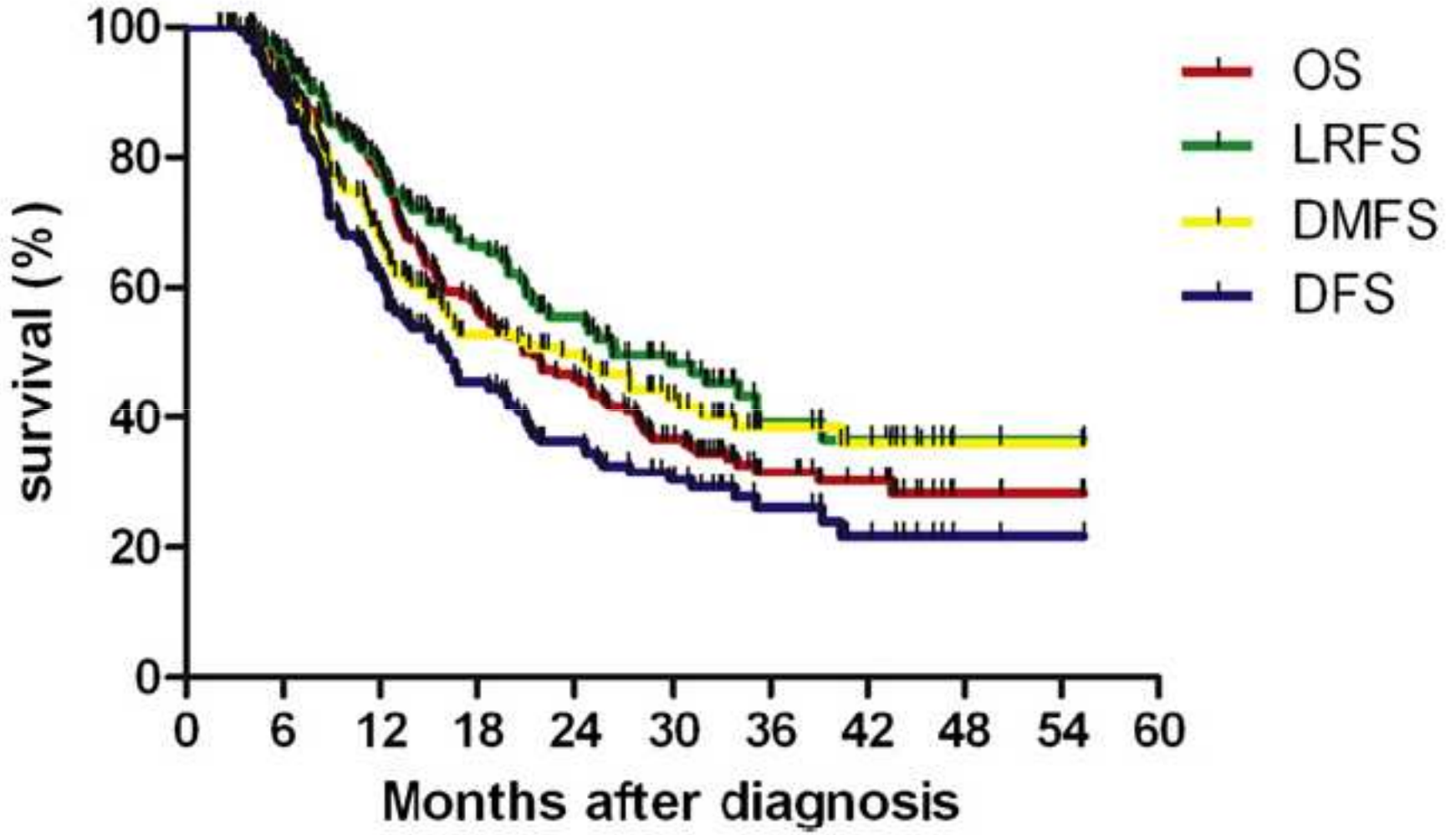
Long term clinical outcomes of IMRT in NSCLC



Jiang et al, Int J Radiat Oncol Biol Phys 2011

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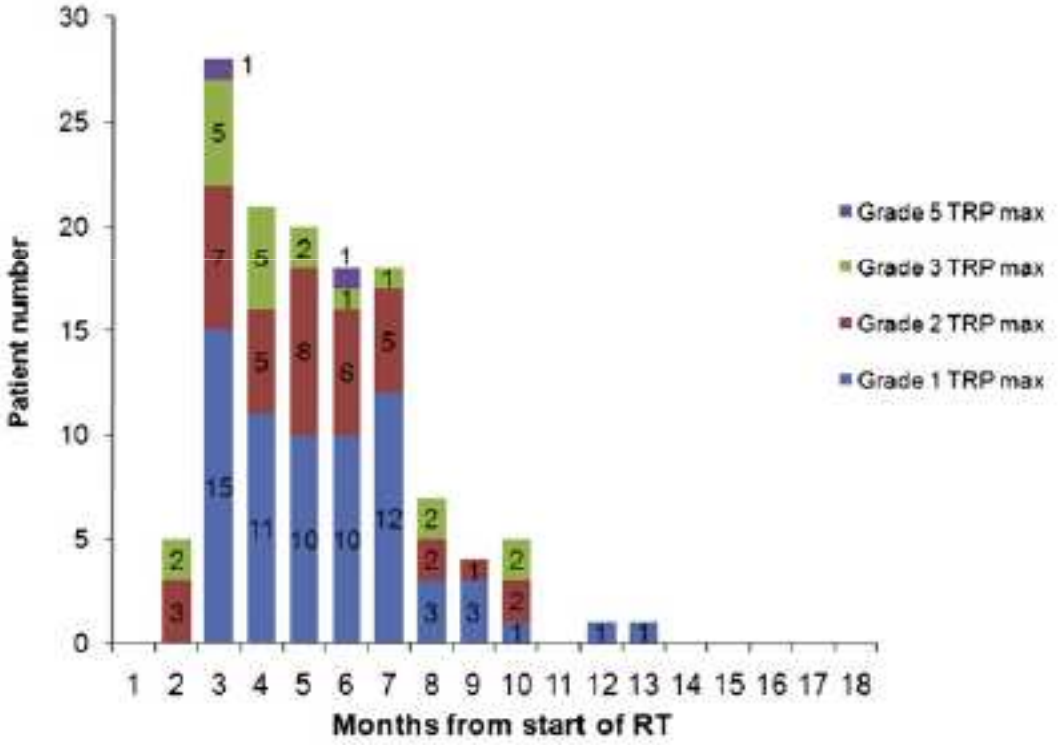
Long term clinical outcomes of IMRT in NSCLC

Toxicity	Patients, n (n = 165)	%
First recorded TRP		
Grade 0	37	22
Grade 1	98	59
Grade 2	23	14
Grade 3	7	4
Grade 4	0	0
Grade 5	0	0
TRP_{max}		
Grade 0	37	22
Grade 1	67	41
Grade 2	39	24
Grade 3	20	12
Grade 4	0	0
Grade 5	2	1
$Esophagitis_{max}$		
Grade 0	20	12
Grade 1	0	0
Grade 2	116	70
Grade 3	29	18
Grade 4	0	0
Grade 5	0	0
$Dermatitis_{max}$		
Grade 0	9	5
Grade 1	92	56
Grade 2	51	31
Grade 3	13	8
Grade 4	0	0
Grade 5	0	0



Jiang et al, Int J Radiat Oncol Biol Phys 2011

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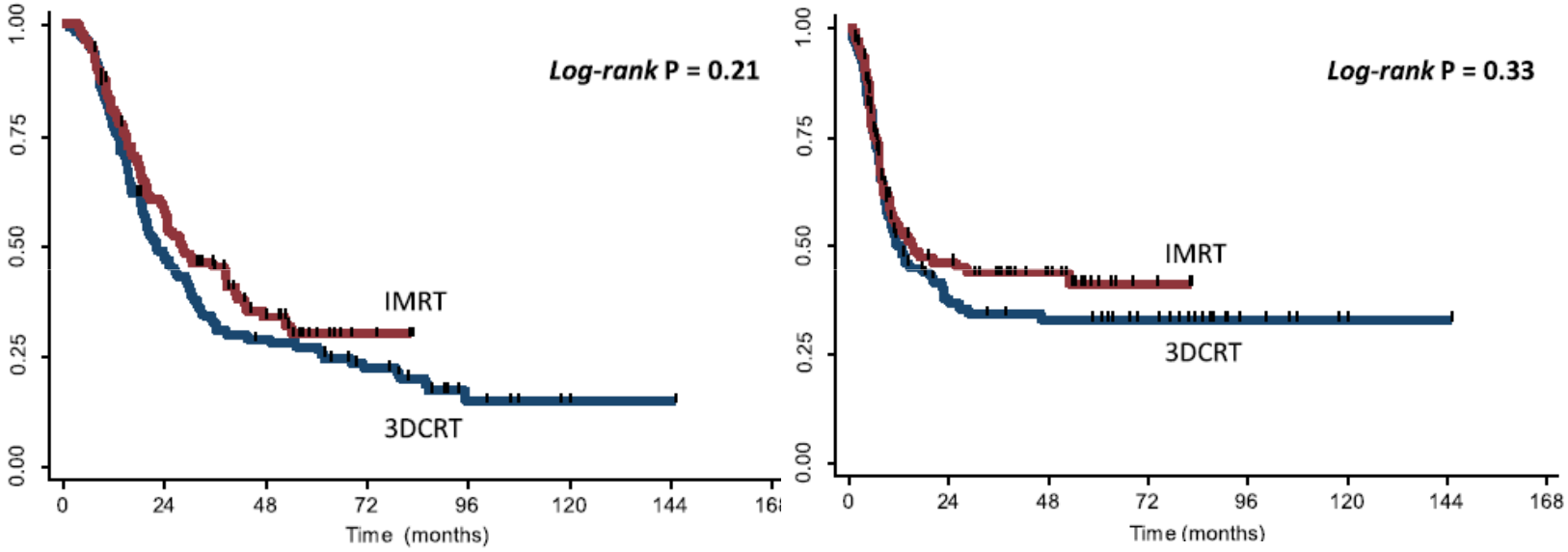
Comparison of 2 Common Radiation Therapy Techniques for Definitive Treatment of Small Cell Lung Cancer



IMRT patients required significantly fewer percutaneous feeding tube placements (5% vs 17%, respectively, p<.005).

Shirvani, IJRBOP 2013; 87: 139-147

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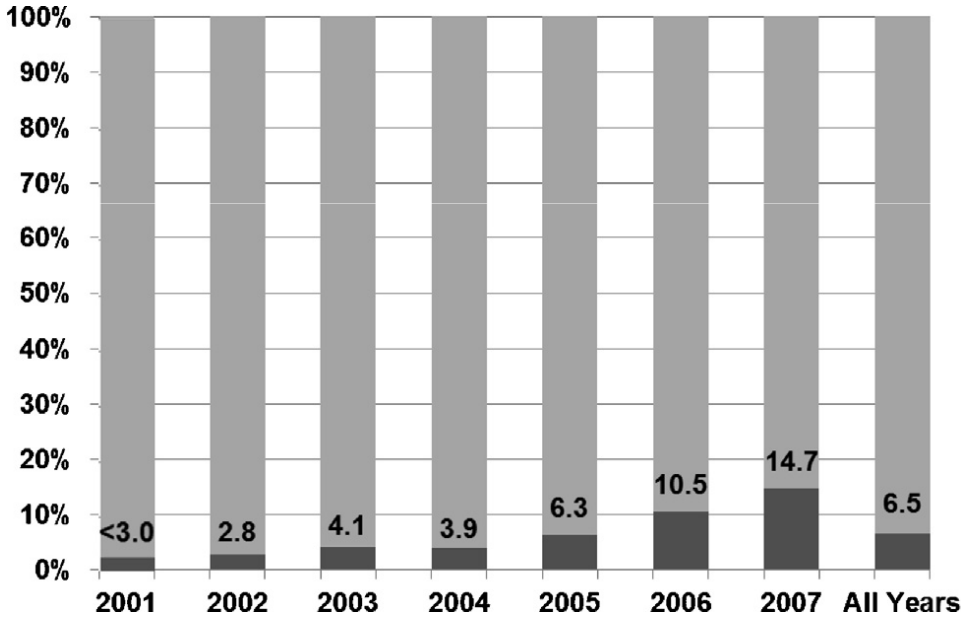
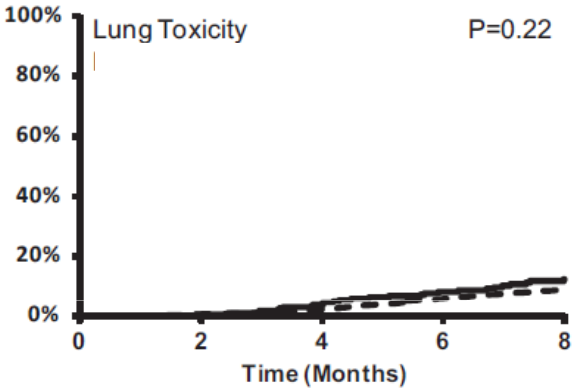
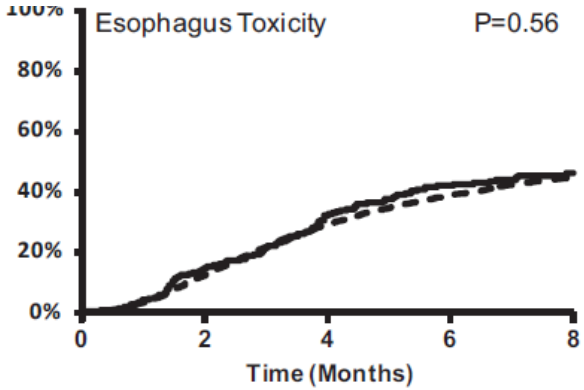
IMRT for NSCLC: toxicity outcomes

Surveillance, Epidemiology and End Results (SEER-) Medicare Records

3986 patients stage III Lung Cancer 2001-2007 (257 IMRT (6.5%)







Shirvani SM, Lung Cancer 2013; 82: 252-259

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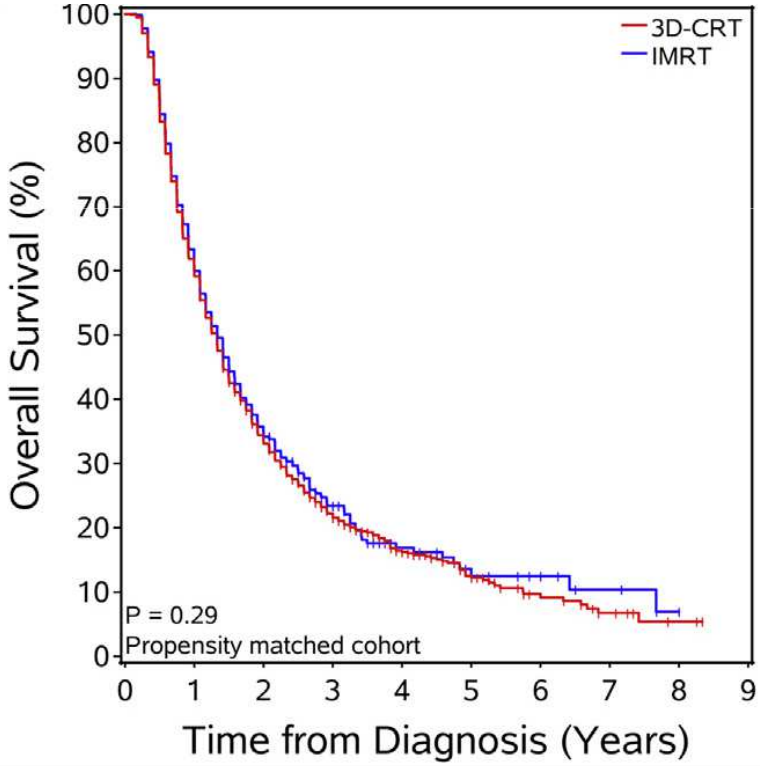
IMRT for NSCLC: survival outcomes

Surveillance, Epidemiology and End Results (SEER-) Medicare Records

6894 patients stage III Lung Cancer 2002-2009 (716 IMRT (10%)



Summary of hazard ratios for IMRT versus 3D-CRT (reference)

	Multivariate adjusted HR (95% CI)	*P*
OS	0.94 (0.85-1.04)	.23
CSS	0.94 (0.85-1.05)	.28
Early UGI toxicity	1.01 (0.87-1.19)	.86
Late UGI toxicity	0.94 (0.87-1.01)	.08
Early pulmonary toxicity	1.14 (0.92-1.43)	.23
Late pulmonary toxicity	1.22 (0.82-1.83)	.33
Cardiac toxicity	0.88 (0.64-1.21)	.44

IMRT is associated with similar toxicities while maintaining good outcomes

Harris JP, IJROBP 2014

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IMRT for NSCLC: clinical outcomes

Outcomes of Intensity Modulated and 3D-Conformal Radiotherapy for Stage III Non-Small Cell Lung Cancer in NRG Oncology/RTOG 0617

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September 8, 2015

IASLC 40 YEARS

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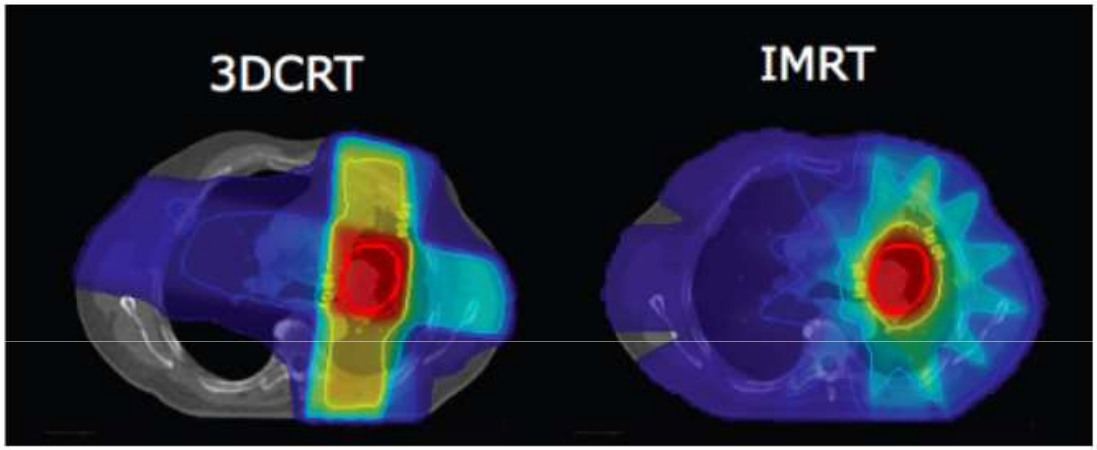
IMRT for NSCLC: clinical outcomes

STUDY RATIONALE/HYPOTHESIS

High
60+ Gy
Intermediate
20 - 50 Gy
Low
5 Gy



- Rationale
  - IMRT improves target conformity and reduces both high and intermediate dose volumes
  - Exchange for large low-dose bath
- Hypothesis: IMRT may improve outcomes in Stage III NSCLC

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938: Outcomes of intensity modulated and 3D-conformal radiotherapy for Stage III NSCLC in NRG/RTOG 0617 – Stephen G. Chun, M.D.

Hu C et al, IALSC 2015

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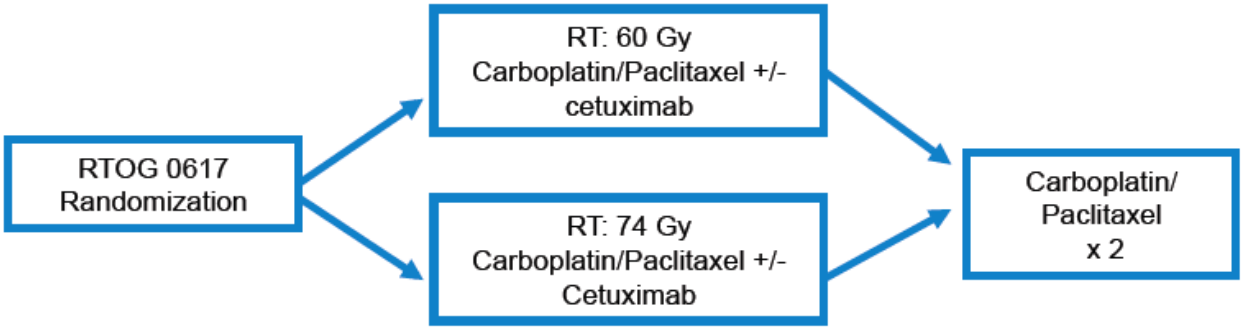
IMRT for NSCLC: clinical outcomes

STUDY METHODS

Secondary Analysis of NRG/RTOG 0617



Compared RT technique in Univariate and Multivariate Analyses

- Stratified: 3D-CRT 53%, IMRT 47% in both RT dose arms
- Endpoints of secondary analysis
  - Survival – overall, progression free, local control
  - Grade 3+ toxicity
  - Amount of chemotherapy administered

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IMRT for NSCLC: clinical outcomes

RESULTS

Baseline Characteristics

Deck stacked against IMRT

Characteristic	3D-CRT	IMRT	P-value
Stage IIIB	30%	39%	0.056
PTV	427 mL	486 mL	0.005
PTV:lung ratio	0.13	0.15	0.013

IMRT likely selected prior to randomization to treat more "difficult" tumors

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IMRT for NSCLC: clinical outcomes

RESULTS

Effect of radiation technique on 2-year outcomes

Multivariate analysis 3D-CRT (reference) vs. IMRT

Outcome	OR (95% CI)	P-value
Overall survival	1.01 (0.8, 1.28)	0.95
Progression free survival	1.12 (0.91, 1.39)	0.28
Local control	0.91 (0.67, 1.23)	0.54
Distant metastasis free	0.92 (0.71, 1.19)	0.52

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Overall and progression free survival similar
in spite of more unfavorable tumors in IMRT group

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Hu C et al, IALSC 2015

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RESULTS

Benefits of IMRT

Outcome	3D-CRT	IMRT	P-value
Grade 3+ pneumonitis	8%	3.5%	0.0462
Heart V40	11.4%	6.8%	0.0026
Full consolidative chemotherapy	29%	37%	0.05

Esophagitis, weight loss, cardiovascular, neurologic adverse effects similar in IMRT and 3D-CRT

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IMRT for NSCLC: clinical outcomes

RESULTS

Multivariate Predictors of Grade 3+ pneumonitis

Co-variate	Comparison	OR (95% CI)	P-value
Technique	3D-CRT vs IMRT	0.44 (0.18, 1.04)	0.0621
Stage	IIIA vs. IIIB	2.35 (1.05, 5.29)	0.0385
Lung V20	Continuous	1.081 (1.02, 1.146)	0.009

Low dose bath bigger with IMRT

Lung V5 – IMRT 62% vs. 3D-CRT 55% ($P < 0.0001$)

Lung V5 did not predict pneumonitis, P = 0.14, OR 1.02, 95% CI (0.994, 1.04)

MLD did not predict pneumonitis

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IMRT for NSCLC: clinical outcomes

CONCLUSIONS

- **IMRT Patient Outcomes**
  - Similar OS and PFS in spite of worse tumors
  - Improved Toxicity
  - Better tolerance of chemotherapy

- **Radiation Treatment planning**
  - Lung doses – V20 was significant
    (Lung V5/MLD was not)
  - Heart doses can be reduced with IMRT

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Hu C et al, IALSC 2015

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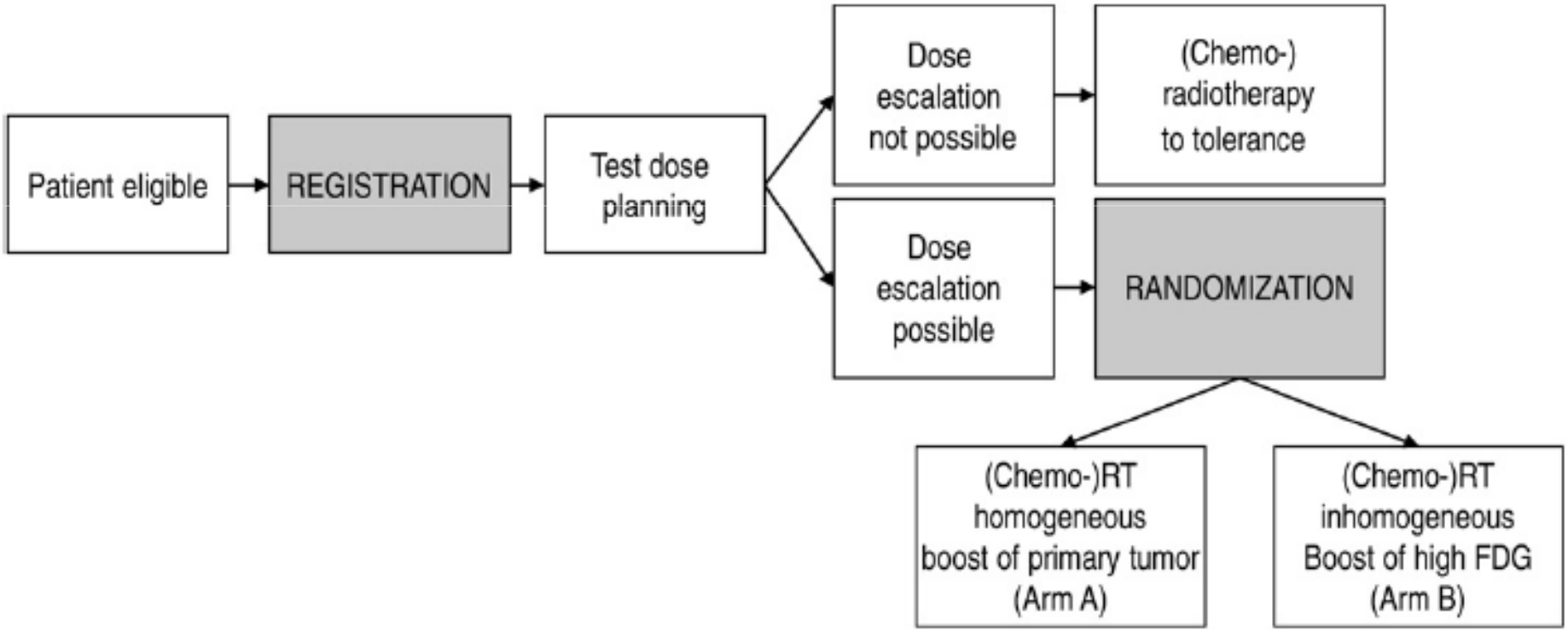
The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer

Wouter van Elmpt [a,*], Dirk De Ruysscher [a], Anke van der Salm [a], Annemarie Lakeman [b], Judith van der Stoep [a], Daisy Emans [a], Eugène Damen [b], Michel Öllers [a], Jan-Jakob Sonke [b], José Belderbos [b]

[a] *Department of Radiation Oncology, Maastricht University Medical Centre, Maastricht;* [b] *Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands*



Van Elmpt et al, Radiother Oncol 2012

Table 2
Dose parameters for the target structures.

Parameter	No escalation possible [$N = 5$]	Uniform boost (arm A) (arm A) [$N = 15$]	PET boost (arm B) (arm B) [$N = 15$]	p-value*
Prescribed dose/24 fractions	2.75 [1 patient 23#] in primary tumour	3.27 ± 0.31 [3.01–4.28] in primary tumour	3.63 ± 0.54 [3.20–5.40] in boost volume	0.001
Mean PTV dose: primary tumour [Gy]	65.5 ± 1.5 [63.3–67.3]	77.3 ± 7.9 [70.2–103.4]	77.5 ± 10.1 [71.4–112.0]	0.950
Mean PTV dose: boost area [Gy]	N.A.	79.2 ± 8.0 [72.0 – 104.9]	86.9 ± 14.9 [74.9–134.9]	0.001
Min. PTV dose ($D_{99\%}$): primary tumour [Gy]	61.3 ± 2.9 [57.8–64.6]	66.7 ± 8.1 [55.0–92.4]	62.0 ± 3.3 [56.0–69.9]	0.001

* The p-values were calculated using a Wilcoxon-Signed Rank test.

Table 3
Dose parameters for the organs at risk.

Organ-at-risk	Dose constraint	Uniform boost (arm A)	PET boost (arm B)	p-value*	Dose-limiting arm A	Dose-limiting arm B
Mean lung dose [mean dose Gy]	20 Gy (corrected to EQD2)	15.8 ± 3.9 [7.3–19.7] (corrected to EQD2)	15.7 ± 4.0 [7.3–19.9] (corrected to EQD2)	0.038	3/15	2/15
	N.A. (physical dose)	16.7 ± 4.3 [7.8–21.5]	16.8 ± 4.4 [7.8–21.9]	0.340	3/15	2/15
PRV mediast. [$D_{0.1\%}$ Gy]	<76 Gy (=EQD2 of 94 Gy)	71.1 ± 11.4 [30.3–75.7]	72.1 ± 10.4 [34.9–76.8]	0.073	13/15	14/15
Spinal cord [$D_{0.1\%}$ Gy]	<51 Gy (=EQD2 of 53 Gy)	41.7 ± 8.4 [25.1–49.7]	42.0 ± 9.2 [22.1–50.1]	0.394	1/15	1/15
Oesophagus [V_{35Gy}]	<80%	38.8 ± 15.5 [10.7–62.8]	39.1 ± 15.8 [12.0–57.0]	0.727	0/15	0/15
Heart [mean dose Gy]	<47 Gy (=EQD2 of 46 Gy)	13.2 ± 12.8 [0.3–30.9]	12.4 ± 11.9 [0.3–29.7]	0.271	0/15	0/15
Brachial plexus [$D_{0.1\%}$ Gy] (if proximity of PTV)	<66 Gy (=EQD2 of 79 Gy)	54.2 ± 14.2 [23.7–65.6]	53.7 ± 16.2 [17.3–65.7]	0.778	3/15	3/15

* The p-values were calculated using a Wilcoxon-Signed Rank test.

Van Elmpt et al, Radiother Oncol 2012

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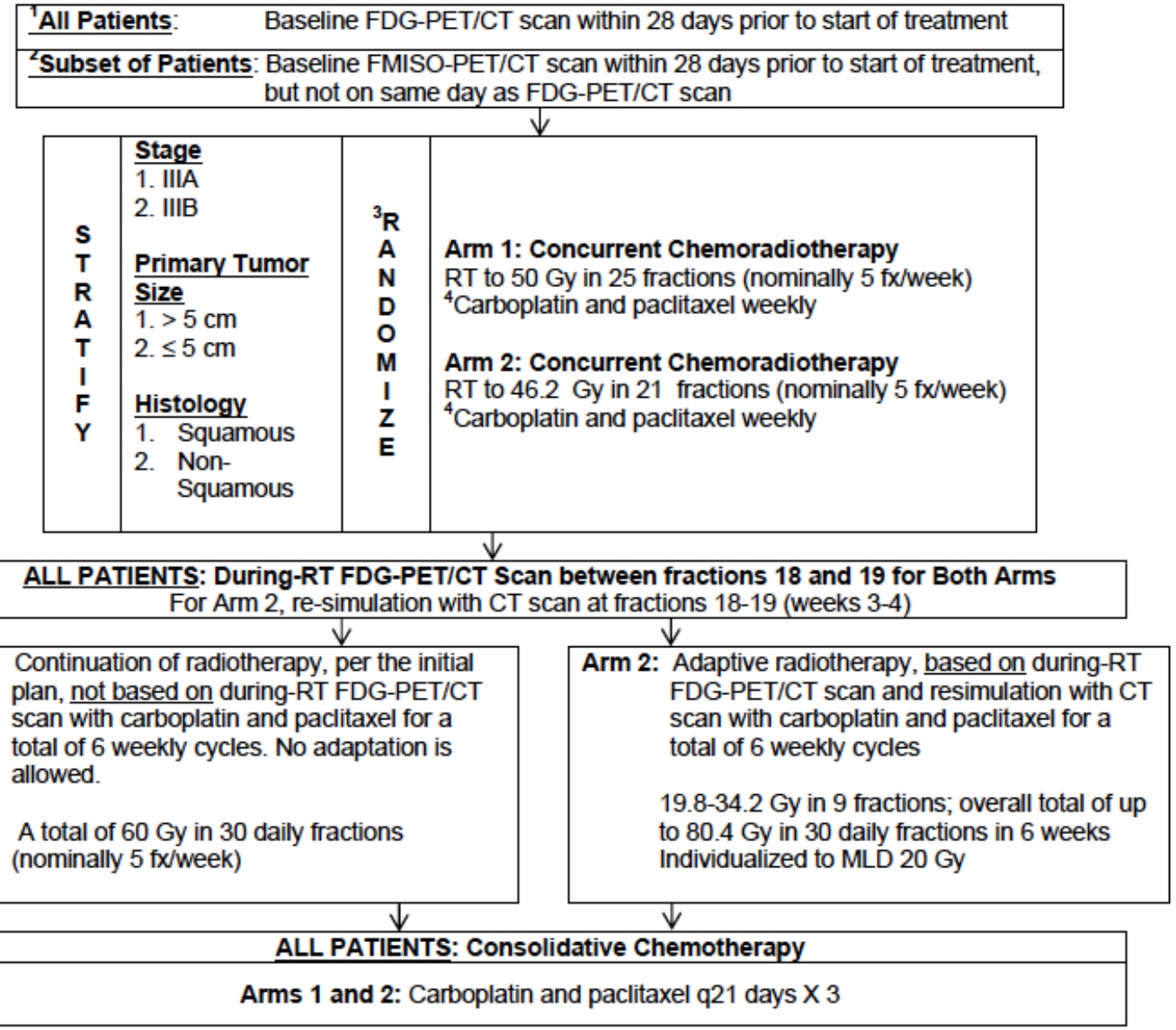
RTOG 1106



Van Elmpt et al, Radiother Oncol 2012

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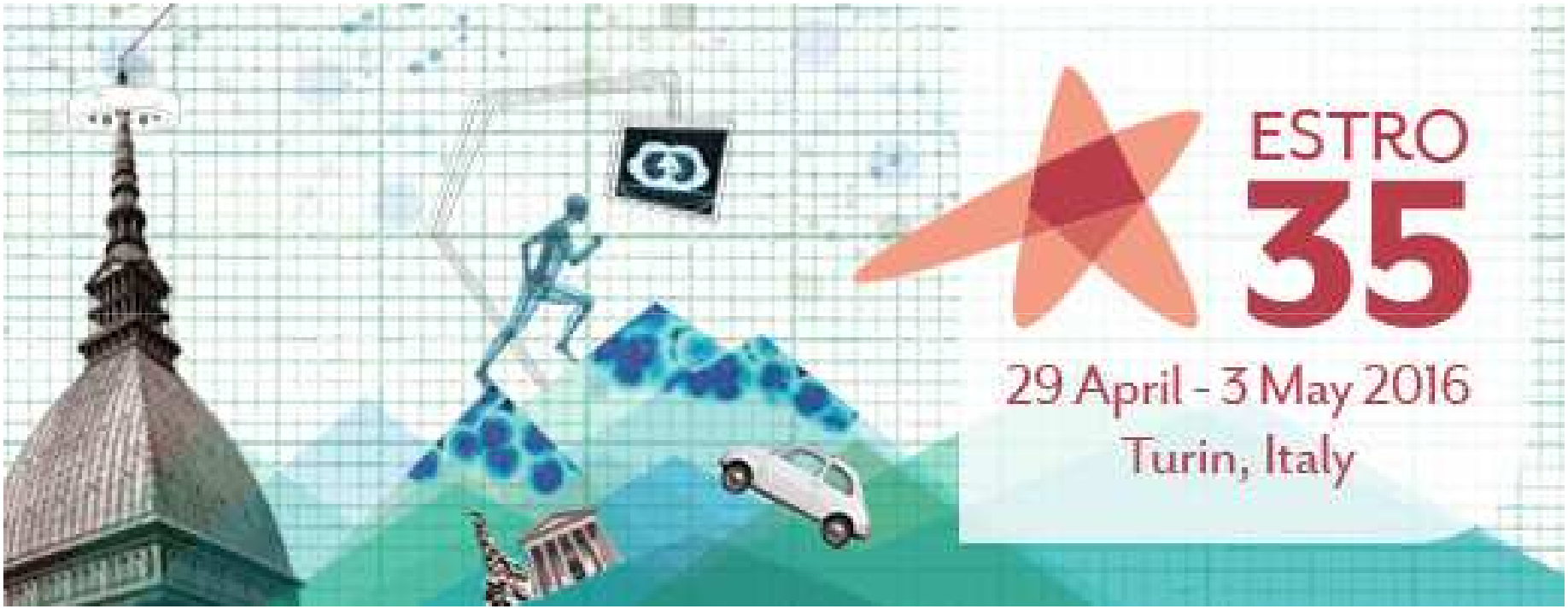
Remarks on IMRT for LA NSCLC

- IMRT is now an accepted standard for LA NSCLC radiotherapy
- IMRT could reduce V20 and heart dose
- IMRT could increase patients' compliance to chemotherapy
- Ongoing trials will clarify us the role of PET-guided hypo-fractionated boost and the best chemotherapy combination (these trials are made possible by the use of IMRT!)
- New drugs will hopefully amplify the benefit of the combined modality approach



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IMRT in Gynae and GI

Gemma Eminowicz

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- Dummies guide
- Upper GI IMRT
- Pelvic IMRT
- Important factors affecting IMRT

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Dummies guide to IMRT

- Better conformity to PTV
- Increased normal tissue sparing
- ?Less toxicity

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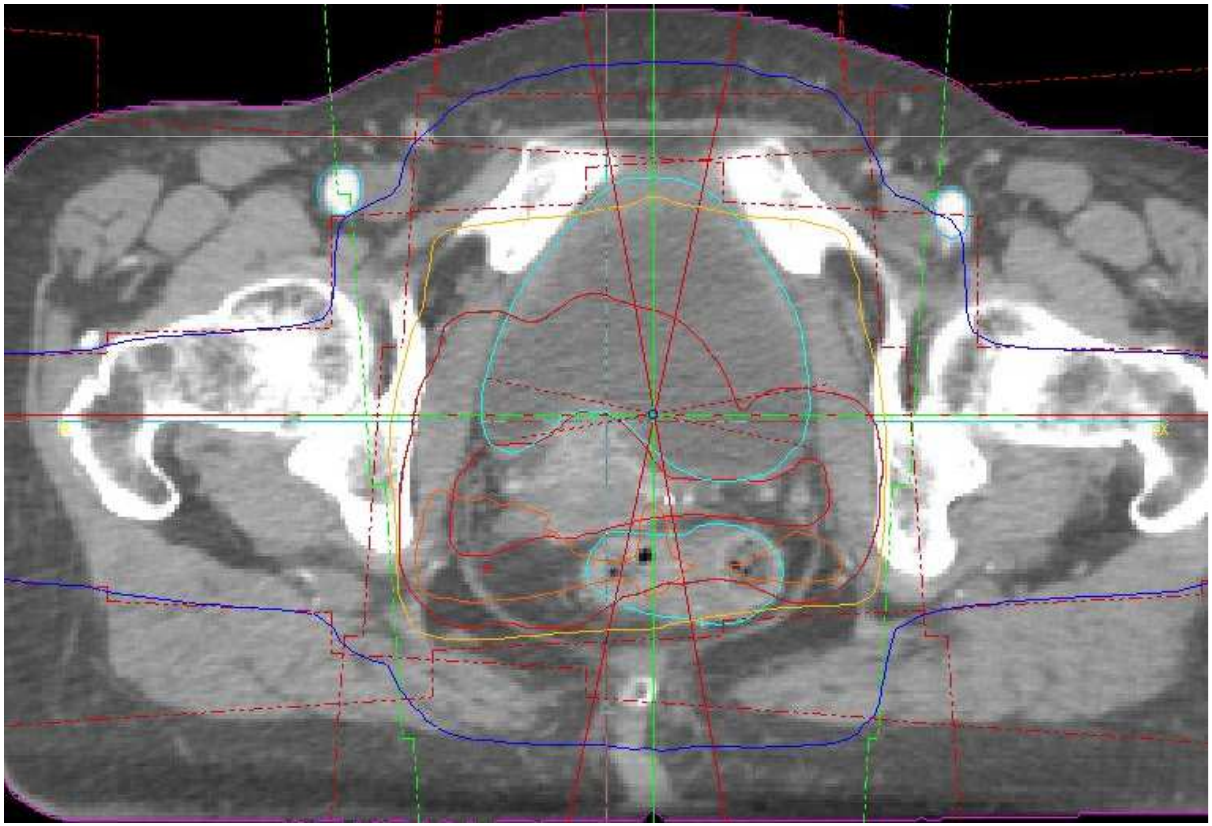
Dummies guide to IMRT

- Better conformity to PTV
- Increased normal tissue sparing
- ?Less toxicity



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Dummies guide to IMRT

- Better conformity to PTV
- Increased normal tissue sparing
- ?Less toxicity

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Dummies guide to IMRT

- Better conformity to PTV
- Increased normal tissue sparing
- ?Less toxicity

BUT

- Better conformity to the delineated PTV
- Planned on snapshot in time
- Balance of PTV dose vs OAR tolerance

Overview: Upper GI IMRT

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- Oesophageal
  - SCOPE 2 trial
  - Cervical tumours
- Pancreatic
  - SCALOP 2 trial

- Pneumonitis
- Hepatitis
- Renal function

- Neuropathy (cervical oesophageal tumours)

Overview: Upper GI IMRT

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- **Oesophageal**
  - SCOPE 2 trial
  - **Cervical tumours**

- Pancreatic
  - SCALOP 2 trial

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Oesophageal tumours

- 50Gy with concurrent chemo
- Cervical oesophageal tumours
  - Spinal cord sparing
- Lung sparing (mean dose)
- Heart sparing (V30, V45)

- Clinical benefit?
  - Less cardiac deaths

Nicolini et al IJROBP 2012;84(2):553. Lin et al IJROBP;84(5):1078

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Study of Chemoradiotherapy in Oesophageal cancer with PET and dose Escalation

Use of IMRT to dose escalate/paint

4D-CT planning

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Pancreatic tumours

- 50.4-60Gy/28-30# with concurrent chemo
- Small bowel sparing (D10%, D15%, V35, V45)
- Kidney sparing (mean, V20)
- Liver sparing (mean, V35)

- Clinical benefit?

Chapman, Med Dosim 2016 ahead of print

University College London Hospitals NHS
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Systemic therapy and Chemoradiation in Advanced LOcalised Pancreatic cancer 2

Recommend 4D-CT or motion management

IMRT priority: duodenum and bowel sparing

Overview: Upper GI IMRT

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- Oesophageal
  - SCOPE 2 trial
  - Cervical tumours
- Pancreatic
  - SCALOP 2 trial

- Pneumonitis
- Hepatitis
- Renal function
- Neuropathy (cervical oesophageal tumours)

PROBABLE CLINICAL BENEFIT

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Overview: Pelvic/abdo IMRT

- Lower GI
  - Anal cancer
  - Rectal cancer
- Vulval
  - Extrapolated from anal ca
- Endometrial
  - Post operative RT using ITV
- Cervical
  - Adaptive RT or ITV

- Bowel toxicity
- Cystitis
- Proctitis
- Haem toxicity
- Skeletal events
- Dermatitis

Overview: Pelvic/abdo IMRT

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- Lower GI
  - **Anal cancer**
  - Rectal cancer
- **Vulval**
  - Extrapolated from anal ca
- **Endometrial**
  - Post operative RT using ITV
- Cervical
  - Adaptive RT or ITV

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Rectal IMRT

- 45-50.4Gy/25-28# with chemotherapy
- 14 prospective studies
  - Reduced irradiated bowel volume (V45, V50)
  - Benefit depends upon bowel proximity to PTV
  - Some suggest improved acute toxicity
- Minimal late toxicity data

- RTOG 0822: Ph II evaluation of pre-operative CRT using IMRT with capox

Teoh Clin Oncol 2016;28:93-102

Rectal IMRT: RTOG 0822

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- Ph II evaluation of pre-operative CRT using IMRT with capox
- Prospective study of IMRT use
- Standardised RTOG contouring atlas
- 79 pts, 68 evaluable, 51% ≥G2 GI toxicity, 18% G3/4 diarrhoea
- NO reduction in rate of GI toxicity

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Hong IJROBP 2015;93:29

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Rectal IMRT

- Ph II evaluation of IMRT-IGRT pre-operative CRT with SIB
- Prospective study of IMRT use
- 108 patients, 54/12 FU
- 9% ≥G3 late gastrointestinal toxicity
- 4% ≥G3 late urinary toxicity
- 13% ≥G3 any late toxicity
- Good LC, survival

Engels et al, Radiother Oncol 2014;110:155-159

Anal IMRT

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- Dose variation
  - Elective dose 30/40Gy
  - T1 40-45Gy
  - T2 50-59
  - T3/4 59-66Gy
- Significant G3/4 toxicity causes delays in RT
  - Haem 61%, Derm 48%, GI 36%, GU 4%
- Published series showing reduced toxicity

Ajani JAMA 2008;299:1914

Anal IMRT

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- RTOG 0529
- Phase 2 dose painting study
- Stat sig lower G2 haem, G3 GI and derm toxicity

- Reduce dose to bowel, bladder, genitalia, bone
- www.analimrtguidance.co.uk

- Single phase IMRT delivered in 28 daily fractions
- 50.4Gy primary, 53.2 if T3/4, 40Gy elective nodes

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Kachnic et al, IJROBP 2013;8(1):27-33

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Vulval IMRT

- Extrapolated from anal
- Complex volume
- Skin and genitalia sparing
- Less acute toxicity therefore less delays in Rx

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Endometrial IMRT

- Post-operative 45Gy/25#
- RTOG 0418 (phase 2 haem toxicity)
- RTOG 0724 (adj chemo after adj CRT)
- ITV from bladder full and empty planning CT
- Reductions in bowel, bladder and rectum dose
- Bowel sparing affected by bladder filling status

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TIME-C trial

- Randomized Ph III Study Of Standard Vs. IMRT Pelvic Radiation For Post-Operative Treatment Of Endometrial And Cervical Cancer (TIME-C)--RTOG CCOP Study 1203

- Week 5 acute GI toxicity (PRO)
- Closed to recruitment 27/8/15 (289 pts)

Cervical IMRT

- 45-50.4Gy/25-28# with concurrent chemo
- Dosimetric benefits
  - Small bowel (V45 halved)
  - Bladder volume (V45 halved)
  - Rectal volume (V45↓7 fold)
  - Pelvic bone dose

Roeske, Radiother Oncol 2003;69:201, Portelance IJROBP 2001;51:261

Cervical IMRT cont

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Clinical benefits

- Stat sig reduced bowel tox (unmatched cohort)
  - Acute 95% to 53%; Chronic 50% to 11%
- Clin sig reduced genitourinary toxicity
  - 7% vs 16%
- Lower G2 white cell toxicity if chemo-RT
  - 60% vs 31%
- Bone complications/QoL

- PA nodal RT (cohorts only, bowel tox)
- Concurrent chemoradiation (haem tox)

Mundt,Gynecol oncol 2001;82:456,IJROBP2002;52:1330, Brixey IJROBP2002;54:1388

Cervical IMRT- Adaptive

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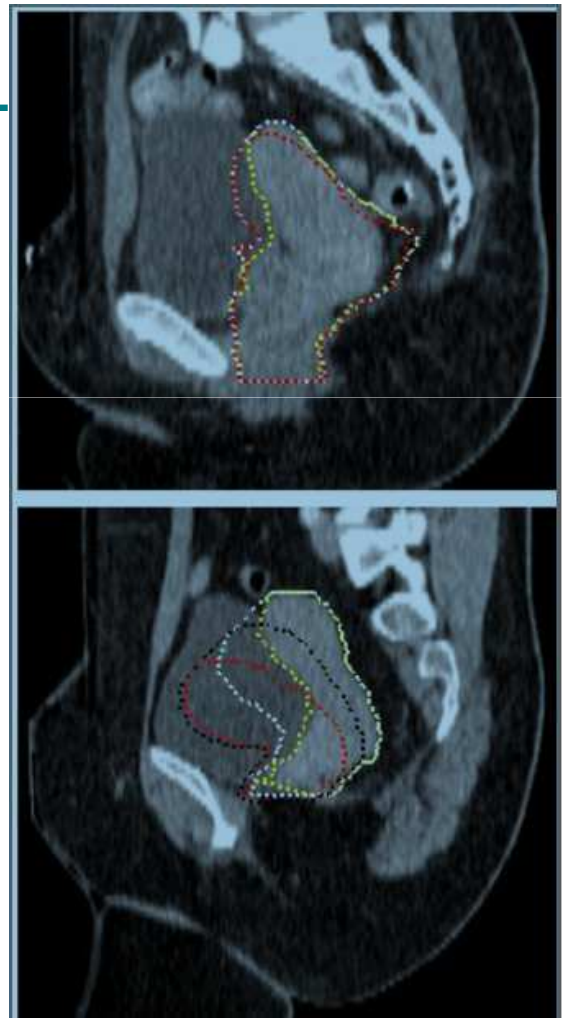
- ITV to cover all bladder filling
- Bladder full & empty planning CT
- Full and empty plan if ‘mover’
- Fiducial markers in cervix
- Soft tissue matching
- 3D-CRT back up plan (18%)
  - uterus out 27.5%
  - markers out 21.3%
  - both out 21.7%
  - poor CBCT 10.5%



Heijkoop, IJROBP 2014; 90: 673-679

Overview: Pelvic/abdo IMRT

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- Lower GI
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  - Adaptive RT for ITV
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CLINICAL BENEFIT

- Bowel toxicity
- Cystitis
- Proctitis
- Haem toxicity
- Skeletal events
- Dermatitis

Guerrero-Urbanno IJROBP 2006;65:907

Important factors affecting IMRT

- Delineation accuracy
- Organ position accuracy

- Tumour regression during RT
- Low dose radiation increase
- Second Cancer Risk

- Cost effectiveness

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Delineation

Delineation

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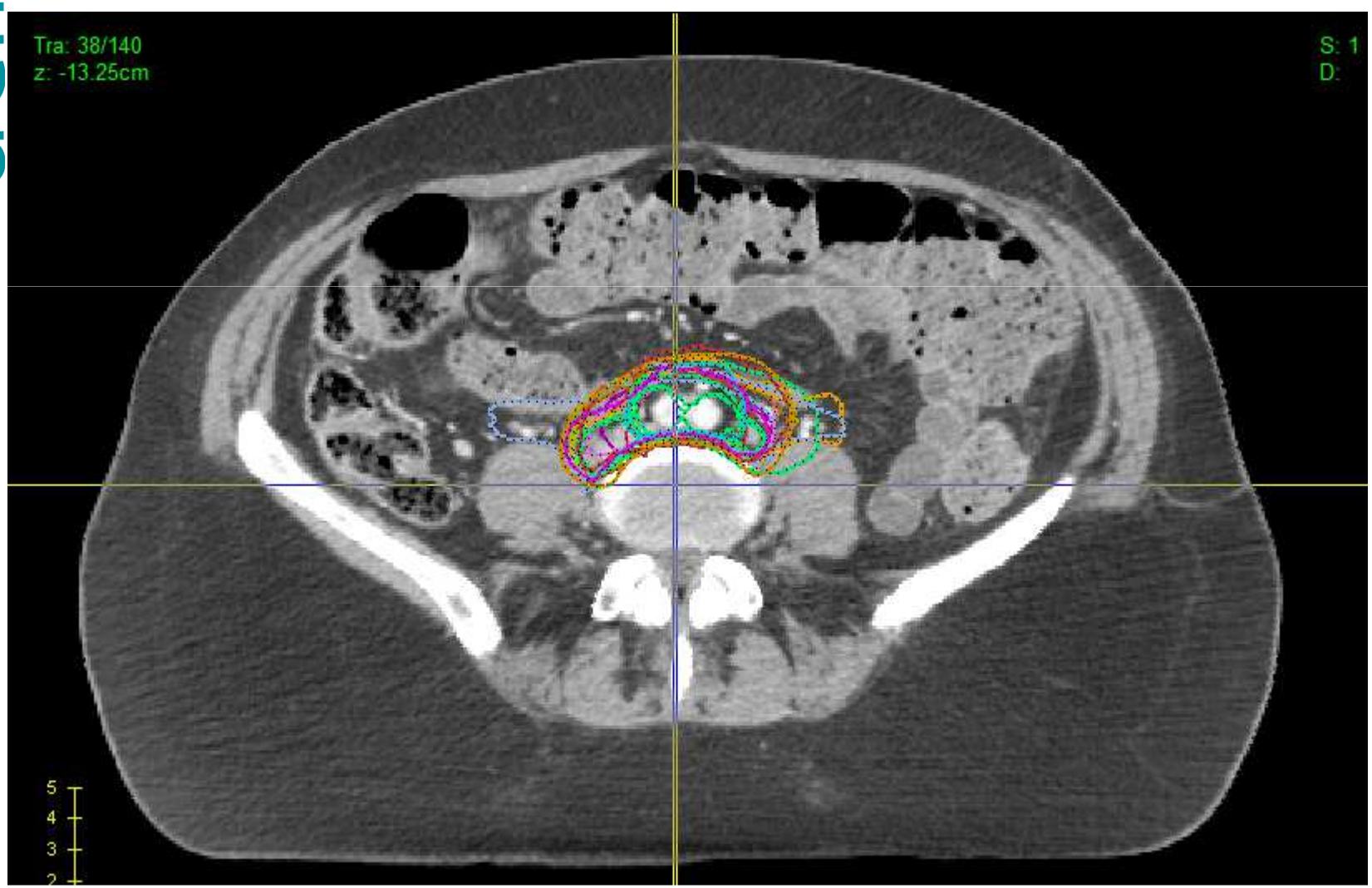

Delineation

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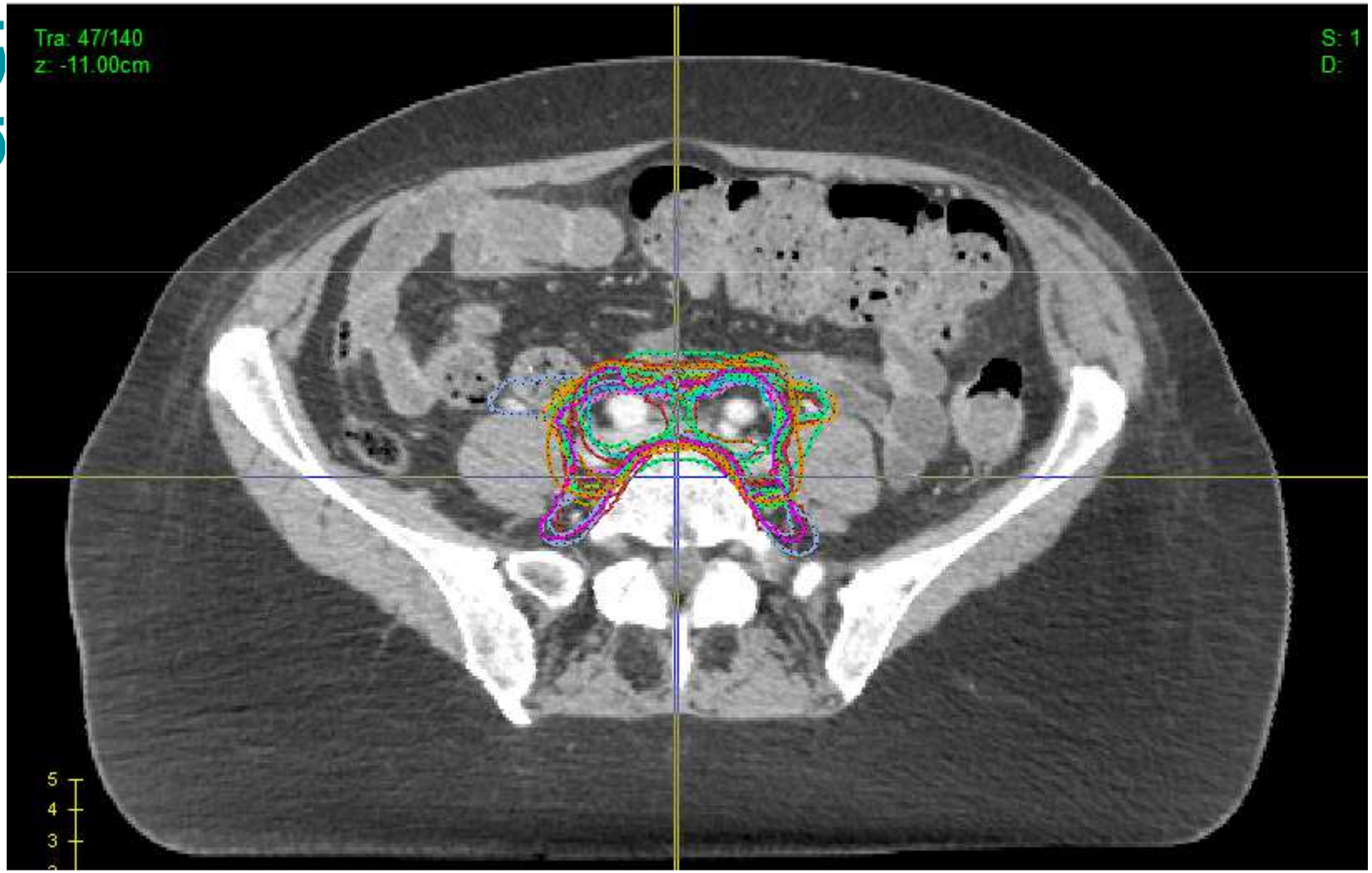

Delineation

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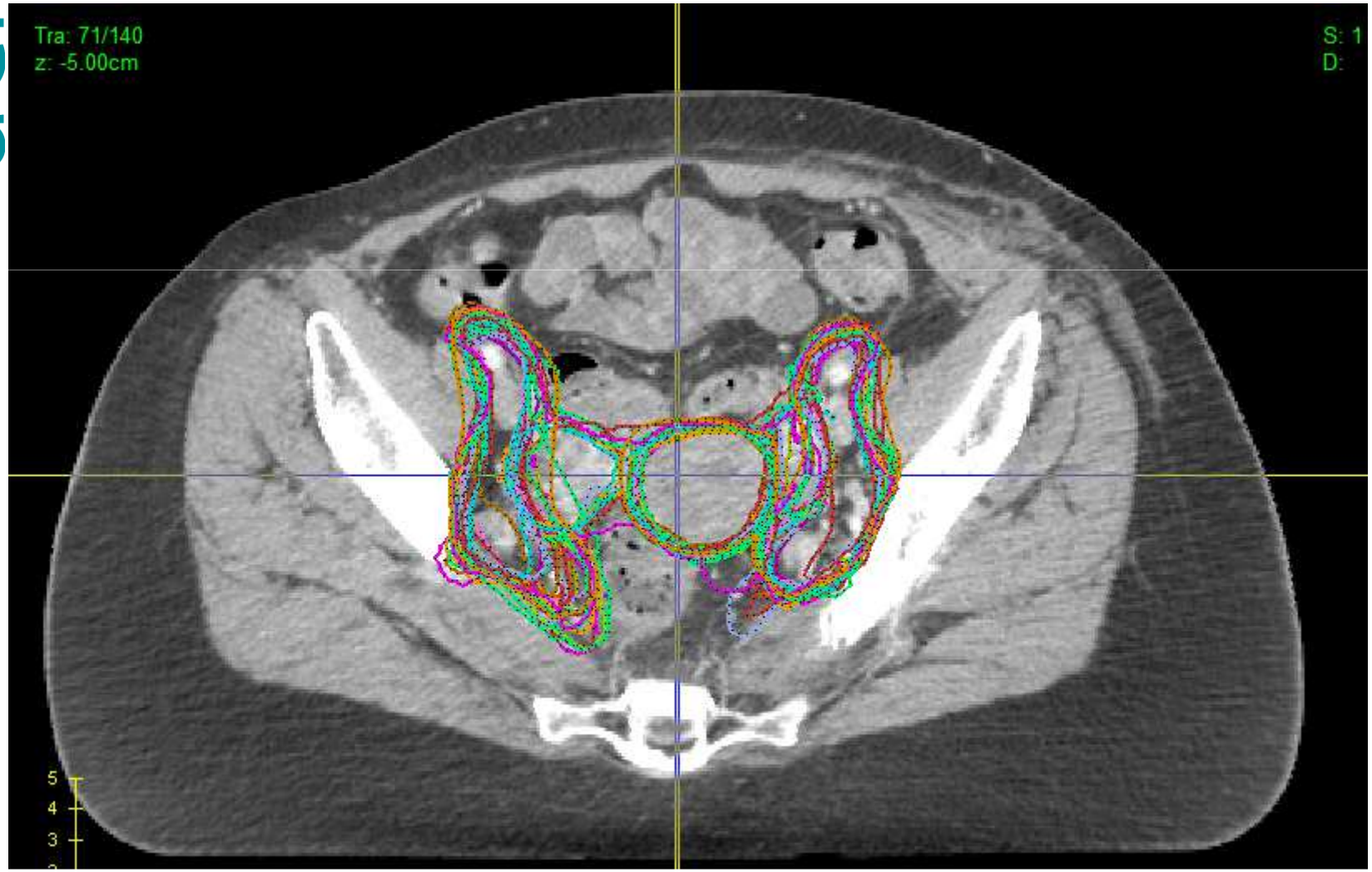

Delineation

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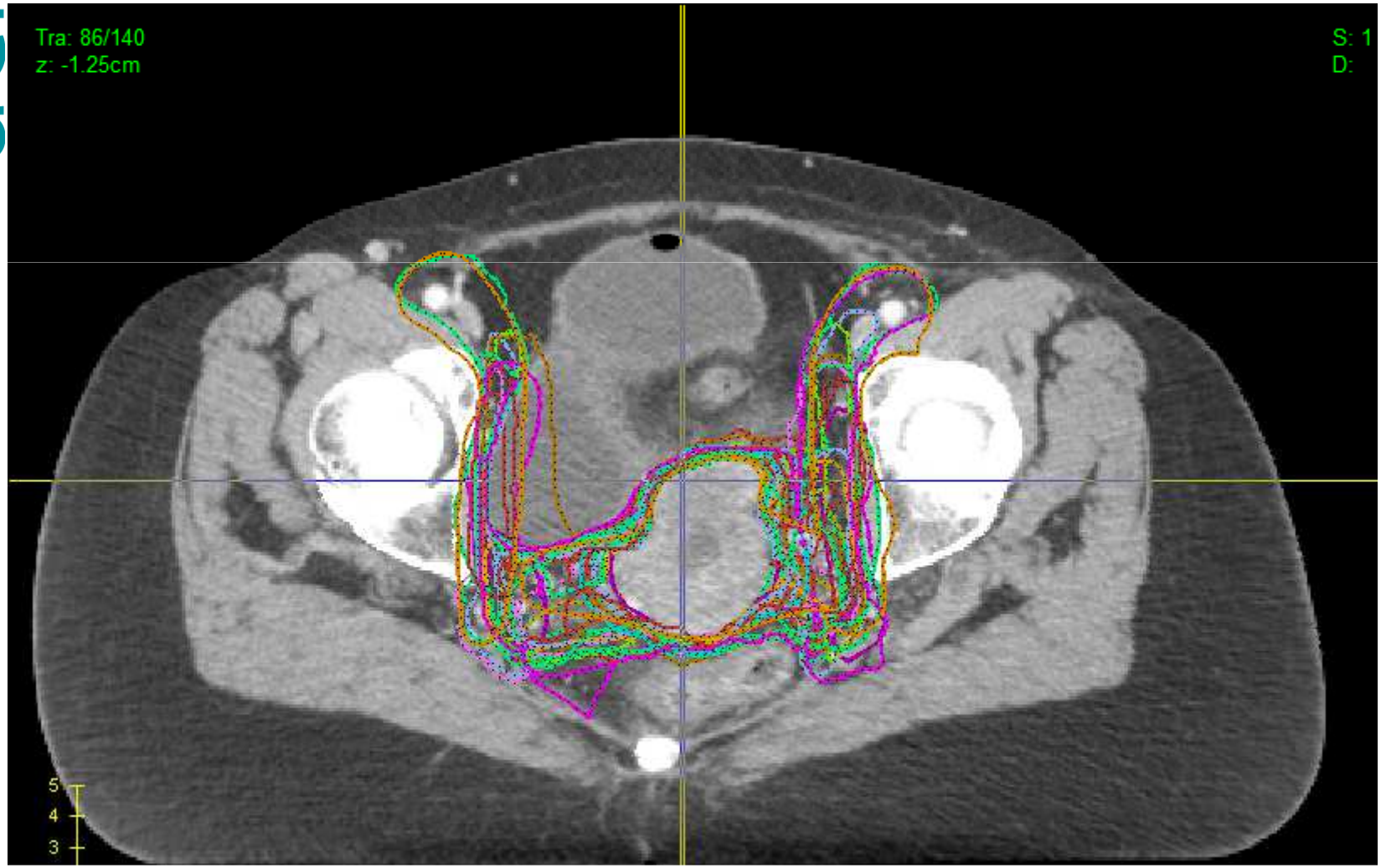

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Delineation

- Largest uncertainty in RT planning

- Cervical cancer
  - Two fold difference in CTV volume
  - Up to 4cm difference in superior border
  - JCI 0.51-0.81 vs gold standard

Eminowicz, Radiother Oncol 2015;117:542-117

Anatomical region	Case 1 (%, 95% CI)	Case 2 (%, 95% CI)	Protocol
Common iliac nodal region	95 (76.2–99.9)	100 (84.6–100)	Yes
Internal iliac nodal region	100 (83.9–100)	100 (84.2–100)	Yes
External iliac nodal region	86 (63.7–97.0)	95 (77.2–99.9)	Yes
Obturator nodal region	52 (29.8–74.3)	50 (28.2–71.8)	Yes
Pudendal nodal region	43 (21.8–66.0)	73 (49.8–89.3)	No
Inguinofemoral nodal region	33 (14.6–57.0)	18 (5.2–40.3)	No
Presacral nodal region	67 (43.0–85.4)	59 (36.3–79.3)	Yes
Sacral foramina	29 (11.3–52.2)	41 (20.7–63.6)	No guide
Aortic bifurcation GS ±0.5 cm	71 (47.8–88.7)	91 (70.8–98.9)	
Vaginal length mean ±0.5 cm	67 (43.0–85.4)	64 (40.7–82.8)	
Overlap with muscle/bone	10 (1.2–30.4)	23 (7.8–45.4)	No
Lateral gaps	24 (8.2–47.2)	23 (7.8–45.4)	No

Eminowicz, Radiother Oncol 2015;117:542-117

Dose effect……

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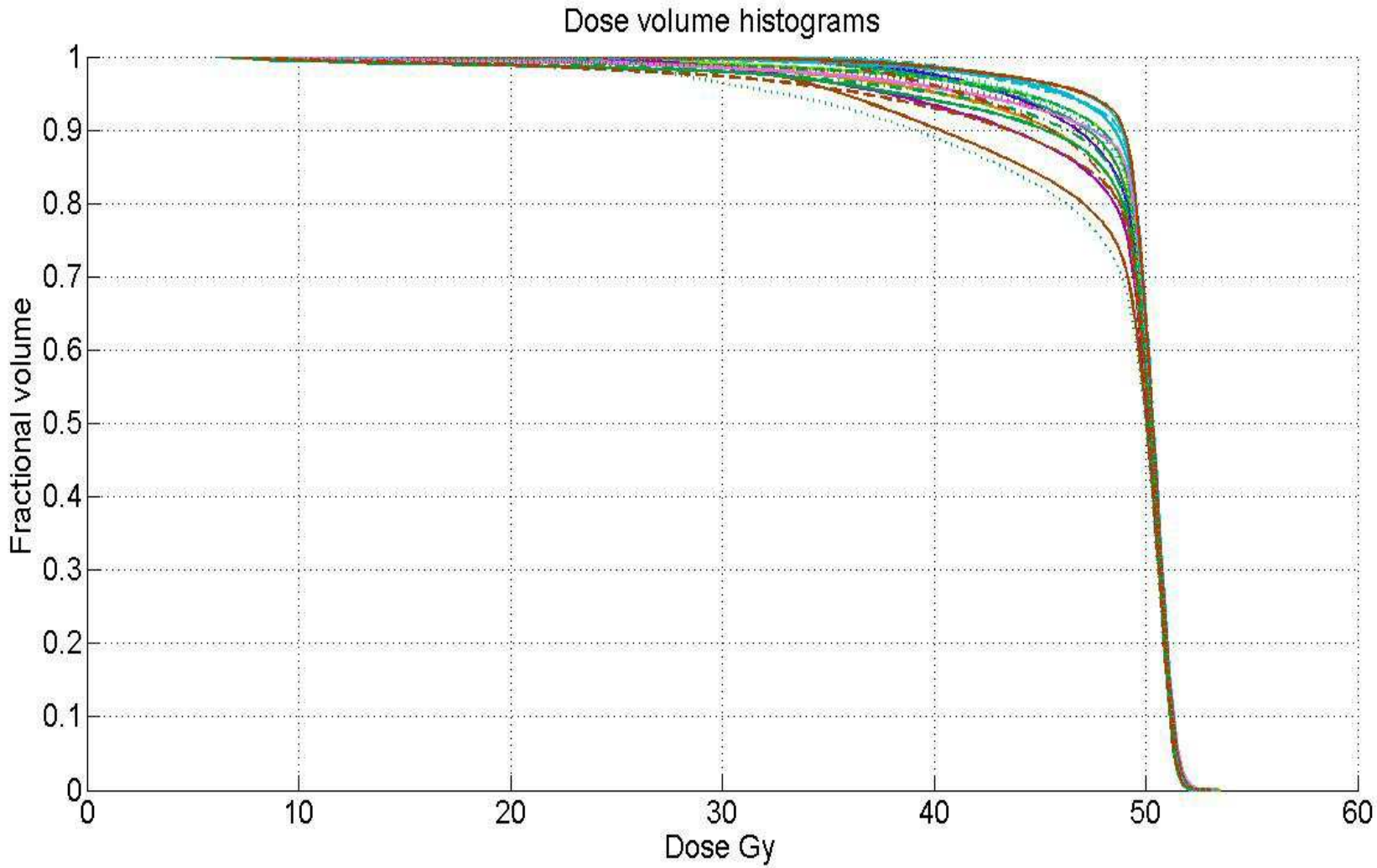
- Cervical ca (21 observers 2 cases):
  - No plans achieved GSPTV V95%≥95%
  - V95%≥90% not achieved in 29% and 36%
  - V95%>80% not achieved in 2 of both cases
  - Mean GSPTV V95%:85.9%/87.9% (range 70-95%)

- Rectal ca (4 observers, 10 cases)
  - Mean V95% to target PTV with IMRT was 86.5%
  - 3D-CRT maintained V95% at 93.7%
  - mean V95% improved to 94.5% with guidelines

Lobefalo Radiat Oncol 2013;8:176

ucl h


Dose volume histograms
Fractional volume
Dose Gy
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0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60

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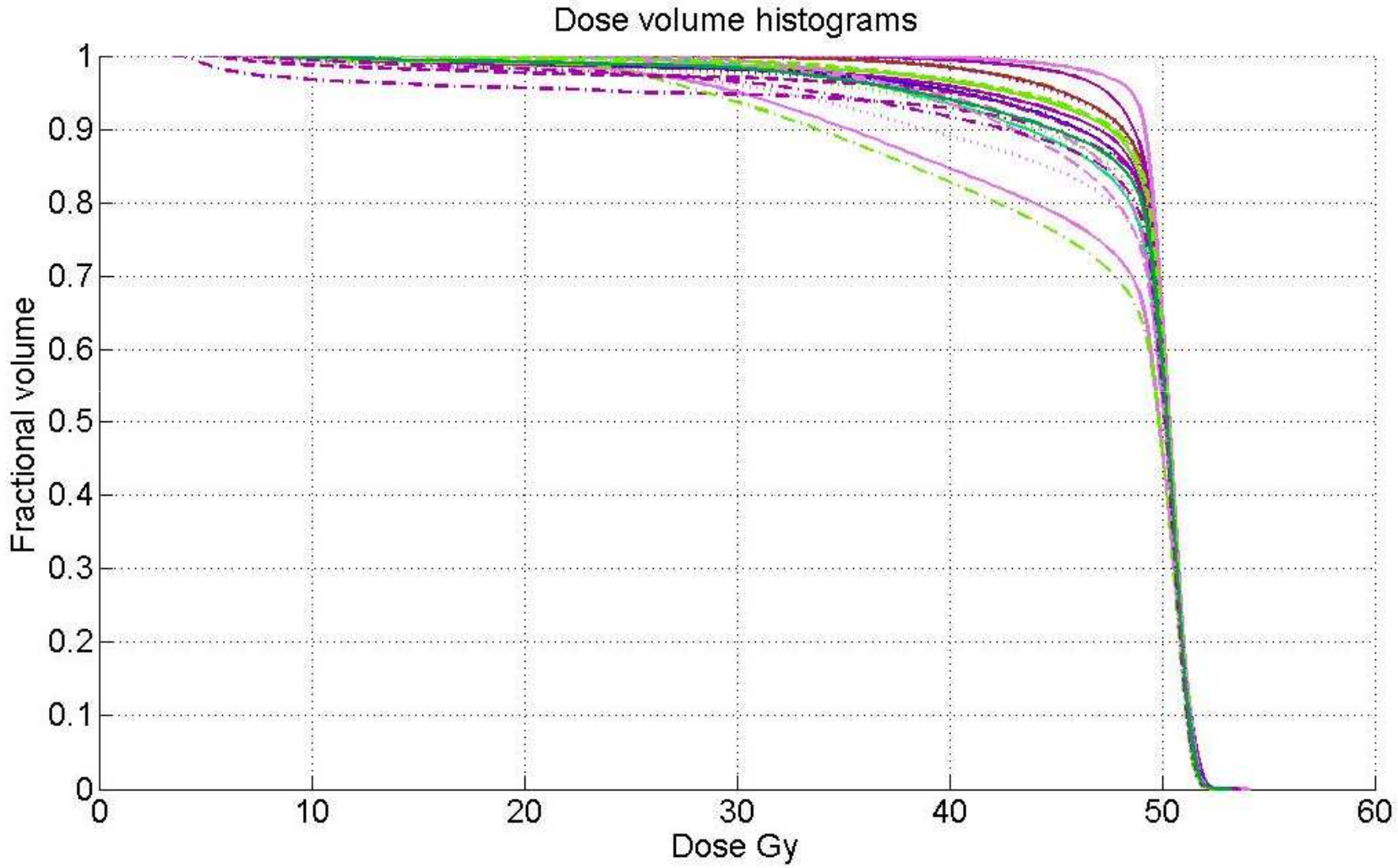
Dose volume histograms
Fractional volume
Dose Gy
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60

Delineation guidance

uclh

- Oesophagus: IJROBP 2015;92(4):911-920
- Rectal:https://www.rtog.org/LinkClick.aspx?fileticket=DgflROvKQ6w%3d&tabid=231
- Cervix: IJROBP 2011;79:348-55. (RTOG)
- Anal: www.analimrtguidance.co.uk
- Trial protocols
  - INTERLACE/EMBRACE2
  - SCOPE2
  - SCALOP2
  - ARISTOTLE

Organ motion

uclh

Organ motion

- Upper GI:
  - Respiratory movements
- Pelvis
  - Bladder filling
  - Rectal/bowel filling

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Compensatory approaches

- Large margins
- Breath-holds/ Respiratory gating/ 4D-CT
- Internal Target Volume
- Plan of the day ‘adaptive RT’

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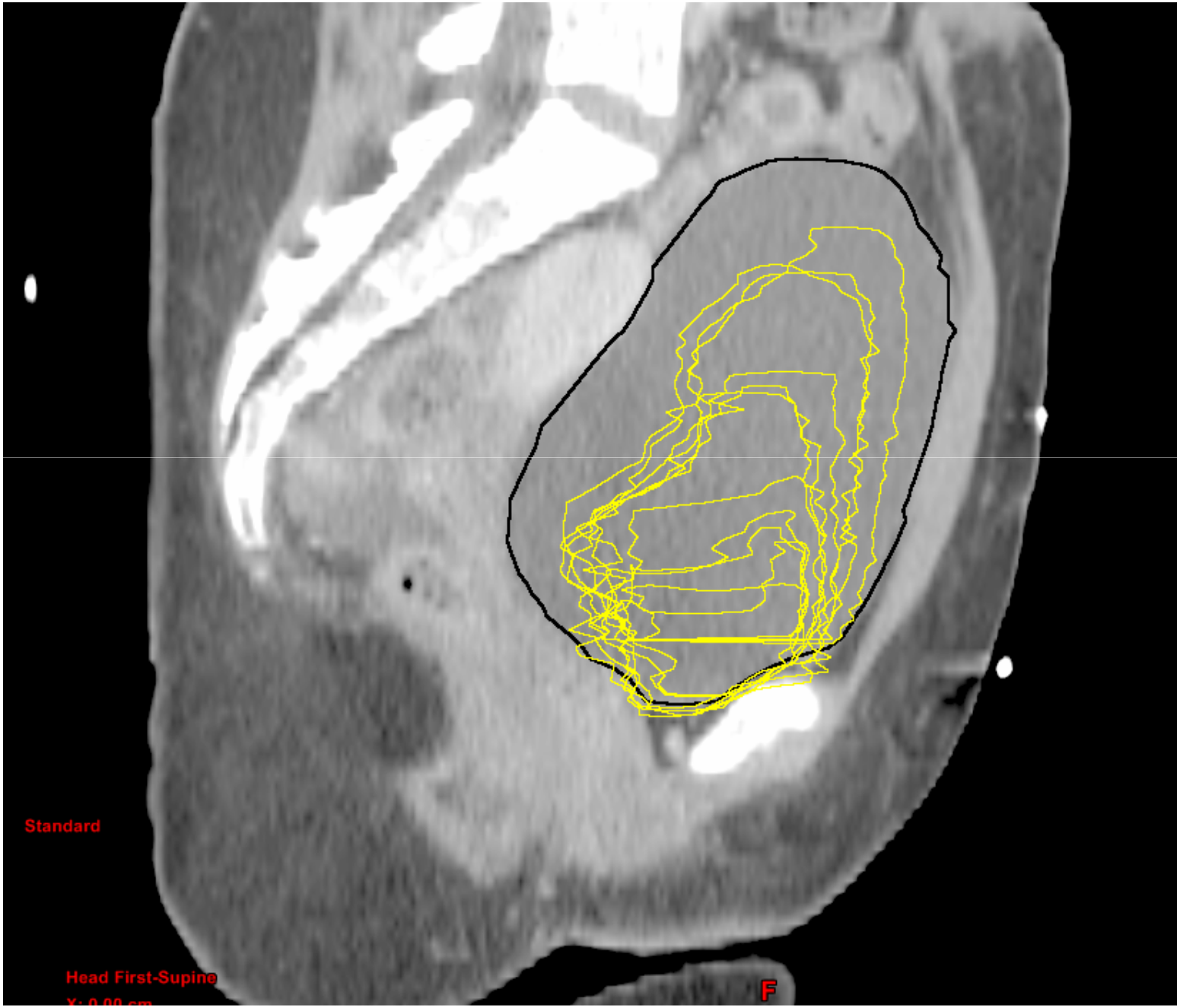
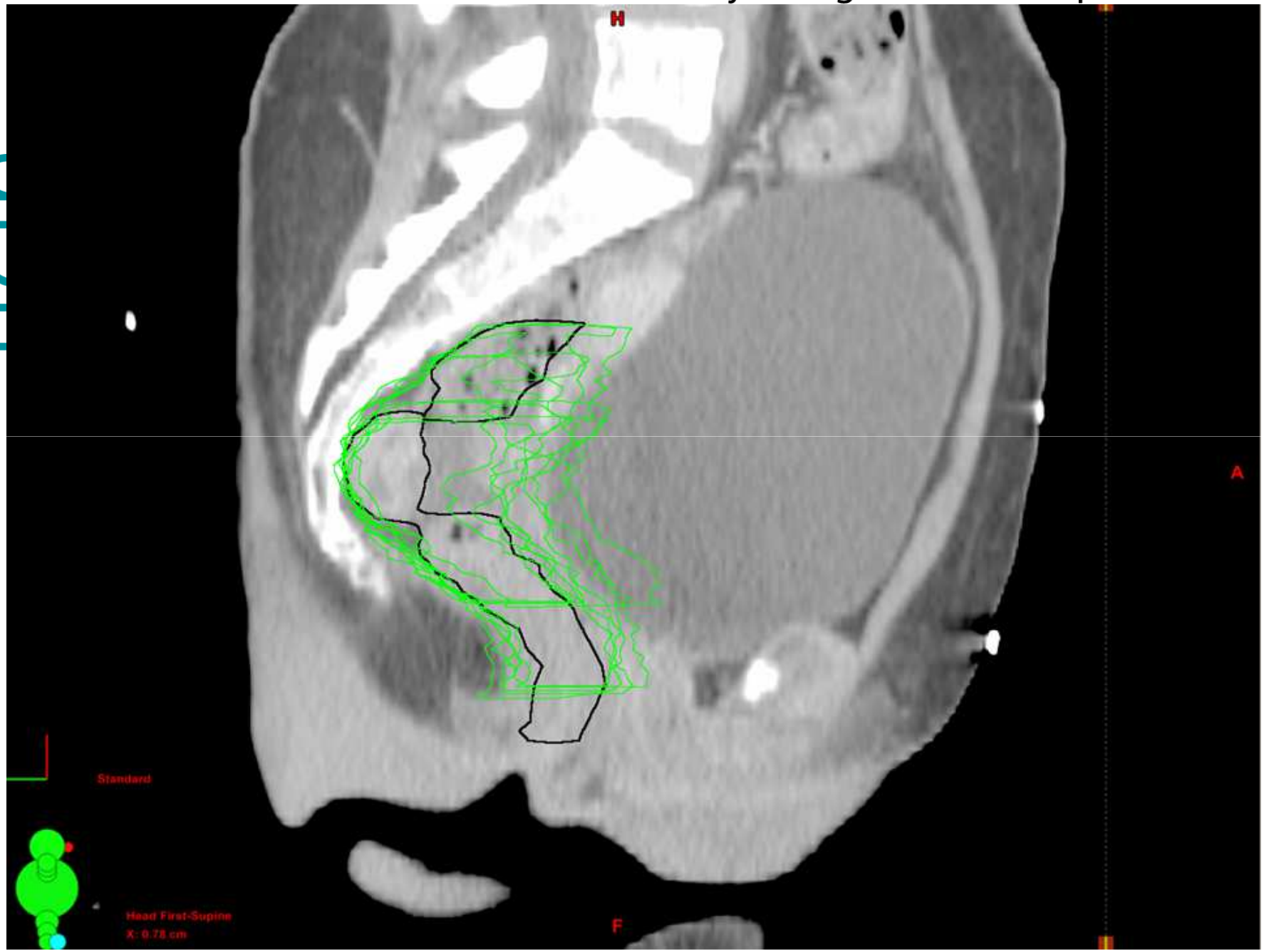
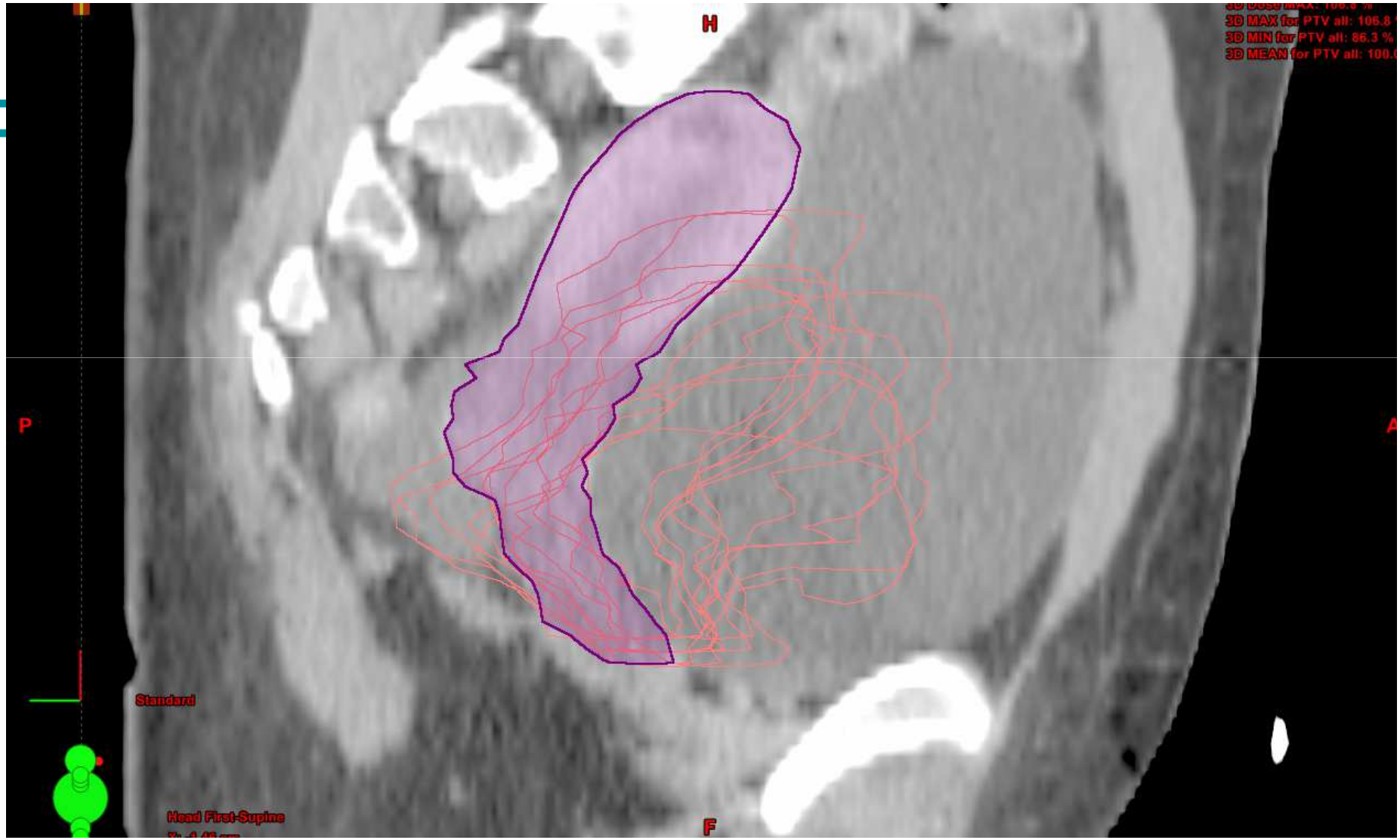
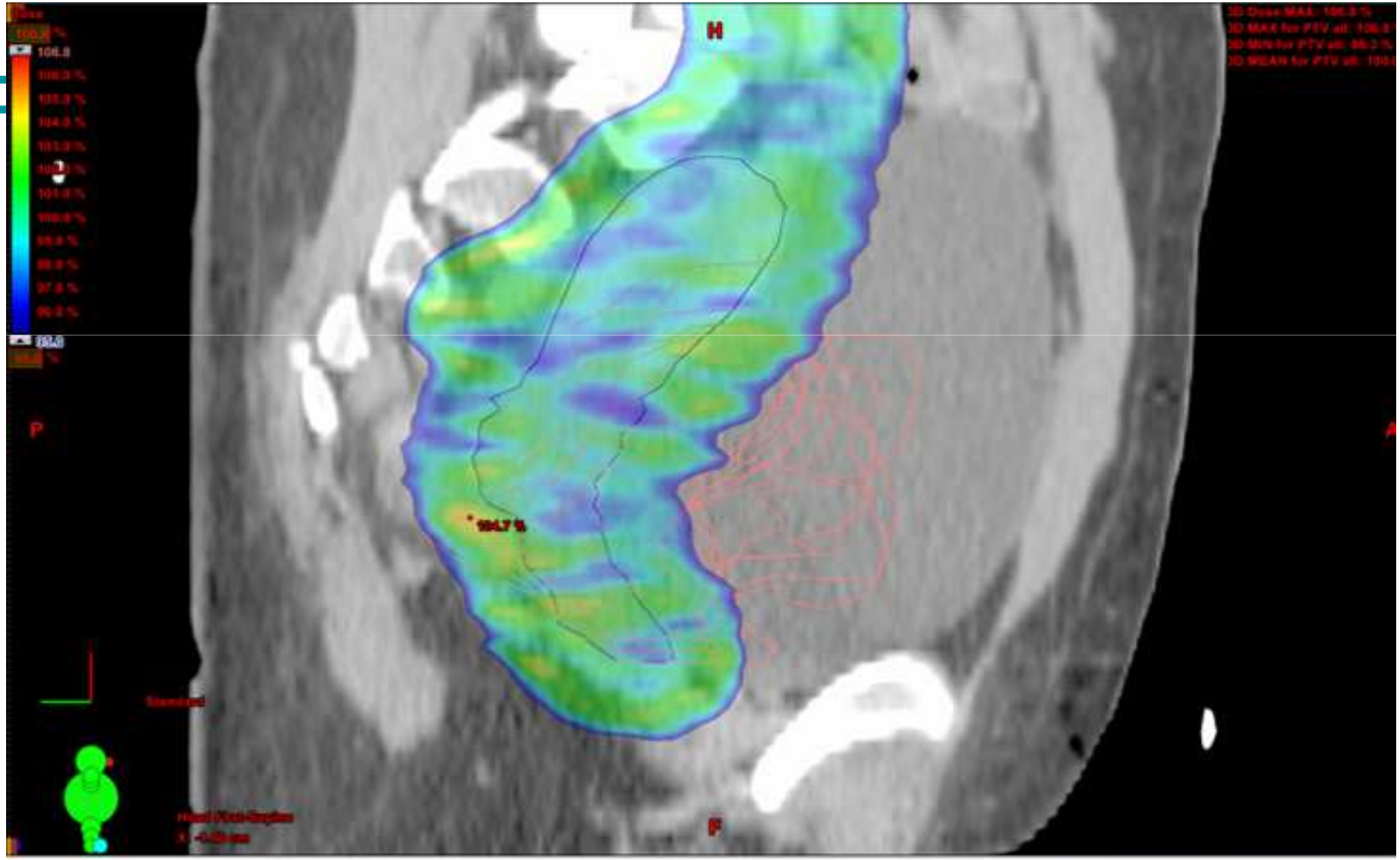



H
A
F
Standard
Head First-Supine
X: 0.78 cm


H
P
A
F
3D MAX for PTV all: 106.8
3D MIN for PTV all: 86.3 %
Standard
Head First-Supine


H
P
F

Tumour regression

- Large radiosensitive tumours decrease in volume during RT

- Cervical tumours reduce 31-70%
- Time to 50% reduction 21/7
- Less fixation → increased mobility?
  - No dosimetric detriment

- Replanning beneficial to spare bowel

Herrera et al 2013; Van de bunt 2006

Unknown late effects

- Increased peripheral dose:
  - 0.12% prescribed dose
  - Less with 6MV vs 15MV
  - Clinical consequence unclear
- Second cancer risk
  - Absolute risk 1.75% at 10 years compared with 1% for 3D-CRT
  - Due to increased low dose volume (0.5%) and MU (0.25%)
  - Higher energy worse; <1% absolute increase risk

Salz et al 2012, Hall et al 2003, Zwahlen et al 2009

Cost effectiveness

- More expensive initial cost

- Gynaecological patients:
- Increasingly cost effective with time
    - Lower toxicity
    - Post operative pts

- Too expensive unless treating PA nodes

Chen et al Gynecol Oncol 2015;136:521. Lesnock et al Gynecol Oncol 2013;129: 574

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Summary

- IMRT improves OAR protection
- Dosimetric benefit
- Clinical benefit likely
- Strict QA necessary
  - Image guidance
  - Delineation accuracy
  - Margins
  - Reproducibility

- Prospective randomised clinical trials needed

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References

University College London Hospitals NHS
NHS Foundation Trust

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Ahamad et al. IMRT after hysterectomy: comparison with conventional treatment and sensitivity of the normal-tissue-sparing effect to margin size. IJROBP 2005; 62: 1117-24.

Georg et al. Factors influencing bowel sparing in intensity modulated whole pelvic radiotherapy for gynaecological malignancies. Radiother Oncol 2006; 80: 19-26

Hall EJ et al. Radiation-induced second cancers: the impact of 3D-CRT and IMRT.IJROBP 2003;56:83-88.

Herrera FG et al. Retrospective feasibility study of simultaneous integrated boost in cervical cancer using Tomotherapy: the impact of organ motion and tumor regression. Radiat Oncol 2013; 8: 5.

Lin et al. Propensity Score-based Comparison of Long-term Outcomes With 3-Dimensional Conformal Radiotherapy vs IMRT for Esophageal Cancer IJROBP 2012;84(5):1078-1085

Muirhead et al, An evidence based UK IMRT solution for anal cancer:the development of the control arm for future UK led clinical trials. NCRI meeting 2013 http://conference.ncri.org.uk

Nicolini G et al. Volumetric modulation arc radiotherapy with flattening filter-free beams compared with static gantry IMRT and 3D conformal radiotherapy for advanced esophageal cancer: A feasibility study. IJROBP 2012;84:553-560.

Salz et al. Does IMRT increase the peripheral radiation dose? A comparison of treatment plans 2000 and 2010. Z Med Phys 2012; 22: 6-12.

Teoh et al. Rectal Radiotherapy–IMRT delivery delineation and doses. Clin Oncol 2016;28:93

Zwahlen DR et al. Effect of intensity-modulated pelvic radiotherapy on second cancer risk in the postoperative treatment of endometrial and cervical cancer. IJROBP 2009; 74: 539-45.

van de Bunt et al. Conventional, conformal, and IMRT treatment planning of external beam radiotherapy for cervical cancer: The impact of tumor regression. IJROBP 2006; 64: 189-96.

IMRT Optimization: Algorithms and Cost Functions

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Disclosure

• I am involved in the development of the treatment planning system HYPERION which is the basis for Elekta Monaco®.

• My department (LMU Munich) currently receives research grants from Elekta and C-RAD.

• I am co-owner of the company SCIENTIFICRT

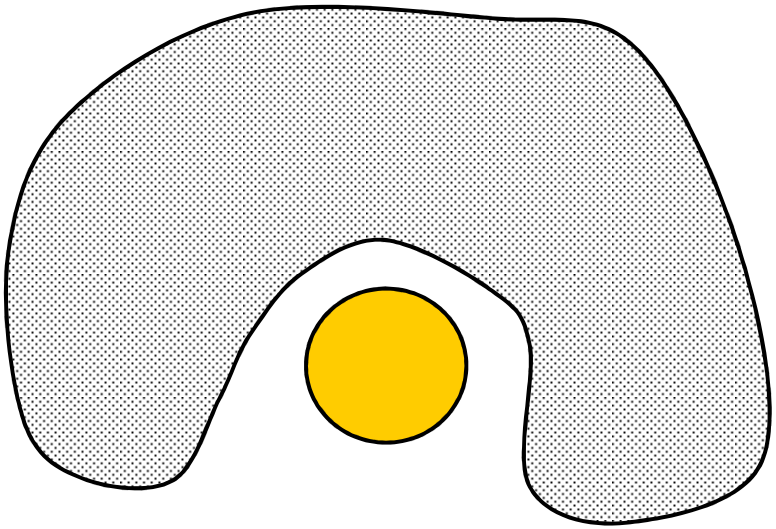
Courtesy *M. Alber*:
Many of the following slides are based on his presentations about "IMRT optimization" and "Costfunctions" at the ESTRO IMRT course 2012

FAQ:

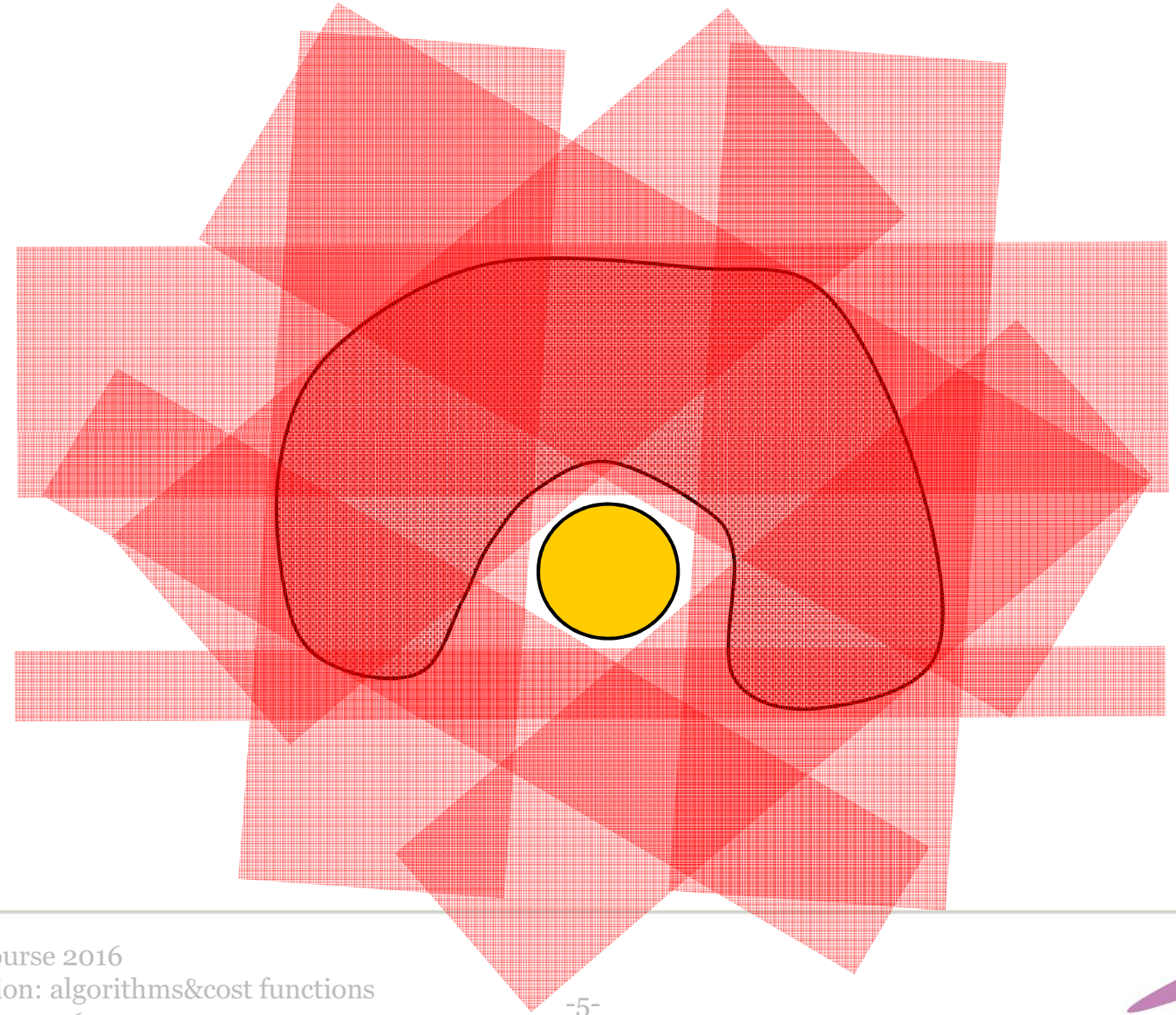
- Why do we need dose optimization if all we want to do is dose planning?

How close are our objectives to a physically feasible dose?

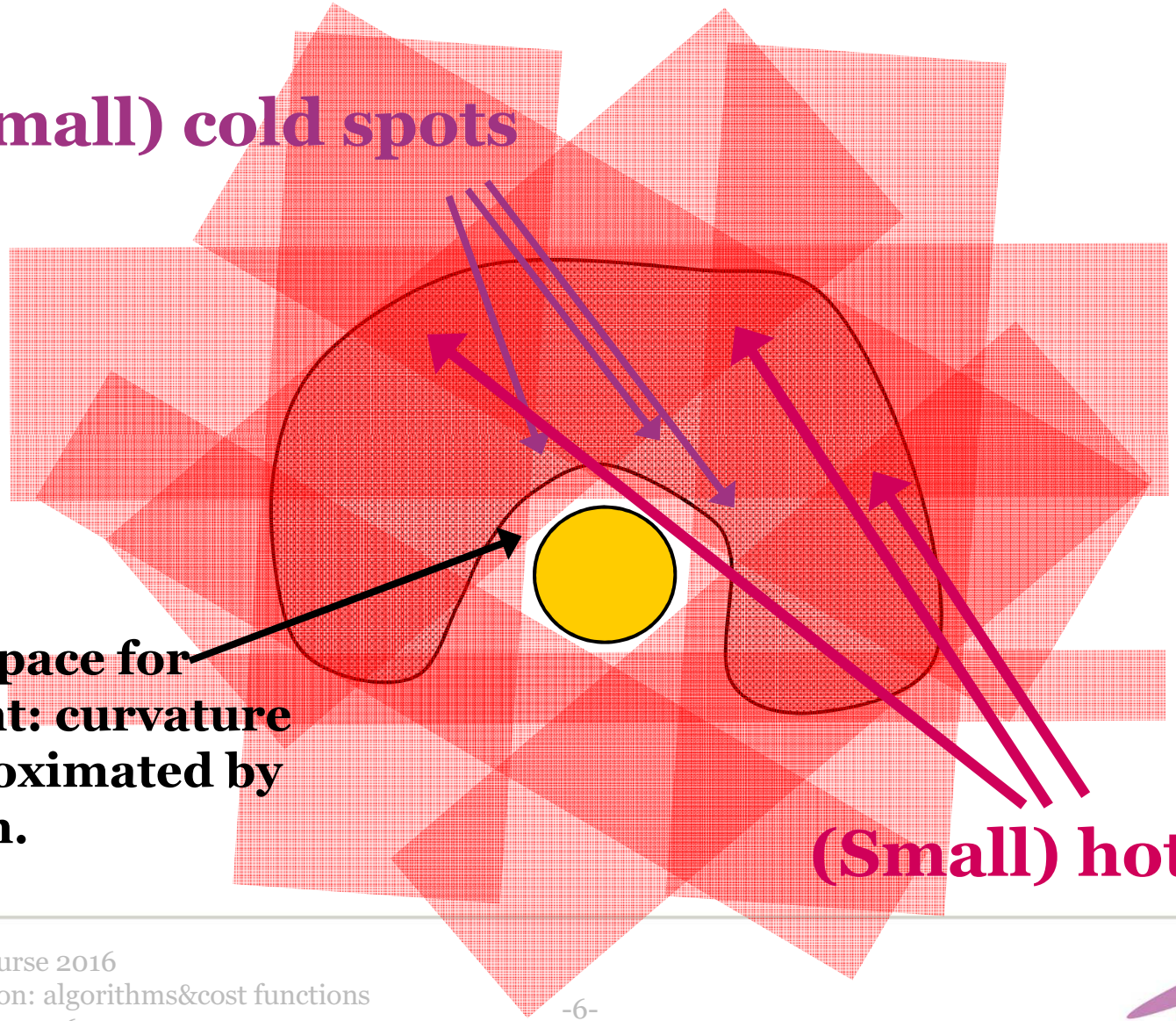
Paint a concave dose gradient!



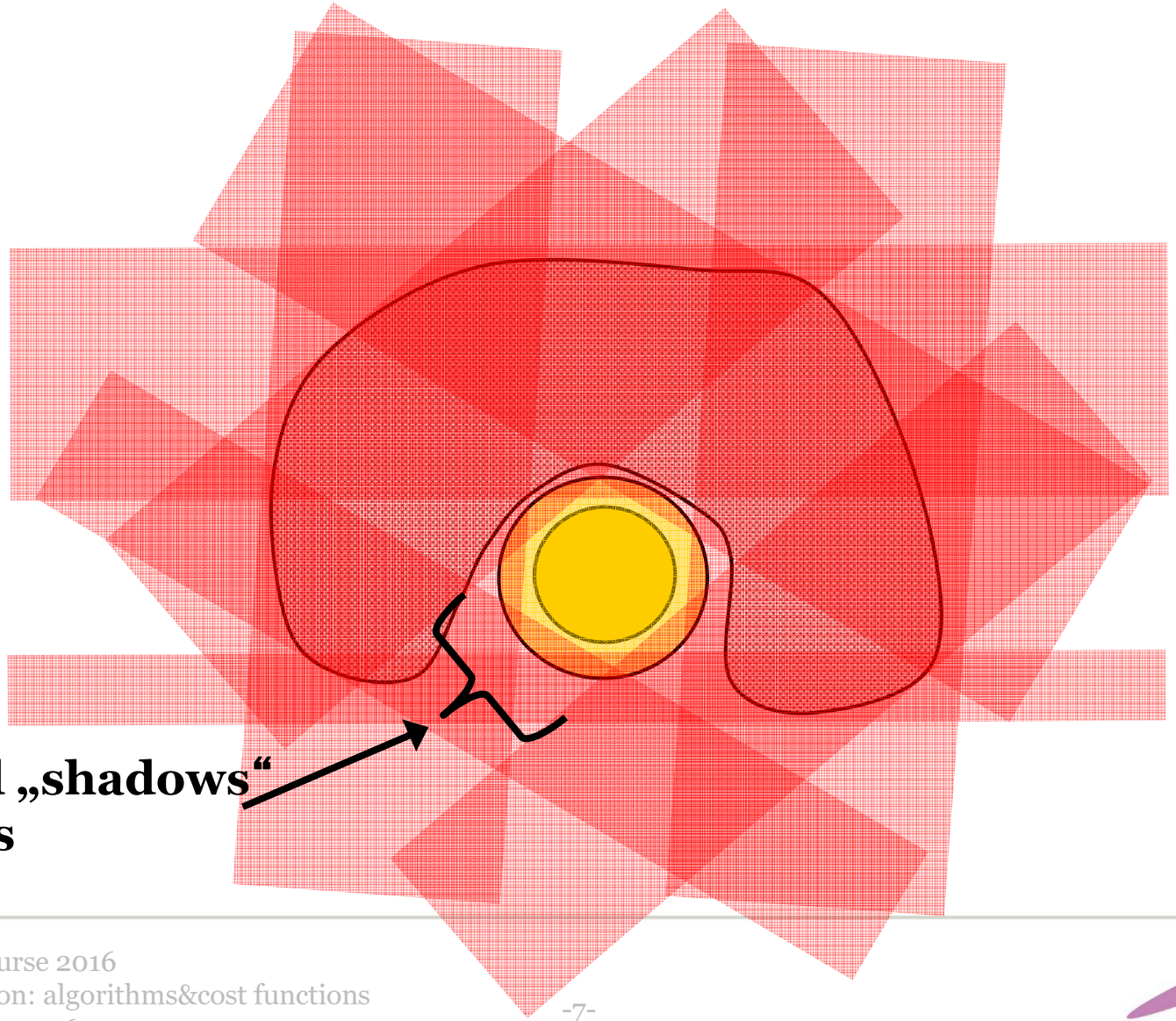
With 4 beams…



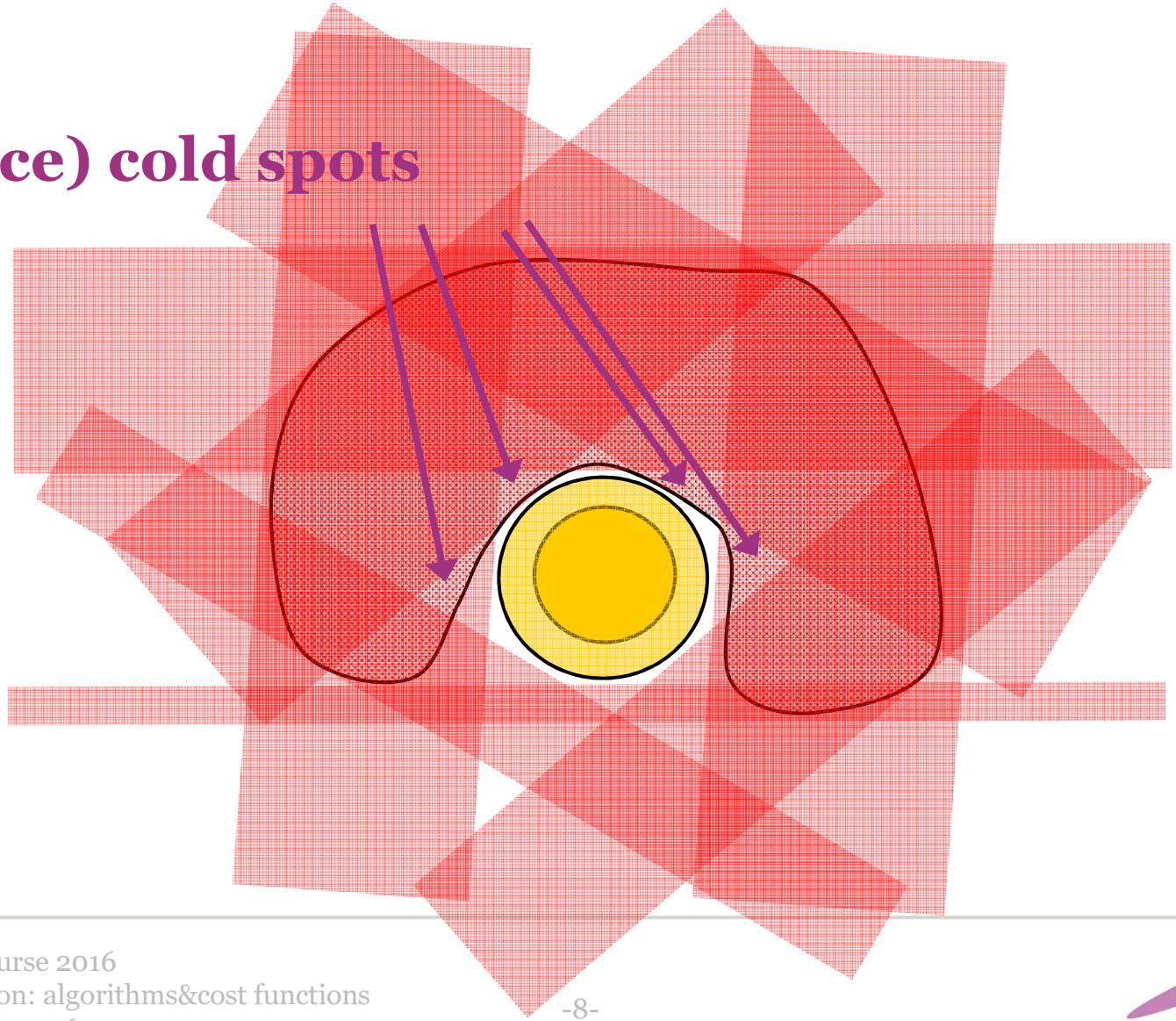
With 4 beams…


(Small) cold spots
Large space for gradient: curvature is approximated by polygon.
(Small) hot spots

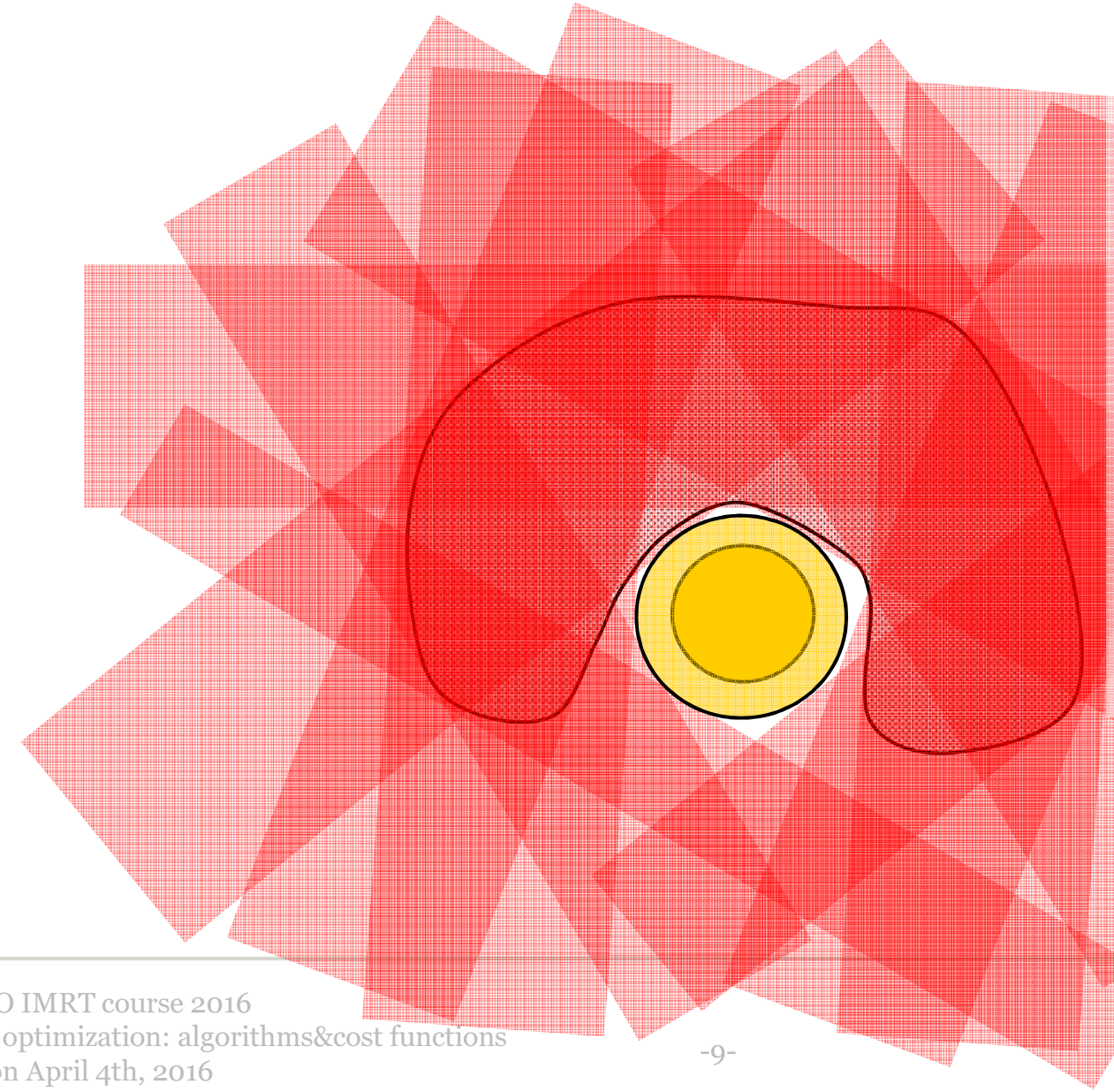
What if the gradient has to be tighter?



What if the gradient has to be tighter?



Solution *for this special case:* Use more beam angles!



What works for this special case might not be a sufficient solution for another case!

Depends on patient geometry, PTV/OAR overlaps, required amount of OAR sparing…

So, why optimization?

The best physical dose distribution depends strongly on the patient geometry, the plan setup and the treatment machine´s capabilities.

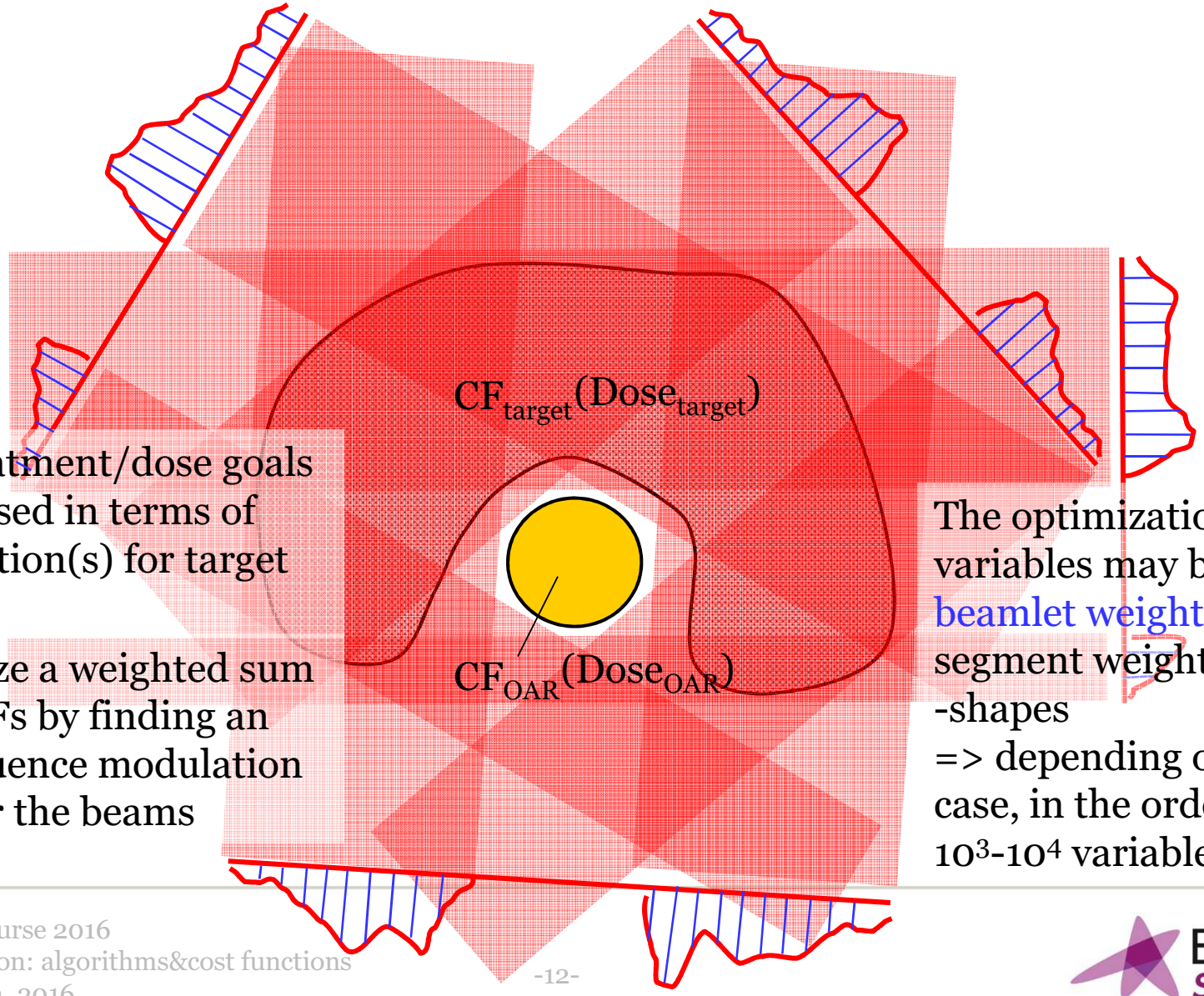
What may be easy for one patient may be infeasible for another.

Therefore, IMRT treatment planning *means exploring the limits of physics* for each patient. The big decisions still have to be made by the experts.

FAQ:

- Why do we need dose optimization if all we want to do is dose planning? √
- What do we actually optimize? Dose? Cost functions? Beamlets?

The IMRT optimization problem: What is optimized, and what are the variables?



(1) the treatment/dose goals are expressed in terms of **C**ost **F**unction(s) for target and OARs.

(2) optimize a weighted sum of these CFs by finding an optimal fluence modulation pattern for the beams

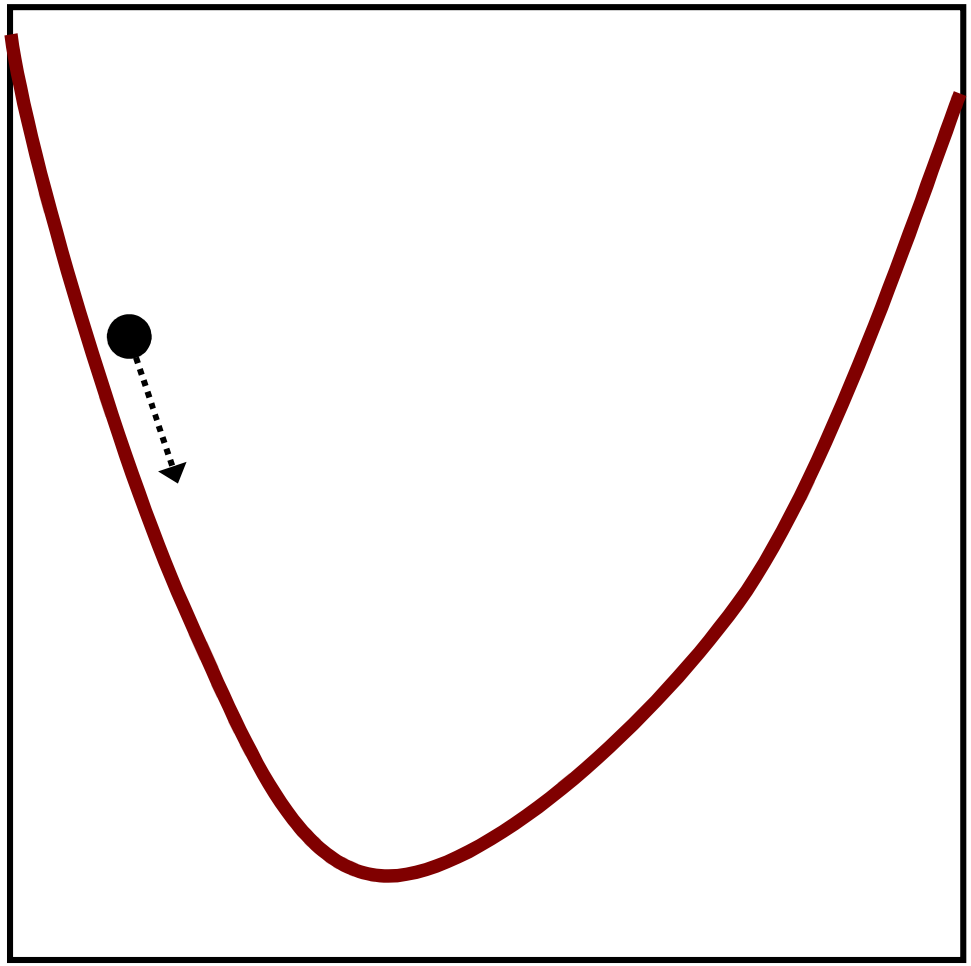
The optimization variables may be beamlet weights or segment weights and -shapes
=> depending on the case, in the order of 10^3-10^4 variables!

FAQ:

- Why do we need dose optimization if all we want to do is dose planning? √
- What do we actually optimize? Dose? Cost functions? Beamlets? √
- What optimization algorithm to use, and why?

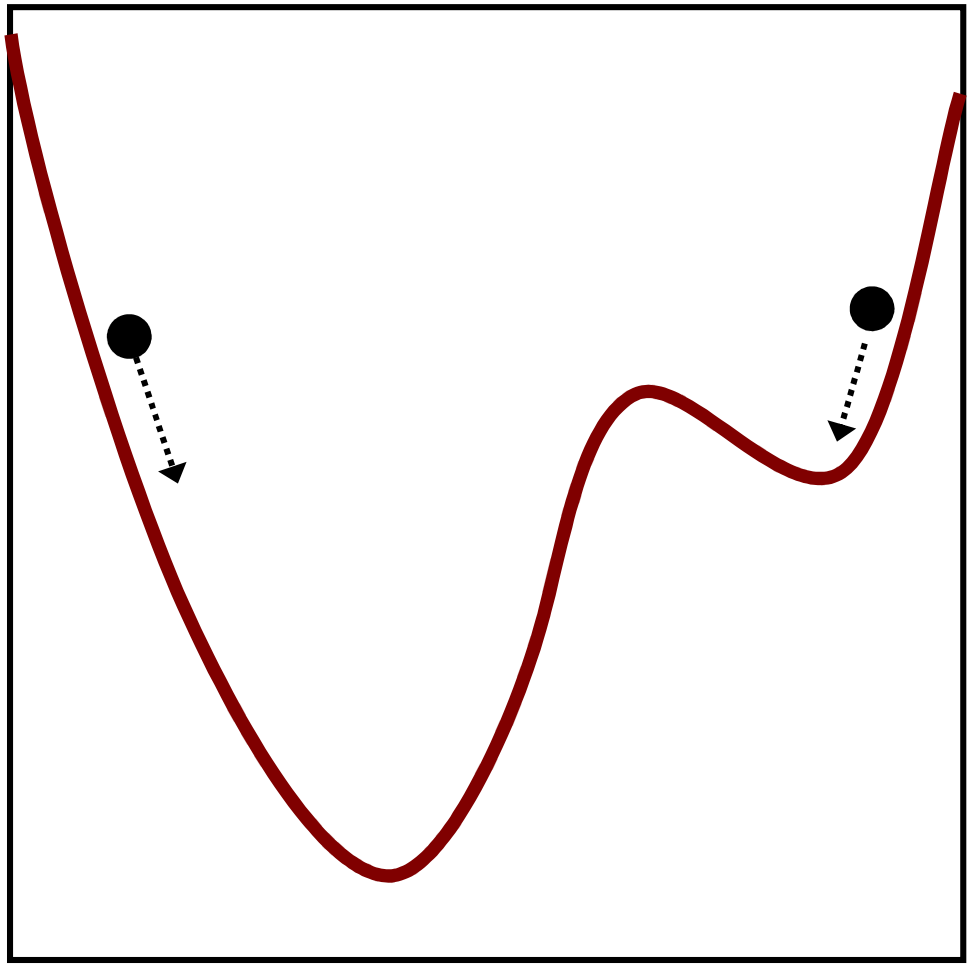
The popular understanding

Reach minimum of cost function
by going downhill in
a well-defined direction
to a well-defined minimum



The popular fear

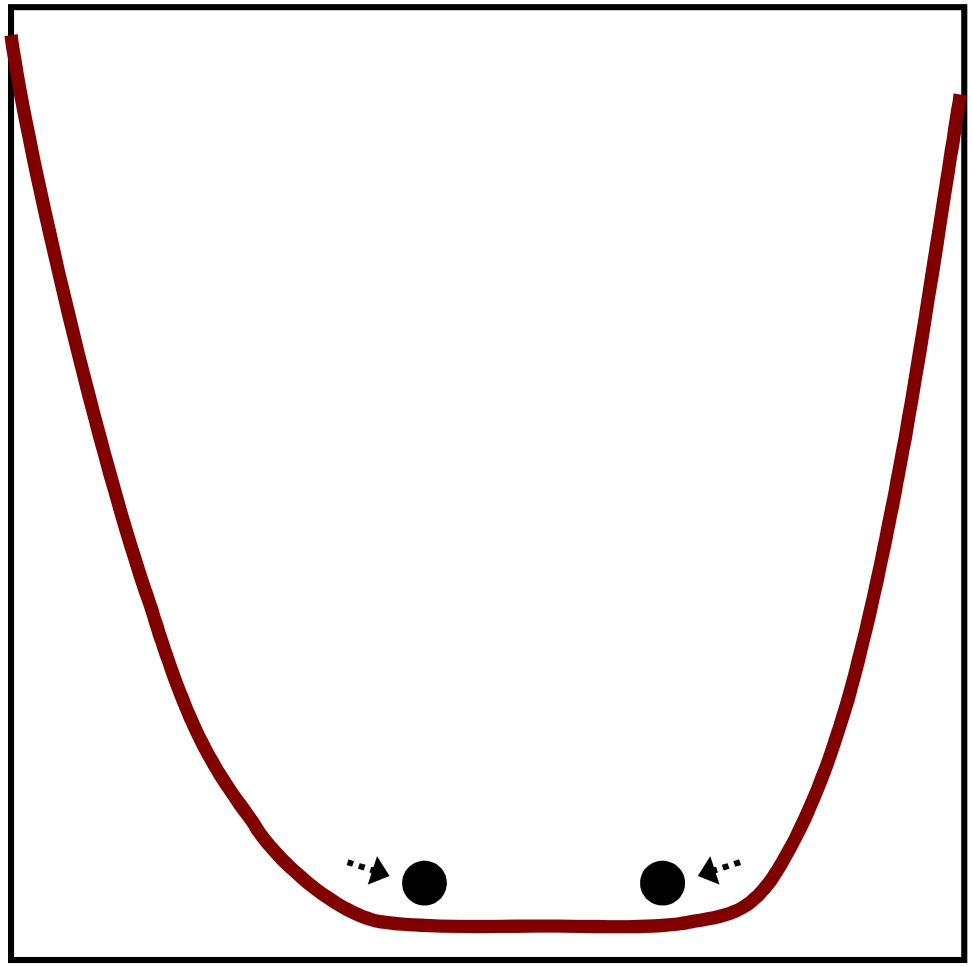
There are multiple minima, some not as good as the global minimum



The truth: degeneracy of the optimization problem, non-uniqueness of the solution

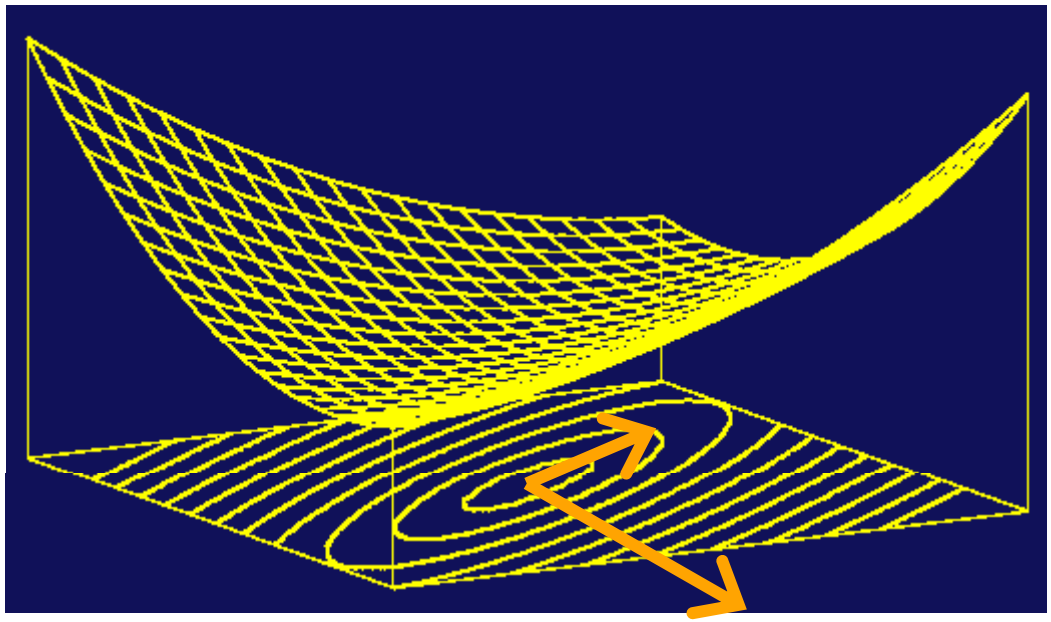
In some directions, the minimum is not sharp at all.

In others, it is.



Fluence profile optimization (No MLC)

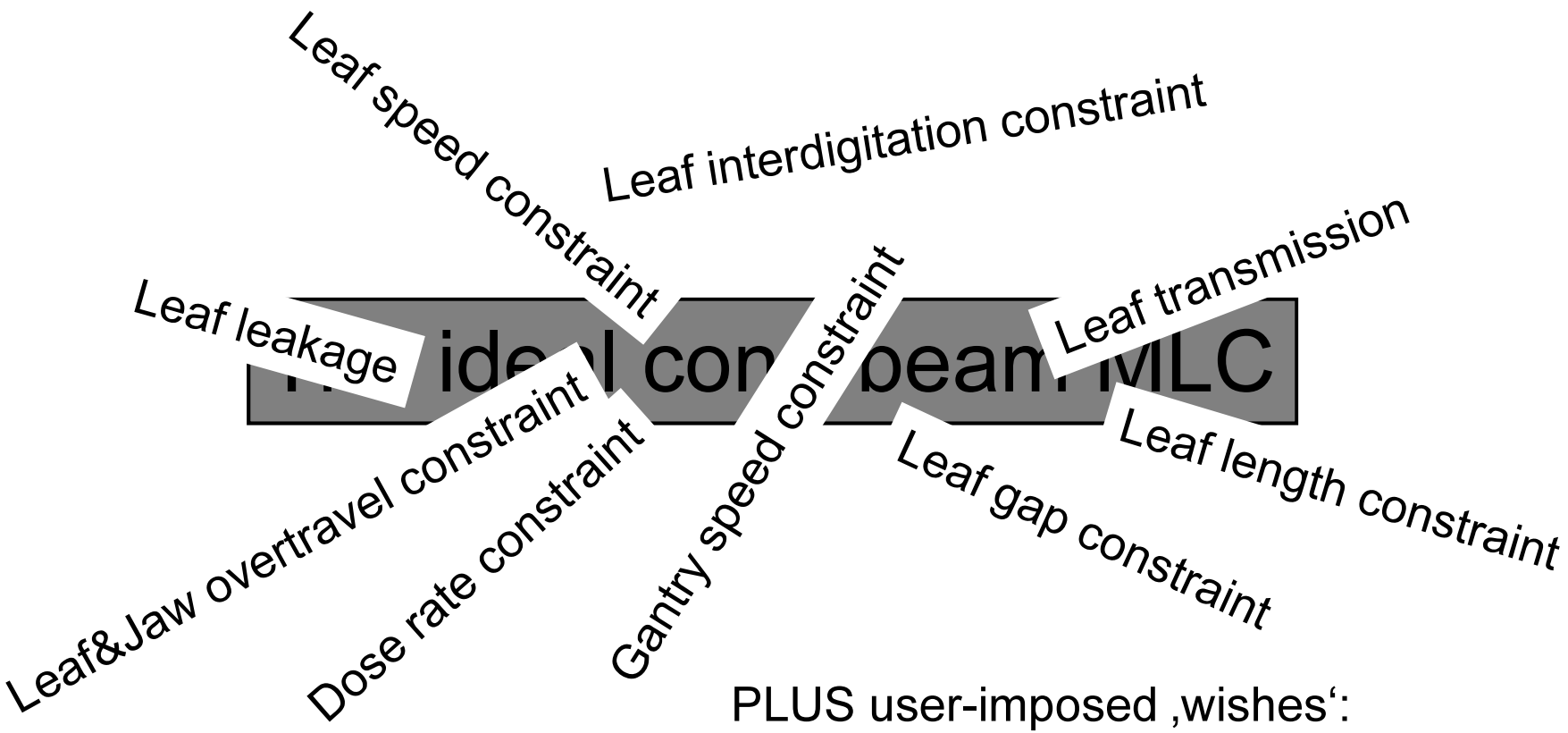
The minimum sits in a flat-pan valley, the search direction is well defined in few (ca. 100), but vague in most dimensions (ca. 10000),
a multiplicity of optimum solutions exists.



Problems for the optimization algorithm:

- **convergence** in end game is very **slow – terminate long before convergence**
- same **solution** may **not be reached** twice, although the cost functions have identical values
- no local minima, but still difficulties to find the optimum!

Next: Sequencing
Add (a lot of!) delivery constraints…



PLUS user-imposed ‚wishes‘:

- max. #segments
- max. #arcs
- minimize #MUs, treatment time...

Principles: The optimization problem for the different IMRT techniques

Static gantry, dMLC: (e.g. sliding window)	no distant local minima for 'easy' MLCs, proven algorithm for solution
Static gantry, step&shoot: ('step&shoot' IMRT)	local minima possible, but good heuristics for avoiding them (MLC sequencer)

(Notice: *algorithm* converges, *heuristic* produces a result)

Rotational-IMRT: (VMAT, Rapid Arc ©...)	So many local solutions that it becomes impossible to *identify* the global one, bold heuristics for avoiding the inevitable: getting trapped in a local minimum.

Optimization Algorithms

- Optimization algorithms find a solution by minimizing a function.
- Virtually all algorithms use gradient information for the downhill search.
- The size of the optimization problem limits the number of available algorithms to *quasi-Newton methods* and *Conjugate Gradient search*. If implemented well, none should be superior to the others.
- These algorithms are deterministic, so that given infinite time, they find a minimum, which is unique in the absence of delivery constraints.
- Some delivery constraints make the problem virtually unsolvable.
- If nothing else helps: stochastic algorithms (like Simulated Annealing) which perform a sparse, random search of the entire solution space (which is very, very big). Stochastic algorithms are the last resort when the problem is otherwise intractable.

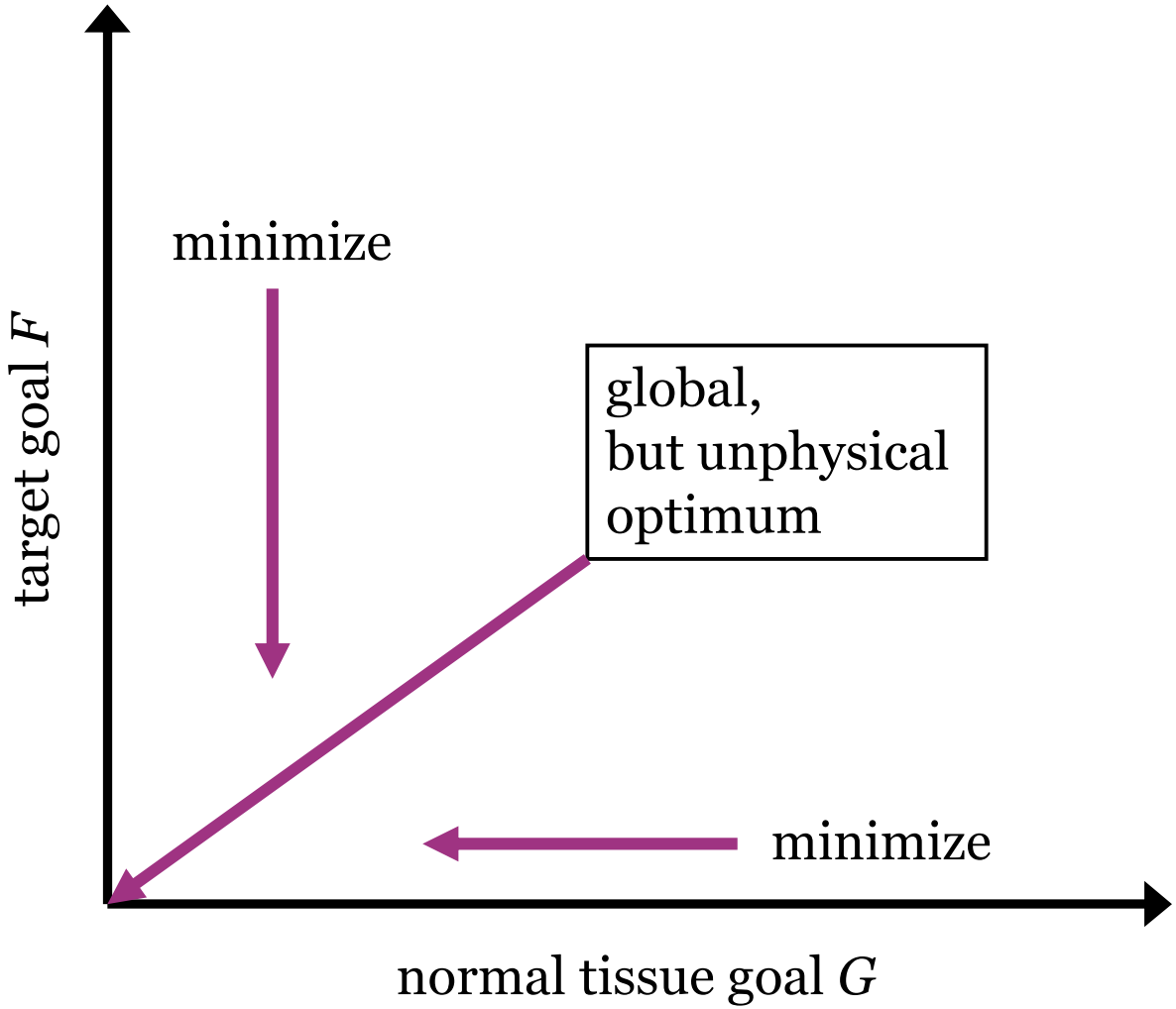
FAQ:

- Why do we need dose optimization if all we want to do is dose planning? √
- What do we actually optimize? Dose? Cost functions? Beamlets? √
- What optimization algorithm to use, and why? √
- Weight Factors, Constraints, Objectives – why is it so complex?

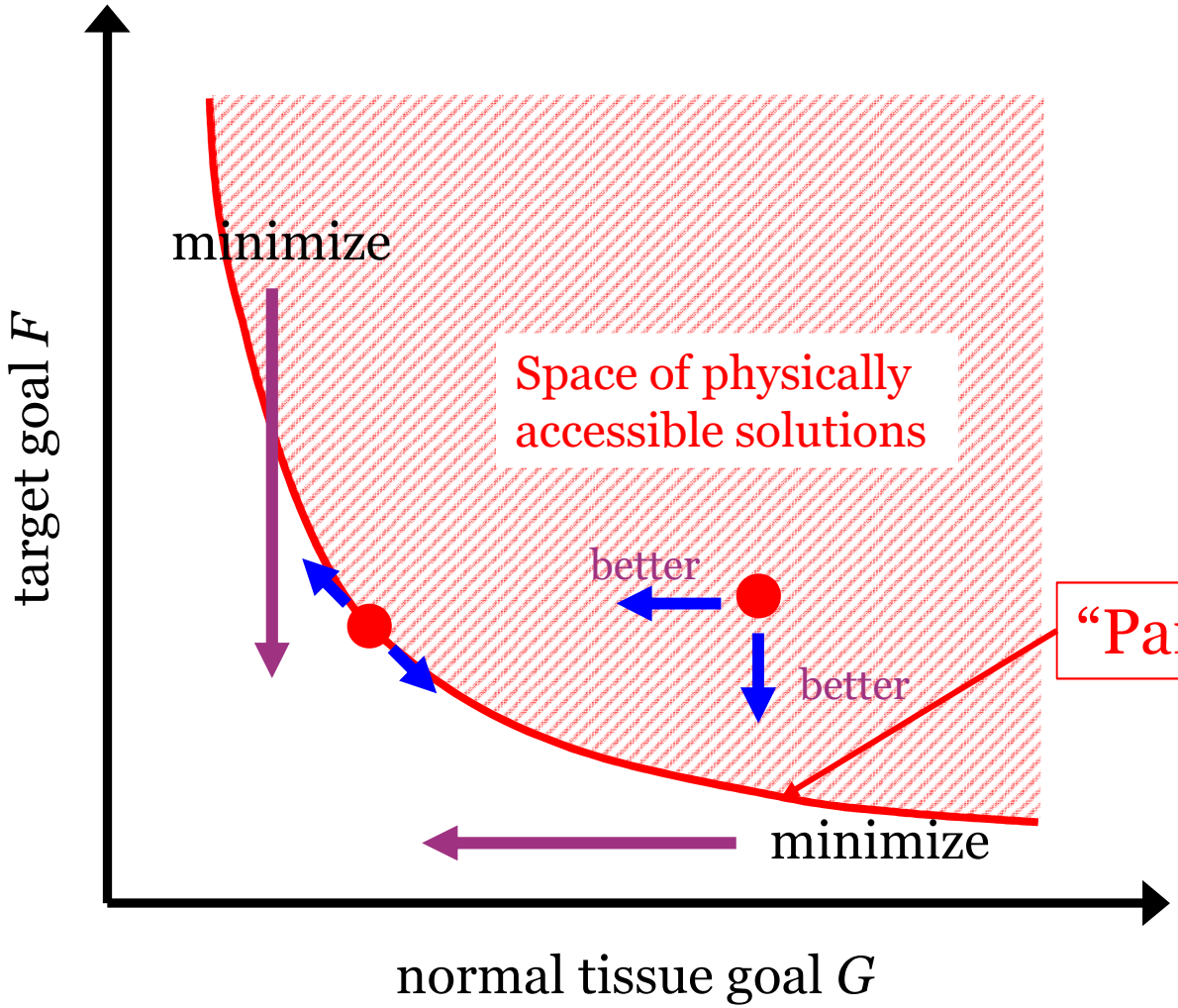
What are typical treatment goals?

Target goal:	achieve a ***sufficient target dose***
Normal tissue goals:	do not ***exceed acceptable doses*** in N ***organs***
Conformality goal:	target dose should be ***conformal***, ***spare generic normal tissue***
Homogeneity goal:	***no large*** or ***excessive hot spots*** in the ***target***

Without the laws of physics, all goals could be fulfilled simultaneously



There exists a boundary that separates physical from unphysical solutions



Any optimum solution lies on this boundary:

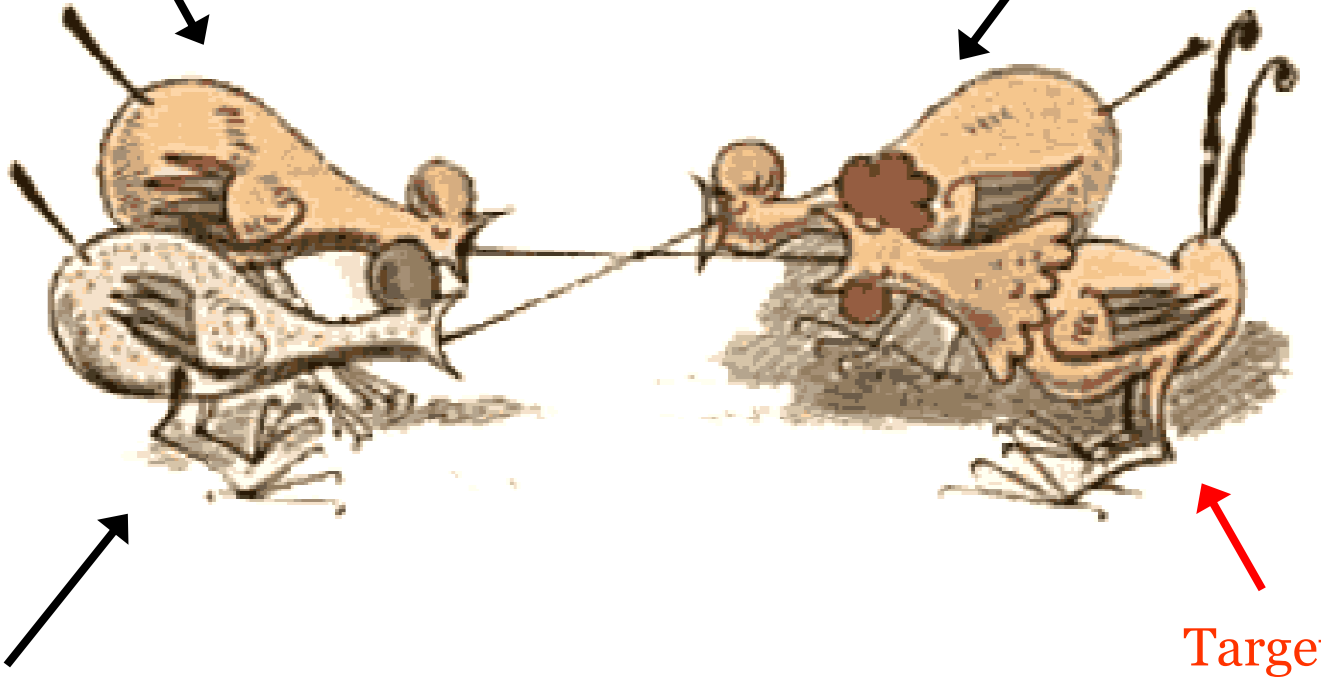
G cannot be reduced without increasing *F* and vice versa.

"Pareto-front"

In other words: Treatment goals contradict each other! How can these be balanced?

Normal Tissue Goals

Target Dose Homogeneity Goal



Dose Conformality Goal

Target Goals: only goal aiming to *increase* dose

Cost Functions can be Balanced by Weight Factors: the Lagrange Function

Combine all goals to one weighted sum:

$$L = \sum_{j=1}^{M} \lambda_j F_j$$

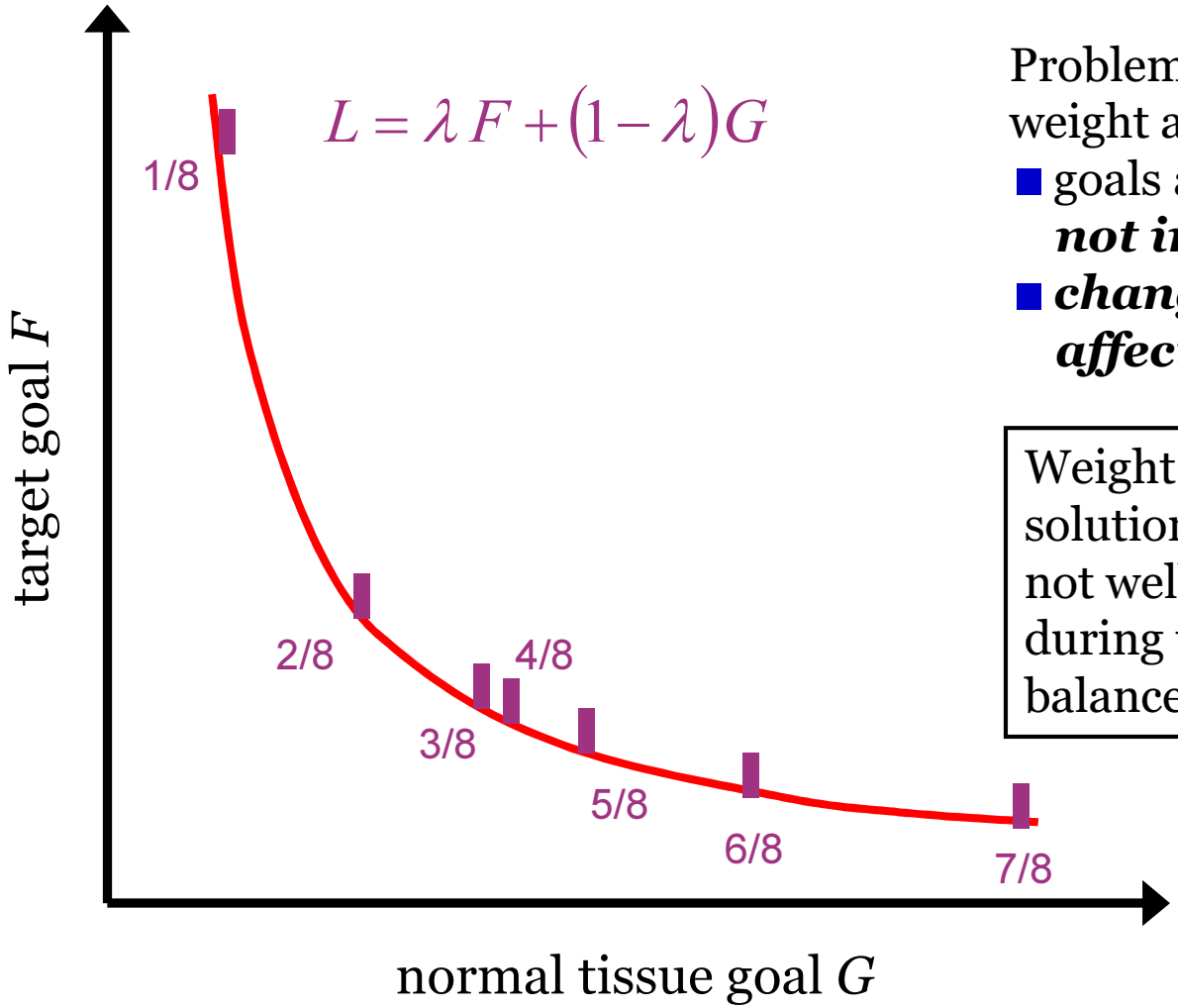
$$\sum_{j=1}^{M} \lambda_j = 1, \quad \lambda_j \geq 0$$

...and minimize the Lagrange Function L.
Tuning the weight factors λ_j makes all solutions in Solution Space accessible.

Problem: find the right set of weights that produces a dose distribution as minimizer of L which is `***closest to the intended***` treatment.

This is a decision to be made by the user, not the software

Parametrisation of the Solution Space by Weight Factors

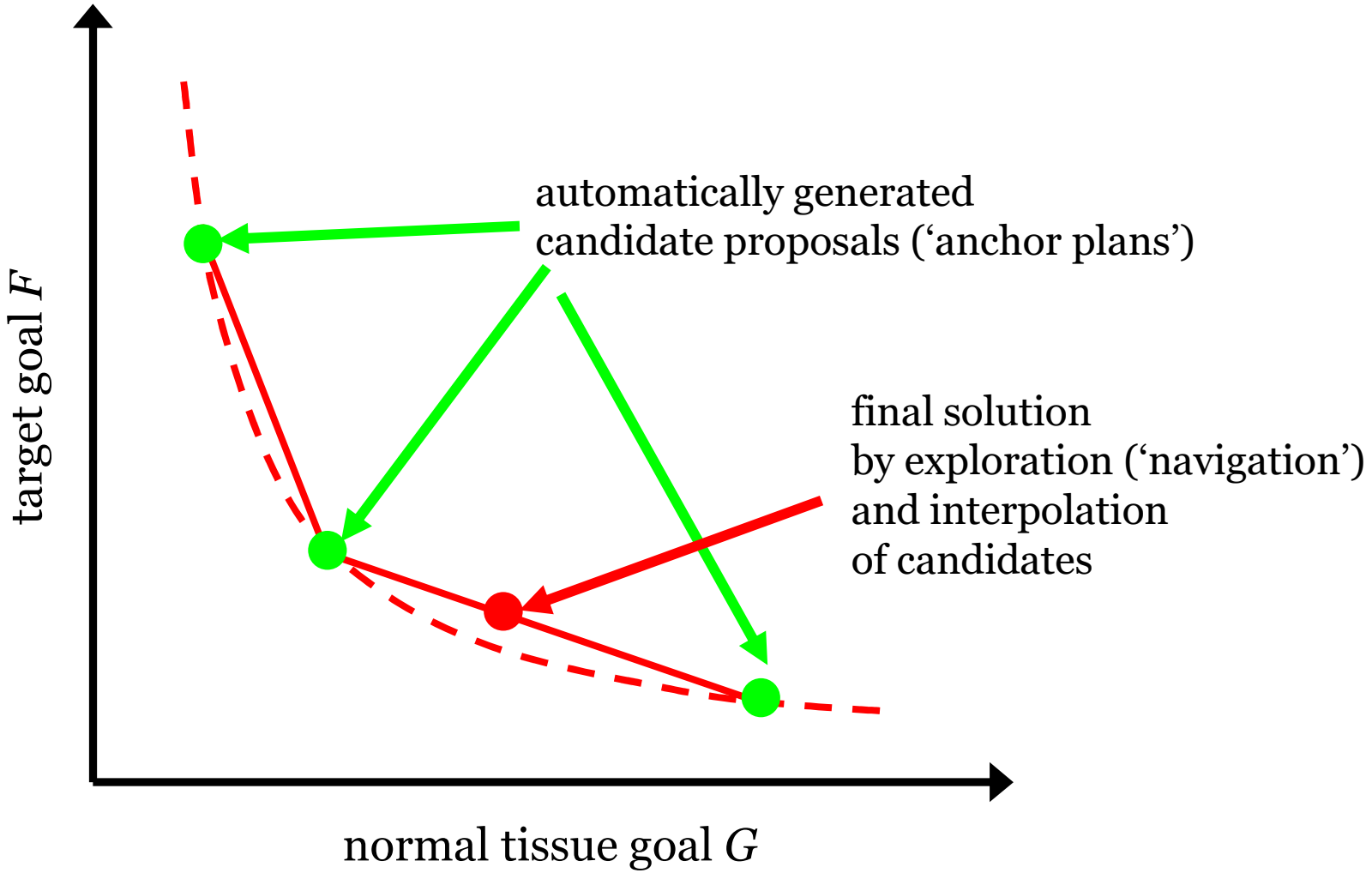


Problems with manual weight adjustments:

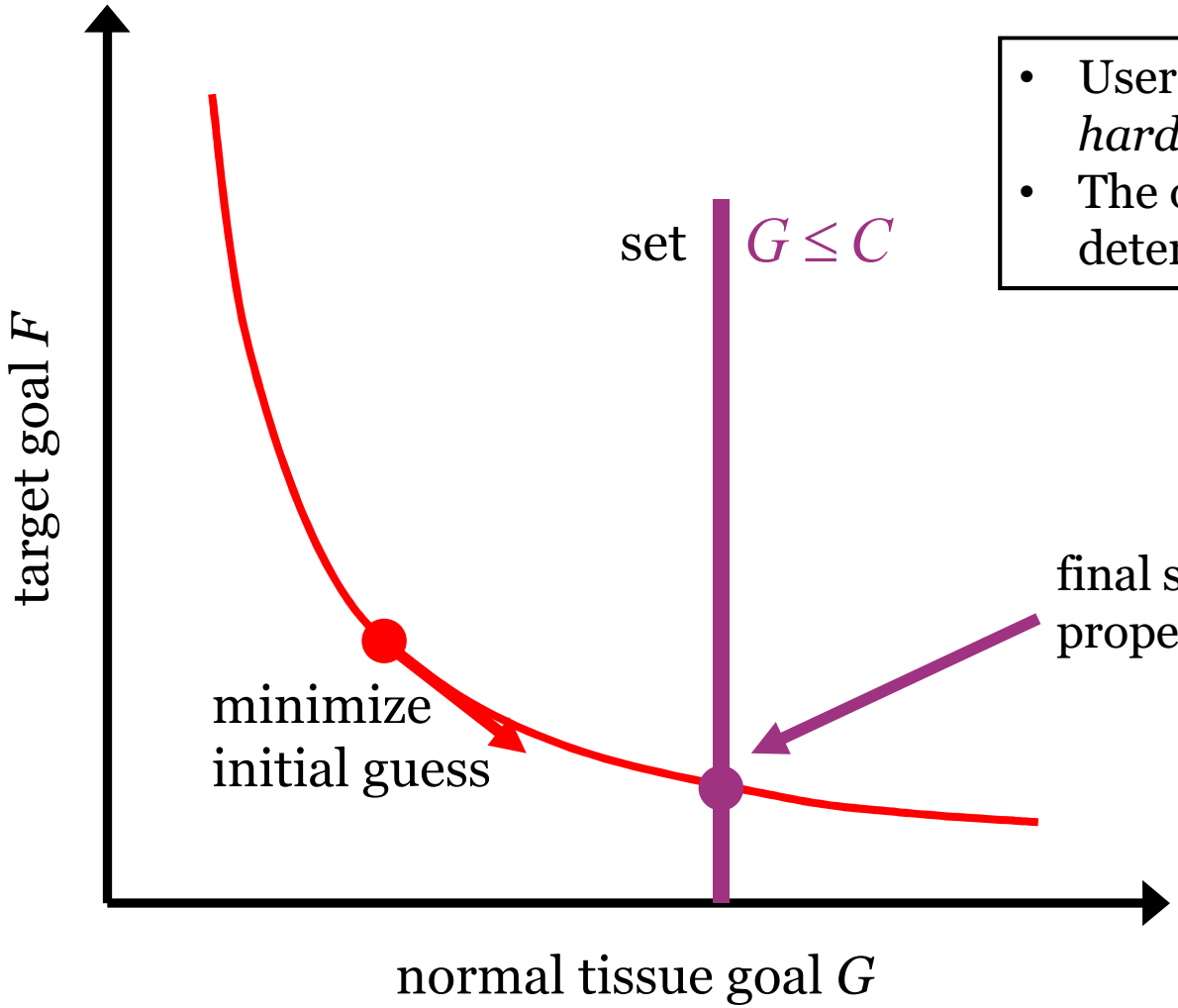
- goals and weight factors are ***not inversely proportional***
- ***changing one*** weight factor ***affects all*** other goals

Weight factors make the solution space accessible, but are not well suited for exploring it during the search for the best balance between goals.

Navigating the Solution Space: Libraries of Proposals ('multicriterial/Pareto-optimization')

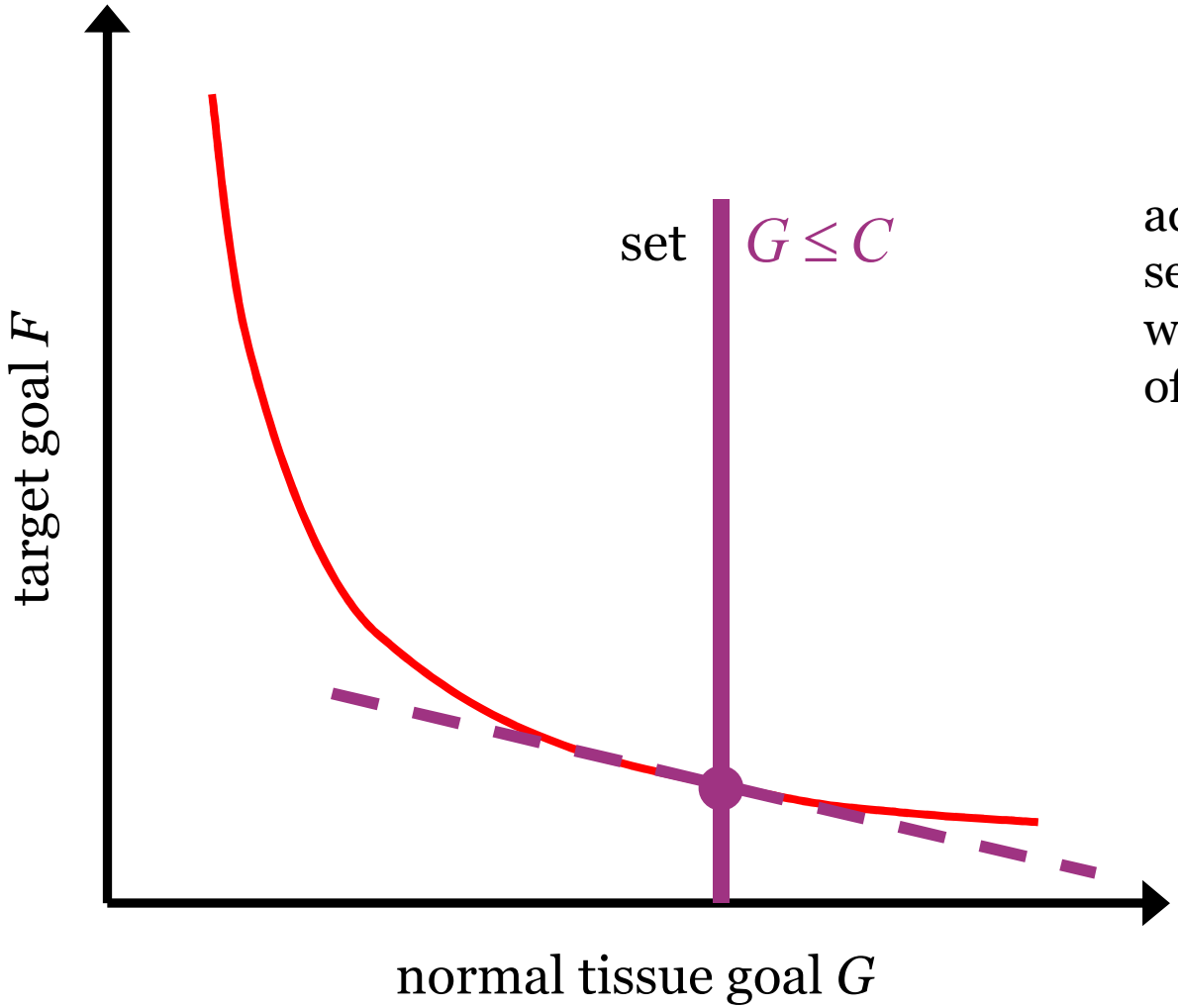


Navigating the Solution Space: Constrained Optimization



- User sets the goals in terms of *hard constraint(s)*
- The optimizer automatically determines the weight factor(s)

Navigating the Solution Space: Constrained Optimization and Sensitivity



additional information:
sensitivity of goal F
with respect to changes
of the constraint G

„Automated planning“

Automatic choice of the „optimal“ pareto-optimal plan!

Basic idea/aim:
Automatically find a patient-specific set of CF-prescriptions/constraints as starting point of an IMRT optimization that will result in the *clinically most acceptable plan* from the solution space of this patient.

How does it work?

- Finding: In a population of patients, a similar compromise of PTV coverage vs. dose constraints will be *realizable* for patients with ‚similar geometry‘
- Use of prior knowledge to predict realizable DVHs/dose presciptions for a new patient
- Algorithm based on database of patients/correlation model/machine-learning/…

To some extent institution-specific; the larger the ‚input‘ patient-database, the better it works…

FAQ:

- Why do we need dose optimization if all we want to do is dose planning? √
- What do we actually optimize? Dose? Cost functions? Beamlets? √
- What optimization algorithm to use, and why? √
- Weight Factors, Constraints, Objectives – why is it so complex? √
- What is the point in optimizing undeliverable fluence profiles first?

Because:

• The ‘free fluence’ optimization problem is well behaved. Fast algorithms can be used.

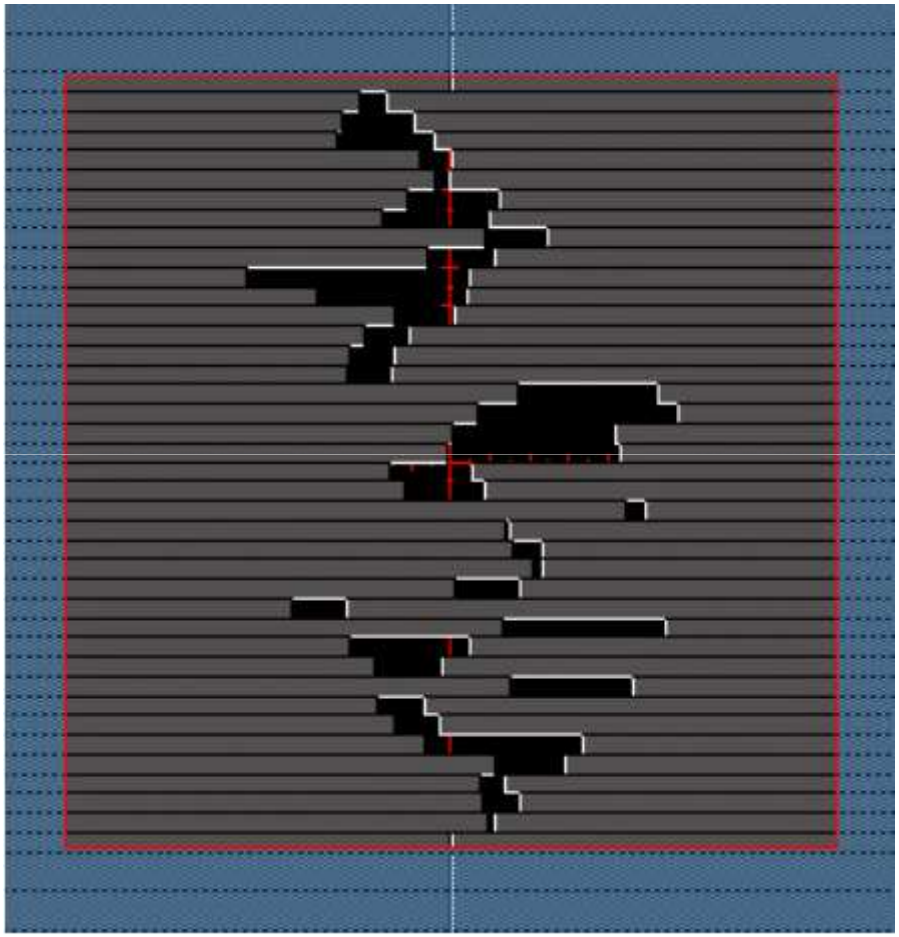
• The solution space needs to be explored in an interactive manner. MLC sequencers and precise dose calculation are too slow yet.

• e.g. ‘Pareto-optimization/navigation’ currently only works for fluence distributions

…vs. Direct Aperture Optimization (DAO), Simulated Annealing (Rapid Arc ©)…:

• It is a long way to go from coarse field shapes to the patient-specific optimum fluence distribution. *It is very easy to get trapped in local minima when directly optimizing field shapes.*

Direct aperture optimization needs a control of segment shapes and good initial segment shapes



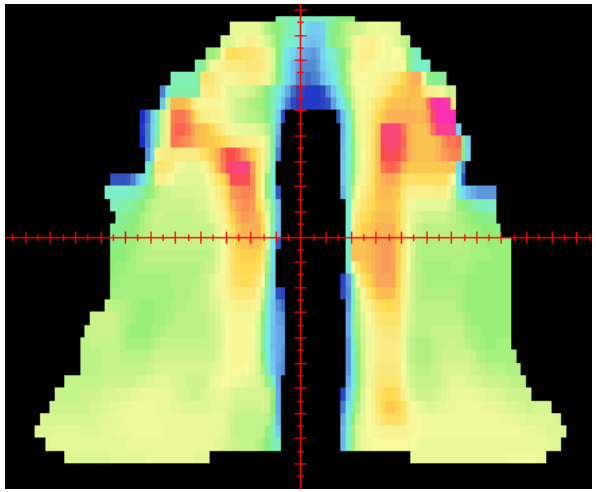
This is what a local minimum looks like

FAQ:

- Why do we need dose optimization if all we want to do is dose planning? √
- What do we actually optimize? Dose? Cost functions? Beamlets? √
- What optimization algorithm to use, and why? √
- Weight Factors, Constraints, Objectives – why is it so complex? √
- What is the point in optimizing undeliverable fluence profiles first? √
- Why does the dose get worse after MLC sequencing?

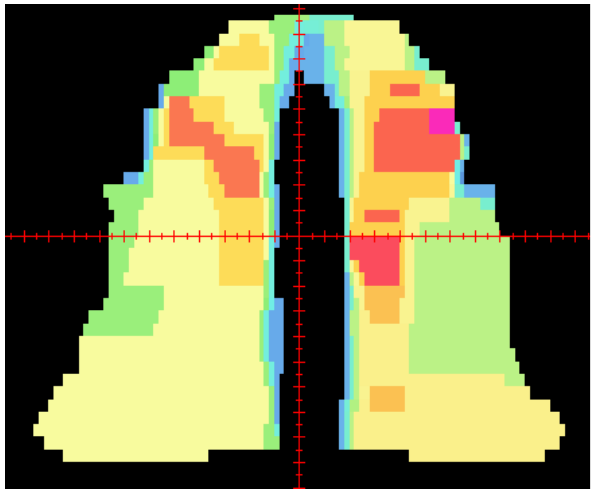
courtesy M. Alber

MLC delivery deviates from the ideal profiles



optimal fluence profile

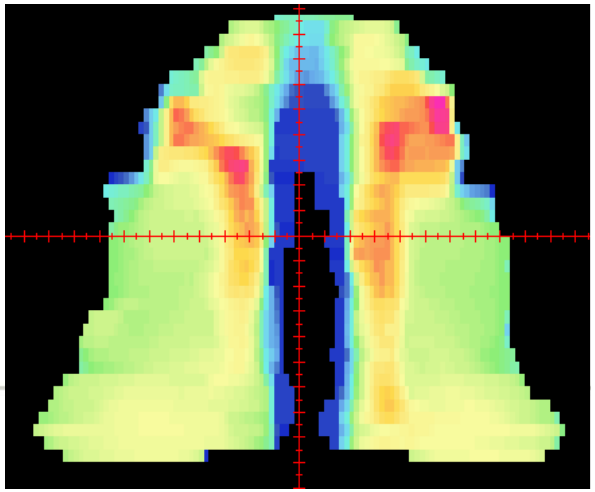
sequencing: translation into (coarser, but deliverable) segments



step and shoot

sliding-window dynamic

improvement

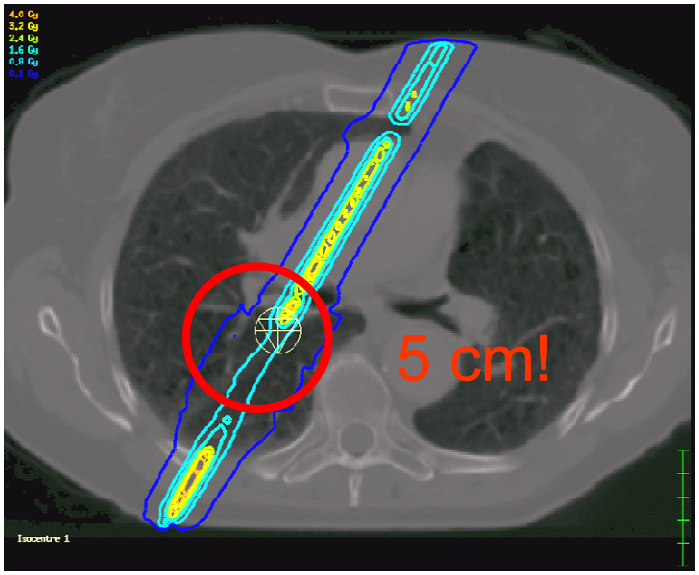


⇒ **(1) Quality loss due to *discretization***

⇒ **(2) Hi-quality dose calculation of segment doses changes dose distribution!**
(usually: to the worse)

Precise dose computation DURING fluence profile optimization is immensely expensive!

- computation time issue
- computer memory issue (10.000 beamlets can be ~Gigabyte memory)



4 mm x 2 mm beamlet, 15 MV, 3D-PB

This is why some planning system calculate simplified beamlet doses:

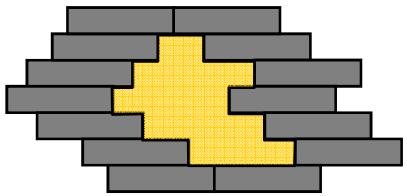
- ➢ too steep and/or truncated penumbra, esp. in presence of inhomogenieties
- ➢ thus, OARs may wrongly appear sufficiently spared
- ➢ the final, more precise dose calculation reveals such initial simplifications!

→ **plan degradation of segmented plan!**

How to tackle these problems…

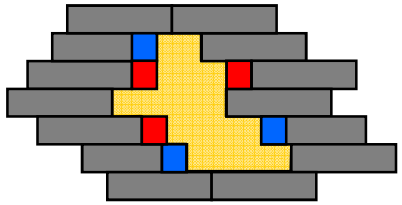
...perform a subsequent **Segment-Shape-Optimization!**

Iterative segment shape (aperture) optimization



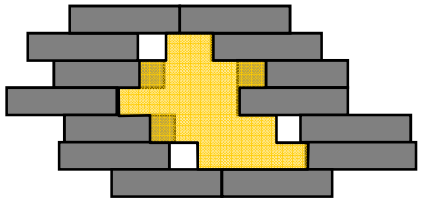
initial field

• *trial-and-error*
(e.g. simulated annealing)
• *derivatives*
• *brute force*



candidates for opening or closing leaves

dose calculation



altered field

chose next field, repeat

This is why…

…most IMRT planning methods follow a two stage process.

Idea:

stage 1 produces a guess of a good solution

stage 2 refines the result of stage 1 (Aperture optimization)

Problem: the longer the way from the initial guess to the end result, the easier it is to get lost.

Rotational IMRT techniques: Alternatives for the creation of initial guesses

+ dynamic conformal arc

+ using the projection of target volumes / organs at risk to the beam apertures (e.g. Elekta ERGO++)

+ translating a fluence profile into sliding-window segments and arranging them on an arc (Philips Pinnacle SmartArc, Elekta Monaco)

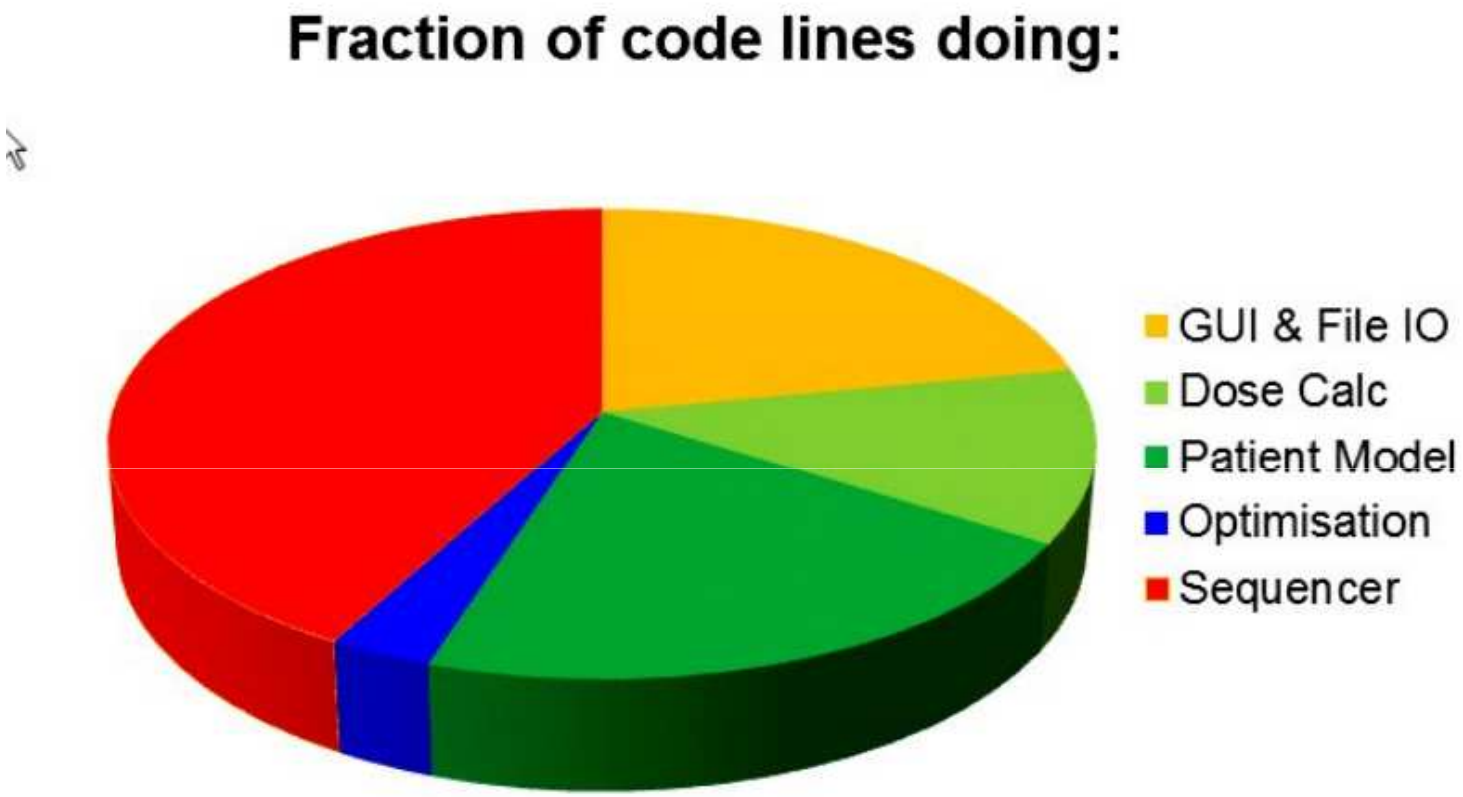
+ an iterative angular resolution refinement, starting from beam shapes at large angular intervals and interpolating them (Varian RapidArc)

FAQ:

- Why do we need dose optimization if all we want to do is dose planning? √
- What do we actually optimize? Dose? Cost functions? Beamlets? √
- What optimization algorithm to use, and why? √
- Weight Factors, Constraints, Objectives – why is it so complex? √
- What is the point in optimizing undeliverable fluence profiles first? √
- Why does the dose get worse after MLC sequencing? √
- How much optimization is actually in an IMRT optimizer?

courtesy M. Alber

How much optimization is in an optimizer?



IMRT-TPS *Hyperion*
(Univ. Tübingen)

FAQ:

- Why do we need dose optimization if all we want to do is dose planning? √
- What do we actually optimize? Dose? Cost functions? Beamlets? √
- What optimization algorithm to use, and why? √
- Weight Factors, Constraints, Objectives – why is it so complex? √
- What is the point in optimizing undeliverable fluence profiles first? √
- Why does the dose get worse after MLC sequencing? √
- How much optimization is actually in an IMRT optimizer? √
- Cost functions: Which one to use when?

Again: What are Typical Treatment Goals?

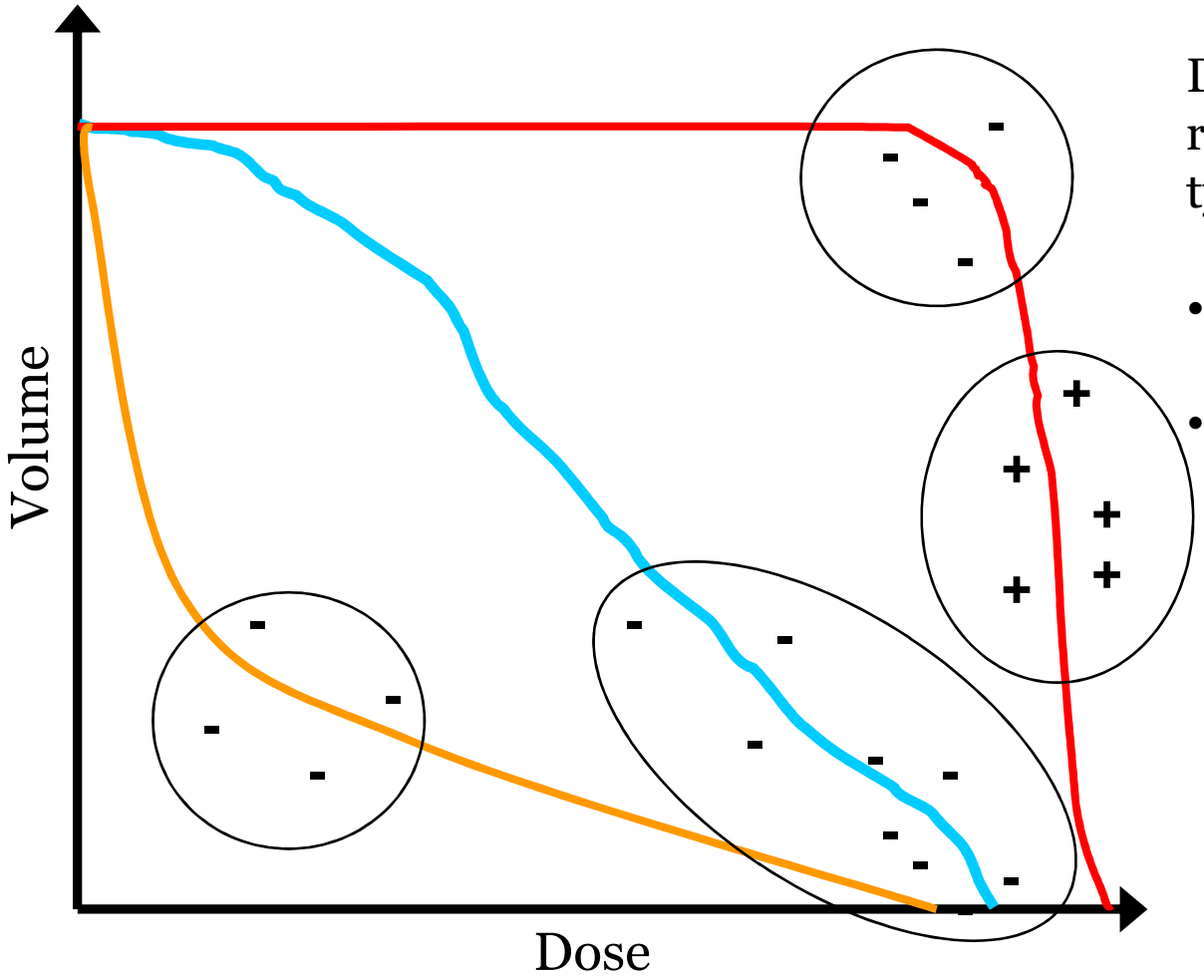
Target goal:	achieve a ***sufficient target dose***
Normal tissue goals:	do not ***exceed acceptable doses*** in N ***organs***
Conformality goal:	target dose should be ***conformal***, ***spare generic normal tissue***
Homogeneity goal:	***no large*** or ***excessive hot spots*** in the ***target***

*These goals need to be communicated to the planning algorithm in a **concise**, **comprehensive**, **transparent** and **numerically expedient** manner.*

↓

Cost Functions!

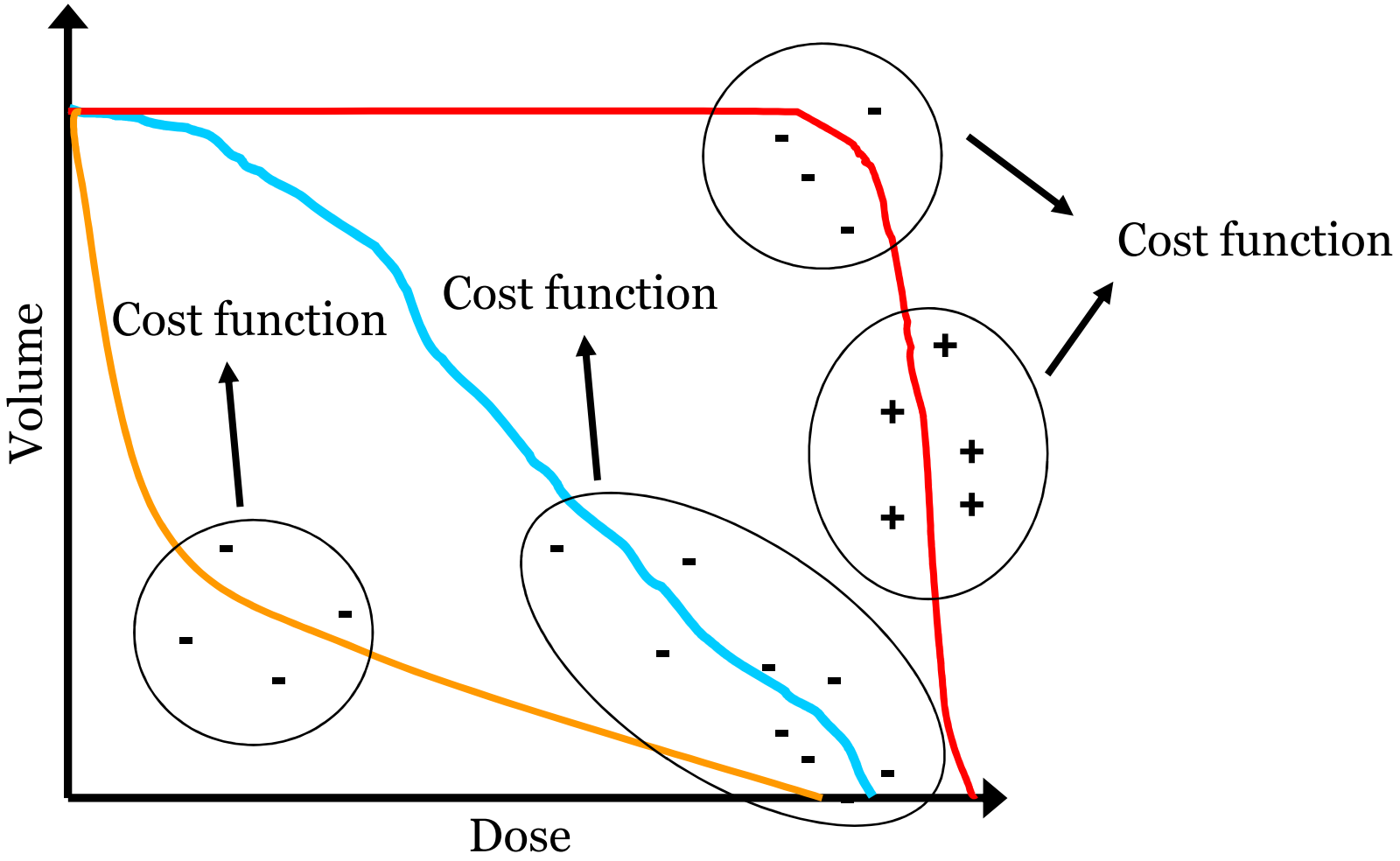
A cost function rewards the positive aspects of a DVH and penalizes the negative ones in a single number



Different goals require different types of cost functions:

- *physical:* dose-, dose/volume-based
- *biological*

A cost function rewards the positive aspects of a DVH and penalizes the negative ones in a single number



Properties of Cost Functions

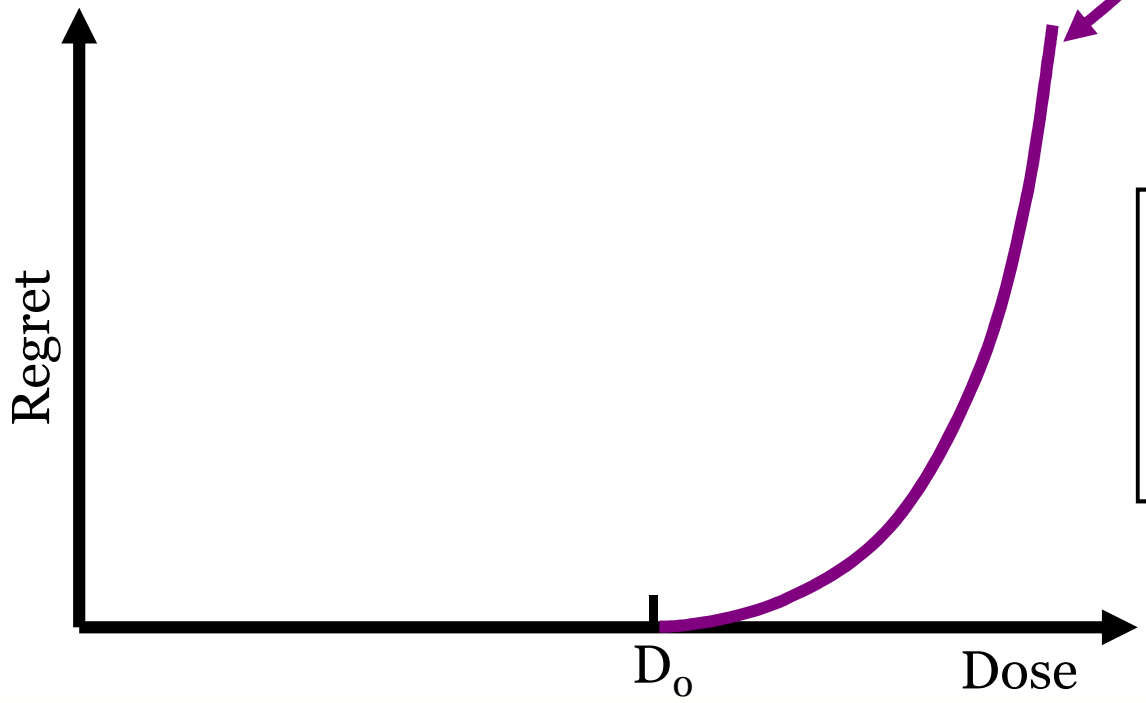
- Purpose: to ***quantify*** our concept of ***quality*** of a dose distribution
- By convention: if D_1 is ***better*** than D_2, then $F(D_1) < F(D_2)$:
  search the ***minimum*** of F.
- Commonly, the cost function has the form:

$$F = \frac{1}{N}\sum_{i=1}^{N} f(D_i)$$

D_i	Dose in volume element i of an organ/tumour
N	Number of volume elements
$f(D)$	number of **regret** assigned to the dose D in this volume element

The most Common Physical Cost Function: One-Sided Quadratic Penalties

$$F_{overdose} = \frac{1}{N}\sum_{i=1}^{N}(D_i - D_0)^2$$

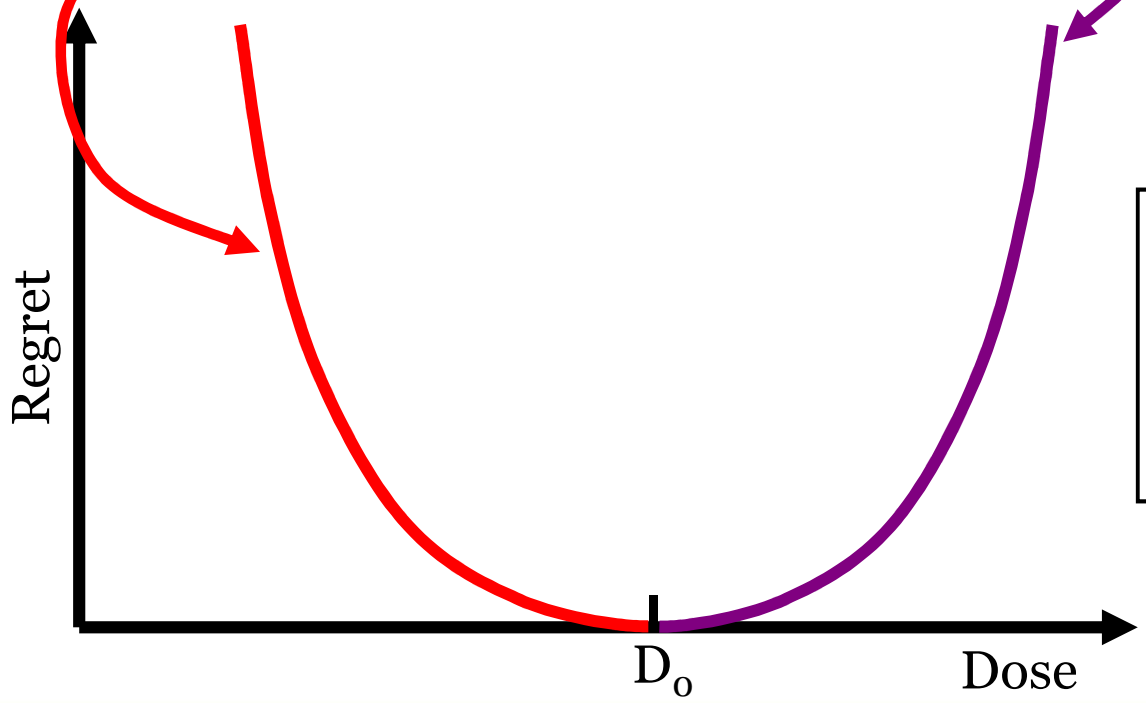


The ***regret grows quadratically*** with the violation of the required/ tolerated dose

The most Common Physical Cost Function: One-Sided Quadratic Penalties

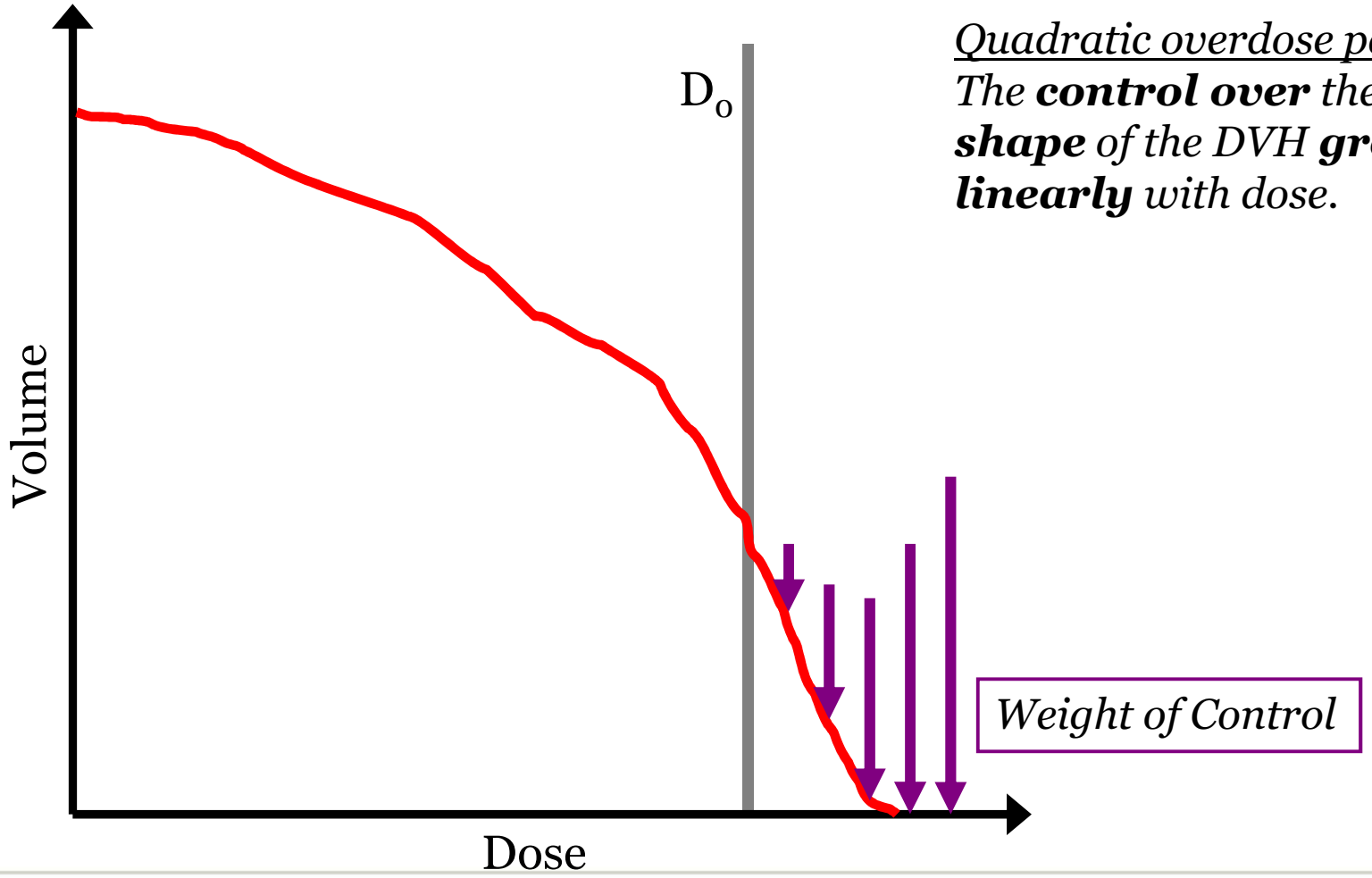
$$F_{overdose} = \frac{1}{N}\sum_{i=1}^{N}(D_i - D_0)^2\,\theta(D_i - D_0)$$

$$F_{underdose} = \frac{1}{N}\sum_{i=1}^{N}(D_i - D_0)^2\,\theta(D_0 - D_i)$$



The ***regret grows quadratically*** with the violation of the required/ tolerated dose

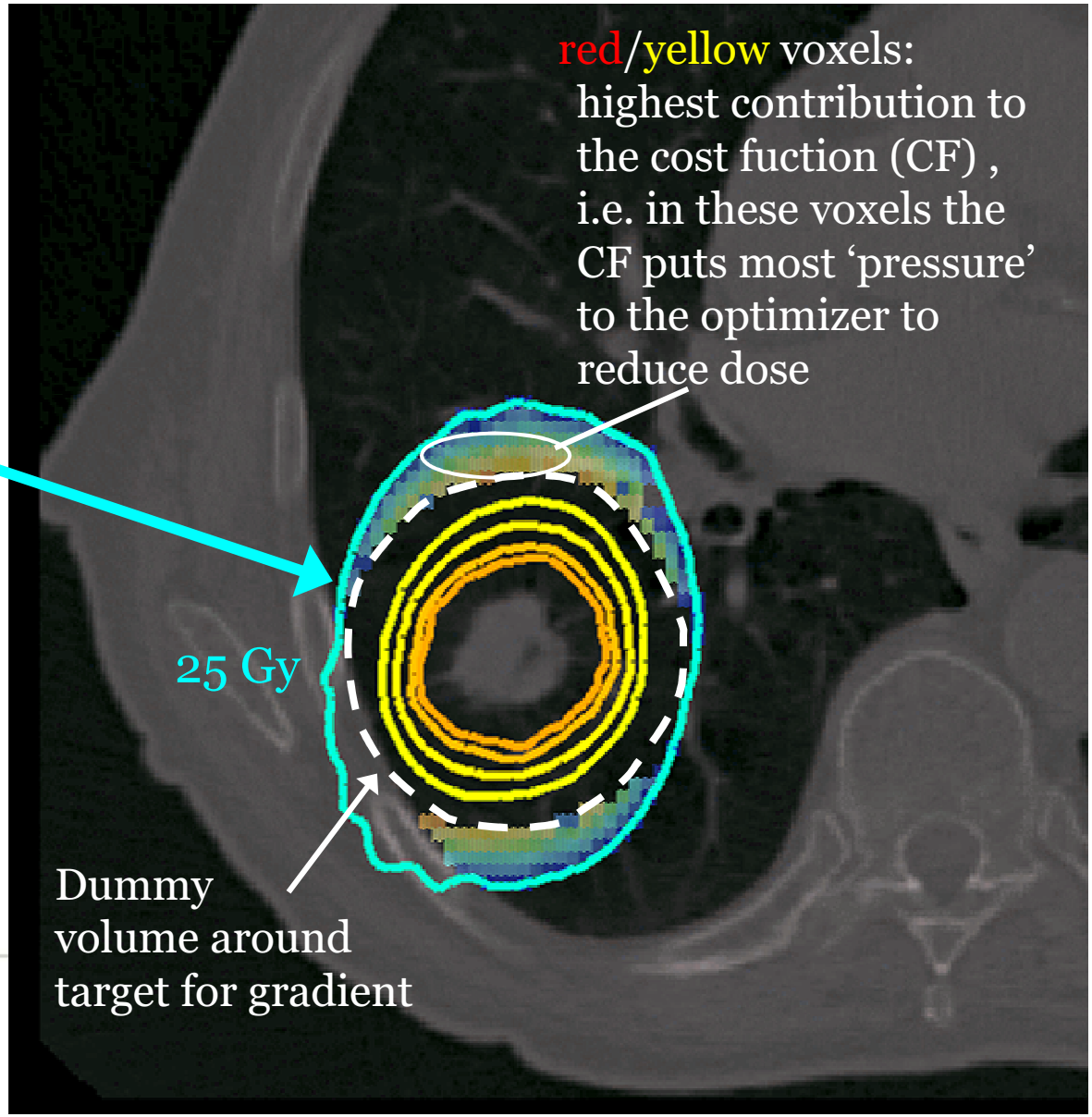
The Purpose of a Cost Function is to control the Shape of the DVH: Control Weights



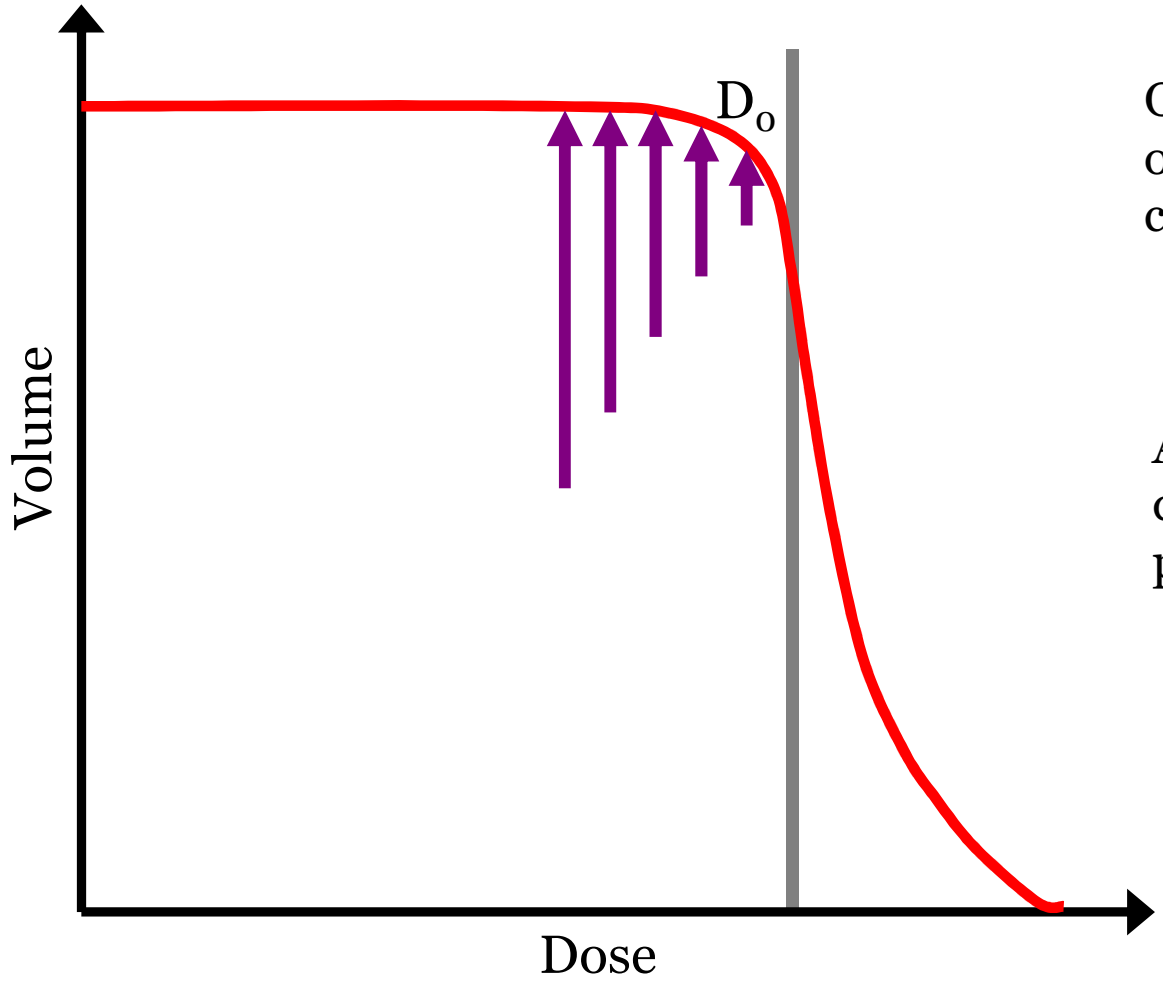
Quadratic overdose penalty:
*The **control over** the **shape** of the DVH **grows linearly** with dose.*

Local Control of a Quadratic Overdose Penalty

example:
quadratic overdose penalty for D_0=25Gy, i.e. area of control only at doses > 25 Gy



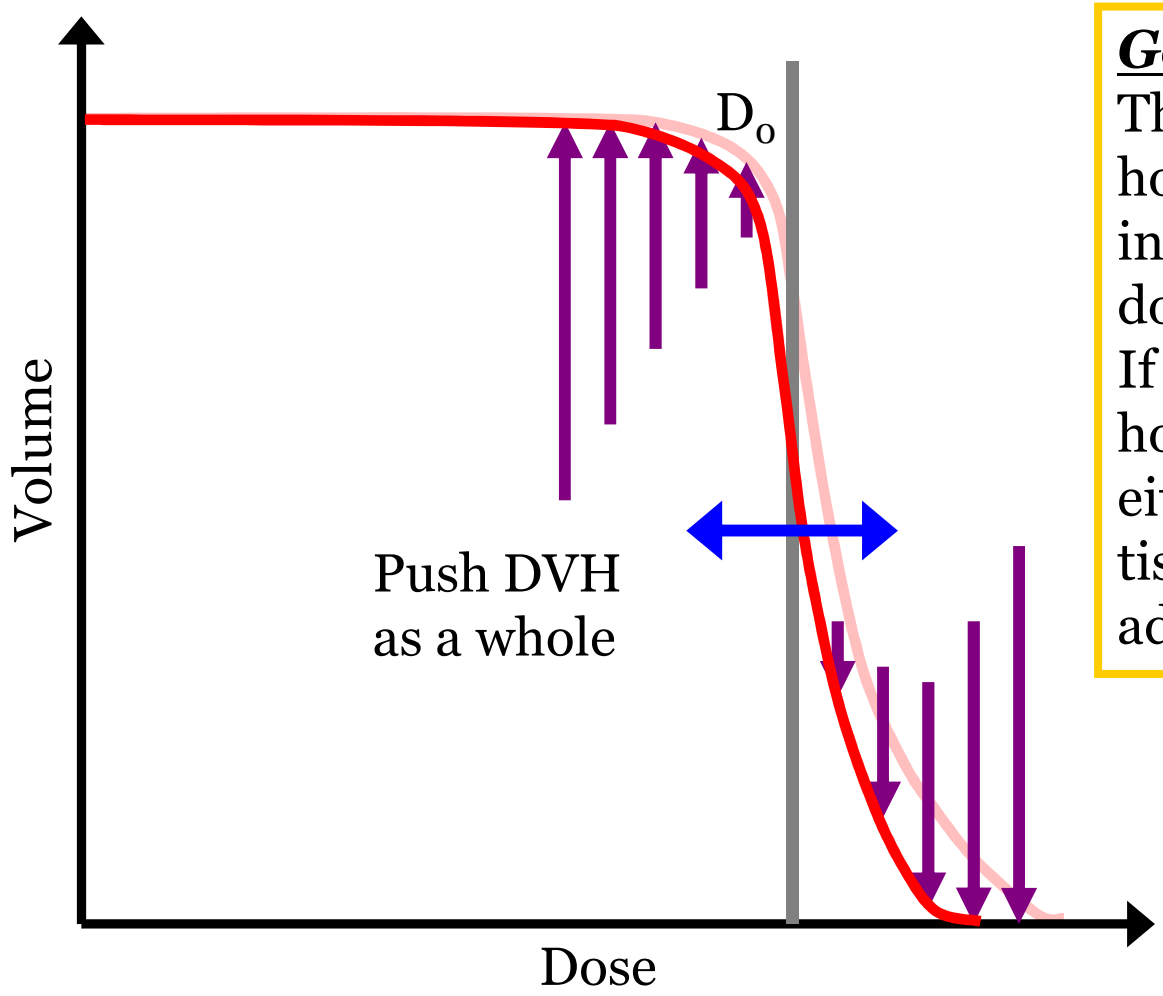
Control of a Target DVH by a One-Sided Quadratic Underdosage Penalty



Only one aspect of the target DVH is controlled.

Add a one-sided quadratic overdosage penalty!

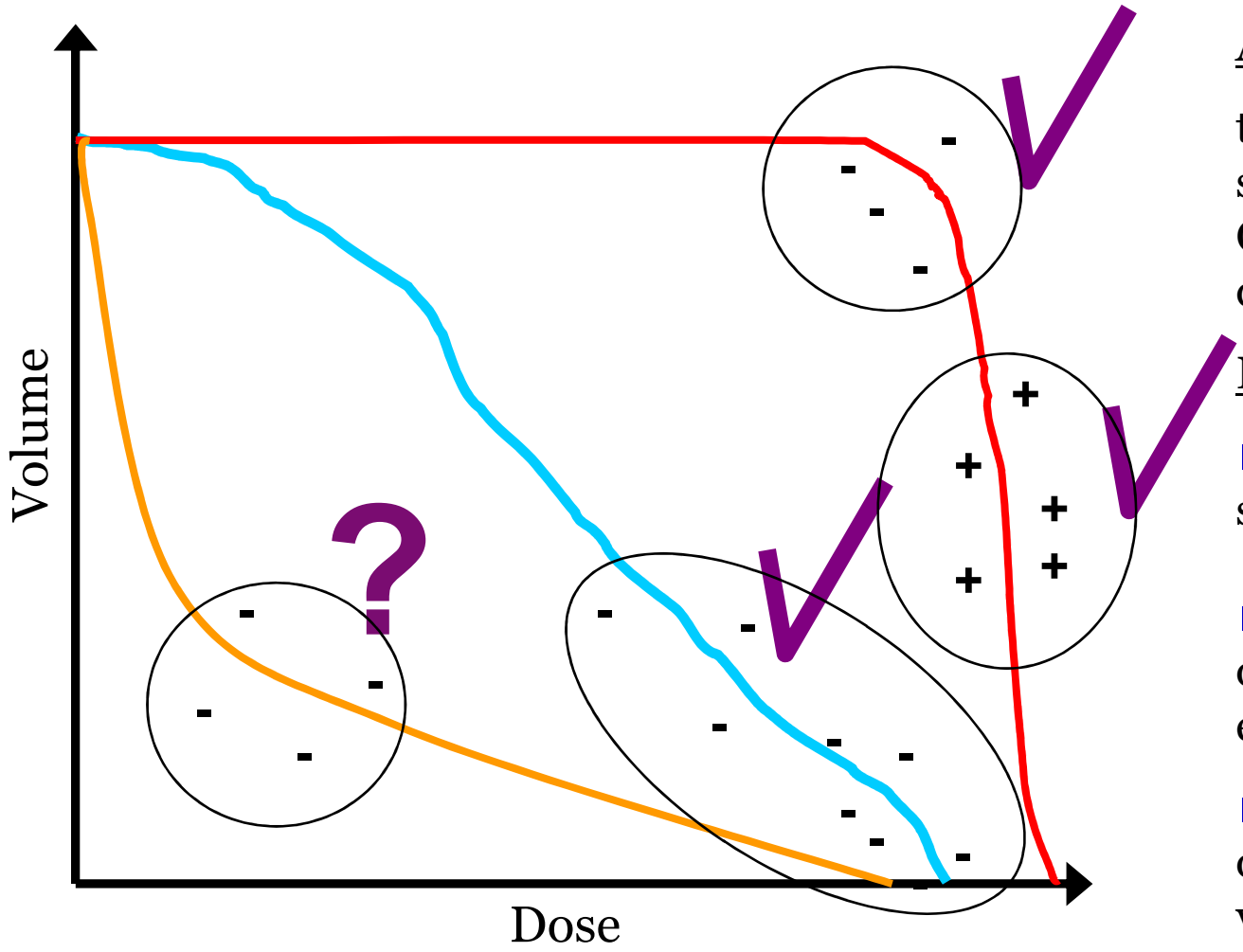
Control of a Target DVH by Two One-Sided Quadratic Penalties



Golden Rule:

The overall target dose homogeneity cannot be influenced by target dose penalties alone.
If the target dose is not homogenous enough, either reduce normal tissue sparing, or add more beams.

Can quadratic penalties control all aspects of dose?



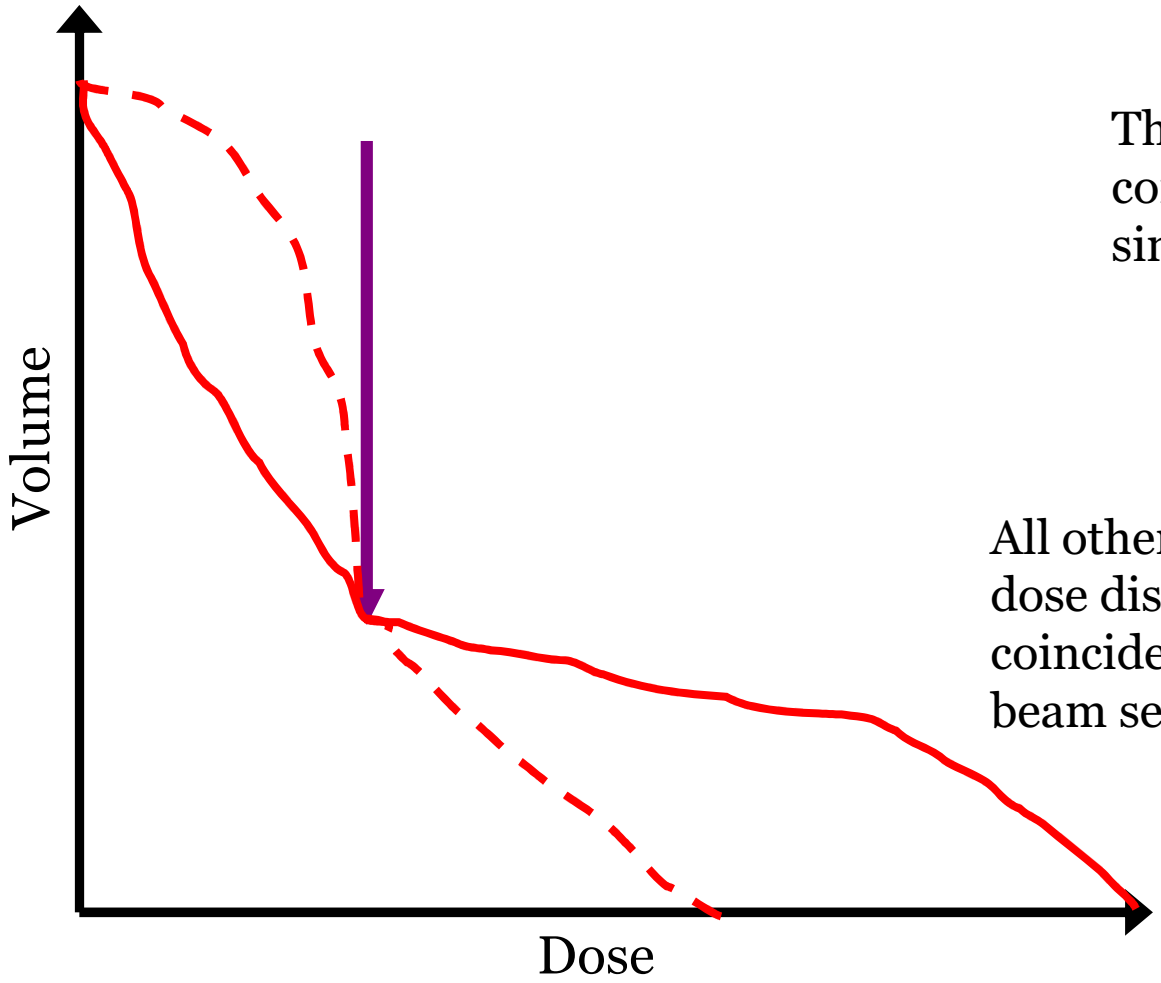
Application:

target hot and cold spots,
OARs with maximum dose restrictions.

Limitations:

- Cannot enforce a strict dose limit.
- Does not express organ specific volume effects.
- Cannot be applied to organs with a large volume effect.

DVH Control for Organs with a Large Volume Effect: DVH Constraints



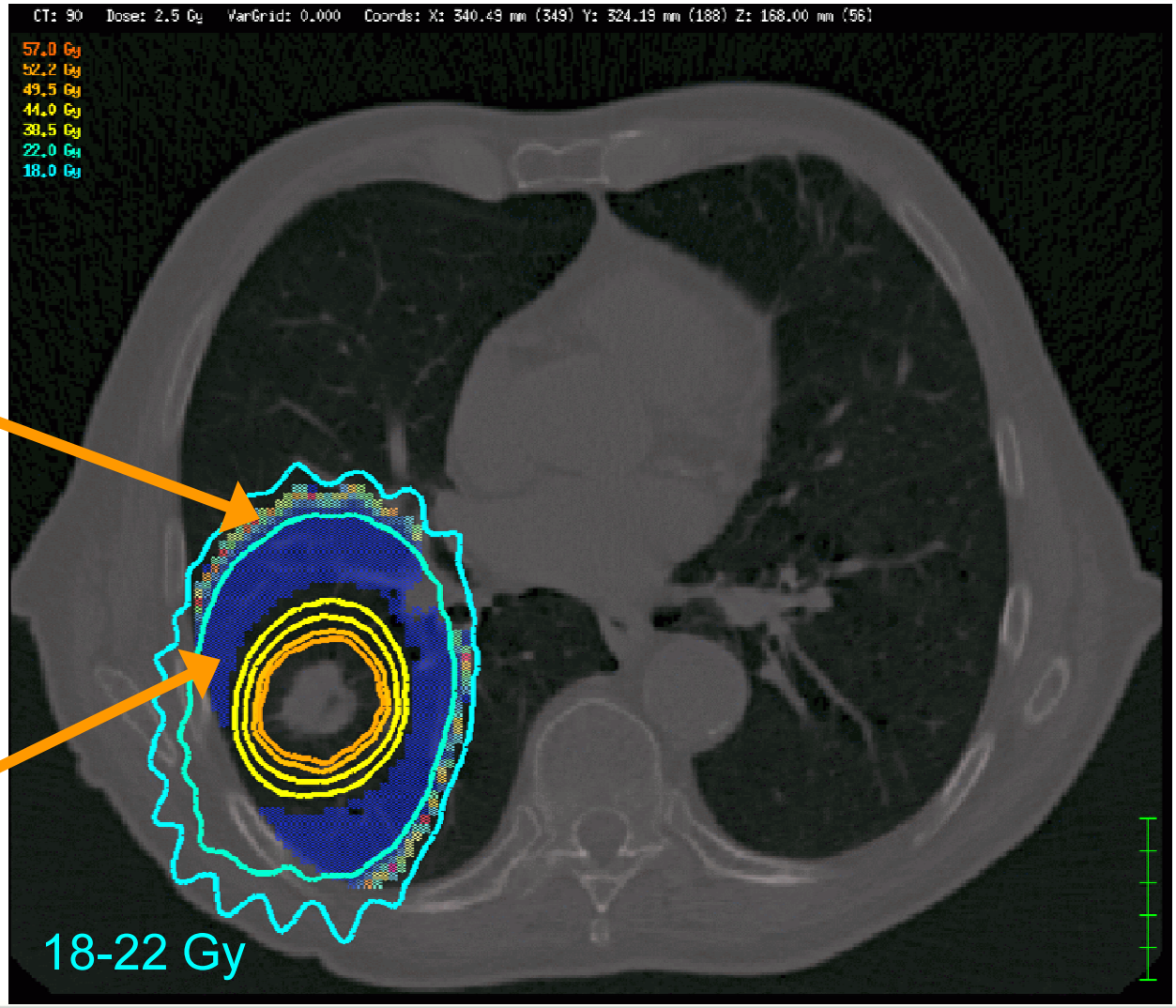
The constraint controls only a single point.

All other aspects of the dose distribution are merely coincidence (patient geometry, beam setup)

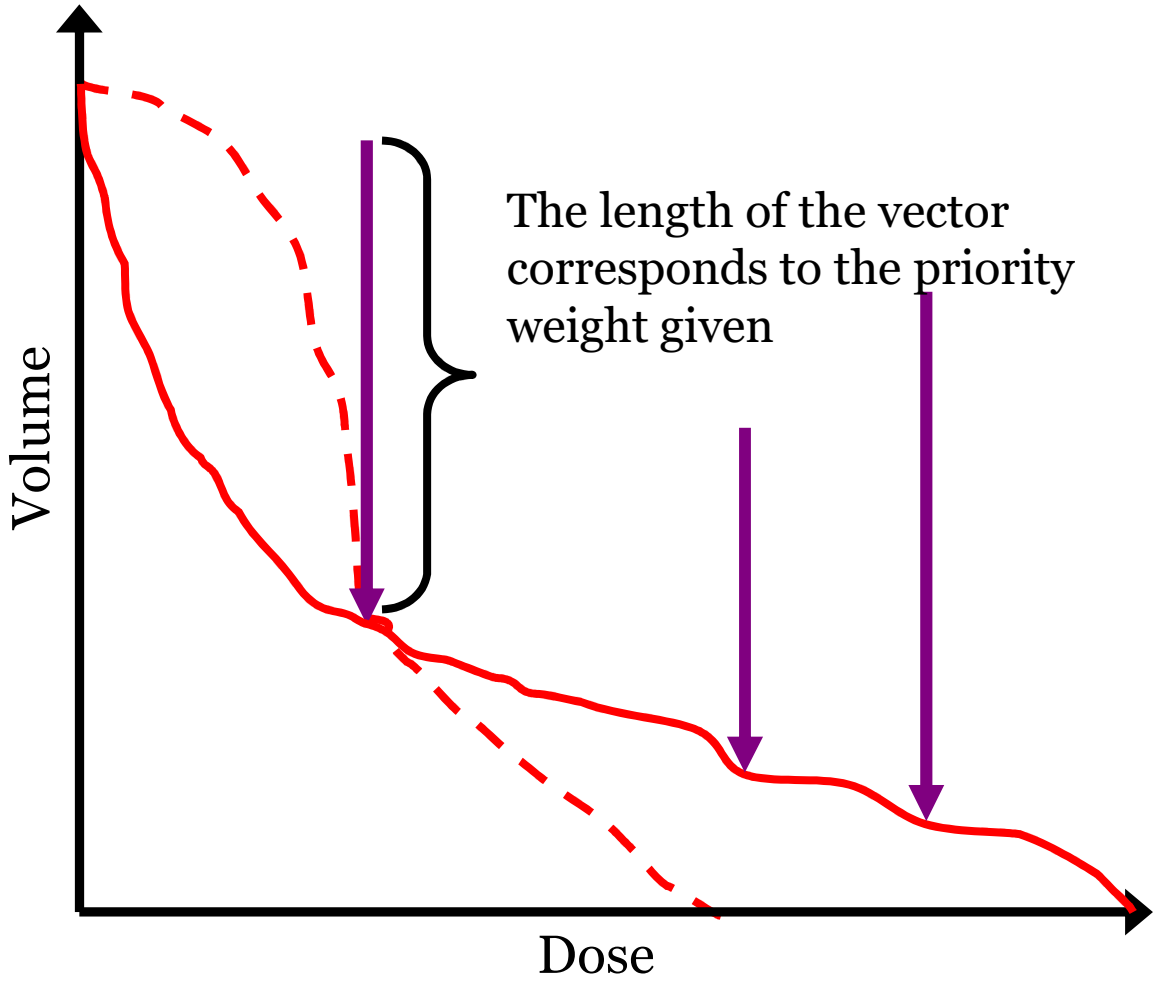
Local Control of a DVH constraint:

example:
constraint to V_{20},
i.e. area of control
only at dose = 20 Gy

Volume given up
by cost function

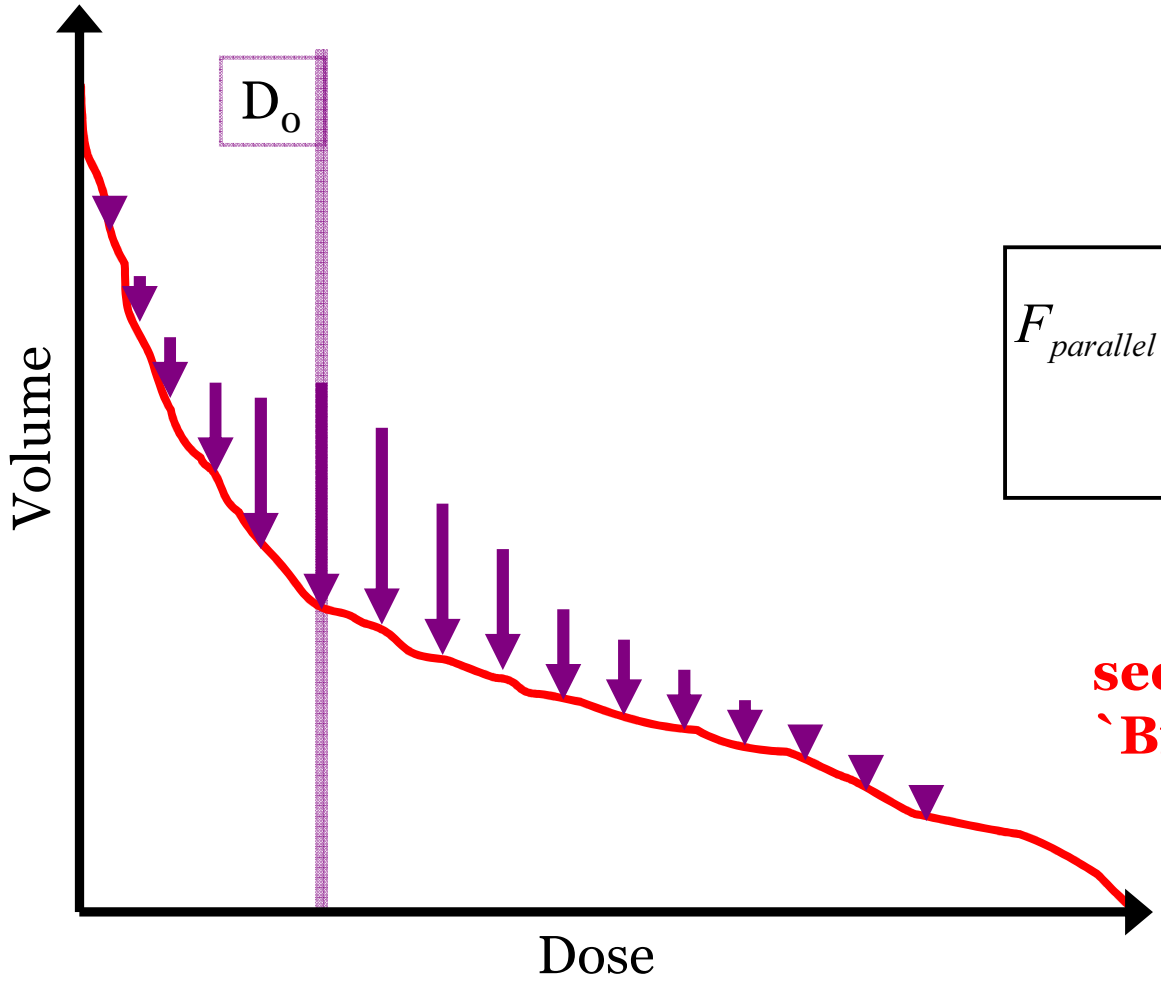


DVH Control for Organs with a Large Volume Effect: Multiple DVH Constraints



Multiple constraints may be combined to enhance control over the dose distribution.

How does a Parallel Complication Model control the DVH?



$$F_{parallel} = \frac{1}{N}\sum_{i=1}^{N}\frac{1}{1+\left(\frac{D_0}{D}\right)^k}, \quad k \geq 1$$

(or similar functions)

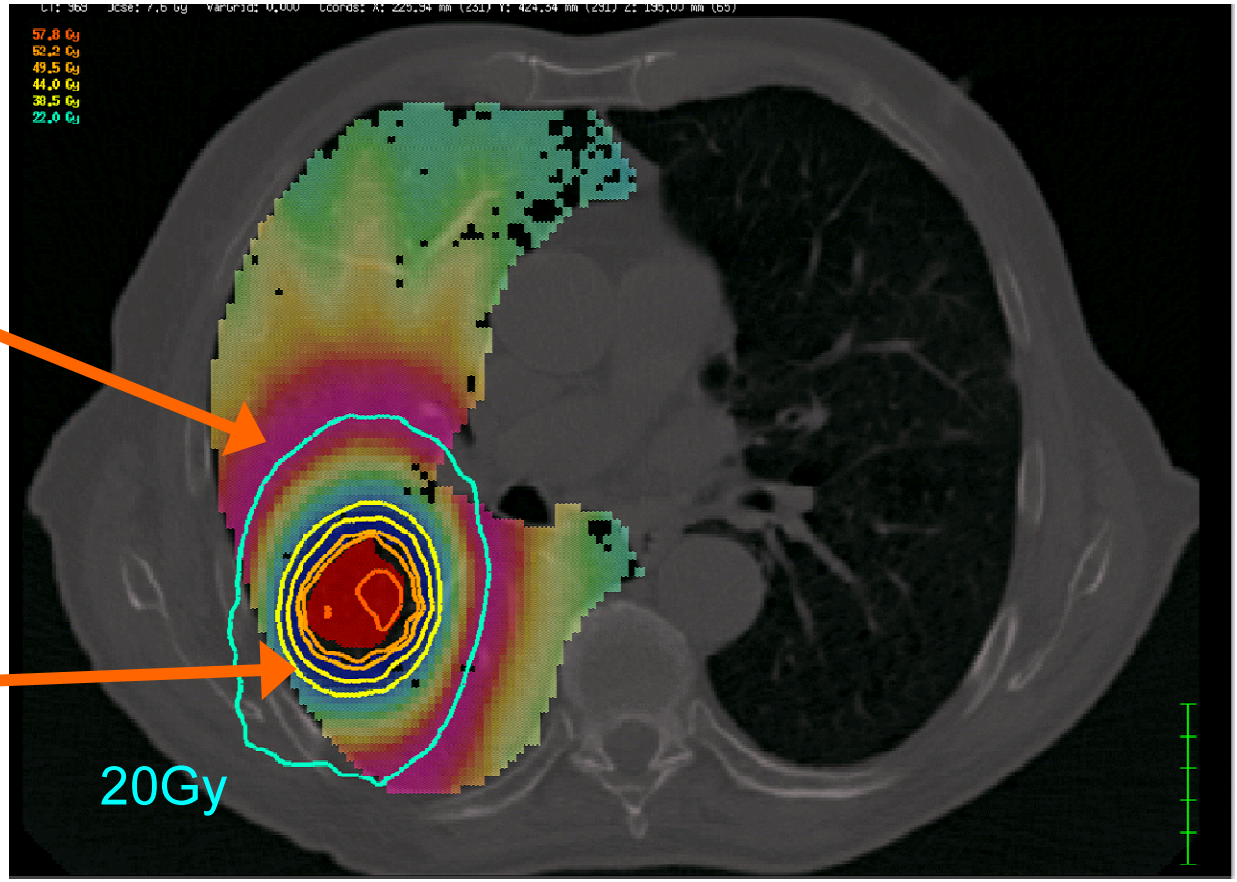
see presentation `Biological Optimization`

Local Control of a Parallel Cost Function

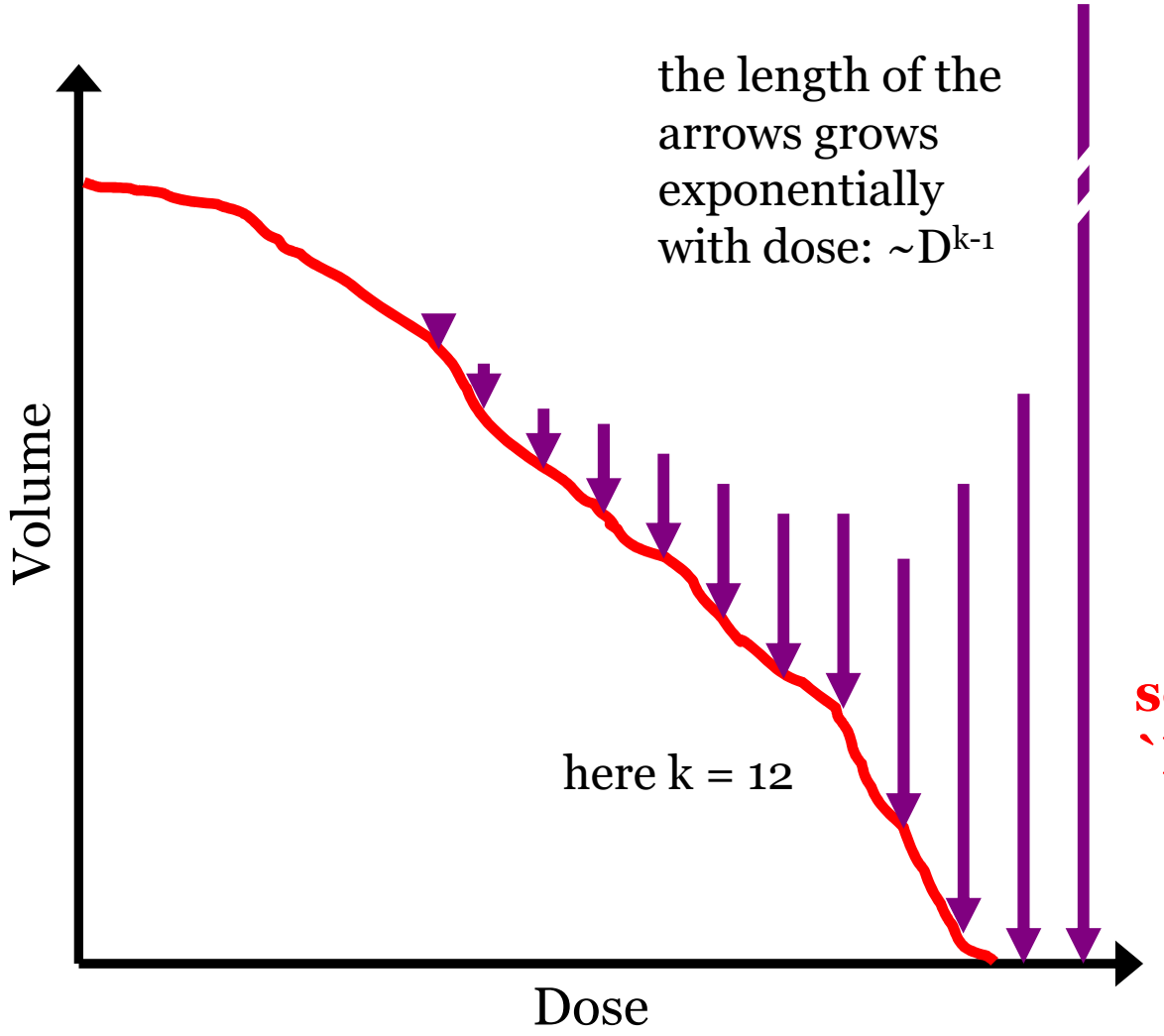
example:
parallel constraint with
D_0=20Gy

Volume of greatest weight in optimization

Volume given up by cost function



How does a Serial Complication Model control the DVH ?

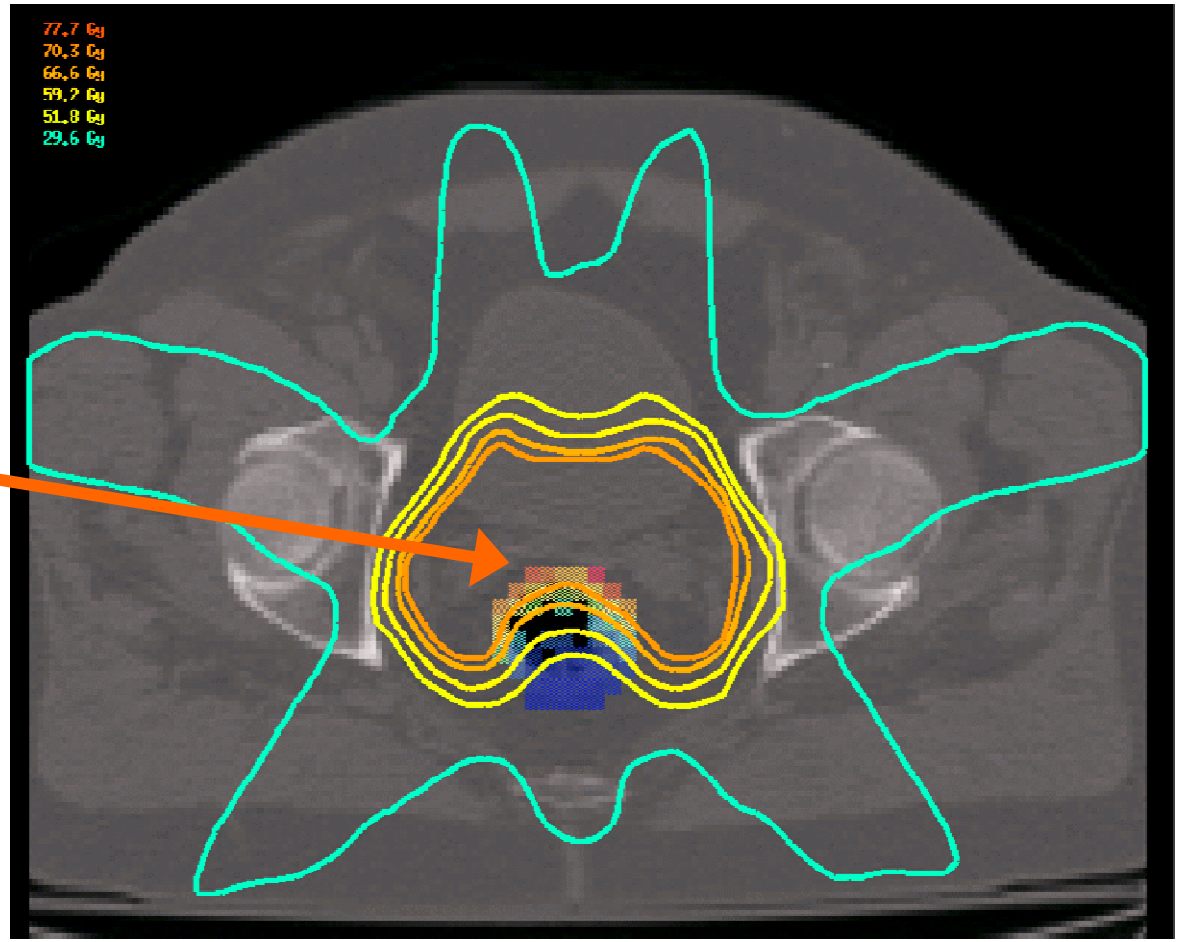


$$F_{serial} = \frac{1}{N}\sum_{i=1}^{N} D_i^{\,k}, \quad k \geq 1$$

see presentation `Biological Optimization`

Local Control of a Serial Cost Function

Volume of greatest weight in optimization



FAQ:

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- What do we actually optimize? Dose? Cost functions? Beamlets? √
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- Weight Factors, Constraints, Objectives – why is it so complex? √
- What is the point in optimizing undeliverable fluence profiles first? √
- Why does the dose get worse after MLC sequencing? √
- How much optimization is actually in an IMRT optimizer? √
- Cost functions: Which one to use when? √
- Do we really need 'complicated' cost functions like the serial complication model CF?

Clinical relevance of the serial cost function

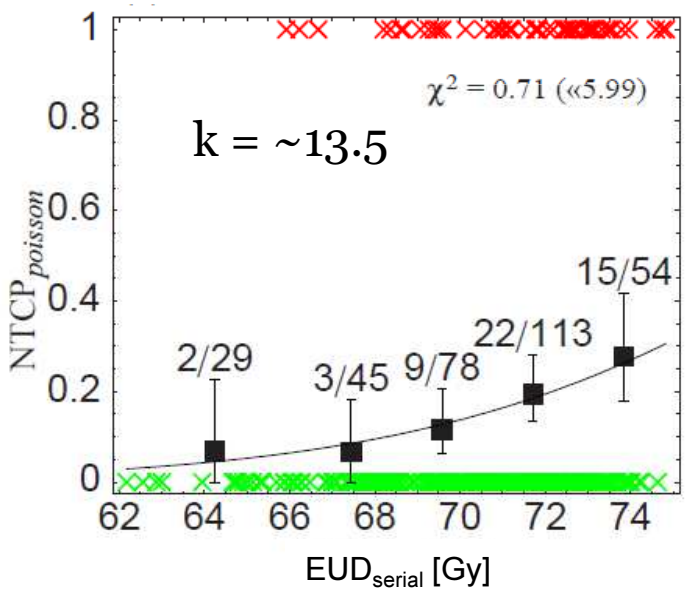
$$F_{serial} = \frac{1}{N}\sum_{i=1}^{N} D_i^{\,k}, \quad k \geq 1$$

directly related to...

$$EUD_{serial} = \sqrt[k]{\frac{1}{N}\sum_{i=1}^{N} D_i^{\,k}}$$

For rectal complications (grade>=2 bleeding) strong clinical evidence, that NTCP is clearly related to rectal EUD!

M. Söhn et al. 2007 (IJROBP 67(4))
Quantec-Report: J. M. Michalski et al. 2010 (IJROBP 76(3))



Summary & Conclusions

- **IMRT treatment planning means *exploring the limits of physics* for each patient**:
  - the 'physics in the patient': Is the desired dose distribution possible? (steepness and placement of gradients,...)
  - Applicability by MLC hardware

- numerous different and partly conflicting target and normal tissue goals need to be balanced — **IMRT *optimization algorithms* are tools to 'navigate' through the solution space**

- *'navigation'*: using weight factors, constraints, or a library of precalculated plans

- different approaches to arrive at applicable, segmented plans: typically a *two-stage optimization-process*

Summary & Conclusions [2]

- Cost functions define numerical rules for the IMRT optimizer, which features of a dose distribution should be rewarded and which ones penalized.
  CFs are essential, because the *ideal* dose distribution does usually not exist

- The dose distribution in a volume results from a complex interplay of the cost functions defined in this volume, and all other cost functions.
  It is therefore extremely important to understand which features of the dose distribution are controlled by a cost function and which are uncontrolled and thus random.

- The ideal dose distribution cannot be arrived at by the perfect set of cost functions, but only in an interactive process of exploring physically possible trade-offs between different treatment goals.

⇒ IMRT optimization is about as much art as it is science
⇒ BUT: experience helps!
⇒ …as does a good TPS: should make the effects of all actions on the dose distribution transparent to the user in order to reduce trial-and-error

Modelling adverse effects after radiotherapy

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ESTRO School

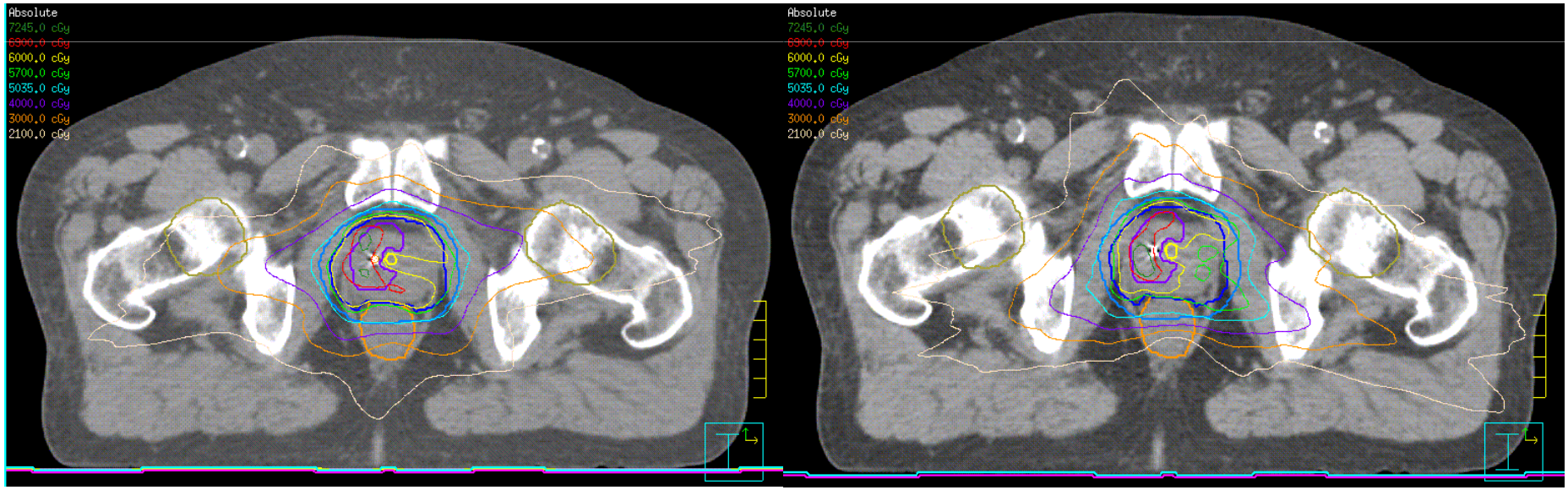
Contents

- Introduction (what, why, when?)
- Organ architecture and the volume effect
- From DVH to normal-tissue complication probability
- Models: LKB, critical volume, relative seriality
- Equivalent uniform dose
- Fractionation correction
- Model accuracy
- Applications

Objective

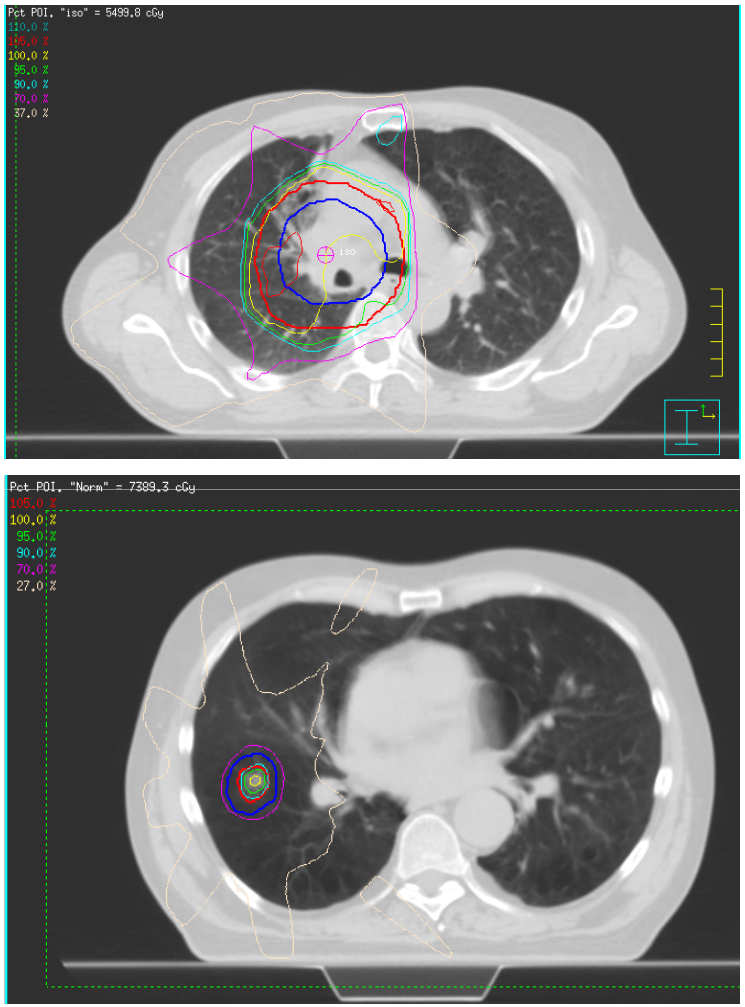
- IMRT/VMAT offers huge flexibility in distributing the dose around the target (many degrees of freedom)
- Optimisation/evaluation requires quantification/representation of the risk from very different dose distributions.

2 plans with equal estimated effect:



Which ‘dose’ is relevant for normal tissues?

- All tumours of a certain type and stage prescribed the same dose
  - based on perceived risk of toxicity in the population
- Wide variation in dose throughout the tissue
- Different anatomy = different dose distribution
- Prescription dose not a good measure of normal-tissue complication probability (NTCP) for an individual
- Good NTCP models could help us limit the risk for each individual



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What is an NTCP model?

Complex models have been developed to describe what happens when you irradiate a patient. These are called *mechanistic* NTCP models.

- Limited understanding of mechanisms limits the scope of the models
- Requires too many parameters to allow fitting to clinical data
- Useful for generating hypotheses and testing methodology

Outcome modelling instead looks for a statistical relationship between treatment plan parameters and the incidence of a particular complication. This is called *empirical* or *phenomenological* NTCP modelling.

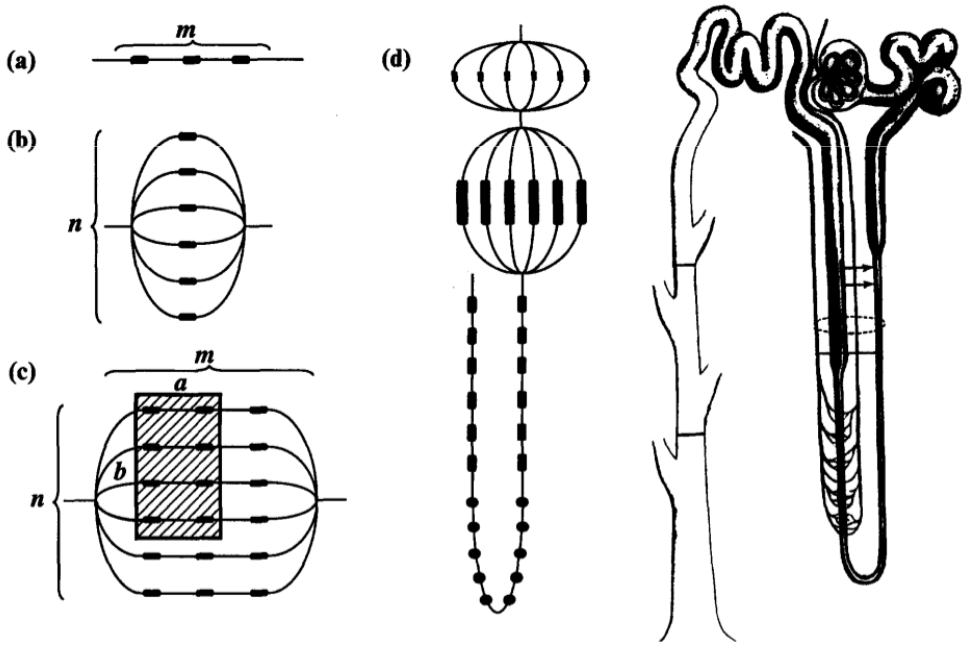
- Regression-type models
- A few parameters fitted to treatment and outcome data
- Can fill the same purpose as dose-volume constraints

This lecture will focus on empirical NTCP modelling.

Organ architecture

- Consider normal tissues as consisting of multiple functional subunits (FSU)*, for tissue repair purposes
- Each organ different in terms of FSU interaction
- Parallel type response like a rope: it can perform its function even if some strands break.
  - Large volume effect
- Serial type response like a chain: function is lost if any one link breaks.
  - Small volume effect
- Kidney: nephron

*Withers et al. 1988



Källman et al. Int J Radiat Biol, 1992

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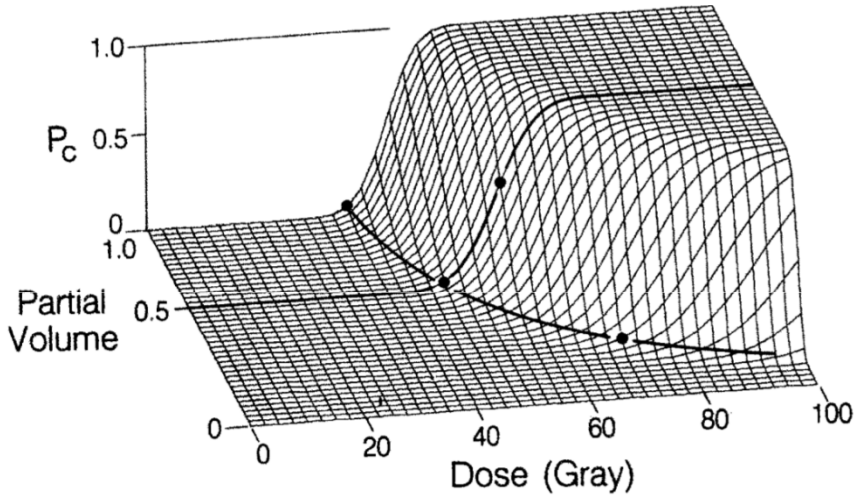
Volume effect

Sigmoid dose-response for partial (uniform) organ irradiation

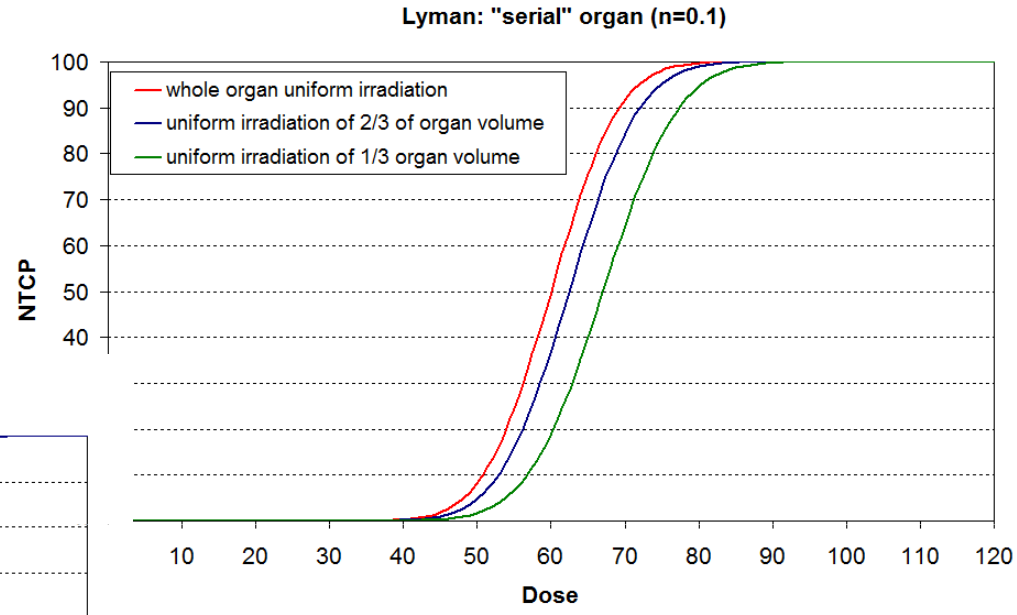


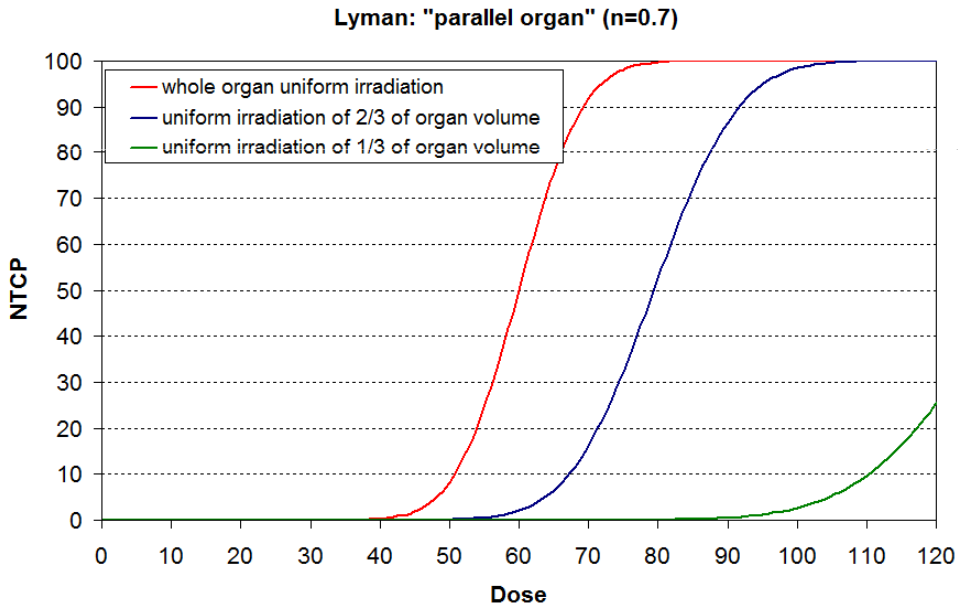
Lyman, Radiat Res Suppl, 1985

The volume effect depends on:

- Functional reserve
- Migration of cells
- Stochastic tissue damage
- Inflammatory response?

Volume effect cont.





Courtesy Giovanna Gagliardi

1991 ⇒ parameters for 28 complications Burman et al, IJROBP

Dose-volume constraints

- The relevant dose-volume parameter depends on the volume effect
- Small volume effect: maximum dose
- Large volume effet: V_x or mean dose
- Emami et al. (IJROBP 1991) published tolerance values for partial organ irradiation
- The QUANTEC initiative (IJROBP 2010) is a special issue with one article per organ

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● *Original Contribution*

TOLERANCE OF NORMAL TISSUE TO THERAPEUTIC IRRADIATION

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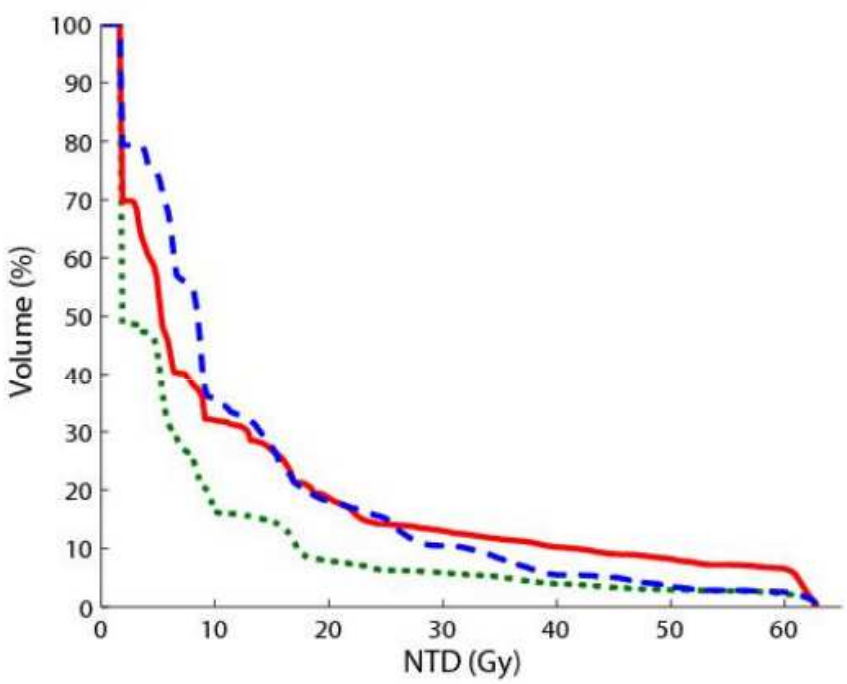
[1]Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO 63110; [2]Memorial Sloan-Kettering Cancer Center, New York, NY 10021; [3]Department of Radiation Therapy, University of Pennsylvania School of Medicine and the Fox Chase Cancer Center, Philadelphia, PA 19111; [4]Massachusetts General Hospital, Department of Radiation Medicine, Boston, MA 02114 and Harvard Medical School; and [5]University of California-Lawrence Berkeley Laboratory, Research Medicine and Radiation Biophysics Division, Berkeley, CA 94720

Dose-volume histogram



Dose-volume histograms (DVHs) are used when evaluating a treatment plan.

- Useful for comparing alternative plans
- If two DVHs overlap it is not clear which one is better.
- Dose-volume constraints are surrogates for a normal-tissue complication probability (NTCP)
- What if we could associate a risk value to each DVH?

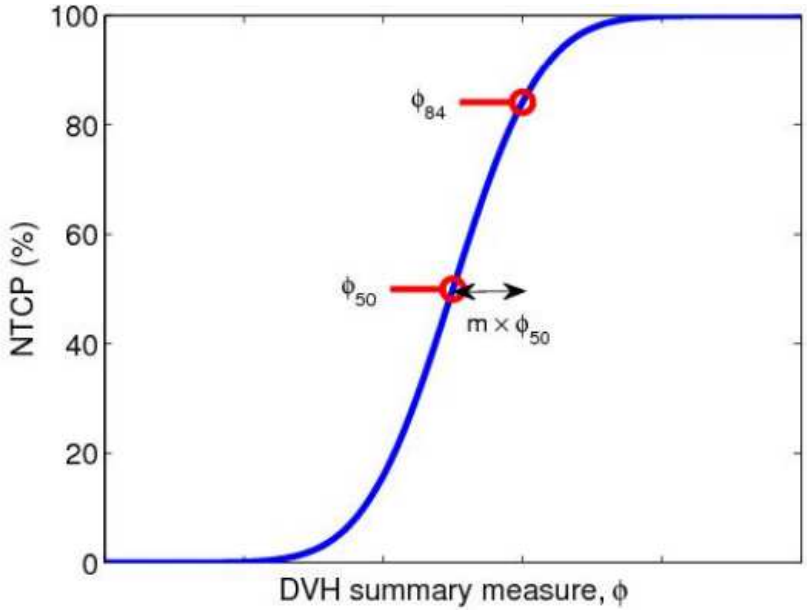
NTCP model structure

Regression models cannot handle 3D dose distributions or DVHs; requires a summary measure φ, e.g. mean dose, which takes the volume effect into account.

The most widely used (Lyman) model uses a cumulative normal function with 2 parameters: φ_{50} and m. Additional parameters might be needed for the DVH summary.

$$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-x^2/2} dx$$

$$t = \frac{\varphi - \varphi_{50}}{m \cdot \varphi_{50}}$$



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LKB model

The Lyman-Kutcher-Burman (LKB) model uses an Equivalent Uniform Dose (EUD)*:

$$EUD = \sum_i \left(D_i^{\frac{1}{n}} \frac{V_i}{V_{tot}} \right)^n$$

- D_i = total dose to bin i
- V_i = absolute volume in bin i
- V_{tot} = total organ volume
- n = volume effect parameter

Parameter 'n' is organ (endpoint) specific

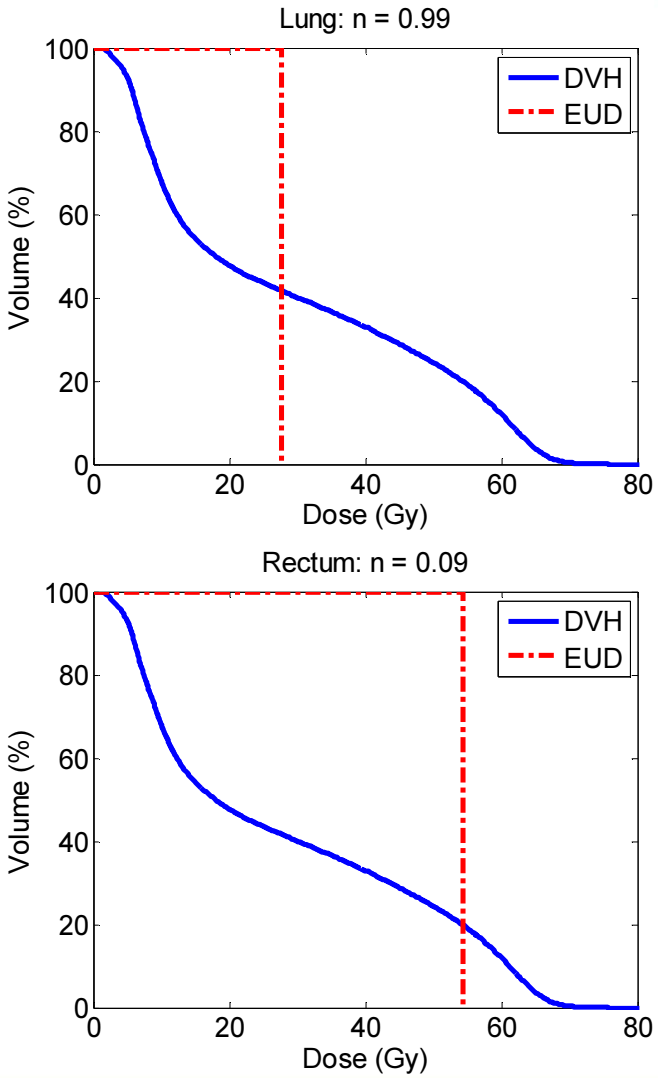
- Low (≈ 0): small volume effect, EUD ≈ max dose
- High (= 1): large volume effect, EUD = mean dose

*Original representation with *effective volume* rather than EUD

Equivalent uniform dose

Note that to apply the LKB model as described, a whole-organ inhomogeneous dose distribution must be converted to a uniform dose, EUD, which has the same likelihood of causing a complication.

The parameter *n* is introduced to represent volume dependence of the organ.



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Generalised equivalent uniform dose

Different expressions for EUD have been proposed, but Niemierko's GEUD has been the most widely implemented.

The parameter 'a' is equivalent to 1/n (the LKB parameter for volume effect).

NTCP scales (non-linearly) with EUD; sufficient to minimise EUD

WE-C2-09

A generalized concept of Equivalent Uniform Dose (EUD)

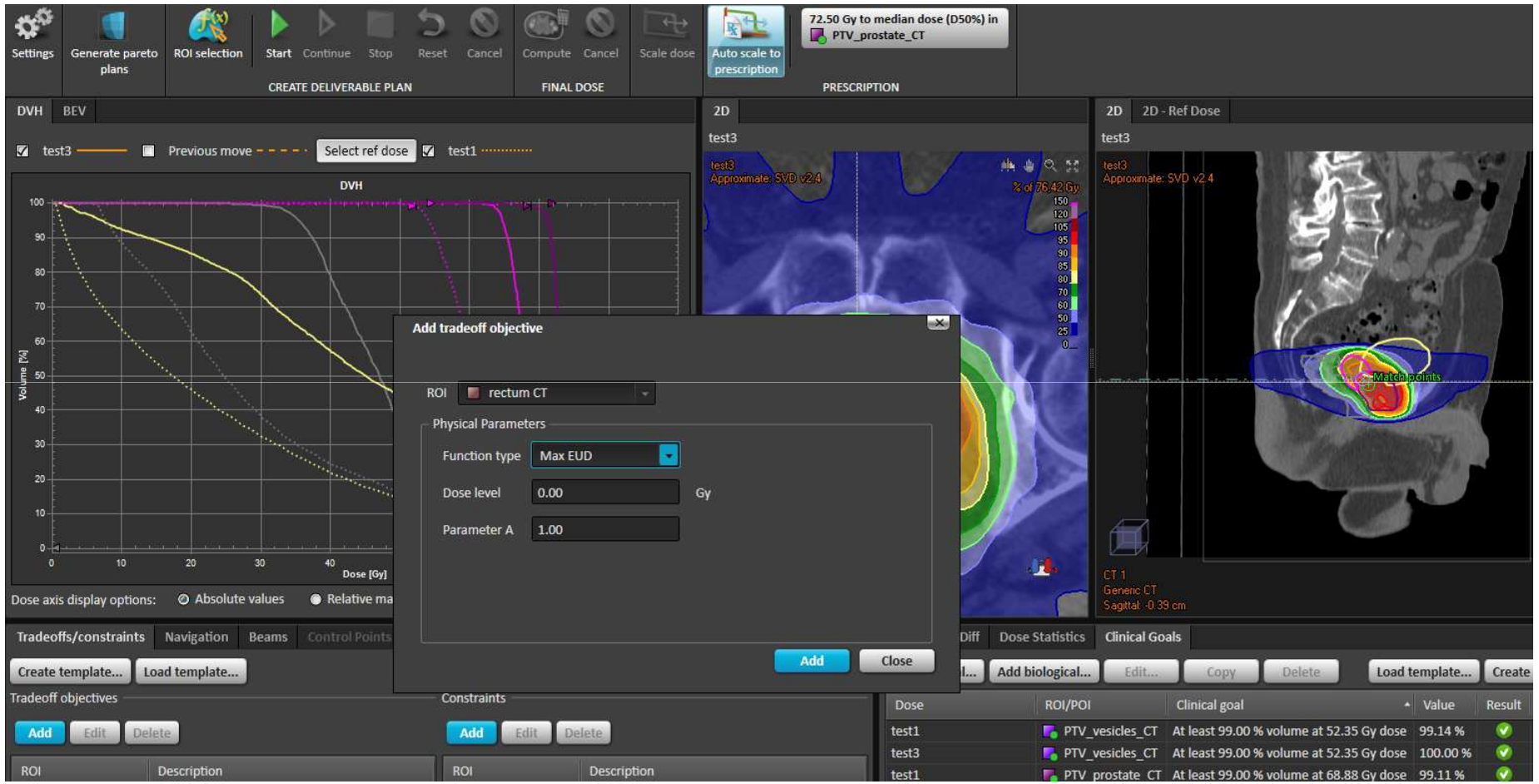
A Niemierko*, Massachusetts General Hospital, Boston, MA

Dose distributions are inherently non-uniform, especially for normal structures. Although IMRT is capable of delivering superior dose distributions tailored to the geometry of irradiated structures; it often produces inhomogeneous target dose distributions. To quantitatively evaluate a treatment plan one needs to know the consequences of dose inhomogeneity for all structures of interest. A concept of Equivalent Uniform Dose (EUD) for tumors, based on models of clonogen survival, has recently been developed and investigated in several clinical settings. Here we report on generalization of the EUD concept that applies to both tumors and normal tissues. Based on the analysis of outcomes for several clinical studies providing volumetric information for tumors and normal organs we propose that EUD for a structure of interest be estimated as:

$$EUD = \left(\frac{1}{N} \sum_{i=1}^{N} D_i^a \right)^{\frac{1}{a}}$$ or, using a differential dosevolume histo[gram] $$EUD = \left(\sum_{i=1}^{N} v_i D_i^a \right)^{\frac{1}{a}}$$

where $\{v_i, D_i\}$ are bins of the histogram and "a" is a tissue-specific parameter. *It is easy to see that EUD is bounded by the minimum and by the* maximum dose, and is equal to the mean dose for "a" equal to one. The parameter "a" is negative for all tumors and it is positive for all normal *structures. We estimated the maximum likelihood values of the parameter* "a" for several tumors and normal structures and they range from –13.1 for control of chordoma tumors to 17.7 for perforation of esophagus. We discuss the rationale for this generalized EUD concept and we will discuss the estimates of the parameter "a" for several important structures and end-points.

EUD plan optimisation



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Critical volume model

In the Critical Volume model the summary measure is a damaged volume, calculated using a local dose-effect function $E(D_i)$.

$$\text{Damaged volume} = \sum_i E(D_i)\frac{V_i}{V_{tot}}$$

- D_i = total dose to bin i
- V_i = absolute volume in bin i
- V_{tot} = total organ volume

Different functions can be used, but the effect increases with dose; FSU inactivation?

Local dose effect functions

$$E(D_i) = \frac{1}{1 + (D_{50}/D_i)^k}$$

2+2 parameters

$\begin{cases} D_{50} = \text{dose causing 50\% local effect} \\ k = \text{parameter for slope of curve} \end{cases}$

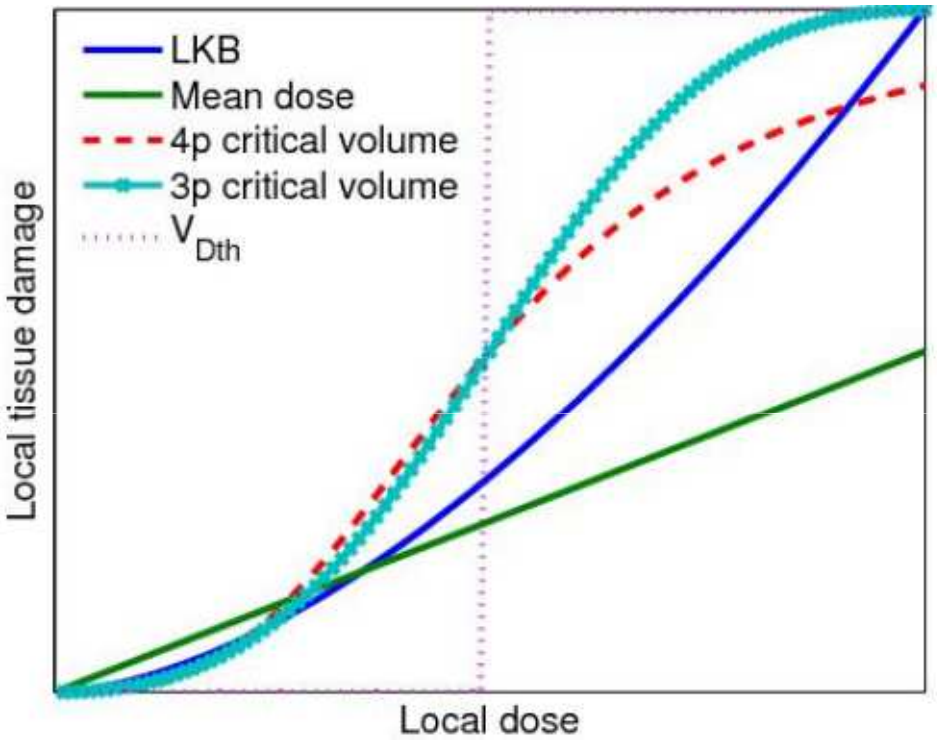
$$E(D_i) = \begin{cases} \dfrac{D_i/D_{50} - 1}{1 + (D_i/D_{50} - 1)^2} + {}^1/_2 & \text{when } D_i < 2D_{50} \\ 1 \text{ when } D_i \geq 2D_{50} \end{cases}$$

2+1 parameters

$$E(D_i) = \begin{cases} 0 \text{ when } D_i < D_{50} \\ 1 \text{ when } D_i \geq D_{50} \end{cases}$$

2+1 parameters

DVH reduction



Models use different DVH summary measures.

A function for DVH reduction can be used based on assumptions about the effect of the local dose on the local tissue (functional subunit inactivation).

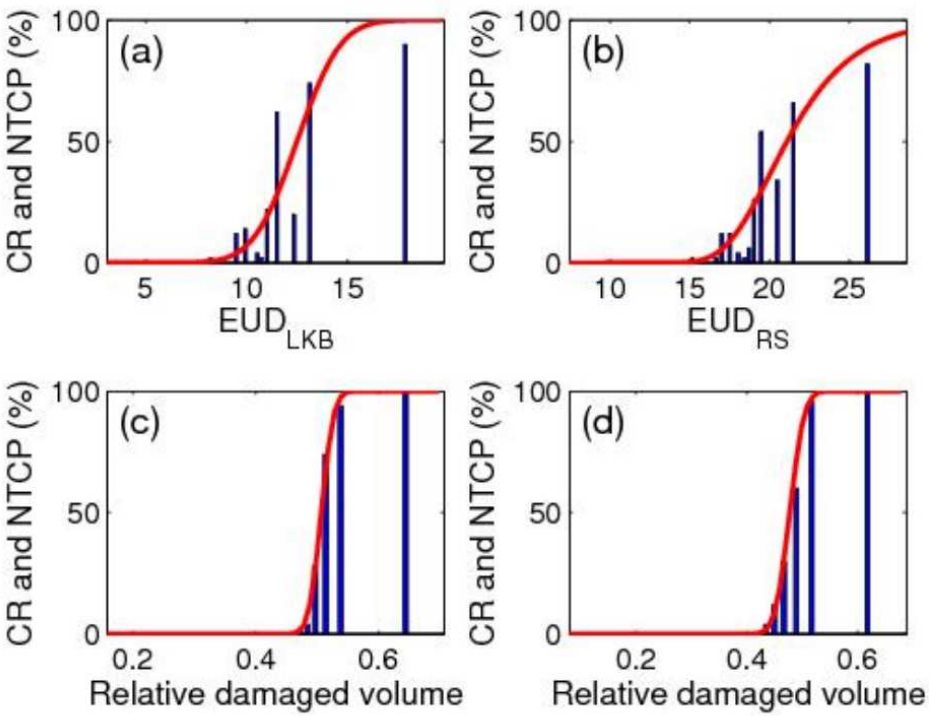
The main difference between models is whether a saturation of the response with dose is assumed.

Choosing a summary measure

A model with a non-representative summary measure estimates the same NTCP for plans with different risk.

- Results in a shallow dose/volume-response function
- Less useful predictive tool
- Makes inefficient use of the data

Example with simulated data



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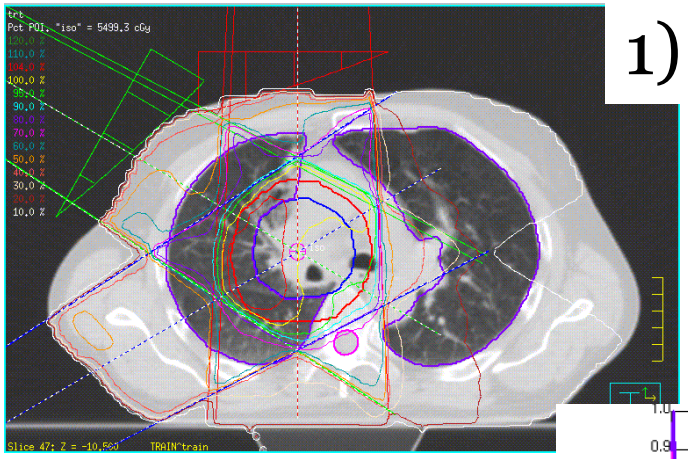
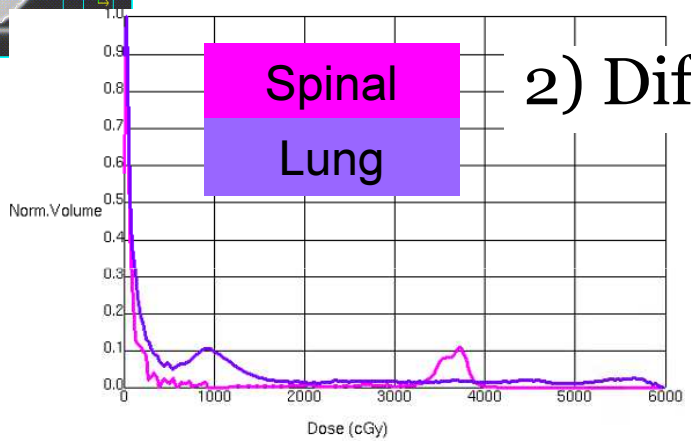


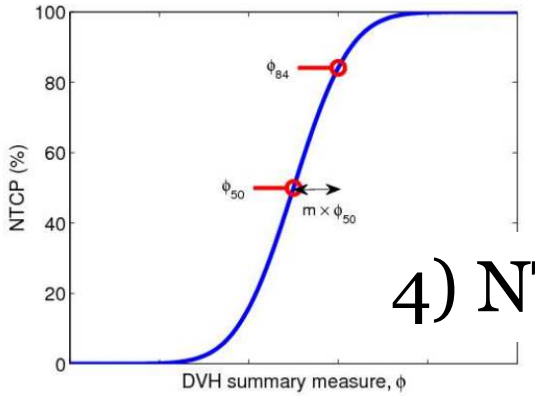
1) 3D organ dose distribution



2) Differential DVH

3) EUD or ‘damaged volume’

Parameters used in the models have been derived from data on previous treatments:
DVHs and outcome.



4) NTCP

The relative seriality model

The Relative Seriality model first calculates a probability of local damage for each dose bin in the DVH:

$$P(D_i) = 2^{-\exp\left(e\gamma\left(1-\frac{D_i}{D_{50}}\right)\right)}$$

- D_i = total dose to bin i
- D_{50} = Dose causing 50% probability
- γ = slope of the curve

Then NTCP is estimated using the relative seriality parameter 's'.

- Serial organs: $s = 1$, high doses to small volume important
- Parallel organs: $s \approx 0$, large irradiated volume important

$$\mathrm{NTCP} = \left(1 - \prod_i (1 - P(D_i)^s)^{\frac{V_i}{V_{tot}}}\right)^{1/s}$$

- V_i = absolute volume in bin i
- V_{tot} = total organ volume
- s = relative seriatlity parameter

How do I calculate NTCP?

- Available in biological packages in some treatment planning systems
- BIOSUITE: standalone executable developed by Dr Uzan and Prof Nahum at Clatterbridge Cancer Centre, UK. Available on request (dr.j.a.uzan@gmail.com).
- Good MATLAB based packages: CERR, DREES www.cerr.info
- VODCA: database software for radiotherapy data analysis www.vodca.ch
- Straightforward to calculate from exported DVHs

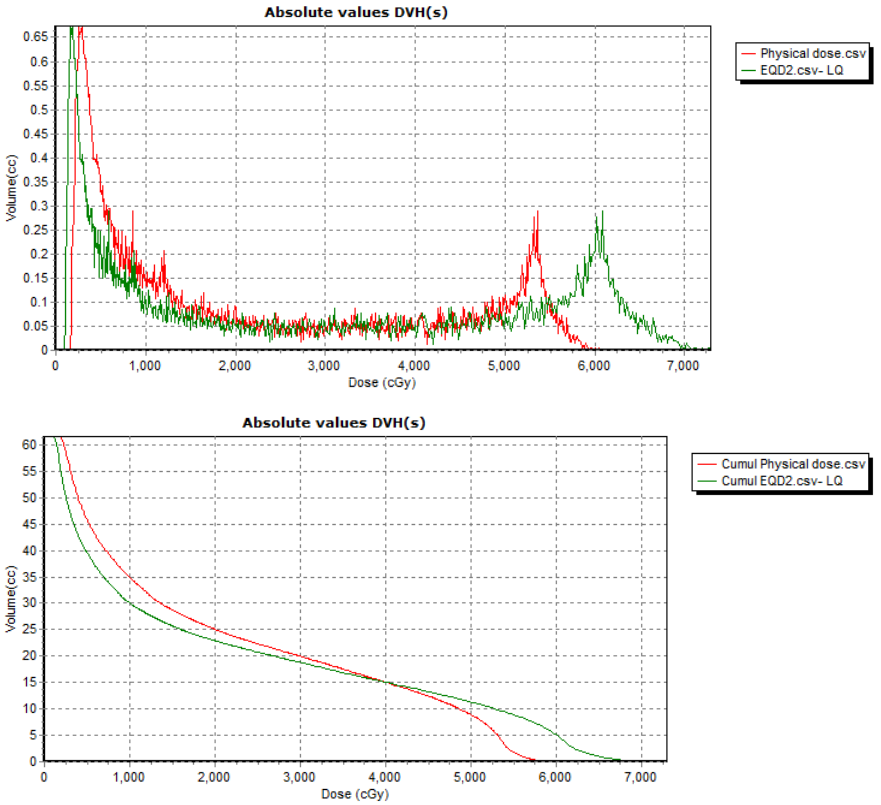
Fractionation correction!

Each bin in the DVH receives a different dose per fraction.

- Convert each dose-bin to 2Gy fraction equivalence (reference conditions).

$$BED = D\left[1 + \frac{d}{(\alpha/\beta)}\right]$$

$$EQD_{2Gy} = D\left[\frac{d + (\alpha/\beta)}{2 + (\alpha/\beta)}\right]$$



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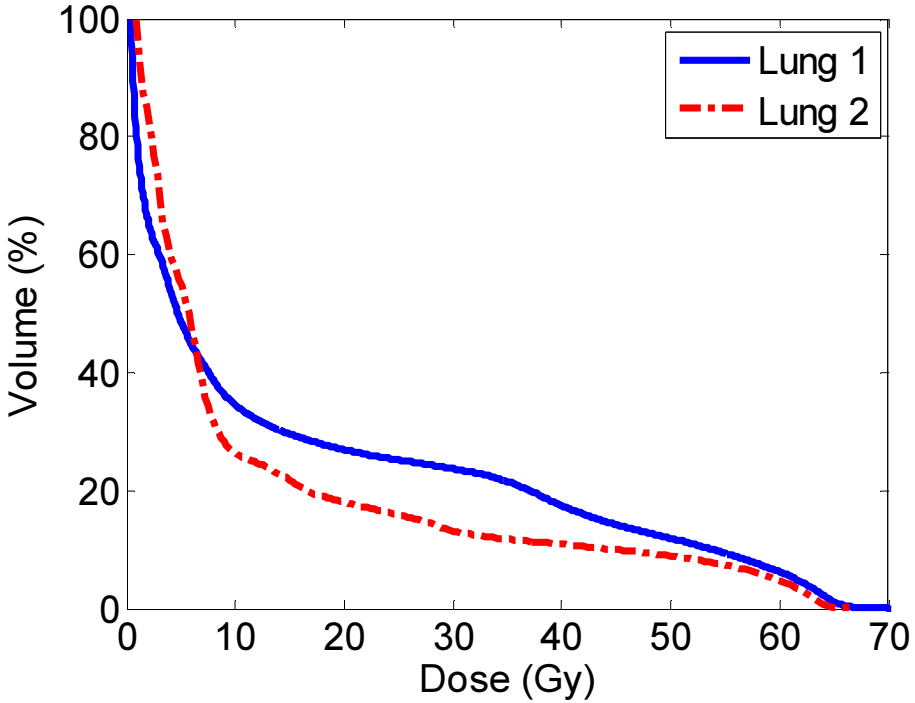
Example

- DVHs for 2 lung cancer patients
- Total lung – GTV
- Fractionation correction (α/β = 3 Gy)
- NTCP estimated using 3 different models
- Parameter values from Seppenwoolde et al. 2003



	Patient 1	Patient 2
LKB	9.2%	5.4%
Critical Volume	9.9%	6.9%
Relative Seriality	8.5%	4.4%

Which model should I use?

- Preferably several
- The LKB model is the most commonly used model and has parameter values published for many organs/endpoints (e.g. QUANTEC)
- All the above models are empirical
  - Statistical fits to clinical data
  - Biological interpretation of DVH reduction method should not be relied on blindly
- The more parameters, the more clinical data needed for parameter fitting; up to 3 parameters often appropriate
- Datasets often in the order of 100-300 patients. The more 'events', the more information to model on

Parameter derivation

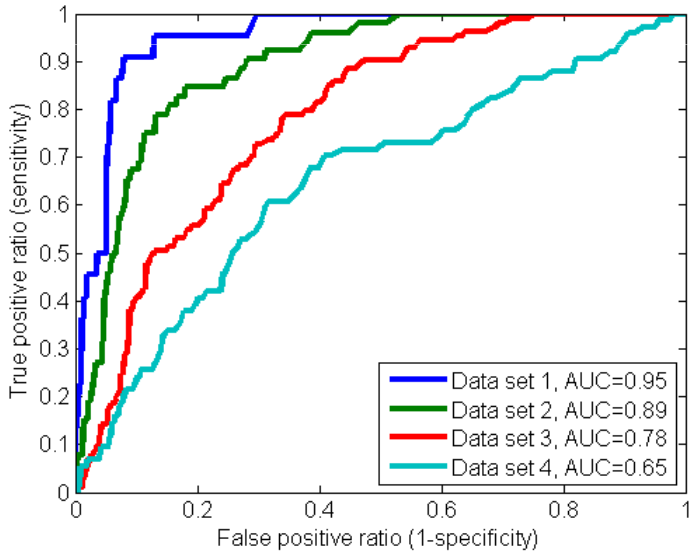
- Parameters are fitted to outcome data and DVHs (fractionation corrected) using the *maximum likelihood* method: finds parameters which makes current observation as likely as possible
- Outcome data generally binary (tox, no tox)
- Model is associated with the characteristics of the registered outcome data:
  - Endpoint, including grade
  - Co-morbidity, concomitant treatments etc.
- The confidence interval of the parameters depend on the quality of the data they're fitted to, and the sample size

Important considerations

- The model is only as good as the data used for parameter fitting.
  - Well-designed study (unbiased, representative)?
  - Sample size, number of events
  - Uncertainties in dose distributions (incl. organ motion, organ definition)
- The model is only reliable for plans reasonably similar to the plans included in the study (also applies to patient specific factors).
- When a model is used without knowledge of these factors, or for a different technique/patient group, the same limitations apply as to empirical 'tolerance doses'.
- NTCP is continuous but the patient outcome is binary
  - NTCP needs to be estimated because of limited information

Model accuracy

- The figure shows how the performance of an NTCP model deteriorates as confounding factors are increased in the patient population to which the model is fitted
- The area under the curve (AUC) is a measure of accuracy, giving the probability that the model will correctly rank sampled 'complicator' & 'non-complicator' pairs from the data set
  - 0.5-0.7: poor
  - 0.7-0.9: moderate
  - 0.9-1: excellent



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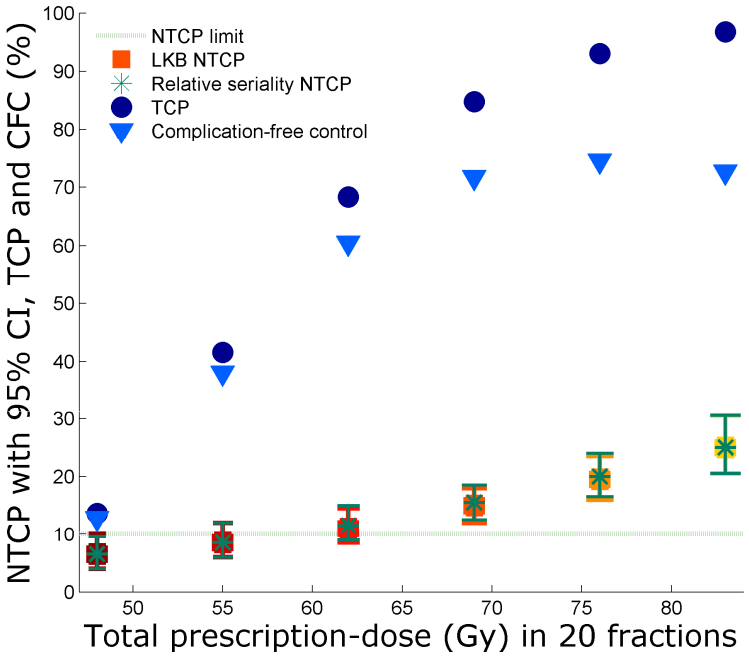
When to use NTCP models

- ICRU report 83: level 3 dose reporting
- Dose-volume constraints
- IMRT/VMAT optimisation
- Ranking treatment plans
- Evaluation of treatment data from clinical studies; derive parameter values locally
  - Better to used locally derived parameter values than published values
- Develop new potential techniques
- Dose prescription

Individualised dose prescription

Where individual dose prescription is adopted NTCP and TCP estimates for individual patients can be used by the clinician.

Due to anatomy differences between patients the TCP and NTCP estimates for a prescription dose will vary.



Complication-free control
= TCP(1-NTCP)

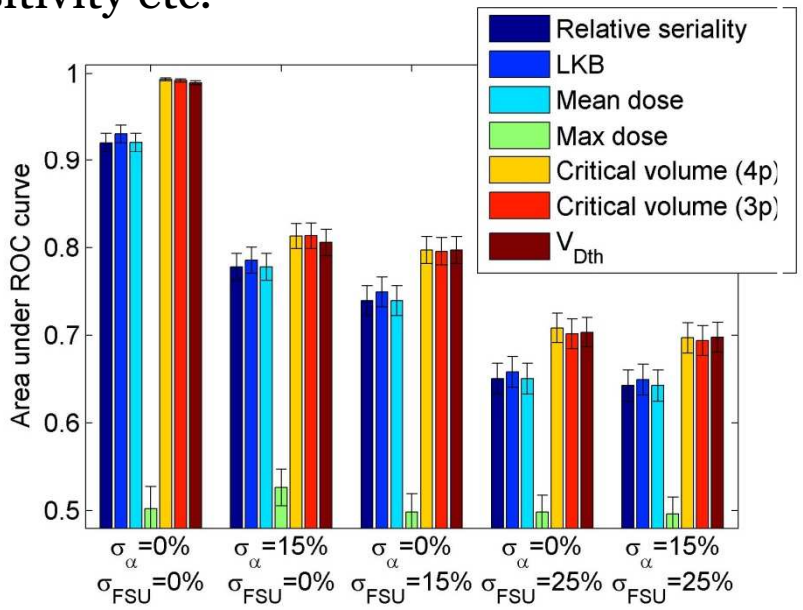
Taking empirical models further

Accounting for confounding factors

- Confounding factors include any non-dosimetric factors (X) influencing the outcome, as these are not modelled.
- Health status, chemo/surgery, radiosensitivity etc.
- Sharper slope, greater certainty

$$\mathrm{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-x/2} \mathrm{d}x$$

$$t = \frac{\varphi - \varphi_{50}}{m \cdot \varphi_{50}} + \beta_2 X_2 + \cdots + \beta_n X_n$$



Onjukka et al. MedPhys 2015

Selected bibliography

Lyman, J. T. Complication probability as assessed from dose-volume histograms. Radiat Res Suppl, 1985, 8, S13-S19

Kutcher, G. J. & Burman, C. Calculation of complication probability factors for non-uniform normal tissue irradiation: the effective volume method. Int J Radiat Oncol Biol Phys, 1989, 16, 1623-1630

Jackson, A. et al. Probability of radiationinduced complications for normal tissues with parallel architecture subject to non-uniform irradiation. Med Phys, 1993, 20, 613–625

Seppenwoolde, Y. et al. Comparing different NTCP models that predict the incidence of radiation pneumonitis. Normal tissue complication probability. Int J Radiat Oncol Biol Phys, 2003, 55, 724-735

Jin, J.-Y. et al. Impact of fraction size on lung radiation toxicity: hypofractionation may be beneficial in dose escalation of radiotherapy for lung cancers. Int J Radiat Oncol Biol Phys, 2010, 76, 782-788

Källman, P.; Ågren, A. & Brahme, A. Tumour and normal tissue responses to fractionated non-uniform dose delivery. Int J Radiat Biol, 1992, 62, 249-262

Onjukka, E. et al. The performance of normal-tissue complication probability models in the presence of confounding factors. Med Phys. 2015, 42, 2326-41

Thank you!

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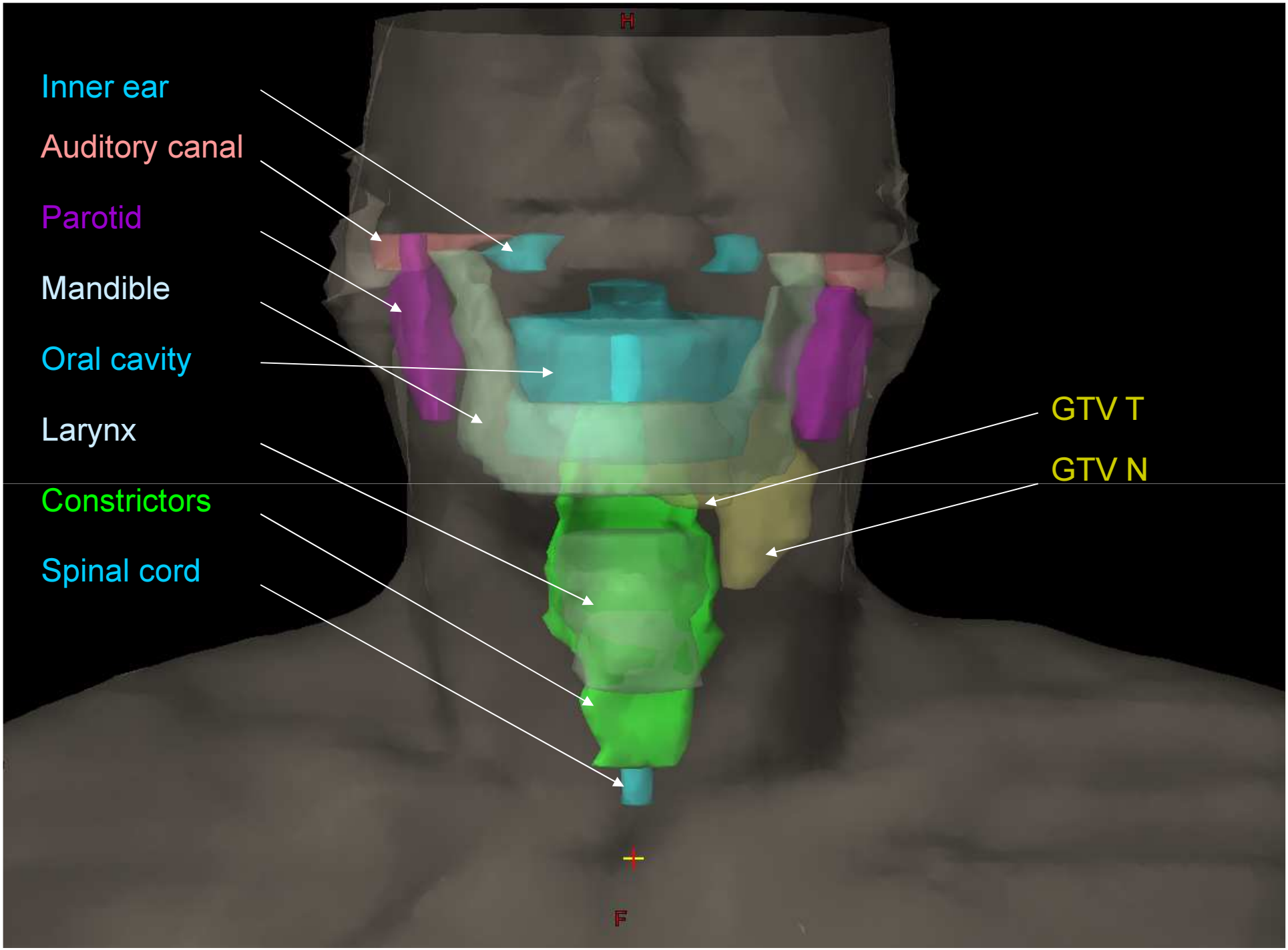
H&N irradiation: dose-volume predictors and NTCP parameters for some complication

Giovanna Gagliardi
Dept of Medical Physics
Karolinska University Hospital, Stockholm

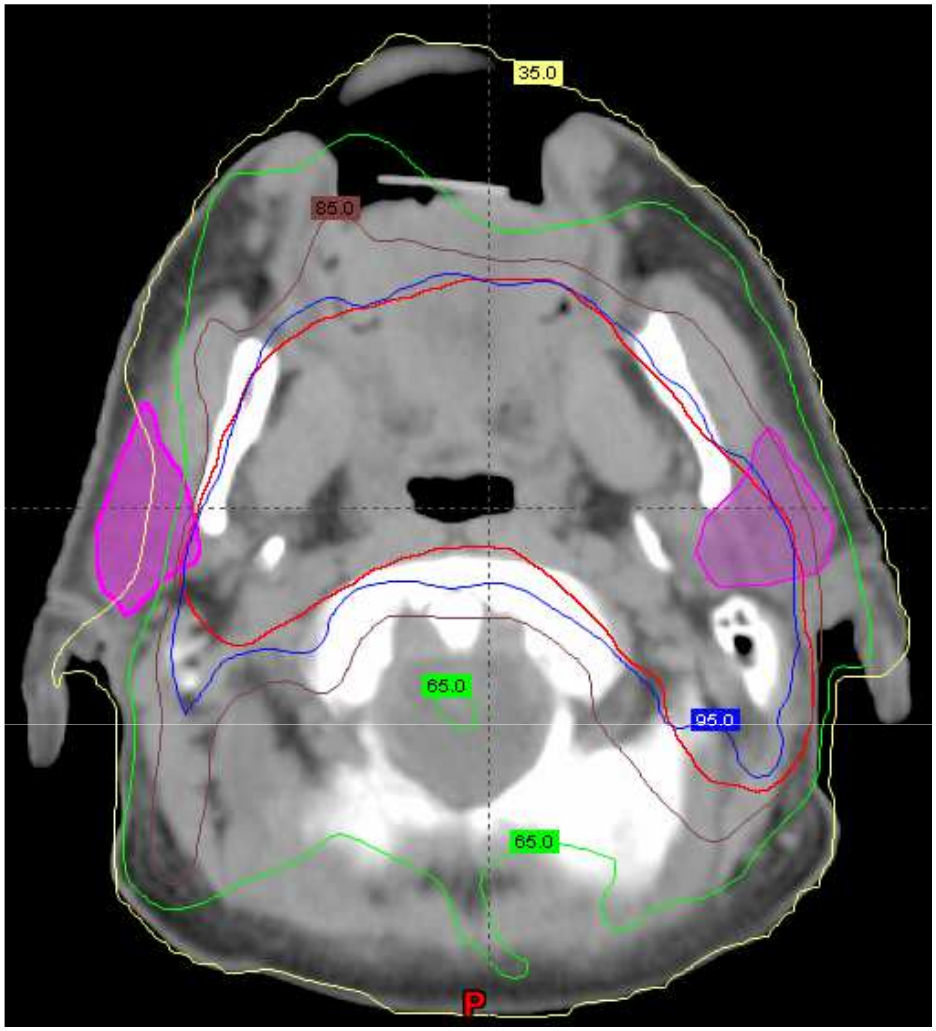
ESTRO IMRT course, 2016

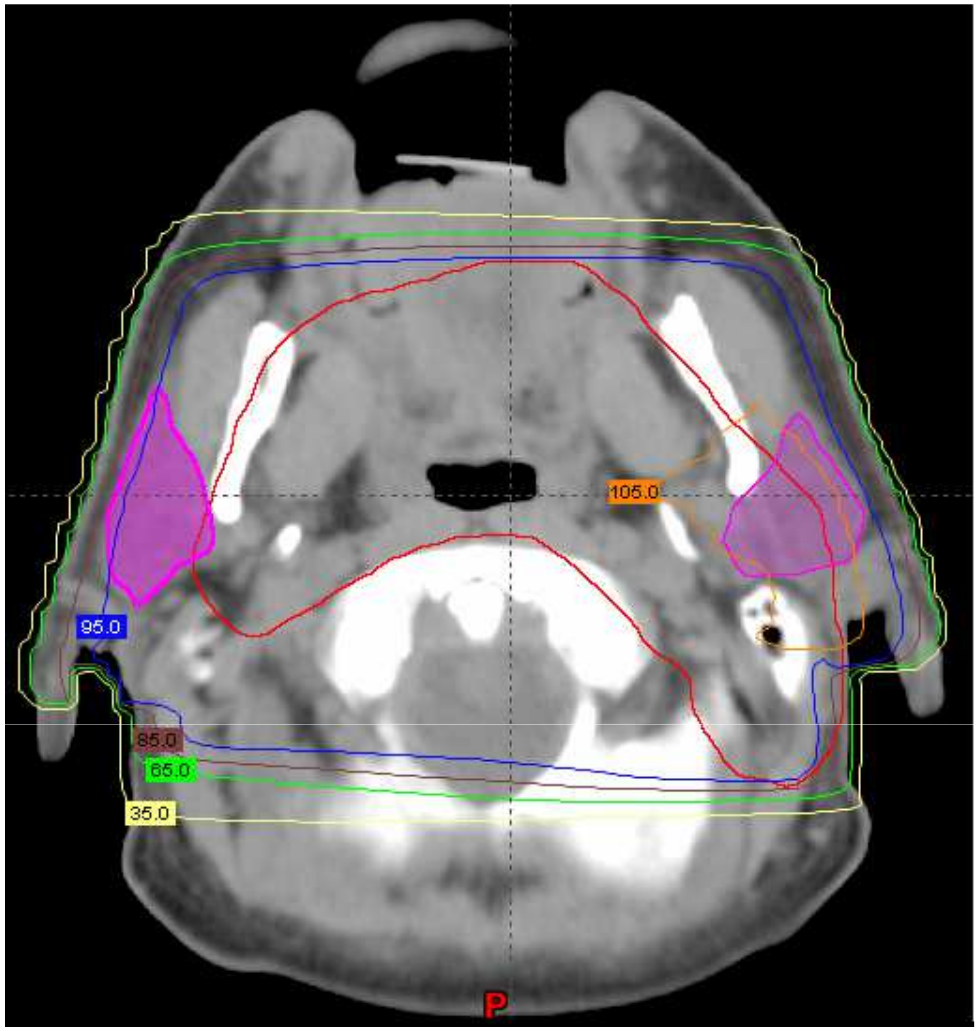

Inner ear
Auditory canal
Parotid
Mandible
Oral cavity
Larynx
Constrictors
Spinal cord
GTV T
GTV N
H
F

- Xerostomia
- Edema
- Swallowing

Parotid glands
Larynx
Pharynx/Mucosa

QUANTEC Supplement 2010





IMRT: Dmean (parotid dx)=18Gy

Parotid (pink) dose limit: D_{mean} 26Gy

3DCRT Dmean(parotid dx)=42Gy

BASELINE
for parotis

Xerostomia - PAROTID GLANDS

- Outcomes:
  reduced salivary output, xerostomia
  alterations in speech and taste, nutritional problems, dental hygien

- Measure of the salivary flow: quantitative information about the secretory capacity of the glands

- Salivary gland: stimulated salivary production (60-70%)
- Submandibulary and sublingual glands: unstimulated salivary production

- Subjective scoring and objective scoring missmatch
  (assessment by questionnaires interviews, patient diaries different from those performed with salivary gland flow rates, scintigraphic activity)

Eisbruch et al, IJROBP 45, 3:577, 1999

Prospective study

- 51 patients, parotid sparing bilateral neck RT
  (advanced head & neck)
  37 patients, unilateral neck RT (small lateral tumors)
- Saliva flow rates measured before and 1 year after RT
- Threshold mean dose to the glands for suppression of the salivary flow: 24 - 26 Gy

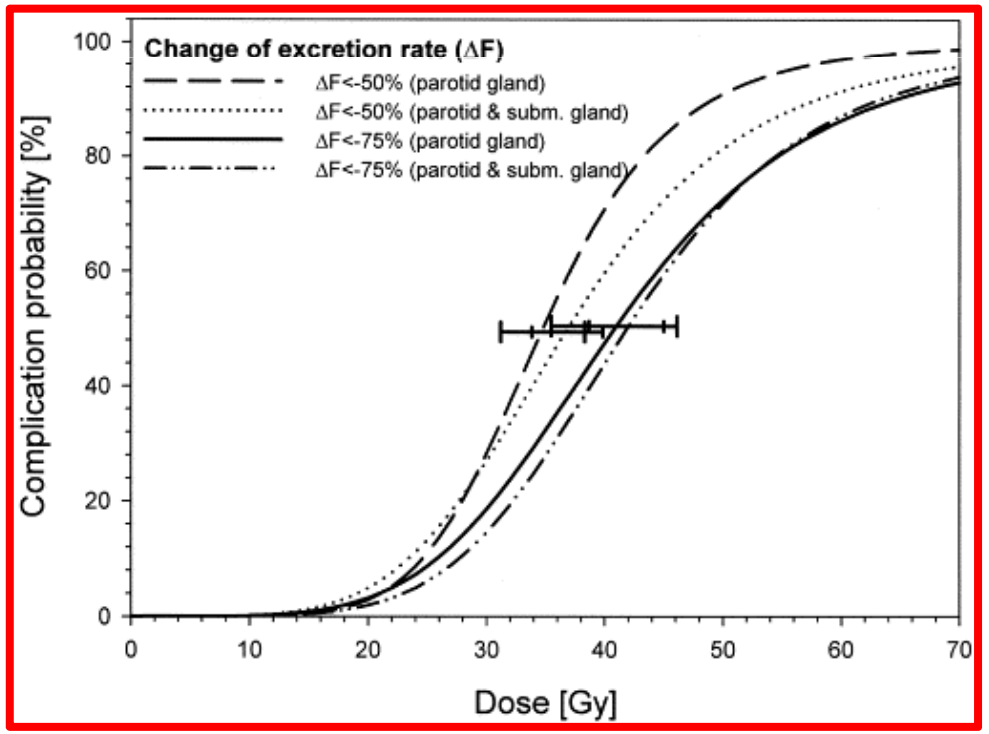
Roesink et al, IJROBP 51, 4:938, 2001

Prospective study

- 180 patients, 174 parotid glands
- Saliva flow rates measured before and after RT
  (6 weeks, 6 months, 1 year)
- Postradiotherapy saliva flow decreased with increasing irradiated volume to a mean dose between 35 and 45
- No threshold mean dose

PAROTID GLANDS

- Large volume effects confirmed in several studies (Munter 2004, 2007, Dijkema 2008,2010)
- Reducing D_{mean} < 25-30 Gy is not sufficient to reduce xerostomia



Parotid glands – xerostomia
NTCP description

LKB model	***TD50***	***m***	n
Emami (1991) No 3D - retrosp.	46 Gy	0.18	0.7
Eisbruch (1999) 88 pts – prosp.	28.4 Gy (25 – 34.7)	0.18 (0.10 – 0.33)	1 (fixed)
Roesink (2001) 180 pts – prosp. 95% CI	39 Gy (34 - 44)	0.45 (0.33 - 0.65)	1 (fixed)

”early” modelling, large volume effect

PAROTID GLANDS – dose-volume recommendations for xerostomia < 20%

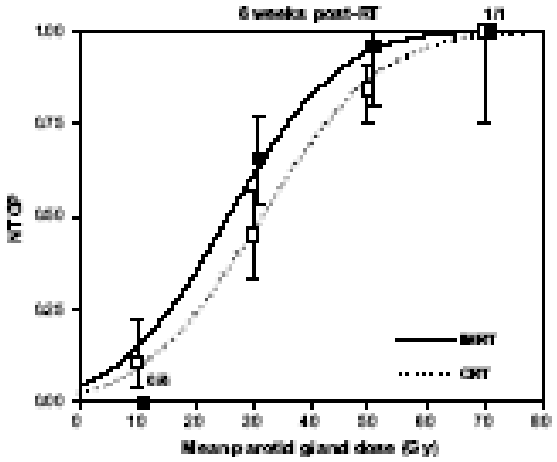
Mean dose to one parotid gland < 20 Gy

Mean dose to both parotid glands < 25 Gy

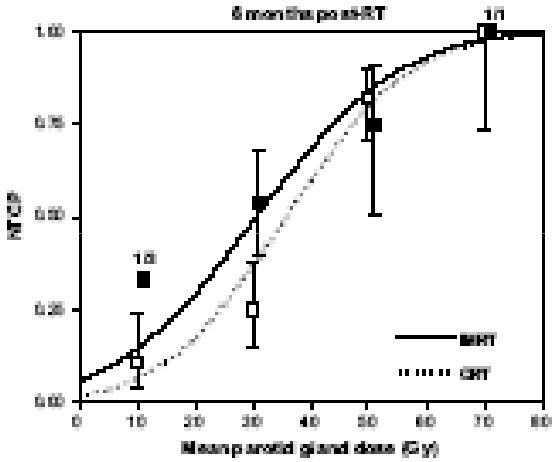
- ? Mean dose to submandibular gland < 35 Gy
- ? Threshold value, < 10 Gy

Large volume effect dependence, related to the parallel architecture of the glands

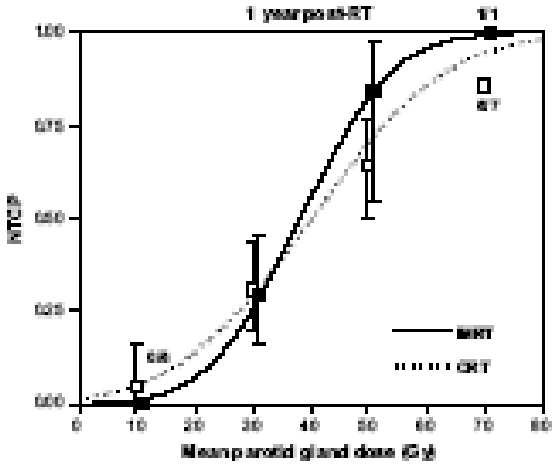
QUANTEC recommendations



6w



6m



1y

Parotids: other updates…

- Utrecht data (221 pts), stimulated flow rates 6w, 6m, 1y.
- 3DCRT (n=157) vs IMRT (n=64)
- NTCP end point: reduction < 25% baseline
- Different behaviour between IMRT and 3D
- Spatial effects (different dose distribution @ same Dmean)…more important for early reactions

Dijkema et al 2008

PAROTID GLANDS –

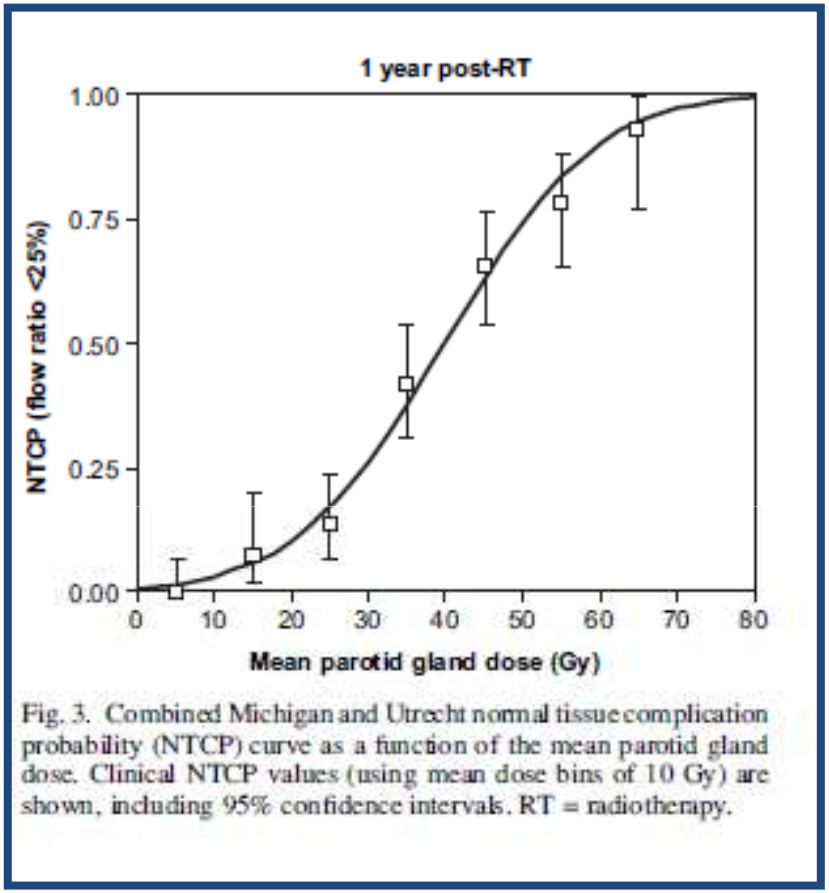


Fig. 3. Combined Michigan and Utrecht normal tissue complication probability (NTCP) curve as a function of the mean parotid gland dose. Clinical NTCP values (using mean dose bins of 10 Gy) are shown, including 95% confidence intervals. RT = radiotherapy.

Table 4. Combined analysis: Parameters TD_{50}, m, and n (95% CI) in terms of mean dose ($n = 1$) and with the full LKB-model (n) for flow data 1 year after radiotherapy

Parameter	Mean dose ($n = 1$)	Full LKB (n unrestricted)
TD_{50} (Gy)	39.9 (37.3–42.8)	39.4 (33.8–41.8)
m	0.40 (0.34–0.51)	0.42 (0.36–0.58)
n	1	1.13 (0.75–14.3)
Δ	339.2	340.6

Abbreviations: CI = confidence interval; LKB = Lyman-Kutcher-Burman model; TD_{50} = the uniform dose to the whole organ resulting in 50% complication probability; m = slope of the complication probability curve; n = volume dependency parameter.
Goodness-of-fit is expressed as the deviance (Δ).

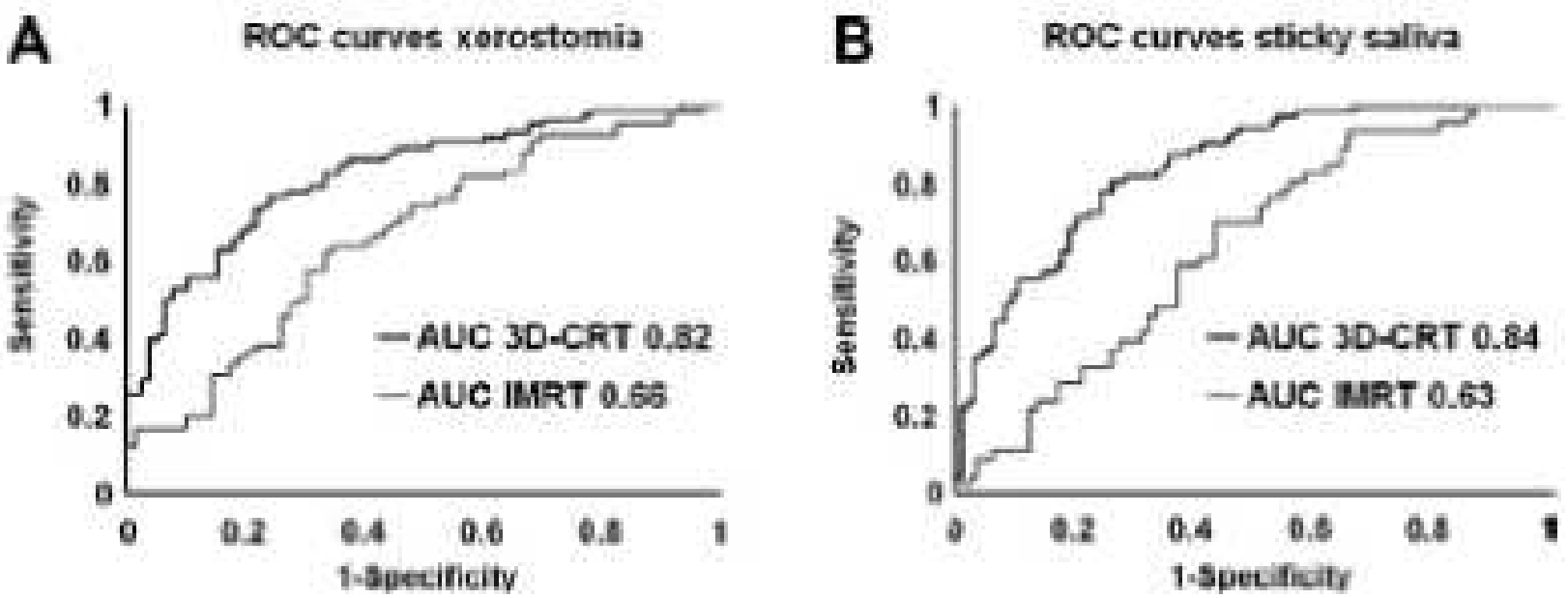
Utrecht & Ann Arbor data, 384 parotids,
Stimulated flow rates 1 year after RT

Endpoint: reduction < 25% baseline

n=1, D mean model ok

Dijkema et al, 2010

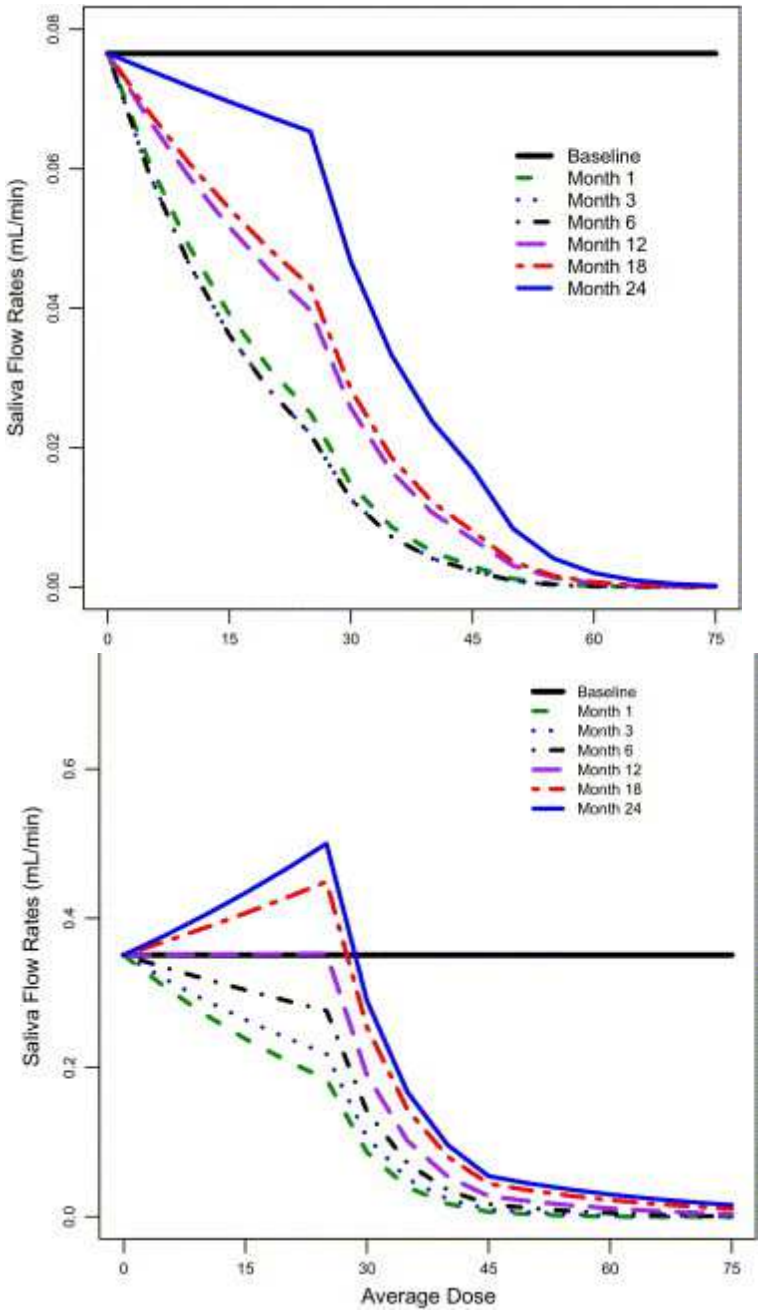
Xerostomia: **spatial effects**? 3D vs IMRT



- are there more sensitive sub regions?
- stem cells only seen in the excretory ducts (Feng 2009)
- selective sparing or stem cell transplanation to reduce xerostomia?

Beetz et al, 2011

Entity and speed of the recovery vs Dmean: a model



Unstimulated saliva
flow rate

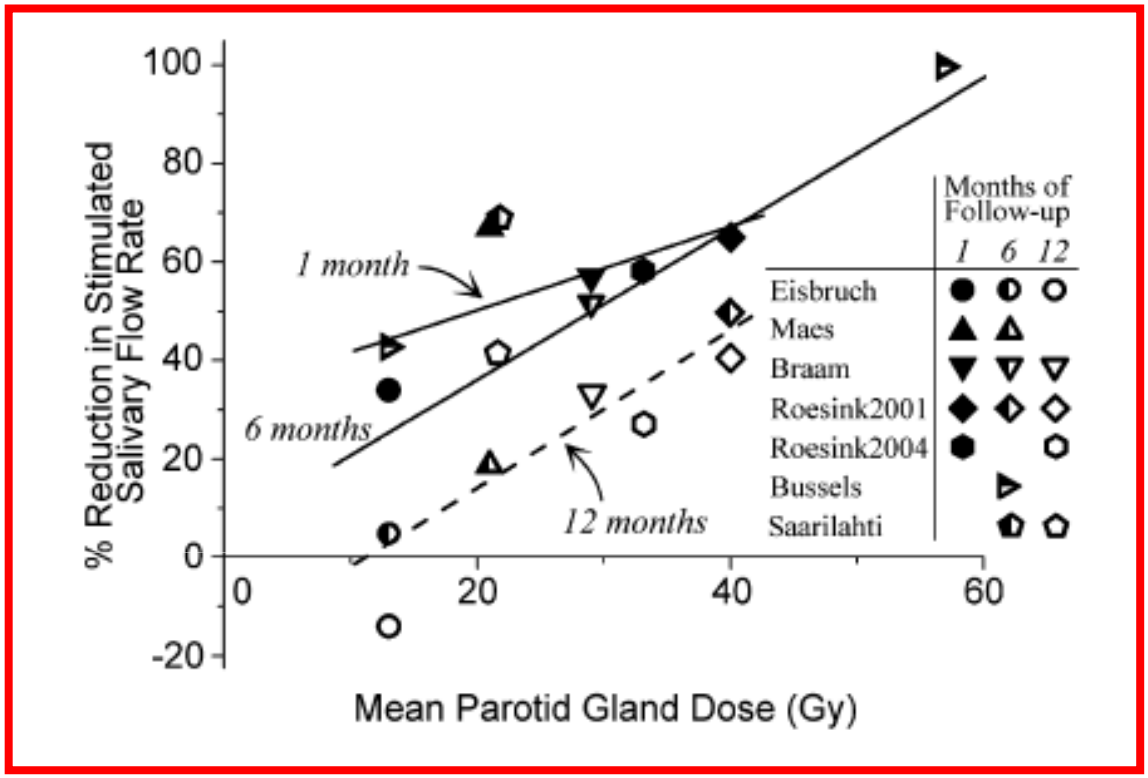
Almost complete recovery at 12-24 months for Dmean < 25-30 Gy

(Li 2007; 266 parotids; 142 pts)

Stimulated saliva
flow rate

Courtesy C. Fiorino

Xerostomia– **time aspects**



Relevance of the time of evaluation of the endpoint

Outcome data (reduction in salivary flow) and sampling time
- @ 1month: almost independent of mean dose
- shift to right: higher mean dose with longer follow-up

Deasy *et al*. IJROBP, vol 76, n3, 2010, S58-S63

PAROTID GLANDS –**shrinkage and CT density**

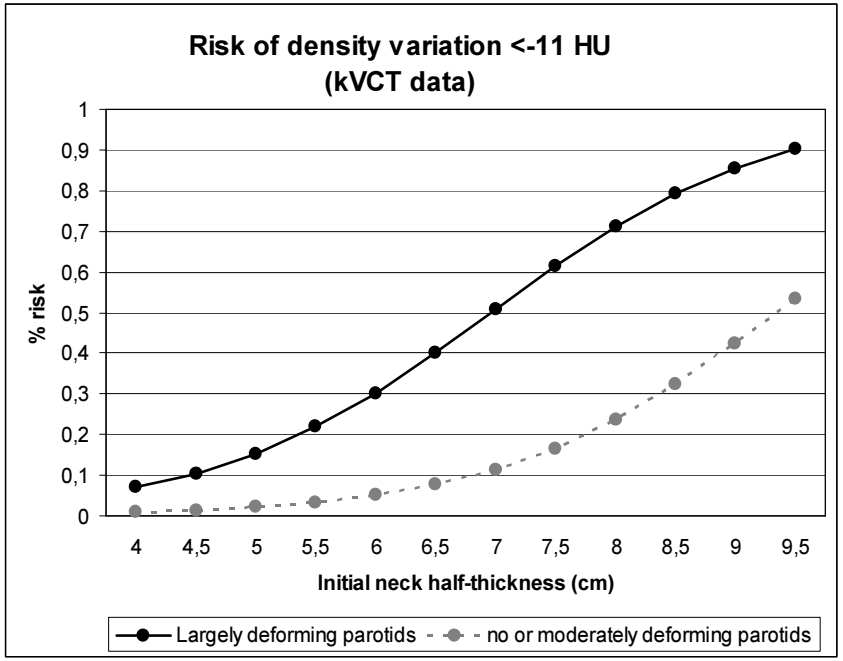
84 pts, (Fiorino *et al*, RO,2012), parotid reduced during IMRT

parotid deformation and average Hounsfield number changes evaluated through MVCT or kVCT diagnostic at treatment start

individual ΔHU highly correlated with degree of local deformation in terms of volume change and with neck thickness variation

individual assessment of density changes reliable with kVCT

density changes to score toxicity?



See also Broggi *et al* 2010

What is the best measure of xerostomia?

- Does the tolerance dose of parotid glands differ between subjective measures, objective measures and patient reported outcomes of xerostomia?

  (data from the first multicenter randomized study of IMRT and conventional RT)

- Patient reported outcomes results are associated with a higher tolerance dose (D50= 33 Gy)

- LENT-SOMA subjective xerostomia is the most useful clinical measure of salivary function (easily measured and strongly associated with the dose-response of the parotid glands)

Miah *et al*, 2013

Less xerostomy (RTOG scale) with tomotherapy than with sliding window IMRT

- 119 pts, oropharingeal ca, concurrent chemo radio: 59 pts sw-IMRT, 60 pts HT

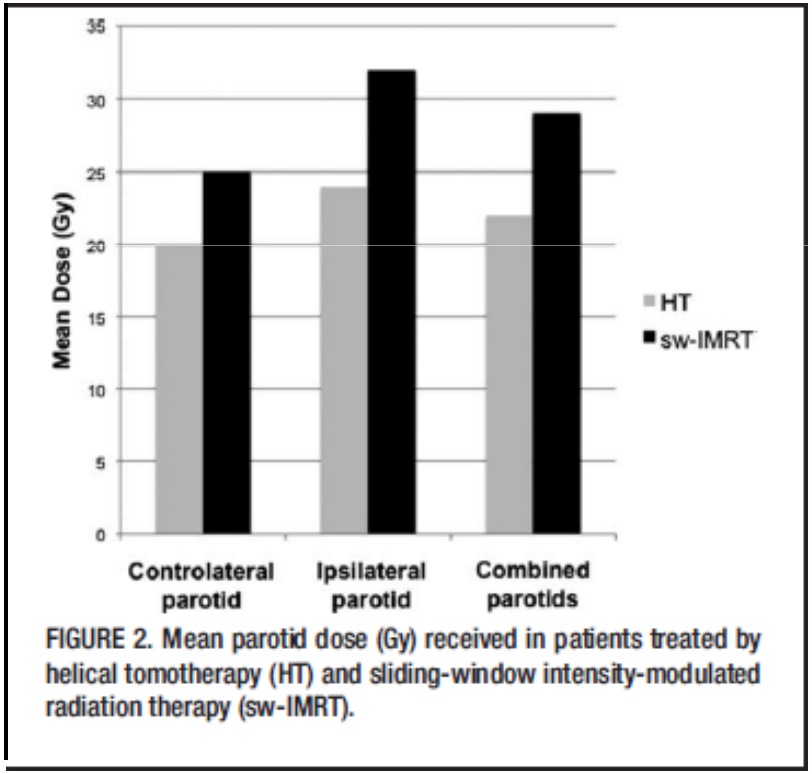


FIGURE 2. Mean parotid dose (Gy) received in patients treated by helical tomotherapy (HT) and sliding-window intensity-modulated radiation therapy (sw-IMRT).

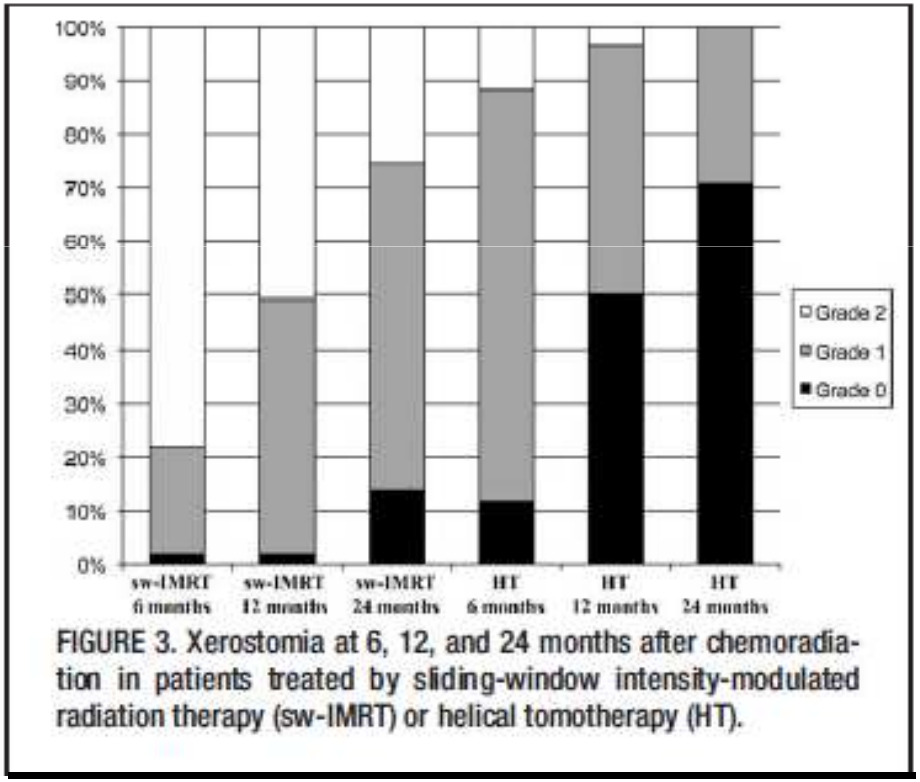


FIGURE 3. Xerostomia at 6, 12, and 24 months after chemoradiation in patients treated by sliding-window intensity-modulated radiation therapy (sw-IMRT) or helical tomotherapy (HT).

Ipsilateral parotid mean dose – HT 24 Gy; IMRT 32 Gy
Controlateral parotid mean dose – HT 20 GY, IMRT 25 Gy

Fortin *et al*, 2013

Validation of QUANTEC guidelines for xerostomia

- Lee F *et al*, R&O, 2013
- 238 pts, EORTG QoL questionnaires
- Validation of LKB parameters,

- Beetz I *et al,* Acta Oncologica, 2014
- 307 pts, chemoradio, 3D CRT (56%), IMRT (44%)
- Significanly **lower rates of xerostomia** in pts treated according to **guidelines**, but the criteria do not completely protect aganist xerostomia

- Moiseenko *et al*, IJROBP 2012
- 66 pts,, flow measurements, gr 4 xerostomia; @3 mths, flow decreases to <25% than pretreatment
- Clinical use of the ”20 Gy spared-gland rule” is justified

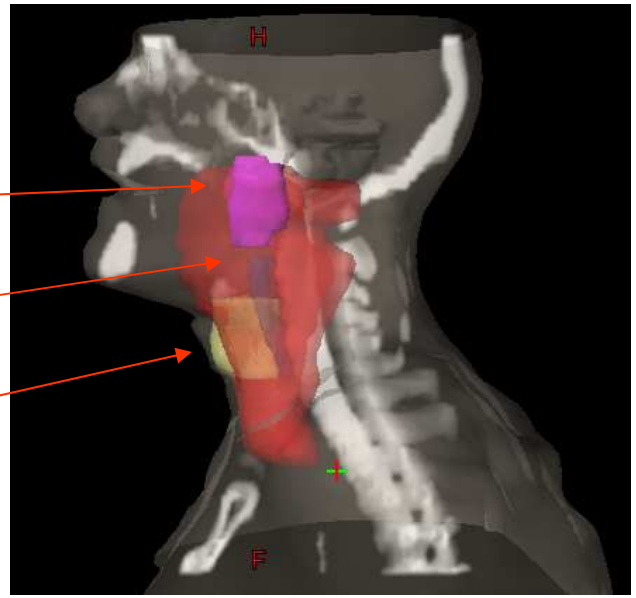
LARYNX AND PHARYNX irradiation (1/4)

- RT advantage: larynx preservation, implying speech and swallowing retention
- RT damage: laryngeal edema/fibrosis, leading in long term to problems in speech and swallowing retention
- Larynx (and pharynx): often partially included in the target

Parotid glands

Pharynx

Larynx



LARYNX, edema

- **Larynx/edema gr 2**:

  66 pts, videofluoroscopy assessed, fu=17.4m
  mean dose or V%> 50 Gy
  & neck stage (multivariate - Sanguineti *et al*, IJROBP 2007)

  V50<27%; mean dose < 43.5 Gy (EQD2)

- **Larynx/vocal disfunction**:

  complex physiology
  ≥66 Gy (prescription): decrease in function but not 3D data (Dornfeld *et al,* IJROBP 2007)

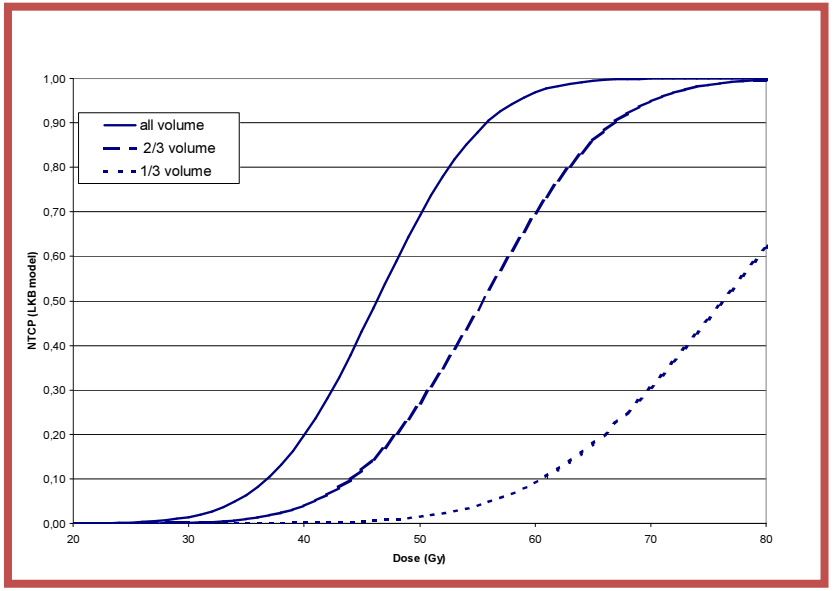
- **Risk factors**:

  concurrent chemo to high dose RT
  ≥double risk of laryngeal edema and vocal dysfunction

Rancati *et al*, IJROBP, vol, 76, n3, S64-S69

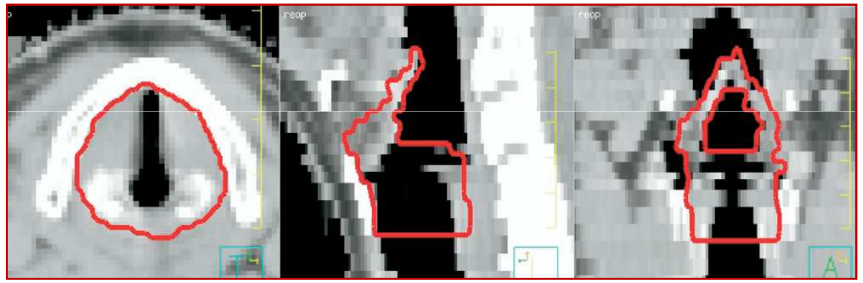
LOGEUD	*TD50*	*k*	
Rancati (2009)	46.0 ± 1.8	9.95 ± 3.46	

LKB	*TD50*	***m***	*n*
Rancati (2009)	46.3 ± 1.8	0.16 ± 0.05	0.45 ± 0.028



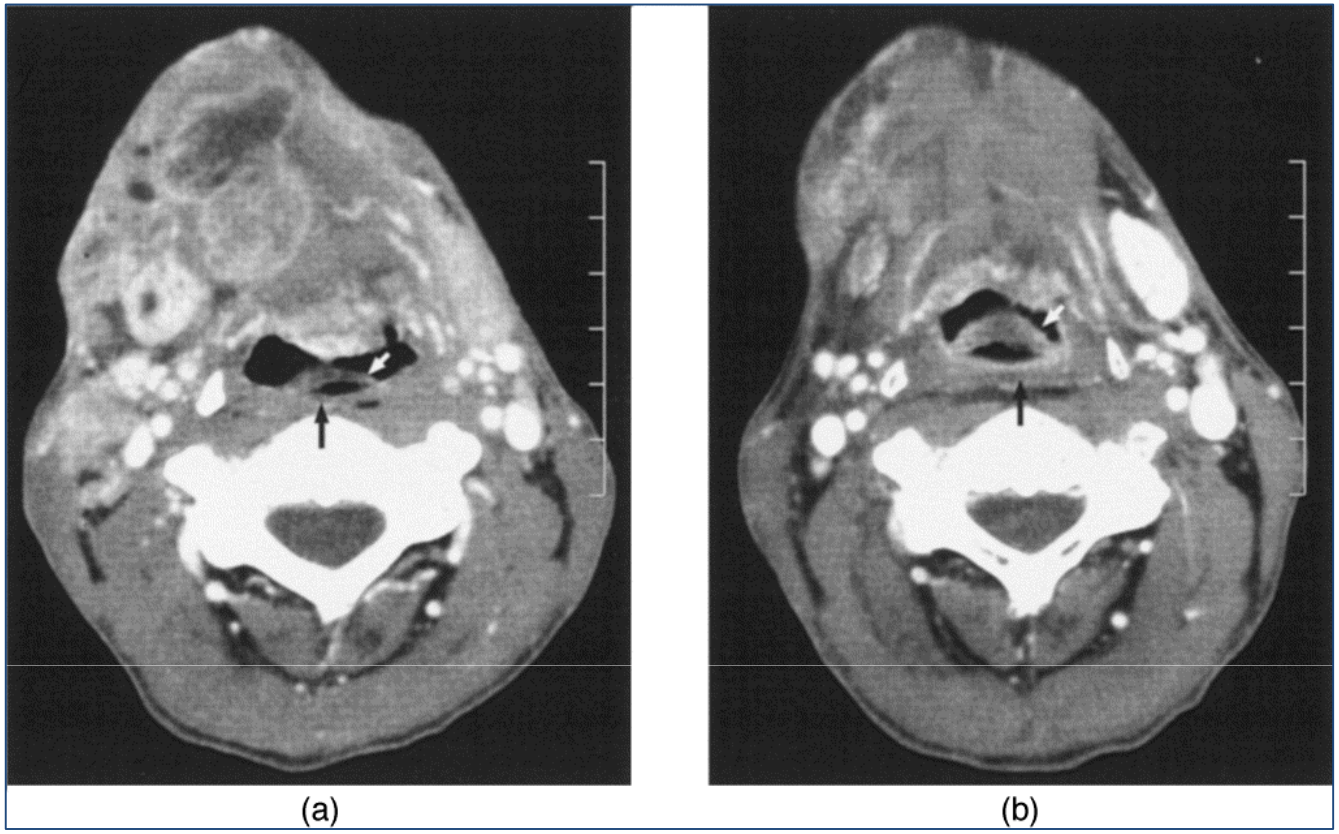
Rancati et al *IJROBP 2009*

Larynx is parallel for edema



Laryngeal edema:

- Large volume effect
  EUD<30-35 Gy (n=0.45)
- V50≤27%;
  mean dose ≤44 Gy



Black arrow, middle pharyngeal constrictor

white arrow, epiglottis….

before (a) and 3 months after treatment (b)

Eisbruch *et al* 2003

DYSPHAGIA

- Organs: supraglottic larynx and constrictor muscles
- Endpoints: aspiration and deglutition
- **Feng et al, 2006 (ASTRO):** evidence of a quantitatively assessed **dose-volume effect** for disphagia & aspiration (36 pts)
- **Aspiration**: **mean dose & V50-V65 to pharingeal constrictors**, supraglottic larynx - correlated.

Most predictive: V65(PC)<50%

Validation of QUANTEC guidelines for dysphagia

- Anderson NJ *et al,* Acta Oncologica 2014
- 76 pts, advanced squamous cell ca,
- **QUANTEC larynx** recommendations: **V50< 27 Gy**, **D mean< 44 Gy**
- Acute dysphagia toxicity, weekly measurements, prospectively scoring

- V50<27 Gy, Dmean>40 Gy, Dmax<66Gy predicted for grade 3 dysphagia
- no clinical risk factors significantly predicted for gr. 3 dysphagia

Usefulness of QUANTEC criteria in predicting acute toxicity

Xerostomia and disphagia after IMRT

Morbidity of head and neck RT

Late dysphagia after IMRT for head and neck cancer and correlation with dose–volume parameters

Hanna R. Mortensen [a,*], Kenneth Jensen [a], Karin Aksglæde [b,c], Marie Behrens [d], Cai Grau [a]

Prospective study, 294 pts, IMRT 2006-2010

EORTC QoL-C30, H&N 35 questionnaires
65 pts: also objective measurements

- QoL data: low degree of disphagia compared to objective measures
- Both subjective and objective measurements of late disphagia correlated with **dose to PCM**, QoL points correlated with **DVH parameters in the glottis/supraglottic larynx**

Both xerostomia and disphagia reduced after introduction of IMRT

PHARYNX irradiation - QUANTEC

Table 3. Organs at risk and dose–volume relationship above which swallowing dysfunction increases significantly

		Dose–volume data						
Investigator/patients (*n*)	Critical organs	Mean dose (Gy)	Median dose (Gy)	V_{50}	V_{60}	V_{65}	Endpoint	Evaluation method
Eisbruch *et al.* (13),	Larynx	60		50%	—	—	Aspiration	VF
Feng *et al.* (14)/36 patients	PC	66		80%	70%	50%	Aspiration	
IMRT + chemotherapy	PC			85%	70%	60%	Stricture	
Caglar (19)/96 patients	Larynx	48*		21%			Aspiration and stricture	VF
IMRT + chemotherapy	IC	54		51%				
Doomaert *et al.* (18)/81 patients	Pharyngeal mucosa and	45					QOL	RTOG/EORTC
RT + chemotherapy	constrictors							C30 and H/N 35
O'Meara *et al.* (20)/148 patients	Pharyngoesophageal inlet		50				Grade 3 plus pharyngoesophageal	RTOG late
2D-RT plus chemotherapy							dysfunction	Toxicity
Levandag *et al.* (15)/81 patients	Superior and middle	55					Grade >3 EORTC	RTOG
3D-CRT/IMRT plus	constrictors						PSS–HN MDADI	QOL
brachytherapy + chemotherapy								QOL
Domfeld *et al.* (7)/27 patients	Aryepiglottic fold	50					Diet score	QOL
IMRT + chemotherapy	False cord						HN QOL	Clinical assessment
	Lateral pharyngeal						Weight loss	
	Wall near false cord						PEG tube	
Jensen *et al.* (16)/25 patients	Larynx/upper esophageal	60					Aspiration	EORTC QOL
3D-CRT	sphincter						QOL	FEES
RT alone								

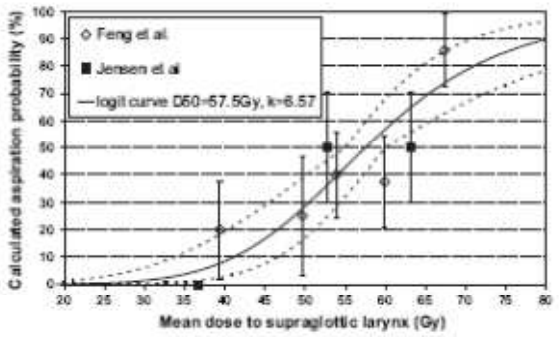


Fig. 1. Dose–effect relationship for dysphagia according to data from Feng *et al.* (14) and Jensen *et al.* (16). Solid line fit to combined data; dotted line fit to 68% confidence area for normal tissue complication probability-logit curve.

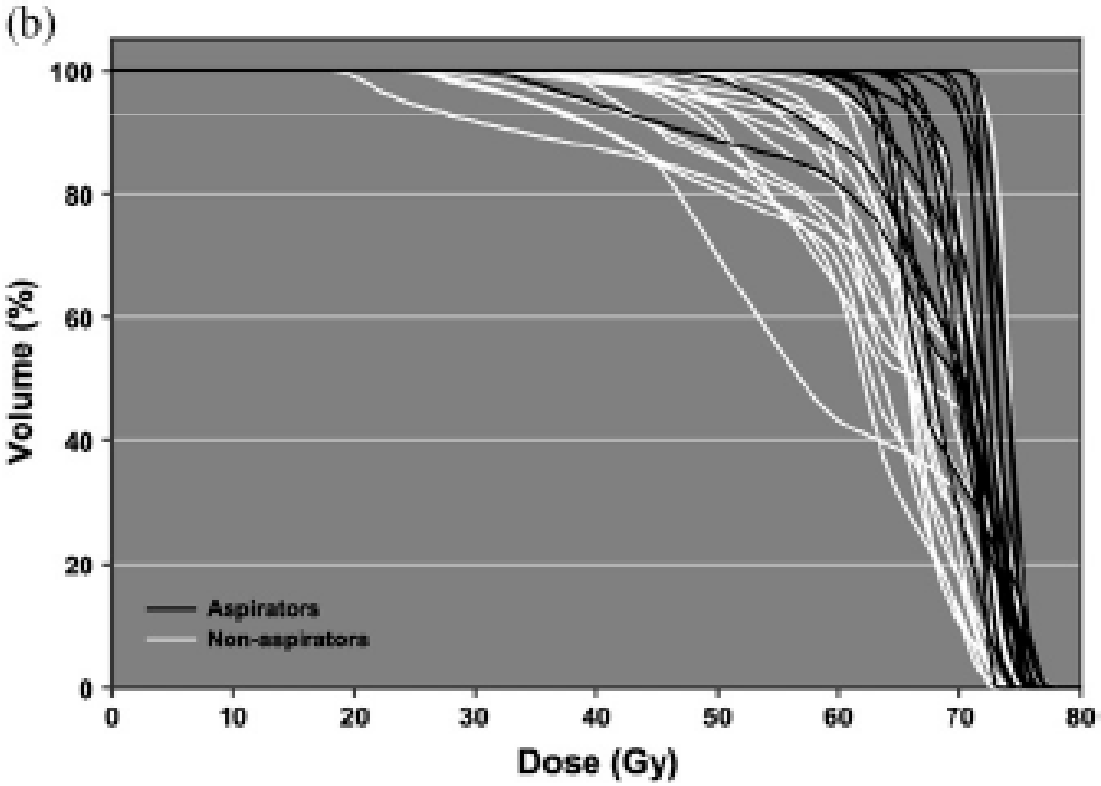
- **Data: Mean dose < 50 Gy < 20% incid.**
- Recommendations: **minimize volume of the constrictors >60 Gy**

  reducing volume receving > 50 Gy

SWALLOWING: **Pharingeal Constrinctors** and **Supraglottyx larynx**

IMRT of HN cancer aiming to reduce dysphagia: early dose–effect relationships for the swallowing structures

(Feng *et al*. IJROBP 2007)

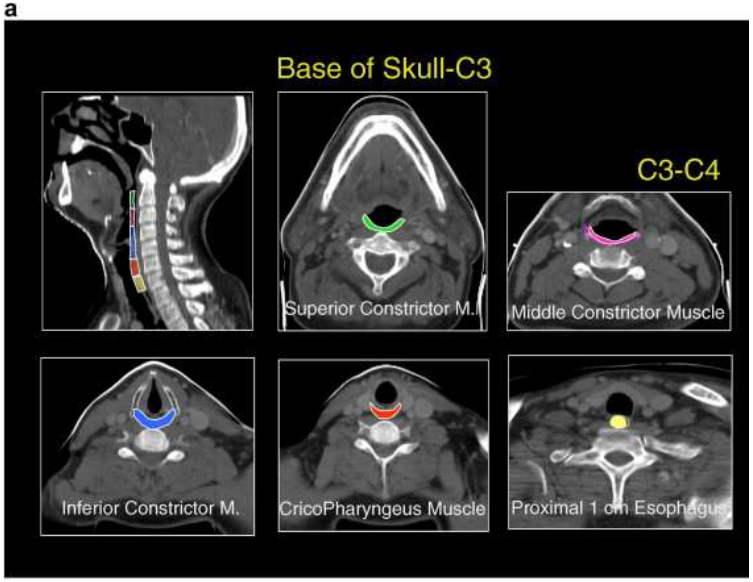


Superior PC most predictive

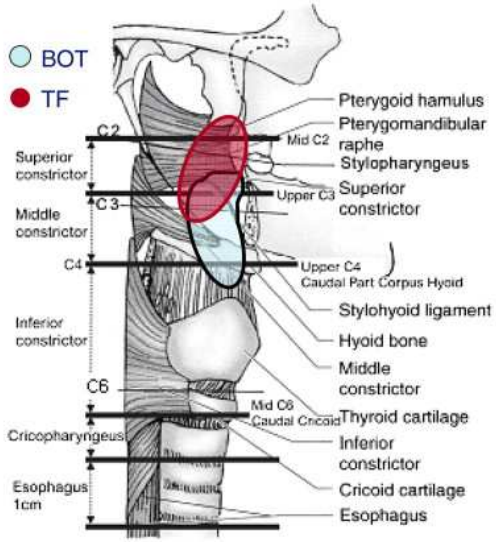
DVHs for the pharyngeal constrictor in patients with stricture (black) or without stricture (white).

SWALLOWING: dose to superior and middle constrictor muscles

a



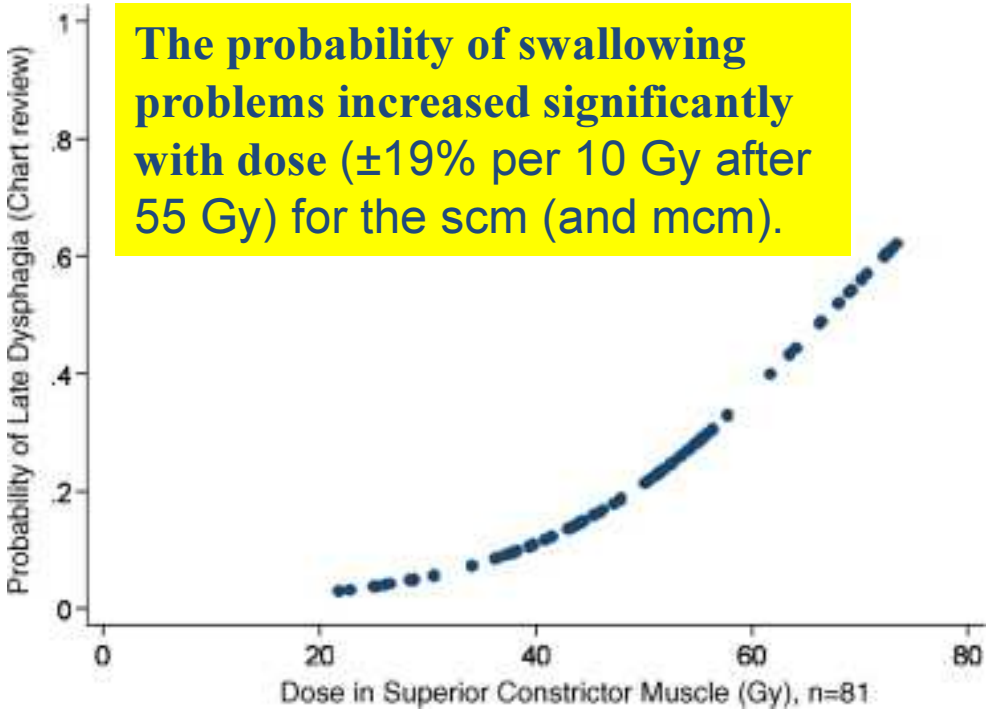
b



Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: A dose-effect relationship

(Levendag, RO, 2007)

The probability of swallowing problems increased significantly with dose (±19% per 10 Gy after 55 Gy) for the scm (and mcm).

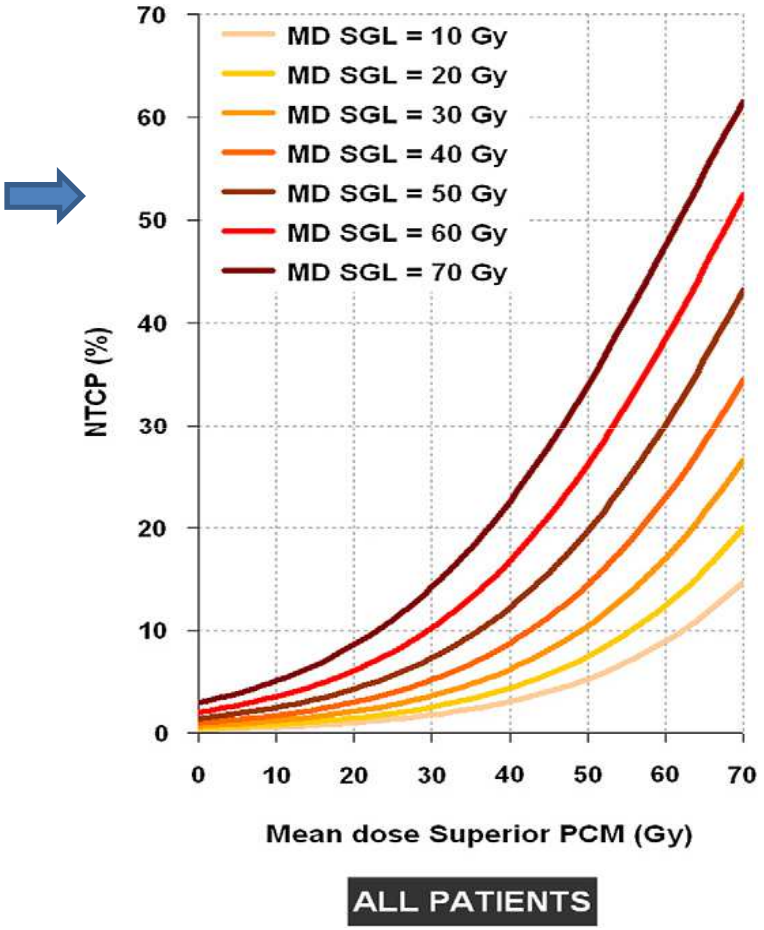


SWALLOWING: predictors

- Christianen *et al*, 2011, prospective study, 354 pts

- Toxicity related to mean dose to superior pharingeal constrictors and supraglottic larynx

- Age, previous symptoms, CHT
- **Oral mucosa irradiation** (Schwartz 2011, Sanguineti 2011)
- **PEG tube insertion** (Percutaneous endoscopic gastrostomic) (Caudell 2010, Sanguineti 2011)



NTCP curves for SWALM6 for each 10 Gy increase in dose to the supraglottic larynx.

SWALLOWING: oral mucosa irradiation/ risk of PEG (Sanguineti *et al*, 2011)

Cut off values:

V 9.5 Gy/week < 64 cm3
V10 Gy/week < 54 cm3

Multivariate analysis:
risk of PEG reduced when Oral Mucosa receives:
V 9.5 Gy/week < 64 cm3

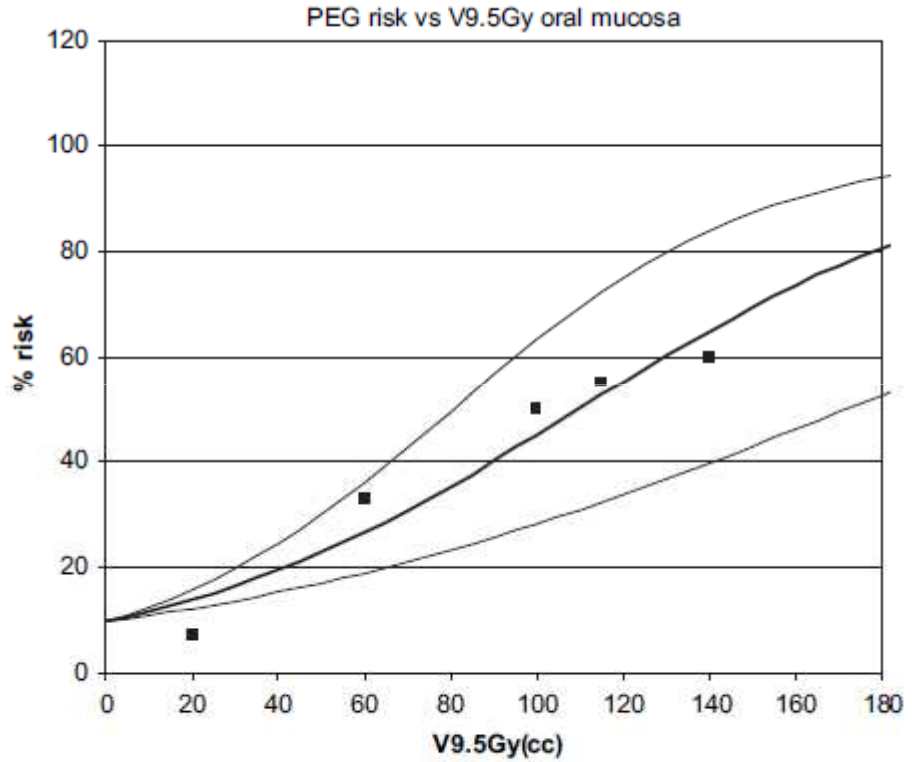
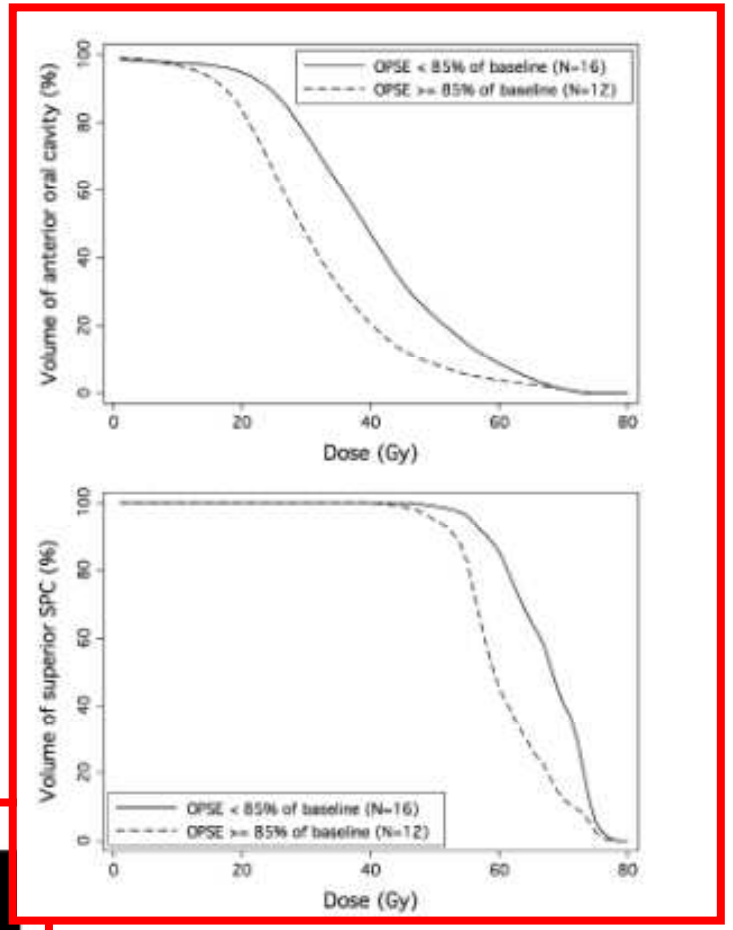
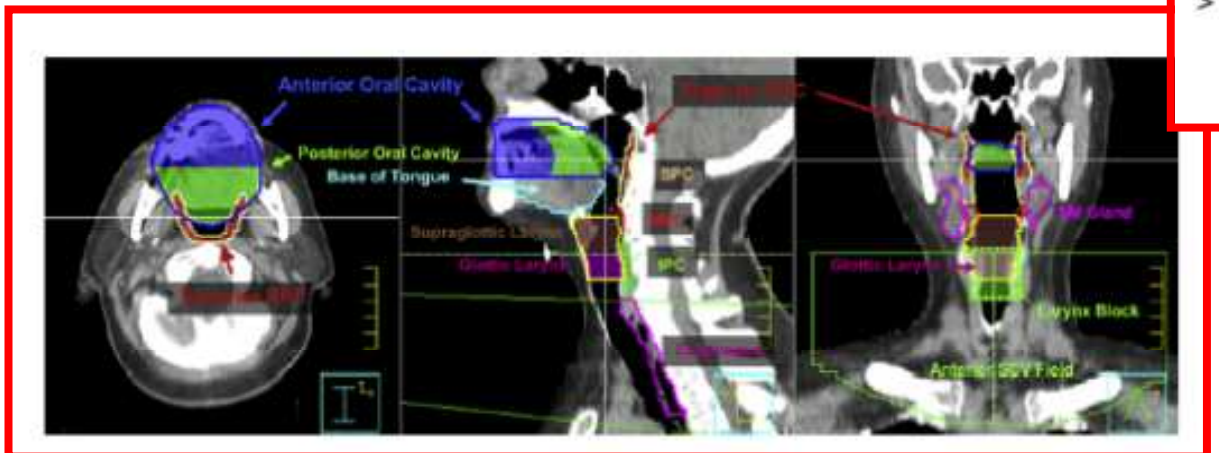


Fig. 3. Risk of percutaneous endoscopic gastrostomy (PEG) tube insertion vs. V9.5 Gy/week of oral mucosa is plotted with the 68% confidence intervals.

Confirming Oral Mucosa DVH related to late swallowing problems

- 31 IMRT pts, IV stage Oro cancer, no CHT (MDA)
- Prospective assessment of swallowing problems
- **Anterior and posterior oral mucosa DVHs as best predictors**
- Constrictors dose also correlated





Schwartz *et al*. 2011

Courtesy of C Fiorino

Summary: HN dose-volume relationships - Xerostomia

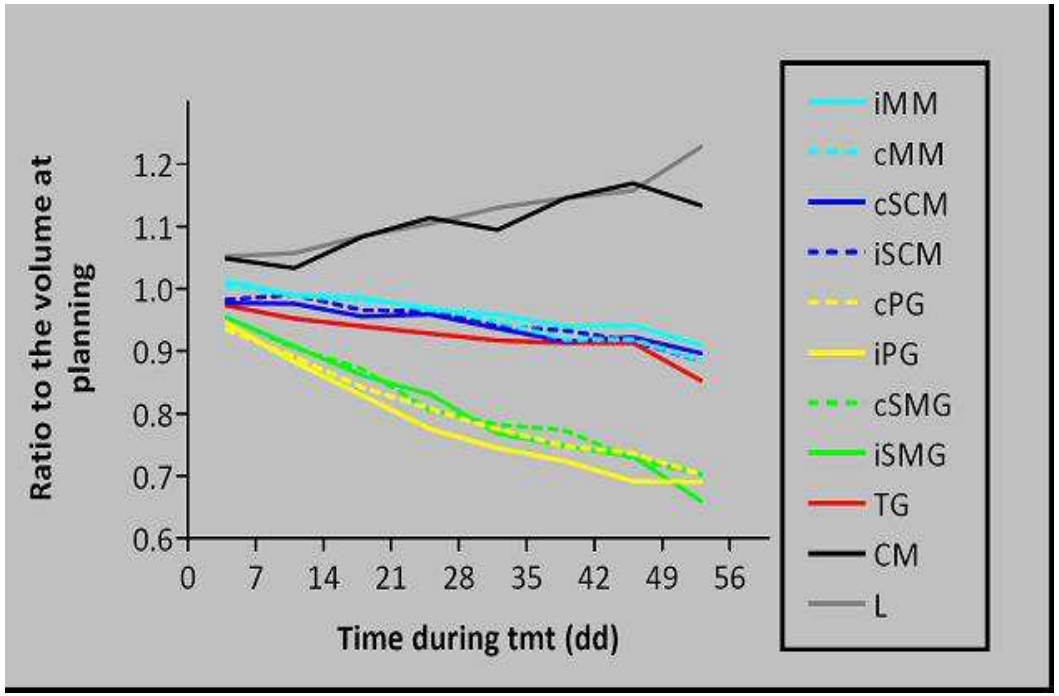
- Consensus : parotid as a parallel organ
- Mean dose, V20-40 best predictors
- Faster recovery of the damage with IMRT
- Different Mean dose vs xerostomia curves between 3DCRT and IMRT pts: spatial effects (?)
- Image-based assessment of early reactions (volumes, density, ….): high potential for better scoring and understanding radiation-induced parotid changes

Summary: HN dose-volume relationships – Disphagia, Larynx edema

- Increasing evidence of dose-volume effects for dysphagia (especially sup. constrictor, larynx)
- Dose-volume effect for Oral mucosa and constrictors in predicting PEG risk/swallowing problems
- Impact of CHT
- NTCP model available for laryngeal edema
- Conformal avoidance approach with IMRT may reduce toxicities (even without quantitative dose-volume relationship)

Volume changes during RT imaged by IGRT to assess normal tissue effects

- Volume variation of parotids and other organs during IMRT for HN cancer



PG: parotid glands
SMG: submandibular glands
TG: thyroid gland
CM: constrictor muscles
SCM:sternocleidomastoid muscles
MM: masticatory muscles
L: larynx
i=ipsi, c=contro

Ricchetti et al. IJROBP 2011

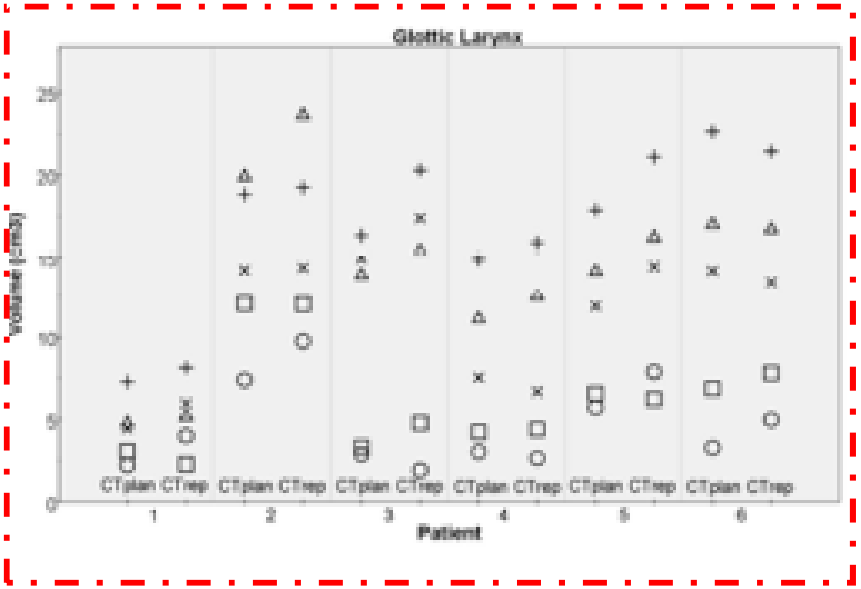
Courtesy C. Fiorino

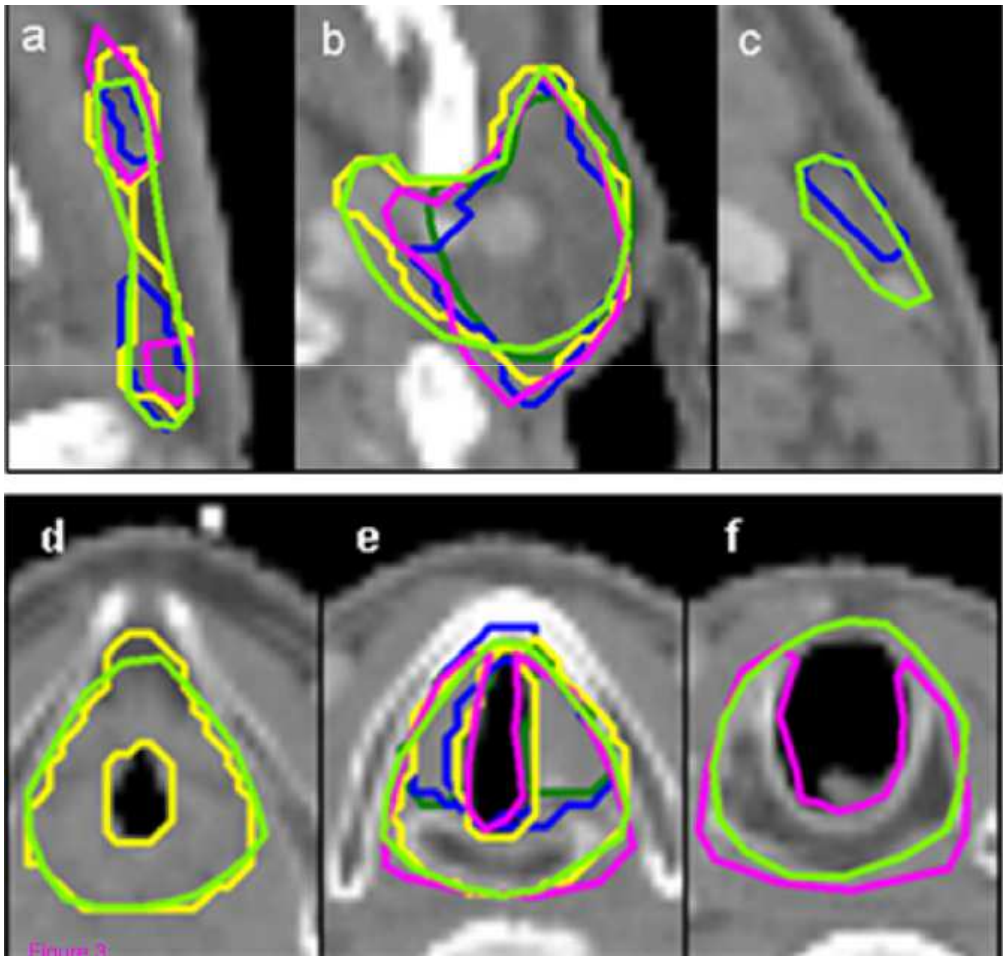
3D Variation in delineation of head and neck organs at risk

Radiation Oncology 2012, **7**:32 doi:10.1186/1748-717X-7-32

Brower et al

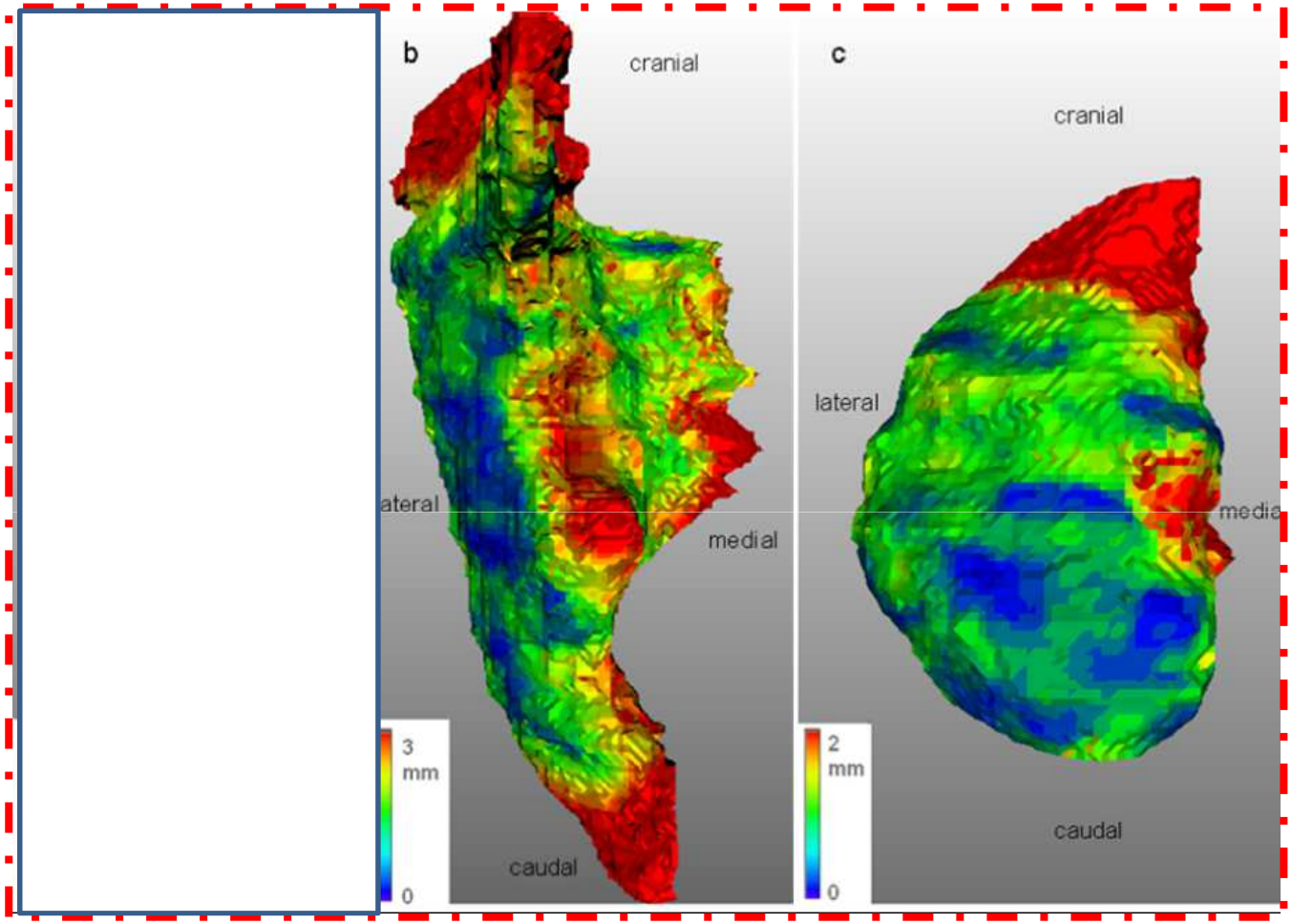
To study the magnitude and 3D localization of interobserver variability in the HN area





a) Larger interobserver variability for the glottix larynx

cranial, caudal and medial regions of the OAR showed larger interobserver variabilities



3D Standard Deviations for a patient

-Right parotid
-Right subman-dibular gland

- parotid glands: image resolution in cc direction
- submandibular gland: poor discrimination in contrast from adjacent tissues

Brower et al

Changes in anatomy over the course of treatment

- 10 H&N – oropharingeal ca pts, IMRT
- Three radiation oncologists delineating OARs, three contouring sessions one week apart
- Mean difference in total volume for each OAR was 1 cm3 for each OAR.
- Considerable spatial differences in contours, ipsilateral parotis and pharingeal constrictors showing most variability.
- **Despite substantial differences in OAR contours, optimization was barely affected with less than a 1 Gy difference in dose** (Feng *et al*, 2012)

Changes in anatomy over the course of treatment

- 10 H&N pts, IMRT
- CTVs and OARs delineated on CBCT at the10th, 15th, 20th, 25th treatment session and then compared with the planning CT
- A statistically significant increase of larynx volume at the 20th and 25th CBCT was observed
- The main benefit of replanning could be to preserve parotis, not to reevaluate the target

- **Check point at the 3rd week of radiotherapy in this pts cohort** (Cozzolino *et al*, 2014)

Changes in anatomy over the course of treatment

- 10 H&N – oropharingeal ca pts, IMRT
- CBCT prospectively acquired weekly, OARs dose/volume compared to the planned CT
- Evaluation of the use of KV CBCT for dose monitoring and examine if dosimetric impact of such changes on the parotid and OARs require replanning
- Patient weight loss (mean:7.5 kg) and parotid volume shrinkage was observed, but no significant excess dose to OAR
- **<u>No need for replanning in this patient cohort</u>** (Ho *et al* 2011)

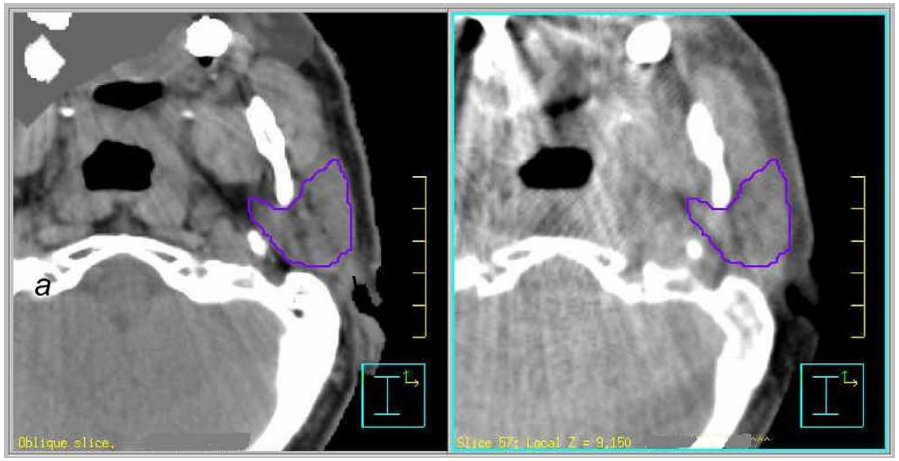
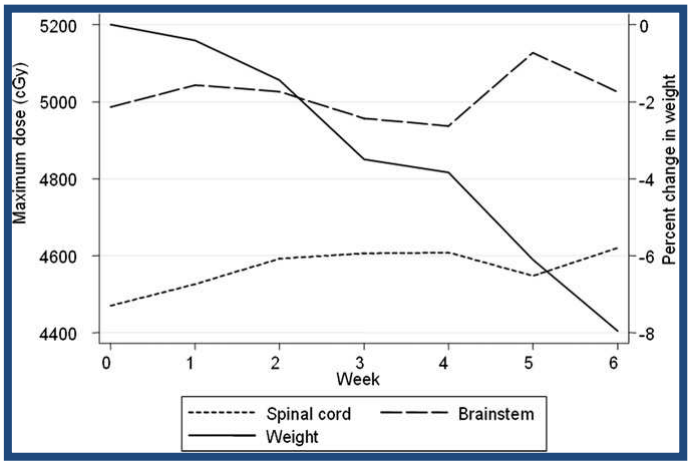


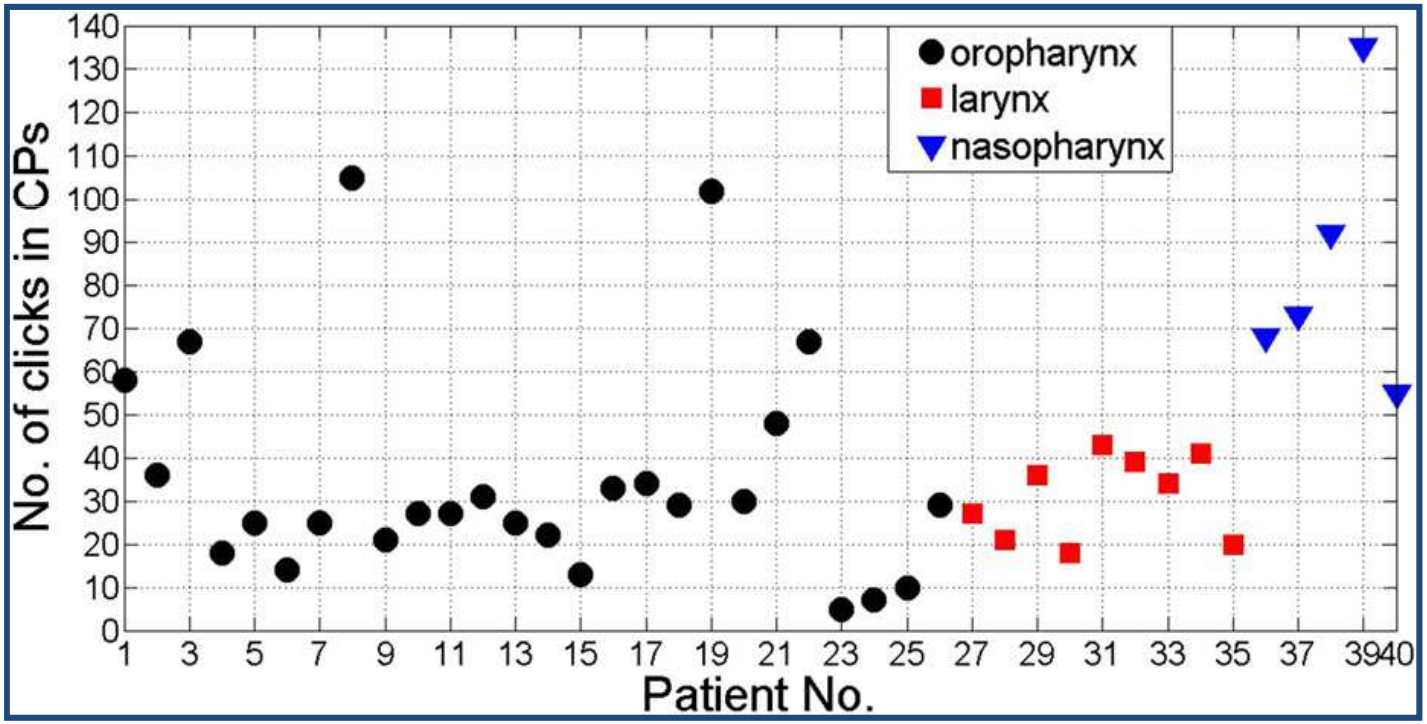
Fig. 1. Contouring parotid on cone beam computed tomography (CBCT) (b) using planning CT (a) as reference.



Automated VMAT planning

- Overlap volume histogram-driven automated planning optimization (Wu *et al*, 2012)
- Purpose: to prospectively determine whether it can be introduced in the clinical workflow
- 40 H&N SIB-IMRT consecutive pts, ; for each pt a fully automated plan (AP), was compared to the clinical plan (CP) used for the treatment.
- The study would show the non-inferiority of APs with respect to PTC coverage and secondary organ sparing (parotid, brachial plexus, esophagus, larynx, inner ear, oral mucosa).
- In APs, average doses to secondary organs were reduced by 1.16%, overall average PTV coverage was increased by 1.26%.

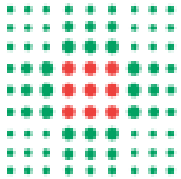
- According to the physician, APs were superior to CP in 27/40 cases
- **The dosimetric results of the APs were not inferior to routinely generated clinical plans.**



Distribution of the number of clicks of the “Start Optimization” button by dosimetrists in clinical planning. Average clicks in oropharynx, nasopharynx, and larynx planning is 35 (SD: 25.7), 84.6 (SD: 31.1), and 31 (SD: 9.7).

Thanks to:

Claudio Fiorino, HSR Milano
Tiziana Rancati, Istituto dei Tumori, Milano
Eva Onjukka, Karolinska University Hospital, Stockholm



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Policlinico

Head and Neck IMRT Tolerance Doses (Parotid Gland, Spinal Cord, Optic Pathways)

Frank Lohr, M.D.
Policlinico Modena

Disclosure

Research and Training Agreement, Expert Testimony and Travel Grants with Elekta/IBA/C-Rad

Board Member of C-Rad

Clinical Application of IMRT

Most important indications and treatment philosophy

1. **Head and Neck Cancer**
   CNS

   Paranasal Sinus Tumors / Integrated Boost
   (Better Tumor coverage and shortening of overall treatment time)

   NPC and other ENT Tumors
   (Parotid sparing when possible, better tumor coverage for NPC)

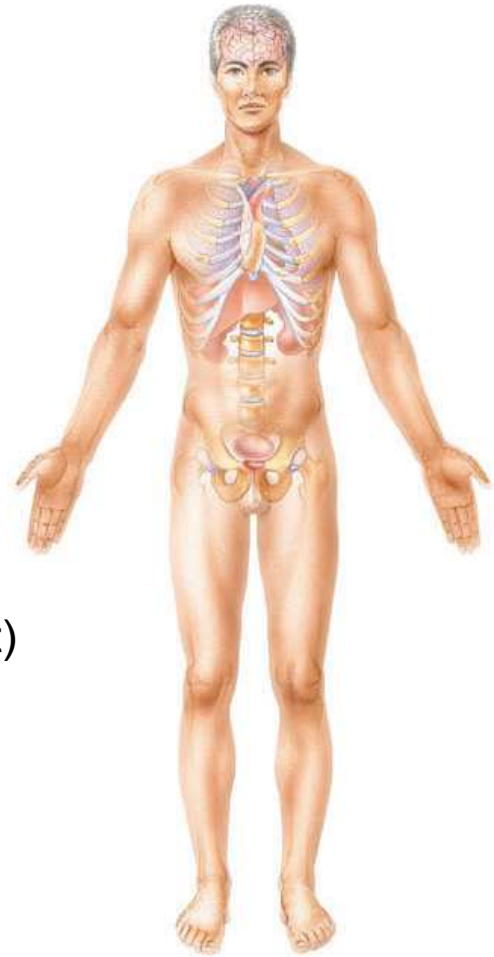
2. **Prostate / Integrated boost**
   (Potentially hypofractionation)

3. **Gastric cancer**
   (Better kidney sparing while treating the whole of the target)

4. **Breast Cancer**

5. **Lung Cancer**

6. **Metastases**



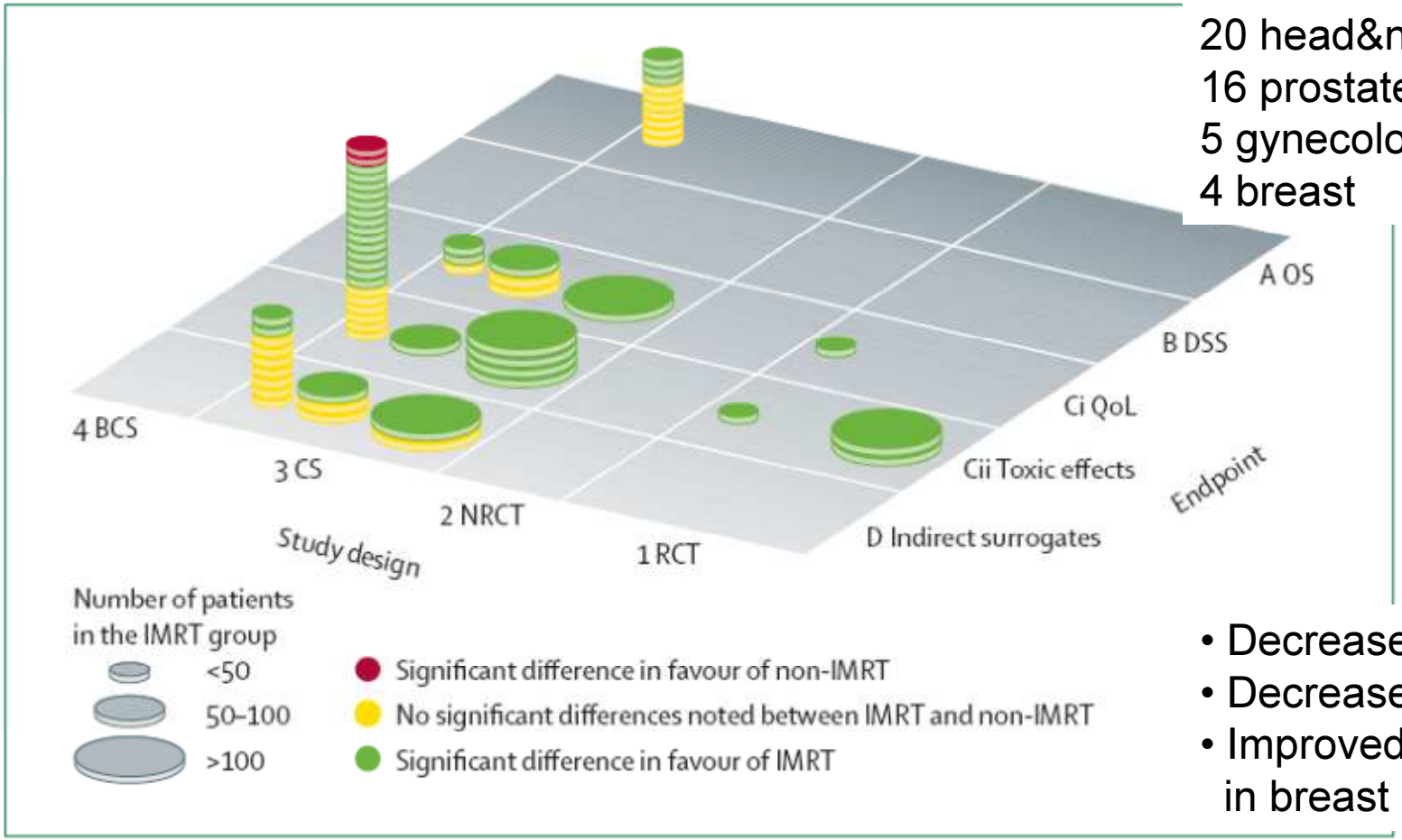
Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies

Liv Veldeman, Indira Madani, Frank Hulstaert, Gert De Meerleer, Marc Mareel, Wilfried De Neve

Lancet Oncol 2008; 9: 367–375

56 studies/reports

20 head&neck	3 lung
16 prostate	5 GI
5 gynecological	3 CNS
4 breast	



- Decreased xerostomia
- Decreased rectal toxicity
- Improved cosmesis in breast cancer

Figure 3: **Evaluation tool for relevance of clinical statements reported in 56 studies of IMRT**
BCS=best case series. CS=case series. NRCT=non-randomised controlled trial. RCT=randomised controlled trial. OS=overall survival. DSS=disease-specific survival. QoL=quality of life.

IMRT clinical outcome

Factors influencing the rational use of IMRT for head-and-neck cancer

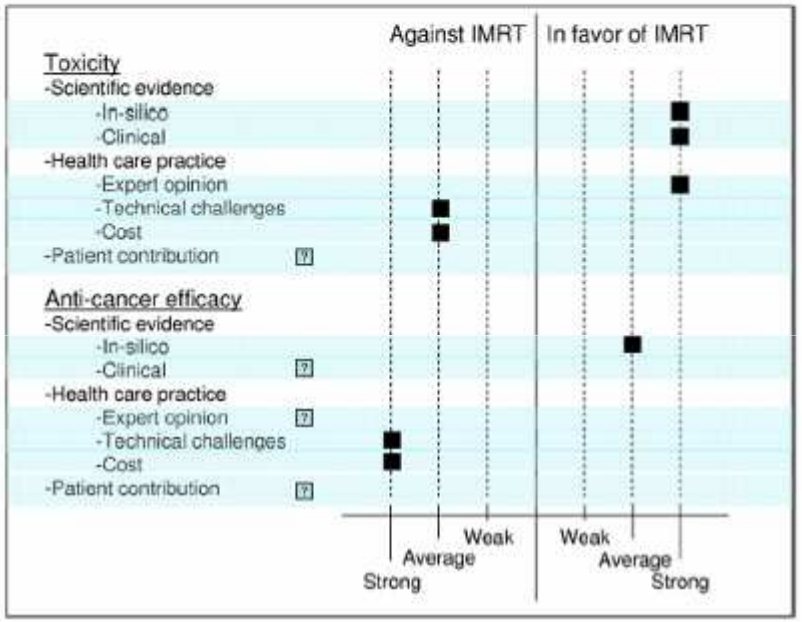


Figure 1 Factors in favor or against IMRT are represented by a rectangle on the right or on the left of the vertical solid line, respectively. A question mark inside a rectangle indicates too much uncertainty for using the factor in the graph.

Factors influencing the rational use of IMRT for whole breast irradiation

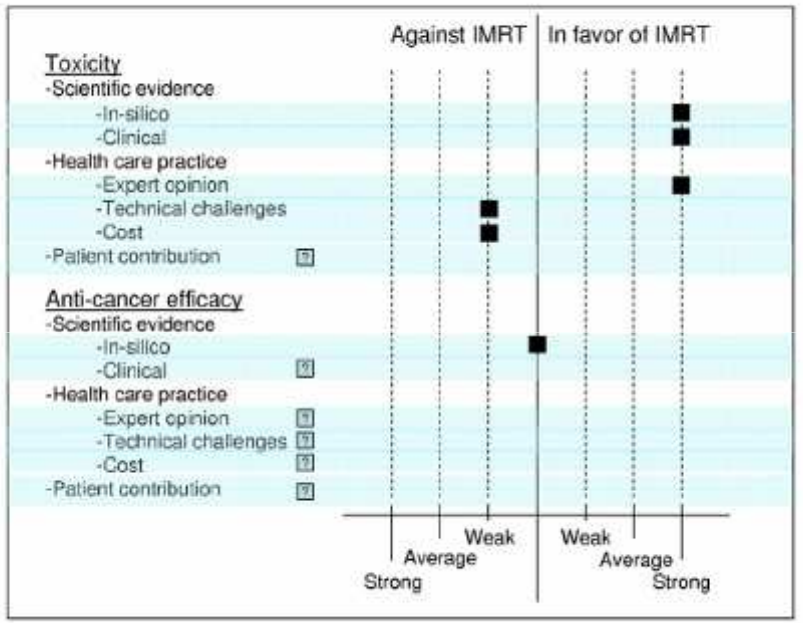


Figure 2 Factors in favor or against IMRT are represented by a rectangle on the right or on the left of the vertical solid line, respectively. A question mark inside a rectangle indicates too much uncertainty for using the factor in the graph.

De Neve et al. Sem Rad Onc, 2012

Canadian H&N IMRT-Review and Consensus

"The case for IMRT in head and neck cancer can be broadly outlined as follows:
1) The data identified in this review, as well as the earlier historical data described in the Introduction, support the contention that IMRT is, at worst, not inferior to two-dimensional CRT with respect to disease control.
2) The data identified in this review, as well as the earlier historical data, support the contention that with IMRT, there are clinically relevant and statistically significant differences in adverse event rates and quality of life compared with two-dimensional CRT."

O'Sullivan et al., Clin Oncol, 2012

Cost Effectiveness of IMRT

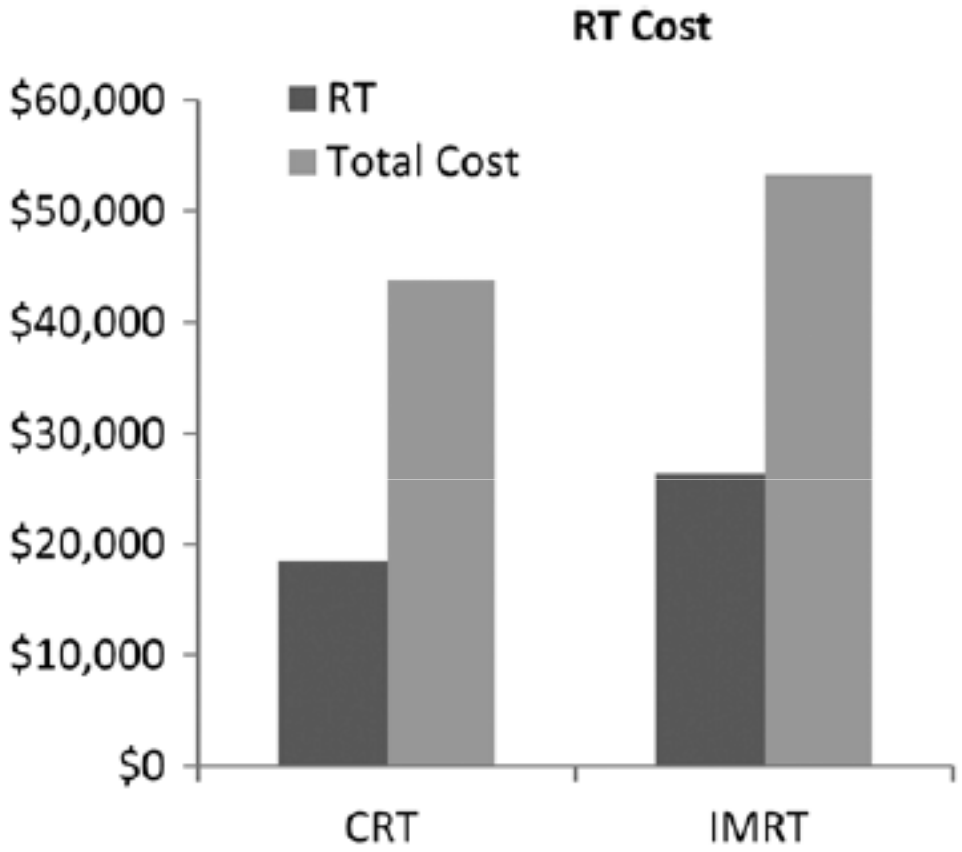


FIGURE 1. Radiation cost as a proportion of total cost from diagnosis through 1 year of follow-up.

-Exaggerated billing

-Cost F/u only recorded until 1 year after RT, therefore long term benefits not accounted for properly

Sheets et al.,
Am J Clin Oncol, 2013

Tumor Localizations

2. Head and Neck

Recent Review

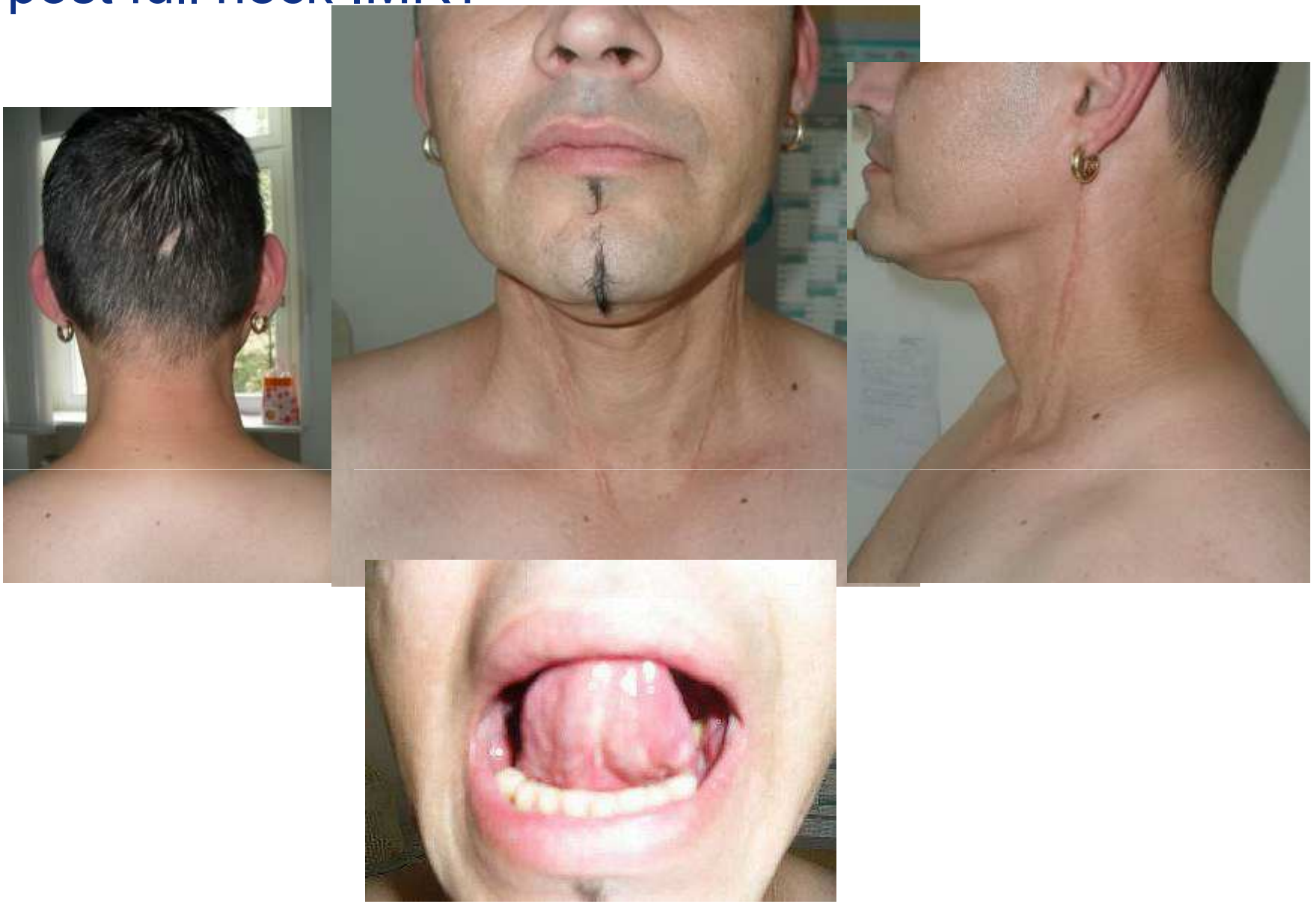
The British Journal of Radiology, 85 (2012), 487–494

REVIEW ARTICLE

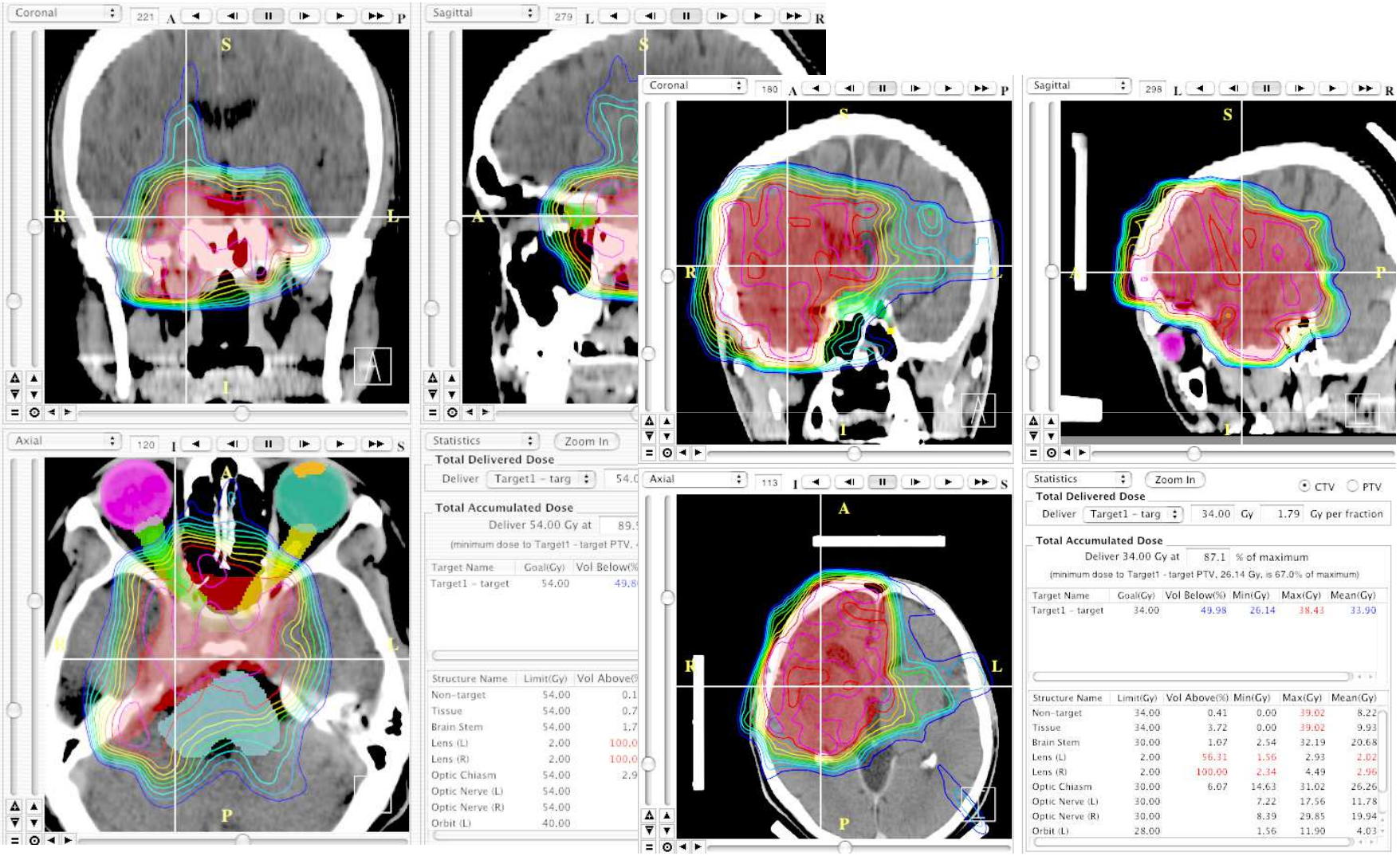
Clinical evaluation of intensity-modulated radiotherapy for head and neck cancers

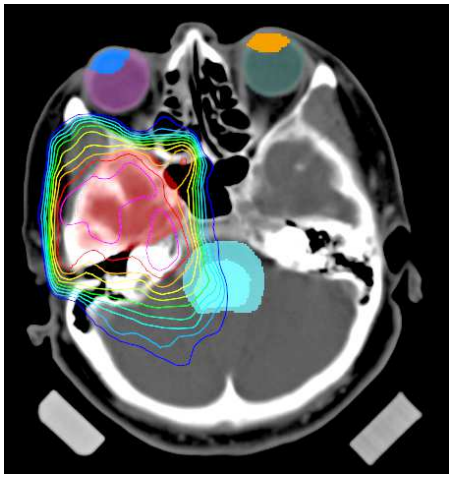
[1]S A BHIDE, PhD, FRCR, [1]K L NEWBOLD, MRCP, FRCR, [2]K J HARRINGTON, PhD, FRCR and [2]C M NUTTING, MD, FRCR

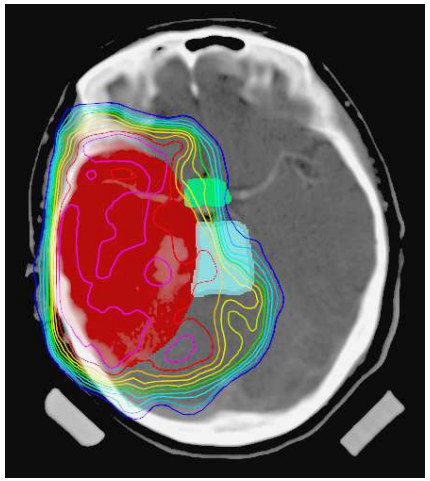
10J post full neck IMRT

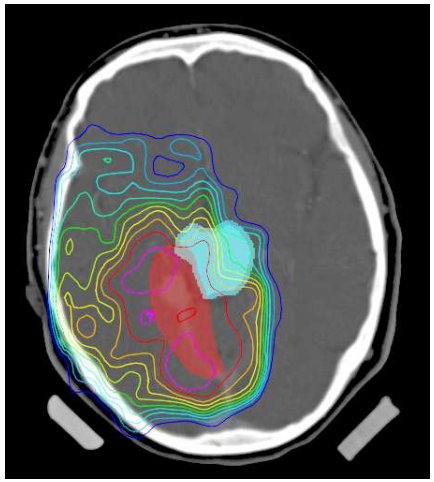


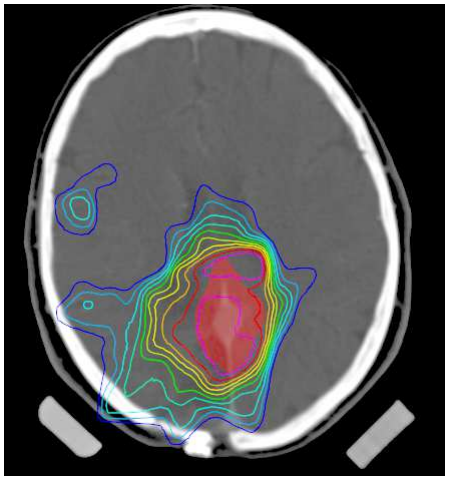
Head and Neck

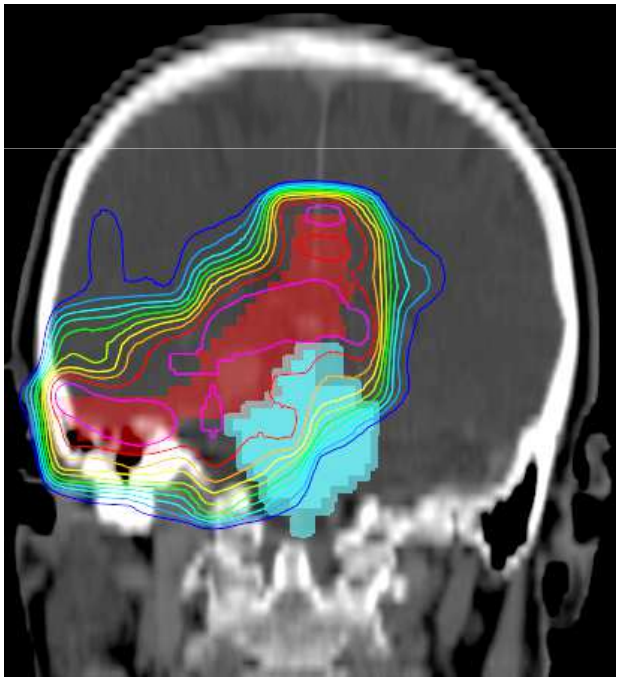


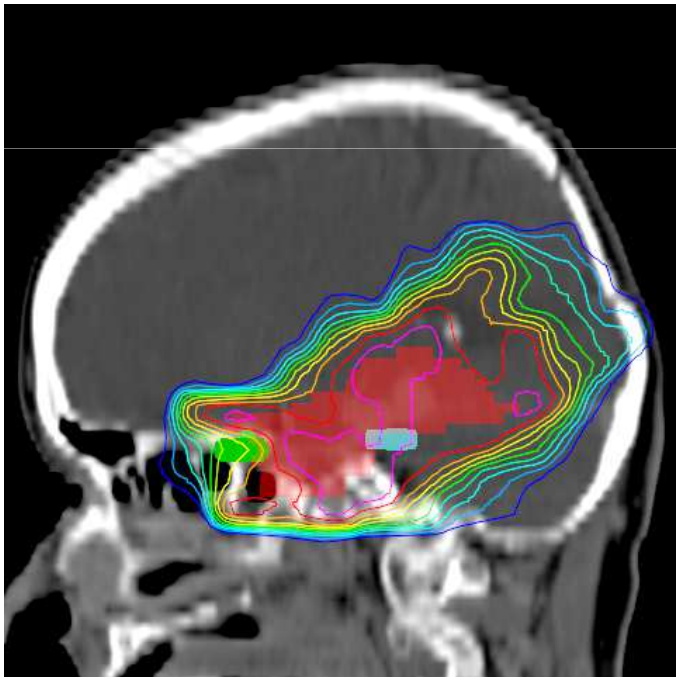


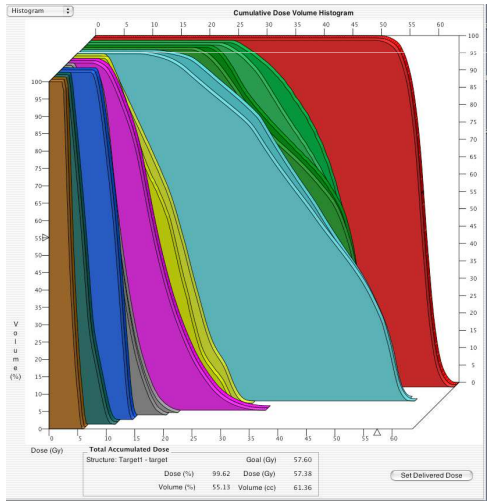











Histogram
Cumulative Dose Volume Histogram
Volume (%)
Dose (Gy)
Total Accumulated Dose
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Dose (%) 99.62
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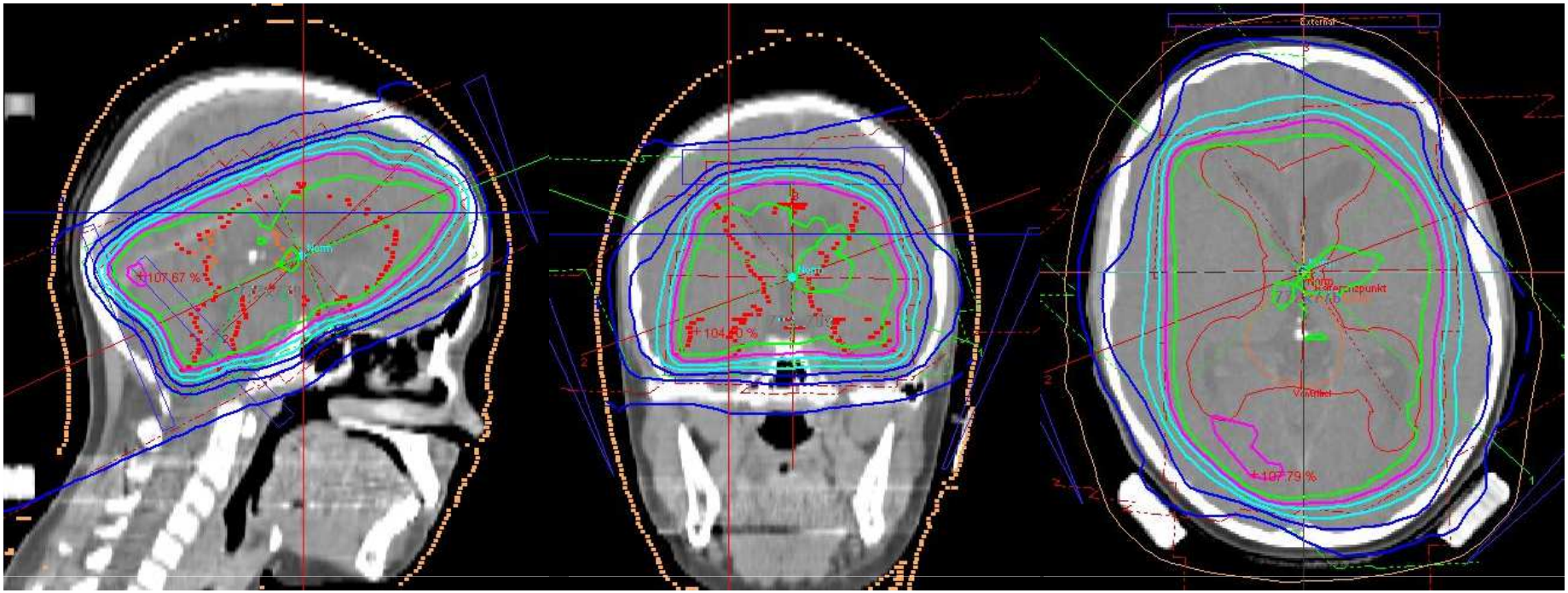
Volume (%) 55.13
Volume (cc) 61.36
Set Delivered Dose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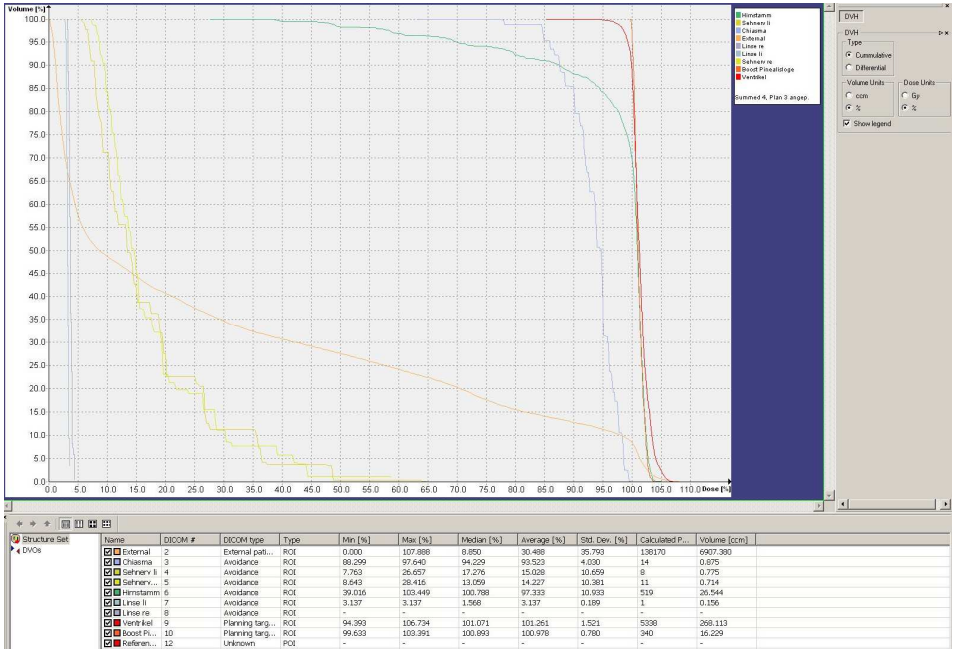
Isozentrumpunkt
Ventrikel
+107.67 %
+104.80 %
+107.79 %


Volume [%]
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Volume Units
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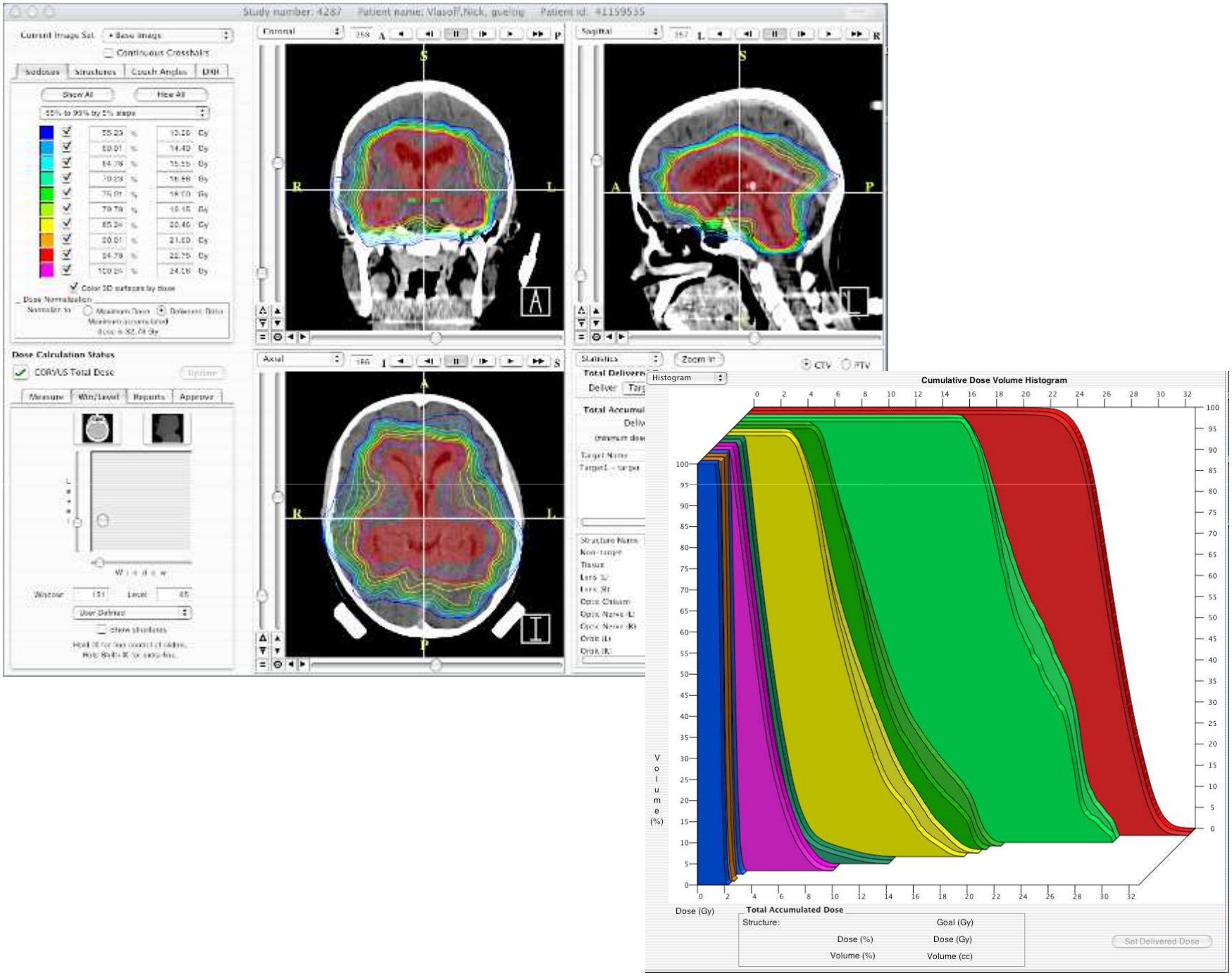
Show legend
Structure Set
DVOs
Name | DICOM # | DICOM type | Type | Min [%] | Max [%] | Median [%] | Average [%] | Std. Dev. [%] | Calculated P... | Volume [ccm]
External | 2 | External pati... | ROI | 0.000 | 107.888 | 8.850 | 30.488 | 35.793 | 138170 | 6907.380
Chiasma | 3 | Avoidance | ROI | 88.299 | 97.640 | 94.229 | 93.523 | 4.030 | 14 | 0.675
Sehnerv li | 4 | Avoidance | ROI | 7.763 | 26.657 | 17.276 | 15.028 | 10.659 | 8 | 0.775
Sehnerv... | 5 | Avoidance | ROI | 8.643 | 28.416 | 13.059 | 14.227 | 10.381 | 11 | 0.714
Himstamm | 6 | Avoidance | ROI | 39.016 | 103.449 | 100.788 | 97.333 | 10.933 | 519 | 26.544
Linse li | 7 | Avoidance | ROI | 3.137 | 3.137 | 1.568 | 3.137 | 0.189 | 1 | 0.156
Linse re | 8 | Avoidance | ROI | - | - | - | - | - | - | -
Ventrikel | 9 | Planning targ... | ROI | 94.393 | 106.734 | 101.071 | 101.261 | 1.521 | 5338 | 268.113
Boost Pi... | 10 | Planning targ... | ROI | 99.633 | 103.391 | 100.893 | 100.978 | 0.780 | 340 | 16.229
Referen... | 12 | Unknown | POI | - | - | - | - | - | - | -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CORVUS Total Dose
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Win/Level
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Target Name
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Optic Nerve (L)
Optic Nerve (R)
Orbit (L)
Orbit (R)
Histogram
Cumulative Dose Volume Histogram
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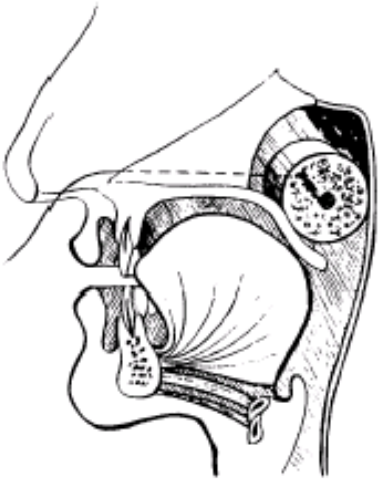
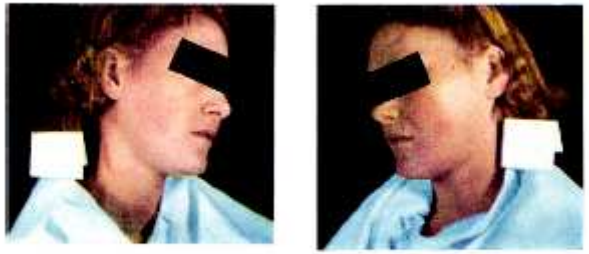
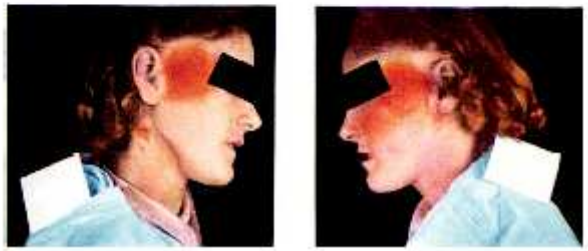


Nasopharyngeal carcinoma: treatments and outcomes in the 20th century

[1]R F MOULD, MSc, PhD and [2]T H P TAI, FRCR, FRCPC

The British Journal of Radiology, 75 (2002), 307–339





Year of publication	Centre	No. of cases	Symptom free cases	
			No.	%
1931	Radiumhemmet, Stockholm	70	8	11.4
1931	Zurich	32	2	6.2
1931	Mayo Clinic	194	4	2.1
1937	Amsterdam	47	5	10.6
1938	Fondation Curie, Paris	38	7	8.4
1940	Memorial, New York	80	20	25.0
1941	New York	42	7	16.7
1943	Copenhagen	37	9	24.3
1944	Copenhagen	266	59	22.2

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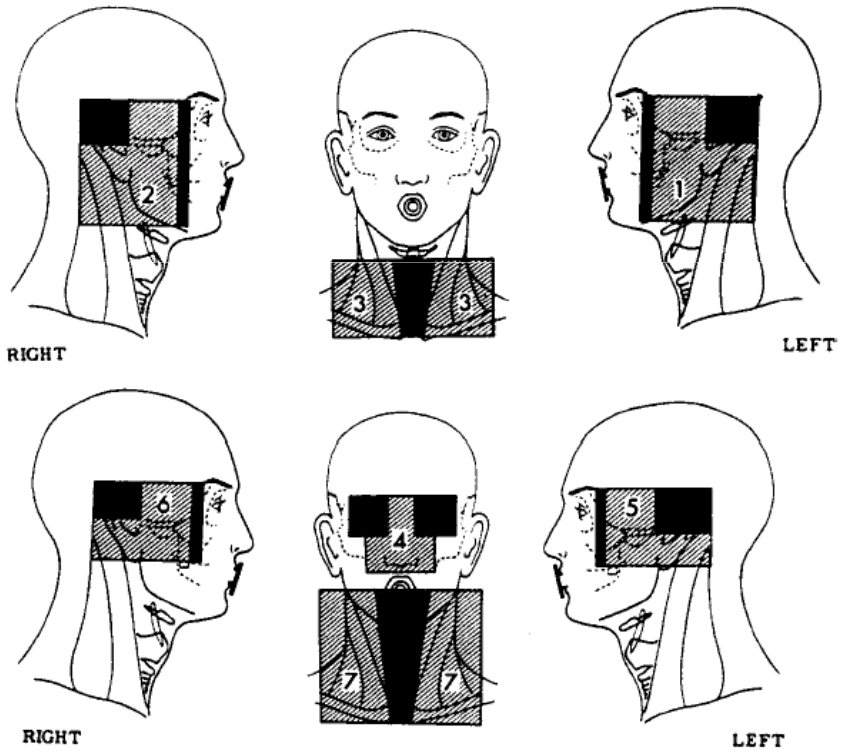

Table 3. Results of a world literature survey after Rosemarie Albrecht of the Head & Neck Clinic, Jena, former German Democratic Republic [41]

Year of publication	Centre	No. of cases	5-year survival	
			No.	%
1943	Mayo Clinic	271	35	12.9
1944	Zurich	40	12	30.0
1947	Innsbruck	18	4	22.2
1951	Boston	83	11	13.3
1951	Bologna	63	7	11.1
1951	Presbyterian & Montefiore, New York	91	23	25.3
1952	Tokyo	68	10	14.7
1952	Milan	72	4	5.5
1954	Fondation Curie, Paris	147	34	23.1
1954	Christie Hospital, Manchester	100	21	21.0
1954	Middlesex Hospital, London	46	7	15.2
1957	Toronto	77	7	9.1
1958	Germany (Albrecht)	397	55	13.8

Table 9a. 5-year local control results from various series

Series	Local control (total No. of patients)			
	T1	T2	T3	T4
[a]Hoppe et al [66], Stanford	87% (38)	94% (16)	68% (19)	44% (9)
[b]Chu et al [67], Louisville	76% (25)	79% (14)	37% (19)	55% (22)
[c]Vikram et al [68], MSKCC	65% (47)		100% (3)	48% (57)
[d]Wang [69], MGH	76% (17)	54% (23)	34% (11)	42% (10)
	[f]67% (14)	[f]84% (30)	[f]78% (12)	[f]52% (12)
[e]Perez et al [70], Mallinckrodt	85% (21)	75% (33)	67% (26)	45% (63)

Table 9b. 5-year survival results from various series

Series	5-year survival results (total No. of patients)			
	T1	T2	T3	T4
[a]Hoppe et al [66], Stanford	76% (38)	68% (16)	55% (19)	0% (9)
[b]Wang [69], MGH	60% (52)	48% (58)	27% (33)	29% (42)

Table 11. 5-year local control rates after radiotherapy as a function of cervical node status

Series	Local control rate (Total No. of patients)		
	N0–N1	N2	N3
Bedwinek et al [73], Mallinckrodt[a]	98% (54)	71% (21)	64% (46)
Mesic et al [71], MD Anderson[a]	95% (65)	88% (59)	81% (111)

Table 12. 5-year disease–free survival rates as a function of cervical node status for two American series and for the Hong Kong series in Table 11

Series	Disease-free survival rate (Total No. of patients)	
	N0–N1	N2–N3
Frezza et al [74], Univ. of Bologna, Italy[a]	80% (36)	30% (42)
Perez et al [70, 75], Massachusetts General[b]	63% (115)	56% (144)
Lee et al [56], Hong Kong[c]	72% (1882)	40% (2848)

Nasopharyngeal carcinoma: treatments and outcomes in the 20th century

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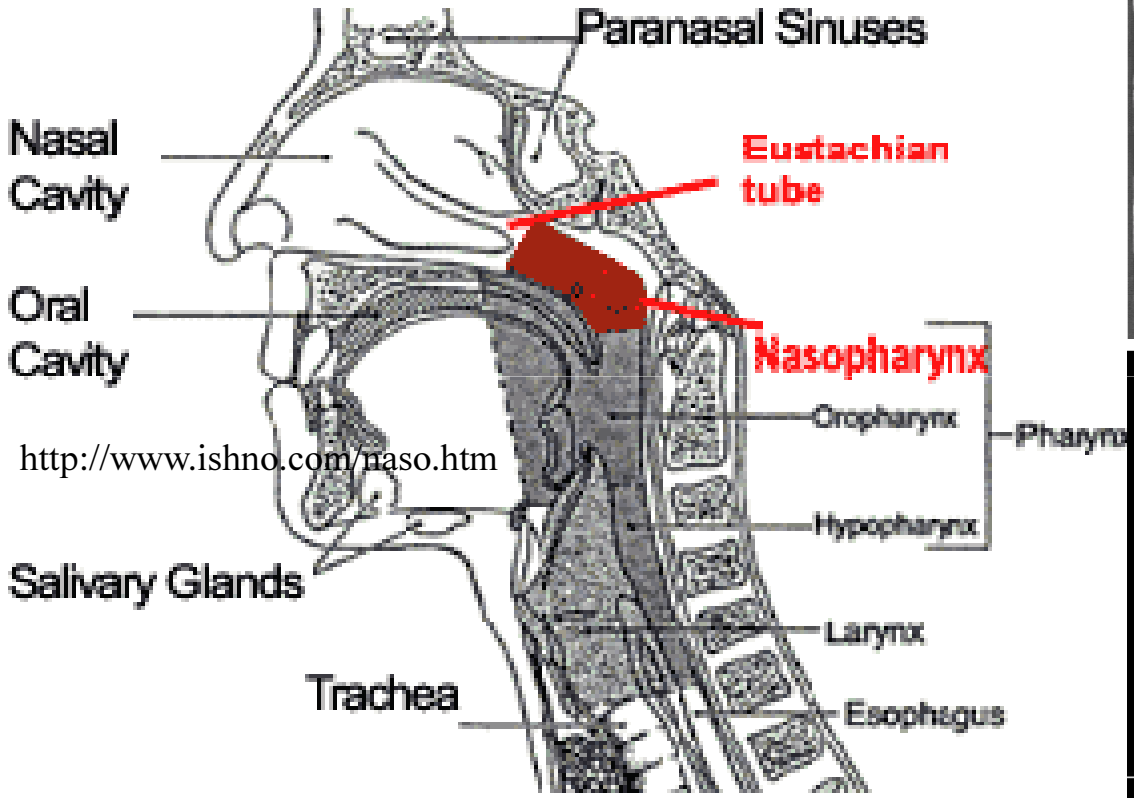
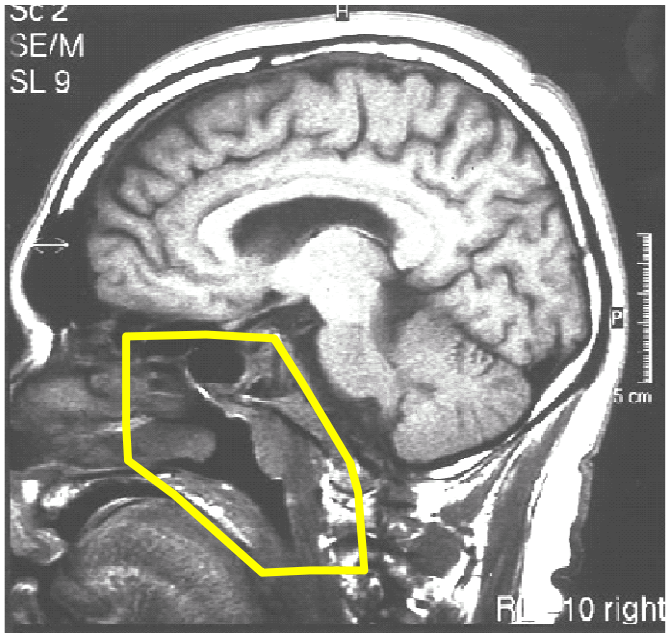
The British Journal of Radiology, 75 (2002), 307–339



http://www.ishno.com/naso.htm



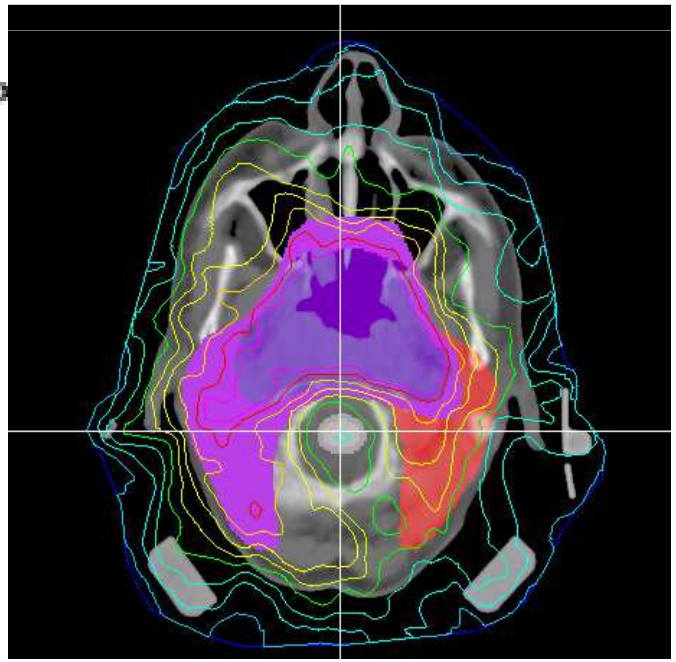


Table 3.1. Comparison between the TNM atlas terminology and the Robbin classification of the lymph nodes of the neck

TNM atlas for lymph nodes of the neck		Robbins classification	
Group No.	Terminology	Level	Terminology
1	Submental nodes	Ia	Submental group
2	Submandibular nodes	Ib	Submandibular group
3	Cranial jugular nodes	II	Upper jugular group
4	Medial jugular nodes	III	Middle jugular group
5	Caudal jugular nodes	IV	Lower jugular group
6	Dorsal cervical nodes along Spinal accessory nerve	V	Posterior triangle group
7	Supraclavicular nodes	V	Posterior triangle group
8	Prelaryngeal and paratracheal nodes	VI	Anterior compartment group
9	Retropharyngeal nodes	–	–
10	Parotid nodes	–	–
11	Buccal nodes	–	–
12	Retroauricular and occipital nodes	–	–

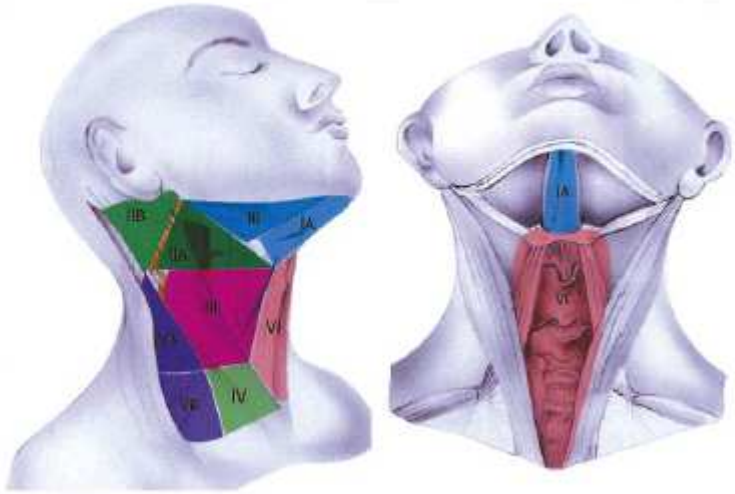


Fig. 3.1. Schematic representation of the various neck node groups: submental (*Ia*) and submandibular (*Ib*); upper jugular (*II*); middle jugular (*III*); lower jugular (*IV*); posterior triangle (*V*); anterior compartment (*VI*)

Table 3.2. Distribution of clinical metastatic neck nodes from head and neck SCC

Tumor site	Patients with N+ (%)	Distribution of metastatic lymph nodes per level (percentage of node-positive patients)					
		I	II	III	IV	V	Other[a]
Oral cavity (*n*=787)	36	42/3.5[b]	79/8	18/3	5/1	1/0	1.4/0.3
Oropharynx (*n*=1479)	64	13/2	81/24	23/5	9/2.5	13/3	2/1
Hypopharynx (*n*=847)	70	2/0	80/13	51/4	20/3	24/2	3/1
Supraglottic larynx (*n*=428)	55	2/0	71/21	48/10	18/7	15/4	2/0
Nasopharynx (*n*= 440)	80	9/5	71/56	36/32	22/15	32/26	15/10

[a] Parotid, buccal nodes
[b] Ipsilateral/contralateral nodes
Redrawn from BATAINI et al. (1985); LINDBERG (1972); SHAM et al. (1990)

Table 3.3. Incidence of retropharyngeal lymph nodes in head and neck primary tumors

Authors	Primary site	Incidence of retropharyngeal lymph nodes (percentage of total number of patients)		
		Overall	N0 neck[a]	N+ neck[b]
MCLAUGHLIN et al. (1995)	Oropharynx			
	Pharyngeal wall	18/93 (19%)	6/37 (16%)	12/56 (21%)
	Soft palate	7/53 (13%)	1/21 (5%)	6/32 (19%)
	Tonsillar fossa	16/176 (9%	2/56 (4%)	14/120 (12%)
	Base of tongue	5/121 (4%)	0/31 (0%)	5/90 (6%)
	Hypopharynx (piriform sinus or post-cricoid area)	7/136 (5%)	0/55 (0%)	7/81 (9%)
	Supraglottic larynx	4/196 (2%)	0/87 (0%)	4/109 (4%)
	Nasopharynx	14/19 (74%)	2/5 (40%)	12/14 (86%)
CHUA et al. (1997)	Nasopharynx	106/364 (29%)	21/134 (16%)	85/230 (37%)
CHONG et al. (1995)	Nasopharynx	Not stated	Not stated	59/91 (65%)

[a] Clinically negative nodes in levels I–V
[b] Clinically positive nodes in levels I–V

V. Grégoire · P. Scalliet · K. K. Ang (Eds.)
Clinical Target Volumes in Conformal and Intensity Modulated Radiation Therapy
A Clinical Guide to Cancer Treatment

Table 3.10. Suggested guidelines for the treatment of patients with head and neck SCC

Location of primary tumor	Appropriate node levels to be treated	
	Stage N0–N1 (AJCC 1997)	Stage N2b (AJCC 1997)
Oral cavity	I, II[a], and III (+IV for anterior tongue tumors)	I, II, III, IV and V[c]
Oropharynx	II, III, and IV (+ retropharyngeal nodes for posterior pharyngeal wall tumors)	I, II, III, IV, V and retropharyngeal nodes
Hypopharynx	II[a], III, and IV (+ VI for esophageal extension)	I, II, III, IV, V and retropharyngeal nodes (+ VI for esophageal extension)
Larynx[b]	II[a], III, and IV (+ VI for transglottic and subglottic tumors)	(I), II, III, IV and V (+ VI for transglottic and subglottic tumors)
Nasopharynx	II, III, IV, V and retropharyngeal nodes	II, III, IV, V and retropharyngeal nodes

[a] Nodes in level IIb could be omitted for N0 patients
[b] T1 glottic cancer excluded
[c] May be omitted if only levels I–III are involved

V. Grégoire · P. Scalliet · K. K. Ang (Eds.)
Clinical Target Volumes in Conformal and Intensity Modulated Radiation Therapy
A Clinical Guide to Cancer Treatment

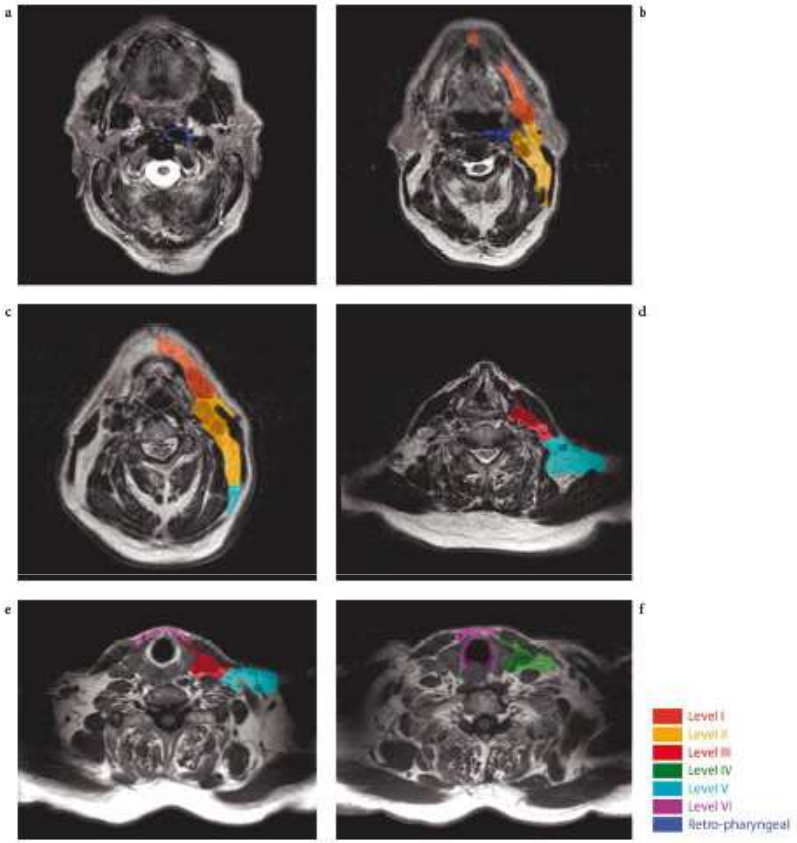


Fig. 3.3. MRI of the same patient with a T1N0M0 glottic SCC (see tumor in *panel d*). The examination was performed on a Gyroscan NT 1.5 T Philips Medical Systems (Eindhoven, the Netherlands) on an axial plane with a slice thickness of 4 mm, a gap of 2 mm, and a field of view of 240 mm. T2-weighted images (TR 7976 ms and TE 90 ms) are displayed in *panels a–d*. *Panels e and f* represent T1-weighted images (TR 500 and TE 12 ms). Sections were taken at the level of the bottom edge of C1 (*panel a*), the upper edge of C3 (*panel b*), mid C4 (*panel c*), the bottom edge of C6 (*panel d*), the bottom edge of C7 (*panel e*), and mid D1 (*panel f*). Neck node levels were drawn on each slice using the radiological boundaries detailed in Table 3.11. The slight difference in the shape of the various levels between Figs. 3.2 and 3.3 is explained by a difference in the positioning of the patient, leading to a slight difference in slice levels. Each node level corresponds to the CTV, and thus does not include a security margin for organ motion or set-up inaccuracy

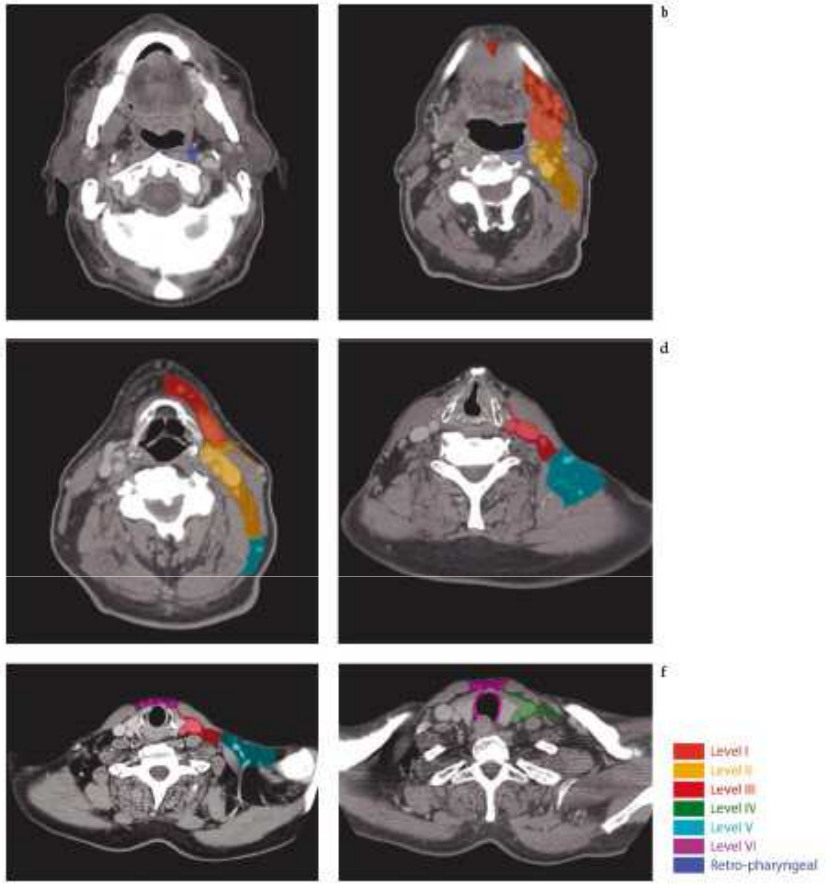


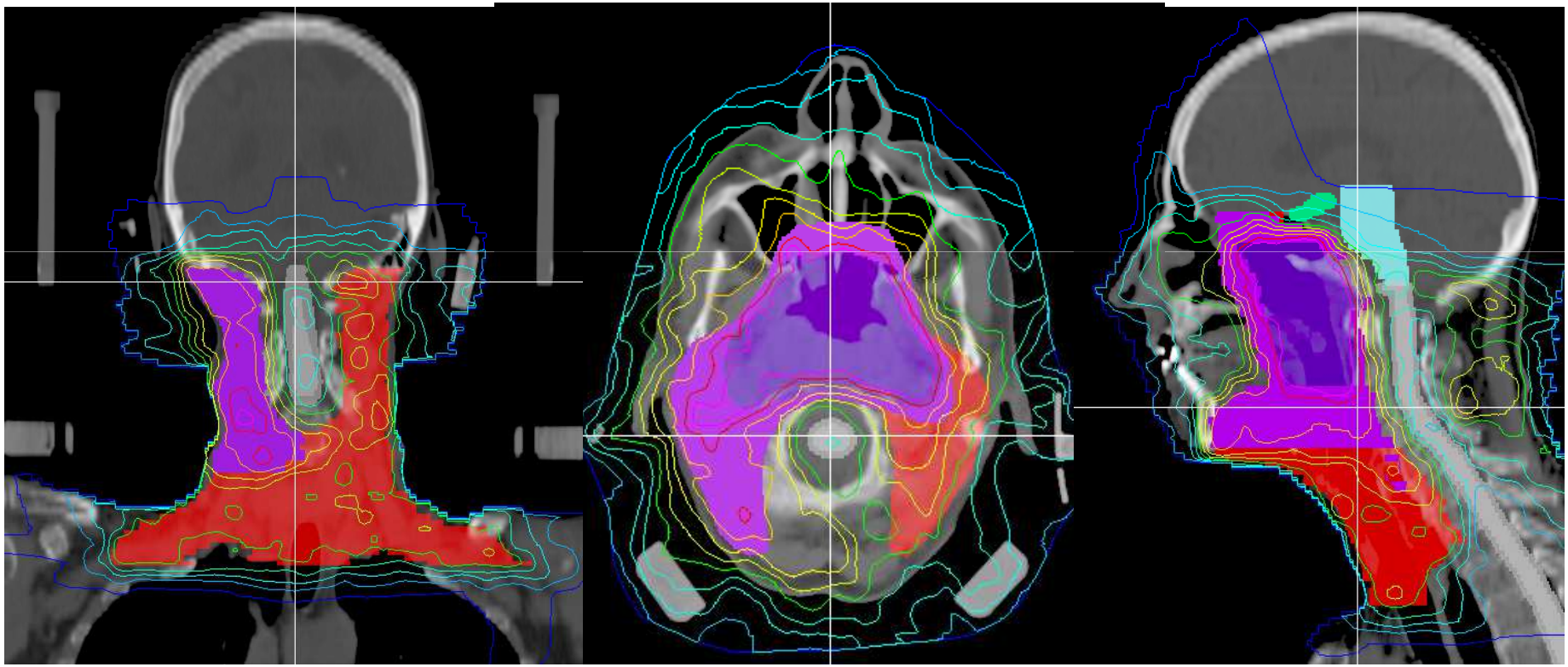
Fig. 3.2. CT imaging of a patient with a T1N0M0 glottic SCC (see tumor in *panel d*). The examination was performed on a dual-detector spiral CT (Elscint Twin, Haifa, Israel) using a slice thickness of 2.7 mm, an interval reconstruction of 2 mm and a pitch of 0.7. Contrast medium was injected intravenously at a rate of 2 ml/s with a total amount of 100 ml. Sections were taken at the level of the bottom edge of C1 (*panel a*), the upper edge of C3 (*panel b*), mid C4 (*panel c*), the bottom edge of C6 (*panel d*), the bottom edge of C7 (*panel e*), and mid D1 (*panel f*). Neck node levels were drawn on each CT slice using the radiological boundaries detailed in Table 3.11. Each node level corresponds to the CTV, and thus does not include a security margin for organ motion or set-up inaccuracy

V. Grégoire · P. Scalliet · K. K. Ang (Eds.)

Clinical Target Volumes in Conformal and Intensity Modulated Radiation Therapy

A Clinical Guide to Cancer Treatment

Nasopharynx
Integrated Boost



Principles of using Integrated Boost

1. If working with several dose levels, try not to move too far away from single doses with which there is clinical experience (e.g. 1.6 to 2.5 Gy)

2. Keep the high-total-dose / high-single-dose volume small and away from (especially serial) critical structures

3. Start with IMRT as early as possible in the course of a patient‘s treatment to keep the single dose spread as low as possible

INTENSITY-MODULATED RADIATION THERAPY FOR HEAD-AND-NECK CANCER: THE UCSF EXPERIENCE FOCUSING ON TARGET VOLUME DELINEATION

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Departments of *Radiation Oncology and †Radiology, University of California-San Francisco, San Francisco, CA

Int. J. Radiation Oncology Biol. Phys., Vol. 57, No. 1, pp. 49–60, 2003

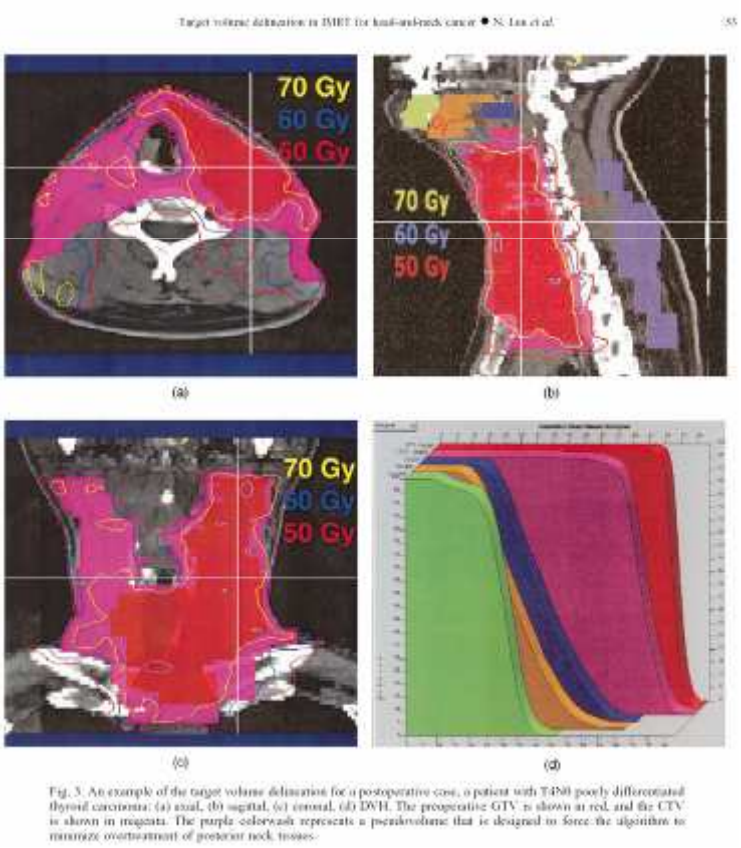


Fig. 3. An example of the target volume delineation for a postoperative case, a patient with T4N0 poorly differentiated thyroid carcinoma: (a) axial, (b) sagittal, (c) coronal, (d) DVH. The preoperative GTV is shown in red, and the CTV is shown in magenta. The purple colorwash represents a pseudovolume that is designed to force the algorithm to minimize overtreatment of posterior neck tissues.

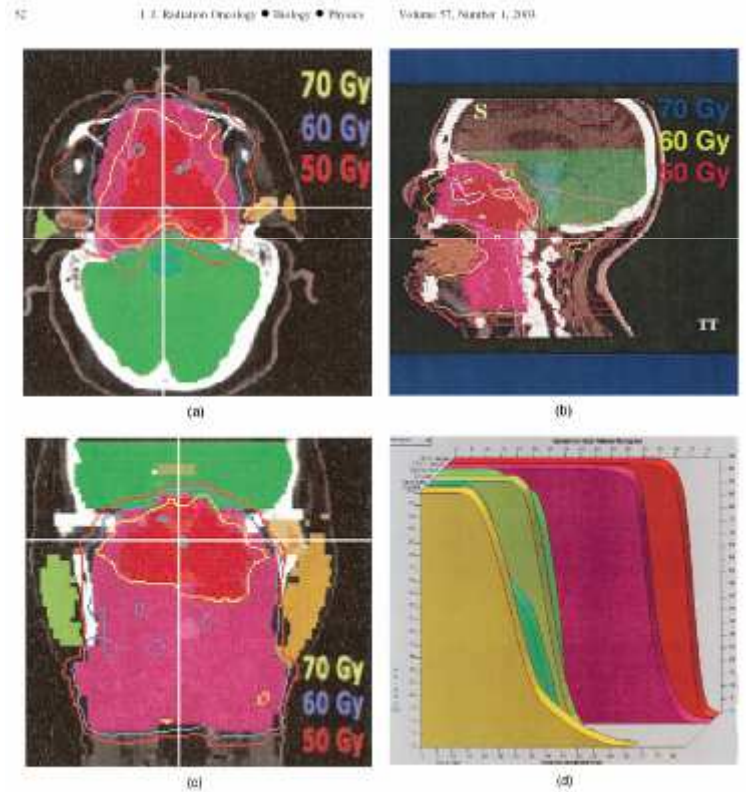


Fig. 2. An example of a target volume delineation for a definitive case, a patient with T3N0 nasopharyngeal carcinoma: (a) axial, (b) sagittal, (c) coronal, (d) DVH. The GTV is shown in red, and the CTV is shown in magenta.

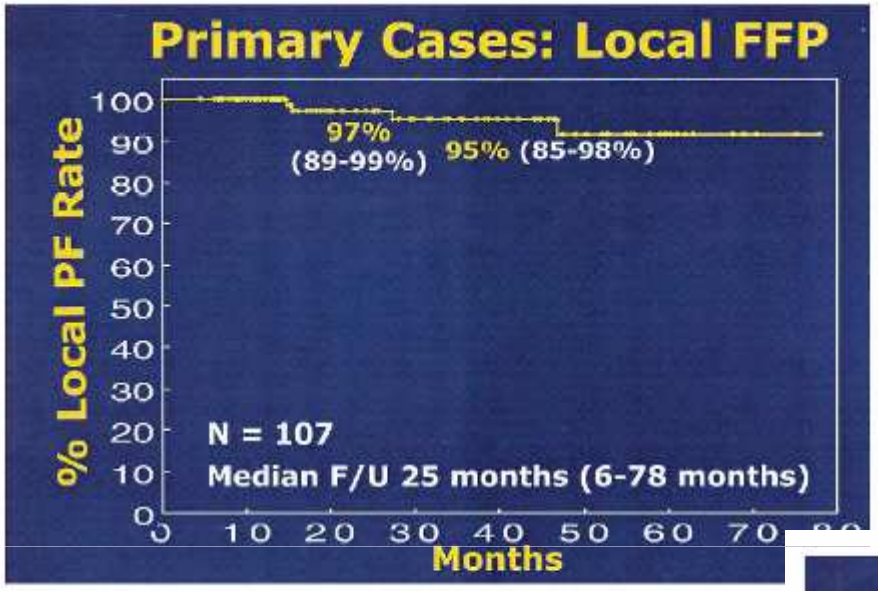


Fig. 4. Kaplan-Meier estimates of local freedom from progression rates for the definiti

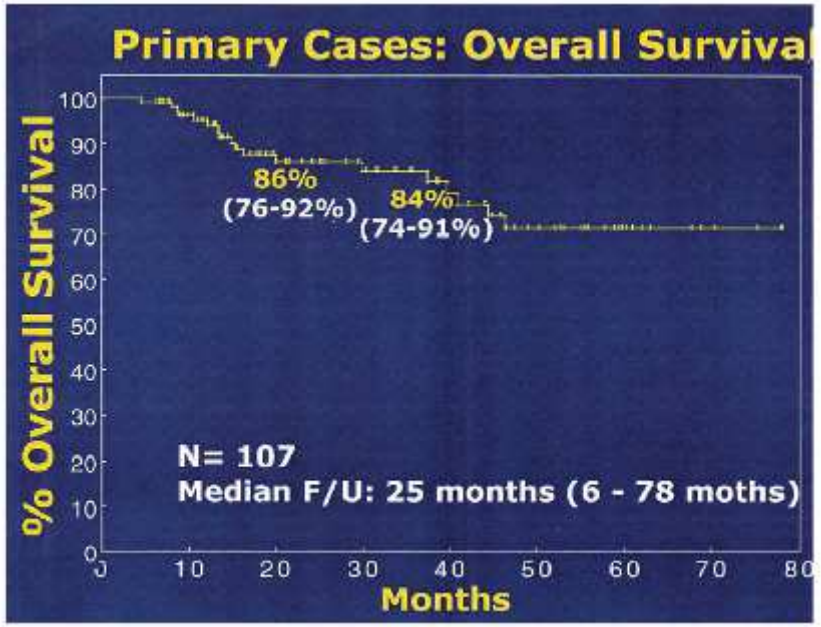
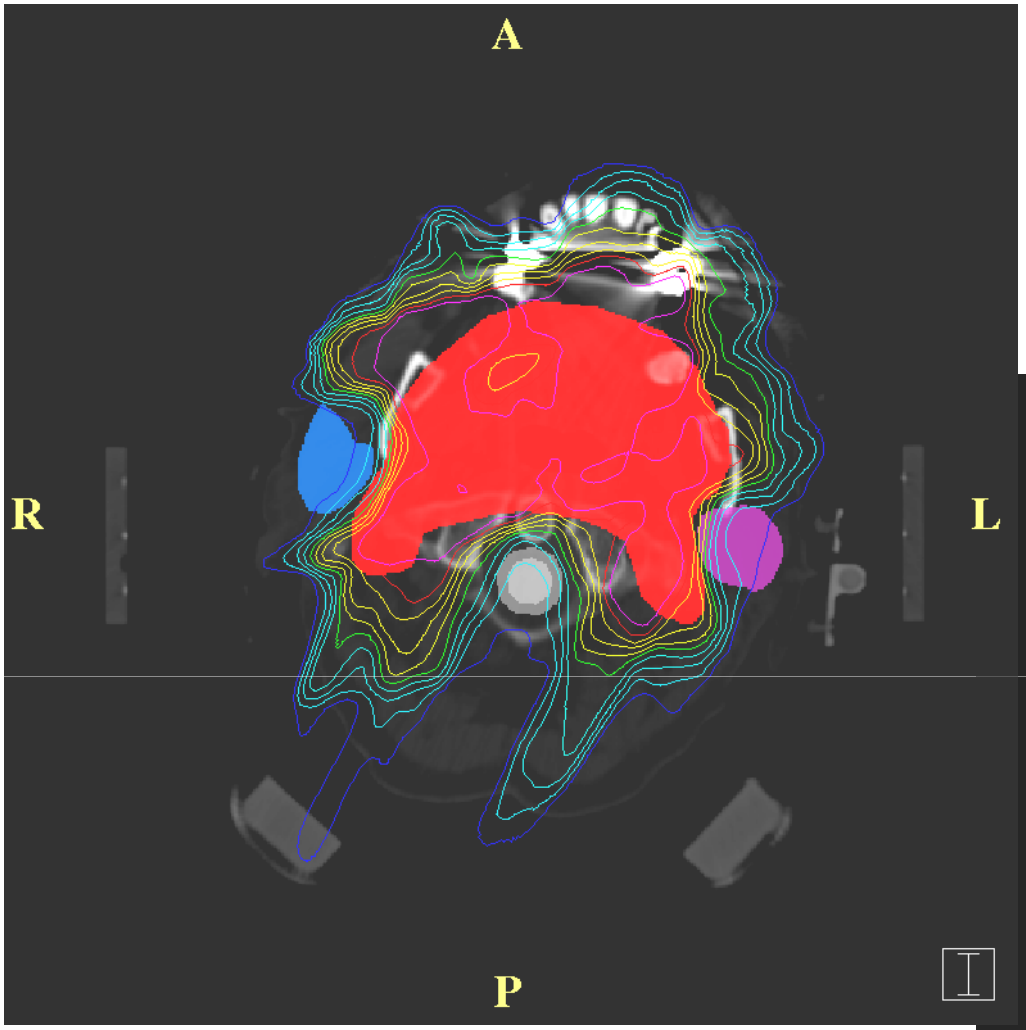
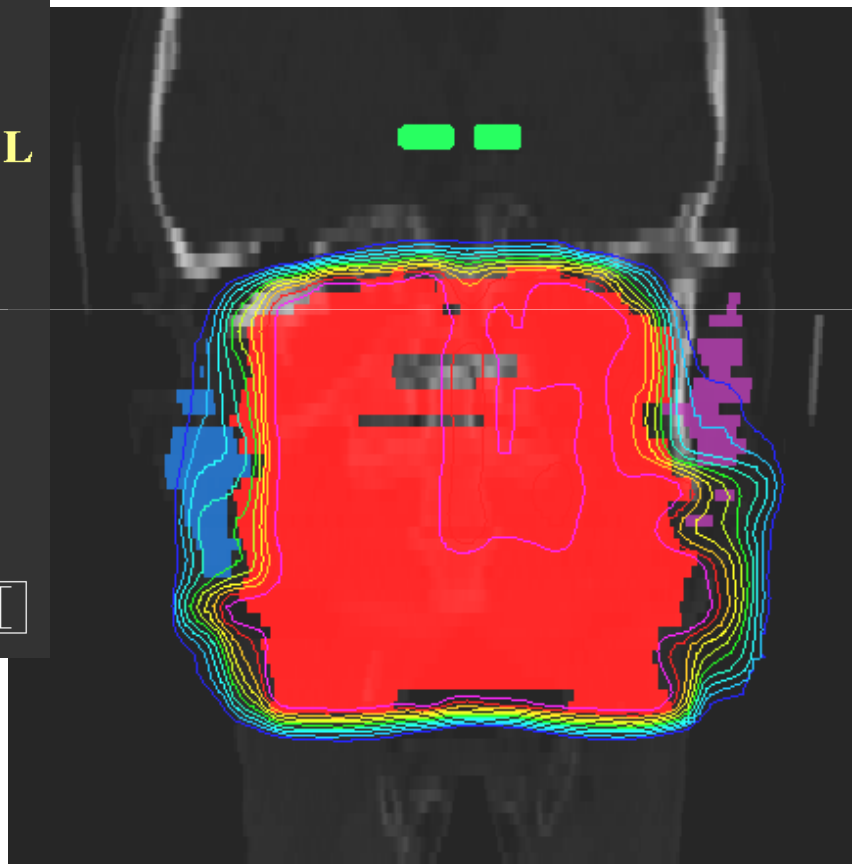


Fig. 5. Kaplan-Meier estimates of overall survival rates for the definitive cases.

Oropharnynx (Tongue) T3N0 Bilateral Parotid Sparing





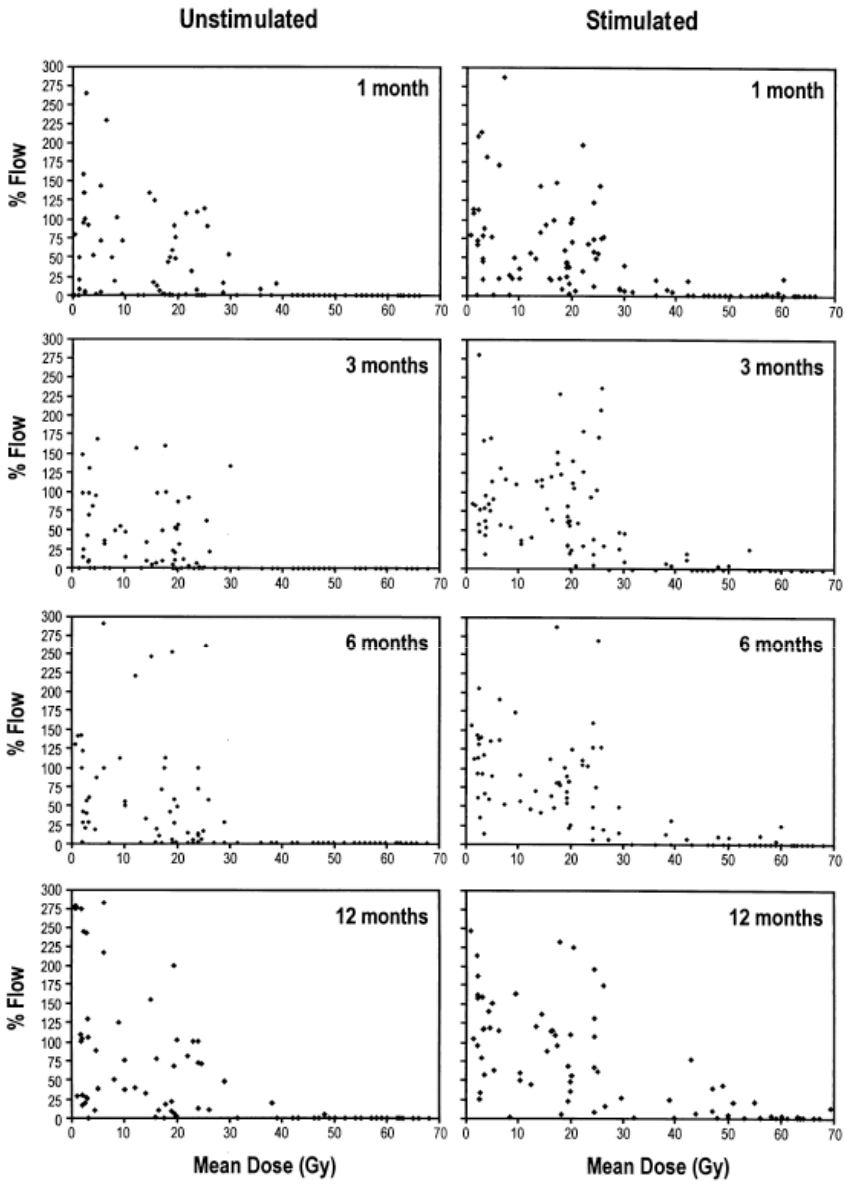


Fig. 2. Salivary flow rates, unstimulated and stimulated, vs. mean parotid gland dose at various time points after the completion of RT. The flows are expressed as the percentage of the pre-RT flow rates for each gland.

Parotid Sparing

–

Clinical Results

Eisbruch et al.,
IJROBP, 1999

-> Aim for a median parotid dose of <26 Gy

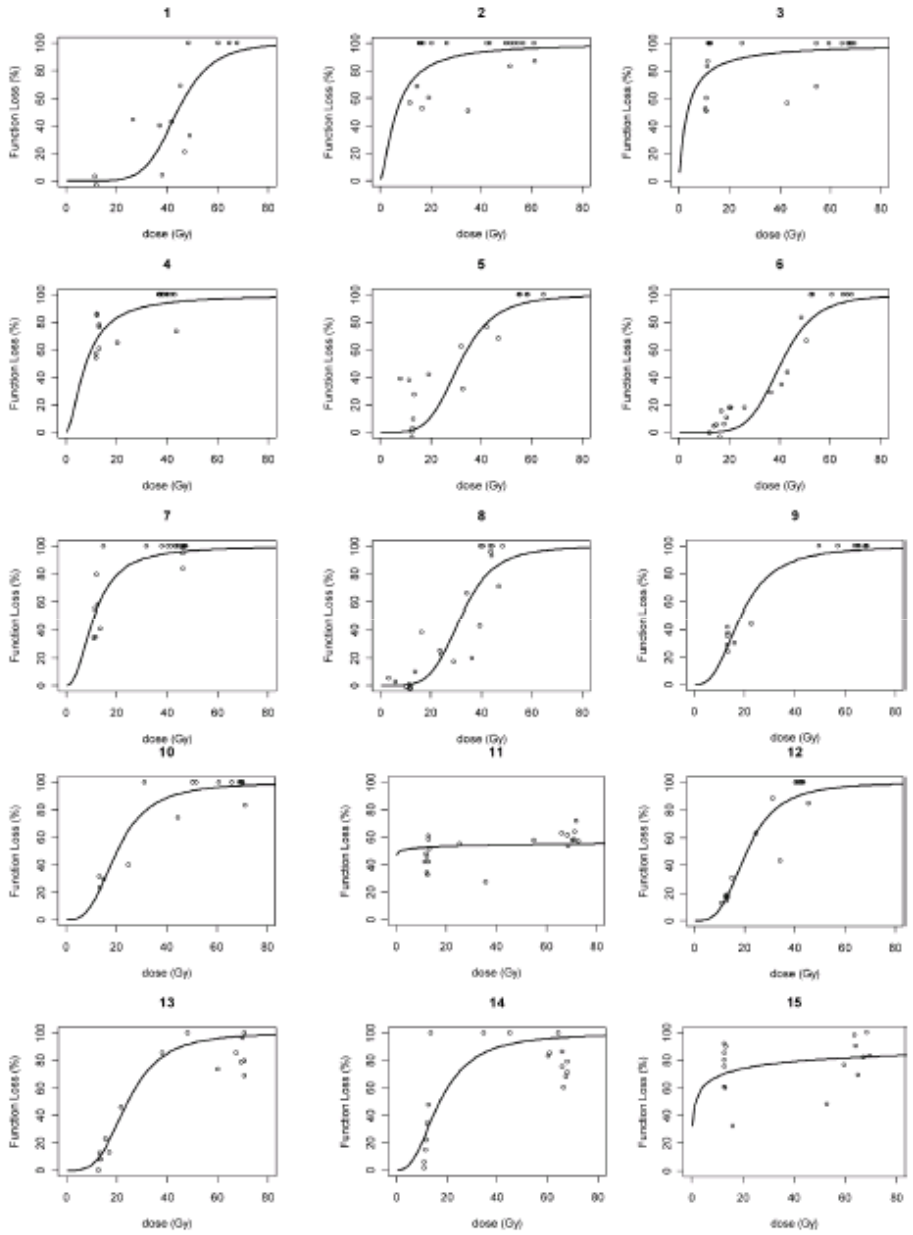


Fig. 5. The figure consists of the dose (Gy: *X*-axis) versus loss of function (dSEF: *Y*-axis) graphs for each of the 15 patients separately.

Parotid Sparing
–
Clinical Results

Bussels et al.,
R&O, 2004

-> Radiosensitivity of Parotid might be individual

->Parotid Tissue that is exposed to a dose that is lower than an individual threshold seems to remain functional

Parotid Tolerance -> The (almost) definitive data….

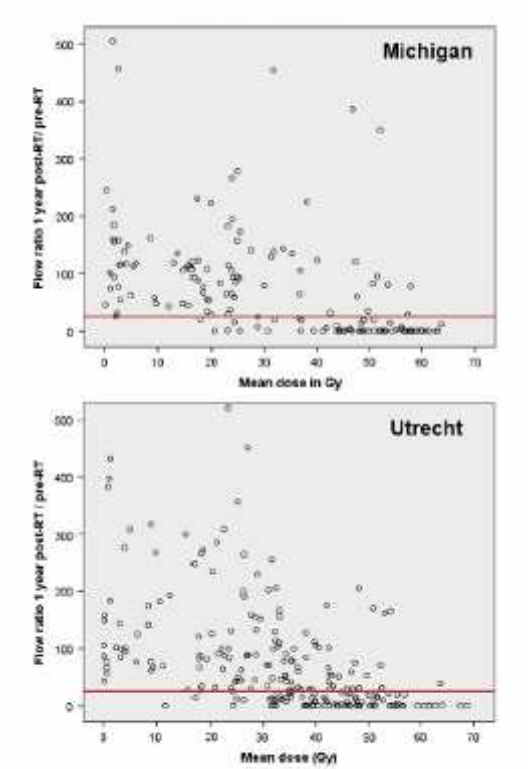


Fig. 1. Parotid flow ratio at 1 year after radiotherapy (RT) as a function of the mean parotid gland dose for Michigan (157 glands) and Utrecht (227 glands). The horizontal line indicates the complication threshold according to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Grade 4 xerostomia (flow ratio <25% of pretreatment).

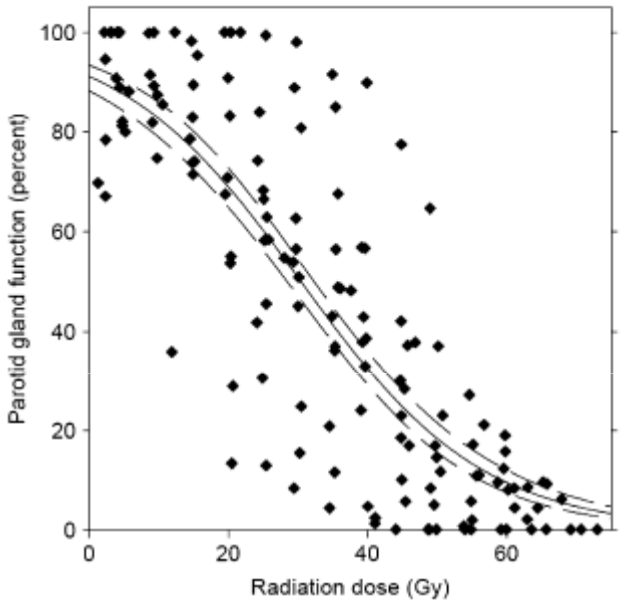


Fig. 4. Population-based dose vs. local function response (salivary function at rest) from imaging study by Buus *et al.* (2). Local functional decline in metabolic clearance of parotid salivary glands vs. local dose, according to voxel-by-voxel estimated time-activity curves of intravenously injected C11-methionine. Data points from 12 patients shown, along with best-fit curve and 95% confidence intervals of curve fit. Individual gland curves reported by Buus *et al.* (2) deviated significantly from this population average curve (reproduced from Buus *et al.* [2], used with permission.) This population curve demonstrated functional decline in salivary function even at low doses.

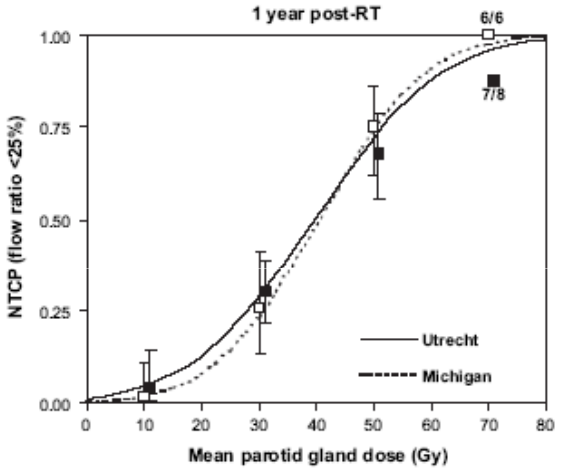


Fig. 2. Normal tissue complication probability (NTCP) curves as a function of the mean parotid gland dose for Michigan (dashed line) and Utrecht (solid line). Clinical NTCP values (using mean dose bins of 20 Gy) are shown for Michigan (open squares) and Utrecht (black squares), including 95% confidence intervals. RT = radiotherapy.

Deasy/Eisbruch, IJROBP, 2010
Dijkema/Eisbruch, IJROBP, 2010

ELSEVIER

Radiotherapy and Oncology 72 (2004) 119–127

www.elsevier.com/locate/radonline

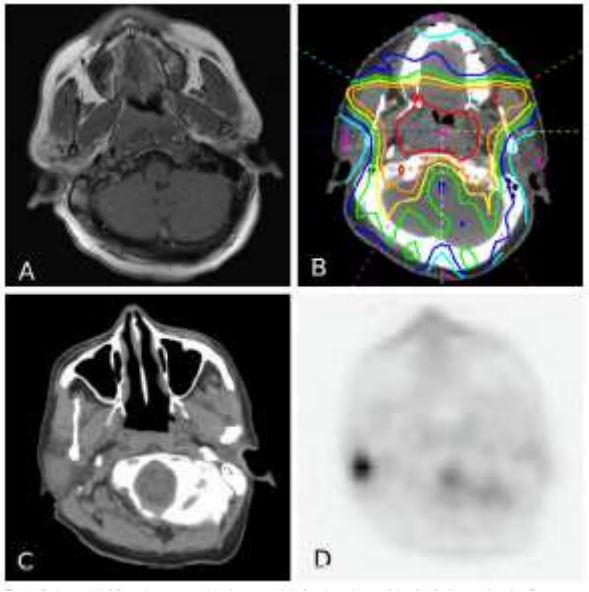
Recurrences after conformal parotid-sparing radiotherapy for head and neck cancer

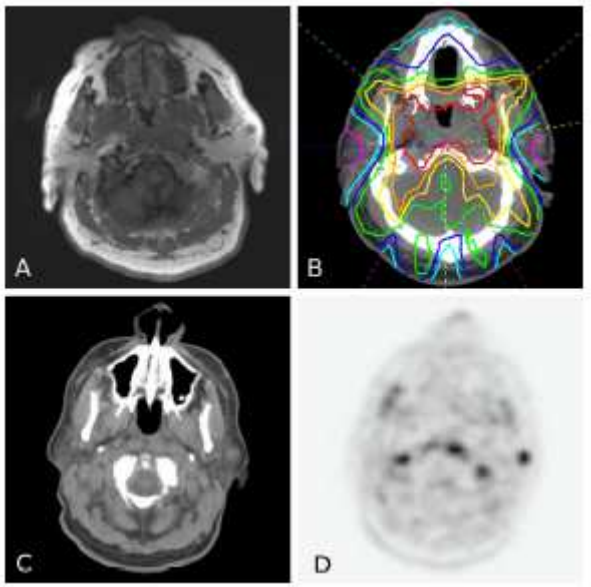
Barbara Bussels[a,*], Annelies Maes[b], Robert Hermans[c], Sandra Nuyts[a], Caroline Weltens[a], Walter Van den Bogaert[a]

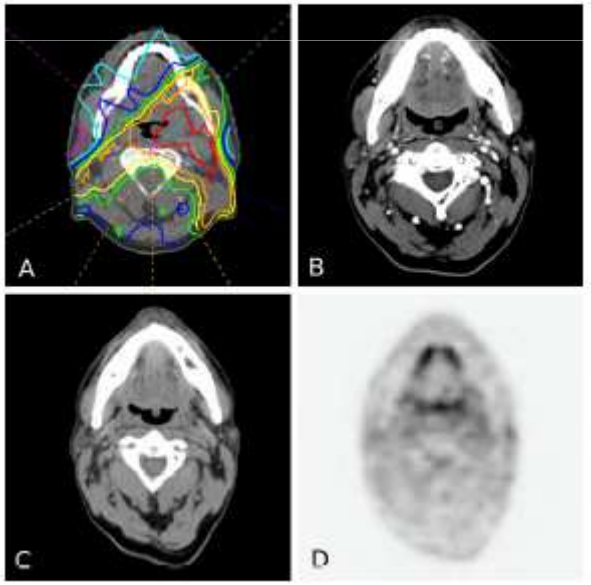
>95% in-field relapse

➢Parotid sparing with correct Patient selection does not seem to increase marginal misses

➢....is it?







„Our experience with the 2
NPC patients suggests that the presence of multilevel nodal disease and periparotid nodules on pretreatment imaging should raise the index of suspicion for subclinical disease, even if the nodules are not hypermetabolic on PET and do not meet radiographic or clinical criteria for possible gross disease. Additional evaluation such as FNA or CT-guided biopsy might be warranted in such situations before proceeding with definitive IMRT.“

Cannon, IJROBP, 2007

It usually is, but you gotta watch out!

Chen et al., IJROBP, 2011

90 Pts
11 In-Field Relapses
6 Marginal Misses

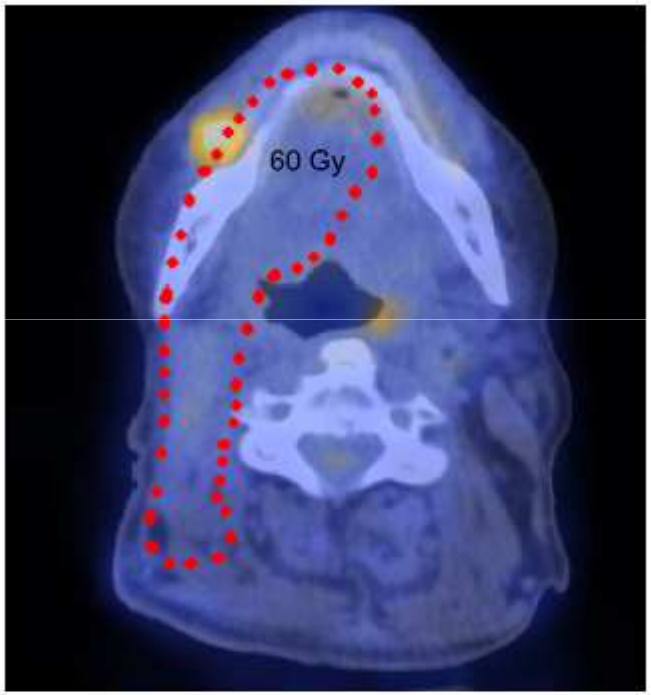


Fig. 4. Case illustration (marginal miss): This 69-year-old male underwent laser CO_2 excision for T1 squamous cell carcinoma of the right buccal mucosa and split-thickness skin grafting. Modified radical neck dissection on the ipsilateral side revealed six lymph nodes involved with malignancy at levels Ib and II with extracapsular extension. He subsequently completed postoperative IMRT with concurrent cisplatin chemotherapy. A dose of 60 Gy in 30 fractions was delivered to the primary tumor site and ipsilateral neck, with 54 Gy delivered to the contralateral left neck. Approximately, 9 months later, the patient presented with a subcutaneous nodule arising from the right anterior aspect of his mandible. PET/CT suggested LRR, which was confirmed by fine-needle aspiration biopsy.

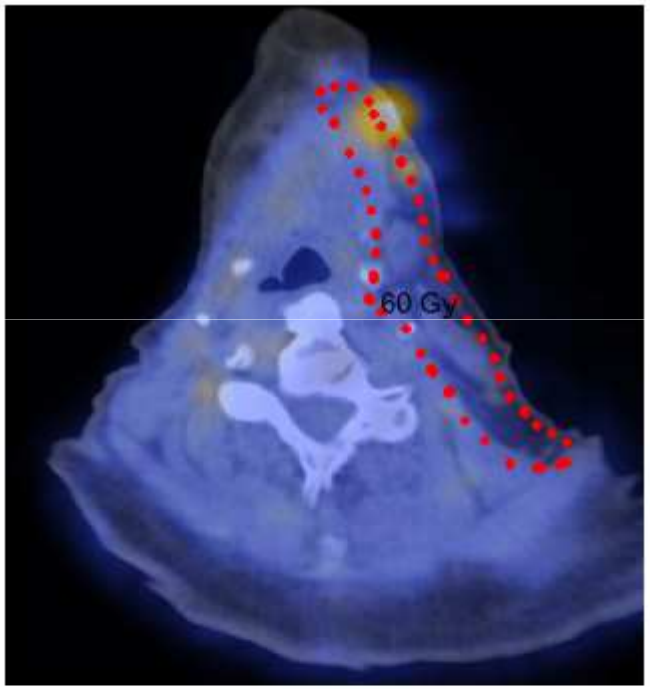


Fig. 5. Case illustration (marginal miss): This 70-year-old male underwent partial glossectomy for a 3.5-cm focus of squamous cell carcinoma involving the left oral tongue. Modified radical neck dissection on the ipsilateral side revealed 3 of 20 lymph nodes involved with disease at level Ib and II. There was no extracapsular extension. Postoperative radiation therapy was delivered to a dose of 60 Gy in 30 fractions to the primary site and ipsilateral cervical neck. The contralateral neck and supraclavicular fossae were treated to 54 Gy. Approximately 6 months after treatment, the patient presented with a suspicious erythematous lesion involving the left neck. PET/CT suggested LRR, which was confirmed by fine-needle aspiration biopsy.

It usually is, but you gotta watch out!

Chen et al., IJROBP, 2011

90 Pts
11 In-Field Relapses
6 Marginal Misses

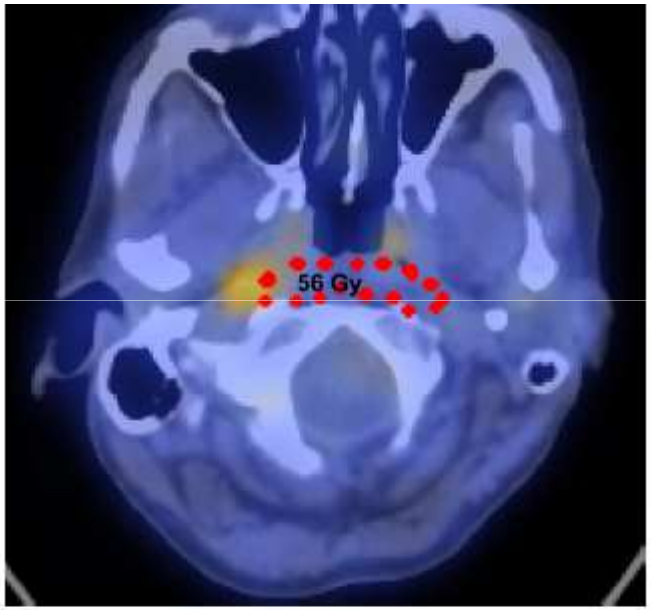


Fig. 2. Case illustration (marginal miss): This 70-year-old female underwent total laryngectomy and bilateral neck dissection for T4aN0 squamous cell carcinoma of the right pyriform sinus with extension through the thyroid cartilage. She subsequently completed postoperative IMRT at a dose of 63 Gy in 35 fractions to the primary surgical bed and 56 Gy (red outline) to the bilateral necks, including the retropharyngeal lymph nodes. A follow-up PET/CT scan performed approximately 12 months after completion of IMRT suggested regional recurrence in the retropharyngeal lymph nodes near the base of the skull. She also developed simultaneous lung metastasis. It should be noted that CTV delineation in this case was inadequate given that the consensus guidelines describe the lateral boundaries of the retropharyngeal nodal region as the medial edge of the internal carotid artery.

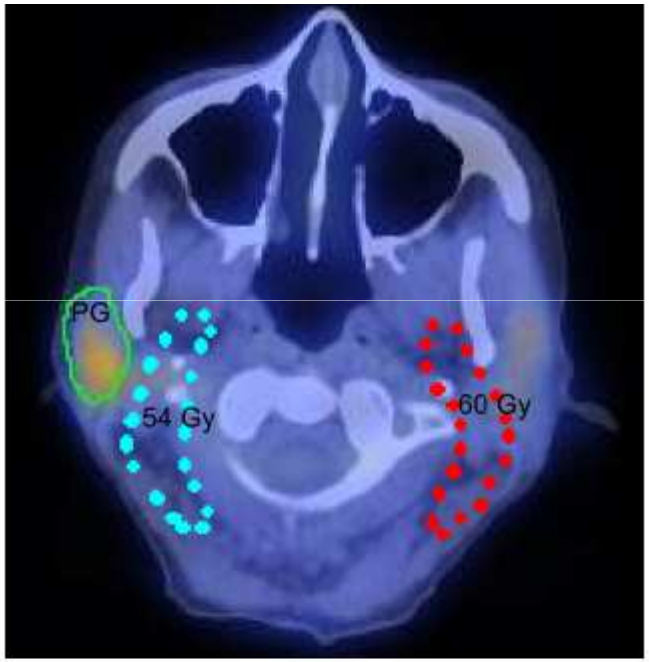
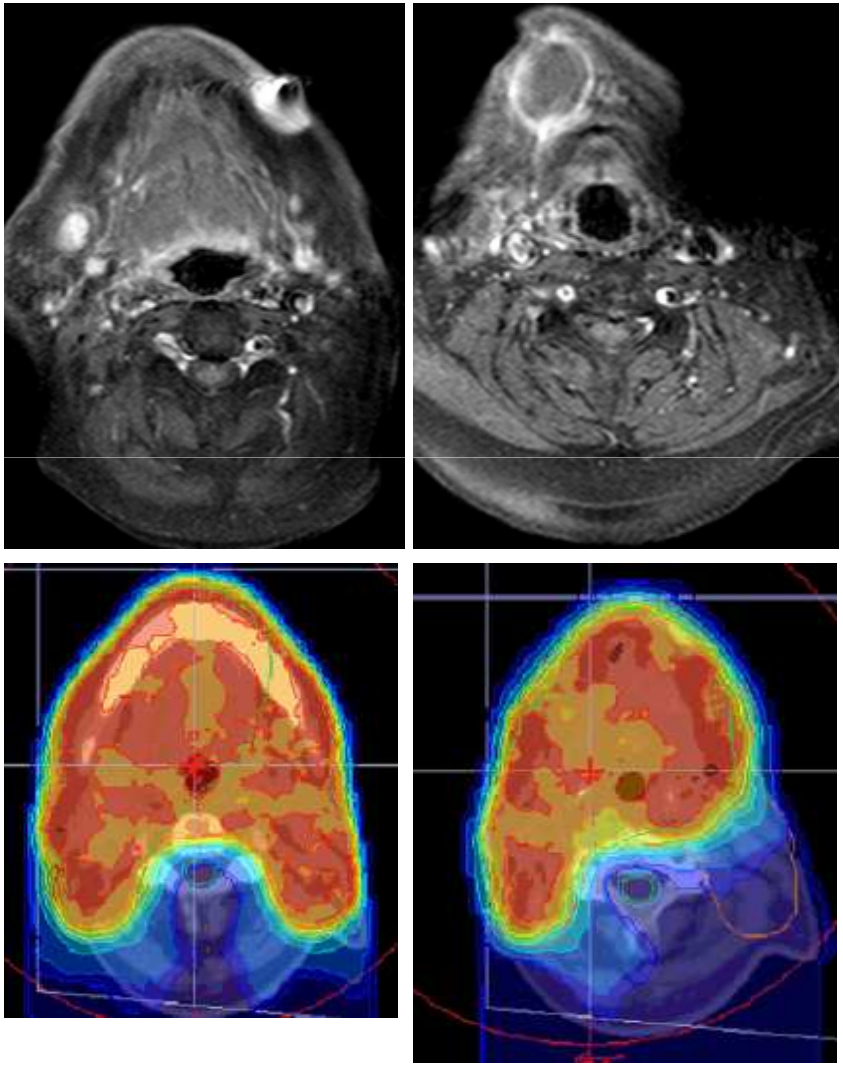


Fig. 3. Case illustration (marginal miss): This 67-year-old male underwent segmental mandibulectomy and open resection of a 3-cm squamous cell carcinoma of the left oral tongue. Modified radical neck dissection on the ipsilateral side revealed 4 of 15 lymph nodes involved at levels II and III. He subsequently completed postoperative IMRT with concurrent cisplatin chemotherapy. A dose of 60 Gy in 30 fractions (red outline) was delivered to the primary tumor site and ipsilateral neck. The contralateral right neck received a dose of 54 Gy (blue outline). Approximately 13 months later, the patient presented with fullness in the right parotid region. PET/CT scan suggested LRR near the region of the spared parotid gland (PG), which was confirmed by fine-needle aspiration biopsy.

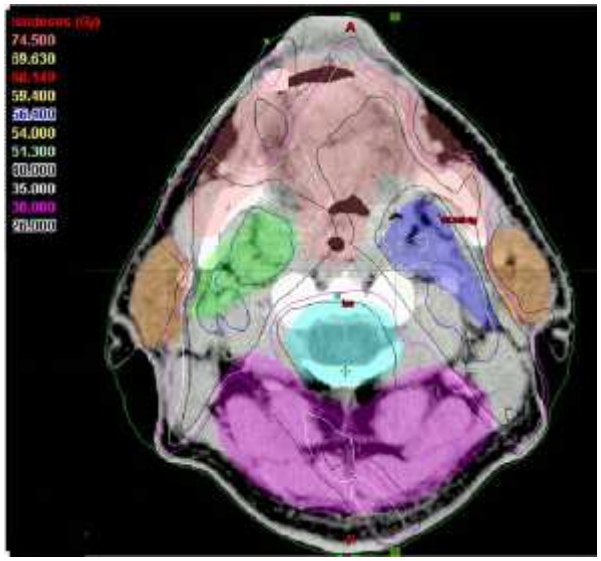
UMM example
– cancer of the lower lip

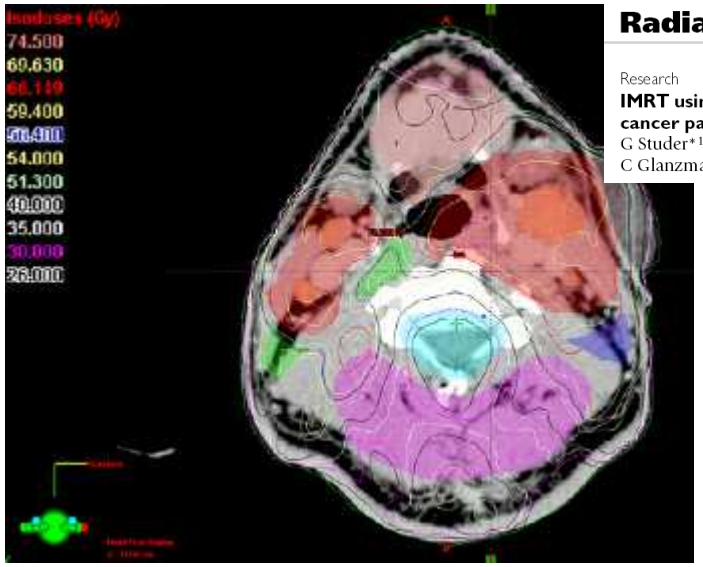


Relapse Pattern OCC - PMH

“Conclusions: Nearly a third (12/38) of LR recurrences were marginal or out-of-field following postoperative IMRT for OCSCC. Postoperative IMRT following gross total surgical resection requires careful and comprehensive target volume delineation, and larger volumes may be needed than the primary RT setting.”

Chan, R&O, 2013





Radiation Oncology

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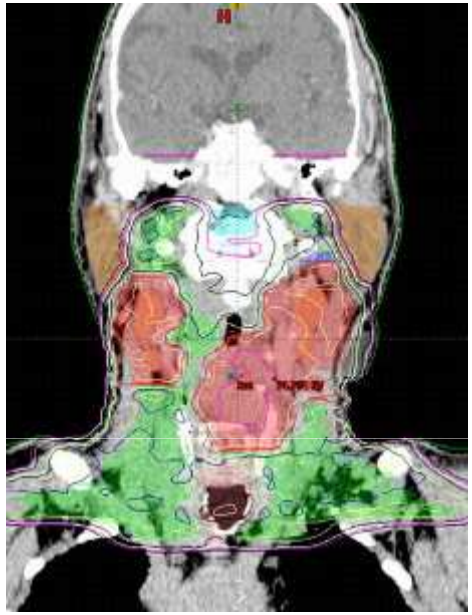
IMRT using simultaneously integrated boost (SIB) in head and neck cancer patients

G Studer*[1], PU Huguenin[1], JB Davis[2], G Kunz[2], UM Lütolf[1] and C Glanzmann[1]



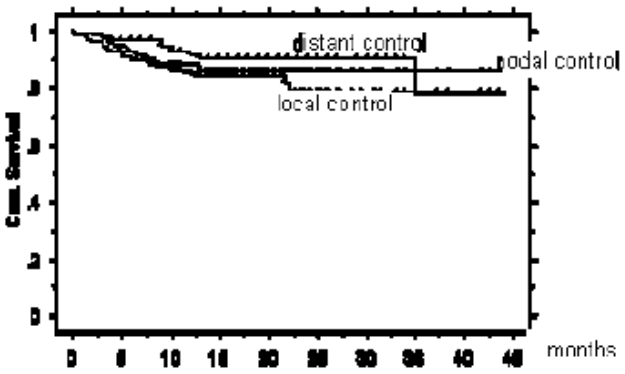


Figure 1
Actuarial 2 year local, nodal, and distant disease free survival: 77 %, 87 %, and 78 %, respectively

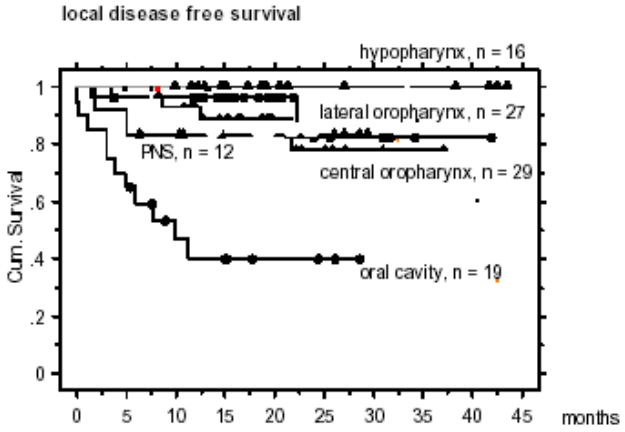


Figure 2
Actuarial 2 year local disease free survival in different HNC entities. Hypopharyngeal tumors revealed the highest local control rates, while oral cavity tumors showed the lowest rate. This fact can not be explained by TN stages or tumor volumes, and is issue of further data anaylses.

Table 3). 5 loco-regionally controlled patients suffered from distant failure.

6% Grade 3/4 late Tox

Kam, JCO, 2007

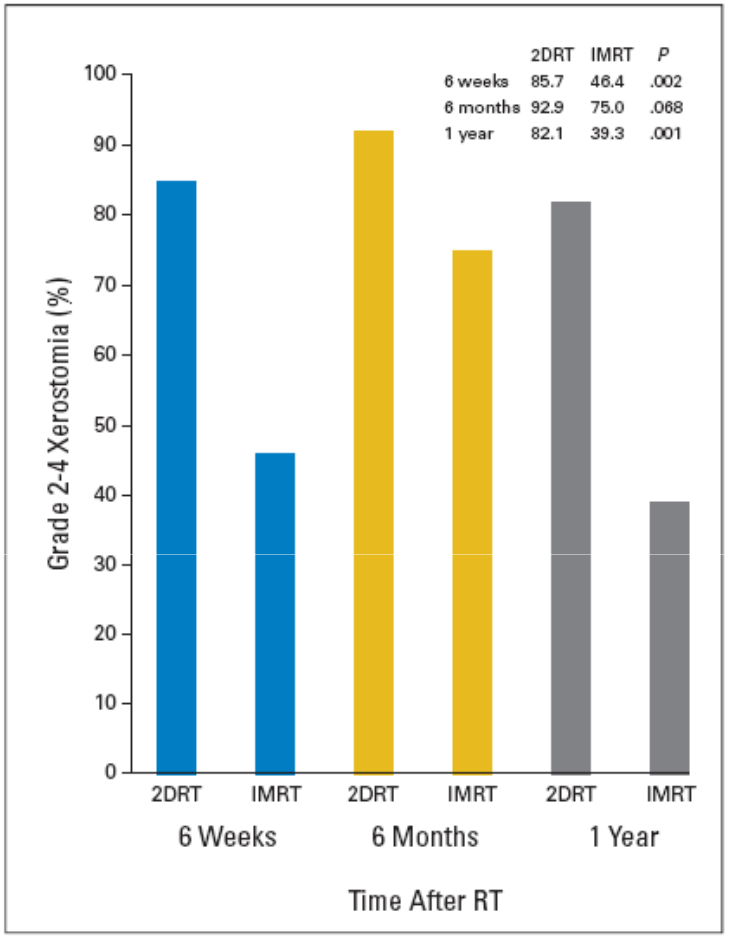


Fig 2. Histogram showing the incidence of Radiation Therapy Oncology Group (RTOG)/European Organisation for the Research and Treatment of Cancer (EORTC) grade 2 to 4 xerostomia in patients treated by two-dimensional radiation therapy (2DRT) and intensity-modulated radiation therapy (IMRT).

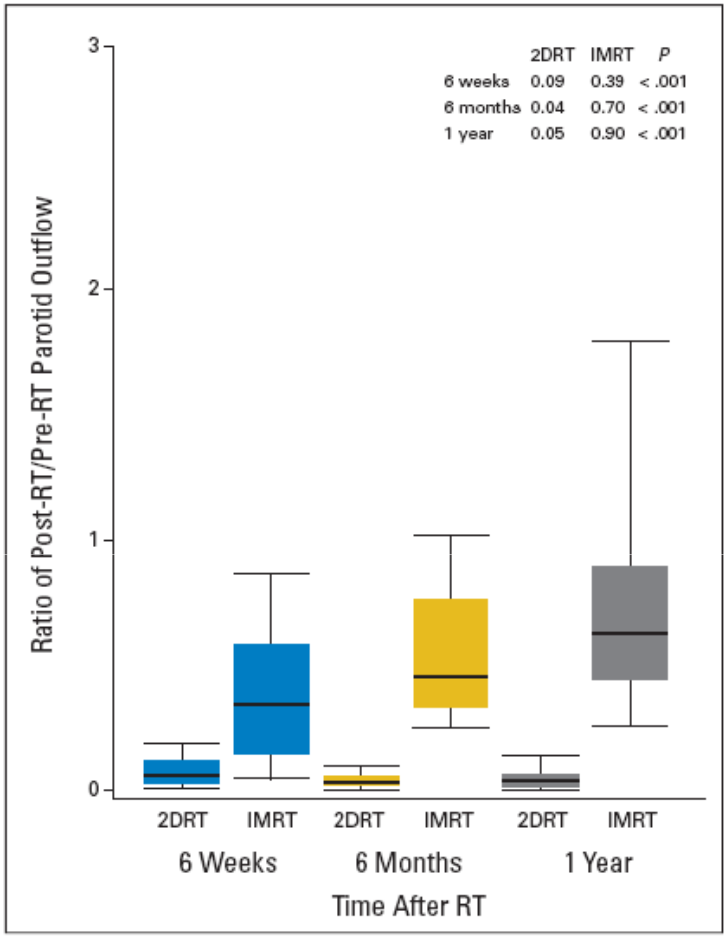


Fig 3. Changes in fractional stimulated parotid flow rate (SPFR) after two-dimensional radiation therapy (2DRT) and intensity-modulated radiation therapy (IMRT). Spread of data denoted by box whiskers plot: box limits represent 25 and 75 percentiles, line within box median, whisker ends 1 and 99 percentiles; comparison of means denoted in inserts.

Good functional parotid sparing with IMRT.....

.....but no subjective gain. Really?

Kam, JCO, 2007

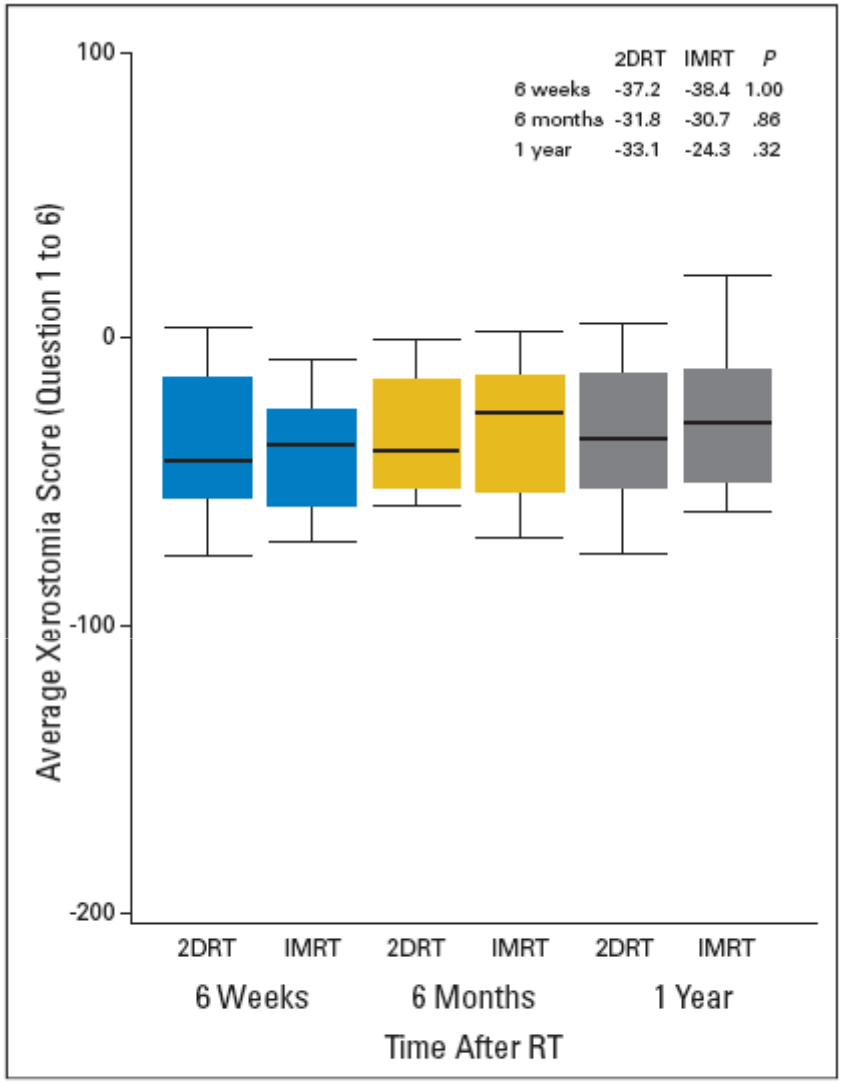


Fig 5. Average scores of the six-item xerostomia questionnaire in two-dimensional radiation therapy (2DRT) and intensity-modulated radiation therapy (IMRT) arms at various time point post-treatment. Positive score indicates improvement and negative score indicates deterioration. Spread of data denoted by box whiskers plot: box limits represent 25 and 75 percentiles, line within box median, whisker ends 1 and 99 percentiles; comparison of means denoted in inserts.

Intensity-Modulated Radiation Therapy in Head and Neck Cancers

Dosimetric Advantages and Update of Clinical Results

Dev R. Puri, MD, William Chou, MD, and Nancy Lee, MD

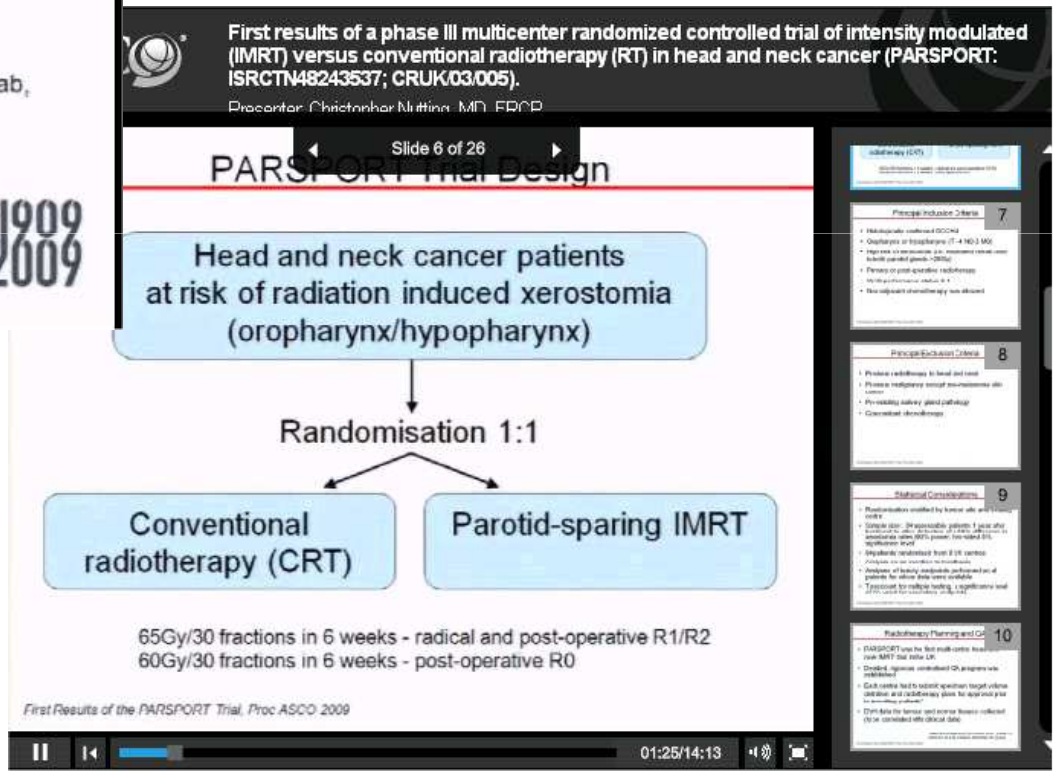
American Journal of Clinical Oncology • Volume 28, Number 4, August 2005

TABLE 2. Results From Series Treating NPC With IMRT +/– Chemotherapy

Study	n	Characteristics	Median Follow-up, mo	Time Point, y	Local Control, %	Regional Control, %	Distant Metastasis-free Rate, %	Overall Survival, %	Comments
Lee et al[6] (United States)	67	All stages	31	4	97	98	66	73	Most stage III/IV and received chemotherapy; GTV received 65–70 Gy; brachytherapy boost given
Kwong et al[14] (Hong Kong)	33	T1N0-N1, M0	24	3	100	92	100	100	Dose to GTV was 68–70 Gy; continuous recovery of salivary flow observed in the first 2 y after IMRT
Kam et al[15] (Hong Kong)	64	All stages	29	3	92	98	79	90	Dose escalation above 66 Gy was a significant determinant of progression-free survival and distant-metastasis free survival for advanced T-stage tumors

NPC, nasopharyngeal cancer; IMRT, intensity-modulated radiation therapy.


First results of a phase III multicenter randomized controlled trial
(IMRT) versus conventional radiotherapy (RT) in head and neck
ISRCTN48243537; CRUK/03/005).
Slide 1 of 26
PARSPORT
First Results of a Phase III Multi-Centre Randomised Controlled Trial of Intensity Modulated vs Conventional Radiotherapy in Head and Neck Cancer: PARSPORT (CRUK/03/005)
C. Nutting, R. A'Hern, M. S. Rogers, M. A. Sydenham, F. Adab, K. Harrington, S. Jefferies, C. Scrase, B. K. Yap, E. Hall, on behalf of the PARSPORT Trial Management Group
CANCER RESEARCH UK
ICR
The institute
1909
2009


First results of a phase III multicenter randomized controlled trial of intensity modulated (IMRT) versus conventional radiotherapy (RT) in head and neck cancer (PARSPORT: ISRCTN48243537; CRUK/03/005).
Slide 6 of 26
PARSPORT Trial Design
Head and neck cancer patients at risk of radiation induced xerostomia (oropharynx/hypopharynx)
Randomisation 1:1
Conventional radiotherapy (CRT)
Parotid-sparing IMRT
65Gy/30 fractions in 6 weeks - radical and post-operative R1/R2
60Gy/30 fractions in 6 weeks - post-operative R0
First Results of the PARSPORT Trial, Proc ASCO 2009
01:25/14:13

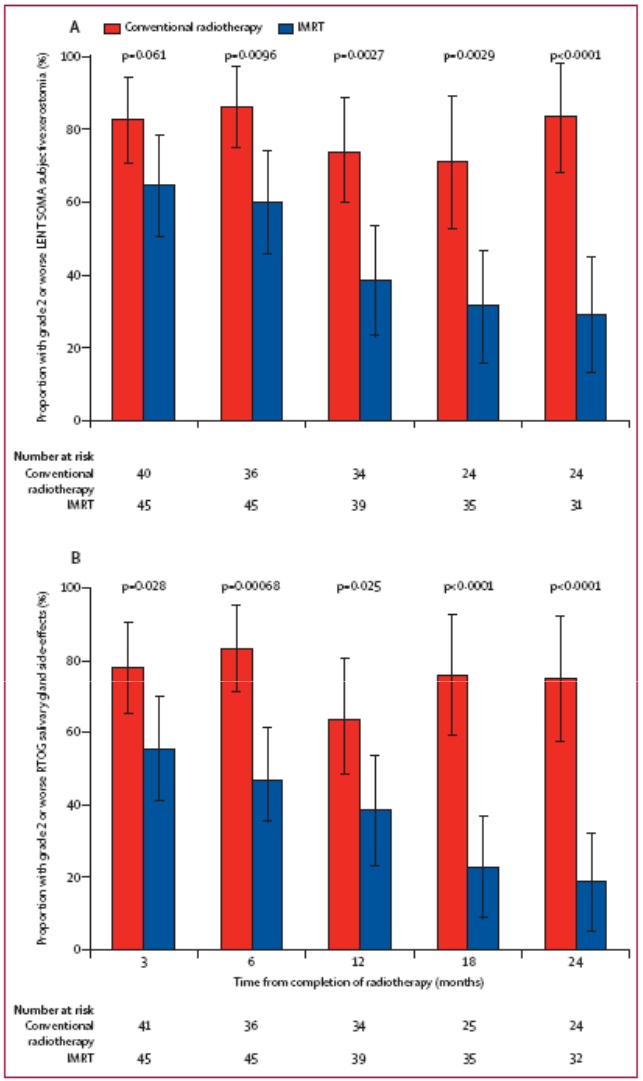


Figure 2: **Proportion of patients reporting grade 2 or worse LENT SOMA subjective xerostomia and RTOG salivary gland side-effects**
p values quoted compare proportions with grade 2 or worse side-effects in each group with a χ^2 test. Error bars represent 95% CIs. IMRT=Intensity-modulated radiotherapy. LENT SOMA=Late Effects of Normal Tissues Subjective-Objective Management Analytic. RTOG=Radiation Therapy Oncology Group.

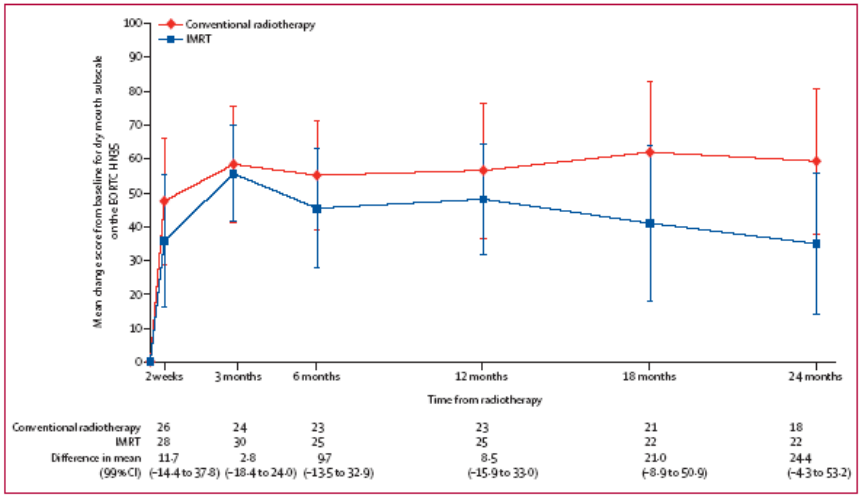


Figure 3: **Mean EORTC HN35 dry mouth subscale score changes from baseline**
IMRT=Intensity-modulated radiotherapy. EORTC HN35=European Organization for Research and Treatment of Cancer head and neck specific module HN35.

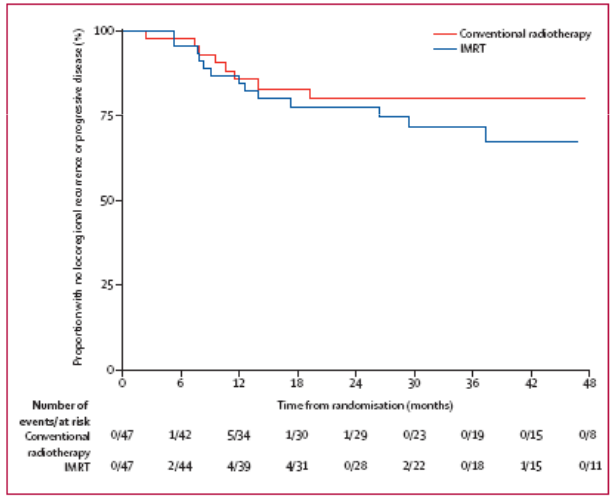


Figure 4: **Kaplan-Meier plot of locoregional progression-free survival by treatment group**
Hazard ratio 1·53 (95% CI 0·63 to 3·70). Log-rank test p=0·34. 2-year locoregional progression-free survival estimates for conventional radiotherapy 80% (95% CI 65 to 90) and for IMRT 78% (62 to 87); absolute difference 3% (−15 to 20). IMRT=Intensity-modulated radiotherapy.

„Unexpectedly, acute fatigue was greater in patients treated with IMRT, which could be due to the greater radiation dose to non-tumour tissues. In an unplanned dosimetry review in a subset of patients, mean radiation doses to the posterior fossa were 20–30 Gy in the patients treated with IMRT compared with about 6 Gy in patients treated with conventional RT“

Nutting et al., Lancet Oncol, 2011

Parsport – Parotid Dose Response Relationship

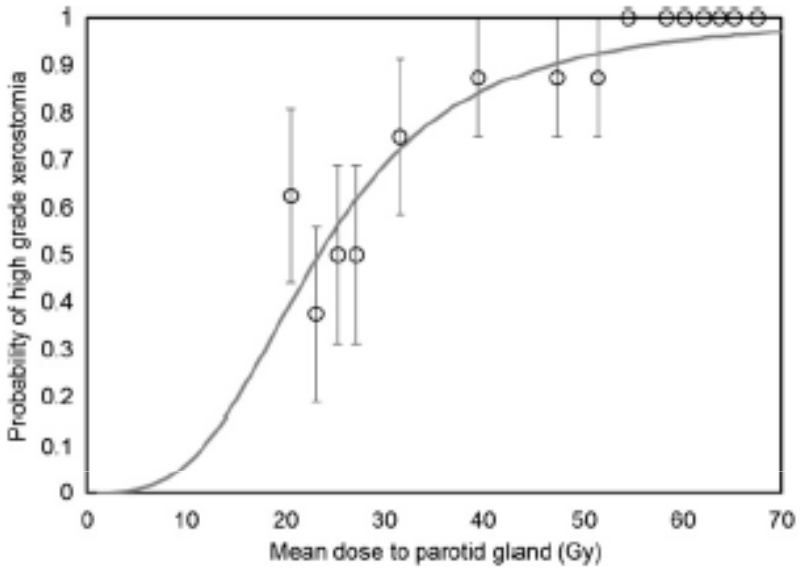


Fig. 3. Dose–response curve for probability of developing high grade xerostomia (no recovery of parotid saliva flow) at 12 months, error bars represent one standard error of mean. $D50 = 23.4$ (95% CI: 20.6–26.2) and $k = 3.2$ (95% CI: 1.9–4.5), line of best fit, $R^2 = 0.85$.

Miah et al., R&O, 2013 (I)

No differenceds +/- Cht

Miah et al., R&O, 2013 (II)

GORTEC 2004-3

Toledano et al., R&O, 2012

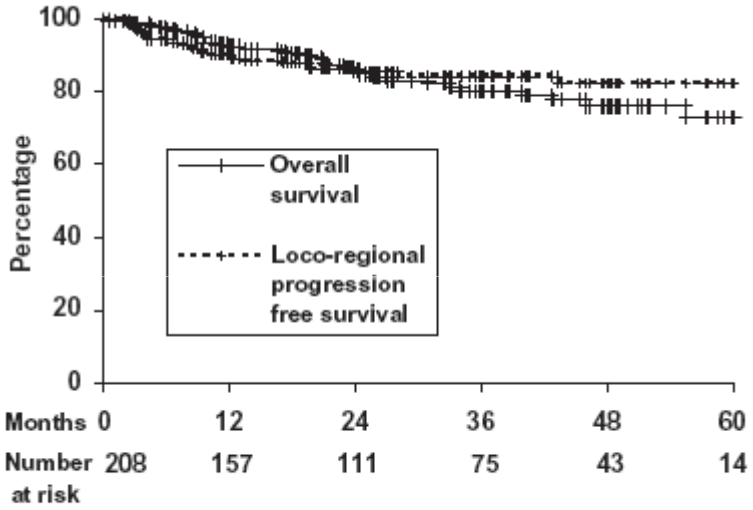


Fig. 1. Overall survival and loco-regional progression free survival (Kaplan–Meier method) of the population (208 patients).

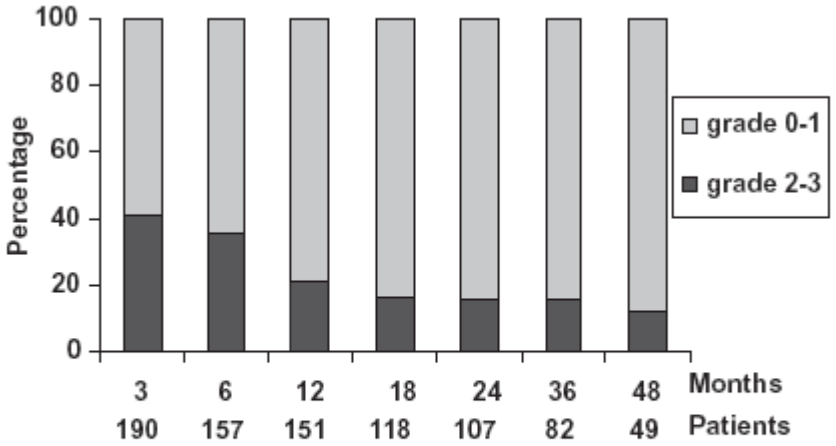


Fig. 3. Xerostomia evolution over the time (RTOG/EORTC classification).

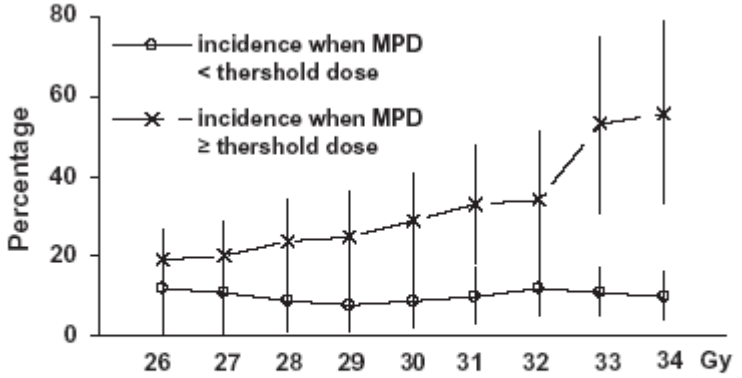


Fig. 4. Grade ⩾2 xerostomia incidence according to the spared-parotid mean dose at 18 months (CI 95%). MPD: mean parotid dose, +3%/Gy of xerostomia grade ⩾2 range 26–32 Gy, +7%/Gy of xerostomia grade ⩾2 above 33 Gy.

Tata Memorial Randomized Trial

Rathod et al.,
Oral Oncol, 2013

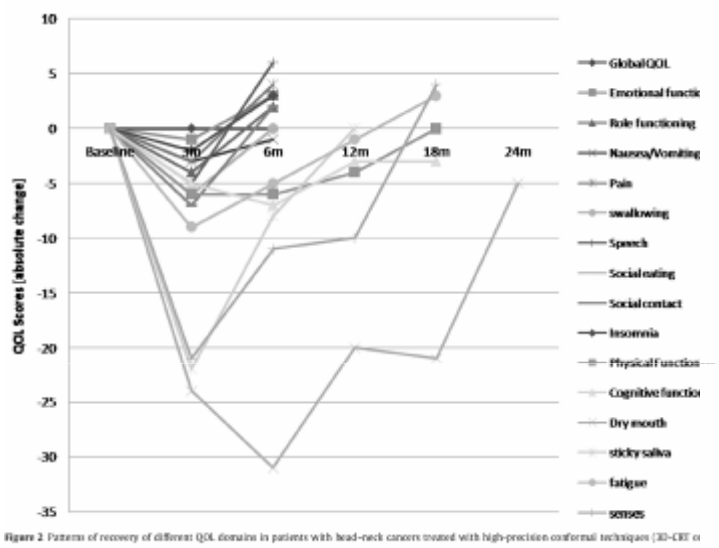


Figure 2 Patterns of recovery of different QOL domains in patients with head-neck cancers treated with high-precision conformal techniques (3D-CRT o

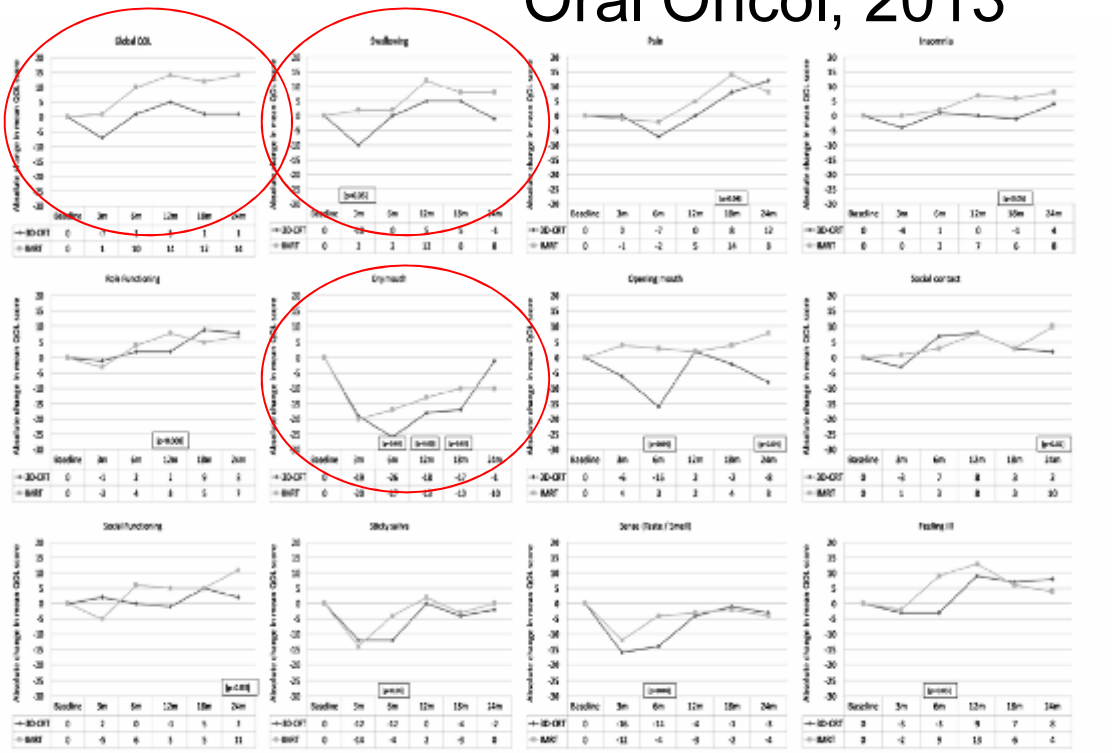


Figure 1 Comparison of absolute change in mean scores for several QOL domains and symptom subscales between 3D-CRT and IMRT at different time points. Statistically significant p-values are presented at appropriate time points.

"Fiftyeight of 60 (96.7%) randomized patients filled at least one QOL questionnaire, while 22 (36.7%) filled the questionnaires at all the six time-points as per protocol"

Tata Memorial Randomized Trial

Rathod et al.,
Oral Oncol, 2013

Caveat:

At a median followup of 40 months (inter-quartile range 26-50 months):

The 3-year estimates of loco-regional control with 95% confidence intervals (95%CI) were
88.2%** (75.4–100%) for **3D-CRT
80.5%** (66.1–94.9%) for **IMRT
(p = 0.45).

And if you want everything in one publication…

go for the Metaanalysis

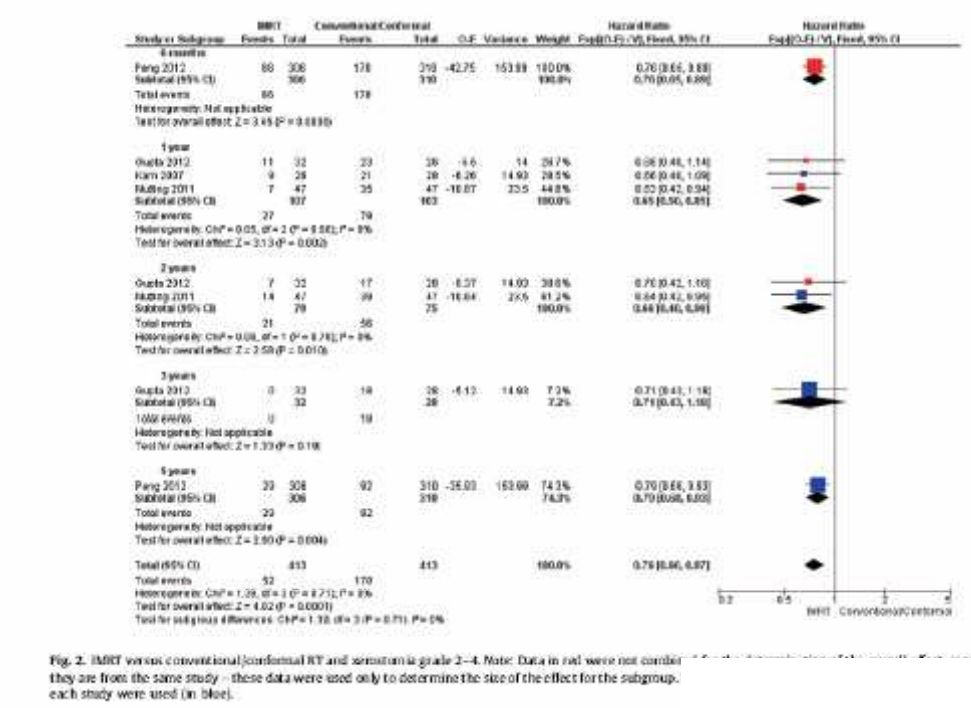


Fig. 2. IMRT versus conventional/conformal RT and xerostomia grade 2–4. Note: Data in red were not combi… they are from the same study – these data were used only to determine the size of the effect for the subgroup. each study were used (in blue).

Marta et al., Radiother Oncol, 2013

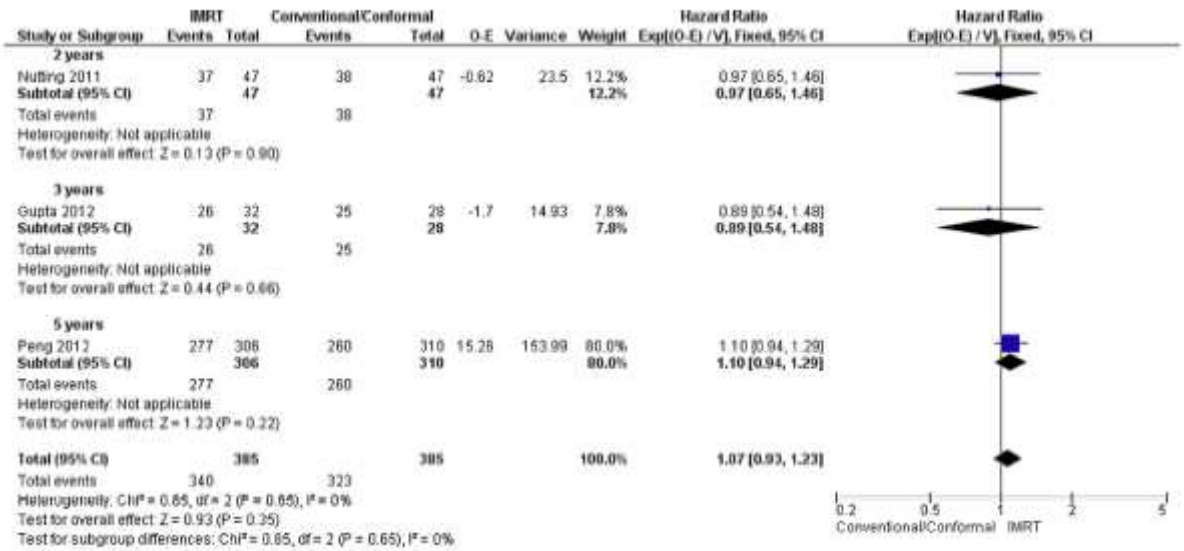


Fig. 3. Conventional/conformal RT versus IMRT and loco-regional control.

So IMRT is evil….is it? The SEER-Database suggests…

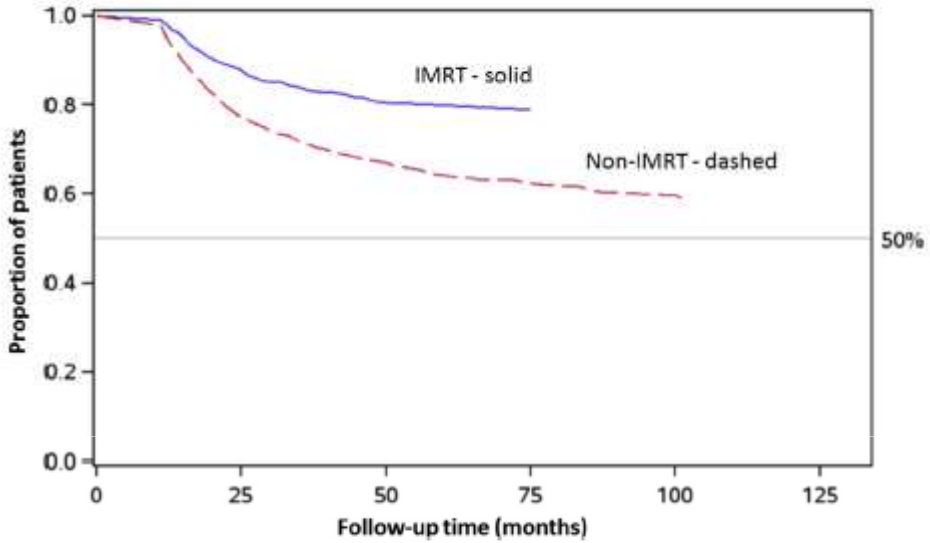
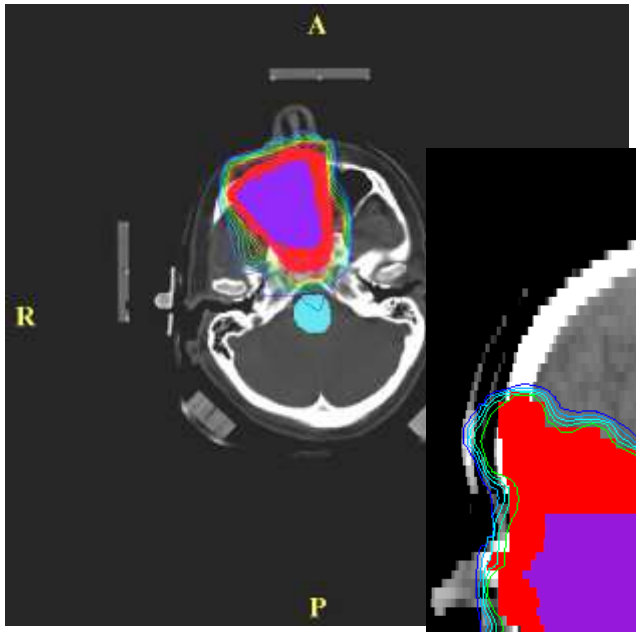
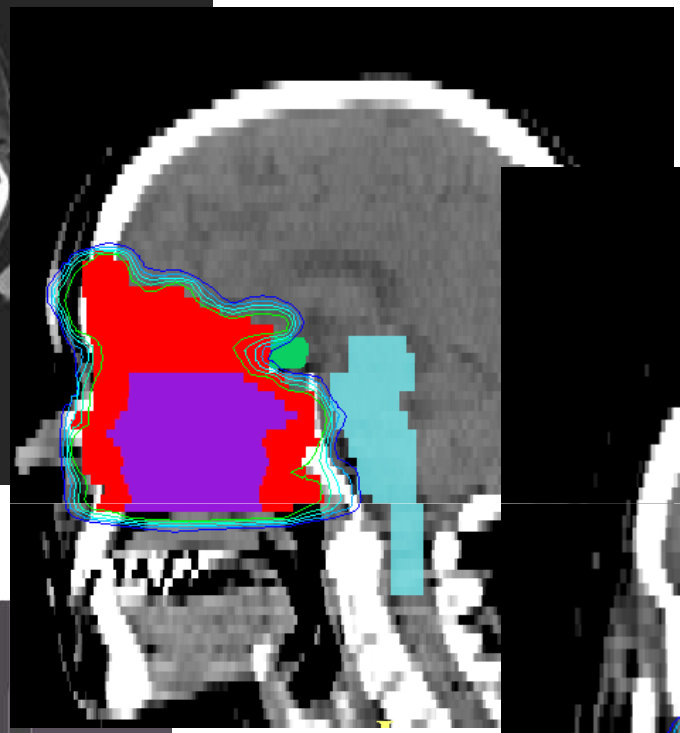


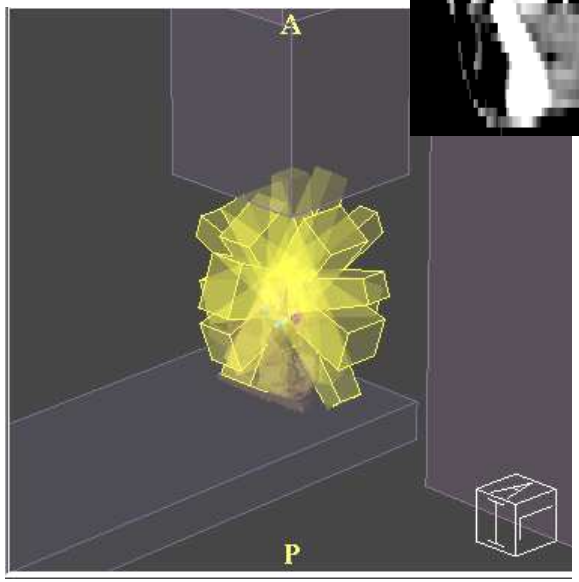
Figure 1. Impact of intensity-modulated radiation therapy (IMRT) on cause-specific survival. Kaplan-Meier curve depicting the cause-specific survival with time for patients treated with IMRT (dashed) compared to those treated with non-IMRT (solid).

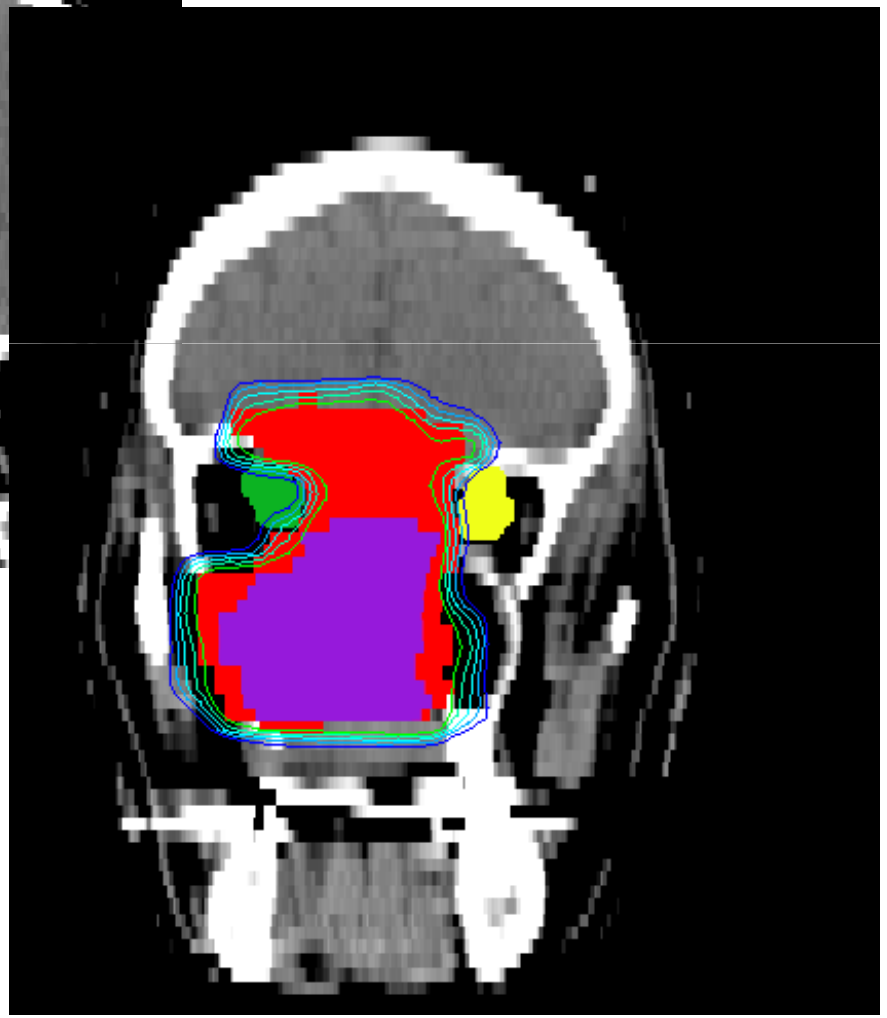
Beadle et al., Cancer, 2014

Paranasal Sinus Integrated Boost

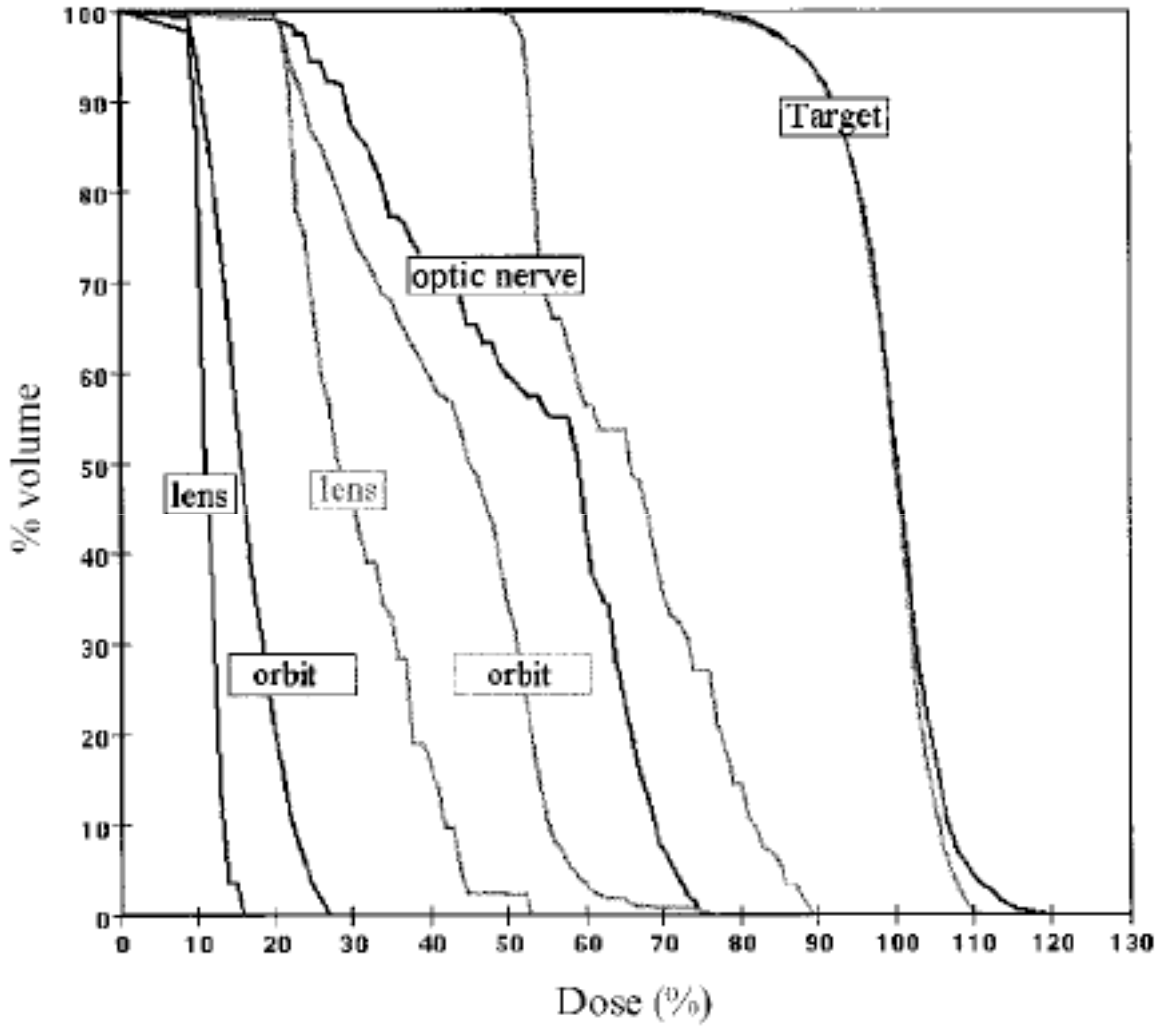




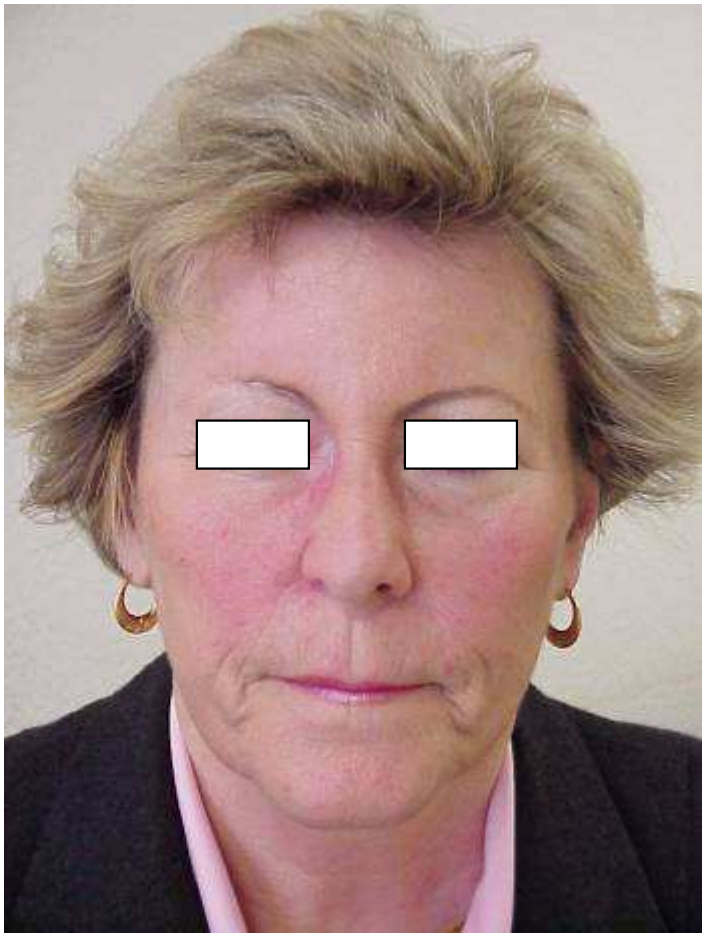




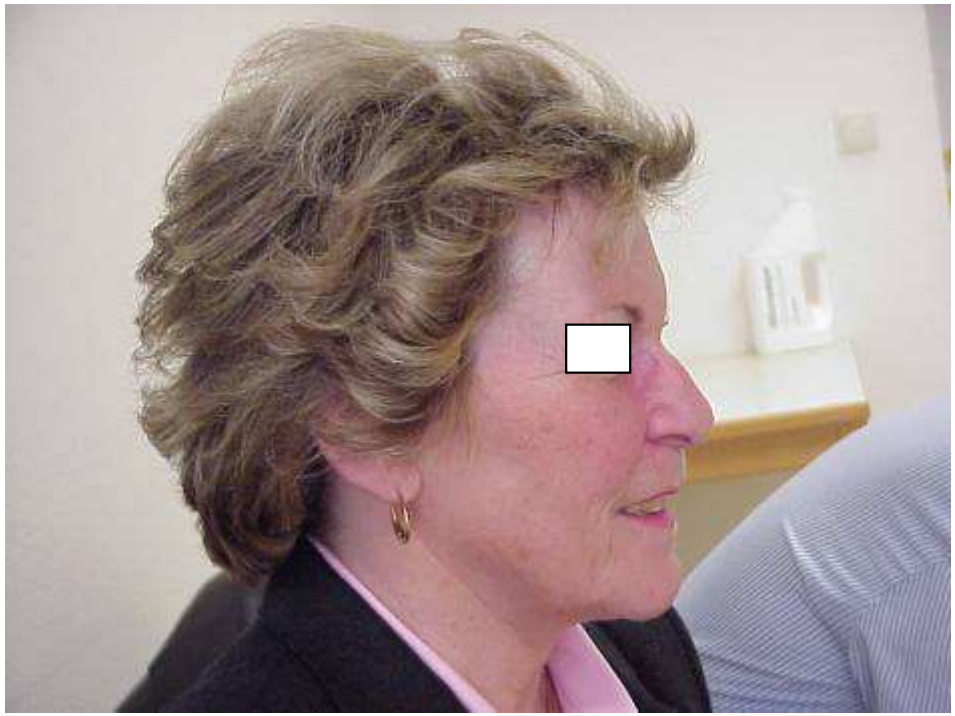
Paranasal Sinus



Zabel et al.,
BJR, 2002



Status 1 Year post RT



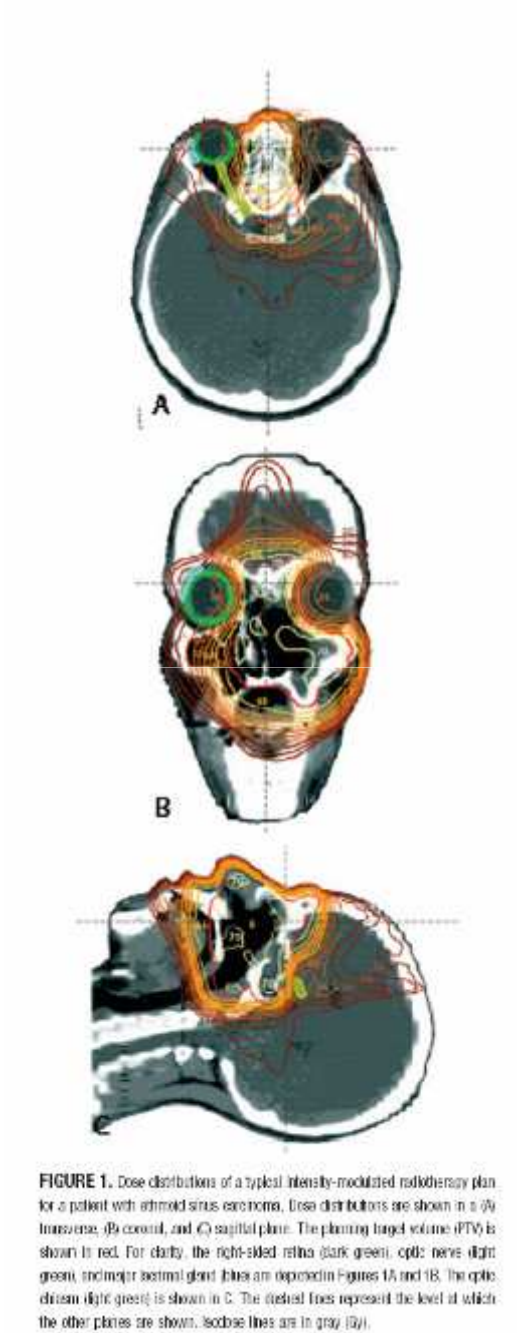


FIGURE 1. Dose distributions of a typical intensity-modulated radiotherapy plan for a patient with ethmoid sinus carcinoma. Dose distributions are shown in a (A) transverse, (B) coronal, and (C) sagittal plane. The planning target volume (PTV) is shown in red. For clarity, the right-sided retina (dark green), optic nerve (light green), and major lacrimal gland (blue) are depicted in Figures 1A and 1B. The optic chiasm (light green) is shown in C. The dashed lines represent the level at which the other planes are shown. Isodose lines are in gray (Gy).

Postoperative Intensity-Modulated Radiotherapy in Sinonasal Carcinoma

Clinical Results in 39 Patients

Wim Duthoy, M.D.[1]
Tom Boterberg, M.D., Ph.D.[1]
Filip Claus, M.D., Ph.D.[1]
Piet Ost[1]
Luc Vakaet, M.D., Ph.D.[1]
Samuel Bral, M.D.[1]
Frederic Duprez, M.D.[1]
Marianne Van Landuyt, M.D.[1]
Hubert Vermeersch, M.D., Ph.D.[2]
Wilfried De Neve, M.D., Ph.D.[1]

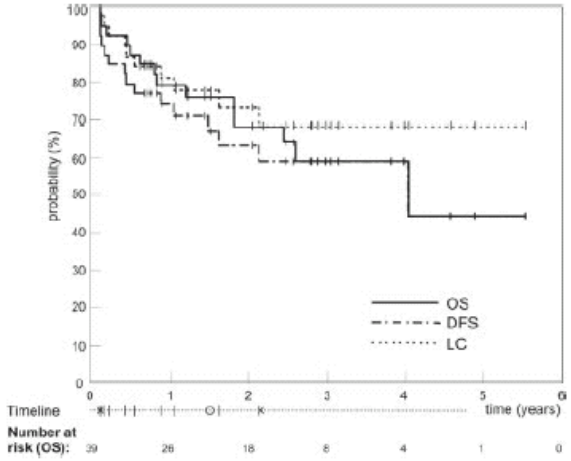


FIGURE 3. Overall survival (OS), disease-free survival (DFS), and local control (LC) for all patients. A timeline is shown, indicating the time of local (I), regional (°) and distant (x) disease recurrence.

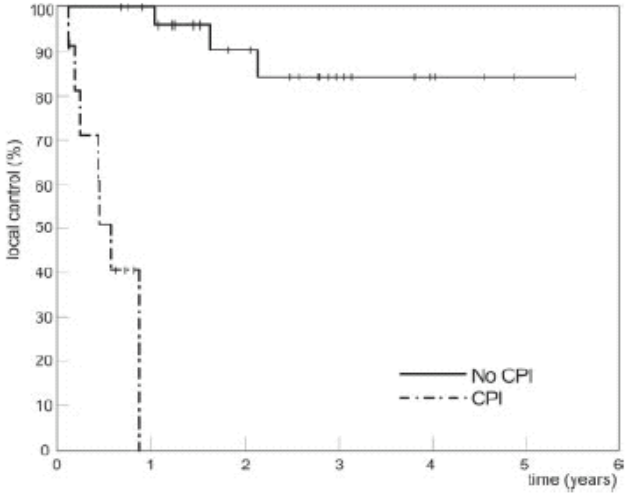


FIGURE 5. Local control in function of the presence of invasion through the cribriform plate (CP).

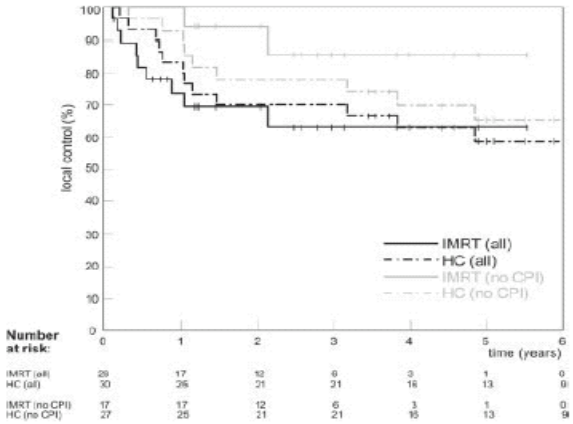


FIGURE 6. Local control for patients treated with IMRT (solid lines) and for patients in the historical cohort (dashed lines). The black lines represent the data for all patients, whereas the gray lines represent the group of patients without invasion of the cribriform plate ("no CPI").

No
Dry Eye
Syndrom

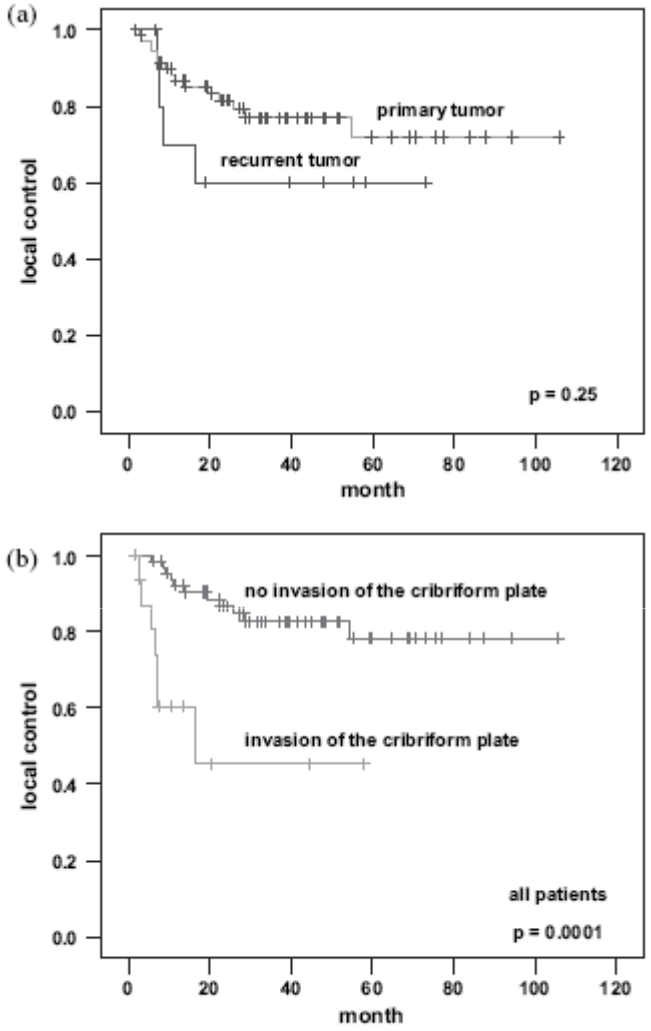


Fig. 1. (a) Local control for patients with primary and recurrent tumors and (b) with and without invasion of the cribriform plate in all patients.

INTENSITY-MODULATED RADIOTHERAPY FOR SINONASAL TUMORS: GHENT UNIVERSITY HOSPITAL UPDATE

INDIRA MADANI, M.D.,* KATRIEN BONTE, M.D.,† LUC VAKAET, M.D., PH.D.,* TOM BOTERBERG, M.D., PH.D.,* AND WILFRIED DE NEVE, M.D., PH.D.*

*Department of Radiotherapy and †Division of Head and Neck Surgery, Ghent University Hospital, Ghent, Belgium

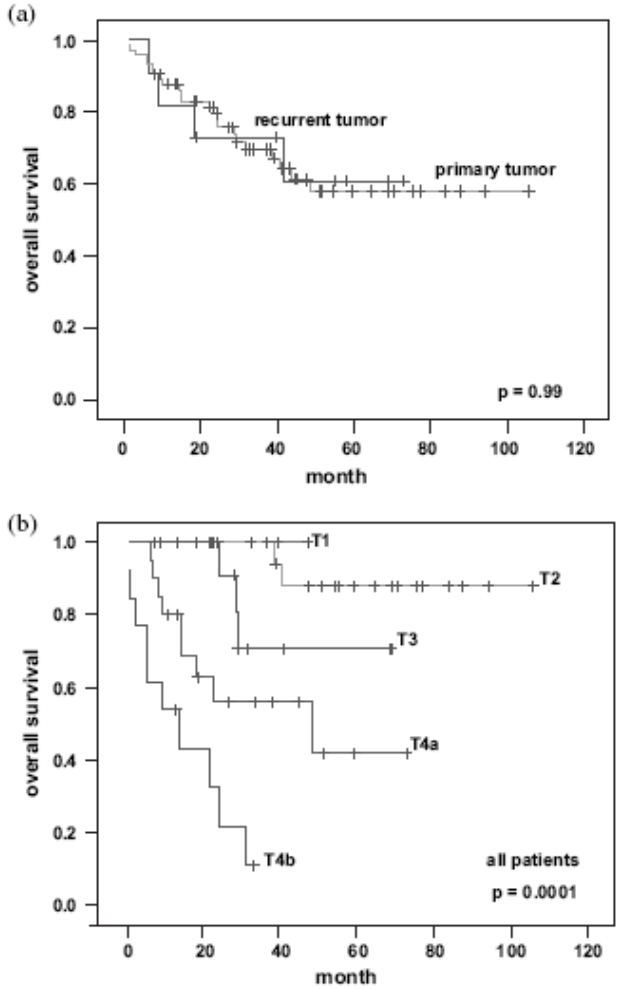


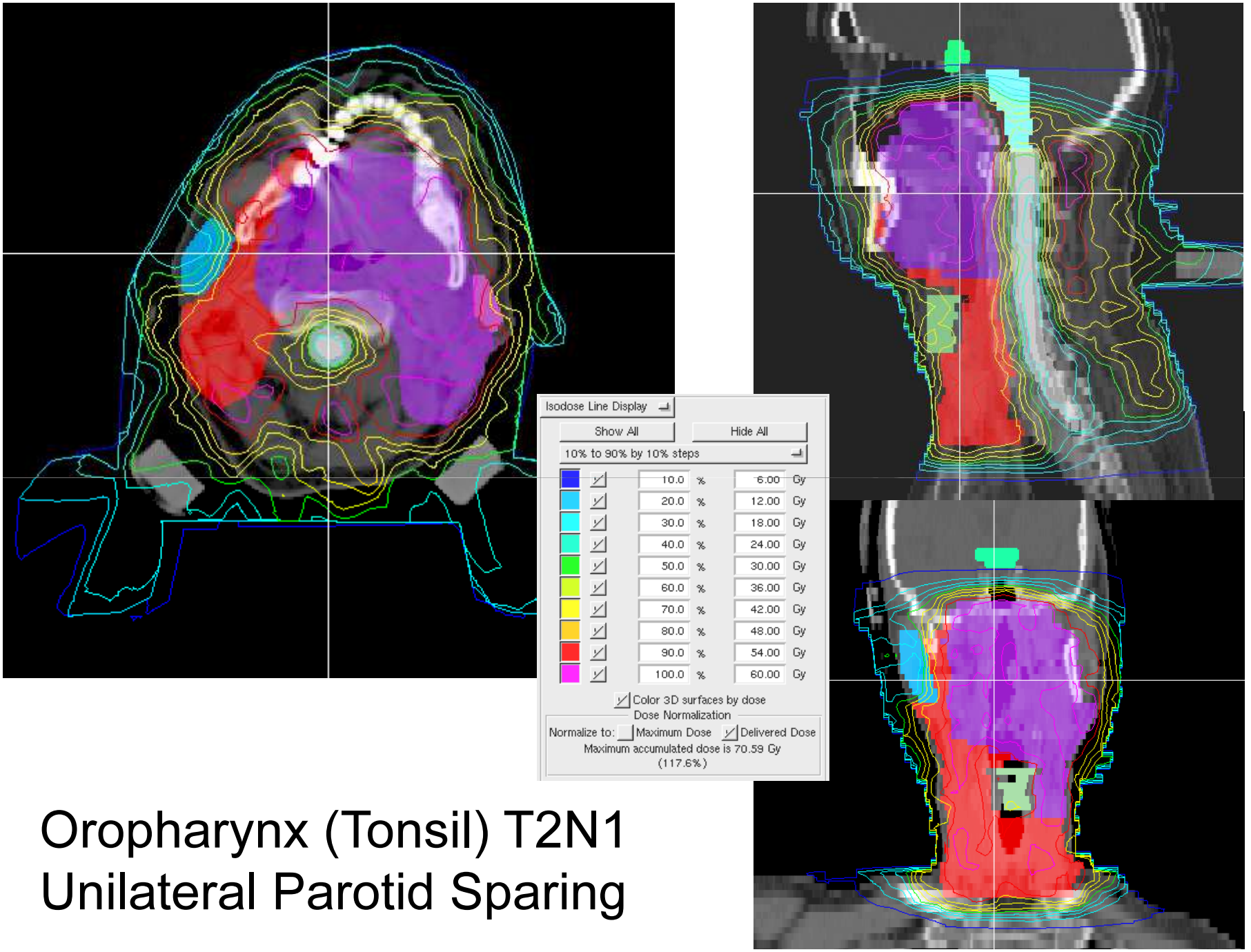
Fig. 2. (a) Overall survival for patients with primary and recurrent tumors, and (b) overall survival by T stage for all patients, except for those with esthesioneuroblastoma.

Table 8. Summary of studies reporting treatment outcome and late severe (grade 3) visual impairment after IMRT for sinonasal tumors

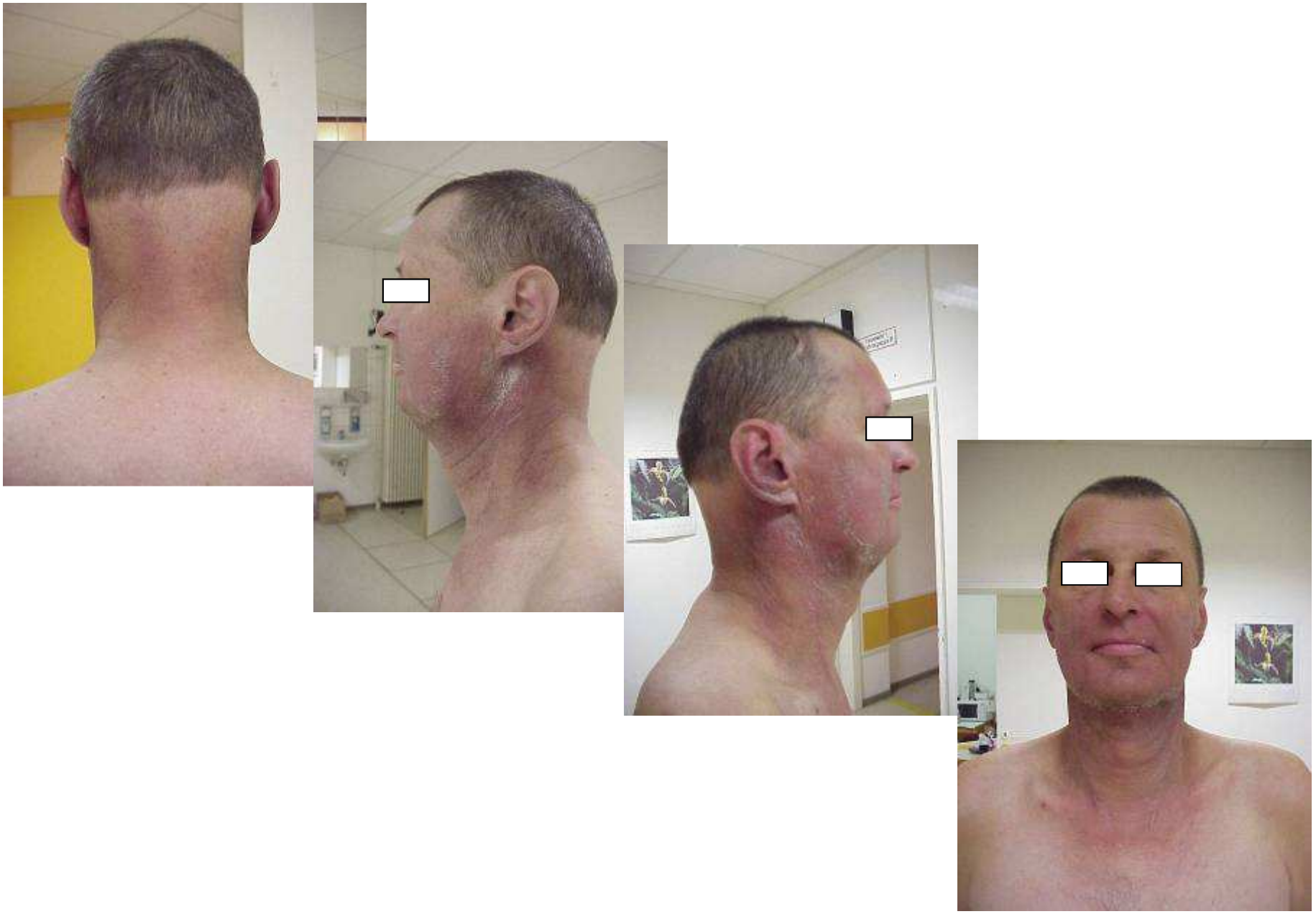
Investigator	Patients (*n*)	Histologic type*	Treatment	Median Dose (Gy)	Follow-up (mo)	Local control rate (y)	Overall survival rate (y)	Grade 3 visual impairment (*n*)
Claus *et al.* (8)	32	ADC (53)	S+IMRT or IMRT	70	15	NR	80% (1)	0
Duthoy *et al.* (9)	39	ADC (79)	S+IMRT	70	31	73% (2)	68% (2)	2
						68% (4)	59% (4)	
Combs *et al.* (22)	46	ACC (43.4)	S+IMRT or IMRT	64	16	85% (1)	96% (1)	0
						81% (2)	90% (3)	
Hoppe *et al.* (21)†	30		S+IMRT	60	23	NR	NR	0
Daly *et al.* (20)	36	SCC (33)	S+IMRT or IMRT	70	39	62% (2)	69% (2)	0
						58% (5)	45% (5)	
Chen *et al.* (19)‡	23		S+IMRT or IMRT	70	44	65% (5)	47% (5)	0
Dirix *et al.* (23)	25	ADC (68)	S+IMRT	60	27	81% (2)	88% (2)	0
Present study	84	ADC (64)	S+IMRT or IMRT	70	40	74.9% (3)	70.2% (3)	1
						70.7% (5)	58.5% (5)	

Abbreviations: S = surgery; IMRT = intensity-modulated radiotherapy; NR = not reported; other abbreviations as in Table 2.
* Most frequent histologic type in patient cohort and its proportion in parentheses.
† Reported treatment outcome in 85 patients treated with three-dimensional conformal RT and IMRT.
‡ Reported treatment outcome in 127 patients treated with conventional, three-dimensional RT and IMRT.

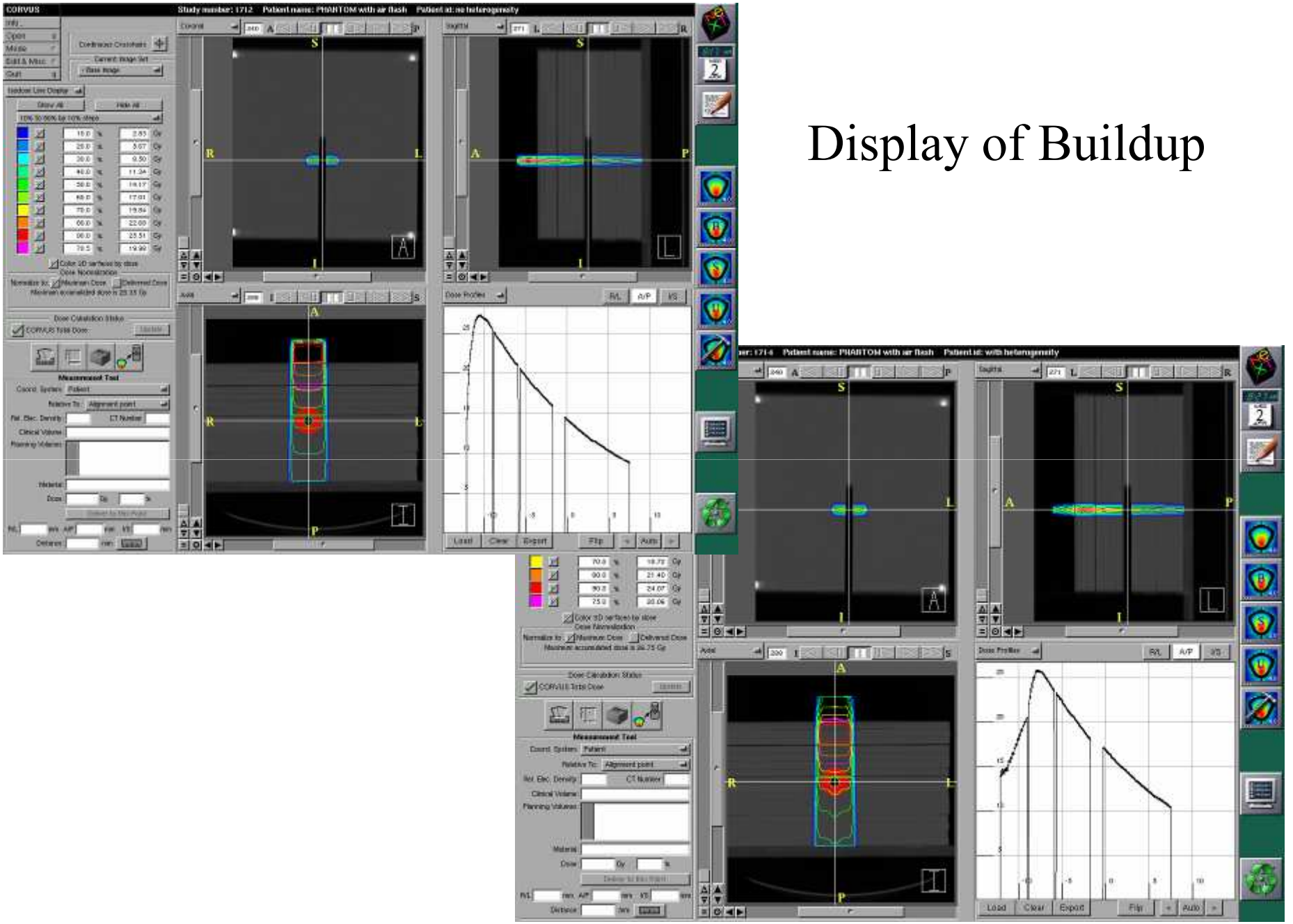
No Grade 3 Dryness !!

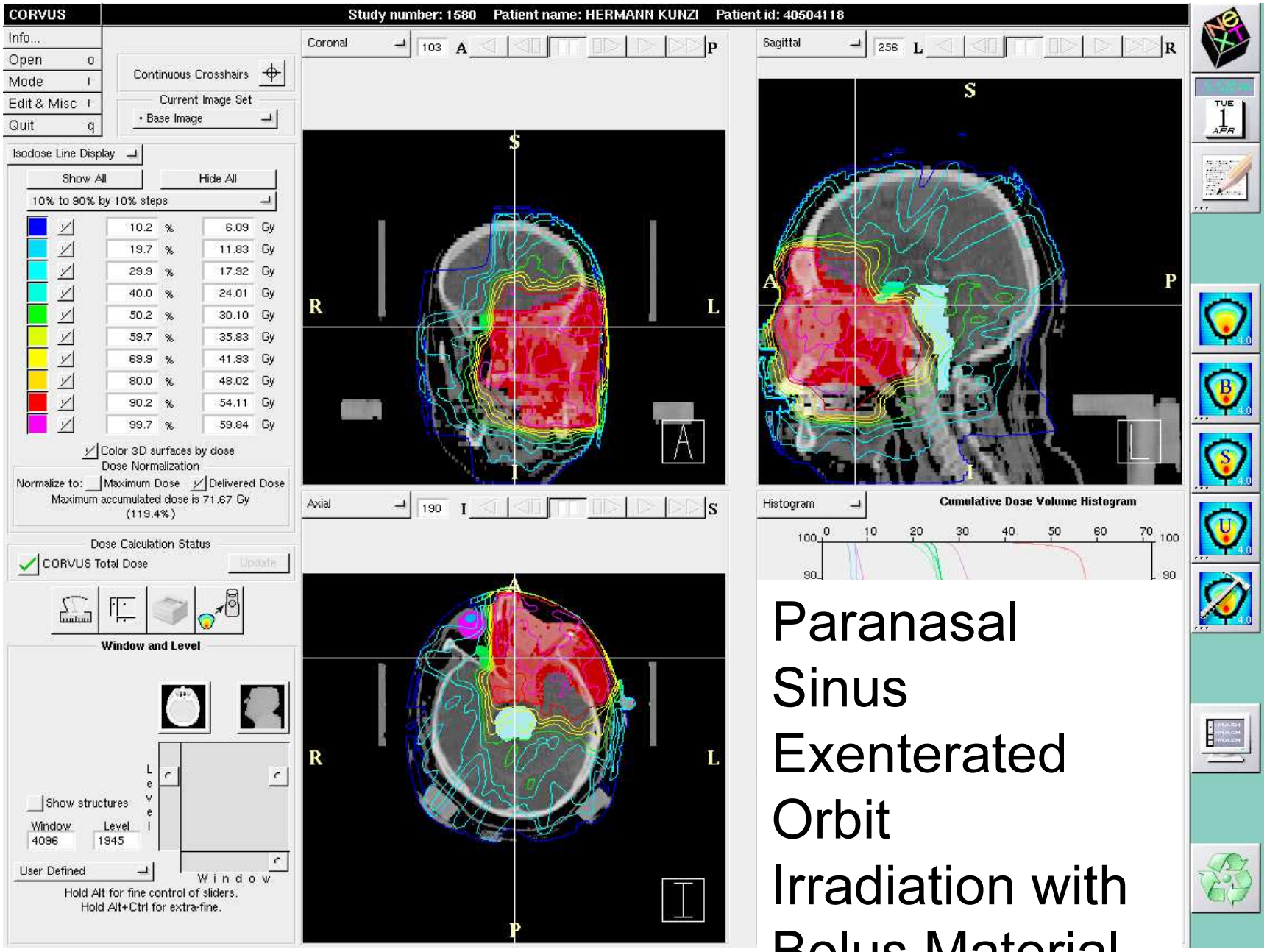


Oropharynx (Tonsil) T2N1
Unilateral Parotid Sparing



Display of Buildup




CORVUS
Study number: 1580 Patient name: HERMANN KUNZI Patient id: 40504118
Info...
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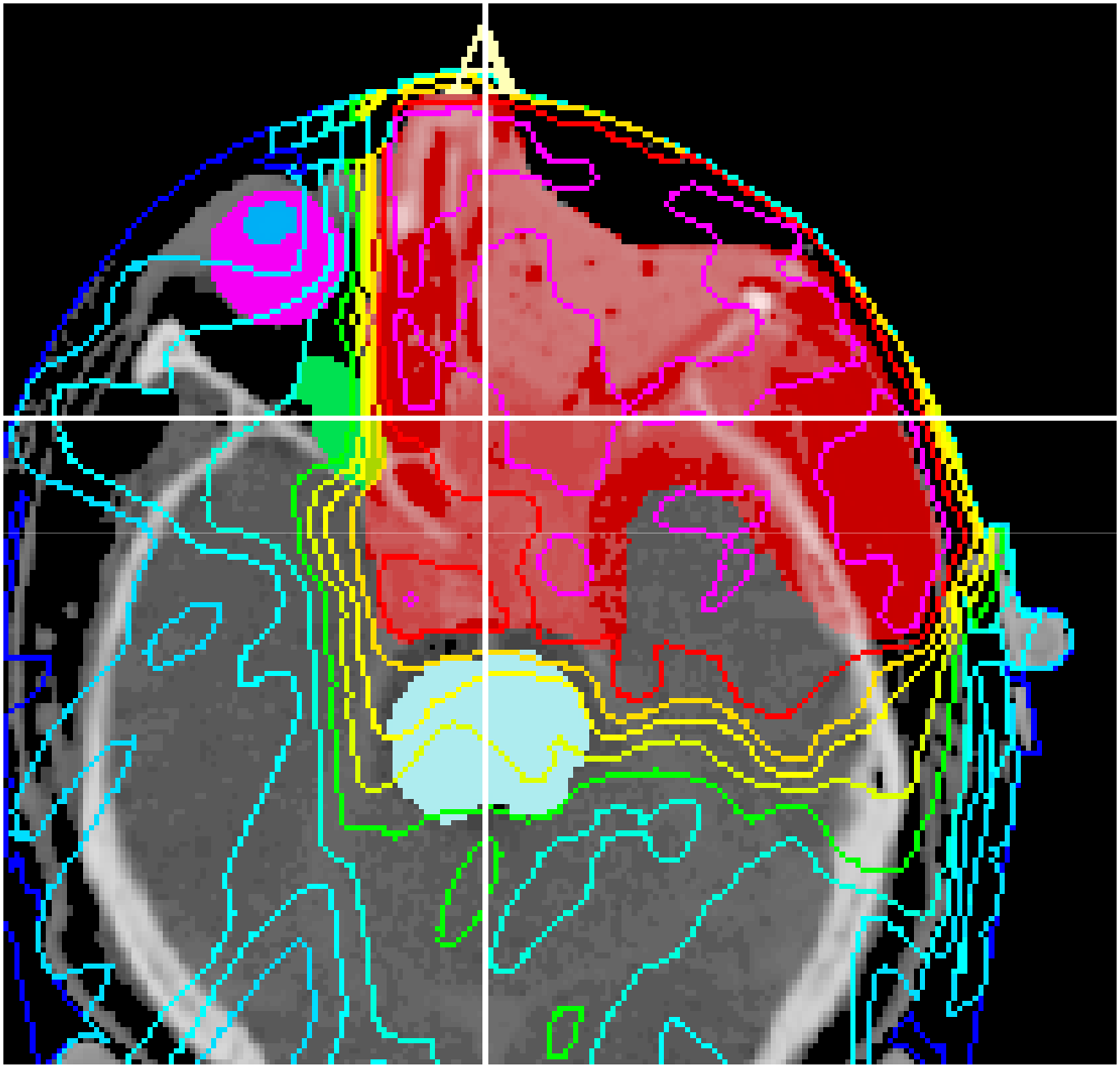
10% to 90% by 10% steps
10.2 % 6.09 Gy
19.7 % 11.83 Gy
29.9 % 17.92 Gy
40.0 % 24.01 Gy
50.2 % 30.10 Gy
59.7 % 35.83 Gy
69.9 % 41.93 Gy
80.0 % 48.02 Gy
90.2 % 54.11 Gy
99.7 % 59.84 Gy
Color 3D surfaces by dose
Dose Normalization
Normalize to: Maximum Dose Delivered Dose
Maximum accumulated dose is 71.67 Gy
(119.4%)
Dose Calculation Status
CORVUS Total Dose
Update
Window and Level
Show structures
Window 4096
Level 1945
User Defined
Hold Alt for fine control of sliders.
Hold Alt+Ctrl for extra-fine.
Coronal 103 A P
Axial 190 I S
Sagittal 256 L R
Histogram
Cumulative Dose Volume Histogram
Paranasal Sinus Exenterated Orbit Irradiation with Bolus Material



Paranasal Sinus Exenterated Orbit Irradiation with Bolus Material

Use Bolus when sufficient dose is desired in superficial tissues. Dose calculation is not reliable in a buildup region

Clinical Normal Tissue Toxicity

An excellent Reference just published:

Seminars in Radiation Oncology
Volume 26, No.2, April 2016

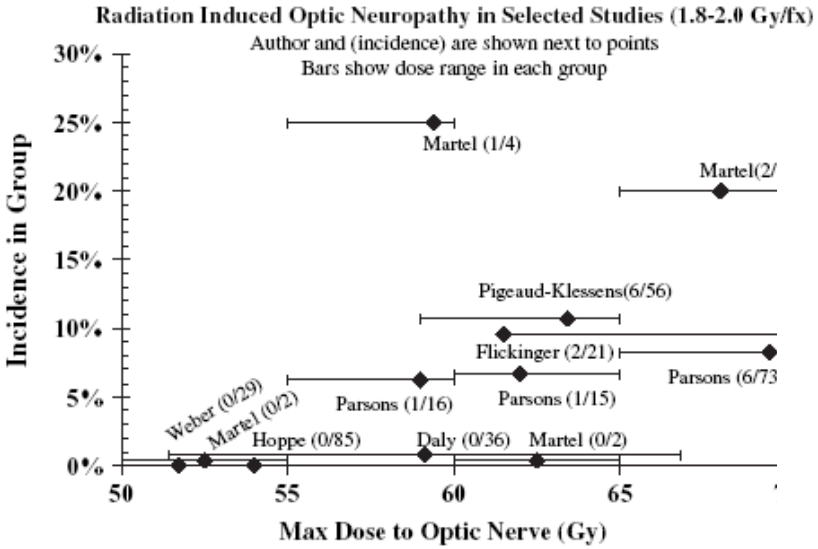
Normal Tissue Toxicity Modelling for SRS and SBRT

Optic Nerve Toxicity: Quantec

Mayo et al., IJROBP, 2010

Few studies have adequate data for dose–volume outcome modeling. The risk of toxicity increased markedly at doses **>60 Gy at >1.8 Gy/fraction** and at **>12 Gy for single-fraction** radiosurgery.

The evidence is strong that radiation tolerance is increased with a reduction in the dose per fraction.



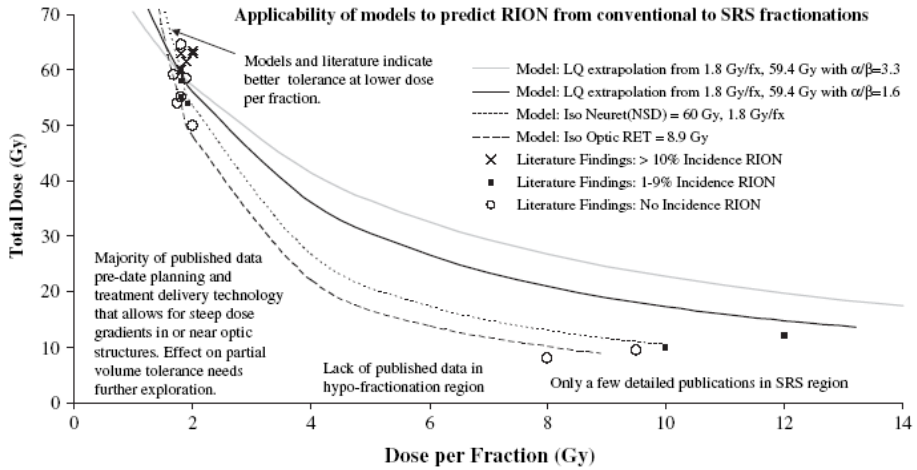


Fig. 2. Isoeffect linear-quadratic model extrapolations and alternative biologically effective threshold models (curves) compared with reported maximum optic nerve/chiasm doses detailing incidence of radiation-induced optic neuropathy (RION) (symbols) for full range of dose per fraction. Linear-quadratic model was unreliable for extrapolating from fractionated (1.8–2.0-Gy/fraction) dose range to single-fraction range. Detailed data needed for low (<1.8 Gy) and hypofractionated regions to better define organ response.

No Optic Neuropathy at <45/1,8 Gy in Nonfunctioning Pituitary Adenoma - High SD are problematic

Van den Bergh, J Neuro-Ophthalmol, 2004

TABLE 2. *Reported cases of radiation optic neuropathy (RON) in irradiated patients with nonfunctioning pituitary adenomas in which radiation treatment characteristics are documented*

Author (year or publication)	Gender	Age at diagnosis of RON (y)	Surgery	Total dose (Gy)	Fraction size (Gy)	Treatment time (d)	Latency of RON (mo)	Visual status† to RON attributable
Crompton, 1961 (52)	F	56	Y	45	N/A	28	12	N/A
Harris, 1976 (24)*	F	41	N	45	2.25	32	6	OD: NFP OS: 20/20
Harris, 1976 (24)*	M	62	Y	45	2.5	26	15	OD: NLP OS: NLP
Harris, 1976 (24)*	M	66	N	45	2.5	26	6	OD: NLP OS: NLP
Harris, 1976 (24)*	F	37	N	45	2.5	26	2	N/A
Aristizabal, 1977 (12)	N/A	N/A	N/A	50	2	35	10	OD: NLP OS: NLP
Martins, 1977 (53)	F	61	Y	67	2.25	37	33	OD: LP OS: 20/20
Martins, 1977 (53)	F	44	Y	65.8	2.2	46	13	OD: NLP OS:20/30
Lorenzo, 1978 (54)	F	28	N	50	NA	35	14	N/A
Fitzgerald, 1981 (22)	F	65	N	50	NA	42	13	OD: 20/20 OS: LP (helical isopters)
Fukamach, 1982 (55)	F	49	Y	50	2	35	10	OD: 20/400 OS: 20/100
Hammer, 1983 (15)	F	52	Y	42.5	2.8	21	13 25	OS: 20/200 OD: NLP
Kline, 1985 (18)	M	73	Y	50	2	38	12	OD: VA: 20/800 OS: 20/20
Kundra, 1990 (56)	M	40	Y	55	2.75	NA	6	N/A
Kundra, 1990 (56)	M	46	Y	55	2.2	NA	±6	N/A
Zimmerman, 1990 (57)	M	64	Y	50.4	1.8	28	14	OD: HM OS: 20/25
Millar, 1991 (58)	F	56	Y	45	1.8	35	10	OD: NLP OS: NLP
Guy, 1991 (21)	M	51	Y	53.4	2	NA	30	OD: 20/20 OS: 20/25
Hudgins, 1992 (59)	F	75	Y	54	1.8	NA	35	OD: N/A OS: 20/20
Sallet, 1992 (60)	F	40	Y	30	NA	NA	8	OD: 20/20 OS: NLP
Hughes, 1993 (61)	N/A	N/A	N/A	50	2.5	N/A	N/A	N/A
Hughes, 1993 (61)	N/A	N/A	N/A	50	2.5	N/A	N/A	OD: 20/20 OS: 20/20 but temporal field defect
McClellan, 1995 (62)	M	67	Y	45	1.8	36	3 7	OD: HM OS: NLP
Colao, 1998 (47)*	N/A	N/A	Y	45	1.8	35	12	N/A
Breen, 1998 (48)*	N/A	N/A	N/A	50	2	N/A	54	N/A

Bold rows indicate patients in whom RON developed with "safe" radiation regimens.
F, female; M, male; Y, yes; N, no; VA, visual acuity; N/A, data not available.
*These references are also included in Table 1, because patient and treatment characteristics were available.
†In some cases, visual acuity was documented as "normal," or when not normal, as attributable to a cause other than RON; for simplicity, 20/20 has been used in all such cases.

No ON at Proton Doses of <55GyE

10% ON risk between 55 and 65GyE
(two of 20 patients in series developed ON at doses of 55 and 65GyE
at SD of <2Gy)

Habrand, IJROBP, 1989

Single Dose vs. Fractionated Tolerance for Meningeoma

Shrieve et al., J Neurosurg, 2004

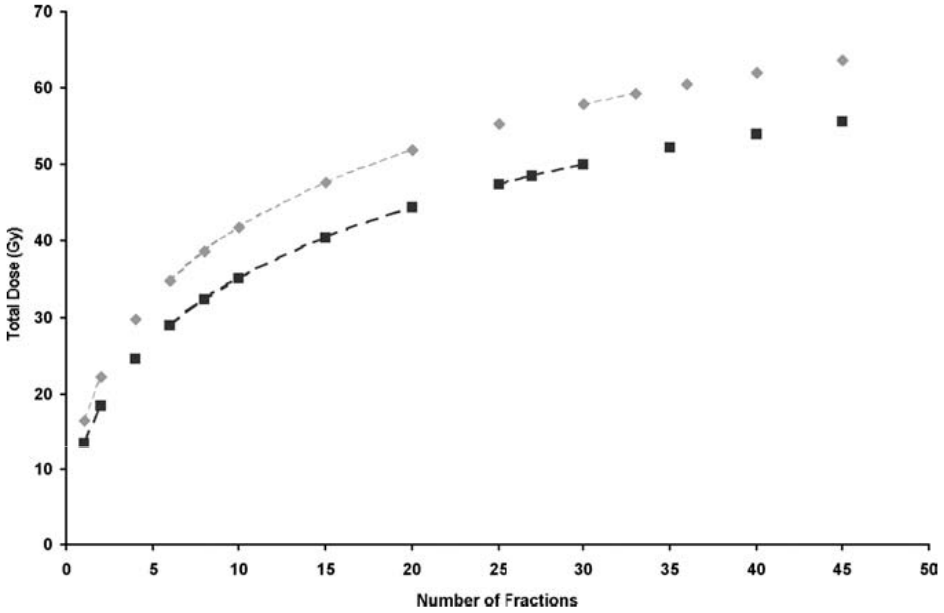


FIG. 4. Graph showing the range of total doses predicted to be associated with excellent control of meningioma *(dotted lines)* compared with the optic nerve tolerance for various equal daily doses *(solid line)*. The therapeutic range exceeds optic nerve tolerance until at least 20 fractions are used.

"Single doses of radiation required to treat benign meningioma optimally (13.5–16.5 Gy) clearly exceed the estimated and reported clinical tolerance of the optic nerves and chiasm. The application of equivalent biological doses in a small number of fractions continues to exceed optic tolerance until at least 25 fractions are applied."

Optic Neuropathy Risk after RS

The risk of developing a clinically significant RON was **1.1%** for patients receiving **12 Gy** or less with a median F/u of 40 months

Patients receiving prior or concurrent EBRT had a greater risk of developing RON after radiosurgery

Stafford et al., IJROBP, 2004

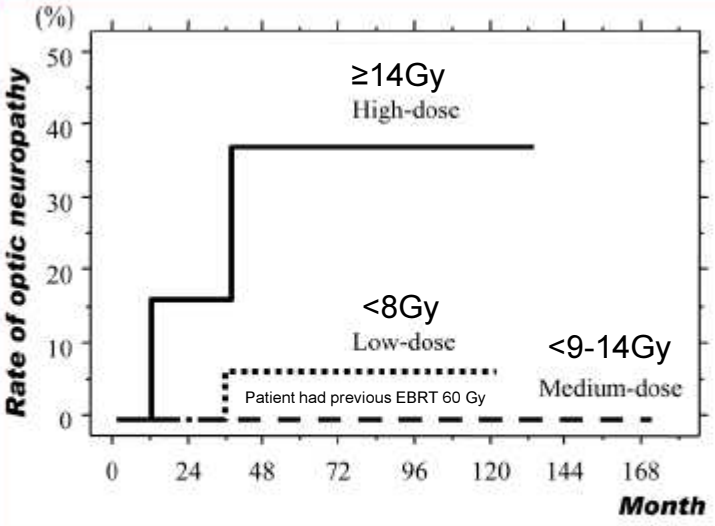


FIGURE 5. *Kaplan-Meier curves demonstrating radiation-induced optic neuropathy rates on the basis of dose groups.*

TABLE 3. Dose to Optic Chiasm (n = 53)

Maximum Dose, Gy	No. of Patients (%)
<5	13 (25)
5-6	13 (25)
7-8	14 (26)
9-10	11 (21)
11-12	1 (2)
13-14	0 (0)
15-16	1 (2)

Hasegawa et al., Nerurosurgery, 2010

Optic Neuropathy Risk - Synopsis

A TD of 45Gy/SD 1.8 Gy and RS with 1 x 8 Gy seem to be completely safe

At TD 50-60Gy/SD <2 Gy and RS with 1 x 10-12 Gy a low incidence of ON is reported

At TD>60Gy with SD < 2 Gy and TD>50 Gy with SD >2 Gy

as well as

RS with >12 Gy,

ON risk increases quickly with dose and SD

Plexopathy

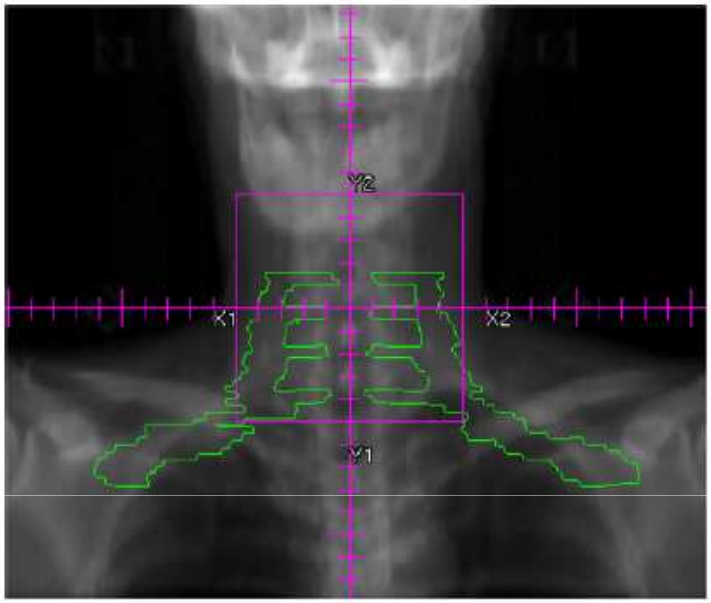


Fig. 3. Coronal section of the head and neck illustrating the anatomic location of the brachial plexus as depicted using the Radiation Therapy Oncology Group contouring atlas (available at www.rtog.org).

The brachial plexus begins at the ventral rami of nerve roots at the fifth cervical vertebrae and continues inferiorly to include the nerve roots exiting the neural foramen of the first thoracic vertebrae (Fig. 3). It then passes inferolaterally between the anterior and middle scalene muscles to innervate the cutaneous skin of the upper extremity and numerous muscles including the latissimus dorsi, pectoralis major and minor, levator scapulae, deltoid, and biceps brachii.

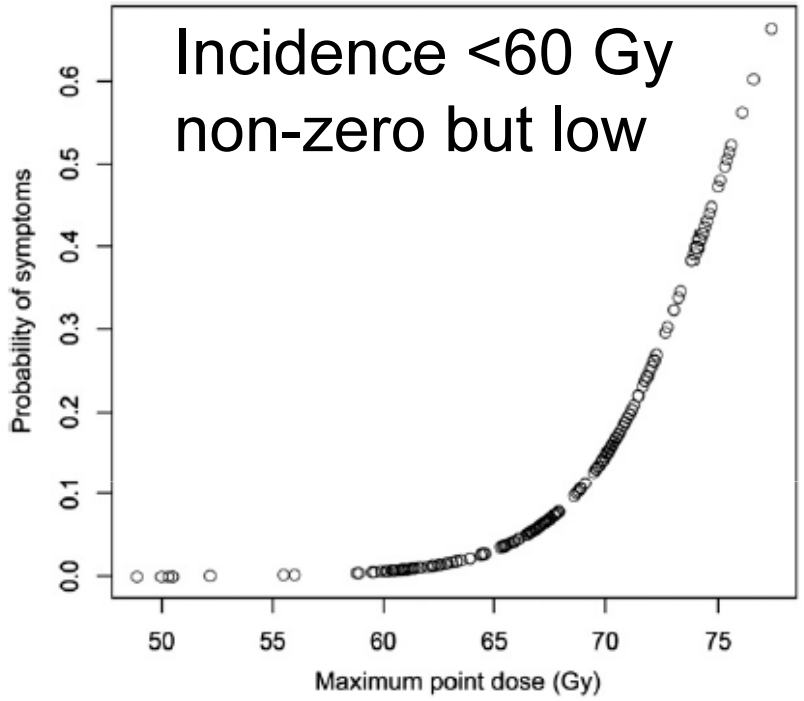
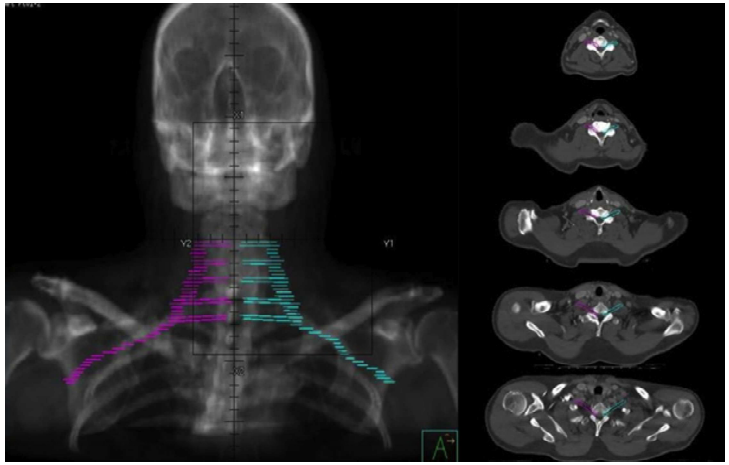


Fig. 2. Relationship between probability of developing neuropathic symptoms and maximum radiation point dose (Gy).

Chen et al., IJROBP, 2012

In this study cohort, at a minimum of two-years follow up, the mean dose of 68.7Gy, a median dose to 69.5Gy to ≤5% of ipsilateral BP, and a median Dmax of 72.96Gy did not result in BP injury when patients were treated with S-IMRT technique.

However, longer follow up is needed.



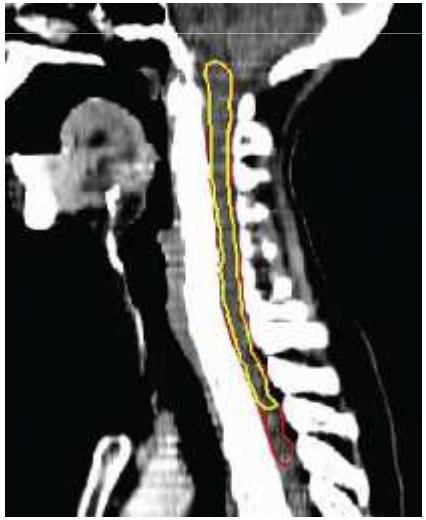
Thomas, Rad Onc, 2015

Start with the close call….

Pak et al., IJROBP, 2012

Lhermitte's (RT+Cht w/ Carbo/Tax)

Plan relateds spinal cord



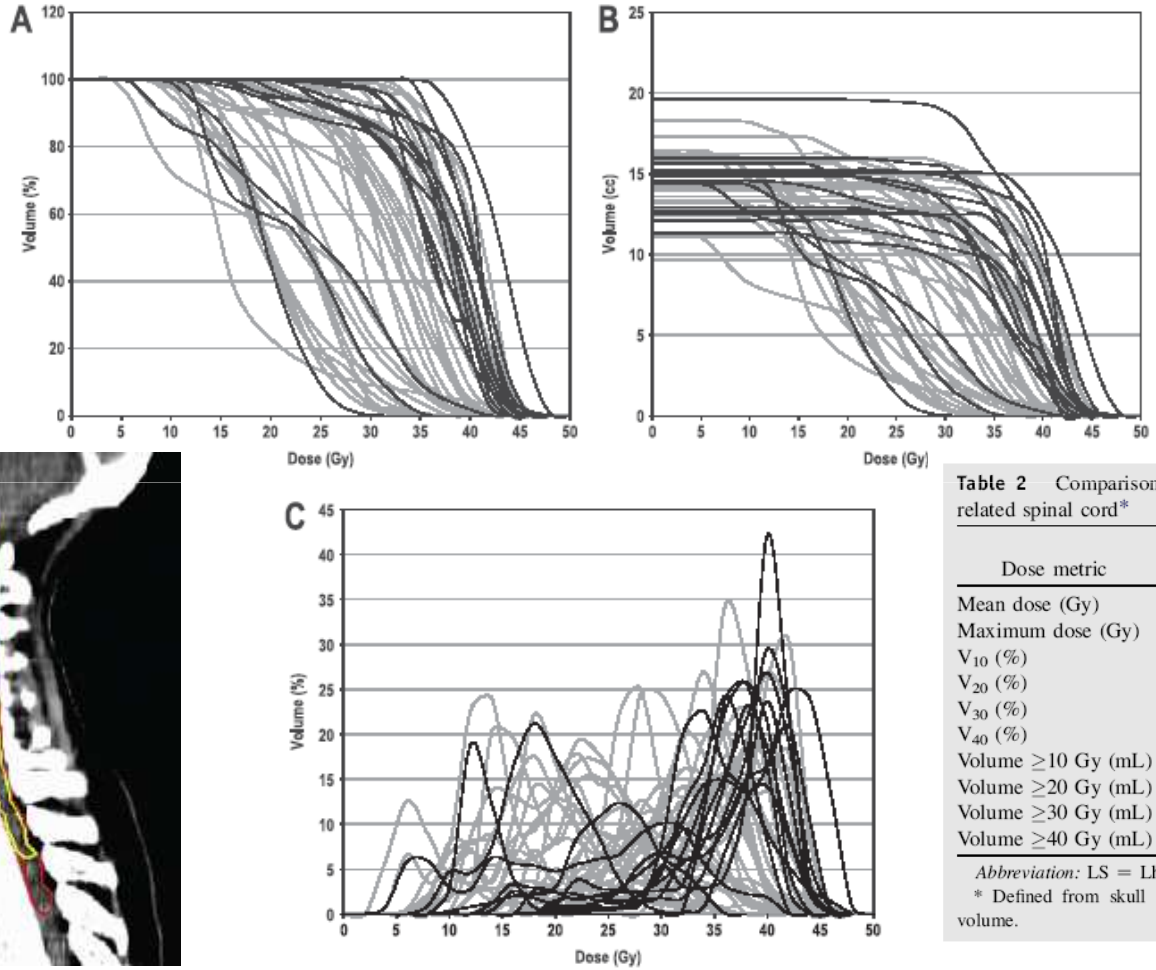


Table 2 Comparison of dose metrics by LS status: Plan-related spinal cord*

Dose metric	Non-LS (n = 34)	LS (n = 15)	p value
Mean dose (Gy)	29.0 ± 6.9	33.6 ± 7.0	0.032
Maximum dose (Gy)	42.2 ± 4.2	43.1 ± 4.5	0.572
V_{10} (%)	99.1 ± 2.6	99.1 ± 3.2	0.451
V_{20} (%)	83.4 ± 22.1	89.9 ± 18.1	0.148
V_{30} (%)	54.9 ± 35.6	76.7 ± 32.8	0.044
V_{40} (%)	12.3 ± 17.5	32.6 ± 24.2	0.005
Volume ≥10 Gy (mL)	14.0 ± 2.0	14.3 ± 2.1	0.421
Volume ≥20 Gy (mL)	11.8 ± 3.5	13.0 ± 3.3	0.157
Volume ≥30 Gy (mL)	7.8 ± 5.2	11.1 ± 5.1	0.048
Volume ≥40 Gy (mL)	1.7 ± 2.5	5.0 ± 3.9	0.006

Abbreviation: LS = Lhermitte sign.

* Defined from skull base to inferior border of planning target volume.

Fig. 2. Dose–volume histograms (DVHs) for plan-related spinal cord: non–Lhermitte sign (LS) patients (gray) and LS patients (black). Cumulative DVHs with (A) percent cord volume and (B) absolute cord volume. (C) Direct DVH with percent cord volume.

Spinal Cord Damage – Review 1

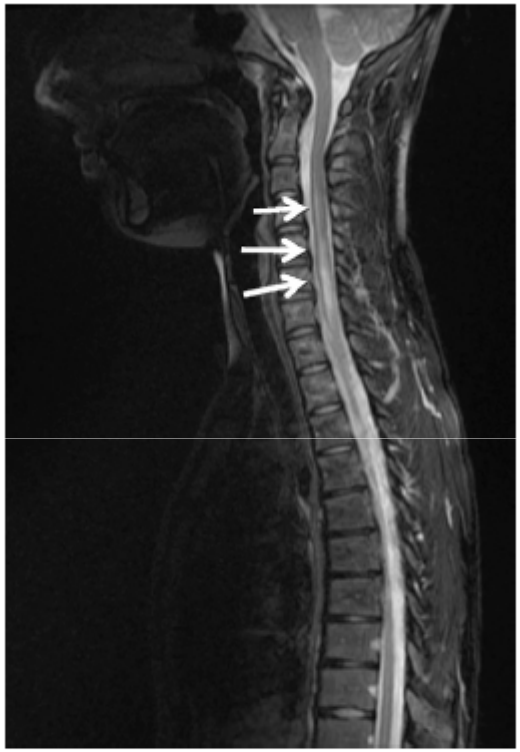


Fig. 1. Paraparésie sensitivomotrice, cinq mois après irradiation en manteleet incomplet d'une adolescente ayant préalablement reçu une chimiothérapie (protocole OEPA/COPP, vincristine, procarbazine, etoposide, prednisone, adriamycine, cyclophosphamide). Dose délivrée : 20 Gy en 11 séances par faisceaux antéropostérieurs de photons de haute énergie. Aspect grêle et hyper T2 de la moelle cervicodorsale avec prises de contraste étagées, compatibles avec une myélite radique. Régression de la symptomatologie après bolus de corticoïdes. Tests de radiosensibilité négatifs (collection de l'institut Gustave-Roussy).

Spinal Cord Damage risk ~0,5%
for full cord exposure to 50 Gy

Habrand et al., Cancer Radiother, 2010

Spinal Cord Damage – Review 2

Dose–volume data for myelopathy in humans treated with radiotherapy (RT) to the spine is reviewed, along with pertinent preclinical data. Using conventional fractionation of **1.8–2 Gy/fraction** to the full-thickness cord, the estimated risk of myelopathy is **<1% and <10% at 54 Gy and 61 Gy**, respectively, with a calculated strong dependence on dose/fraction (a/b = 0.87 Gy.)

Reirradiation data in animals and humans suggest partial repair
of RT-induced subclinical damage becoming evident about 6 months post-RTand increasing over the next 2 years.

Reports of myelopathy from **stereotactic radiosurgery** to spinal lesions appear rare **(<1%)** when the maximum spinal cord dose is limited to the equivalent of **13 Gy in a single fraction or 20 Gy in three fractions**. However,long-term data are insufficient to calculate a dose–volume relationship for myelopathy when the partial cord istreated with a hypofractionated regimen.

Kirkpatrick et al., IJROBP, 2010

How much RT can I give after conventional RT?

Table 2. Risk score for development of radiation myelopathy

	Score									
Factor	0	1	2	3	4	5	6	7	8	9
Cumulative BED (Gy_2)	≤120	120.1–130	130.1–140	140.1–150	150.1–160	160.1–170	170.1–180	180.1–190	190.1–200	>200
Interval <6 mo					X (4.5)					
One BED course ≥102 Gy_2					X (4.5)					

Abbreviation: BED = biologically effective dose.

50 Gy ~BED 100
-> low risk at 50+20Gy

Group	Score	Myelopathy (%)
Low risk	≤3	0/24 (0)
Intermediate risk	4–6	2/6 (33)
High risk	>6	9/10 (90)

Nieder et al., IJROBP, 2005

Maximum Doses to Spinal cord of 20 Gy in 1-3 SD
Lower than expected Tox – high parallelity of Spinal Cord

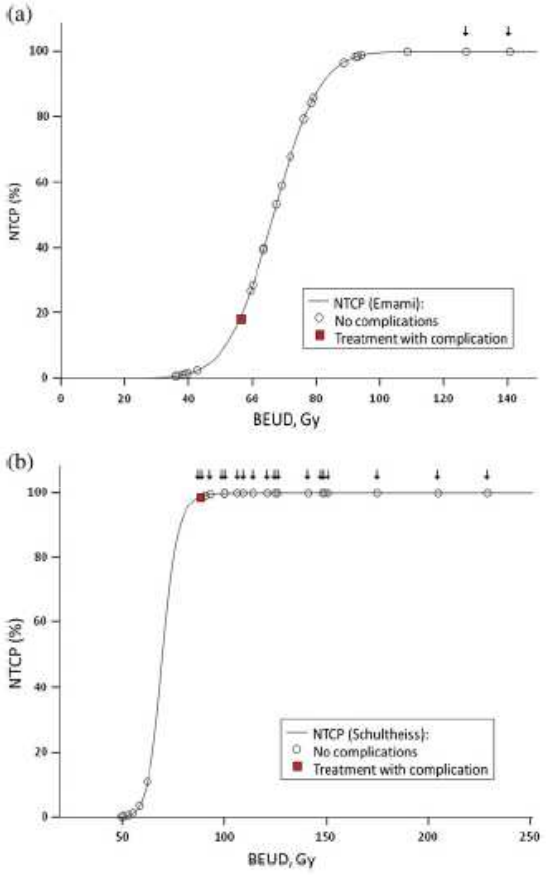


Fig. 1. a, Predicted normal tissue complication probability (NTCP) for spinal cord with NTCP modeling of clinical outcomes based on parameters of Emami (3). One cord toxicity was observed clinically (square) (with an NTCP of 19%). Seventeen other lesions with a higher NTCP, including two lesions with 100% NTCP (arrows), did not have toxicity. Therefore these modeling parameters were not predictive of the clinical outcomes. b, Predicted NTCP for spinal cord with NTCP modeling of clinical outcomes based on parameters of Schultheiss (5). One cord toxicity was observed clinically (square) (with an NTCP of 99.8%), whereas seventeen other lesions without toxicity had an NTCP of greater than 99% (arrows). These NTCP values overestimated the toxicity rates observed clinically. BEUD = biologically equivalent uniform dose.

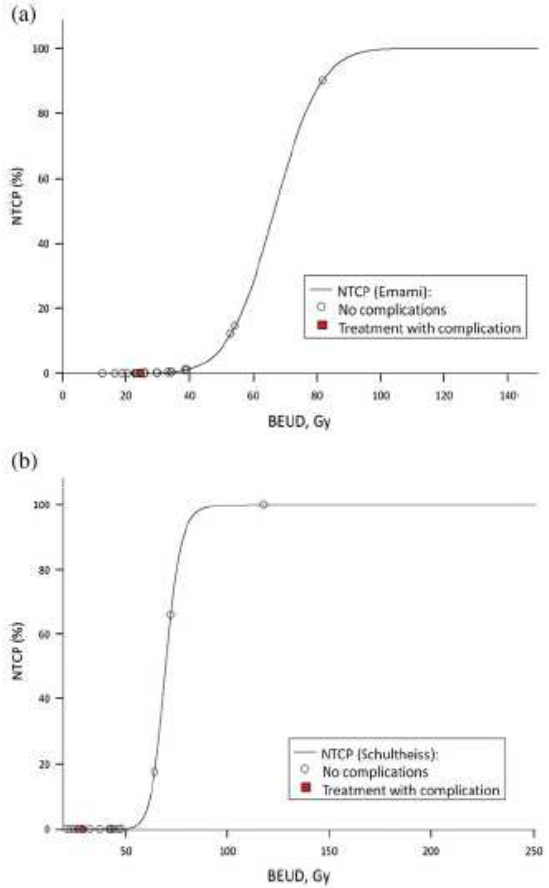


Fig. 2. a, Predicted normal tissue complication probability (NTCP) for spinal cord with NTCP modeling of clinical outcomes based on parameters of Emami (3), with optimization of the volume parameter ($n = 0.31$), assuming a greater degree of parallel organization of the spinal cord. Although this optimization provided a better fit of the NTCP to the clinical data, these NTCP parameters continued to overestimate the risk of complications. b, Predicted NTCP for spinal cord with NTCP modeling of clinical outcomes based on parameters of Schultheiss (5), with optimization of the volume parameter ($n = 0.43$), assuming a greater degree of parallel organization of the spinal cord. These modified parameters continued to overestimate the risk of complications observed clinically. BEUD = biologically equivalent uniform dose.

Table 2. Predicted and observed number of complications

Parameter used	No. of complications predicted	No. of complications observed
Emami	13	1
Schultheiss $n = 0.05$	18	1
Schultheiss $n = 0.43$	2	1
Emami with α/β of 13.2 Gy	0.7	1

Abbreviation: n = volume parameter.

Spinal cord D_{max} [median (range)] (Gy)	
1 Session	22.7 (17.8–30.9)
2 Sessions	22.0 (21.3–26.6)
SF-BED (LQ model)	16.1 (15.6–19.4)
SF-BED (LQ-L model)	19.5 (18.8–24.1)
3 Sessions	21.3 (20.2–25.4)
SF-BED (LQ model)	13.2 (12.6–15.6)
SF-BED (LQ-L model)	16.3 (15.2–20.4)
Spinal cord V_{10} [median (range)] (mm^3)	
1 Session	454 (226–2,543)
2 Sessions	711 (114–1,216)
3 Sessions	926 (780–1,240)
Spinal cord D_{500} [median (range)] (Gy)	
1 Session	9.5 (5.3–22.5)
2 Sessions	12.8 (2.9–15.0)
3 Sessions	13.2 (12.3–14.1)

Daly et al., IJROBP, 2012

Partial Volume Spinal Cord Reirradiation

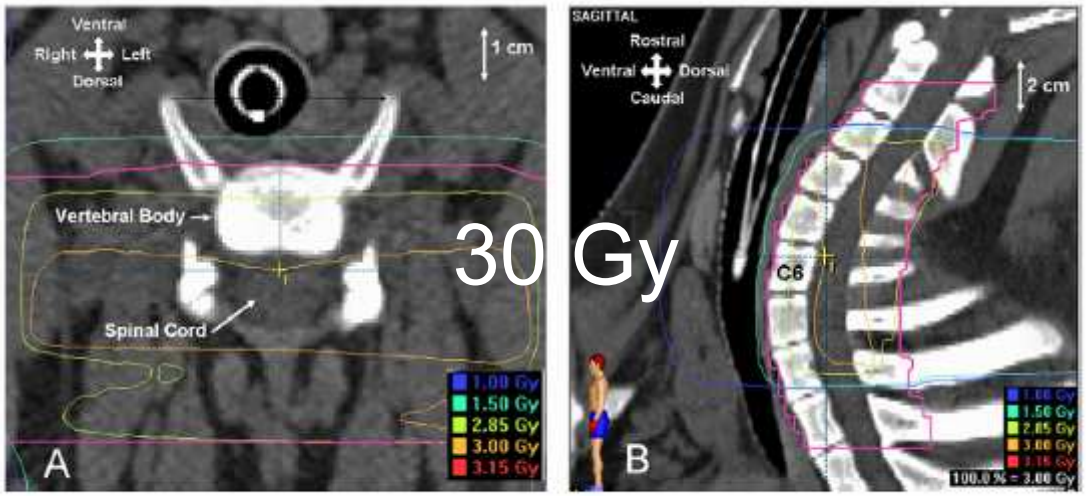


Fig. 1. Dose distribution for 30 Gy in 10 fractions in the axial (A) and sagittal (B) planes.

1 Year

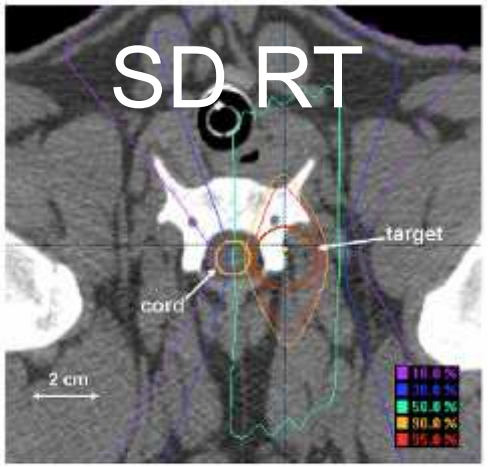


Fig. 2. Dose distribution for single-fraction radiosurgery in the axial plane is shown.

Medin et al, IJROBP, 2012

„No deficits were noted on the unirradiated (right) side of any animal“

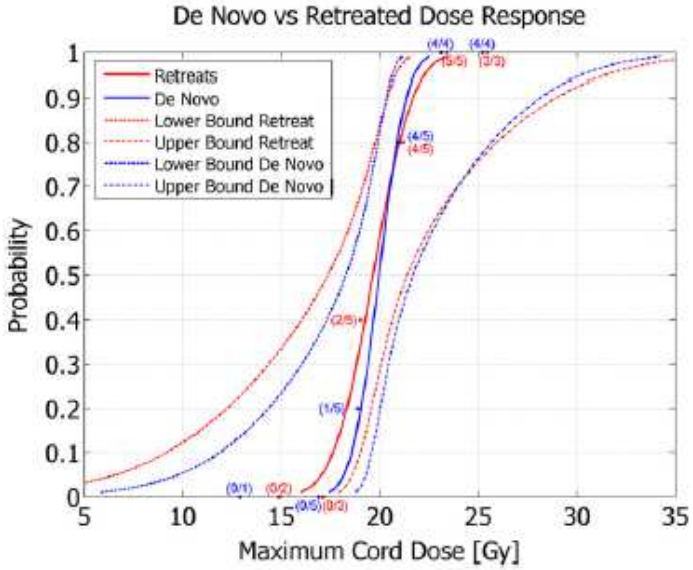


Fig. 3. Dose-response curves with 95% confidence limits for de novo radiosurgery versus retreatment are shown.

How much SBRT can I give after conventional RT?

Table 6. Reasonable reirradiation SBRT doses to the thecal sac P_{max} following common initial conventional radiotherapy regimens

Conventional Radiotherapy (nBED)	1 fraction: SBRT dose to thecal sac P_{max}	2 fractions: SBRT dose to thecal sac P_{max}	3 fractions: SBRT dose to thecal sac P_{max}	4 fractions: SBRT dose to thecal sac P_{max}	5 fractions: SBRT dose to thecal sac P_{max}
0*	10 Gy	14.5 Gy	17.5 Gy	20 Gy	22 Gy
20 Gy in 5 fractions ($30\ Gy_{2/2}$)	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
30 Gy in 10 fractions ($37.5\ Gy_{2/2}$)	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
37.5 Gy in 15 fractions ($42\ Gy_{2/2}$)	9 Gy	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
40 Gy in 20 fractions ($40\ Gy_{2/2}$)	N/A	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
45 Gy in 25 fractions ($43\ Gy_{2/2}$)	N/A	12.2 Gy	14.5 Gy	16.2 Gy	18 Gy
50 Gy in 25 fractions ($50\ Gy_{2/2}$)	N/A	11 Gy	12.5 Gy	14 Gy	15.5 Gy

Abbreviations: N/A = not applicable; nBED = normalized biologically effective doses; SBRT = stereotactic body radiotherapy.

* These dose limits are based on our prior publication for spinal cord tolerance in patients treated with SBRT and no prior history of radiation (7).

Saghal et al., IJROBP, 2012

Daily vs. less frequent Imaging: Spinal cord dose

Duma et al., IJROBP, 2013

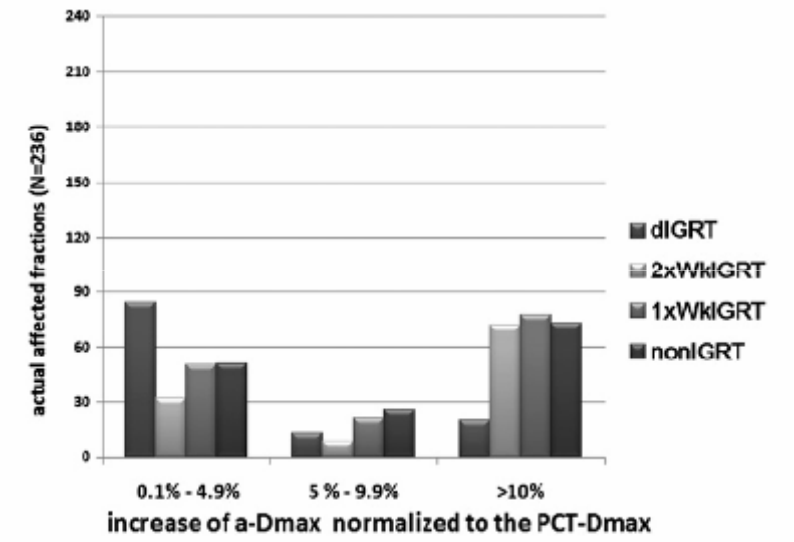


Fig. 2. The a-Dmax is higher than the planned Dmax. a-Dmax = actual delivered Dmax; plan-Dmax = Dmax on the planning kVCT.

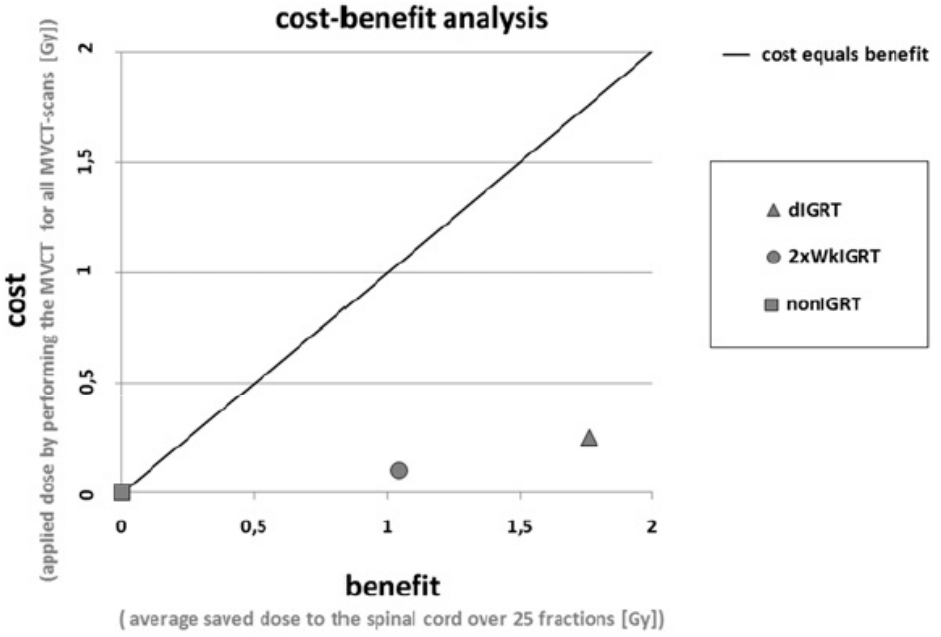


Fig. 4. Cost-benefit analysis of dIGRT and 2×WkIGRT compared to non-IGRT. Compared to the non-IGRT, the dIGRT and 2×WkIGRT scenarios save, on average, 1.76 and 1.04 Gy, respectively. That is calculated by the higher-than-planned Dmax for the non-IGRT (5.6%) minus the higher-than-planned Dmax for the dIGRT (1.2%); *e.g.*, 2.24 Gy − 0.48 Gy = 1.76 Gy; and for 2×WkIGRT, 2.24 Gy − 1.2 Gy = 1.04 Gy. The cost of one MVCT scan in the coarse mode is 0.01 Gy (dIGRT = 0.25 Gy; 2×WkIGRT = 0.12 Gy).

ART (IMRT) – Dosimetric Benefits

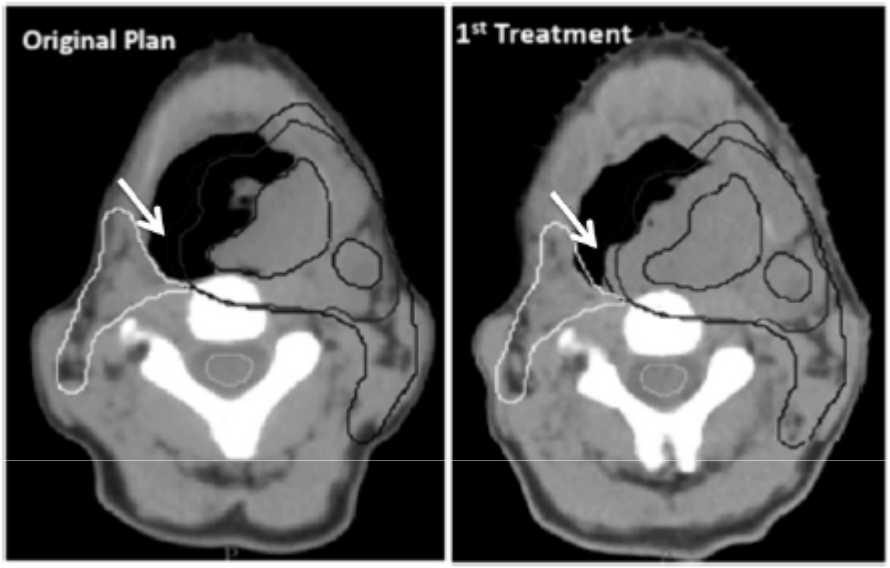


Fig. 1. Detection of rapid tumor progression prior to start of treatment. The original plan is shown to the left; patient's anatomy on first treatment day is shown on the right. Primary GTV progressed by >50%. Arrows designate site of geographic miss for CTV1.

Try to keep Interval between CT and 1st RT short (2-3 days is possible)

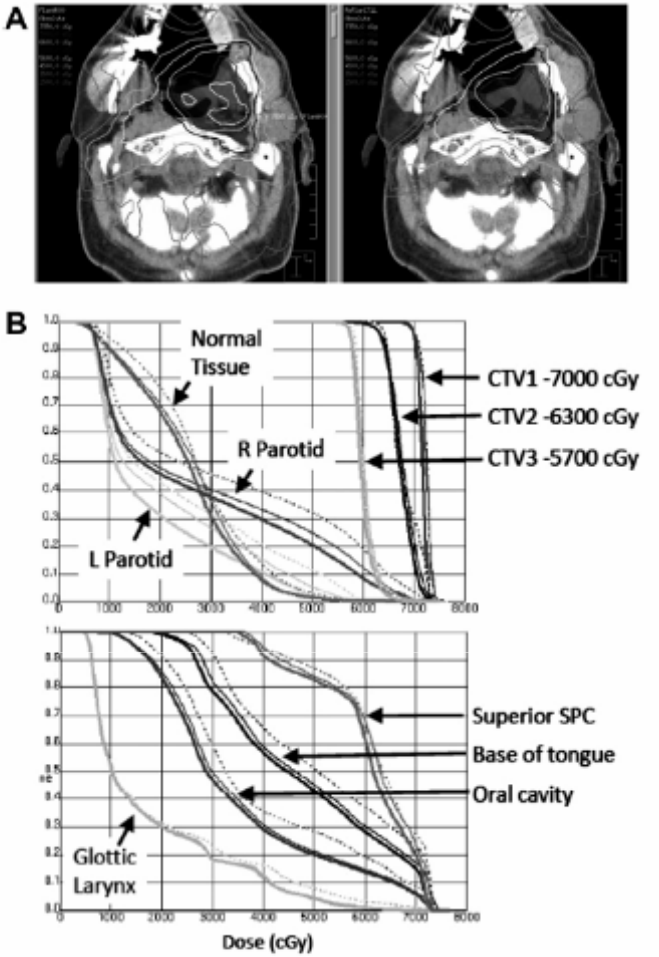


Fig. 3. (A) *Right:* Emergence of dose heterogeneity within high-risk CTV1 in a tonsillar carcinoma case at treatment fraction #11; *Left:* Restoration of intended dose distribution within CTV1 by adaptive replanning without PTV margin expansions. (B) DVH comparison for the original IMRT plan of this case (dotted lines), ART1 replan designed on treatment day 15 (thin solid lines), and the ART2 replan (thick solid lines), all re-calculated on CT anatomy obtained on 25th treatment day.

Schwartz et al., R&O, 2013

IMRT vs. Protons?

Table 1 Method to calculate toxicity for the *IMPT if efficient* strategy: Illustrated for xerostomia 6 months after radiation therapy

	Probability of xerostomia (%)		ICER	Preferred	Probability of xerostomia (%)
Patient	IMPT	IMRT	IMPT vs IMRT (€)	IMPT/IMRT	*IMPT if efficient**
1	25.5	41.3	93,302	IMRT	41.3
2	18.9	36.6	169,448	IMRT	36.6
3	23.6	55.2	44,358	IMPT	23.6
4	26.7	37.2	150,041	IMRT	37.2
↓	↓	↓	↓	↓	↓
25	25.8	45.1	89,593	IMRT	45.1
Mean probability of xerostomia for the IMPT if efficient strategy					37.1%

Abbreviations: ICER = incremental cost-effectiveness ratio; IMPT = intensity modulated proton radiation therapy; IMRT = intensity modulated radiation therapy with photons.

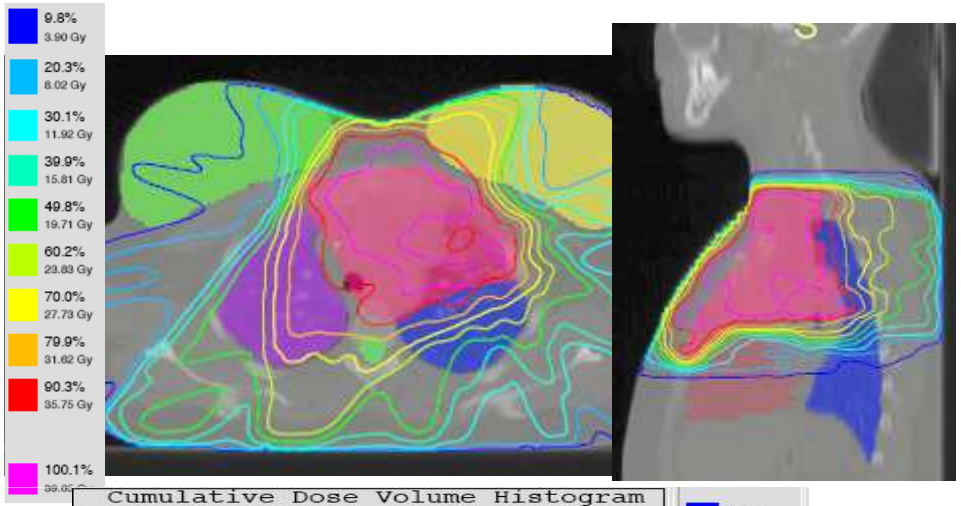
* Patients will only receive IMPT in this scenario if IMPT is expected to be cost-effective compared with IMRT (grey fields), thus if the ICER is below the threshold of 80,000 per QALY gained.

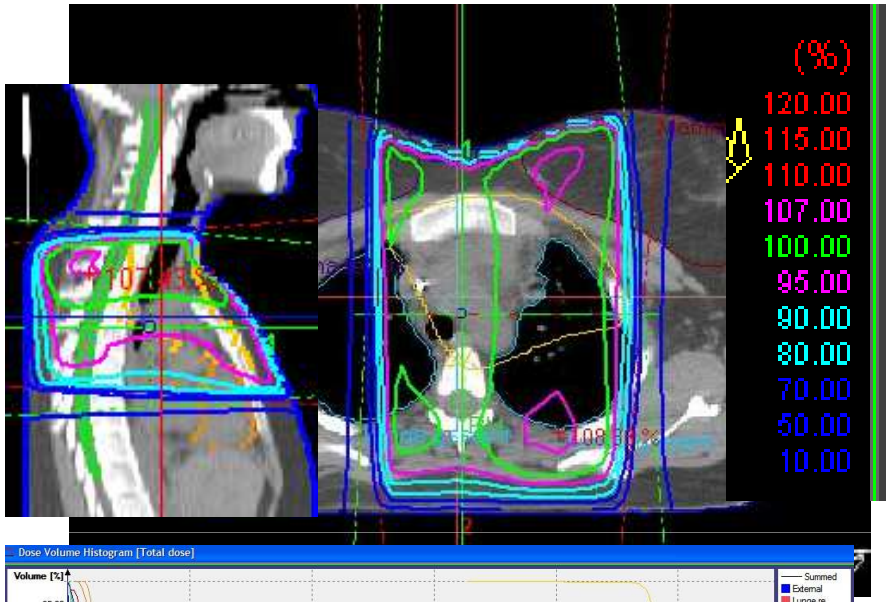
Ramaekers et al., IJROBP, 2013

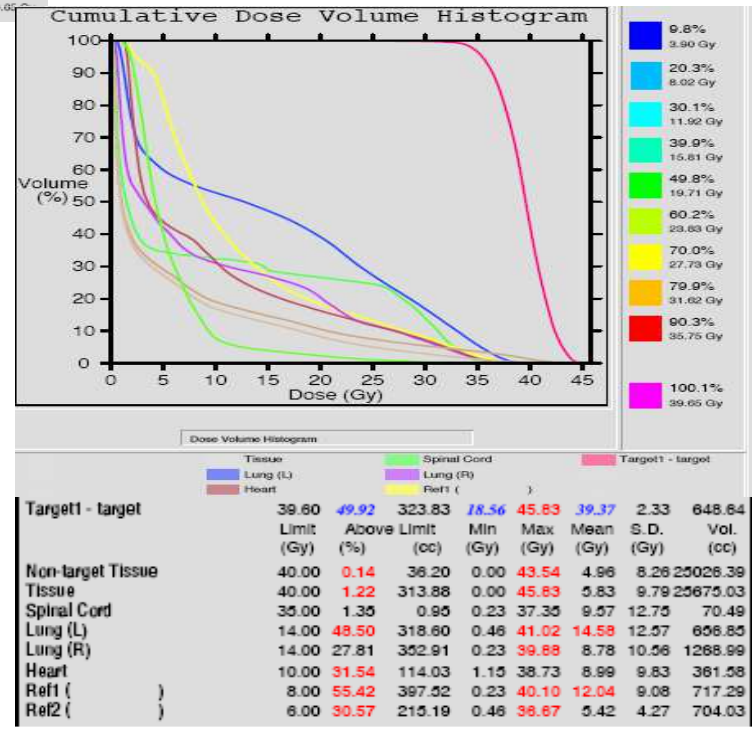
Mediastinal Tumors: Hodgkin‘s Disease

Koeck et al., IJROBP, 2012

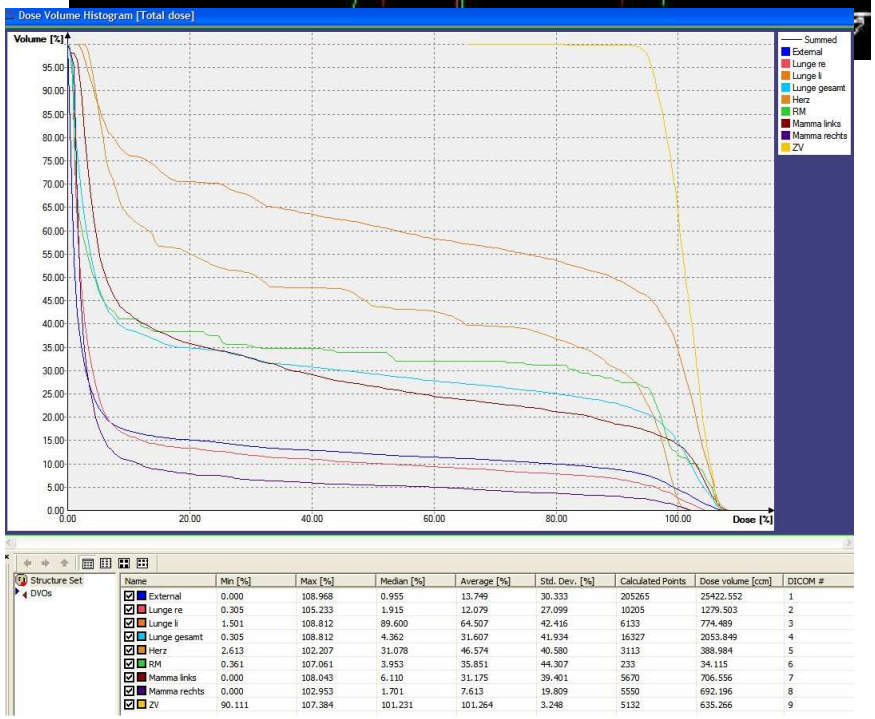
Elevated median but reduced mean breast dose as a result of improved heart protection -> Consequences???







Target1 - target	39.60 Limit (Gy)	49.92 Above Limit (%)	323.83 Limit (cc)	18.56 Min (Gy)	45.83 Max (Gy)	39.37 Mean (Gy)	2.33 S.D. (Gy)	648.64 Vol. (cc)
Non-target Tissue	40.00	0.14	36.20	0.00	43.54	4.96	8.26	25026.39
Tissue	40.00	1.22	313.88	0.00	45.83	5.83	9.79	25675.03
Spinal Cord	35.00	1.35	0.95	0.23	37.35	9.57	12.75	70.49
Lung (L)	14.00	48.50	318.60	0.46	41.02	14.58	12.57	656.85
Lung (R)	14.00	27.81	352.91	0.23	39.88	8.78	10.56	1268.99
Heart	10.00	31.54	114.03	1.15	38.73	8.99	9.83	361.58
Ref1 ( )	8.00	55.42	397.52	0.23	40.10	12.04	9.08	717.29
Ref2 ( )	6.00	30.57	215.19	0.46	36.67	5.42	4.27	704.03



Name	Min [%]	Max [%]	Median [%]	Average [%]	Std. Dev. [%]	Calculated Points	Dose volume [ccm]	DICOM #
External	0.000	108.968	0.955	13.749	30.333	205265	25422.552	1
Lunge re	0.305	105.233	1.915	12.079	27.099	10205	1279.503	2
Lunge li	1.501	108.812	89.600	64.507	42.416	6133	774.489	3
Lunge gesamt	0.305	108.812	4.362	31.607	41.934	16327	2053.849	4
Herz	2.613	102.207	31.078	46.574	40.580	3113	388.984	5
RM	0.361	107.061	3.953	35.851	44.307	233	34.115	6
Mamma links	0.000	108.043	6.110	31.175	39.401	5670	706.556	7
Mamma rechts	0.000	102.953	1.701	7.613	19.809	5550	692.196	8
ZV	90.111	107.384	101.231	101.264	3.248	5132	635.266	9

AMERICAN SOCIETY OF RADIATION ONCOLOGY RECOMMENDATIONS FOR DOCUMENTING INTENSITY-MODULATED RADIATION THERAPY TREATMENTS

IMRT Documentation Working Group, Timothy Holmes, (Chairman), Ph.D.,* Rupak Das, Ph.D.,† Daniel Low, Ph.D.,‡ Fang-Fang Yin, Ph.D.,§ James Balter, Ph.D.,‖ Jatinder Palta, Ph.D.,¶ and Patricia Eifel, M.D.,# FASTRO

IJROBP, August 2009

Prescription

Version: August 6, 2007

Treatment Planning Directive: Head and Neck

Type: ☐ IMRT ☐ IMRT PROTOCOL ☐ 3D Conformal ☐ Post-Op ☐ Palliative

Imaging: CT ☐ MRI ☐ Other_____

Target/Etc:	Dataset	Target Descriptions
☐ GTV #___	☐ CT or ☐ MR	
☐ CTV1 #___	☐ CT or ☐ MR	
☐ CTV2 #___	☐ CT or ☐ MR	
☐ Other	☐ CT or ☐ MR	
☐ PTV		
☐ GTV/CTV1/CTV2 + 0.3cm or _____ cm		
☐ Other _____		

Normal Structures:	Parameter	Limit to 1% of volume
☐ Cord :	Max	≤45Gy or_____
☐ Cord+0.5cm	Max	≤50Gy or_____
☐ Brainstem+0.5cm	Max	≤54Gy or_____
☐ Optic Chiasm+0.3cm	Max	≤50Gy or_____
☐ Rt Optic Nerve +0.3cm Max	Max	≤50Gy or_____
☐ Lt Optic Nerve +0.3cm Max	Max	≤50Gy or_____
☐ Rt Parotid:	Mean	≤24Gy or Alara
☐ Lt Parotid	Mean	≤24Gy or Alara
☐ Subman Glands Mean	Alara	or_____
☐ OralCav/Non-involved	Mean	≤30Gy or Alara
☐ Larynx	Mean	≤50Gy or Alara
☐ Pharyngeal Constr.	Mean	≤50Gy or Alara
☐ Esophagus	Mean	≤45Gy or Alara
☐ Mandible	Max	≤70Gy or_____
☐ Lips	Mean	≤30Gy or Alara
☐ Eyes	Mean	≤50y or_____
☐ Non Specified	Max	≤95% prescription
☐ Other: _____		

Target Goals:
PTV(s) ☐ +/- 5% ☐ Min to 1% of target = 99% of prescription dose or_____
☐ Max +7% or _____

Dose Prescription:
☐ Sequential Plans – 2.5/fx, 2.0/fx,1.8/fx or ____ ☐ Single plan, differentially dosed targets

☐ GTV 70 Gy or ____Gy	☐ GTV 70 Gy/2.0fx or ____Gy/___fx
☐ CTV1 60 Gy or ____Gy	☐ CTV1 63 Gy/1.8fx or ____Gy/___fx
☐ CTV2 50 Gy or ____Gy	☐ CTV2 59 Gy/1.7fx or ____Gy/___fx
☐ Other ____Gy	☐ Other ____Gy/___fx

Plan Parameters:
Beam Energy: ☐ 6x ☐ 10x ☐ 6 MV (IMRT) ☐ As planning dictates
Density Correction: ☐ On or ☐ Off
Tx Devices: ☐ MLC/block ☐ Bolus ☐ hard block ☐ open fields

Considerations: ☐ Previous tx ☐ Pacemaker ☐ Multiple tx sites ☐ Concurrent chemo ☐ Special Procedures
Medical Necessity _____

*(Special Treatment procedures include: Hyperfractionation (BID treatment), brachytherapy, planned combination with chemotherapy or other combined modality therapy, stereotactic radiotherapy, radiation response modifier, IMRT, retreatment of same site, concurrent multiple site treatment, any other special time-consuming treatment plan)

Other Instructions: _____

Staff Physician/Date _____

Reporting

Patient Name			John Doe		MRN	12345		
Site:			Head and Neck					
Plan			Composite					
Prescriptions (Gy)			PTV					
		Total	60					
ROI	Margin (mm)	Volume (c.c)	Goal	Objective Dose (Gy)	Meet Goal			
PTV		100.0						
Plan		95.0	95% Vol > Rx(t)	60.0	YES	95% Vol =	60.0	Gy
		99.0	99% Vol >93% Rx(t)	55.8	YES	99% Vol =	58.0	Gy
		20.0	20% Vol ≤ 110% Rx (t)	66.0	YES	20% Vol =	12.0	Gy
		10.0	%Vol≥110% Rx(t)	66.0		Vol=	10%	%
Cord(M)	2		0.1 cc Vol ≤ 50Gy		YES	0.1 cc Vol=	30.0	Gy
Brainstem(M)	2		0.1 cc Vol ≤ 55Gy		YES	0.1 cc Vol=	26.0	Gy
Chiasm(M)	0		0.1 cc Vol ≤ 50Gy		YES	0.1 cc Vol=	10.0	Gy
Parotid_RT(M)	3	25.0	Mean dose ≤ 26Gy		*	Mean dose=	30.0	Gy
Parotid_RT(M)<30Gy	3	12.0	% Vol of 30Gy ≤ 50%		YES	%Vol of 30Gy=	48.0	%
Parotid_RT(M)-P	3	10.0	Volume ratio outside PTV		YES	Vol=	40.0	%
Parotid_LT(M)	3	27.0	Mean dose ≤ 26Gy		YES	Mean dose=	12.0	Gy
Parotid_LT(M)-P	3	12.0	Volume ratio outside PTV		YES	Vol=	44.4	%

Patient Name			Pedro Prostate		MRN	23456		
Site:			Prostate					
Plan			Composite					
Prescriptions (Gy)			77.4					
ROI	Margin (mm)	Volume (c.c)	Goal	Objective Dose (Gy)	Meet Goal			
PTV		33.0						
		31.4	95% Vol > Rx	77.4	YES	95% Vol =	77.4	Gy
		32.7	99% Vol >93% Rx	72.0	YES	99% Vol =	77.4	Gy
		6.6	20% Vol ≤ 110% Rx	85.1	YES	20% Vol =	22.0	Gy
		1.0	%Vol≥110% Rx	85.1		Vol=	3%	%
Rectum Wall(M)	3		10 cc Vol ≤ 70Gy		YES	10 cc Vol=	65.0	Gy
Bladder Wall(M)	0		30 cc Vol ≤ 30Gy		*	30 cc Vol=	32.0	Gy
Femoral Heads(M)	0		0.1 cc Vol ≤ 55Gy		YES	0.1 cc Vol=	41.0	Gy

Fig. 2. Examples of an intensity-modulated radiation therapy (IMRT) dosimetry summary for head-and-neck and prostate cancer cases using a spread sheet with predefined treatment goals (provided with permission of the Department of Radiation Oncology, University of Florida).

Current ASTRO Practice Guideline

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Modena
Policlinico

REVIEW ARTICLE

American College of Radiology (ACR) and American Society for Radiation Oncology (ASTRO) Practice Guideline for Intensity-modulated Radiation Therapy (IMRT)

Alan C. Hartford, MD, PhD, James M. Galvin, DSc,† David C. Beyer, MD,‡ Thomas J. Eichler, MD,§ Geoffrey S. Ibbott, PhD,‖ Brian Kavanagh, MD,¶ Christopher J. Schultz, MD,# and Seth A. Rosenthal, MD***

Am J Clin Oncol, 2012

Patient-specific QA

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Karolinska University Hospital

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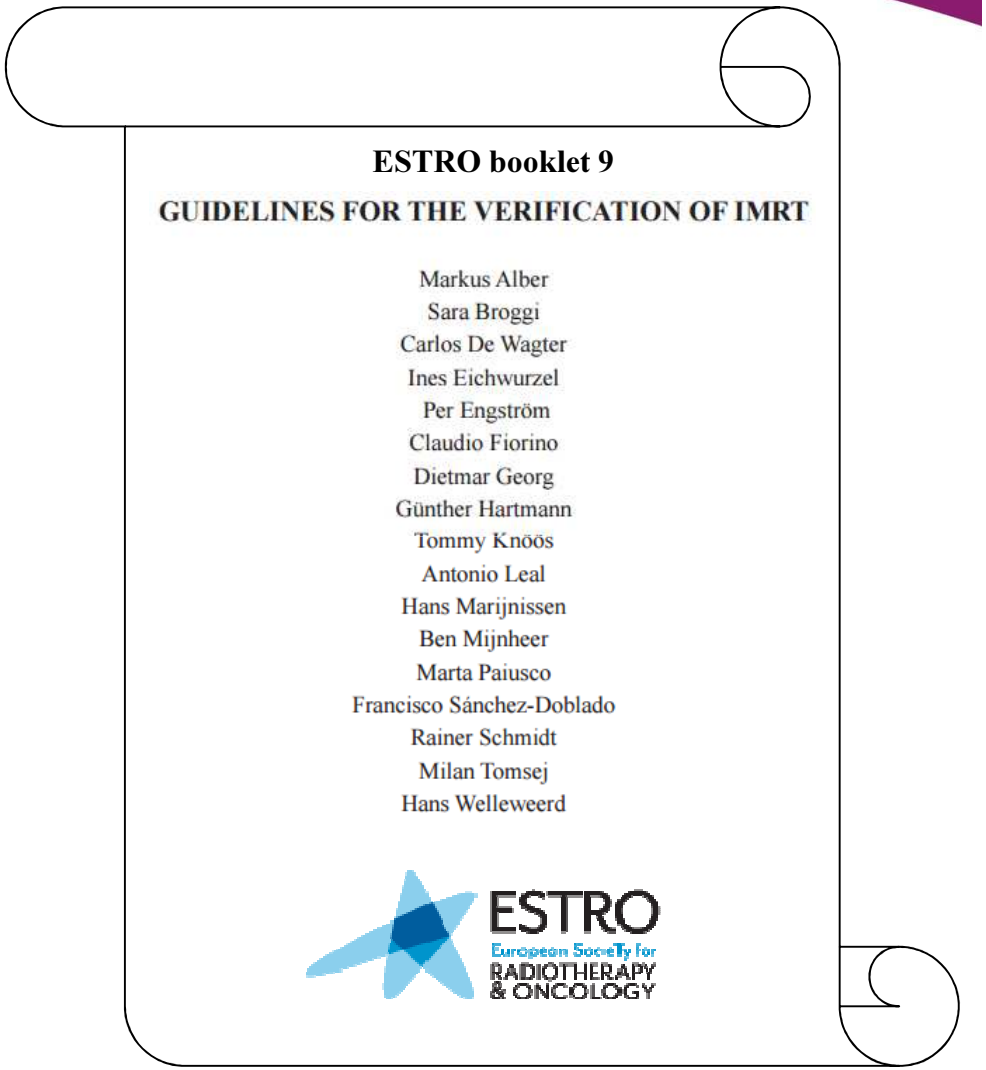
ESTRO School

Contents

- What's special about IMRT?
- IMRT verification systems
- Data analysis: the gamma index
- The value of patient-specific QA



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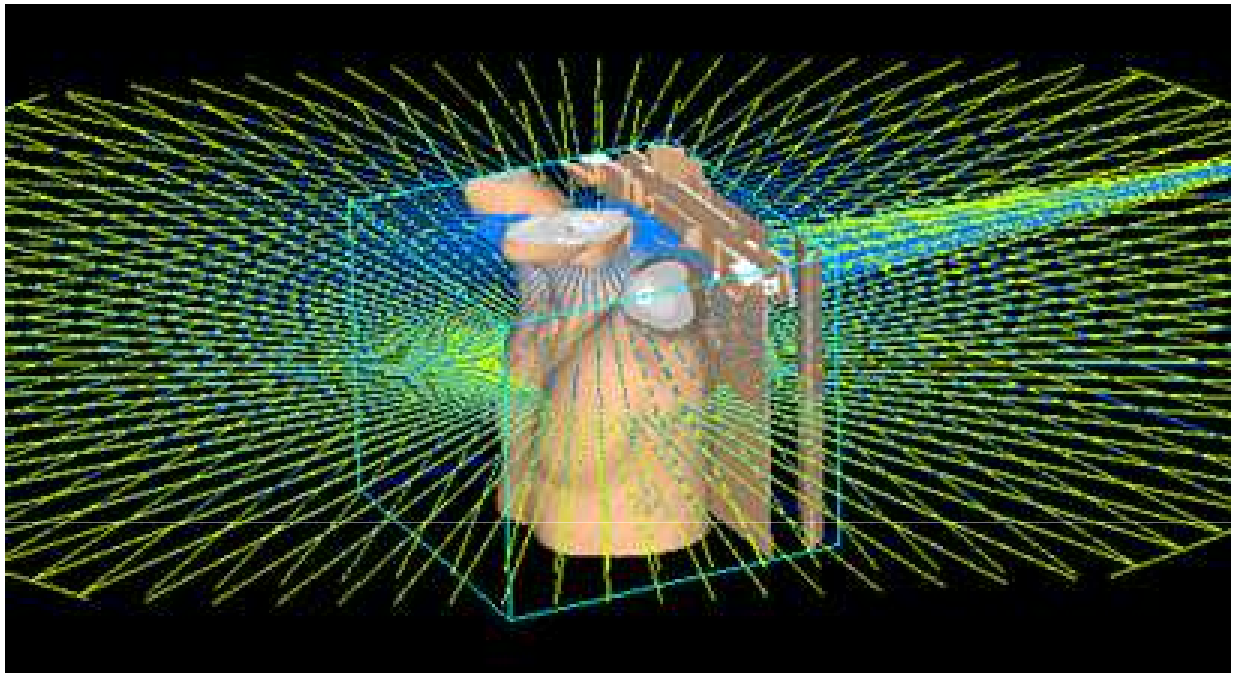
QA in the 3D-CRT era

- Successful radiotherapy requires correct delivery of planned dose
- Achieved through commissioning of treatment-planning system (TPS) and treatment machines
- Stable performance of machines monitored through a quality assurance (QA) programme
  - Absolute and relative dose
  - Collimator positions
- Plan check routines make sure patients get correct treatment plans
- Patient-specific QA an option but not necessarily a requirement

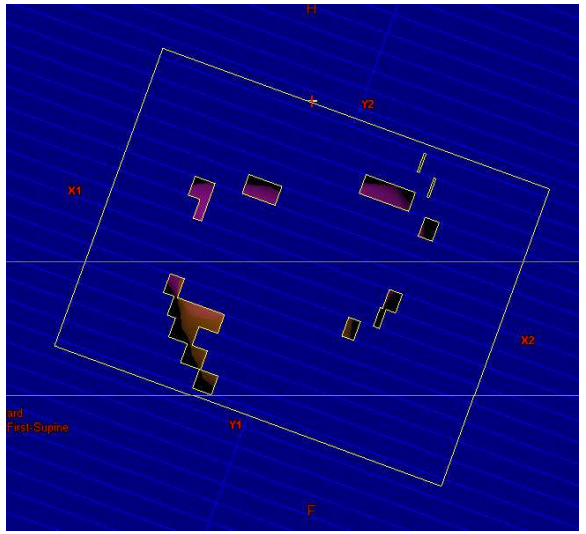


WHAT'S DIFFERENT ABOUT IMRT?

Modulation

Total dose delivered by multiple small beamlets

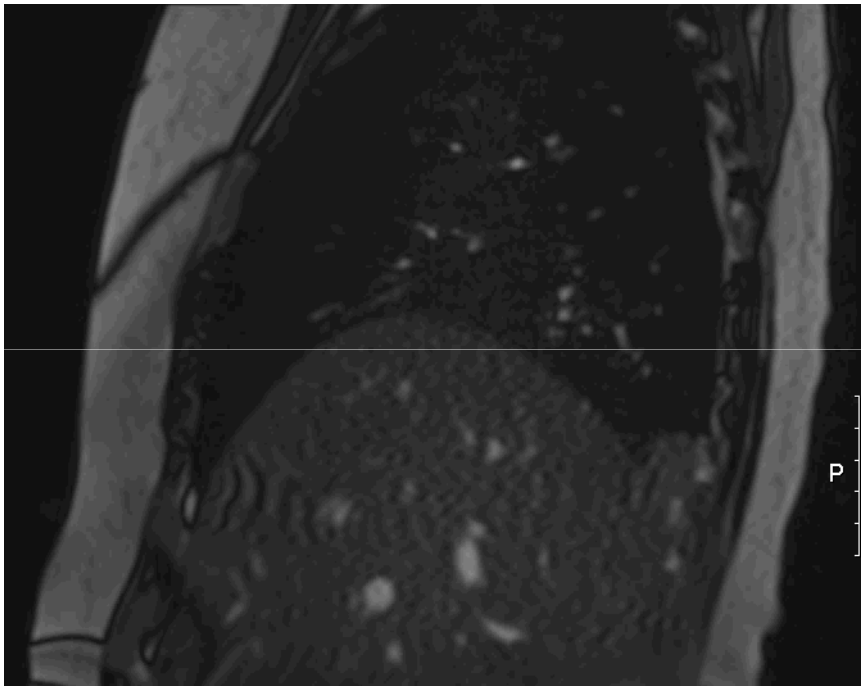
1. Output factor for very small fields difficult to measure/model
2. Field penumbra directly in the target
3. Inter-leaf leakage exposing the target
4. Secondary dose calculation complicated
5. Interplay effect

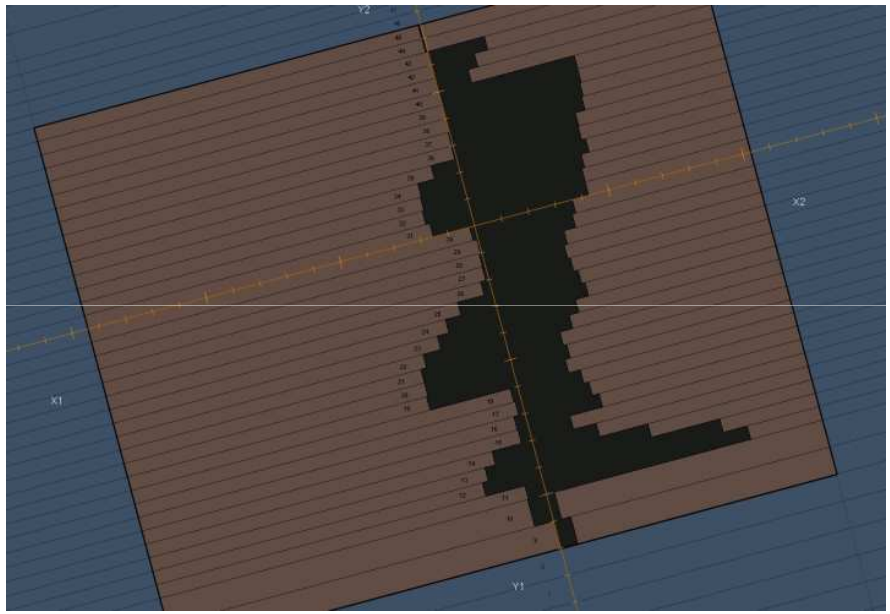


Limitations in beam modelling more important for IMRT.

Monte Carlo beam model could address 1-3 above.

Interplay effect



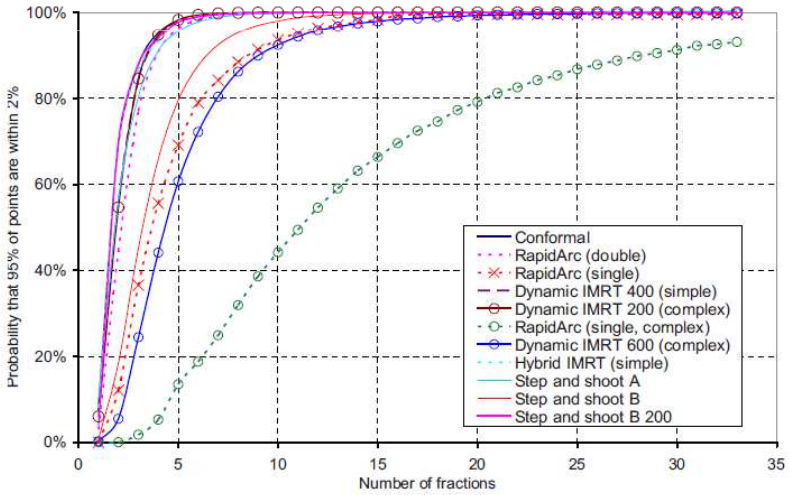


Interplay effect

- Total dose distribution relies on different areas of the target being selectively exposed at different times
- Intrafraction motion would lead to the dose accumulating in a different distribution than planned

In reality, the interplay effect is rarely a problem:

- Over many fractions the dose averages out
- SABR: few fractions but longer delivery times (e.g. more breathing cycles)
- Very heavily modulated plans, single-arc VMAT
- Avoid by limiting modulation



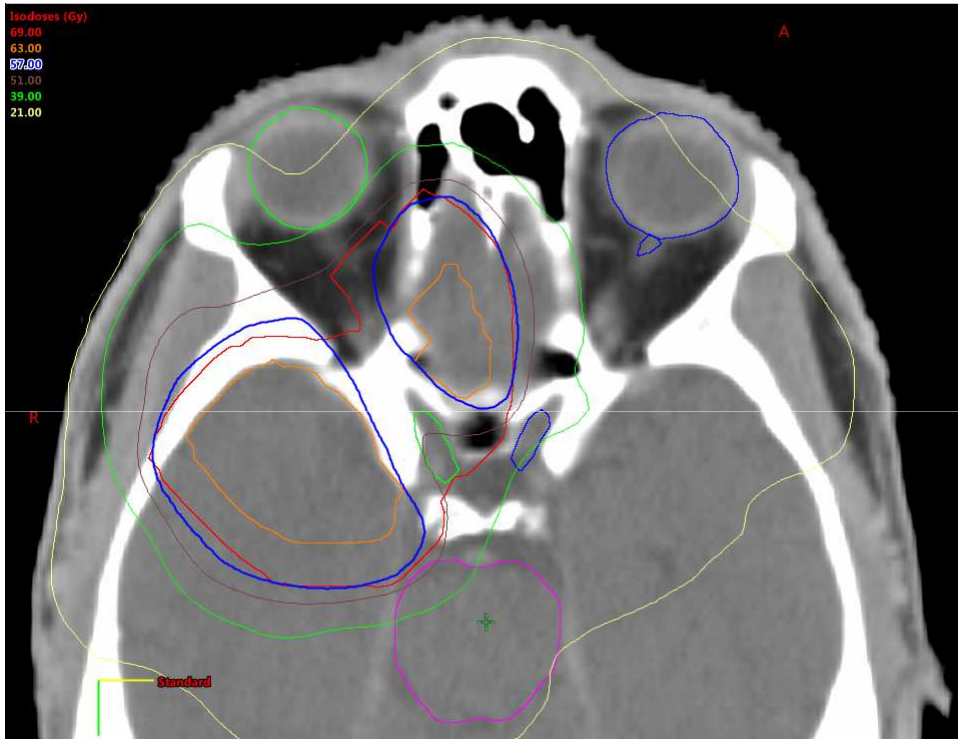
Court et al. MedPhys 2010

Static or dynamic delivery

- Step-and-shoot IMRT
  - Multitude of low-weighted beamlets
  - Quick ramp-up of accelerator performance required
- Sliding window IMRT and VMAT
  - Dose-rate, MLC motion and gantry motion need to be perfectly syncronised
  - Influence of gravity on MLCs
  - MLC QA, e.g. picket fence test
  - Analysis of MLC log files
- Standard IMRT/VMAT plan measured regularly on phantom/array

Complex modality

- Potentially high dose wrapping close around critical organs
- Sensitive to set-up errors
- High accuracy in delivery of planned dose *particularly* important for IMRT
- Difficult for treatment staff to discover mistakes



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IMRT audit results

- Dose determination audits with anthropomorphic phantoms show , in the target volume, an agreement between different centres of:
  - About 3% (1 standard deviation) for 3D-CRT
  - Up to 8% (1 standard deviation) for IMRT
- 30% of clinics failed to deliver correct IMRT H&N plans (7%/4mm) according to Ibbot et al. (IJROBP 2008), due to:
  - Incorrect output factors and percent depth dose data
  - Inadequate modeling of the penumbra at MLC leaf ends
  - Incorrect application of QA calculations or measurements
  - Inadequate QA of multileaf collimator
  - Incorrect patient positioning
  - Errors in treatment planning software

Why patient-specific QA?

The agreement between planned and delivered dose may depend on plan-specific parameters, like the level of modulation

Seems unavoidable at least until:

- Stable history of machine QC for dynamic MLC and gantry
- Monte Carlo dose calculation algorithm
- Convenient secondary dose calculation
- Extensive experience of high pass rates for patient-specific plan measurements
- New history of patient-specific QA needs to be aquired after new class solution is introduced

May be a legal requirement in your country

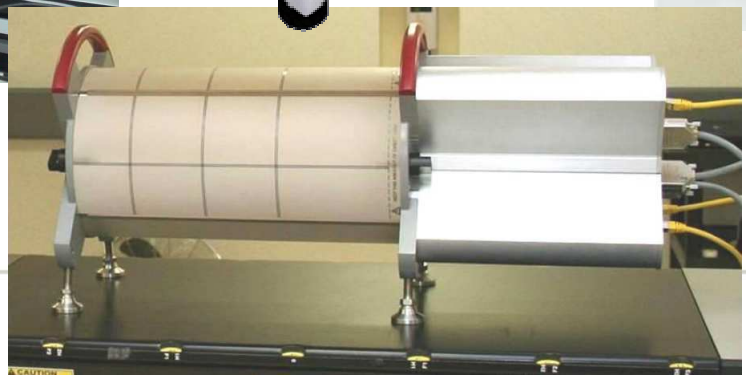
EURATOM directive 97/43

IMRT treatment plan verification strategies

- Single field- versus composite-field verification
  - Ease of evaluation and investigation
  - Both fill the purpose of plan verification
- 1D, i.e. point measurement: too simplistic
- 2D, i.e. film, detector arrays, EPID: most common
- 3D, i.e. gels and similar: less common
- Pre-treatment verification and/or in-vivo verification

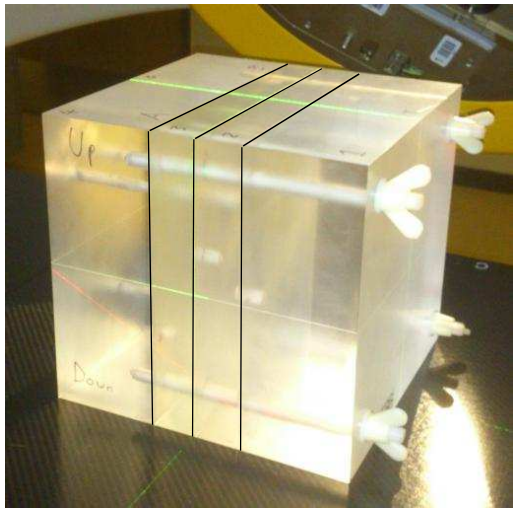
2D verification systems: detector arrays

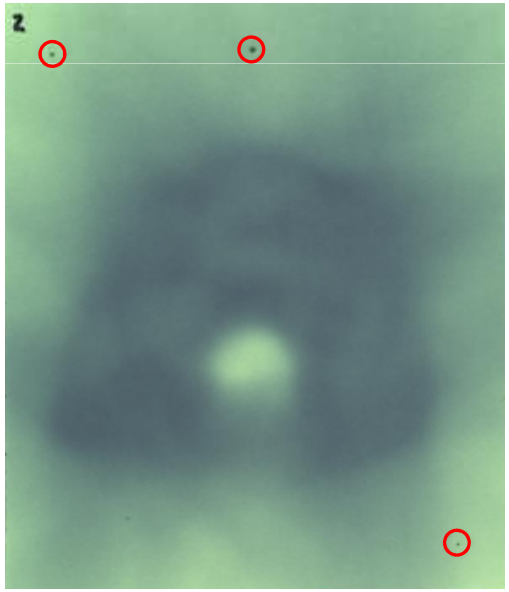
- Detector arrays can be integrated in a phantom or attached to the gantry
- Patient plan copied, unmodified, onto a phantom scan and the dose calculated. This 'hybrid' plan is compared to measurement.
- Convenient, large sample of measurement points

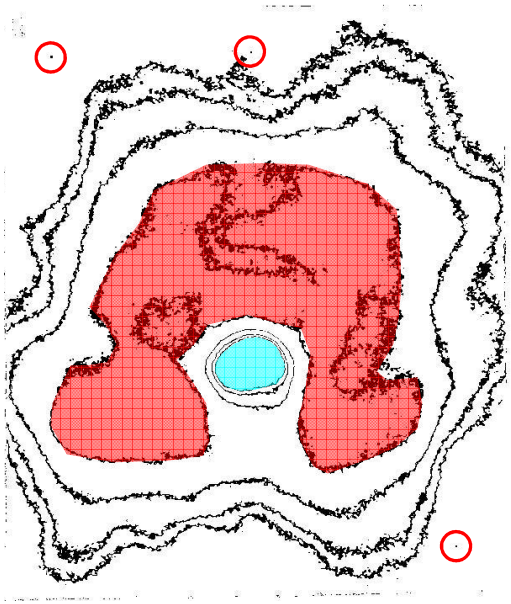


2D verification systems: Radiochromic film

- Radiographic film was used extensively at the dawn of IMRT
- Today radiochromic film more commonly used
- Great spatial resolution, less convenient than detector arrays
- Allows verification of steep dose gradients



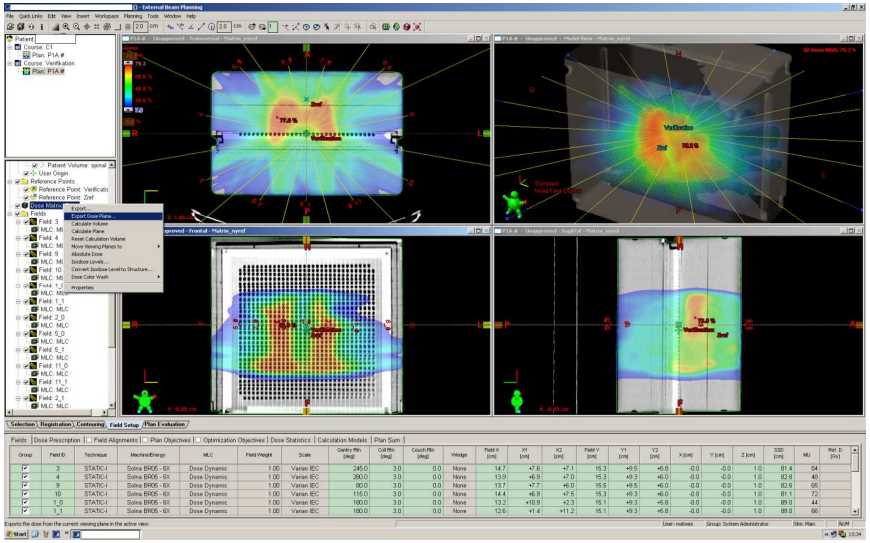


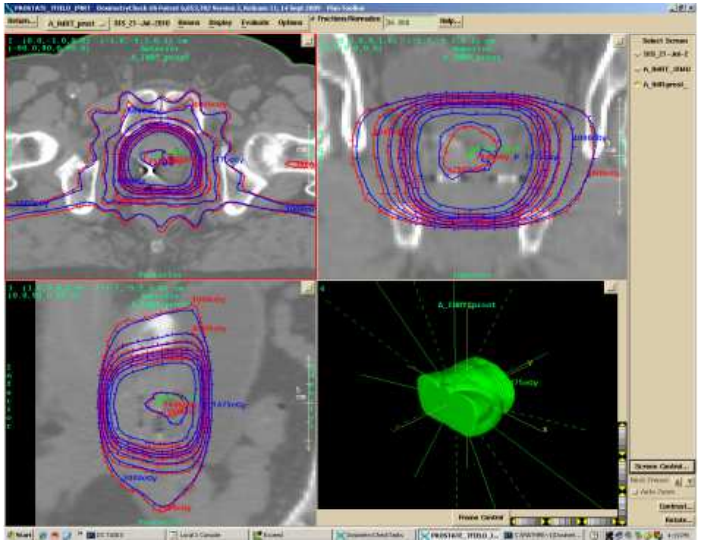


Courtesy Jonny Lee

2D verification systems: EPID

- The electronic portal imaging device (EPID) can be used for dose measurement, if correctly calibrated
- Higher resolution than detector arrays, not independent of gantry rotation
- Quick and convenient measurement, potentially integrated analysis tools
- Can also measure the exit dose during treatment: 3D in-vivo dosimetry





3D verification systems

A few 3D dosimetry systems available:

- Ferrous gel (Fricke)
- Polymer gels (PAG)
- Radiochromic plastics (Presage)

Read-out with MRI or optical CT

Takes time and requires specific equipent and expertise

Suitable for commissioning/end-to-end tests rather than patient-specific QA

Vandecasteele PhysMedBiol 2013

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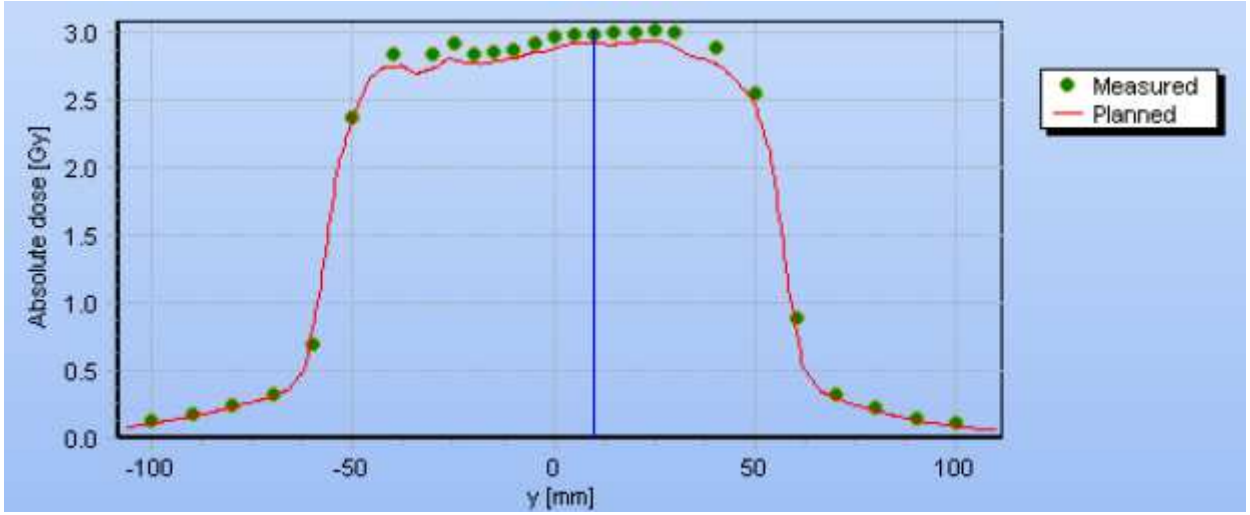
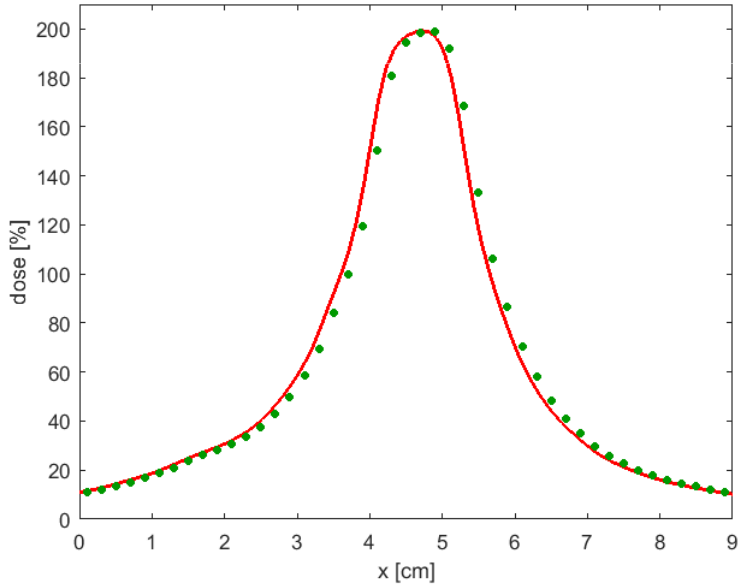
Data analysis: local dose difference

- IMRT verification measurements need to be compared to planned 3D dose distributions
- Agreement can be assessed qualitatively by overlaying isodose lines or comparing dose profiles
- Quantitative evaluation of many measurement points?



Data anlysis: DTA

- Dose difference can be large at steep dose gradients for realistic phantom set-up uncertainties
- Distance to agreement (DTA) between pixel/voxel values a more relevant measure



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Data analysis: gamma index

A gamma analysis compares each calculated value to all measured values, both in terms of dose deviation and DTA.

$$\Gamma(r_m, r_c) = \sqrt{\frac{r^2(r_m, r_c)}{\Delta d_m^2} + \frac{\delta^2(r_m, r_c)}{\Delta D_m^2}}$$

- r_m= point in measured distribution
- r_c= point in caculated distribution
- $r(r_m,r_c)$= distance between r_m and r_c
- $\delta(r_m,r_c)$= dose deviation in r_m to r_c
- Δd_m= DTA criterion
- ΔD_m= dose deviation criterion

For each r_m, the r_c with the lowest gamma value is identified.

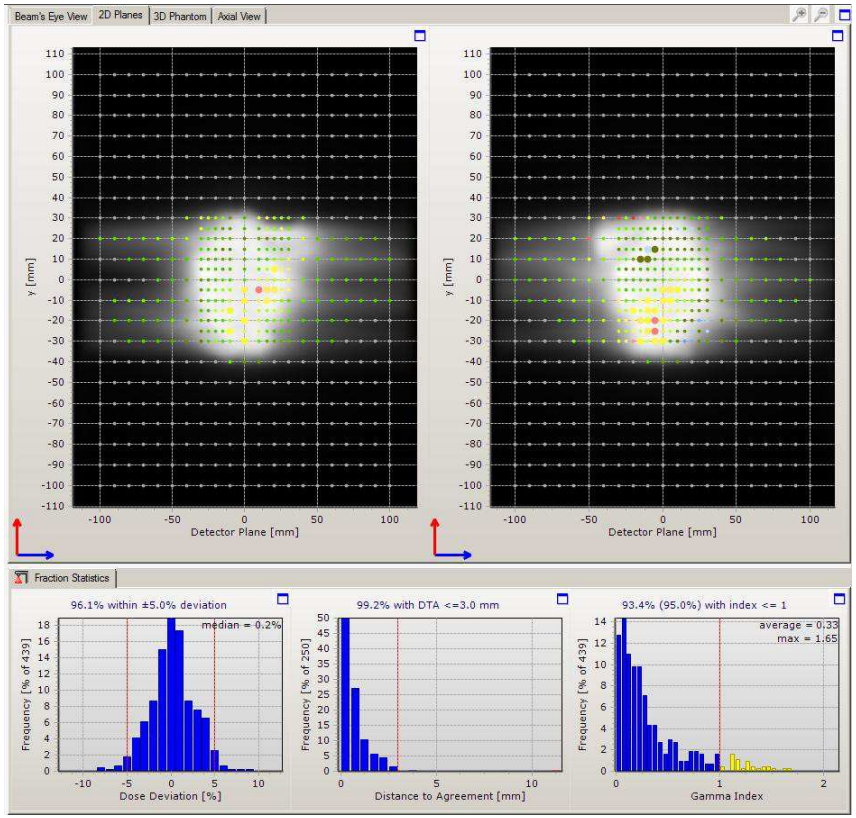
$$\gamma(r_m) = \min\{\Gamma(r_m, r_c)\} \forall \{r_c\}$$

All r_m with $\gamma \leq 1$ have passed the combined gamma criterion. The percentage of acceptable γ-values can be used as an over all agreement measure.

Gamma analysis considerations

- Local or global dose deviation can be used
  - Global: deviation expressed as percentage of maximum or prescribed dose
  - Local: deviation expressed as percentage of local dose
  - Global dose deviation more forgiving, especially in low-dose region
- Gamma analysis fails extensively in the low-dose region, but this may not be of interest: cut-off often applied
- Can be performed in 2D or 3D: slightly better pass rates with 3D
- Adjustment for the linac output of the day?
- Adjust spatial registration of dose distributions for best result?

Example



- 5%/3mm gamma analysis of VMAT plan
- 2D analysis with the Delta4 system
- Low-dose cut-off
- Pass rate: 93.4%
- Failed the 95% limit of the clinic

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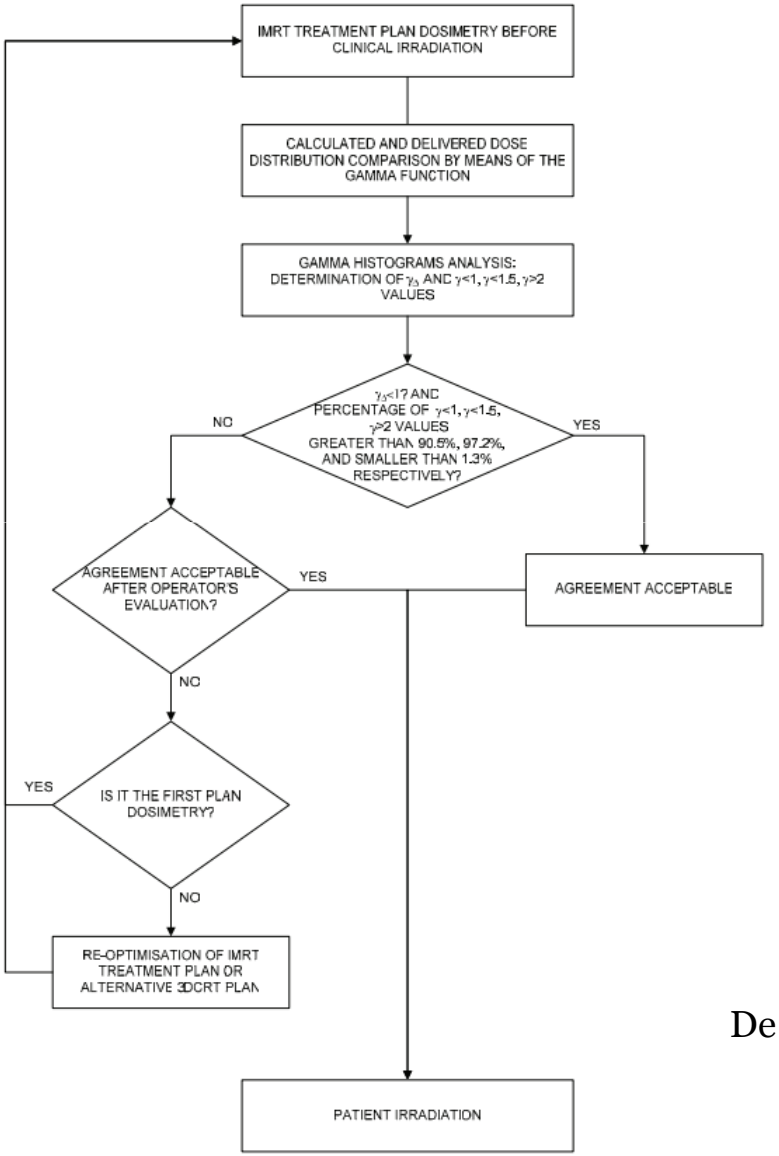
Decision protocol



De Martin et a. RadiotOncol 2007

Comparison between QA solutions

TABLE III. Comparison between calculated and measured dose distributions. Percentage of points satisfying Γ (3%, 3 mm) <1: Statistics for all plans and all dosimetric systems. The average pass-rate obtained over seven ERGO++ and seven Oncentra plans optimized for the same treatment cases is shown separately, and indicated as comparative study.

	ERGO++				Oncentra Vmat			
	All plans	Average (%) Comparative study	Max (%)	Min (%)	All plans	Average (%) Comparative study	Max (%)	Min (%)
EDR2	95.1	96.1	100.0	83.0				
EBT2	91.1	92.9	98.5	80.0	91.7	92.1	98.9	85.2
MAPCHECK	97.4	98.0	100.0	92.0	96.3	97.8	99.7	86.2
DELTA4	99.3	99.4	100.0	93.0	95.4	96.2	100.0	89.3
SEVEN29	99.6	99.8	100.0	99.1	98.0	97.5	100.0	88.0

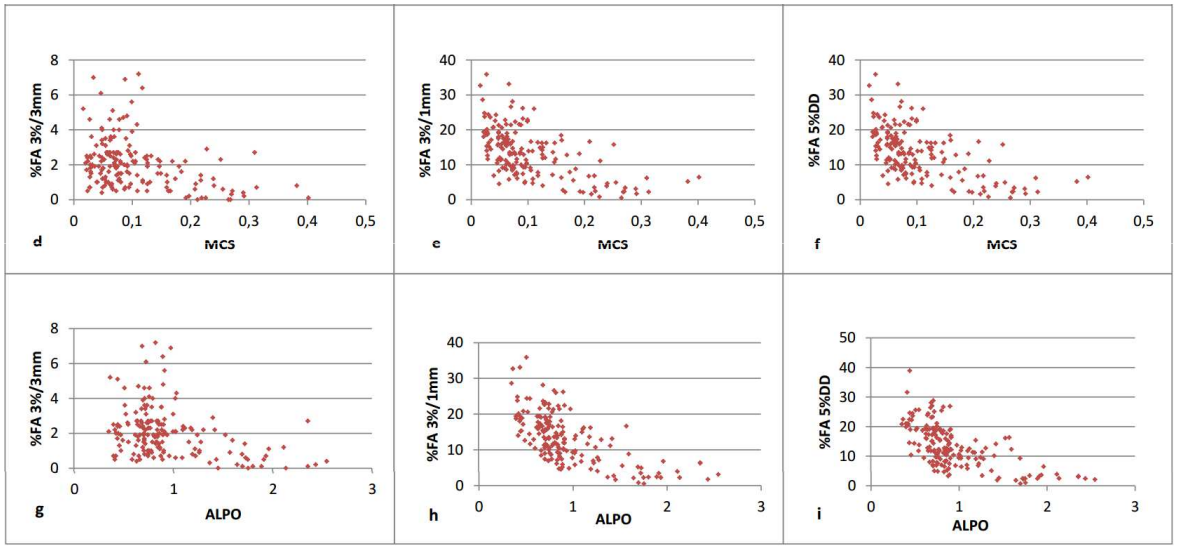
Masi et al. Medical Physics 2011

Gamma analysis physically relevant?

- What do we want to detect with patient-specific QA?
- Do we have confidence in our MLCs?
  - Perhaps better addressed with machine QA
  - Thourough commissioning of IMRT with challenging plans and several measurement systems
  - Constancy checks with challenging plan
- Do we have confidence in our dose calculation algorithm?
  - Aware of limitations
  - Impact depends strongly on the individual plan
  - The gamma index seems to correlate with plan complexity/modulation
  - Gamma pass rates can probably highlight challenging cases

Robust IMRT plans

- The Gothenburg group is looking at correlations of the gamma index to the modulation complexity score (MCS), and the average leaf pair opening (ALPO)



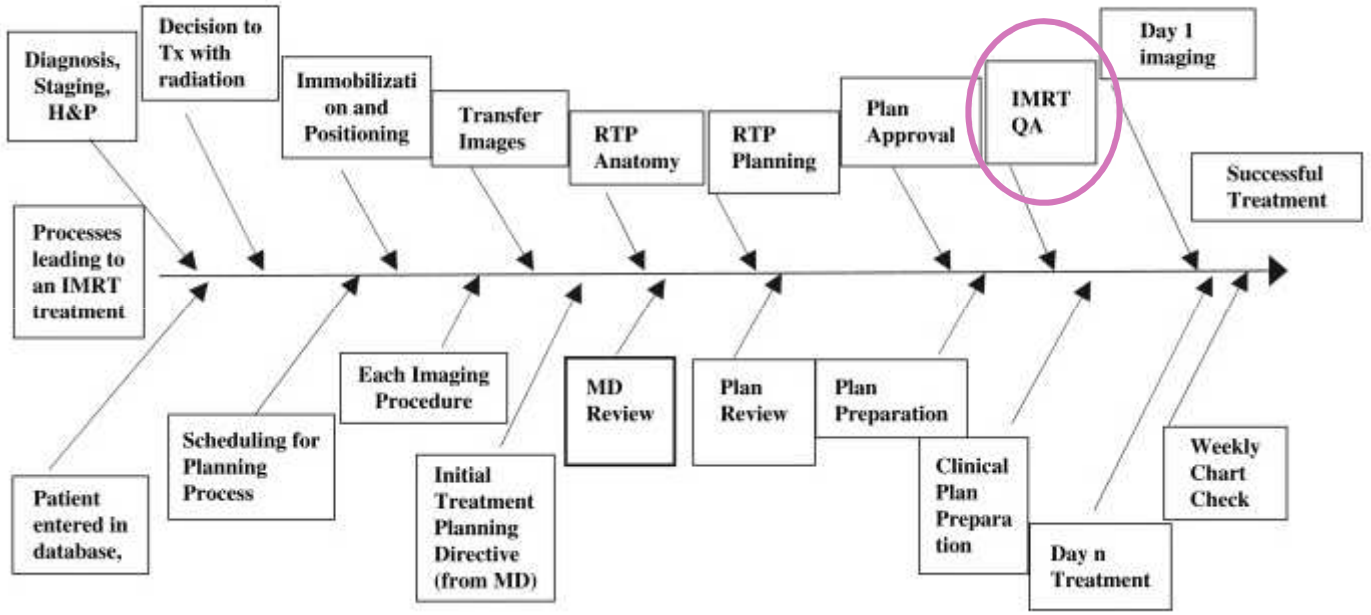
Olofsson, MSc thesis 2012

- For purposes of robustness, don't use more modulation than necessary
- Larger beamlets result in a better agreement between planned and delivered dose, and mitigates the interplay effect

Gamma analysis clinically relevant?

- Studies have shown that clinically relevant parameters do not correlate well with gamma pass rates (Nelms et al. MedPhys 2011, Carver et al. RadiatOncol 2011)
- Dose deviation tolerance usually at a few percent
- Tumour control probability depends strongly on the dose deviation
- Comparison of isodoses is important for critical organs at risk
- Not sensitive to small systematic differences

One piece of the puzzle

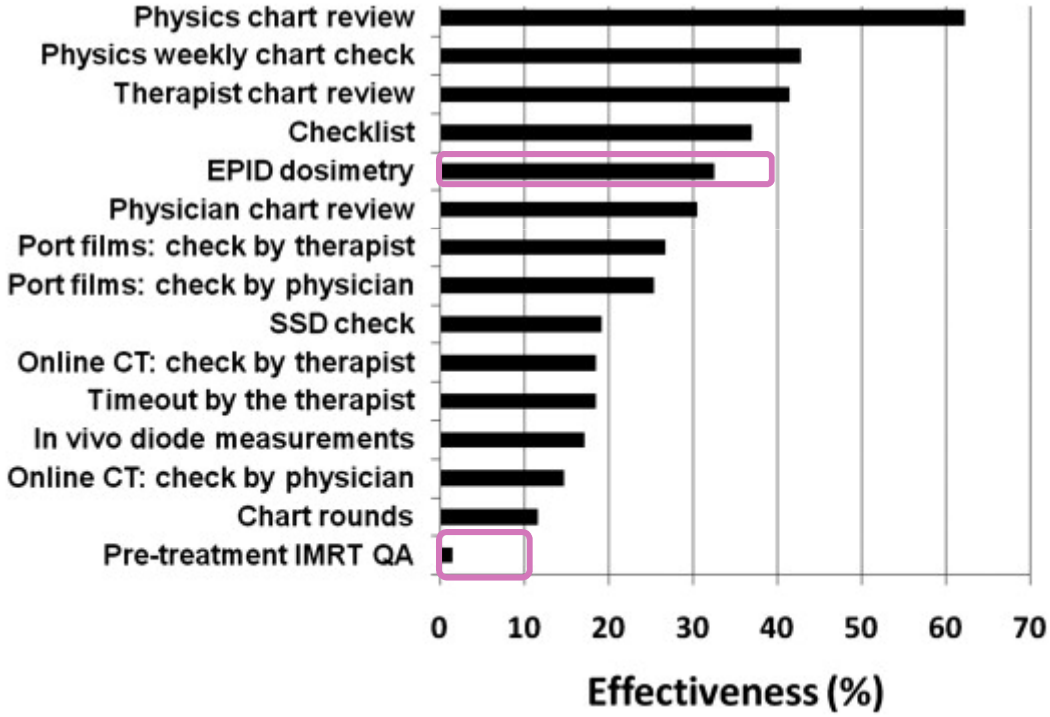


Huq et al. IJROBP 2008

Error-detection efficiency

Few errors are spotted using pre-treatment IMRT QA.

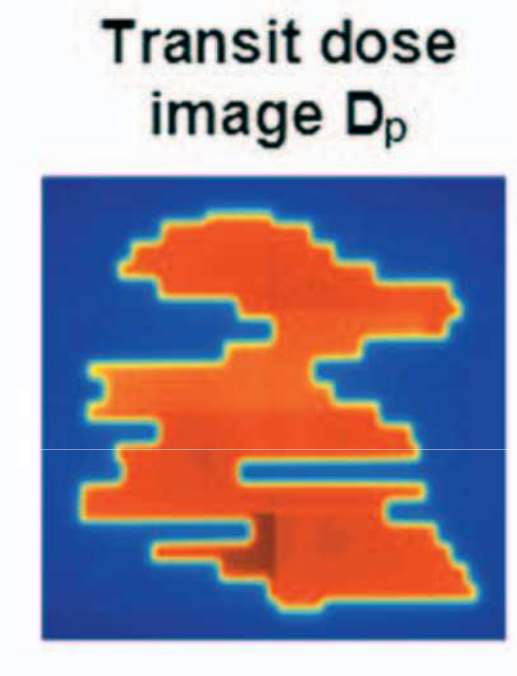
EPID-based in-vivo dosimetry ranks highly, on the other hand.



Ford et al. IJROBP 2012

Transit dosimetry

- Transit dose measurement with the electronic portal imaging device (EPID)
- 2D: model to convert gray scale image to portal dose
- 3D: Reconstruction of dose in 3D using CBCT
- In-vivo dosimetry using only the equipment integrated on the linac, using the treatment field itself
- Commercial solutions being developed
- Generates a huge amount of data to be analysed
- Do we know how to address discrepancies?



Nijsten MedPhys 2007

Conclusions

- Ideally, in-vivo plan verification should be performed for all techniques
- IMRT potentially pushes the delivery- and planning equipments to their limits
- Confidence in the whole chain should be built through, at least, patient-specific pre-treatment plan verification
- Convenient 'IMRT QA' systems exist
- Gamma analysis is useful for a high-throughput QA programme
- Limitations of the gamma index require attention to dose deviation in selected cases
- Consider patient-specific QA as one among several important components of the QA programme

Conclusions cont.

After initial successful learning phase, the QA programme might consist of:

- Regular machine QC, including dynamic MLC tests
- Monthly challenging standard plan measurement
- Secondary dose calculation of all plans
- Ideally, if possible, in-vivo dosimetry for all patients
- For new class solutions: patient-specific pre-treatment measurements for some time

Guidelines

ESTRO Booklet 9, Guidelines for the verification of IMRT, 2008

http://www.estro-education.org/publications/Documents/Booklet9_Physics.pdf

IPEM Project 527, Guidance for the Clinical Implementation of Intensity Modulated Radiation Therapy, IPEM 2008

AAPM Task Group 120: Dosimetry tools and techniques for IMRT. MedPhys. 38, 1313-1338, 2011

Questions

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WWW.ESTRO.ORG/SCHOOL

Geometric uncertainties in IMRT

Koen Tournel - Physicist
Radiotherapy Department UZ Brussel

ESTRO School

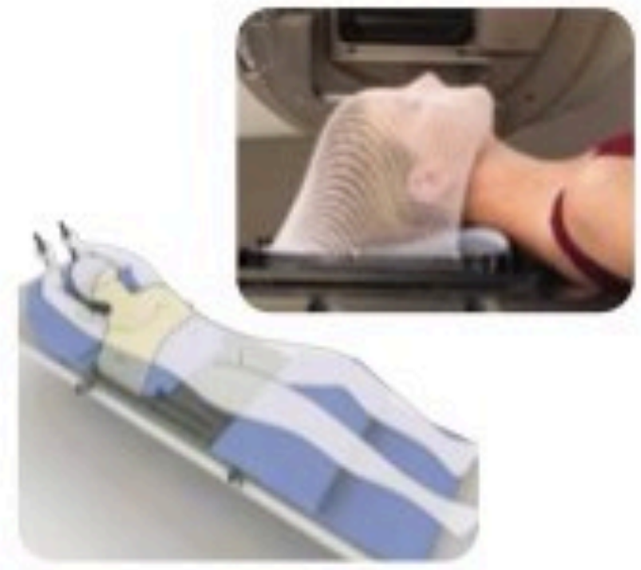
‘The snapshot paradigm’

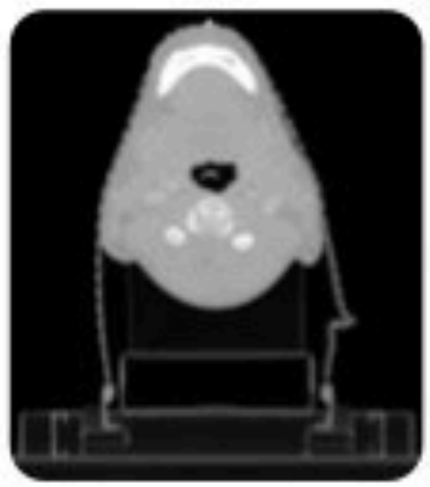
Simulation

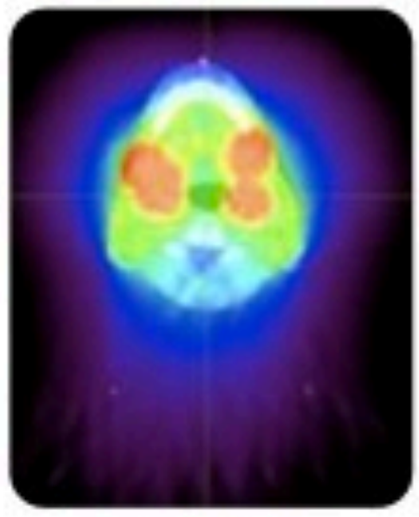
Planning CT

Treatment Planning

Treatment

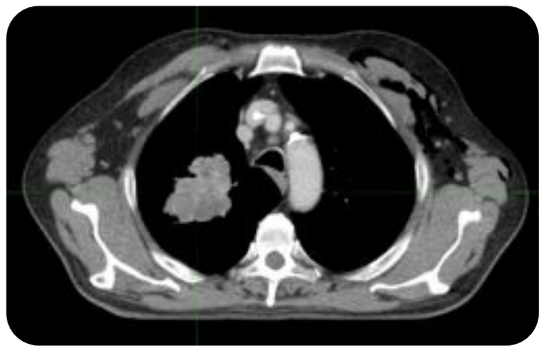


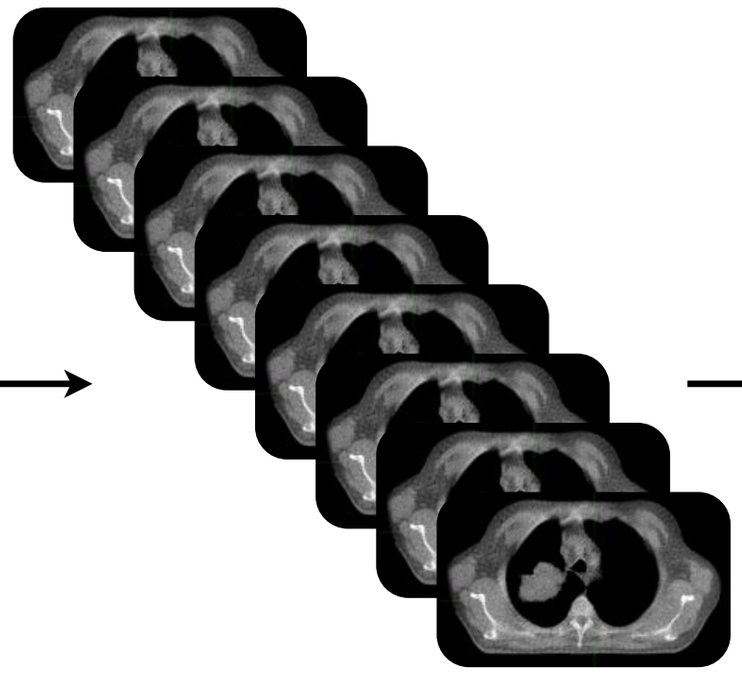




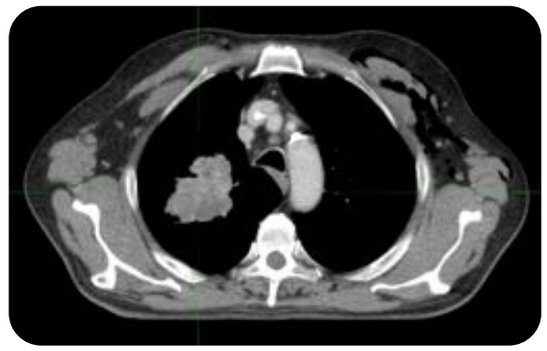
Treatment fractions

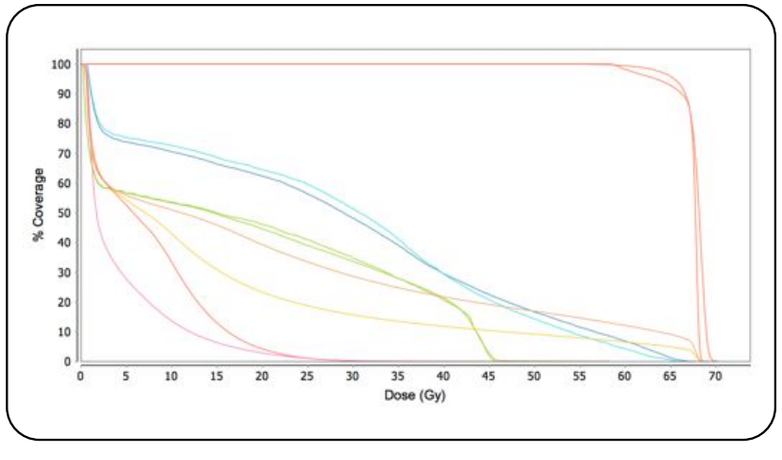
Start

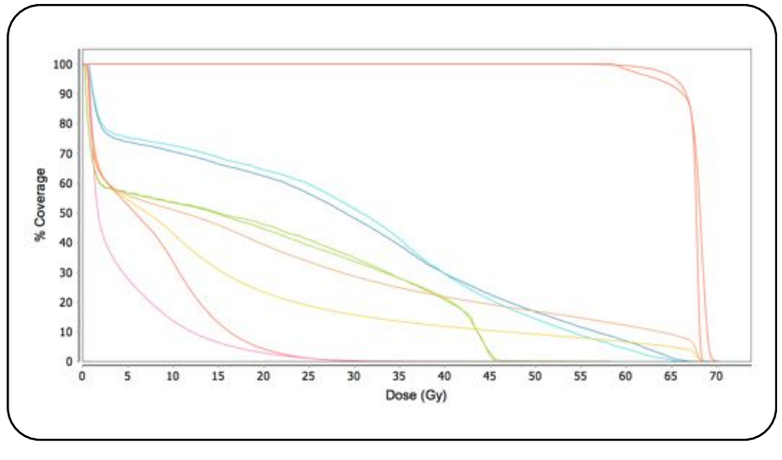




End





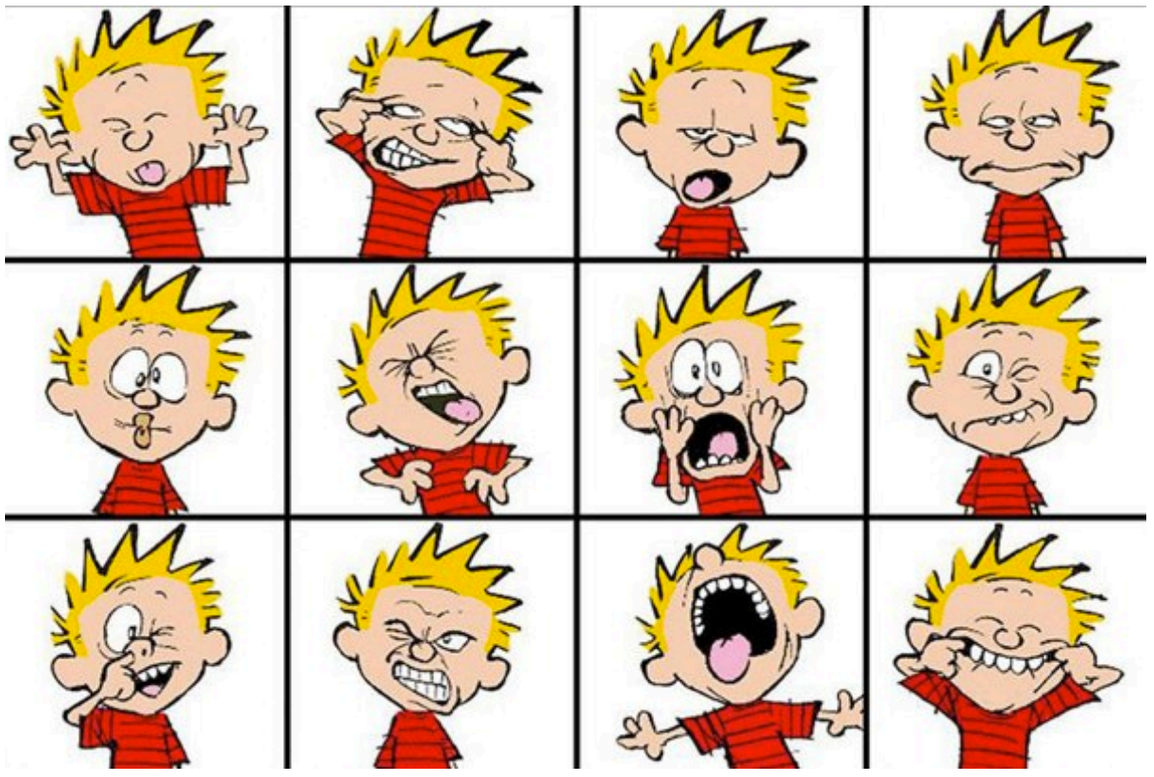


Problem

- IMRT planning is based on a -well defined and researched - snapshot of reality.
- This snapshot has to be reproduced during the entire treatment chain.
- This ain't just gonna happen....we can't be that lucky

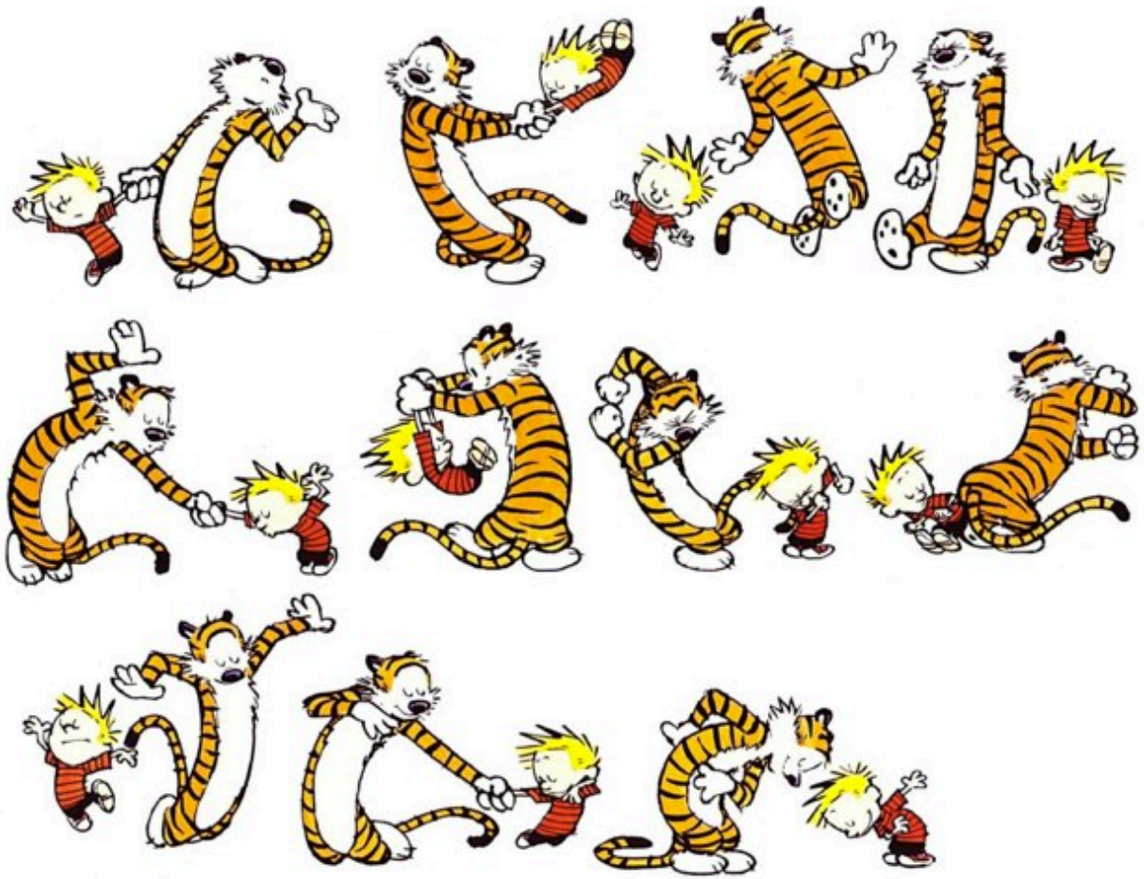
Types of uncertainties

- Movement
  - (Rigid)Interfractional (positioning errors)
  - The position/shape of our tumor will vary day by day



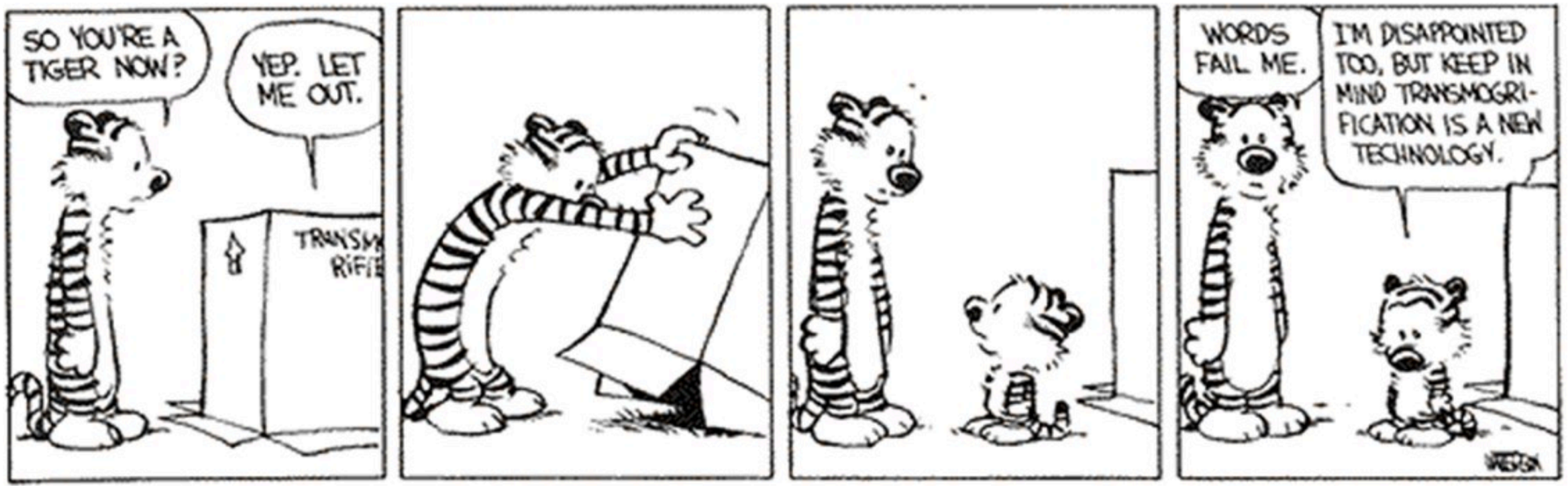
Types of uncertainties

- Movement
  - Intrafractional (periodic or non-periodic)
  - Tumor and OAR are moving while we are treating them

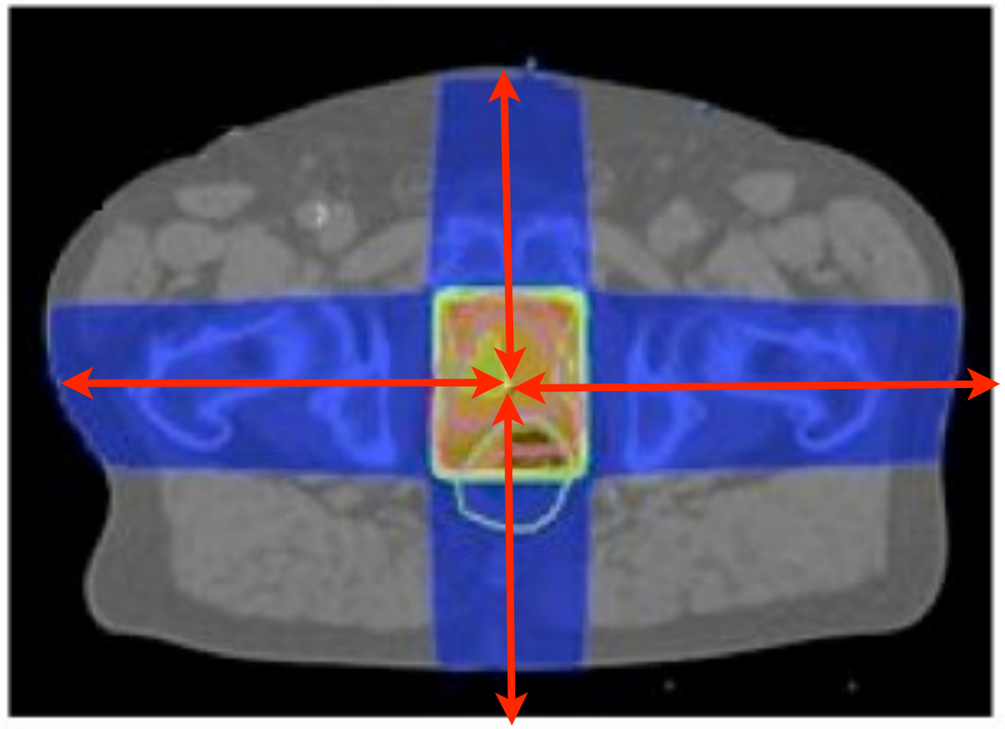


Types of uncertainties

- Deformation
  - Tumors and OARs will change shape



What do we do in normal conventional RT?



Open fields, normalized at isocenter, MU scaled on beam axis.

Conventional RT

- For movement there's the PTV concept.
- Minimization through movement management
  - IGRT, off-line/on line protocols
  - Gating/tracking
- Dose delivery will not change a lot when the radiological pathlength of the central axis does not change a lot
- Robustness of the dose

Patient geometric uncertainties: homogeneous dose distributions

$$\mathbf{m_{ptv}} = \alpha\Sigma + \beta\sigma - \beta\sigma_{\mathbf{p}}$$

Systematic errors

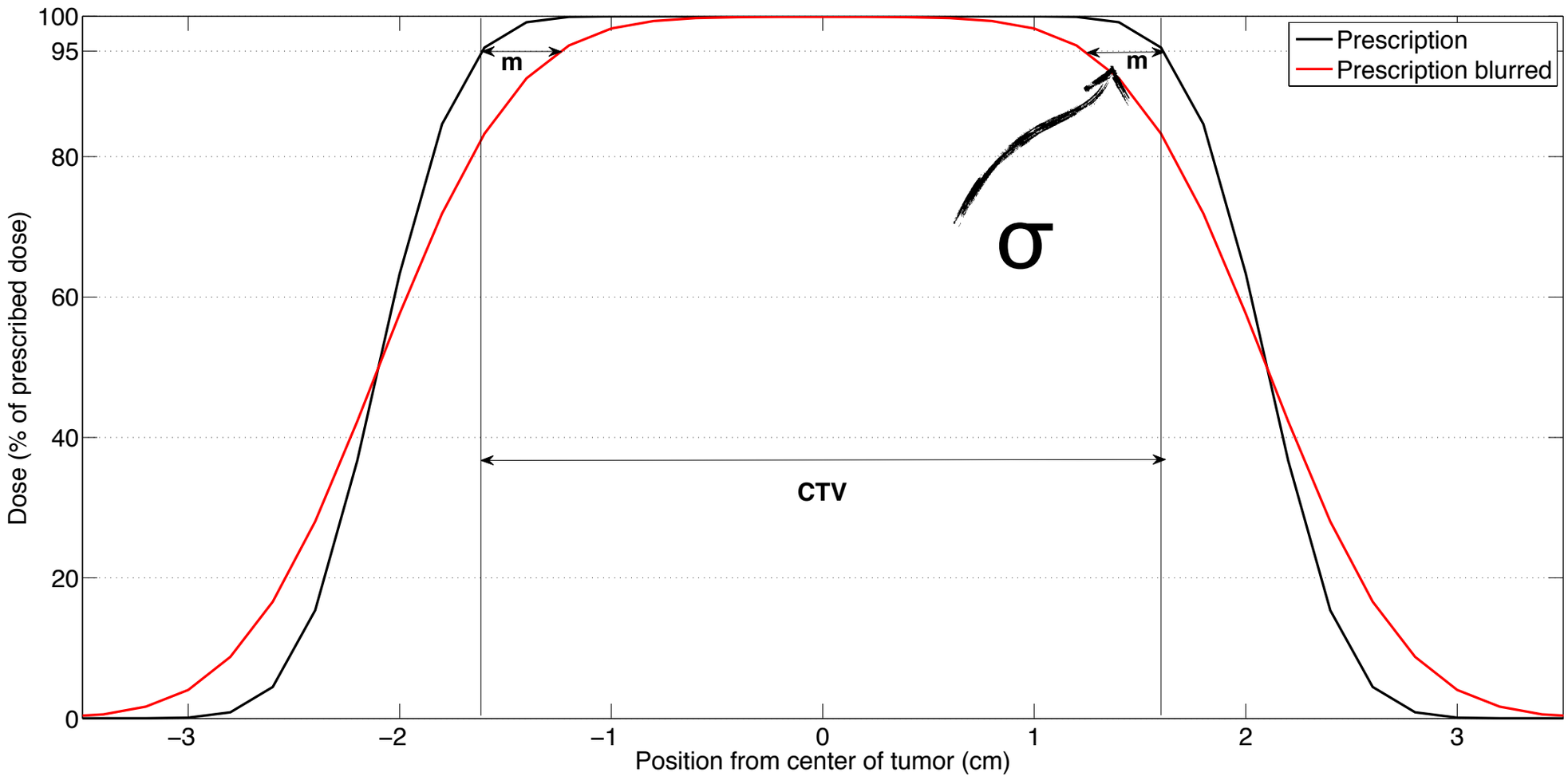
Random errors

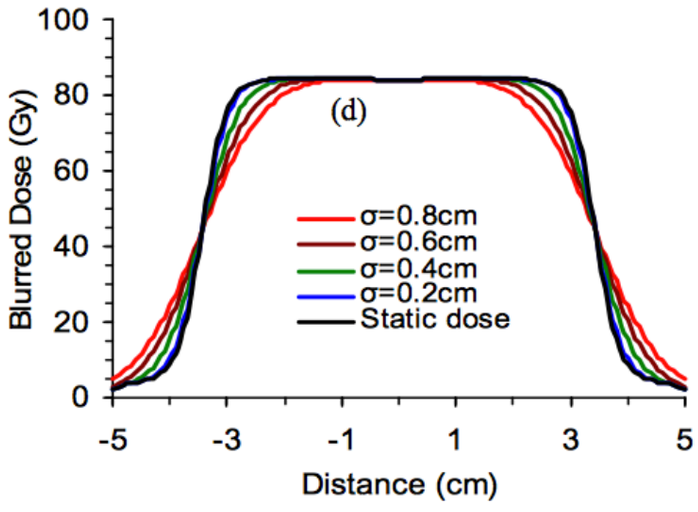
Shift

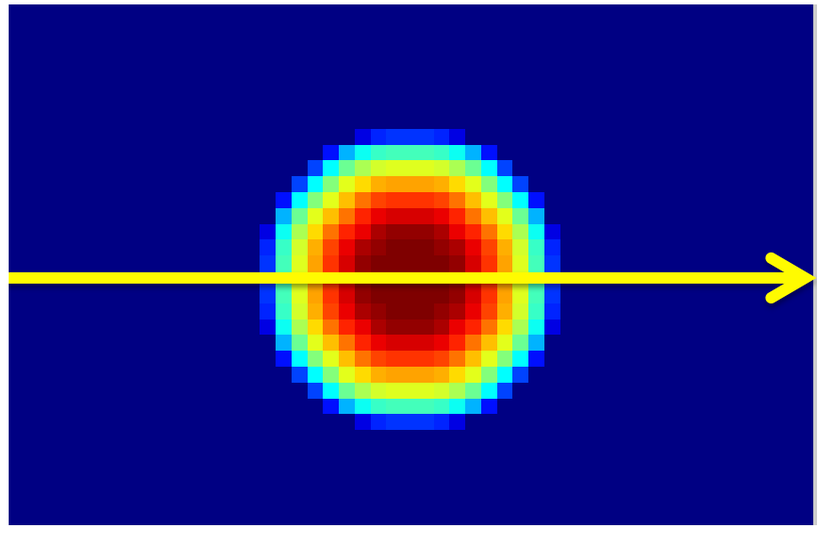
Smoothing

Assuming margins such that 90% of the population receives 95% of prescribed dose α=2.5 and β=1.64 (Van Herk et al)

effect of random errors - homogeneous precription

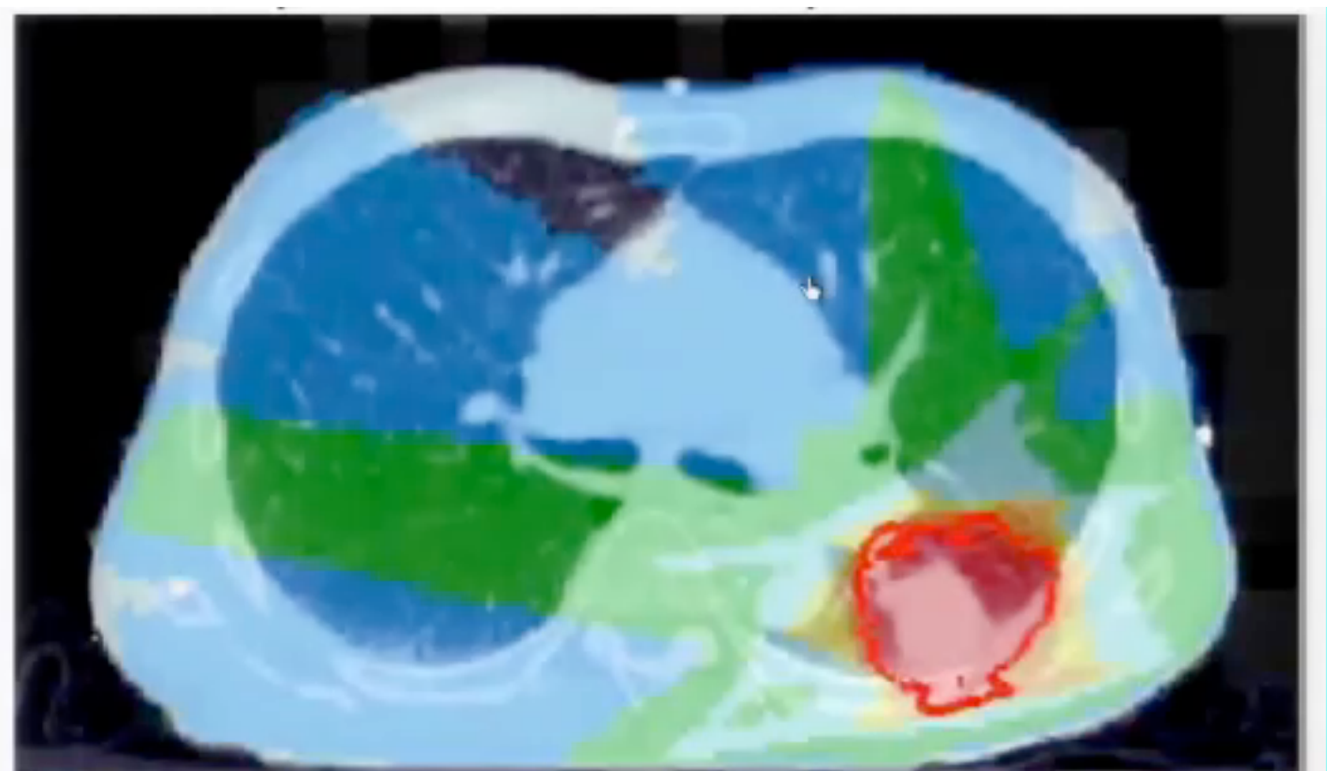






“Dose Cloud”

- Movement inside our nice, homogeneous dose region....robustness.
- In other phases dose will deform, but CTV will keep coverage



NO modulation

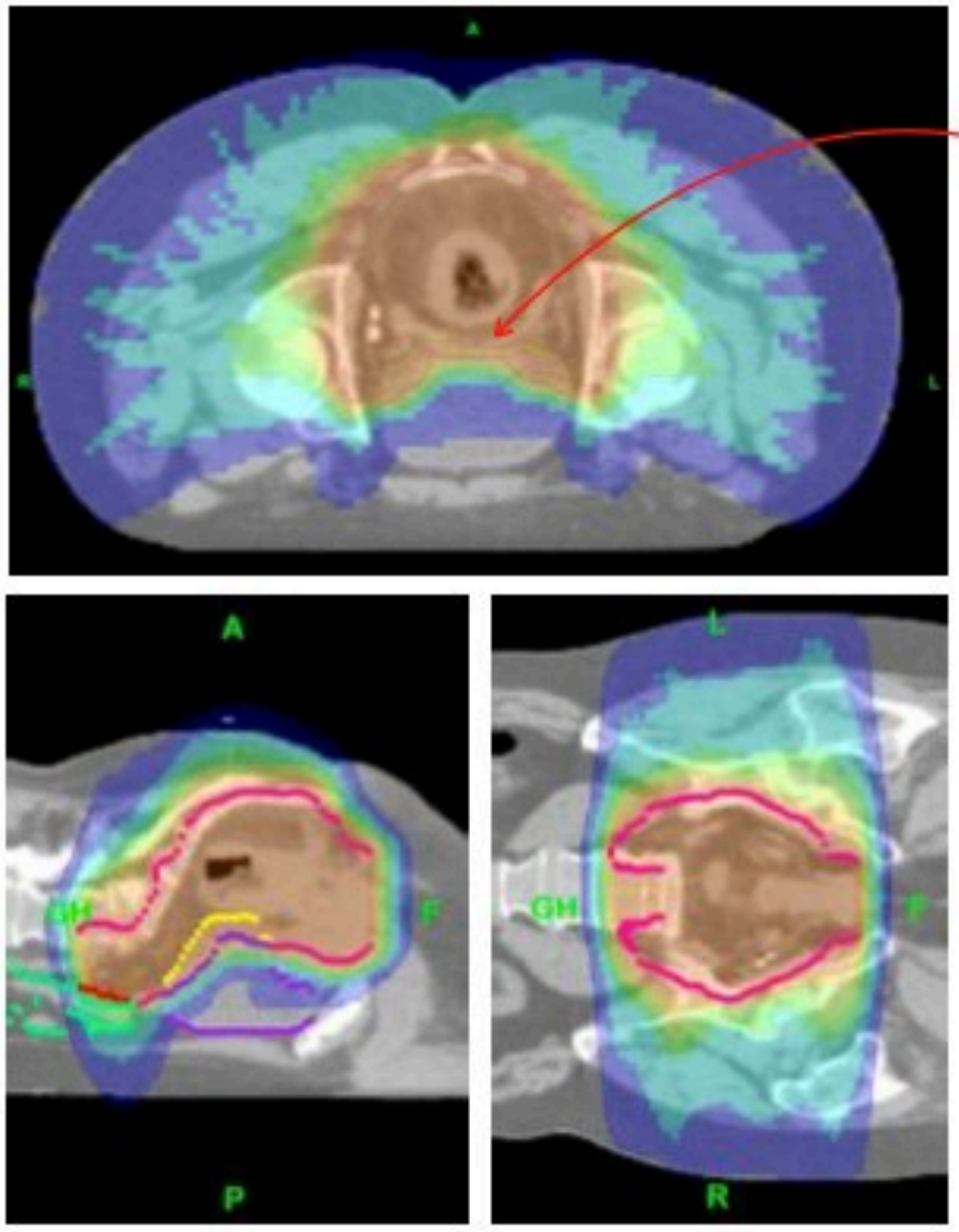
IMRT

- “More money, more problems”
- Beamlets are optimized on one particular pathlength, on particular scatter conditions

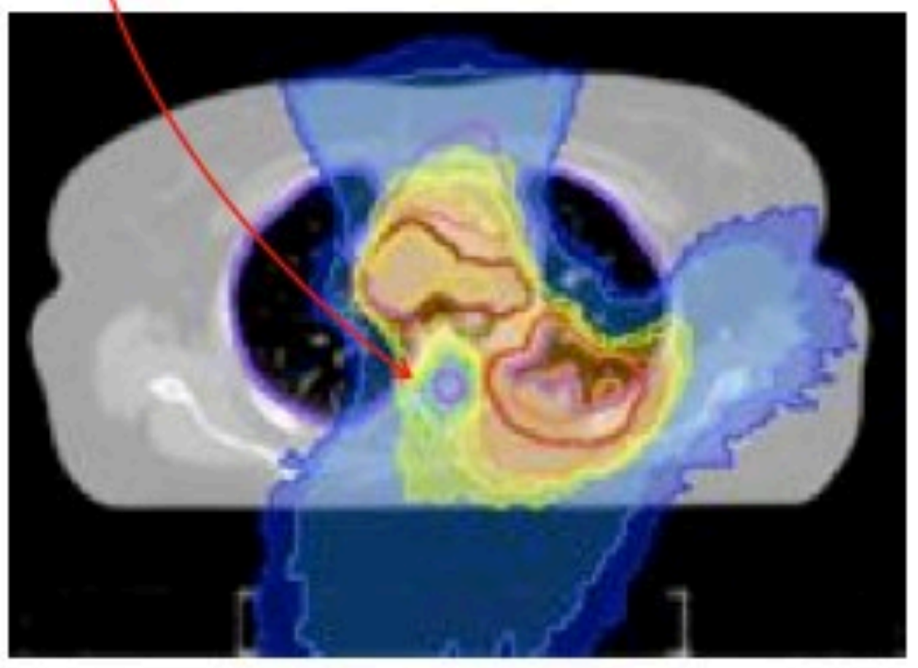
IMRT

- A lot of movement.
  - Tumor moves
  - OARs move
  - Leaves move (DMLC)
  - Gantry moves (VMAT/Tomo)
  - Table moves (Tomo/VMAT?)

All at different frequencies/speeds



Sharp gradients



(NO IMRT without IGRT)

The BIG question

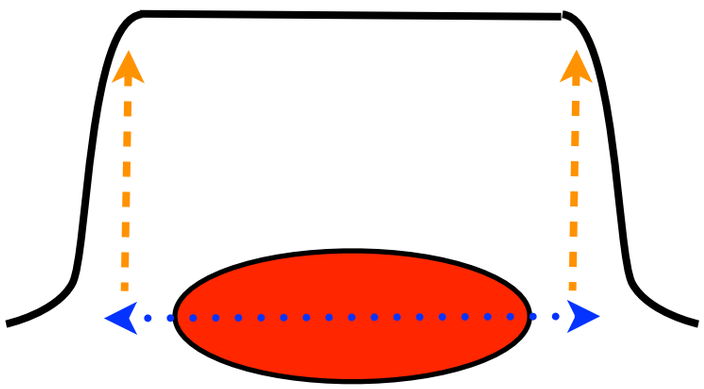
What is the effect of all of these geometric uncertainties on the IMRT dose distribution?

The answer

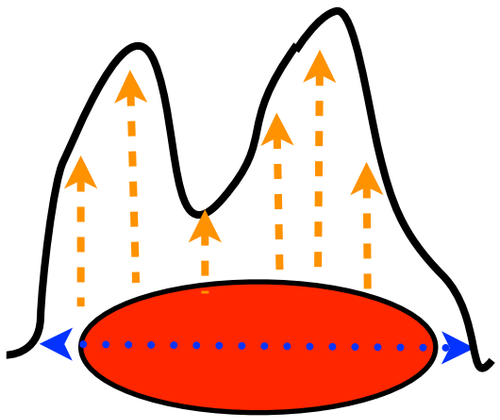
- ~~42~~
- Interfraction movement
- Intrafraction movement
- Deformation
- Robust Planning

PTV Margin?

Conventional



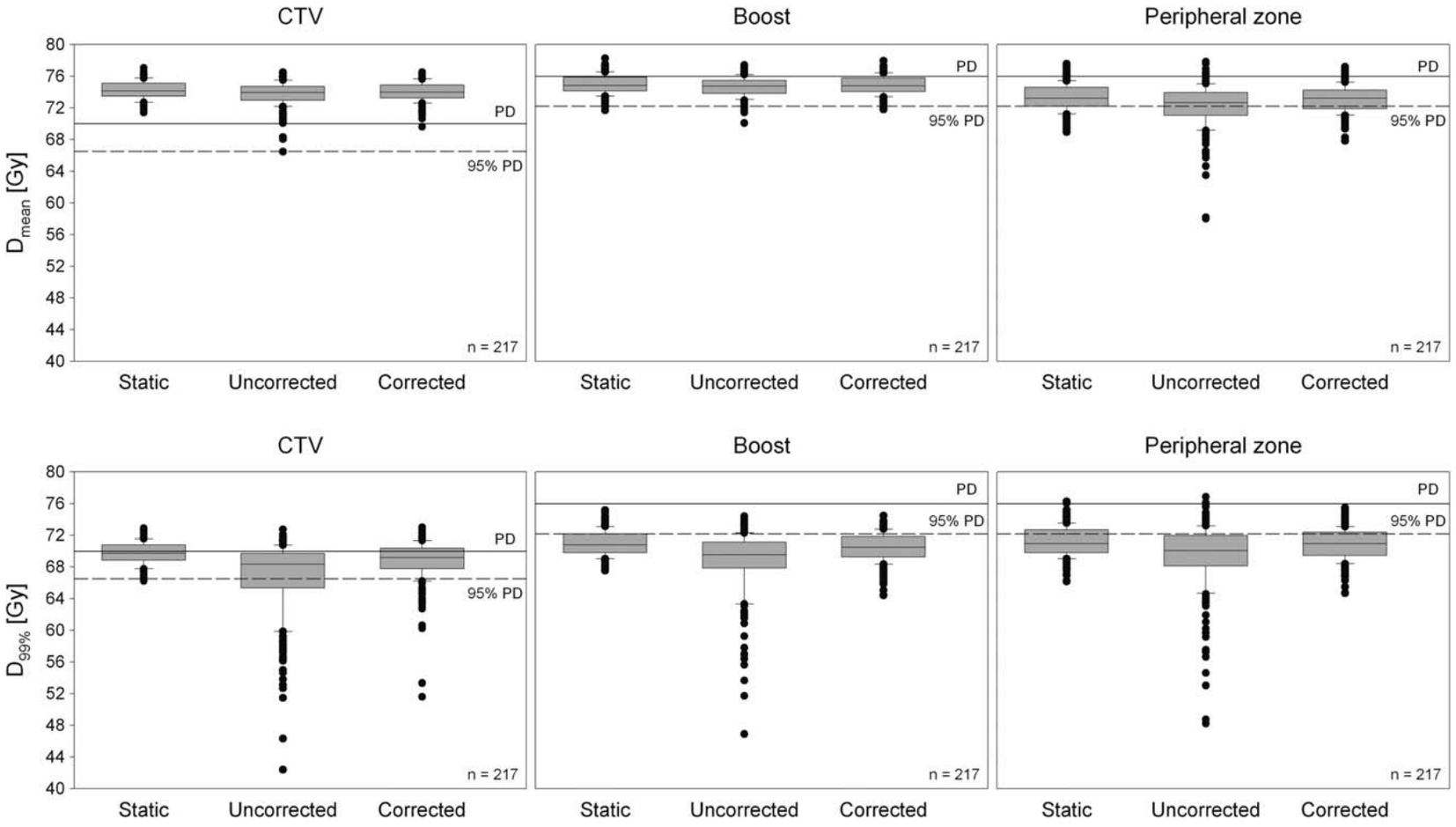
IMRT

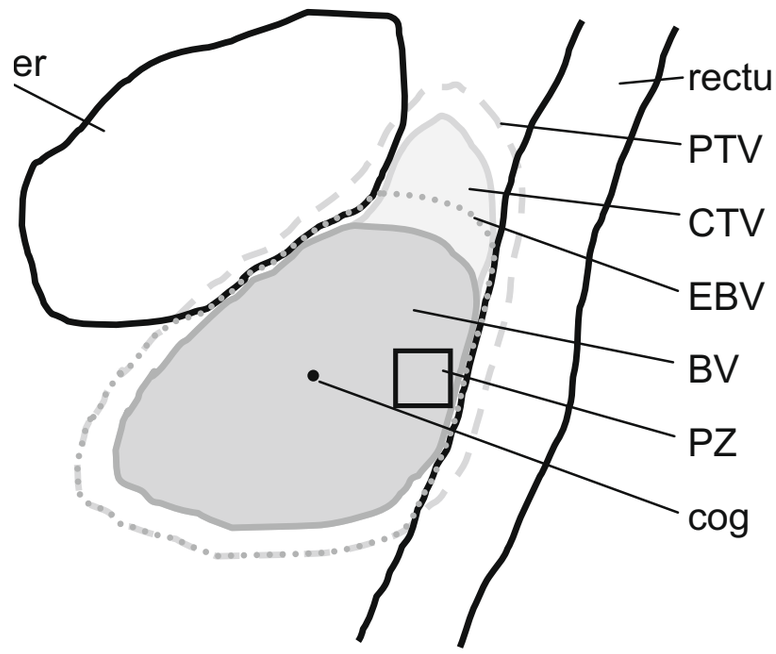


Interfraction Movement/setup errors

- NOT deformations
- Different effect of random and systematic errors
  - Systematic error : your gradient could end up somewhere else
  - random : averaging effect

Prostate





215 patients

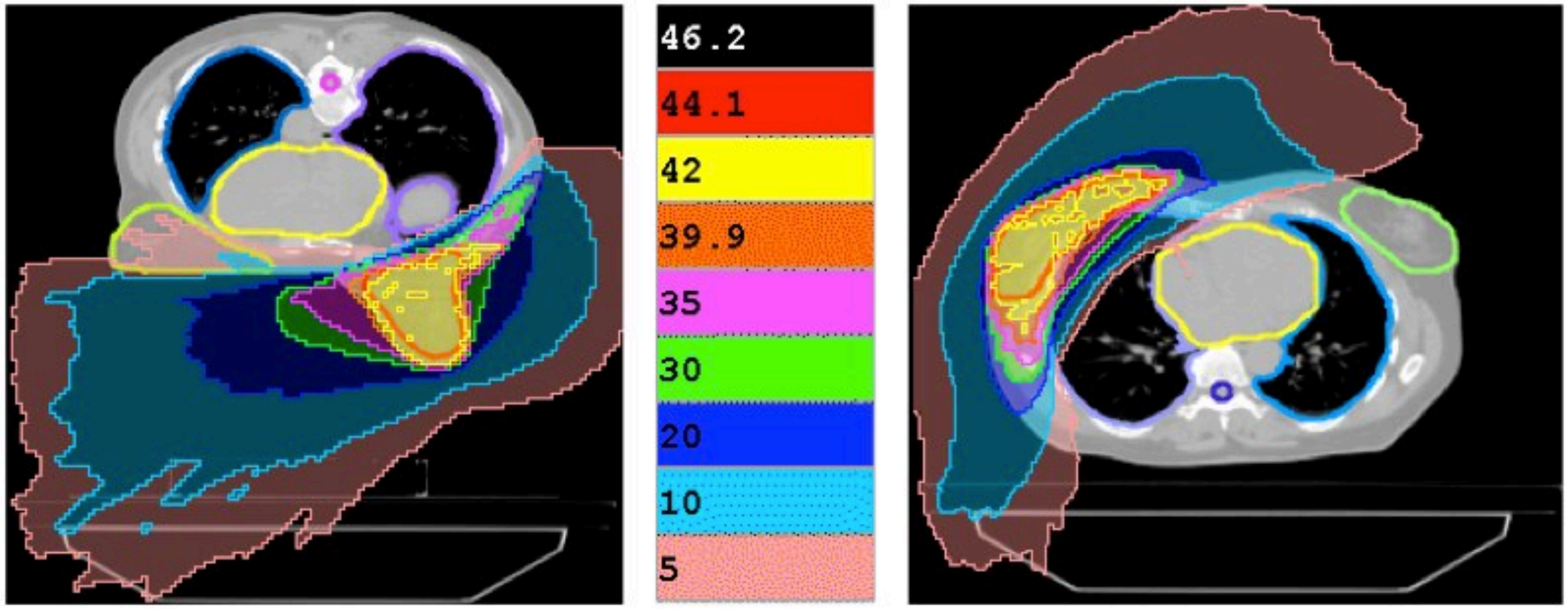
Changes can be accounted for by correction (IGRT) protocols or sufficient margins, when movement is limited <10mm

P.M.A. van Haaren et al./Radiotherapy and Oncology 90 (2009) 291–298

Prostate

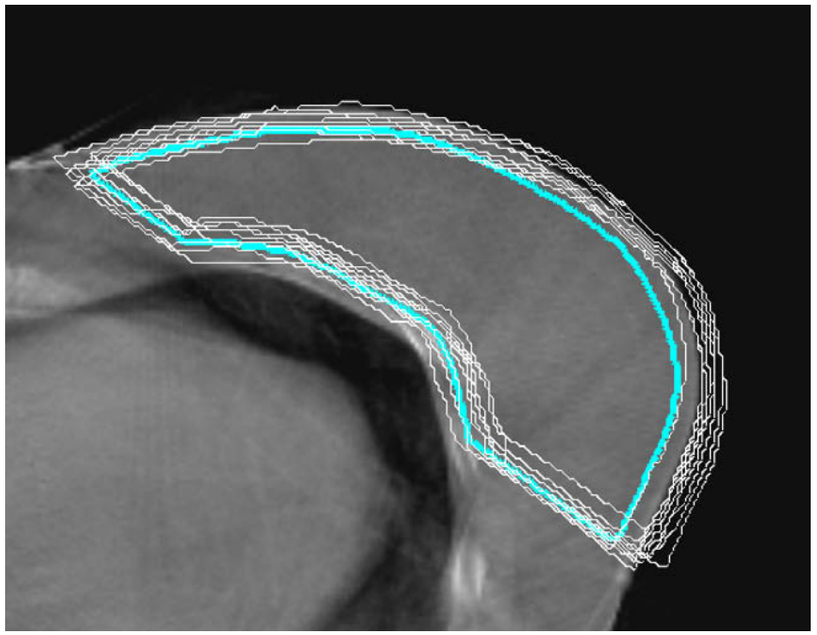
- "homogeneous region"
- Isodoselines are quite robust if the anatomy will not change.
- Watch out for systematic errors

Breast IMRT

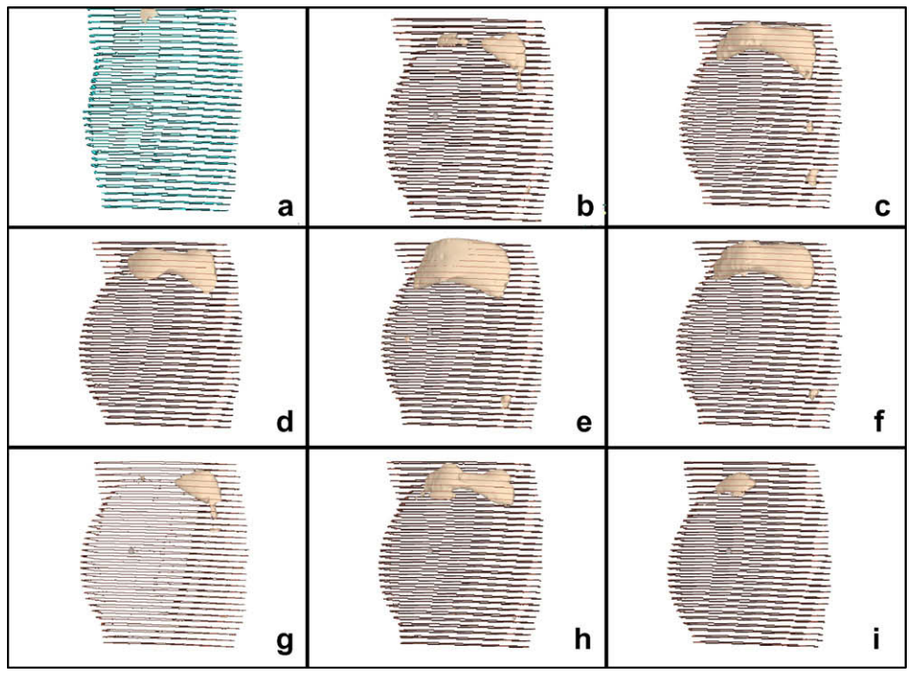


- Improves homogeneity
- You have to be sure that the extra few segments end up at the right place
- Susceptibility to movement?

Breast IMRT

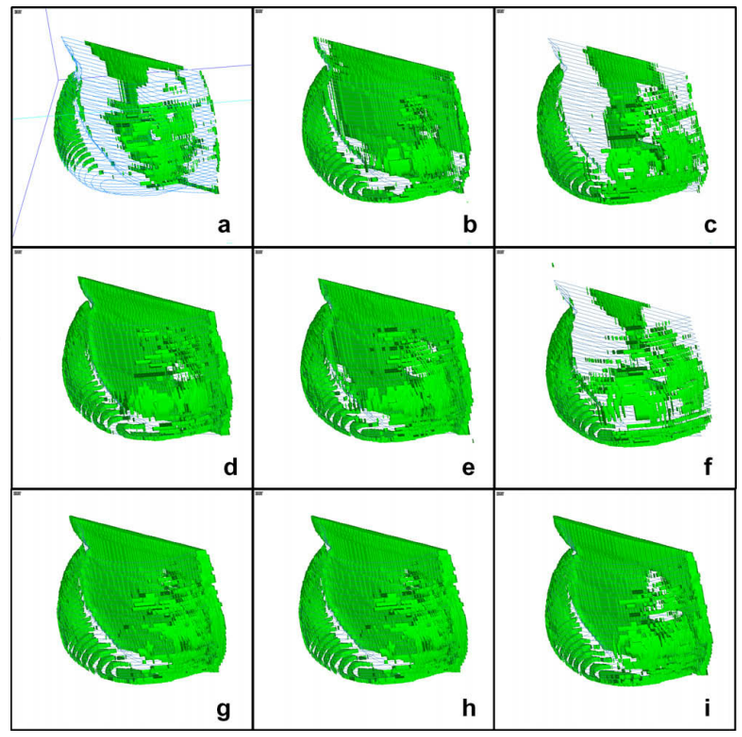


PTV position



High dose

Low Dose



Impact of daily PTV variations upon IMRT and conventional RT plans.

Isodose level	IMRT plan		Standard tangential RT plan	
	Mean planned volume (% PTV)	Mean delivered volume (% PTV)	Mean planned volume (% PTV)	Mean delivered volume (% PTV)
>107%	0.1	0.3 ± 0.6	4.0	4.4 ± 1.9
>105%	0.5	1.8 ± 2.0	15.7	15.6 ± 3.7
>95% <105%	96.7	89.5 ± 5.1	82.5	79.3 ± 5.1
<95%	2.7	8.6 ± 4.0	1.8	5.1 ± 2.6
<90%	0.3	2.7 ± 2.9	0.2	1.9 ± 2.0

P. Jain et al./Radiotherapy and Oncology 90 (2009) 93–98

Breast IMRT

Technique	D_{mean}, mean (SD), Gy	*p*	V_{95}, mean (SD), %	*p*	V_{107}, mean (SD), %	*p*
Wedge	-0.2 (± 0.1)	**<0.01**	-0.2 (± 0.2)	**<0.01**	-1.4 (± 0.9)	**<0.01**
FIF	-0.2 (± 0.2)	**<0.01**	+0.1 (± 0.7)	0.74	0.0 (± 0.4)	0.69
Hybrid IMRT	-0.5 (± 0.3)	**<0.01**	-2.5 (± 3.7)	**<0.01**	0.0 (± 0.1)	0.65
Full IMRT	-0.6 (± 0.3)	**<0.01**	-4.3 (± 5.1)	**<0.01**	-0.1 (± 0.2)	0.38

Nakamura et al., 2010

Modulation vs. robustness to dose?

- Less is more?
- Max 20% modulation seems to preserve robustness
- Cave : internal mammary nodes
  - Sharon et al (IJROBP) : 28% change in V45 for M.I.
- What with SIB treatments?

Interfractional movement

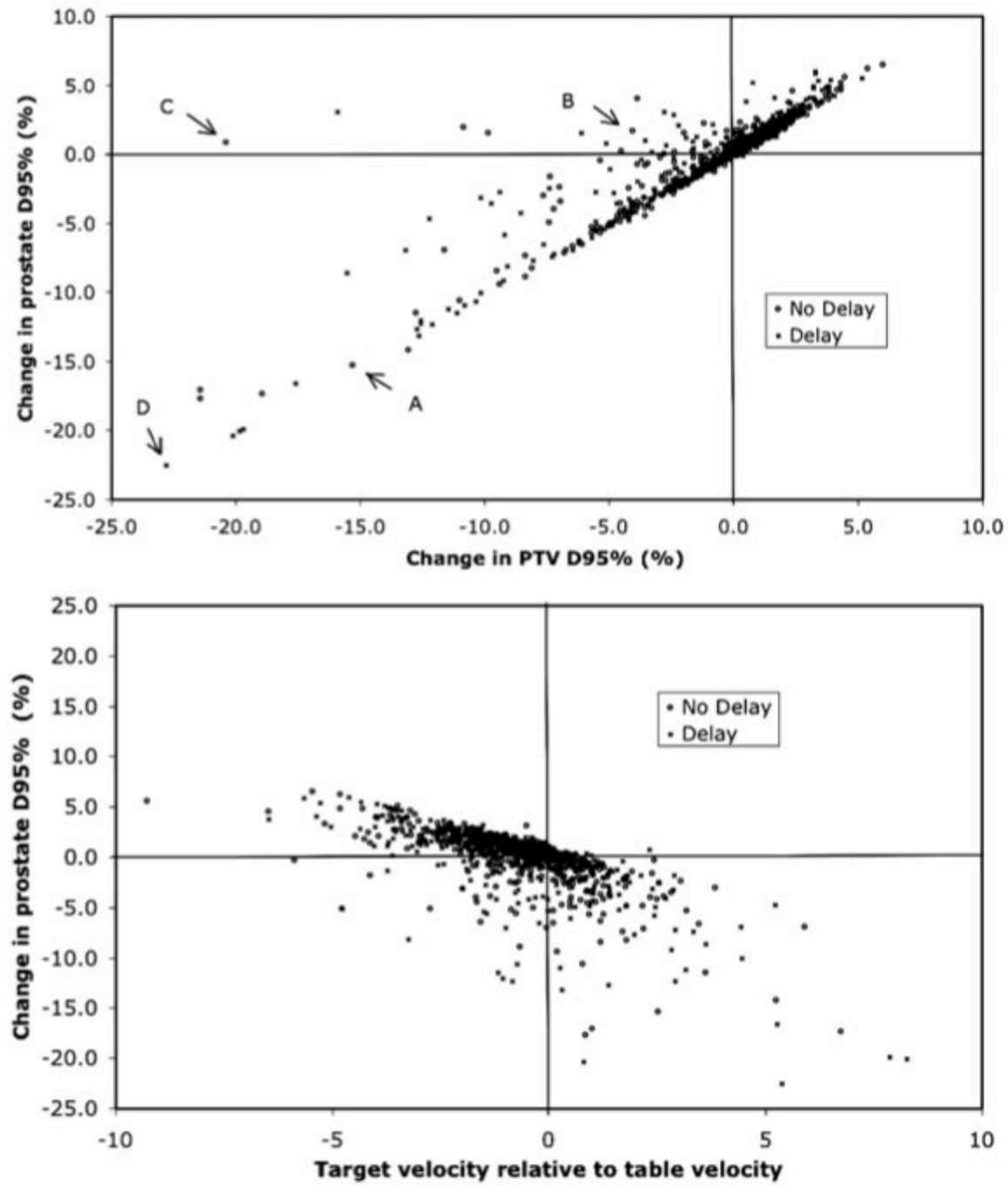
- As long as we are working in homogenous regions....
- or the modulation is not too large
- our concept of the robust dose cloud keeps up
- IGRT to the rescue

Intra-fraction movement

Prostate (tomotherapy)

Effect not limited to the periphery

Margins???



Relative movement table vs. target

Correlation between ampunt of motion and effect not straightforward (dep. direction...)

Phys. Med. Biol. **53** (2008) 7073–7086

"For prostate and HT, there CAN be a significant dosimetric effect in the cranio-caudal direction because table speed and tumor motion are of the same magnitude." However....

#fx	Movement	Impact (dose)
1/3	<3mm	5%
2/3	<5mm	10%

Correction schemes not feasible! We don't know when (which fraction and timing in the fraction) to interrupt an correct

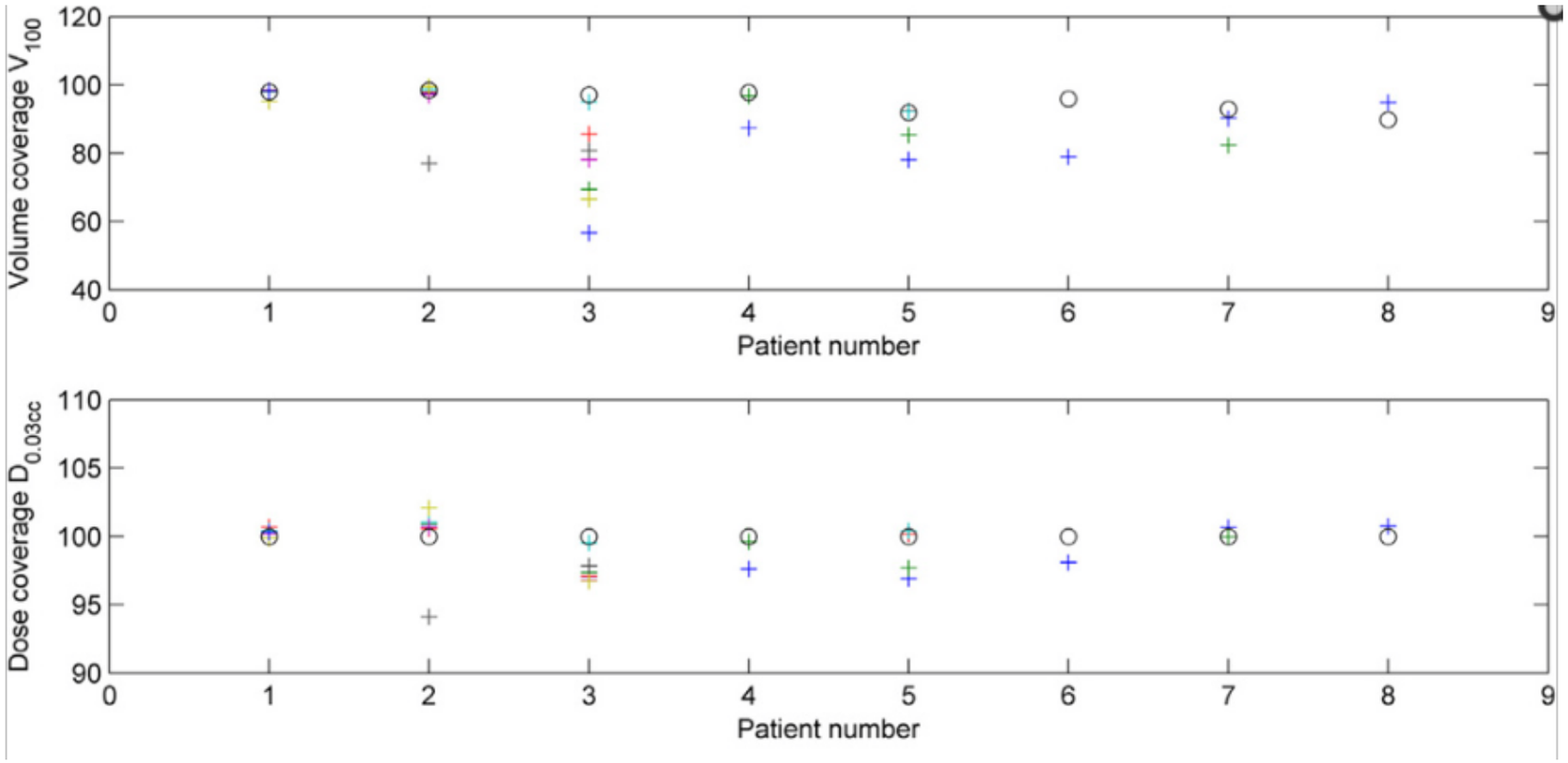
Prostate (S&S)

- 486 fractions
- Mean deviation at $D(95\%)_{CTV}$ =0.2+/- 0.5% (1SD)
- Poor correlation between movement parameters and $D(95\%)_{CTV}$
- No threshold possible

Langen et al , Int J Radiat Oncol Biol Phys. 2012 Dec 1;84(5):1220-5

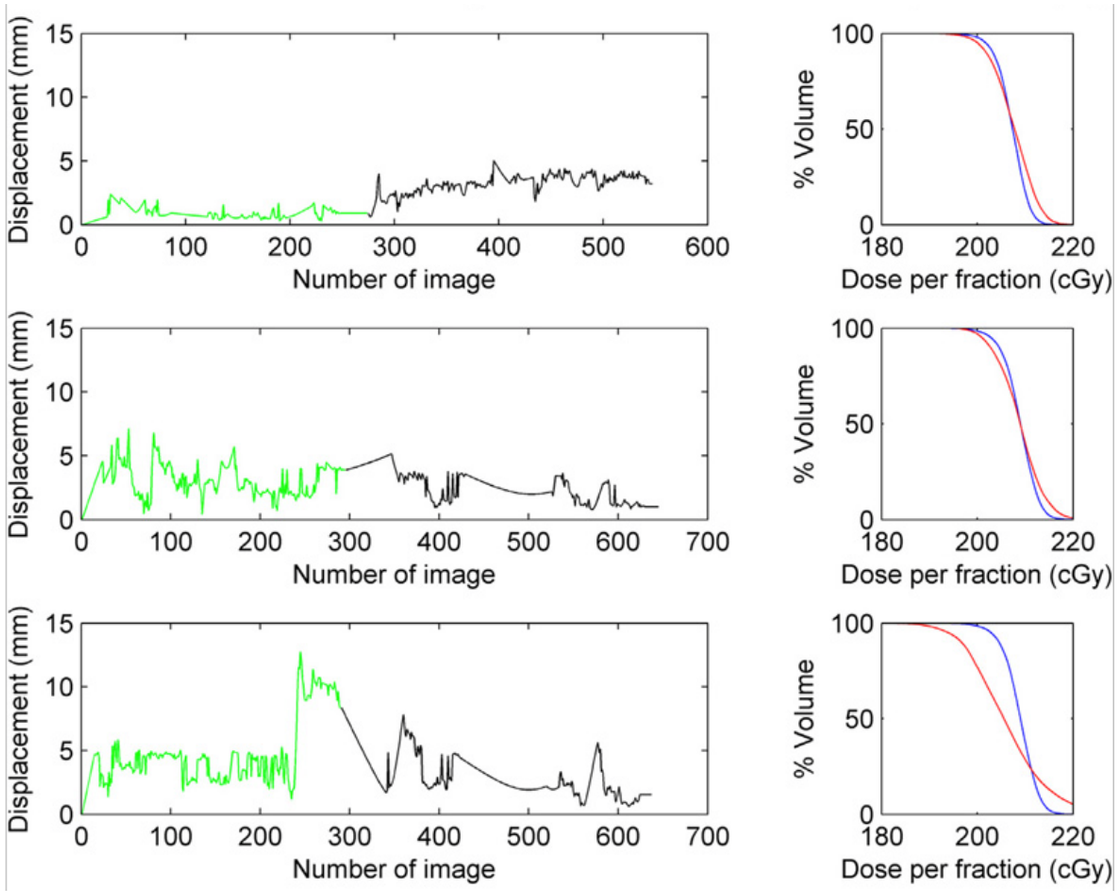
Intrafraction movement VMAT - prostate

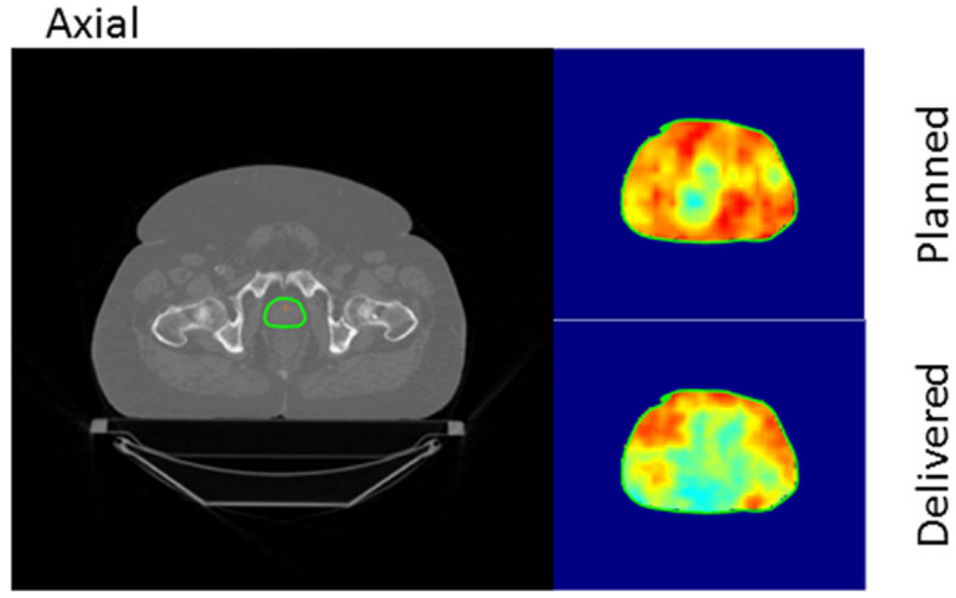
- Fiducial detection
- Linked to control points
- Recalculated using MC

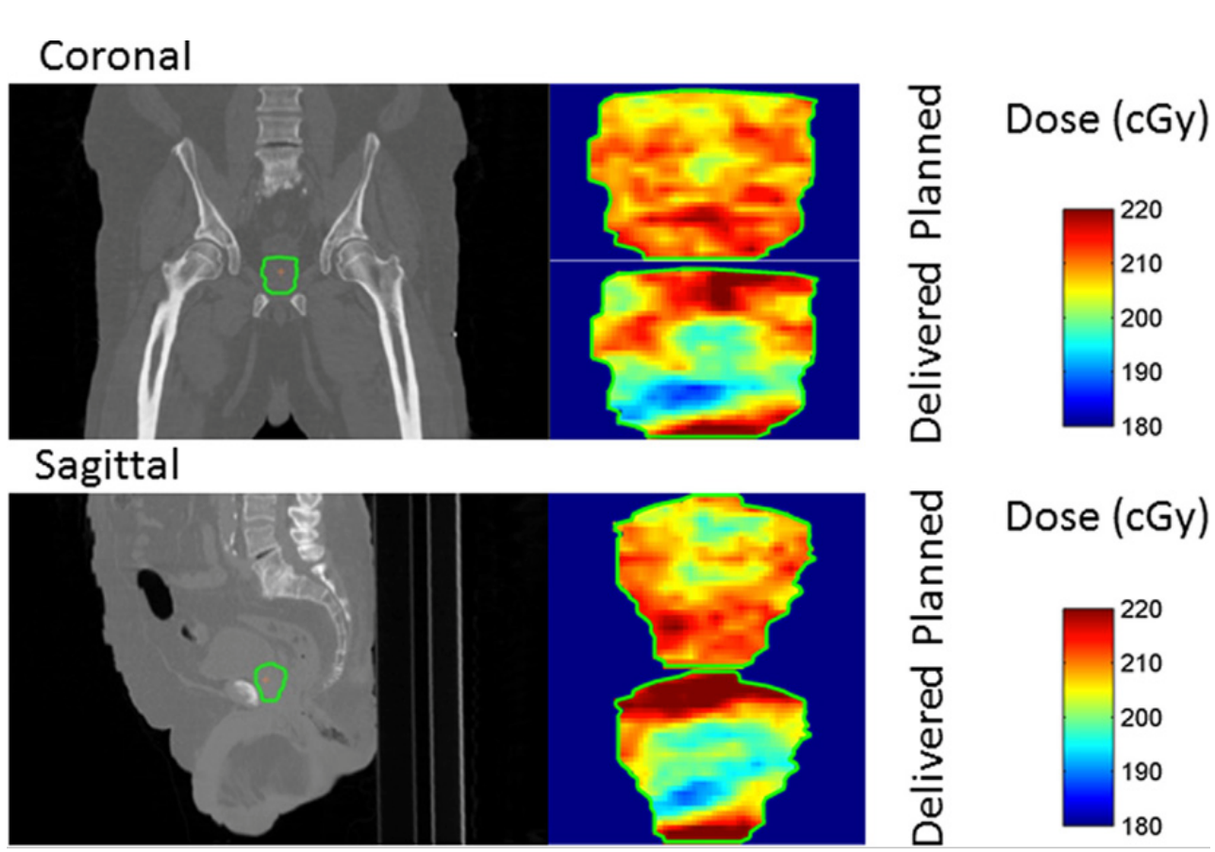


Azcona et al 2015

Intrafraction effect - VMAT prostate







- Possible large effects in single fractions
- Effect is reduced over 7-8 fractions
- Prostate tracking?

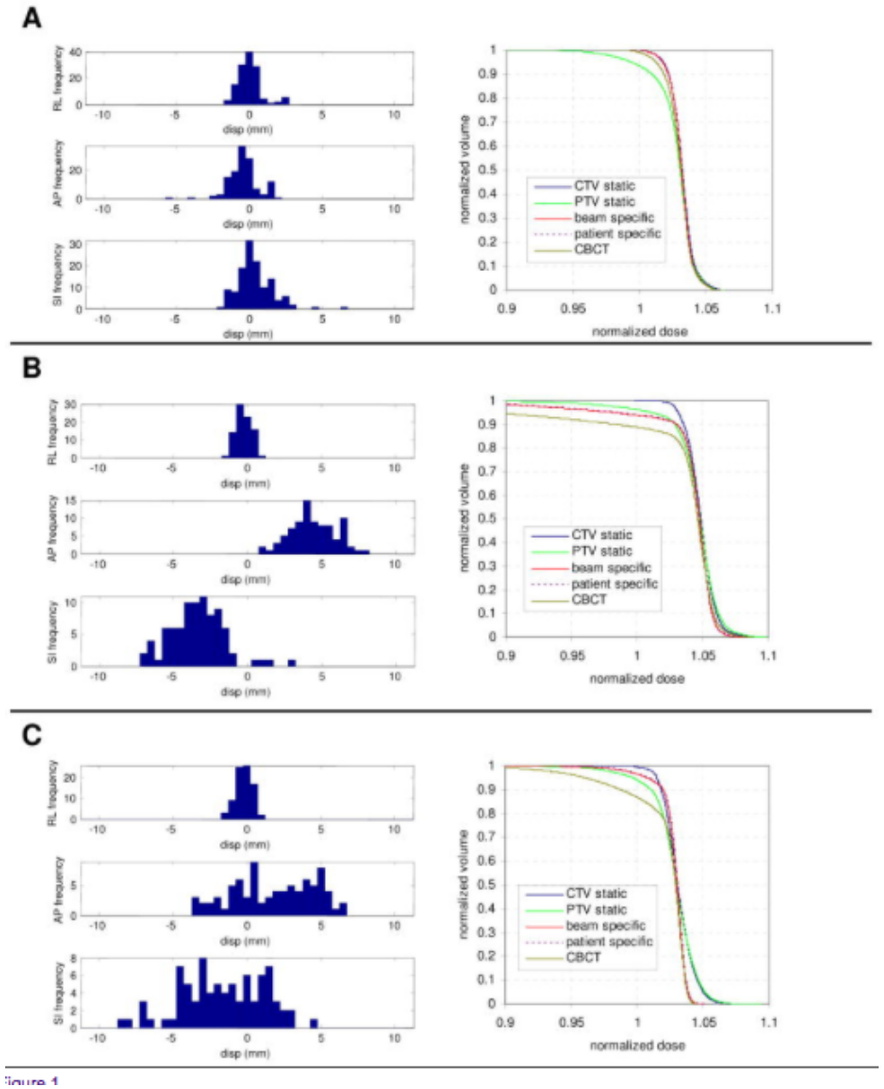
Azcona et al 2015

Intrafraction movement VMAT - prostate

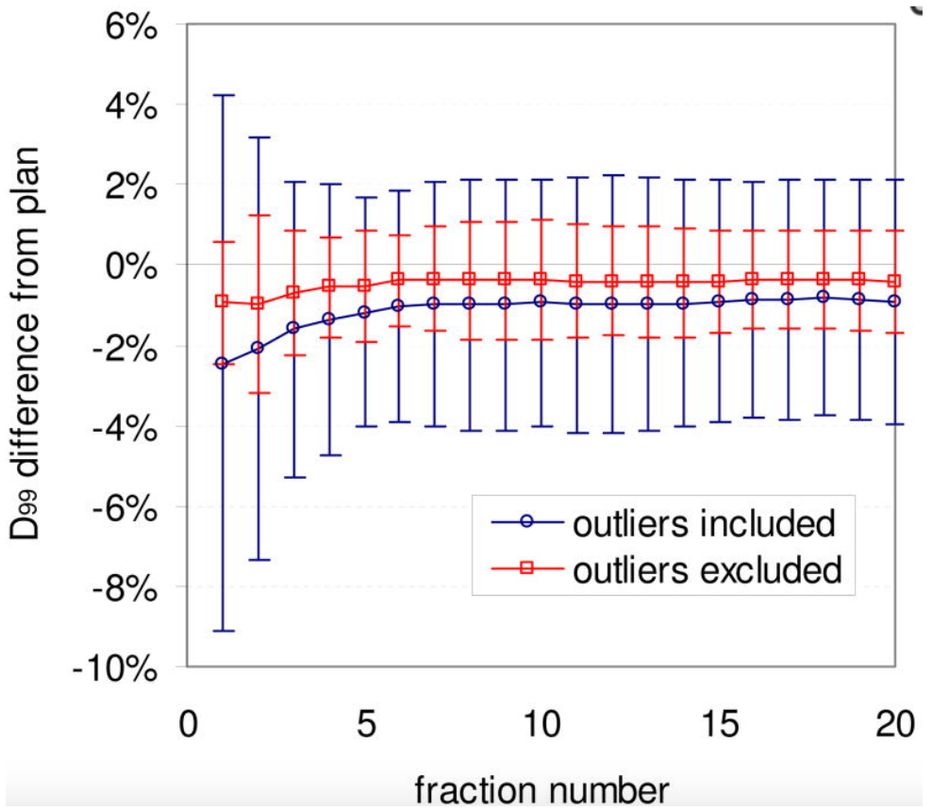
DOSIMETRIC EFFECT OF INTRAFRACTION MOTION AND RESIDUAL SETUP ERROR FOR HYPOFRACTIONATED PROSTATE IMRT WITH CBCT IMAGE GUIDANCE

Justus Adamson, PhD,[1,2,3] Qiuwen Wu, PhD,[1,3] and Di Yan, Dsc.[1]

PDF constructed using pre-and post CBCT



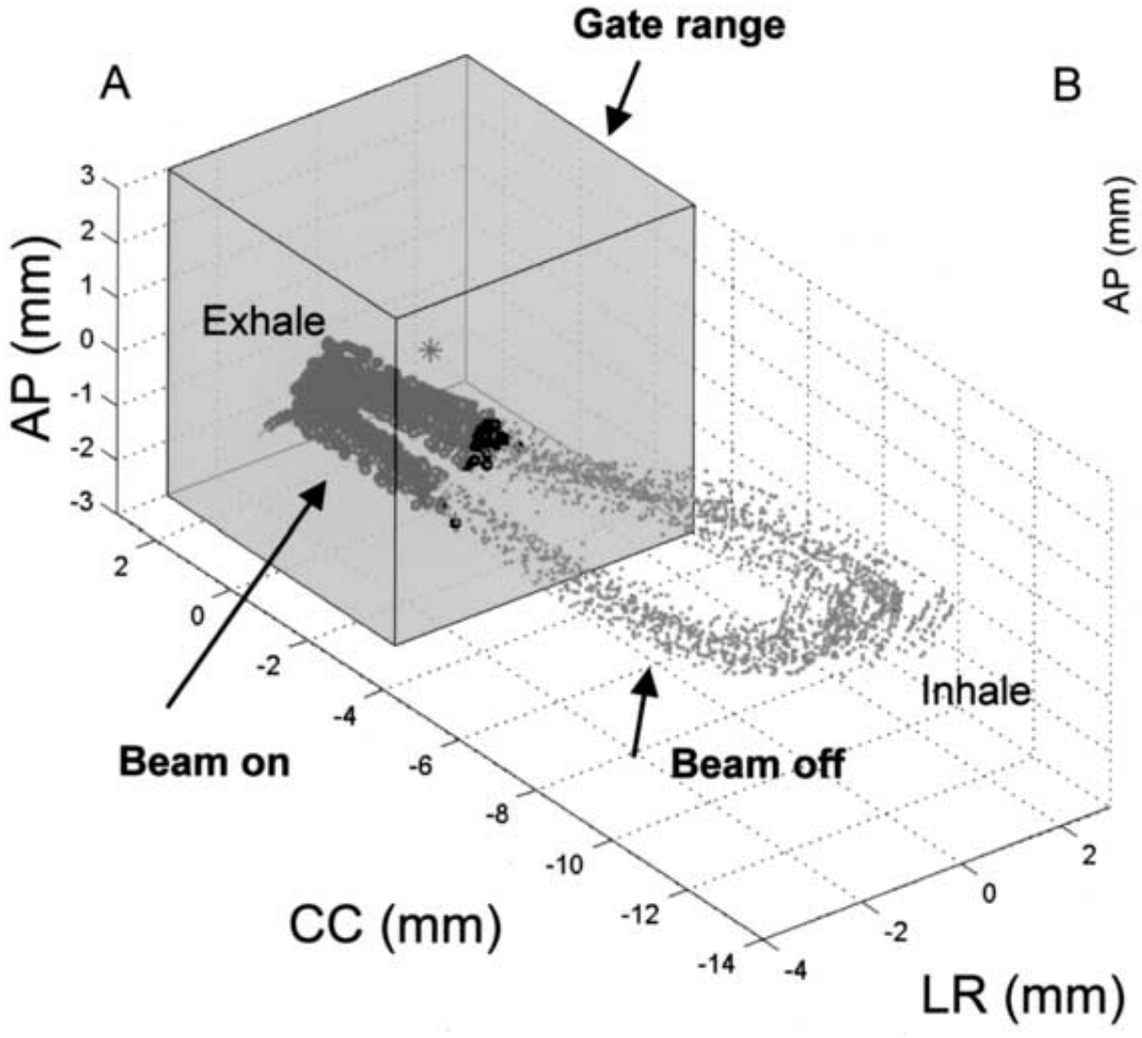
Results



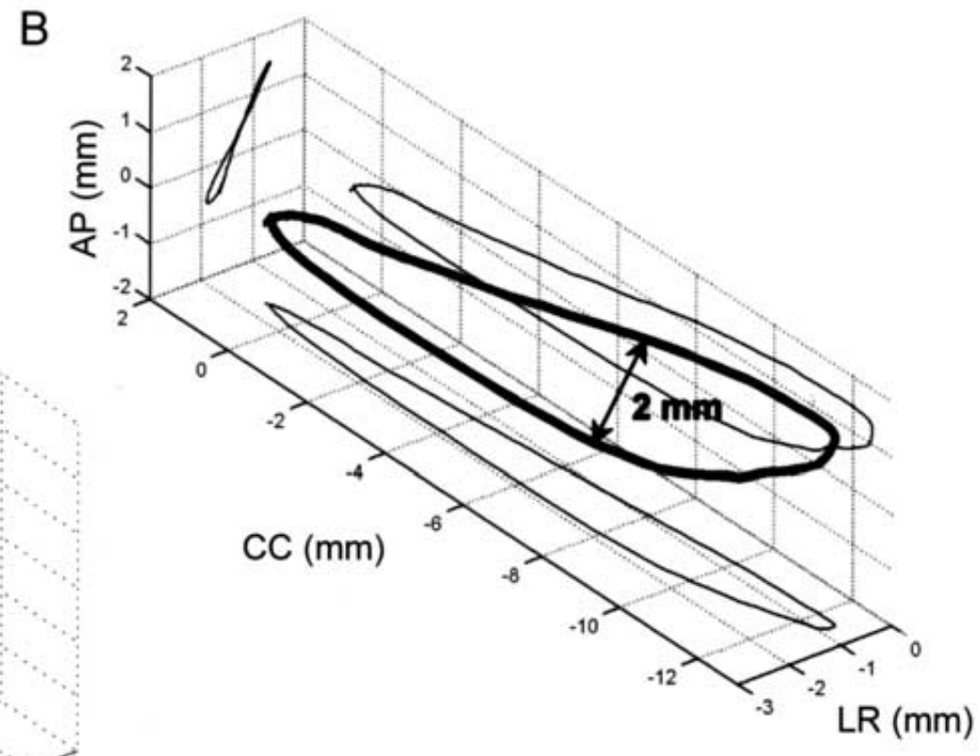
Intrafraction movement

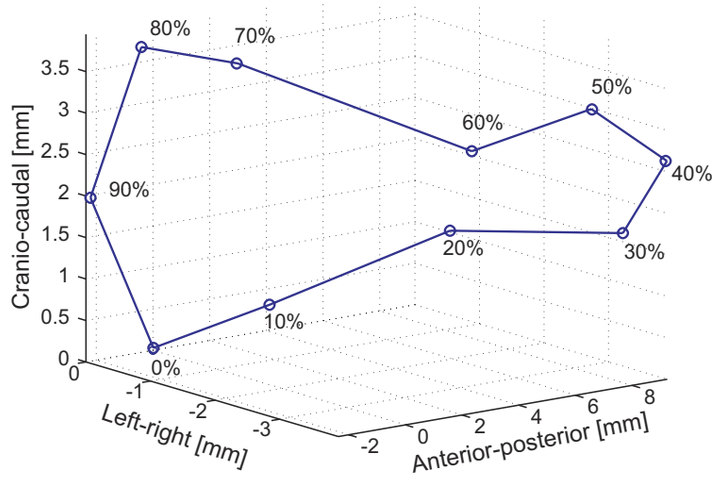
- Pretty good example : breathing motion
- (quasi)-periodic, around 8BPM
- not limited to craniocaudal axis, although a large CC-component is in there

movement in lung



Seppenwoolde et al 2002



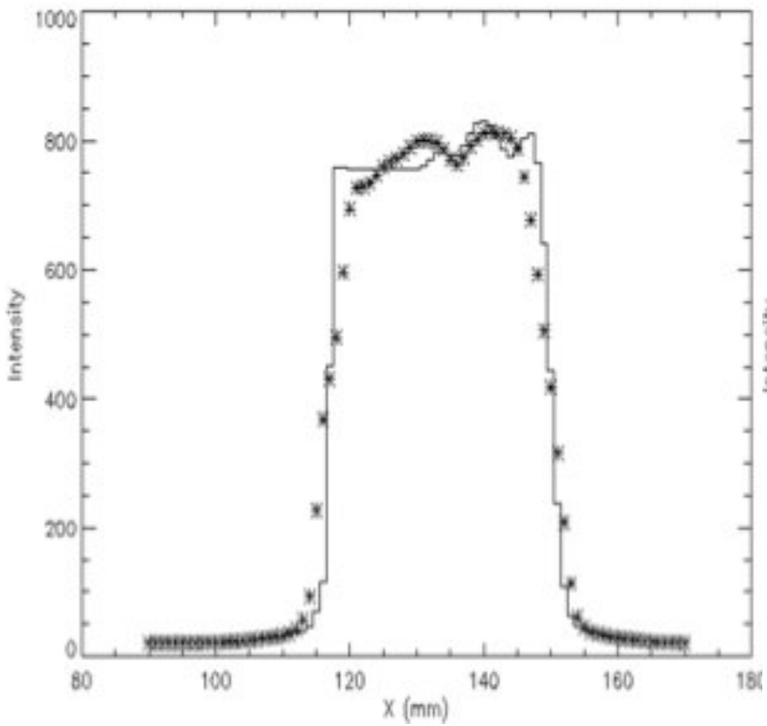


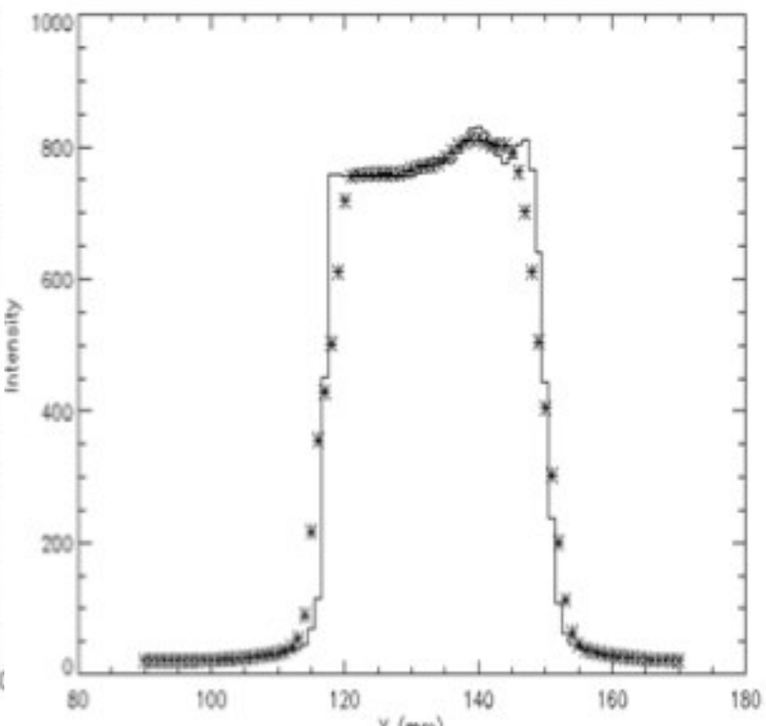
Wolthaus et al

Effect of delivery techniques

- Step and shoot
  - Leaves are not moving during irradiation
  - Smoothing, broadening of penumbra
    - Relatively small effect

1fx





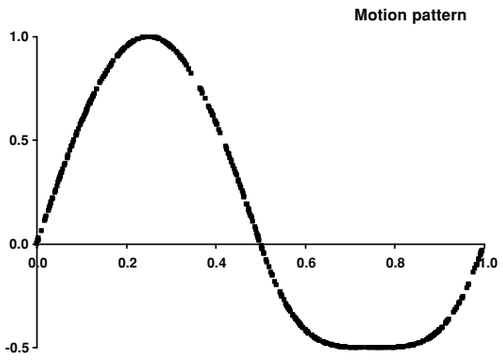
30fx

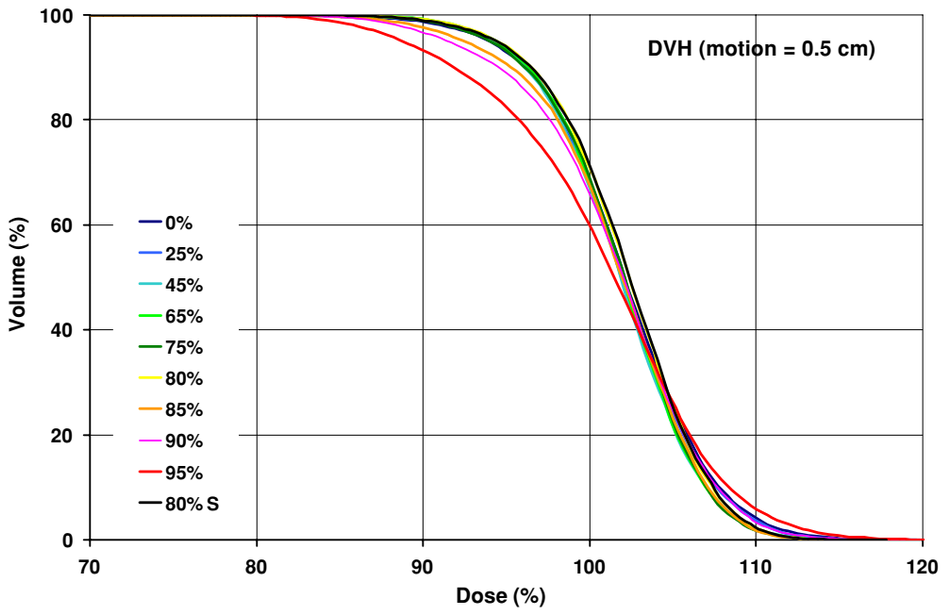
Chui et al , 2003

Effect of delivery techniques

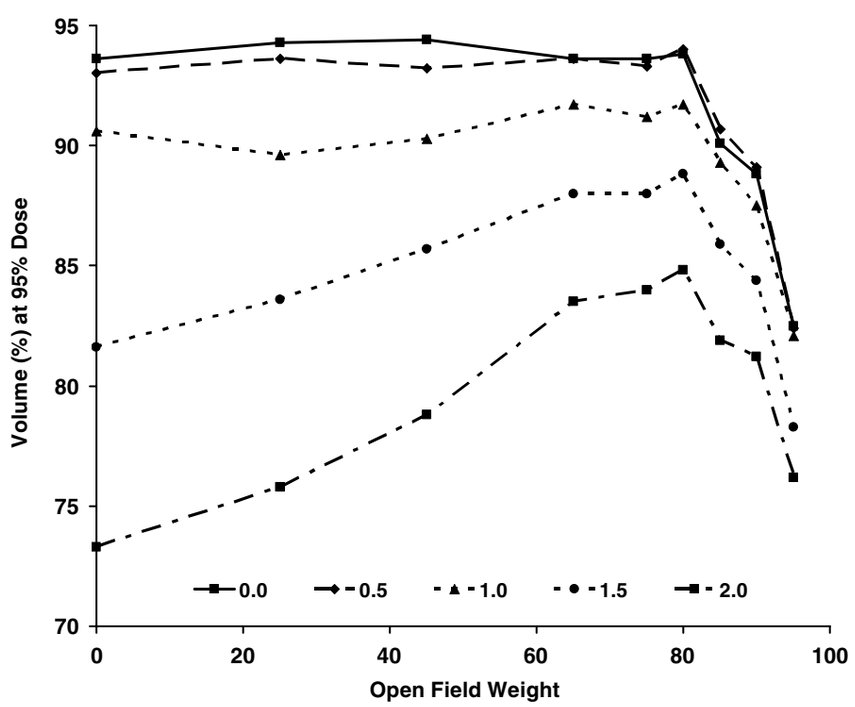
- Dynamic MLC
  - Leaves are moving during irradiation
  - Leafspeed and tumor speed is in the same range
  - Interplay effects
  - Depending on relative direction of movement

Respiratory Movement in breast IMRT



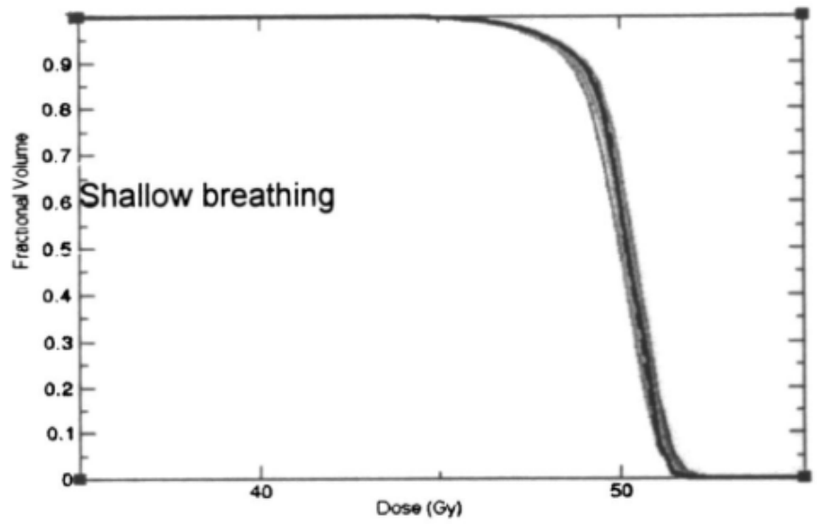


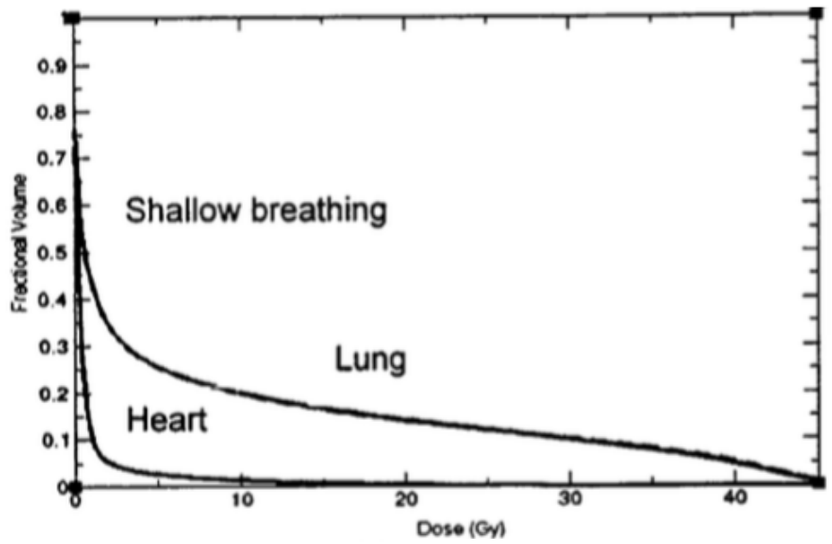
- 7 segment DAO
- Effect of open field weight
- Breath-hold, breathing limiting devices, prone...

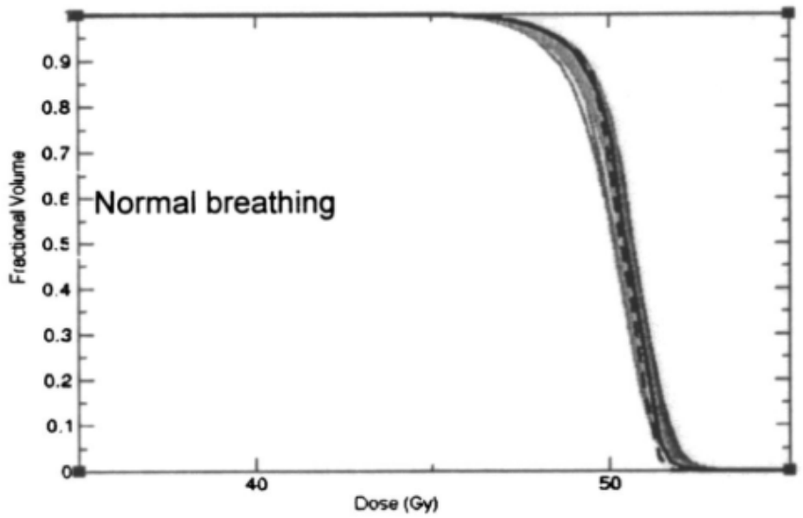


Zhang et al, 2006 Phys. Med. Biol. 51

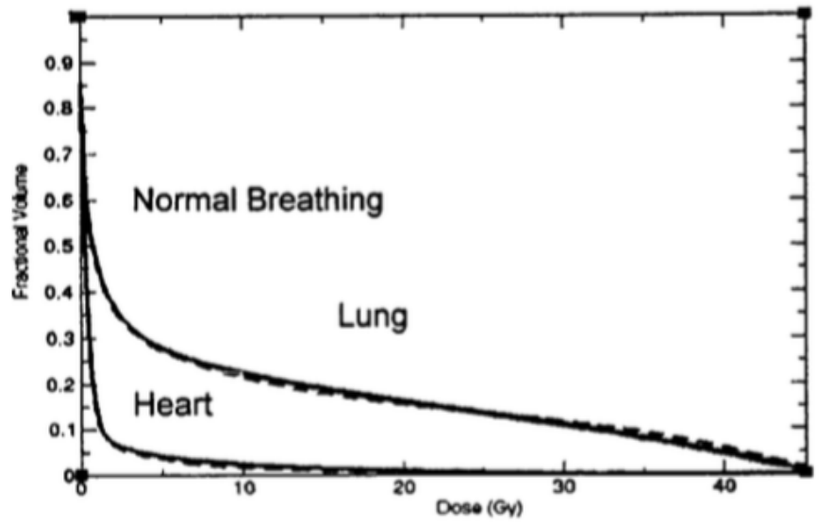
reast DML



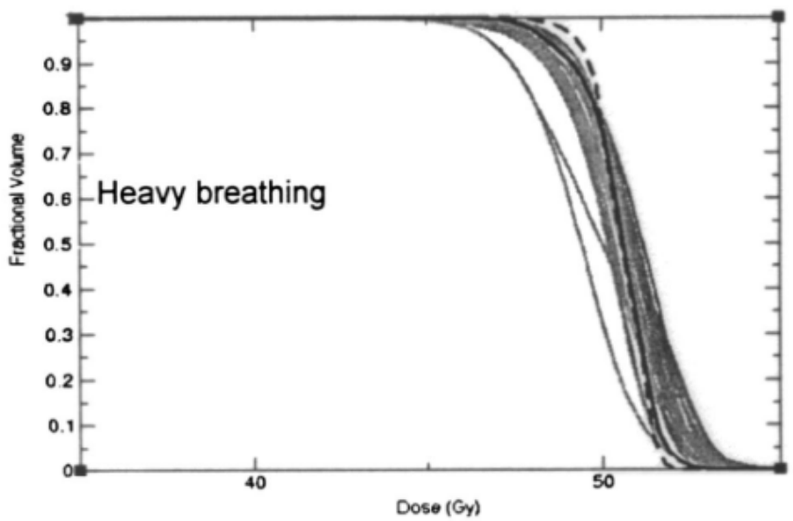




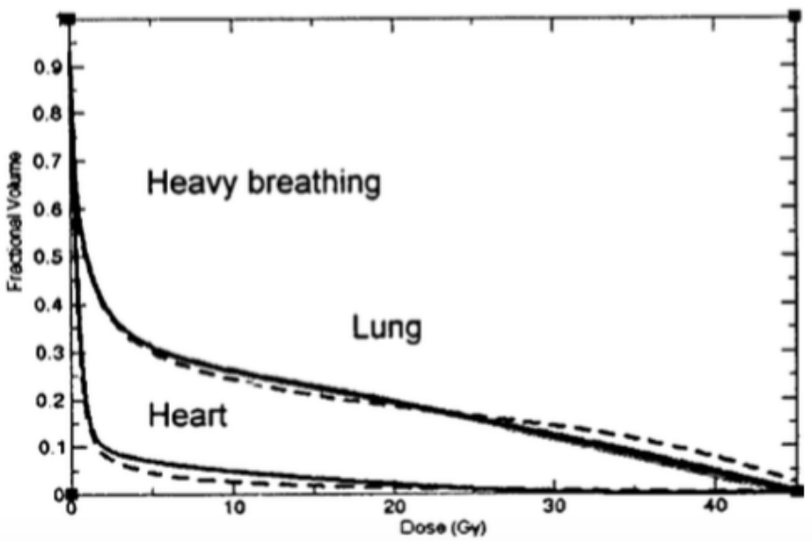
(b)



(b)



(c)



George et al.

DMLC tracking

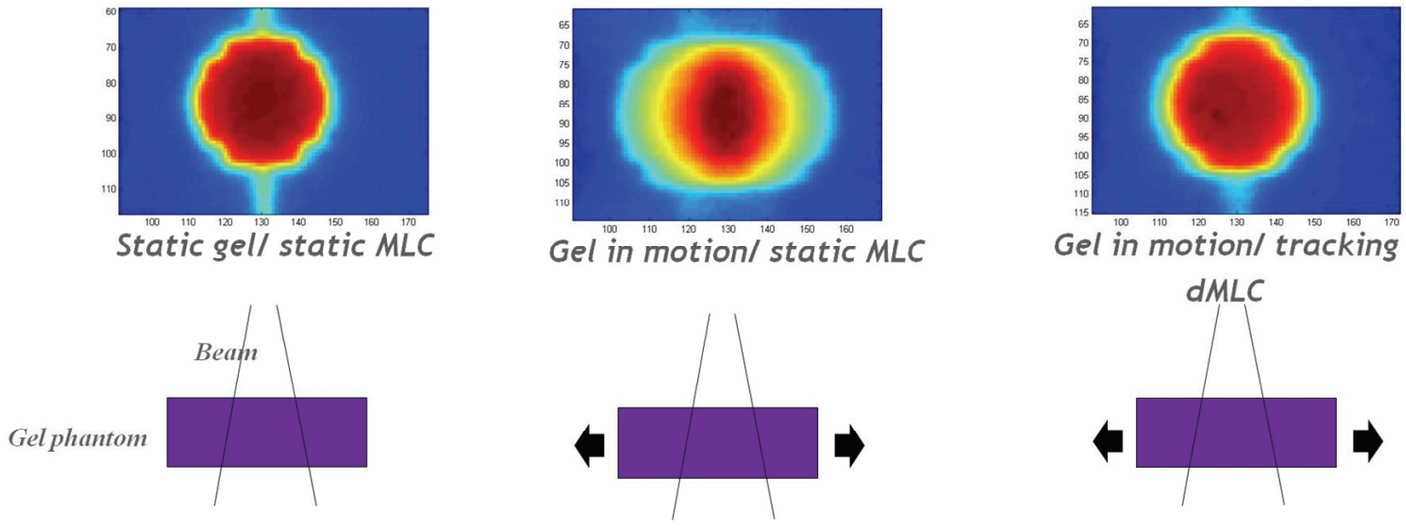
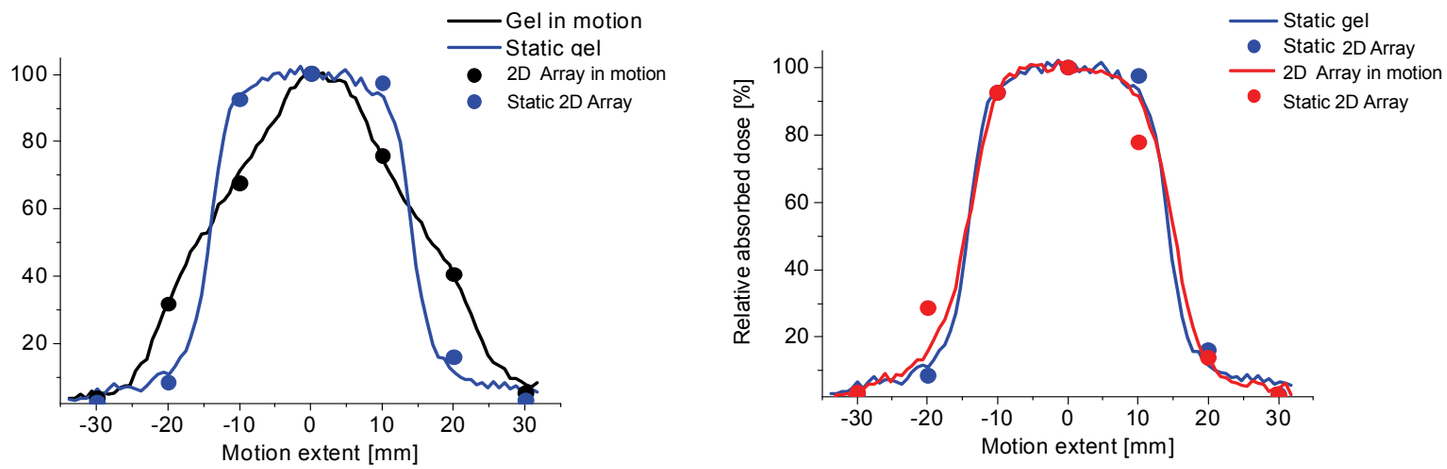


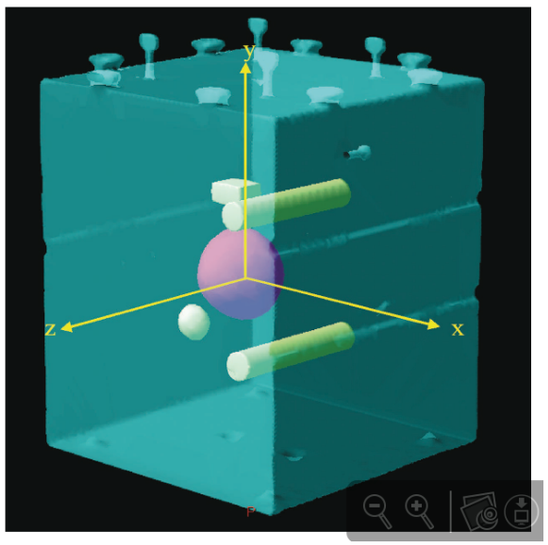
Figure 16. Dose distributions measured using gel dosimetry with and without the DMLC-tumour tracking connected.



Ceberg et al *Phys. Med. Biol. 53: N387–N396, 2008*

DMLC and breathing motion

Duan et al,med phys 2006



- DMLC on phantom
- 5, 7, 9 an 10field-plan
- Measured over differen
- with and without breath

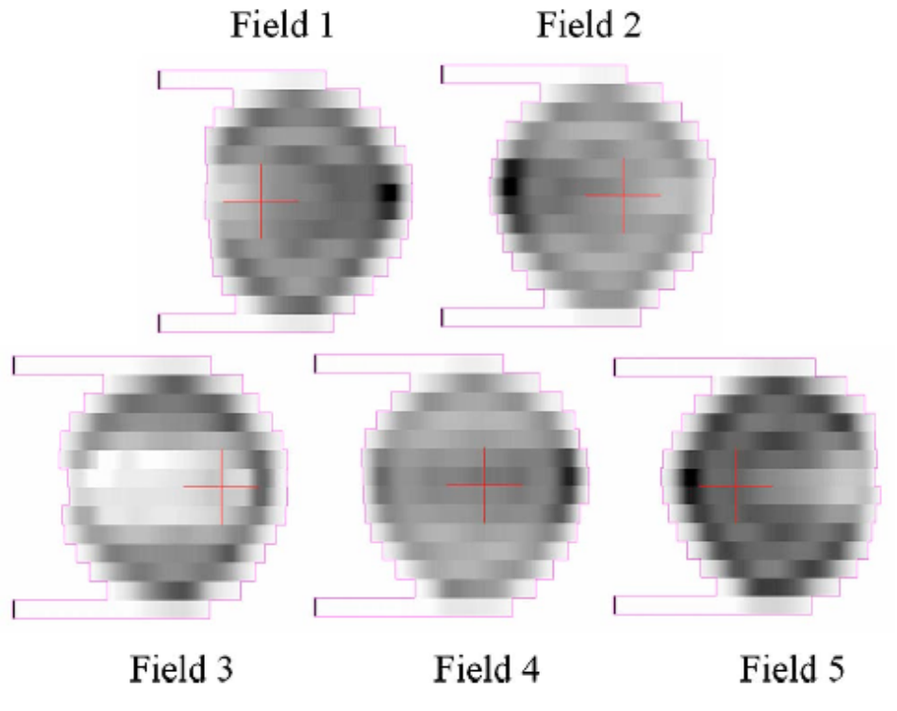
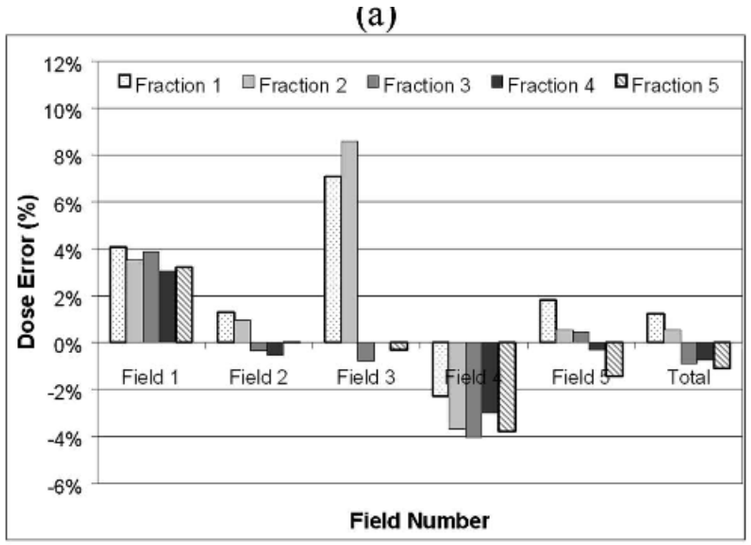
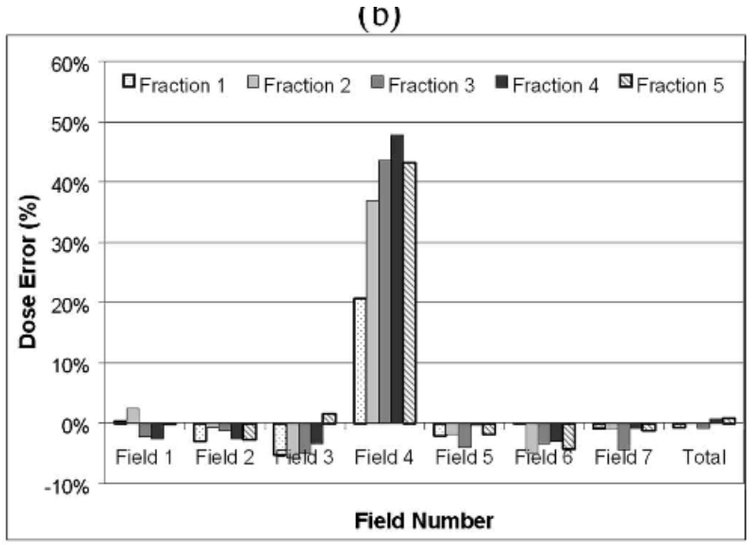


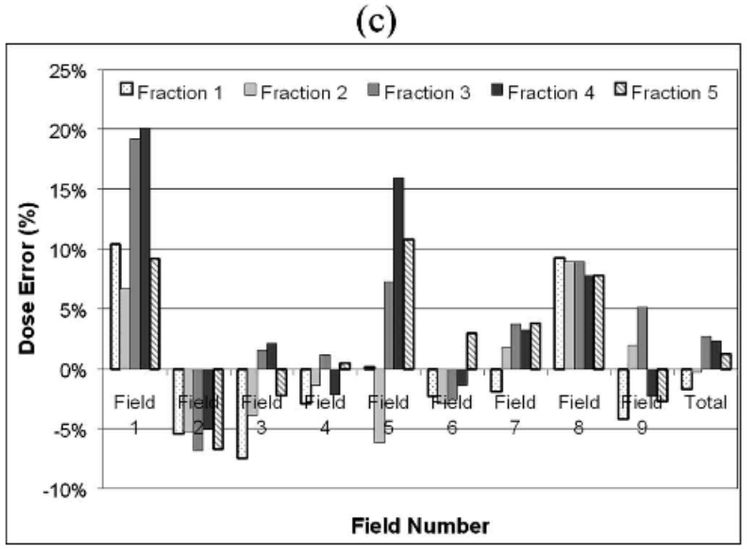
FIG. 2. Fluence maps for the five-field plan.

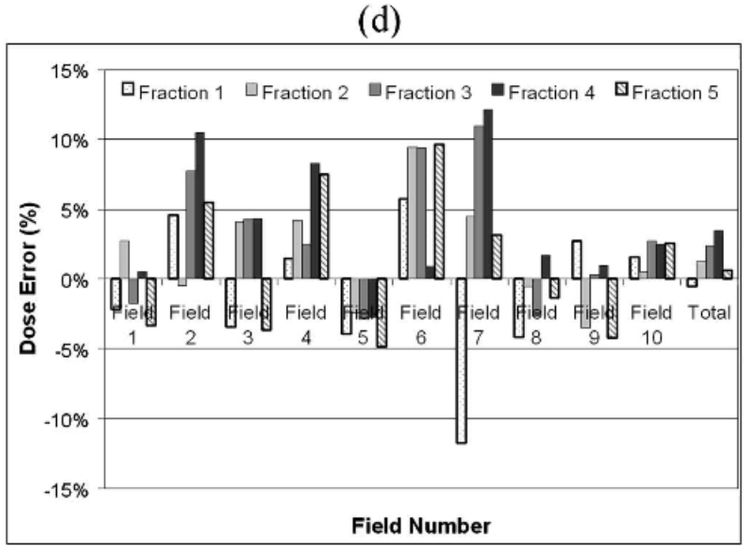
DMLC and breathing

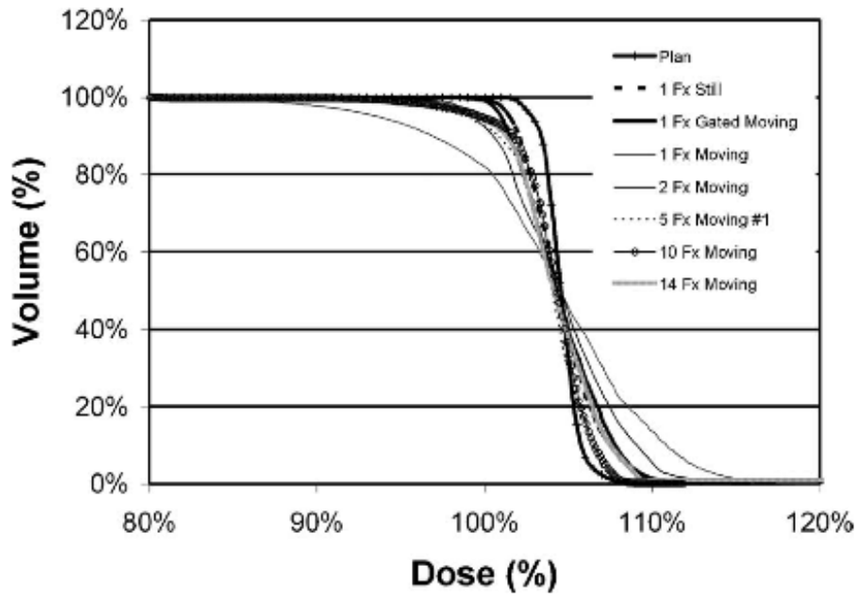




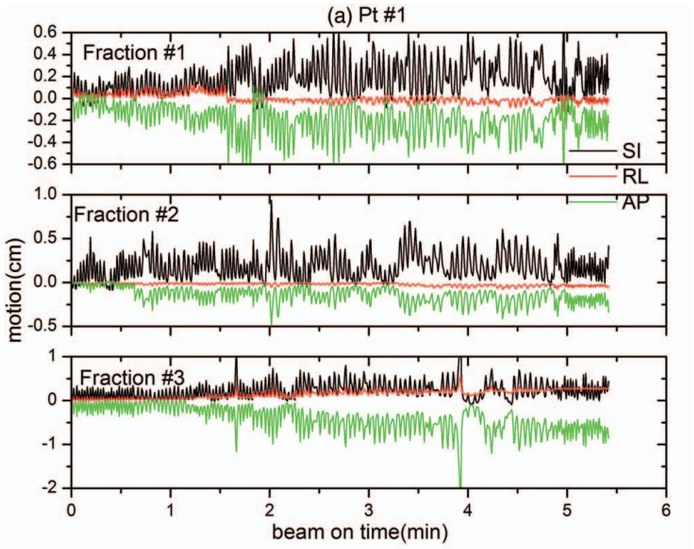
Field number	Treatment plan			
	Five fields	Seven fields	Nine fields	Ten fields
All	−0.2%	−0.1%	0.9%	1.4%
1	3.5%	−0.5%	13.1%	−0.8%
2	0.3%	−2.1%	−5.9%	5.6%
3	2.9%	−3.6%	−2.0%	1.1%
4	−3.4%	38.4%	−1.0%	4.8%
5	0.2%	−2.1%	5.6%	−3.4%
6		−3.2%	−1.2%	7.0%
7		−1.7%	2.1%	3.8%
8			8.5%	−1.4%
9			−0.4%	−0.7%
10				2.0%



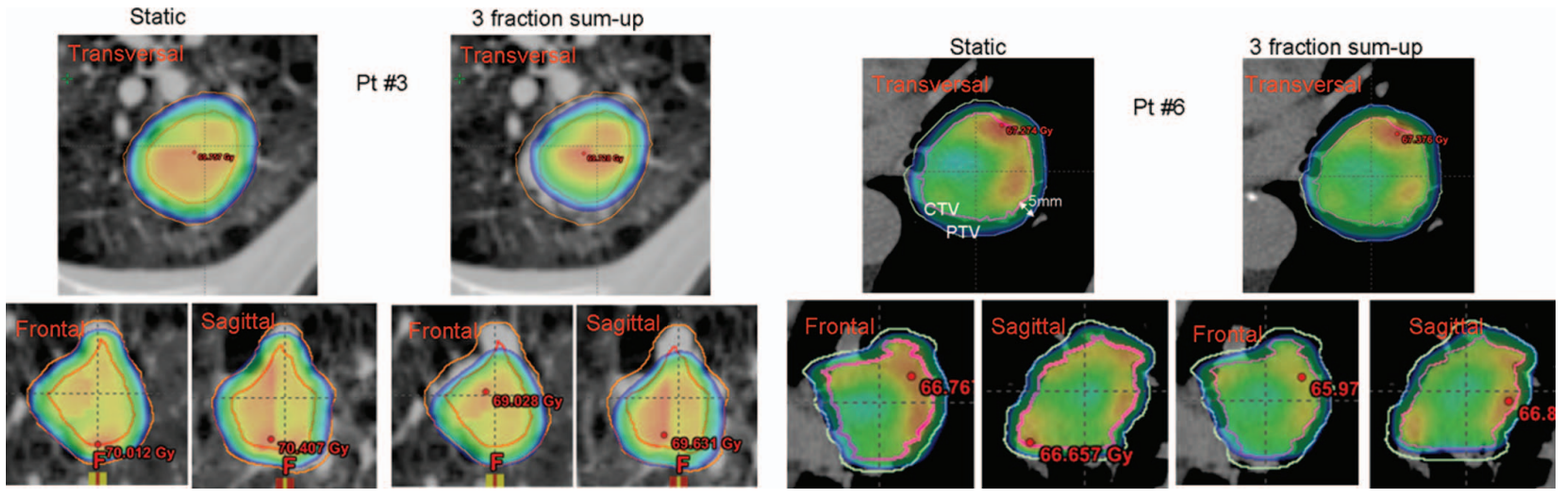




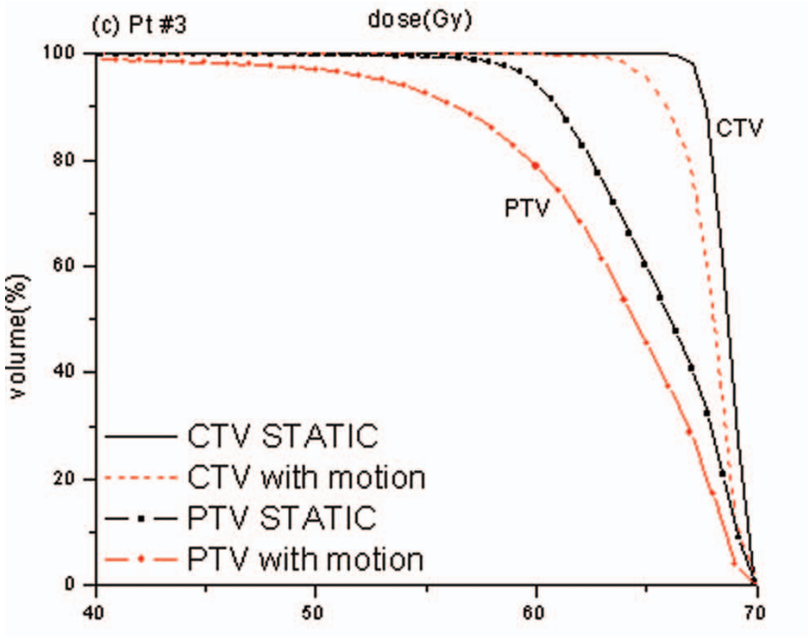
DMLC Movement simulation



Movement tracks from Cyberknife

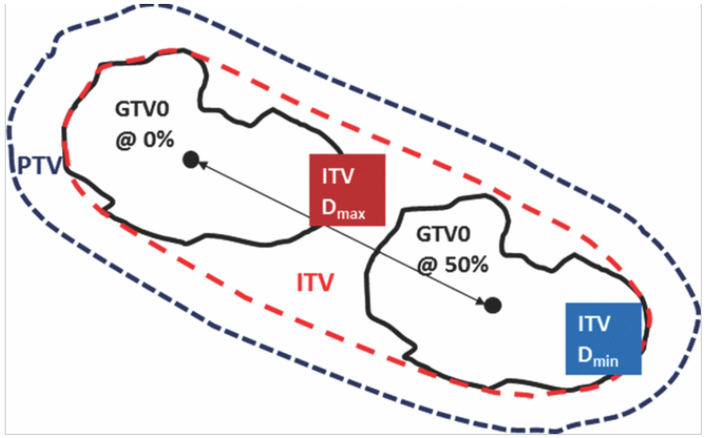


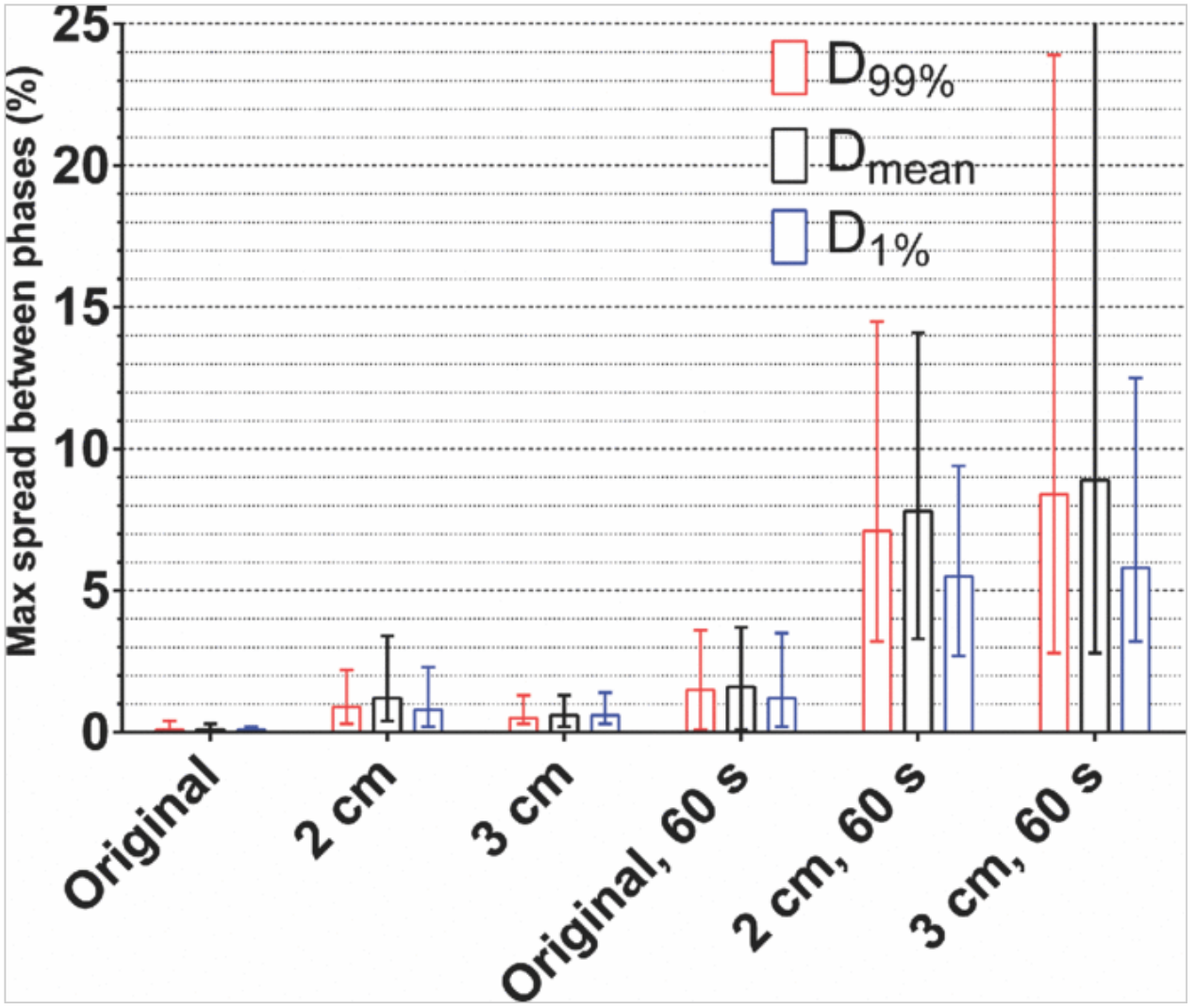
- Target motion converted into leaf motion using PDF from movement tracks
- Segment per segment modified
- Recalculation



Zhao et al, **Medical Physics, Vol. 39, No. 11,**

VMAT SBRT - interplay effect





- Motion kernels 4DCT
- Original and forced -unrealistic- interplay
- eliminated gradient effects
- Diminished effect for large # fractions

Stambaugh et al 2015

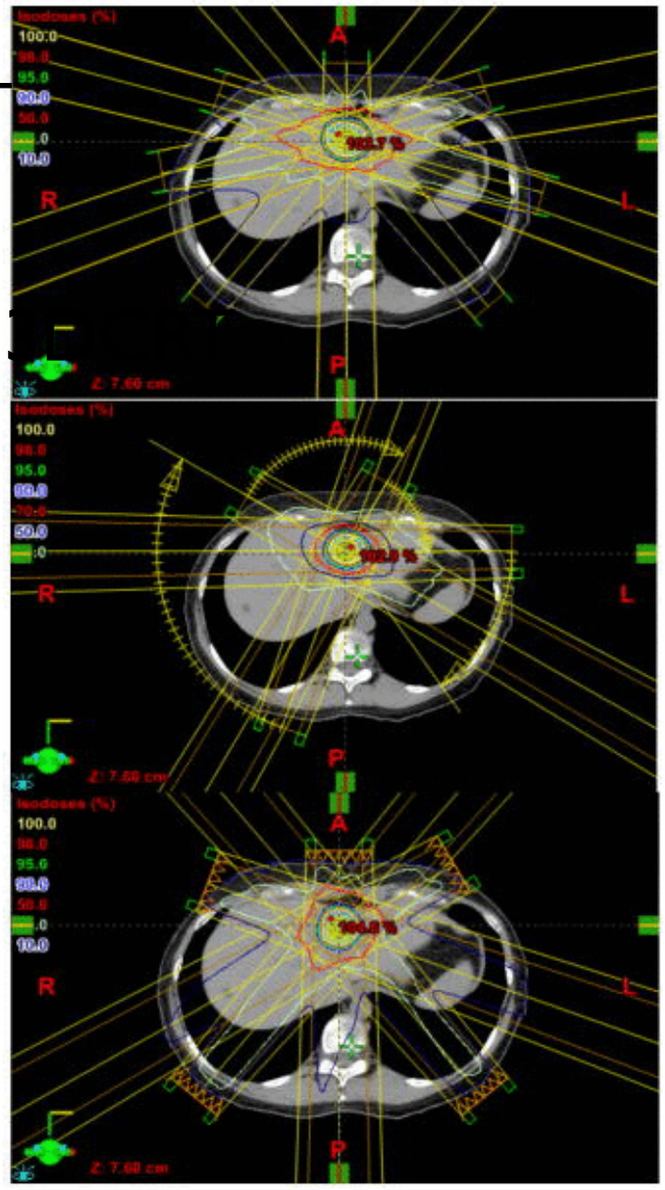
The impact of respiratory motion and treatment technique on stereotactic body radiation therapy for liver cancer

Wu et al Med. Phys. **35**, 1440 (2008)

3DCRT

DArc

VMAT

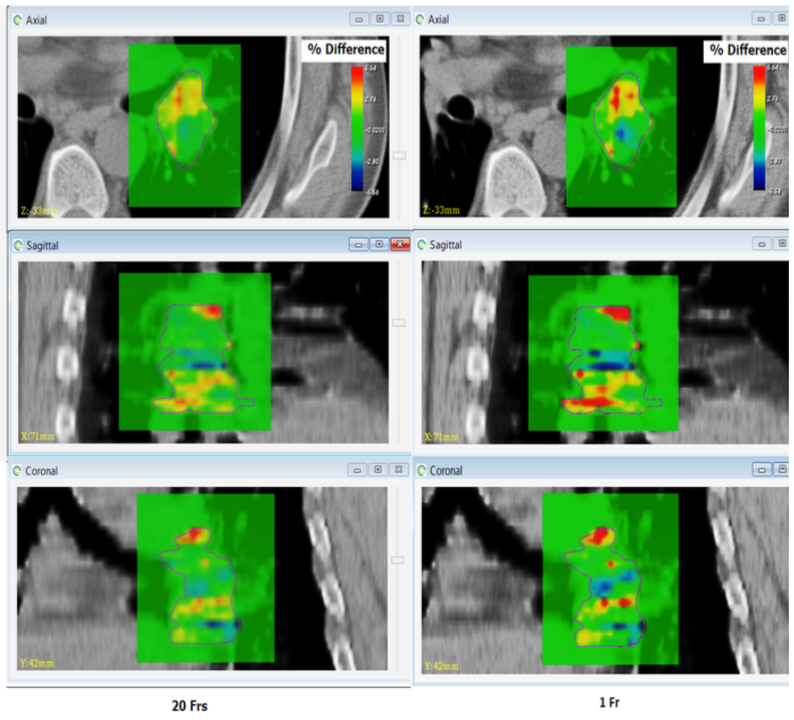


Case No.	Technique	PTV					CTV				
		$\Delta D99$	$\Delta D95$	$\Delta D90$	ΔDmax	ΔMean	$\Delta D99$	$\Delta D95$	$\Delta D90$	ΔDmax	ΔMean
1	3DCRT	−3.5	−1.5	−1.4	−0.4	−0.6	−0.9	−0.7	−0.4	−0.2	−0.3
	DARC	−6.3	−2.4	−1.4	−0.4	−0.6	−1.4	−0.7	−0.5	−0.2	−0.3
	IMRT	−10.0	−3.9	−3.0	−0.7	−1.3	−2.7	−1.7	−1.0	−0.2	−0.4
2	3DCRT	−0.3	−0.2	−0.1	0.0	−0.1	−0.2	0.0	−0.1	0.0	−0.1
	DARC	−0.5	−0.3	−0.2	−0.1	−0.1	−0.3	−0.1	−0.2	−0.1	−0.1
	IMRT	−2.4	−1.2	−0.9	−0.1	−0.3	−1.9	−0.9	−0.5	−0.1	−0.2
3	3DCRT	−1.3	−1.1	−0.8	−0.1	−0.3	−1.0	−0.7	−0.4	−0.1	−0.2
	DARC	−2.8	−1.8	−1.2	−0.1	−0.4	−2.4	−1.2	−0.8	−0.1	−0.3
	IMRT	−0.1	0.0	−0.1	0.0	0.0	−1.0	−0.7	−0.1	0.0	−0.1
4	3DCRT	−4.5	−3.1	−2.2	−0.6	−1.0	−1.8	−1.4	−1.1	−0.4	−0.6
	DARC	−3.3	−2.2	−1.6	−0.6	−0.8	−0.9	−0.7	−0.6	−0.3	−0.4
	IMRT	−16.9	−8.7	−7.0	−1.0	−2.6	−9.3	−5.5	−3.1	−0.4	−1.1
5	3DCRT	−8.1	−4.9	−2.9	−0.4	−1.1	−2.2	−1.6	−1.2	−0.5	−0.6
	DARC	−15.4	−9.9	−5.6	−0.6	−1.9	−4.7	−3.8	−2.5	−0.6	−1.0
	IMRT	−14.8	−12.6	−9.2	−1.4	−3.1	−8.9	−8.3	−6.3	−0.9	−2.0

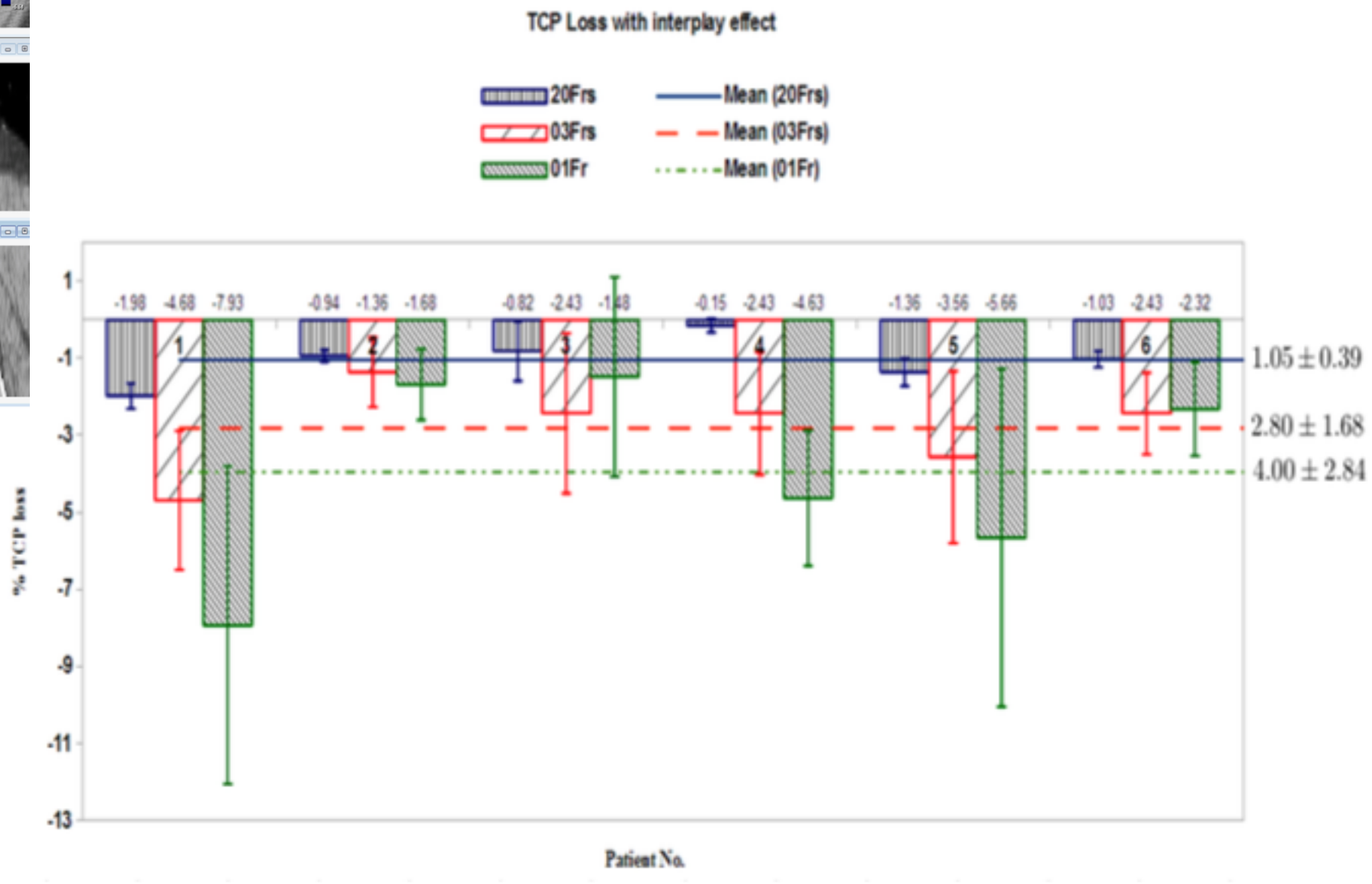
VMAT SBRT an overview…

	Technique	Effect	Comment
Li et al	VMAT/FFF	PTV degraded up to 7%	Minimum margin of 5mm necessary
Riley et al	VMAT	<2%	4DCT tracks. Larger eff
Ong et al	2-arc VMAT SBRT	98.5% for large modulated plans met gamma 3%, 99.5% for low modulation	not homogeneous
Rao et al	VMAT	<1% for GTV	mapping on 4DCT
Zhao et al	VMAT	Mostly OK, some outliers in single patients	Simulation using CK-tracks
Yang et al	DMLC	<3%	6 patients
Ehrbar et al	VMAT	GTV<3.8% average	

Lung DMLC



MC simulation
Connection to TCP

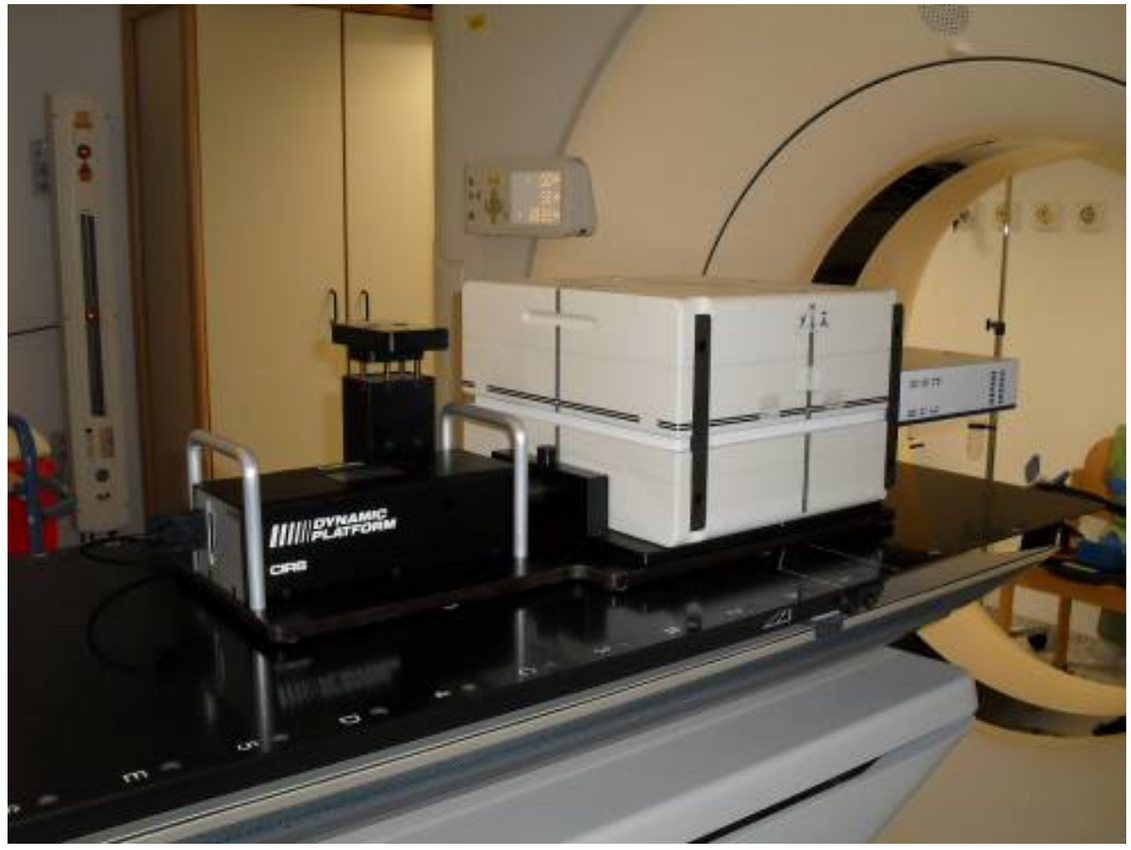


Selvaraj et al (2013)

Measurement setup

Fleckenstein et al., submitted

- IBA Matrixx Evolution
- IBA Multicube
- CIRS dynamic platform model 008PL (accuracy 0.05mm)
- VMAT plan generated in Monaco 2.0.3.beta

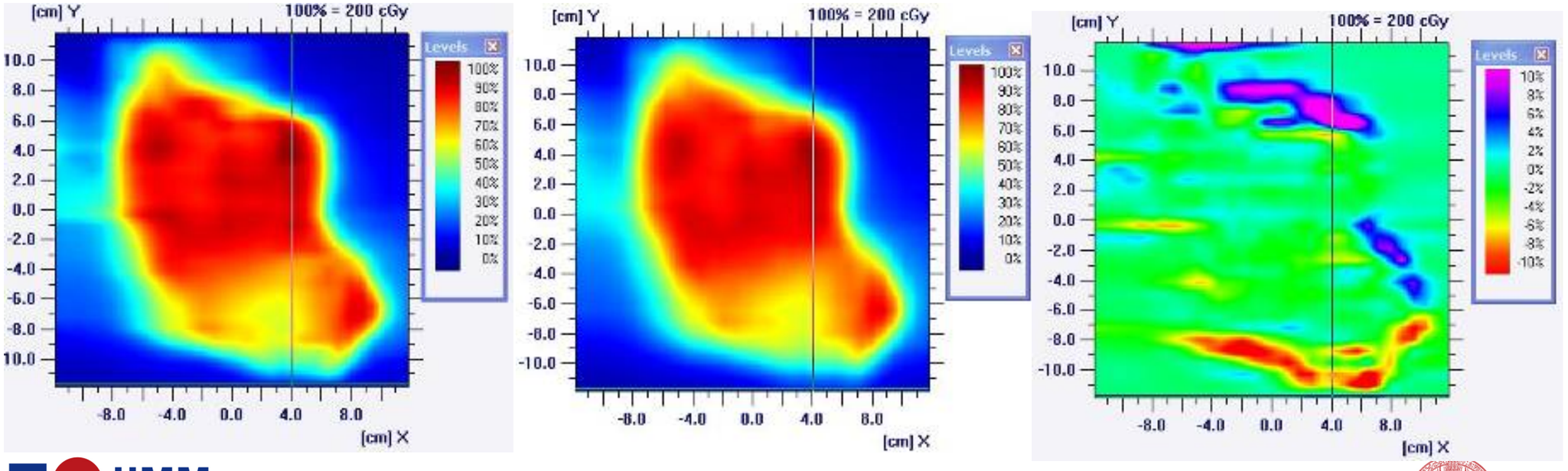


Court. Frank Löhr

Fleckenstein et al.,

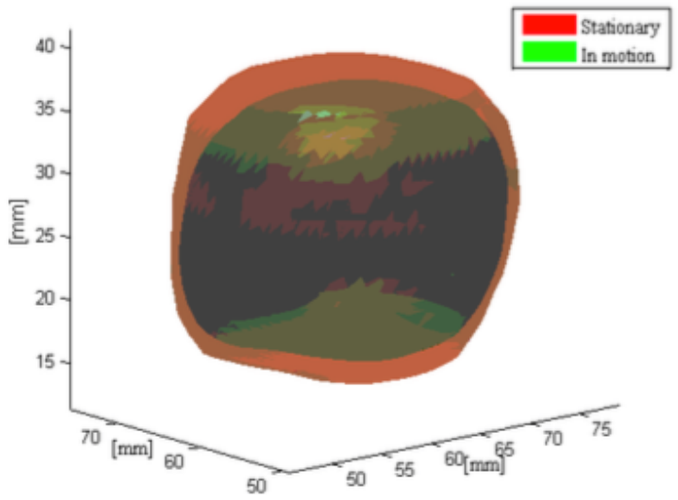
A=10mm, T=3.6s, cos4-motion trajectory

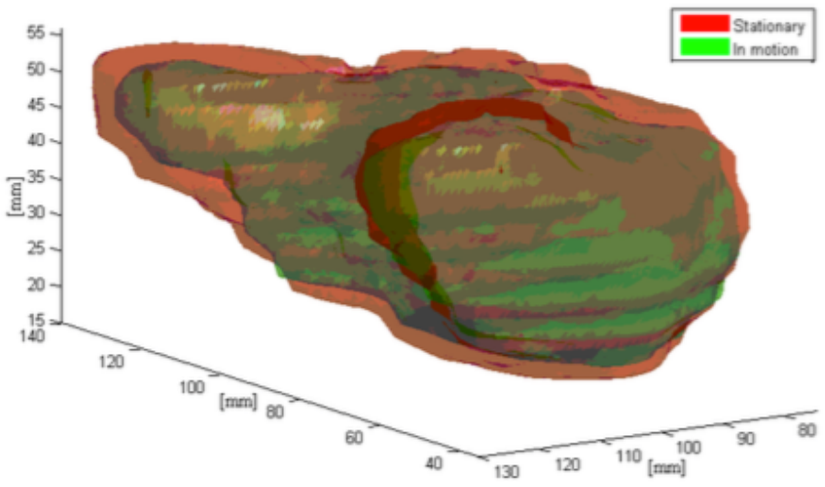
static case with motion difference map



Court. Frank Löhr

VMAT- interplay effect : gel measurements





Lung, 1cm/4s

Prostate, 2cm/5s

$$D_{IP} = \frac{(D_{duringmotion} - D_{convolvedstat.})}{D_{convolvedstat.}} \times 100$$

$D_{static,corr} \otimes F_{motion}$

	Lung	Prostate
Motion blurring+IP+ME	2.5%	3-4%
Interplay Effect	1.4%	2.3%

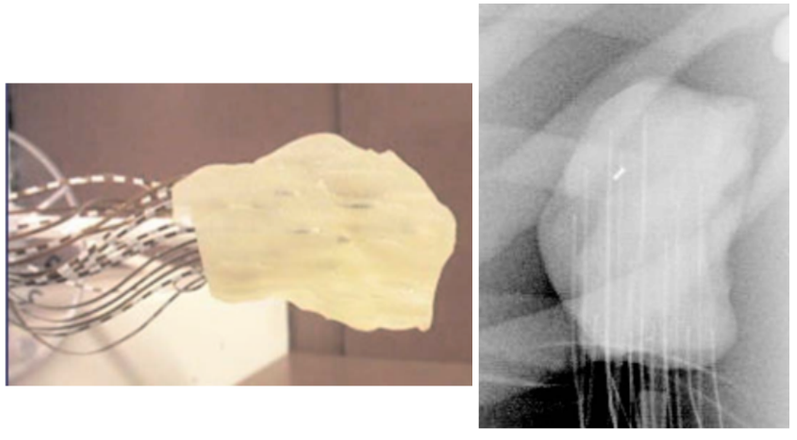
S.Ceberg (2013)

Phantom dependence?

TABLE I. Characteristics of the nine treatment plans created in this study. Minimum GTV dose and hot spot are point doses. The only difference between plans 3 and 3a and between plans 5 and 5a is the dose rate.

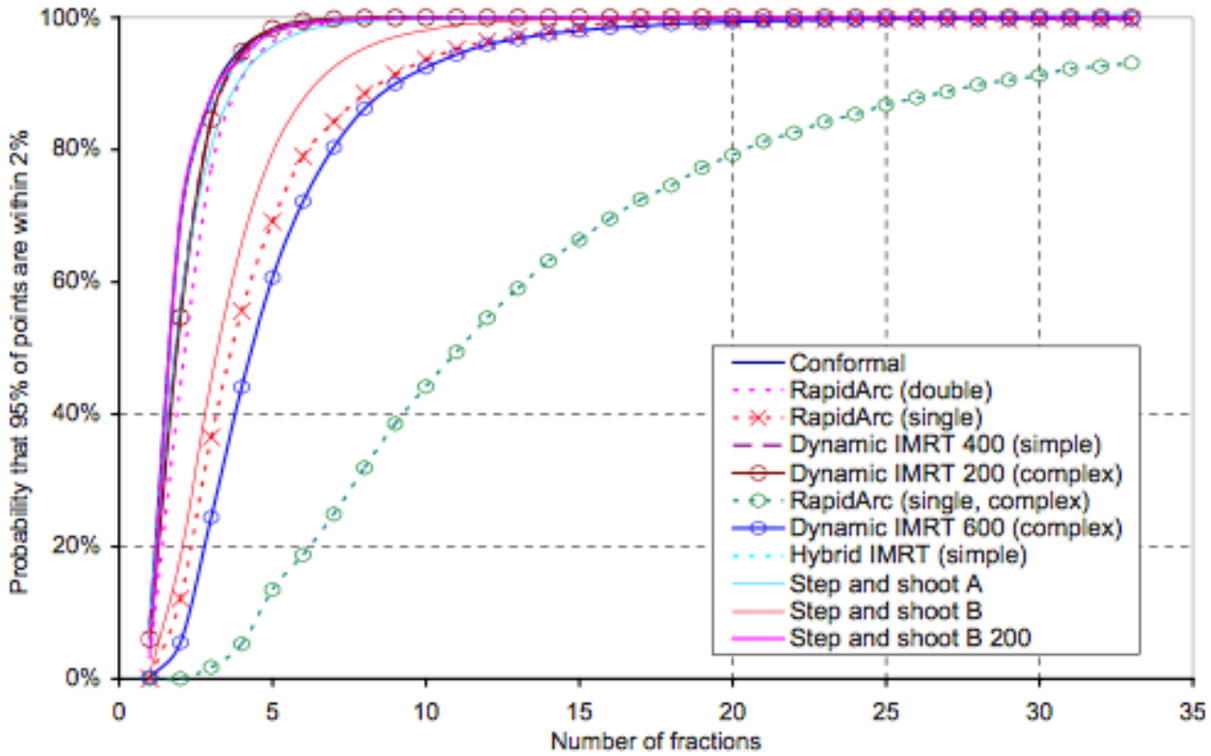
	Treatment plan	TPS	Linac	Number of fields	Dose rate (MU/min)	Total MU	Minimum GTV dose (%)	Hot spot (%)
1	Conformal RT	Eclipse	Tx	6	600	289	97	122
2	Step-and-shoot IMRT A	Pinnacle	iX	5	600	1696	92	118
3	Step-and-shoot IMRT B	XiO	iX	5	600	680	90	114
3a	Step-and-shoot IMRT B (low dose rate)	XiO	iX	5	200	680	90	114
4	Dynamic IMRT (simple)	Eclipse	Tx	6	400	503	98	117
5	Dynamic IMRT (complex)	Eclipse	Tx	8	600	818	97	123
5a	Dynamic IMRT (complex, low dose rate)	Eclipse	Tx	8	200	818	97	123
6	Hybrid IMRT	Eclipse	Tx	2/3 (conformal/IMRT)	600/400	137/259	99	119
7	RapidArc (single)	Eclipse	Tx	1	600	438	97	124
8	RapidArc (double)	Eclipse	Tx	2	600	435	97	127
9	RapidArc (single, complex)	Eclipse	Tx	1	600	980	95	130

Court et al (2010)

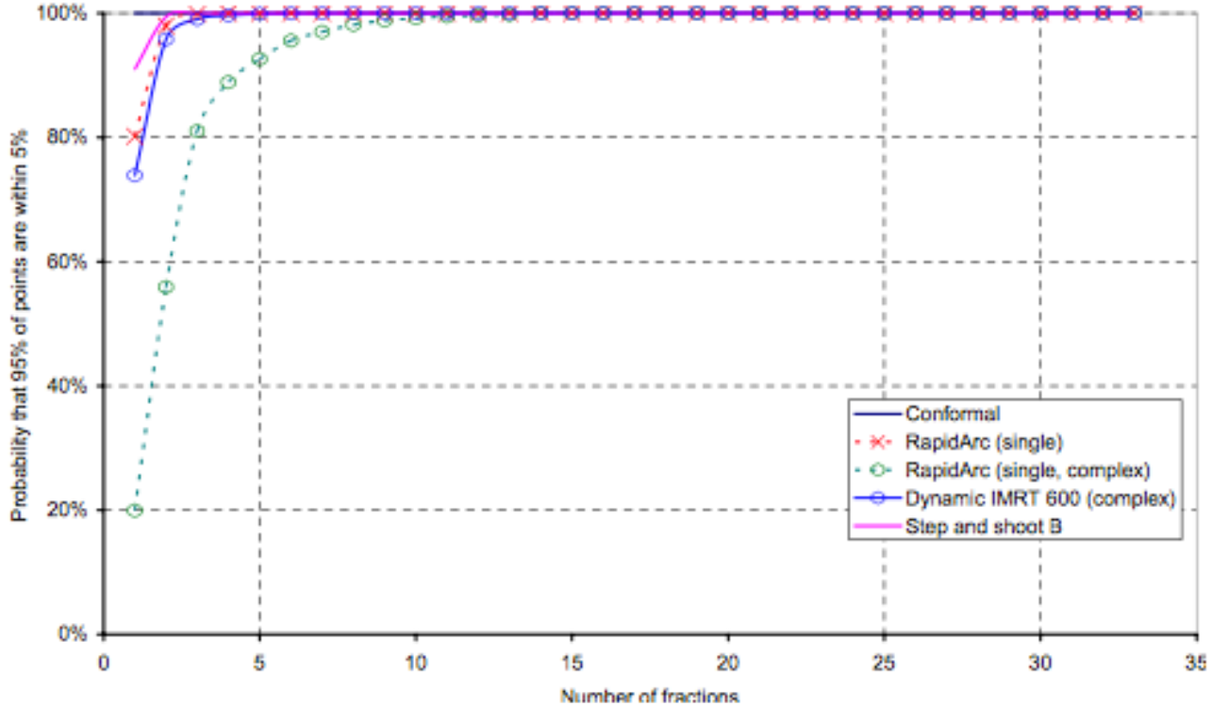


Results

2%



5%



- All but 1 complex VMAT plan converged
- Result dependant on technique, doserate and modulation

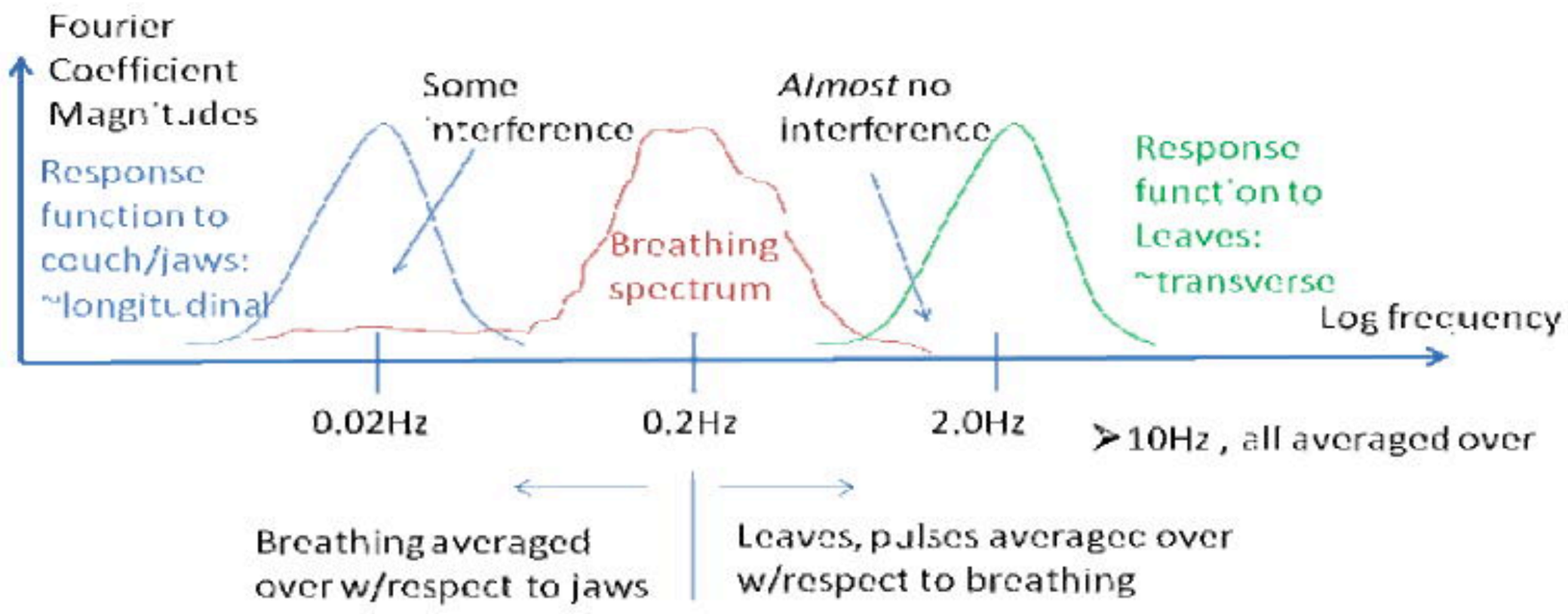
Court et al (2010)

DMLC and breathing

- Interplay effect is there for single fields and single fractions.
  - Depending on degree of modulation
  - Depending on gantry angle
  - levelled out by blurring effect over larger number of fractions

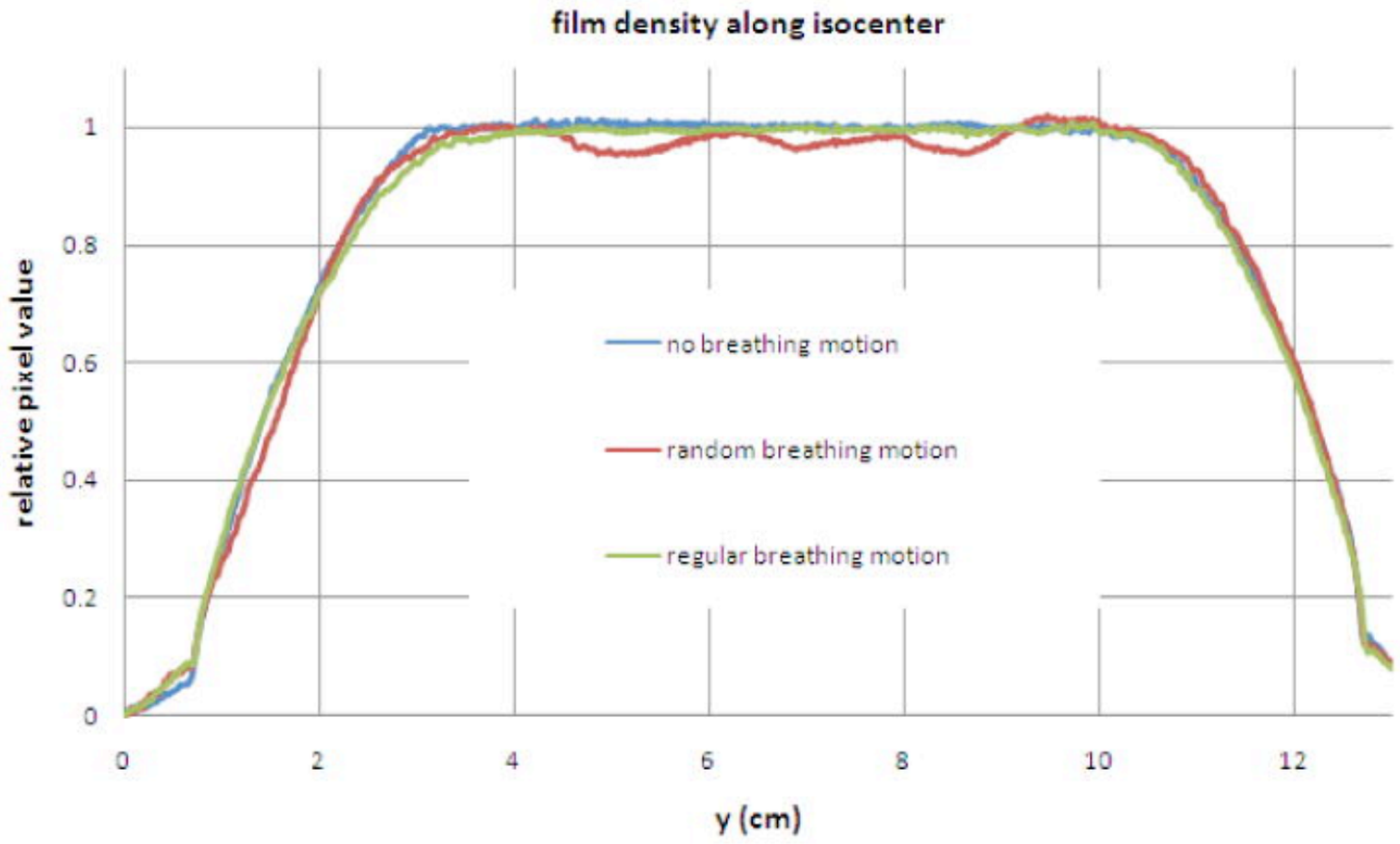
TomoTherapy

- Helical treatment, binary MLC
- Lateral modulation : leaf open times
- Longitudinal modulation : Table/Pitch

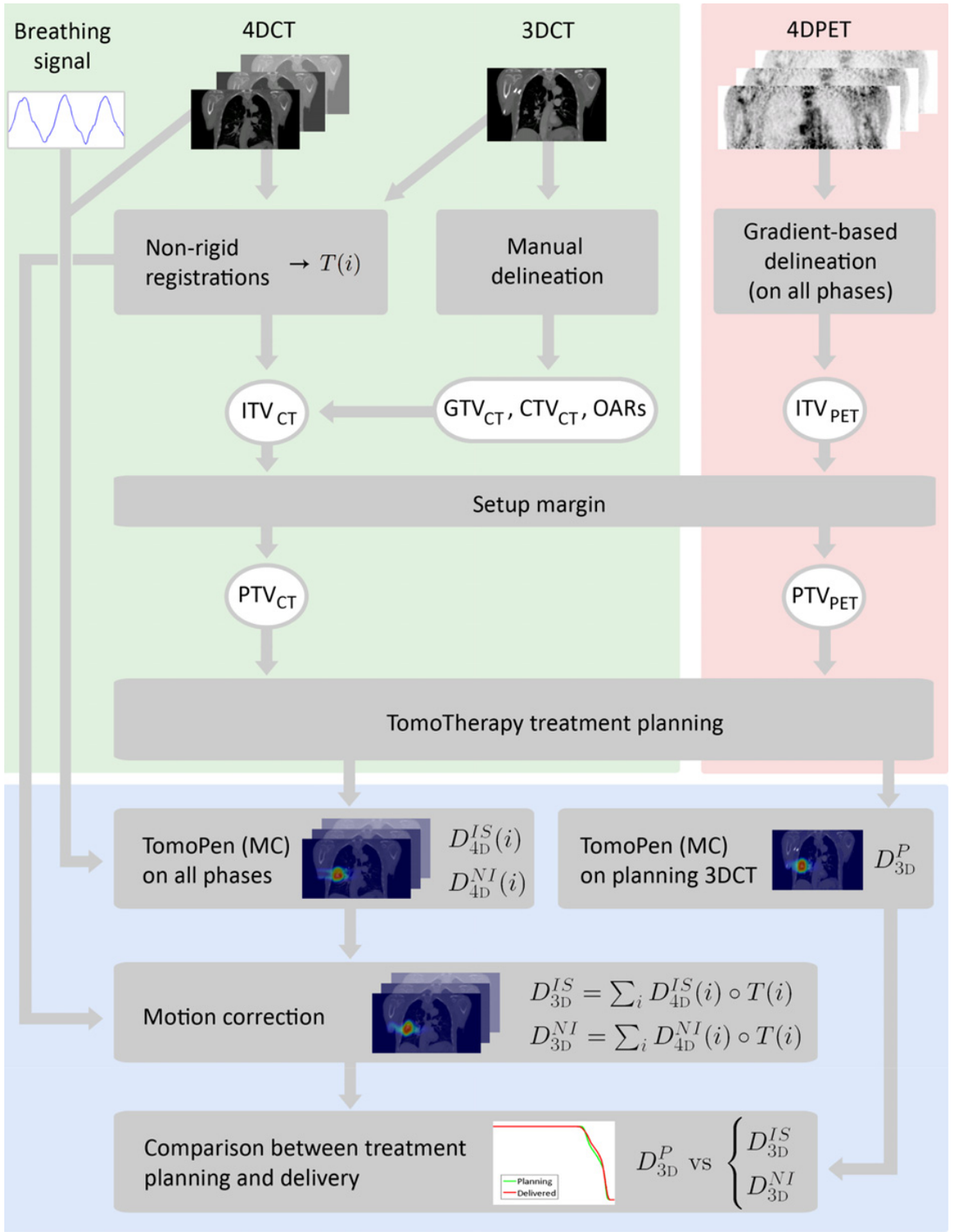


TomoTherapy

- Regular Motion : small blurring
- irregular motion: small discrepancies when large as relative to fieldsize (2.5cm)



Monte Carlo sim.



Tech.	Δ (Dp,ptv - Dc,ctv) Interplay	Δ (Dp,ptv - Dc,ctv) Mov. only
4DCT-SIB	0.45% (-1.3,2.7)	0.47% (-1.4,2.7)
4D-PET SIB	-0.34% (-1.2, 2.6)	-0.29% (-2.4,2.1)
SBRT 3x18Gy	1.19% (-1.5,2.8)	1% (-2,2.8)

Sterpin et al.,Radiotherapy and Oncology 104 (2012) 173–180

Intrafraction movement in lung

- Dosimetric effects are linked to the relative frequencies of all the movements.
- There seems to be a possible problem with leaf/ movement interplay in DMLC techniques (VMAT/ DMLC) which can not be solved by PTV-margins.
- The size of this effect is dependent on the relative movement (size and speed).
- VMAT : depending on whatever your leaves are doing (can have low modulation)
- Possible solutions can be found in tracking, gating ...

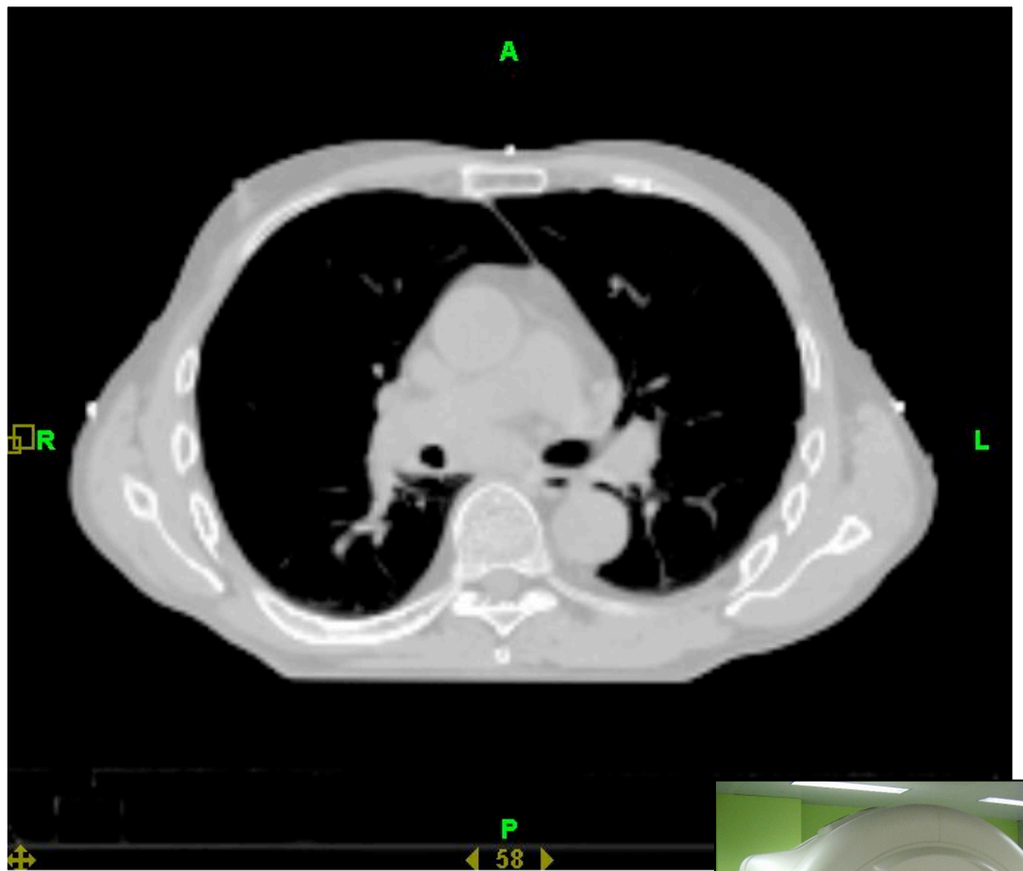
In total…

- Effects on the dose distribution are not straightforward.
  - Depending on frequency, modulation, patient
  - Over all fractions things do not look that bad….
  - Are homogeneous phantom studies a good way to study these effects? There is no change of scatter conditions there.

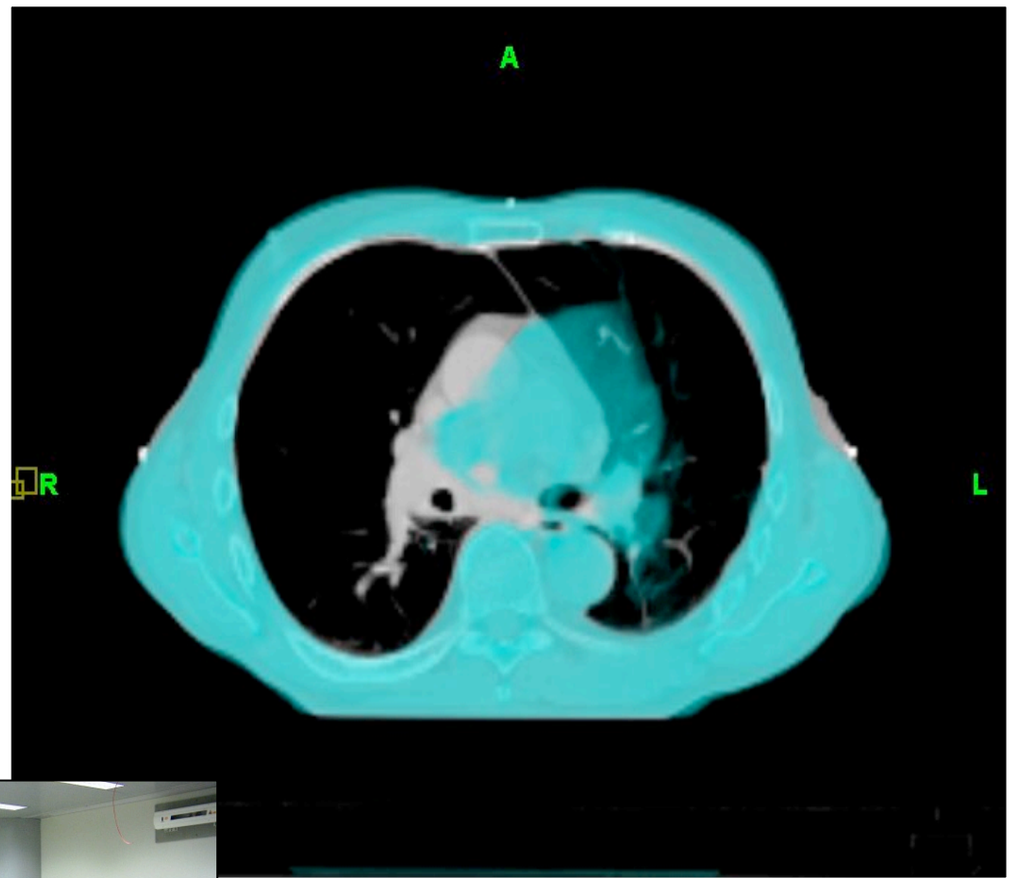
Anatomical Deformations

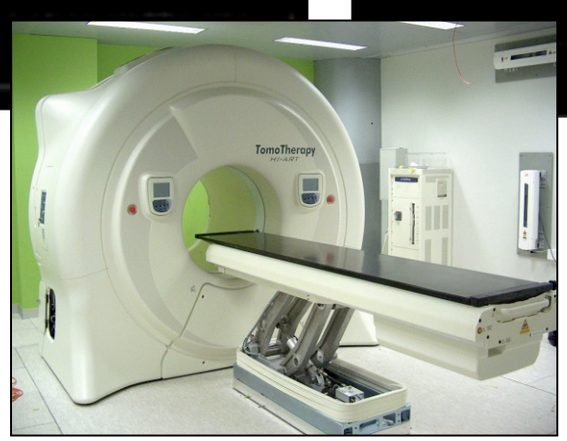
Anatomical deformation

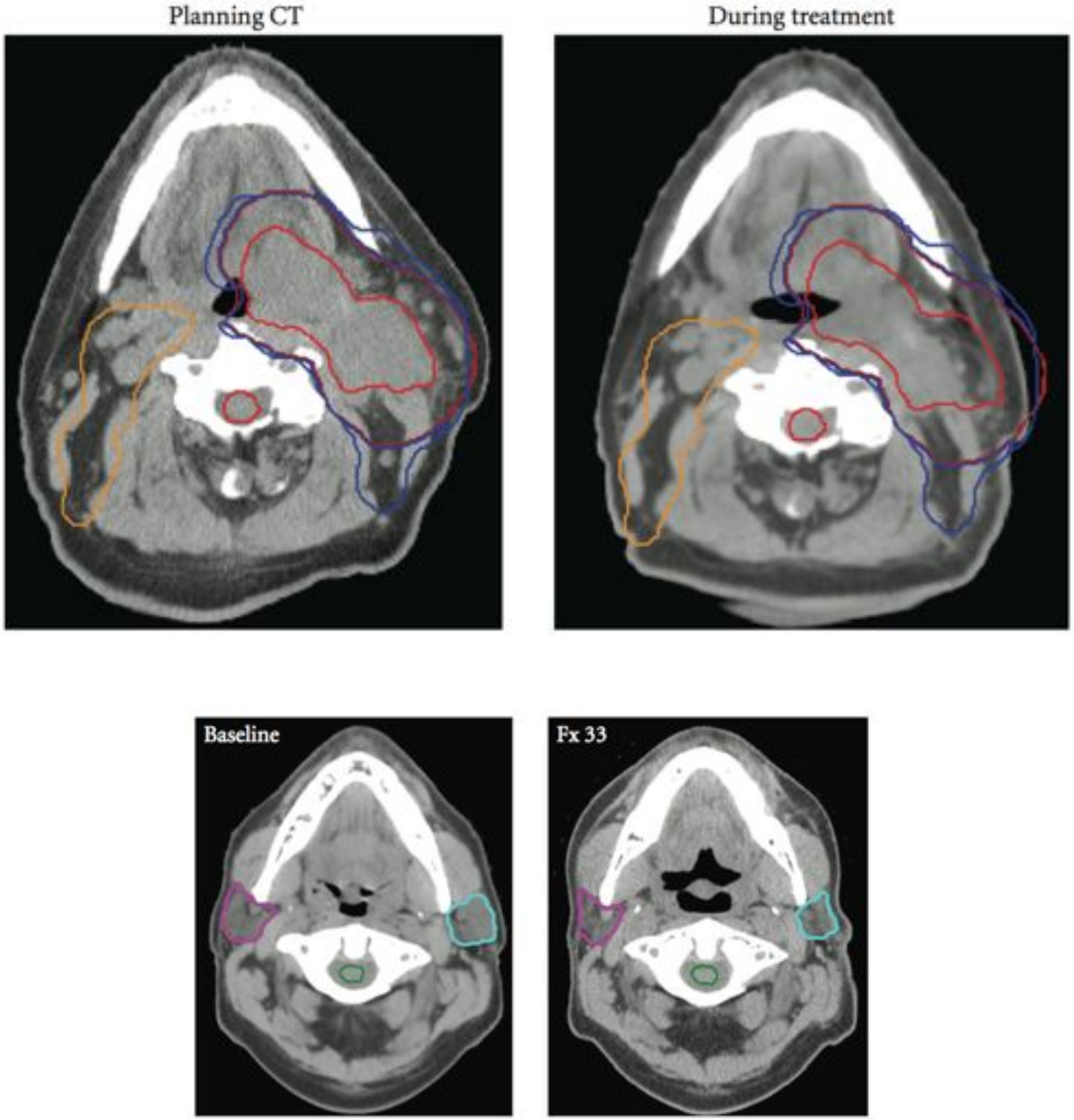
Planning CT



Day 2 of treatment

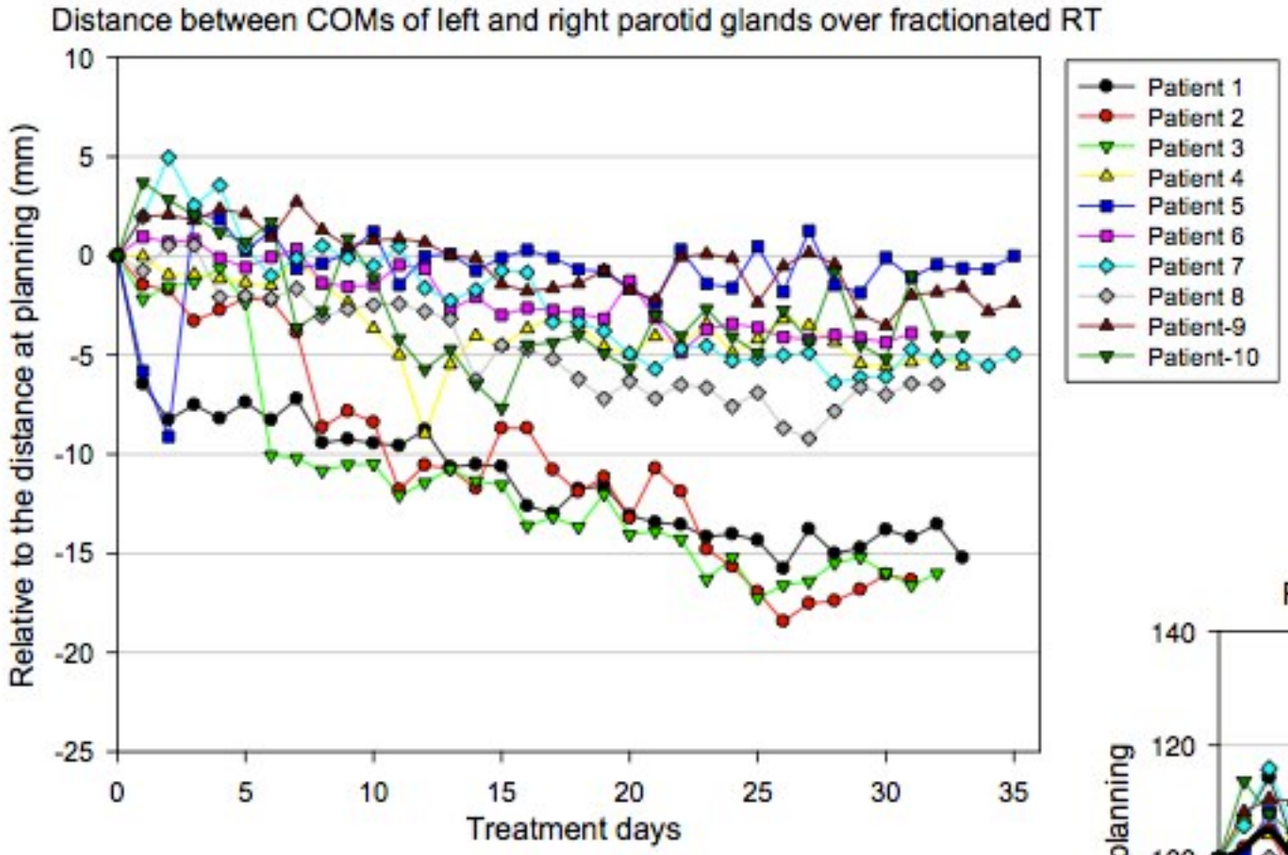


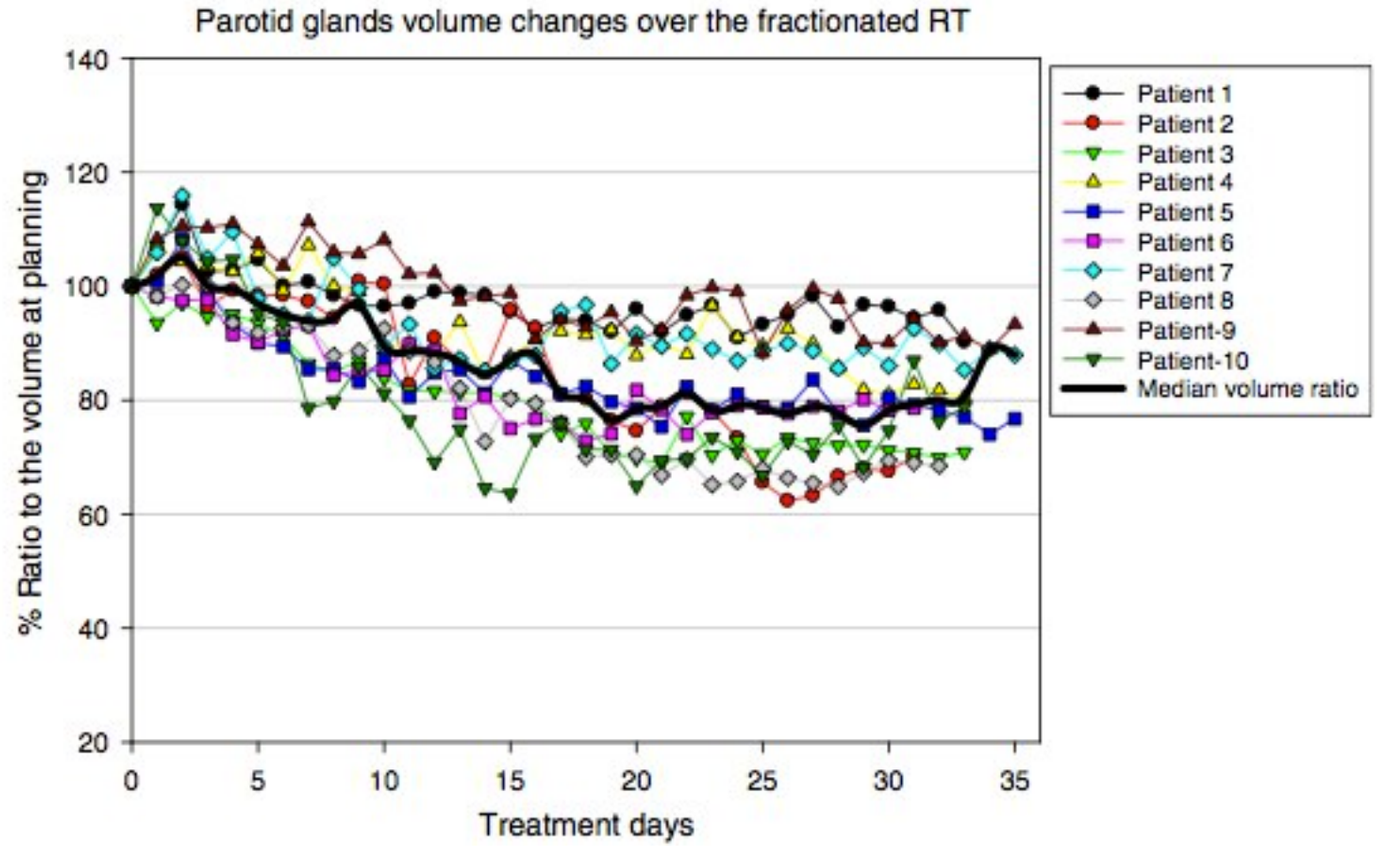




Schwartz et al. ‘Adaptive radiotherapy for head and neck cancer – Can an old goal evolve into a new standard?’ Journal of oncology 2011

QOL : Parotids

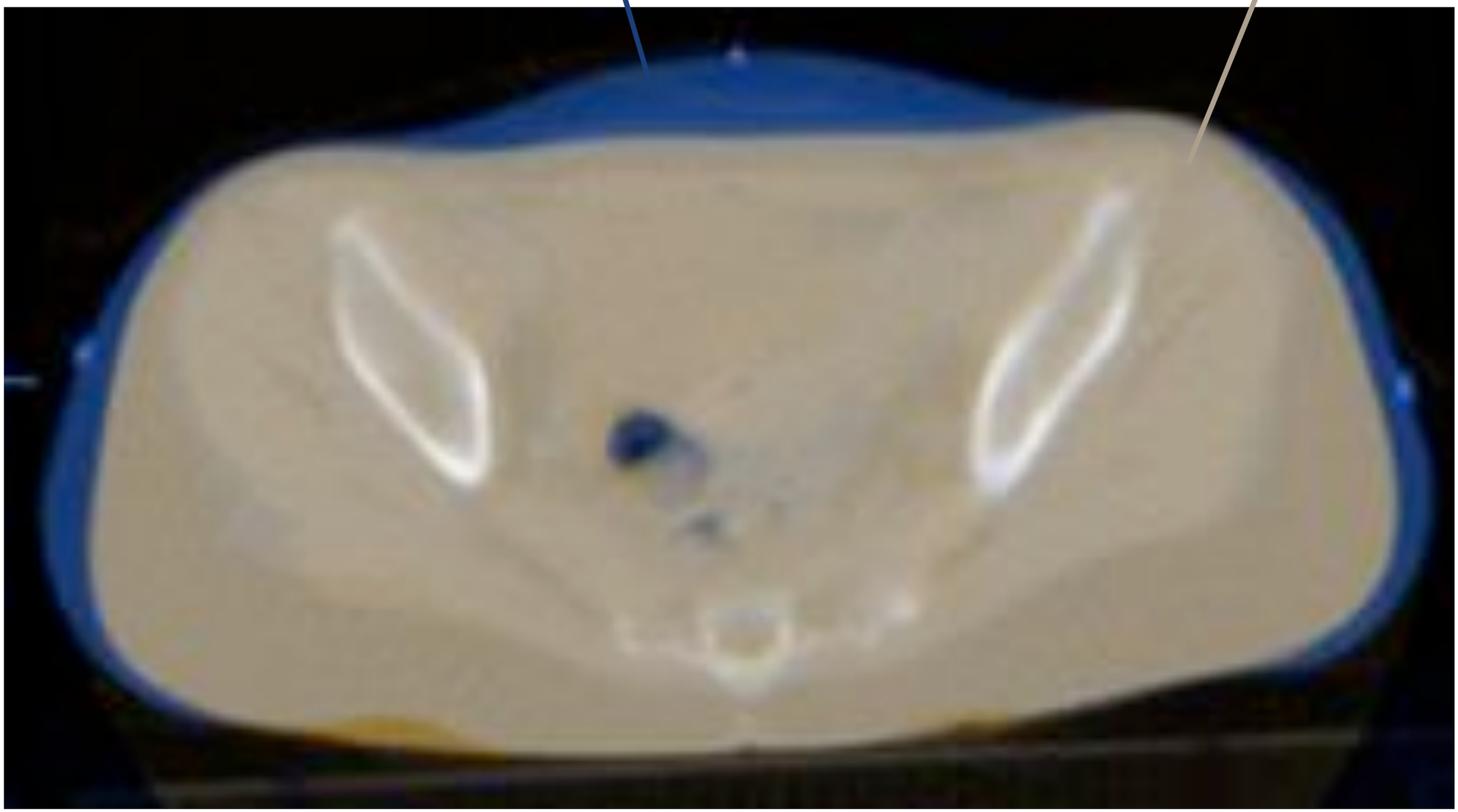




Lee et al Radiotherapy and Oncology 89 (2008) 81—88

kV planning CT

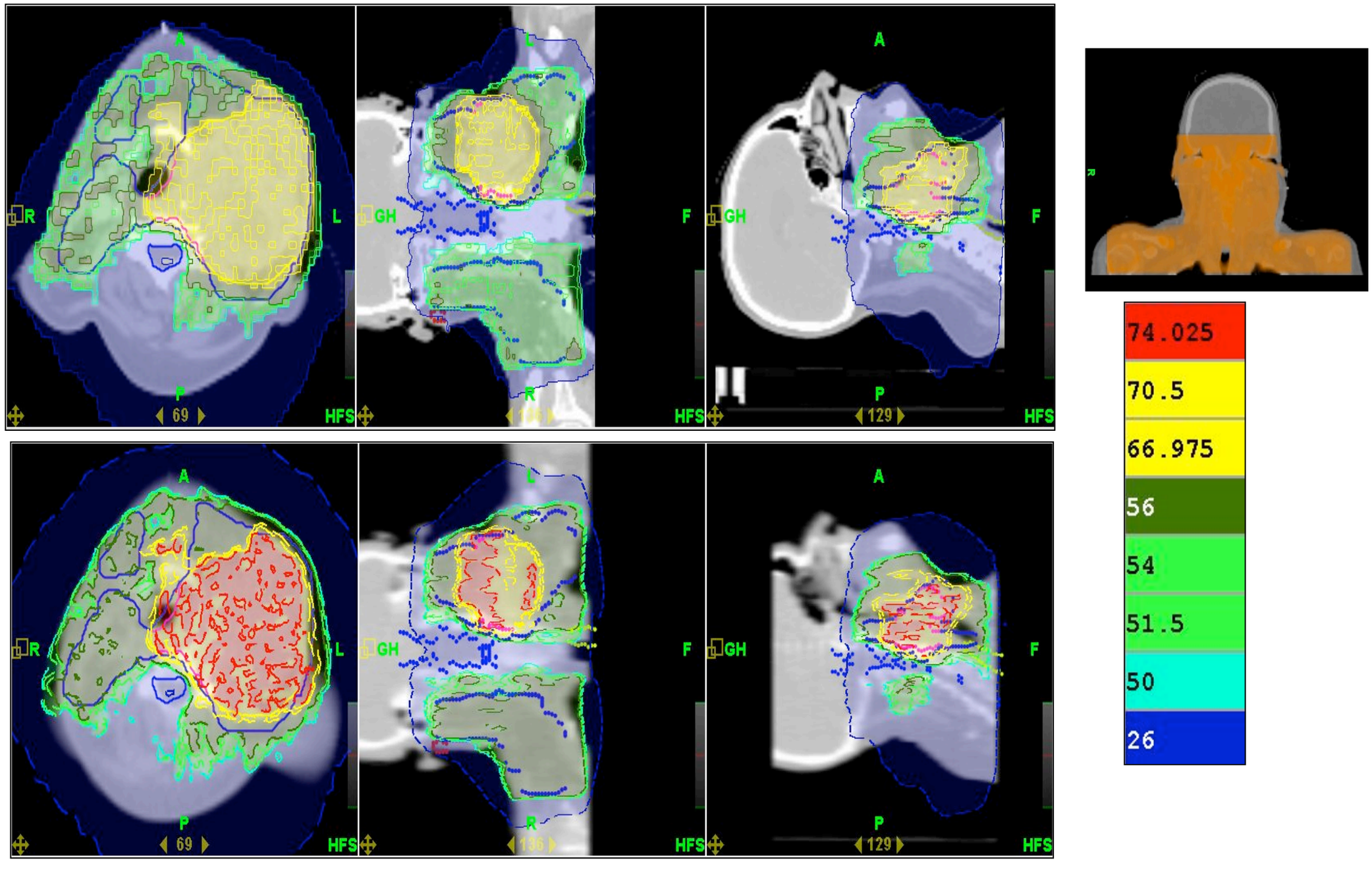
MVCT

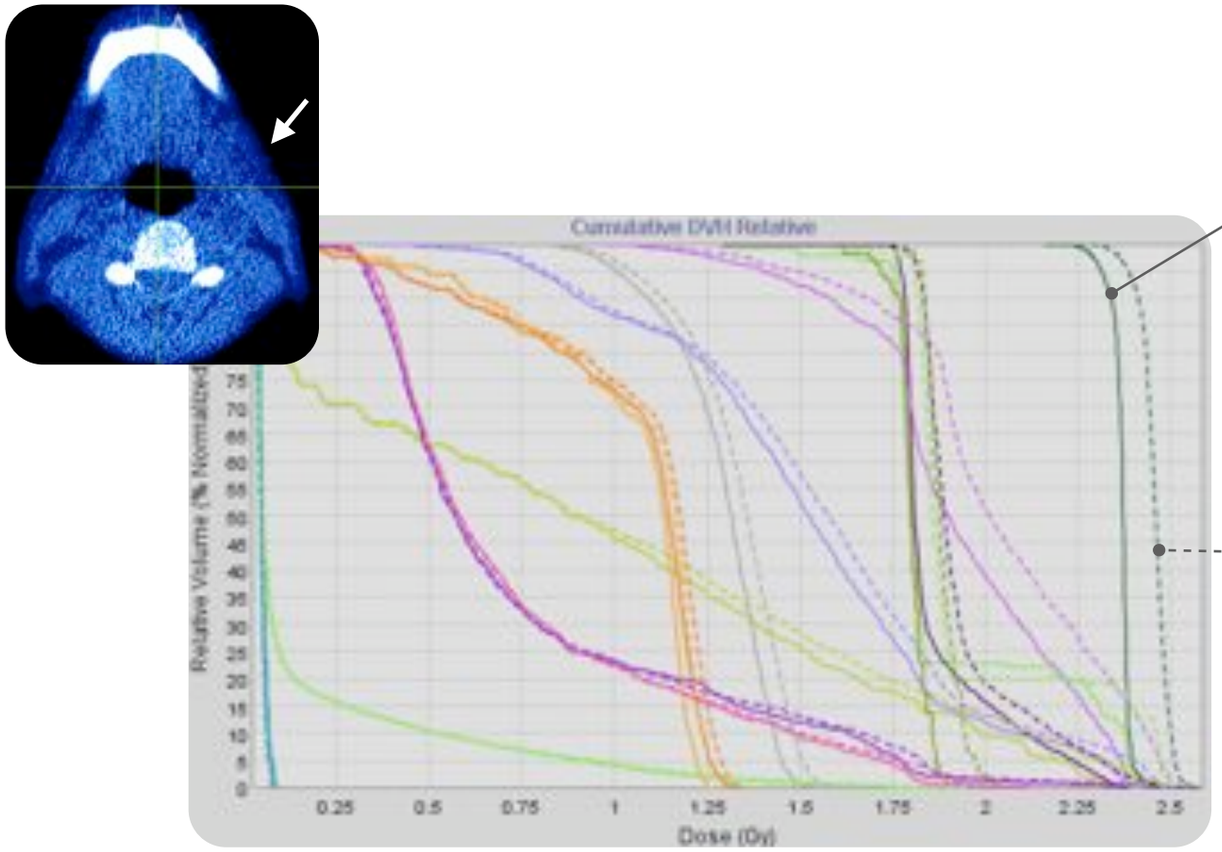


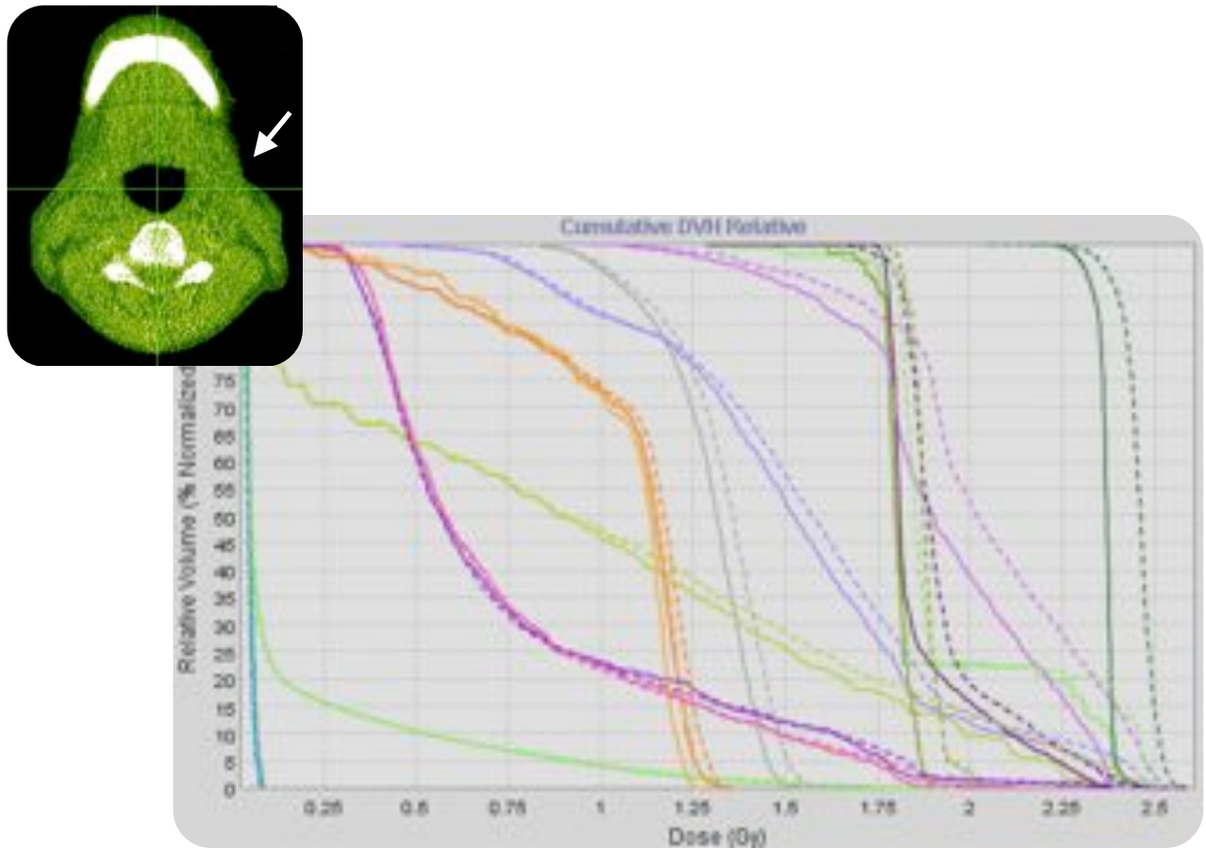
Toolbox

- Deformable registration
  - Volumes
  - Dose (NOT verified)
- ART
  - Dose Recalculation
  - Plan of the day-approach

Dose Recalculation

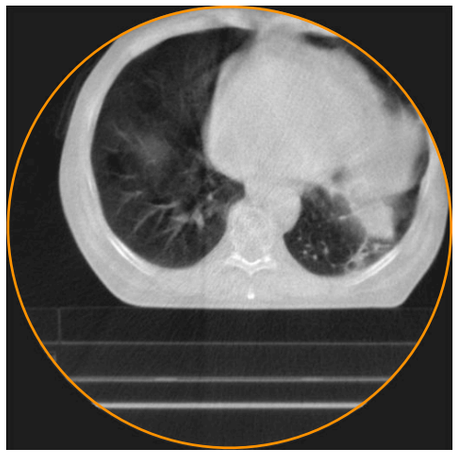



Cumulative DVH Relative
Relative Volume (% Normalized)
Dose (Gy)
kV calculated dose
MV calculated dose


Cumulative DVH Relative
Relative Volume (% Normalized)
Dose (Gy)

What's the catch?

- Adaptive strategies allow us to recalculate daily dose and see the immediate effect of deformations or geometrical uncertainties.
- Since this was a "buzzword" vendors were aching to have us spend our cash on these expensive options.
- Are they feasible in clinical routine?
  - MVCT : Duchateau *et al* 2010 *Phys. Med. Biol.* **55** N329
  - ConeBeamCT
    - Daily calibration
    - Check contouring
    - Missing information



Deformations : comment

ART will only work if there exists a clear, automatic workflow that is integrated in planning, imaging, treatment and follow-up.

Deformable registration

- The basis for a successful Adaptive Strategy
- The algorithm should be
  - usable in clinical routine
  - verified

Verification

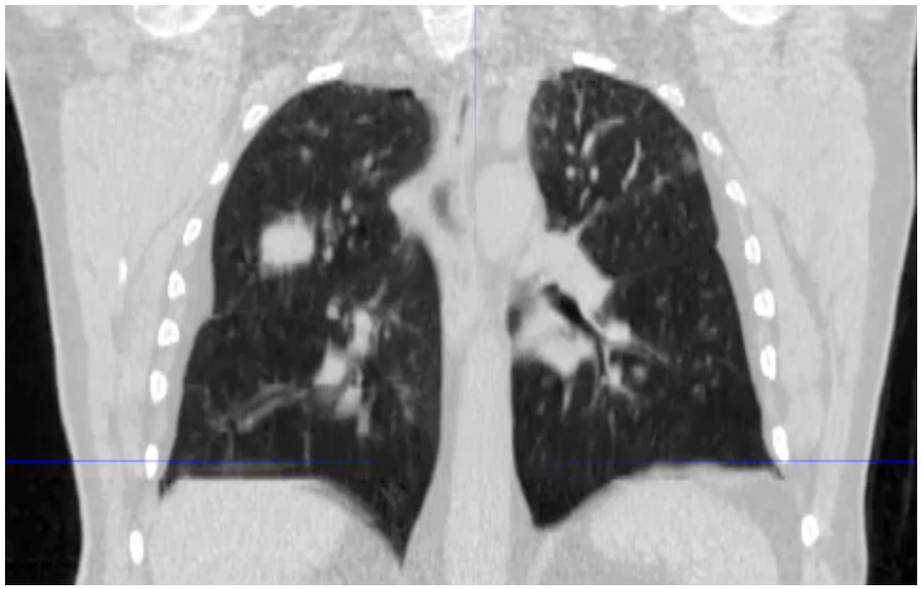
1. http://www.creatis.insa-lyon.fr/rio/popi-model

2. 6 4DCT Sets
   - 3 with 100 POI - All phases
   - 3 with 100 POI - In and exhale

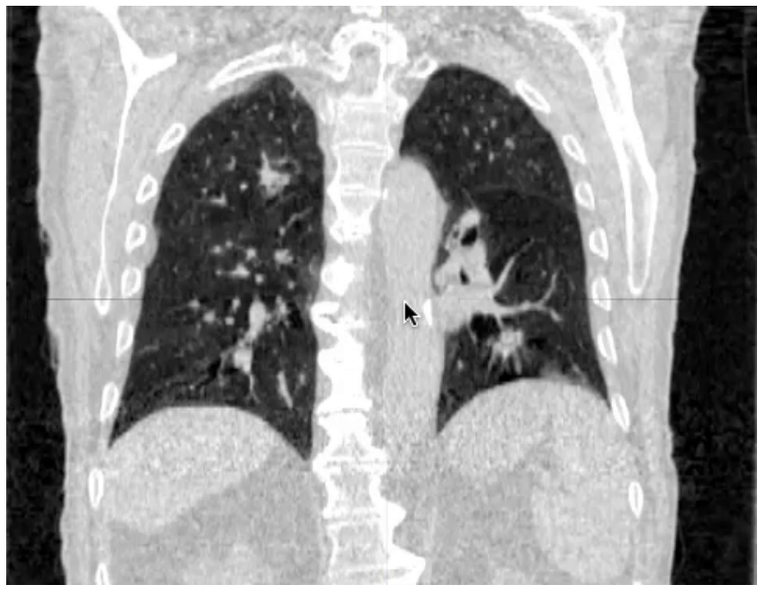
3. POI on vessel and bronchial bifurcation

4. For everyone to download !

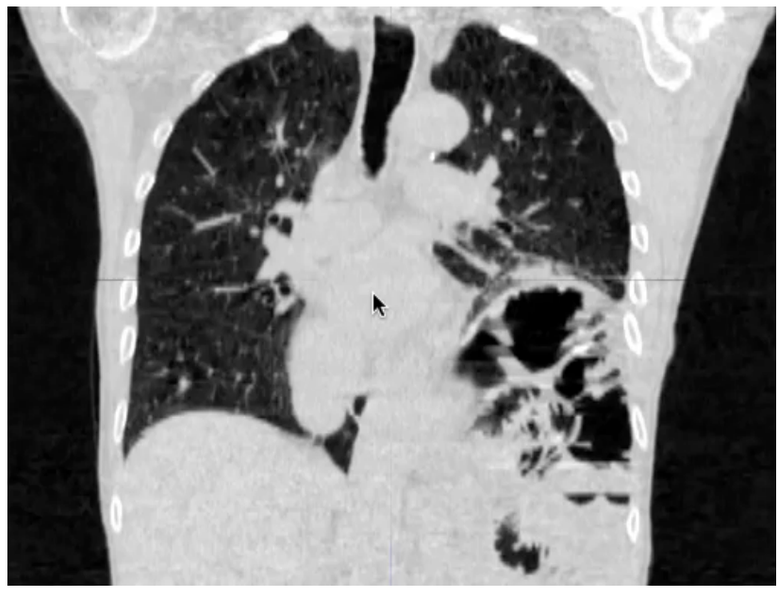
Popi 1

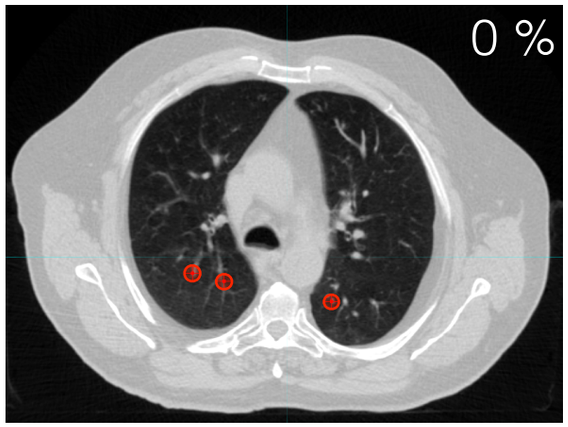


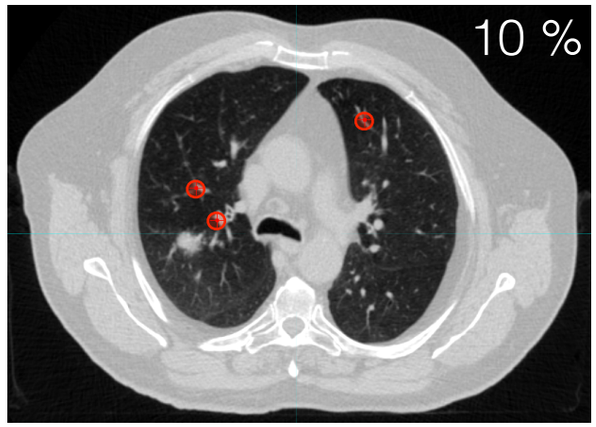
Popi 2

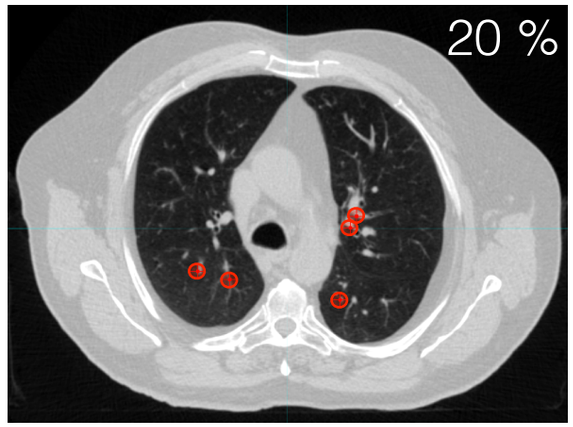


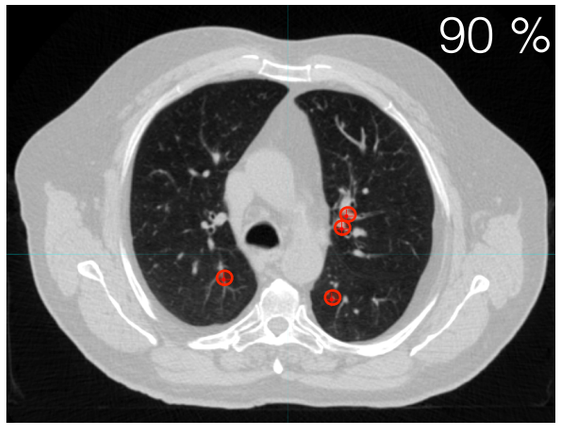
Popi 3









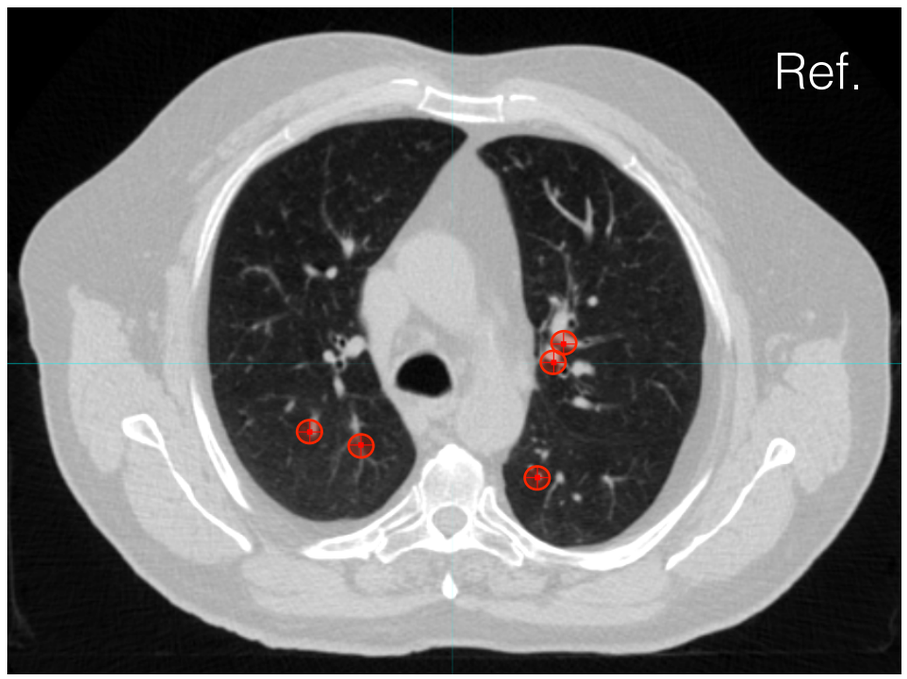


deformable

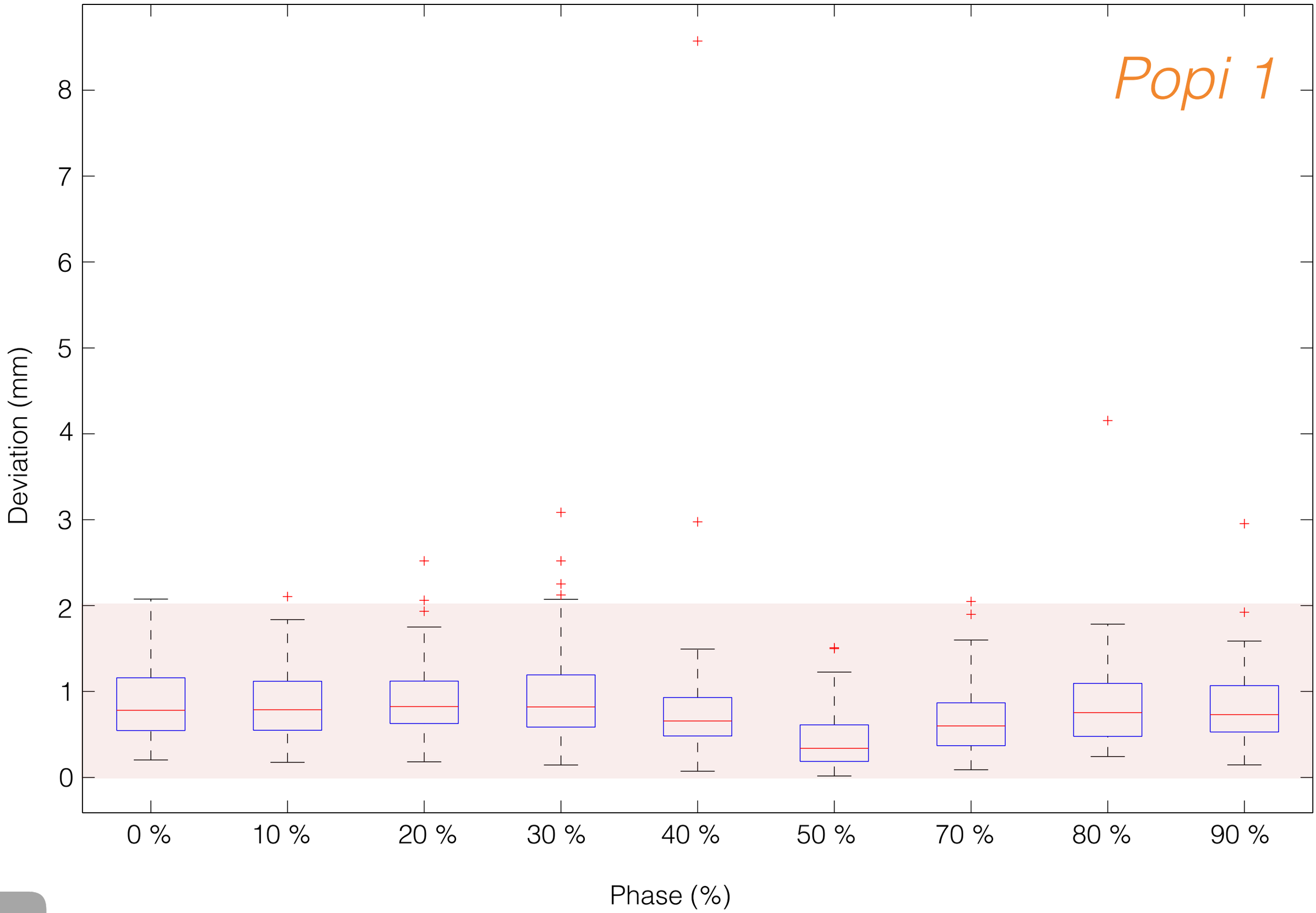
deformable

deformable

deformable

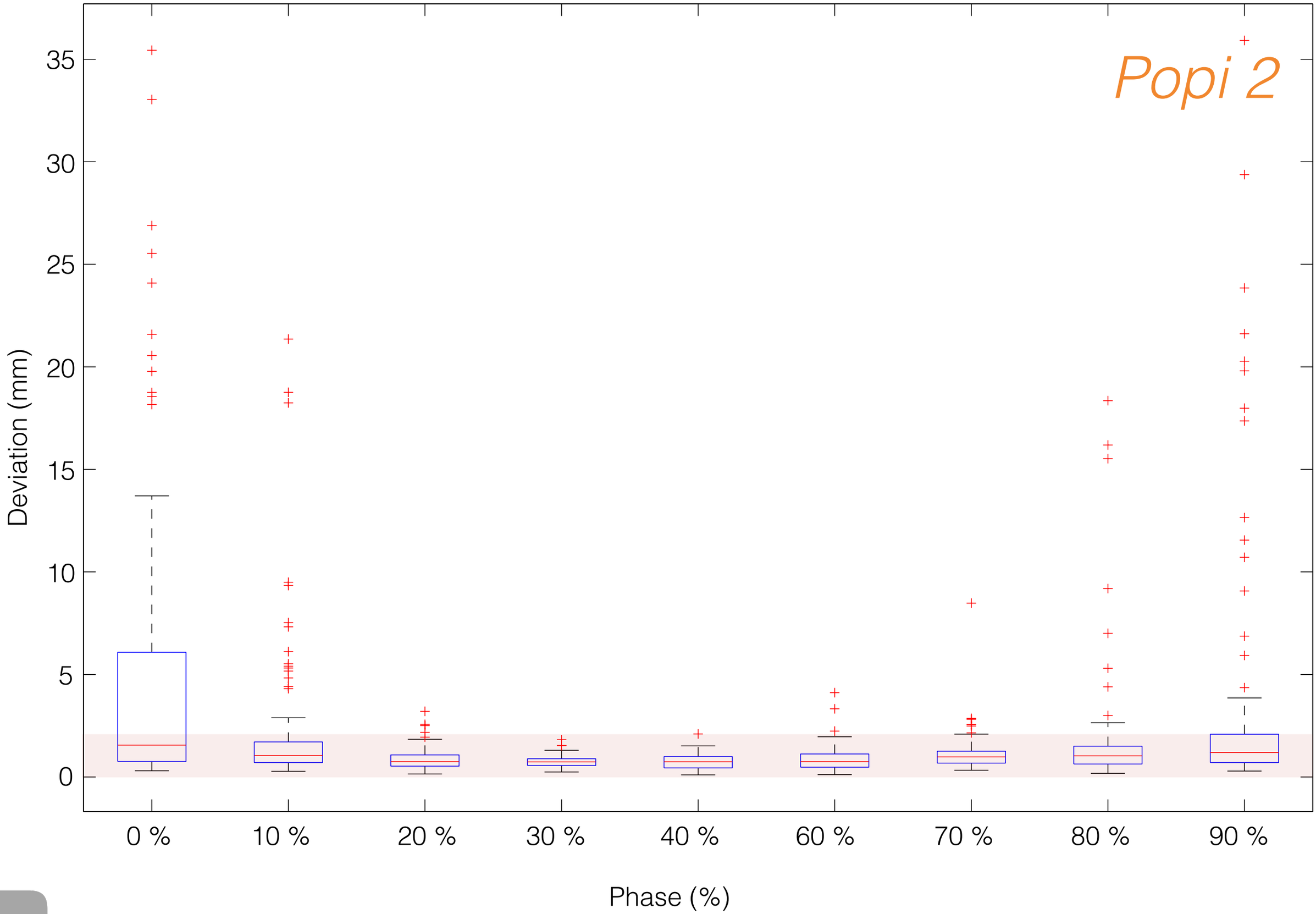


$$d(p,q) = \sqrt{(p1-q1)^2 + (p2-q2)^2 + (p3-q3)^2}$$



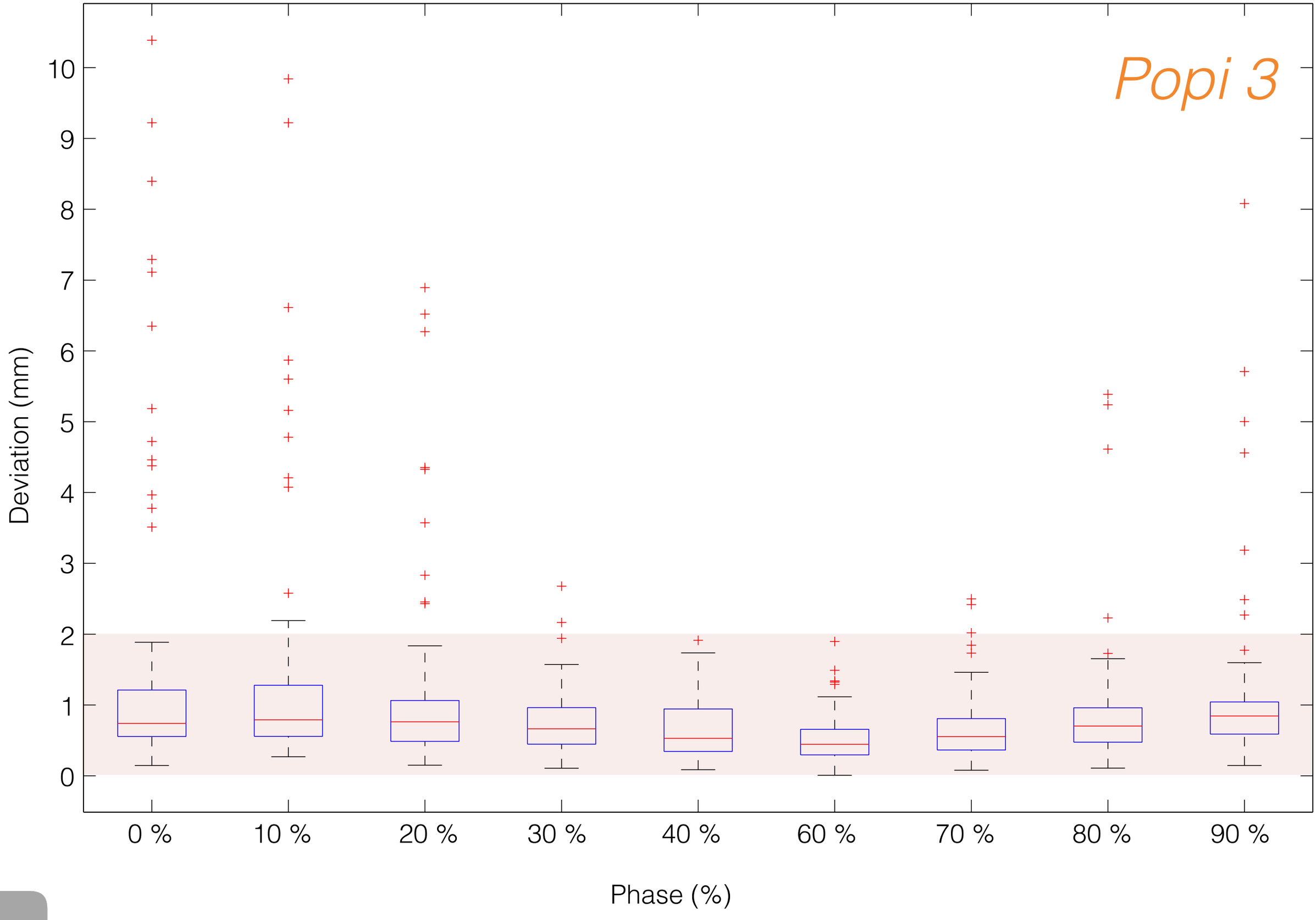
MIM SOFTWARE™

MIM Software, Cleveland, OH, United States.



MIM SOFTWARE™

MIM Software, Cleveland, OH, United States.



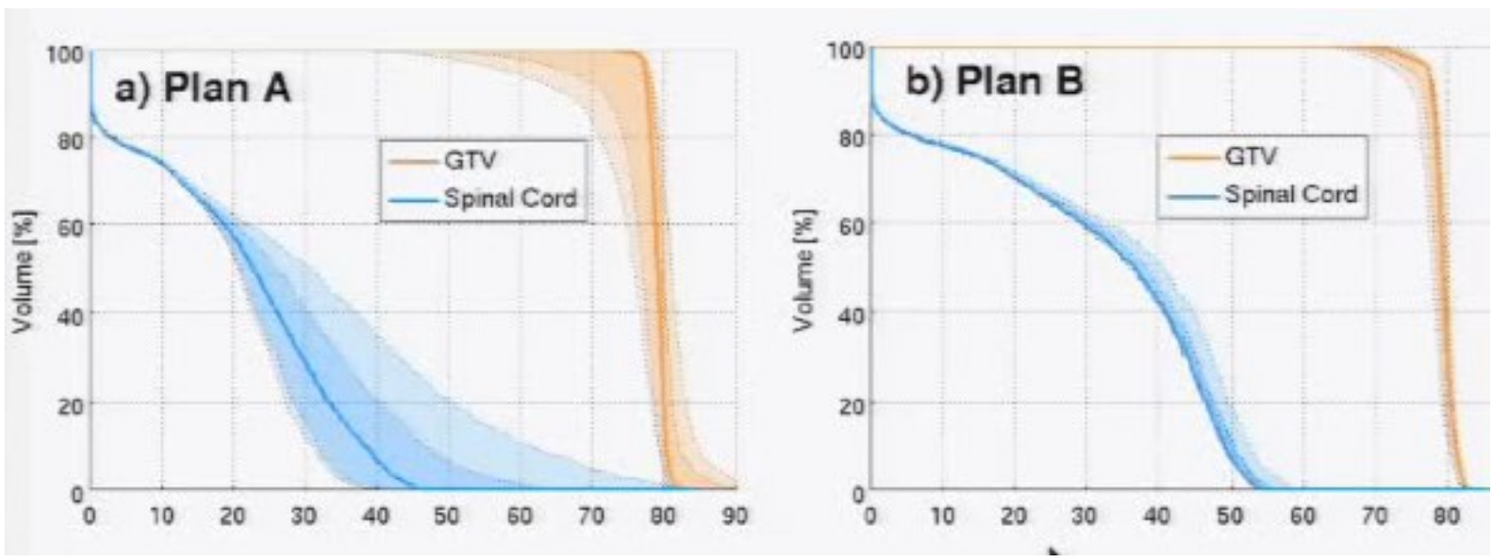
MIM SOFTWARE™

MIM Software, Cleveland, OH, United States.

Robust Planning

Statistical models/Robust Planning

- Taking into account the possible geometric deviations (random and setup errors) at the planning stage.
- Creating a dose distribution that will be "robust" or "immune" against the "most likely" movements of the target volume



Trofimov, Phys Med Biol 2011

How can we achieve this?

- Stochastic programming : statistical method, using defined probability density functions for all uncertainty parameters (e.g. gaussian model for setup errors, breathin cycle...). Feed this to our IMRT objective function.
- Worst case approach : make sure that constraints are always fulfilled, obtain the best plan in the worst case.

Stochastic method

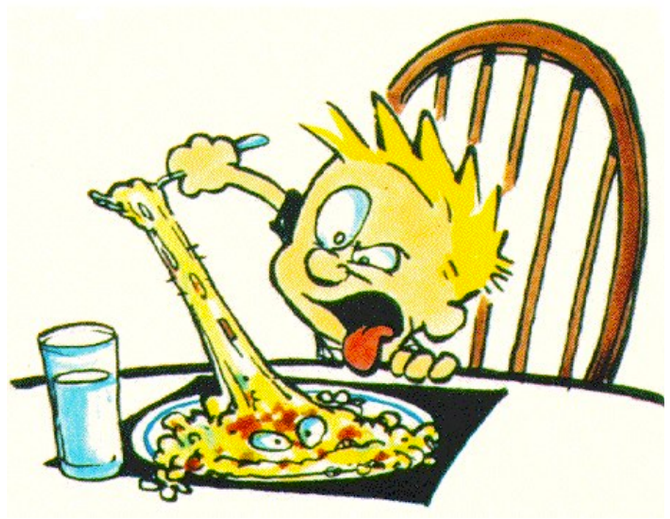
Normal Optimization

$$d_i(x) = \sum_j D_{ij} x_j$$

Dose in voxel i is a sum of the doses coming out of each bixel, weighed with the constraints

$$f(d(x))$$

Is our IMRT objective function which has to be minimized



Robust Optimization

$$d_i^s(x) = \sum_j D_{ij}^s x_j$$

Dose is calculate for all different scenarios = e.g. all possible positions

$$< f >= \sum_s p_s f(d^s(x))$$

The objective function is now minimized over all possible scenarios, weighed with the probability function

Worst case approach

$$d_i^s(x) = \sum_j D_{ij}^s x_j$$

Dose is calculate for all different scenarios = e.g. all possible positions

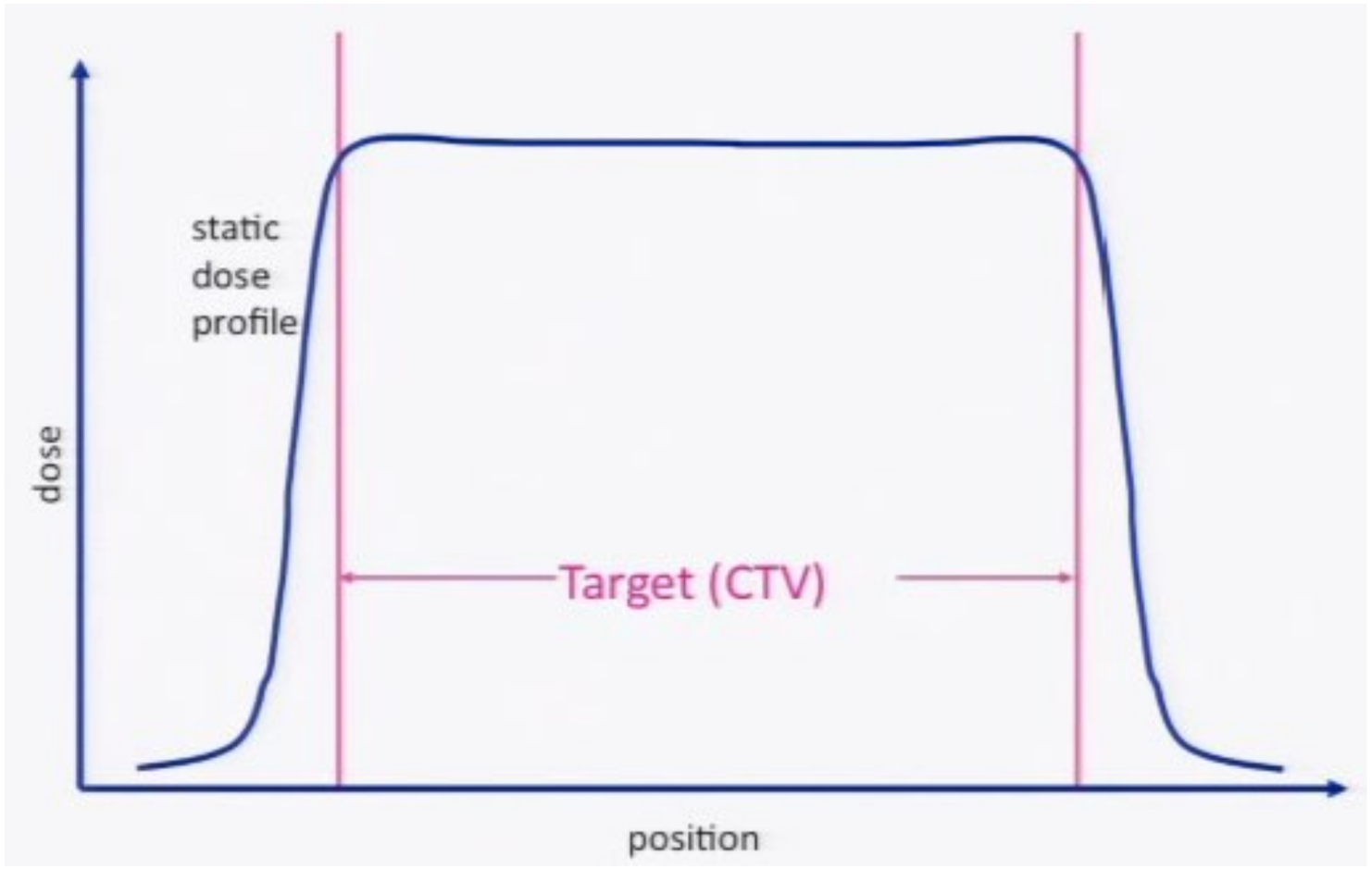
$$\left[\max_s f(d^s) \right]$$

Function is minimized for the WORST possible case

The plan that comes out will fit the worst patient situation, but is probably too strict

Example : Lung

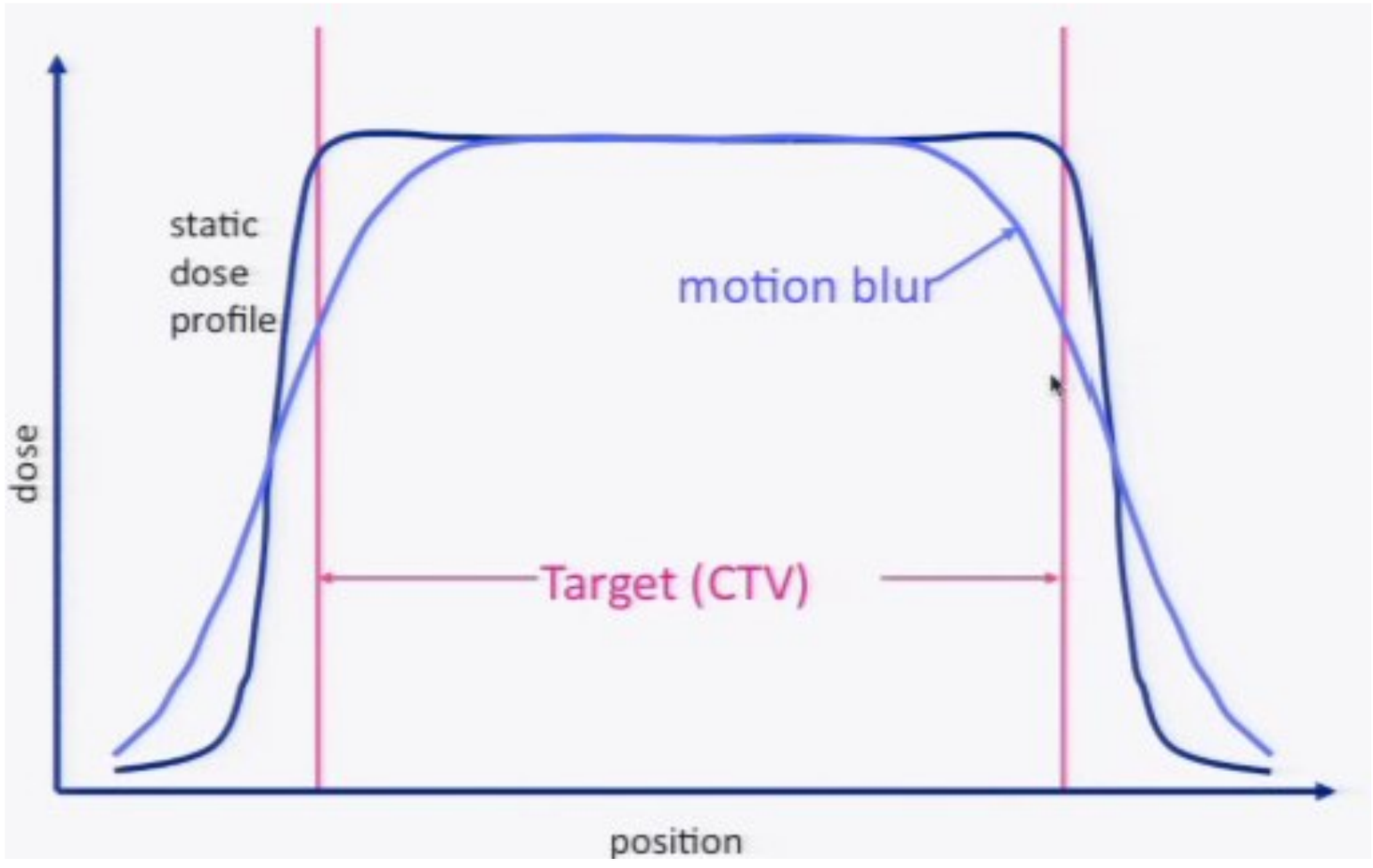
Static



Court. of T.Bortfeld

Example : Lung

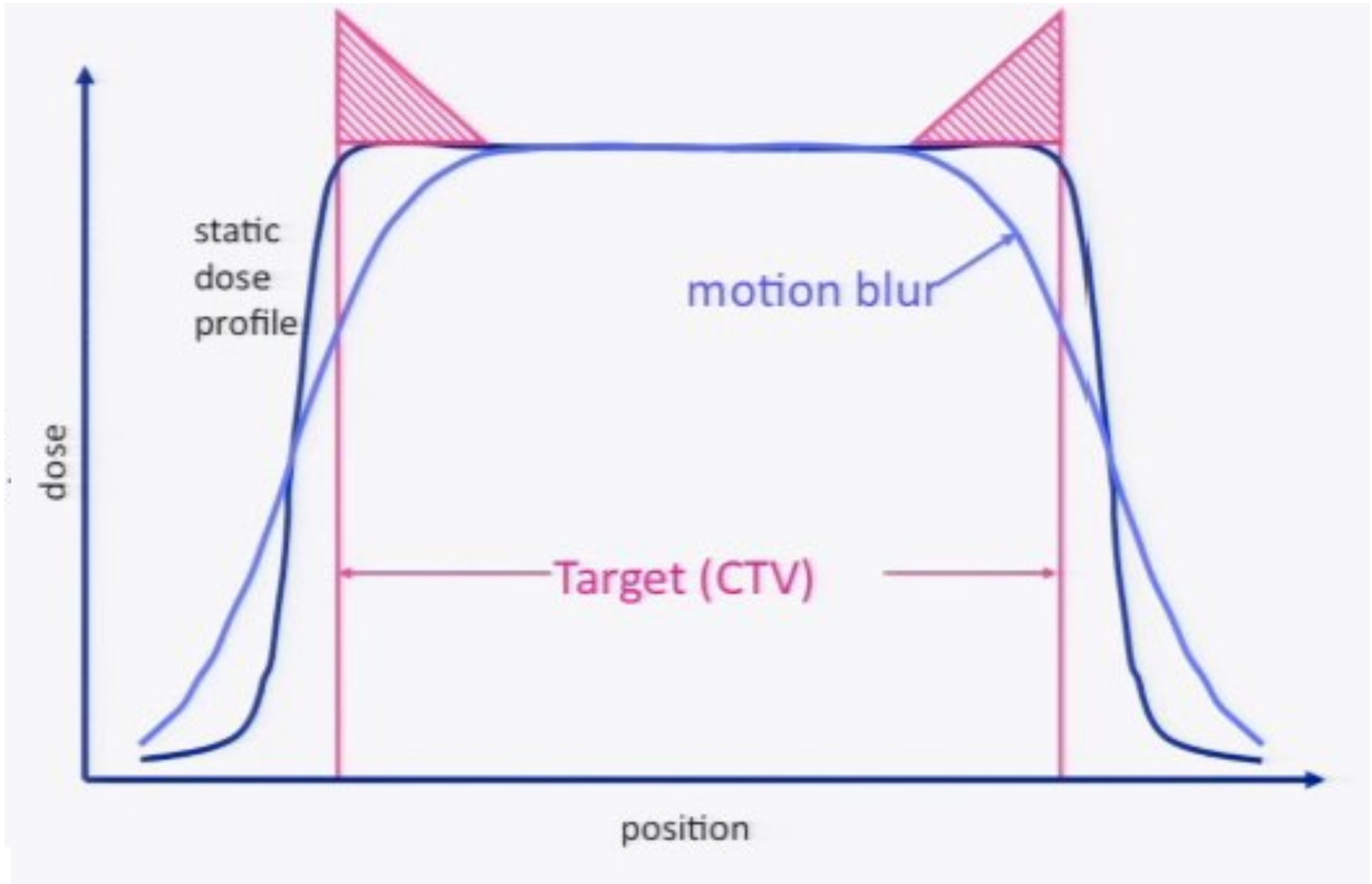
Movement : Dose Blurring



Court. of T.Bortfeld

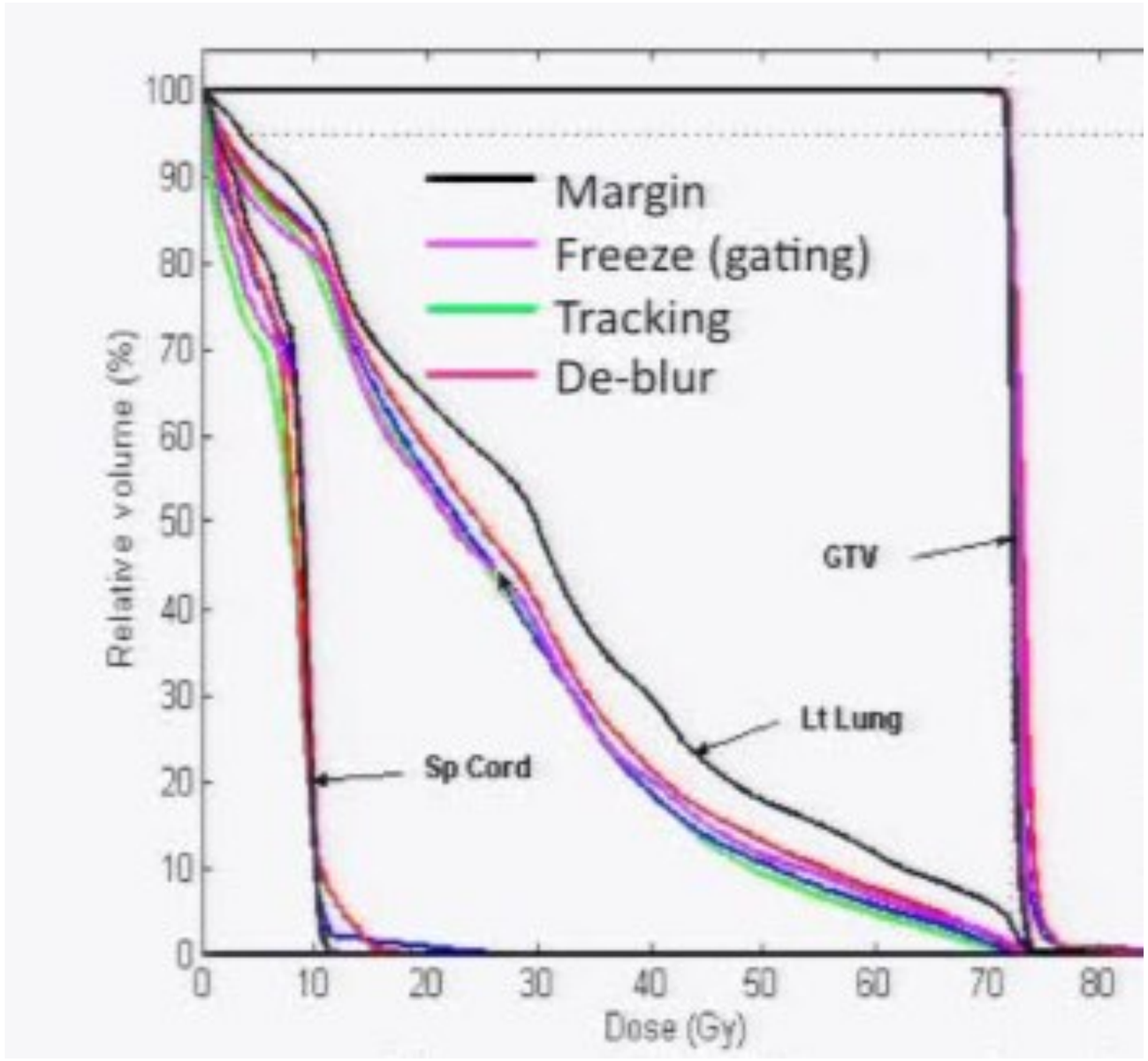
Example : Lung

Deblurring with IMRT : horns



Court. of T.Bortfeld

Dose Volume Histogram : lung case



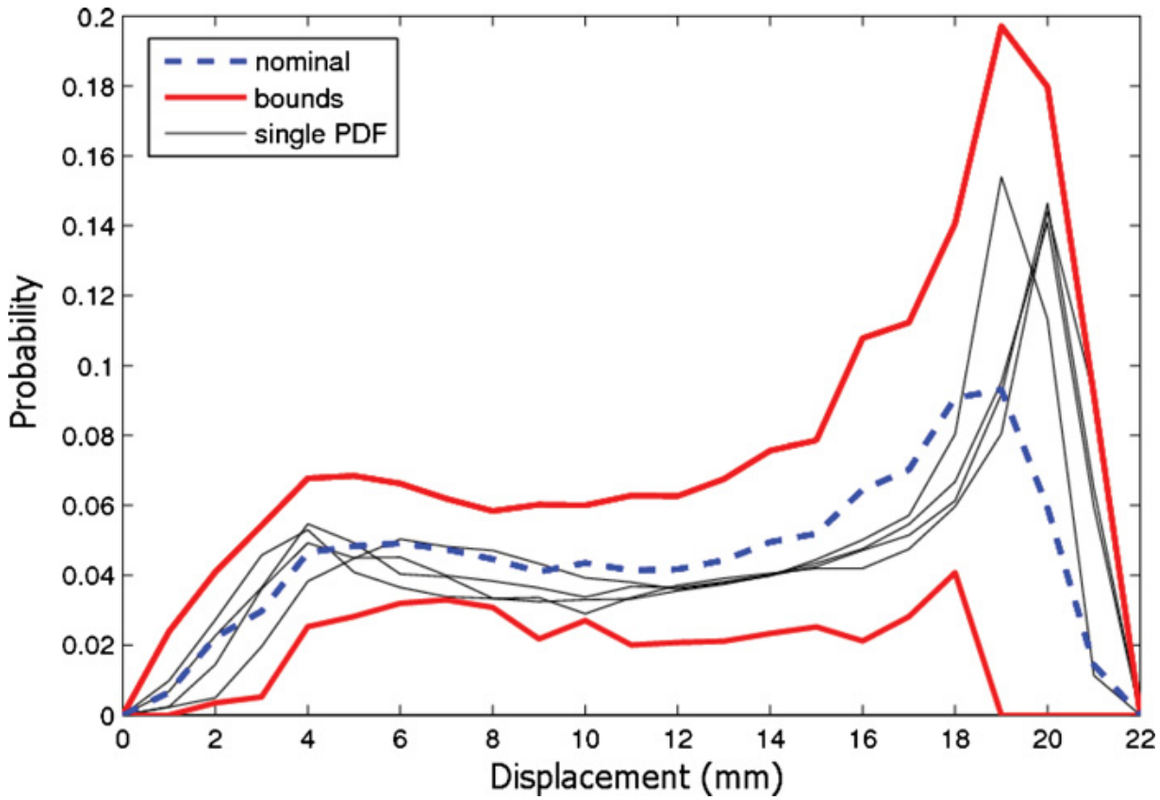
Mean dose to left lung is reduced by 20% a.r.t. adding margin

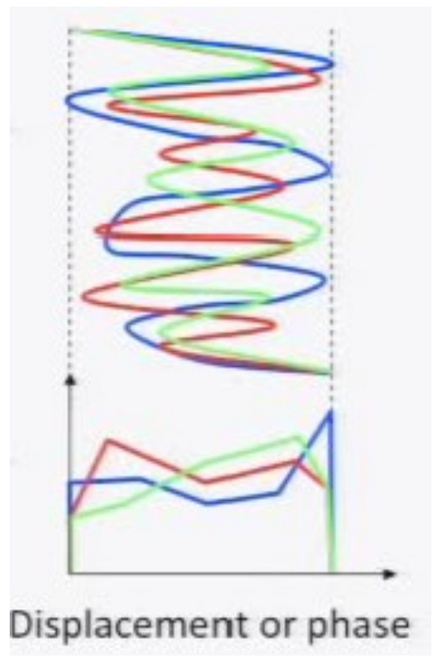
Trofimov et al., Phys Med Biol. 50:2779-98, 2005

Assumptions

- Based on probability functions for the breathing
- Has to be known perfectly
- Incorporation of this uncertainty

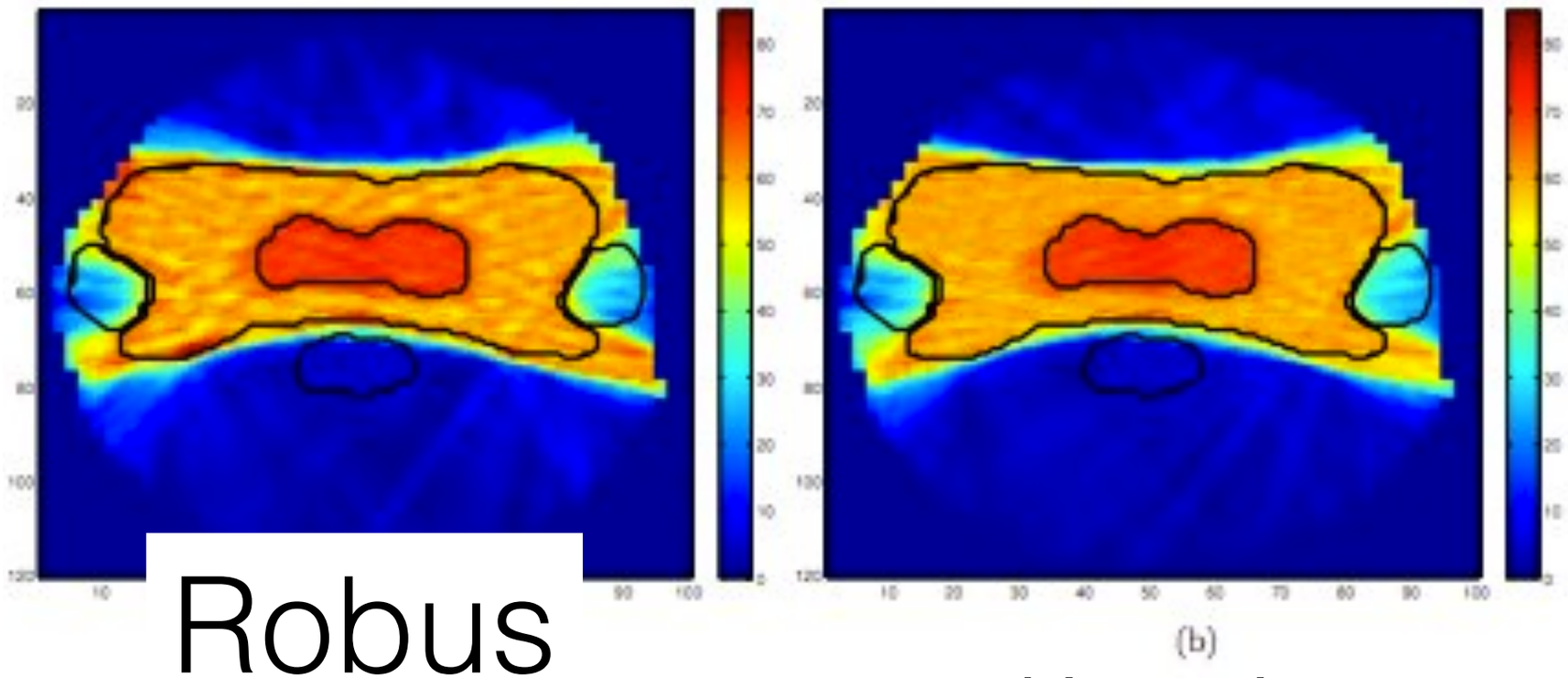
- Combination of horns and margins





Vrancic et al 2009 Phys. Med. Biol. 54 2901

Example H&N

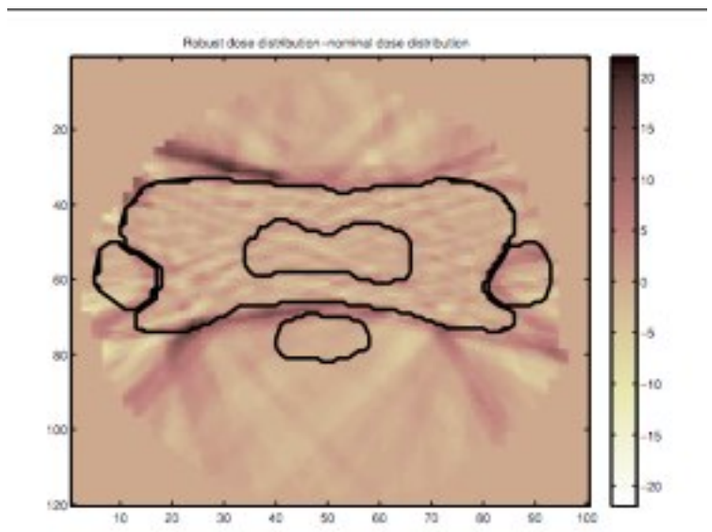


(b)

Robust

Non-robust

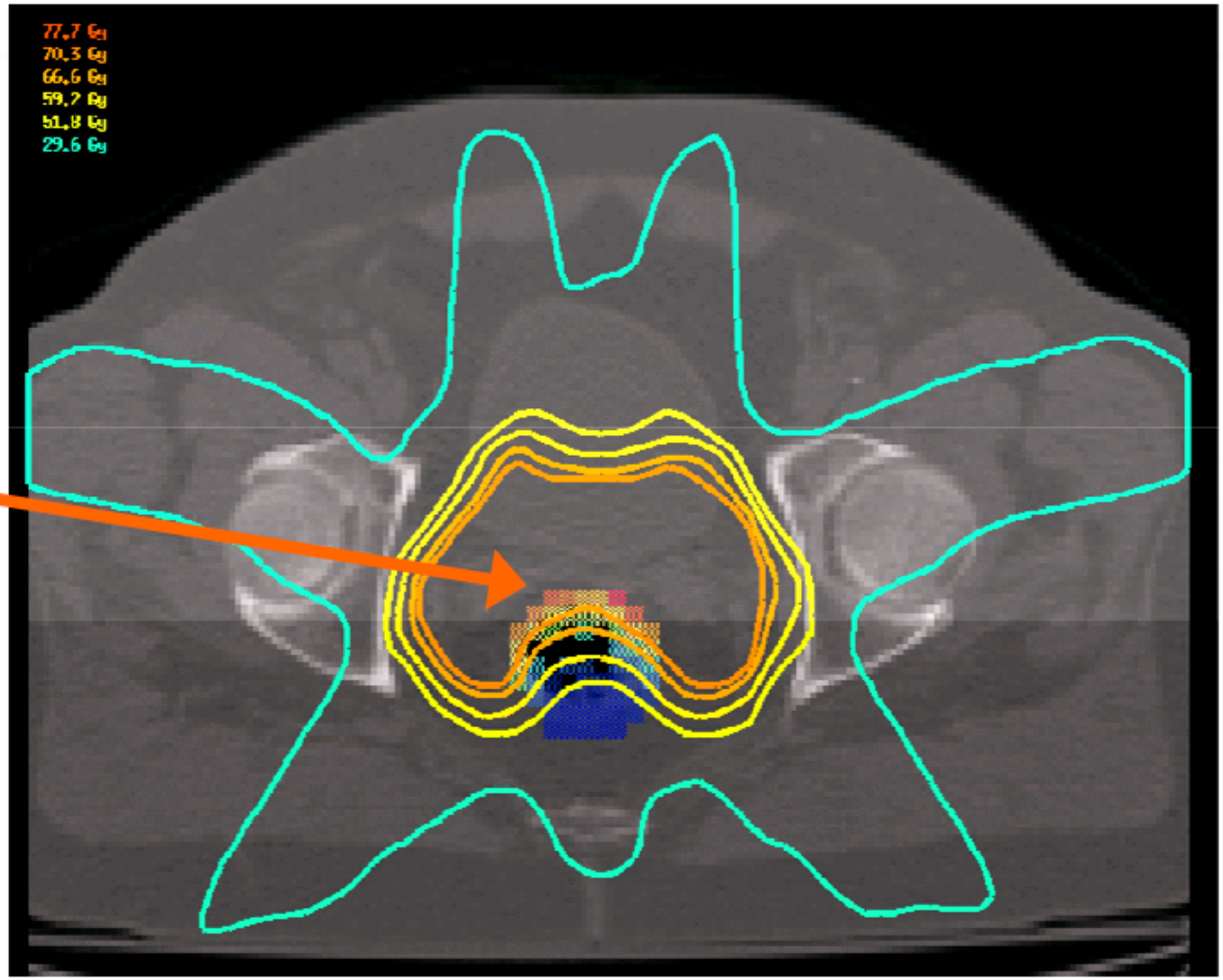
Difference



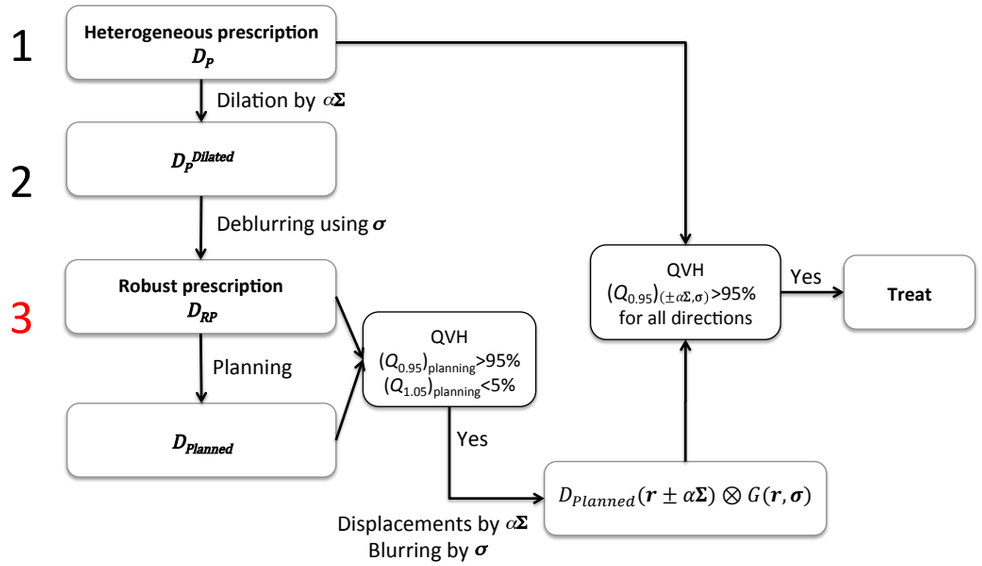
Olaffson et al,2006 Phys. Med. Biol. 51 5621

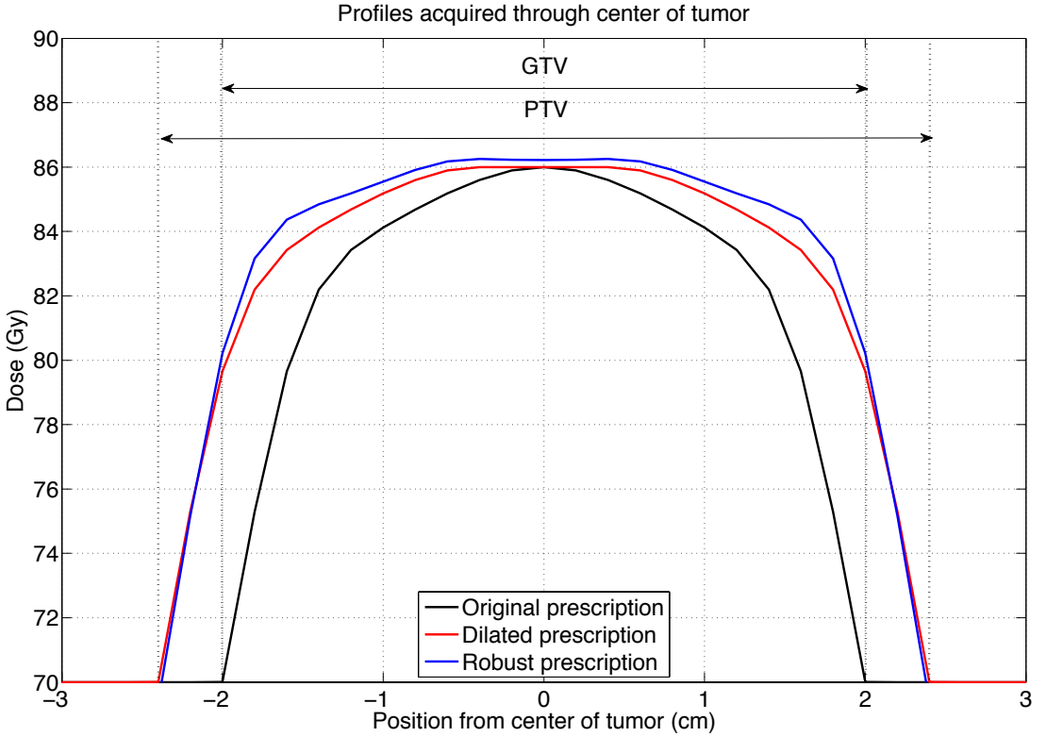
….look at the optimisation function!

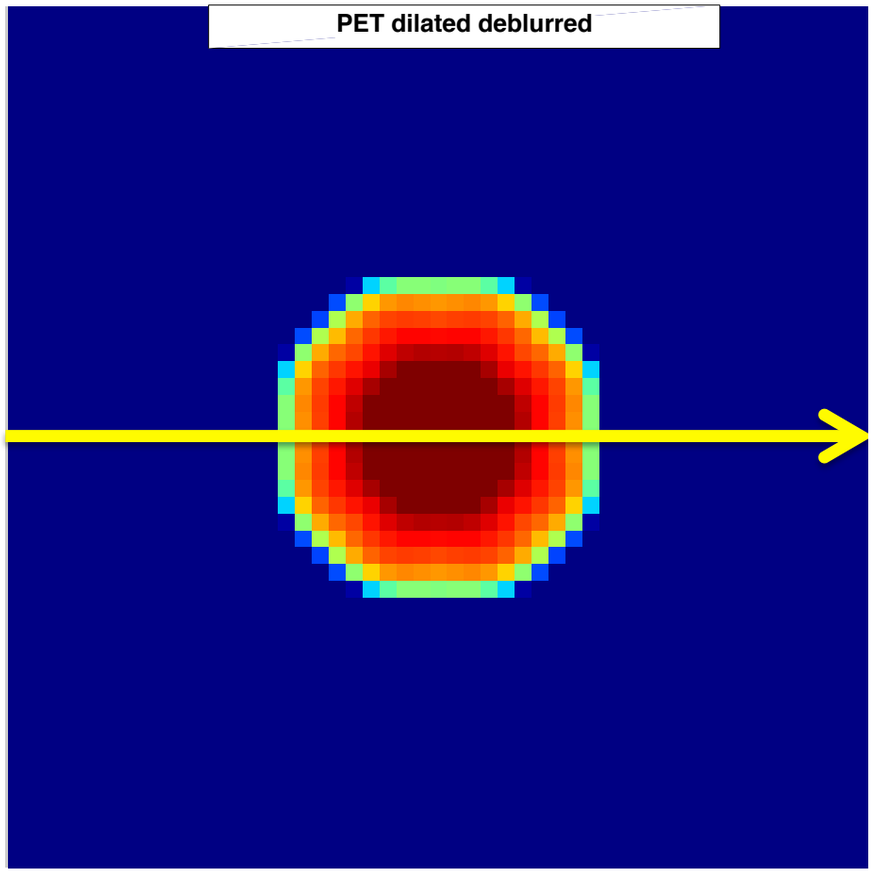
Volume of greatest weight in optimization



Alternative : robust prescription







Spherical tumor

Only dependent on σ and Σ
independant of TPS

Court. of E.Sterpin,

Conclusions

- In cases with small movements IGRT strategies will counter the effects on the dose distribution.
- In Other cases the PTV concept might not suffice in maintaining coverage
- Effects depend on interplay between the frequencies and amplitudes of the different processes
- Gating and tracking might be a possible countermove in selected cases.

Some wilder conclusions…

- Robust planning and optimisation could be the starting point of a new way of planning and evaluating dose distributions.
- Possibility of incorporating uncertainties into the planning phase (and very wild: dump the PTV notion?)
- To allow this uncertainties have to be known in a pretty high degree.
- to be continued…

A wise man's words…

"Simulating the effect of geometrical uncertainties on the individual patient plan should become part of the standard pre-treatment verification procedure."

(M.Schwarz, 2006)

Pelvis irradiation: overview of dose-volume predictors and NTCP parameters

Giovanna Gagliardi
Dept of Medical Physics
Karolinska University Hospital, Stockholm

ESTRO IMRT course, 2016

Organs at risk

- Rectum
- Bladder
- Small bowel
- Penil bulb

Radiotherapy and Oncology 93 (2009) 153–167

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

Dose–volume effects for normal tissues in external radiotherapy: Pelvis

Claudio Fiorino [a,*], Riccardo Valdagni [b], Tiziana Rancati [b], Giuseppe Sanguineti [c]

RECTUM – main complications

- rectal bleeding
- foecal incontinence
- stool frequency

- ca. prostate /cervival ca

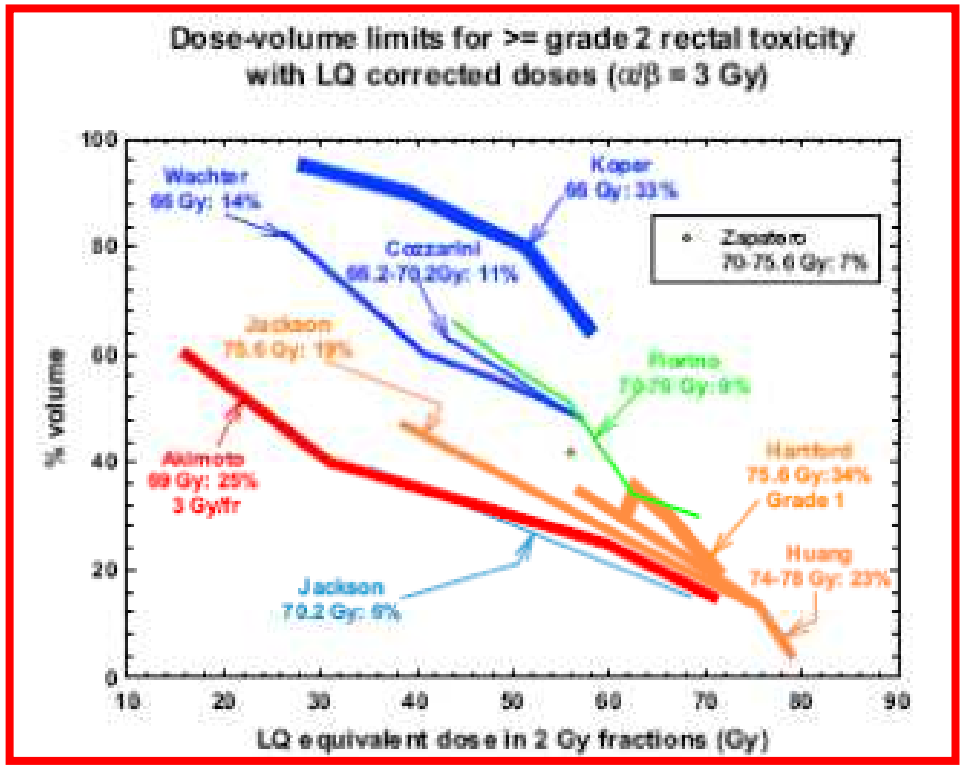
- acute: diarrhea, pain, superficial ulcerations, treatment for anemia, transfusion
- late (3-4 ys after RT): stricture, diminished rectal compliance, fecal incontinence

Rectal bleeding

- Grade 2: moderate diarrhea or colic, bowel movement, excessive rectal mucus, intermittent bleeding
- Grade 3: obstruction, bleeding requiring surgery

- **risk factors** for late rectal toxicity: hormonal therapy, diabetes, severe acute toxicity, advanced age, prior abdominal surgery

RECTUM, late rectal bleeding
DVH description



Thicker lines indicate
higher rates of overall toxicity

- Late rectal toxicity: doses $\geq$ 60 Gy
- Convergence at the high dose range < 70 Gy and volumes < 20%
- Uncertaint interpretation of the role of the intermediate doses?

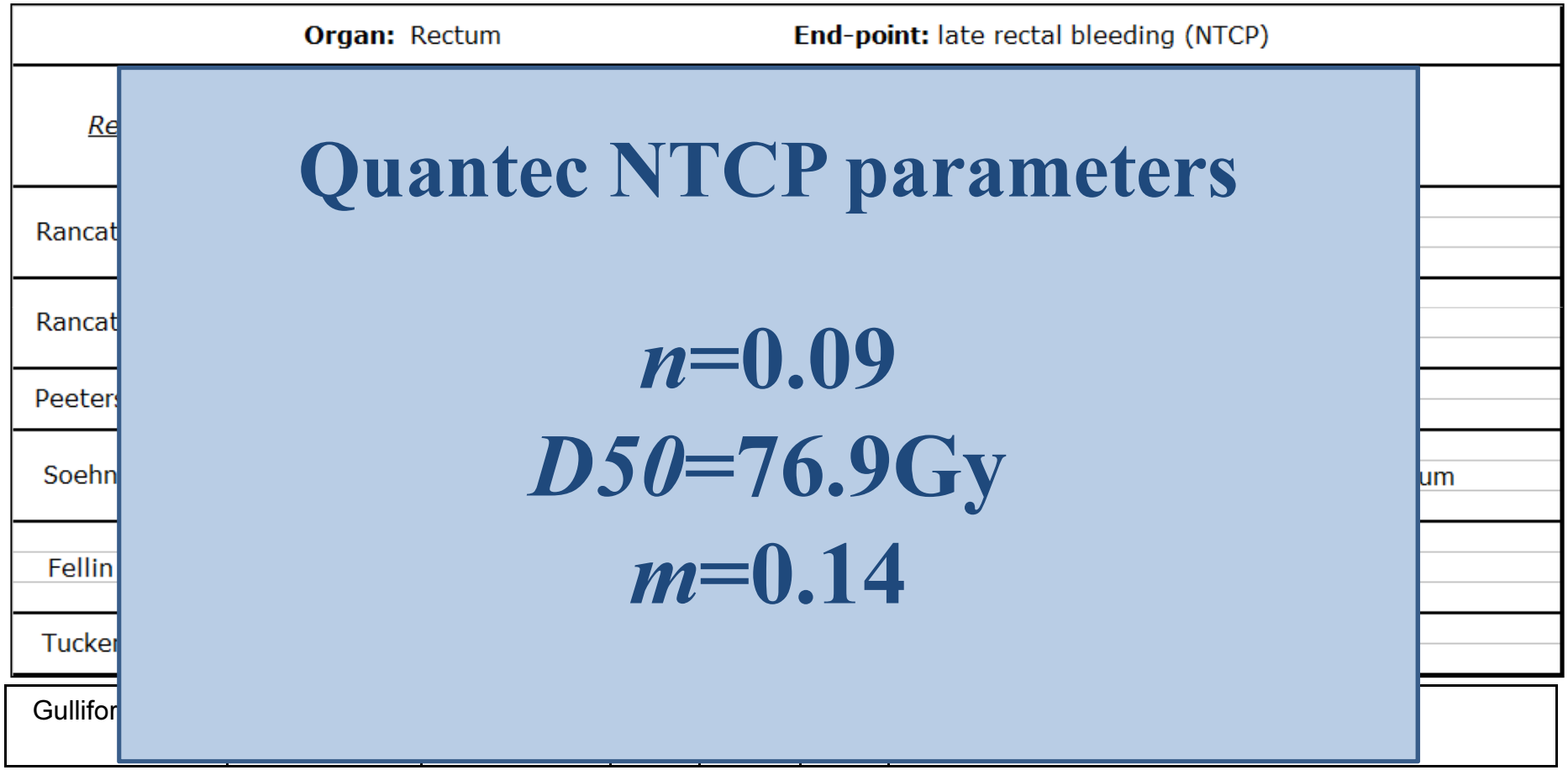
Michalski *et al, IJROBP vol 76, n3, S123-S129, 2010*

QUANTEC Supplement 2010

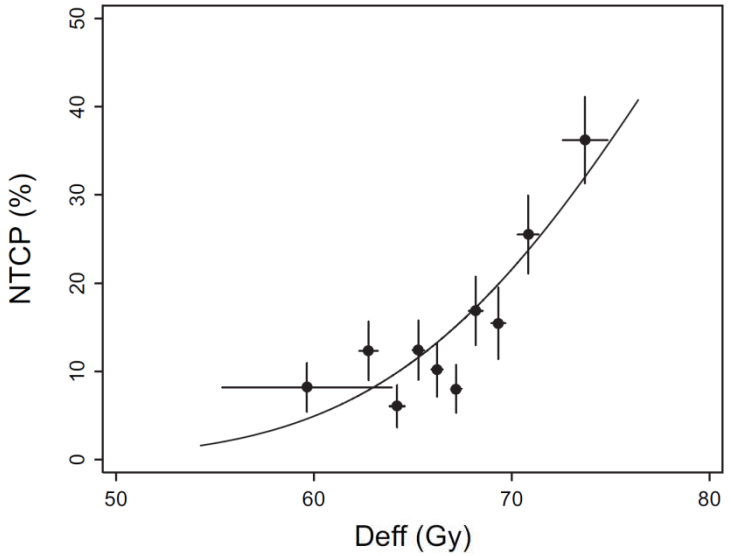
RECTUM, late rectal bleeding
NTCP description

Organ: Rectum			**End-point:** late rectal bleeding (NTCP)			
Ref.	*n° pts*	*Dose range*	*LKB model parameters*			*Comments*
			n	*D50(Gy)*	*m*	
Rancati 2004	547	64-79.2 Gy 1.8-2Gy/fr	0.24	81.9	0.19	**G2-G3 late rectal bleeding;** solid rectum including filling; including 90 non-conformal patients
Rancati 2004	547	64-79 Gy 1.8-2Gy/fr	0.06	78.6	0.06	**G3 late rectal bleeding;** solid rectum including filling; including non-conformal patients
Peeters 2006	468	68-78 Gy 2 Gy/fr	0.13	80.7	0.14	**G3 late rectal bleeding;** *rectal wall*
Soehn 2007	319	70.2-79.2 Gy 1.8 Gy/fr	0.08	78.4	0.11	**G2-G3 late rectal bleeding;** rectal wall defined starting from solid rectum contours + 3-4mm thickness
Fellin 2008	1119	64-81.6 Gy 1.8-2 Gy/fr	0.085	97.7	0.27	**G2-G3 late rectal bleeding;** solid rectum including filling; including 90 non-conformal patients
Tucker 2010	1010	68.4 -79.2Gy 1.8 Gy/fr	0.077	79.1	0.146	**G2-G3 late rectal bleeding;** solid rectum including filling
Gulliford 2012	388	64-74 Gy 2Gy/fr	0,12	68.2	0.14	**G2 late rectal bleeding** solid rectum including filling

RECTUM, late rectal bleeding
NTCP description

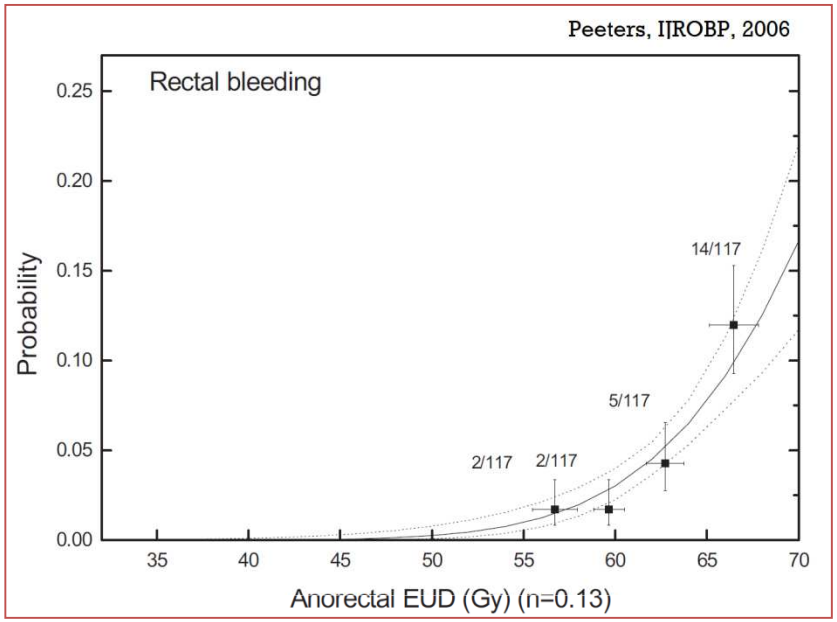


Tucker et al. IJROBP 2010

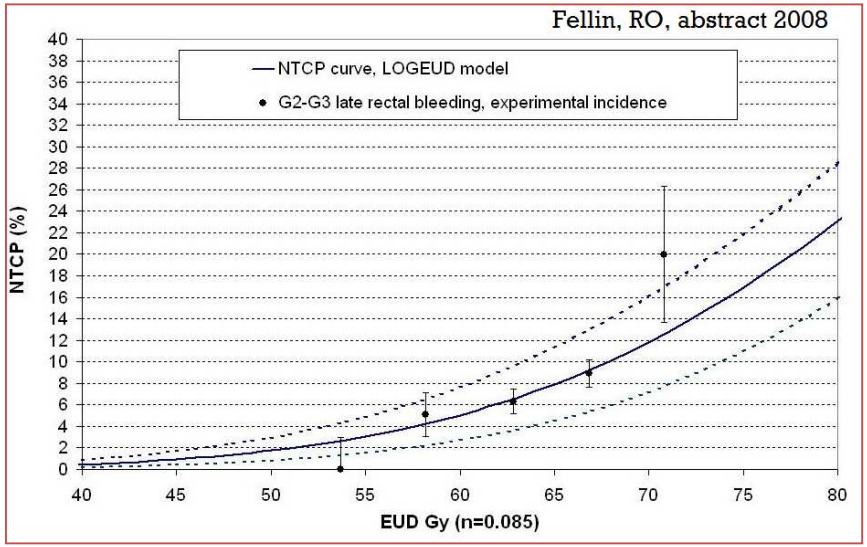


Incidence of Grade ≥2 late rectal toxicity at 8 years in each of 10 subgroups of 101 patients each, grouped by D_{eff} (equation 3), computed using $n = 0.077$. Points are plotted at the mean value of D_{eff} per subgroup. Horizontal error bars show ±1 standard deviation; vertical error bars show ±1 standard error.

Peeters, IJROBP, 2006

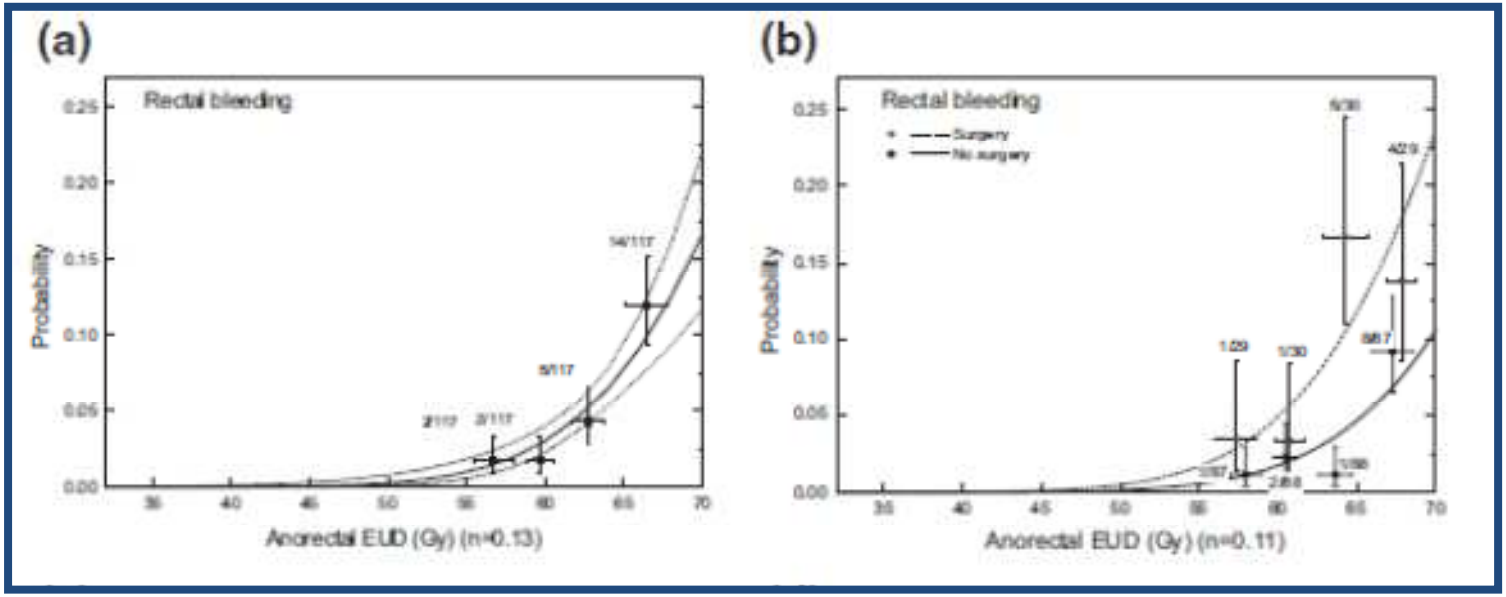


Fellin, RO, abstract 2008



Large data collections

RECTUM late rectal bleeding
DVH + clinical risk factors (abdom. surgery)

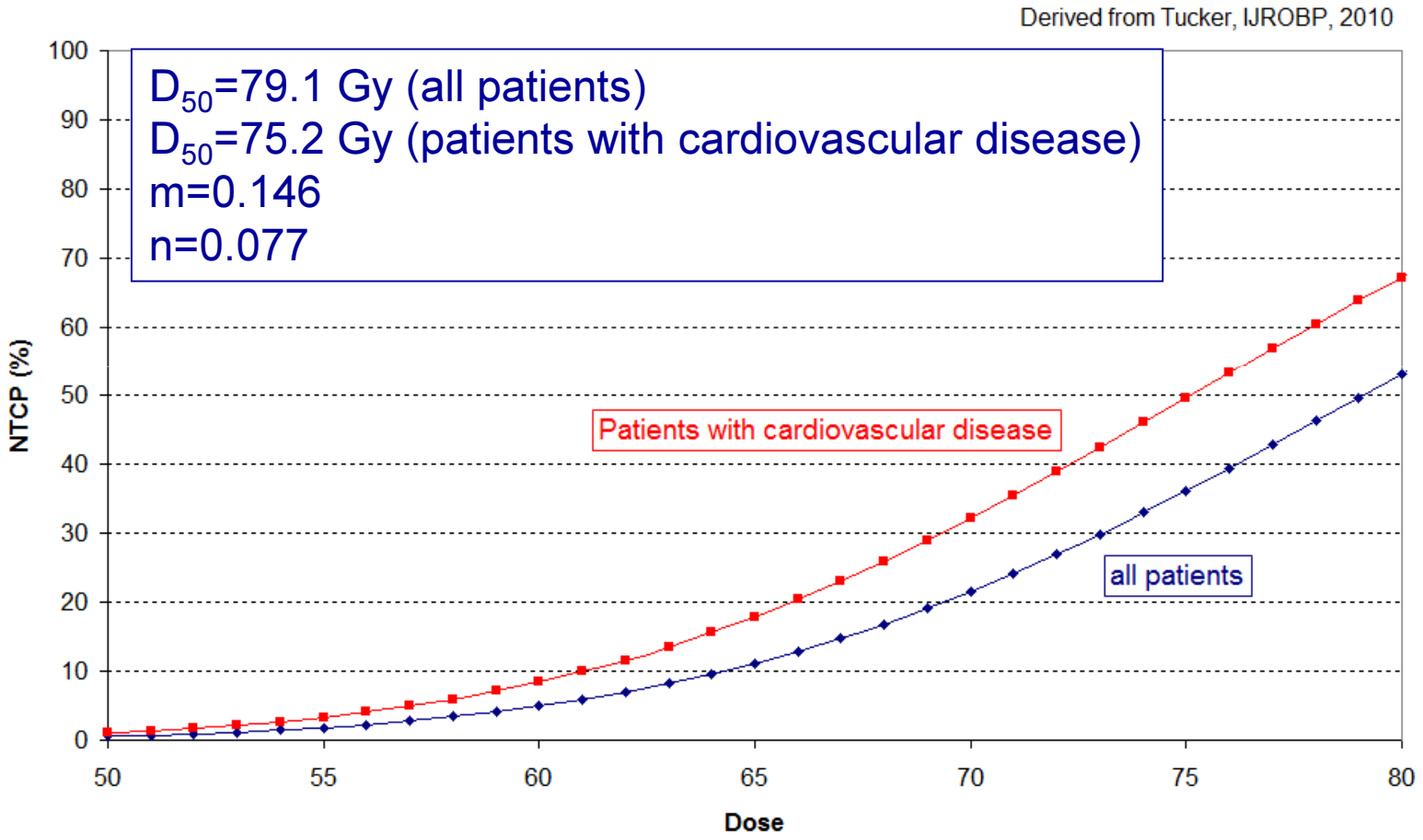


LKB	*TD50 (Gy)*	*m*	*n*
Observed	**81 (75-90)**	**0.14 (0.11-0.19)**	**0.13 (0.04-0.25)**
w/o previous abd. surgery	**85 (78-96)**	**0.14 (0.11-0.19)**	**0.11 (0.02-0.23)**
with previous abd. surgery	**78 (72-89)**		

Including clinical risk factor: lower tolerance to radiation (also for fecal incontinence)

Peeters *et al, IJROBP, 2006*

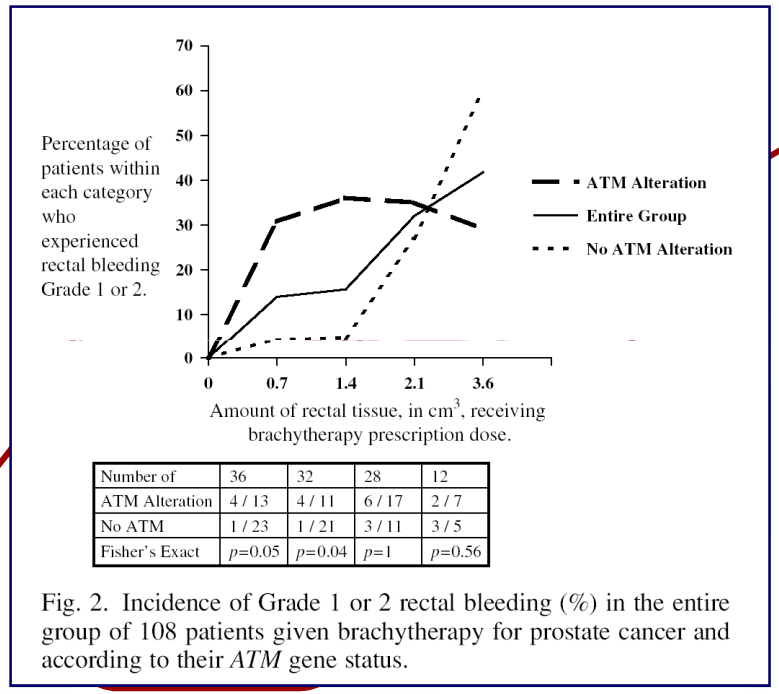
RECTUM: late rectal bleeding
DVH + clinical risk factors (cardiovascular disease)



Is there a genetic component in late rectal bleeding?

The data seem to confirm Cesaretti et al's findings (in brachytherapy) on the possible genetic component of rectal bleeding

Percentage of patients within each category who experienced rectal bleeding Grade 1 or 2



Number of	36	32	28	12
ATM Alteration	4 / 13	4 / 11	6 / 17	2 / 7
No ATM	1 / 23	1 / 21	3 / 11	3 / 5
Fisher's Exact	p=0.05	p=0.04	p=1	p=0.56

Fig. 2. Incidence of Grade 1 or 2 rectal bleeding (%) in the entire group of 108 patients given brachytherapy for prostate cancer and according to their *ATM* gene status.

EUD (Gy)

High-dose region: the genetic makeup plays a minor role and the dose the major role

LSM7 alteration

Entire population

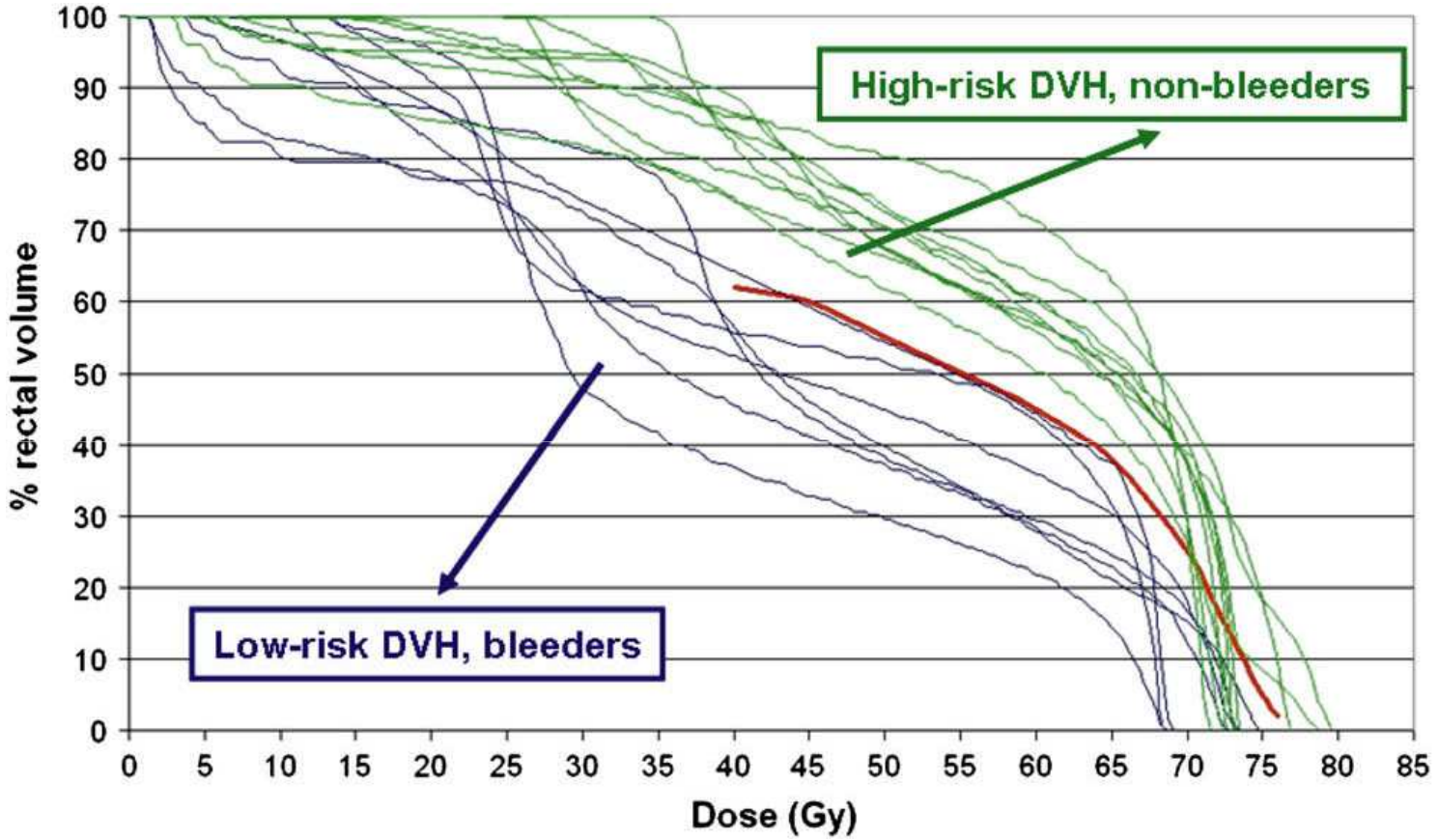
no LSM7 alteration

Low-dose region: the genetic makeup might play the major role

When more pts are available, it might be reasonable to unveil the double nature of the dose-response relationship also for external radiation

Courtesy of Riccardo Valdagni, Milan

TO BLEED OR NOT TO BLEED – Valdagni *et al*, Int.J Rad Onc Biol Phys, feb 2009



Dose–volume histograms (DVHs) for patients belonging to the low-risk bleeder (blue lines) and high-risk nonbleeder groups (green line). The red line is the cut-off DVH value that can be derived from literature-based dose–volume constraints.

Rectum, summary

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Rectum	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity,	V50 <50%	<15	Prostate cancer treatment
			Grade ≥ 3 late rectal toxicity		<10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity,	V60 <35%	<15	
			Grade ≥ 3 late rectal toxicity		<10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity,	V65 <25%	<15	
			Grade ≥ 3 late rectal toxicity		<10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity,	V70 <20%	<15	
			Grade ≥ 3 late rectal toxicity		<10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity,	V75 <15%	<15	
			Grade ≥ 3 late rectal toxicity		<10	

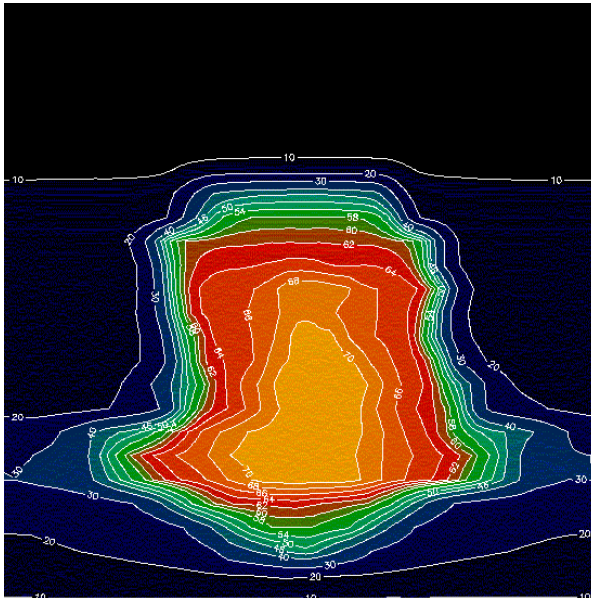
Recommendations:

- Organ definition, from above the anal verge to the turn in the sigmoid colon
- V_{50}<15%, V_{60}<35%, V_{65}<25%, V_{70}<20%, V_{75}<15%

  for $\leq$ 15% Gr.$\geq$ 2 late tox

  for <10% Gr. $\geq$ 3 late tox
- IMRT: intermediate (40-60 Gy) doses for pts <78Gy ?

Rectal bleeding: dose-volume, dose-surface or dose wall?



- Empty rectum: DWH ≈ DVH
- Full rectum: DWH ≈ DSH

Robust solutions:

Empty the rectum at plan CT scan and use DVH

Use DSH for distended rectum (rectal balloon)

Several prospective studies ongoing

Sanchez-Nieto B, Fenwick J F, Nahum A E *et al* 2001
Biological dose surface maps: evaluation of 3D dose data
for tubular organs *Radiother. Oncol.* **61** S52

FOECAL INCONTINENCE

- Volume(s) definition
- Quantification: need prospective studies/self reported toxicities/symptoms persistency
- Risk factors: age, baseline situation
- Complex anatomy and radiobiology

- Occur in ca 5% pts, but chronic symptoms
- V40< 80% (or mean rectal dose < 45-50 Gy)

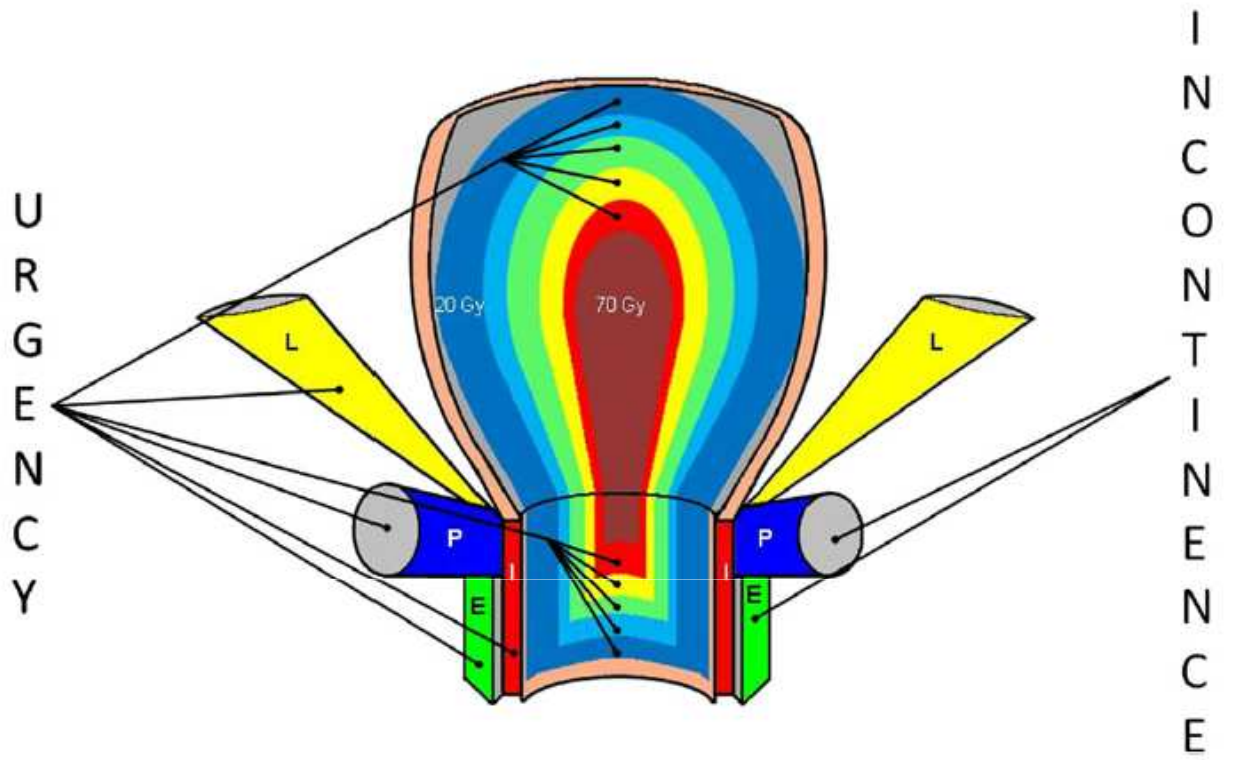


Fig. 2. Schematic image shows rectum, anal canal, and individual pelvic floor muscles. I = internal anal sphincter; E = external anal sphincter; P = puborectalis muscle; L = levator ani muscles. Lines represent associations between complaints and subsites.

- 48 pts, separate delineation of specific pelvic floor muscles
- Toxicity scale, scoring every 6 months
- EQD corrected doses

Smeenk *et al*, 2012

Foecal incontinence

- Occurrence of urgency correlated to incontinence and frequency
- No significant different toxicities with conv vs IRMT
- All mean doses higher in the group with urgency
- Mean dose ≤30 Gy to the internal anal surface,
  ≤10 Gy to the external anal surface
  ≤50 Gy to the puborectalis muscle
  ≤40 Gy to levator ani muscle

Constraints to **pelvic muscle floor** to reduce incontinence related complaints

- Endorectal balloon: fewer complaints in this group (28pts)

Smeenk *et al*, 2012

Foecal incontinence

- **Prospective** study **(> 500 pts**), self reported questionnaires
- Taking into account **severity** and **duration** of symptoms
- **V40>80%**: predictor of Mean Incontinence Score together with previous bowel symptoms, antiypertensive, surgery

- **Two patterns for occurrence of foecal incontinence after RT**:
  - 1: consequent to **acute effects** and mainly responsible for **peak events** (ca ½ pts recovering from symptoms)
  - 2: needs longitudinal analysis- it results form the irradiation of large fraction of the rectum at intermediate doses (V40), presence of pretreatment bowel symptoms, previous abdominal-pelvivc surgery for chronic incontinence
    - Vascular damage, more than damage to sacral nerve (hypertensive drugs work)

Fiorino *et al*, 2011

Summary RECTUM: dose-volume response relationships

- Late rectal bleeding: **serial** description
- DVH/NTCP description: consistent (10^3 pat)
- Abdominal/pelvic surgery- important predictor, modified dose-volume constraints and NTCP

- Foecal incontinence: seems parallel
- V40, D mean best predictors
- Clinical predictors important
- Longitudinal definitions of the endpoints
- Spatial aspects?

BLADDER

4. REVIEW OF DOSE–VOLUME DATA

To date, no studies have comprehensively reported the true three-dimensional (3D) bladder dosimetry in relation to toxicities. A single 3D image set (SimDVH) is of questionable validity. Data for whole-bladder RT vs. partial-bladder doses are discussed by cancer type.

QUANTEC, IJROBP, 2010

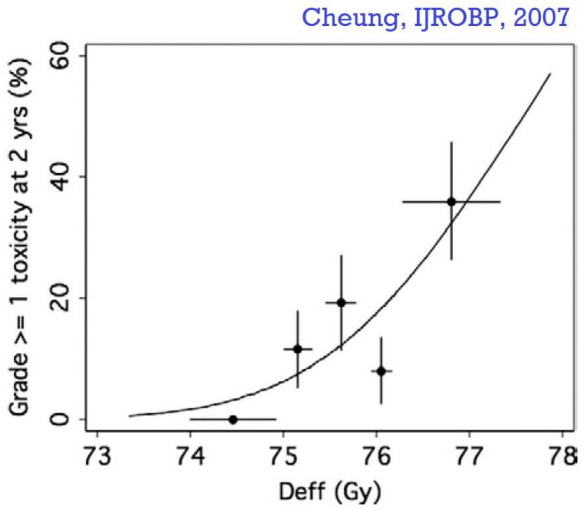
3-years GU (G2-3) toxicities correlated with both high and "low" dose if empty bladder (Harsolia, IJROBP, 2007)

V30Gy < 33.5 cc	2%	G3
V30Gy > 33.5 cc	20%	G3
V82Gy < 2.5 cc	2%	G3
V82Gy > 2.5 cc	12%	G3

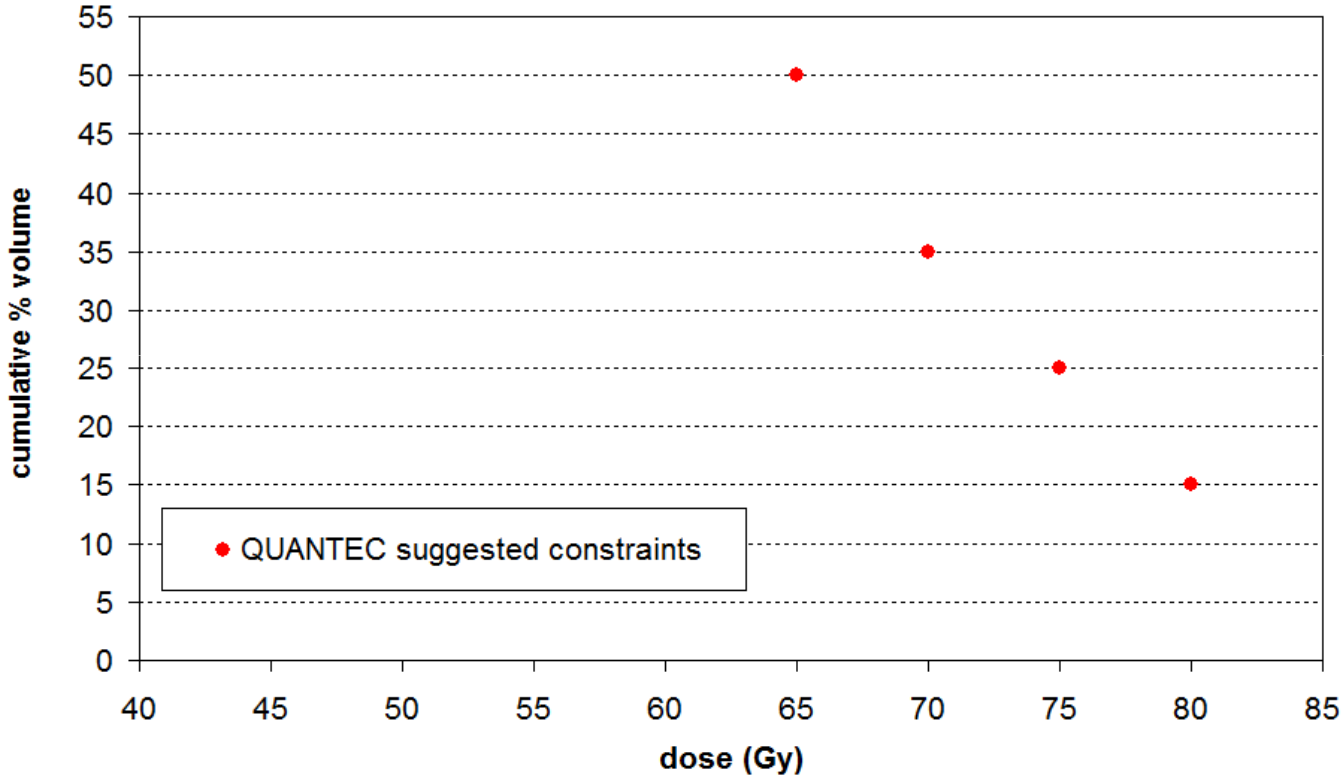
---

8 years GU (G1-3) toxicities correlated with "**hottest volume**"

V78Gy < 2.9 %	25 % 8-years risk
V78Gy > 2.9 %	50 % 8-years risk

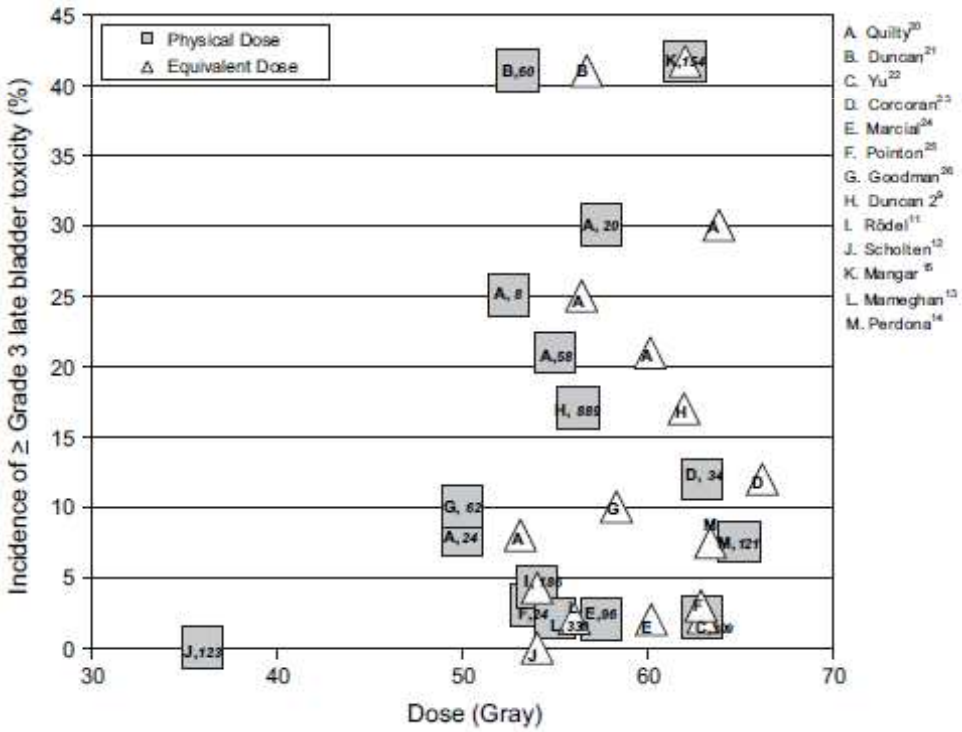


BLADDER: urinary toxicity
QUANTEC constaints (based on RTOG 0415)



GU toxicity- what do we know?

- Quantec summary: not much….
- Whole bladder irradiation: 55Gy threshold for late grade 3 RTOG tox
- Clinical factors hardly influence the outcome
- Variable filling?
- 8 ys fu: hottest volume
- 3 ys fu: both high and low dose



Quantifying Unnecessary Normal Tissue Complication Risks due to Suboptimal Planning: A Secondary Study of RTOG 0126

Moore *et al*, IJROBP, 2015

QC study on: a) treatment planning

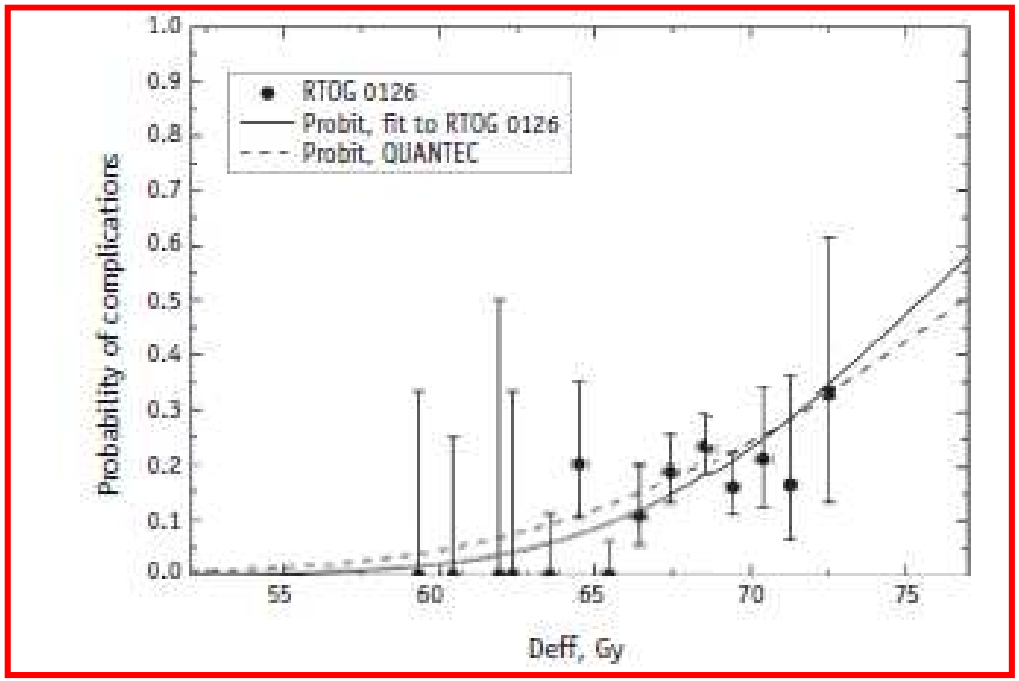
b) QUANTEC guidelines for rectal complications >2gr

- Purpose - Effect of suboptimal planning in IMRT (frequency and clinical severity of quality deficiencies)
- Material - RTOG 0126, 219 pts from the high dose arm (79.2 Gy in 44 frcs)

(RTOG0126: Phase 3 randomised study of High Dose 3D CFRT/IMRT vs Standard Dose 3D CFRT/IMRT)

- Plans analyzed with knowledge-based DVH predictions, based on differences (dose metrics and NTCP values) between the predicted ”best practice” plan and the clinical plan.

Plan quality deficiencies in RTOG 0126 exposed patients to substantial excess risk for rectal complications (less for bladder)



QUANTEC validation for rectal complication > gr 2: **ok!**

Fig. 2. Validation of QUANTEC LKB NTCP model. Observed grade ≥2 late GI toxicities agree with predictions based on QUANTEC (17) recommended LKB parameters (dotted line). Dose-response curve obtained with parameters fitted to RTOG 0126 data is shown for comparison (solid line). Vertical error bars are 68%

…more results from large studies!

Gastrointestinal Dose-Histogram Effects in the Context of Dose-Volume–Constrained Prostate Radiation Therapy: Analysis of Data From the RADAR Prostate Radiation Therapy Trial

Dataset: multicentral trial, **754 pts**, TROG 0304 RADAR LENT and SOMA **toxicity assessment**

- Anatomical dependence of specific GI toxicities
- Dose-volume constraints for different (parts of) OAR

Ebert *et al*, IJROBP, 2014

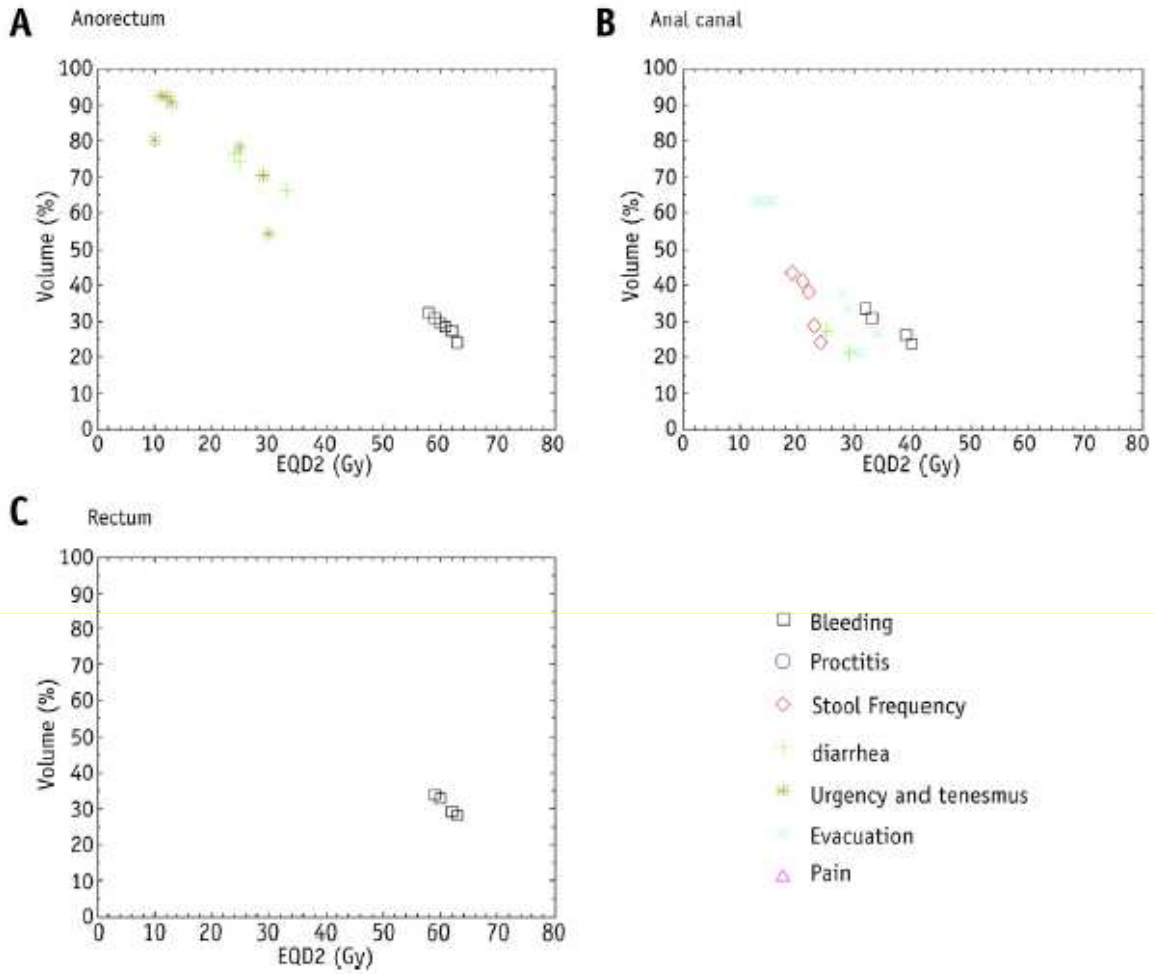


Fig. 5. Important relative dose-volume constraints identified by multivariate regression for 3 GI regions, (a) anorectum, (b) anal canal, and (c) rectum. All values are for peak toxicity and have an OR > 1. EQD2 is for $\alpha/\beta = 3.0$ Gy. EQD2 = equivalent dose in 2-Gy fractions; OR = odds ratio.

Ebert *et al*, IJROBP, 2014

BOWEL: dose-volume effect

Ref.	No. of pts	Doses[a]	Suggested constraints
Baglan [122]	40	45 Gy	Grade 3 CTC 3.0: V15Gy < 150 cc (V40Gy < 125 cc)
Roeske [123]	40	45 Gy	⩾ Grade 2 RTOG: V45Gy < 150–200 cc
Tho [126]	41	45 Gy	⩾ Grade 2 CTC 3.0: V15Gy < 100 cc (risk < 20%)
Huang [125]	80	39.6–45 Gy	⩾ Grade 2 diarrhoea CTC 3.0: V16–18Gy and V40–45Gy independently predictive for pts without/with previous surgery, respectively
Robertson [127]	91	45 Gy	Grade 3 diarrhoea CTC 3.0: V15Gy < 120 cc V25Gy < 105 cc V40Gy < 71 cc
Sanguineti [124]	149	0/54 Gy[b]	⩾ Grade 2 CTC 2.0: V15Gy < 1186 cc
Fiorino [128]	175	50.4–54 Gy	⩾ Grade 2 RTOG: Intestinal cavity outside PTV/Whole cavity V50Gy < 35 cc/100 cc V45Gy < 100 cc/250 cc V40Gy < 150 cc/350 cc V30Gy < 300 cc/500 cc

Fiorino, RO, 2009

DOSE–VOLUME RELATIONSHIPS FOR ACUTE BOWEL TOXICITY IN PATIENTS TREATED WITH PELVIC NODAL IRRADIATION FOR PROSTATE CANCER

CLAUDIO FIORINO, PH.D.,* FILIPPO ALONGI, M.D.,†‡ LUCIA PERNA, PH.D.,* SARA BROGGI, PH.D.,* GIOVANNI MAURO CATTANEO, PH.D.,* CESARE COZZARINI, M.D.,† NADIA DI MUZIO, M.D.,† FERRUCCIO FAZIO, PROF, M.D.,† AND RICCARDO CALANDRINO, PH.D.*

Table 1. Modified Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer acute toxicity scoring criteria used to assess bowel symptoms in current study

Grade 0	1	2	3	4
No change	Increased frequency or change in habits not requiring medication	Diarrhea requiring drugs/mucous discharge not necessitating sanitary pads/abdominal pain requiring analgesic	Diarrhea requiring parenteral support/severe mucous discharge requiring sanitary pads	Acute or subacute obstruction/abdominal pain or tenesmus requiring surgery

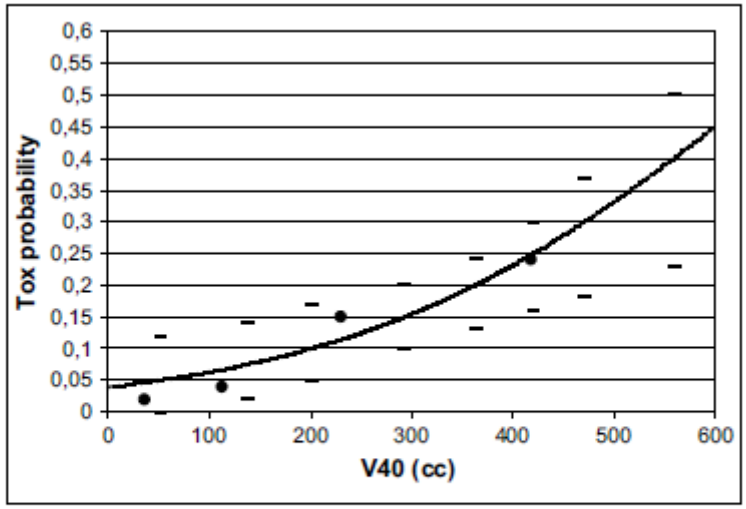
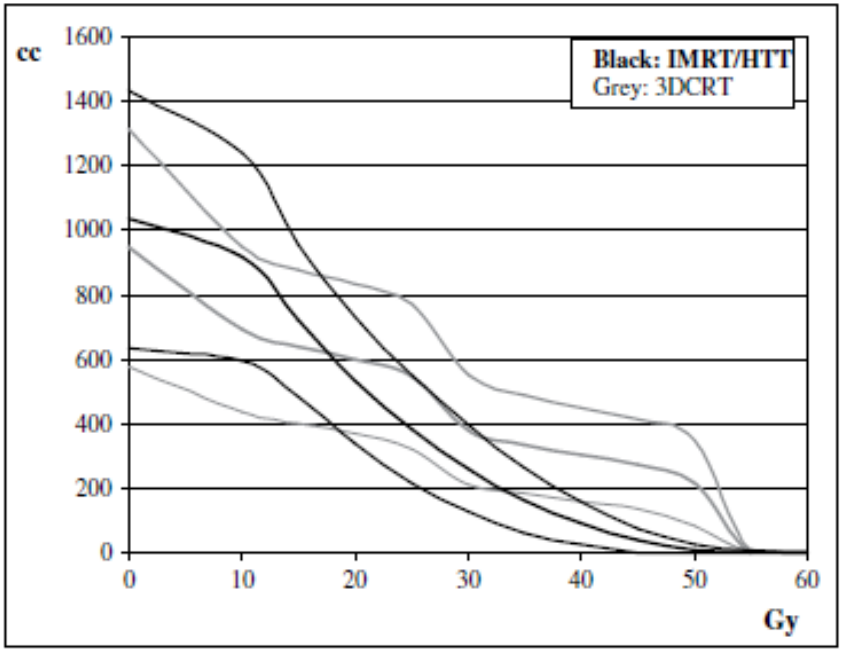


Fig. 1. The relationship between the V40 of the intestinal cavity (outside the planning target volume) and the risk of Grade 2–3 acute bowel toxicity is plotted, together with 95% confidence intervals (logistic curve).



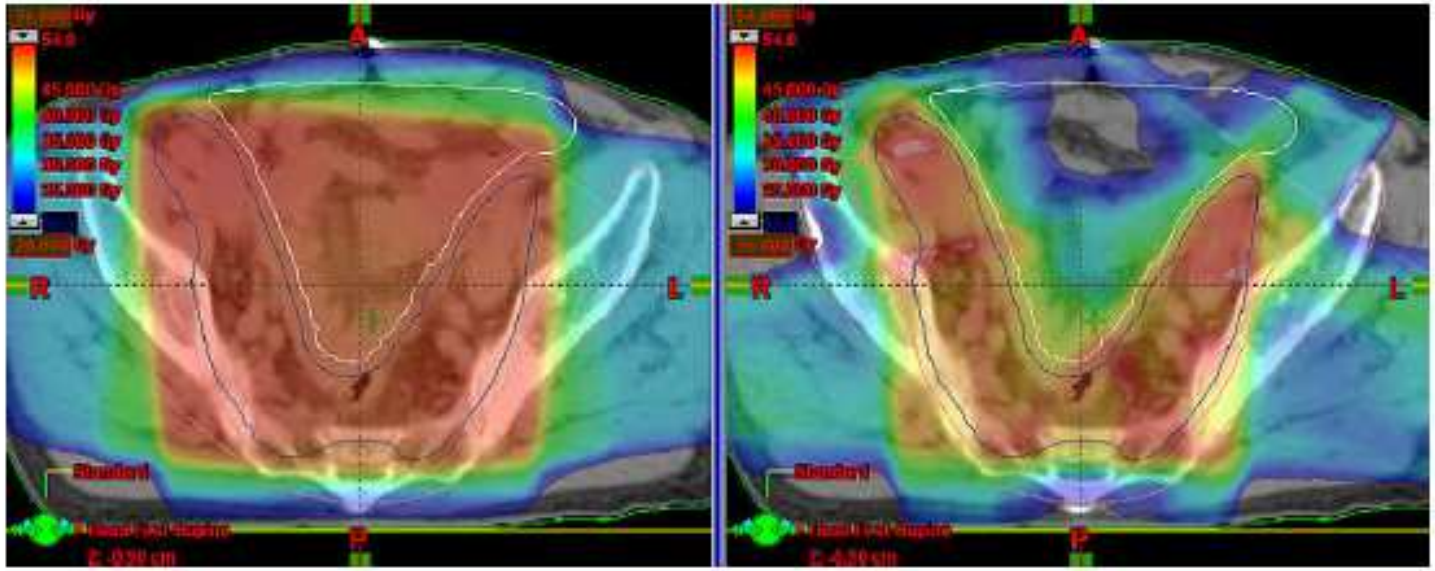
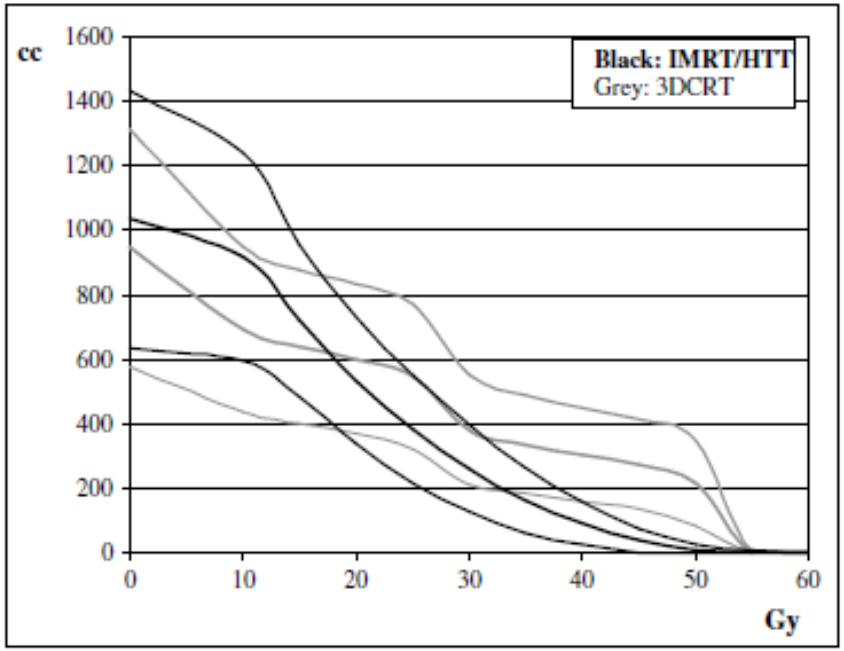
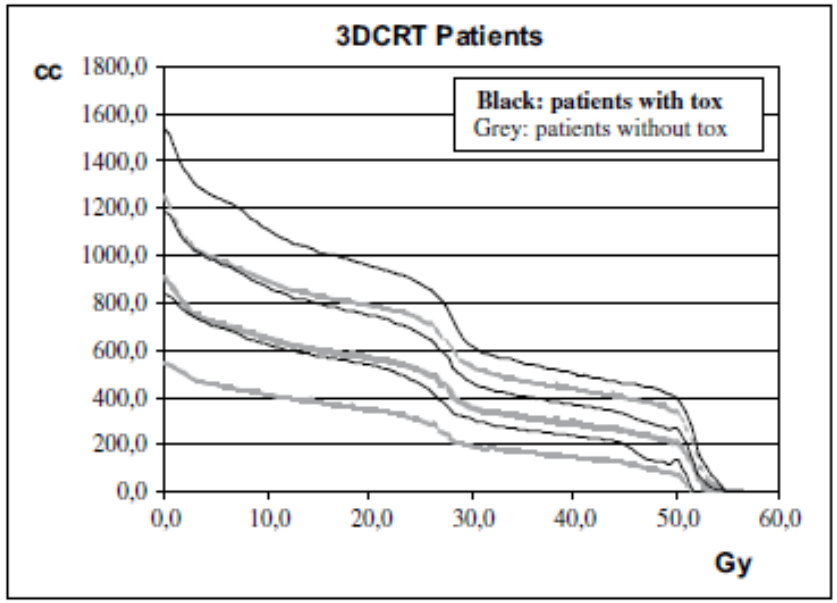
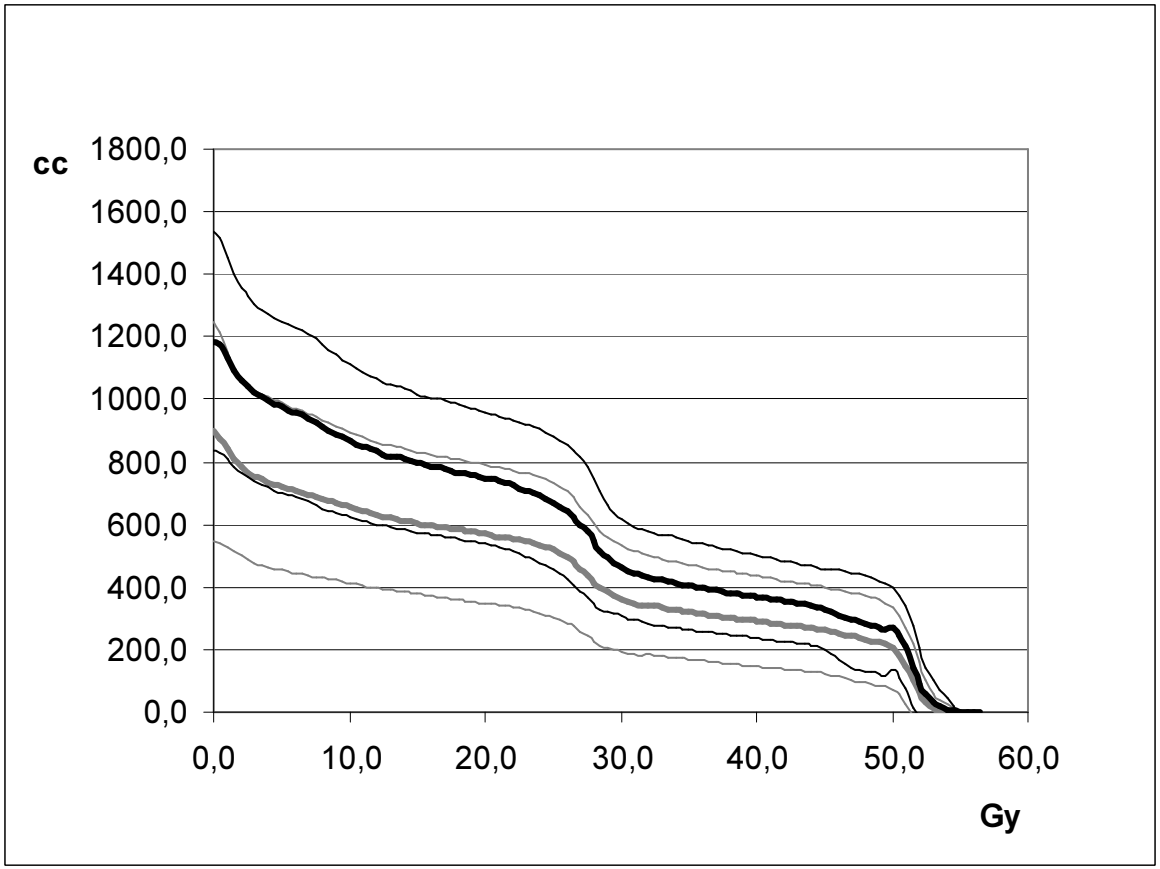


Fig. 5. An example of the dose distribution for three-dimensional conformal radiation therapy (3DCRT) and intensity-modulated radiation therapy (IMRT) on an axial slice passing through the pelvis: the 15- to 54-Gy dose range is shown in color wash. Dark contour = planning target volume (PTV); white contour = intestinal cavity outside PTV (IC).







Black: pts with tox

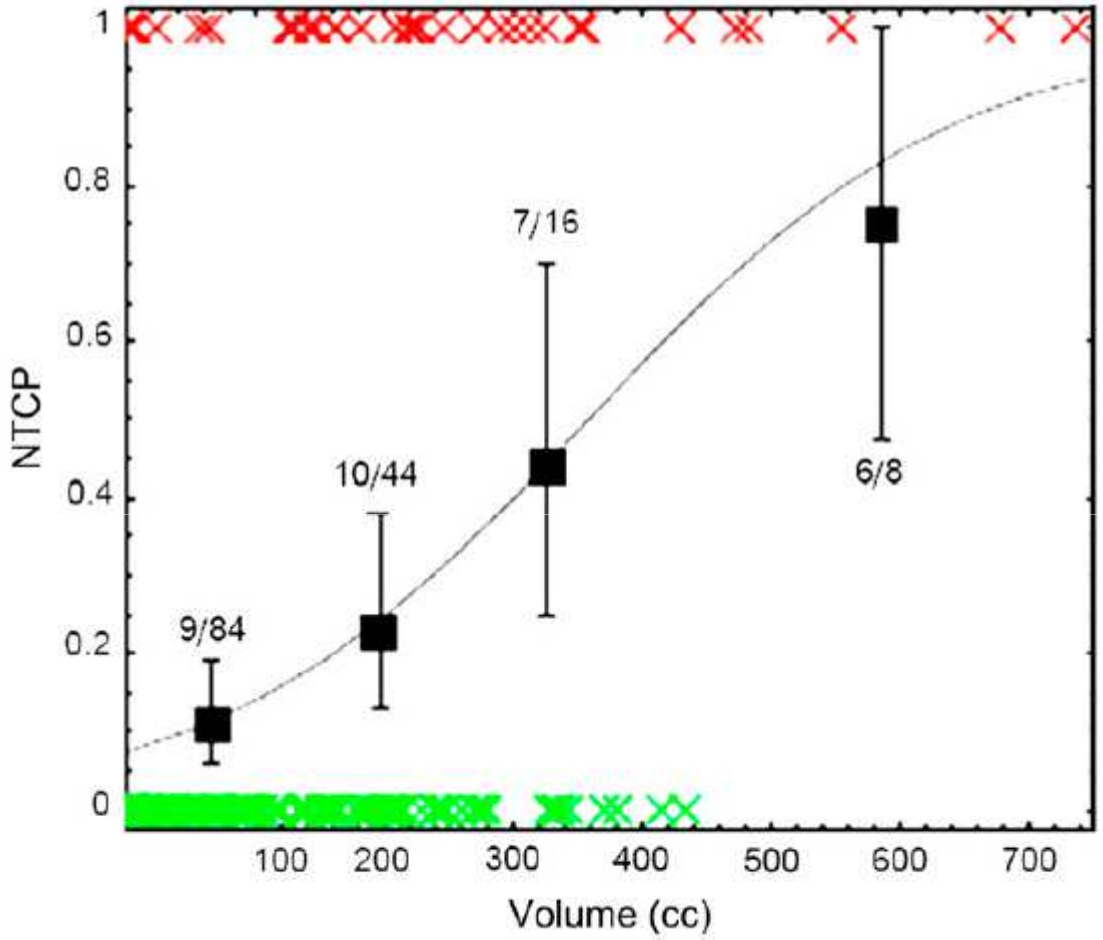
Grey: pts without tox

UVA: V15 best predictor compared to V40-V50…..due to larger differences at low doses (geometry…no biology !!!!)

V15 AS A SURROGATE OF THE HIGH-DOSE REGION IN THE BOX TECHNIQUE

NO BIOLOGICAL MEANING - DONT USE IT (ALONE) IN IMRT OPTIMIZATION…

BOWEL: dose-volume effect



V15Gy, rectal cancer patients, acute G3 diarrhea
Concomitant chemotherapy
Robertson IJROBP 2010

PENILE BULB: erectile dysfunction

Erectile dysfunction (ED), the consistent inability to attain or maintain an erection of sufficient quality to permit satisfactory sexual intercourse, is a common complication resulting from radiotherapy (RT) for prostate cancer (1). Many patients choose RT for their clinically localized prostate cancer because they believe there may be a lower risk of ED compared with radical prostatectomy (RP); however, this remains controversial. Posttreatment ED rates have been reported to be approximately 24% (brachytherapy alone), 40% (brachytherapy plus external RT), 45% (external RT alone), 66% (nerve-sparing RP), 75% (non–nerve-sparing RP), and 87% for cryosurgery, but physician-reported rates are known to be less reliable than patient-reported outcomes, so the optimal comparison studies have yet to be done (2).

QUANTEC 2010

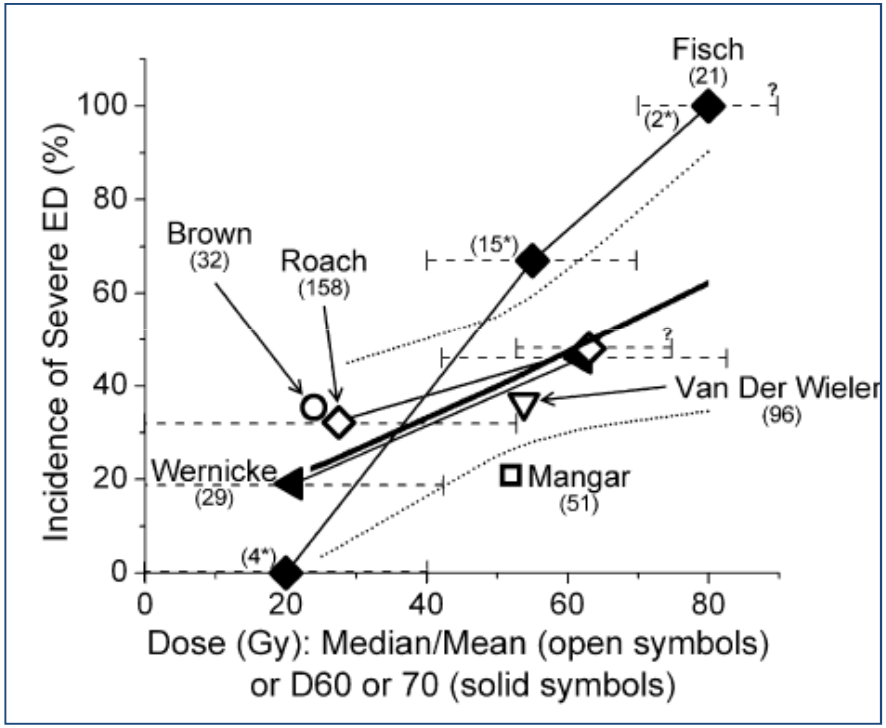
Table 1. Erectile dysfunction after external-beam radiotherapy and correlated parameters

First author, year (reference)	N	Assessment method*	Prescribed dose, treatment	OAR definition	Severe ED rate (%)	Correlated parameters	
						Dose–volume	Clinical
Fisch, 2001 (7)	21	Questionnaire†	65–72 Gy, 3D	Penile bulb	33‡	D70 ≥70 Gy§	No other endpoints analyzed
Roach, 2004 (10)	158	Patient report, (RTOG)‖	68.4 Gy, 73.8 Gy, 3D	Penile bulb¶	41	Median penile bulb dose ≥52.5 Gy¶	No other endpoints analyzed
Wernicke, 2004 (14)	29	Questionnaire†	66.6– 79.2 Gy, 3D	Penile bulb#	NS	D30 ≥67 Gy¶ D45 ≥63 Gy¶ D60 ≥42 Gy¶ D75 ≥20 Gy¶	Alcohol and smoking not significant, dose and volume significant
Selek, 2004 (11)	28	Questionnaire†	78 Gy, 3D	Penile bulb#	35.7% at 2 y	Mean dose to penile structure 38.2 Gy, no dose–volume effect was found#	Up to 68% may have had ED posttreatment? ED correlated with hypertension
Mangar, 2006 (8)	51	Questionnaire†	64 Gy, 74 Gy, 3D	Penile bulb, crura and cavernosum**	24	D15, D30, D50, D90 of penile bulb¶	Adjusted for age, bulb volume, hypertension, and previous pelvic surgery
Zelefsky, 2006 (15)	561	Patient report (NCI)††	81 Gy, IMRT	‡‡	49	Not evaluated	Hormone therapy
Brown, 2007 (5)	32	Questionnaire†	NS, IMRT	Penile bulb	34	No relationship noted	Hypertension, pre-RT erectile function
Cahlon, 2008 (6)	478	Patient report (NCI)††	86.4 Gy, IMRT	‡‡	30	Not evaluated	Age >70 y, diabetes, hormone therapy
van der Wielen, 2008 (13)	70	Questionnaire†	68 vs. 78 Gy	Penile bulb	36	No correlations between ED and dose–volume of crura, or the penile bulb#	Adjusted for diabetes and history of cardiovascular disease
Pinkawa, 2009 (9)	123	Questionnaire†	70.2–72 Gy, 3D	NS	73§§	Not evaluated	Age, diabetes

QUANTEC 2010

Suggestion: D>40-50 Gy to the whole bulb associated with increased toxicity,
Observe: several studies do **not** find any correlation with dose

Erectile dysfunction – dose response relationship?



8. RECOMMENDED DOSE/VOLUME LIMITS

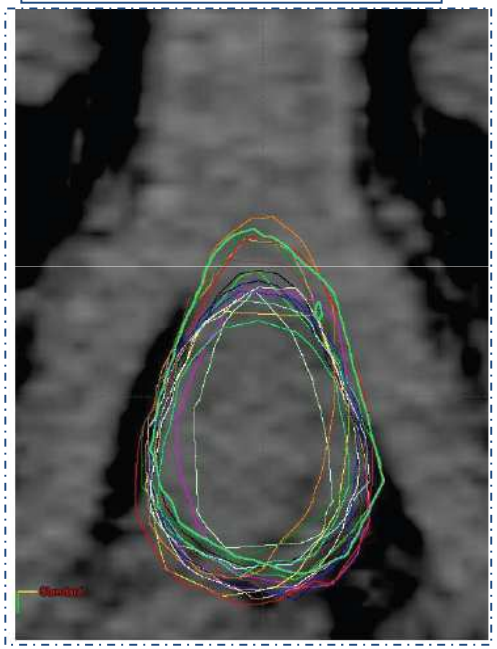
On the basis of the data available, it is prudent to keep the mean dose to 95% of the PB volume to <50 Gy. It may also be prudent to limit the D70 and D90 to 70 Gy and 50 Gy, respectively. It is acknowledged that the PB may not be the critical component of the erectile apparatus, but it seems to be a surrogate for yet to be determined structure(s) critical for erectile function for at least some techniques.

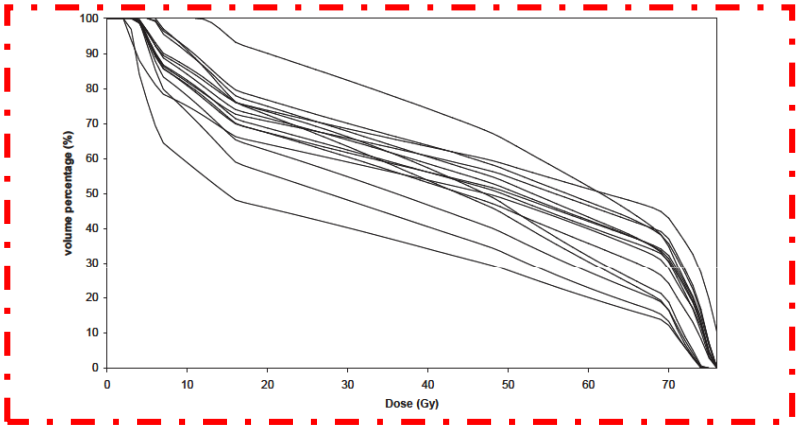
QUANTEC 2010

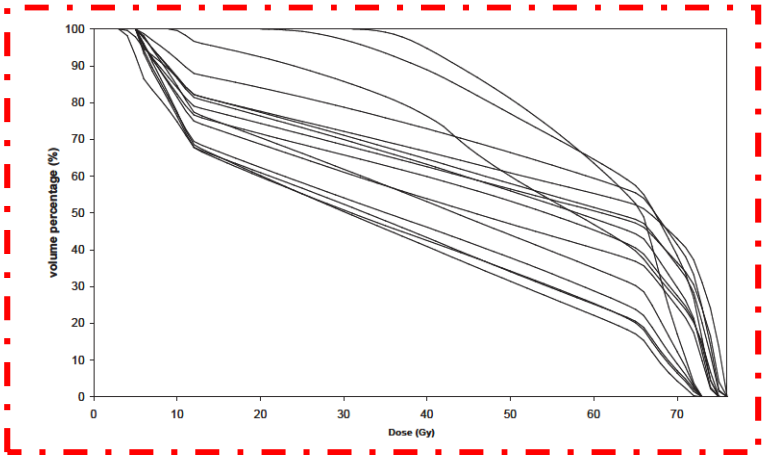
Inter-observer variability in contouring the penile bulb on CT images for prostate cancer treatment planning

Pema *et al. Radiation Oncology* 2011, **6**:123

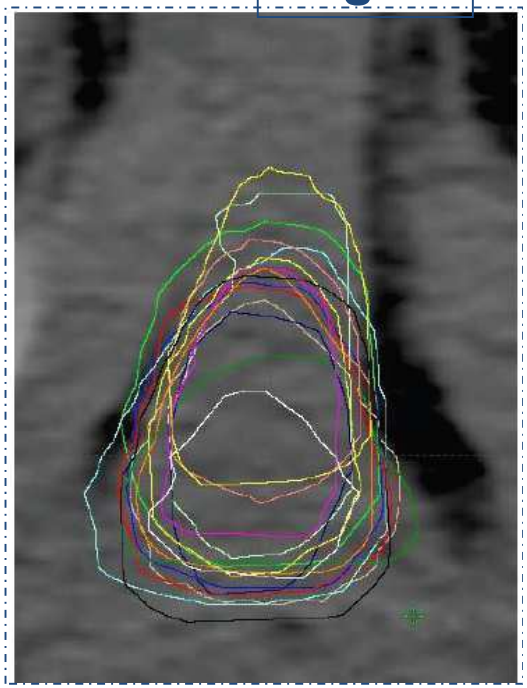
lowest







largest



•Penile bulb volume: 5-20cc

- Contouring: interobserver variability larger than interpatient variability
- Dose-metrics: interpatient variability larger than interobserver variability
- % DVH should be used, not absolute DVH in cc

Pema *et al. Radiation Oncology* 2011, **6**:123

Acknowledgments:

Claudio Fiorino, HSR, Milano
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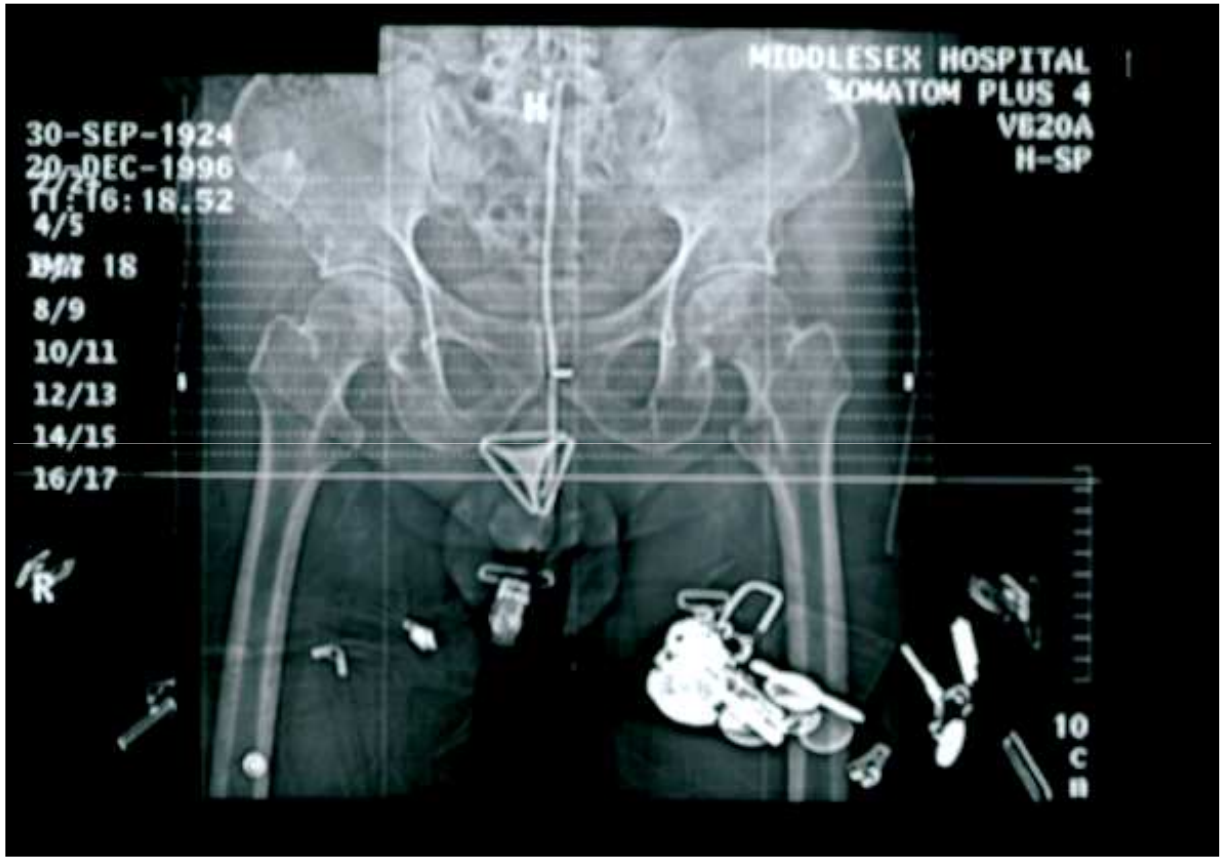
Eva Onjukka, Medical Physics Department, Karolinska University Hospital, Stockholm

IMRT - Prostate Cancer

Heather Payne
Clinical Oncology -UCH

The Historical Efficacy and Toxicity of Conventional EBRT in Prostate Cancer was not good!


MIDDLESEX HOSPITAL
SOMATOM PLUS 4
VB20A
H-SP
30-SEP-1924
20-DEC-1996
11:16:18.52
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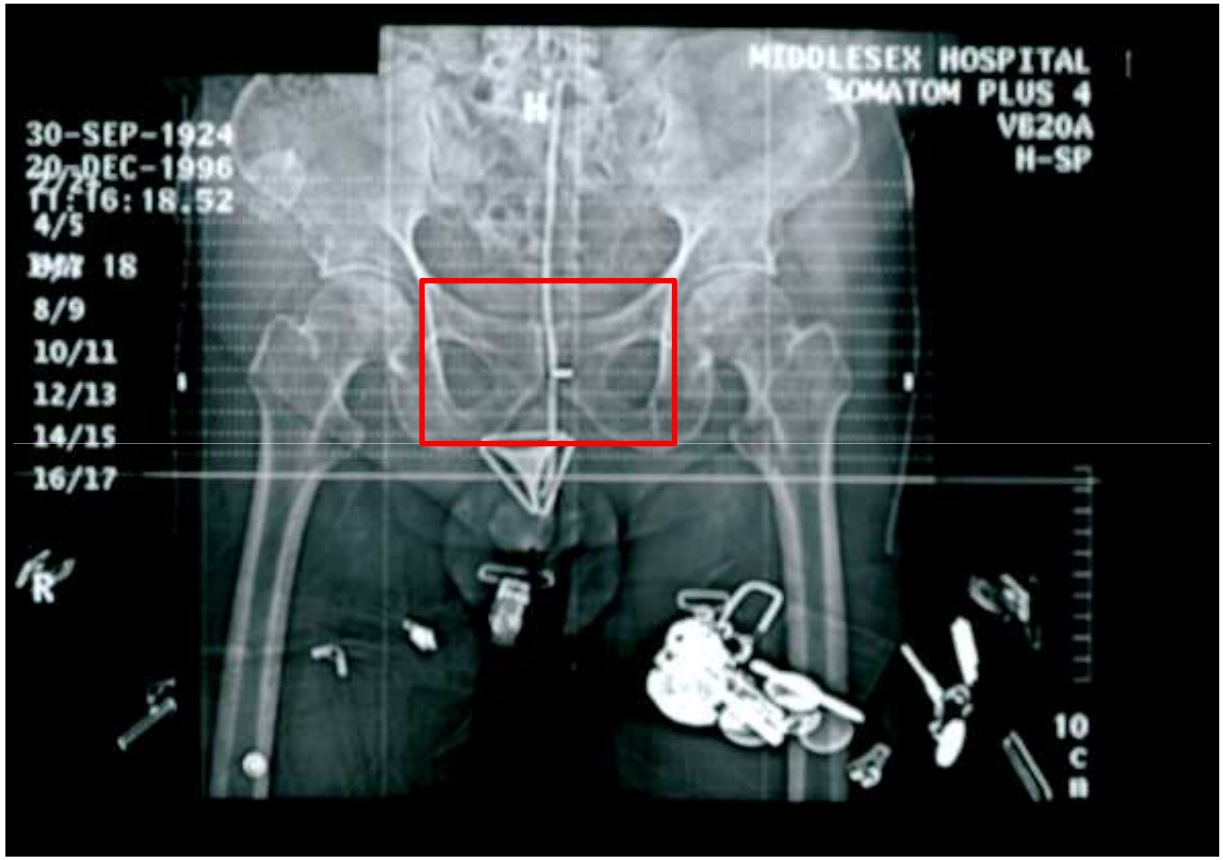
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SOMATOM PLUS 4
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30-SEP-1924
20-DEC-1996
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14/15
16/17
R
10 cm

Results Radiotherapy Series

– *Hanks et al*

682 pts – 10 year follow up

SURVIVAL	5 YRS	10YRS
A	83%	62%
B	73%	46%
C	**58%**	**38%**

Results - *Hanks 2*

Infield Recurrence –even worse!

	5yrs	10yrs
A	3%	3%
B	14%	26%
C	**26%**	**31%**

Improving the Results of RT

- PROBLEMS

1. Inadequate dose delivered so poor efficacy despite the fact that it was known that dose escalation beneficial – calculated that increasing the dose of radiation by 10% can increase local control by 20%

2. Inability to dose escalate without unacceptable toxicity to surrounding normal structures

3. High risk disease also recurrence at nodal and distant sites

Recent improvements in RT

- Innovative techniques allow dose escalation while sparing normal tissue:[1,2]

3D conformal RT (3D-CRT)
- Minimises organ damage
- Allows higher radiation dose

Image-guided RT (IGRT)
- Fiducial markers
- Cone-beam imaging
- Tomotherapy

High dose rate (HDR) brachytherapy boost

Cyberknife and Proton Boost under investigation

Intensity-modulated RT (IMRT)
- Optimised form of 3D-CRT
- Dose distribution shaped more precisely to target than 3D-CRT to spare organs at risk

Hypofractionation

Volumetric arc therapy

Combined RT and ADT
- Can delay progression and improve overall survival
- Concomitant and adjuvant ADT mandatory for RT of high-risk PCa[1]

: Androgen deprivation therapy, PCa: prostate cancer, RT: Radiotherapy

1. Heidenreich A, et al. Eur Urol 2011; 59:61–71; 2. Pinkawa M et al. Strahlenther Onkol 2011;187:479–484

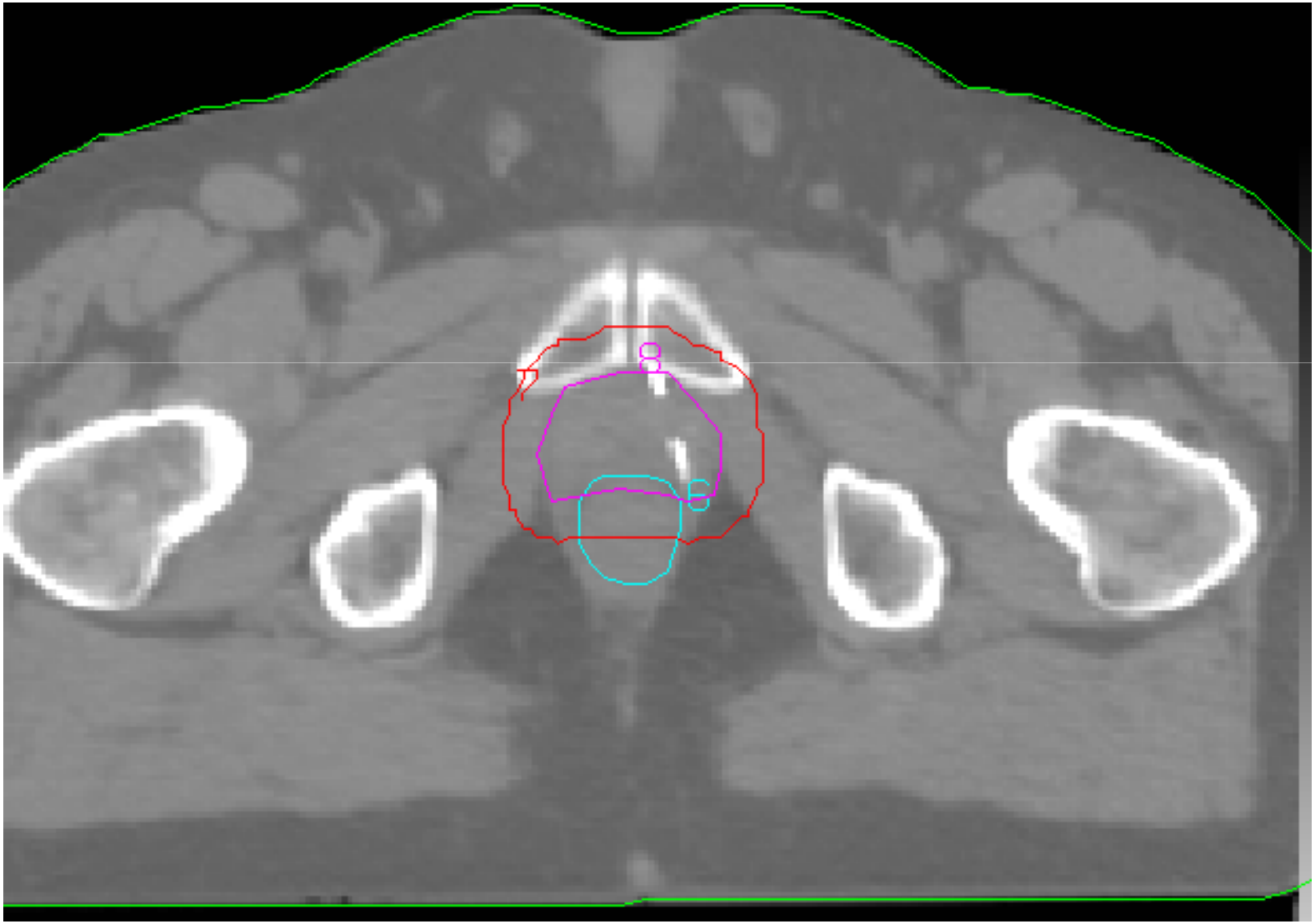
3D-CRT and IMRT

- **3D-CRT:**
  - better targeting of RT using 3D imaging to define target volume and critical organs at risk (OAR); multiple beams conform to the 3D tumour shape and maximally avoid the OAR[1]
- **IMRT:**
  - optimized high-precision form of 3D-CRT
    - allows better dose distributions and improved ability to conform treatment volume to concave shapes
    - Individual beamlets allow varying doses to exploit differences in position of tumour vs. normal tissue[2]
- **IMRT +IGRT:**
  - IGRT may improve outcome by reducing set-up error and accounting for organ motion[2]

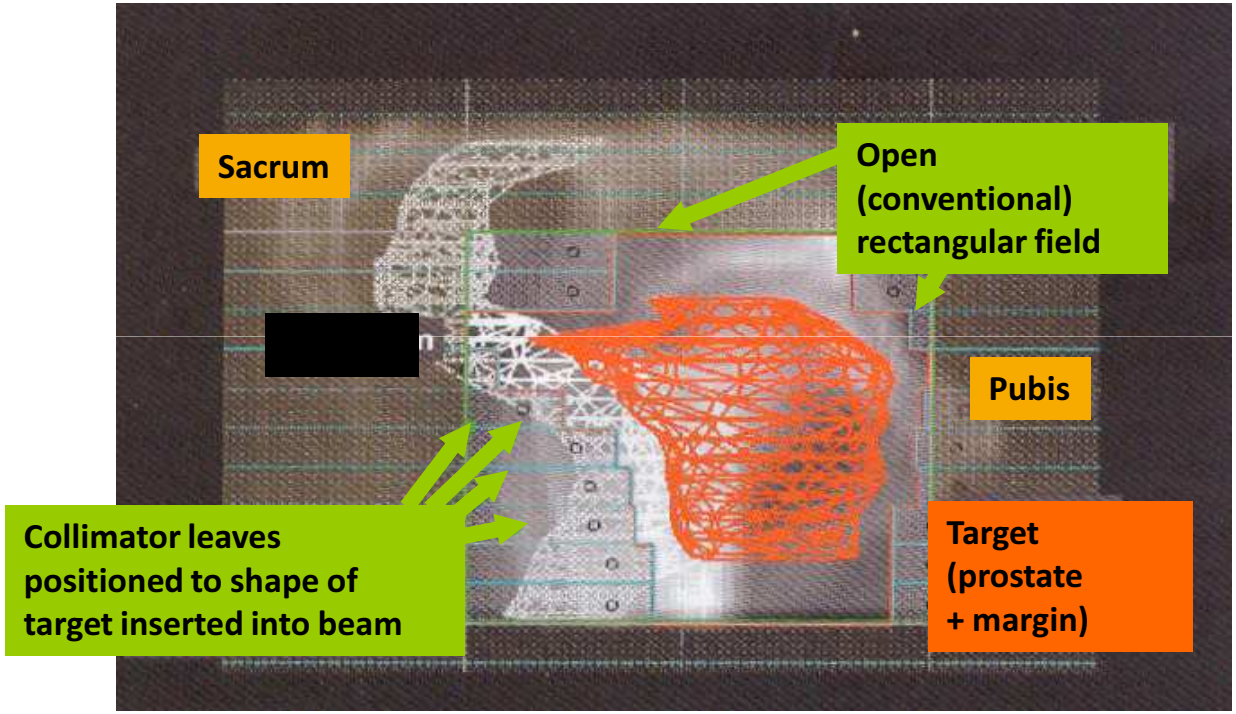
3D-CRT, 3-dimensional conformal RT ; IMRT, Intensity modulated RT; IGRT, image-guided RT

1. Hummel S, et al. Health Technol Assess 2010;14(47);
2. Wolff JM et al. BJU Int 2012; 109 (Suppl 6): 33–41

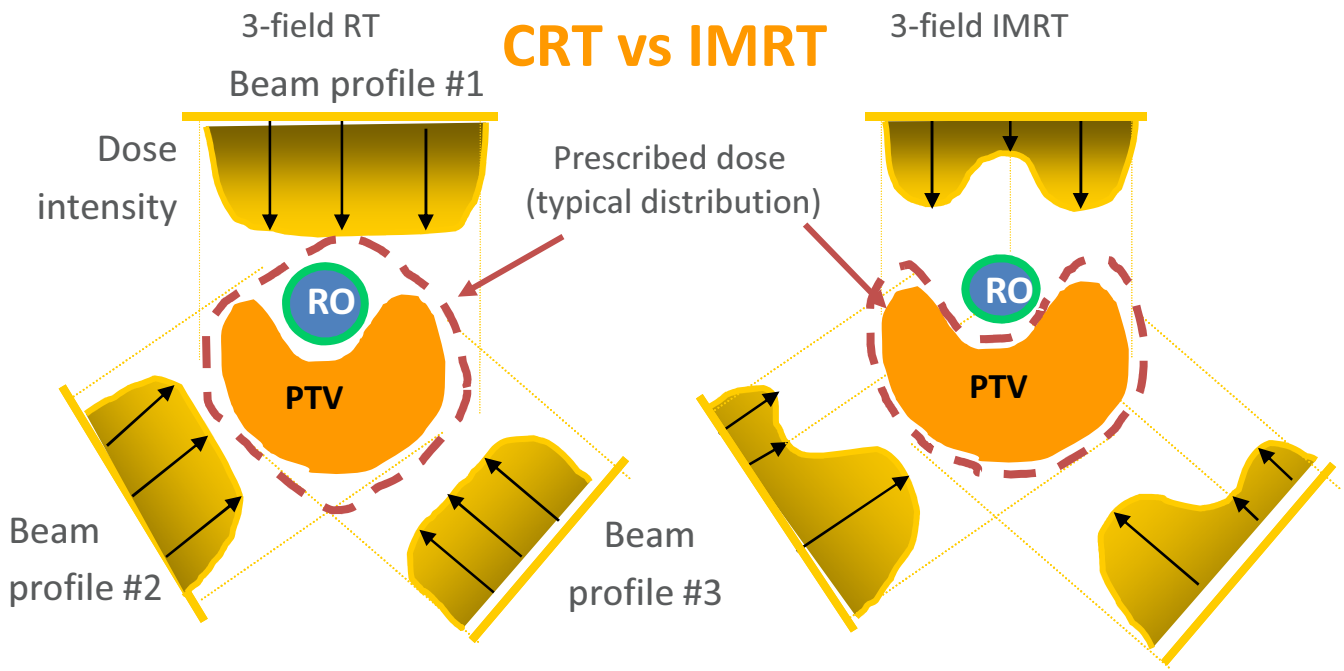
E



Conformal Radiotherapy



IMRT allows dose distribution to be shaped to the target, sparing at-risk organs



CRT: Conformal radiotherapy. IMRT: Intensity-modulated radiotherapy.
PTV: Panning target volume. RO: Risk organ

Volumetric modulated arc therapy (VMAT)

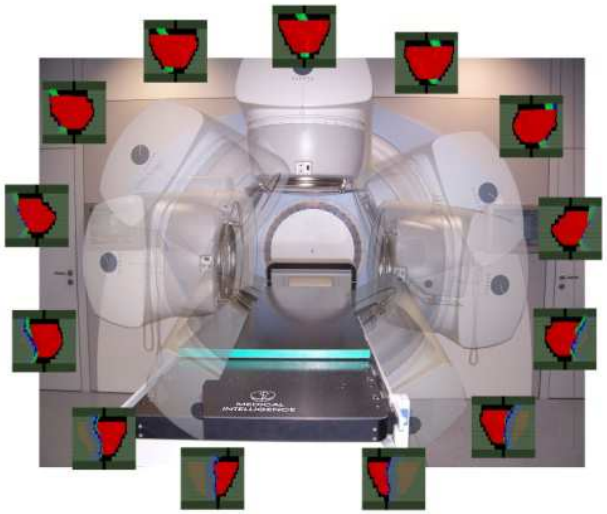
- Treatment of whole target volume using 1 or 2 arcs
- Simultaneous variation of 3 parameters:[1]
  - ➔ Gantry rotation speed
  - ➔ Treatment aperture shape via movement of multileaf collimators*
  - ➔ Dose rate
- Highly conformal dose distributions with improved target volume coverage and sparing of normal tissues vs. conventional RT techniques;
  - ➔ Potential to reduce treatment delivery time vs. conventional static field IMRT[1]

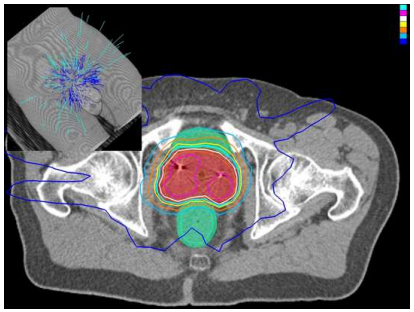
1. Teoh M, et al. British J Radiol 2011;84:967–996

* Each radiation beam is modulated by continuously moving multileaf collimators

13

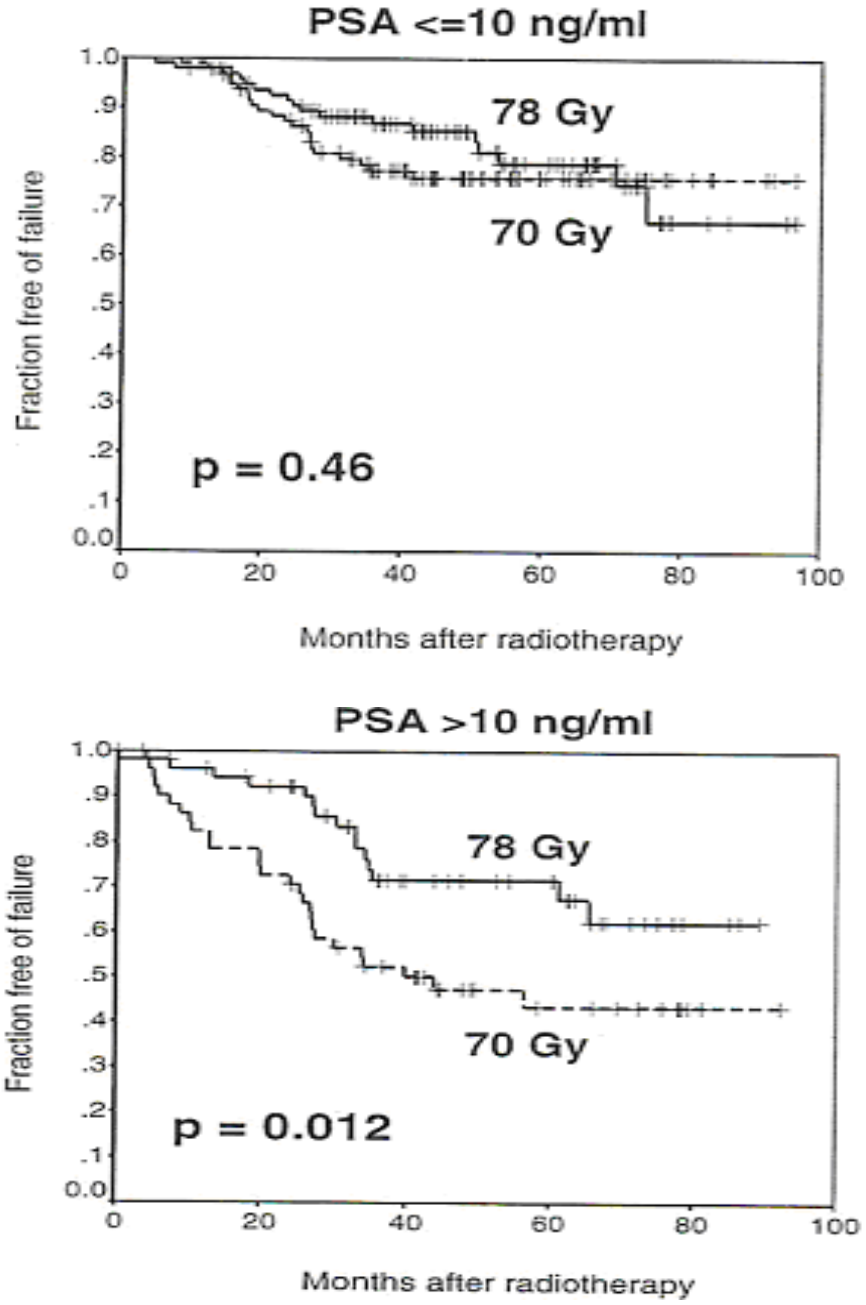
VMAT images





Conformal Dose Escalation

- MD Anderson 1000 patients treated 87 –97 patients T2 –T4 disease
- 4 year bNED
- Up to 67 Gy = 54%
- 67-77 Gy =71%
- Above 77 Gy = 74%
- Good prognostic patients showed no additional benefit.
- Grade 3 morbidity = 1%


PSA <=10 ng/ml
78 Gy
70 Gy
p = 0.46
Fraction free of failure
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
0.0
0
20
40
60
80
100
Months after radiotherapy
PSA >10 ng/ml
78 Gy
70 Gy
p = 0.012
Fraction free of failure
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
0.0
0
20
40
60
80
100
Months after radiotherapy

Prostate cancer-specific mortality in RCTs for dose escalation

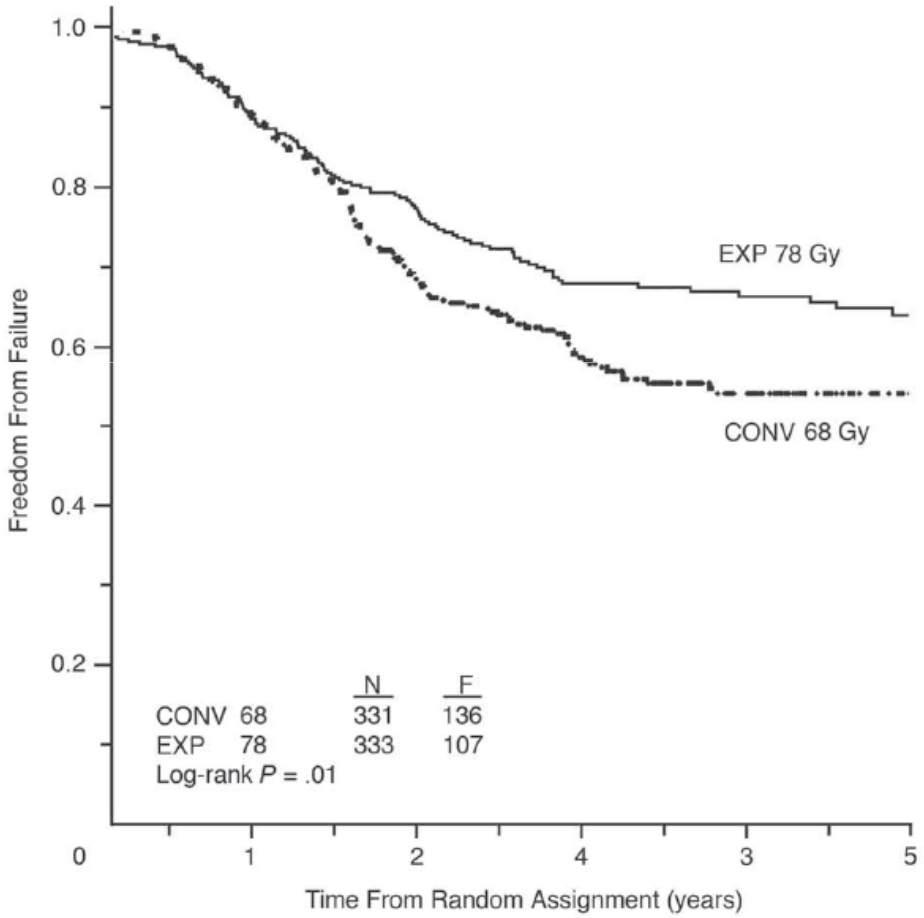
Trial	No.	Follow-up	High risk	PCa deaths
PROG[1]	393	9 yr	5%	4 (1%)
MDA[2]	305	9 yr	33%	10 (3%)
RT01[3]	843	5 yr	44%	36 (4%)
NKI[4]	669	5.8 yr	55%	87 (13%)
RT01[5]	843	10 yr	44%	91 (11%)
ICR/RMH[6]	126	14 yr	59%	19 (15%)

RCT; randomized clinical trial

. Zietman AL, et al. J Clin Oncol 2010;28:1106–11; 2. Kuban DA, et al. Int J Radiat Oncol Biol Phys 2011;79:1310–7; 3. Dearnaley DP, et al. Lancet Oncol 2007;8:475–87; 4. Peeters ST, et al. J Clin Oncol 2006;24:1990–6; 5.Dearnaley DP et al. ECCO/ESMO Sept 2011. Abstract 21LBA; 6. Creak AL, et al. ESTRO May 2011

Netherlands Cancer Institute (NKI) study: Freedom from failure significantly better in dose-escalated arm

Freedom from failure*



Biochemical failure was defined according to the ASTRO definition with backdating
EXP, experimental; CONV, conventional; F, failures
Peeters ST, et al. J Clin Oncol 2006;24:1990–6

RT01 trial: 5-year follow-up: Improved bPFS with dose-escalation (44% high risk)

Median follow-up: 5 years	Standard dose CFRT 64 Gy/32 fractions (n=421)	Escalated-dose CFRT 74 Gy/37 fractions (n=422)	HR (95% CI)
bPFS at 5 years	60%	71%	0.67 (0.53-0.85) p<0.0007
bPFS events	149	108	
Clinical PFS	87%	90%	0.69 (0.47-1.02) p=0.064
Freedom from salvage androgen suppression	80%	84%	0.78 (0.57-1.07) p=0.12

At 5 years, using CFRT to increase RT dose from 64 Gy to 74 Gy had substantially improved prostate-cancer control in terms of bPFS

bPFS, biochemical progression-free survival; CFRT, conformal radiotherapy; HR, hazard ratio; all comparisons expressed relative to patients in standard group (i.e. HR <1・0 indicates decreased risk of event for escalated group)
Dearnaley DP et al. Lancet Oncol 2007;8:475–87

RT01 trial: 10-year follow-up: No improvement in long-term survival with dose-escalation (44% high risk)

Median follow-up: 10 years	Standard dose CFRT 64 Gy/32 fractions (n=421)	Escalated-dose CFRT 74 Gy/37 fractions (n=422)	HR (95% CI)
Deaths	120	119	
Overall survival at 10 years	70%	70%	0.99 (0.77-1.28) assumption of proportional hazards met: p=0.337
bPFS at 10 years	42%	54%	0.688 (0.56-0.84) p<0.0001
bPFS events	224	172	
Long-term HT	220 men overall: fewer men starting HT and later in escalated-dose group		0.77 (0.59-1.00) p=0.05

In the longer-term perhaps 74 Gy is not a sufficient dose escalation

No mandated IGRT

bPFS, biochemical progression-free survival; CFRT, conformal radiotherapy; HR, hazard ratio; all comparisons expressed relative to patients in standard group (i.e. HR <1・0 indicates decreased risk of event for escalated group); HT, hormone therapy

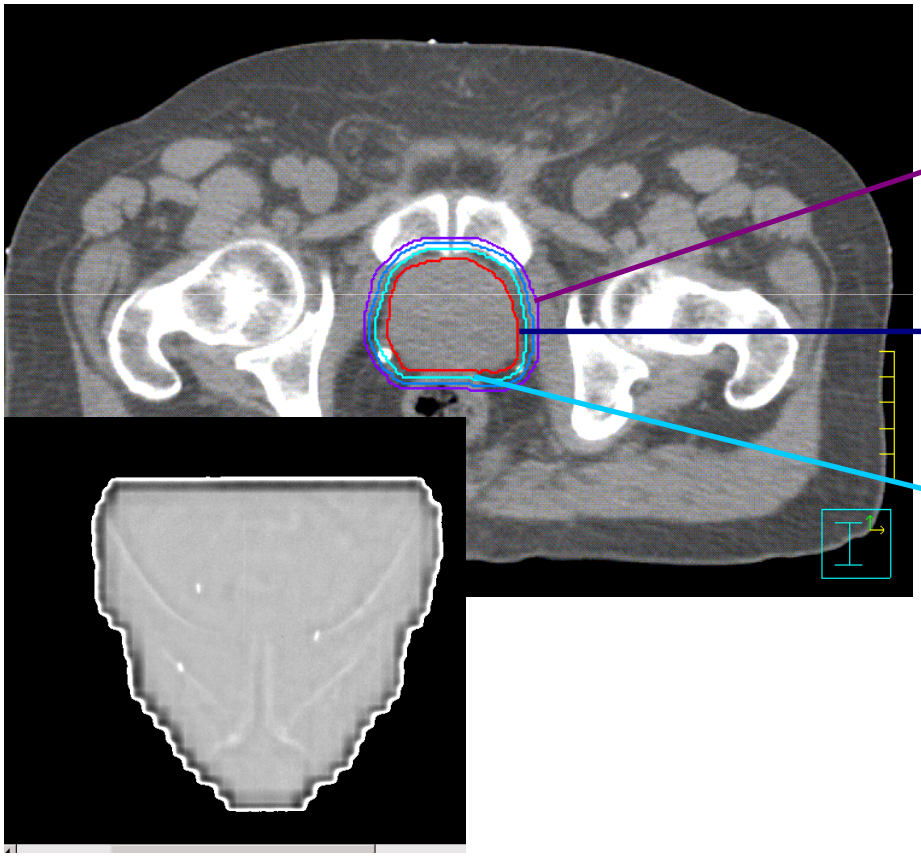
Dearnaley DP et al. ECCO/ESMO Sept 2011. Abstract 21LBA

IGRT

- Fiducial markers
- CT Cone Beam Imaging
- Tomotherapy
- Combinations…….

IGRT gold seed fiducial markers and margin reduction

CHHiP IGRT



10 mm margin

7 mm margin
34% reduction in volume

5 mm margin
55% reduction in volume

3 mm margin
74% reduction in volume

IGRT, image-guided RT

IMRT for Prostate Cancer

PATIENT SELECTION CRITERIA

Histologically confirmed non-metastatic prostate cancer

All patients referred for prostate +/- seminal vesicle radiotherapy +/- nodal therapy or prostate bed radiotherapy to be considered for inverse planned IMRT

WHO performance status 0 or 1

EXCLUSION CRITERIA

Previous pelvic radiotherapy

Inflammatory Bowel Disease?

Prior major pelvic surgery (e.g. Colectomy, colostomy, cystectomy)???

Significant bladder instability or urinary incontinence?????

Bilateral Hip Replacements????

IMRT for Prostate Cancer

PRE-TREATMENT ASSESSMENT

TNM stage
Pathology – Gleason Score
PSA at presentation

Neo-adjuvant androgen deprivation for 3- 6 months prior to RT
Discuss adjuvant androgen deprivation therapy according to risk category

Prostate fiducial marker implant 3-4 weeks prior to CT planning scan
Ciprofloxacin antibiotics to be prescribed in clinic and started by patient the evening before fiducial marker insertion.
Patients on anticoagulation require switching from warfarin to S/C heparin prior to fiducial marker insertion.

Bowel and bladder preparation appointment booked 1 week before planning scan

Consent form signed in clinic scanned onto CDR as a permanent record

IMRT for Prostate Cancer

Prostate and Seminal Vesicles

IMRT for Prostate Cancer

DECISION FOR TREATMENT VOLUME

Roach Formula: Seminal vesicle risk (%) = PSA + [(Gleason Grade – 6) x 10]

Seminal Vesicle Low risk group
Clinical stages T1b/c or T2a/b and with PSA + [(Gleason Grade – 6) x 10] <15

Seminal Vesicle Moderate/High risk group
Clinical stages T1b/c or T2a/b and with PSA + [(Gleason Grade – 6) x 10] >15
T2c or T3a

PATIENT RISK DEFINITION

Patients with **low risk disease** - T1-T2b, Gleason Grade ≤ 6, PSA ≤ 10

Patients with **intermediate risk disease** - T2c, Gleason Grade 7, PSA 10-20

Patients with **high risk disease** -T3a-T4 Gleason Grade ≥ 8, PSA ≥20

IMRT for Prostate Cancer

POSITIONING AND IMMOBILISATION

The patient will be immobilised head first supine on the combifix.

RADIOTHERAPY PLANNING

CT planning scan of the pelvis with 2.5 mm slice thickness

Bladder and rectal filling - Comfortably full bladder (350mls of water 30 minutes before scan) and empty rectum achieved using microlette enemas)

Rescan the patient if the bladder is empty or the rectum is >5cm. Consider rescan if rectum > 3.5cm and rectum is deforming prostate.

Scanning levels: From the top of the L3 vertebral space to 5cm below the ischial tuberosities.

IMRT for Prostate Cancer

VOLUME DELINEATION

The volumes will be delineated with the aid of CT images

The clinician will outline
Gross tumour volume (GTV)
Clinical tumour volume (CTV)
Planning target volume (PTV)

The normal tissue organs at risk of radiation exposure will be outlined- rectum, bladder, femoral heads, bowel, urethral bulb, penile shaft

IMRT for Prostate Cancer

PLANNING TARGET VOLUMES

Low and Intermediate Risk Patients:

GTVp	Prostate alone
GTVpb	Prostate and base of seminal vesicles
CTVpb	GTVpb+0.5cm (excluding rectum)
PTV74	GTVp + 0.5cm (excluding rectum)
PTV71	CTVpb + 0.5cm (isotropic)

High Risk Patients:

GTVp	Prostate alone +/- any involved disease
GTVpsv	Prostate and seminal vesicles
CTVpsv	GTVpsv+0.5cm (excluding rectum)
PTV74	GTVp+0.5cm (excluding rectum)
PTV71	CTVpsv+0.5cm (isotropic)

IMRT for Prostate Cancer

STRUCTURES TO BE OUTLINED AS ORGANS AT RISK

RECTUM

The circumference of the rectum should be outlined entirely. If the anterior-posterior diameter of the rectum is > 5cm at any level adjacent to the prostate, or is >3.5cm and deforming the prostate, the patient should be re-scanned. The outlining should extend to the bottom of the ischial tuberosities to the recto-sigmoid junction. At the recto-sigmoid junction, the rectum and the sigmoid will be outlined as different structures. The recto-sigmoid junction will be defined as the level at which there is an anterior inflection of the bowel.

IMRT for Prostate Cancer

STRUCTURES TO BE OUTLINED AS ORGANS AT RISK

BLADDER

The outside of the bladder wall should be outlined. The entire bladder should be included.

BOWEL (SMALL BOWEL AND COLON)

The small and large bowel should be outlined on all slices. The small and large bowel should be outlined as separate structures where possible. However, the combined structure will be used for the bowel dose constraint. The outlining will include the small bowel, large bowel and the sigmoid colon down to the level of the recto-sigmoid junction. The superior extent should be 3cm above the superior limit of the PTV.

FEMORAL HEADS

The femoral heads should be outlined to the bottom of the curvature of their heads.

PENILE SHAFT AND BULB

The penile shaft and penile bulb

IMRT for Prostate Cancer

RADIOTHERAPY TREATMENT

Inverse planned VMAT/IMRT using dynamic MLC, 6MV photons

VMAT: 1-2 Arcs

IMRT: 5-7 co-planar fields

Gantry: 0°, 52°, 100°, 157°, 203°, 260°, 308° (7 fields)

180, 91-100, 30, 330, 260-269 (5 fields)

Energy: 6 MV photons

IMRT for Prostate Cancer

RADIATION PRESCRIPTION

Low and intermediate risk patients

74Gy to MTD in 37# at 2Gy per # over 7.5 weeks

PTV74	74Gy in 37# to target mean (2.0)
PTV71	71Gy in 37# to target mean(1.92)

High risk patients

74Gy to MTD in 37# at 2Gy per # over 7.5 weeks

PTV74	74Gy in 37# to target mean (2.0)
PTV71	71Gy in 37# to target mean (1.92)

IMRT for Prostate Cancer

DOSE REQUIREMENTS

PTV 74

99% of the volume to be covered by 95-105% of prescribed dose (70.3 – 77.7Gy)

Median dose = 74Gy +/- 0.5Gy

Minimum dose to 99% volume = ≥ 95% (70.3Gy)

Maximum dose to 1% volume = <105% (77.7Gy)

PTV71

99% of the volume to be covered by 95% of 71Gy (67.45Gy)

Median dose = 71Gy +/ - 1Gy

IMRT for Prostate Cancer

MAXIMUM DOSE LIMITS FOR OAR

RECTUM

V30	80%
V40	70%
V50	60% (Should aim to achieve < 50%)
V60	50% (Should aim to achieve < 40%)
V65	30%
V70	15%
V74	3%

BLADDER

V50	50%
V60	25%
V74	5%

FEMORAL HEADS

V50	50%
Max	55Gy

IMRT for Prostate Cancer

BOWEL GRADE	0	(Grade1)
V45	78cc	158cc
V50	17cc	110cc
V55	14cc	28cc
V60	0.5cc	6cc
V65	0cc	0cc

Aiming to meet Grade 0 values

Urethral Bulb

V50	50%
V60	10%

DVH LIMITS FOR OAR

No hotspots (>103%) to occur in bowel

No dose > 105% to any OAR

Any hot spots outside the PTV should not to exceed 105%. Unexpected cold spots should be avoided.

RT Prostate

Morbidity

Acute

- Lethargy
- Proctitis
- Urethritis
- Cystitis
- Diarrhoea

Late

- Erectile Dysfunction– 40-50%
- Bowel Disturbance – 20%
- Surgery to Bowel – <1%
- Surgery to Bladder – <1%
- Risk Second Malignancy

EORTC GI Toxicity Scores

- 0 = None
- 1 = Mild diarrhoea, Mild cramping, Bowel movement 5 times daily, Slight rectal discharge or bleeding
- 2= Moderate diarrhoea and colic, Bowel movement >5 times daily, Excessive rectal mucus or intermittent bleeding
- 3 =Obstruction or bleeding requiring surgery
- 4= Necrosis/ Perforation Fistula

GI Toxicity

Dutch CKVO96-10 PMID 18718725 -- "Role of intensity-modulated radiotherapy in reducing toxicity in dose escalation for localized prostate cancer." (Al-Mamgani A, Int J Radiat Oncol Biol Phys

- Dutch randomized dose-escalation trial, subset treated at same institution to 78 Gy using 2 techniques: 3D-CRT and IMRT

- Outcome: 5-year bPFS IMRT 70% vs 3DCRT 61% (NS)

- Acute toxicity: G2+ IMRT 20% vs. 3DCRT 61% (SS)
  G3+ 0% vs 13%

- Late toxicity: G2+ IMRT 21% vs. 3DCRT 37% (NS); GI G3+ 0% vs 7%
  G3+ 0% vs 7%

  Conclusion: IMRT reduced toxicity without compromising outcomes

Hypofractionation

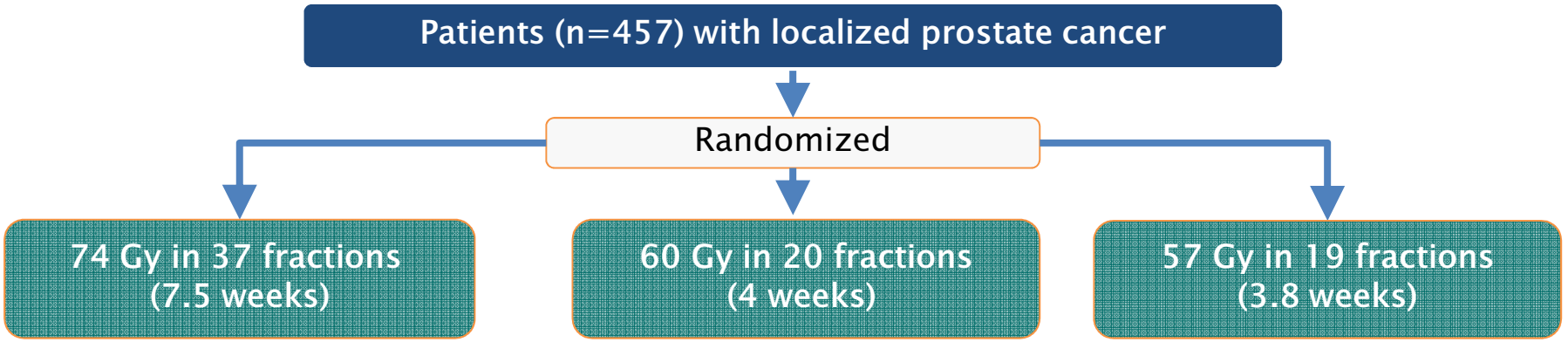
- Hypofractionation: delivery of larger doses of radiation (>2 Gy) per fraction to reduce the overall length of treatment[1]
- A lower alpha/beta ratio* in prostate cancer means that a larger dose of radiation per treatment may provide improved efficacy in terms of tumour control[1,2]
- Advantages include reduced health care costs and improved patient convenience[2]

1. Ritter M, et al. Cancer J 2009;15(1):1–6
2. Aneja S et al. Oncology: Perspectives on Best Practices 2012; 6:1-9

40

CHHiP Study

3 x RT dose fractionations combined with
3–6 months of neoadjuvant hormone therapy



- Safety results (median follow-up 50.5 months):

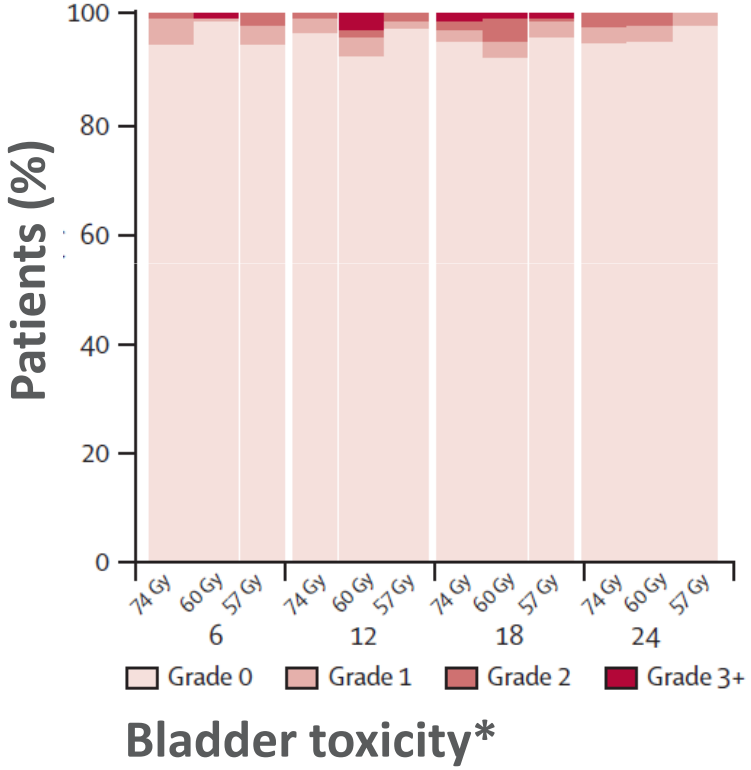
	RT dose		
	57Gy	60Gy	74Gy
Grade 2+ bowel toxicity	1.4%	3.6%	4.3%
Grade 2+ bladder toxicity	0%	2.2%	2.2%

- N

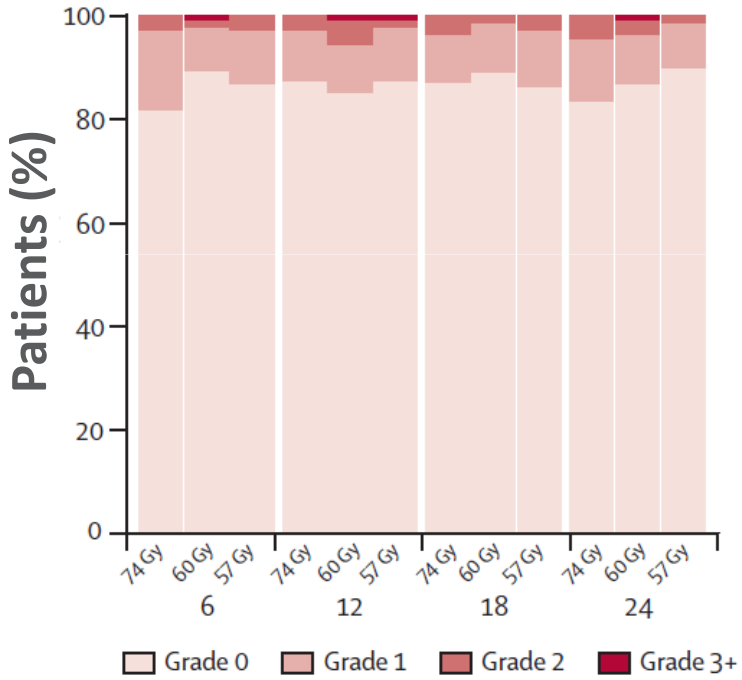
Dearnaley D, et al. Lancet Oncol 2012;13(1):43-54

CHHiP study comparing standard and hypofractionated RT+ADT

- No increased toxicity for hypofractionated regimes at 2 years – efficacy results awaited



Bladder toxicity*



Bowel toxicity*

CHHiP Study

3216 men randomised
Risk group 15% low, 73% intermediate, 12% high.
Median duration of hormone therapy was 5.6m.
Median follow up of 62.3m

5yr progression-free rate
74Gy: 88.3% (86.0%, 90.2%)
60Gy: 90.6% (88.5%, 92.3%)
57Gy: 85.9%(83.4%, 88.0%)

CHHiP Study

Late Toxicity

RTOG G2+ bowel toxicity at 2yr 74Gy (3.8%) 60Gy(2.9%) 57Gy (1.8%)

No significant difference at 5yr 74Gy (1.3%) 60Gy (2.3%) 57Gy (2.0%)

G2+ bladder toxicity showed NSD at 2yr or 5yr.

Analysis of LENT-SOM and PROs supported these results.

Conclusions: After 5 years follow-up treatment with 60Gy/20f is non-inferior to 74Gy/37f for PCa progression and is not associated with significant differences in late toxicity. 57Gy/19f has not been shown to be non-inferior to 74Gy/37f. All schedules had a low side effect profile using trial specified IMRT techniques. 60Gy/20f appears effective and safe and may be recommended as a new standard of care.

Neoadjuvant (NHT) and/or adjuvant (AHT) hormone therapy

- NHT, before definitive local treatment with curative intent, aims:
  - To reduce tumour bulk and prostate volume. Short-term ADT (3-4 m) reduces prostate size by 25-50%;[1] this may allow more focused RT
  - To treat micrometastatic disease and the primary lesion
- NHT responders may be candidates for AHT after surgery or RT
- NHT and/or AHT plus RT improves disease progression and/or overall survival vs. RT alone in high-risk localized and locally advanced PCa[2]
- Intermediate-risk patients may also benefit from combined RT and short-term ADT

Key trials of neoadjuvant HT plus RT

BM1

Trial	Follow-up	HT duration	Improved	Not improved
RTOG 86-10[1]	10 years	4 months	Disease-specific mortality, DFS, biochemical failure	OS, median survival time
TROG 96.01[2]	10 years	3 or 6 months	Local progression, event-free survival (3 and 6 months) All-cause mortality, prostate cancer mortality (6 months)	Prostate cancer-specific mortality, all-cause mortality (3 months)

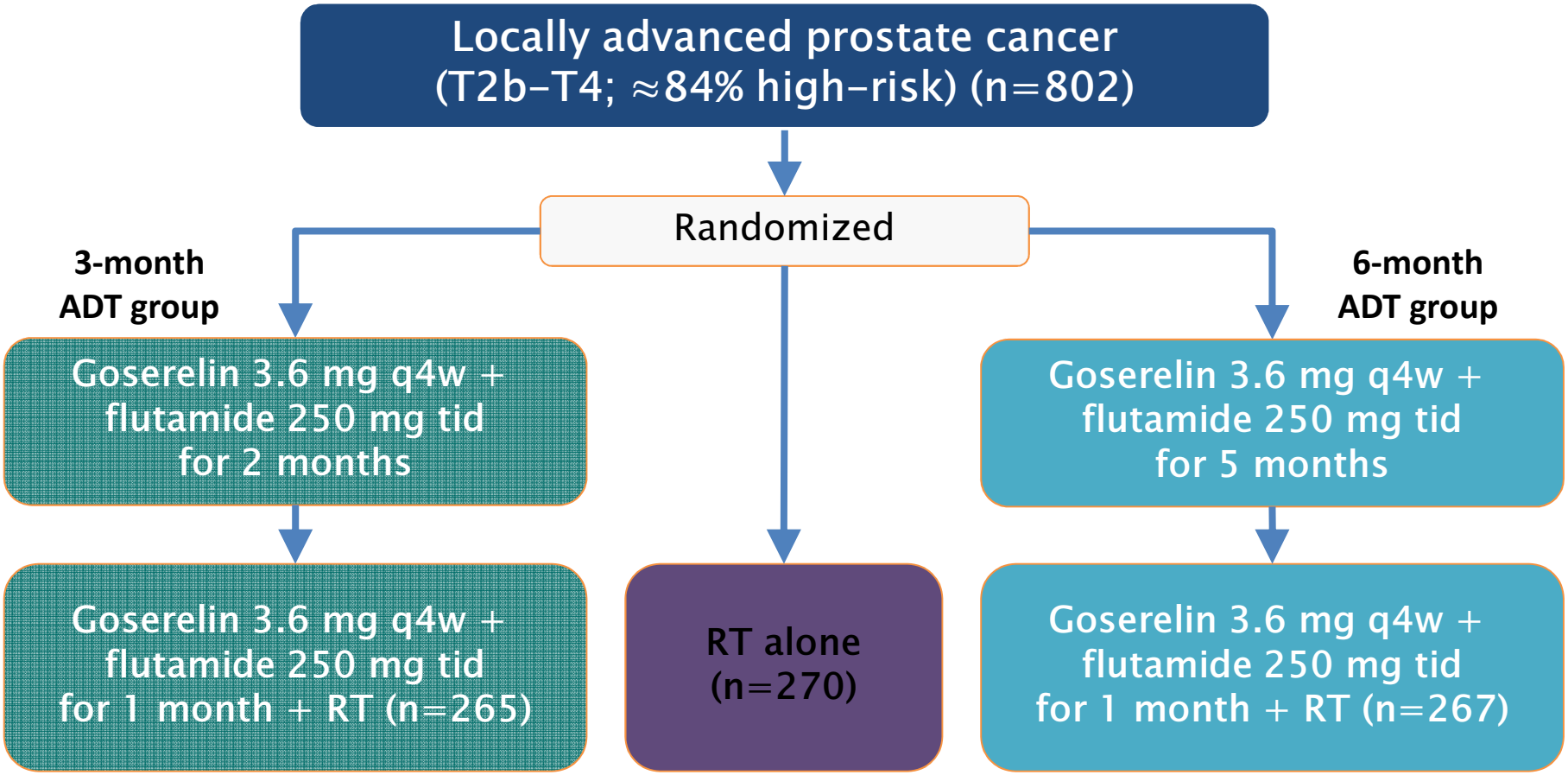
DFS, disease-free survival; HT, hormone therapy
OS, overall survival; RT, radiotherapy

1. Roach M, et al. J Clin Oncol 2008;26:585-91
2. Denham JW, et al. Lancet Oncol 2011;12:451-9

Slide 46

BM1 Created overview table. Suggest to remove following 5 slides (have hidden).
Bioscript Medical; 12-01-16

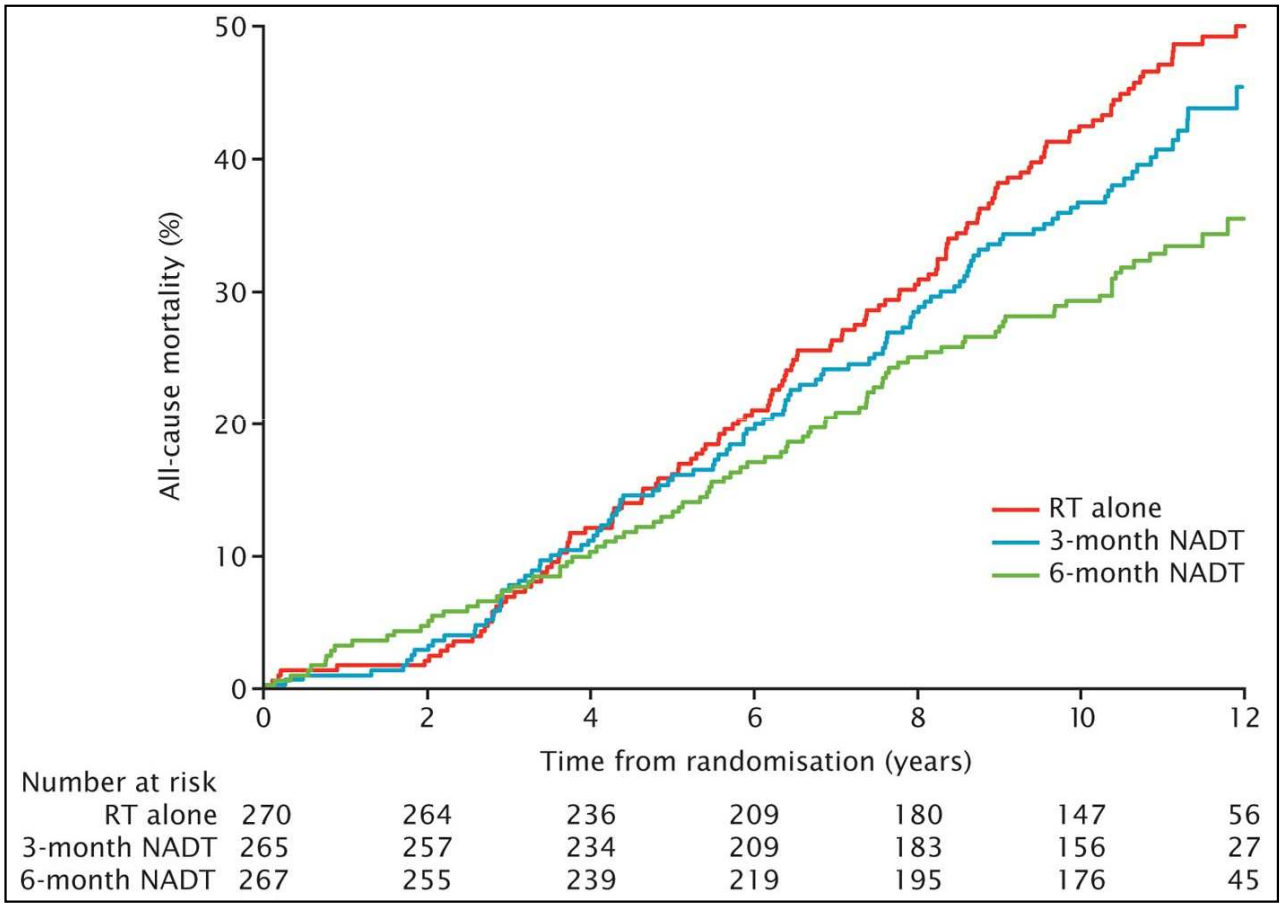
TROG 96.01: Neoadjuvant HT (3 or 6 months) plus RT vs RT alone



ADT, androgen deprivation therapy
HT, hormone therapy; q4w, every 4 weeks
RT, radiotherapy; tid, three times daily

Denham JW, et al. Lancet Oncol 2011;12:451-9

TROG 96.01: 10-year all-cause mortality



6-month ADT + RT vs RT alone: p=0.0008[a]

3- and 6-month ADT significantly reduced PSA progression, local progression and improved event-free survival

6-month ADT also significantly improved distant progression and prostate cancer mortality

[a]From multivariate model with covariates of treatment group, age, Gleason score, initial PSA and prostate cancer stage
NADT, neoadjuvant androgen deprivation therapy
PSA, prostate-specific antigen; RT, radiotherapy

Denham JW, et al. Lancet Oncol 2011;12:451-9

Adjuvant HT plus RT versus RT in high-risk PCa: 10-year results

- Significant reduction in most 10-year endpoints

Trial	Treatment groups	Local failure (%)	Distant metastases (%)	DFS (%)	OS (%)
EORTC 22863[1,2]	RT (n=208)	NR	70	23	40
	RT + goserelin for 36 months [+ AA for 1 month] (n=207)	NR	49‡	48‡	58†
RTOG 85-31[3]	RT (n=489)	38	39	23[a]	39
	RT + indefinite goserelin (n=488)	23‡	24†	37‡[a]	49**
RTOG 92-02[4,5]	Goserelin + AA for 4 months before and during RT, then:				
	– No further adjuvant HT (n=763)	22	23	23	52
	– Goserelin for 24 months (n=758)	12‡	15‡	13‡	54

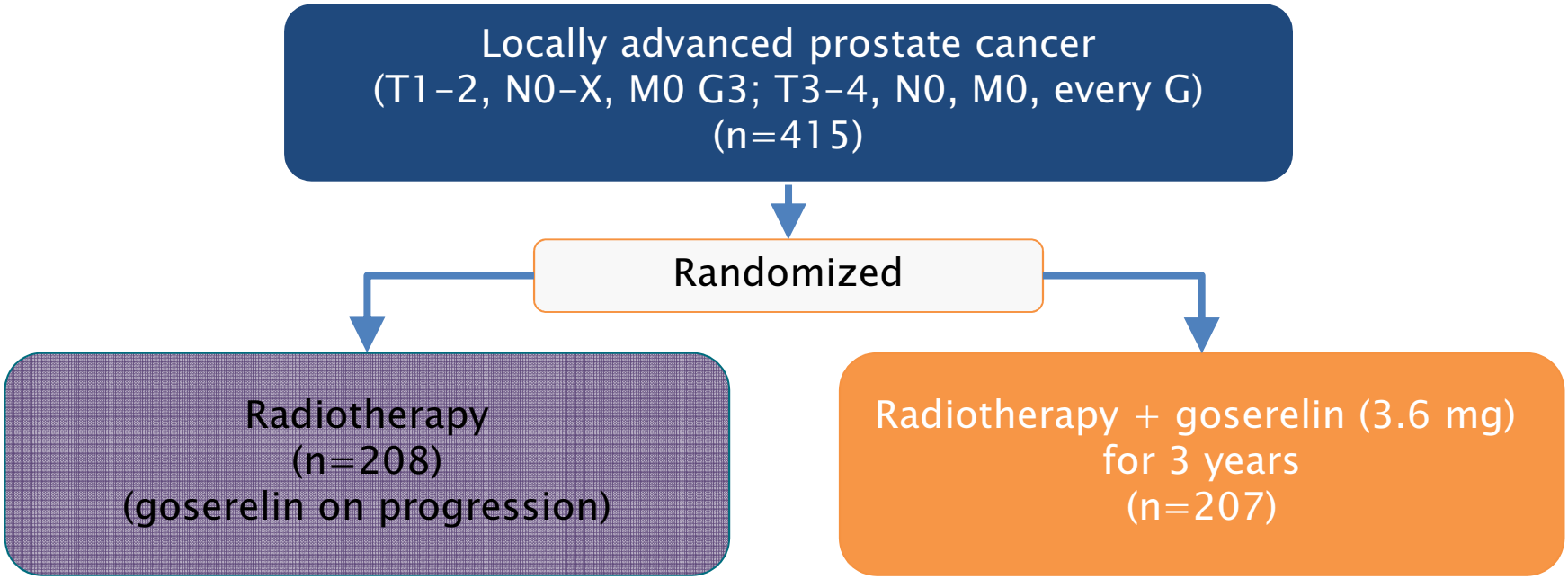
[a]No evidence of disease survival: survival in absence of locoregional failure/distant metastases

**P<0.01; †P<0.001; ‡P<0.0001 vs RT alone

NR, not reported
DFS, disease-free survival
OS, overall survival

1. Bolla M, et al. Lancet 2002;360:103-8; 2. Bolla M, et al. Lancet Oncol 2010;11:1066-73; 3. Pilepich MV, et al. Int J Radiat Oncol Biol Phys 2005;61:1285-90; 4. Hanks GE, et al. JCO 2003;21:3972-8 5. Horwitz EM, et al. JCO 2008;26:2497-504

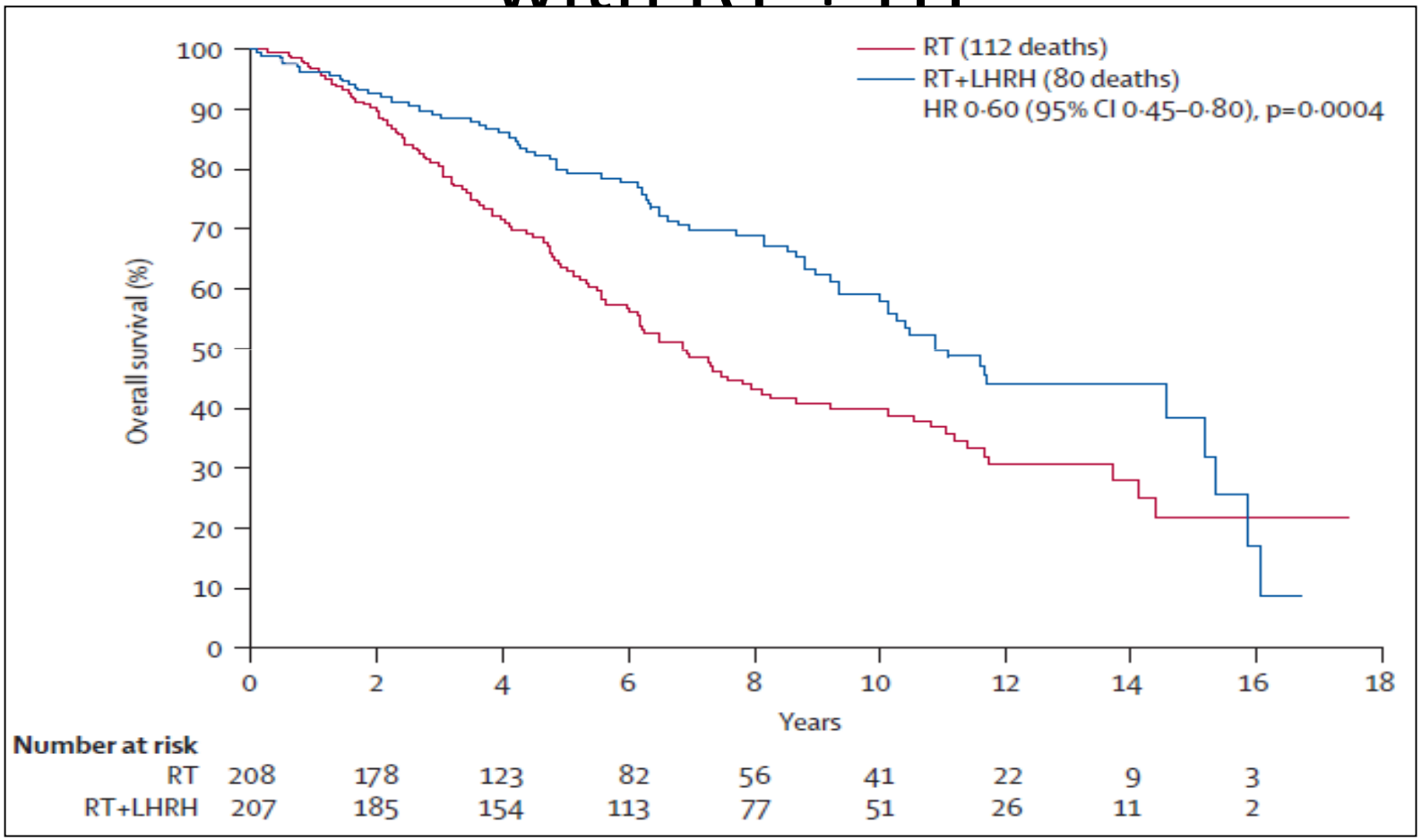
EORTC 22863: RT + concomitant and adjuvant HT vs RT alone



HT, hormone therapy; RT, radiotherapy

Bolla M, et al. N Engl J Med 1997;337:295–300

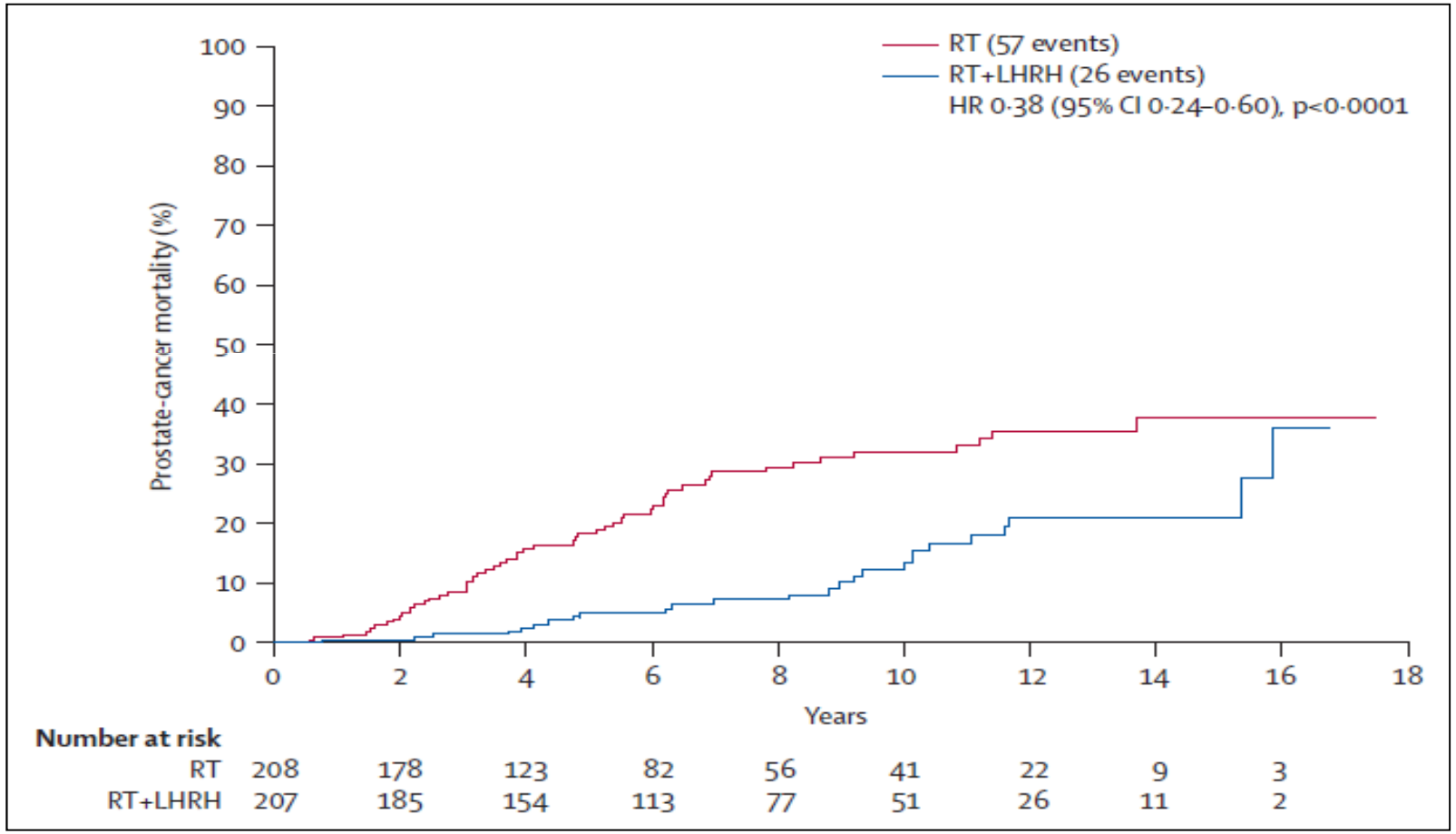
EORTC 22863: Improved overall survival with RT + HT



HT, hormone therapy; RT, radiotherapy

Bolla M, et al. Lancet oncol 2010;11:1066–73

EORTC 22863: Decreased prostate cancer mortality with RT + HT

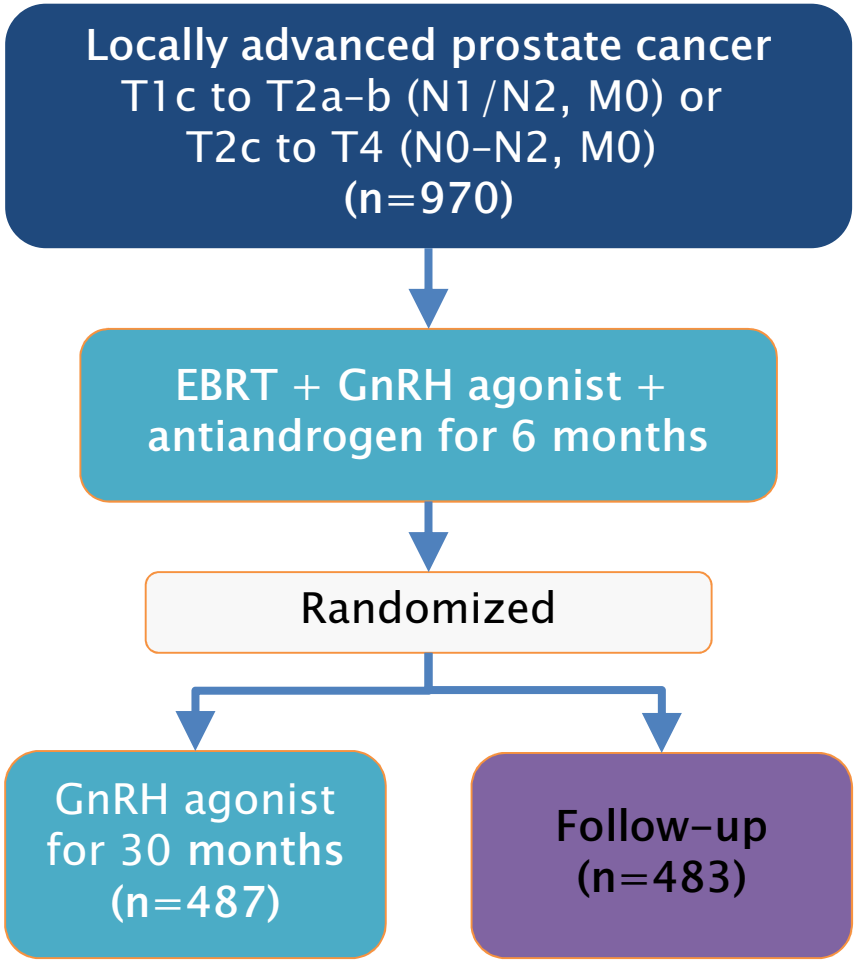


HT, hormone therapy; RT, radiotherapy

Bolla M, et al. Lancet oncol 2010;11:1066–73

BM13

EORTC-22961: Superior survival with long-term adjuvant HT



- PCa mortality for short- and long-term adjuvant HT was 4.7% and 3.2%, respectively
  - Significant difference in PCa survival (HR=1.71; p=0.002)
- 5-year overall mortality was 19.0% and 15.2% short- and long-term groups, respectively
  - HR=1.42 (p=0.65 for non-inferiority)

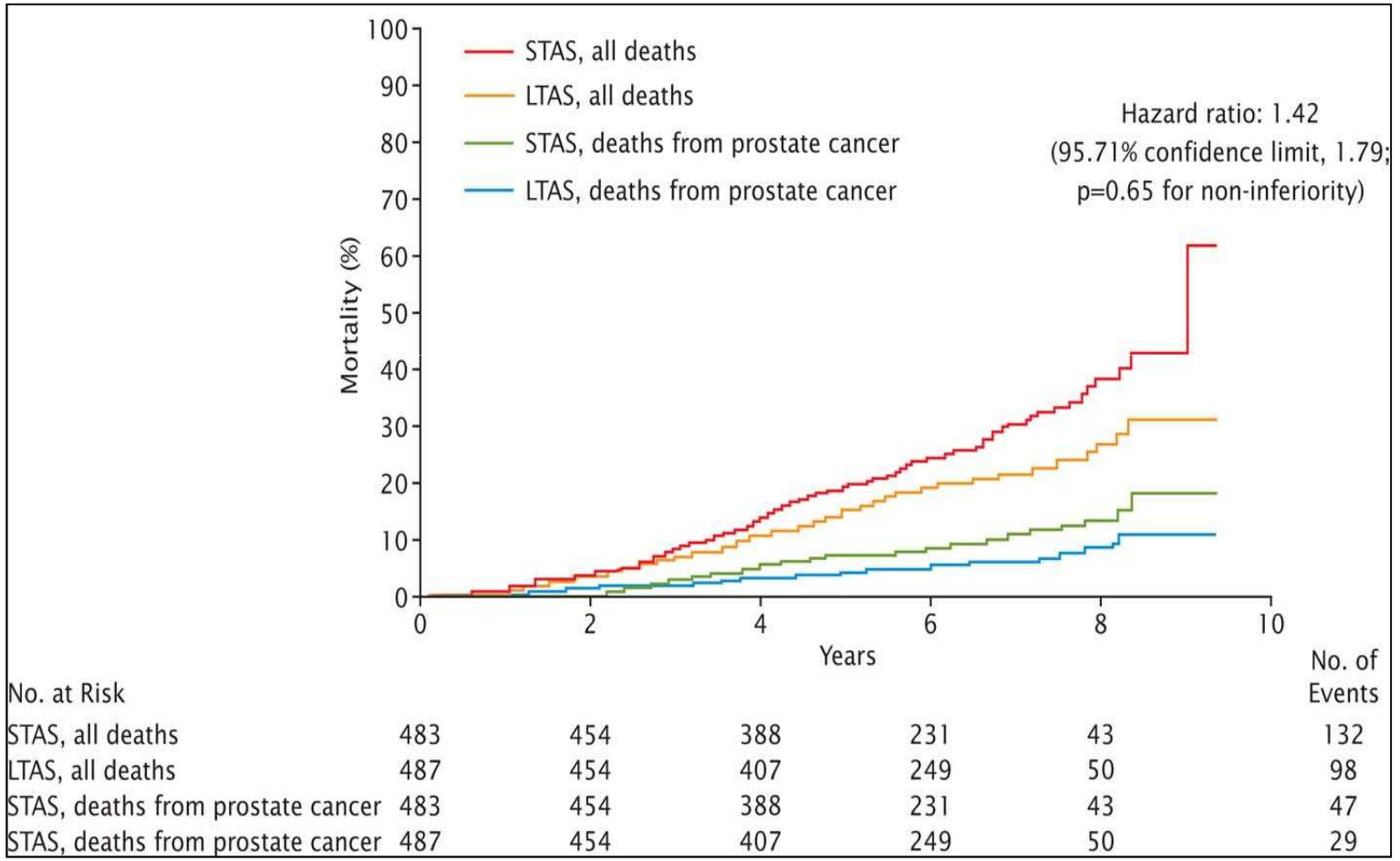
EBRT, external-beam radiotherapy; HT, hormone therapy

Bolla M, et al. NEJM 2009;360:2516–27

Slide 53

BM13 Added text from slide 49.
Bioscript Medical; 13-01-16

EORTC-22961: Increased overall survival and reduced prostate cancer mortality with long-term adjuvant HT

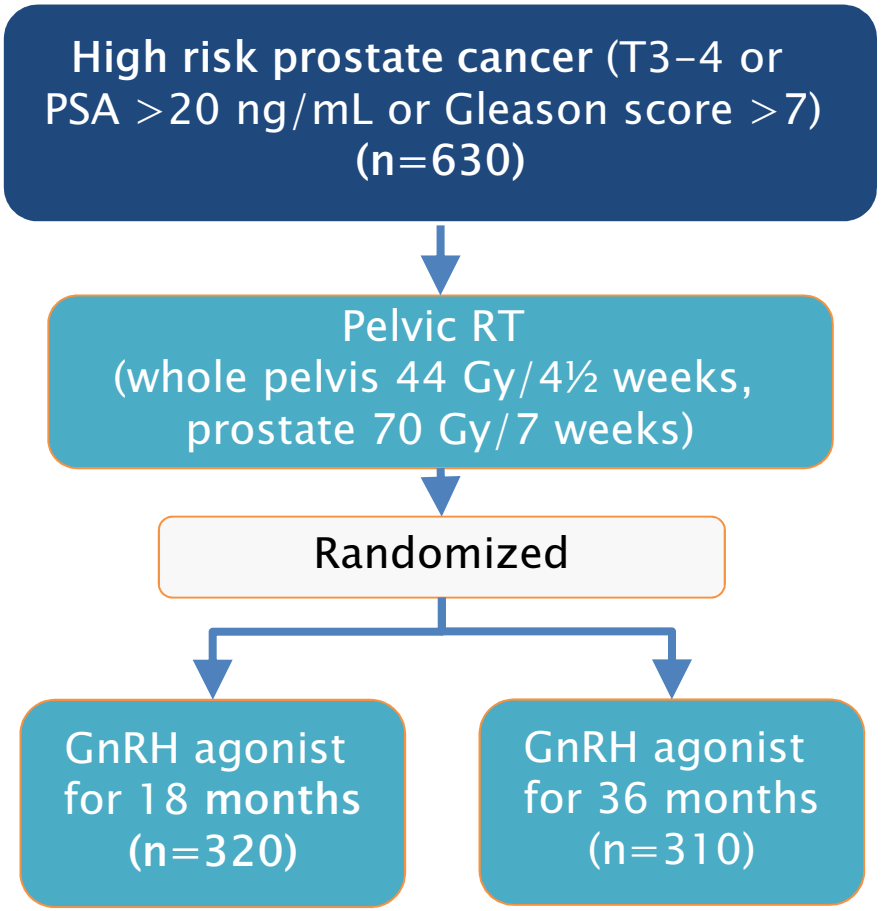


No. at Risk						No. of Events
STAS, all deaths	483	454	388	231	43	132
LTAS, all deaths	487	454	407	249	50	98
STAS, deaths from prostate cancer	483	454	388	231	43	47
STAS, deaths from prostate cancer	487	454	407	249	50	29

HT, hormone therapy; STAS: short-term androgen suppression LTAS: long-term androgen suppression

Bolla M, et al. NEJM 2009;360:2516–27

Adjuvant HT: 18 vs 36 months (PCS IV trial)



- Median follow-up 77 months
- 10 year overall survival
  - 63.6% (18 months) vs 63.2% (38 months), p=0.429
- 10 year disease-specific survival
  - 87.2% (18 months) vs 87.2% (36 months), p=0.838
- No significant differences in biochemical, regional or distant failure between arms

HT, hormone therapy; RT, radiotherapy

Nabid A, et al. ASCO GU 2013; Abstract 3

Conclusions

- The benefits of EBRT can be enhanced by dose escalation:

  Improves biochemical and/or clinical failure in localized or locally advanced PCa, with acceptable genitourinary and rectal safety[1-]

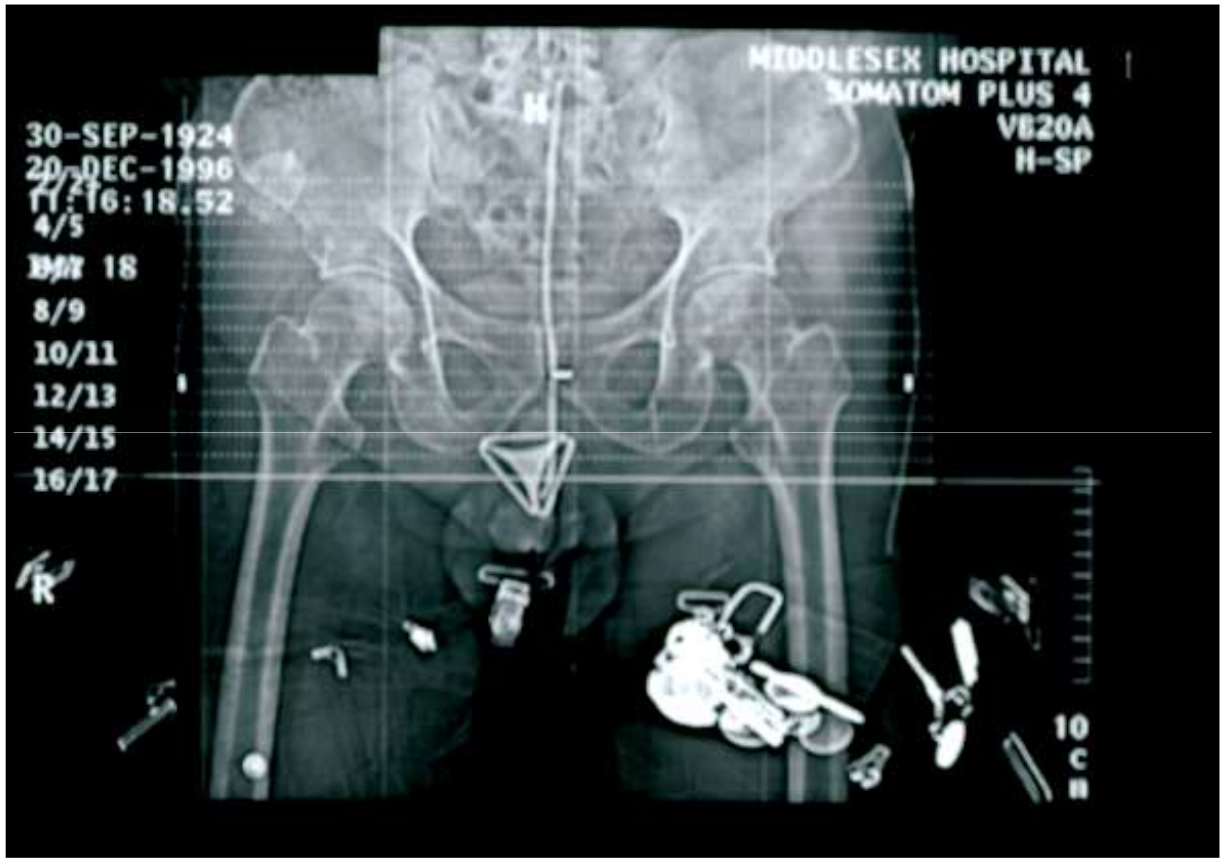
- The benefit of adding ADT to RT is established

  The exact timing and duration of ADT is still under investigation

  It remains to be established whether combining these approaches improves Prostate Cancer outcomes further

Heidenreich A et al. EAU guidelines 2012; 3. Pinkawa M et al. Strahlenther Onkol 2011;187:479–484;
4. Payne H, Mason M Br J Cancer 2011;105):1628-34; 5. Smith MJ et al. Prostate Cancer 2012; article ID 280278 Epub 2012

Are we on the…..
‘The Node to Nowhere’


MIDDLESEX HOSPITAL
SOMATOM PLUS 4
VB20A
H-SP
30-SEP-1924
20-DEC-1996
11:16:18.52
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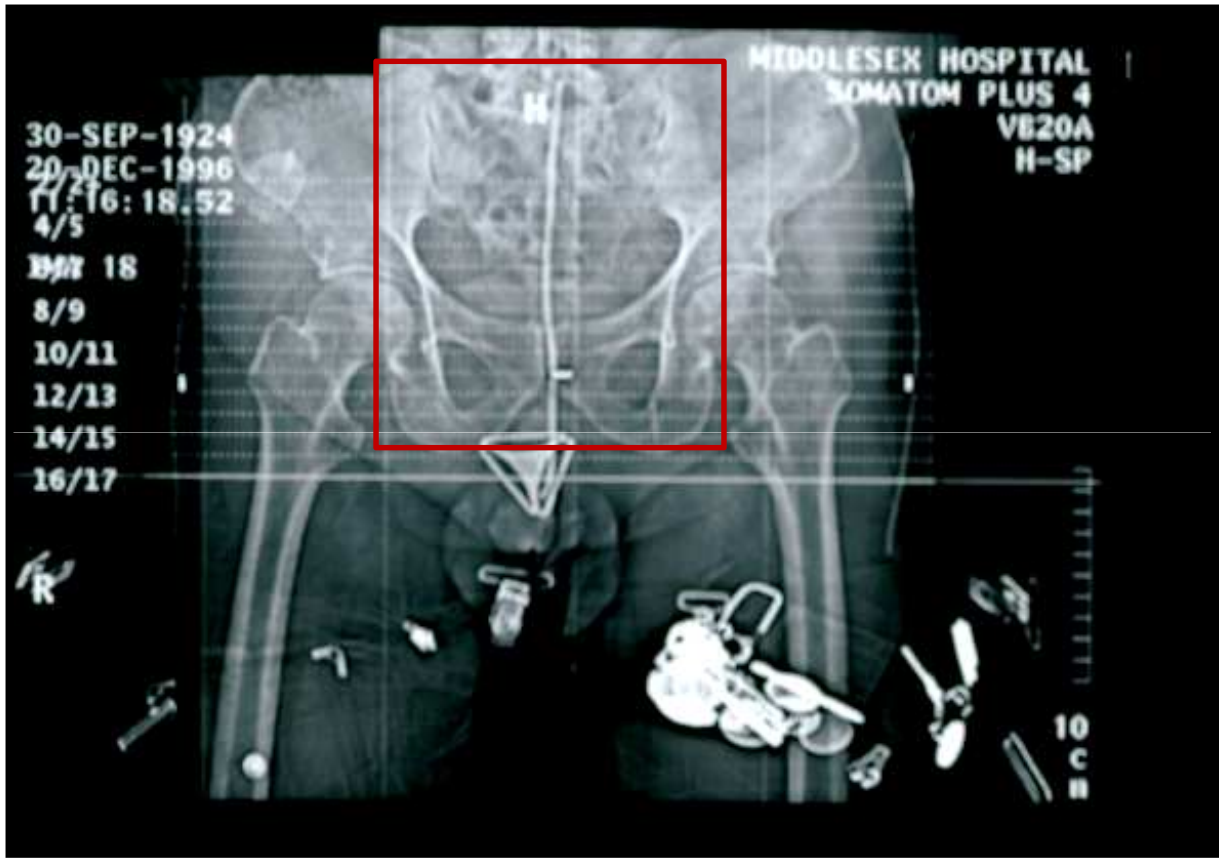
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SOMATOM PLUS 4
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20-DEC-1996
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10/11
12/13
14/15
16/17
R
10 cm

WPRT vs. PORT: Retrospective Studies - Positive

Table 3
Retrospective studies showing a benefit from WPRT

Study	Population	Field	No	DFS (%)	*P*	Survival (%)	*P*
McGowan [67]	T2-T3	WPRT	91	63 (5 years)	0.1	NA	NA
		PORT	44	35 (5 years)			
Ploysongsang [91]	T2	WPRT	32	68 (5 years)	NA	92 (5 years)	0.25
		PORT	60	NA		70 (5 years)	0.0004
	T3	WPRT	82	63 (3 years)	0.0004	72 (5 years)	
		PORT	41	30 (3 years)		40 (5 years)	
Seaward [105]	15% < LN+	WPRT	117	34.3°	0.0001	NA	NA
		PORT	84	21.0°		NA	NA
Seaward [106]	15% < LN+ < 35%	WPRT	70	39.5	<0.0001	NA	NA
		PORT	60	22.5°			
	35% < LN+	WPRT	47	27.2°	NS	NA	NA
		PORT	24	20.8°			
Pan [76]	5% > LN+	WPRT	243	79.3 (5 years)	0.73	NA	NA
		PORT	466	79.0 (5 years)			
	5% < LN+ < 15%	WPRT	176	60.2 (5 years)	0.02	NA	NA
		PORT	87	47.9 (5 years)			
	15% < LN+	WPRT	274	45.7 (5 years)	0.57	NA	NA
		PORT	35	45.3 (5 years)			

Dirix et al. Radiother Oncol 2006;79(1):1-14

WPRT vs. PORT: Retrospective Studies - Negative

Table 4
Retrospective studies failing to show a benefit from WPRT

Study	Population	Field	No	Recurrence (%)	*P*	DFS (%)	*P*
Aristizabal [4]	All stages	WPRT	58	12	NA	NA	NA
		PORT	160	7.5	NA		
Rosen [99]	T2	WPRT	29	10	NS	60 (5 years)	NS
		PORT	48	12.5		60 (5 years)	
	T3	WPRT	49	14	NS	45 (5 years)	NS
		PORT	38	21		65 (5 years)	
Zagars [120]	T3	WPRT	202	NA	NA	54 (10 years)	NS
		PORT	233	NA		43 (10 years)	
Zagars [121]	T1b,c or T2	WPRT	22	NA	NA	92 (5 years)	NS
		PORT	55	NA		87 (5 years)	
Rasp [95]	+LN>15%	WPRT	52	NA	NA	35 (5 years)	NS
		PORT	52	NA		29 (5 years)	

Dirix et al. Radiother Oncol 2006;79(1):1-14

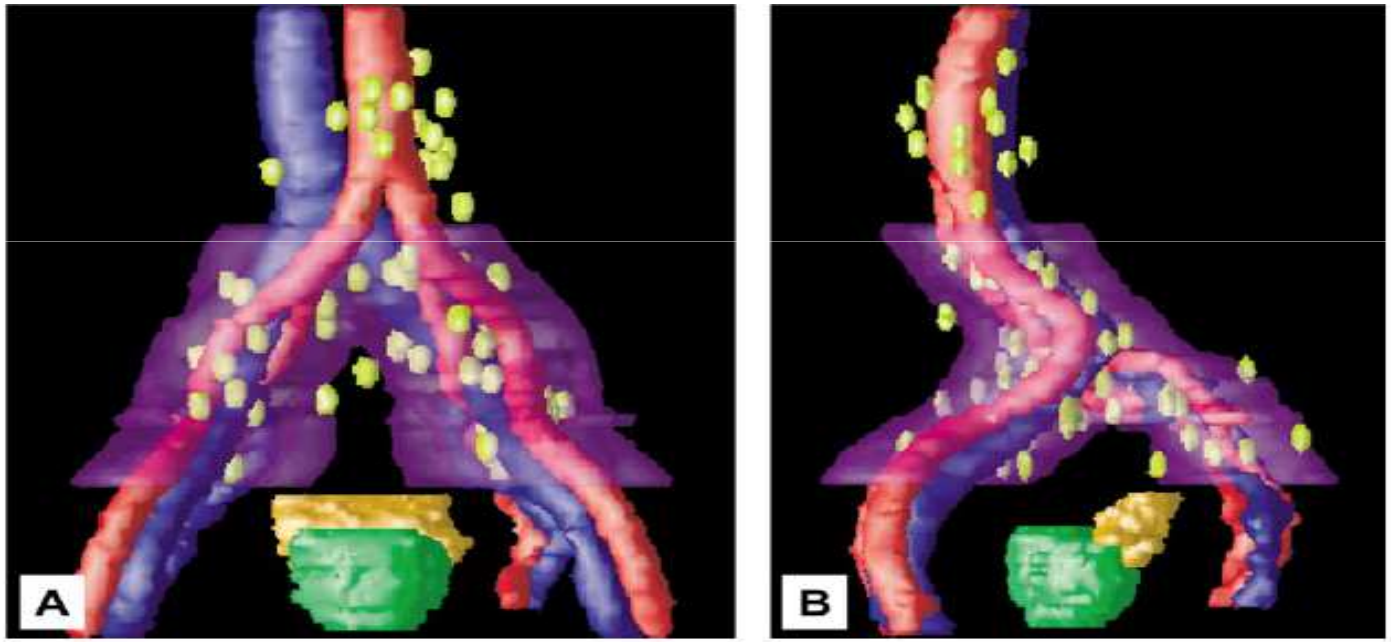
What were the problems with these trials ?

- Recruitment of patients with low risk of LN mets (GETUG)
- Low doses of RT to prostate and pelvis approx. 66-70GY and 46-48Gy
- Inadequate treatment of some LN groups
- Interaction with scheduling of hormone treatment (RTOG)
- Some favourable subgroup analyses for LN RT

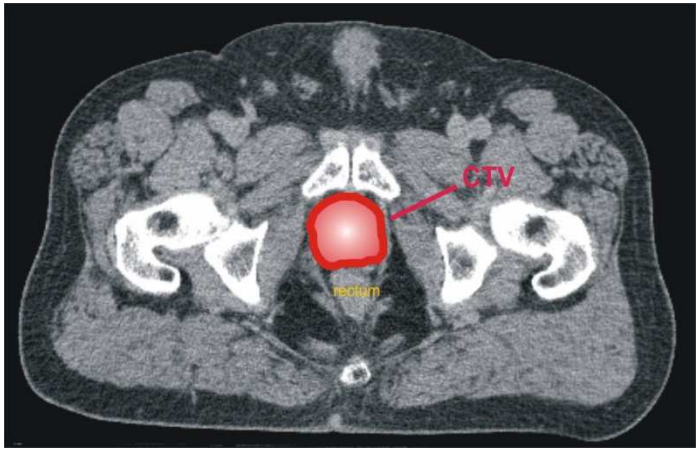
N0/N1 – non metastatic prostate cancer

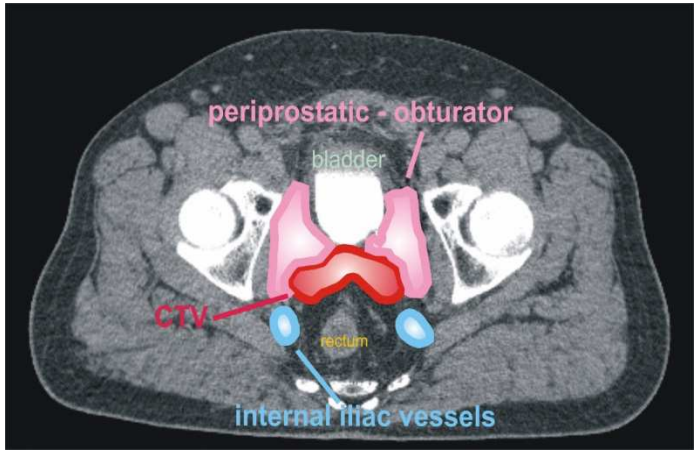
- Evidence unclear for concomitant RT to whole pelvis to treat pelvic LN for N0/N+ - studies N0 with different dose and RT techniques
- Historically associated with high toxicity
- Inadequate dose
- N0 to N+ - detection and imaging utilised
- N+ to N0 with neoadjuvant ADT= treat microscopic disease
- No RCT has assessed the role of RT N+ M0 patients and none are planned.

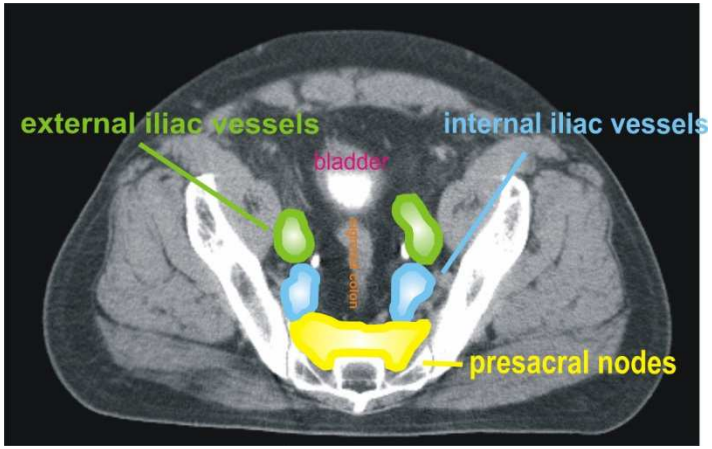
Target volume for Treatment of pelvic lymph nodes

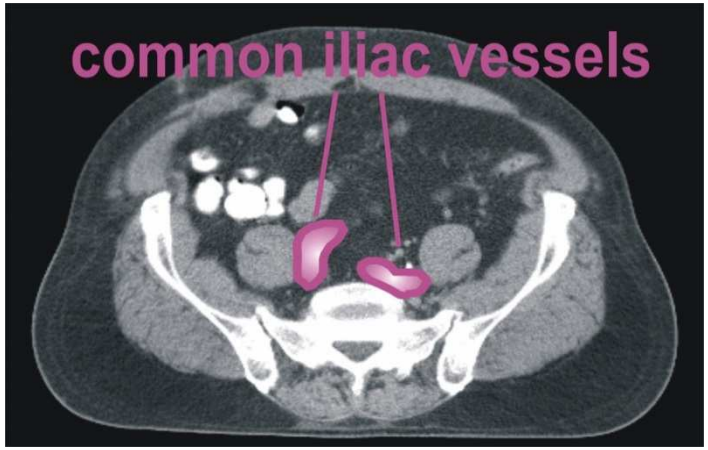


Metastatic nodes referenced to pelvic vessels with a 2.0-cm clinical target volume expansion to the region

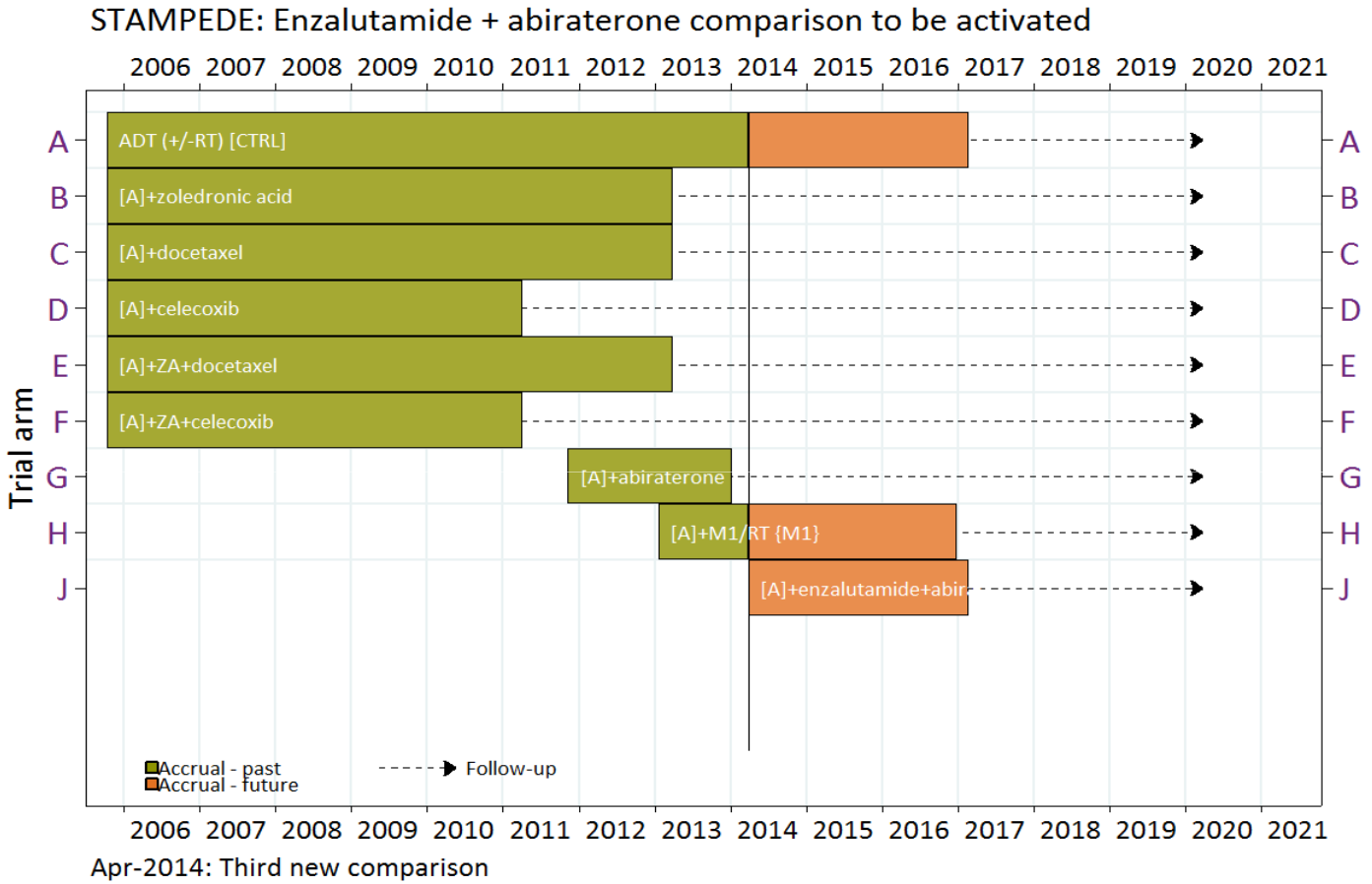








Courtesy of Gert De Meerleer


STAMPEDE: Enzalutamide + abiraterone comparison to be activated
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021
Trial arm
A
B
C
D
E
F
G
H
J
ADT (+/-RT) [CTRL]
[A]+zoledronic acid
[A]+docetaxel
[A]+celecoxib
[A]+ZA+docetaxel
[A]+ZA+celecoxib
[A]+abiraterone
[A]+M1/RT {M1}
[A]+enzalutamide+abir
Accrual - past
Accrual - future
Follow-up
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021
Apr-2014: Third new comparison

Patient Characteristics

1%	WHO PS 2	[s]
21%	WHO PS 1	[s]
65yr	Median age (min 40, max 84)	[s]
61%	Metastatic (85% Bony mets)	[s]
15%	N+M0	
24%	N0M0	
98%	LHRH analogues	[s]
29%	Planned for RT (72% of N0M0 pts)	[s]
6%	Previous local therapy	

Balanced by arm

[s] Stratification factors + hospital + NSAID/aspirin

STAMPEDE

- Recruits men from 4 groups starting long-term ADT:
  1. High-risk localised (T3/4, PSA >40 or Gleason 8-10)
  2. Node-positive (N+) prostate cancer
  3. Newly-diagnosed metastatic (M1)
  4. High risk recurrence post surgery or RT

- Tests addition of further treatments to standard care

- Radical radiotherapy in standard care:
  - N0M0 patients; optional Oct 2005 – Nov 2011, mandatory from Nov-2011
  - N+M0 patients; optional

Impact of node status and radiotherapy on failure-free survival in patients with newly-diagnosed non-metastatic prostate cancer: Data from >690 patients in the control arm of the STAMPEDE trial (MRC PR08, CRUK/06/019)

Nicholas James , MR Spears, NW Clarke, MR Sydes, CC Parker, DP Dearnaley, JM Russell, AWS Ritchie, G Thalmann, JS De Bono, G Attard, C Amos, MK Parmar, MD Mason and the STAMPEDE Investigators

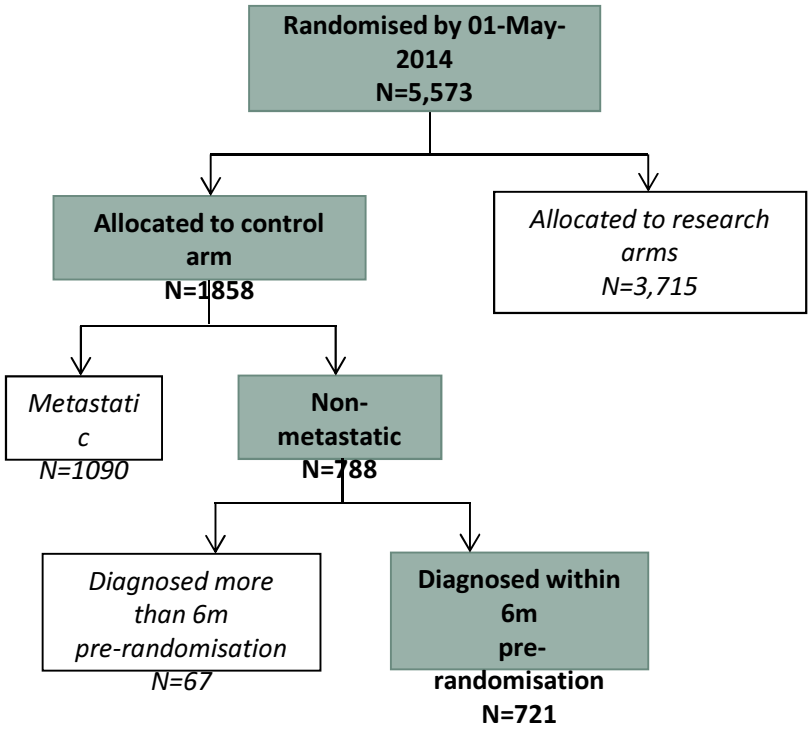
Aims

1. Describe prognosis for men with newly-diagnosed high-risk M0 disease

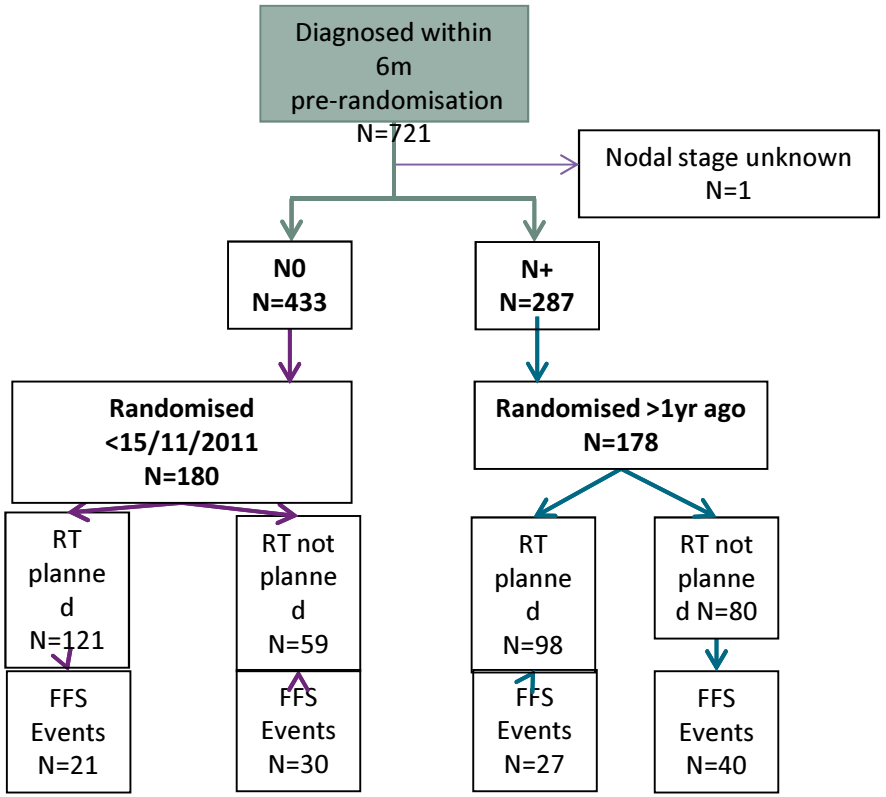
2. Describe impact of planned radical RT (6-9 months from randomisation) on time to progression
   - split by nodal status N0/N+

Results

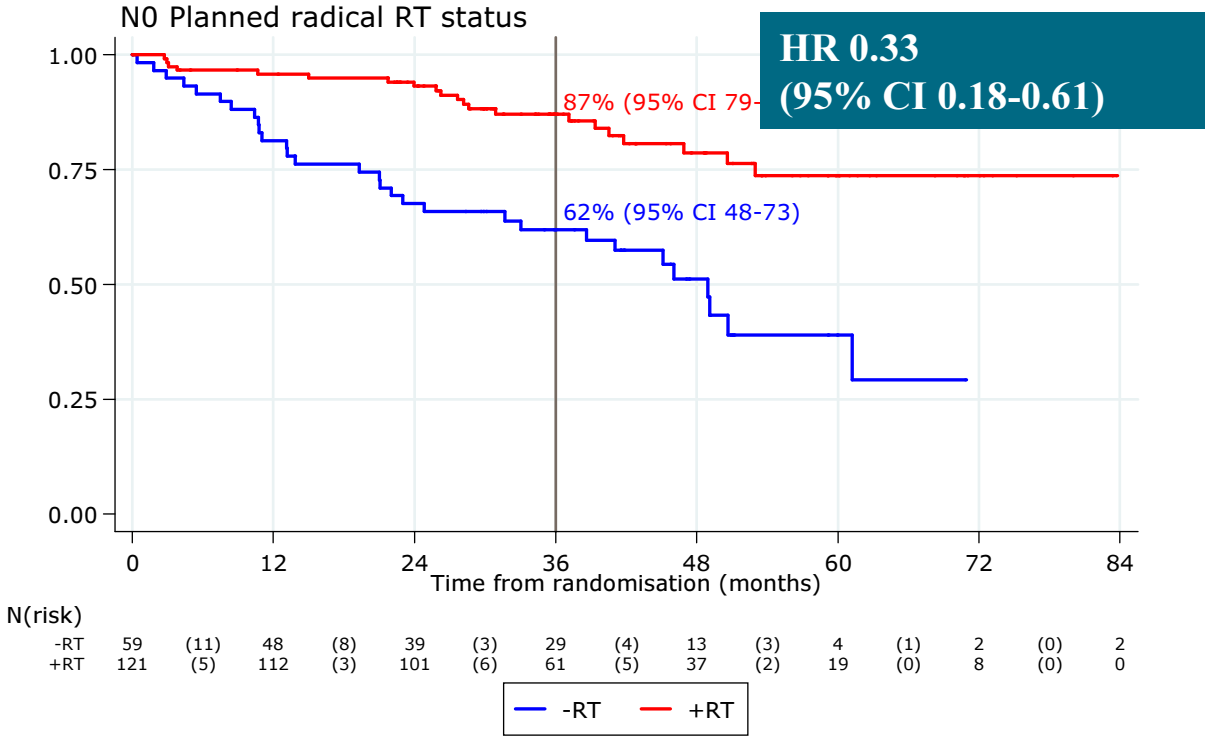
- Prognosis of newly-diagnosed high-risk M0 disease
- Cohort selection:



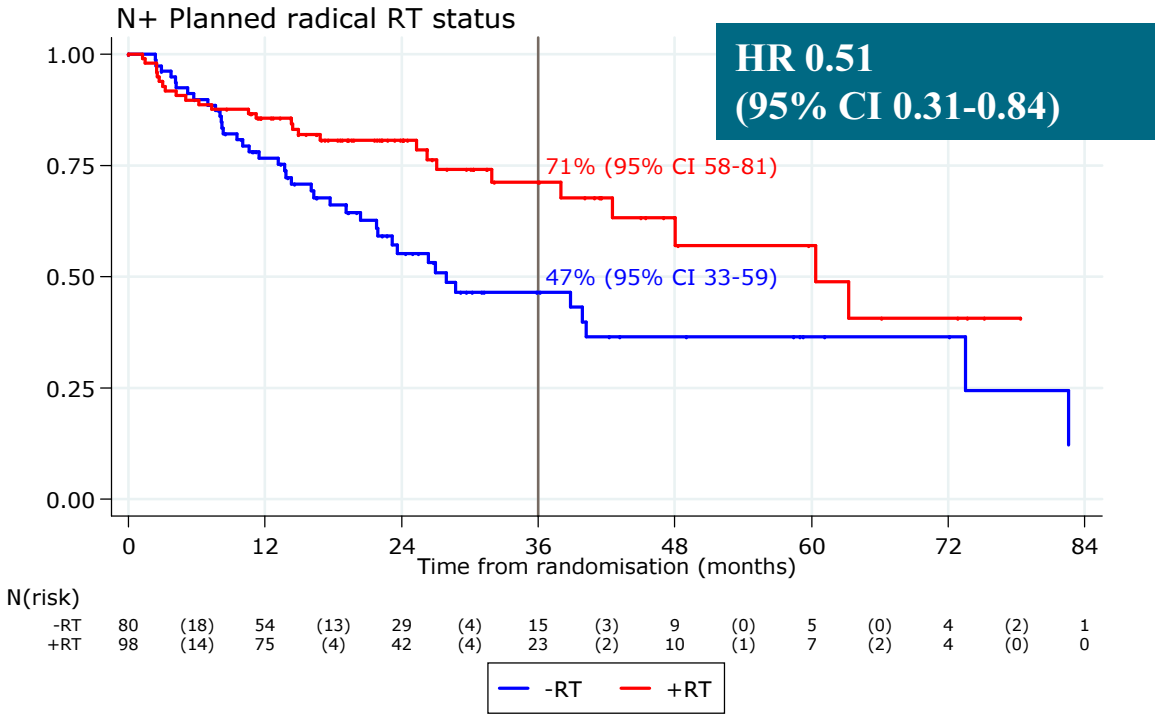
Nodal Subgroups



FFS by RT status: Node-negative cohort



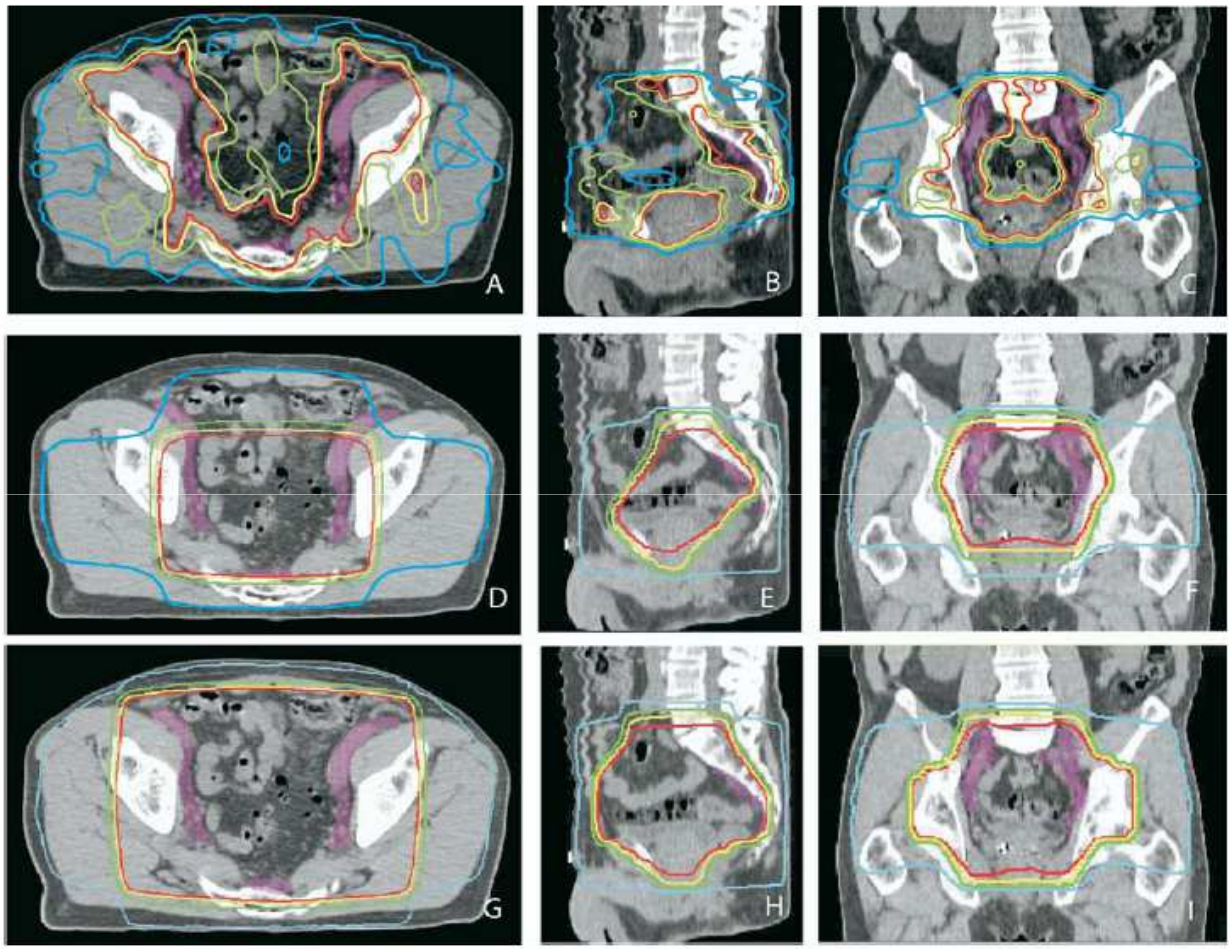
FFS by RT status: Node-positive cohort



Conclusions

- Survival better than anticipated at trial inception in 2005
  - In M0, control arm patients
- Effect of RT in N0M0 patients consistent with effect seen in previous large RCTs
- Effect of RT in N+ patients similar to effect in N0 patients
- Strongly supports routine use RT in node-positive prostate cancer
  - How best to administer?

ND James et al Proc ASTRO 2014.



Pagliarullo et al. JCO 2006; 24: 2735 - 2742

IMRT to Pelvic Lymph Nodes

- PLANNING TARGET VOLUMES

- GTVnodes GTV nodes - vessels
-
- CTVnodes GTVnodes + 0.7cm with trim for muscle and bone. Superiorly CTV extends to lower border of L5,as seen on the sagital view of the planning CT; inferiorly to the obturator nodes at superior extent of seminal vesicles.

- PTV55 = CTVnodes+ 0.5cm-0.7cm (to be specified on planning note)

CONCLUSIONS

- RT to N+ pelvic lymph nodes – emerging data but no RCT – extrapolation of data
- Neoadjuvant ADT to reduce LN – treat microscopic disease
- EBRT can now be given with reduced toxicity
- Role of chemotherapy
- Role of Surgery

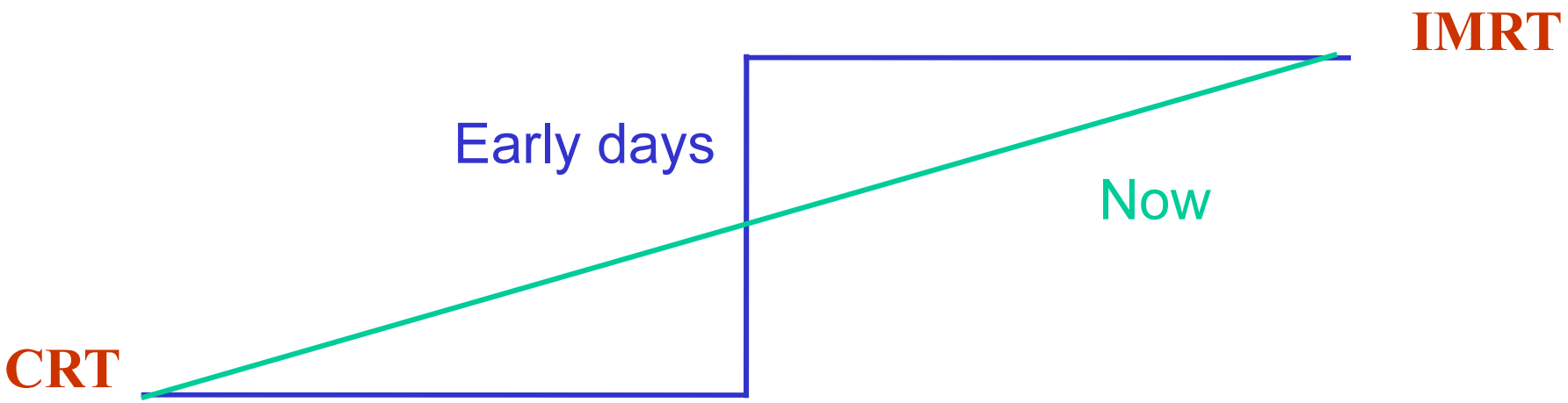
Thank You

Azienda Provinciale per i Servizi Sanitari
Trento, Italy

Practical IMRT planning and 'biological optimization'

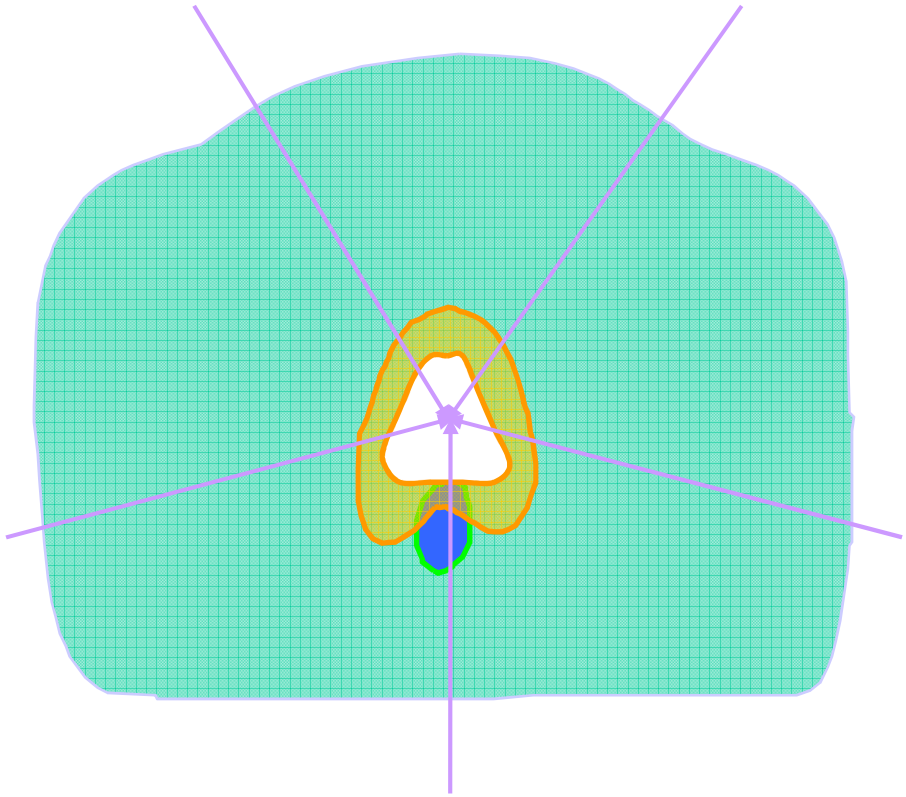
Marco Schwarz
Marco.schwarz@apss.tn.it

‘IMRT’: one word for a number of different approaches



Choosing where to stay on this line will make quite some difference also in terms of treatment planning

IMRT to solve simple problems

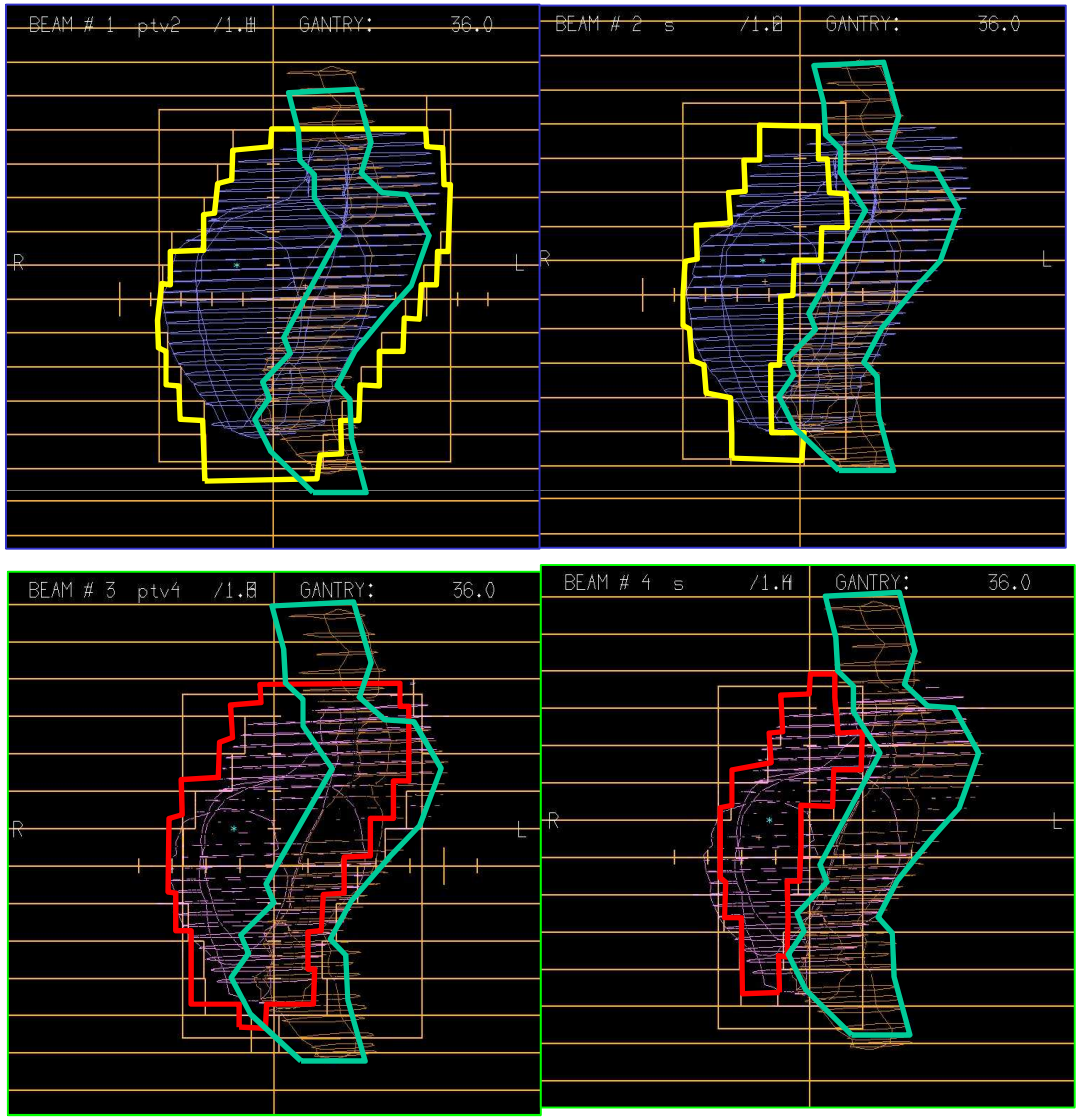


The problem:

Deliver 78 Gy to prostate (± SV) + margin

CRT too risky for the rectal wall

1 conflict to deal with
(PTV minimum dose vs high doses in the rectum)



Possible solution:

‘Forward planning’ does work

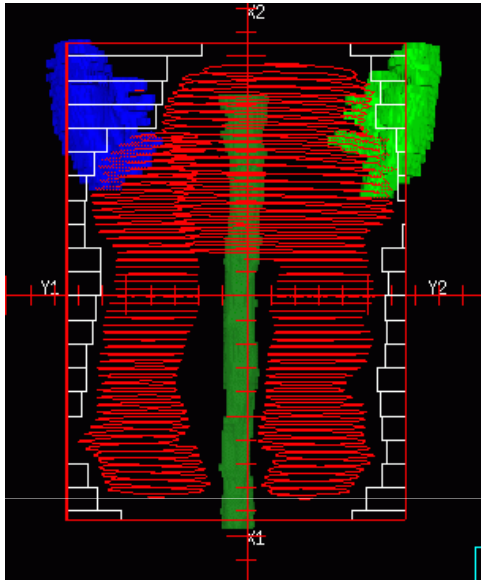
Class solution for beam direction and segment shape

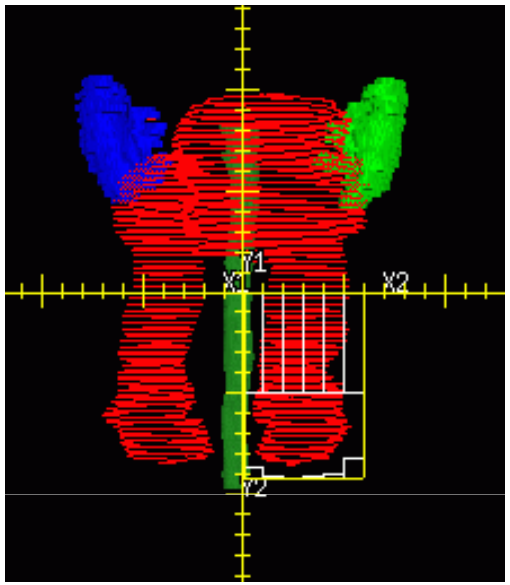
Simple cost function

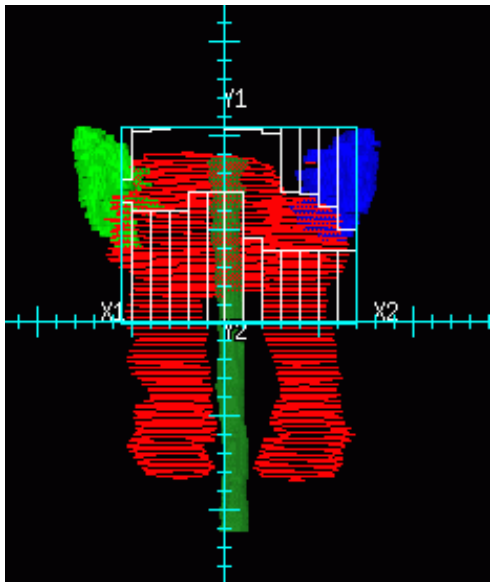
12-18 segments overall

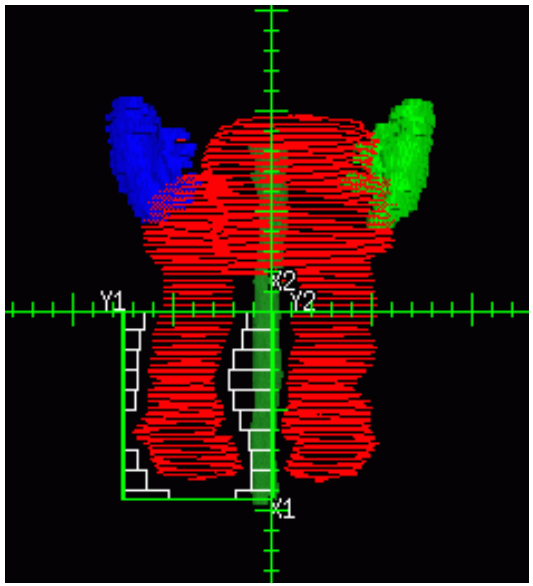
Simple plan verification

… more complex problems









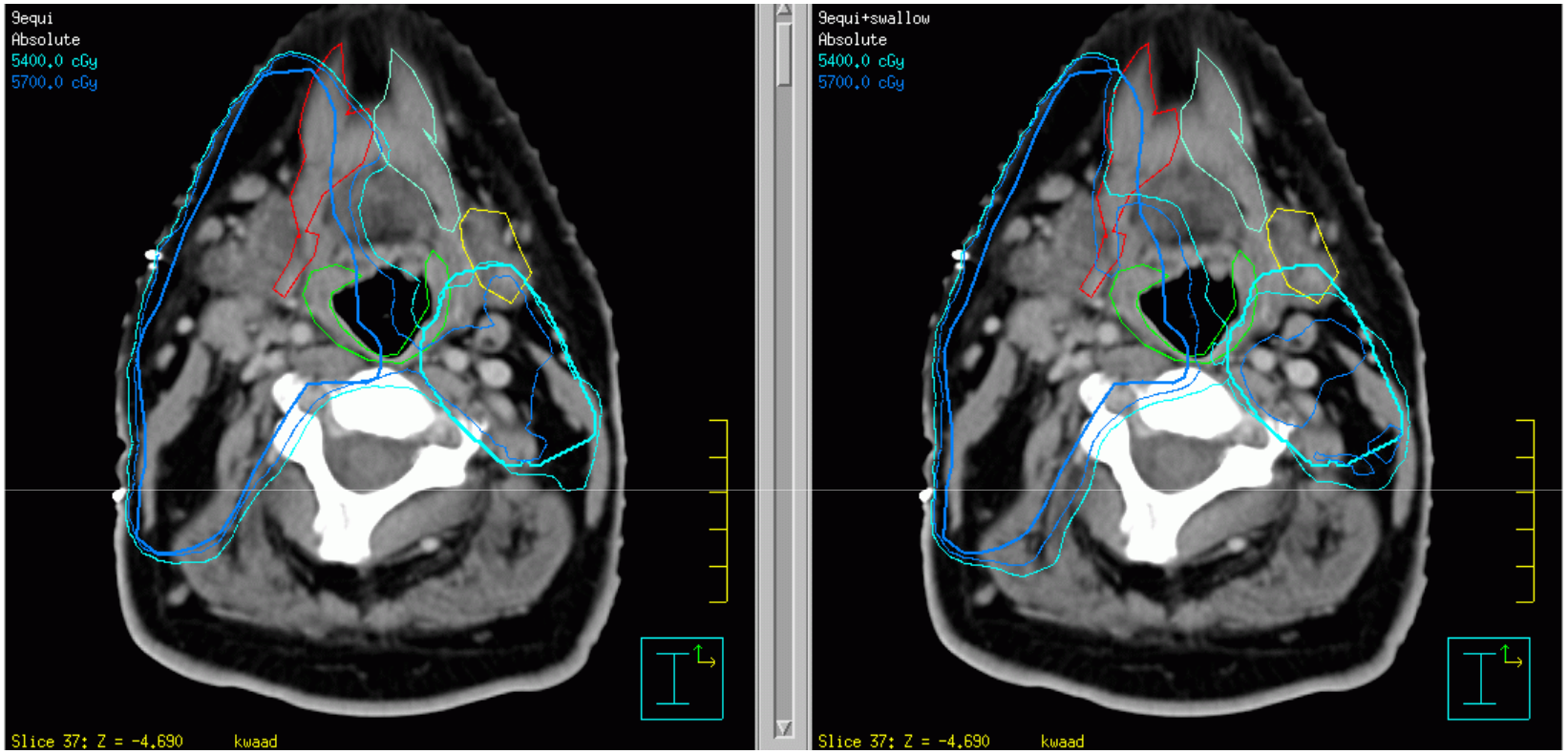
'forward planning' sort of works, but tricky without

automatic segment definition

and

segment shape optimisation

… even more complex problems



Complex IMRT cases require

- Elaborate cost functions,
- Efficient optimisation and segmentation techniques,
- Segment shape optimisation and
- Tools for sensitivity analysis.

Defining the treatment goals - Cost function

One should define a cost function …

1. Specific enough

To define the boundaries of the search space.

Example: Define the dose limits for the OAR over the whole dose range.

2. General enough

Not to artificially restrict the solution space

Example: if you want to obtain a specific OAR mean dose, do not set objectives for this OAR with DVH points.

Common sense and implicit knowledge must be made explicit

Cost function vs. plan evaluation

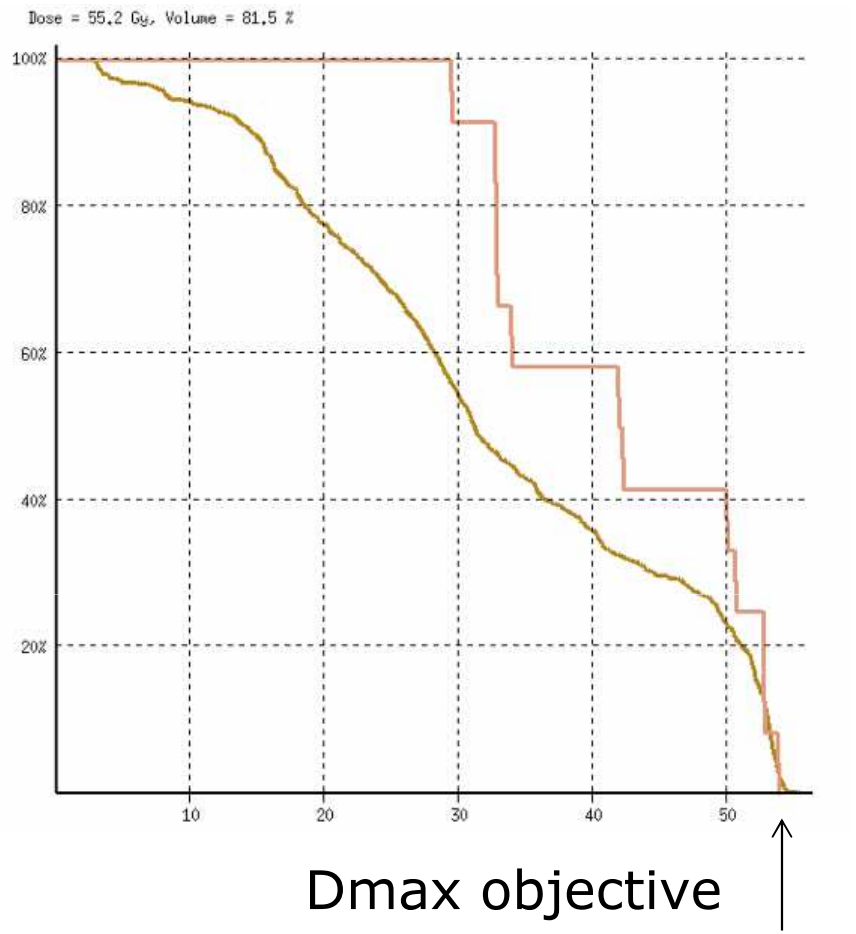
The dose distribution resulting from (unconstrained) optimisation typically contains

- Features you requested and you obtained
- Features you requested and you did not obtain

!!!!!!!

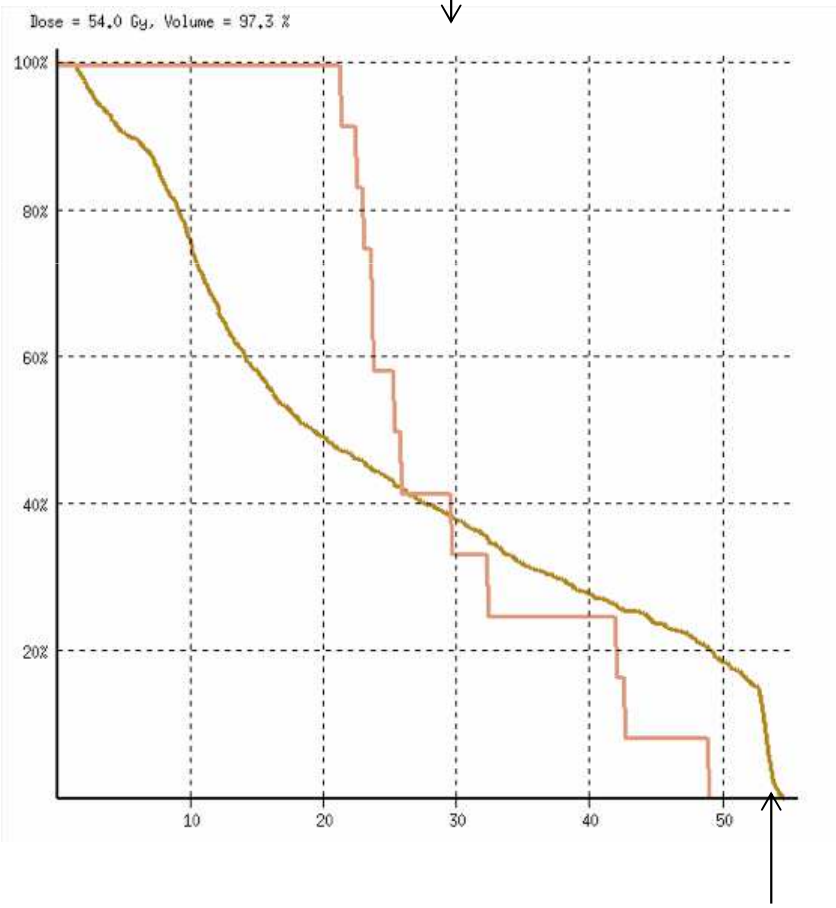
- Features you did **not** request
  - Neutral features
  - Negative features (you left a ‘hole’ in the cost function, and the optimisation took advantage from it)
  - Positive features (you got them ‘for free’, as a byproduct of other features)

?????



Dmax objective

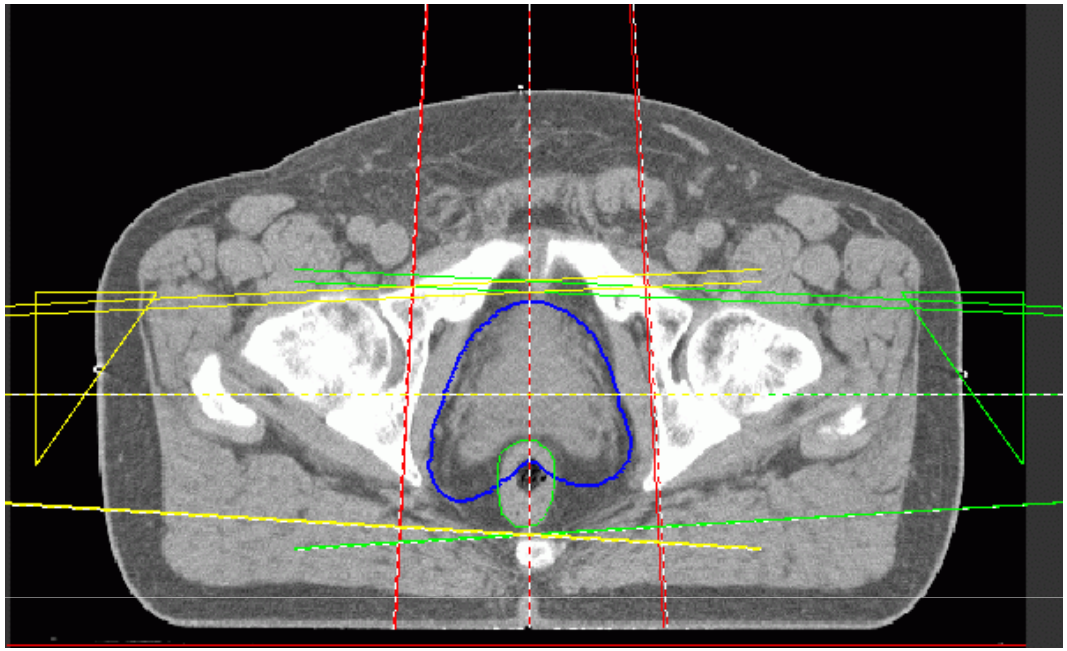
Dmax + Dmean objective



Think about this problem when you read paper on treatment planning studies

Defining the treatment goals - VOI definition

PTV: advantages



Forced people to incorporate geometrical uncertainties into treatment planning

ICRU concepts quite rapidly became a standard

Very appropriate tool for CRT: not too simple, not too complex.

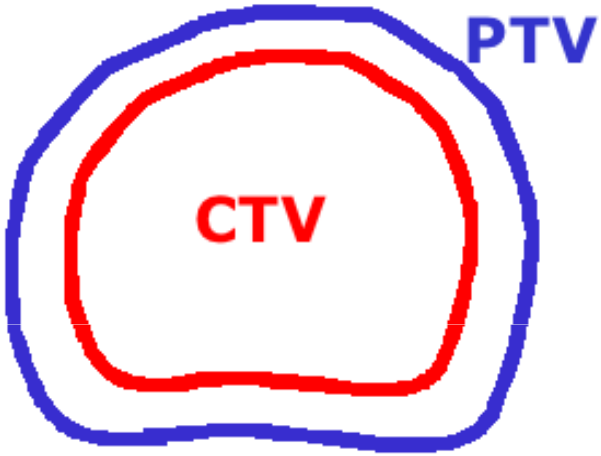
PTV: disadvantages

The PTV concept works only when

a)The dose is homogeneous

b)The dose is invariant after translations/rotations

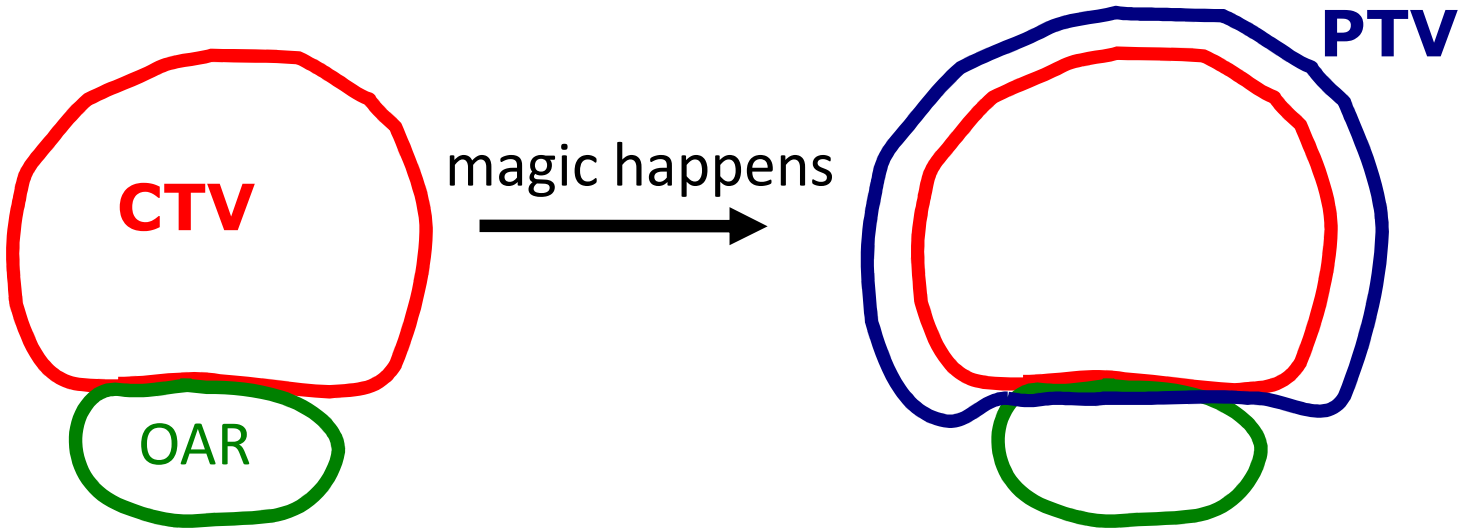
c)Margins are defined correctly w.r.t. the geometrical uncertainties



The tradeoff between target coverage and OAR sparing is unbalanced

N.B. IGRT aims at reducing PTV margins but does not address the shortcomings of PTV-based RT

To compensate for the unbalance between target coverage and OAR sparing, we often cheat



As if one should prefer
homogeneous doses in the wrong PTV instead of
heterogenous doses in the right PTV

We just shift the problem from planning to dose delivery and dose reporting

Reduced local control in prostate XRT with 3mm margin and daily IGRT (Engels IJROBP 2009)

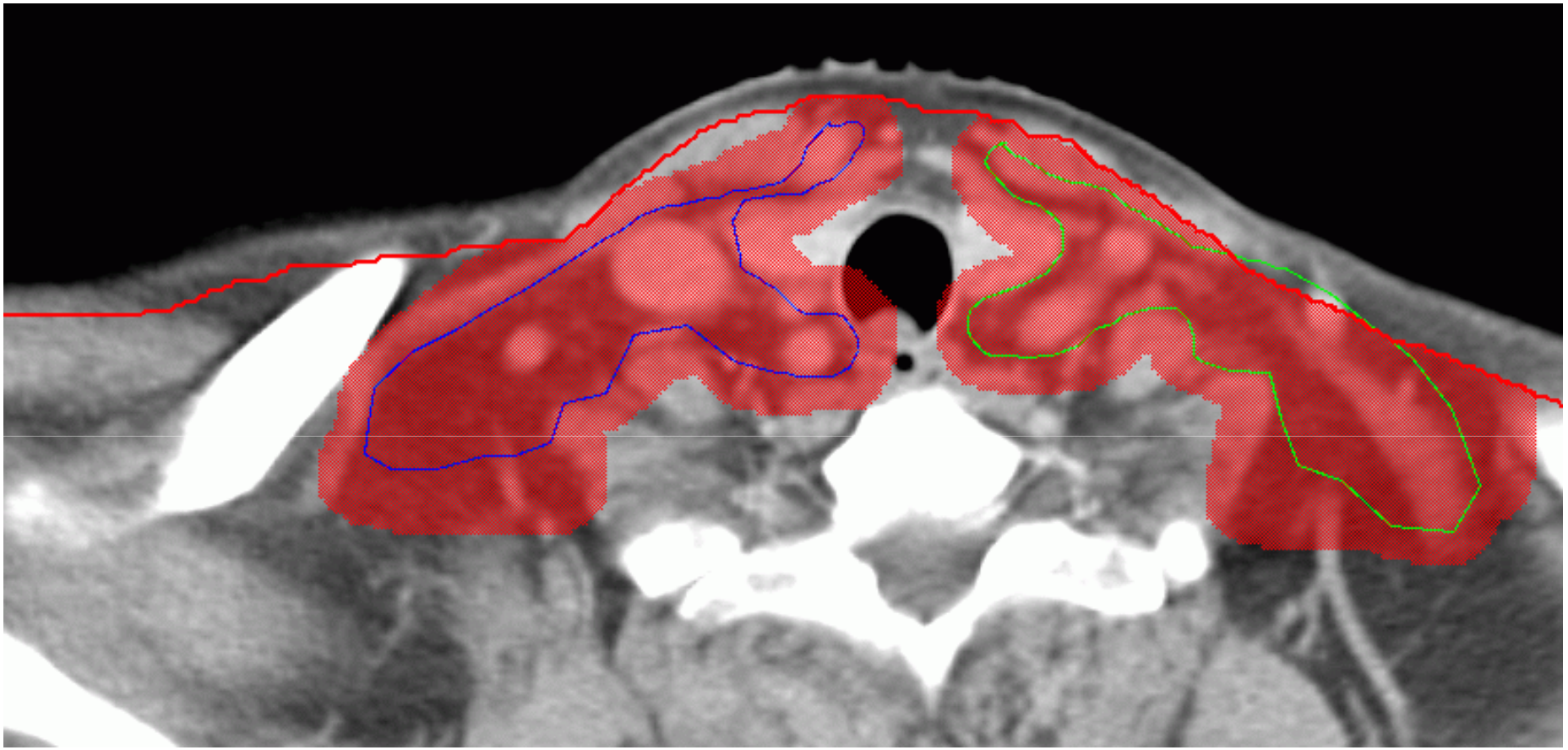
CLINICAL INVESTIGATION **Prostate**

CONFORMAL ARC RADIOTHERAPY FOR PROSTATE CANCER: INCREASED BIOCHEMICAL FAILURE IN PATIENTS WITH DISTENDED RECTUM ON THE PLANNING COMPUTED TOMOGRAM DESPITE IMAGE GUIDANCE BY IMPLANTED MARKERS

BENEDIKT ENGELS, M.D., GUY SOETE, M.D., PH.D., D. VERELLEN, PH.D., AND GUY STORME, M.D., PH.D.

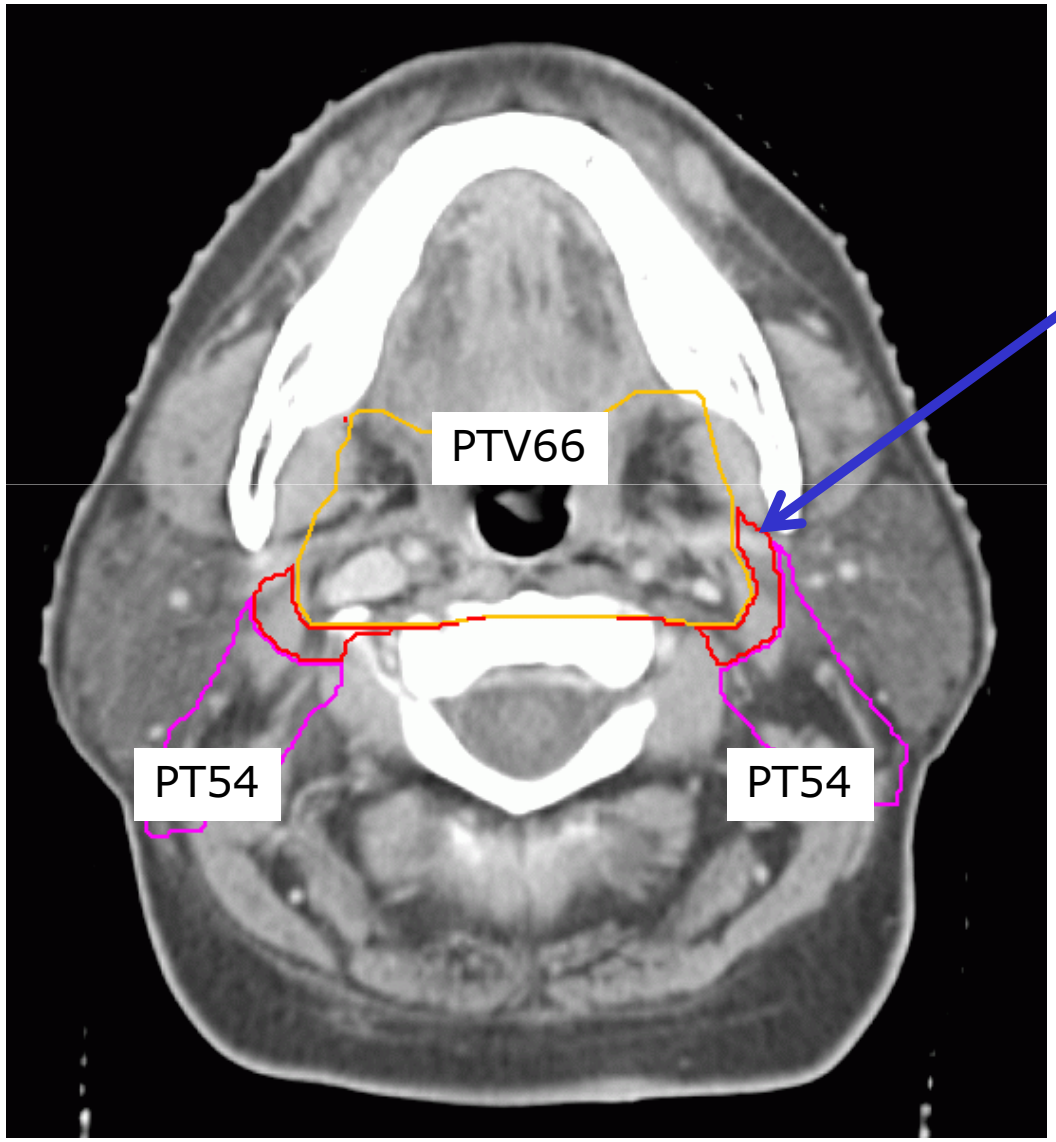
Department of Radiotherapy, University Hospital Brussels, Brussels, Belgium

VOI definitions & c.f. – build up region



When the PTV is shallower than the depth of Dmax, defining an ad-hoc volume + using the ‘skin flash’ feature of your TPS will help defining better plans

SIB & dose gradients in the PTV



IF

You want to control the Dmax in PTV 54

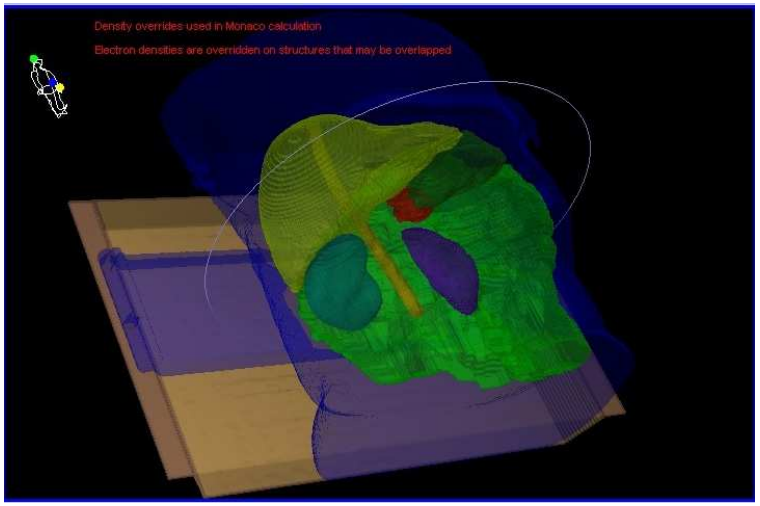
AND

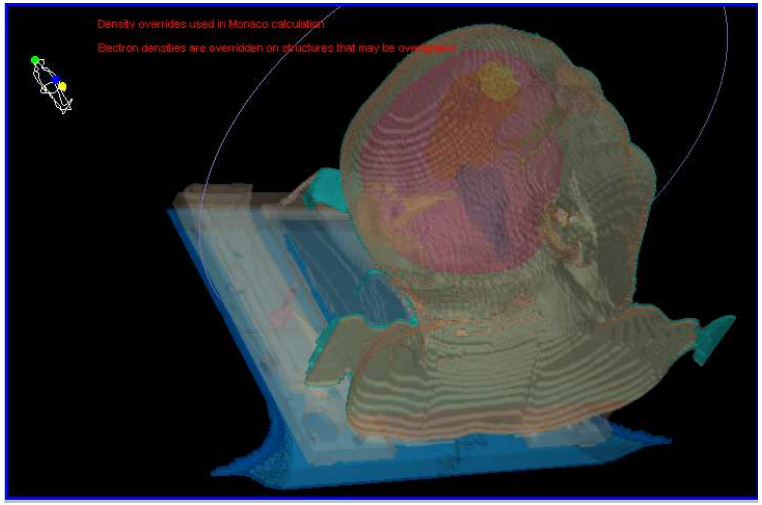
Dmin in PTV66

THEN

You need to make room for the dose gradient

Treatment couch modelling





With VMAT there is an increased need in accounting for the couch top (attenuation, increased skin dose, and target coverage effects).

Dosimetric effects caused by couch tops and immobilization devices: Report of AAPM Task Group 176

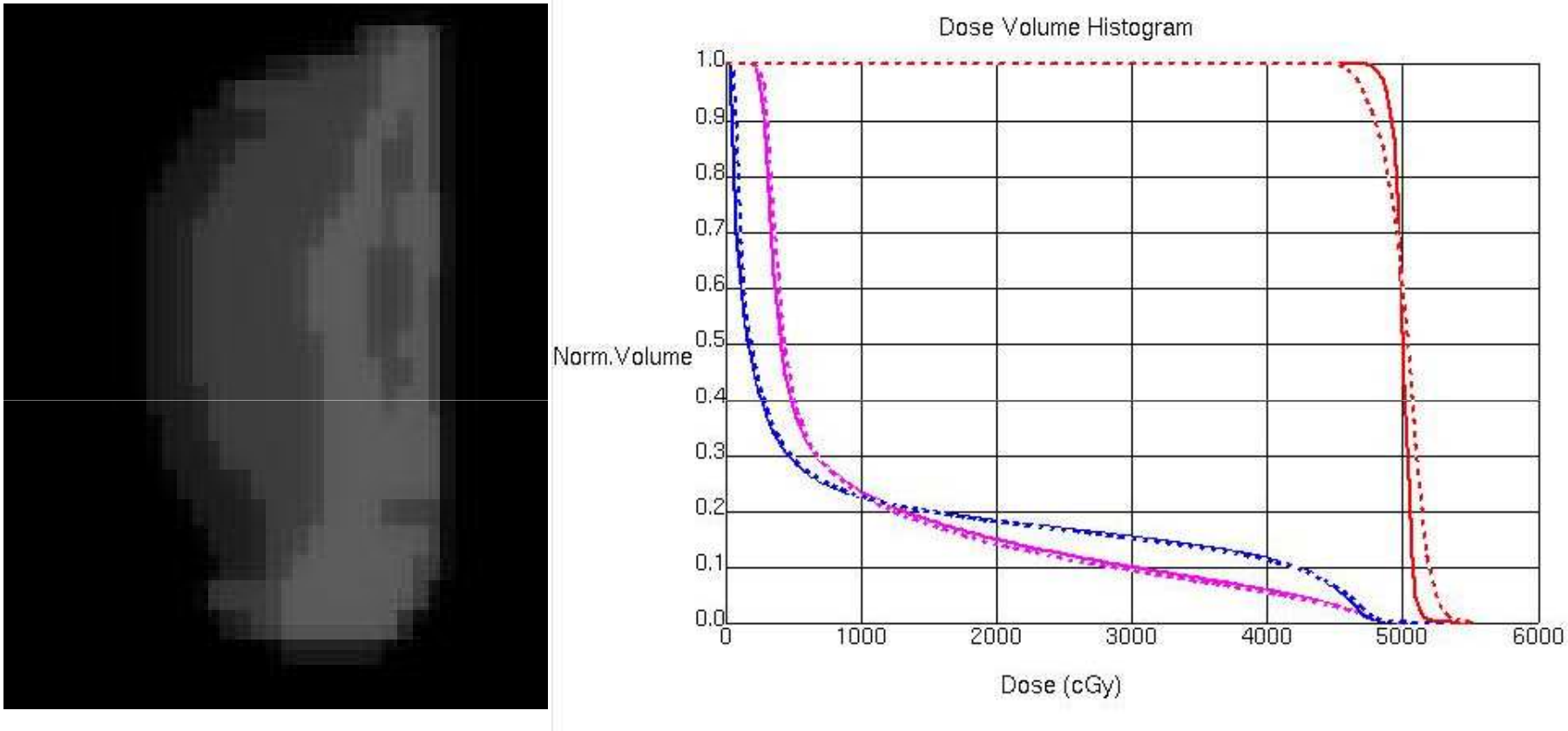
Arthur J. Olch[a)]
Radiation Oncology Department, University of Southern California and Children's Hospital Los Angeles, Los Angeles, California 90027

Med Phys 2014

Urban legends on IMRT /1

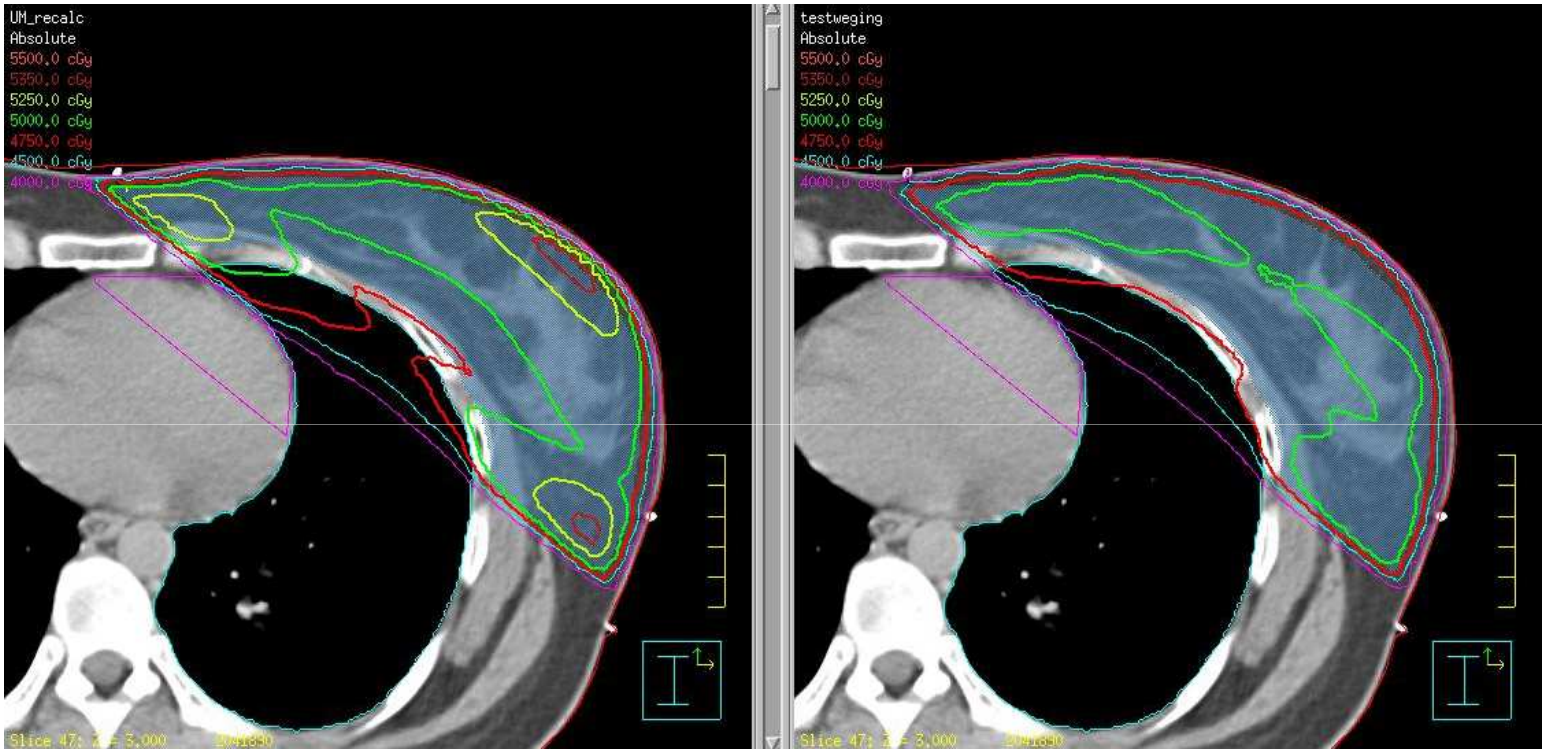
"IMRT = dose heterogeneity in the PTV. Live with that."

IMRT to increase PTV dose homogeneity



B. van Asselen

IMRT to increase PTV dose homogeneity

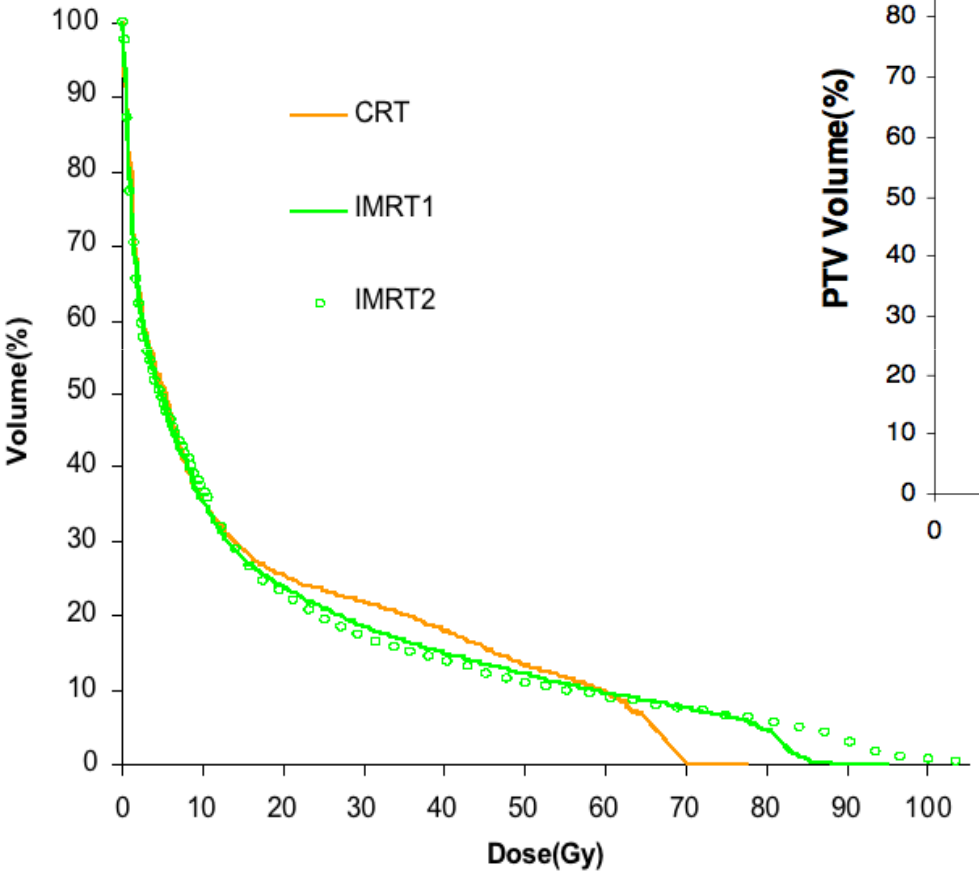


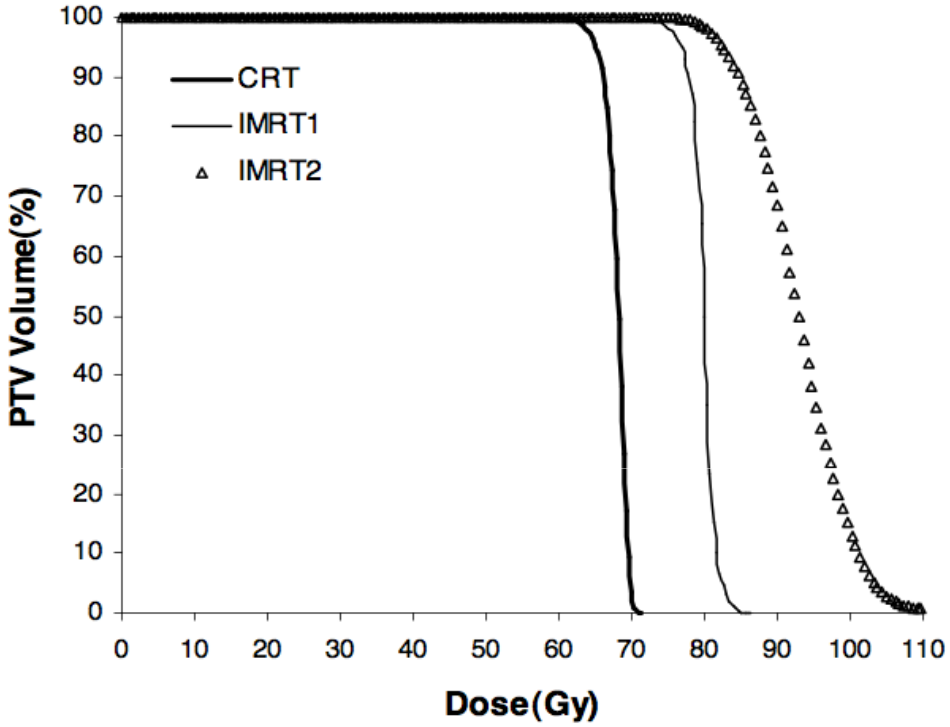
CRT

IMRT

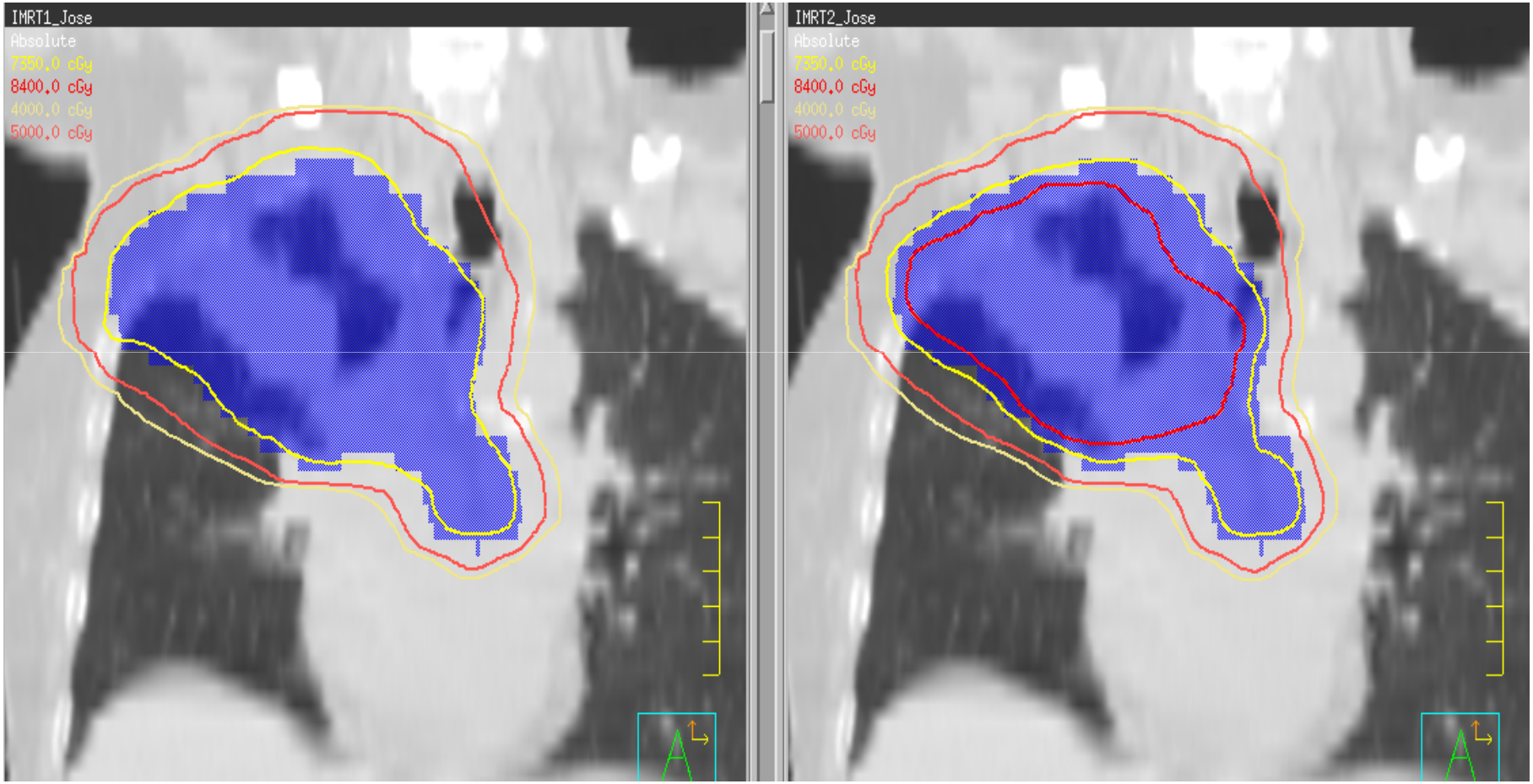
van Asselen et al, R&O 2006

Dose heterogeneity is a feature, not a bug





IMRT & dose heterogeneity in the PTV



"IMRT = dose heterogeneity in the PTV. Live with that."

Quite the contrary.

IMRT allows excellent dose homogeneity as long as you are willing to pay the price for it, so ask for homogeneity only if you actually need it.

Urban legends on IMRT /2

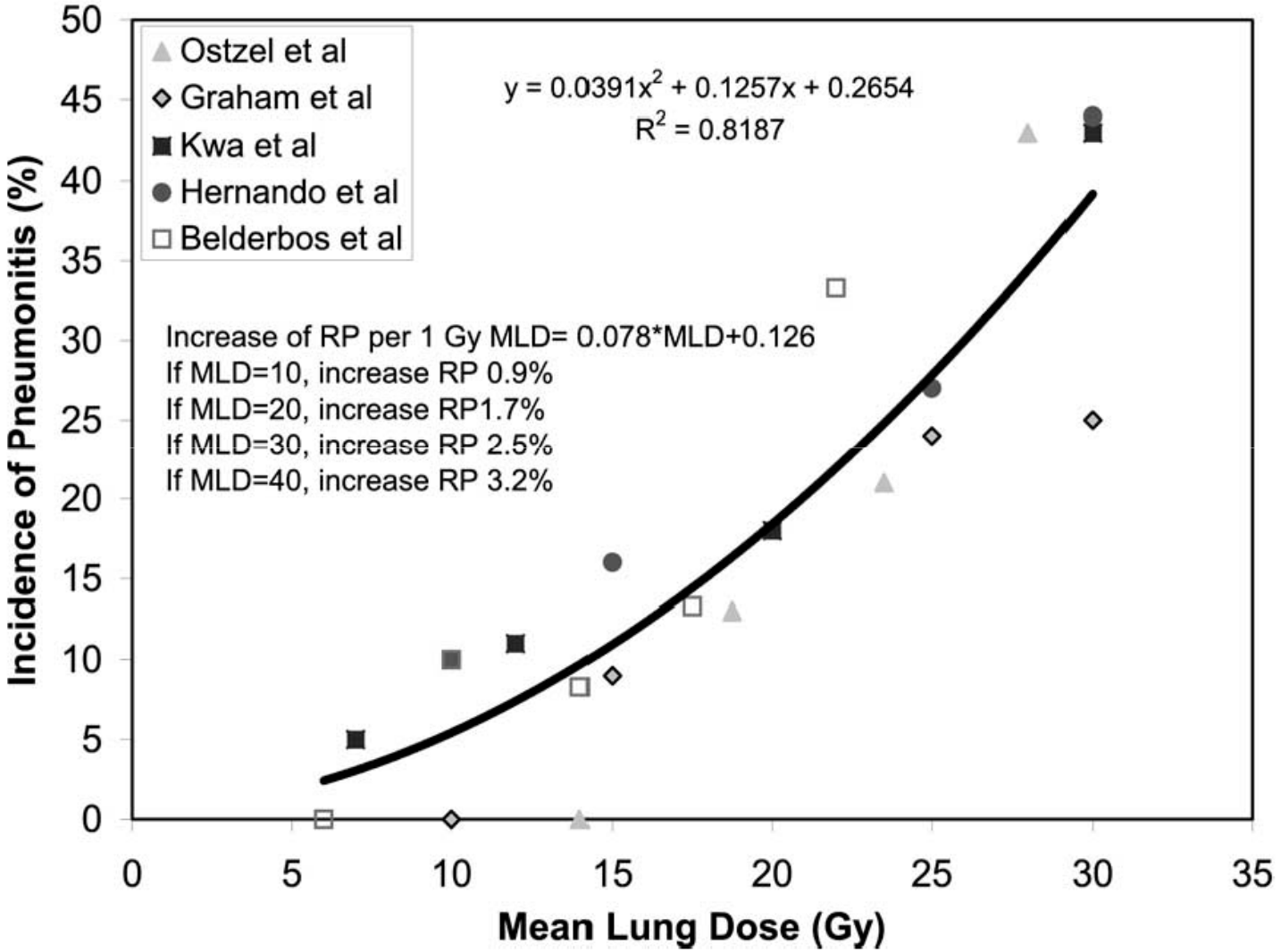
"We are not yet ready for EUD/'biological' optimisation in the clinical practice"

For some OARs the estimates for the volume effect parameter is consistent

Study	m	n	TD50
Rancati 2004	0.06	0.06	78.6
Peeters 2006	0.14	0.13	80.7
Sohn 2007	0.11	0.08	78.4
Tucker 2007	0.08	0.08	78
Rancati 2008	0.27	0.085	97.7

Rectum NTCP parameters with the LKB model

Mean lung dose model



Kong et al, Sem. Rad. Oncol 2005

Generalized EUD (gEUD)

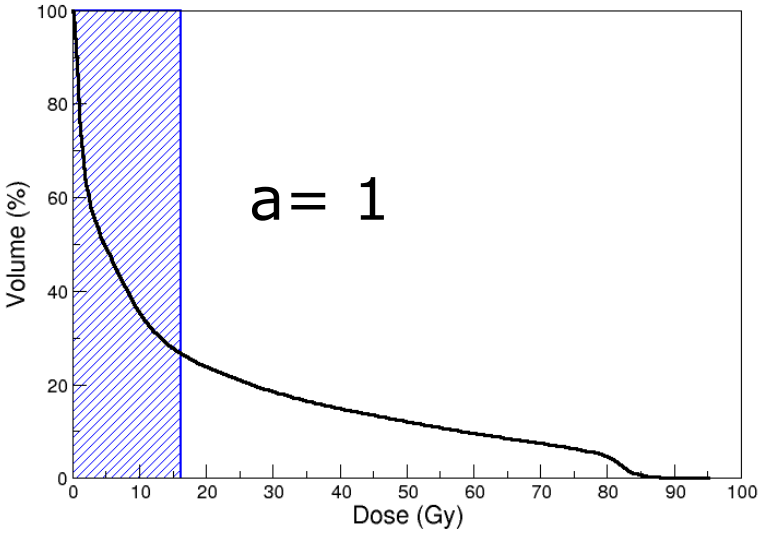
$$gEUD(Gy) = \left(\sum_{i=1}^{n} v_i D_i^a \right)^{1/a}$$

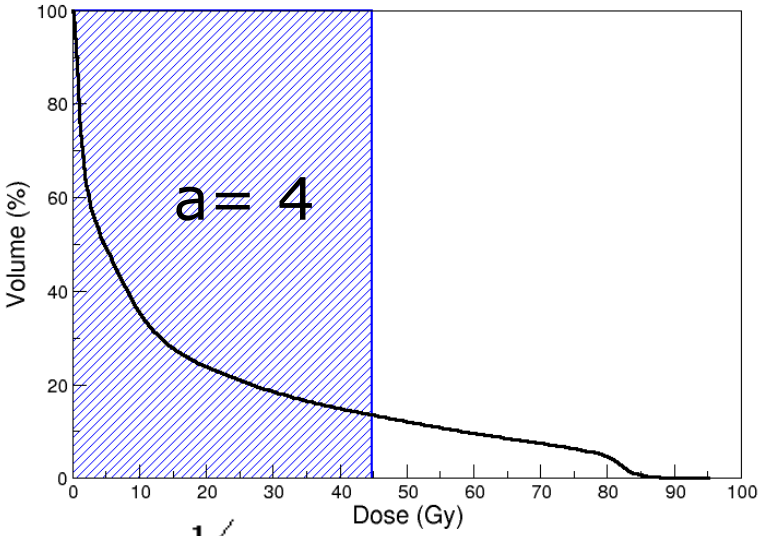
Niemierko 2000

a = 1	EUD = Dmean
a --> -∞	EUD --> Dmin
a --> +∞	EUD --> Dmax

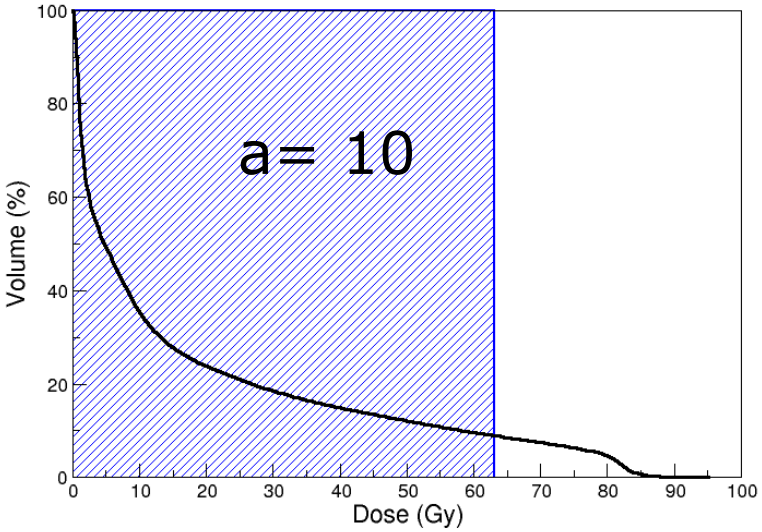
gEUD : phenomenological description
of the biological response to the radiation

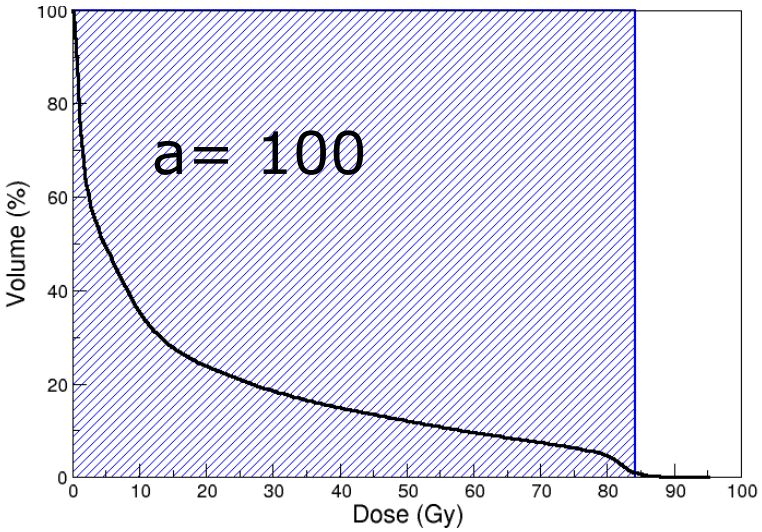
In principle applicable to target volumes and OARs

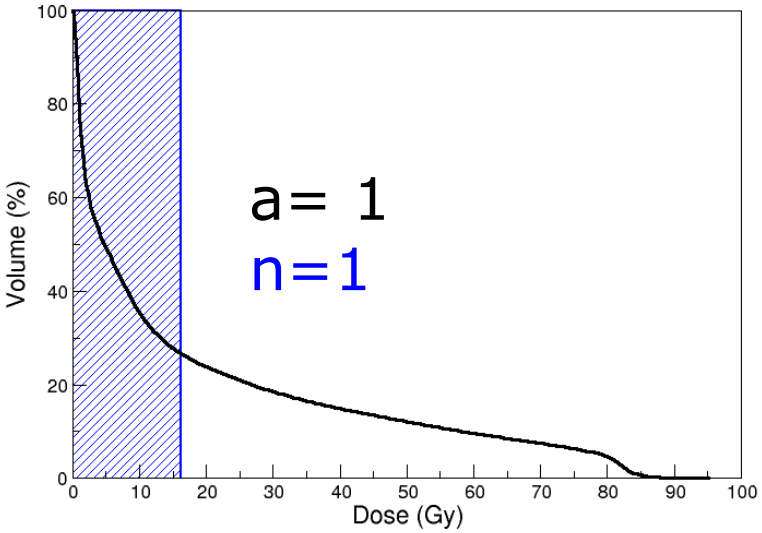


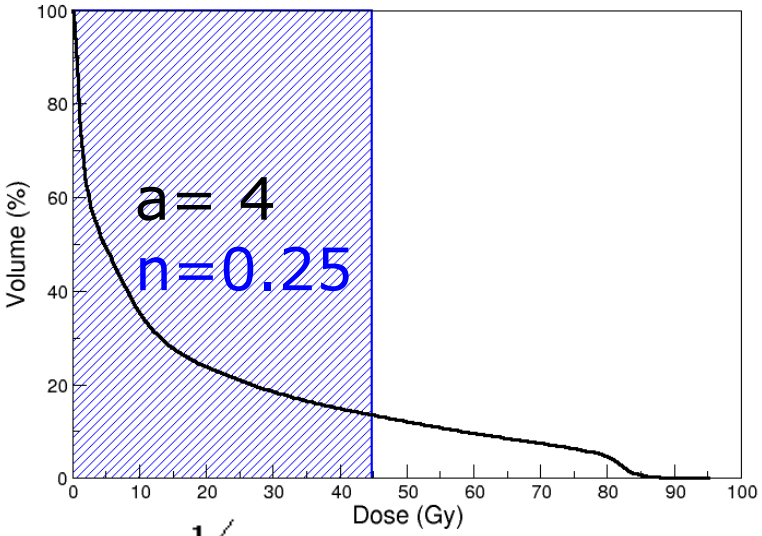


$$gEUD(Gy) = \left(\sum_{i=1}^{n} v_i D_i^a \right)^{1/a}$$

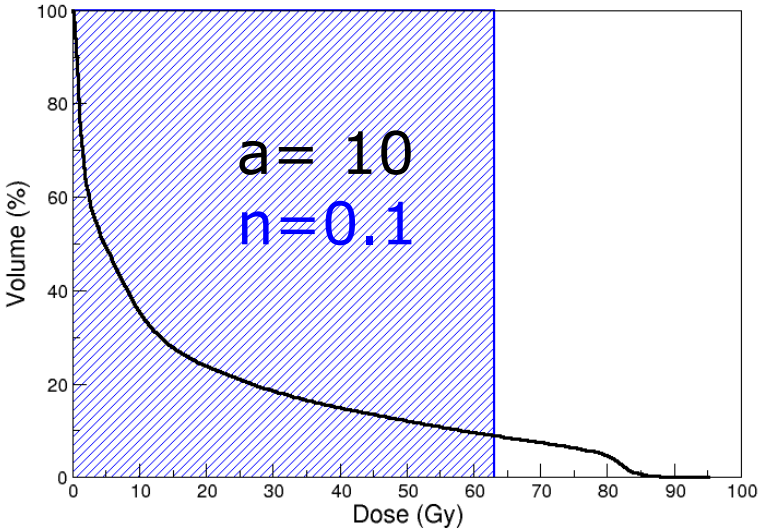


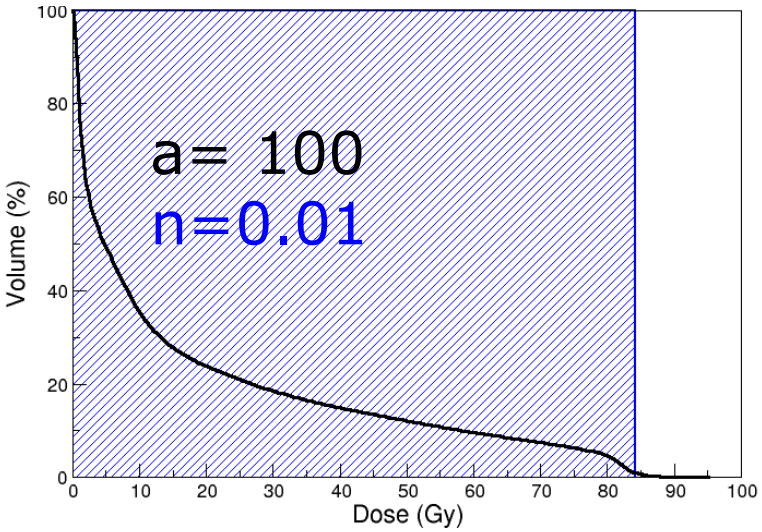




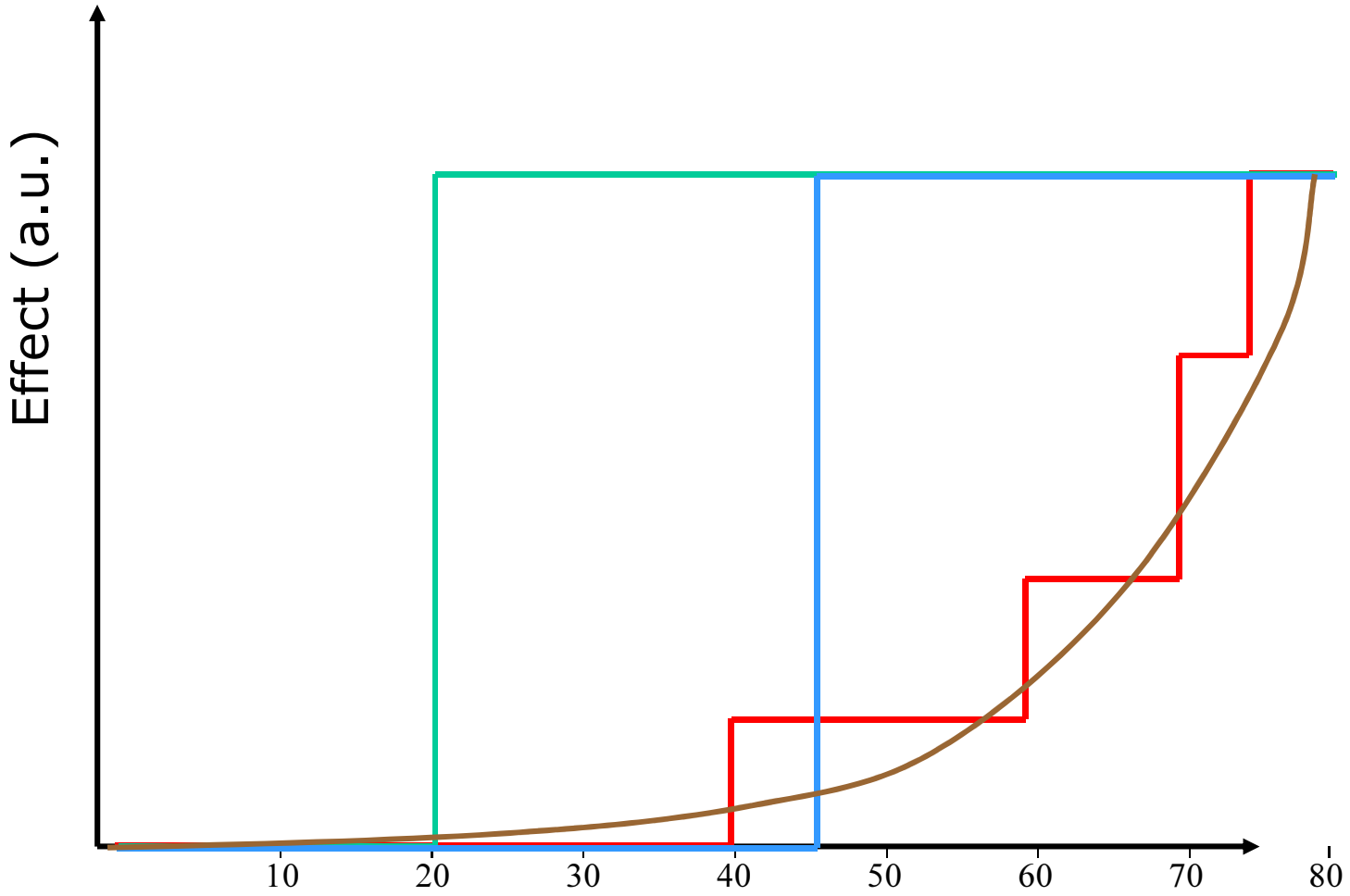


$$gEUD(Gy) = \left(\sum_{i=1}^{n} v_i D_i^a \right)^{1/a}$$





gEUD as a way to lock the relation between different DVH points (and getting rid of weigths!)



Commercial implementations - 1 (Philips/Raysearch/(Varian?))

(g)EUD optimisation for target and OARs as an add-on to DVH-based optimisation

$$F(\mathrm{E}UD)=\Theta(\mathrm{E}UD\text{-}\mathrm{E}UD_0)\left(\frac{\mathrm{E}UD\text{-}\mathrm{E}UD_0^2}{\mathrm{E}UD_0}\right)$$

Unconstrained optimisation

Evaluation tool including TCP, NTCP & P+

Commercial implementations - 2 (Elekta-Monaco)

EUD_{target}= Poisson EUD,

Serial model=gEUD,

Parallel model $$Isoeffect=\frac{1}{n}\sum_{i=1}^{n}\left(1+\left(\frac{d_0}{d_i}\right)^k\right)^{-1}$$

Constrained (OAR) or multicriteria (target) dose optimisation

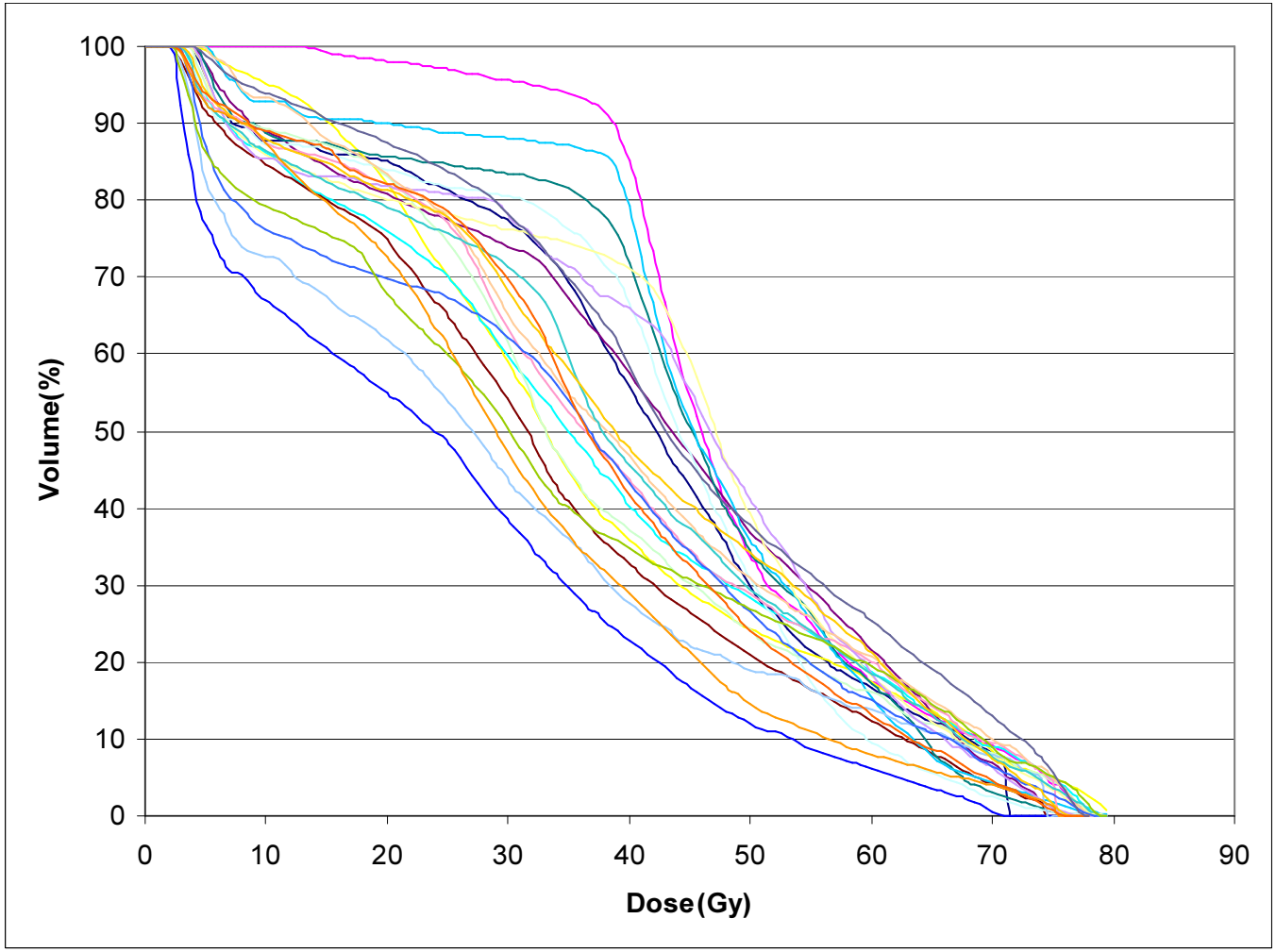
Tool for sensitivity analysis

(DVH constraints are available too.)

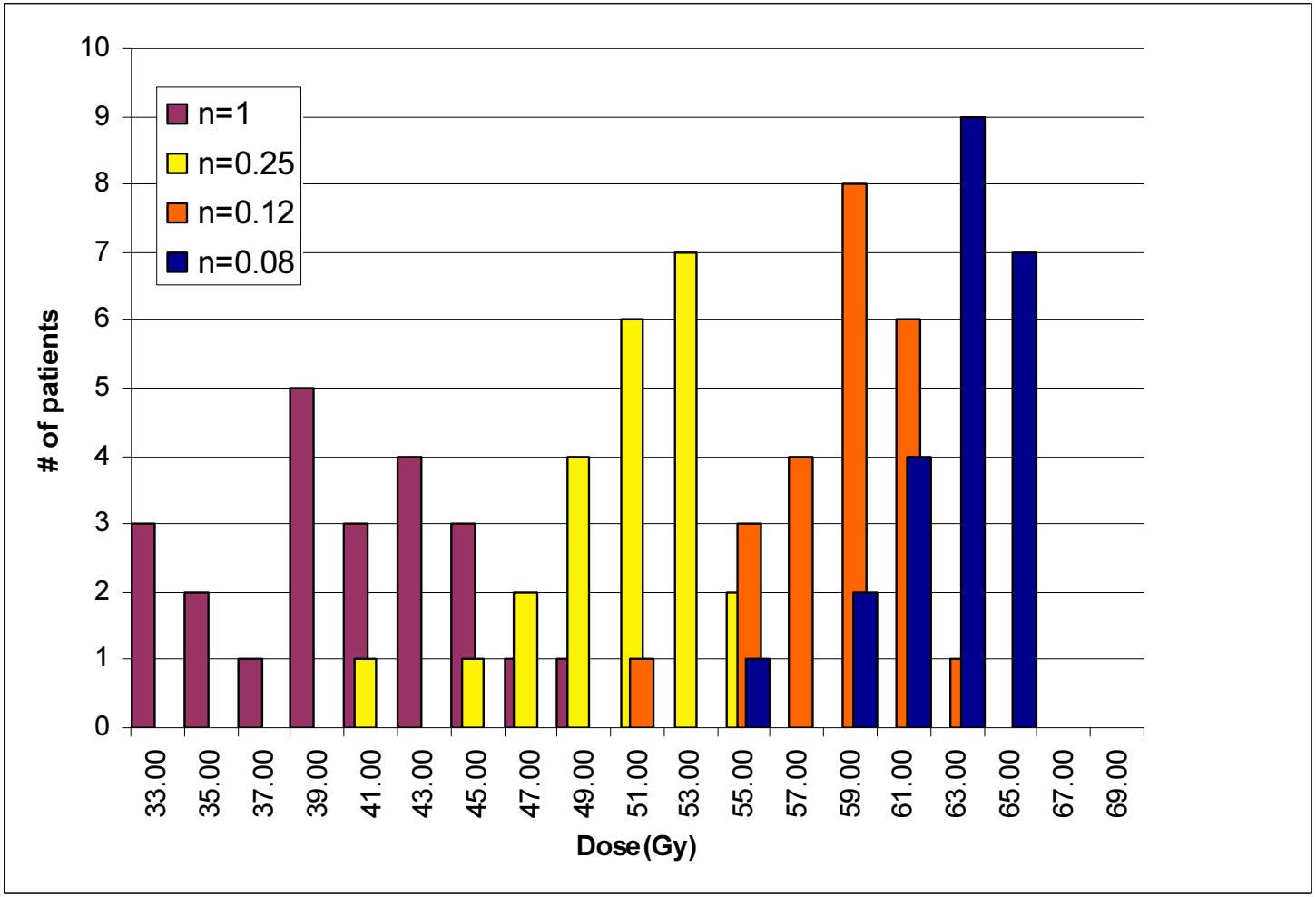
Fine, let’s try EUD optimisation.

Where should I start?

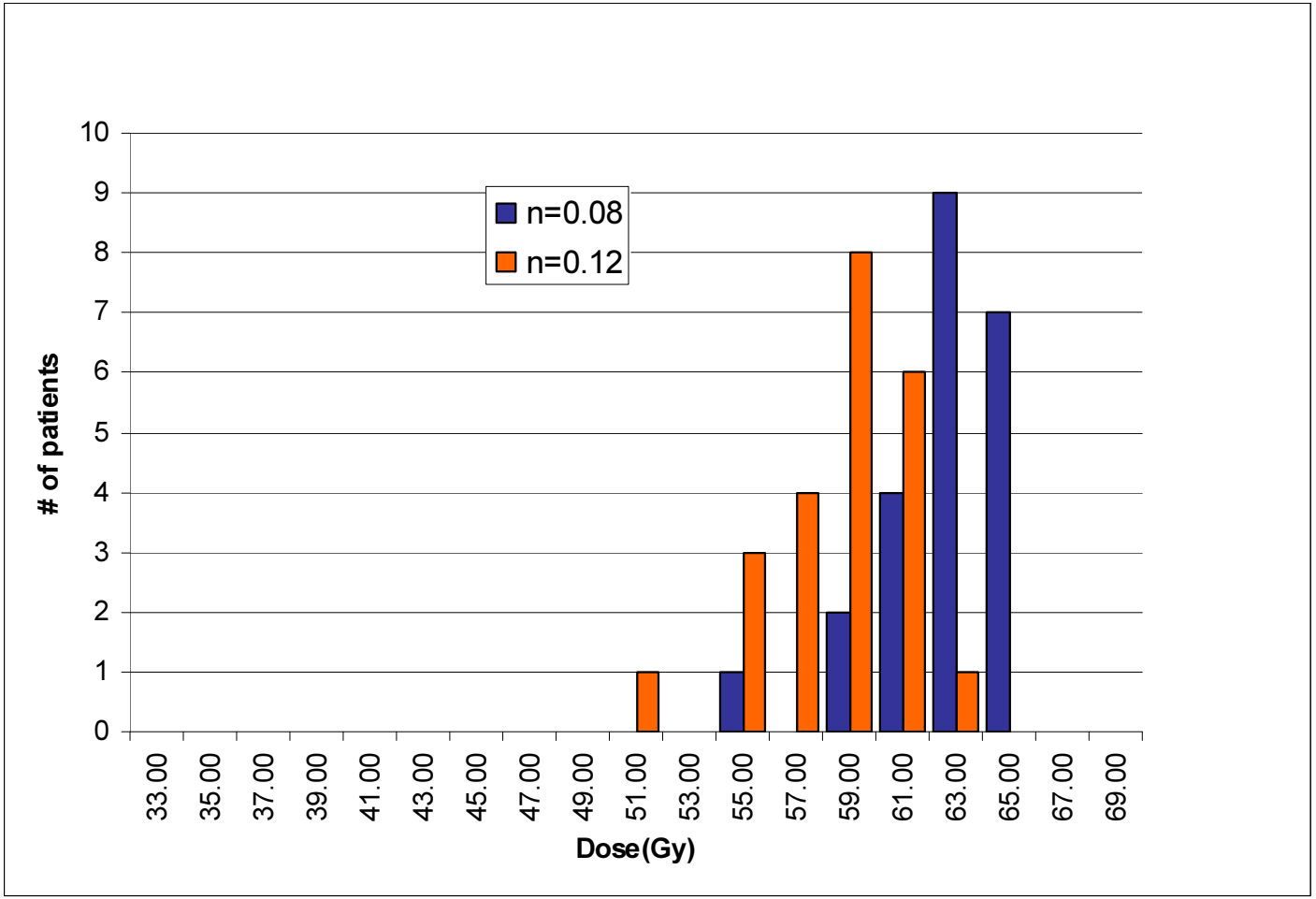
Start from your existing clinical practice.



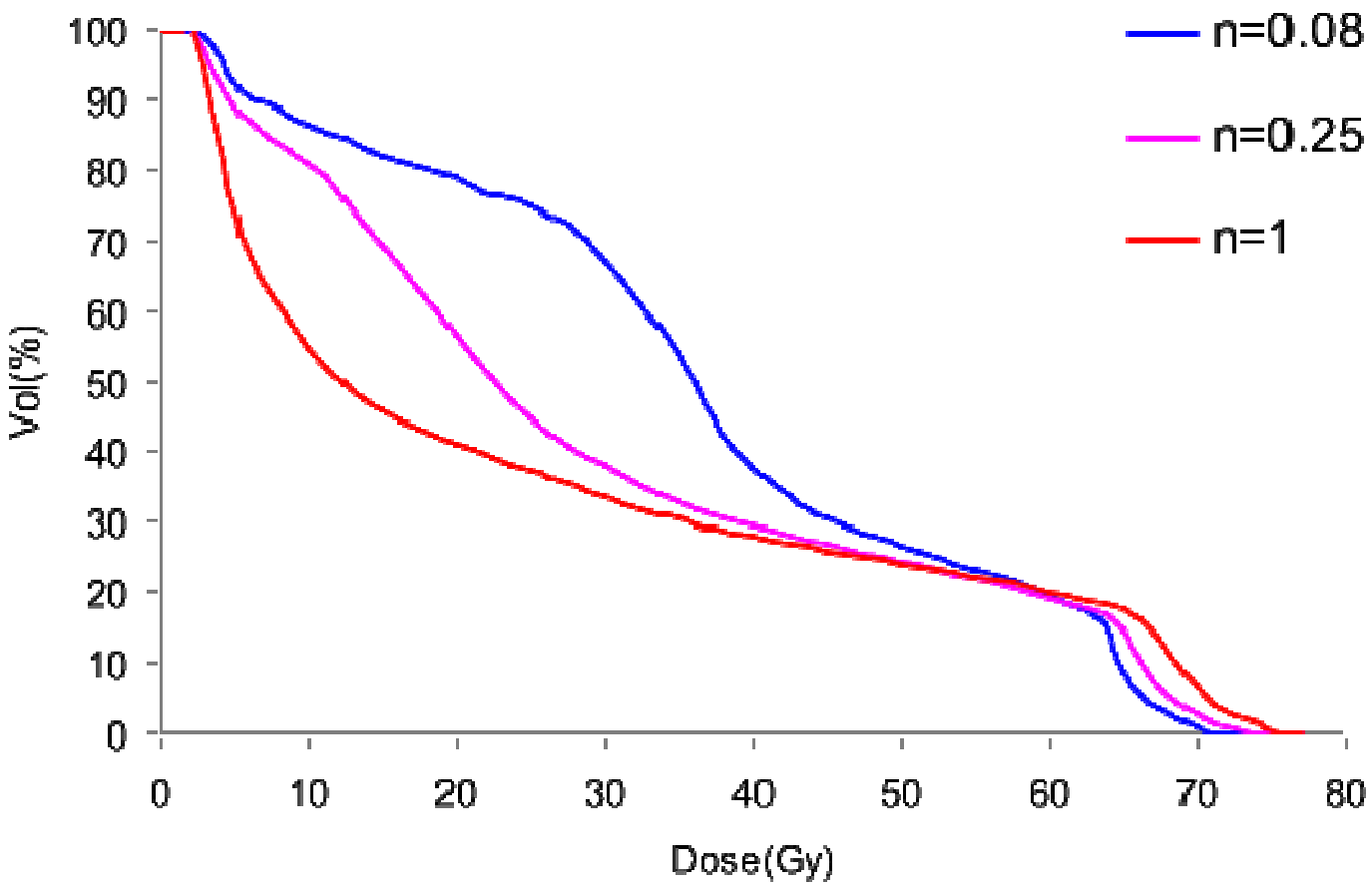
Calculate EUD values for your plans



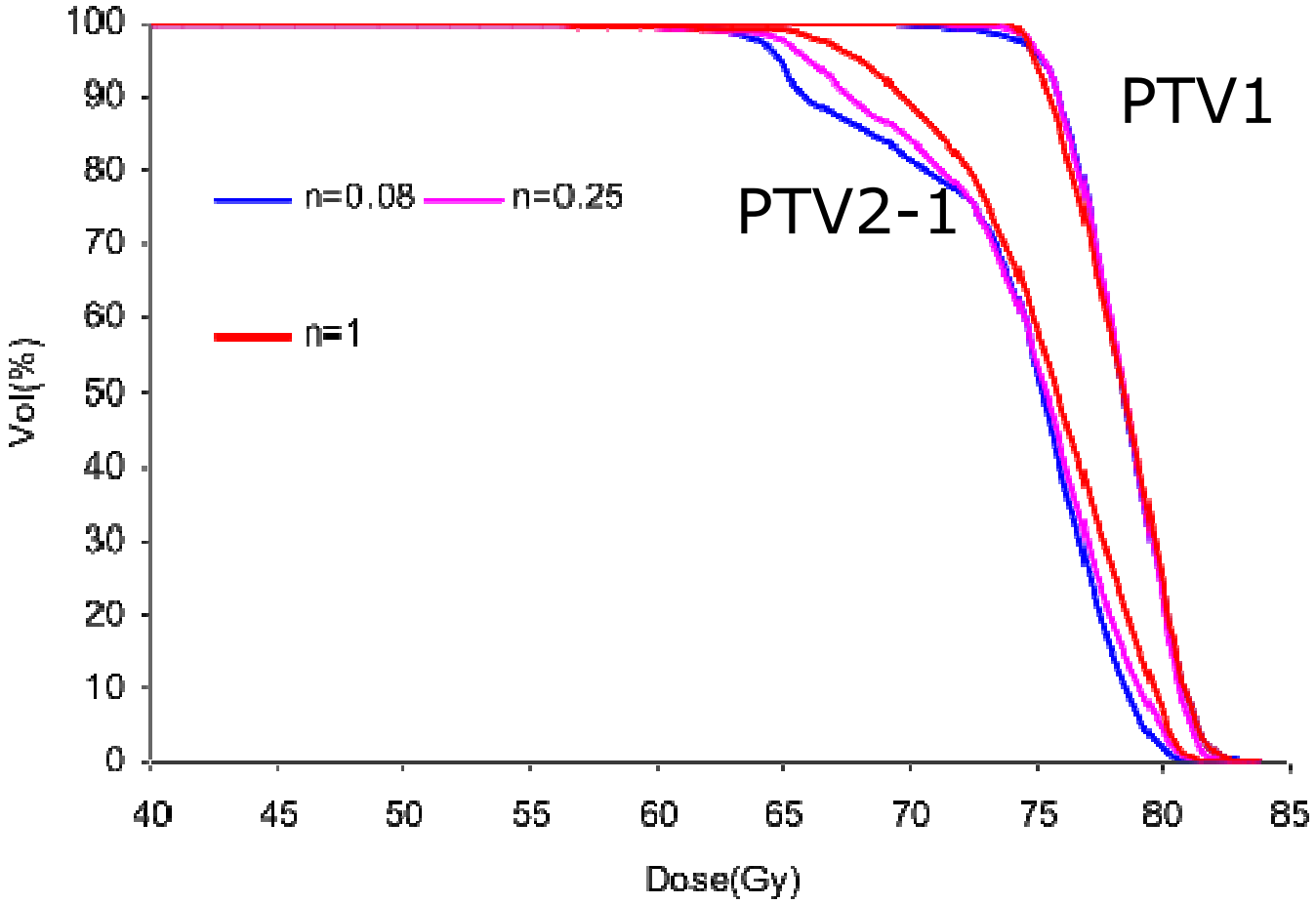
Do the n *values suggested in the literature make sense ?*



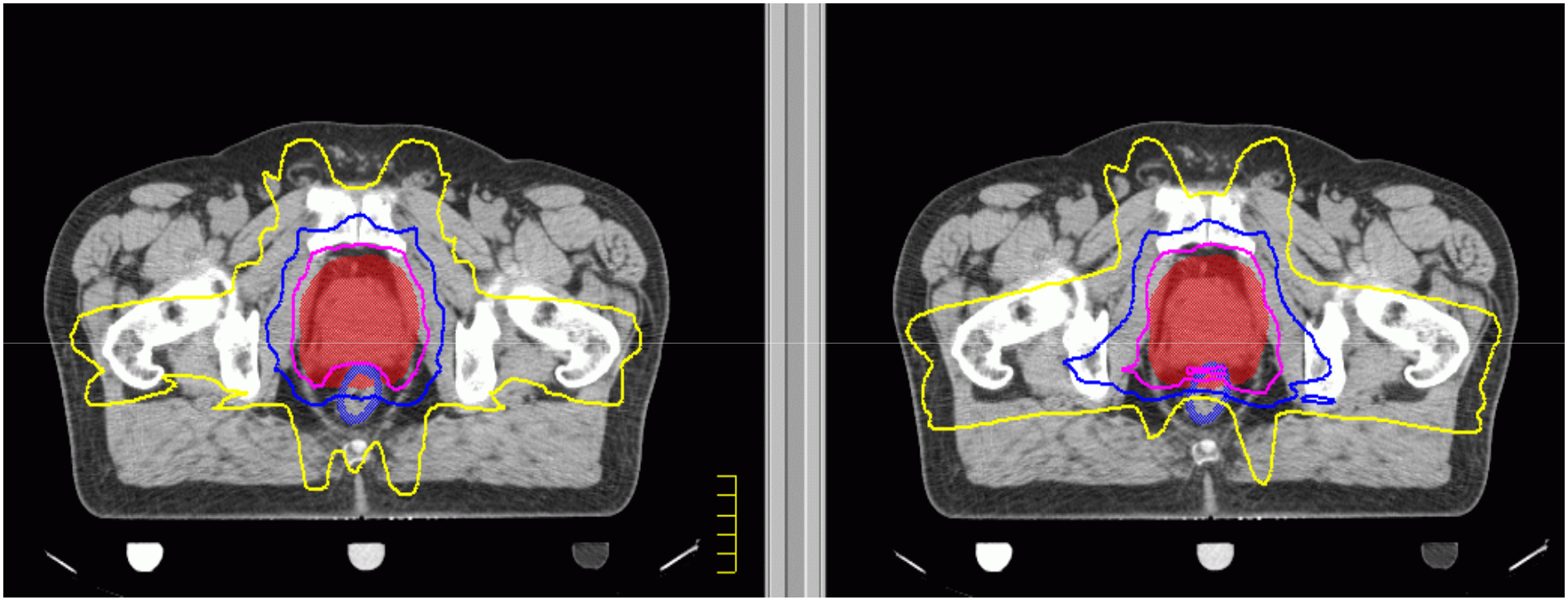
Run a sensitivity analysis



PTVs


100
90
80
70
60
50
40
30
20
10
0
Vol(%)
n=0.08
n=0.25
n=1
PTV1
PTV2-1
40
45
50
55
60
65
70
75
80
85
Dose(Gy)

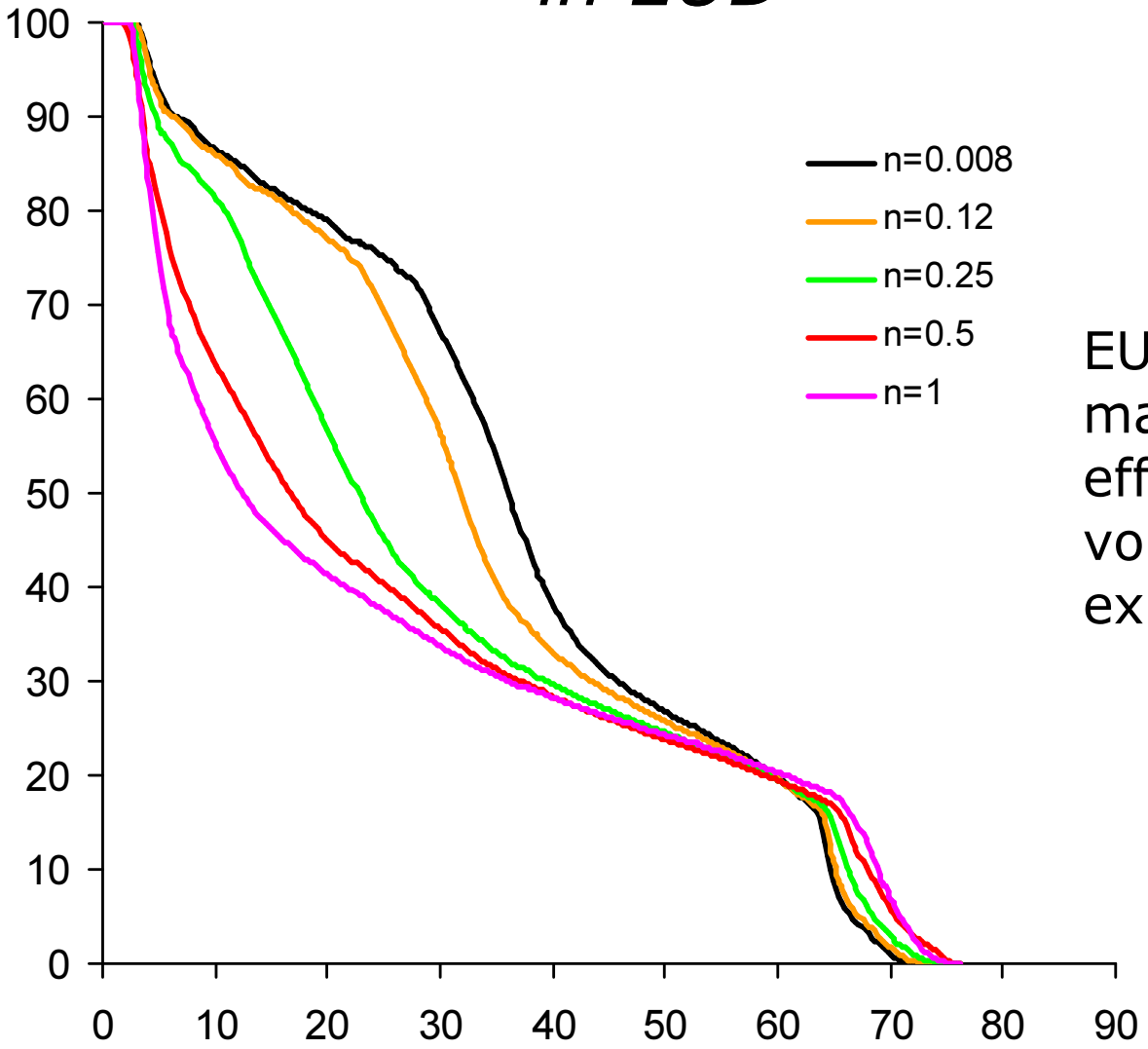
2D dose distributions



***n* = 0.08**

***n* = 1**

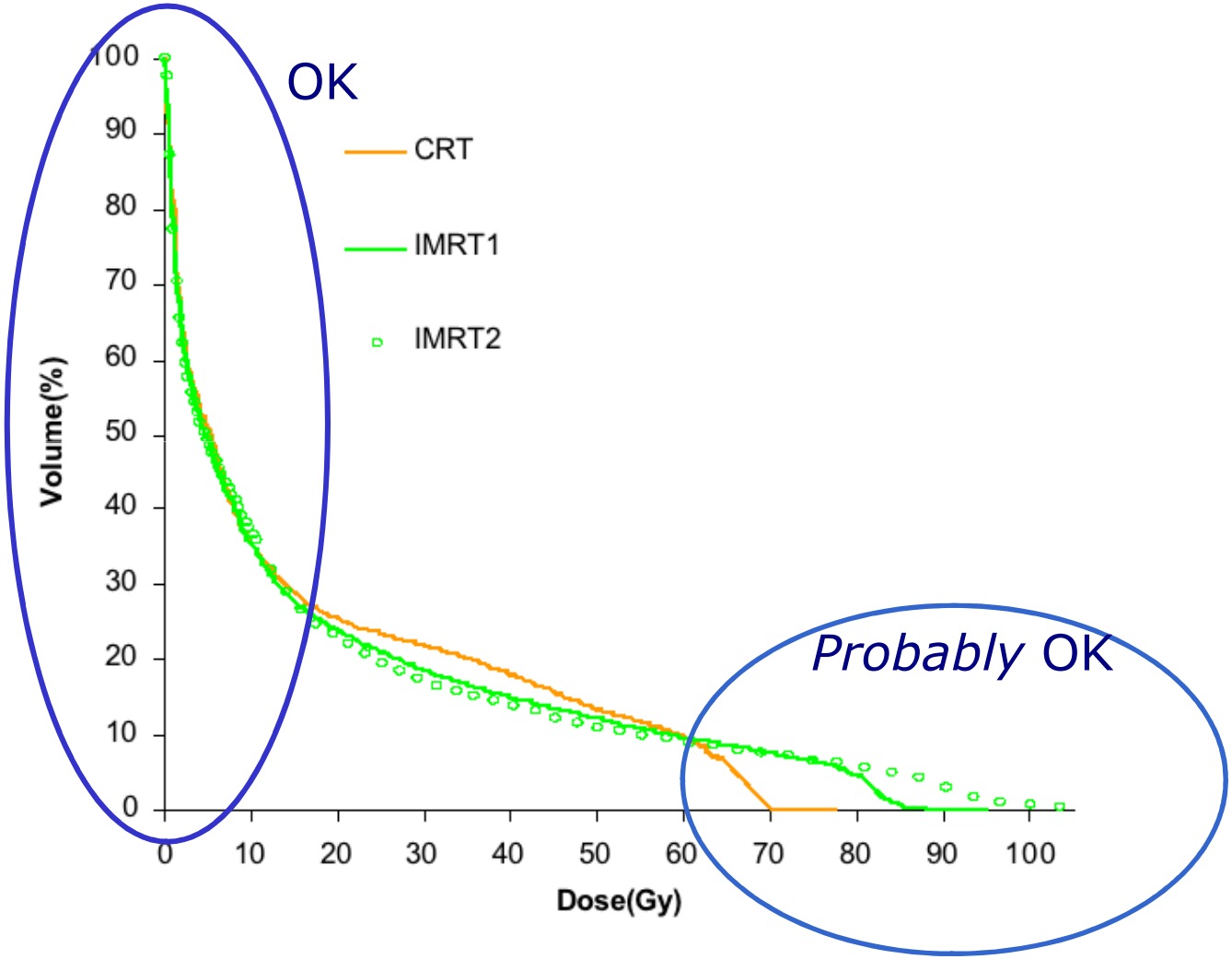
There's no magic in EUD



EUD it's all about making volume effects (i.e. dose-volume tradeoffs) explicit

“IMRT optimisation can not be based on data obtained in the 3D-CRT era.”

Don't make the dose-response models break



... but don't get stuck either

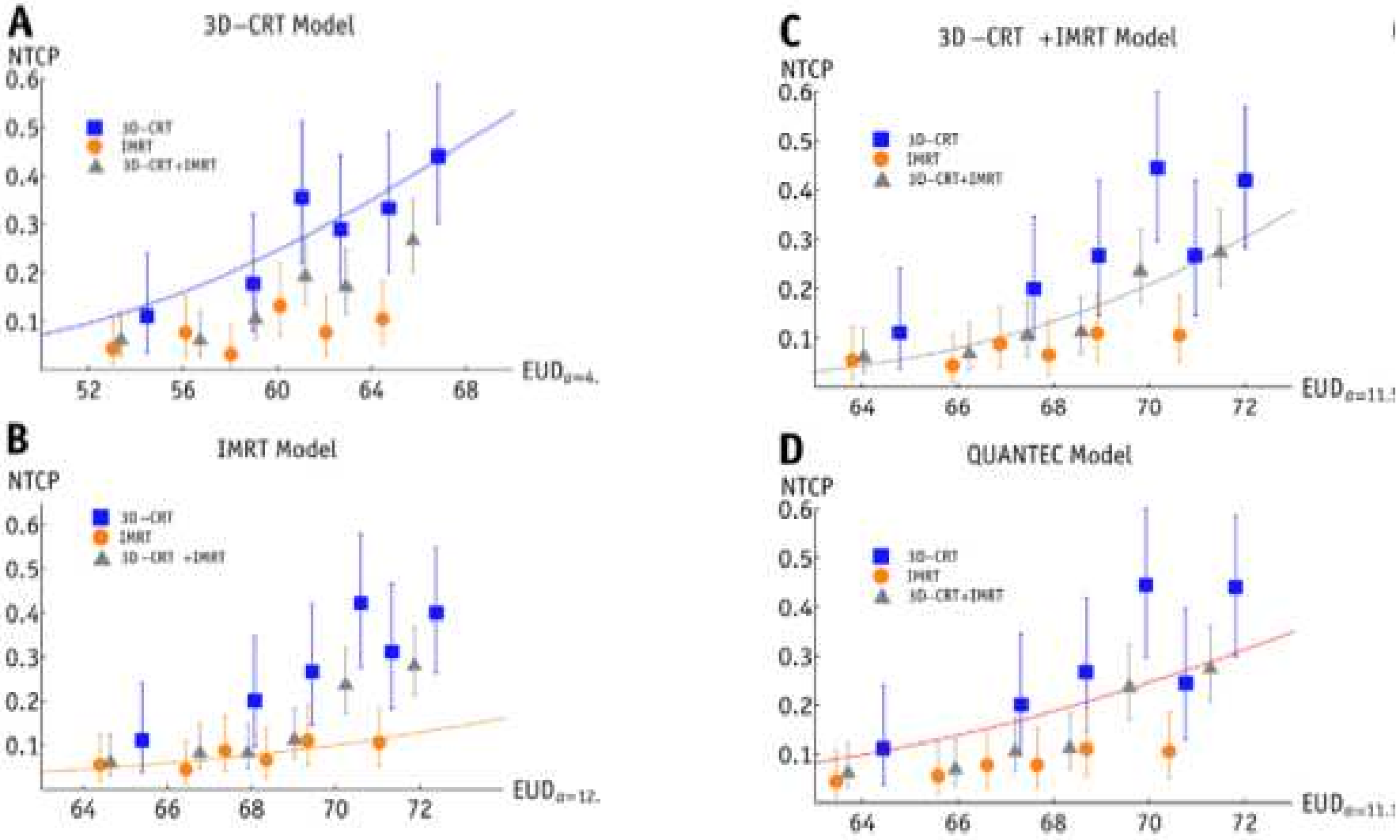
1. One uses IMRT to create plans as similar as possible to CRT

2. CRT-like dose distributions are delivered to patients

3. The follow up will provide further data on the effect of ... CRT-like dose distribution

The smaller the dose effect for a complication, the least you should be worried about potentially undue extrapolations

... And then you learn about puzzling results



Troeller IJROBP 2015

General references

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Journal of the ICRU

ICRU REPORT 83

Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT)

The use and QA of biologically related models for treatment planning: Short report of the TG-166 of the therapy physics committee of the AAPM[a)]

X. Allen Li[b)]
Radiation Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin 53226

Med Phys 2012

Plan reporting

Current plan reporting (e.g. recent ASTRO recommendation) does not include ‘error bars’.

If there are uncertainties in the planning procedure, they should be reflected in plan reporting.

E.g., reporting the PTV dose is correct only if

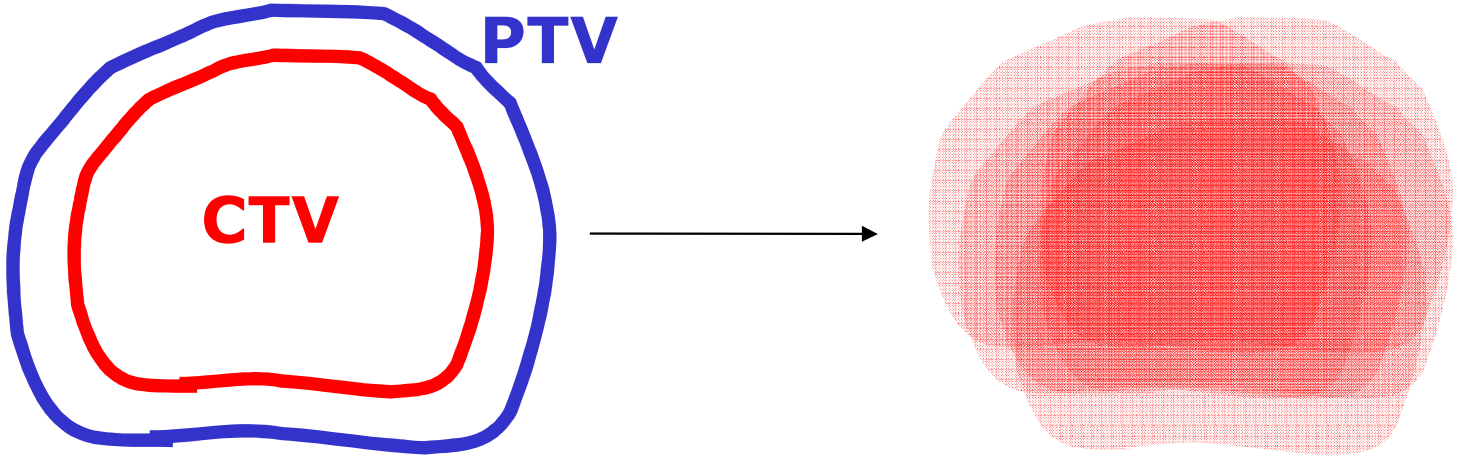
- The margins are correct
- The dose distribution is invariant for traslations/rotations
- The dose in the PTV is homogeneous

The same holds for ‘biological planning’:

- Uncertainty in the optimisation parameters (e.g. ‘a’) should result in a robustness analysis of the results.

Current and future developments

IMRT planning & geometrical uncertainties



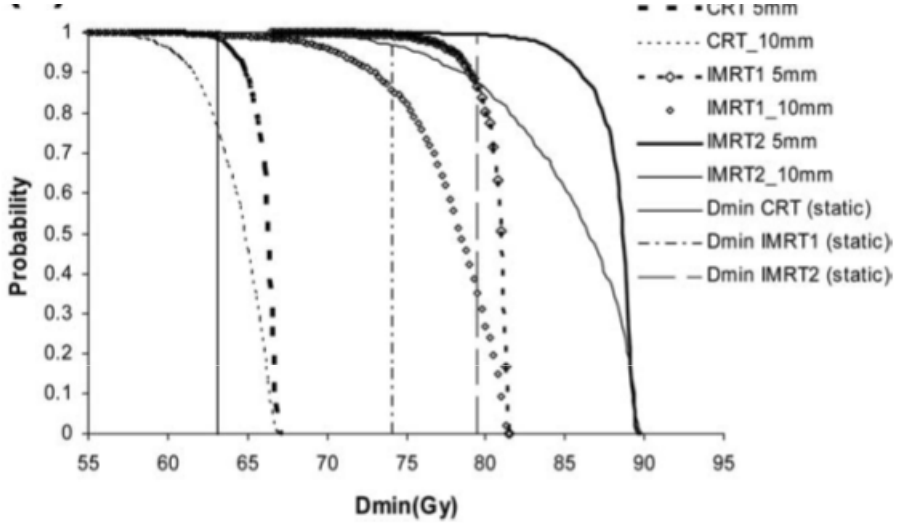
The PTV is an appropriate tool for CRT, but in IMRT one can do better than that.

'Robust optimisation' is an emerging field

Alternatives to the PTV particularly needed for charged particle therapy (e.g. p+).

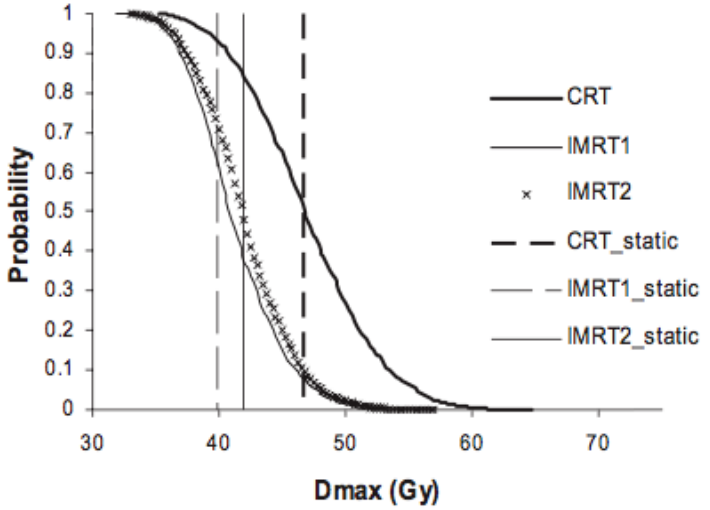
Current target dose reporting assumes homogeneous dose distributions in the appropriate PTV.

If **either** of the two is missing, we should report the dose differently.



Probabilistic dose reporting?

In the meantime, report the dose for the correct volumes



Schwarz et al IJROBP 2006

Conclusions

Class solutions ± 'forward planning' might facilitate a gradual transition to IMRT

Appropriate cost function and VOI definition are critical in 'steering' the optimisation in the desired direction.

‘Biological’ planning can be incorporated in everyday practice

Automatic planning is coming. Fast.

Dose Calculation in Static and Rotational IMRT

Matthias Söhn, PhD

Radiation Oncology, Medical Physics
University Hospital Grosshadern
LMU Munich, Germany

Disclosures

• I am involved in the development of the treatment planning system HYPERION which is the basis for Elekta Monaco®.

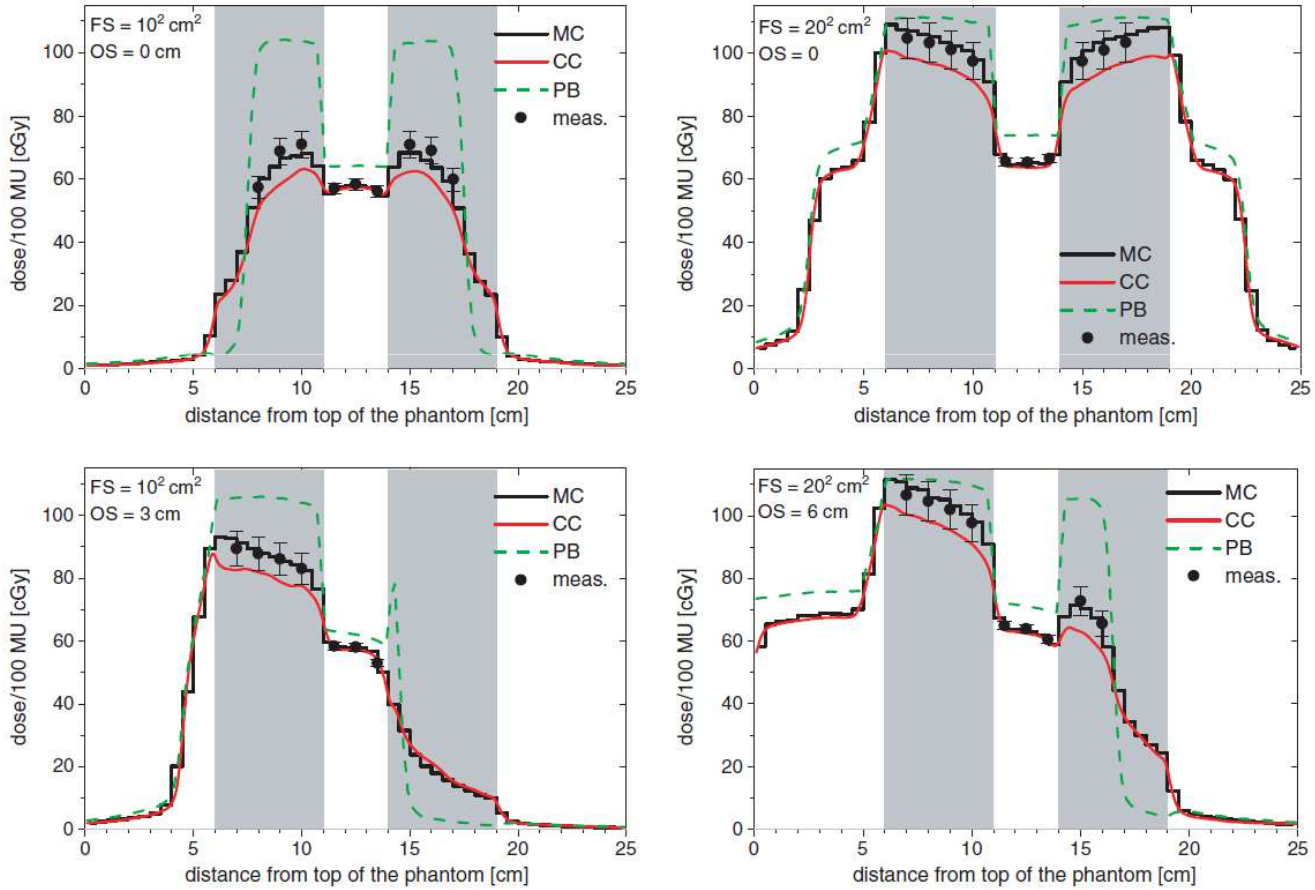
• My department (LMU Munich) currently receives research grants from Elekta and C-RAD.

• I am co-owner of a company SCIENTIFICRT which specializes in the field of Monte-Carlo dose calculation

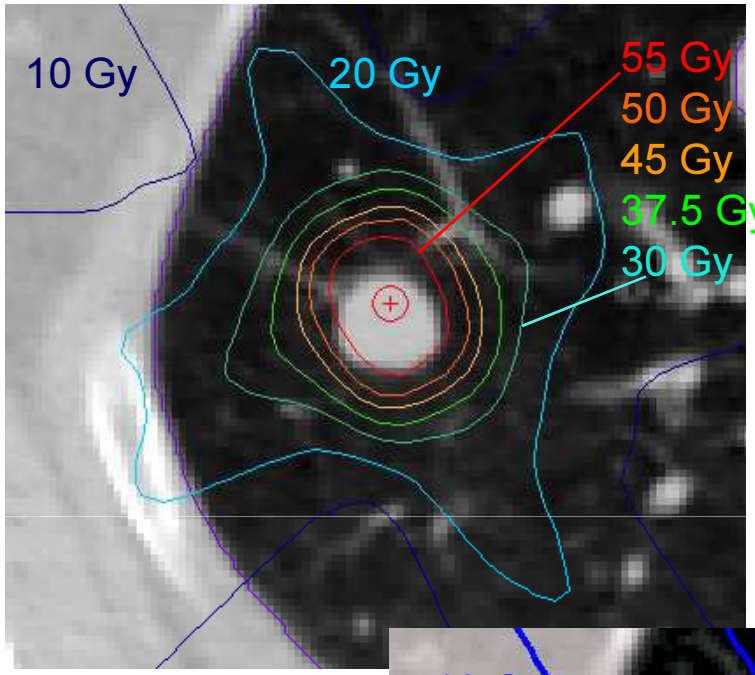
Differences in Dose calculation algorithms – A clinically relevant issue?

Krieger and Sauer 2005 (PMB 50(5))

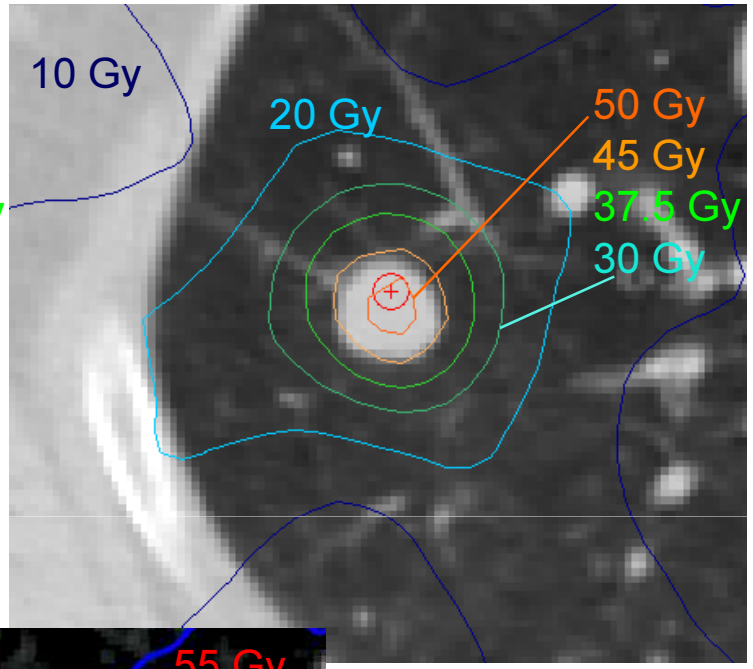
Pencil Beam vs. Collapsed Cone vs. Monte Carlo vs. measurement in a heterogeneous multi-layer phantom



Differences in Dose calculation algorithms – A clinically relevant issue?



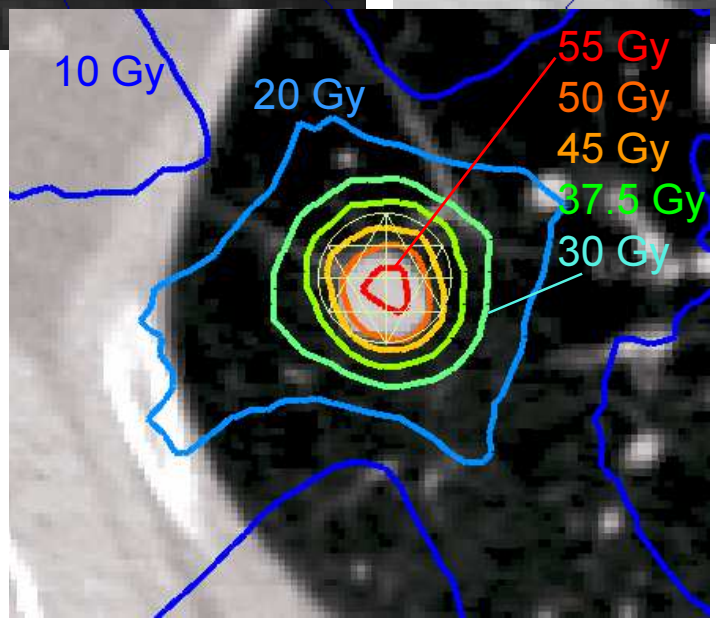
Pencil Beam



Collapsed Cone

Patient example:

- small lung lesion
- fully surrounded by low density tissue

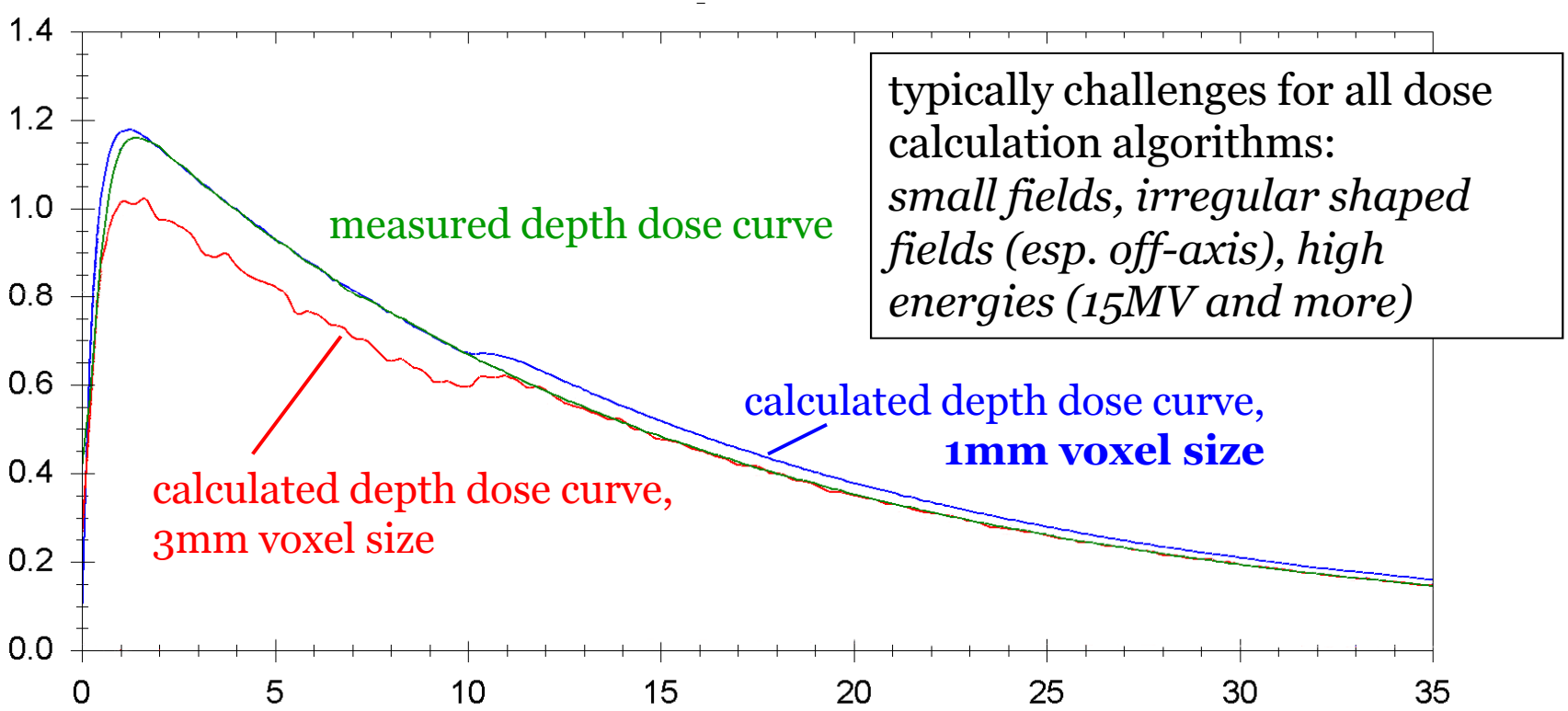


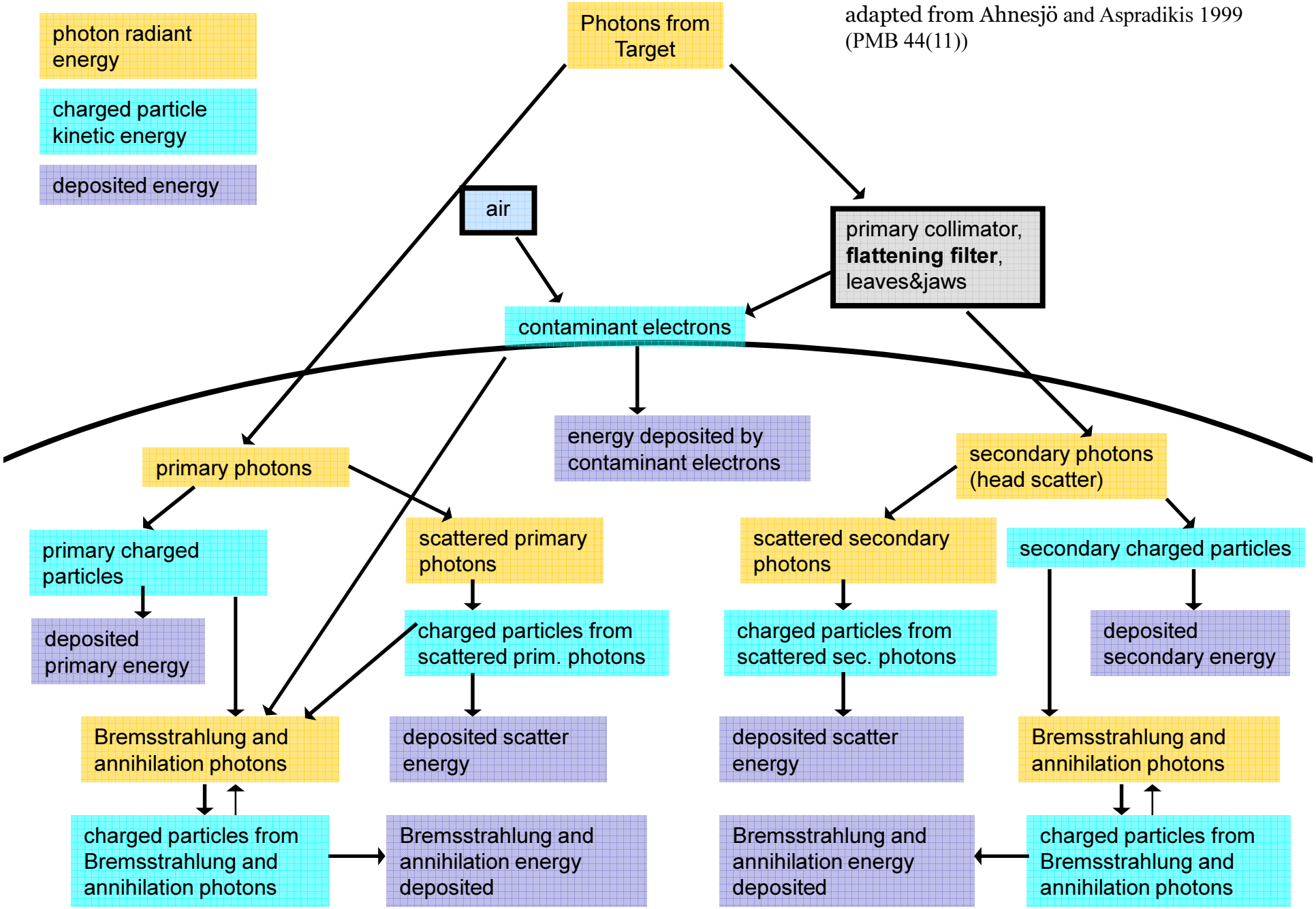
Monte Carlo

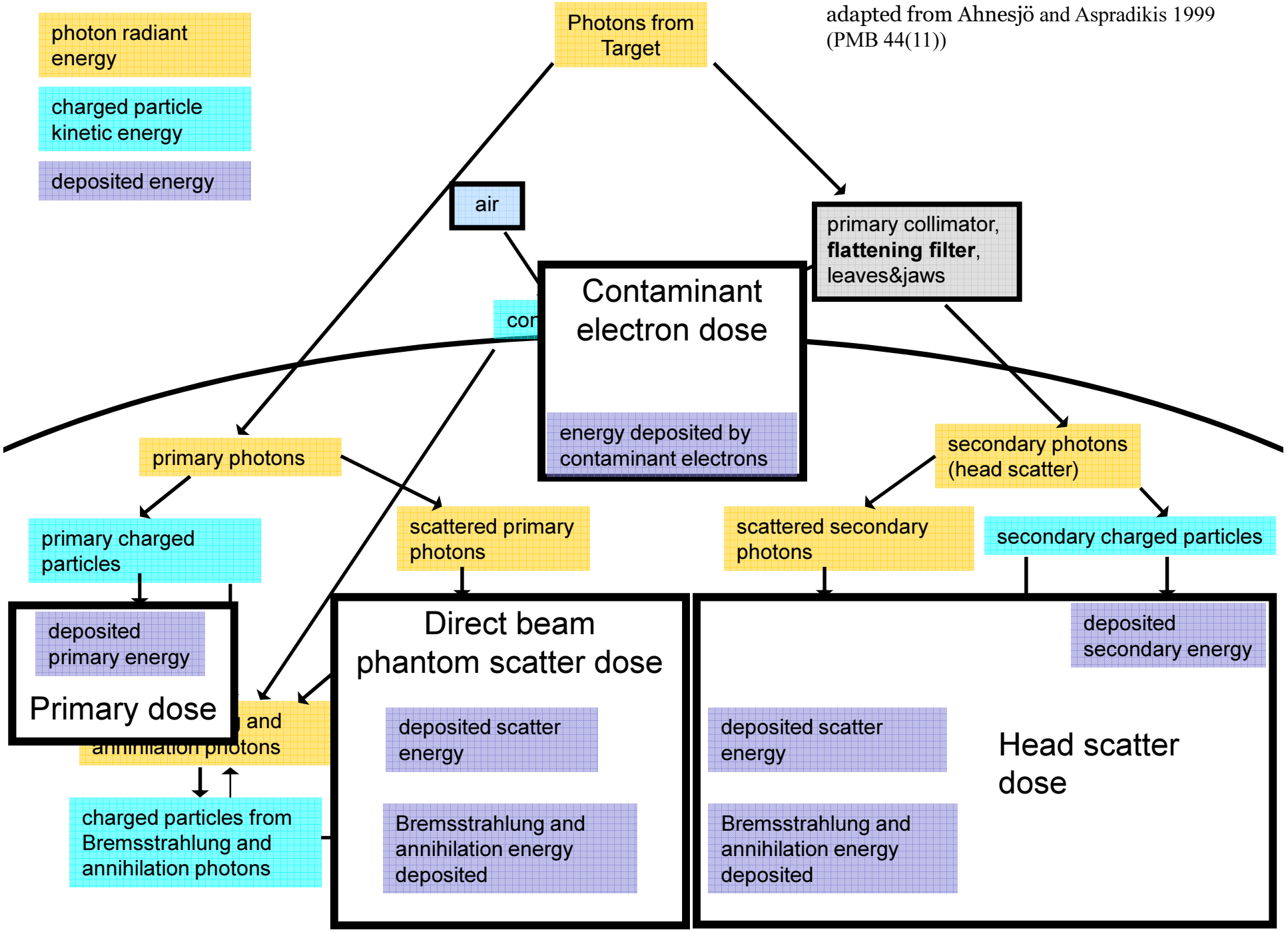
Precise dose calculation is still a challenge: Be aware of potential software BUGS!

courtesy P. Lang, C. Heinz (LMU Munich)

Example: depth dose curve *in water* for a central **1x1 cm field**, 6MV
results of a dose calc. algorithm (here: CC) of a widely used commercial TPS...




photon radiant energy
charged particle kinetic energy
deposited energy
Photons from Target
adapted from Ahnesjö and Aspradikis 1999 (PMB 44(11))
air
primary collimator, **flattening filter**, leaves&jaws
contaminant electrons
energy deposited by contaminant electrons
primary photons
secondary photons (head scatter)
primary charged particles
deposited primary energy
scattered primary photons
charged particles from scattered prim. photons
deposited scatter energy
scattered secondary photons
charged particles from scattered sec. photons
deposited scatter energy
secondary charged particles
deposited secondary energy
Bremsstrahlung and annihilation photons
charged particles from Bremsstrahlung and annihilation photons
Bremsstrahlung and annihilation energy deposited
Bremsstrahlung and annihilation photons
charged particles from Bremsstrahlung and annihilation photons
Bremsstrahlung and annihilation energy deposited


photon radiant energy
charged particle kinetic energy
deposited energy
Photons from Target
adapted from Ahnesjö and Aspradikis 1999 (PMB 44(11))
air
primary collimator, **flattening filter**, leaves&jaws
Contaminant electron dose
energy deposited by contaminant electrons
primary photons
secondary photons (head scatter)
primary charged particles
scattered primary photons
scattered secondary photons
secondary charged particles
deposited primary energy
Primary dose
Direct beam phantom scatter dose
deposited secondary energy
deposited scatter energy
deposited scatter energy
Head scatter dose
charged particles from Bremsstrahlung and annihilation photons
Bremsstrahlung and annihilation energy deposited
Bremsstrahlung and annihilation energy deposited

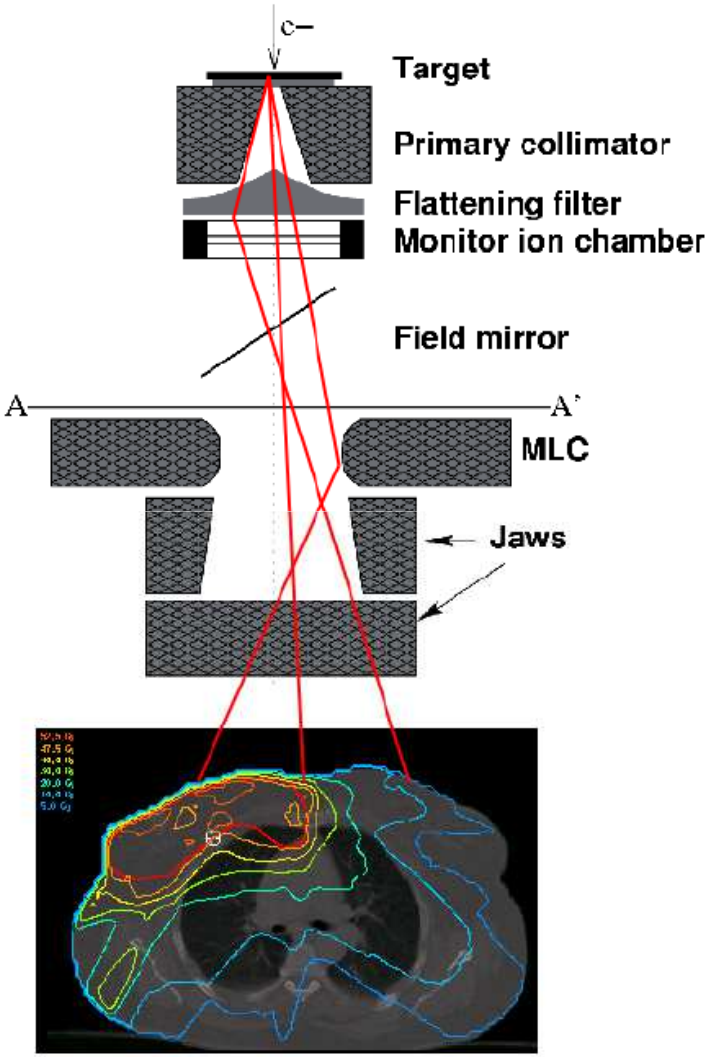
Technical background: Typical components of an accelerator head

accelerator head

particle source

beam modulators

Patient



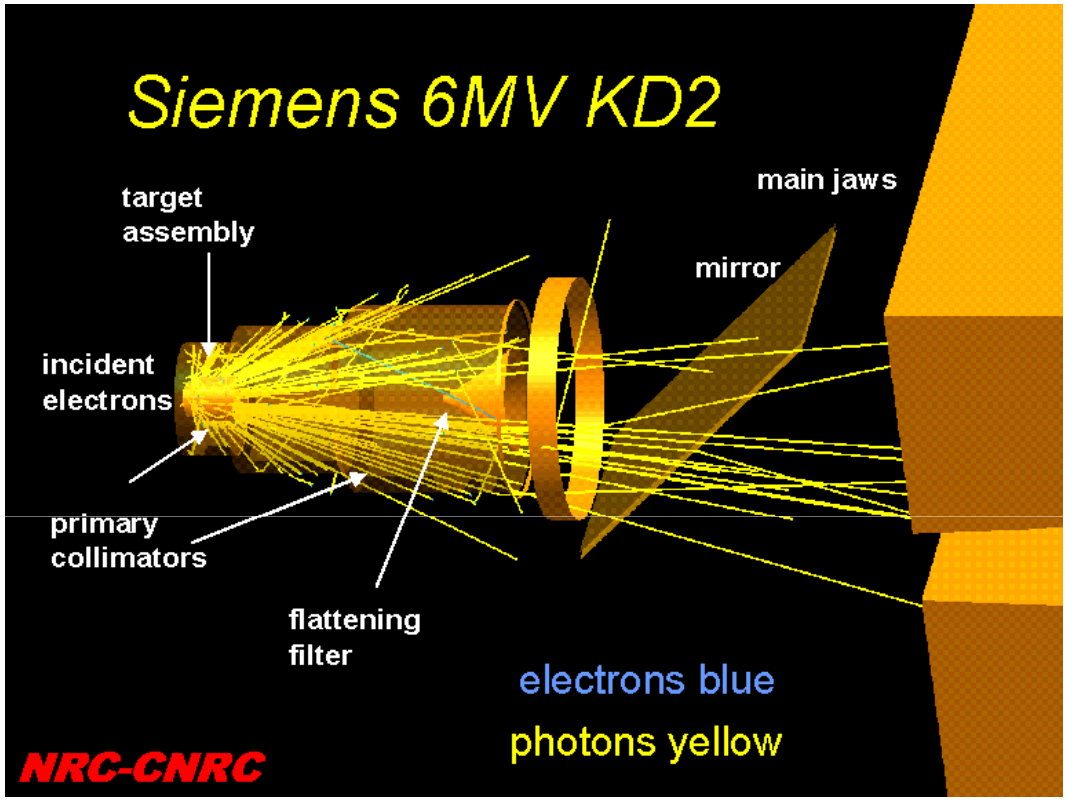
Dose calculation algorithms...

model of accelerator head

radiation transport in the patient model for (pencil beam, collapsed cone superposition, Monte Carlo, ...)

Is it really important to focus *mainly* on radiation transport in the patient?

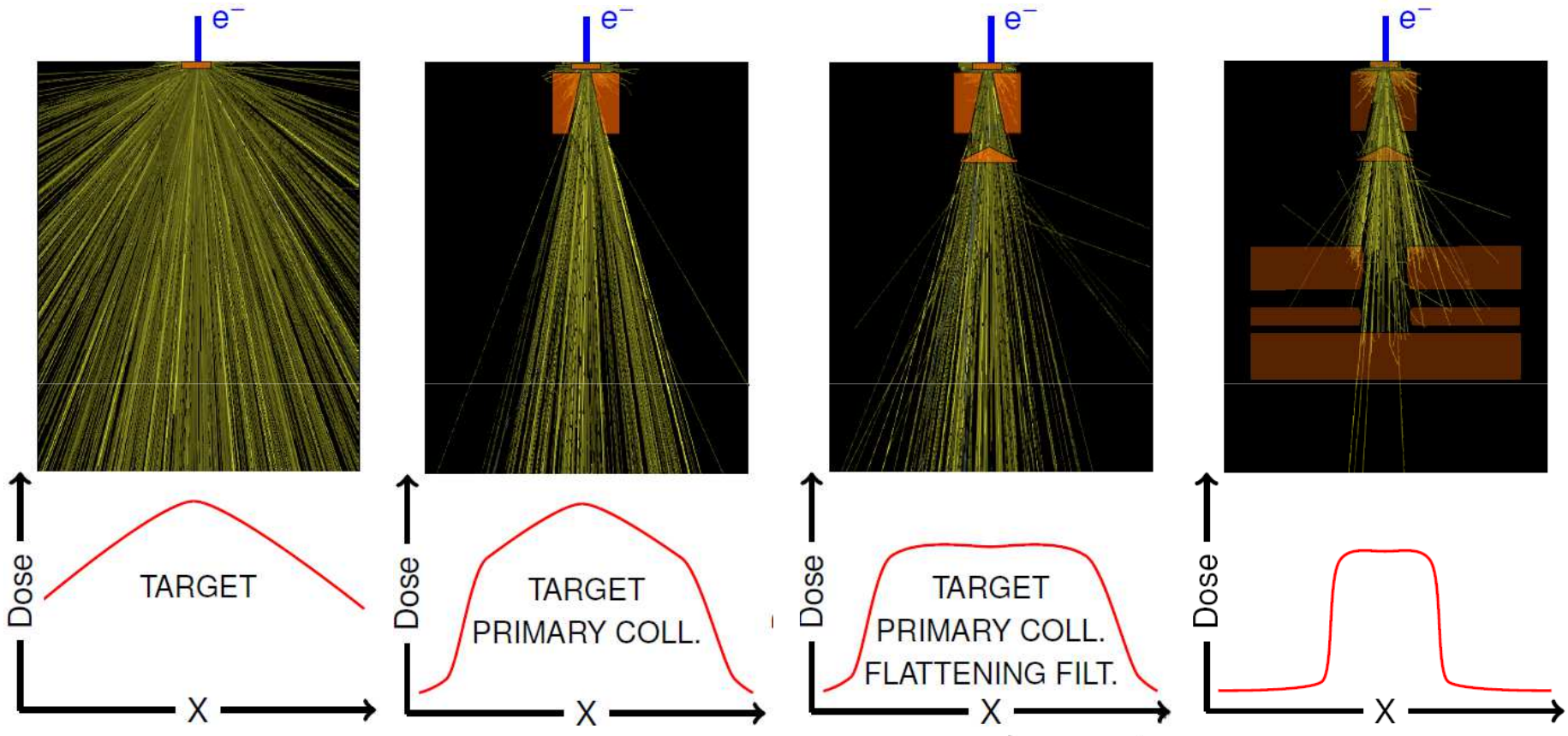
Monte Carlo simulations of a linac with BEAMnrc allow separate dose calculation for *primary photons*, *secondary photons* ('head scatter') and *contaminant electrons*



The following slides:
Appropriate modelling of what happens in the accelerator head is of major importance for dose calculation accuracy!

courtesy M. Sikora

Monte Carlo simulations of the accelerator head

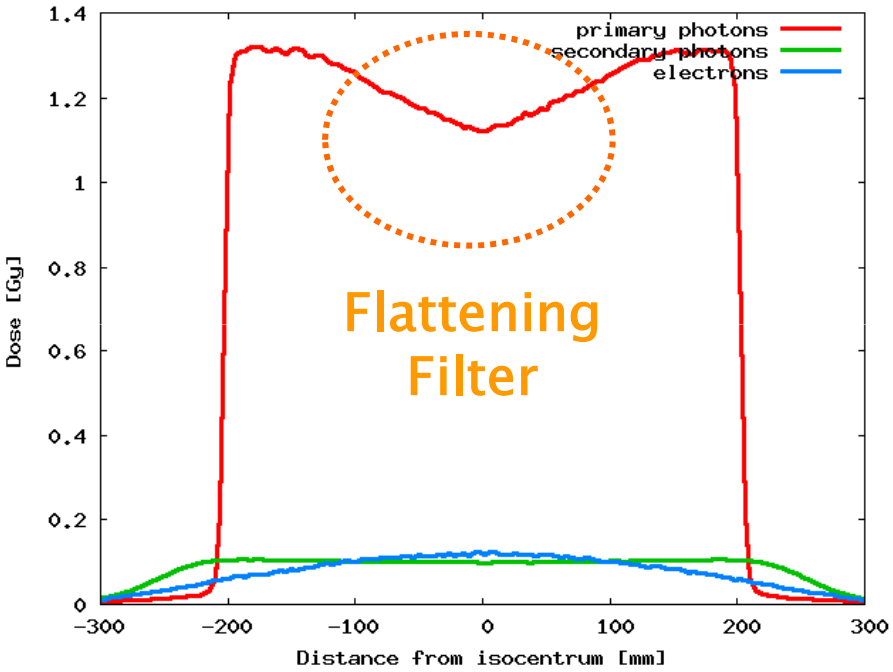


Crossprofiles and depth dose curves by components

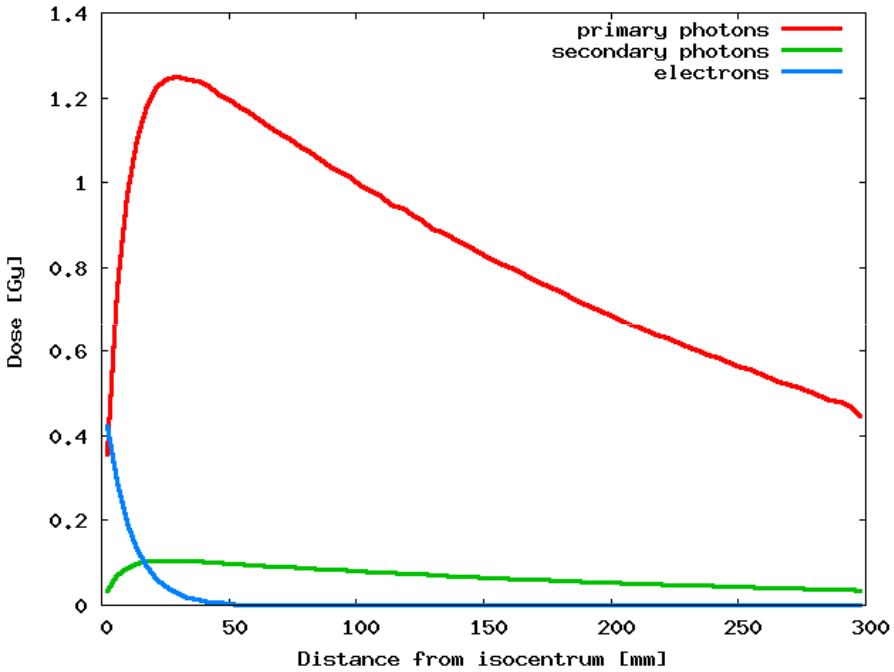
courtesy M. Sikora

energy: 15 MV

cross-profiles, depth: 15 mm



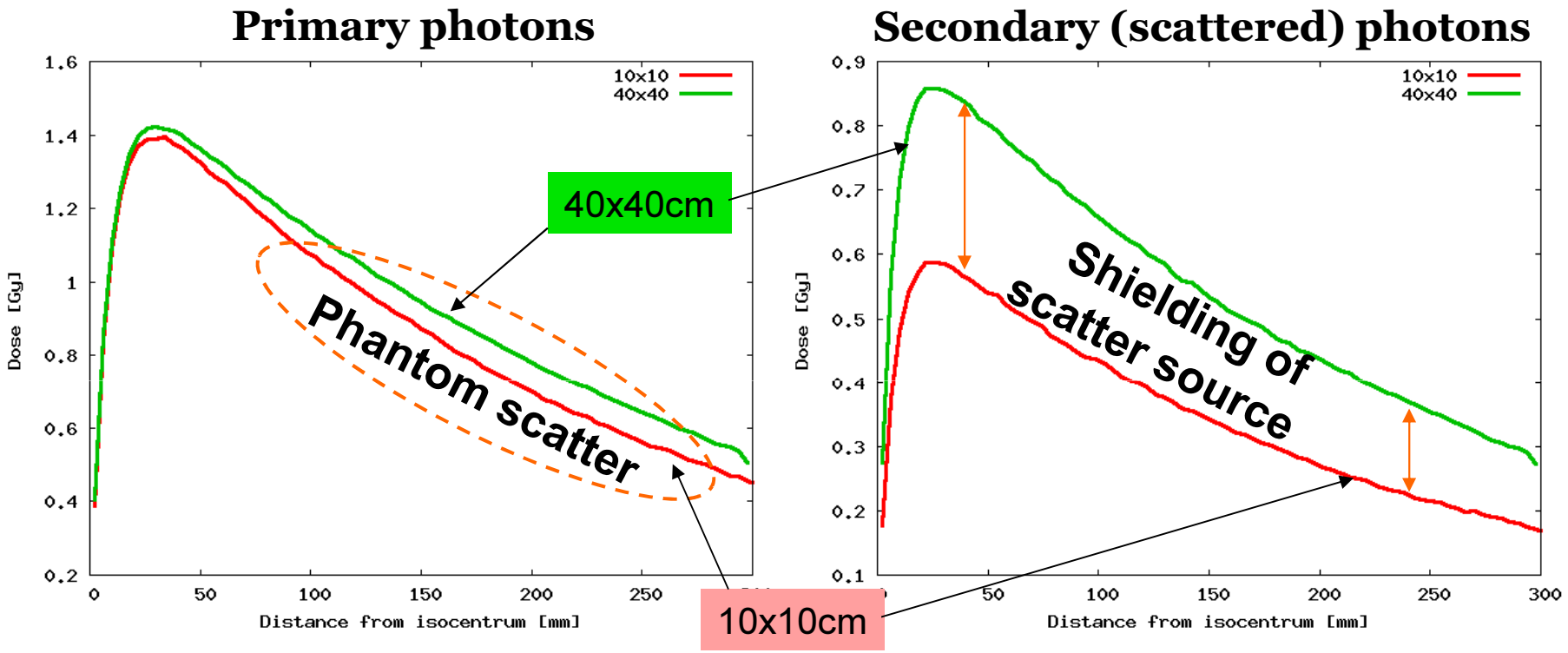
depth dose curves



primary photons: do not scatter in the treatment head since creation in target
secondary photons and electrons: scatter/interact anywhere since

Variation of the output factor for primary and secondary photons

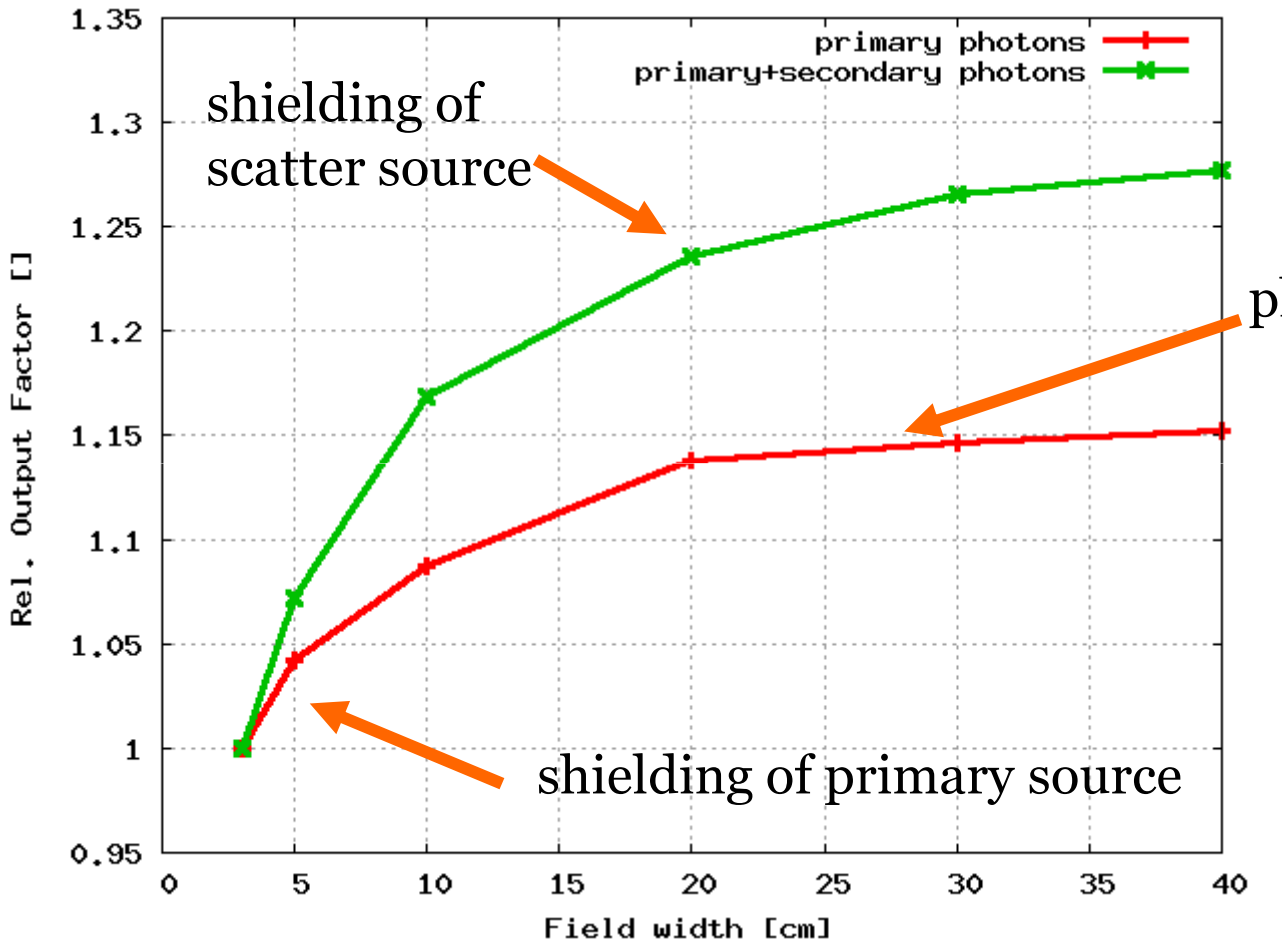
courtesy M. Sikora



$$\text{OutputFactor} = \frac{\text{Dose(field size)}}{\text{Dose(reference field size)}}$$

Output factors by Components

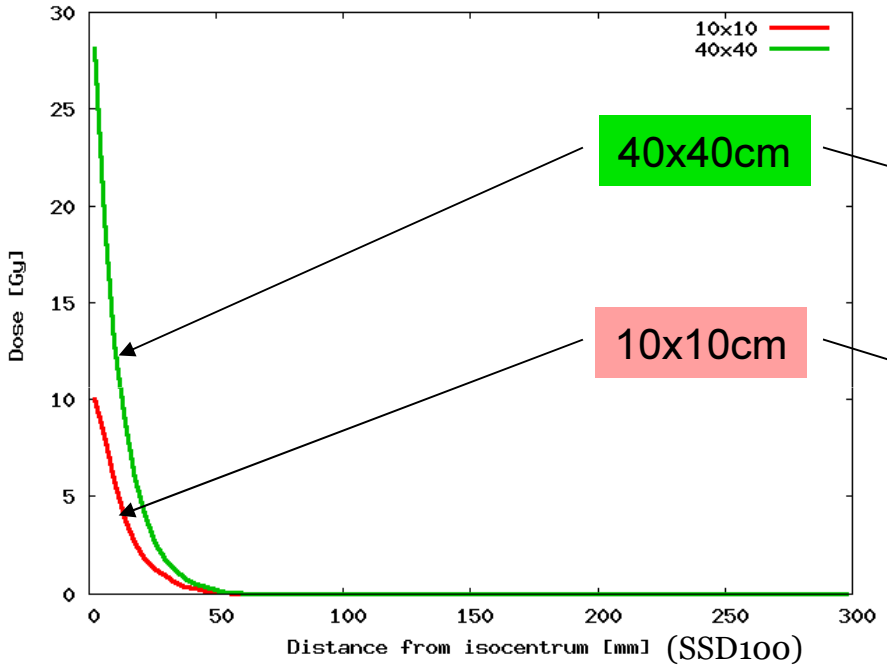
courtesy M. Sikora



Electron contamination

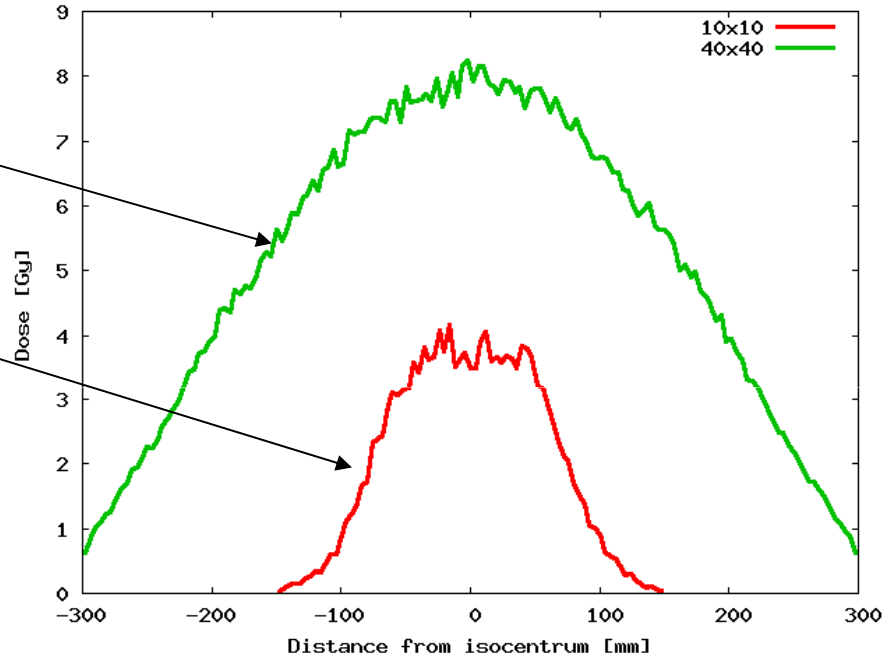
courtesy M. Sikora

depth dose curves



(SSD100)

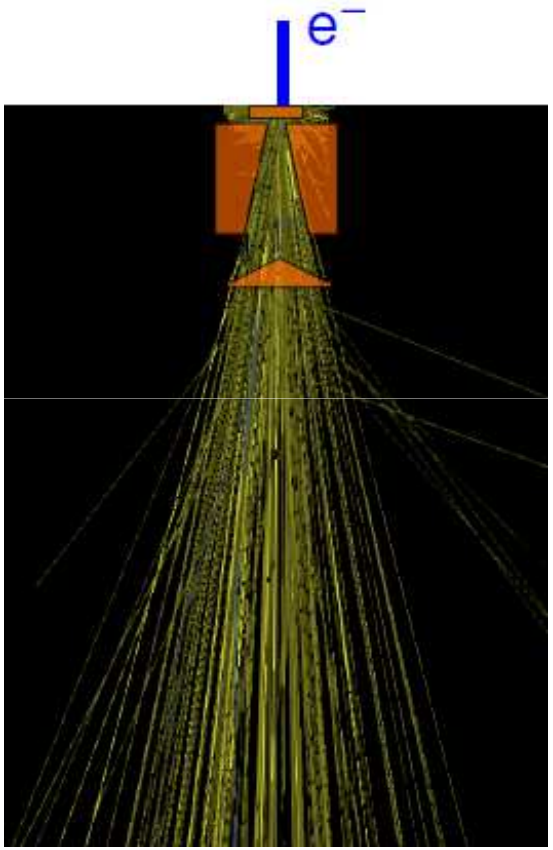
cross profiles

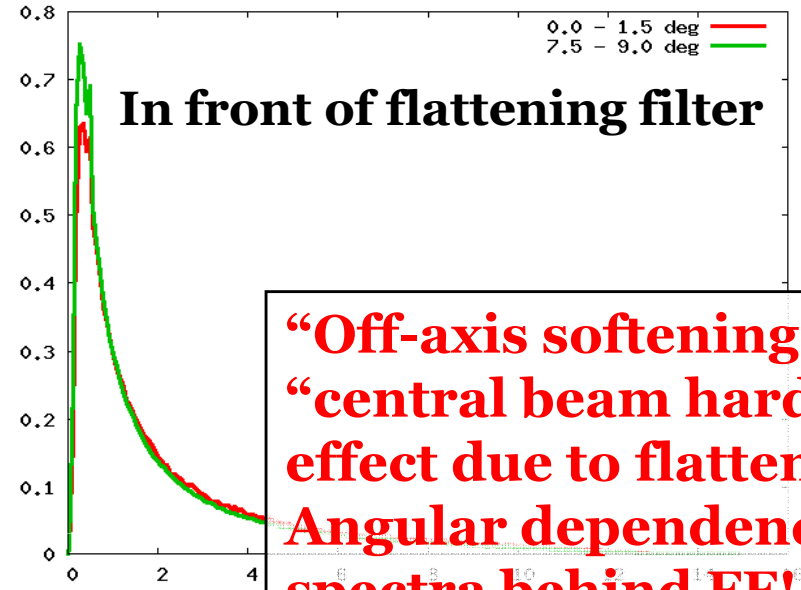


Contaminant electrons account for about 1% of the total energy fluence,
with decreasing mean energy for larger fields

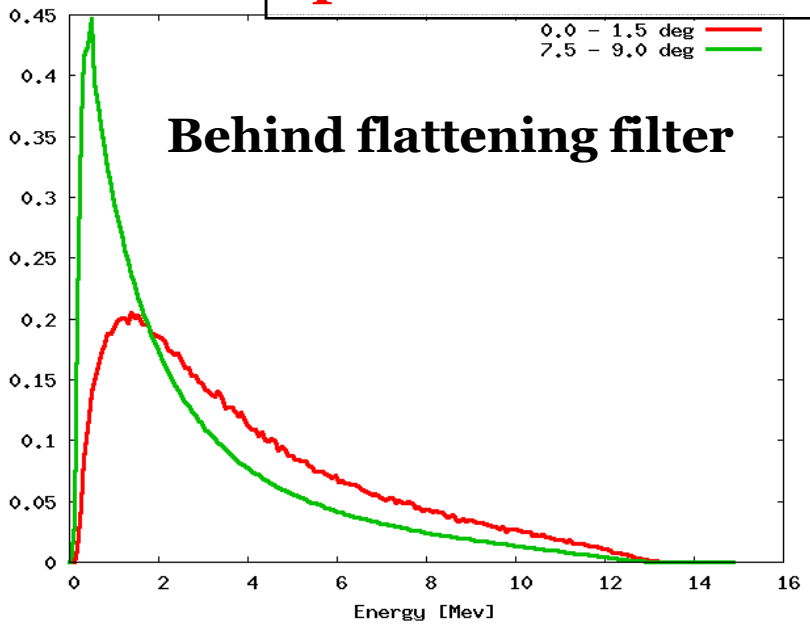
Energy spectra of primary photons: Angular dependence

courtesy M. Sikora



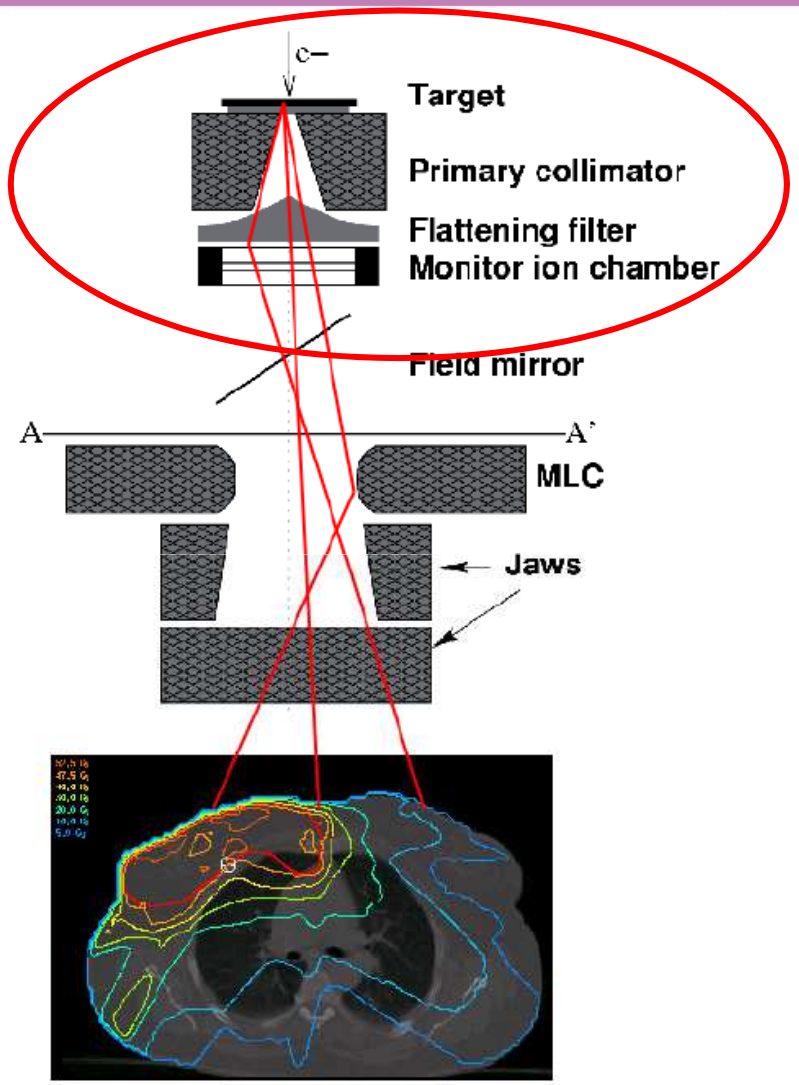


"Off-axis softening" (or: "central beam hardening") effect due to flattening filter: Angular dependence of energy spectra behind FF!



ESTRO School

Important Conclusion so far

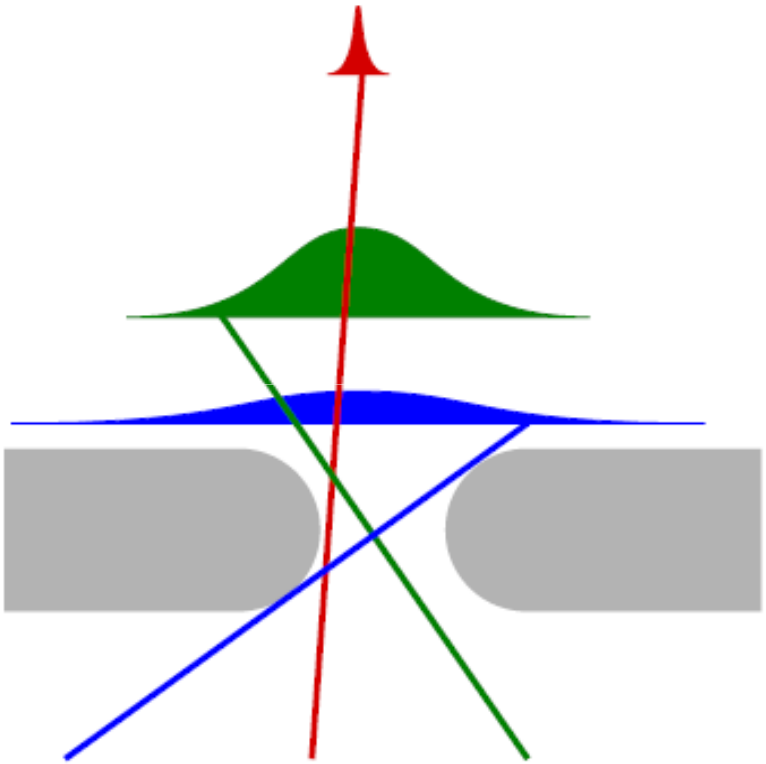


- **<u>A lot</u>** happens in the accelerator head already!

- Thus, independent of the specific algorithm (pencil beam/collapsed cone/MC/…), dose calculation in the patient can only as good as the *head model*

Usual model of the radiation source

courtesy M. Sikora



Gaussian photon sources:

primary source (→target)

secondary source (→ head scatter, predominantly from flattening filter)

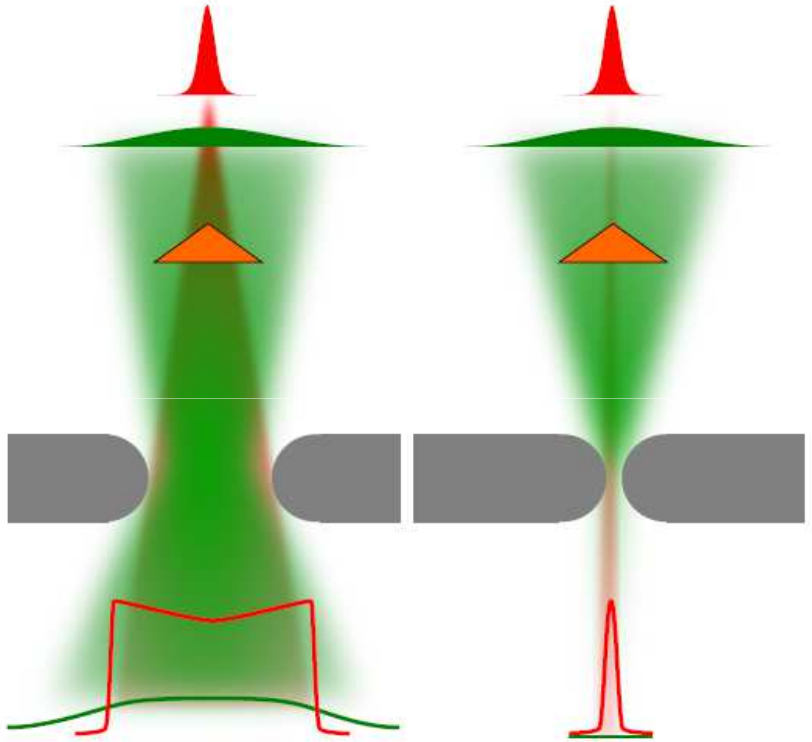
contamination electron source

- Description of energy fluence distribution
- Description of the spectra of all sources, including its angular distribution

Field-size depenence of Output-factor 'explained' …

courtesy M. Sikora

large fields:
• primary source fully visible
• OF-dependence mainly due to partial shielding of secondary source



small fields:
• secondary source almost shielded (=only minimal head scatter contribution)
• OF-dependence mainly due to partial shielding of primary source

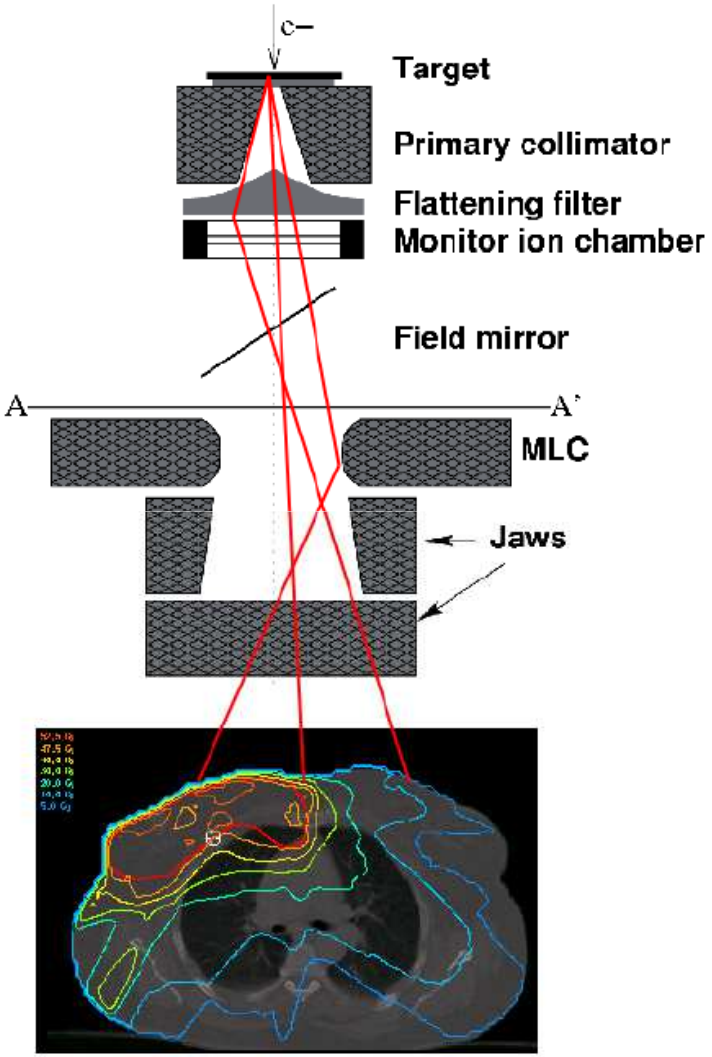
Technical background: Typical components of an accelerator head

accelerator head

particle source

beam modulators

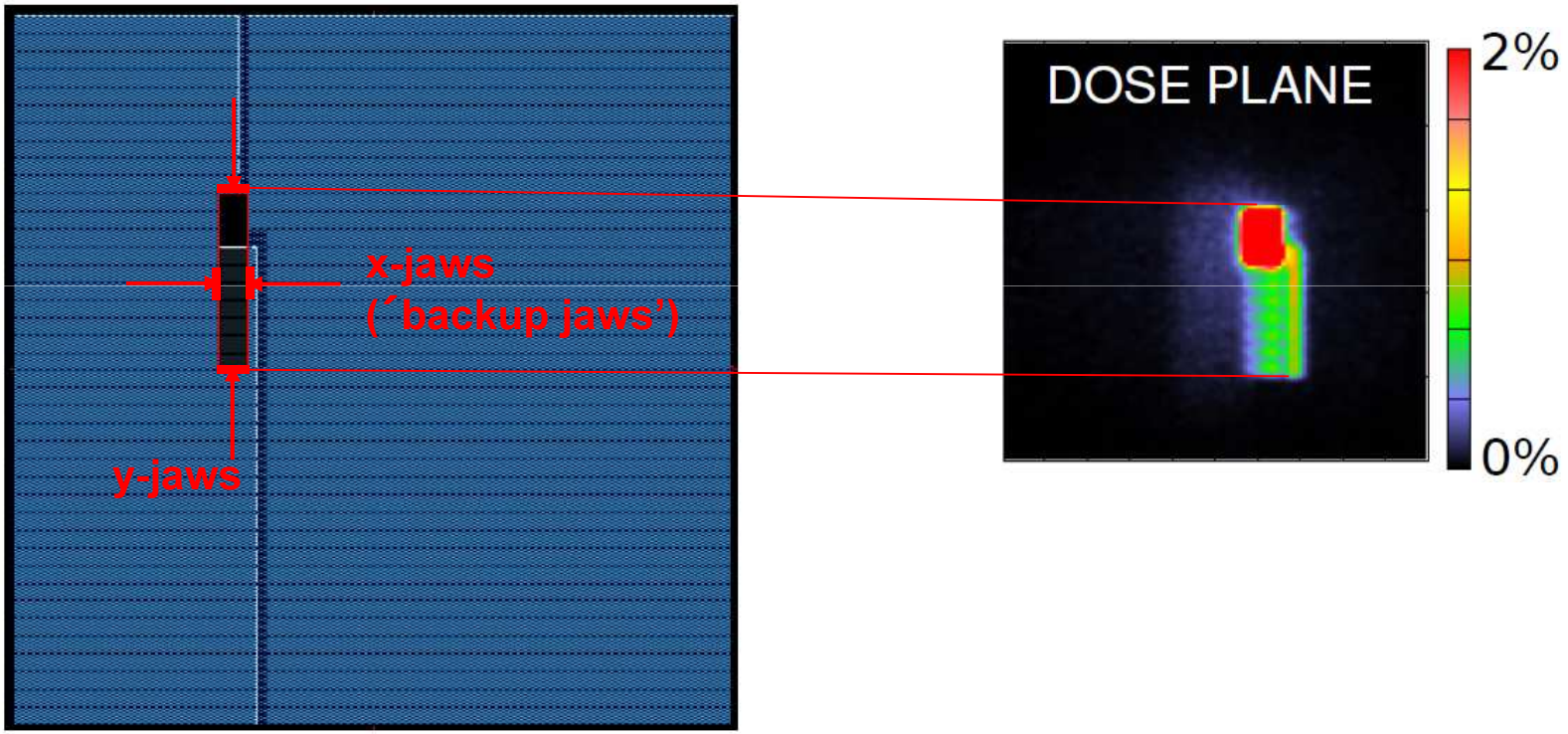
Patient



Example:
Leaf and jaw transmission, inter-leaf leakage

courtesy M. Sikora

3 x 1 cm off-axis segment



Effects of the beam modulating elements that need to be modeled for high-precision dose calculation

- leaf transmission, (jaw transmission)
- inter-leaf leakage
- leaf/jaw tip factors (influence on penumbra shapes)
- tongue-and-groove
- systematic leaf offsets
- correction factors for MLC/jaw backscatter into Monitor chamber

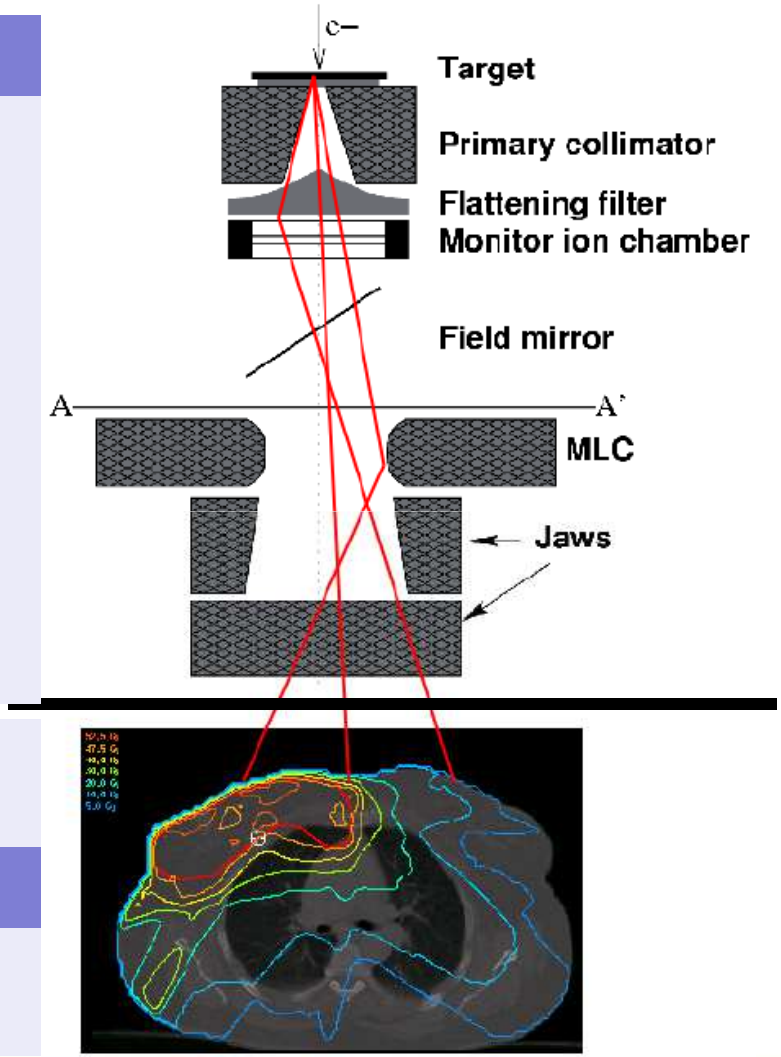
→ *most of these effects were discussed in the presentations of Marco Schwarz:*
"IMRT delivery techniques"
"TPS commissioning"

Where are we now?

accelerator head

particle source

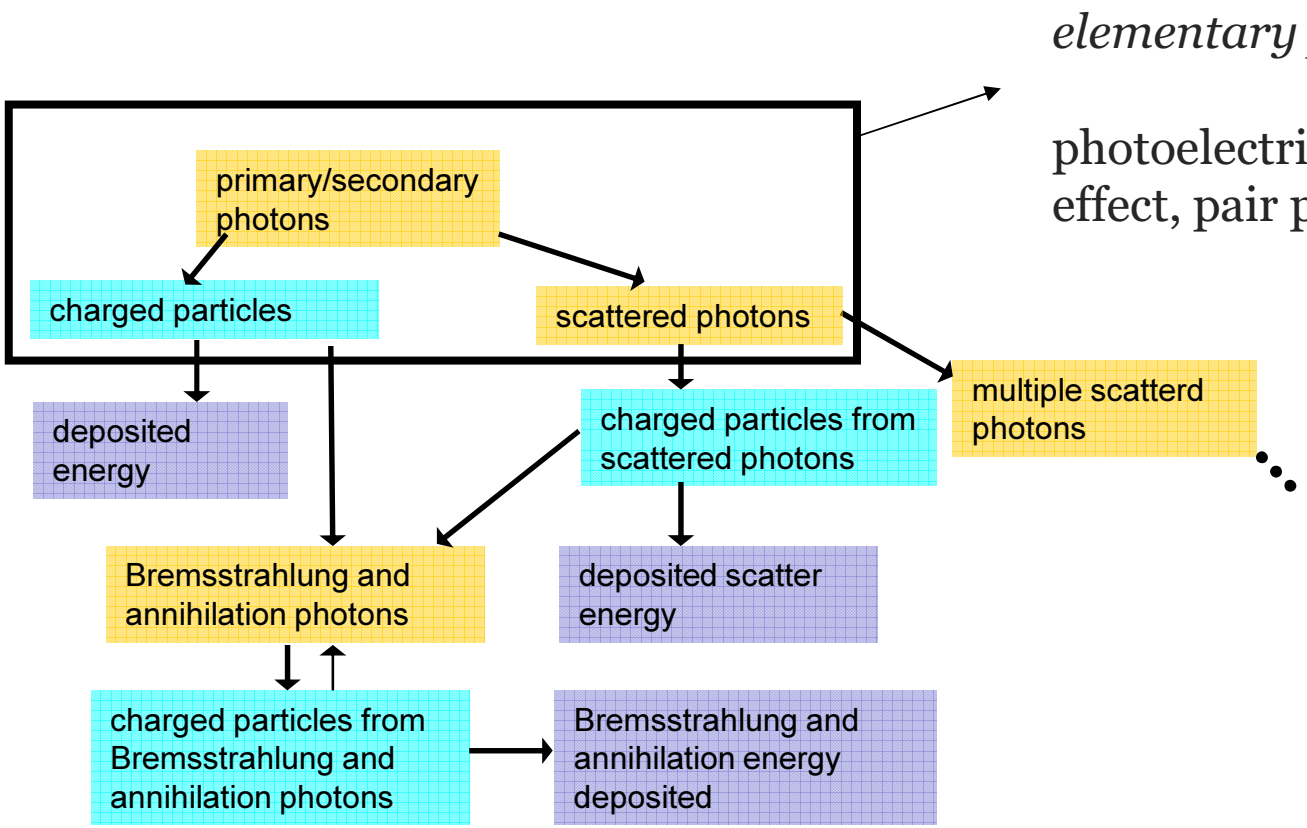
beam modulators



Patient

‘Beam phase space’

What happens in the patient…



elementary physical processes:

photoelectric effect, Compton effect, pair production

Modelling particle transport in the patient: Dose calculation methods

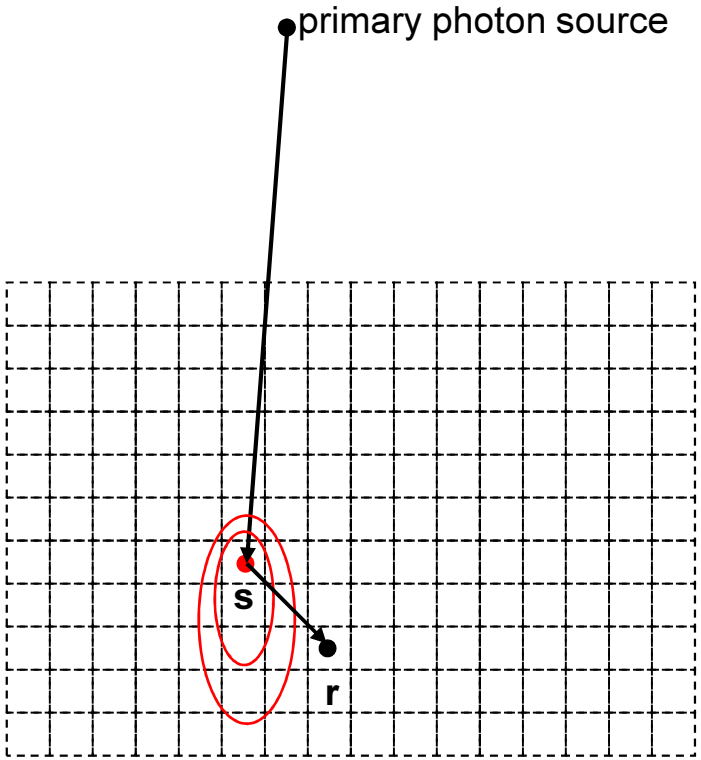
Implicit, Kernel-based methods:

- Collapsed Cone Convolution Superposition
- Pencil Beam

Explicit methods:

- stochastic particle transport modelling: Monte Carlo
- deterministic particle transport modelling: Boltzmann Transport Equation (LBTE) Solvers

Kernel-based methods: Separation of Photon-fluence and energy deposition



TERMA~photon fluence

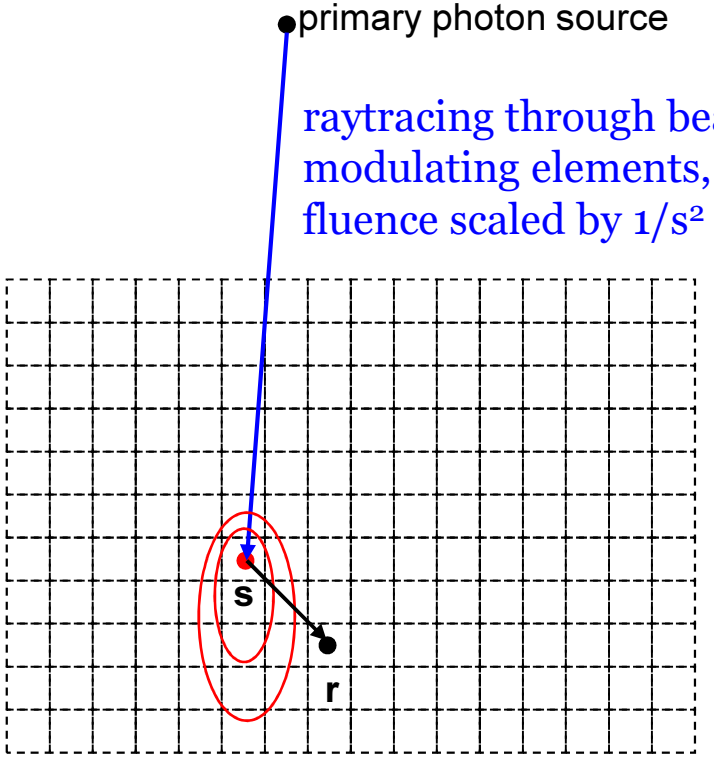
Photon transport from the primary photon source (or a secondary source) to an interaction point *s*

Energy release through physical interactions in medium

Energy transport from *s* to point *r* through secondary particles (photons and electrons)

KERNEL

Kernel-based methods: The TERMA concept



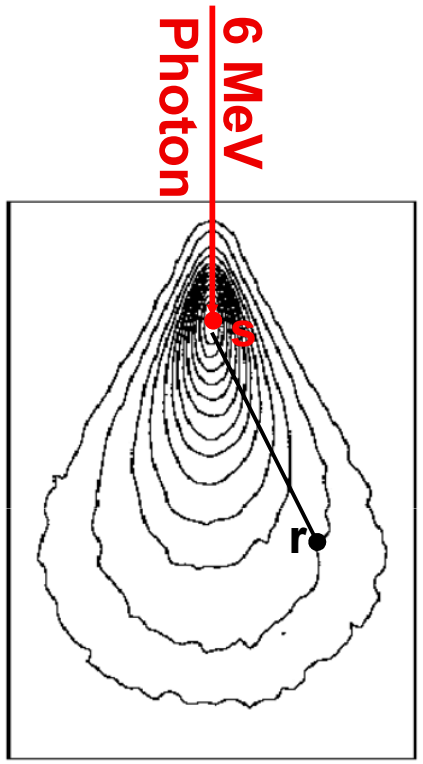
$$T(E,\vec{s}) = \underbrace{\frac{\mu(E,s)}{\rho(\vec{s})}}_{\text{mass attenuation coefficient}} \cdot \underbrace{E \cdot \Phi^{prim}(E,\vec{s})}_{\text{primary fluence}}$$

TERMA:
Total **E**nergy **R**eleased per **MA**ss

all energy released at *s* through physical interactions of the ***primary*** photon with the medium: *photons, electrons, (positrons)*

Neglected in most commercial dose calc. algorithms

Kernel-based methods: Energy deposition *point kernel*



$$h^{water}\left(E,\vec{r},\vec{s}\right) = h^{water}\left(E,\vec{r}-\vec{s}\right)$$

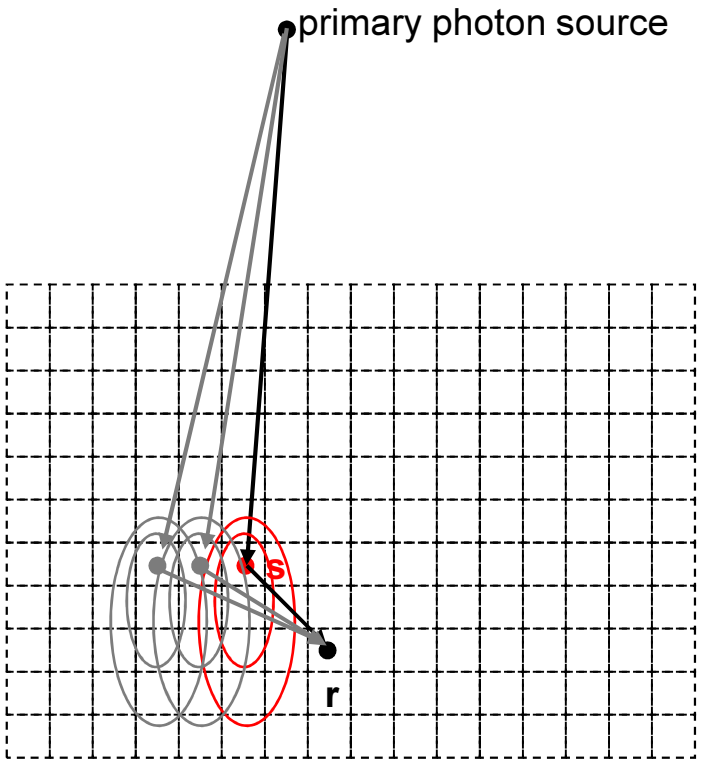
homogeneous medium (water)
→ symmetrical PSF!

The *point kernel* - also called *point spread function* (PSF)- summarizes energy deposition of all physical interaction processes:

- pre-calculation e.g. with Monte Carlo dose calculation in water
- parameterization for efficient use

Kernel-based methods: Convolution/Superposition

Simplest possible situation:
Monoenergetic incident photons,
Homogeneous medium



Dose in point *r*...

$$D(\vec{r}) = \int d^3 s \; T(\vec{s})\, h(\vec{r} - \vec{s})$$

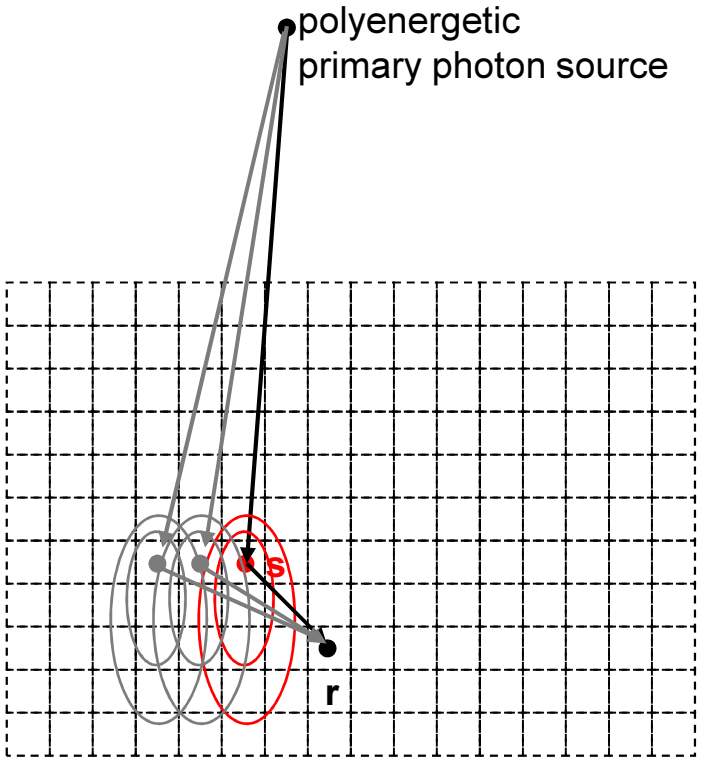
...*superposition* of all point kernels originating around all possible points *s*

mathematically: 3D-*convolution integral*

→ very efficient numerical implementation via fast fourier transform!
BUT necessary condition: point kernel independent of location (homogeneous medium)

Kernel-based methods: Convolution/Superposition

more realistic situation:
***Poly*energetic** incident photons,
Homogeneous medium (water)



Dose in point *r*...

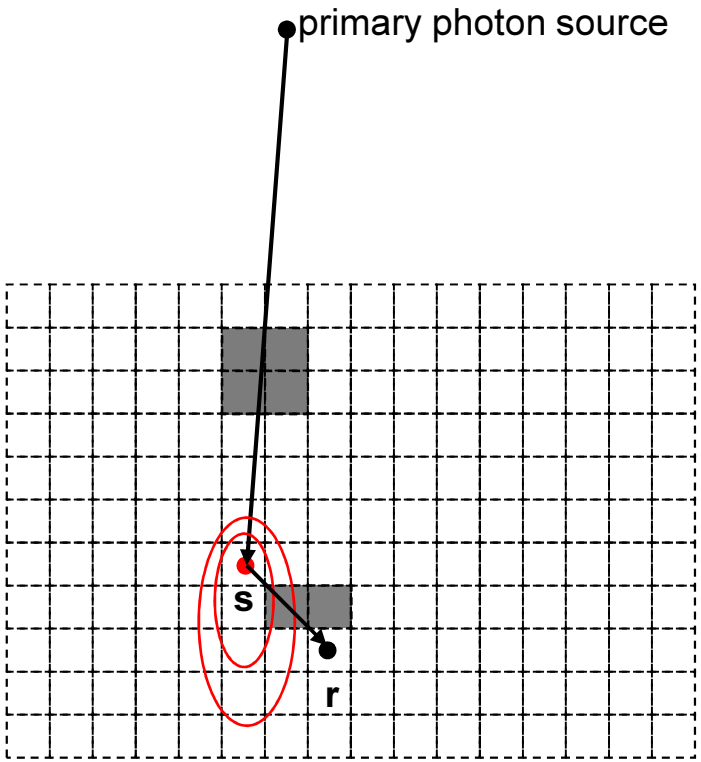
$$D(\vec{r}) = \int dE \int d^3s \; T(E,\vec{s})\, h(E,\vec{r}-\vec{s})$$

3+1D-*superposition:*

weighted superposition of dose contributions for different energies

→ numerical less expedient than the previous idealized situation

Kernel-based methods:
Dose calculation in inhomogeneous media



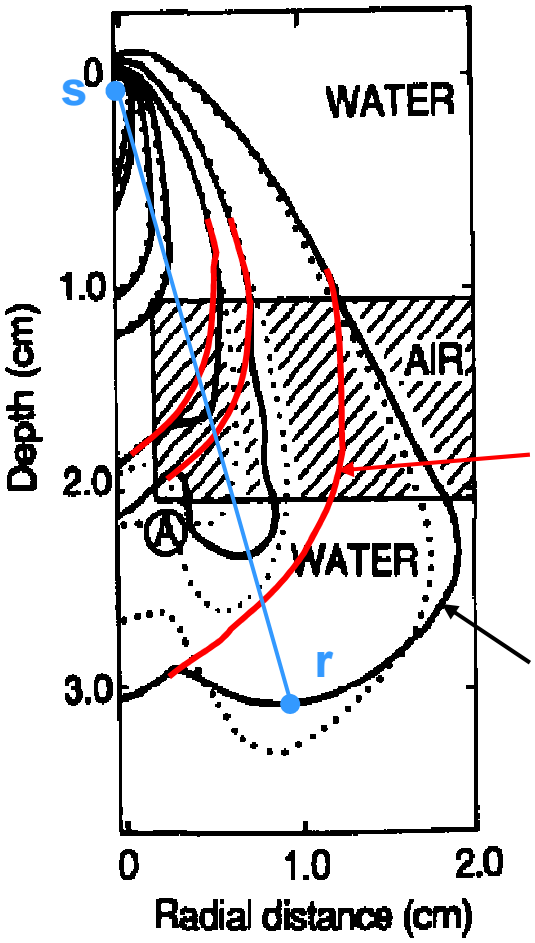
How to handle inhomogeneous media in the kernel formalism?

(1) rescale fluence according to the *effective pathlength* corrected by densities-along-the-way of raytracing

(2) 'rectilinear' density rescaling of kernel

Kernel-based methods: Rectilinear density rescaling of the kernel

adapted from Woo and Cunningham 1990 (Med. Phys. 17(2))



$$h(E,\vec{r},\vec{s}) = \frac{\rho(\vec{r})}{\rho_{water}} \cdot \bar{\rho}^{2}{}_{rel}(\vec{r},\vec{s}) \cdot h^{water}\left(E, \bar{\rho}_{rel}(\vec{r},\vec{s}) \cdot (\vec{r}-\vec{s})\right)$$

this would be the kernel dose in a homogeneous medium: h^{water}!

...and after rectilinear rescaling

'Rectilinear' rescaling with the *mean relative density* along the path between s and r:

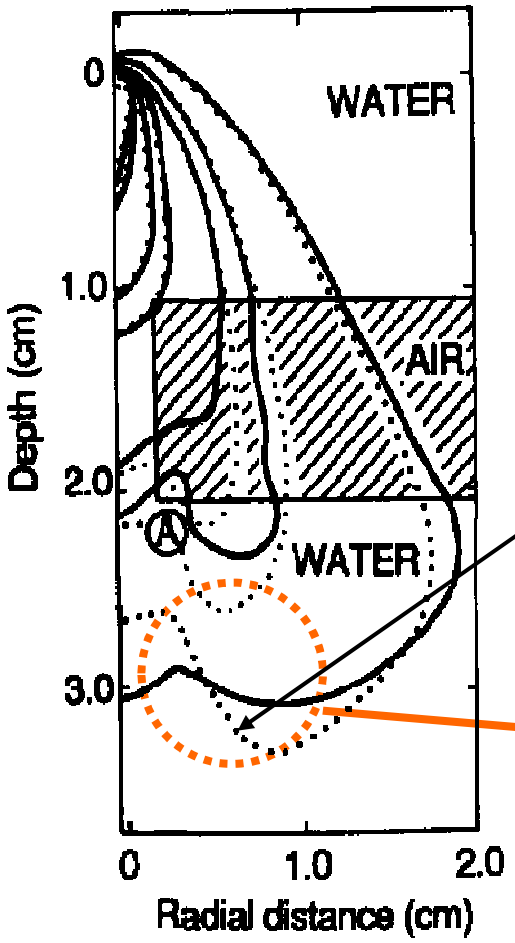
$$\bar{\rho}_{rel}(\vec{r},\vec{s}) = \frac{1}{|\vec{r}-\vec{s}|}\int_{\vec{r}}^{\vec{s}} d\vec{s}' \, \frac{\rho(\vec{s}')}{\rho_{water}}$$

→ The point kernel dose *is dependent on location* inside of inhomogeneous media (patient!)

→ efficient numerical dose calculation w. fast fourier transform not possible without further approximations

Kernel-based methods: Rectilinear density rescaling of the kernel

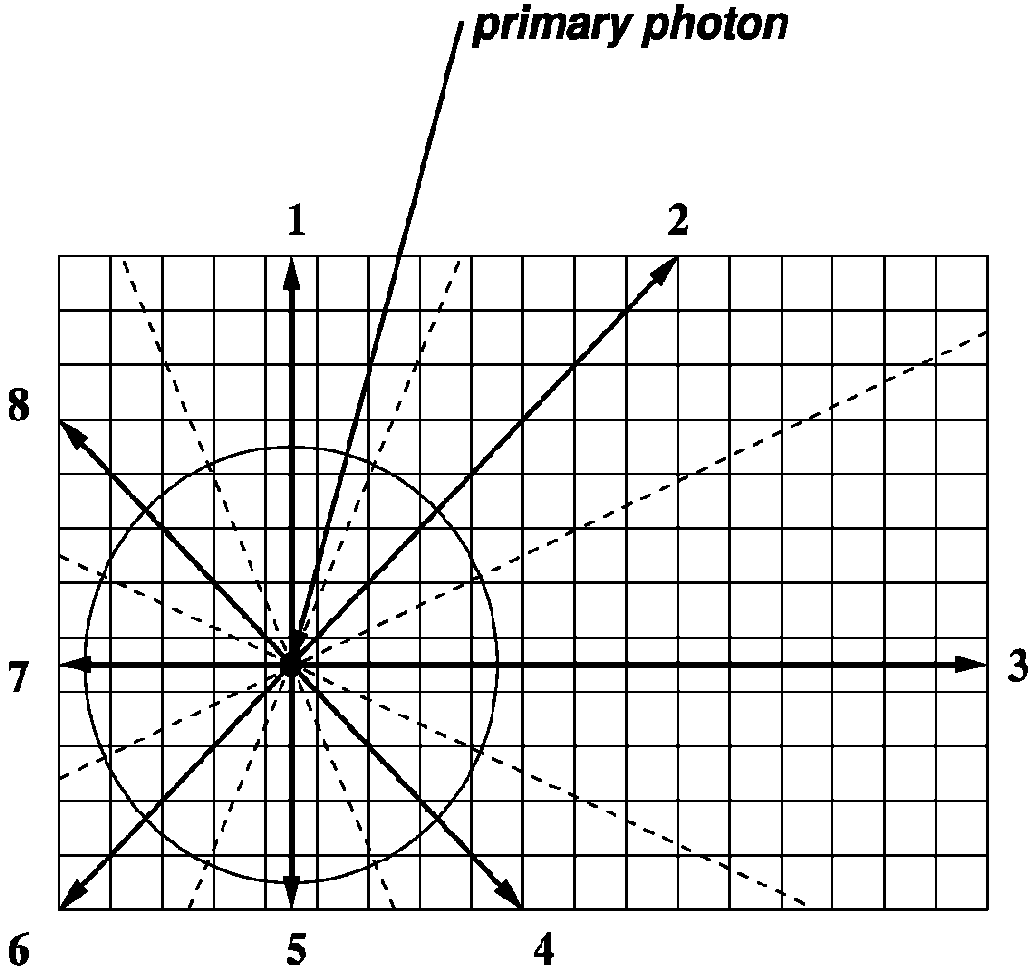
Woo and Cunningham 1990 (Med. Phys. 17(2))



…dotted isodose lines: 'exact' point kernel dose from Monte Carlo calculations

Electrons do not move linearly on straight tracks!
Multiple scattering effects not exactly handled

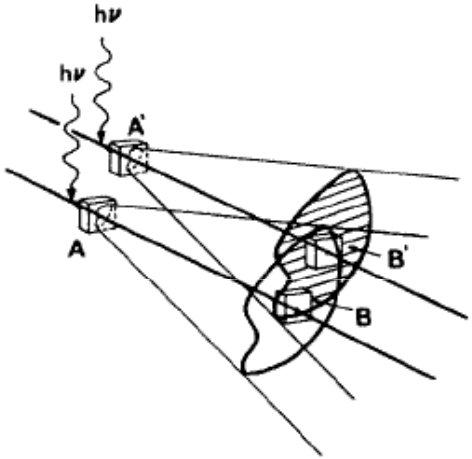
Kernel-based methods:
'Collapsed Cone' approximation for efficient density rescaling

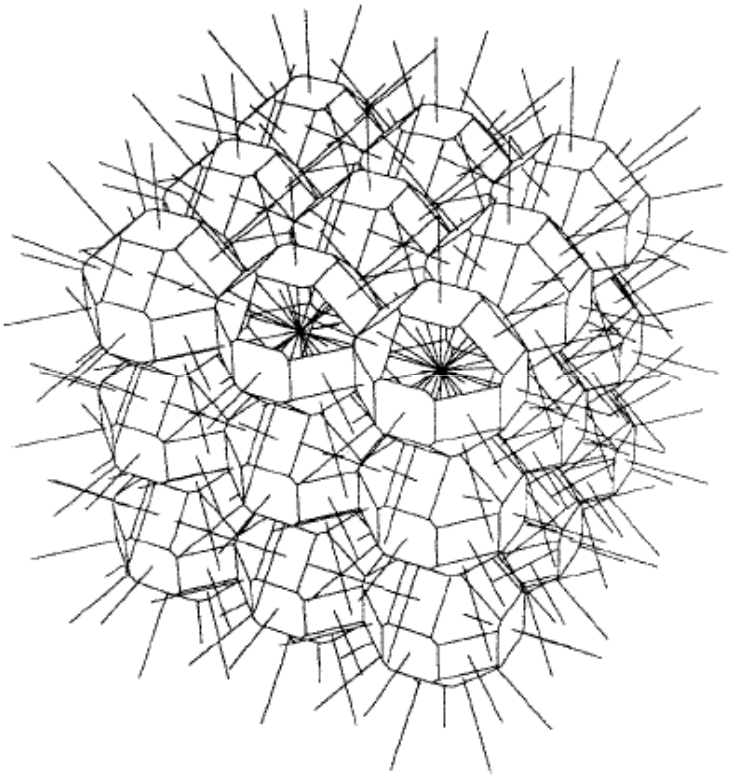


- Discretization of the point kernel into angular sectors ('cones')
- density rescaling only done for voxels on the central cone axis, i.e. the cones are 'collapsed' to their central axis
- precision and calculation time depend on resolution

Kernel-based methods:
'Collapsed Cone' approximation for efficient density rescaling

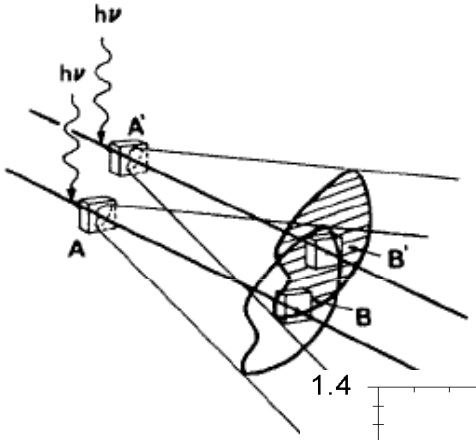
Ahnesjö and Aspradakis
1999 (PMB 44(11))

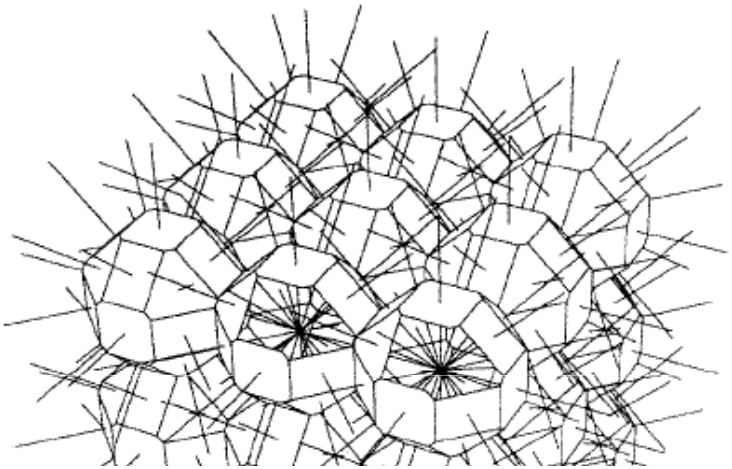


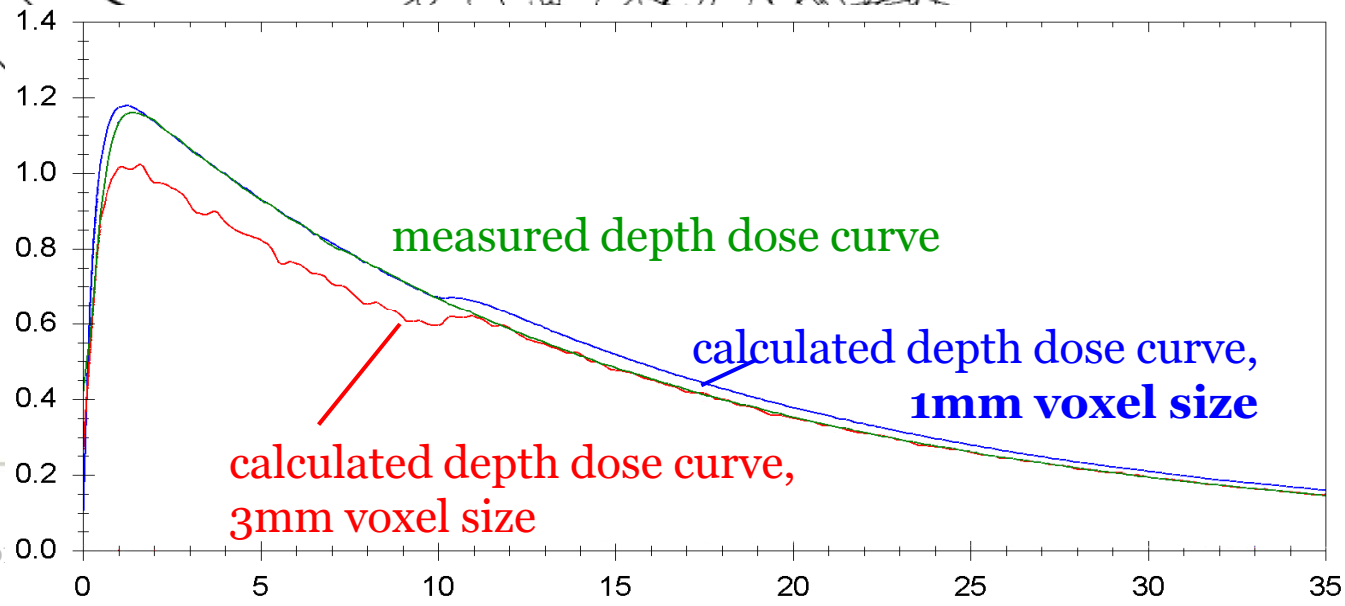


Kernel-based methods:
'Collapsed Cone' approximation for efficient density rescaling

Ahnesjö and Aspradakis
1999 (PMB 44(11))





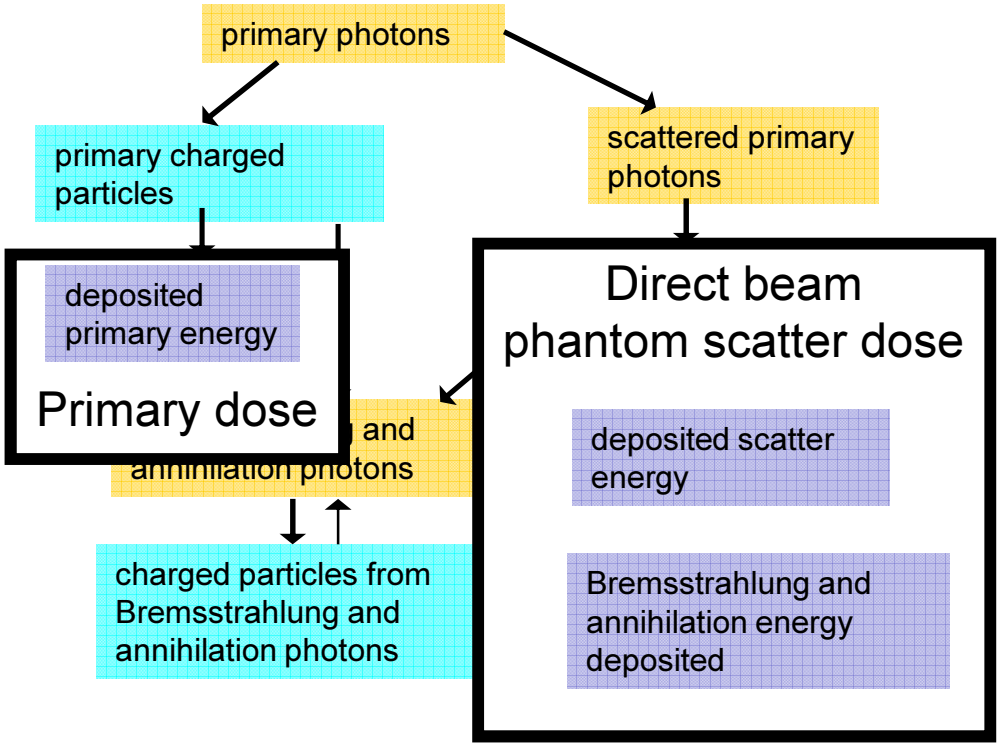


Kernel-based methods:
'Collapsed Cone' approximation for efficient density rescaling

Further 'smart' approximations for efficient numerical implementation:

- separate treatment of deposited primary enery and deposited phantom scattered dose

- further approximations for polyenergetic photon beams (details depend on implementation): Energy-averaged TERMA and point kernel; approximate or no modelling of beam hardening; ...



More details: Ahnesjö and Aspradakis 1999 (PMB 44(11))

Important to realize:
There is not >>THE<< Collapsed-Cone algorithm

The specific accuracy of different *implementations* of Collapsed Cone algorithms does vary!

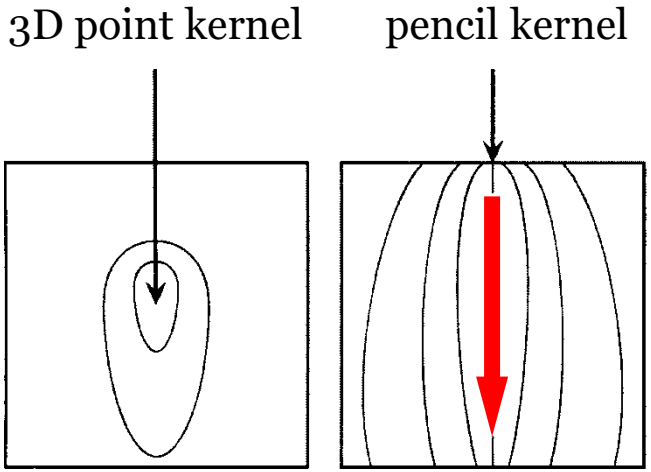
In fact, this is also true for Pencil Beam, and – to some extent (esp. head model) – for Monte Carlo…

Further readings e.g…

- Vanderstraeten et al. 2006: Accuracy of patient dose calculation for lung IMRT: A comparison of Monte Carlo, convolution/superposition, and pencil beam computations. Med. Phys. 33(9), 3149-3158

- Huang et al. 2013: Investigation of various energy deposition kernel refinements for the convolution/superposition method. Med. Phys. 40, 121721

Kernel-based methods:
2D-superposition methods: Pencil Kernel algorithms



Integrate 3D point kernels along beam direction ('pre-convolution'):

→ patient-specific *local* lateral scatter cannot be modelled well!

Dose calculation becomes a 2D-integration (superposition integral):

$$D(\vec{r}) = \int d^2s \; \Psi(\vec{s}) \; p(\vec{r}, \vec{s})$$

$\Psi(\vec{s})$: Fluence on the patient surface

$p(\vec{r}, \vec{s})$: Pencil Beam kernel

Kernel-based methods:
2D-superposition methods: Pencil Kernel algorithms

As for 3D point kernel methods, the superposition integral is a convolution integral, if the pencil kernel in spatially invariant (**homogeneous media**)

→ **very fast dose calculation** using Fast Fourier Transformation

approx. ***dose deposition in the patient***

Approximate methods to handle **inhomogeneous media:**

- density corrections: mainly effective path length rescaling along beam direction
- simplified modelling of phantom scatter: local *lateral scatter* effects not modelled correctly
- neglect energy spectrum changes
- simplified modelling of head scatter: requires *correction factors for the output-factor*

...and approximations to the ***head model***

Modelling particle transport in the patient: Dose calculation methods

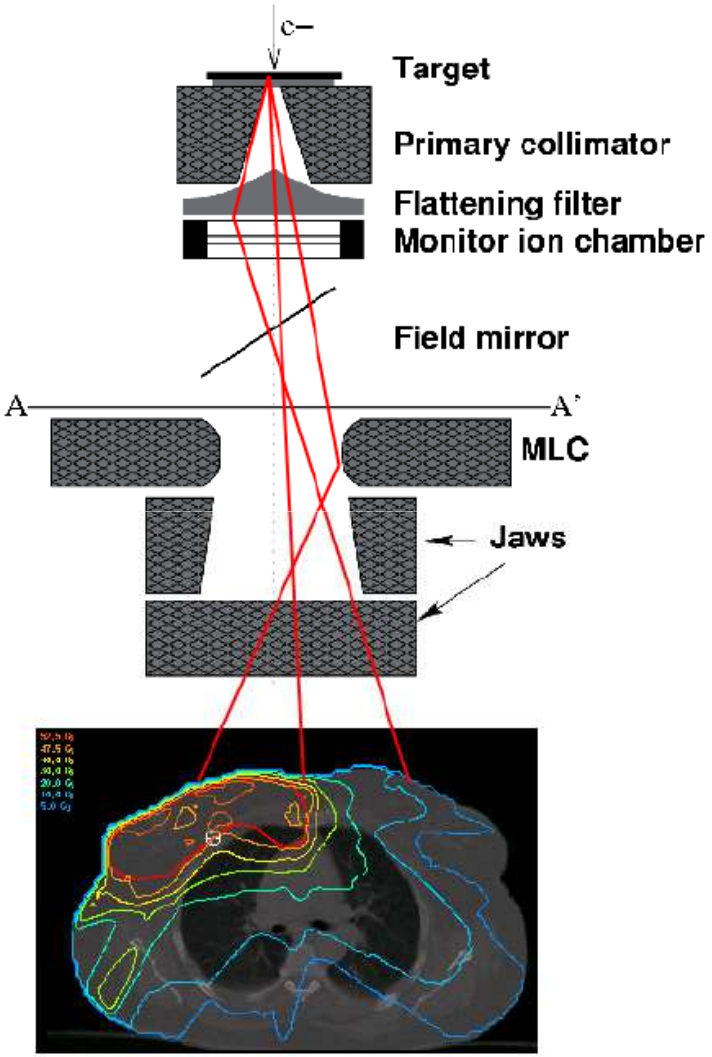
Implicit, Kernel-based methods:

- Collapsed Cone Convolution Superposition
- Pencil Beam

Explicit methods:

- stochastic particle transport modelling: Monte Carlo
- deterministic particle transport modelling: Boltzmann Transport Equation (LBTE) Solvers

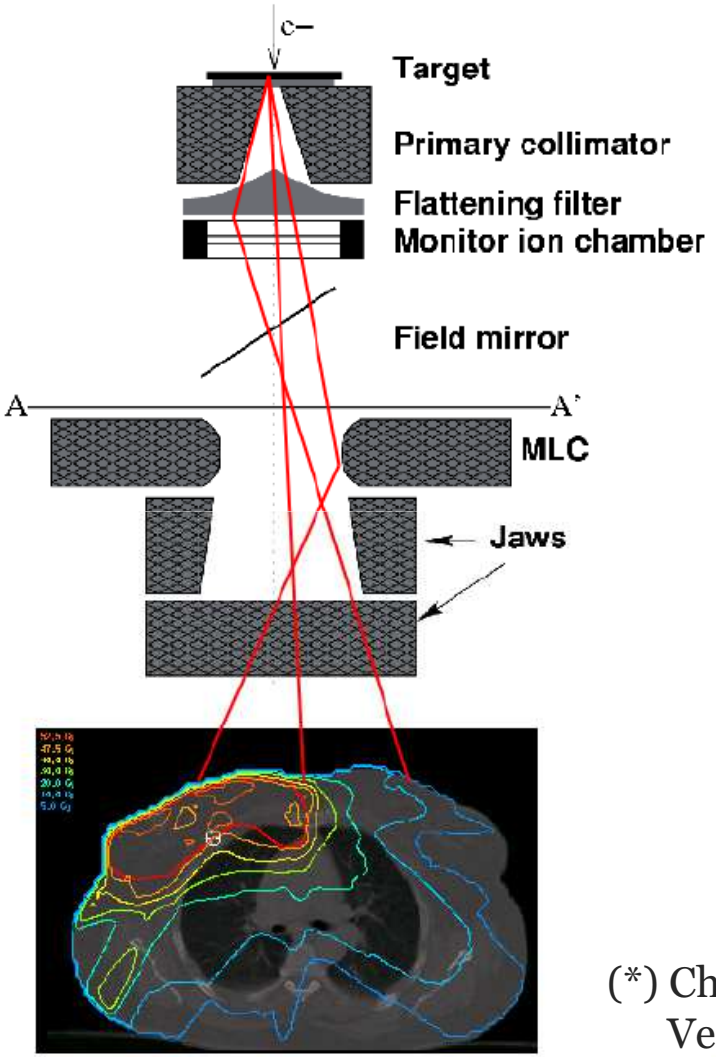
Monte Carlo Dose Calculation



'Full' Monte Carlo methods:

Explicit simulation of all physical interactions of all particle histories (photons, electrons, positrons and cross-sections of interactions)
starting from electrons hitting the target
ending with all local elementary dose depositions in the patient, considering exact material compositions

Monte Carlo Dose Calculation



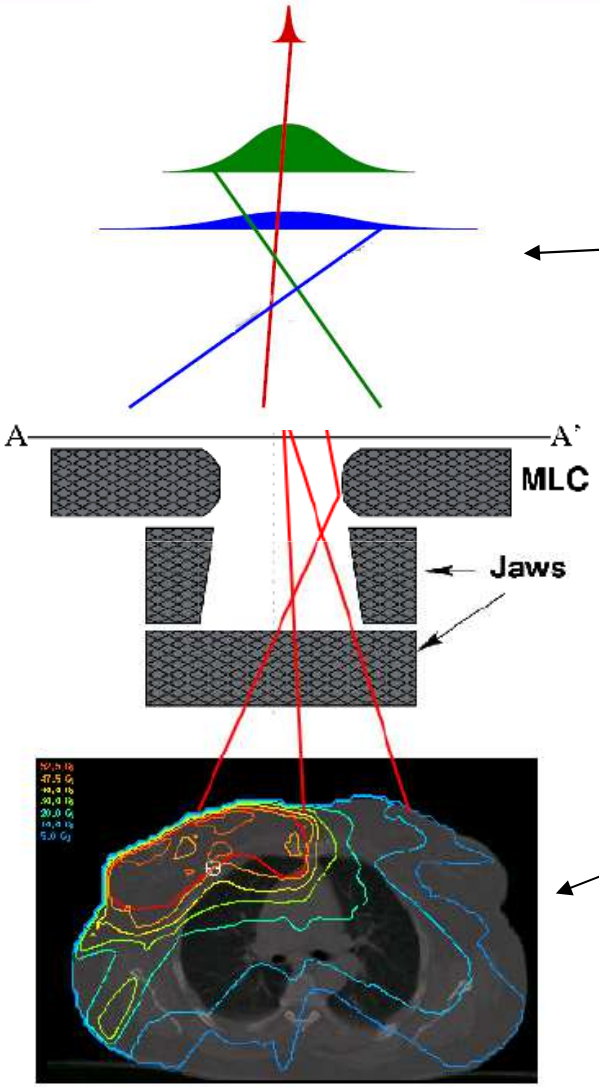
'Full' Monte Carlo meth

Explicit simulation
interactions of al
histories (pho ,
positrons a ns of
interacti
starti ns hitting the
tar
local elementary
ions in the patient,
g exact material
sitions

'Gold standard' (*)
(if all geometries, material compositions etc. are correctly modelled, which is a challenge in itself!)
BUT: very time consuming

(*) Chetty et al. 2007, Med. Phys. 34(12)
Verhaegen and Seuntjens 2003, PMB 48(21)
Fraass et al. 2003, Med. Phys. 30(12)

Monte Carlo Dose Calculation



Fast Monte Carlo codes:

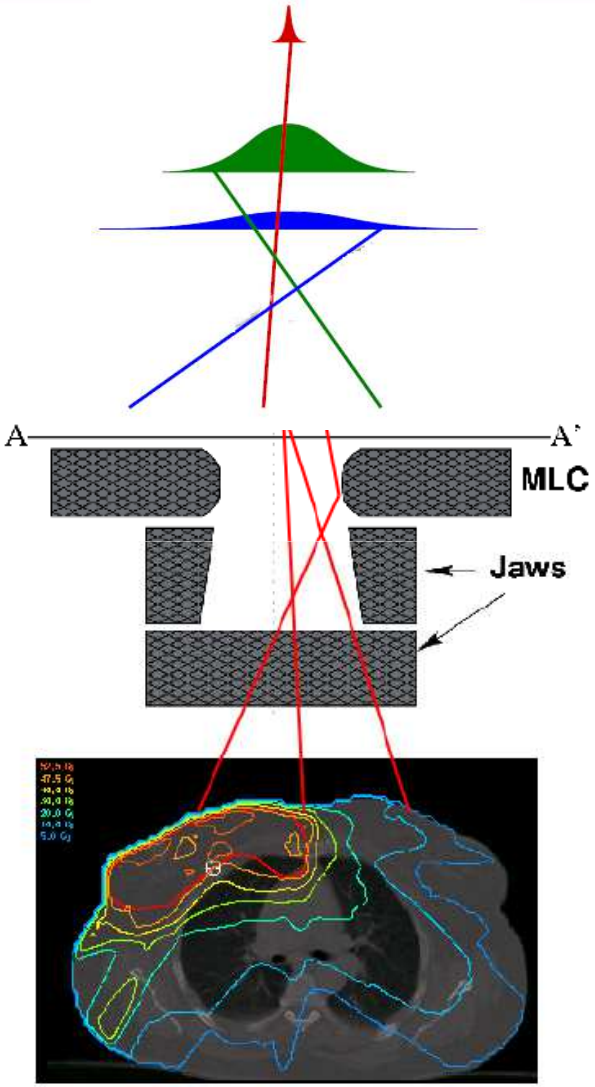
Virtual Source Model (VSM)

efficient (approximate) modelling of effects of beam modulating elements (transmission maps etc.)

In the patient: variance reduction techniques, history repetition; optimized for voxel geometries; optimized for energy range typical in RT and material compositions in human tissue, ...

see e.g. Fippel 1999, Med. Phys. 26(8)
Kawrakov and Fippel 2000, PMB 45(8)

Monte Carlo Dose Calculation



Fast Monte Carlo codes·

Virtual Source Mod

potentially eff
effects of b
element etc.)

In ·· .eduction
petition;
. geometries;
.ergy range typical
.terial compositions
i. .ssue, ...

...MUCH faster and for all practical purposes in RT (typical energy range 6~20MeV, human tissue and tissue-like materials) same accuracy as full Monte Carlo

see e.g. Fippel 1999, Med. Phys. 26(8)
Kawrakov and Fippel 2000, PMB 45(8)

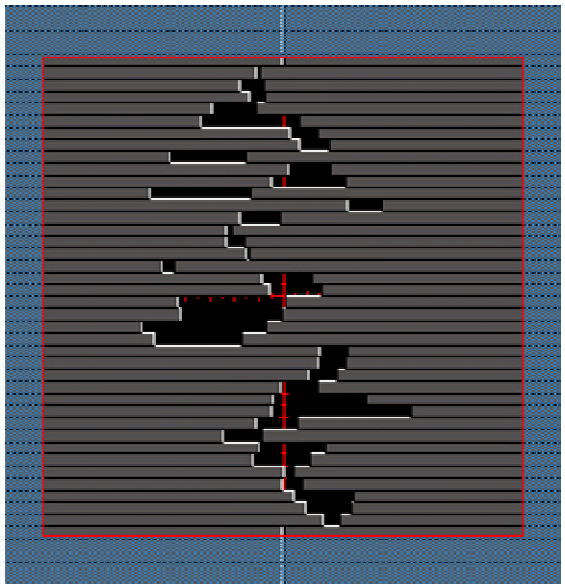
Special issues for Rotational IMRT

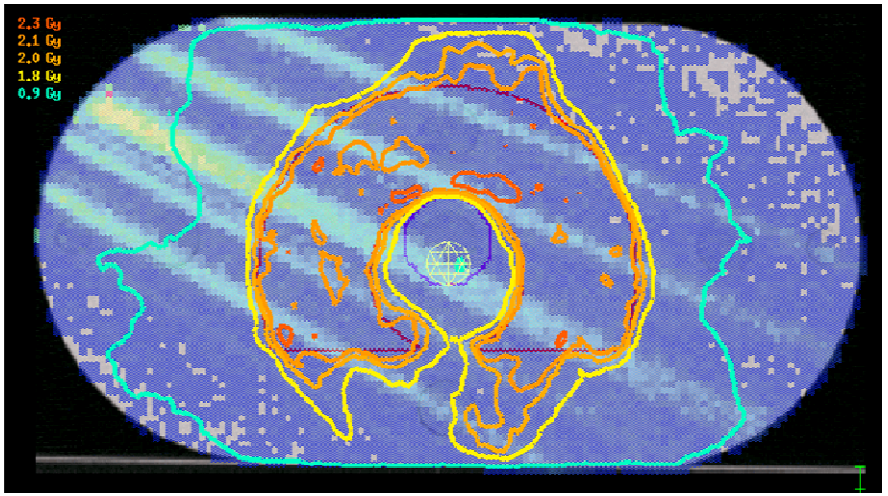
courtesy C. Fiorino, M. Alber

Modern IMRT techniques, especially rotational IMRT:

- Complexity of field shapes are a challenge for dose calculation algorithms
- simple field-size dependent Output-Factor corrections (e.g. Pencil Beam) difficult!

→ good head model required!





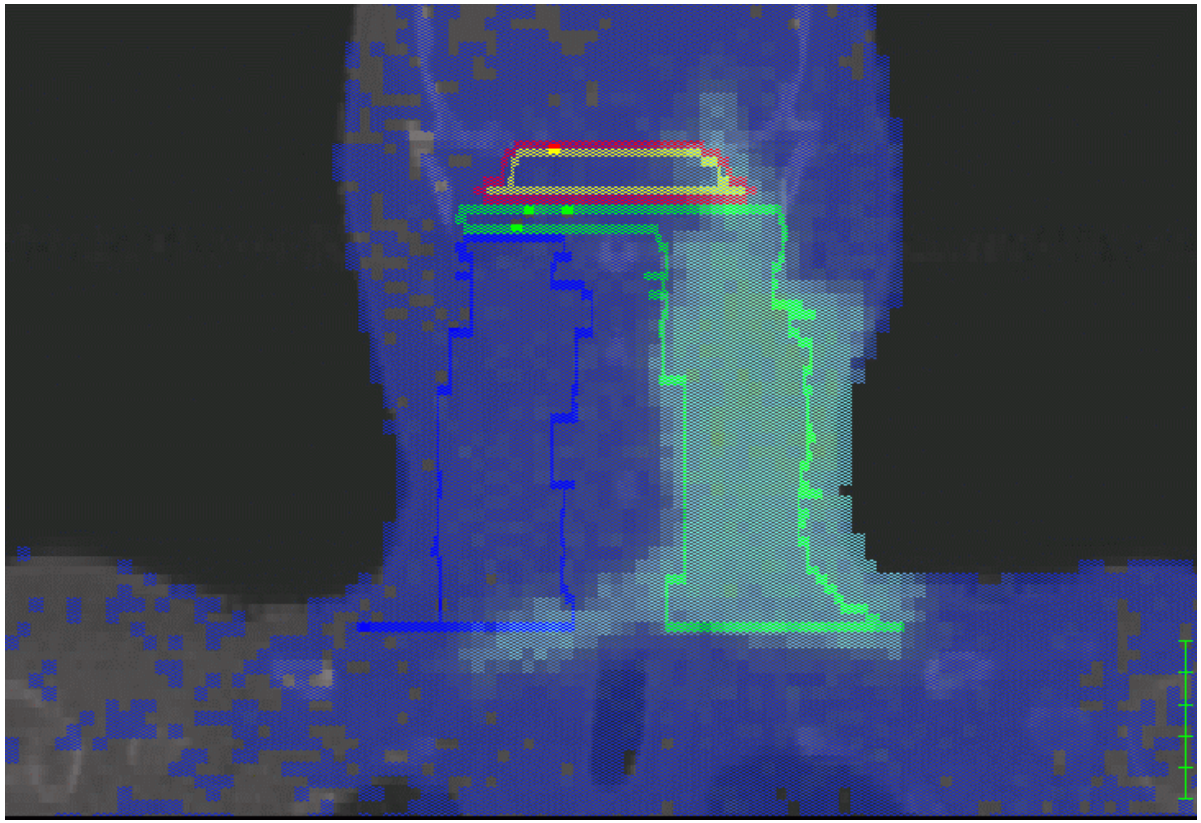
Treatment field obtained from Varian RapidArc and its dose distribution in the patient

Special issues for Rotational IMRT: Discretized Arc vs. Continuous Arc Dose Calculation

courtesy M. Alber

Most algorithms calculate the dose of an Arc as sum of segment dose contributions from *discrete beam angles*

Monte Carlo: Beam angle can be treated as additional random variable!
→ simulation of the rotating, dynamically modulated beam without discretization of the motion



Pinnacle SmartArc treatment plan, recomputed with Monte Carlo

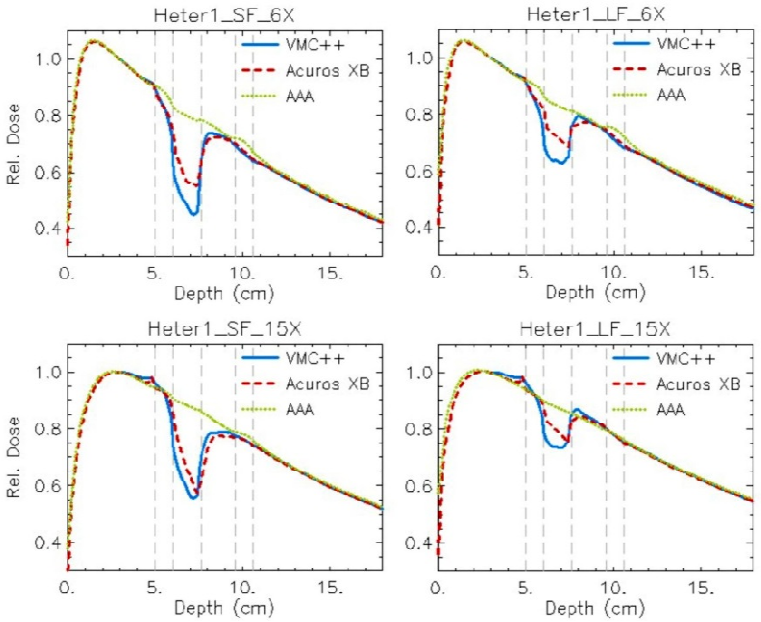
HYPERION

ESTRO School

Linear Boltzmann Transport Equation (LBTE) Solvers

Dose Calculation as Energy Transport: *Explicit, deterministic 'solution'* of the Boltzmann equation vs. its *stochasic 'solution'* via Monte Carlo.

- Raytracing of incident photons and electrons from virtual sources in the accelerator head
- same head model as other 2-3-4D superposition algorithm can be used
- approximations in modelling of phantom scatter: weakly variable, thus rough discretization of raytracing possible
- *explicit modelling of local electron transport* — no kernel density rescaling necessary
- first implementation in clinical TPS as Varian Acuros XB



from Fogliata et al. 2011 (6:82)

further reading…

about
Monte Carlo…

sources the most demanding candidate for direct use of Monte Carlo dose calculations. Long calculation times are a pronounced problem in conformal therapy where optimization of dose distributions using iterative algorithms requires the dose to be recomputed many times during the planning procedure. Hence, it is likely that for another decade photon Monte Carlo will be used for beam characterization, benchmarking and other special studies rather than routine treatment planning. Nevertheless, a very ambitious Monte Carlo treatment planning

Anders Ahnesjö and Maria Mania Aspradakis 1999:
Dose calculations for external photon beams in radiotherapy
Phys. Med. Biol. **44**(11), R99-R155

…and LDPE
Solvers…

number of iterations is proportional to the number of interactions. Hence, to completely solve the dose deposition in photon beams numerically by purely deterministic methods the electron transport must be solved by a more suitable method such as the phase space evolution originally developed for dose calculation in electron beams (Huizenga and Storchi 1989, McLellan *et al* 1992, Janssen *et al* 1997). The complexity and computational burden for such a complete deterministic approach would probably exceed that of the Monte Carlo approach (Börgers 1998).

Summary and Conclusions

- As clinical **users**, we don't have to know all details of dose calculation algorithms

The few things you should know and be aware of:

- Major effects happen in the accelerator head already
  – importance of a good head model!
- Pencil beam algorithms are very fast, but have major problems with accuracy in regions of the body with large density inhomogenieties (lung/thorax!, head-and-neck)
- thus, the final dose calculation should be done with Collapsed Cone algorithms, Linear Boltzmann Transport Equation Solvers or Monte Carlo algorithms
- be aware: There is not "THE" Pencil Beam or "THE" Collapsed Cone algorithm
  – accuracy and performance depend on vendor-specific implementational details
- finally, and most importantly: *Always keep a critical eye on what is calculated!* (Appendix)

Appendix

Dose calculation issues ‚in practice‘

Dose calculation issues ‚in practice‘

Even when using allegedly ‘precise’ dose calculation algorithms:

DON’T TRUST YOUR DOSE TOO MUCH!

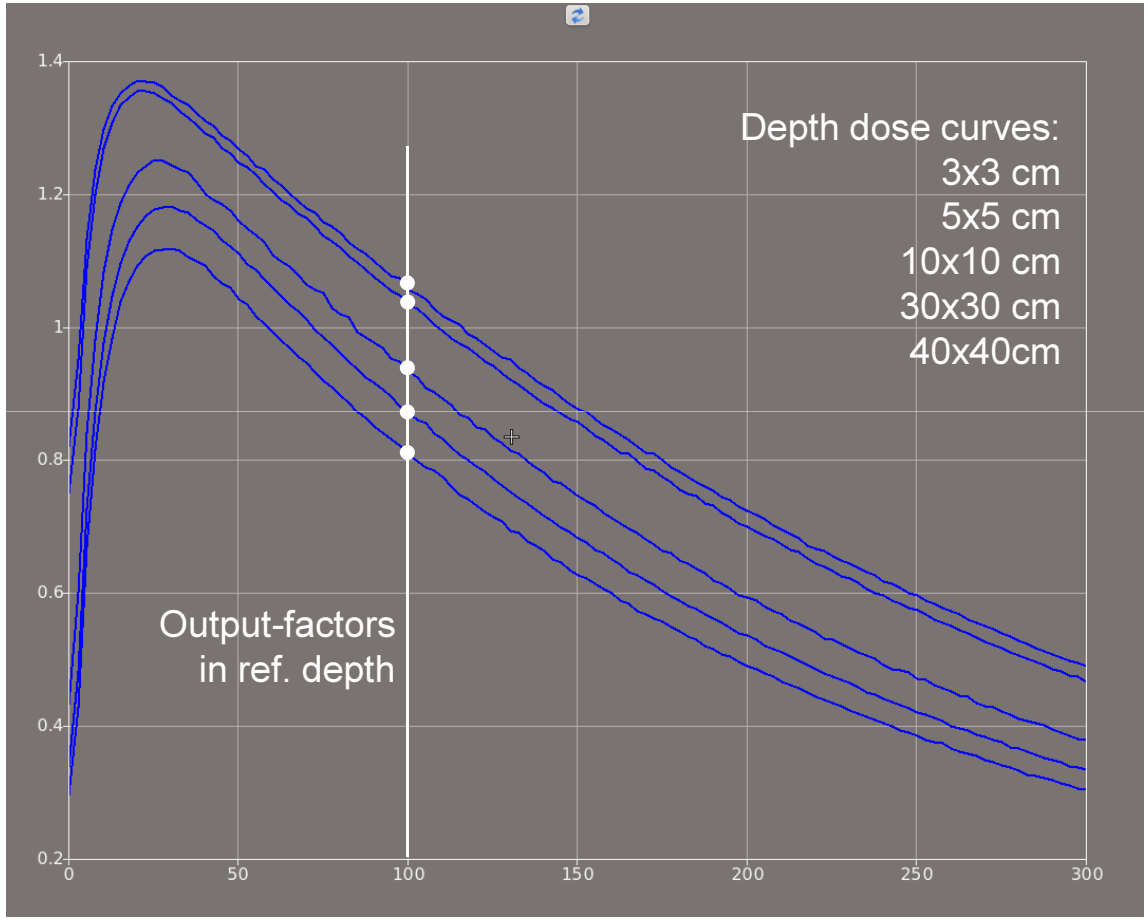
[i.e. always keep a critical eye on what is calculated]

Some examples for situations which need special care:

- small fields, irregular shaped fields (esp. off-axis), …
- potential systematic errors in measured base-data
- air in rectum
- dose calculation in lung in presence of breathing motion (‘4D’ dose)
- dose absorption in the patient table/couch
- dose calc in presence of CT artifacts: dental&hip implants
- HU errors in CT-calibration

Base-data for dose-calculations algorithms

Key-input for all types of dose-calculation algorithms: DDCs, OFs…



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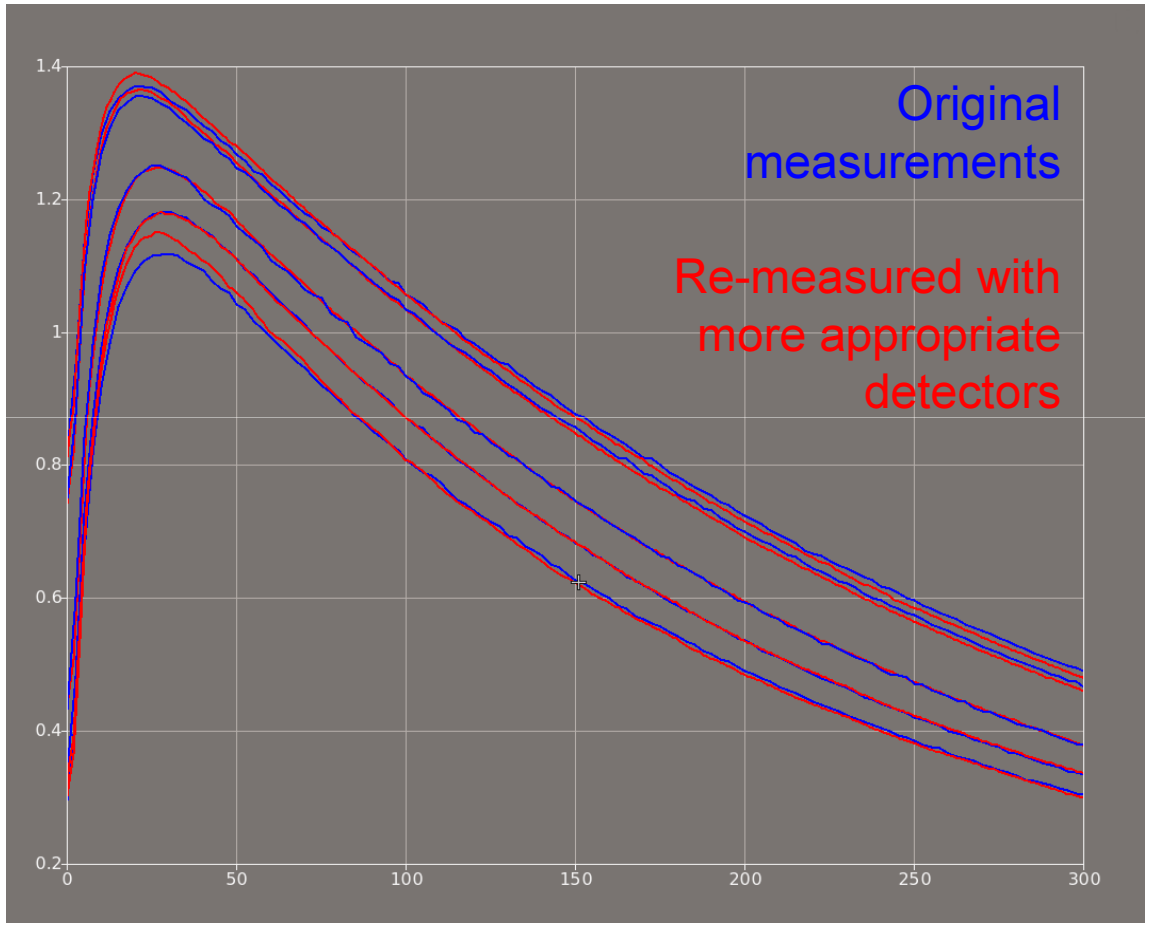
Base-data for dose-calculations algorithms

...a classical *garbage-in garbage-out* problem:



...non-trivial optimal choice of detector(s) (ionisation chamber, diode, diamond, ...):

- Energy-dependence
- Field size
- DDC vs. cross-profile
- ...

ESTRO School

Dose calculation issues ‚in practice‘: Prostate RT: Rectal gas filling in planning CT

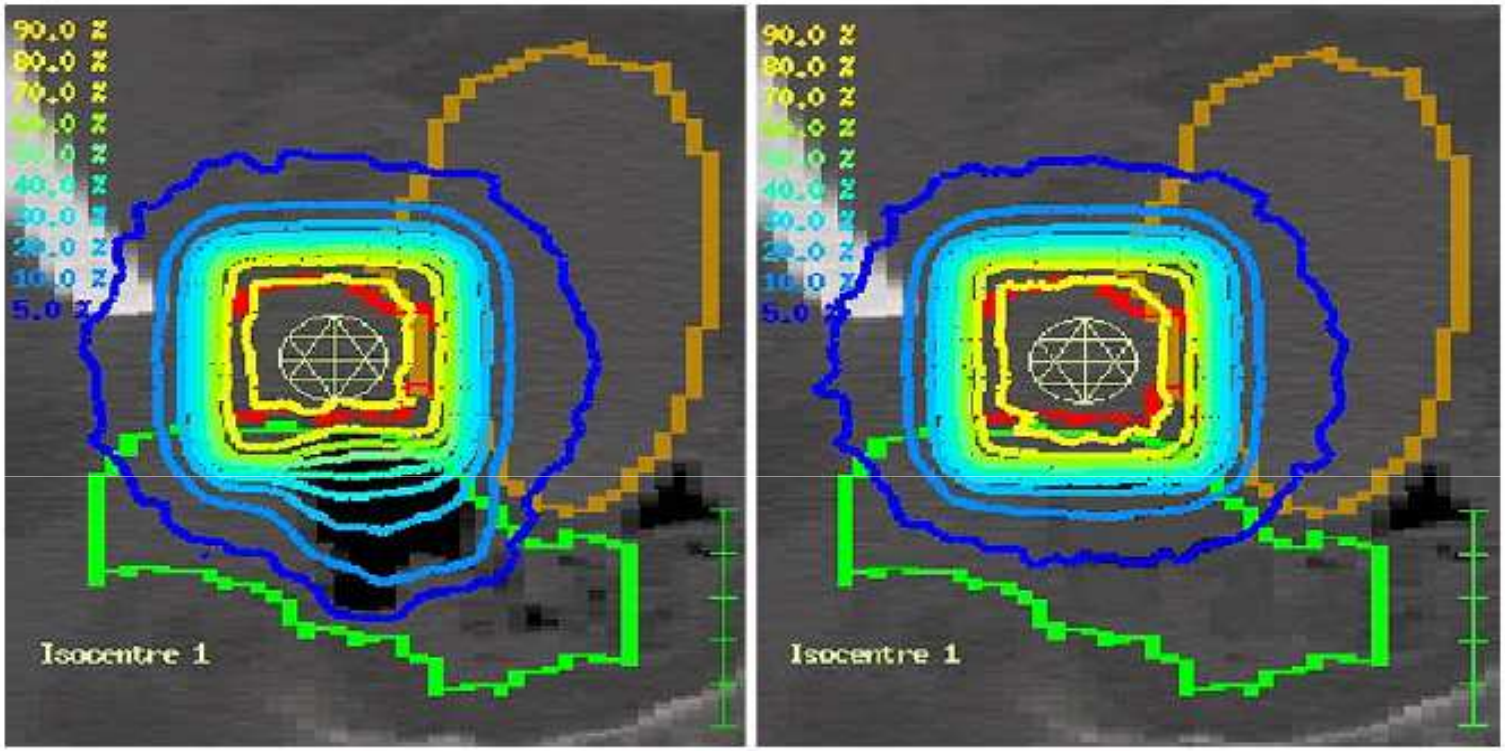
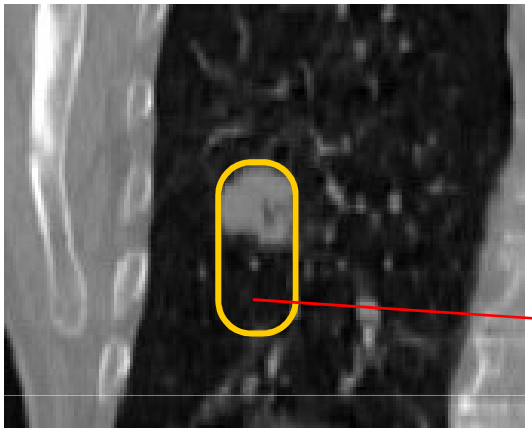


Fig. 4. Isodose distribution from sagittal view in isocentric plane for 5 × 5 cm^2 photon field (gantry 90°). (Left) Original computed tomography (CT) scan. (Right) Density overwrite of rectal gas filling with water-equivalent density. Difficulty arises if planning target volume overlaps with cavity as optimizer compensates for dose loss resulting from lateral scatter.

Further reading: Soukup et al. 2009 (IJROBP 75(3))

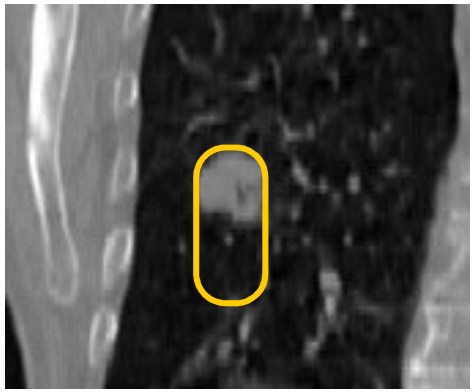
Dose calculation issues ‚in practice‘: Dose calculation for lung lesions

A fundamental problem of the PTV-concept:

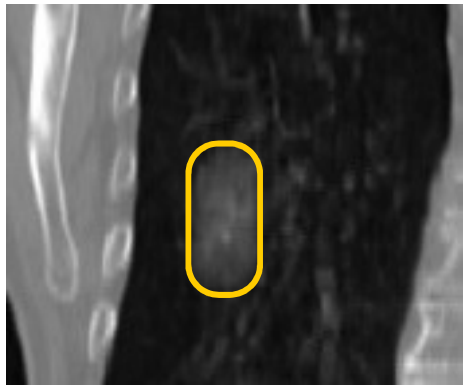


In the ICRU concept the PTV is a *virtual, non-anatomical* planning volume

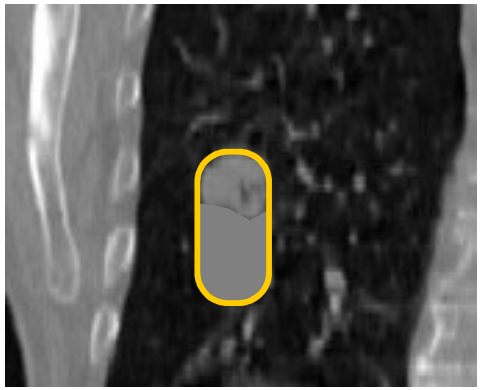
- generally extends into low density region: lung tissue/air
- *What density should be used for planning, so that reported PTV dose is well representative for the dose-to-moving-tumour?*



as-is (no density override)



average density CT based on RCCT



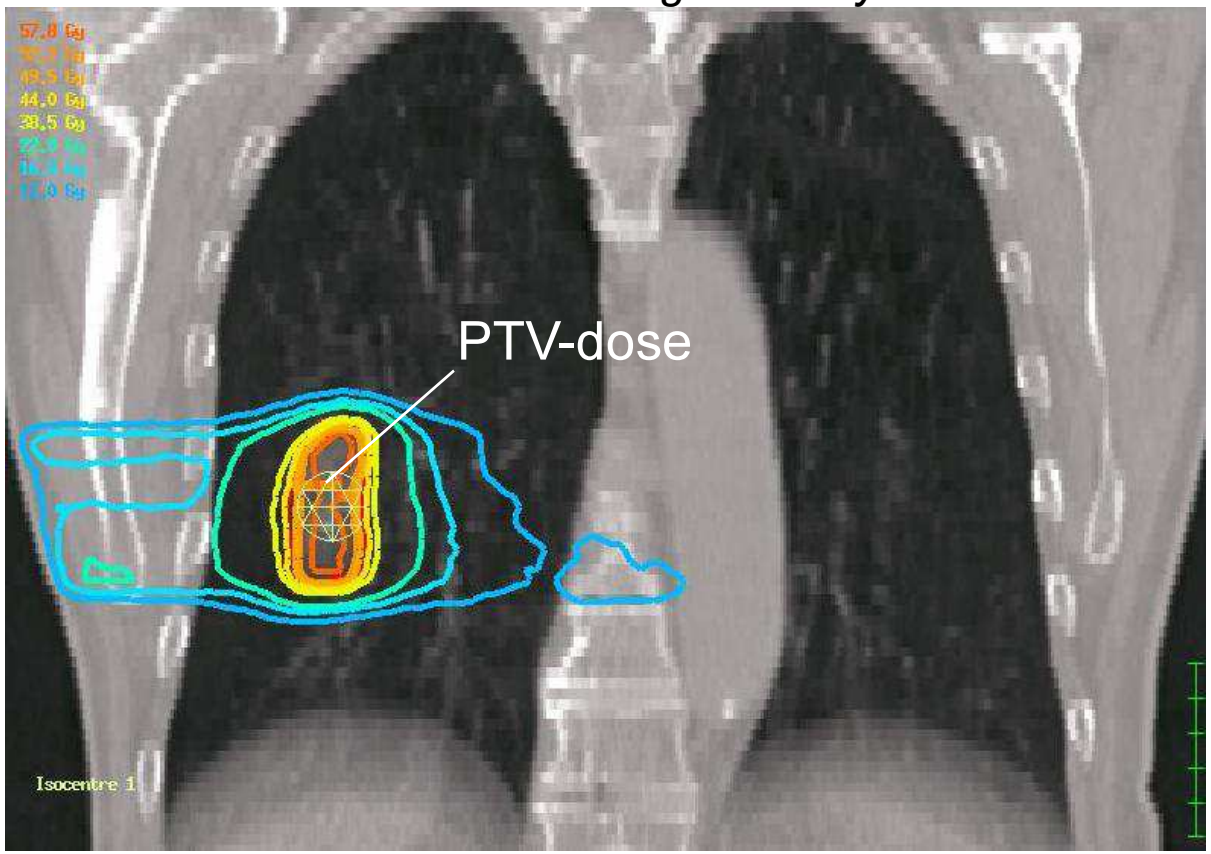
virtual density overwrite

???

Dose calculation issues ‚in practice‘: Dose calculation for lung lesions

What is planned…

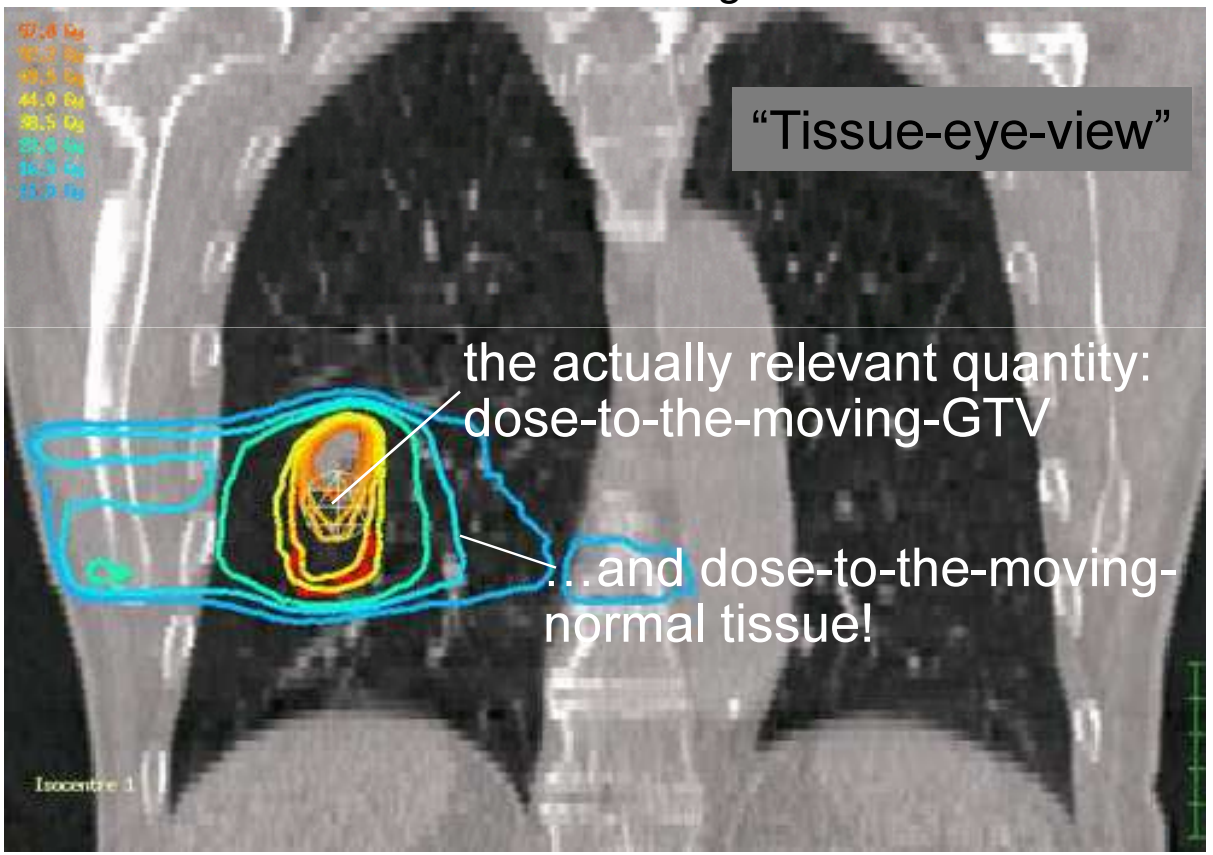
dose distribution of static PTV plan…
calculated on average density CT



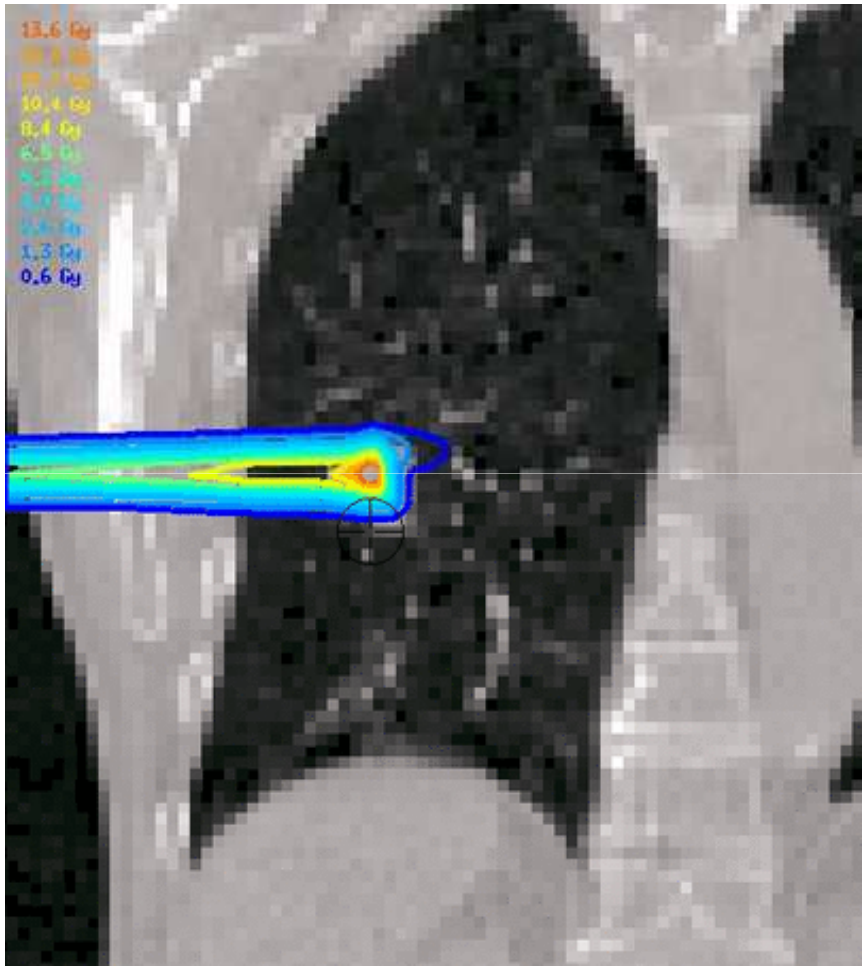
Dose calculation issues ‚in practice‘: Dose calculation for lung lesions

…and what actually happens:

dose distribution of static PTV plan…
calculated in the different instance geometries of a 4D-CT

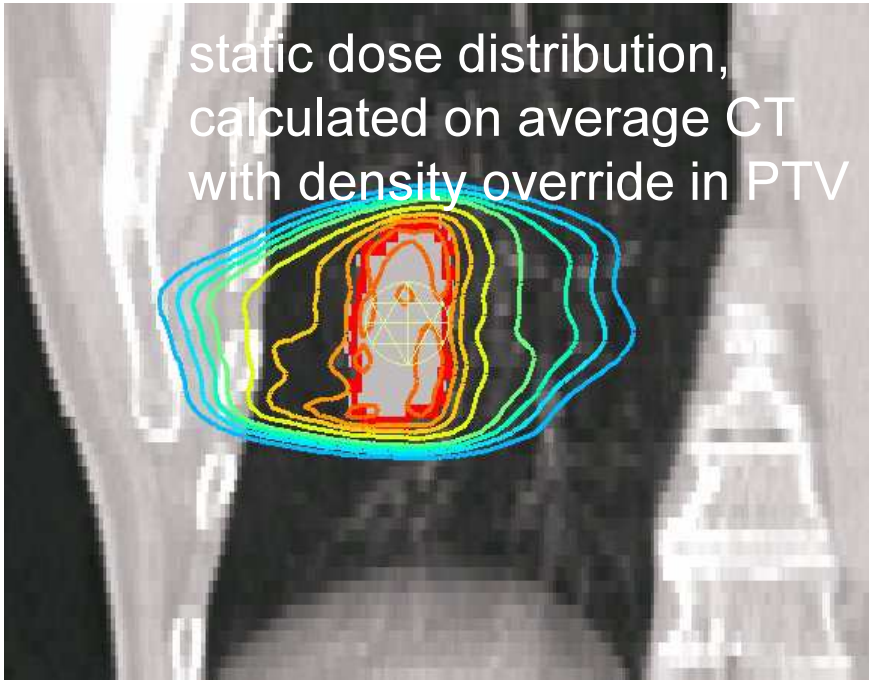


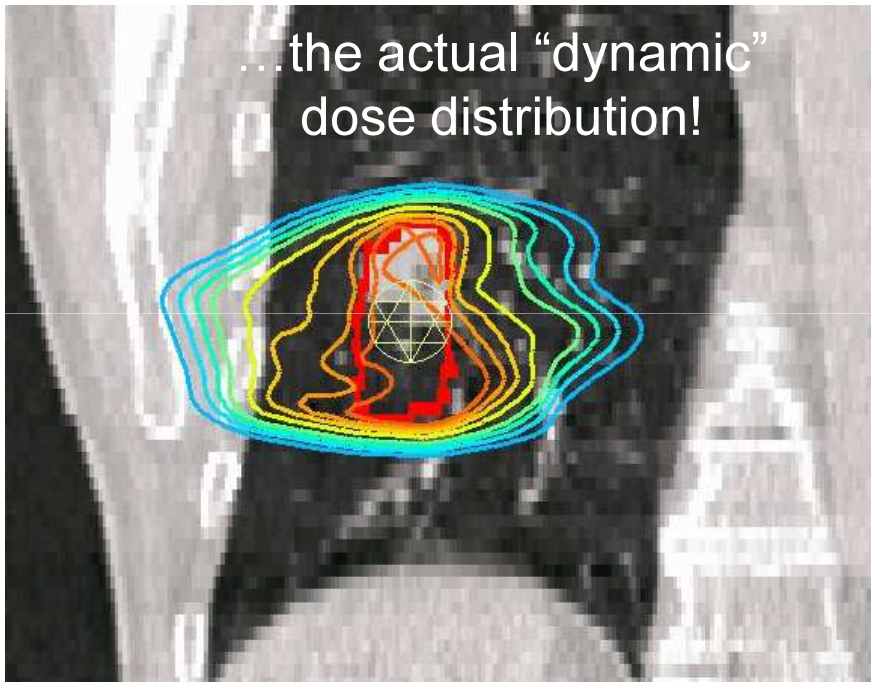
Side track: Proton therapy of moving targets



example:
single proton pencil beam of an IMPT plan (Intensity Modulated Proton Therapy)

Side track: Proton therapy of moving targets





Dose calculation issues ‚in practice‘: Dose calculation for lung lesions

Further reading:

• Choice of optimal density inside of PTV for static dose calculation by evaluating actual 4D-MC-doses; recommendation: raise density in voxels below 0.4 g/cm^3 to this value:

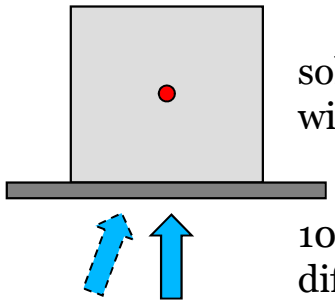
Sikora et al. 2009 (Radiat. Oncol. 4:64):
Monte Carlo vs. Pencil Beam Based Optimization of Stereotactic Lung IMRT

• related -- highly recommended -- reading: Static (3D-)dose-to-GTV representative for actual 4D-dose (based on Collapsed Cone dose calculation):

Guckenberger et al. 2007 (IJROBP 69(1)):
Four-Dimensional Treatment Planning For Stereotactic Body Radiotherapy

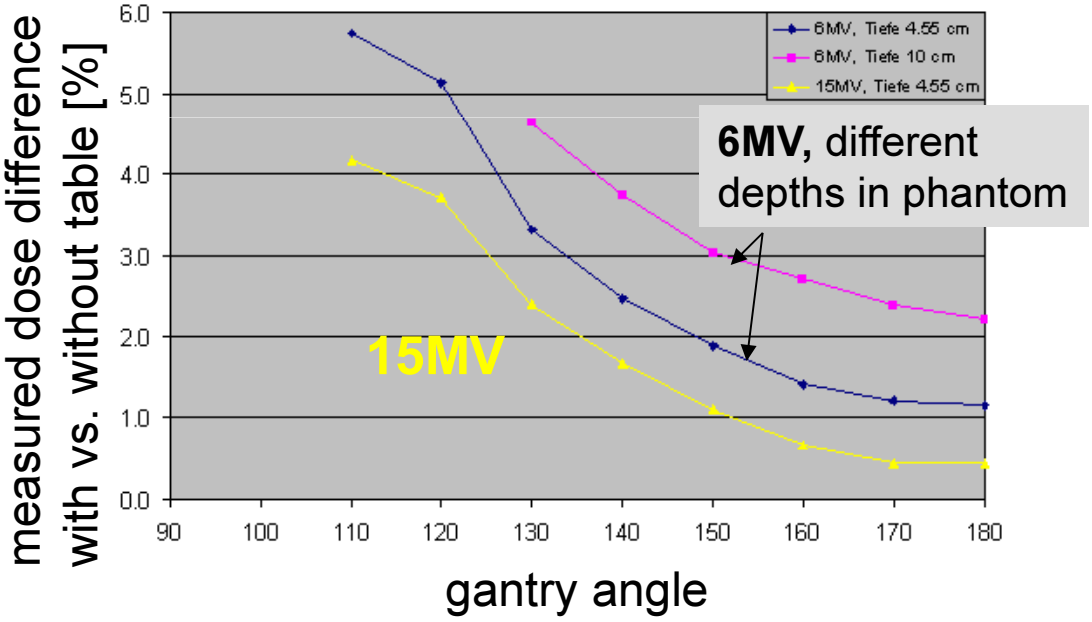
Dose calculation issues ‚in practice‘: Dosimetric effects of the treatment table/setup devices

Reiner et al., DEGRO 2013



solid water phantom
with ionisation chamber

10x10 cm field,
different beam angles

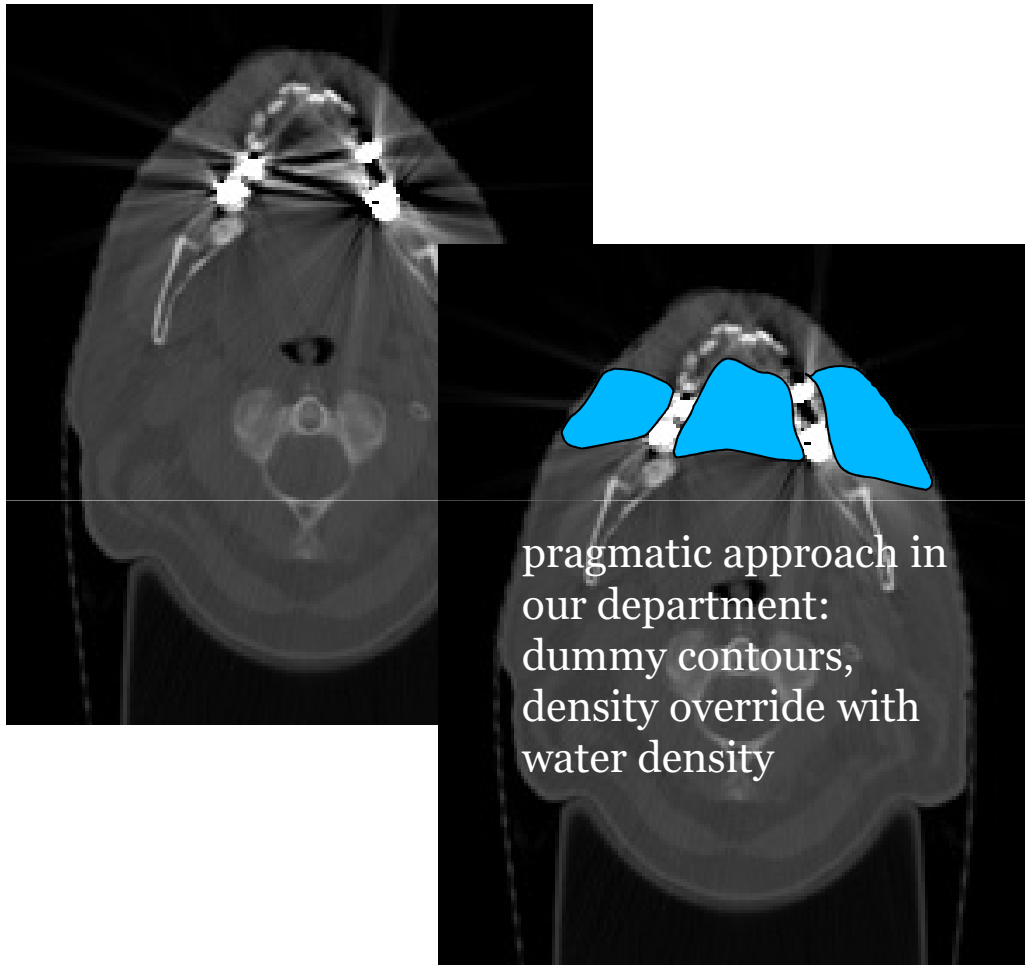


- depending on the vendor/model, treatment tables can have a water-equivalent thickness of ~1 cm w.r.t dose absorption
- depending on beam angle, dose absorption of several percent

→ should be explicitly considered for dose calculation, especially for rotational techniques (VMAT), where oblique angles through the table cannot be avoided

- Methods: Dose calculation with table/setup devices ‘as in CT’, or dummy contour with water density override. MIND: evaluate optimal method for your TPS/dose calculation algorithm!

Dose calculation issues ‚in practice‘: Dose calculation in presence of CT artifacts



- typical cases in RT: dental metal implants, hip implants
- significant dose calculation errors possible in soft tissue artifact regions due to wrong Hounsfield (CT-) values
- Hounsfield values of metal structures itself wrong as well AND usually dose calculation algorithms do not model radiation transport through metal correctly

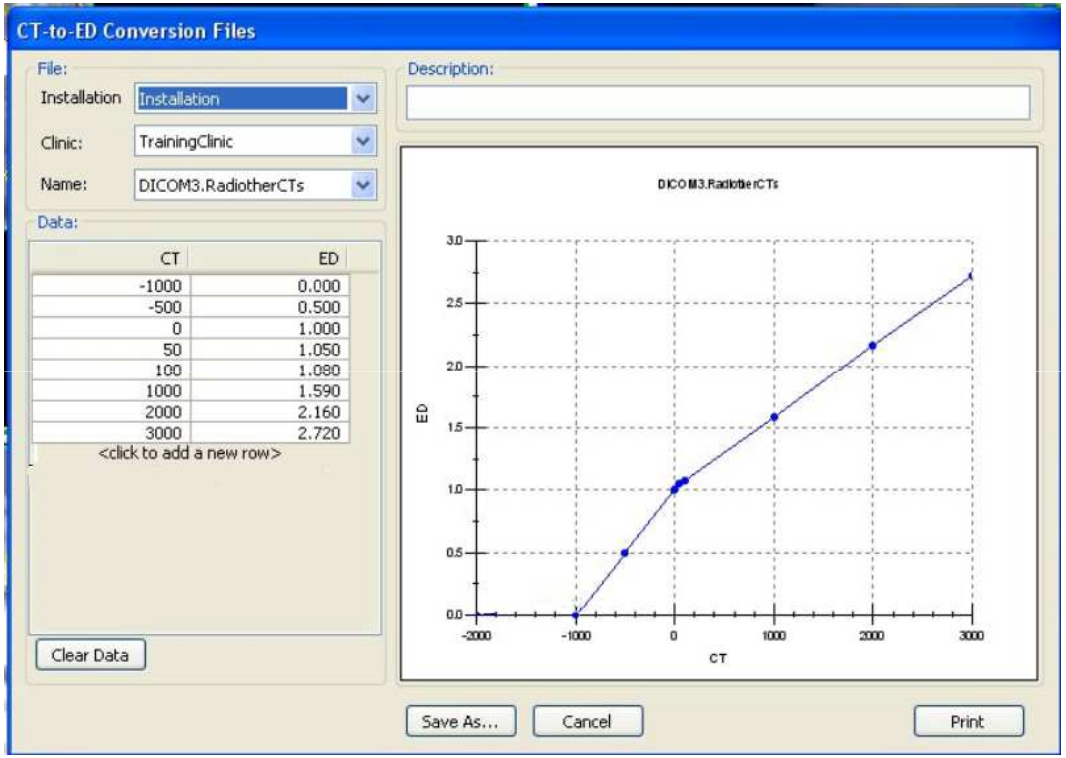
→ do not trust your dose ‘behind’ metal structures!

→ if possible (hip implants), try to avoid beam directions passing metal structures

further reading e.g. Kim et al. 2006 (Radiother. Oncol. 79(2))

Dose calculation issues ‚in practice‘: Hounsfield (CT-) value calibration

...a sometimes (!?) underrated issue!



- input for clinical dose calculation algorithms: local *electron or mass densities* in the patient
- these are typically determined based on the Hounsfield (CT-) values via calibration curves

→ MIND potential errors in calibration curve, or Hounsfield stability problems of CT hardware

Related issue: Dose calculation based on Cone Beam CTs!

Adaptive Radiotherapy

Matthias Söhn, PhD

Radiation Oncology, Medical Physics
University Hospital Grosshadern
LMU Munich, Germany

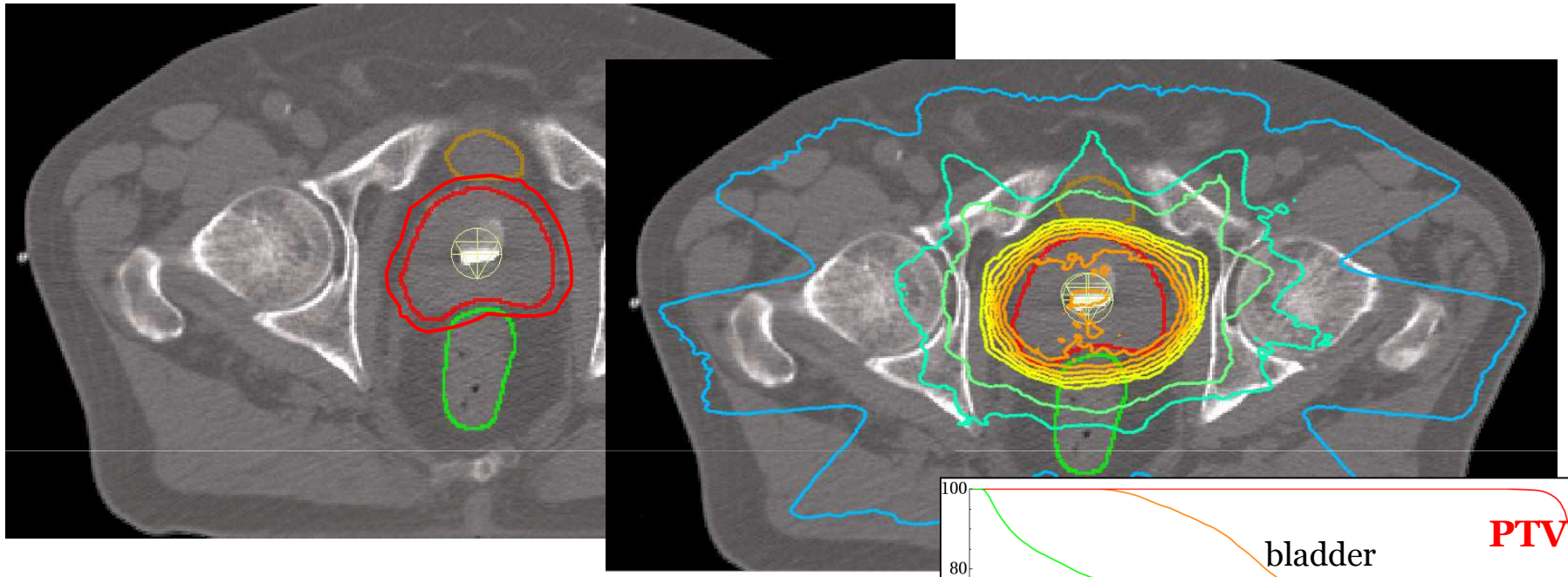
Disclosure

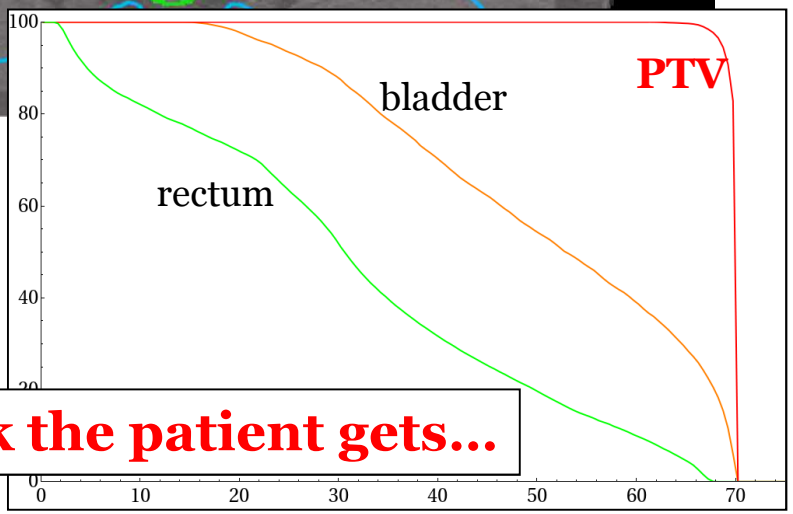
• I am involved in the development of the treatment planning system HYPERION which is the basis for Elekta Monaco®.

• My department (LMU Munich) currently receives research grants from Elekta and C-RAD.

• I am co-owner of the company SCIENTIFICRT

The common planning approach





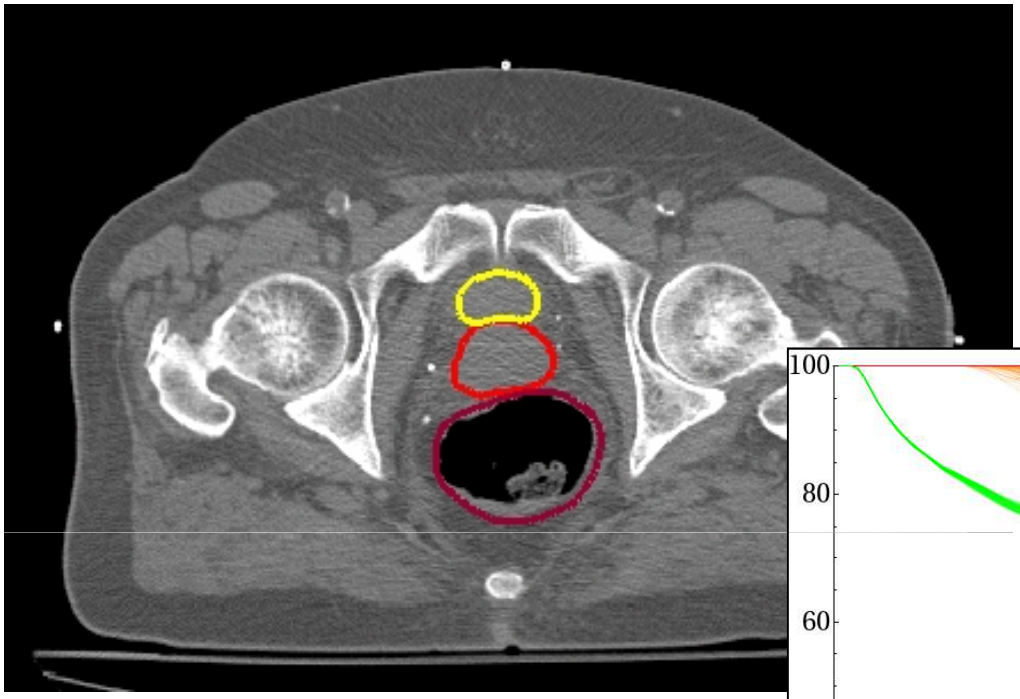
(1) planning CT

(2) add a margin

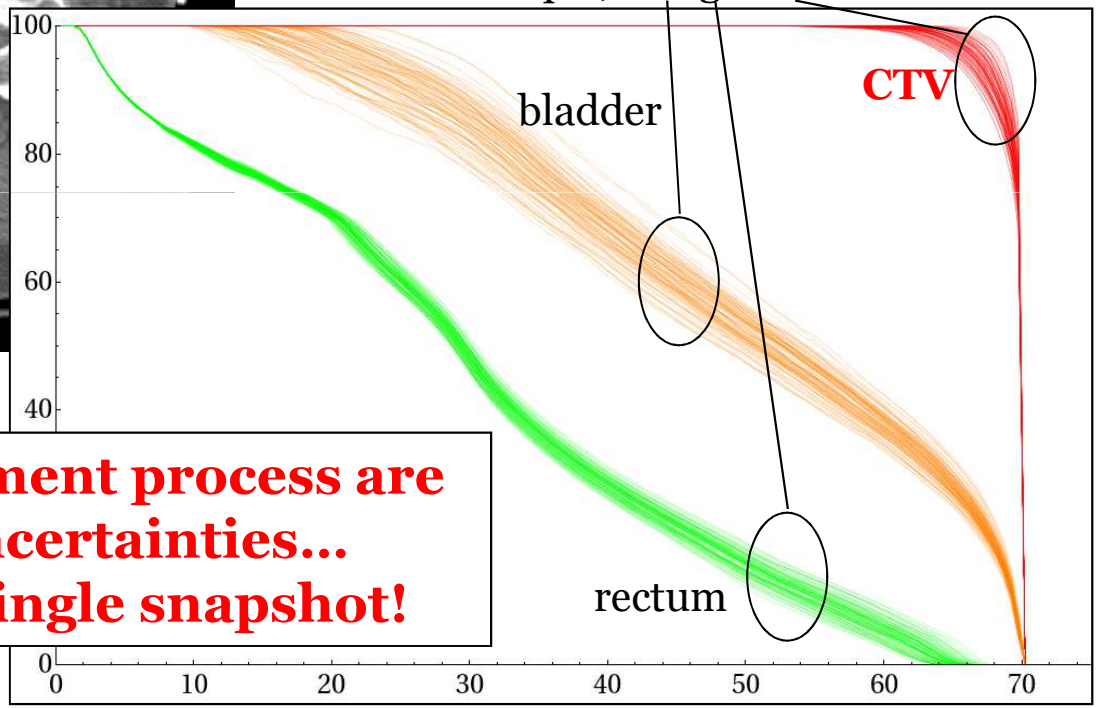
(3) make a plan!

This is the dose we may think the patient gets…

This is what actually happens!



Uncertainties depend on patient, treatment technique, margin size…



Reason: Patient and treatment process are not a *static*, all kinds of uncertainties…
The planning CT is just a single snapshot!

Classification of errors&uncertainties according to their *stochastic* nature

Systematic errors:

most deleterious!

Imaging, segmentation, planning, application, patient-setup, organ-motion&deformation, …

Random errors:

Application, patient-setu… motion&deformation, …

Most of this: patient-dependent!

Non-stationary ('trending') errors:

anatomic changes, functional changes, …

‘Adaptive RT’: How it all started

Phys. Med. Biol. **42** (1997) 123–132. Printed in the UK PII: S0031-9155(97)67292-9

Adaptive radiation therapy

Di Yan†, Frank Vicini, John Wong and Alvaro Martinez
Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, MI 48073, USA

Received 11 August 1995, in final form 29 August 1996

Abstract. Adaptive radiation therapy is a closed-loop radiation treatment process where the treatment plan can be modified using a systematic feedback of measurements. Adaptive radiation therapy intends to improve radiation treatment by systematically monitoring treatment variations and incorporating them to re-optimize the treatment plan early on during the course of treatment. In this process, field margin and treatment dose can be routinely customized to each individual patient to achieve a safe dose escalation.

…and follow-up papers

Phys. Med. Biol. **43** (1998) 1605–1628. Printed in the UK PII: S0031-9155(98)80274-1

An adaptive control algorithm for optimization of intensity modulated radiotherapy considering uncertainties in beam profiles, patient set-up and internal organ motion

Johan Löf, Bengt K Lind and Anders Brahme
Department of Medical Radiation Physics, The Karolinska Institute and University of Stockholm, PO Box 260, S-171 76 Stockholm, Sweden

Received 9 December 1996

Adaptive RT:
The fundamental, yet abstract picture…

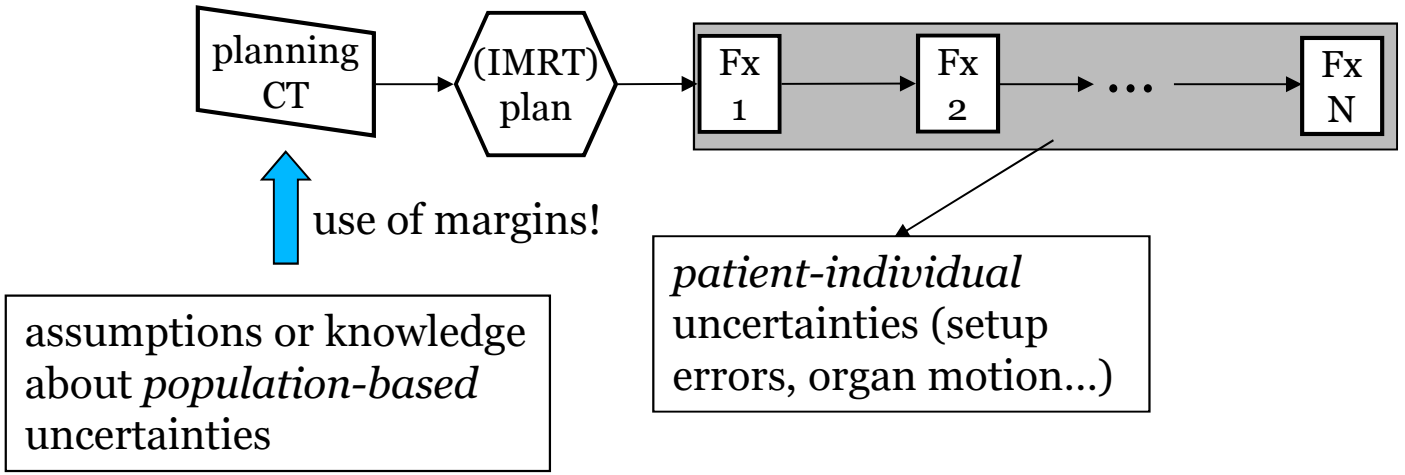
Adaptive radiotherapy:

- explicitly acknowledge that radiotherapy treatment as a whole is a **process**
- this process is performed in presence of all kinds of **uncertainties**
- the uncertainties can be strongly **patient-dependent**
- uncertainties are understood as – stationary or non-stationary – random processes

⇒ new understanding of an *radiotherapy treatment process* as
'feedback control strategy'

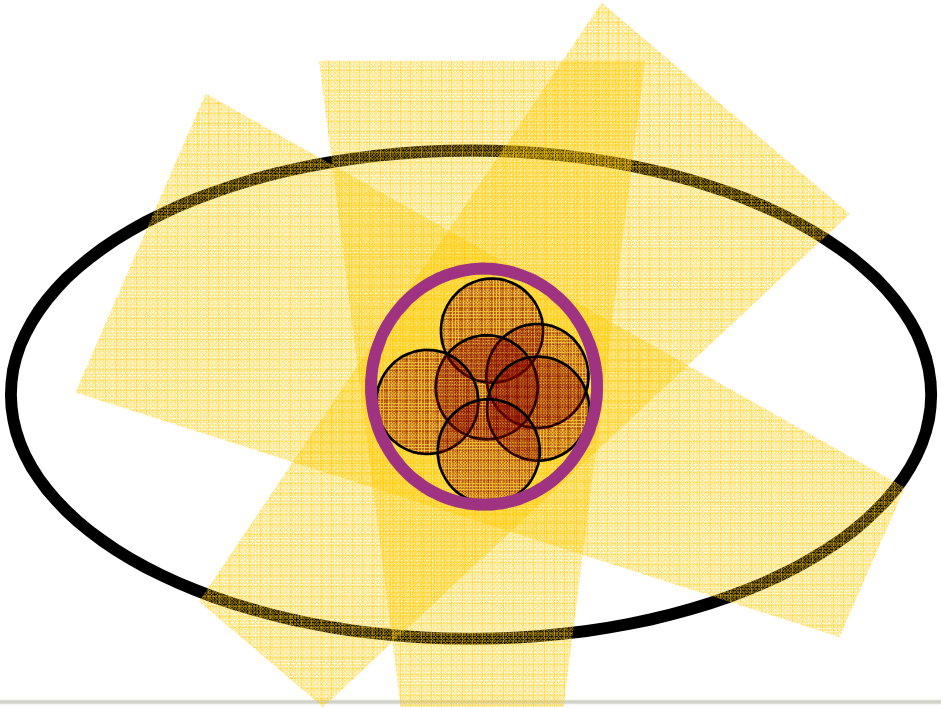
…versus the conventional approach:
single planning in the beginning without further actions/corrections later

The simplest, non-adaptive planning approach as *process*



Margins: The PTV-concept

Irradiate a volume, which is large enough, such that the CTV will (almost) always stay inside!



How large does the margin have to be?

A typical 'margin recipe'...:

systematic errors are more deleterious than random errors!

$$R = 2.5\,\Sigma + 0.7\,\sigma$$

Σ systematic setup errors

σ random setup errors

M. van Herk et al. 2000: The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. IJROBP 47(4)

Which assumptions are behind this formula?

$$R = 2.5\,\Sigma + 0.7\,\sigma$$

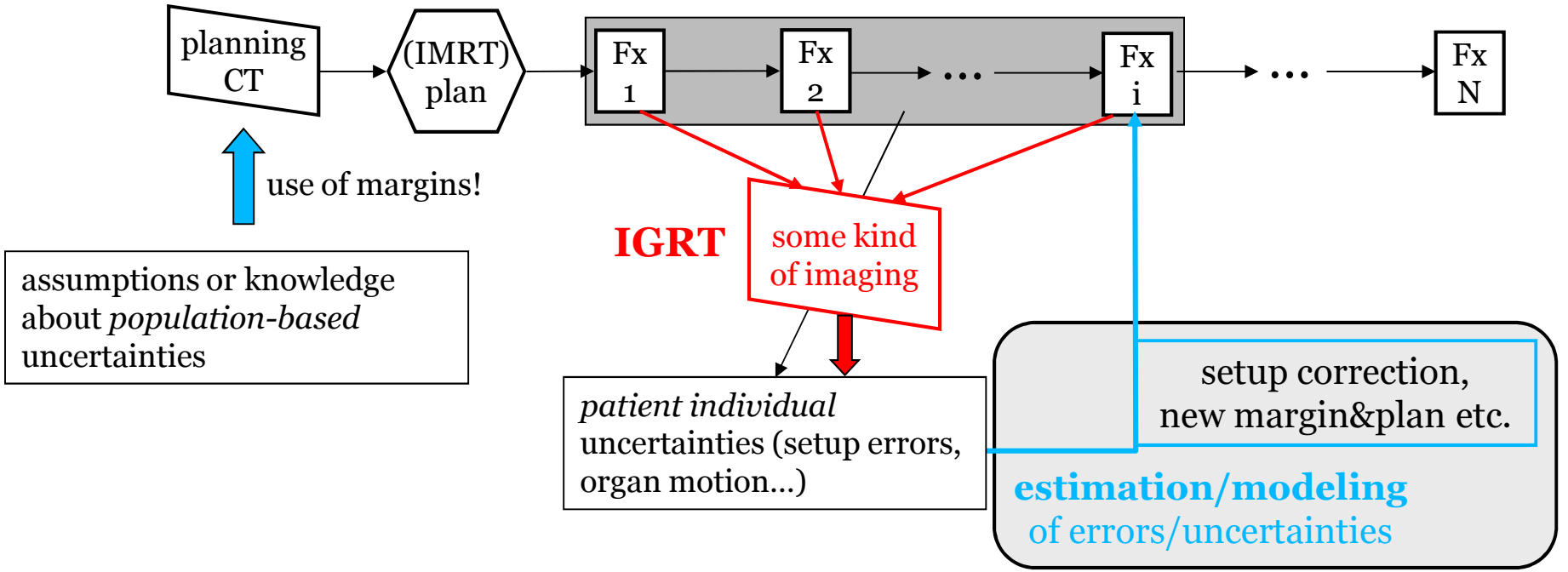
Σ systematic setup errors

σ random setup errors

- round CTV moves around within idealized round dose distribution with idealized penumbra, which drops to zero to all sides
- **population-based uncertainties**, effect quantized as TCP of a population

For the individual patient, the margin will be either too large, or too small…

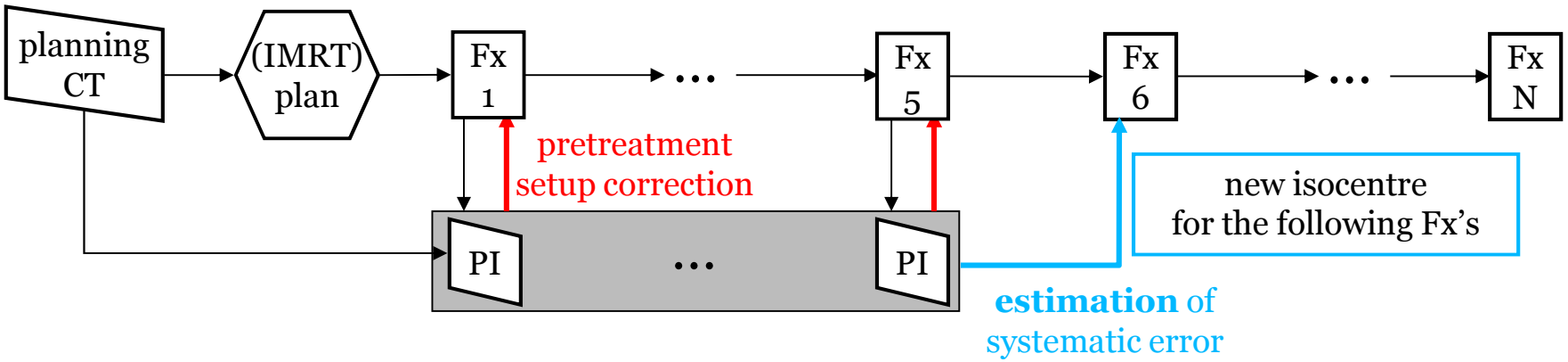
This is where adaptive RT comes in!



"Feedback-loop"!
This makes it 'adaptive RT'!

Adapting the isocentre: Setup correction protocols

An early adaptive RT workflow:
Patient-individual reduction of systematic and random setup errors via portal imaging!

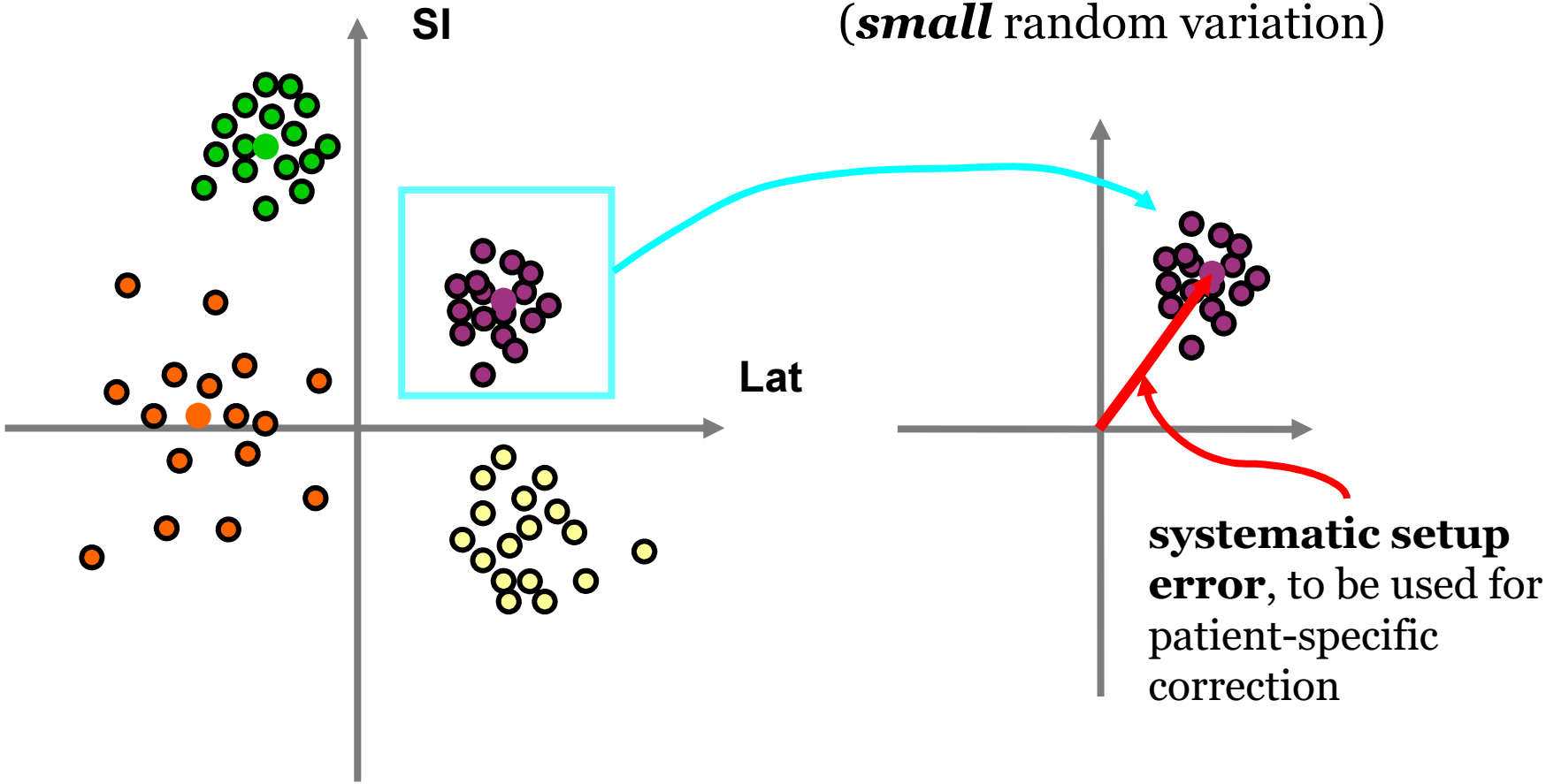


courtesy D. Lockman/D. Yan (WBH)

Estimation of the patient-individual setup error

Population distribution of setup errors

Patient-specific distribution (***small*** random variation)

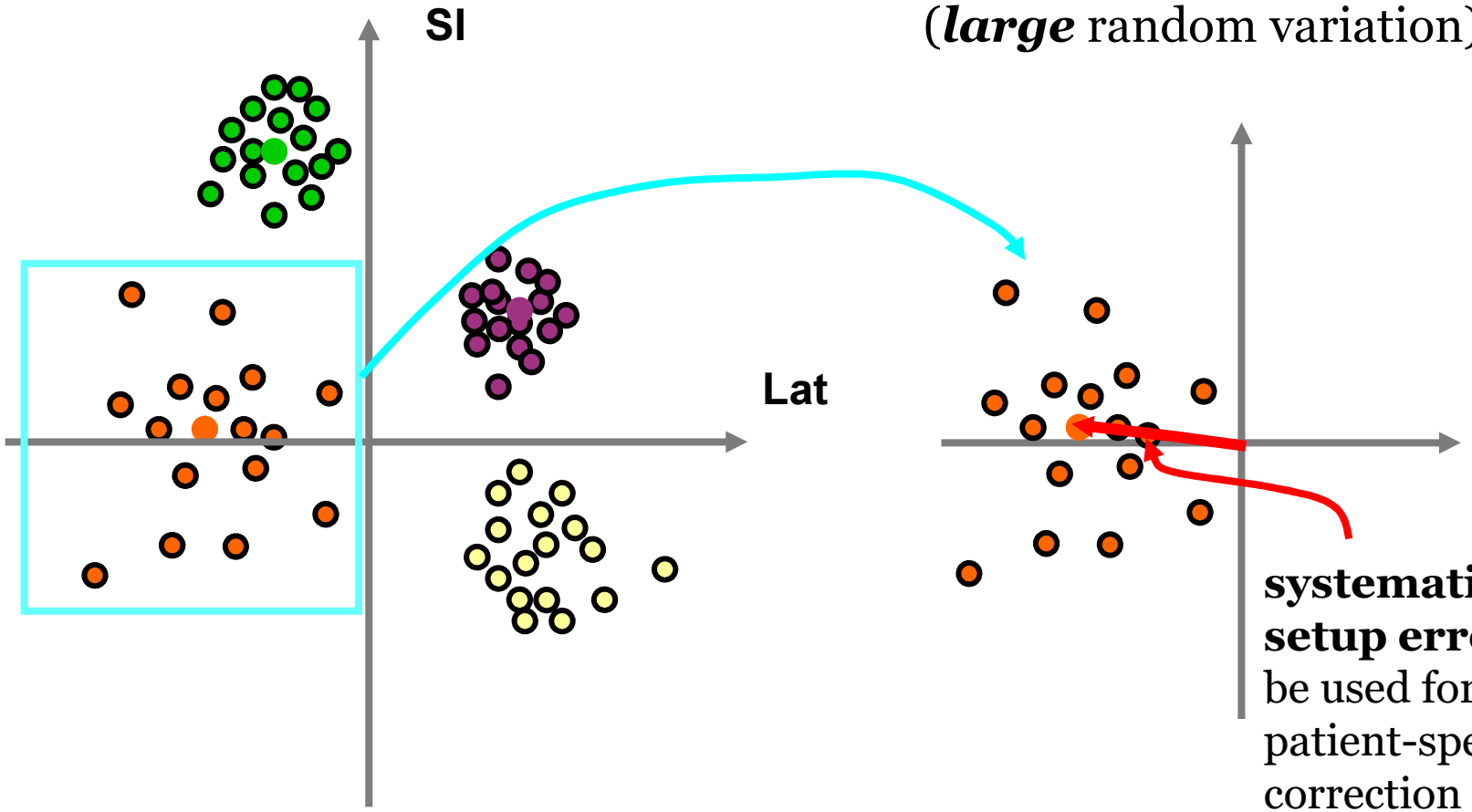


courtesy D. Lockman/D. Yan (WBH)

Estimation of the patient-individual setup error

Population distribution of setup errors

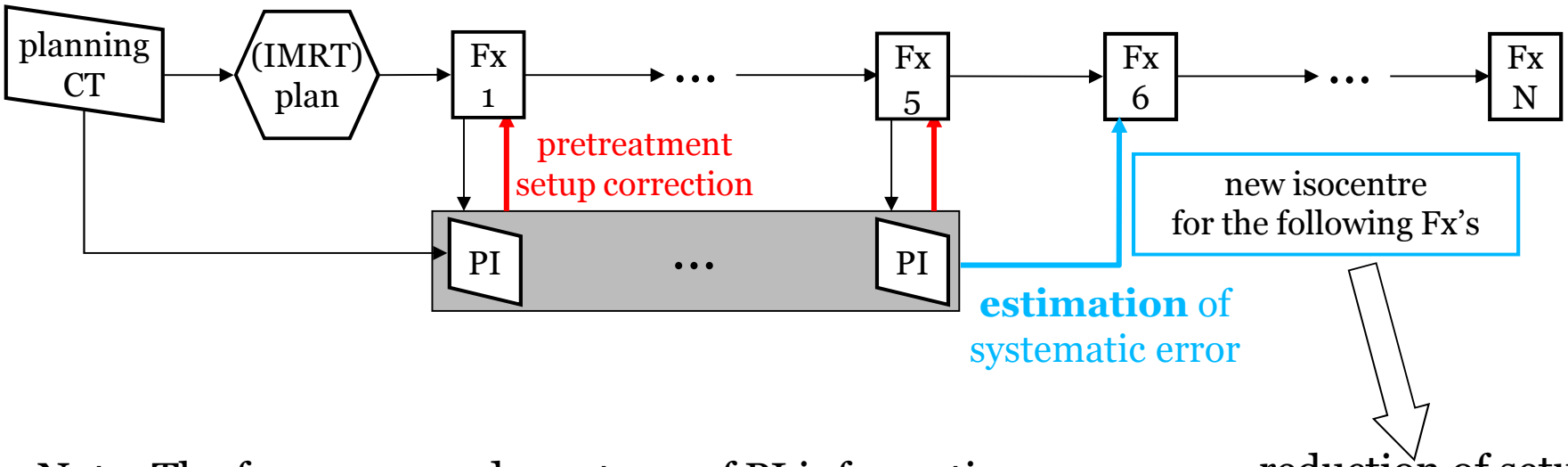
Patient-specific distribution (***large*** random variation)



systematic setup error, to be used for patient-specific correction

Adapting the isocentre: Setup correction protocols

An early adaptive RT workflow:
Patient-individual reduction of systematic and random setup errors via portal imaging!



Note: The frequency and exact use of PI information depends on the **setup protocol** used!

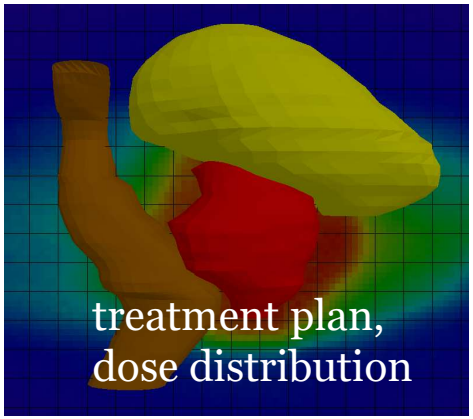
Some proposed setup protocols…

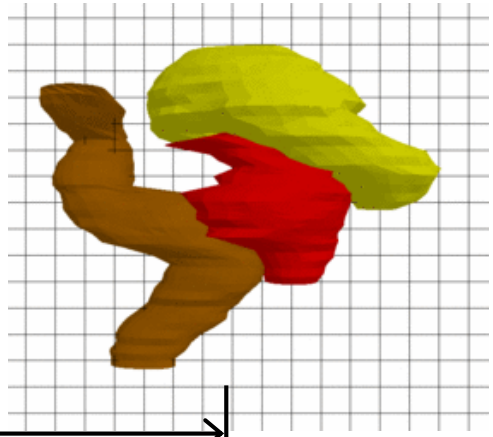
Offline setup protocols (e.g. DRR-PI match):

no action level:	correct setup by the average setup error after n days
shrinking action level:	correct setup by the average setup error after n days, if above a threshold S(n)
Newcastle:	correct setup by the average setup error after n days, if the assumption of 'zero' error is not in confidence interval of estimated error distribution

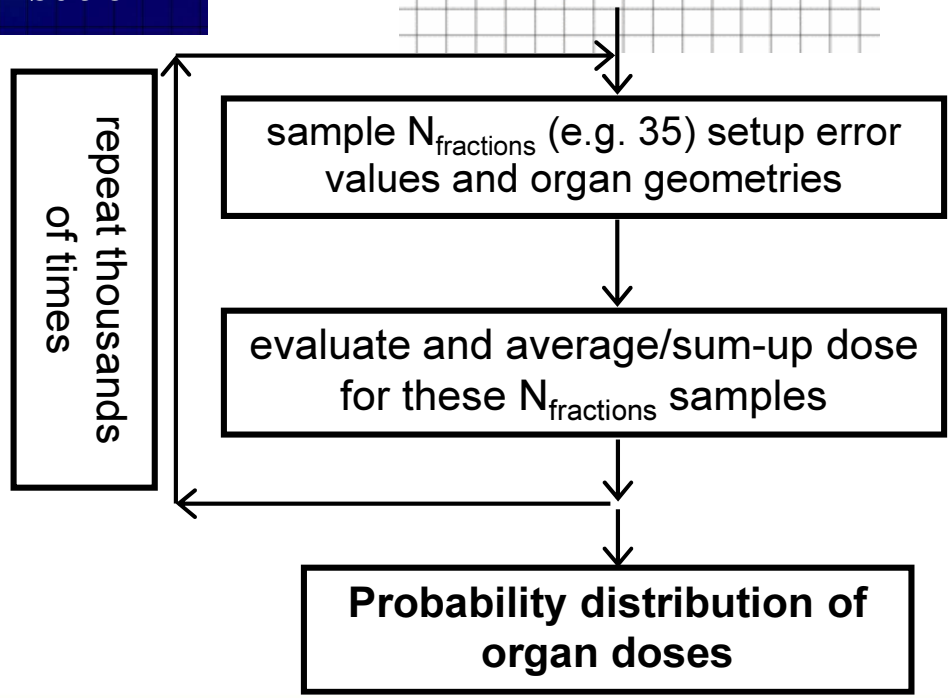
…

How to evaluate and find the best strategy?: Treatment course simulation approaches





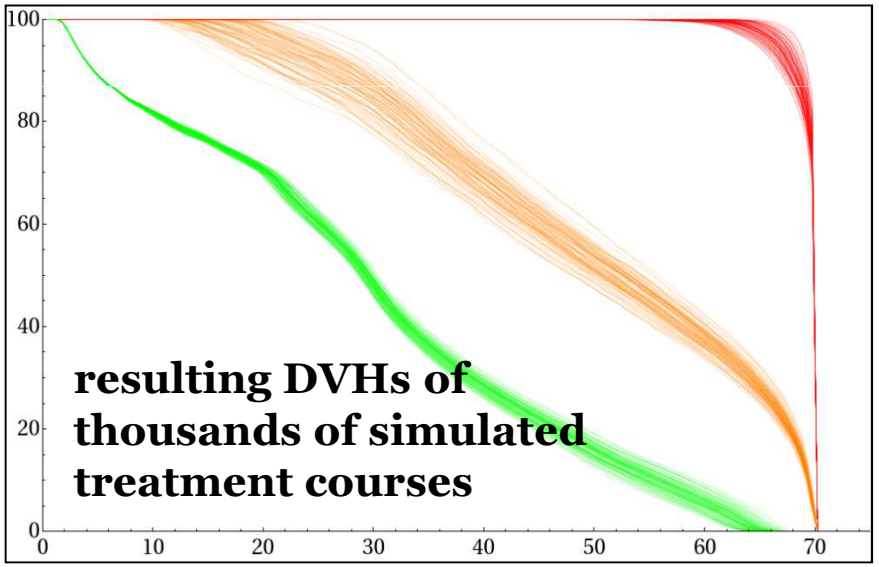
multiple organ contours and setup errors values
- either measured in a patient study
- and/or simulated based on *motion model*

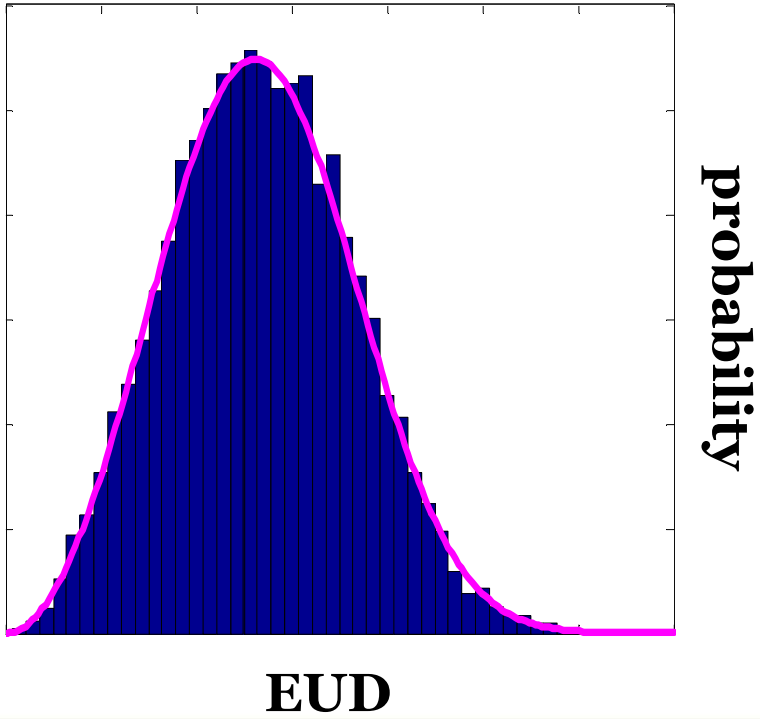


How to evaluate and find the best strategy?: Treatment course simulation approaches

Every treatment course realizes a dose distribution with a certain probability.

Purpose of treatment course simulations: Estimate the probability distribution for a given plan and given uncertainties!





Treatment course simulations for use of different setup protocols

C. Baum et al. 2005: Dosimetric consequences of the application of off-line setup error correction protocols and a hull-volume definition strategy for intensity modulated radiotherapy of prostate cancer.
Rad. Onc. 76(1)

→ Almost all setup correction protocols are similarly efficient in ensuring CTV coverage in presence of setup errors!

Important conclusion for clinical practice:
No need to do especially sophisticated and complicated corrections, but instead implement a workflow with a few simple corrections in a thorough way!

no correction

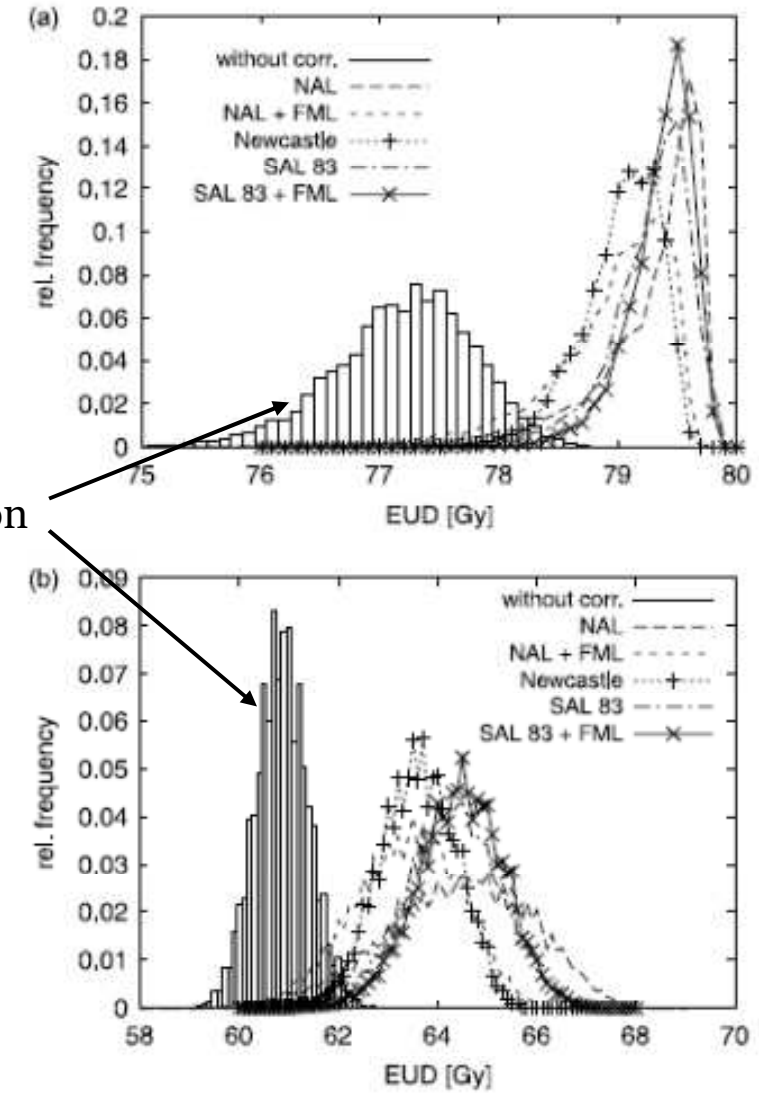
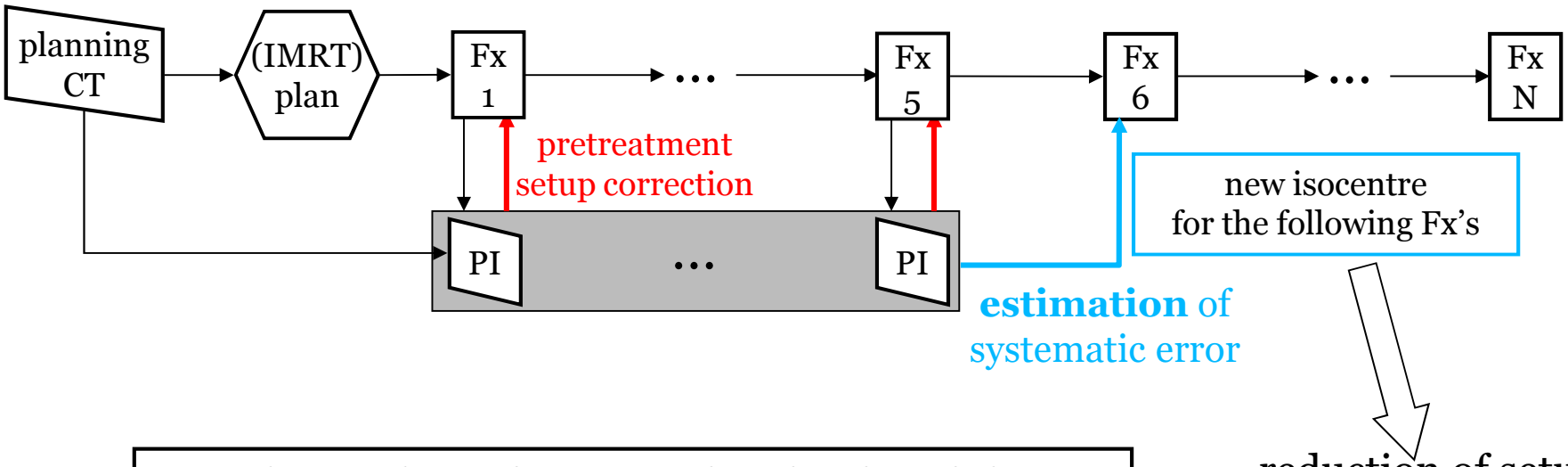


Fig. 4. Distribution of EUD of (a) CTV_hull and (b) Rectum_hull for artificial patient A6 of treatment simulations with and without setup correction.

The ‘Toolbox’ of Adaptive RT

- IGRT – imaging!
- prediction methods/models
- evaluation approaches: prospective studies on real (and realistic!) patient data of a study cohort, treatment course simulations, motion models

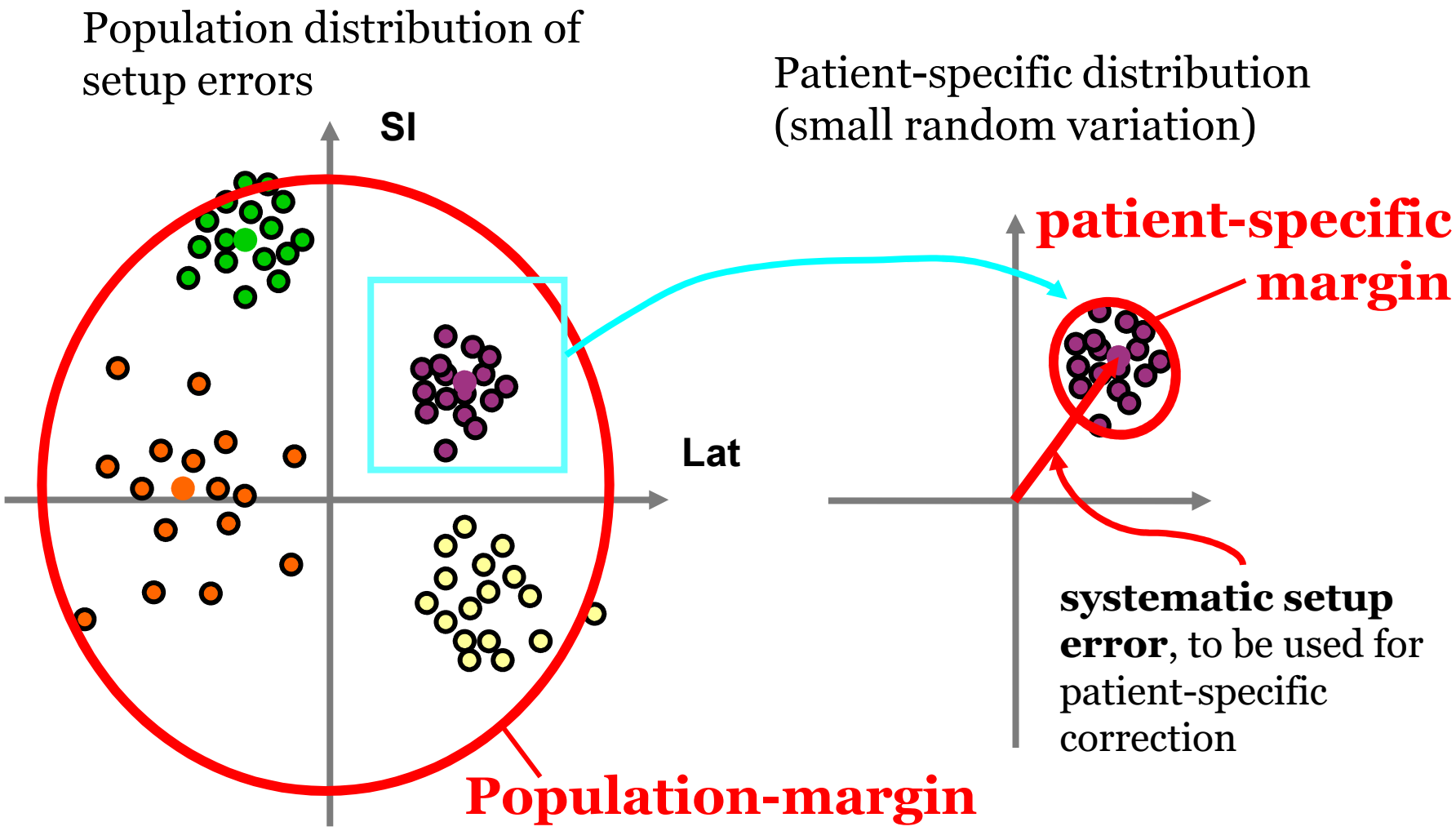
One step further: Margin adaption



Now that we have determined and reduced the patient-individual systematic error:
Why not also reduce/adapt the margin???

Margin adaptation 'visually'

courtesy D. Lockman/D. Yan (WBH)

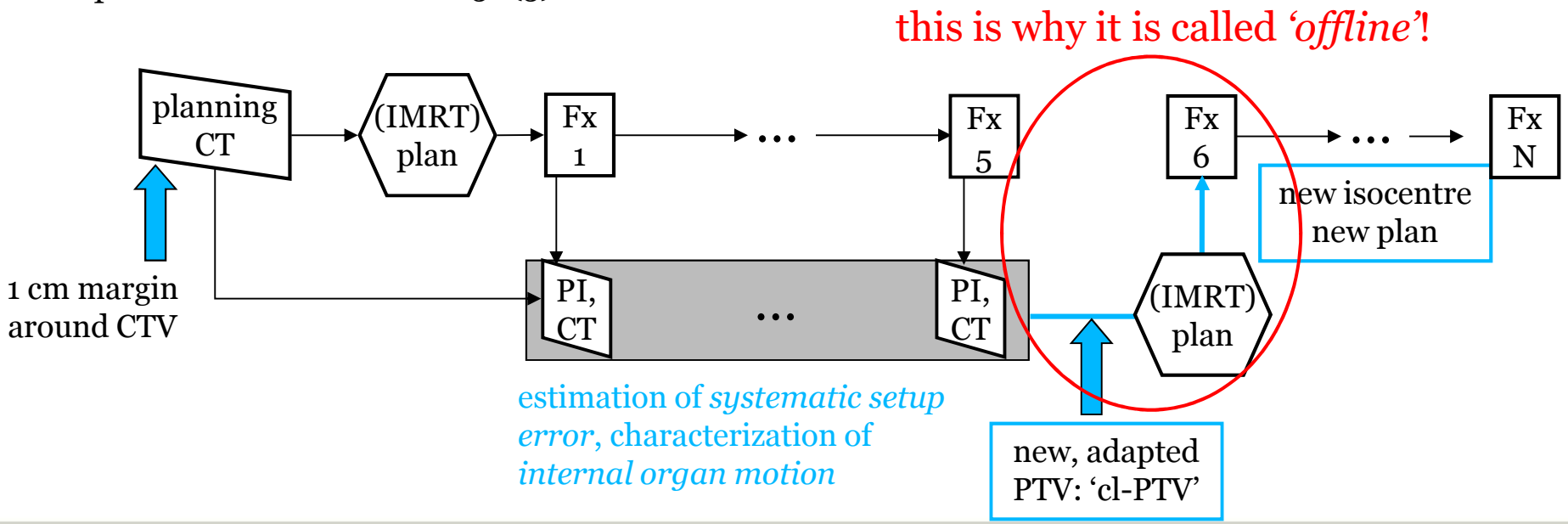


The Beaumont offline adaptive RT approach

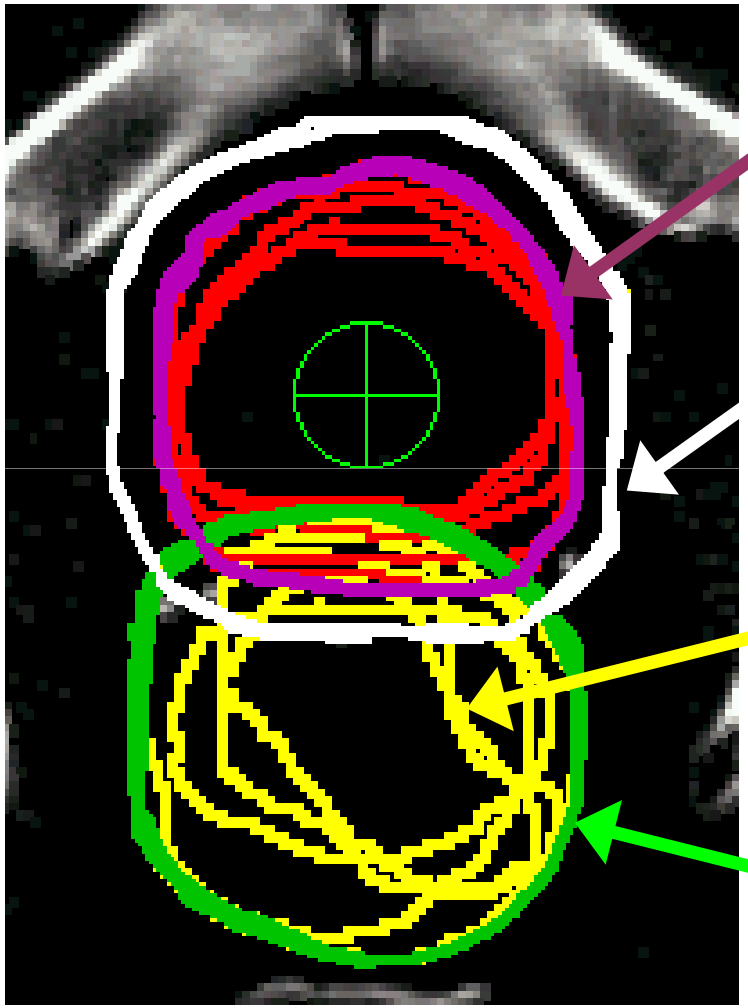
First systematic clinical adaptive RT implementation
at Beaumont Hospital, Royal Oak, Michigan: since 1997!

Yan et al. 2000: An off-line strategy for constructing a patient-specific planning target volume in adaptive treatment process for prostate cancer. IJROBP 48(1)

Martinez et al. 2001: Improvement in dose escalation using the process of adaptive radiotherapy combined with three- dimensional conformal or intensity-modulated beams for prostate cancer. IJROBP 50(5)



The Beaumont offline adaptive RT approach: Eliminate systematic errors of the organ geometry!



CTV_hull = hull of 3-5 prostate contours (planning CTV and first days of treatment)

PTV = CTV_hull + patient-individual margin, adapted according to setup errors measured during first 5 fractions (~5mm)

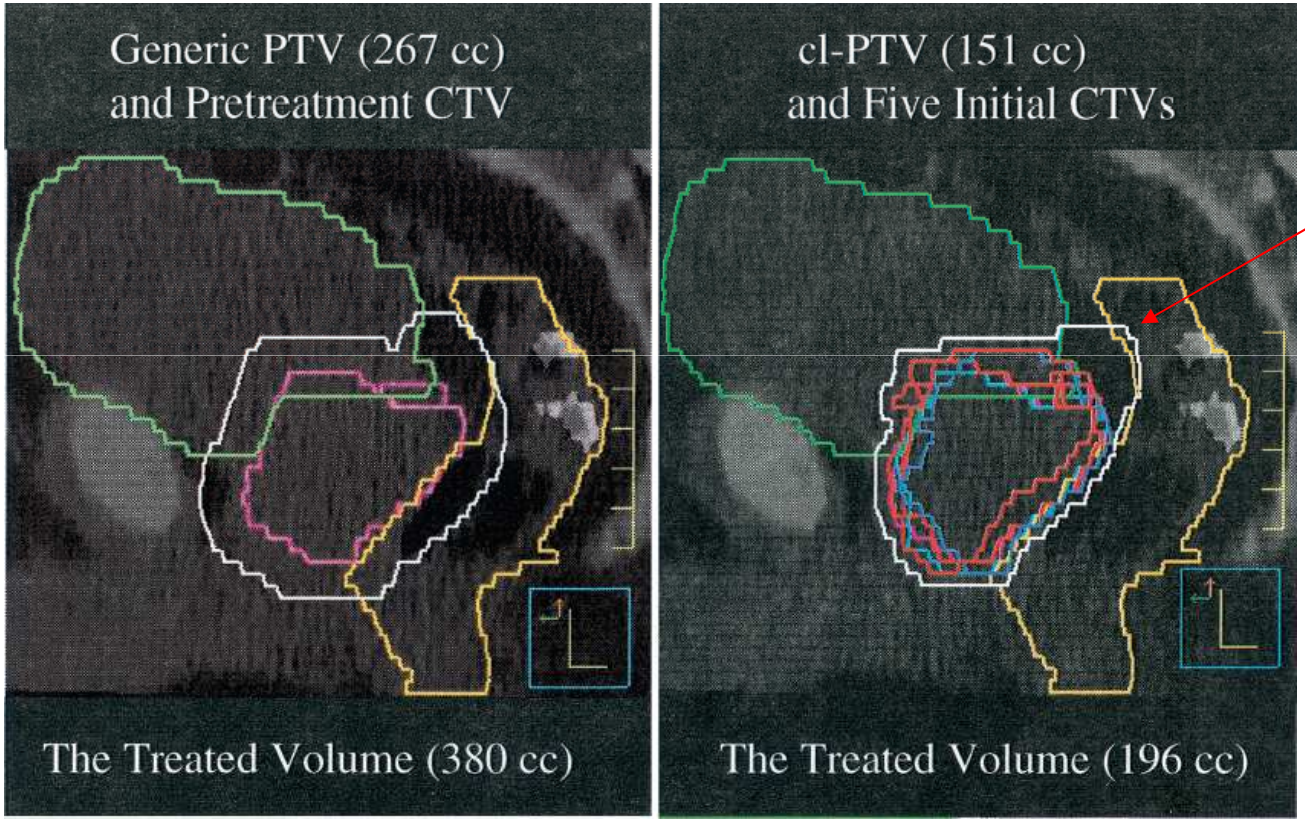
corresponding rectum contours of the first 3-5 treatment days;
Beaumont approach: dose constraint to rectal-wall structure as in planning CT

alternative approach:
constraints to Rectum_hull = hull of 3-5 rectum contours, no PRV margin

The Beaumont offline adaptive RT approach

Martinez et al. 2001 (IJROBP 50(5))

average PTV volume reduction (150 patients): 24%



BUT:
may also be larger
- locally
- or for 'large mover' patients!

=> adaptation to the patient-individual interfractional 'motion pattern'

What are the clinical benefits?

NKI-AVL dose escalation study, **no margin adaptation** (1cm, 0-5mm for boost):

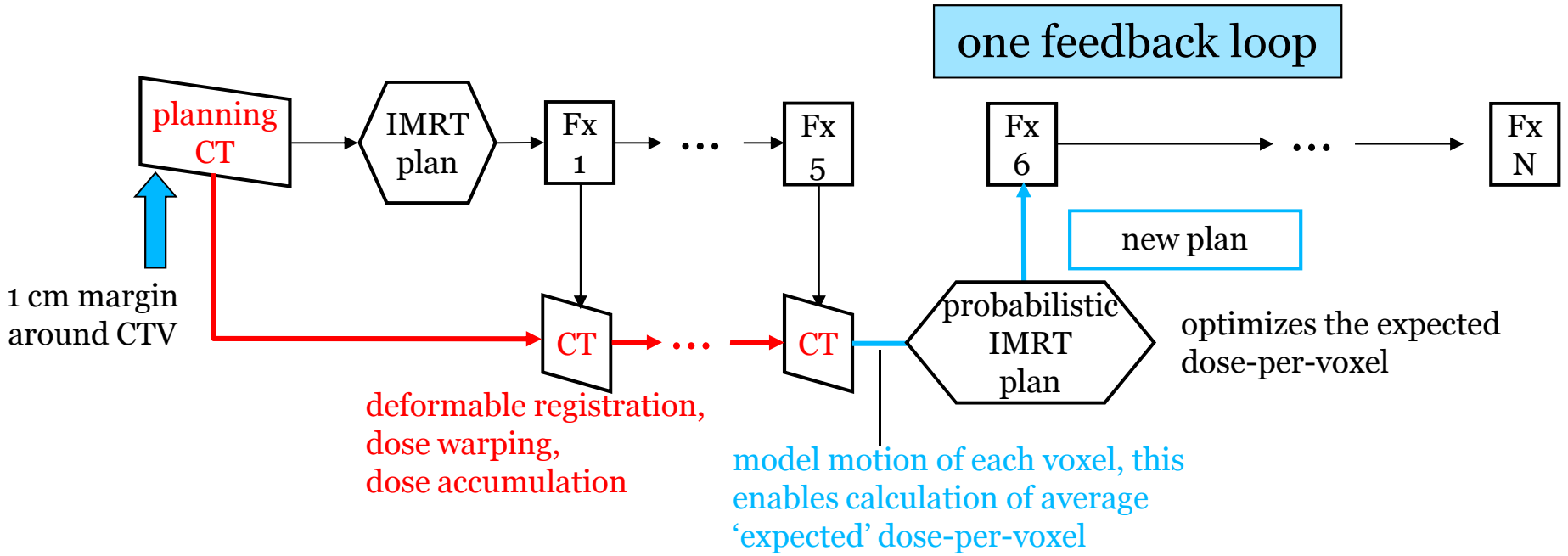
W. Heemsbergen et al. 2007: Increased risk of Biochemical and clinical failure for prostate patients with a *large rectum at radiotherapy planning*: results from the dutch trial of 68 Gy versus 78 Gy.
IJROBP 67(5)

...versus clinical long-term follow-up results of Beaumont offline ART:

S. S. Park et al. 2012: Adaptive Image-guided Radiotherapy (IGRT) Eliminates the Risk of Biochemical Failure Caused by the *Bias of Rectal Distension* in Prostate Cancer Treatment Planning: Clinical Evidence.
IJROBP 83(3)

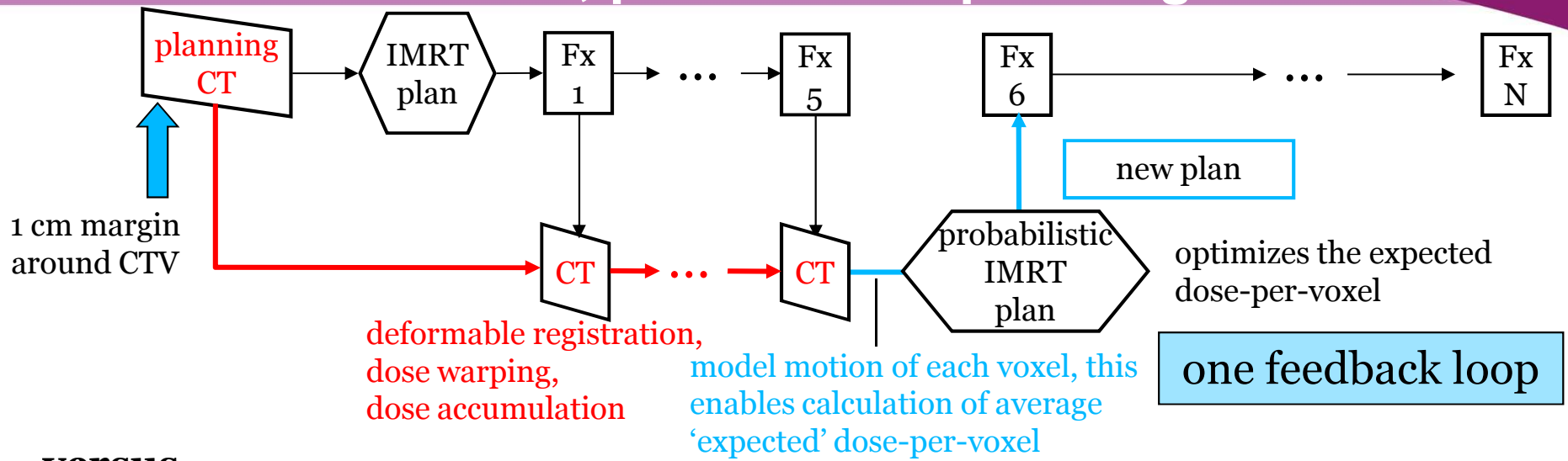
The next step: more than one re-optimization, dose accumulation, probabilistic planning

M. Birkner et al. 2003: Adapting inverse planning to patient and organ geometrical variation: algorithm and implementation.
Med. Phys. 30(10)

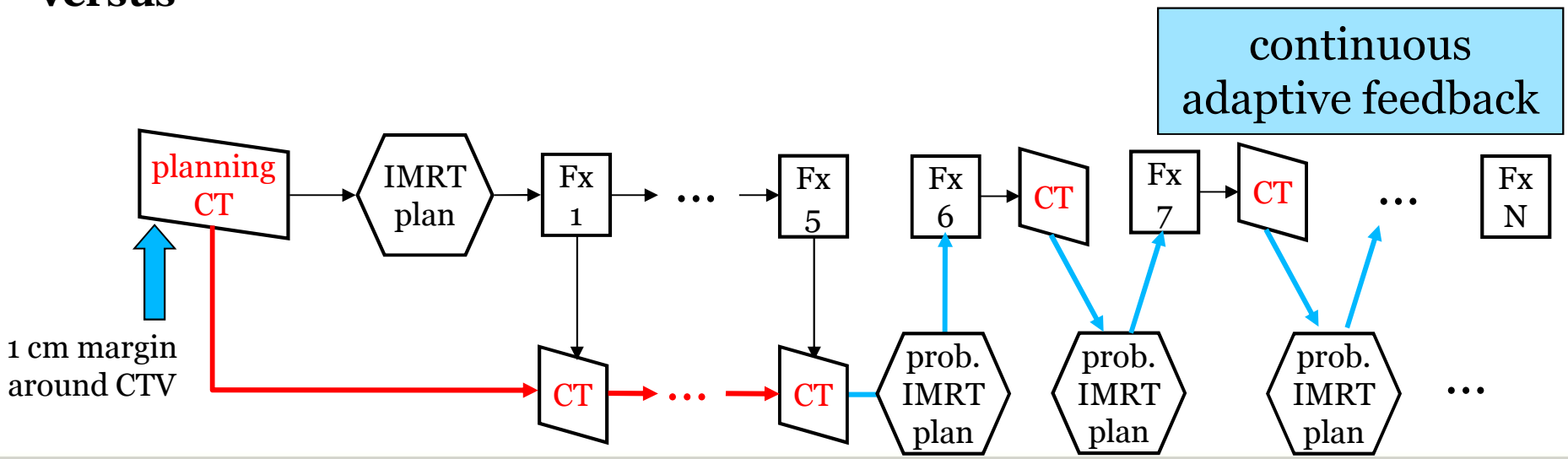


The next step: more than one re-optimization, dose accumulation, probabilistic planning

Birkner et al. 2003 (Med. Phys. 30(10))



versus



The next step: more than one re-optimization, dose accumulation, probabilistic planning

Birkner et al. 2003
(Med. Phys. 30(10))

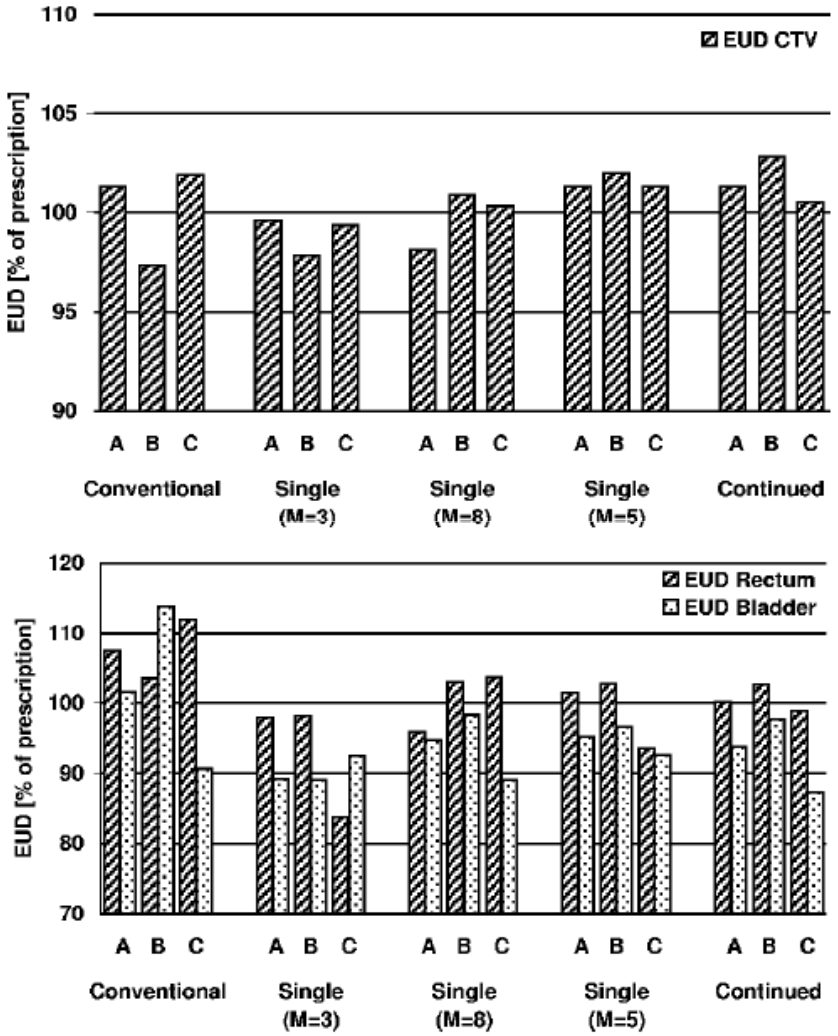


FIG. 4. Comparison of treatment prescription and treatment outcome for treatment strategies: Conventional IMRT planning (PTV=CTV+1 cm) without feedback, single adaptive feedback re-optimization after 3, 8, and 5 fractions, and continued adaptive feedback from fraction 6 to final fraction. All three patients (A, B, C) show a similar trend of convergence of CTV coverage with increasing number of feedbacks (top). For the critical structures (bottom), treatment outcome comes closer to the prescribed 100% EUD level with any adaptive feedback strategy, while at the same time inter-patient variability is reduced. Differences between single re-optimiztion after $M=5$ fraction and continued feedback strategies are marginal.

→ one plan adaptation after 5 fractions almost 'does the full job',
no significant additional benefits from more than one re-planning

The 'Toolbox' of Adaptive RT

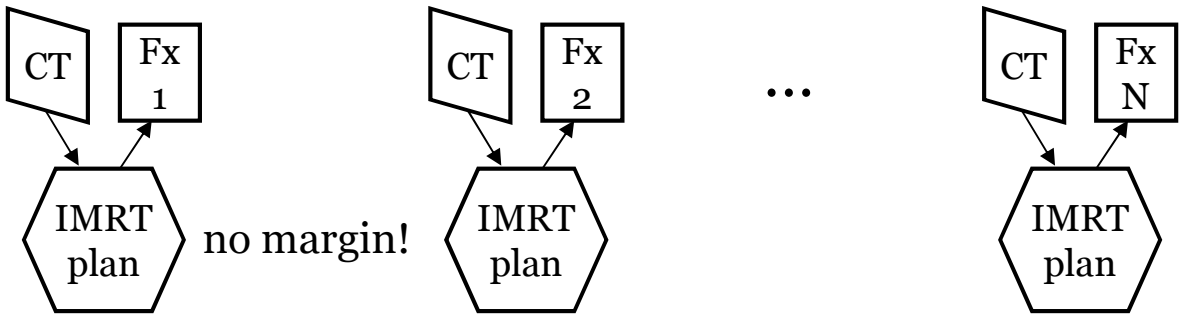
- IGRT – imaging!
- prediction methods/models
- evaluation approaches: prospective studies on real (and realistic!) patient data of a study cohort, treatment course simulations, motion models
- deformable registration, dose warping, dose accumulation
- probabilistic and robust planning approaches

This was all offline ART…
Now: Online Adaptive Re-Planning

M. Ghilezan et al. (2004): Online image-guided intensity-modulated radiotherapy for prostate cancer: How much improvement can we expect? A theoretical assessment of clinical benefits and potential dose escalation by improving precision and accuracy of radiation therapy. IJRPBP 60(5)

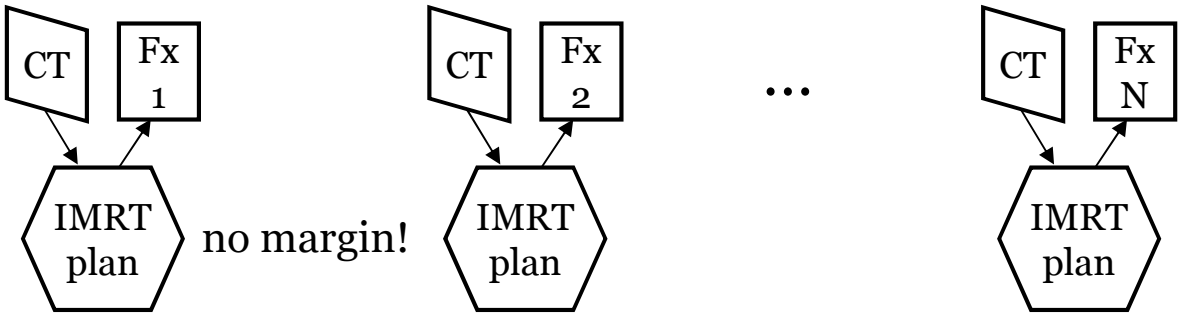
Idealized assumptions to investigate a 'gold-standard' benchmark online ART scheme:

- daily pre-treatment imaging and online IMRT replanning
- no intrafractional or other uncertainties => no PTV-margin necessary
- evaluation using deformable dose accumulation of multiple CTs of 18 patients



This was all offline ART…
Now: Online Adaptive Re-Planning

Ghilezan et al. 2004
(IJROBP 60(5))



Results (in short):

- average dose escalation by 13% possible, but with large interpatient variation (5-41%).
- 27% of the patient would have only minimal benefit (<5% dose escalation), 32% would have significant benefit (>15% dose esc.)

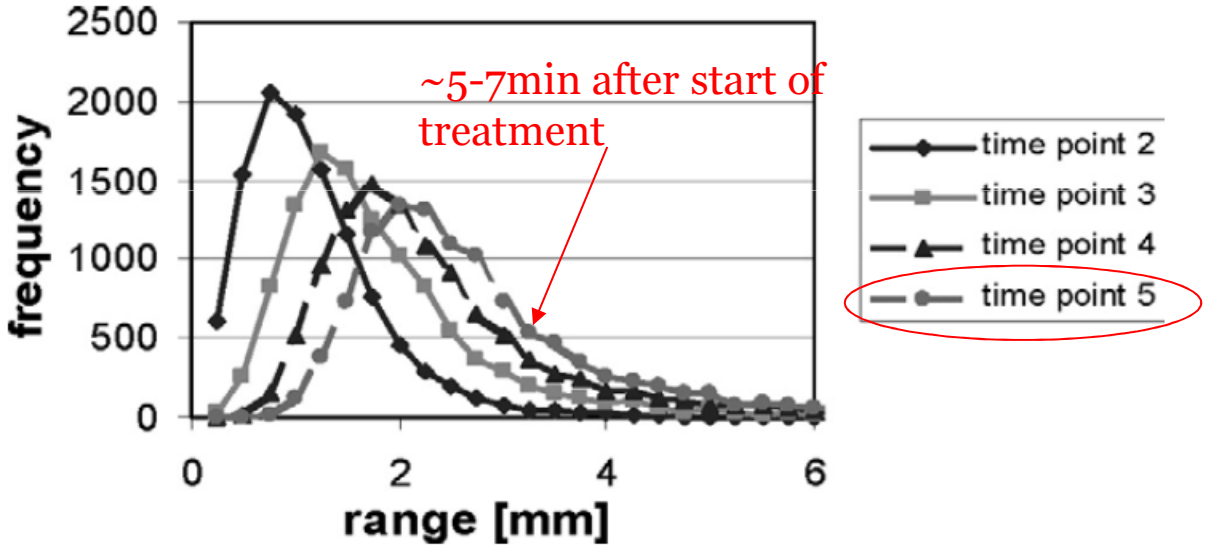
Note!:

- comparison relative to non adaptive standard IMRT (1 cm margin), not to offline adaptive IMRT.
- no margin, intrafraction motion and all other uncertainties neglected

Zero Margins in daily online ART/IGRT?
Intrafraction motion: prostate

A. N. T. J. Kotte et al. 2007: Intrafraction motion of the prostate during external-beam radiation therapy: Analysis of 427 patients with implanted fiducial markers. IJROBP 69(2)

Motion of implanted fiducial markers as seen with PIs:
11426 fractions of 427 pts.



- intrafraction motion range >2mm in 66% of all fractions, >3mm in 28%
- conclusion of the authors: lower limit of 2 mm for margins

Zero Margins in daily online ART/IGRT?
Intrafraction motion: prostate

D. Skarsgard et al. 2010: Planning target volume margins for prostate radiotherapy using daily electronic portal imaging and implanted fiducial markers. Radiat Oncol. 5:52

RESULTS:
Without image guidance, margins of 0.57 cm, 0.79 cm and 0.77 cm, along the left-right, superior-inferior and anterior-posterior axes respectively, are required to give 95% probability of complete CTV coverage each day. With the above image guidance strategy, these margins can be reduced to 0.36 cm, 0.37 cm and 0.37 cm respectively. Correction of all isocenter placement errors, regardless of size, would permit minimal additional reduction in margins.

Zero Margins in daily online ART/IGRT?
Intrafraction motion: prostate

...this was all portal-image based visualization of implanted fiducial markers.
*Improvements by daily **Cone-Beam-CT**-based setup?*

J. Adamson et al. 2011: Dosimetric effect of intrafraction motion and residual setup error for hypofractionated prostate intensity-modulated radiotherapy with online cone beam computed tomography image guidance. IJROBP 80(2)

CONCLUSIONS:
For protocols with CBCT guidance, RL, AP, and SI margins of 2, 4, and 3 mm are sufficient to account for translational errors; however, the large variation in patient-specific margins suggests that adaptive management may be beneficial.

Note: This is not resulting from geometric considerations (CTV appropriately covered by PTV), but from dosimetric considerations: coverage by 95% isodose line.
→ Influence of planning strategy and TPS!

Further limitations of daily rigid isocentre adaptations: Deformable uncertainties

again: prostate…

G. J. van der Wielen et al. 2008:Deformation of prostate and seminal vesicles relative to intraprostatic fiducial markers. IJROBP 72(5)

CONCLUSION:
Although prostate deformation with respect to implanted fiducial markers was small, the corresponding deformation of the seminal vesicles was considerable. Adding marker-based rotational corrections to on-line translation corrections provided a limited reduction in the estimated planning margins.

Further limitations of daily rigid isocentre adaptations: Deformable uncertainties

Head-and-neck…

S. van Beek et al. 2010: First clinical experience with a multiple region of interest registration and correction method in radiotherapy of head-and-neck cancer patients. Radiother. Oncol. 94(2)

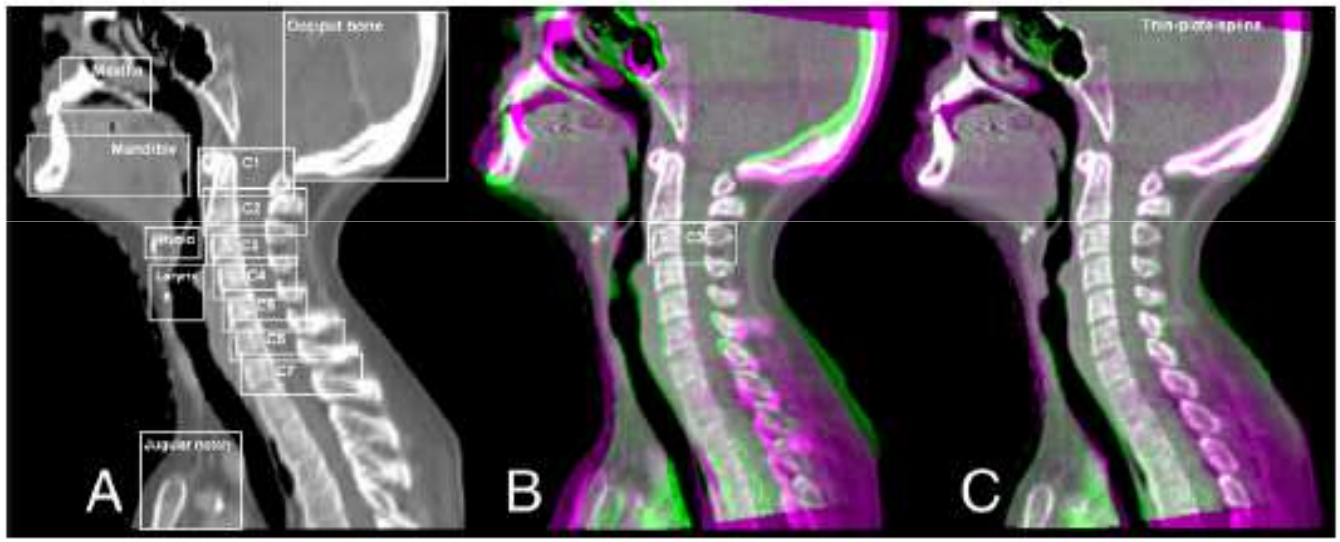


Fig. 1. Multiple regions of interest registration method on bony structures. (A) Definition of 13 regions of interest in the sagittal view. (B) Example registration of vertebrae C3 in green/purple overlay, note that other bony structures are not aligned. (C) Single assessment of all registration with a thin-plate-spline-based deformation.

In 40% of the CBCTs scans the errors in one or more subregions exceeded 5mm / 5°!

Daily rigid isocentre adaptations/IGRT: Conclusions

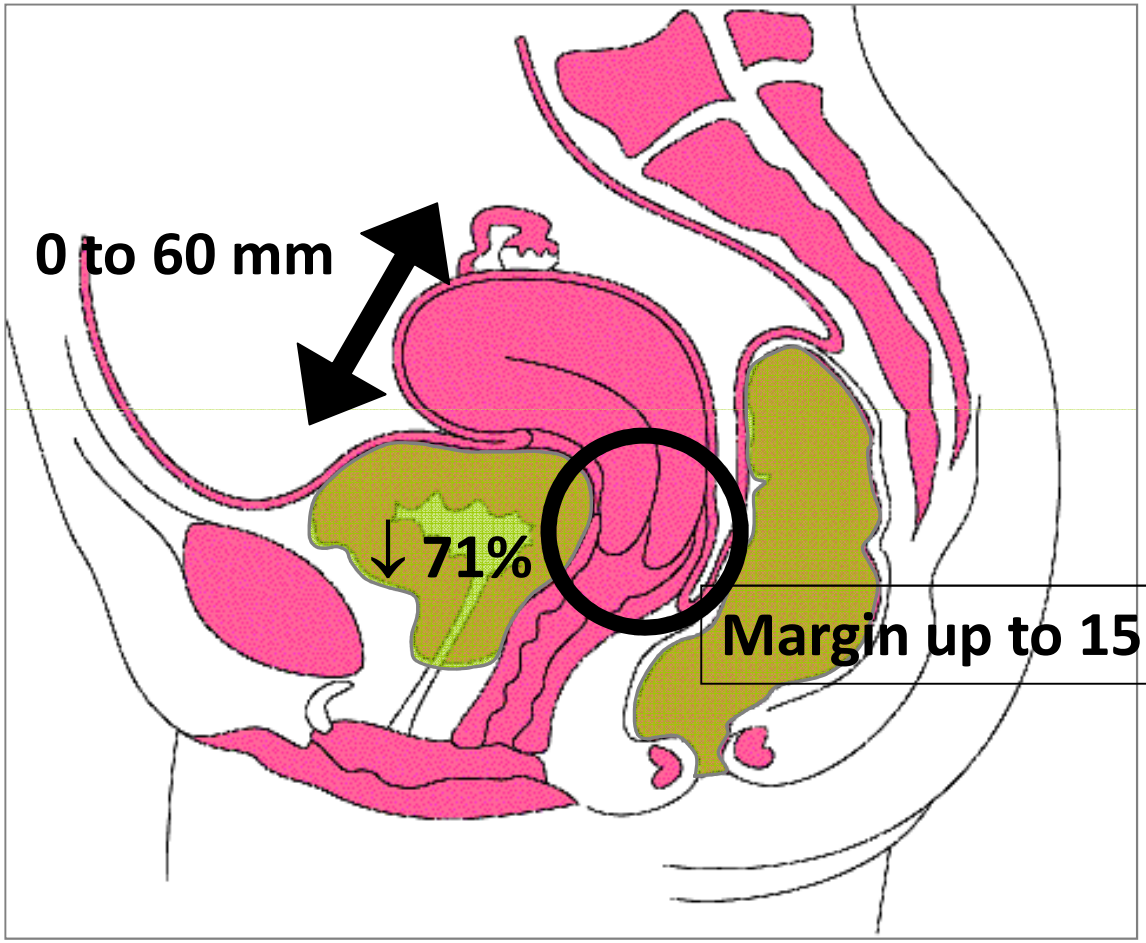
- Daily online adaptive concepts further *reduce* uncertainties, but *do not remove uncertainties completely*
- *there is still a lower limit for margin size* – treatment with 'zero margin' is not safe even with online imaging efforts
- too much margin reduction might be dangerous for other reasons as well: extra-capsular extension, see Chao et al. 2006 (IJROBP 65(4))

My personal opinion:
Even with advanced daily IGRT possibilities, there is still a need for 'smart' *probabilistic and robust planning approaches* – beyond the margin approach – due to the remaining uncertainties.

Treatment of targets with large interfractional deformations: Plan-selection strategies

courtesy M. Hoogeman (Erasmus MC)

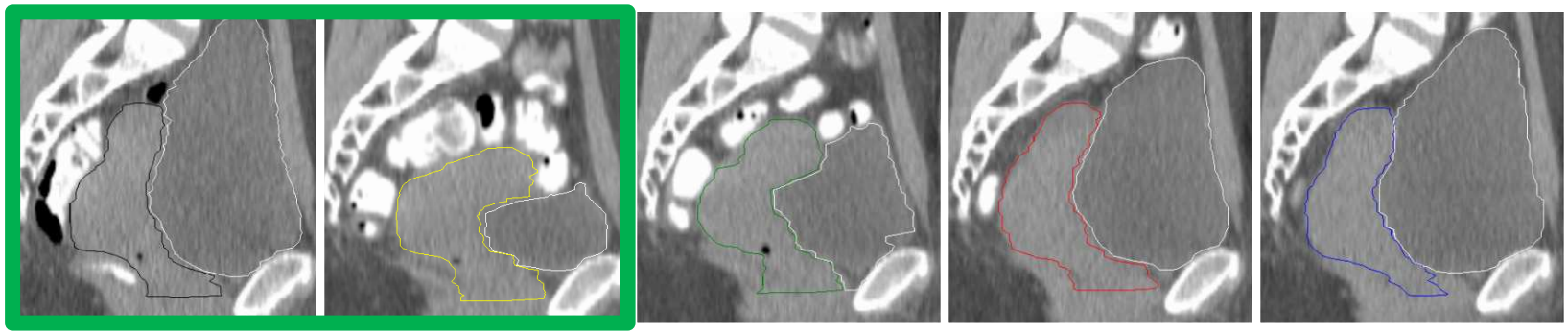
Example: female pelvis



Langerak et al.

Treatment of targets with large interfractional deformations: Plan-selection strategies

Example: female pelvis



Bondar et al. 2011 (Rad. Onc. 99(2)); courtesy M. Hoogeman (Erasmus MC)

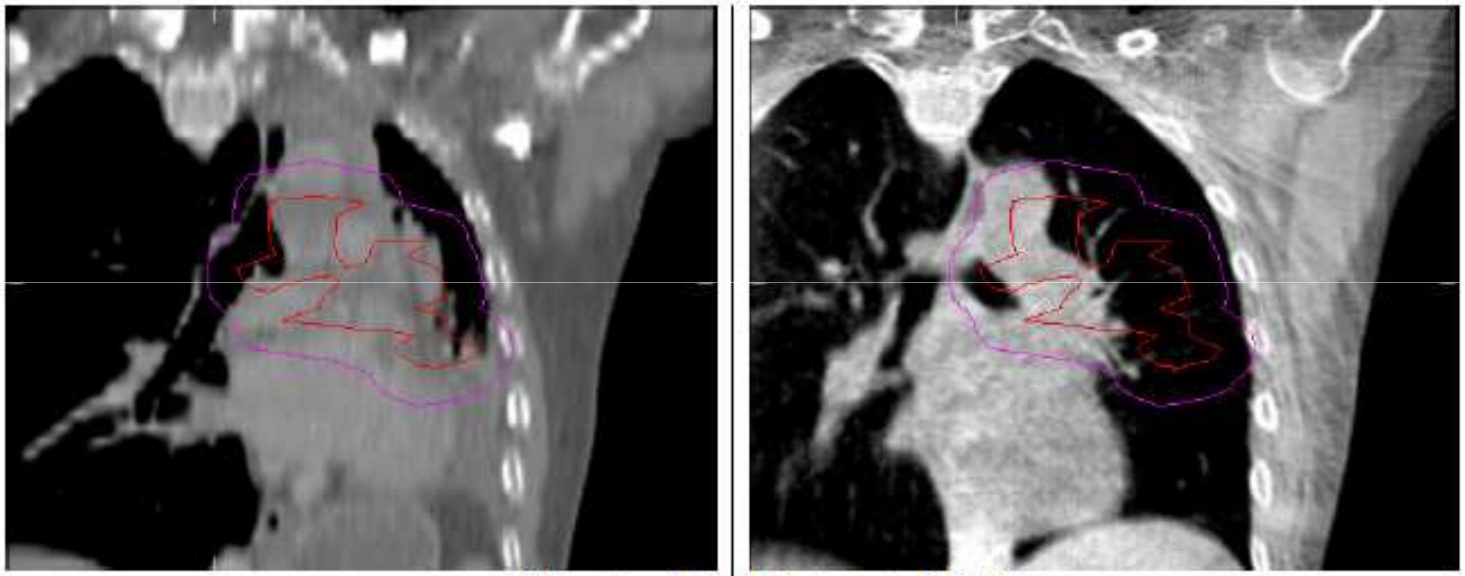
- ART for cervical cancer: For 90% of pts. with CTV coverage of >=95%...
  * non-ART population based **CTV-PTV volume 1702±274ml** (38mm margin)
  * online-adaptive 2-plan library: **CTV-PTV volume 764 ±165ml** (7mm margin)
  (Bondar et al. 2012, IJROBP 83(5))

- ART for bladder cancer, online adaptive 3-plan library:
  compared to non-ART, **V_{57Gy} of body tissue reduced by 34%**
  (Vestergaard et al. 2013, Rad. Onc. 109(3))
  and **median PTV volume reduction by 30%**
  (Vestergaard et al. 2014, Acta Oncol. 53(8))

Anatomical changes of trending nature

Sonke and Belderbos 2010
(Sem. Rad. Onc. 20(4))

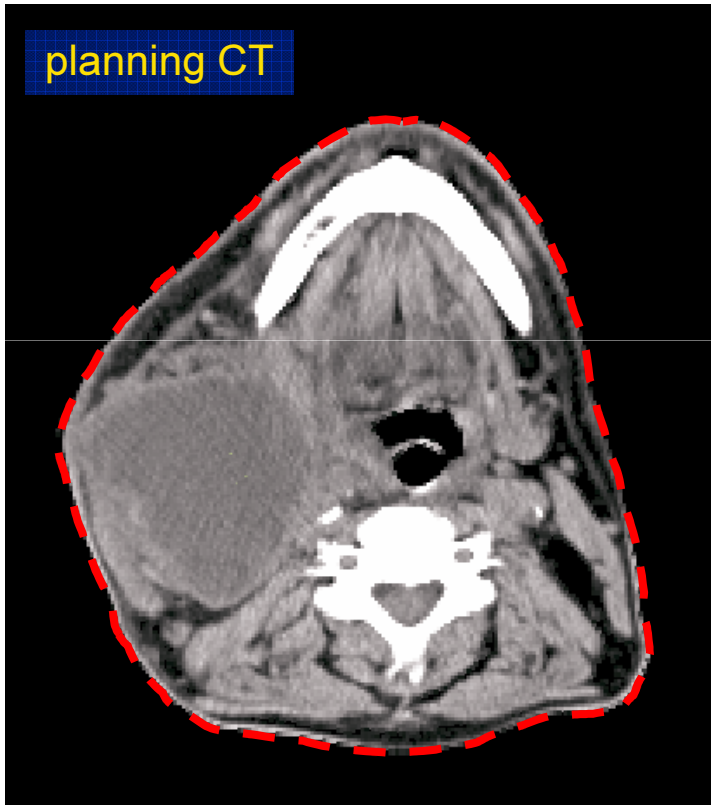
example: lung

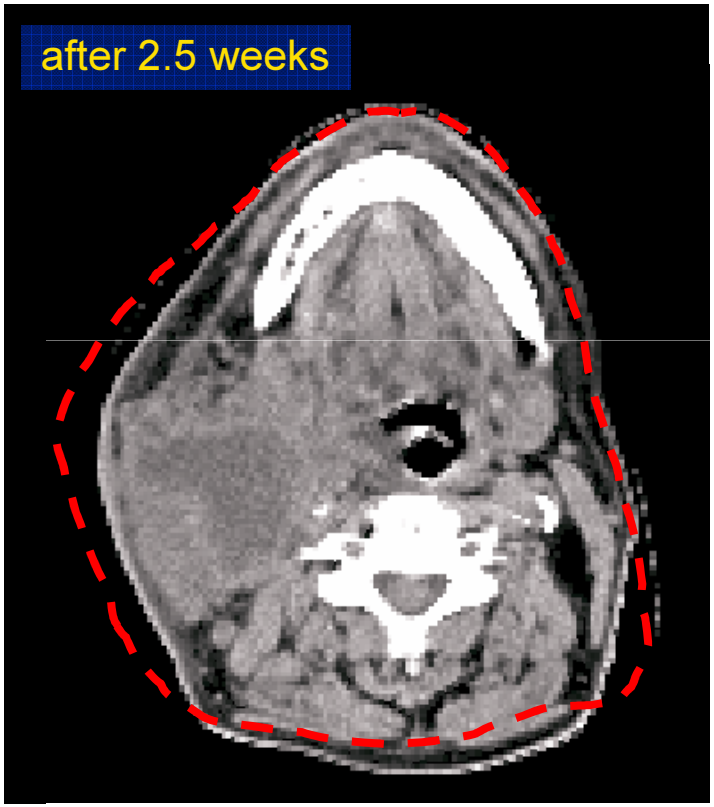


Planning CT | First week CBCT

Anatomical changes of trending nature

example: head-and-neck

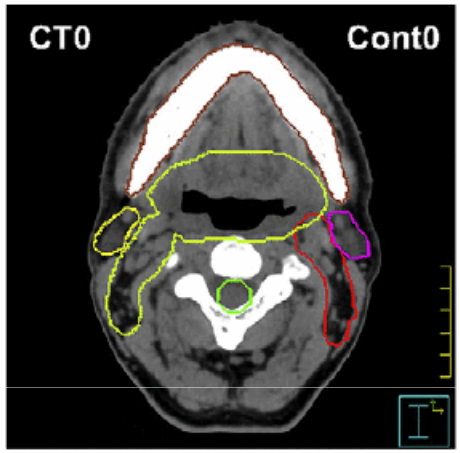


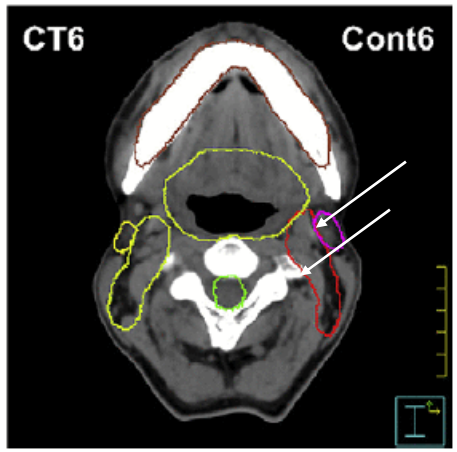


Anatomical changes of trending nature

Wu et al. 2009
(IJROPB 75(3))

example:
planning CT and 6 weeks later…





- systematic shrinkage of tumor/parotid volumes during treatment course, OARs move into high dose
- overdosage of OARs as compared to planning, and potential partial misses of CTVs
- more serious esp. for IMRT due to steep dose gradients

My personal opinion:
High(est) potential for clinical improvements by repeat imaging and multiple replanning/adaptation.

Wishful for the future: 'flag'/red light identifying patients who benefit most from one or multiple adaptations

Biologically Adapted Radiotherapy

Å. Søvik et al. 2010
(Sem. Rad. Onc. 20(4))

- adaptation by patient-individual biological/functional feedback

- **tumor:** changes in perfusion, hypoxic areas/re-oxigenation, tumor cell metabolism
- early predictive discrimination between 'responders' and 'non-reponders'
- **normal tissues:** e.g. lung perfusion changes, early detection of potential radiation-induced toxicity

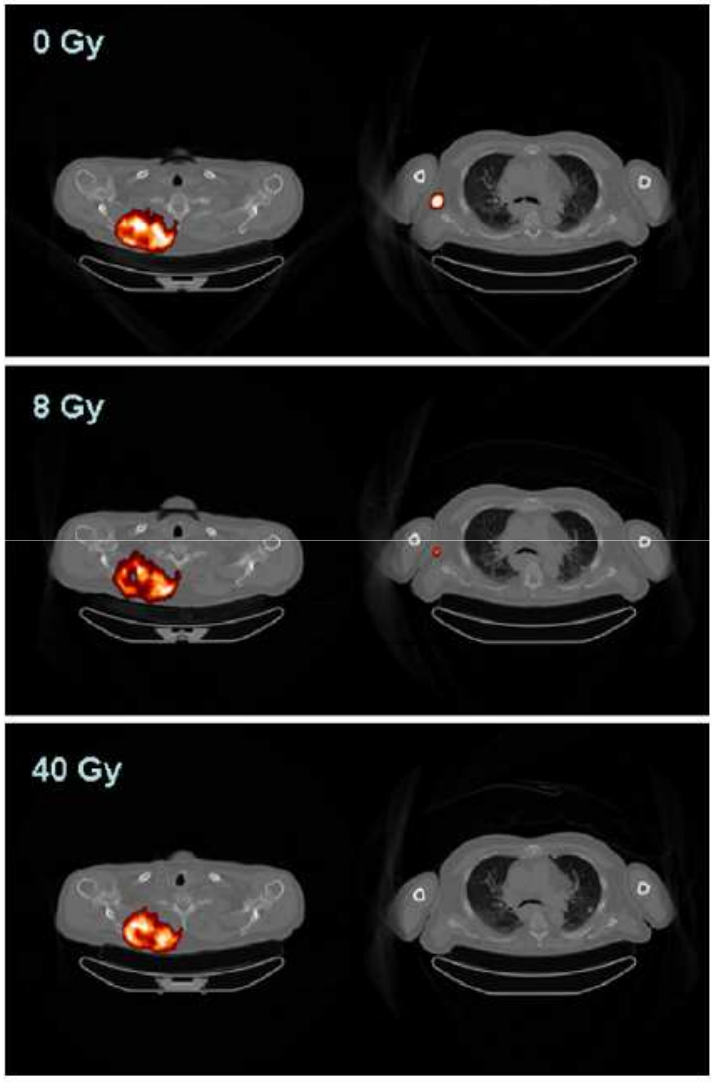


Figure 1 ^{18}F-FDG-PET/CT images of a patient with a sarcoma in the right scapula and a lymphoma in the right axillary lymph node. Images were taken before the start of radiotherapy, after 8 Gy (early treatment) and after 40 Gy (late treatment). PET/CT images courtesy of Jan Rødal.

Further reading…

Issue on 'Adaptive Radiotherapy' in *Seminars in Radiation Oncology*, Vol. 20(4), 2010, p. 215-88

Beyond others, site-specific articles about Adaptive Radiotherapy of…

- Head and Neck cancer
- Lung cancer
- Liver cancer
- Bladder cancer
- Cervical Cancer
- Prostate Cancer

Conclusions

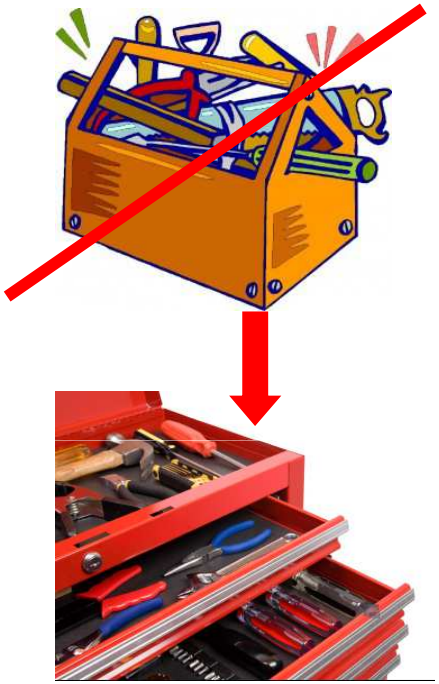
- *offline adaptive* setup correction and margin adapting protocols with clinically proven benefits and high efficiency to reduce systematic errors

- *online adaptive* schemes can further reduce uncertainties for the price of more frequent imaging, but there is a lower limit for margin reduction

provocative thought: a single adaptation – if well implemented and its effects evaluated thoroughly – is better than some 'latest' complex IGRT/ART scheme with daily imaging and repeat adaptations
– unless its benefits are clearly proven with treatment simulation approaches/patient data.

Conclusions [2]

- A real broad, clinical implemention of full adaptive schemes probably won't happen before vendors provide easy, yet robust and mature software solutions for meaningful adaptive workflows



Finally: Some (more) words of caution

The ‘latest-and-greatest’ ART schemes use methods from the ‘toolbox’, that start to find its way into commercial products and thus into clinical practice.

BUT be aware…

- Deformable registration errors => dose warping errors!
  Deformable registration is especially challenging for prostate/rectum
- Thus: Are hot/cold spots in an accumulated dose real? Should these be actively compensated for?
- Dose calculation on cone beam CT data: no high-precision dose calculation possible, thus dose-of-the-day calculation is subject to errors

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Modena
Policlinico

IGRT for IMRT

Frank Lohr, M.D.
University Medical Center Mannheim

Disclosure

Research and Training Agreement, Expert Testimony and Travel Grants with Elekta/IBA/C-Rad

Board Member of C-Rad

Basic treatment techniques

K. Bratengeier

In: Kiricuta, Definition of Target Volumes, 2001

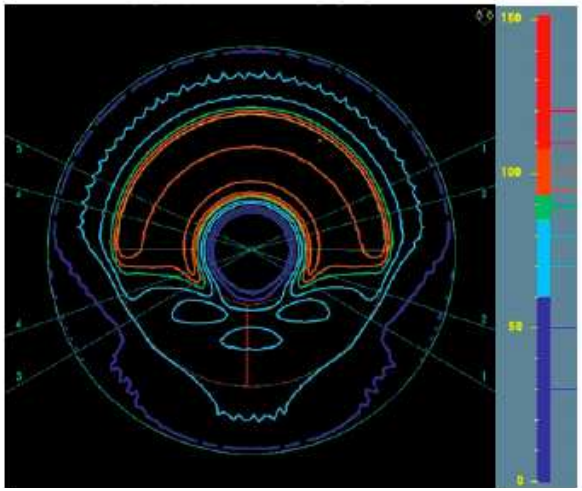
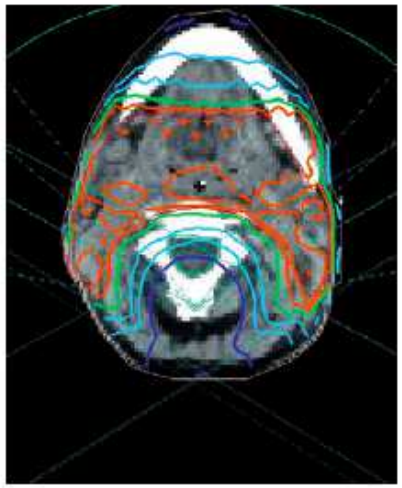
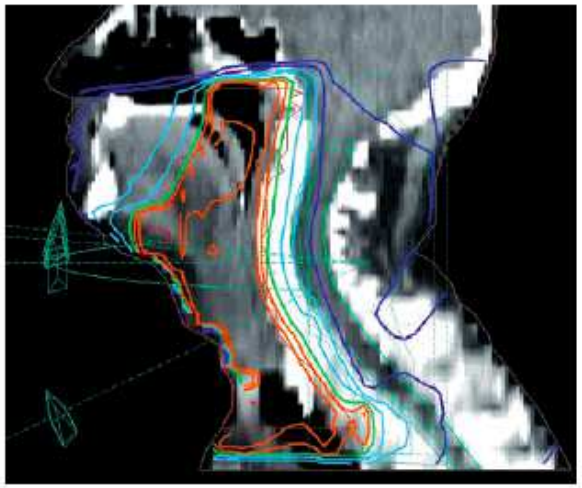


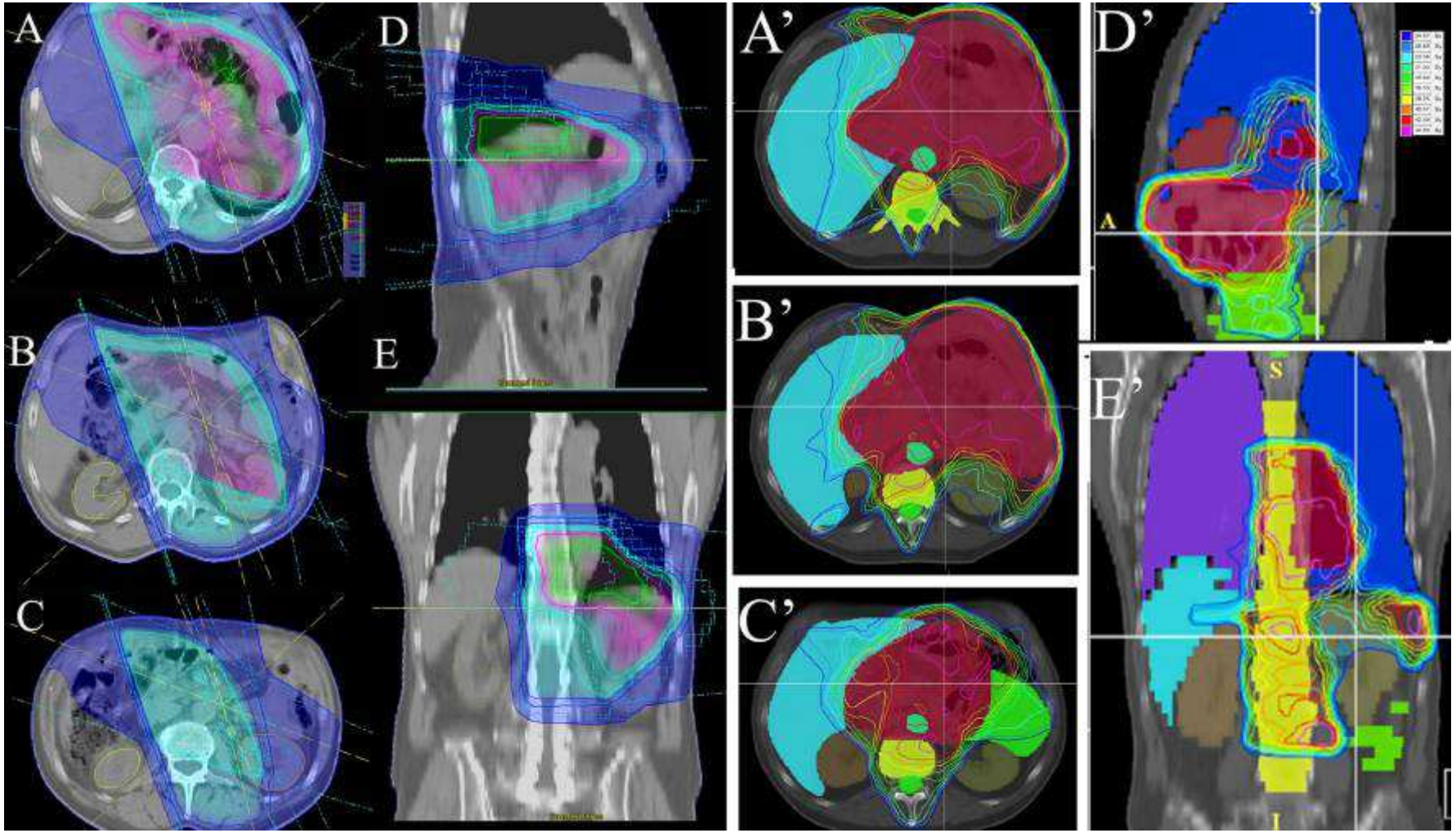
Figure 8. *Two-step IMAT in the case of a patient with Hypopharynx-Carcinoma. Left: transversal plane. Right: sagittal plane; 30%, 50%, 70%, 80%, 90% and 95% isodoses are shown in the same colors as labelled in figure 7.*





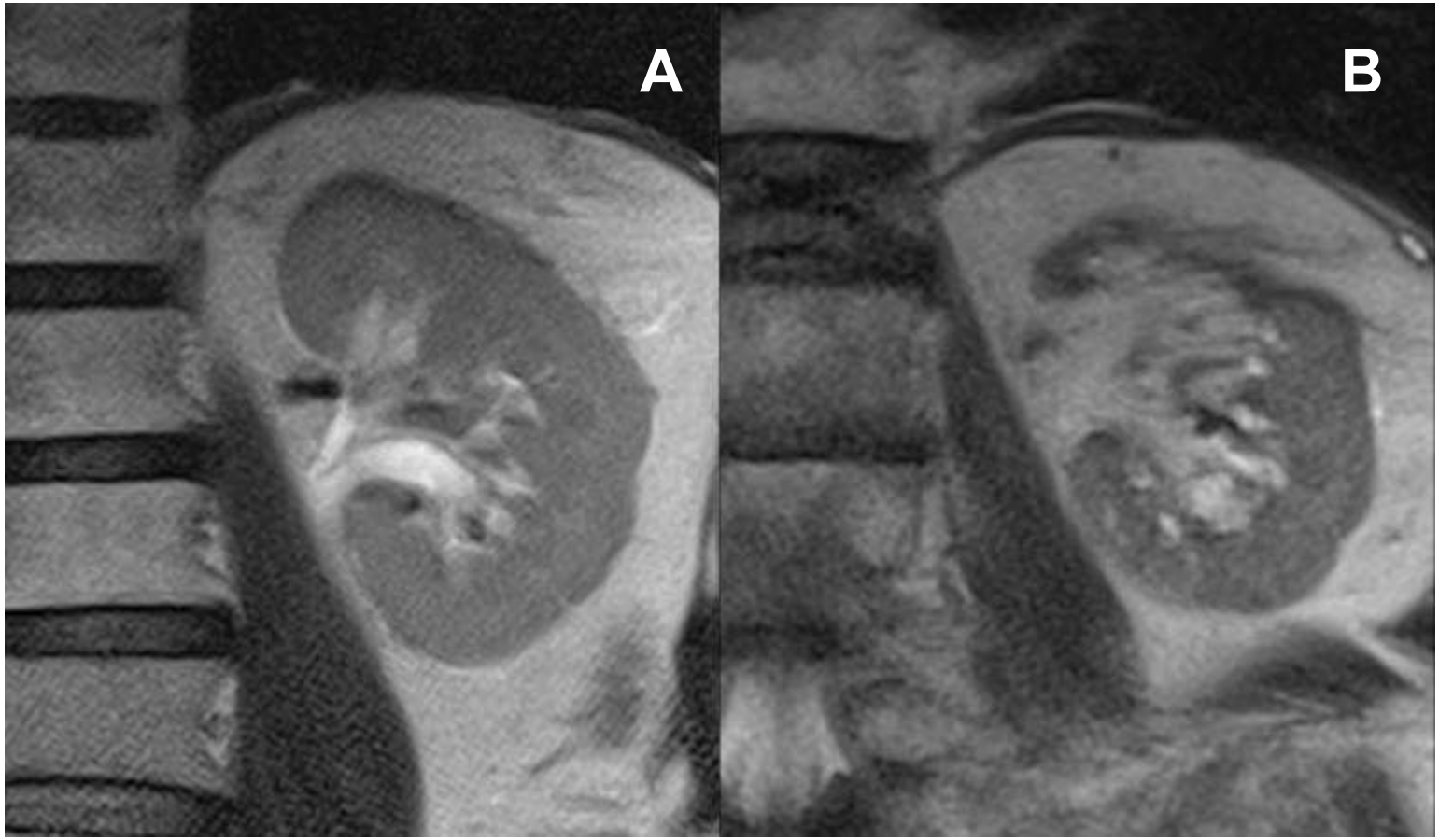
3DCRT

IMRT



	Right Kidney (Gy)							Left Kidney (Gy)						
	Median	Mean	D30	D60	Cranial part	Middle part	Caudal part	Median	Mean	D30	D60	Cranial part	Middle part	Caudal part
3DCRT-1	2.52	3.18	3.3	2.4	5	<5	<5	41.07	36.9	46.3	38.4	47.8	45.3	25.2
3DCRT-2	3.2	7.76	8.1	2.7	22.5	4.5	<4.5	25.8	22.95	27	18	45	42.7	36
IMRT-1	1.49	1.61	1.77	1.39	11	5	0	20.25	22.18	26.68	18.15	29	26	9
IMRT-2	14.77	16.12	17.4	13.8	13	8	4	23.84	23.28	27.7	21.2	26.8	18.5	13.5

T2w: (A) IMRT vs. (B) 3D

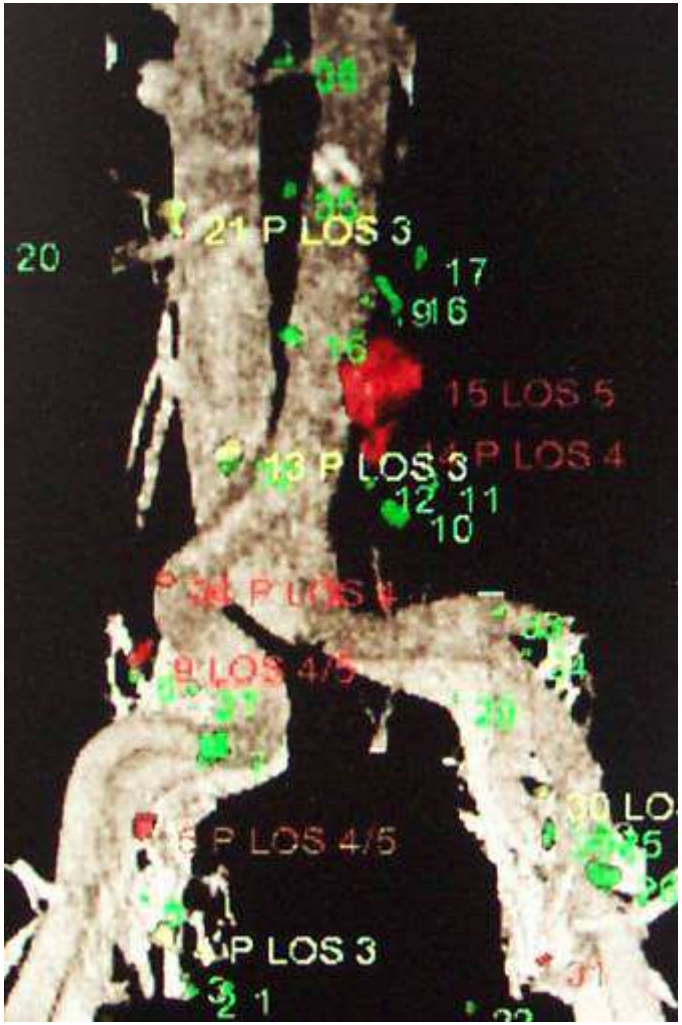


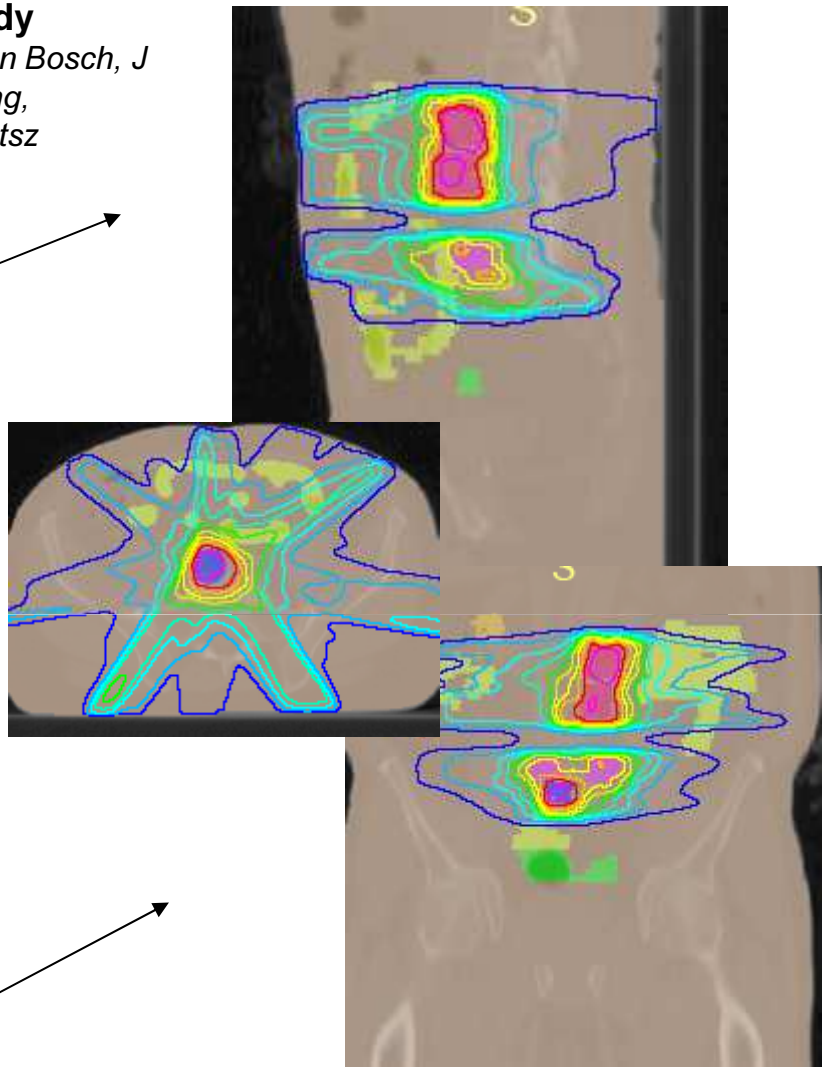
Haneder et al., SUON, 2012

MRI with a lymph-node-specifi c contrast agent as an alternative to CT scan and lymph-node dissection in patients with prostate cancer: a prospective multicohort study

Roel A M Heesakkers, Anke M Hövels, Gerrit J Jager, Harrie C M van den Bosch, J Alfred Witjes, Hein P J Raat, Johan L Severens, Eddy M M Adang, Christina Hulsbergen van der Kaa, Jurgen J Fütterer, Jelle Barentsz

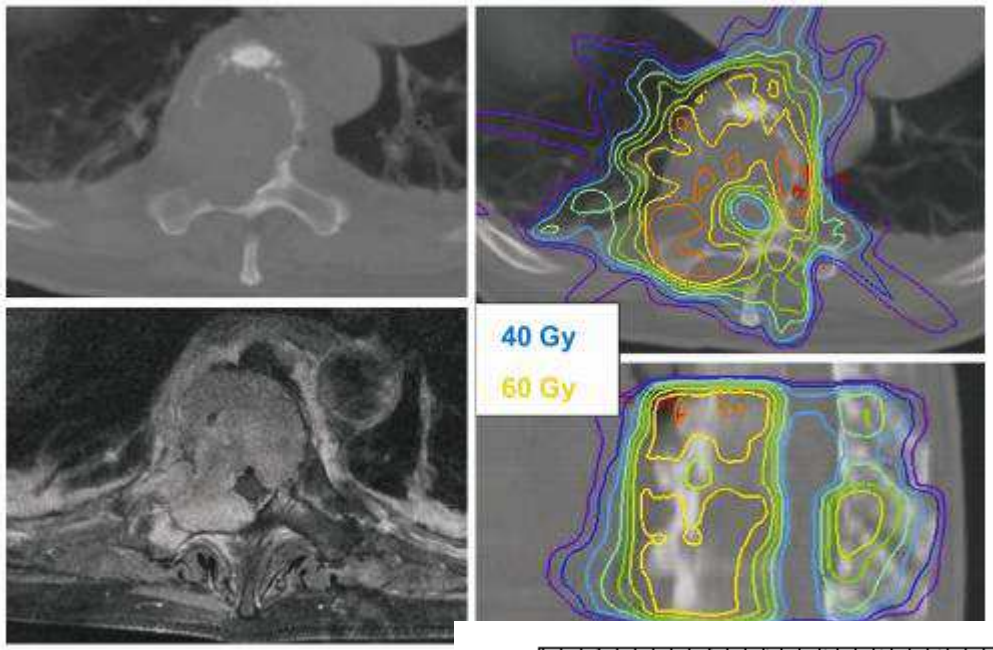
9/2008





Weidner et al., SUON, 2011

Dose-Escalated Irradiation of Paraspinal Metastases



Guckenberger et al., 2009

40 Gy in the spinal canal in 2 Gy
>50 Gy in PTV in SD > 2 Gy

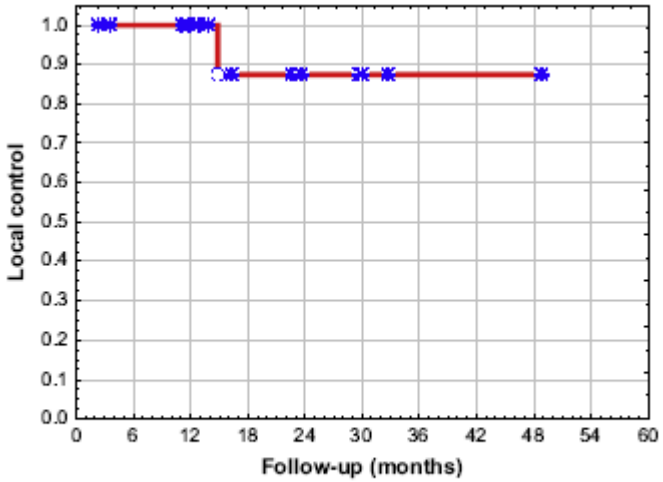


Fig. 2. Local control for all patients with spinal metastasis ($n = 15$).

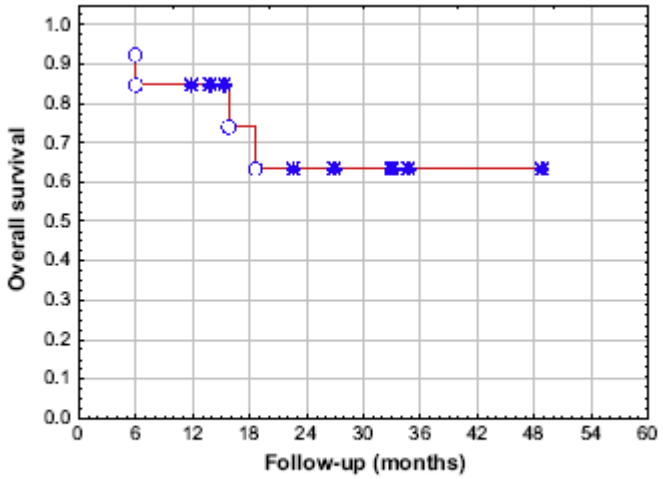


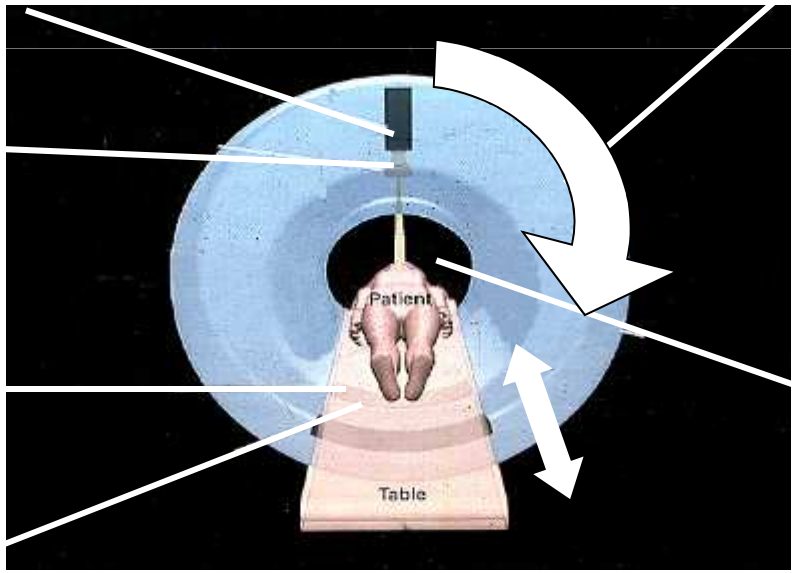
Fig. 4. Overall survival after radiotherapy for spinal metastasis ($n = 13$).

MIMiC

www.nomos.com

The HI•ART TomoTherapy System

CONTOURED CT/MR/PET IMAGE INPUT → IMRT DOSE OPTIMIZATION FOR TOMOTHERAPY → HELICAL DELIVERY OF RT



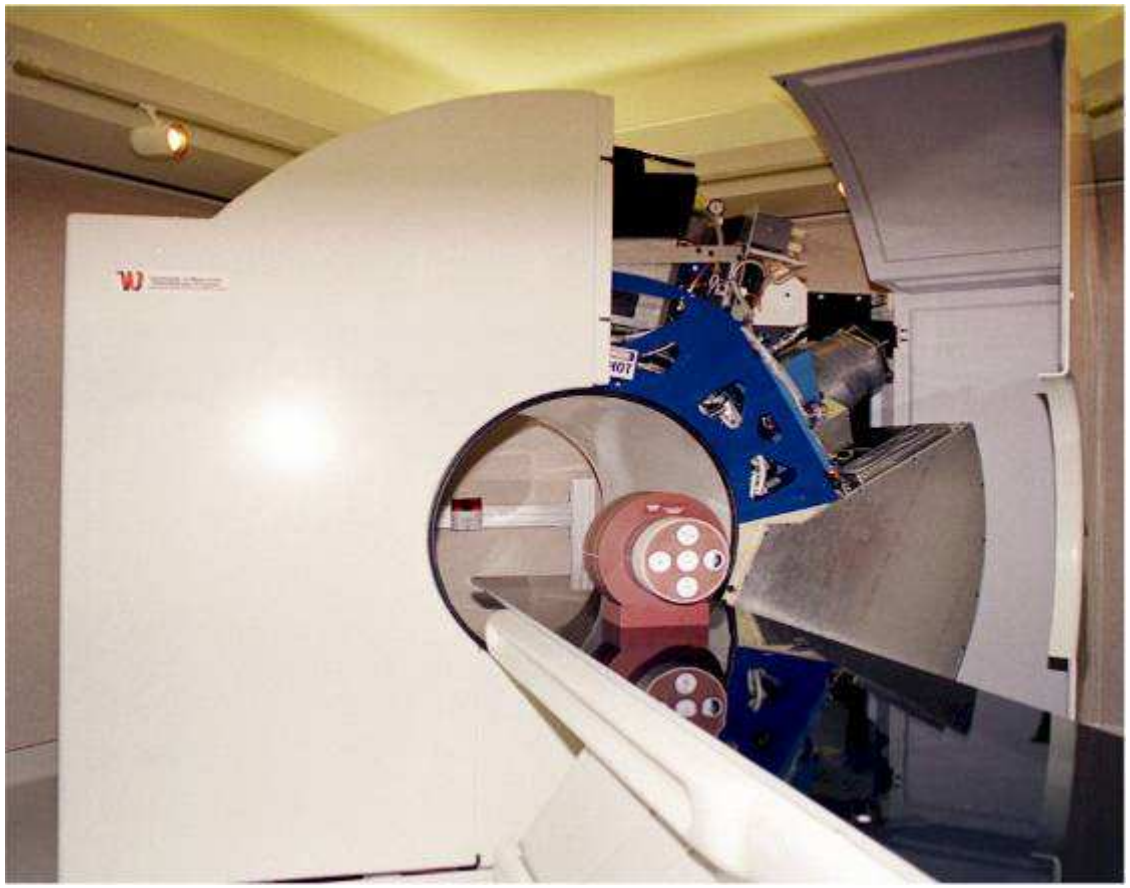
The HI•ART TomoTherapy System

Dr. T. Rock Mackie with the University of Wisconsin
Tomotherapy Research Unit

www.tomotherapy.com

The HI•ART TomoTherapy System

UW Tomotherapy Research Unit

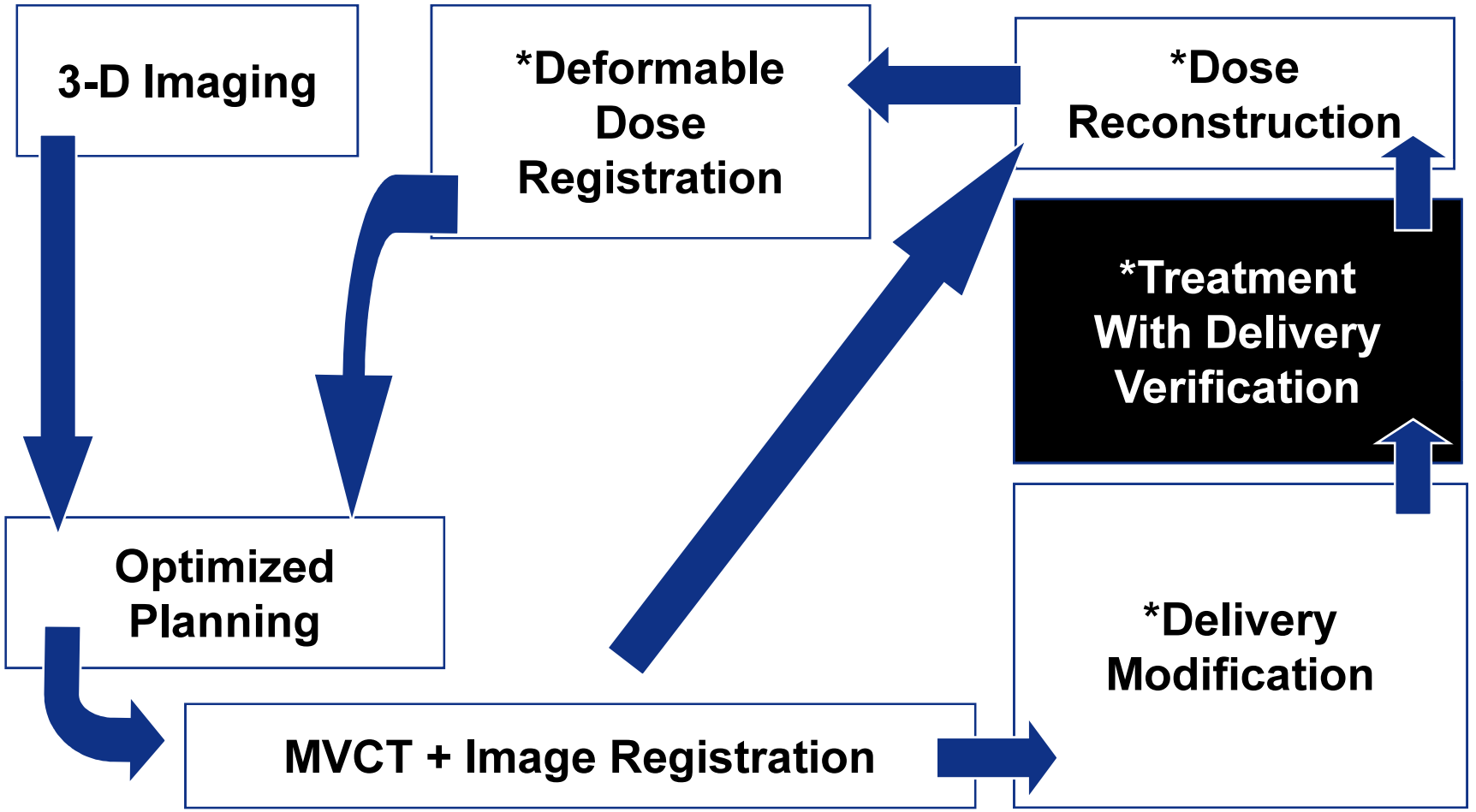


www.tomotherapy.com

Adaptive Radiotherapy

www.tomotherapy.com

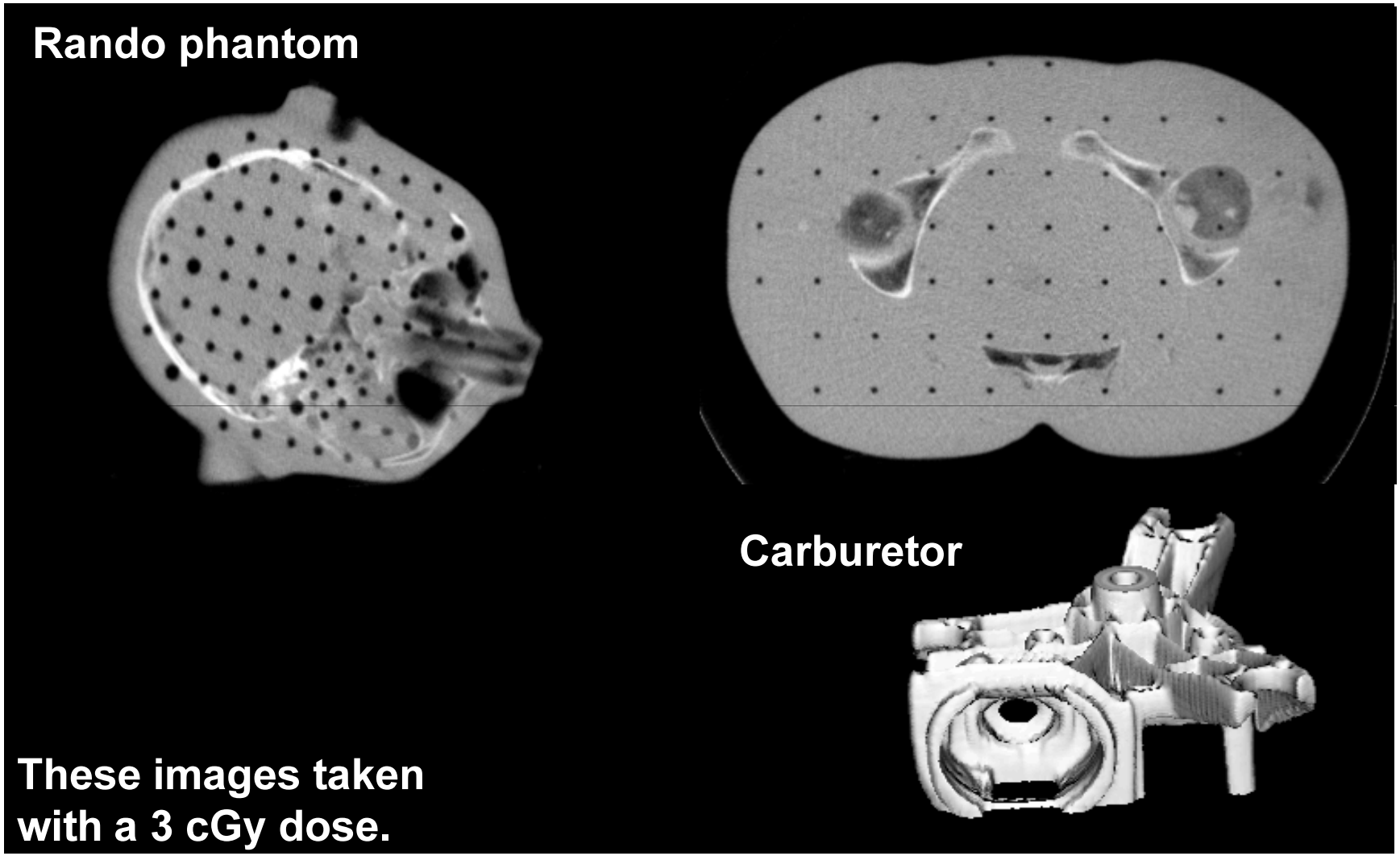
This is where we want to go



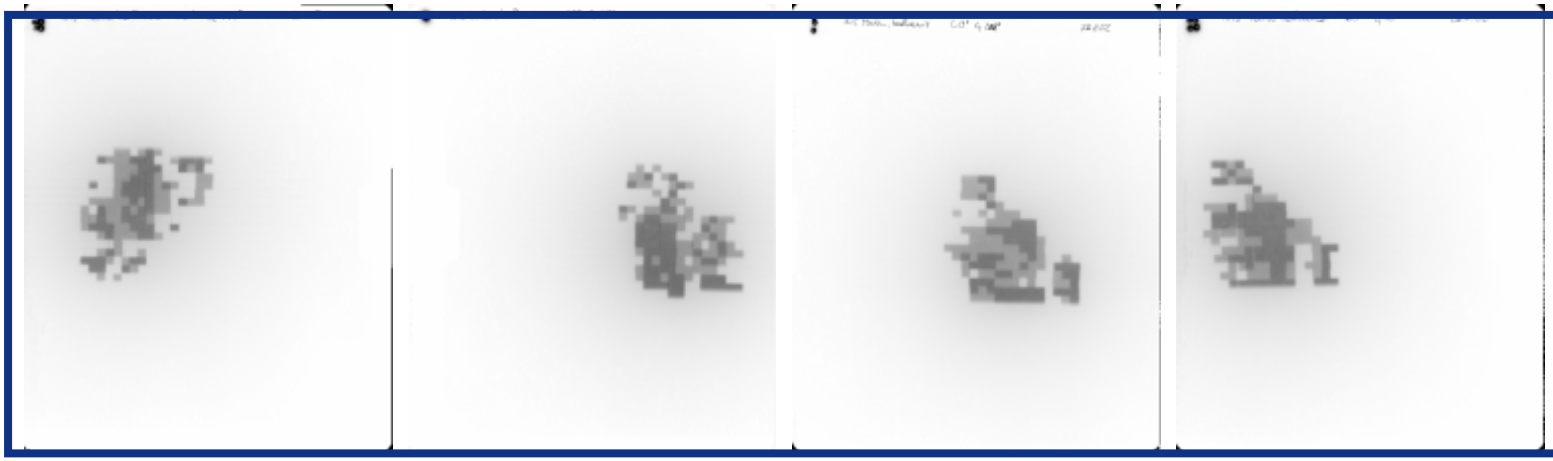
(*These concepts are work in progress – product not available for sale.)

Megavoltage CT Images

www.tomotherapy.com

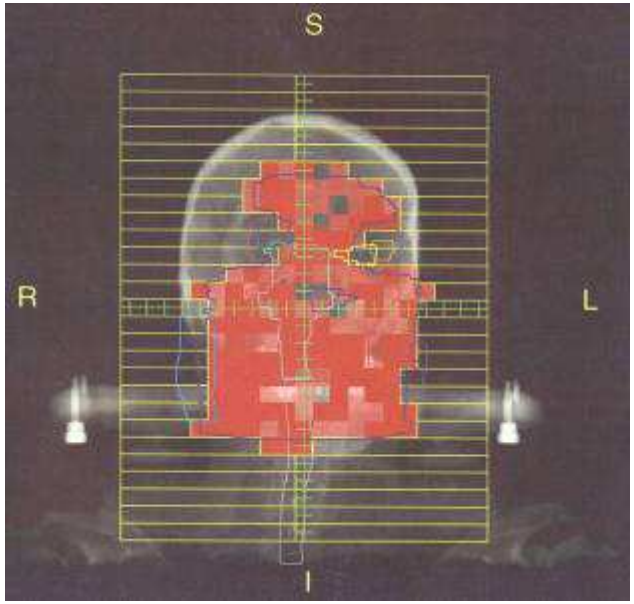


Verification/QA



Primary Fluence as detected with trayhold-mounted films

DRR with superimposed Intensity Matrix



Respective Double Exposure of actual treatment

Positioning Errors


CTV
PTV
PTV
IG

How to minimize

PTV_{IG}

Interfractional Error

Intrafractional Error

Interfractional Error

Systematic Error
Random Error

Intrafractional Error

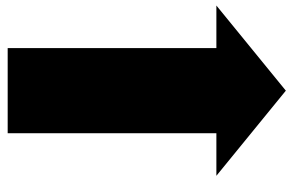
➡ **PTV_{IG}**

Interfractional Error

~~*Systematic Error*~~

Random Error

Intrafractional Error



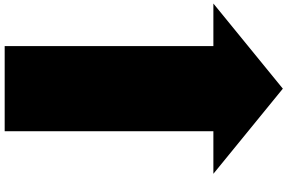
PTV_{IG}

Interfractional Error

~~*Systematic Error*~~

~~*Random Error*~~

Intrafractional Error



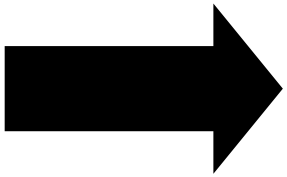
PTV_{IG}

Interfractional Error

~~*Systematic Error*~~

~~*Random Error*~~

~~Intrafractional Error~~



PTV_{IG}

And for a more detailed Discussion of Positioning Errors please turn to:

Errors and Margins in Radiotherapy

Marcel van Herk

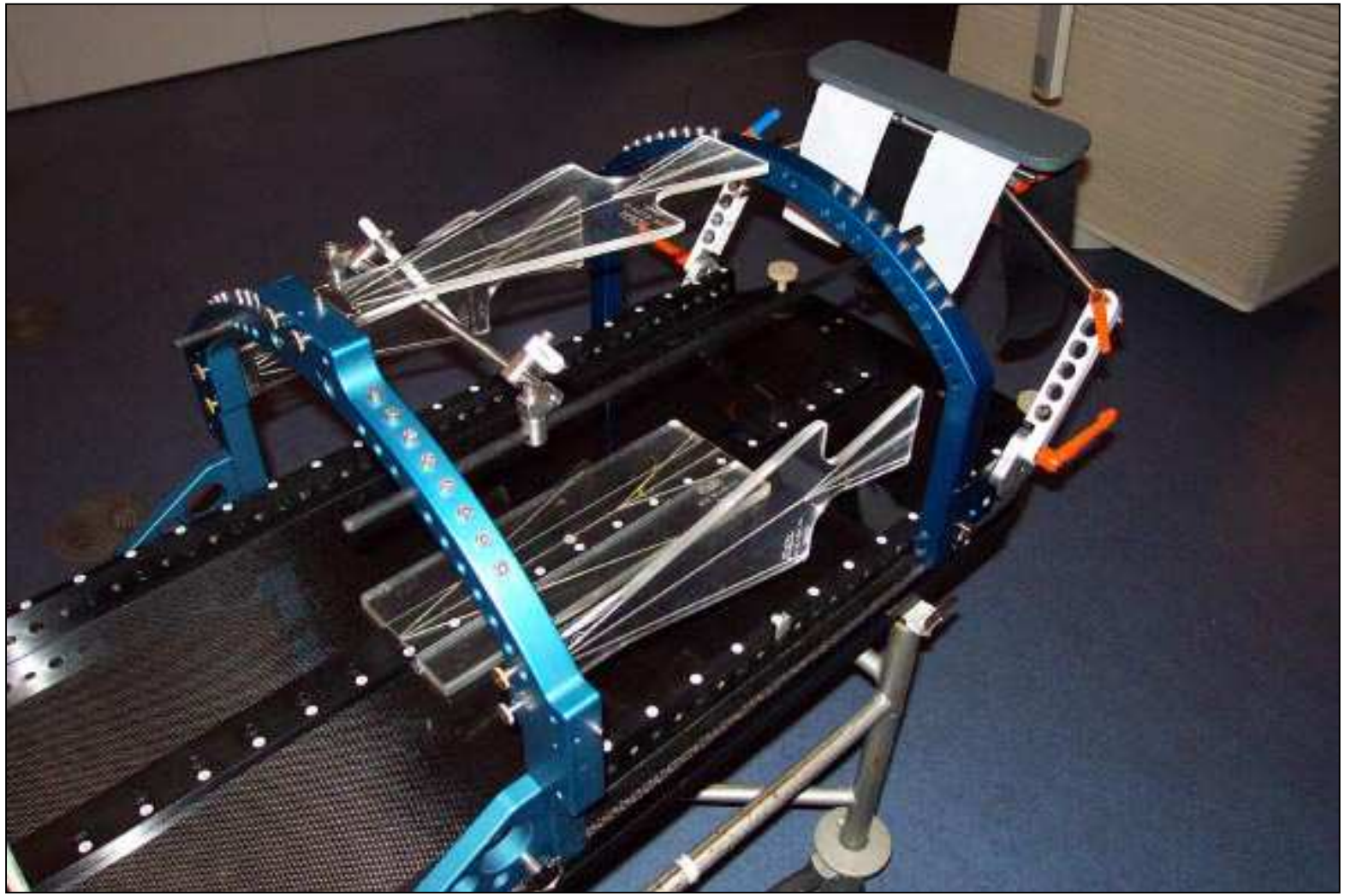
Clinical radiotherapy procedures aim at high accuracy. However, there are many error sources that act during treatment preparation and execution that limit the accuracy. As a consequence, a safety margin is required to ensure that the planned dose is actually delivered to the target for (almost) all patients. Before treatment planning, a planning computed tomography scan is made. In particular, motion of skin with respect to the internal anatomy limits the reproducibility of this step, introducing a systematic setup error. The second important error source is organ motion. The tumor is imaged in an arbitrary position, leading to a systematic organ motion error. The image may also be distorted because of the interference of the scanning process and organ motion. A further systematic error introduced during treatment planning is caused by the delineation process. During treatment, the most important errors are setup error and organ motion leading to day-to-day variations. There are many ways to define the margins required for these errors. In this article, an overview is given of errors in radiotherapy and margin recipes, based on physical and biological considerations. Respiration motion is treated separately.

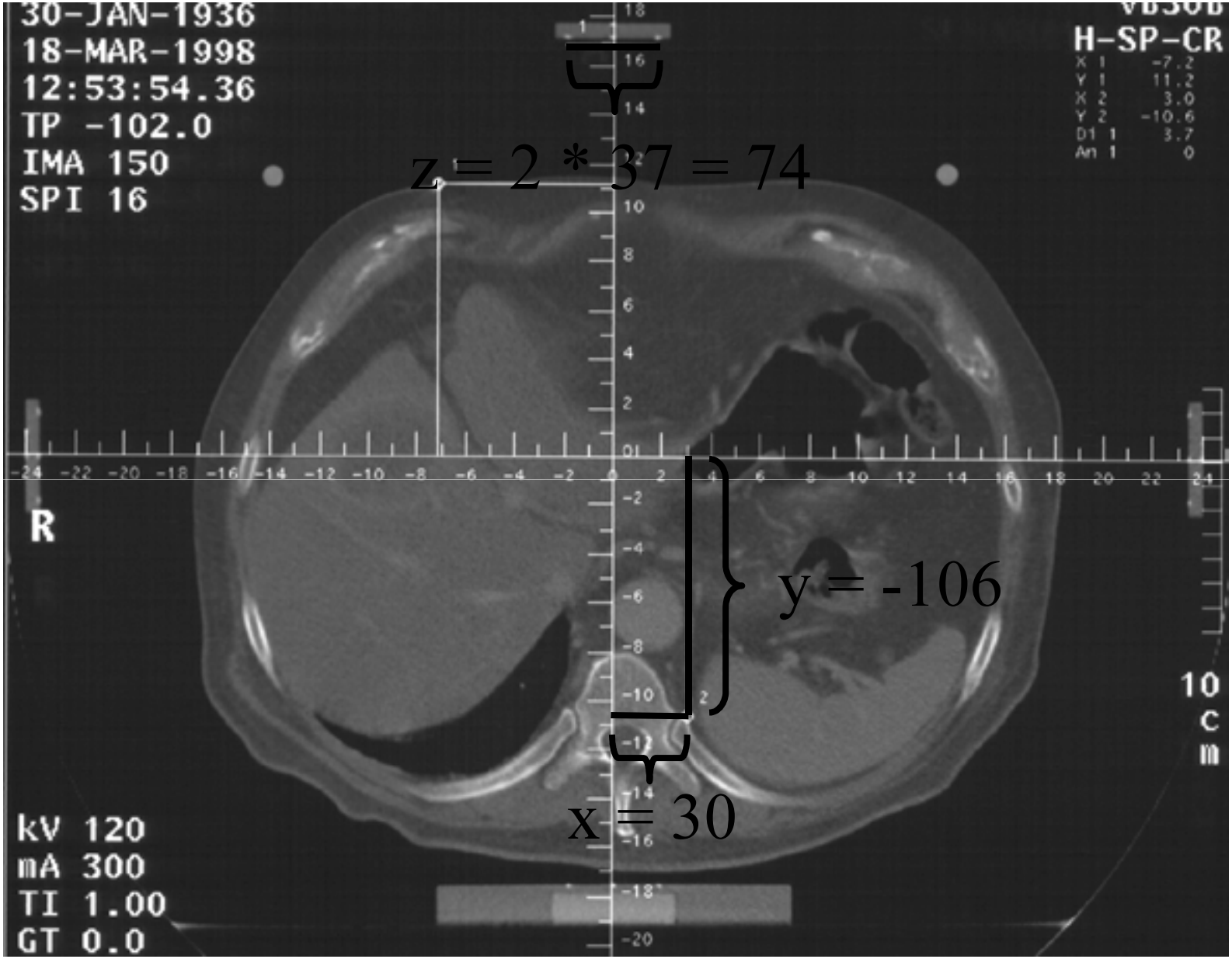
Sem Rad Onc, 2004

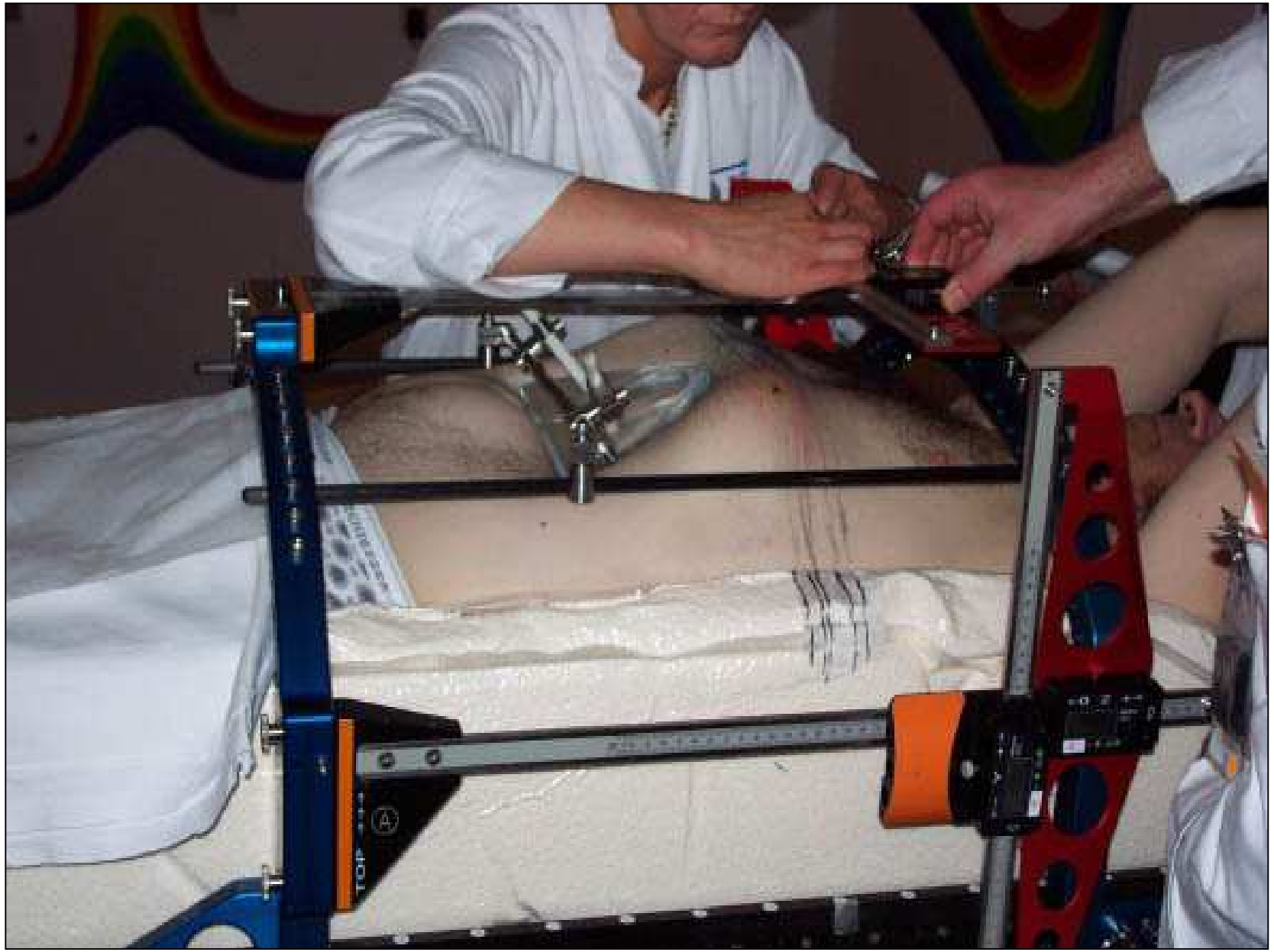
„Will positioning errors ever be zero?“

Well, for photons we are getting sufficiently close to zero…

ECS Basis-System



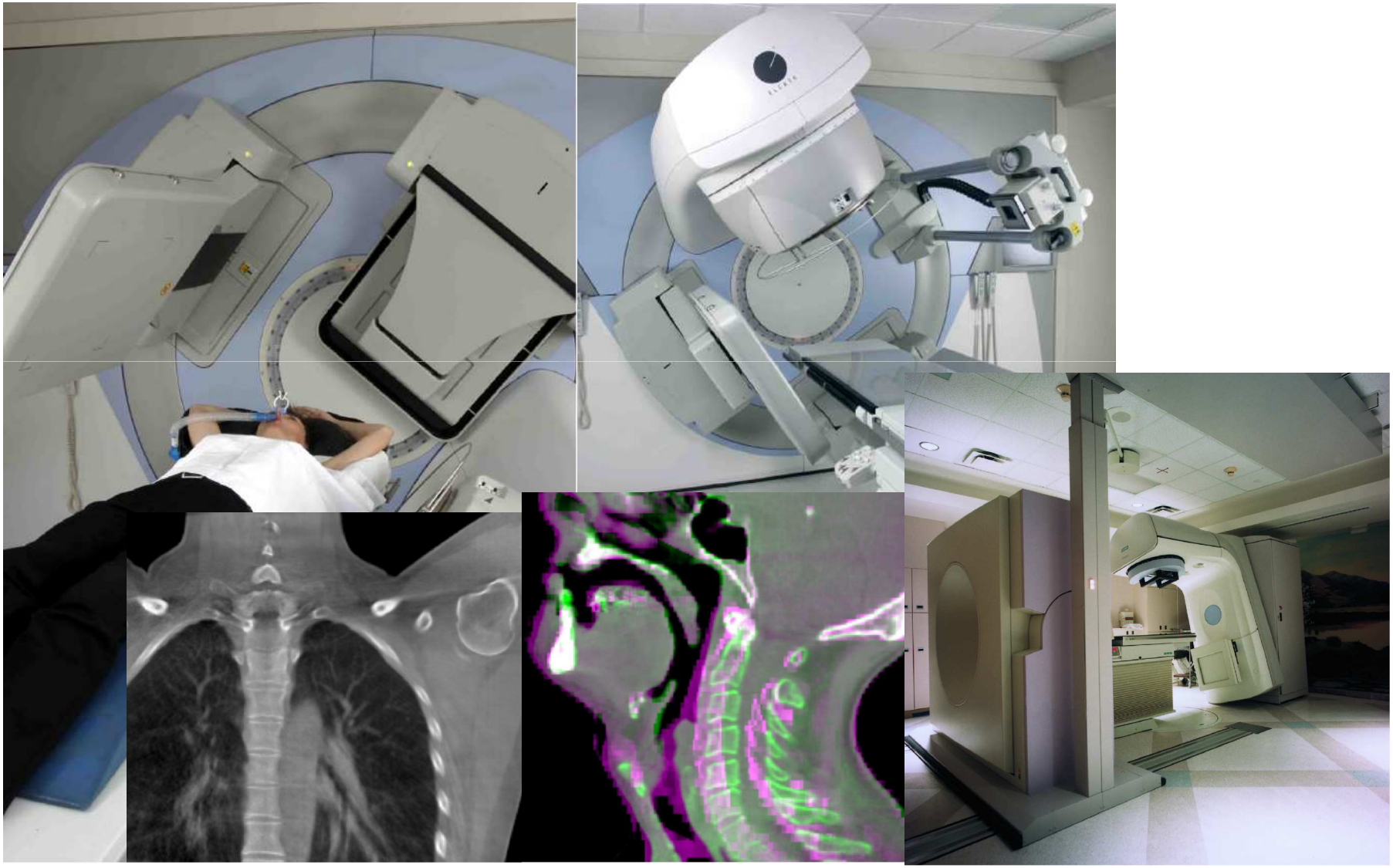

30-JAN-1936
18-MAR-1998
12:53:54.36
TP -102.0
IMA 150
SPI 16
H-SP-CR
X 1 -7.2
Y 1 11.2
X 2 3.0
Y 2 -10.6
D1 1 3.7
An 1 0
z = 2 * 37 = 74
y = -106
x = 30
R
10 cm
kV 120
mA 300
TI 1.00
GT 0.0


TOP

Stereotactic Ultrasound-System

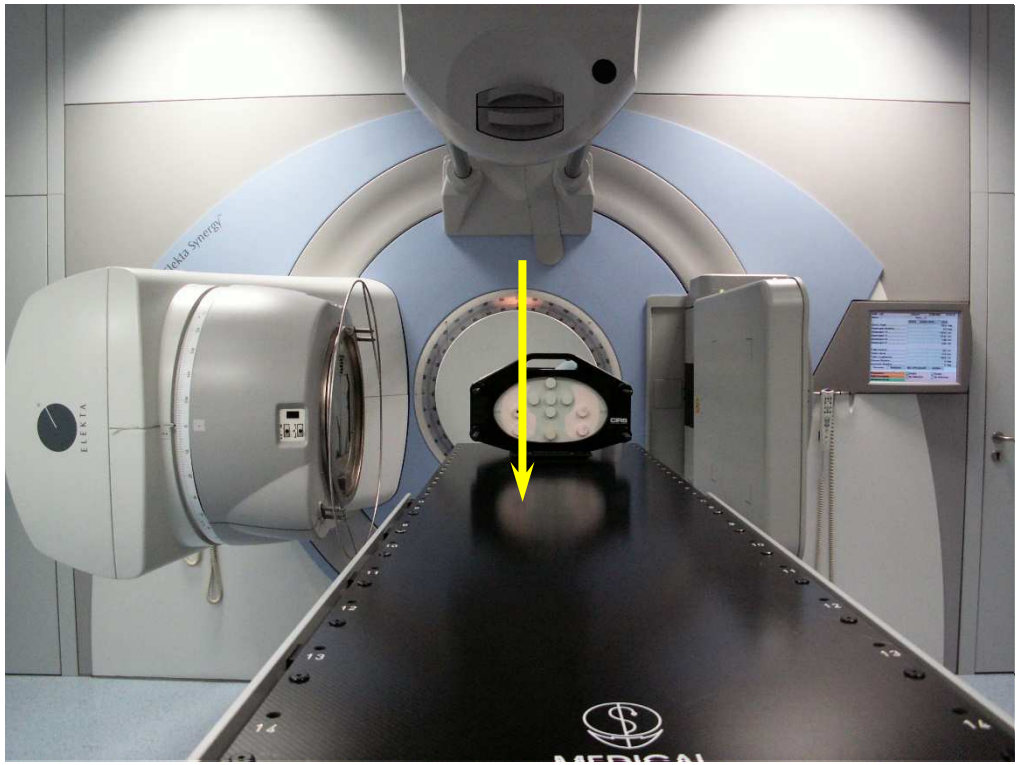
Stereotactic Ultrasound-System
„BAT“

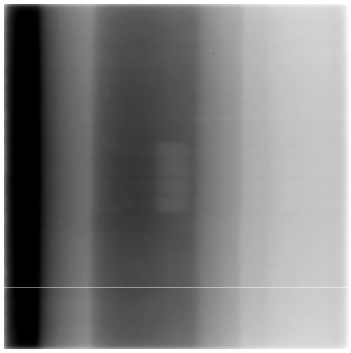
Image Guided Radiotherapy (IGRT)



Dipl. Phys. C. Walter

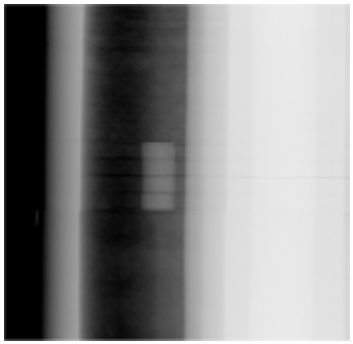
Motiavation for kV-Imaging…





MV-Image

(projection)

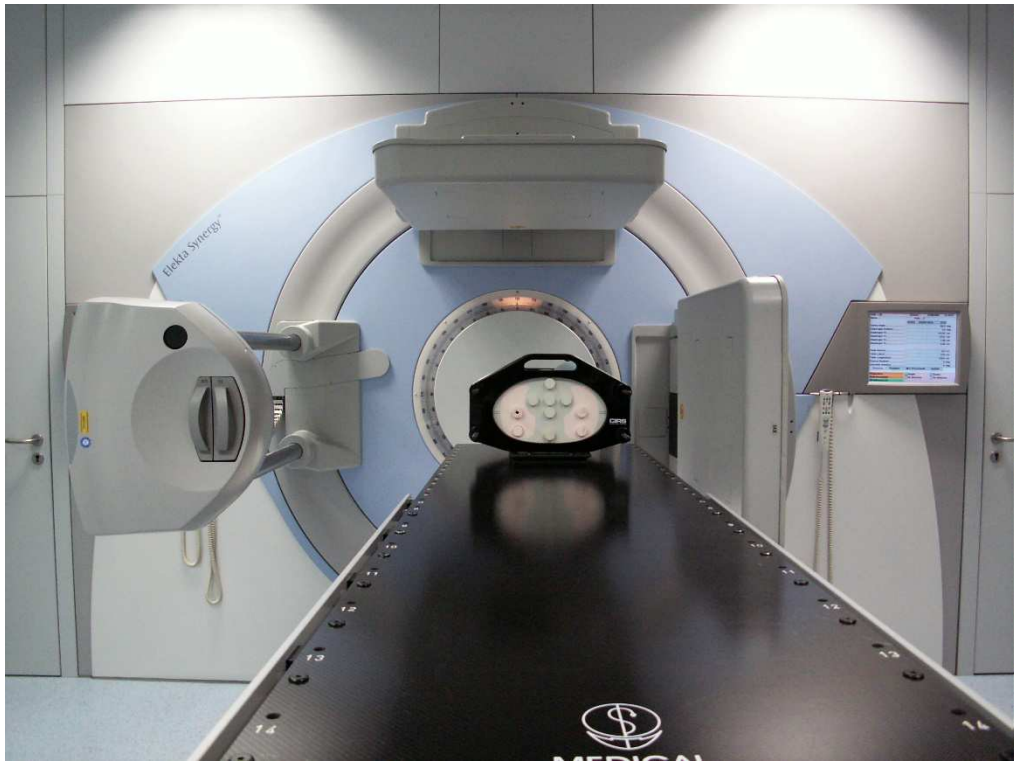


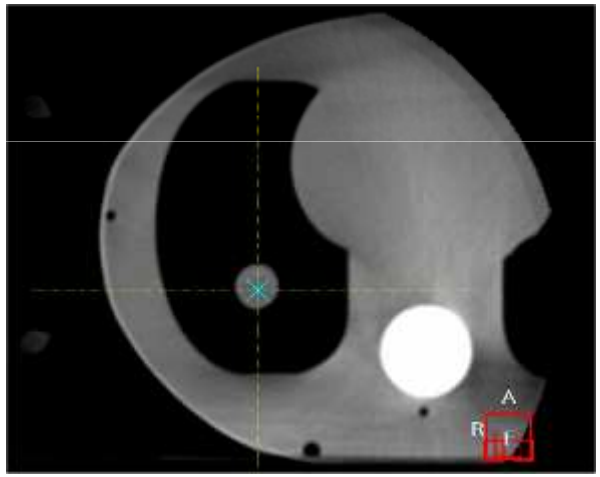
kV-Image

(projection)

Dipl. Phys. C. Walter

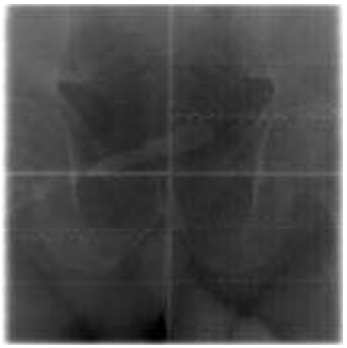
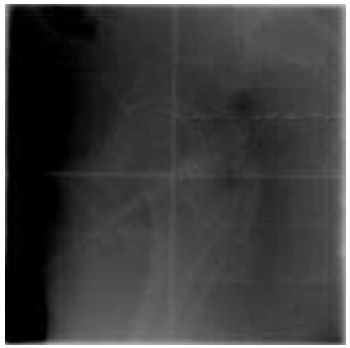
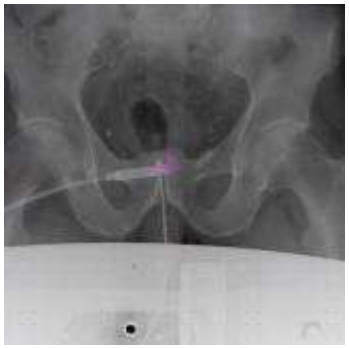
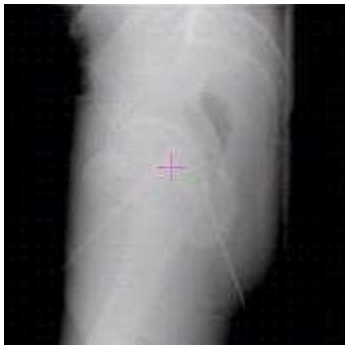
… and cone-beam scanning





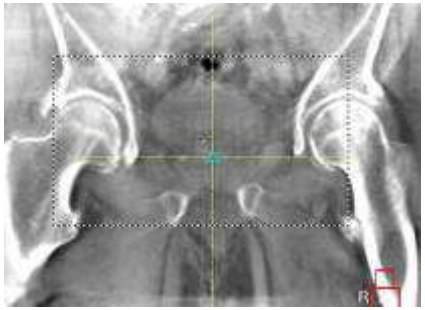
Dose for positioning verification I

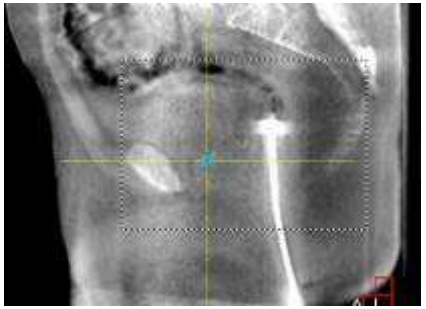
Walter et al., IJROBP, 2006

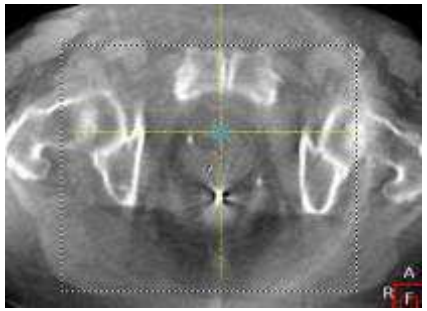
	6 MeV Photons		120 keV Photons	
	ap	lateral	ap	lateral
				
skin [mGy]	57.8	69.4	0.7	1.1
rectum [mGy]	33.9	31.7	0.2	0.1

RBE of 2 for kV radiation

cone-beam CT in-vivo dose measurement

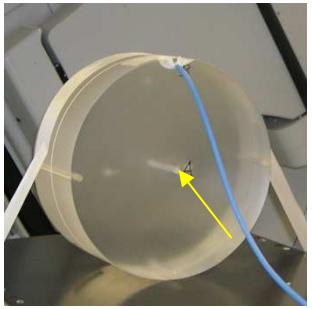




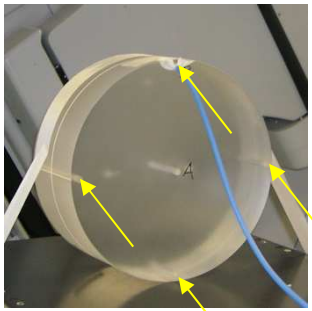


dose inside rectum: 17.2 mGy

cone-beam CT phantom dose measurement



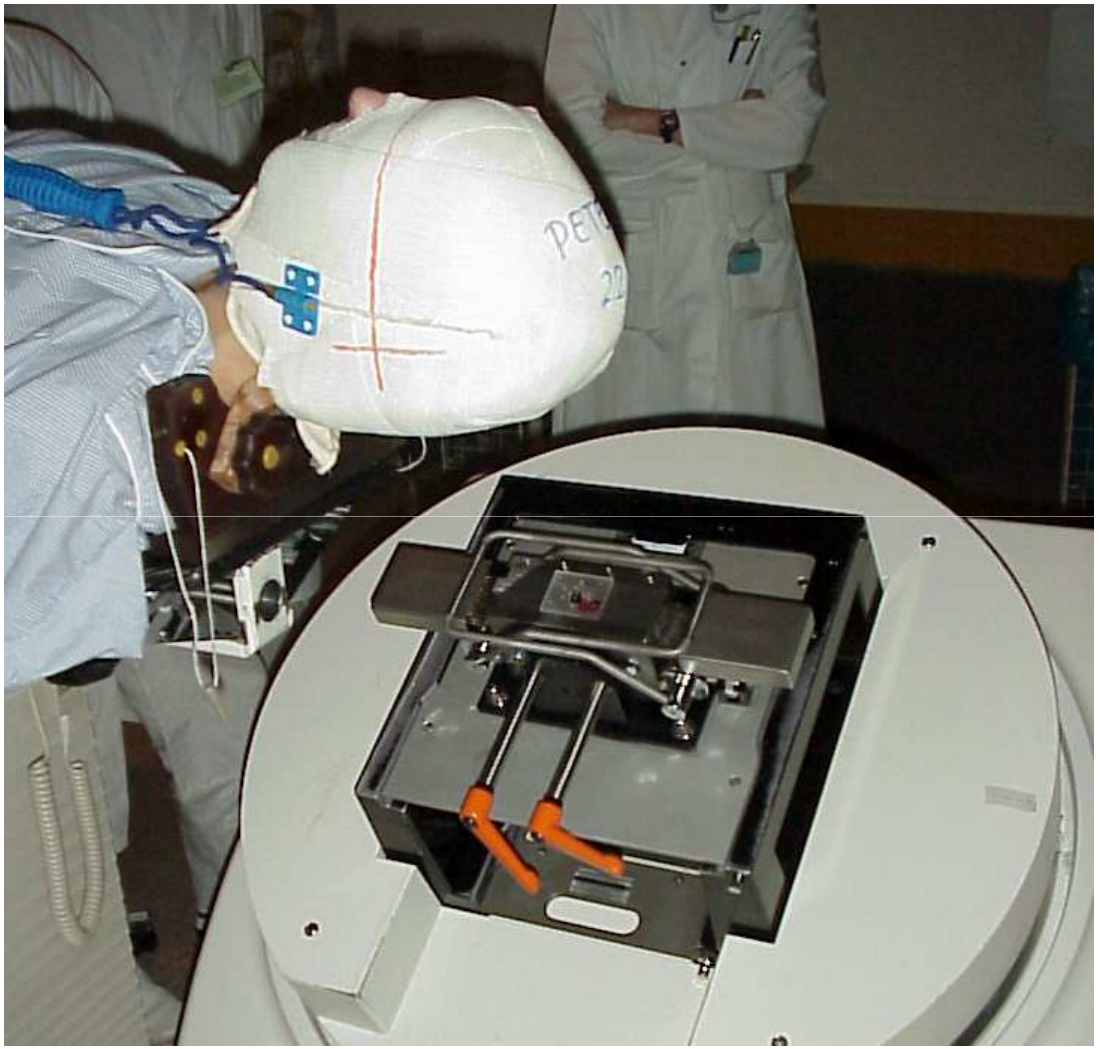
central dose: 11.4 mGy



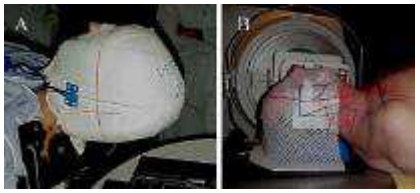
peripheral dose: 25.4 mGy

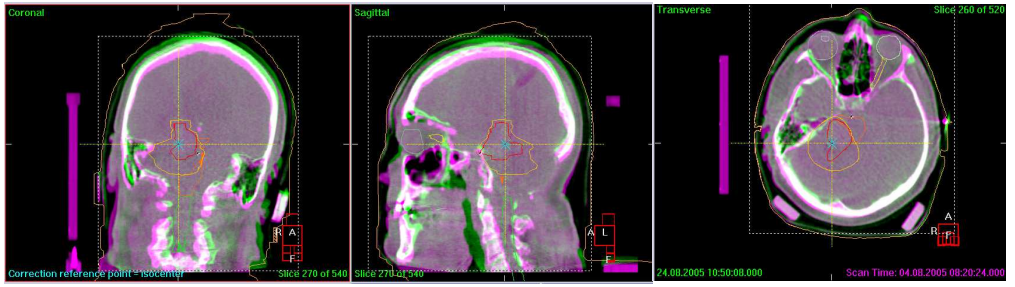
weighted dose: 20.7 mGy

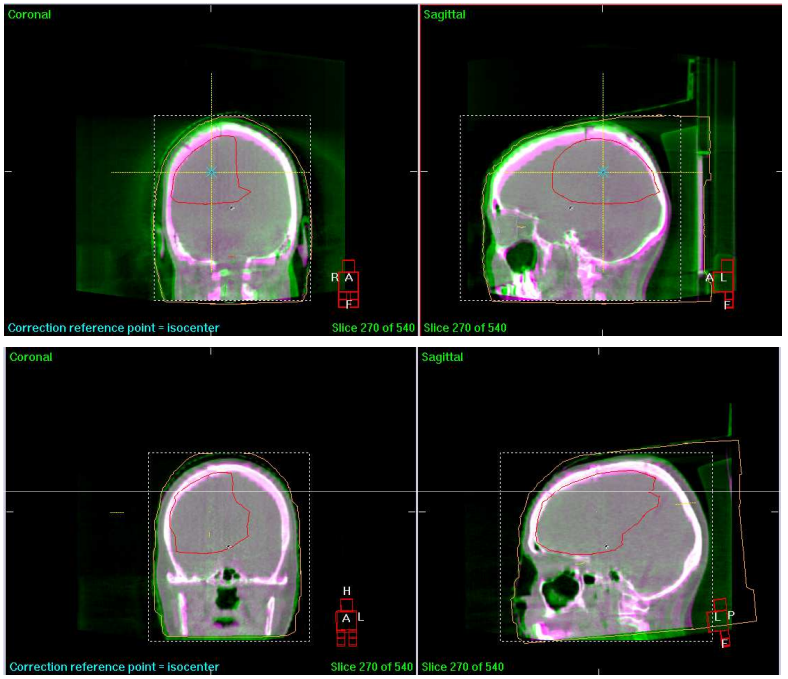
Target / Organ Motion



J. Boda-Heggemann, IJROBP, 2006



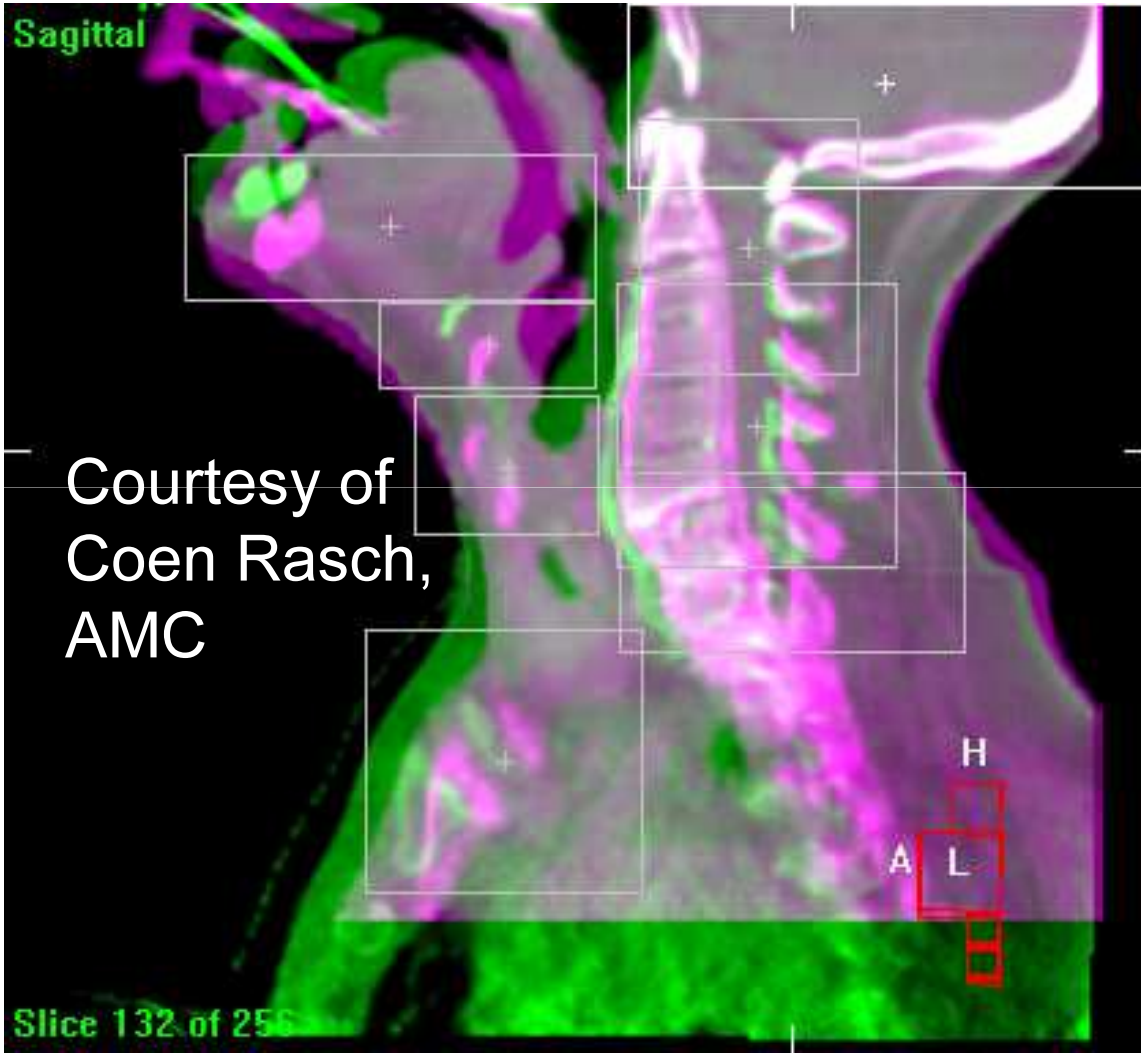




	Translation (MV±SD, cm)				Rotation (degrees)		
	x	y	z	**Vector (cm)**	x	y	z
Delta-Cast™ (Intracranial)	0.039±0.175	0.083±0.232	0.005±0.174	**0.312±0.152**	0.073±1.018	0.13±1.653	-0.25±0.0881
Thermoplastic masks (intracranial)	-0.02±0.227	0.23±0.233	-0.154±0.277	**0.472±0.174**	-1.47±1.75	-0.13±1.921	-0.06±2.18
Delta-Cast™ (neck)	-0.158±0.207	0.225±0.241	0.179±0.479	**0.586±0.294**	1.027±3.527	1.013±2.556	1.257±3.008
Thermoplastic masks (neck)	0.205±0.298	0.407±0.516	0.142±0.393	**0.726±0.445**	-0.2±2.31	-1.3±2.69	-1.09±2.02

Table 1. Results with the example of automatic bony registration

Neck Flexibility



Daily vs. less frequent Imaging: Spinal cord dose

Duma et al., IJROBP, 2013

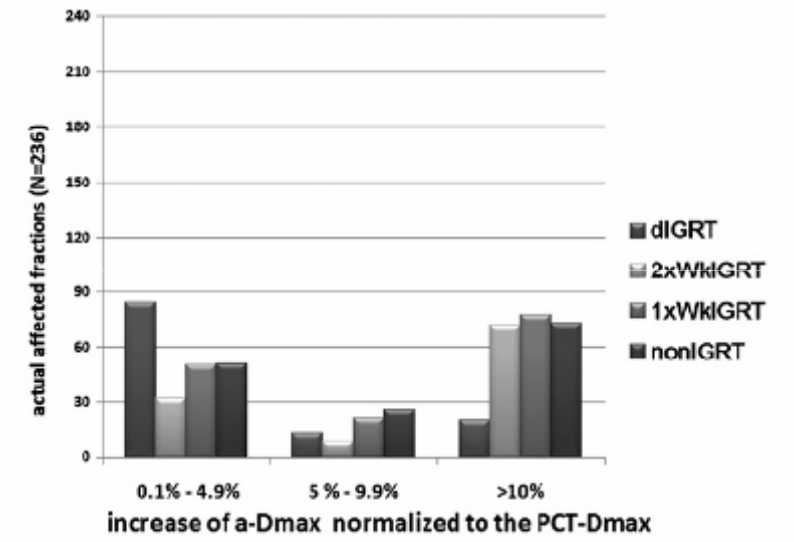


Fig. 2. The a-Dmax is higher than the planned Dmax. a-Dmax = actual delivered Dmax; plan-Dmax = Dmax on the planning kVCT.

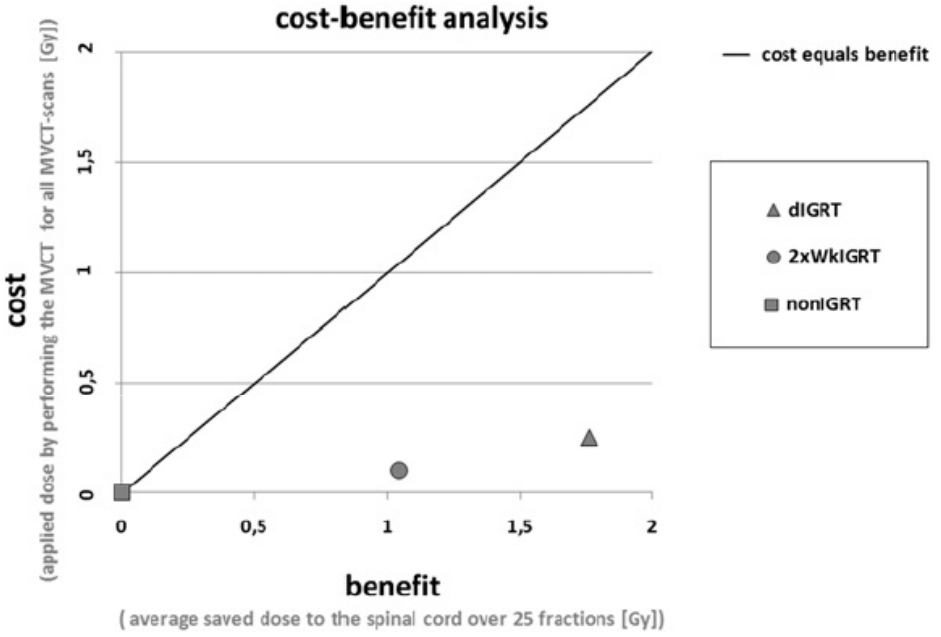


Fig. 4. Cost-benefit analysis of dIGRT and 2×WkIGRT compared to non-IGRT. Compared to the non-IGRT, the dIGRT and 2×WkIGRT scenarios save, on average, 1.76 and 1.04 Gy, respectively. That is calculated by the higher-than-planned Dmax for the non-IGRT (5.6%) minus the higher-than-planned Dmax for the dIGRT (1.2%); *e.g.*, 2.24 Gy − 0.48 Gy = 1.76 Gy; and for 2×WkIGRT, 2.24 Gy − 1.2 Gy = 1.04 Gy. The cost of one MVCT scan in the coarse mode is 0.01 Gy (dIGRT = 0.25 Gy; 2×WkIGRT = 0.12 Gy).

ART (IMRT) – Dosimetric Benefits

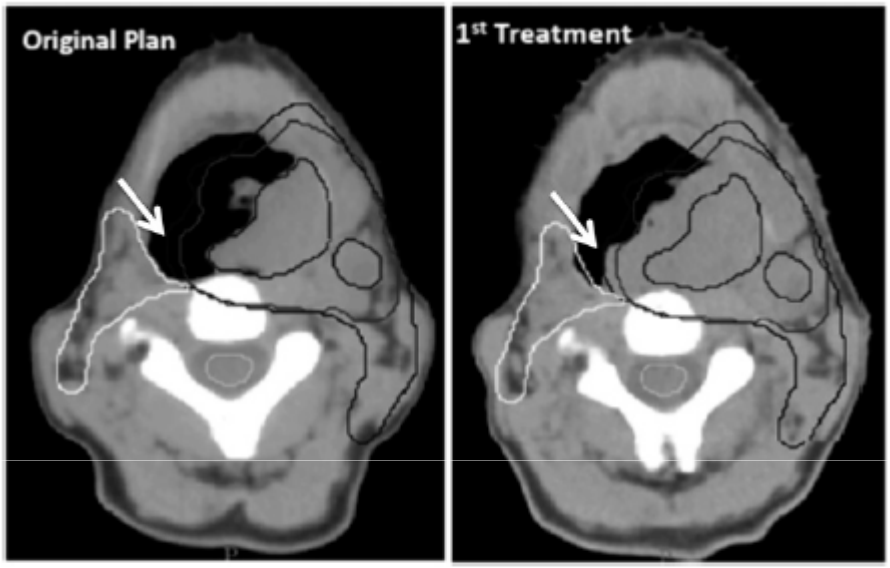


Fig. 1. Detection of rapid tumor progression prior to start of treatment. The original plan is shown to the left; patient's anatomy on first treatment day is shown on the right. Primary GTV progressed by >50%. Arrows designate site of geographic miss for CTV1.

Try to keep Interval between CT and 1st RT short (2-3 days is possible)

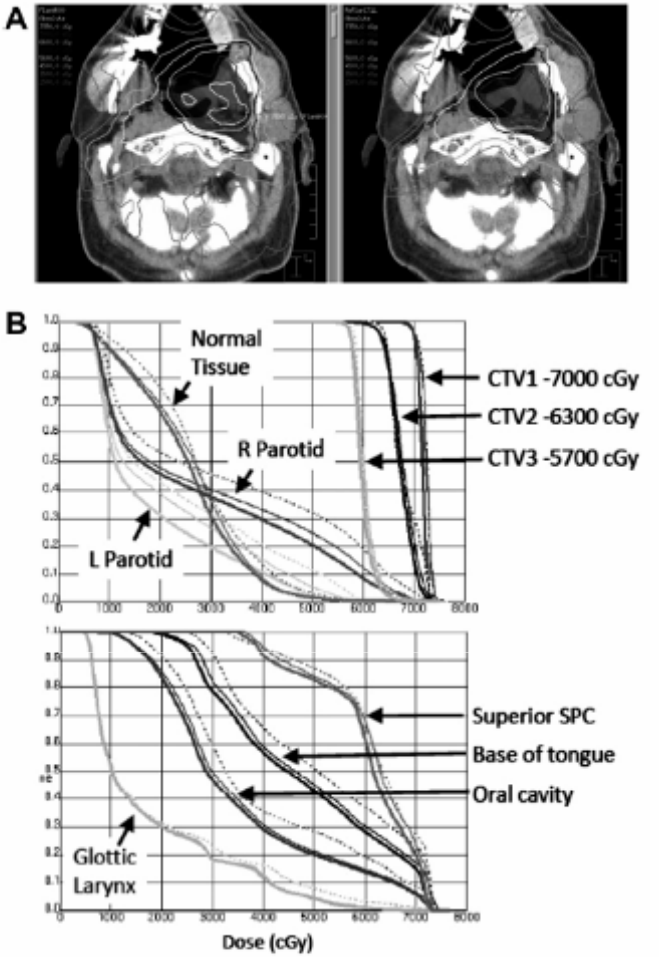
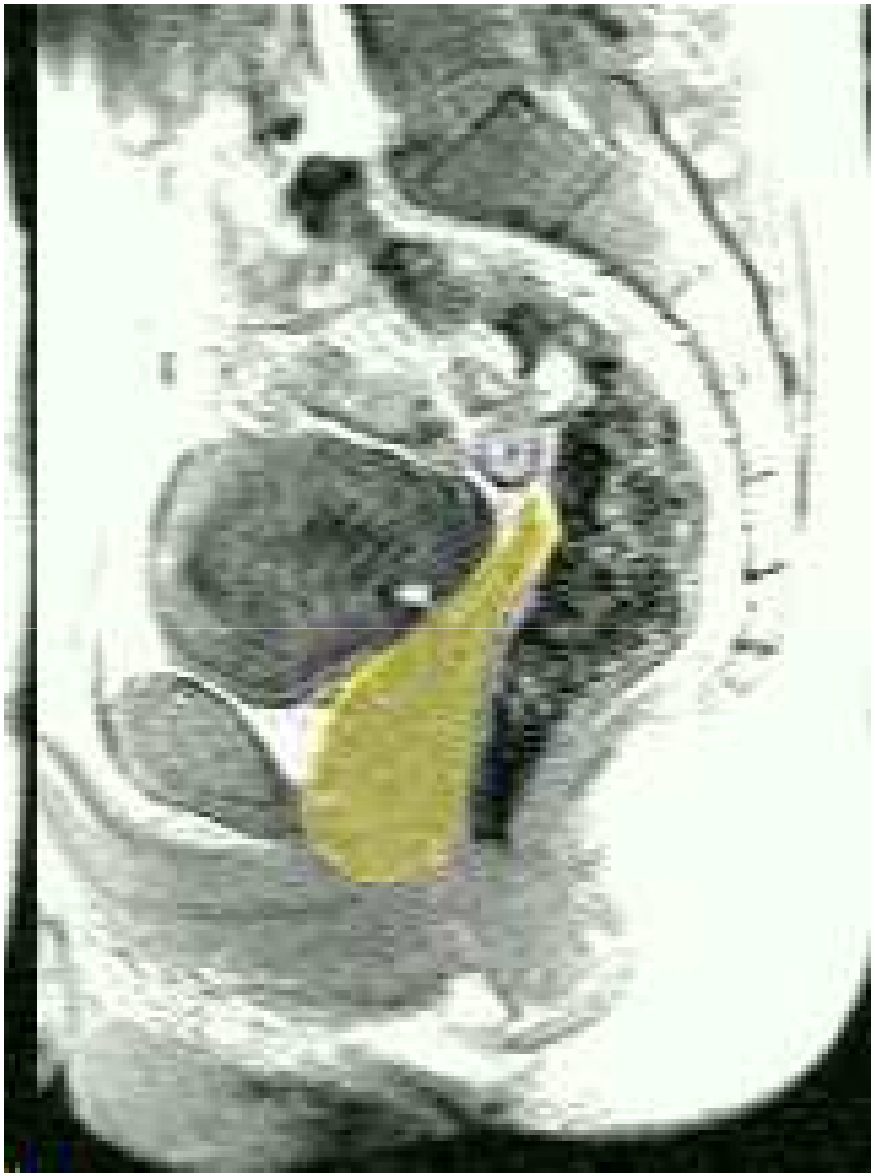
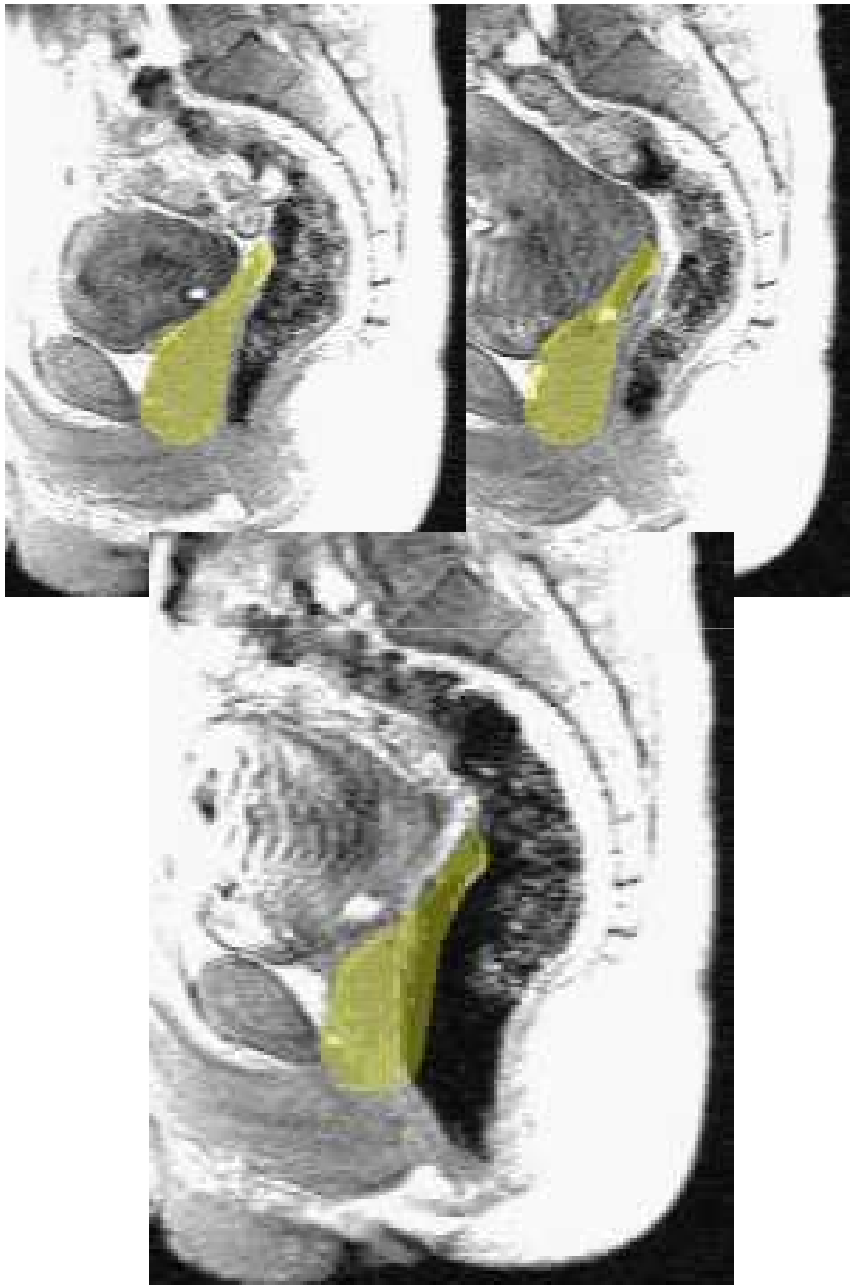
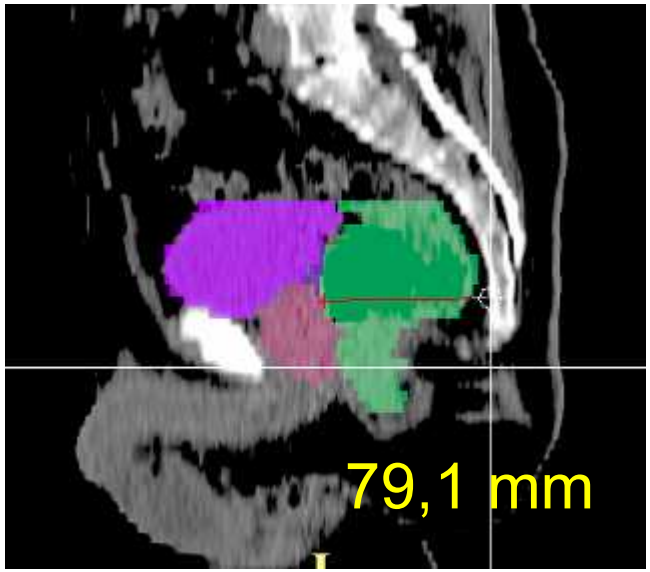


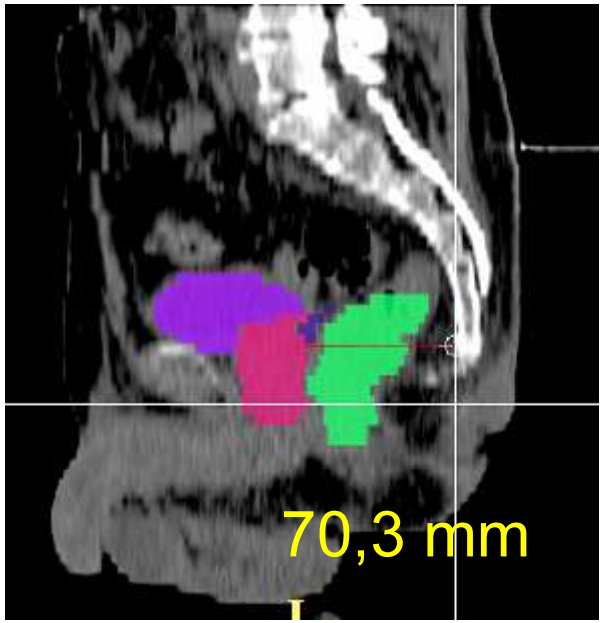
Fig. 3. (A) *Right:* Emergence of dose heterogeneity within high-risk CTV1 in a tonsillar carcinoma case at treatment fraction #11; *Left:* Restoration of intended dose distribution within CTV1 by adaptive replanning without PTV margin expansions. (B) DVH comparison for the original IMRT plan of this case (dotted lines), ART1 replan designed on treatment day 15 (thin solid lines), and the ART2 replan (thick solid lines), all re-calculated on CT anatomy obtained on 25th treatment day.

Schwartz et al., R&O, 2013

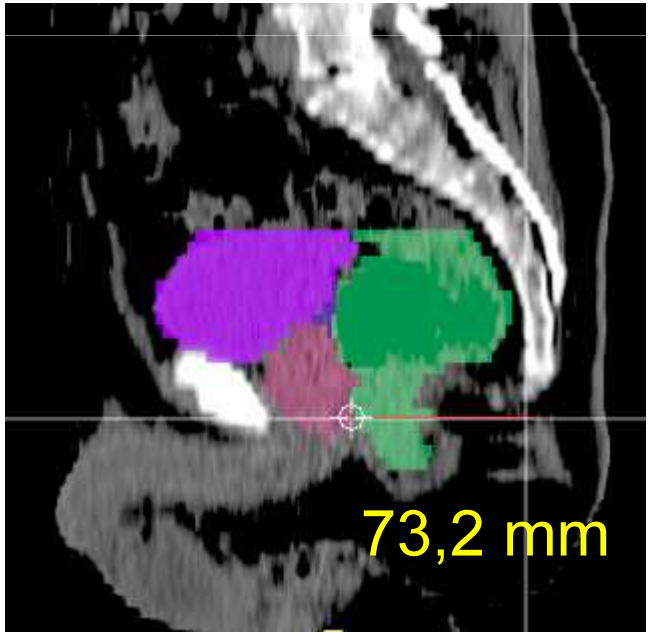


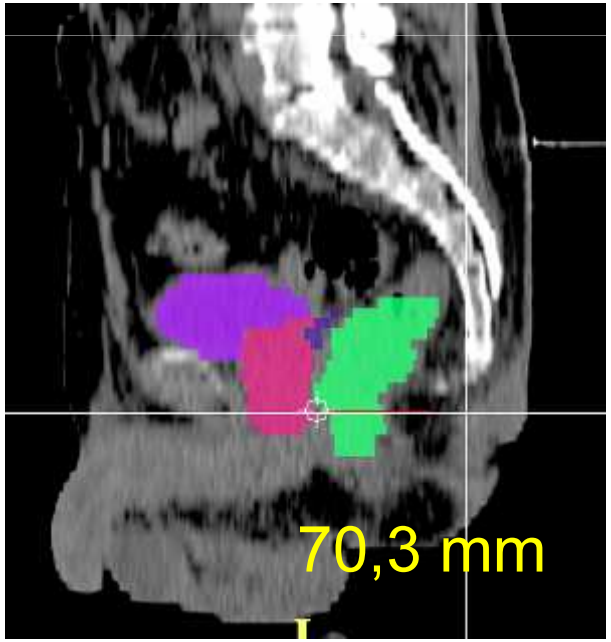






Δ=8,8 mm

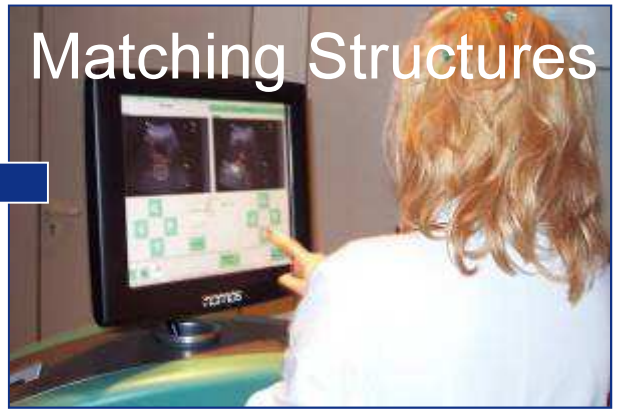




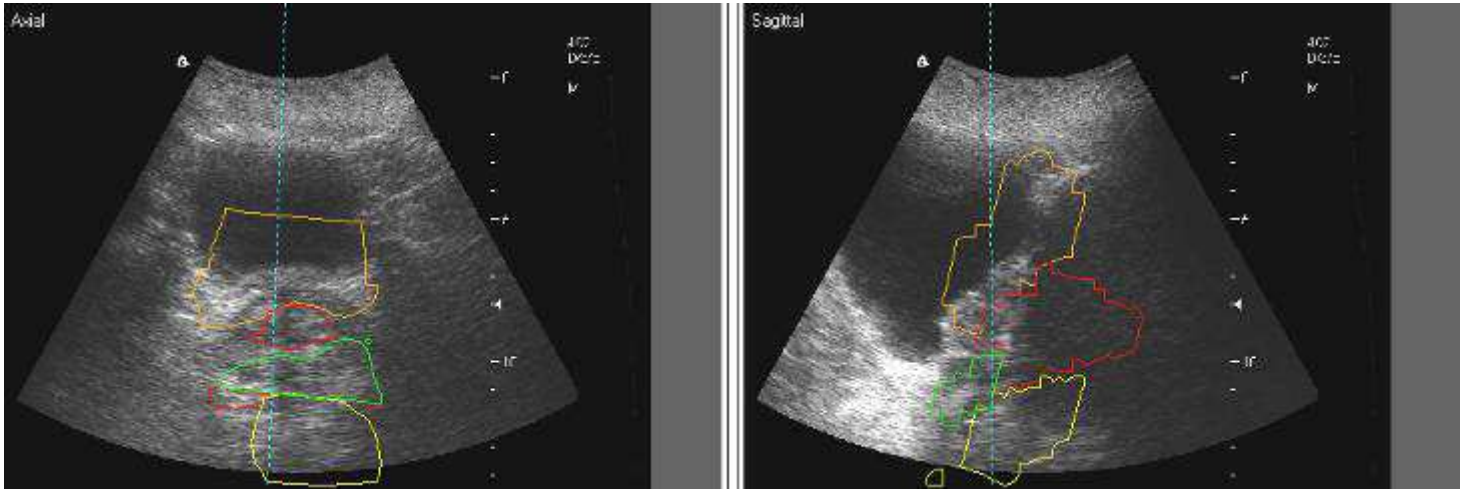
Δ=1,9 mm

Precision Immobilizatin for Pelvic Tumors

BAT-Procedure



Status pre Correction



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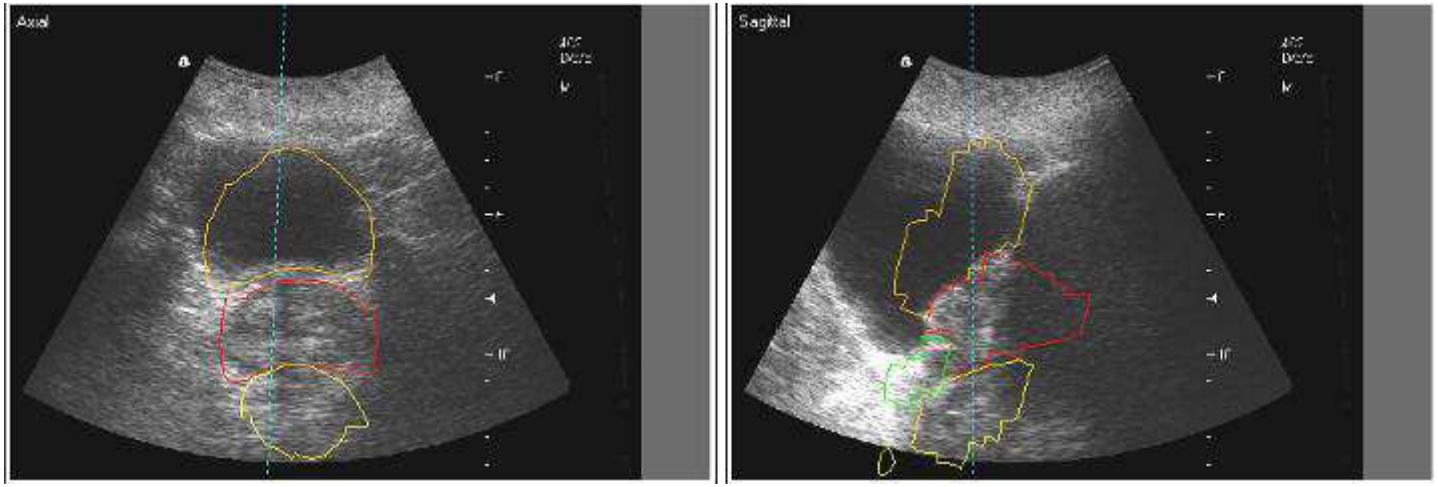
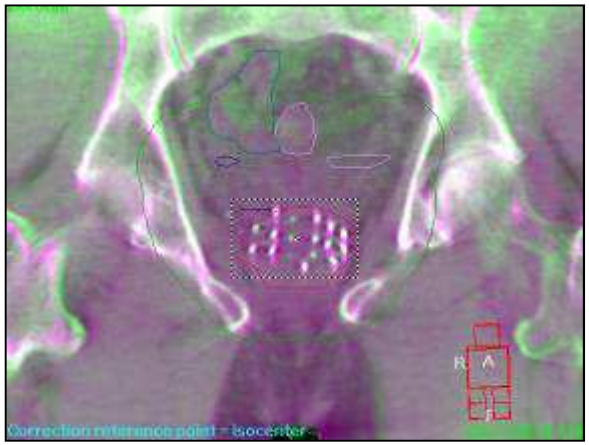
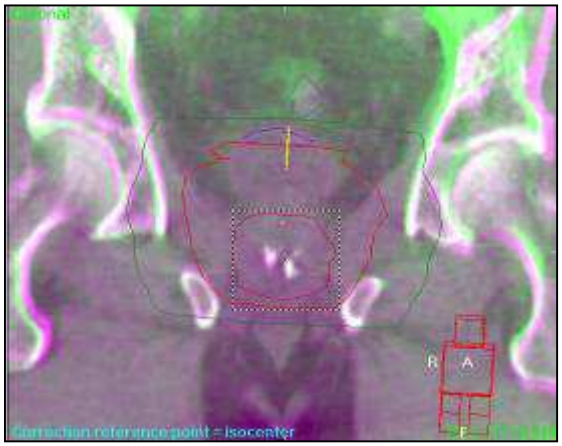


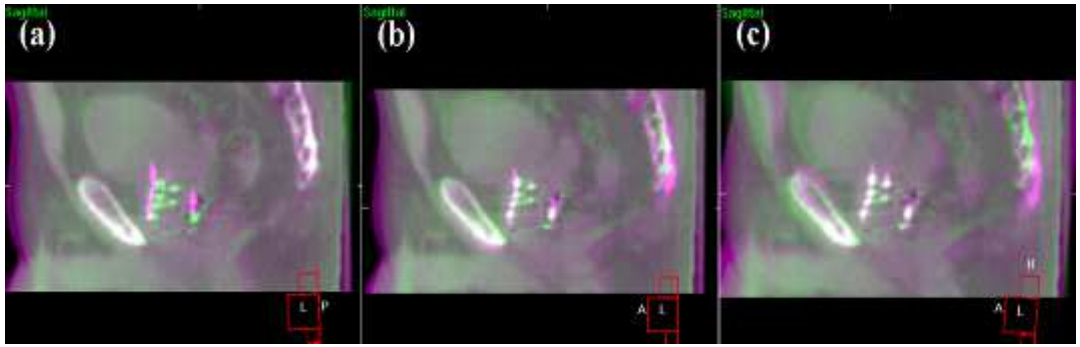
XVI with natural or aetificialFiducials

J. Boda-Heggemann/F. Köhler, IJROBP, 2008

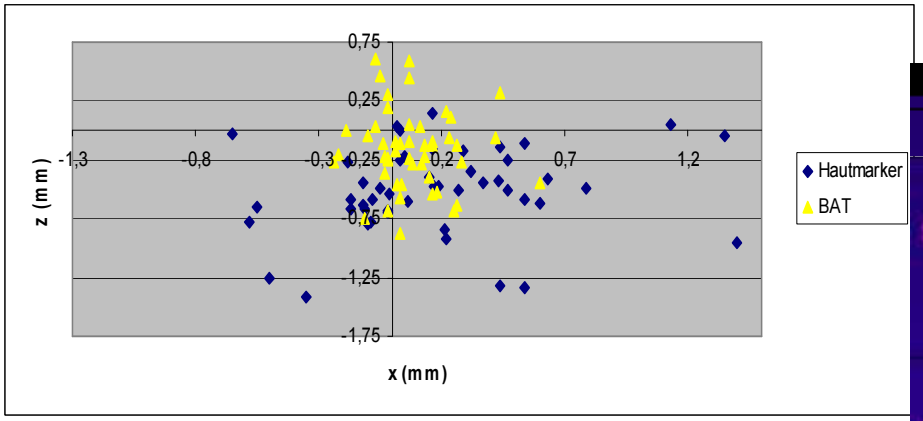




Correlation Ultrasound/XVI

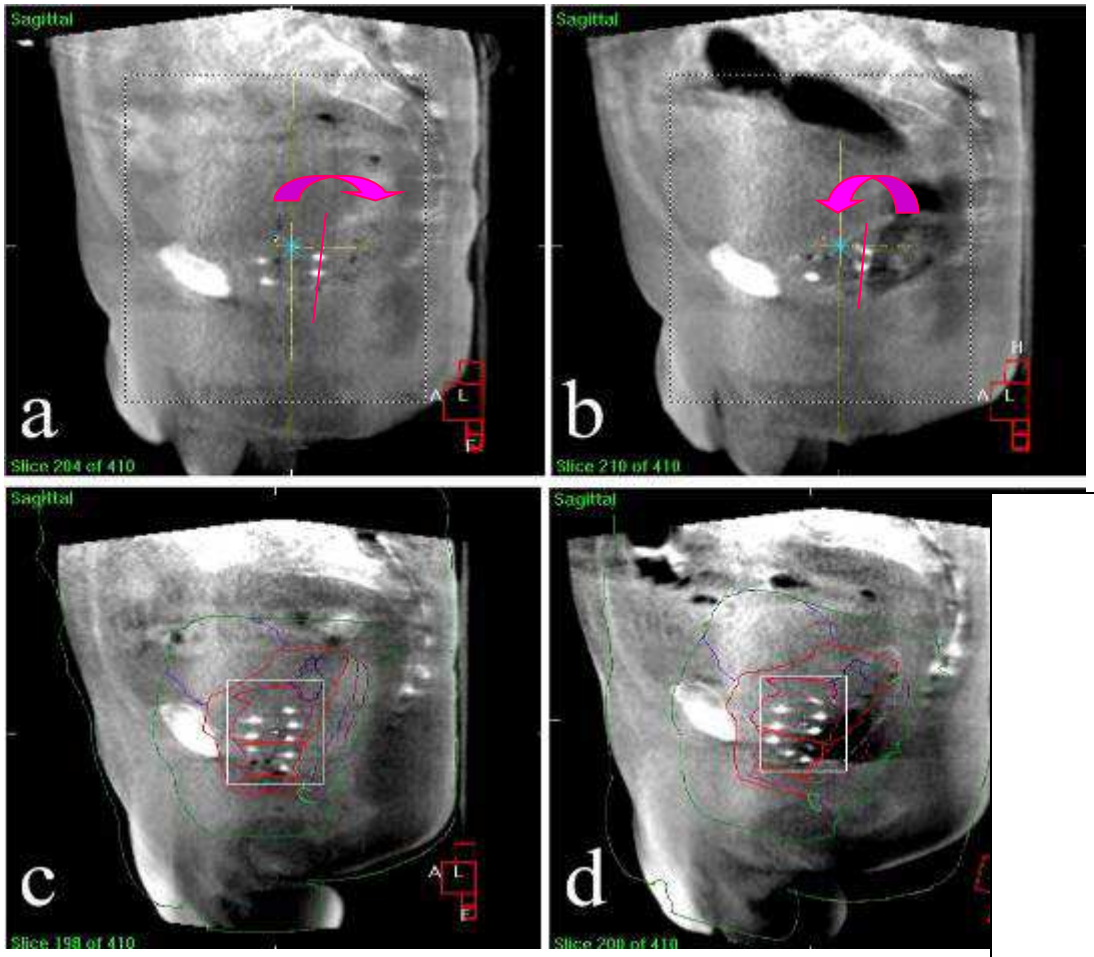


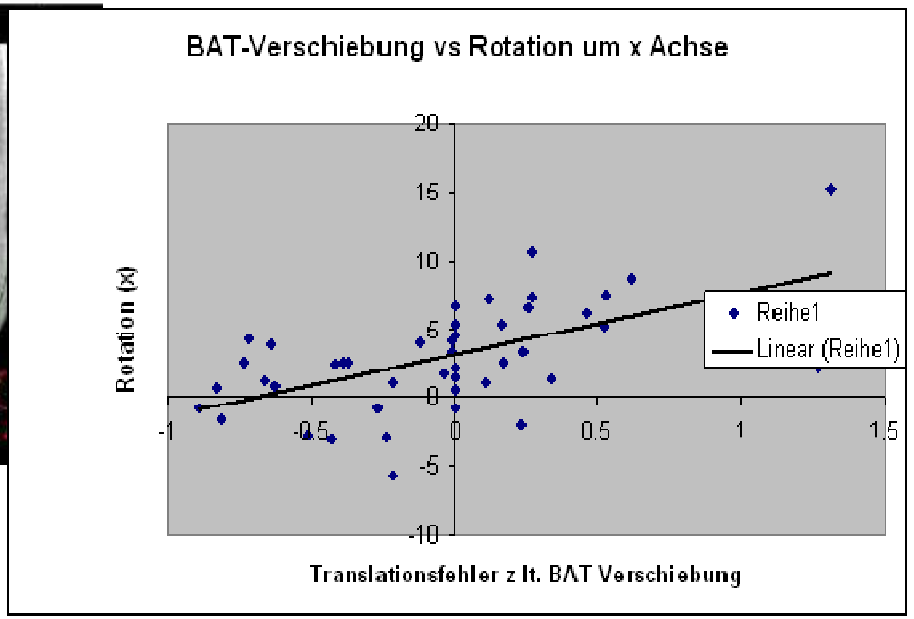
J. Boda-Heggemann/F. Köhler,
IJROBP, 2008

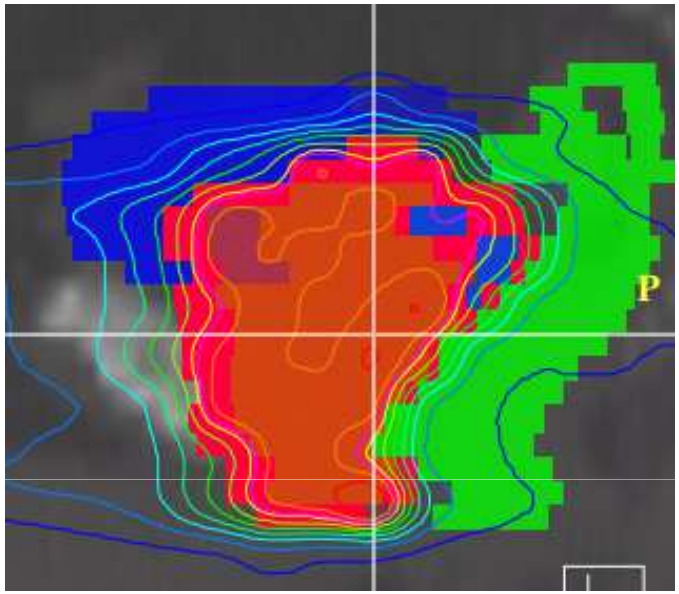


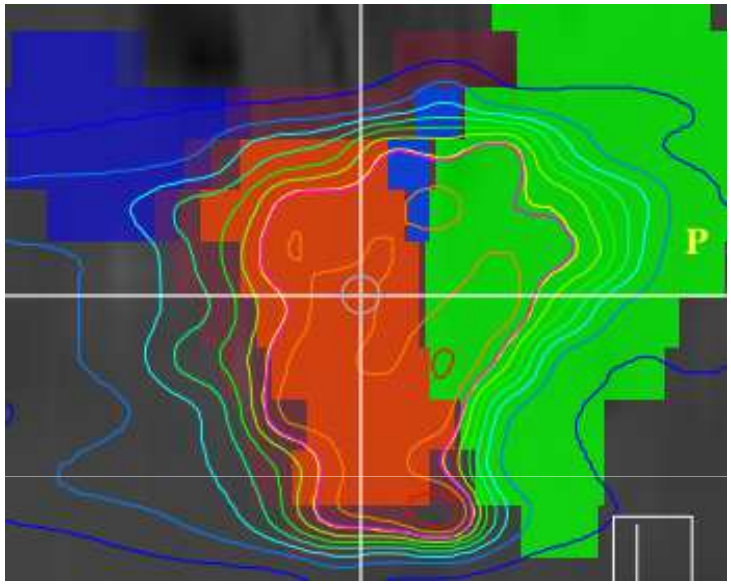
		Translation (mm)		
n=54		x	y	z
Skin marks	overall MV±SD	2.1±4.6	-4.8±8.5	-5.2±3.6
	M	2.7	-4.4	-4.8
	Σ	3.3	3.7	1.7
	σ	3.9	6.7	3.5
Bony anatomy	overall MV±SD	0.1±1.8	-3.5±6.8	-1.9±5.2
	M	0.2	-3	-2
	Σ	0.9	1.8	1.3
	σ	1.1	3.7	4
Soft tissue Repositioning (BAT®)	overall MV±SD	0.6±1.7	0.9±3.2	-1.7±3.5
	M	0.5	0.5	-1.7
	Σ	0.8	2.2	2.3
	σ	1.4	2.8	3

Boda-Heggemann, Köhler et al.,
Radiotherapy & Oncology, 2007






P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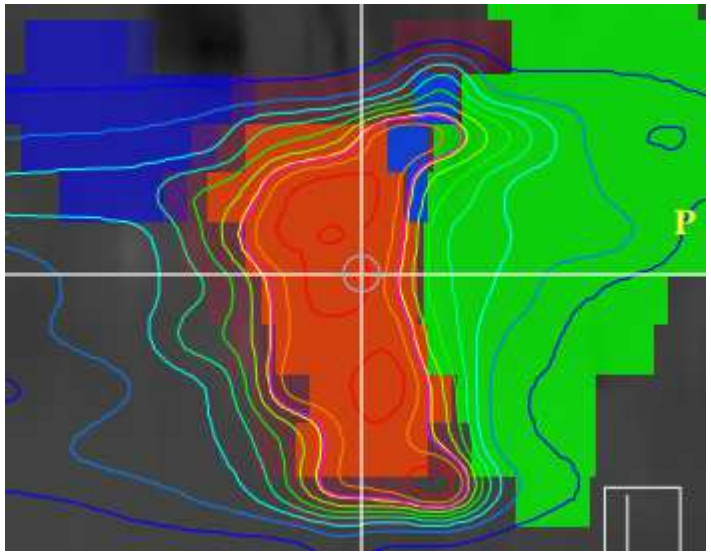
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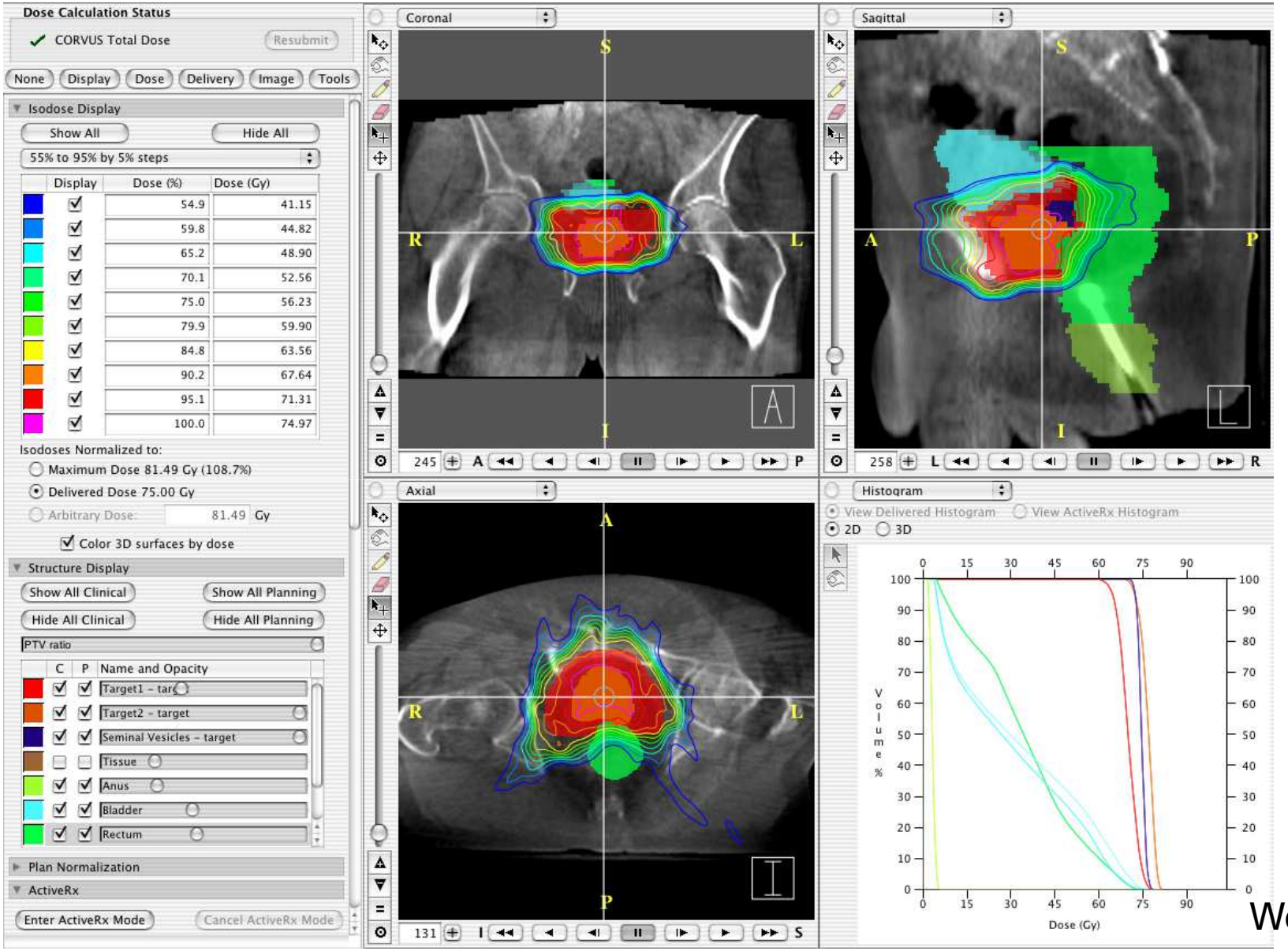
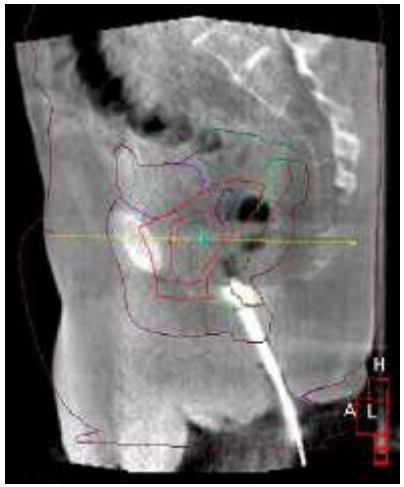


Wertz/
Abo
Madyan

HexaPOD®

CBCT Volume-Scan



Position Error	Translation (cm)		Rotation (dg)
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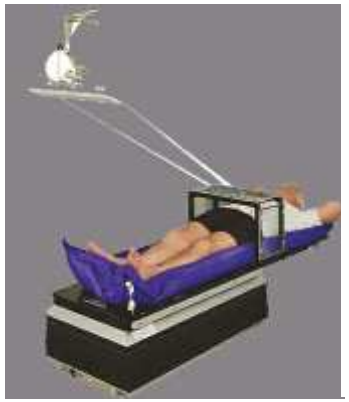
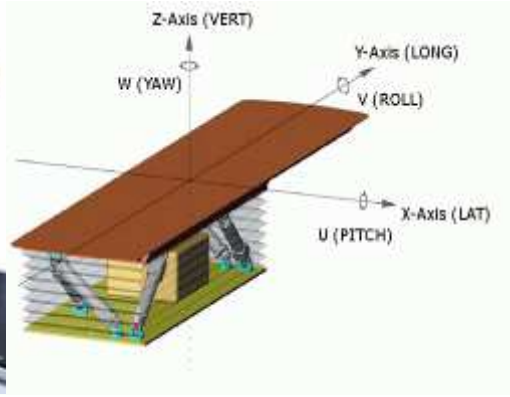
Y	-1.25	Y	-0.9
Z	-1.14	Z	1.1

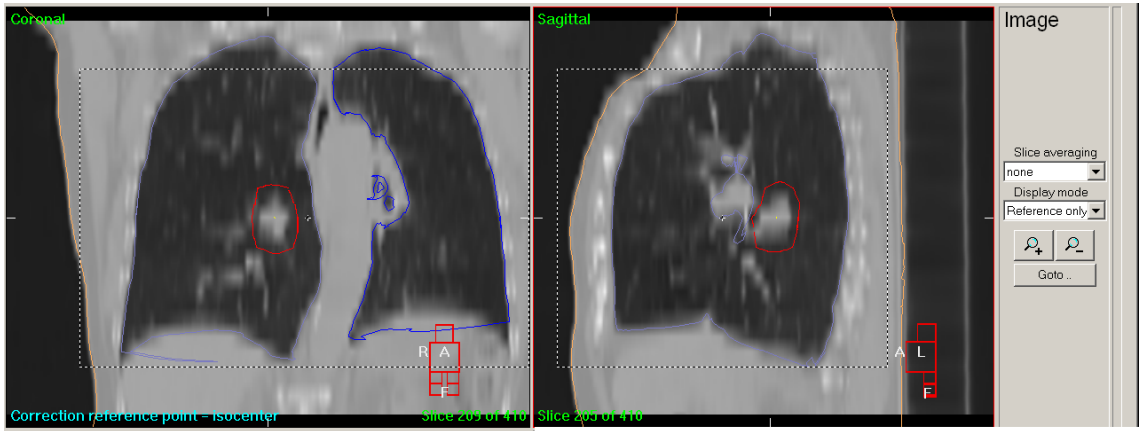
Verschiebungs- und Rotationsfehler



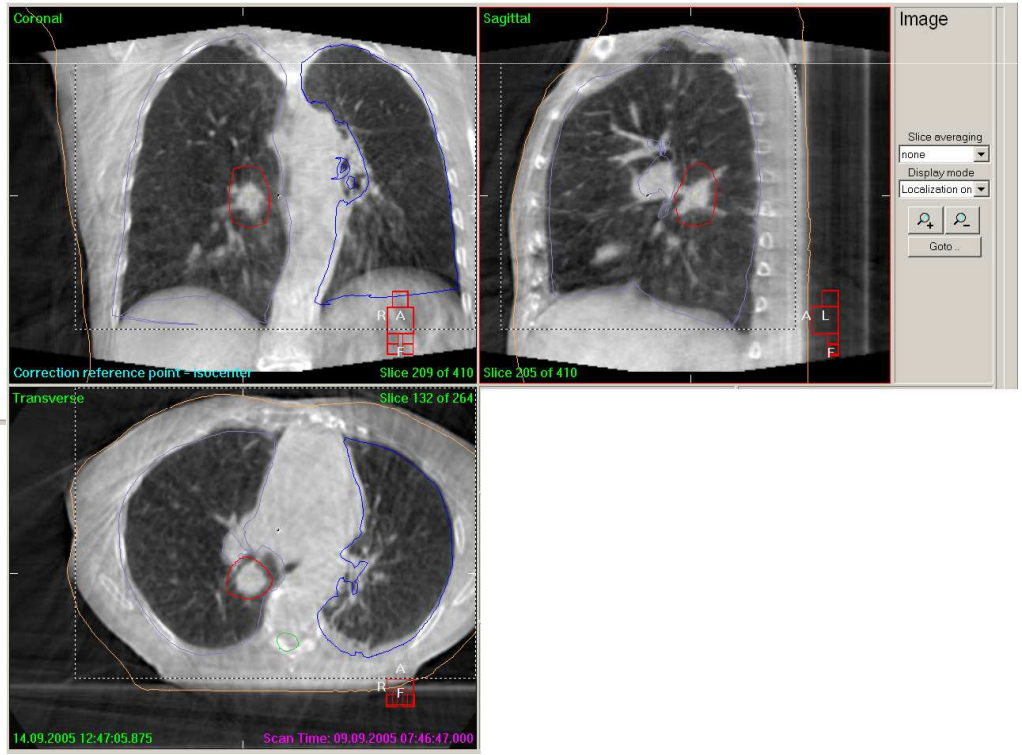


Positionskorrektur in 6 Freiheitsgraden (HexaPOD®)

IGRT: CBCT

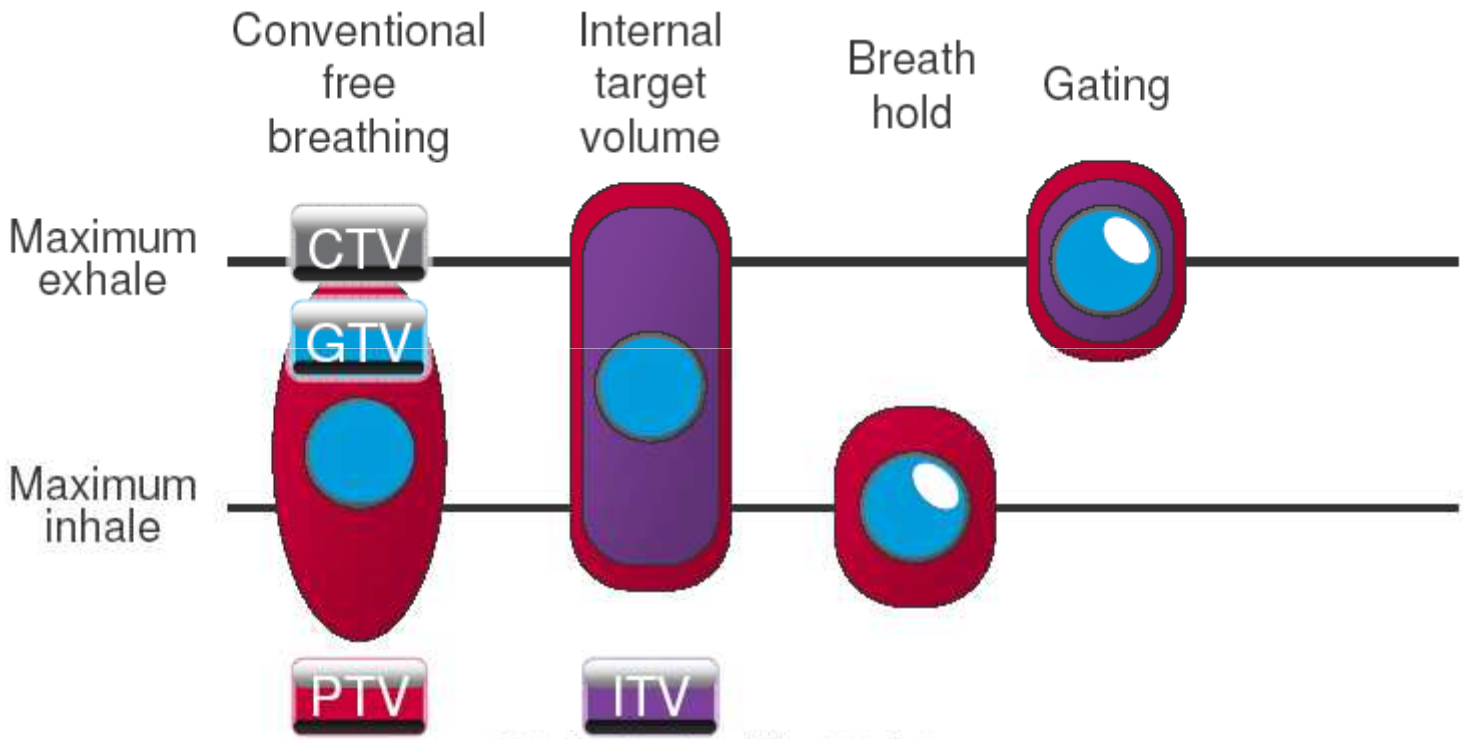


Fuss, Boda Heggemann, Salter
Medical Dosimetry, 2006



Why?

Planning Concepts – current techniques

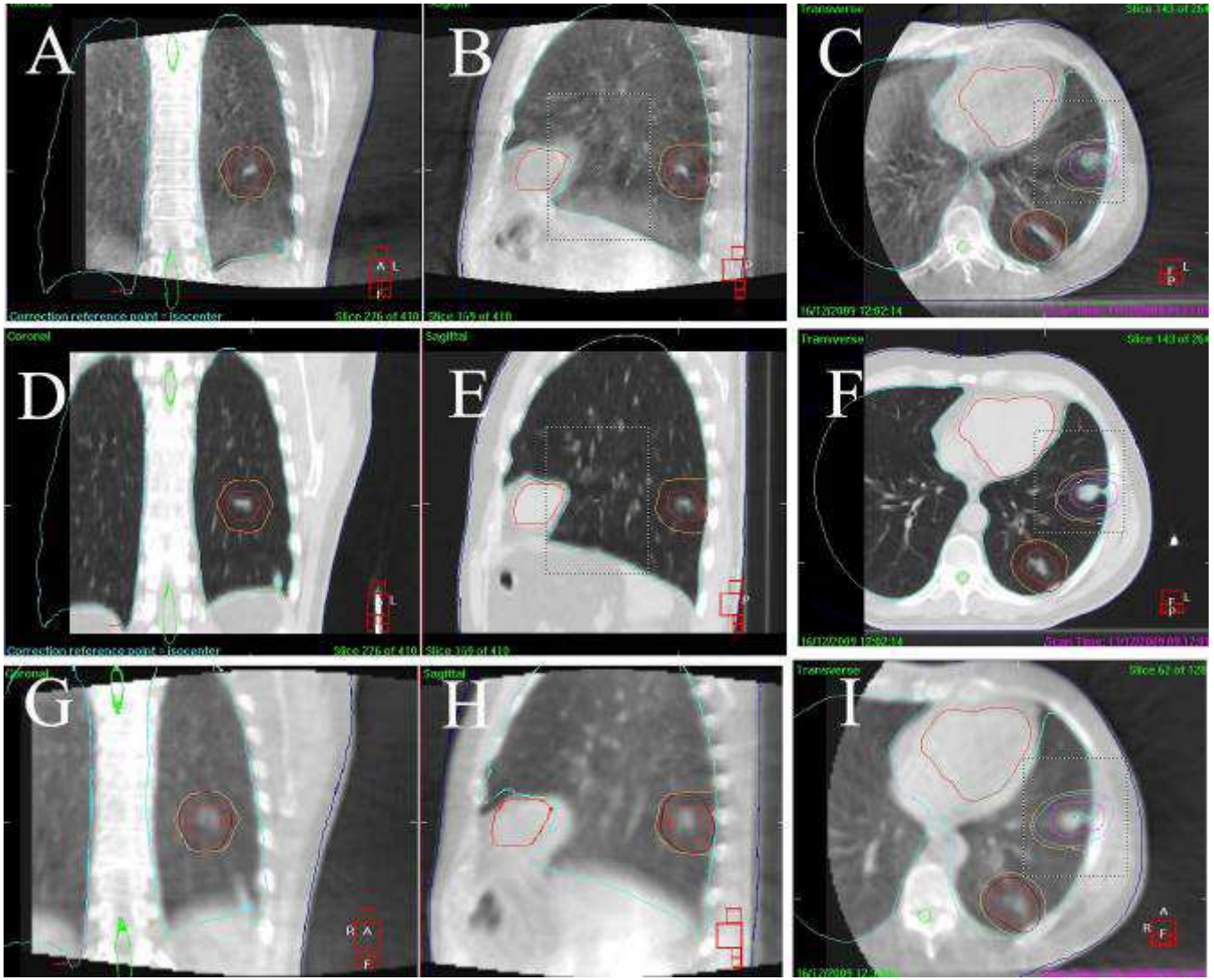


Adapted from Comparison of different strategies to use four-dimensional computed tomography in treatment planning for lung cancer patients. Wolthaus et al.

ELEKTA ONCOLOGY

Boda Heggemann et al., Strahlentherapie, 4/2006
Küpper, MTA, 2/2006 & 4/2006

Boda-Heggemann et al., Radiother Oncol, 2011

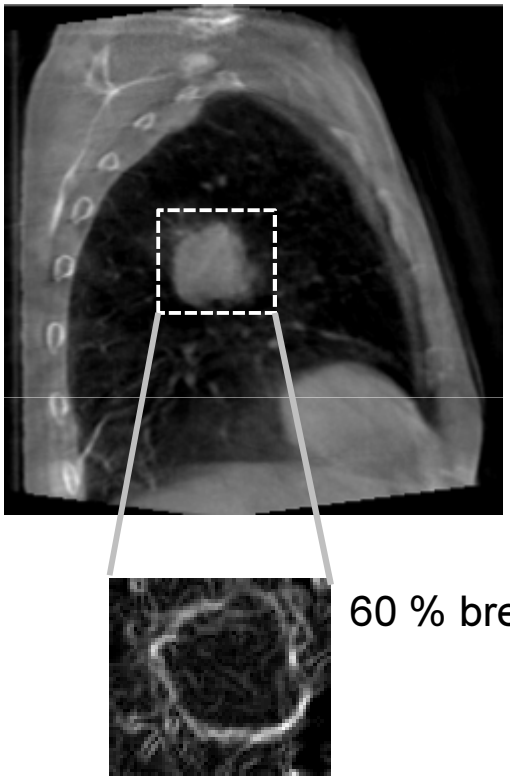


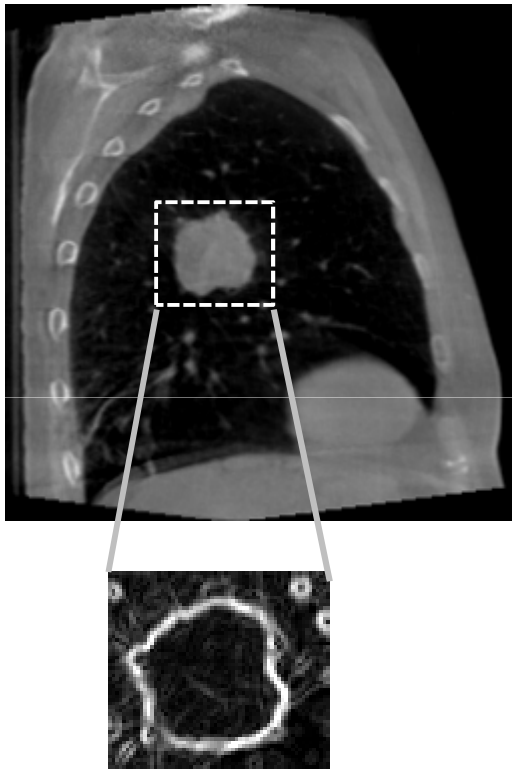
CBCT
(ABC Breath hold)

Planning CT
(ABC breathhold)

CBCT
Free breathing

CBCT (XVI) with ABC
in partial breath-hold vs. total breath-hold





deep inspiration
60 % breath-hold vs. 100 %

gradient image

Boda-Heggemann, Jahnke et al.,
ASTRO/DEGRO 2014

4D-CBCT

Sweeney et al., Radiation Oncol, 2012

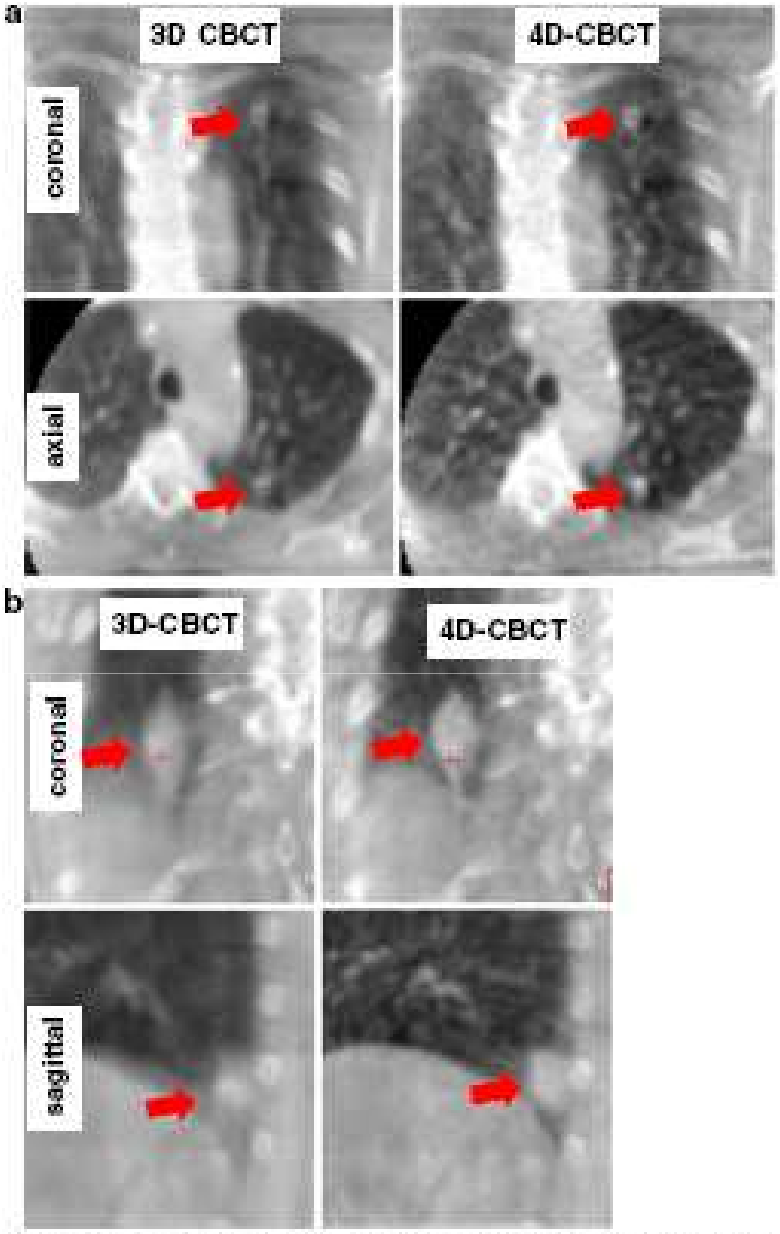
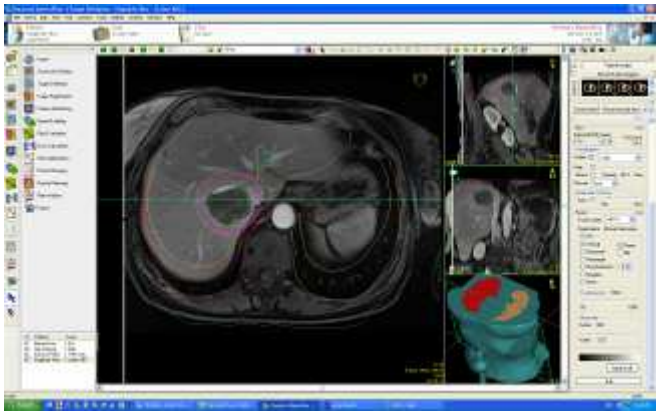
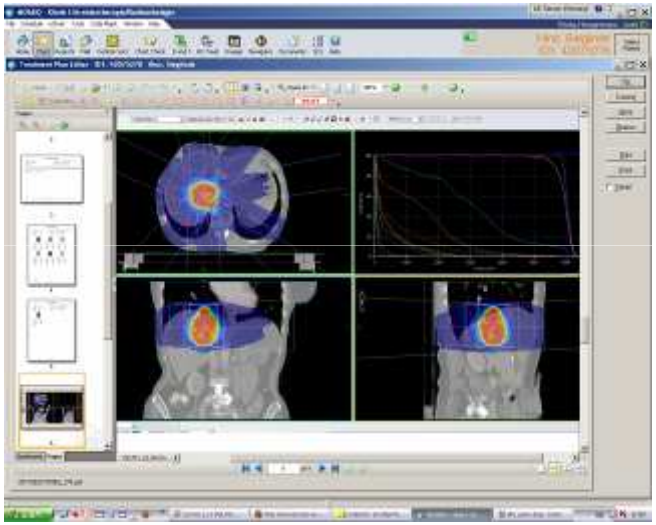
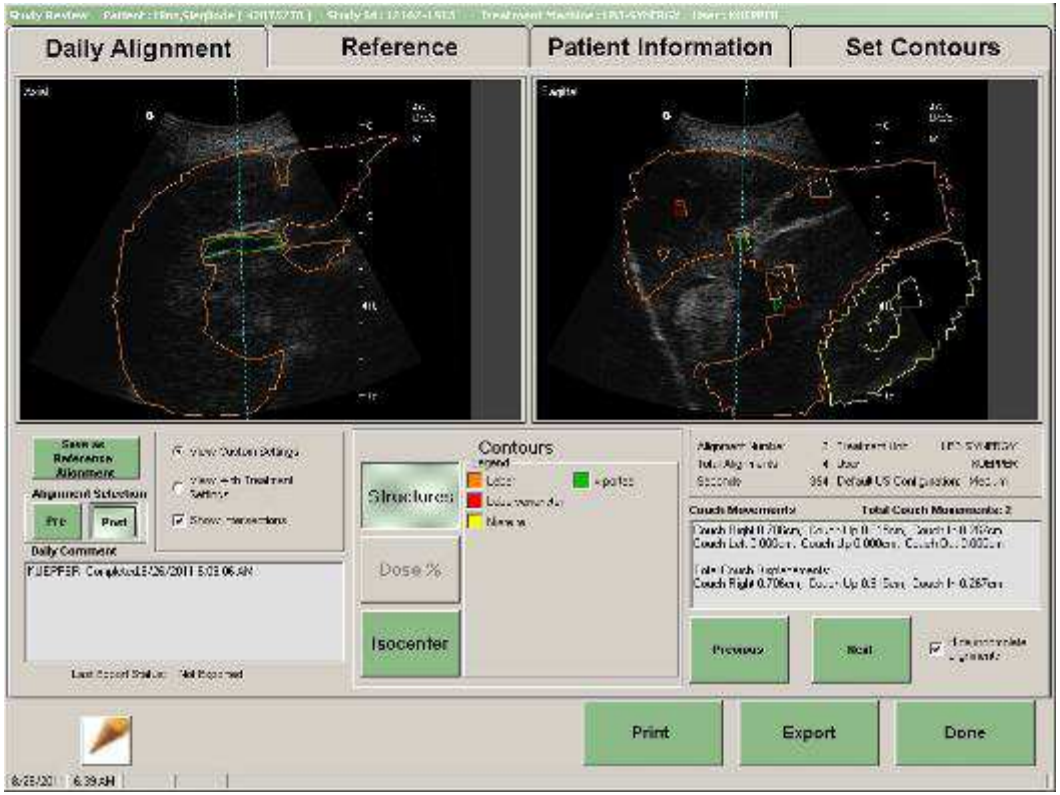
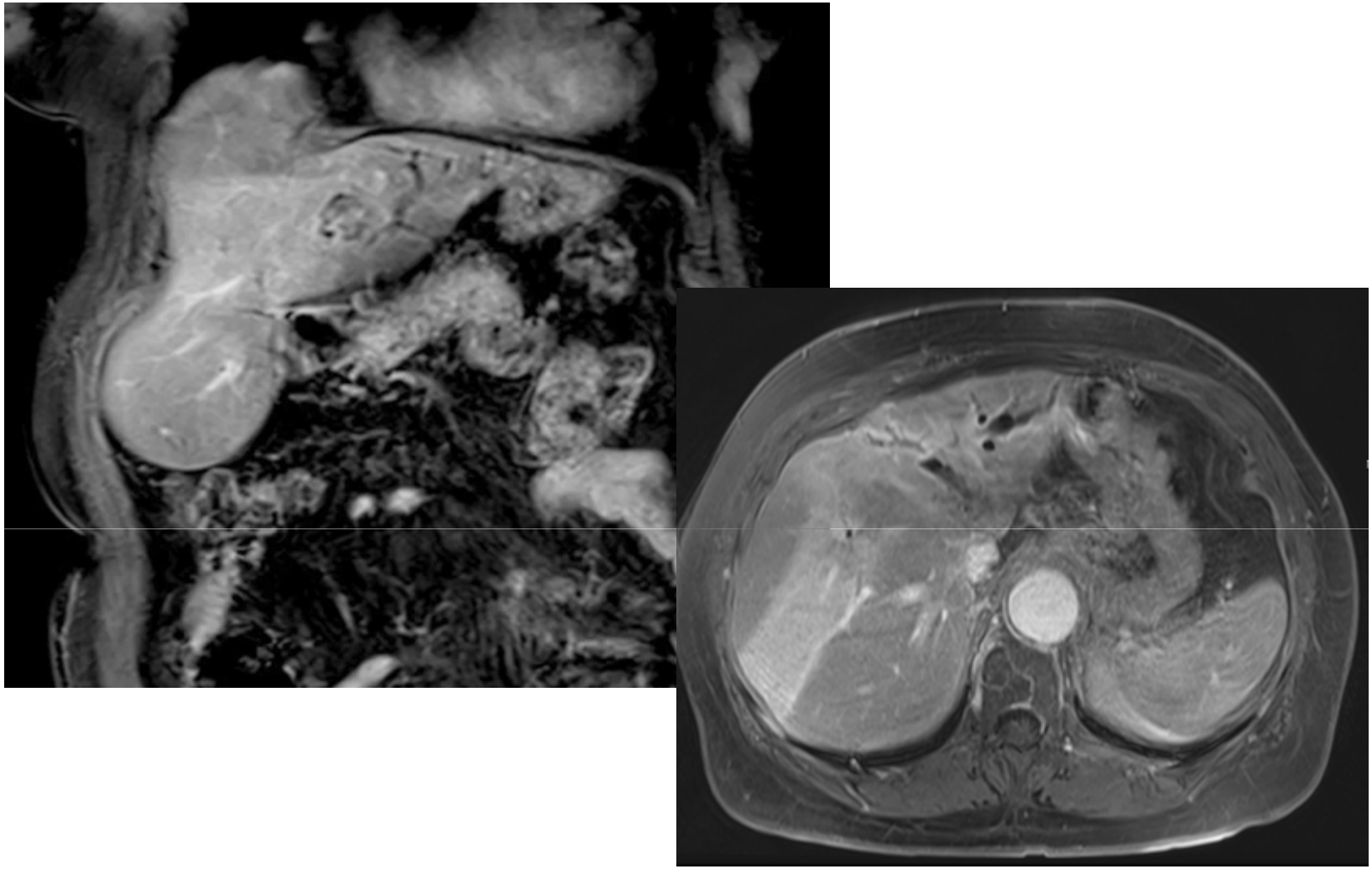


Figure 4 Examples of image quality in 3D-CBCT and 4D-CBCT. The arrow indicates the position of the target. a) Small target in the upper lobe with a 3D motion amplitude of 9.3 mm, where averaged image quality was 3.0 and 1.8 in 3D-CBCT and 4D-CBCT, respectively. b) Target in the lower lobe immediately superior to the diaphragm with a 3D motion amplitude of 16.6 mm, where averaged image quality was 3.0 and 1.3 in 3D-CBCT and 4D-CBCT, respectively.

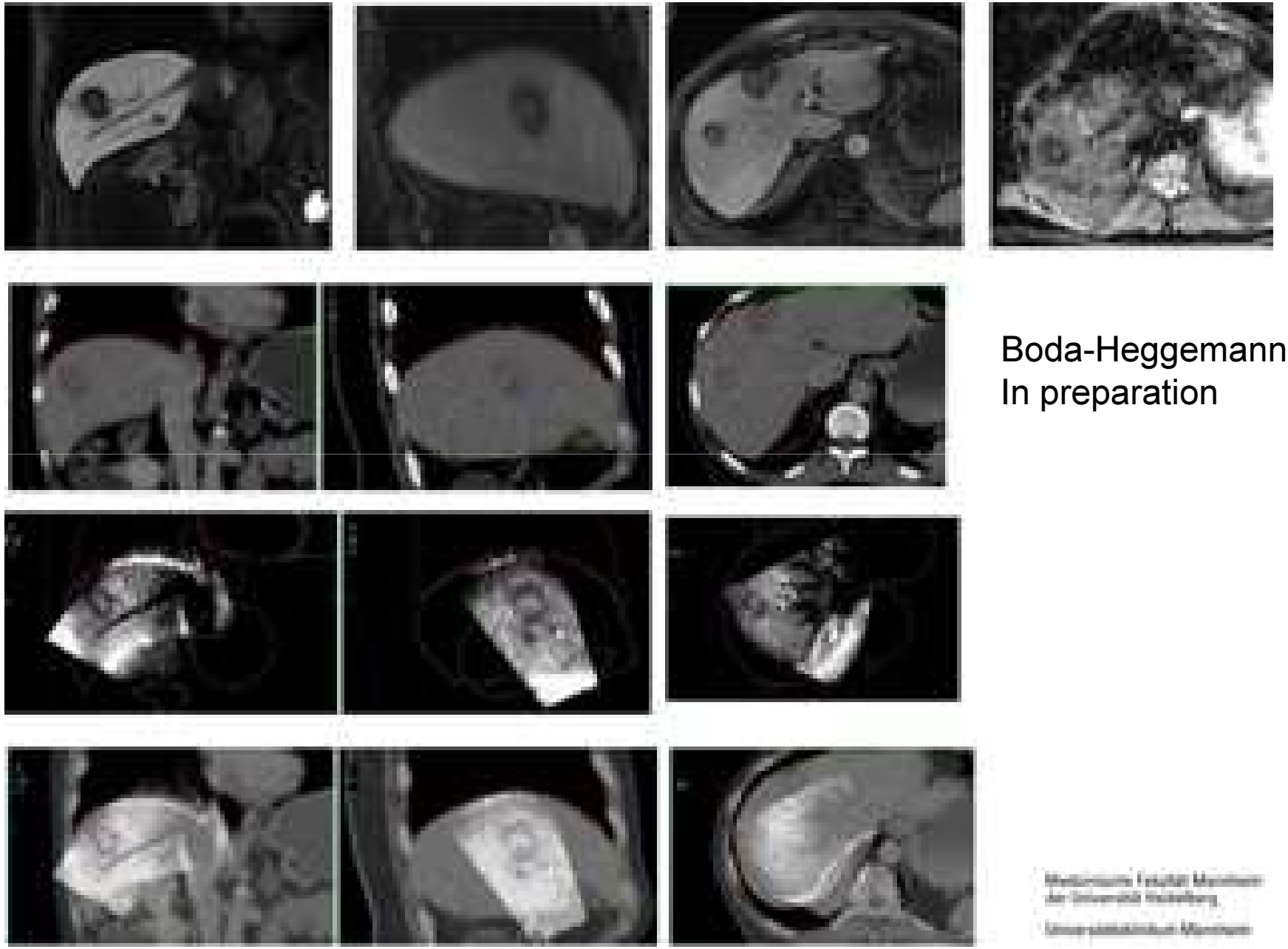





Daily Alignment
Reference
Patient Information
Set Contours
Contours
Structures
Dose %
Isocenter
Previous
Next
Print
Export
Done



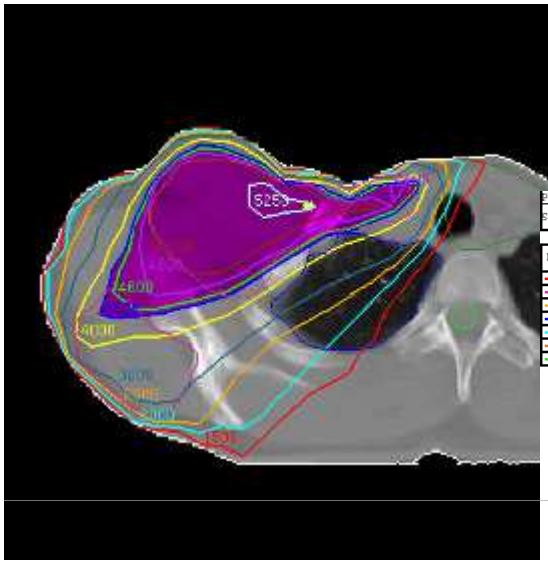

Lebowski, Duderino (280512b)
Clarity Guide
Prostate Treatment
29-May-2012 14:45
Clarity
Out of thresholds.
Verify prostate position.
Hide Contours
6.7
LT
mm
0.6
ANT
mm
4.7
mm
INF
Patient
Scan
Segment
Setup
Position
R&V
Monitoring
Done
User no password
Server

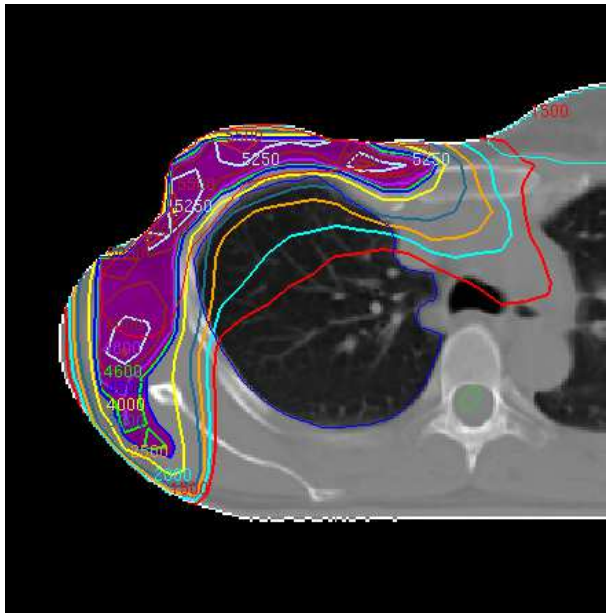


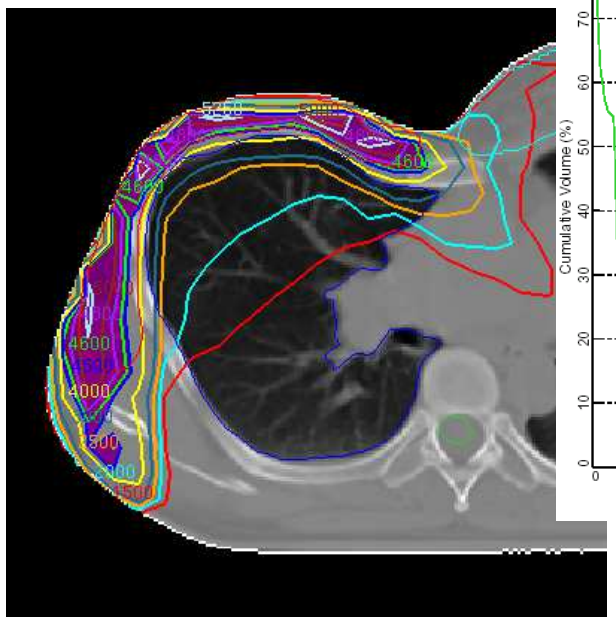
Boda-Heggemann et al.,
In preparation

Medizinische Fakultät Mannheim
der Universität Heidelberg
Universitätsklinikum Mannheim

Thoracic Wall IMRT

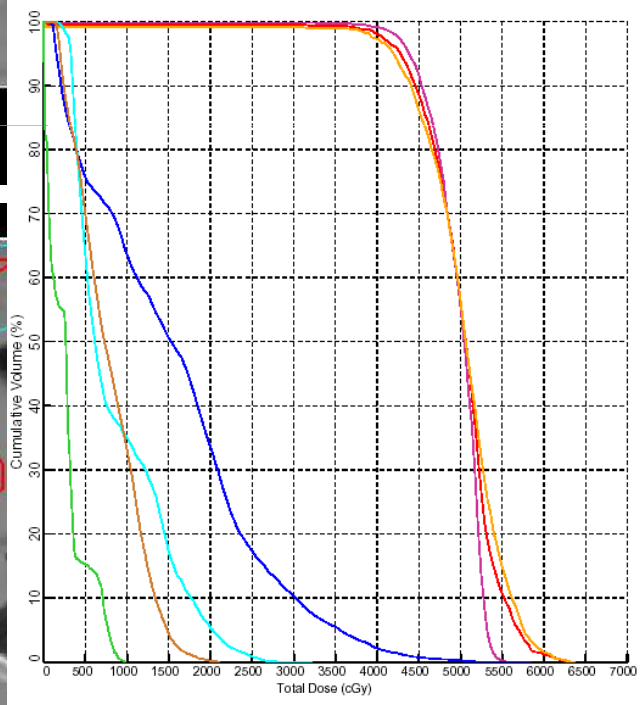




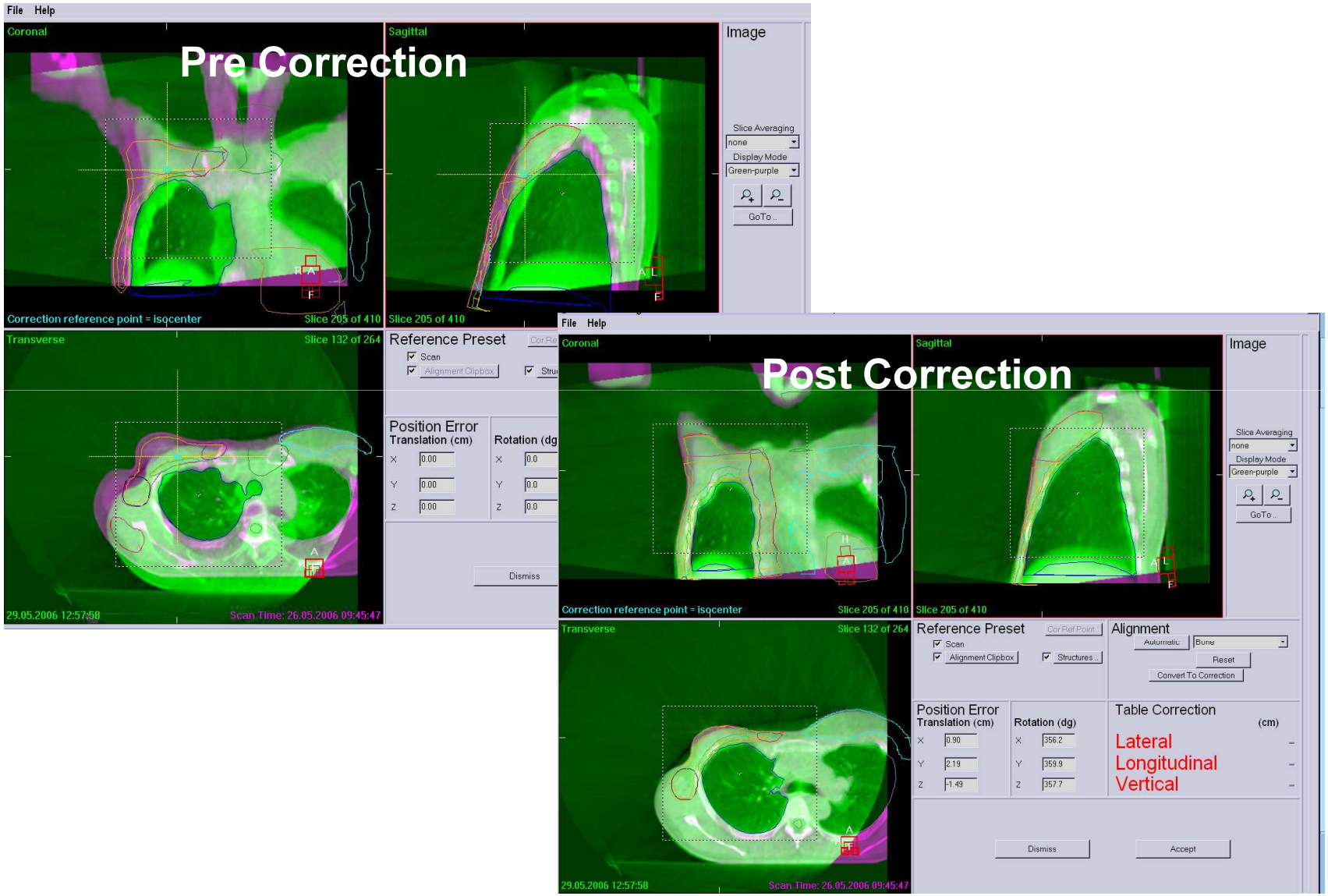


Plan: 37	plan 36 - hot spots out	Plan Date	23-MAY-2006 22:54
Signature	8 Beams - 35 segments - purged for <3 MUs - Flash region added		

Key	Structure	Plan	Min Dose[cGy]	Max Dose[cGy]	Mean Dose[cGy]	Total Vol [cc]
	PTV	Renken Heike(37) Whole PTV	0	6288	5800	774.4
	SCLN	Renken Heike(37) Supraclavicular LNs	0	5545	4962	261.3
	PTV 2	Renken Heike(37) Chest Wall	0	6336	5800	461.1
	Lunge re	Renken Heike(37) Ipsilateral Lung	107	5775	1552	1635.0
	L Breast	Renken Heike(37) Contralateral Breast	0	3186	886	632.5
	Herz	Renken Heike(37)	141	2090	785	409.3
	RM	Renken Heike(37)	0	963	258	60.8

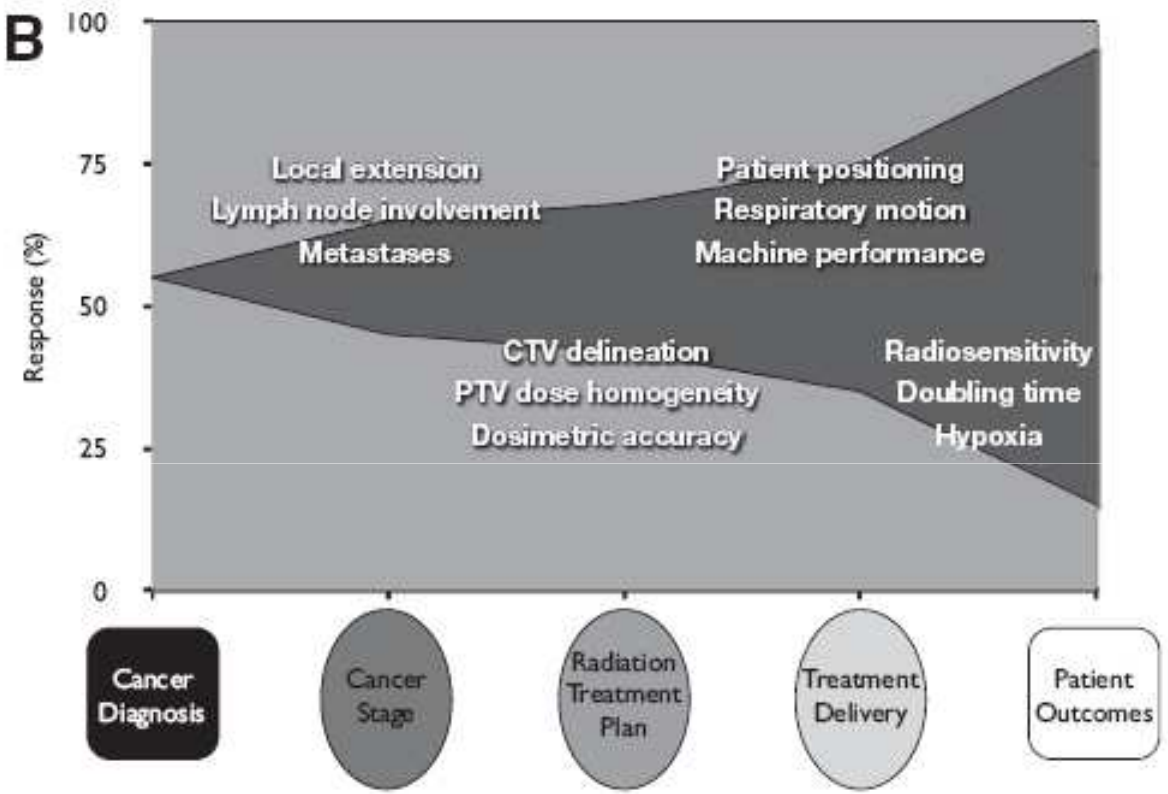


Positioning for Thoracic Wall IMRT



Influence of IGRT on clinical outcome

„Although it may be difficult to directly evaluate the limited evidence for IGRT it is possible to examine improved clinical outcomes that have been enabled by IGRT“

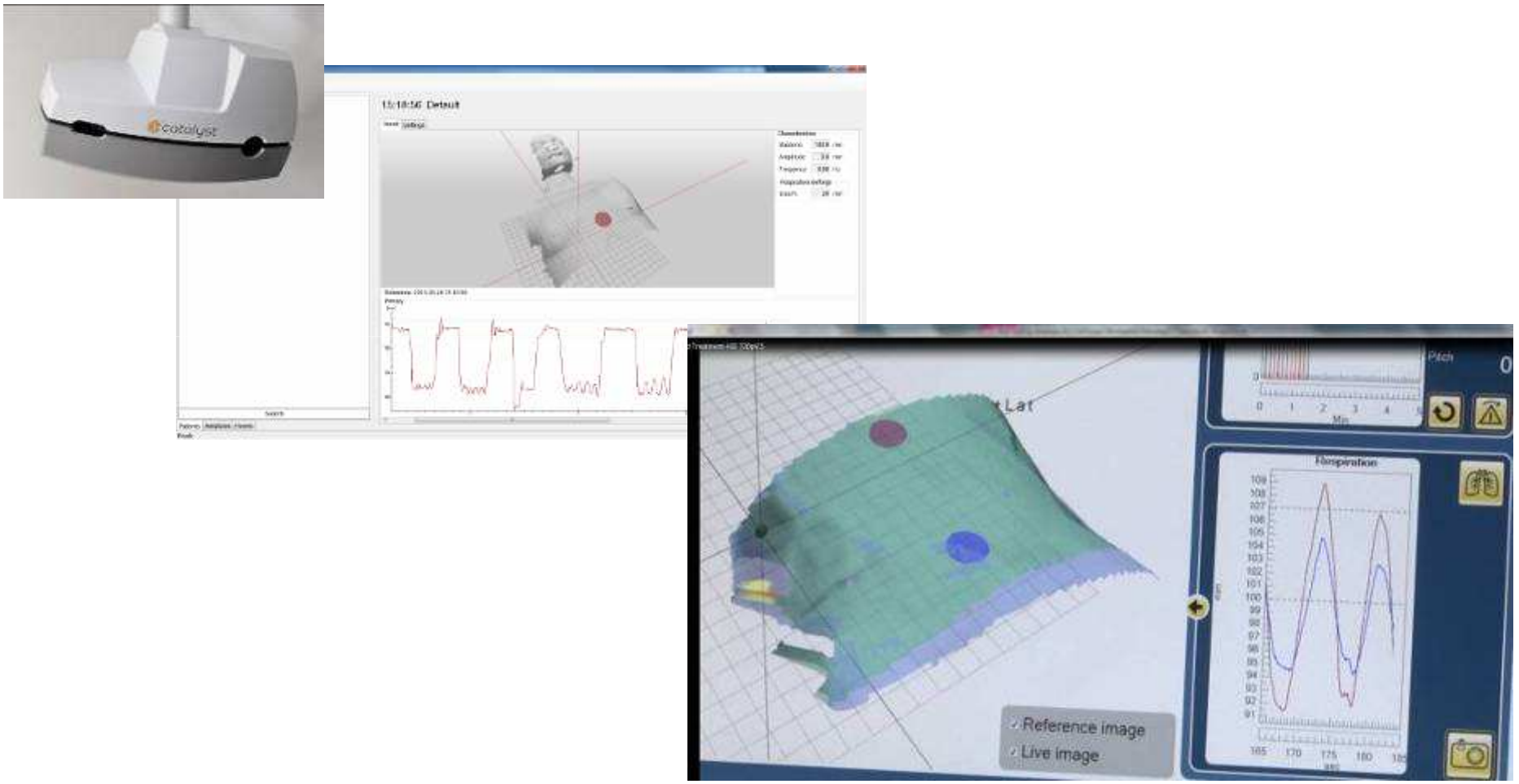


Bujold, Craig, Jaffray, Dawson, Sem Rad Onc, 2012

“Although there are many guidelines for the quality assurance of IGRT equipment, there are few that specifically highlight the role of IGRT as quality assurance or the potential of IGRT to reduce patient treatment incidents”

Bujold, Craig, Jaffray, Dawson, Sem Rad Onc, 2012

Surface-based Surveillance



Catalyst Characteristics

Stieler et al., submitted

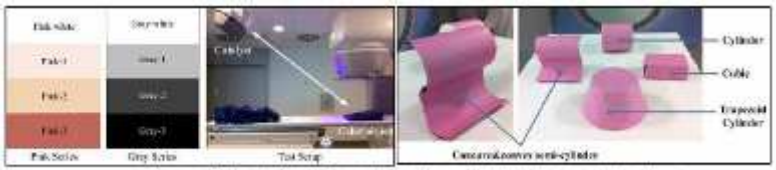


Figure 2a,b: Left: colour test setup. Right: shape test setup

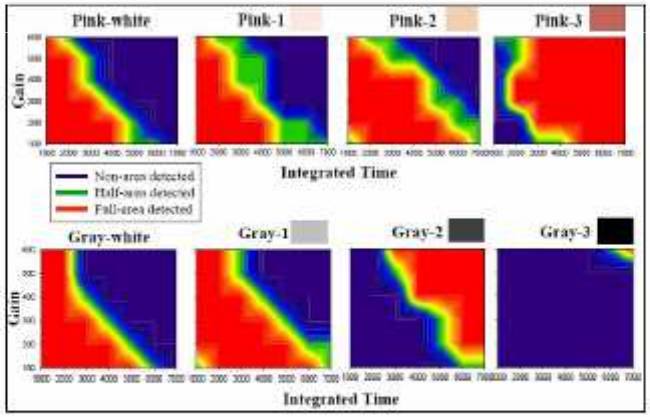


Figure 3: Plots of the color tests depending on gain and IT. Scans with settings that result with values in the blue area are not visible; scans with results in the red area are full visible.

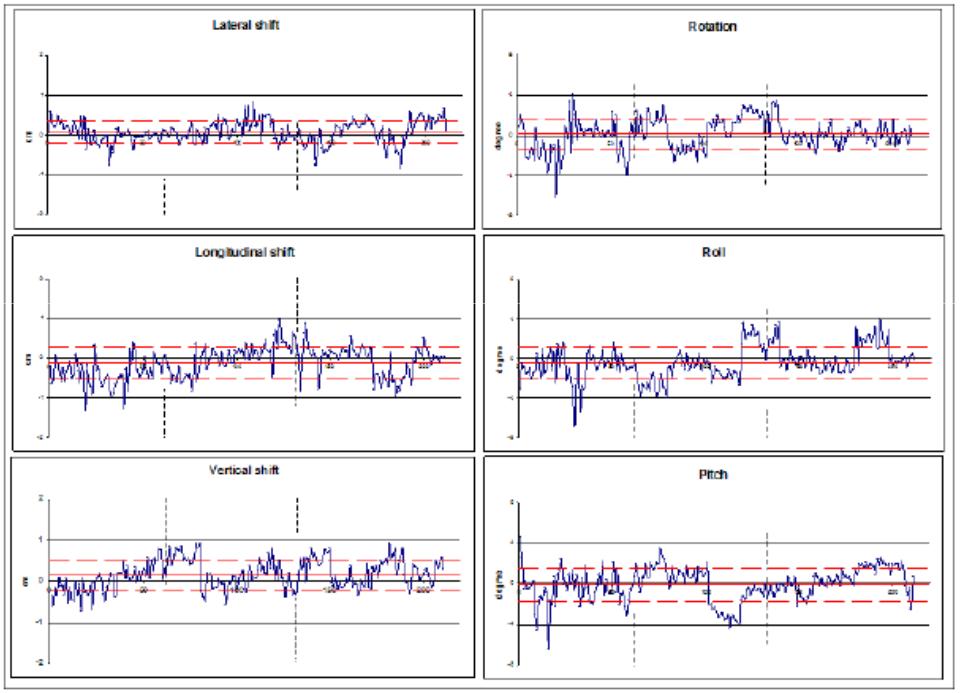
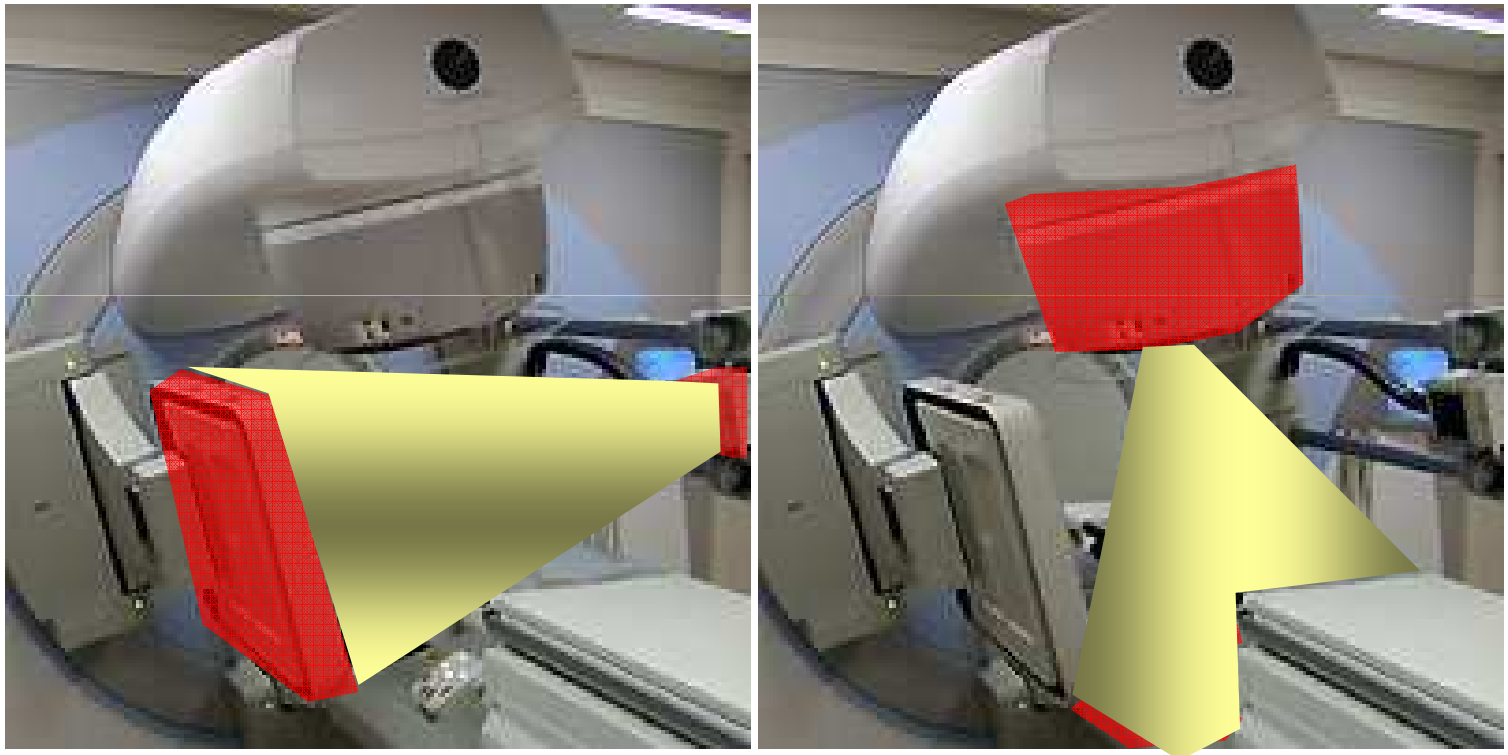


Figure 6: Shift vector in cm respectively degree for the 224 fraction for 3 translation directions (lateral, longitudinal and vertical) and 3 rotational directions (rotation, roll and pitch). First block: head-and neck targets, second block pelvic targets and third block thoracic targets.

Ansatz kV+MV-Rekonstruktion

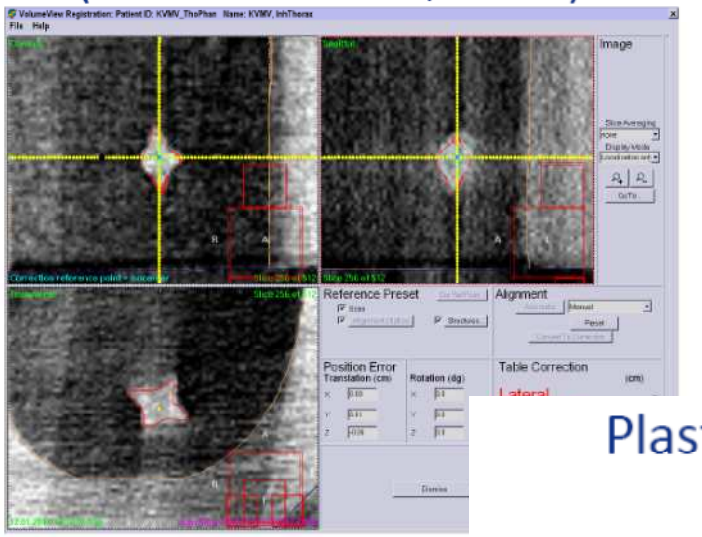
kV

MV

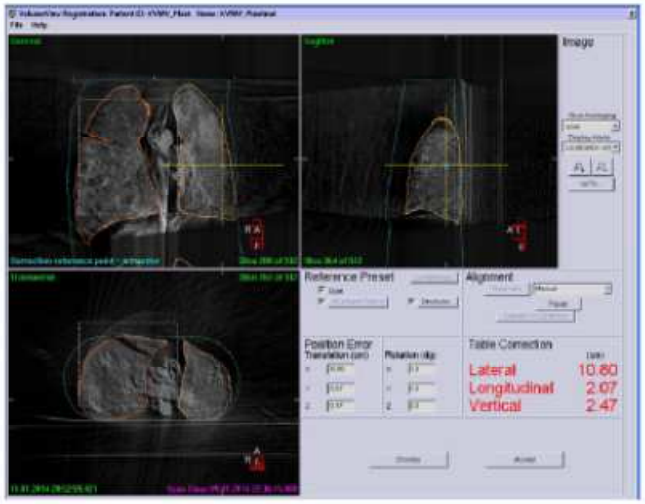


http://www.elekta.com/healthcare_international_beaumont_work_results_breakthrough.php

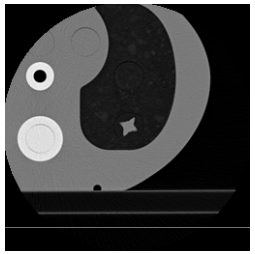
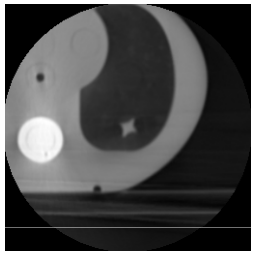
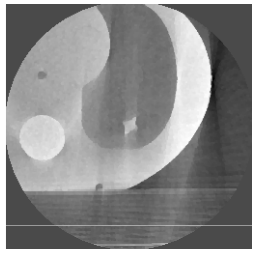
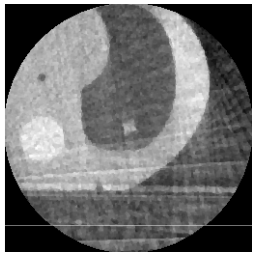
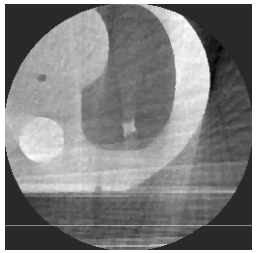
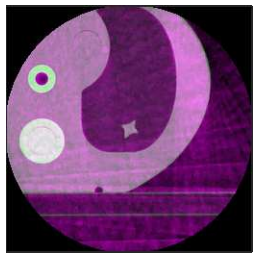
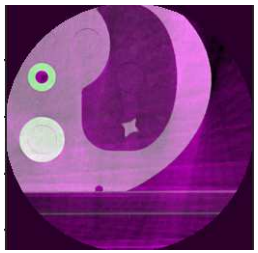
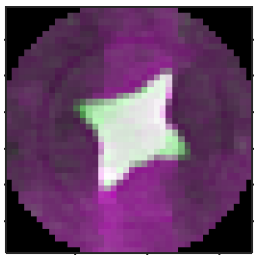
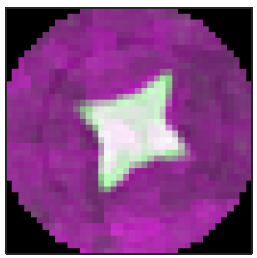
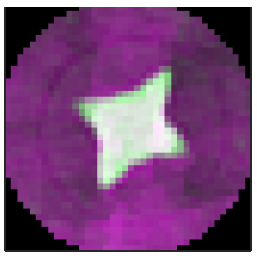
Thorax phantom: star shaped inlay
(15s kV-MV scan, 5 MU)



Plastinated Thorax (15s kV-MV mode, 5MU)
different level/window settings

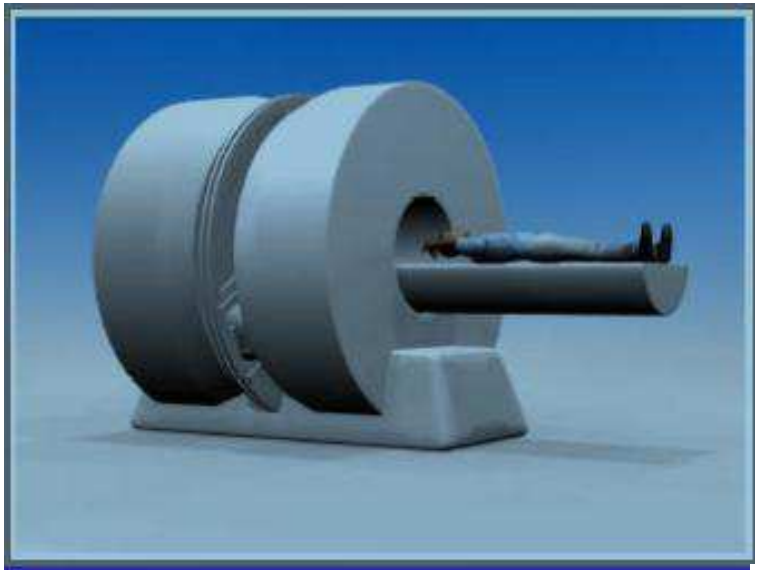


Beispiel: Tumor shape Star10, after registration of iso-shift 1
(automatic registration with in-house developed software - Matlab)

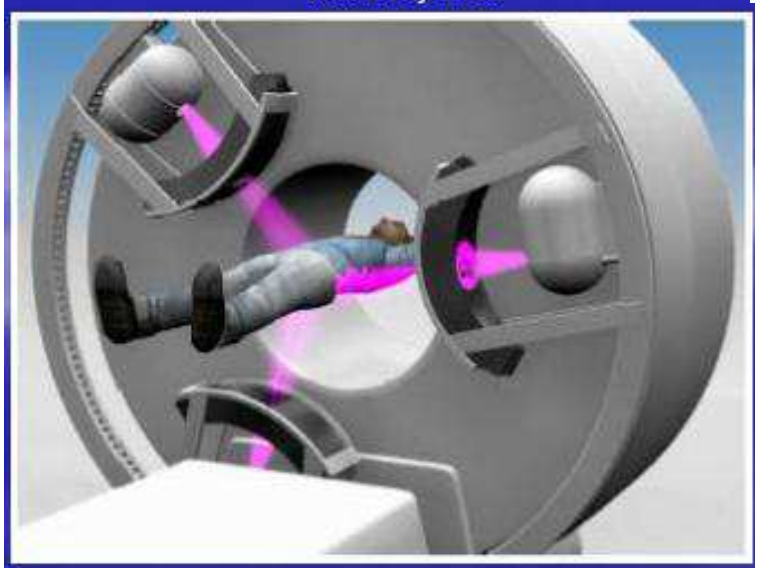
	pCT	kV-Chest CBCT * (360°) (*clinical preset)	kV-only CBCT (180°)	MV-only CBCT (180°)	Combined kV-MV CBCT (90°)
Full Phantom (registered)					
Full phantom registration overlay	pCT CBCT				
Full tumor registration overlay	pCT CBCT				

NOTE: kV-only, MV-only and combined kV-MV CBCT were simultaneously acquired → MV-scatter in kV-contribution

1- MRI guided Radiation Therapy



Renaissance™ System 1000
ViewRay Inc.

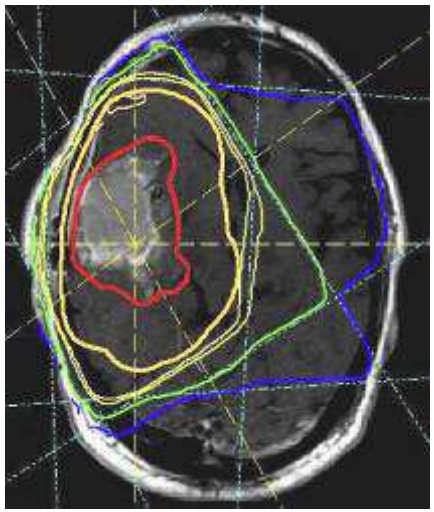


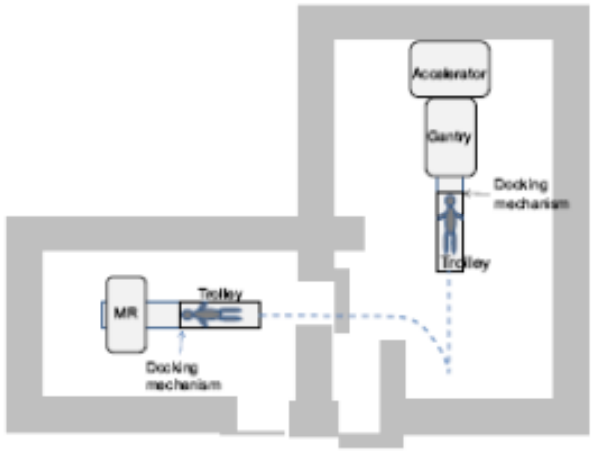
MR scanner /^{60}Co

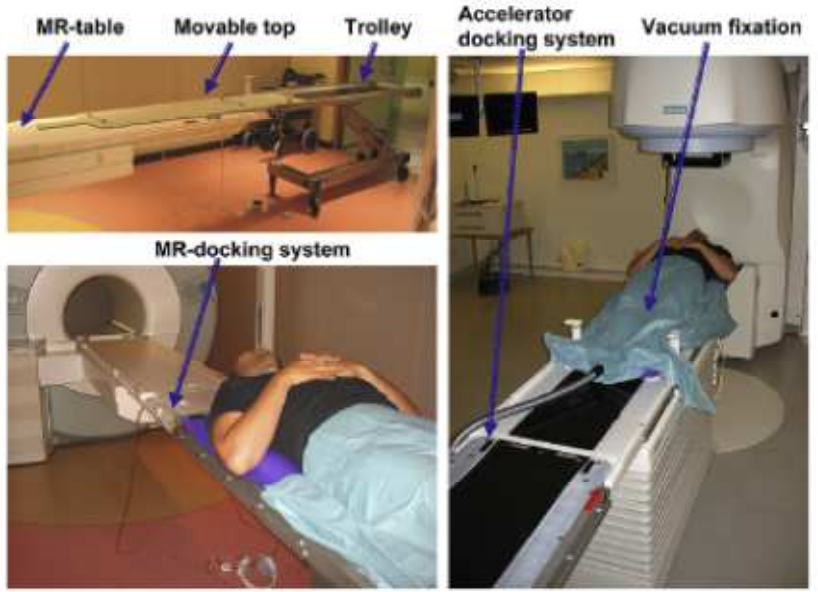
2- MRI and LINAC

Karlsson M. et al. Int. J. Radiation Oncology Biol. Phys. 2009

1.5-T Siemens Espree unit
Siemens ONCOR (LINAC)

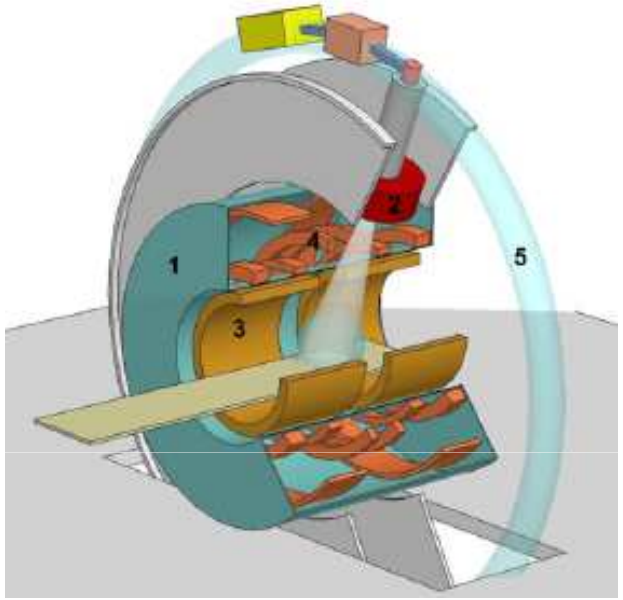


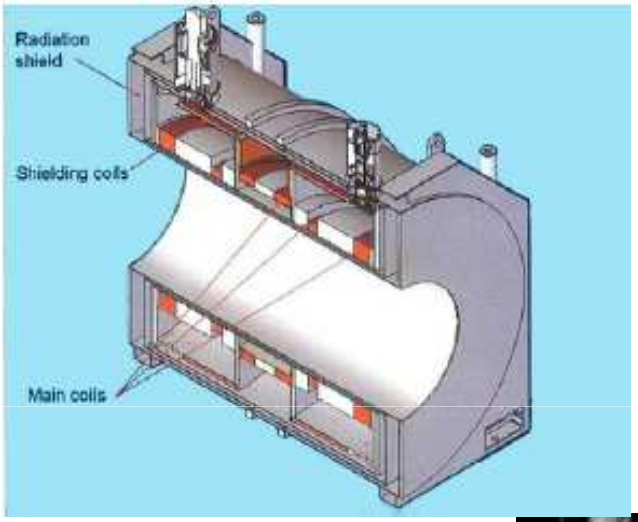


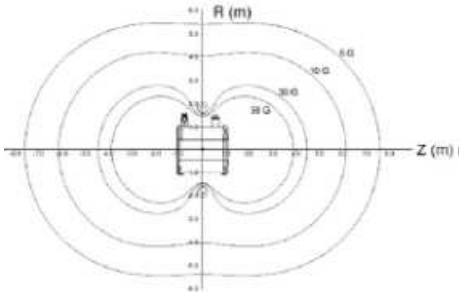


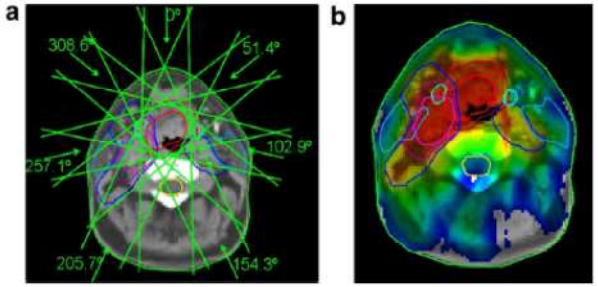
3- MR LINAC

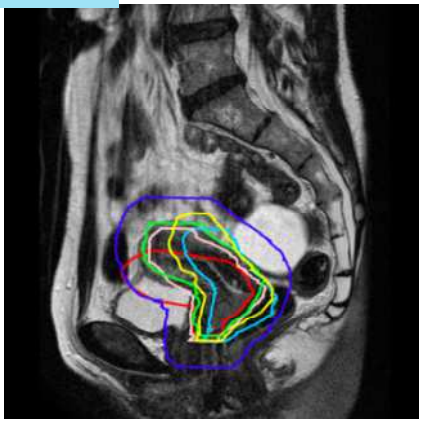
Lagendijka JW et al. Oncology, 2008
Raaymakers BW et al, Phys. Med. Biol. 2009
Crijns SPM et al, Phys. Med. Biol. 2012

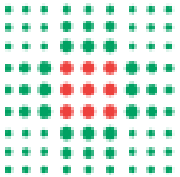












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