Physics for Modern Radiotherapy

A joint course for clinicians and physicists

4-8 June 2017 | Bucharest, Romania

2017
ESTRO SCHOOL
LIVE COURSE

COURSE AIMS

The lectures aim to:

- Provide knowledge and understanding of physics relevant to modern clinical radiotherapy
- Provide comprehensive overviews of imaging and volume concepts in radiotherapy
- Discuss modern dose delivery techniques, such as IMRT, rotational therapy (VMAT, helical tomotherapy), S(B)RT, IGRT, adaptive therapy (ART), particle therapy and brachytherapy
- Discuss safety issues in lectures on commissioning and QA/QC, radiation protection, in vivo dosimetry and induction of secondary tumours.

Complimentary to the lectures, this course has clinical case discussions as an important component. The case discussions aim at teaching physics by practical application in treatment planning.

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PROGRAMME
PHYSICS FOR MODERN RADIOTHERAPY
Bucharest, Romania – June 4-8, 2017

Sunday 4 June	***Morning Chairs: A. Henry, B. Heijmen*** ***Afternoon Chairs: S. Hafeez, V. Hansen***	
	Topic	***Speaker***
08.30 – 08.45	Welcome address	
08.45 - 09.00	Introduction to the course	All teachers
09.00 - 10.00	ENTRANCE EXAM	B. Heijmen
10.00 - 10.30	*Coffee break*	
10.30 - 11.15	Volumes in EBRT and introduction to GTV definition	S. Hafeez
11.15- 12.00	Imaging for treatment preparation and planning	E. Troost
12.00 - 12.45	IGRT - tumor set-up correction strategies	B. Heijmen
12.45 - 14.00	*Lunch*	
14.00 - 14.45	IGRT - equipment for in-room imaging	A. Henry
14.45 - 15.30	PTV margin calculation	B. Heijmen
15.30 - 16.00	*Coffee break*	
16.00 - 16.45	**Clinicians:** Basics of radiation physics for clinicians	S. Molinelli
	Physicists: Modern dose calculation algorithms	M. Tomsej
16.45 - 17.30	**Clinicians:** Principles of Radiotherapy Equipment	M. Tomsej
	Physicists: Oncological Concepts	E. Troost
17.30 – 18.30	Welcome Drink	
Monday 5 June	***Morning Chairs: Esther Troost, S. Molinelli*** ***Afternoon Chairs: A. Henry, M.Tomsej***	
	Topic	***Speaker***
08.30 - 09.15	Radiobiology in the clinic	**A. Henry**
09.15 - 10.00	IMRT – Physics aspects	V. Hansen
10.00 - 10.30	*Coffee break*	
10.30 - 11.15	IMRT - clinical application and impact	S. Peeters
11.15 - 12.00	Challenges in dose prescription and plan evaluation	A. Henry
12.00 - 12.45	Field junctions: how, when, and alternatives	S. Hafeez / B. Heijmen
12.45 - 14.00	*Lunch*	
14.00 - 15.30	**Group 1**: Discussions on H&N case -	A. Henry / M. Tomsej
	Group 2: Discussions on H&N case -	S. Hafeez / V. Hansen
	Group 3: Discussions on H&N case -	E. Troost / B. Heijmen
	Group 4: Discussions on H&N case -	S. Peeters / S. Molinelli
15.30 - 16.00	*Coffee break*	
16.00 - 16.45	Stereotactic radiotherapy	S. Peeters
16.45 – 17.30	Rotational therapy and flattening filter free dose delivery	S. Molinelli

19.30	Social Dinner	
Tuesday 6 June	***Afternoon Chairs: S. Peeters, V. Hansen***	
	Topic	***Speaker***
09.30 - 13.15	FREE MORNING	
13.15 – 14.00	Imaging for GTV definition	S. Hafeez
14.00 – 15.30	**Group 1**: Discussions on lung case	S. Hafeez / V. Hansen
	Group 2: Discussions on lung case	E. Troost / B. Heijmen
	Group 3: Discussions on lung case	S. Peeters / S. Molinelli
	Group 4: Discussions on lung case	A. Henry / M. Tomsej
15.30 - 16.00	*Coffee break*	
16.00 - 16.45	Physics aspects of proton-, ion-, and electron beam therapy	S. Molinelli
16.45 – 17.30	Clinical aspects and evidence for particle therapy and other novel technology	E. Troost
Wednesday 7 June	***Morning Chairs: E. Troost, S. Molinelli*** ***Afternoon Chairs: S. Peeters, B. Heijmen***	
	Topic	***Speaker***
08.30 - 09.15	Commissioning and QA/QC of equipment and software	M. Tomsej
09.15- 10.00	In-vivo dosimetry	V. Hansen
10.00 - 10.30	*Coffee break*	
10.30 - 12.00	**Group 1**: Discussions on breast case	E. Troost / B. Heijmen
	Group 2: Discussions on breast case	S. Peeters/ S. Molinelli
	Group 3: Discussions on breast case	A. Henry / M. Tomsej
	Group 4: Discussions on breast case	S. Hafeez / V. Hansen
12.00 - 12.45	Adaptive Radiotherapy	S. Hafeez
12.45 - 14.00	*Lunch*	
14.00 – 14.45	**Clinicians***:* Physical principles of advanced Radiotherapy	S. Molinelli
	Physicists*:* Reference Dosimetry	B. Heijmen
14.45 – 15.30	**Clinicians:** Dose calculation principles	V. Hansen
	Physicists*:* QA for advanced delivery techniques	M. Tomsej
15.30 - 16.00	*Coffee break*	
16.00 - 16.45	**Clinicians:** Calculation of dose in the TPS	V. Hansen
	Physicists*:* Non-reference dosimetry	B. Heijmen
16.45 – 17.30	MEET THE TEACHERS – INFORMAL DISCUSSIONS ON TOPICS BROUGHT UP BY PARTICIPANTS	All teachers
Thursday 8 June	***Morning Chairs: S. Hafeez, M. Tomsej***	
	Topic	***Speaker***
08.30 - 09.15	Brachytherapy	A. Henry
09.15 - 10.00	Radiation Protection	S. Molinelli
10.00 - 10.30	*Coffee break*	
10.30 - 11.15	Radiotherapy dose and induction of secondary tumors	S. Peeters
11.15 - 12.15	EXIT EXAM	B. Heijmen
12.15- 12.30	Distribution of certificates of attendance	All teachers

Volumes in EBRT and introduction to GTV definition

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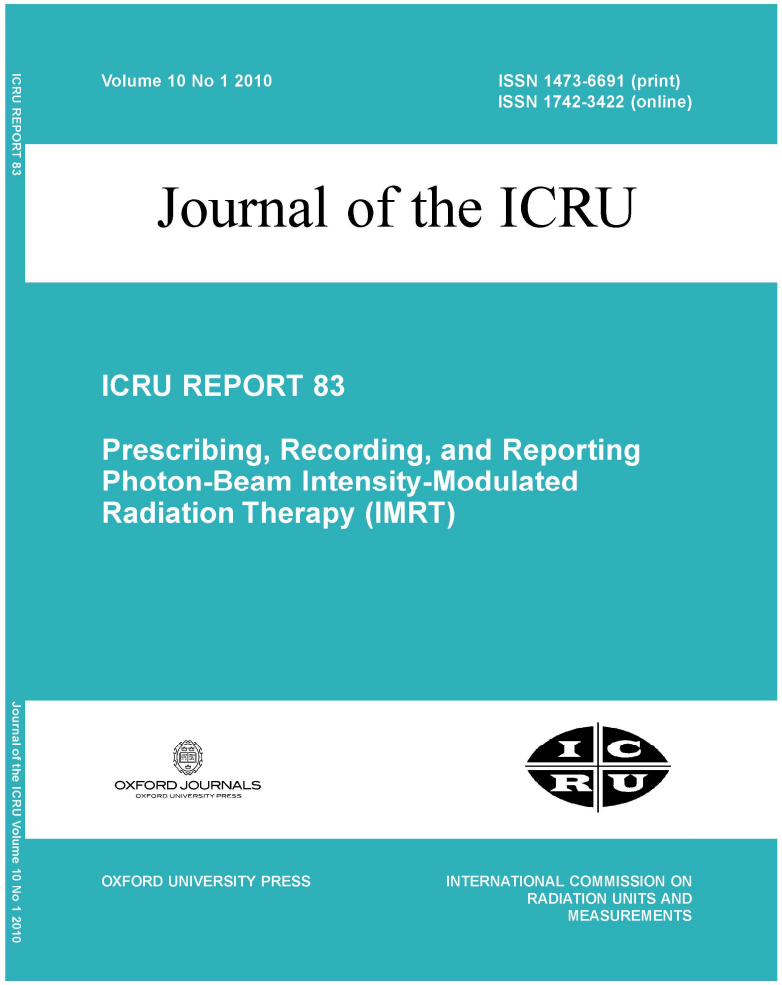
Physics for Modern Radiotherapy, Bucharest, 2017

ICRU Reports



- Common international language for describing target volumes
- Dose prescribing, recording, reporting

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ICRU Reports

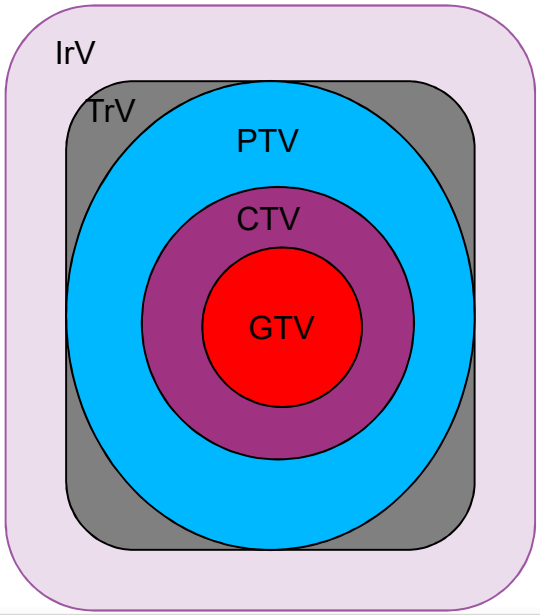
Standardisation of radiation therapy terminology and dose specification

Aim:

- Maintain a consistent treatment policy which may be improved with experience
- Enable comparison of treatment results within department and between RT centres
- Particularly useful for multi-centre studies and publication

Volume definition

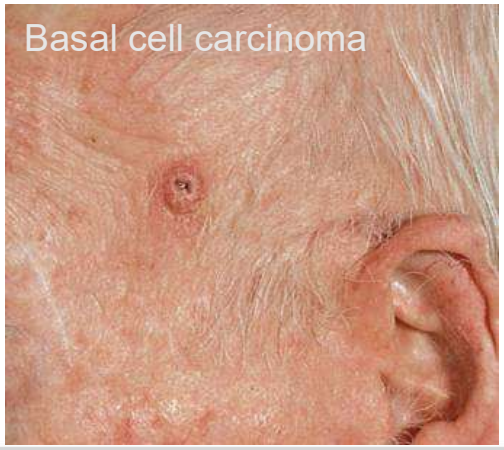
Standardisation of radiation therapy terminology and dose specification

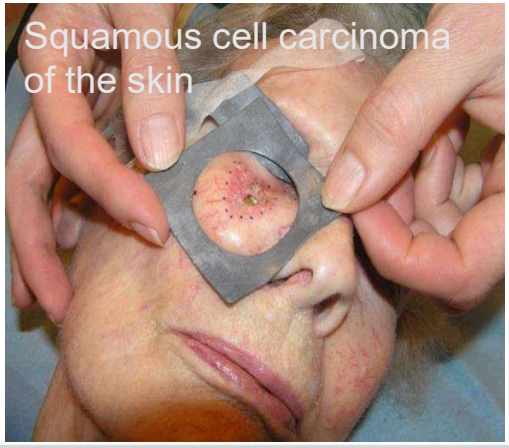


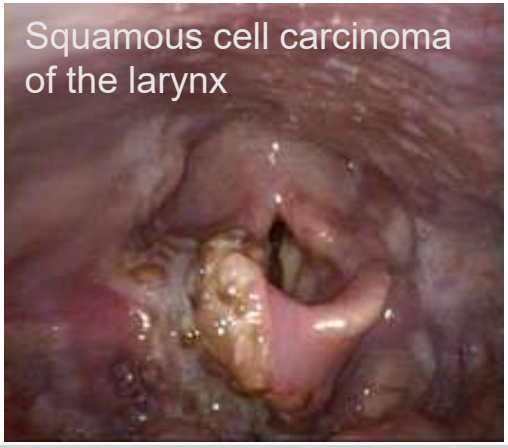
Volume definition: Gross Tumour Volume (GTV)

GTV

- The gross palpable, visible or demonstrable extent of malignant disease
- May consist of primary tumour, nodal, or metastases
- No GTV if tumour has been removed







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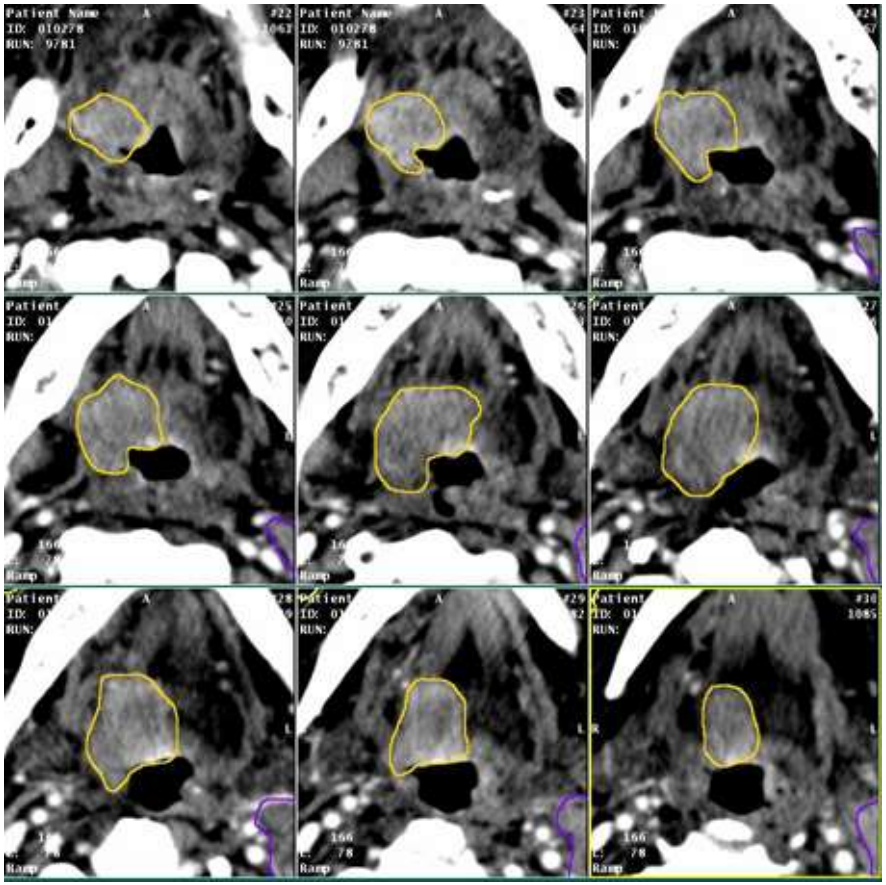
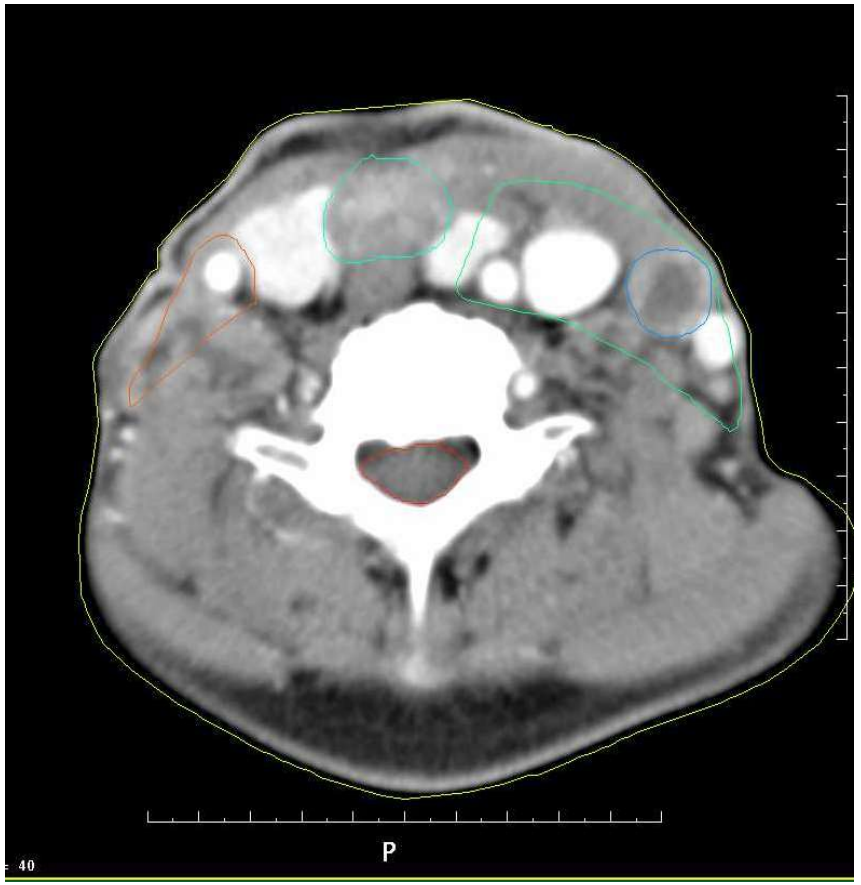
Delineating the GTV



CT (with contrast)- visualisation of gross primary (GTV-T)



CT (with contrast)- visualisation of gross nodal disease (GTV-N)

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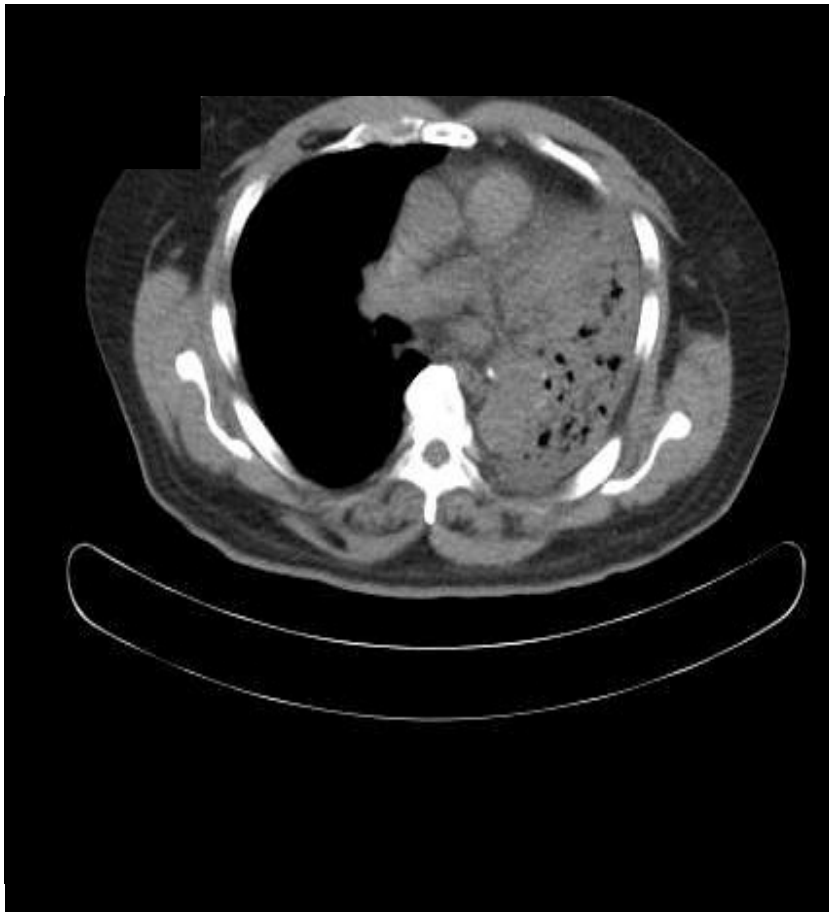
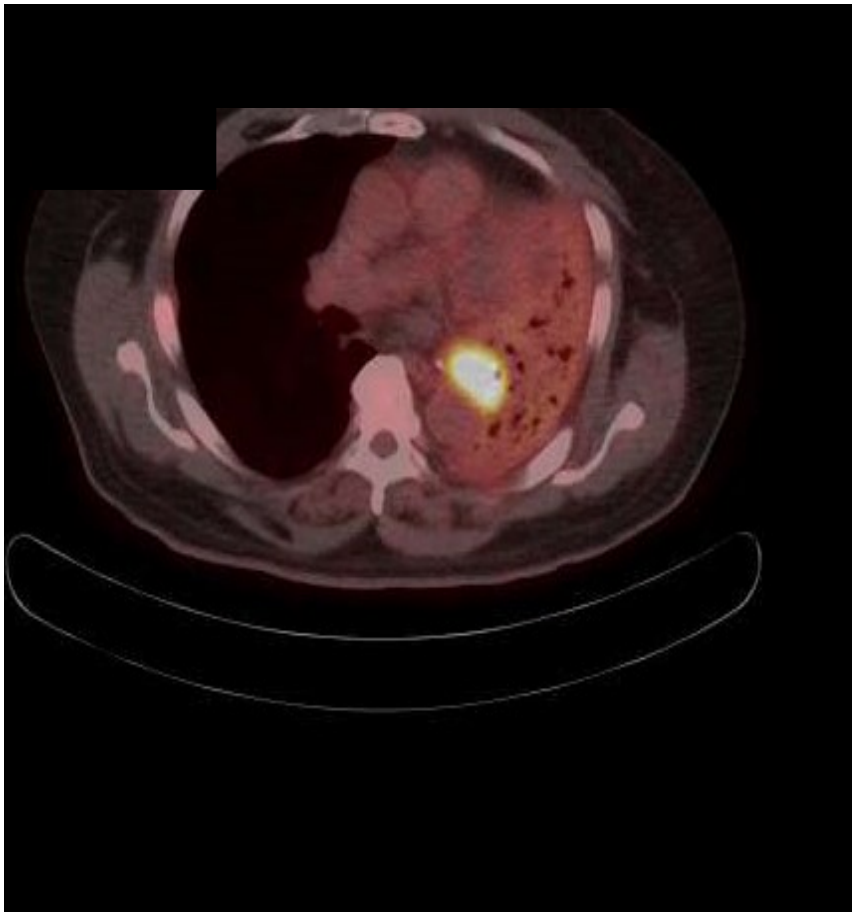
Delineating the GTV- variation with modality



Planning CT

GTV-T (CT, 0Gy)



FDG-PET-CT

GTV-T (FDG-PET-CT, 0Gy)

Chiti A, Kirienko M, Gregoire V. Clinical use of PET-CT data for radiotherapy planning: what 90 are we looking for? Radiother Oncol. 2010;96(3):277–9. De Ruysscher D, Kirsch CM. PET scans in radiotherapy planning of lung cancer. Radiother 88 Oncol. 2010;96(3):335–8. Bradley J, *et al*: A phase II comparative study of gross tumor volume definition with or without PET/CT fusion in dosimetric planning for non-small-cell lung cancer (NSCLC): primary analysis of Radiation Therapy Oncology Group (RTOG) 0515. *Int J Radiat Oncol Biol Phys* 2012, **82**(1):435-441 e431.

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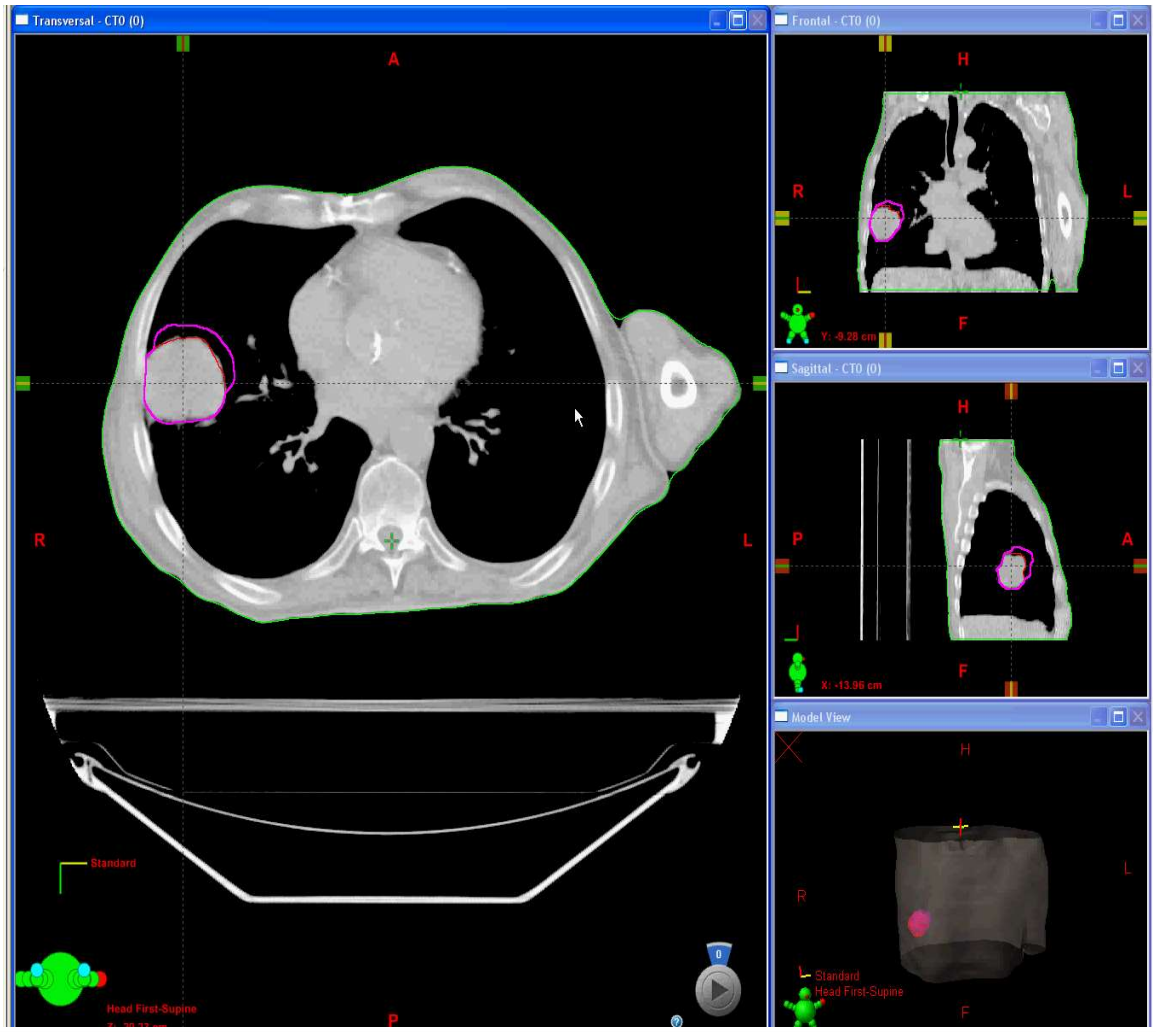
Delineating the GTV- variation with time



Delineating the GTV- variation with person

Inter clinician variation

- Variation observed between radiologist & radiation oncologists

Intra clinician variation

- Variation seen with single observer
- Training
- Delineation workshops

Logue et al., Clinical variability of target volume description in conformal radiotherapy planning. *Int J Radiat Oncol Biol Phys* 1998, 41(4):929-931. Vinod S et al., Uncertainties in volume delineation in radiation oncology: A systematic review and recommendations for future studies. *Radiotherapy and Oncology* 2016

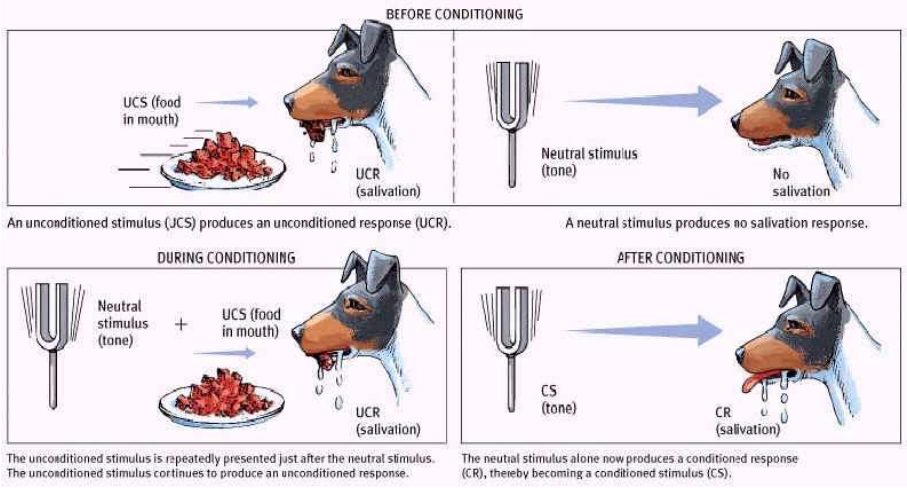
Delineating the GTV- a representation

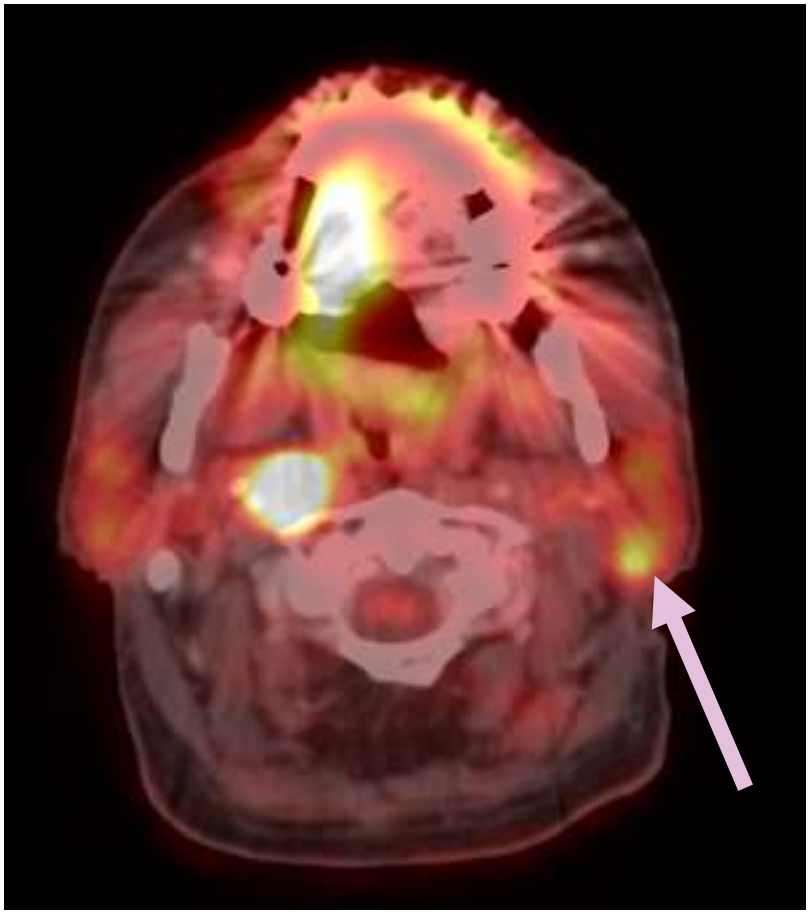
The Treachery of of Images (1928-1929)
Belgian surrealist René Magritte

Target volumes for radiotherapy (GTV, CTV & OAR) are purely oncological or anatomical concepts, a representation of these volumes is used in the planning process

Delineating the GTV- a representation

Classical conditioning





You see a spot

You draw a contour

You irradiate it

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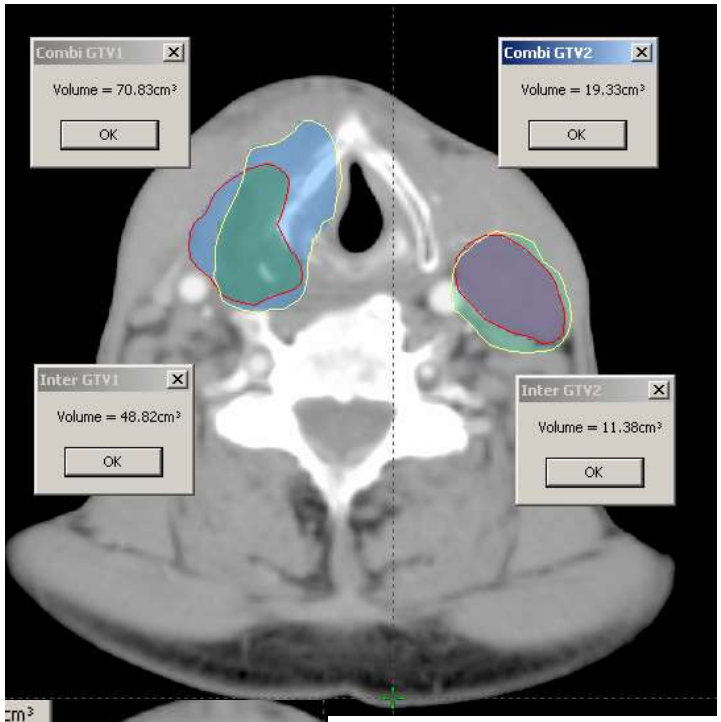
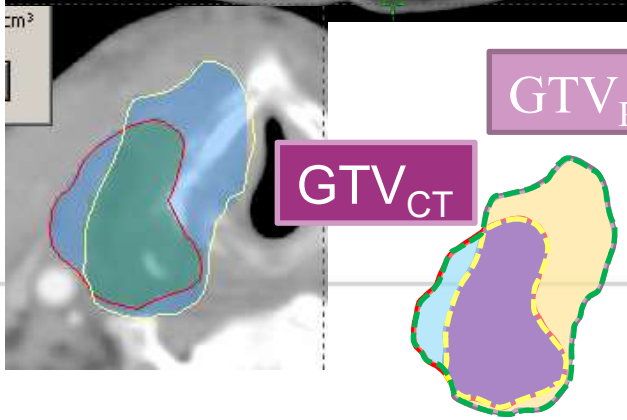
Metrics for volumetric comparisons





Parameter		Formula	Interpretation
Ratio PET/CT		GTV_{PET}/GTV_{CT}	
Ratio CT/PET		GTV_{CT}/GTV_{PET}	
Discrepancy index (DI)		EV/OV	= 1 Perfect concordance = ∞ Complete disagreement
Conformity index (CI)		OV/EV	= 1 Perfect conformity = 0 Complete disconformity
Overlap Fraction (OF) or "coverage"	OF_{CT}	OV /GTV_{CT}	Proportion of GTV_{CT} covered by GTV_{PET}
	OF_{PET}	OV /GTV_{PET}	Proportion of GTV_{PET} covered by GTV_{CT}
Mismatch Fraction (MF)	$MF_{CT/PET}$	1 - OF_{CT}	Volume enclosed by GTV_{CT} but not by GTV_{PET} relative to GTV_{CT}
	$MF_{PET/CT}$	1 - OF_{PET}	Volume enclosed by GTV_{PET} but not by GTV_{CT} relative to GTV_{PET}

$OV = GTV_{PET} \cap GTV_{CT}$ Intersection

$EV = GTV_{PET} \cup GTV_{CT}$ Conjunction

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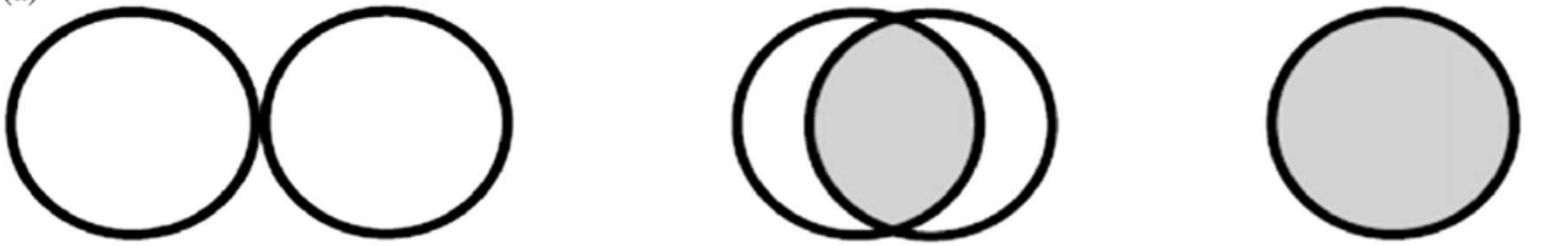
Conformity index

(a)

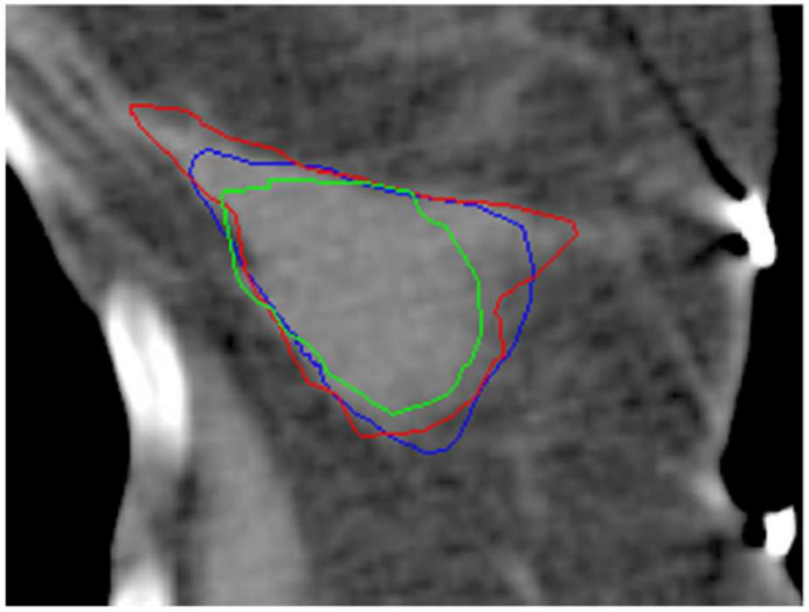


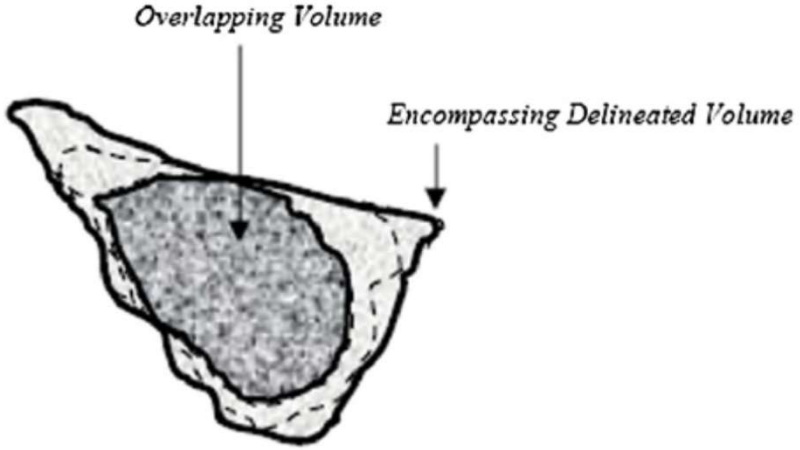
CI = 0 (0% concordance)

CI = 0.5 (50% concordance)

CI = 1 (100% concordance)

(b)





Petersen RP et al., Target volume delineation for partial breast radiotherapy planning: clinical characteristics associated with low interobserver concordance. *Int J Radiat Oncol Biol Phys* 2007, 69(1):41-48.

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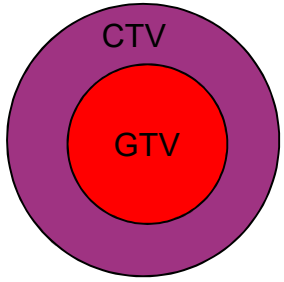
Volume definition: Clinical Target Volume (CTV)

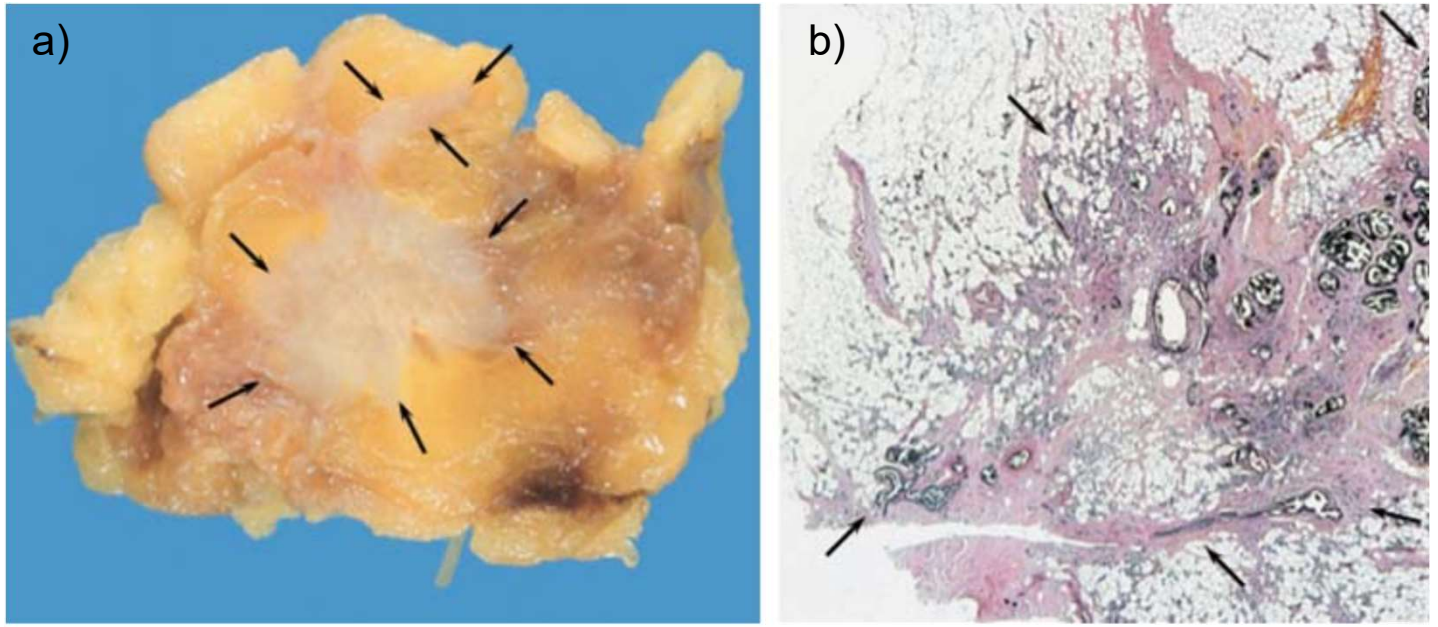
CTV

- Volume containing GTV, and/or subclinical disease with certain probability of occurrence
- Occult disease >5-10% considered
    - Clinical judgement
    - Type of malignancy
    - Local failure consequence
    - Salvage feasibility



Volume definition: Clinical Target Volume (CTV)

Subclinical malignant disease



Breast tumour (a) macroscopic and (b) microscopic view ICRU 83

Volume definition: Clinical Target Volume (CTV)

Subclinical malignant disease

Microscopic tumour spread

Beyond **primary-tumour GTV**

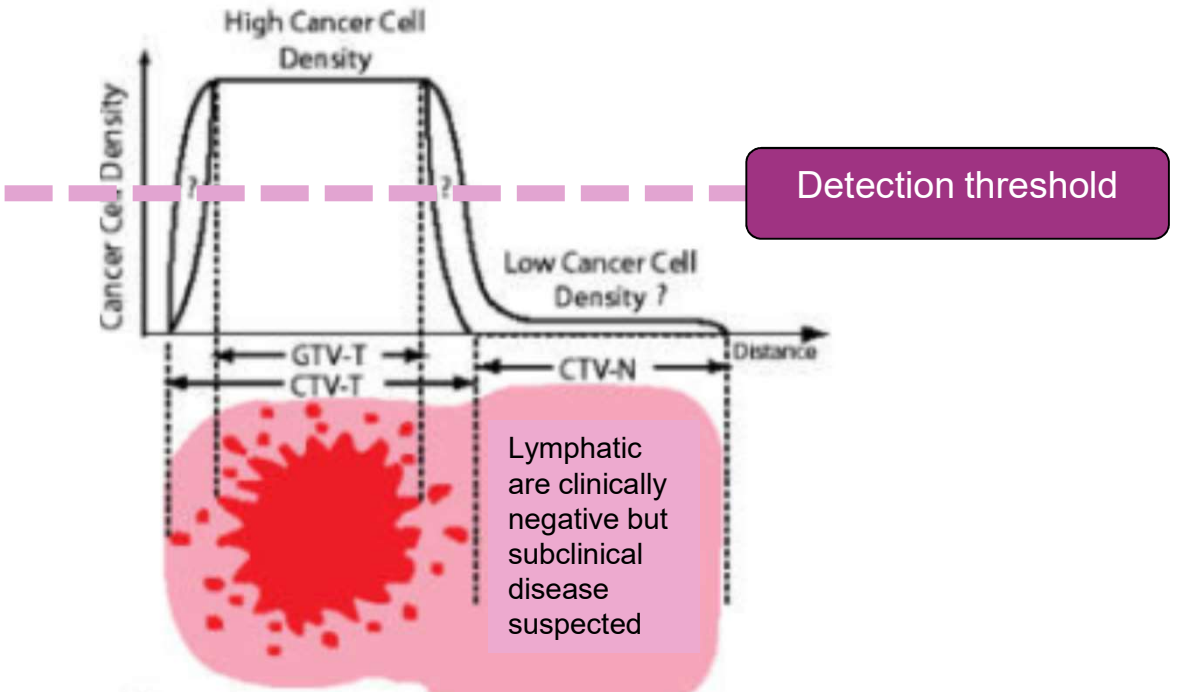
Possible **regional lymph nodes**

Post operative (R0, R1)

Potential **metastatic involvement** of other organs (brain)

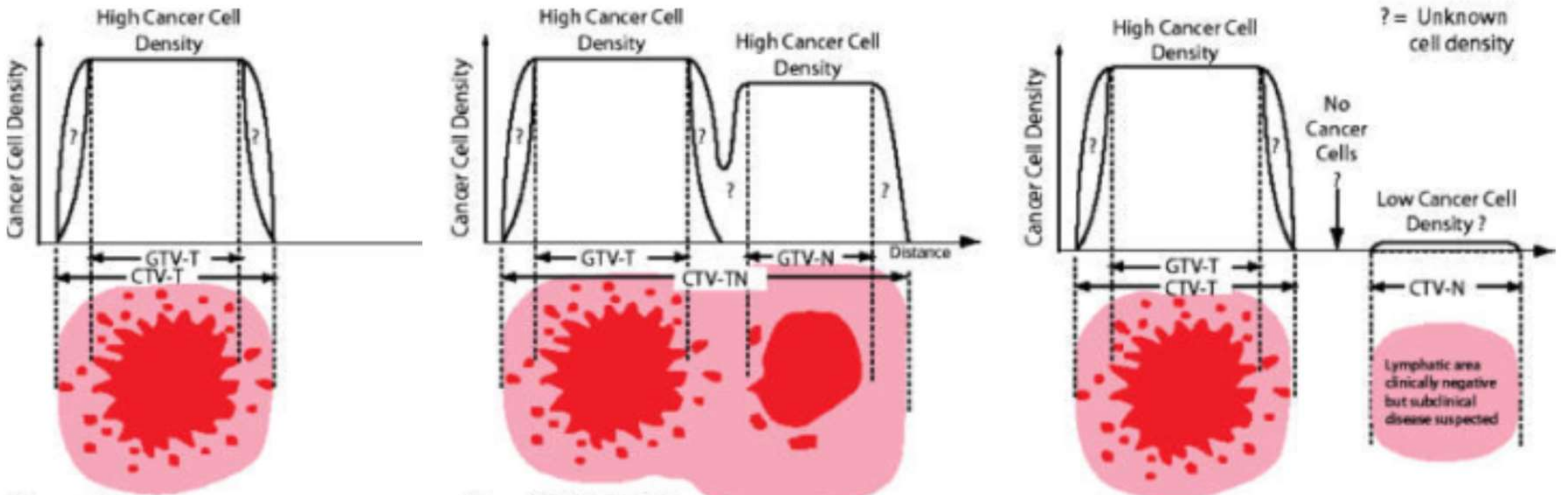
Despite normal appearance on clinical examination and radiology

Determining the CTV



Adapted from ICRU 71

Determining the CTV



Adapted from ICRU 71

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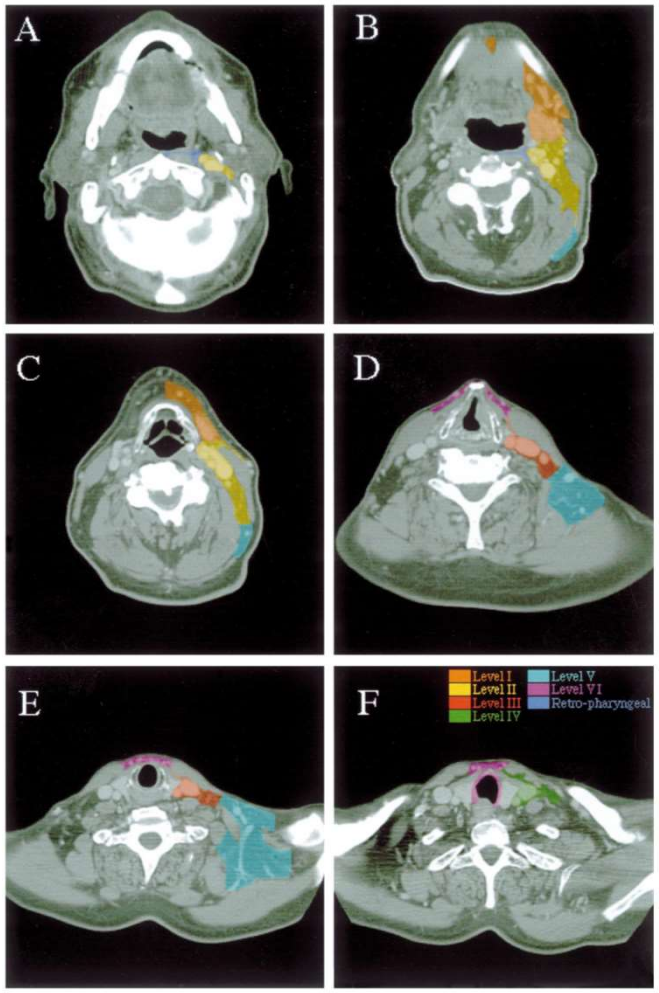
CTV margin assessment

Determining risk of microscopic tumour infiltration

- Biological behaviour
- Clinical behaviour
- Surrounding anatomical barriers
- Can not be modified
- Require cooperation with surgeons

CTV margin determination-surgical experience



Suggested guidelines for the treatment of the neck of patients with head and neck squamous cell carcinomas (AJCC 1997)

Location of primary tumor	Appropriate node levels to be treated	
	Stage N0–N1	Stage N2b
Oral cavity	I, II, and III (+IV for anterior tongue tumors)	I, II, III, IV and V[a]
Oropharynx	II[b], III, and IV (+retropharyngeal nodes for posterior pharyngeal wall tumors)	I, II, III, IV, V and retropharyngeal nodes
Hypopharynx	II[b], III, and IV (+VI for esophageal extension)	I, II, III, IV, V and retropharyngeal nodes (+VI for esophageal extension)
Larynx[c]	II[b], 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] May be omitted if only levels I–III are involved.
[b] Nodes in level IIb could be omitted for N0 patients.
[c] T1 glottic cancer excluded.

Gregoire V, Coche E, Cosnard G, Hamoir M, Reychler H: Selection and delineation of lymph node target volumes in head and neck conformal radiotherapy. Proposal for standardizing terminology and procedure based on the surgical experience. *Radiother Oncol* 2000, 56(2):135-150.

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CTV margin determination-surgical experience

Examples

Lung

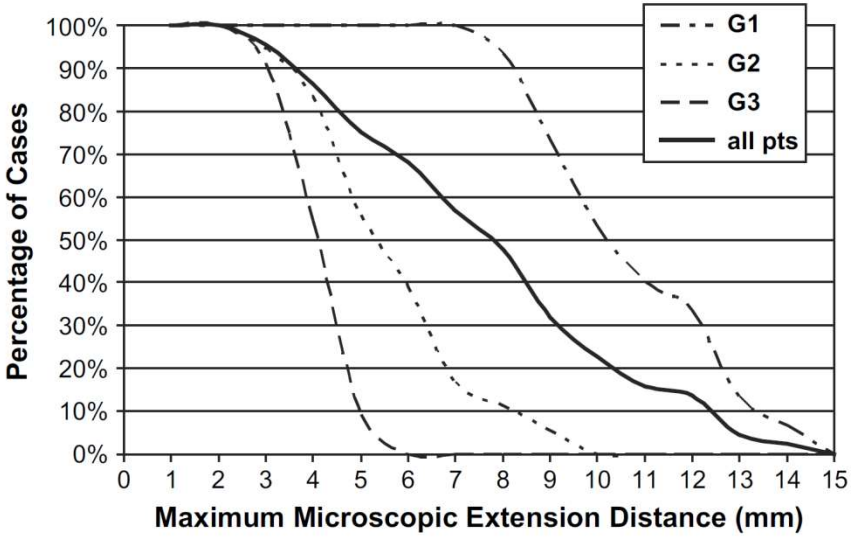

Fig. 2. Relationship between nuclear grade and distance of microscopic extension beyond gross tumor edge.

- 35 patients with T1N0 NSCLC underwent wedge resection plus immediate lobectomy.
- GTV and microscopic extension distance beyond the gross tumor were measured.
- Grade analyzed for association with microscopic extension.

Grills IS, Fitch DL, Goldstein NS, Yan D, Chmielewski GW, Welsh RJ, Kestin LL: Clinicopathologic analysis of microscopic extension in lung adenocarcinoma: defining clinical target volume for radiotherapy. Int J Radiat Oncol Biol Phys 2007, 69(2):334-341.

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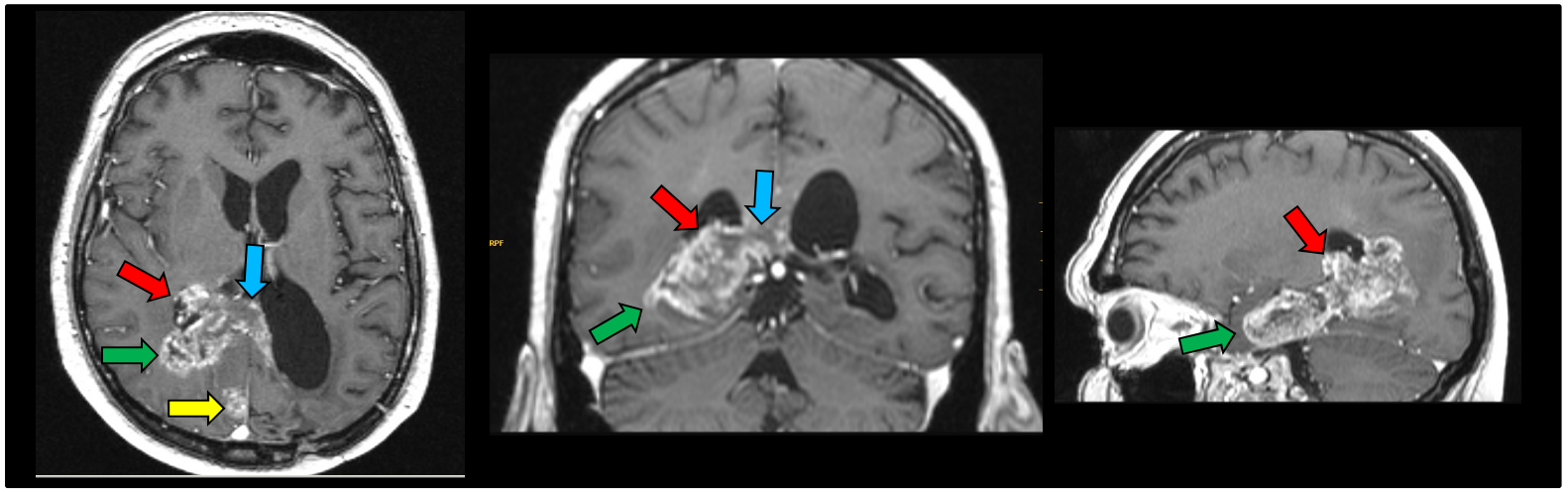
CTV margin determination-patterns of relapse

Examples

Glioblastoma

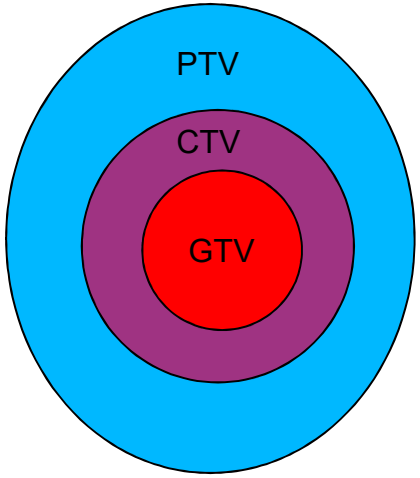


Extension though corpus callosum
Extension subependimal
Extension through white matter (fascículum temporo-occipital)
Recurrence multicentric

Volume definition: Planning Target Volume (PTV)

PTV

- A geometrical concept
- Defined to select appropriate beam arrangement and size which ensures that the CTV will receive the prescribed dose, when all geometric variations are included



Volume definition: Planning Target Volume (PTV)

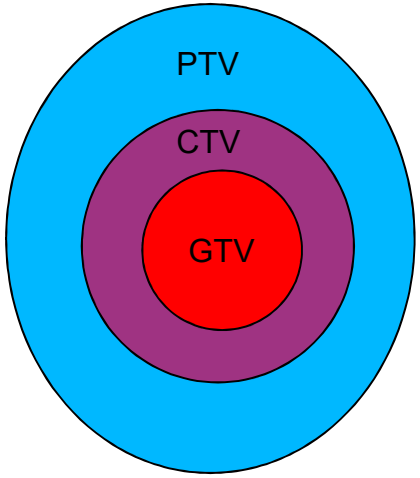
PTV

- A geometrical concept, margin added to take into account

Internal variation

Change in CTV

- Position
- Shape
- Size



External variation

- Patient positioning
- Beam variation

Volume definition: Planning Target Volume (PTV)

ICRU		Uncertainties
Report 29 (1978) – 2D RT	TV Target Volume	Biological + repositioning
Report 50 (1993) – early 3D RT	CTV Clinical Target Volume	Biological
	PTV Planning Target Volume	Repositioning
Report 62 (1999) – advanced 3D RT	CTV Clinical Target Volume	Biological Subclinical extension
	ITV Internal Target Volume	Organ motion Respiration – Bowel - Bladder
	PTV Planning Target Volume	Repositioning Set-up

PTV is a geometrical concept

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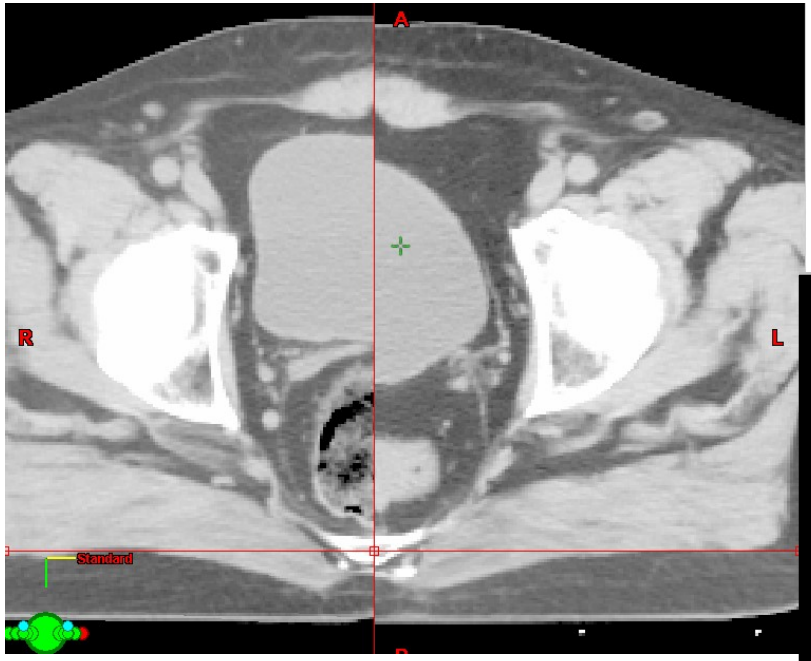
Volume definition: Planning Target Volume (PTV)

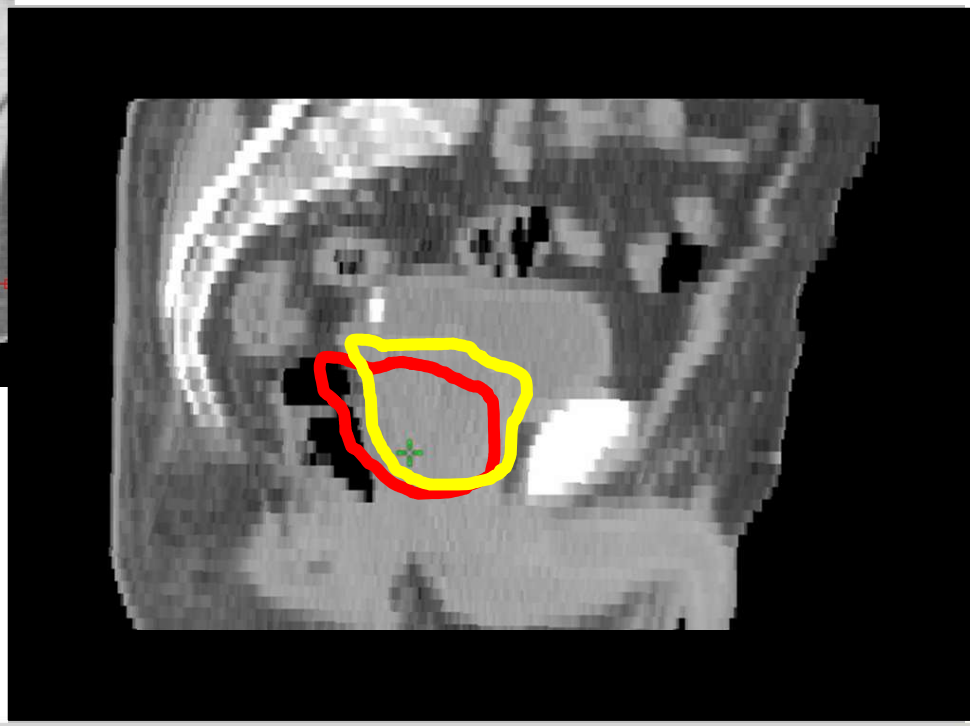
In ICRU 62, CTV to PTV margin split into

- **Internal Margin**
  takes into account inter- and intra-fraction organ motion

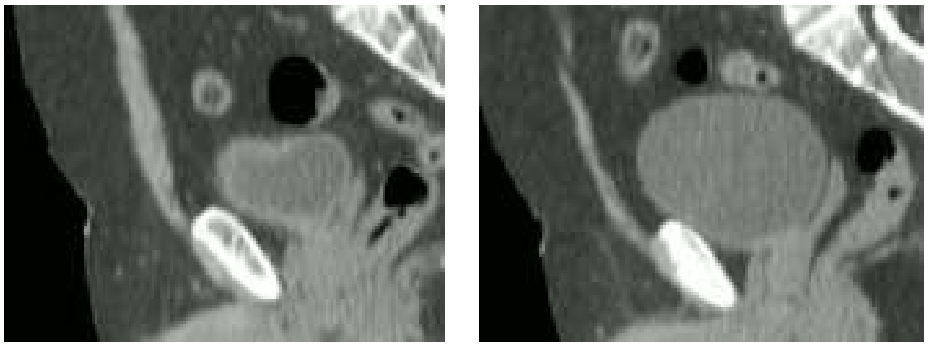
- **Set Up margin**
  takes into account machine tolerances, set-up error

Internal margin (IM)- The challenges

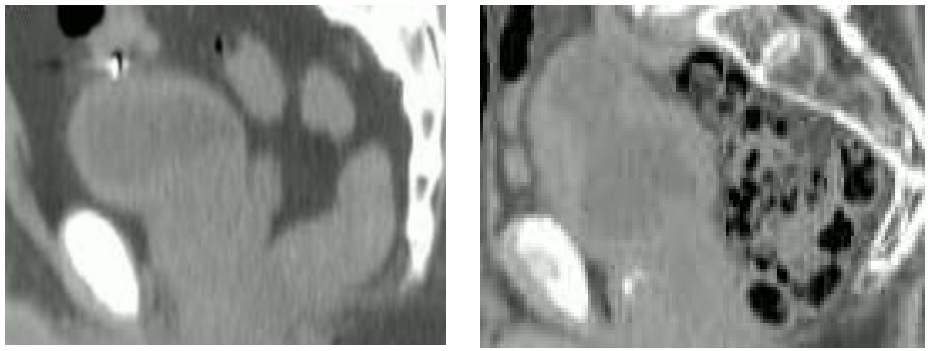




Internal margin (IM)-The challenges



Presumed empty bladder on two different occasions



Influence of rectal filling

Methods to reduce variations:

- Drinking protocol
- Rectal enemas
- Respiratory gating
- Breath hold technique

- Adaptive strategy: repeat the CT (or CBCT), repeat contouring, co-register

- Probabilistic strategy: measure, statistics

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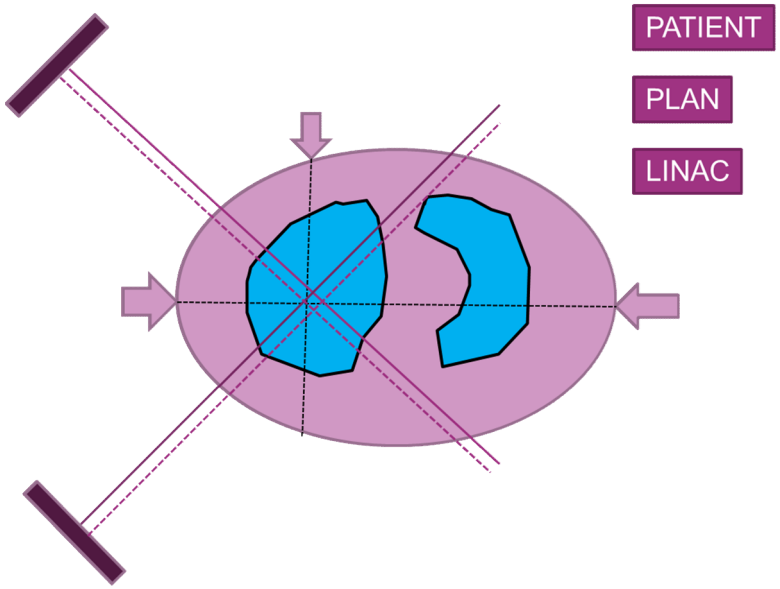
Set-up margin (SM)

Set Up Margin (SM)

Varies from centre to centre (and possibly from machine to machine)

Factors to reduce SM

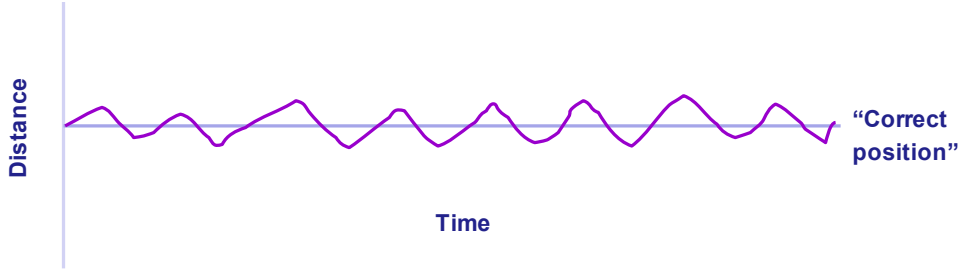
Immobilisation devices
Quality control programs
Online correction for set-up errors



Set-up margin (SM)- Quantifying uncertainties

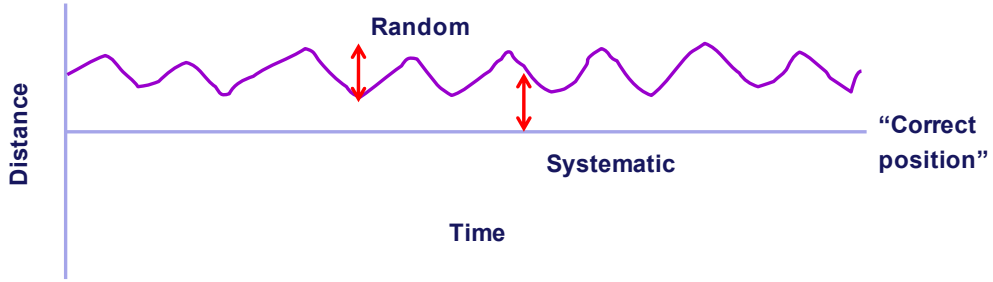
Random variations

- Statistical fluctuations around a point
- Difficult to correct for



Systematic variations

- Reproducible inaccuracy
- Usually due to a persistent problem
- Steps can be taken to reduce this further



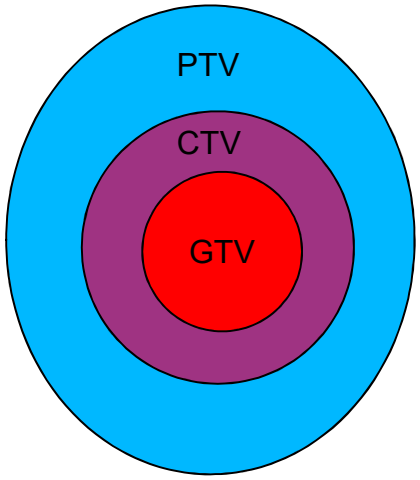
PTV margin recommendations

Author	Region	Recipe
Bel *et al.* (1996)	PTV	0.7σ
Antolak and Rosen (1999)	PTV	1.65σ
Stroom *et al.* (1999a)	PTV	$2\,\Sigma + 0.7\sigma$
van Herk *et al.* (2000)	PTV	$2.5\,\Sigma + 0.7\,\sigma$ (or more correctly): $2.5\Sigma + 1.64$ $(\sigma - \sigma_e)$
McKenzie (2000)	PTV	$2.5\,\Sigma + \beta + (\sigma - \sigma_e)$
Parker *et al.* (2002)	PTV	$\Sigma + \sqrt{(\sigma^2 + \Sigma^2)}$
van Herk *et al.* (2002)	PTV	$2.5 + \Sigma + 0.7\sigma + 3$ mm (or more correctly): $\sqrt{2.7^2\Sigma^2 + 1.6^2\sigma^2} - 2.8$ mm

Influence of margins on volume

- Third-power relationship between radius of a sphere and volume ($4/3\pi r$)
- Small reduction in margin (5mm) yields a 50% reduction in volume
- The volume of the outer layer equals the volume of the core of the orange

- GTV, 2 cm diameter, volume 4.2 cm^3
  - Add 1 cm to
- CTV, 4 cm diameter, volume 33.5 cm^3
  - Add 1 cm to
- PTV, 6 cm diameter, volume 113 cm^3



Verellen D, Ridder MD, Linthout N, Tournel K, Soete G, Storme G: Innovations in image-guided radiotherapy. Nat Rev Cancer 2007, 7(12):949-960.

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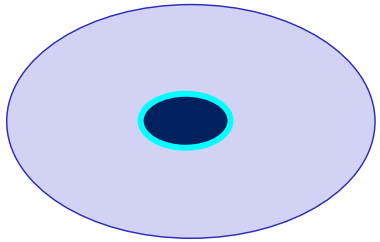
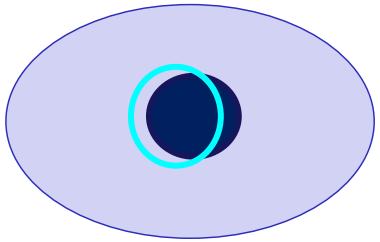
Volume definitions

Parameter	Definition
Treated Volume (TV)	Volume enclosed by a high isodose envelope (95% or 98%)

"Perfect" Treated Volume

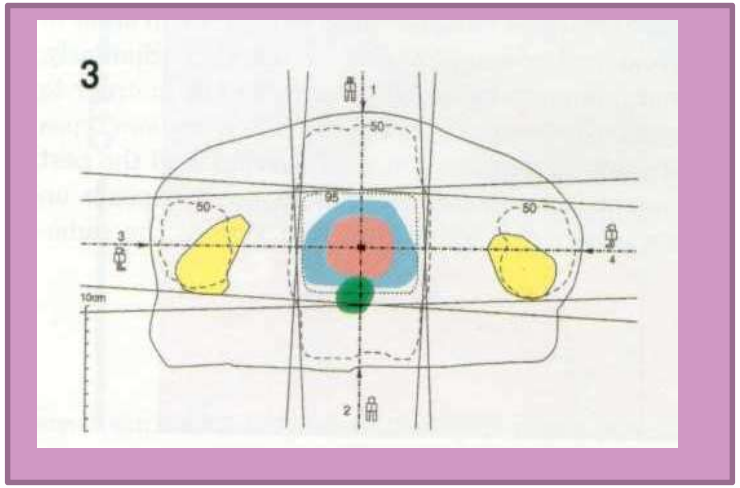


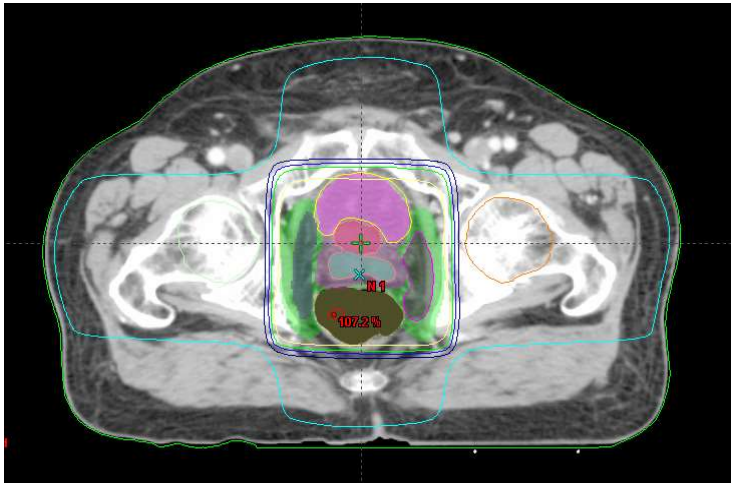
Inadequate Treated Volume



Treated volume & “in field” recurrence

- Reasons to identify the Treated Volume
  - Relation between TV and PTV is an important **optimisation parameter**
  - Recurrence in Treated Volume may be considered a true **“in field” recurrence** (inadequate dose), and not a **marginal recurrence** (inadequate volume)





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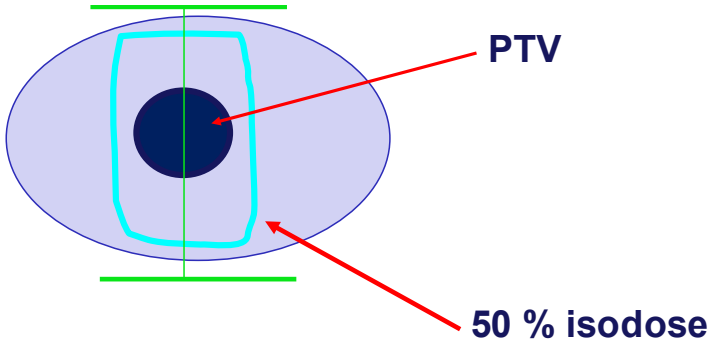
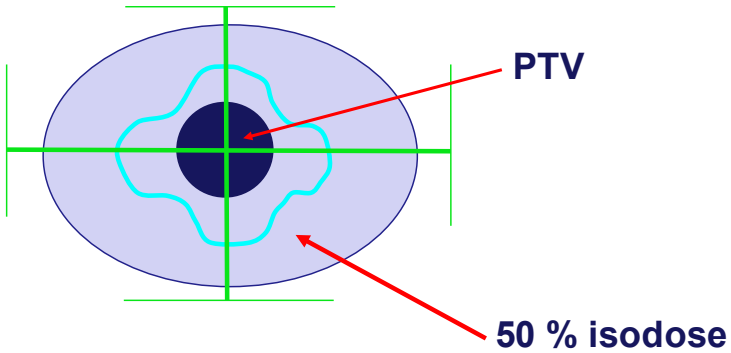
Volume definitions

Parameter	Definition
Irradiated volume (IV)	Volume enclosed by a significant isodose envelope (20% - 50%)

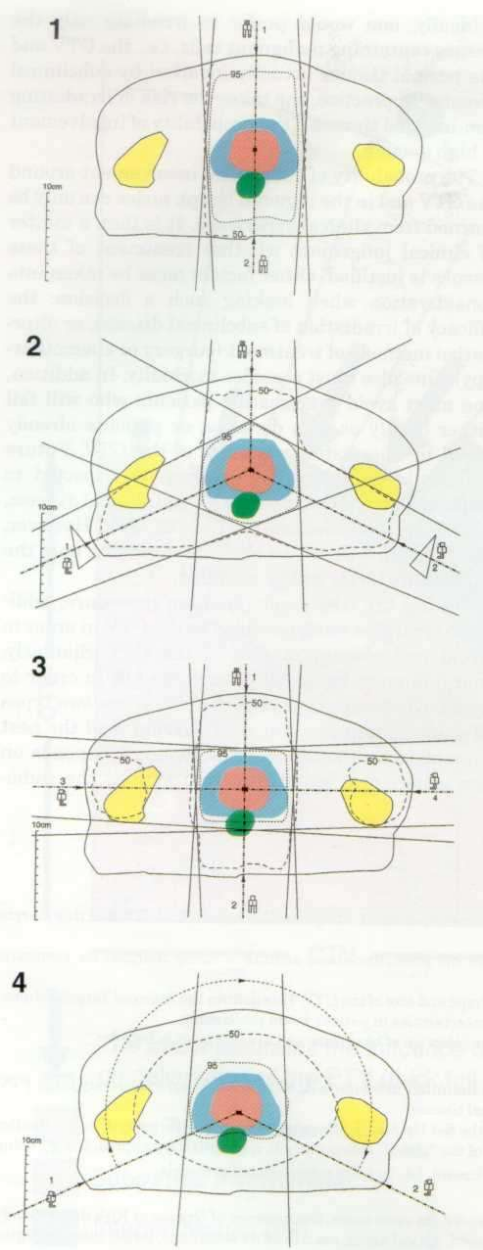
2D representation of irradiated volume for parallel opposed fields



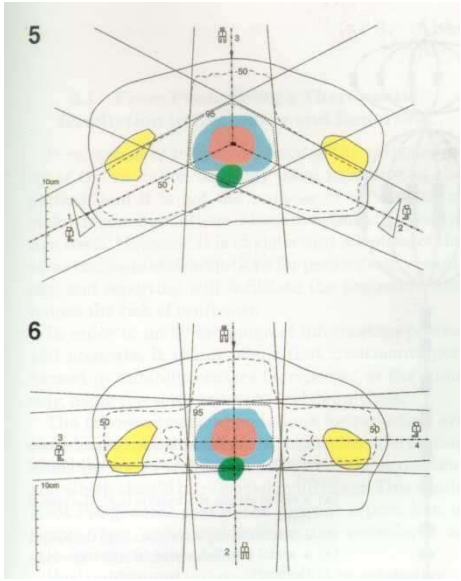
2D representation of irradiated volume for 4 field technique



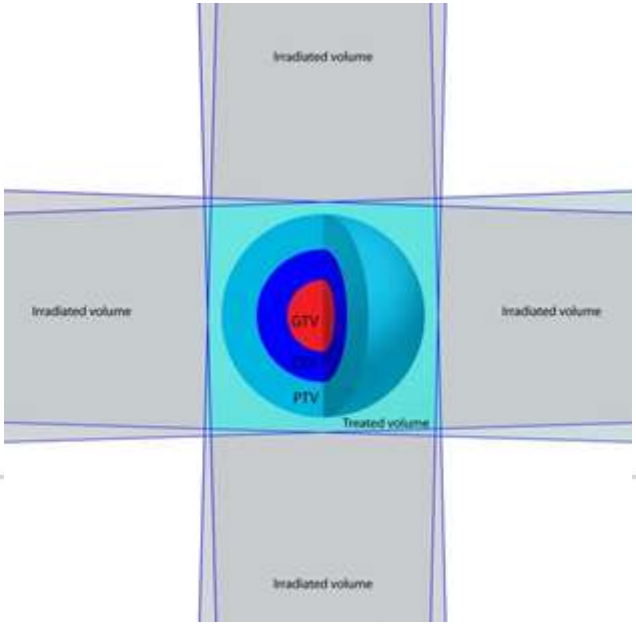
Optimization parameters



	TV/PTV	IV/PTV
1	4.35	8.56
2	2,61	11.9
3	2.61	9.58
4	2.18	9.14



	TV/PTV	IV/PTV
5	1.74	7.40
6	1.60	6.38



Volume definition: Organs at risk (OAR)

- **OAR**
  - Normal tissue whose radiation sensitivity may significantly influence treatment planning and/or prescribed dose

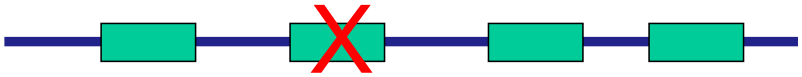
- **Organisation/Functional Subunit Concept**
  - Serial
  - Parallel
  - Serial-Parallel

Schultheiss TE et al., Models in radiotherapy: volume effects. Med Phys 1983, 10(4):410-415. Withers HR et al., Treatment volume and tissue tolerance. Int J Radiat Oncol Biol Phys 1988, 14(4):751-759.

Organs at risk (OAR)-serial organisation

- **Serial organisation-Functional Subunit Concept**

Serially organised organs tolerate a maximal dose.



Necessitates organ receiving high dose delineated consistently

D_{max} has often been reported, $D_{2\%}$ (whole organ delineation)

Example - Spinal Cord

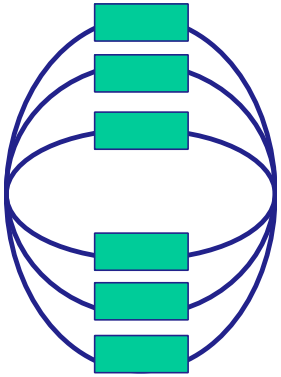
Organs at risk (OAR)-parallel organisation

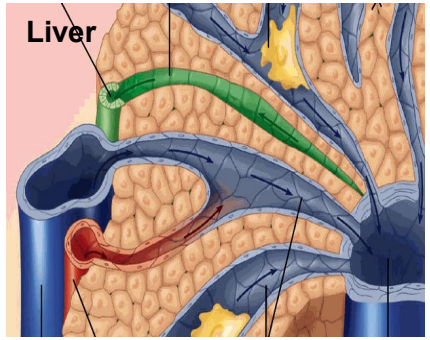
- **Parallel organisation-Functional Subunit Concept**

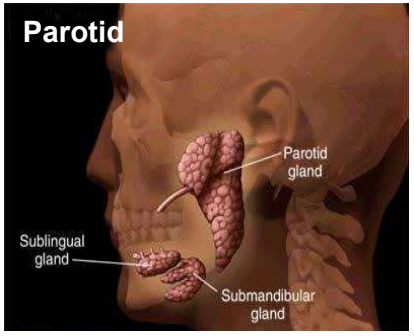
Concerned about organ proportion receiving dose (V_D)

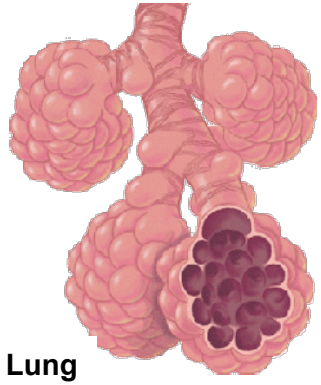
Necessitates whole organ delineation

Example-Lung volume receiving 20 Gy < 35% i.e. V_{20Gy} < 35%









Organs at risk (OAR)-serial-parallel organisation

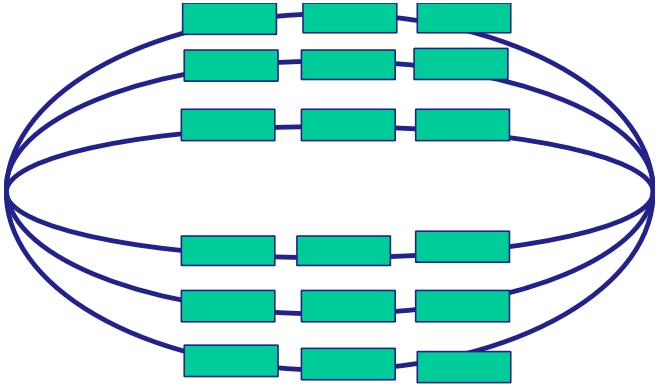
•Serial-parallel organisation-Functional Subunit Concept

Most organs are not clearly serial-like or parallel-like structure,

Examples- Heart (myocardium- parallel, coronary arteries –serial); Kidney (glomerulus- parallel, tubules-serial)

Report at least three dose – volume specifications

Include D_{mean}, $D_{2\ \%,}$ and, V_D (which if exceeded has high probability of serious complication)



For tubular types of organ (e.g., the rectum), delineation of the wall is preferred to whole-organ delineation.

Emami B et al.,Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991, 21(1):109-122. Bentzen SM, et al., Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys 2010, 76(3 Suppl):S3-9.

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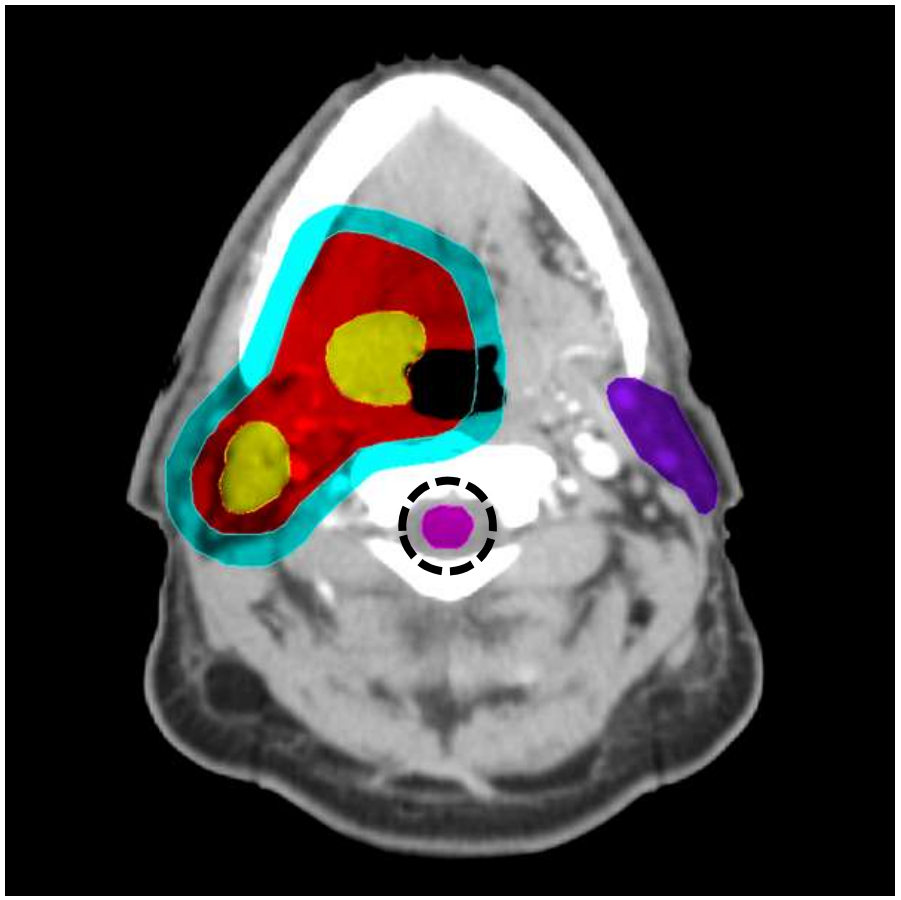
Planning Organ at Risk volume (PRV)

- PRV to OAR is analogous to the PTV
- Aim is account for movement of OAR due to change is size, shape, and setup
- For reporting, the PRV should be described including the size of the combined margins.
- PTV and PRV margins should be based on clinical measurements



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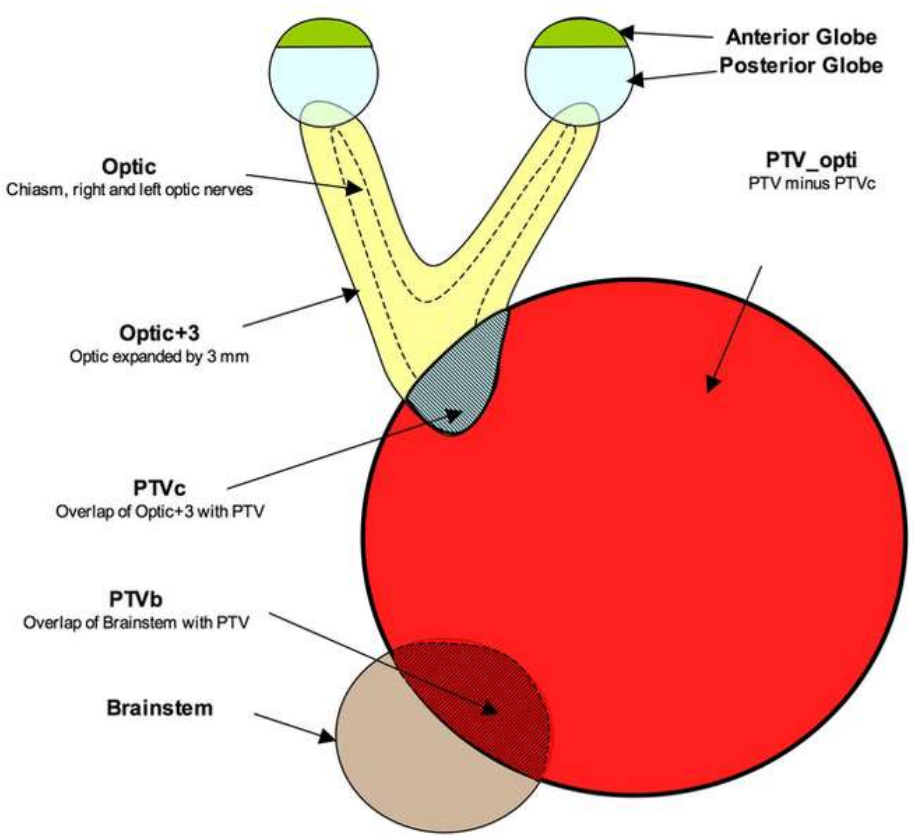
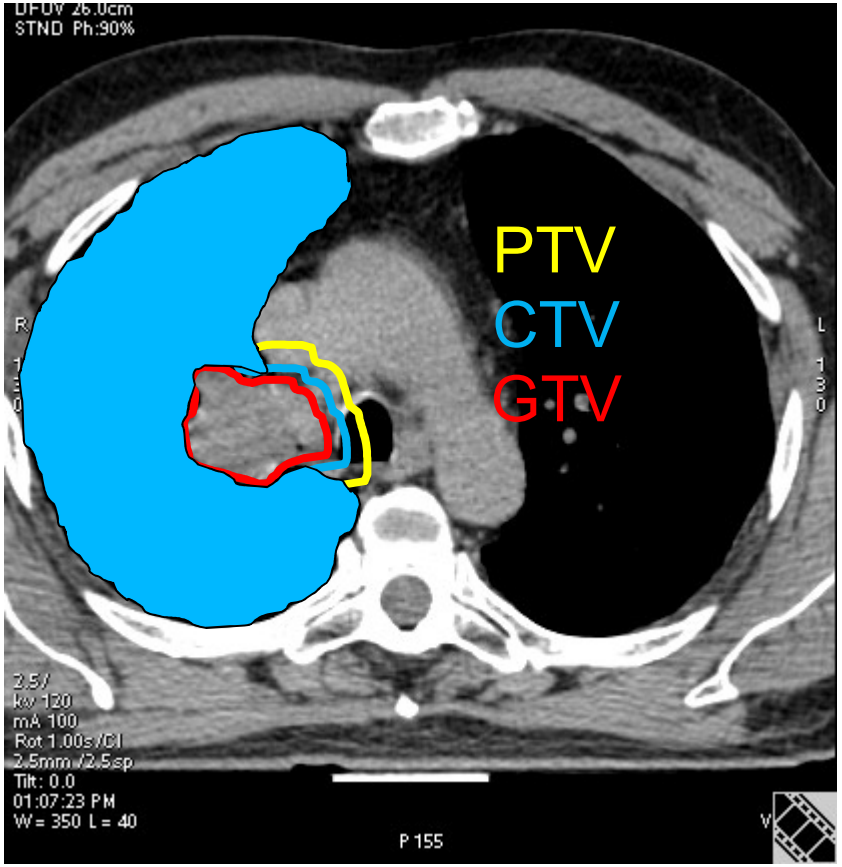
PRV-Overlapping volumes





http://www.jacmp.org/index.php/jacmp/article/view/3826/2563

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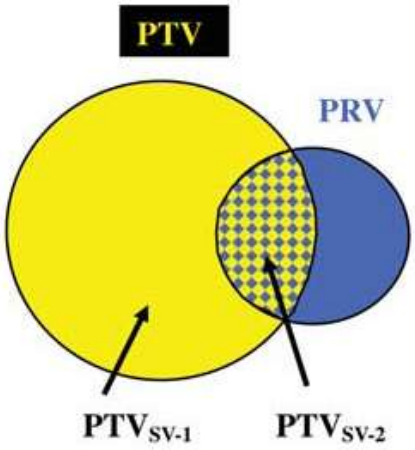
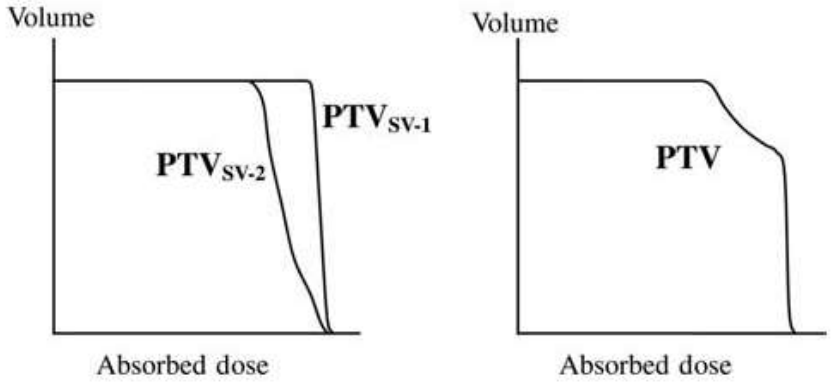
How to deal with overlapping volumes



$$PTV = PTV_{SV-1} + PTV_{SV-2}$$



ICRU 83 strongly recommends no compromise to margins when delineating the PTV or PRV

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Remaining volume at risk (RVR)

- All normal tissue that could potentially be irradiated
- Tissues not included in the CTV or not delineated as dose limiting OARs should still be specifically delineated and named the remaining volume at risk (RVR).
- Dose–volume constraints applied to the RVR avoid unsuspected regions of high dose.
- The absorbed dose to the RVR can be useful in estimating the risk of late effects, such as carcinogenesis.

RVR = Body – (CTV + OARs)

ICRU report, colour convention

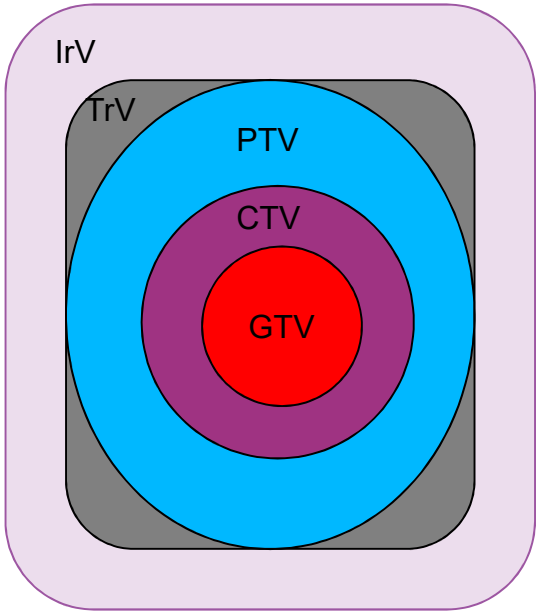
ICRU 62

GTV **CTV**

ITV **PTV**

OR **PRV**

Volume definition-summary



- GTV- demonstrable tumour
- CTV- GTV + subclinical tumour
- PTV- CTV + margin for uncertainties (internal margin & set-up margin)
- TrV- volume enclosed by specified isodose
- IrV- tissue volume receiving dose deemed significant in relation to normal tissue tolerance
- OAR- critical structure
- PRV- planning organ at risk volume

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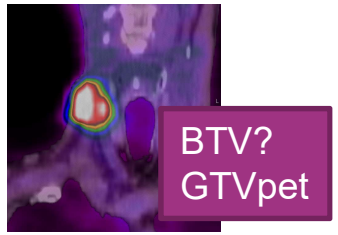
How to deal with counturing?

1. Elapsed time Prep/Tx as short as possible
2. Consult the radiologist / Nuclear medicine physician
3. Follow guidelines / protocols
4. Follow consensus (local - natl. – internatl.)
   - Use standardised terms (unambiguous – understandable)
5. Practicalities
   - Adequate clinical work-up (Complete staging)
     - Included physical exam
   - Supervise thoroughly image acquisition (position, scanning protocol, contrasts,…)
   - Before start contouring…
     - Room darkened
     - High-quality screen for side-by-side reviews of diagnostic images
     - Appropriate zooming
   - Get your contours reviewed by a senior

International Commission on Radiation Units and Measurements, Inc.



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Imaging for treatment preparation and planning

Esther Troost, MD PhD

Bucharest, June 2017

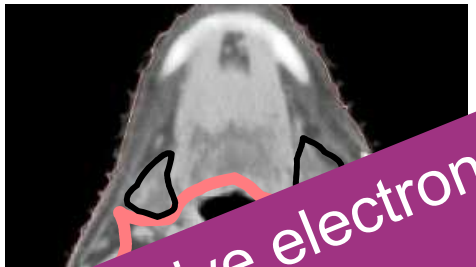
OncoRay Radiation Research in Oncology
HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF
NCT
ESTRO School

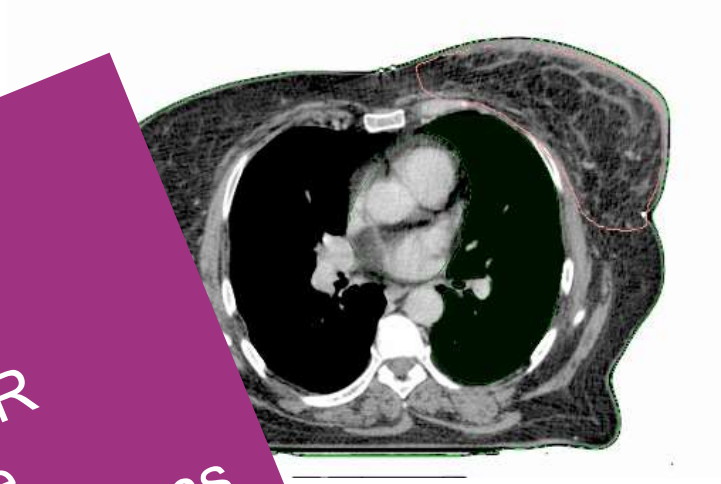
Index

Anatomical and functional imaging modalities

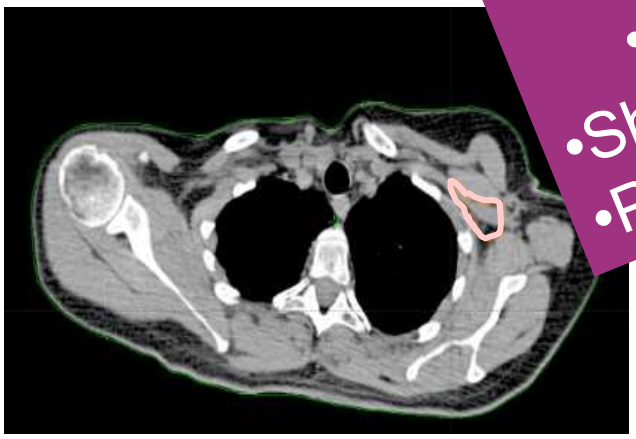
Image registration

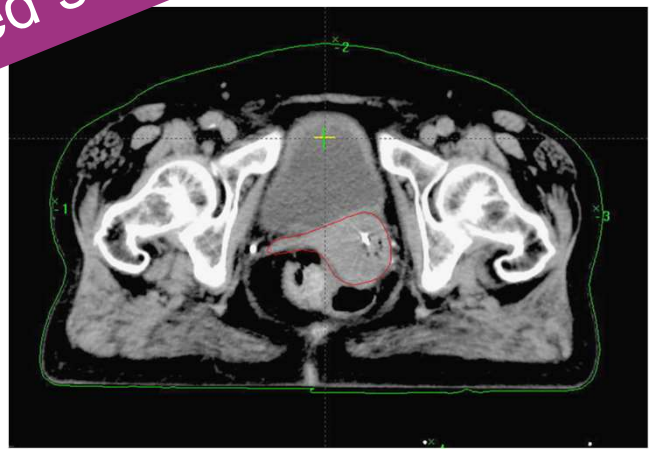
CT scan for contouring





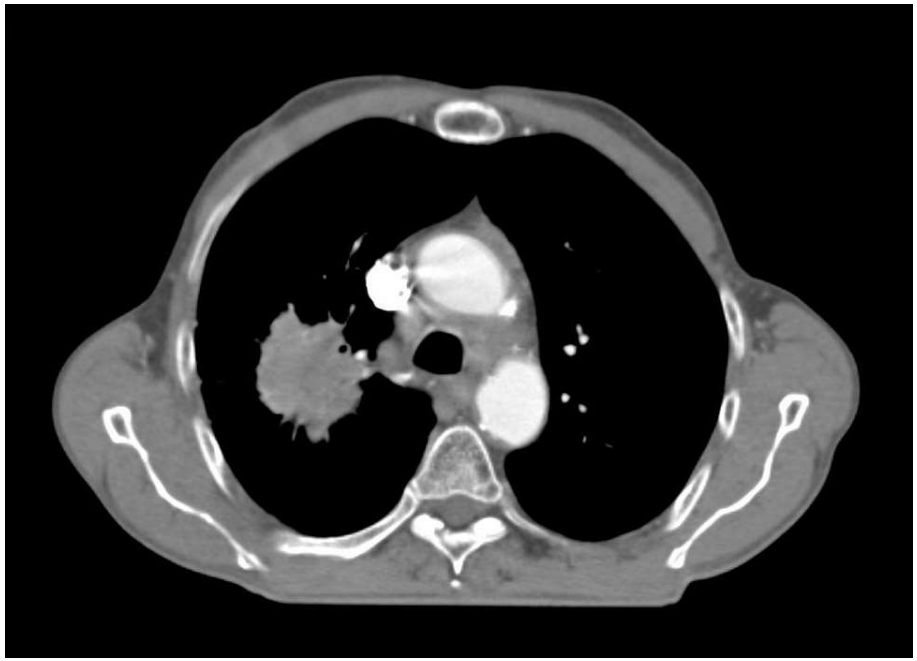
- Provide relative electron density
- Dose calculation
- Directly create DRR
- Short acquisition time
- Perform time resolved scans



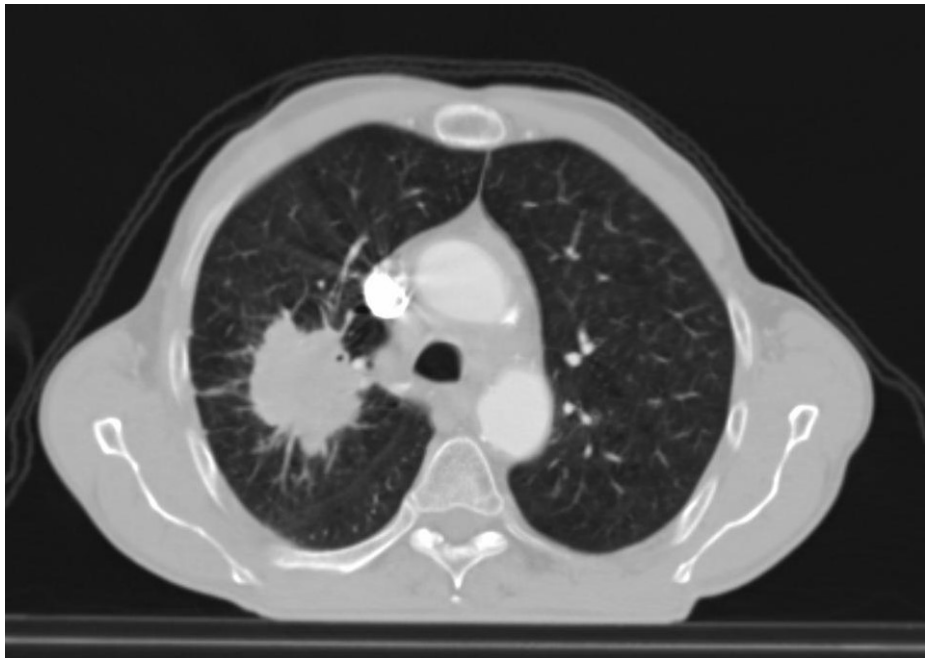


CT scan: window-level setting

- lung window for lung interfaces
- soft tissue window for mediastinal and hilar interfaces

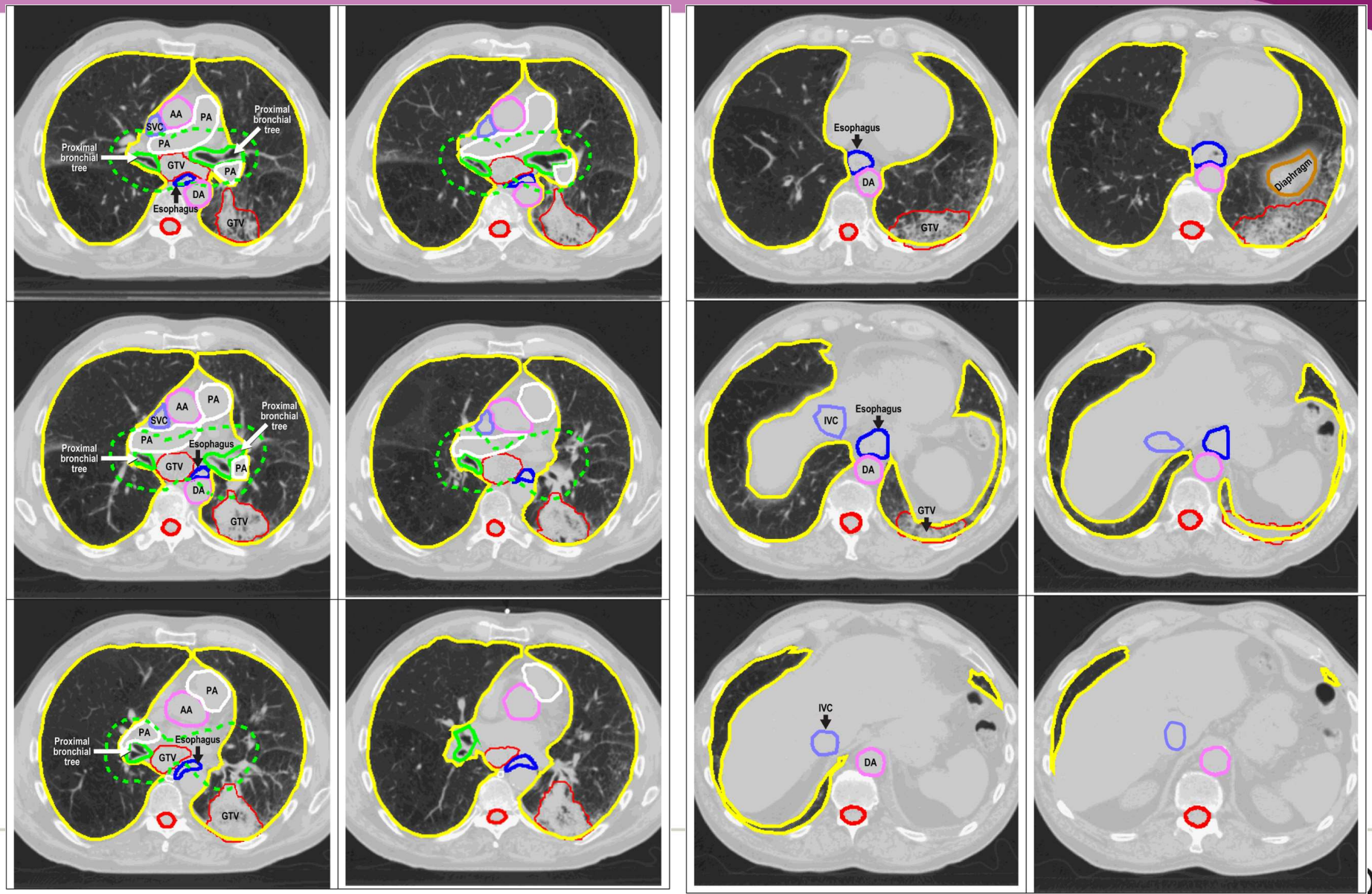


soft tissue window



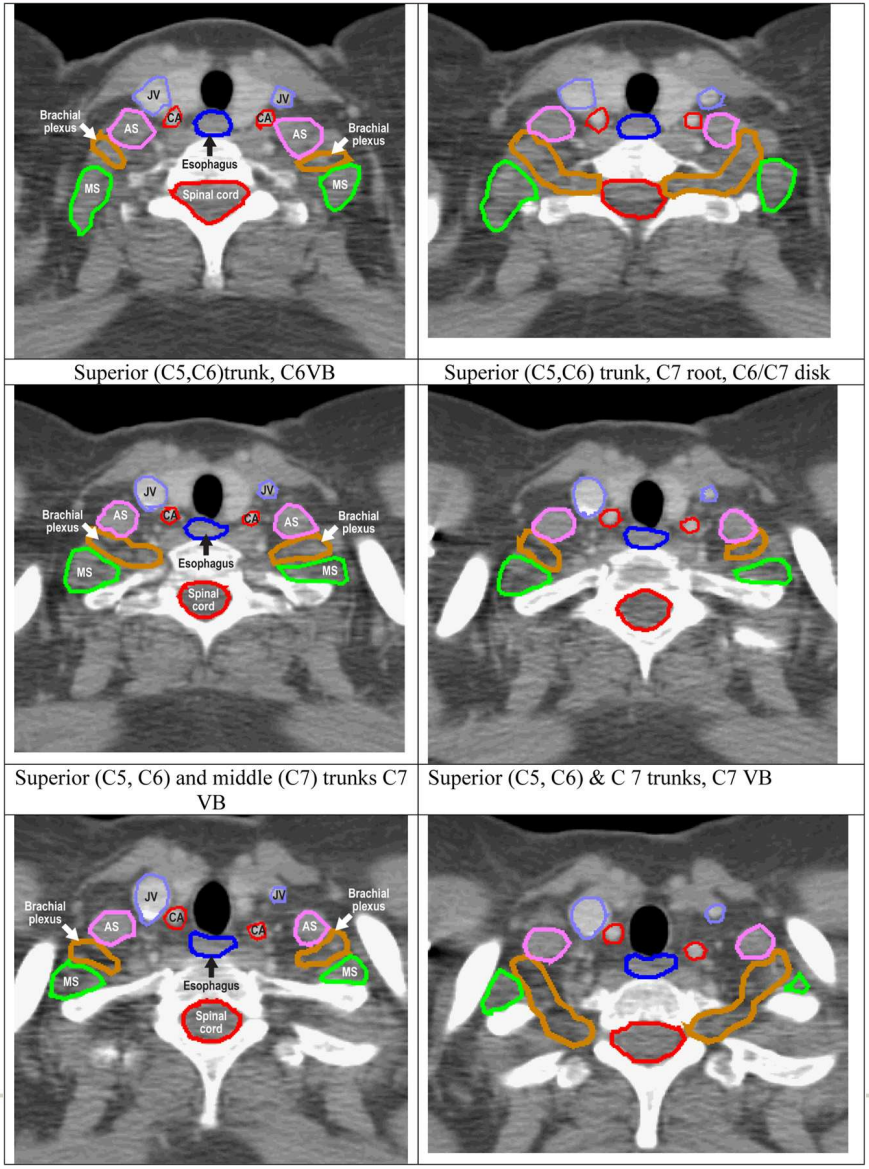
lung window

CT scan: delineation of OARs



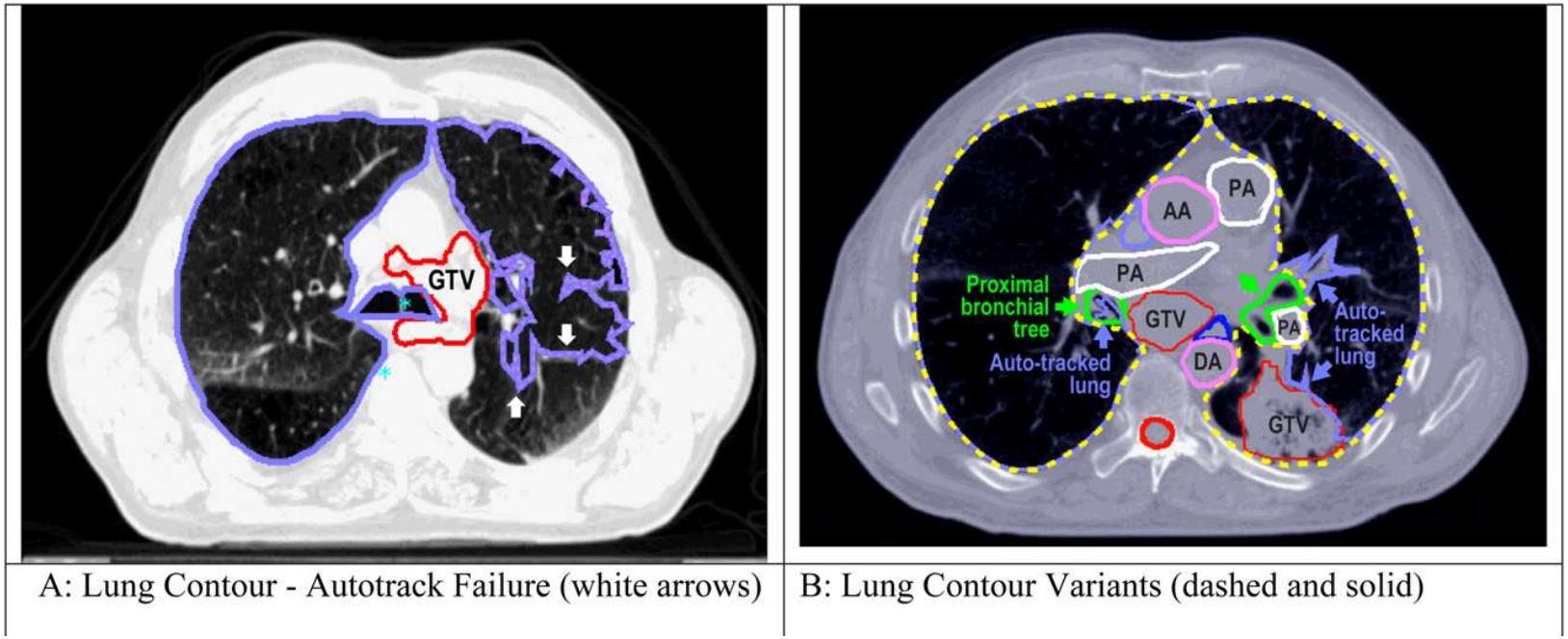
Kong *et al.*, Int J Radiat Oncol Biol Phys 2011

CT scan: delineation of brachial plexus



Kong *et al.*, Int J Radiat Oncol Biol Phys 2011

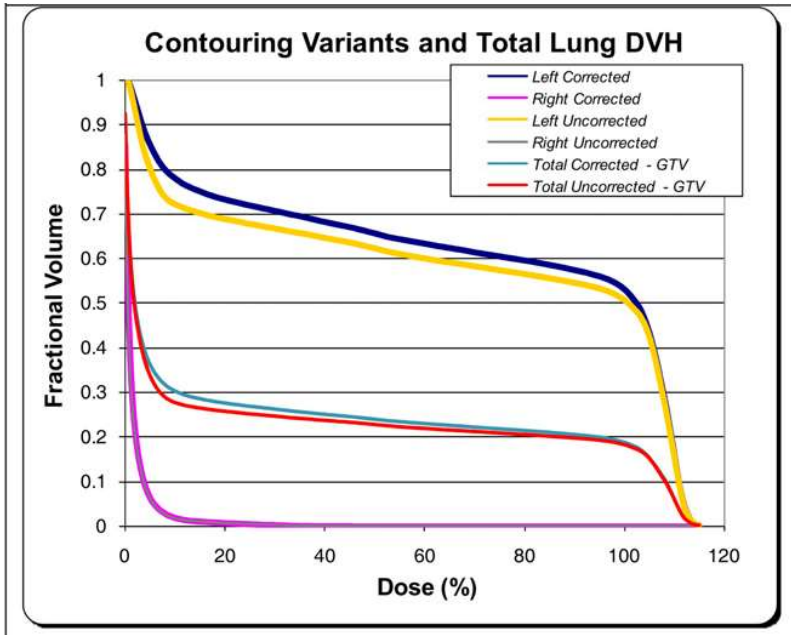
CT scan: accurate delineation!



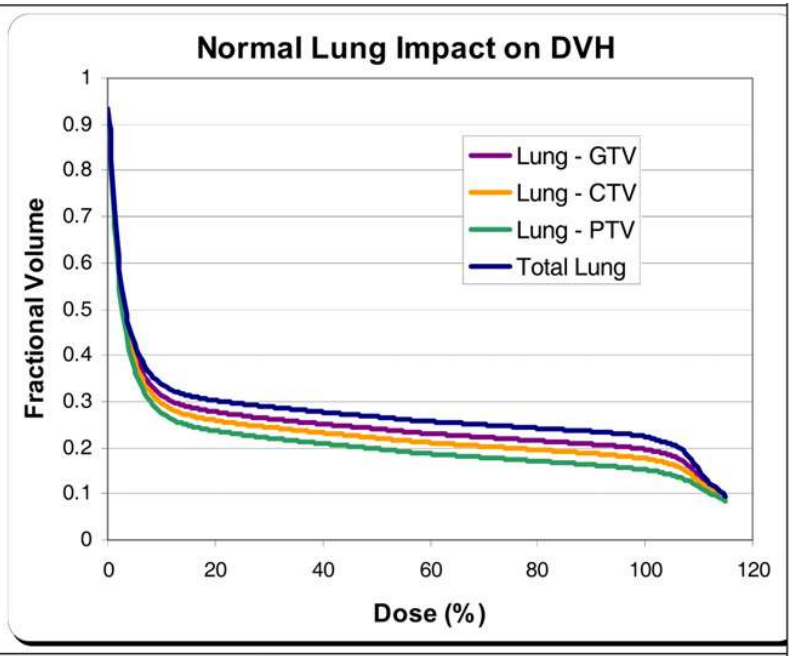
A: Lung Contour - Autotrack Failure (white arrows) | B: Lung Contour Variants (dashed and solid)

Kong *et al.*, Int J Radiat Oncol Biol Phys 2011

CT scan: accurate delineation



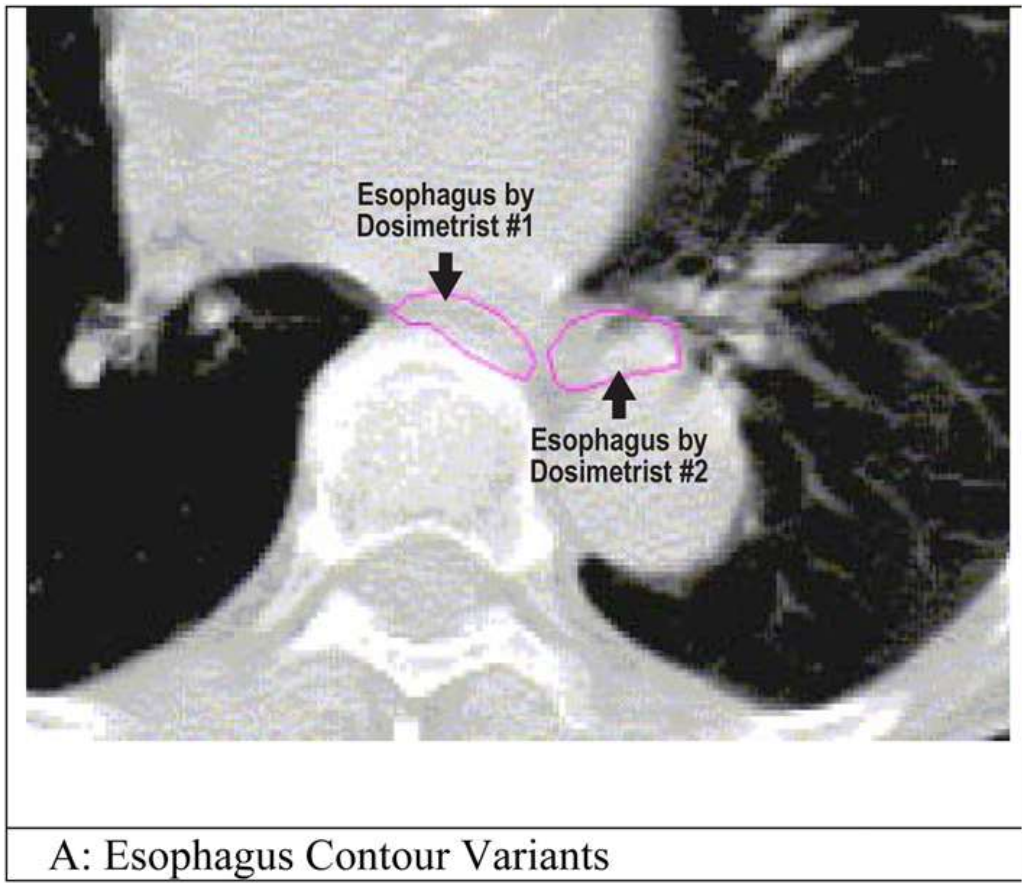
C: Lung DVH differences of contouring variants



D: Lung DVH differences on target consideration

Kong *et al.*, Int J Radiat Oncol Biol Phys 2011

CT scan: variations and motion of OARs

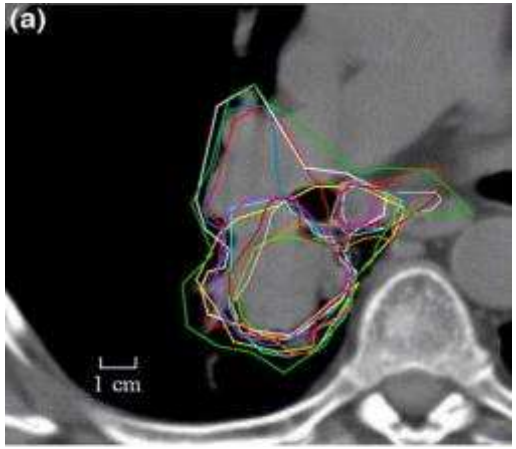


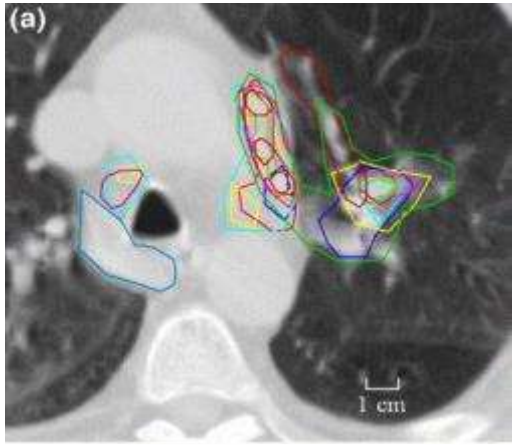
A: Esophagus Contour Variants

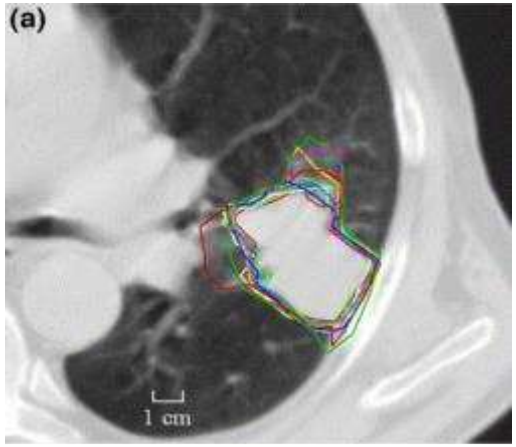
Kong *et al.*, Int J Radiat Oncol Biol Phys 2011

^{18}FDG-PET in NSCLC: target volume delineation

SD 10.2 mm



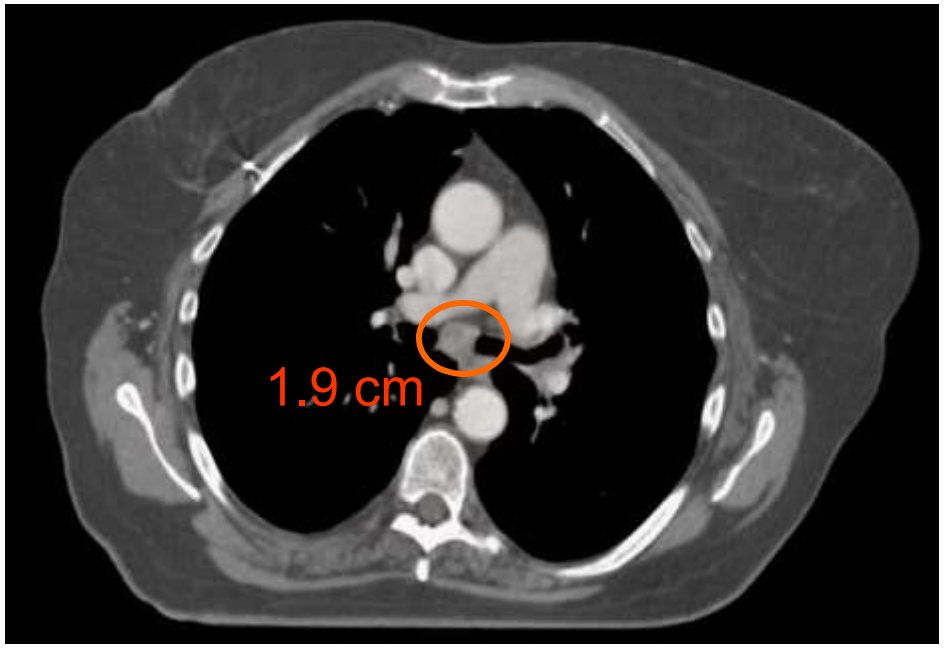


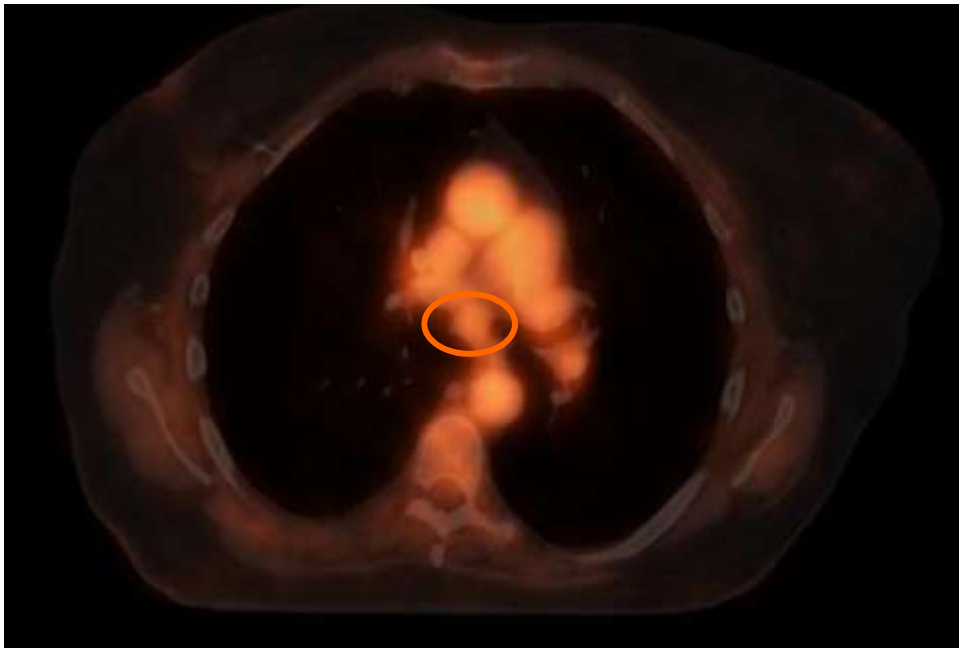


PET: reduced interobserver variability

[Steenbakkers *et al.*, 2006]

^{18}FDG-PET in NSCLC: lymph node contouring

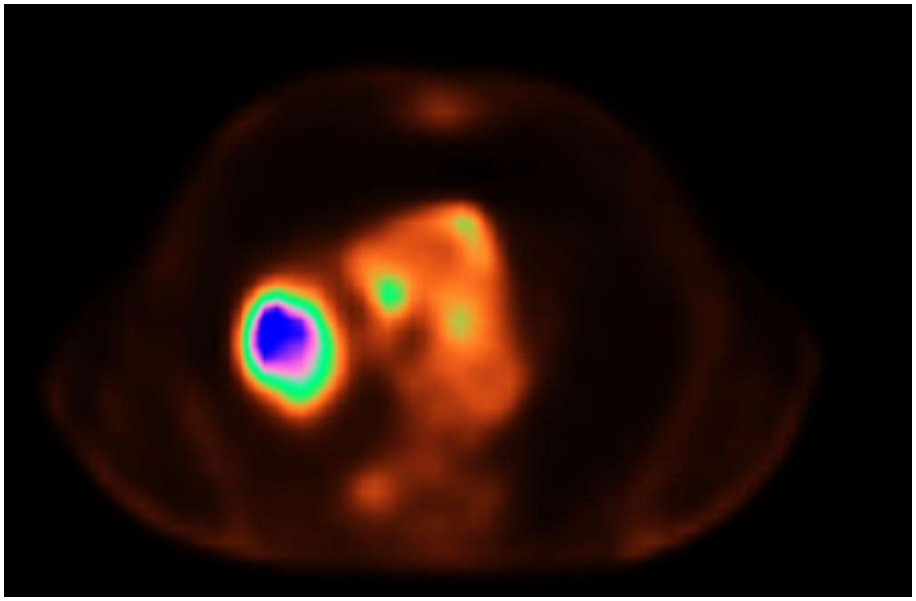


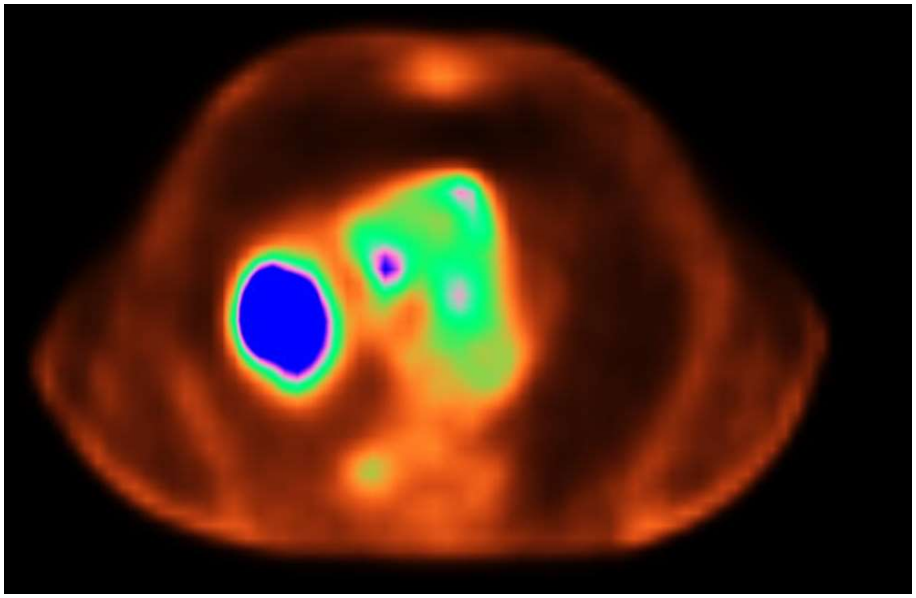


Isolated nodal recurrences following 3D-CRT and IMRT: 2.2 – 2.3%!

[De Ruysscher *et al.* 2005, Belderbos *et al*. 2006, Martinussen *et al.* submitted]

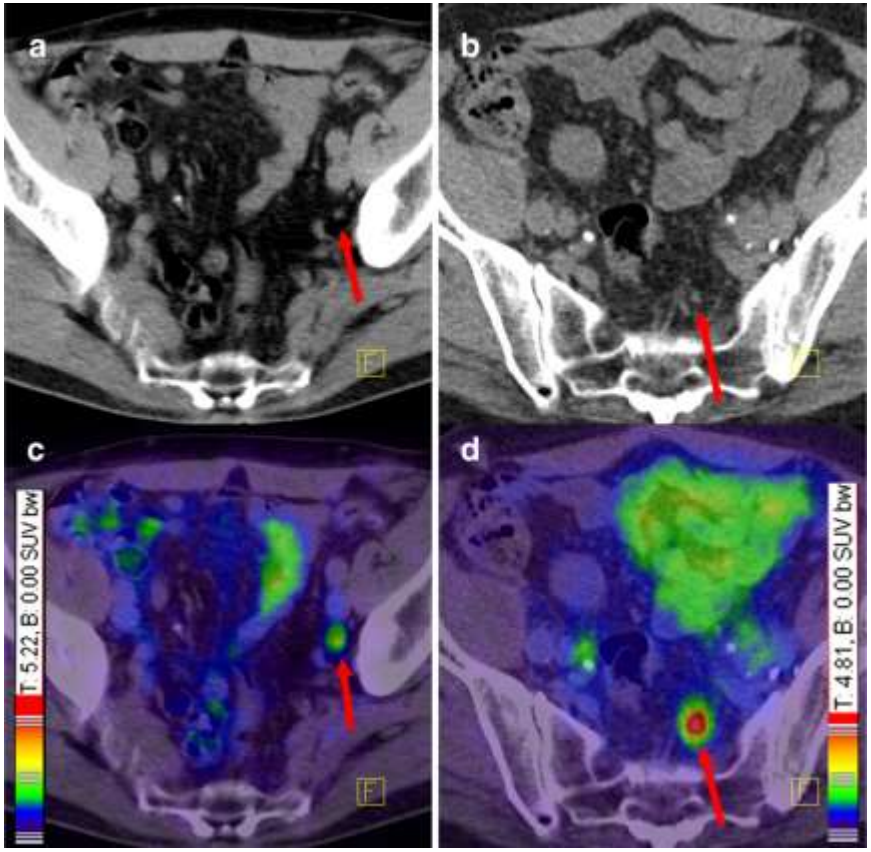
PET: window-level setting

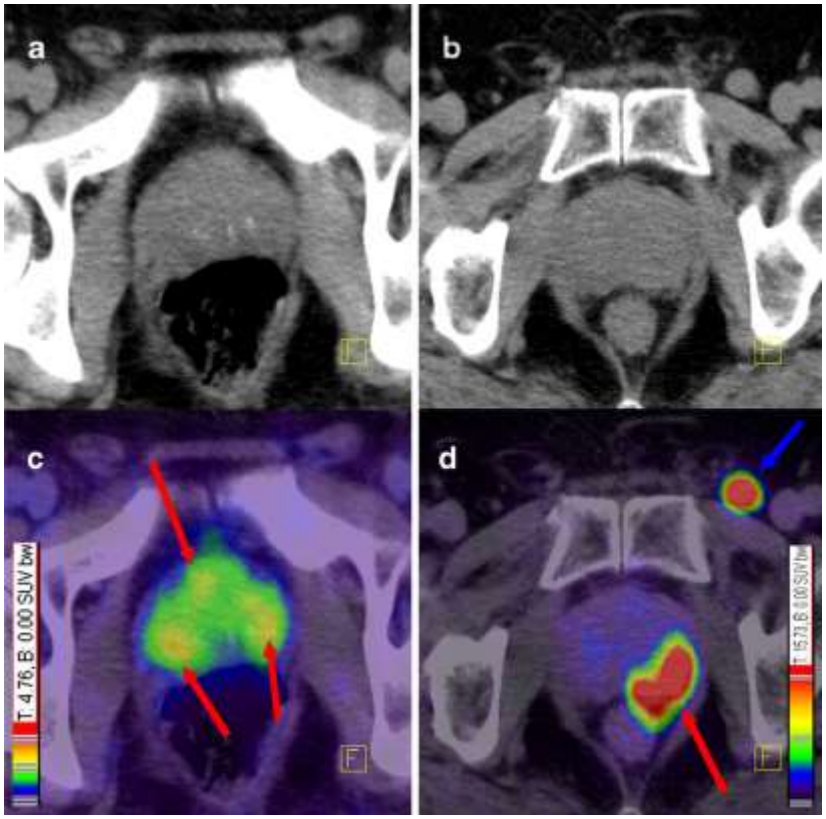




Same tumor, different settings

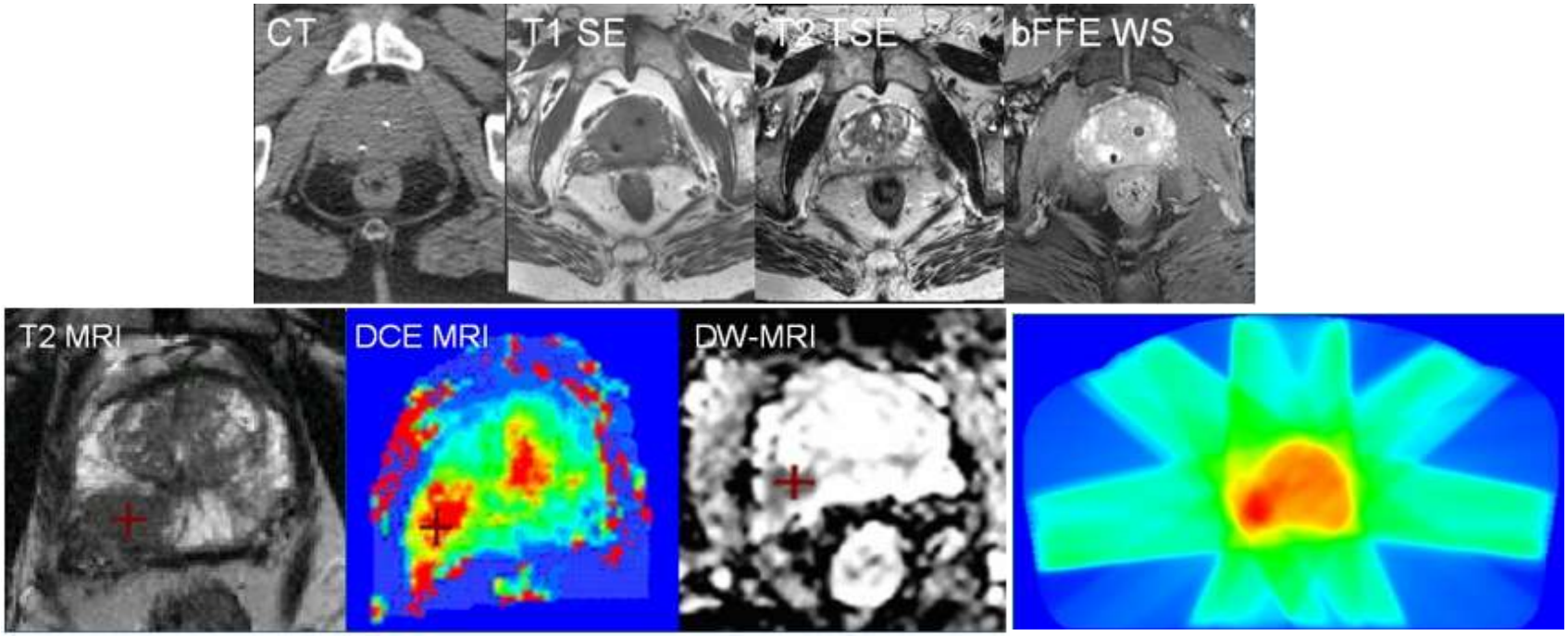
^{68}Ga-PSMA-PET: detection of recurrence





[Afshar-Oromieh *et al*., 2015]

MRI for prostate cancer



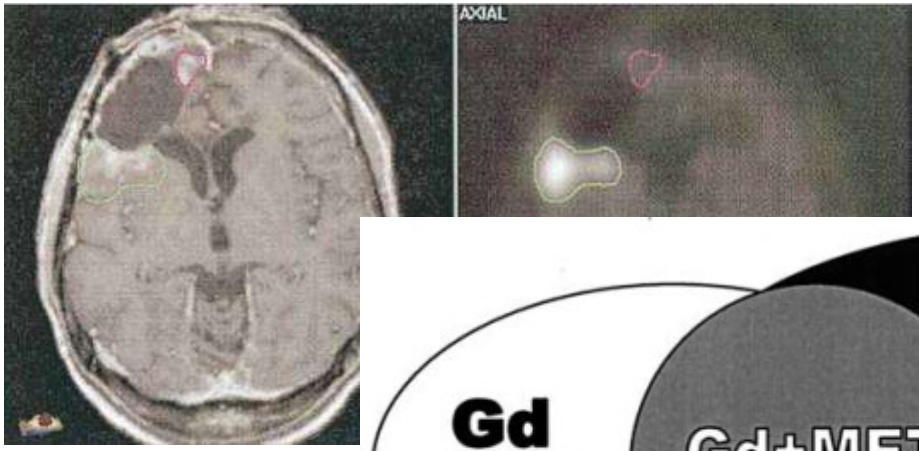
FLAME

N=566 patients

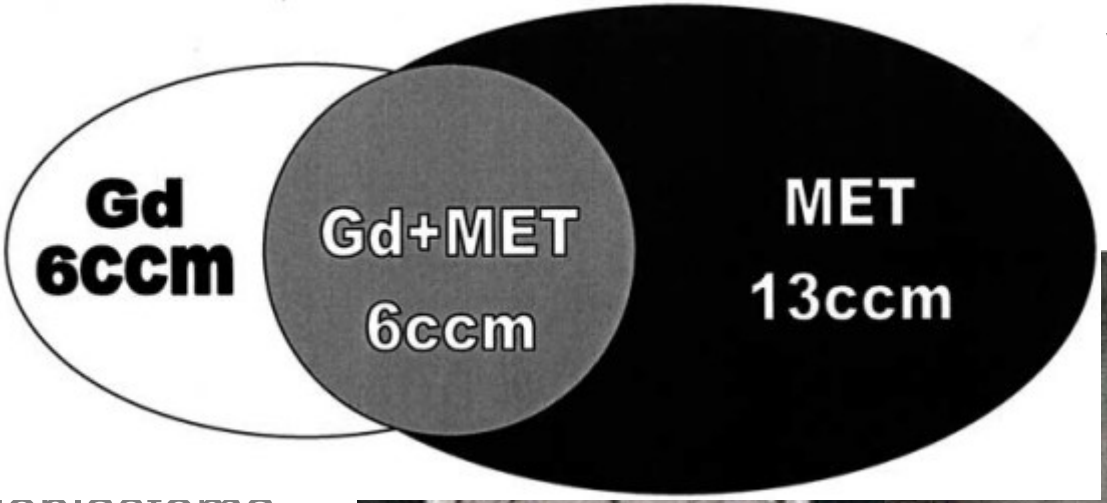
Arm A: 77 Gy / 35 fractions
Arm B: 77 Gy + boost up to 95 Gy in 35 fractions

[UMC Utrecht]

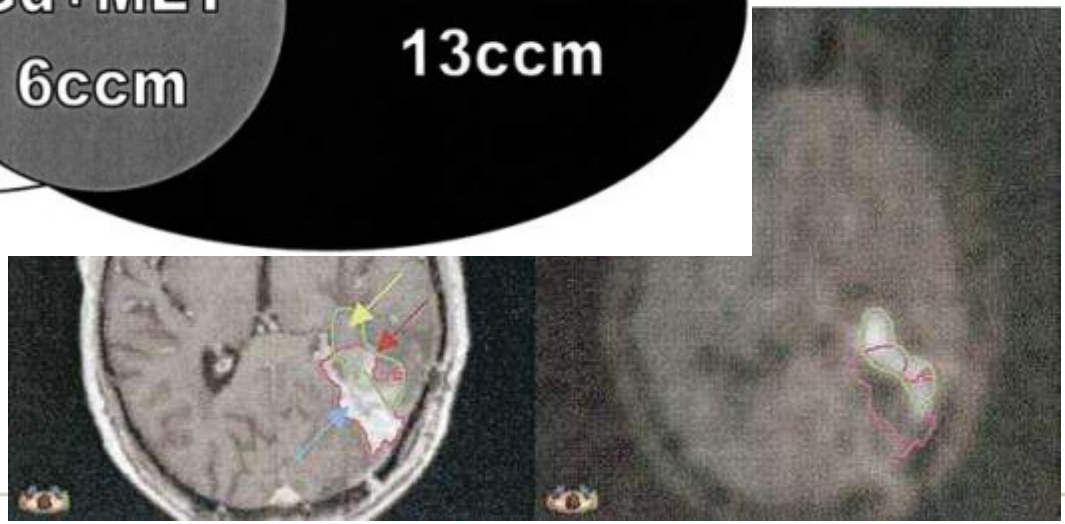
^{11}C-Methionine-PET



Grade III astrocytoma
T1-MRI with Gd
Imaging 2 weeks
y

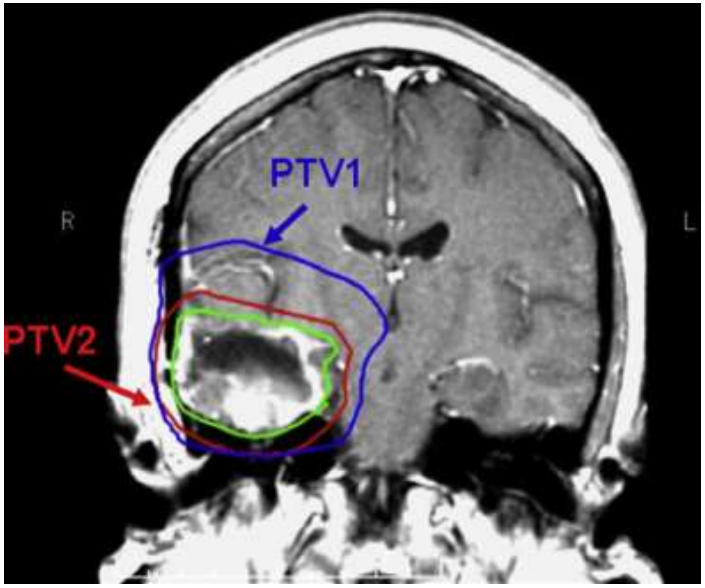


Grade IV glioblastoma
T1-MRI with Gd
Imaging 4 weeks
postoperatively



[Grosu *et al*. 2005]

^{11}C-Methionine-PET



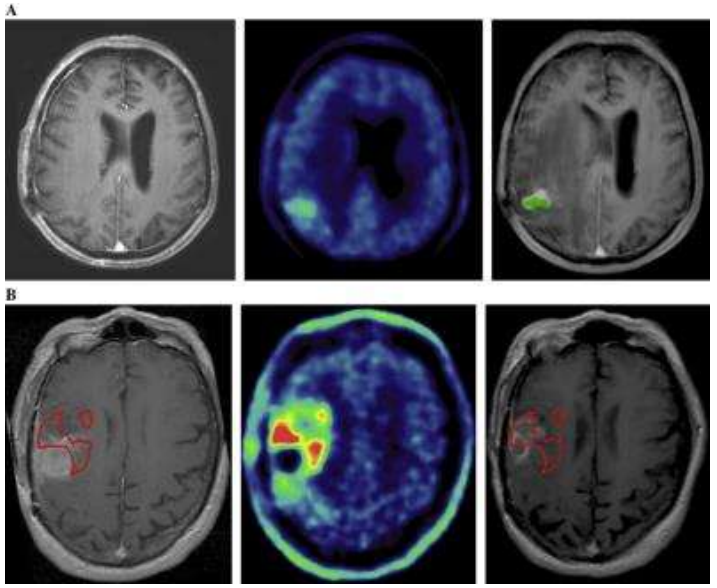


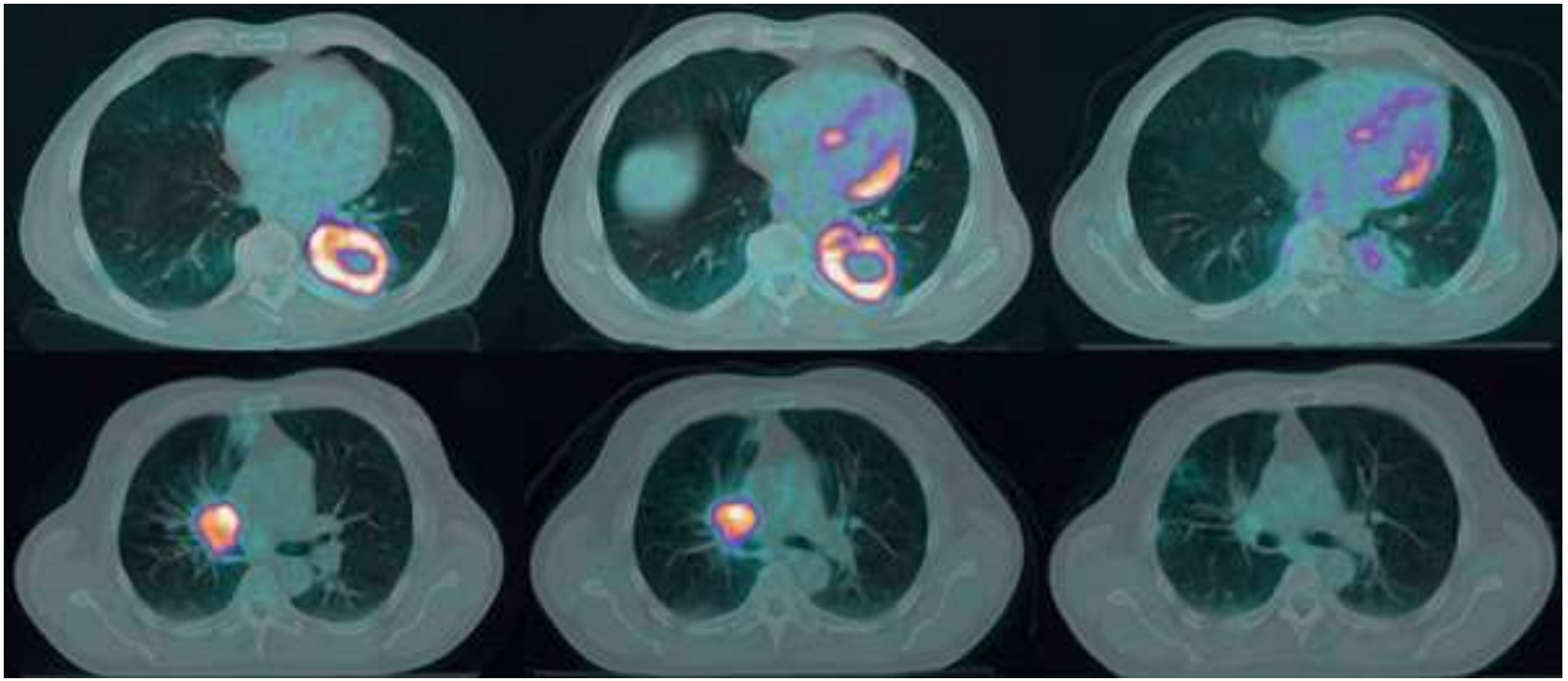
Table 2. Patterns of Failure and PET-GTV Coverage

	Central	In-field	Marginal
> 95% PET-GTV within 95% IDS	9	1	1
< 95% PET-GTV within 95% IDS	0	2	3

$P = 0.004$ (Fisher exact test)

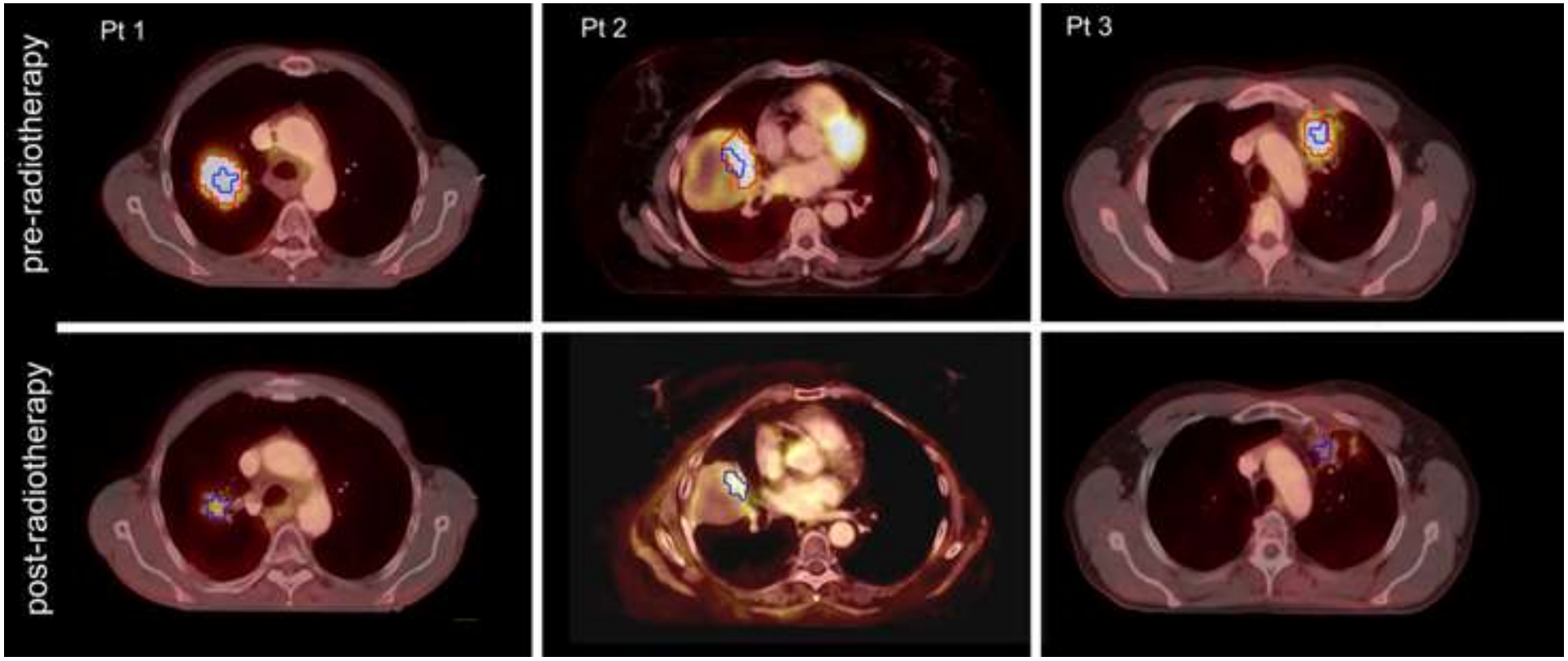
[Lee *et al*. 2009]

^{18}FDG-PET in NSCLC: response assessment



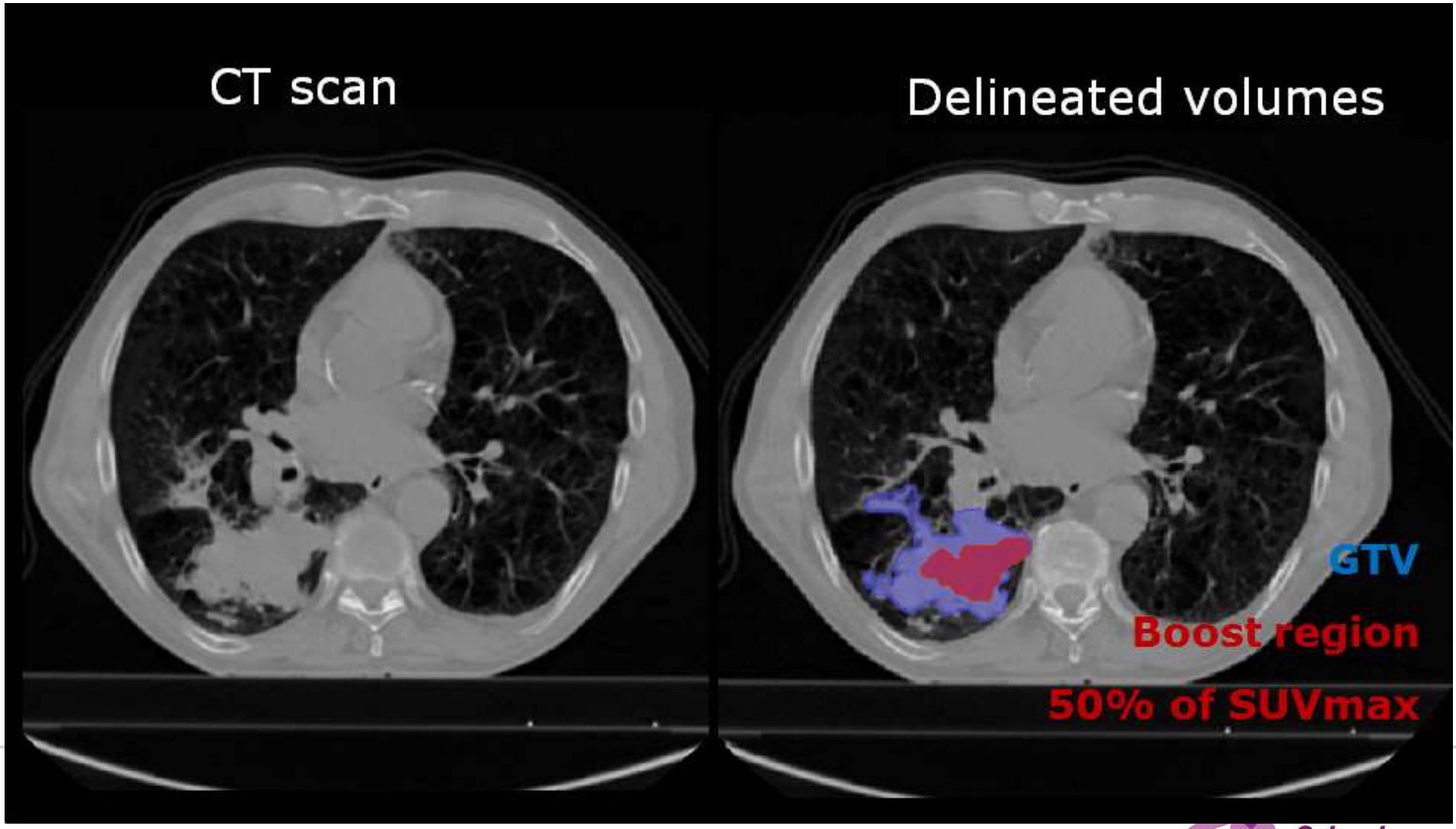
[Grootjans *et al.* 2015]

Correlation residual FDG-uptake and recurrence



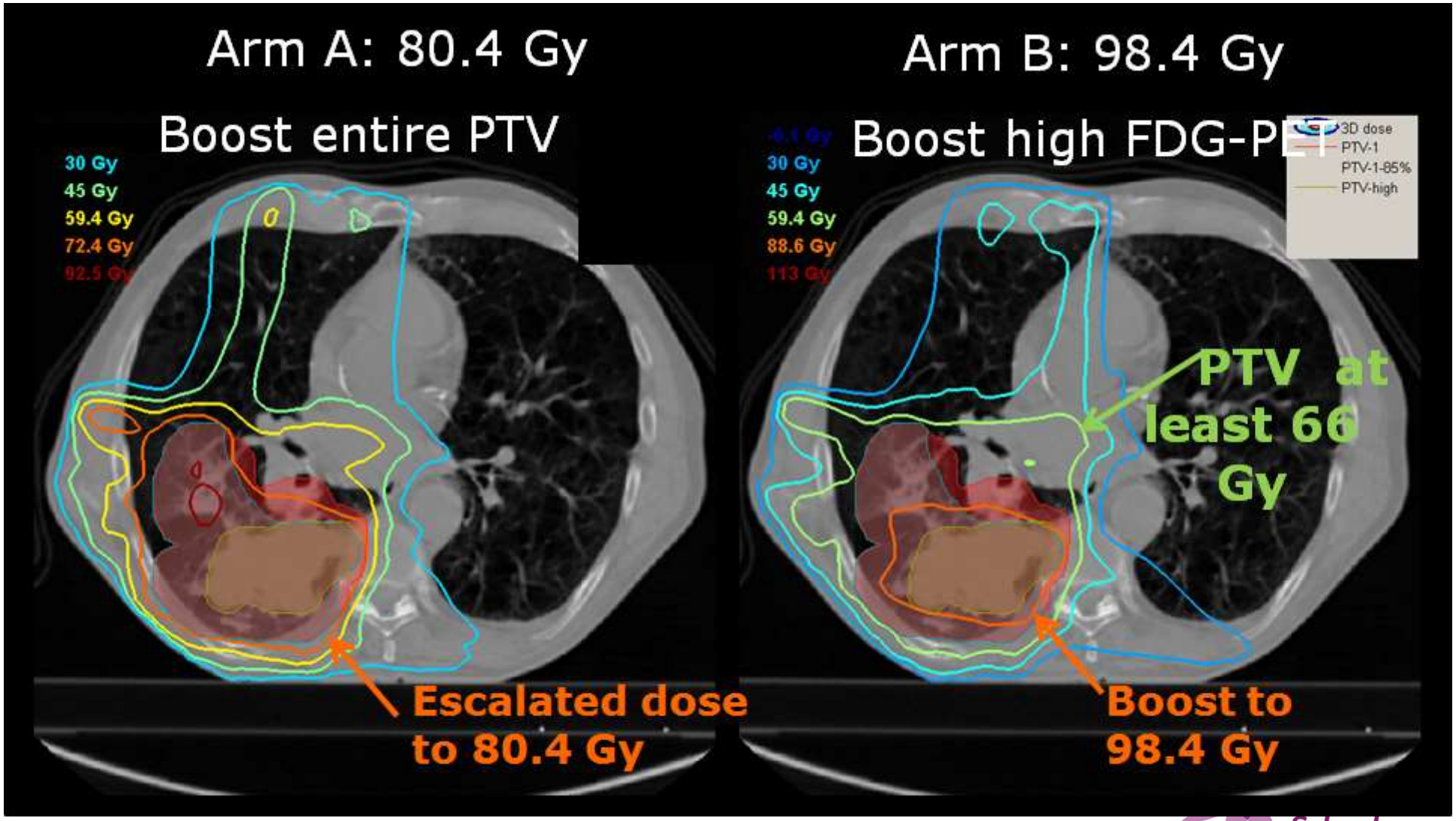
Aerts *et al*., *Radiother Oncol* 91: 386-392, 2009

PET-Boost study



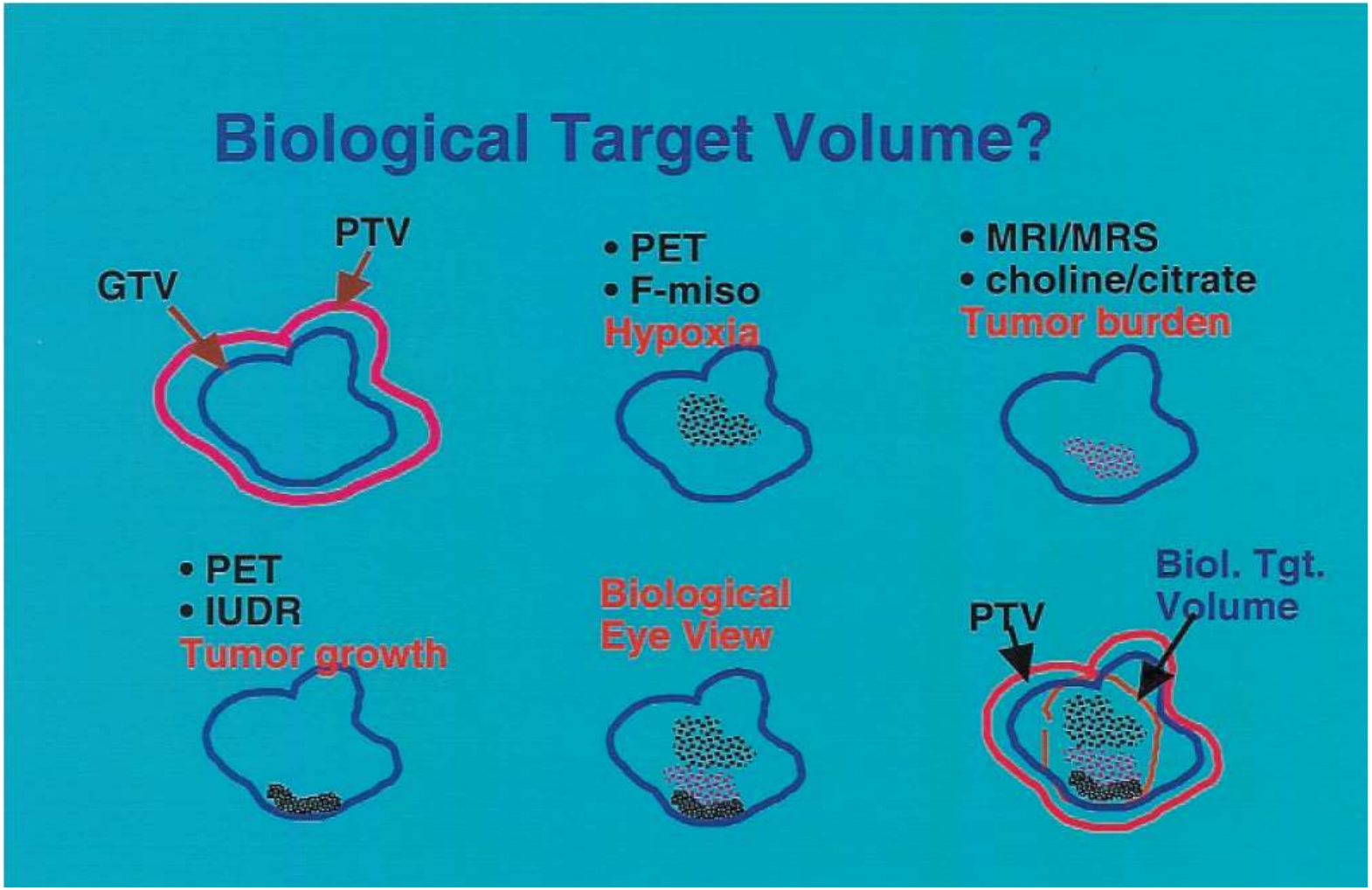
Van Elmpt, *et al.* Radiother Oncol 2012;104(1):67-71

PET-Boost study



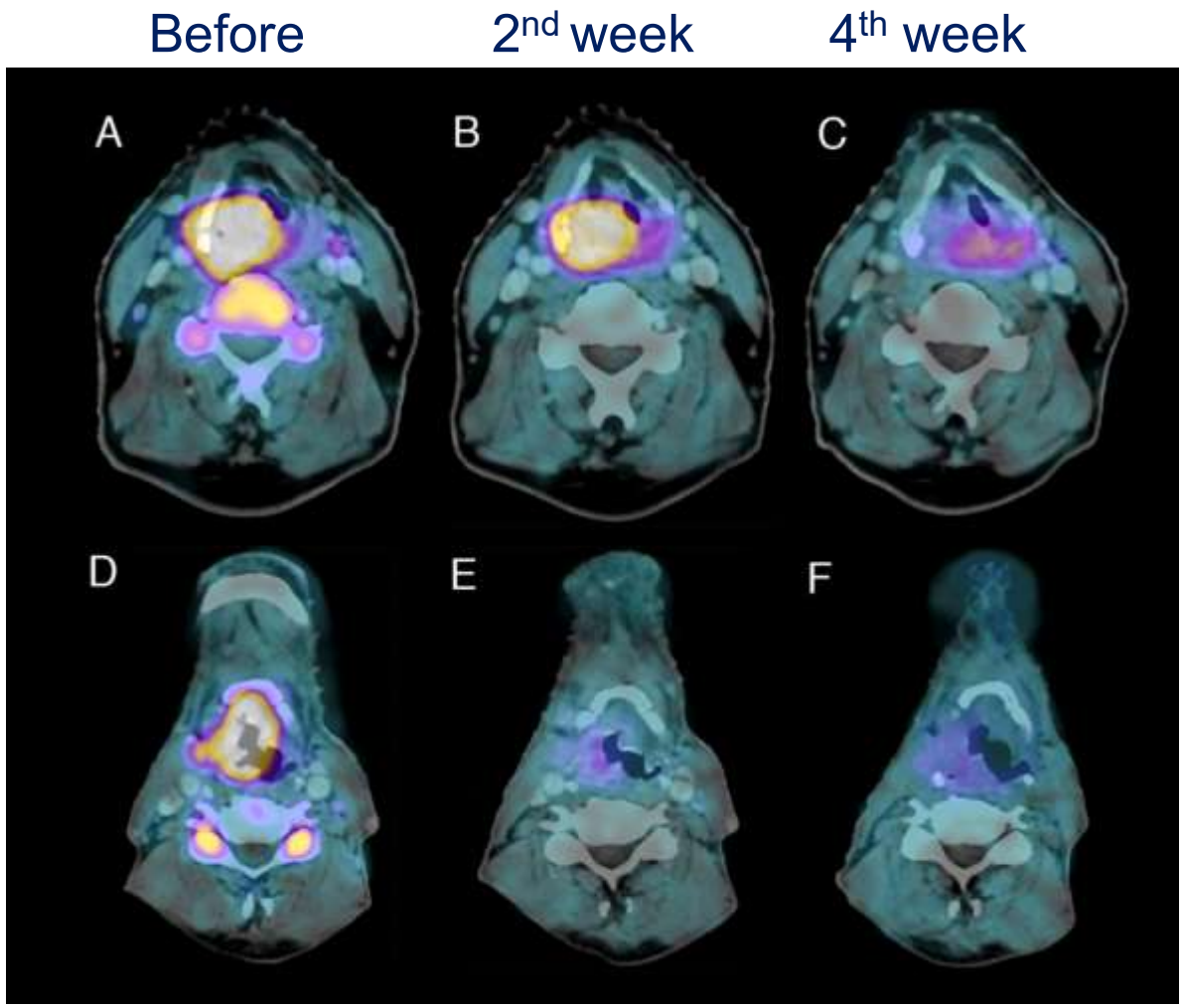
Van Elmpt, *et al*. Radiother Oncol 2012;104(1):67-71

Functional imaging for biology-adapted RT



[Ling C. 2000]

Tumor cell proliferation – ^{18}FLT-PET

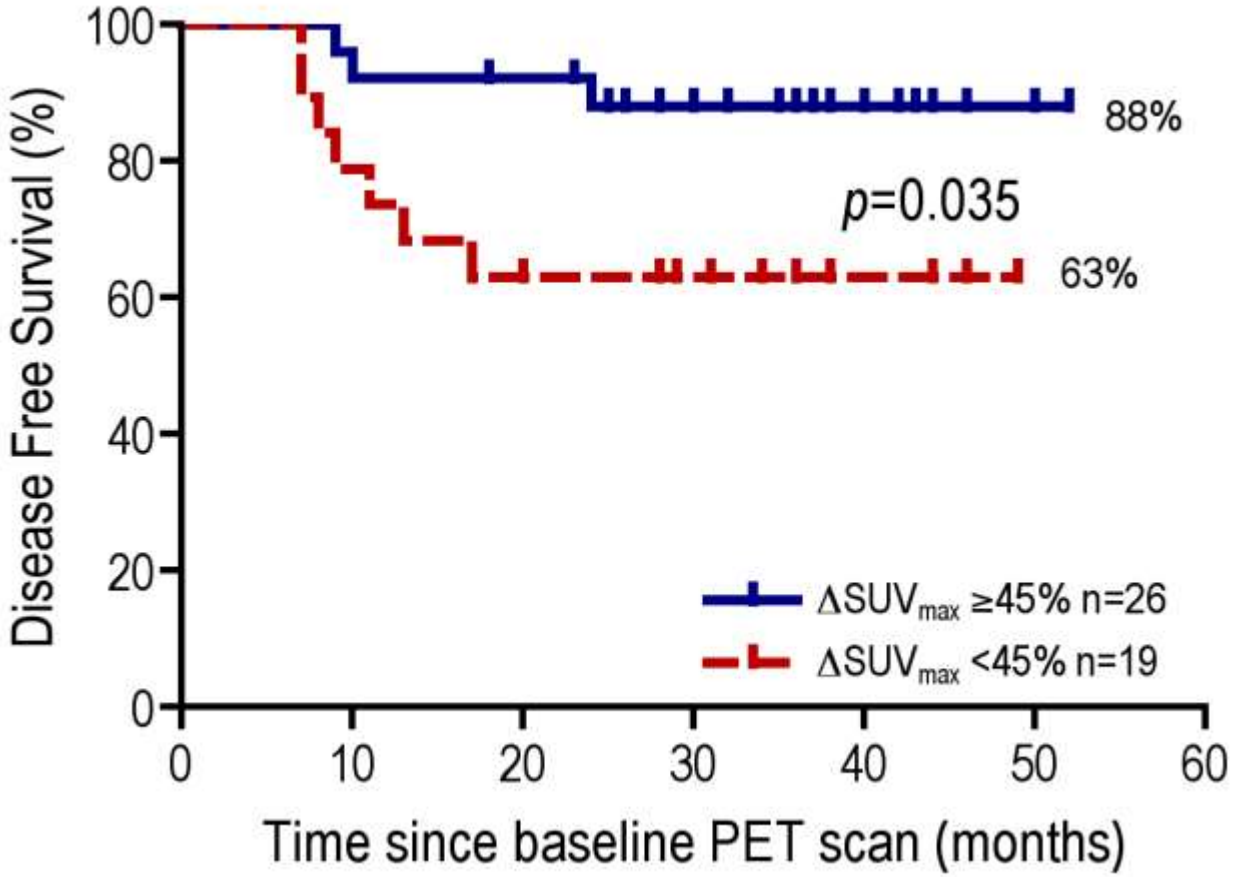


Radiochemotherapy
Local recurrence
after 7 months, M+
lateron

Radiotherapy
After 32 months **no recurrence**

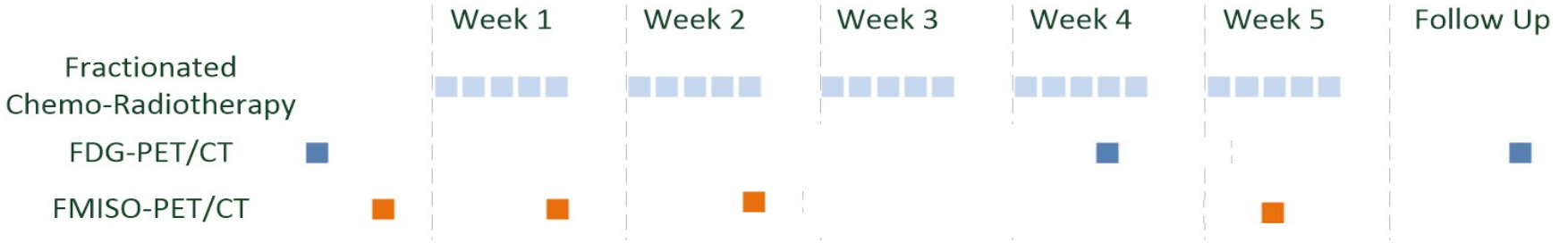
[Hoeben, Troost *et al*. 2013]

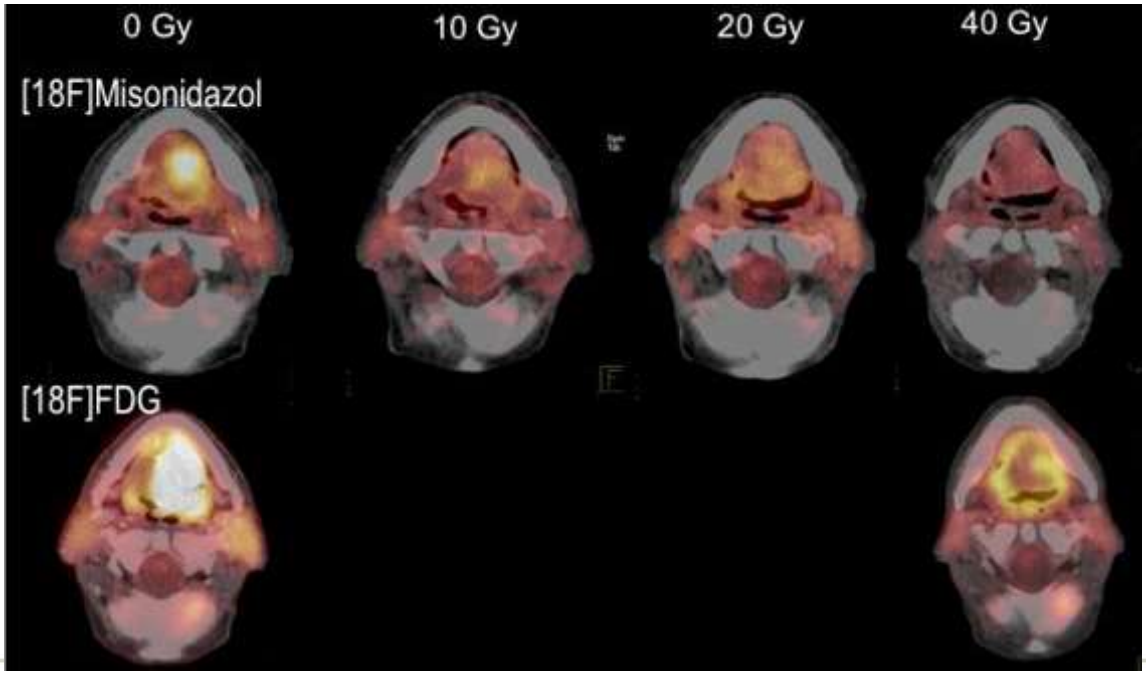
^{18}FLT-PET and disease-free survival



[Hoeben, Troost *et al*. 2013]

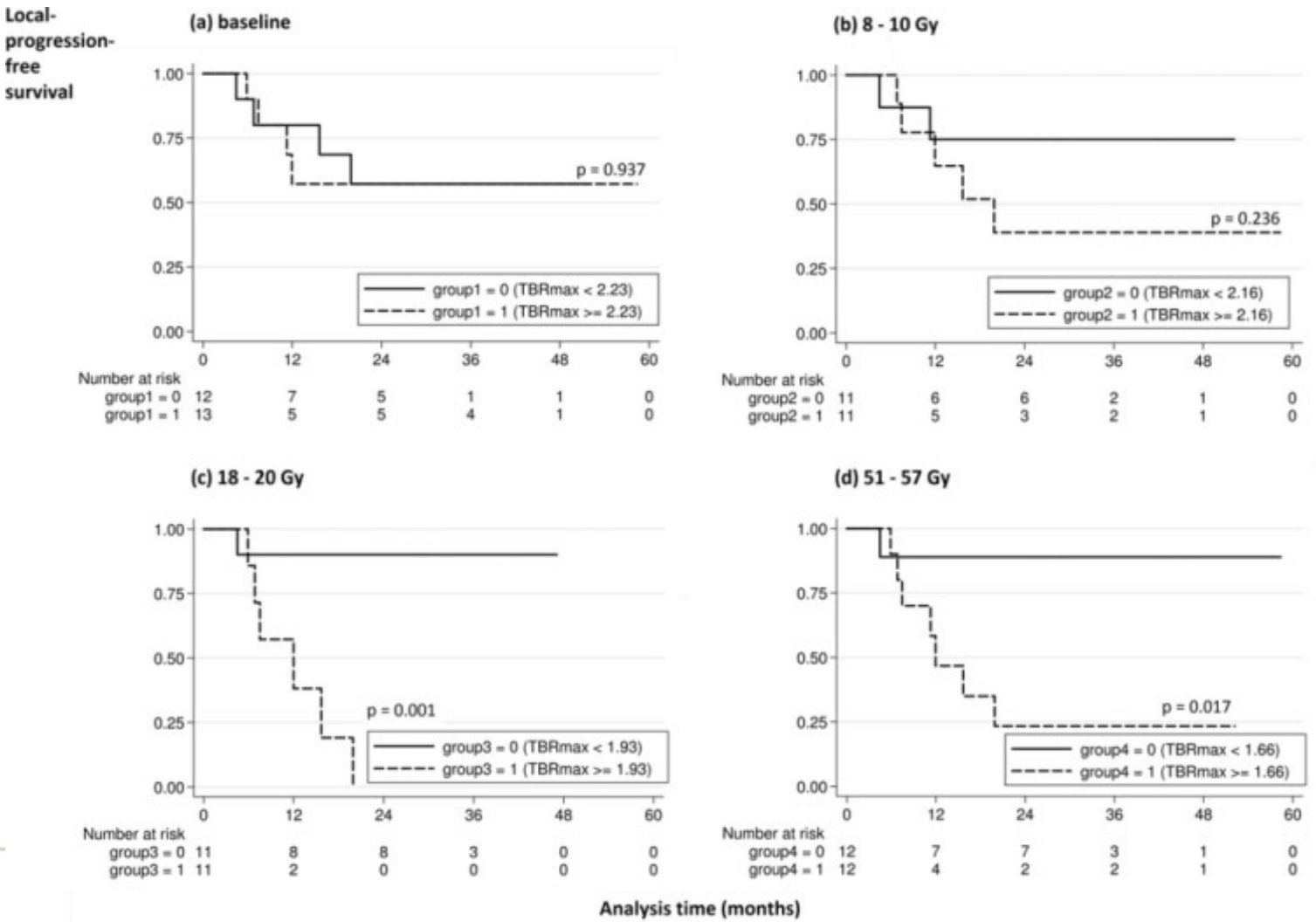
^{18}FMISO exploration- and validation study





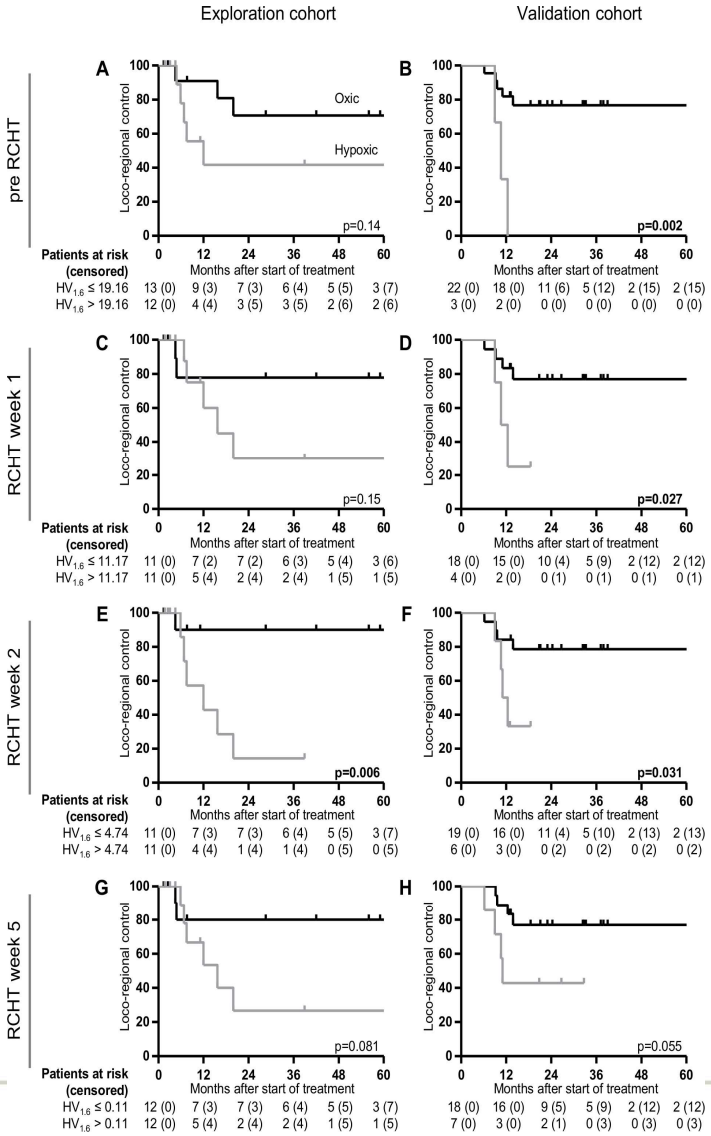
[Zips *et al.*, 2012]

^{18}FMISO – exploration cohort



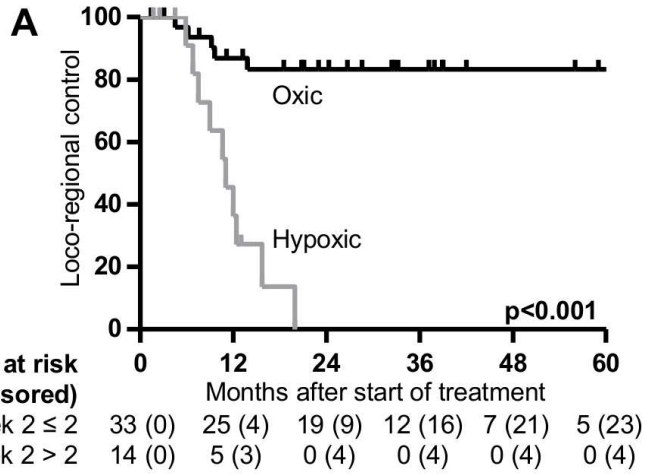
[Zips *et al.*, 2012]

^{18}FMISO – exploration and validation cohorts

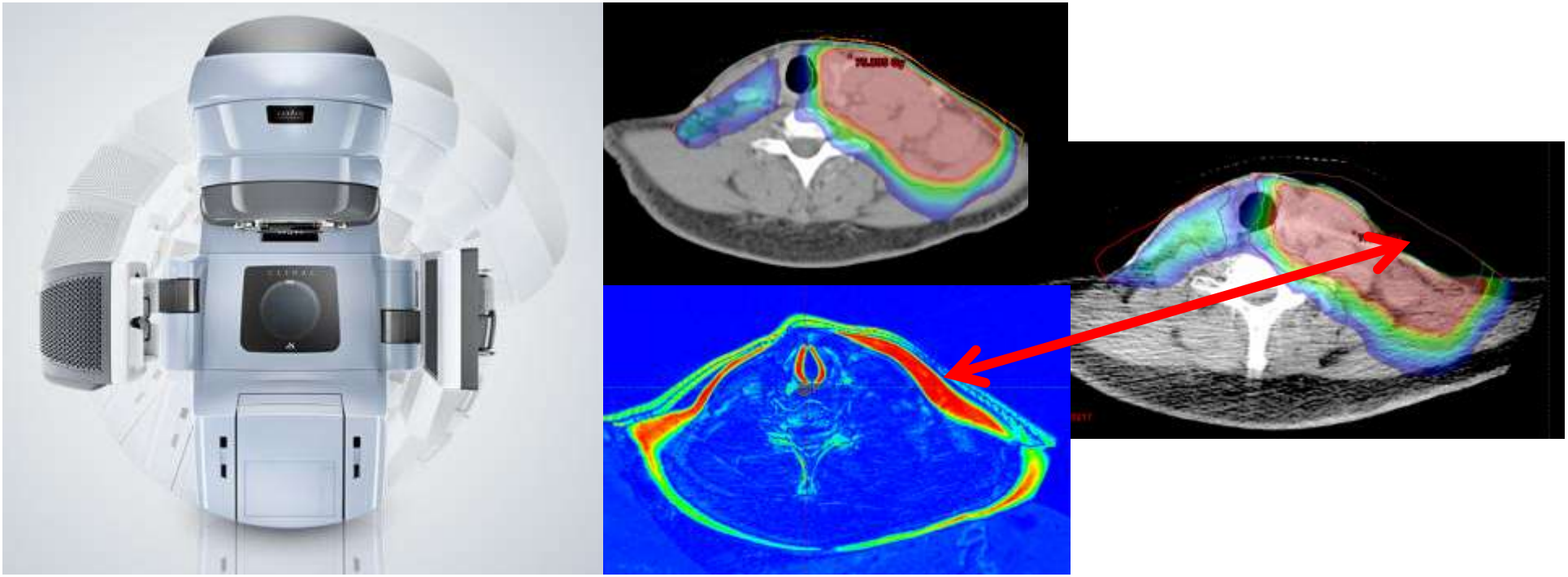


[Zips *et al.*, 2012; Löck *et al.*, under review]

Pooled cohorts in 2nd week of RCHT

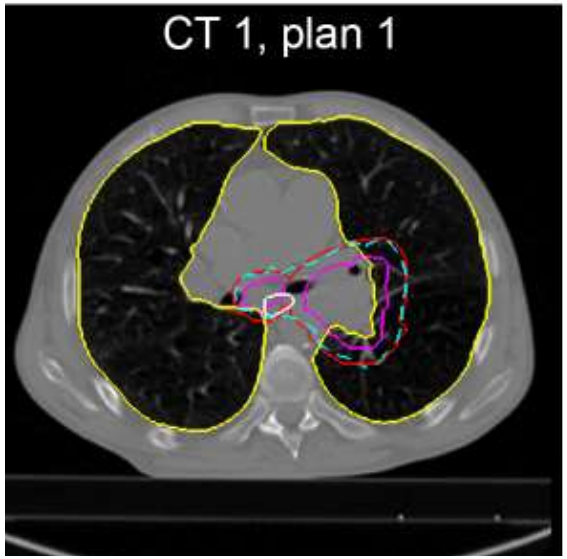


Dose-guided RadioTherapy



[VARIAN; MAASTRO clinic]

Dose-guided RadioTherapy



[Persoon *et al.*, 2013]

Target volume adaptation in NSCLC

Overall goal: lower NTCP and higher TCP due to dose escalation

- Tumor regression 0.6%-2.4% per day, fast decrease in tumor volume is associated with worse outcome (non-adenocarcinoma patients)
- Measurable tumor regression occurs in 40% of the patients (progression only in 1%), and is mostly visible in the fourth week of radio(chemo)therapy
- Tumor volume decrease is larger in patients simultaneously treated with radiochemotherapy than in those treated sequentially (50.1% *versus* 33.7%, p=0.003)
- Planning studies on possible dose escalation have reported different results

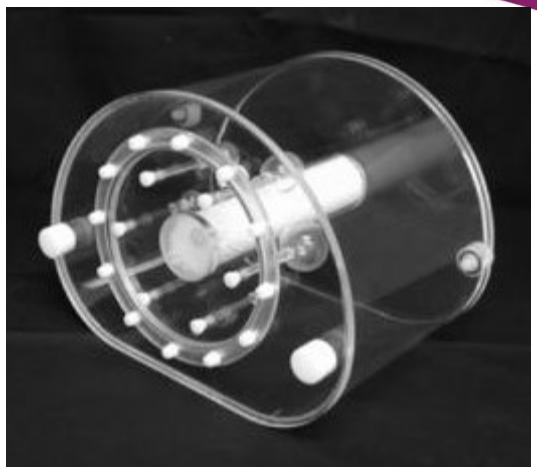
Sonke, Belderbos. Sem Radiat Oncol 2011; Brink, *et al*., Radiother Oncol 2014; Zwienen, *et al*. Int J Radiat Oncol Biol Phys 2008; Berkovic, *et al*. Acta Oncol 2015

First clinical results following adaptive RT in NSCLC

- N=104 (N)SCLC patients, 52 ART with PTV margin 4mm for primary tumor, 52 bone match with 10mm PTV margin
- Follow-up CT scans in three-monthly intervals
- Median follow-up 16 months (3-35 months), treatment adaptation in 12/52 ART-patients
- Locoregional recurrence 35% ART, 53% in non-ART (p=0.05), marginal recurrence in 1 *versus* 4 patients
- Overall survival: 10 *versus* 8 months
- Grade ≥ 2 pneumonitis: 18% *versus* 22% (p=0.6)

Tvilum *et al*., Acta Oncologica 2015

PET - resEARch 4 Life



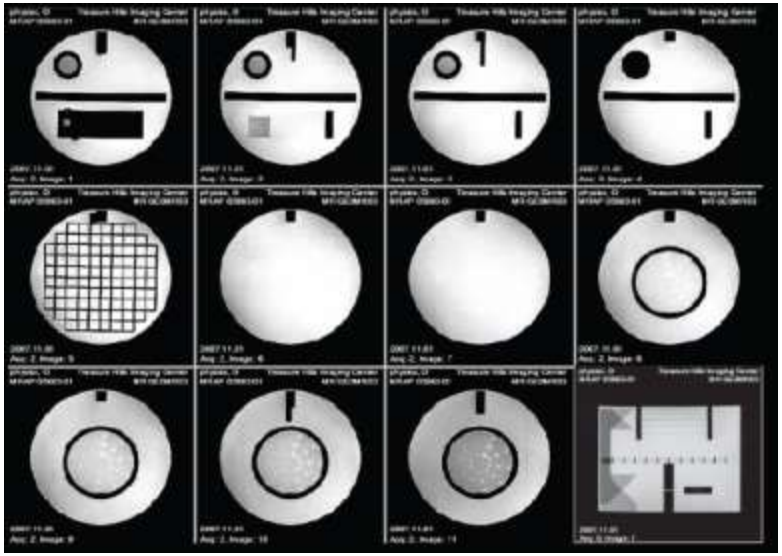
- Developed in 2010 by EANM
- Till July 2014, 96 centers with
  107 PET-CT scanners had been accredited

Aims:

- Independent **quality control** by imaging experts
- **Comparable** scanner performance between centers, harmonization of acquisition and interpretation of FDG-PET/CT scans
- **Accurate, reproducible and quantitative assessment**
- **Quality seal** of EARL-certified centers

Anatomical MRT - ACR Phantom

1	2	3	4
5	6	7	8
9	10	11	12



[http://elsc.huji.ac.il/enu/blog/2013/02/ready-go]

Index

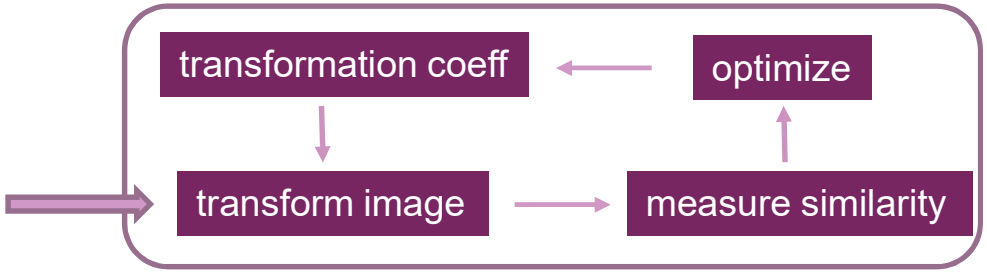
Anatomical and functional imaging modalities

Image registration

Image registration

The three core components of image registration:

1. Spatial/geometrical transformation T
2. Similarity measure/cost function
3. Optimization algorithm

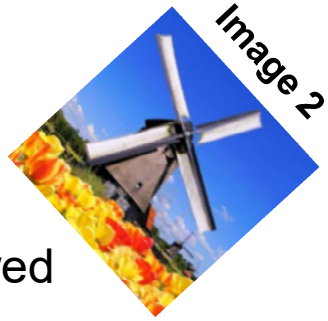


1. Geometrical transformation

Image 1

Rigid

- no deformation
- only translations and rotations are allowed



(3 rotations, 3 translations → (max) 6 independent parameters)

- **Affine**
  - shearing, stretching

(3 rotations, 3 translations, 3 stretches, 3 shears → (max) 12 parameters)

1. Geometrical transformation

- **Deformable /non-rigid**
  - e.g. elastic
    (milions of parameters!)

Image 2

Image 1

Applications

Intrafraction

- example: breathing (automatic propagation of lung tumor in 4DCT image set)

Interfraction

- example: tumor regression
  future: online adaptive RT
  dose mapping/accumulation

Interpatient

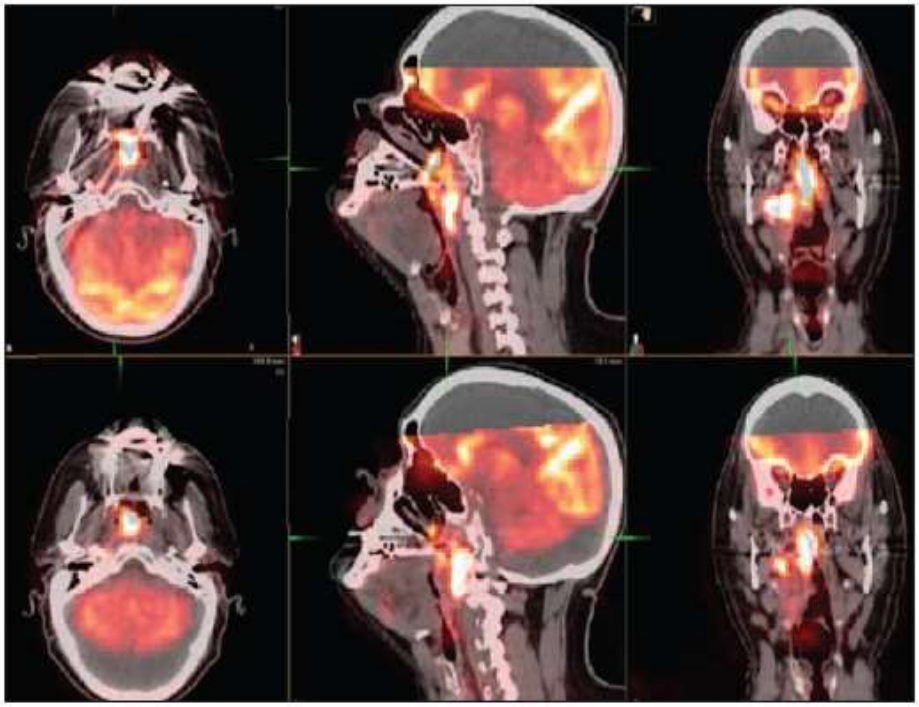
- atlas based segmentation

1. Geometrical transformation

Example: deformable registration of diagnostic PET and CT

deformable

rigid



Schoenfeld et al, AJR 2012

2. Similarity measure

Similarity measure quantifies degree of similarity between 2 images

Different methods exist:

- FEATURE – based
- INTENSITY – based (grey values)
- MODEL – based

2. Similarity measure

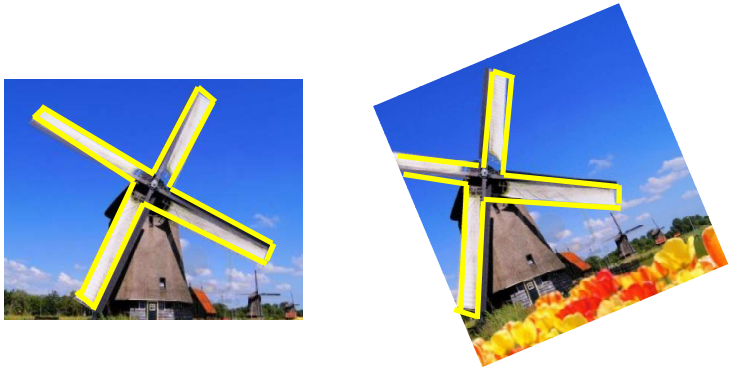
Feature-based method

- extract feature from images & evaluate distance between features
- employed when local accuracy is important
- dependent on accuracy of feature extraction

2 types:

Landmark-based method

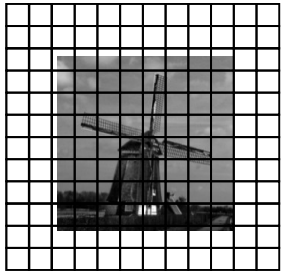
Segmentation-based method

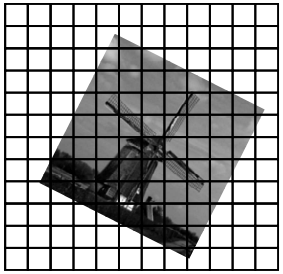


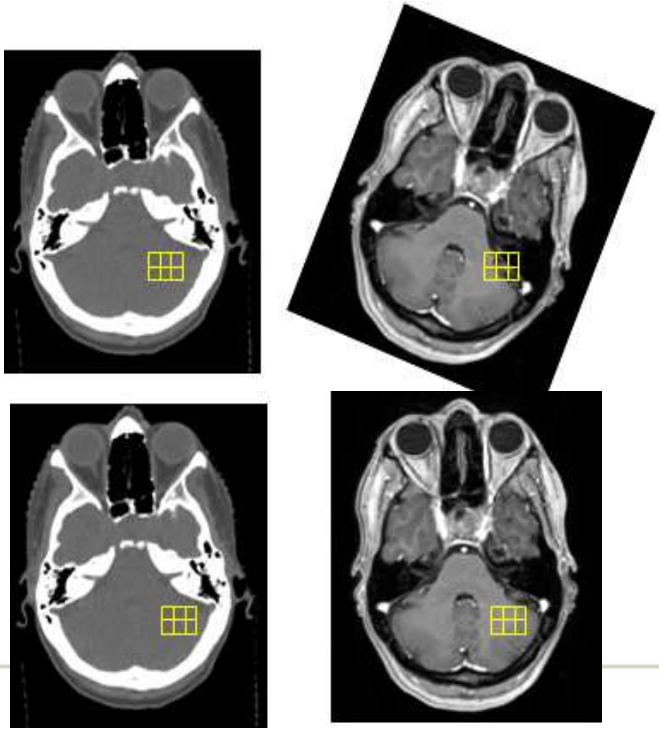
2. Similarity measure

Intensity-based method (grey values)

- all pixels in overlapping regions are utilized
- does not require detection of geometric features
- time consuming







e.g. *mutual information*

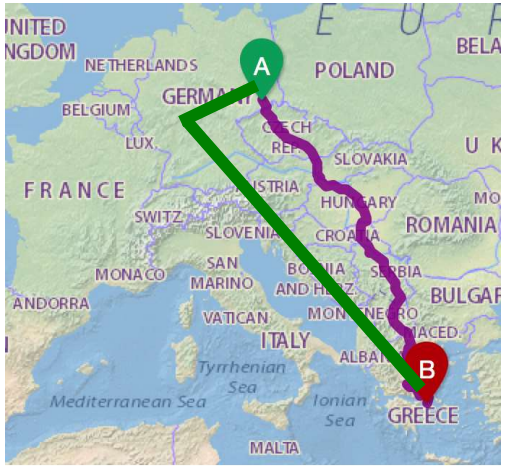
2. Similarity measure/COST FUNTION

description of problem in **mathematical terms**

value of cost function reflects quality of registration: smallest value = best solution

Example:

find shortest way to Athens → cost function = Σ path lengths



possible route: Dresden → Athens

2168 km
23h20
265.14 €

answer: purple

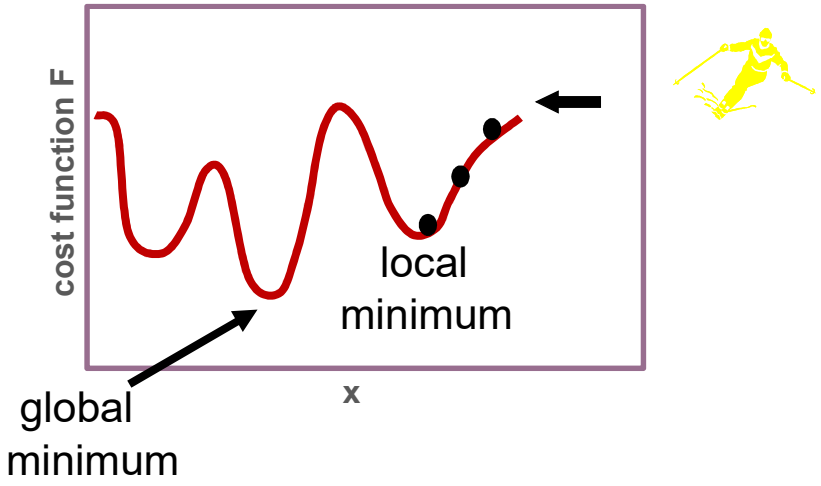
find fastest way to Athens → extra parameter: plane permitted

answer: green

3. Optimizer/optimization algorithm

optimizer finds smallest value of cost function (= “optimal” transformation)

example: gradient descent



simplified

Image registration in the RT chain

Initial diagnosis and staging	Preparation/planning (delineation)	Delivery (position verification)	Adaptive RT

Quantification of organ motion/
organ motion analysis

Format: Summary **Sort by**: Most Recent **Send to**

Search results

Items: 1 to 20 of 1568

<< First < Prev Page 1 of 79 Next > Last >>

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Take home messages

Anatomical and functional imaging modalities

- CT
- MRI
- PET
- Quality assurance

Image registration

- Different methods exist, (dis)advantages
- Numerous registration steps in RT - **beware of errors!**

Thank you for your attention

IGRT – tumor set-up correction strategies

- ✓ approaches to improve daily tumor set-up relative to linac isocenter
- ✓ set-up errors measured with in-room imaging (EPID, CBCT, …).

only ***inter***-fraction variations, no ***intra***-fraction motion

Ben Heijmen

Erasmus MC
University Medical Center Rotterdam

IGRT – tumor set-up correction strategies

Outline

- Introduction
- Random and systematic set-up errors
- Set-up correction protocols

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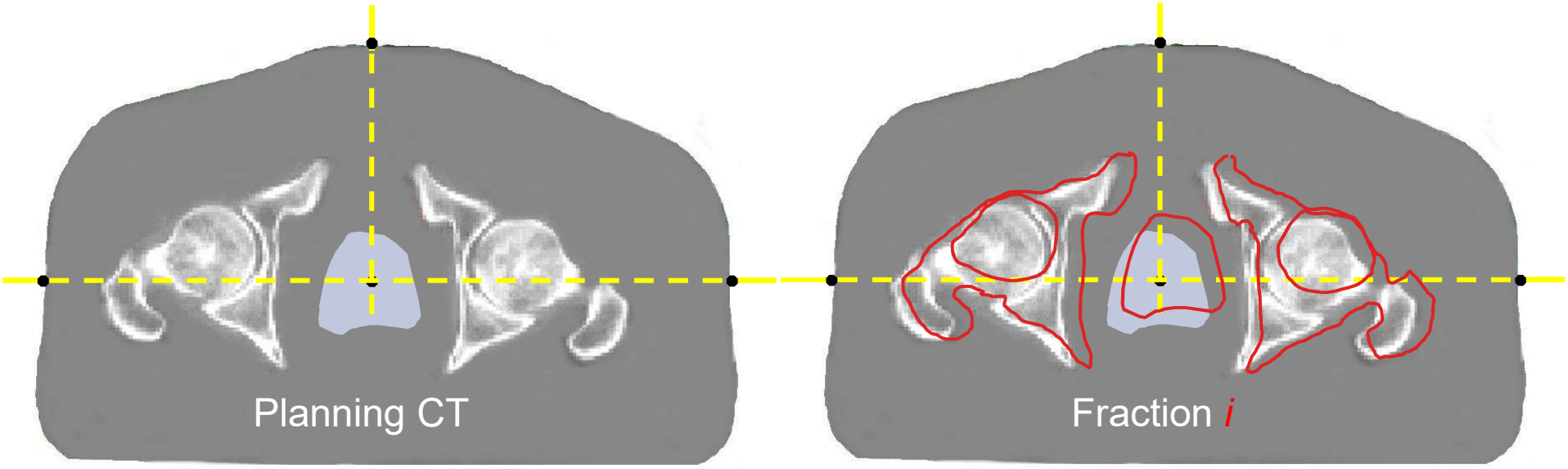
Aims of in-room set-up measurements and corrections

1) detect ***in first fraction*** mistakes in treatment preparation
e.g. error in prescription of set-up of immobilization device

2) reduce statistical variations in tumor set-ups ➔ plan and treat with reduced CTV-to-PTV margin



This presentation focuses on 2)

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IGRT – tumor set-up correction strategies

Outline

- Introduction
- Random and systematic set-up errors
- Set-up correction protocols

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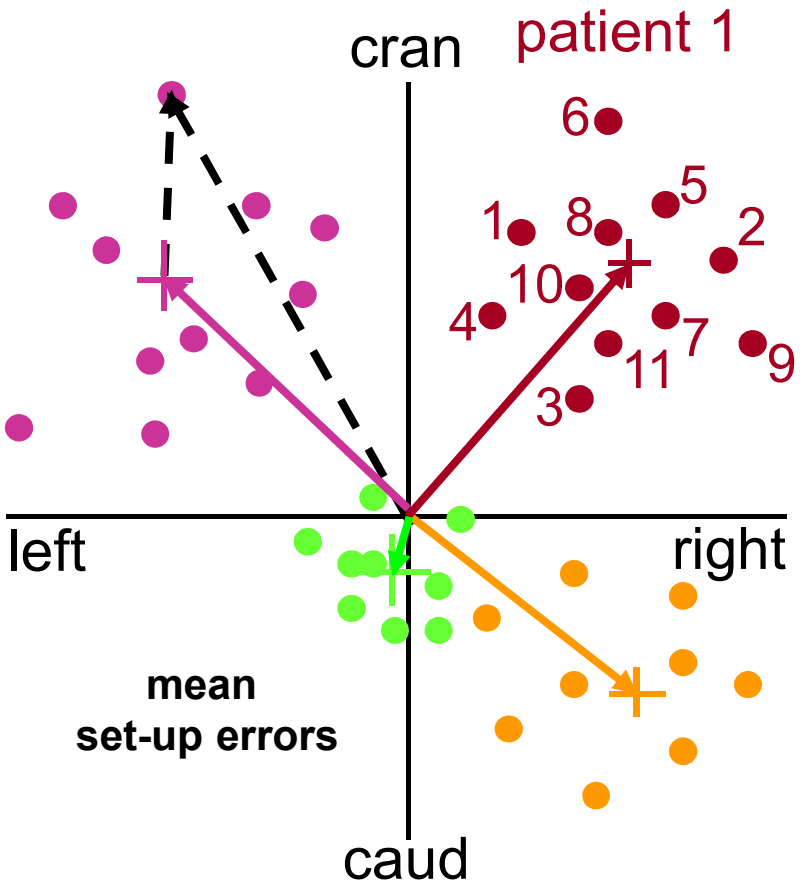
Systematic and random errors

- patient's systematic error $\stackrel{\text{def}}{=}$ mean error

- in each fraction:

  total set-up error =

  systematic error + random error



patient set-up errors 2D:
each fraction: •

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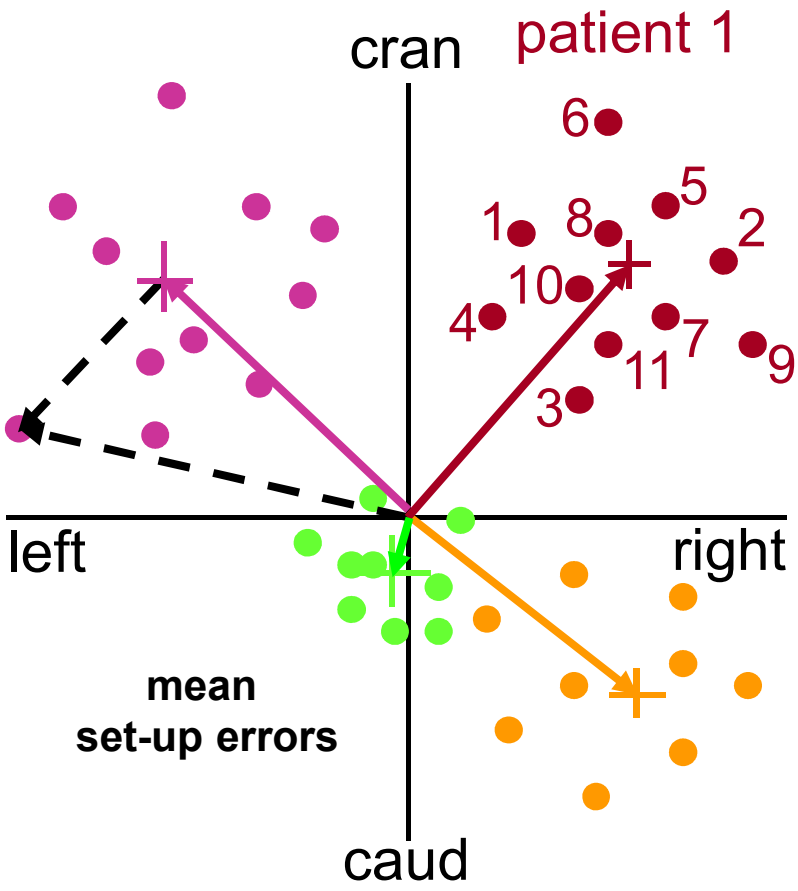
Systematic and random errors

- patient's systematic error $\stackrel{\text{def}}{=}$ mean error

- in each fraction:

  total set-up error =

  systematic error + random error



patient set-up errors 2D:
each fraction: •

- for each patient: systematic error is a fixed error, occuring every day

- random errors are day-to-day variations around the systematic error

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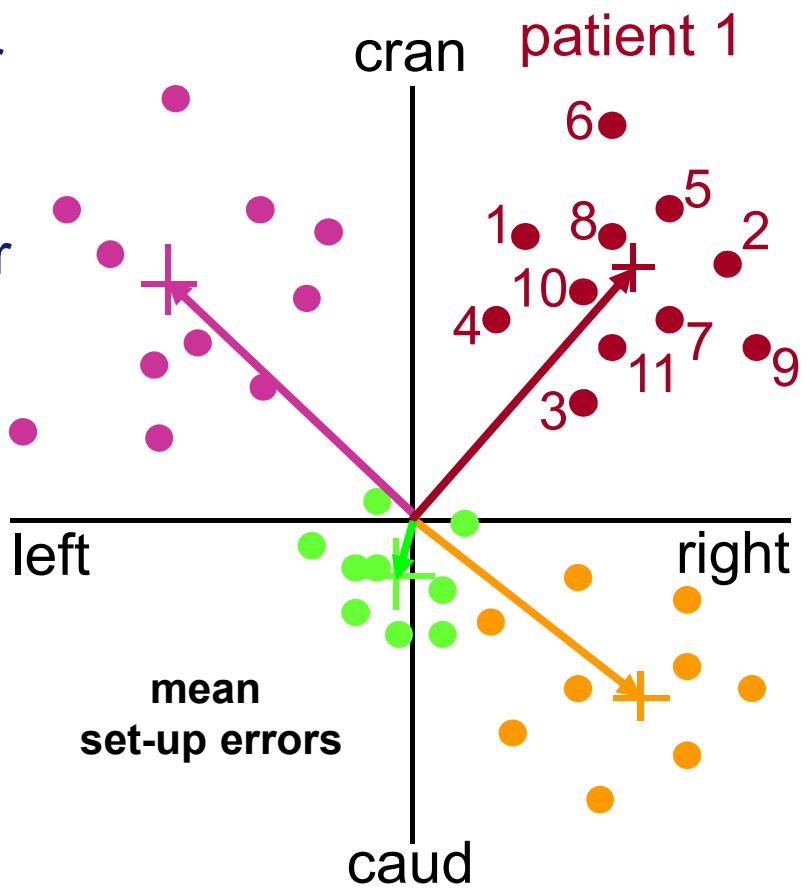
Systematic and random errors

- patient's systematic error $\stackrel{\text{def}}{=}$ mean error

- systematic error can only be known after completion of fractionated treatment

- systematic error cannot be upfront corrected, i.e. prior to start with fractionated treatment



patient set-up errors 2D:
each fraction: •

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Parameters to describe SYSTEMATIC and RANDOM errors in the patient population:

Random error:

$$\sigma_x = \sqrt{\frac{\sum_i \sigma_{i,x}^2}{N}}$$

$$\sigma_y = \sqrt{\frac{\sum_i \sigma_{i,y}^2}{N}}$$

Systematic error:

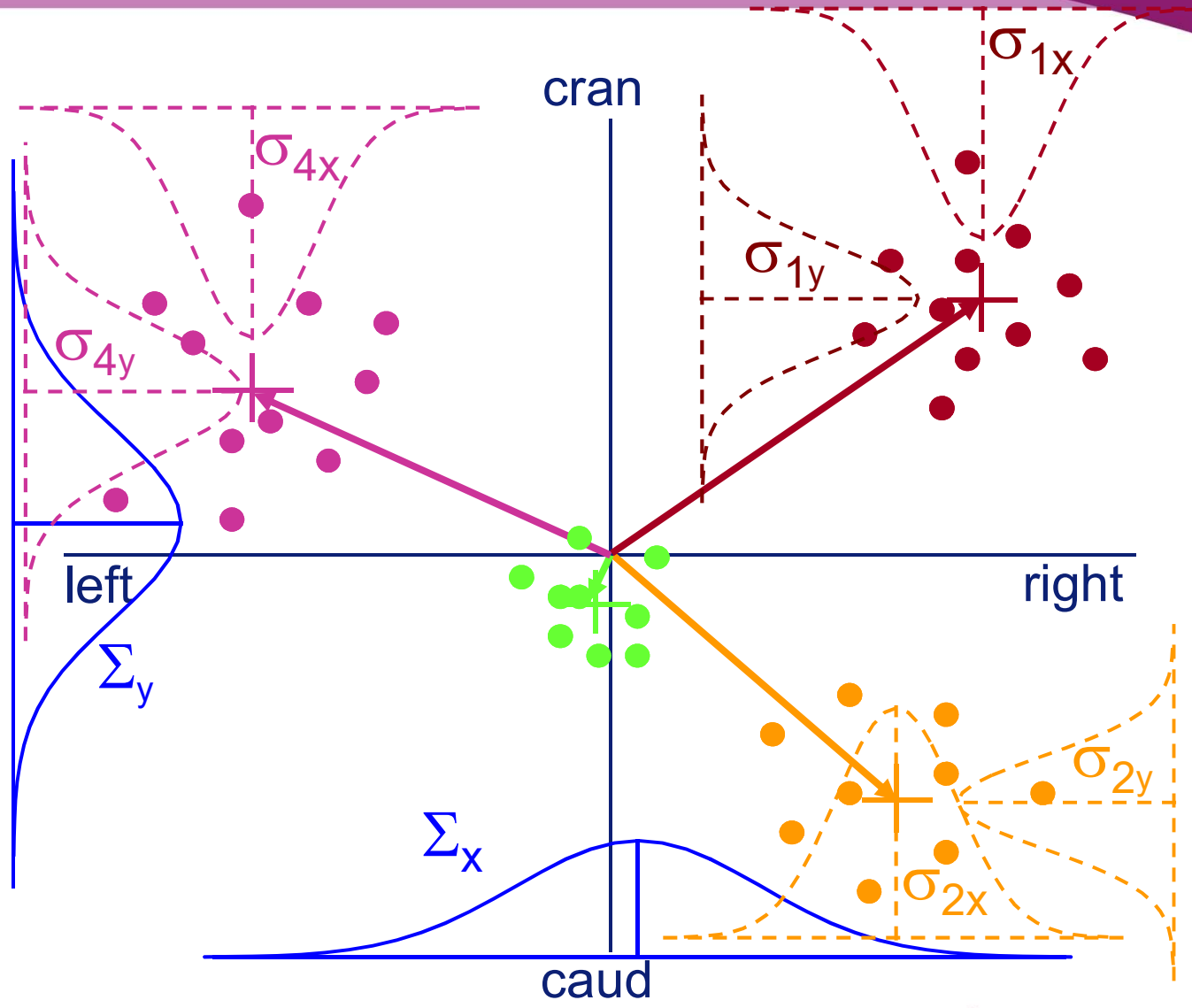
Σ_x: SD($m_{i,x}$)

Σ_y: SD($m_{i,y}$)

Mean error:

$\mathbf{M_x}$: $\langle m_{i,x} \rangle \approx 0$

$\mathbf{M_y}$: $\langle m_{i,y} \rangle \approx 0$



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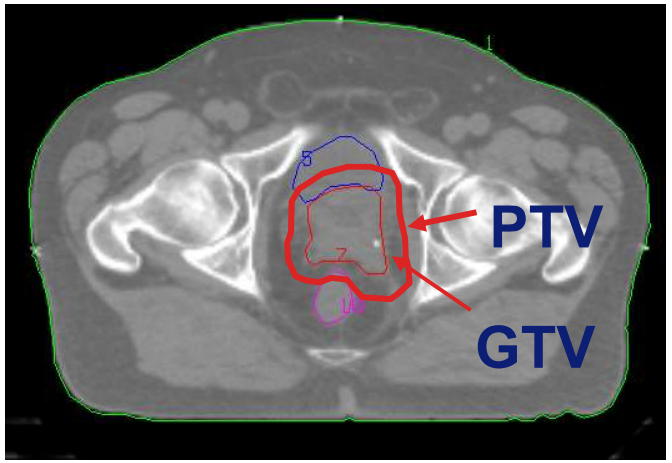
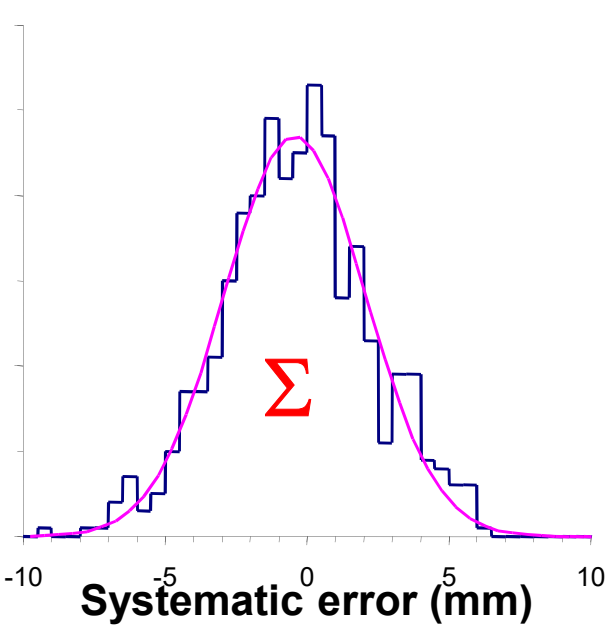
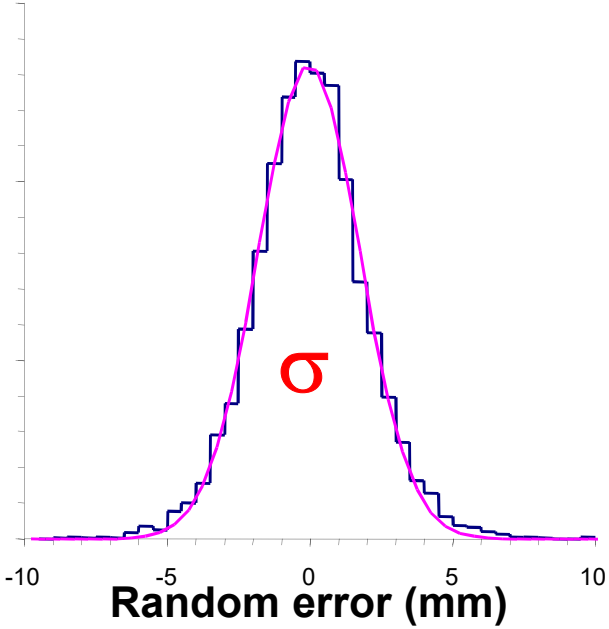
Relevance of Σ and σ?

$$M_{PTV} = 2.5\,\Sigma + 0.7\sigma$$



Measured in previously treated patients:





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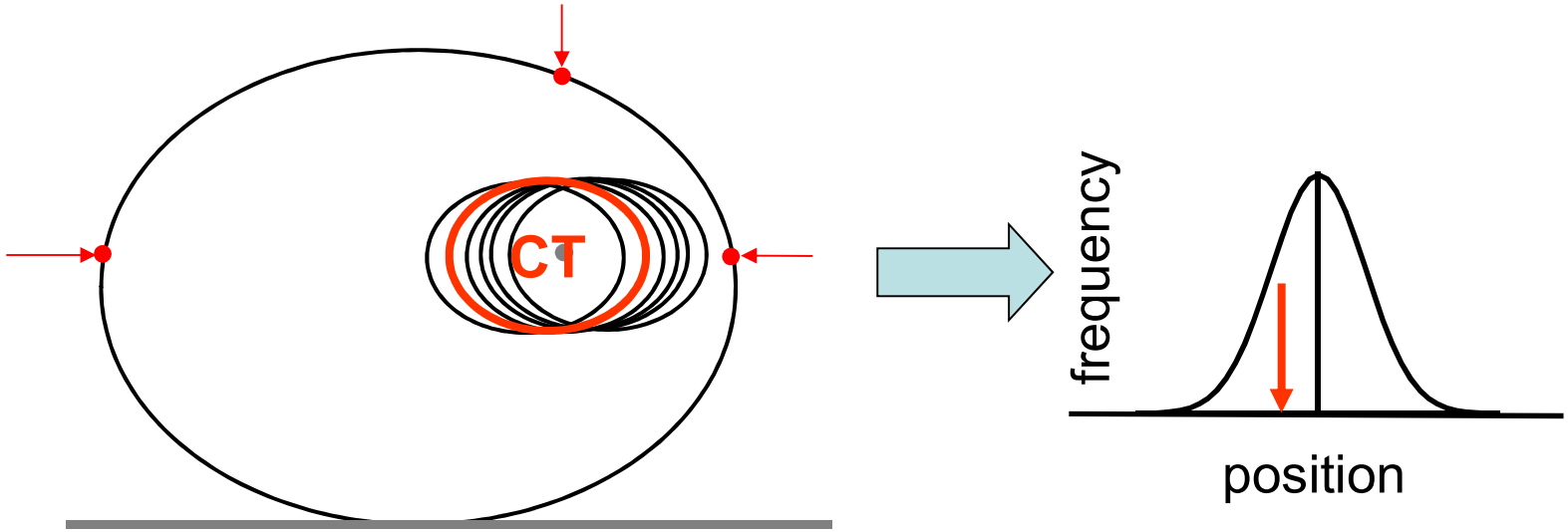
Systematic and Random errors

Intermezzo 1: systematic set-up errors are to be expected, even with perfect daily set-up based on tattoos:

tumor set-up variations with repeated perfect daily patient set-up



The **random** position of the tumor at the CT yields a **systematic** error during treatment

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IGRT – tumor set-up correction strategies

- **Introduction**
- **Random and systematic set-up errors**
- **Set-up correction protocols:**
  - on-line protocol
  - off-line protocols

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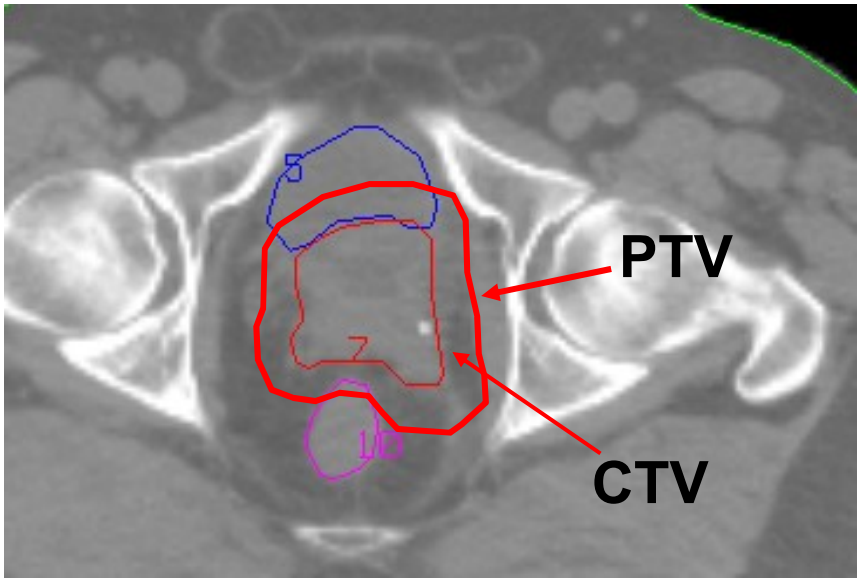
Aim of all strategies: reduce set-up errors and thereby the required planning margin

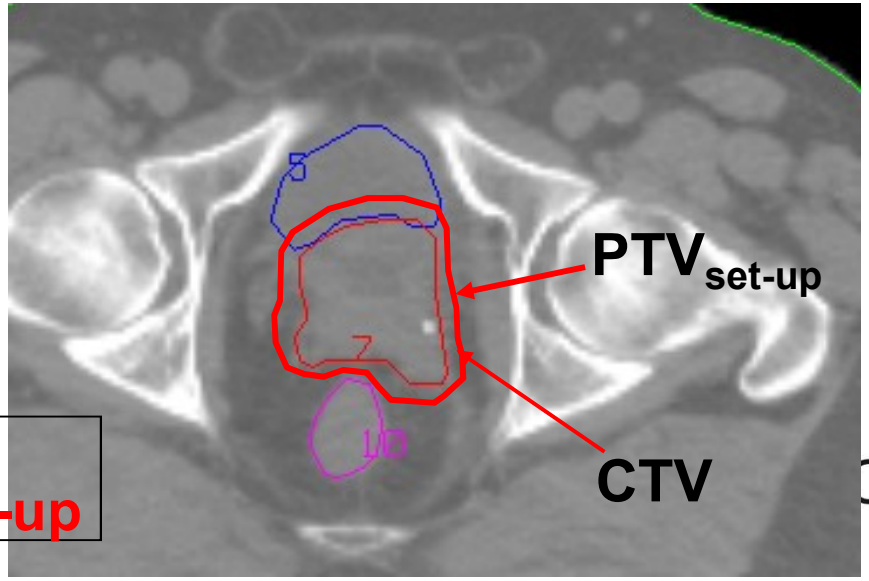
$$M = 2.5\,\Sigma + 0.7\sigma$$

Stroom et al.
van Herk et al.



- different strategies have different impact on Σ and σ

- Reduction of Σ has the largest impact on the margin M



$$M_{set\text{-}up} = 2.5\,\Sigma_{set\text{-}up} + 0.7\sigma_{set\text{-}up}$$

ON-LINE protocol:

- daily imaging and daily correction (couch shift)

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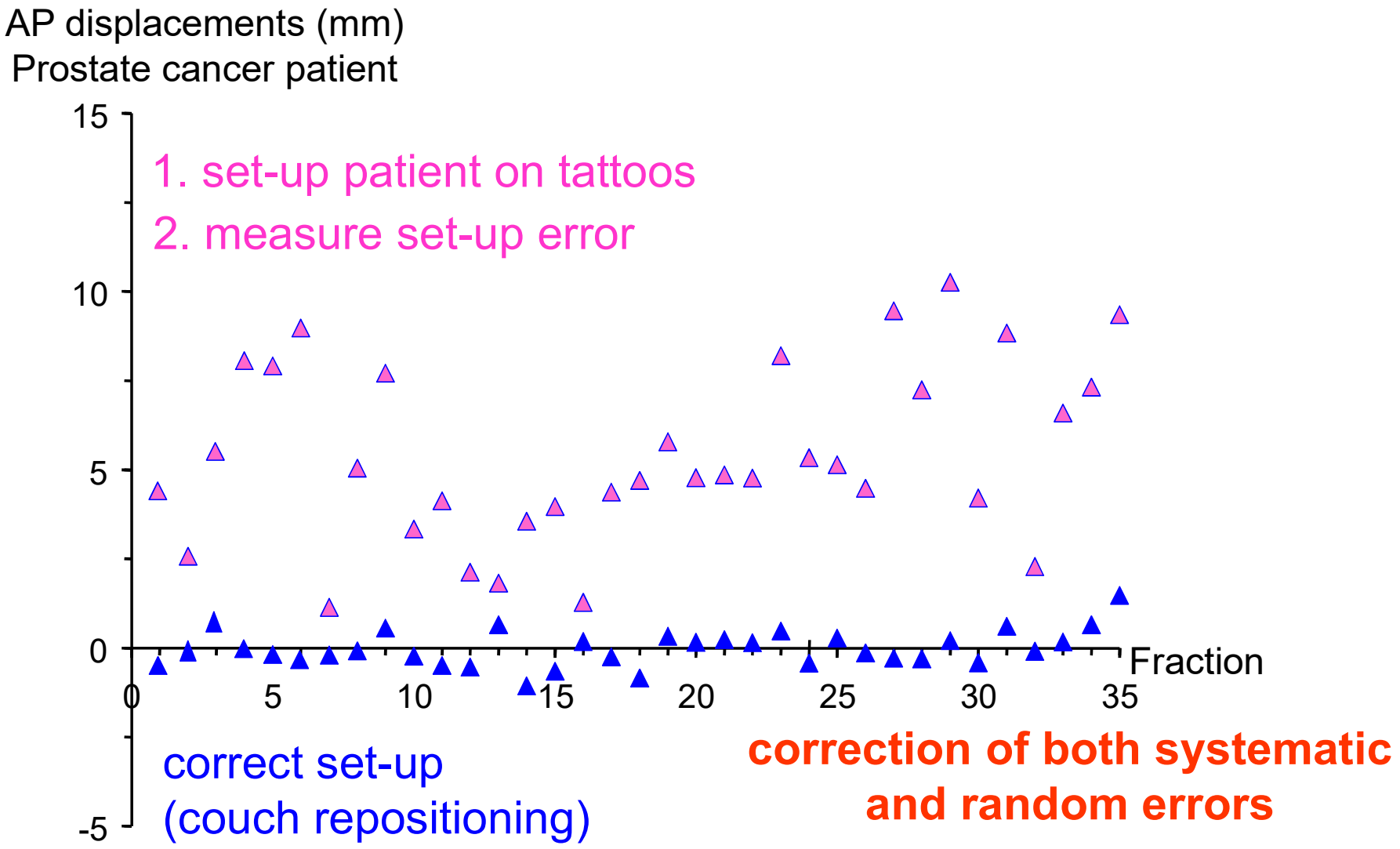
Mechanism of on-line



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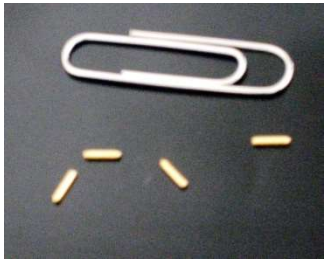
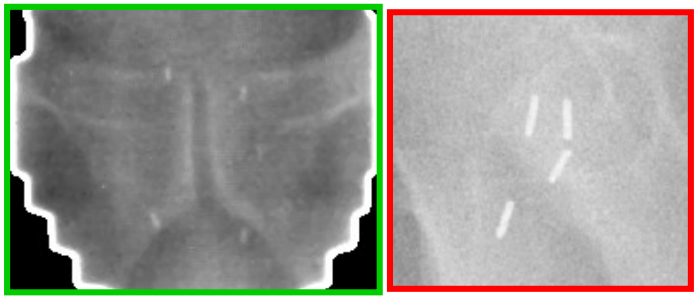
Daily on-line prostate re-positioning using StereoGraphic Targeting (SGT)

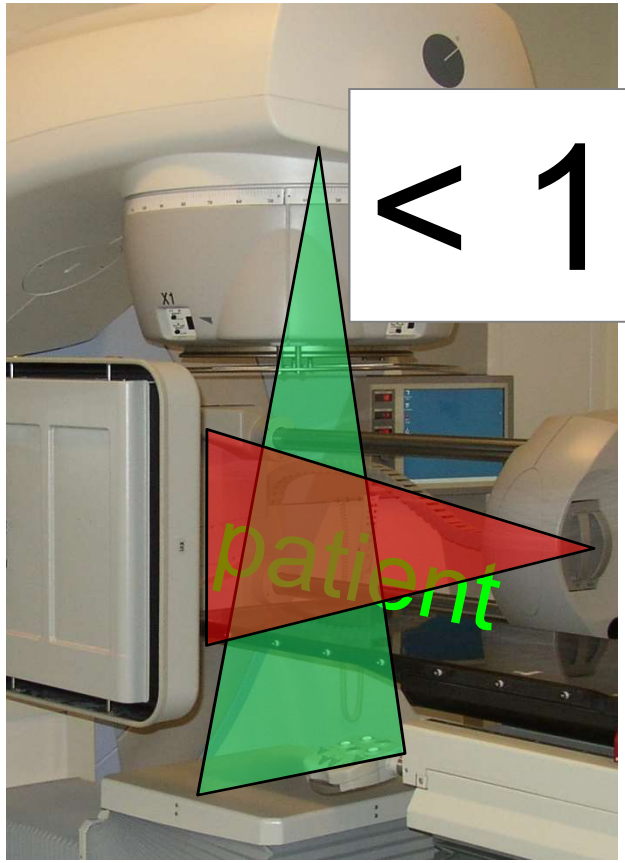
Mutanga et al, 2008



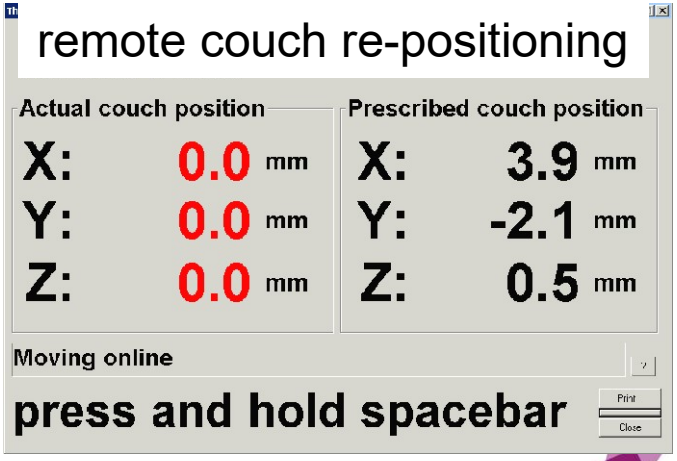


registration < 1 sec

ate: 98%



< 1 minute



techs do not enter treatment room

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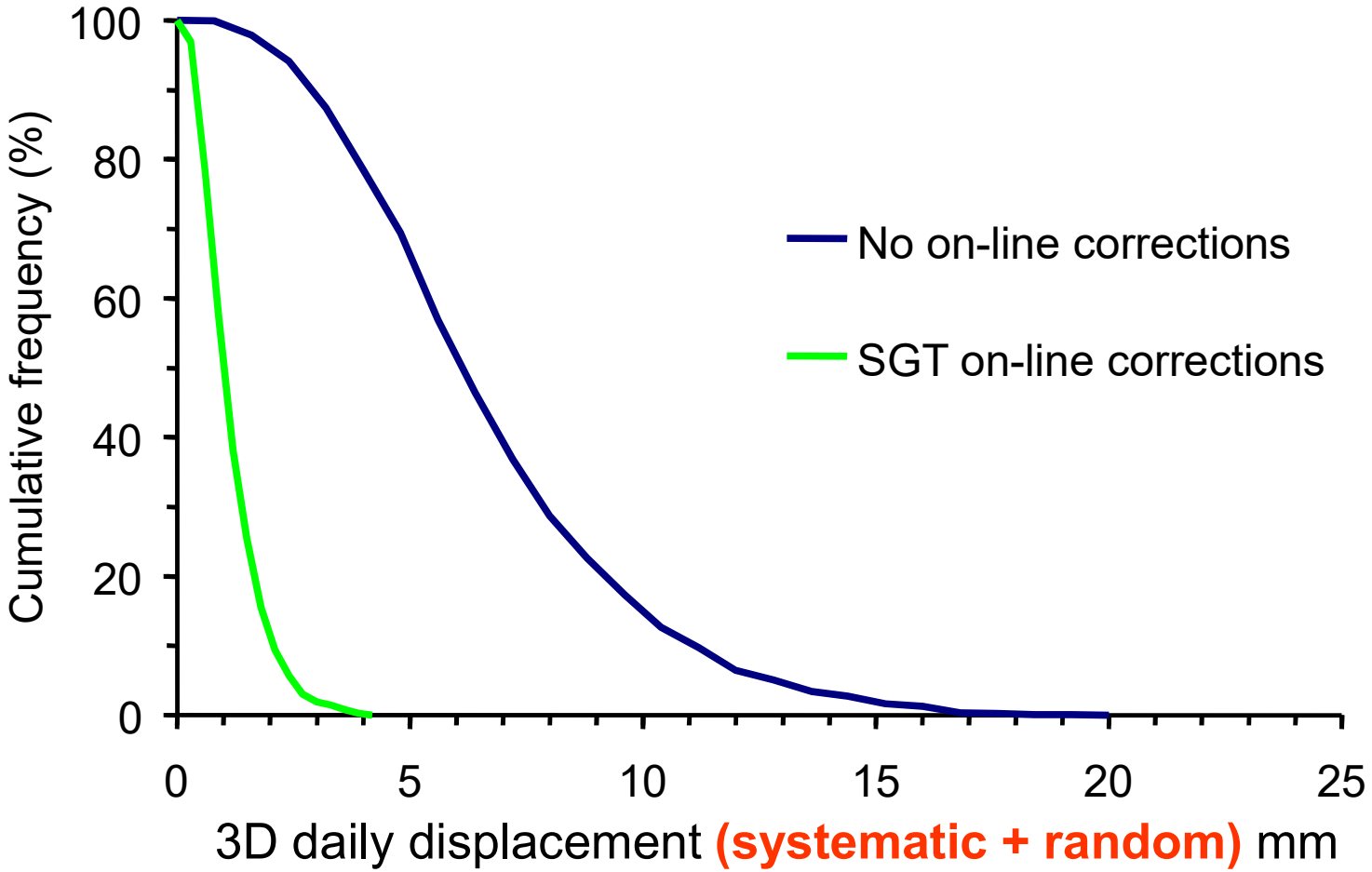
Reductions in systematic + random prostate displacements derived from verification measurements



De Boer, Mutanga, Heijmen et al., 2007

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OFF-LINE protocols

- imaging in limited number of fractions (at least first N fractions)
- measured errors are only used for correction in future fractions
- corrections not used same day ➔ off-line image analysis

OFF-LINE protocols

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OFF-LINE protocols

- imaging in limited number of fractions (at least first N fractions)
- **measured errors are** only **used for correction in future fractions**
- corrections not used same day ➔ off-line image analysis

in all fractions i: $E(i) = s + r(i)$

s = patient's systematic set-up error, $r(i)$ = random error in fraction i

➔ of *measured* $E(i)$, only s-component is relevant for future fractions

➔ use *measured* $E(i)$ to estimate s

➔ correct in future fractions with estimate of s

AIM: reduction of **systematic** set-up errors

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IGRT – tumor set-up correction strategies

- **Introduction**
- **Random and systematic set-up errors**
- **Set-up correction protocols:**
  - general aspects
  - on-line protocol
  - off-line protocols
    - a too simple off-line protocol
    - No Action Level (NAL) protocol
    - eNAL (extended NAL) protocol

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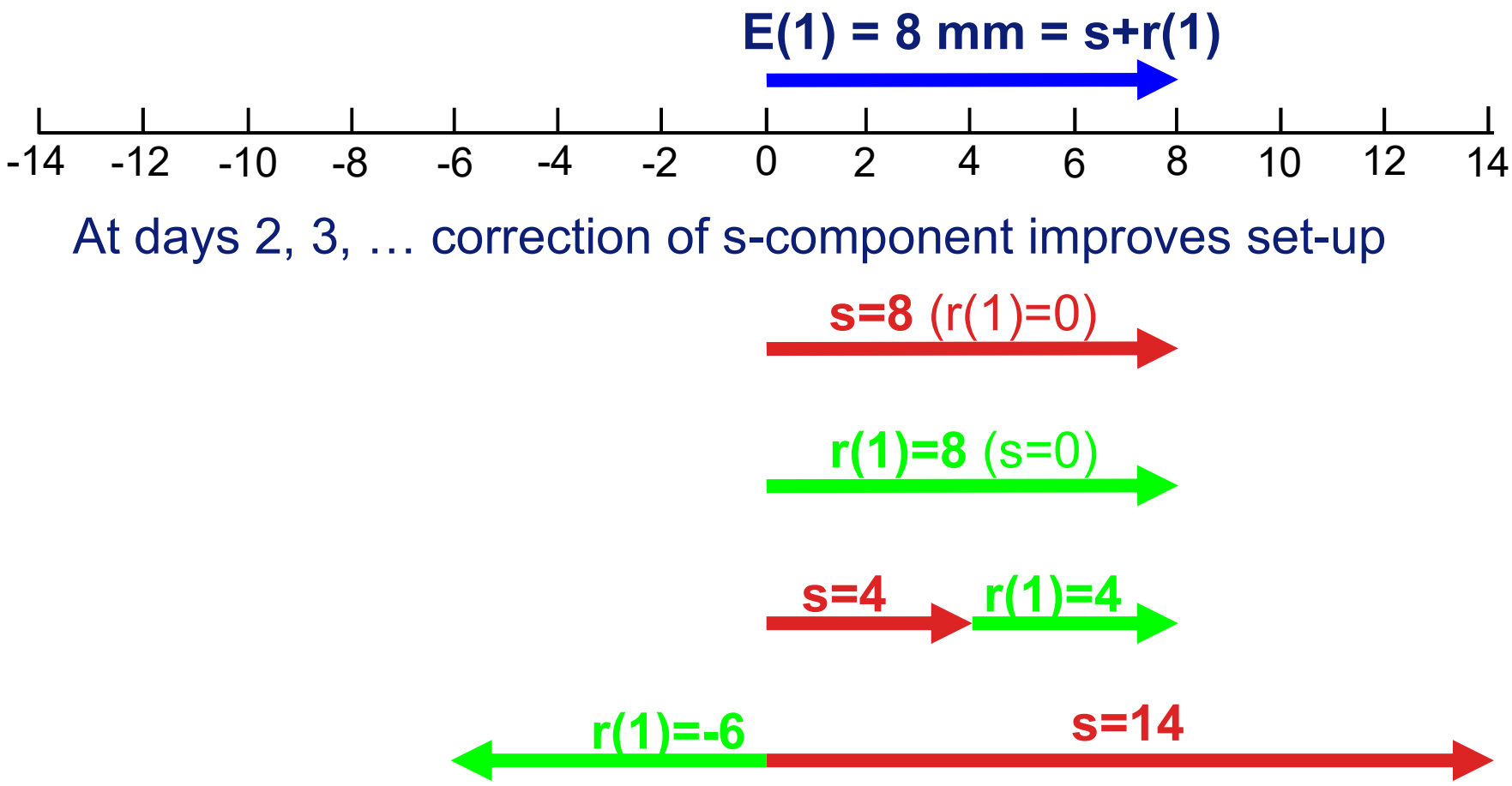
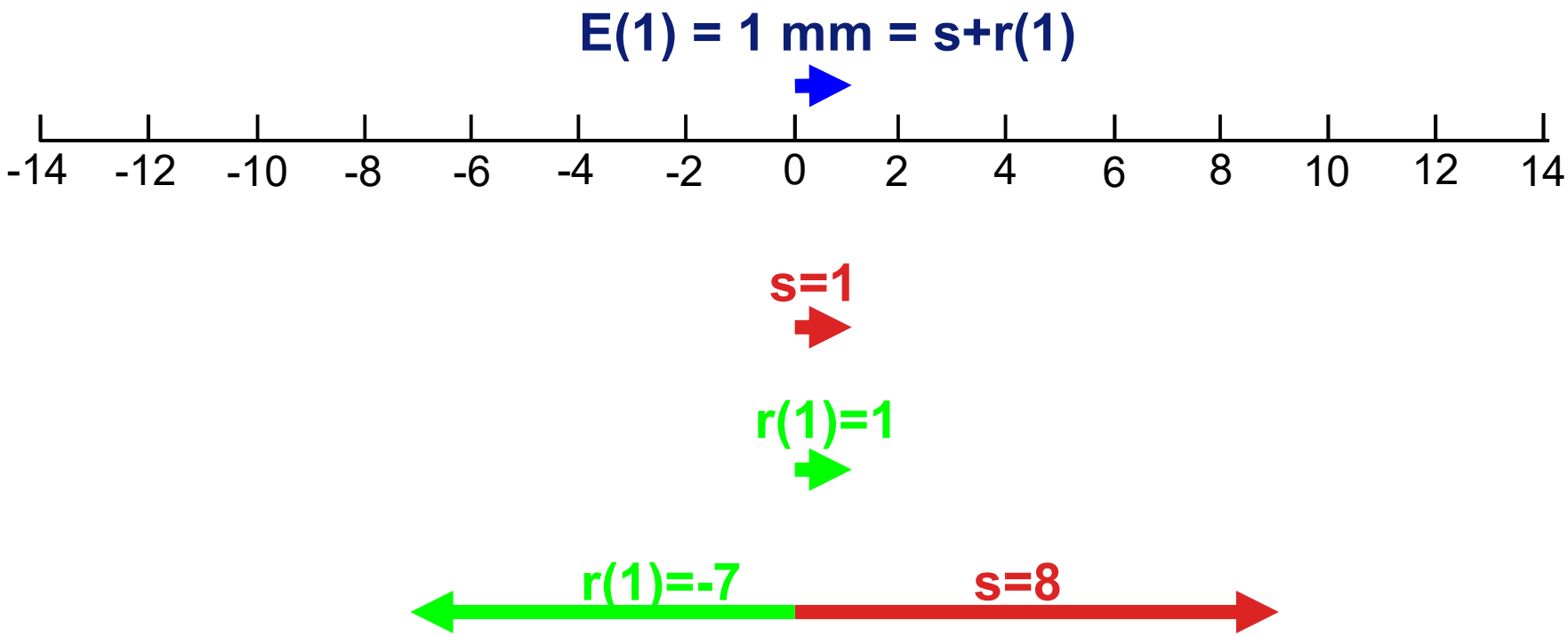
too simple off-line protocol: measure day 1, correct on days 2,3,…
without new measurements, what to do in following fractions?



systematic and random components unknown,
set-up correction on next days = ??

Erasmus MC

too simple off-line protocol: measure day 1, correct on days 2,3,…
without new measurements, what to do in following fractions?



a small measured set-up error does **NOT** necessarily imply a small problem

Erasmus MC

A SINGLE MEASUREMENT CANNOT BE USED FOR SET-UP CORRECTIONS IN FOLLOWING FRACTIONS

You cannot use it to estimate the patient's systematic error s.

If it is huge, then find out reason, do not simply correct.

Erasmus MC

IGRT – tumor set-up correction strategies

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  - off-line protocols
    - a too simple off-line protocol
    - No Action Level[1] (NAL) protocol
    - eNAL (extended NAL) protocol

[1]de Boer, Heijmen, IJROBP, 2001

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No Action Level (NAL) off-line protocol

- first 3 fractions:
  - set up patient on *original* tattoos
  - image, no corrections
  - **off-line**: analyze images of first 3 fractions (Erasmus MC: by RTTs), and calculate mean set-up error:

$$\bar{E} = \frac{E(1)+E(2)+E(3)}{3}$$

- after fraction 3:
  - patient set-up on *original* tattoos
  - correct with $-\bar{E}$ (no imaging)

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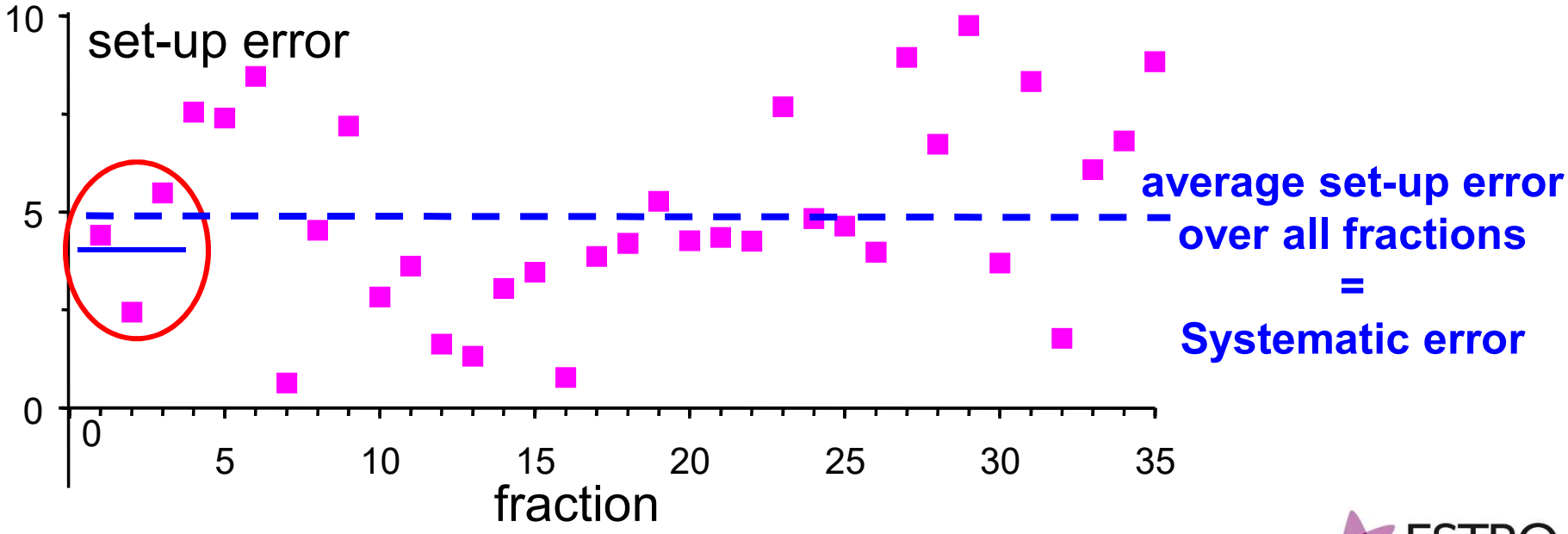
No Action Level (NAL) off-line protocol

$$\text{NAL Correction} = -\frac{E(1)+E(2)+E(3)}{3}$$

Logics:

- average set-up error in first 3 fractions = estimate of ***systematic*** error



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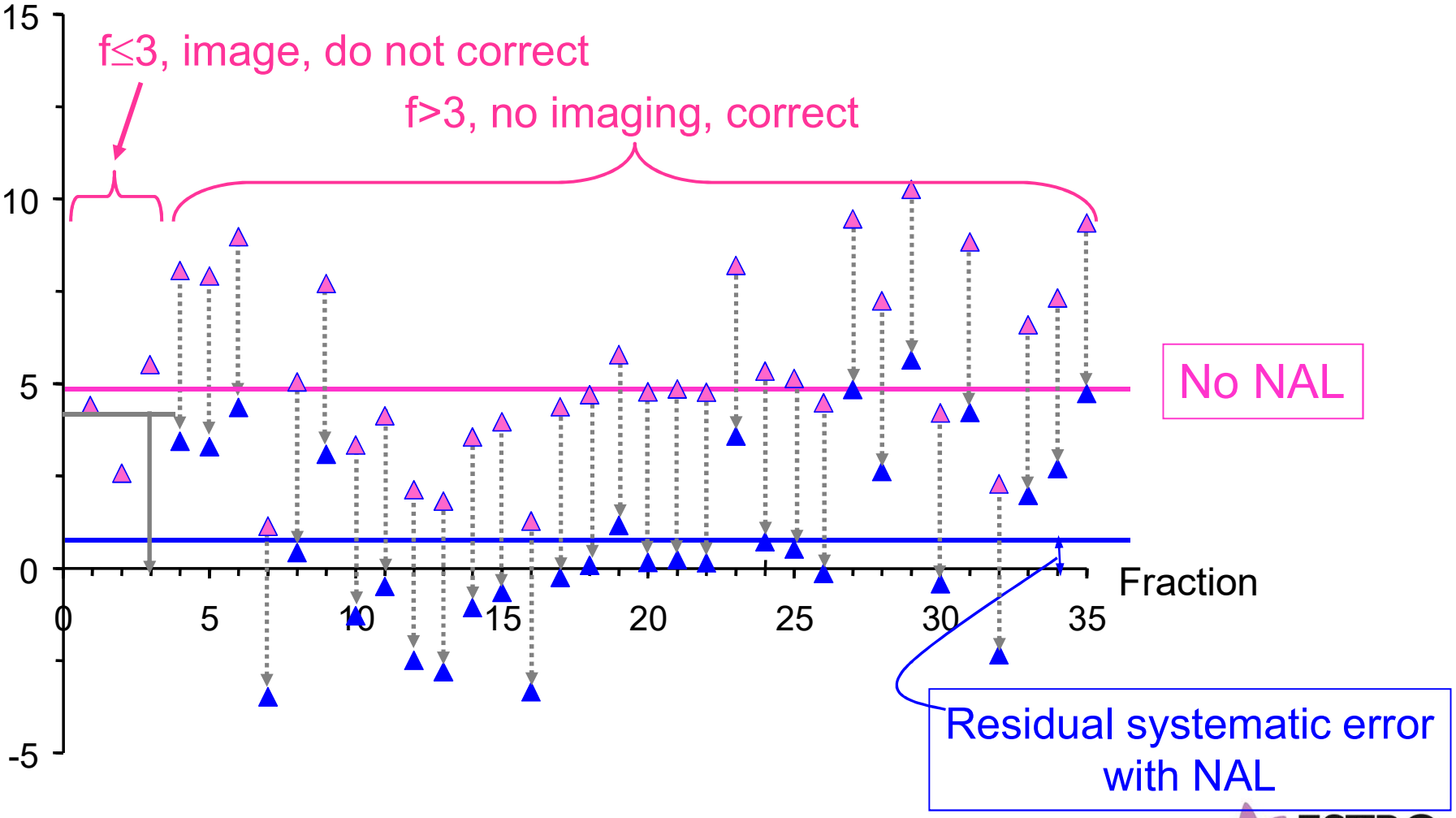
Mechanism of NAL

AP displacements (mm)
Prostate cancer patient

NO REDUCTION OF RANDOM ERROR



▲: initial set-up on (original) tattoos (prior to NAL correction)
▲: after NAL a priori setup correction

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Setup uncertainties Erasmus MC: NAL works

(residual) displacements [mm]:

		LR	CC	AP
Prostate[1]	σ	1.7	2.1	2.5
	Σ_{res}	1.0	1.3	1.5
Cervix[2]	σ	2.7	2.9	3.5
	Σ_{res}	1.5	2.1	2.9
Lung[3]	σ	2.0	2.4	2.4
	Σ_{res}	1.3	0.6	1.2
head & neck[4]	σ	1.6	1.6	1.4
	Σ_{res}	1.0	1.1	1.2

[1] De Boer et al. 2005

[2] Ahmad et al. 2012

[3] De Boer et al. 2003

[4] De Boer et al. 2004

(dis)advantages of on-line and NAL

Both protocols: in first fraction, detection of gross errors/mistakes

On-line protocol
- daily correction of full error (random + systematic components)
- maximal reduction of PTV margin
- if not automated: unacceptable increase of treatment time, large workload

NAL protocol
- no image analysis at treatment unit, no increased fraction duration
- imaging only f≤3, image analysis workload low
- significant (but partial) reduction of systematic errors and hence PTV margin ($\Sigma_{res} \approx \sigma/\sqrt{N}$)
- no reduction of random errors

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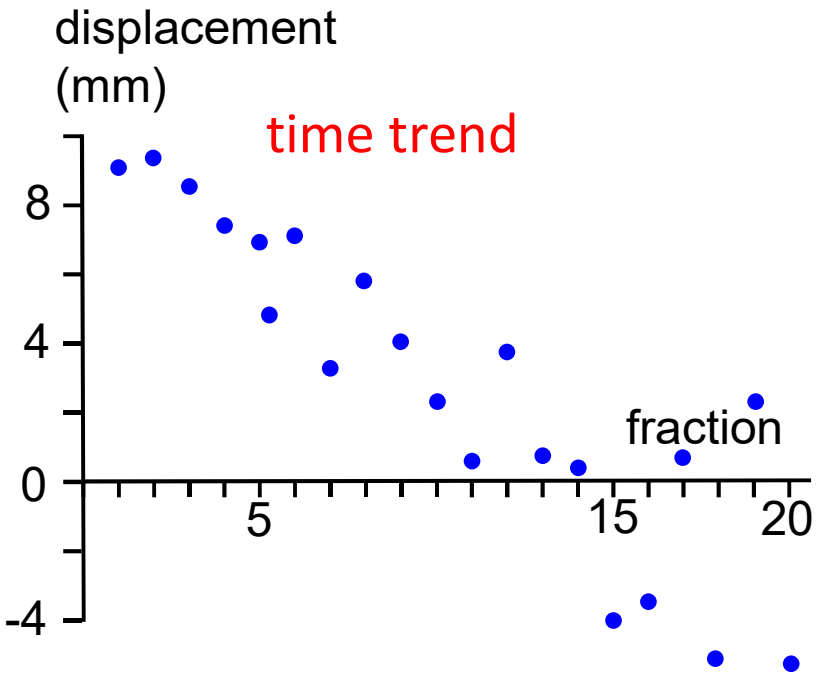
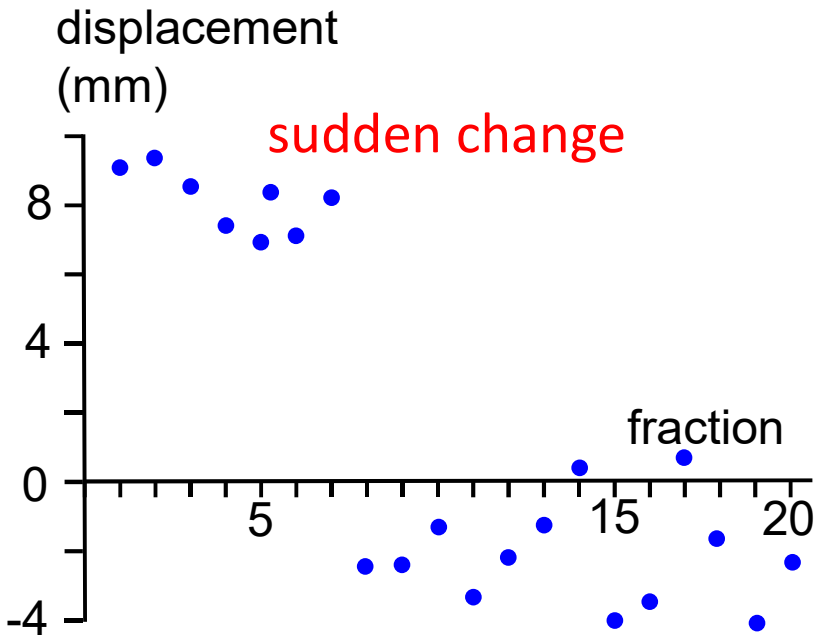
Potential limitations of NAL





On other hand: on-line corrections may involve too much workload and prolongation of fraction duration

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eNAL

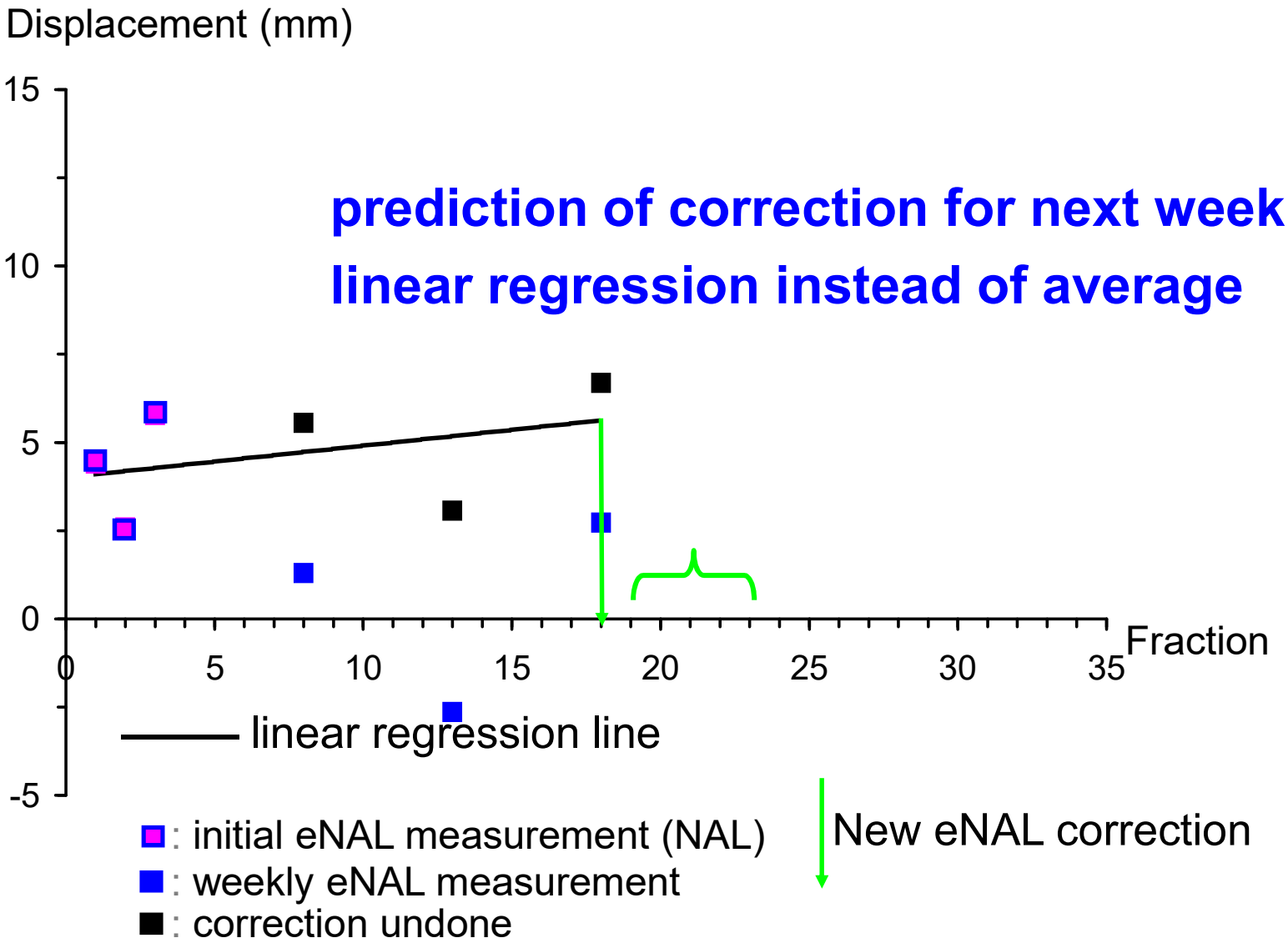
eNAL: *extended* NAL

- ***extended***: measurements in first 3 fractions ***+ once a week***

Protocol:

- start with NAL for one week
- every week: adjust correction vector for next week, based on **new measurement & all old measurements**

eNAL in 4th week: establishment of correction vector



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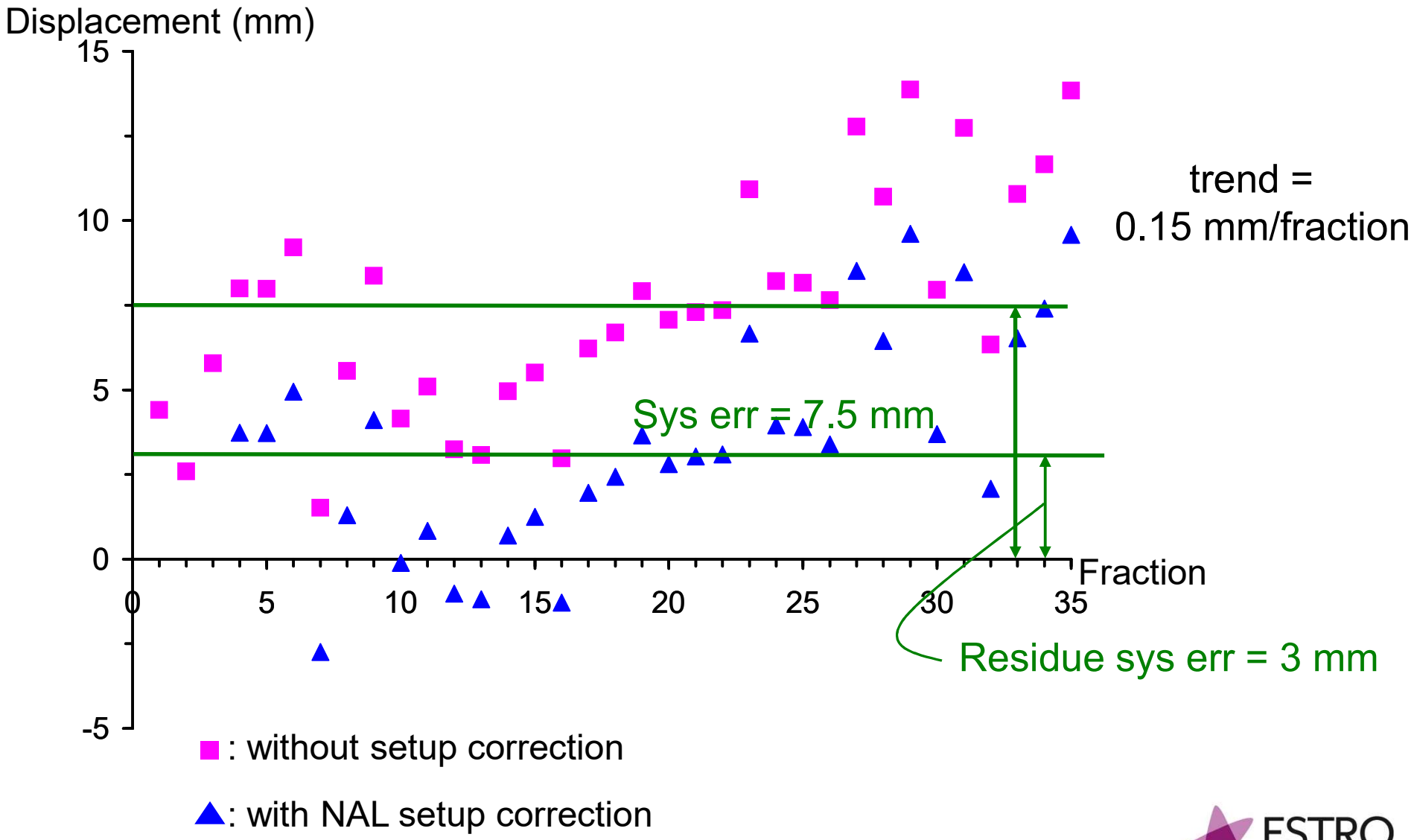
Performance NAL and eNAL in presence of time trend



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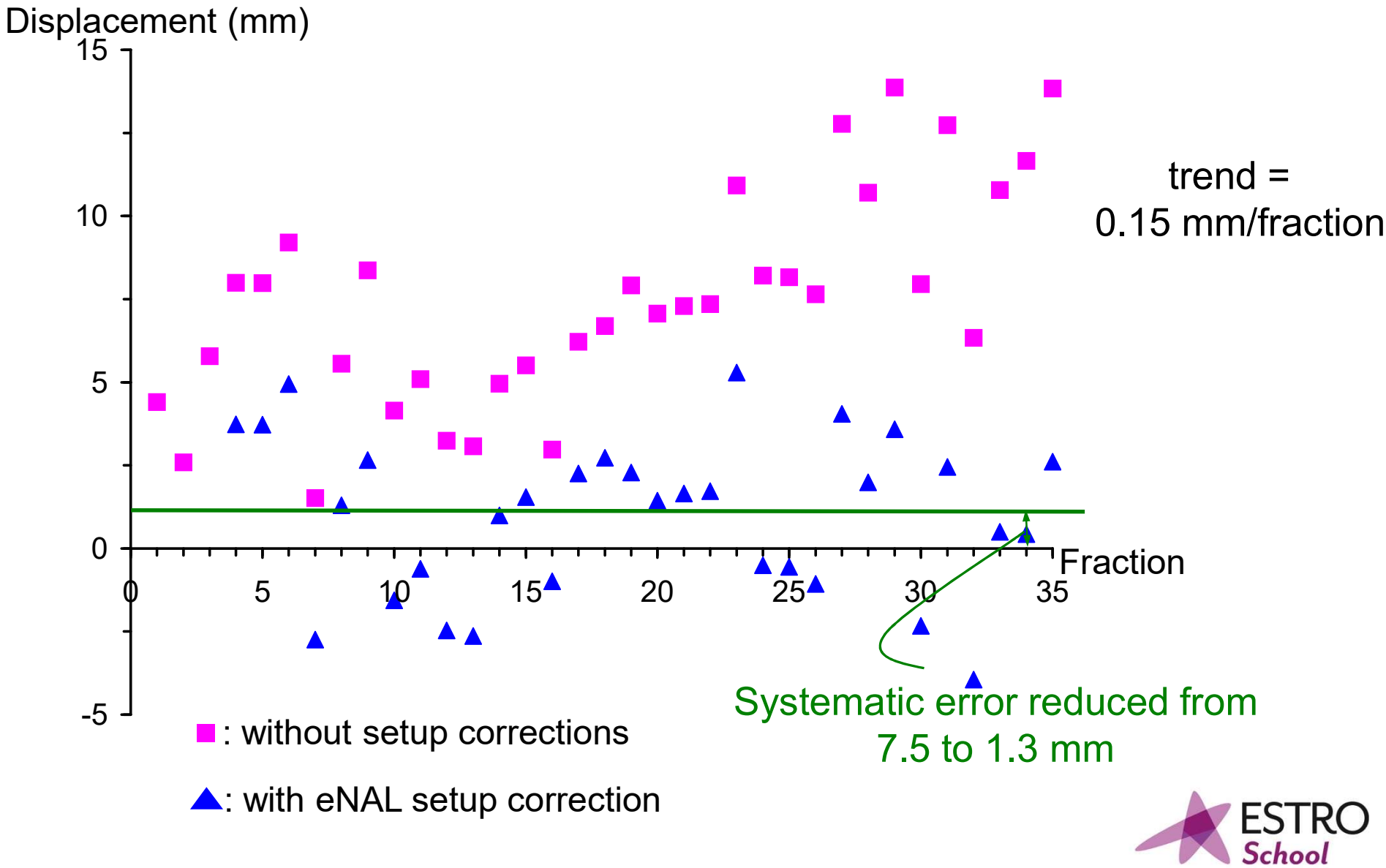
Performance NAL and eNAL in presence of time trend



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Erasmus MC, Rotterdam:

- almost all patients in off-line protocol, large majority eNAL, some NAL (neurological tumors)
- prostate, breast DIBH, palliative $\leq$ 5 fractions, rectum 5x5Gy (TME), cervix routinely in on-line protocol
- switch from off-line to on-line in case of large day-to-day variations detected in first fractions
- bladder cancer: on-line CBCT verification whether bladder is in PTV
- Cyberknife (lung, liver, cranial): tumor tracking

IGRT: Equipment for in-room imaging

Dr Ann Henry

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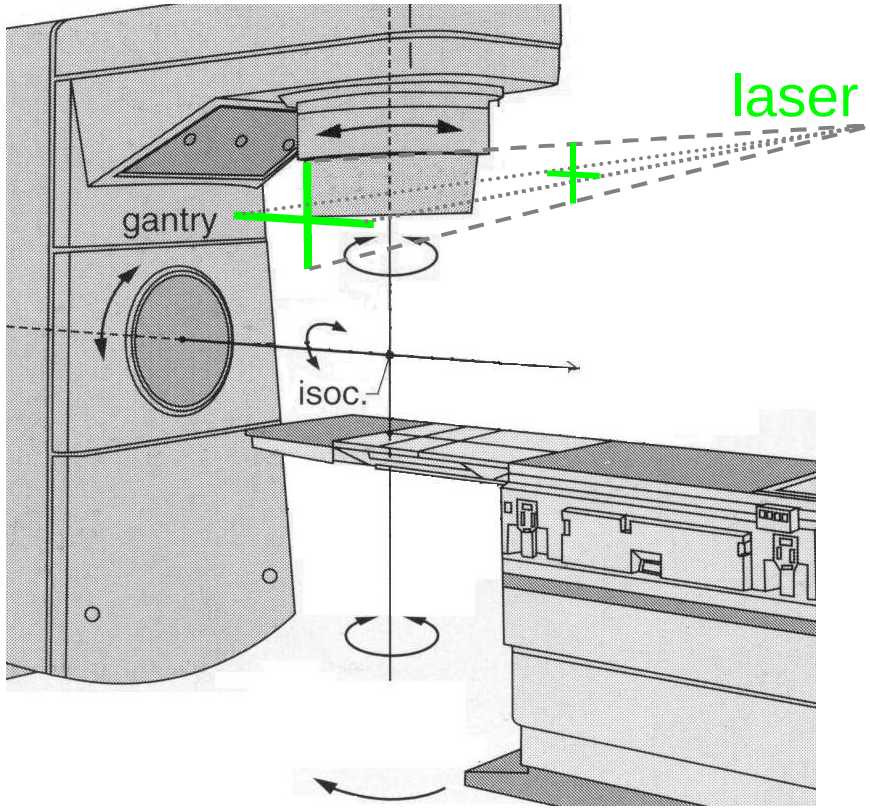
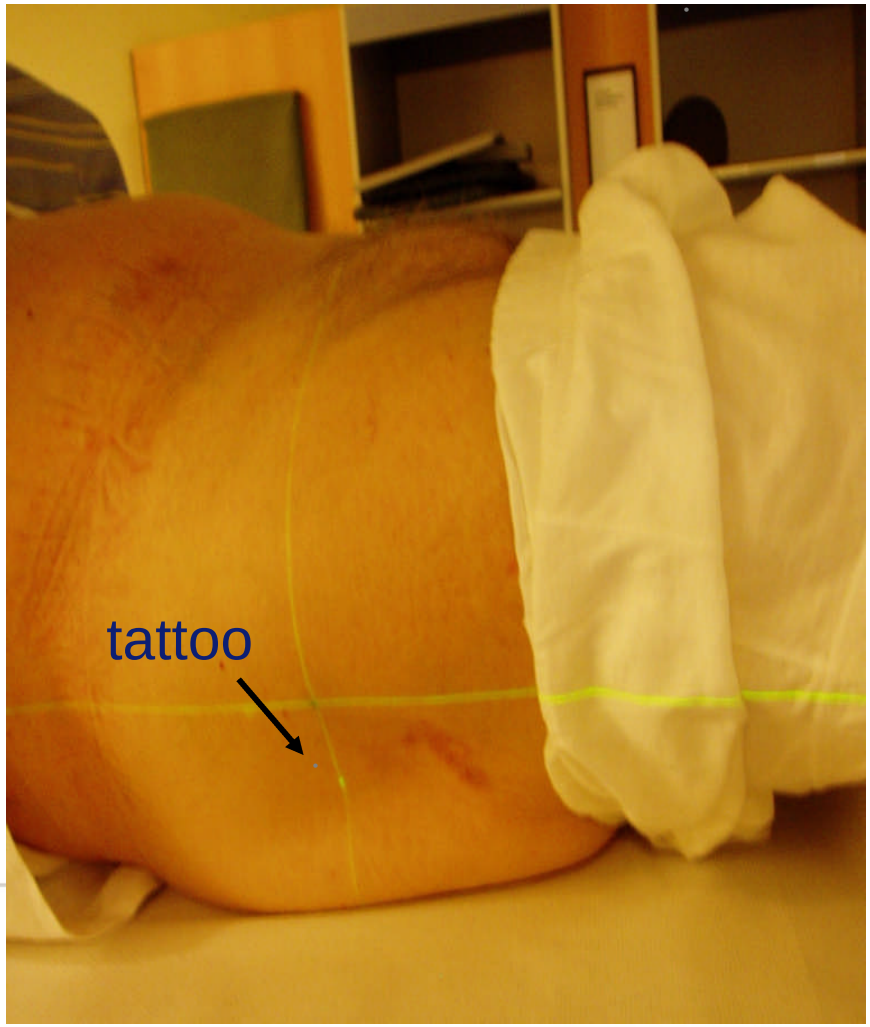
Overview: IGRT technologies

- 2D Electronic Portal Imaging (EPI)
- 2D EPI and implanted markers
- 3D/Volumetric imaging
- 4D/Tracking
- Non-ionising imaging
  - Ultrasound
  - Surface sensing
  - Implanted radio-emitters
  - MR

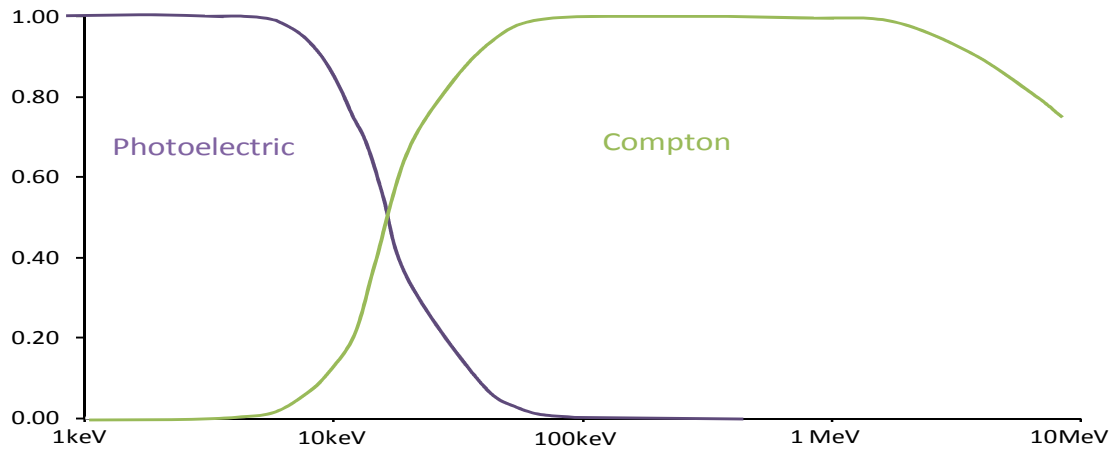
External anatomy and laser set-up



left, right and top lasers



Impact of increasing energy on interactions



- The nature of the x-ray image obtained is related to the type of interaction which occurs.
- At X-ray energies in the kilovoltage (kV) range the interaction is predominately via the **photoelectric effect.** As the X-ray energy increases to megavoltage (MV) levels the most likely interaction is via the **Compton interaction.**
- Results in poorer soft tissue contrast with MV imaging

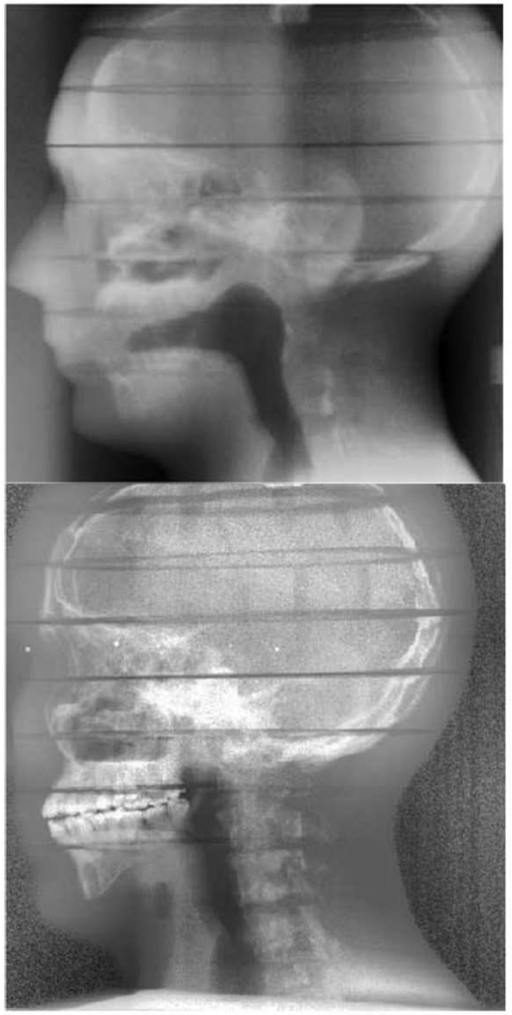
MV imaging: higher dose and less detail

Anthropomorphic head phantom imaged with

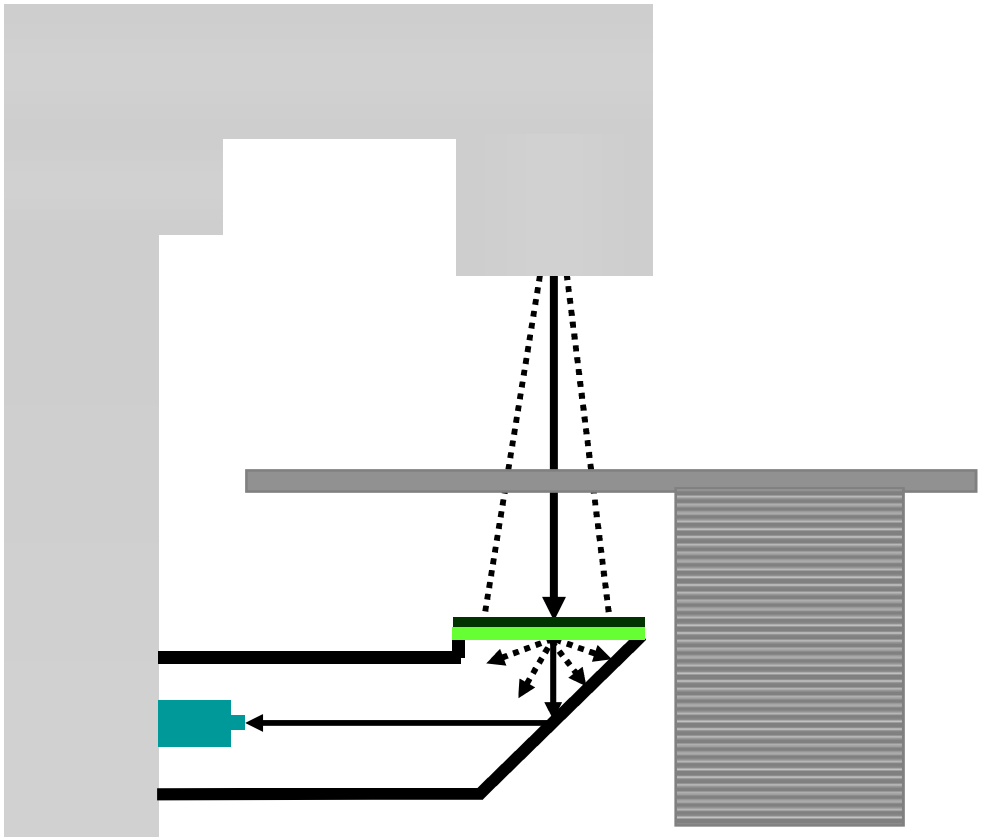
6MV X-rays
100kVp X-rays.

•The dose used for MV is approximately 3000 times higher than used for kV.

•Much greater contrast detail is observed in kV image.

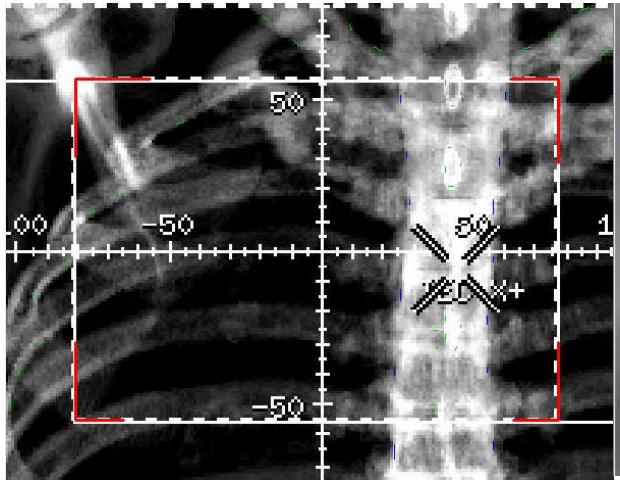


MV EPID: most systems now use aSi FPI

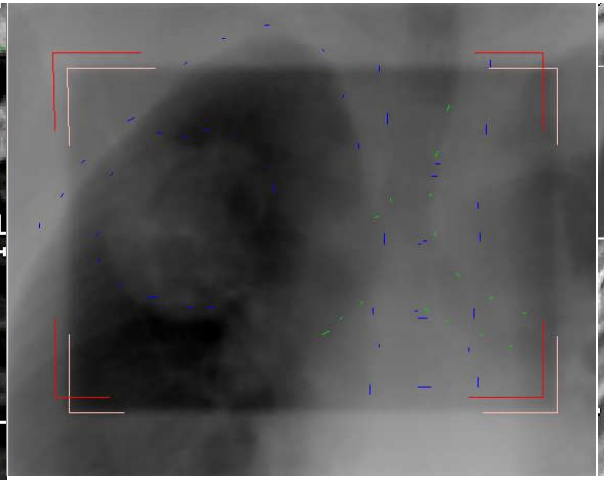


Reference imaging

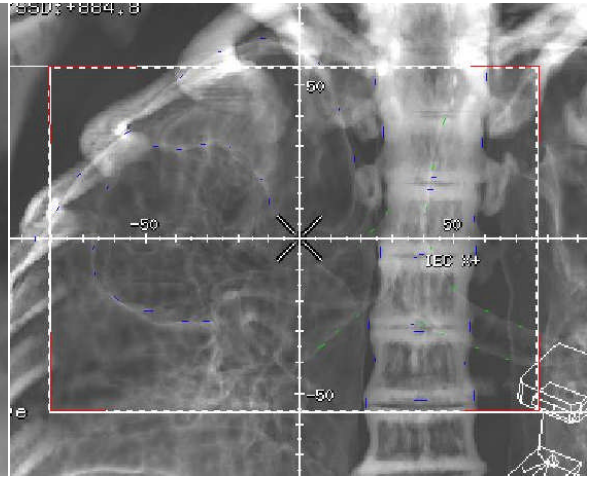
- 2D Reference Image (Digitally Reconstructed Radiograph)
- Shows the planned geometry of the treatment field placement relative to bony anatomy.
- Soft tissue anatomy can also be seen for some treatment sites.



Bony DRR



Electronic Portal Image (EPI)



Soft Tissue DRR

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2-D Verification

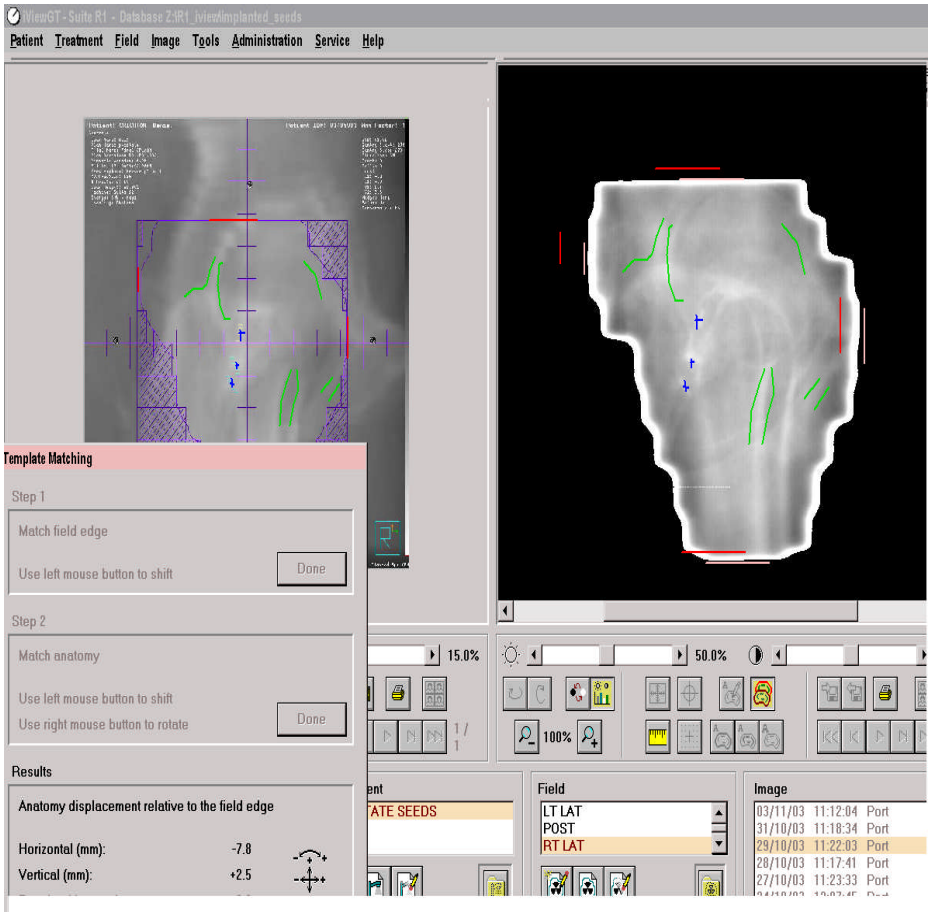
- Visualisation of bony anatomy, some soft tissue, implanted radio-opaque markers.
- Only suitable for tumours closely related to bony anatomy and/or restricted tumour movement.
- Used for
  - QA: Measurement of beam shape
  - In vivo dosimetry
- Orthogonal portal images acquired at cardinal angles allow field placement assessment in 3 directions:
  - AP for LR and SI displacement;
  - LAT for AP and SI displacement.
- It may be necessary to produce fields for imaging purposes only.

Surrogates of target position

- Used when the target object cannot be seen directly using the imaging technologies available, commonly MV portal imaging or kV planar imaging.
- Implanted markers in, or close, to the structure of interest may be used as surrogates.
- **Surgical clips** may be placed in the tumour cavity of a breast patient at the time of surgery.
- **Gold markers** are used in prostate patients with EPI or CBCT.
- The BrainLab and Cyberknife systems use **implanted markers** to track tumour movement.
- Small **wireless transmitters** have been used in both prostate and lung.

Prostate markers

- Widely used, 3-4 inserted trans-rectally or trans-perineally
- Allows correction for prostate organ motion using 2D equipment available in all centres
- Markers need to have high specific gravity e.g. Au or Pt if used with MV rather than kV imaging
- Automated detection software available



2D orthogonal images gives 3D position

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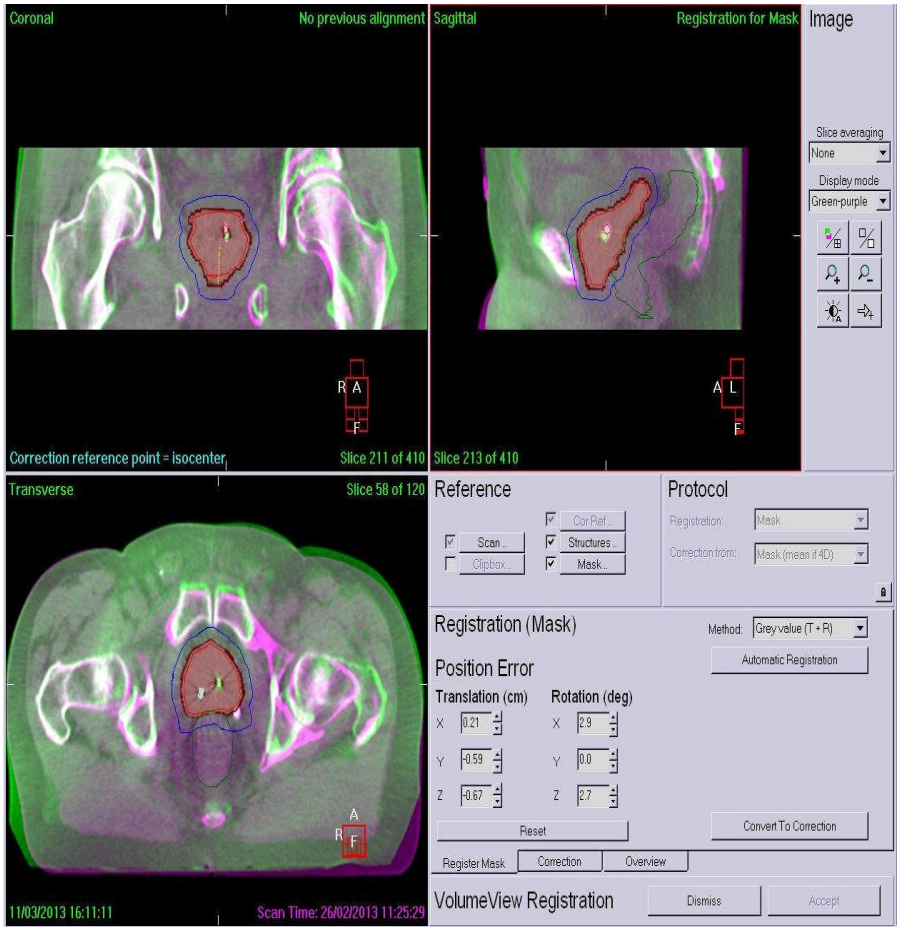


Limitations of 2D Verification

- Measurement of set-up errors is subjective depending on the quality of the reference compared with the portal image.
- Without markers, only bony anatomy is available as a surrogate for the tumour or target volume.
- Awareness of tumour motion, changes in target volume, proximity of surrounding OARs to the high-dose region, and the impact of patient weight-loss is very limited.
- Portal images are often restricted by treatment field orientation. The alternative is the labour-intensive production of imaging-only fields.

3-D / 4-D IGRT

- Preferred for tumours close to organs at risk
- Mobile tumours (4th dimension is time) e.g. lung, lower oesophagus, liver
- Valuable for target volumes prone to changes in size and shape e.g. bladder, prostate, lung
- Essential for soft tissue tumours surrounded by soft tissue e.g. pancreas
- Essential for extra-cranial stereotactic XRT
- May enable reduction in planning margins which may improve treatment outcome and prognosis.

3D Volumetric imaging

Available equipment includes:

kV fan beam CT

- Siemens CTVision

kV cone beam CT

- Elekta Synergy™, Varian OBI™

MV cone beam CT

- Varian Halycon™

MV fan beam CT

- TomoTherapy

(In-room) kV Fan Beam CT

Siemens
CTVision

Advantages

Diagnostic image quality

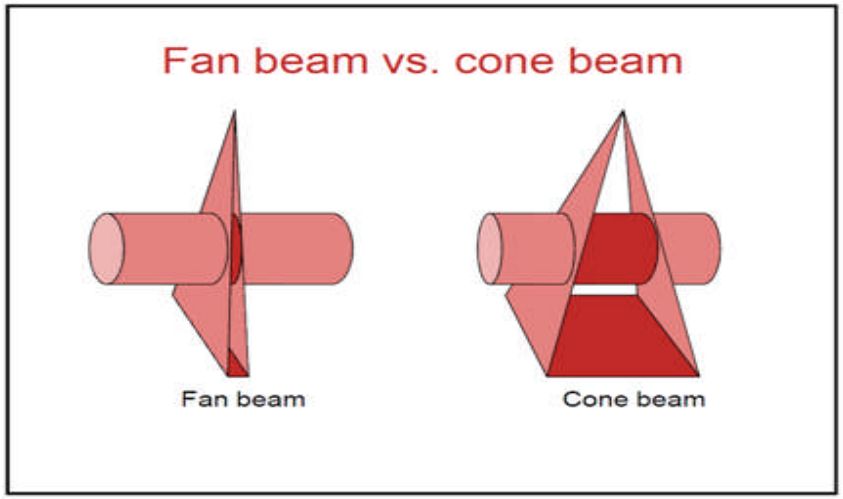
Limitations

Patient moved between imaging and treatment

Interference between slice based imaging and patient movement

Artefacts from high density objects

Needs larger room size



Conventional CT:

‘Fan beam’ highly collimated

Multiple gantry rotations. Most now multi-slice resulting in broadening of fan beam approaching a cone beam

Cone Beam CT:

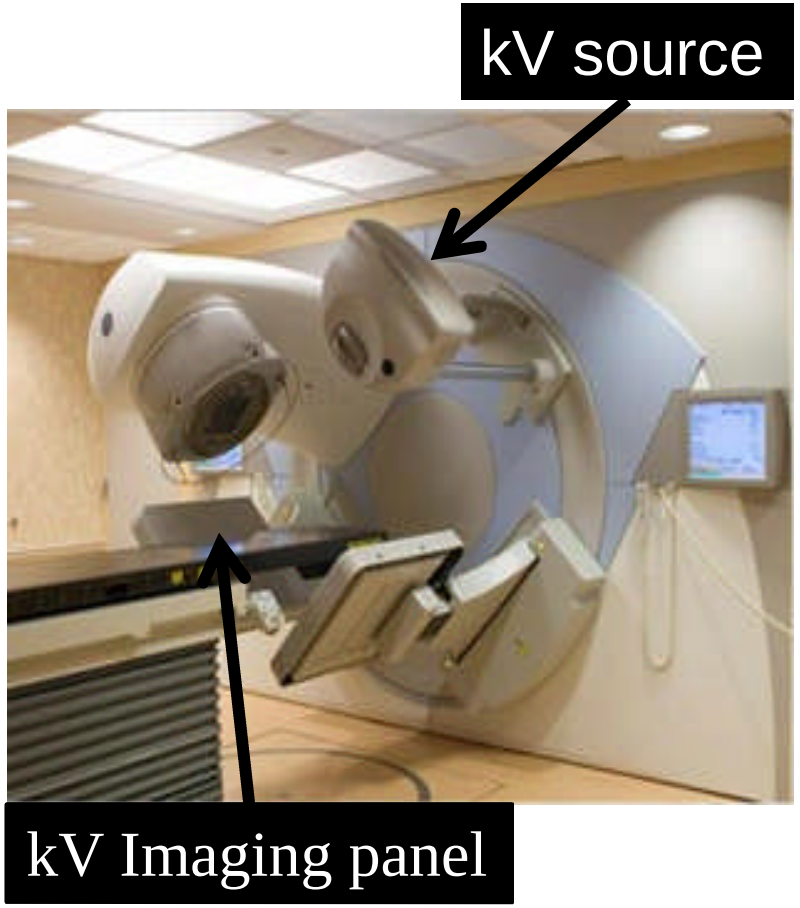
Single gantry rotation with 2D rows/planar detectors

‘cone beam’ poorly collimated with scattered photons results in reduced image quality

Also available with 4D mode

kV cone beam CT

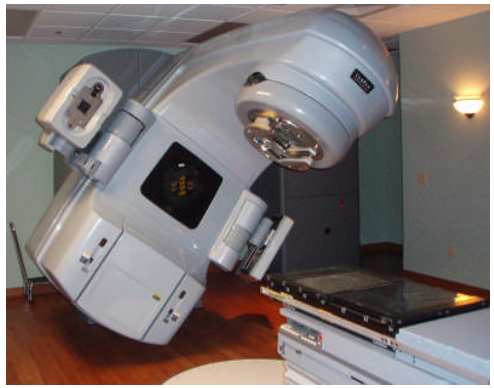
- kV imager and panel at 90º to the linac head
- 3D volumetric kV cone beam image can be acquired and compared to planning CT data
- Also provides MV EPI, static kV imaging and movies
- 4D kV cone beam CT
- Acquisition of kV images during treatment delivery available



kV Cone Beam CT

Elekta XVI

Varian OBI

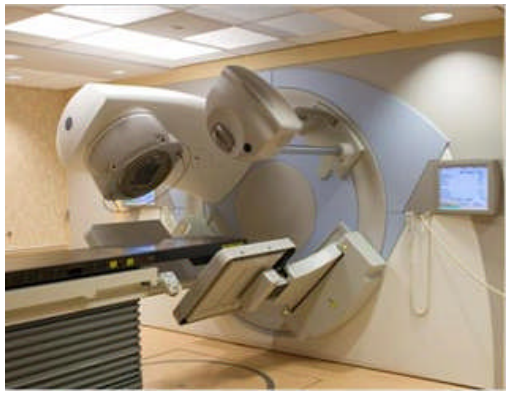


Advantages

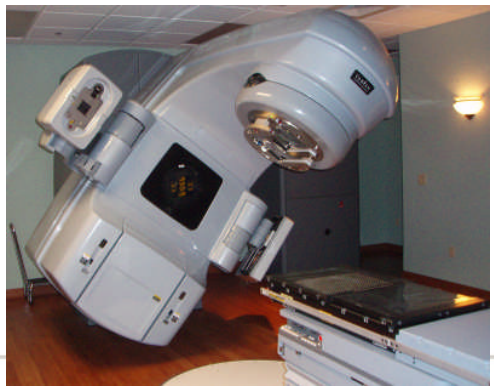
- kV imaging (better contrast at lower dose)
- Patient in treatment position
- kV and MV systems mechanically integrated
- Radiographic/Fluoroscopic modes
- More control over imaging parameters with a range of voltage and current settings to choose from

kV Cone Beam CT

Elekta XVI



Varian OBI

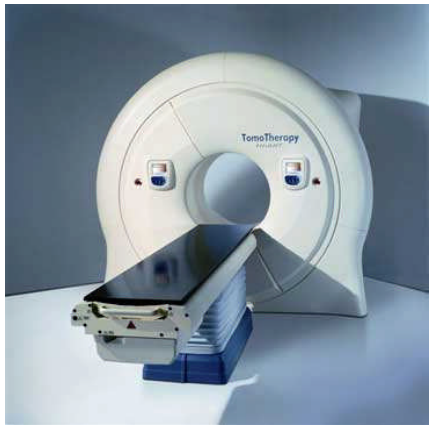


Limitations

- Cone beam scatter
  - Reduced contrast
  - Reduced HU number accuracy
- Artefacts from high density objects
- Slow image acquisition
  - Artefacts from moving objects
- Artefacts from flat-panel

MV Fan Beam CT

Tomotherapy

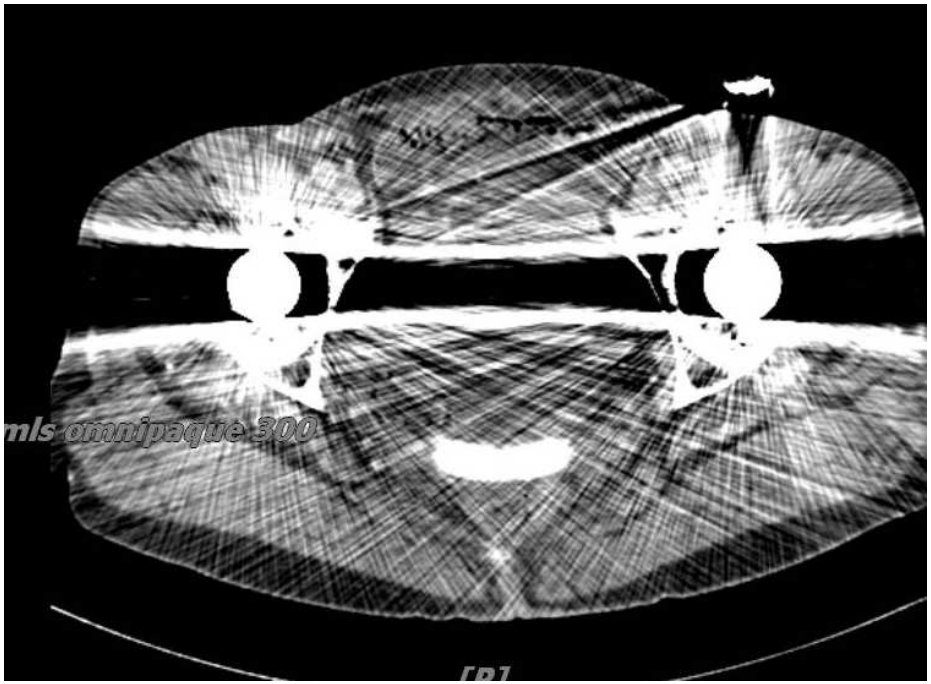


- MV treatment beam used (reduced to 3.5MV for CT acquisition)
- Slice thickness of 2,4 and 6mm
- Fan beam with co-incident treatment and imaging iso-centres
- No artefact from high density objects e.g. hip prosthesis

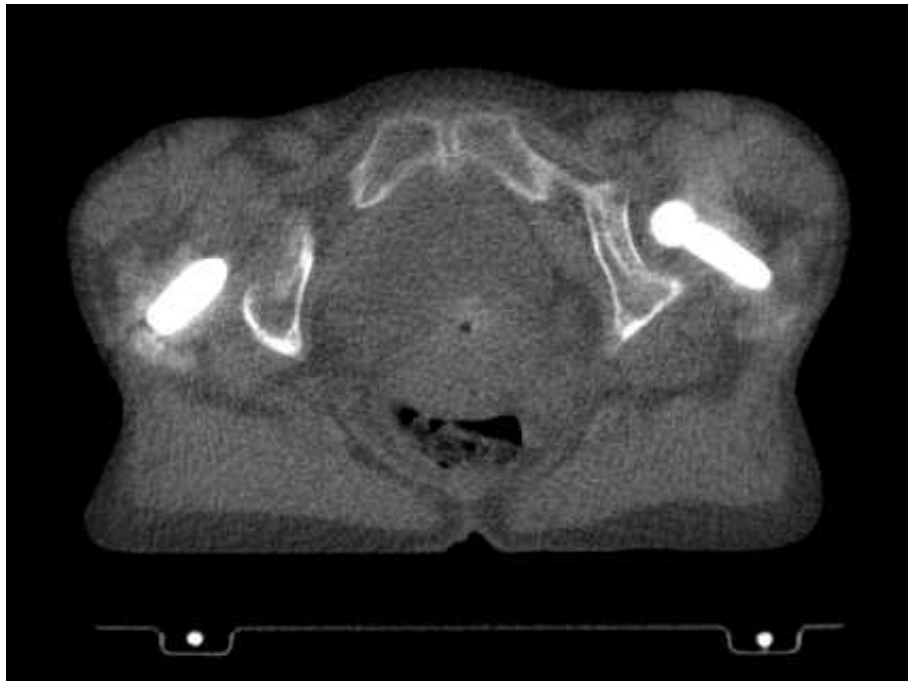
Limitations

- MV contrast
- Slow image acquisition (5s per slice)
- Image quality vs. dose? (1-3cGy)
- Longitudinal artefacts from resp motion

Bilateral hips

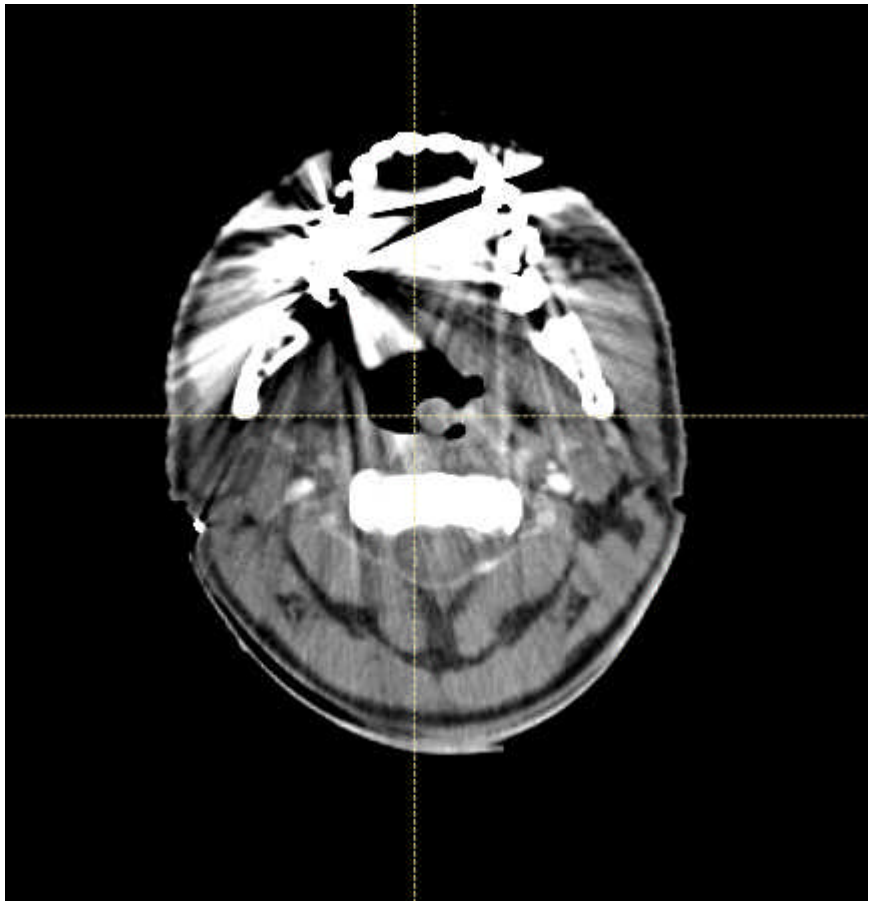


kVCT image

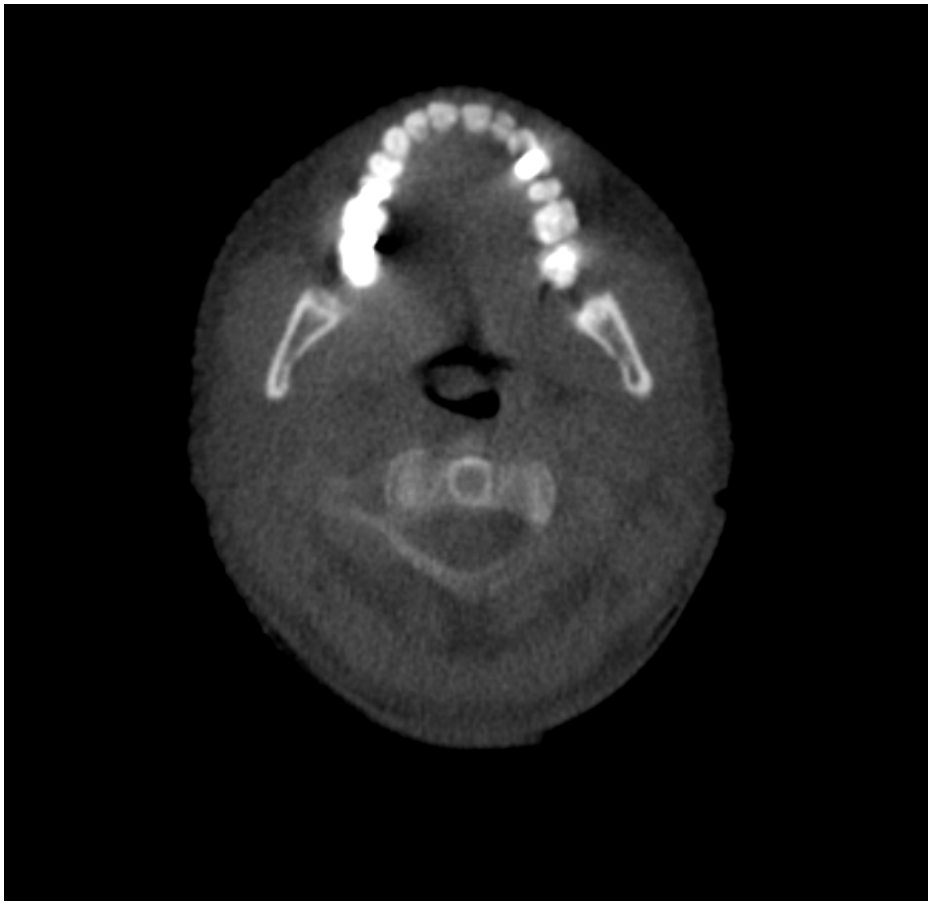


MVCT image

Dental amalgam artefacts

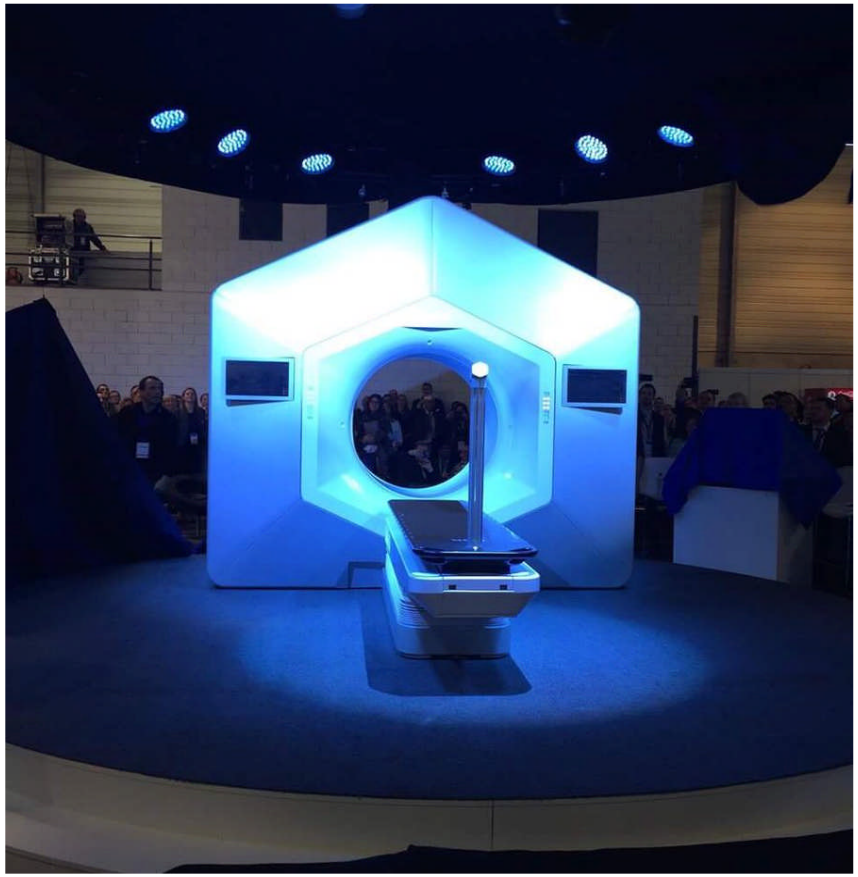


kVCT image



MVCT image

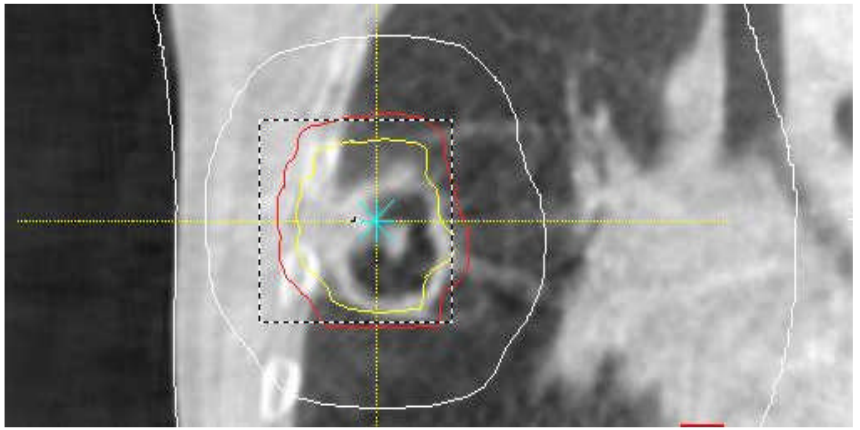
Varian Halycon™

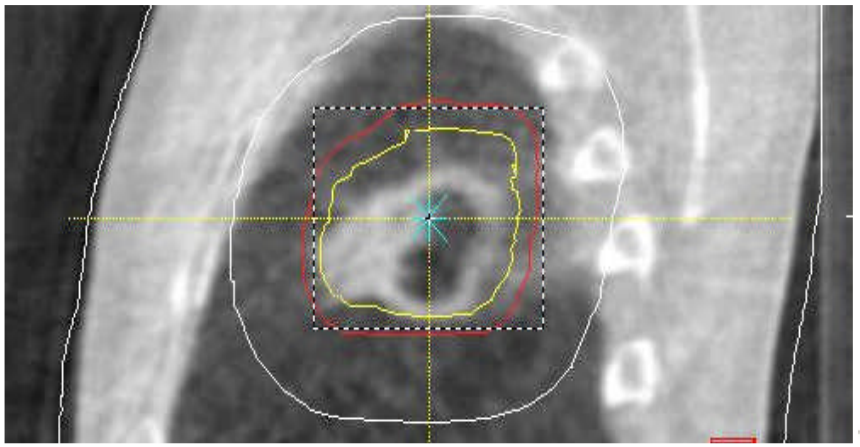


- Launched ESTRO 2017
- Uses ring technology rather than C-arm
- Reported:
- MV volumetric images in approx 15s
- Wider 100cm bore
- Delivered pre-commissioned with less shielding requirements

Clinical example: Stereotactic lung

- 3D imaging essential
- kV cone beam CT acquired on-line and correction applied
- Imaging after any correction, during treatment and at end





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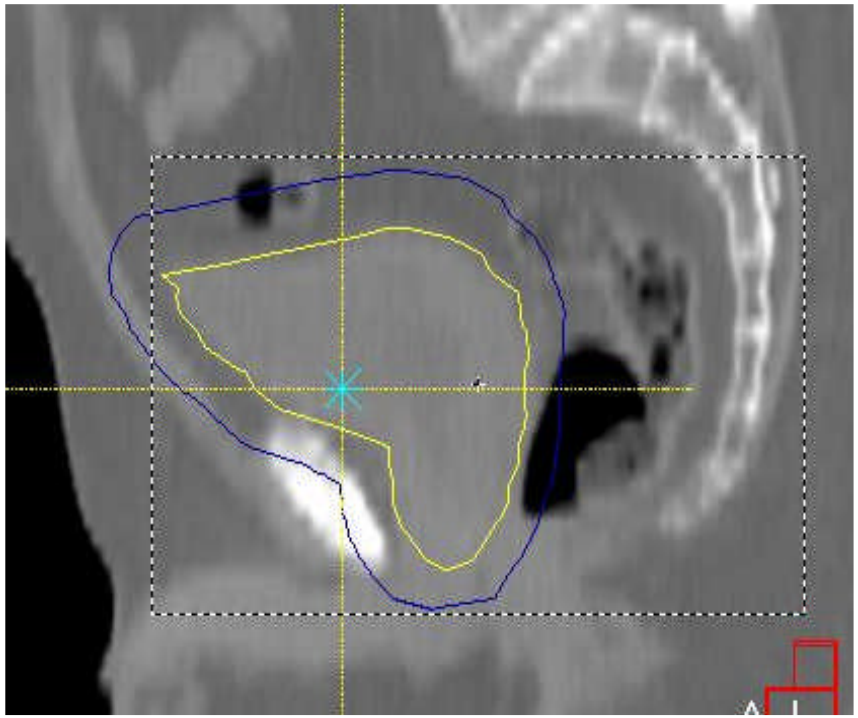
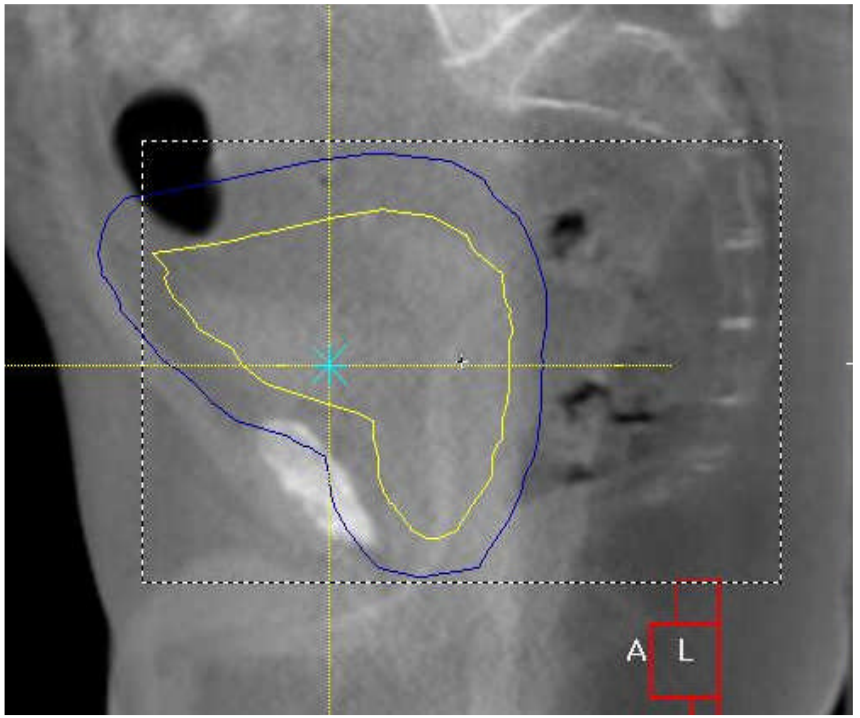
Clinical example: Bladder XRT



Sagital planning CT image with bladder (yellow) and PTV (blue)



On-treatment kV cone beam scan after patient catheterised: Bladder now smaller and needs re-plan

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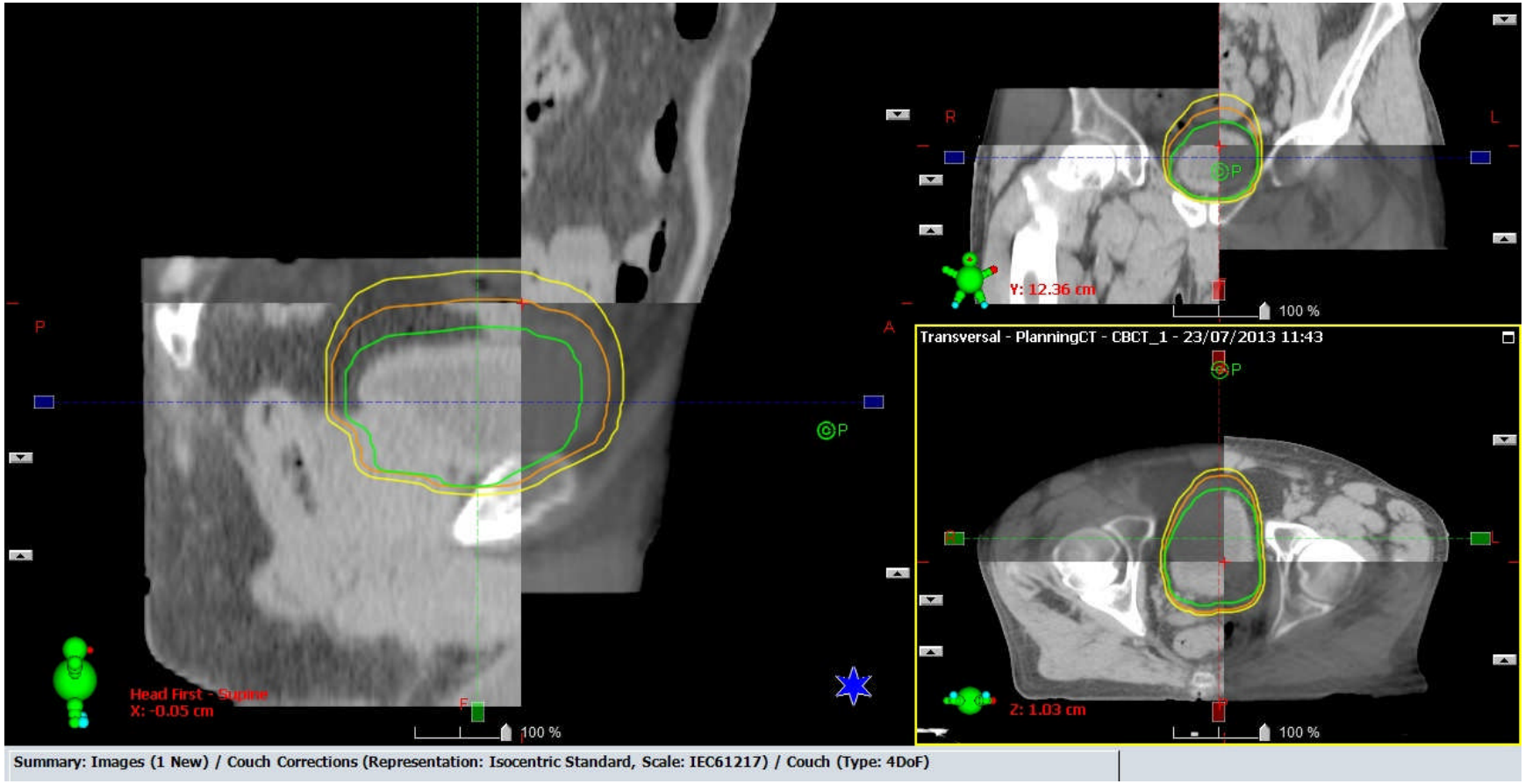
Complex IGRT: Plan of the day for bladder RT



Library of plans (small, medium and large) available and best fitting plan chosen at each treatment

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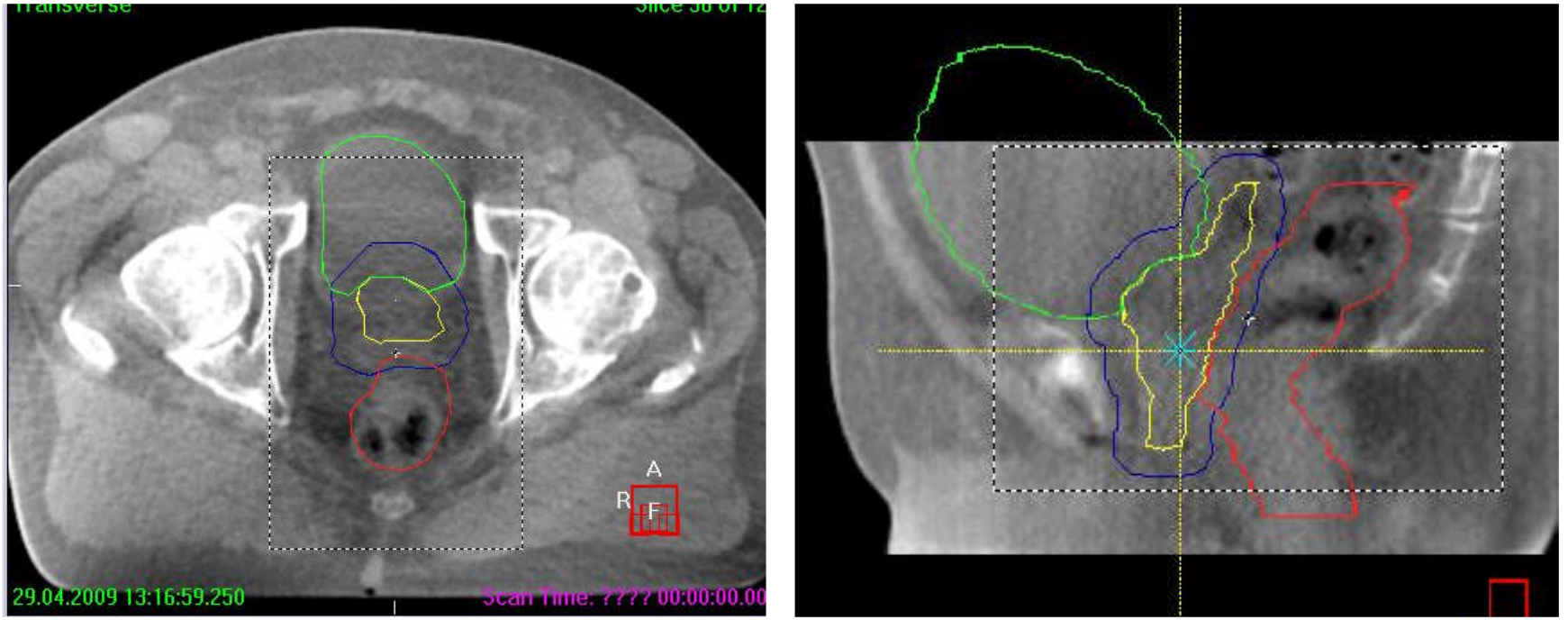
Clinical example: Prostate XRT



Transverse and Sagital kV cone beam CT images with bladder (green), prostate (yellow), PTV (blue) and rectal contours (red) superimposed. Can be difficult to identify edge of prostate but rectal-prostate interface is easily seen

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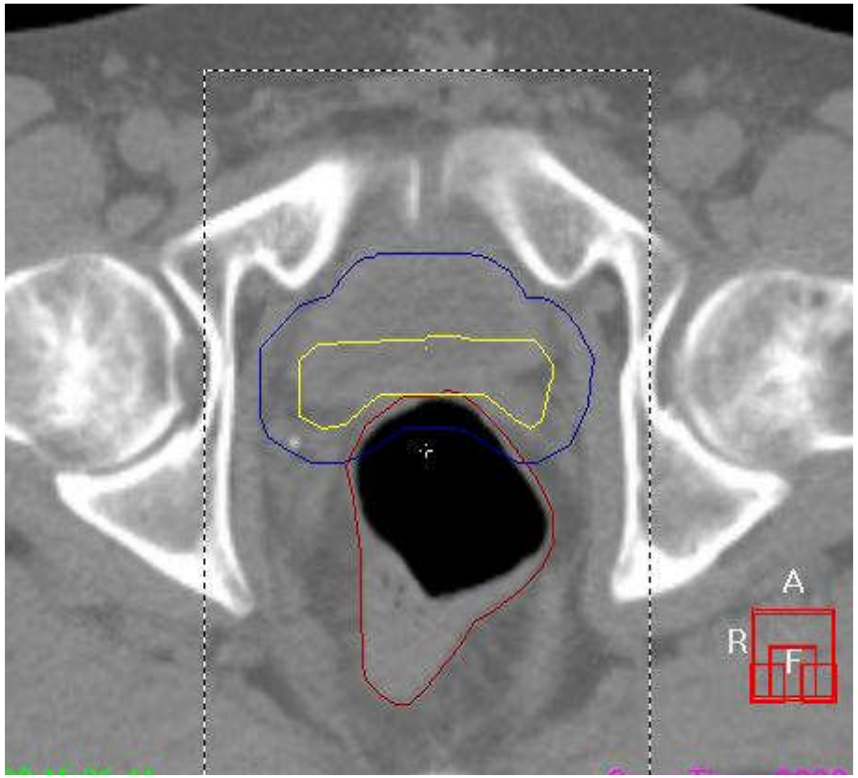
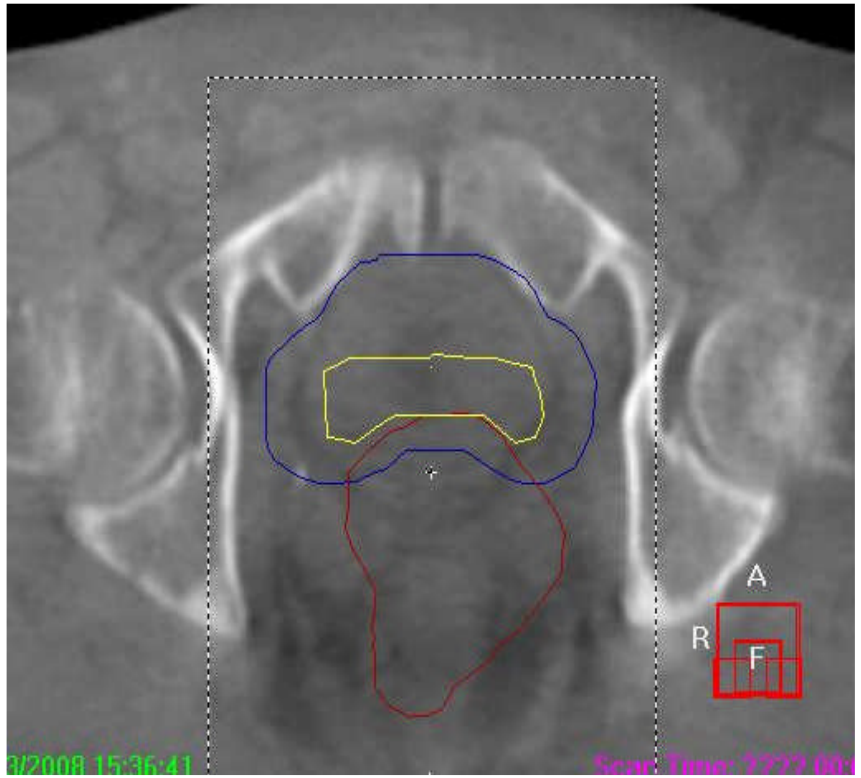
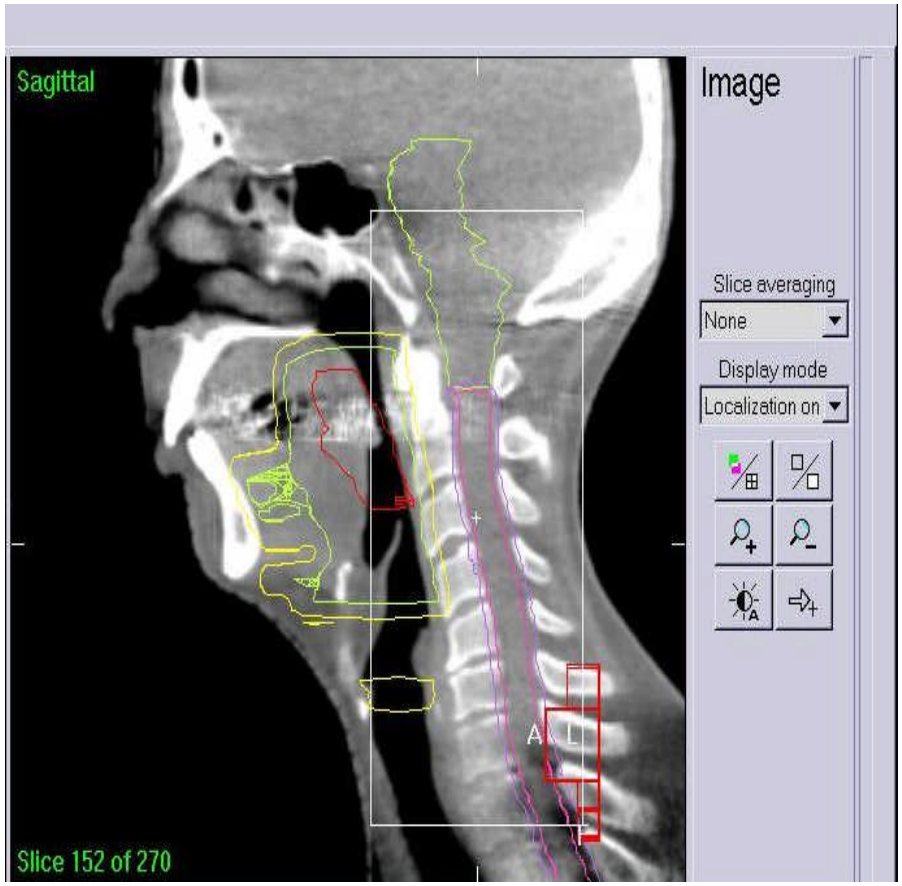
Prostate XRT: First image is planning scan and the second kV CBCT demonstrating the rectum has decreased in size and seminal vesicles now moved out of PTV





Head and neck

- kV CBCT image of a patient undergoing IMRT for cancer of the tonsil.
- A clipbox can be used to localise the volume to be matched.
- The rectangular clipbox here is used to match with the main OAR, the spinal cord rather than tumour.



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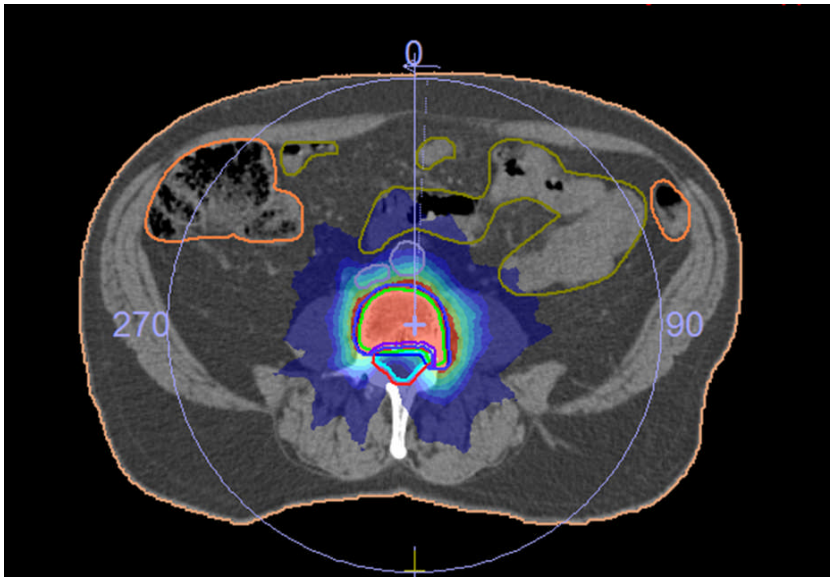
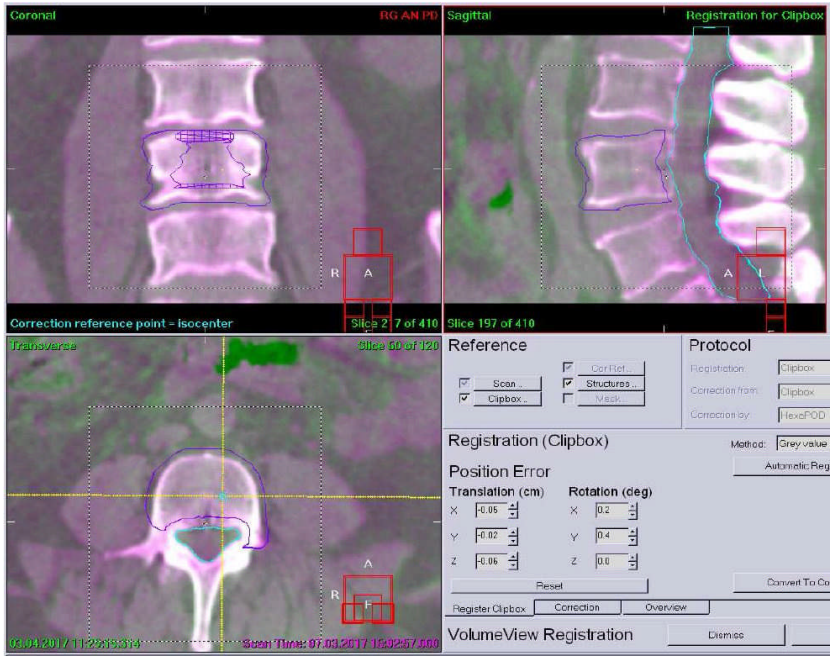
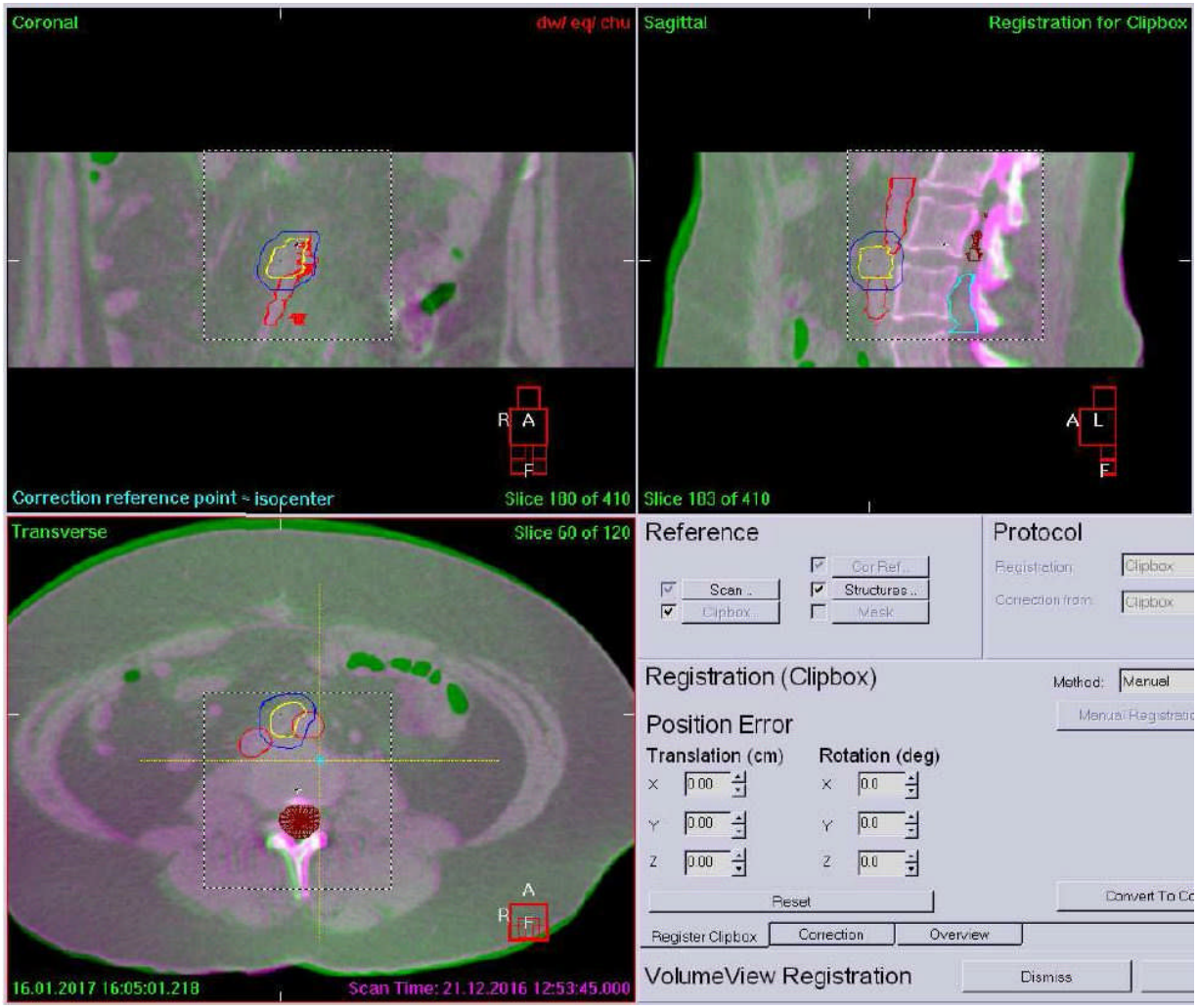
kV CBCT IGRT for spinal SABR





kV CBCT IGRT for abdominal node SABR



4D-CBCT

Max Expiration

Max Inspiration

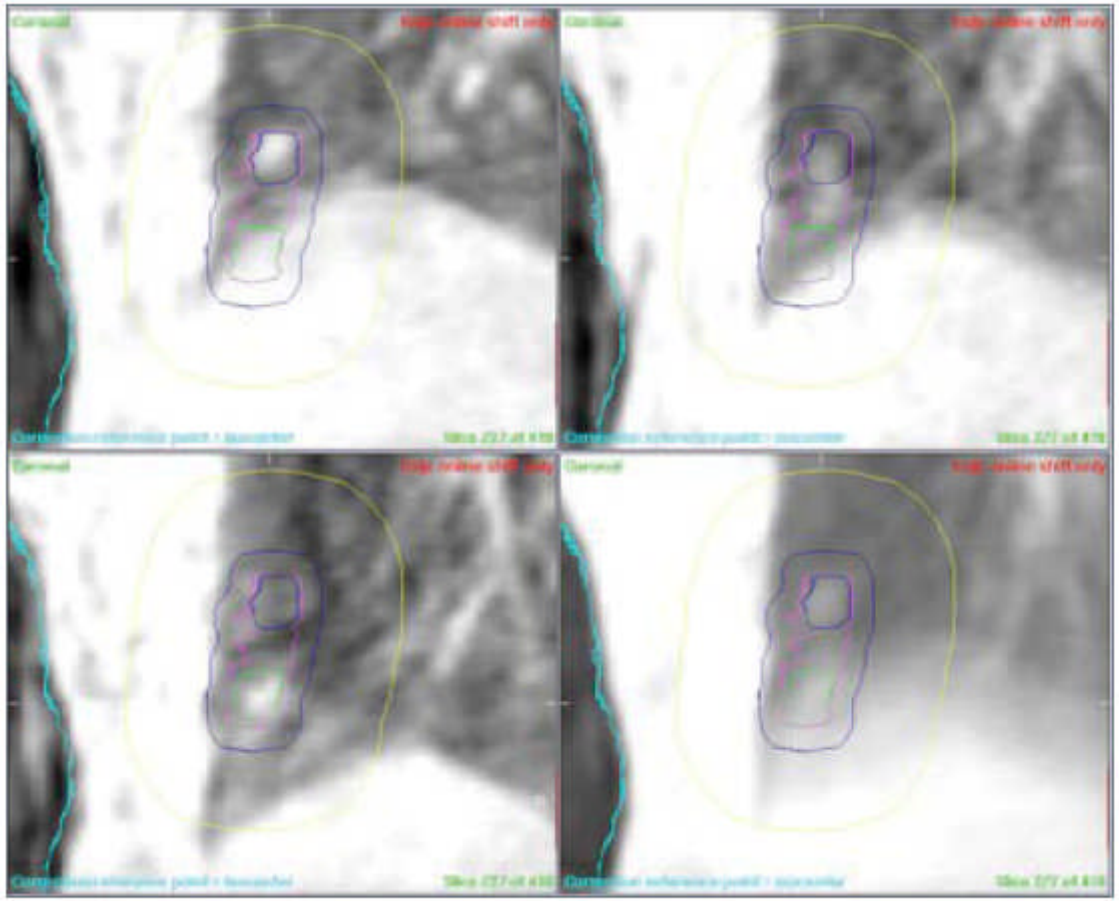


Figure 4. Coronal views of 4D-XVI (Top left = max expiration, top right = 40% expiration, bottom left = max inspiration and bottom right = average of all phases). The respective GTV's (blue and green), ITV (pink), and PTV (blue) are shown.

Mid-ventila

Average of all phases. Equivalent to 3D-CCT

4D CyberKnife image guidance

X-ray images are compared with DRRs

Robot can correct:

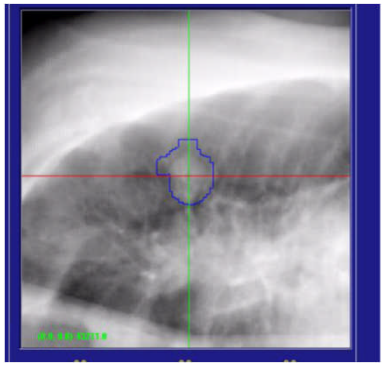
- ± 10 mm
- ± 1° roll
- ± 1° pitch
- ± 3° yaw

Robot corrects after each stereographic X-ray image acquisition during treatment

Cyberknife features

Tumour motion management with on-going imaging and automated corrections during treatment

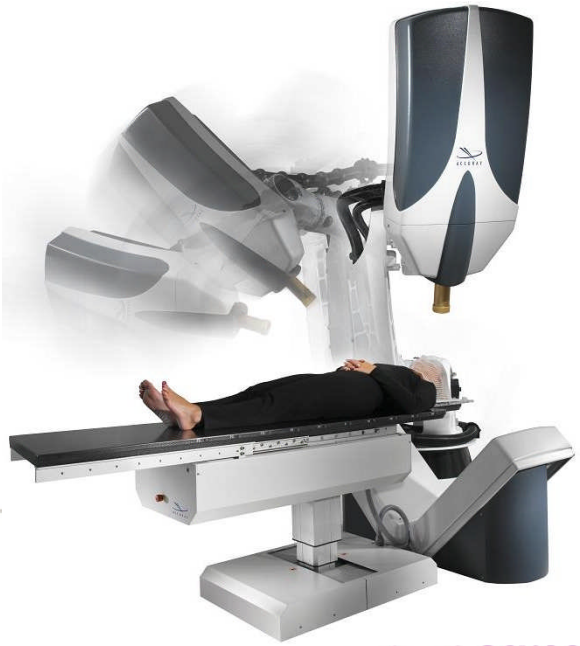
- Skull tracking
- Implanted fiducials
- external-internal markers for compensation of respiratory motion



Non-coplanar beam set-ups

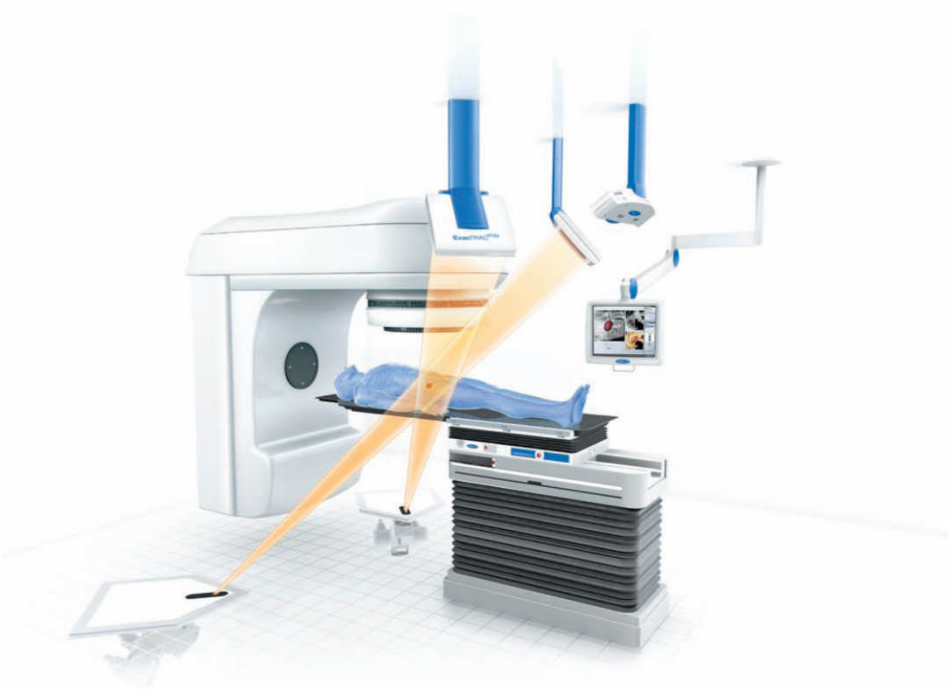
Clinical focus:

Hypofractionation- Lung, Para spinal, prostate

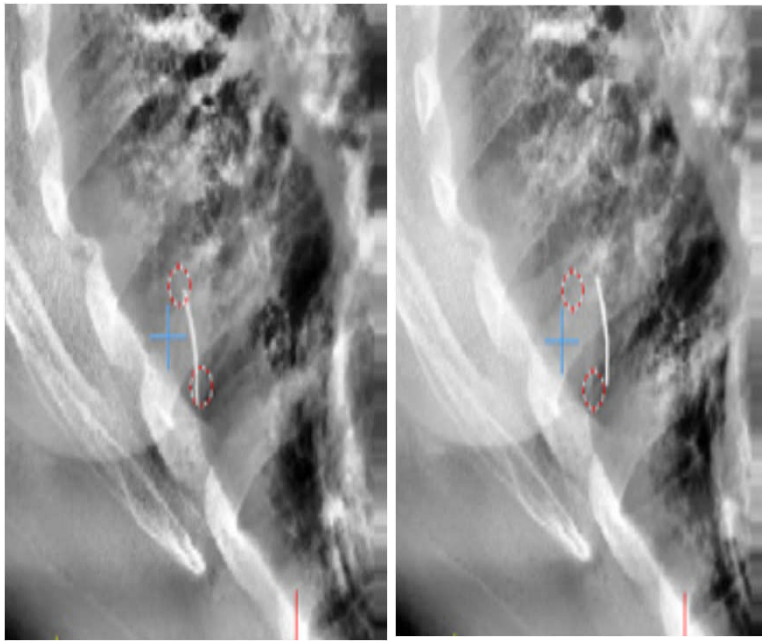


ExacTrac™ (BrainLAB)

- 2 kV imagers recessed in floor
- 2 ceiling mounted aSi FPI
- Allows tracking of bone and markers
- Respiratory gating



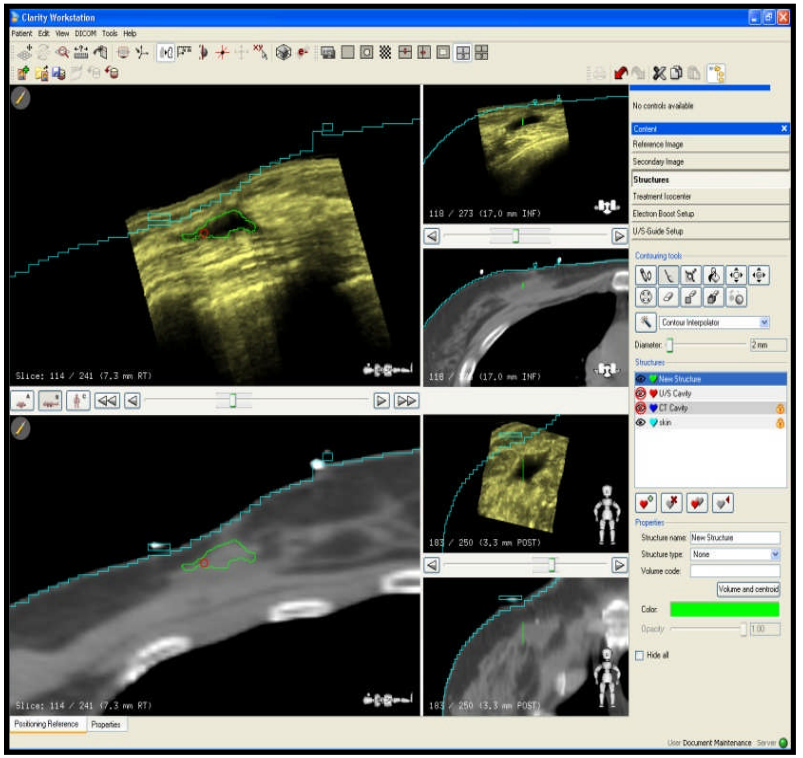
- Fluoroscopic images showing a lung fiducial marker indicating the position of a lung tumour .
- In the second image the marker has moved away from the reference position.



Images from www.brainlab.com

Ultrasound (US) 2D and 3D imaging

- Mobile cart that can be moved between simulator and linac
- Ceiling mounted scanners to localise 3D position
- Can use both CT and US to identify target
- Breast boost example



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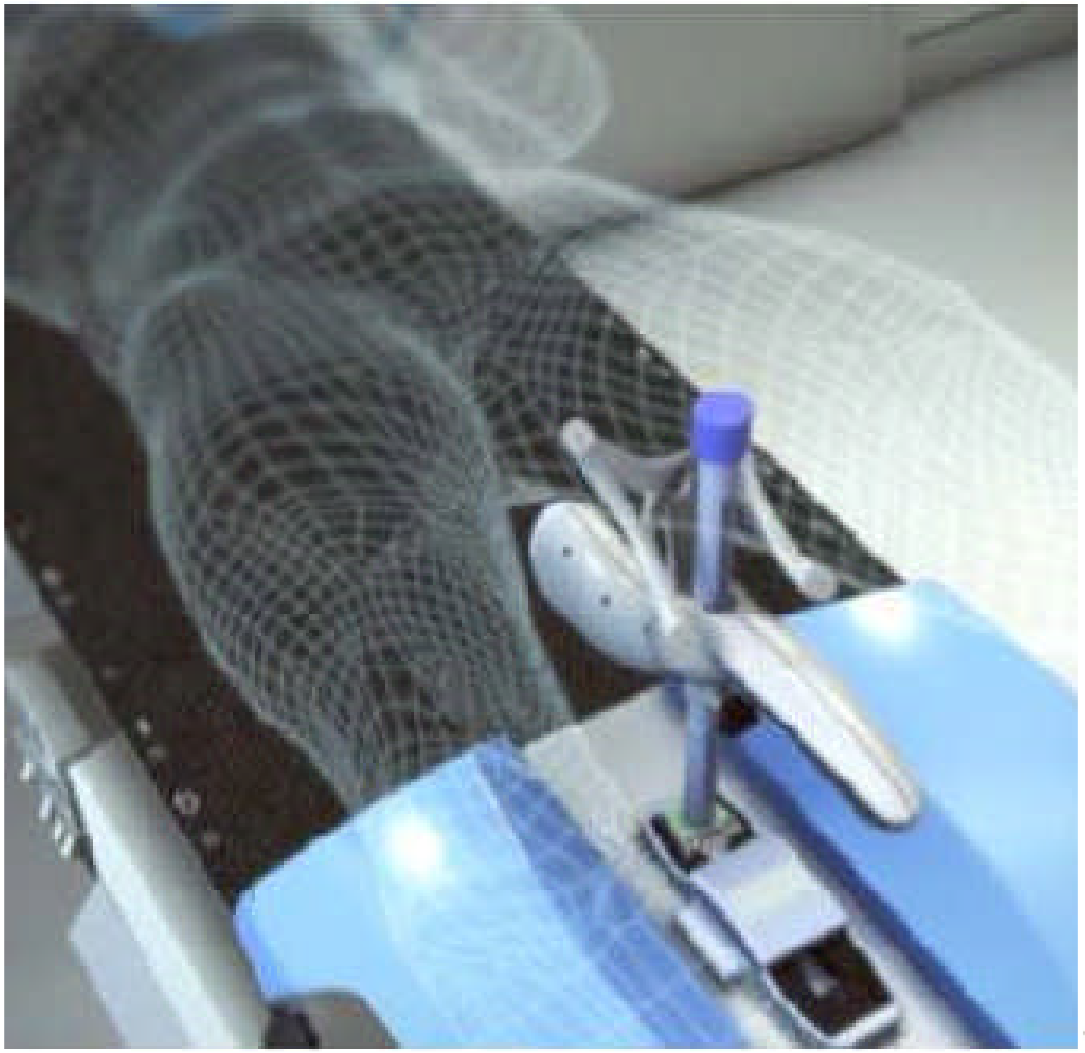
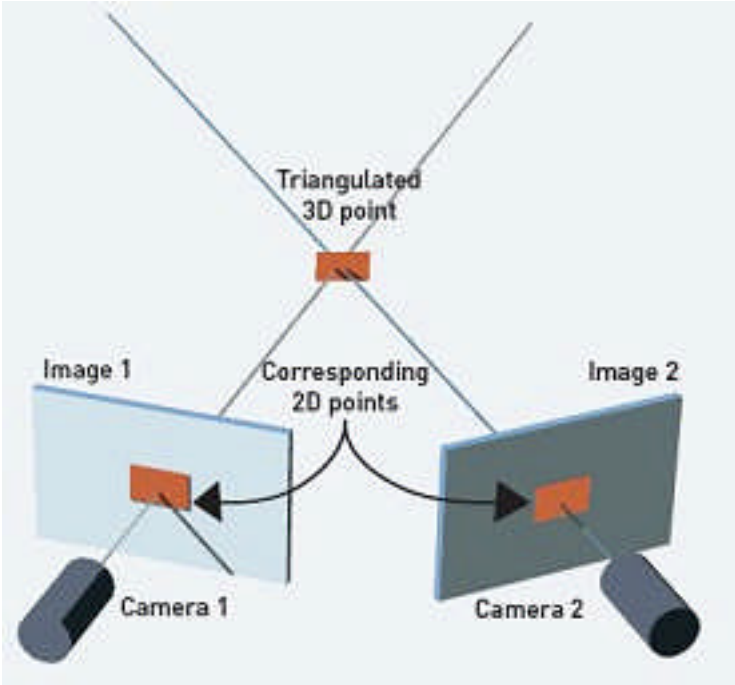
Clarity system

- Used transperineally for prostate
- Can both CT and US to ID target volume at planning
- Check and correct for inter-fraction motion
- Monitor intra-fraction motion with alert thresholds



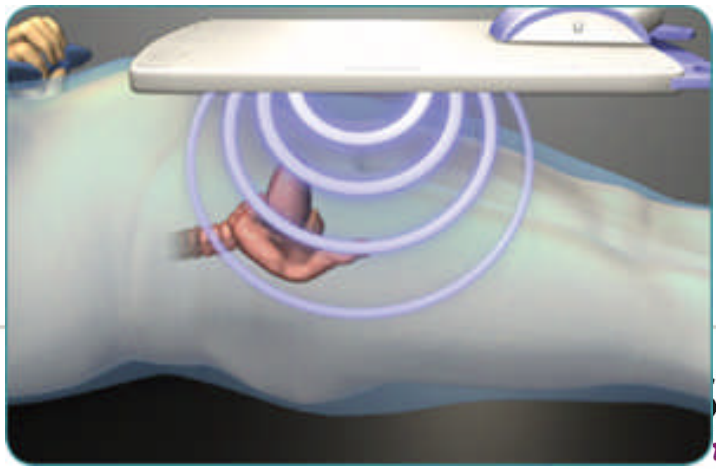
Surface sensing/optical tracking

- Skin surface monitored in real-time
- Infrared-reflecting markers or patterned light viewed using stereoscopic cameras calibrated to isocentre
- Movements exceeding tolerance can led to intervention
- Advantages: non-invasive with no additional radiation



Implanted radio-emitters

- Calypso system
- 3 EM transponders inserted into prostate
- Monitored continuously
- Can check whether gland moves out of pre-defined tolerance



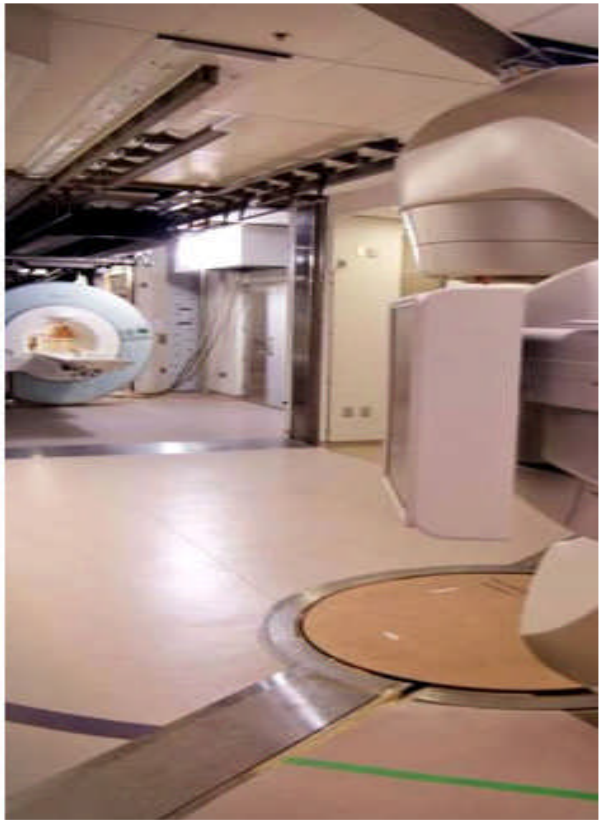
Incorporating in-room MR

- Many sites soft tissue contrast not optimal with CT

- Interest in MR
  - High soft tissue contrast
  - Imaging could be repeated during XRT
  - Functional imaging/early response assessment

- Challenges
  - Primary photon beam not affected by field but secondary electrons experience Lorentz force
  - Field also affects dose response of ionisation chambers
  - Geometric accuracy would need to be sub-mm

Work around solution: MR on rails

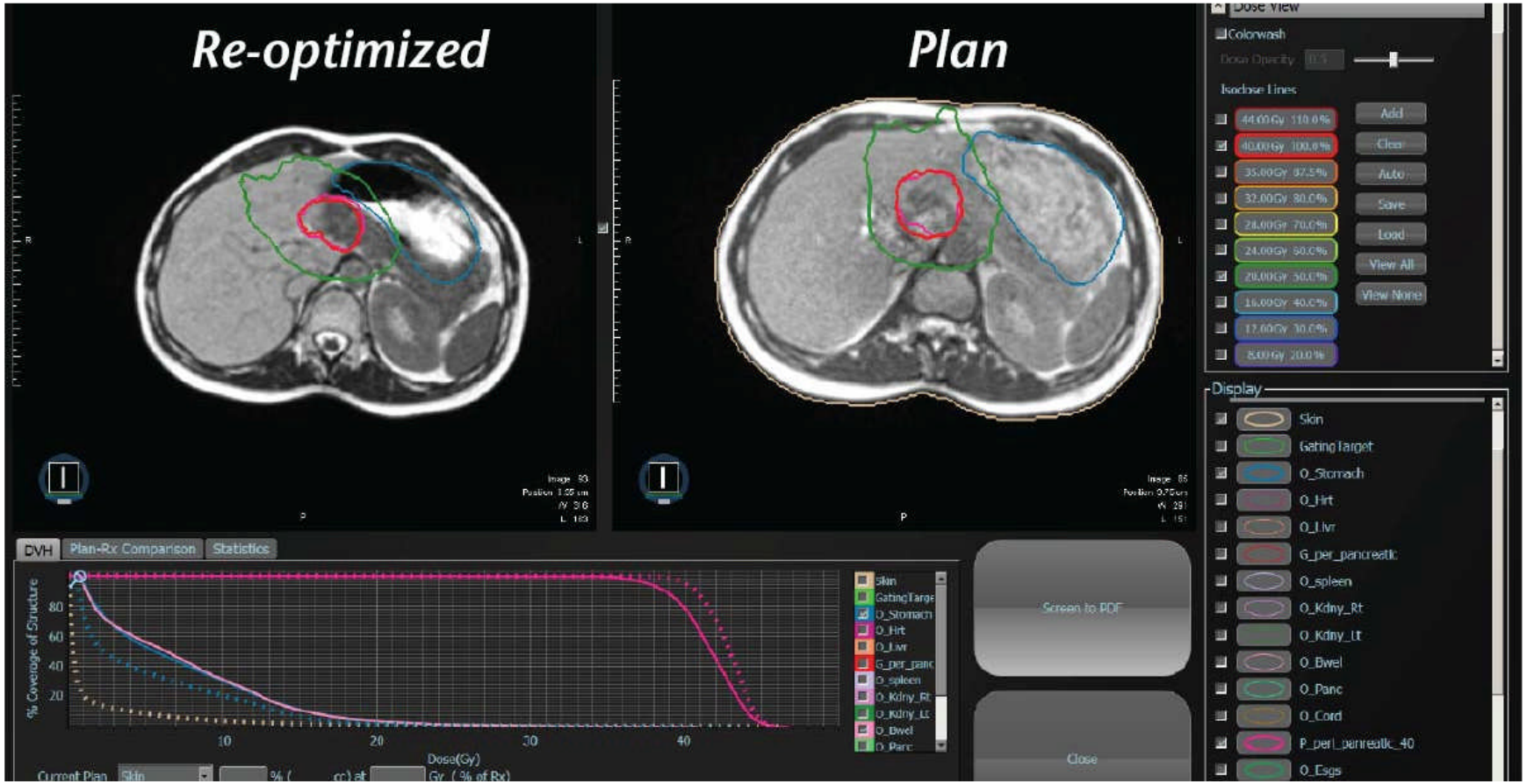


- MRgRT
- Varian and PMH Toronto
- Ceiling mounted 1.5T MR on rails
- Moves between linac and HDR brachytherapy suite

Work around solutions: Viewray MRIdian™

- 0.35T split magnet MR
- 3 Co-60 heads with fully divergent MLCs (minimises penumbra)
- Large imaging FOV and treatment volume
- Conformal RT and IMRT
- Tumor tracking
- Integrated planning system
  - Only MC dose calculations
  - Fast optimization and calculation (9field plan approx. 90s)
- Clinical focus in hypofractionated RT
- Linac version available shortly

ViewRay MR images



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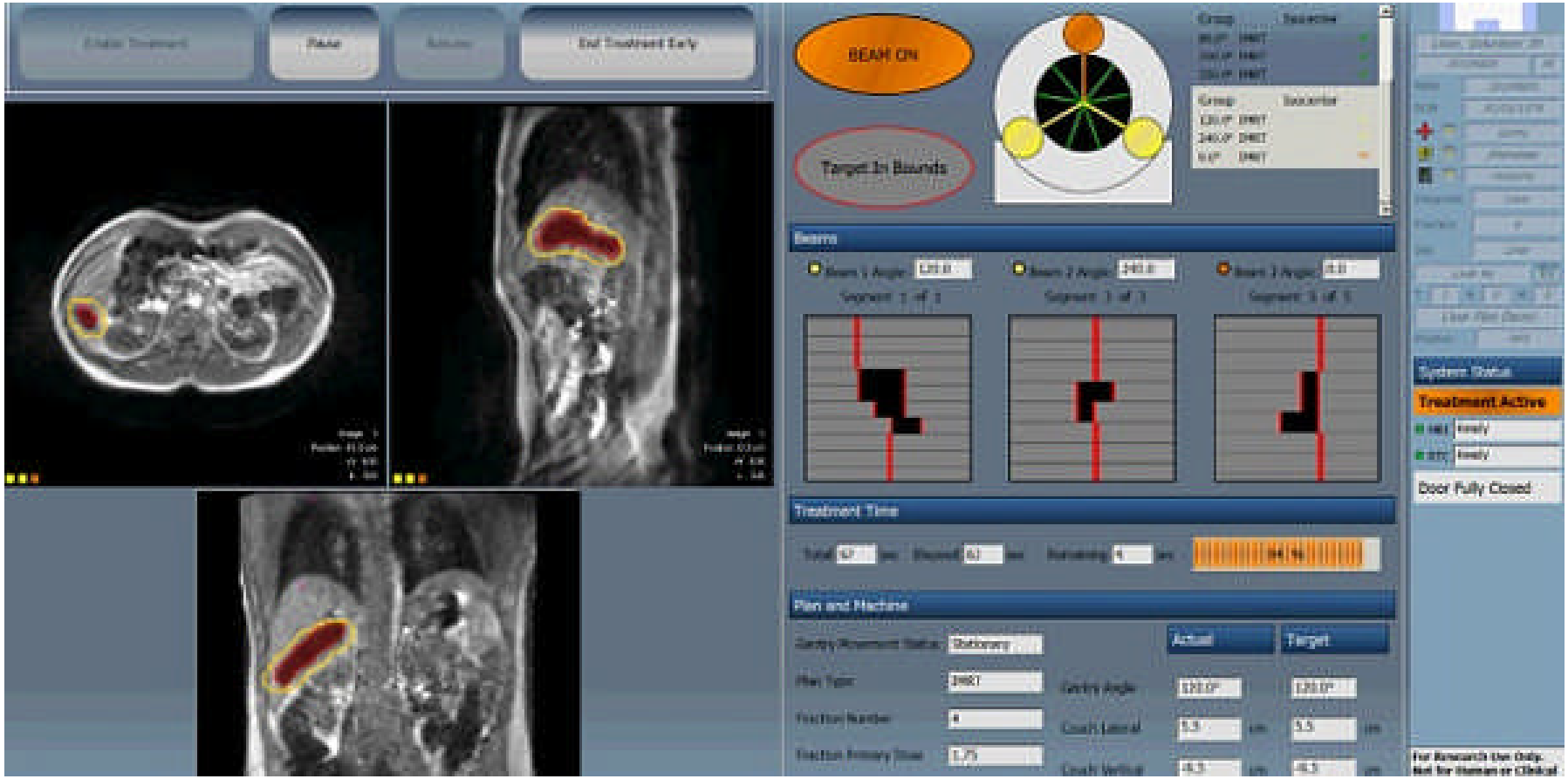
ViewRay system



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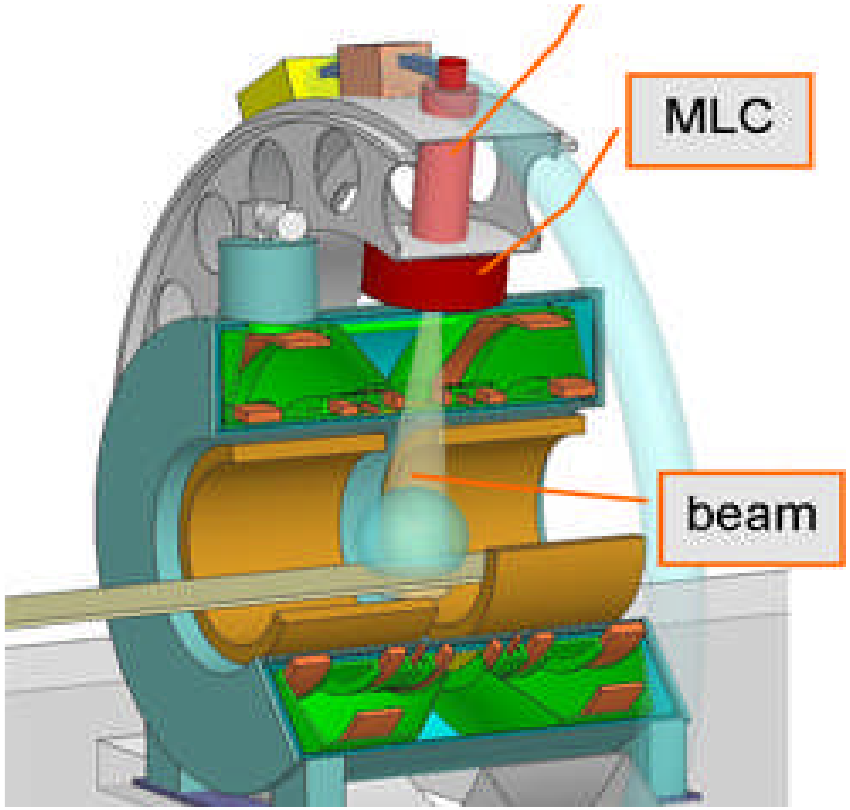
Elekta MR linac development



- Elekta / Phillips collaboration with UMC Utrecht
- Elekta Unity (MR/RT)
- 1.5 T MRI combined with 6MV linac in ring gantry design
- Inter and intra-fraction MR imaging would be available
- Installations underway and CE mark later in 2017

Conclusions

- A range of IGRT equipment and techniques are available however, the choice of which to use is dependent on the frequency of imaging and the type of motion which is to be measured.
- Superior image quality and greater soft tissue information can be obtained by using 3D imaging and kV x-ray.
- kV x-ray imaging, ultrasound, optical and electromagnetic marker systems can be used to measure intra-fraction motion.
- Optical techniques assume a correlation between external features and internal organ motion.
- Increasing number of solutions aiming to use in-room MR

PTV margin calculation

Ben Heijmen

Erasmus MC
University Medical Center Rotterdam

Physics for Modern Radiotherapy
Bucharest, 2017

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PTV margin calculation

- Introduction
- Derivation of $M_{PTV} = 2.5\Sigma_i + 0.7\sigma_i$, i = x, y, z
- Clinical examples Erasmus MC:
  - prostate cancer
  - breast cancer
- Margins and respiratory motion
- Final remarks

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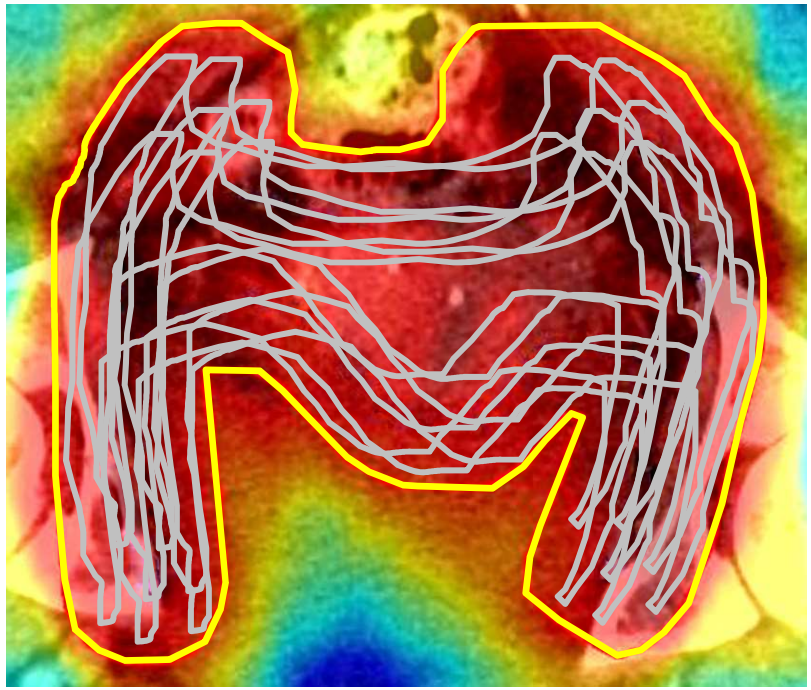

PTV prescribes planning high dose volume,
is fixed in space, and centred around the linac isocenter.

PTV = CTV + margin

CTV most of the times in high dose volume

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Parameters to describe SYSTEMATIC and RANDOM errors in the patient population:

Random error:

$$\sigma_x = \sqrt{\frac{\sum_i \sigma_{i,x}^2}{N}}$$

$$\sigma_y = \sqrt{\frac{\sum_i \sigma_{i,y}^2}{N}}$$

Systematic error:

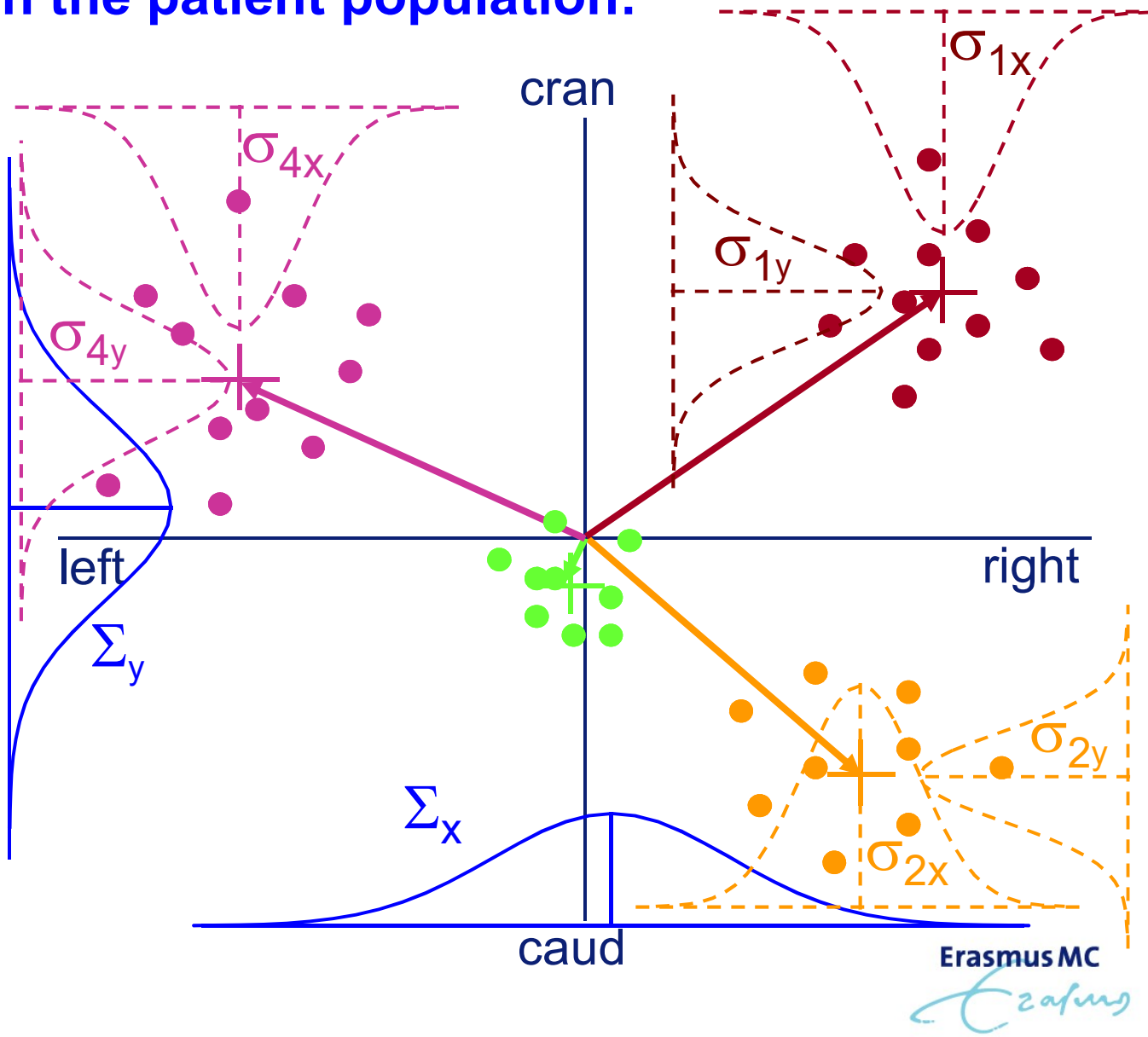
Σ_x: SD($m_{i,x}$)

Σ_y: SD($m_{i,y}$)

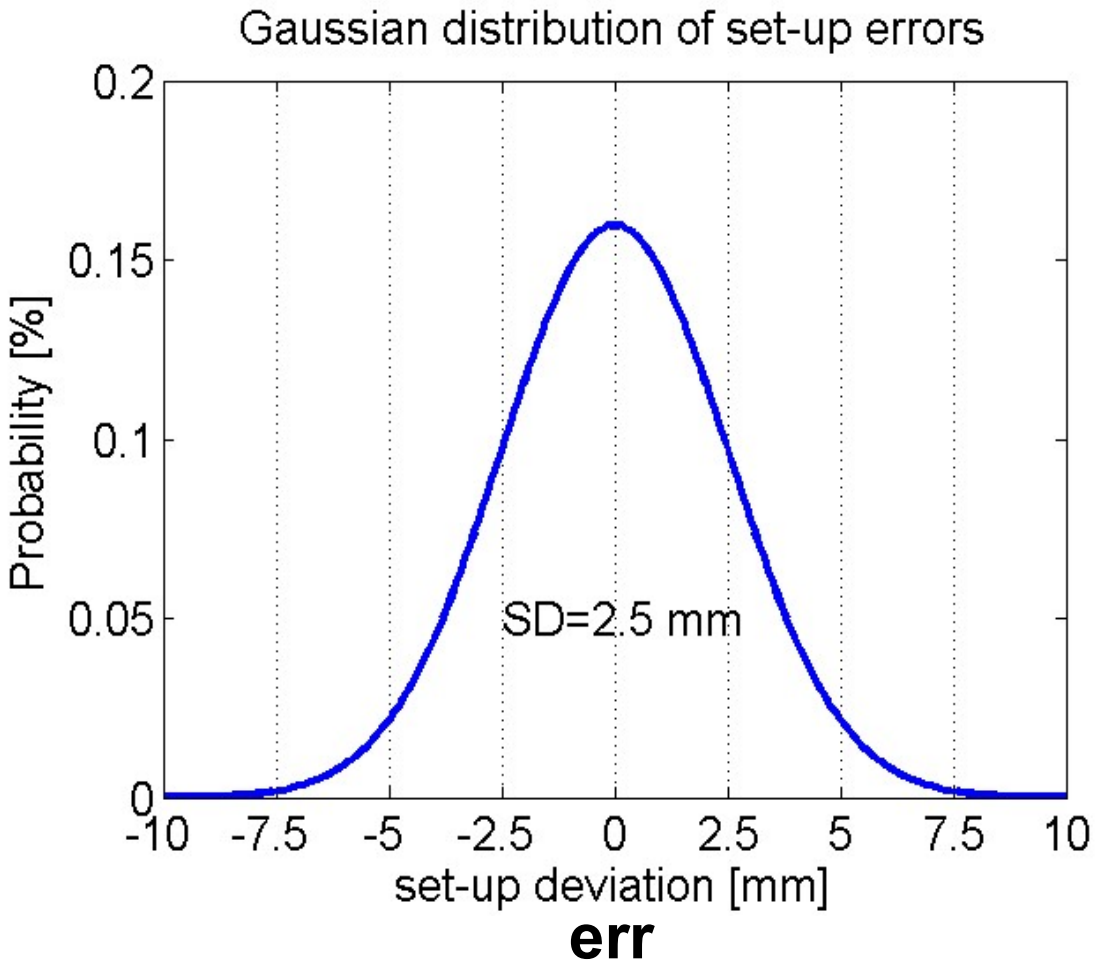
Mean error:

M_x: $\langle m_{i,x} \rangle \approx 0$

M_y: $\langle m_{i,y} \rangle \approx 0$



Gaussian probability distributions with SD = Σ or σ



$$P(err) = \frac{1}{SD\sqrt{2\pi}} \cdot e^{-\frac{err^2}{2 \cdot SD^2}}$$

- systematic errors: SD = Σ
- random errors: SD = σ

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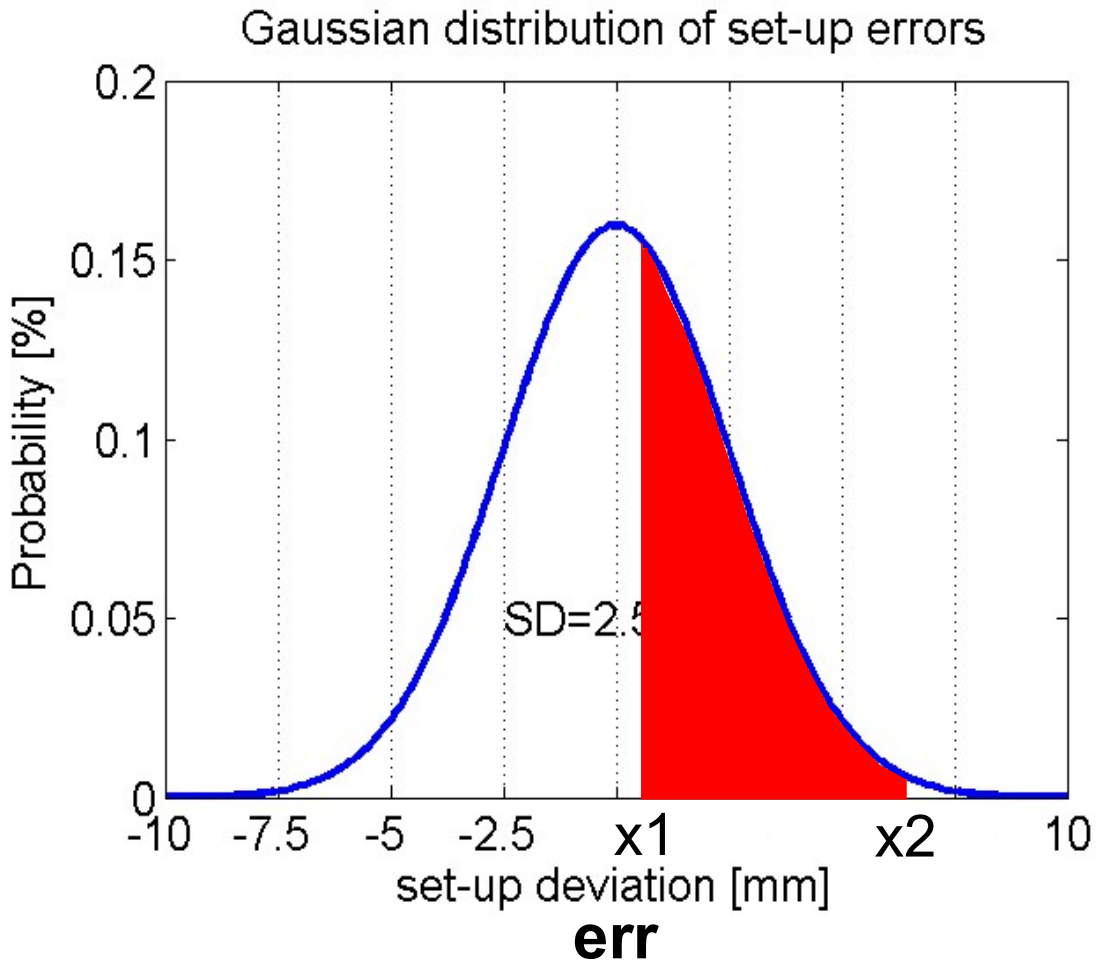
Introduction – Gaussian probability distributions with SD = Σ or σ



$$P(x1 < err < x2) = \int_{x1}^{x2} P(x)dx$$

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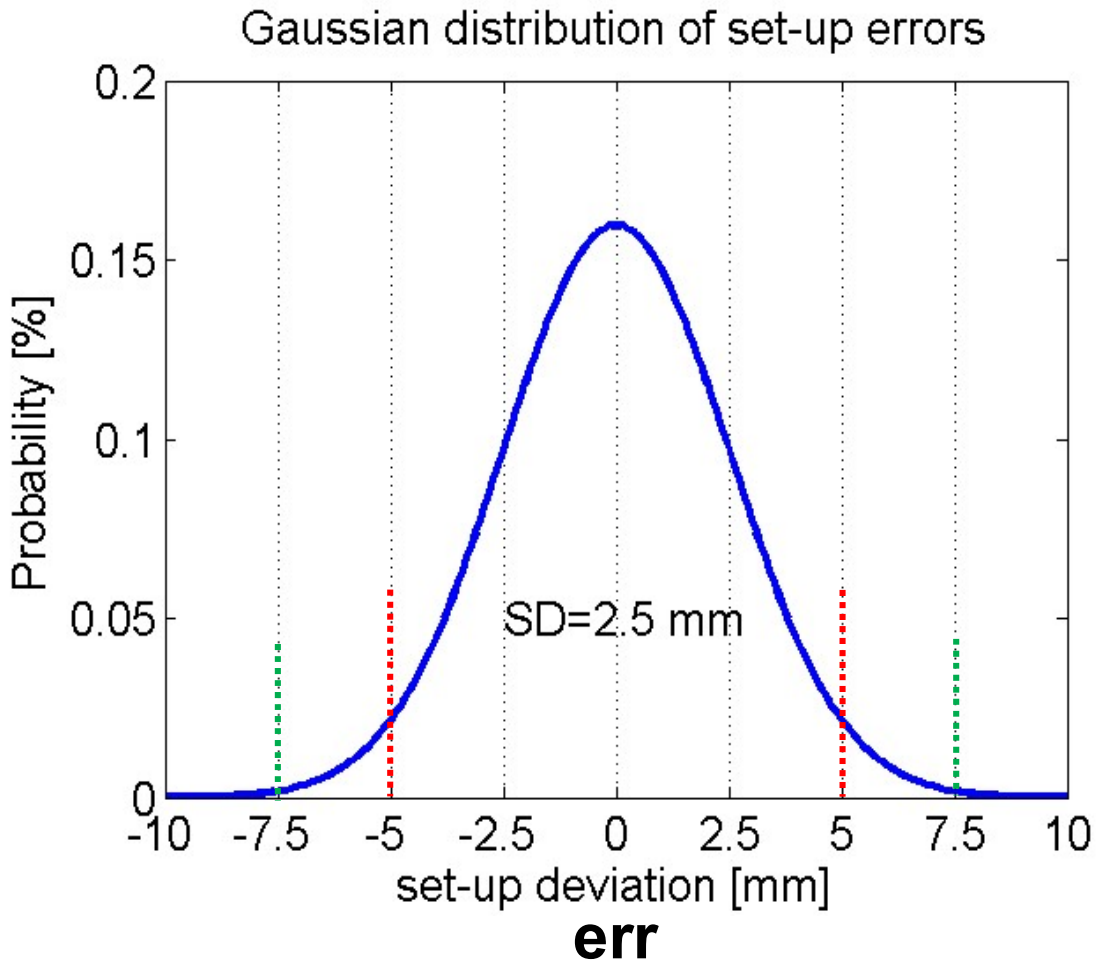
Introduction – Gaussian probability distributions with SD = Σ or σ



$$P(x1 < err < x2) = \int_{x1}^{x2} P(x)dx$$

P(-2SD <err< 2SD) = 0.95

P(|err| > 5 mm) = 5%

P(-3SD <err< 3SD) = 0.997

P(|err| > 7.5 mm) = 0.3%

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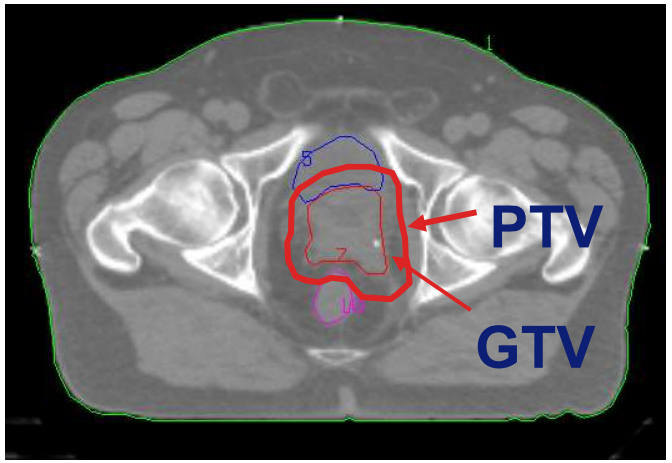
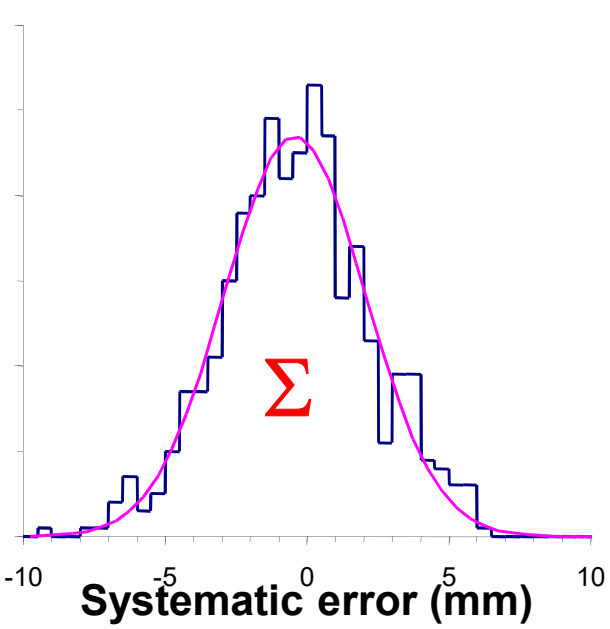
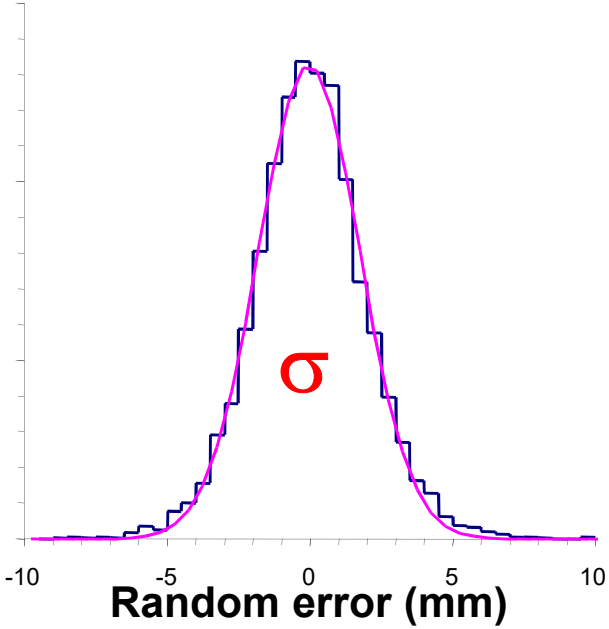
Use of Σ and σ for margin calculation

$$M_{PTV} = 2.5\,\Sigma + 0.7\sigma$$



Measured in previously treated patients:





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PTV margin calculation

- Introduction
- Derivation of $M_{PTV,i} = 2.5\Sigma_i + 0.7\sigma_i$, i = x, y, z
- Clinical examples Erasmus MC:
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Assumptions/simplifications in derivation of $M_{PTV,i} = 2.5\Sigma_i + 0.7\sigma_i$:

- large number of fractions
- spherical tumor
- ideal conformality:
  - 95% isodose is a spherical surface coinciding with PTV surface
    (ICRU-50: 100% of PTV should get dose ≥ 95%)
- only translational set-up errors:
  - no tumor rotations
  - no deformations
    (derived margin often has to be considered as lower limit)

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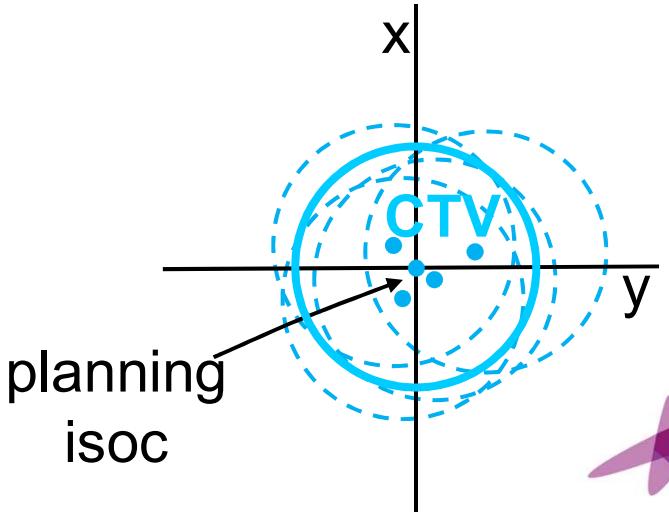
Consider systematic errors only ➔ $M_{PTV,sys} = 2.5\Sigma$

For spherical tumor: systematic set-up errors described by 3D Gaussian with SD=Σ.

the larger r, the lower the probability



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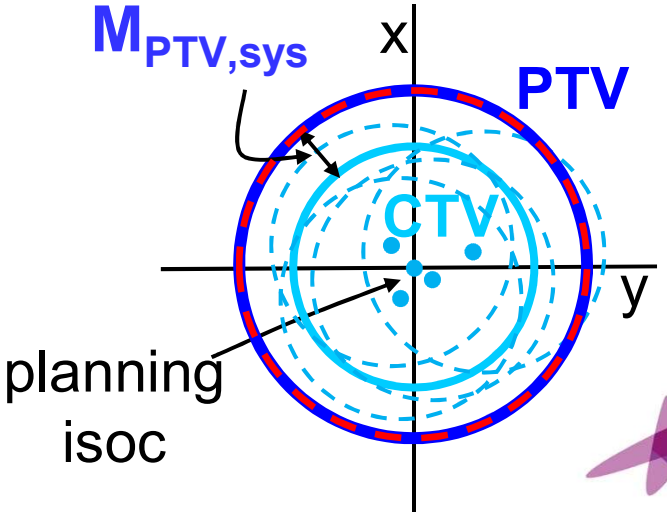
Consider systematic errors only ➔ $M_{PTV,sys} = 2.5\Sigma$

How to choose $M_{PTV,sys}$ for planning?

van Herk et al (2000):
allow a probability of 10% that CTV sticks (partially) outside the PTV

➔ probability of 10% that part of the CTV gets dose < **95%**



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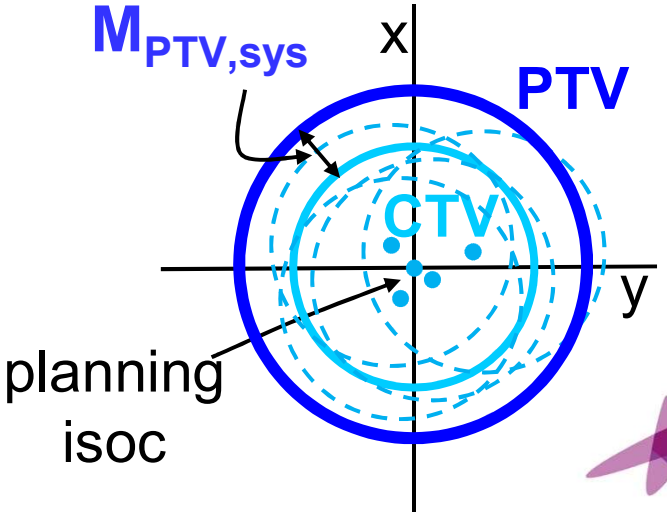
Consider systematic errors only ➔ $M_{PTV,sys} = 2.5\Sigma$

How to choose $M_{PTV,sys}$ for planning?

$$1 - \int_0^{M_{PTV,sys}} \frac{r^2}{\sqrt{\frac{\pi}{2}} \cdot \Sigma^3} \cdot e^{-\frac{r^2}{2\Sigma^2}} dr = 0.1$$



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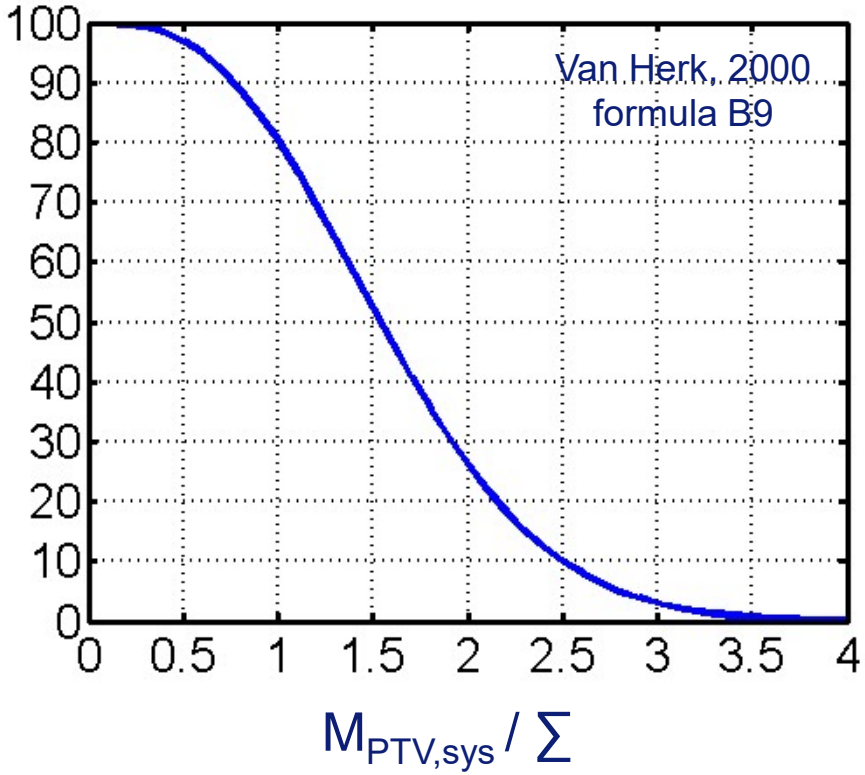
Consider systematic errors only ➔ $M_{PTV,sys}$ = 2.5Σ

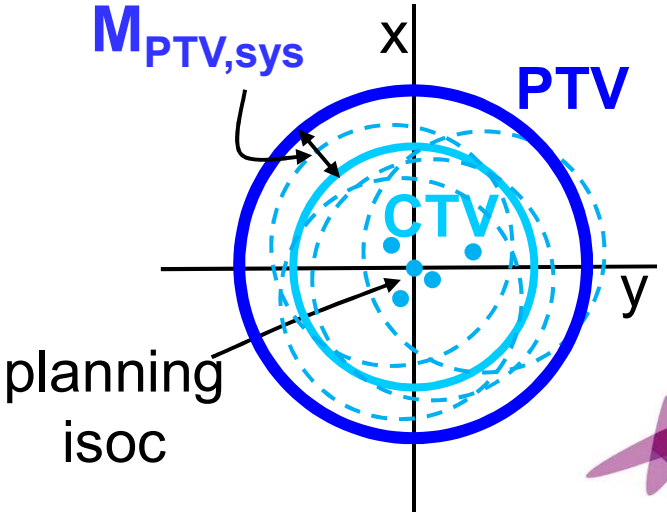
% of cases with CTV partially outside PTV



20%	2.16Σ
10%	2.50Σ
5%	2.79Σ
1%	3.36Σ

0% ➔TBI

$M_{PTV,sys}$ = 2.5Σ



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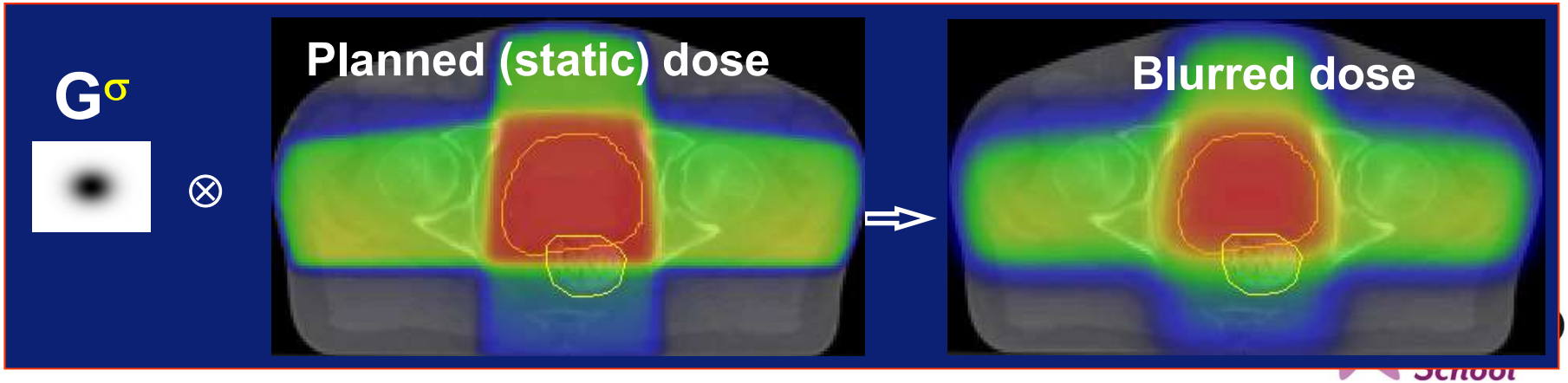
Add random errors ➔ $M_{PTV} = 2.5\Sigma + 0.7\sigma$

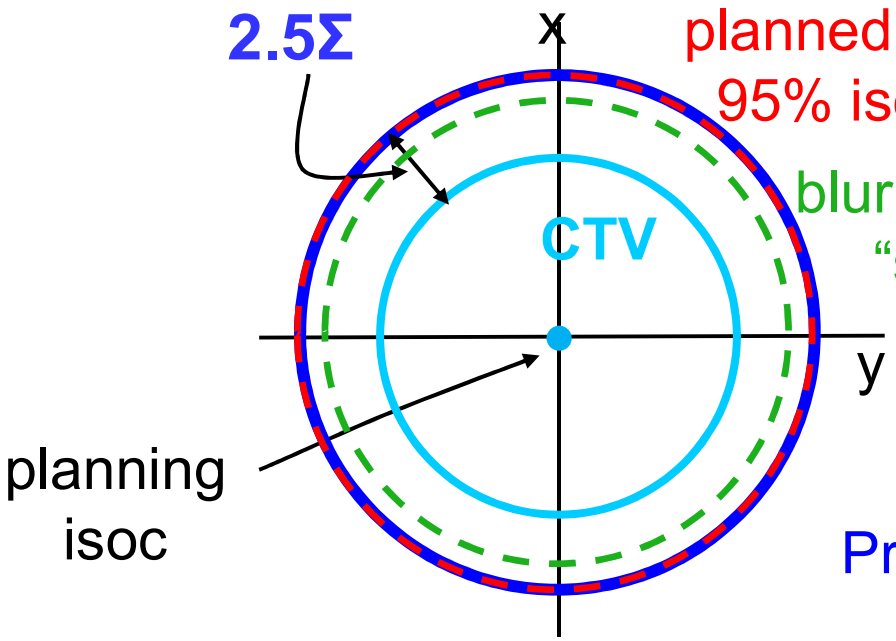
Impact of random motion on tumor dose:

- Narrow PTV-margin: cells at PTV edge get >95% in some fractions, << 95% dose in others (asymmetric)
- Effectively, tumor experiences the planning dose distribution that is blurred

For an infinite number of fractions:



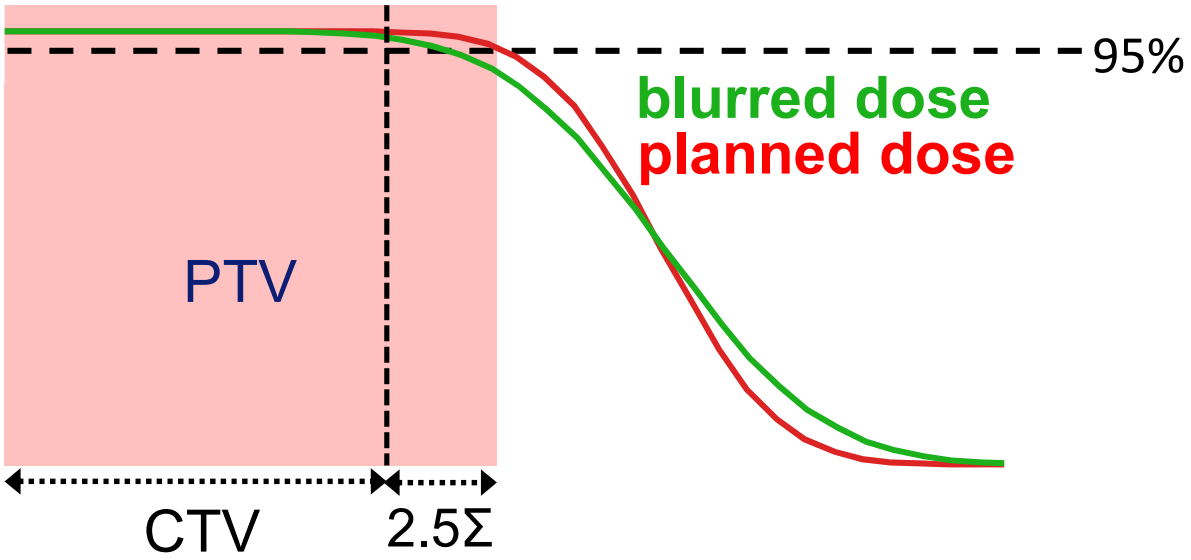
Add random errors ➔ $M_{PTV} = 2.5\Sigma + 0.7\sigma$



planned (static)
95% isodose

blurred 95% isodose
"seen by" CTV

Probability of CTV underdose > 10%



Solution:

$M_{PTV} = 2.5\Sigma + \ldots$

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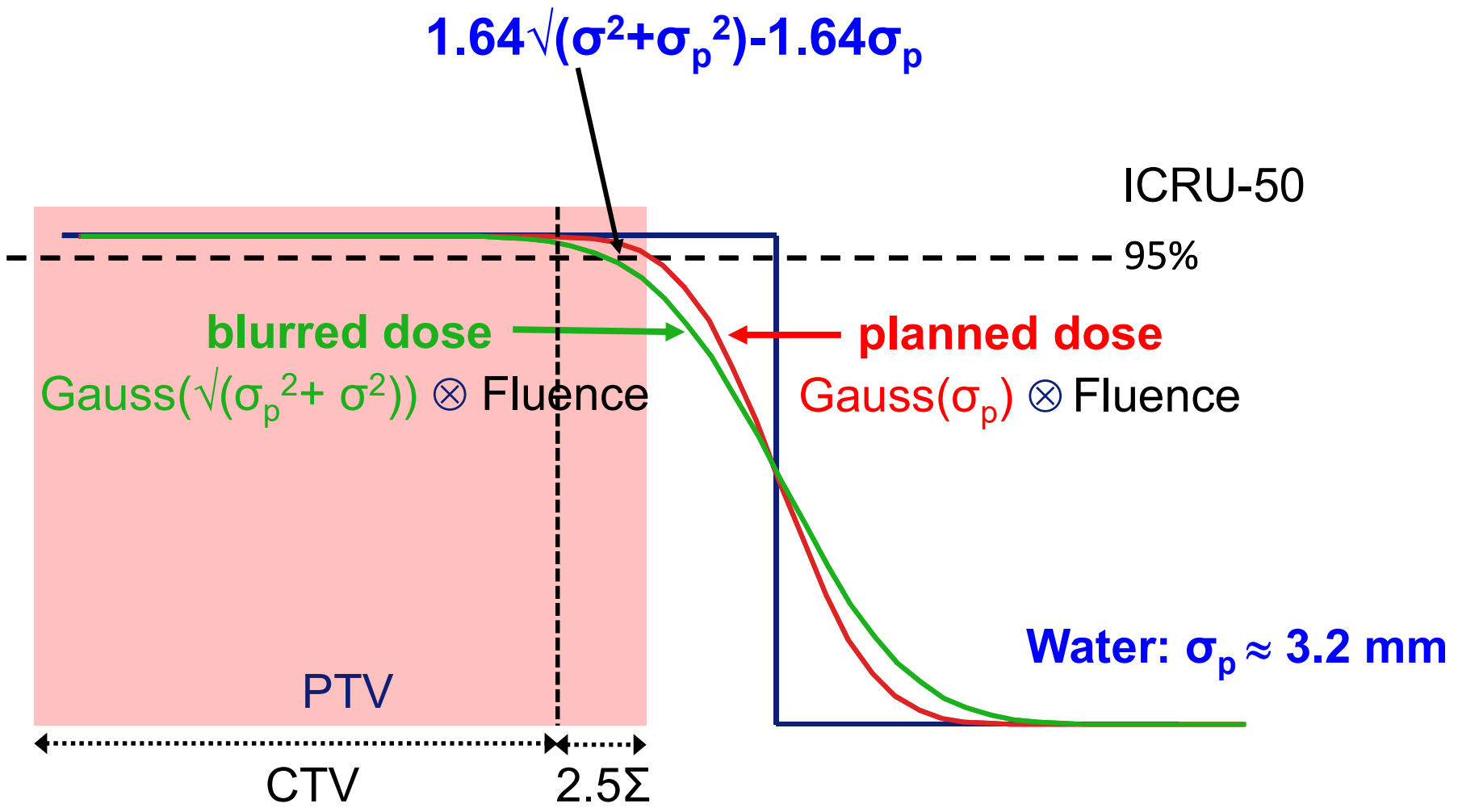
Add random errors ➔ $M_{PTV} = 2.5\Sigma + 0.7\sigma$



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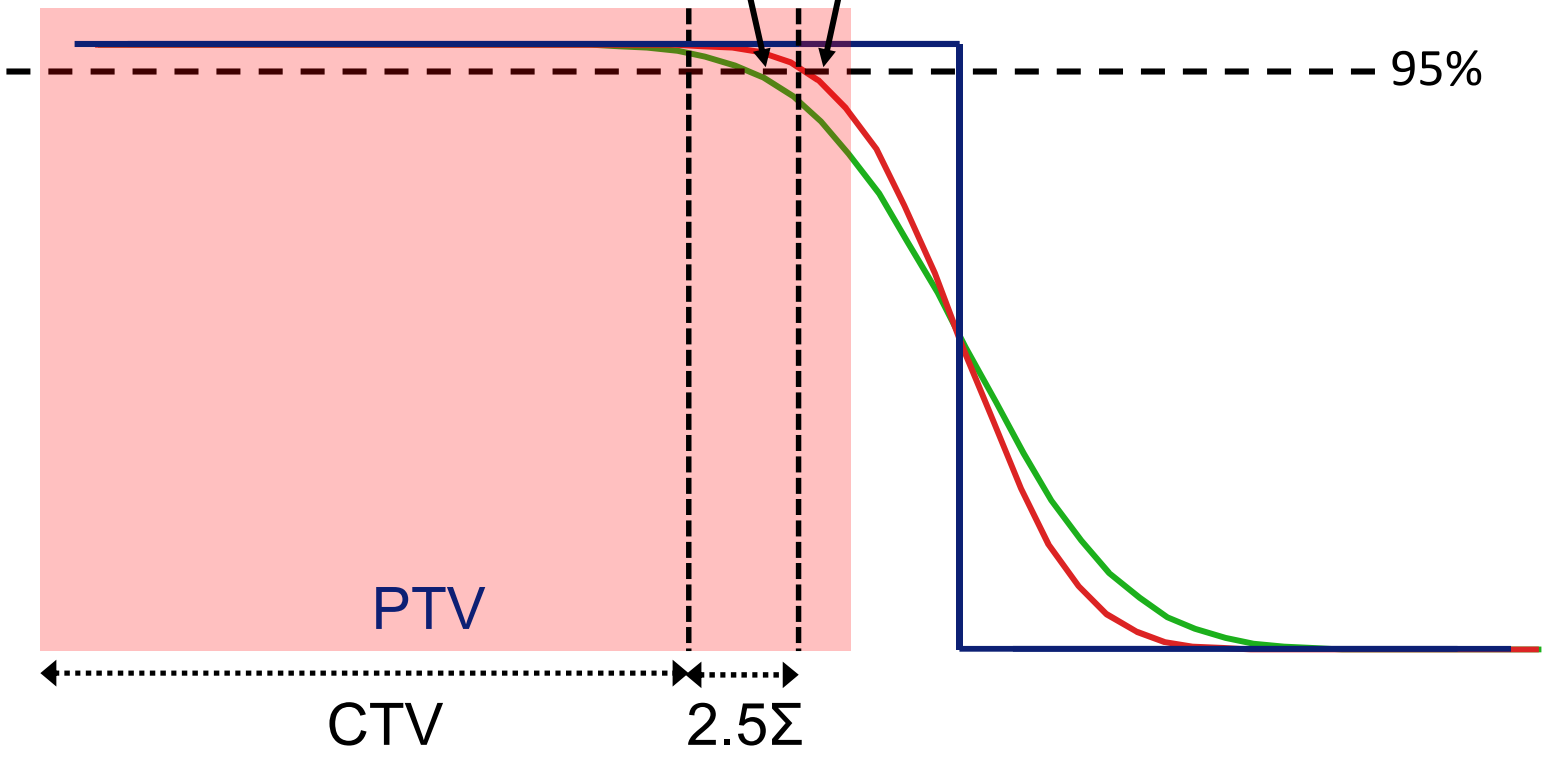
Add random errors ➔ $M_{PTV} = 2.5\Sigma + 0.7\sigma$

$$M_{PTV,random} = 1.64\sqrt{(\sigma^2+\sigma_p^2)} - 1.64\sigma_p$$



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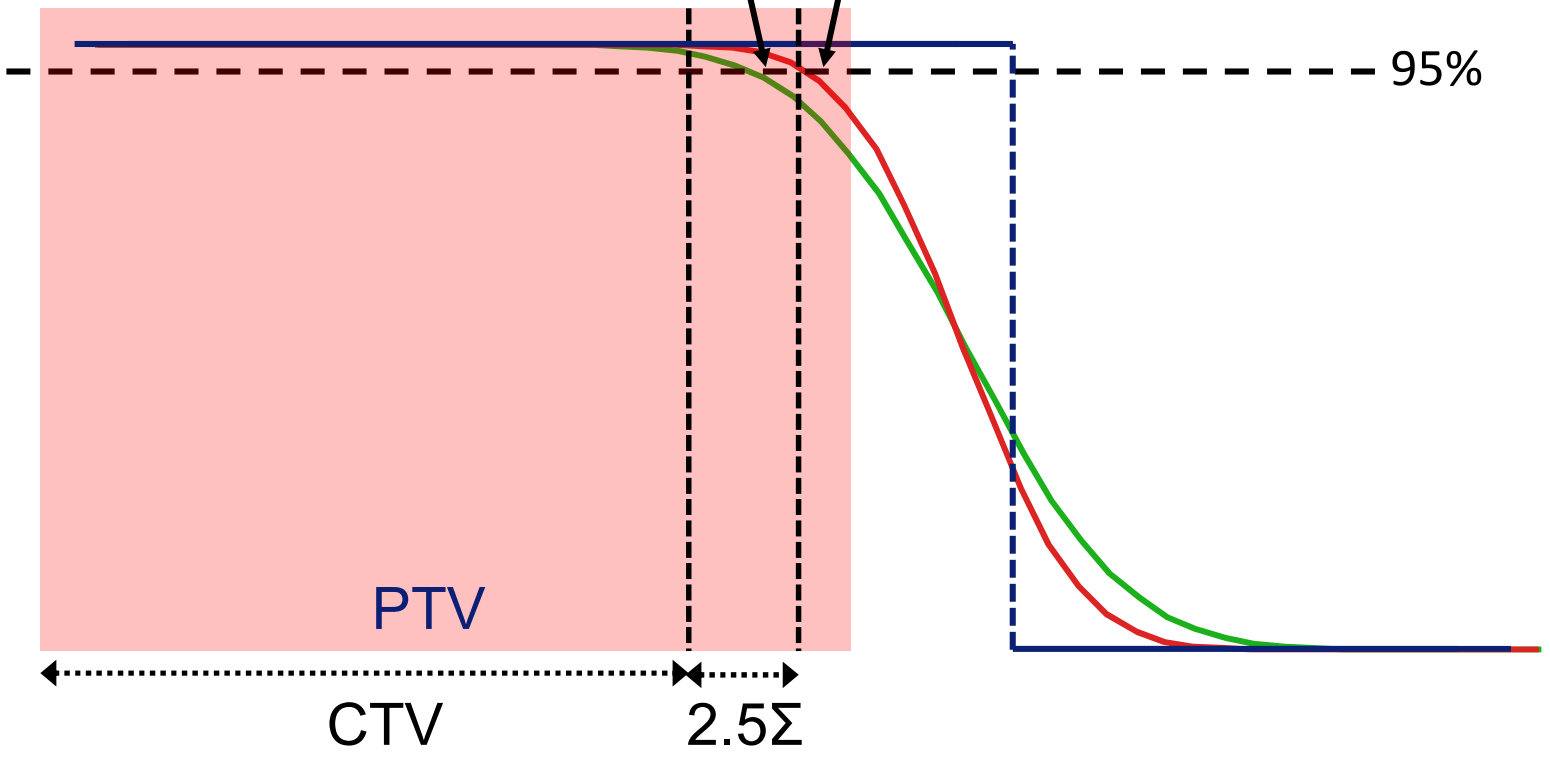

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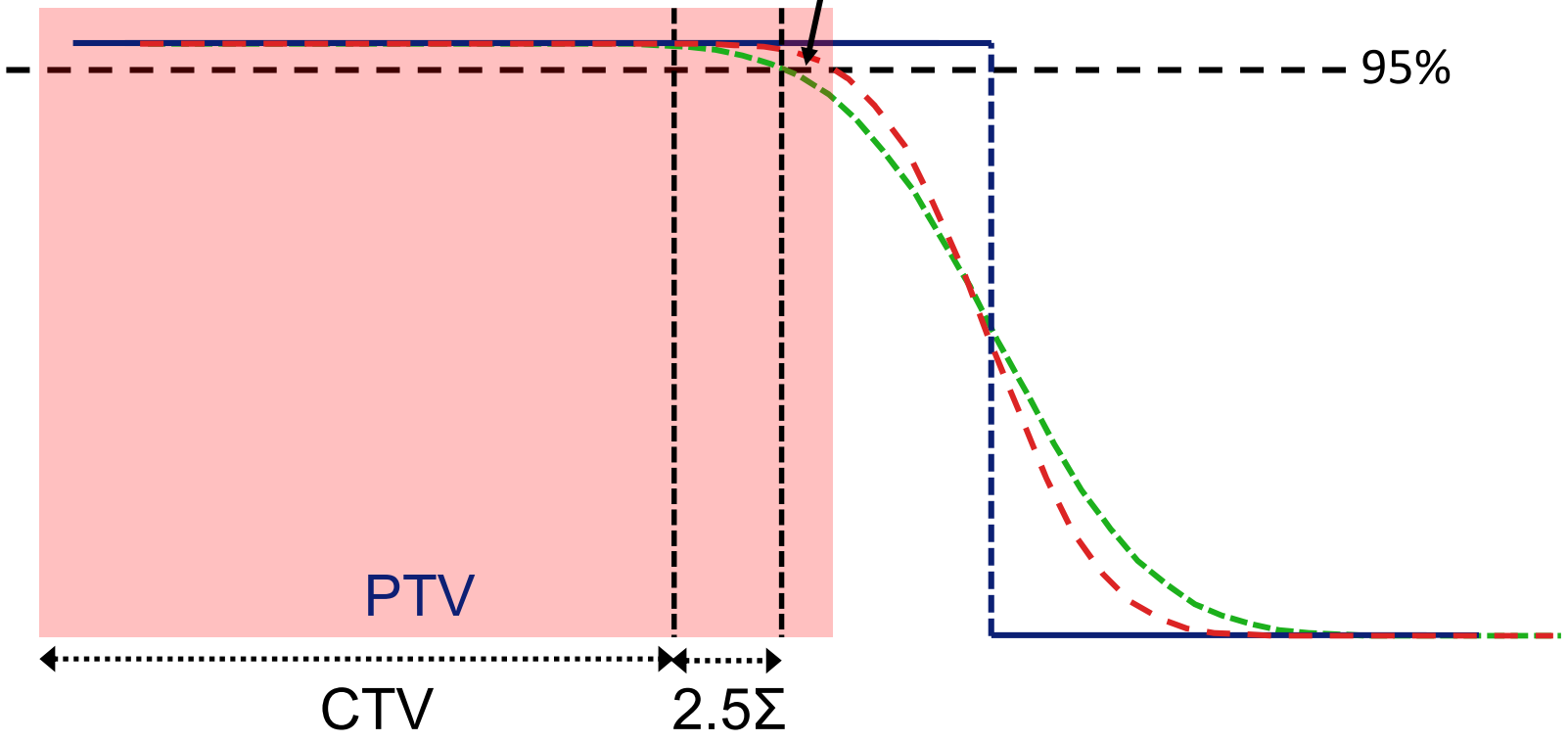
Add random errors ➔ $M_{PTV} = 2.5\Sigma + 0.7\sigma$

$$M_{PTV,random} = 1.64\sqrt{(\sigma^2+\sigma_p^2)}-1.64\sigma_p$$



$$M_{PTV} = 2.5\Sigma + 1.64\cdot(\sqrt{(\sigma^2+\sigma_p^2)} - \sigma_p)$$

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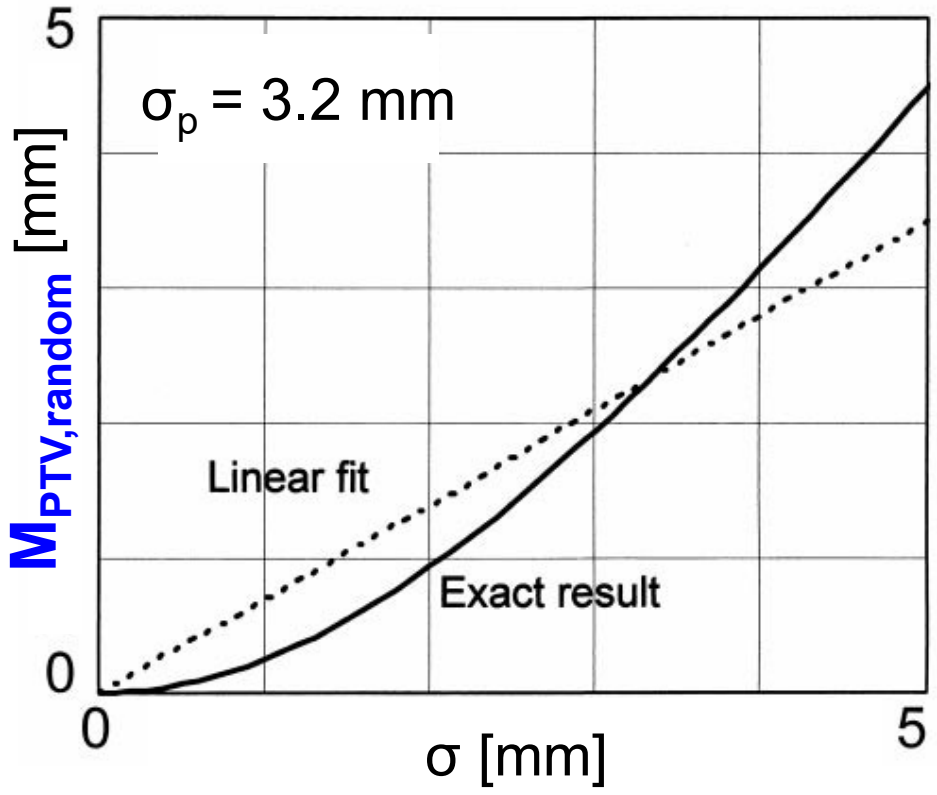
Add random errors ➔ $M_{PTV} = 2.5\Sigma + 0.7\sigma$

$$M_{PTV,random} = 1.64 \cdot (\sqrt{(\sigma^2 + \sigma_p^2)} - \sigma_p)$$



$$M_{PTV,random} \approx 0.7\sigma$$

$$M_{PTV} = 2.5\Sigma + 0.7\sigma$$

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choose M_{PTV} such that

in 10% of cases the CTV sticks (partially) outside the real (= blurred) 95% isodose

Why this choice, what about the other 10%?

- real dose distributions are **not** maximally conformal
- Also for maximally conformal dose distributions, dose is not zero outside the 95% isodose
  small pieces may get dose lower than 95% but still high

PTV margin calculation

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Combining error sources:

Example: prostate moves because of

A. motion of the pelvic bony anatomy relative to isocenter
B. motion of the prostate relative to bony anatomy (internal motion)

$$M = 2.5 \cdot \Sigma_{tot} + 0.7 \cdot \sigma_{tot}$$

$$\sigma_{tot} = \sqrt{(\sigma_A)^2 + (\sigma_B)^2}$$

$$\Sigma_{tot} = \sqrt{(\Sigma_A)^2 + (\Sigma_B)^2}$$

Stroom&Heijmen
R&O 2002

With A, B error sources

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Prostate margins – historic example Erasmus MC

- set-up verification and correction using EPIDs and off-line set-up corrections of bony anatomy displacements
  ➔ σ_{bone}, Σ_{bone}
- repeat CT study for a group of 20 patients to measure internal motion
  ➔σ_{int}, Σ_{int}

Stroom, Heijmen, et al., R&O, 1999

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Prostate margins – historic example Erasmus MC

	σ_{bone}	Σ_{bone}	σ_{int}	Σ_{int}
LR	1.6	1.3	0.6	0.5
AP	2.2	1.5	2.8	2.5
CC	1.5	1.4	2.5	2.7

$$M = 2 \cdot \Sigma_{tot} + 0.7 \cdot \sigma_{tot}$$

(formula by Stroom et al: 2Σ instead of 2.5Σ)

$$\sigma_{tot} = \sqrt{(\sigma_{bone})^2 + (\sigma_{int})^2}$$

$$\Sigma_{tot} = \sqrt{(\Sigma_{bone})^2 + (\Sigma_{int})^2}$$

Stroom, Heijmen, et al., R&O, 1999

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Prostate margins – historic example Erasmus MC

* 10 Gy boost

	σ_{bone}	Σ_{bone}	σ_{int}	Σ_{int}	σ_{tot}	Σ_{tot}	M^{cal}	M^{clin}
LR	1.6	1.3	0.6	0.5	1.7	1.4	**4.0**	**10/5***
AP	2.2	1.5	2.8	2.5	3.6	2.9	**8.3**	**10/0-5***
CC	1.5	1.4	2.5	2.7	2.9	3.0	**8.1**	**10/5***

CKVO
Kassim, Heijmen et al.
R&O 2009

$$M = 2 \cdot \Sigma_{tot} + 0.7 \cdot \sigma_{tot}$$

(formula by Stroom et al: 2Σ instead of 2.5Σ)

$$\sigma_{tot} = \sqrt{(\sigma_{bone})^2 + (\sigma_{int})^2}$$

$$\Sigma_{tot} = \sqrt{(\Sigma_{bone})^2 + (\Sigma_{int})^2}$$

Stroom, Heijmen, et al., R&O, 1999

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Prostate margins – current situation Erasmus MC

daily kV/MV imaging, on-line correction of marker COM set-up error (4 implanted gold markers)

	σ_{pre}	Σ_{pre}	σ_{post}	Σ_{post}	$\mathbf{M_{pre}}$	$\mathbf{M_{post}}$	$\mathbf{M_{clin}}$
LR							**5**
AP	0.7	0.5	1.8	1.7	**1.5**	**4.7**	**5**
CC	0.7	0.5	1.9	1.4	**1.5**	**4.1**	**5**

pre: derived from lateral kV acquired immediately after kV/MV based on-line set-up correction

post: derived from lateral kV acquired immediately after delivery last beam

Differences between pre and post due to intrafraction motion

Mutanga, Heijmen, et al, IJROBP, 2011, 2012

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PTV margin calculation

- Introduction
- Derivation of $M_{PTV} = 2.5\Sigma_i + 0.7\sigma_i$, i = x, y, z
- Clinical examples Erasmus MC:
  - prostate cancer
  - breast cancer
- Margins and respiratory motion
- Final remarks

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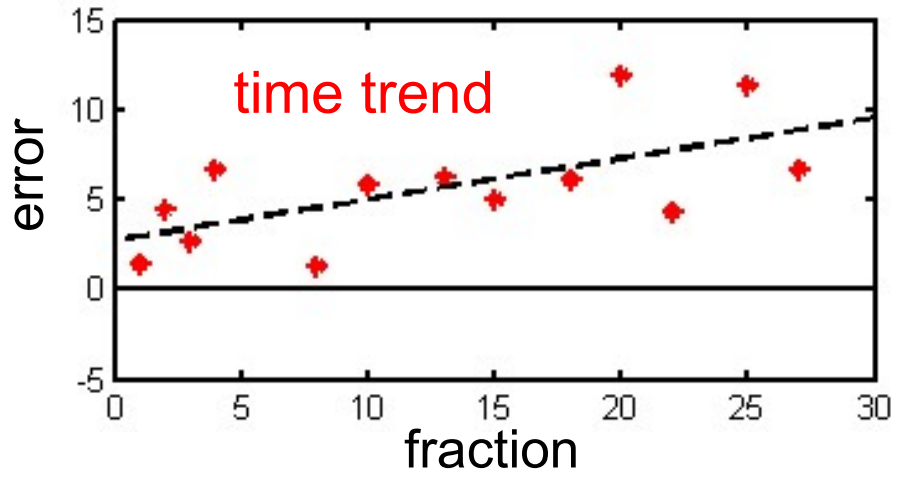
Breast margins – SIB-technique in Erasmus MC

- 28-31 fractions
- in each fraction: whole breast tangential field + boost
- IGRT: 3 or more implanted markers to demarcate tumor bed
- IGRT: 2 orthogonal kV beams (also 1 MV beam for whole breast acquired)
- eNAL (with refinements) corrections applied both tumor bed and whole breast



IJROBP 82, p1031–1037, 2012

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Breast margins – SIB-technique in Erasmus MC
residual set-up errors for 80 eNAL patients

		Tumor bed (boost)			Whole breast	
		LR (mm)	CC (mm)	AP (mm)	U (mm) ⊥ Th wall	V (mm) CC
	σ	2.1	2.0	2.3	2.0	1.8
No corrections	Σ	2.6	2.5	3.4	3.5	2.3
	M=2.5Σ+0.7σ	8.0	7.7	10.1	10.2	7.0
eNAL markers	Σ	0.8	0.6	0.9	1.9	2.1
	M=2.5Σ+0.7σ	3.5	2.9	3.9	6.2	6.5
Clinical	M	5.0	5.0	5.0	5.0 mm LR, CC, AP	

IJROBP 82, p1031–1037, 2012

PTV margin calculation

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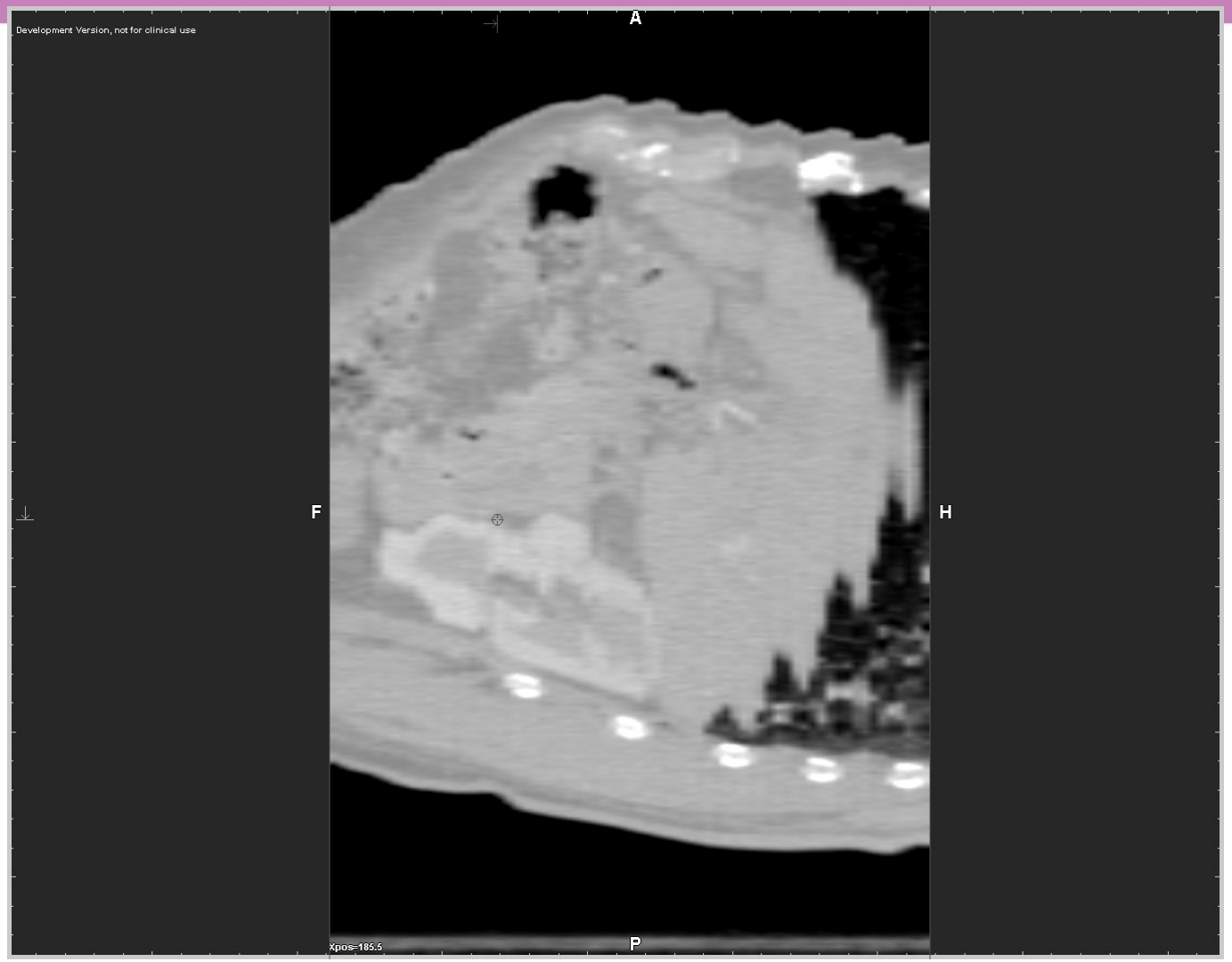
Breathing motion artefacts in planning CT-scan



➔ **Systematic uncertainty in tumor size, shape and position**

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Avoid motion artifacts in planning CT-scan (i.e. avoid systematic errors)

- breathhold scanning: multislice CT-scanner, only 3D scan in 1 phase
- gated free-breathing scanning: single slice scanner, only 3D scan in 1 phase
- 4DCT scanning: multislice CT-scanner, 10 3D CT-scans in 10 breathing phases

Include respiratory motion as intra-fraction random error in PTV margin

Random lung tumor motion because of
- random ***inter***-fraction set-up variations
- random ***intra***-fraction respiratory motion

Combine errors:

$$M = 2.5\Sigma + 0.7 \cdot \sigma_{tot}$$

$$\sigma_{tot} = \sqrt{(\sigma_{inter})^2 + (\sigma_{resp})^2}$$

$$\sigma_{resp} = 0.358 \cdot R$$

with R top-top respiratory motion amplitude

For R > 1cm, see reference

Van Herk et al. IJROBP 57-5: 1460–1471, 2003

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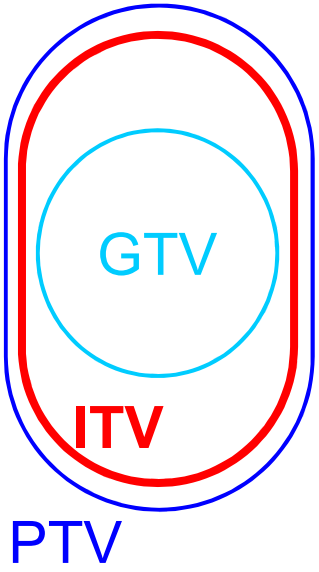
The ITV concept



ITV often applied in lung SBRT:

- derived from a 4DCT scan
- ITV encloses the full CTV in all respiratory phases
- use of ITV may result in too large PTV: Wolthaus et al, 2008, Sonke et al, 2009

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PTV margin calculation

- Introduction
- Derivation of $M_{PTV} = 2.5\Sigma_i + 0.7\sigma_i$, i = x, y, z
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Final remarks

- this is not more than an introduction, see Bibliography for further reading
- important ommission: how to deal with tumor deformations
  - establish $\Sigma(j)$ and $\sigma(j)$ for various parts j of the tumor and use $M(j)=2.5\Sigma(j)+0.7\sigma(j)$
  - Monte Carlo simulations including models for non-rigid motion derived for multiple CT-scans per patients: Mutanga et al 2012
- If tumor moves then also surroundig tissues move: omit margins and incorporate motion distributions for tumor and OAR in cost functions for IMRT optimization (robust planning)
- IT ALL STARTS WITH MEASURING ERRORS!!!

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Sonke et al. FRAMELESS STEREOTACTIC BODY RADIOTHERAPY FOR LUNG CANCER USING FOUR-DIMENSIONAL CONE BEAM CT *GUIDANCE Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 2, pp. 567–574, 2009*

Van Herk et al. BIOLOGIC AND PHYSICAL FRACTIONATION EFFECTS OF RANDOM GEOMETRIC ERRORS. *Int. J. Radiation Oncology Biol. Phys., Vol. 57, No. 5, pp. 1460–1471, 2003*

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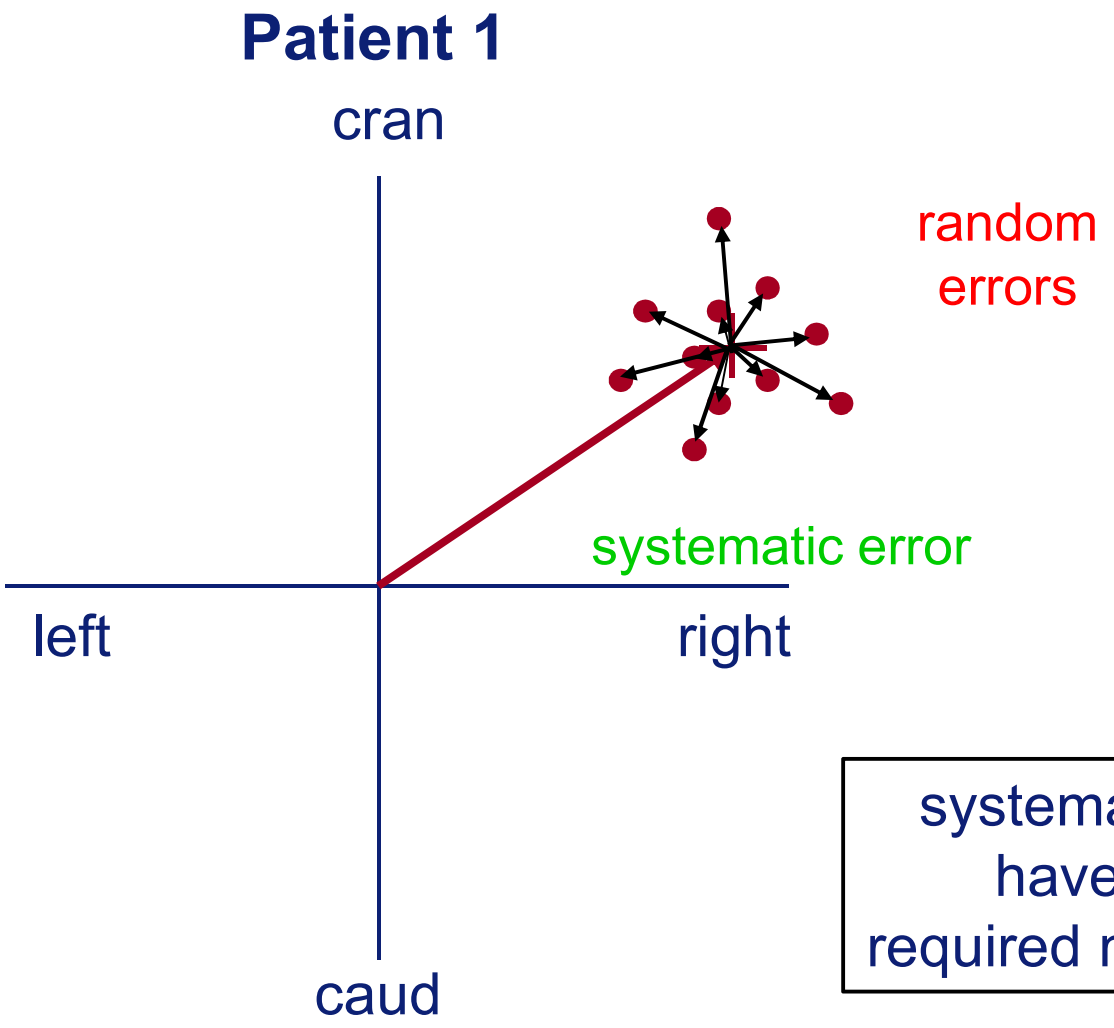
Systematic and random errors in previously treated patients



systematic and random errors have different impact on required margin of future patients

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Systematic and random errors in previously treated patients

Random error:

σ_x

σ_y

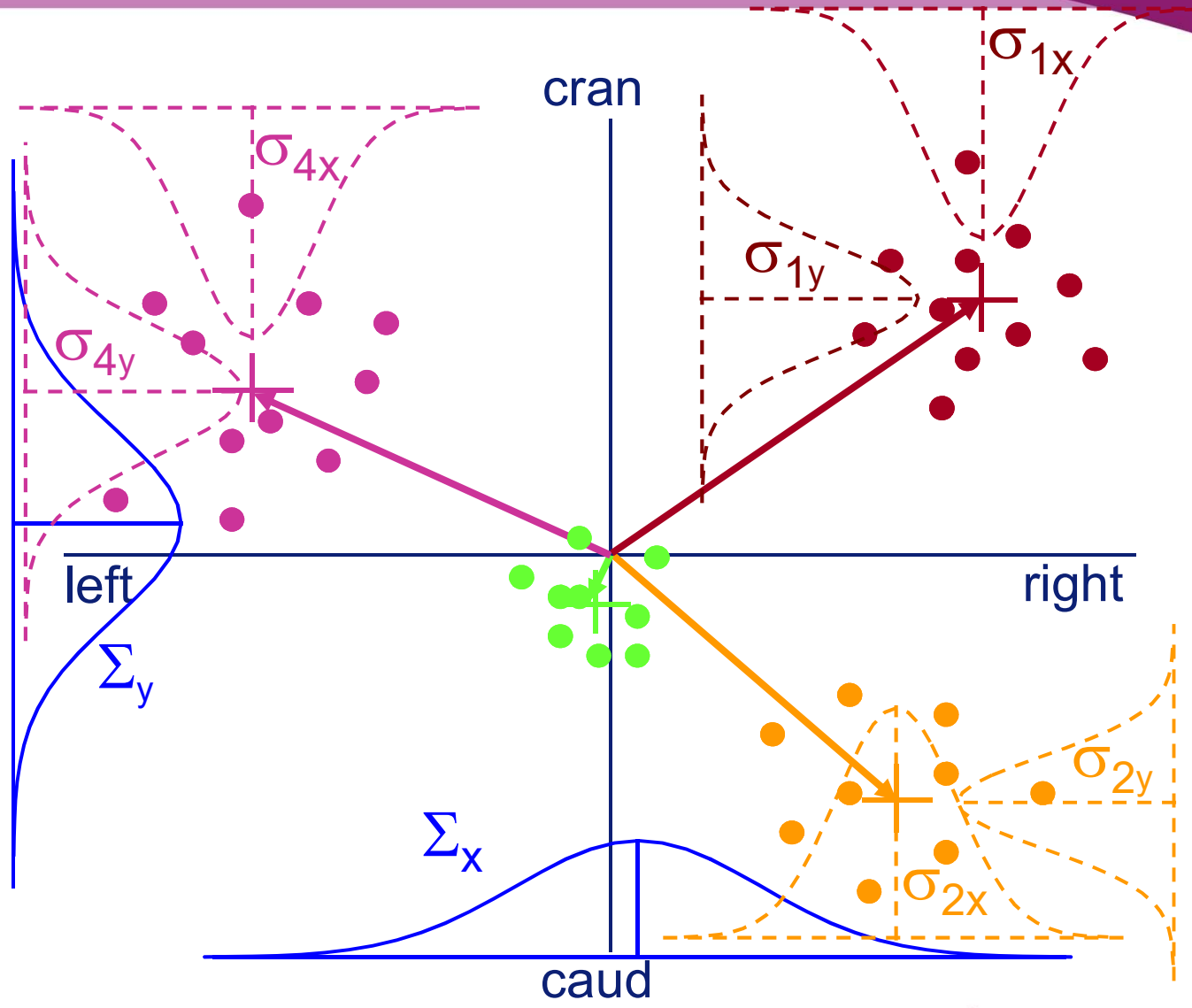
σ_z

Systematic error:

Σ_x

Σ_y

Σ_z



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Basics of Radiation Physics for clinicians

Silvia Molinelli
Medical Physics Unit, CNAO - Pavia, Italy

Physics for Modern Radiotherapy
Bucharest, Romania - 4 - 8 June 2017

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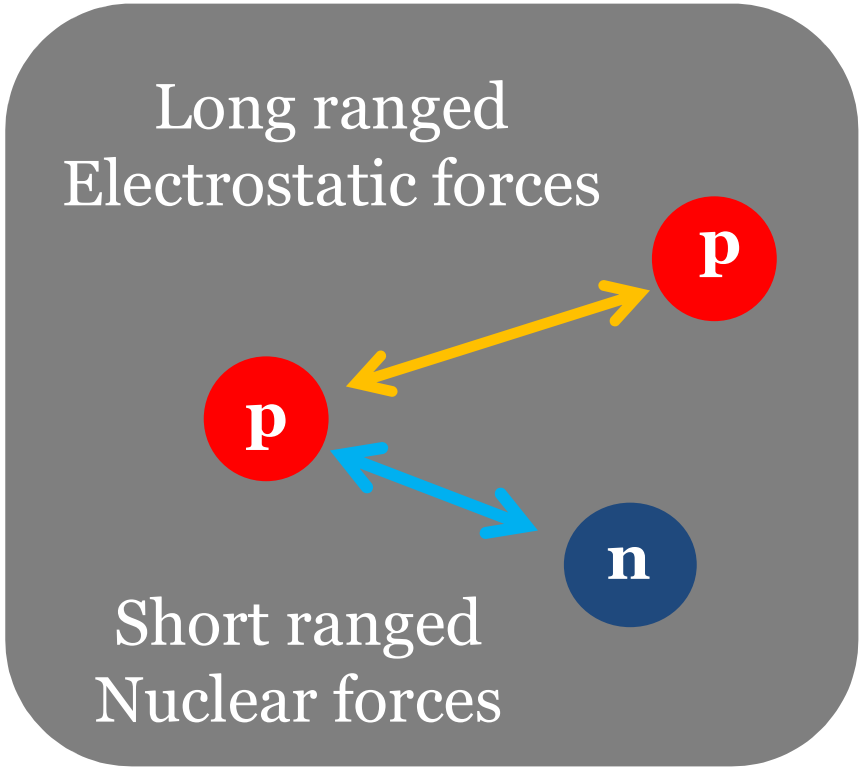
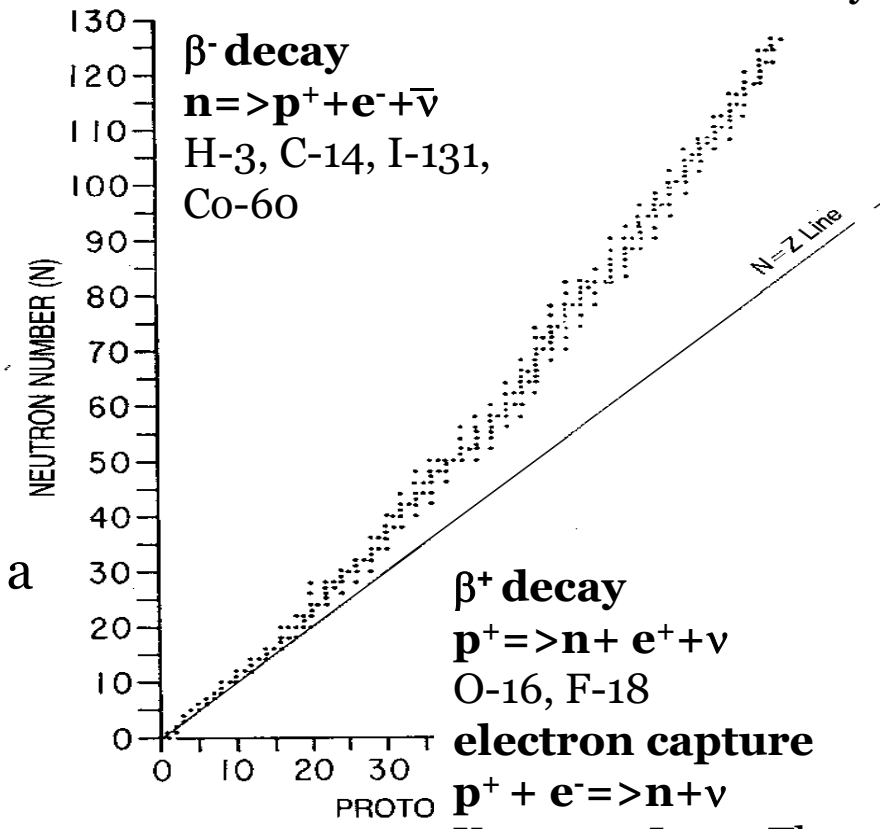
Contents – Physics behind clinical applications

- Radioactivity
- Ionizing radiation and external beam RT
- Dose
- Photons interaction with matter
- Energy deposition

Stability: equilibrium of forces



Line of stability



a

β⁻ decay
n=>p⁺+e⁻+ν̄
H-3, C-14, I-131, Co-60

β⁺ decay
p⁺=>n+ e⁺+ν
O-16, F-18

electron capture
p⁺ + e⁻=>n+ν
Xe-125 → I-125, Tl-201

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Activity

Radioactivity is a random event which can only be adequately described using statistics

• **Activity:** total number of disintegrations (decays) per unit time - SI unit is the Becquerel (Bq) - nuclear transformation per second – (Curie (Ci) activity of 1 gr of Ra-226)

$$\mathbf{1\ Ci\ =\ 37 \times 10^{9}\ Bq\ =\ 37\ GBq}$$

•**Activity →** $\underline{\mathbf{A(t) = \lambda N(t)}}$
where N(t) is the number of radioactive nuclei at time t

• **Decay constant** λ **→** characteristic parameter that describes how fast a particular nucleus transforms (probability of disintegration per unit time)

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Radioactive Decay

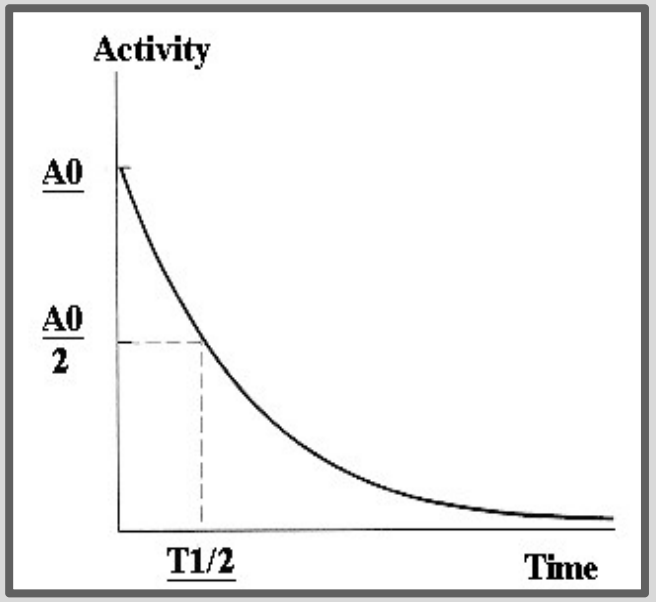
It is only possible to determine the probability of decay in a certain time.
In a sample of N nuclei the number of decays per unit time is:

A =-dN/dt

$$\frac{dN}{dt} = -N \cdot \lambda$$

$$N(t) = N_0 \cdot e^{-\lambda \cdot t}$$

$$T_{1/2} = \frac{\ln 2}{\lambda}$$



Half Life: The time it takes for half the amount of a radioactive material to decay
Effective half life (Te) = TpTb/(Tp+Tb)
Tp= radioactive decay
Tb= biological transport or elimination from the specific site

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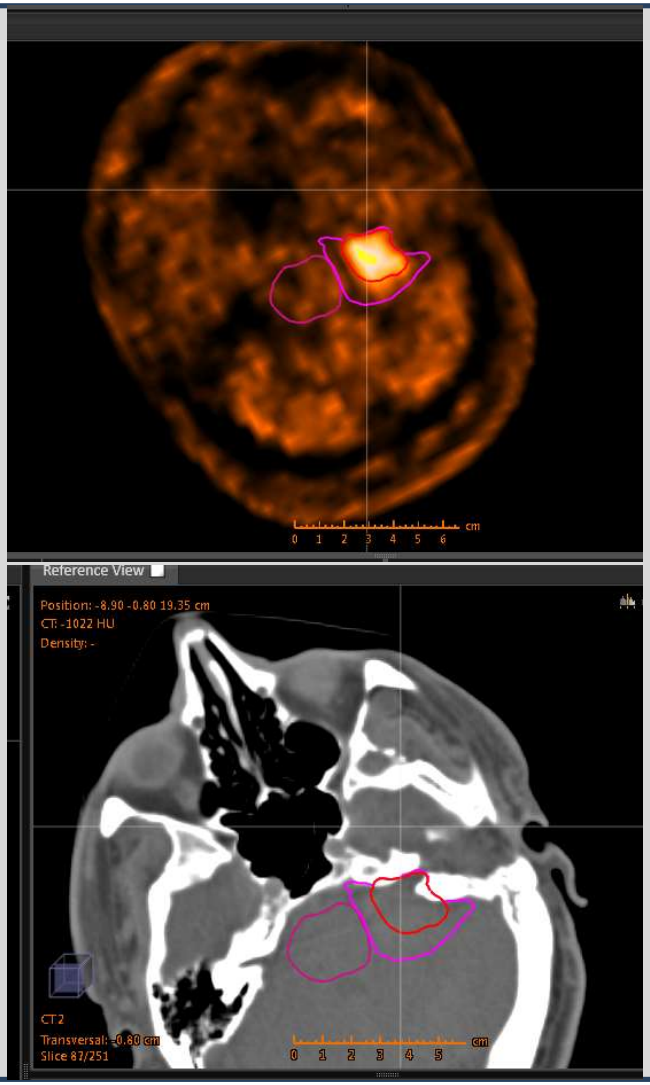
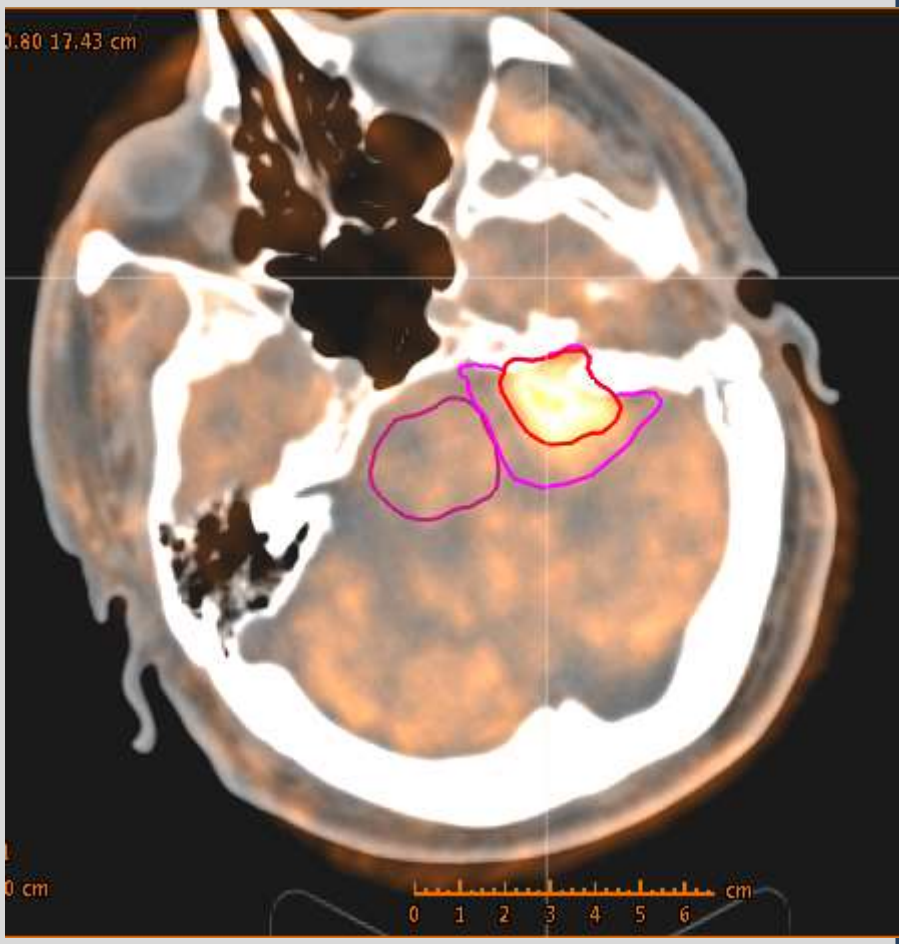
Radionuclides – Multymodality Imaging

PET

CT





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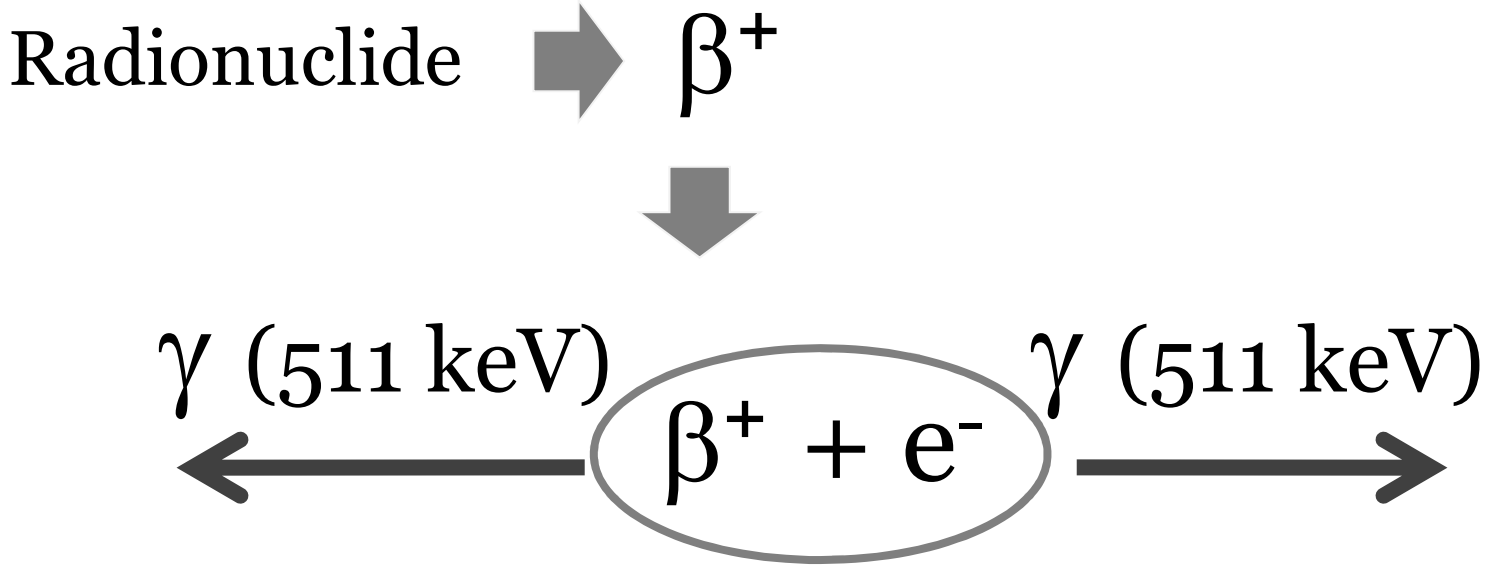
Annihilation



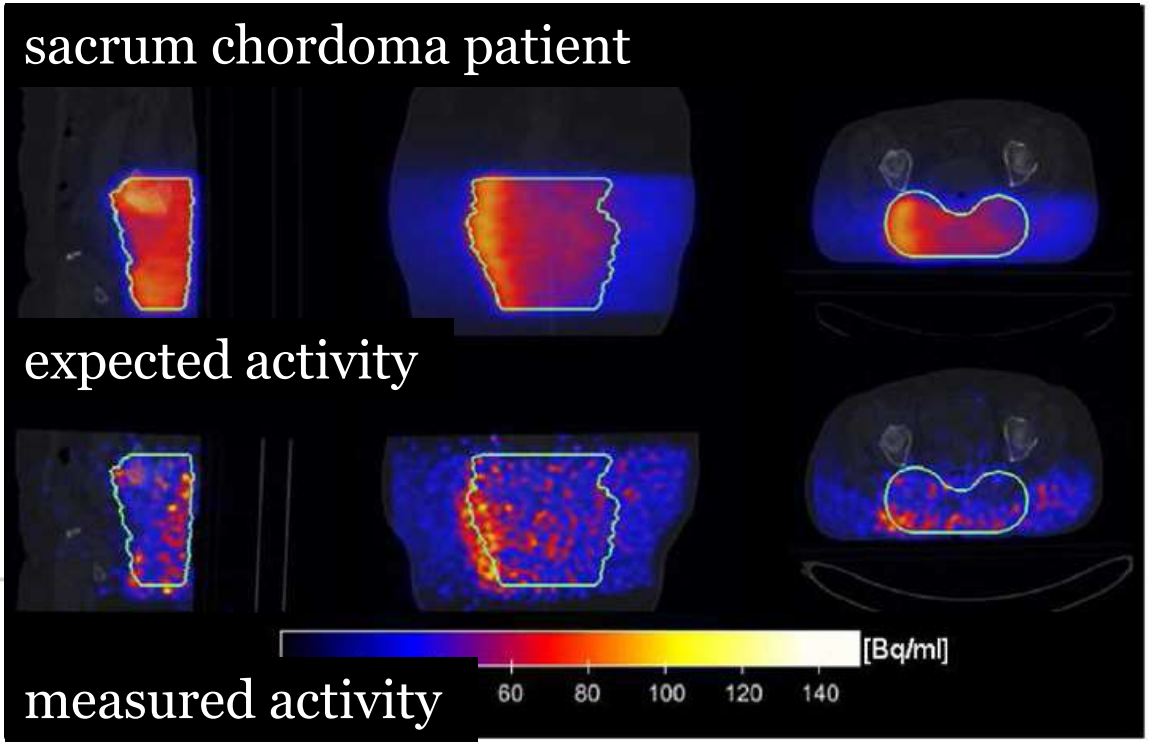
Electron–positron annihilation occurs when an electron (e^-) and a positron (e^+) collide. The result of the collision is the annihilation of the electron and positron, and the creation of gamma ray photons

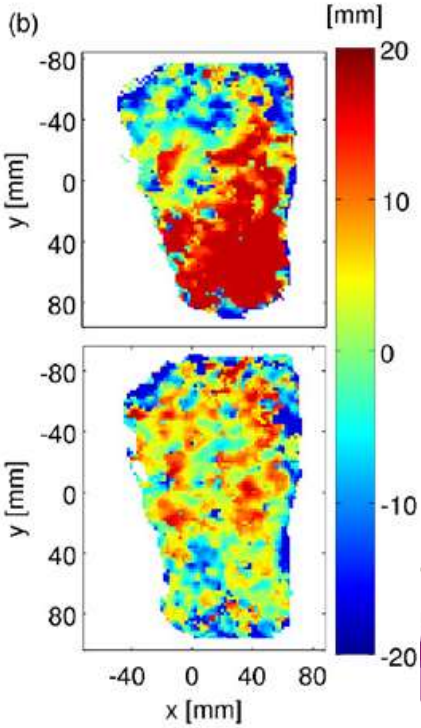
In vivo PET dosimetry
Range evaluation in Particle Therapy

Proton and Carbon-ion beams induced β^+ activities

most relevant β^+ active isotopes of rather long half-lives

^{15}O ($t_{1/2}$ = 2.03 min), ^{11}C ($t_{1/2}$ = 20.38 min), ^{13}N ($t_{1/2}$ = 9.96 min), ^{38}K ($t_{1/2}$ = 7.6 min), ^{30}P ($t_{1/2}$ = 2.5 min) and ^{34}Cl ($t_{1/2}$ = 32.0 min)





Frey K. et al.
Phys. Med. Biol. 59 (2014)

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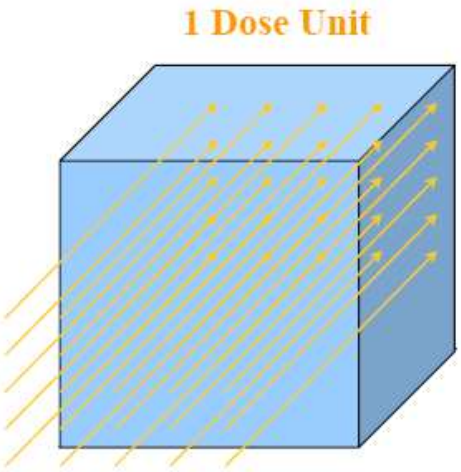
Types of Radiation in EBRT

- X rays and gamma rays = photons

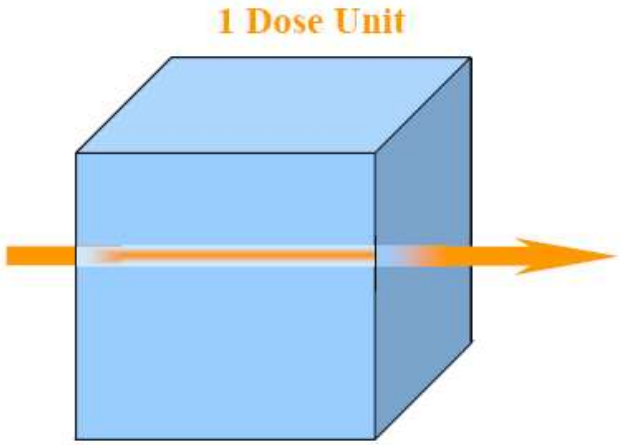
- electrons and beta particles - negative charge
- neutrons (20000 Pts → too severe late effects)
- protons - positive charge (≈ 100000 Pts)
- alpha and heavy charged particles (> 10000 Pts with C-ion)

The Fundamental Concept of Dose Can Be Fallacious

- Dose is defined as energy absorbed per unit mass
  (irrespective of the spatial distribution of the absorbed energy)



Low LET radiation deposits energy in a uniform pattern



High LET radiation deposits energy in a non-uniform pattern

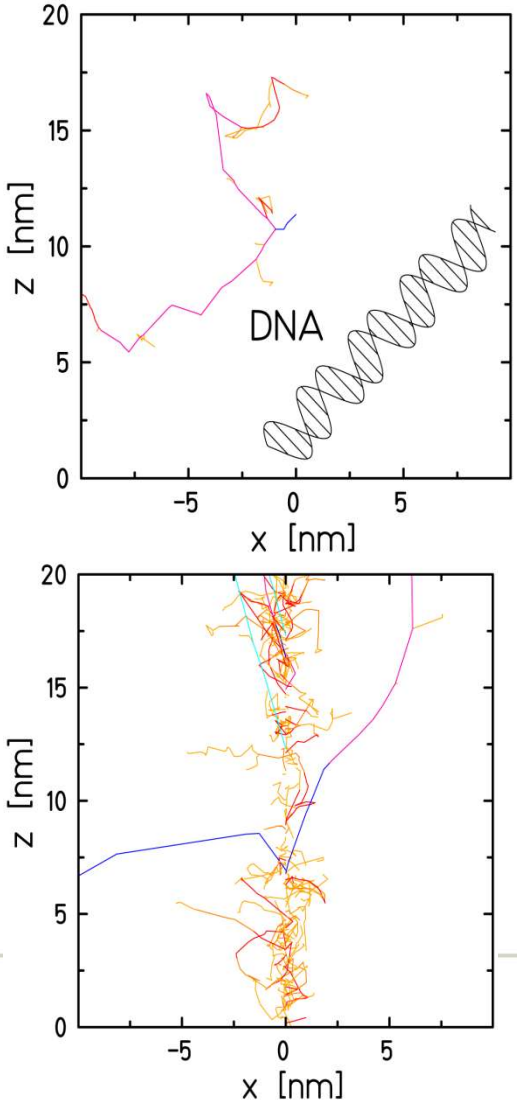
Gy

⬇

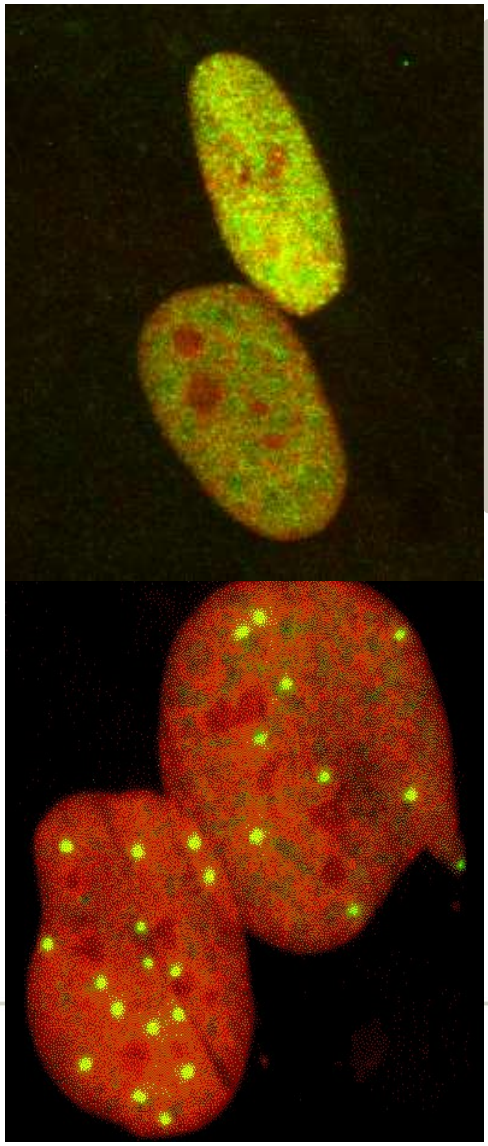
Gy (RBE)?

Linear Energy Transfer (LET): Energy transferred per unit of particle path length (keV/μm)

Ionization tracks



Damage in nucleus



Low LET
Sparsely ionizing

↓

Homogeneous deposition of dose

High LET
Densely ionizing

↓

Local deposition of high doses

M. Scholz et al.
Rad. Res. 2001

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Relative Biological Effectiveness (RBE) - particles

RBE-weighted Dose (Gy (RBE)) = Absorbed Dose (Gy) x RBE

$$\mathbf{RBE} = \left. \frac{D_{(\text{Co-60; 250kV})}}{D_{(\text{p-ions})}} \right|_{\text{Biological effect (cell inactivation)}}$$

RBE is the ratio of the dose of photons, e.g., ^{60}Co-rays or linear accelerator X-rays, relative to that of protons/ions required to produce a defined biologic response

RBE is a function of LET, Z, cell type, dose, endpoint

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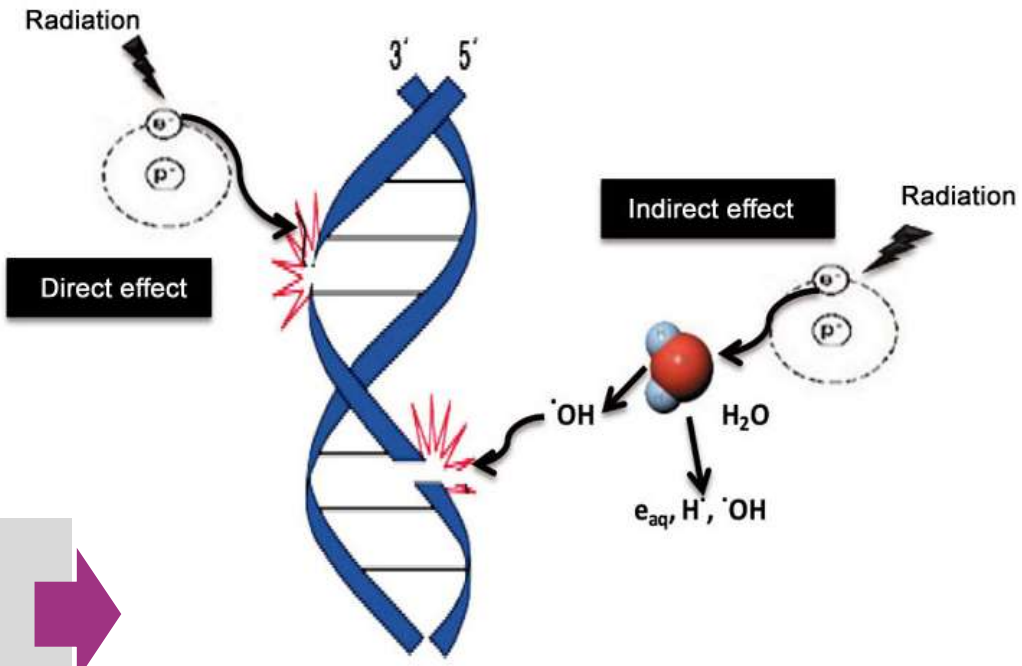
Ionizing Radiation (direct - indirect Effect)

Sufficient energy to ionize atoms (eject an electron or add an additional one)

This leaves a charged ion that will upset chemical bonds

If this affects critical molecules such as DNA it can result in cell damage, mutation or death



Ionizing Radiation (IR)

- **Directly ionizing:** (charged particles) electrons, protons, light ions …

Radiation deposits energy in the medium through direct Coulomb interactions (→ charged) with orbital electrons of atoms in the medium

- **Indirectly ionizing:** (neutral particles) photons, neutrons

Radiation deposits energy in the medium through a two step process: a charged particle is released in the medium ($\gamma \rightarrow e^-, e^+$; n → p or heavier ions) the released charged particle acts as a directly ionizing radiation

Physics problem in RT

Focus the dose on the target
(in space and time)

Dose localization:
ability to deliver dose precisely and accurately to a region of interest in the patient

Target definition:
- Tumor delineation
- Organ Motion
- Organ filling
- Tumor shrinkage

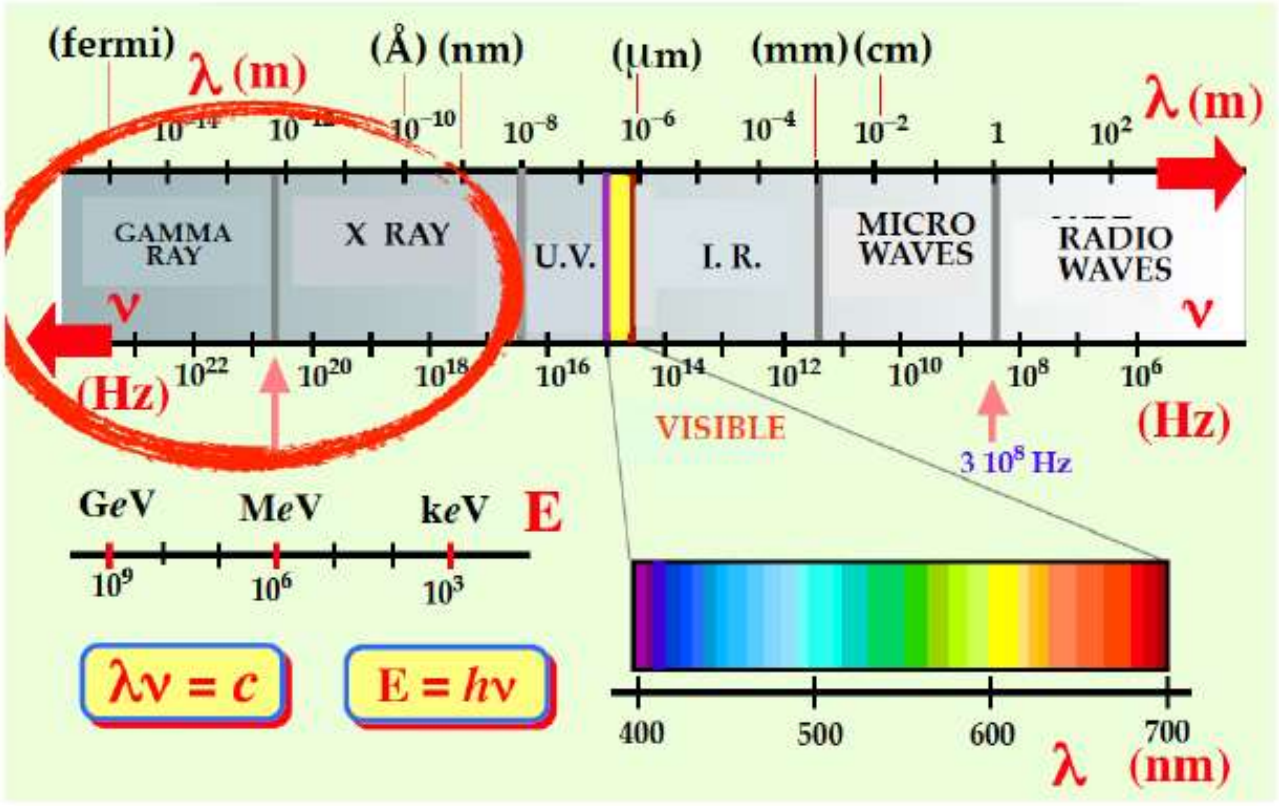
Imaging – treatment planning - delivery technology

radiation physical properties – technological inventions

The interaction processes of each type of radiation determine

→ penetration in matter (how much radiation reaches a target)
→ the amount of dose deposited in the target
→ Dose conformation around the target (dose to the OARs)

Electromagnetic radiation



NB: λ (or ν) does not in itself make the EM wave more or less penetrating!

→ the key is its interaction with matter, or more specifically, whether the photon energy is right to excite some transition of a charged particle

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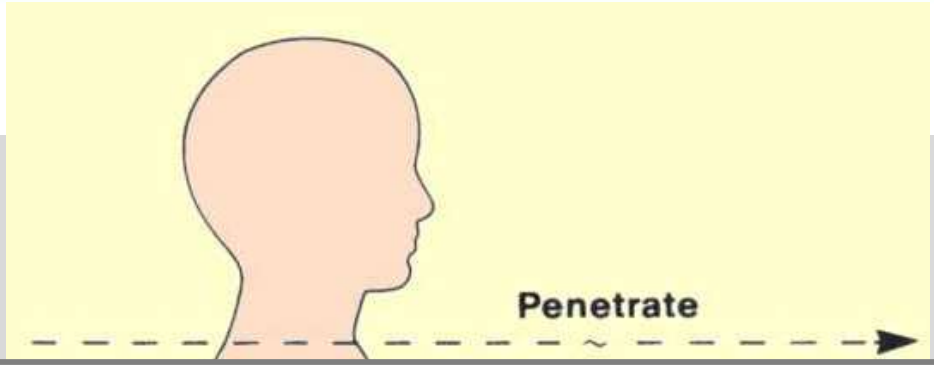
Photons interaction with matter

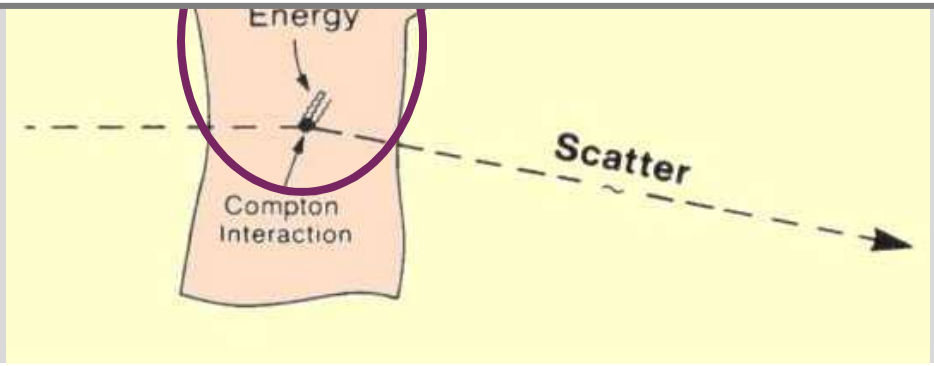
Transmission



Interactions are governed by stochastic laws
→ no prediction of the fate of a single photon
→ prediction of the fraction of transmitted photons

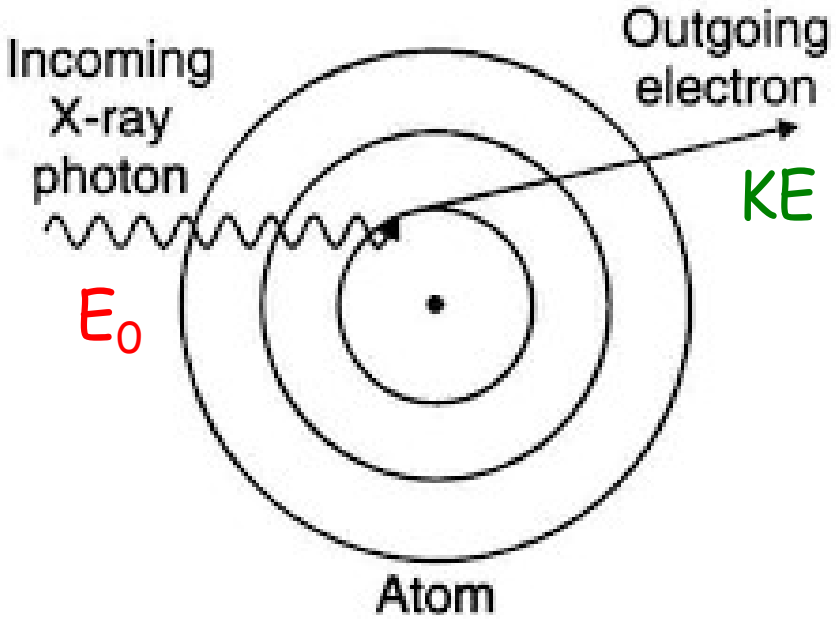
Scattering

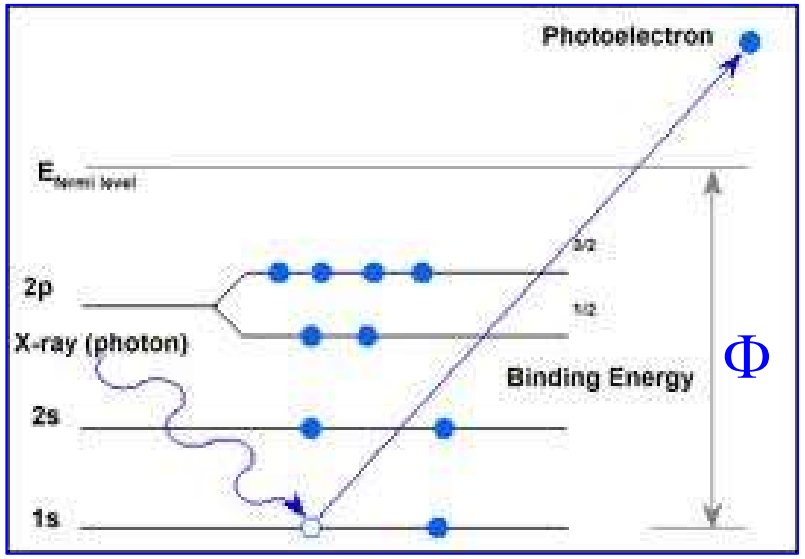
- Compton effect
- Coherent (Rayleigh)



Photons: photoelectric effect

- A photon is absorbed by an atomic electron, which is rejected from the atom
- The process needs the electron to be bound
- Kinetic energy of the ejected photoelectron KE is equal to the incident photon energy E_0 - the binding energy of the orbital electron Φ : $KE = E_0 - \Phi$





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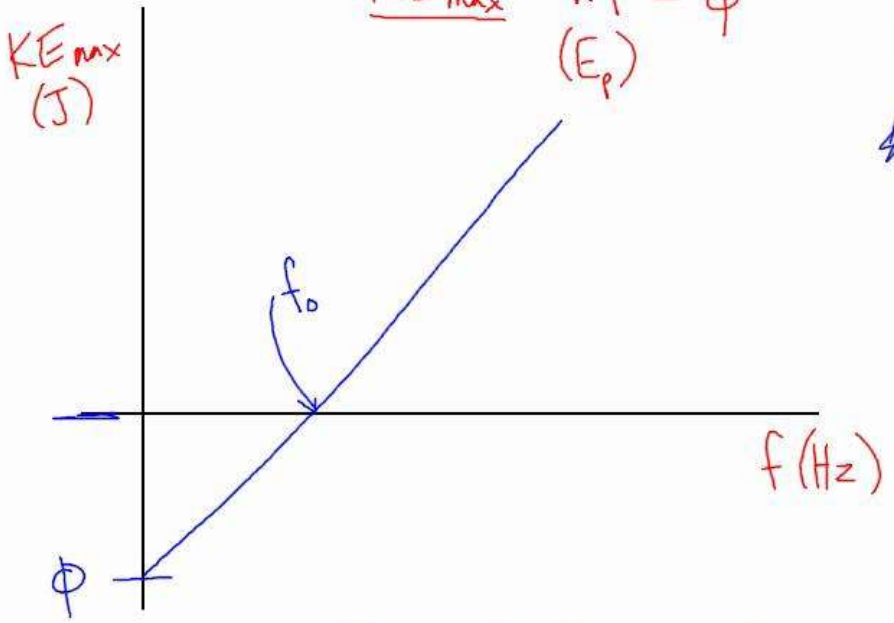
Photoelectric effect → split Personality of Light!

Graphs of Photoelectric Effect Phenomena

$y = mx + b$

$KE_{max} = hf - \phi$ (E_p)



Key Elements to Recognize

- slope = h
- y-int. = ϕ
- x-intercept = f_0 "threshold frequency" min. f_p that will result in e^- ejection

$c = f_0 \lambda_0$

λ_0 = "cutoff" wa

KE_{max} = Max KE of e's ejected from metal

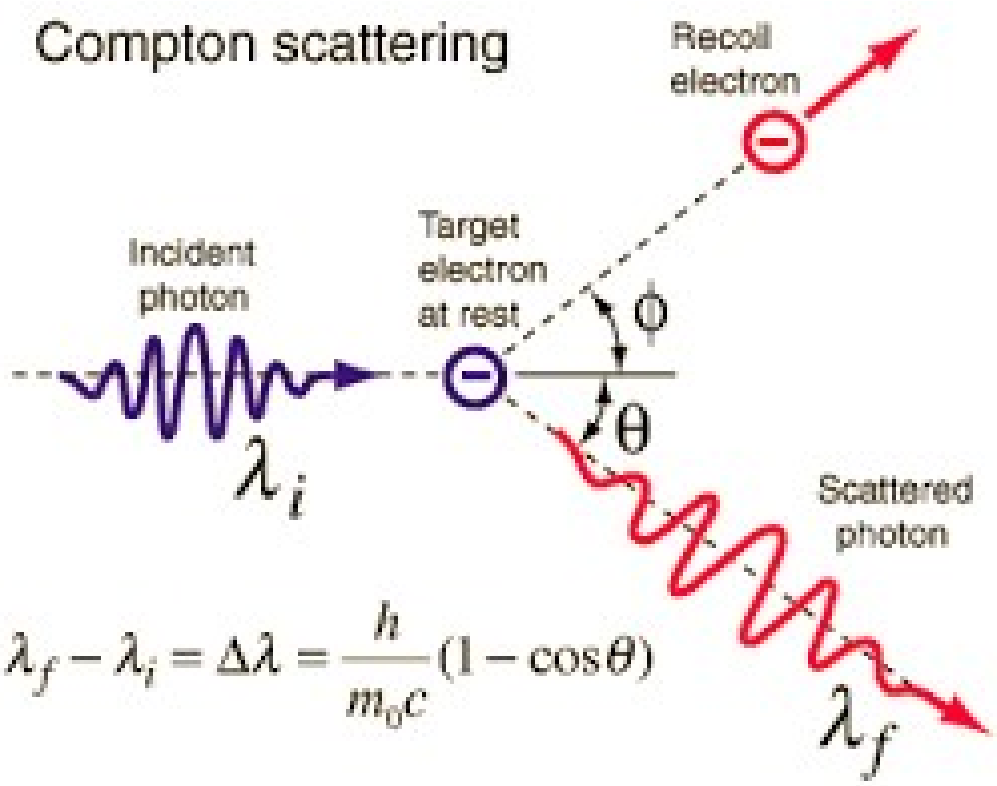
f = frequency of incident photons.

ϕ = "Work function" of metal. E required simply to remove an e^- from metal

Compton Effect

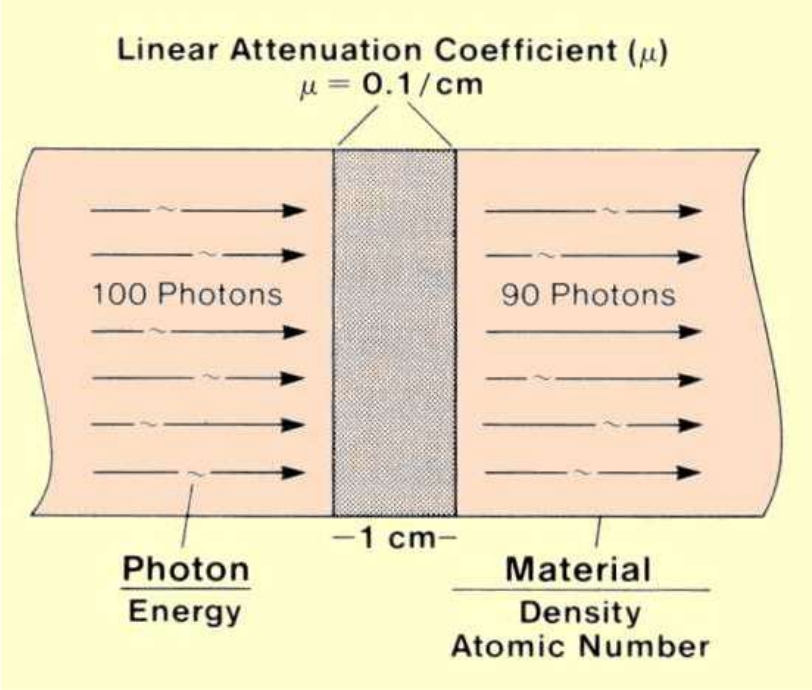
Inelastic scattering of a photon with a quasi-free electron

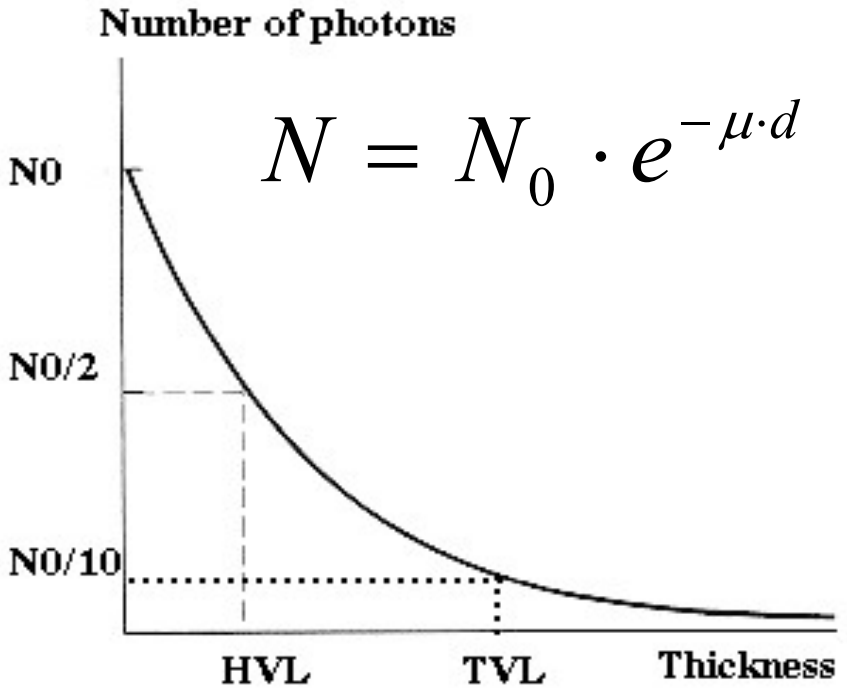
Decrease in photon energy → Part of the photon energy is transferred to the recoiling electron



Photons – linear attenuation coefficient

μ = interaction probability per unit path lenght (cm^{-1})





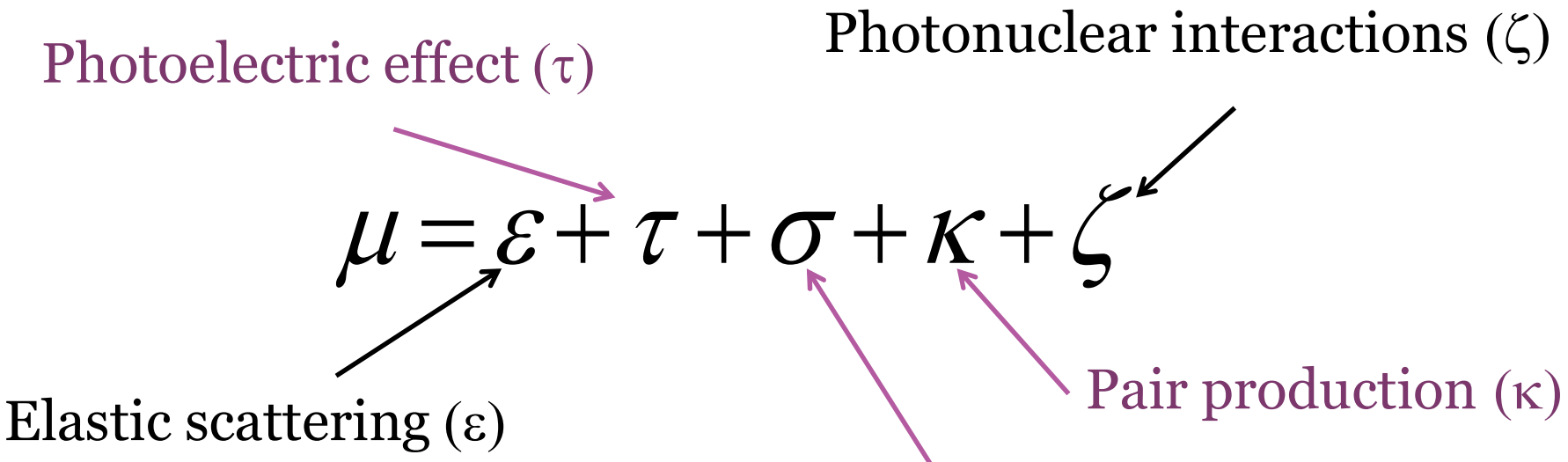
$$N = N_0 \cdot e^{-\mu \cdot d}$$

d: absorber thickness
μ: μ(E,Z): linear attenuation coefficient
HVL: half value layer
TVL: tenth value layer

School

Attenuation coefficient μ

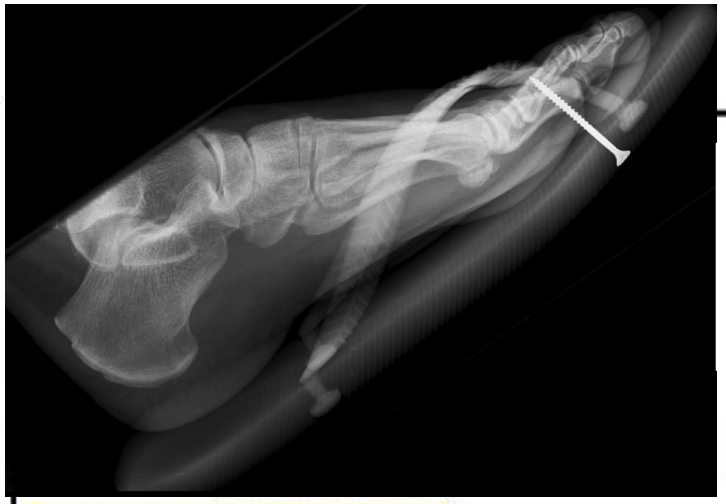
- Each photon interaction process it's represented by its own attenuation coefficient (ε,τ,σ,κ,ζ). The sum of coefficients gives μ
- Photoelectric absorption, Compton effect and Pair production are dominant in the energy range of interest (0.1 – 100 MeV)



Photons Attenuation - Radiography

• Attenuation is the most important property for medical imaging.

• Differences in the number of photons behind an inhomogeneous absorber create contrast.



$$I(x) = I_0 e^{-\mu x}$$

FIGURE XVI-1. Diagram showing how the primary radiological image is produced.

$\mu = \mu(E,Z) \Rightarrow$ same E

$\mu_{lead} > \mu_{bone} > \mu_{softT} > \mu_{air}$

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Photons interaction with matter

Photon interaction with matter for the energy range of gamma and x-radiation (Z = atomic number, A = atomic mass, except for hydrogen one can use as a first approximation A = 2Z). The atomic number and energy dependence is an approximation only and varies with each other.

Interaction type	dependence on atomic number	dependence on photon energy	secondary particles
Classical scattering	$Z^{2.5}/A$	E^{-2}	
Photo effect	Z^4/A	E^{-3}	electrons, characteristic x-rays, Auger-electrons
Compton effect	Z/A	$E^{-1/2}$	electrons, scattered photons
Pair production	Z^2/A	E > 1022keV log E	electrons, positrons, annihilation radiation
Nuclear photo effect	depends on material	E > threshold for particular material	neutrons, protons, fission, ...

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μ: μ(E,Z)

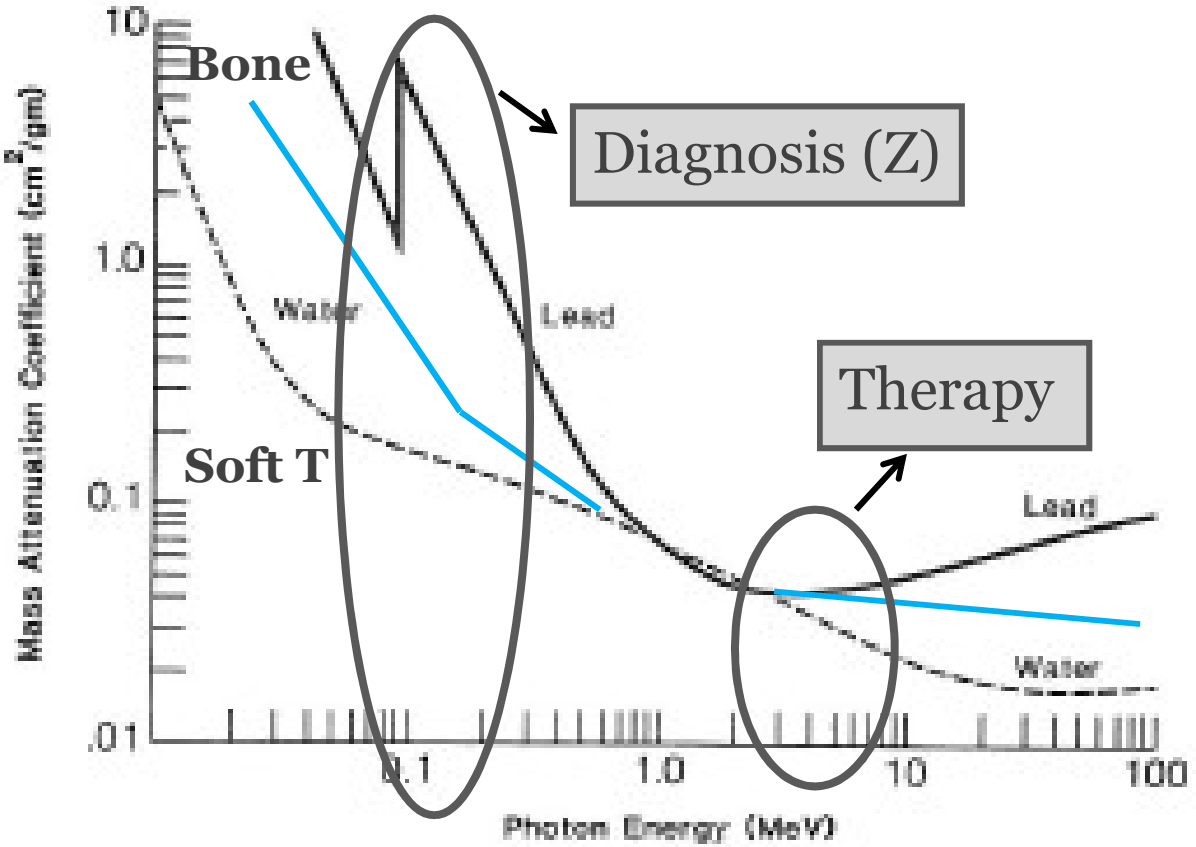

Figure 5.12. Plot of total mass attenuation coefficient (μ/ρ) as a function of photon energy for lead and water. Reprinted with permission from Johns HE, Cunningham JR. The physics of radiology, 3rd ed. Springfield, IL: Charles C Thomas, 1969.

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The dominant photon interaction process

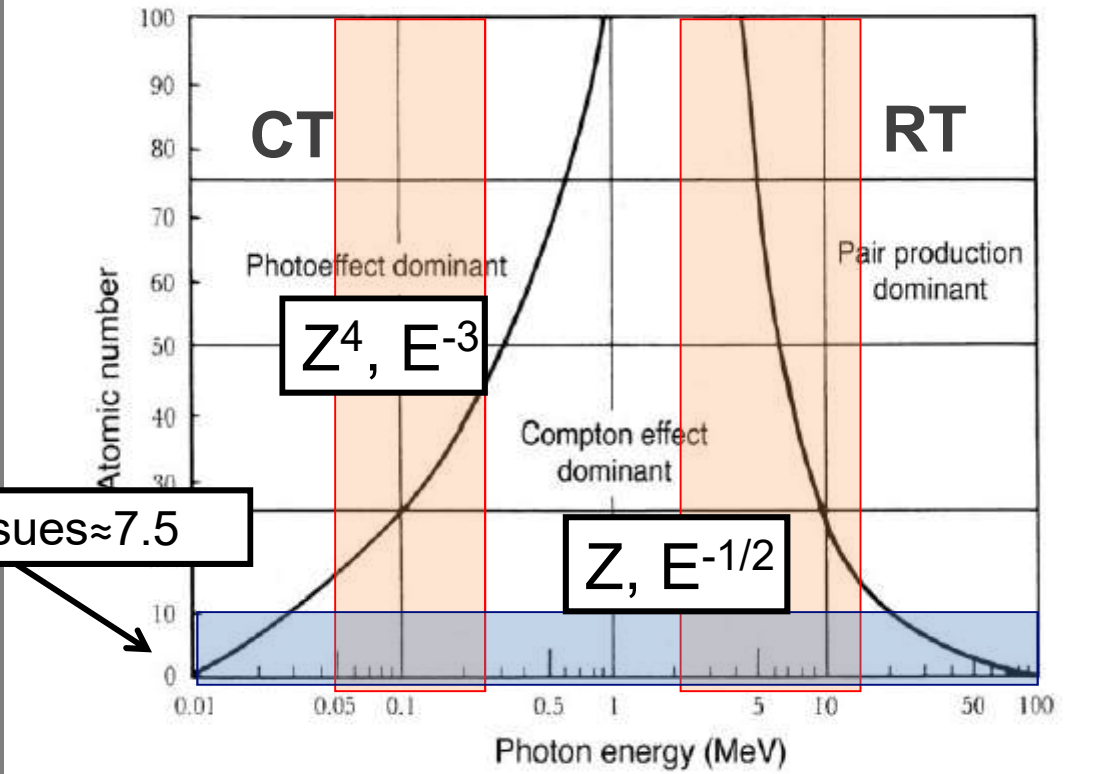

FIG. 1.8. Regions of relative predominance of the three main forms of photon interaction with matter. The left curve represents the region where the atomic coefficients for the photoelectric effect and Compton effect are equal ($_a\tau = {}_a\sigma_C$), the right curve is for the region where the atomic Compton coefficient equals the atomic pair production coefficient ($_a\sigma_C = {}_a\kappa$).

Z_{eff} water eq tissues≈7.5

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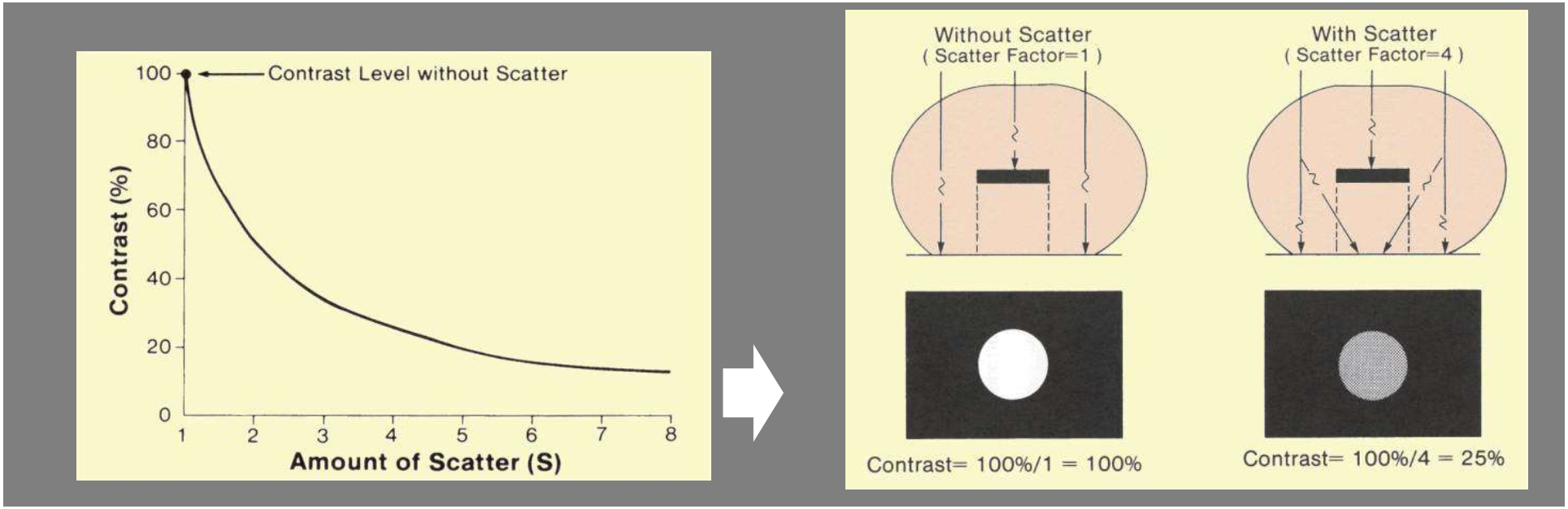
Consequences

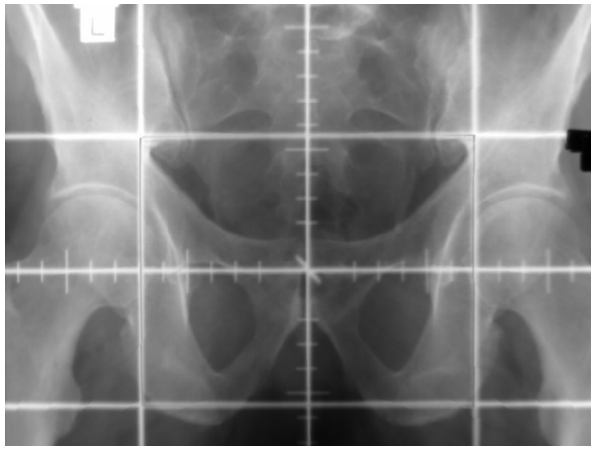
- Importance of the compton process in the interaction with soft tissue (Z<10) → all imaging modalities will have problems with scattered radiation



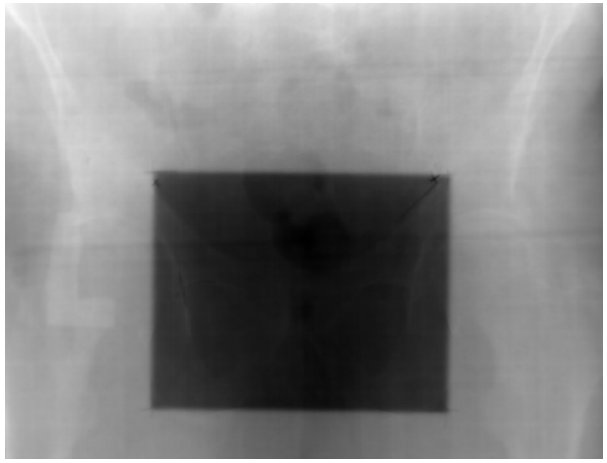
Consequences

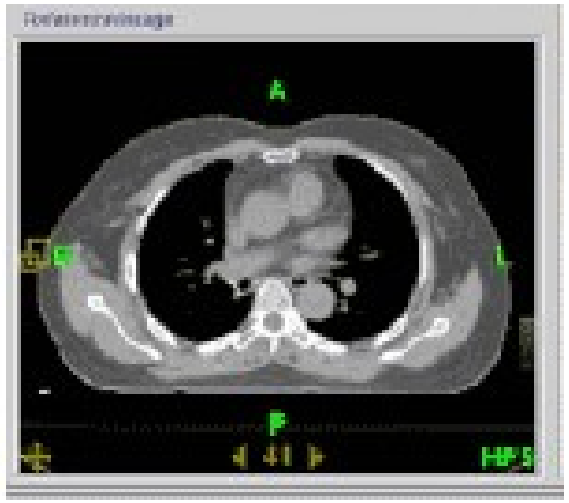
- MV photons are less suitable for imaging

Reference simulator film



Check portal film





kV CT

MV CT

Conversion of μ to CT number

μ values are scaled to that of water to give the CT number (Hounsfield Unit)

$$\text{CT number} = 1000 \times \frac{\mu_{tissue} - \mu_{water}}{\mu_{water} - \mu_{air}}$$

TPS: The relative electron density of the irradiated medium can be determined from the CT data set via the conversion between CT numbers and ρ_e

Tissue	CT-number (HU)
Air	-1000
Lung	-300
Fat	-90
Water	0
White Matter	30
Gray Matter	40
Muscle	50
Trabecular Bone	300-500
Cortical Bone	600 -3000

Photons are indirectly ionizing

Photons deposit energy in the medium through a two step process:

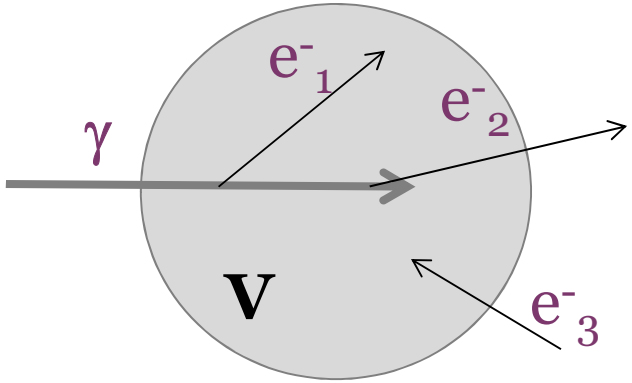
1. energy is transferred to charged particles released in the medium
2. the released charged particles act as directly ionizing radiation

KERMA: **K**inetic **E**nergy **R**eleased per unit **Ma**ss (J/kg = Gy)

Sum of initial kinetic energies transferred from *indirectly ionizing* radiation to charged particles (electrons) in a sample of matter

- initial kinetic energies of e^-_1 and e^-_2 contribute to the **KERMA** as both were generated in V, e^-_3 was generated outside V, so does not contribute

- e^-_1 and e^-_3 contribute to the **Dose** in V, while e^-_2 deposits energy outside V, so does not contribute



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KERMA vs Absorbed Dose

absorption of energy does not take place at same location as energy transfer by **KERMA**

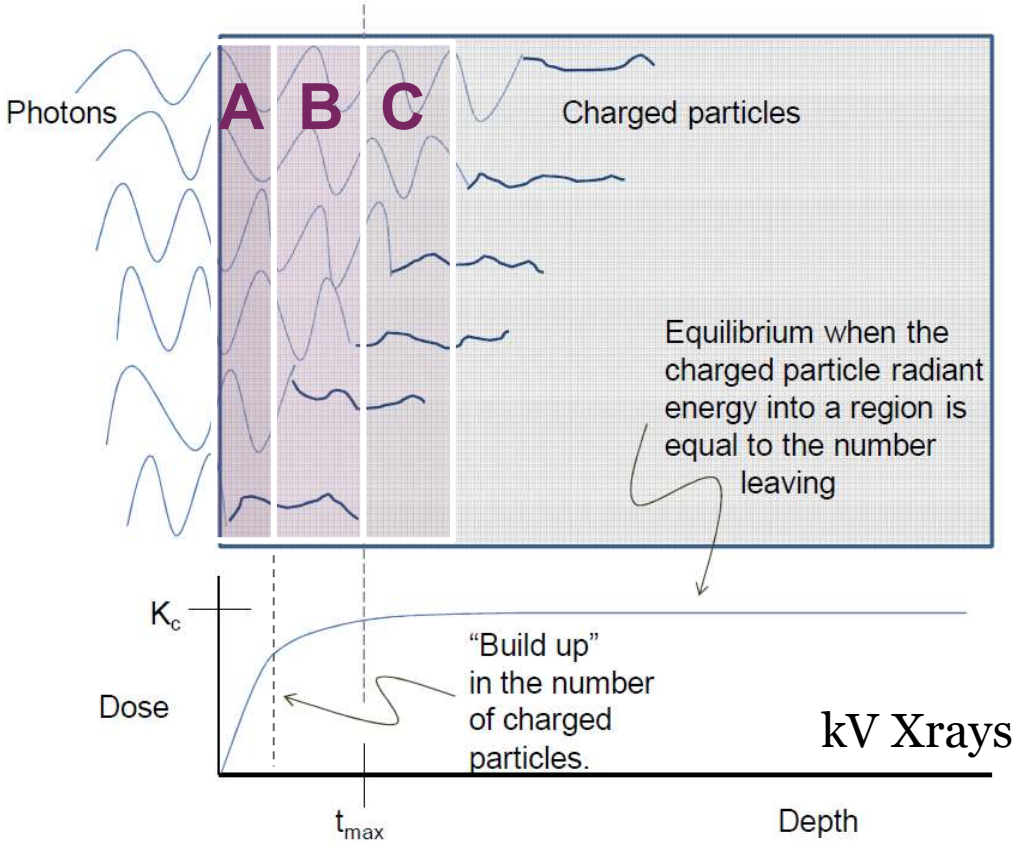
→ electrons travel in the medium and deposit energy along their tracks, the subsequent imparting of energy to matter (**absorbed Dose**) is spread over distances determined by the ranges of charged particles

Charged Particle Equilibrium

Charged particle equilibrium (CPE) exists if for each charged particle with energy **E** leaving a volume **V**, there is an identical particle with same energy **E** entering **V**

- only a fraction of electron track deposits energy in voxel **A** → dose is low
- in voxel **B**, a new electron starts but there is also part of electron track which started upstream in voxel A → dose is higher B
- kinetic energies leaving voxel C is balanced by kinetic energies entering in this volume → equilibrium is reached at **C**

at C → Dose ≈ KERMA



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Depth Dose Profiles - Photons

Build up

$z < z_{max}$

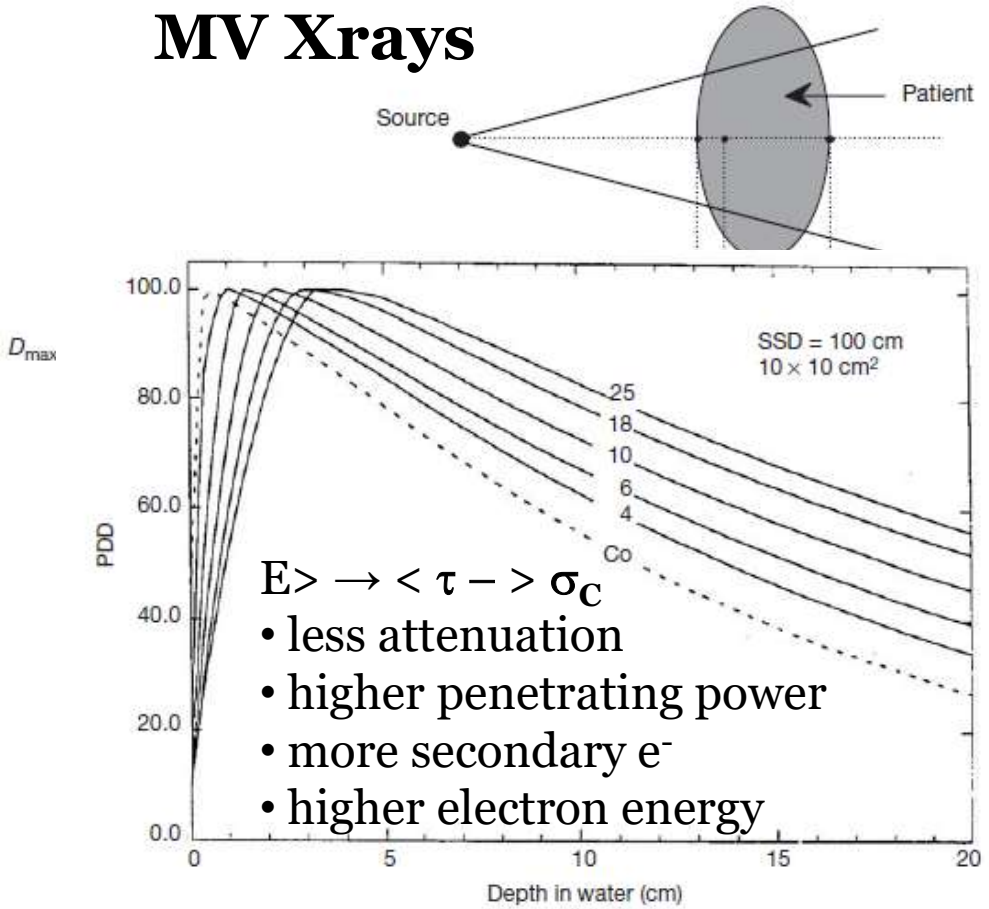
- Absorbed dose is much smaller than the transferred energy (KERMA)
- Dose buildup results from the relatively **long range** of secondary charged particles that first are released in the patient by photon interactions and then deposit their kinetic energy in the patient

D_{max} -> $z=z_{max}$ ≈ range of secondary particles

$z > z_{max}$

Dose decrease for photons attenuation in the patient

MV Xrays



E> → < τ – > σ_C

- less attenuation
- higher penetrating power
- more secondary e^-
- higher electron energy

FIG. 6.10. PDD curves in water for a 10 × 10 cm² field at an SSD of 100 cm for various megavoltage photon beams ranging from ^{60}Co γ rays to 25 MV X rays.

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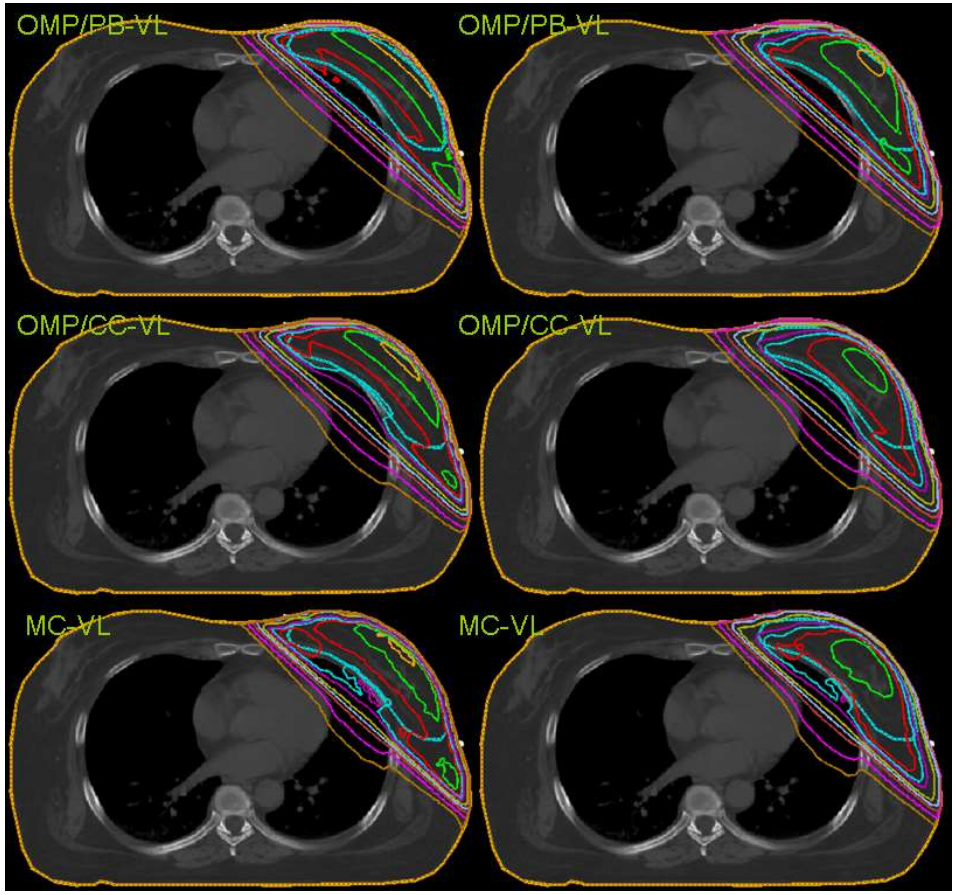
e^- disequilibrium at tissue interfaces

6 MV 18 MV



Pencil beam

Collapsed cone

MC simulations

Knoos T et al. Phys. Med. Biol. 51 (2006)

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e^- disequilibrium at tissue interfaces

Soft tissue – lung interface

→ Less attenuation → Increase in primary beam intensity

→ Reduction of scattering material

→ Different electron transport and longer range

→ lateral loss of e^- equilibrium

NB: Higher γ E → higher e^- range → penumbra broadening → wider margins required to compensate for e^- disequilibrium (increased dose calculation uncertainty – worst for smaller target volumes)

Sources and References

- **IAEA**

Radiation protection of Patients
http://rpop.iaea.org/RPOP/RPoP/Content/
Radiation Oncology physics handbook
http://www-naweb.iaea.org/nahu/dmrp/

- **The Physics of Radiation Therapy**

Faiz M Khan (Lippincott Williams & Wilkins)

- **The physical principles of medical imaging**

http://www.sprawls.org/resources

Sources and References

credits to

Giorgio Baiocco (Physics department, UniPV)
Andrea Mairani (CNAO and HIT)

Photons interaction with matter

Table illustrating importance of various interactions with energy in H_2O*

Photon Energy (MeV)	Relative number of interactions (%)		
	τ	σ	κ
0.01	95	5	0
0.026	50	50	0
0.060	7	93	0
0.150	0	100	0
4.00	0	94	6
10.00	0	77	23
24.00	0	50	50
100.00	0	16	84

* F. Khan, The Physics of Radiotherapy

Radiation through matter – how they interact

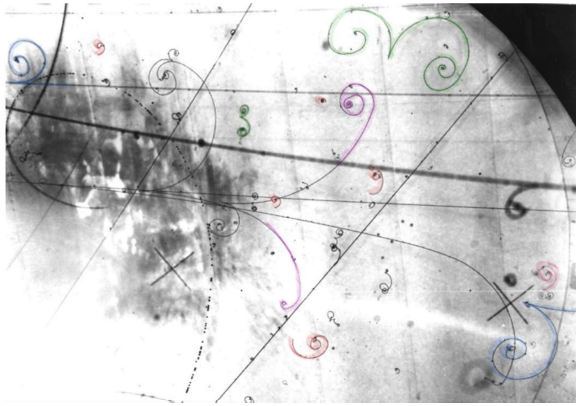
- Electromagnetic radiation
- Charged particles

ELECTROMAGNETIC interactions
in particular inelastic collision with the atomic electrons
(Strenght and Range of the Coulomb force)
+
NUCLEAR interactions

- Neutrons

NUCLEAR interactions

Modern Dose Calculation Algorithms



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Charleroi

BELGIUM

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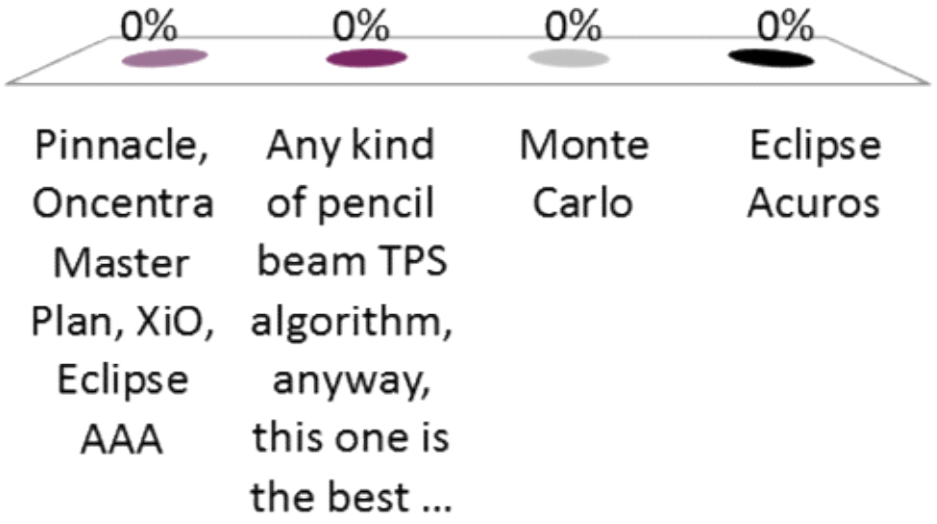
Question 1: Which RT Planning System (for photon beams) do you have ?

A. Pinnacle, Oncentra Master Plan, XiO, Eclipse AAA

B. Any kind of pencil beam TPS algorithm, anyway, this one is the best …

C. Monte Carlo

D. Eclipse Acuros



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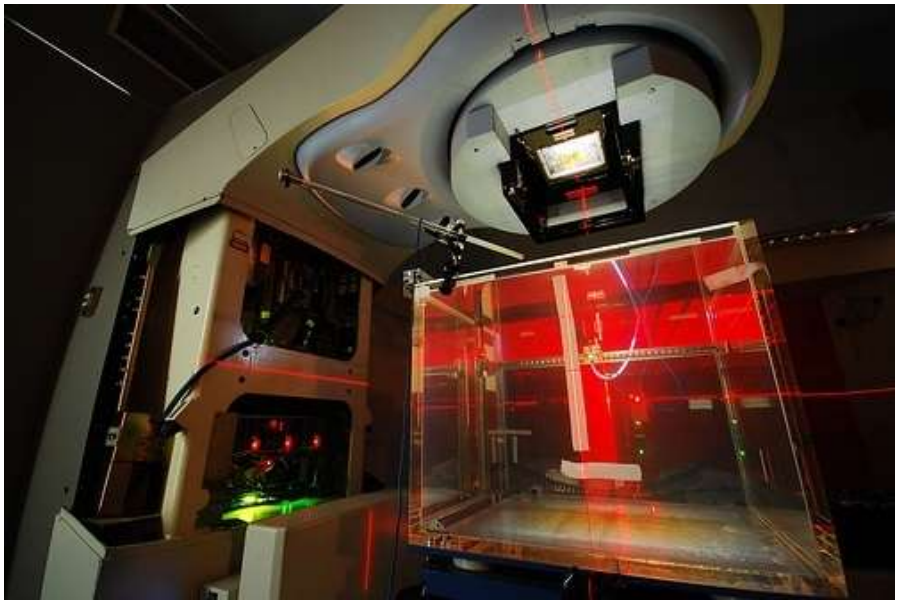
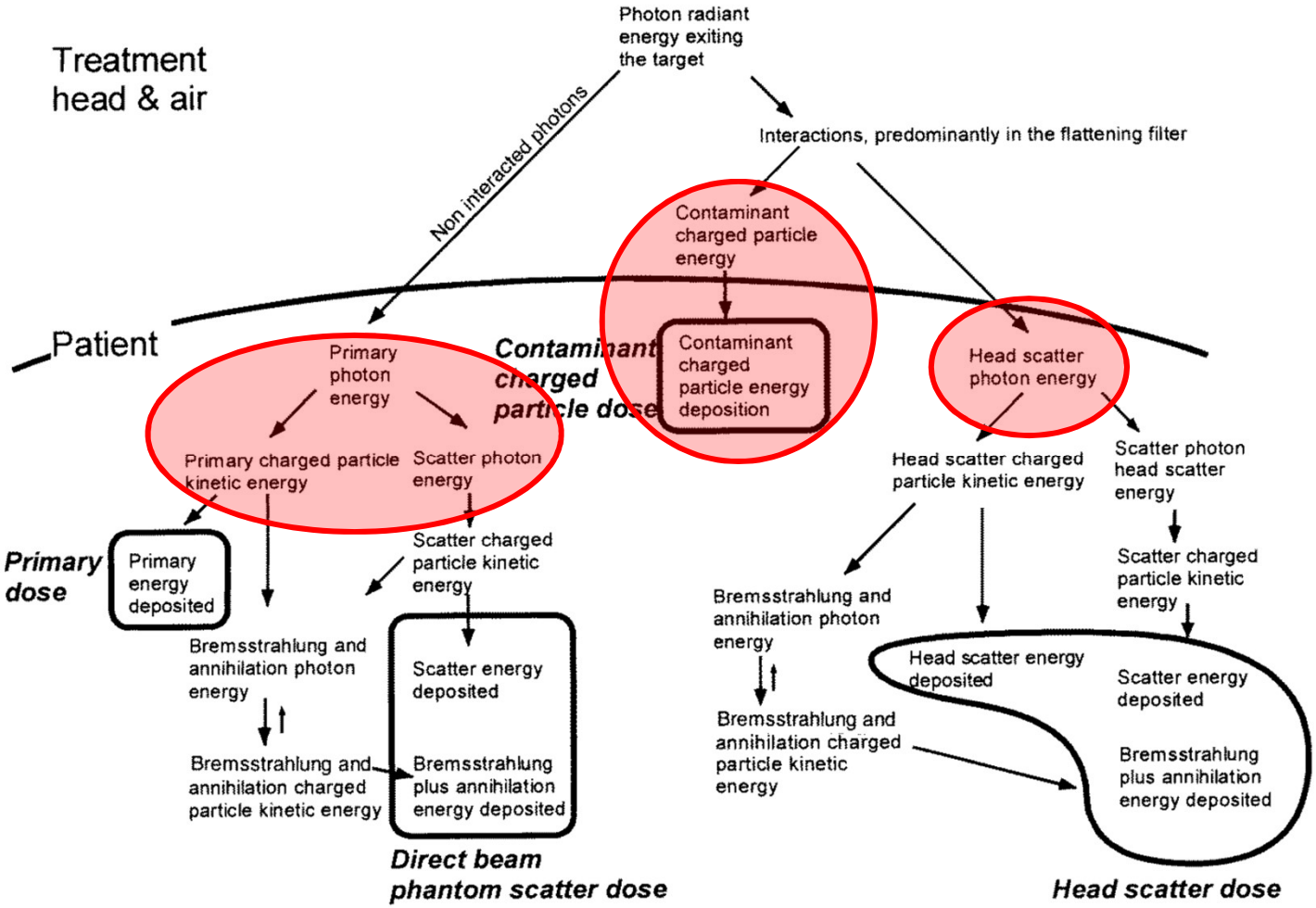
From Measurement to Dose in the Patient



- Based on the knowledge of the dose in a phantom, how can the relative and absolute dose be determined in patients?

Interaction for Clinical Photon Beams



From: A. Ahnesjö and M.M. Aspradakis, Dose calculations for external photon beams in radiotherapy. Phys Med Biol 44 (1999), pp. R99–R155.

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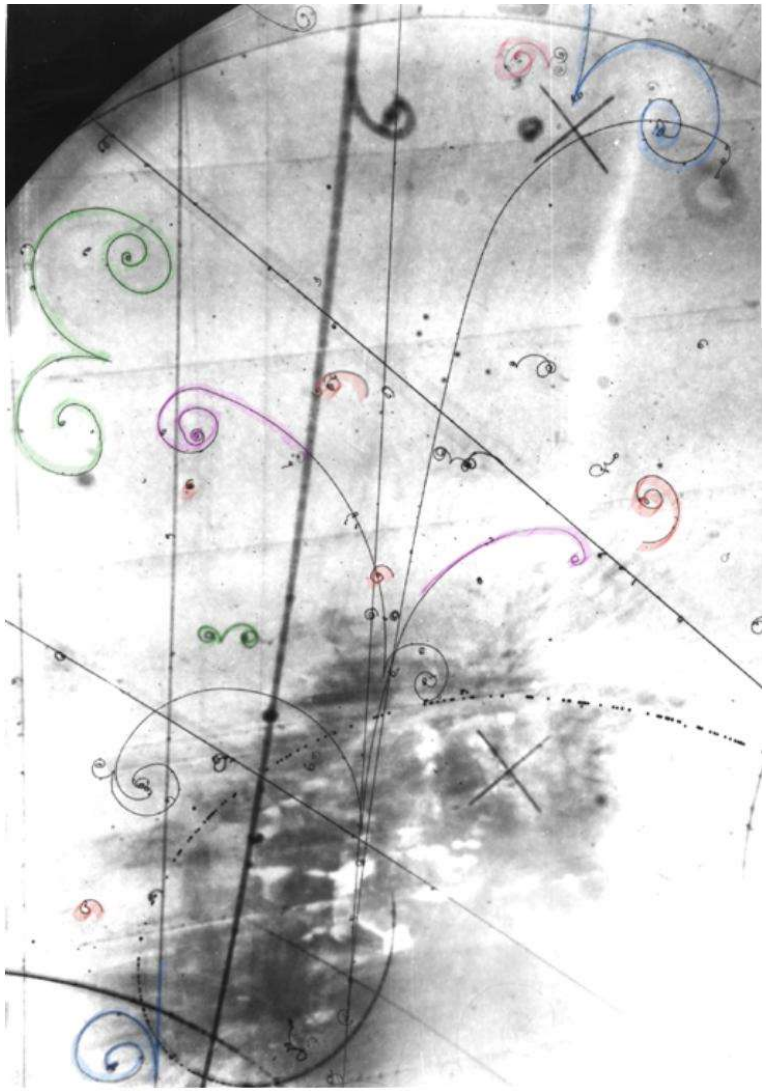
Absorbed Dose

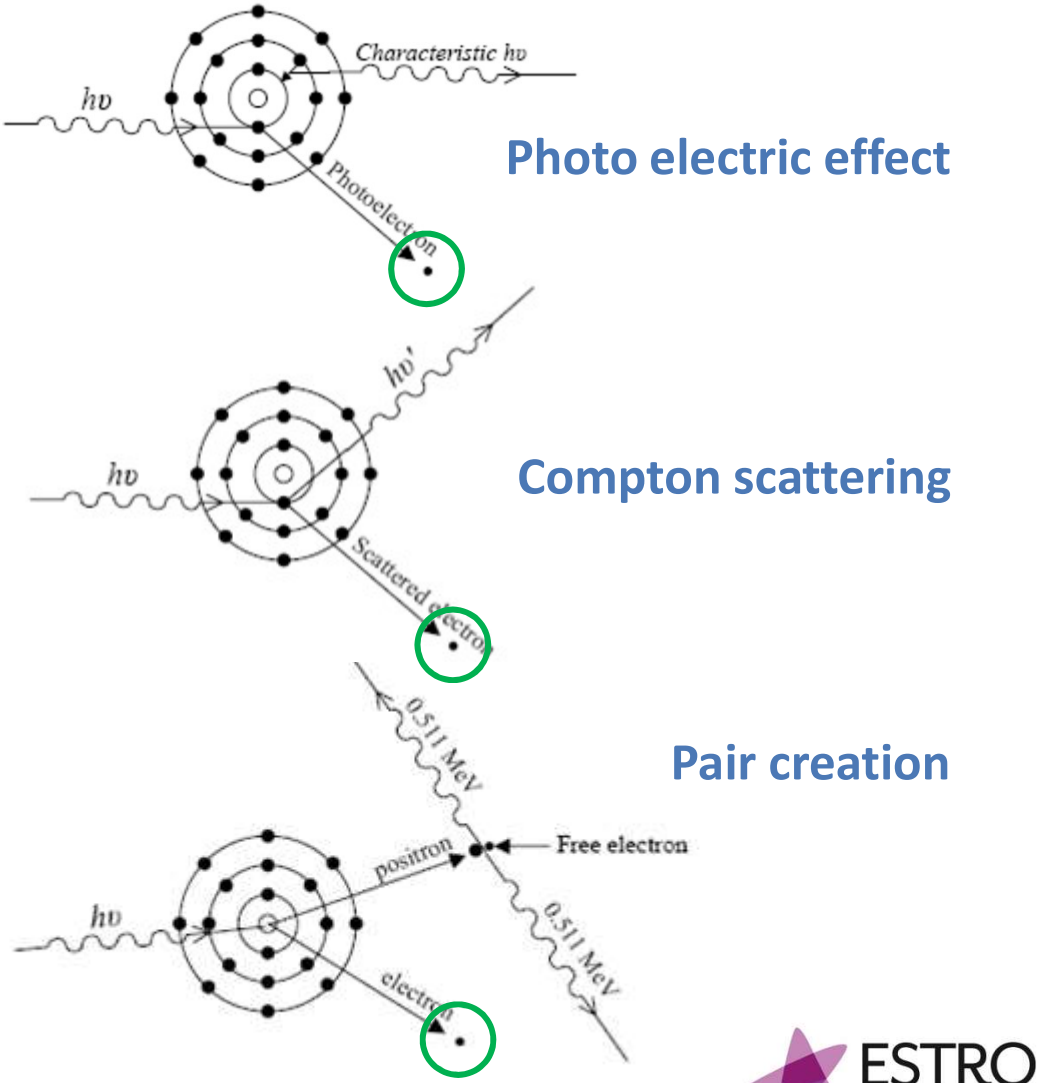
- **Absorbed dose** (also known as total ionizing dose) is a measure of the **energy deposited** in a medium by **ionizing** radiation.

- It is equal to the energy deposited per unit mass of medium, and so has the unit J/kg, which is given the special name Gray (Gy).

charged particles

Mechanisms of Interaction





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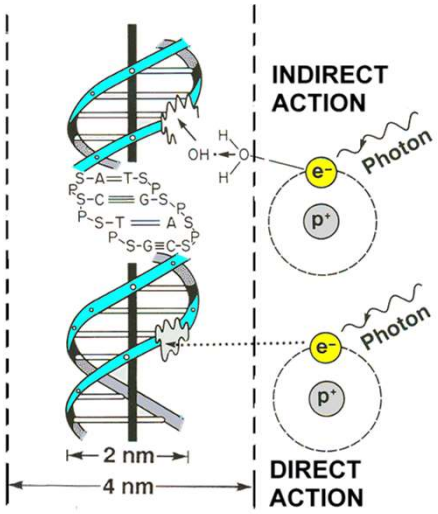
What Happens to the Electrons?

- Electrons move away **from the point of creation** leaving a trail of **ionized** atoms.
  - This is where cell damage is done in a patient
  - *The amount of cell damage is related to the amount of ionizations or energy deposited (absorbed dose!)*



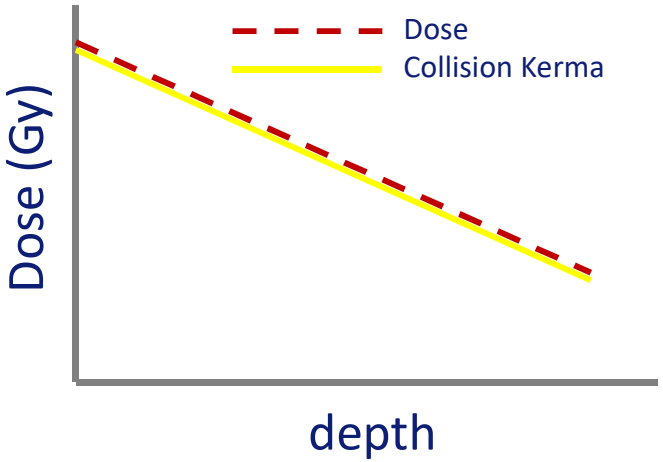
Basic Theorems and Principles

- **ABSORBED DOSE**: kinetic energy transferred per unit mass (J/kg = Gy)
  - Charged particles (created by primary photons) **transfer** some of kinetic **energy to medium** -> absorbed dose and lose some of their energy in the form of radiative losses (bremsstrahlung, etc)
  - Absorbed dose is the mean energy transfer imparted by ionizing radiation to matter with volume V
    - Mean energy transfer = E(entering V) – E(leaving V)
  - Because electrons travel in the medium and deposit energy along their tracks, **absorption of energy does not take place at same location as energy transfer by KERMA (Energy transfer from indirectly ionizing radiation to directly ionizing)**

Charged Particle (=Electronic) Equilibrium

- **Charged particle equilibrium** (CPE) exists if for each charged particle with energy **E leaving a volume**, there is an **identical** particle with **same** energy **E entering that volume**
- **Low** energy beam enters surface: **KERMA** is max because fluence is greatest at surface
- **Low** energy beam: **KERMA = Dose** because the energy is deposited at the interaction point

Low energy



Ignoring brehmsstralung

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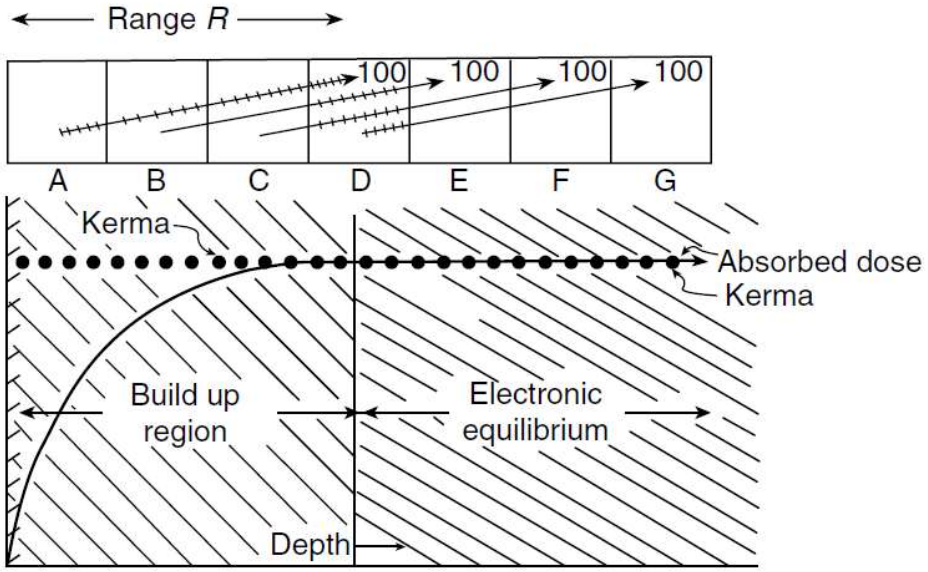
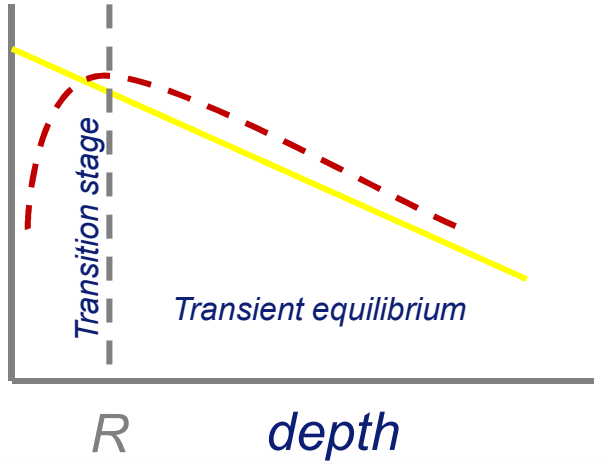
Charged Particle (=Electronic) Equilibrium

- **High** energy beam enters surface: **KERMA** is max because fluence is greatest at surface
- **High** energy: energy is **deposited in front** of the interacting photon → lack of energy deposition at the surface
- Dose at surface is low (contamination: charged particles generated in linac head)





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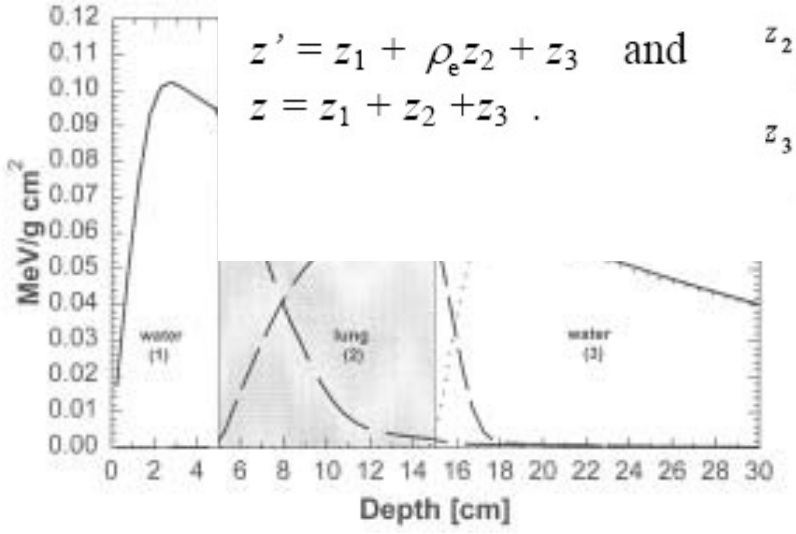
Analytical Methods for Photon Beam Calculation

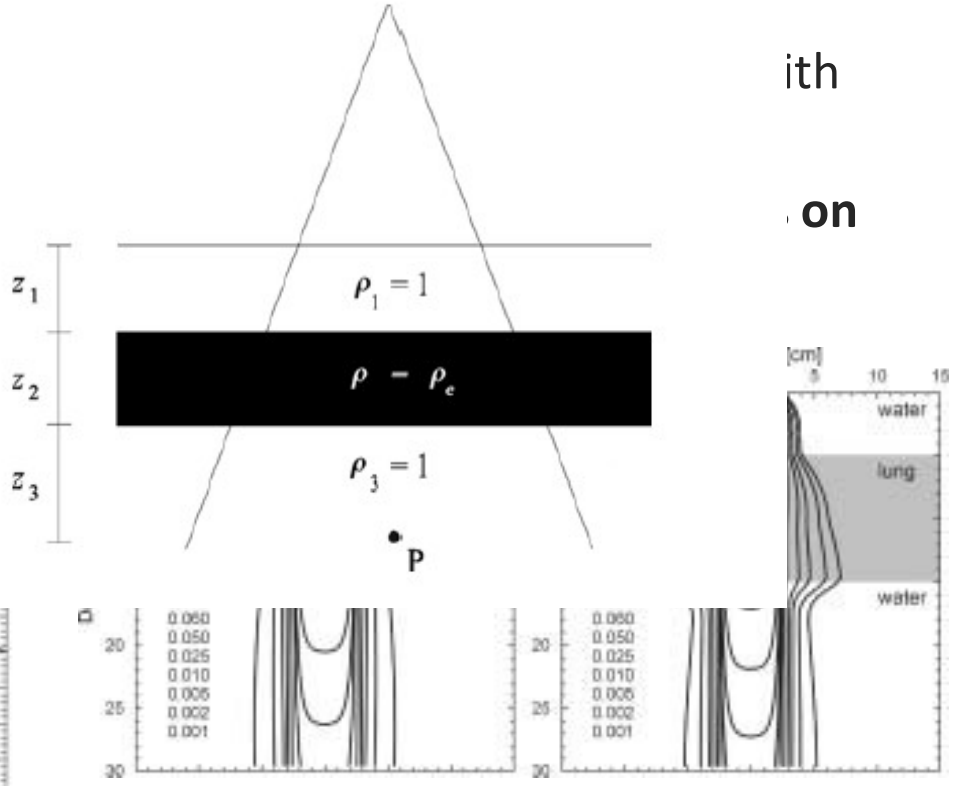
- **Early** methods of dose calculation
  - Based on **separating** the dose into **primary** and **scatter** component usi
  - **Inh** ith **de**
  - **Wo** **on sca**

$$CF = \frac{TAR(z', r_d)}{TAR(z, r_d)}$$

where

$$z' = z_1 + \rho_e z_2 + z_3 \quad \text{and}$$
$$z = z_1 + z_2 + z_3 \ .$$





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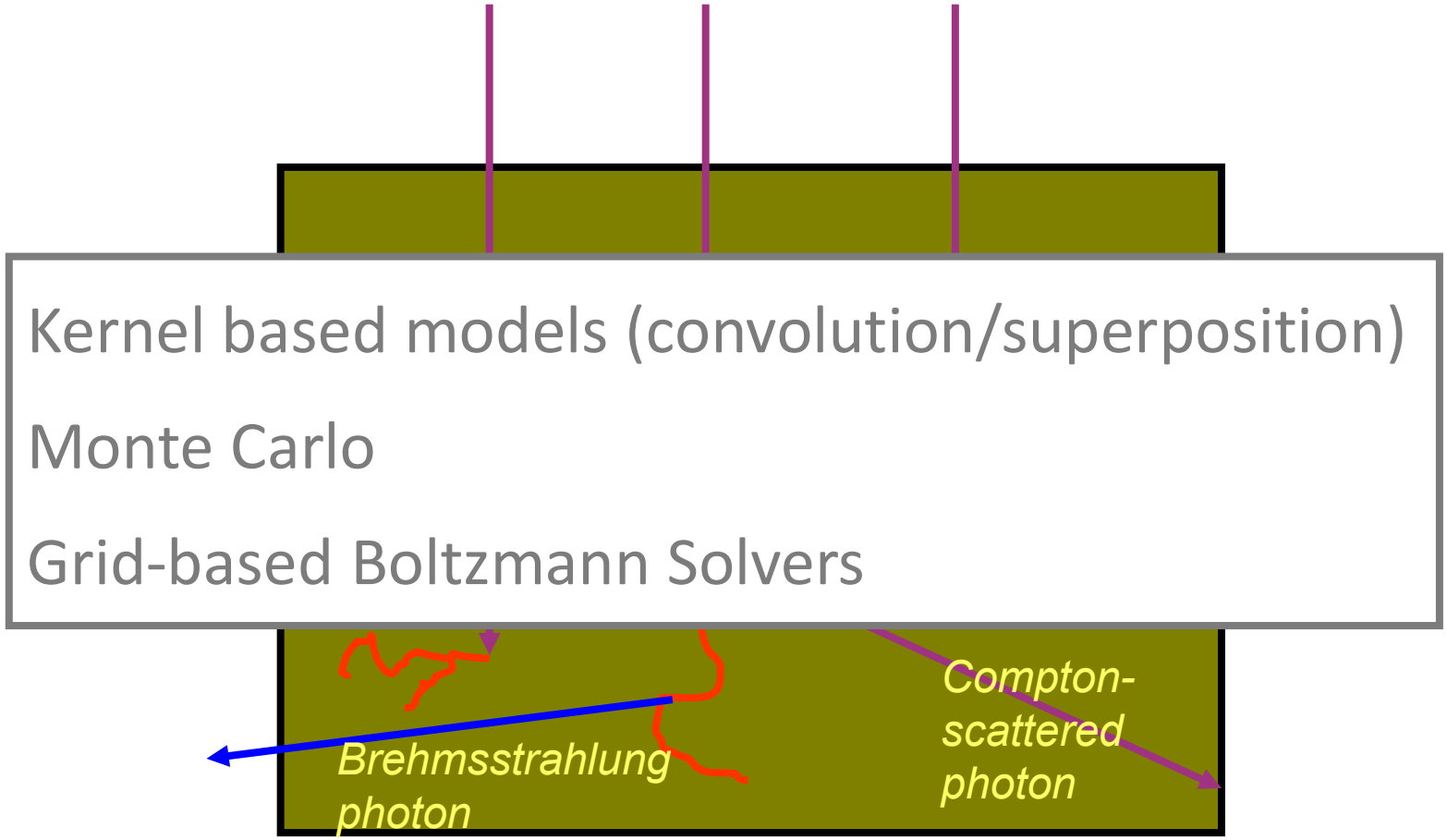
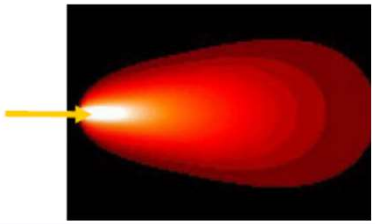
Modeling of Complex Physical Processes

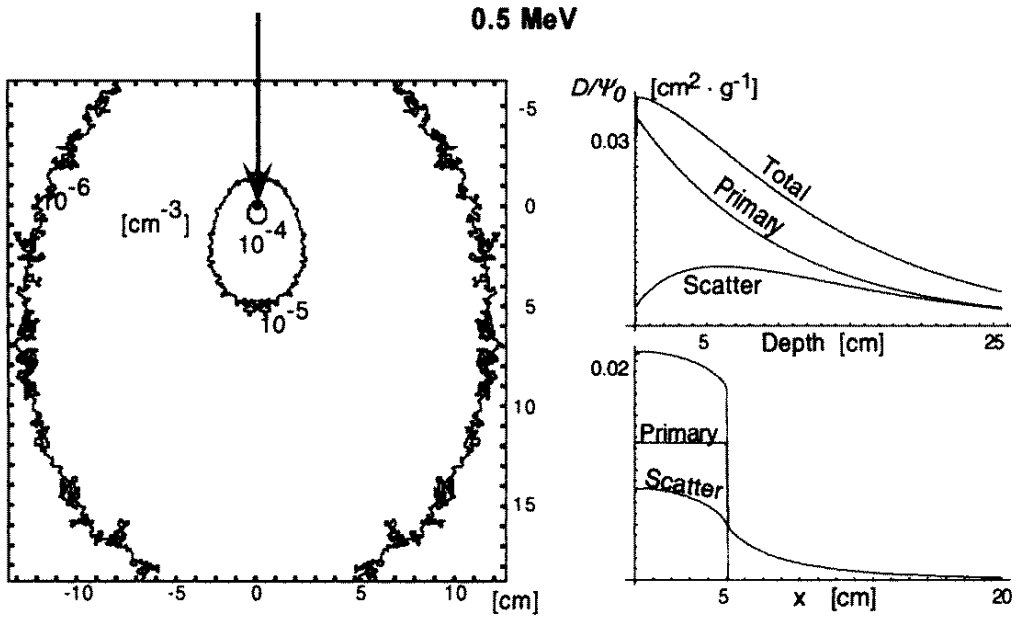


Kernel-Based Methods

- Combine an **analytical** calculation of the primary photon interactions with the subsequent transport and **energy deposition** by secondary particles described by **pre-calculated kernels**
- Point-spread **kernel**: Absorbed dose from **both** secondary **electrons** and **photons** around the interaction point
- Calculated by **Monte Carlo** in infinite medium of water since **too chaotic** (sometimes photoelectric, Compton, …)
- Energy spectrum derived from measurements (pdd)



Dose Deposition Kernel Low Energy



- **Low energy**: electron range much shorter than photon mean free path
- Small primary dose region (short BU distance and steep penumbra)
- Wide scatter dose region (high dose outside field)
- Isotropic isolevels (large amount of backscatter)

From: A. Ahnesjö and M.M. Aspradakis, Dose calculations for external photon beams in radiotherapy. Phys Med Biol 44 (1999), pp. R99–R155.

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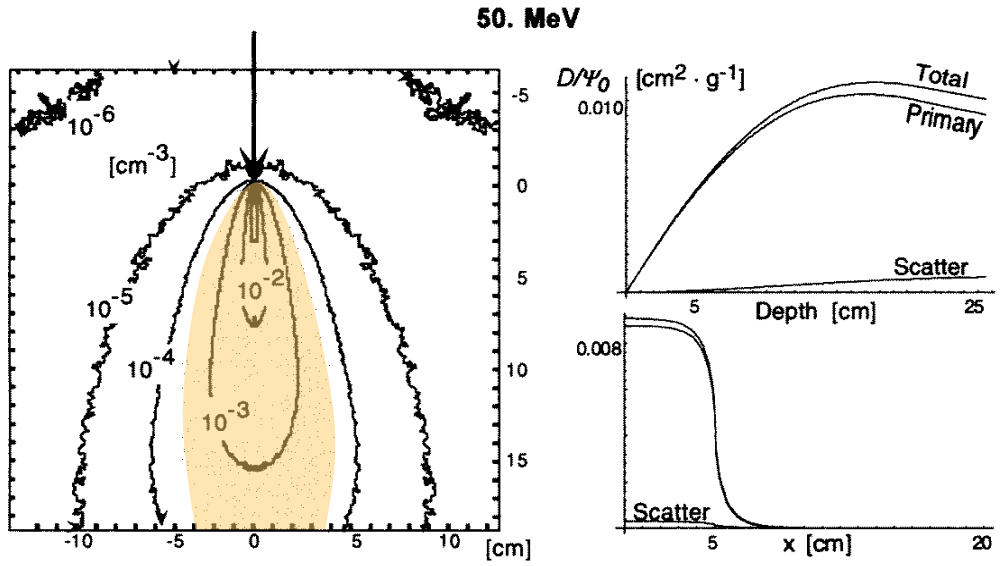
Dose Deposition Kernel High Energy



- **High energy**: electron track lengths are of the same order as the photon mean free paths
- Large primary dose region (long BU distance & broad penumbra)
- Narrow scatter dose region (low dose outside field)
- Forward directed isolevels (small amount of backscatter)

From: A. Ahnesjö and M.M. Aspradakis, Dose calculations for external photon beams in radiotherapy. Phys Med Biol 44 (1999), pp. R99–R155.

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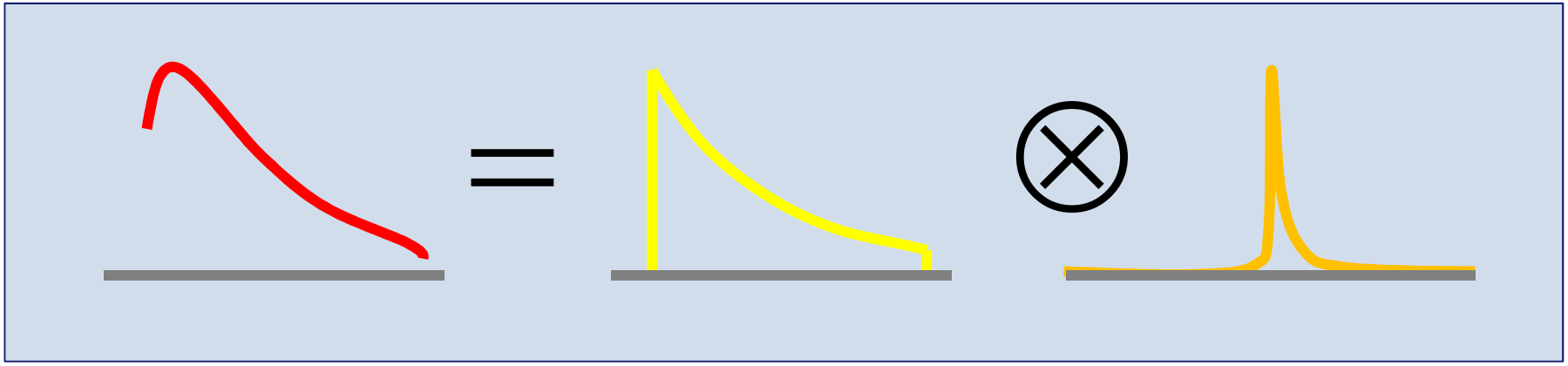
Principle of Convolution (1D)

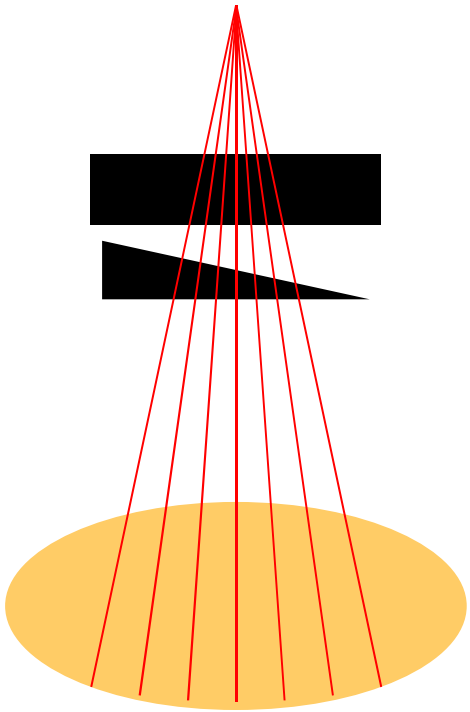


$$D(x) = \int T(x') \cdot K(x - x') dx'$$

D = Dose Distribution
T = Terma Distribution
K = Dose Deposition Kernel

TERMA

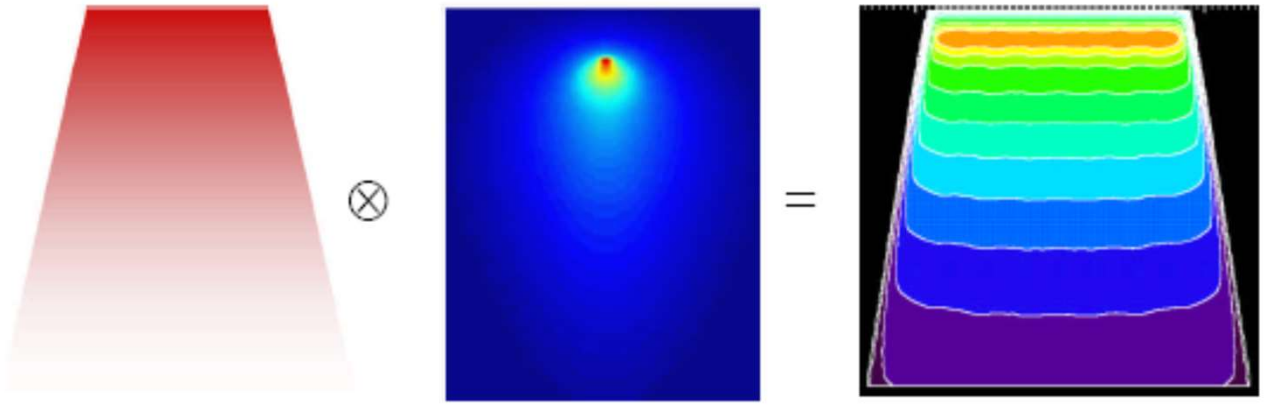
- **T**otal **E**nergy **R**eleased in **M**ass
- The primary photon energy fluence is calculated by ray-tracing primary photon trajectories, including beam modulators, etc.



$$T_E(r) = \frac{\mu}{\rho}(E, r)\Psi_E(r)$$

Kernel-Based Methods

Energy deposition in homogeneous media can be described through a **convolution** of the energy released by the **primary beam** with an energy deposition **kernel**



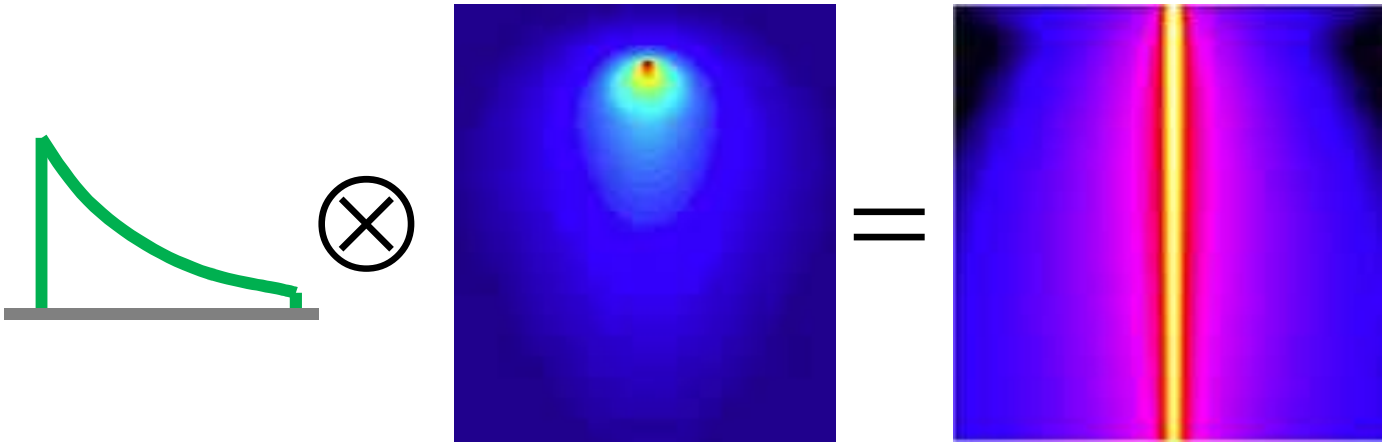
Photon fluence

Point spread function (Kernel)

Dose

Pencil Beam Approximation

- Irradiation field decomposed in **thin pencil** beams
- **Superposition** of **longitudinal** pencil beam **kernels** in 2D (much faster since 2D integration)
- **Summation** of individual narrow beams
- Kernel creation by deconvolution of measurements (or MC)
- Pencil beam kernel cannot be modified locally (i.e. for inhomogeneities), does **not** take the changes of **lateral scattering** effects into consideration



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Generalization for Primary Beam Spectral Variations

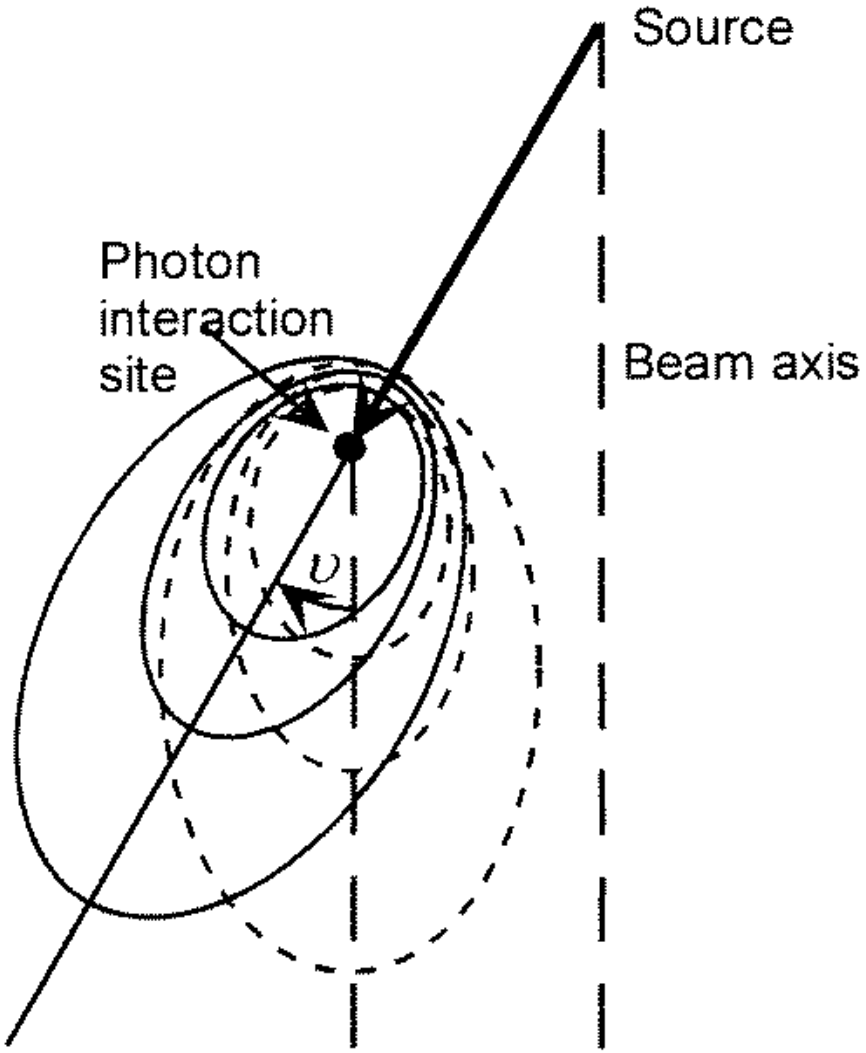
$$D(\boldsymbol{r}) = \int_E \iiint_V T_E(\boldsymbol{s}) h(E, \boldsymbol{r} - \boldsymbol{s})\, \mathrm{d}^3 s\, \mathrm{d}E$$

$$T_E(\boldsymbol{r}) = \frac{\mu}{\rho}(E, \boldsymbol{r}) \Psi_E(\boldsymbol{r})$$

- In practice use five energy bins
- Beam hardening accounted for in terma and approximated by precalculated correction factors (Papanikolaou 1993)

Papanikolaou N, Mackie T R, Meger-Wells C, Gehring M and Reckwerdt P 1993 Investigation of the convolution method for polyenergetic spectra Med. Phys. 20 1327–36.

Beam Divergence



- Kernels should ideally be tilted
- Approximated by taking inverse square factor at dose deposition site instead of interaction site (Papanikolaou 1993)
- Errors above 3% for small SSD, large field size and high energy (Sharpe 1993)

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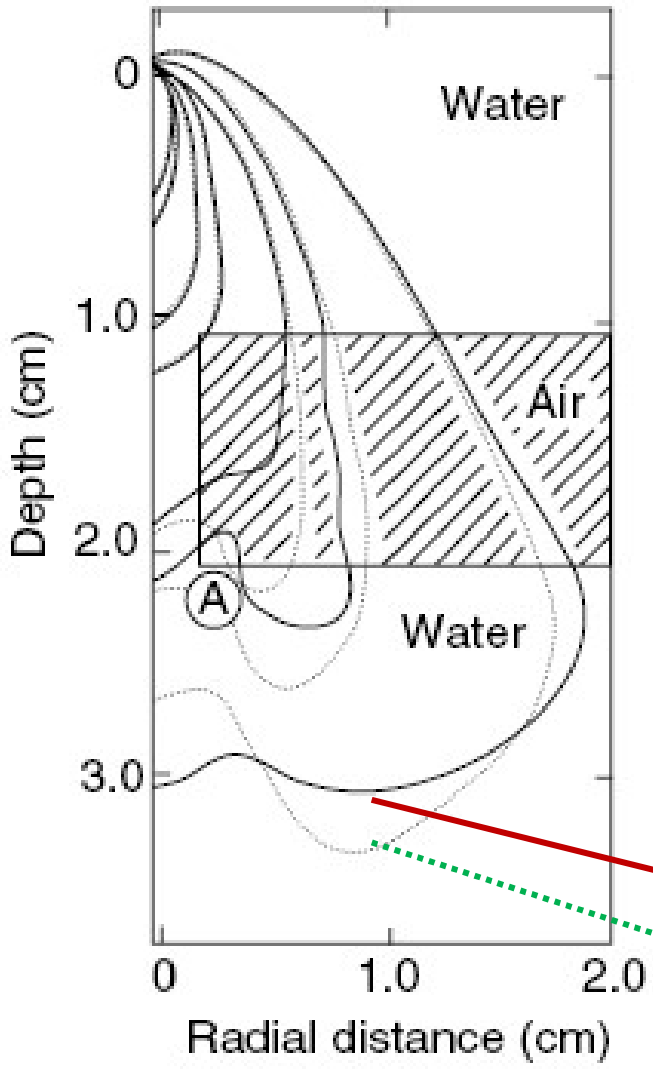
Heterogeneity Correction



- All dose fractions of a point kernel are scaled by the mean electron density between the point s of energy release and the point r of energy deposition
- Approximation for exact kernel for every situation
- Convolution/superposition : 100^7 calculations for 30cm x 30cm x 30cm, 3mm grid size …, **need approximations !**

Exact

Range scaling

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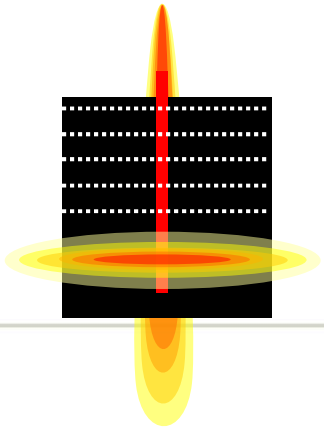
AAA Algorithm of Eclipse (Varian)

- Analytical Anisotropic Algorithm
  - Three separate sources
    1. primary photons
    2. extra-focal photons
    3. and contaminating electrons
  - **Effective path length** method is used to account for **heterogeneities (but only longitudinal)**
  - **Lateral** scatter: **spread** of kernels are scaled based on the density



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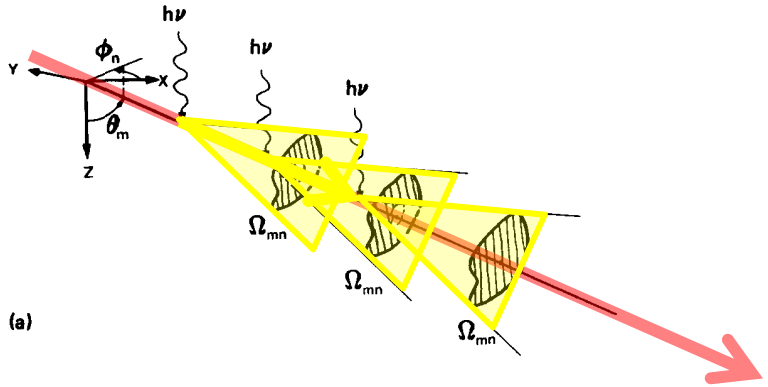
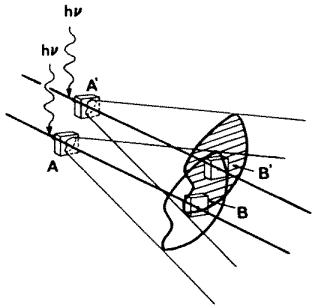
Collapsed Cone Algorithm (approximation !)

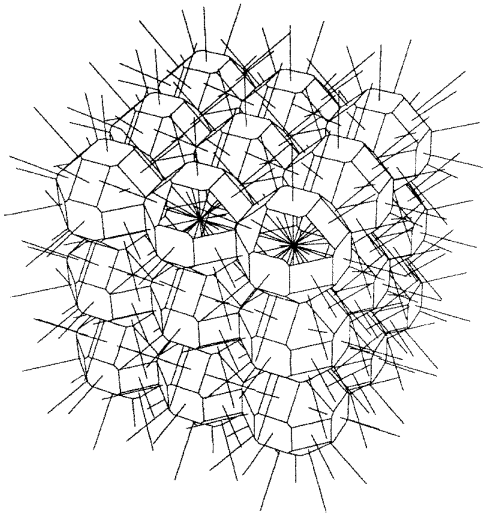
- Applies an angular discretisation of a parameterized kernel

$$\iint_{\Omega_i} \frac{h_{\rho_0}}{\rho}(r, \Omega) r^2 \, \mathrm{d}^2\Omega = A_{\Omega_i} \mathrm{e}^{-a_{\Omega_i} r} + B_{\Omega_i} \mathrm{e}^{-b_{\Omega_i} r}$$

- All energy inside a specified solid angle will be transported along a line
- Collapse cones of equal direction into a common pipe (ie 128 in CMS)
- During **each step of the transport** along a pipe, kernel energy is **picked up** and **attenuated** and **deposited** according to kernel parameters
- **Heterogeneities** are accounted for by **density scaling**
- Dose Calculation time ~MxN^3







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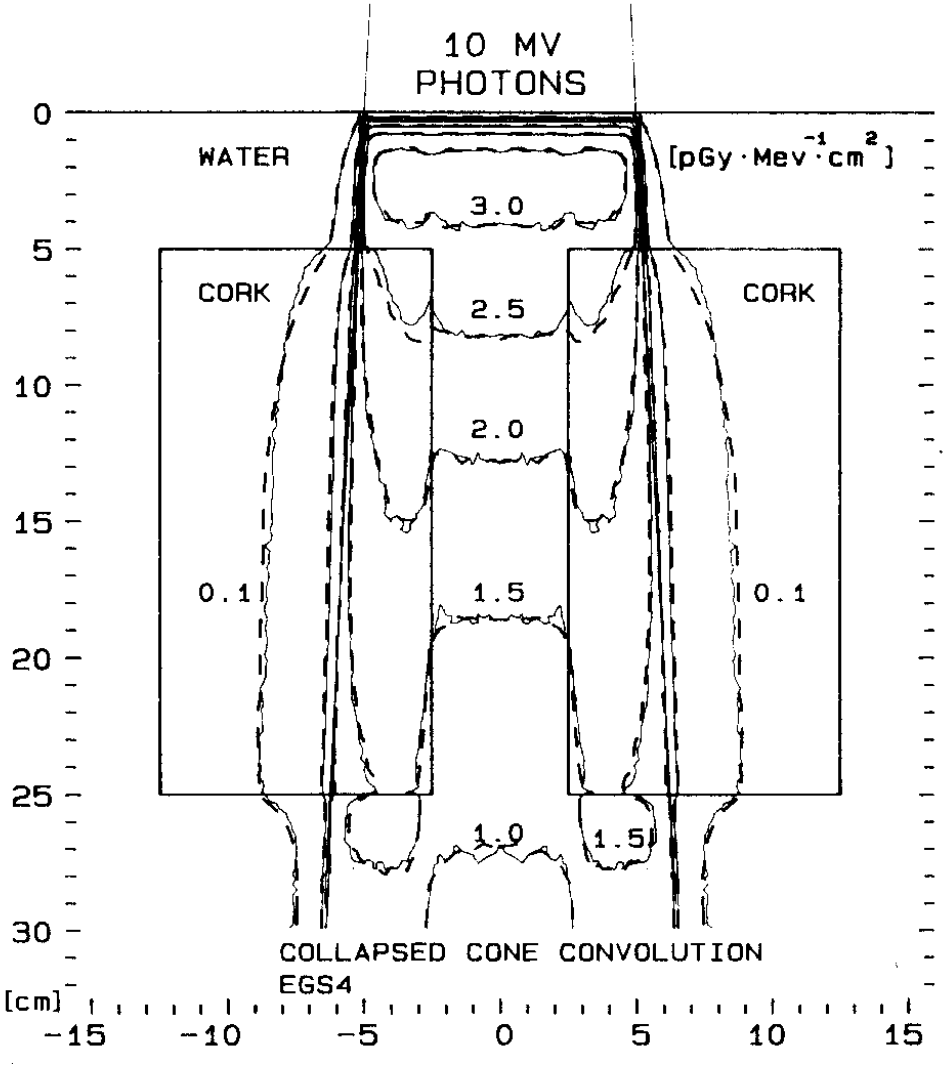
Collapsed Cone – Test Geometries



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Two Model Types

- Knöös et al.:

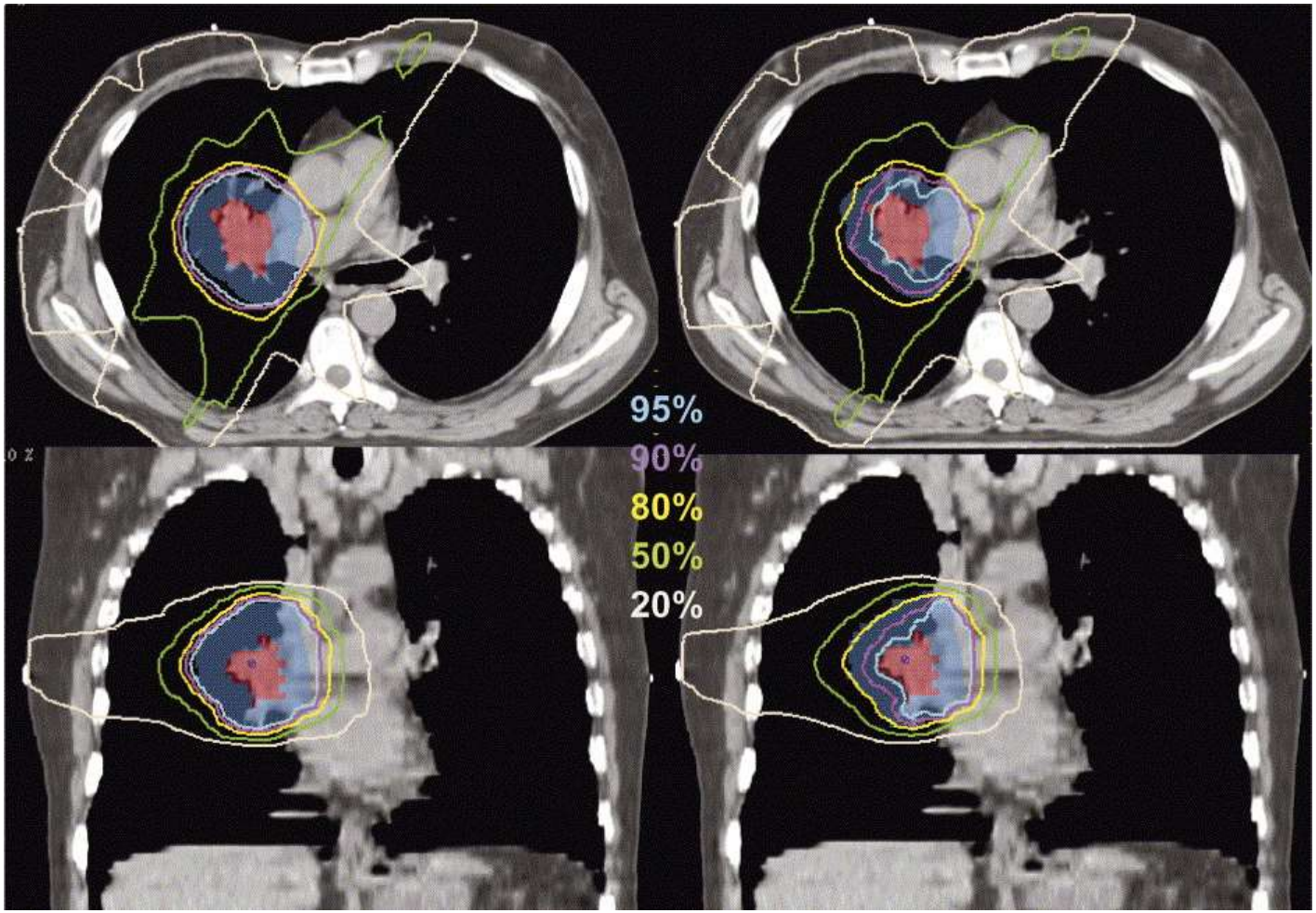
  A. Models primarily based on **equivalent path length** for inhomogeneity corrections, where **electron transport** is **not** separately **modeled**, and the density changes are sampled along the 1D **(longitudinal)** primary rays.

  Ex: Eclipse PB, OMP PB, XiO Convolution

  B. Models able to treat in an approximate way the **electron transport as well as the secondary photon transport in the medium** accounting for density changes, sampled along the full three dimensions **(longitudinal and lateral)**.

  Ex: Pinnacle CC, Eclipse AAA, OMP CC, XiO Convolution/Superposition

Clinical Example (Model A vs. Model B)



Katrien De Jaeger, Mischa S Hoogeman, Martijn Engelsman, Yvette Seppenwoolde, Eugène M.F Damen, Ben J Mijnheer, Liesbeth J Boersma, Joos V Lebesque, Incorporating an improved dose-calculation algorithm in conformal radiotherapy of lung cancer: re-evaluation of dose in normal lung tissue, Radiotherapy and Oncology, Volume 69, Issue 1, October 2003, Pages 1-10

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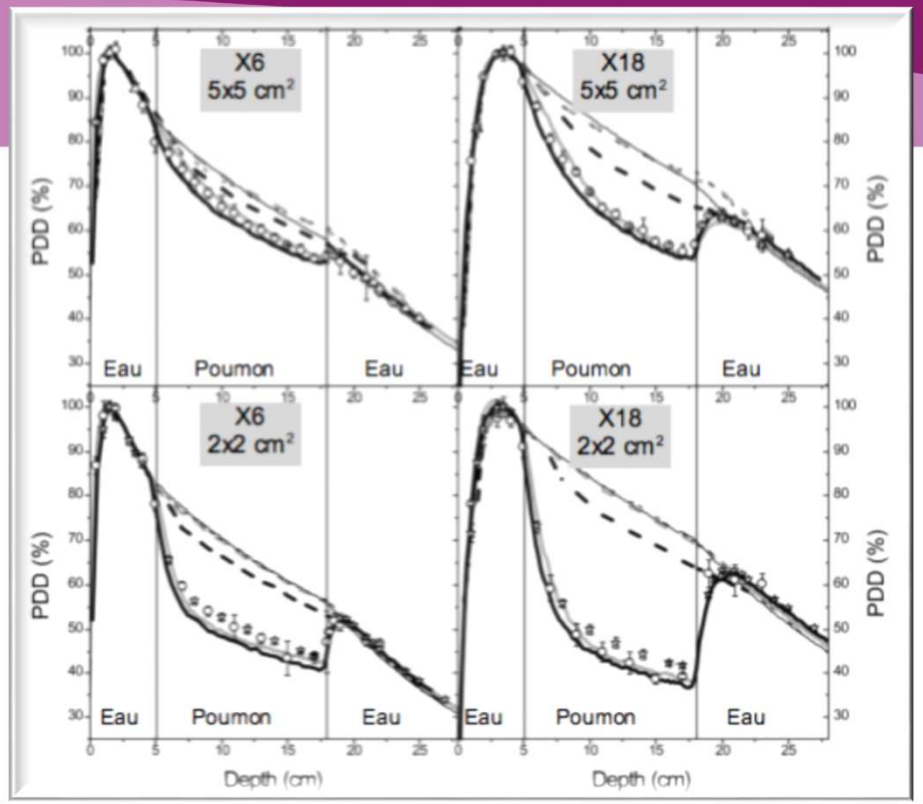
Tested Methods

- Anisotropic Analytical Algorithm, version 8.6, Eclipse, Varian (Eclipse AAA)
- Collapsed Cone, version 3.1 sp3, Oncentra MasterPlan, Nucletron (OTP CC)
- Pencil Beam, version 3.1 sp3, Oncentra MasterPlan, Nucletron (OTP PB)
- Collapsed Cone, version 8.0m, Pinnacle, Philips (Pinnacle CC)
- Multigrid Superposition, version 4.40, XiO, CMS (XiO Sup)
- Fast Fourier Transform Convolution, version 4.40, XiO, CMS (XiO FFT)

T. Nielsen et al. Influence of dose calculation algorithms on the predicted dose distributions and NTCP values for NSCLC patients Med. Phys. 38 (5), May 2011.

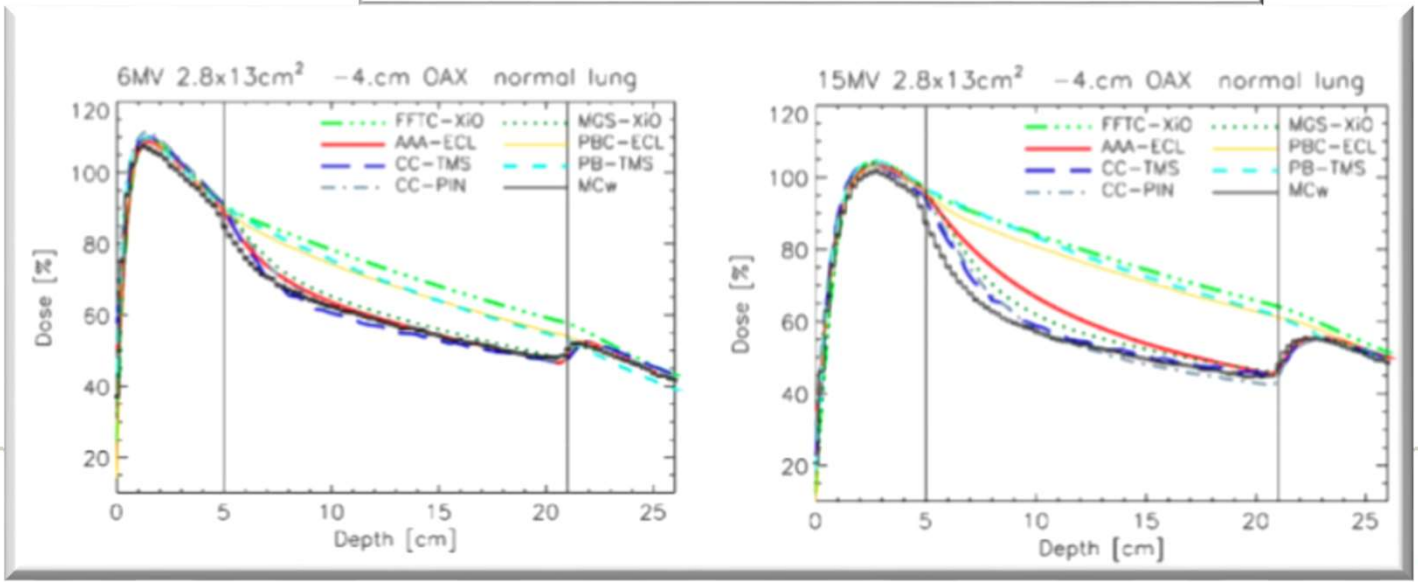


Pencil Beam

Collapsed cone

Monte Carlo

o o o o o *TLD*



Fogliata

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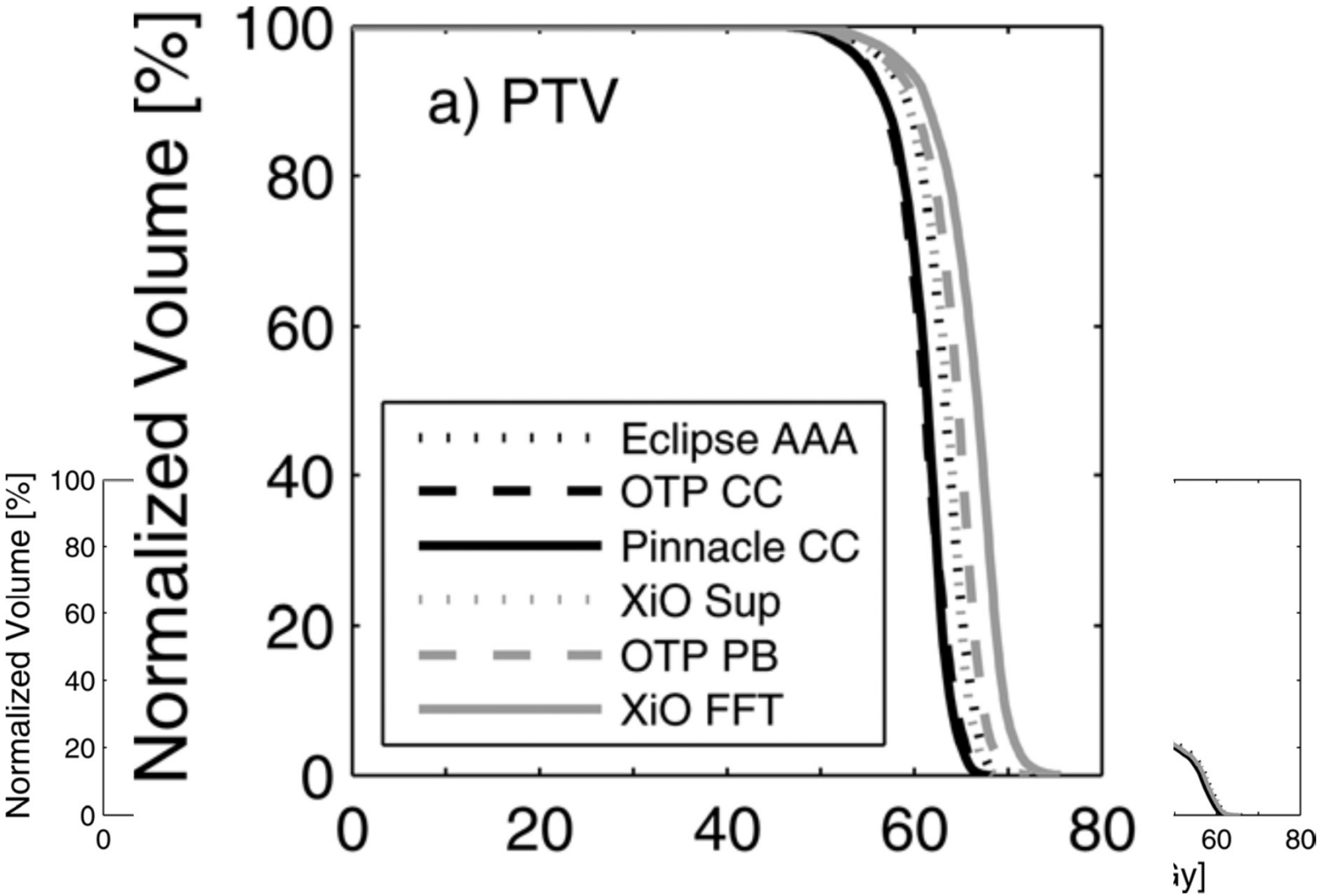
Clinical Lung Case (Example)



Rationale for Monte Carlo

- *Convolution/superposition…*

$$D(\mathbf{r}) = \iiint_V T(\mathbf{s})h(\mathbf{r}-\mathbf{s})d^3s$$

- 100% accurate for parallel monoenergetic beams in an infinite homogeneous phantom

But !!!!!!

Patients are not infinite

Beams are not parallel

Beams are not monoenergetic

Integral too complex
→ need for approximations (pencil beam, collapsed cone…)

What about highly modulated beams in inhomogeneous media (patients…)?

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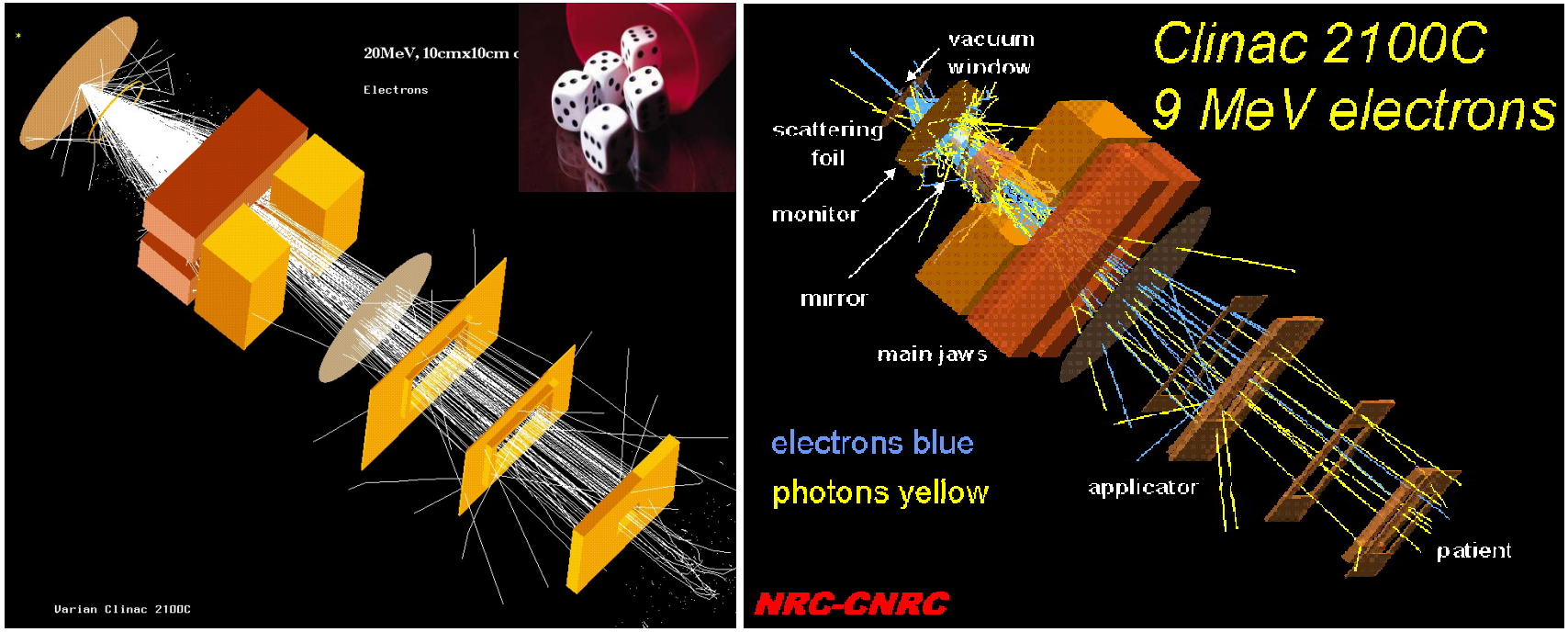
Explicit Modeling of Scattered Particle Transport

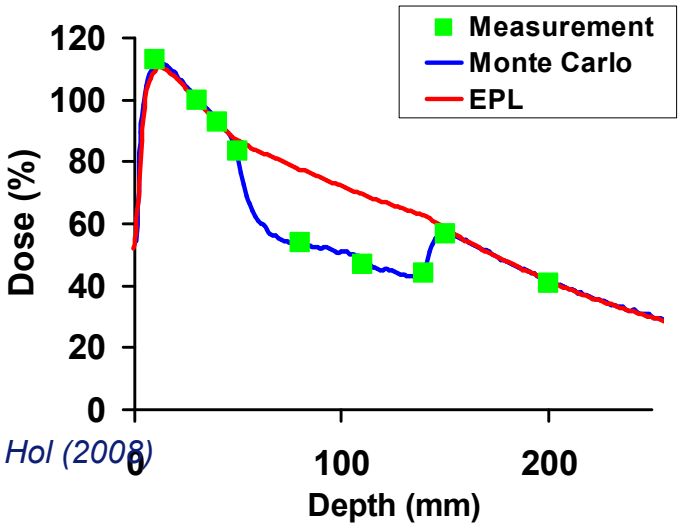
- Monte Carlo



Why Monte Carlo Treatment Planning?

Accuracy

- Dose calculation should be accurate within 2% to 3%
- MC dose calculation engines can be even more exact than 3%
- Regardless of the treatment setup



Hol (2008)

Uncertainties and Causes

- Imperfect matching of the MC beam to the Linac **within 1%**
- Uncertainties in the cross section libraries **negligible**
- Limited number of simulated 'events'

  ~number of histories
- Uncertainties in the conversion of CT data to the material composition and density **difficult to quantify**

Basic Monte Carlo Steps

- The position of the photon is updated with the travel distance **l**
- The type of interaction will be selected based on the cross section data for the different interactions
- The energies and angles of the produced particles will be generated

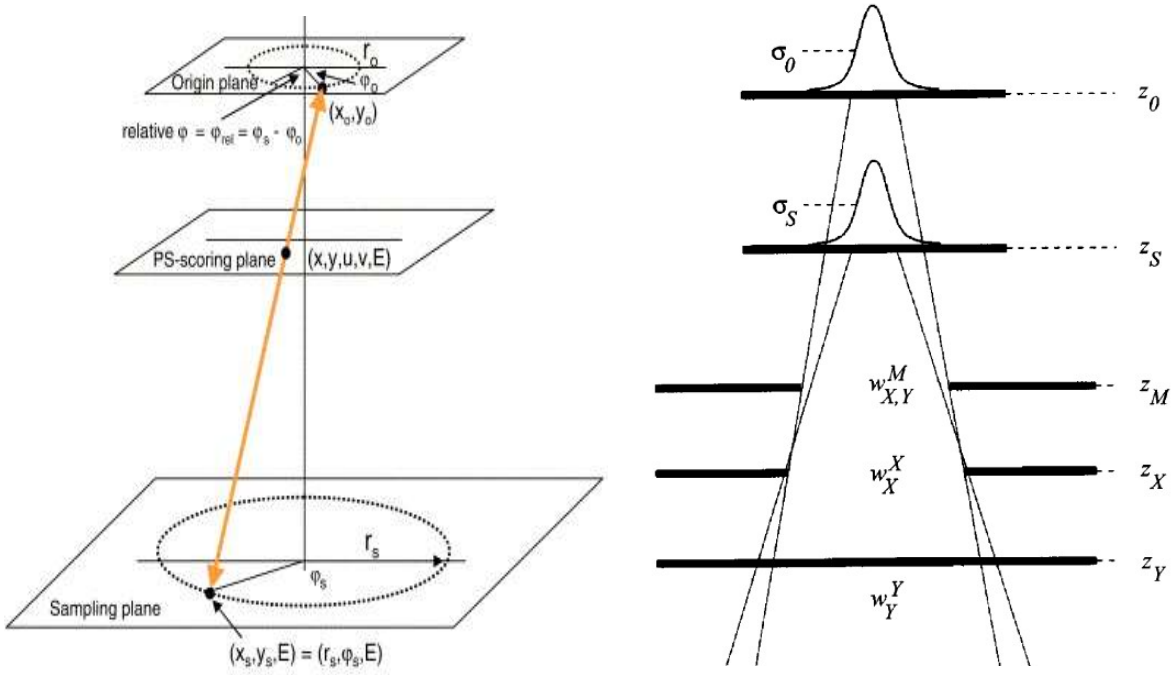
Input Particles

- **Modelling** of radiation source consists of sampling the required information about initial particles (**type of particle**, **starting** coordinates, **direction** cosines, **energy**, charge and particle **weight**)
- The **linac** can be divided into:
  - **Upper** part - components that remain fixed for all possible beams settings **(Patient independent)**
  - **Lower** part - beam modifiers **(Patient dependent)**

- The **upper** part is modeled only **once** and a **phase-space file** is generated at the entrance of the lower part
- This file is then used as an **input** for the MCTP calculation (the lower part and the patient are handled in one process)

Virtual Source Model

- Parameterization of a phase space file
- Several sub-sources serves as a particle generator



Virtual source model from XVMC with two virtual sources, i.e. target and flattening filter

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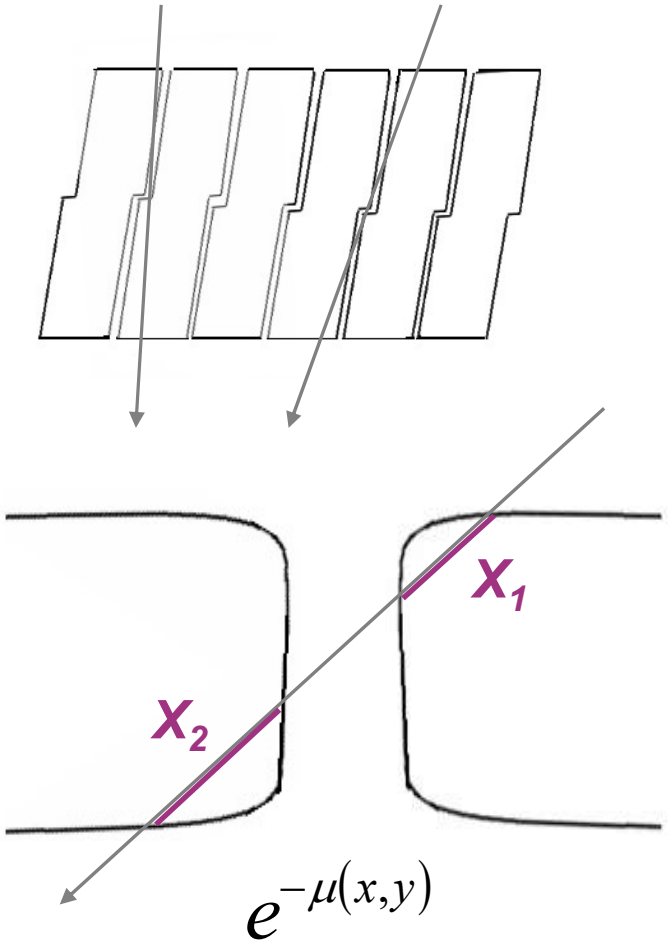
Beam Modifiers

- Most of the **calculation time** of a MCTP system is spent in the **jaws and MLC** (when tracking photons and electrons through high-Z materials many particles are lost, so it requires a lot of **CPU time to obtain sufficient particles** that manage to cross these parts)
- To avoid waste of CPU time on photons and electrons tracking through MLC and other collimating devices approximations are introduced
  - Chen et al (2000): MCDOSE Ray-tracing based method for calculating transmission through MLC geometry (only works with virtual source model)

Beam Modifiers Approximations

- A line can be drawn from a sub-source through the MLC to the isocenter plane
- In the MLC this line is split up into many short intervals. For each end point of an interval it is determined whether the point falls inside or outside tungsten
- One simply sums the geometric path lengths X_1 and X_2 in the leaf material to apply an attenuation correction



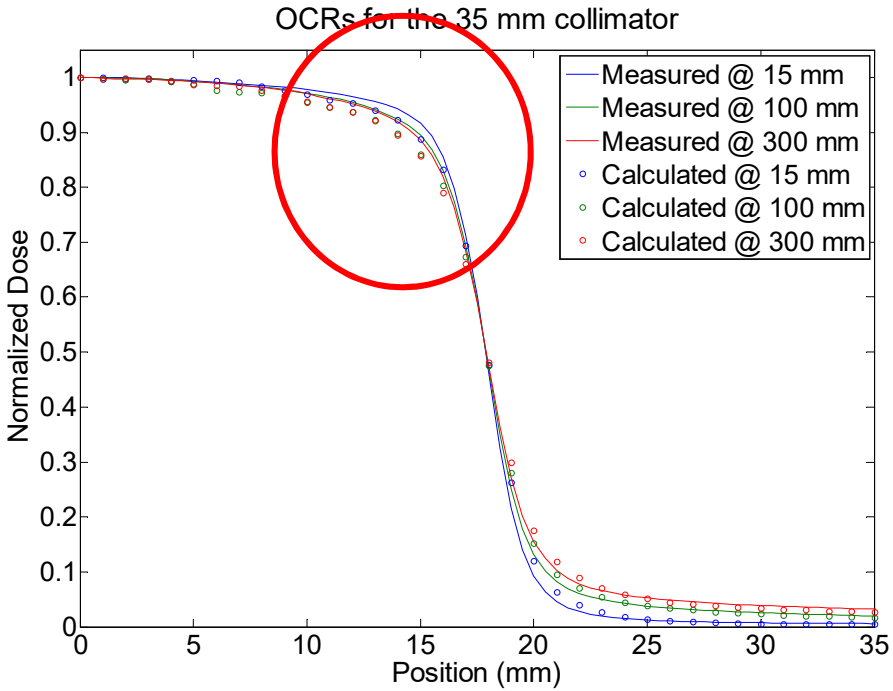
Variance Reduction Techniques

- **Particle Splitting**
  - To get more particles to the patient
  - Split particle close to the patient and simulate track for both particles independently
  - Statistical weight is adjusted
  - Often used for the brehmsstrahlung photons in the target inside the linac head
- **History Repetition**
  - Applied to electrons
- …

Danger of not probing all parts of the geometry
Reducing calculation time per history means simplifying the physics

Why Monte Carlo Treatment Planning?

- **Antolak**
  - When one speeds up the MCTP, it is no more exact
- **Mohan**
  - Approximations introduce no bias
  - Resolutions up to 2 or 3 mm can be reached within a few minutes



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Grid-based Boltzmann Equation Solver

Validation of a new grid-based Boltzmann equation solver for dose calculation in radiotherapy with photon beams

Oleg N Vassiliev[1,3], Todd A Wareing[2], John McGhee[2], Gregory Failla[2], Mohammad R Salehpour[1] and Firas Mourtada[1]

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Received 23 July 2009, in final form 1 December 2009
Published 7 January 2010
Online at stacks.iop.org/PMB/55/581

Stochastic vs. Deterministic Methods

- Stochastic and deterministic methods:
  - both converge to the same solution
  - same accuracy

- **Stochastic (MC)**
  - Particle tracking process
  - Errors come from insufficient number of interactions simulated and voxel size
  - Stochastic errors
  - Low efficiency in large attenuation regions and volumes

- **Deterministic (AXB)**
  - Solve full phase-space solution everywhere
  - Errors come from insufficient refinement of discretized variables
  - No statistical noise
  - High efficiency in large attenuation regions and volumes

From: Fogliata Antonella

Evolution of calculation algorithms

Manual – 1D

↓

2D → pencil beam (ECLIPSE – SPB, HELAX (OTP) – TMS, …) 1D heterogeneity correction

↓

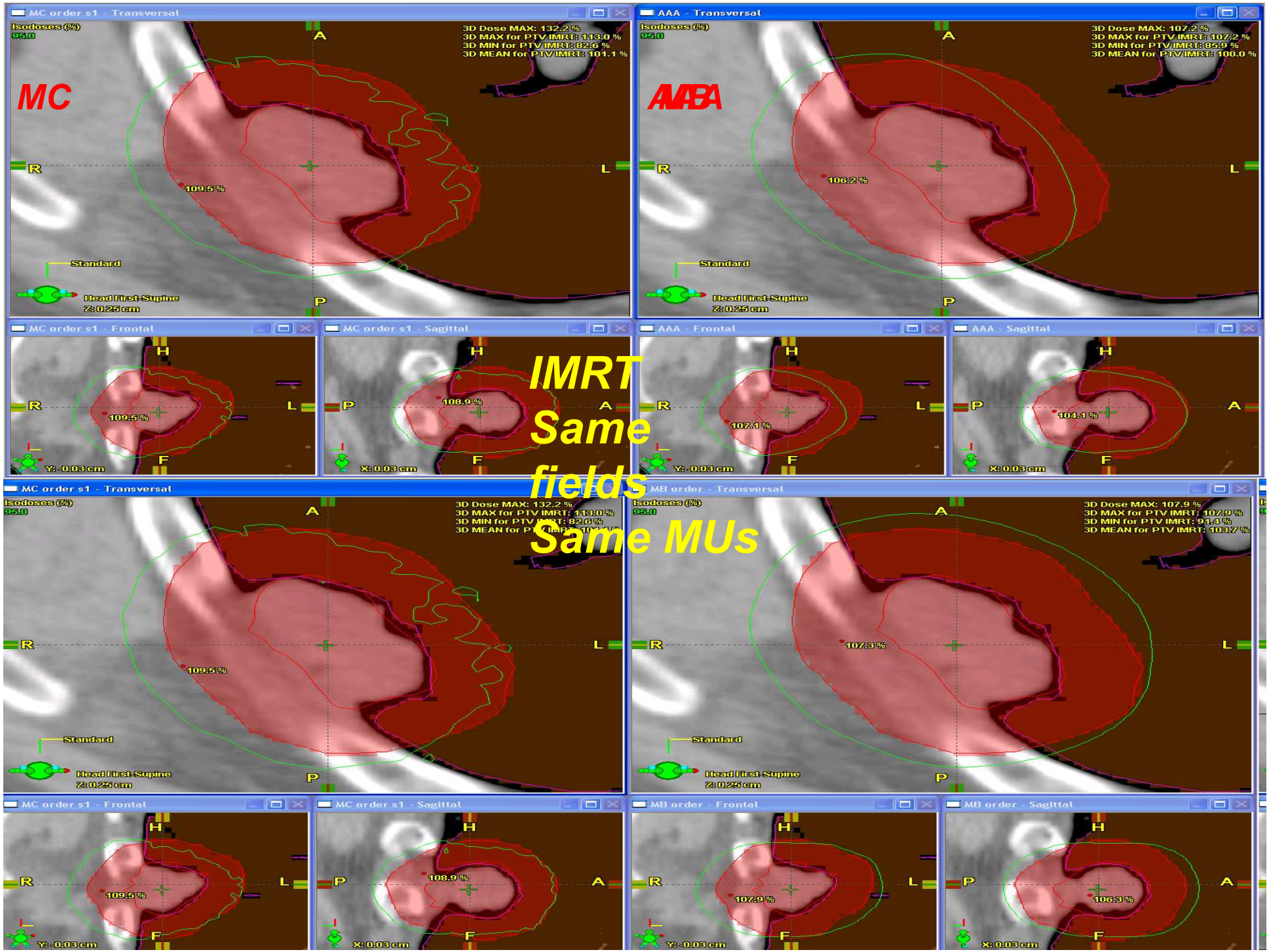
2,5 D → ECLIPSE-AAA (pencil beam but with heterogeneity correction ~3D)

↓

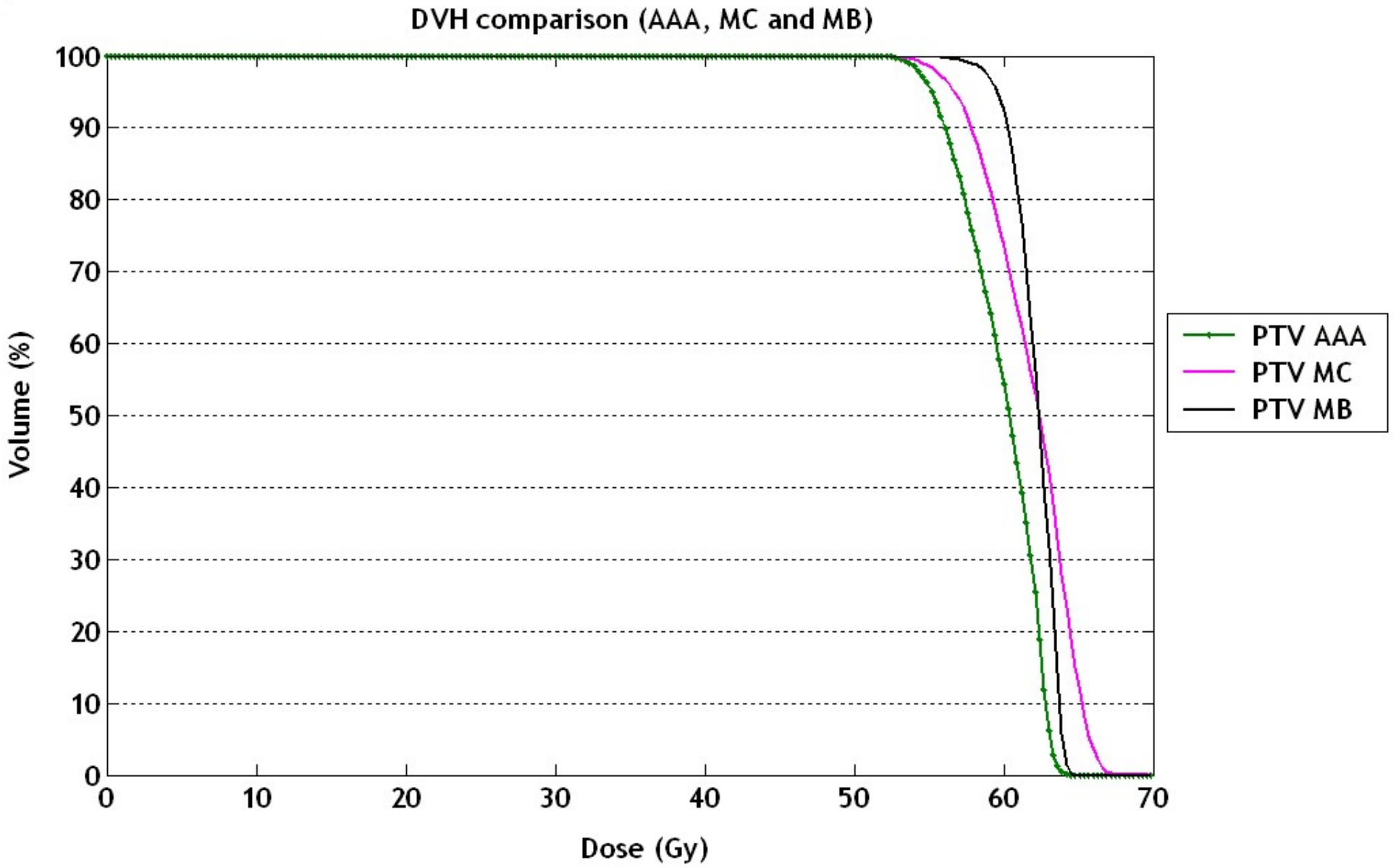
3D → convolution/superposition, collapsed cone (CMS, Pinnacle, HELAX (OTP) – CC, Tomotherapy) 3D heterogeneity correction

↓

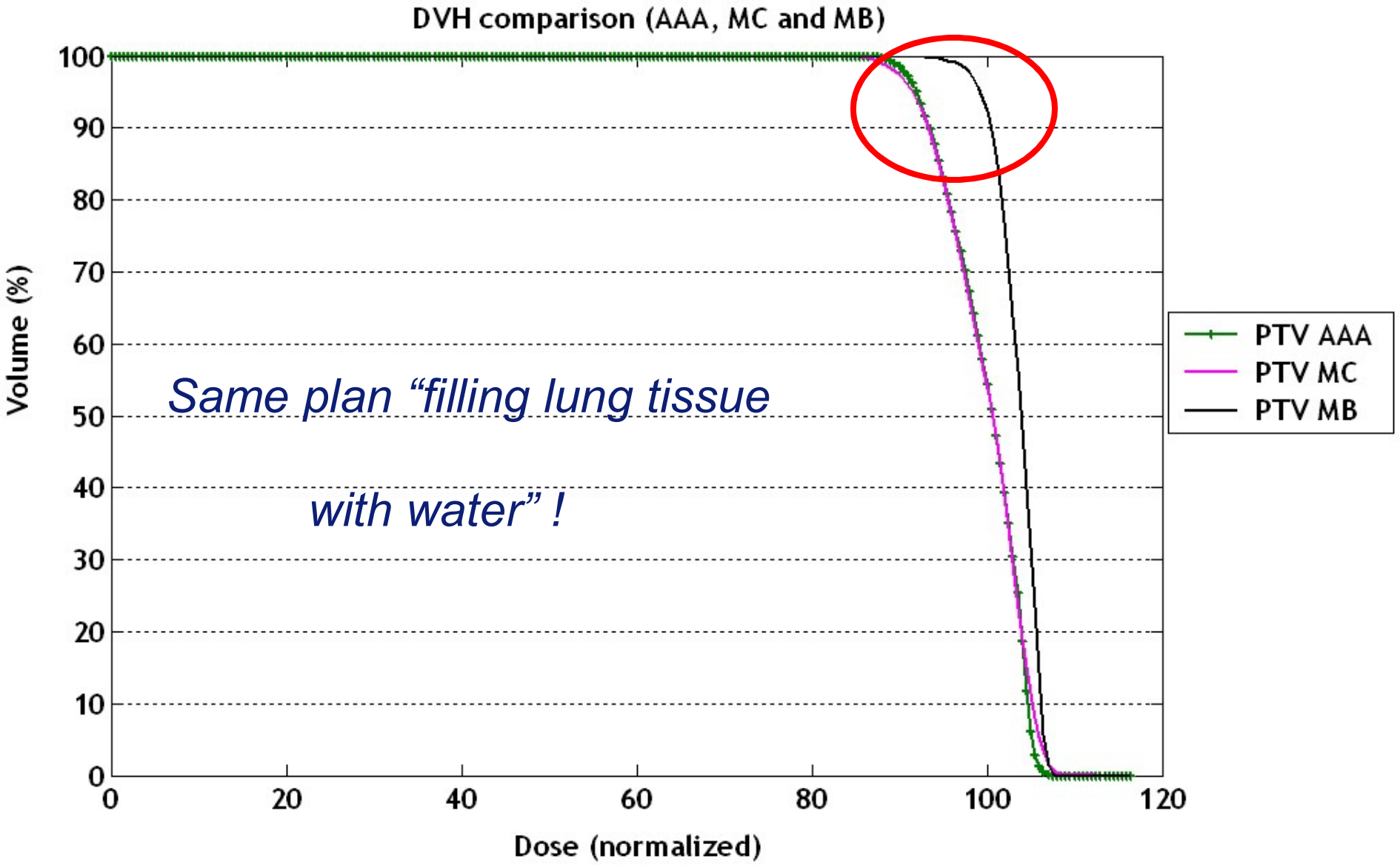
Monte Carlo and Grid Based Boltzmann Equation solver

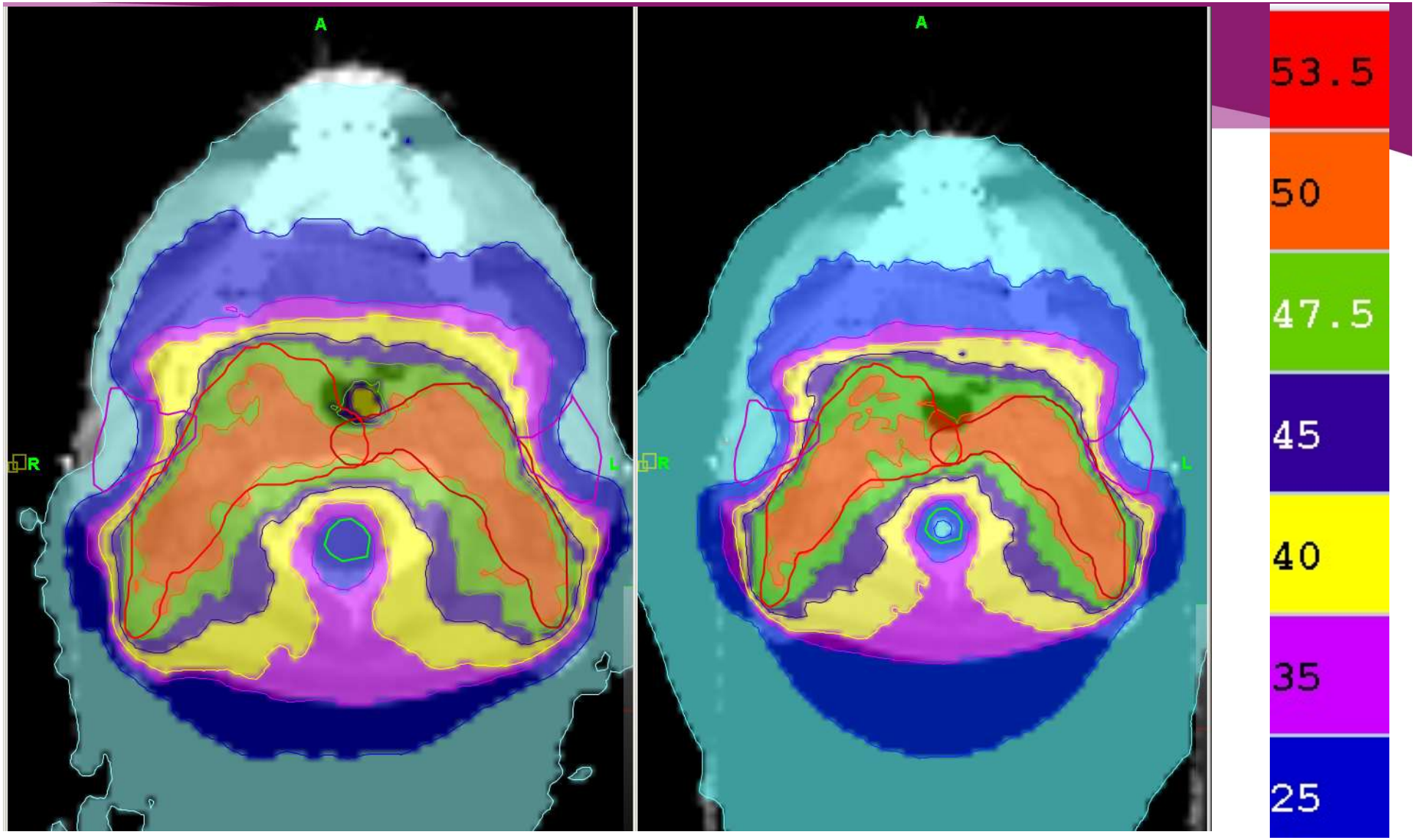

MC order s1 - Transversal
Isodoses (%)
95.0
3D Dose MAX: 132.2 %
3D MAX for PTV IMRT: 113.0 %
3D MIN for PTV IMRT: 82.6 %
3D MEAN for PTV IMRT: 101.1 %
MC
109.5 %
Standard
Head First-Supine
Z: 0.25 cm
AAA - Transversal
3D Dose MAX: 107.2 %
3D MAX for PTV IMRT: 107.2 %
3D MIN for PTV IMRT: 85.9 %
3D MEAN for PTV IMRT: 100.0 %
AAA
106.2 %
MC order s1 - Frontal
109.5 %
Y: -0.03 cm
MC order s1 - Sagittal
108.9 %
X: 0.03 cm
AAA - Frontal
107.1 %
AAA - Sagittal
104.1 %
IMRT
Same
fields
Same MUs
MB order - Transversal
3D Dose MAX: 107.9 %
3D MAX for PTV IMRT: 107.9 %
3D MIN for PTV IMRT: 91.4 %
3D MEAN for PTV IMRT: 103.7 %
107.3 %
MB order - Frontal
107.9 %
MB order - Sagittal
106.3 %

AAA : 2(b) Small lung tumor



AAA : 2(b) Small lung tumor





Monte Carlo

Convolution/Superposition

Presribed dose = 70 Gy

Computation time: 6hrs (2.5GHz)

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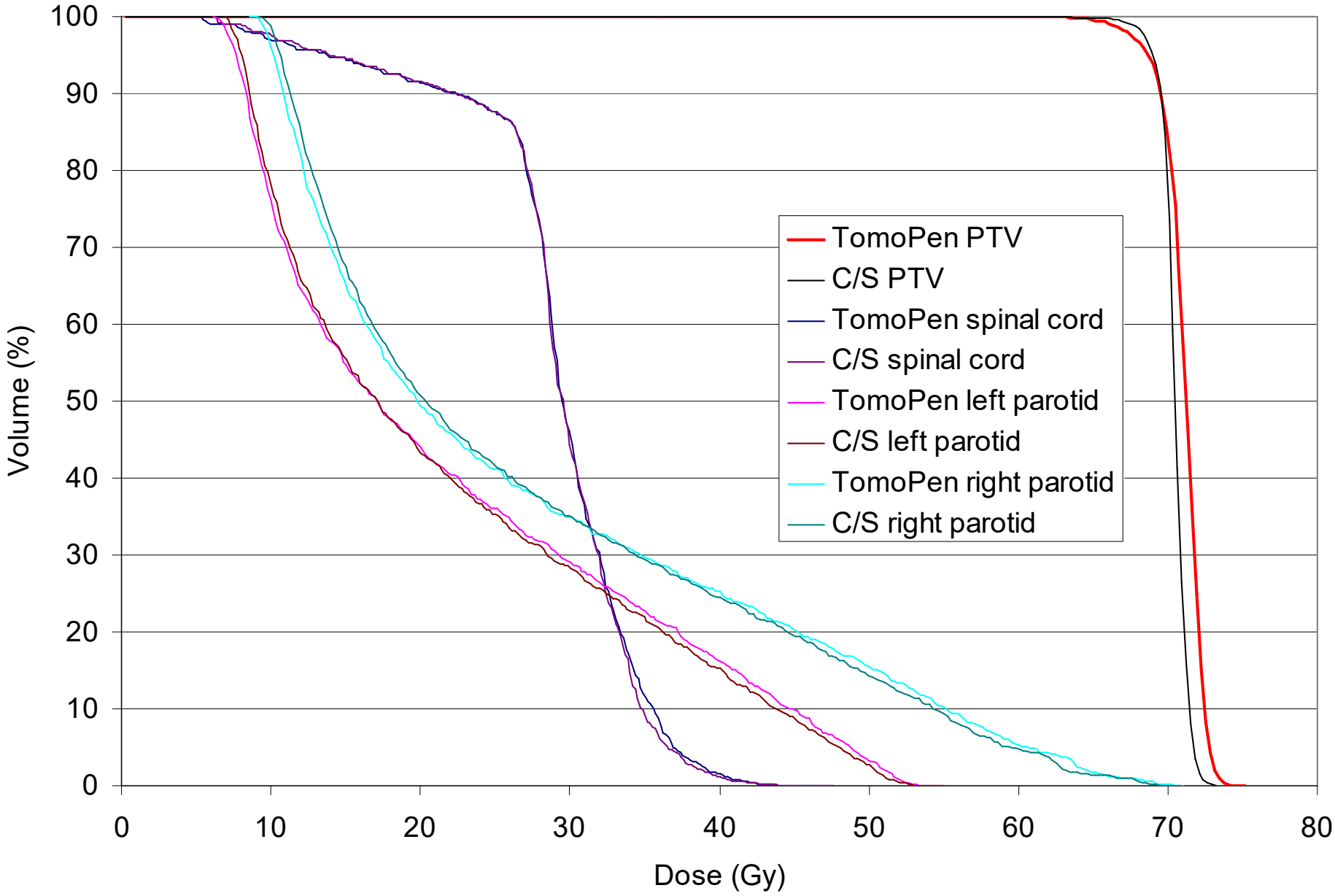
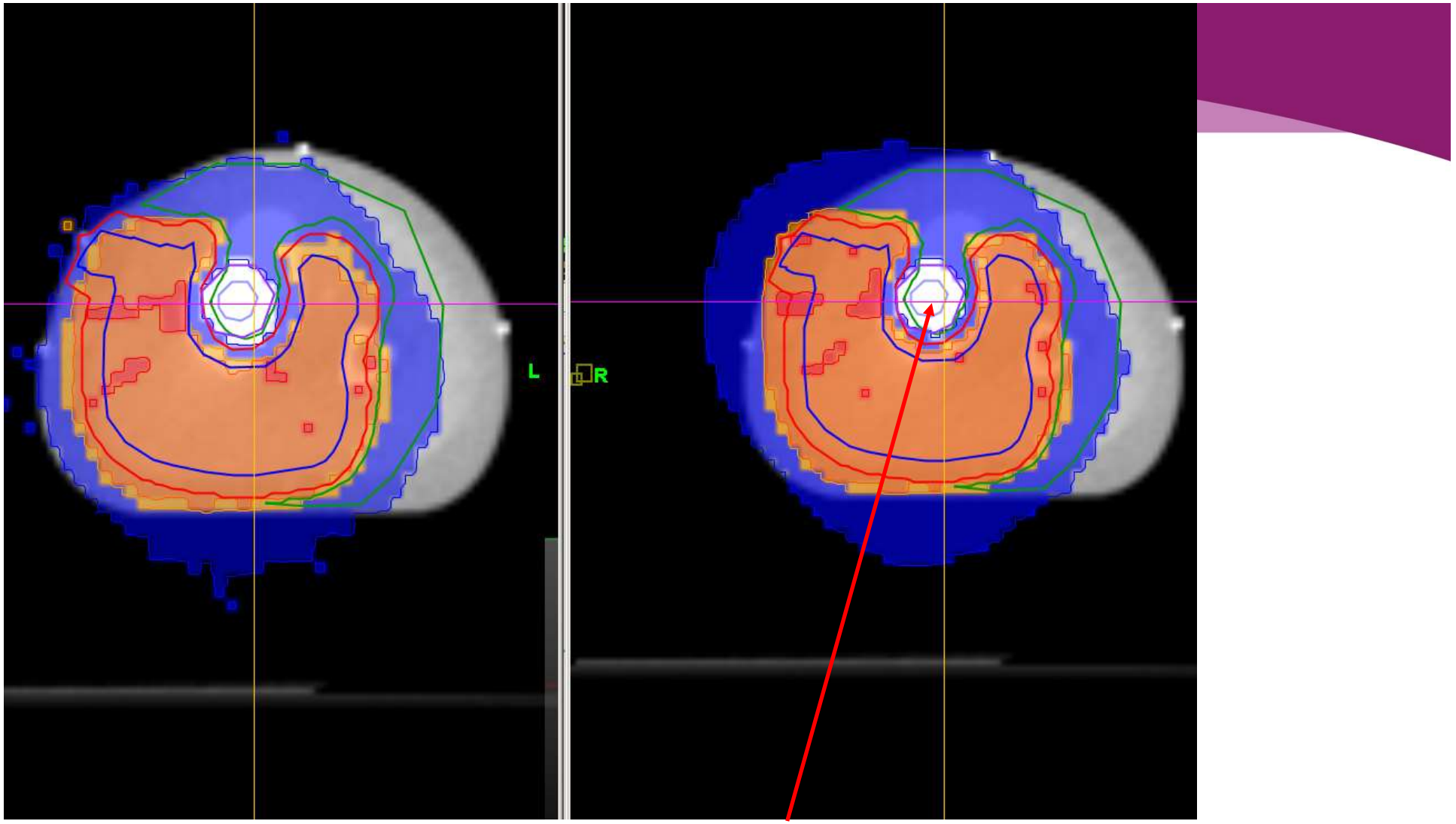

100
90
80
70
60
50
40
30
20
10
0
Volume (%)
0
10
20
30
40
50
60
70
80
Dose (Gy)
TomoPen PTV
C/S PTV
TomoPen spinal cord
C/S spinal cord
TomoPen left parotid
C/S left parotid
TomoPen right parotid
C/S right parotid



Monte Carlo

High density prosthesis

Convolution/S uperposition

Prescribed dose = 45 Gy

Calculated on MVCT !

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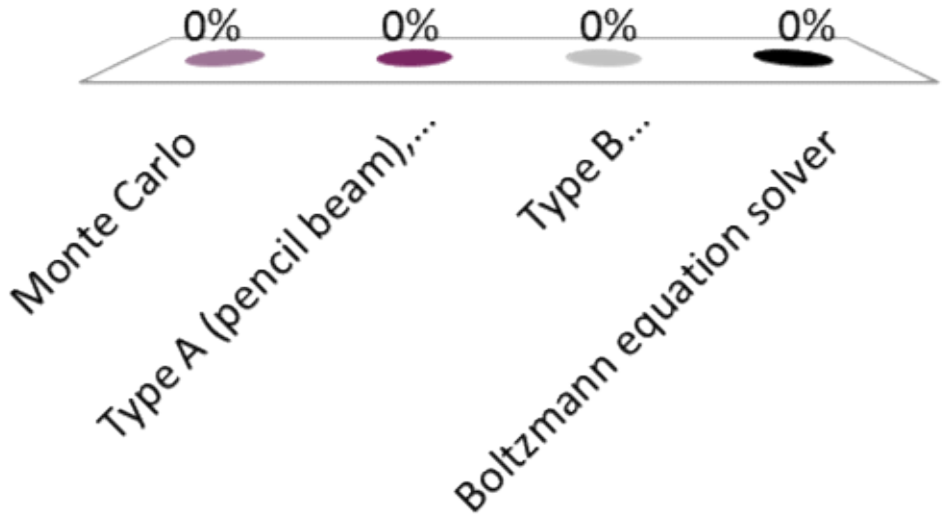
Question 2: For this clinical case, I mandatorily need the following algorithm:

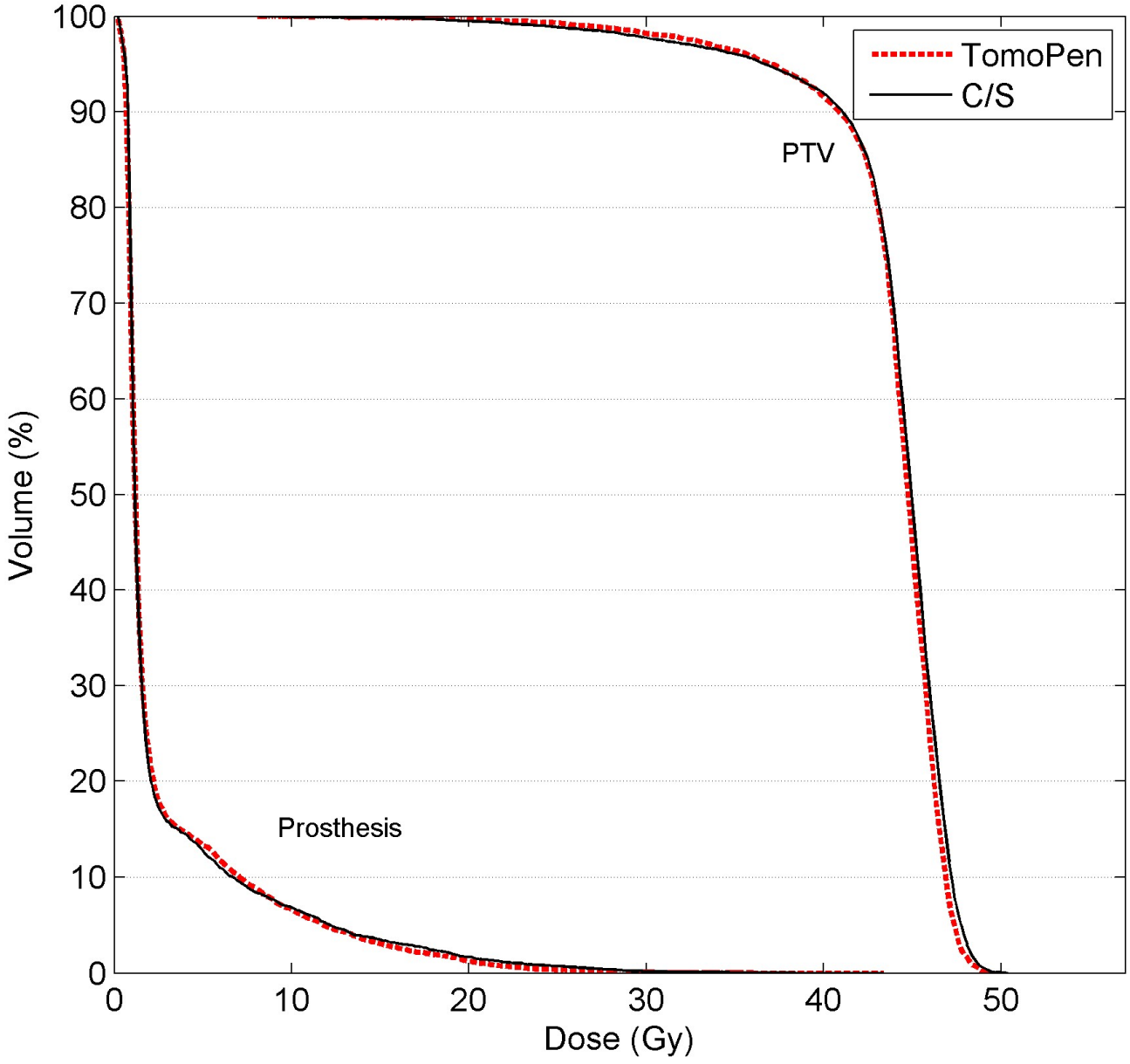
A. Monte Carlo

B. Type A (pencil beam), that's enough accuracy …

C. Type B (Convolution/superposition, AAA, …) of course, with such density inhomogeneities

D. Boltzmann equation solver




TomoPen
C/S
PTV
Prosthesis
Volume (%)
Dose (Gy)
0
10
20
30
40
50
60
70
80
90
100

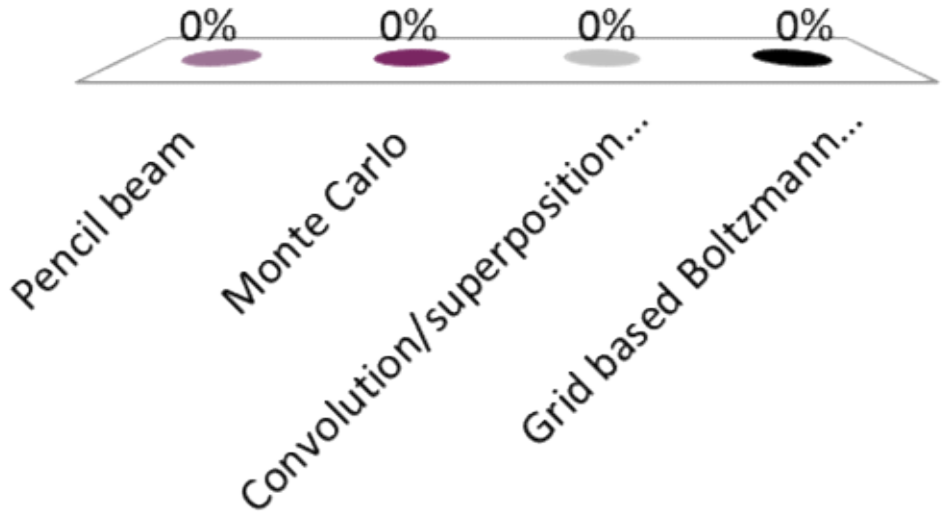
Question 3: I want to treat a lung case with 18MV and small field sizes, I would never use the following algorithm

A. Pencil beam

B. Monte Carlo

C. Convolution/superposition, collapsed cone

D. Grid based Boltzmann equation solver



Conclusions/take-home message

- Convolution/Superposition algorithm (pre-calculated kernels)
  - High accuracy with density inhomogeneities
- Collapsed Cone algorithm: why ?
- AAA : significant gain of accuracy compared to PB. Good accuracy overall
- PB: OK for prostate, head and neck (…?)
  - Used to oversome limitations with irregular fields, only AAA takes lateral scatter into account
- Added-value of MC : certainly for small lung tumors, IMRT QA ?
- High level C/S sufficient in majority of cases …

Thank you!

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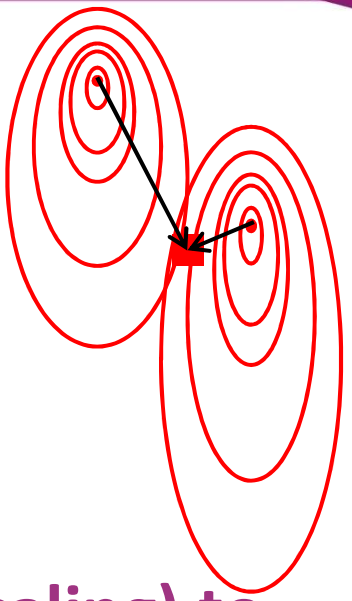
Kernels are not Invariant in Space

- Energy distribution varies with position in beam
  - Beam hardening at depth
  - Off-axis softening
- Kernels are tilted
- Kernels vary with density



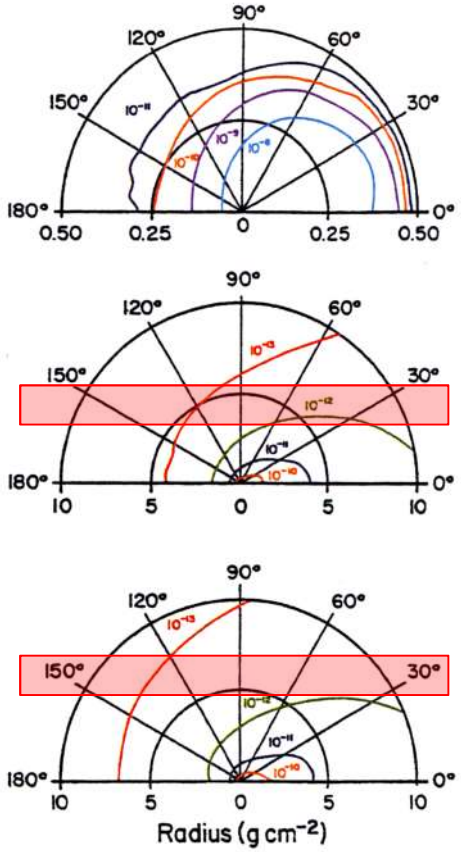
- **N^7 operations (including kernel density scaling) to calculate results in N^3 points**

Fast Point Kernel Convolution (CMS)

Fast Fourier Transform ($N^3 \log_2 N$)

- Requires invariant kernel

- **Separate calculations**
  - Primary kernel
    - High resolution
    - Short range
  - Scatter kernel
    - Low resolution
    - Large range



Basic Monte Carlo Steps (Inside LINAC Head)

- Sample energy of photon created by electron
- Sample angles φ and θ between incoming electron and created photon
- Select distance to the first interaction
- Probability that the photon will travel a distance **l** without interaction is **exp(-μ l)**
- m dl is the probability to interact
- Probability to interact between **l** and **l+dl** is given by μ **exp(-μ l) dl**

$$P(l) = \int_0^l \mu e^{-\mu s} ds = \ldots = 1 - e^{-\mu l}$$

$$r = 1 - e^{-\mu l} \Rightarrow l = -\frac{1}{\mu}\ln(1-r) = -\frac{1}{\mu}\ln(r')$$

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Basics of Monte Carlo

- **Photon Transport**
  - Small number of interactions
  - Compton scattering, pair production, …
- **Electron Transport**
  - Large number of interactions
  - Elastic scattering
  - Inelastic collision causing excitation or ionization
  - Brehmsstrahlung and emission of X-rays or Auger electrons

Modern Radiation Therapy Equipment

Milan TOMSEJ

CHU A. Vésale

Charleroi

BELGIUM

ESTRO School

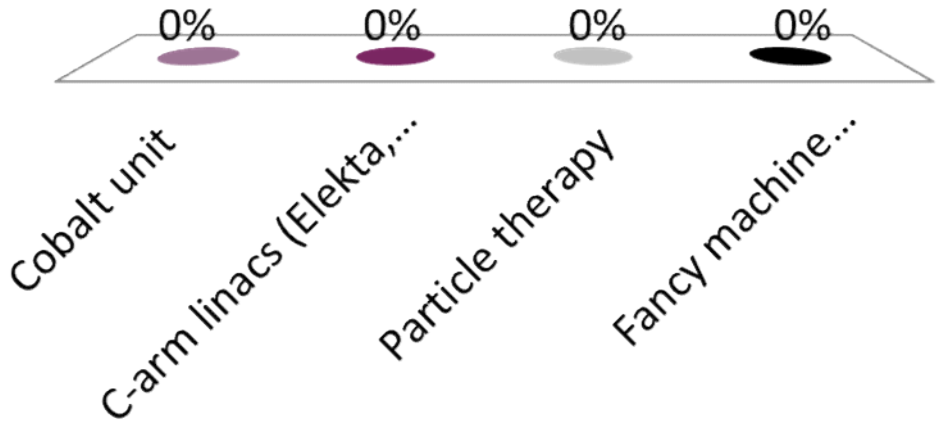
Question 1: What kind of treatment machine do you have for EBRT ?

A. Cobalt unit

B. C-arm linacs (Elekta, Varian, Siemens)

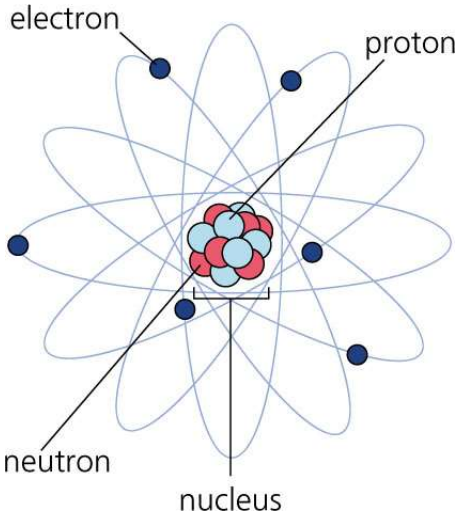
C. Particle therapy

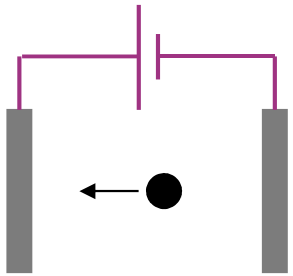
D. Fancy machine (Tomotherapy, Cyberknife, Vero, …)



Introduction

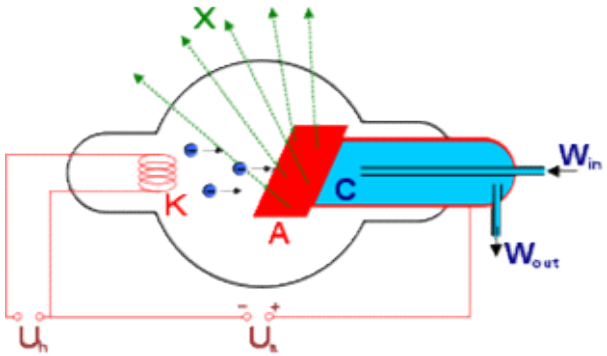
- Photons (X-rays) cannot be accelerated
- Charged particles, e.g. electrons can be accelerated
  - What is an electron?
  - How to create/free an electron?
  - How to accelerate an electron?

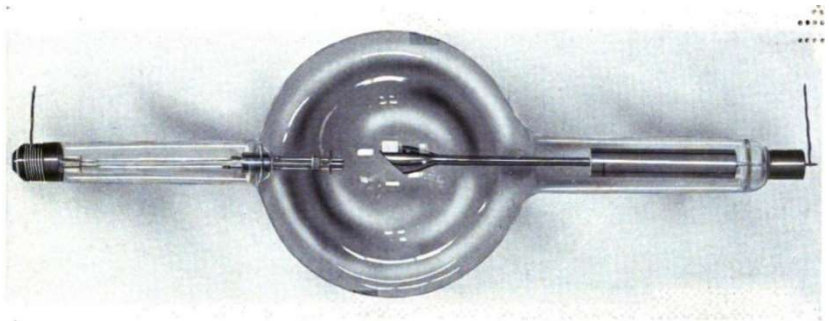




electron mass = 9.1×10^{-31} kilograms

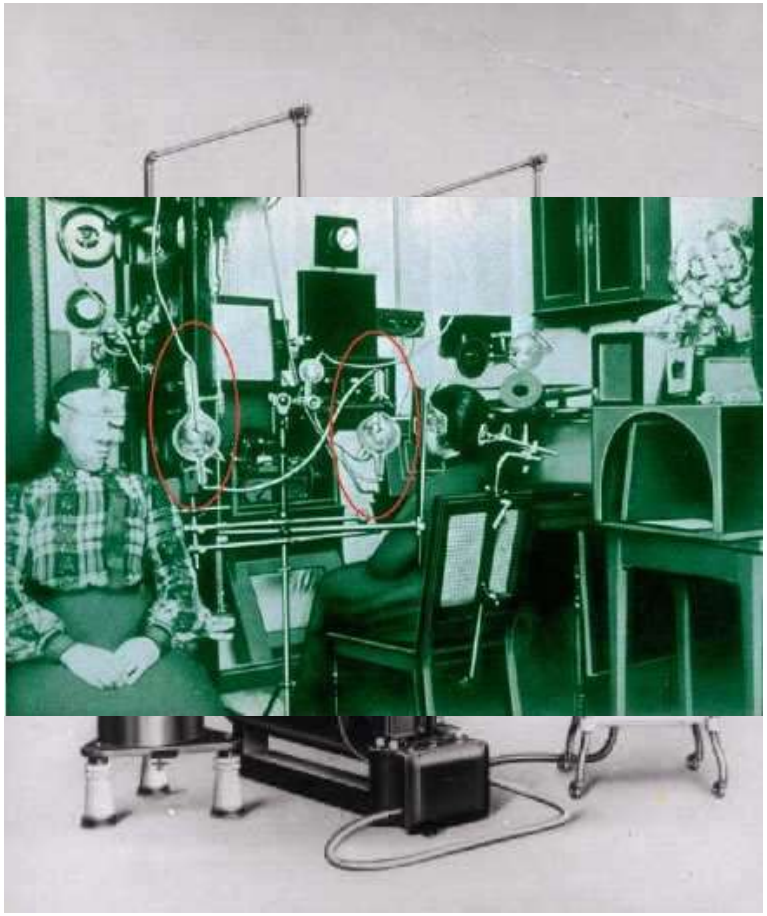
X-ray Tube



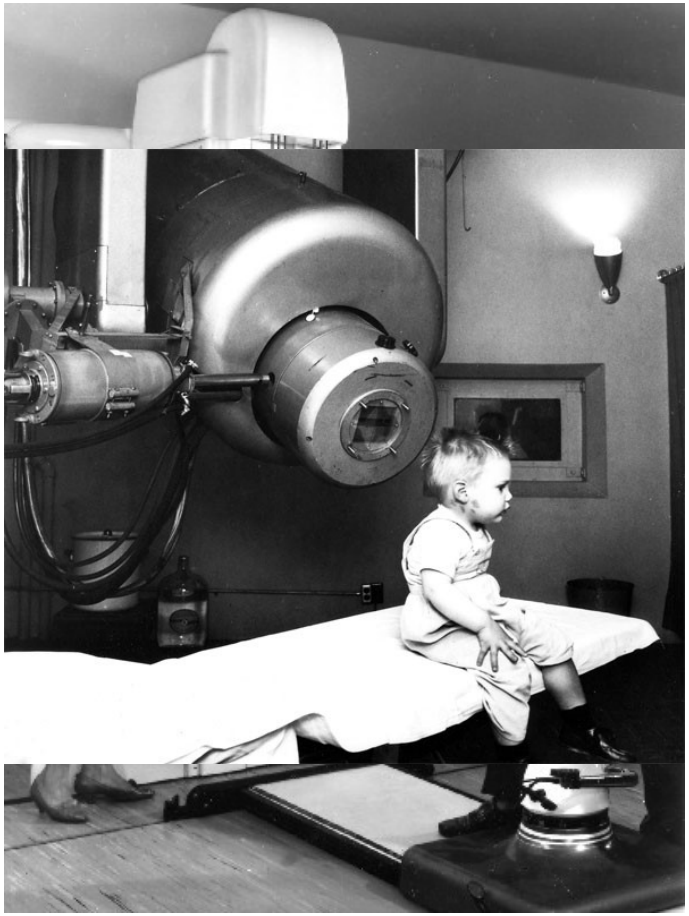


Coolidge X-ray tube, from around 1917. The heated cathode is on the left, and the anode is right. The X-rays are emitted downwards.

Early devices

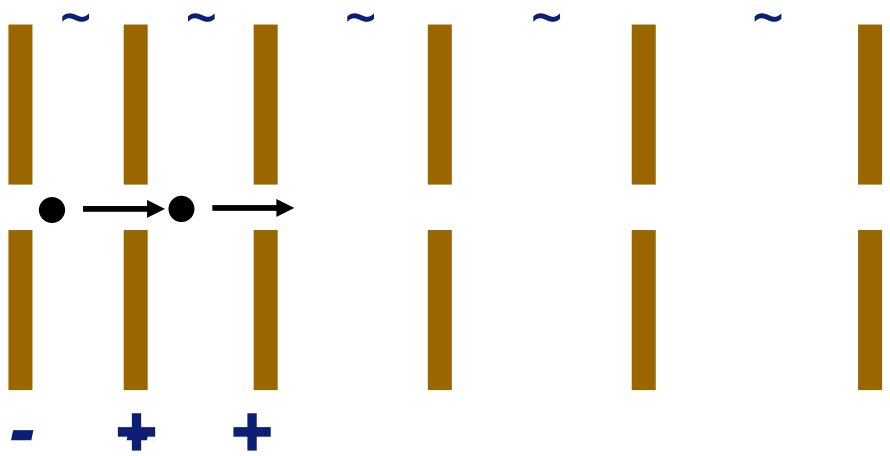


Stabilivolt (200 kV)

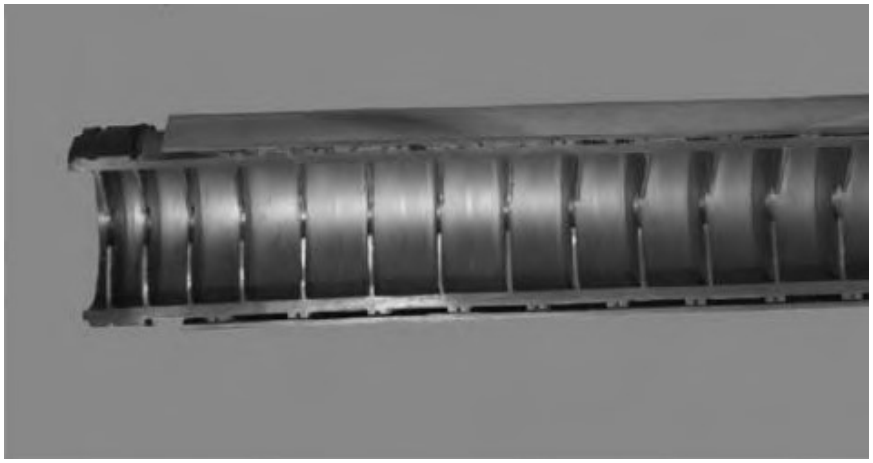


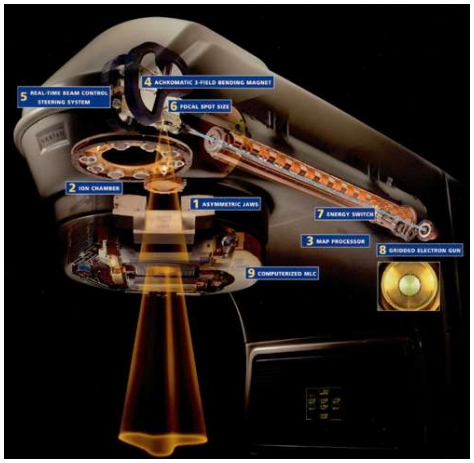
Betatron

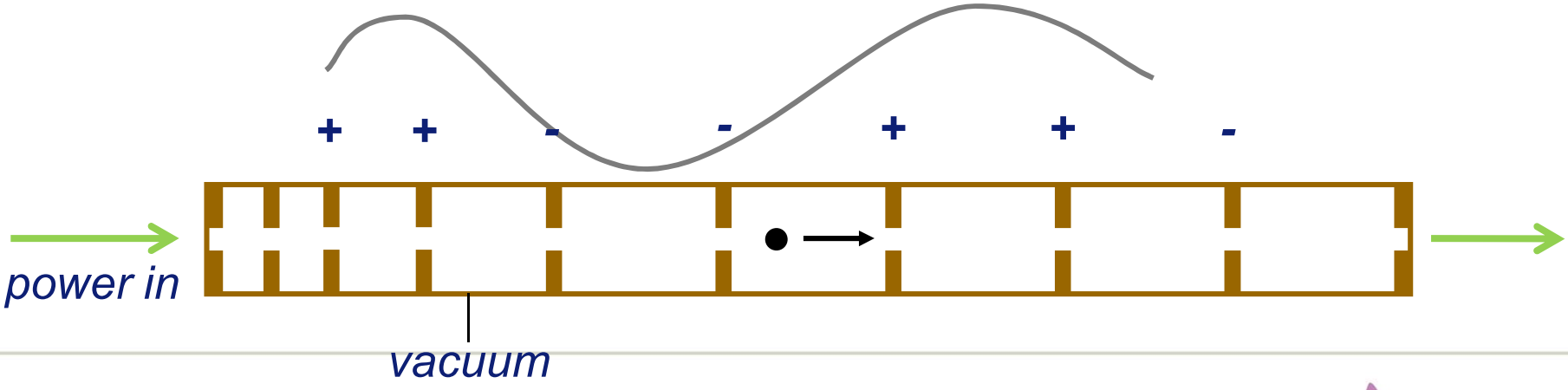
Schematic Accelerator Structure



Traveling Wave Accelerating Guide







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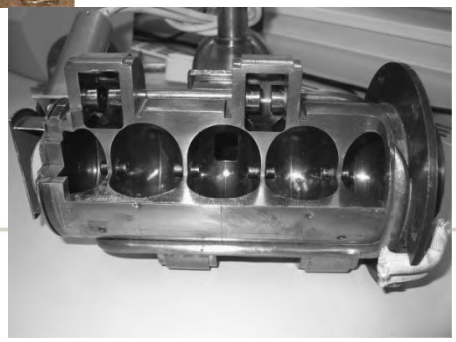
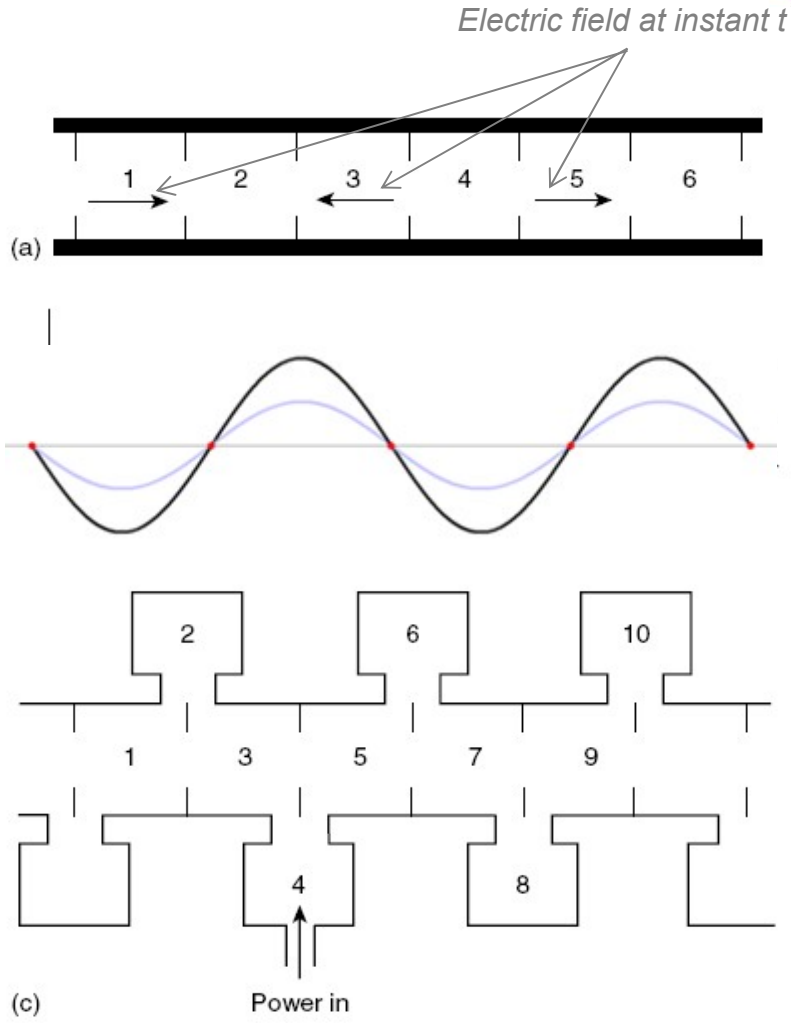
Standing Wave Guide

- End of waveguide terminated by conducting disc
  - → reflected with π/2 phase
- Electrons in 2, 4, 6 will receive no acceleration
  - Serve only as coupling cavities
  - Can be moved out to the side of waveguide
- Half cycle later: situation has reversed





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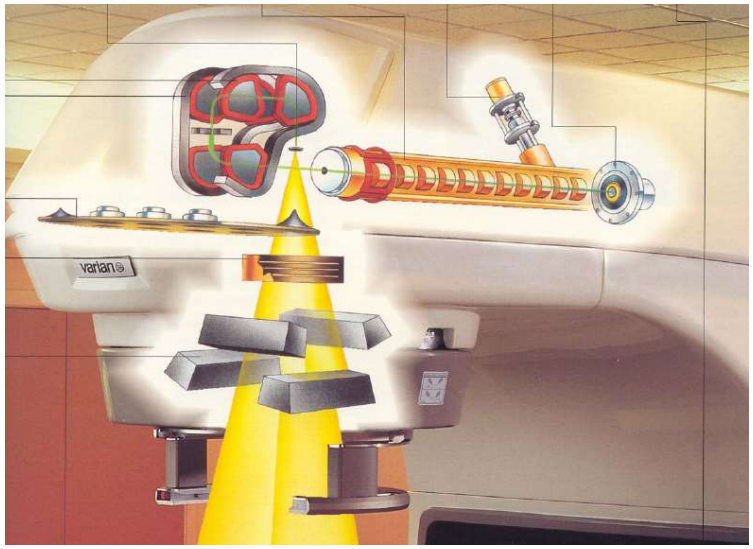
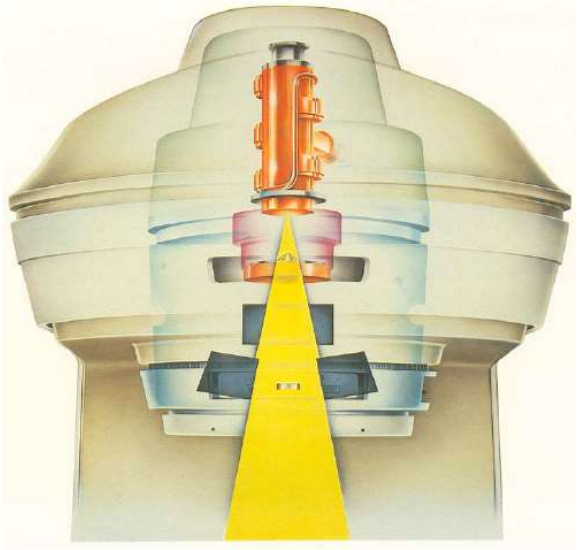
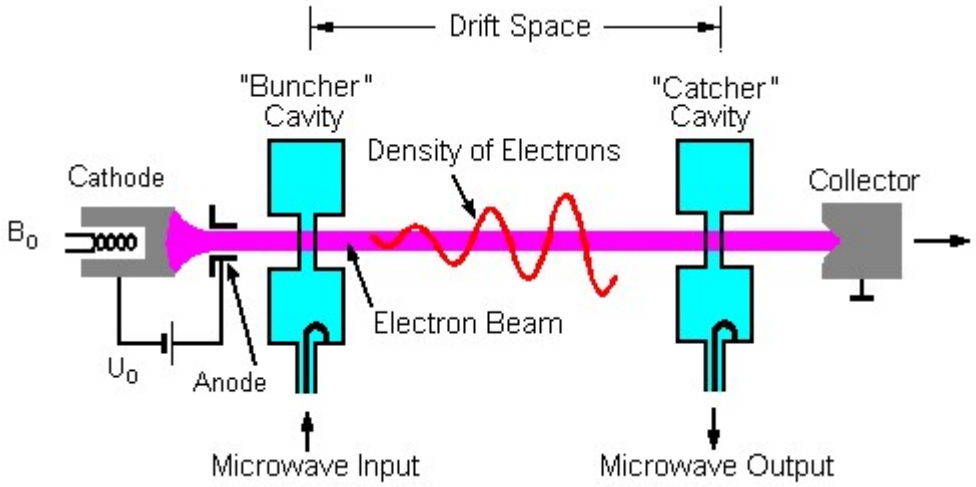
Traveling vs. Standing Wave Guides

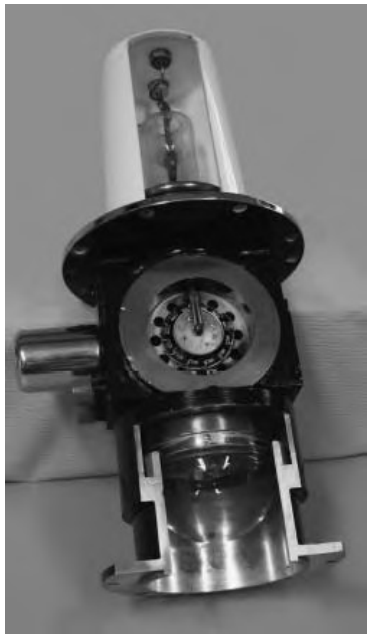




- Traveling Wave Guides (Elekta)
  - Easier, less costly
- Standing Wave Guides (Varian, Accuray)
  - More efficient

Powering the System: Klystron and Magnetron





10.000 hrs

2.000 hrs

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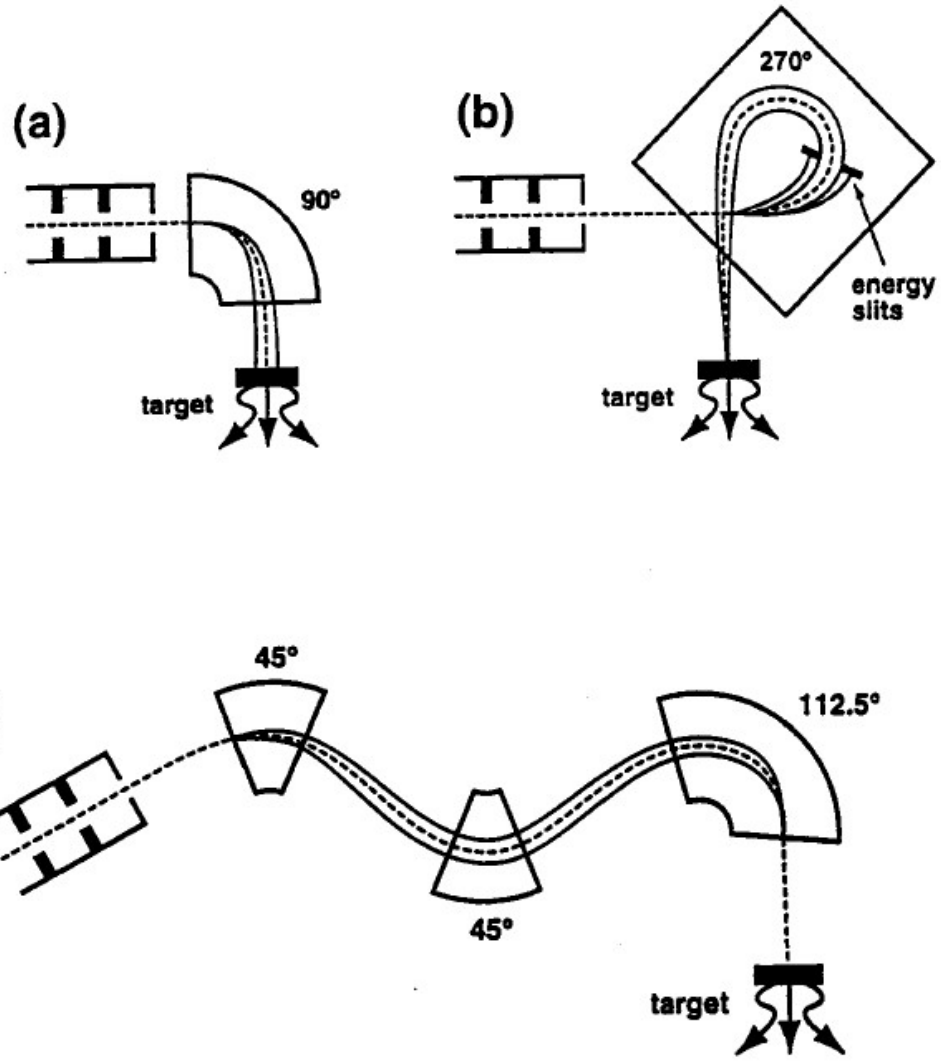
Beam Transport (Chromatic and Achromatic 90° Bending)



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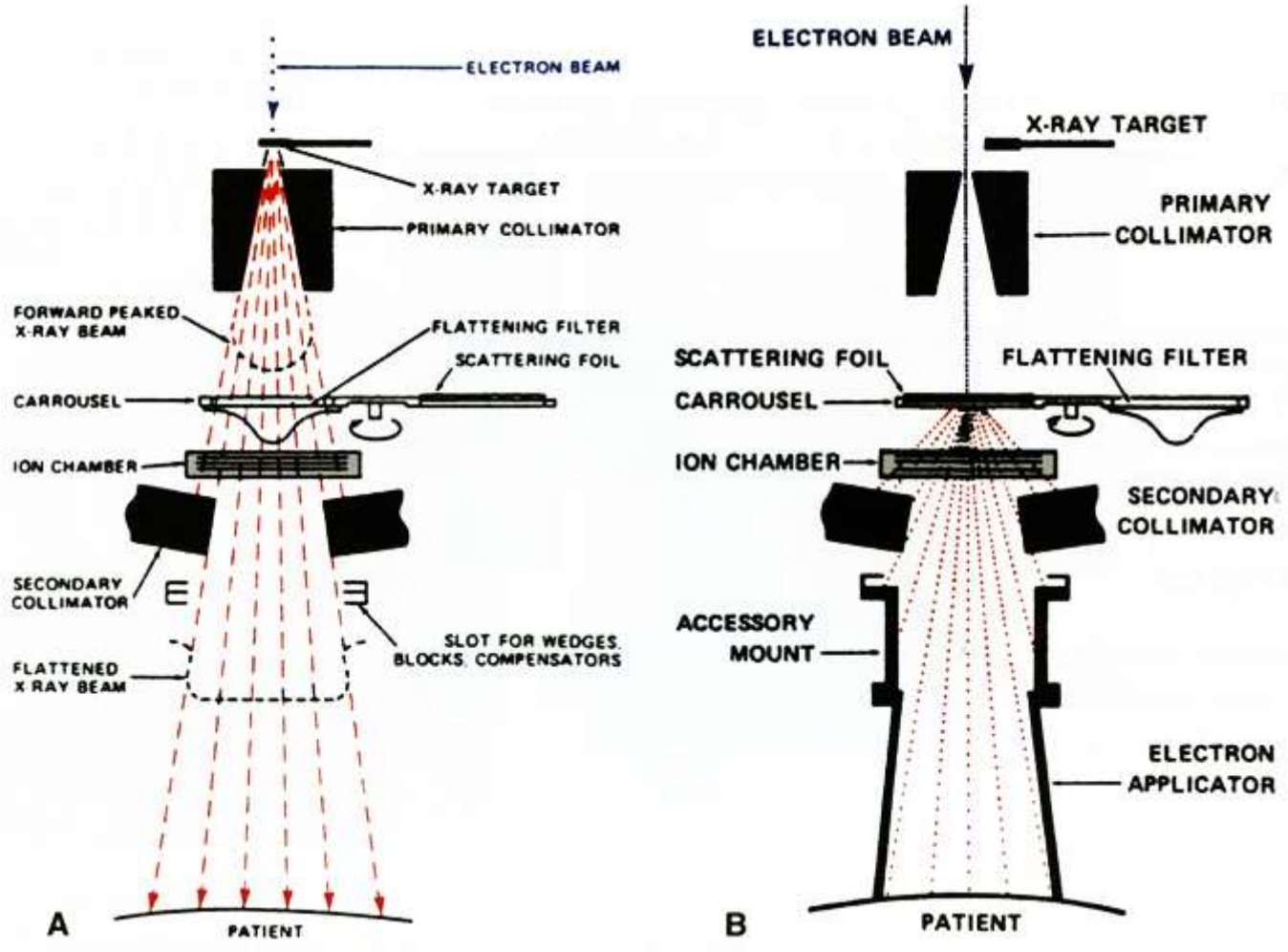
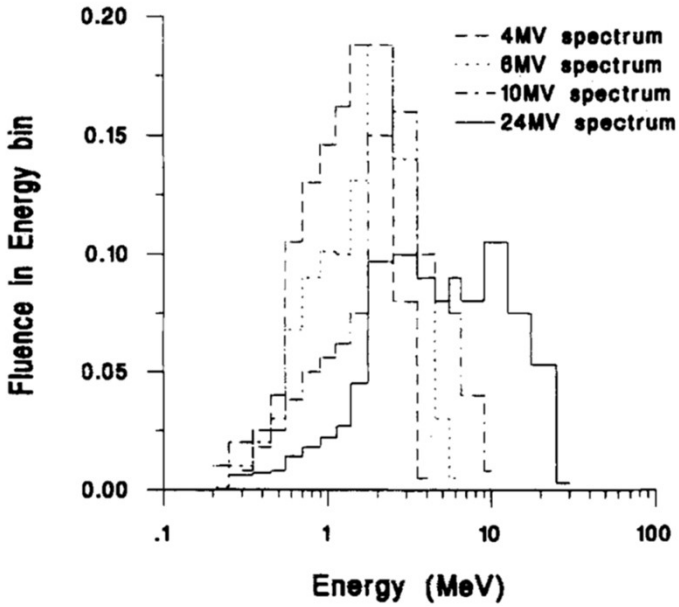
Linac Head



Photons **Electrons**

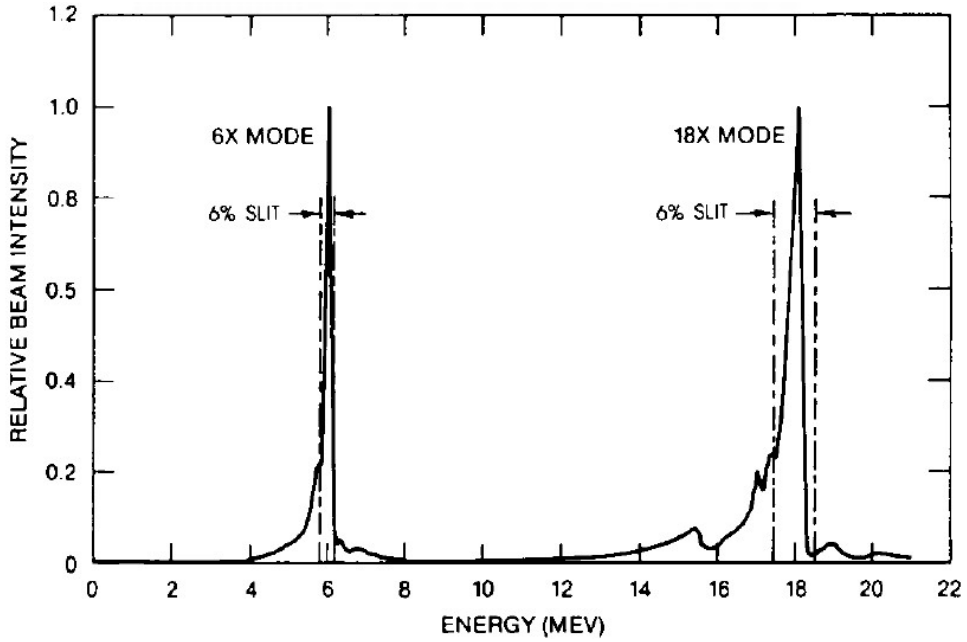
Energy Distribution Photons vs. Electrons

Photons



Papanikolaou (1993)

Electrons



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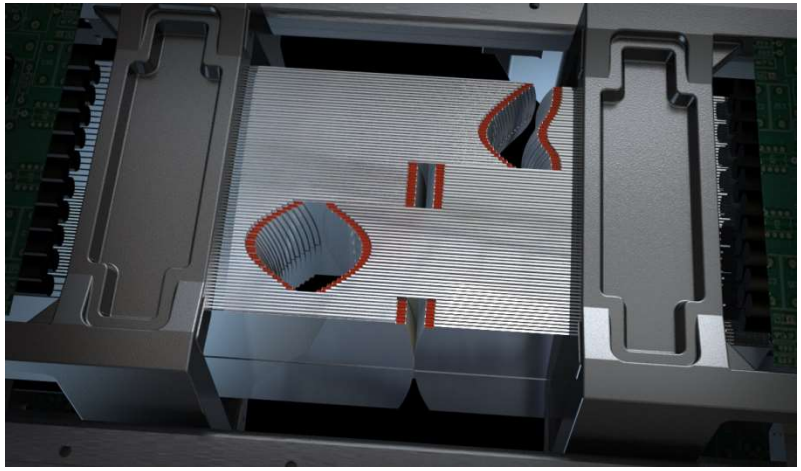
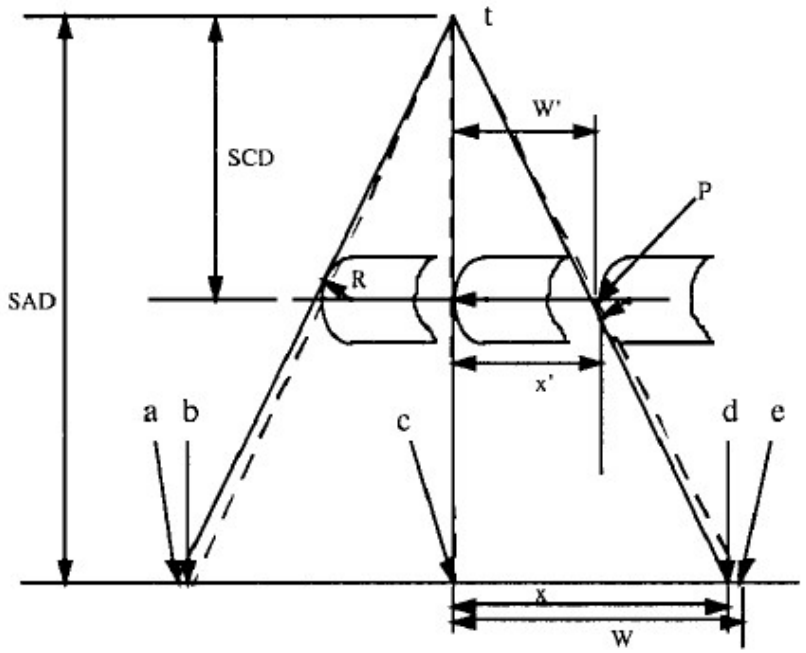
Beam Collimation (ext Helical Tomotherapy)

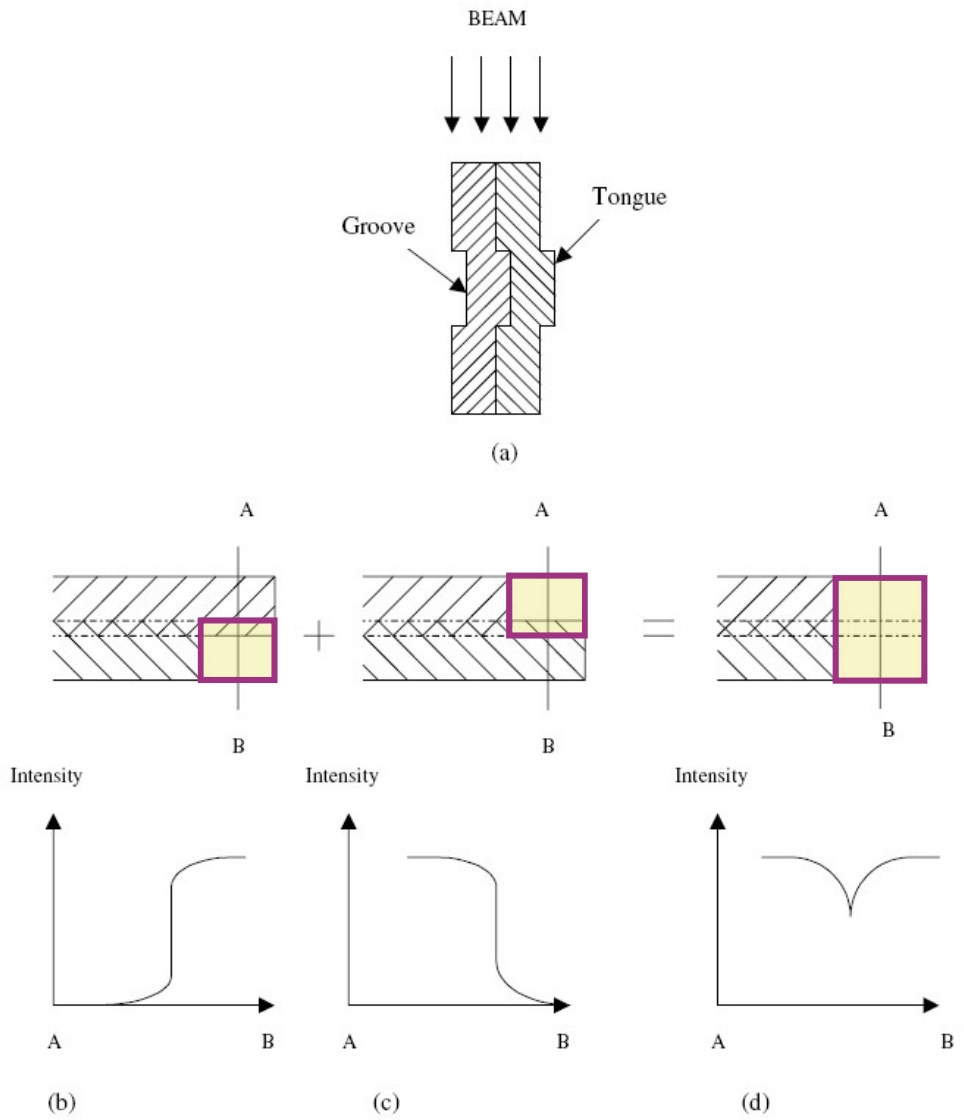
- Leaf width 2.5-4-5-10 mm
- High leaf velocity required for high dose rate with unflattened beams
- Interdigitation



- Rounded leafs

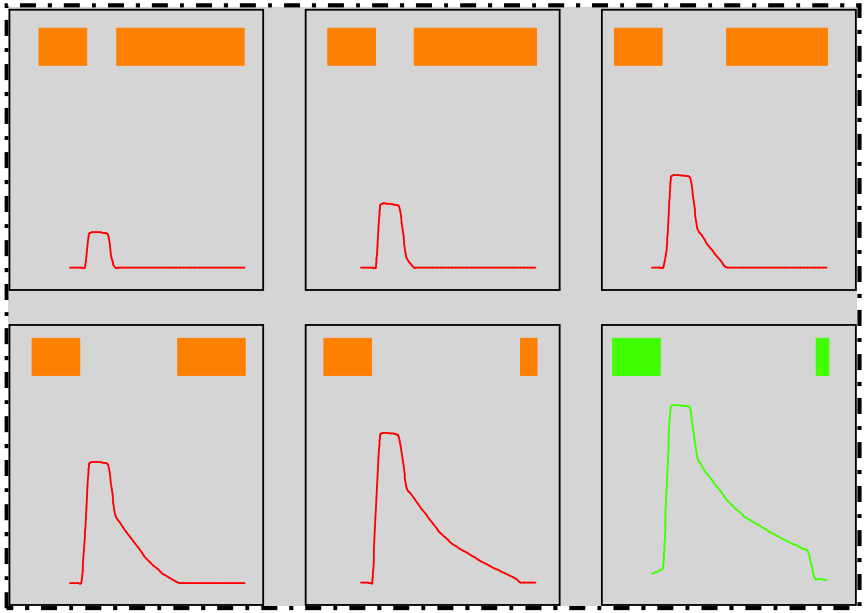


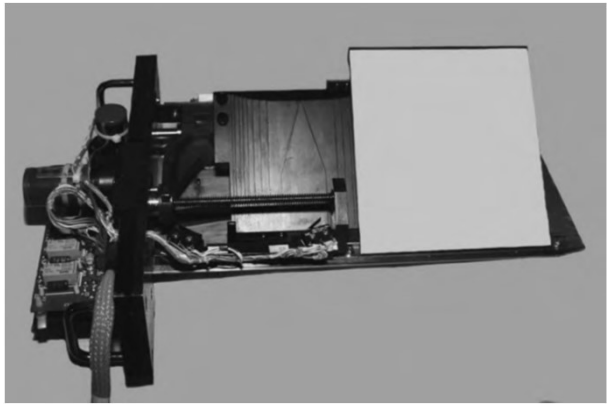
Tongue and Groove Effect

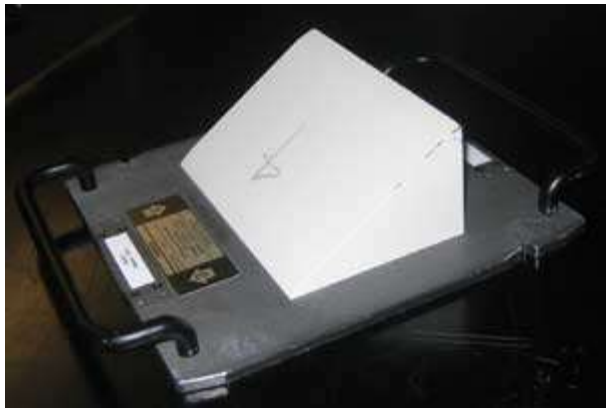


Wedge

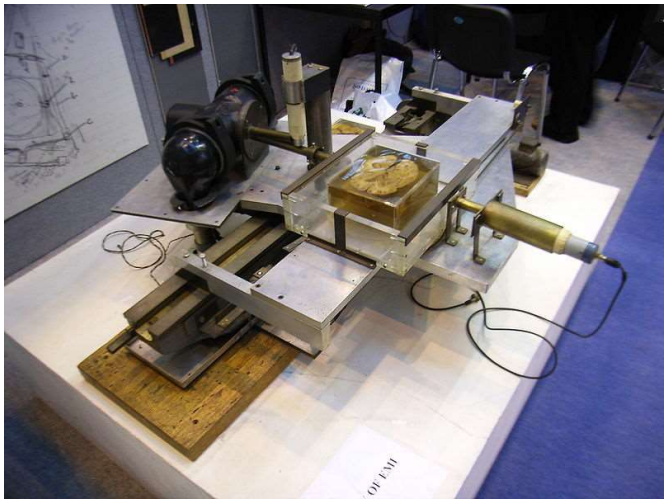
- Mechanical fixed wedge
- Motorized wedge
- Dynamic wedge

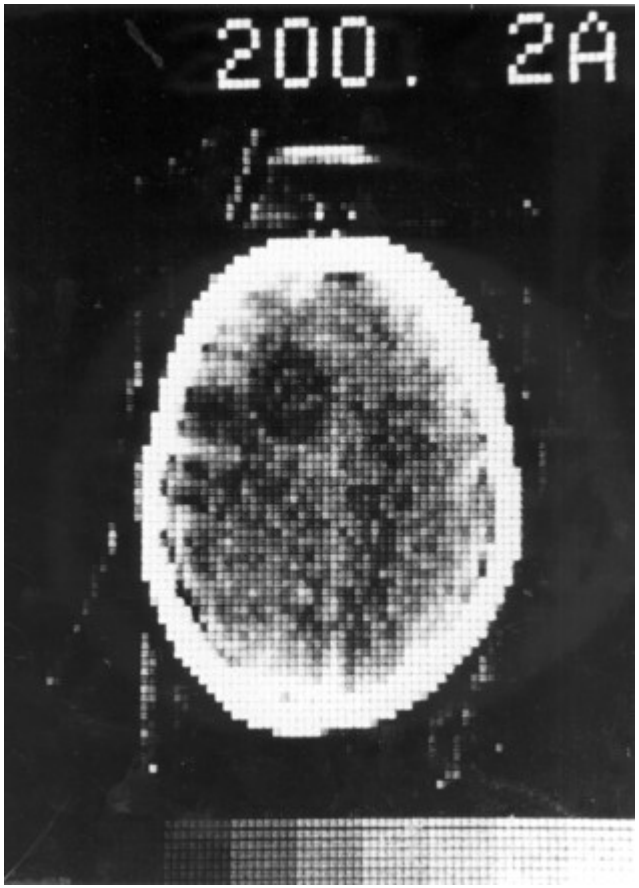


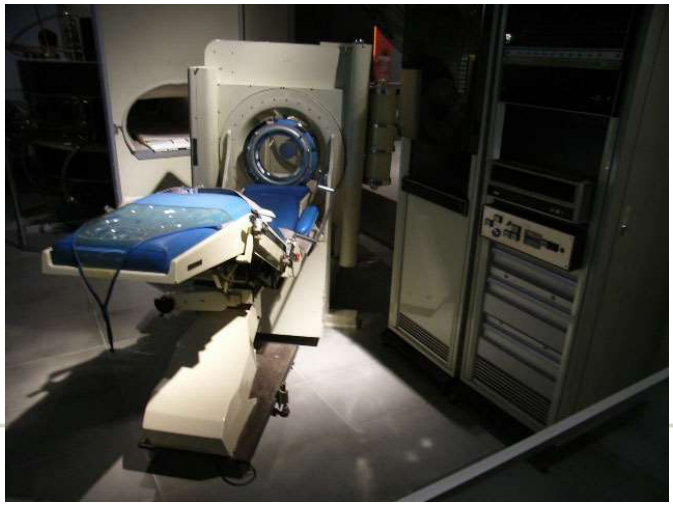




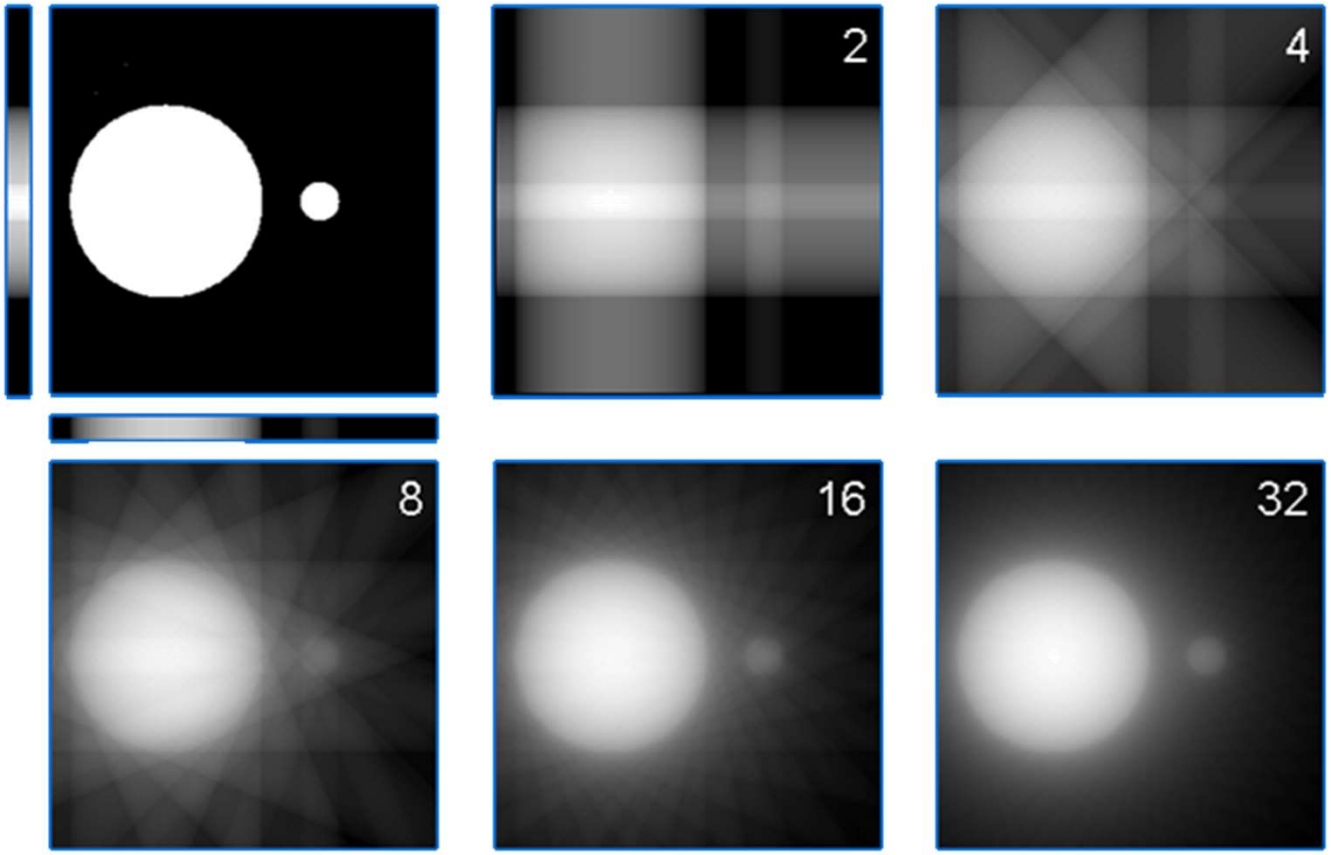
CT Scanner of Hounsfield





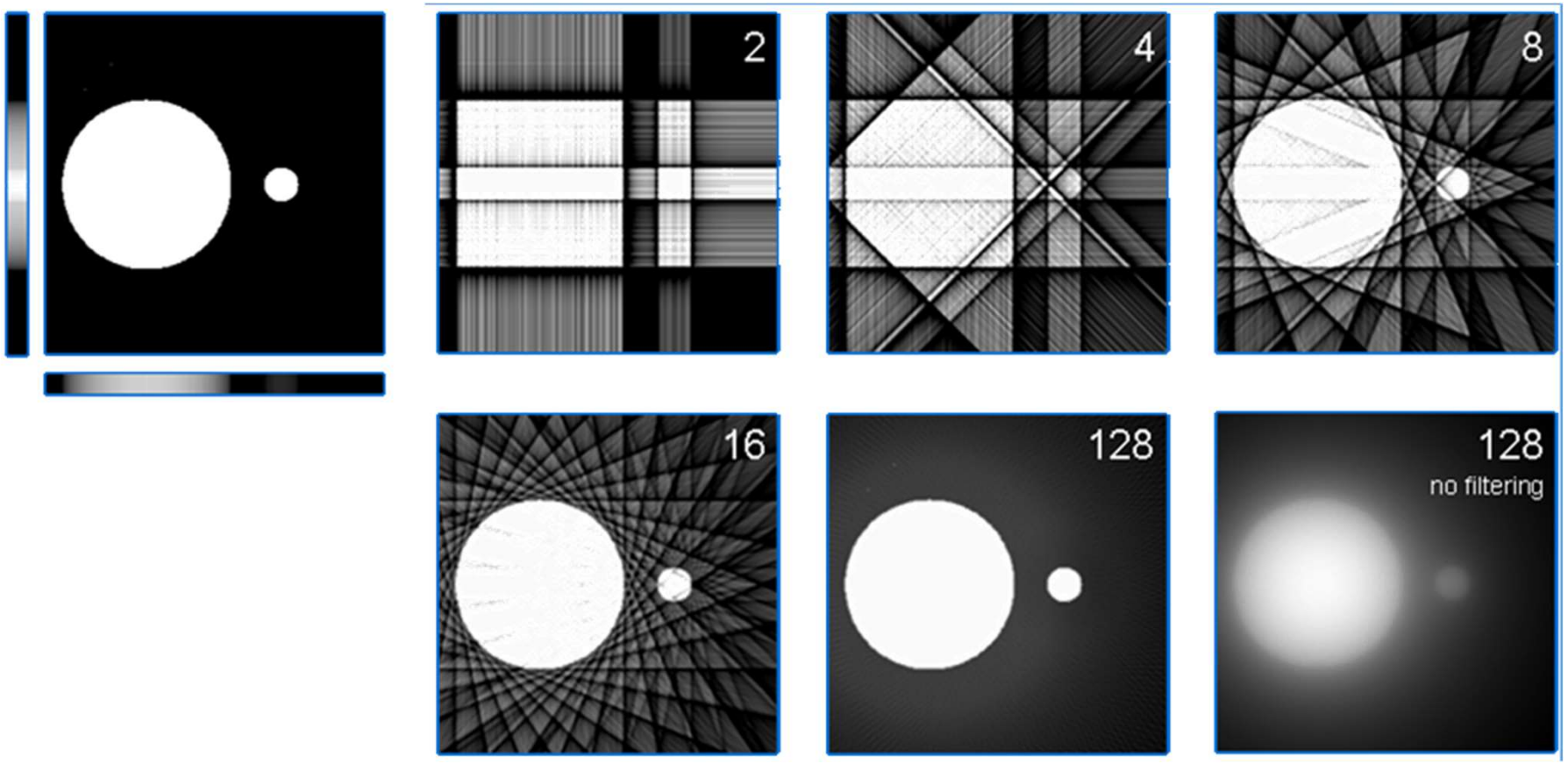


Back Projection



http://www.impactscan.org/impactcourse.htm

Filtered Back Projection



http://www.impactscan.org/impactcourse.htm

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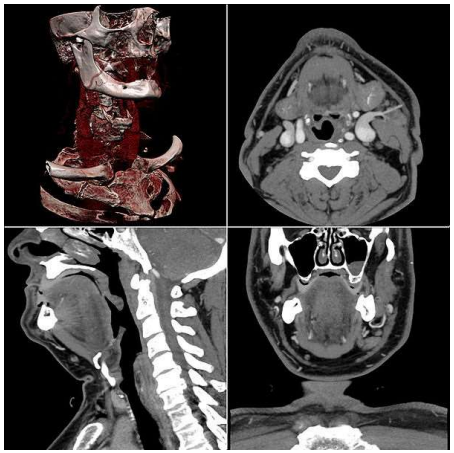
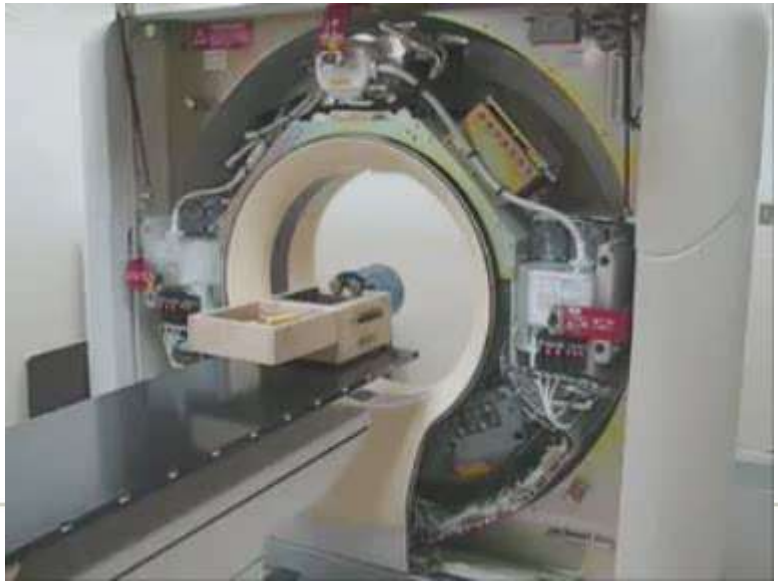
Modern CT Scanners for Radiotherapy

- Flat couch top & positioning devices
- Wide bore
- CT simulation software
- External positioning lasers
- 4D and Respiratory gated CT



- 64 Multislice
- Spiral acquisition
- Dual Energy



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Special Techniques / Treatment Machines

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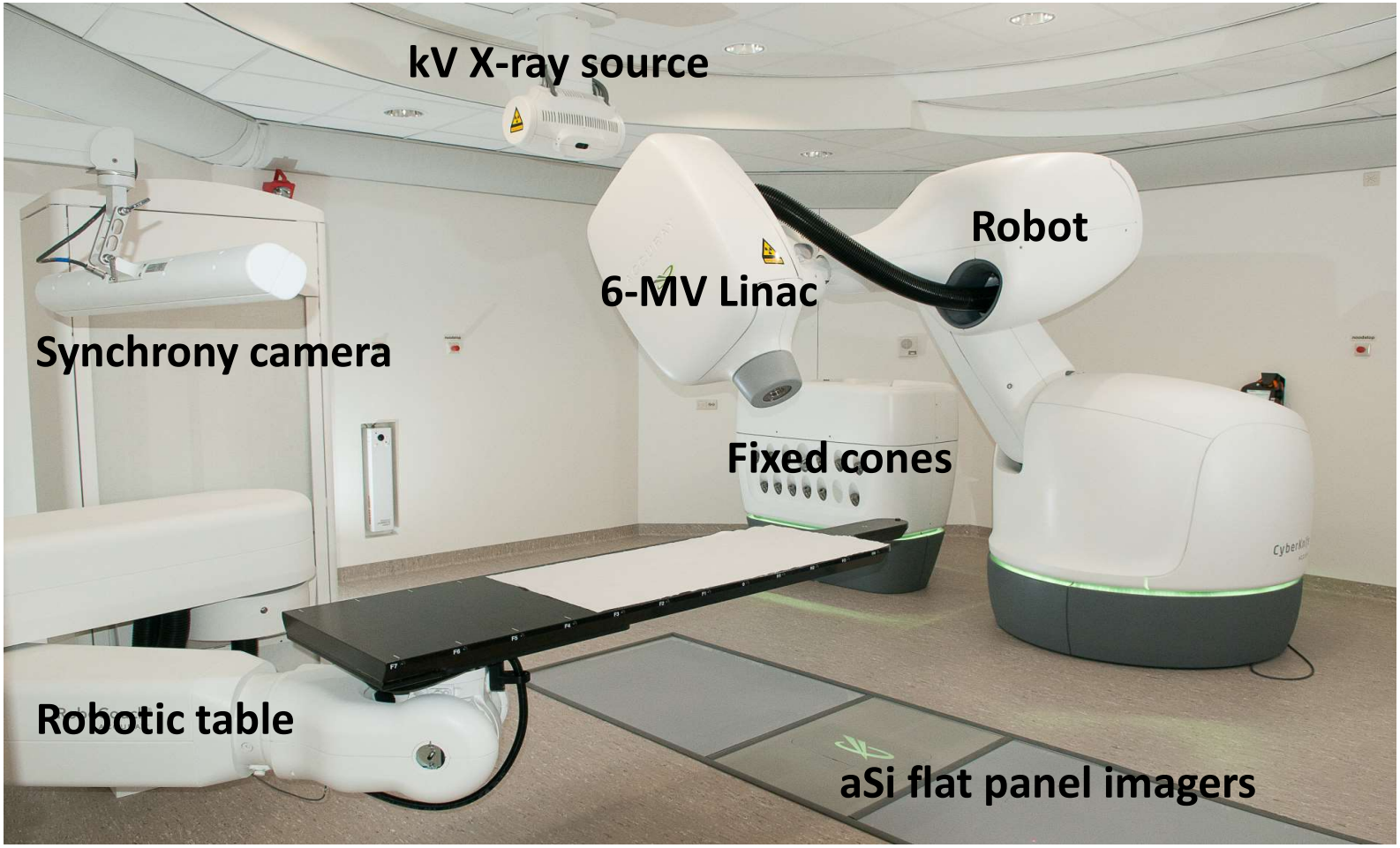
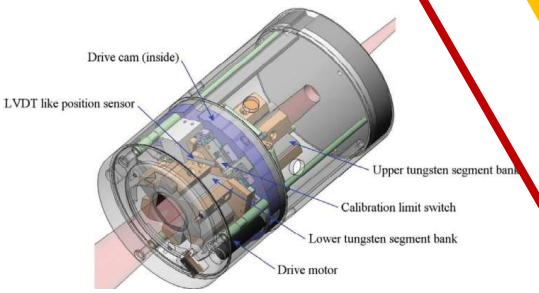
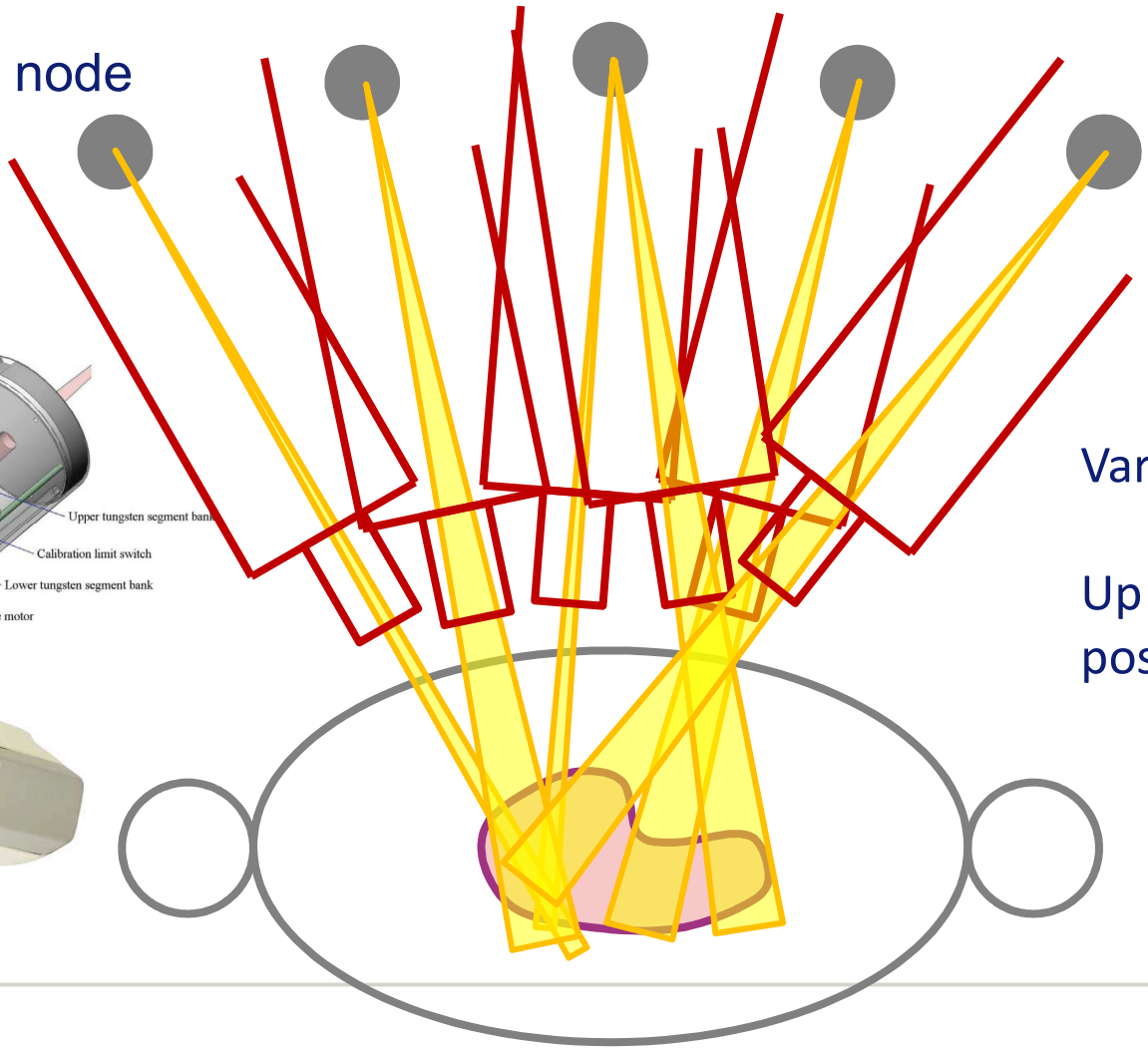
CyberKnife System Components



CyberKnife





Various node sets

Up to 180 node positions

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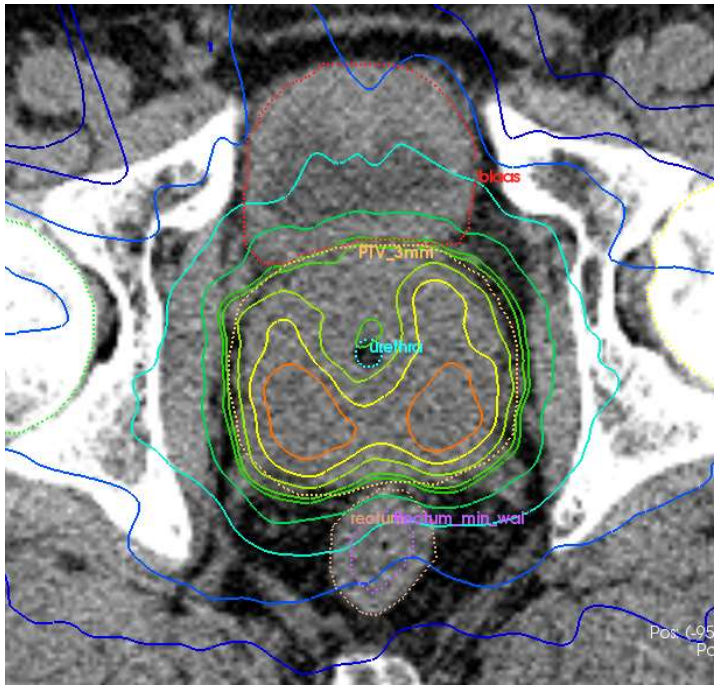
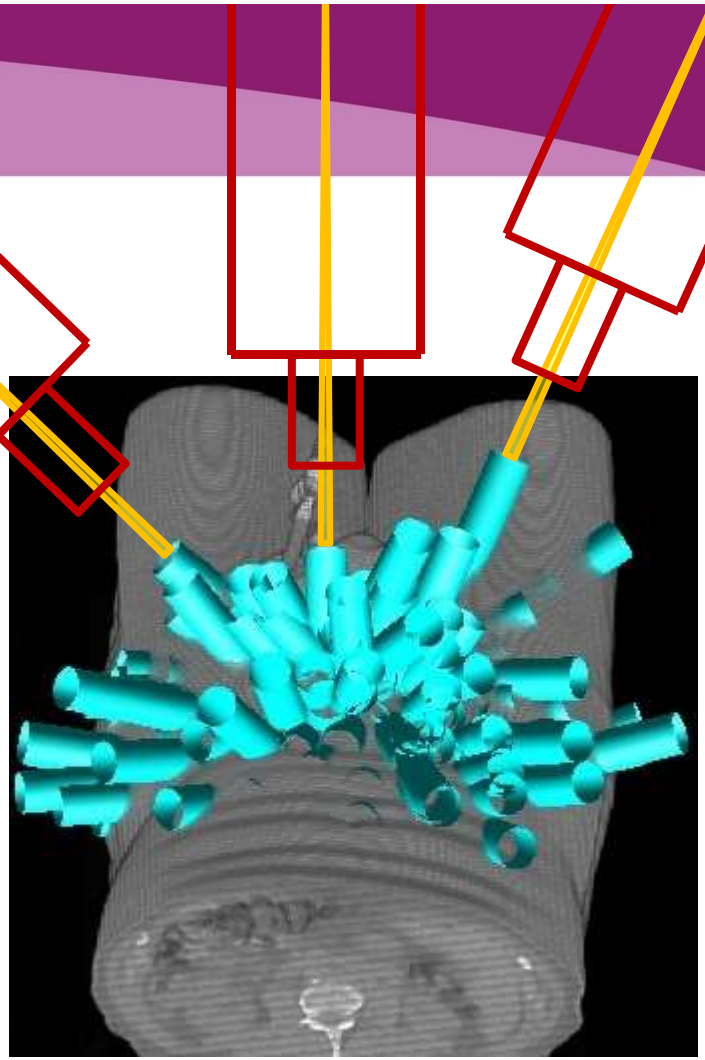
CyberKnife prostate

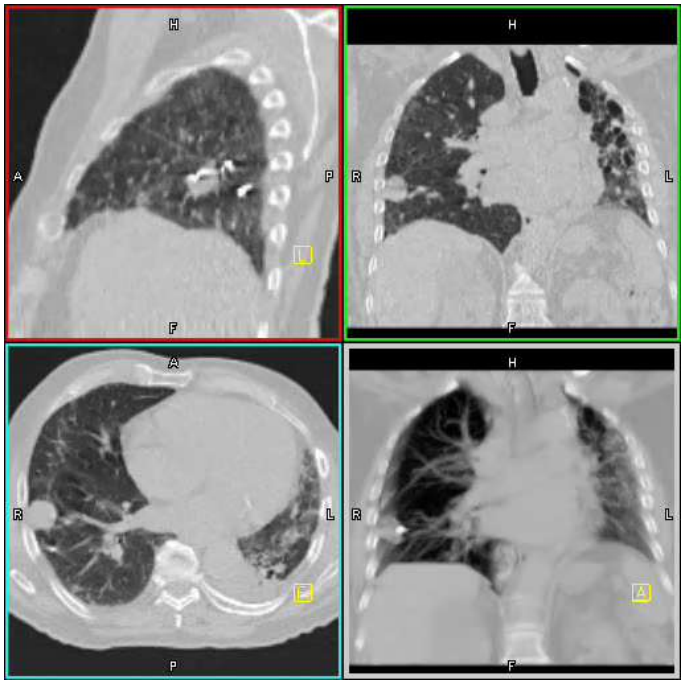




4 x 9.5 Gy @ 60%

Tracking tumors that move with respiration

- Beam moves with moving tumor



Accuracy better than 3 mm
Hoogeman et al. IJROBP 2009

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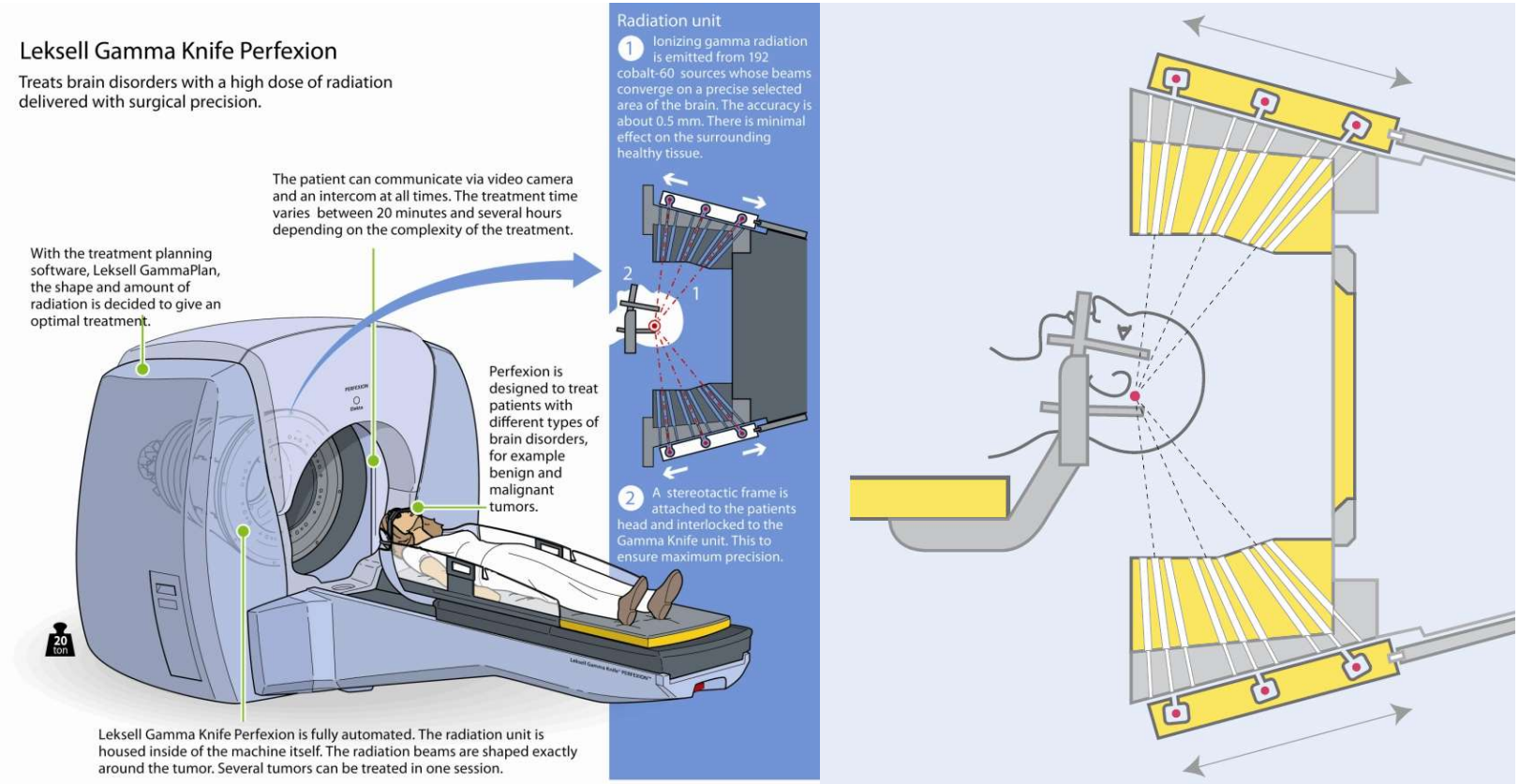
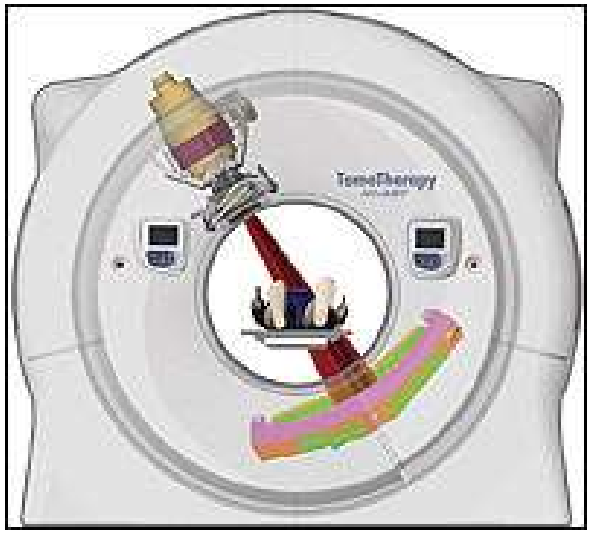
GammaKnife (Elekta)

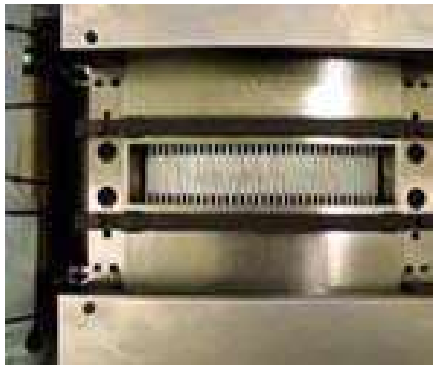
- Invented by Lars Leksell (1967)
- Contains 192 Co-60 sources (half-life is 5.27 years)

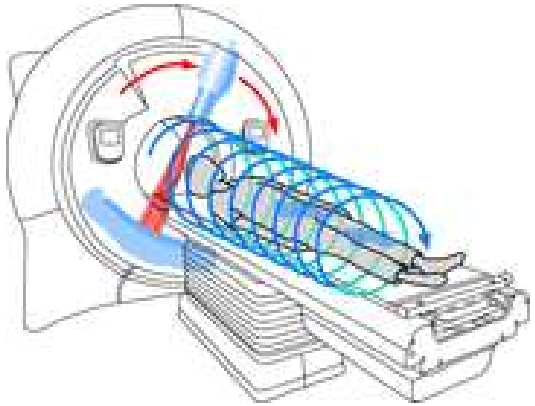


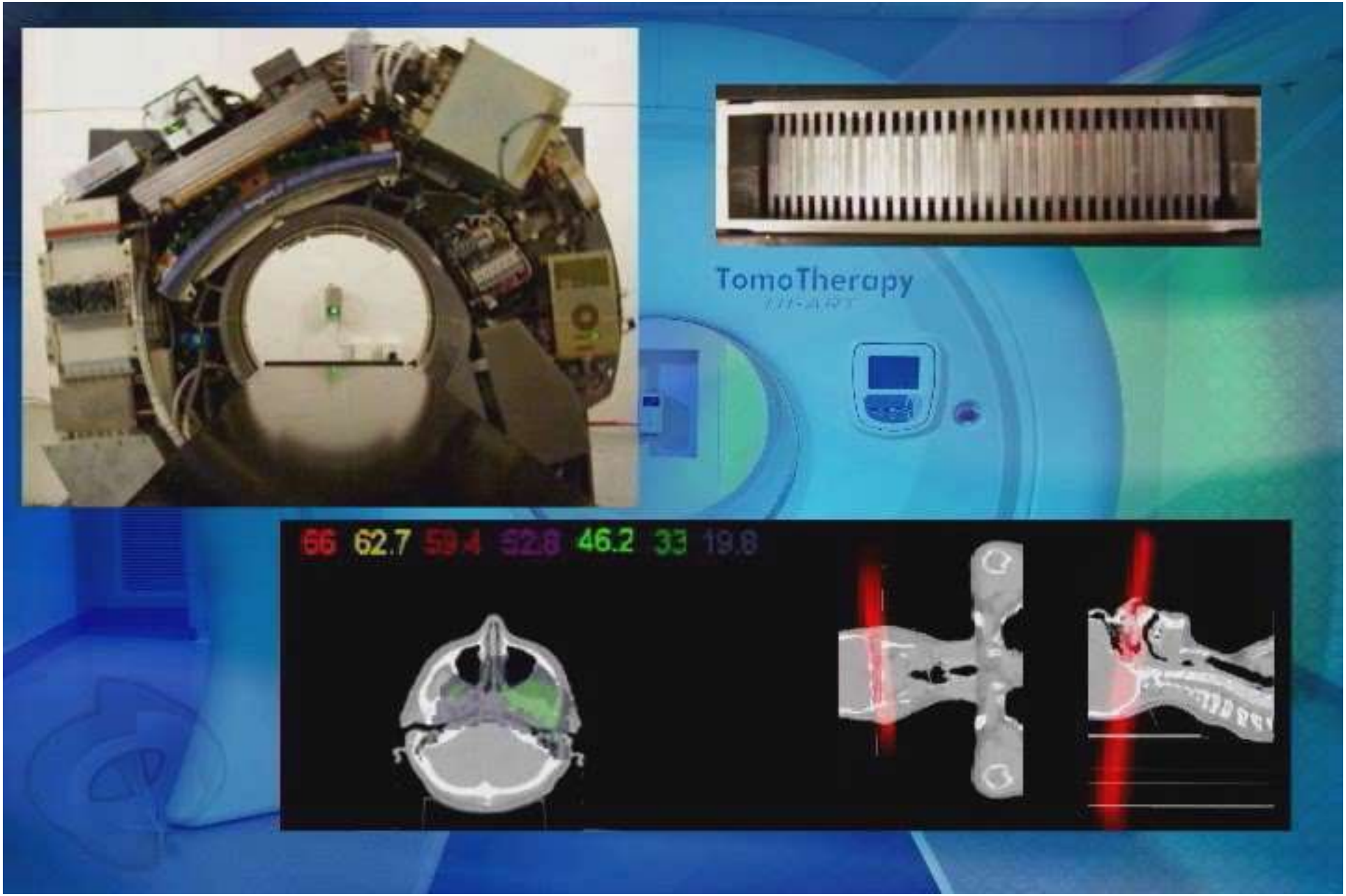
Tomotherapy (Accuray)

- Fan beam with binary MLC
- Helical delivery of dose by fan beam
- MVCT
- See lecture on rotational techniques









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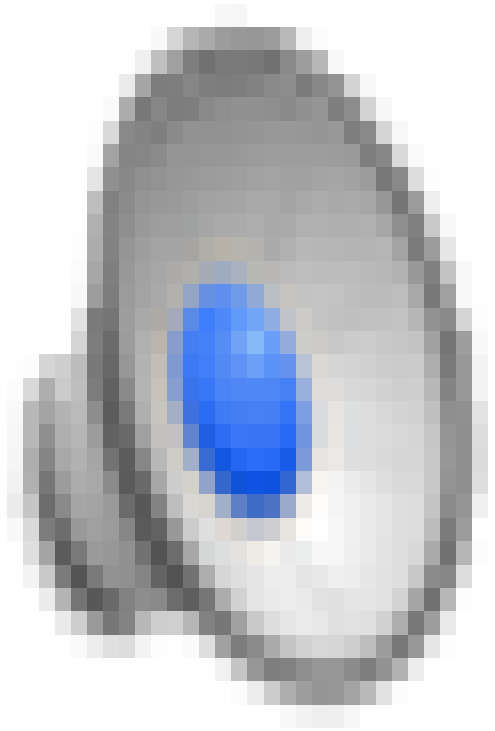
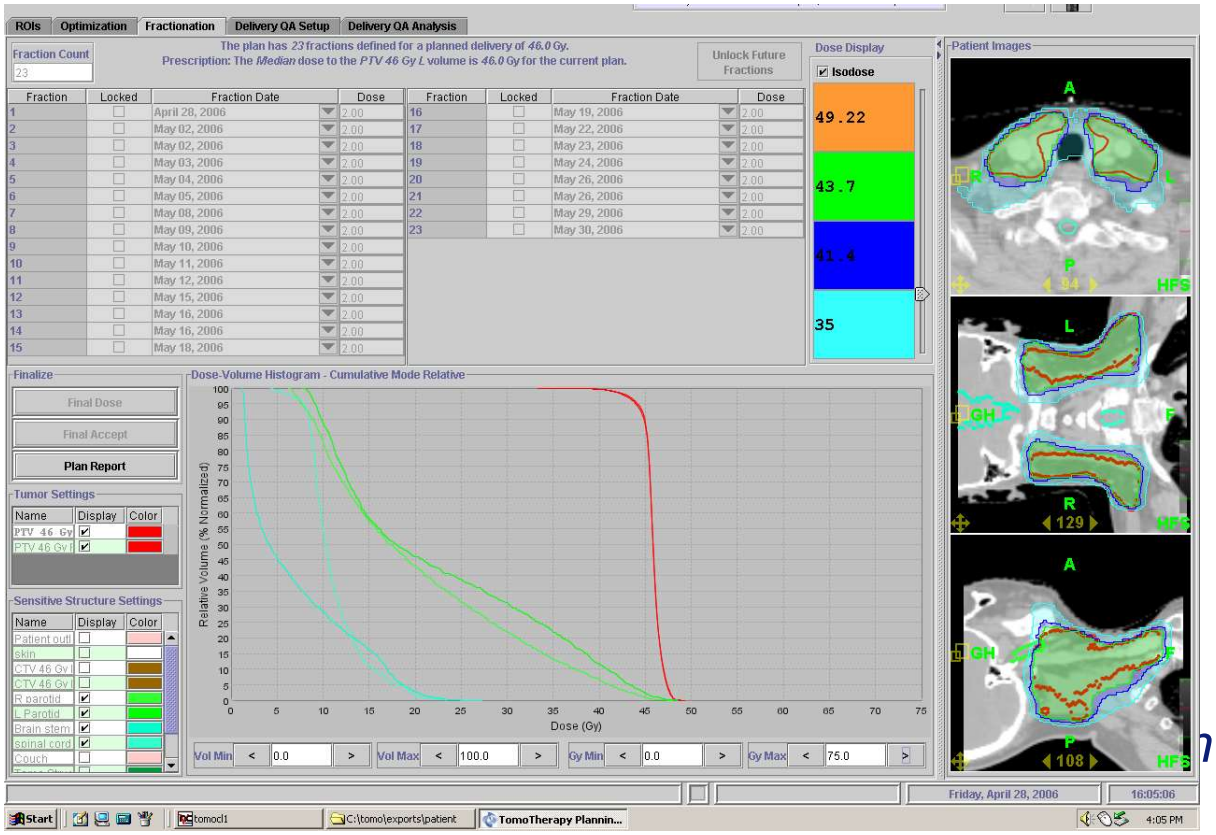
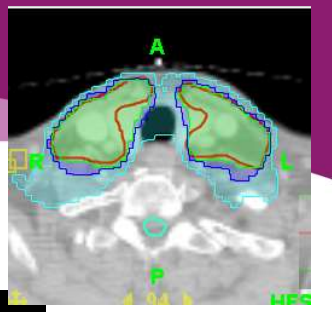
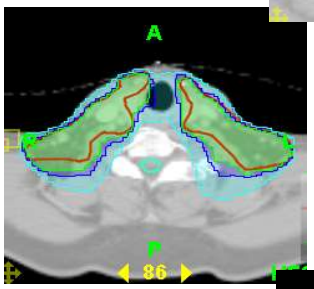
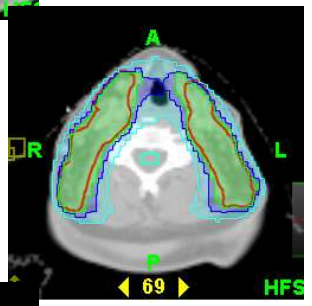


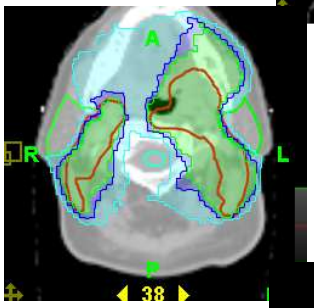
- Head and neck case

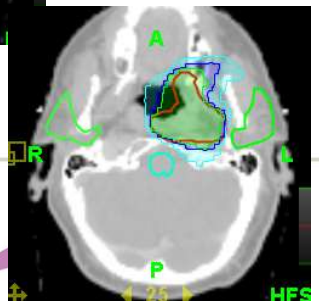




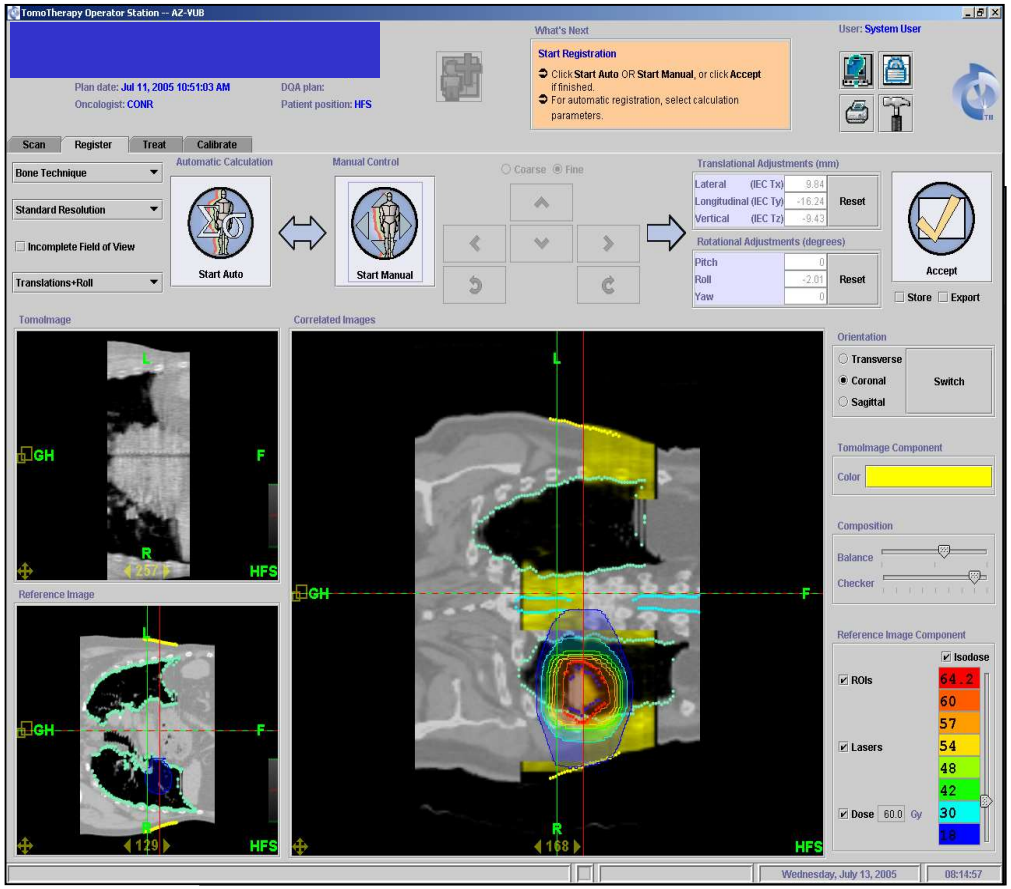








Advantages of MVCT



- Actual treatment beam also used for imaging
- No surrogate required

  (soft tissue visualization)
- 3D volumetric imaging
- CT-CT registration, similar information
- Registration of dose distribution and anatomy
- Patient dose: ≈ 1-2 cGy

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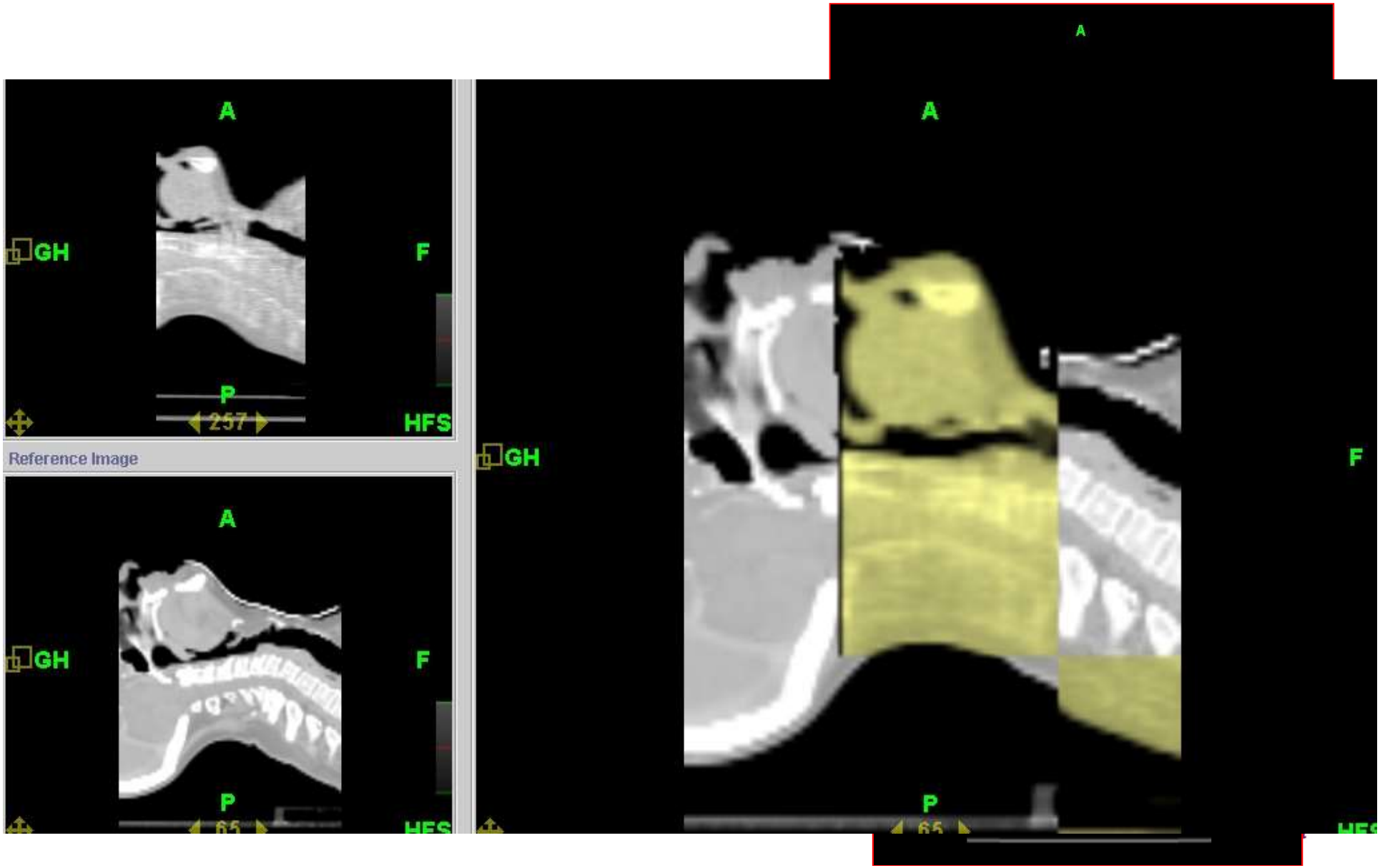
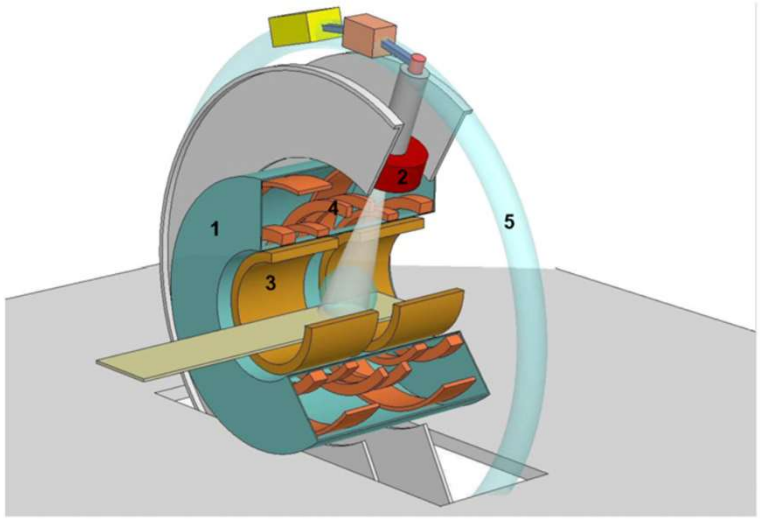
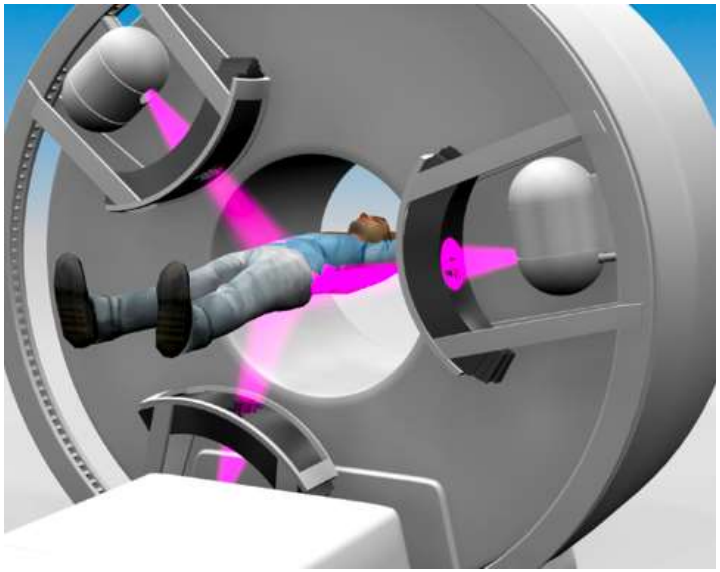
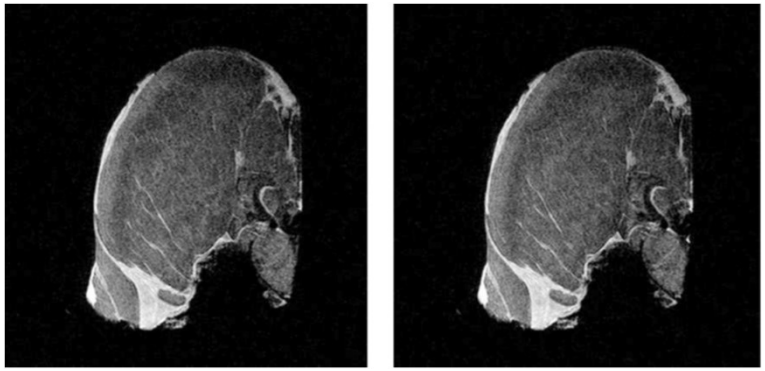
Patient positioning



Linac Integrated MRI





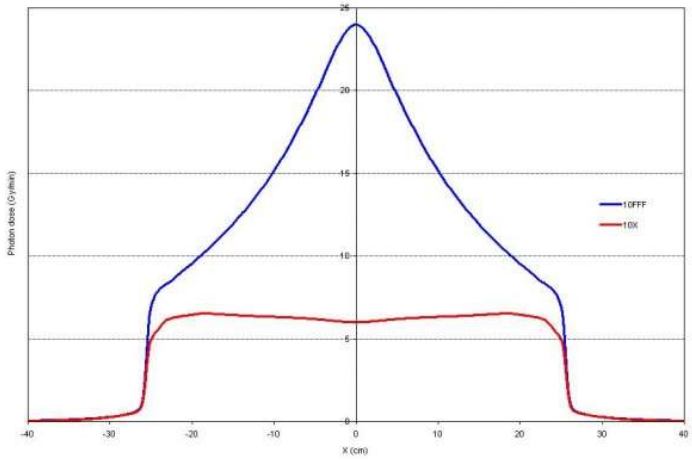


Raaymakers Phys Med Biol (2009)

Linac Integrated MRI

Truebeam STx (Varian)

No flattening filter!



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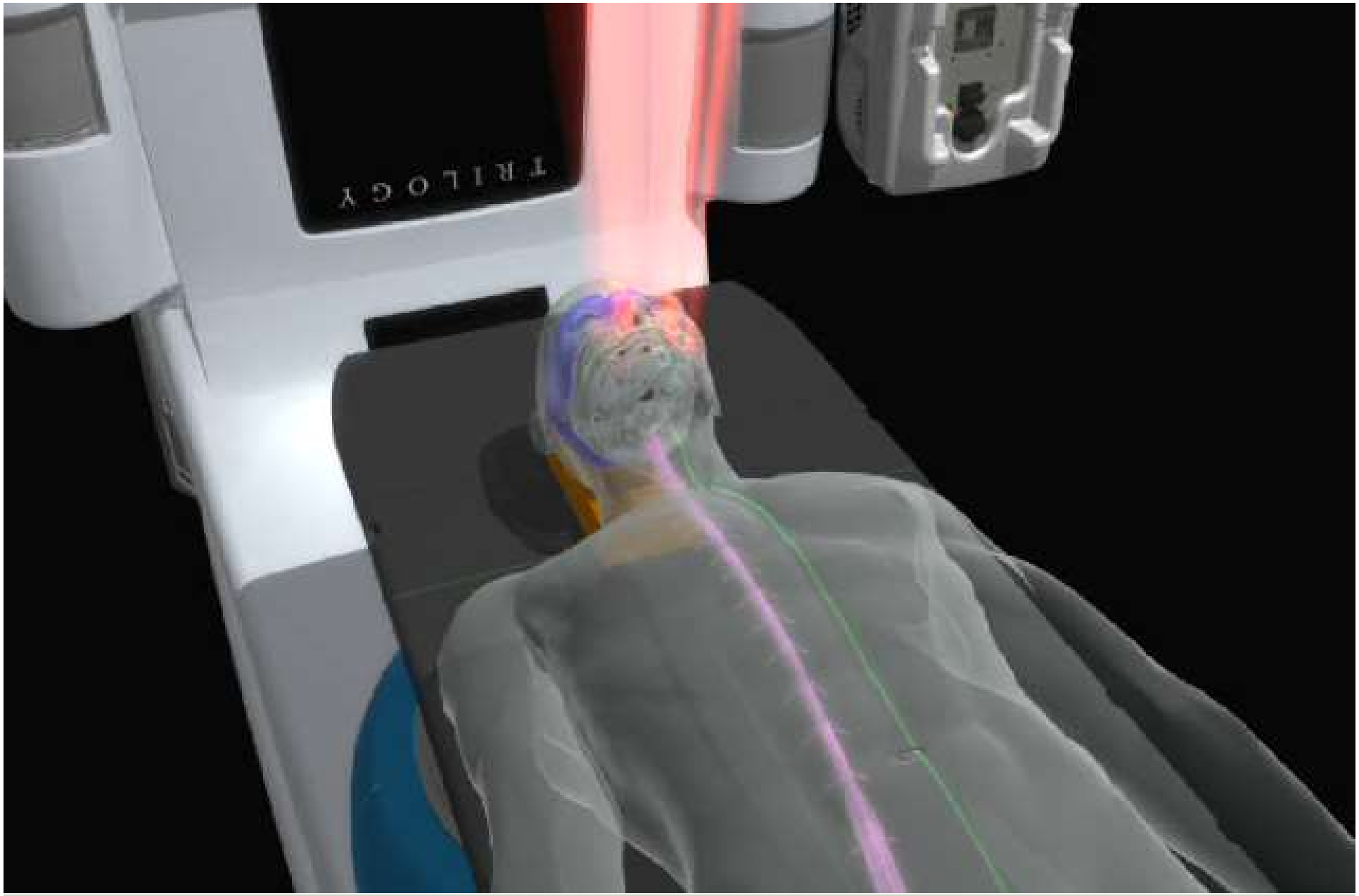

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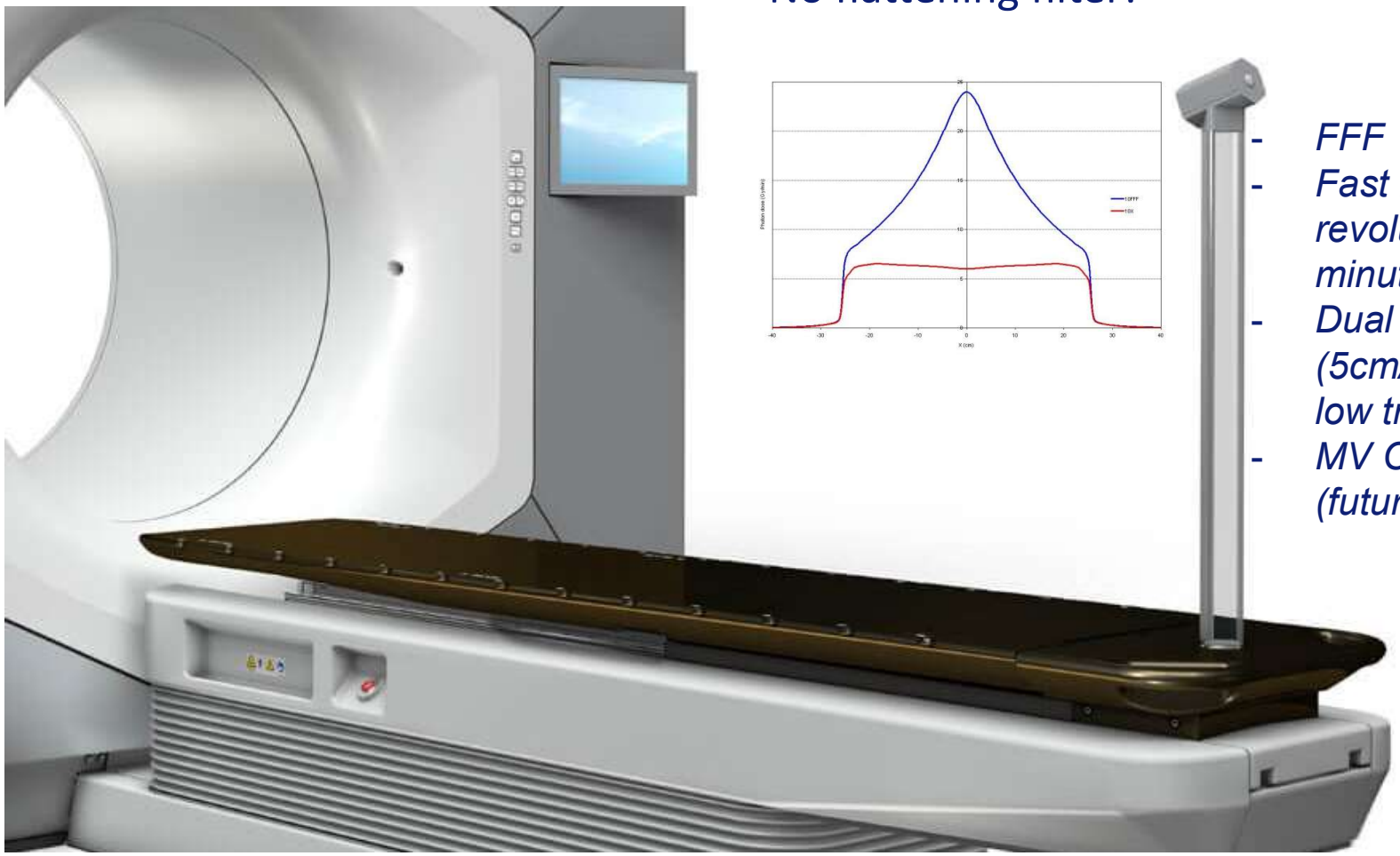
HALCYON (Varian)

No flattening filter!



- *FFF*
- *Fast rotation ! (4 revolutions per minute)*
- *Dual layer MLC (5cm/sec), very low transmission*
- *MV CBCT (future:kV CBCT)*

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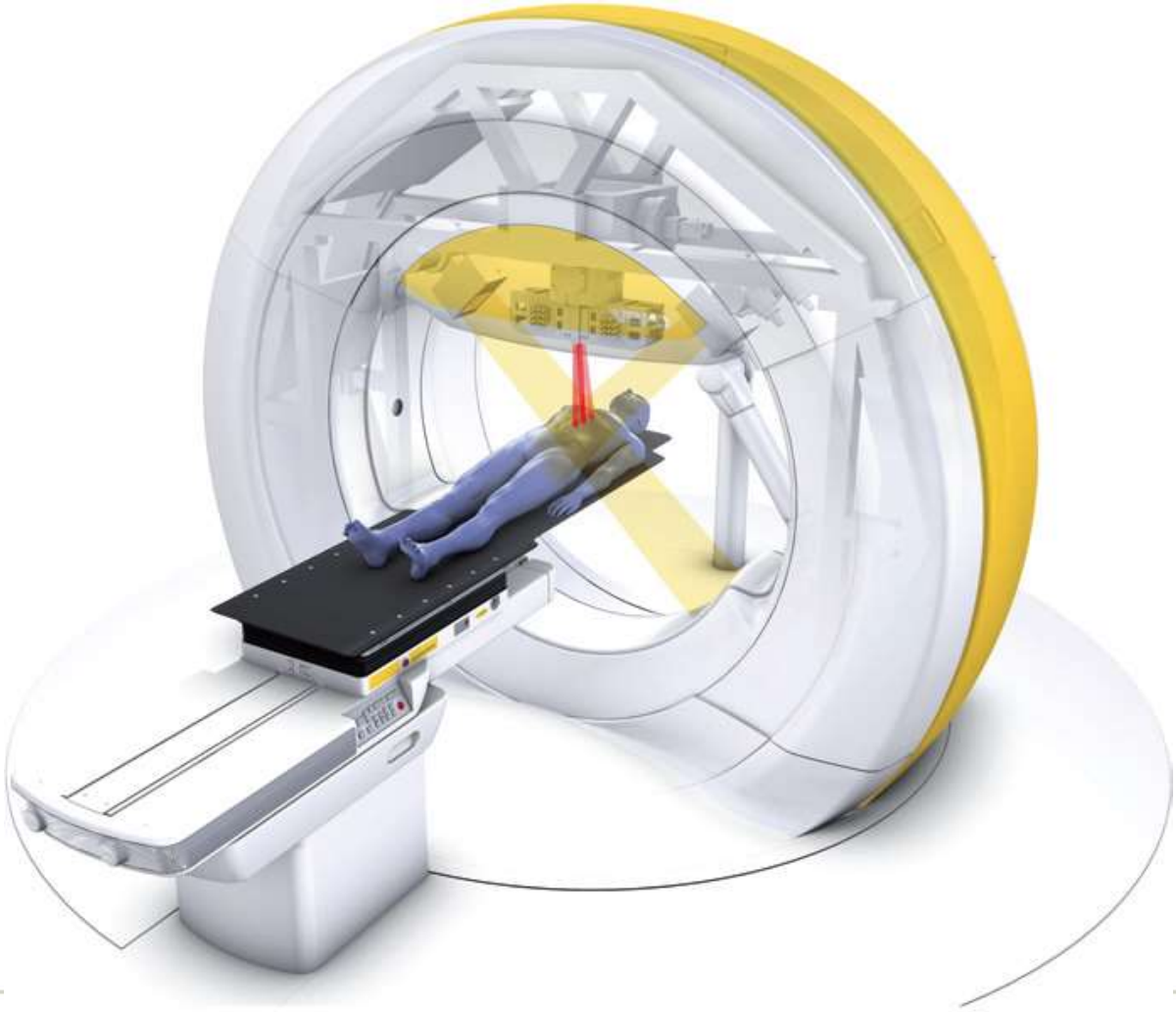
Vero (Brainlab/Mitsubishi)



- Dual orthogonal kV X-ray system
- Stereoscopic imaging
- Fluoroscopy
- kV CBCT

- Gimbaled LINAC/MLC for real-time tumor tracking

- Static conformal beam
- Arc therapy
- IMRT
- Non-coplanar ARC

Particle Therapy

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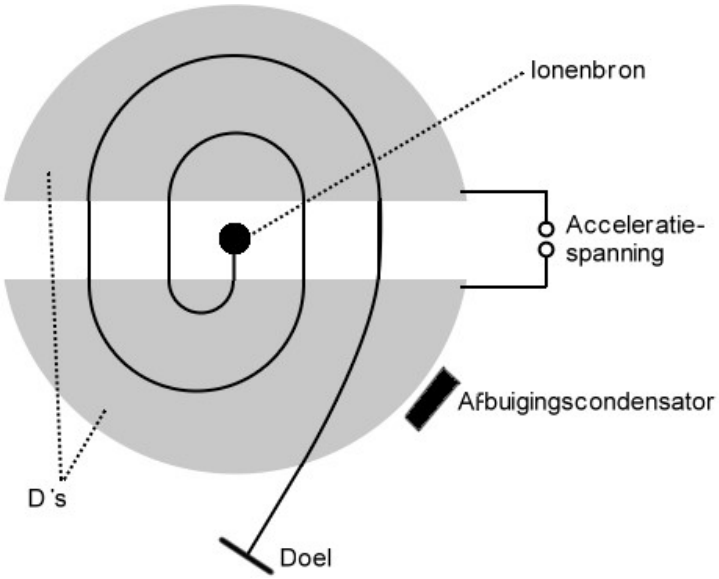
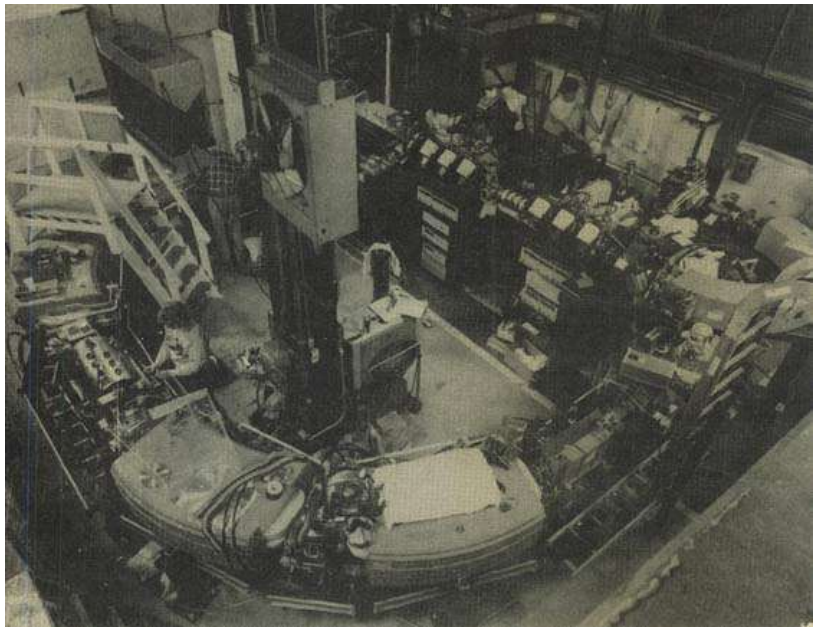
Cyclotron

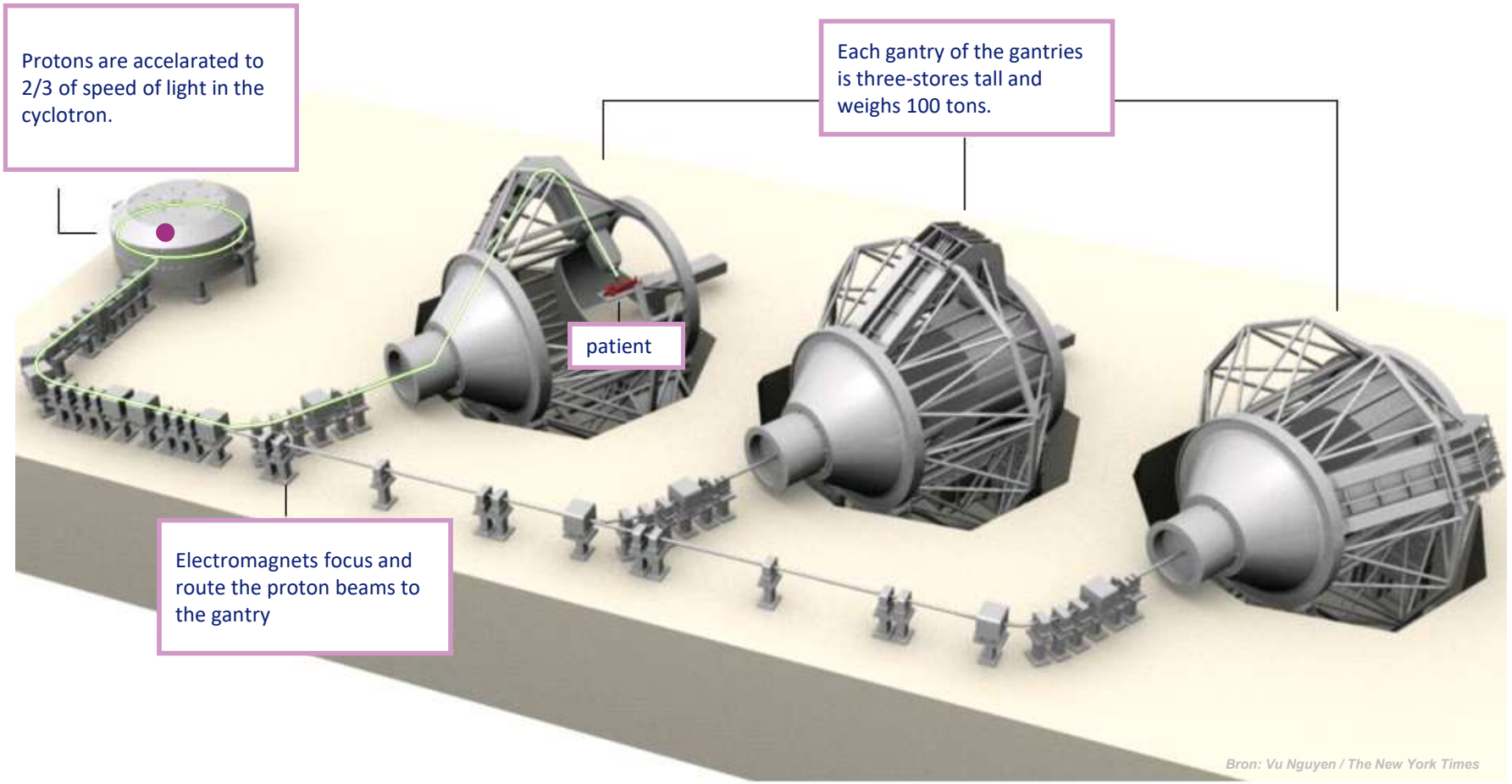

Ionenbron
Acceleratie-
spanning
Afbuigingscondensator
D's
Doel

Proton Accelerator

- Cyclotron: constant fixed energy
- Synchrotron: variable energy, spills



Proton Facility



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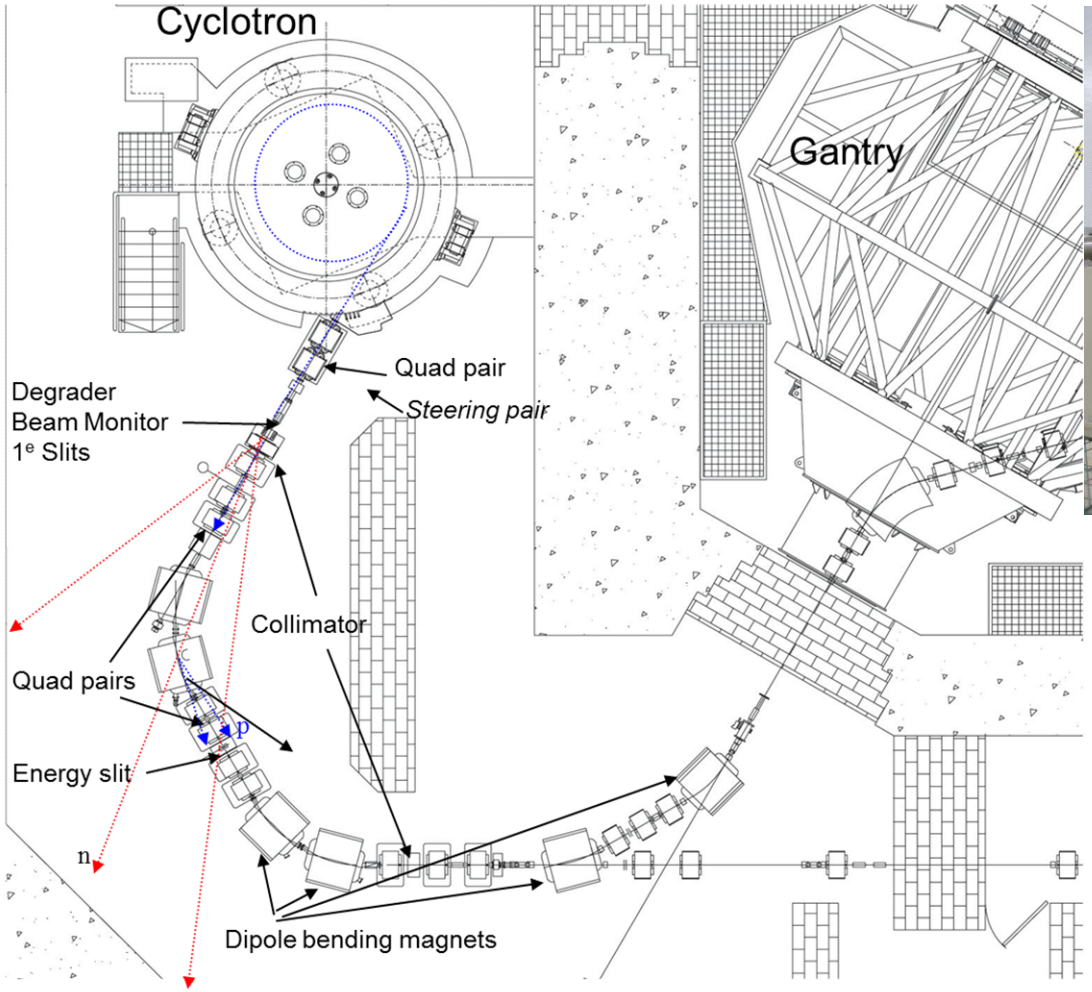
Beam line



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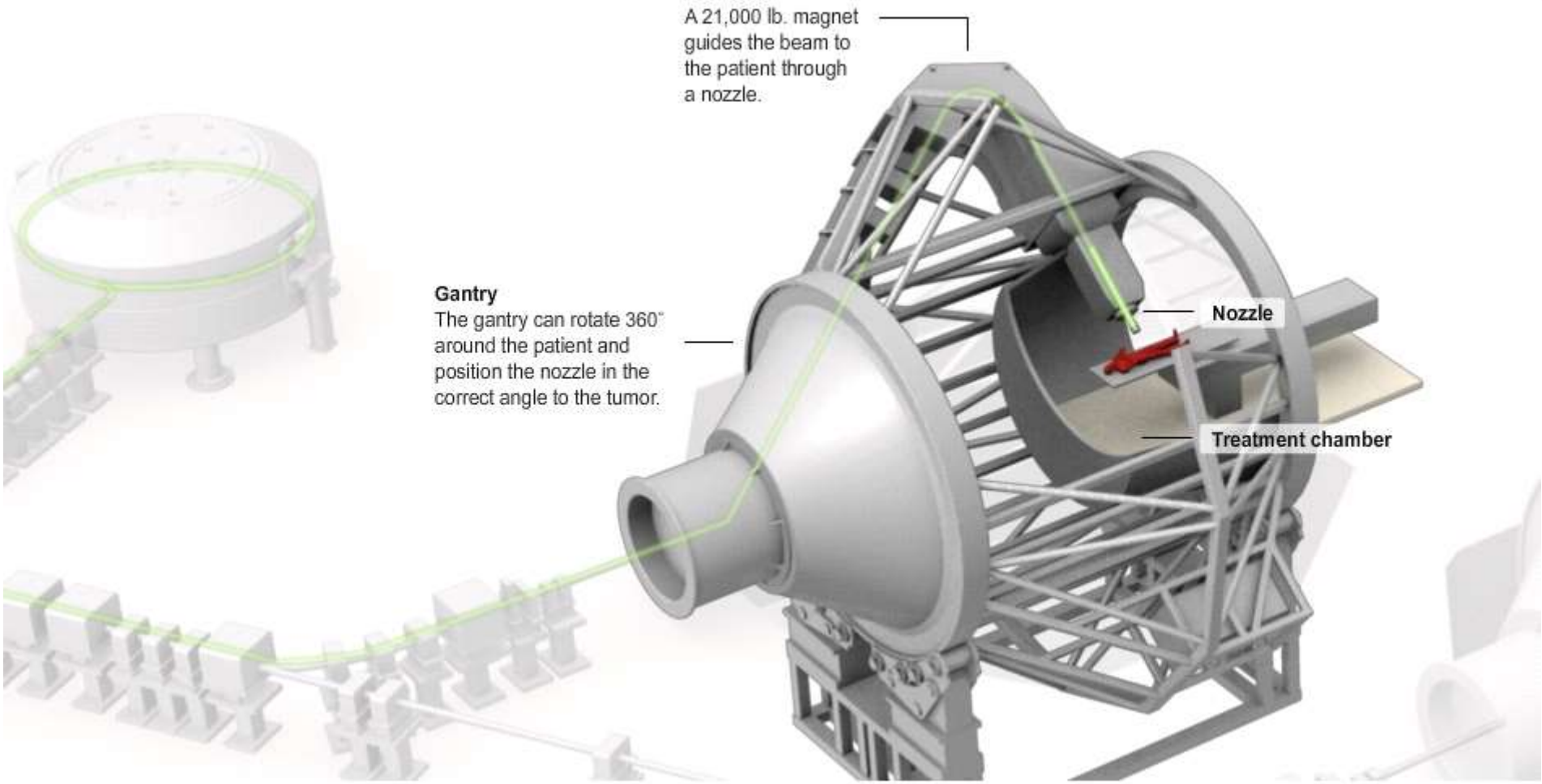
Gantry



From: New York Times

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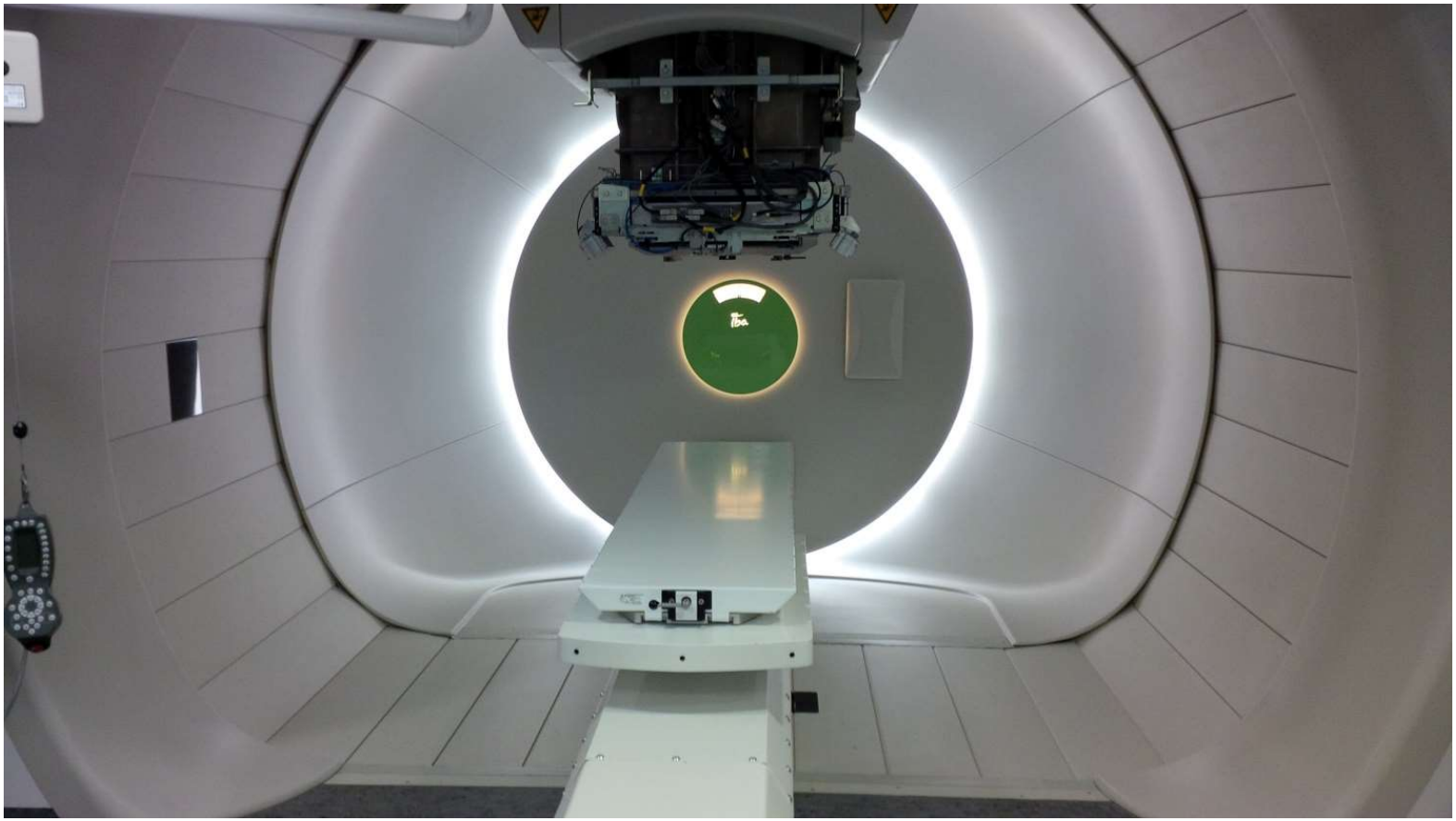
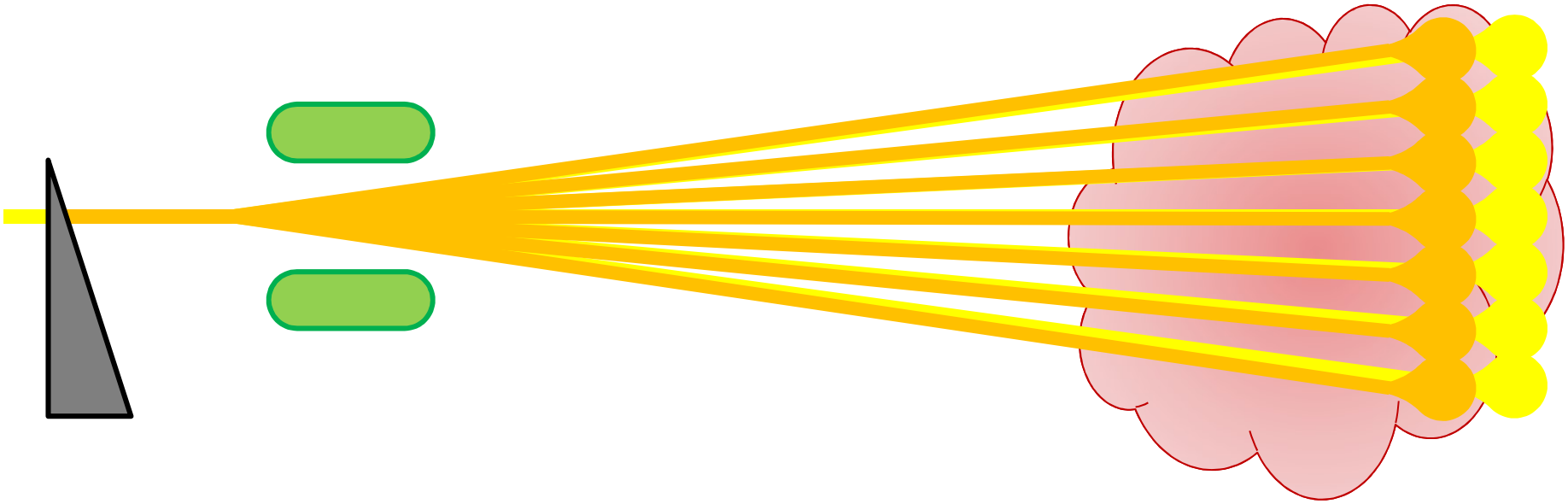
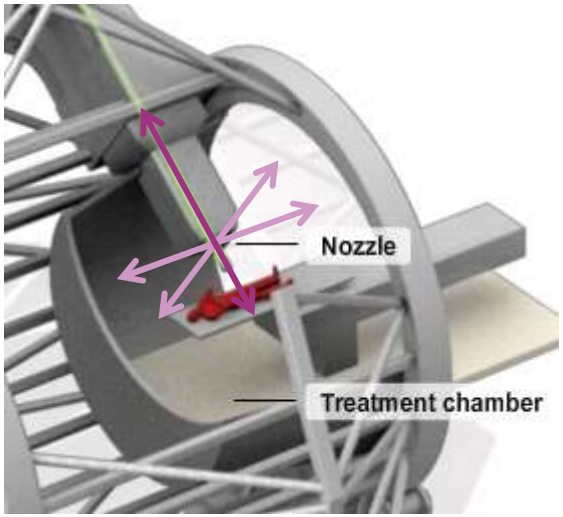
Gantry (IBA, Essen)

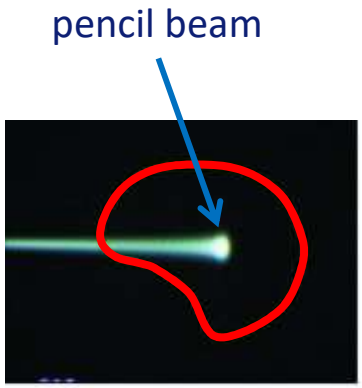


Pencil Beam Scanning

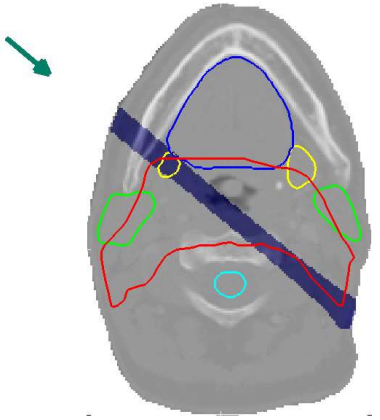


Pencil beam scanning





Eros Pedroni, PSI



Superconducting Synchrocyclotron

- ***TriNiobium Core proton source***
- ***High field strength accelerator***
- ***Beam characteristics optimized for RT***
  - ***250 MeV protons***
  - ***Conventional dose rate: 2-4+ Gy/min***
  - ***Low power requirements***
  - ***High stability and reliability***

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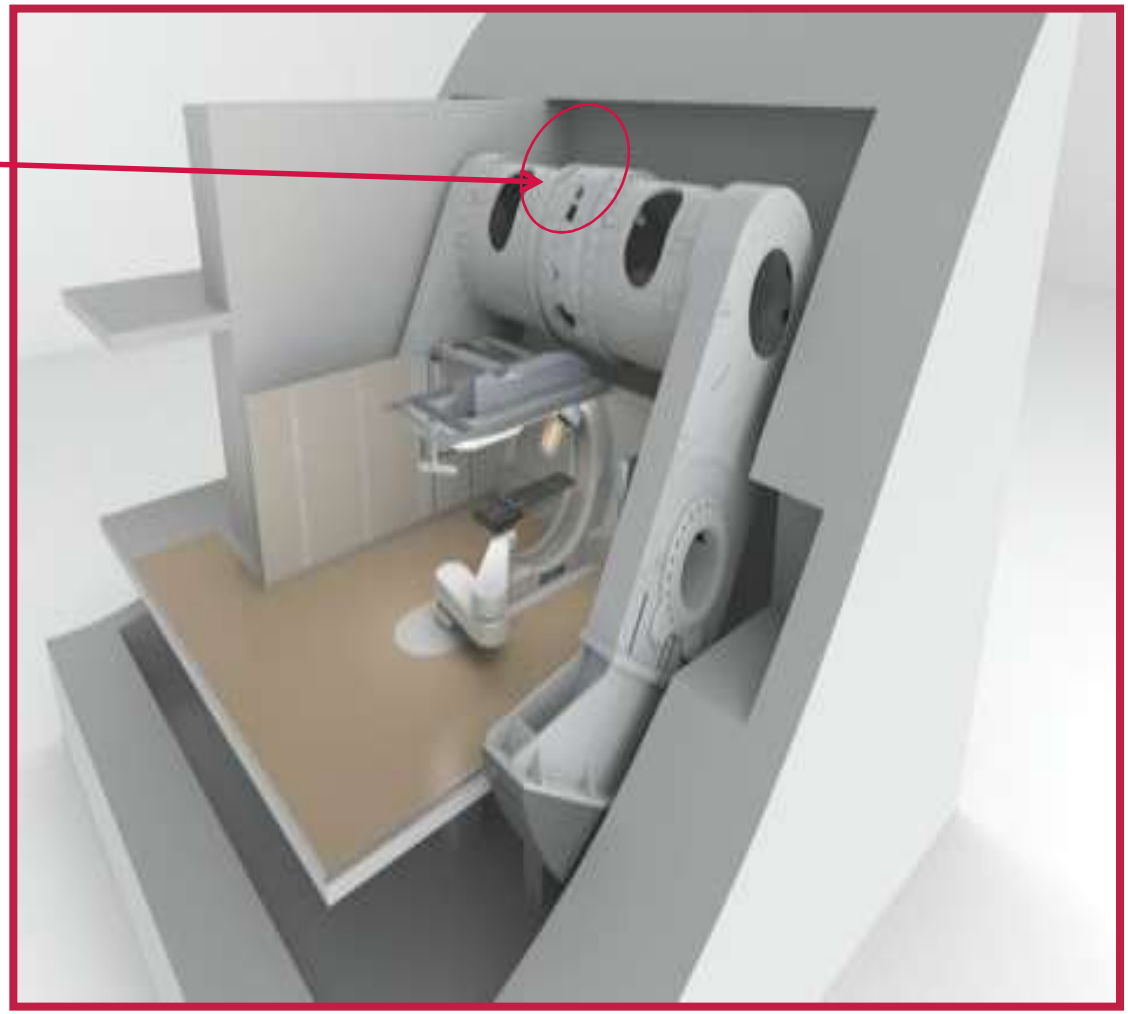
Gantry Mounted

Limited size and weight of the cyclotron, can be mounted onto a gantry, thereby having ALL equipment in just ONE room



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Conclusions

- Essential to deliver optimal doses to all patients, and ensure quality of care
- Era of use of VERY complex radiotherapy techniques
- New technologies are not limited anymore to academic centers and are rapidly assimilated in diverse clinical sites
- “one is left applying manufacturers procedures” (International codes of practice for dosimetry not accomodated)
- Some high tech machines should not be used for all clinical needs

Thank you!

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Oncological concepts

Esther Troost, MD PhD

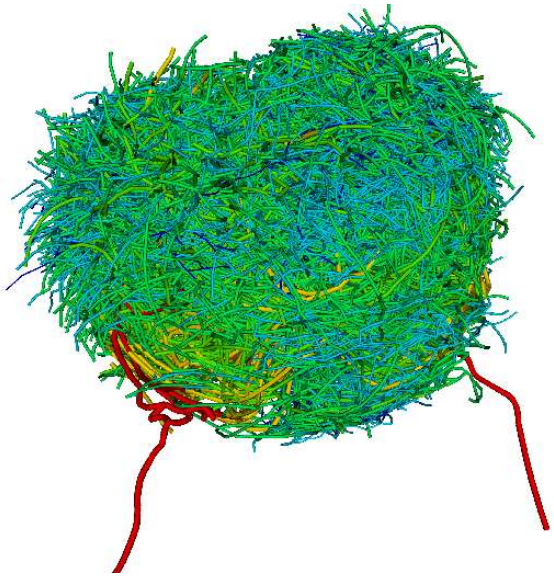
Bucharest, June 2017

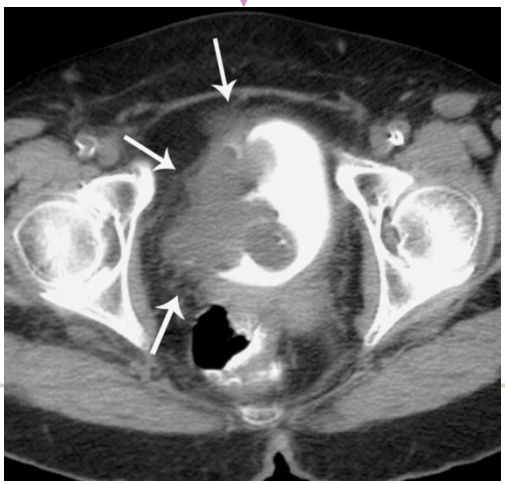
Index

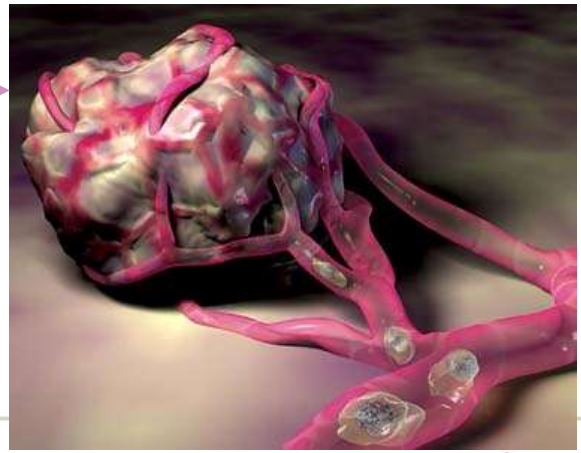
Part 1: What is Cancer?

Group of diseases characterized by

1. Uncontrolled cellular growth
2. Local tissue invasion
3. Systemic metastasis



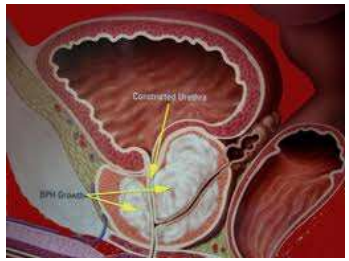




Cancer is a process "*plasia*" = formation

Hyper-plasia

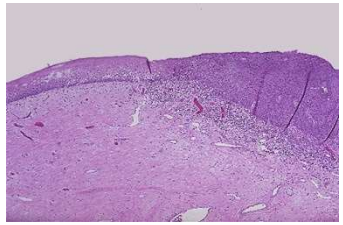
Increase in the number of cells in a tissue or organ



Benign Prostatic Hyperplasia

Dys-plasia (δυσ = "difficulty")

Disturbance in size, shape and organization of cell and tissue



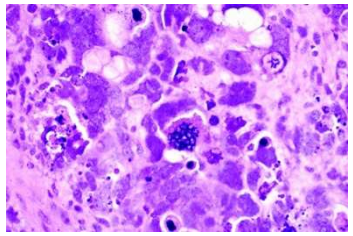
Cervical Dysplasia

Ana-plasia (ἀνά = "new")

Loss of structural organization and useful function of a cell

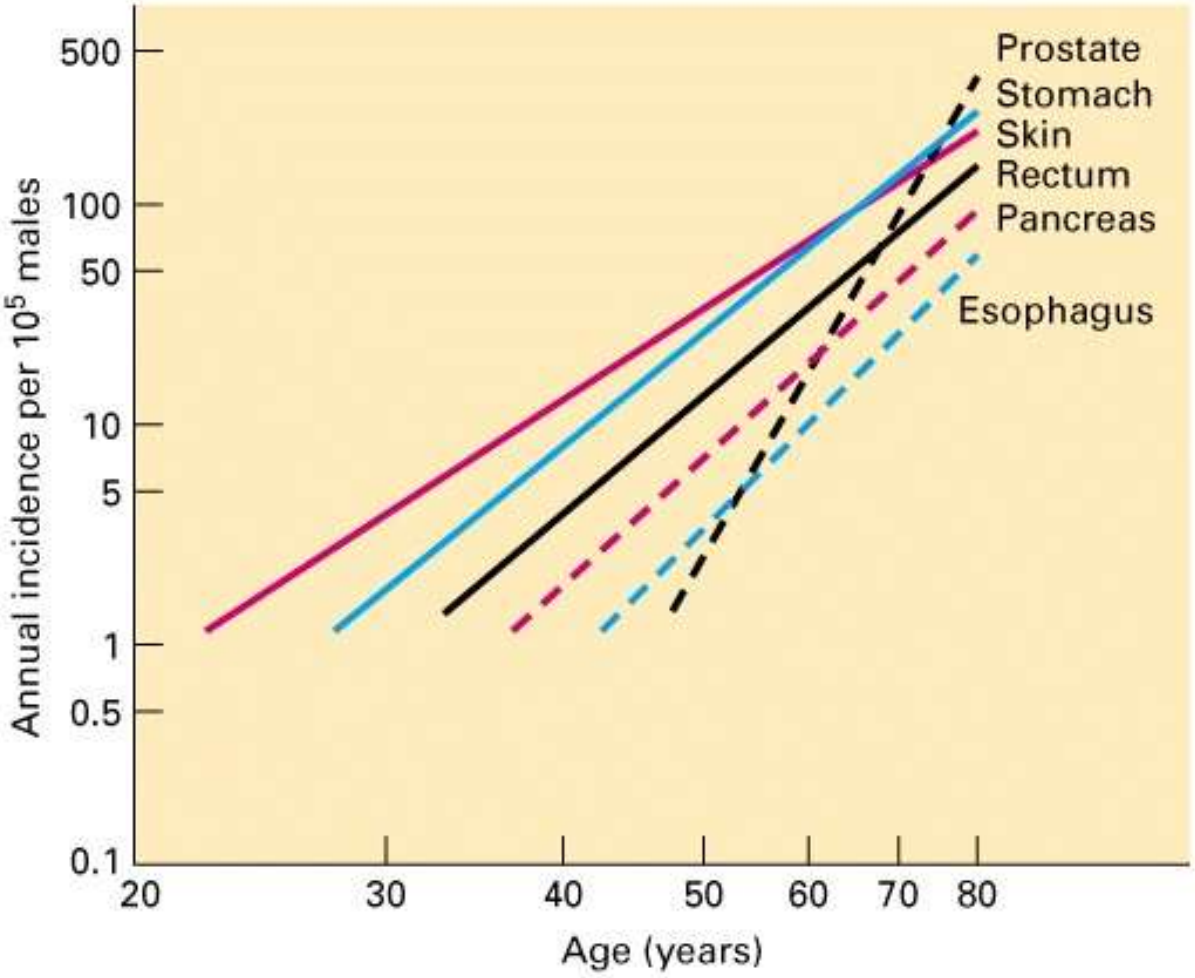
Neo-plasia (νεός = "new")

Pathologic process resulting in the formation and growth of a tumor



Anaplastic Rhabdomyosarcoma

Cancer requires multi-step process



Tumorigenesis = multi-step process

Tumor initiation

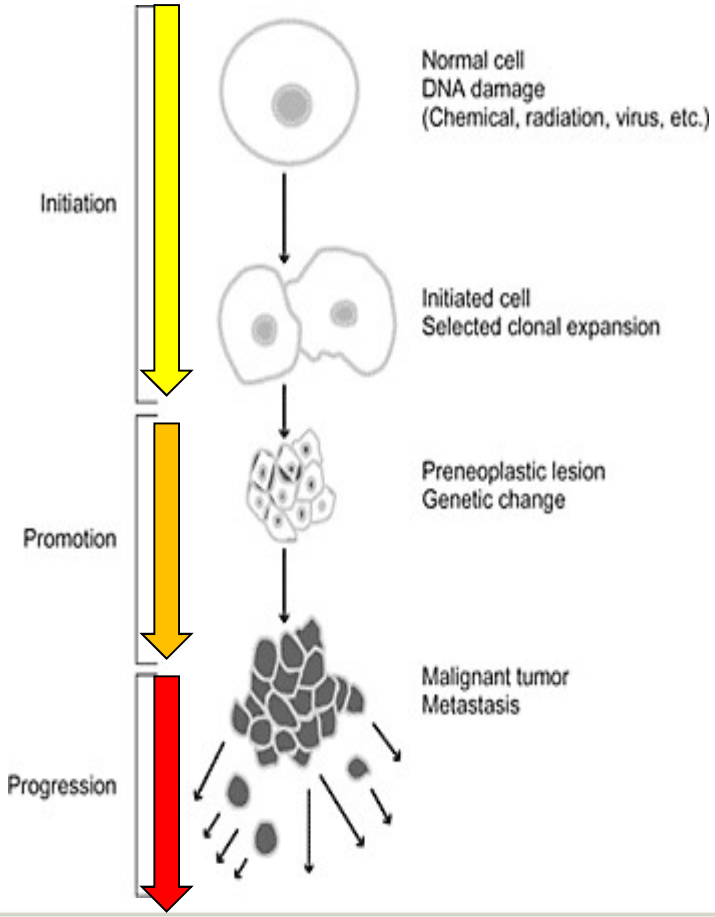
- Cell at risk (which?)
- Cooperative DNA lesions (Mutations)

Tumor promotion

- Perpetuation of genetic lesions (No repair)
- Addition of genetic lesions
- Autonomous proliferation
- Altered differentiation

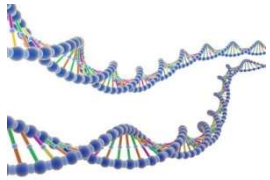
Tumor progression

- Invasion
- Angiogenesis
- Metastases



Tumor initiation

Genetic (Mutational)



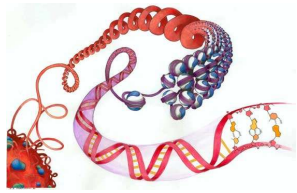
Irreversible DNA damage in critical gene(s)

Environmental carcinogens

Spontaneous mutations

Inherent error rate in DNA replication or repair

Epigenetic (No mutational)



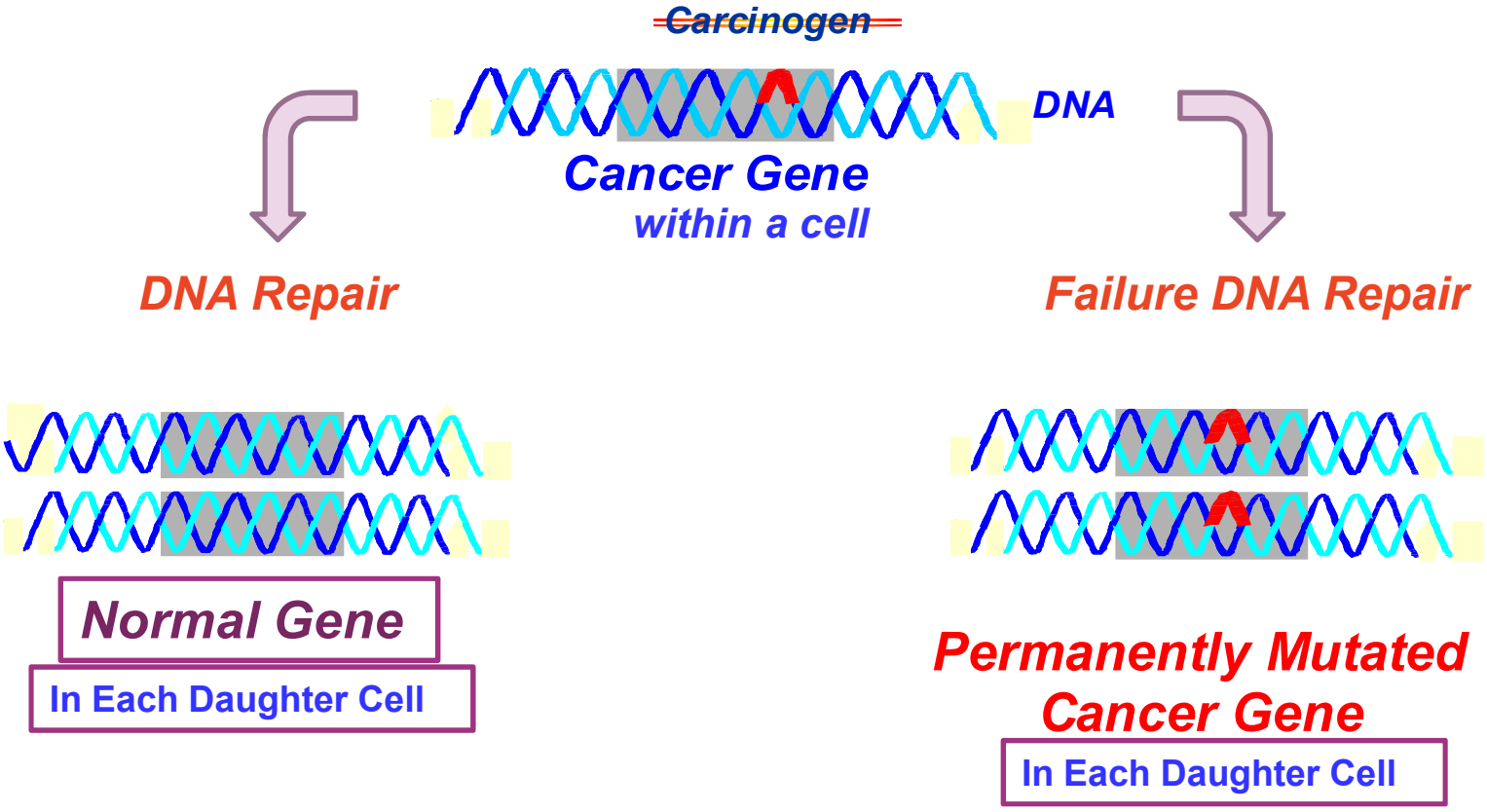
Modulation of DNA expression

Addition of a methyl group to CpG dinucleotides

Removal of acetyl groups from histone tails

Initiation (mutational)

Barbour S Warren, PhD



Rate and efficiency of repair systems

ONLY 30%!!! population develops cancer

- The estimated rate of single strand DNA breaks and base loss is up to 10^4 / cell / day
- A human body (70 kg) is comprised of 10^{14} cells
  - 100.000.000.000.000
- The number of blood and small intestinal cells produced per day is 10^{10}–10^{11}, respectively

Suit, H. Radiother & Oncol 2011

Cell at risk

Cancer Stem Cell (CSC) hypothesis

- Tumors are stem cell-based tissues, like any other tissue
  - Hierarchical structure within the tumor
  - Not all the tumor cells are equally competent for regenerating the tumor
  - Only a tumor subpopulation (stem cells) is responsible for the cancer recurrence after treatment

Treatment failure

- CSCs are more resistant to antiproliferative therapies than other tumor subpopulations
- Normal stem cells are sensitive to antiproliferative therapies
- To erradicate the CSCs would require to eliminate normal stem cells (Toxicity)

How is the risk of cancer increased?

Larger number of mutations

- Increased initiation & progression

Greater level of proliferation

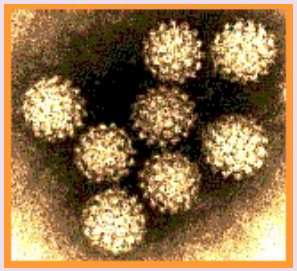
- Increased promotion & progression

Increase number of cells at risk

Increase the time of high risk for tumor initiation

- Increased initiation events

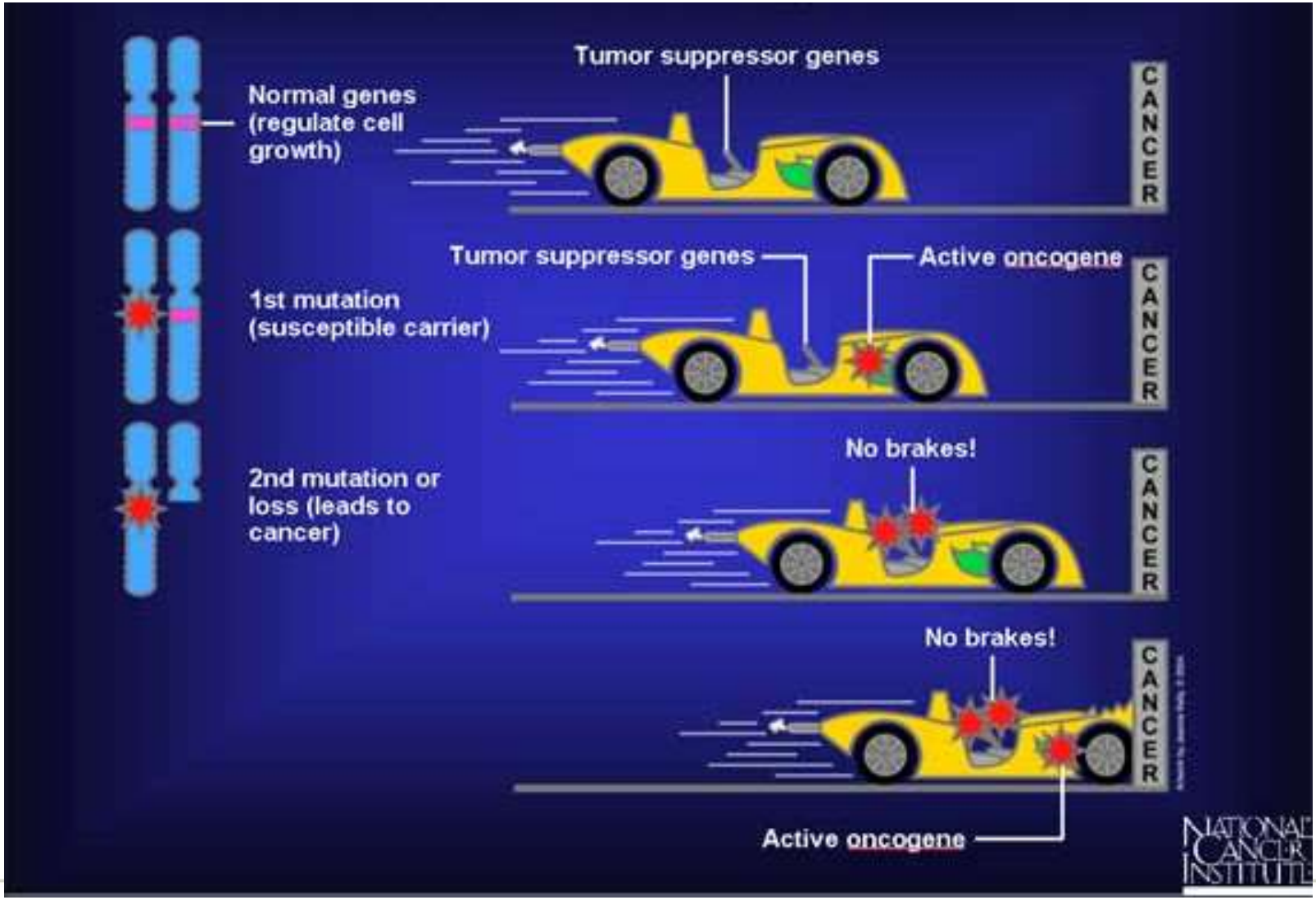
Initiators = Carcinogens

Agent		Cancer
Viruses 	HTLV-1 & HTLV-2 HIV Hepadnaviruses HPV EBV KSHV	Leukemia (ATL) --- Hepatocellular ca. Cervical ca. (…) Burkitt's lymph. – NPC Kaposi's sarcoma
Chemicals	Tobacco 	Lung, Bladder, HN
Physical	X-rays UV light Asbestos	Sarcomas, Breast (…) Skin Mesothelioma
Inflammation		Oesophagus, Gastric
Dietary factors		??

Carcinogenic substances either

- trigger oncogenes (genes that cause cells to grow out of control) or
- hinder the activity of tumor suppressor genes (genes that regulate a multitude of processes to work against cancerous cell growth)

Oncogenes and Tumor suppressor genes



Oncogenes (Tumor Inducing Genes)

- **Proto-oncogen**
  - normal gen
  - aid in the differentiation and growth regulation in cells
- **Oncogenic mutation**
  - Mutation in a proto-oncogene resulting in an oncogene
- **Types of mutations**
  - Insertions
  - deletions
  - point mutations

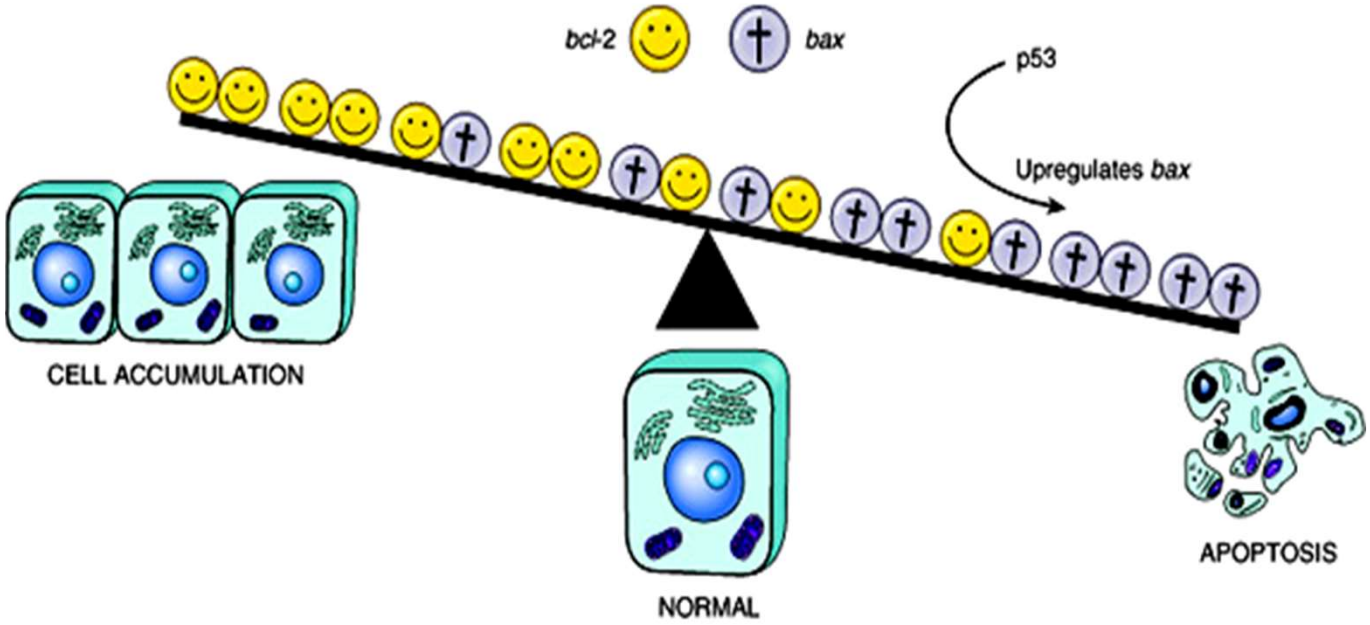
  Increased transcription rate
  - gene amplification or duplication (extra copies)
  - chromosomal translocation (a section of one chromosome is detach and reattach itself to another chromosome)
- **How does a mutation activate an oncogene?**
  - Increased enzyme or protein activity
  - Regulation loss
  - Increased protein concentration

Oncogenes

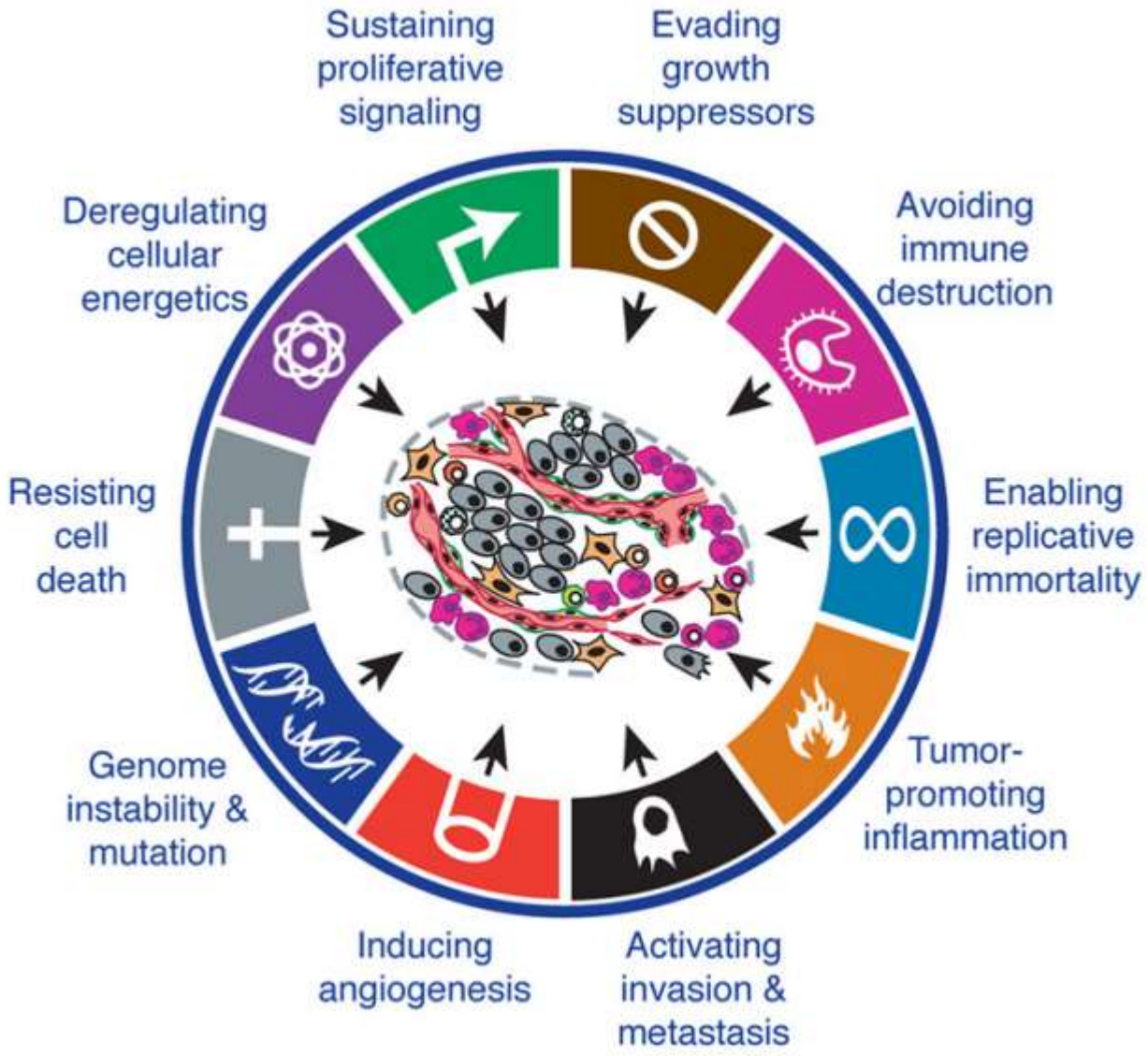
- **A few important oncogenes:**
  - **HER-2/neu**, encodes for a cell surface receptor that can stimulate cell division. The HER-2/neu gene is amplified in up to 30% of human breast cancers.
  - **RAS**, involved in kinase signaling pathways that ultimately control transcription of genes, regulating cell growth and differentiation.
  - **MYC**, a transcription factor and controls expression of several genes.
  - **SRC**, a tyrosine kinase, which regulates cell activity.
  - **hTERT**, codes for an enzyme (telomerase) that maintains chromosome ends.

- **A few important tumor-suppressor genes:**
  - **p53**: a transcription factor that regulates cell division and cell death.
  - **Rb**: alters the activity of transcription factors and therefore controls cell division.
  - **APC**: controls the availability of a transcription factor.

Cell division – Cell death



Hallmarks of Cancer



Hanahan, Weinberg, 2011

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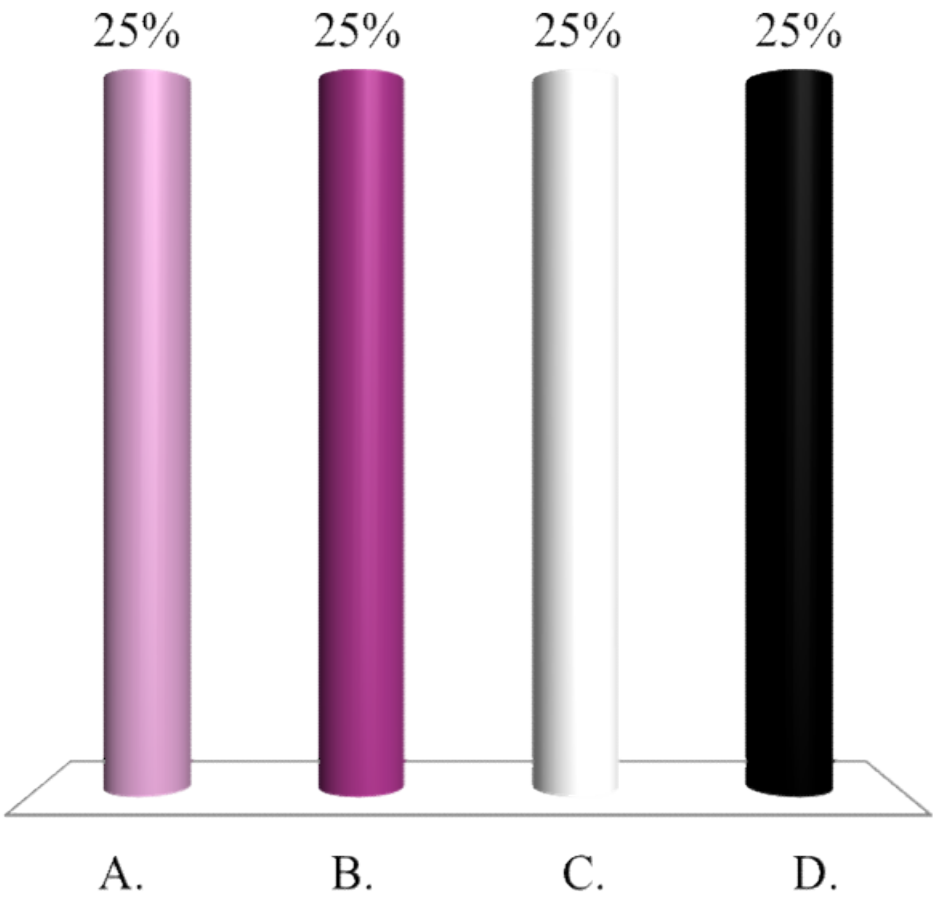
Q1. Which is NOT a cause of cancer?

A. Increasing age
B. Smoking
C. Activation of tumor suppressor gene
✓ D. Infection with virus



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Concepts in Radiation Therapy

- **Curative**
  - Aimed at curing the patient from his/her disease
  - Treatment schedules may be multimodal and last for numerous weeks
  - Side-effects can be severe

- **Palliative**
  - Aimed at alleviating symptoms caused by the tumor
  - Treatment schedules are usually limited to one modality and last for a couple of weeks
  - Treatment-related side-effects should be mild-moderate

Curative concepts in Radiation Therapy

- **Primary Radiotherapy**
  - Radiotherapy is the only treatment modality
  - Early laryngeal or prostatic carcinoma

- **Primary Radiochemotherapy**
  - Radiochemotherapy is the treatment modality
  - Advanced stage head-and-neck cancer, (non-)small cell lung cancer

- **Neoadjuvant Radiochemotherapy**
  - Radiochemotherapy is applied prior to surgery
  - Advanced stage esophageal or rectal cancer

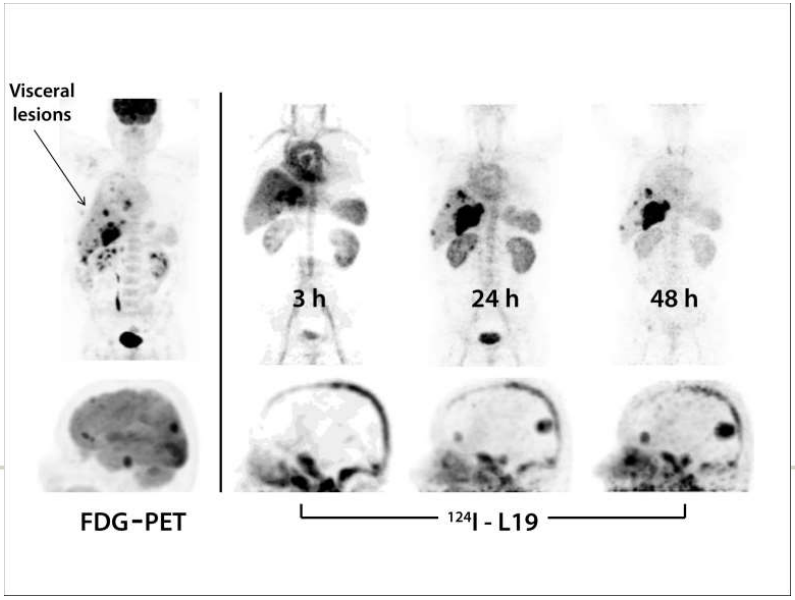
Curative concepts in Radiation Therapy

- **Adjuvant Radio(chemo)therapy**
  - Radio(chemo)therapy is given after surgery, *e.g.*, when likelihood of residual tumor cells is high
  - Advanced stage head-and-neck cancer with extranodal spread, unexpected N2-disease in non-small cell lung cancer, positive circumferential resection margin (CRM) in rectal cancer

"Nurse, get on the internet, go to SURGERY.COM, scroll down and click on the 'Are you totally lost?' icon."

Abscopal effect in Radiation Therapy

- Oligometastatic solid tumors (max. 5 metastasis; primary tumors: NSCLC, HNSCC, renal cell carcinoma, melanoma, colorectal)
- High dose stereotactic RT induces immune response
- The combination with immune-modulatory agents may eliminate microscopic disease and prolong progression-free survival



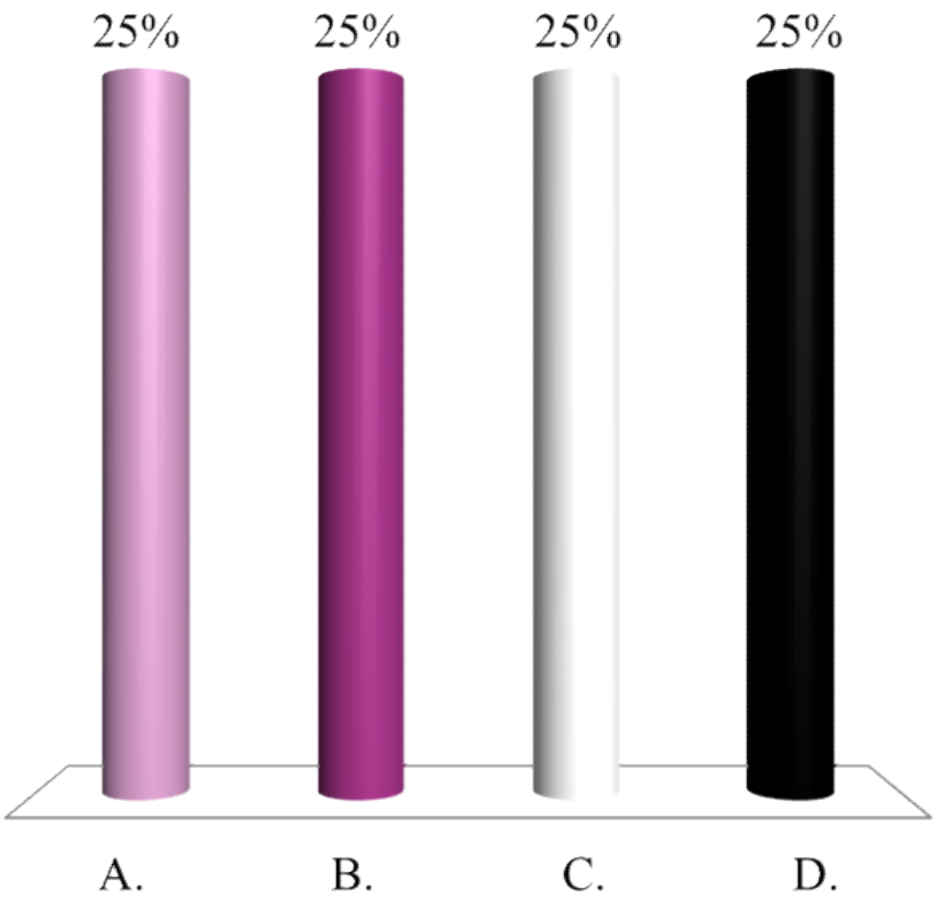
Q2. Which statement is true?

A. Adjuvant treatment is given before surgery

✓ B. Palliative treatment aims at alleviating pain

C. Primary radiotherapy is given after surgery

D. The abscopal effect is frequently observed in radiotherapy



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Compulsory data for treatment decision

- **Patient**
  - Age
  - Performance status
  - Medical history

- **Tumor**
  - Histology and grade
  - TNM staging

Classification of patients

Performance status: global assessment of a patient's ability for self-care and ambulation

Several different scales are in use

- ECOG
- Karnofsky scale

Used for a variety of purposes:

- patient selection and stratification for cancer clinical trials
- life quality evaluations
- definition for treatment intention

Which diagnostics are required?

Would it be better to provide best supportive care only?

Eastern Cooperative Oncology Group

G	ECOG
0	**Fully active**, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and **able to carry out work** of a light or sedentary nature, e.g., light house/office work
2	Ambulatory and capable of all selfcare but **unable to carry out any work** activities. Up and about more than 50% of waking hours
3	Capable of only **limited selfcare**, confined to bed or chair more than 50% of waking hours
4	**Completely disabled**. Cannot carry on any selfcare. Totally confined to bed or chair
5	**Dead**

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

http://www.ecog.org/general/perf_stat.html

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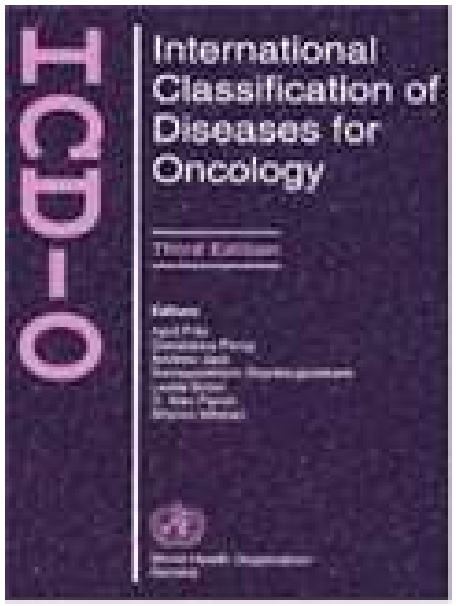
Classification of tumors: Topography and Morphology

To register
- Topography
- Morphology

To predict
- Prognostic factors
  - **Grading**
  - **Staging systems**
  - Residual disease
  - Prognostic score
  - (...)

ICD-O



World Health Organization

http://www.who.int/classifications/icd/adaptations/oncology

http://training.seer.cancer.gov/module_icdo3/icdo3_home.html

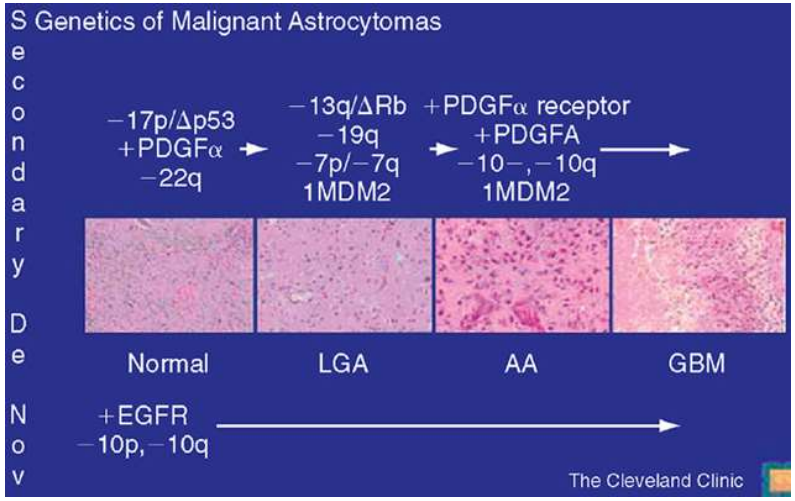
Grading

Degree of differentiation and an estimate of growth rate (mitotic index):

- Grade I-- 75% to 100% differentiation
- Grade II-- 50%-75% differentiation
- Grade III-- 25%-50% differentiation
- Grade IV-- 0%-25% differentiation

Also based on

- amount of infiltration and
- amount of stromal tissue in and around the tumor

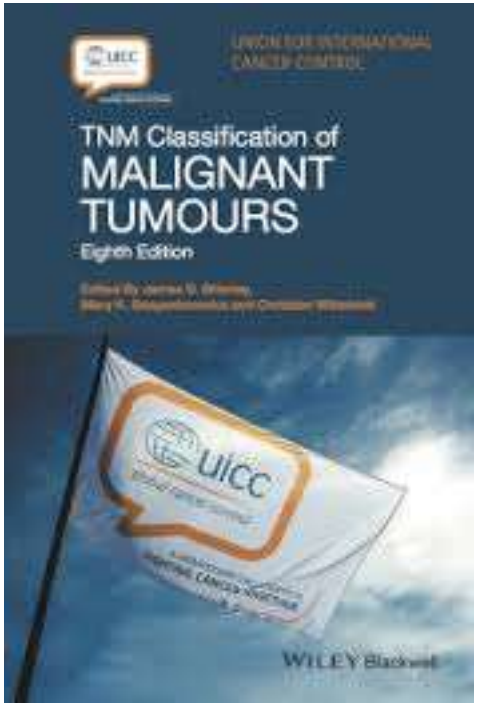


Staging

TNM – AJCC (American Joint Committee on Cancer)

Other staging systems

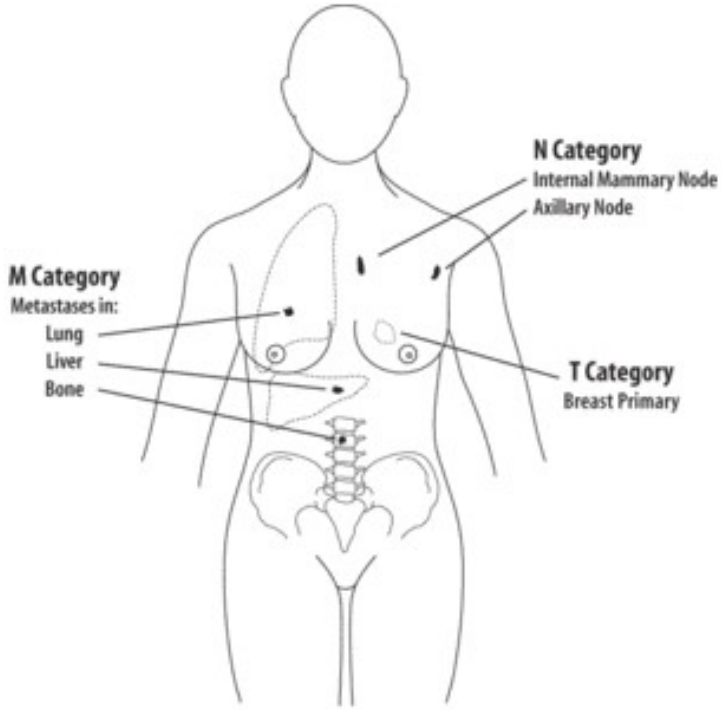
FIGO Staging of Gynecologic Tumors
Dukes' Staging of Colorectal Cancer
Jewett Staging for Bladder Cancer
Prostate Staging Schemes
Melanoma Staging Schemes
Pediatric Staging
Lymphoma Staging Scheme



TNM Classification

TNM: Tumor, Nodes, Metastases

Primary tumour	(**T**)
Regional lymph nodes	(**N**)
Distant metastasis	(**M**)



T category

TX

Minimum requirements to assess the primary tumor cannot be met

T0

No evidence of primary tumor

Tis

Carcinoma *in situ*

T1, T2, T3, T4

Progressive increase in tumor size or involvement

T (early stage)

- malignancy limited to the organ of origin;
- no spread beyond organ of origin;
- infiltration past basement membrane of epithelium into stroma of organ.

T1-T2

T (advanced stage)

- Tumor extension beyond limits of organ of origin.
- Invasion through entire wall of organ into surrounding organs and/or adjacent tissues ("direct extension" or "contiguous spread").

T3-T4

N (regional spread)

- Tumor invasion of walls of lymphatics where cells can travel through lymphatic vessels to regional lymph nodes where they are "filtered" out and begin to grow in the nodes.

N staging

NX

Minimum requirements to assess lymph nodes cannot be met

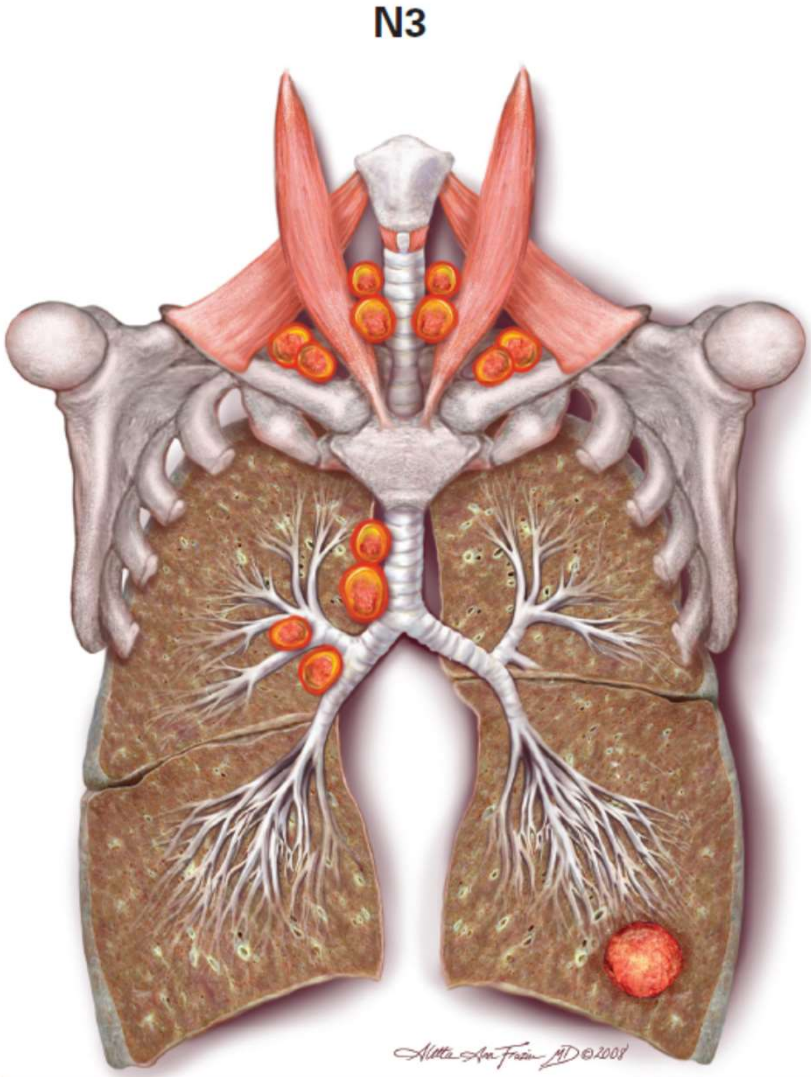
N0

No evidence of regional node involvement

N1, N2, N3

Increasing abnormality of lymph nodes (size, characteristics, location)

N staging in lung cancer



N3 Metastasis to

- contralateral mediastinal, contralateral hilar, contralateral scalene or supraclavicular lymph node(s)

- ipsilateral scalene or supraclavicular lymph node(s)

M (distant spread)

- Spread to areas of the body distant or remote from the primary tumor.
- Distant metastases are comprised of tumor cells which have broken away from the primary tumor and have traveled to other organs.
- Also called remote, disseminated, diffuse, metastatic.
- Methods of spread:
  - Travel in lymph channels beyond the first drainage area
  - Hematogenous or blood-borne metastases
  - Spread through fluids in a body cavity

M category

MX

Minimum requirements to assess presence of distant metastases cannot be met

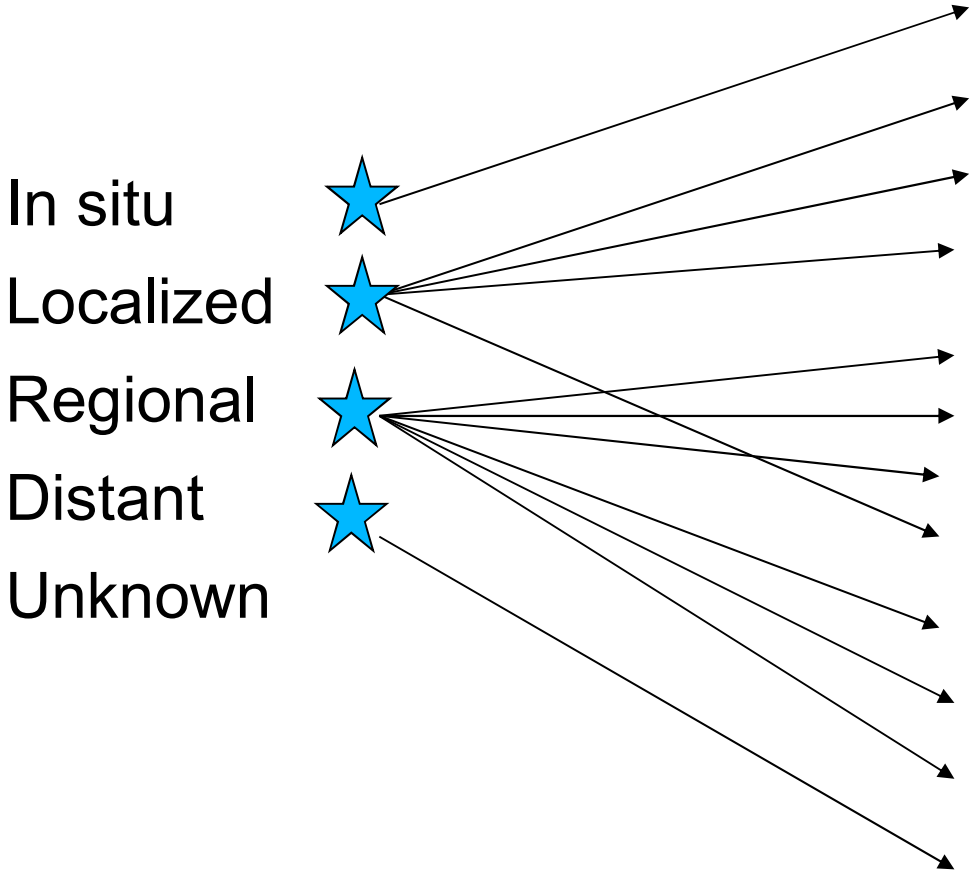
M0

No evidence of distant metastases

M1

Presence of distant metastases

Stage grouping, *e.g.*, laryng



STAGE GROUPING - Larynx			
0	Yis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IV	T4	N0	M0
	T4	N1	M0
	Any T	N2	M0
	Any T	N3	M0
	Any T	Any N	M1

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Staging – What is it for?

- responsibility of the oncologist to assess the extent of cancer
- aid the clinician in classifying the tumor in order to plan the treatment
- give an indication of prognosis
- assist in the evaluation of the results of treatment
- facilitate the exchange of information

TNM clinical & pathological

TNM is a dual system with:

- (pretreatment) Clinical classification (cTNM or TNM)
- (postsurgical histopathological) Pathological classification (pTNM).

Both classifications are retained unaltered in the patient's record.

- The former is used for the choice of treatment
- The latter is used for the estimation of prognosis and the possible selection of adjuvant therapy

Residual disease after surgery

"Cancer cells that are left over after surgery"

RX:

Presence of residual tumor can not be assessed.

R0:

No residual tumor.

R1:

Microscopic residual tumor.

R2:

Macroscopic residual tumor.

Classification of effects on the tumor

Uniform criteria for reporting response, recurrence, disease-free interval, and toxicity were proposed in 1979 after a meeting on the Standardization of Reporting Results of Cancer Treatment and were subsequently widely accepted.

These response criteria, known as the World Health Organization (WHO) criteria, are based largely on tumor measurements in two dimensions (the longest perpendicular diameters in the axial plane).

WHO: WHO Handbook for Reporting Results of Cancer Treatment. Geneva, Switzerland, World Health Organization, **WHO offset publication 48, 1979**

Miller AB, Hoogstraten B, Staquet M, et al: Reporting results of cancer treatment. **Cancer 47:207-214, 1981**

RECIST criteria: only the longest diameter

CR (complete response)
disappearance of all target lesions

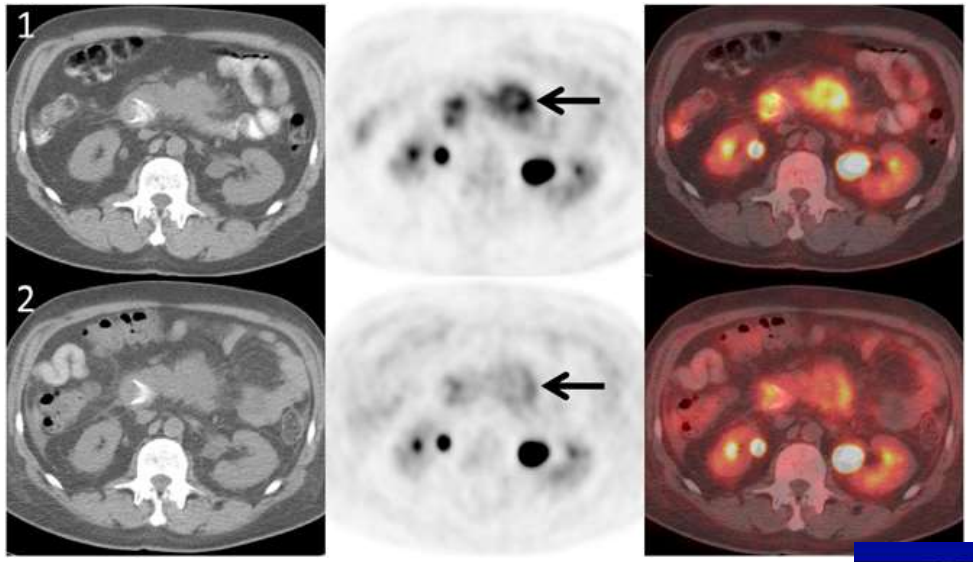
PR (partial response)
30% decrease in the sum of the longest diameter of target lesions

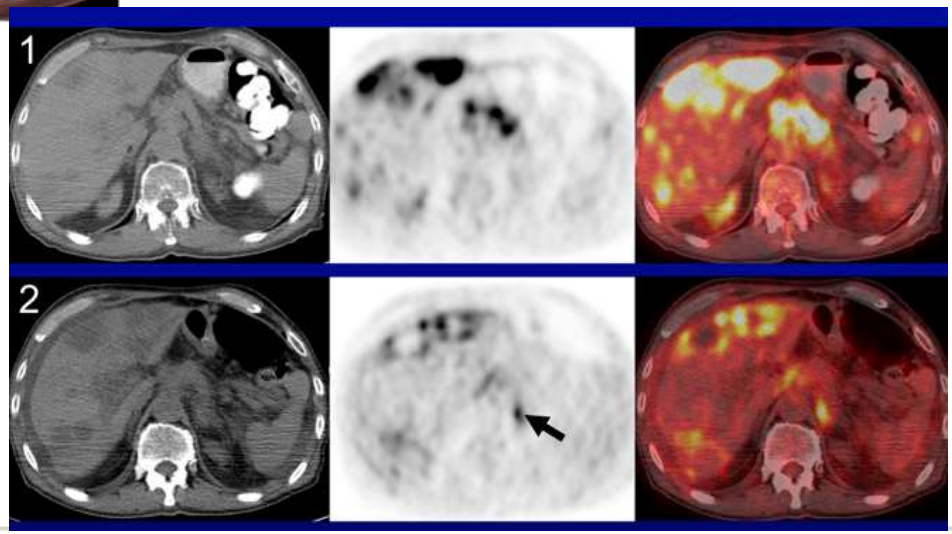
PD (progressive disease)
20% increase in the sum of the longest diameter of target lesions

SD (stable disease)
small changes that do not meet above criteria

Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada.
J Natl Cancer Inst 92:205-216, 2000

PERCIST criteria: including PET





Wahl RL, et al. **J Nucl Med 2009**

Classification of Toxicity

Physician rated instruments

Scoring-Grading systems

- WHO
- NCI – CTC
- RTOG-EORTC
- LENT-SOMA

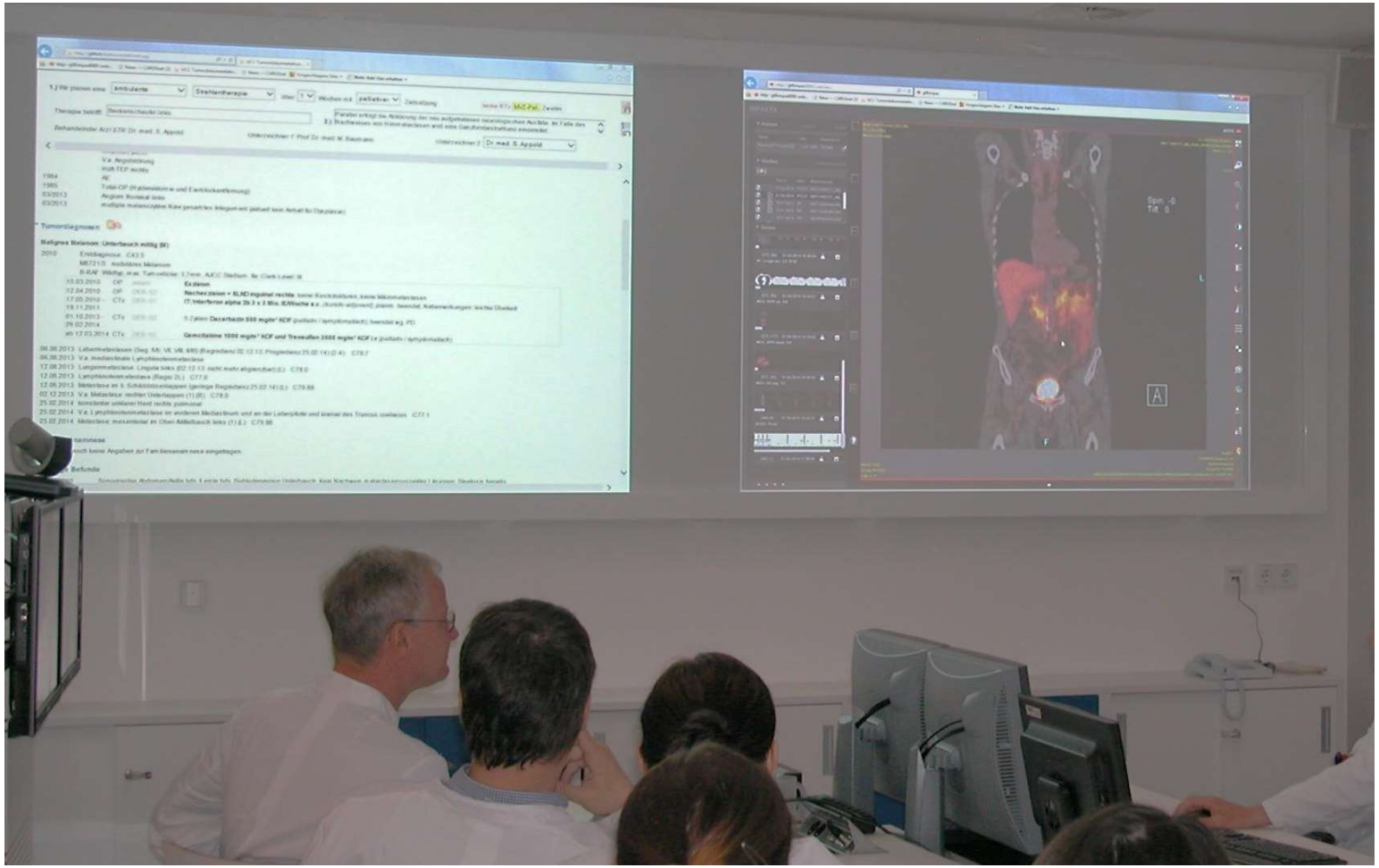
Patient rated instruments

CTCAE v4.03

QOL tests (Quality of Life)

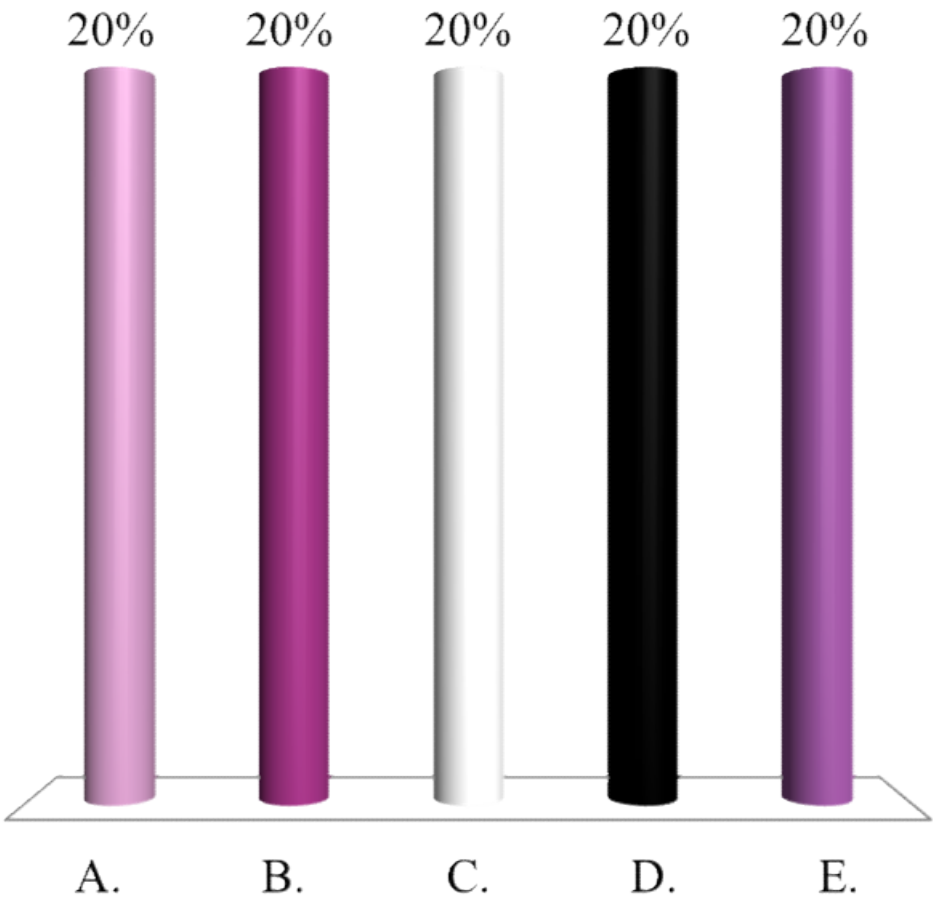
- Subjective
- Modulated by patient's ability to adapt to adversity

Multidisciplinary tumor board



Q3. Which statement is false? This patient and tumor information is crucial for a treatment decision:

A. Patient performance status
B. Tumor histology
C. cTNM staging
✓ D. Patient's health insurance company
E. Other illnesses



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Thank you for your attention

Radiobiology in the clinic

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Leeds Cancer Centre and University of Leeds, UK
a.henry@leeds.ac.uk

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Overview

- Practical applications of radiobiology
- Therapeutic ratio, NTCP models
- LQ alpha/beta
- Fractionation
- Equivalence
- Dealing with gaps

Understand the practical application of radiobiology in radiotherapy

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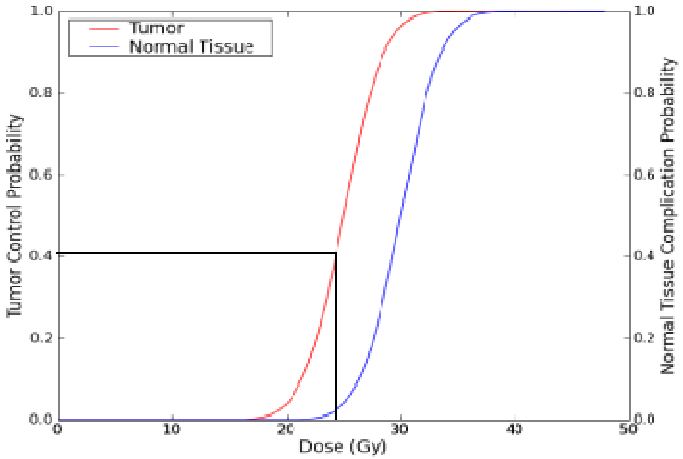
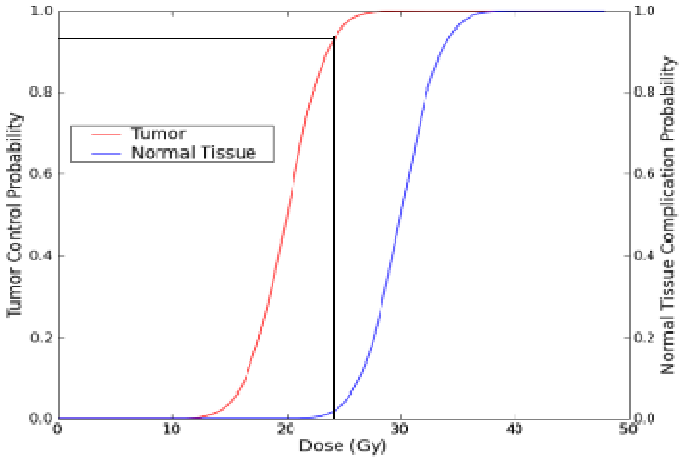
Therapeutic ratio

- TR describes the probability of tumour control (TCP) versus normal tissue complication (NTCP). Aim to cure with minimal late side-effects
- Higher doses increase TCP but also NTCP: usually accept a 5% risk of severe late normal tissue toxicity except for spinal cord (<1%)
- Clinical ways of therapeutic ratio
  - Fractionation
  - Concurrent chemotherapy/biological agents
  - reducing volume of normal tissue irradiated or dose delivered e.g. Conformal, Stereotactic XRT or brachytherapy





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Normal Tissue Tolerance

- The maximum radiation dose or intensity of fractionated radiotherapy that is deemed to produce an acceptable level of normal tissue toxicity.
- Often specified as the dose that can be delivered with a risk of damage no higher than 5% at 5 years (TD5/5) or the dose that can be delivered with a risk no higher than 50% at 5 yrs (TD50/5).
- Emami (1991) reviewed the tolerances for partial and whole organ irradiation.
- **Q**uantitative **E**stimates of **N**ormal **T**issue **E**ffects in **C**linic : Joint AAPM-ASTRO initiative published
- Int J Rad Oncol Biol Physics 76 No.3 supplement 2010

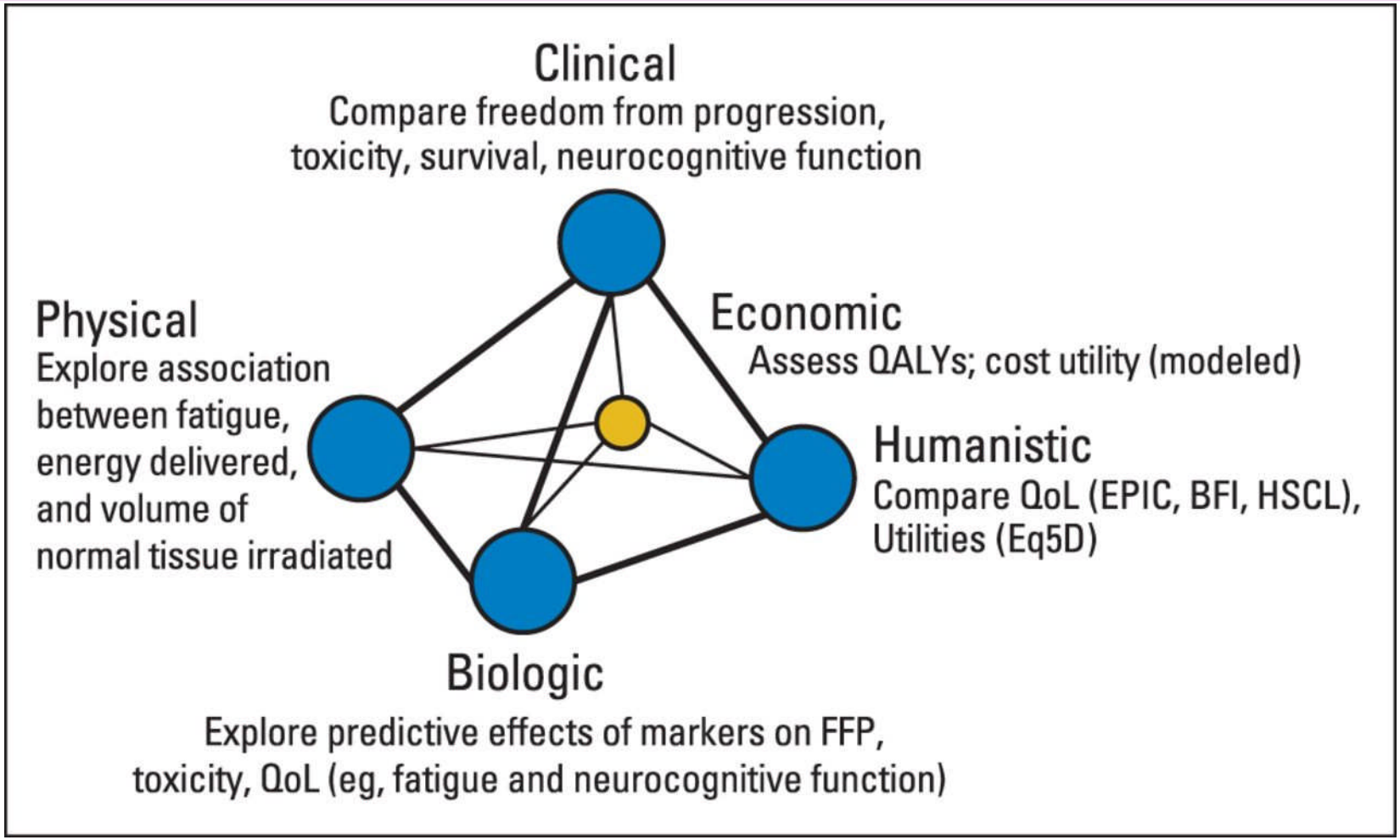
Toxicity scoring

- Toxicity an increasing survivorship issue
- Often under-reported and under-recorded even in clinical trials
- US National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0 – dictionary for recording and grading side effects
- Aims for consistency in reporting toxicity between centres and trials

Patient Reported Outcome Measures

- Know as PROMs or PROs
- Need to be validated on relevant population
- Ensure reliable, easy to complete and acceptable
- Can be challenging to translate into other languages
- Can measure changes in radiation specific toxicity such as breast changes, rectal bleeding or pneumonitis, demonstrate a dose response
- Overlap with Health Related Quality of Life (QoL includes issues such as social support and spirituality)

The Radiation Therapy Oncology Group outcomes model.

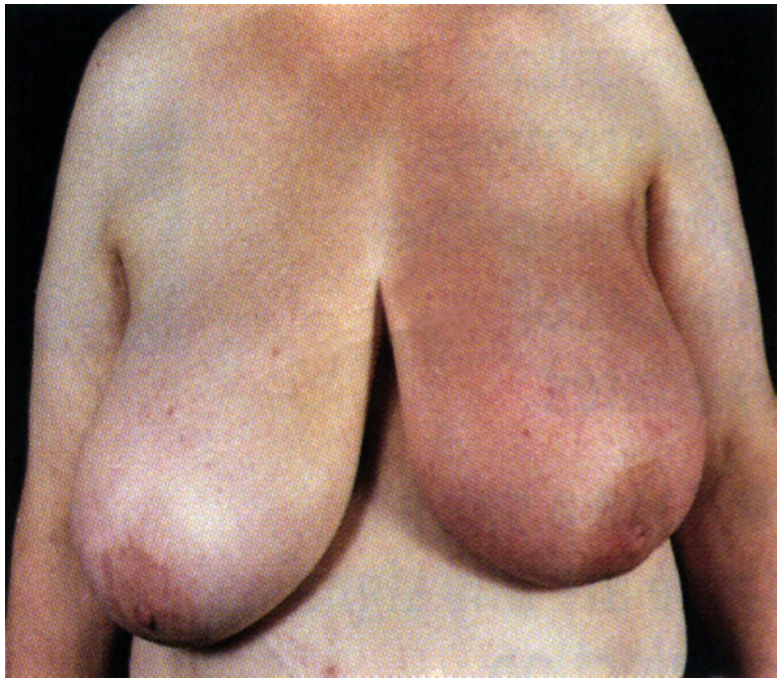


Farzan Siddiqui et al. JCO 2014;32:2920-2927

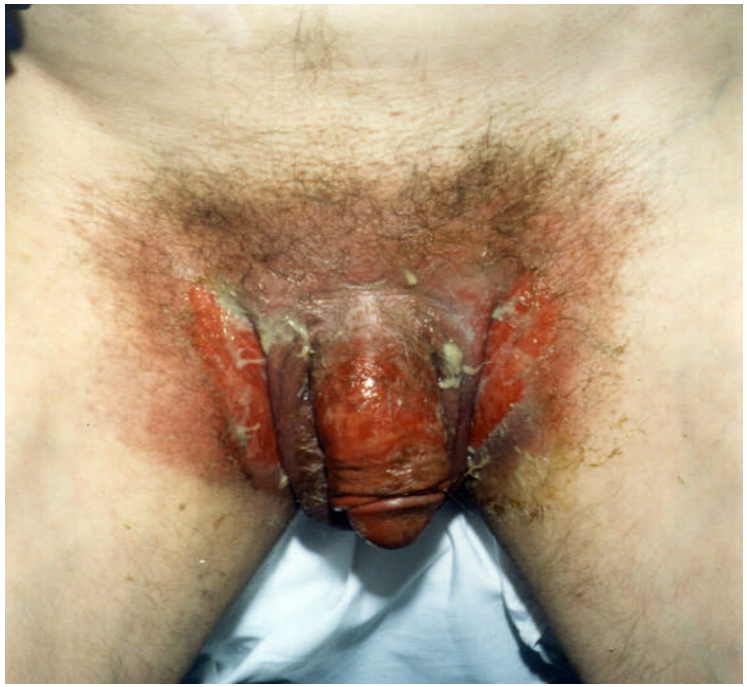
Early therapeutic radiation reactions

- Occur during or shortly after completion
- Due to rapid cell loss
- Associated with oedema and exudation
- Seen in skin, gastrointestinal tract and bone marrow
- Repair due to cell renewal via intact basal cells
- Healing usually complete but can result in *consequential late reactions*. Seen in skin, bladder and oral mucosa when persistent damage remains long-term after severe acute damage

Grading acute skin toxicity



CTCAE grade 1: Faint erythema



CTCAE grade 3: Confluent moist desquamation

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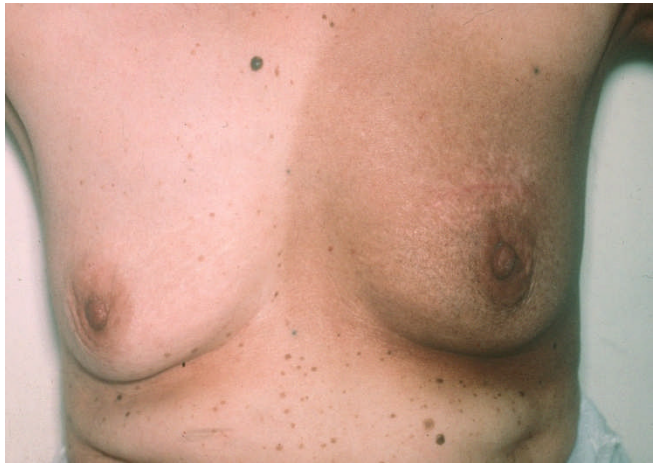
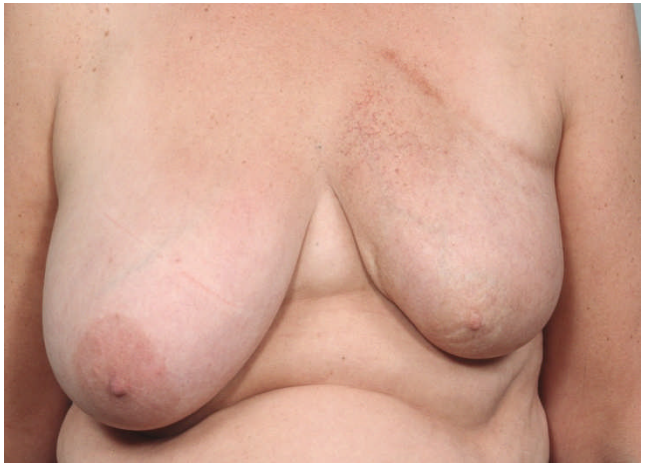
Late effects of therapeutic radiation

- Occur > 90 days after treatment completion
- Cause more complex: Due to cell loss, vascular effects and premature differentiation
- Generally irreversible
- Fibrosis and organ atrophy often seen which continues to progress over years
- Occur in all tissues but most commonly seen in lung, kidney, heart, liver, CNS and skin



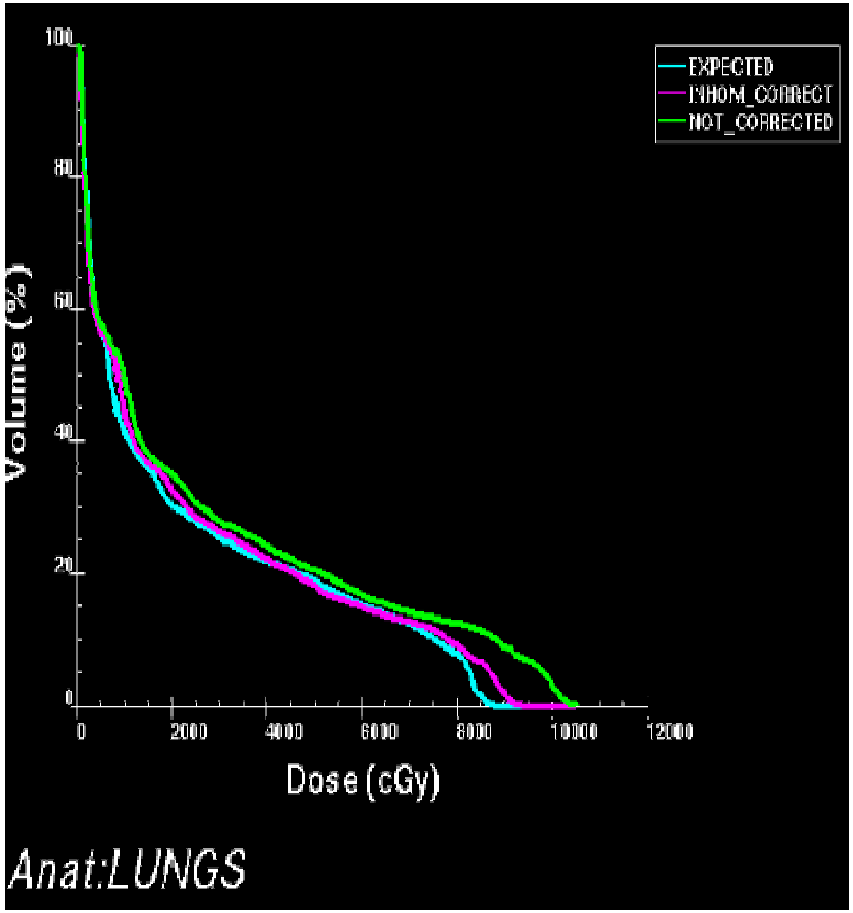


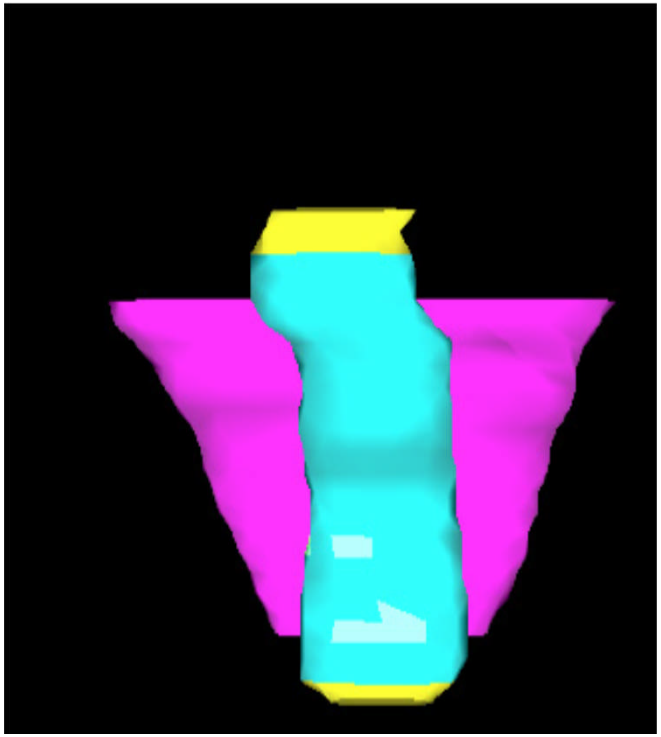
Comparison of different scoring systems: Breathlessness

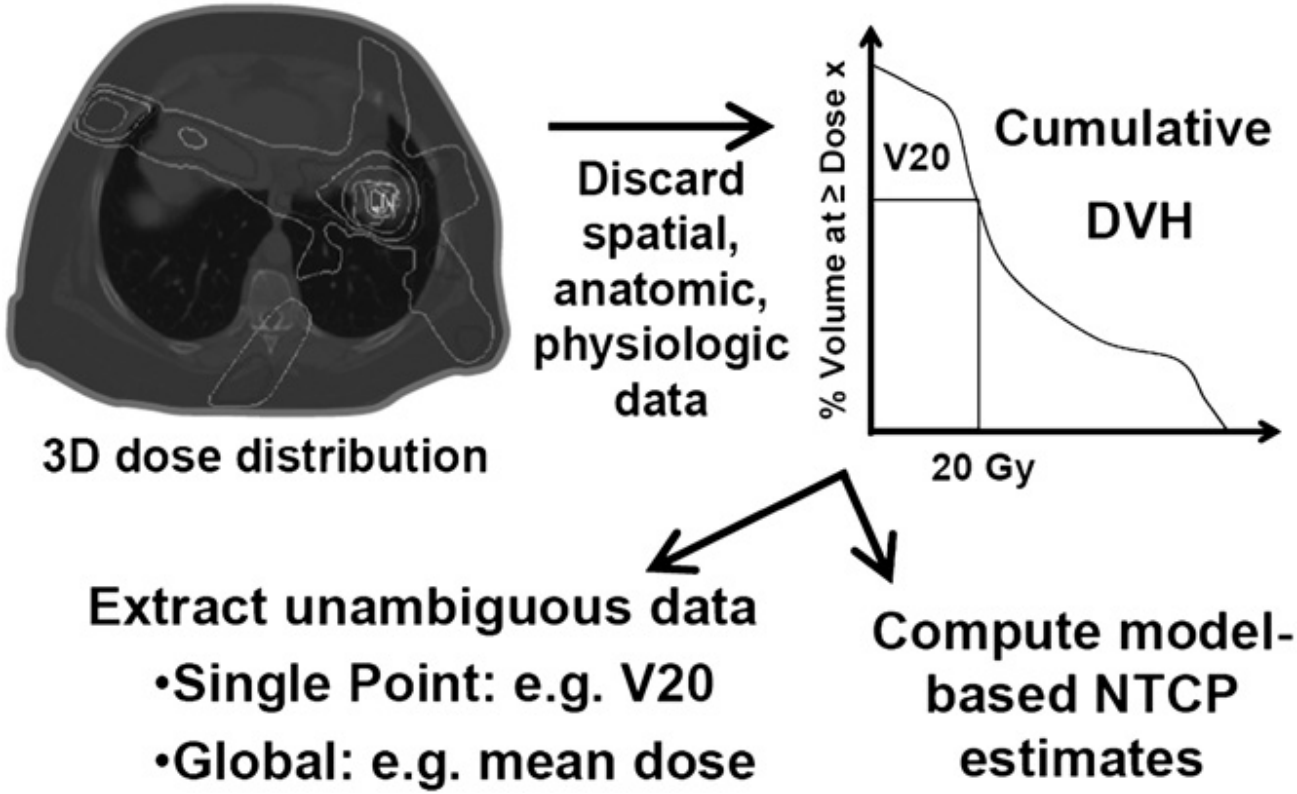
GRADE	NCI CTCAE v4.0	RTOG
0	None	None
1	SOB with moderate exertion	Mild dry cough, SOB on exertion
2	SOB with minimal exertion; limiting ADL	Persistent cough, SOB at rest
3	SOB at rest; limiting self care ADL	Severe cough requiring steroids/ O_2
4	Life threatening; Urgent intervention needed	Severe respiratory insufficiency requiring continuous O_2 or ventilation
5	Death	Death

www.fda.gov/cder/cancer/toxicityframe.htm

Variations in contouring OAR and dose calculations



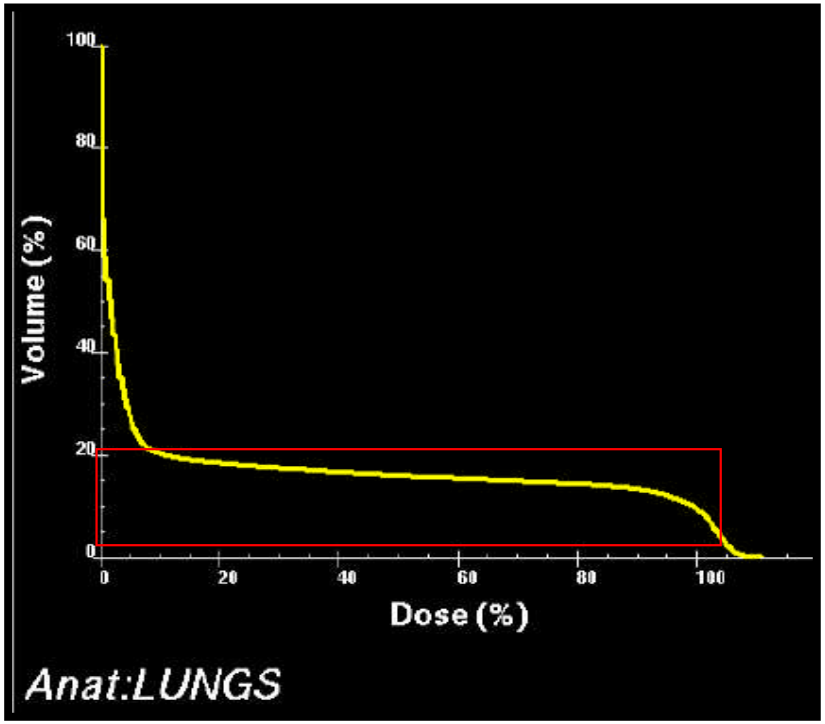




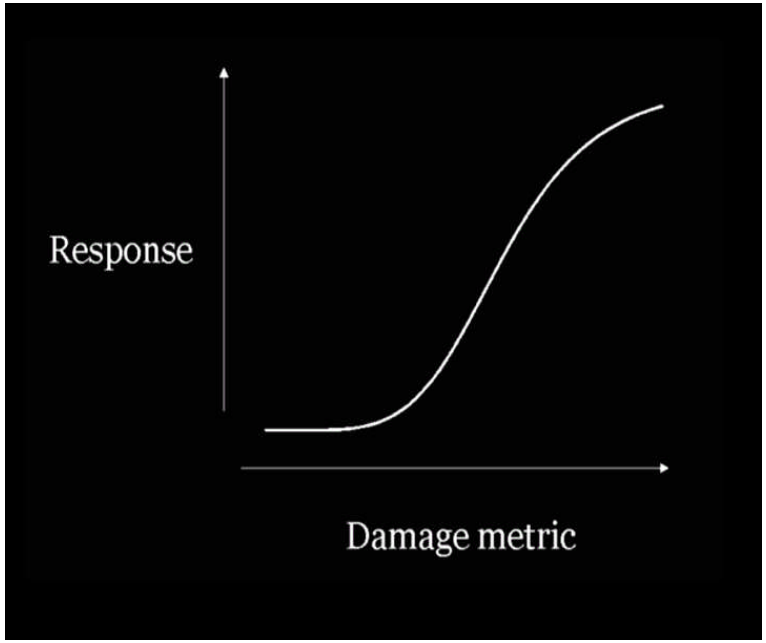
From LB Marks et al, Int J Rad Oncol Biol Physics, 76(3), 2010

NTCP models

- Burman (2001) published companion paper using Emami consensus dose volume data fitted to Lyman model
- Partial volume irradiation: Basis of Lyman model
- Valid in simple treatments using parallel opposed pair of beams with homogeneous dose distribution
- Assumes
  - uniform dose D to Volume fraction, v
  - zero dose to volume fraction = 1-v



The NTCP volume effect model (LKB model)



- Sigmoidal dose response curve, parameters include
  - Slope parameter, m
  - TD50 parameter (tolerance dose for 50% response)
  - Volume parameter, n where n=0 no volume effect to n=1 large volume effect
  - Reference volume of whole organ
- Equation which reduces dose heterogeneity to a single number

But most 3D and IMRT treatments unlike partial irradiation: The idea of the “Equivalent Uniform Dose”

What dose, given uniformly, would have the same biological effect as the actual non-uniform dose distribution?

Can be used to calculate NTCP and TCP

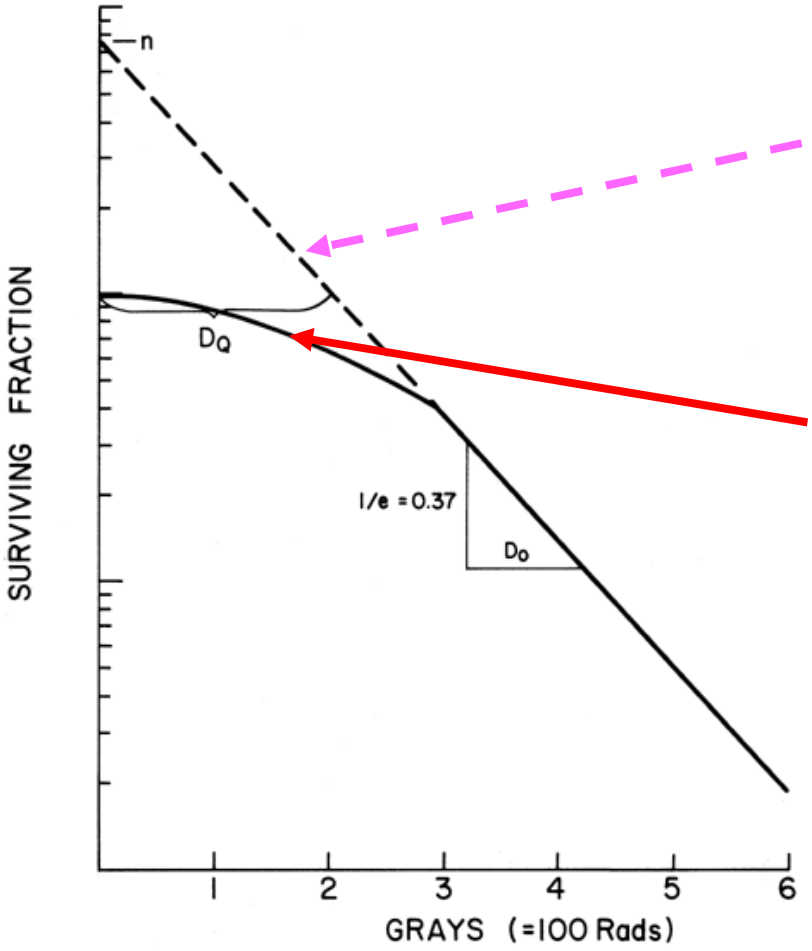
Linear – Quadratic Model

- Quantitative explanation of many aspects of radiotherapy observed at the macroscopic (clinical) level, e.g. fractionation and dose-rate effects, divergence of response between tumours and normal tissues, etc.

- Model continues to be developed, e.g. to incorporate effect of oxygen effects, tumour repopulation, etc.

- Limitations
  - Response at low doses per fraction (<2Gy) – underestimates biological response
  - Response at high dose per fraction (>10Gy) – not modelled well
  - Brachytherapy– steep dose gradients

Cell Survival: Mathematical Models



Bacteria colonies: Constant exponential function
(NB: constant proportional kill rather than constant number)

Mammalian cell curves have 'shoulder' effect in low dose region

- Less effective cell killing
- At higher doses repair mechanism saturated and more lethal lesions occur

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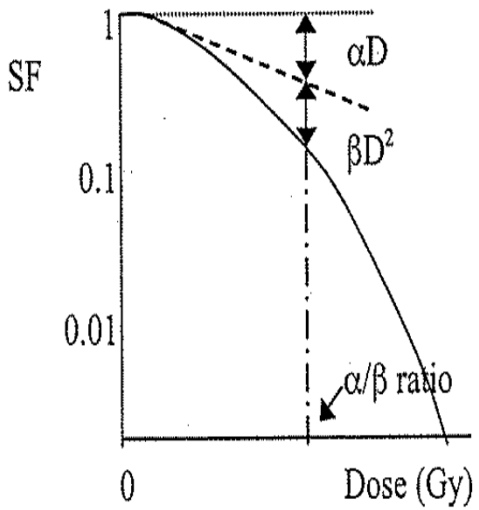
Linear Quadratic Model of cell survival

- Second order polynomial with a zero constant term so SF = 1 at zero dose
- Models in vivo and in vitro responses well
- α – probability of damage due to single track event
- β – probability of damage due to two independent track events
- Key features of graph
  - Continuously bending
  - Semi-log plot
  - α/β (Gy) is dose where linear component to damage (αD) = quadratic component (βD^2)

Probability of survival, P(survival) = exp ($-\alpha D - \beta D^2$)



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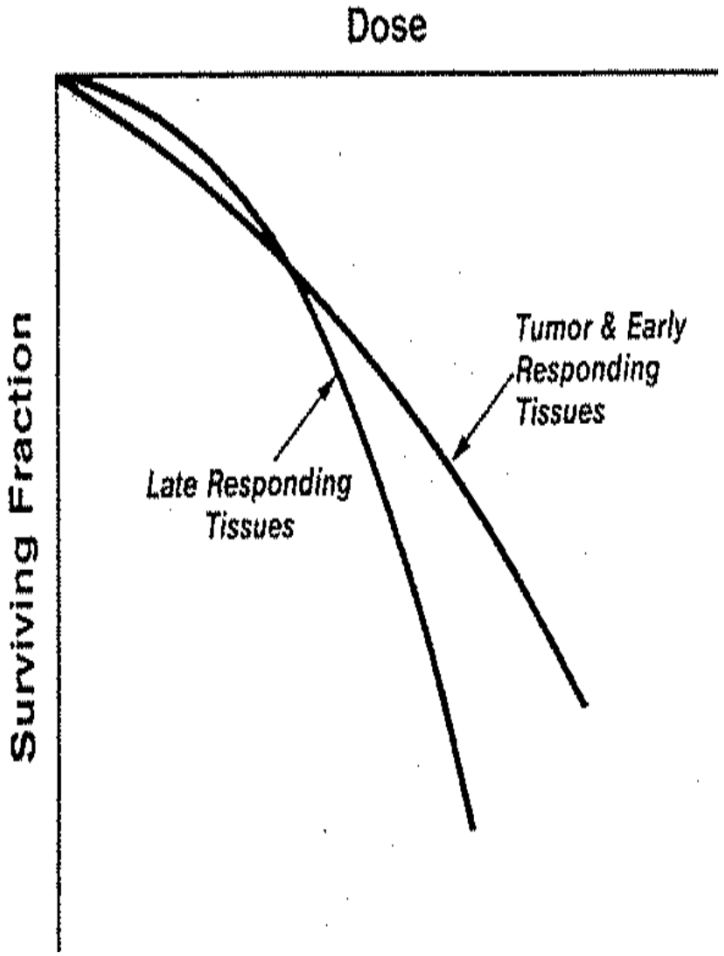
α/β ratio: Fractionation sensitivity in tumours and normal tissues

- DR curve more bendy for late responding tissues – LQ translates into lower α/β ratio
- Late responding normal tissues (spinal cord, kidney): 1-4 Gy
- Most tumours: 8-15 Gy
- Other tumours such as melanomas, liposarcomas, prostate adenocarcinoma: 1-4 Gy
- Early responding normal tissues (skin, mucosa): 8-15 Gy
- Decrease dose per fraction (or dose rate)
  - Tissues with lower □/□ ratios will be preferentially spared compared to those with higher □/□ ratios. – i.e. reduction in cell kill



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Types of modified fractionation

Hyperfractionation (HF)

Accelerated fractionation (AF)

Hybrid schedules

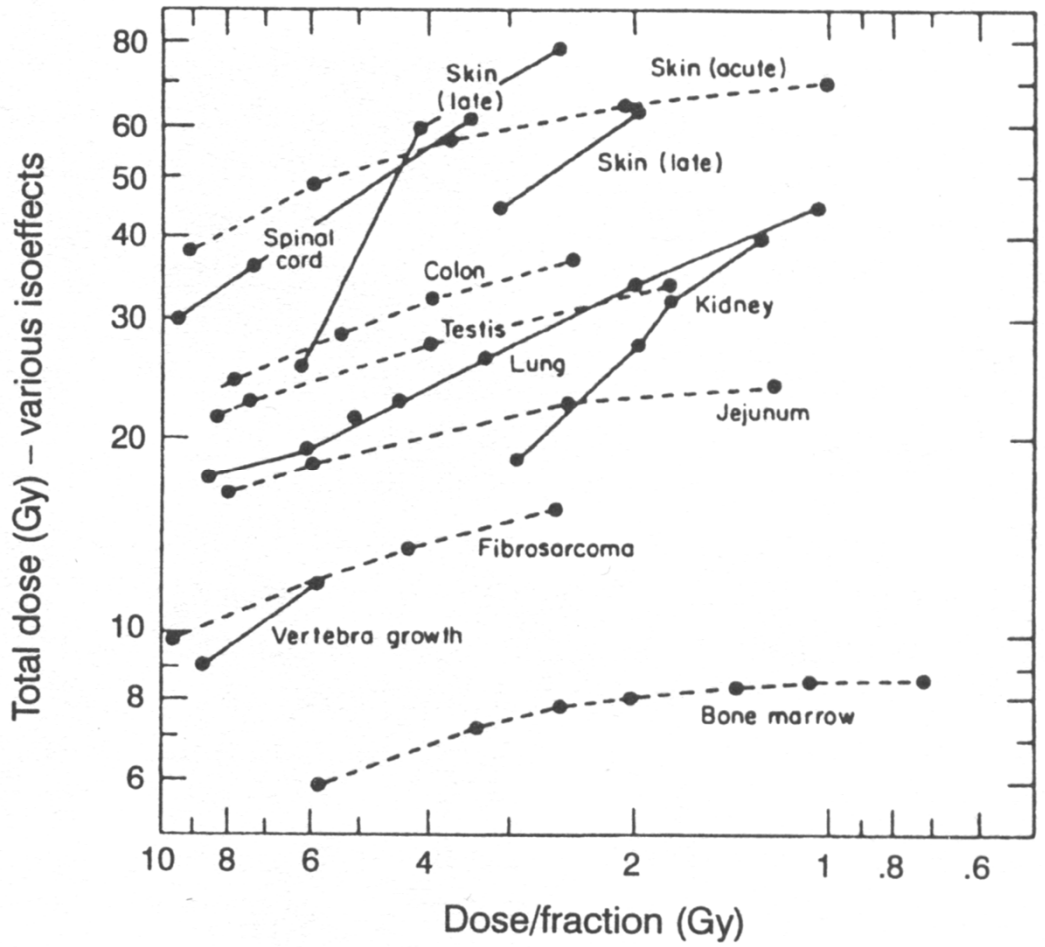
Hypofractionation

Brachytherapy

Why does fractionation reduce risk of late effects?

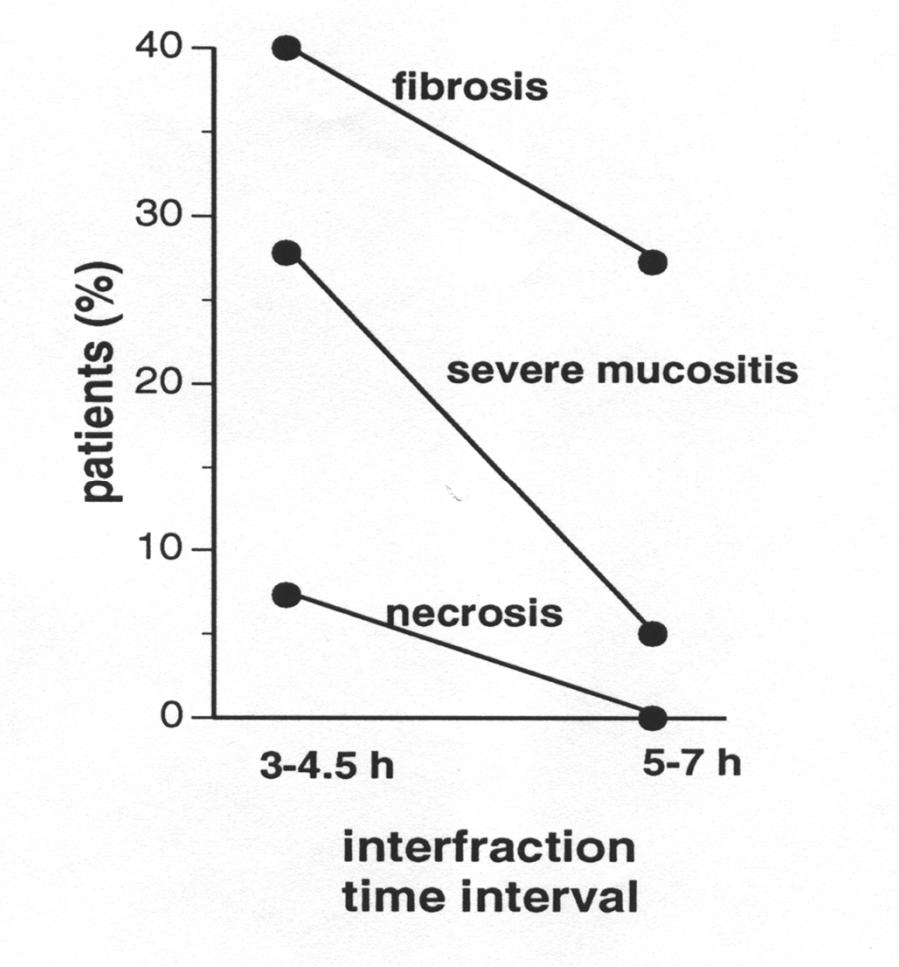
- Individual dose fractions create lethal (fixed) and sub-lethal (repairable) damage.
- Sub-lethal damage (SLD) repairs between one fraction and the next.
- Normal tissues generally have a greater capacity to repair SLD than tumours.
- The process of fractionation therefore “spares” the normal tissues relatively more than the tumour.
- If fewer, larger fractions are delivered, normal tissue damage *may* be excessive, i.e. tolerance may be exceeded.

Dose per fraction: normal tissues



Thames et al. 1982

Data from RTOG HN studies



Incomplete repair with short intervals requires 6-8 hours between #

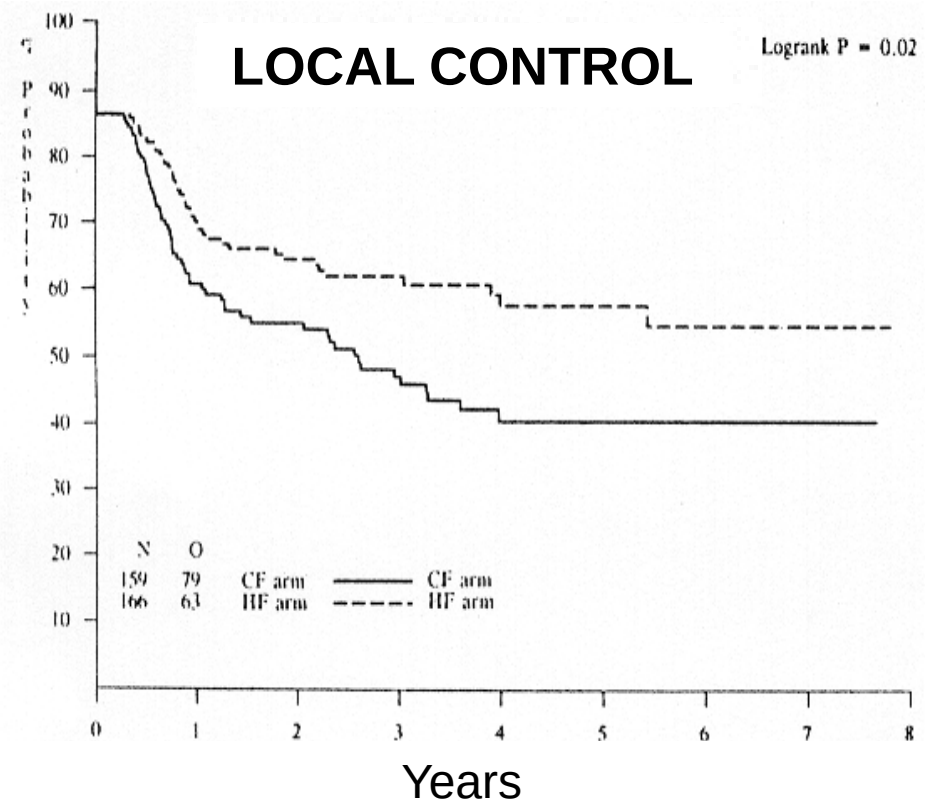
Hyperfractionation (HF)(<1.8 Gy per fraction)

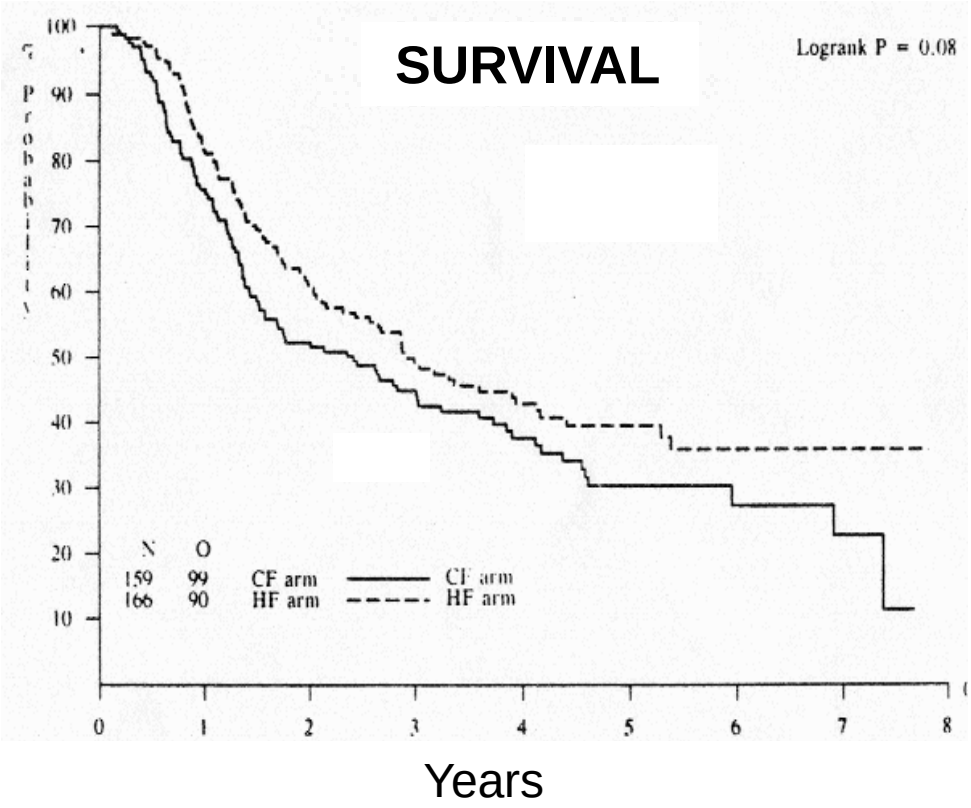
CF	HF
70Gy, 2.0 Gy, 7w	80.5Gy, 2 x 1.15 Gy, interval = 6h, 7w

Expectations (dose-escalated HF):

- Increased tumor control
- More severe early reactions
- Unchanged or less late reactions

Oropharyngeal Ca T2-3, N0-1, n= 356
70 Gy, 35 x 2 Gy, 7w vs. 80.5 Gy, 70 x 1.15 Gy, 4-6 h, 7w





EORTC 22791; Horiot et al., *Radiother. Oncol.* 25: 231-241, 1992

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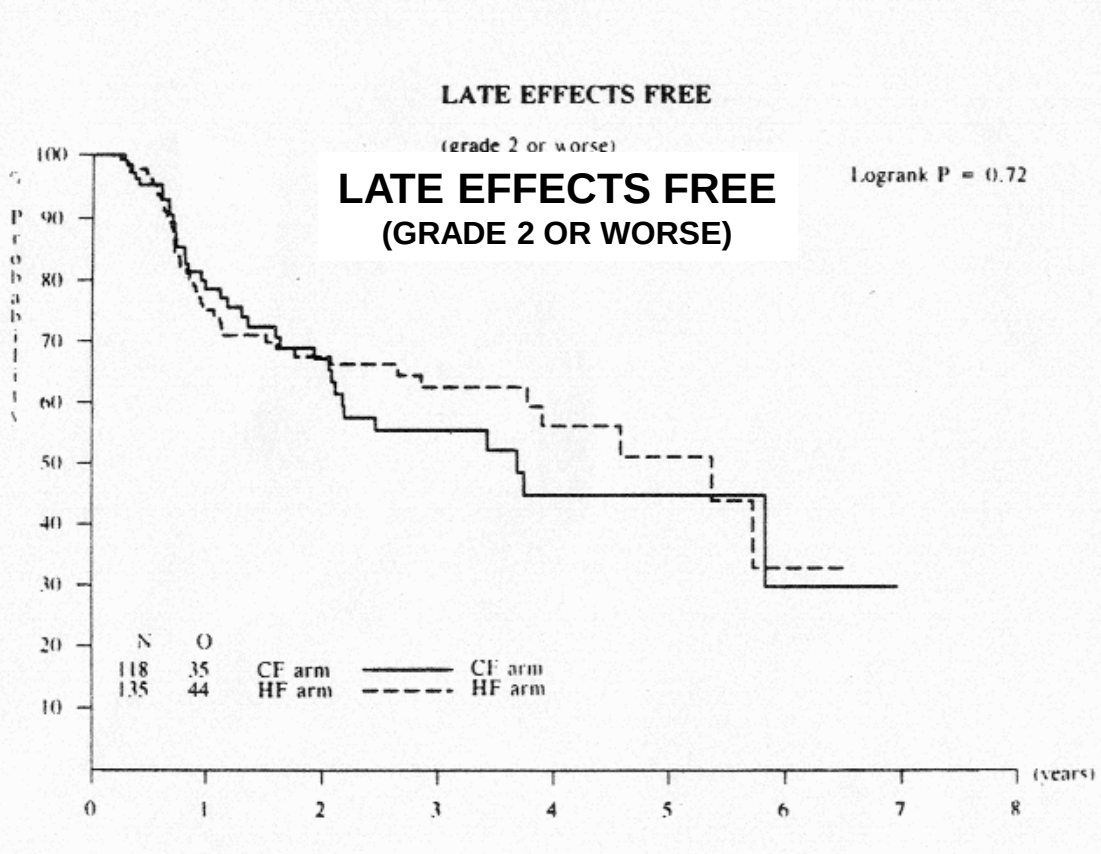
Oropharyngeal Ca T2-3, N0-1, n= 356
70 Gy, 35 x 2 Gy, 7w vs 80.5 Gy, 70 x 1.15 Gy, 4-6 h, 7w



Years

No increase of fibrosis with hyperfractionation

Accelerated fractionation (AF): Shortened overall treatment time, dose per week >10 Gy

CF	70 Gy, 2.0 Gy, 7 w	Conventional
AF	70 Gy, 2.0 Gy, 5 w	Concomitant boost
AF/HF	54 Gy, 3 x 1.5 Gy, interval = 6 h, 12 d	CHART: Continuous hyper-fractionated

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Accelerated fractionation (AF)
Shortened overall treatment time, dose per week >10 Gy

CF 70 Gy, 2.0 Gy, 7 w

AF

70 Gy, 2.0 Gy, 5 w

AF/HF

54 Gy, 3 x 1.5 Gy,
interval = 6 h, 12 d

Expectations:

Increased tumor control

Increased early reactions

Unchanged or decreased late damage
(AF/HF and/or reduced total dose)

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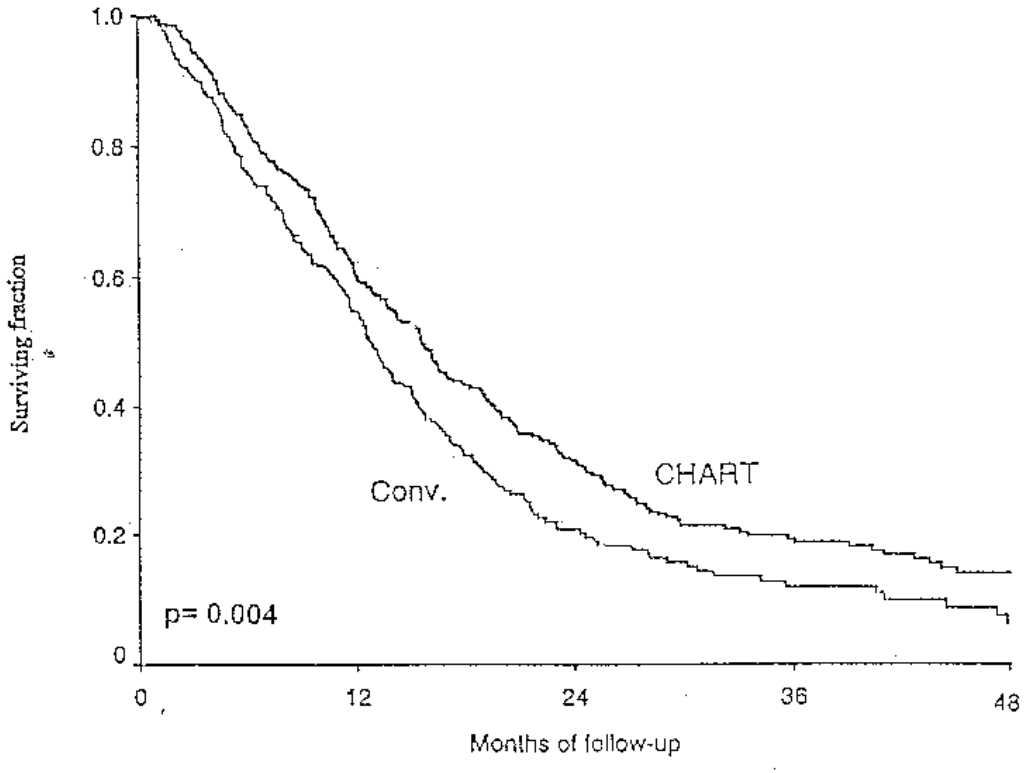
CHART Bronchus trial (MRC, UK): Inoperable NSCLC



IIIII IIIII IIIII IIIII IIIII IIIII
60 Gy, 2.0 Gy, 6 w

IIIIIIIIIIII
IIIIIIIIIIII
IIIIIIIIIIII
54 Gy, 3 x 1.5 Gy,
interval = 6 h, 12 d

Saunders et al., *Lancet* 350: 161-165, 1997

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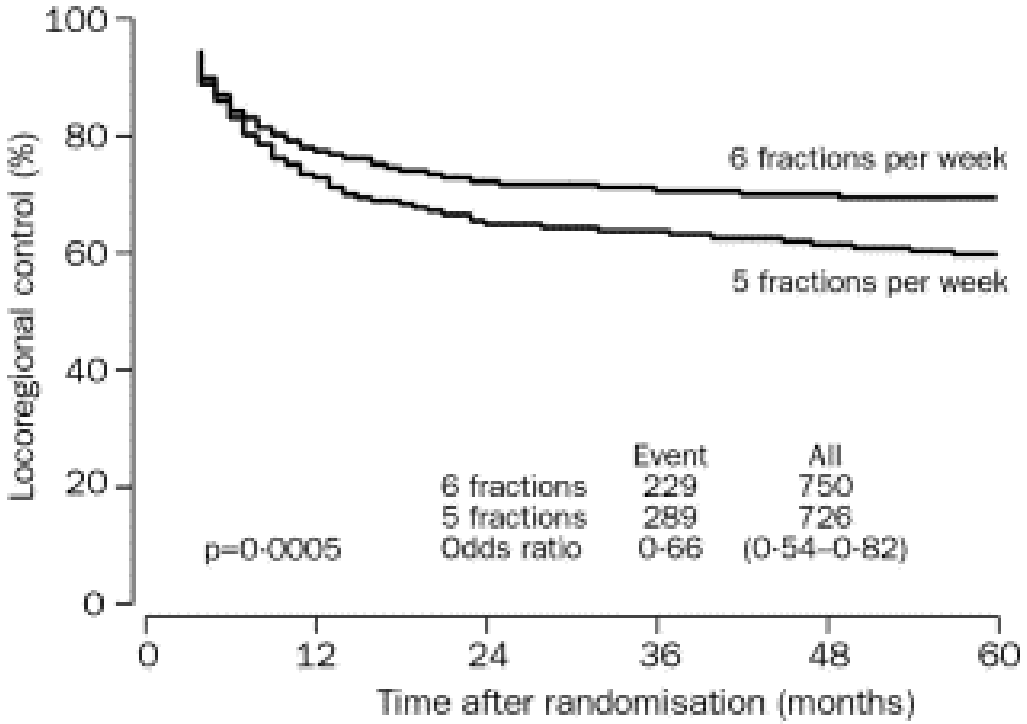
DAHANCA 6-7, loco-regional control

Overgaard 2003

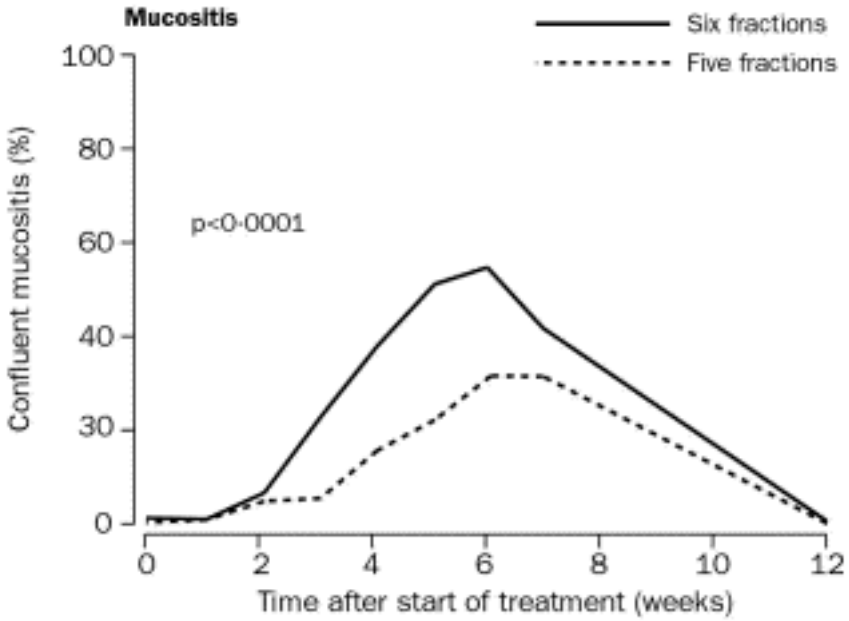


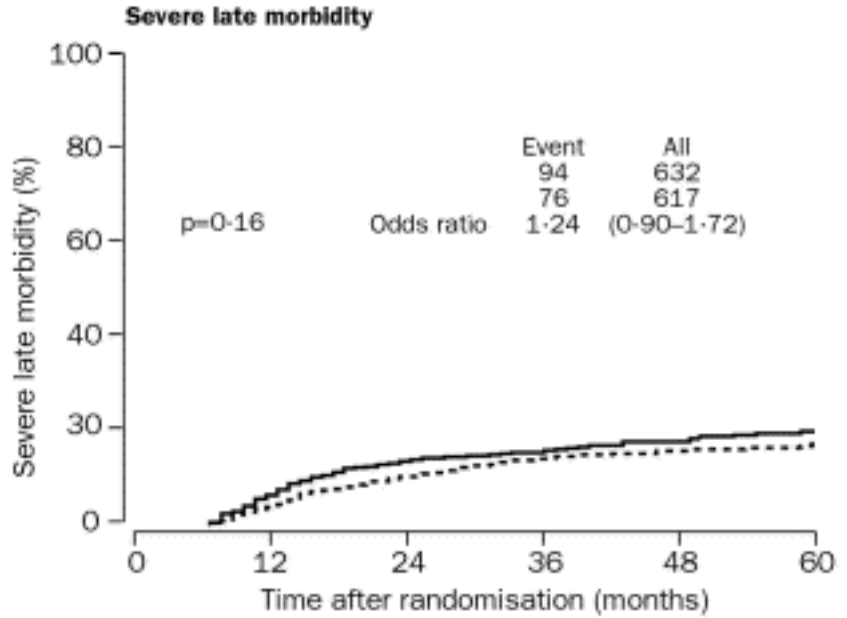
Patients at risk

6 fractions per week					
750	520	440	363	296	193
5 fractions per week					
726	492	400	334	283	182

DAHANCA 6-7, acute and late morbidity

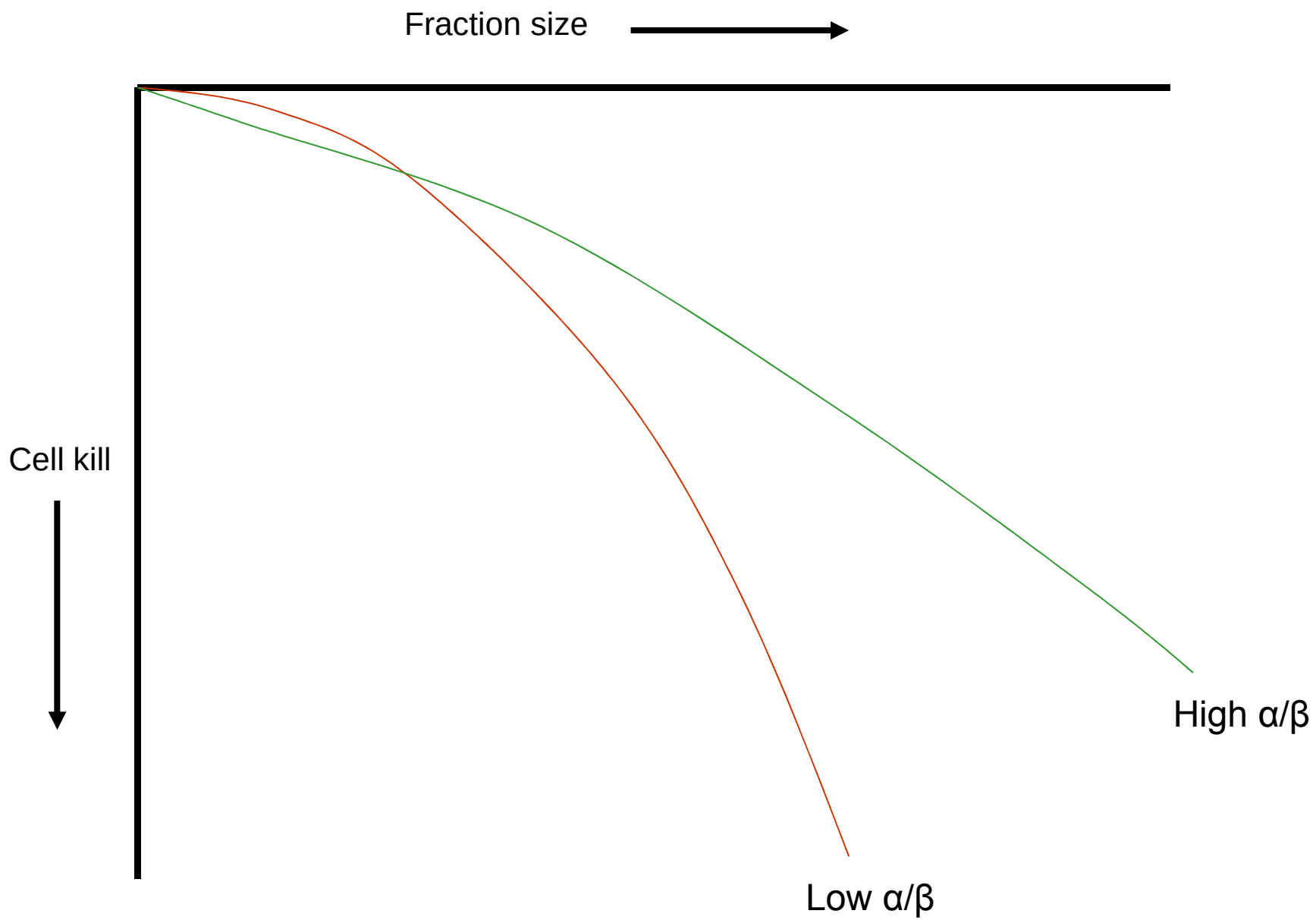
Overgaard 2003

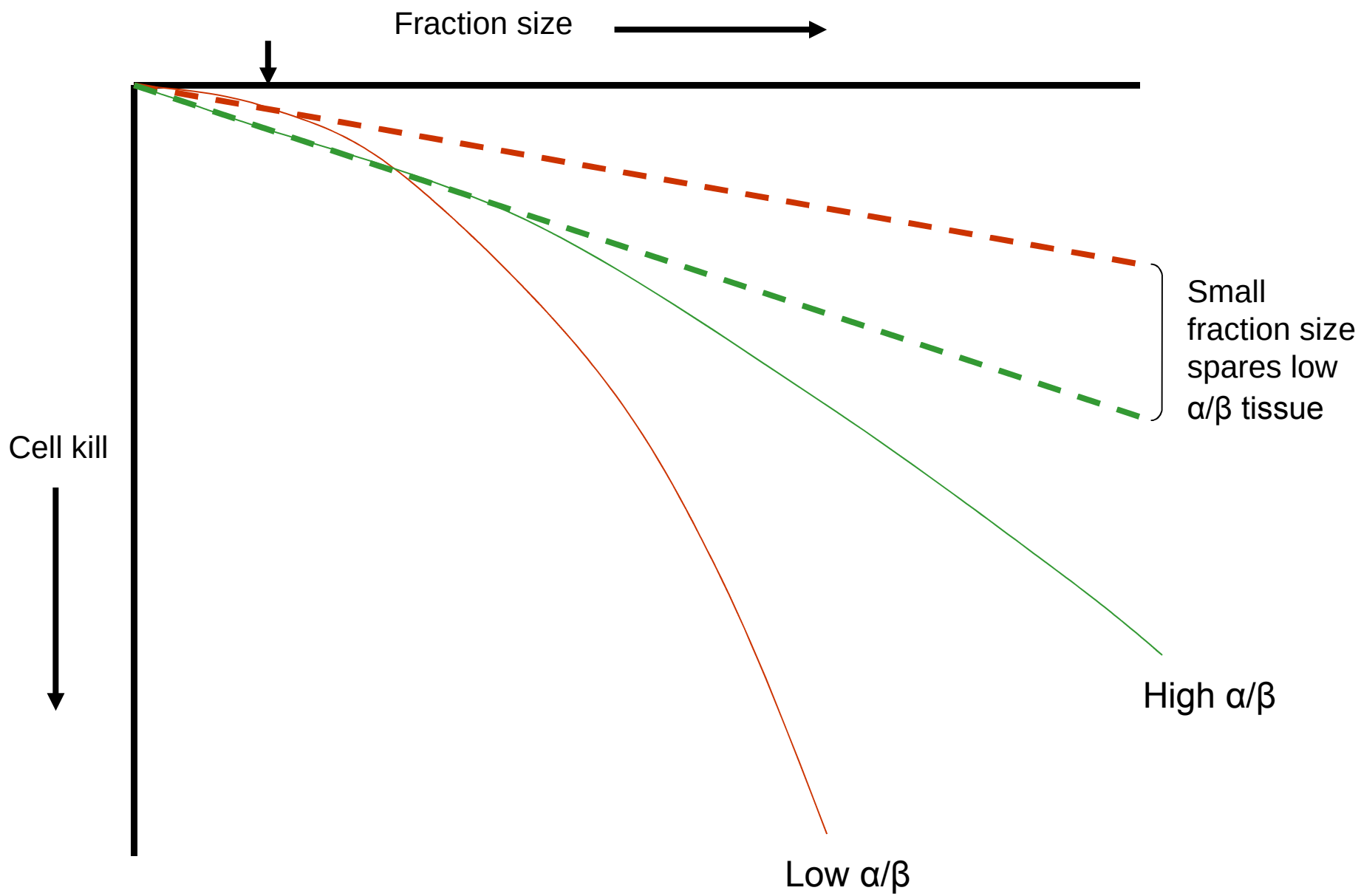


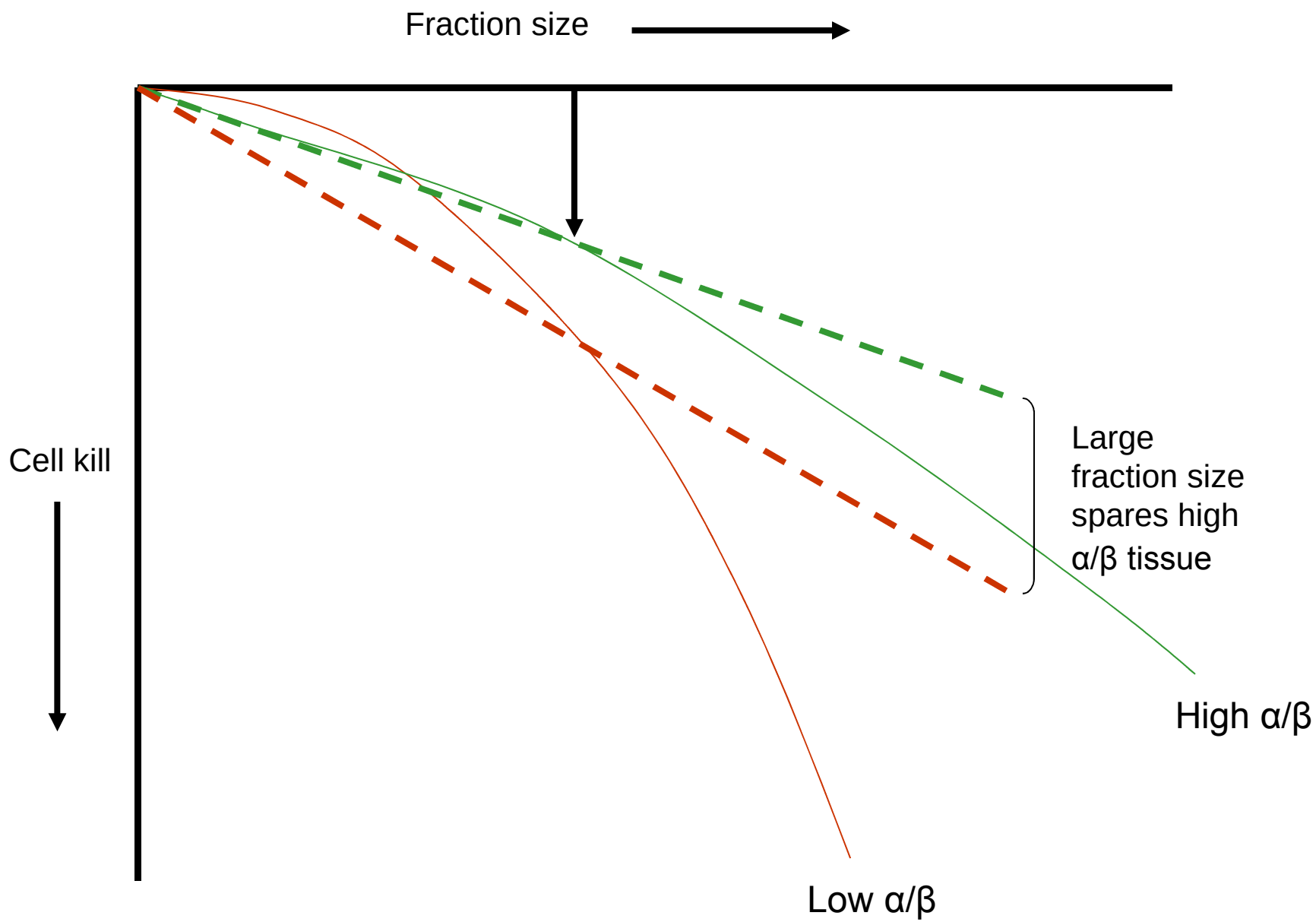


Patients at risk

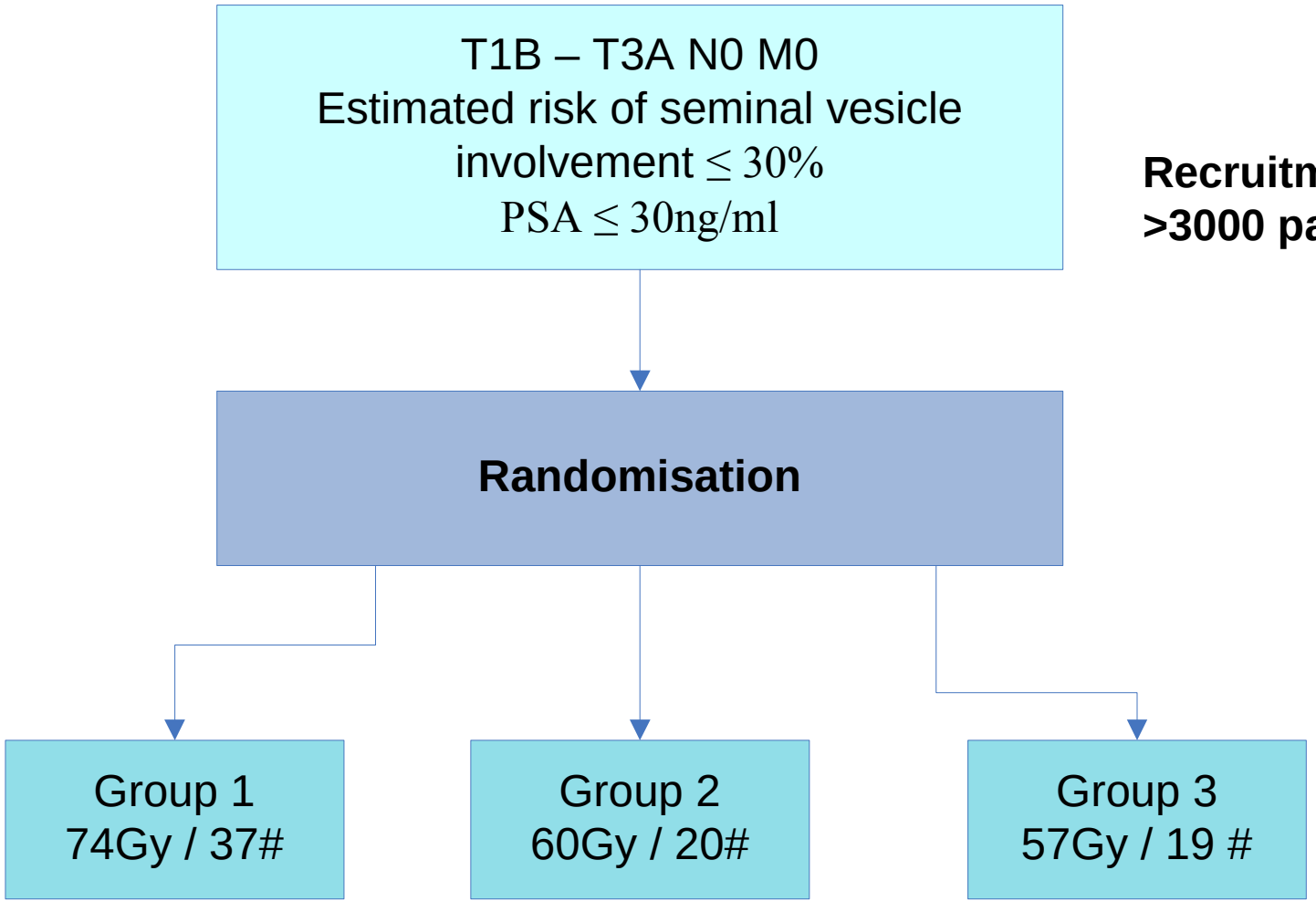
6 fractions per week	632	485	398	347	292	184
5 fractions per week	617	475	382	332	280	177


Fraction size
Cell kill
High α/β
Low α/β


Fraction size
Cell kill
Small fraction size spares low α/β tissue
High α/β
Low α/β


Fraction size
Cell kill
Large
fraction size
spares high
α/β tissue
High α/β
Low α/β

Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHiP) Trial Design



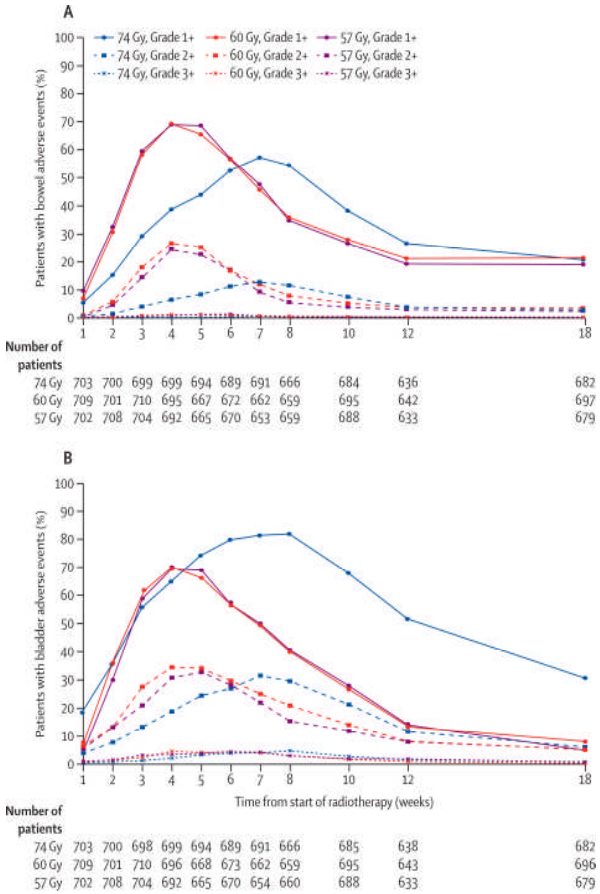
Recruitment >3000 patients

Moderate hypo-fractionation in prostate RT (<4Gy/fx)

With 3Gy x 20 delivered daily using IMRT

1. Acute GI toxicity peaks earlier and higher but resolves quicker
2. Acute GU toxicity peaks earlier but resolves quicker
3. No difference noted in late toxicity

Note: HYPRO study ↑ toxicity with 3.4Gyx19 3 times per week



Dearnaley et al. and Incrocci et al
Both Lancet Oncology 2016 DOI.org/10.1016/S1470-2045

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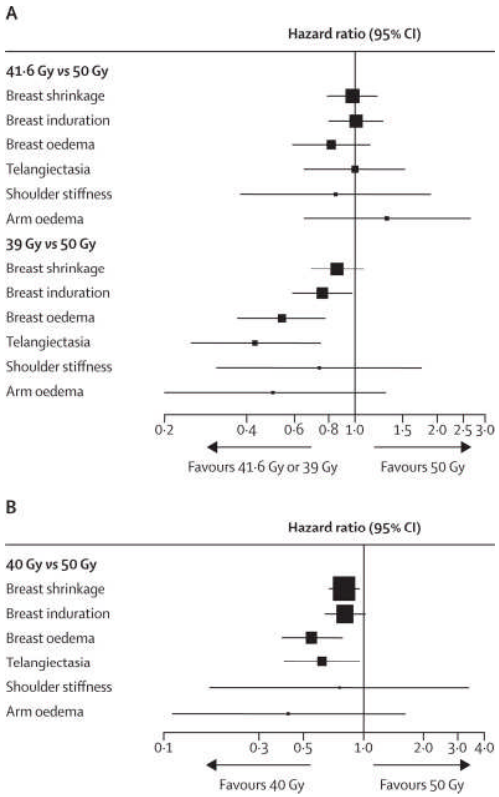
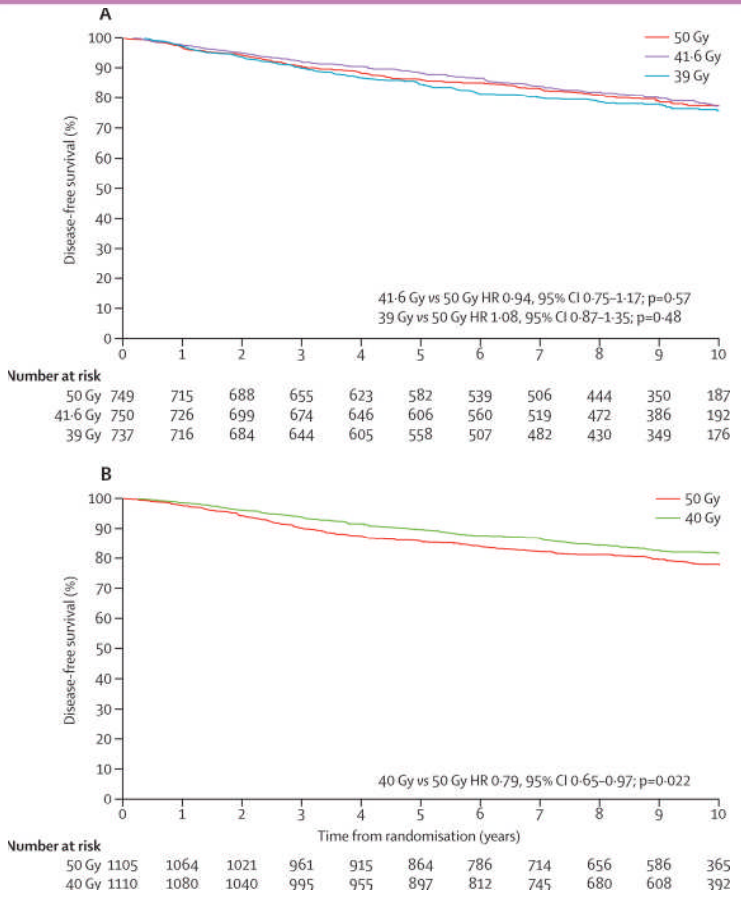
Moderate hypo-fractionation in breast RT





15 fractions results in less long term SE and similar long term control compared to 25 fractions

The Lancet Oncology 2013 14, 1086-1094DOI: (10.1016/S1470-2045(13)70386-3)

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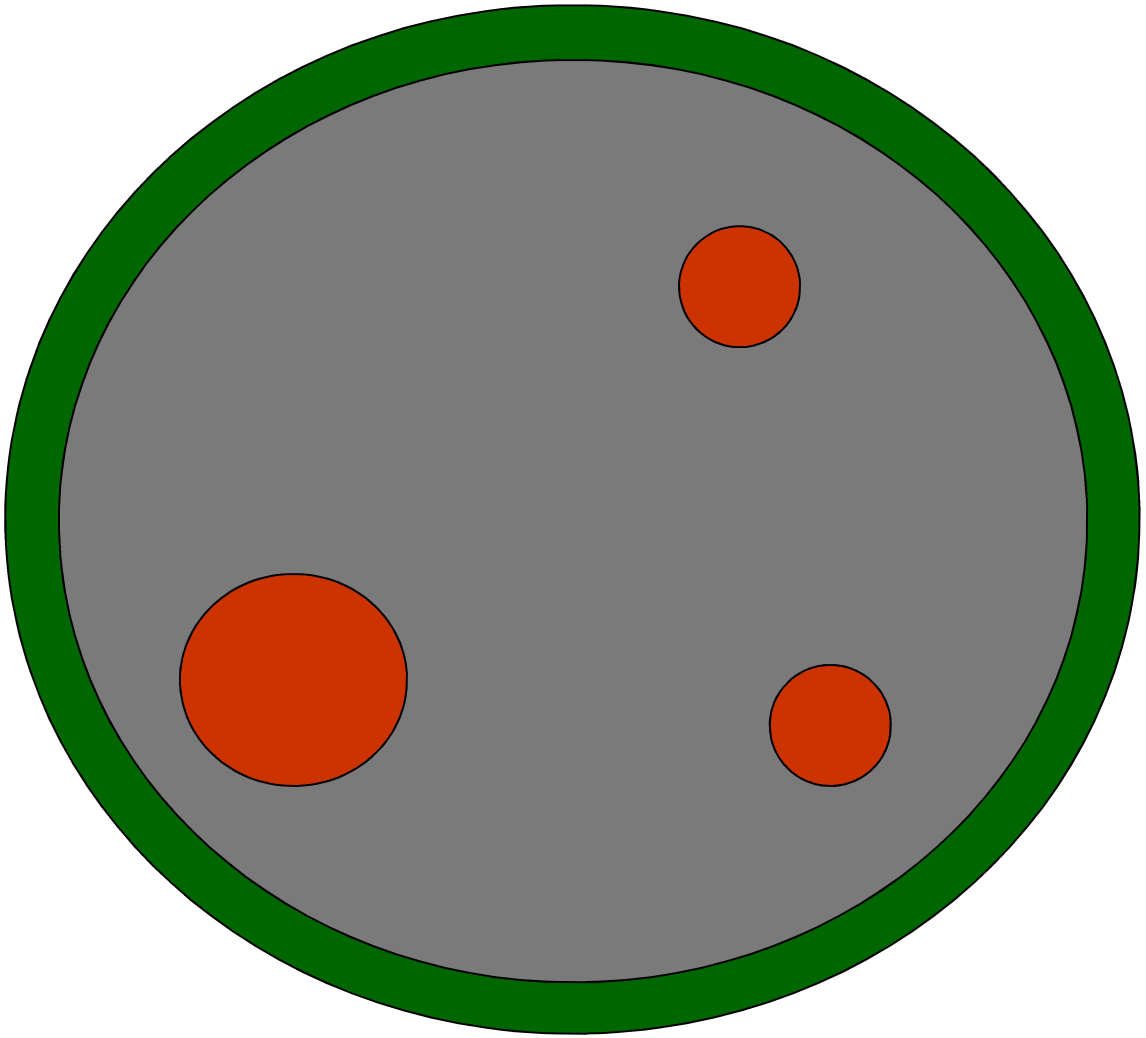
Extreme hypo-fractionation

1. Known as SBRT or SABR
2. Usually delivered in 3,5, or 8 fractions
3. Use of multiple beams, IMRT and IGRT means reduced normal tissue treated
4. Established for NSCLC
5. Same principles apply with brachytherapy

GTV

CTV

PTV

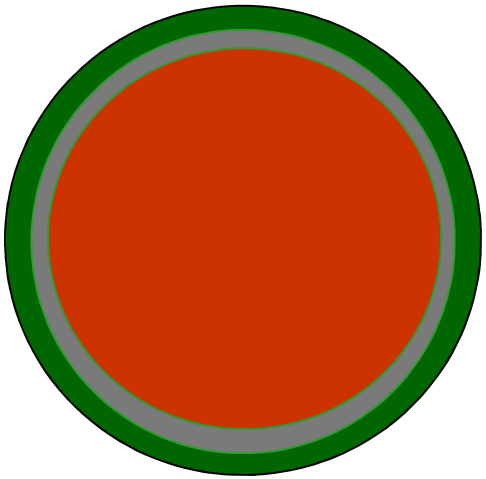


Big volume and lots of normal tissue in PTV then small fraction size makes sense

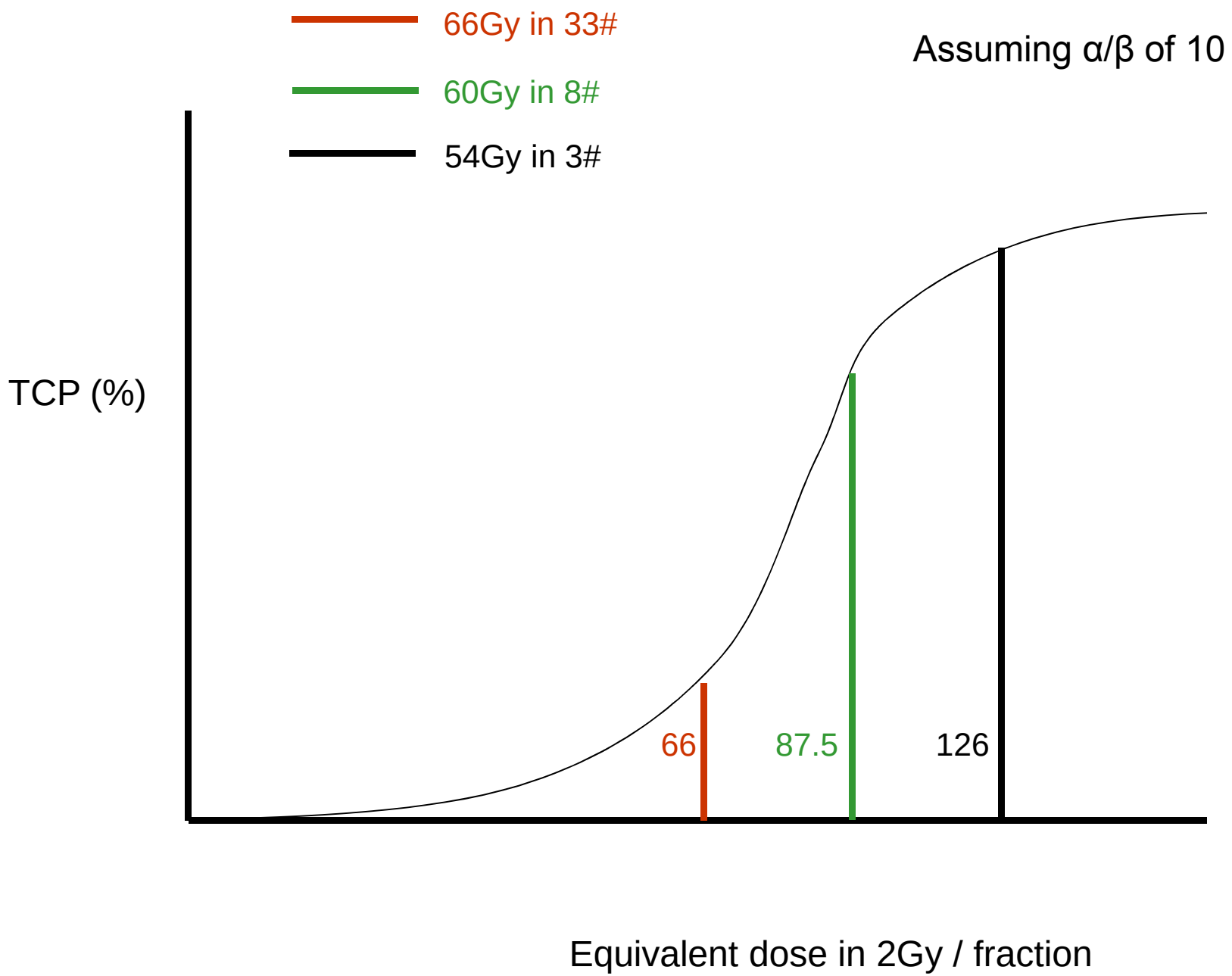
GTV

CTV

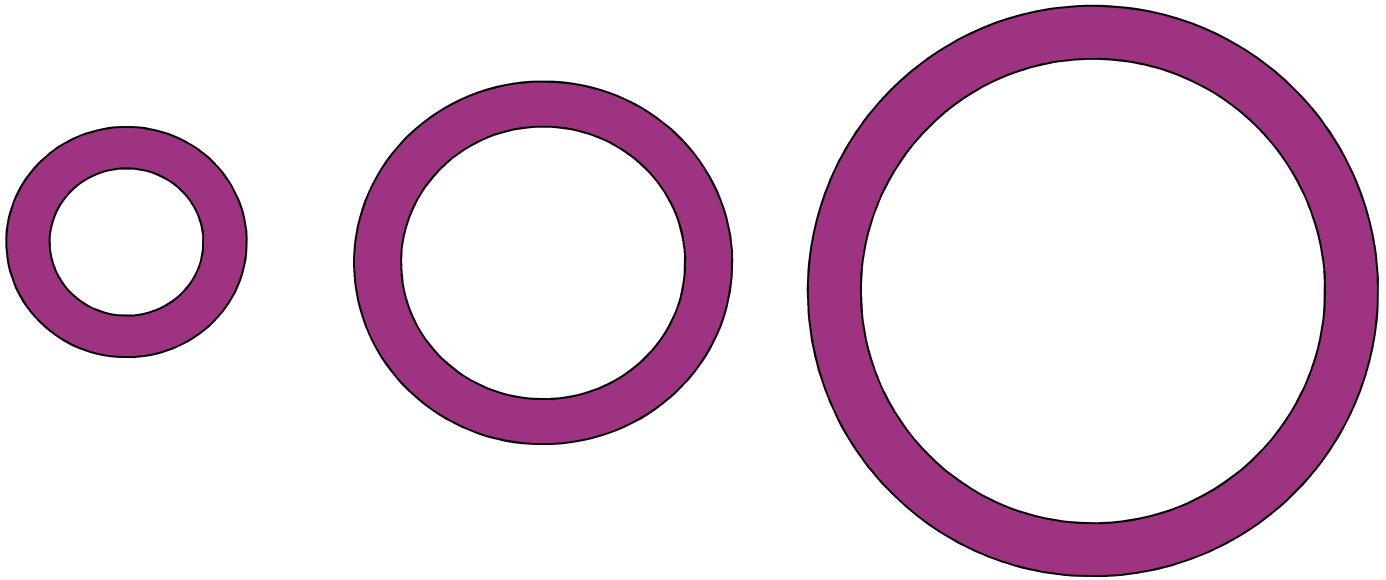
PTV



Small volume with limited volume of normal tissue then large fraction sizes may have advantages (e.g. small primary with low risk of metastasis or small isolated metastasis)


66Gy in 33#
60Gy in 8#
54Gy in 3#
Assuming α/β of 10
TCP (%)
66
87.5
126
Equivalent dose in 2Gy / fraction

CTV to PTV = 0.5cm

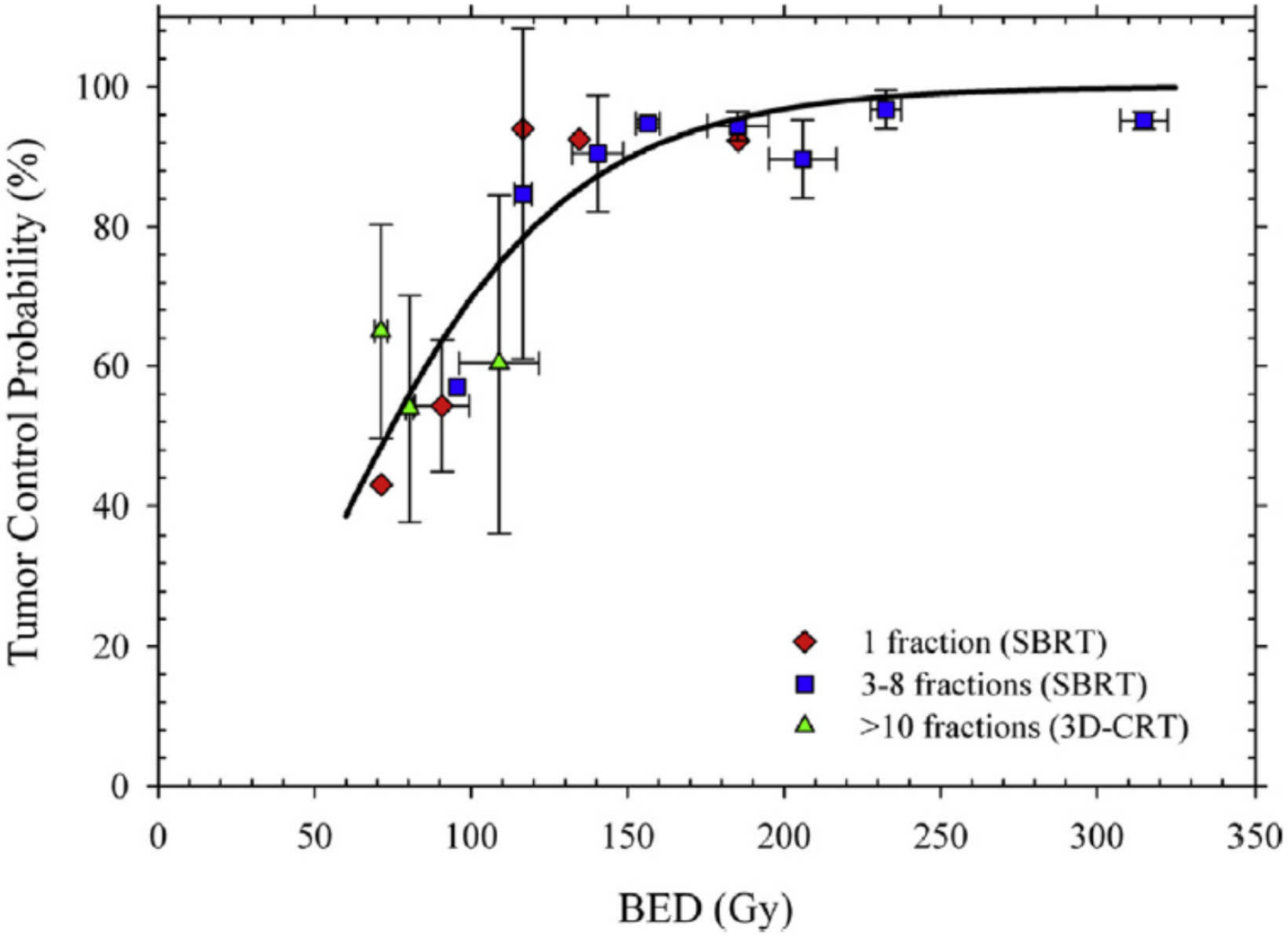


Diameter of CTV	1 cm	2 cm	3 cm
Volume of CTV	~0.5 cm^3	~4 cm^3	~14 cm^3
Volume of PTV	~4 cm^3	~14 cm^3	~33 cm^3
PTV - CTV	~3.5 cm^3	~10 cm^3	~19 cm^3

- The LQ model. Still valid for big fraction sizes?
  Most data are for fraction sizes 1-5 Gy. Controversial if alternative models required at higher fraction sizes.

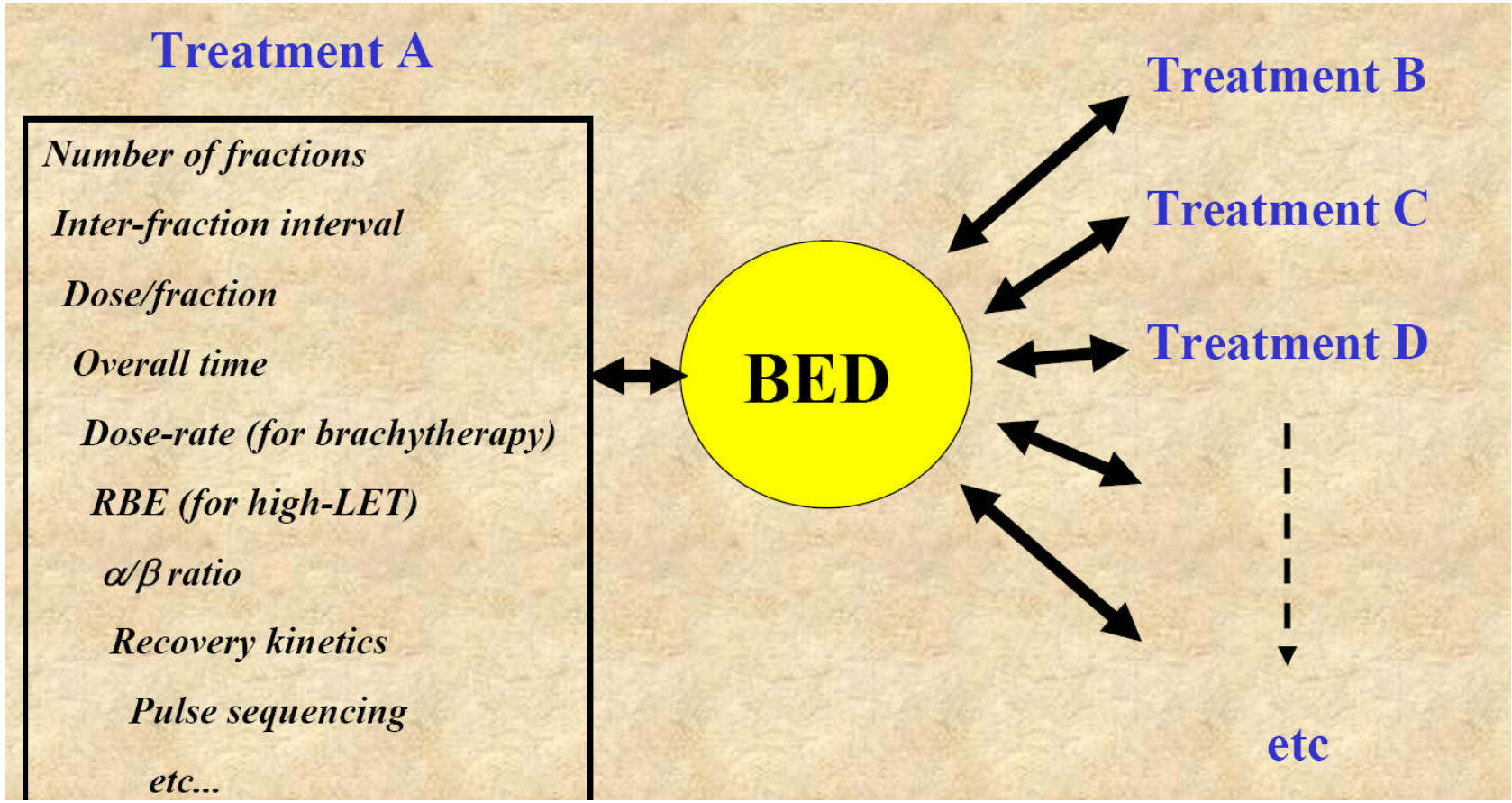
- At big fraction sizes the lack of re-oxygenation would predict worse outcomes than we see.
  - Perhaps endothelial damage (apoptosis) important?
  - Vascular damage causes secondary tumour cell killing?
  - Immune effect?

- How significant is tumour hypoxia – especially for single fraction treatment.



Brown, J.M., D.J. Brenner, and D.J. Carlson. 2013. *Int J Radiat Oncol Biol Phys*. 85:1159-1160.

Biological Effective Dose allows comparison of regimes



Comparing fractionation

$$BED = D \times \left(1 + \frac{d}{\alpha/\beta}\right)$$

Where

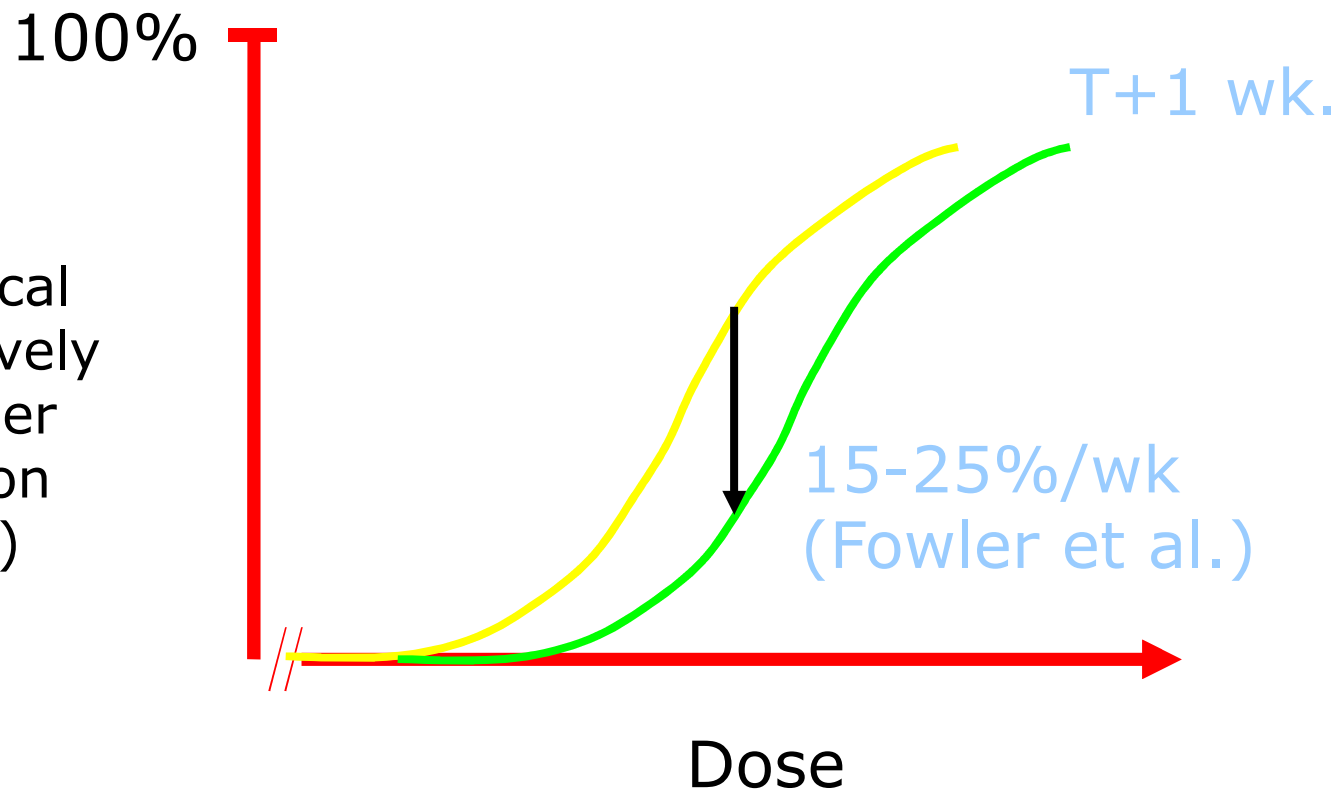
D=total dose

d= dose per #

α/β chosen for tumour or toxicity endpoint

The impact of time on local control

Reduction in local control: effectively about 0.6 Gy per day prolongation (Bentzen et al.)



Compensating for unscheduled gaps

- Prolonging treatment times in the following tumours results in ↓local control and cure rates: SCC head and neck, SCC cervix/vagina, NSCLC, medulloblastoma, oesophageal and skin cancers and possibly TCC bladder

- Prevent gaps by ensuring adequate resources, plan machine down time/treatment schedules and have a clear departmental policy

- Gaps can be compensated for by:
  - Treating over a weekend or twice daily
  - Use of EQD_2 formulae in fewer fractions to achieve planned overall treatment time
  - Deliver additional fractions/dose where compensation can't be achieved within the overall planned treatment time

Further reading

Quantitative **E**stimates of **N**ormal **T**issue **E**ffects in **C**linic : Joint AAPM-ASTRO initiative published Int J Rad Oncol Biol Physics 76 No.3 supplement 2010

Burman C, Kutcher B, Emami B et al. Fitting of normal tissue tolerance data to an analytical function. Int J Radiat Oncol Biol Physics 21: 123-35, 1991.

Dale RG et al. Practical methods for compensation for missed treatment days in radiotherapy with particular reference to head and neck schedules. Clin Onc 14:382-93, 2002.

Emami B, Lyman J, Brown A et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 21: 109-22, 1991.

Kong et al. Physical models and simpler dosimetric descriptors of radiation late toxicity. Semin Radiat Oncol 17(2):108-120, 2007.

Milano MT, Constine LS, Okunieff P. Normal tissue tolerance dose metrics for radiation therapy of major organs. Semin Radiat Oncol 17(2): 131-40, 2007.

Nieder C, Grosu AL, Andratschke NH et al. Update of human spinal cord re-irradiation dose based on collection of data from 38 patients. Int J Radiat Oncol Biol Physics 66: 1446-49, 2006.

Joiner M and van der Kogel A (4th Edition) Basic Clinical Radiobiology. London : Hodder Arnold, 2009.

Yorke ED. Modelling the effects of inhomogeneous dose distributions in normal tissues. Semin Radiat Oncol 11:197-209, 2001.

IMRT physics aspects

By Vibeke Nordmark Hansen and Tom Depuydt

The ROYAL MARSDEN
NHS Foundation Trust

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IMRT overview

- Why IMRT?
- The concept of IMRT
- Inverse planning
  - Formulating the math behind cost functions
  - Optimisation
- Automatic planning and knowledge based planning

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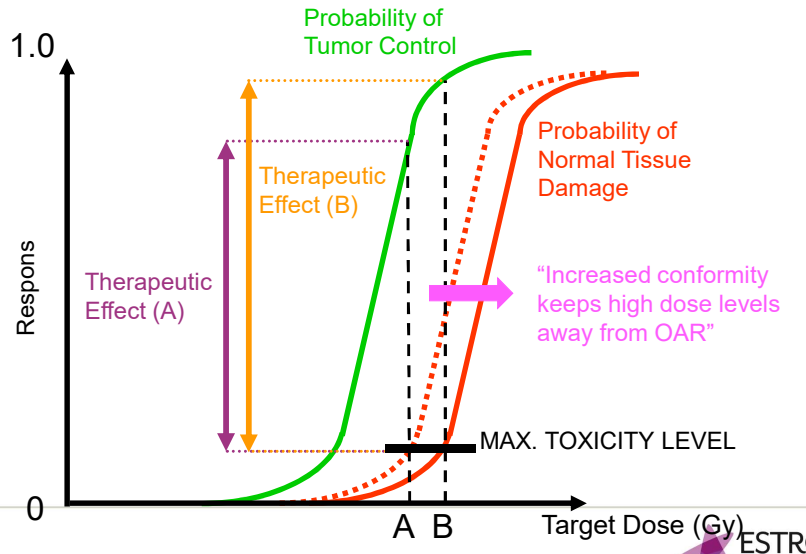
IMRT – Why?
The biological argument, dose escalation

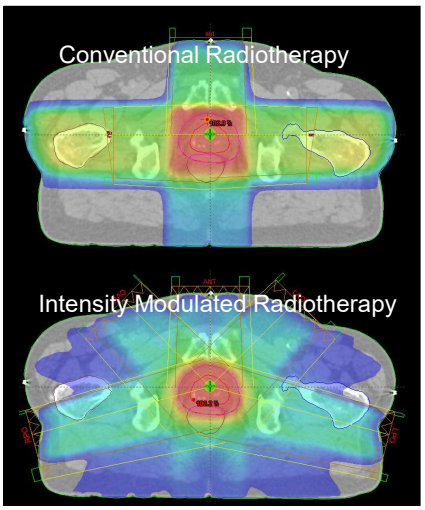


IMRT – Why? Looking at conformity

"Conformity index" is a measure of how well confined to the target volume:

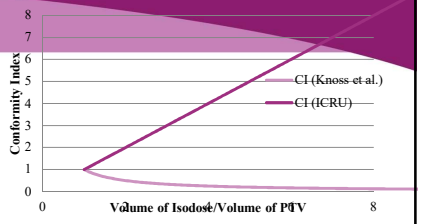
$CI = V_{target}/V_{treated}$

Conventional RT gives a low CI whereas the CI of IMRT approached unity.



Knoos T, Kristensen I, Nilsson P: **Volumetric and dosimetric evaluation of radiation treatment plans: radiation conformity index**
Int J Radiat Oncol Biol Phys 1998, 42(5):1169-1176

Conformity Index



NOTE:

Conformity index is defined differently in different texts:

RTOG /ICRU:

$$CI = V_{\text{treated to specific Iso-dose}} / V_{\text{target}}$$

The "specific Iso-dose" is often prescription dose, 95% dose or 50% dose

Both definitions CI close to 1 is ideal, provided ALL of PTV is covered.

BE careful not to only look at CI, as lack of PTV coverage may lead to CI near 1.

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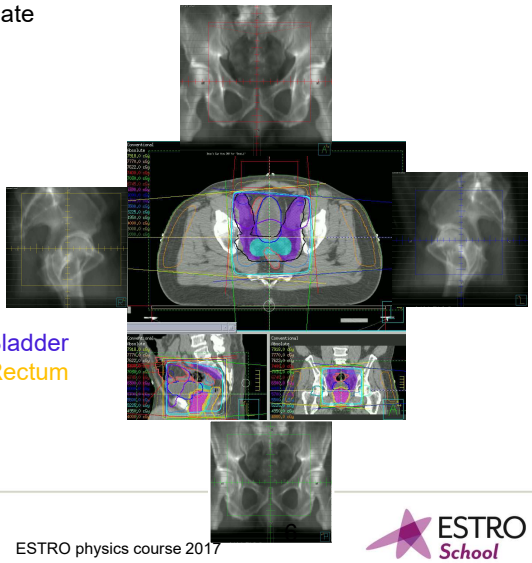
Conventional RT

Only Jaws to limit the beam apertures, wedges to modulate the intensity

$$CI_{95\%} = \frac{2315.76}{626.3} = 3.7$$



Bladder
Rectum

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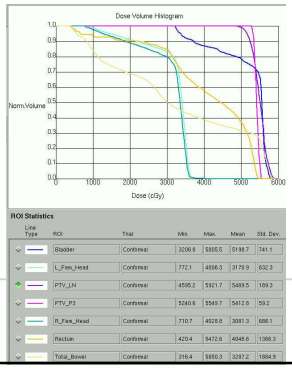
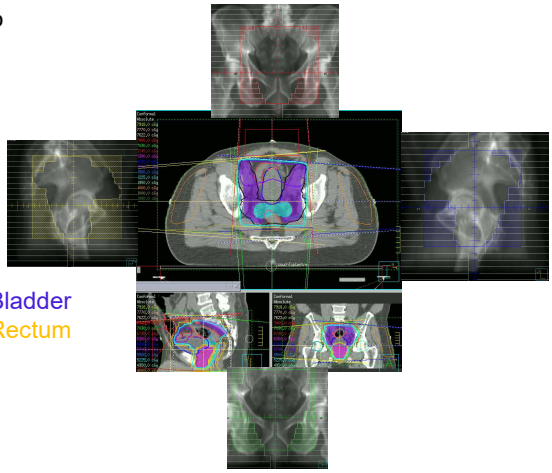
Beam shaping and modulating techniques

Conformal RT

Use of physical blocks or MLC to shape the beam apertures, wedges to modulate the intensity

$$CI_{95\%} = \frac{1035.35}{626.3} = 1.65$$





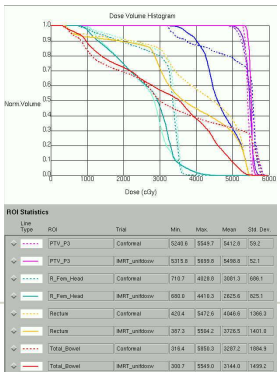
Bladder
Rectum

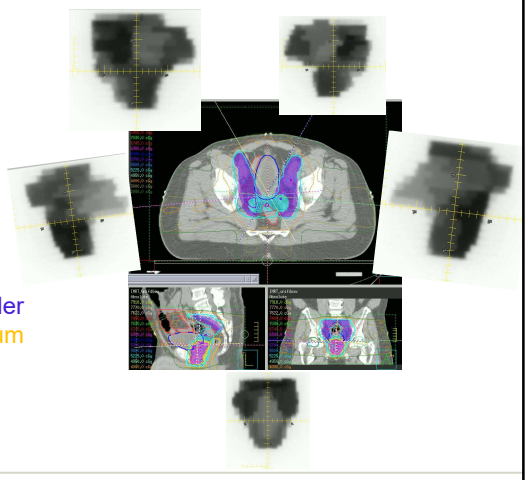
IMRT Intensity Modulated RT

Step and shoot IMRT

Multiple segments per beam

$$CI_{95\%} = \frac{782.8}{626.3} = 1.25$$





Bladder
Rectum

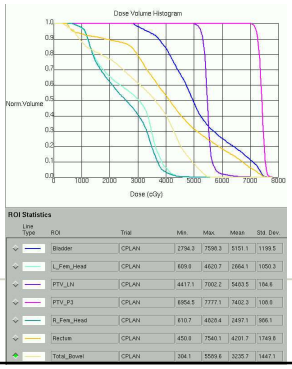
IMRT Intensity Modulated RT Simultaneous integrated boost SIB

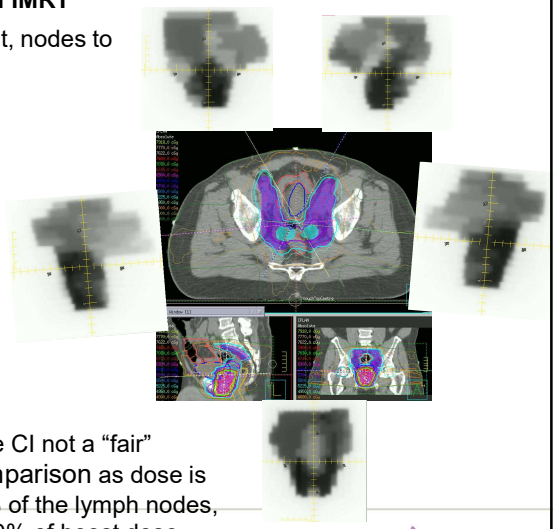
Increase dose allowed because of IMRT

Step and shoot with integrated boost, nodes to 55Gy, Prostate to 74 Gy

Dose escalation

$$CI_{95\%} = \frac{877.5}{626.3} = 1.4$$



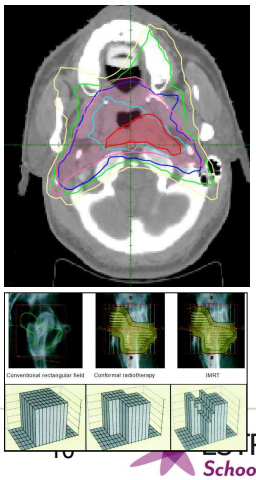


Note CI not a "fair" comparison as dose is 95% of the lymph nodes, ie 70% of boost dose

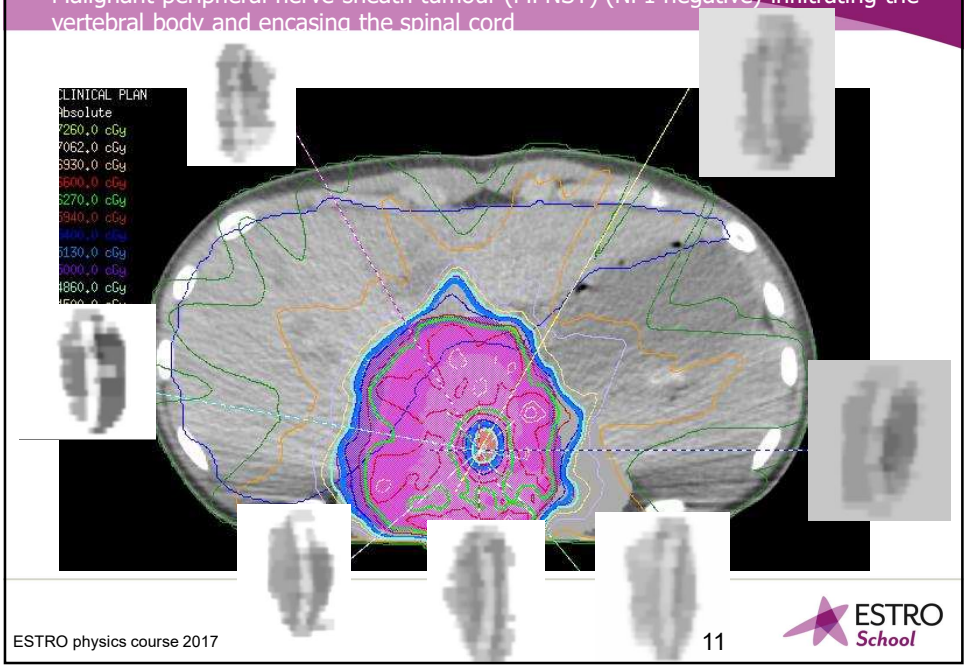
IMRT – Why?

Intensity-modulated radiation therapy is a technique that allow confinement of the high dose region to that of the target volume.

- IMRT is a **further development** of conformal RT.
- IMRT can conform to complex and in particular concave target volumes.
- IMRT can avoid normal tissue.
- IMRT can improve dose homogeneity.
- IMRT can facilitate Simultaneous integrated boost (SIB).



Case where IMRT is only option for a curative dose, 66Gy.
Malignant peripheral nerve sheath tumour (MPNST) (NF1 negative) infiltrating the vertebral body and encasing the spinal cord



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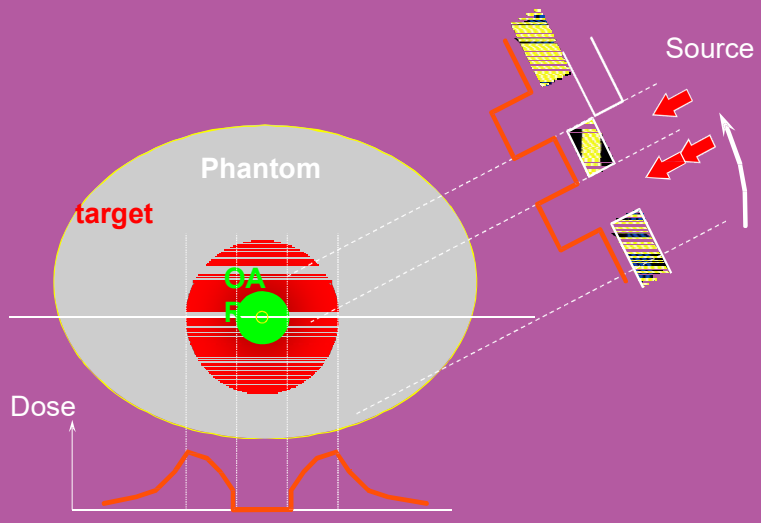
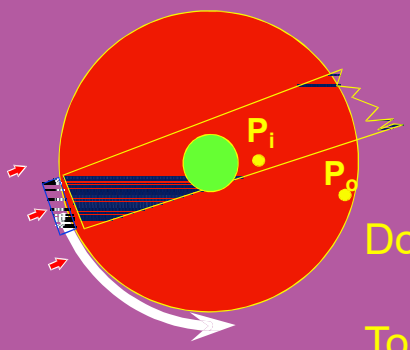
Rotationtherapy: central block



Courtesy of Uwe Oelfke

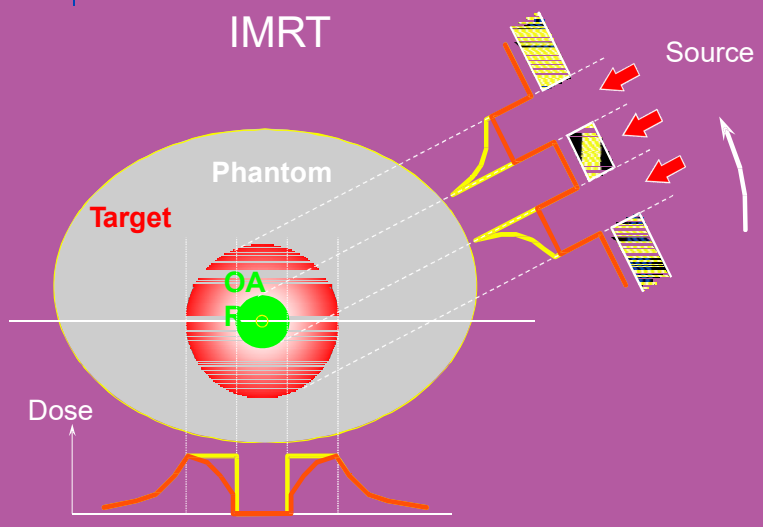


Dose (P_i) < Dose (P_o) !!

To get uniform dose to donut irradiate more dose near sparing structure.

Courtesy of Uwe Oelfke

IMRT



Courtesy of Uwe Oelfke

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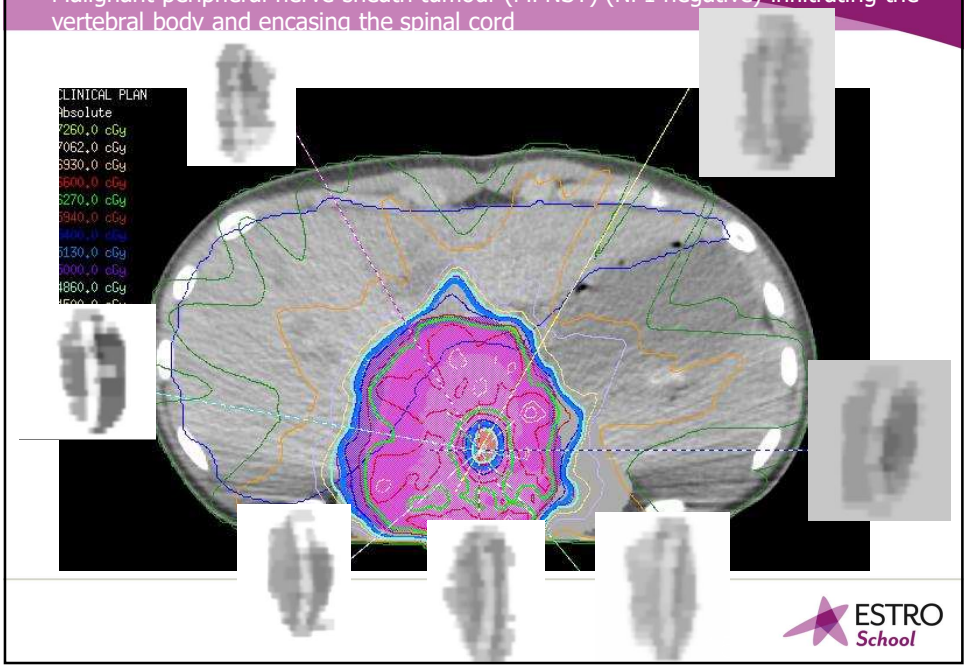

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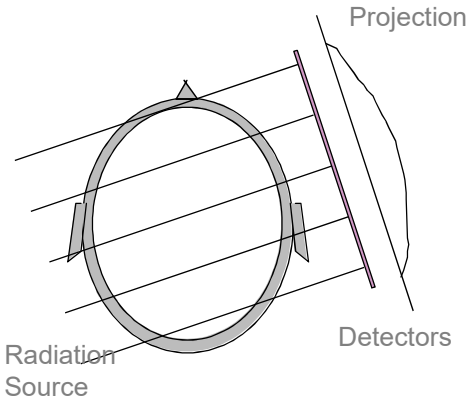
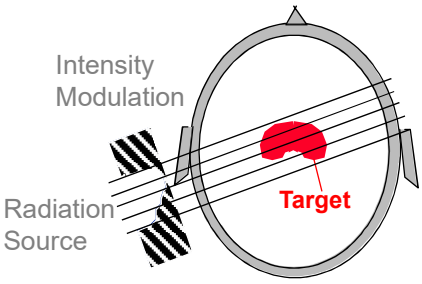
IMRT – the concept of "inverse planning"

Computer Tomography (CT)



Conformal Radiotherapy



CT:
From multiple projections a 2D/3D image is formed

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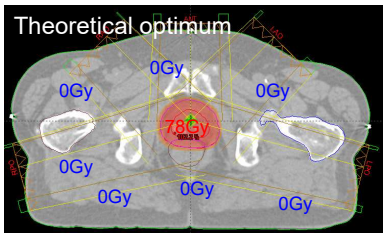
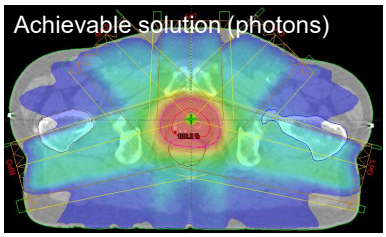
The inverse problem

- The ideal dose distribution is not real
- So, the best clinical result is not possible
- So, compromise …
- Try and get the best approximation to the ideal dose distribution
- Define treatment goals mathematically with a function whose minimum corresponds to our definition of the best plan
- The name of such a mathematical function is **COST FUNCTION** or **OBJECT FUNCTION** or **SCORE FUNCTION**





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The inverse problem

A simple optimization problem:
*"A manufacturer needs to make a cylindrical can that will hold 1.5 liters of liquid. Determine the dimensions of the can that will minimize the amount of material used and as such the **COST** of its construction."*

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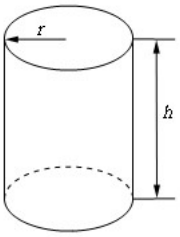
The inverse problem

A simple optimization problem:

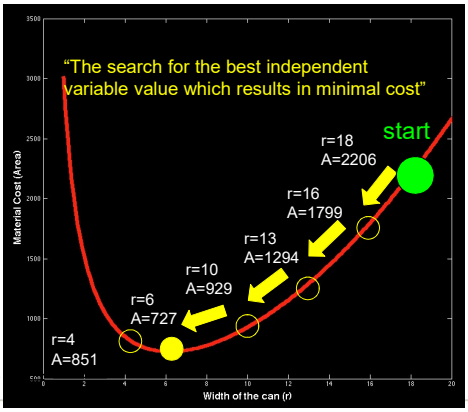
*"A manufacturer needs to make a cylindrical can that will hold 1.5 liters of liquid. Determine the dimensions of the can that will minimize the amount of material used and as such the **COST** of its construction."*



$$V = (\pi r^2)(h) = \pi r^2 h$$
$$A - (2\pi r)(h) - 2\pi rh$$

$$\text{Minimize} : A - 2\pi rh + 2\pi r^2$$
$$\text{Constraint} : 1500 = \pi r^2 h$$

$$\Rightarrow \quad \text{Minimise } A = \frac{3000}{r} + 2\pi r^2$$



The analytic result is 6.20350491

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The inverse problem

Independent variables

Optimization can involve:

Intensity profiles

Beam weights, segment weights

Beam angles (gantry angle, couch angle)

Number of beams

Energy (especially in charged particle therapy)

Type of radiation (photons, electrons, ...)

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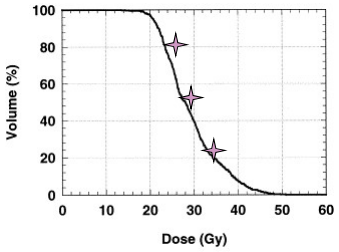
The inverse problem

Optimise:

Physical dose
- Target coverage (min, max, …)
- Target homogeneity
- OAR exposure (max, …)
- Surrounding tissues
- …

Biological effect
- TCP, NTCP
- EUD
- …



DVH goals

Cost function

β Is the relative weight factor

Penalty for not having uniform dose d_0
(optimising uniformity in target)

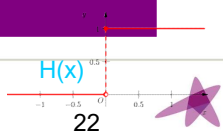
$$C = \beta_T \frac{1}{n_T} \sum_{i \in T} (d_i - d_0)^2 +$$

Penalty for any dose to OAR
(minimising the mean of the OAR)

$$\beta_{OAR1} \frac{1}{n_{OAR1}} \sum_{i \in OAR1} d_i +$$

$$\beta_{OAR2} \frac{1}{n_{OAR2}} \sum_{i \in OAR2} \mathrm{H}(d_i - d_0)(d_i - d_0)$$

Penalty for dose above "tolerance dose d_0 " in OAR
(keeping max dose below d_0)



Cost function for biological constraints

Generalized Equivalent Uniform Dose (gEUD)

$$gEUD(Gy) = \left(\sum_{i=1}^{n} v_i D_i^a \right)^{1/a}$$

Niemierko 1997,1999
Med.Phys

a = 1	EUD = Dmean
a --> -∞	EUD --> Dmin
a --> +∞	EUD --> Dmax

EUD can be optimised to "equal", (gEUD-D_0), "maximum" or "minimum"

gEUD : phenomenological description
of the biological response to the radiation

In principle applicable to target volumes and OARs

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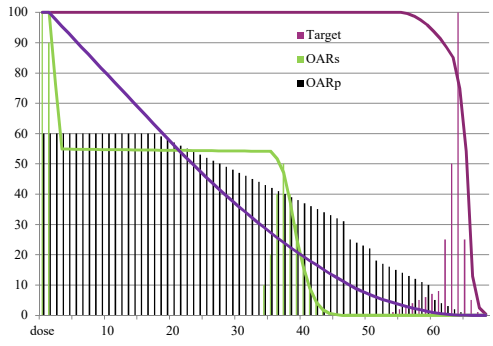
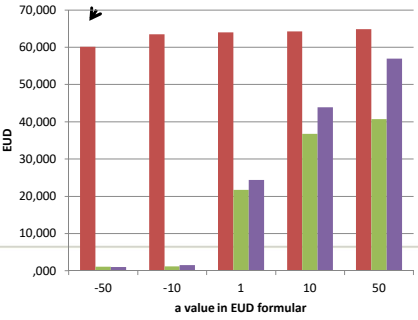
Simple gEUD for 3 structures

Differential and cumulative DVH



gEUD value

Min dose
(55Gy,1Gy,1Gy)
seen at low a



Max dose
(68Gy, 47Gy,
65Gy) at high a

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The inverse problem

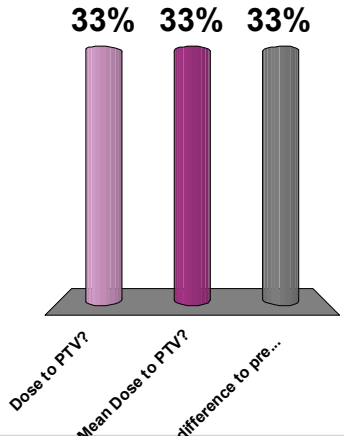
Optimization can be based on a 'Cost Function'

- a figure of merit based on the specification for target and sensitive organ dose requirement.

- Clearly there may be many terms for the target and each OAR, and there may be more than one minimum

What will you minimise for PTV?

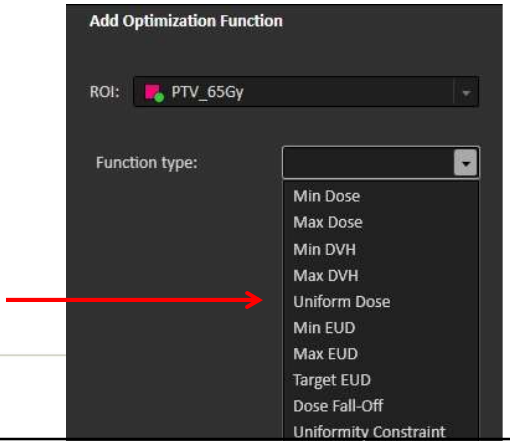
A. Dose to PTV?
B. Mean Dose to PTV?
C. Dose difference to prescription dose?



What will you minimise for PTV?

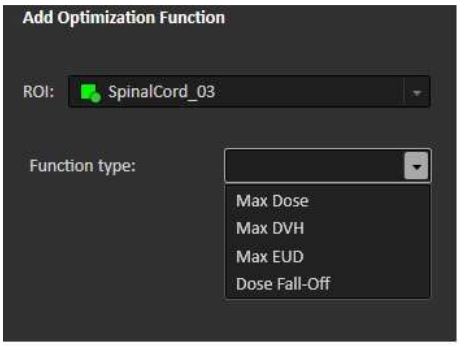
Dose difference to prescription dose

We aim for uniform dose.



What will you optimise for OAR?

For OAR you always want “As low dose as possible”



Cost function

The cost function is universal for RT planning and independent of the plan.

If it is IMRT or VMAT the cost function may be the same.

You have the same aim for your plan.

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Setting up your IMRT plan

Number of beams

Beam orientation

Following influence the optimisation time and plan modulation:

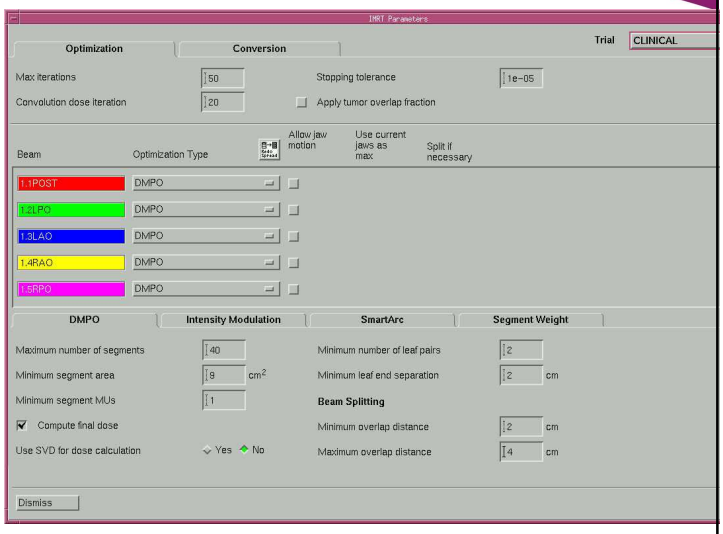
Total number of segments

Minimum segment area

Minimum segment MU

Minimum leaf pairs

Minimum leaf separation



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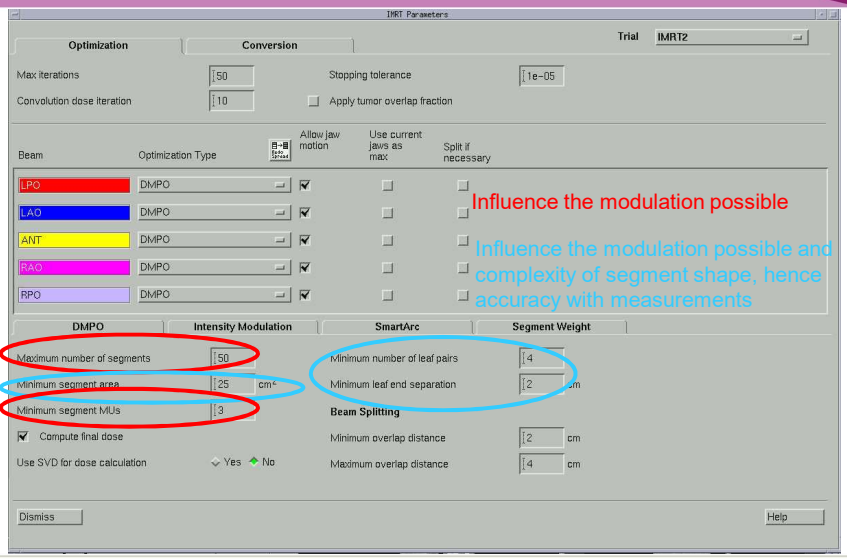
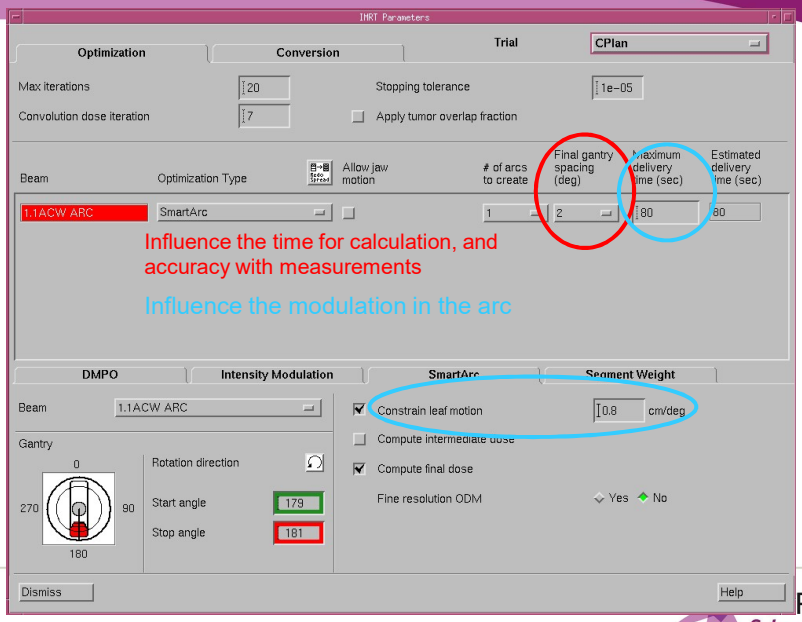
IMRT parameters



SMARTARC



Courtesy of Dr James Bedford, RMH

Optimisation methods

Gradient descent

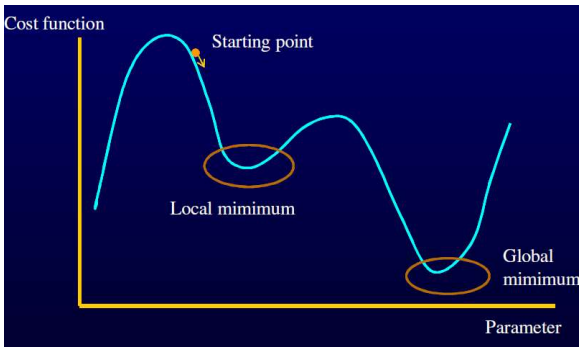
Only accepts parameter changes which reduce cost function

Simulated annealing

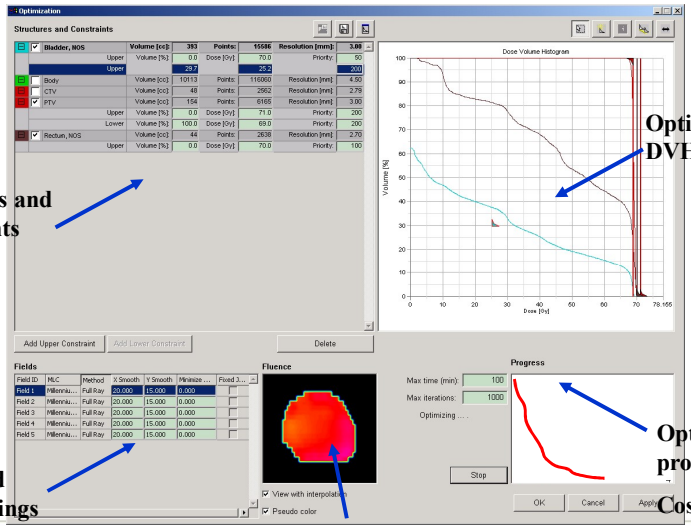
Will allow increases in cost function with reducing probability

The inverse problem

Gradient descent can end in a local minima, whereas simulated annealing will allow, some "uphill" – like running down a ski slope.



The inverse problem



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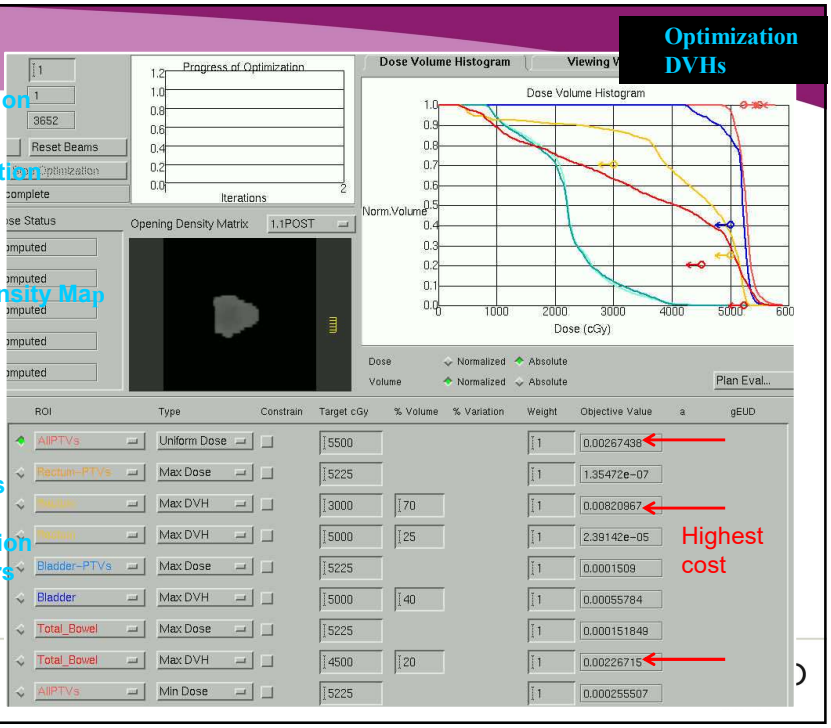
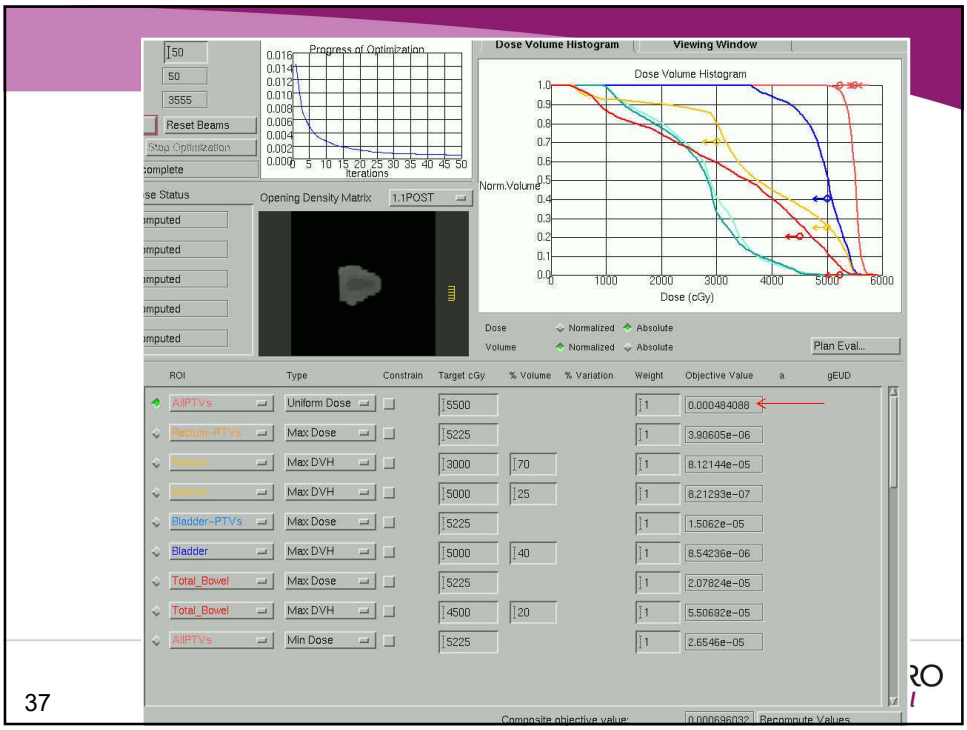
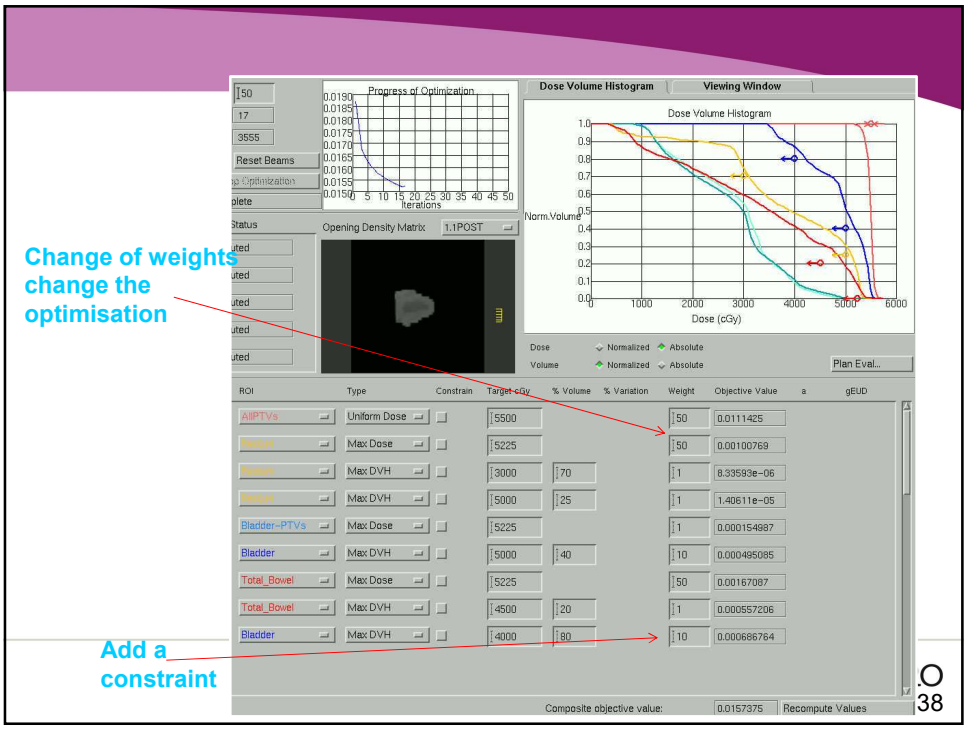


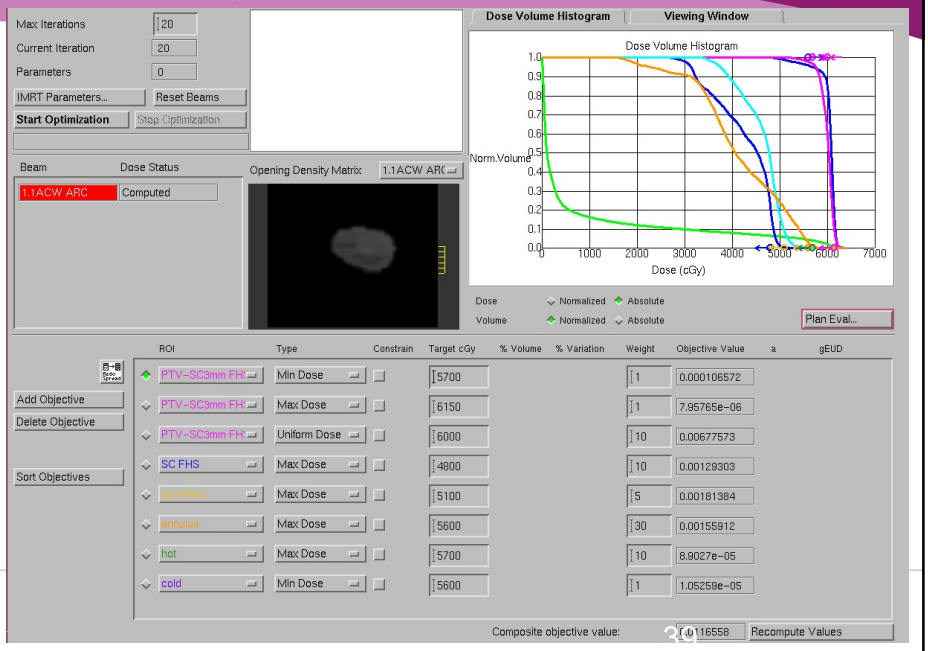

Progress of Optimization
Iterations
Dose Volume Histogram
Viewing Window
Dose Volume Histogram
Norm.Volume
Dose (cGy)
Reset Beams
Opening Density Matrix
1.1POST
Plan Eval...
ROI
Type
Constrain
Target cGy
% Volume
% Variation
Weight
Objective Value
a
gEUD
AllPTVs
Uniform Dose
5500
0.000484088
Max Dose
5225
3.90605e-06
Max DVH
3000
70
8.12144e-05
5000
25
8.21293e-07
Bladder-PTVs
1.5062e-05
Bladder
40
8.54236e-06
Total_Bowel
2.07824e-05
4500
20
5.50692e-05
Min Dose
2.6546e-05
Recompute Values

37


Change of weights change the optimisation
Add a constraint
Progress of Optimization
Iterations
Dose Volume Histogram
Viewing Window
Dose Volume Histogram
Norm.Volume
Dose (cGy)
Reset Beams
Opening Density Matrix
1.1POST
Plan Eval...
ROI
Type
Constrain
Target cGy
% Volume
% Variation
Weight
Objective Value
a
gEUD
AllPTVs
Uniform Dose
5500
0.0111425
Max Dose
5225
0.00100769
Max DVH
3000
70
8.33593e-06
5000
25
1.40611e-05
Bladder-PTVs
0.000154987
Bladder
40
0.000495085
Total_Bowel
0.00167087
4500
20
0.000557206
4000
80
0.000686764
Composite objective value:
0.0157375
Recompute Values

38

SMARTARC, VMAT – same optimisation window as IMRT



Potential of beam angle optimization?

1. Decision about the number of beams by a radiation oncologist
2. Automated optimization of beam orientations

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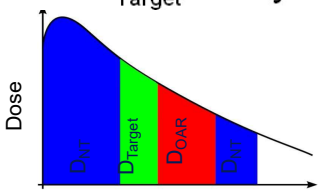
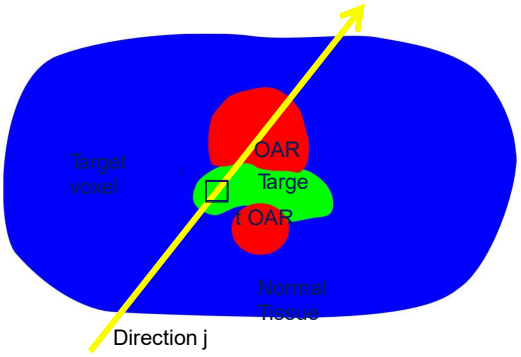
Beam angle optimization with a patient specific score for every target voxel…

$$s = \frac{D_{NT} + 100 \cdot D_{OAR}}{D_{Target} + 1Gy \cdot m}$$





By computing the score for a set of candidate directions, the ideal irradiation angle for target voxel i is defined as the direction with the minimum score.

Courtesy of Uwe Oelfke

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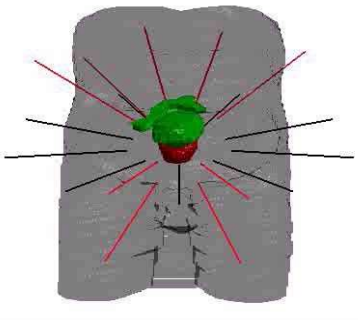
Treatment plan comparison for a prostate lesion – 9 coplanar equi-spaced beams versus 9 non-coplanar beams



- 9 coplanar equi-spaced beams
- 9 optimized beams

Courtesy of Uwe Oelfke

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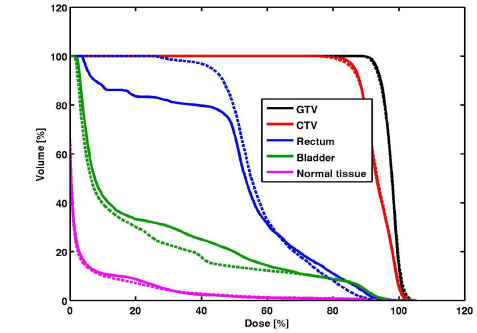
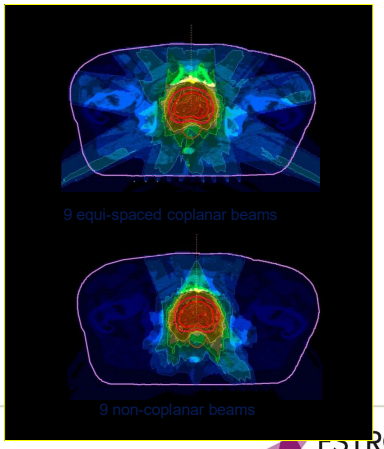
Treatment plan comparison for a prostate lesion – 9 coplanar equi-spaced beams versus 9 non-coplanar beams



Solid lines: 9 coplanar equi-spaced beams Dashed lines: 9 optimized beams



Courtesy of Uwe Oelfke

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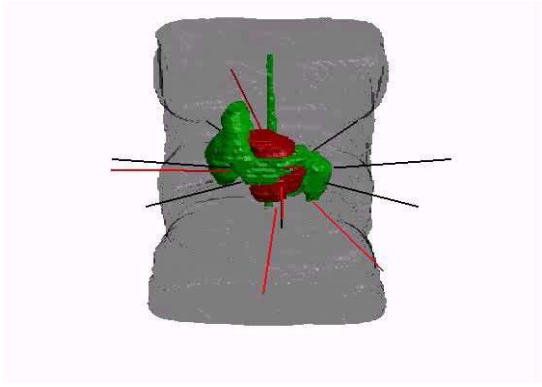
Treatment plan comparison for an abdominal lesion – 7 coplanar equi-spaced beams versus 5 non-coplanar beams



- 7 coplanar equi-spaced beams
- 5 optimized beams

Courtesy of Uwe Oelfke

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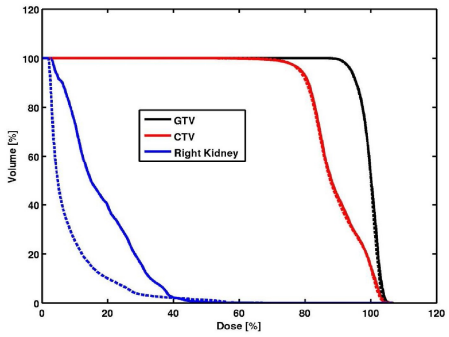
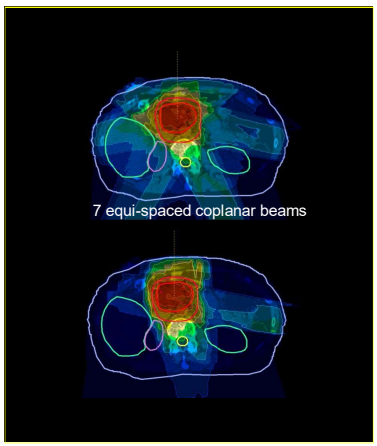
Treatment plan comparison for an abdominal lesion – 7 coplanar equi-spaced beams versus 5 non-coplanar beams

While non-co-planar beams do offer improvement in dose distributions, Delivery times with standard linacs needs to be considered



Solid lines: 7 coplanar equi-space d beams
Dashed lines: 5 optimized beams



5 non-coplanar beams

Courtesy of Uwe Oelfke

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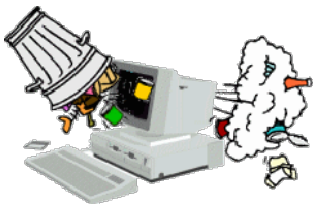
The inverse problem

Factors Affecting Optimization Results

- Number of beams
- Beam orientation



- Optimization parameter and dose constraints
- Optimization algorithm and objective function
- Experience is gold!

•Planning studies are a good way of gaining experience.

Experience can be fed into "Class solutions" or automated planning

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Summary on inverse optimisation

- Inverse planning means DVH or biological optimisation according to clinically motivated constraints
- Constraints are expressed by the objective function
- Optimisation is achieved with fast gradient algorithms if beam directions are pre-selected

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Knowledge based solutions

- Practical problem: Planning is time consuming
- Knowledge based planning: Use your previous planning expereince and start with a very good initial plan
- Based on achieved DVH from a library of plans (already done)

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Knowledge based planning

Evaluation of a Knowledge-Based Planning Solution for Head and Neck Cancer

Jim P. Tol, MSc, Alexander R. Delaney, BSc,

Max Dahele, et al, VU University Medical Center, Amsterdam, The Netherlands

Int J Radiation Oncol Biol Phys, Vol. 91, No. 3, pp. 612e620, 2015

RapidPlan knowledge-based treatment plans were comparable to CP if the patient's OAR-planning target volume geometry was within the range of those included in the models.

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Class Solutions or Automatic planning

- Practical problem: Planning is time consuming
- For a given tumor site (i.e. prostate or H&N) a
  - class solution‘ includes:
    - fixed dose prescriptions
    - initial values for all parameters that define the objective function
    - Define their relative importance
    - E.g. for H&N
      - Sparing of Spinal cord and Brain stem
      - PTV coverage
      - Parotid sparing
      - Larynx sparing
      - Oral cavity sparing

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Class Solutions

Class solutions depend on and are specific to:

- Clinical cases of similar irradiation geometries
- Your clinical goals
- Your treatment planning system
- Dose delivery method (practical constraints)

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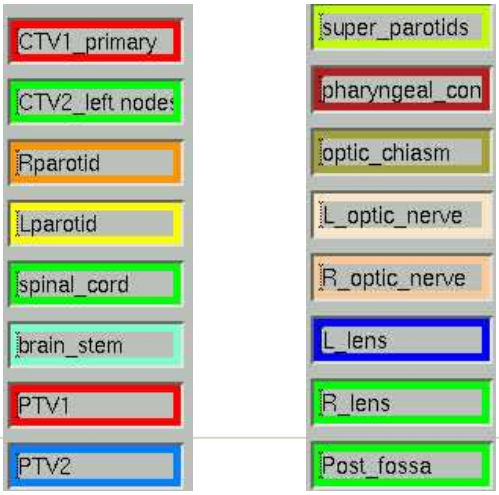
RMH experience for class solutions for H&N

First ensure that the clinicians use a pre-defined script for naming all structures



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Standardizing Naming Conventions in Radiation Oncology

L Santanam et al.

International Journal of Radiation Oncology biology physics pp 1344-49 **83** ,4 2012

Standard names	Description	Standard names	Description
AnalCanal	Anal Canal	**Esophagus_Middle**	**Middle Esophagus**
A_Pulmonary	**Pulmonary Artery**	External	Skin
A_Carotid	**Carotid Artery**	**Eye**	**Eye**
A_Brachiocephali	**Brachiocephalic Artery**	Femur	Femur
A_Coronary	**Coronary Artery**	**FemoralJoint**	**Femoral Joint**
A_Subclavicular	**Subclavicular Artery**	**FrontalLobe**	**Frontal Lobe**
A_Hypophyseal	**Hypophyseal Artery**	**GHJoint**	**Glenohumeral Join**
Aorta	**Aorta**	Globe	Eye Globe
AnalSphincter	**Anal Sphincter**	Glottis	Glottis
Atrium	**Atrium**	GreatVessel	Great Vessel
Bladder	Bladder	Heart	Heart
BladderWall	**Bladder Wall**	**Hippocampus**	**Hippocampus**
BrachialPlexus	Brachial Plexus	**Hypothalamus**	**Hypothalamus**
Brain	Brain	Kidney	Kidney
BrainStem	Brain Stem	LargeBowel	Large Bowel
Breast	Breast	Larynx	Larynx
BronchialTree	Bronchial Tree	LacrimalGland	Lacrimal Gland
BaseOfTongue	**Base of Tongue**	Lens	Eye Lens
Carina	Carina	Lips	Lips
CaudaEquina	Cauda Equina	Liver	Liver
Cerebellum	Cerebellum	Lung	Lung
Cerebrum	Cerebrum	Mandible	Mandible
Chiasm	Optic Chiasm	**MassMuscle**	**Masseter Muscle**
CN_VII	Seventh Cranial Nerve	**Mediastinum**	**Mediastinum**
CN_VIII	Eighth Cranial Nerve	MainBronchus	Main Bronchus
Cervix	**Cervix**	**OccipitalLobe**	**Occipital Lobe**
Cochlea	Cochlea	OpticNerve	Optic Nerve
Colon	**Colon**	OralCavity	Oral Cavity
ConstrMuscle	**Constrictor Muscle**	Ovary	Ovary
Cornea	Cornea	**Parametrium**	**Parametrium**
Duodenum	Duodenum	**ParietalLobe**	**Parietal Lobe**
Ear_Middle	Middle Ear	**Pancreas**	**Pancreas**
Ear_External	External Ear	Parotid	Parotid
Esophagus	Esophagus	**PelvicBones**	**Pelvic Bones**
Esophagus_Upper	**Upper Esophagus**	PenileBulb	Penile Bulb
Esophagus_Lower	**Lower Esophagus**	**Penis**	**Penis**

Perineum	Perineum
Pericardium	**Pericardium**
Pharynx	Pharynx
PharynxConst	**Pharyngeal Constricto**
Pituitary	Pituitary
Prostate	Prostate
PubicSymphysis	**Pubic Symphysis**
Rectum	Rectum
RectalWall	**Rectal Wall**
Retina	Retina
Rib	Rib
Sacrum	Sacrum
SalivaryGland	**Salivary Glands**
SeminalVesicle	Seminal Vesicle
SmallBowel	Small Bowel
SpinalCord	Spinal Cord
Spleen	**Spleen**
Stomach	Stomach
Submandibular	Submandibular Gland
Supertentorial	**Supertentorial**
TemporalLobe	Temporal Lobe
Testis	Testis
Thyroid	Thyroid
TMjoint	Temperomandibular Joi
Trachea	Trachea
Tongue	Tongue
Urethra	Urethra
Uterus	**Uterus**
V_Azygos	**Azygos Vein**
V_CavaInferior	**Inferior vena cava**
V_CavaSuperior	**Superior vena cava**
V_Pulmonary	**Pulmonary Vein**
V_SubClav	**SubClavicular Vein**
Vagina	**Vagina**

RMH experience for class solutions for H&N

Planning ”HELP” structures

Run script to

create Body contour

PTV with appropriate margins

Create margins on OAR,

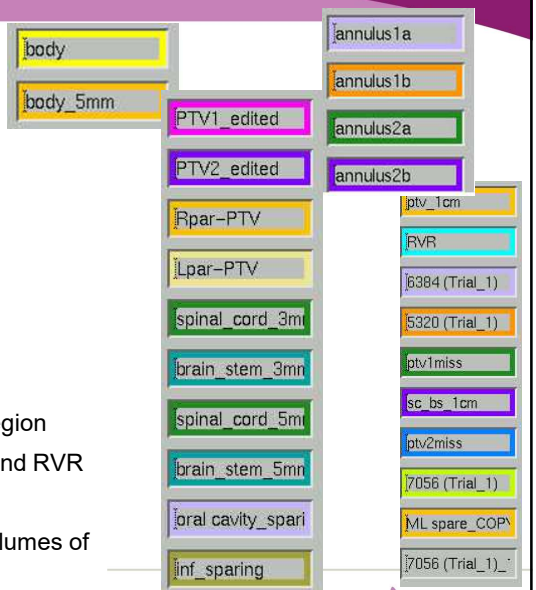
Create volumes for optimisation:

OAR – excluding PTV

“edited PTV” to exclude build-up region

Create rings / annuli around PTV and RVR

After some optimisations create volumes of hot and/ or cold spots



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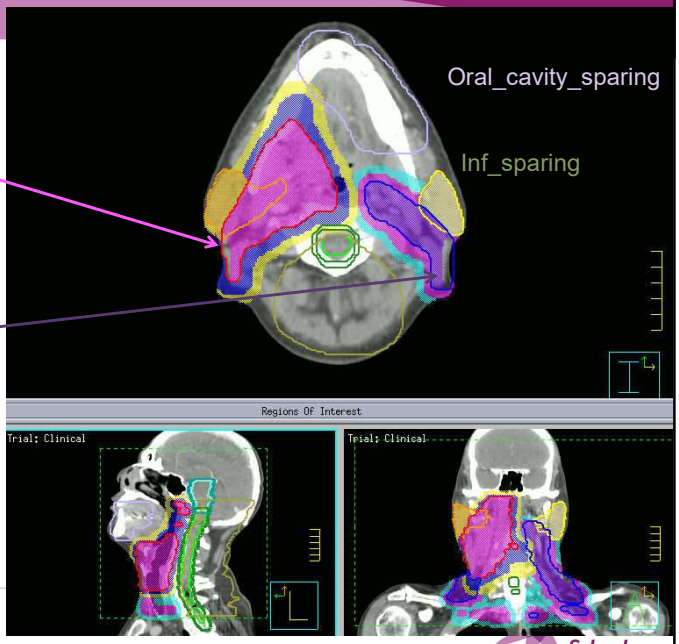
H&N outlines

PTV1
PTV1_edited
Rparotid
Rpar-PTV

PTV2
PTV2_edited
Annulus1a
Annulus1b
Annulus2a
Annulus2b
spinal_cord
spinal_cord_3mm
spinal_cord_5mm

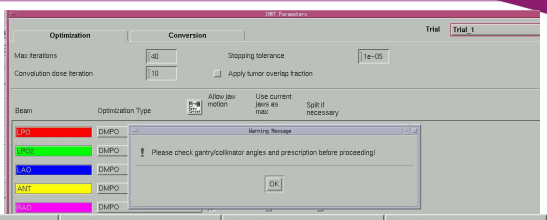


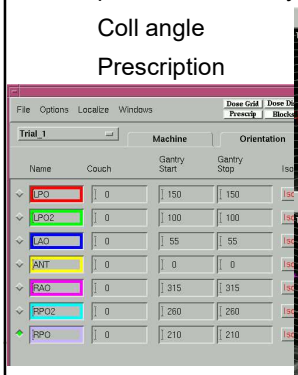
School

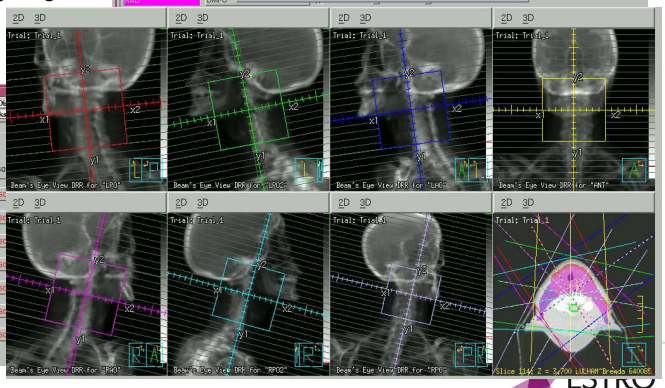
RMH experience for class solutions for H&N

Run script to set up beams

Class solution is 7 fields,
pre-defined Gantry angles
Coll angle
Prescription







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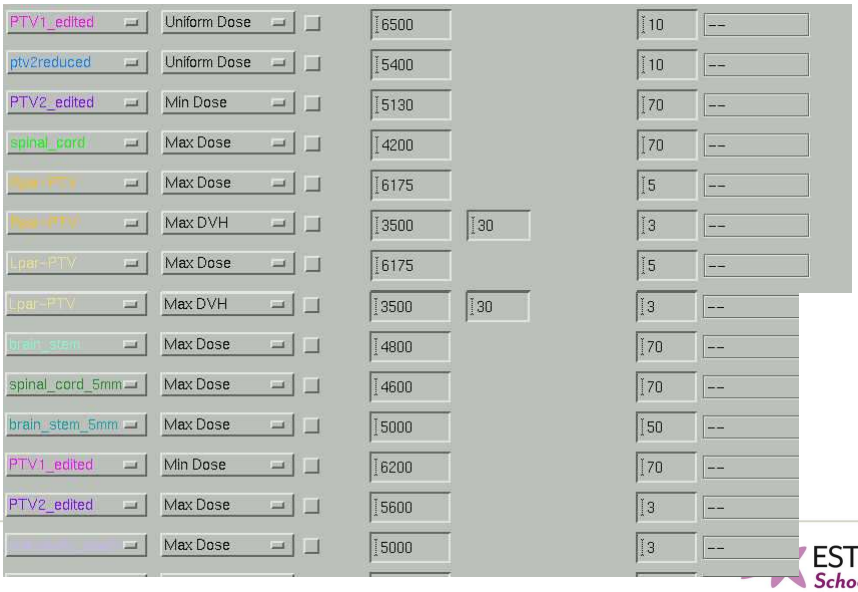
RMH experience for class solutions for H&N

Run protocol for all optimisation parameters:



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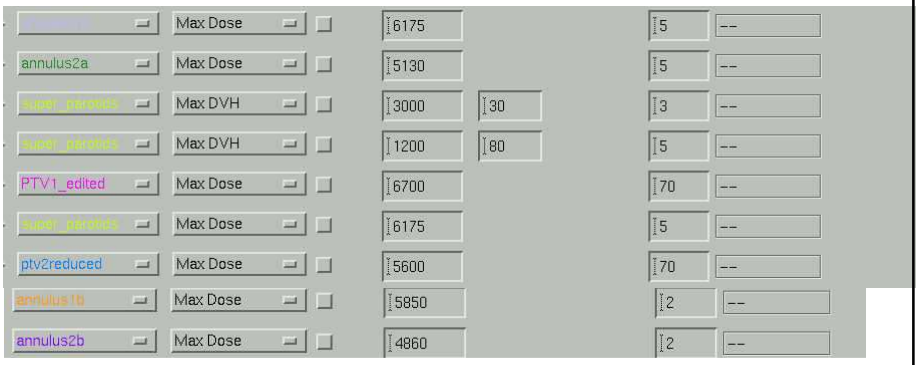
More Optimisation creteria:



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Check the plan – does it meet your clinical dose constraints?

Run scripts to check if all dose constraints are met

ROI	Dose Statistic Type	Value	Unit		Constraints Opt	Rqd	Result	Unit
Primary PTV 65GY								
PTV1	D	99	%	>	58.5		61.1	Gy
PTV1_edited	D	99	%	>		58.5	61.1	Gy
PTV1	D	95	%	>	61.8		62.8	Gy
PTV1_edited	D	95	%	>		61.8	62.8	Gy
PTV1	D	50	%	=	65+/-1		65.3	Gy
PTV1_edited	D	50	%	=		65+/-1	65.3	Gy
PTV1	D	5	%	<	68.2		66.8	Gy
PTV1_edited	D	5	%	<		68.2	66.8	Gy
PTV1	D	2	%	<	69.5		67.1	Gy
PTV1_edited	D	2	%	<		69.5	67.1	Gy
Nodal PTV 54GY								
PTV2	D	99	%	>	48.6		45.6	Gy
PTV2_edited	D	99	%	>		48.6	51.0	Gy
PTV2	D	95	%	>	51.3		50.9	Gy
PTV2_edited	D	95	%	>		51.3	52.2	Gy
PTV2	D	50	%	=	54+/-1		54.1	Gy
PTV2_edited	D	50	%	=		54+/-1	54.2	Gy
ORGANS AT RISK								
Rparotid	Mean			<	24	30	32.1	Gy
Ipsilateral Parotid/Contralateral Parotid	(please indicate)							
Lparotid	Mean			<	24	30	33.6	Gy
Ipsilateral Parotid/Contralateral Parotid	(please indicate)							

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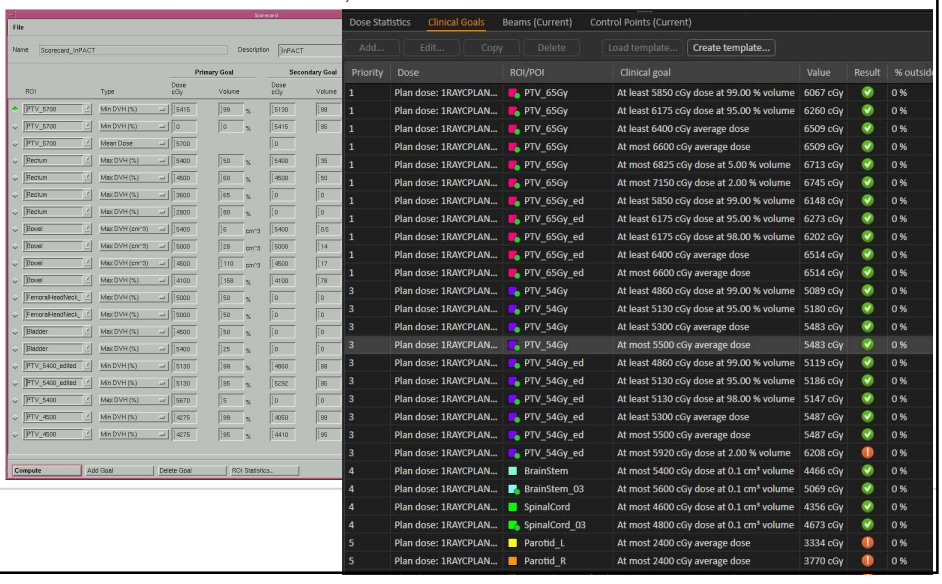
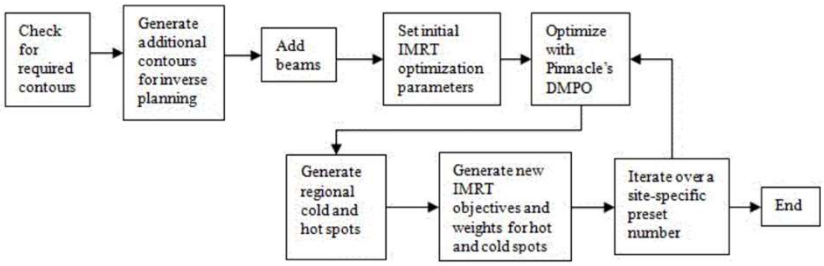
Check the plan – does it meet your clinical dose constraints?

We have been calling these dose stat checks, but manufacturers calls it “Dose score cards”, or “Clinical Goals”



JOURNAL OF APPLIEDCLINICAL MEDICAL PHYSICS, 14, 2013
Automated IMRT planning with regional optimization using planning scripts
Ilma Xhaferllari, Eugene Wong, Karl Bzdusek, Michael Lock, and Jeff Z. Chen



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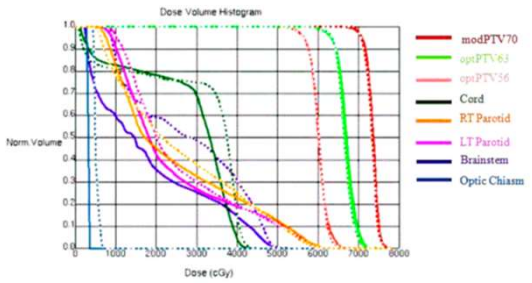
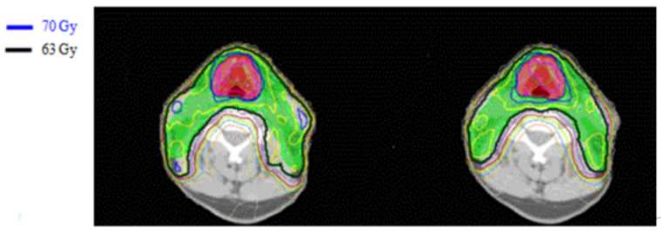
Xhaferllari et al.





Manually generated plan Automatically generated plan

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Xhaferllari et al

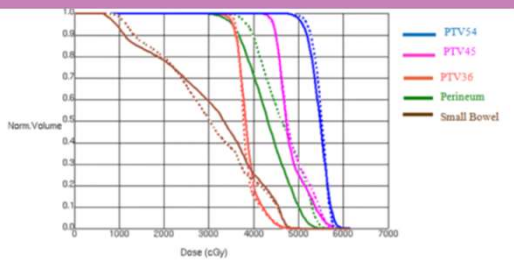
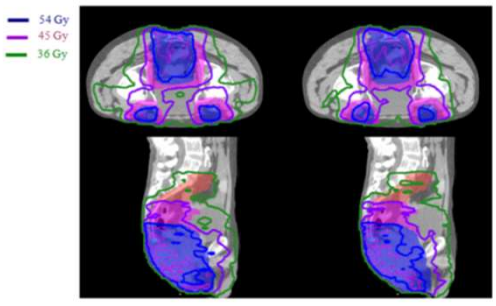


Fig. 7. DVH comparison for an anal canal irradiation between manually (dashed line) and automatically generated IMRT plans (solid line).



Manually generated plan Automatically generated plan

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Automatic planning of head and neck treatment plans

26 prev treated H&N plans were re-planned using the Automatic planning.

The user can define the following parameters in a Technique:

- Derived regions of interest (ROIs) (e.g., PTV or expanded cord)
- - Prescriptions
- Beam geometries, settings, and optimization options
- Prioritized optimization goals

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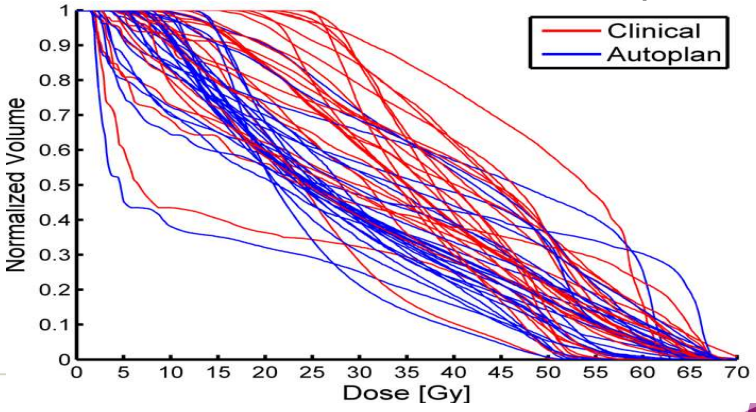
All plans were clinically acceptable and 94% of cases scored higher or equal to clinical plans by two blinded senior clinicians.

PTV mean and coverage was similar.

For nodal PTV the stdev was lower for the automatic plan.



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	Clinical	*Auto*	*p*
	Spinal Cord		
Mean (Gy)	26.03±5.13	21.13±4.55	**<0.001**
Max (Gy)	42.35±1.56	39.60±3.62	**<0.001**
$D_{2\%}$ (Gy)	40.50±1.45	36.23±3.60	**<0.001**
V_{35Gy}	0.46±0.19	0.09±0.10	**<0.001**
	Submandibular Contralateral		
Mean (Gy)	47.33±7.66	40.41±6.87	**<0.001**
V_{30Gy}	0.94±0.20	0.79±0.19	**<0.001**
V_{39Gy}	0.85±0.25	0.56±0.21	**<0.001**
V_{60Gy}	0.08±0.16	0.05±0.12	0.074
	Submandibular Ipsilateral		
Mean (Gy)	57.62±6.78	54.54±9.18	**0.001**
V_{30Gy}	0.99±0.03	0.92±0.11	**<0.001**
V_{39Gy}	0.94±0.12	0.84±0.20	**<0.001**
V_{60Gy}	0.53±0.33	0.49±0.30	0.072
	Parotid Contralateral		
Mean (Gy)	30.48±5.71	26.55±4.02	**<0.001**
V_{5Gy}	0.96±0.07	0.94±0.08	**0.033**
V_{26Gy}	0.60±0.19	0.46±0.11	**<0.001**
V_{35Gy}	0.42±0.16	0.30±0.12	**<0.001**
	Parotid Ipsilateral		
Mean (Gy)	35.54±6.84	29.73±5.57	**<0.001**
V_{5Gy}	0.96±0.09	0.94±0.12	**0.007**
V_{26Gy}	0.71±0.19	0.51±0.11	**<0.001**
V_{35Gy}	0.52±0.16	0.37±0.12	**<0.001**

Hazell et al

JOURNAL OF APPLIED CLINICAL MEDICAL PHYSICS, VOLUME 17, 2016

IMRT Class solutions and automatic planning, summary

Class solutions are specific to clinical sites, and prescriptions

Class solutions are based on experience, clinical goals and may need adaptation

Automatic planning builds on class solutions

In many situations IMRT is being replaced by VAMT

Class solutions are still required for the optimisation parameters for VMAT

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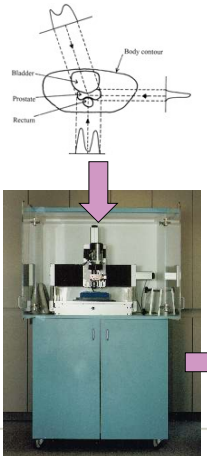
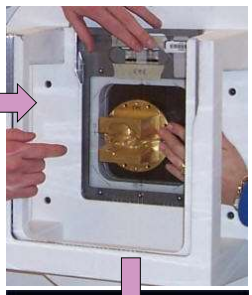
IMRT delivery methods

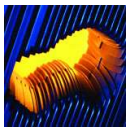
IMRT with compensators

Treatment plan





IMRT delivery methods using MLC



Static

beam off during leaf/gantry/couch motion

slower, simpler

Dynamic

beam on during leaf motion , per beam

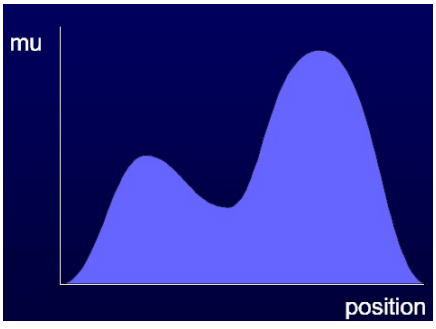
faster, less efficient per MU, more complicated to check dose

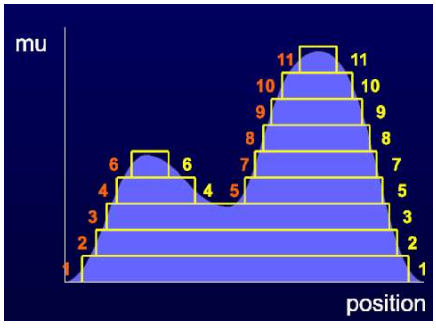
Dynamic VMAT

beam on during leaf/gantry motion

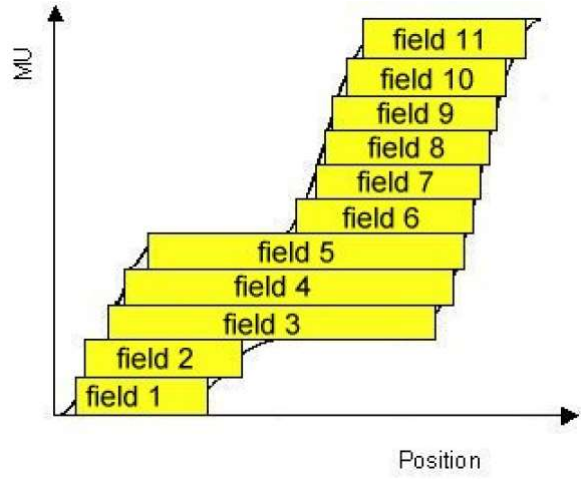
faster, more complicated to check dose

SMLC – close-in sequence



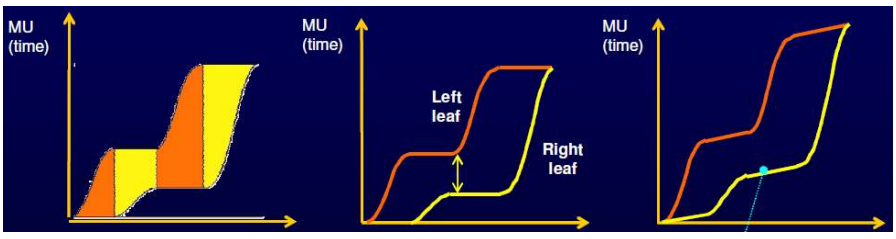


SMLC – leaf sweep technique



Dynamic MLC fields

MLC leaves and possibly also collimator jaws move during irradiation, scanning a variable –width aperture



Distance between curves represents intensity level

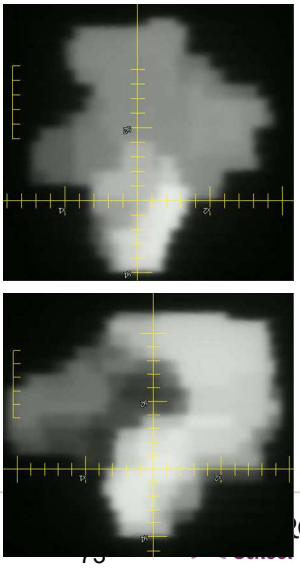
Minimum gradient needed equal to maximum MLC leaf speed

IMRT fields = 2D modulation

Could (potentially) consider each leaf pair separately

Preferable to consider 2D matrix and group leaves

- maximise segment area
- minimise number of segments



IMRT delivery methods

Dynamic

More versatile - more intensity levels

Faster overall treatment time - beam stays on

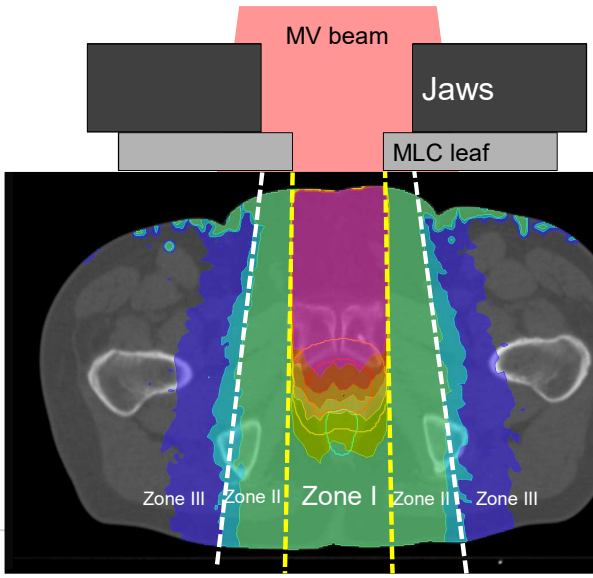
Smooth transition - but depends on leaf speed

MU efficiency lower

Gantry rotation

VMAT/ RapidArc

MU efficiency and leakage



Exposure outside beam aperture

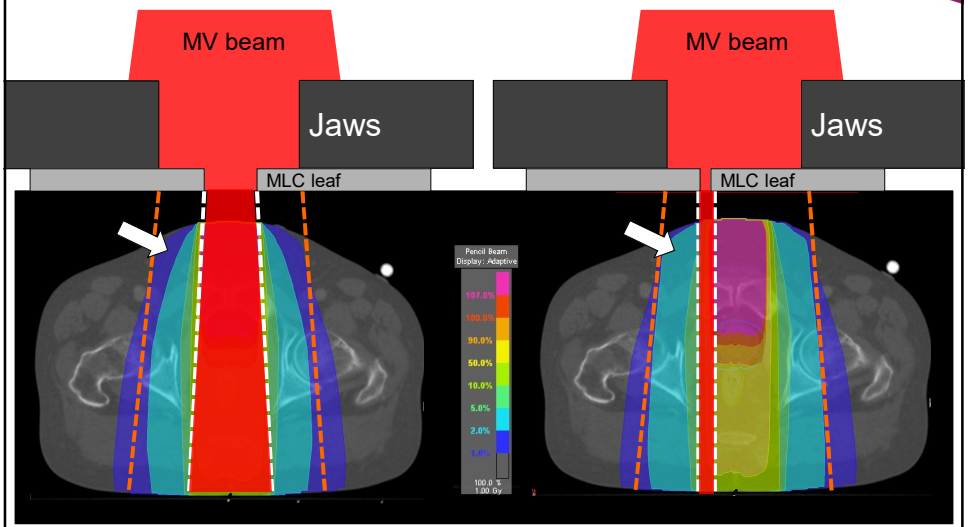
Head/Jaw leakage 0.1%
MLC leakage 0.5% to 3%

Zone I: Primary beam
"**Wanted** dose" to target
"**Unwanted** dose" to healthy tissue and OAR in the beam path

Zone II: MLC/Collimator Leakage + scatter
"**Unwanted** dose"

Zone III: Linac head leakage + scatter
"**Unwanted** dose"

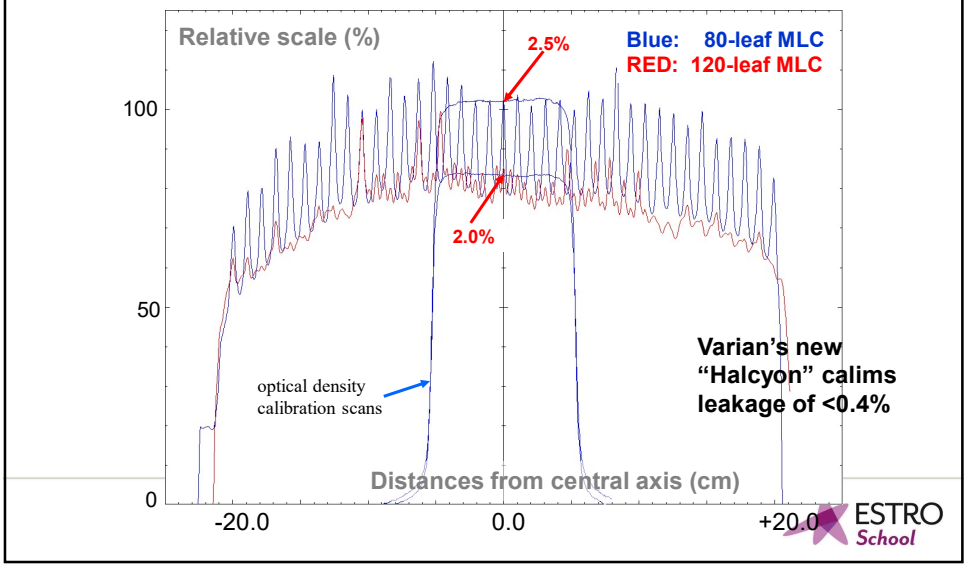
MU efficiency and leakage



Open beam: 140 MU

Sliding window (1 cm): 680 MU

Varian leakage: comparison between 120- and 80-leaf MLCs



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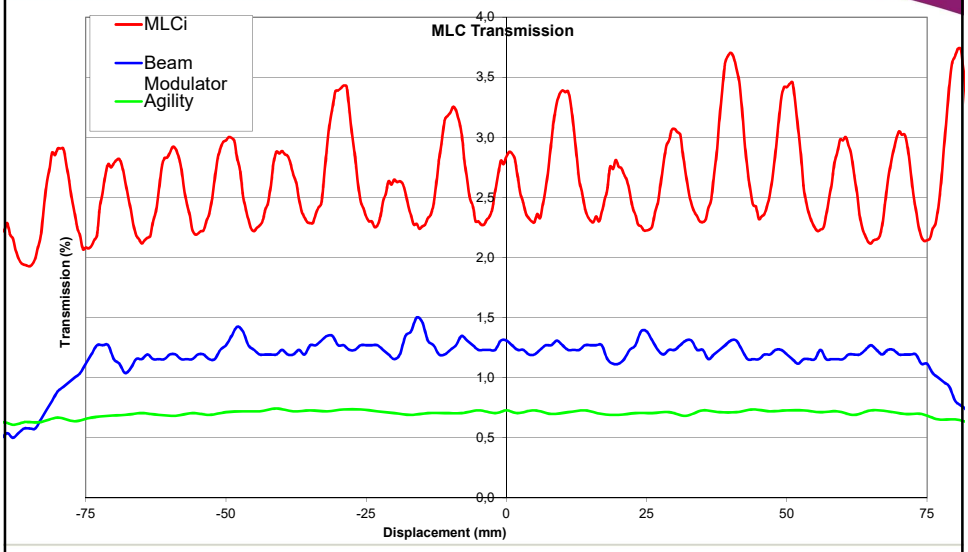
Elekta leakage: comparison between MLCi, Beam Modulator and Agility



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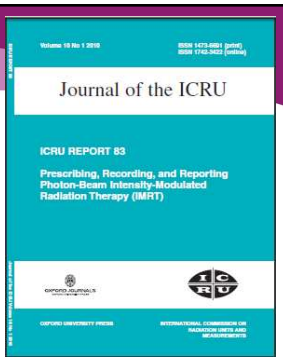
IMRT quality assurance

Machine related QA:

- Small field effects
- Small number of monitor units
- Tongue and groove effects
- Verify Leaf Positions
- Output tolerance tighter
- Isocenter, mechanical tolerance tighter (smaller target)
- Dosimetric accuracy

- Immobilization

ICRU 83
Patient specific QA A.2.3



Individual beams

No agreement on pass–fail criteria for the gamma value

Absorbed dose in Phantom

Dosimetric accuracy of 5%

Independent absorbed-dose calculation

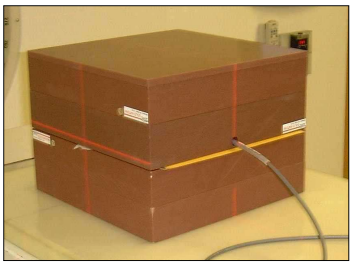
The independent absorbed dose calculation must be able to compute the absorbed dose in 3D so that the calculation can be tested at a statistically relevant number of points

In vivo dosimetry

TLD, Diode, MOSFET, EPID Dosimetry

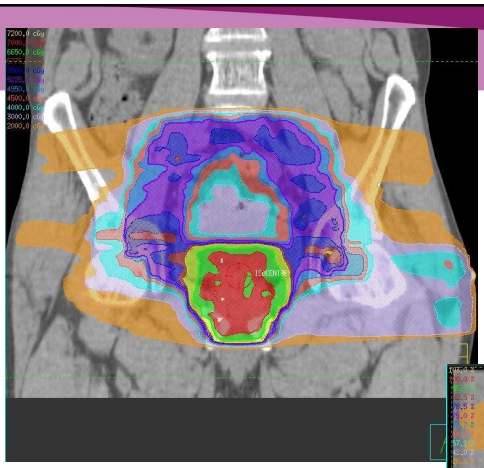
Creation of a phantom plan

In TPS there is a function to copy the IMRT plan to a phantom.

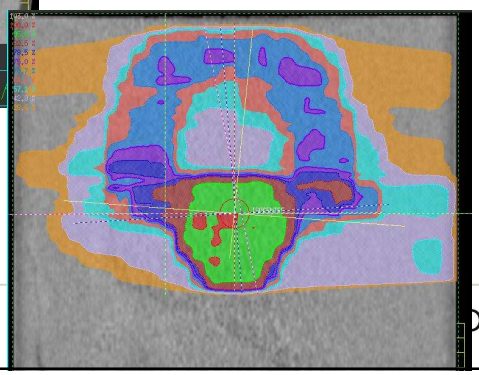


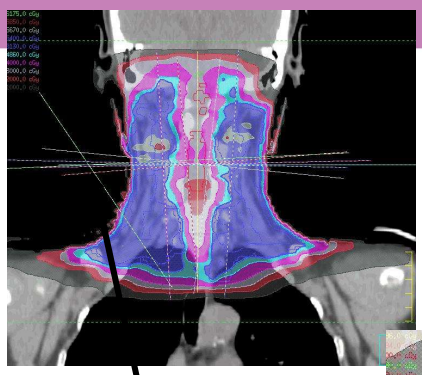
We use standard 30*30 cm water equivalent slabs of different heights

User sets the position of the isocentre

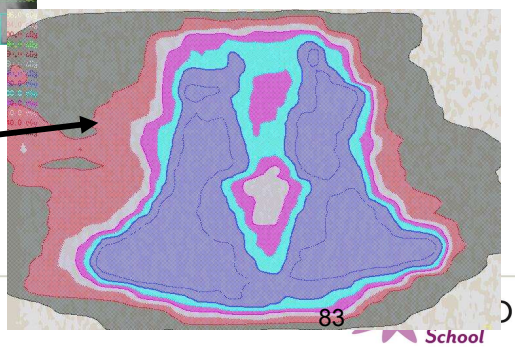


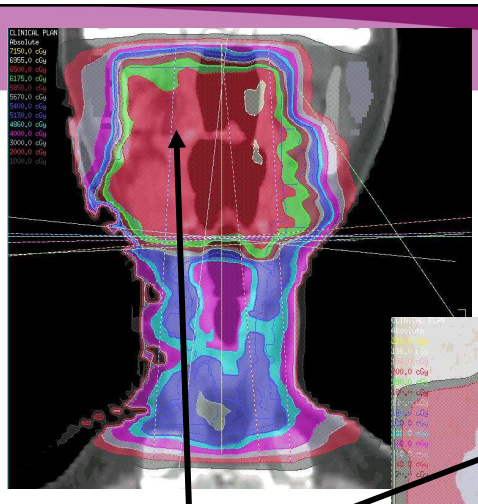
For Prostate and Pelvic node plans the Block phantom has very similar dose distribution as the patient plan



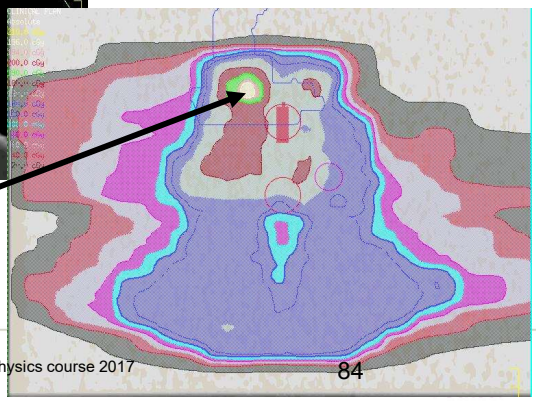


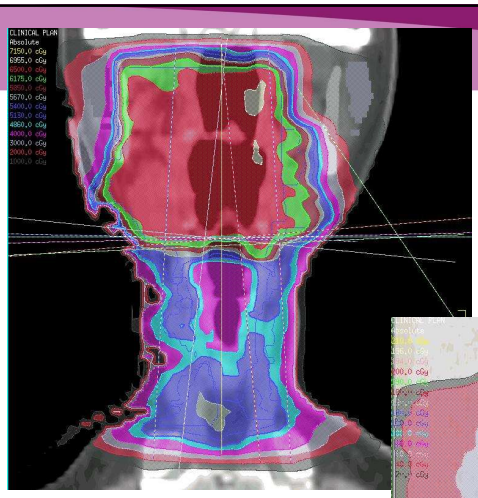
For Head and Neck plans the square block phantom differs in the dose distribution to the patient plan





Both outside the patient and often also in the high dose region due to the difference in shape and heterogeneity of the phantom and the patient

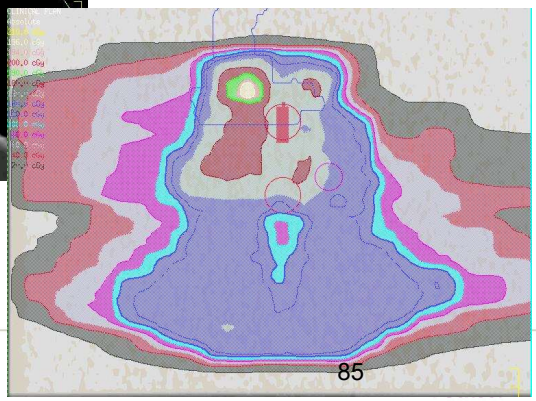




Dose homogeneity in high dose region

2.7% standard dev on Patient

16.0% Standard dev on Phantom

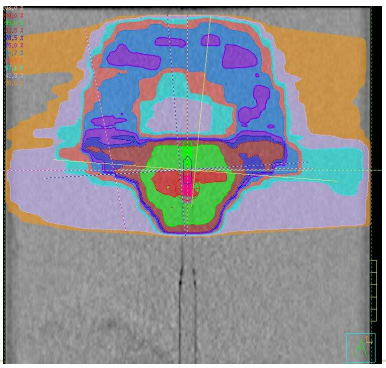


Ion chamber measurement

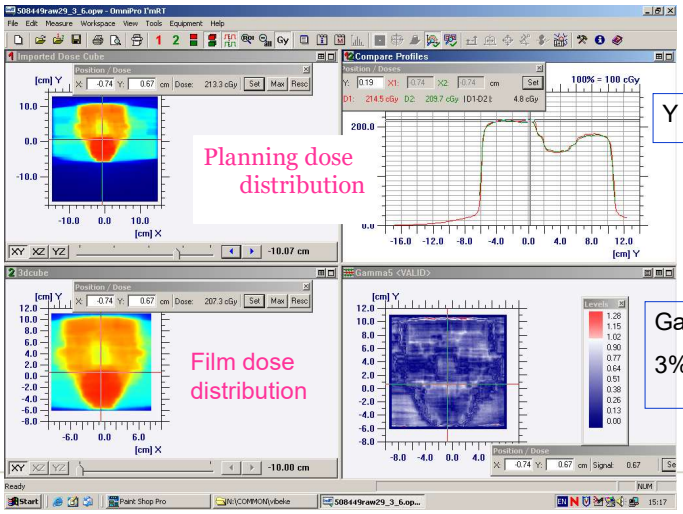
Gives instant result and provide absolute dose for a point.

Measure in high dose

Region



Prostate and pelvic nodes



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ScandiDos

Delta4 is a registered trademark of ScandiDos AB

Delta 4

ArcCHECK

More than 2D

–but not True 3D!

School

Ideally In-vivo dosimetry

Wait for the lecture on
In-Vivo Dosimetry ……..

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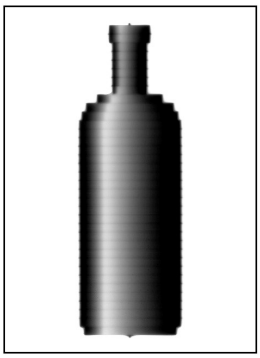
What IMRT can do……..



ABSOLUT DMLC.

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REFERENCES:

- ICRU 83, 2010
- IPEM report 96 “Guidance for the Clinical Implementation of Intensity Modulation Radiation Therapy”, 2008
- Estro Physics Booklets Booklet 9 Guide for the Verification of IMRT http://www.estro-education.org/publications/Documents/Booklet_n9_P3.pdf

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Thank you for your attention

Any questions?

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ESTRO Teaching Course on Physics for Clinical Radiotherapy, Bucharest 2017

IMRT
clinical application & impact

Stéphanie Peeters

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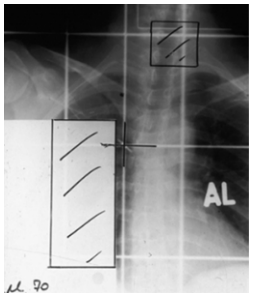
Challenge in Radiotherapy

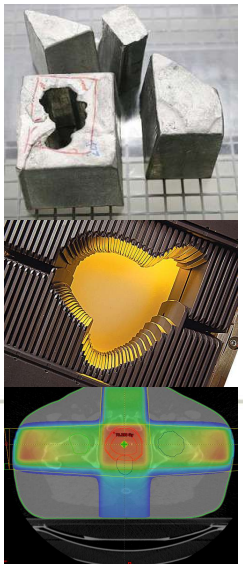
to create a dose distribution that closely conforms to the shape of the target volume in 3 dimensions to give a higher dose to the target, and/or lower doses to the surrounding normal tissues

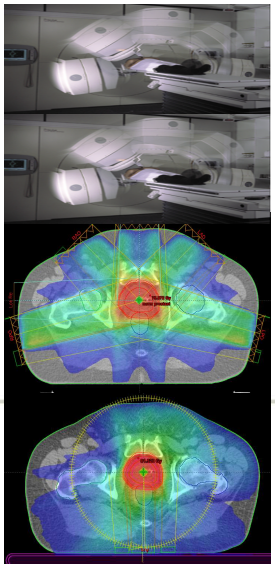
Evolution in radiotherapy

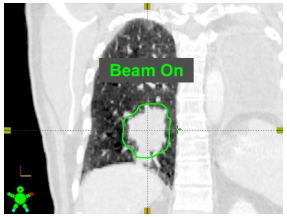
Personalized medicine

2D box | 2D Standard shielding | 3D individualized shielding | 3D Intensity-modulated/arc therapy | 4D Motion management | …









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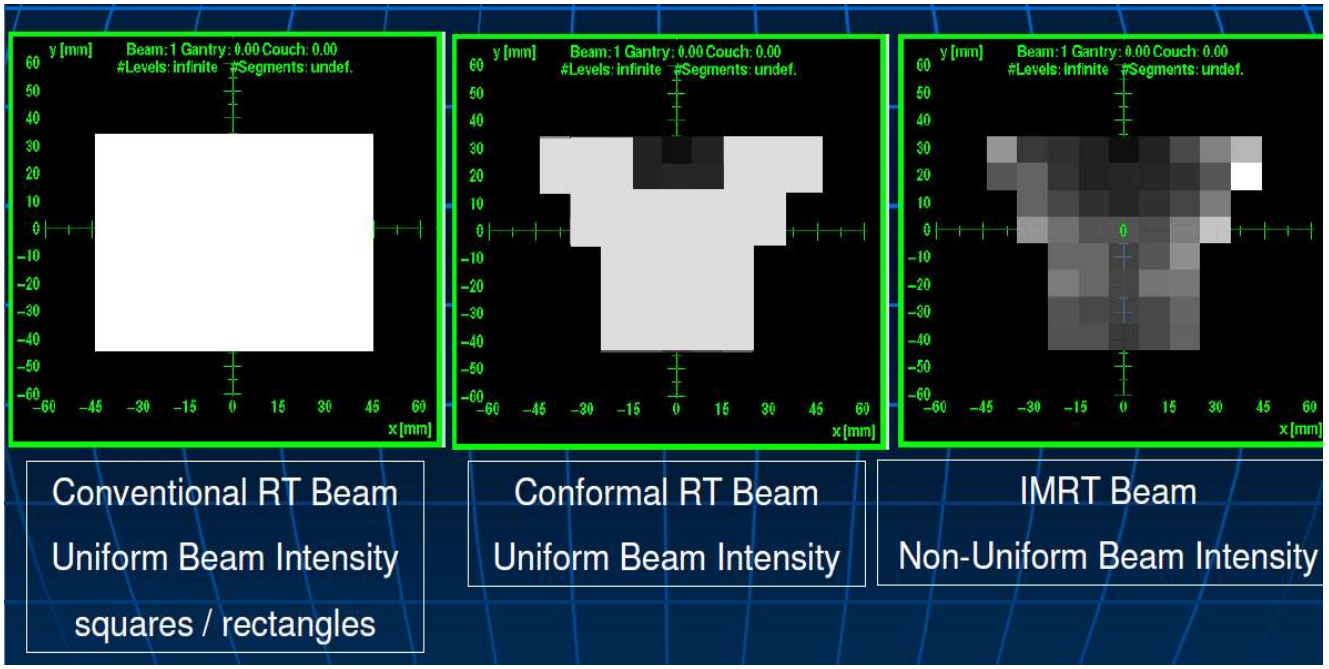
From 2D → 3D-CRT → IMRT

CT shielding

2D-RT 3D-CRT IMRT



Goal: Delivery of higher dose to the tumour and a lower dose to the OAR

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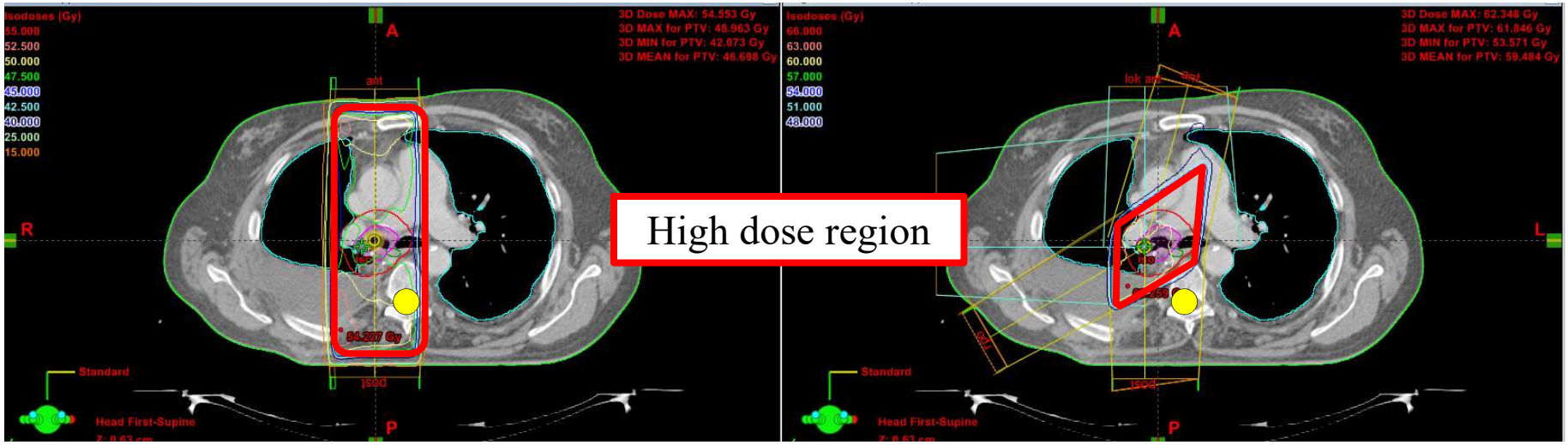
From 2D → 3D-CRT → IMRT



- 2D
- APPA
- PD max 50Gy/2Gy

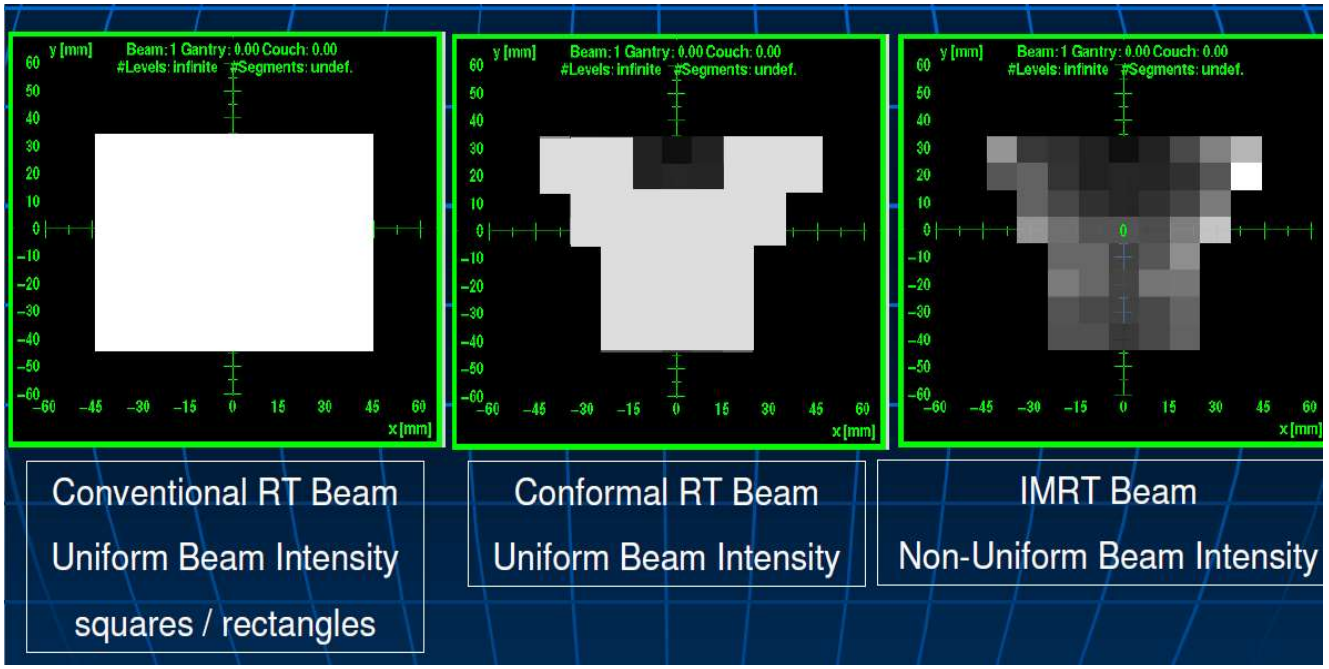
- 3D
- 3 fields
- PD > 50Gy/2Gy

From 2D → 3D-CRT → IMRT

CT shielding

MLC Inversed planning

2D-RT 3D-CRT IMRT



Goal: Delivery of higher dose to the tumour and a lower dose to the OAR

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Intensity-Modulated Radiotherapy

= advanced form of 3D-CRT

= use of **NON-uniform radiation beam fluence** profiles to better shape the dose distribution in the target and OAR

rotational treatments = further development of the IMRT concept

optimization = dialogue of coverage vs. constraints

Brahme et al.

- First paper on 'IMRT' 1982
- Inverse planning

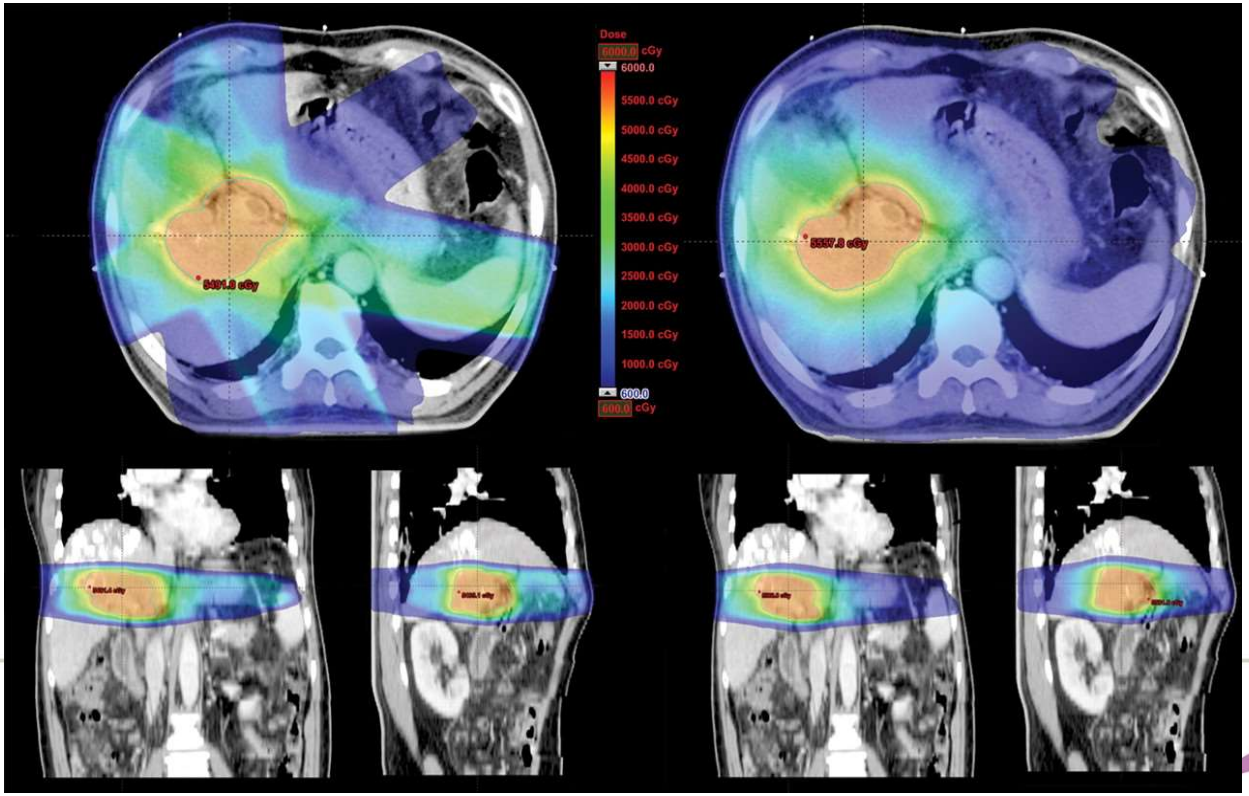
Intensity-Modulated Radiotherapy Delivery

"Classic" IMRT

- step and shoot
- sliding window

Rotational IMRT

- VMAT (Volumetric Arc Therapy)
- Tomotherapy (helical dose delivery)



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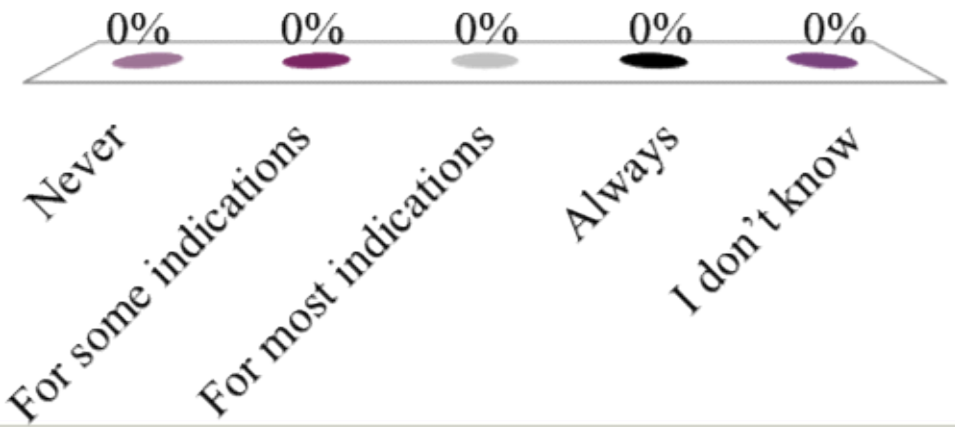
How often IMRT is used in your center?

A. Never
B. For some indications
C. For most indications
D. Always
E. I don’t know



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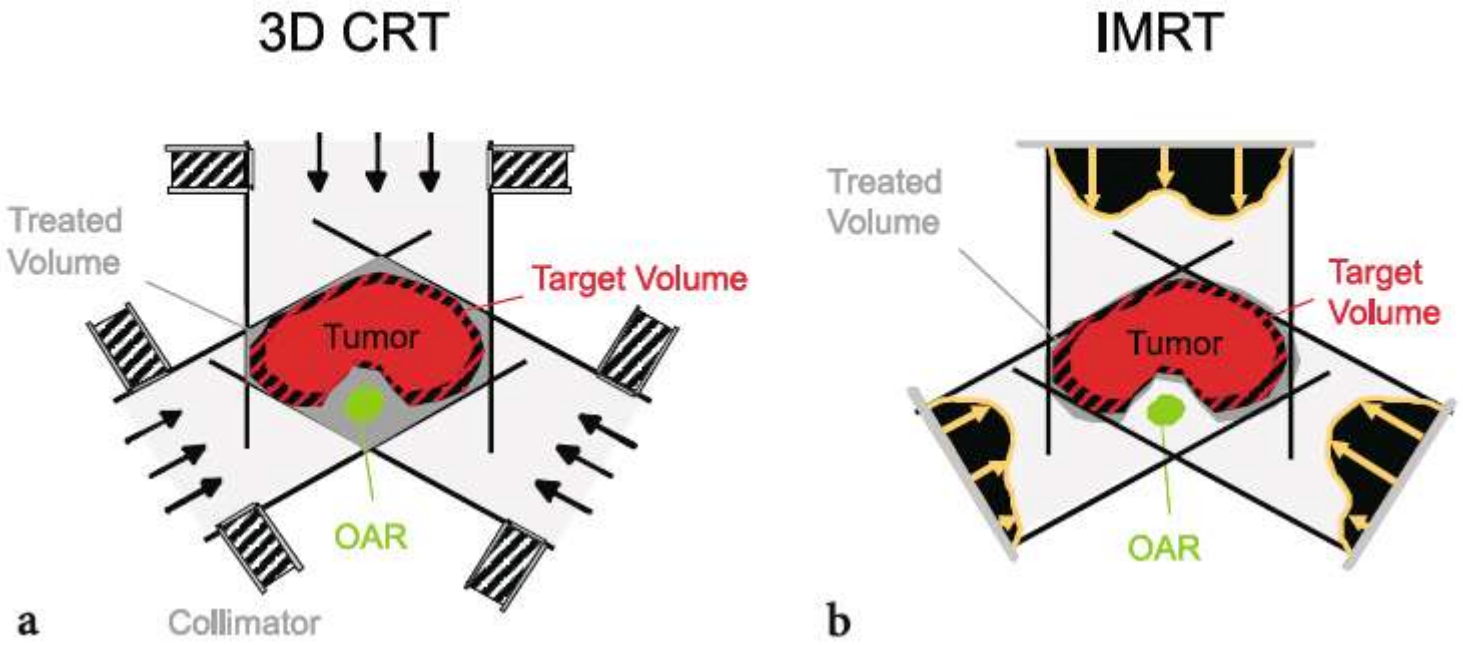
Overview

- Potential of IMRT
- Scientific evidence
- Potential risks of IMRT
- Cost
- Take home messages

Potential of IMRT

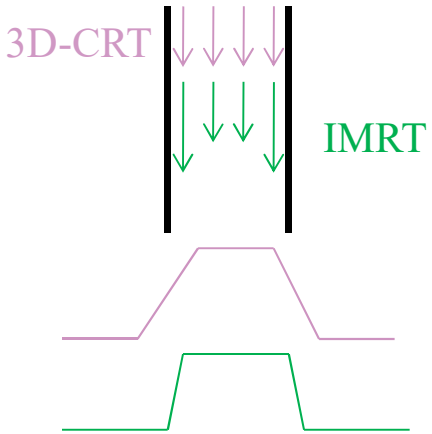
↑ conformality



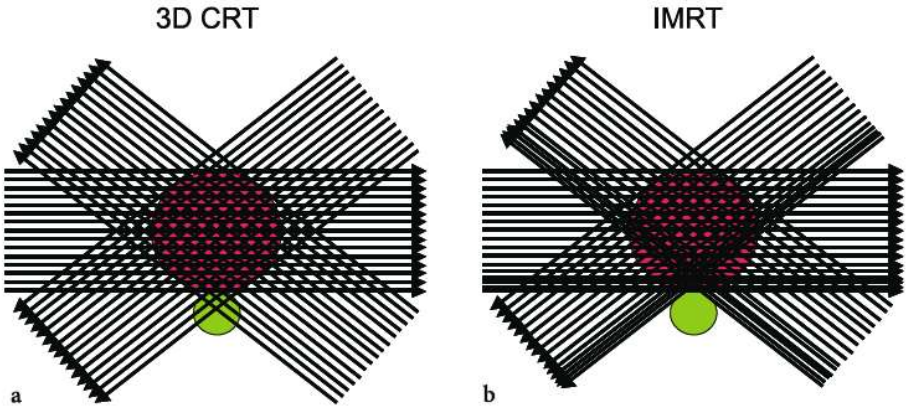
From: Image-Guided IMRT, T. Bortfeld, Springer

Potential of IMRT

Sharper dose fall-off



Compensation for the lateral disequilibrium by increasing boundary fluence



From: Image-Guided IMRT, T. Bortfeld, Springer

Potential of IMRT

Homogeneity

More homogeneous dose-distributions

- ~ Severity of constraints on OAR & proximity to PTV
- ~ Dose-escalation
- ~ Complexicity of anatomy
- ~ Number of beams

Clinically relevant?

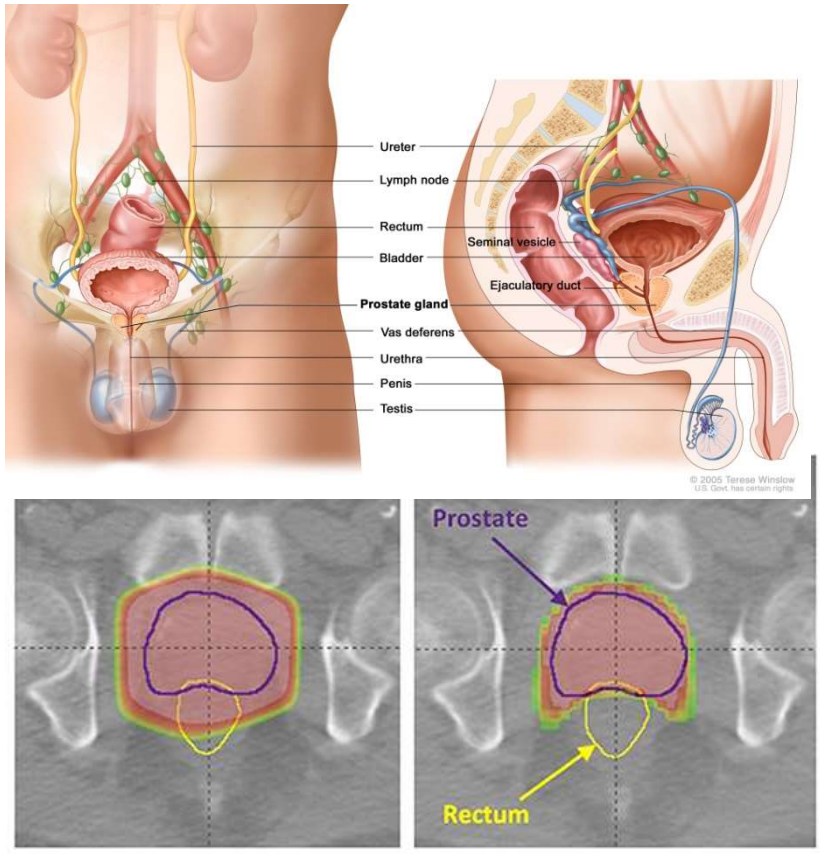
Homogeneity
Conformality
Steep dose gradient

Applications	Examples
I. Coverage of concave PTV with better sparing of OAR	prostate (rectum), head neck (spinal cord), pelvis
II. Better coverage of tumors near critical structures (also convex)	nasopharyngeal, prostate, head-neck cancer,...
III. Intentionally inhomogeneous dose distributions	SIB, multiple GTV/CTVs...
IV. Re-irradiation of locally recurrent tumors	spine, head-neck,...
V. Compensation of plans	brachytherapy

→ delivery of conventional doses with ↓ toxicity
→ delivery of higher doses without ↑ toxicity

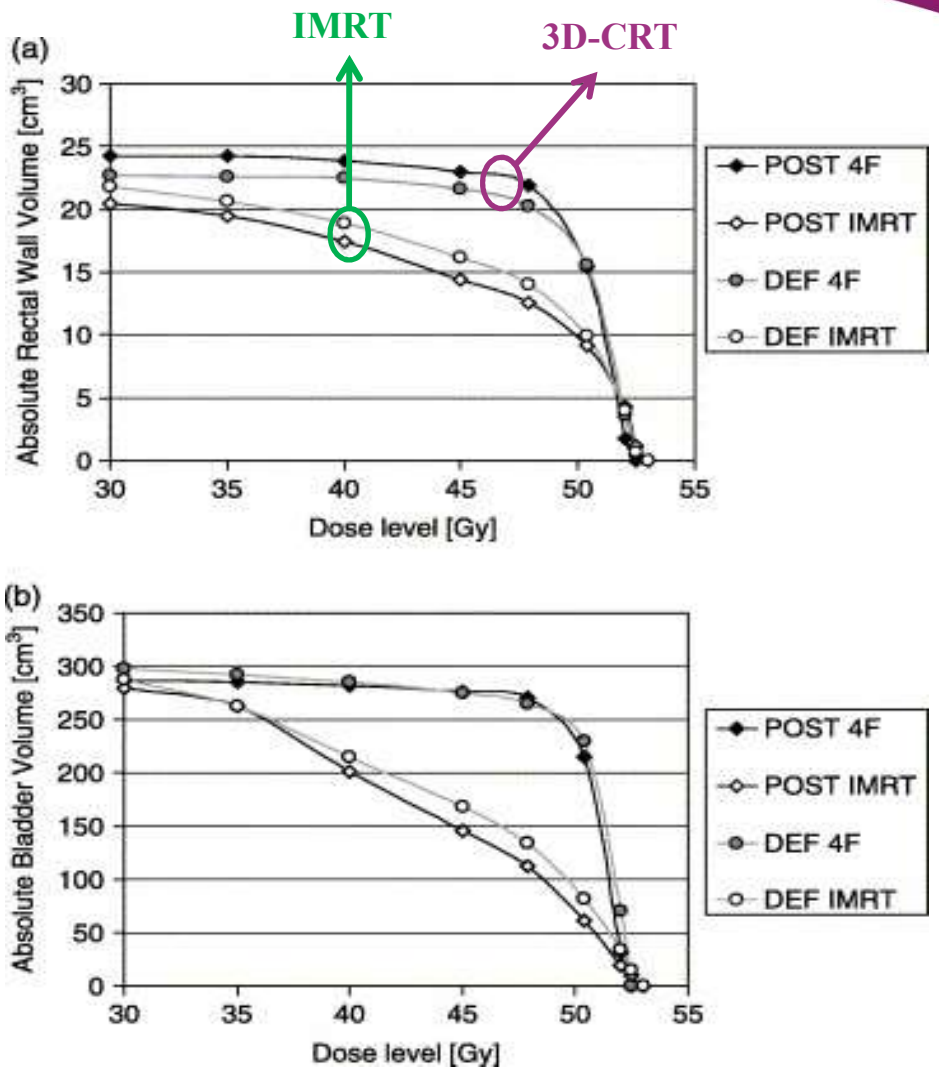
I. Better sparing OAR

- H&N
  - spinal cord
  - parotid gland
  - ...
- Prostate
  - rectum
  - Bladder
  - Small bowel
  - Penile bulb



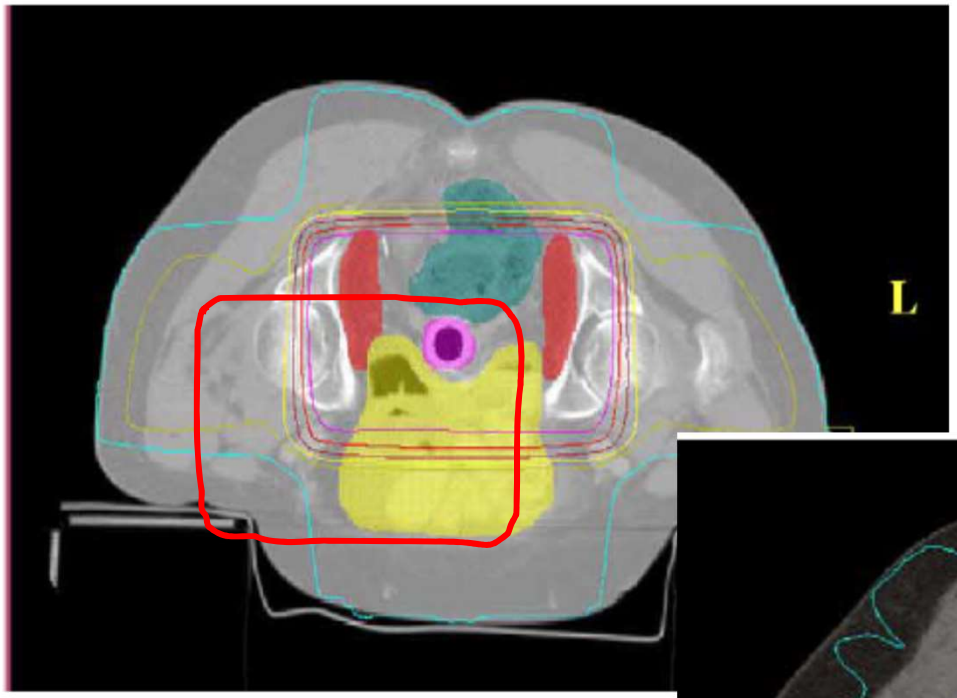
I. Better sparing OAR

- Gynecology
  - rectum
  - bladder



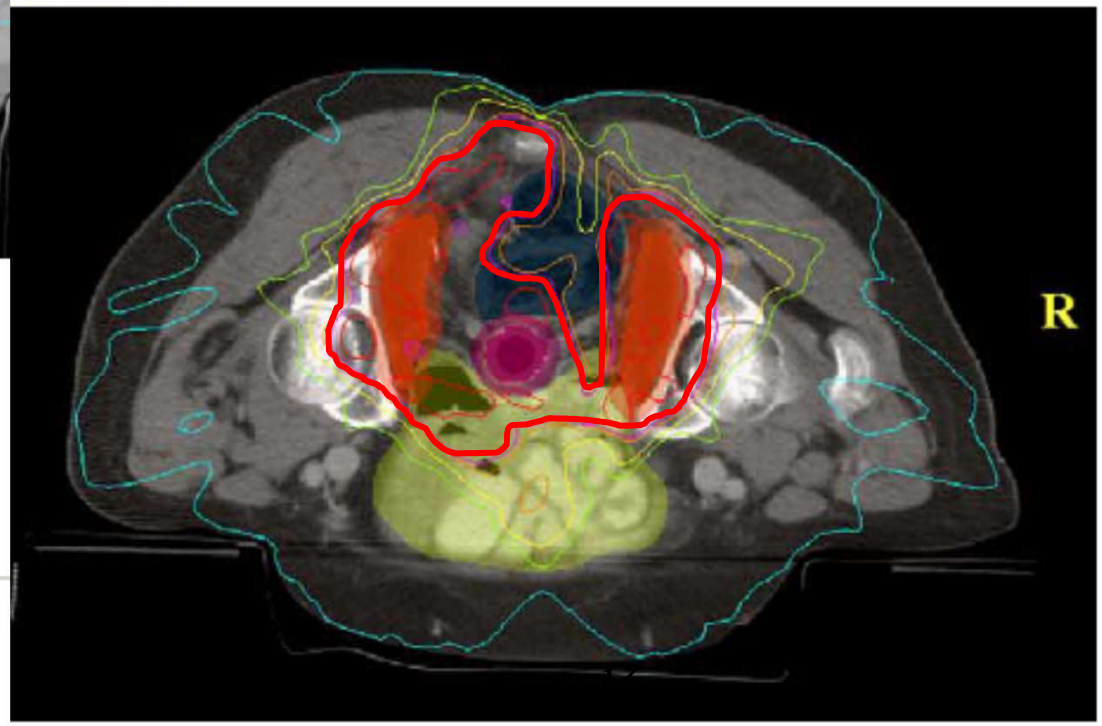
Georg et al. Radioth Oncol 2006

I. Better sparing OAR



"Conventional 3D-CRT vs. IMRT for the adjuvant treatment of gynecologic malignancies: a comparative dosimetric study of dose-volume histograms"

Heron, Radiat Oncol, 2003



I. Better sparing OAR

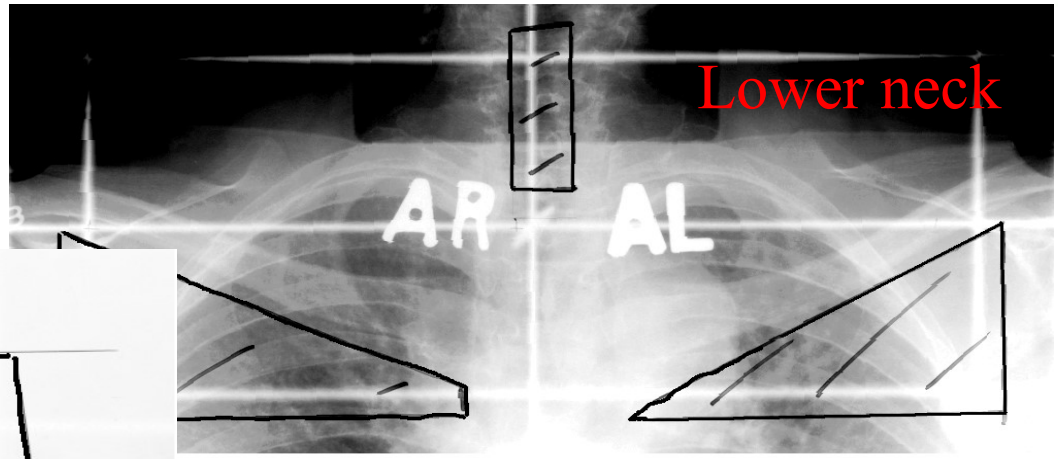
NSCLC

- Sparing of OAR
  - spinal cord
  - lungs
  - heart
- Treatment of previously untreatable patients
- Dose escalation

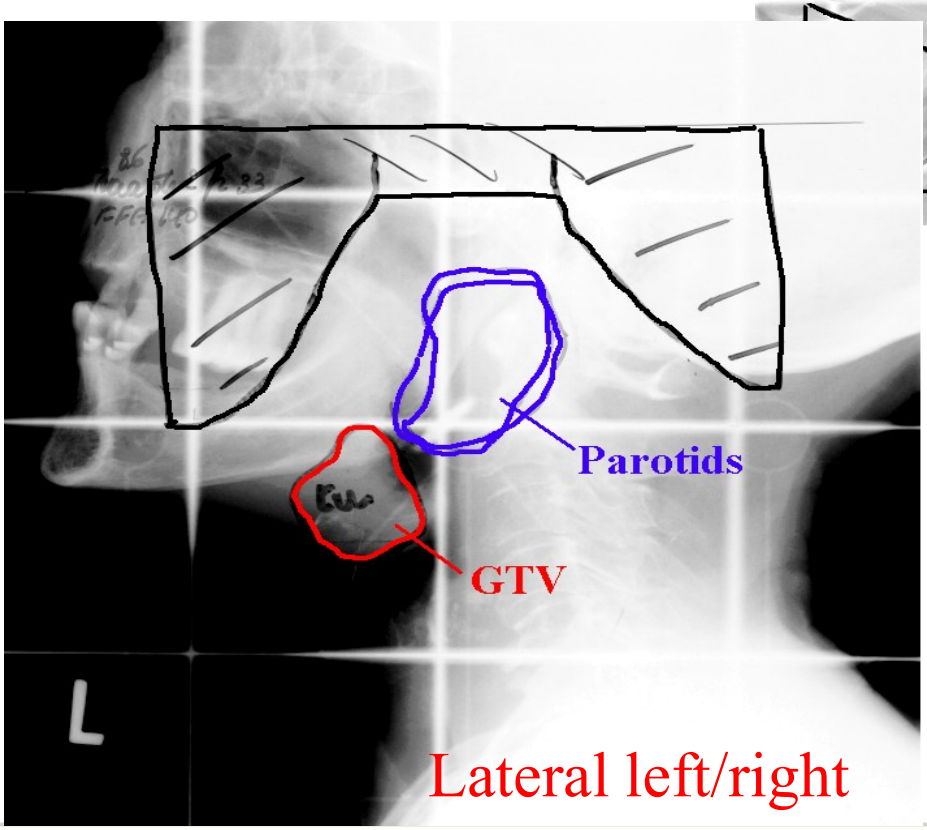
II. Better coverage of tumors near critical structures

- H&N

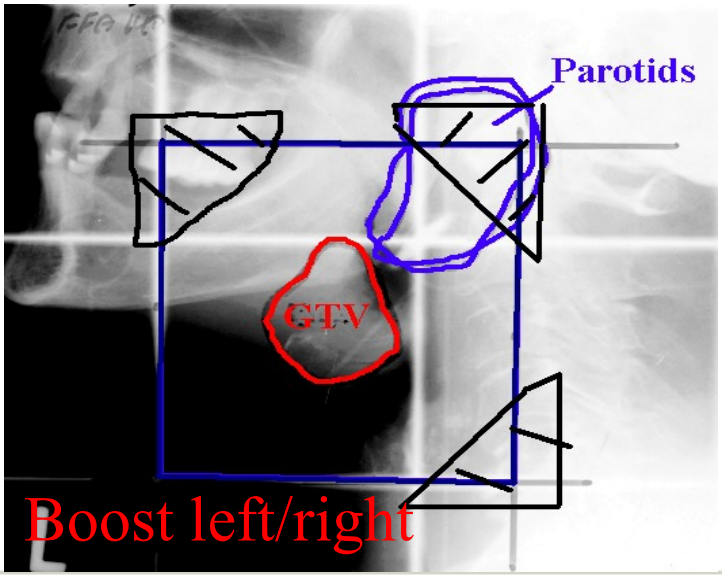
Conventional radiotherapy



Lower neck



Lateral left/right



Boost left/right

Evidence

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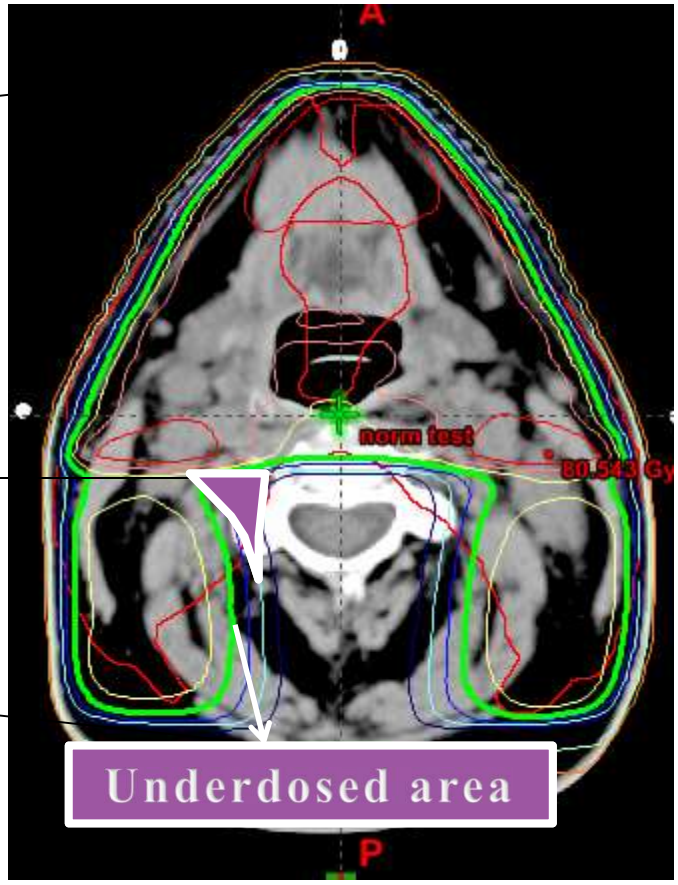
II. Better coverage of tumors near critical structures

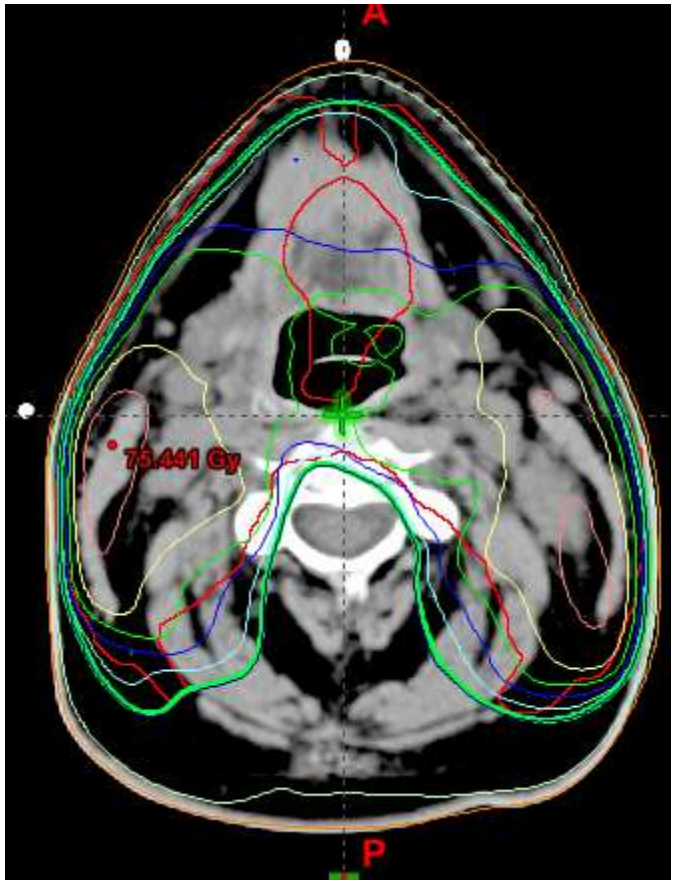
Conventional radiotherapy

IMRT

photons

electrons

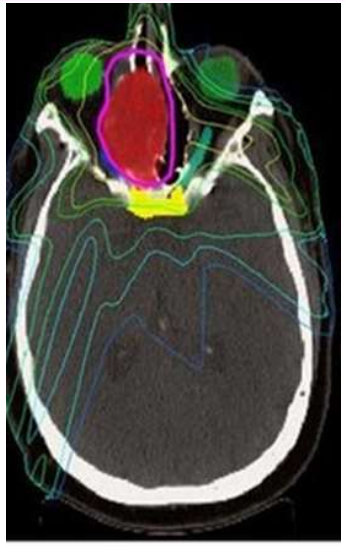




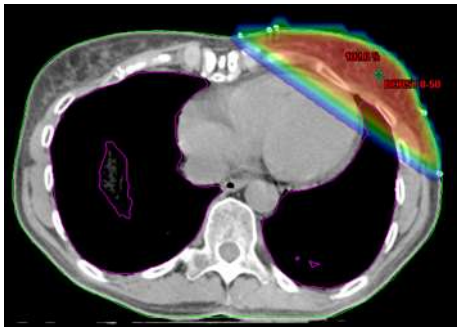
Better coverage of the target

II. Better coverage of tumors near critical structures

- Nasopharyngeal cancer
  - Optical nerve
  - Eyes
  - Chiasm

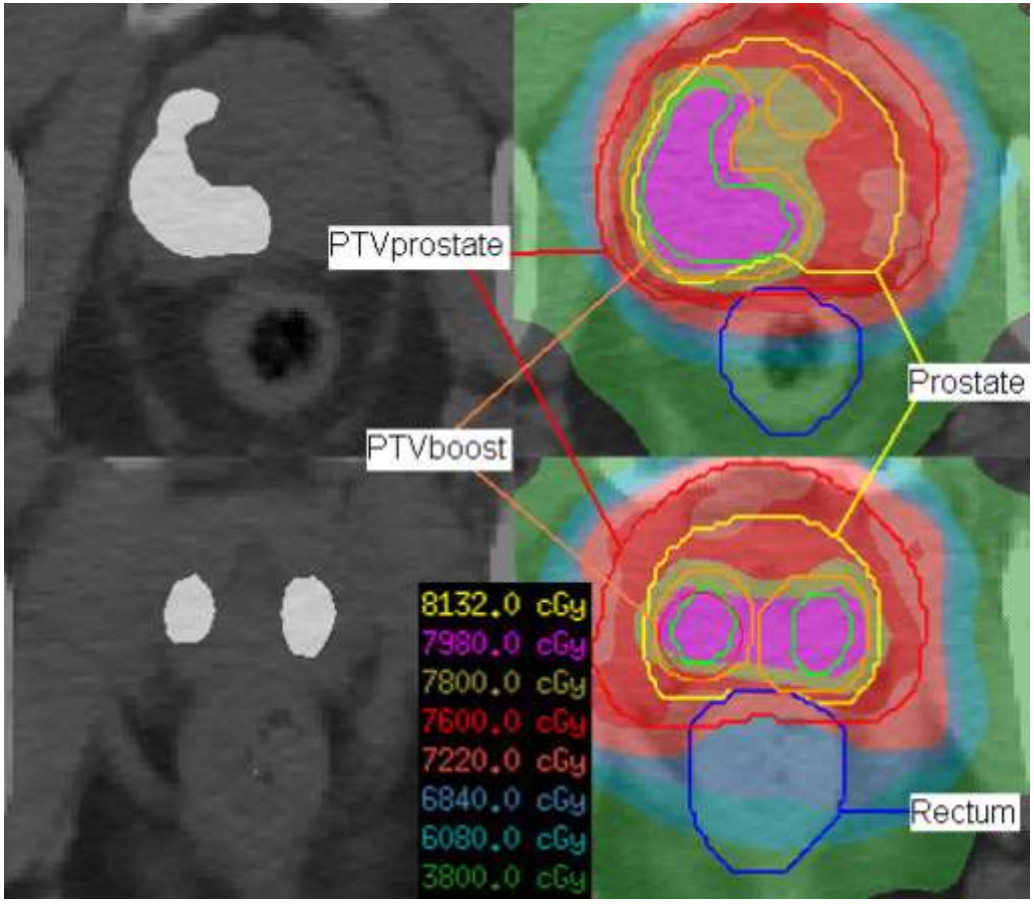


- Breast cancer
  - Lung
  - heart
  - contralateral breast



III. Inhomogeneous dose distributions

- Prostate cancer:
  Simultaneous integrated boost = SIB
- = inhomogeneous dose distribution in the prostate



Pinkawa Radioth Oncol 2012

III. Homogeneous dose distributions

- Breast: delivery of conventional doses ***more homogenously*** with less toxicity

forward planning IMRT with two tangential fields

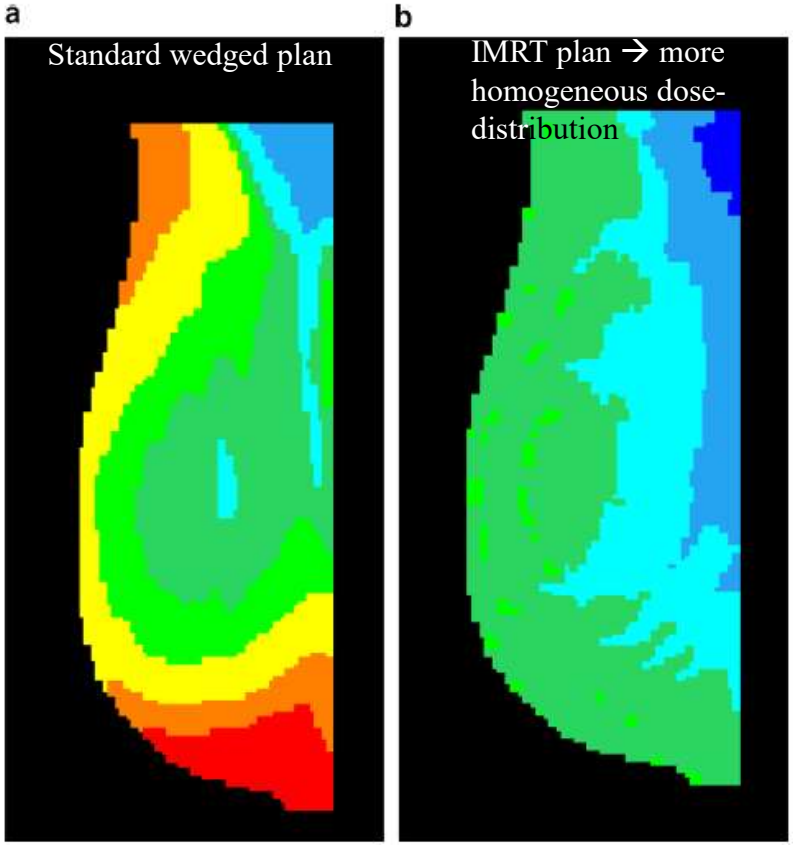


Fig. 4. Examples of sagittal dose distribution for (a) standard wedged plan and (b) IMRT plan. Data are from the in-house program for one patient. Colour scale: dark blue = 90%, mid blue = 95%, light blue = 98%, mid green = 100%, light green = 102%, yellow = 105%, orange = 110%, red = 112%.

Donovan Radioth Oncol 2007

Clinical use of IMRT: What's the scientific evidence?

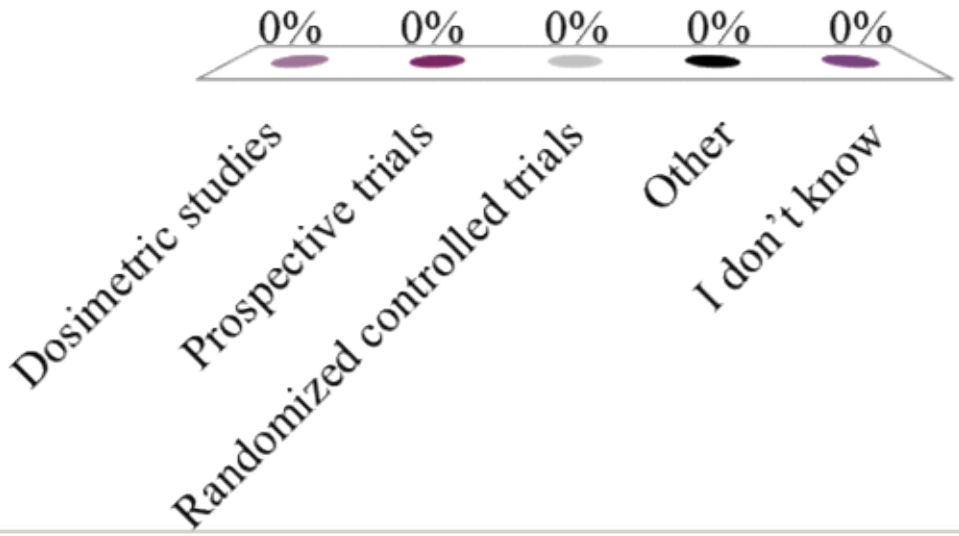
Planning studies:

Improved dose distribution → clinical benefit?

- Organ avoided → less toxicity?
- Better target coverage → better tumor control?
- Lower toxicity → dose-escalation?
- …

What type of scientific evidence is needed?

A. Dosimetric studies
B. Prospective trials
C. Randomized controlled trials
D. Other
E. I don't know



Clinical use of IMRT: What's the scientific evidence?

Planning studies:
Improved dose distribution → clinical benefit?

- Organ avoided → less toxicity?
- Better target coverage → better tumor control? Or maybe worse?
- Lower toxicity → dose-escalation?
- …

Randomized controlled trials

IMRT vs. Non-IMRT?

Clinical use of IMRT: What's the evidence?

Improved dose distribution → clinical benefit?

→Review 2012 on **IMRT vs. non-IMRT**:

- 61 comparative studies; only 6 RCT
  - 3 RCT in *LA-H&N* (205 pts),
  - 3 RCT in *breast cancer* (1809 pts)
- Primary endpoints: acute and late toxicity
- Not powered to detect differences in tumor control

Staffurth Clin Oncol 2010
De Neve Semin Radiat Oncol 2012

Clinical use of IMRT: What's the evidence?

Scientific evidence for:

- Head Neck
- Breast
- Prostate
- Gynecology
- NSCLC

Evidence

Scientific evidence: 4 RCT

Study	Organ	IMRT/ non-MRT	Primary endpoint Other endpoints	IMRT	Non-IMRT	p
Nutting 2011 (PARSPORT)	oropharynx hypopharynx	47/47	**Xerostomia ≥2 (2y)** Acute fatigue 2y OS	29% 74% 78%	83% 41% 76%	<0,001 0,002 NS
Kam 2007	nasopharynx	28/28	**Xerostomia ≥2 (1y)**	39%	82%	0,001
Gupta 2012 Rathod 2013	oropharynx hypopharynx larynx	32/28	**Acute xerostomia ≥2** Xerostomia ≥2 (2y) SC fibrosis (2y) 3y OS QOL	59% 23% 14% 71% better	89% 59% 56% 68%	0,003 0,02 0,005 NS <0,05
Pow 2006	nasopharynx	46/50	Saliva flow QOL	better better		0,002 <0,001

(& comparative case studies)

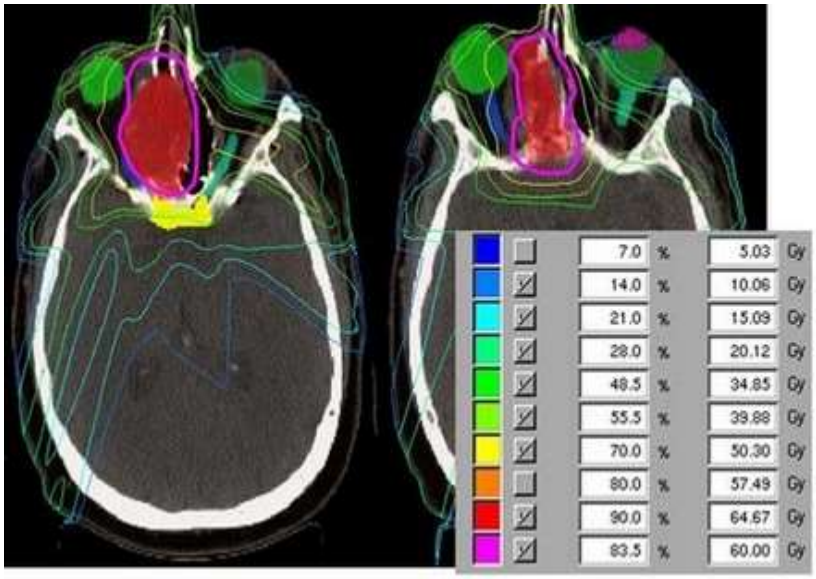
Head & Neck cancer

Evidence

O'Sullivan et al, Review.

15 trials, 1555 patients.

IMRT > 2D for xerostomia, blindness, osteoradionecrosis and QOL



O'Sullivan Clin Oncol 2012, review

Head & Neck cancer: Reirradiation

Evidence

Table 5. Summary of selected clinical series

REIRRADIATION

Author/year	No. patients	Treatment	Median OS (median follow-up for survivors)	2-y LRC/OS	Grade 4
Unresectable disease					
De Crevoisier *et al.* (1998) (13)	169	65 Gy alone (27 pts), 60 Gy/5-FU, OH-urea (106 pts), 60 Gy/CDDP, Mito-C, 5-FU (36 pts)	10 months (70 months)	11% (PF	ssue, nage
Dawson *et al.* (2001) (12)	40	60 Gy (median dose); 35% with chemo	12.5 mo		10% acute, 20% chronic soft tissue, 3% carotid hemorrhage
Spencer *et al.* (2003) (16)	52	60 Gy/5-FU, OH-urea		NR/15%	2% acute, 8% chronic soft tissue
Kramer *et al.* (2005) (15)	38	60 Gy/paclitaxel, CD	ths)	37%/35%	16% acute, 29% chronic soft tissue, 5% carotid hemorrhage
Salama *et al.* (2006) (8)	66		All patients—11 months (67 months)	36%/11%	All patients—13% chronic soft tissue/neuro, 5% carotid hemorrhage
Lee *et al.* (2007) (33)		71% mo, 70% with IMRT	All patients—15 months (35 months)	19%/12%	All patients—4% chronic neurologic
RTOG 96- Spencer *et*		60 Gy/5-FU, OH-Urea	8.2 months (16.3 months)	NR/16.2%	23% grade 4, 7% grade 5 (hematologic)
RTOG 99-1 Langer *et al.*	99	60 Gy/Paclitaxel, CDDP	12.1 months (23.6 months)	NR/25.9%	28% acute, 9% deaths, 2% carotid hemorrhage
Sulman *et al.* (current series)	54	66 Gy (median dose); 66%	25.3 months (25.2 months)	58%/54%	32% acute/chronic, 0% fatal

Favorable outcome BUT substantial severe toxicity

Sulman IJROBP 2007

Scientific evidence: 3 Randomized controlled trials

Study	Significant Endpoints	n	IMRT	Non-IMRT	P-value
Donovan R&O 2007	Change in breast appearance (serial photographs)	306	40%	58%	0,008
Pignol Breast 2008	Moist desquamation	351	31%	48%	0,002
Mukesh JCO 2013	Teleangiectasia (grade 2-3) Cosmesis (poor)	1145	8% 12%	14% 22%	0,02 0,03

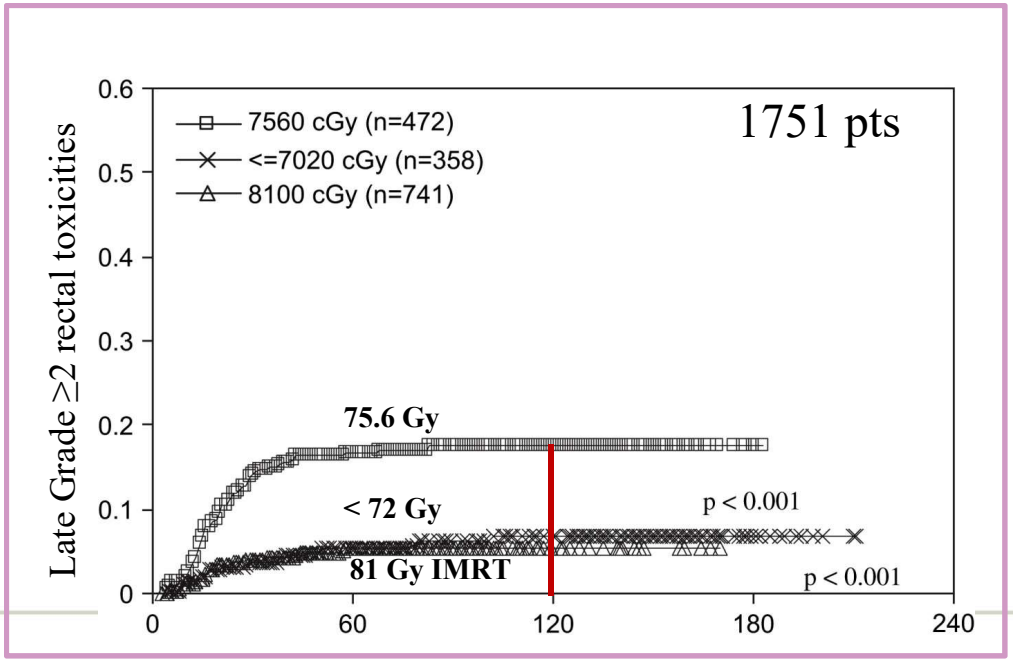
(& comparative case studies)

Scientific evidence:

No RCT; many comparative studies

Consistent results with :

- ↓ acute and late GI toxicity
- =/↓ acute and = late GU toxicity
- ↑ biochemical control with dose-escalation



Zelefsky IJROBP 2008

Gynecological cancer

Scientific evidence: 1 small RCT, 44 pts

Table 3 Acute gastrointestinal and genitourinary toxicity in WP-CRT and WP-IMRT arms

Toxicity	WP-CRT arm, n (%)	WP-IMRT arm, n (%)	*P* value	Effect size	95% CI of the difference
Vomiting grade ≥2	8 (36.4)	2 (9.1)	**.034**	**0.273**	**0.016 to 0.521**
Vomiting grade ≥3	1 (4.5)	1 (4.5)	.756	0	−0.135 to 0.131
GI grade ≥2	14 (63.6)	7 (31.8)	**.034**	**0.318**	**0.002 to 0.604**
GI grade ≥3	6 (27.3)	1 (4.5)	**.047**	**0.228**	**0.003 to 0.447**
GU grade ≥2	7 (31.8)	5 (23.8)	.404	0.08	−0.202 to 0.361
GU grade ≥ 3	3 (13.6)	0 (0)	.125	0.136	−0.019 to 0.291

Abbreviations: GI = gastrointestinal; GU = genitourinary; WP-CRT = conventional whole pelvic radiation therapy; WP-IMRT = whole pelvic intensity modulated radiation therapy.

Gandhi et al. IJRBOP 2013

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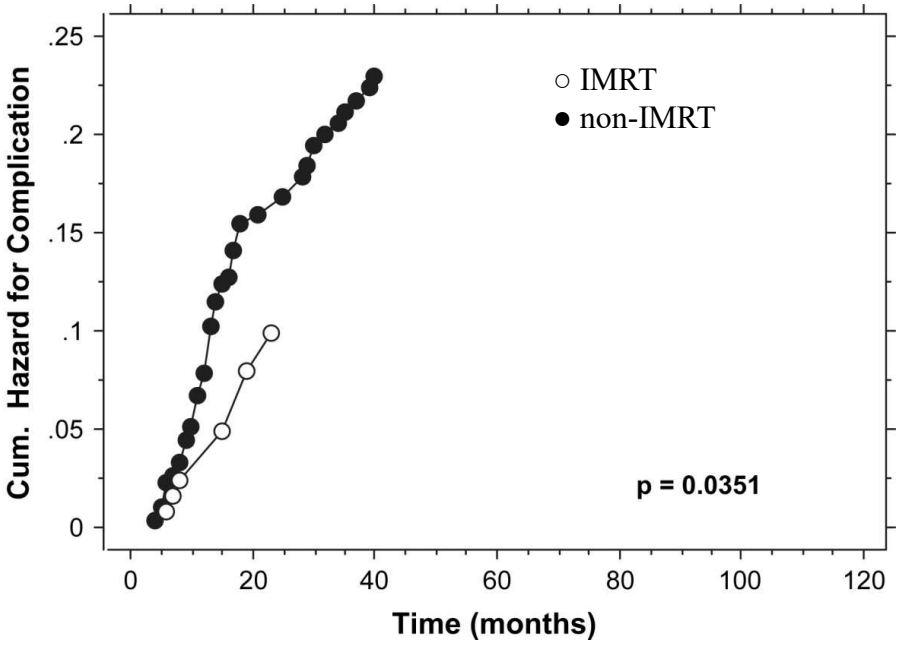
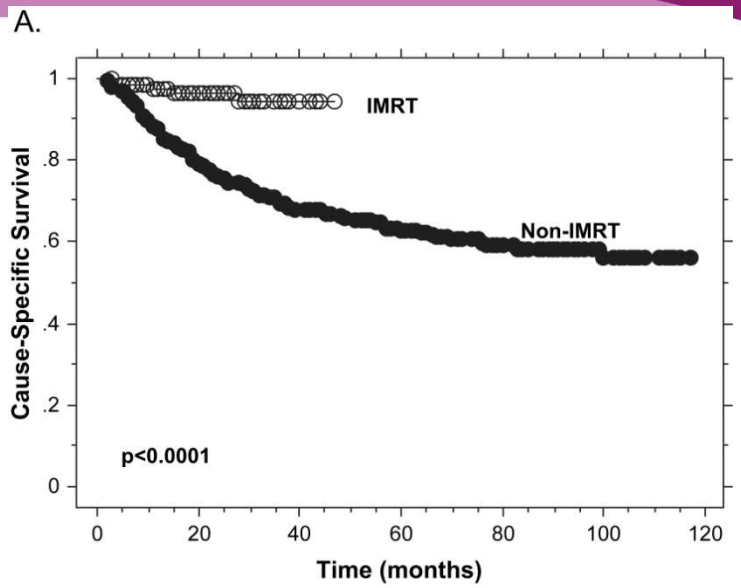
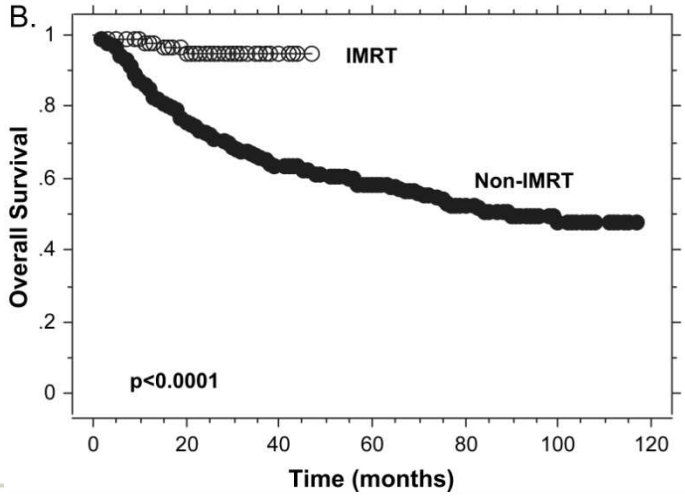
Scientific evidence

Kidd et al. IJROBP 2010
Prospective cohort study
N° pts: 135 IMRT, 317 non-IMRT







*Imbalance in LN involvement & use of PET

Lung cancer

Evidence

Dosimetric studies:

Lung: ↓ V20

V5: variable results

Spinal cord: ↓ Dmax

Heart: variable results

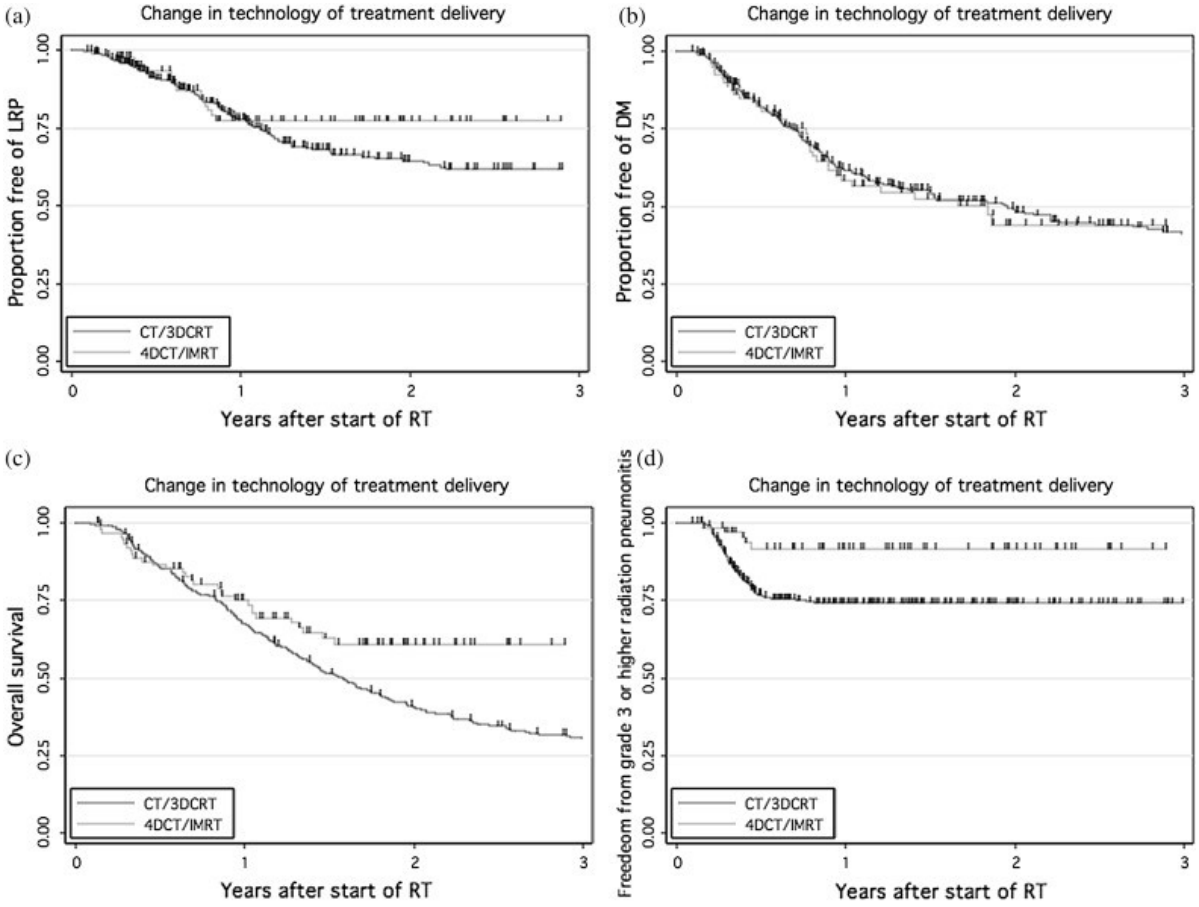
Clinical studies:

No RCT, most info from retrospective studies : less toxicity, better OS

Chan JTO 2014

Retrospective comparative study NSCLC at MDACC

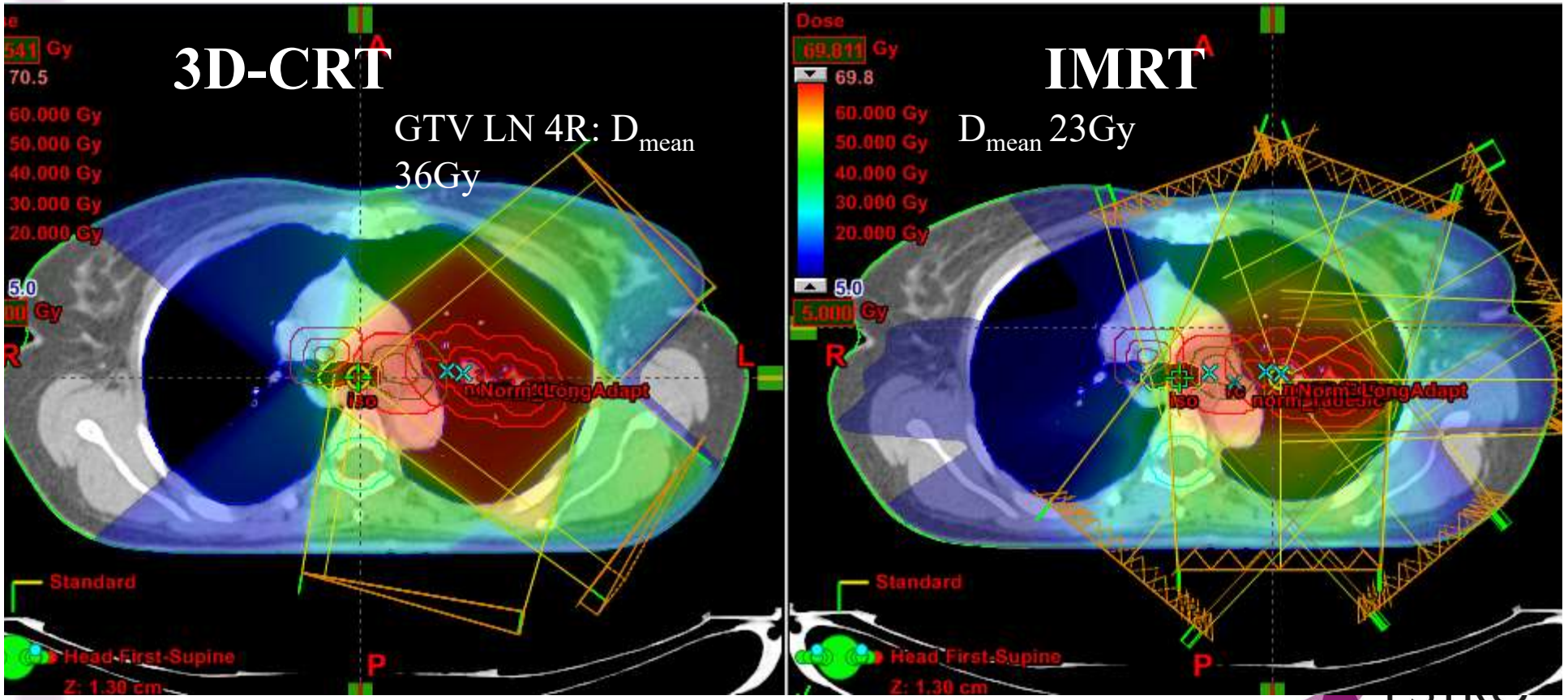
N° pts:
-318 3D-CRT
-91 4D-CT + IMRT



Liao IJROBP 2010

Lung Cancer

Prospective study: selective mediastinal node irradiation in stage III NSCLC using IMRT → results in a low in-field incidence of INF (2.2%), similar to 3D-CRT, and may thus be considered safe.



Potential risks of IMRT

TABLE 1. Advantages and Disadvantages of IMRT for Lung Cancer

Advantages	Disadvantages
Ability to spare organs at risk	Increased contouring, planning, and quality assurance time
Better coverage of irregular shaped targets	Increased need to accurately delineate clinical target volumes and involved nodes requiring treatment
Ability to dose escalate	Need for image guidance
Able to treat synchronous primary tumors and multiple targets simultaneously	Sharp dose gradient—may lead to under-treatment of micrometastatic disease
Enables treatment of larger radiotherapy volumes to radical dose	Potential interplay effects depending on fractionation and complexity of IMRT technique used
	Need for rigorous quality assurance programme
	Low-dose radiotherapy bath

IMRT, intensity-modulated radiotherapy.

Chan JTO 2014: lung cancer

ESTRO School

Potential risks of IMRT

- Increased need of accurate delineation

  Risk of geographical miss because of high conformality, especially in case of positioning uncertainties and motion

- Need for image guidance

  High doses in close proximity of OAR → Higher risk of injury

- Low dose radiotherapy bath

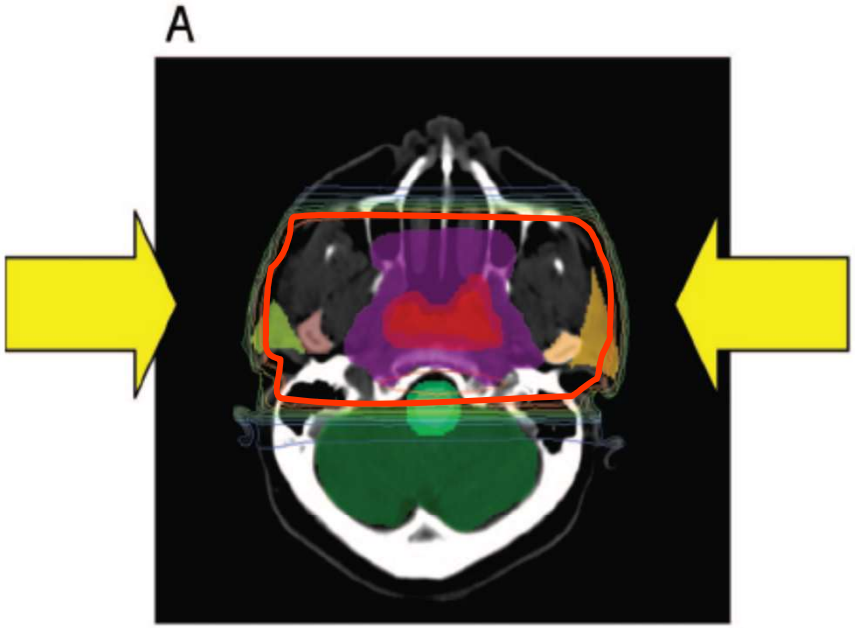
  Larger volume of normal tissues receive low dose RT

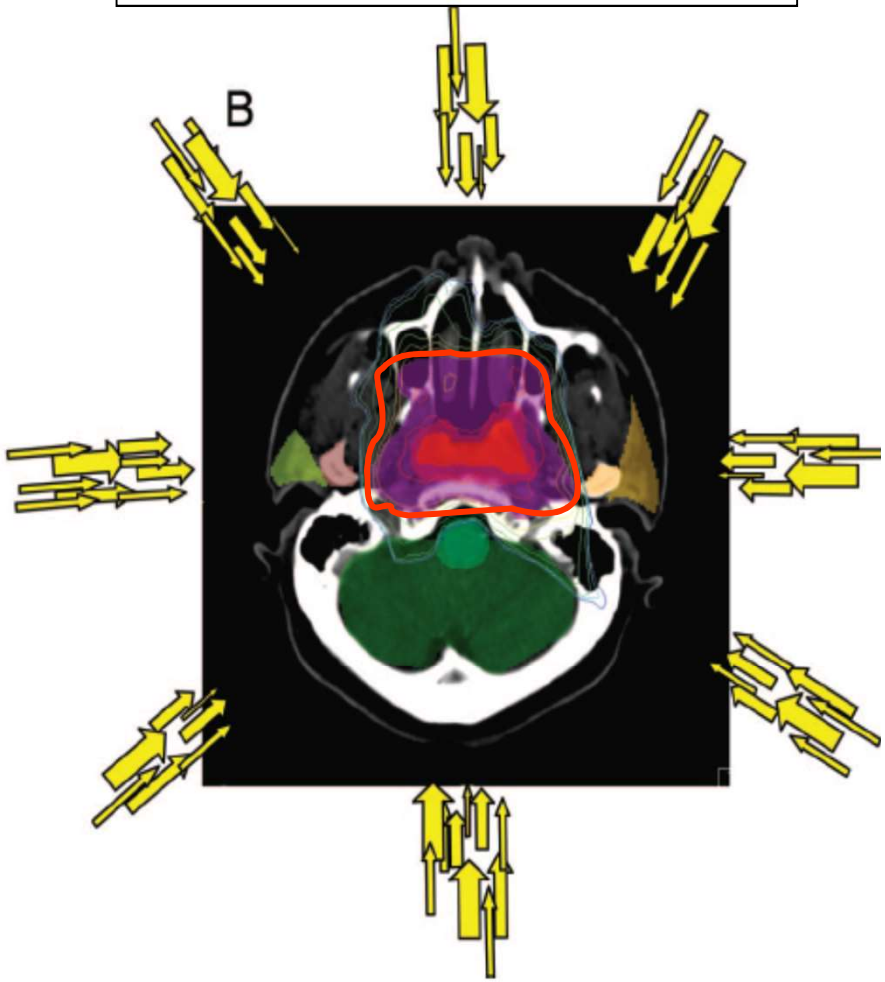
- Interplay effect (lung)

Contouring

Conventional RT
(2D / 3D-CRT)
= dose coverage
goes BEYOND the target

IMRT
= tumoricidal doses EXACTLY
track the target !!





Bucci, CA Cancer J Clin, 2005

Contouring

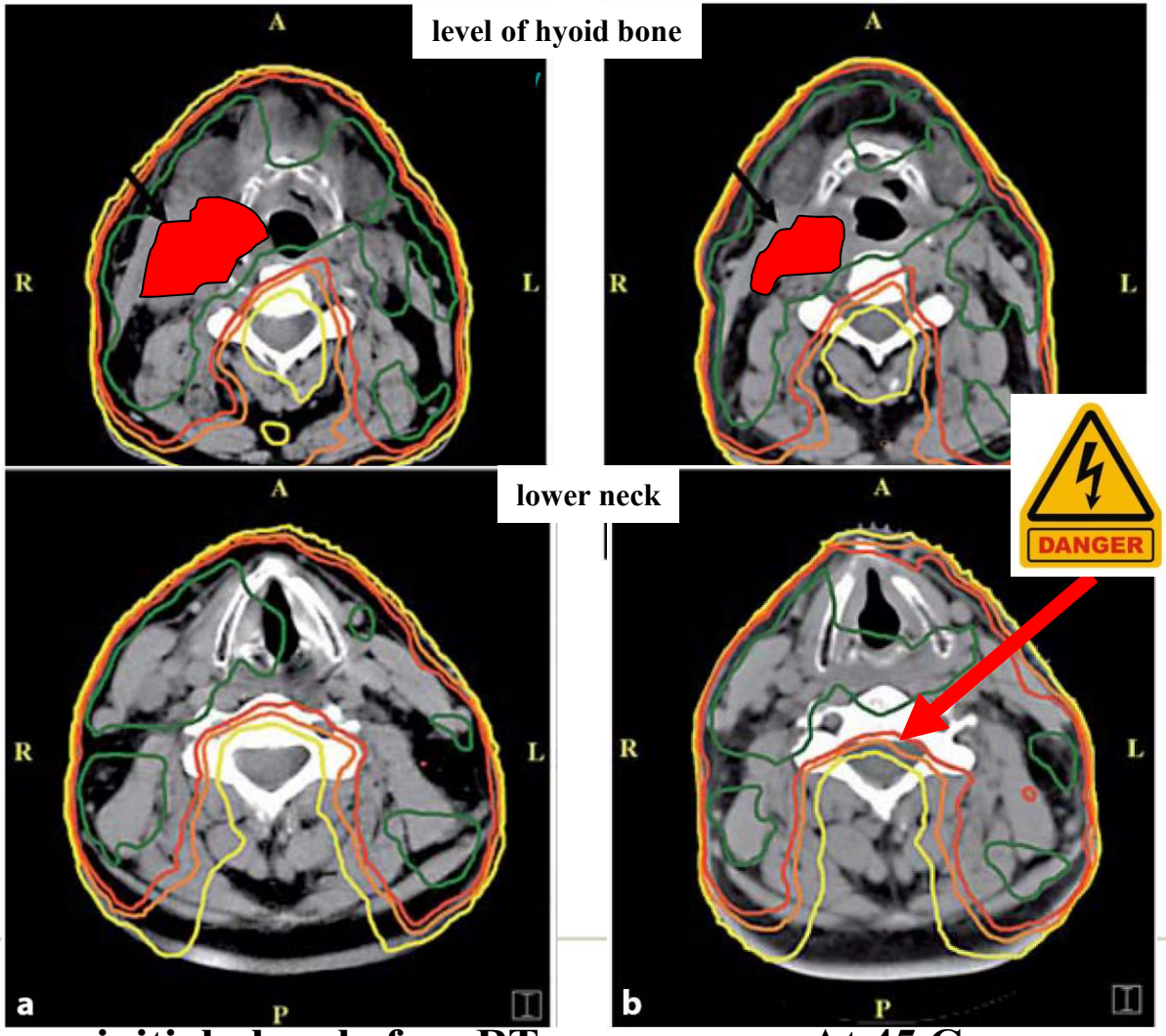
- Delineate on appropriate **imaging modality**
- Use (or design) **guidelines** for delineation of target and OAR to reduce inter- an intraobserver variation

Note: PTV margins account for:

Equipment tolerances
Planning errors
Setup errors
Organ motion
Target volume delineation

Need for image guidance

High doses in close proximity of OAR → Higher risk of injury...



initial plan, before RT

At 45 Gy

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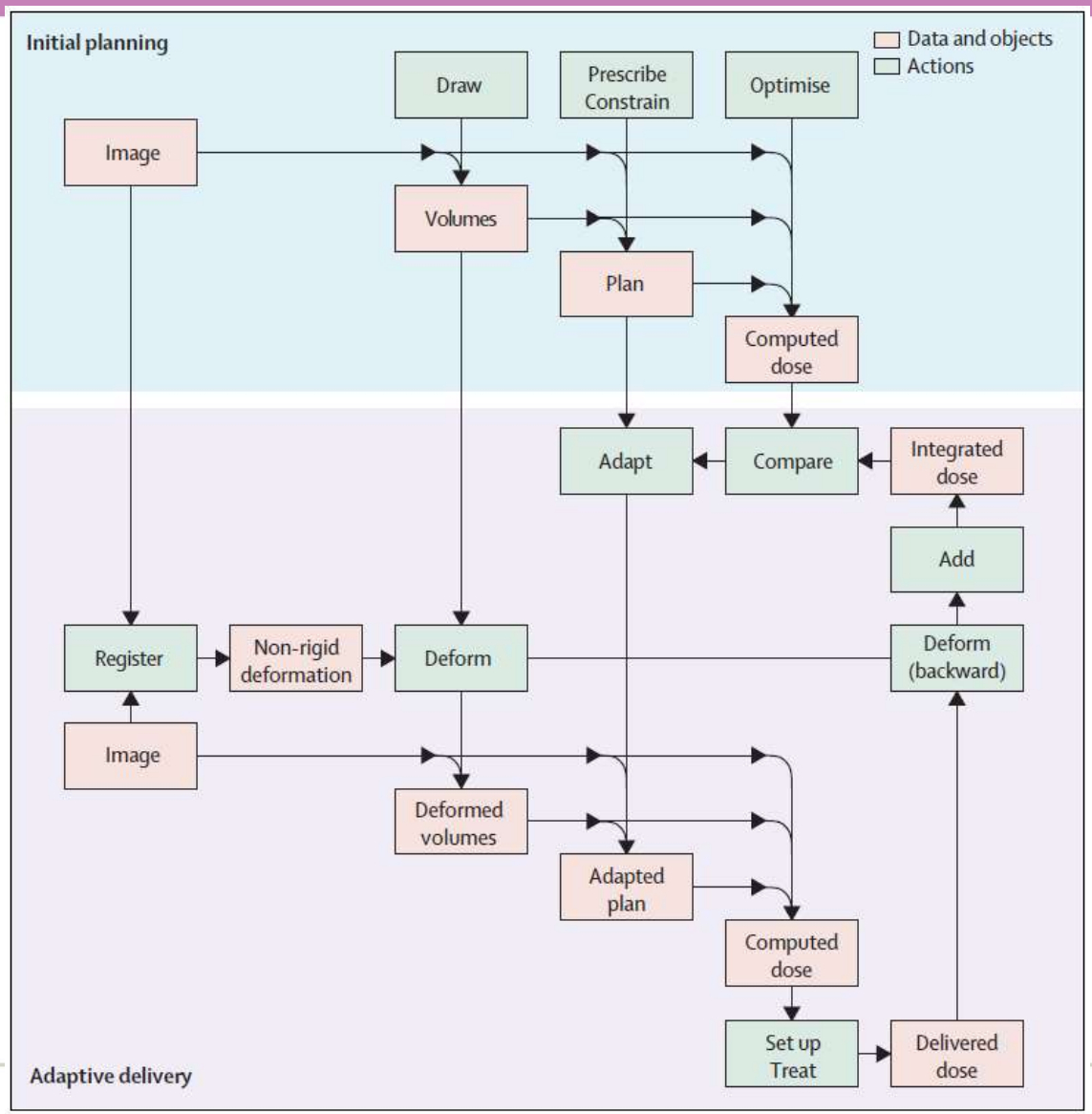
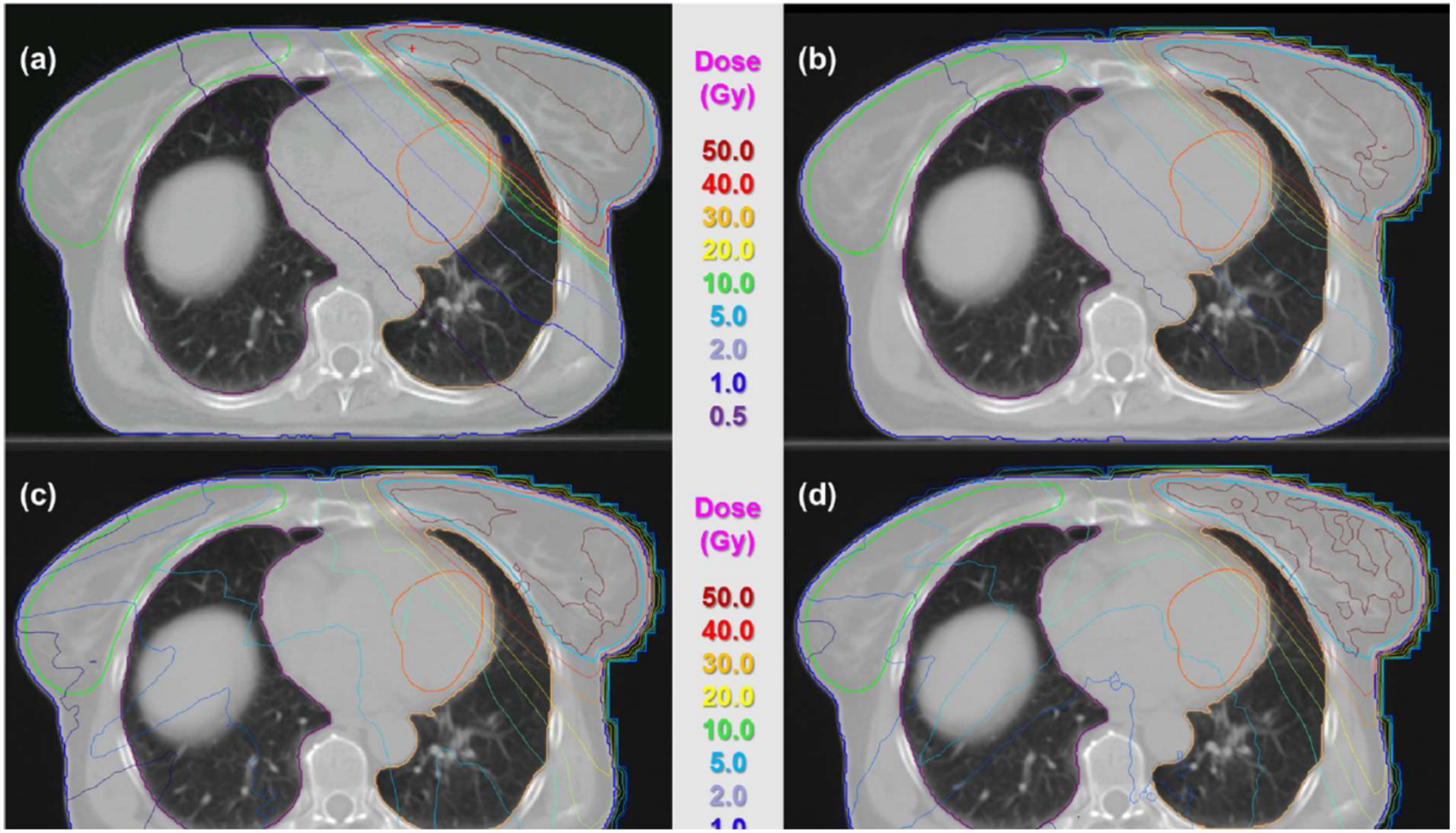
Head & Neck: Adaptive approach?



Gregoire Lancet Oncol 2012

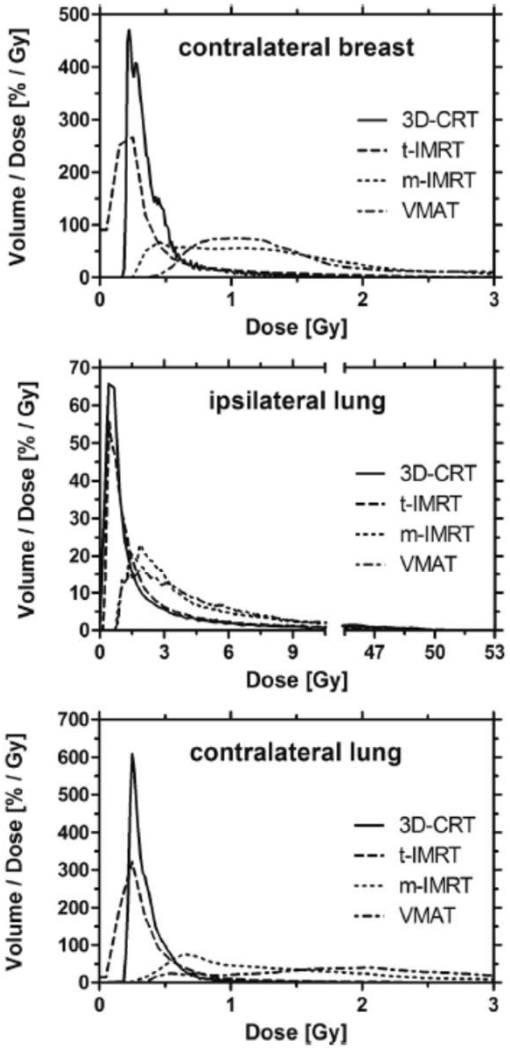
Low dose bath: more toxicity?



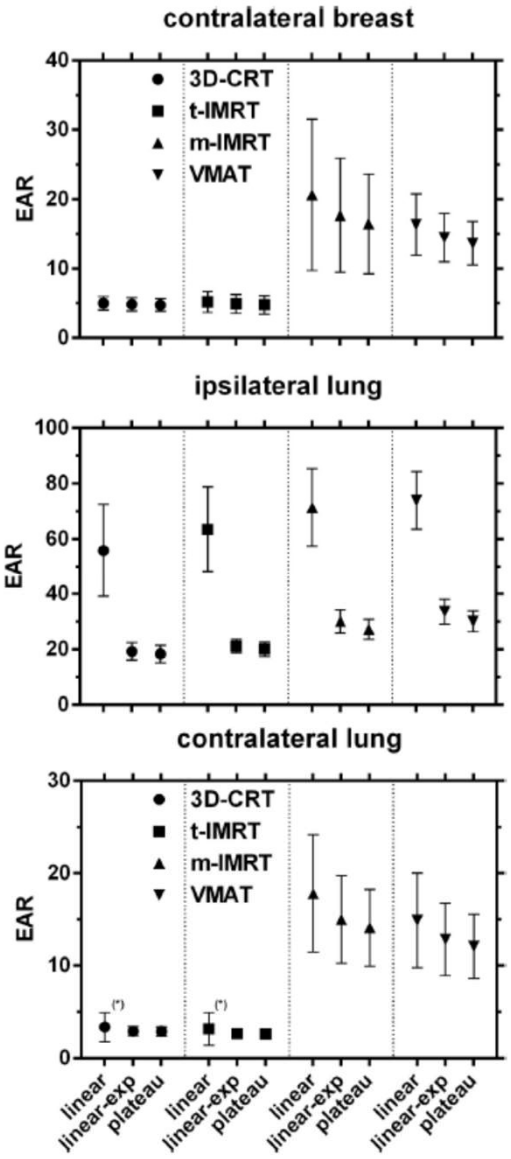
(a) 3D-CRT, (b) tangential IMRT, (c) multibeam IMRT and (d) VMAT.

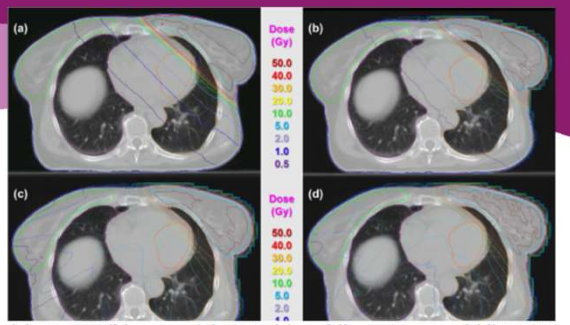
Abo-Madyan 2014

Low dose bath: risk of 2nd cancer

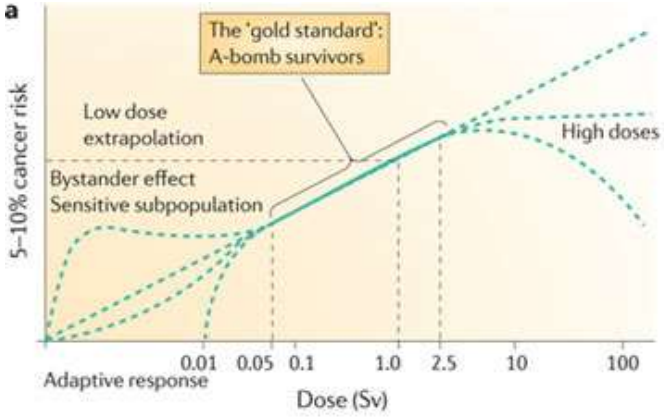


2. Differential DVHs of the representative patient for irradiation of contralat- breast, ipsilateral and contralateral lung for 3D-CRT, tangential IMRT, multi- m IMRT and VMAT.





(a) 3D-CRT, (b) tangential IMRT, (c) multibeam IMRT and (d) VMAT.



Abo-Madyan 2014

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Interplay effect: Lung cancer

- Studies show that interplay effect can alter the dose distribution of a single fraction, but not a fractionated course of treatment.

  → Dose variation (Jiang et al.)

  1 fraction, 1 field: 30%

  1 fraction, 5 fields: 18%

  30 fractions: 1-2%

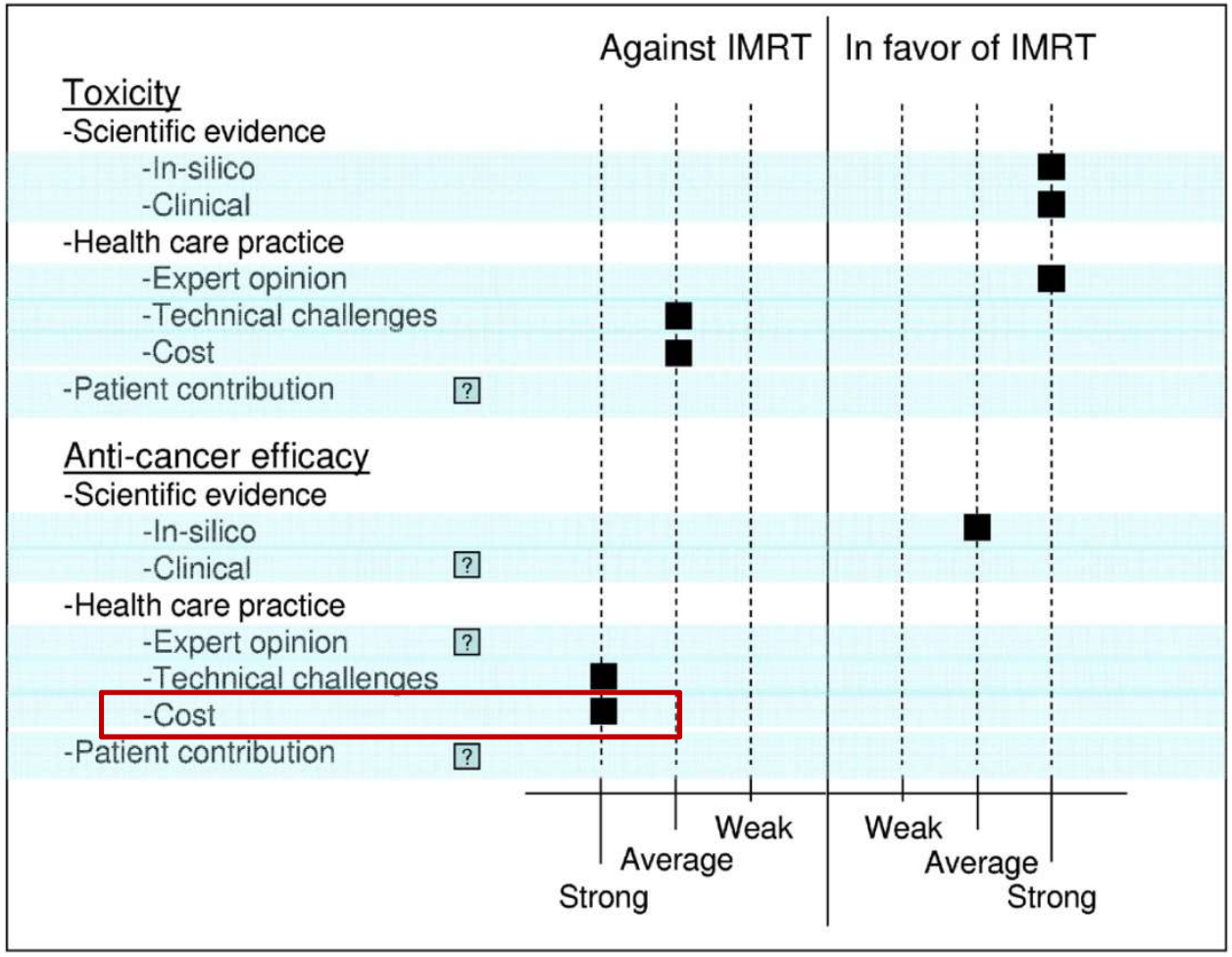
- SABR: interplay effect is negligible, effects are averaged out due to
  - larger number of MU
  - increased treatment time

- Strategies to reduce interplay effect:
  - ↑ n° of arcs
  - ↓ dose rate → prolonging treatment time
  - avoid MLC motion perpendicular to the tumor motion.

Chan JTO 2014, Jiang Phys Med Biol 2003

Other factors influencing the use of IMRT

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



Costs

De Neve Semin Radiat Oncol 2012

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Are costs an issue?

Average product costs and examples of specific costs per product in 2009 compared with 2000.

Product	Nr. of fractions	2009 (€)	2000[a] (€)	% (2009 vs. 2000)	Technical changes
Palliative 1 × 8 Gy	1	648	540	120	
Palliative 5 × 4 Gy	5	1175	994	118	
Palliative 10 × 3 Gy	10	2006	1479	136	With CT scan
Breast tangential + boost	25 + 8 (boost)	5242	4028	130	3D-CRT
Lung involved field	35	6900	4779	144	Daily online PI and correction
Lung coin lesion	33	–	4602		
Lung coin lesion	20	4351	–	95	Hypofractionation
Prostate	25 + 10 (boost)	–	4180		
Prostate IMRT	37	7862	–	188	Daily online PI and correction, IMRT
Head and neck glottis	25	3951	3257	121	
Head and neck	25 + 10 (boost)	–	5662		
Head and neck IMRT	35	6825	–	121	IMRT
Head and neck IMRT	44	7814	–	138	Hyperfractionation, IMRT
Average of all products	20	3656	2731	134	

+ 88%

+ 38%

Abbreviations: 3D-CRT: three-dimensional conformal radiotherapy; PI: portal imaging; IMRT: intensity-modulated radiation therapy.

[a] € costs are adapted to the evolution in Belgian Consumer Price Index.

COST of RT / TOTAL COST of ONCOLOGY = **5 %**

E. Van de Werf et al. Radioth Oncol 2012; Norlund 2003

Cost of toxicity?

IMRT vs. 3D-CRT in gynecological cancer (retrospective)

Cost-effectiveness analysis for 3DCRT versus IMRT.

Timing	Treatment	Cost	Incremental cost	Effectiveness (QALY)	Incremental effectiveness (QALYs)	Incremental C/E ratio
1 year	IMRT	$44,072	$17,172	0.827	0.073	$235,233
	3DCRT	$26,900		0.754		
2 years	IMRT	$42,705	$16,112	1.502	0.141	$114,270
	3DCRT	$26,593		1.361		
3 years	IMRT	$38,080	$11,711	2.035	0.155	$75,555
	3DCRT	$26,369		1.88		

- IMRT: ↑ treatment cost
- IMRT : ↓ late overall toxicity (without compromising clinical outcome) → ↓ toxicity cost
- IMRT was not cost-effective during the early chronic toxicity phase, but it became more cost-effective over time.

Costs

Chen Gyn Onc 2015

Take home messages…

IMRT is an advanced technique, which only in a limited extent has been tested in a randomized manner

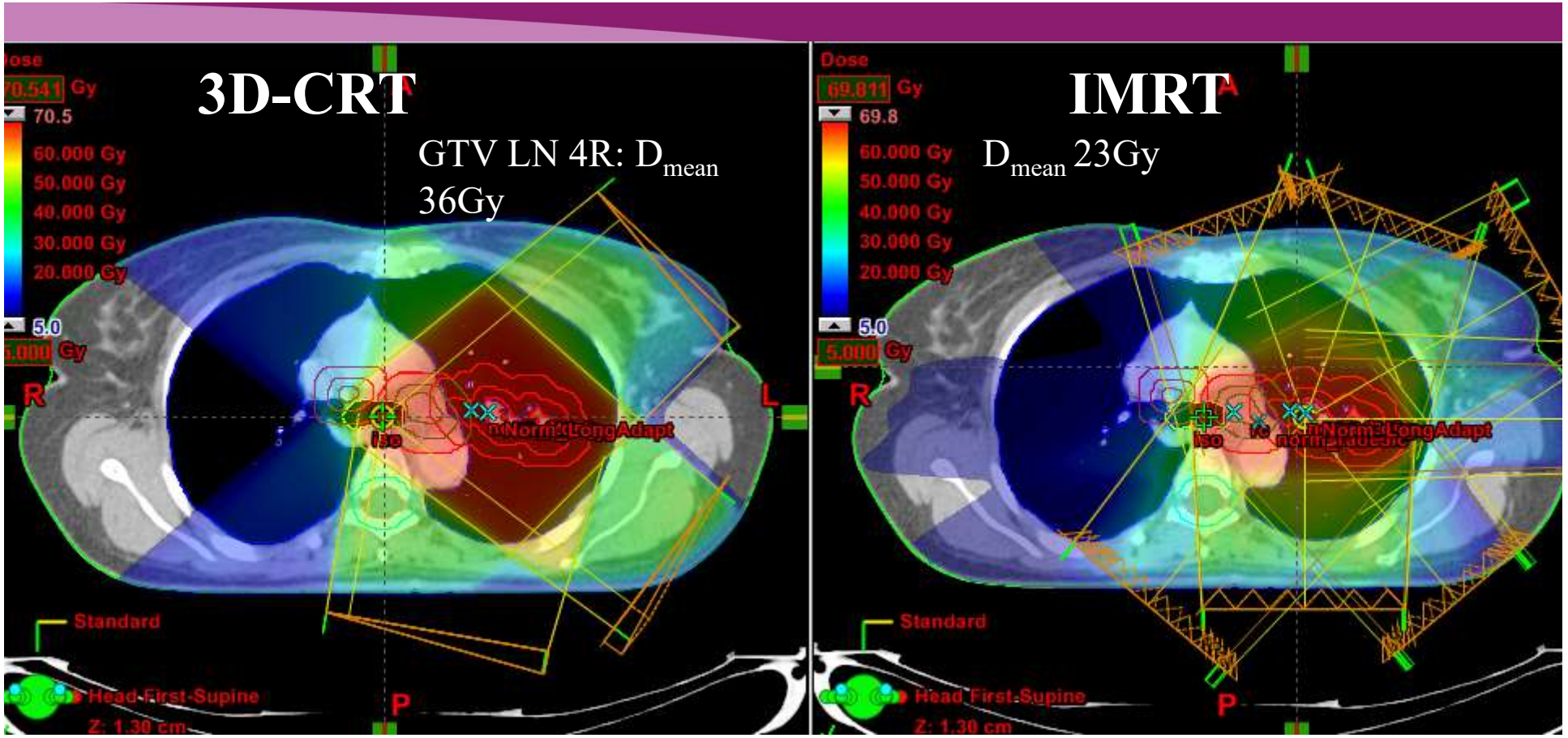
↓ toxicity (H&N, breast)

OS: no robust clinical data

IMRT/RA is a more resource intense and complex technique

Indications for the use of IMRT/RA should be considered, weighing potential gains and risks according to treatment site, patient characteristics, aim, resources, equipment…

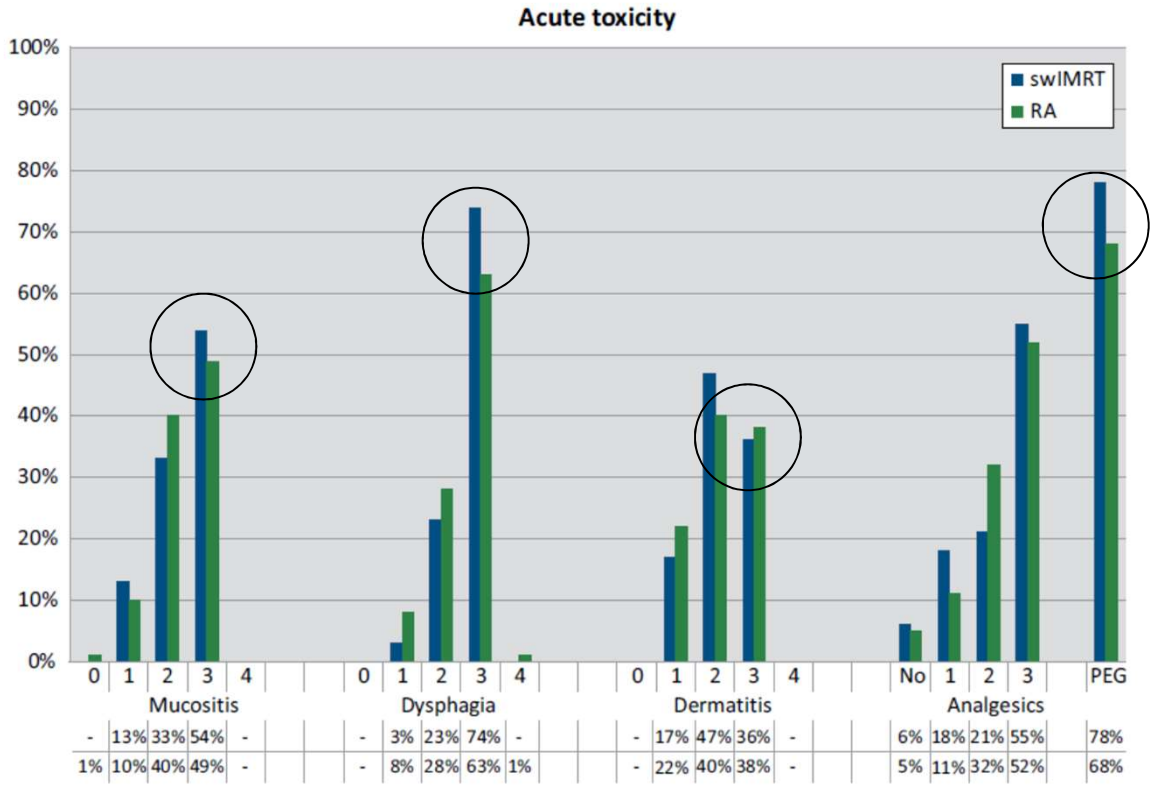
Not all radiotherapy treatments require the highest order of accuracy that is technologically achievable and fiscally affordable.


3D-CRT
GTV LN 4R: D_{mean} 36Gy
IMRT
D_{mean} 23Gy
Dose
69.811 Gy
69.8
60.000 Gy
50.000 Gy
40.000 Gy
30.000 Gy
20.000 Gy
5.0
5.000 Gy
R
L
A
P
Iso
Standard
Head First-Supine
Z: 1.30 cm

Head & Neck

157 pts
swIMRT vs. RA

RA:
↑ target coverage
↑ homogeneity
= conformity



Smet Strahl Onk 2015

Head & Neck

Table 5 Overview of published planning studies comparing IMRT and RA

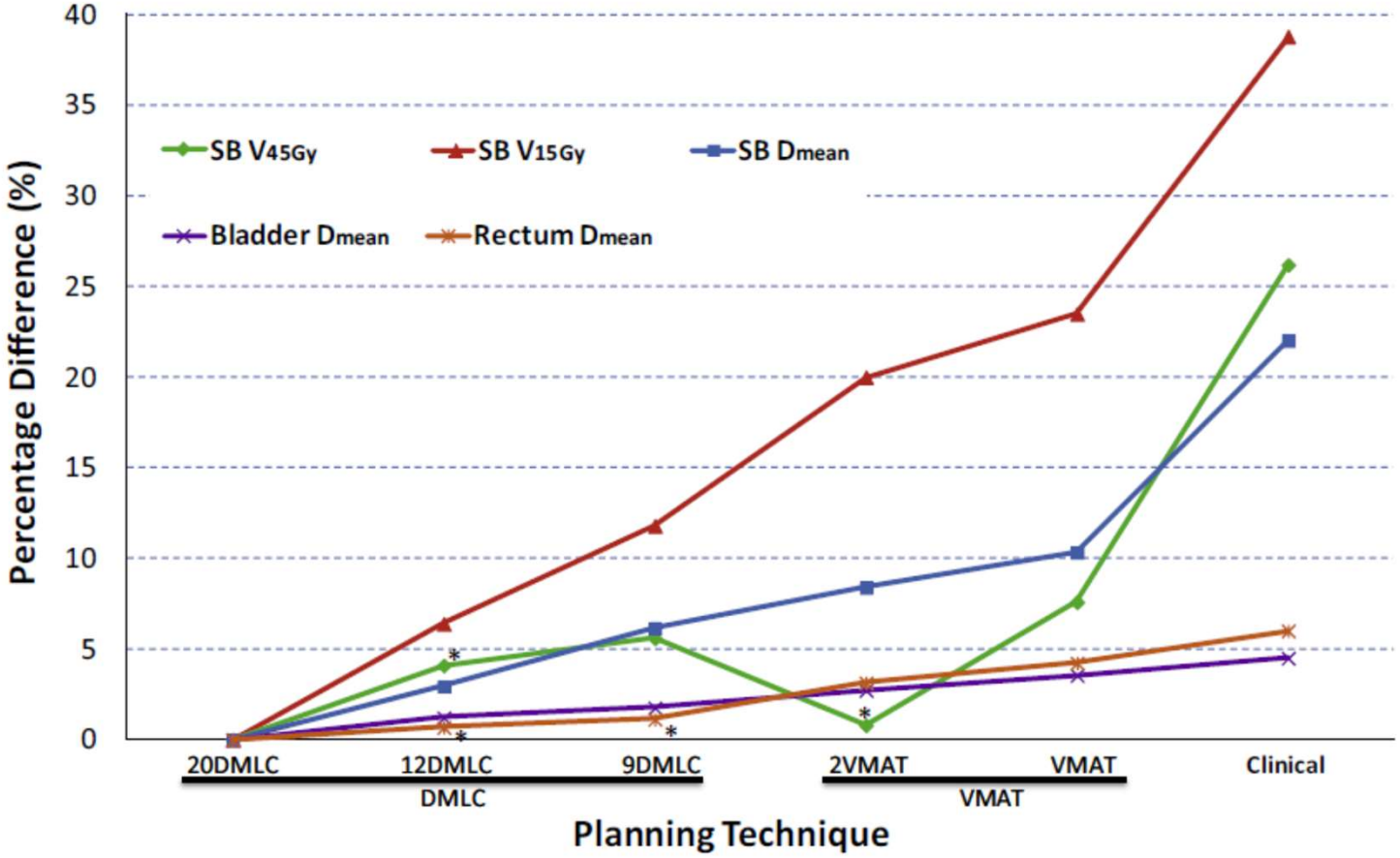
Study	n	Technique	PTV			OAR sparing	MU
			Coverage	CI	HI		
Vanetti et al. [9]	29	sw IMRT sa VMAT da VMAT	Similar	Similar	da VMAT	da VMAT	1126 vs 463 vs 584
Verbakel et al. [8]	12	sw IMRT sa VMAT da VMAT	Similar	Similar	da VMAT	Similar (Parotis: da VMAT)	1108 vs 439 vs 459
Johnston et al. [10]	10	sw IMRT da VMAT	Similar	sw IMRT	sw IMRT	Similar (Contralateral parotis: da VMAT)	529 vs 1628
Fung Kee Fung et al. [11]	20	sw IMRT RA	Similar	sw IMRT	Similar	Similar	542.85 vs 1612.58
Van Gestel et al. [12]	5	ss IMRT RA sw IMRT SA Tomo	Tomo (swIMRT and RA similar)	RA	Tomo (swIMRT and RA similar)	Tomo (RA better than swIMRT)	415 (RA) vs 1125 (swIMRT)
Wiehle et al. [29]	15	ssIMRT da VMAT	da VMAT	daVMAT (conformity function)	/	da VMAT	/
Guckenberger et al. [13]	15	ssIMRT 1–3 arc VMAT	Post-op: 3 arc pharynx: 3 arc = IMRT	/	ssIMRT	Similar	430–688 vs 358–440 vs 460–519 vs 506–560
Our study	157	swIMRT RA	RA	similar	RA	RA	375 vs 987

CI conformity index, *HI* homogeneity index, *OAR* organs at risk, *MU* monitor units, *swIMRT* sliding-window IMRT, *sa VMAT* single arc volumetric-intensity modulated therapy, *da VMAT* double arc VMAT, *RA* RapidArc, *ssIMRT* step and shoot IMRT, *Tomo* tomotherapy

IMRT vs. VMAT

Cervix cancer

Planning study on 10 pts comparing 5 techniques:
9, 12 & 20 beam IMRT, single and dual VMAT



Sharfo et al. Radioth Oncol 2015; SB = small bowel

Challenges in dose prescription and plan evaluation

Dr Ann Henry

Associate Professor in Clinical Oncology

Leeds Cancer Centre and University of Leeds, UK

a.henry@leeds.ac.uk

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Talking the same language

NASA lose $125 million Mars Climate Orbiter because non-SI units were used in calculations

We can easily do the same either for individual patients or for groups of patients!

Need to achieve consensus and ‘Talk the same language’

Quality of RT affects outcome

VOLUME 28 · NUMBER 18 · JUNE 20 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results From TROG 02.02

Lester J. Peters, Brian O'Sullivan, Jordi Giralt, Thomas J. Fitzgerald, Andy Trotti, Jacques Bernier, Jean Bourhis, Kally Yuen, Richard Fisher, and Danny Rischin

Very important results

Poor compliance to RT protocols resulted in poorer patient outcomes with 20% reduction in overall survival

Quality of RT affects outcome

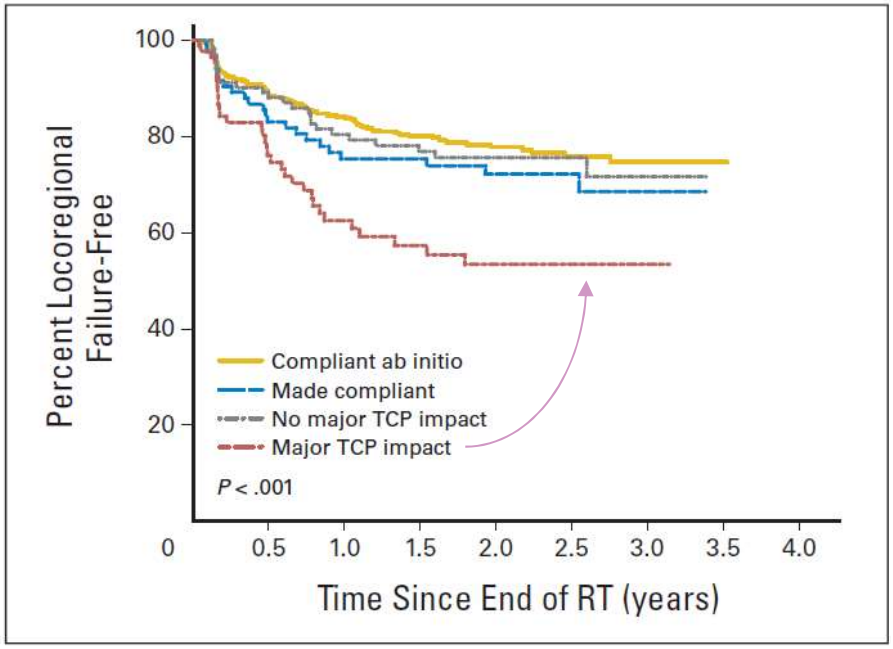

Fig 3. Time to locoregional failure by deviation status

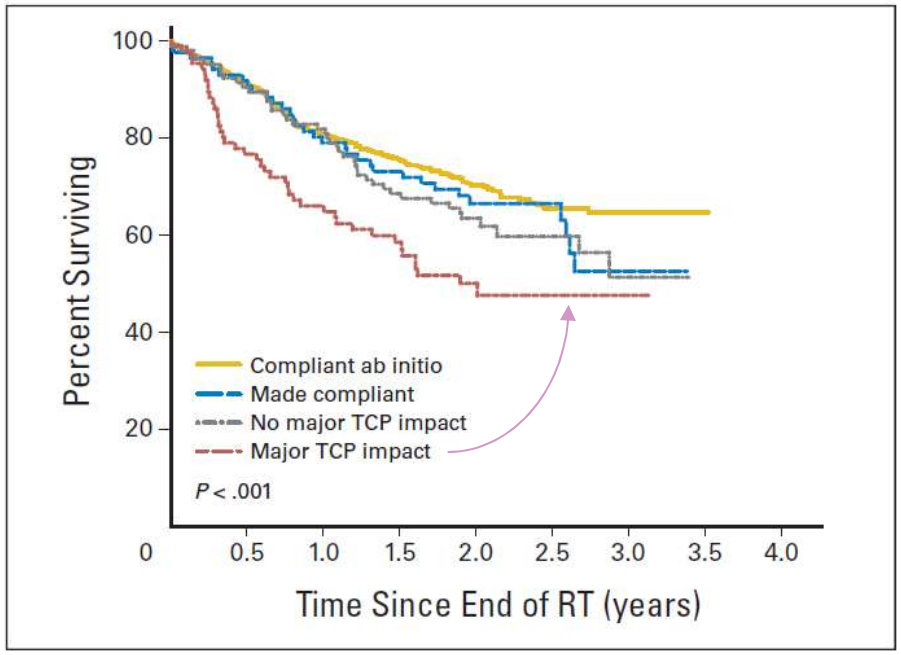

Fig 2. Overall survival by deviation status:

Poor radiotherapy in 12% of patients in study

Overwhelmed effect of the drug being tested!

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Overview

- Aims of ICRU reports
- ICRU 50 and 62 recommendations
- From 3D CRT to IMRT and SBRT
- Aims ICRU 83
- Clinical examples

The importance of definitions

- Increasingly complex treatments
  - IMRT, SABR/SBRT and new delivery systems
- Need common methodology
  - Uniform practice within and between departments
- Common language
  - Allows comparison of patient outcomes using different techniques and dose prescriptions
  - Aids safe implementation of new techniques and dose prescriptions

Need consistent and unambiguous treatment summary

What does the ICRU recommend

- International Commission on Radiation Units and Measurements (ICRU) develop guide-lines for prescribing, recording, and reporting absorbed dose for radiation therapy
- ICRU 50, 1993 defined GTV/CTV/PTV
- ICRU 62; 1999 added PRV, IM and setup margin
- Dose prescribed to
  - 100% (ICRU ref point)
  - Range 95-107%
- These documents recommended concepts and procedures for
  - tumour and normal tissue delineation
  - margins to take into account potential tumour invasion, organ motion, and setup error.

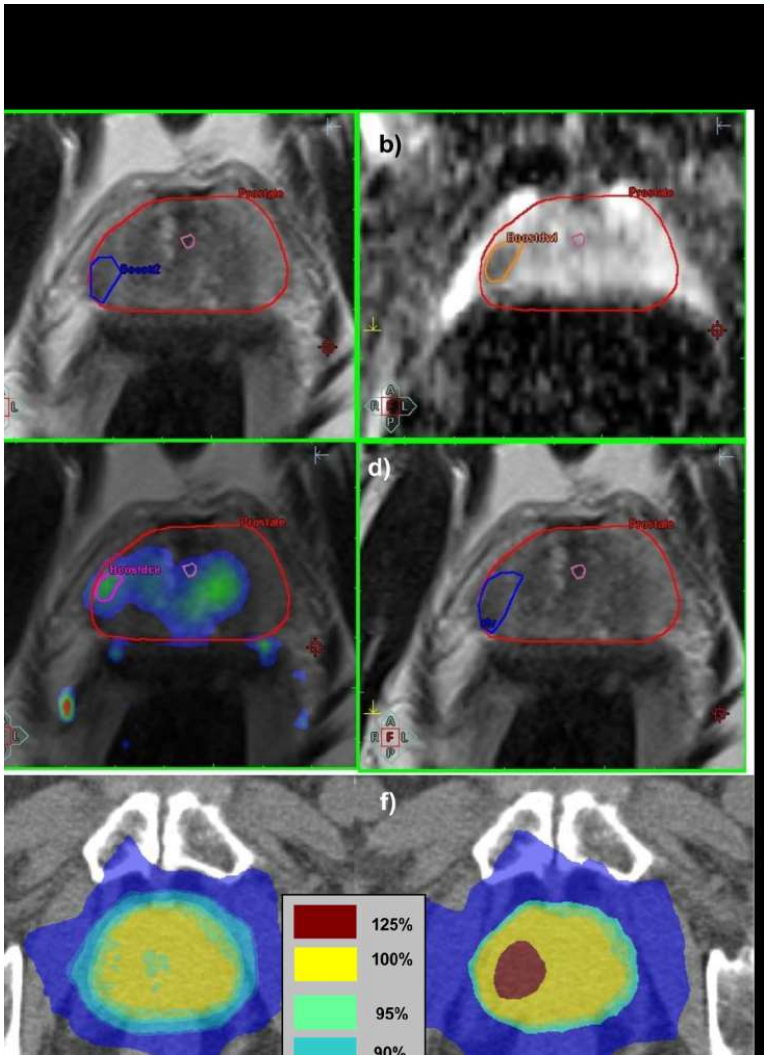
Moving to IMRT and SBRT

Conventional XRT

- Homogeneous dose
- Prescribed to 95% on PTV edge
- Fractionated
- 3-4 co-planar beams

IMRT and SBRT

- Inhomogeneous dose
- Prescribe to iso-volume (80-95%)
- Hypo-fractionated
- Multiple (+/- non-coplanar) beams



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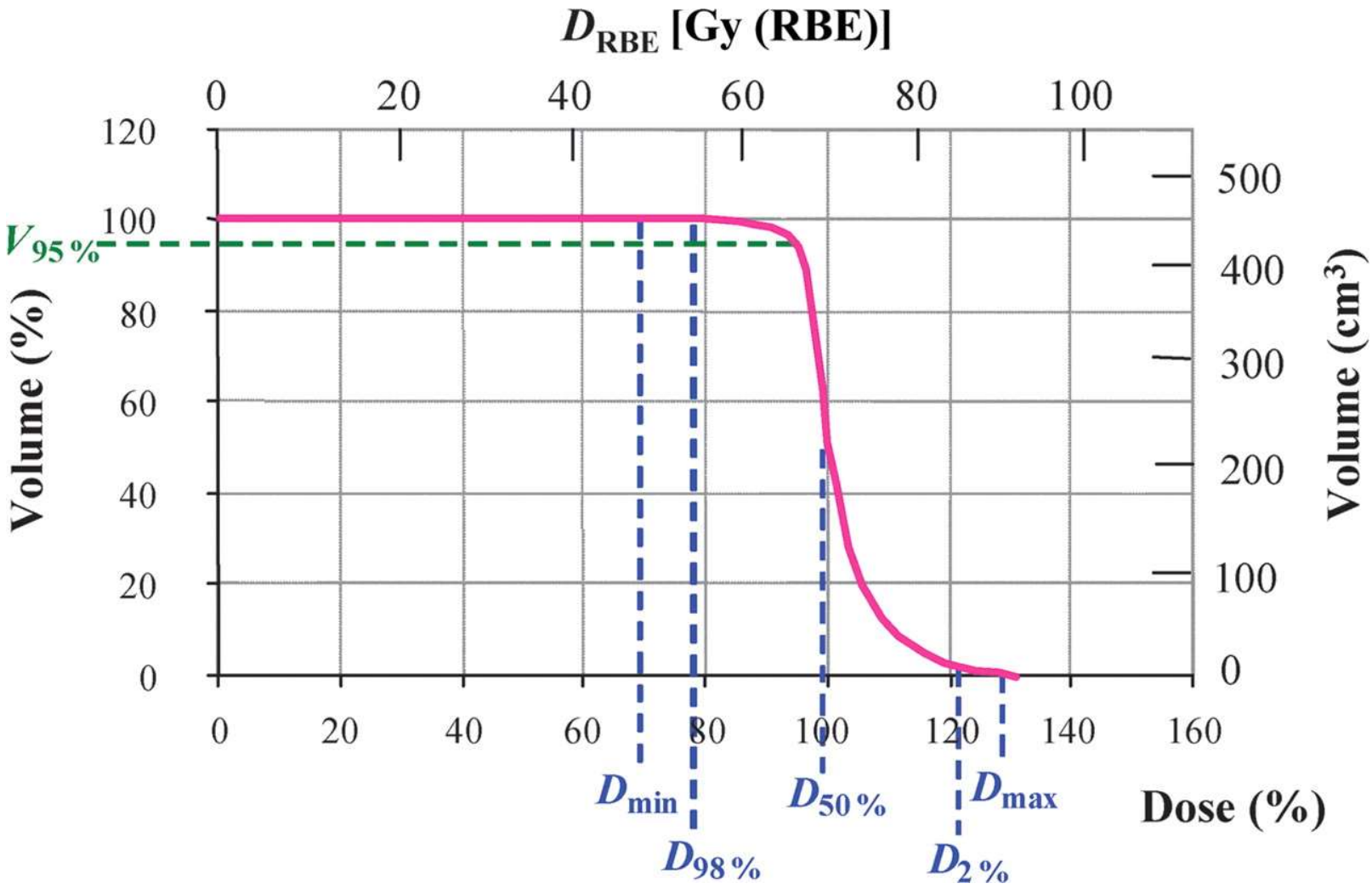
ICRU 83 aims

- To provide the information necessary to standardize IMRT techniques and procedures
- To harmonize the prescribing, recording, and reporting of IMRT
- Moves from single spatial dose point reporting (ICRU ref point, min and max doses) to dose volume reporting
- **ICRU83**: report
  - D50% (D median /mean)
  - D98%
  - D2%



Journal of the ICRU 2007;7:83-94

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Preparation

- Preparation
  - Get it correct at the beginning
  - Outline all structures (ICRU83)
  - Think about
    - Proximity of the PTV to normal structures
    - Dose constraints and objectives
    - Steep dose gradients
  - Clear instructions
  - Good communication

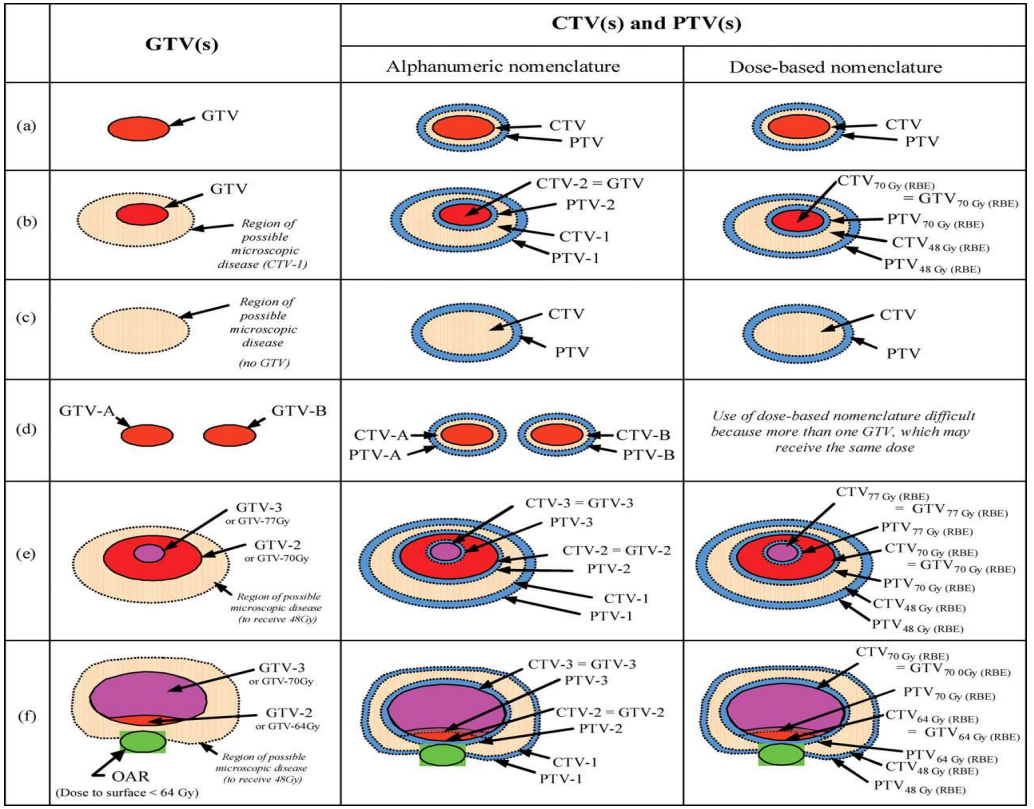
Complexities of target volume definitions

Need to get GTV right!

Consensus on clinical indications for treatment

Develop clinical protocols

Review of contouring



Journal of the ICRU 2007;7:83-94

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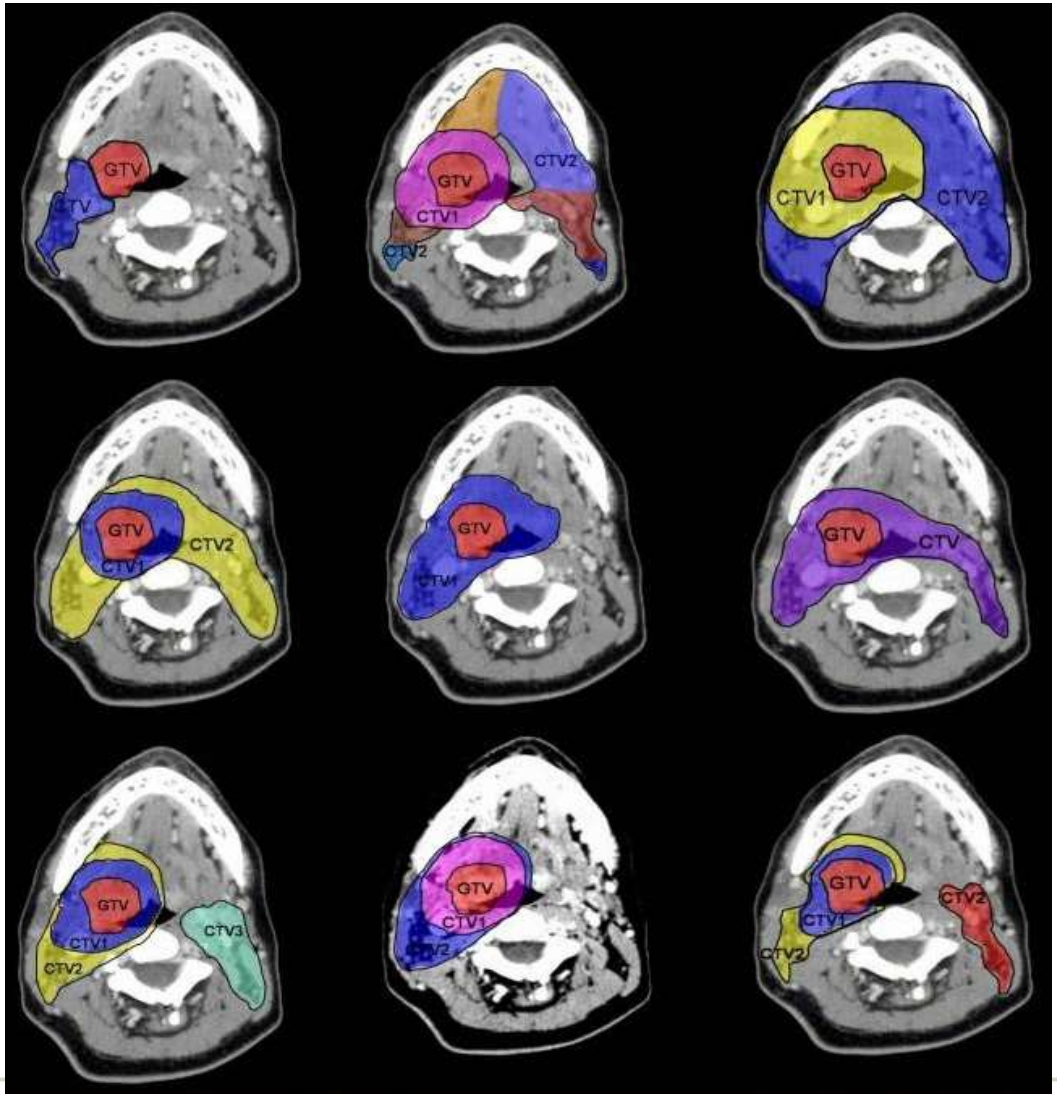
Outlining



Agree target volume definitions

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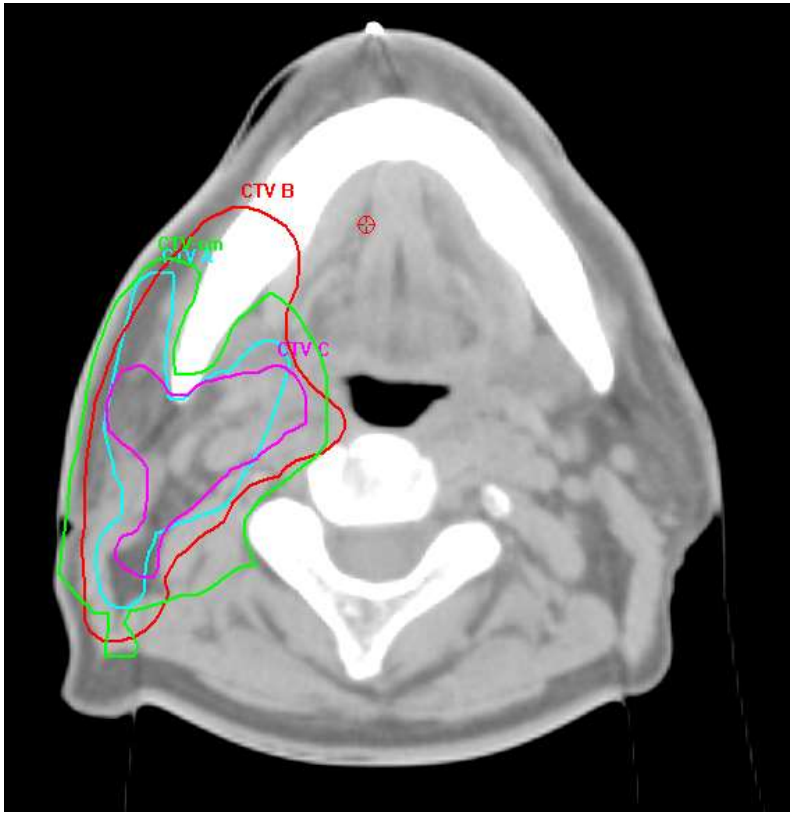
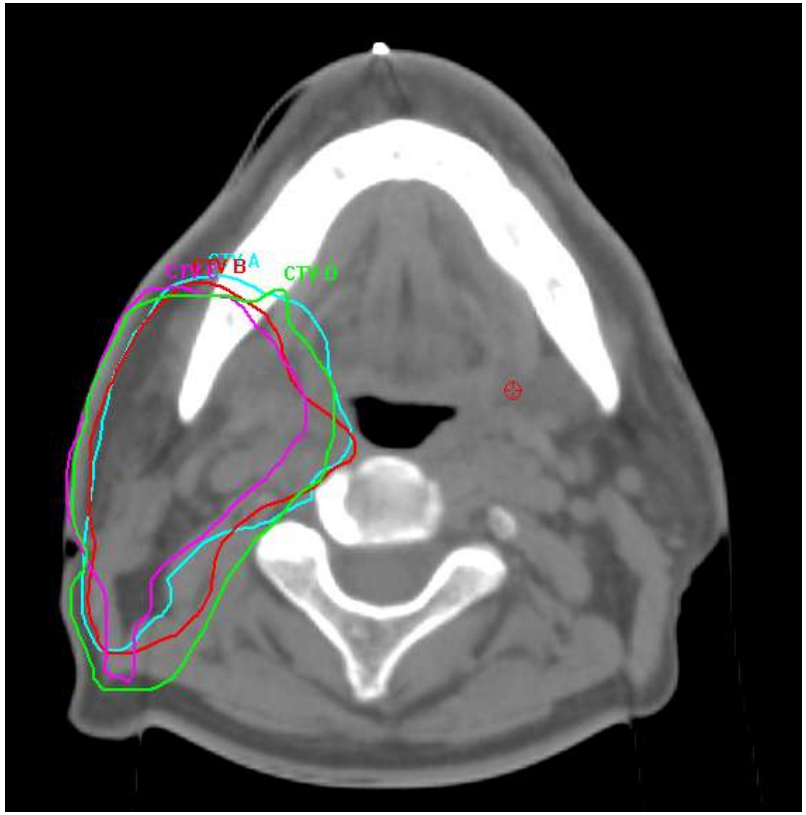
Outlining





Interobserver variation in clinical target volume and organs at risk segmentation in post-parotidectomy radiotherapy: can segmentation protocols help?
M Mukesh et al, BJR 2012

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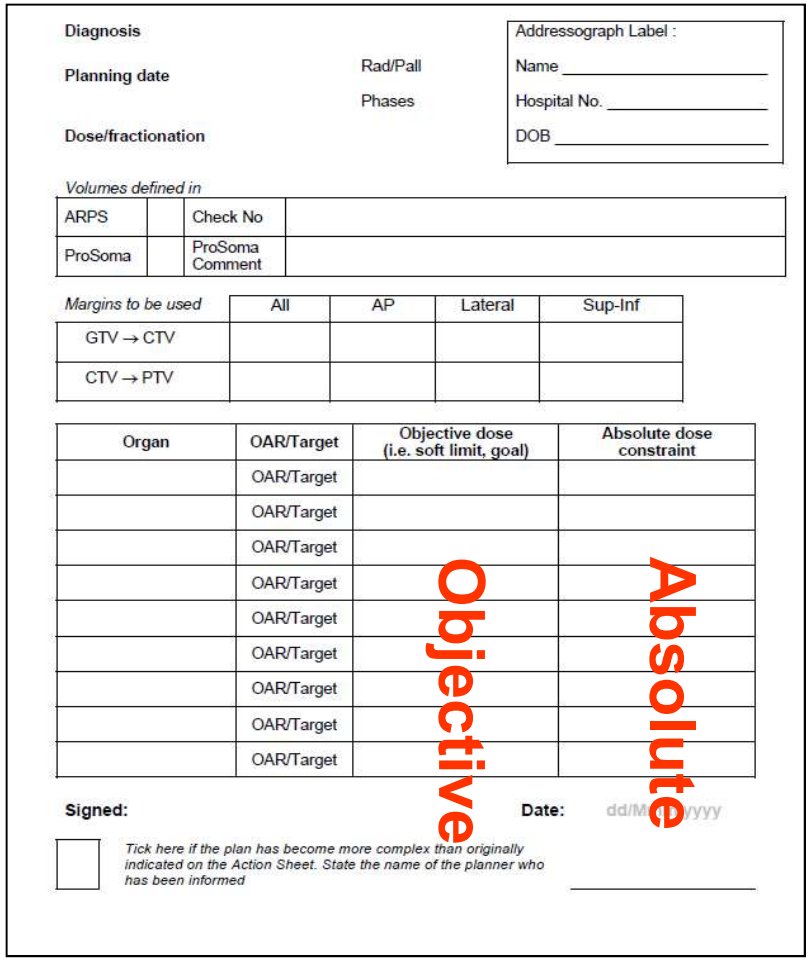
Planning Form

- Planning form to specify
  - Margins
  - Dose constraints
  - Objective (desirable) dose
  - Absolute dose constraints



Diagnosis

Planning date Rad/Pall

Phases

Dose/fractionation

Addressograph Label :

Name _____

Hospital No. _____

DOB _____

Volumes defined in

ARPS		Check No	
ProSoma		ProSoma Comment	

Margins to be used	All	AP	Lateral	Sup-Inf
GTV → CTV				
CTV → PTV				

Organ	OAR/Target	Objective dose (i.e. soft limit, goal)	Absolute dose constraint
	OAR/Target		
	OAR/Target		
	OAR/Target		
	OAR/Target		
	OAR/Target		
	OAR/Target		
	OAR/Target		
	OAR/Target		
	OAR/Target		

Objective

Absolute

Signed: **Date:** dd/M yyyy

Tick here if the plan has become more complex than originally indicated on the Action Sheet. State the name of the planner who has been informed

_____

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Prostate Planning

Organ	OAR/Target	Objective	Dose 74Gy	Dose 60Gy
Rectum	**OAR**	3% vol > 100% dose	74Gy	60Gy
Rectum	**OAR**	<25% vol ≥ 95% dose	70Gy	57Gy
Rectum	**OAR**	<30% vol ≥ 90% dose	67Gy	54Gy
Rectum	**OAR**	<50% vol ≥ 75% dose	55.5Gy	45Gy
Rectum	**OAR**	60% does not cross posterior rectal wall	44.4Gy	36Gy
Bladder	**OAR**	<25% vol > 100% dose	74Gy	60Gy
Bladder	**OAR**	<50% vol > 90% dose	67Gy	54Gy
Femoral Heads	**OAR**	dose to ≥ $2cm^3$	<55Gy	<45Gy
PTV 1 and 2	**Target**	95-107% isodose to cover		
Volumes will not be considered if not outlined				

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IMRT Plan Evaluation

Check plan against dose constraints

- Have objectives / constraints been met

Isodoses

- Scroll through specific isodose levels
- Identify hot spots
- ? dose dumped into an unexpected place

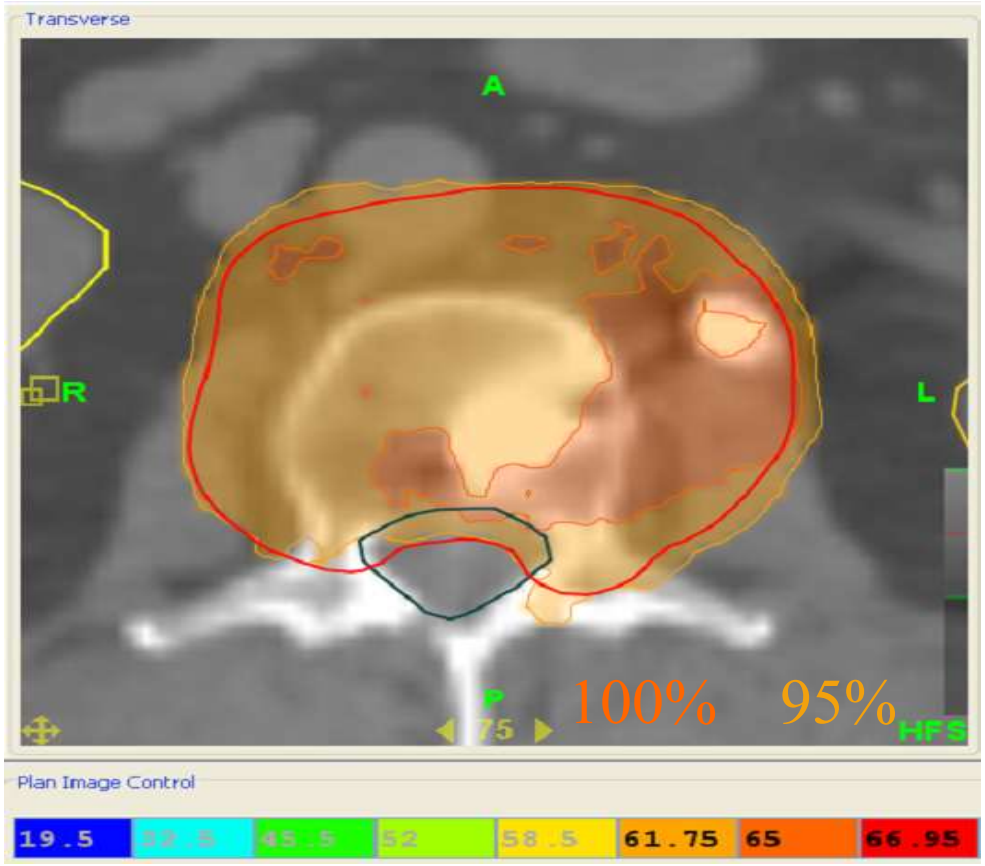
Look at Dose Volume Histogram

Check for unexpected

- Things that you had not thought of!

Isodoses

- Use isodoses specific to the task
- Evaluate PTV coverage
- Select colours to differentiate isodose levels
- Underdose <95% seen more easily without extra colours



95%100%
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Dose volume histograms

- 3D plan information can be summarised into a 2D graph
  - but remember some spatial information is lost
  - a DVH only tells you information about the structures you have accurately contoured

- Volume and dose statistics can be read off from a DVH
  - D_V (absorbed dose in fraction V of the volume)
  - V_D (volume receiving at least an absorbed dose D)

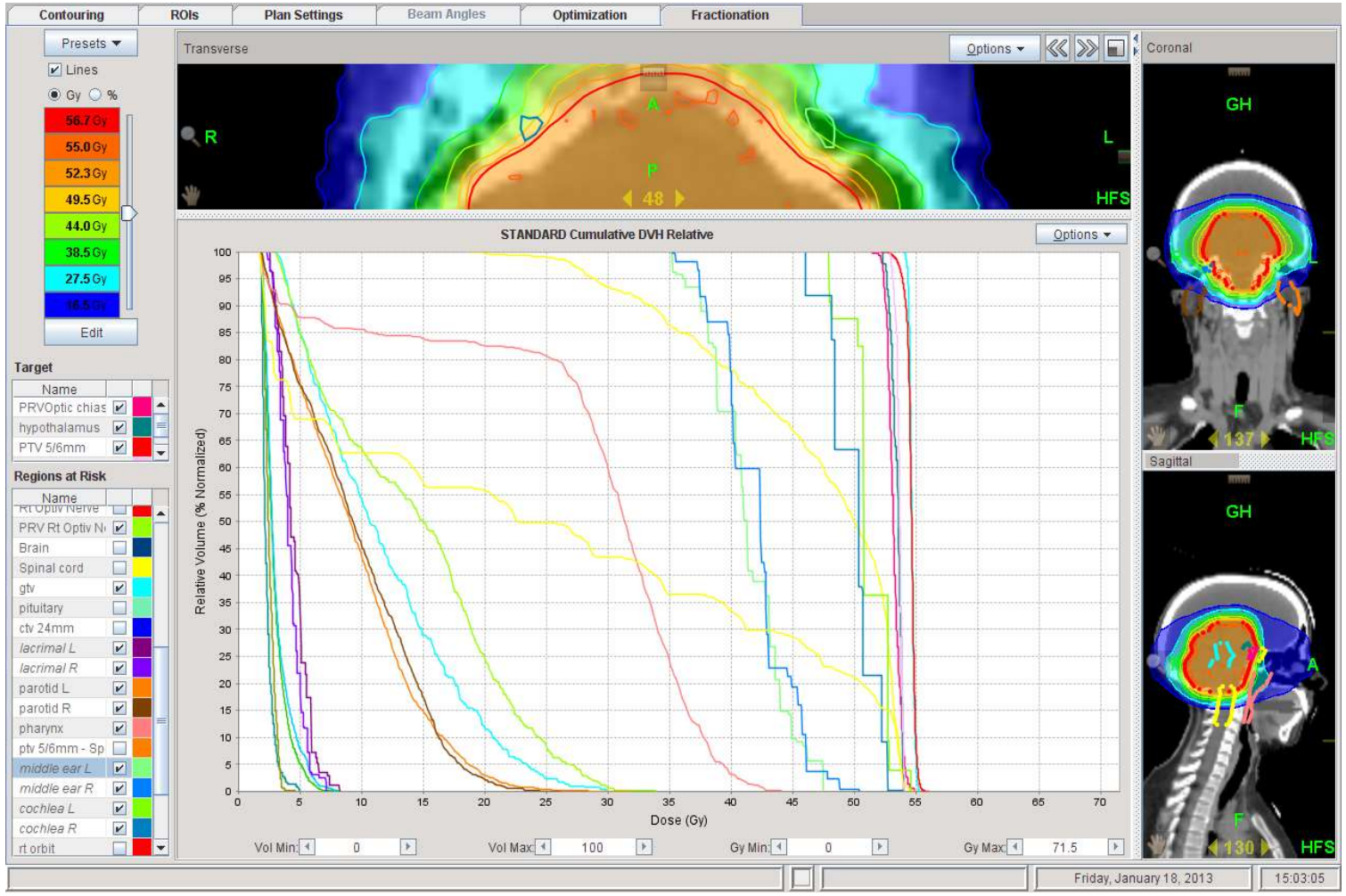
- D50% is identical to Dmean/median

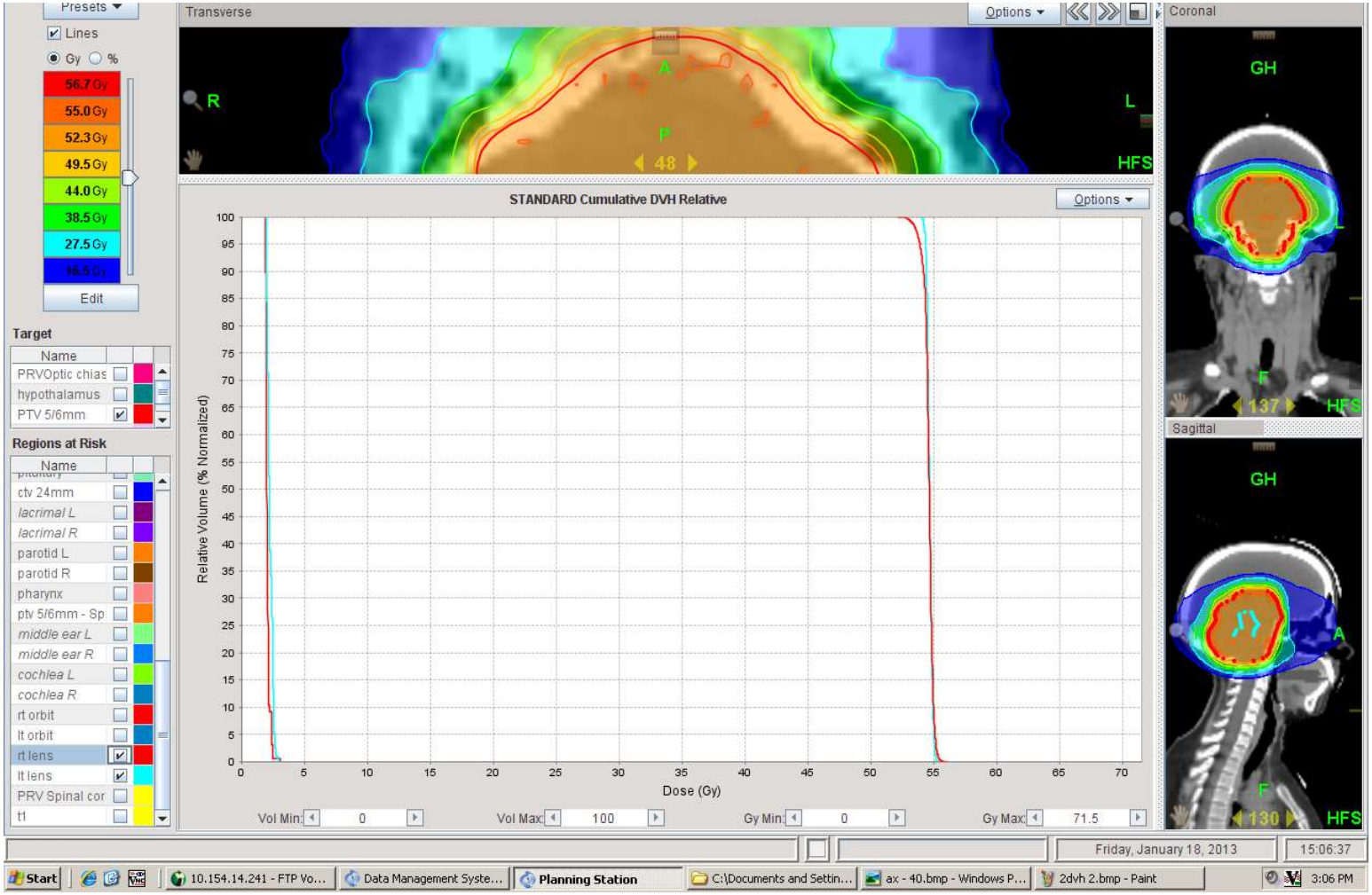
- Dmin and Dmax are identical to D100% and D0%, respectively

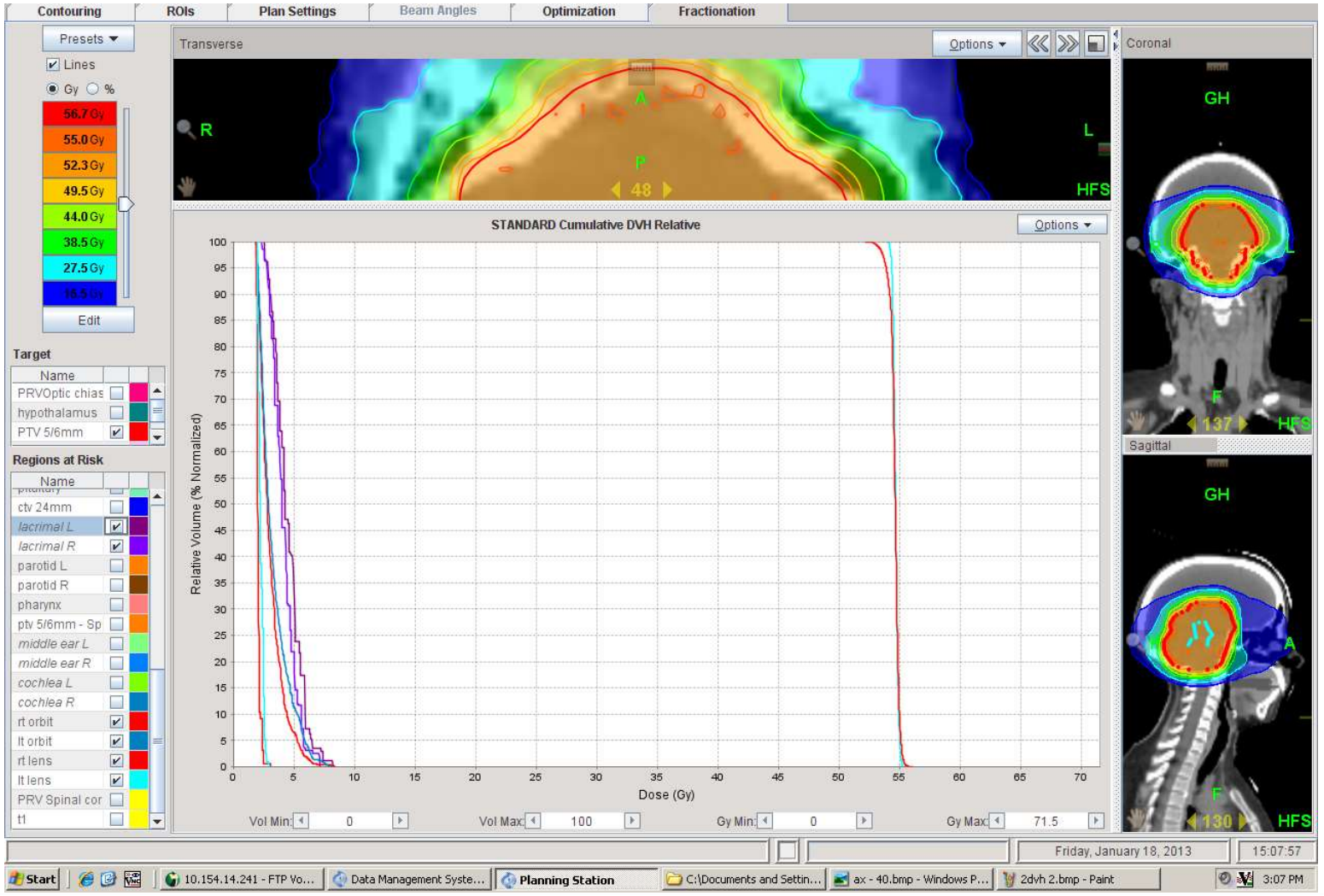
Using Dose Volume Histograms for plan evaluation

- **Complications with a weak volume dependence**
  - Use high-dose end of the DVH
  - D_{max}, D_{05}
  - E.g. spinal cord
- **Complications with strong volume dependence**
  - mean dose
  - other features (e.g. V20), from clinical studies
  - E.g. lung
- **Intermediate volume dependence**
  - Other features (V_D = % volume getting > dose D)
  - E.g. rectum

- Remember spatial aspects not included in DVH but may matter:
- Circumferential irradiation of oesophagus
- Hotspots in un-contoured areas


Contouring
ROIs
Plan Settings
Beam Angles
Optimization
Fractionation
Presets
Lines
Gy
%
56.7 Gy
55.0 Gy
52.3 Gy
49.5 Gy
44.0 Gy
38.5 Gy
27.5 Gy
Edit
Target
Name
PRVOptic chias
hypothalamus
PTV 5/6mm
Regions at Risk
Name
PRV Rt Optiv N
Brain
Spinal cord
gtv
pituitary
ctv 24mm
lacrimal L
lacrimal R
parotid L
parotid R
pharynx
ptv 5/6mm - Sp
middle ear L
middle ear R
cochlea L
cochlea R
rt orbit
Transverse
Options
R
L
A
P
48
HFS
STANDARD Cumulative DVH Relative
Options
Relative Volume (% Normalized)
Dose (Gy)
Vol Min: 0
Vol Max: 100
Gy Min: 0
Gy Max: 71.5
Coronal
GH
137
HFS
Sagittal
GH
A
130
HFS
Friday, January 18, 2013
15:03:05


Presets
Lines
Gy
%
56.7 Gy
55.0 Gy
52.3 Gy
49.5 Gy
44.0 Gy
38.5 Gy
27.5 Gy
16.5 Gy
Edit
Target
Name
PRVOptic chias
hypothalamus
PTV 5/6mm
Regions at Risk
Name
ctv 24mm
lacrimal L
lacrimal R
parotid L
parotid R
pharynx
ptv 5/6mm - Sp
middle ear L
middle ear R
cochlea L
cochlea R
rt orbit
lt orbit
rt lens
lt lens
PRV Spinal cor
t1
Transverse
Options
R
L
A
P
48
HFS
STANDARD Cumulative DVH Relative
Options
Relative Volume (% Normalized)
Dose (Gy)
Vol Min: 0
Vol Max: 100
Gy Min: 0
Gy Max: 71.5
Coronal
GH
F
137
HFS
Sagittal
GH
A
F
130
HFS
Friday, January 18, 2013
15:06:37
Start
10.154.14.241 - FTP Vo...
Data Management Syste...
Planning Station
C:\Documents and Settin...
ax - 40.bmp - Windows P...
2dvh 2.bmp - Paint
3:06 PM



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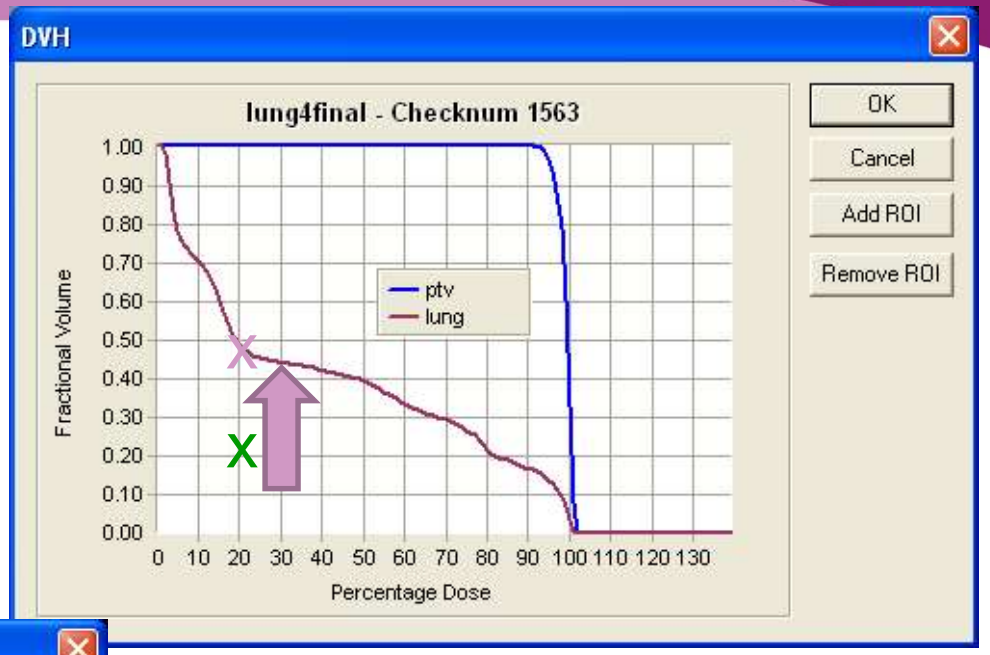
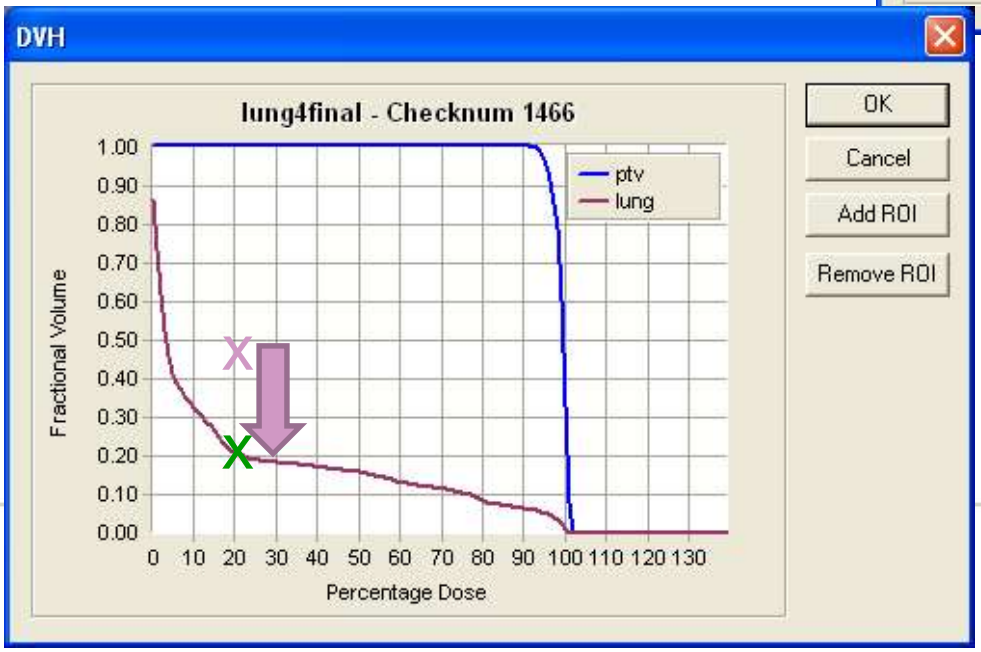
IMRT Plan Evaluation

- Outlining
  - Organs must be outlined or they will be ignored
    - Planner may notice, computer will not!
      - Salivary glands, oesophageal sphincters, cochlea, mandible
  - The whole organ of interest must be outlined
    - Easy not to outline whole lung – conservative, but not ideal
  - Dangerous to ‘over outline’
    - Easy to ‘over outline’ rectum – under-estimate dose

- Lung outlined only over length of PTV
- DVH ‘poor’
  - Underestimates volume





- Whole lung outlined
- DVH ‘acceptable’
- V20 < 25%

  (30% of 66Gy)

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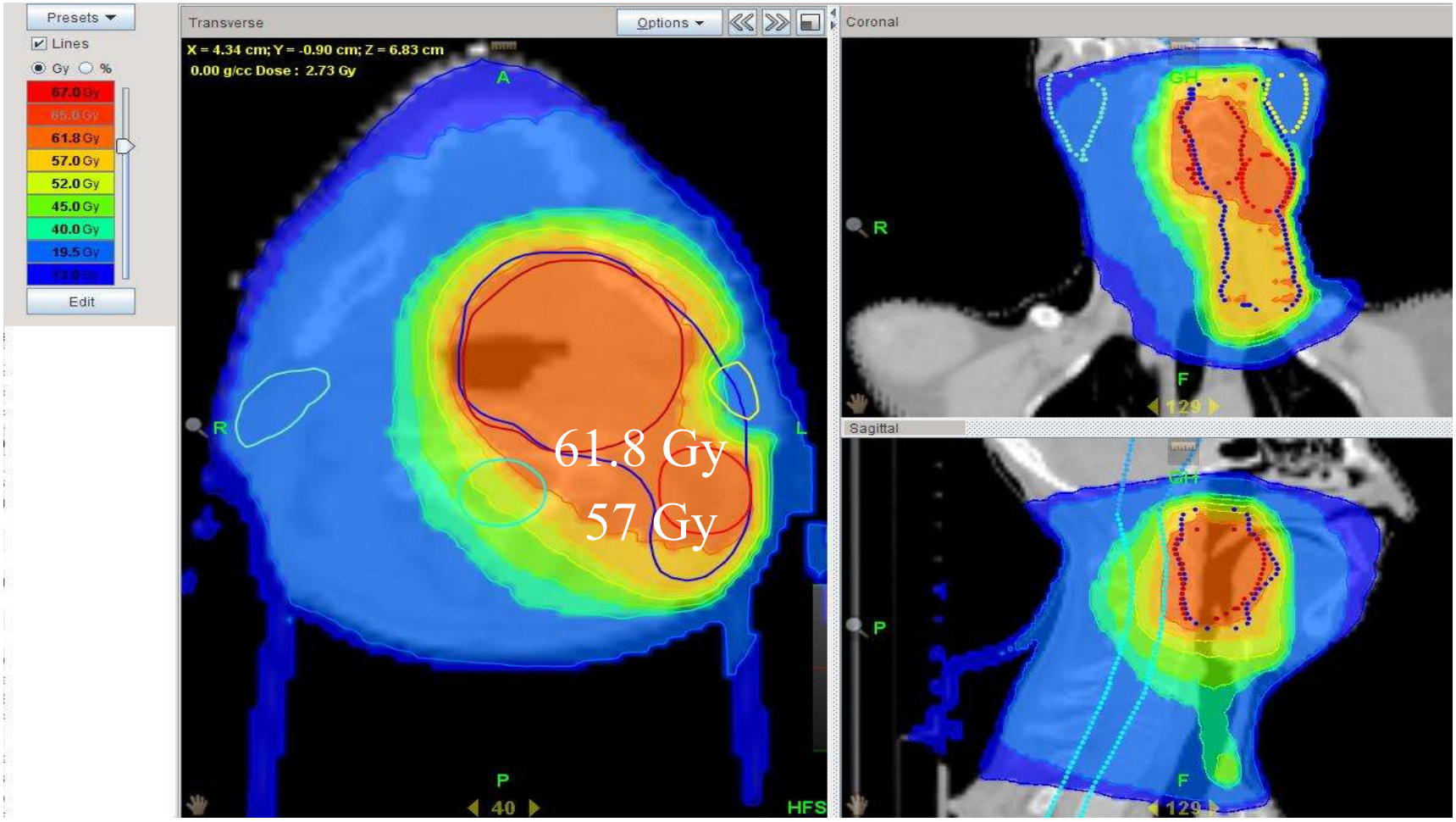
Pitfalls

Things to look out for:

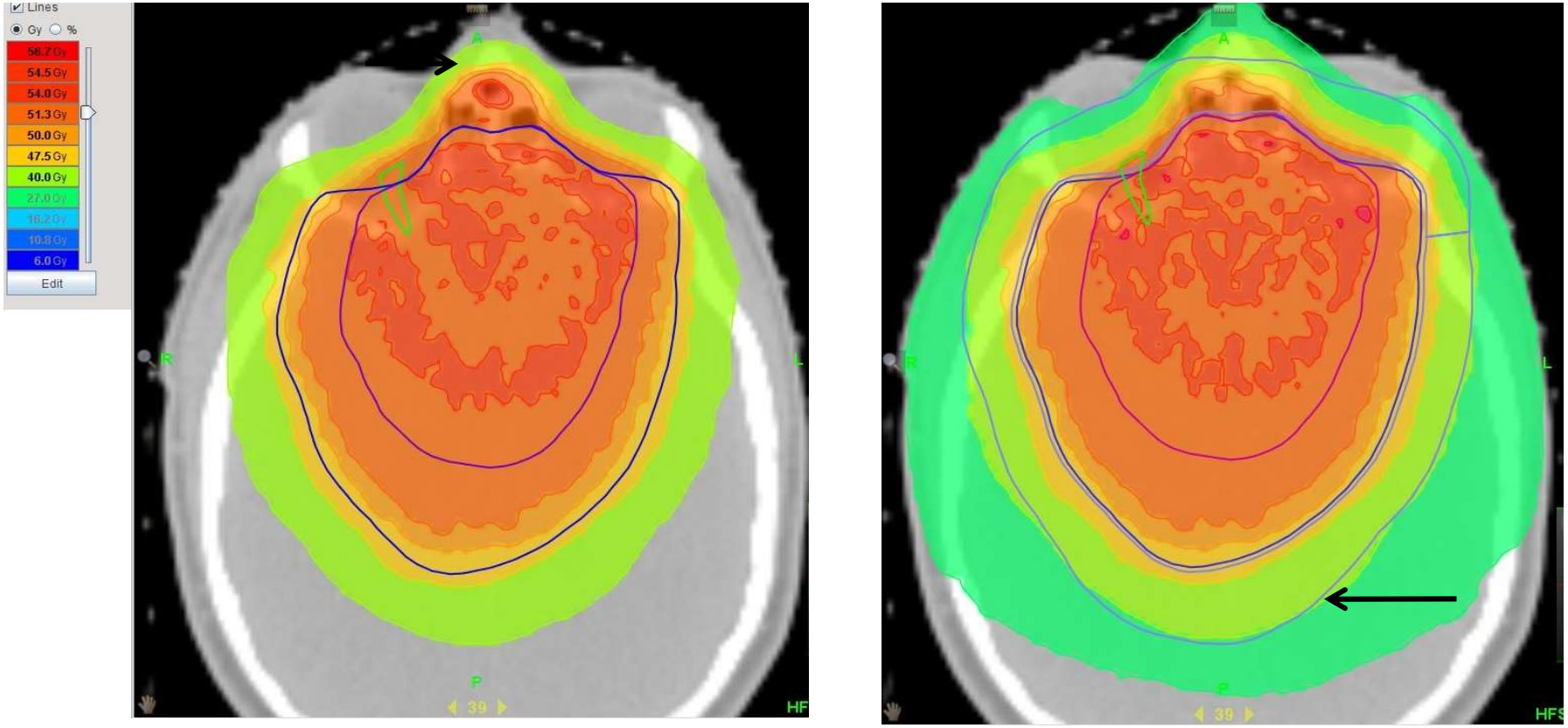
- Structures undefined / unclear nomenclature
- Over complication
- Hot spot outside PTV
- Baggy PTV coverage
- Build up region
- Bolus

Head and neck case



Cord dose too high (NB cord not cord PRV)

Low grade glioma



Hotspot outside PTV

Improvement by addition of a ‘rind’ or ‘planning’ ring structure

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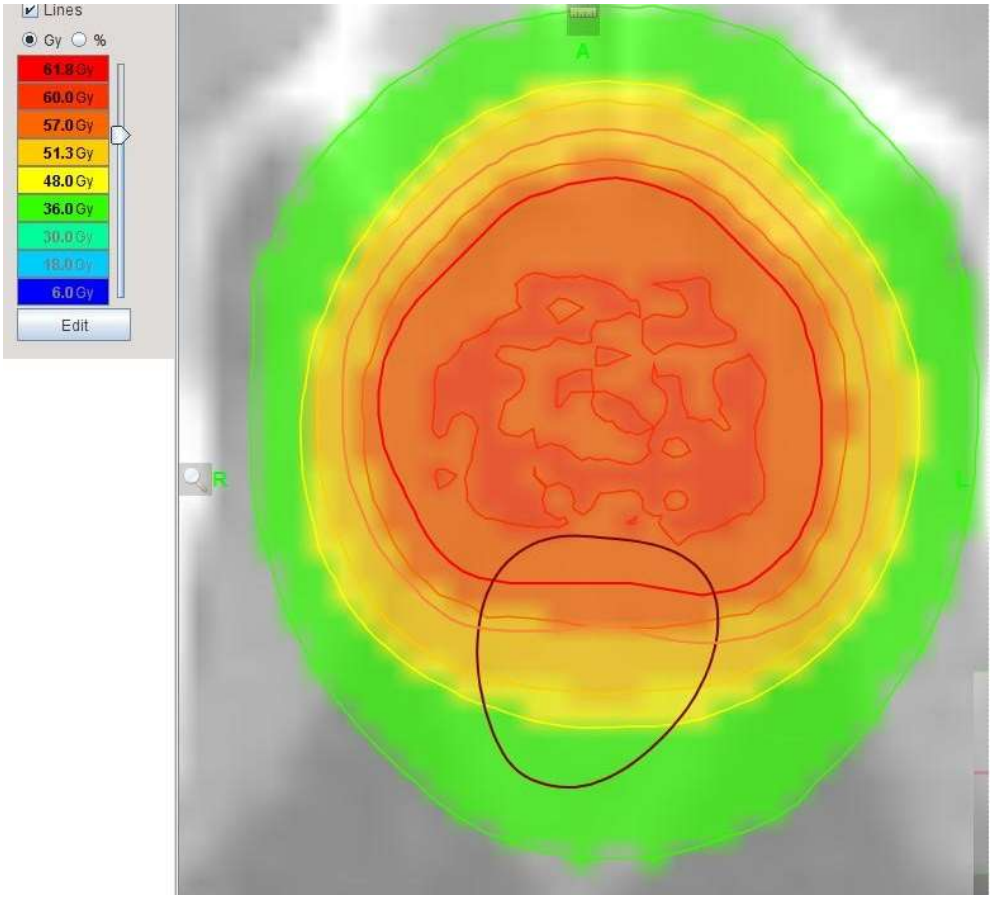
Prostate

Prostate

60Gy in 20#

Posterior rectal wall has unnecessarily high dose

60% (36 Gy) isodose is too ‘baggy’



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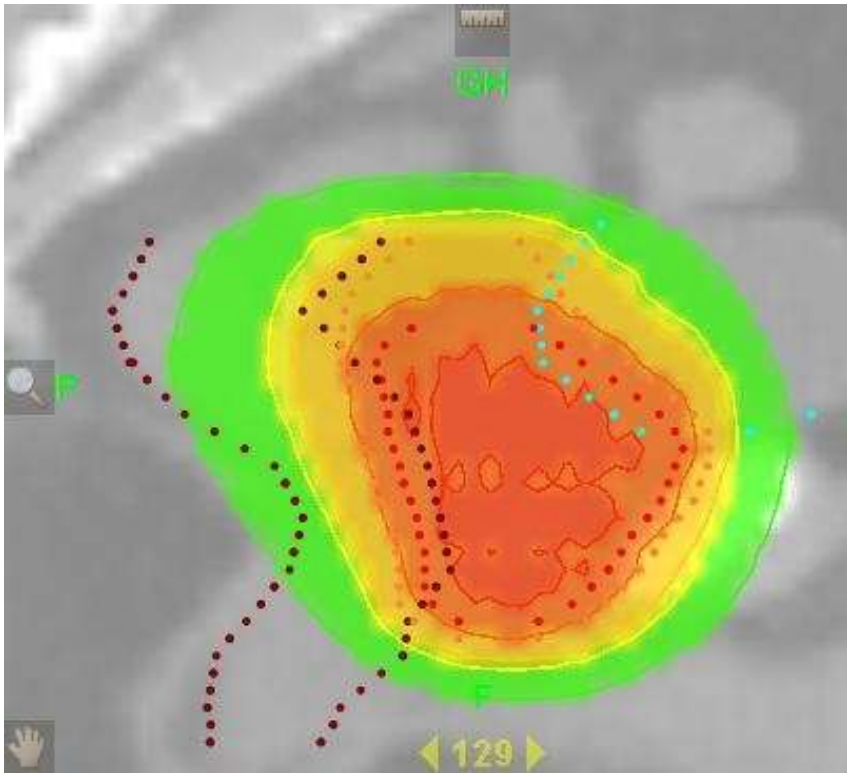
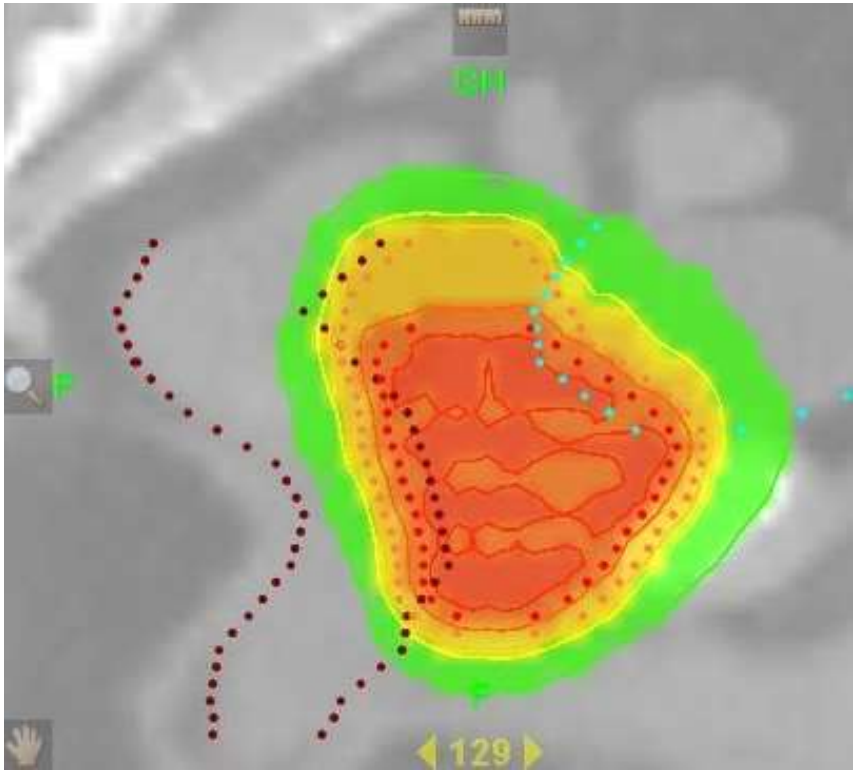
Prostate





Baggy' PTV (green = 60%)

Improved by up weighting the importance of the rectum

General issues

PRV concept works best for serial structures such as cord or brain stem which depend on D max

More complex to use for parallel structures with a volume dependence

Many TPS optimization reduce dose adjacent to where OAR is so get minimums which may be in target areas

- ? How to compensate
- ? Allow dose to spill out in volumes away target

Can automation help standardisation ?

Standardisation:

treat each patient with the
technically best possible *individualised* plan

Technically best possible:

- for treatment unit available
- based on evidence and/or (inter)national guidelines, the institution's policy, or the doctor's point of view
- independent of
  - optimal use of a TPS
  - experience of the planner
  - planner's subjective preferences
  - allotted time for planning

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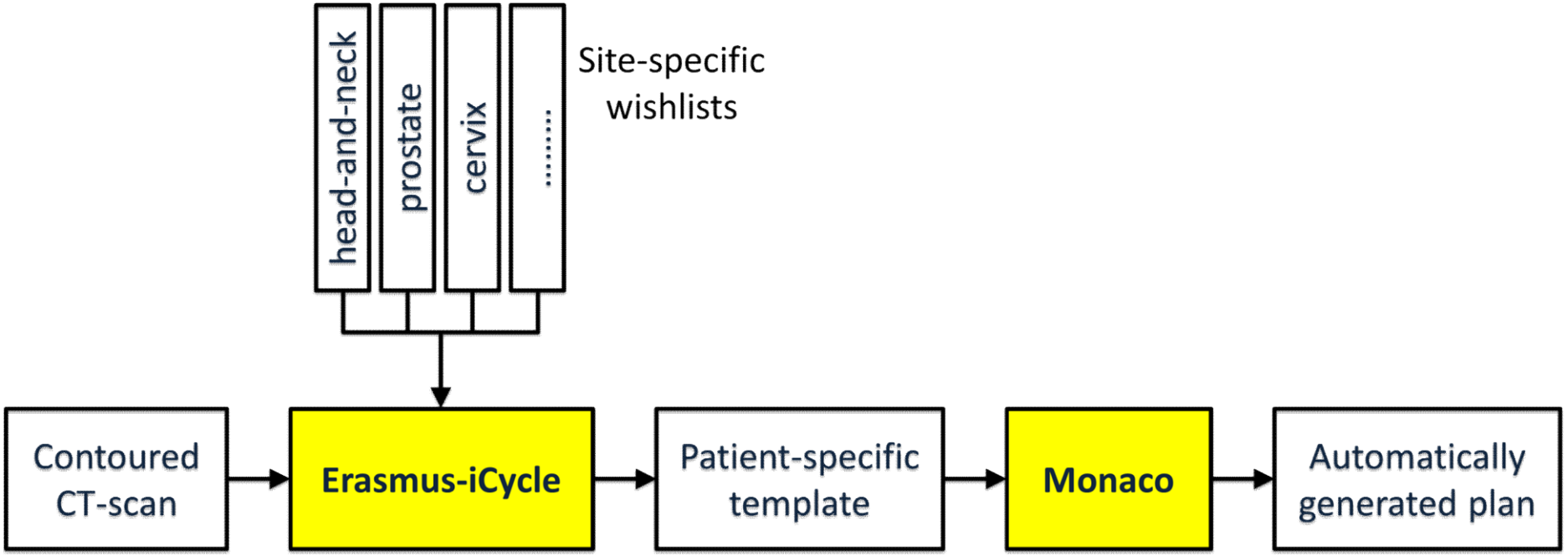
Fully automated multi-objective treatment plan generation

Erasmus-iCycle/Monaco



Erasmus-iCycle: Breedveld S, Storchi PR, Voet PW, Heijmen BJM. iCycle: Integrated, multicriterial beam angle, and profile optimization for generation of coplanar and noncoplanar IMRT plans. Med Phys. 2012; 39(2): 951-963.

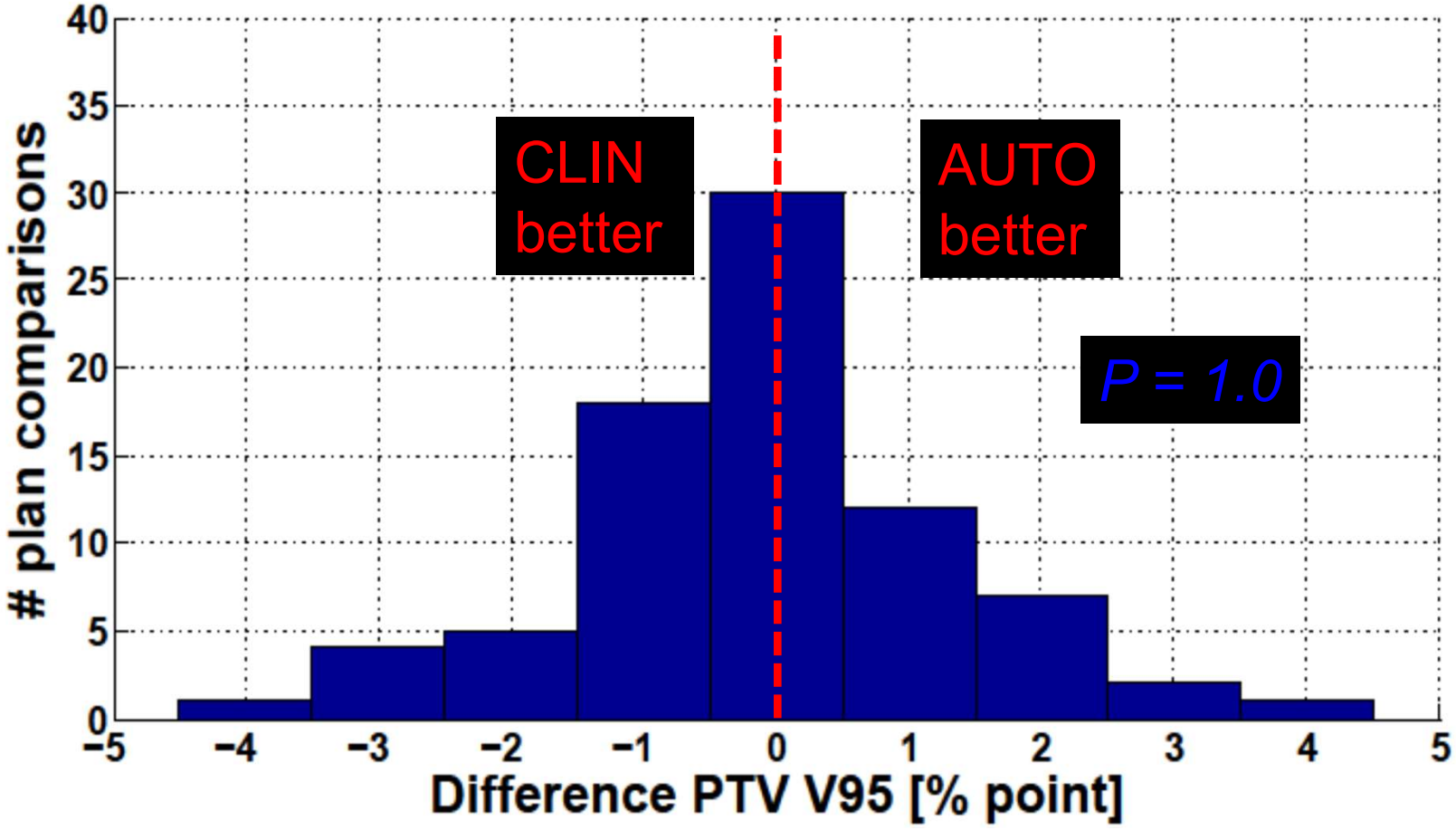
Monaco: Elekta AB, Stockholm, Sweden

International validation study
automated VMAT planning for prostate cancer

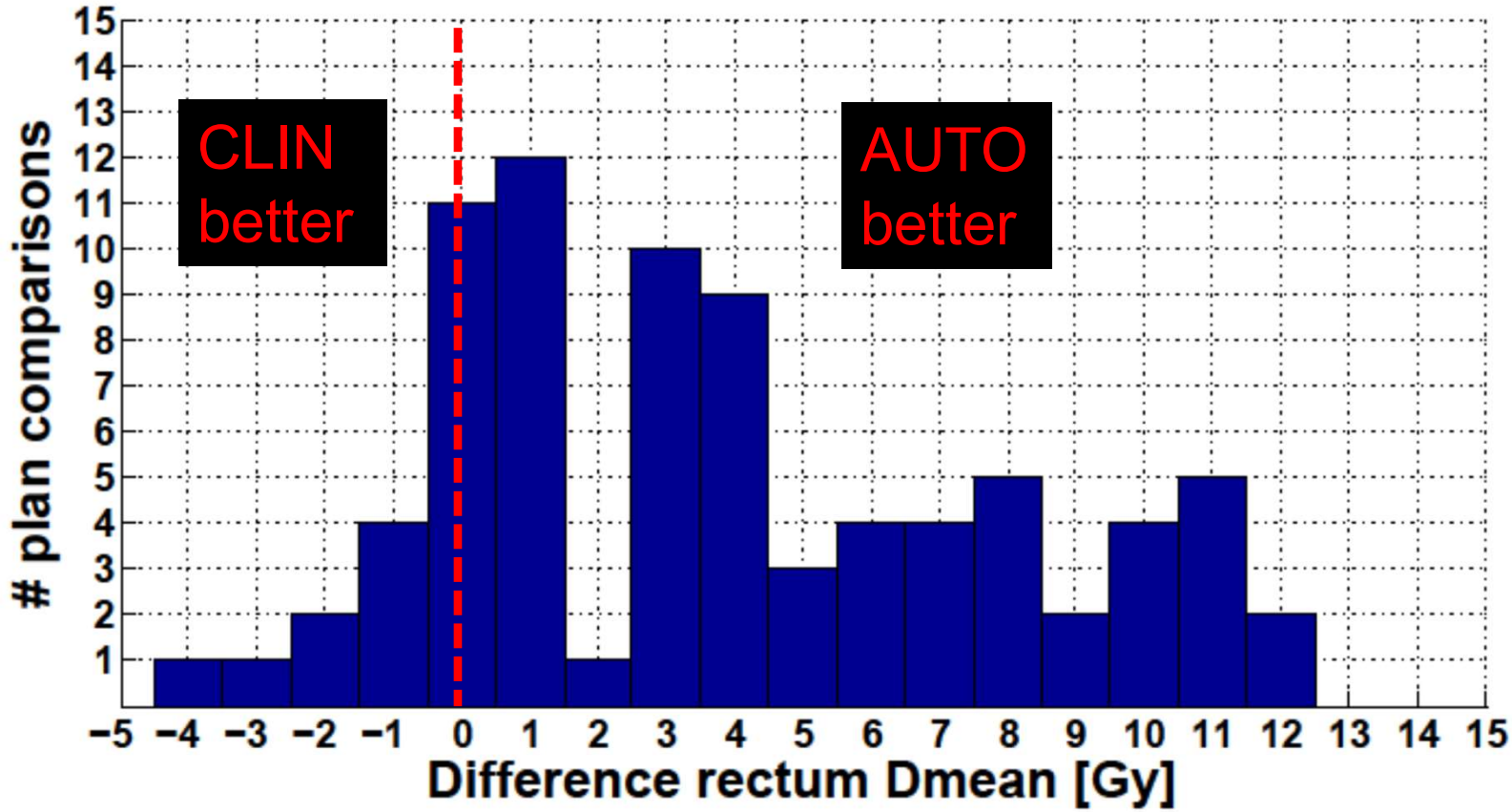
Study Protocol:

For all 4 centers:

- Include VMAT plans of 30 recently treated patients (manual planning with Monaco)
- 10/30 *training* patients used for configuring Erasmus-iCycle/Monaco for plan generation according to center's treatment approach
- For other 20/30 *evaluation* patients:
  - generate AUTOVMAT plan (for local treatment unit)
  - dosimetric comparisons (DVH): CLINICAL vs. AUTO
  - physician side-by-side plan comparisons with scoring: CLINICAL vs. AUTO
    (plan comparisons in Monaco, in the center)



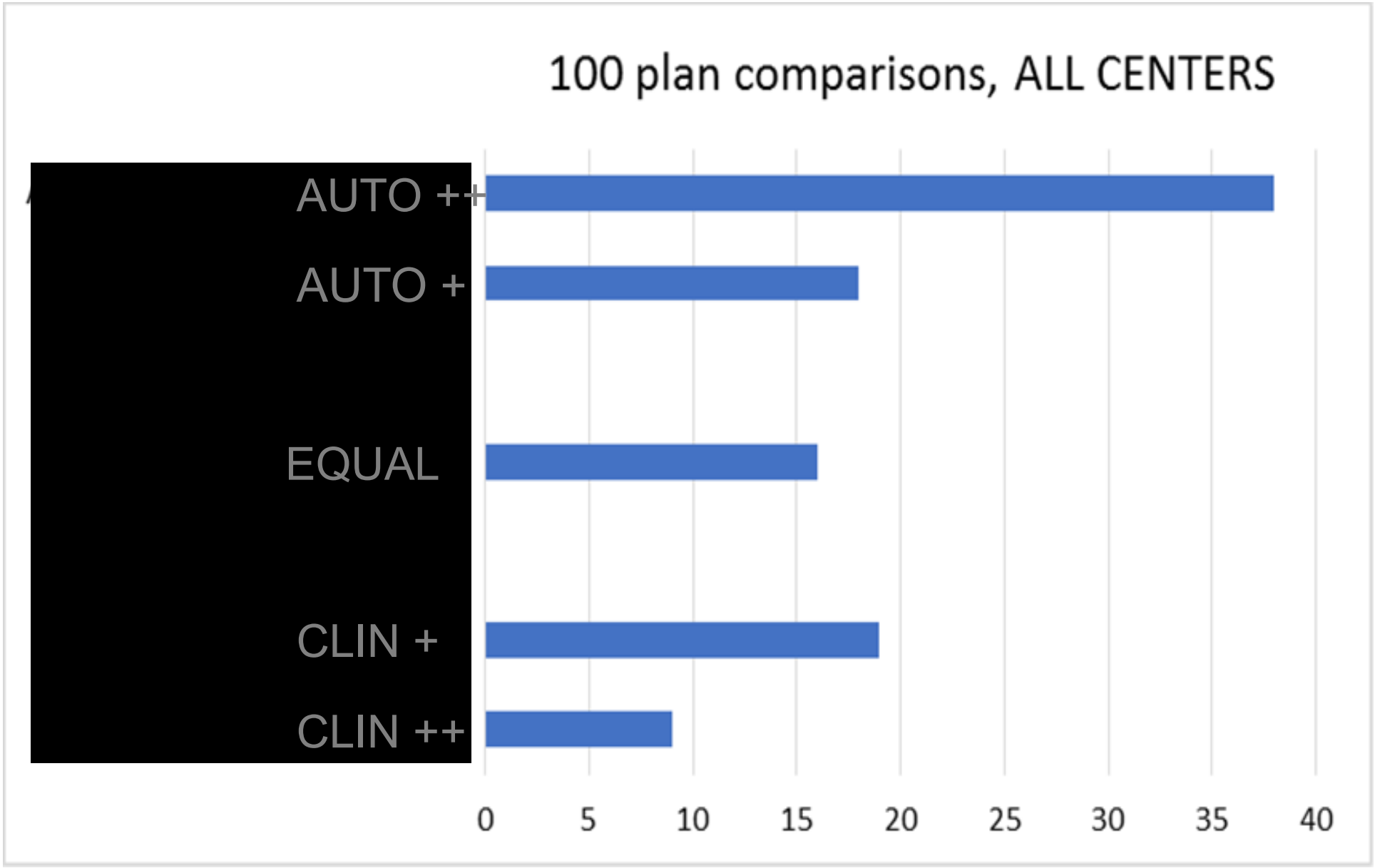
Priorities of all 4 centres:
1. PTV 2. Rectum 3. Bladder



$\Delta D\downarrow mean$ = 3.9 Gy

$P < 0.001$

Physician scoring : CLINICAL VMAT vs AUTOVMAT



Fully automated VMAT plan generation - an international multi-institutional validation study

Conclusions:

Both dosimetric comparisons and scoring by physicians point at substantial plan quality gain with automated planning

Erasmus-iCycle/Monaco automated planning works well in multi-centre setting

Future role of planners in treatment planning?

- Planners remain more important than ever!
- *NOT* for routine planning; prostate, lung, breast, …
- Expert planners with deep understanding remain crucial:
  - Configuration AUTO-planning: expertise and good manual planning

    (Sub-optimal configuration ➔ systematic dose "error" for patient group)
  - New treatment protocol ➔ new configuration
  - Software updates: new possibilities to improve plans ➔ update configuration
  - Software updates: undesirable changes in software
  - Manual planning remains essential, e.g. 5-10% of patients
    - Preserve expertise and skills
    - QA and improvement of AUTO-planning configurations
  - More time for manual planning of "unique", compex cases (re-irradiation, ….)

Conclusions

- Safety is improved by uniformity in reporting radiation dose distributions
- Patient outcomes will improve with high quality and more consistent RT delivery
- IMRT and SBRT deliver complex non-uniform dose distributions to target : ICRU83 can be used as basis for reporting
- We all need to ‘Talk the same language’

Erasmus MC
University Medical Center Rotterdam

ICR The Institute of Cancer Research

The ROYAL MARSDEN
NHS Foundation Trust

Field junctions: how, when, and alternatives

Ben Heijmen, Shaista Hafeez

ESTRO - Physics for Modern Radiotherapy
Bucharest, 2017

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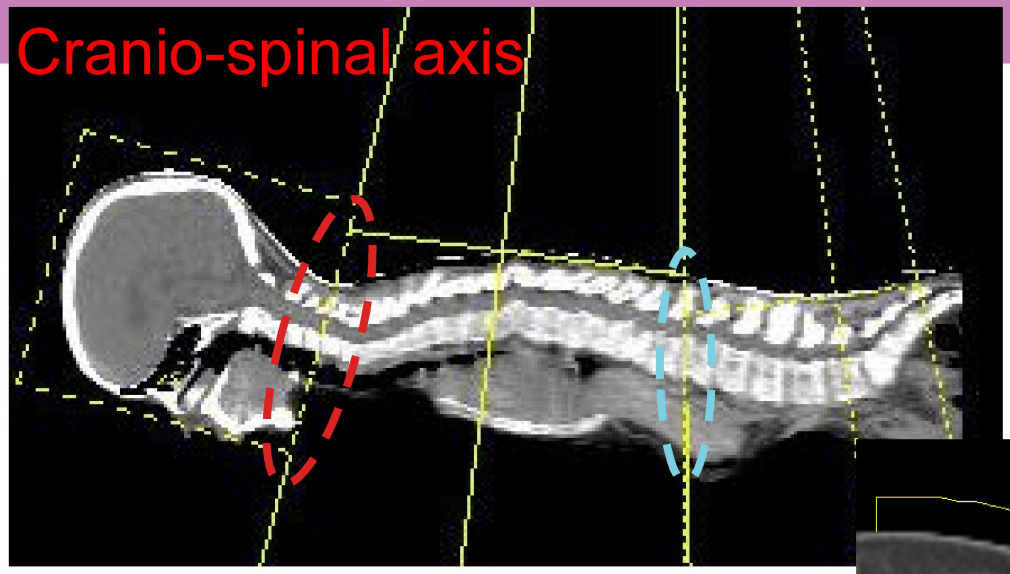
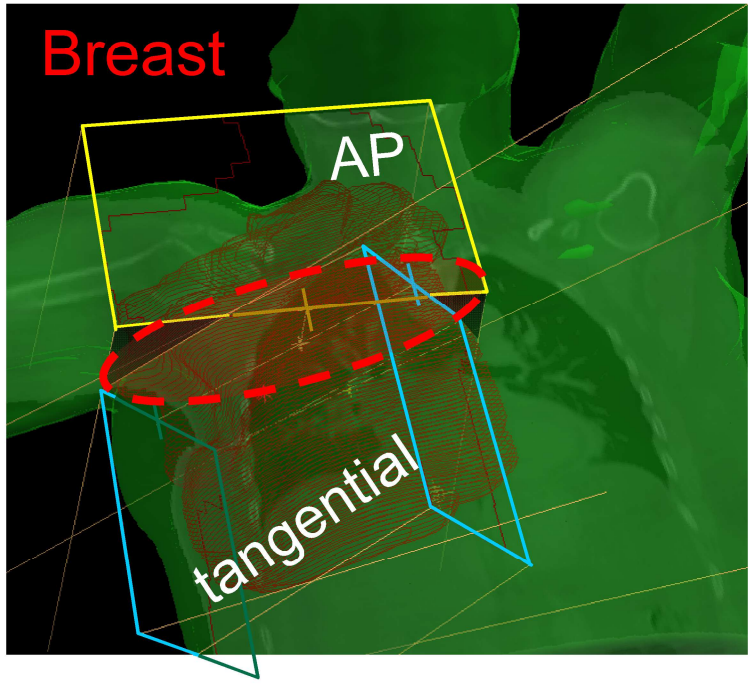
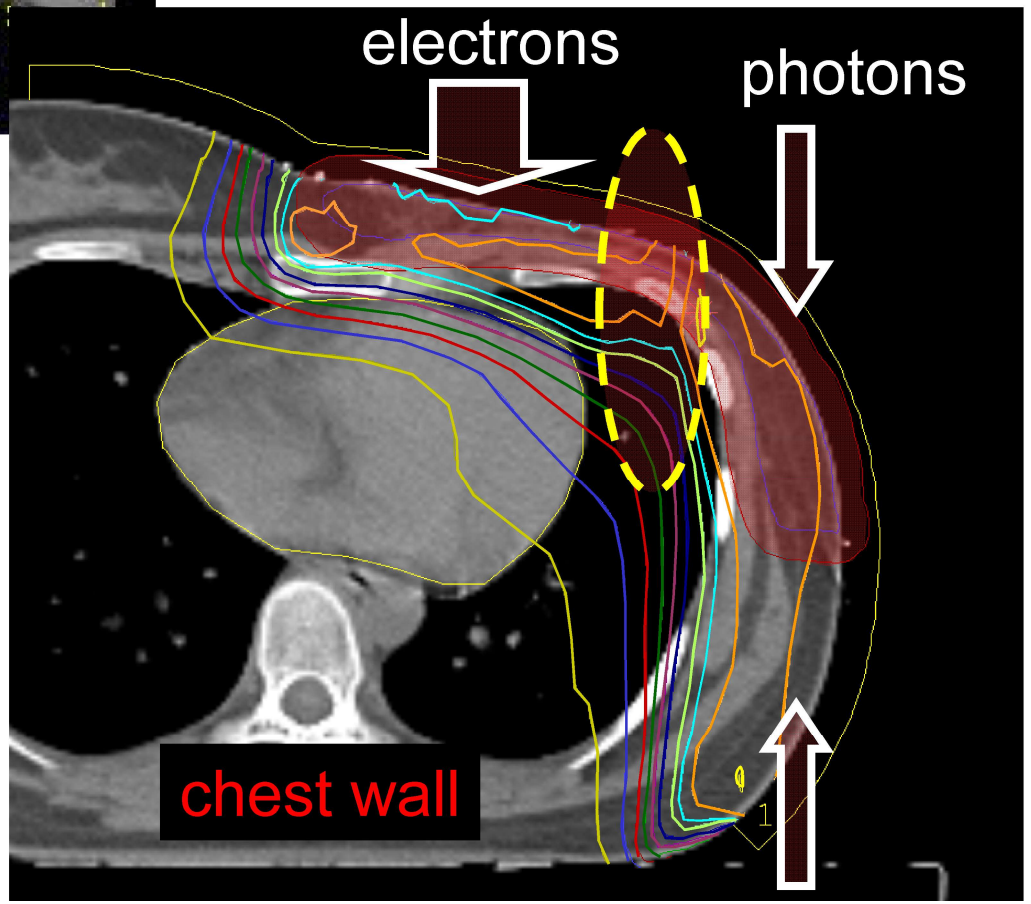
Clinical examples for the use of junctions

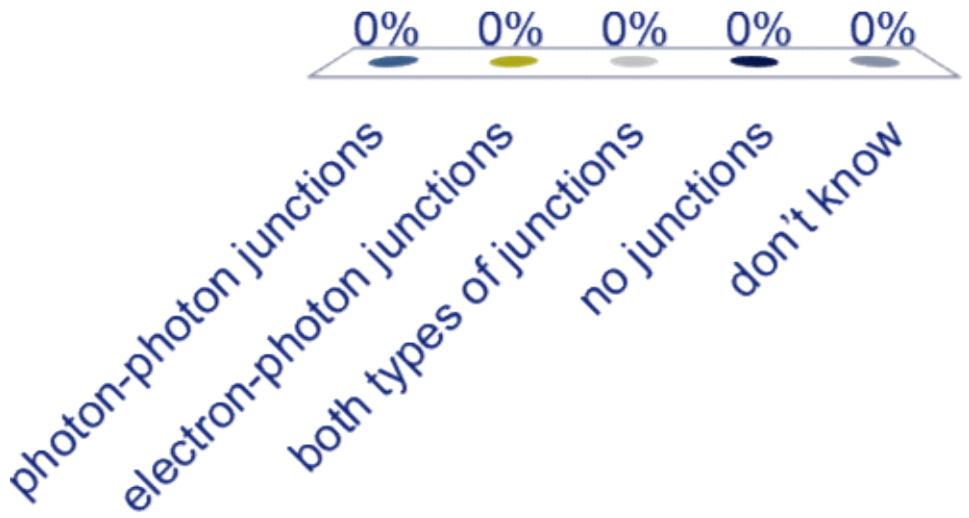






In my institution we use

A. photon-photon junctions
B. electron-photon junctions
C. both types of junctions
D. no junctions
E. don’t know



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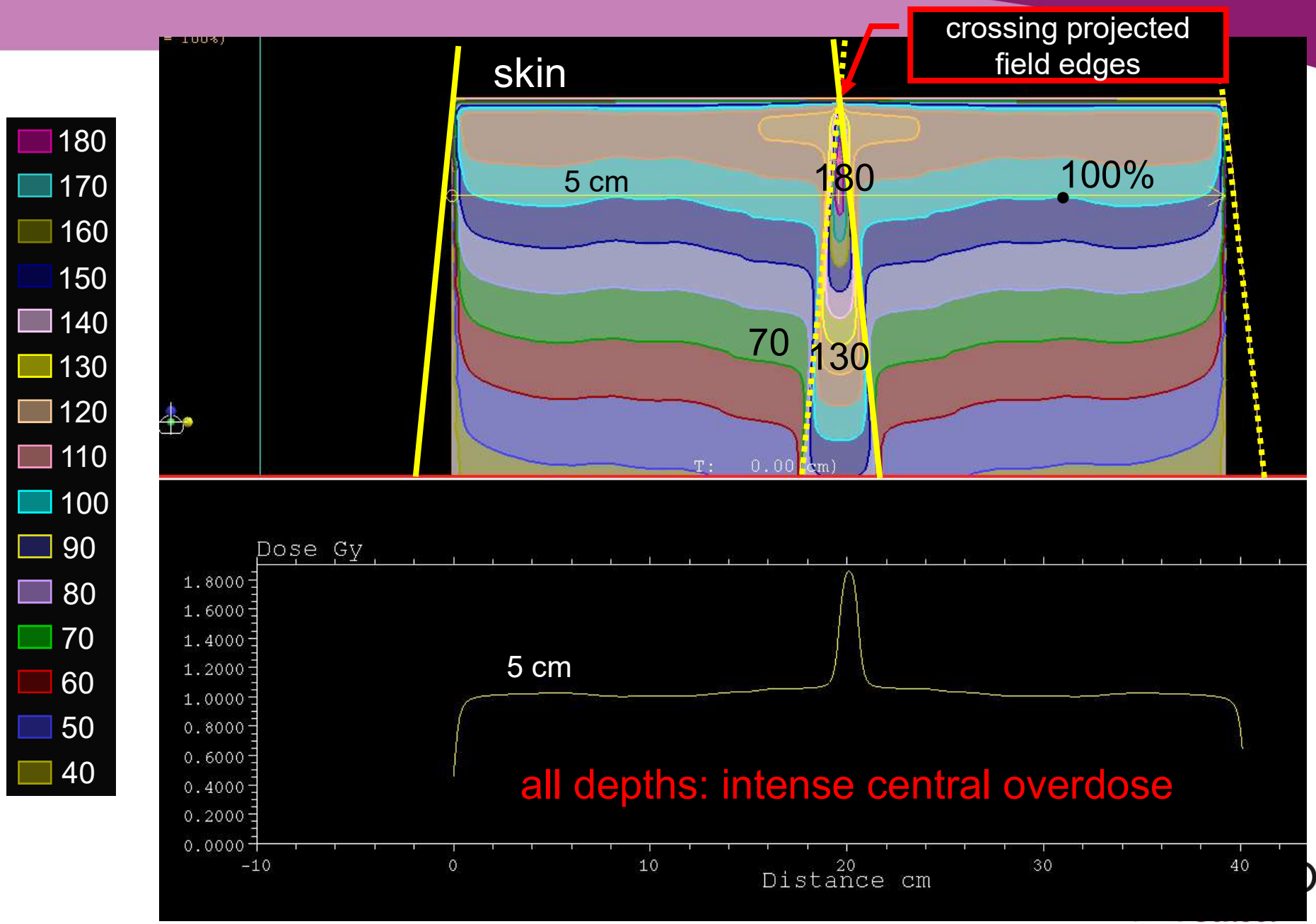
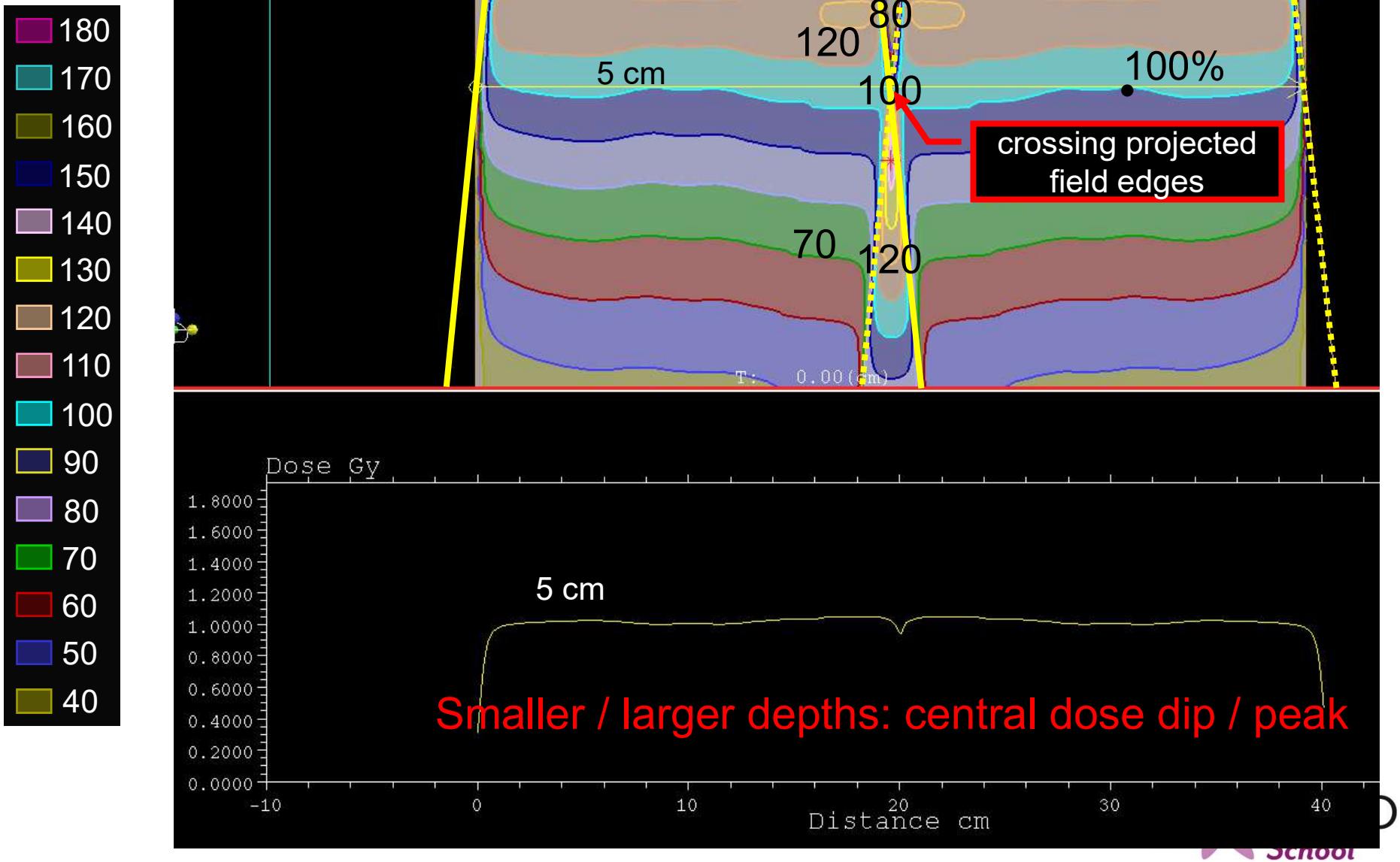
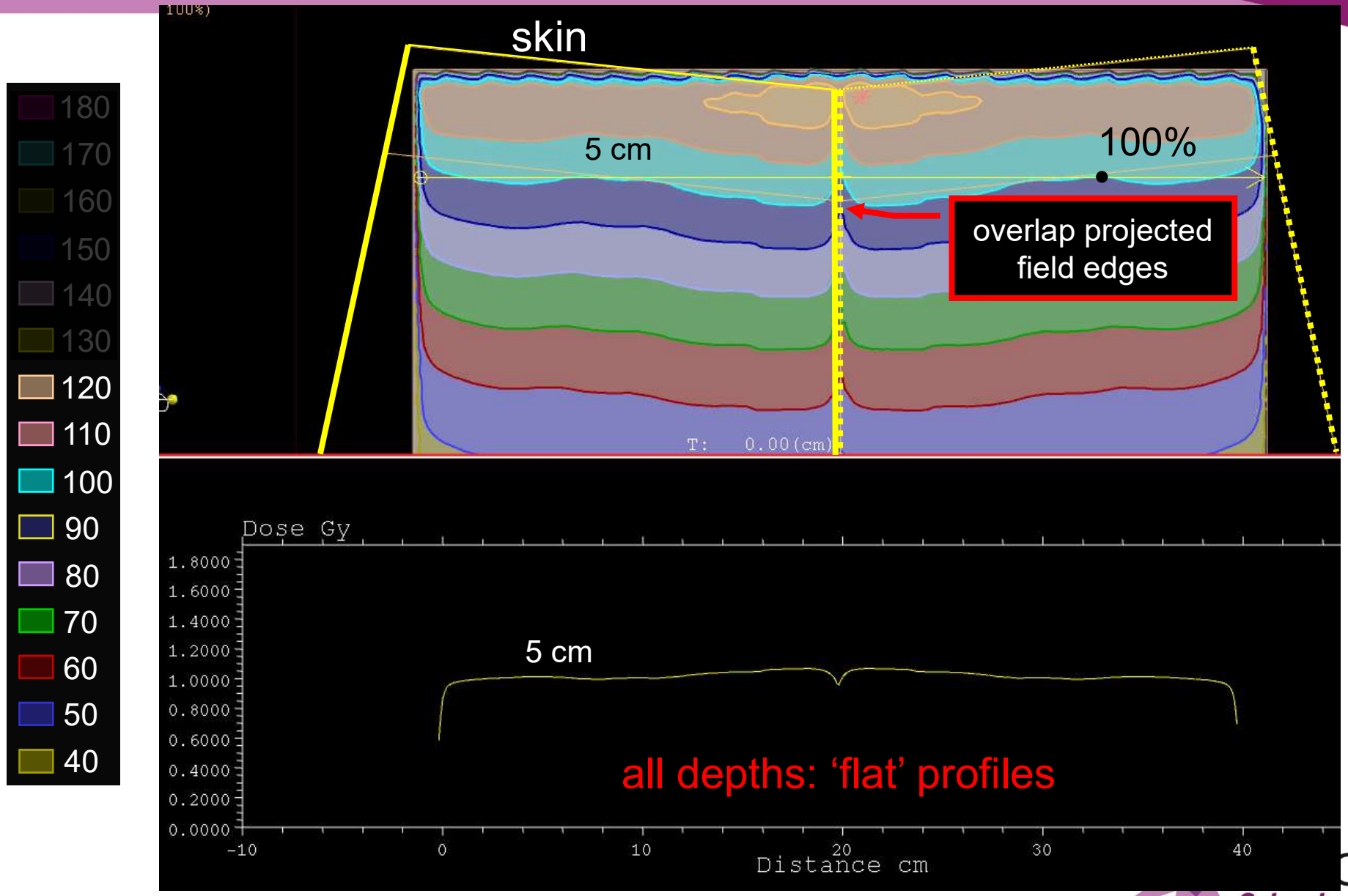
beam overlap caused by divergence: area of huge overdose



gap/overlap caused by divergence: areas of huge under/overdose



exact field edge match by field rotation : ‘flat’ profiles at all depths



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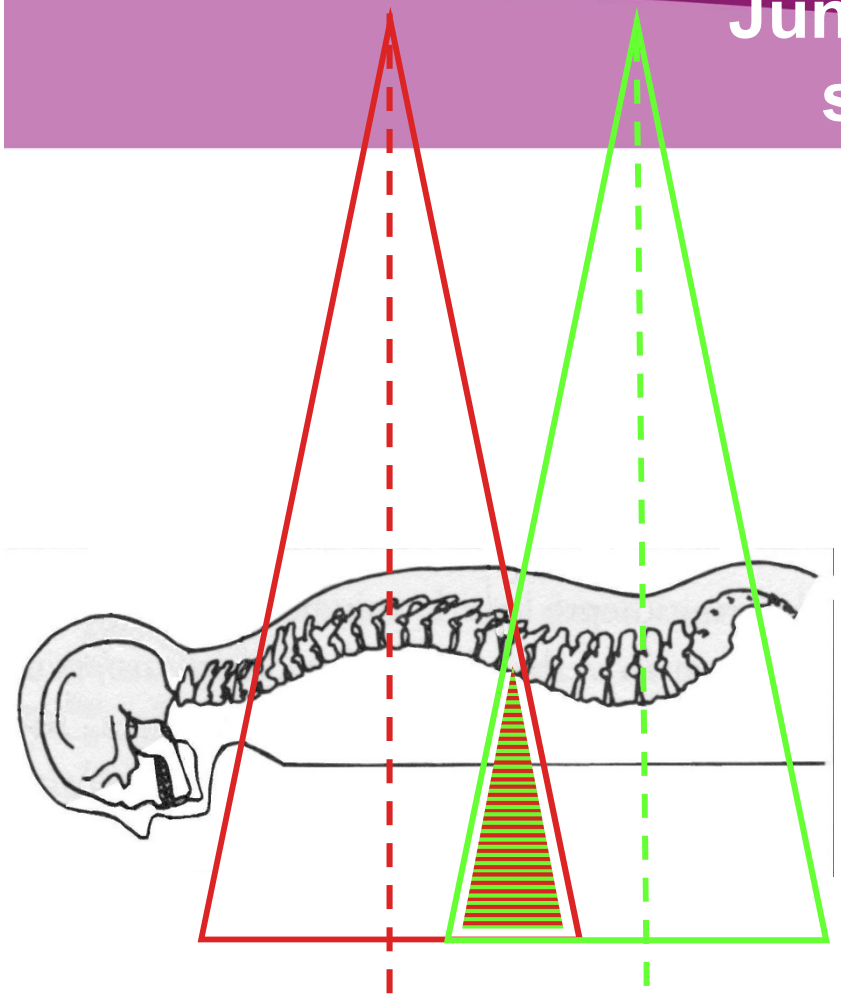
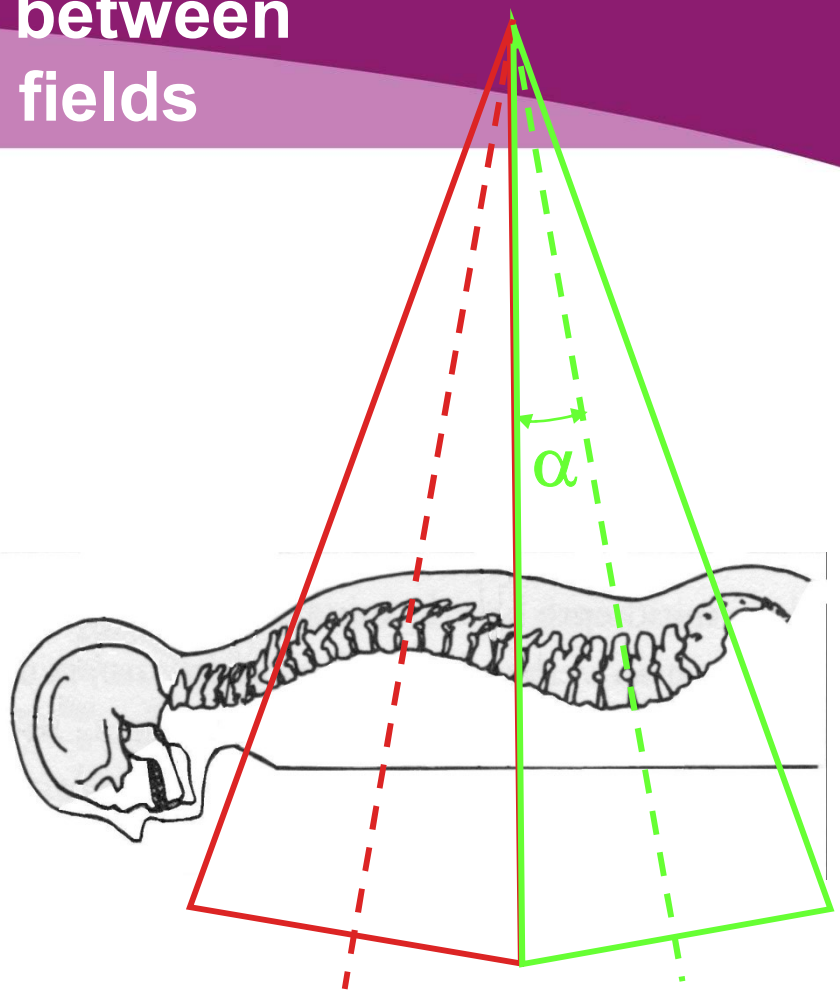
Junction between spinal fields



Crosssing at 1 depth :

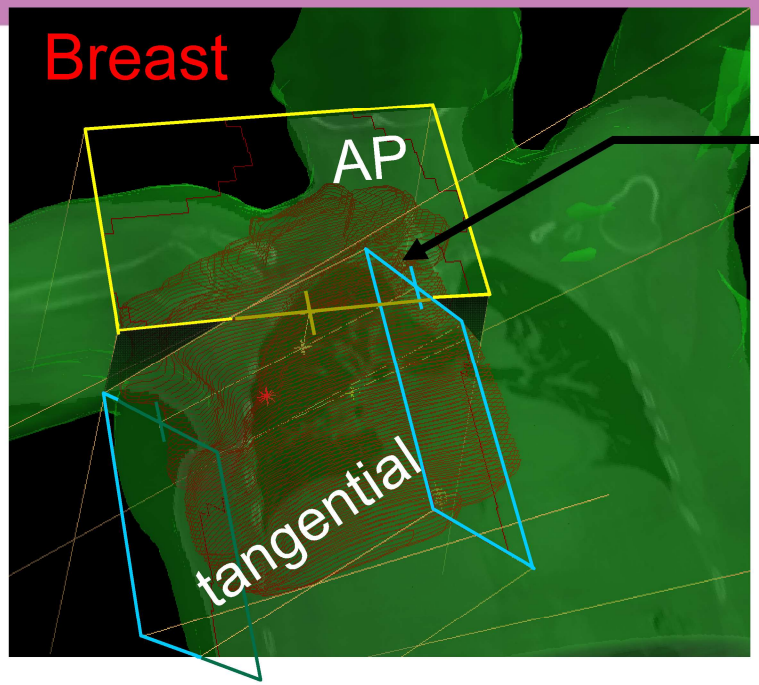
- treatment couch 0°
- gantry 0°
- in between fields couch translation



Exact match of field edges by rotation:

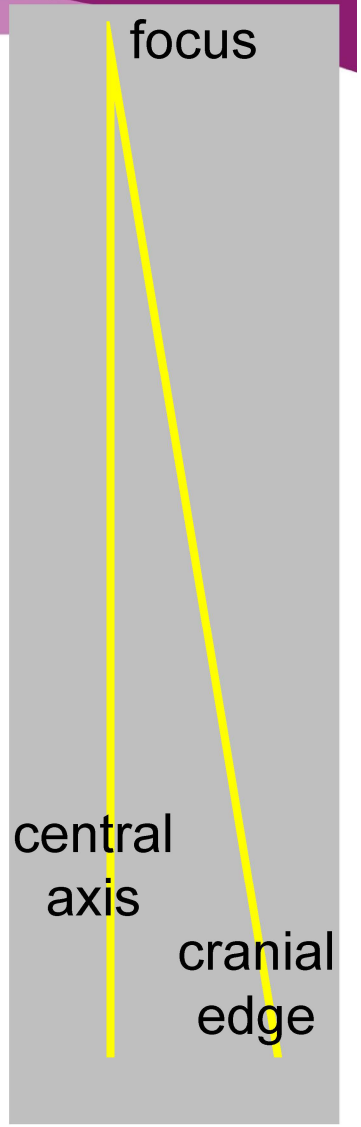
- treatment couch 90°
- gantry ± α°
- in between fields, couch translation and gantry rotation

Exact match of field edges using ‘half’ beams



junction plane through isocenter

‘half’ beam



Simple geometry, complex dosimetry

- couch always at 0°
- AP-field: only use upper half of collimator
- tangential fields: only use lower half of collimator
- in junction plane exact match, defined by sides of leaves (independent of leaf calibrations)

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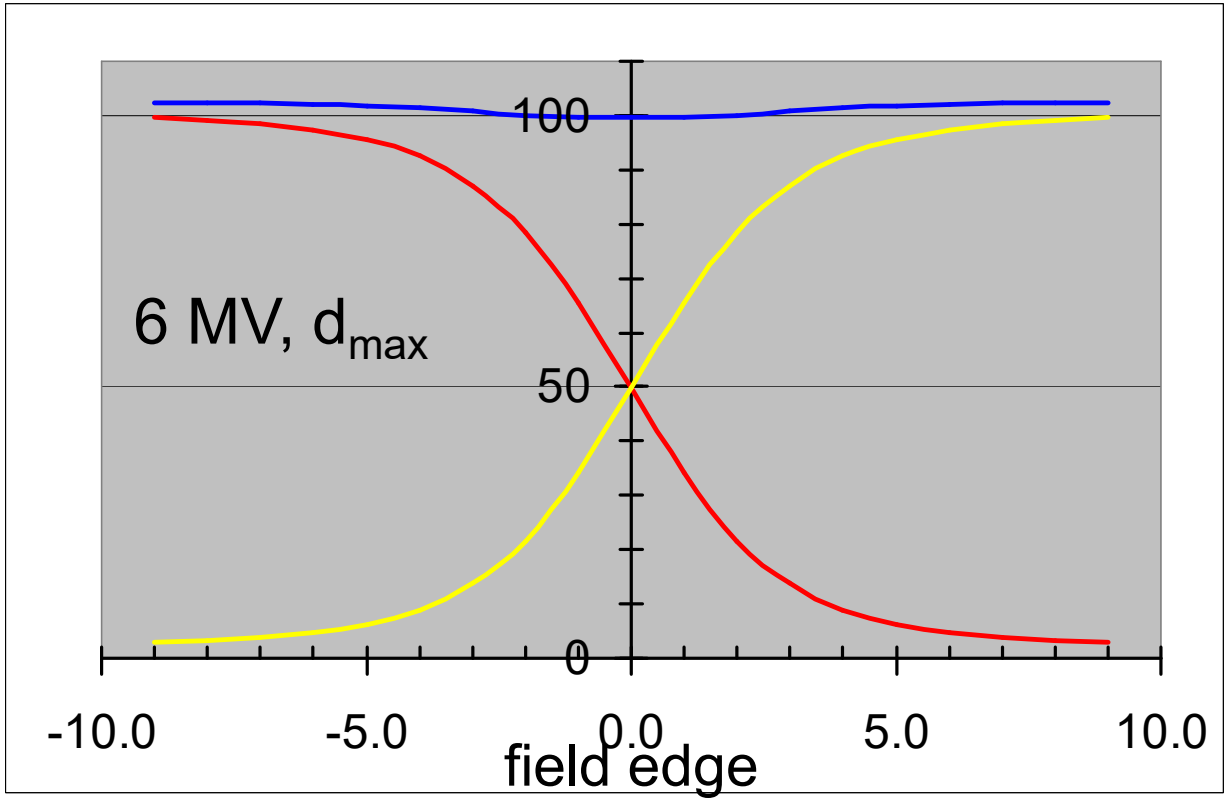
Why are profiles flat in case of exact field edge match?

almost point symmetric profiles at projected field edges, which correspond to ~50% of on-axis dose



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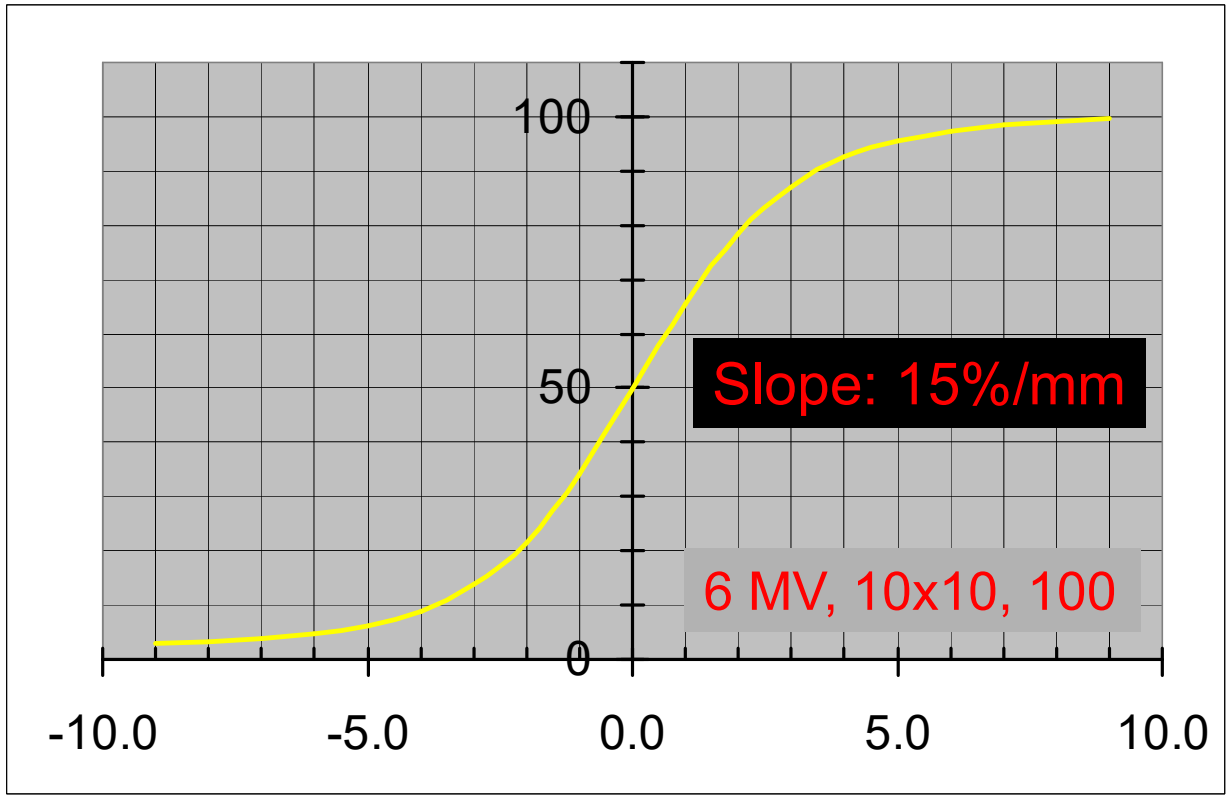
Exact matches may be highly sensitive to geometrical uncertainties and inaccuracies

- Uncertainty/inaccuracy in gantry angles, leaf positions
- Patient motion in between delivery of fields

- Uncertainty/inaccuracy in field edge



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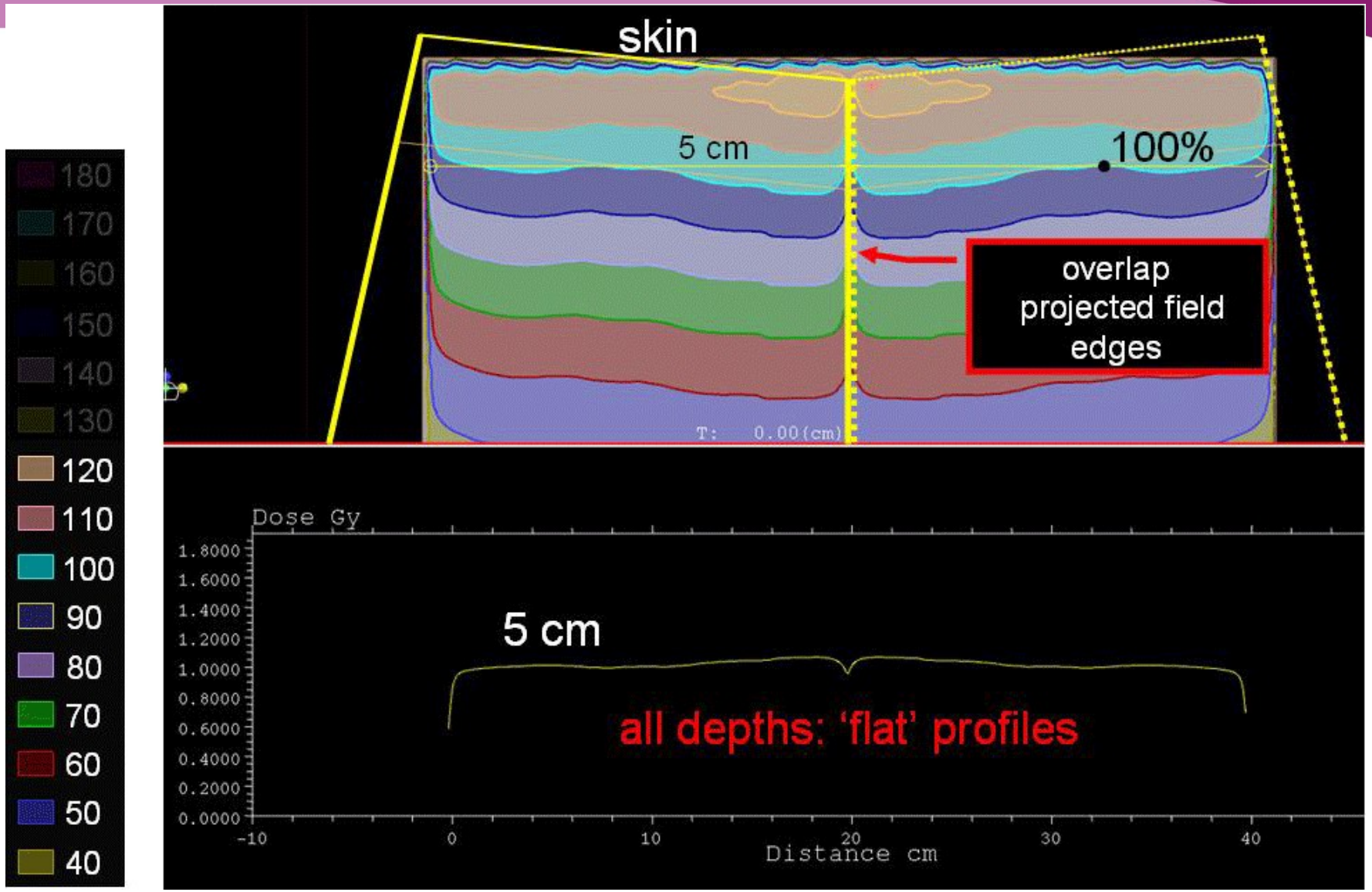
Dosimetric impact of 2 mm gap between fields



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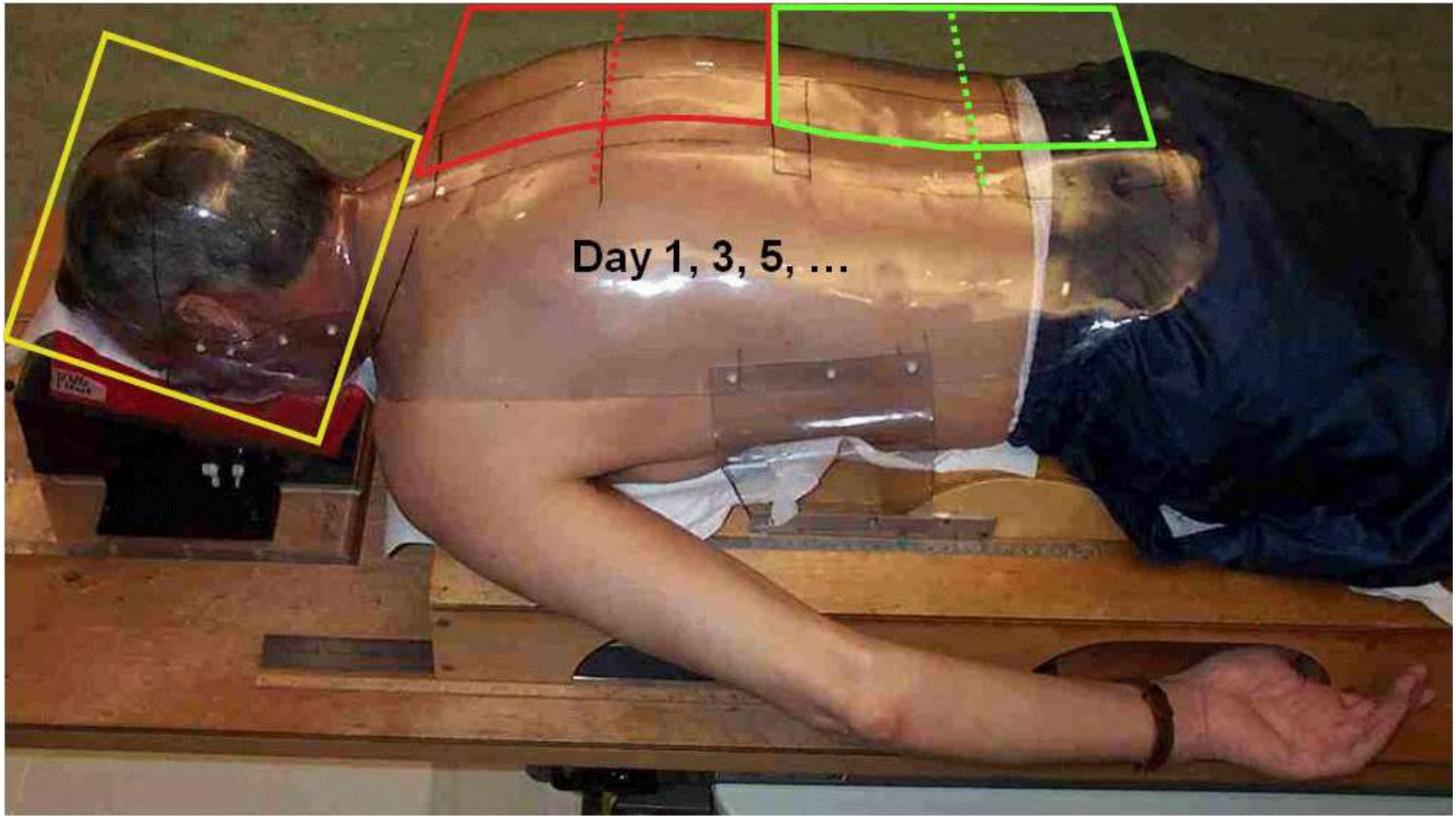
How to avoid dosimetric problems due to geometrical issues:

- Accurate calibration and regular QA of:
  leaves, blocks, couch positioning, gantry rotation
- Proper patient immobilisation
- Broaden photon beam penumbra

Other quality issues:

- Perform measurements in phantoms
- in-vivo dosimetry (TLD)

Effective photon beam penumbra broading to smear out dosimetric problems related to block calibration, patient motion, etc. (old technique)



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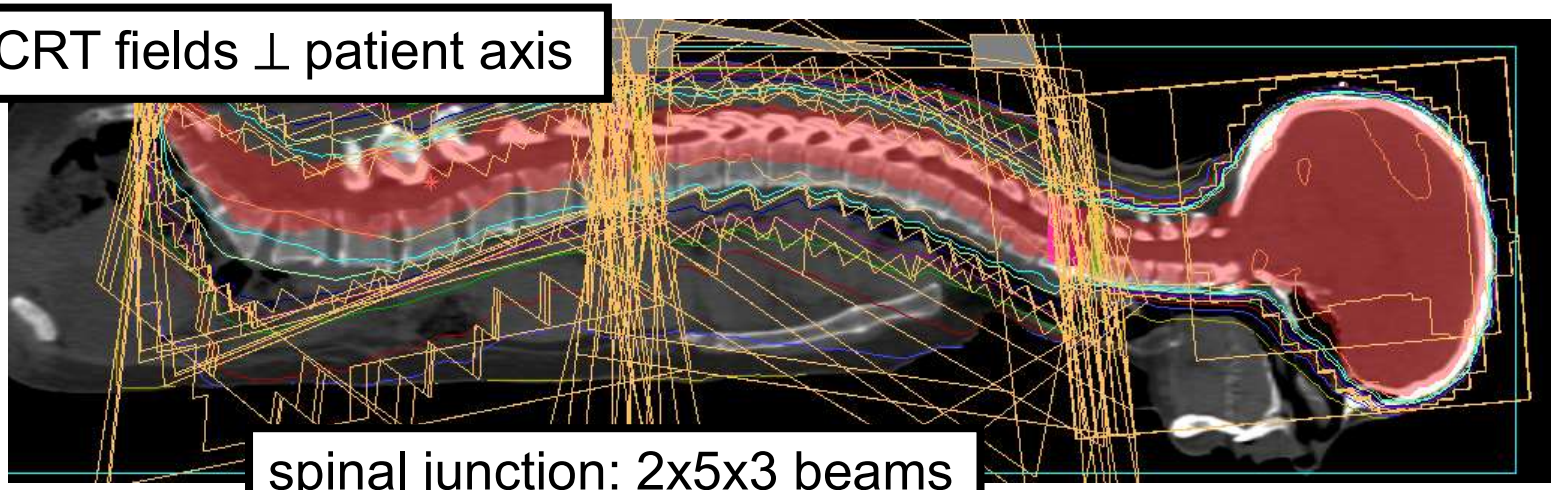
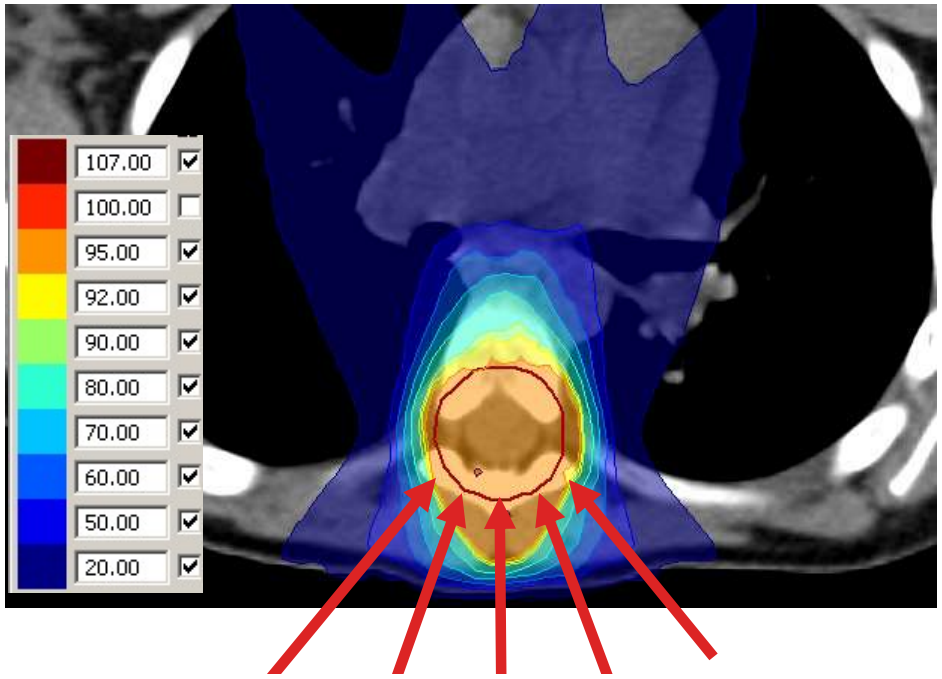
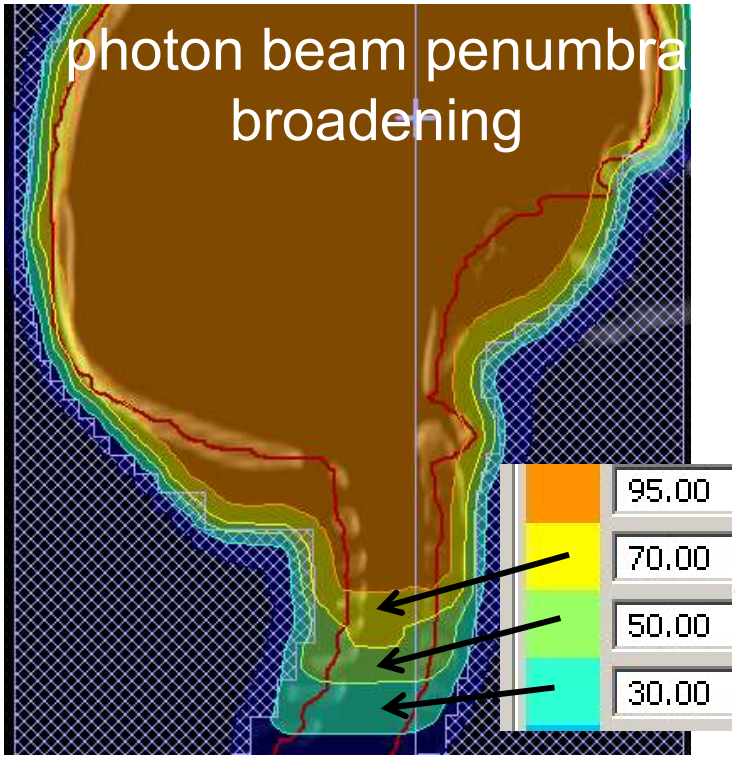
Effective photon beam penumbra broading to smear out dosimetric problems related to block calibration, patient motion, etc. (new technique)

39 3DCRT fields ⊥ patient axis



spinal junction: 2x5x3 beams

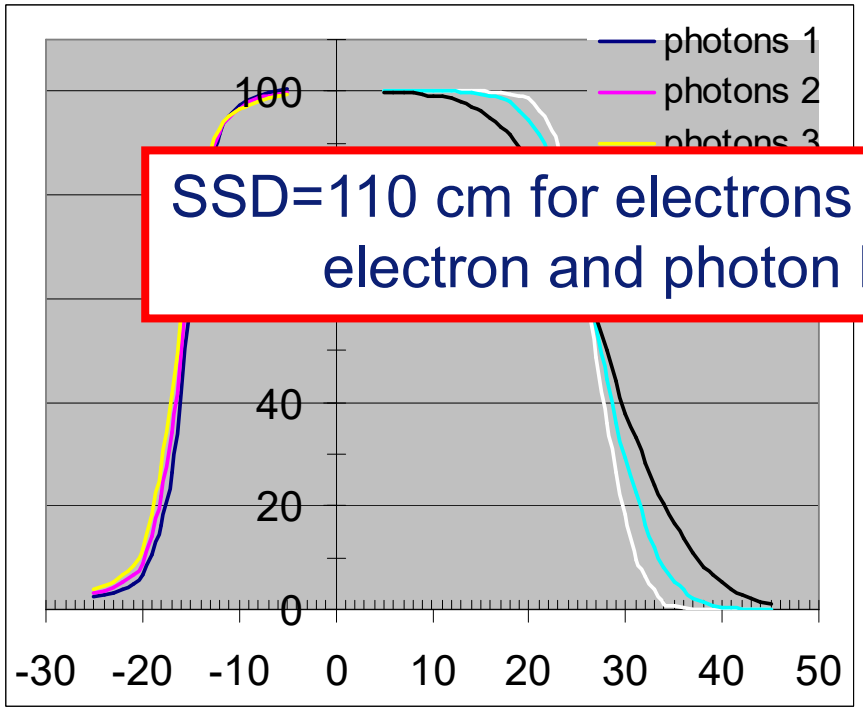




photon-electron junctions

SSD=**100** cm
electrons: applicator-skin=**5** cm

6 MV 10 MeV

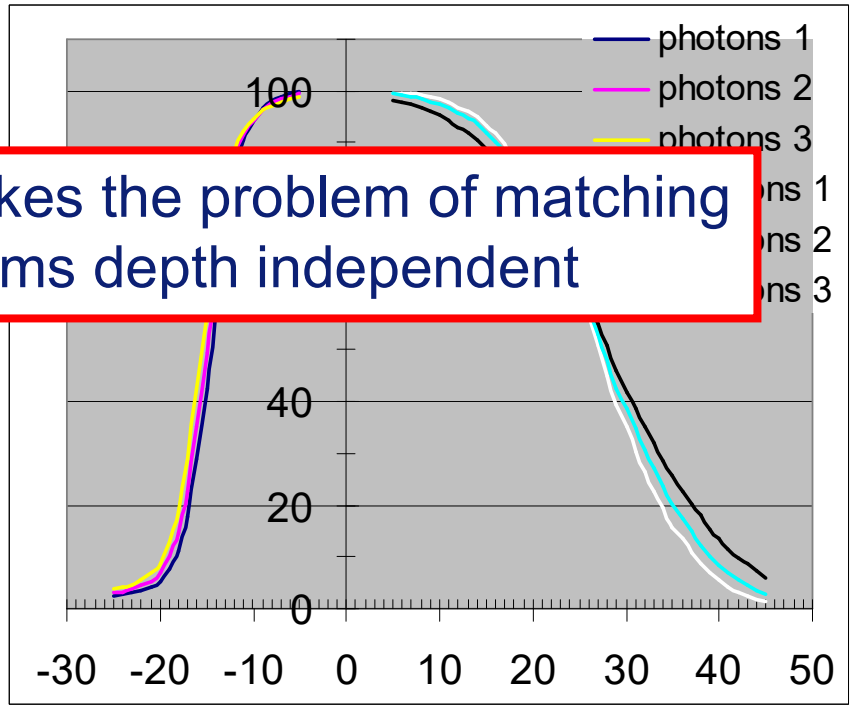


SSD=110 cm for electrons makes the problem of matching electron and photon beams depth independent

- strong dependence electron beam penumbra on depth

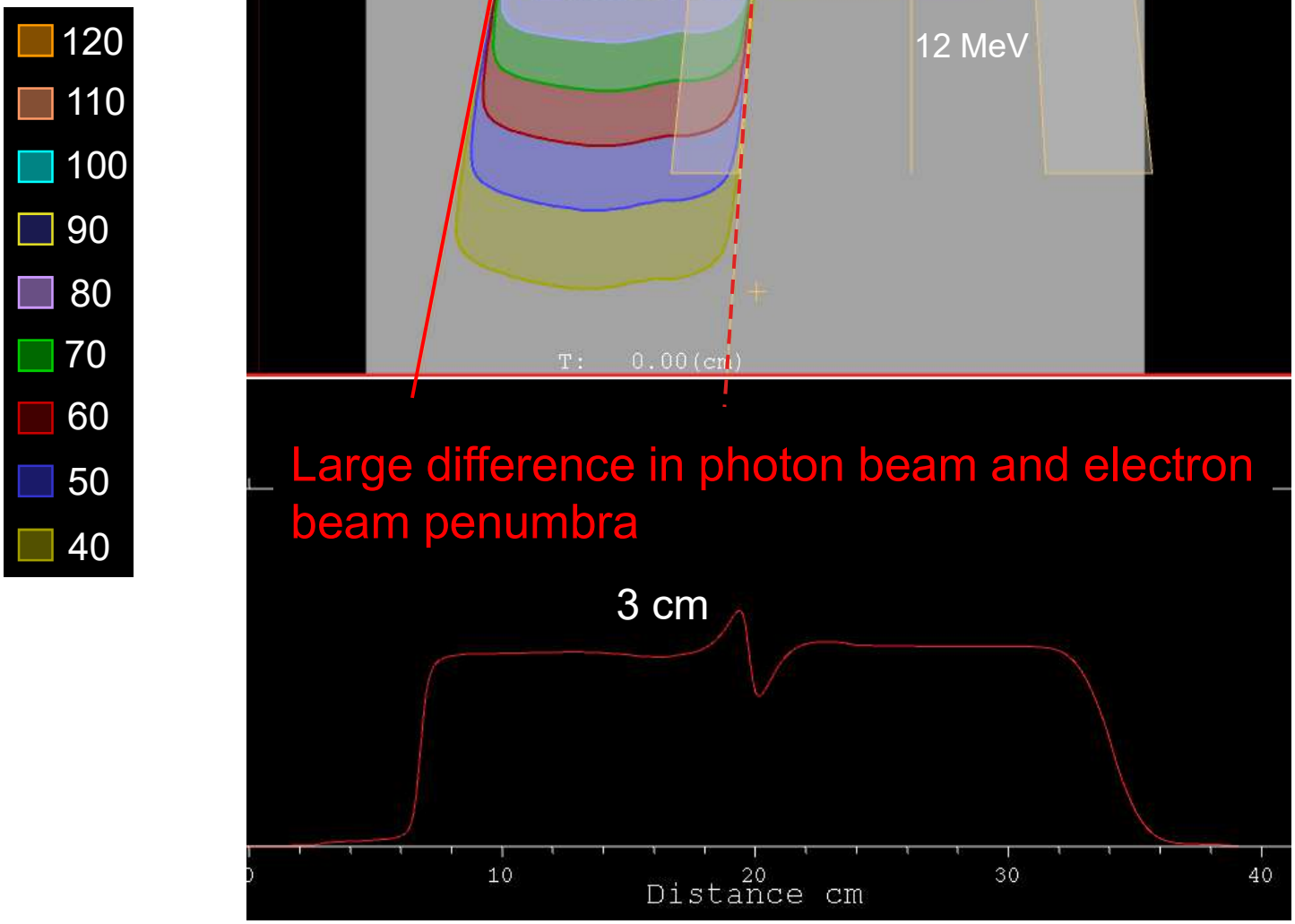
SSD=**110** cm
electrons: applicator-skin=**15** cm

6 MV 10 MeV



- reduced dependence electron beam penumbra on depth
- electron beam penumbra more shallow

6 MV – 12 MeV junction



SSD=110

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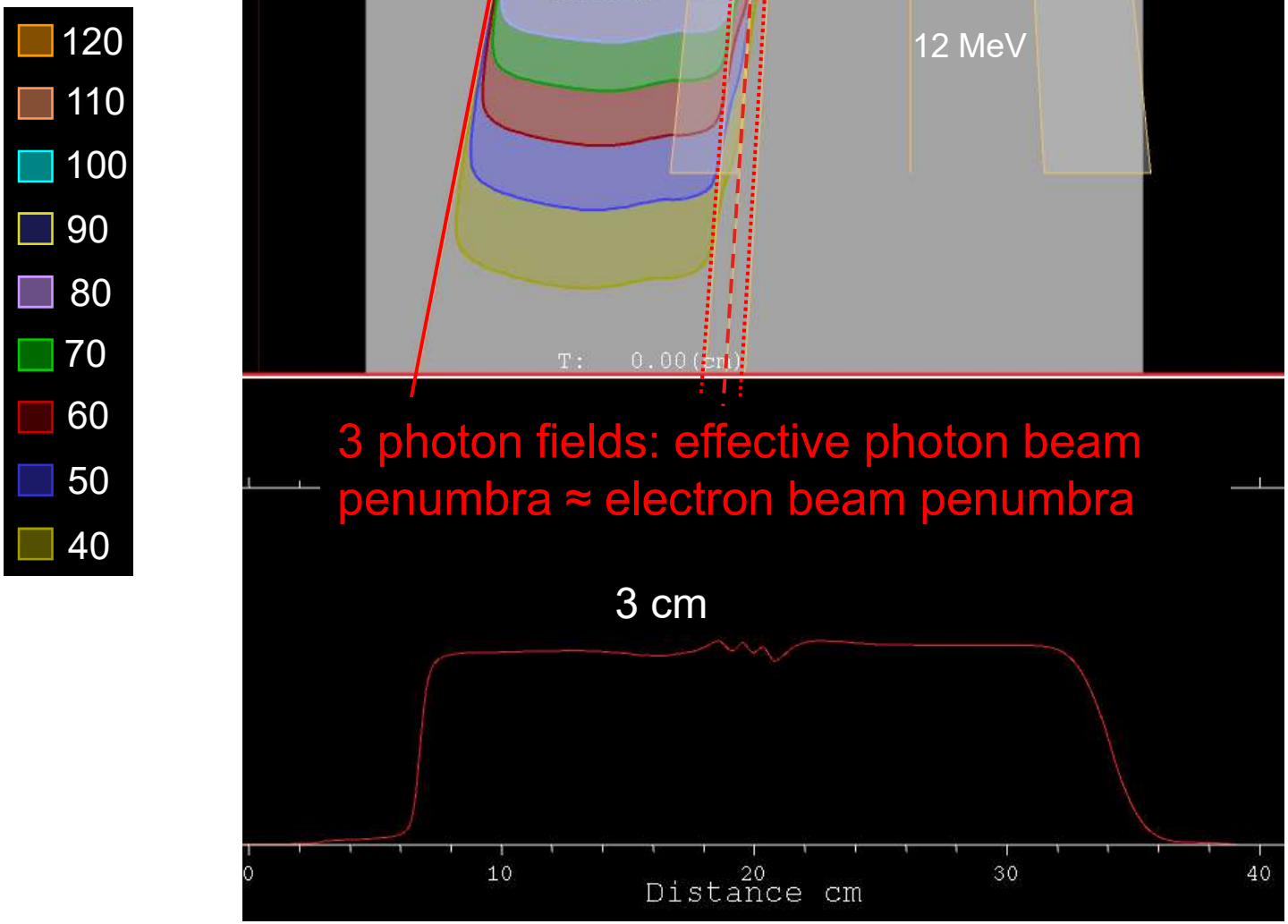
6 MV – 12 MeV junction



SSD=110

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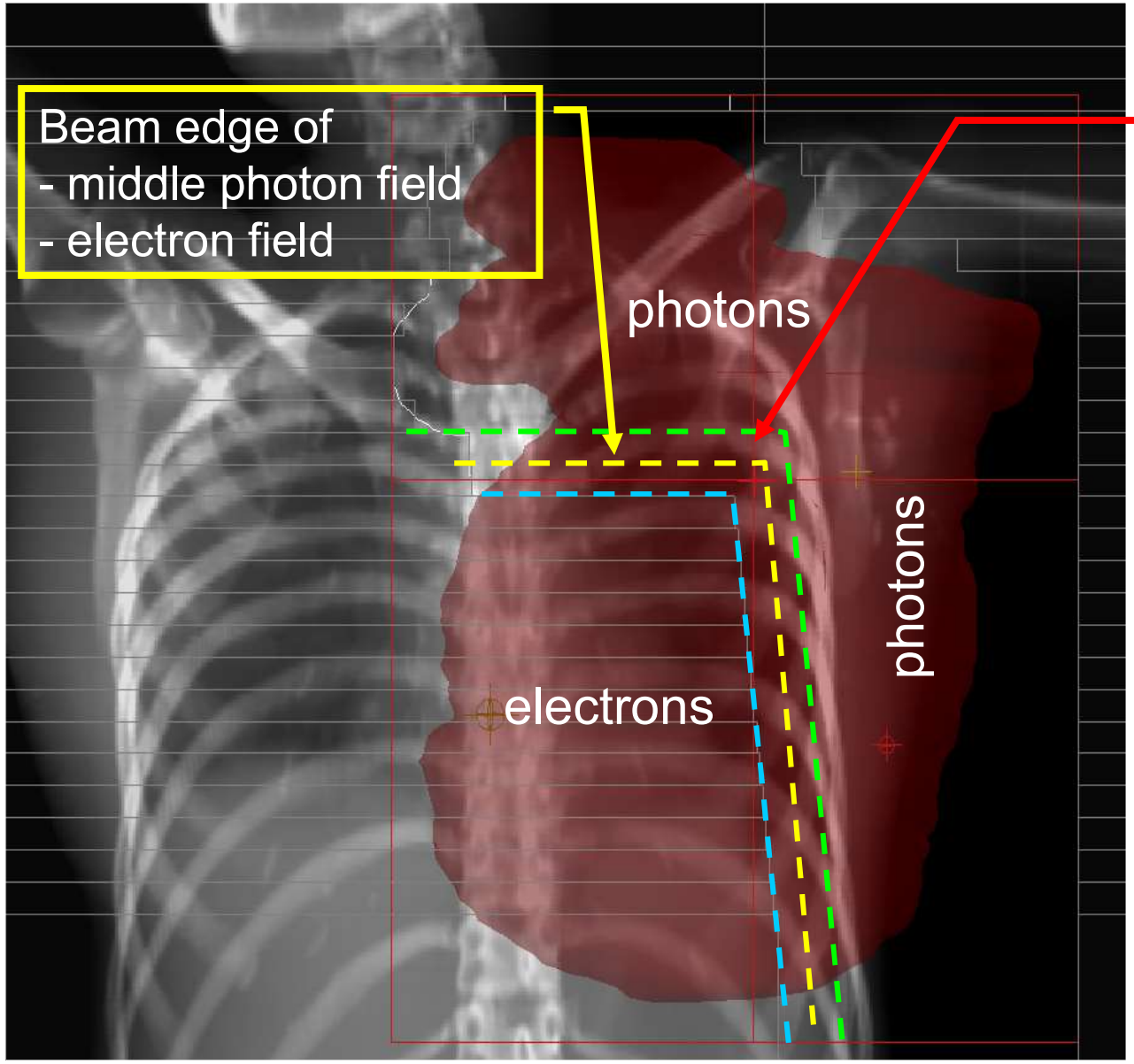
6 MV – 12 MeV junction



3 photon fields for penumbra broadening

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ICR The Institute of Cancer Research

The ROYAL MARSDEN NHS Foundation Trust

Field Junctions: Practical aspects

Shaista Hafeez MRCP, FRCR, PhD
Clinician Scientist Precision Radiotherapy, Radiation Oncologist, London. UK
shaista.hafeez@icr.ac.uk

Physics for Modern Radiotherapy, Bucharest, 2017

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The challenge

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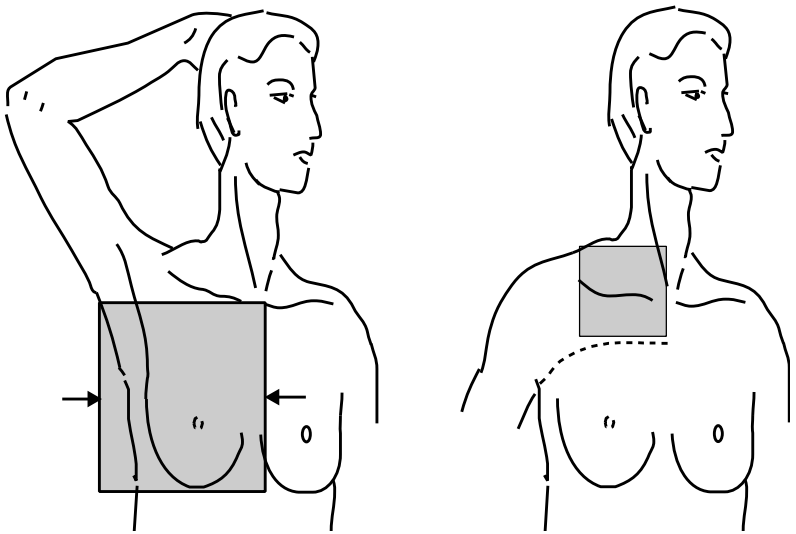
When things go wrong-a lesson from history

OVER DOSAGE

- Example brachial plexus neuropathy (BPN) due to radiation
- Overlap of radiation fields as a result of change in position between treatment of chest wall and nodes
- BPN developed in 75%
    - 100% with major move
    - 63% with moderate move



Moderate move between fields

UNDER DOSAGE

- BPN due to disease recurrence

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Why use abutted fields?

- Large targets
- Complex geometry
- Risk organs close to target organs
- No other options
- More frequent before CT simulation and IMRT
- Current uses
  - **Head and Neck cancer**
  - **Breast**
  - **Craniospinal irradiation**

Site specific consideration

- Breast and Head and Neck cancer
  - Complex geometry of the body shape
  - Different depths of targets
  - Close proximity of target and organs at risk

- Craniospinal irradiation
  - ’Long target’ extension (>100 cm)
  - Complex geometry of the body shape
  - Different depths of target

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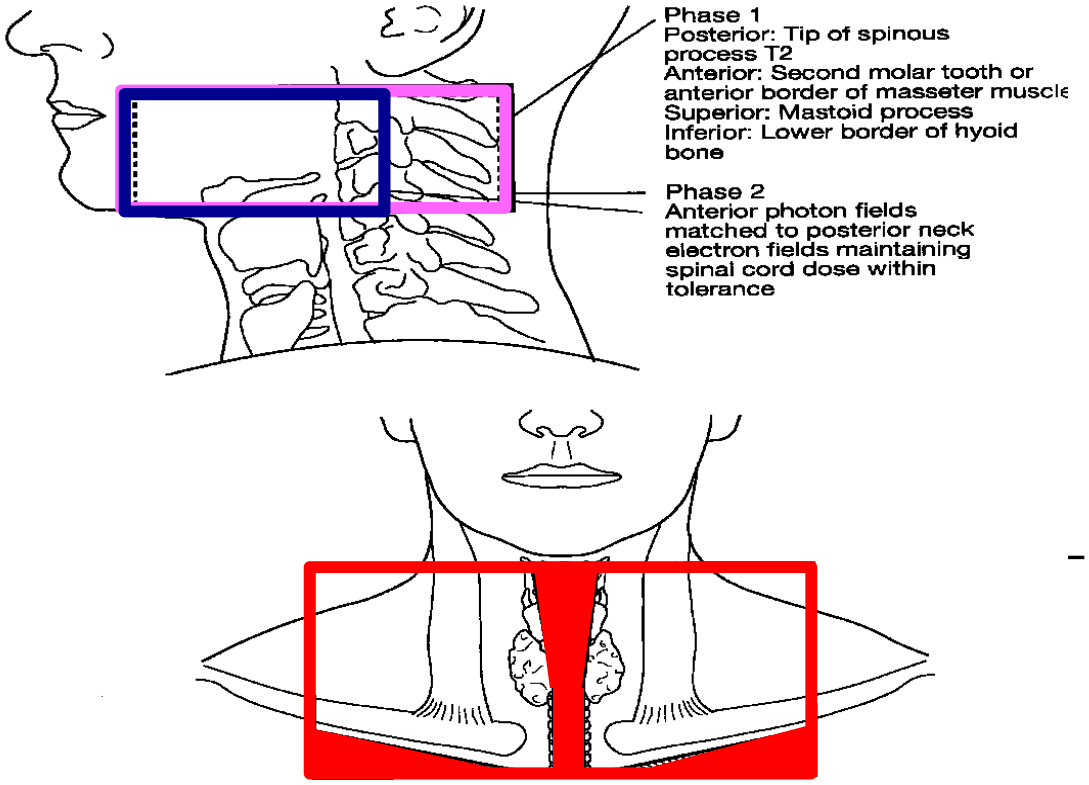
Head and neck cancer (historic-conventional)

T2N2(a)M0 SCC of tonsil



- Phase 1
  - POP to neck
  - Anterior matched field at level of hyoid with central midline shielding (spinal cord and larynx)
  - Avoid junction in high risk areas
- Phase 2
  - POP to neck (anterior to cord)
  - Match posterior electrons

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Head and neck cancer (historic-conventional)

T2N2(a)M0 SCC of tonsil

Issues to consider for matching

Ant beam used to treat low neck needs to be matched with sup field (photon-photon)

- Solutions

  Single isocentre technique,

  - Ant neck beam and sup field half beam block (asymmetric jaw)
  - = match at isocentre without pneumbra or beam divergence

  Calculate angles required so that both beam edges diverge perpendicular to matched plane,

  - = slight overlap at depth as width of pneumbra increases

  Match beams at 50% (light beam) isodose

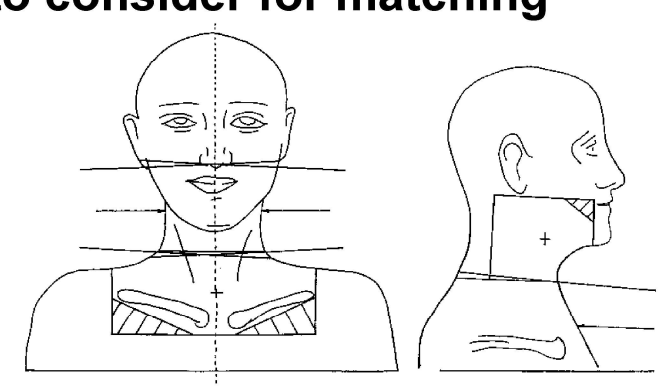
  Gap at skin surface (5-10mm)

  - =match at one depth but underdose ant to this and overdose post

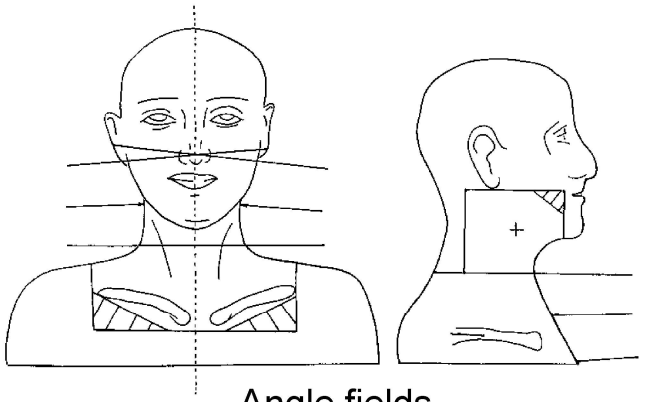
Head and neck cancer (historic-conventional)

T2N2(a)M0 SCC of tonsil

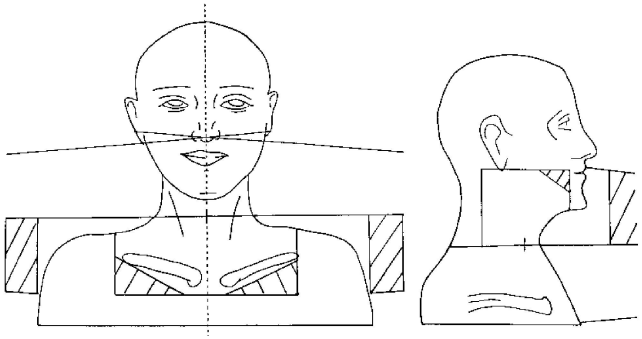
Issues to consider for matching



Straight fields



Angle fields



Mono-isocentric

Zhu Ph.D L, Kron Ph.D T, Barnes Dip.App.Sc K, Johansen B.App.Sc S, O'Brien Fracr P: Junctioning of Lateral and Anterior Fields in Head and Neck Cancer: A Dosimetric Assessment of the Monoisocentric Technique (Including Reproducibility). International Journal of Radiation Oncology*Biology*Physics 1998, 41(1):227-232.

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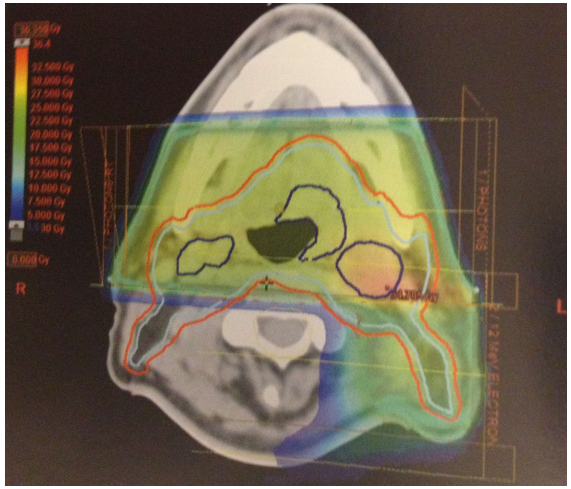
Head and neck cancer (historic-conventional)

T2N2(a)M0 SCC of tonsil

Issues to consider for matching

Post beam used to treat post neck nodes (9-12MeV) overlying the spinal cord (esp if prescribed dose i.e 55Gy in 25f to neck exceeds spinal cord tolerance) matched to beam (electron-photon)

- Solutions
  - **Match beams at 50% (light beam) isodose**
  - =Match edges of 2 light beams on the surface of shell



High dose PTV extends post to spinal cord- - hot spot created by lat bowing of electron isodoses at depth and unavoidable matching close to GTV.

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Most frequent use

- Breast
  - Complex geometry of the body shape
  - Different depths of targets
  - Close proximetry of target and organs at risk

- Craniospinal irradiation
  - ’Long target’ extension (>100 cm)
  - Complex geometry of the body shape
  - Different depths of target

T3N2M0 invasive ductal carcinoma of breast

Complex target

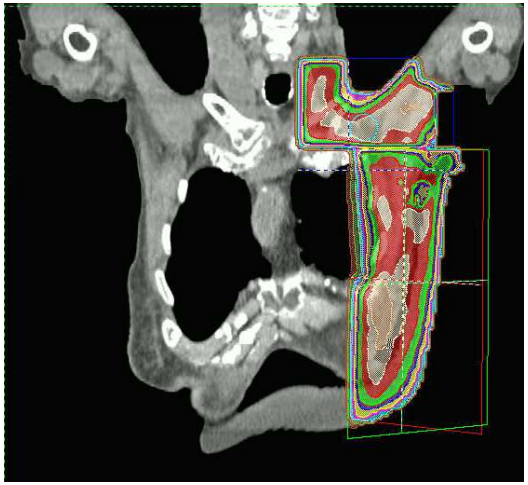
Issues to consider

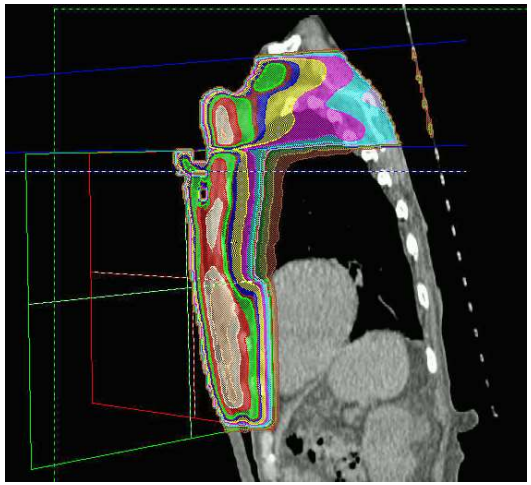
- Thoracic wall
- Supra clavicular nodes
- Axillary nodes
- Internal mammary nodes

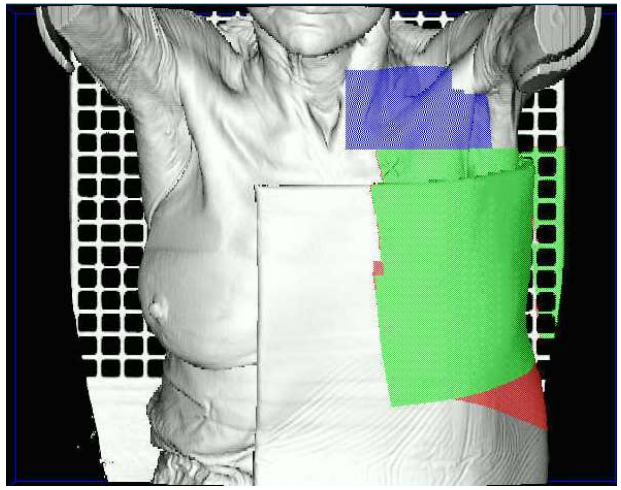
Breast

T3N2M0 invasive ductal carcinoma of breast (post mastectomy)

Target (CTV)- adjuvant chest wall, SCF, and axillary LN







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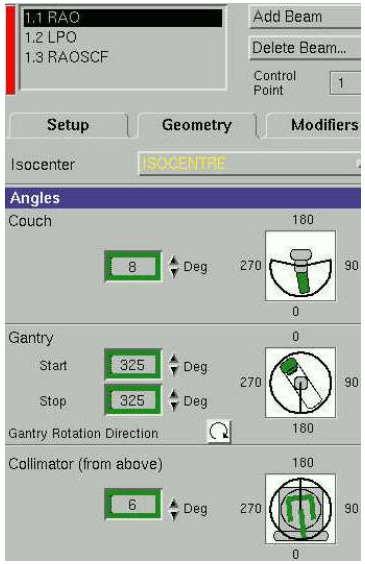
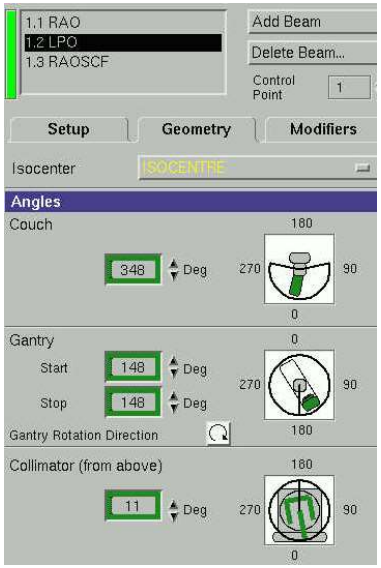
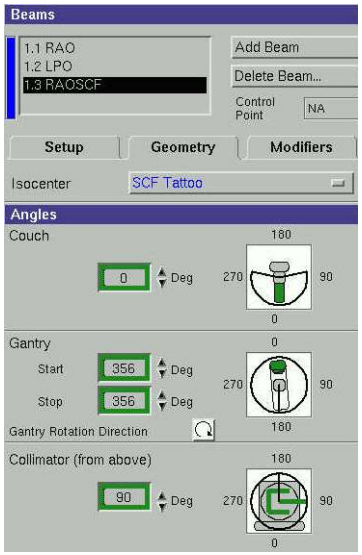
Breast

T3N2M0 invasive ductal carcinoma of breast (post mastectomy)

Name	Couch	Gantry Start	Gantry Stop	Isocenter	SAD (cm)	Start SSD (cm)
1.1 RAO	8	325	325	ISOCENTRE	100.0	96.38
1.2 LPO	348	148	148	ISOCENTRE	100.0	86.63
1.3 RAOSCF	0	356	356	SCF Tattoo	100.0	97.78







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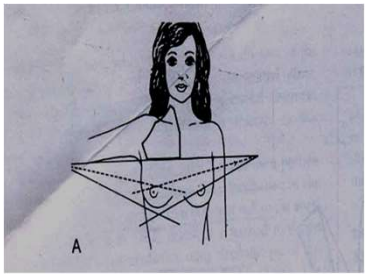
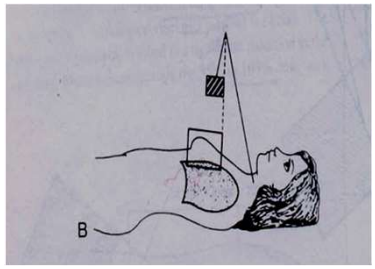
Complex target

Issues to consider for matching
Superior edge of tangential field to inf edge of nodal field.

Solutions
Angulation
By inferior angulation of the tangential fields
Calculated angles for couch, gantry and collimator to keep match plane at junction





Half beam block technique (single isocentre)
Blocking the supraclav field's inferior half, eliminating its divergence inferiorly

?Leave a gap
Risk of under dosing

Complex target

Internal mammary LN (IMN)

- If IMN is to be included in the treatment great care should be taken to minimise dose to heart and lungs
- Usually ipsilateral IMN are treated

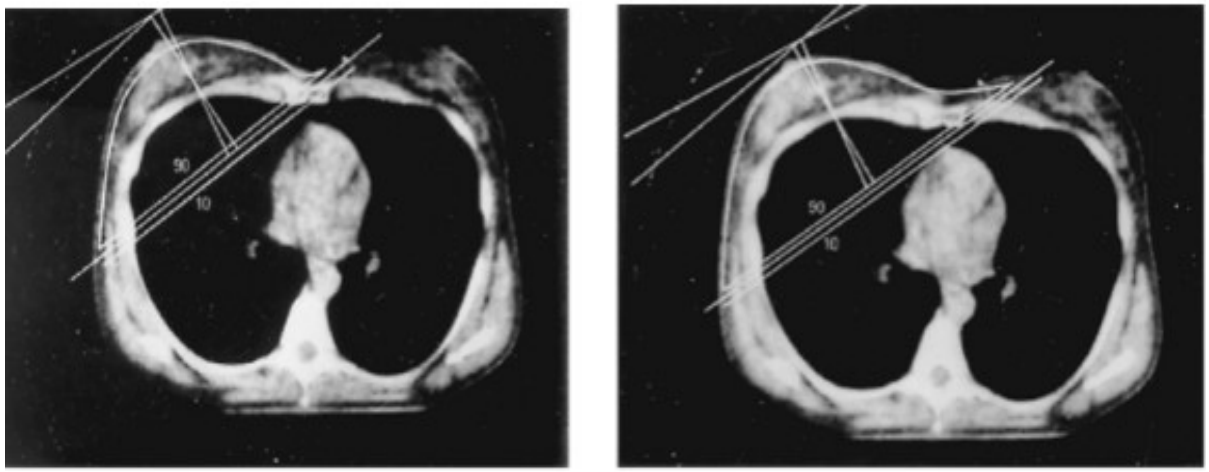
Solutions

1. Extension of tangential fields– by extending medial border – 3cm across midline or by using imaging techniques
2. Separate field –

- Medial border – midline , matching with tangential field border
- Lateral border – 5-6cm from midline
- Superior border – abuts inferior border of supraclav field or at 1st ICS (superior border of head of clavicle) if only IMNs are to be treated
- Inferior border – at xiphoid or higher if 1st three ICS covered

Complex target

Deep tangent for IMN-limitations

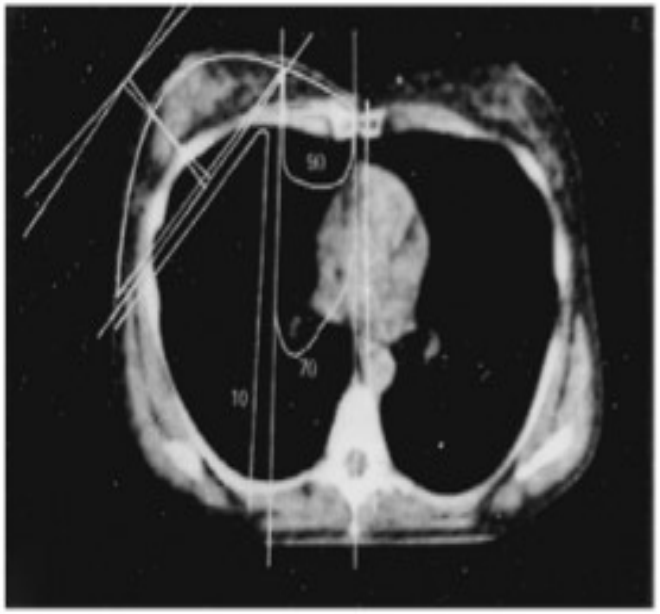


More normal tissue is being irradaited. (lung, heart and contralateral breast)

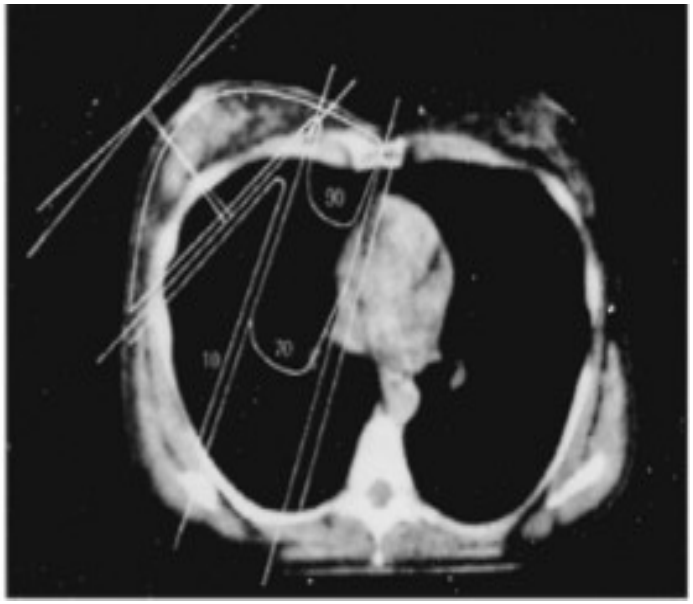
Complex target

- IMN-solution

Anterior field



Oblique field



The dose to the IMN field (45 to 50 Gy at 1.8 to 2 Gy per day) is calculated at a point 4 to 5 cm beneath
Ideally based on CT scan localization
Electrons in the range of 12 to 16 MeV are preferred

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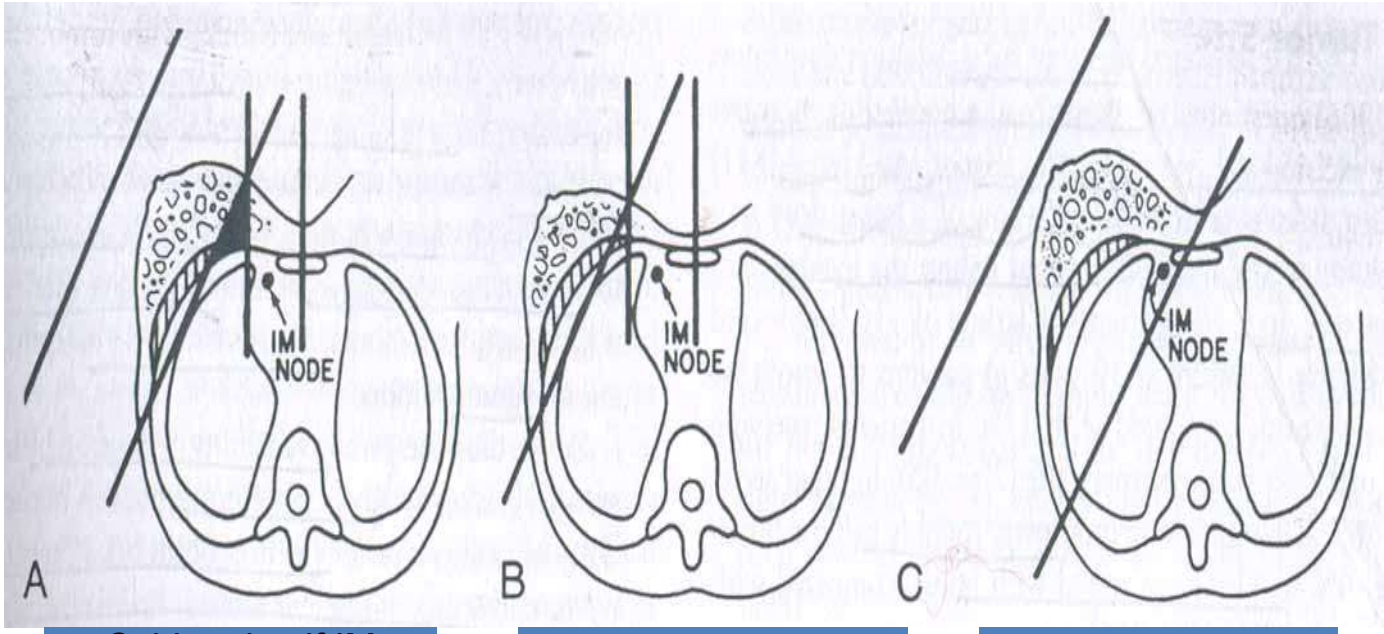
Breast

Complex target

- IMN-solution
- **Issues to consider for matching**



Cold region if IM tangential matching overlies large amt of breast tissue

Cold area negligible if thin breast tissue beneath match-line

Lack of separate IM field - irradiation of Excessive lung vol

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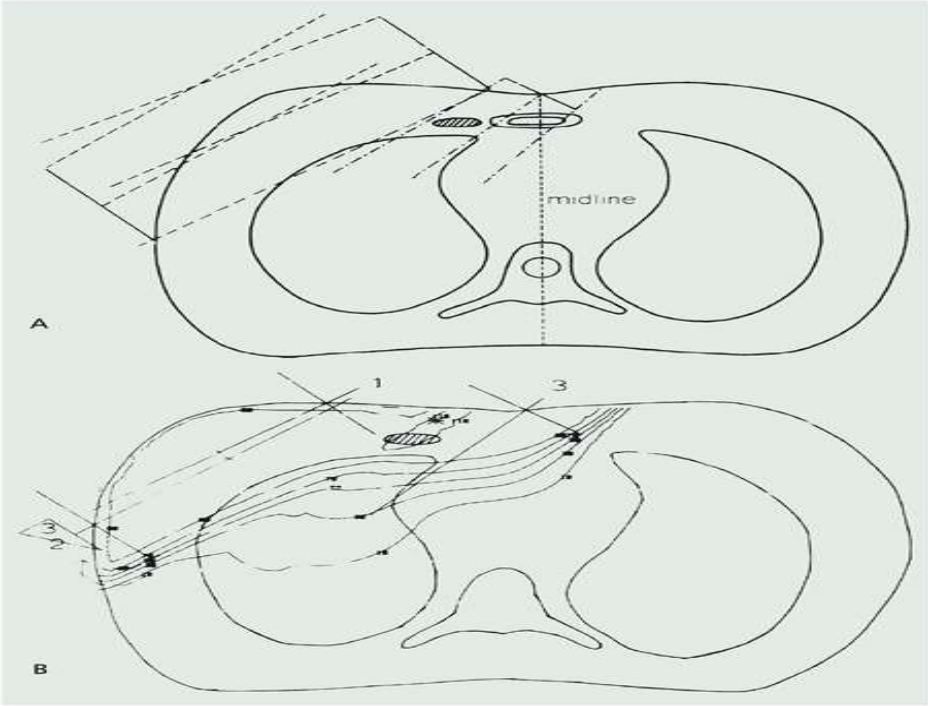
Breast

Complex target

- IMN-solution
- **Issues to consider for matching**
  - **Oblique electron field matching**



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Other solutions: IMRT?

Advantage

- With IMRT - better conformation of dose to target tissues, increased sparing of normal tissues , limiting dose to lungs & heart
- Studies have shown – 50% reduction in cardiac mortality rate
- % of ipsilateral lung volume receiving >20% of isocentre dose can be decreased to 3.4%

Considerations

- Breast is a **mobile organ** (organ motion effects)
- **ACTIVE Breathing Control (ABC)** costly apparatus required or voluntary breath hold (low tech)
- **Geometric uncertainties** as per patients and lumpectomy cavity position
- Uncertainties regarding **surgical clips displacement / lumpectomy cavity**

Craniospinal irradiation

Medulloblastoma

- Primitive neuro-ectodermal tumour which arises most commonly in the cerebellum
- Most common primary CNS tumour in children (20%) but uncommon in adults (0.5 cases per 100,000)

- Most commonly arises in the posterior fossa
  - Spread commonly in craniospinal axis
  - Systemic metastasis is uncommon but reported
  - Presenting symptoms:
    - Hydrocephalus related symptoms
    - Cerebellar symptoms
    - Leptomeningeal symptoms

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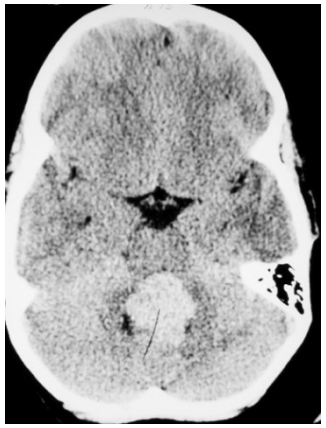
Craniospinal irradiation

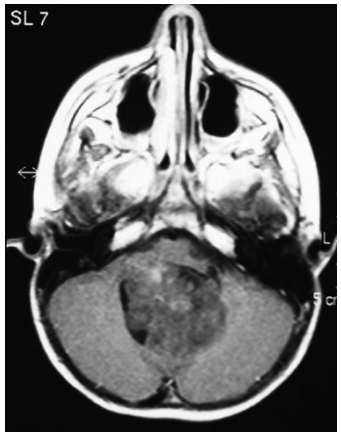
Medulloblastoma

- Optimal neurosurgical debulking: Residual tumour >1.5 cm² (MRI) has a worse prognosis.
- All patients receive cranio-spinal radiotherapy & chemotherapy

CT Head



MRI Head



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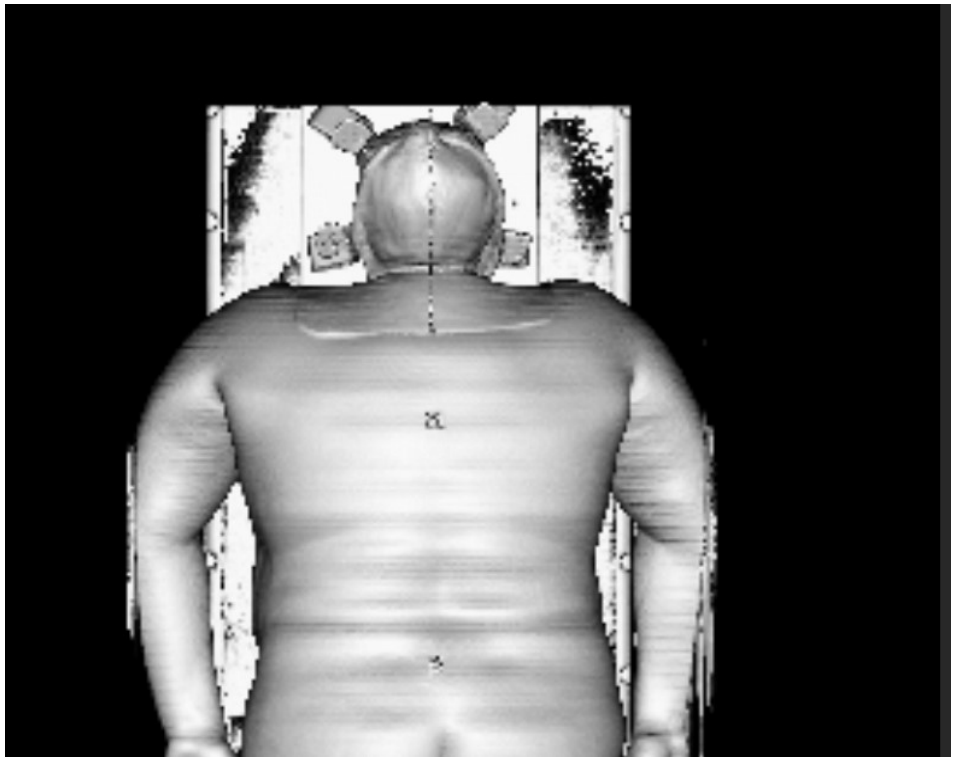
Craniospinal irradiation

- Commonly treated prone
- Head and spine are straight to allow reproducible set up
- Head is extended to avoid spinal fields exiting through the mouth, teeth and jaw
- Shoulders are pulled down to allow flexibility in defining the site of cranio-spinal junction



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Craniospinal irradiation

Target volume

- Entire CSF space as common spread via CSF fluid
- 2 Phase technique
  - Phase 1: Cranial & spinal fields
  - Phase 2: Posterior fossa boost

- **Standard risk group (paeds)**
  - Phase 1: 23.4 Gy/13#
  - Phase 2: 30.6 Gy/17#

- **High risk group (paeds)**
  - Phase 1: 34.2Gy/19#
  - Phase 2: 21.6 Gy/12#
  - Metastatic deposit: 10.8Gy/6#

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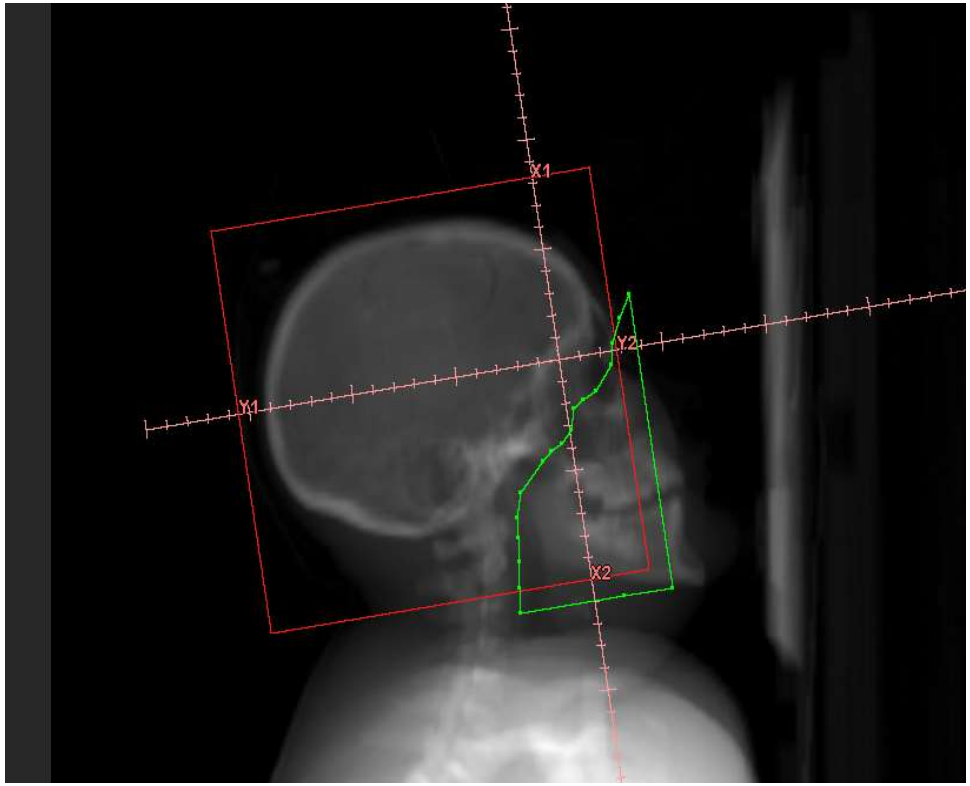
Craniospinal irradiation

Cranial field

- Parallel opposed lateral fields with customised lead blocks to spare the radiosensitive lens, facial tissue, jaw and teeth
- Ensure the field centre is adjacent to the orbit to minimise divergence to the contralateral eye



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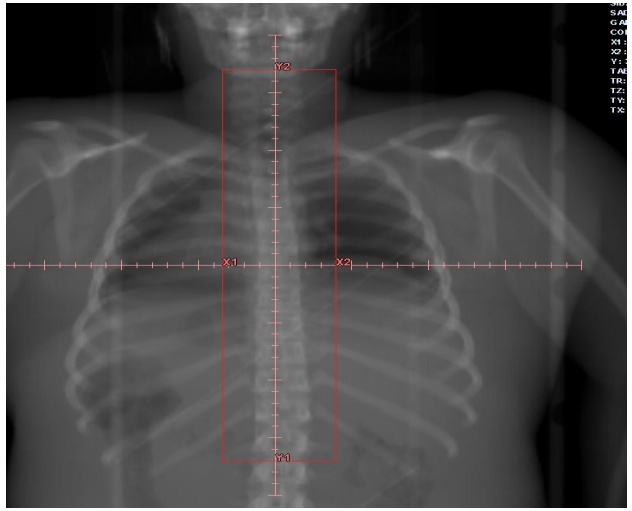
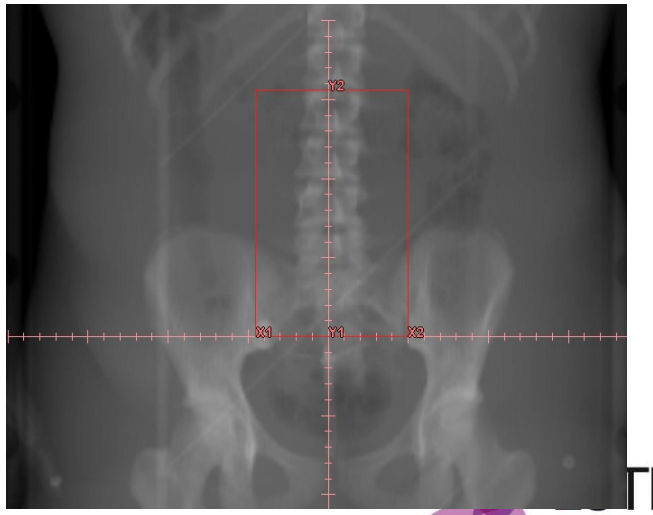
Craniospinal irradiation

Spinal field

- Direct posterior field prescribed at depth (depends on MRI)
- Superior: Match the lower border of the cranial field (usually at C3-C4 junction)
- Lateral: cover the dural recess so extend to the transverse process
- Inferior: 1 cm below the lower end of the thecal sac

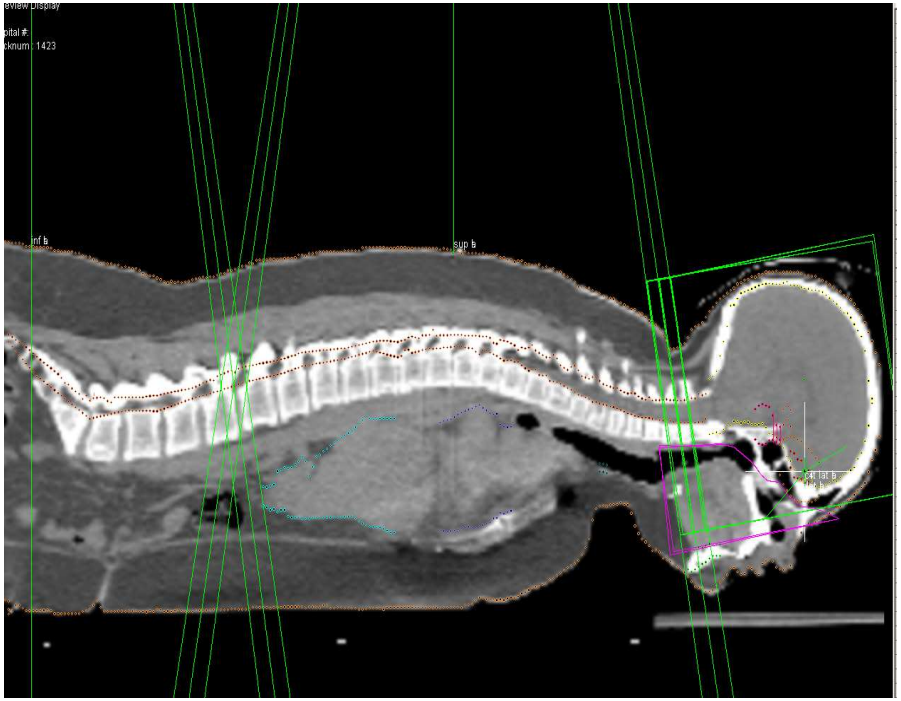




Craniospinal irradiation

Spinal field

- In adults may need extended SSD or 2 spinal beams
- Dose prescribed to anterior spinal cord.
- It should vary by <10%, otherwise use compensators
- As matching is not perfect, the cranial and spinal field junction is moved daily to three different positions



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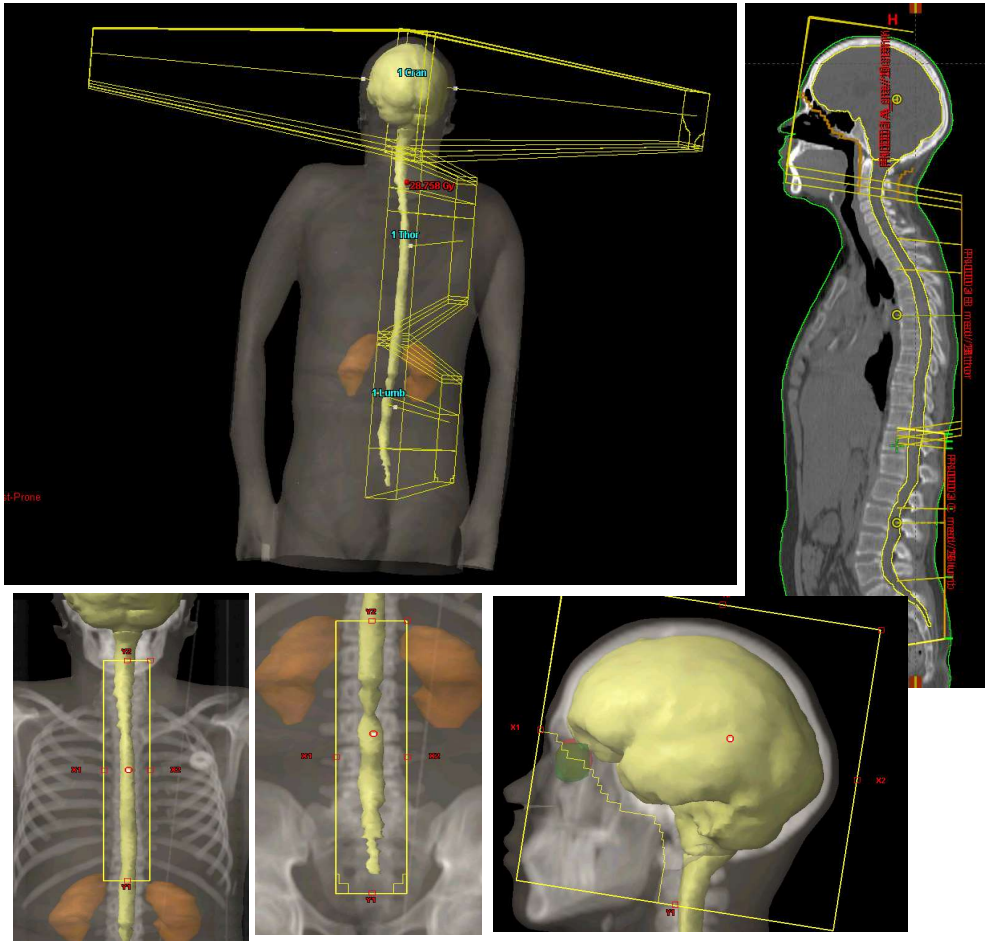
Craniospinal irradiation

Field set up technique



- 3 plans, each with 4 fields (6 MV). The field junctions are moved between the 3 plans
- 2 lateral cranial 90º and 270º with a collimater rotation of 9º
- 1 thoracic fied
- 1 lumbar field
- Separate ’Set up’ fields for each field in each plan

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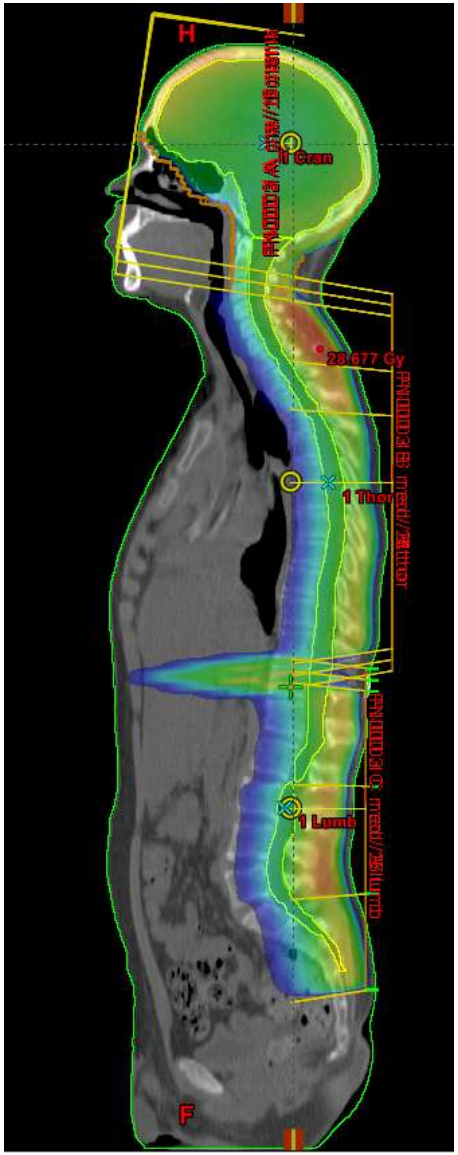
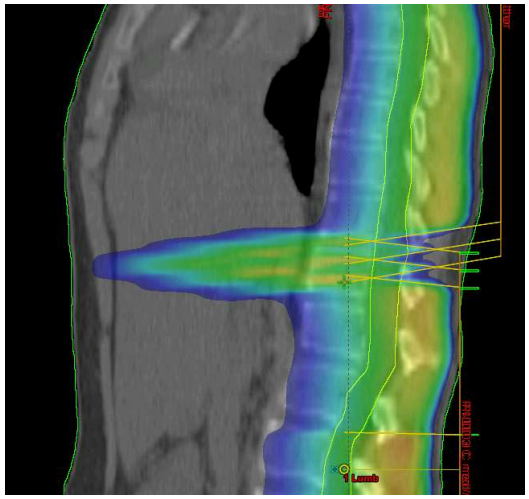
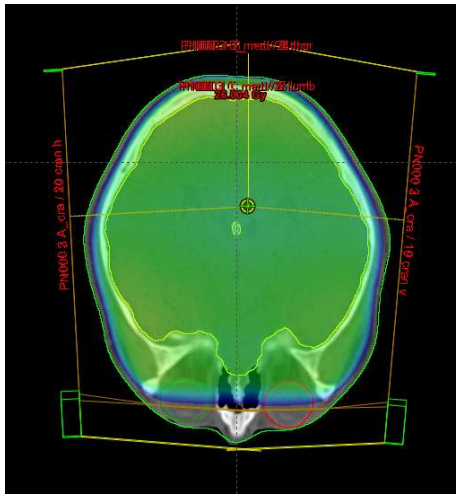
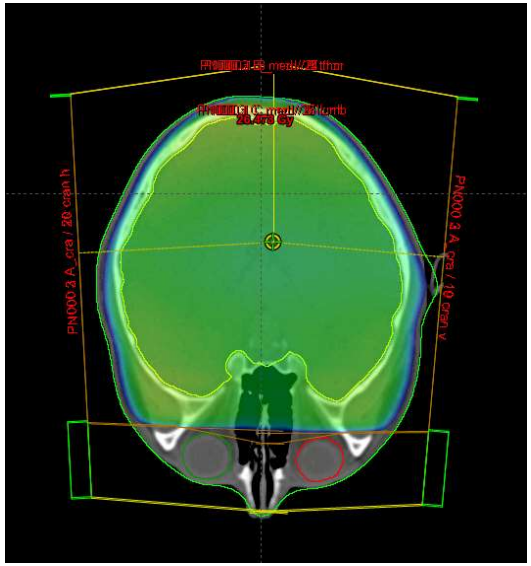
Dose distribution shown 20 – 24 Gy









Organs at risk:
Kidneys
Eyes

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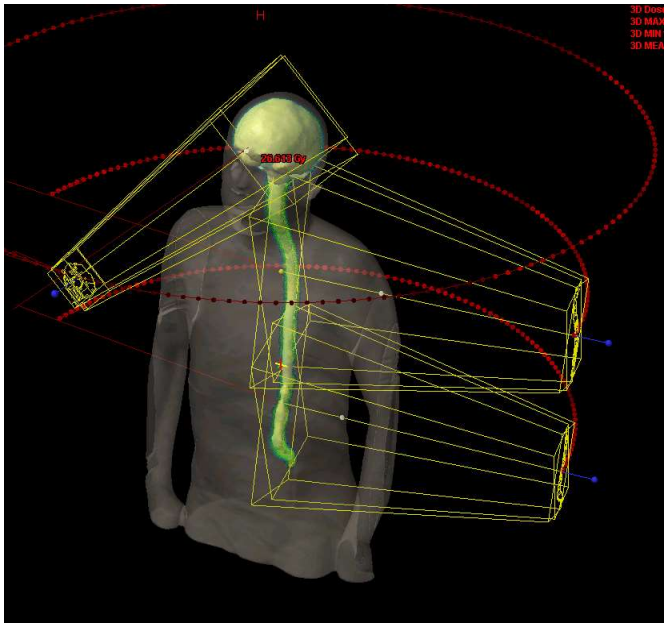
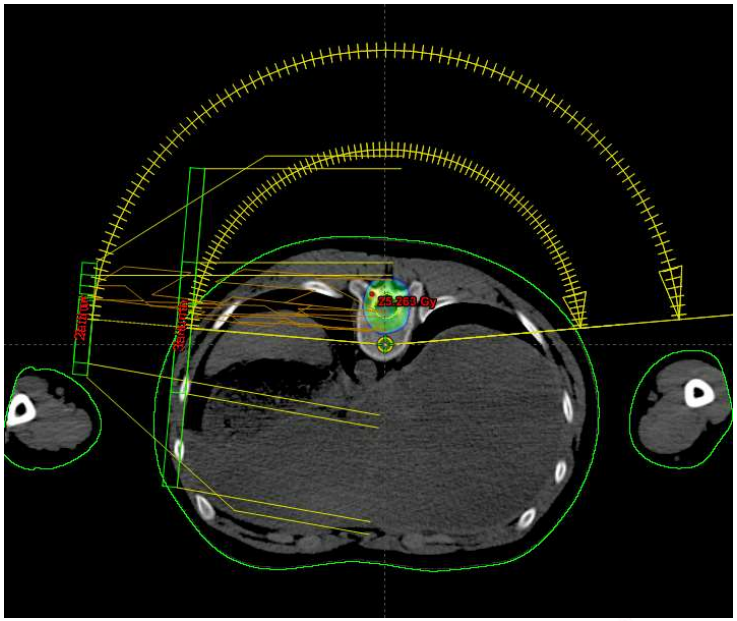
Other options: IMRT, arc therapy tomotherapy and protons

- Arc treatment 6 MV – again 3 plans where the field junctions are moved between the 3 plans
  - Full arc on cranial area
  - Half arc on thoracic and lumbar regions





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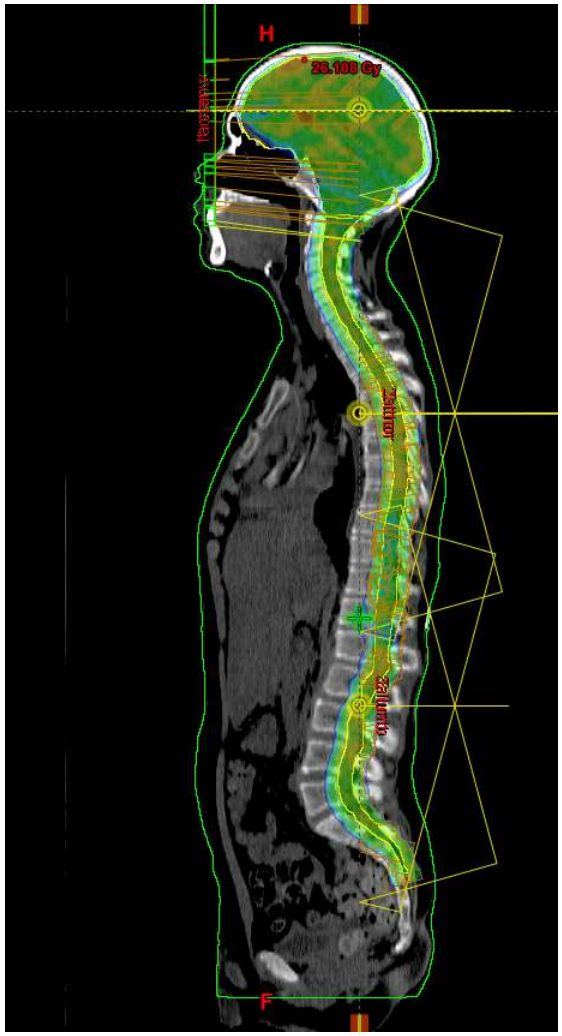
Dose distribution shown 20 – 24 Gy



- OAR: lungs, kidney, eyes,
- More homogenous dose
- No underdosage of target and overdose of OAR
- but –a challenge in designing the correct QA for check of dose delivery in the junctions.

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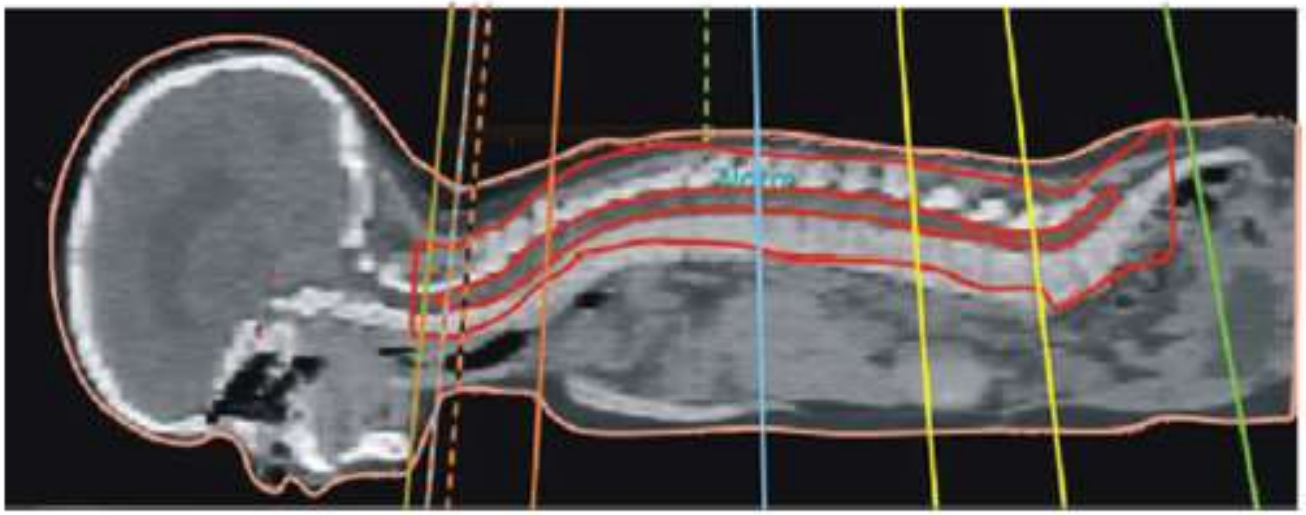
Craniospinal irradiation using a forward planned segmented field technique

Wilkinson JM et al – Br J of Radiology 2007 80:209-215



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Helical tomotherapy for craniospinal radiation

Bauman G et al – Br J of Radiology 2005 78:548-552

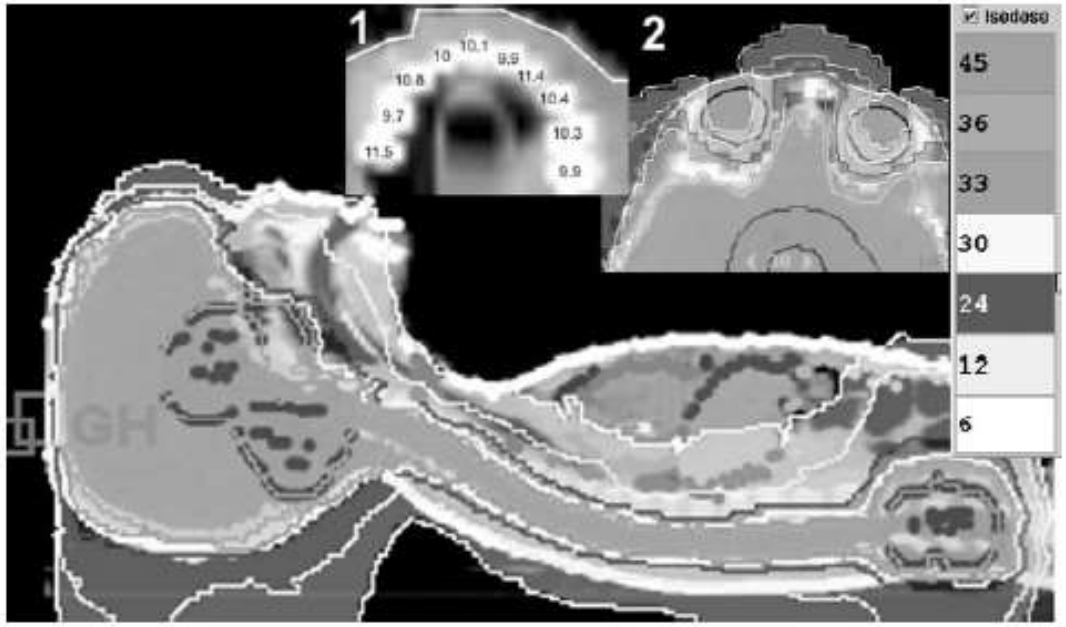

Figure 3. 25 mm helical tomotherapy plan demonstrating excellent conformality in sagittal plane. The chosen fan beam width thickness results in compromises in cribiform plate coverage in order to respect eye dose volume constraints (Inset 2).

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ESTRO Teaching Course on Physics for Clinical Radiotherapy, Ljubljana 2015

Essentials of stereotactic radiotherapy

Stéphanie Peeters

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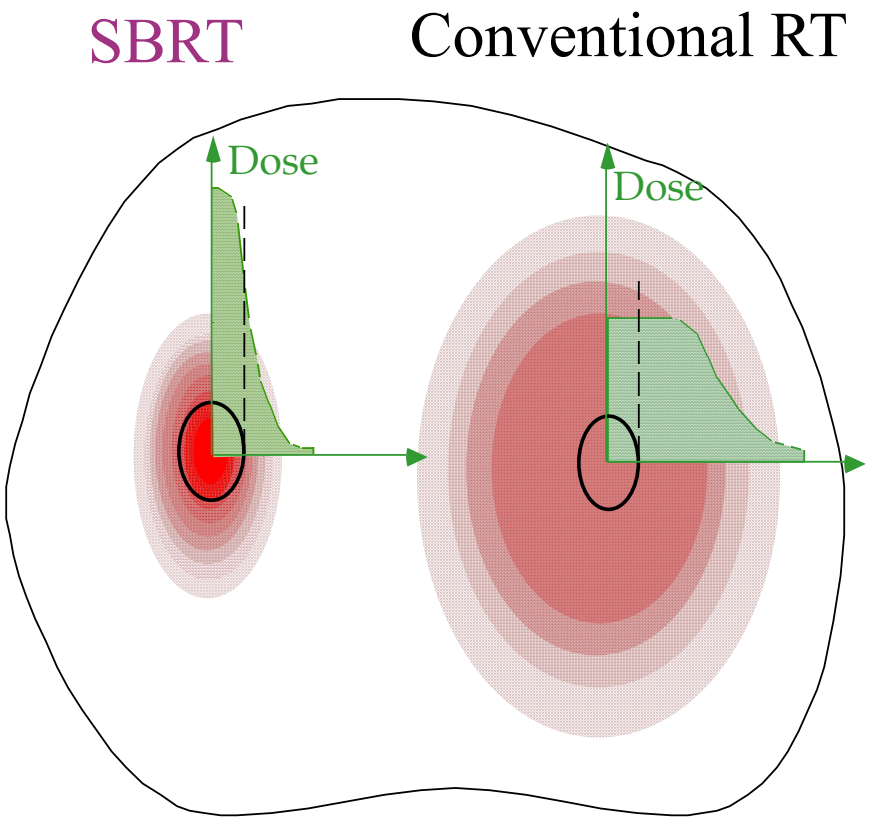
Overview

- What is stereotactic radiotherapy?
- History
- Some features of SABR
  - Radiobiology
  - Target definition
  - Motion control
  - Planning aims
- SABR modalities
- Indications & evidence
  - Cranial: benign, malignant
  - Extracranial: lung, liver, (para)spinal, oligomets…

What is stereotactic radiotherapy?



- Small number of fractions (1-5)
- High dose per fraction, short overall treatment time
- High biological dose (ablative)
- High precision/advanced imaging procedure
- Extremely conformal dosimetry with sharp gradients from high to low dose regions

What is stereotactic radiotherapy?

Stereotactic radiotherapy = **SRT**

Stereotactic ablative radiotherapy = **SABR**

Stereotactic radiosurgery = **SRS**

- Brain
- 1 session

Stereotactic body radiotherapy= **SBRT**

- Body
- fractionated

What is stereotactic radiotherapy?

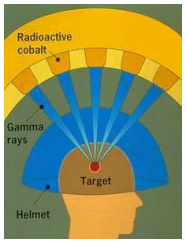
The term “stereotactic” refers to the correlation between

the tumour target position

and reliable fiducials with known position.

These fiducials define a **coordinate system** used to target the tumour, orient the treatment planning process and ultimately guide the therapy toward the intended location in the body.

SABR history & developments



SRS concept *Lars Leksell*

Animal studies

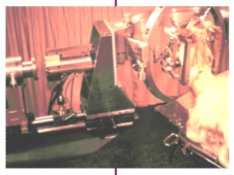
First gamma knife treatment

SBR frame stereotactic body frame *Blomgren Lax*

IGRT Onboard imaging 4D CT, gating, tracking

Equipment
Cyberknife
Tomotherapy
Varian Trilogy
Electa Synergy
Brainlab Exactrac
…

Clinical studies in SBRT:
RTOG
EORTC
NORDIC
Int. guidelines



1949 1968 1991

History

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Features of SABR

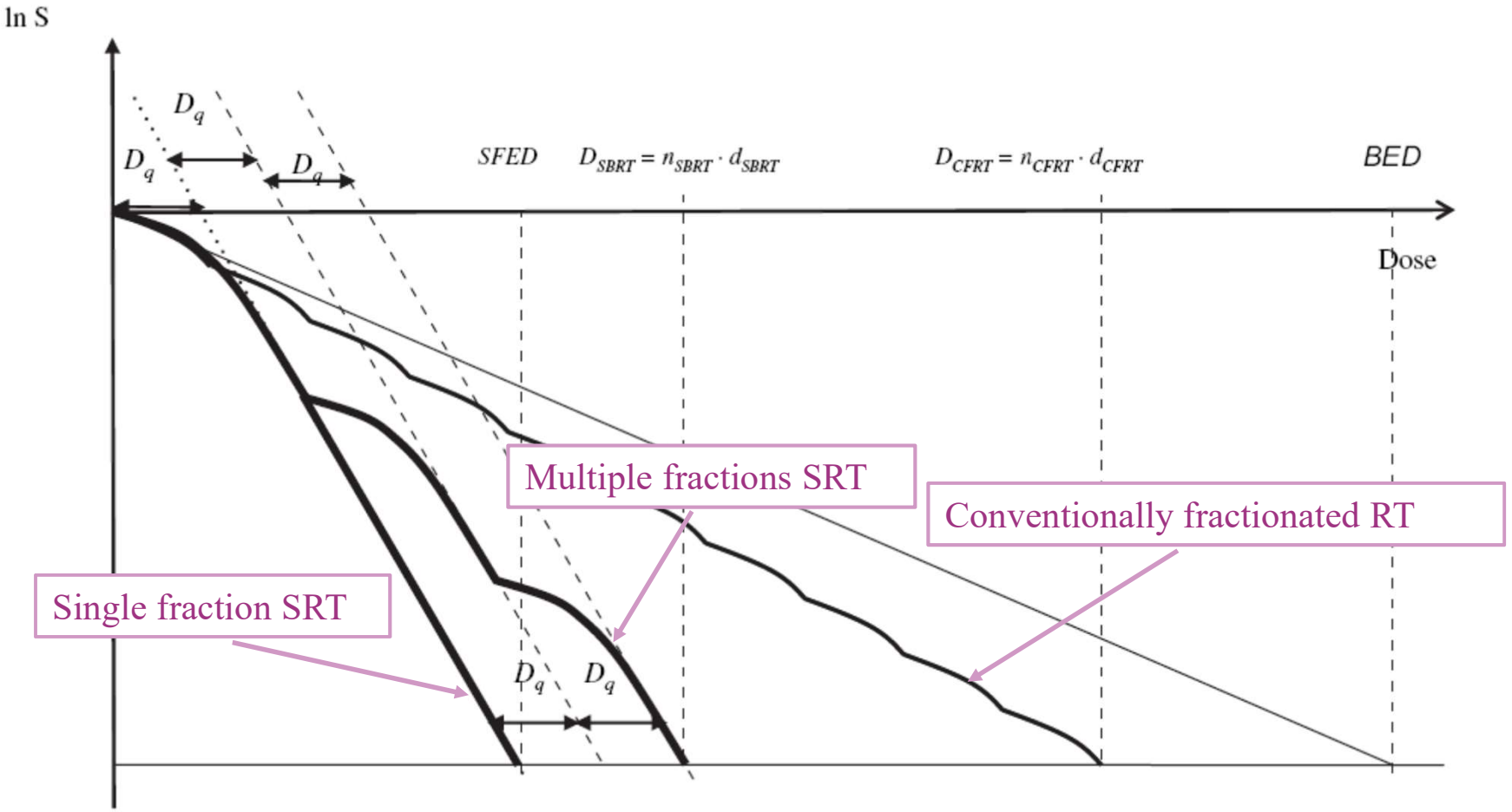
S(B)RT is a little about "stereotaxy"

and a lot about

target definition,
motion control (4D),
image-guidance,
conformal and compact dose distributions,
high levels of quality assurance during treatment

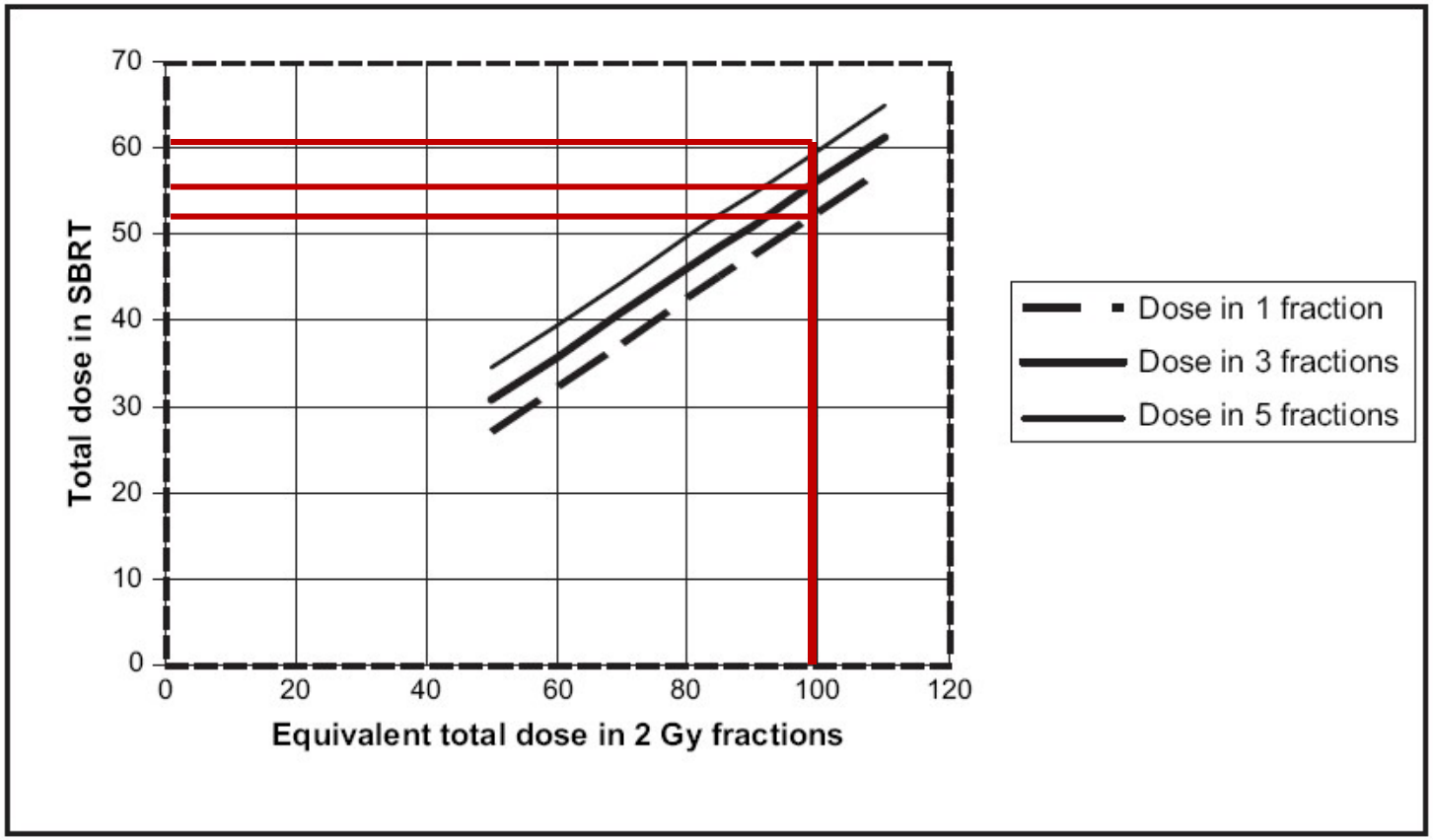
to be able to deliver **ablative doses**

Radiobiology



Park C., et al, IJROBP 2008

Radiobiology



EQ D2 = 100Gy

51Gy
54Gy
60Gy

Fig. 5. Graph representing relationships between biologically equivalent dose for stereotactic body radiotherapy (SBRT) and dose for conventionally fractionated radiotherapy. Three stereotactic body radiotherapy fractionated schemes displayed for stereotactic body radiotherapy delivered in one, three, and five fractions).

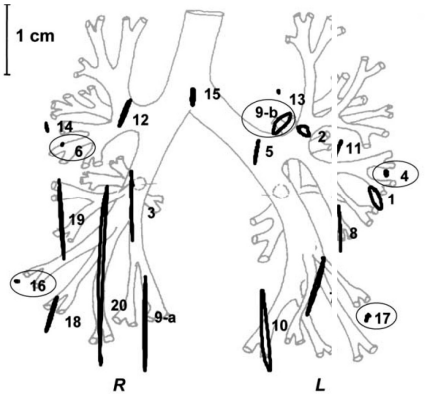
Park C., et al, IJROBP 2008

Target definition

- **GTV**
- No prophylactic or elective treatment
- Adjacent **CTV** is treated by dose fall-off
- **PTV**: setup uncertainty and motion
- **OAR/PRV**

Motion control (extracranial)

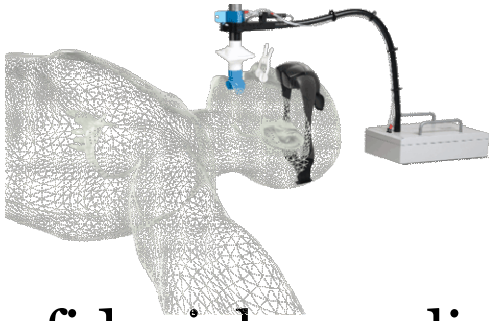
- Breathing, digestion…



Seppenwoolde et al. IJROBP 2002

- Strategies to account for this motion:

Modify respiration/ adaptive interaction	Active Breathing Control (ABC) Breath hold Gating Tracking	planning & treatment
Adequate expansion of PTV	4D-CT: ITV, MidV, MidP…	planning

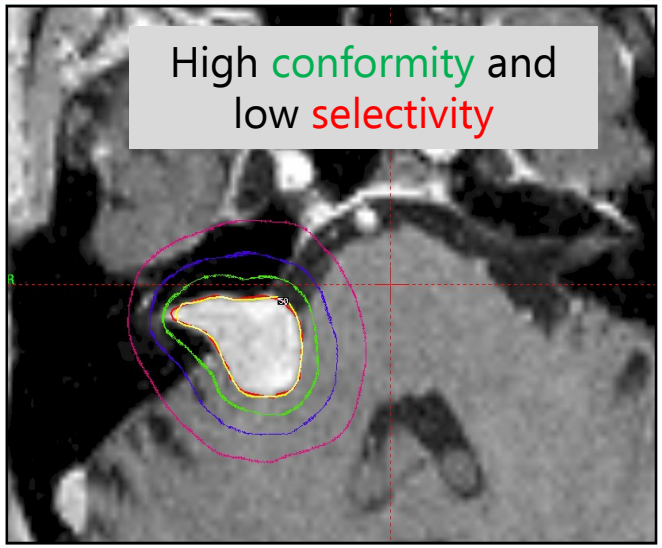


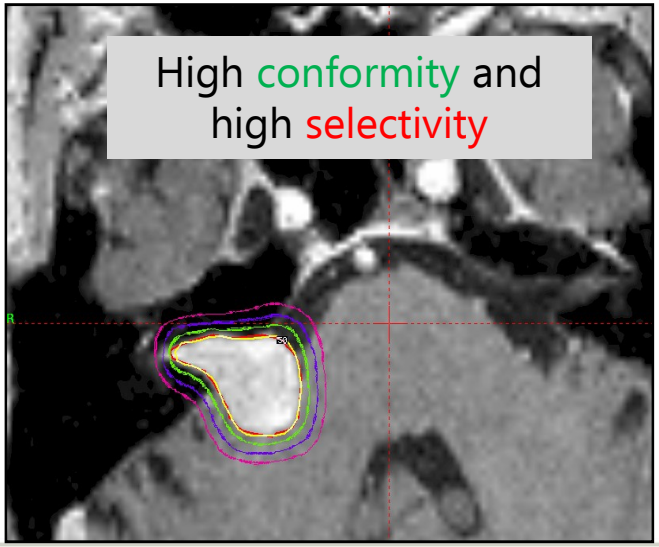
- Consider fiducials, e.g. liver

Planning aims

Conformity describes only how well the prescription dose is fitted to the target volume, whereas

selectivity also takes irradiation to normal tissue into account.





Question

Which statement about planning of a stereotactic ablative radiotherapy (SABR) treatment is correct.

For the planning of a SABR treatment…

A. the dose is prescribed to the isocenter

B. a steep dose gradient has to be achieved

C. the maximum allowed dose within the PTV is 107% of the prescription dose

D. a homogeneous dose distribution within the PTV has to be achieved

Which statement about planning of a stereotactic ablative radiotherapy (SABR) treatment is correct?

For the planning of a SABR treatment…

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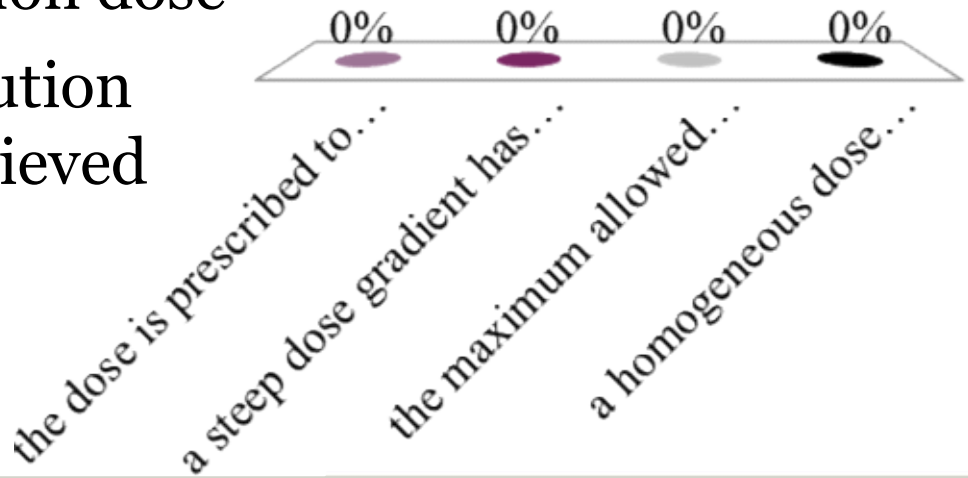

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Planning aims

Dose normalization

Prescription dose (D_{pr}) to %volume of PTV

95% of PTV should be covered by D_{pr}

99% of PTV should receive ≥ 90% of D_{pr}

Common prescription levels: 65-85% isodoseline

High dose constraints

Dose > 105% of D_{pr} must be inside PTV

D_{max} < 125-140% of D_{pr}

Dose calculation:

type B algorithm is advised (especially lung)

Planning aims

In literature different ways of prescribing dose for SBRT are used:

to isodoseline ≠ to isocenter

D_{pr} ≠ D_{pr}

Dose fractionation regimens and crude local control.

	Patient (#)	Median FU (months)	Tumor size (cm)	Prescribed dose/# fractions	Prescription	BED_{iso} (Gy_{10})	$BED_{periphery}$ (Gy_{10})
Median follow-up ⩾30 months							
Baumann et al. [29]	138	33	⩽9 Median 3.7	45 Gy/3 30 Gy/3 40 Gy/4	100% isodose at PTV periphery; 140–150% at the isocenter	219.4 112.5 150	112.5 60 80
Baumann et al. [30]	57	35	⩽5 Median 2.5	45 Gy/3	67% isodose line at PTV periphery	219.4	112.5
Fakiris et al. [31]	70	50.2	⩽7	T1: 60 Gy/ 3 T2: 66 Gy/3	80% isodose includes ⩾95% PTV	262.5 309.4	180 211.2
Kopek et al. [32]	89	44	n/a	45 Gy/3 67.5 Gy/3	Isocenter	112.5 219.4	60.5 113.4
Koto et al. [33]	31	32	⩽5	45 Gy/3 60 Gy/8	Isocenter	112.5 105	95.2 90.5
Nagata et al. [34]	45	30	⩽4	48 Gy/4	Isocenter	105.6	n/a
Nyman et al. [35]	45	43	⩽6	45 Gy/3	100% isodose at PTV periphery; 140% at the isocenter	195.3	112.5
Onishi et al. [36]	257	38	⩽5.8 Median 2.8				
Salazar et al. [37]	102	38	<5				
Takeda et al. [38]	63	39	n/a	50 Gy/5	80% isodose at PTV periphery	140.6	100
Uematsu et al. [39]	131	90	n/a	50–60 Gy/5–10	80% isodose at PTV periphery	?101.6–200.2	?75–140.6
Chen et al. [40]	65	47	n/a	48–64 Gy/6–15	95% isodose at PTV periphery	80.1–123.6	75.0–115.2

Take care when comparing results

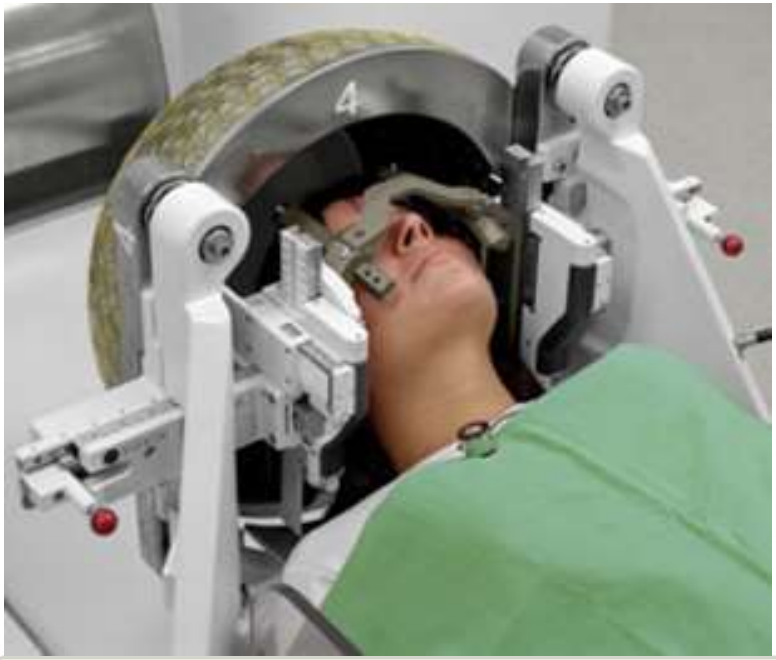
Chi et al. Radioth Oncol 2011

SRT modalities

- Gamma knife
- LINAC
- Cyberknife
- Tomotherapy
- …

Gamma Knife

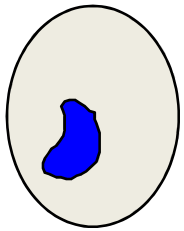
-Designed for brain tumours
-201 cobalt sources, gamma rays
-Energy: 1.25MeV
-Helmet
-1 session
-Isocentric



LINAC

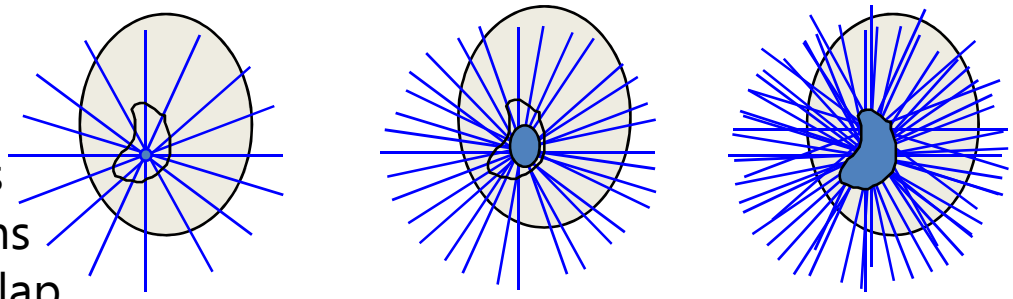
- Brain & body
- Isocentric – 1 source
- Variable energy
- 1 or multiple sessions

Gamma Knife vs. LINAC

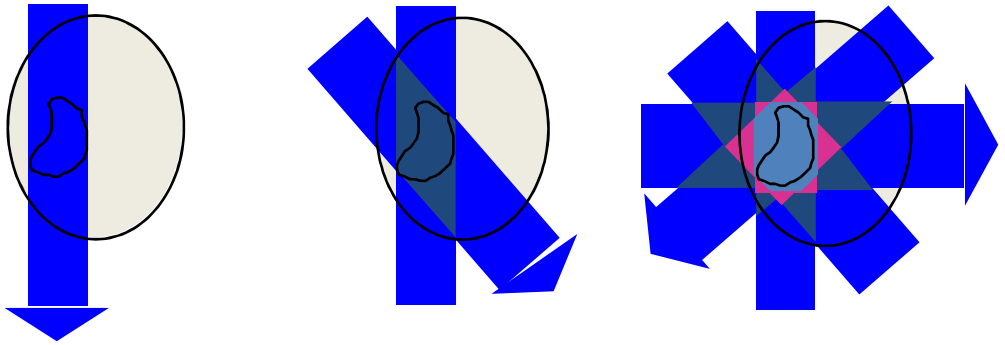


Target in head

Leksell Gamma Knife®
Multiple isocenters using narrow beams
= small beam overlap



Linac µMLC
One isocenter with several wide beams individually shaped
= large beam overlap

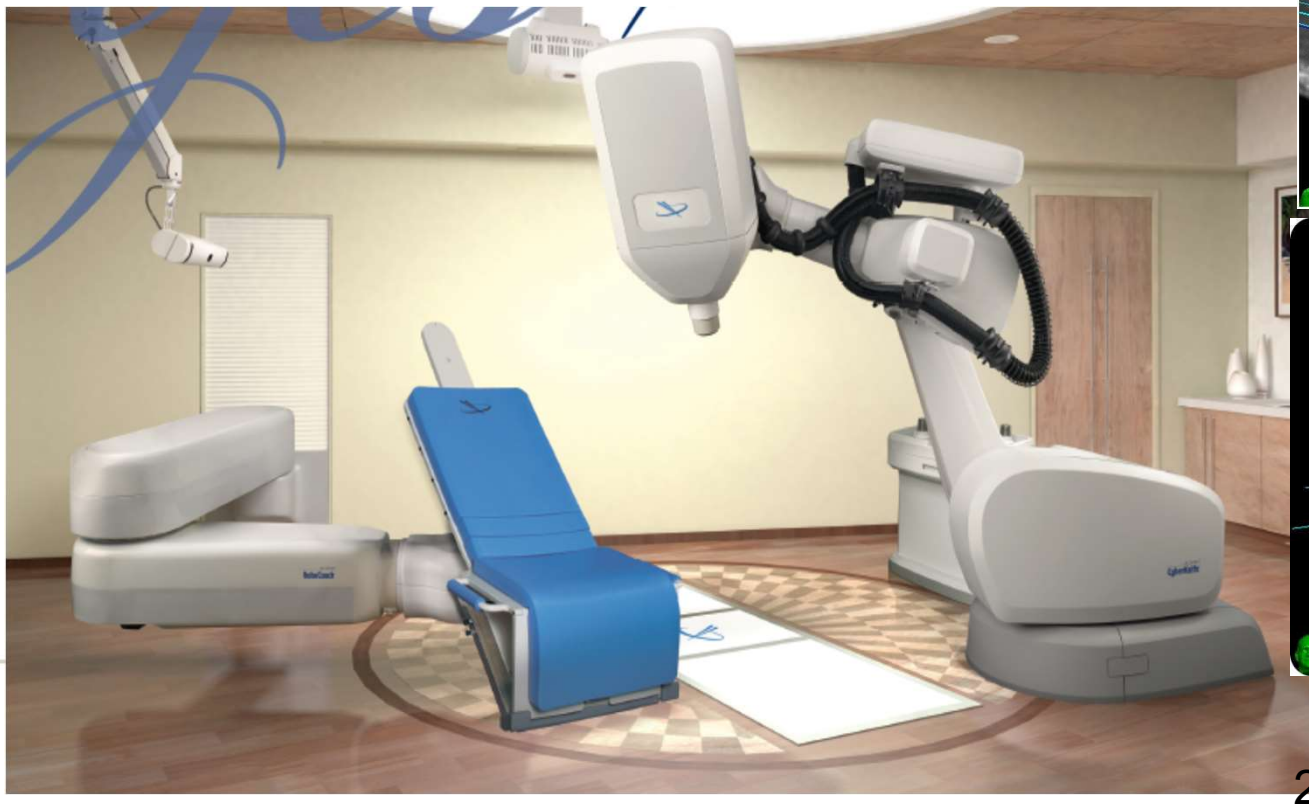


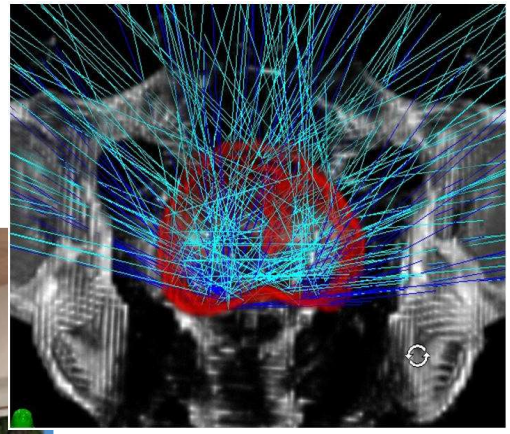
Time

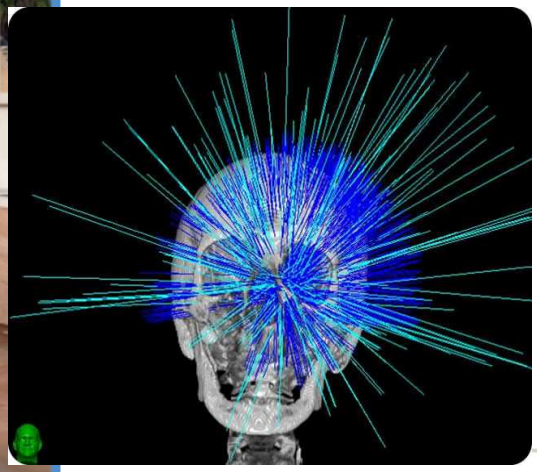
Cyberknife

Brain & body
Energy 6 MV
Robotic table and accelerator arm
Image guidance – tracking
Frameless

Non-isocentric
Several degrees of freedom
No posterior beams
Long treatment times

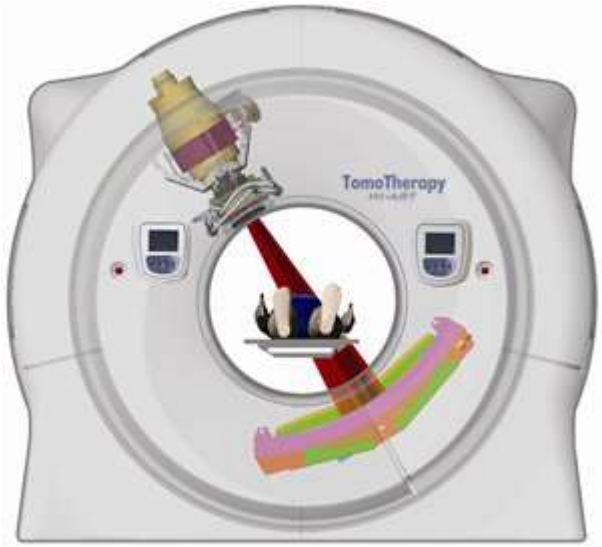






Tomotherapy

Irradiation delivered slice-by-slice (tomo = *greek*, slice)
Beam rotates around the body of the patient and simultaneously the treatment couch moves into the gantry.
Large cranio-caudal penumbra



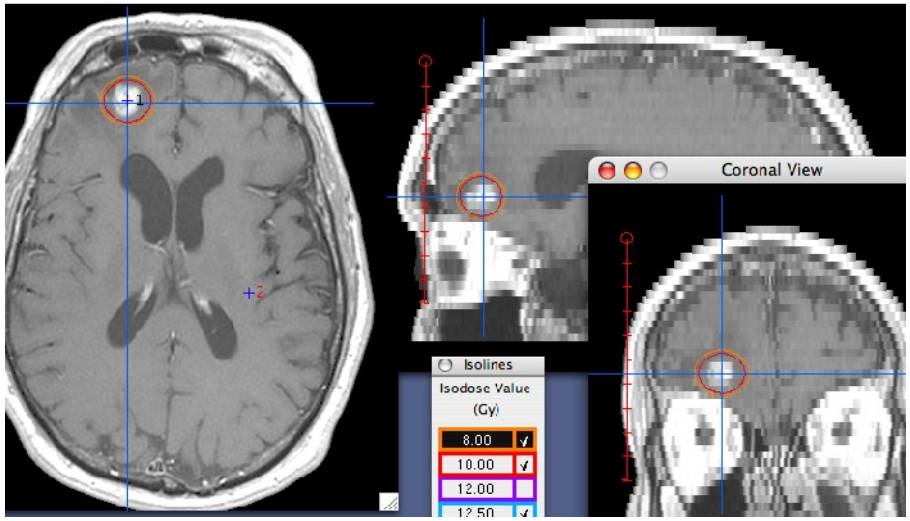
Clinical indications

- Cranial
  - Malignant
  - Benign
- Extracranial
  - Lung
  - Abdomen: liver, pancreas, kidney,...
  - Spinal/Paraspinal
  - Oligometastases
  - ...

Cranial

MALIGNANT TUMORS

Gliomas
Brain metastasis (single/multiple)



BENIGN LESIONS

"Benign" Tumors
Meningiomas
Acoustic neurinomas
Pitiutary Adenomas
Craniofaryngiomas
Glomus
Coroidal plexus papillomas
Schwannomas

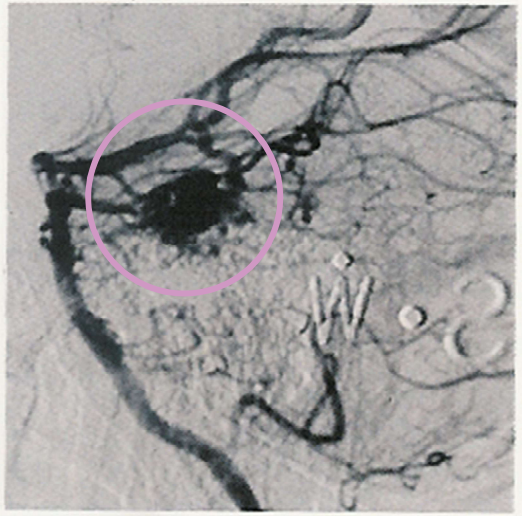
Vascular lesions
Arteriovenous malformations
Arteriovenous fistulas
Cavernomas

Functional diseases
Trigeminal neuralgia
Parkinson & other tremors
Seizure disorders

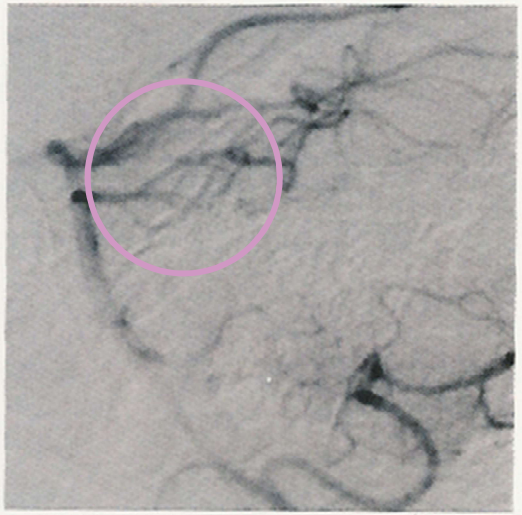
Cranial

Clinical indications

AVM

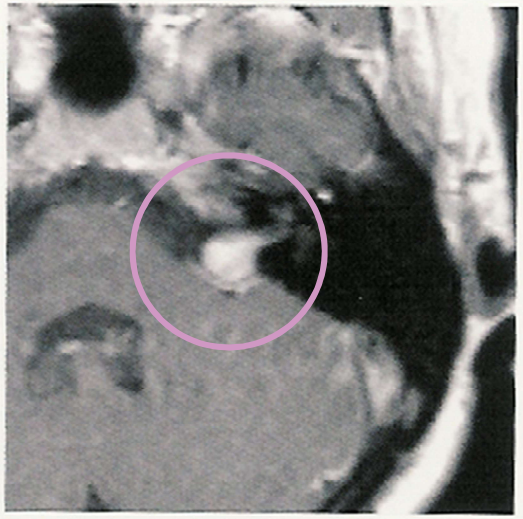


Pre-SRS treatment

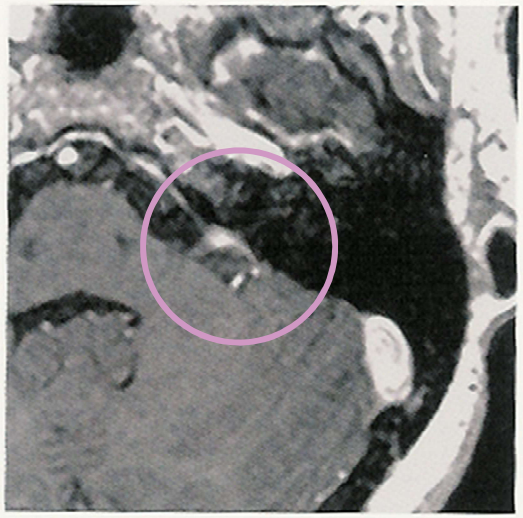


36 months post-SRS

Acoustic Neurinoma

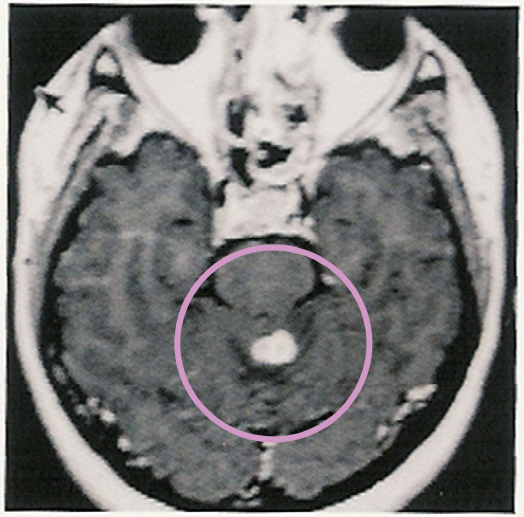


Pre-SRS treatment

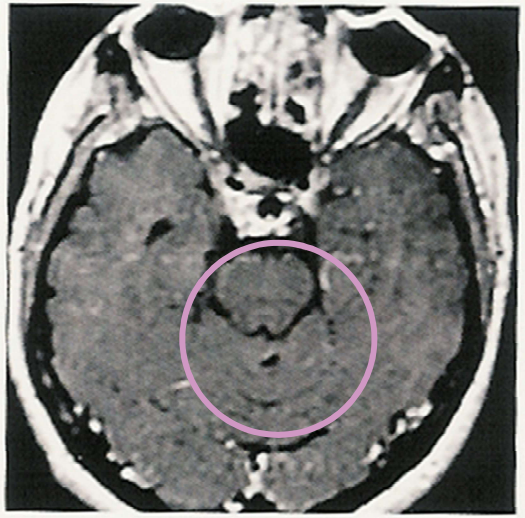


36 months post-SRS

Brain Metastasis



Pre-SRS treatment



36 months post-SRS

Brain metastasis

Surgery

Advantages	Tissue for diagnosis Removes mass immediately Improves local control Retreatment of previously irradiated pts Large lesions can be treated
Disadvantages	Invasive Longer hospital stay Limited to 1-3 M+ Risk of hemorraghe, infection

Radiosurgery

Advantages	Minimally invasive No hospitalisation Cost effective Improved local control Treats surgically inaccessible tumors Avoids general anesthesia
Disadvantages	Only small tumors Longer time to resolve mass effect Limited number of M+?

Brain metastasis

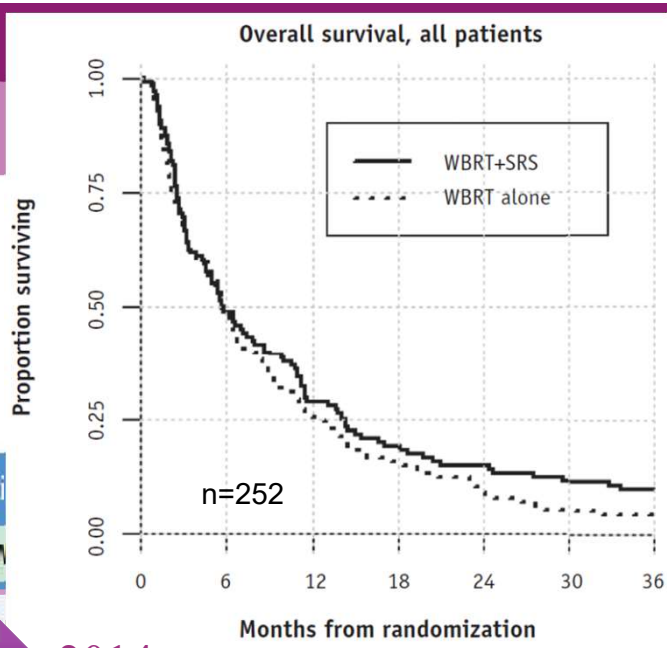
Clinical indications

Whole brain RT +/- radiosurgery

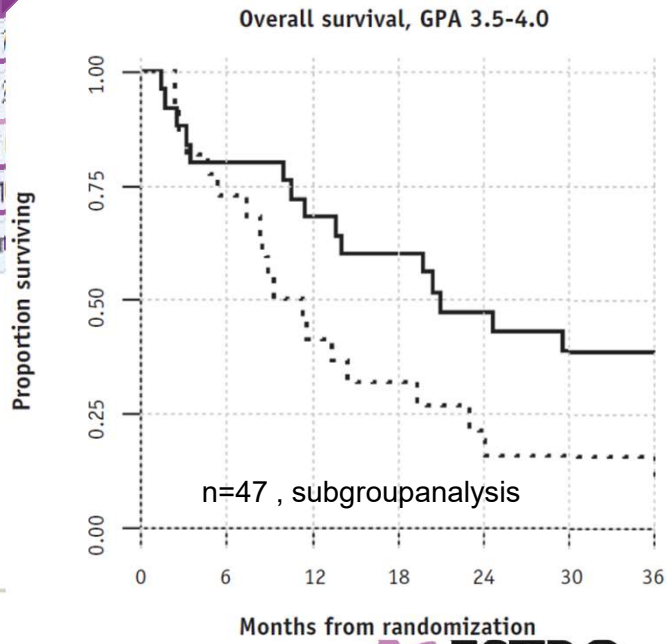
LC ↑
OS =

Table 2. WBRT with or Without SRS in the Treatment of Patients with Single or Multi

Author/Study Type	# BM	Study Endpoints	W
Andrews et al., 2004 (1)/ randomized	1–3	Overall MS	6.5
		1-year local control rate	
		6-months KPS rate	
Kondziolka et al., 1999 (16)/ randomized	2–4	MS	7.5
		1-year local failure rate	1
		Median local recurrence time	6



2014



Elaimy et al. World Neurosurg 2011, Sperduto IJROBP 2014

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Brain metastasis

Radiosurgery +/- whole brain radiotherapy

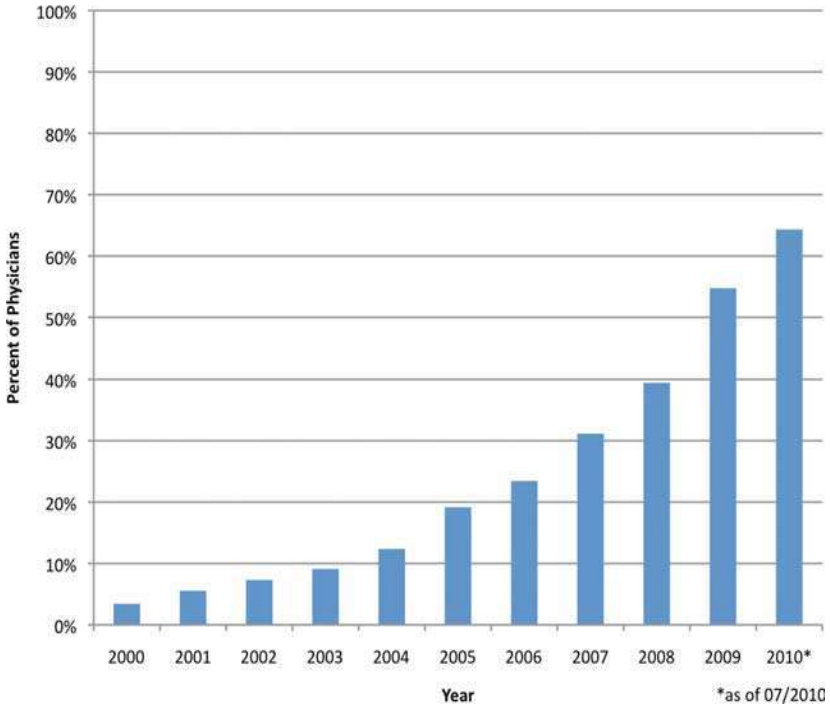
SRS with or without WBRT in the treatment of patients with single of multiple brain metastases

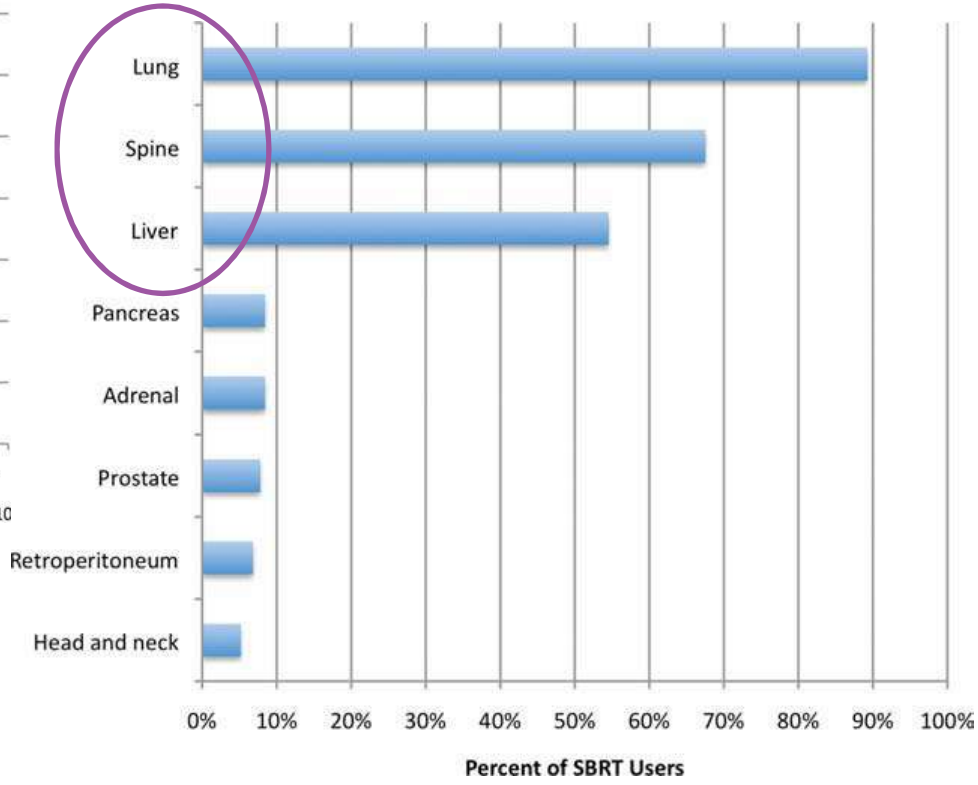
Randomized trials	# BM	Study endpoint	SRS	SRS+WBRT	p
Aoyama JAMA 2006	1-4	MS (months)	8	7.5	NS
		1 year overall recurrence rate	76.4%	46.8%	<0.001
		Neurological death rate	19.3%	22.8%	NS
		1y KPS > 70	27%	34%	NS
EORTC 22952-26001 Kocher JCO 2011	1-3	Median OS (months)	10.7	10.9	NS
		2y relapse at initial site	31%	19%	0.04
		2y relapse at new intracranial site	48%	33%	0.02
		2y Survival with functional independance	22.3%	22.6%	NS

Clinical indications

Extracranial SBRT: indications?

Cumulative adoption of SBRT in the USA





No randomized trials

Most publications on Lung

Pan Cancer 2011

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Primary lung cancer

Table 1. Local control rates of stereotactic radiotherapy for primary lung cancer

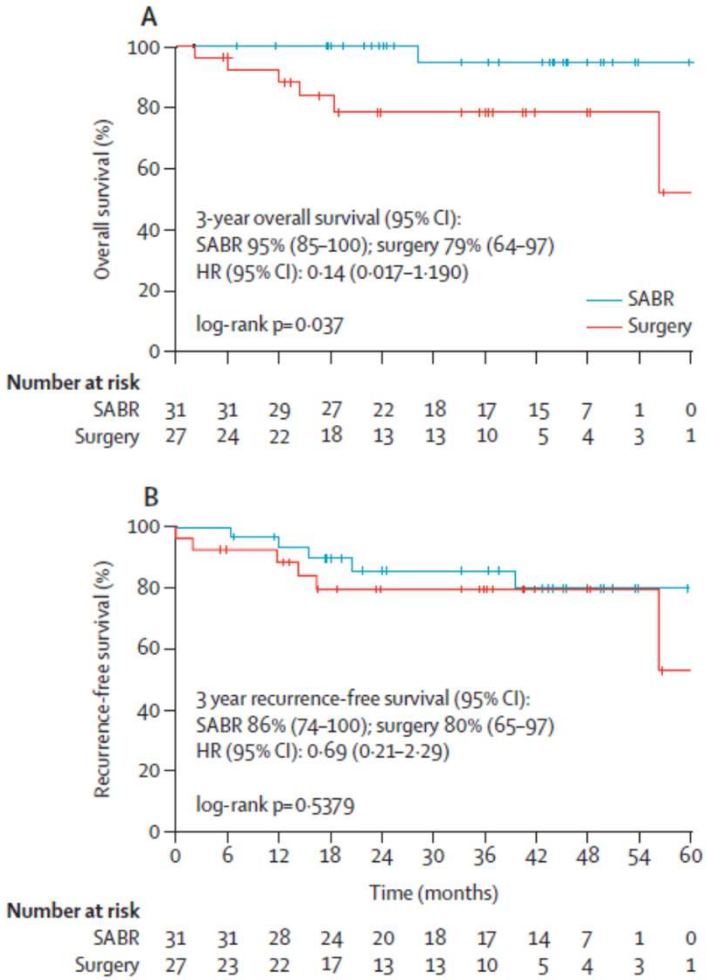
Study	Total dose (Gy)	Daily dose (Gy)	Reference point	Local control	Median follo
Uematsu *et al.*, 2001 (21, 23)	50–60	10	80% margin	94%(47/50)	36 mo
Arimoto *et al.*, 1998 (24)	60	7.5	Isocenter	92%(22/24)	24 mo
Timmerman *et al.*, 2003 (19)	60	20	80% margin	87%(30/37)	15 mo
Onimaru *et al.*, 2003 (25)	48–60	6–7.5	Isocenter	80%(20/25)	17 mo
Wulf *et al.*, 2004 (26)	45–56.2	15–15.4	80% margin	95%(19/20)	10 mo
Nagata *et al.*, 2005 (28)	48	12	Isocenter	97%(44/45)	30 mo
Lee *et al.*, 2003 (27)	30–40	10	90% margin	90%(8/9)	21 mo
Fakiris *et al.*, 2009 (29)	60–66	20–23	80% margin	88%(70)	50 mo
Baumann *et al.*, 2009 (30)	45	15	67% margin	92%(57)	35 mo
Timmerman *et al.*, 2010 (31)	60	20	80% margin	98%(54/55)	36 mo

Nagata IJROBP 2011

Primary lung cancer

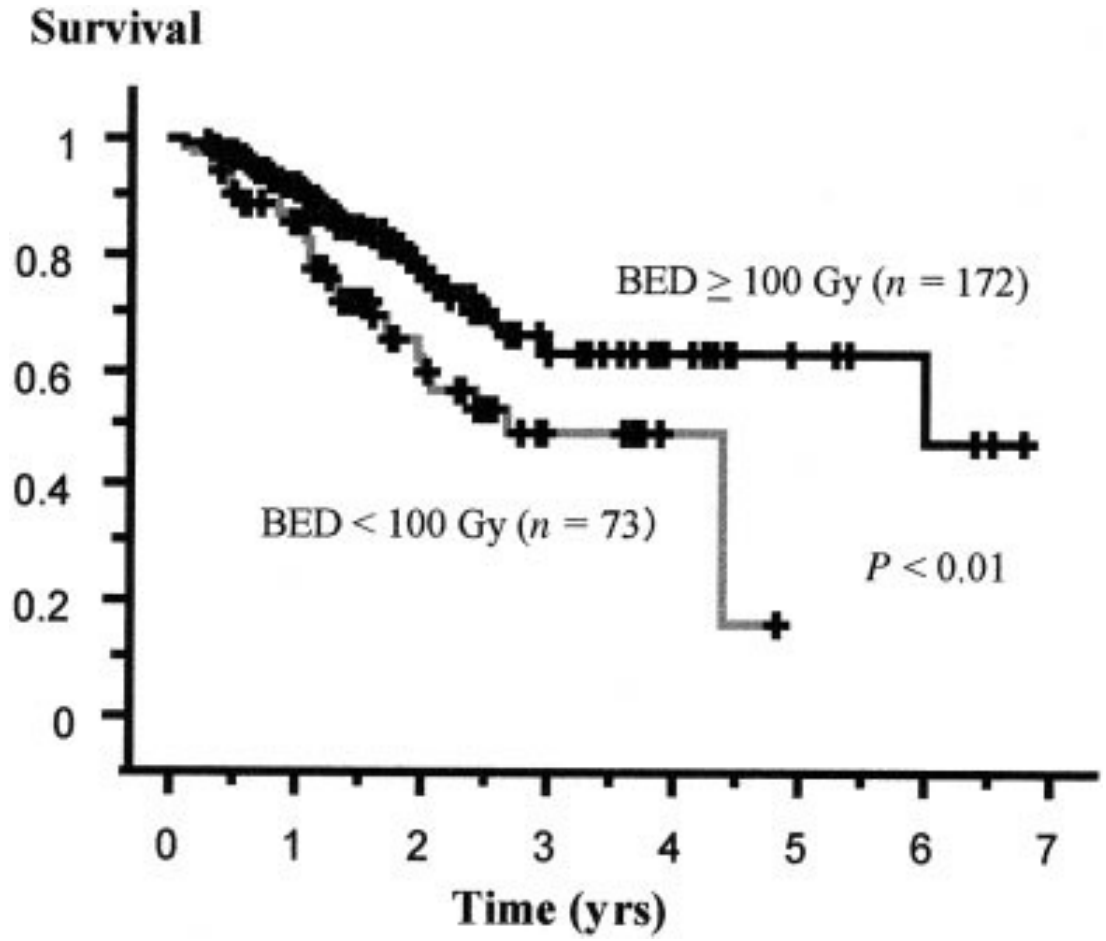
2 RCT (STARS & ROSEL) closed prematurely because of poor accrual → pooled data of both trials

	SABR	surgery
N° pts	32	27
Fup (m)	40	35
Death	1	6
3y OS	95%	79%
3y RFS	86%	80%
Recurrences Local Regional node Distant	 1 4 1	 0 1 2
Toxicity Grade 3 Grade 4 Grade 5	 3 0 0	 10 1 1
	54Gy/3fr 50Gy/5fr 60Gy/5fr	Lobectomy



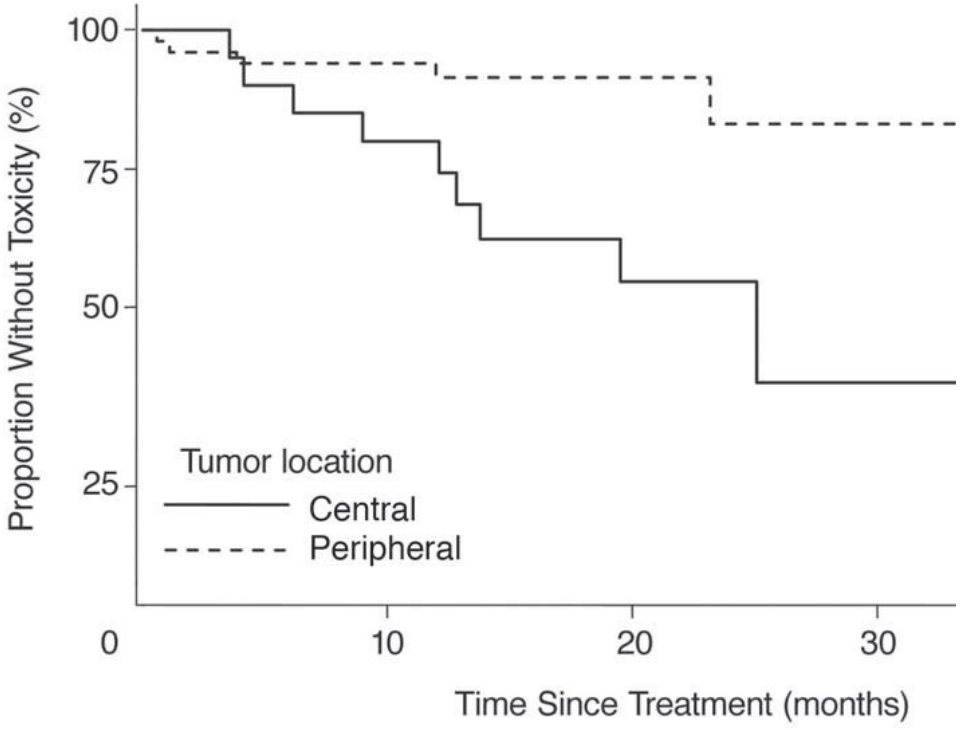
Chang Lancet Oncol 2015

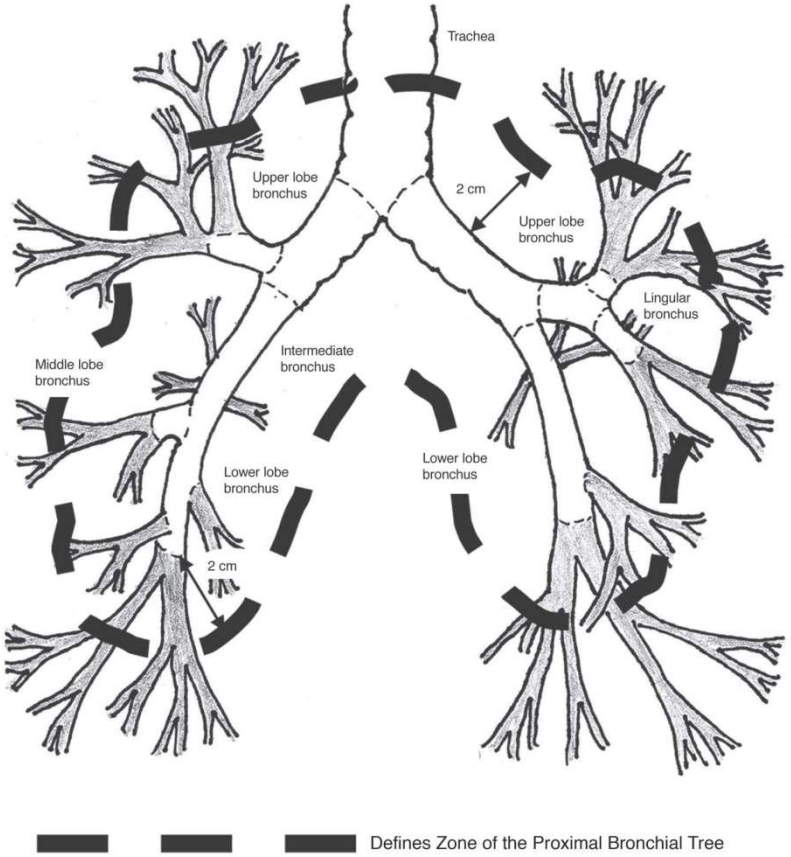
Primary lung cancer



Onishi Cancer 2004

Primary lung cancer: toxicity



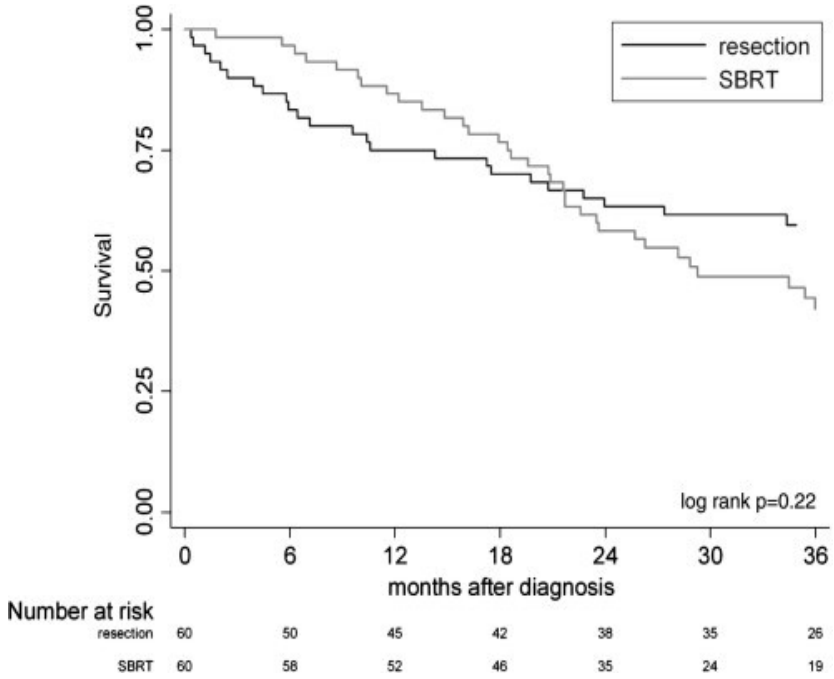


→ Altered fractionation schedules & lower doses for centrally located tumors

Timmerman JCO 2008

Primary lung cancer: elderly

>75y
2005-2007



Palma Radiother Oncol 2011

Panel: Key considerations in local treatment decisions

Surgery

Pros:

- Definitive pathological diagnosis
- Enables invasive nodal staging in all cases
- Appropriate delivery of adjuvant therapy in node-positive disease

Cons:

- Procedure-related morbidity and mortality
- Invasive procedure for possibly benign disease

SABR

Pros:

- 5-year local disease control rates of more than 90%
- Outpatient procedure with mild acute toxicity
- Preservation of lung function and quality of life

Cons:

- Treatment without definite pathological verification
- Post-treatment fibrosis masking local disease recurrence

Senan R&O 2014

Lung metastasis

	Rusthoven JCO 2009	Hof Strahl Onk 2007	Hoyer Acta Oncol 2006	Nuyttens IJROBP 2015
Study	Phase I/II	Phase I/II	Phase II	Phase II
Inclusion	≤ 3 lesions, cum diam max 7cm Extrathoracic disease allowed if low burden…	Max 4 cm No other M+ site Inoperable	Max 6 cm Lung & liver Inoperable 1-4 mets Primary tu treated	Max 2 organs, 5 lesions, Metachronous, Primary controlled …
Dose	48-60 Gy / 3fr	12-30 Gy / 1 fr (isocenter dose)	45 Gy / 3 fr	30 Gy /1 fr 60 Gy / 3 fr or 5 fr 56 Gy / 7 fr
Pts/lesions	38/63	61/71	65/142	37/57
Toxicity grade 3	8% (3 pts)	5% (3 pts)		5 pts
Median fup	15.4 months	14 months	4.3 years	36 months
2 y Local Control	96%	74%	86%	90% (3-7 fr) 75% (1 fr)
2 y OS	39%	65%	38%	63%
Primary	various	various	colorectal	Various (colorectal)

Liver metastasis

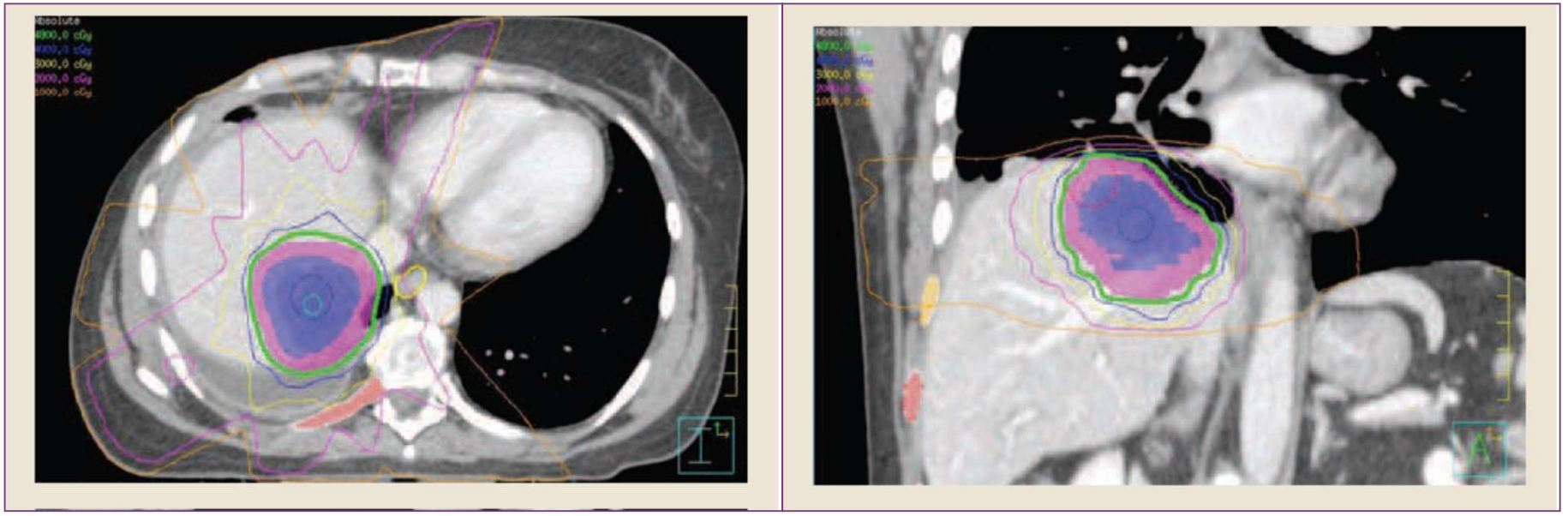
Current standard: surgical resection

Alternatives

Radiofrequency ablation (RFA): < 3 cm

Chemotherapy (up to 12,5% M+ may become resectable)

SBRT



Liver metastasis: outcome

Study	Pts/ targets	Dose	Median FUP	LC	OS	Primary colorectal
Herfarth JCO 2001						
Kavanagh Acta Oncol 2006						
Mendez-Romero Acta Oncol 2006						
Katz IJROBP 2007						
Rusthoven JCO 2009						
Lee JCO 2009						
Van der Pool Br J Surg 2010						
Vautrevas-Dewas IJROBP 2011						

Inclusion criteria usually:
-Inoperable patients
-Maximal lesion diameter 6-7 cm
-Maximal number of M+1-3
-M+ confined to liver, or liver most life-threatening
-Adequate liver function
-Life expectancy > 6m
-KI > 70
-After having failed one or more courses of chemotherapy
-Concurrent chemo not allowed

Liver metastasis: toxicity

Study	Pts/ targets	Dose	Grade 3 hepatic toxicity
Herfarth JCO 2001	37/60	14-26 Gy/ 1fr	0
Kavanagh Acta Oncol 2006	21/28	36-60 Gy / 3fr	0
Mendez-Romero Acta Oncol 2006	17/34	37.5 Gy / 3 fr	2 pts
Katz IJROBP 2007	69/174	50 Gy / 5fr	0
Rusthoven JCO 2009	47/63	36-60 Gy / 3fr	1 pt
Lee JCO 2009	68/141	27.7-60 Gy / 6 fr	2 pts
Van der Pool Br J Surg 2010	20/31	37.5-45 Gy / 3 fr	2 pts

Typical acute toxicity:

-Fatigue
-Nausea
-Abdominal pain
-Fever
-Liver enzymes ↗
-Erythema
-Gastritis/oesophagitis/colitis

Rare severe toxicity:

-RILD
-Liver function decline
-GI ulceration
-GI perforation

Outcome after standard therapies

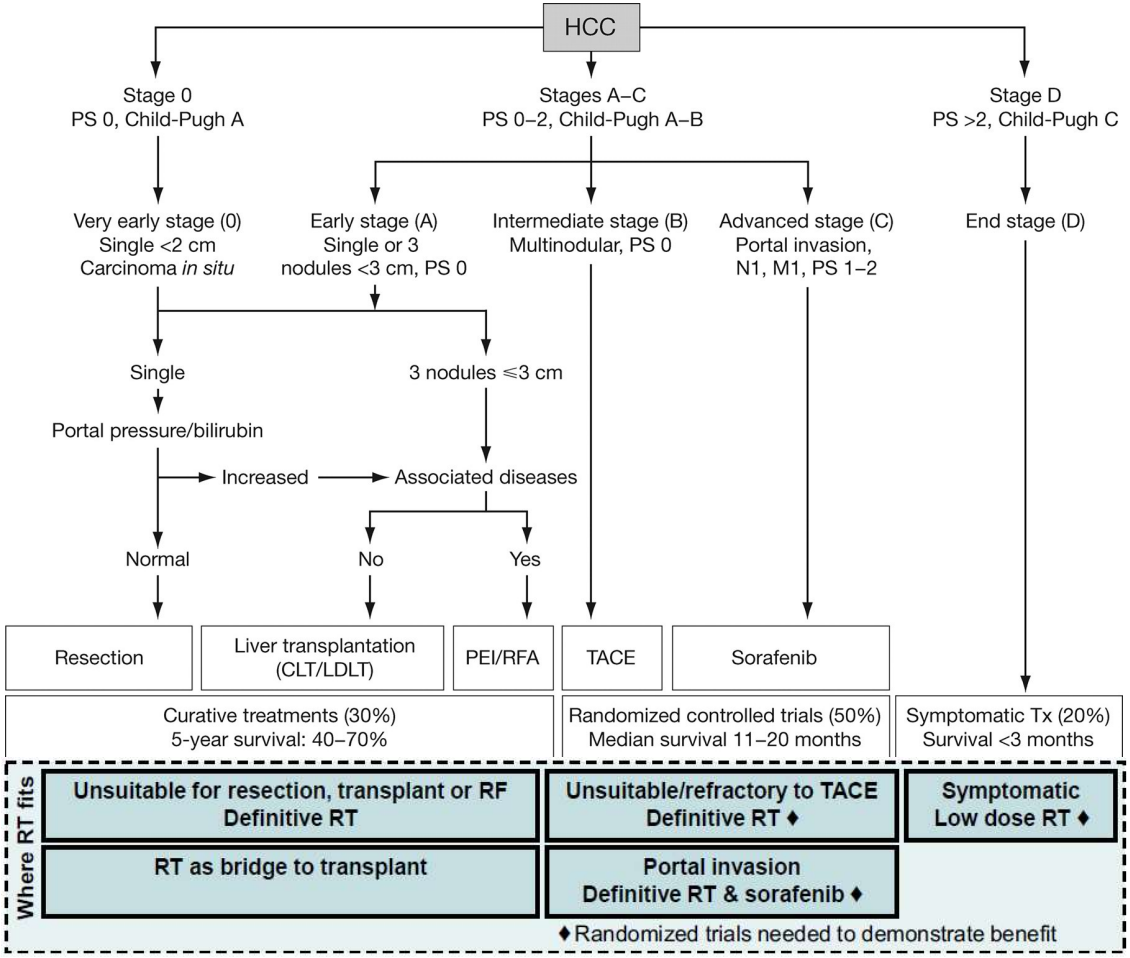
Table 1 Outcome Estimates for HCC (Child-Pugh A)

	Survival, 5 Years (%)	Hepatic Recurrence (%)
Transplant	70-75	8
Resection	45-60	68
RFA	50	5-20 (local recurrence)
TACE	<2 (31-63 at, 2 y)	~100
sorafenib	~0	~100

Dawson Radiat Oncol 2011

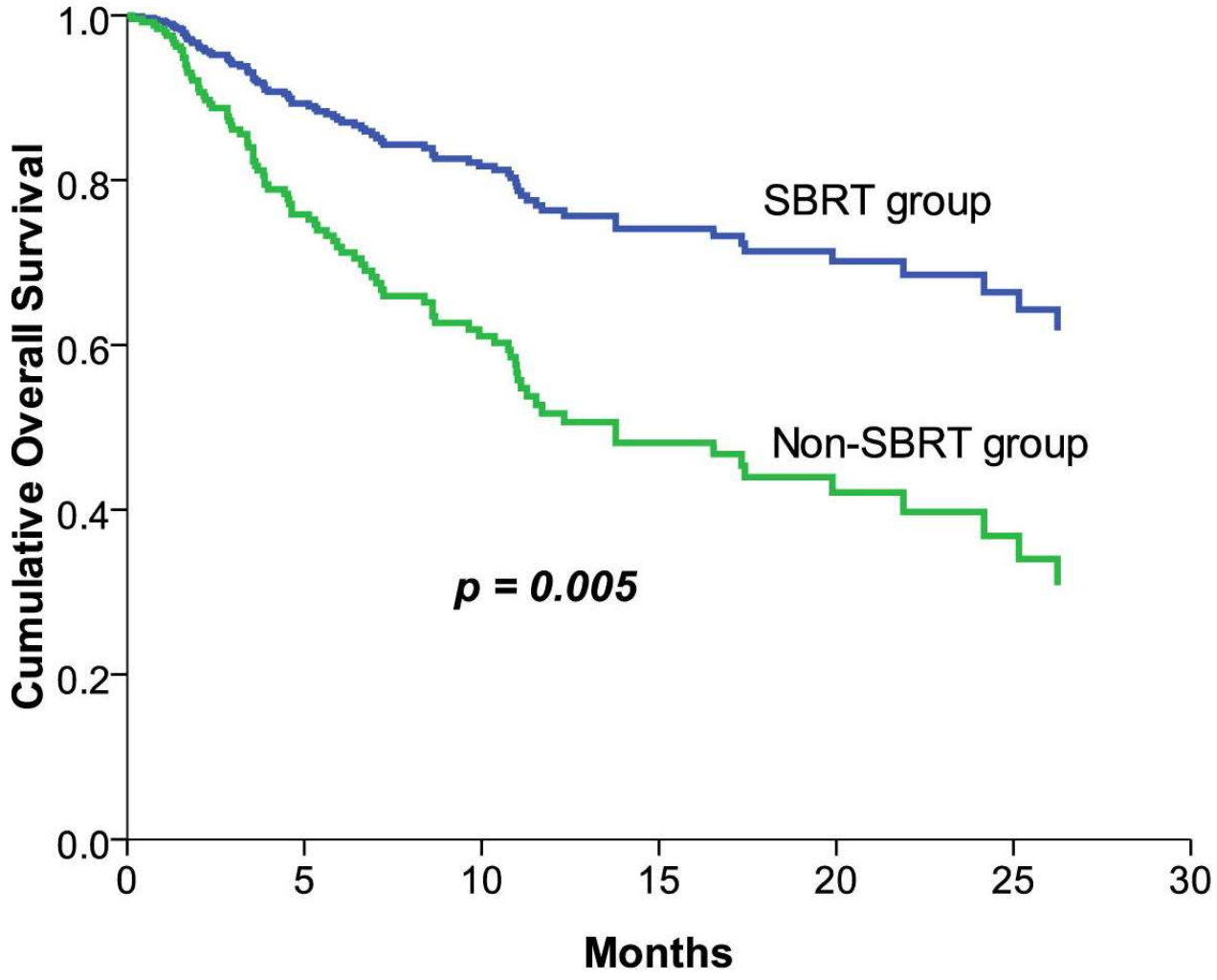
Liver HCC

Figure 1. Barcelona Clinic Liver Cancer staging system and recommended treatment strategy



Lencioni The Oncologist 2010
Dawson Radiat Oncol 2011
Tanguturi The Oncologist 2014

Recurrent HCC

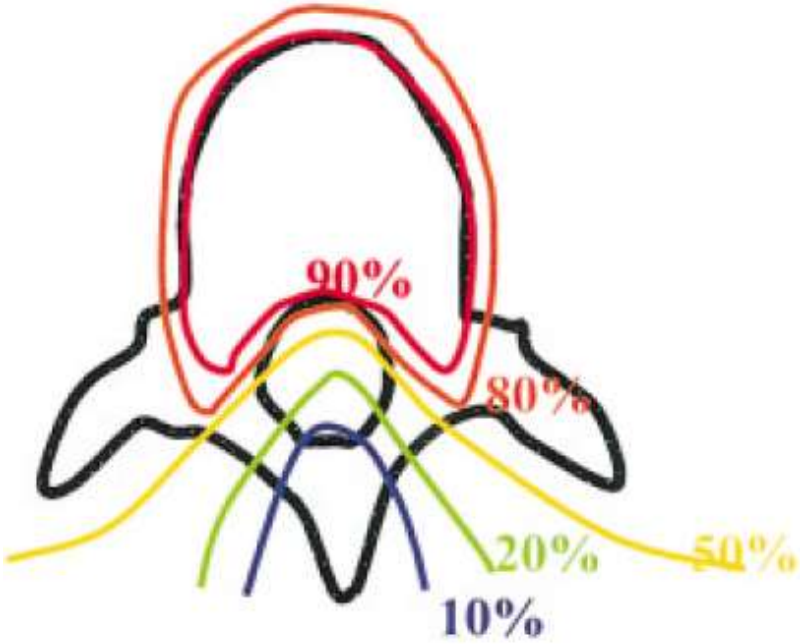


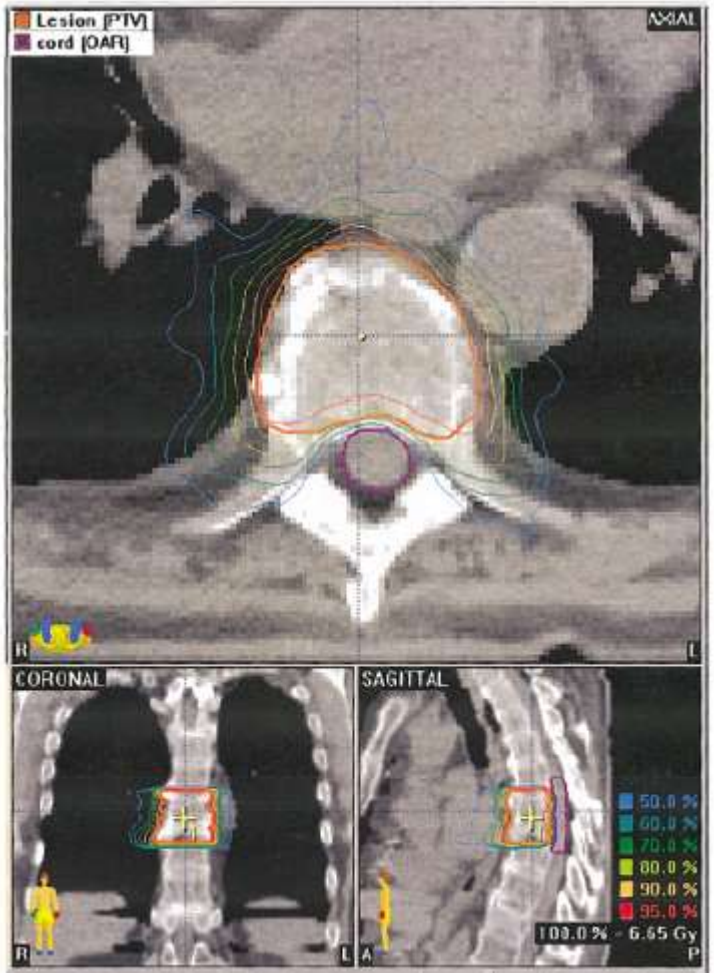
Huang et al. IJROBP 2011

Spinal/paraspinal

Potential indications:

- Durable pain control
- Tumor control (good prognosis)
- Post surgery for residual tumor
- Progression after other treatment





Harel Eur J Ca 2010; Ryu 2003 & 2015

Spinal/paraspinal

Clinical indications

Treated area depends on tumor localisation

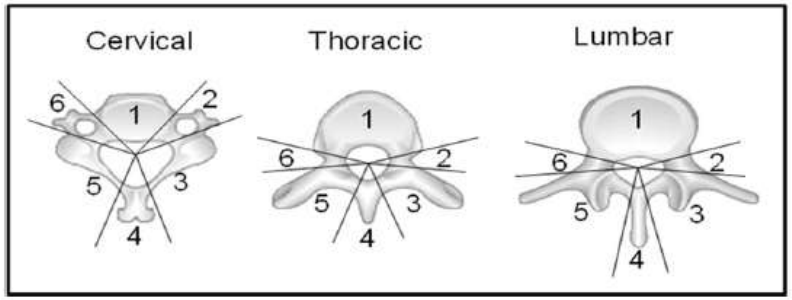


Fig. 1. International Spine Radiosurgery Consortium anatomic classification system for consensus target volumes for spine radiosurgery.

Table 3 Guidelines for spinal SRS bony CTV delineation

GTV involvement	ISRC GTV anatomic classification	ISRC bony CTV recommendation	CTV description
Any portion of the vertebral body	1	1	Include the entire vertebral body
Lateralized within the vertebral body	1	1, 2	Include the entire vertebral body and the ipsilateral pedicle/transverse process
Diffusely involves the vertebral body	1	1, 2, 6	Include the entire vertebral body and the bilateral pedicles/transverse processes
GTV involves vertebral body and unilateral pedicle	1, 2	1, 2, 3	Include entire vertebral body, pedicle, ipsilateral transverse process, and ipsilateral lamina
GTV involves vertebral body and bilateral pedicles/transverse processes	3	2, 3, 4	Include entire vertebral body, bilateral pedicles/transverse processes, and bilateral laminae
GTV involves unilateral pedicle	2	2, 3 ± 1	Include pedicle, ipsilateral transverse process, and ipsilateral lamina, ± vertebral body
GTV involves unilateral lamina	3	2, 3, 4	Include lamina, ipsilateral pedicle/transverse process, and spinous process
GTV involves spinous process	4	3, 4, 5	Include entire spinous process and bilateral laminae

Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; ISRC = International Spine Radiosurgery Consortium.

Cox IJROBP 2012

Spinal/paraspinal

Clinical indications

TABLE 2: Literature review of the current evidence, including only studies reporting on spinal metastases*

Authors & Year	Total No. Tumors/ No. Pts	No. Tumors w/ Retx/ No. Pts	No. Postop Pts	FU in Mos (range)	Local Control/Criteria†	Tumor Dose/No. Frx/Rx Isodose	Pain Response (pain assessment tool)
postop SBRT							
Moulding et al., 2010	21/21	0	21	median 10.3	17 of 21 (81%) w/ 1-yr local control 90.5%/imaging	median 24 Gy/1/80%	NS
Rock et al., 2006	18/18	1/1	18	median 7 (4–36)	17 of 18 (94%)/imaging &/or clinical	4 of 18: EBRT 25 Gy/10 frx + SBRT boost; median 6 Gy/1/90%; 14 of 18: SBRT only; median 14 Gy/1/80%	6 of 18 w/ CR (NS)
Gerszten et al., 2005[17]	26/26	7/7	26	median 16 (11–24)	24 of 26 (92%)/imaging & pain	mean 18 Gy/1/80%	improved in 24 of 26 (VAS)
total	65/65	8/8	65		58 of 65 (89%)		
SBRT for tumors w/ no prior radiation							
Yamada et al., 2008	103/93	0/0	0	median 15 (2–45)	90% at 15 mos, ~93 of 103/imaging	median 24 Gy/1/80%	NS
Ryu et al., 2004	61/49	0/0	NS	median 6.4 (6–24)	57 of 61 (93%)/imaging & pain	10–16 Gy/1/80%	85% comb CR/PR rate (VAS)
Ryu et al., 2003	10/10	0/0	NS	mean 6 (3–12)	10 of 10 (100%)/imaging & pain	EBRT 25 Gy/10 frx + SBRT boost; 6–8 Gy/1/90%	5 of 9 w/ CR, 4 of 9 w/ PR (NS)‡
Sahgal et al., 2009[45]	23/14	0/0	5	median 9 (1–26)	18 of 23 (78%)/imaging &/or pain§	median 24 Gy/3/67%	NS
total	197/166	0/0			178 of 197 (90%)		
SBRT for tumors w/ prior radiation							
Mahan et al., 2005	8/8	8/8	0	mean 15.2	8 of 8 (100%)/NS	median 30 Gy/15/NS	6 of 8 w/ CR, 2 of 8 w/ PR (NS)
Milker-Zabel et al., 2003	19/18	19/18	0	median 12 (4–33)	18 of 19 (95%)/imaging	median 39.6 Gy/2 (aim was 90% coverage)	13 of 16 (NS)
Hamilton et al., 1995	5/5	5/5	0	median 6 (1–12)	5 of 5 (100%)/imaging &/or clinical	median 10 Gy/1/80%	NS
Sahgal et al., 2009[45]	37/25	37/25	0	median 7 (1–48)	34 of 37 (92%)/imaging &/or pain	median 24 Gy/3/60%	NS
total	69/56	69/56	0		65 of 69 (94%)		

* BPI = brief pain inventory; comb = combined; CR = complete pain relief; FFP = freedom from progression; FU = follow-up; NS = not specified; PR = partial pain relief; pts = patients; Retx = reirradiation; VAS = visual analog scale.
† Local control for postoperative patients in those nondedicated postoperative mixed cohort series: 4/5 in Sahgal et al.[45]; 10/15 in Nguyen et al.; 23/29 in Chang et al.
‡ One patient obtained pain relief from surgery prior to SBRT; therefore, the number of cases was 9.
§ Details provided by primary author of the publication, although not specified in the paper.
¶ Assumed that the number of patients is the same as number of tumors treated for those not specified, to give a rough estimate to the reader.

Sahgal JNS 2011

Spinal/paraspinal: summary

A. Local control/pain control is high in all categories > 85-92 %

→ rapid pain control within days (FU short, diff pain instr.)

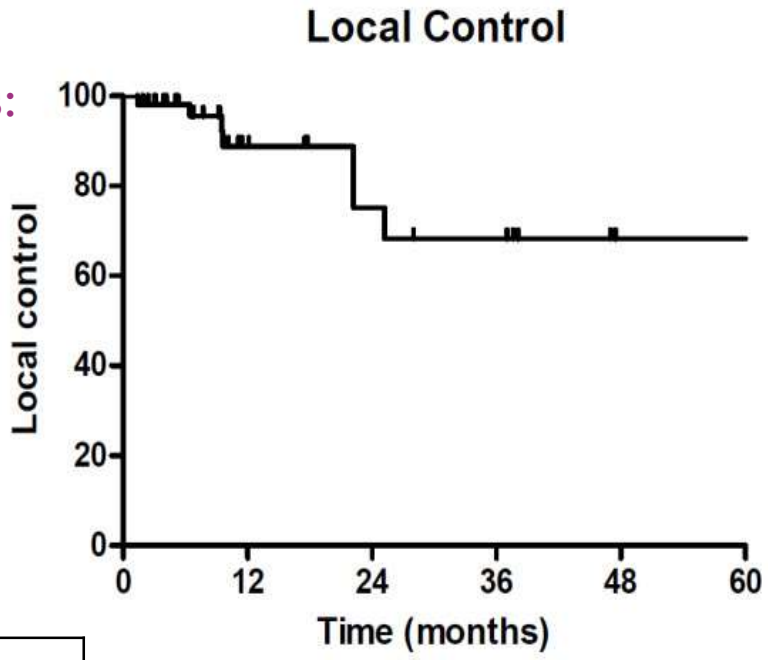
B. Not known if LC is better w conventional radiation (ongoing).

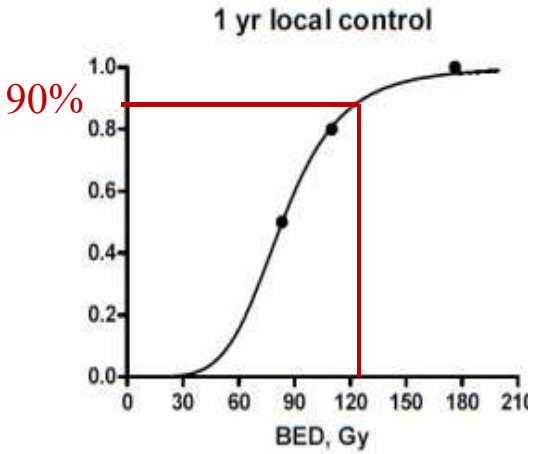
C. Optimal dose unknown; 14-24 Gy x 1 or 8 Gy x 3-4 or …

D. Local failure pattern (short FU); Adjacent vertebra (< 4 %), at epidural space 5-10 %, failure where anatomy was intentionally excluded as posterior elements of VB 3-10%.

RCC/Melanoma

Metastastic pts with "radioresistant" tumors:
-17 melanoma pts – 28 lesions
-13 RCC pts – 25 lesions
Lung > liver > bone mets
Dose: 3-5 fr; 40-60 Gy
No severe toxicity (sorafenib, sutinib…)
Median fup: 28 m





Ex.	BED
5 x 8 Gy	72 Gy
3 x 20 Gy	180 Gy
3 x 16 Gy	125 Gy

Stinauer Radiat Oncol 2011

Oligometastases

Standard treatment for metastatic cancer

= systemic therapy…

Subset of patients with limited metastatic sites =oligometastases

= local treatment? (SBRT…)

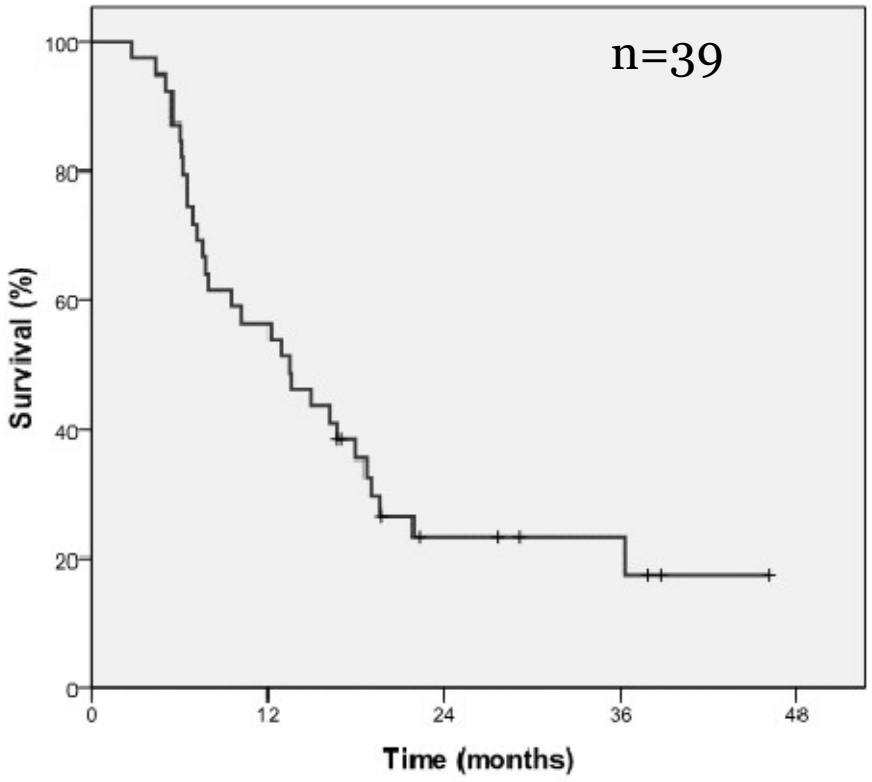
Definition oligometastatic:

A limited number of clinically detectable metastatic tumors where the extent of disease exists in a transitional state between localized and widespread systemic disease

Lo, Expert Rev Anticancer Ther. 2009
Hellman & Weichselbaum 1995

Oligometastases

Prospective single-arm phase II trial; Stage IV NSCLC synchronous M+ < 5



De Ruysscher JTO 2012

ESTRO School

Take home messages SABR

Technical requirements:

- Use adequate imaging modality for delineation (e.g. liver MRI)
- Motion management
- Consider fiducials (e.g. liver)
- Planning:
  - Dose calculation algorithm: type B is advised (especially in lung tumors)
  - Prescription to isodoseline
  - Inhomogeneity – steep dose gradients
- Pretreatment imaging and verification is mandatory
- QA (see AAPM reports)

Clinical indications:

- Cranial: RCT
- Extracanial: no randomized controlled trials
  - Most data on lungs:
    - Excellent LC similar to surgery
    - Low toxicity rate (cave: central tumours)

    → standard of care for inoperable T1-T2a lung tumors
  - Other sites: good LC, low toxicity, often small studies → promising

Rotational therapy and flattening filter free dose delivery

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Medical Physics Unit, CNAO - Pavia, Italy

Physics for Modern Radiotherapy
Bucharest, Romania - 4 - 8 June 2017

ESTRO School

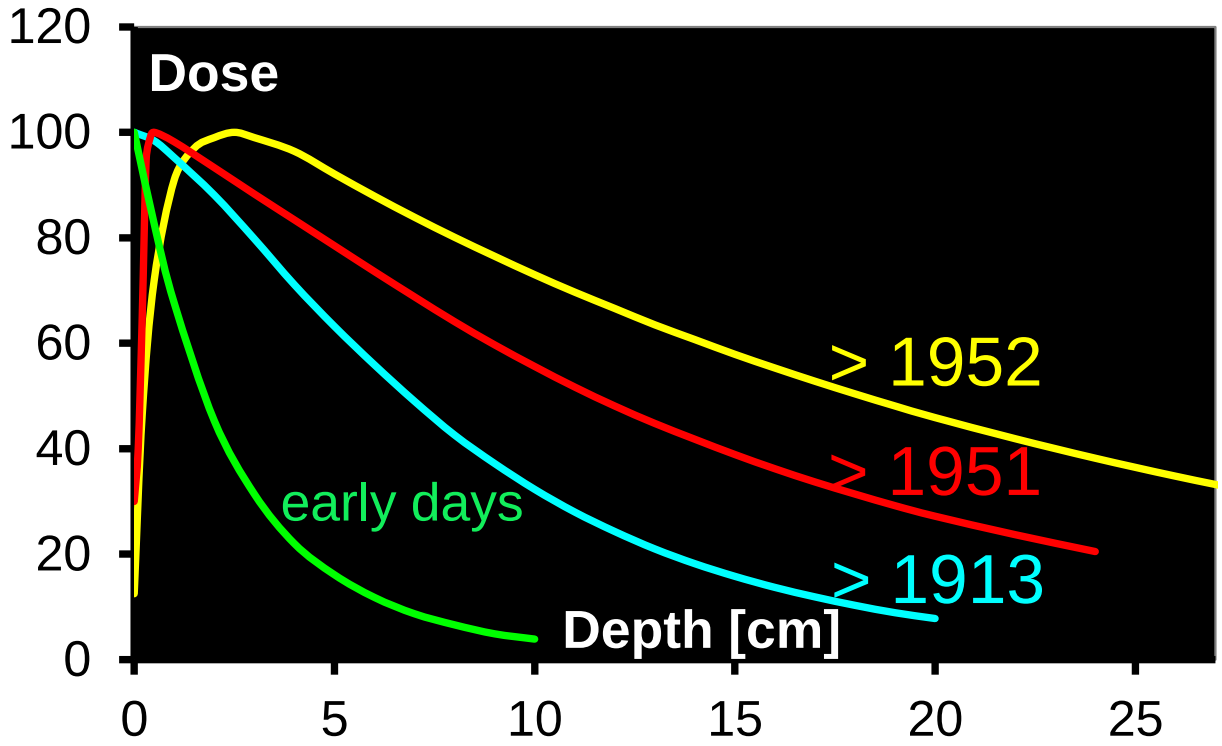
Rotational Therapy - Outline

- Rotational therapy - Rational
- IMRT Rotational techniques
  - Volumetric Modulated Arc Therapy
  - Helical Tomotherapy
- FFF modalities
- Comparison of competing techniques

ESTRO School

Reason 1) before 1951 many beams to reduce skin dose

1895: discovery X-rays
1913: 140 kV, Coolidge: vacuum tube, heated kathode
1921: 200 kV
1925: 300 kV } orthovoltage
1951: first cobalt treatment unit
1952: first clinical linear accelerator (Increase Energy → reduce skin dose)



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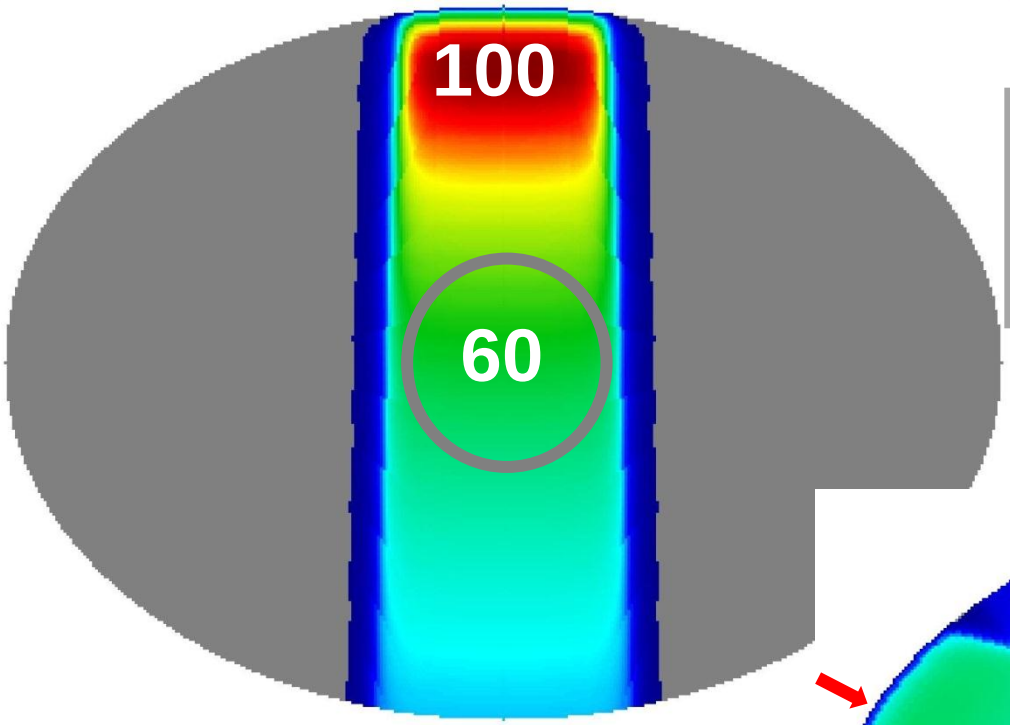
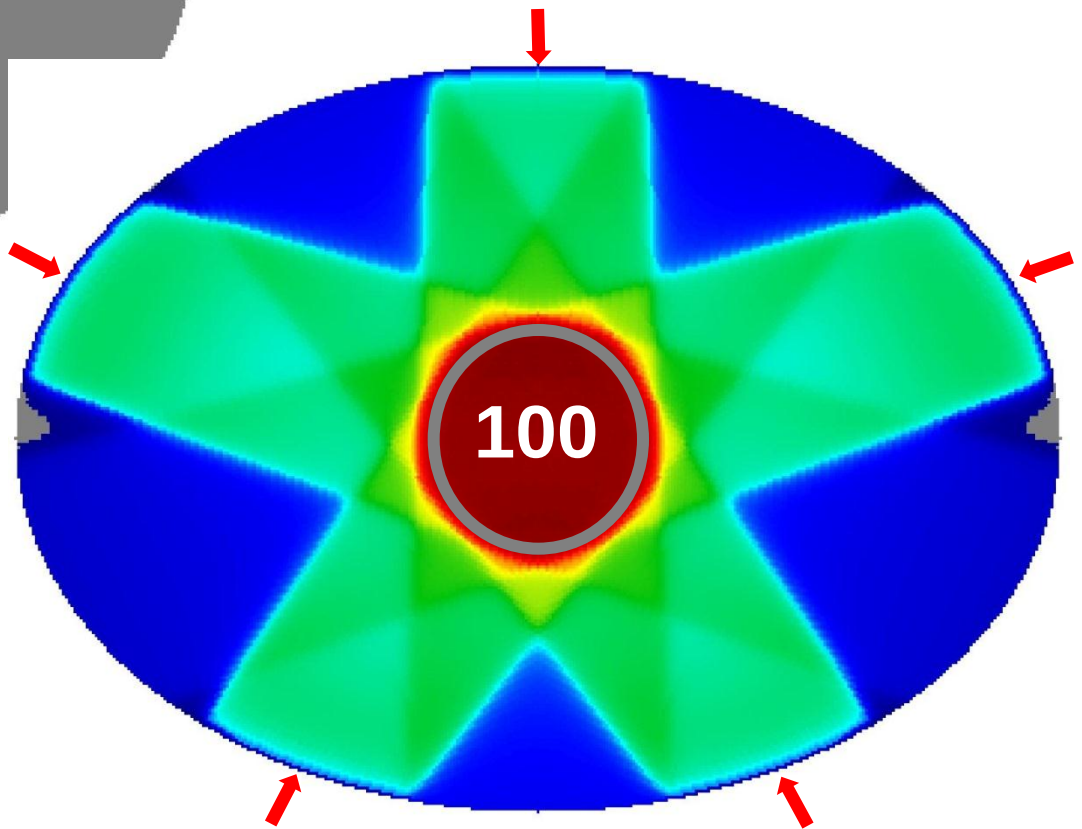
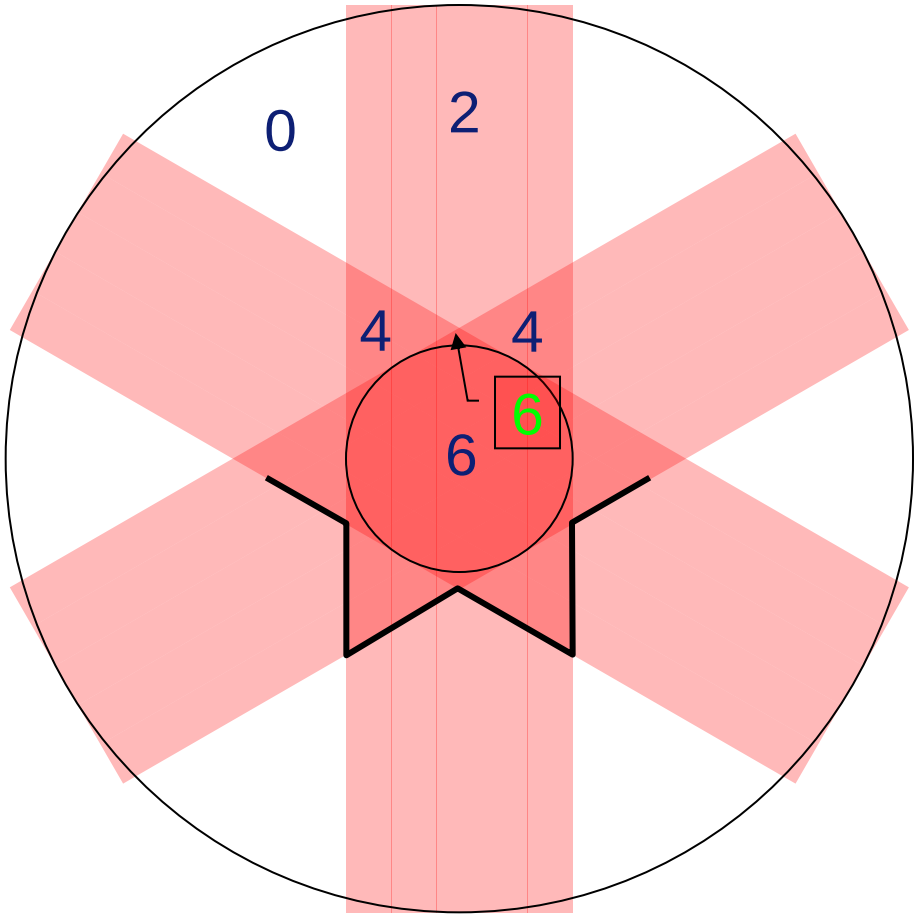
Reason 1) many beams to spread out entrance dose



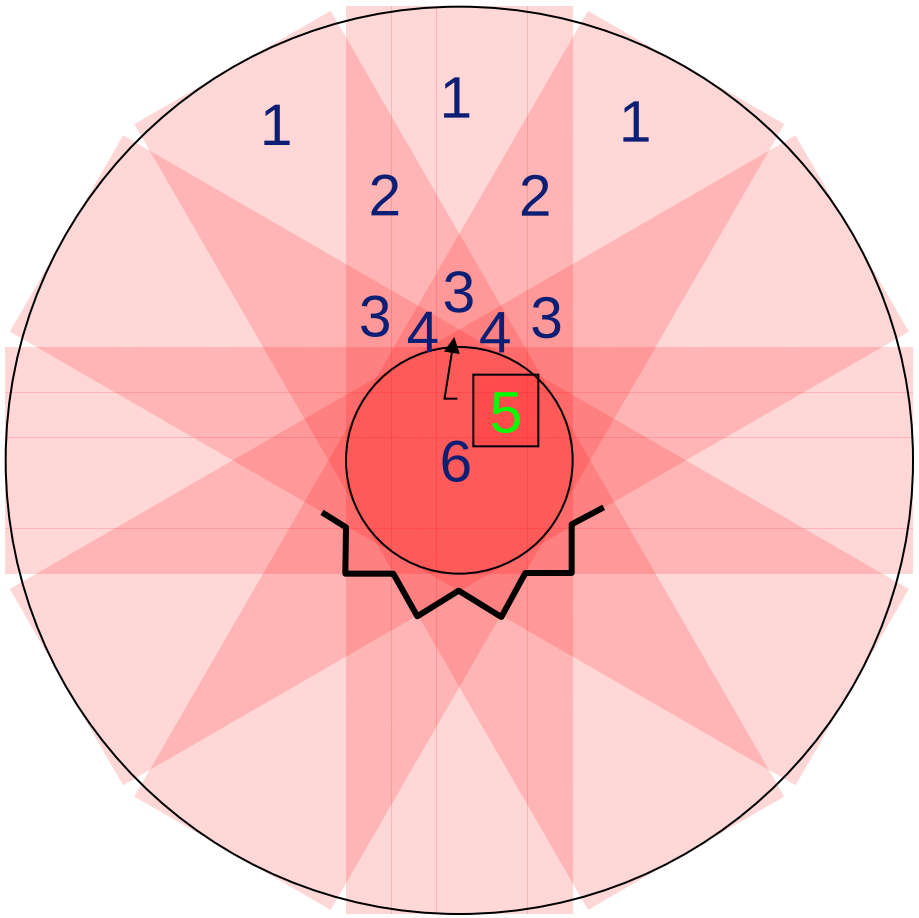
Problem in external beam RT: single beam → low dose in deep seated tumors



Reason 2) many beams to increase dose conformality

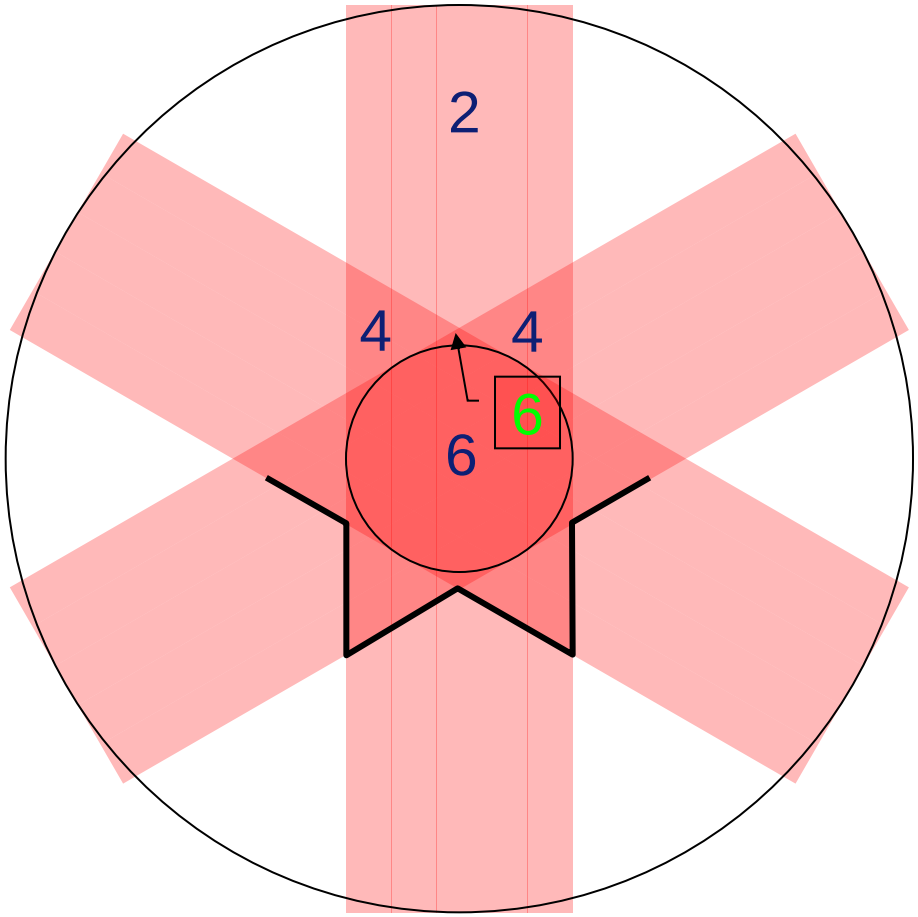


3x2 beams

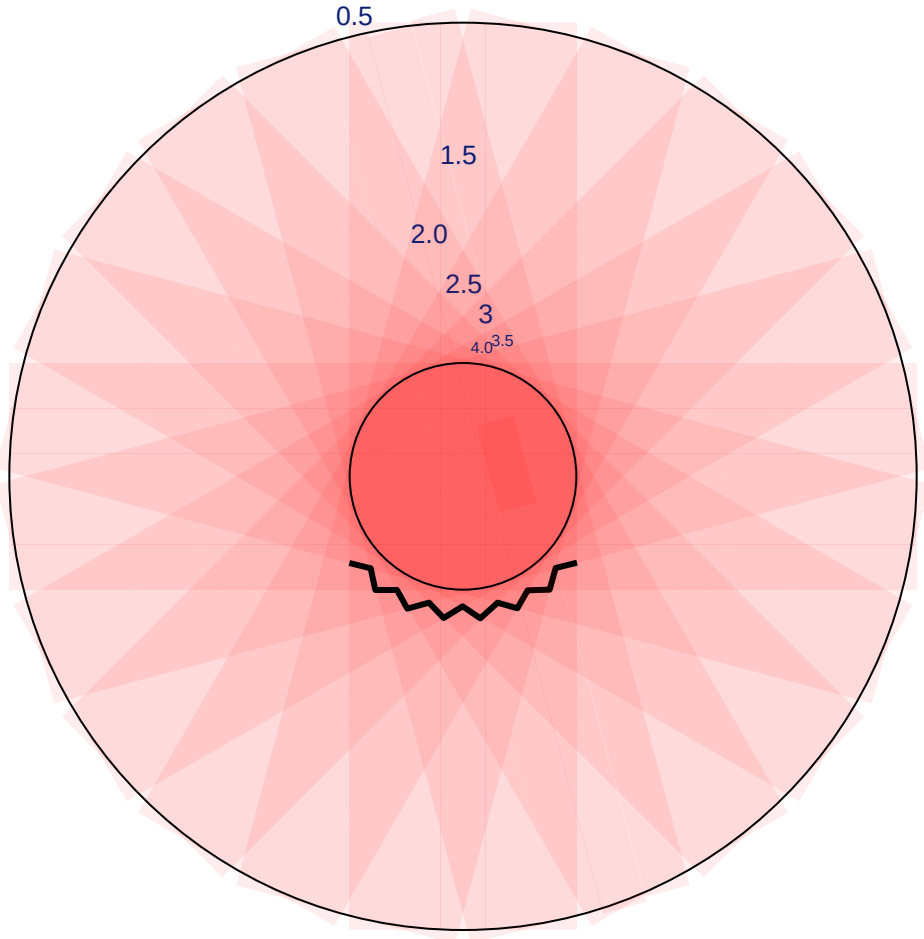


6x2 beams
weight 0.5

Reason 2) many beams to increase dose conformality



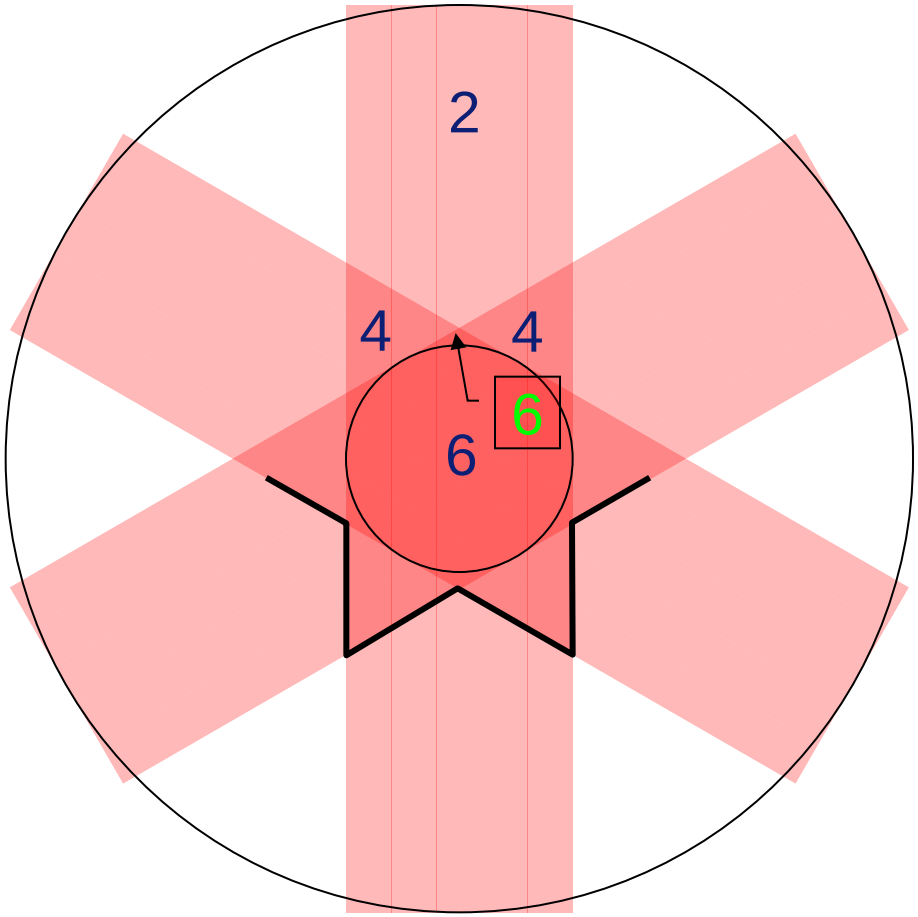
3x2 beams



12x2 beams
weight 0.25

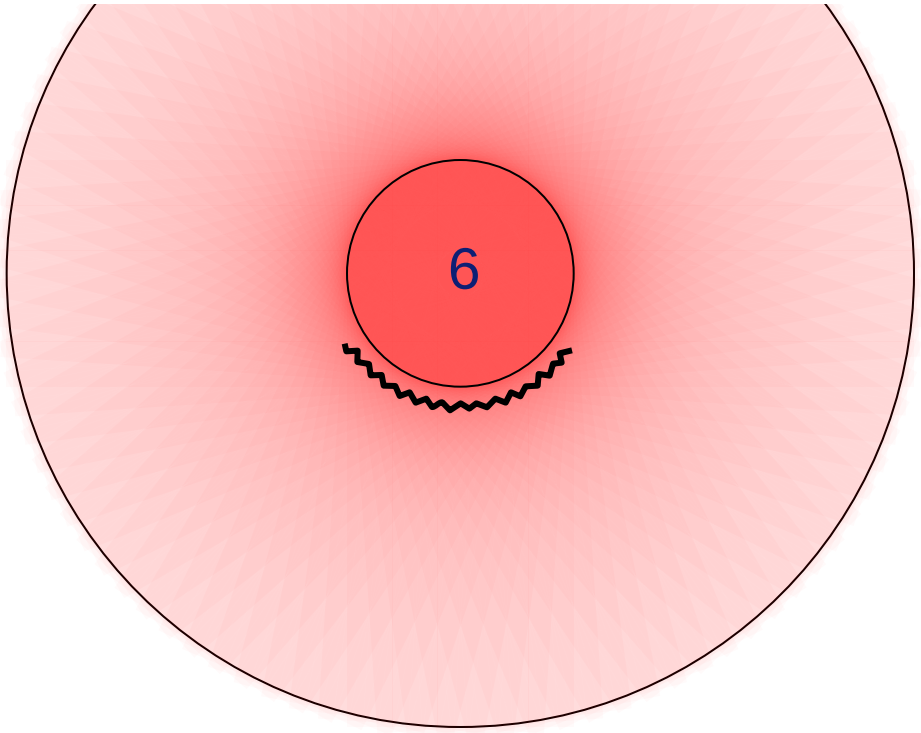
ESTRO School

Reason 2) many beams to increase dose conformality



3x2 beams

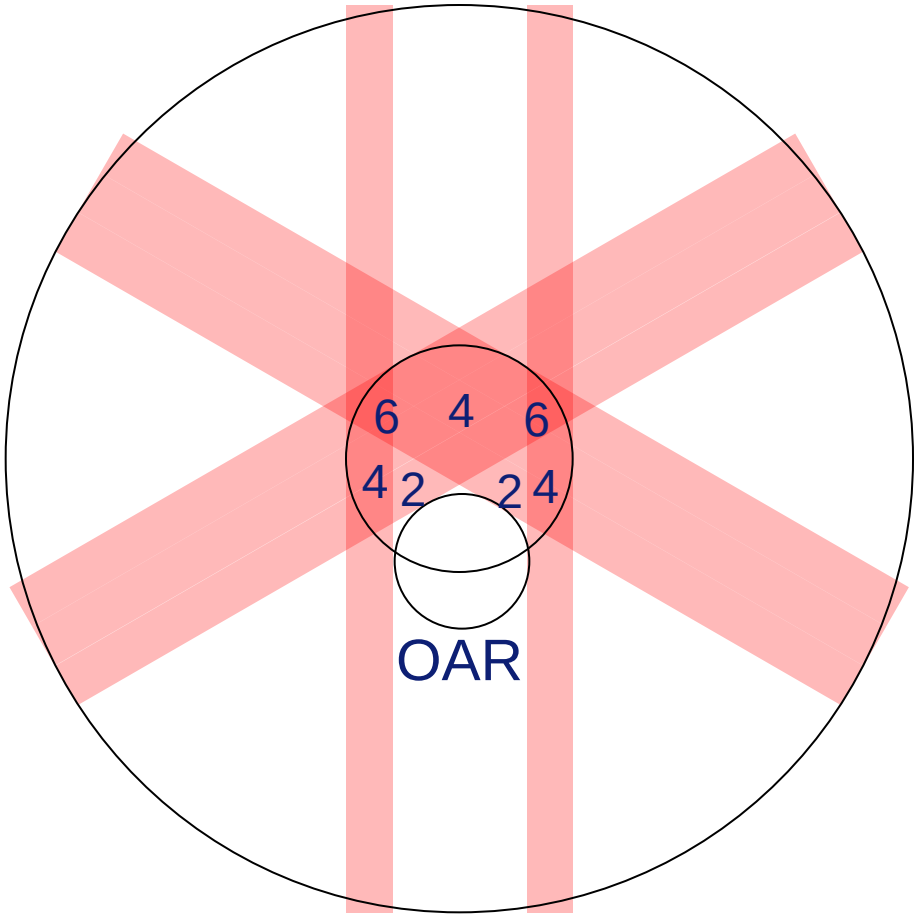
many beams:
- high conformality of high dose volume
- entrance dose maximally smeared out



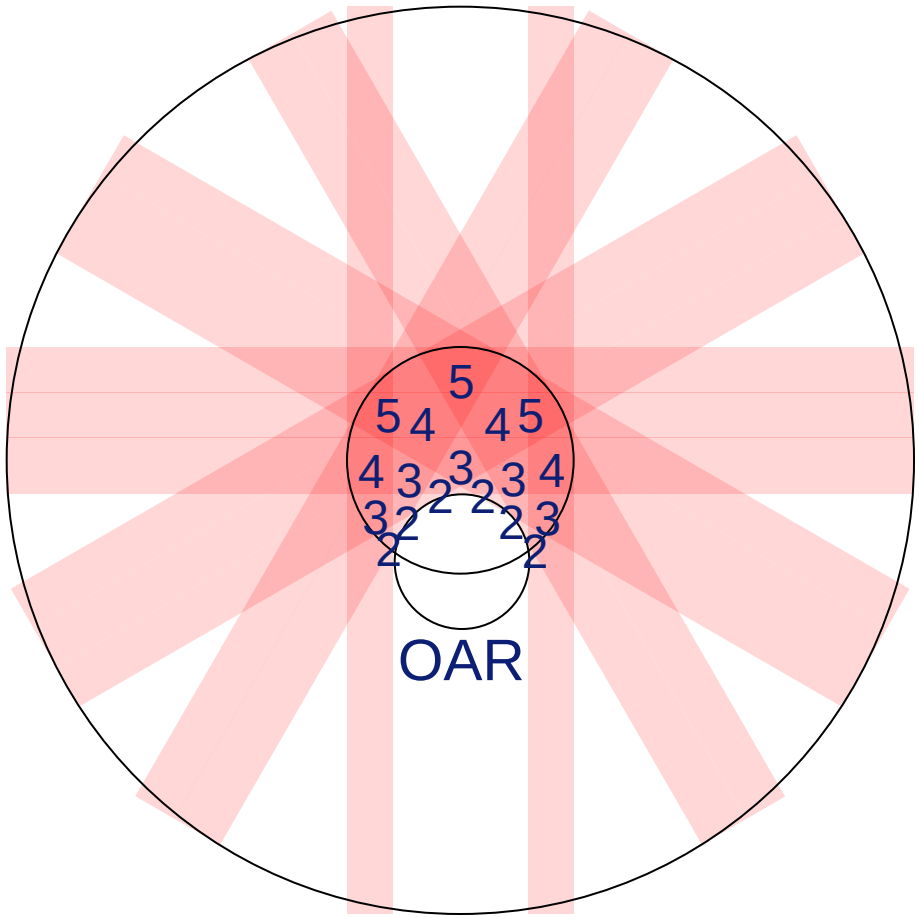
24x2 beams
weight 0.125

ESTRO School

Reason 3) many beams to increase dose homogeneity in IMRT

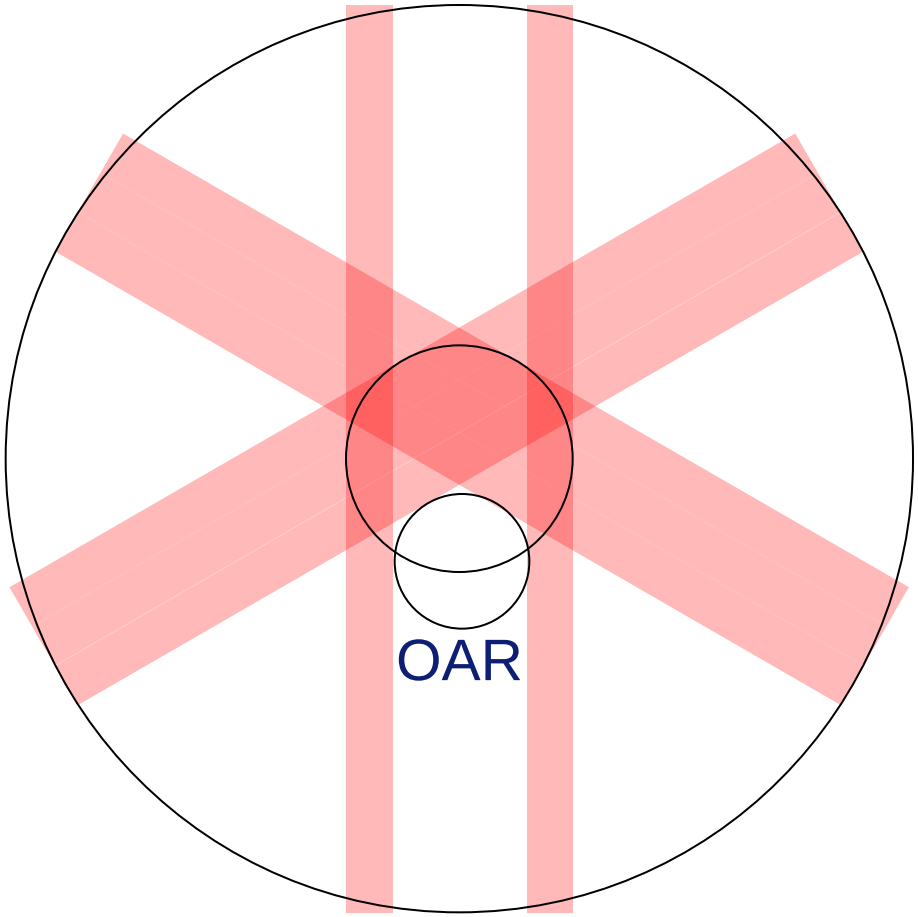


3x2 beams

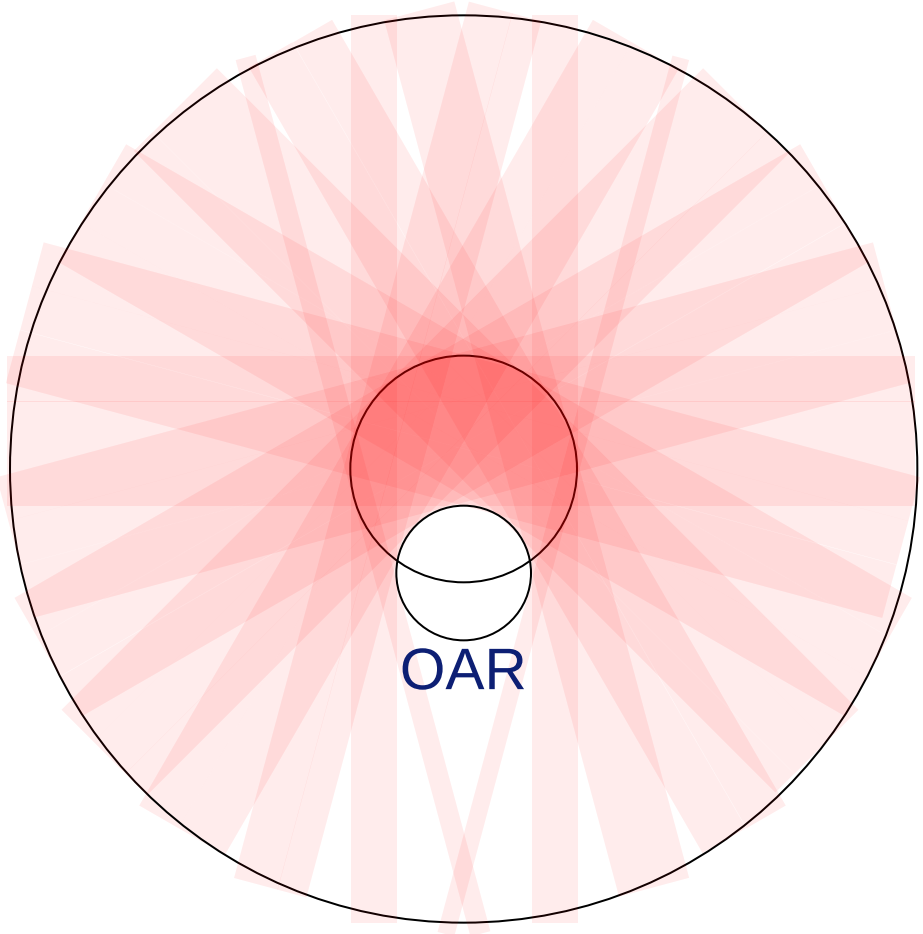


6x2 beams
weight 0.5

Reason 3) many beams to increase dose homogeneity in IMRT



3x2 beams



12x2 beams
weight 0.5

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Reasons 4 - 5

- 4) No need for beam angle selection (difficult for planner but also mathematically with computer).
- 5) Compared to standard IMRT, rotational IMRT with modern linacs (VMAT) may be much faster in delivery. (standard IMRT: flat solution space, often no drive to select plan that is fast in delivery).

Static and Rotational IMRT - Principle

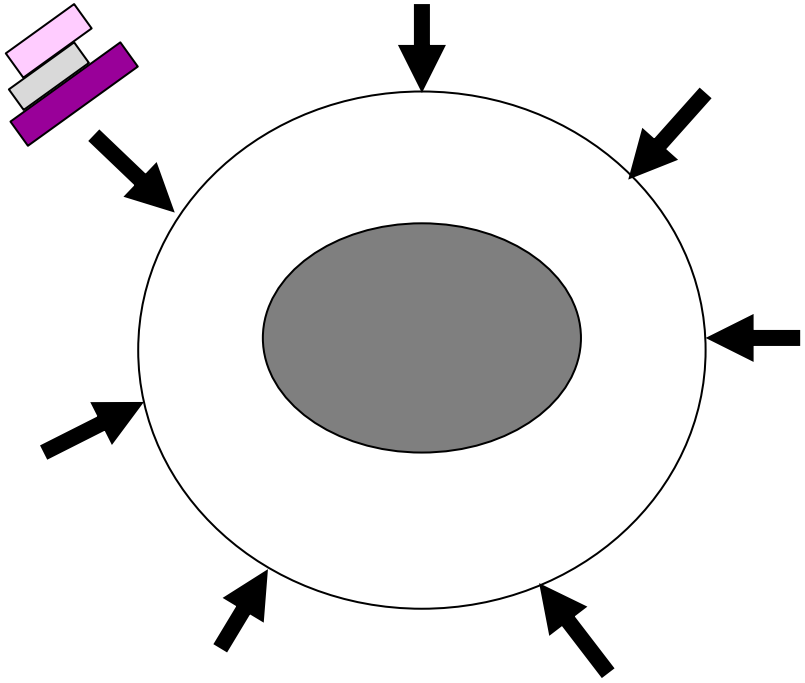
The DVHs or subsequently derived biological scores depend on the total number of **strata** → the product of the **number of beams and the intensity levels within each beam**.
As the number of beams increases, the number of intensity levels required to obtain optimal dose distributions should be reduced.

Yu, CX, Phys. Med. Biol., 40: 1435-49, 1995

→What matters is the total number of aperture shape changes (and dose rate variations)

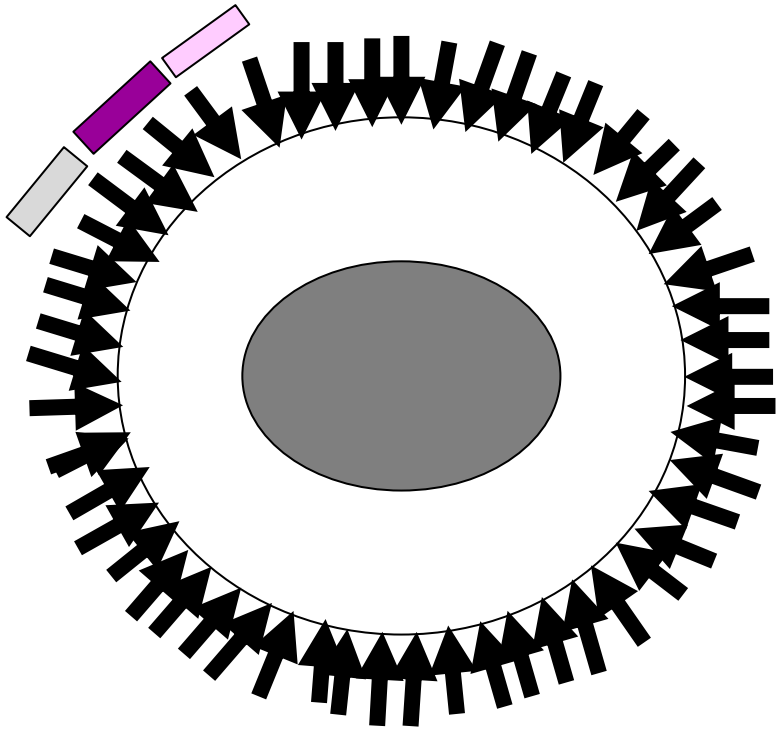
Static and Rotational IMRT - Principle

Static Gantry IMRT



Multiple apertures at each angle

VMAT-Rotational IMRT



One aperture at each angle

Ying Xiao, Thomas Jefferson Univ Hospital, Philadelphia

Static and Rotational IMRT - Principle

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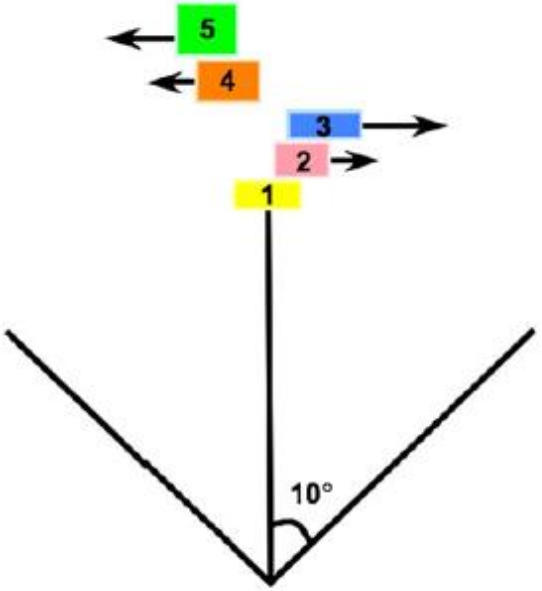
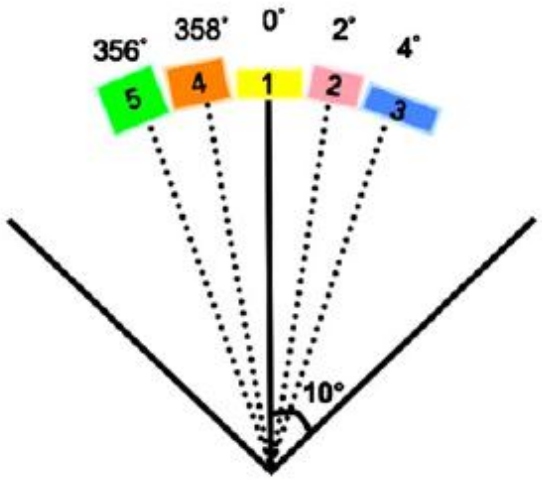
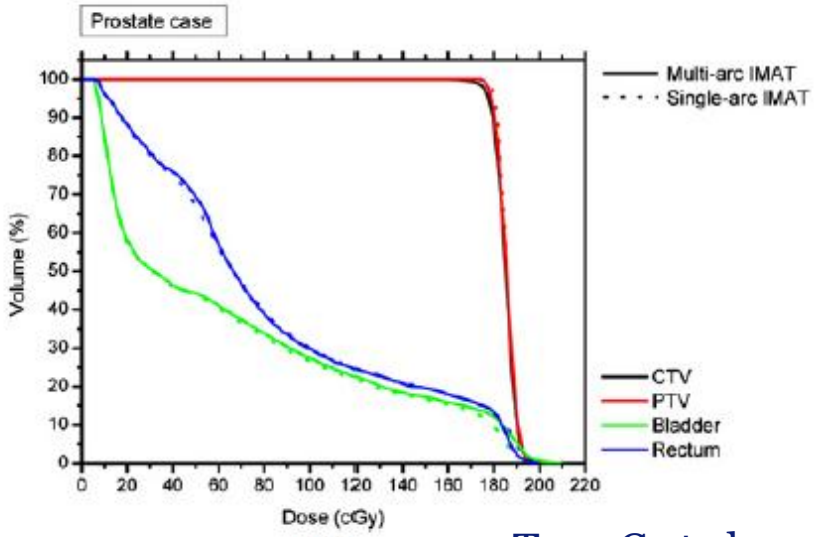


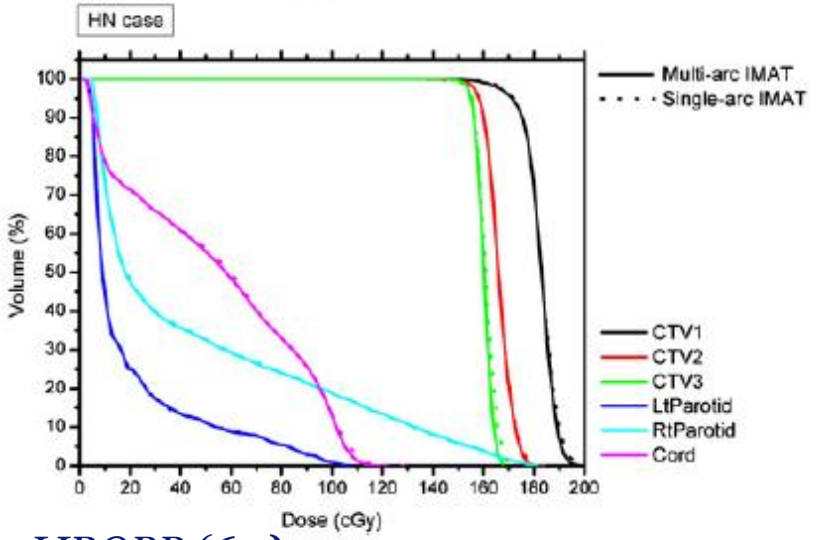
(a)



(b)



(c)



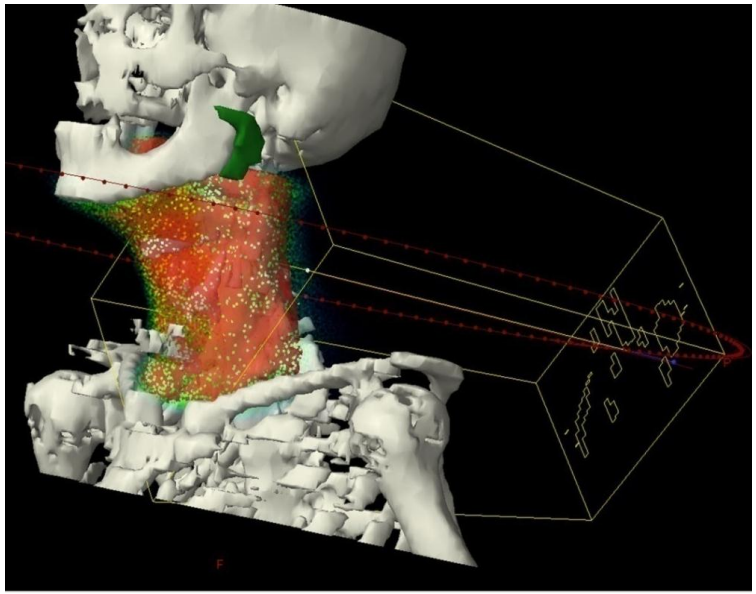
(d)

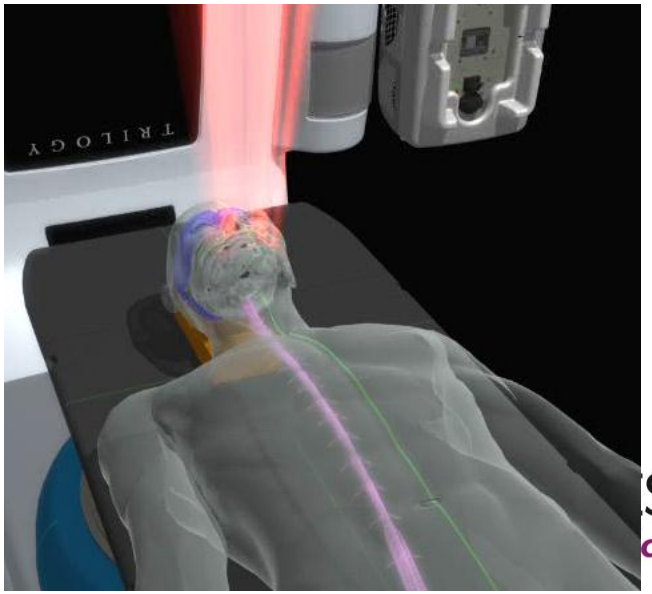
Tang G et al 2007 *IJROBP* ***(69)***

Rotational Therapy - Volumetric Modulated Arc Therapy

- Techniques that delivers IMRT through rotational delivery using regular linacs (and MLC), with optimized field shapes for all angles, each irradiating part of the tumor (not conformal)
- **Volumetric** irradiation → cone beam - long fields
- While rotating, continuous dynamic variation of:

field size/shape (MLC) - dose rate - gantry speed





VMAT

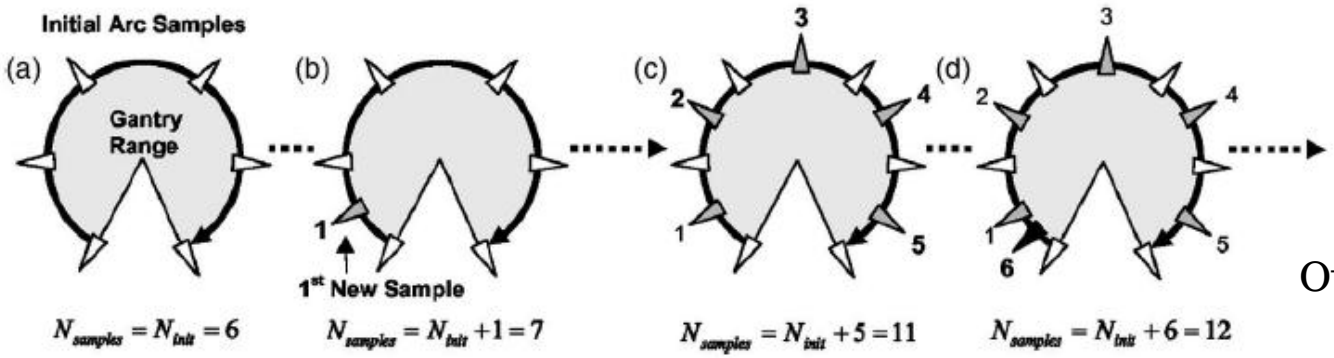
Beam fluence:
1. The MLC leaf trajectories as a function of time
2. The gantry angle as a function of time
3. The dose rate as a function of time

Aperture weights (MU) variation: ⇄ Gantry speed (mechanical limitations)
Dose rate variations

Transition between adjacent apertures: MLC motion trajectories

→ as the gantry rotates the beam is on → the subfields of adjacent beam angles should not require the MLC leaves to travel long distances (ensuring smooth leaf motion in the leaf-sequencing algorithm)

VMAT – Plan optimization



Otto K et al. Med Phys 2008

- The algorithm is based on progressive beam angle sampling to optimize a large number of apertures using direct aperture optimization (coarse-to-fine scheme)
- starts with a small number of beams and large angular spacing, and gradually inserts new beam angles to be optimized
- Geometric connectivity is facilitated by initializing the shapes of new apertures with shape interpolation between its neighbors and by constraining maximum leaf travel near the end of the optimization process

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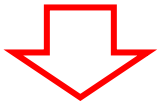
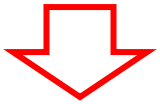
VMAT - Planning (static) vs Delivery (dynamic)

→ **Dynamic** delivery is planned as a sequence of multiple **static** segments coded as **control points** CP (modulation of linac position, field shape, dose rate)



aperture connectivity
number of beams used to approximate an arc



Deliverability AND **calculation accuracy**

VMAT - Planning vs Deliverability

degrees of freedom

- **MLC motion** and **MU** variation are to be constrained between gantry samples to preserve continuous delivery → efficiency constraints to the solution space
- Maximum gantry **rotation speed** or jaws/MLC **modulation speed** can be a limiting factor to the maximum specified dose rate

- Optimization→ find a trade off between deliverable - time consuming – complexity - modeling **Accuracy**

VMAT - Planning vs Deliverability

One arc or more arcs? (coplanar – non-coplanar – partial arcs)

- For most of the commercial planning solutions, no more than 2-arcs are needed
- For complex cases, 2-arcs make it easier to connect the apertures thereby offering the optimizer more freedom, leading to significantly improved dose conformality and homogeneity

- Pushing the **quality** of the treatment plan decreases **monitor unit efficiency** and increases **treatment time**

VMAT QA – a point of caution

NB: Synchronization of both dose rate and gantry motion with MLC movement

new and **different QA** steps relative to conventional IMRT

Acceptance Testing, Commissioning, and Routine QA

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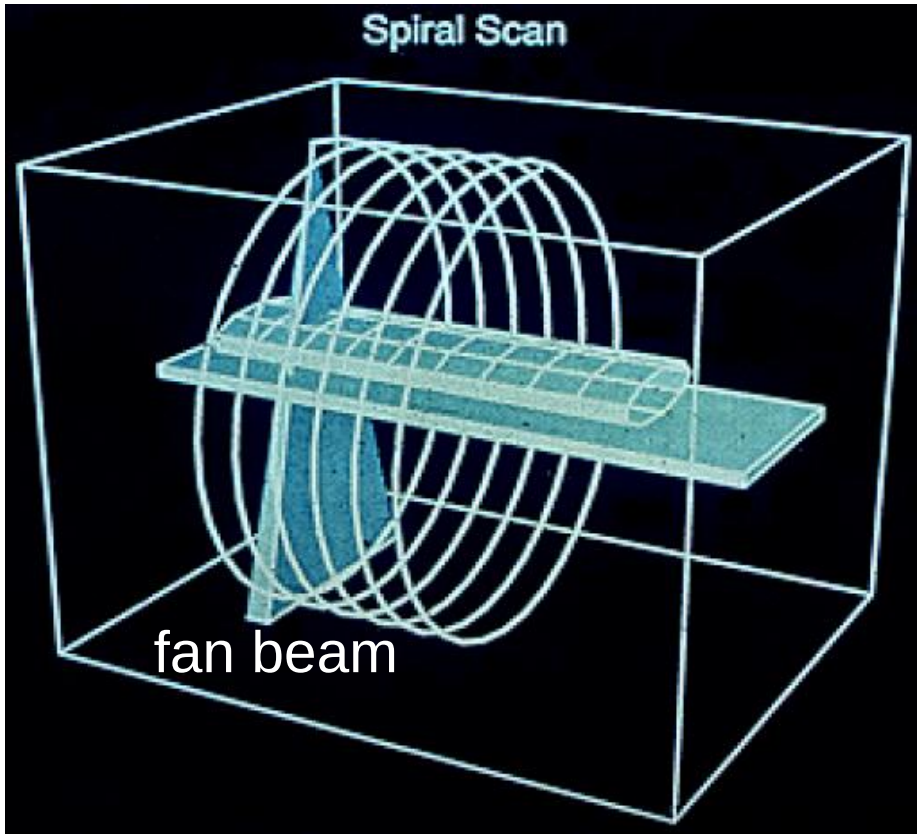
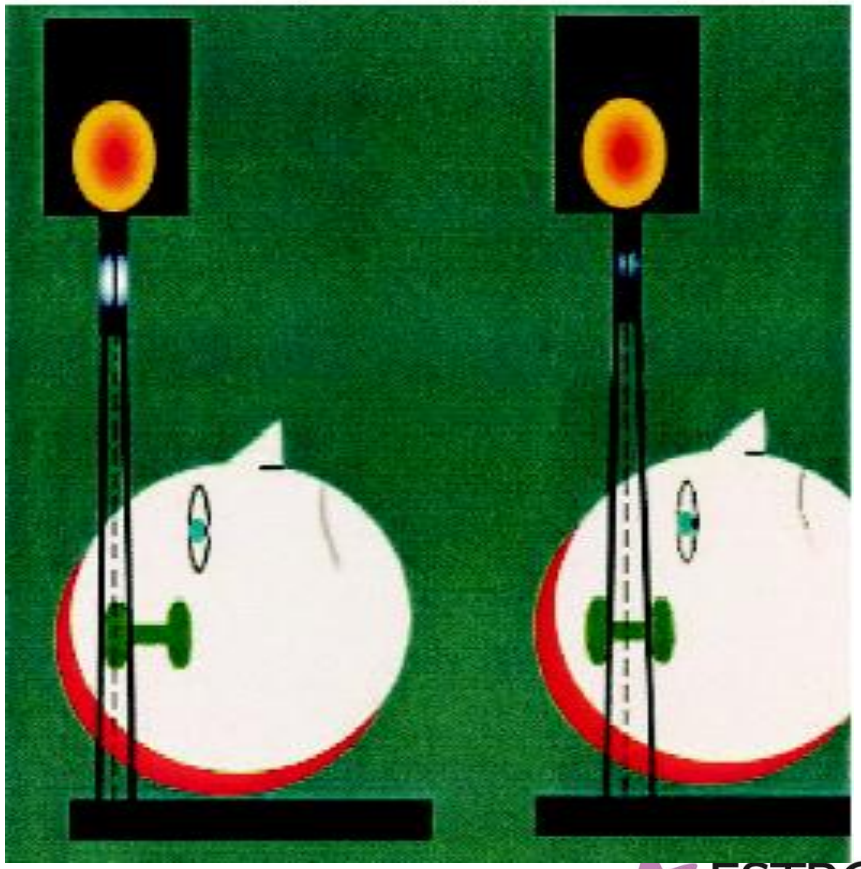
Rotational Therapy – Helical Thomotherapy

- literally tomotherapy means ‘slice therapy’: use of fan beam
- helical: effectively there is a spiral delivery





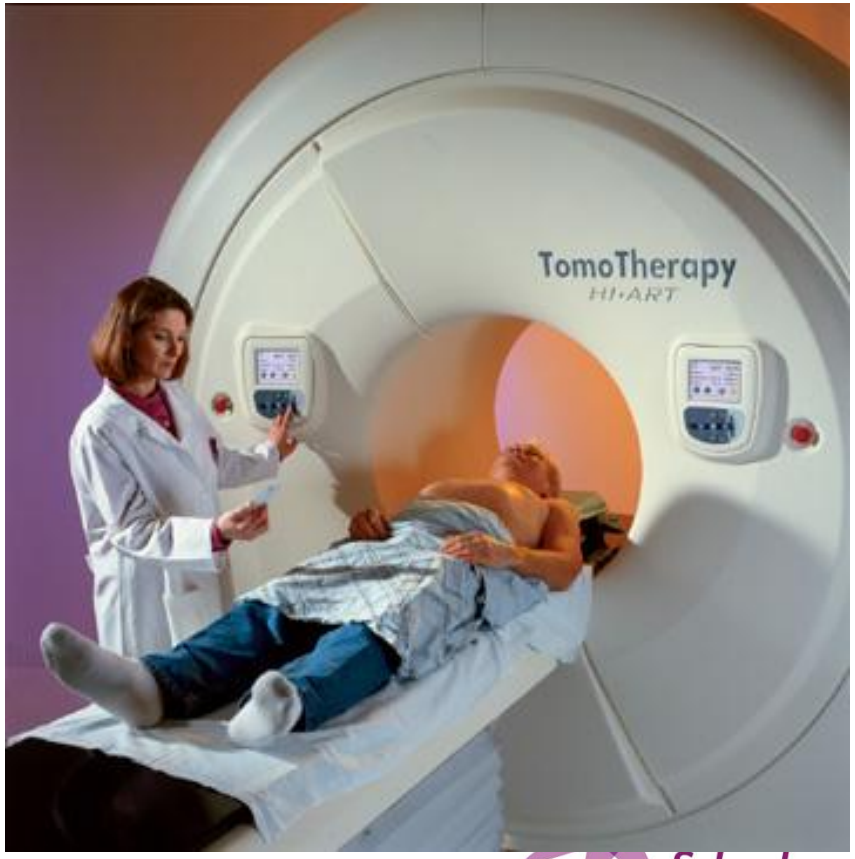
Helical Thomotherapy - Hi-Art Tomotherapy Inc (Accuray)

T.R. Mackie, T.W. Holmes, S. Swerdloff, P. Reckwerdt, J.O. Deasy, J. Yang, B. Paliwal, T. Kinsella.

Tomotherapy: A New Concept for the Delivery of Conformal Radiotherapy

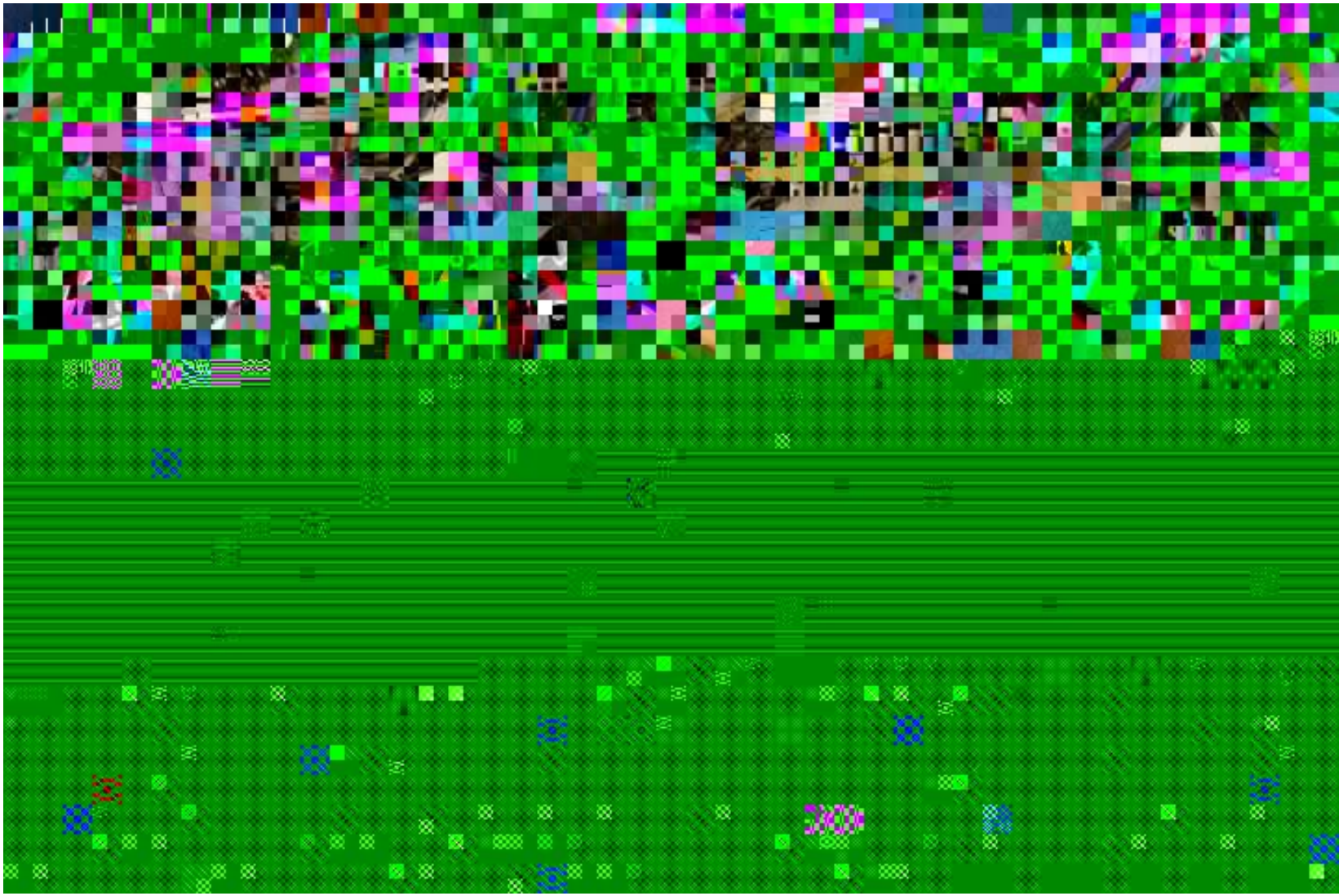
Med. Phys. 20, 1709-1719 (1993).

The dose is delivered by translating the patient in a continuously rotating fan beam which is modulated by a binary MLC for a maximum of 51 different configurations during every rotation.



School

Helical Thomotherapy - Hi-Art Tomotherapy Inc (Accuray)



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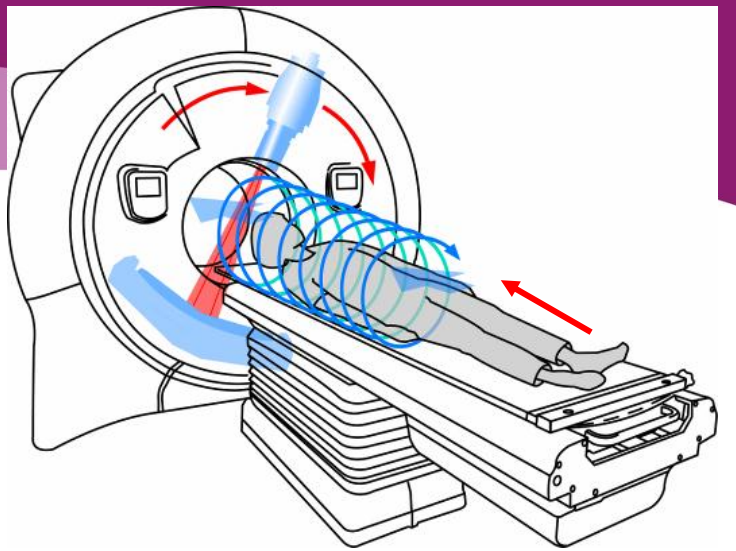
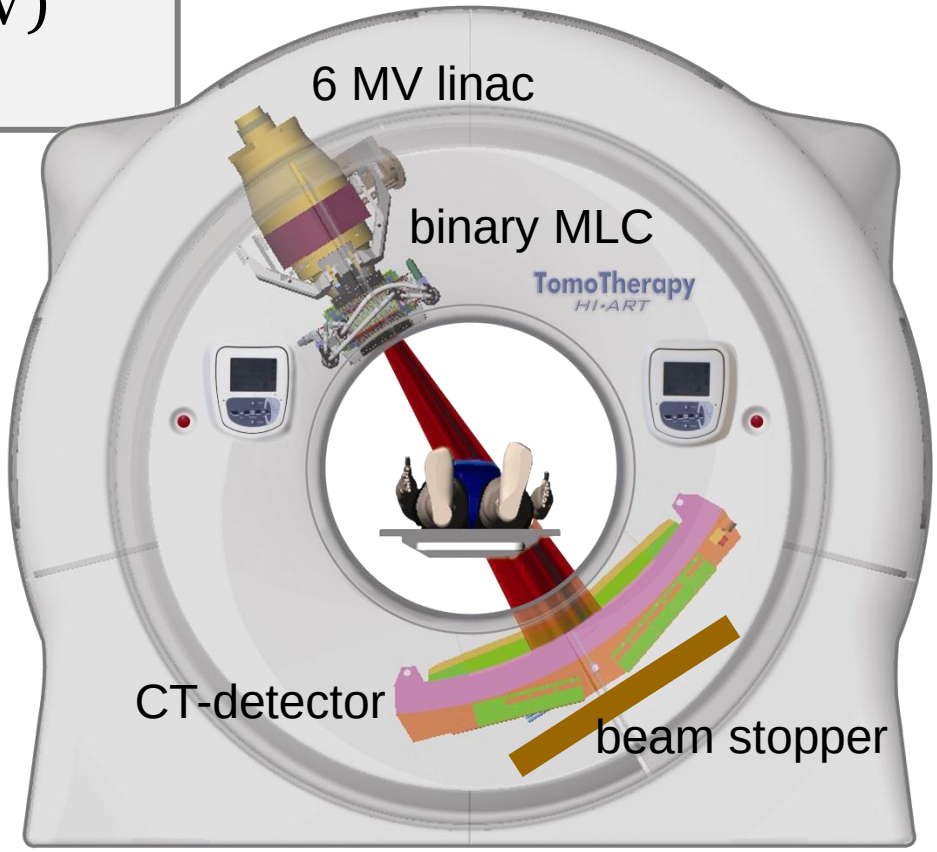
Helical Tomotherapy - features

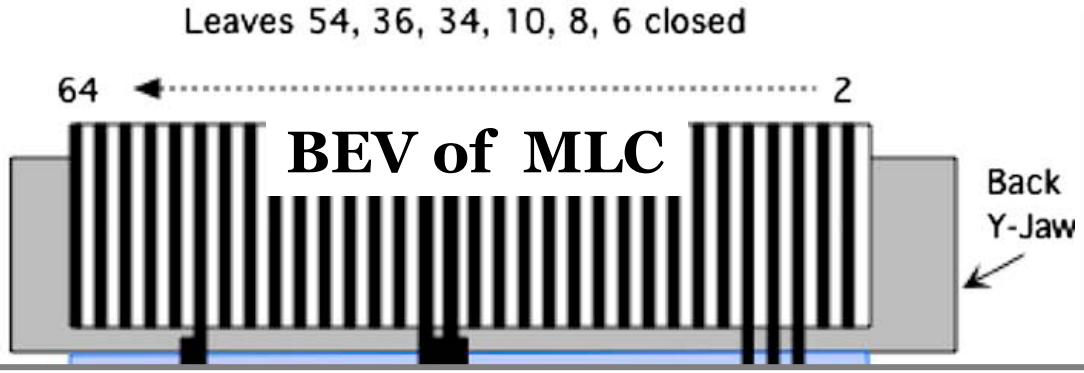
- bore diameter = 85 cm
- 6 MV linac
- SAD=85 cm
- dose rate at axis: 8.5 Gy/min (FFF)
- integrated MV CT-scanner (3 MV)
- binary MLC for IMRT

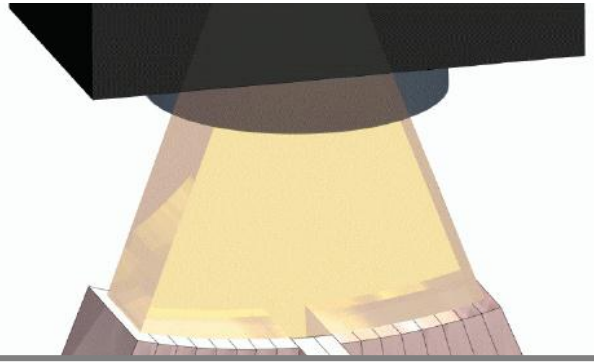




Helical Tomotherapy - binary MLC

accounts for beam divergence in lateral direction



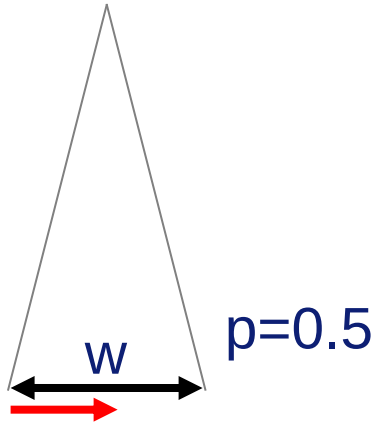


- leaves 95% tungsten, thickness 10 cm
- leaf width projected at isocenter: 0.625 cm
- y-jaws collimate the beam to 1.0, 2.5 or 5.0 cm at isocenter
- leaves are either fully closed or fully opened, when closed: stop under opposite y-jaw
- **IMRT: treat with optimized leaf specific opening times**

Helical Tomotherapy - treatment planning

Definitions:

- T = gantry rotation time: 10-60 s
- w = longitudinal field width: 1, 2.5, 5 cm
- pitch, p = (couch displacement in T)/w
  e.g., p = 0.2 → each point "sees" 5 rotations



- projection: each rotation is divided in 51 projections ('fields'), 1 every 7°
- for each projection 64 binary MLC leaves can be moved IN or OUT with a 0 – 100% intensity modulation

- modulation factor, MF= ratio between maximum intensity in a projection and the mean of the non-zero intensities

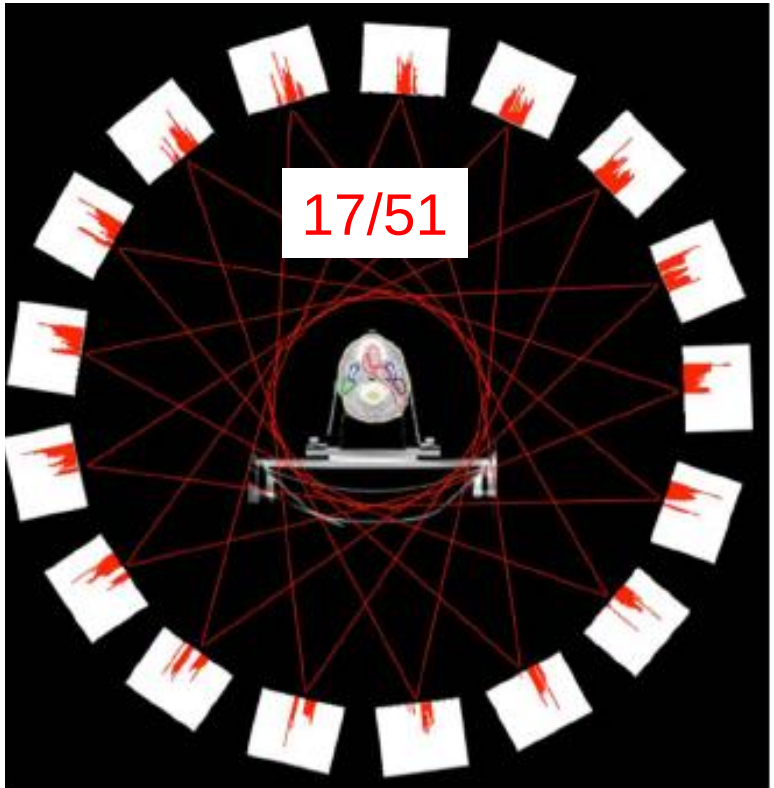
Helical Tomotherapy - treatment planning

Input parameters

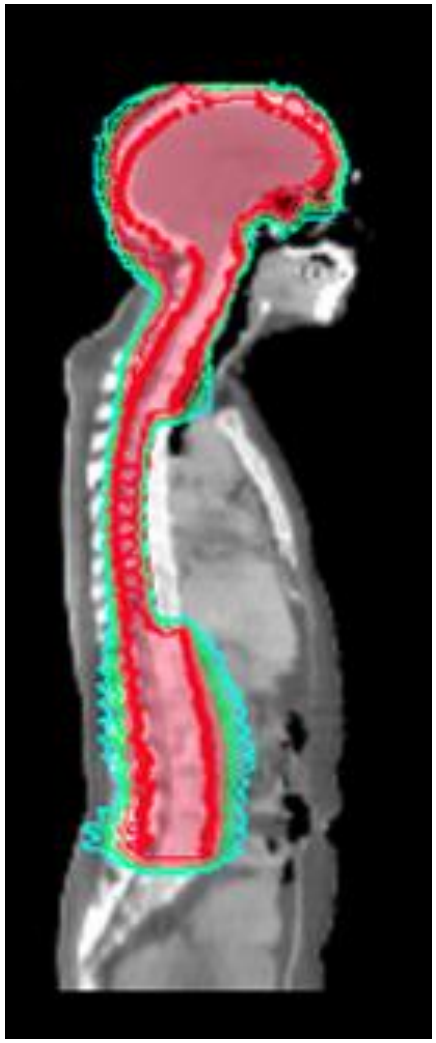
- w: 1.0, 2,5, 5.0 cm (frequently commissioned)
- p: 0.2-0.5 (typically used values)
- maximum MF: 1.5-3.5 (typically used values)
- blocking of selected OAR (beamlet weight=0)

Output

- leaf opening times per projection and rotation for total dose
- maximum leaf opening time and fractionation determine T
- couch velocity, v= (p·w)/T



Helical Tomotherapy - long treatment fields



Maximum couch travel: **160 cm**

→ treatment of long targets without field junctions

Craniospinal axis Irradiation

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Helical Tomotherapy - TomoDirect

Fan beam
Ring gantry
Binary MLC

Flexible modulation
Fully-automated delivery
Continuous Couch Motion

Discrete
Gantry Angle

Continuous
Gantry Rotation

TomoDirect

TomoHelical

Helical Tomotherapy - a point of caution

- Helical Tomotherapy is a helical slice-by-slice treatment
- Delivery time depends on target extension
- Large dose delivery errors may occur in case of substantial intra-fraction changes in the tumor set-up (e.g. if patient moves while treated)
- This may also relate to respiratory motion

FFF
Flattening Filter Free dose delivery

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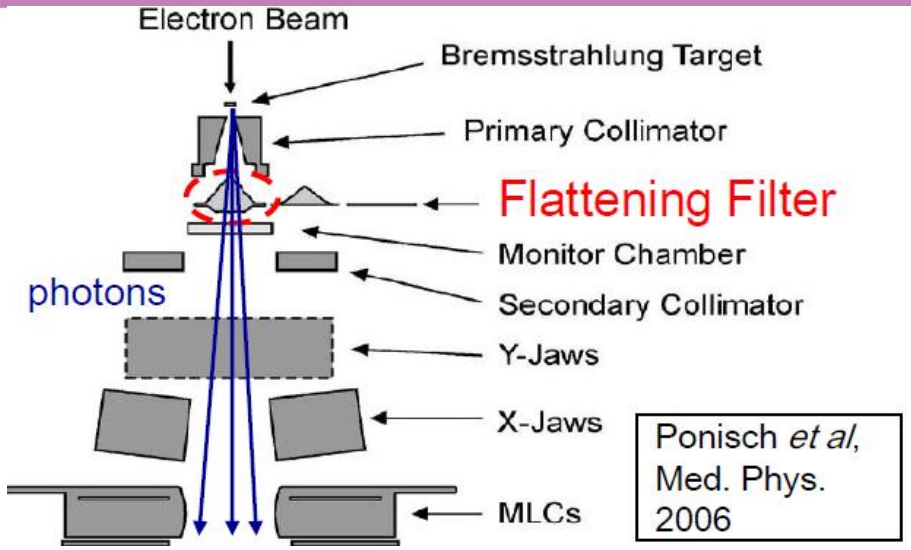
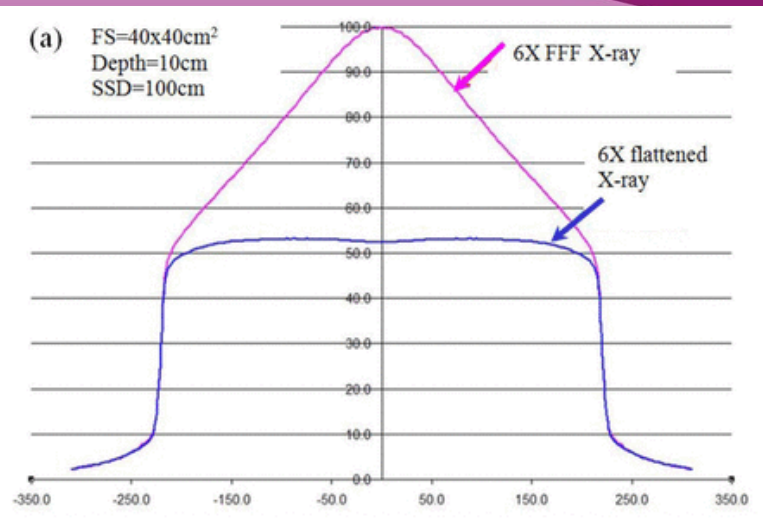
Flattening Filter





Wang Y, JACMP2012

In the FF

- Photons are absorbed → reduced efficiency
- Photons are scattered (head scatter 3-10% of photon fluence)→ increased contamination radiation
- Neutrons are produced (high MV)→ increased contamination radiation

Flat profile

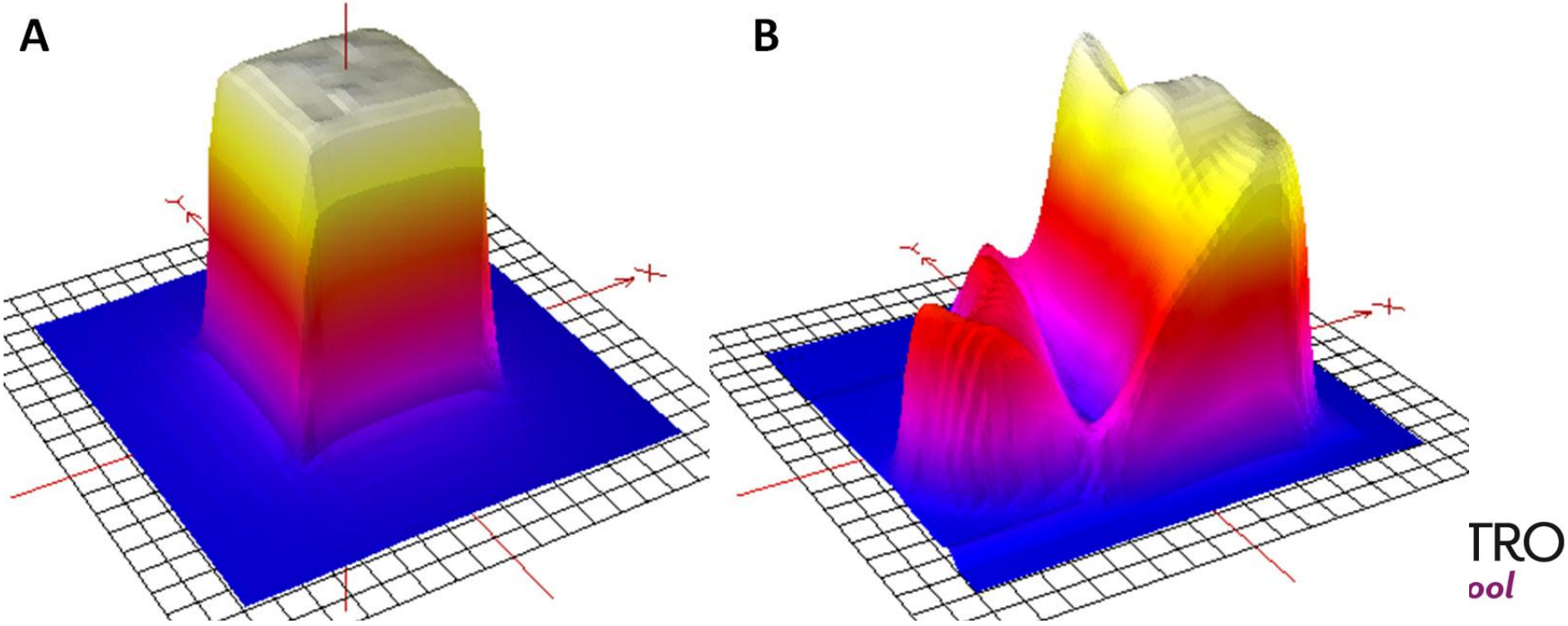
- Only flat at one depth
- Patients and tumors aren't flat

Rational

Plus …

• Stereotactic treatments are often based on inhomogeneous dose delivery and small fields may be sufficiently flat regardless of FF
• IMRT and VMAT vary fluence pattern across the beam

→ If large field homogeneity is not needed anymore → remove the FF



TRO pool

FFF beams

If we remove it, what will happen?

- Less head scatter

- No beam hardening in the central region
  → lower mean energy (if the same e^- beam is used)
  → uniform energy spectra across the field

→ Beam quality
PDD
Profiles
Output factors
Beam contamination
Out of field dose

- Higher dose rate (FF ≈ 600 MU/min)
  → 6MV FFF ≈ 1400MU/min
  → 10MV FFF ≈ 2400MU/min

→ Faster Delivery

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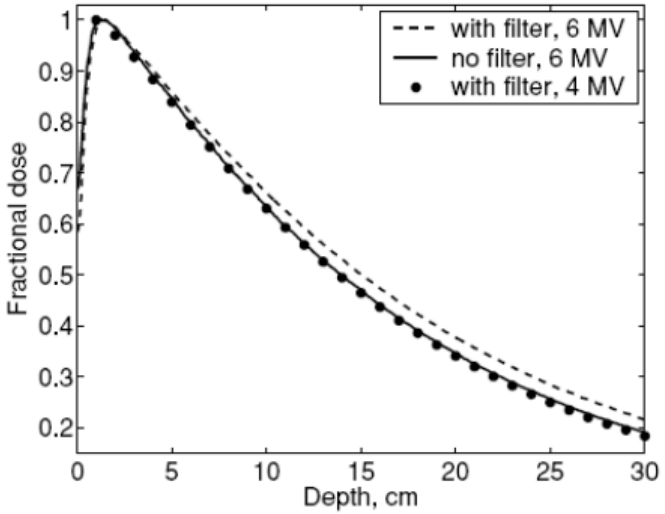
Percent Depth Dose

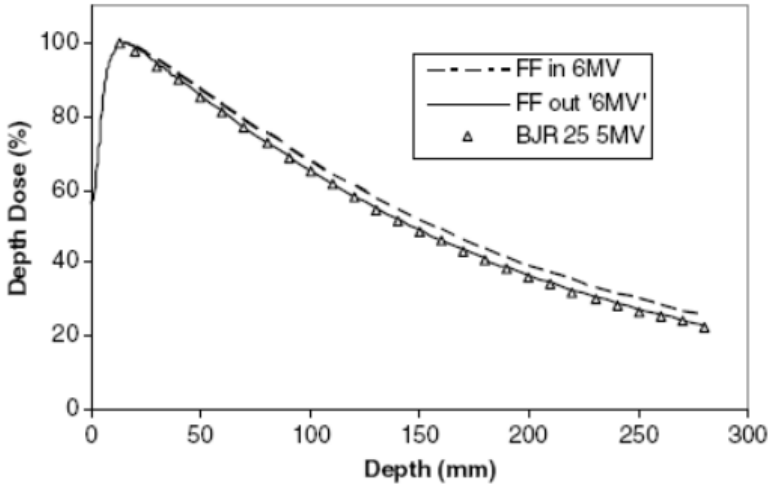
- Softer spectrum
- Steeper dose curve
- D_{max} closer to the surface (balance between no beam hardening and less head scatter)
- Lower beam quality (presence of low energy photons)

Varian



Vassiliev ON et al, PMB 2006; 51

Elekta



Cashmore J. et al, PMB 2008; 53

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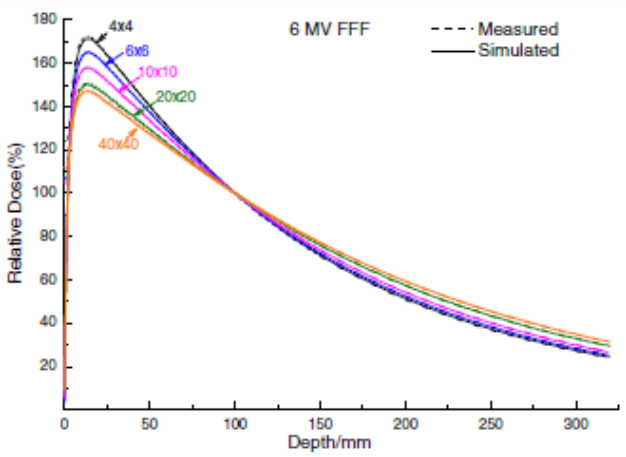
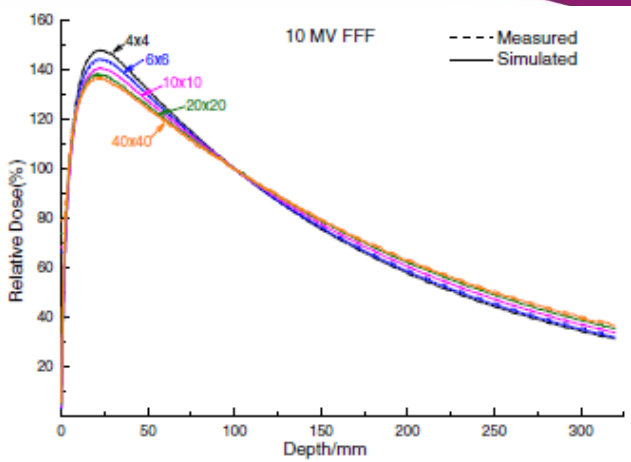
PDD vs Field size

Feng *et al. Radiation Oncology* (2016) 11:30

- D_{max} varies less with field size (lower e^- contam.)





- Surface dose is higher for small field sizes (softer spectrum)
- Surface dose varies less with field size (less head scatter) almost equal or lower for large filed sizes

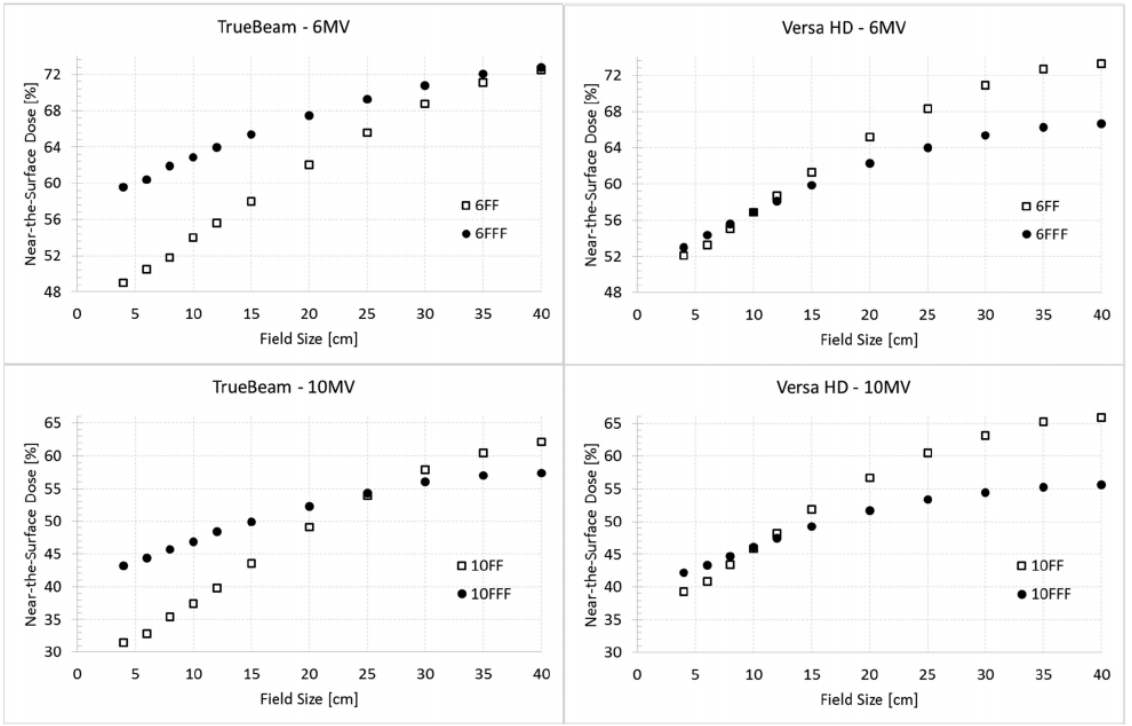


Fig. 4. Near-the-surface doses at 1 mm depth for the two units and the two beam qualities.

Fogliata et al. Med Phys 2016, 43

Energy spectra and output factors

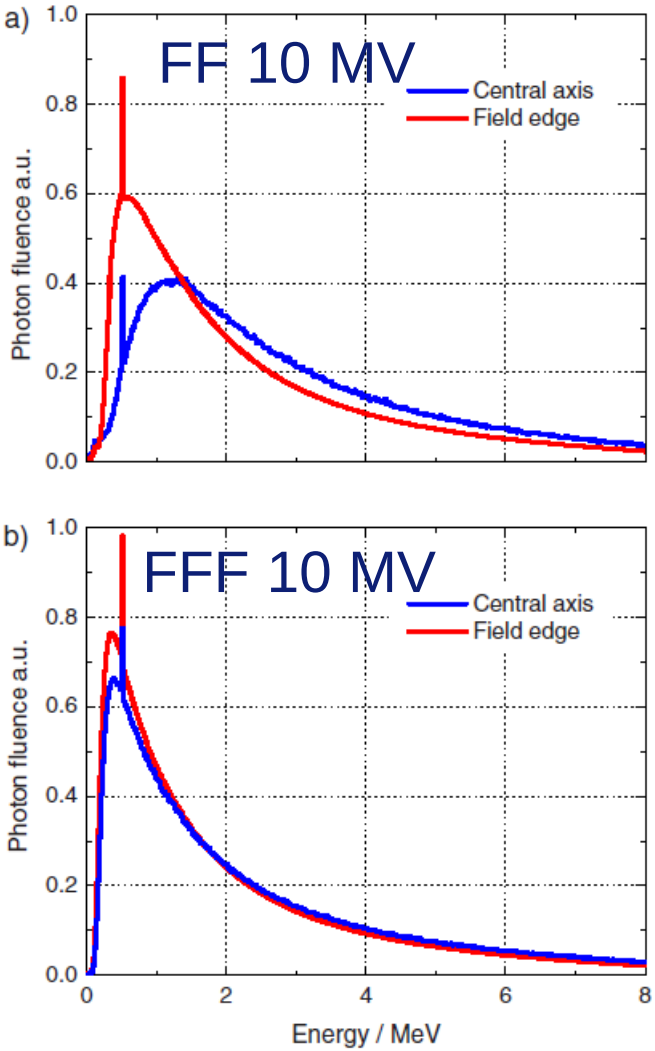


FIG. 1. Comparison of Monte Carlo simulated x-ray spectra on the central beam axis and the field edge of (a) flattened and (b) unflattened 10 MV beams provided by an Elekta linac. More details concerning the MC simulations w.r.t. this figure can be found in Dalaryd *et al.* (Ref. 32).

- Uniform energy spectra across the field
- Lower output factor variation with field size (< head scatter)

Georg et al Med Phys 2011

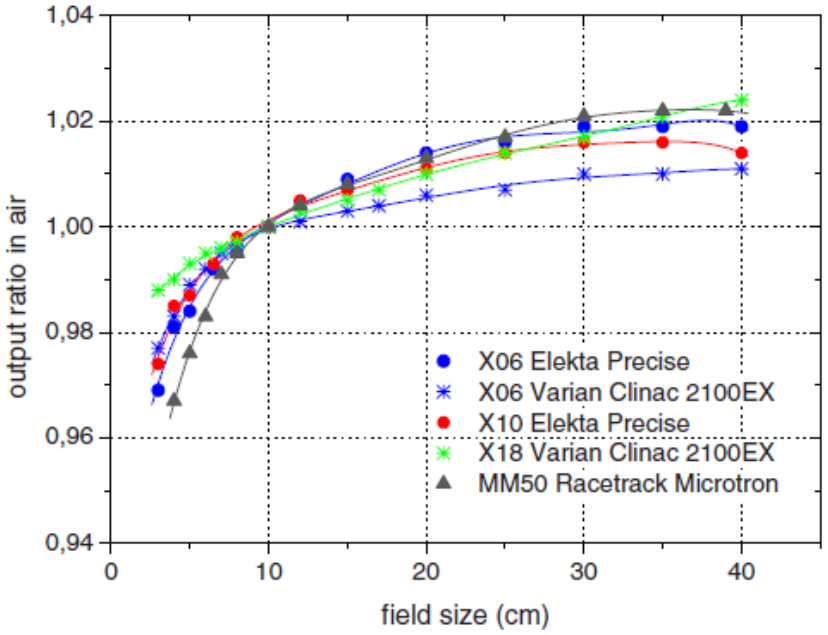
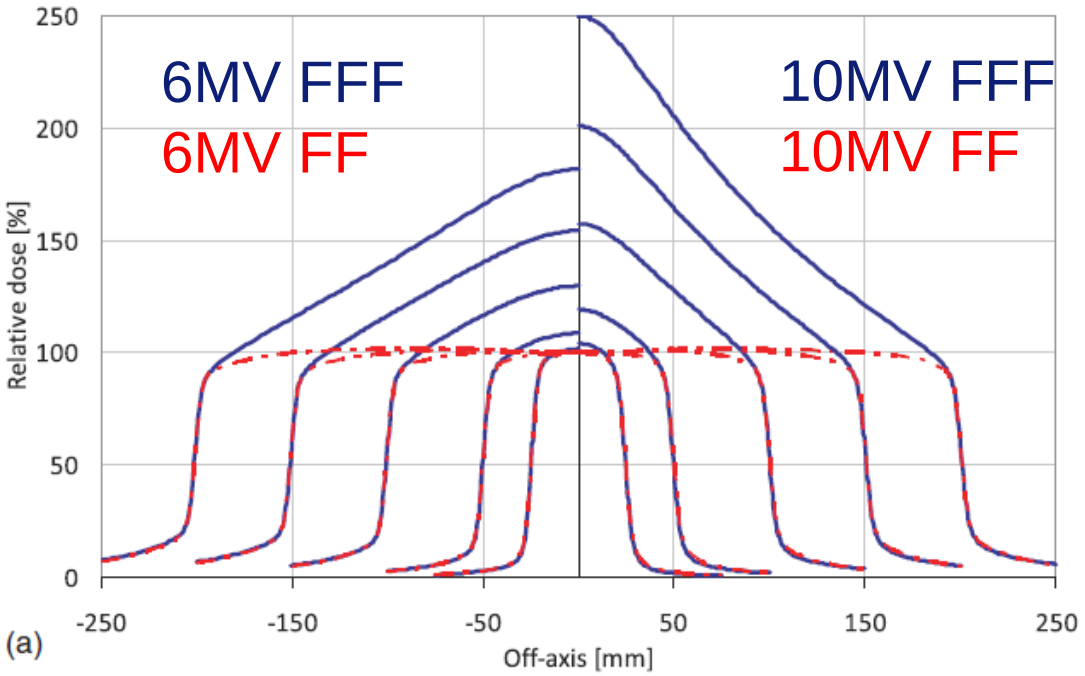


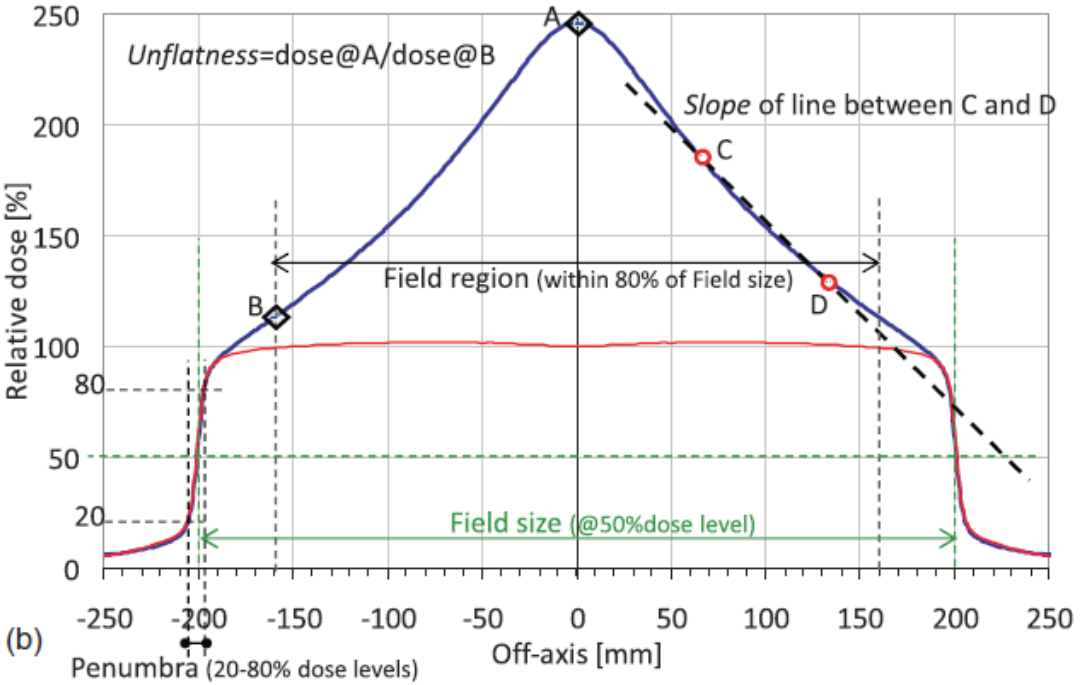
FIG. 2. Variation of the output factor in-air with field size for several flattening filter free treatment units. The given data were extracted from literature (see Refs. 21, 41, and 61).

Lateral Profiles

- Profiles are forward peaked
- Non-flattened shape becomes more pronounced with increasing of field size and beam energy
- Profiles are minimally depth dependent (spectra consistent)
- Flatness is similar when field size is small (4x4 cm²)

New beam parameters





Fogliata et al. Med Phys 2012, 39

Dosimetric characteristics → Clinical implications

- **Higher DR**

→ Dosimetric equipment (dose rate dependence?– P_{ion}-k_q-partial volume)
→ Radiobiology of HDR? No correction factor recommended
→ Main advantage FFF for **SRT (high fraction dose-small fields**–no modulation)
→ **Motion management** – reduced treatment time (but interplay?)

- **Softer spectrum-low energies not removed**

→ Lower effective energy if the electron beam is the same (shallower D_{max})
→ Higher skin dose
→ But purer spectrum (+ < e^- contamination) and easier to model
→ Reduced variation of energy spectrum across field size (due to different hardening in the field)

- **Reduced head scatter**

→ Reduced treatment head leakage
→ Reduced variation of output ratio in air with field size
→ Lower out of field dose to surrounding tissues (Kragl et al. Z Med Phys 2011;21)

- **Less neutron dose** (less photon fluence/dose and no neutron generated in the FF)

→ use of higher energy photons?

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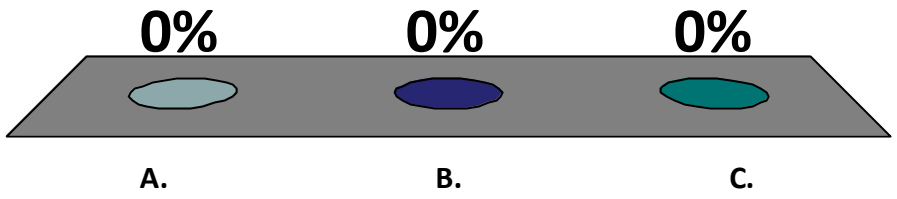
Which of the delivery description is correct?

A. HT delivery time is independent from target size
B. VMAT treats the whole target without couch translation
C. The flattening filter removal causes an average 50% increase in the head scatter component



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How to judge treatment plan quality?

Comparison – Evaluation Criteria

- Dosimetric parameters
- Planning efficiency
- Delivery efficiency, complexity and reliability: **time** and planned **MU**
- Versatility
- Total leakage radiation received by the patient outside the target
- QA protocols (Dynamic leaf motion + gantry rotation + speed and DR variation)
- IGRT – adaptive work flow integration?

NB: How much depends on the optimizer expertise?

Comparison of competing techniques

CRT, Standard IMRT, VMAT

- IMRT (HT-VMAT) vs conventional CRT

→ highly conformal dose distributions → improved target volume conformity and OARs sparing
→ ability to produce inhomogeneous dose distributions → simultaneous delivery of different doses per fraction to separate areas within the target volume

- VMAT vs fixed field IMRT

→ improved **delivery efficiency** → reduction in MU and treatment delivery time (almost universal finding in all planning studies)
→ inferior sparing of low dose levels

- FFF vs FF

→ reduced treatment time
- highly significant for stereotactic treatments with high doses per fraction
- potential advantages for motion management techniques

→ comparable plan quality and accuracy

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Comparison of competing techniques

Prostate

Table 1. Comparative planning studies in prostate cancer

Paper [ref] *VMAT commercial system*	Number of patients	Site and dose	Comparison	PTV	OAR	MU per fraction	Treatment time per fraction
Palma et al [51] *Predecessor to RapidArc*	10	Prostate alone 74 Gy in 37 fractions	3D-CRT *vs* IMRT(5F,SW) *vs* CDR-VMAT (SA) *vs* VDR-VMAT (SA)	IMRT and VMAT – similar PTV coverage and homogeneity (homogeneity inferior to 3D-CRT). Conformity best with IMRT and VDR-VMAT	VDR-VMAT best (compared with IMRT for sparing of rectum and femoral heads; compared with CDR-VMAT for sparing of bladder and rectum)	CDR-VMAT, 491.6; VDR-VMAT, 454.2; IMRT, 788.8; 3D-CRT, 295.5	
Zhang et al [52]	11	Prostate + prox imal SV 86.4 Gy	IMRT (5F,SS) *vs* VMAT (SA)	IMRT – slightly higher dose to PTV (V95%, D95%, mean dose and TCP) and better homogeneity compared with VMAT	VMAT better then IMRT (sparing of rectum, bladder, femoral heads)	VMAT, 290; IMRT, 642	VMAT, 1 min; IMRT, 5 min
Kjaer-Kristoffersen et al [53] *RapidArc*	8	Prostate + SV, 78 Gy (5 pts); 74 Gy (1 pt) Prostate bed, 66 Gy (2 pts)	IMRT (5F,SW) *vs* VMAT (partial SA)	IMRT – slightly better PTV coverage (V95%) but VMAT better in PTV minus rectum coverage. Hotspots higher in VMAT plans.	VMAT better than IMRT (sparing of bladder, rectum). Integral dose to body similar. Low dose bath (V5 Gy) to body larger for VMAT	VMAT, 529; IMRT, 647	
Hardcastle et al [54] *SmartArc*	10	Prostate 78 Gy in 39 fractions	IMRT (7F,SS) *vs* VMAT (SA)	IMRT and VMAT – similar PTV coverage (except D95% where VMAT had lower values).	VMAT better than IMRT at rectal sparing at doses <50 Gy. VMAT – higher doses to femoral heads. No significant difference in bladder doses.	VMAT, 417; IMRT, 526	VMAT, 1.3 min; IMRT, 4.5 min
Ost et al [55]	12	Prostate + SV (76 Gy) and IPL boost (82 Gy). Additional IPL dose level >85 Gy	IMRT (3F,5F,7F,SS) *vs* VMAT (SA)	IMRT (5F,7F) and VMAT – similar PTV coverage and all better than IMRT 3F. Dose escalation up to 95 Gy to IPL with VMAT	VMAT better at rectal sparing (significant at rectal volumes receiving 20–50 Gy). No difference in integral dose to body.	For 6 MV: VMAT, 447; IMRT (3F), 362; IMRT (5F), 407; IMRT (7F), 434	VMAT, 1.95 min; IMRT (5F), 3.85 min; IMRT (7F), 4.82 min
Weber et al [56] *RapidArc*	7	Recurrent prostate carci noma 56 Gy in 14 fractions	IMRT (5F,SW) *vs* IMPT *vs* VMAT (SA)	IMPT best for PTV coverage, VMAT better than IMRT for GTV and PTV coverage. VMAT (high definition MLC) – best for homogeneity. IMRT, VMAT better than IMPT for conformity	IMPT and RA better than IMRT (sparing of rectum, urethra, bladder). Integral doses to body lowest with IMPT. IMPT best at sparing penile bulb		
Kopp et al [57] *RapidArc*	292	Prostate 77.4 Gy in 43 fraction	IMRT (7F,SW) *vs* VMAT (SA)	VMAT and IMRT similar PTV coverage (VMAT less homogeneous). VMAT – slightly higher D2%	VMAT better than IMRT (sparing of rectum at high doses, bladder, femoral heads, penile bulb)		
Yoo et al [58] *RapidArc*	10	Prostate, SV and LN (primary) 46.8 Gy; prostate and SV (boost) 28.8 Gy (1.8 Gy per fraction)	IMRT (9F,7F) *vs* VMAT (SA) *vs* VMAT (DA)	Primary plans – IMRT better than VMAT (PTV coverage, conformity). Boost plans – similar PTV coverage, homogeneity; IMRT had worse conformity compared to VMAT	Primary plans-IMRT better than VMAT (sparing of bladder, rectum, small bowel). Boost plans – IMRT and DA VMAT better than SA VMAT. Higher integral doses to body with VMAT	Primary plans: VMAT (SA), 429; (DA), 444; IMRT, 1300. Boost plans: VMAT (SA), 443; VMAT (DA), 484; IMRT, 777	Primary plans: VMAT (SA), 1.5 min; VMAT (DA), 3.1 min; IMRT, 8.1 min. Boost plans: VMAT (SA), 1.5 min; VMAT (DA), 3.1 min; IMRT, 4.9 min.

Teoh M et al Brit J Rad, 84 (2011)

Comparison of competing techniques

H&N

Table 3. Comparative planning studies in head and neck cancer

Paper [ref] *VMAT commercial system*	Number of patients	Primary tumour site	Comparison	PTV	OAR	MU per fraction	Treatment time per fraction
Verbakel et al [91] *RapidArc*	12	Nasopharynx, oropharynx and hypopharynx	IMRT (7F,SW) *vs* VMAT (SA) *vs* VMAT (DA)	Similar PTV coverage. DA VMAT better than SA VMAT and IMRT for homogeneity	No significant difference. Parotid dose lower with DA VMAT (by average 2Gy) compared with SA VMAT and IMRT	VMAT (SA), 439; VMAT (DA), 459; IMRT, 1108	
Vanetti et al [92] *RapidArc*	29	Oropharynx, hypopharynx and larynx	IMRT (7–9F,SW) *vs* VMAT (SA) *vs* VMAT (DA)	Similar PTV coverage and conformity. DA VMAT better than SA VMAT and IMRT for homogeneity (SA VMAT slightly inferior to IMRT)	VMAT better than IMRT at sparing spinal cord (D2%, mean dose), brainstem (D2%, mean dose) and parotid glands (mean dose). DA VMAT better than SA VMAT. VMAT – lower integral doses to body	VMAT (SA), 463; VMAT (DA), 584; IMRT, 1126	VMAT (SA), 1.2–1.5 min; VMAT (DA), 3 min; IMRT, 15 min
Johnston et al [93] *RapidArc*	10	Nasopharynx and oropharynx	IMRT (9F,SW) *vs* VMAT (DA)	Similar PTV coverage IMRT slightly better than VMAT for conformity and homogeneity	No significant differences for spinal cord, brainstem doses. VMAT better than IMRT for contralateral parotid gland sparing	VMAT, 529; IMRT, 1628	
Guckenberger et al [94] *SmartArc*	15 (of 20)	Post-operative pharynx/ larynx, primary pharynx, paranasal sinus	IMRT (9F,SS) *vs* VMAT (1–3 arcs)	For PTV coverage and homogeneity: (post-operative pharynx/larynx) SA VMAT inferior to IMRT, DA VMAT = IMRT TA VMAT better than IMRT; (primary pharynx) SA and DA VMAT inferior to IMRT TA VMAT= IMRT; (paranasal sinus) All VMAT plans inferior to IMRT; (decreased coverage between orbits)	(Post-operative pharynx/larynx, primary pharynx) No significant difference (SA VMAT inferior to DA VMAT; TA VMAT and IMRT) (paranasal sinus) All VMAT plans inferior to IMRT for lens sparing	IMRT, 430–688; VMAT (SA), 358–440; VMAT (DA), 460–519; VMAT (TA), 506–560	IMRT, 9.55–12.25 min; VMAT (SA), 1.85–2 min; VMAT (DA), 3.83–3.98 min; VMAT (TA), 4.42–4.58 min
Bertelsen et al [95] *Smartarc*	25	Oropharynx and hypopharynx	IMRT (5–7F,SS) *vs* VMAT (SA)	Similar PTV coverage and homogeneity. VMAT better than IMRT for elective PTV coverage and conformity	VMAT better than IMRT at sparing spinal cord, parotid glands, submandibular glands at high dose levels. VMAT – lower volumes of normal tissue (outside PTV) irradiated to higher doses	VMAT, 460; IMRT, 503	VMAT, 4.02 min; IMRT, 6.2 min
Alvarez-Moret [96] *Oncentra Masterplan*	4	Oral cavity, hypopharynx, nasal cavity	IMRT (7–9F,SS) *vs* VMAT (SA) *vs* VMAT (DA)	IMRT and DA VMAT similar PTV coverage, homogeneity (SA VMAT inferior to IMRT and DA VMAT)	IMRT and DA VMAT largely similar OAR sparing (SA VMAT inferior to IMRT and DA VMAT)	VMAT (SA), 491.3; VMAT (DA), 596.4; IMRT, 575.4	VMAT (SA), 1.86 min; VMAT (DA), 3.64 min; IMRT, 11.7 min

Teoh M et al Brit J Rad, 84 (2011)

Comparison of competing techniques

Standard IMRT, Tomotherapy, VMAT

- Tomotherapy has greater flexibility of shaping dose in axial slices than both standard IMRT and VMAT: full IMRT per beam direction, and beams can come from all co-planar directions
- Tomotherapy may in longitudinal direction be more restricted because of field width, if w=1cm → longer treatment times
- Tomotherapy and VMAT have larger spreading of low doses over large volumes than standard IMRT
- In contrast with standard IMRT, Tomotherapy and VMAT do not require selection of limited number of optimal beam directions
- For simple cases, VMAT seems substantially faster than standard IMRT with comparable plan quality for PTV and OAR (but spreading)
- In complex cases, single-arc VMAT with short treatment times may compromise quality of the dose distribution.
- Only standard IMRT allows “free” use of non-coplanar beams

Bortfeld and Webb, 2009

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Credits to Ben Heijmen

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Imaging for GTV definition

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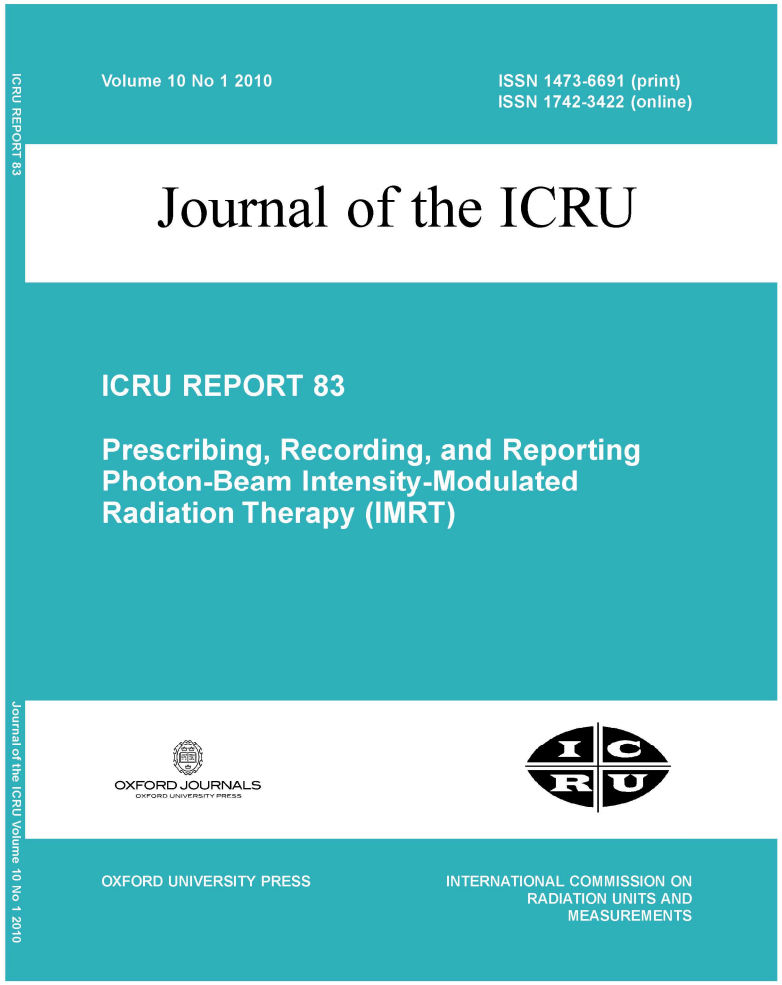
Physics for Modern Radiotherapy, Bucharest, 2017

ICRU Reports



- Common international language for describing target volumes
- Dose prescribing, recording, reporting

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Overview

Imaging for target definition

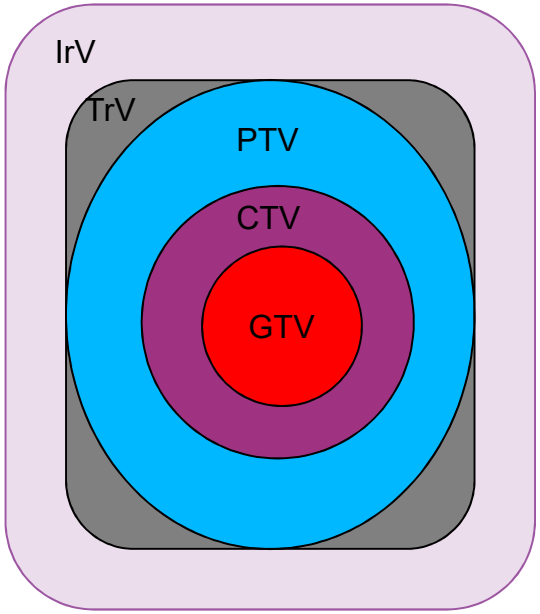
- GTV definition
- Use of functional imaging
- The challenges to overcome

Volume definition: Gross Tumour Volume (GTV)

GTV

- The gross palpable, visible or demonstrable extent of malignant disease
- May consist of primary tumour, nodal, or metastases
- No GTV if tumour has been removed

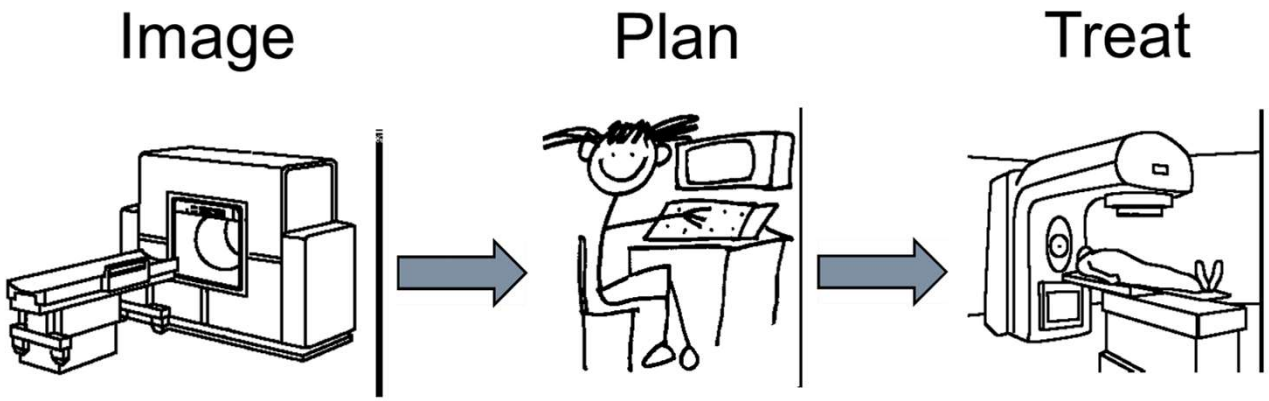
Volume definition-summary



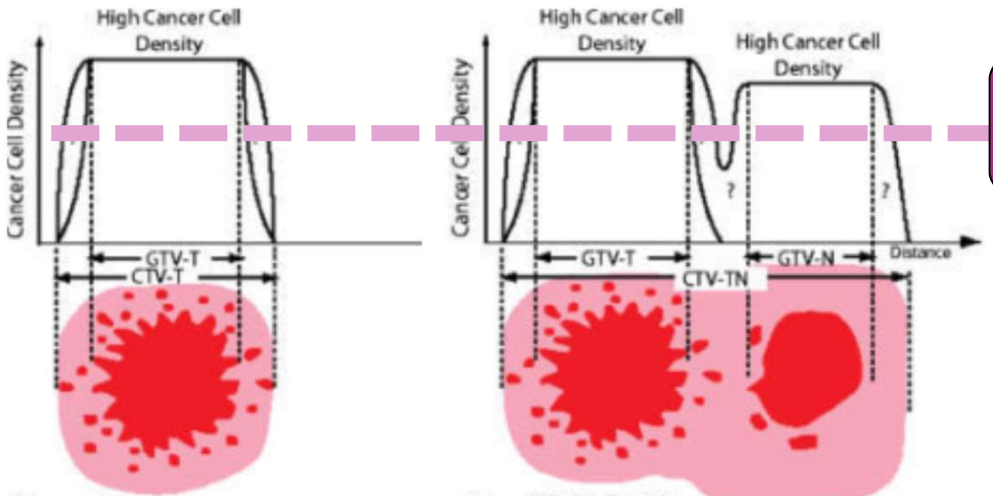
- GTV- demonstrable tumour
- CTV- GTV + subclinical tumour
- PTV- CTV + margin for uncertainties (internal margin & set-up margin)
- TrV- volume enclosed by specified isodose
- IrV- tissue volume receiving dose deemed significant in relation to normal tissue tolerance

Anatomical imaging

- **Fundamental basis of modern radiotherapy is anatomical imaging (mostly CT with some MRI)**
- Used to define target (and normal tissue)
  - AIM
    - Deliver high dose to tumour to achieved local control
    - Keep normal tissue toxicity within reasonable limits



Determining the GTV



Imaging detection threshold

Adapted from ICRU 71

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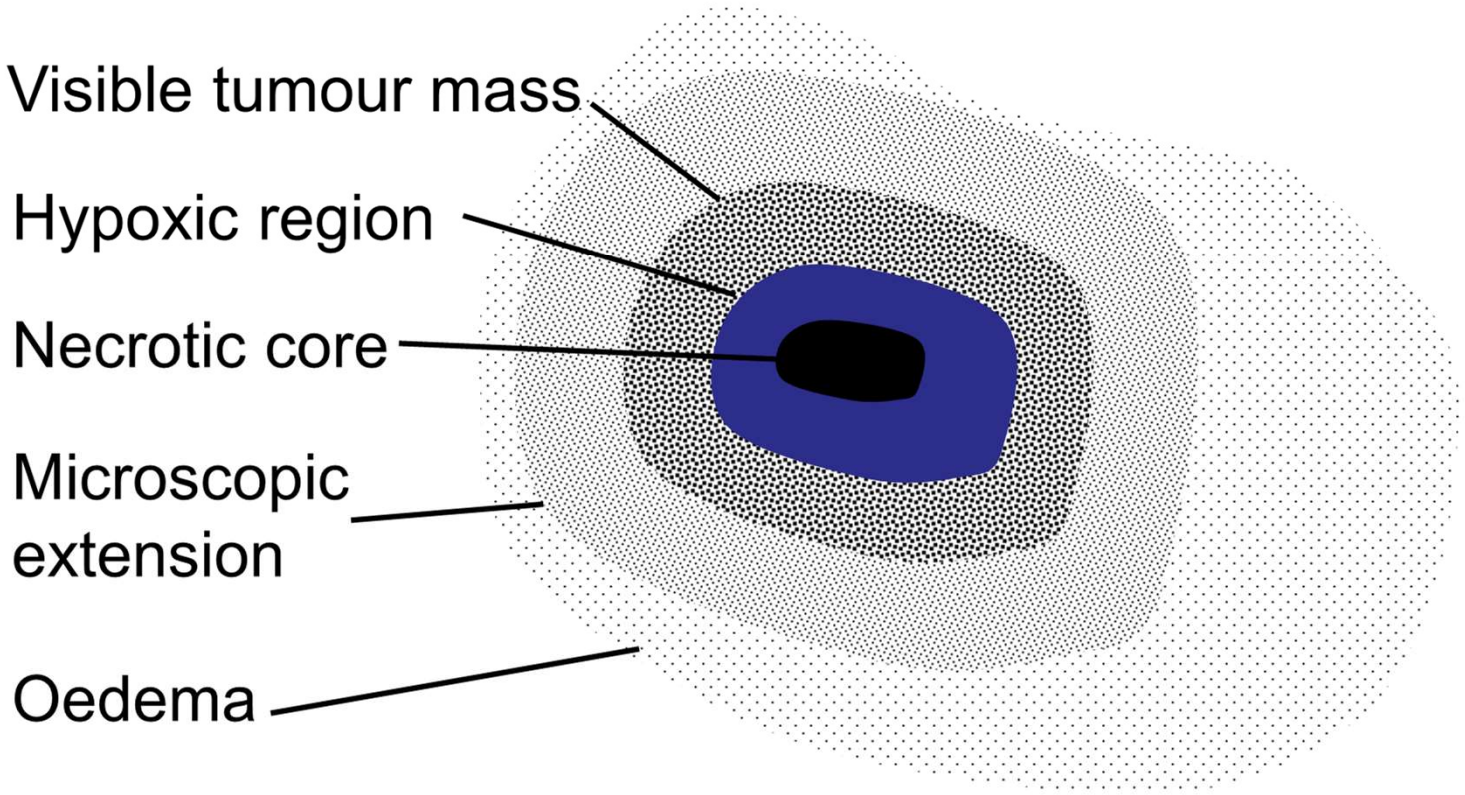
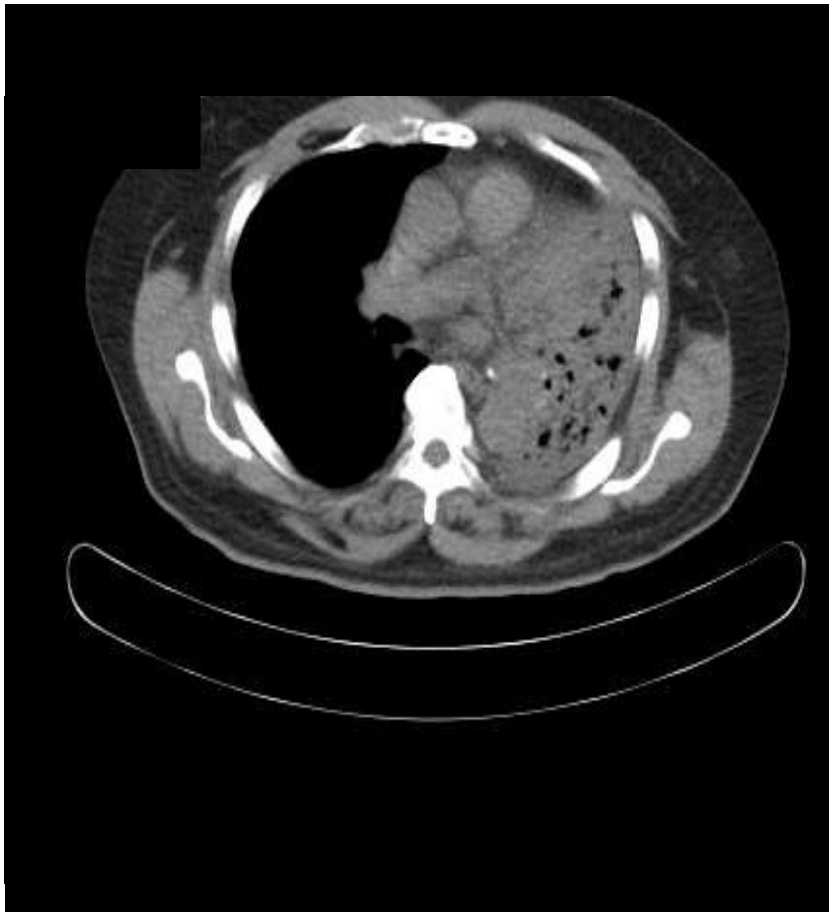
Determining the GTV

Tumour mass is heterogeneous

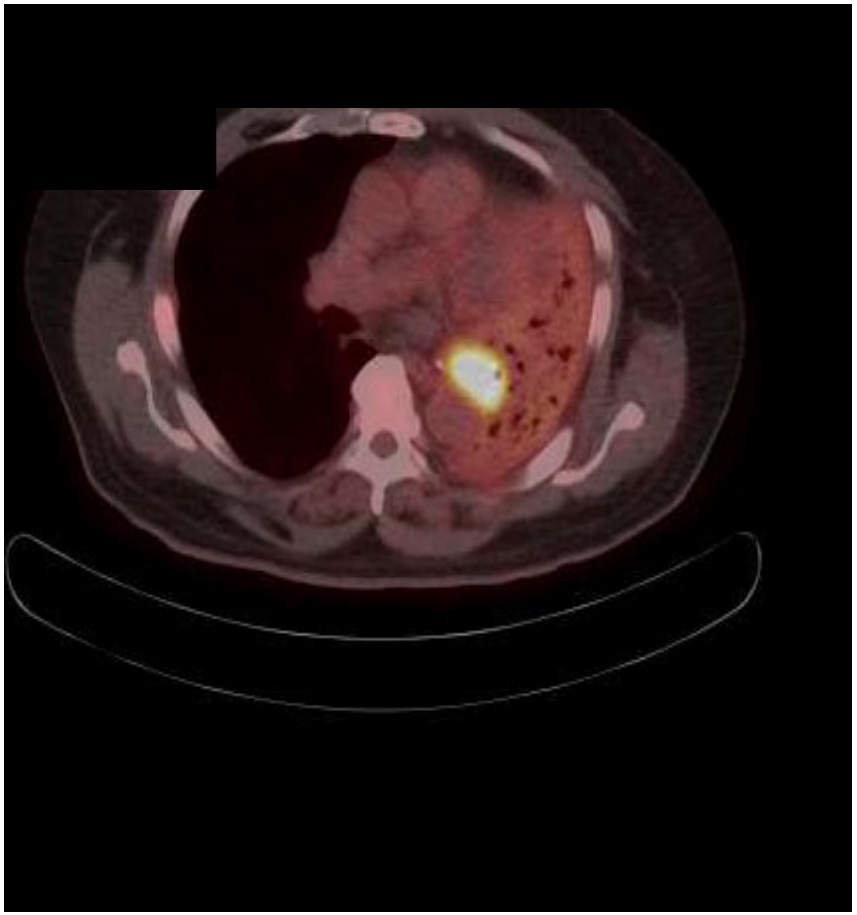


Delineating the GTV- variation with modality



Planning CT

GTV-T (CT, 0Gy)



FDG-PET-CT

GTV-T (FDG-PET-CT, 0Gy)

Chiti A, Kirienko M, Gregoire V. Clinical use of PET-CT data for radiotherapy planning: what 90 are we looking for? Radiother Oncol. 2010;96(3):277–9. De Ruysscher D, Kirsch CM. PET scans in radiotherapy planning of lung cancer. Radiother 88 Oncol. 2010;96(3):335–8. Bradley J, *et al*: A phase II comparative study of gross tumor volume definition with or without PET/CT fusion in dosimetric planning for non-small-cell lung cancer (NSCLC): primary analysis of Radiation Therapy Oncology Group (RTOG) 0515. *Int J Radiat Oncol Biol Phys* 2012, **82**(1):435-441 e431.

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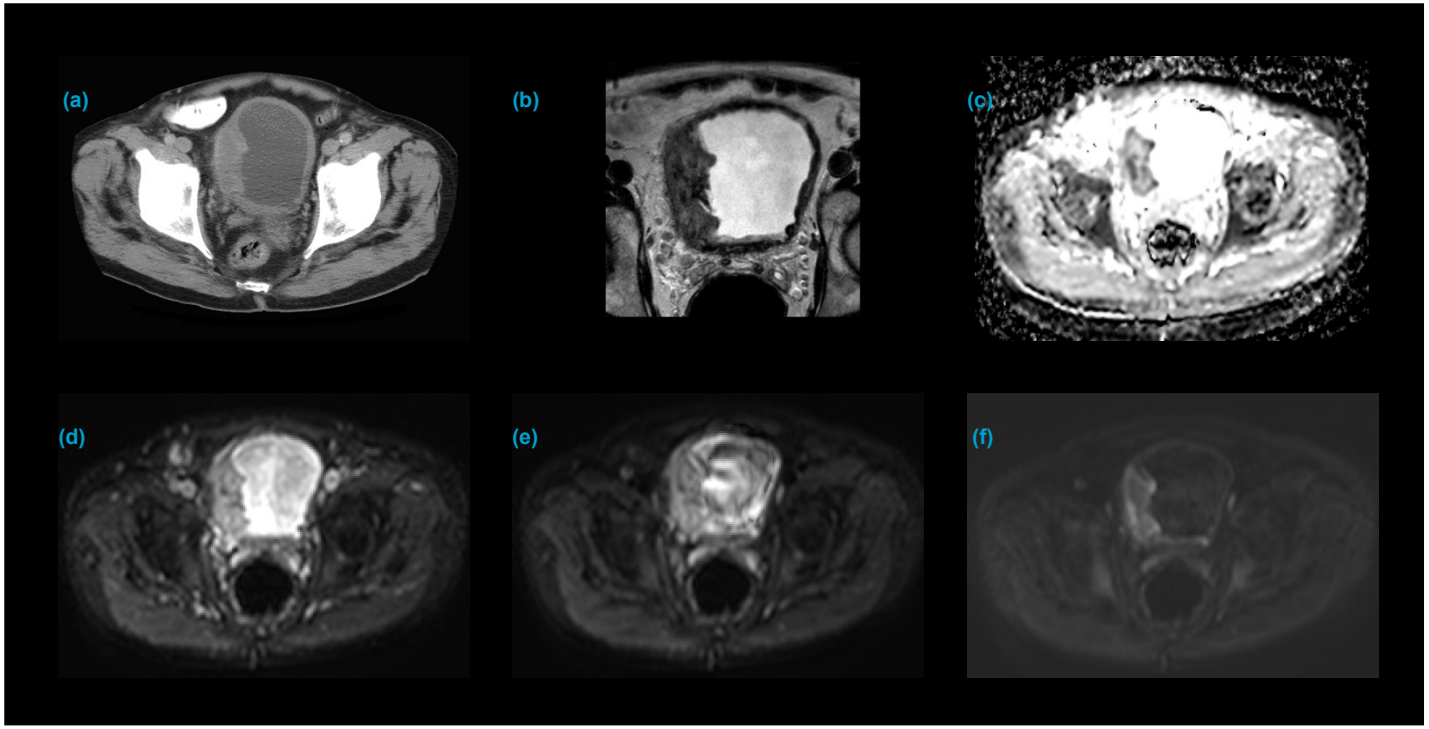
Challenges to be resolved in radiotherapy

Target definition



T3 N0 M0 bladder cancer (right bladder wall) (a) contrast enhanced CT scan, (b) axial T2 weighted image performed on a 1.5T MRI unit, (c) corresponding ADC map, (d) axial DW MRI at b-value=0, (e) axial DW MRI at b-value=100, (f) axial DW MRI at b-value=750

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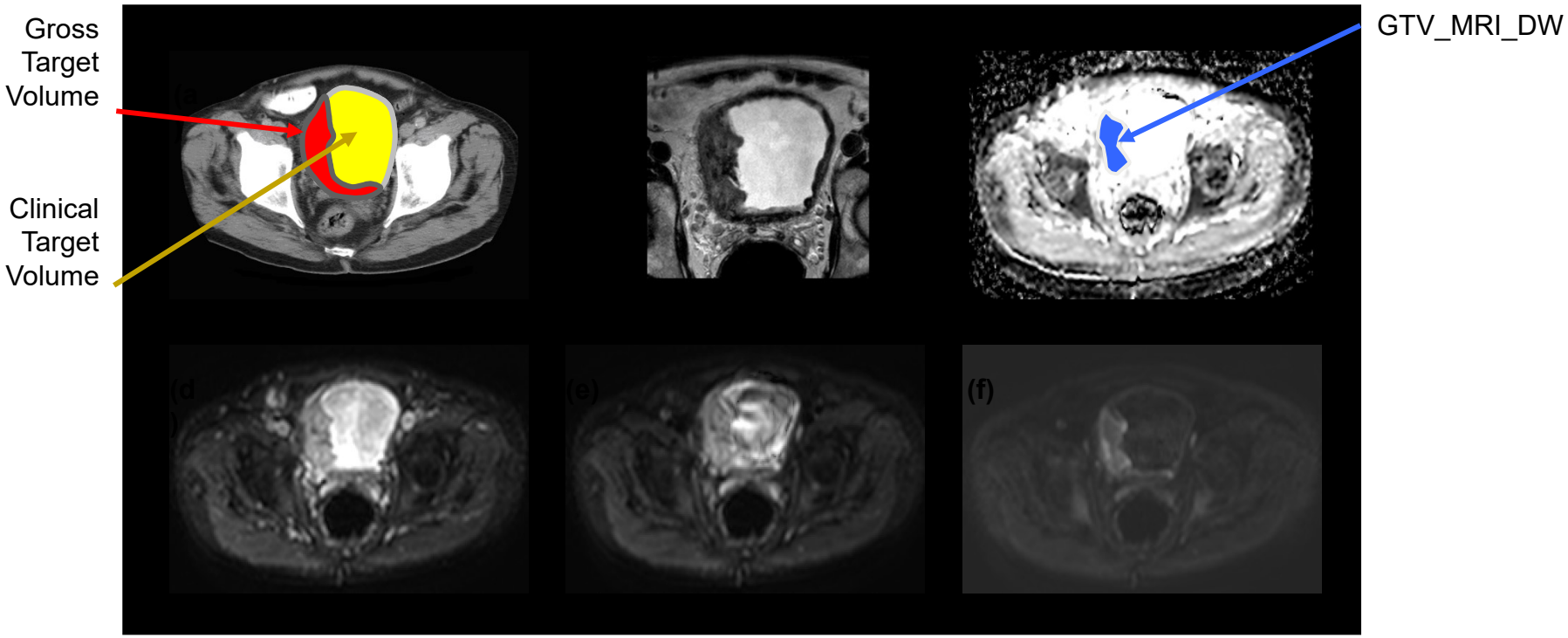
Challenges to be resolved in radiotherapy

Target definition



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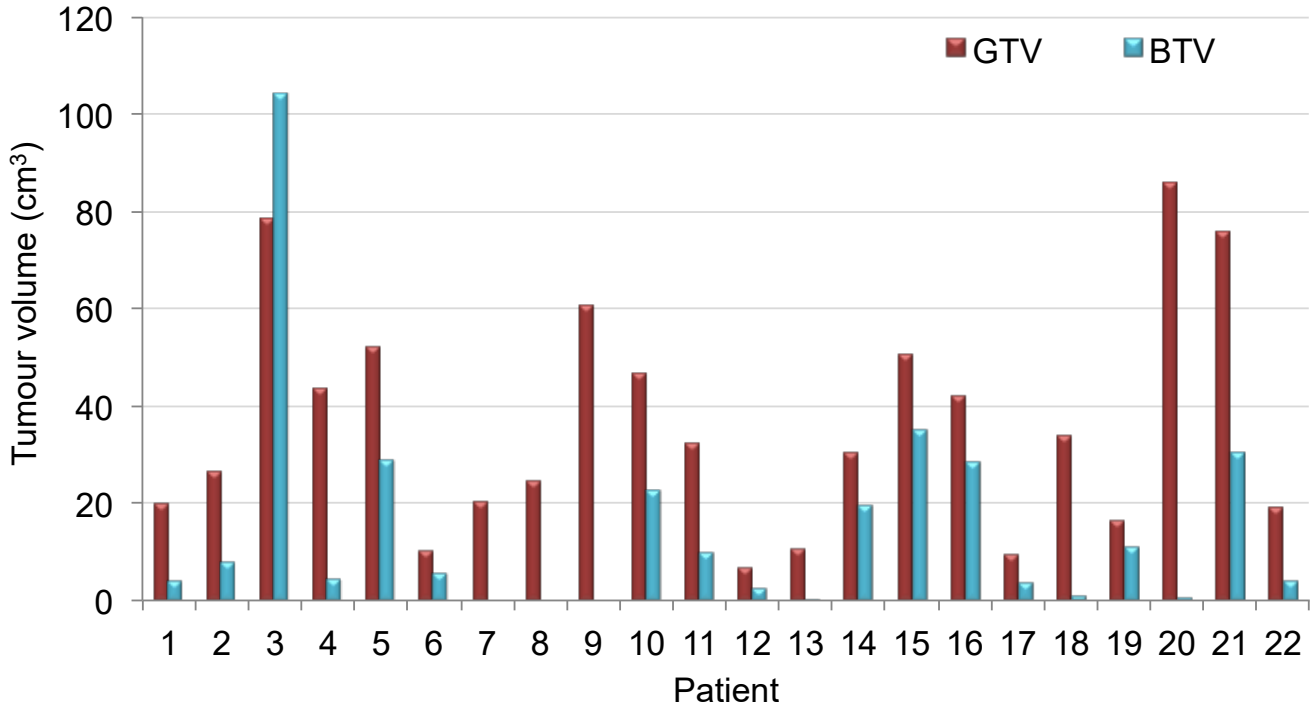
Challenges to be resolved in radiotherapy

Target definition

Proof of concept study



~45% volume reduction (p=0.002)

Hafeez et al., Characterisation of tumour boost with diffusion weighted MRI (DW-MRI) to inform biological target volume for radical radiotherapy in muscle invasive bladder cancer (MIBC) NCRI 2015.

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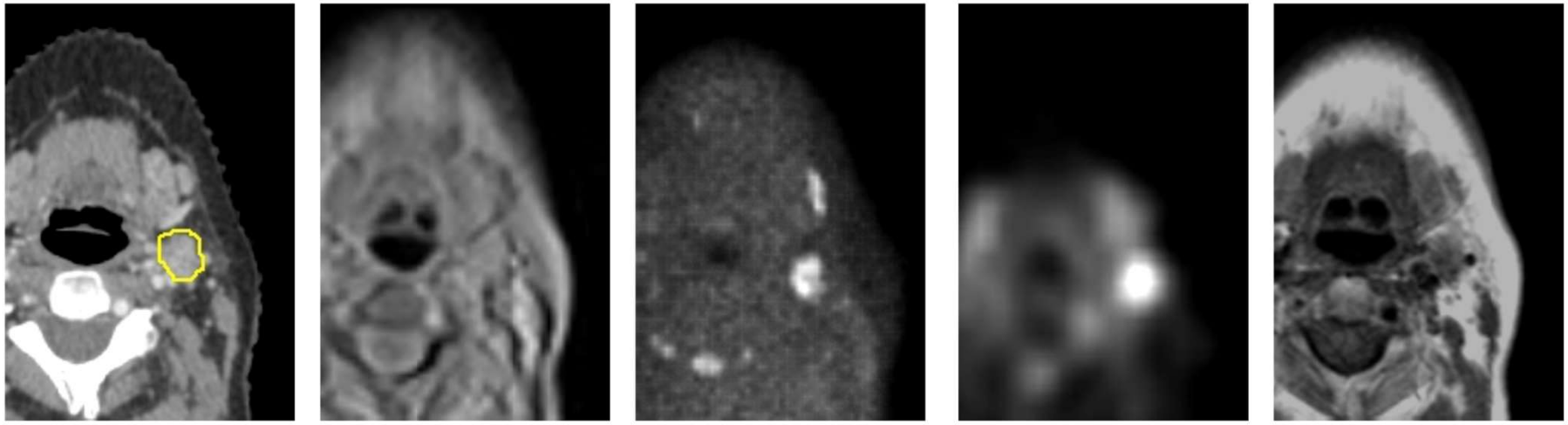
Challenges to be resolved in radiotherapy

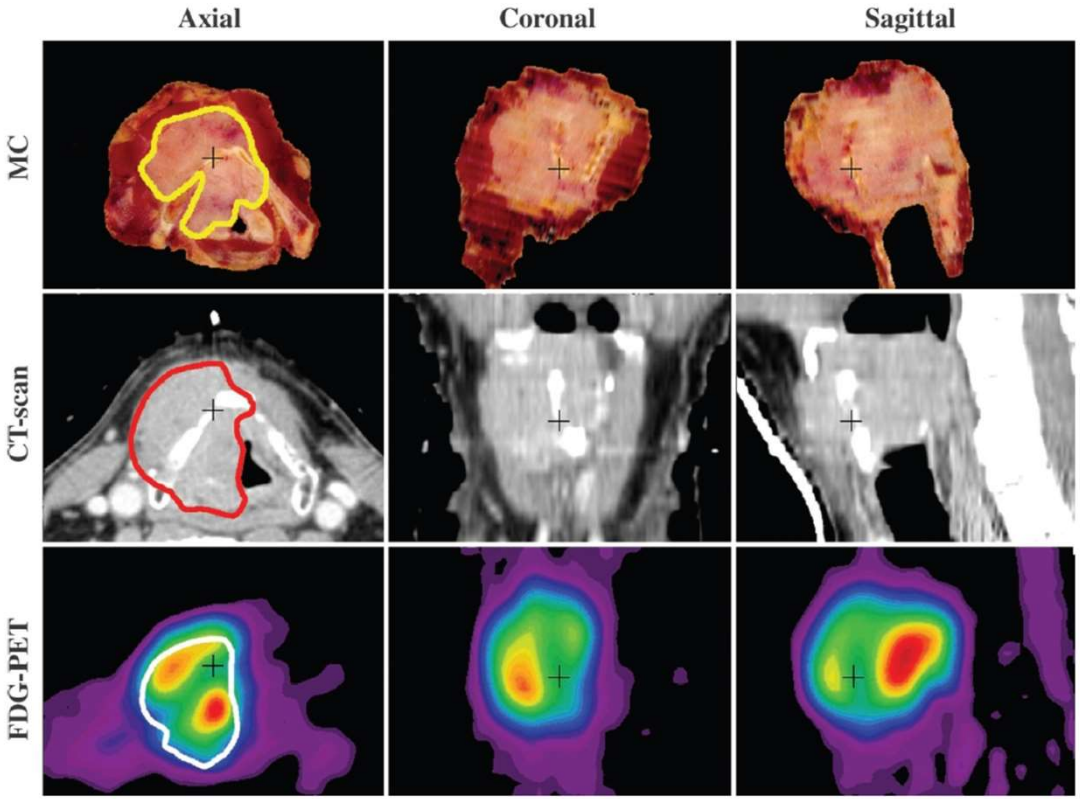
So which is the target?



CT DCE MR DW MR FDG PET T2 MR

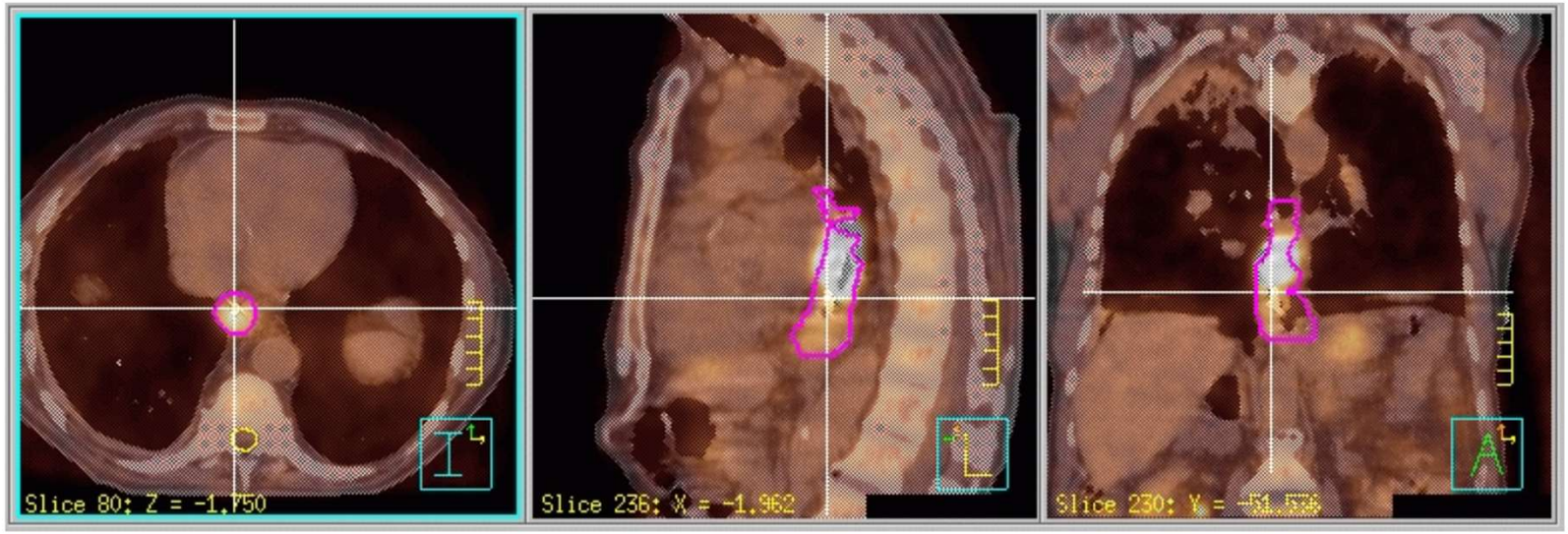
Challenges to be resolved in radiotherapy

Histopathological correlation?



Imaging to assist volume definition

Oesphagus



GTV_PTV_0Gy

Functional imaging to assist volume definition

Considering FDG-PET

Advantages -Accuracy in disease delineation

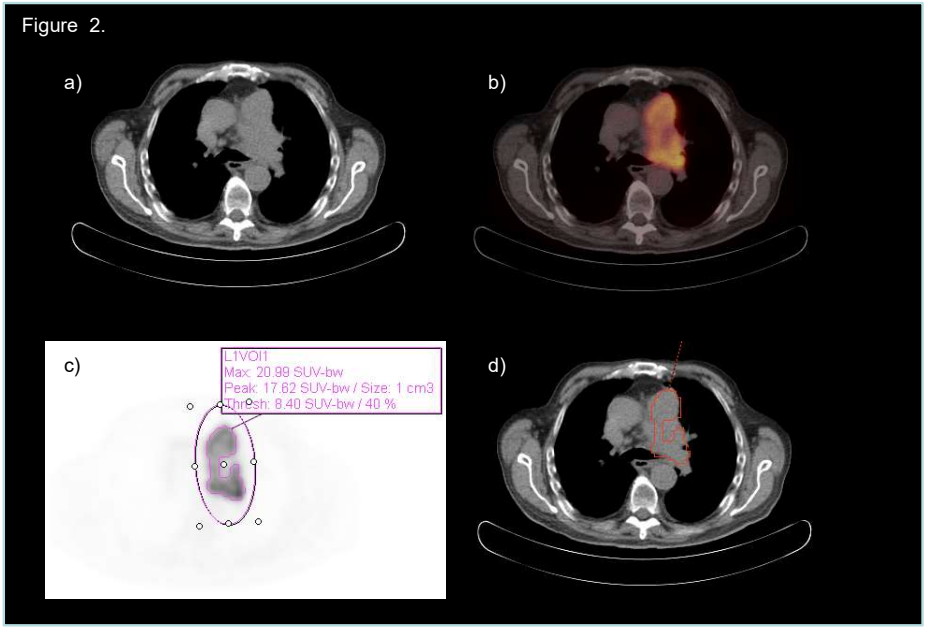
- PET-CT can more closely reflect pathological staging
- Improve inter-observer concordance
    - Tumour
    - Involved lymph node delineation
- Certainty results in smaller treatment volumes
- Less normal tissue irradiation
- Commonly used for radical radiotherapy planning
    - difficulties in distinguishing tumour,
    - necrosis,
    - atelectasis
    - normal tissue boundaries

Functional imaging to assist volume definition

Considering FDG-PET

Advantages- Individualisation

- PET-CT offers ability to identify biological sub-volumes
- Dose shaping with non-uniform dose



Functional imaging to assist volume definition

Advantages- Proposed individualisation

- Alternative tracers
  - Hypoxic tumour regions demonstrate intrinsic radio-resistance, ^{64}Cu-ATSM (sub-volume for dose escalation)

- ‘dose painting by contours’
  - PET based volume is treated to a specified dose level while keeping the mean dose to the remaining target constant

- ‘dose painting by numbers’
  - an inhomogeneous dose across the target volume is informed by the PET voxel intensity

Functional imaging to assist volume definition

Numerous planning studies shown feasibility to inform radiotherapy planning

No randomized clinical trials translates to improving local disease control and toxicity for patients

Functional imaging to assist volume definition

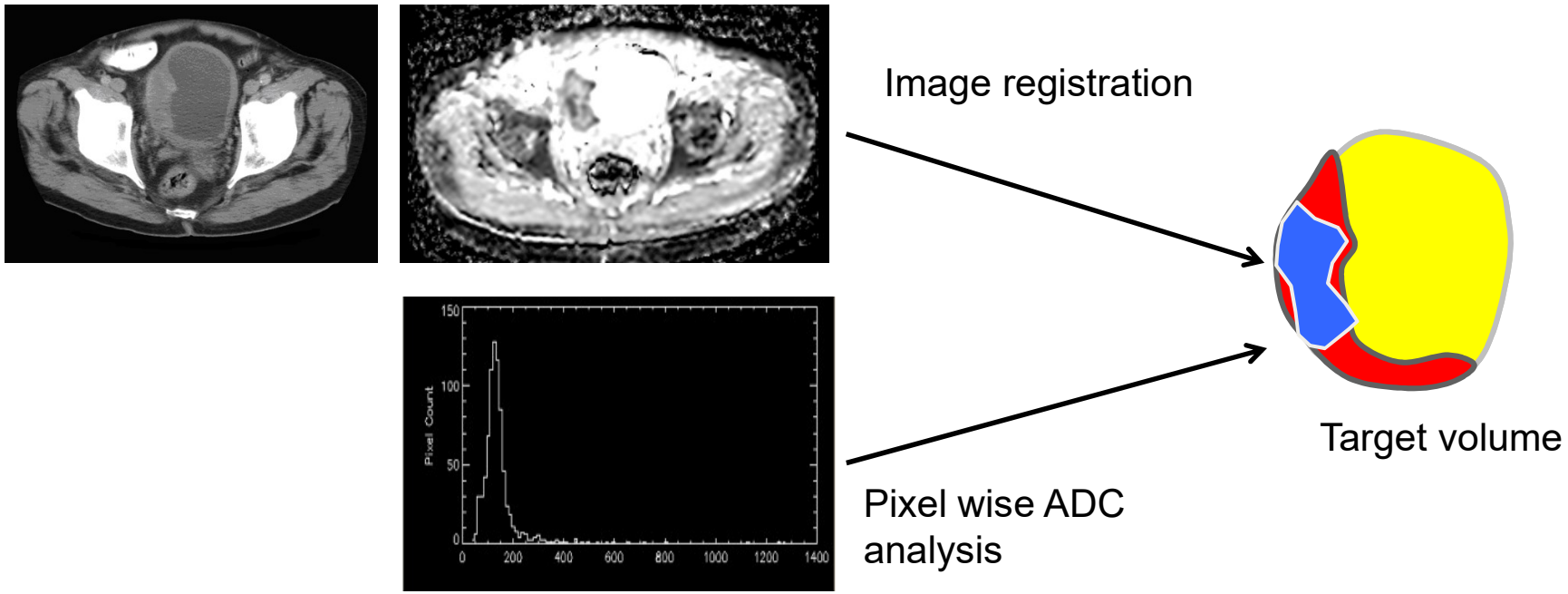
Limitations

- Given planning CT provides the only electron density information from which dose calculations are currently made
- Functional images require precise registration to the planning CT.

Challenges to be resolved in radiotherapy

Target definition

Proof of concept study



Hafeez et al., Characterisation of tumour boost with diffusion weighted MRI (DW-MRI) to inform biological target volume for radical radiotherapy in muscle invasive bladder cancer (MIBC) NCRI 2015.

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Functional imaging to assist volume definition

Considerations

- Rigid registration,
  - patient scanning takes place with identical setup to that of radiotherapy planning and treatment i.e. flat top couch, immobilisation devices, light lasers and tattoos as appropriate.

- Deformable registration
  - algorithms accommodate for any spatial difference between the volume elements of the different scans

Functional imaging to assist volume definition

Considerations

- Disease sites subject to significant respiratory motion can introduce uncertainty and artefact.
    - SUV may be underestimated or the volume over-estimated
    - motion mitigation strategies should be considered particularly for thoracic tumours as they are in radiotherapy

- Quantitative analysis of the SUV is also subject to a number of other potential errors
    - extravasation or incomplete injection,
    - longer uptake period
    - patient's blood glucose in circumstances where ^{18}FDG-PET is used

Functional imaging to assist volume definition

Considerations

- Contouring with PET-CT can be operator dependent
- no robust standard for display thresholds
- Adjustments to the image windowing settings are often arbitrary
- can easily make the tumour appear bigger or smaller introducing a potential systematic error
- Alternative is use automatic or semi automatic segmentation methods (different volumes depending on method used)

Functional imaging to assist volume definition

Considerations

- The other fundamental issue is that the metabolic state of tumours is likely to be dynamic
- A hypoxic sub-region for one fraction may be in a different for the subsequent fractions
- ?Dynamic dose painting approaches.

Functional imaging to assist volume definition

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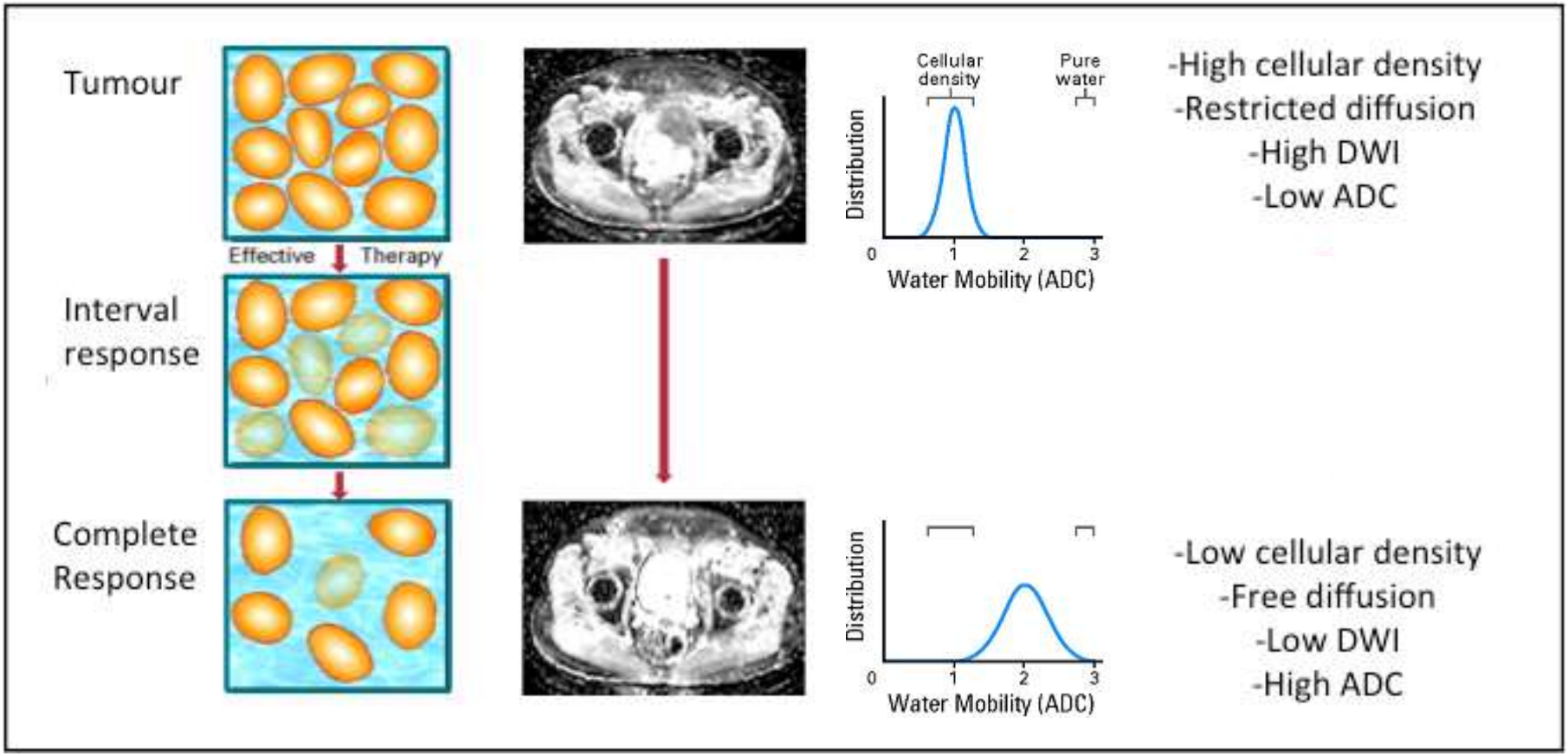
Delineating the GTV- biological adaptation



Hafeez et al., Use of diffusion weighted-MRI (DW-MRI) as a prognostic biomarker of survival and time to cystectomy in muscle invasive bladder cancer (MIBC) following organ conserving treatment. ECCO 2017.

Hafeez et al., Use of diffusion weighted-MRI (DW-MRI) as a biomarker of clinical outcome in muscle invasive bladder cancer (MIBC). NCRI 2015. Awarded NCRI prize 2015

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Physics aspects of electron, proton and ion beam therapy

Silvia Molinelli
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Physics for Modern Radiotherapy
Bucharest, Romania - 4 - 8 June 2017

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Contents

Electrons

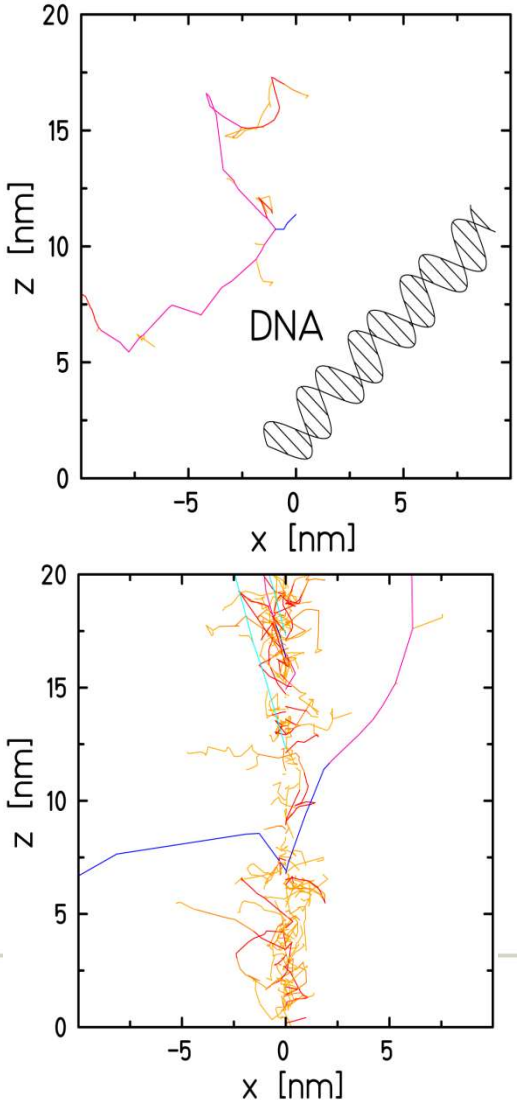
- Interaction with matter
- Dose deposition

Protons and carbon ions

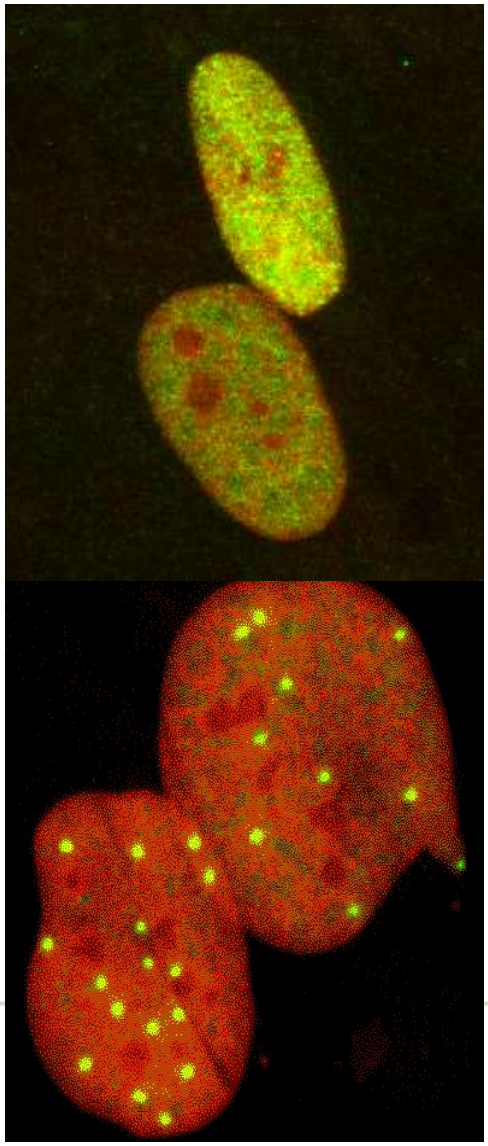
- Dose deposition and beam modeling
- Dose delivery techniques
- Uncertainties
- Relative Biological Effectiveness

Linear Energy Transfer (LET): Energy transferred per unit of particle path length (keV/μm)

Ionization tracks



Damage in nucleus



Low LET
Sparsely ionizing

Homogeneous deposition of dose

High LET
Densely ionizing

Local deposition of high doses

M. Scholz et al.
Rad. Res. 2001

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Electron interaction with matter

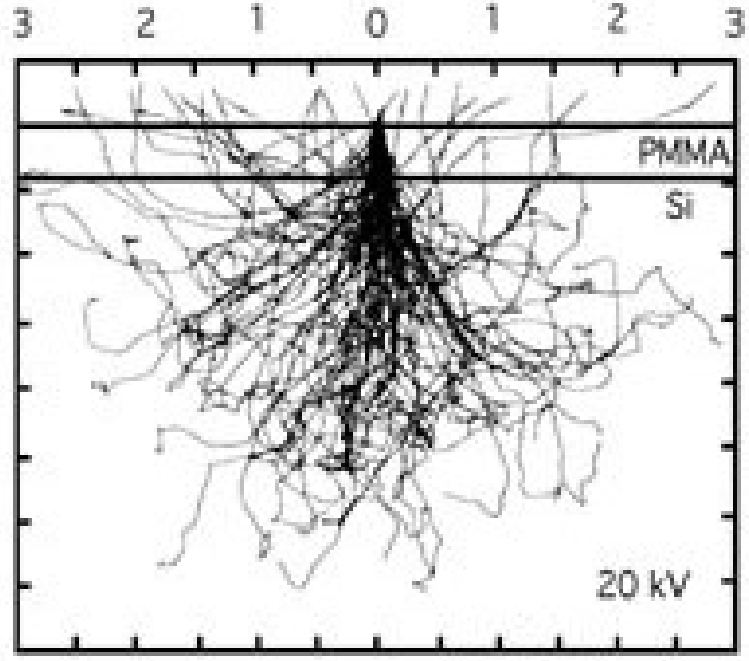
e^- propagating through an absorbing medium interact with atoms by a variety of elastic or inelastic Coulomb force interactions classified as:

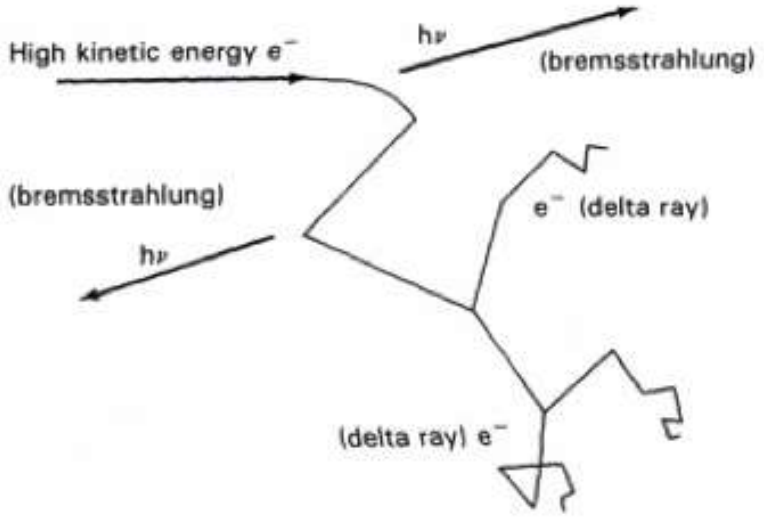
- Inelastic collisions with orbital e^- (ionization loss).
- Inelastic collisions with nuclei (radiative loss).

- Elastic collisions with orbital e^- .
- Elastic collisions with nuclei (nuclear coulomb scattering).

Electron interaction with matter

- Same mass of the atomic e- to which they transfer energy in collisional events
- Multiple elastic collisions of a high-energy e^- **(multiple scattering)** produce multiple small angle deflections
- The e^- follows a zigzag path (it can also be back-scattered) while it continuously loses kinetic energy through inelastic collisions with atoms
- Individual depositions are small and an electron may deposit energy at $>10^4$ locations

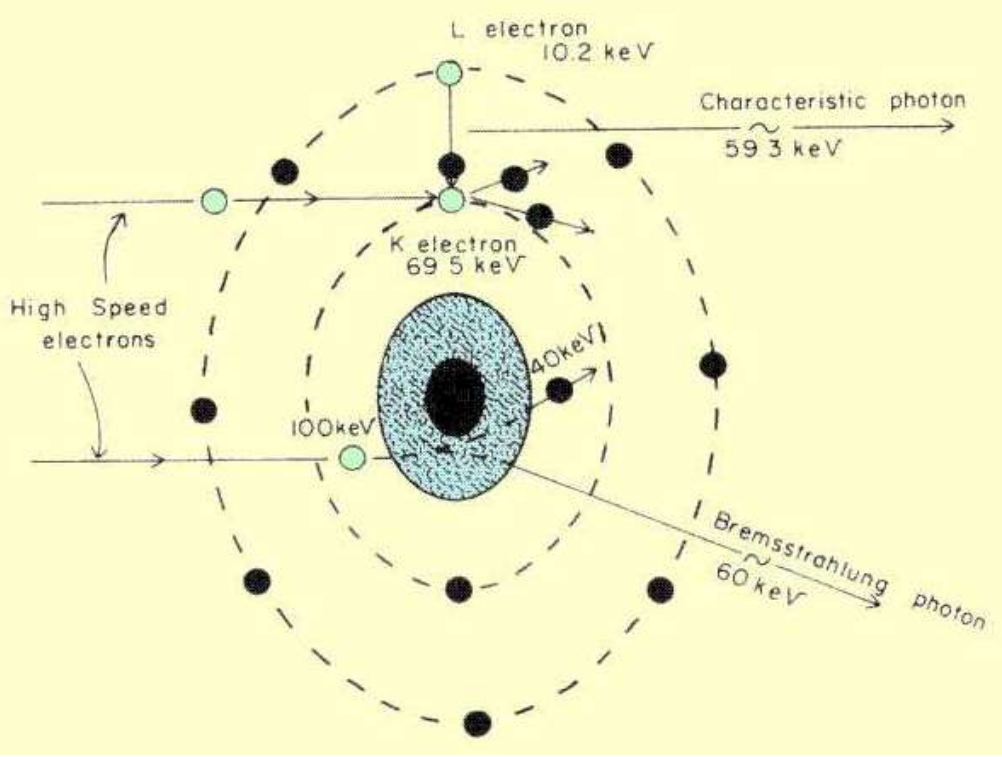




Electron interaction in matter: Inelastic collisions

Bremsstrahlung

- Bremsstrahlung X rays result from Coulomb interactions between the incident e^- and the nuclei of the target material.
- The incident e^- is deflected and decelerated and loses part of its kinetic energy in the form of photons (radiative loss).
- Photons with energy ranging from 0 to the incident e^- energy are generated



X-ray production

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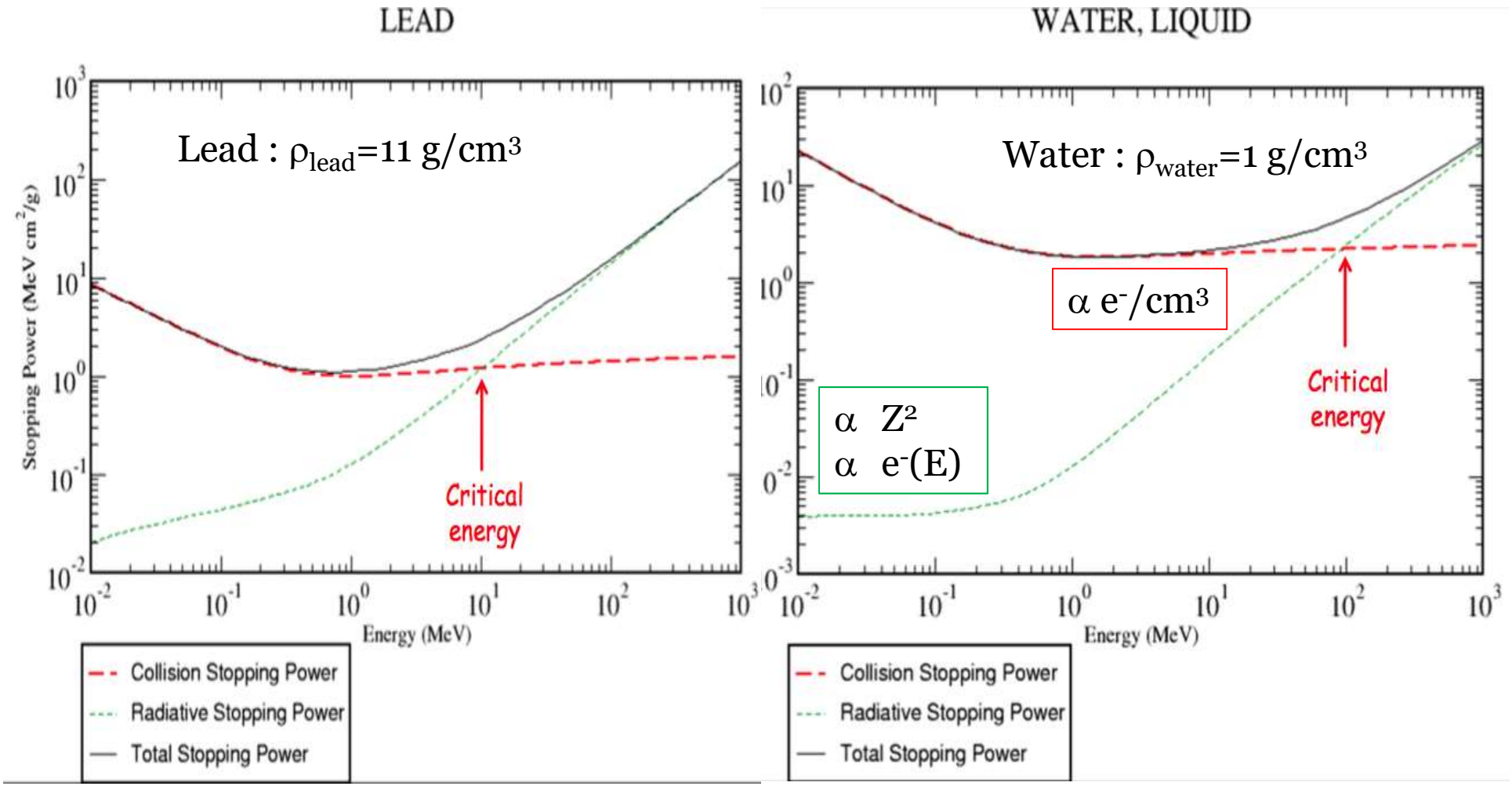
Electron energy loss: Mass Stopping power



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Electrons - Energy spectrum

- $(E_p)_o$ is the most probable energy at the surface – kinetic energy possesed by most of the electrons incident at the surface
- The average E_o is <
  → the energy spectrum is skewed towards lower energies

The Physics of Radiation Therapy (Faiz M. Khan)

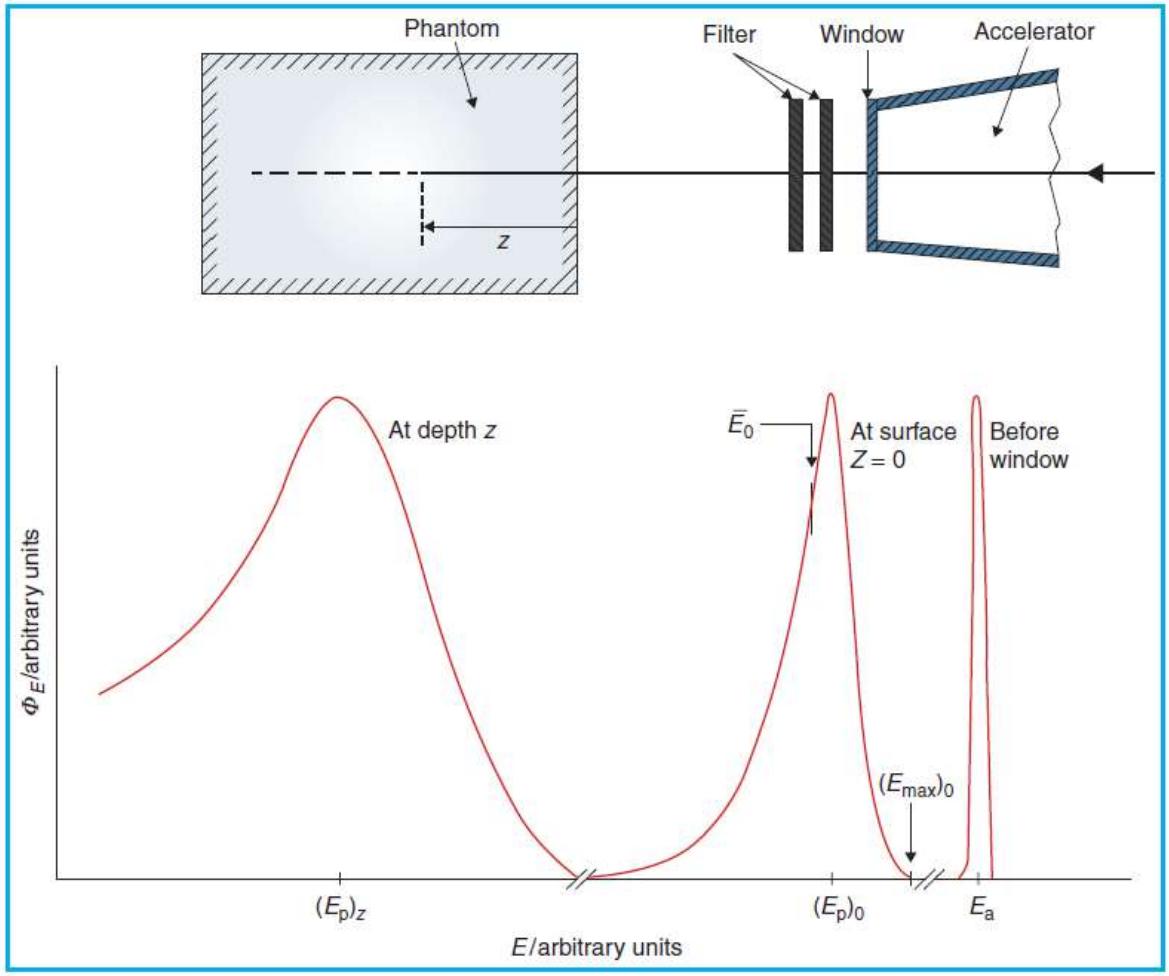


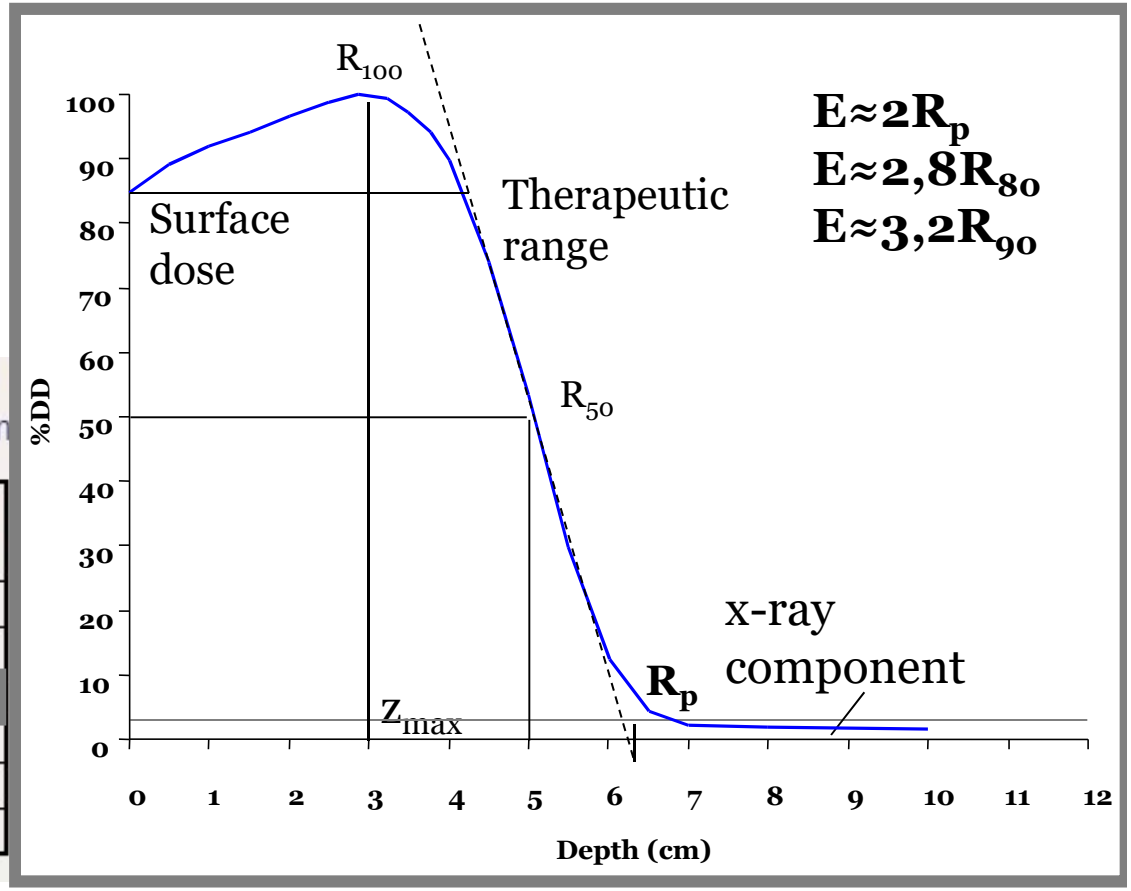
Figure 14.2. Distribution of electron fluence in energy, ϕ_E, as the beam passes through the collimation system of the accelerator and the phantom. (From International Commission on Radiation Units and Measurements. *Radiation Dosimetry: Electrons with Initial Energies between 1 and 50 MeV.* Report No. 21. Washington, DC: International Commission on Radiation Units and Measurements; 1972, with permission.)

Electrons Energy - Range

- Maximum range: R_{max}
- Practical range: R_p
- *R90, R80 and R50*

Typical electron beam depth dose parameters that should be measured for each clinical electron beam

Energy (MeV)	R_{90} (cm)	R_{80} (cm)	R_{50} (cm)	R_p (cm)	$\bar{E}(0)$ (MeV)	Surface dose %
6	1.7	1.8	2.2	2.9	5.6	81
8	2.4	2.6	3.0	4.0	7.2	83
10	3.1	3.3	3.9	4.8	9.2	86
12	3.7	4.1	4.8	6.0	11.3	90
15	4.7	5.2	6.1	7.5	14.0	92
18	5.5	5.9	7.3	9.1	17.4	96



Electron beam PDD

• High surface dose (75-95)% - No skin sparing effect → Skin Targets
< E means < D_s (≠ photons)

• Dose builds up to a maximum at depth
• Beyond z_{max} the dose drops off rapidly and levels off at small low level dose component (Bremsstrahlung tail)

• Plateau region should extend to treatment depth across target region
(PDD = 90% - Therapeutic Range**)**

• Gradient depends on energy

• Dose beyond practical range due to Bremmstrahlung (linac head, air, pt)

4 MeV < 1%
10 MeV < 2.5%
20 MeV < 4%

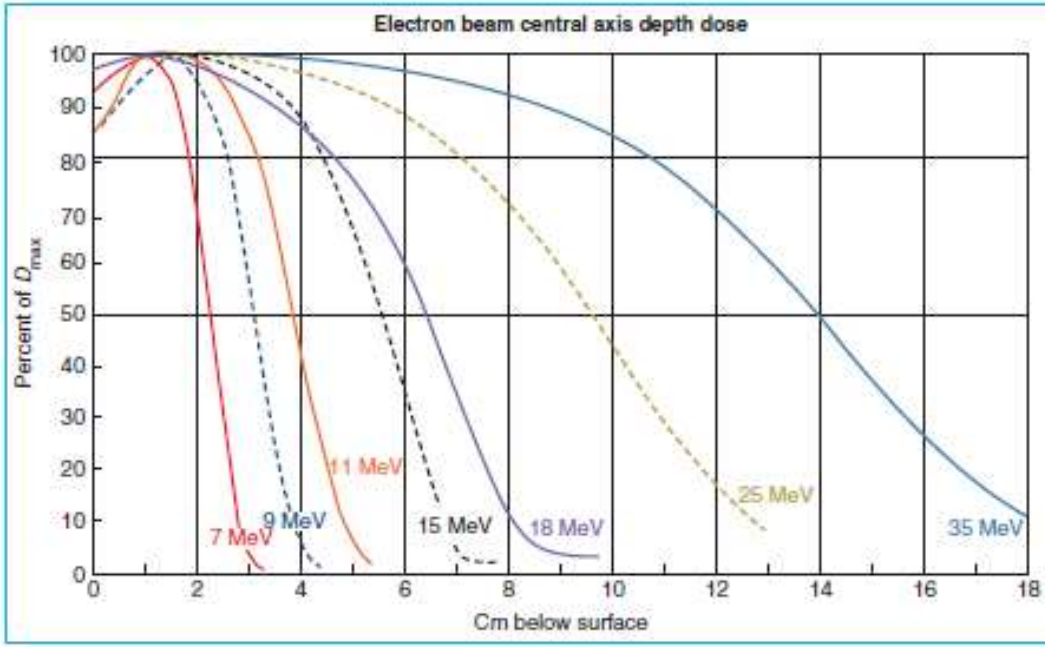


Figure 14.11. Comparison of central axis depth dose distributions of the Sagittaire linear accelerator (*continuous curves*) and the Siemen's betatron (*dashed curves*). (From Tapley N, ed. *Clinical Applications of the Electron Beam*. New York, NY: John Wiley & Sons; 1976, with permission.)

The Physics of Radiation Therapy (Faiz M. Khan)

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Particle Therapy - Rational

Photons	p^+, C^{6+}

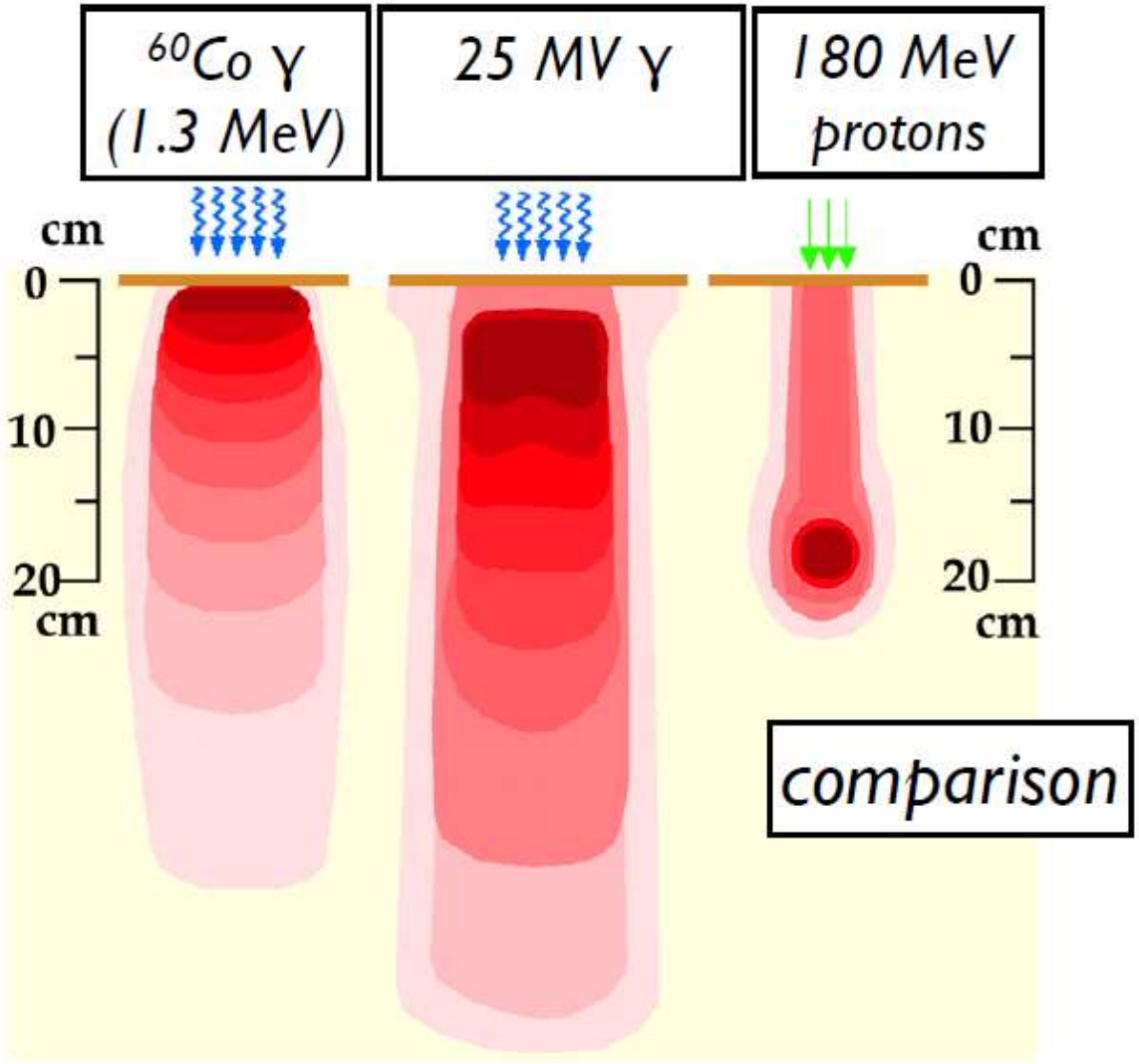
1) Superior physical dose deposition properties

Exponential dose fall off after build up	Inverse dose profile with a maximum energy deposition in the Bragg Peak → Dose at depth (target) is greater than dose at surface → Steep distal dose fall off (they stop)

2) Higher relative biological effectiveness (RBE)

Reference radiation RBE	RBE > 1

Rational – dose distribution



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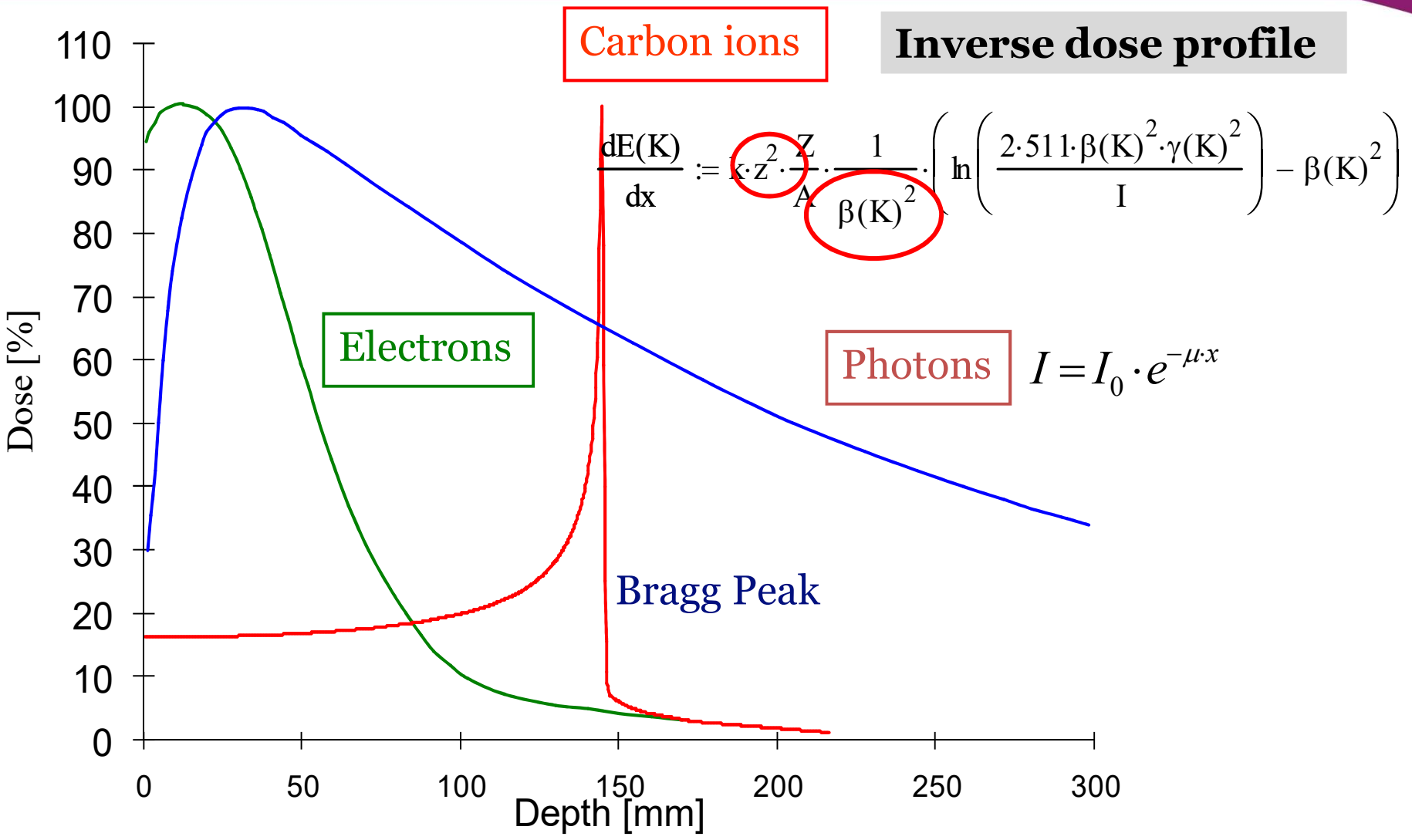
Particle Therapy



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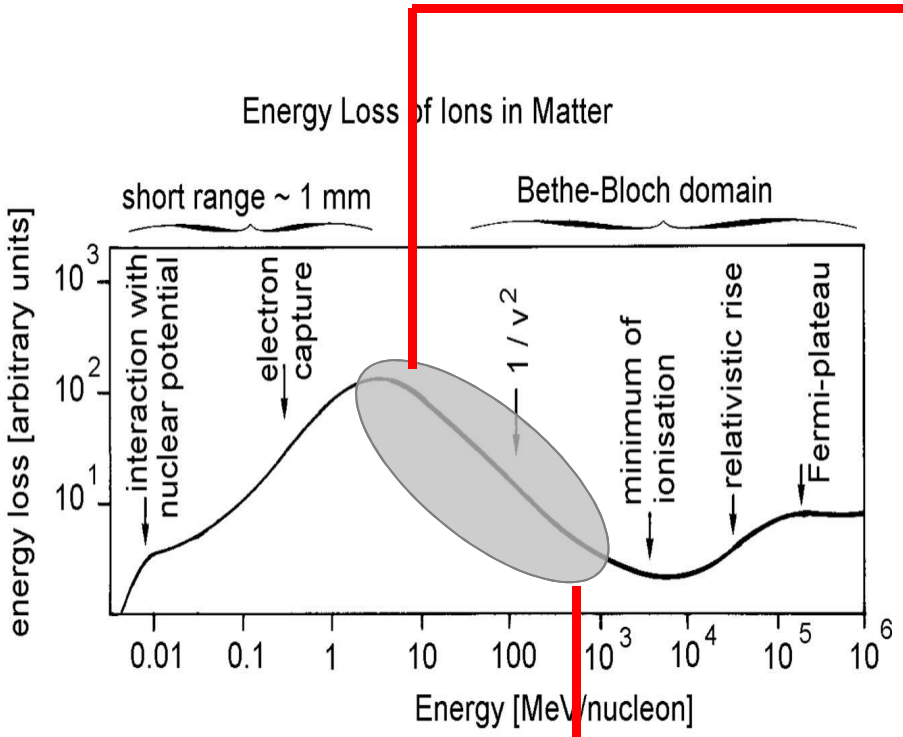
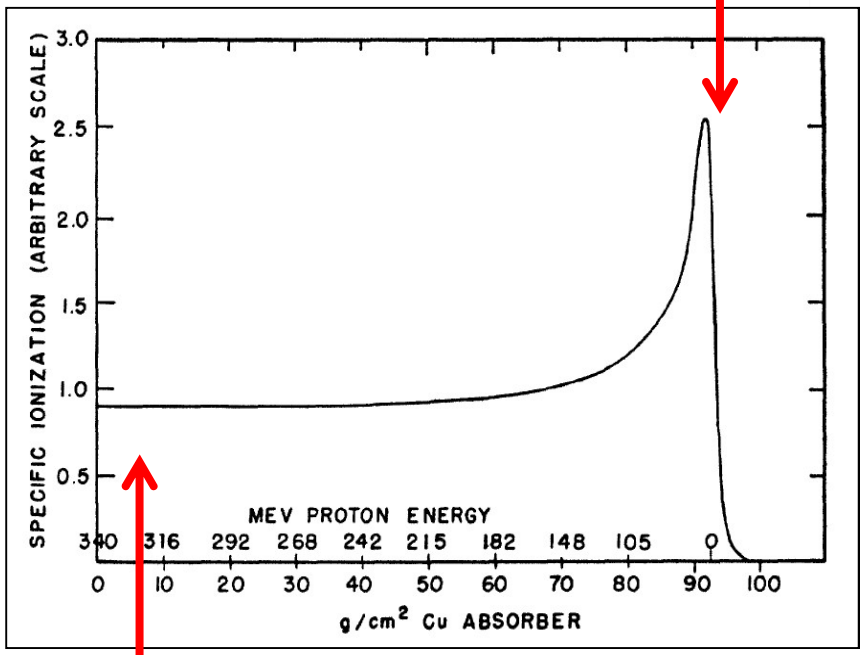
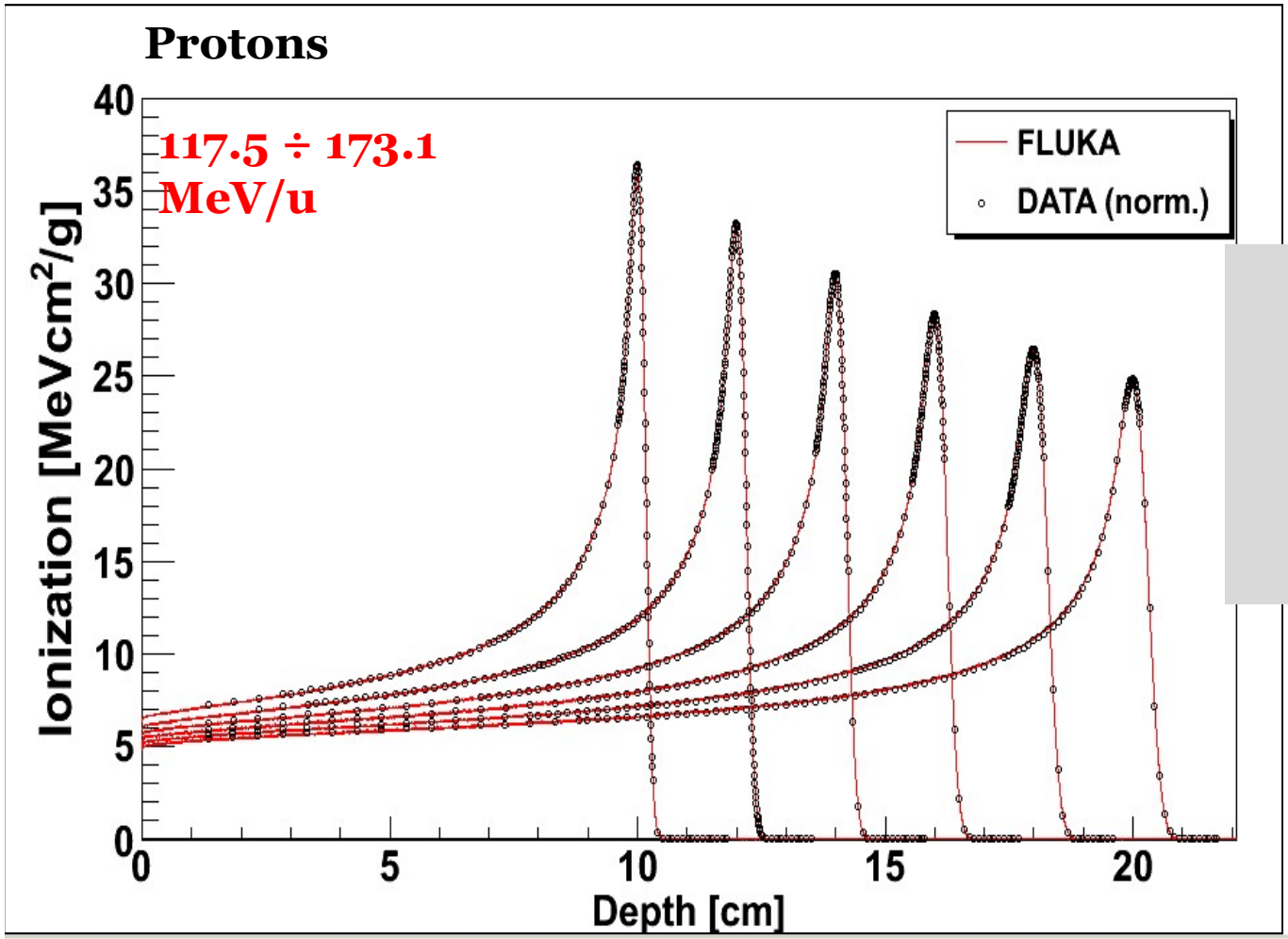
Actual dE/dx of heavy particles ($1/\beta^2$)





Penetration depth

Depth Dose Profiles



Energy dependence
→ BP Position
→ Height
→ FWHM

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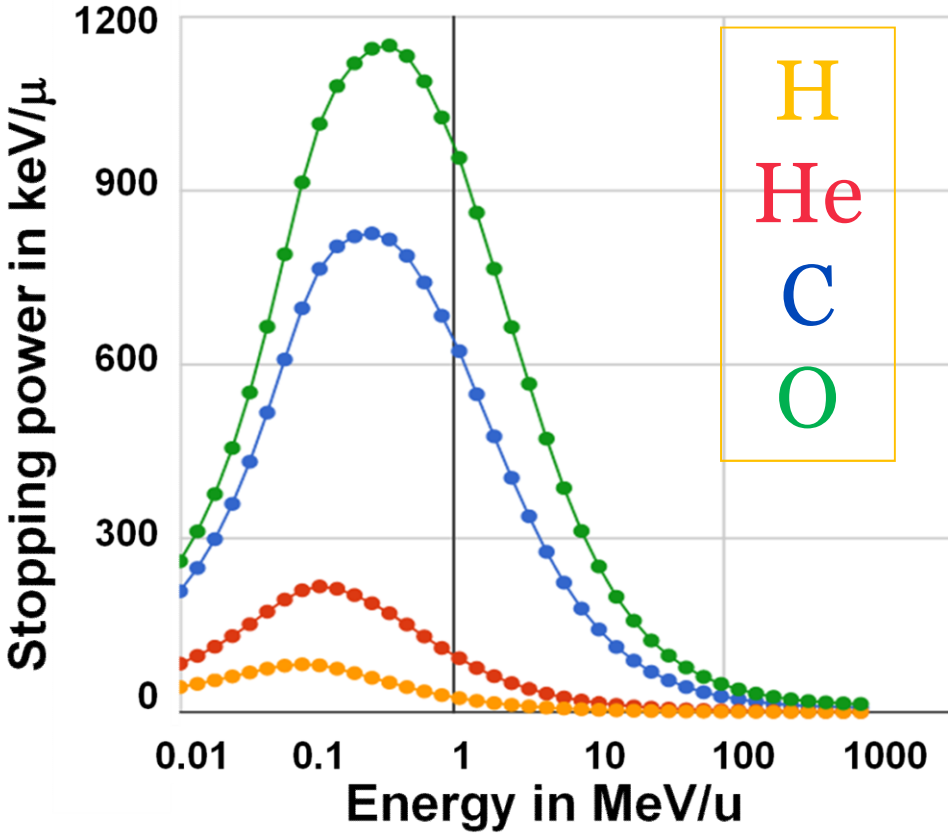
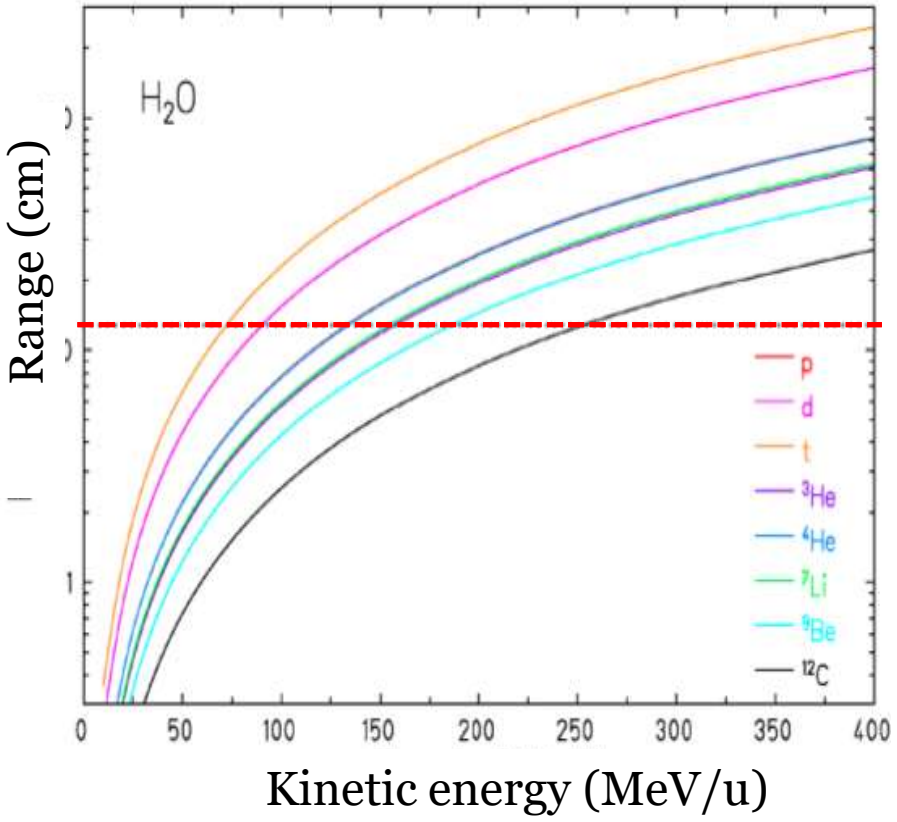
Actual dE/dx of heavy particles (z^2)





Increase with z in the needed energy to reach the same depth in water due to z^2 in the B.B.

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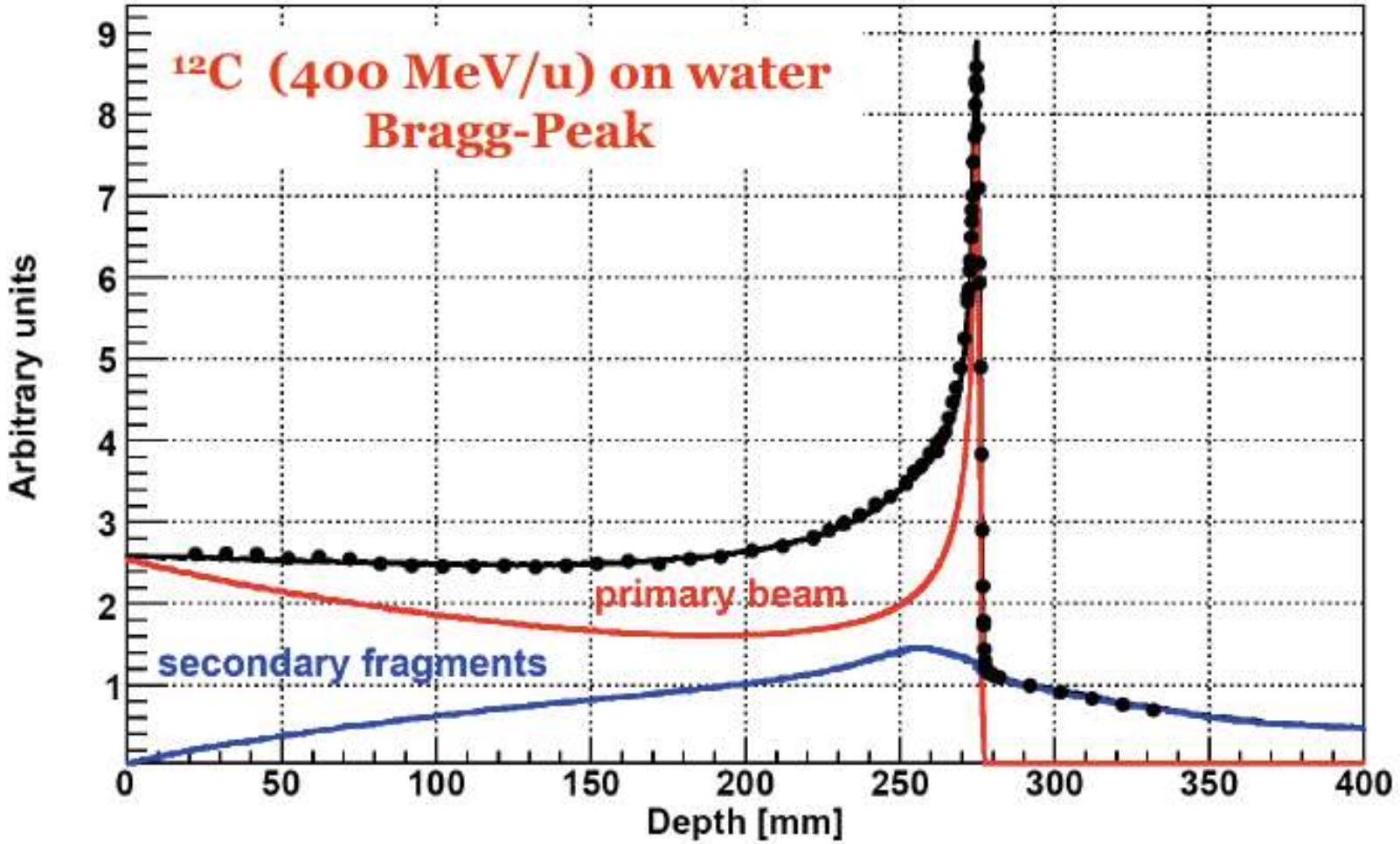
Ion Beam Therapy: ^{12}C ions Mixed Radiation Field



Exp. Data (points) from Haettner et al, Rad. Prot. Dos. 2006

Simulation: A. Mairani PhD Thesis, 2007, Nuovo Cimento C, 31, 2008

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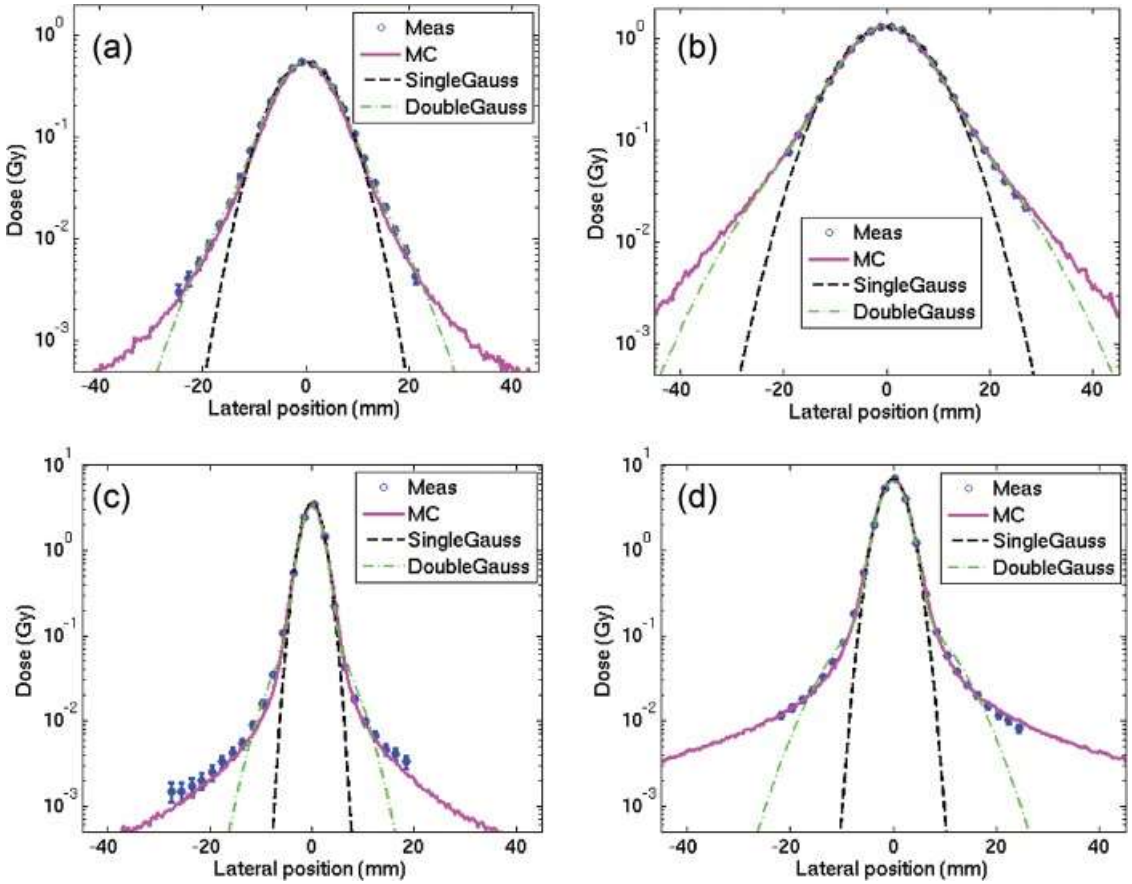
p vs ^{12}C ion lateral dose profiles

p 157.53 MeV/u

C 299.94 MeV/u



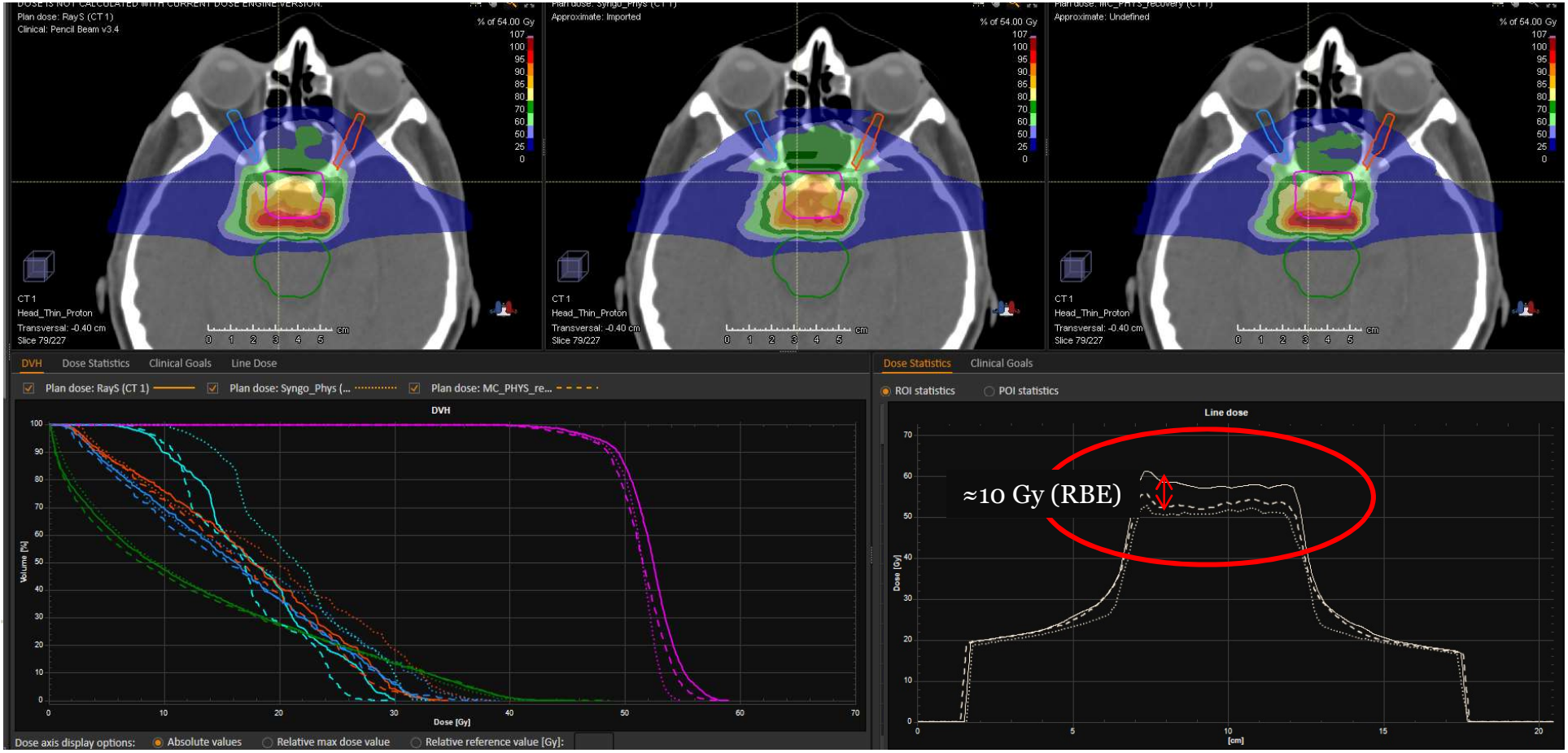
~1.5 cm in the entrance channel

~16.5 cm shortly before the Bragg peak

Parodi K et al. Radiat Res (54) 2013

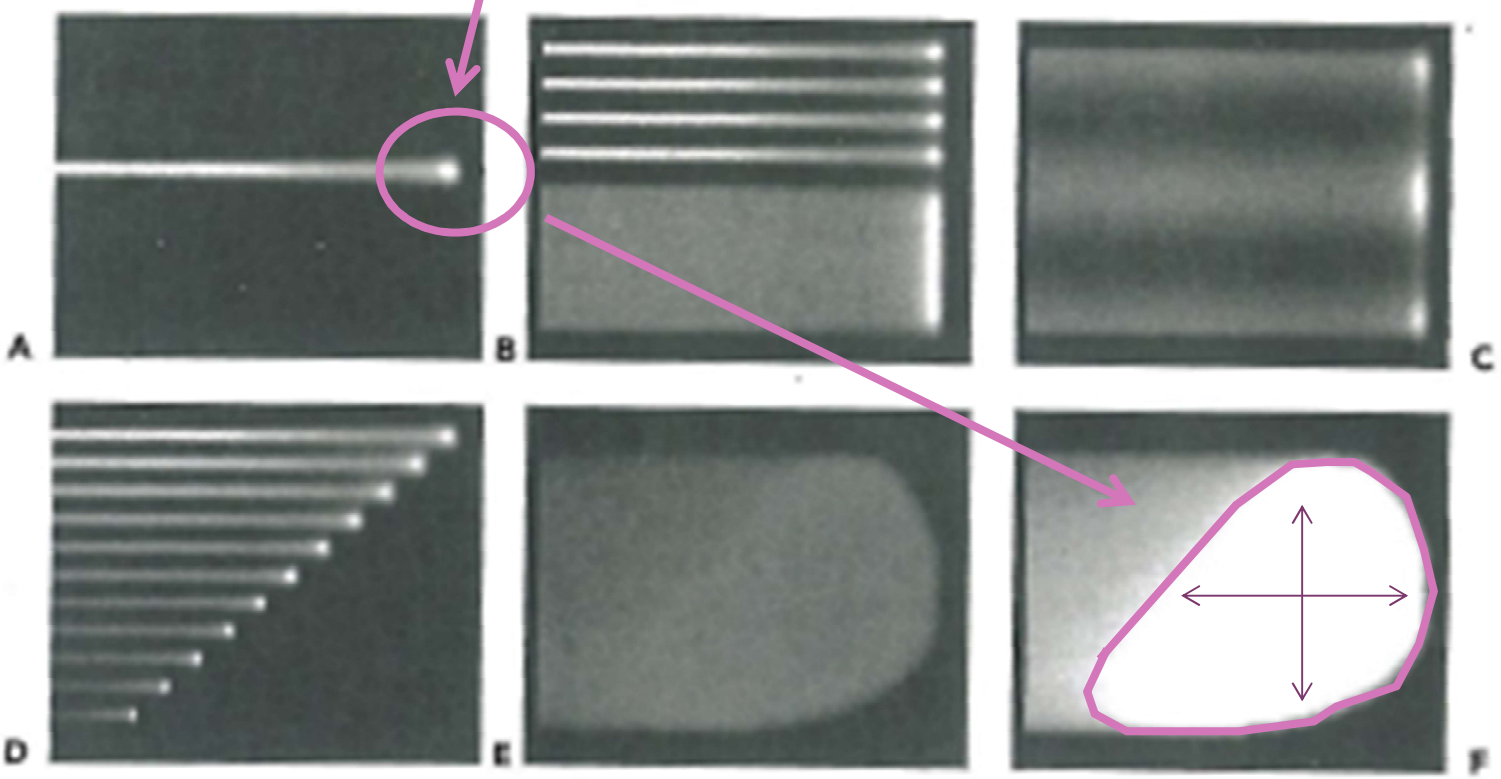
Protons Head case - 2 opposed fields (IMPT)

RayStation	Syngo (Siemens)	MC
19 sub-spots approx	Double Gaussian model	FLUKA simulation



Dose Delivery: Passive vs Active

The monoenergetic pencil beam is not enough



we need to spread the dose laterally and along the beam direction to cover a 3D target volume

DeLaney and Kooy
Proton and Charged Particle Radiotherapy; Lippincott Williams&Wilkins 2008

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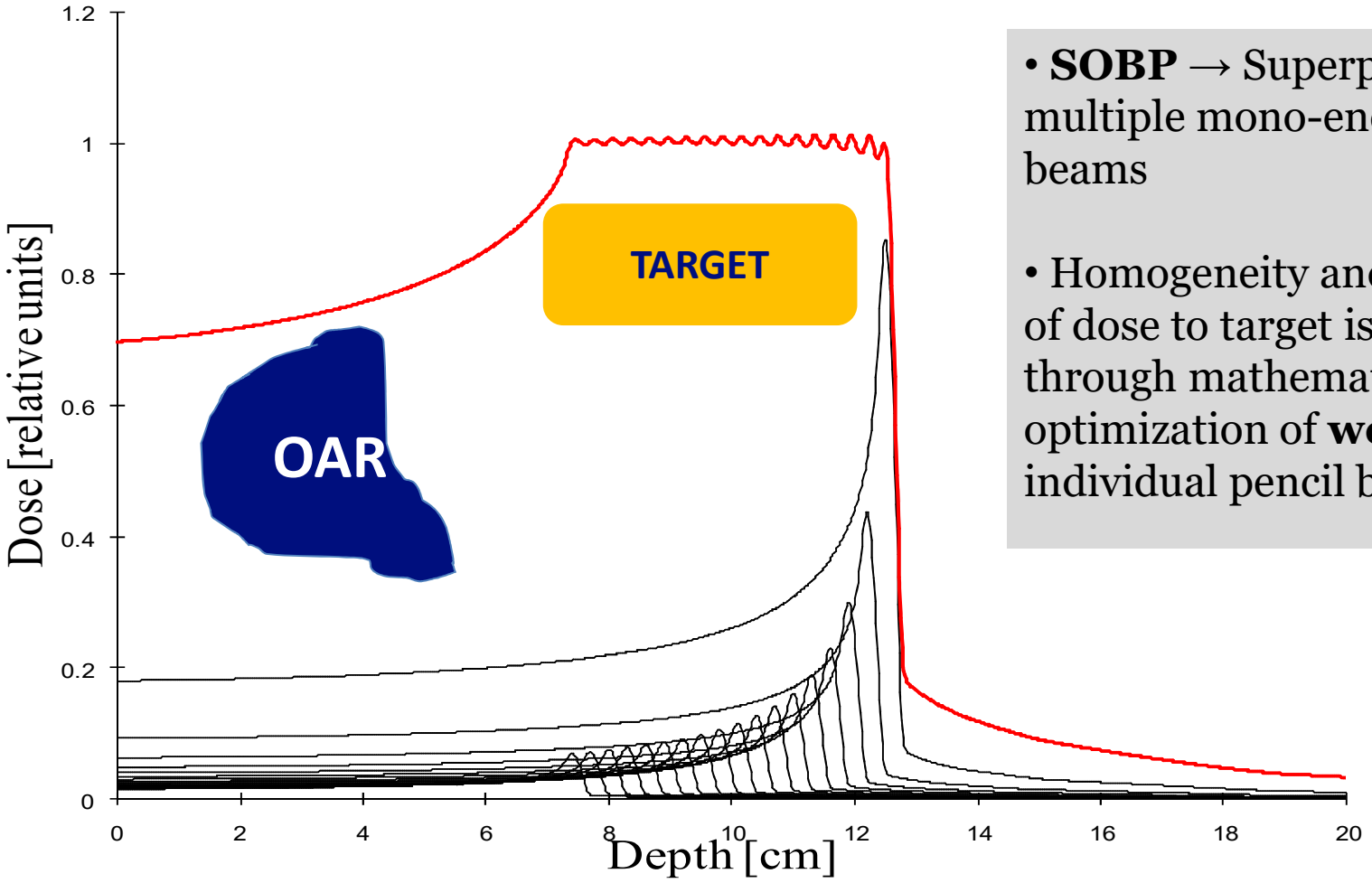
Longitudinal - Spread Out Bragg Peak



- **SOBP** → Superposition of multiple mono-energetic pencil beams

- Homogeneity and conformation of dose to target is achieved through mathematical optimization of **weights** of individual pencil beams

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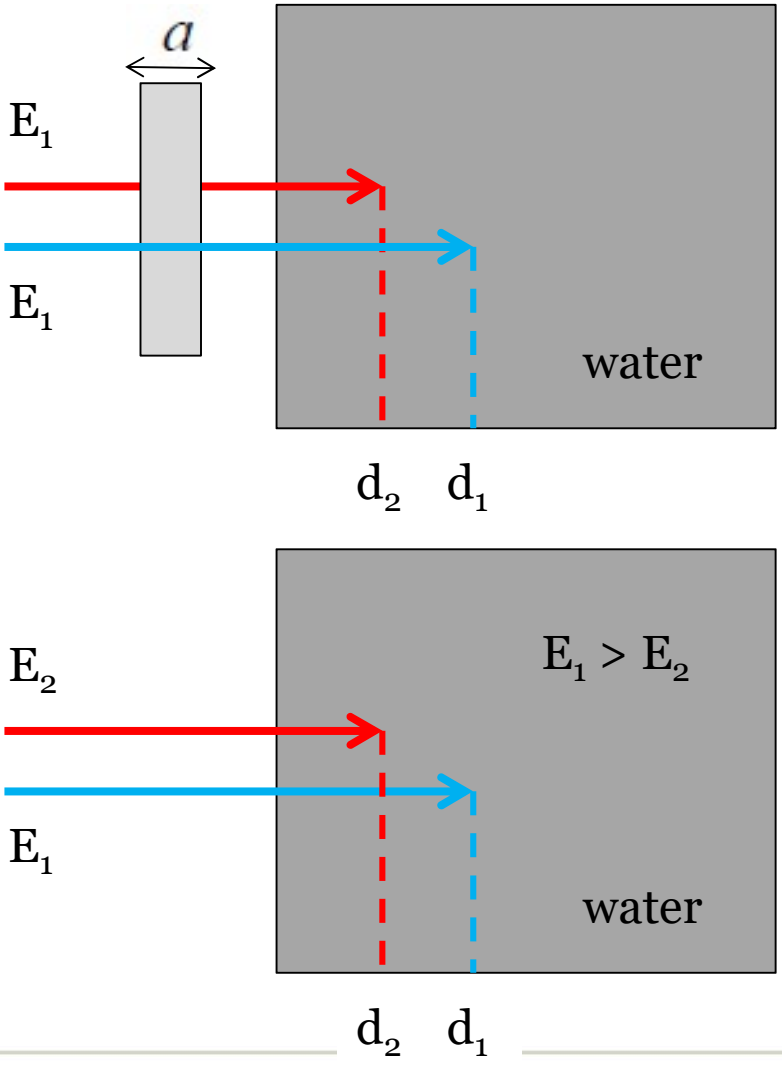
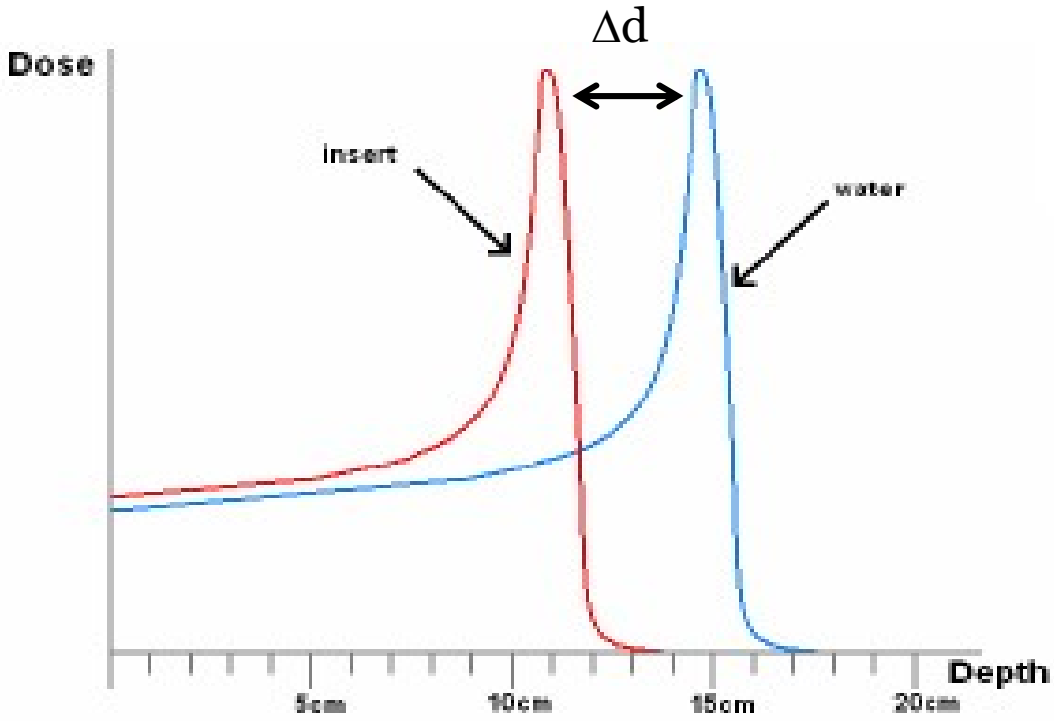
Longitudinal - Spread Out Bragg Peak



> a → < d

WEPL=Δd/a



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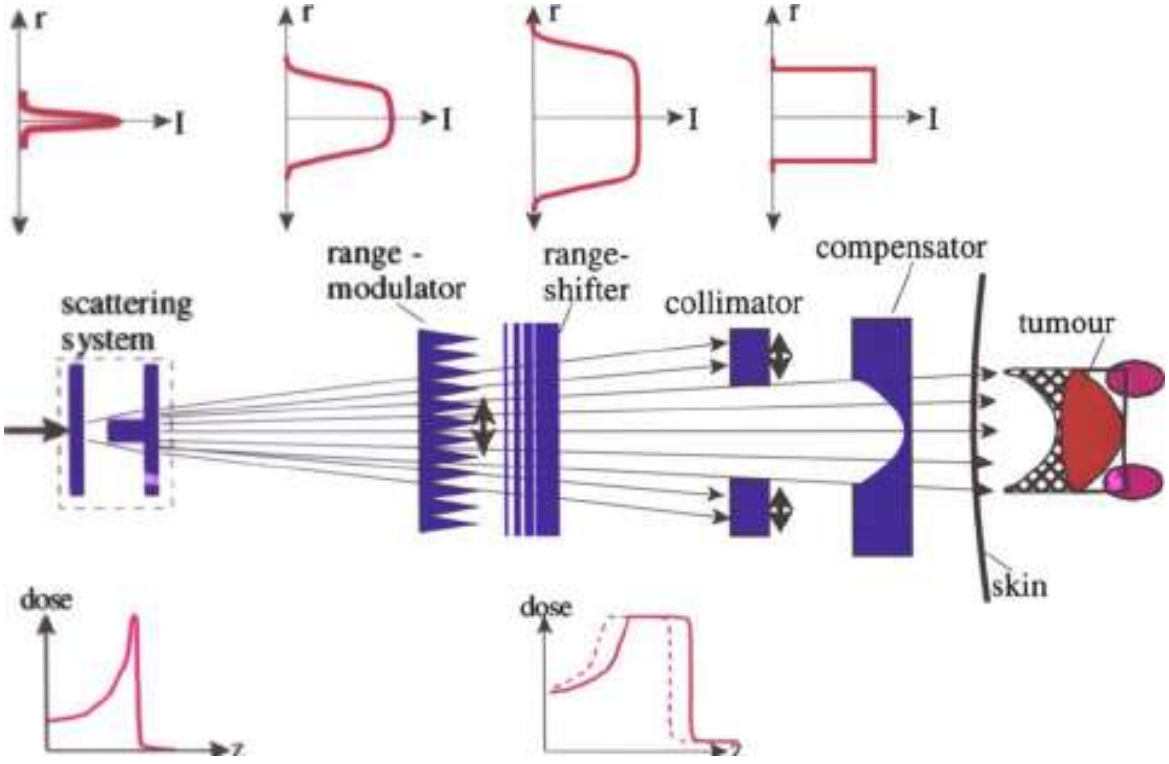
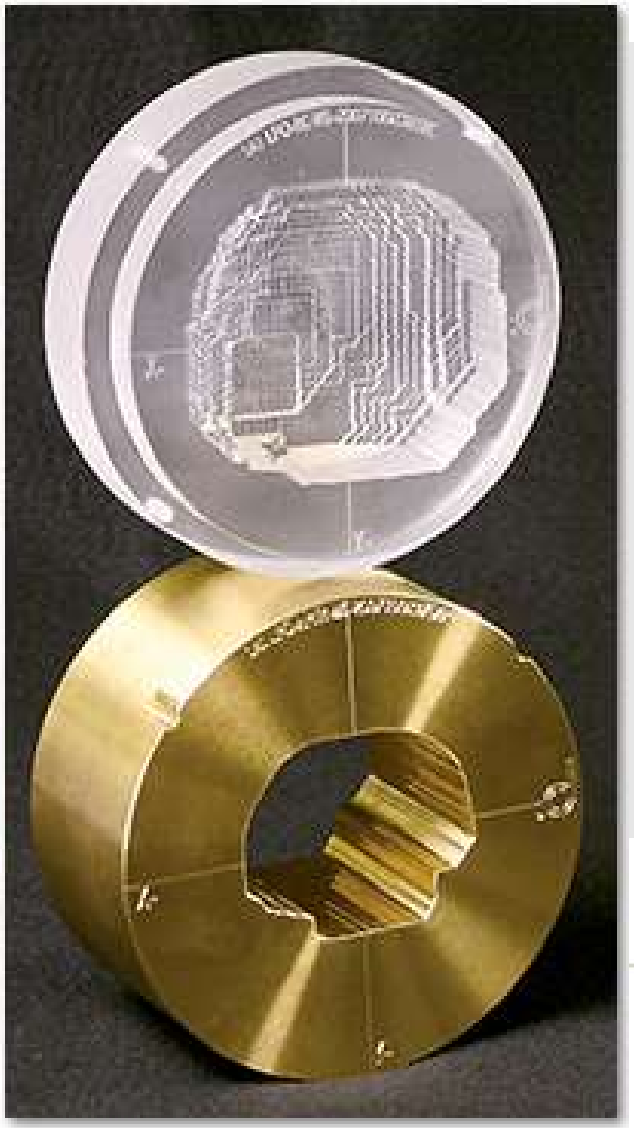
Dose Delivery: Passive

→ The complete target volume is irradiated nearly simultaneously

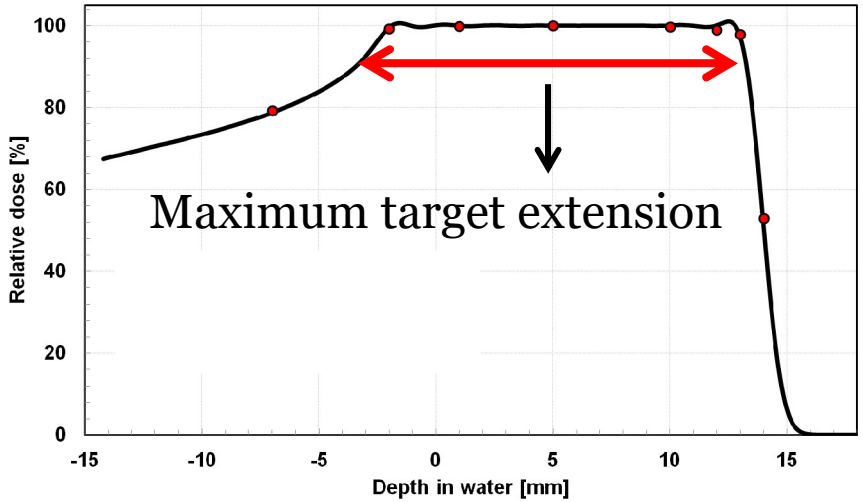




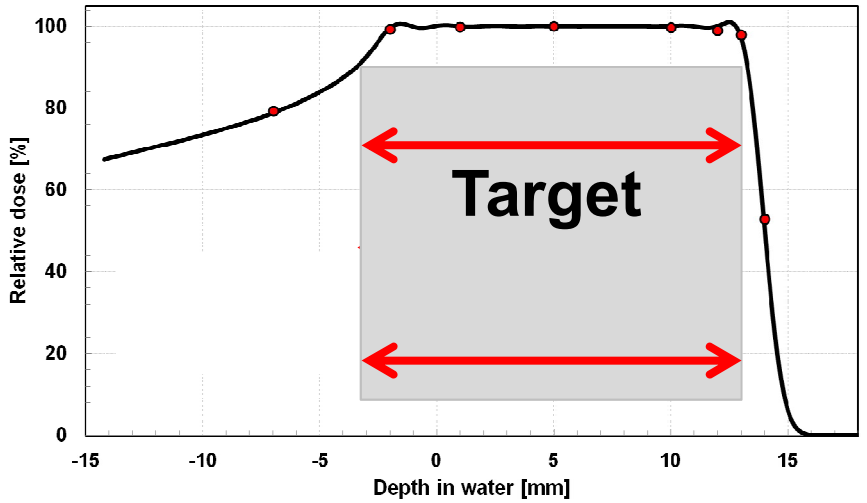
Shardt D et al Review of Modern Physics (82) 2010

Proximal dose modulation?

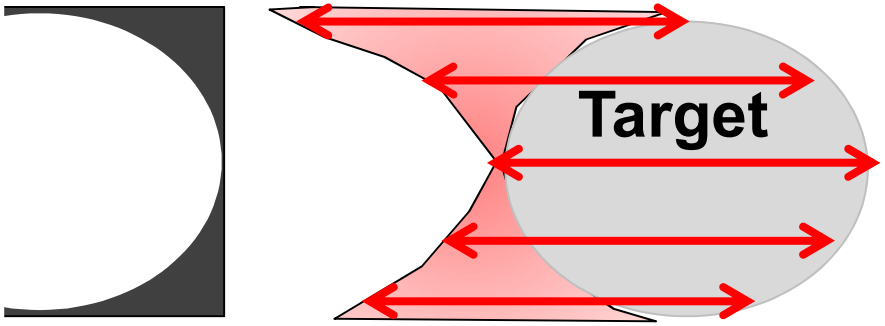
1) Create the SOBP of a **fixed** thickness with a specific ridge filter



2) Shift the SOBP to reach the distal target position with the required range shifter

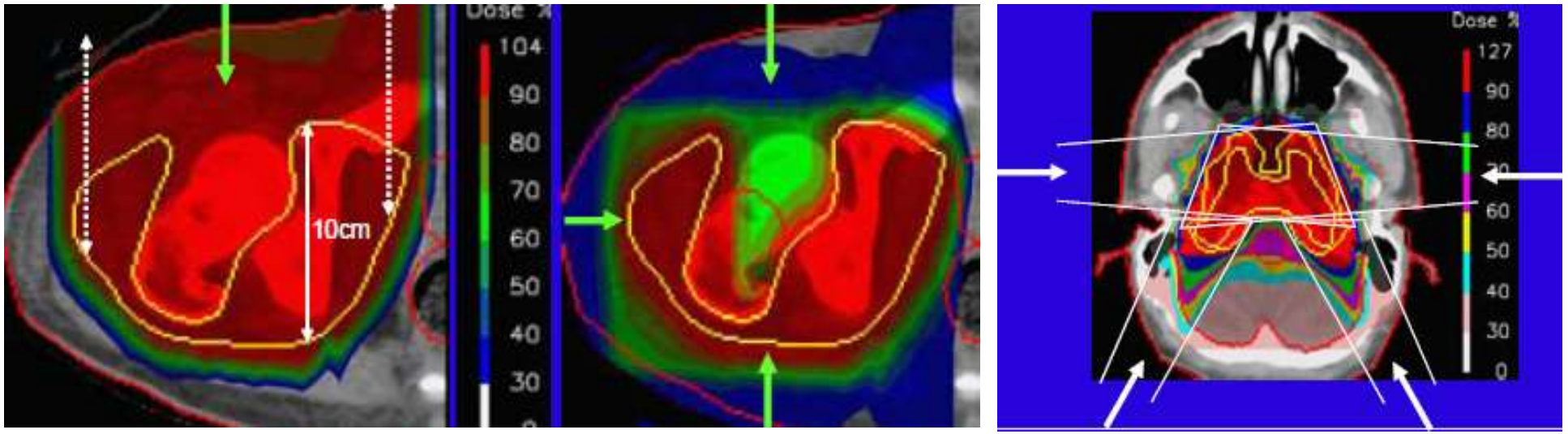


3) Modulate the SOBP with a beam-specific compensator to conform with the distal target shape



Dose Delivery: Passive ↔ 3DCRT

Single field Multiple fields Patch fields



Increase number of beams to improve dose conformity and OAR sparing

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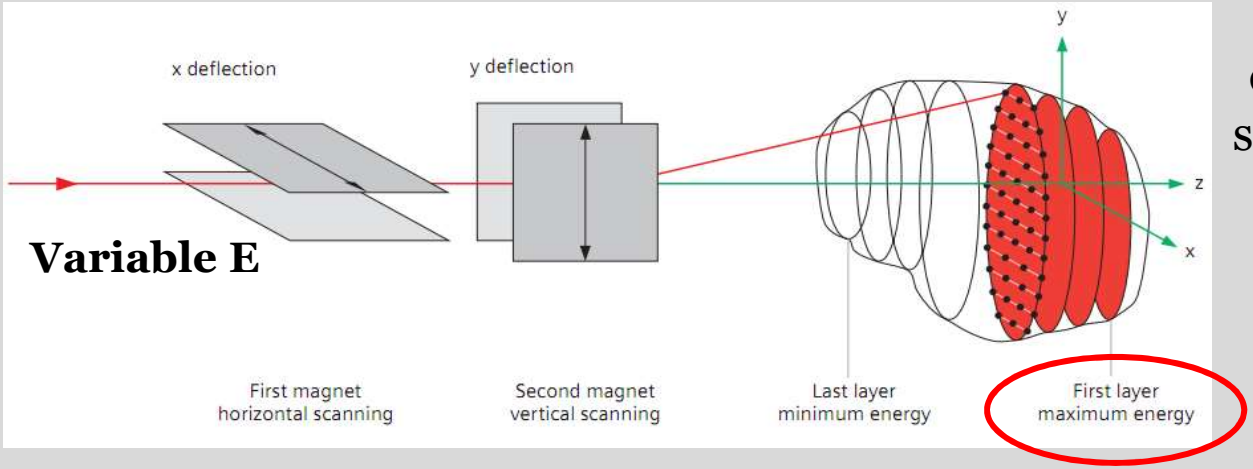
Dose Delivery: Active Scanning

→ The target volume is irradiated sequentially



3D dose distributions are dynamically obtained by the superposition of thousands of p/c "pencil" beams having different energies which are scanned across the target volume according to a **selected path.**

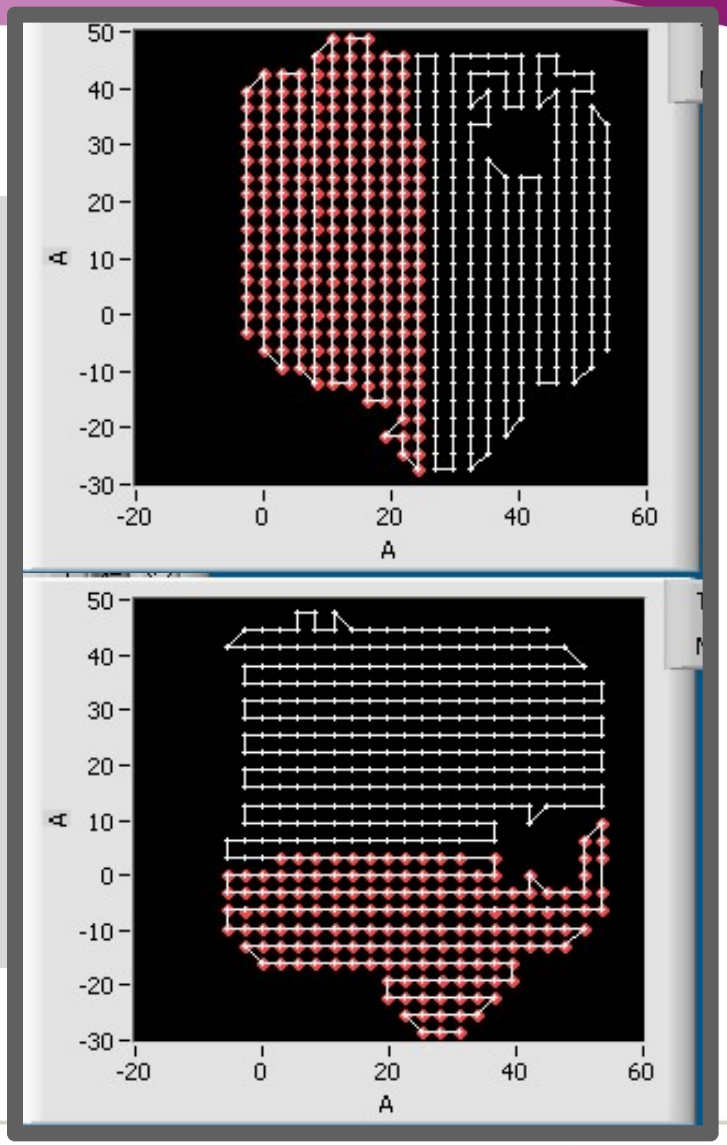
Iso Energy Slice (WE geometry) – Number of Particles per Spot

Lateral - Iso-Energy Slice

• The target is irradiated slice by slice moving the beam on a transversal plane (2D) through a scanning magnets system

• The active scanning follows a pre-calculated optimized path

• **NB:** A stable and precise beam monitoring system is required in order to control with a high frequency beam intensity, position and dimension



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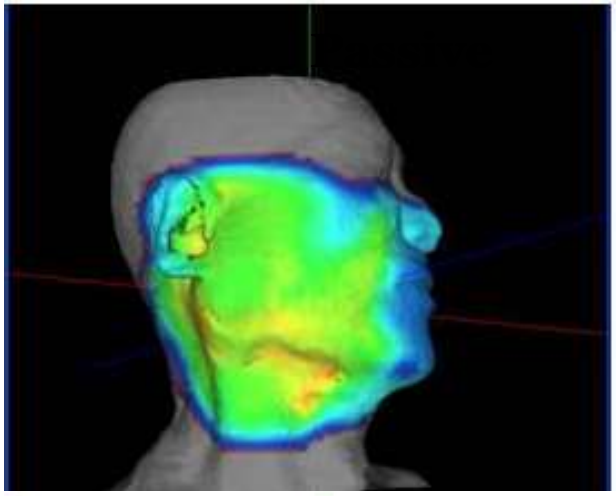
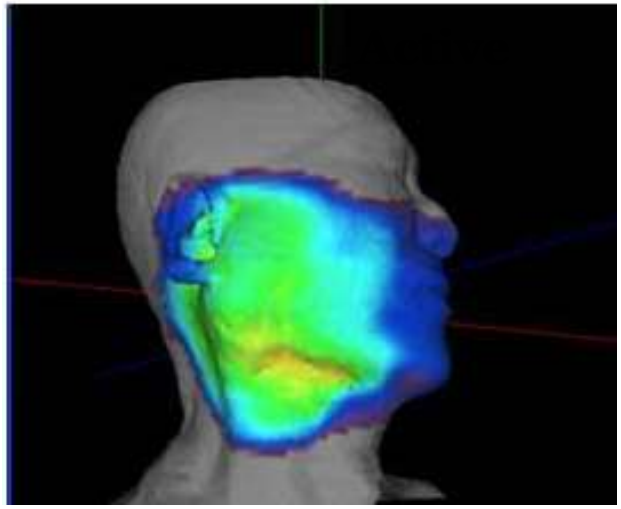
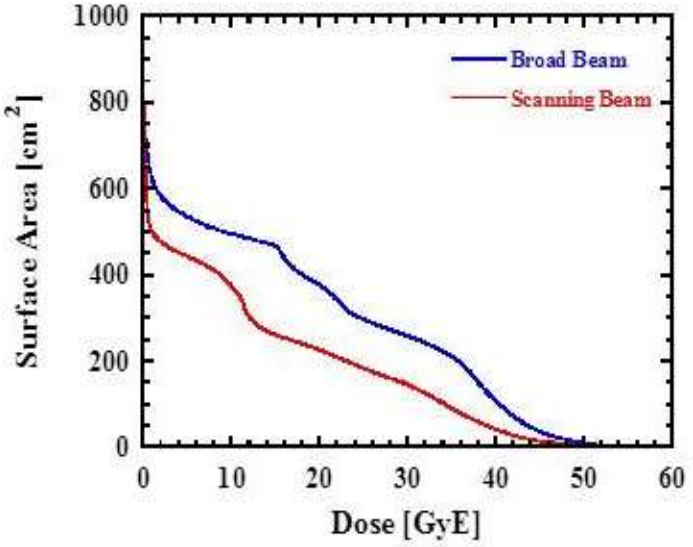
Passive vs Active: dose shaping





Proximal conformation

Skin Sparing



Dose-Surface Area Histogram

Courtesy of Dr Mizoe J, Nagoya Proton Therapy Center, Japan

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Active - Optimization

SFUD (Single field uniform dose optimization): intensities of pencil beams of each beam (number of particles per spot distribution) are optimized individually to deliver a uniform beam dose to the target volume and minimize the dose outside

IMPT (Intensity-modulated particle therapy): intensities of all beams are optimized simultaneously -> uses pencil beams or spots (from all beams) with individually optimized weights to balance the dose and dose-volume objectives of normal tissues and target volumes

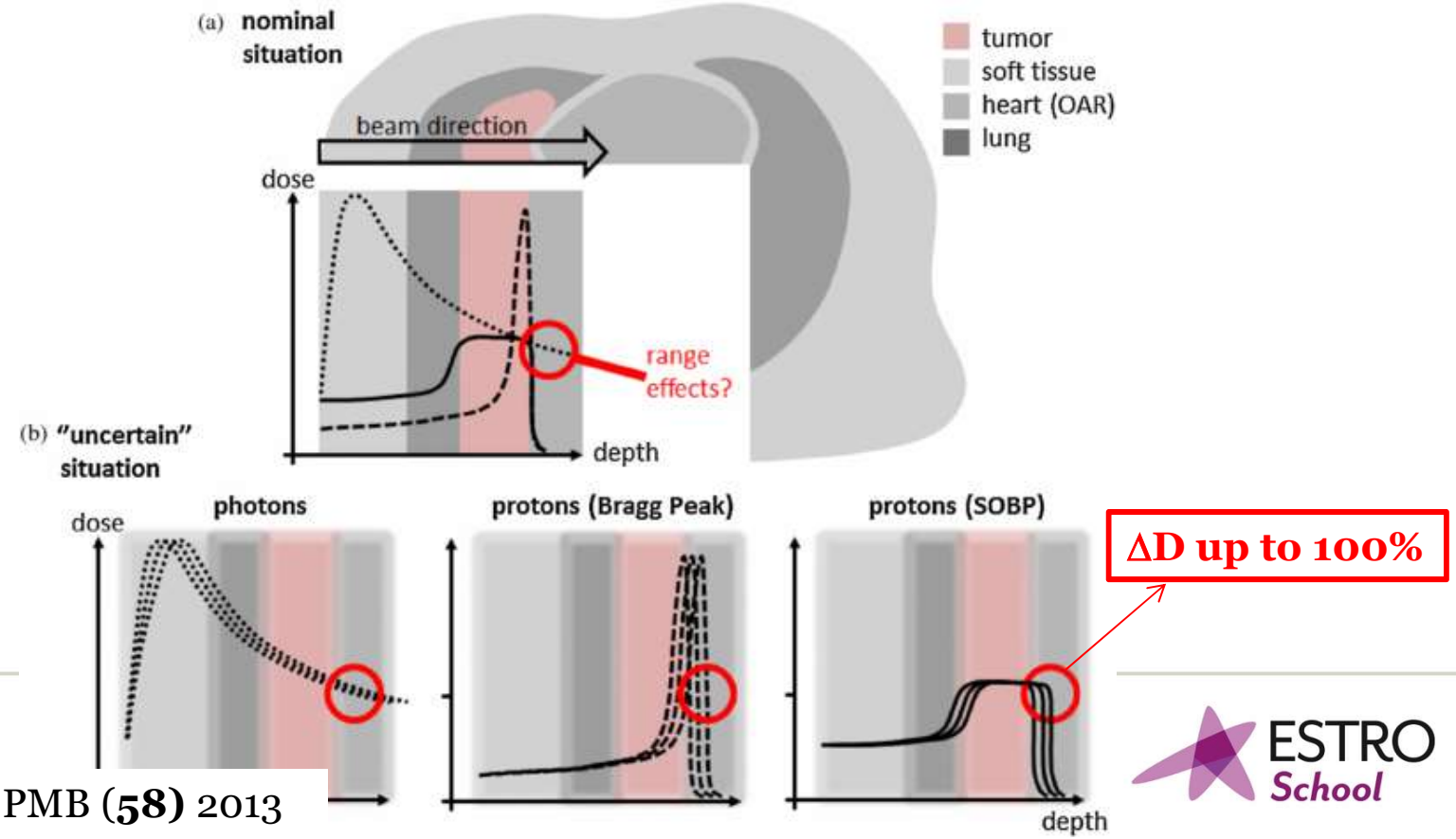
+ **Flexibility** of arbitrarily setting nonuniform intensities of pencil beams of a sequence of energies of multiple beams incident from different directions

- Intensities of spots (and dose distribution) per beam can be highly inhomogeneous -> Higher **sensitivity** to range, set-up and treatment delivery uncertainties

Influence on the radiological pathlength

Moving anatomical districts with strong inhomogeneities may cause variation in BP deposition → Particles stop before/beyond the expected position.

→ Uncorrect Dose Distribution



Knopf and Lomax PMB (**58**) 2013

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Issues?

How to manage uncertainties?
Can we use the PTV concept?

- In particle therapy target alignment is only a partial solution!

- PTV works for photons since the spatial nature of photon dose distributions is minimally perturbed by uncertainties –(Maleike et al PMB 2006)
  Hp: the CTV will BE 95% of the times INSIDE the PTV →the PTV dose distribution and DVH are the worst case scenario for the CTV

- Patient misalignment + density heterogeneities → **dose SHIFT+ DISTORSION**

  → Particle dose distribution is significantly perturbed (DEFORMED) not only distally or proximally, but within and outside the target volume
  → The PTV-based optimization do not consider **range uncertainties.** It considers setup uncertainties implicitly but ignores the deformation of dose distributions caused by them.

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Robust Optimization

Aim Mitigate the influence of uncertainties in IMPT and limit dose degradation due to un-intended range variations

How Include uncertainties in the optimization process

Robust optimization Errors in patient positioning (setup errors) and range errors are explicitly included in plan optimization, optimizing the expected value or worst-case value of the objective function or individual objectives
NB the optimization target is the CTV

E.g. Worst case scenario – minimizes the penalty of the worst scenario (among a limited number of error scenarios), with no regards to the probabilities of the scenarios. It may result in overlay conservative plans

Price of robustness? OARs dose, but could be better than the PTV approach

Robust evaluation: Incorporate the impact of uncertainties when evaluating an IMPT plan

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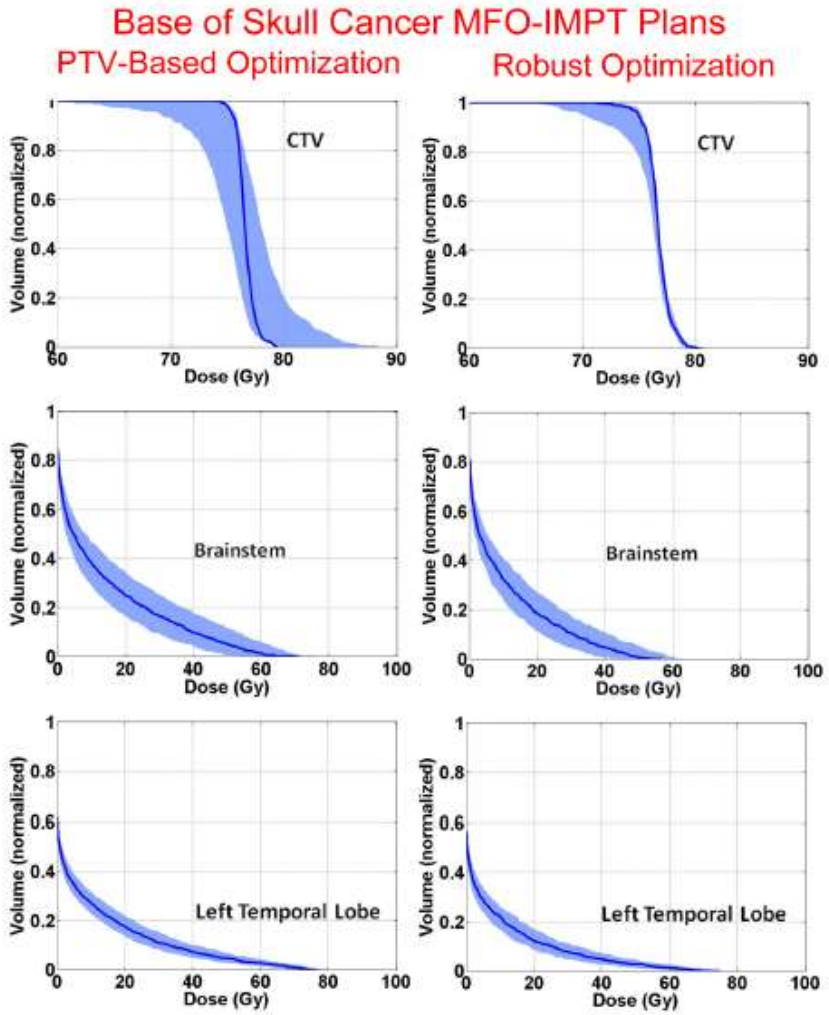
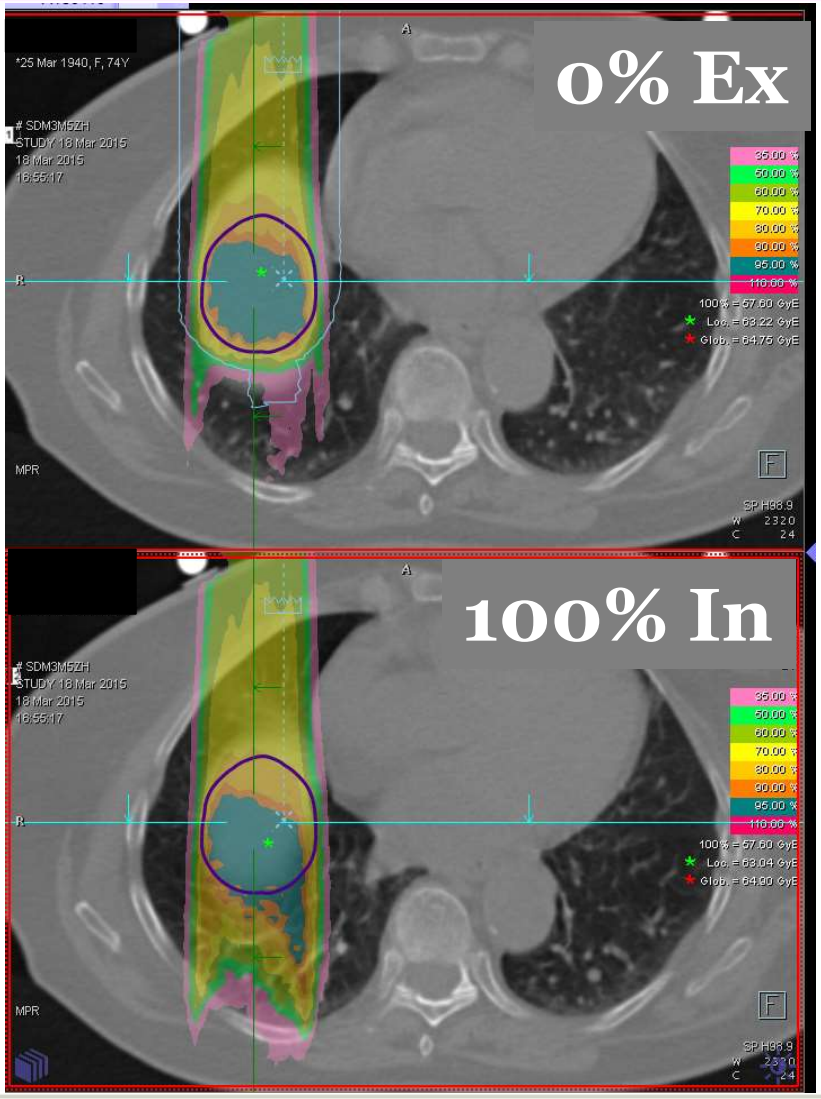
Sensitivity to uncertainties

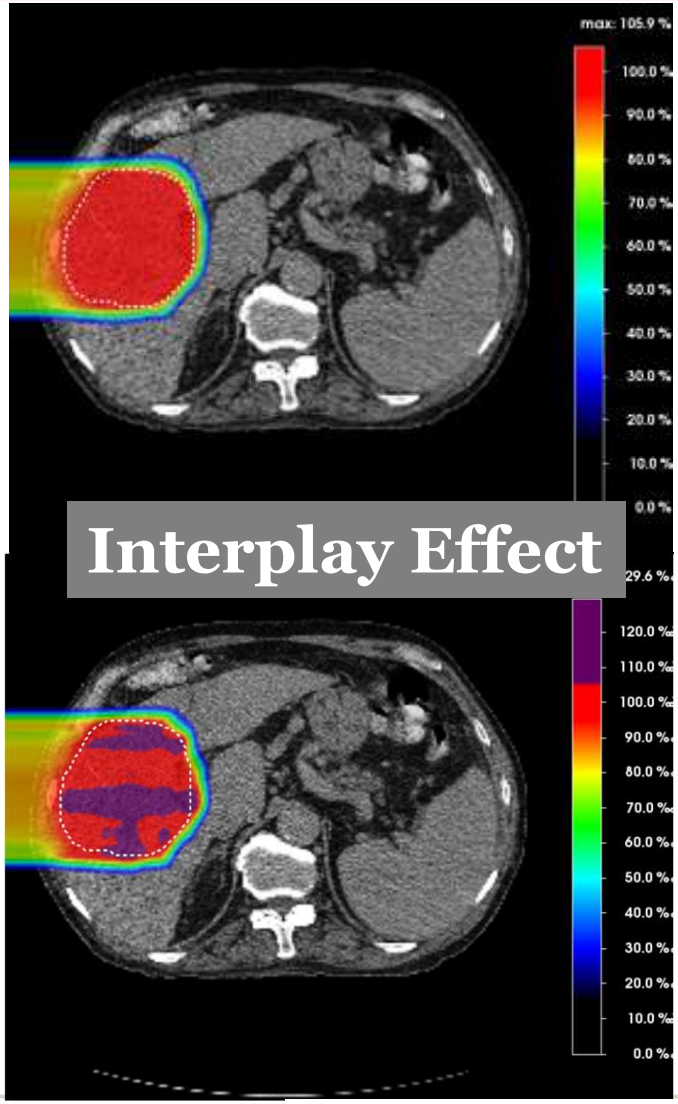
- Families of DVHs covering all setup and proton range uncertainties considered
- Bands are an effective measure of the sensitivity to uncertainty → the wider the band, the greater the sensitivity
- Solid lines are DVHs for the nominal dose distribution
- CTV coverage for the robustly optimized plans is less sensitive to uncertainties



Liu et al. Med Phys 2012 (39)

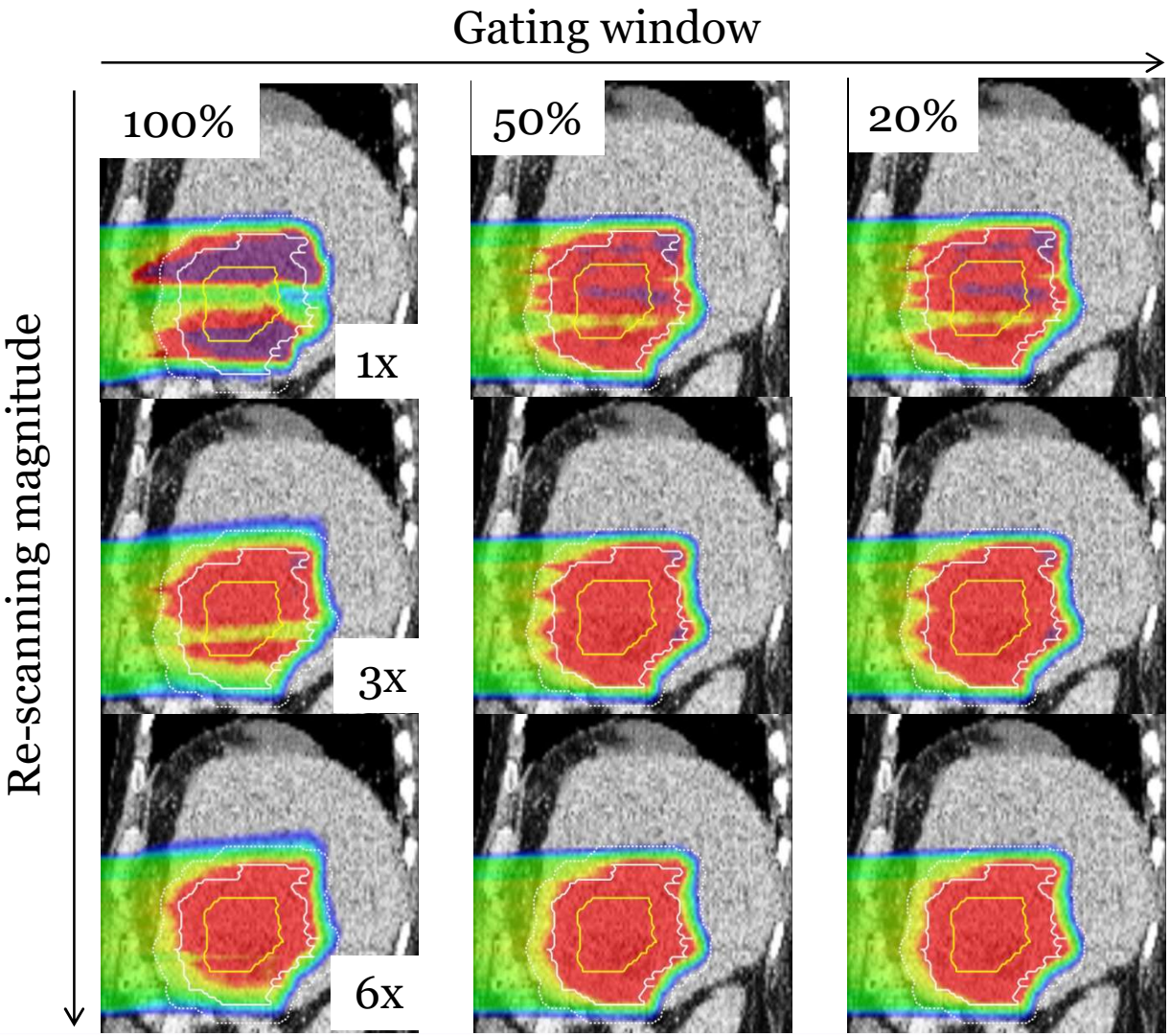
Organ motion





Boye et al, Med. Phys. 40, 2013

Motion mitigation – Gating and Re-scanning



Ye Zhang, PhD thesis, PSI, 2013 – Tony Lomax ESTRO course Particle Therapy

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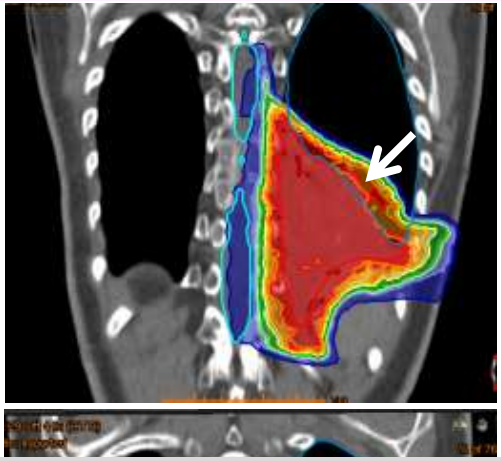
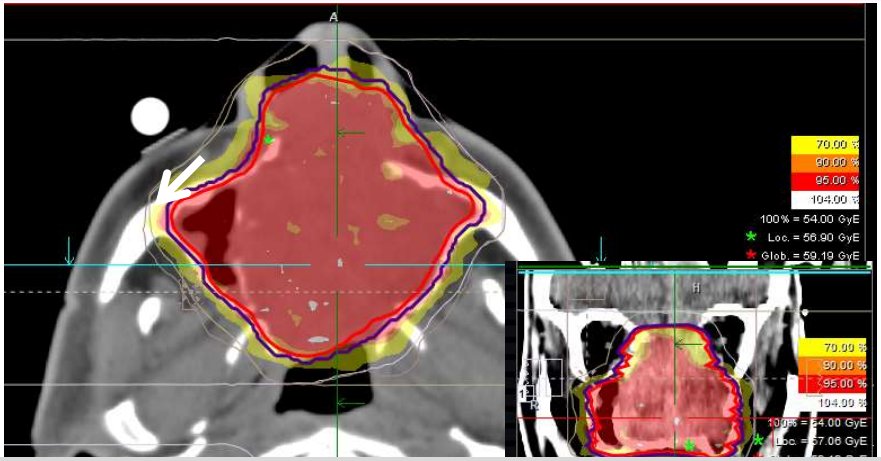
Anatomical changes – Influence on the radiological path length

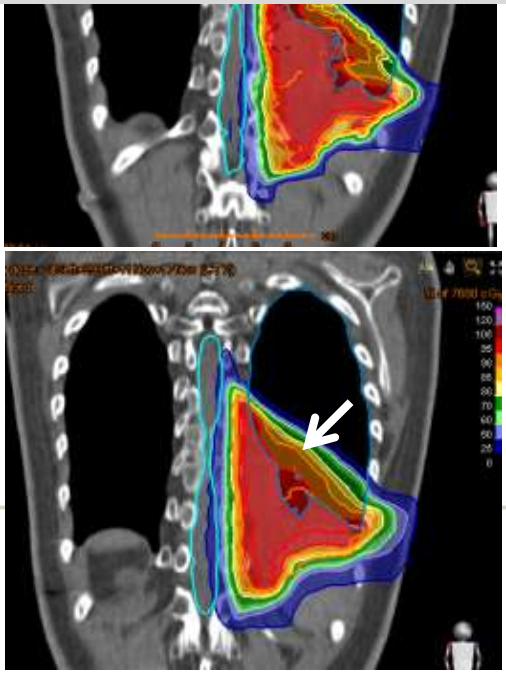
GTV
437.29 cc

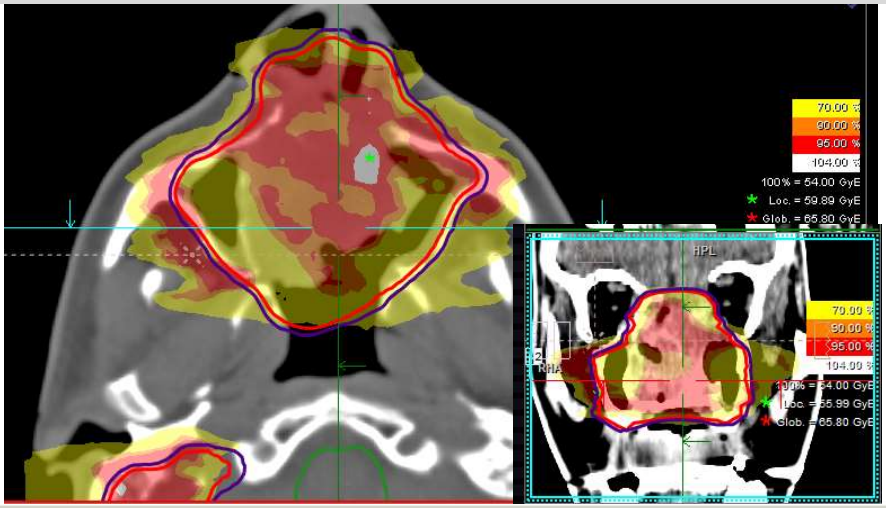




Nodal linkage

You need to replan!





Tumor

GTV
329.14 cc

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Relative Biological Effectiveness (RBE) - particles

RBE-weighted Dose (Gy (RBE)) = Absorbed Dose (Gy) x RBE

$$\mathbf{RBE} = \left. \frac{D_{(\text{Co-60; 250kV})}}{D_{(\text{p-ions})}} \right|_{\text{Biological effect (cell inactivation)}}$$

RBE is the ratio of the dose of photons, e.g., ^{60}Co-rays or linear accelerator X-rays, relative to that of protons/ions required to produce a defined biologic response

RBE is a function of LET, Z, cell type, dose, endpoint

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Protons Gy (RBE) – constant value ICRU 78 - 2007

Protons → D_{eff} (Gy (RBE))= D_{abs} (Gy) x 1.1

All protons are equal

→ the RBE of protons is 1.1

(independent on LET, dose, end point, α/β)…

- Available evidence → the magnitude of RBE variation with treatment parameters is small relative to our abilities to determine RBE.
- There is agreement that there is a measurable increase in RBE over the terminal few millimeters of the SOBP, which results in an extension of the bio-effective range of the beam in the range of 1–2 mm.

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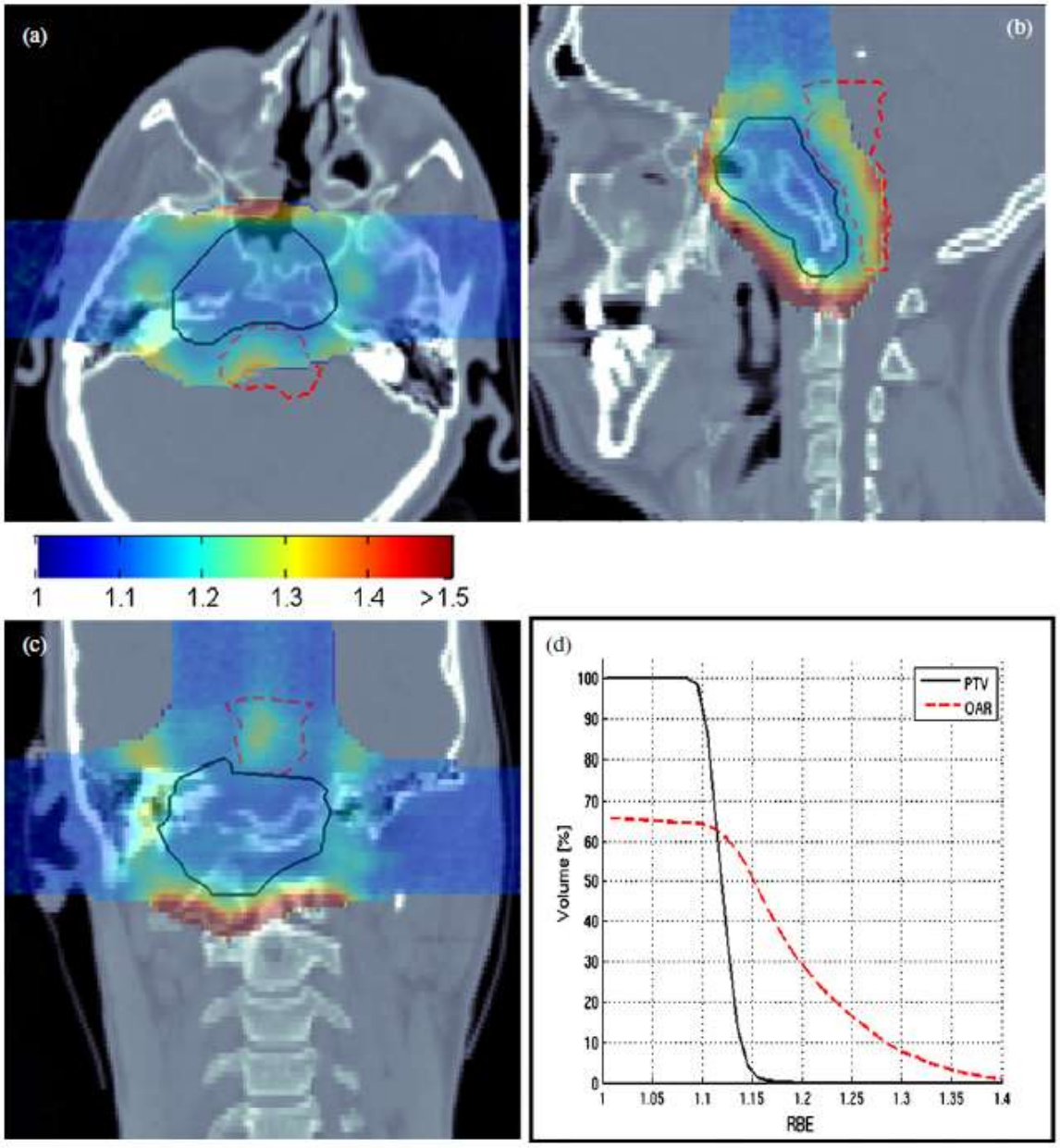
Protons Gy (RBE) – constant value

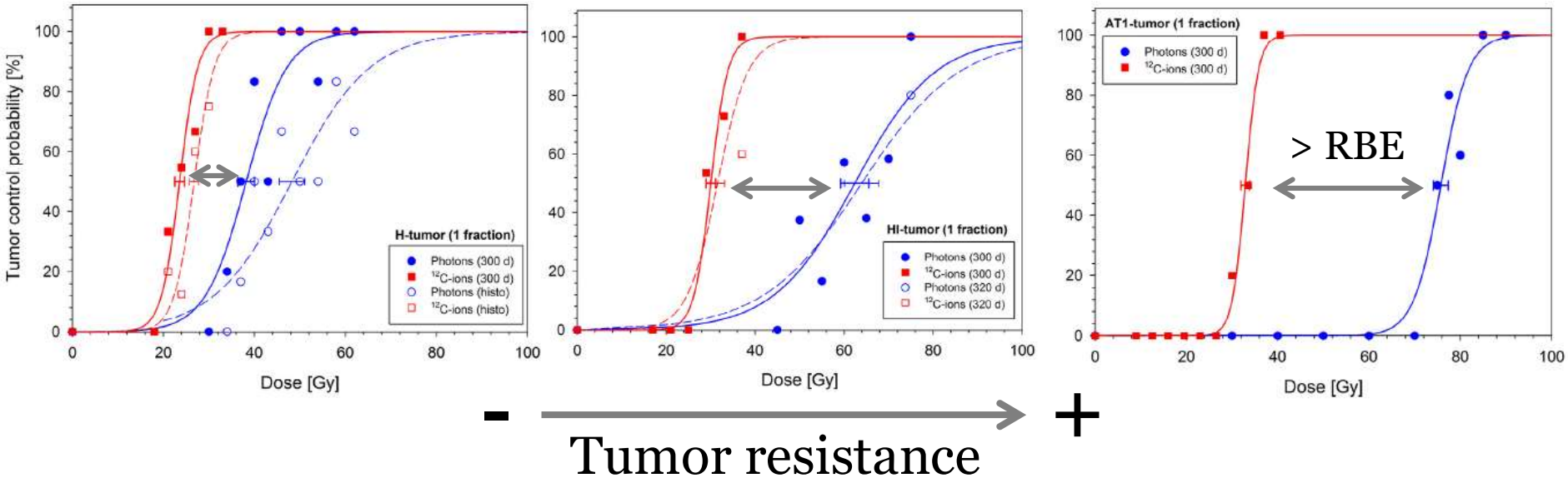


RBE as predicted by LEM for absorbed doses larger than 10% of prescribed dose

Mairani et al. PMB (58) 2013

Carbon ions effectiveness

In-vivo Local control of 3 sublines of prostate carcinoma after 1 fx of photons and C-ions



- The response to C-ions is less dependent on resistance factors as well as on heterogeneity between and within tumor sublines as compared to photons.
- Correlation between decreasing differentiation status and increasing RBE.

Glowa et al. Cancer Letters (378) 2016

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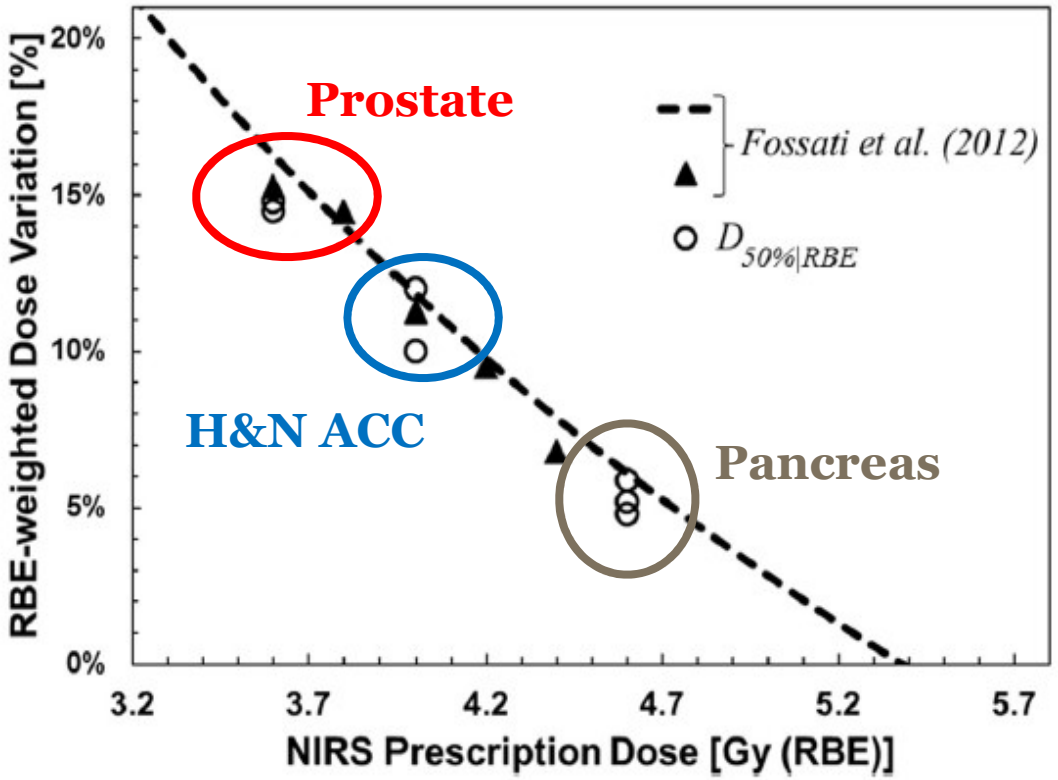
Carbon ions Gy (RBE) – 3D Radiobiological Model ?

→ same effectiveness of carbon ion beams
→ same physical dose distribution
→ different RBE model

RBE-weighted dose differences can range from **15% to 5%** depending on the dose level

Target median RBE-weighted dose difference Japanese vs European RBE adopted models



Molinelli et al. R&O 2016

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Credits to

Giorgio Baiocco (UniPV)
Tony Lomax (PSI)
Andrea Mairani (CNAO and HIT)

University
Protonen Therapy
Dresden

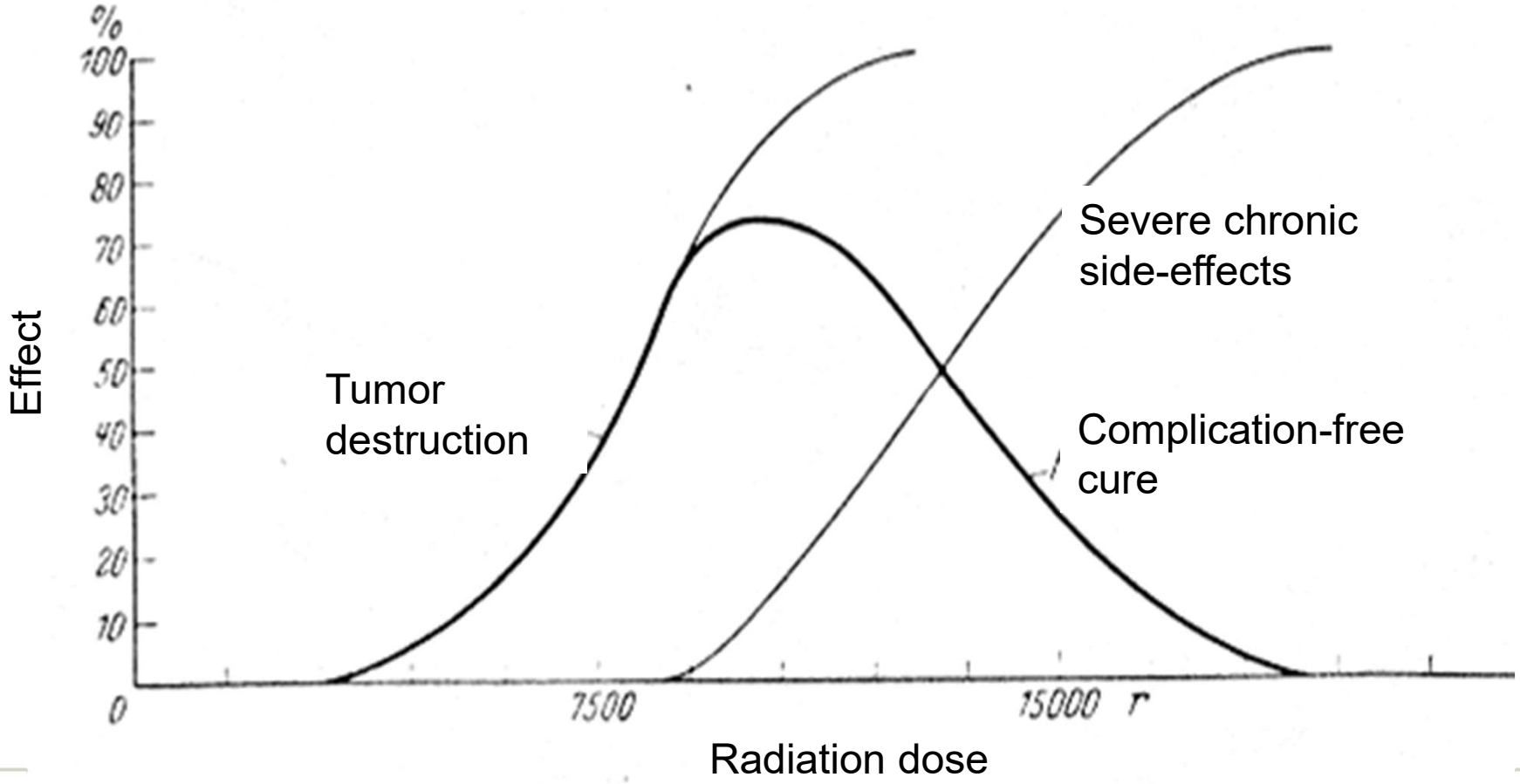
Clinical aspects and evidence for particle therapy and other novel technology

Esther Troost, MD PhD

Bucharest, June 2017

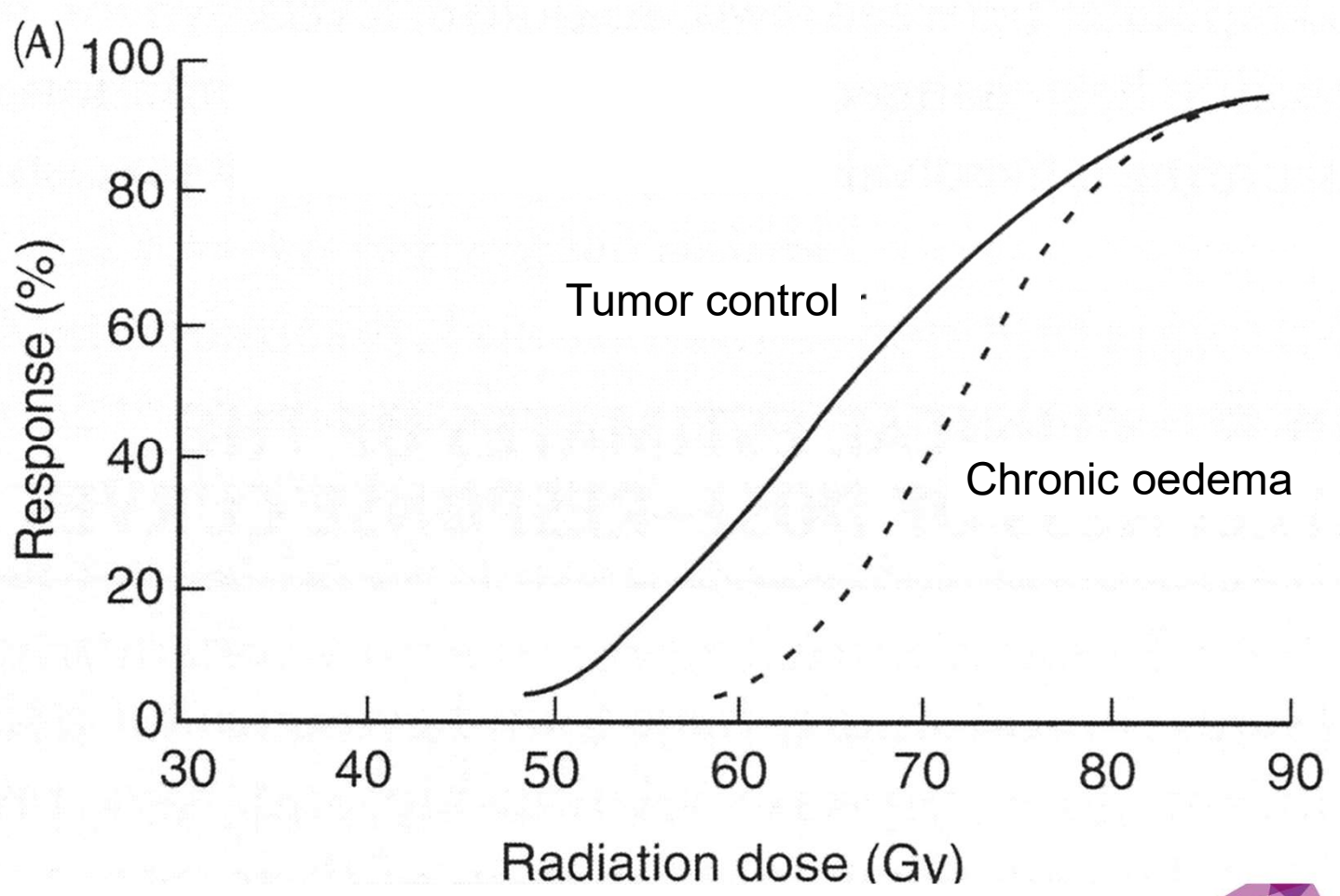
OncoRay Radiation Research in Oncology
HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF
KREBSCENTRUM DRESDEN
NCT
ESTRO School

Goal in RT: cure with little complications



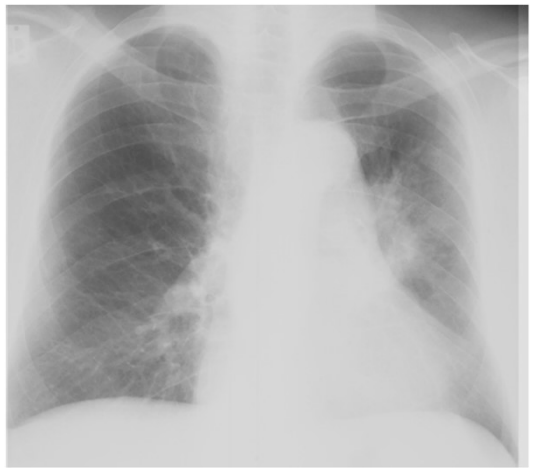
Holthusen, *Strahlentherapie* 57: 254-268,1936

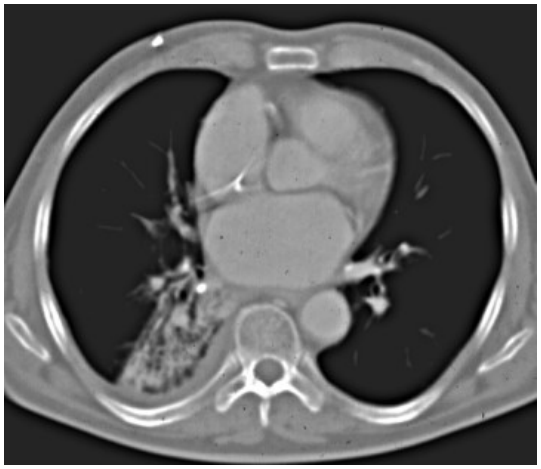
NTCP increases more rapidly than TCP

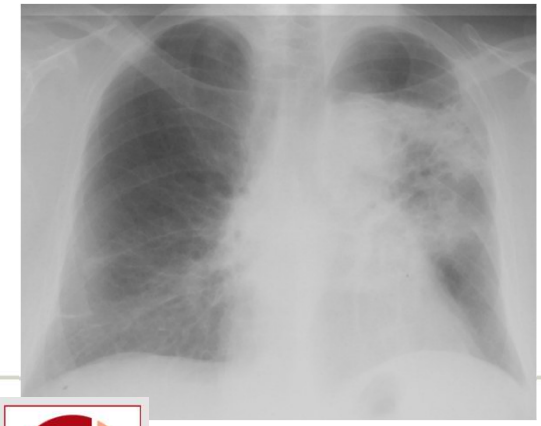


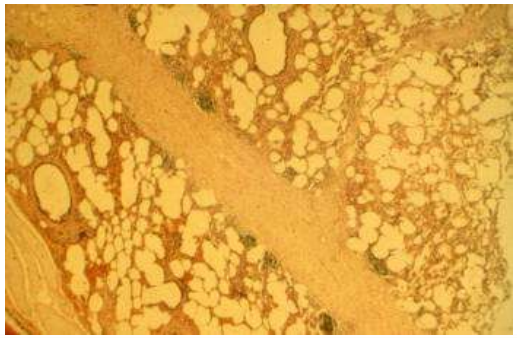
Overgaard et al., *Acta Oncol* 1988; Bentzen, *Basic Clinical Radiobiology*: 94-104, 2002

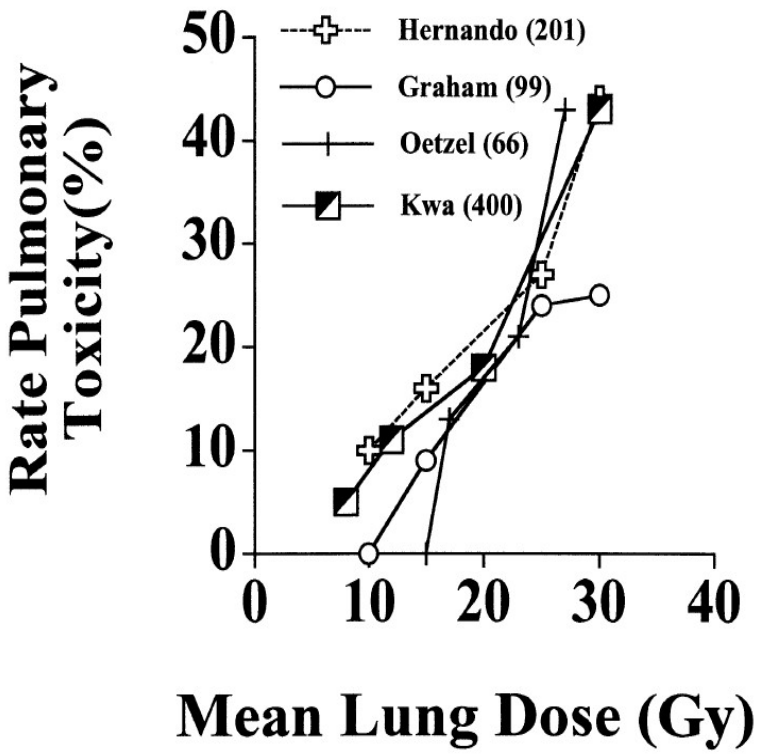
NTCP increases with increasing volume











Hernando et al., *IJROBP*, 2001

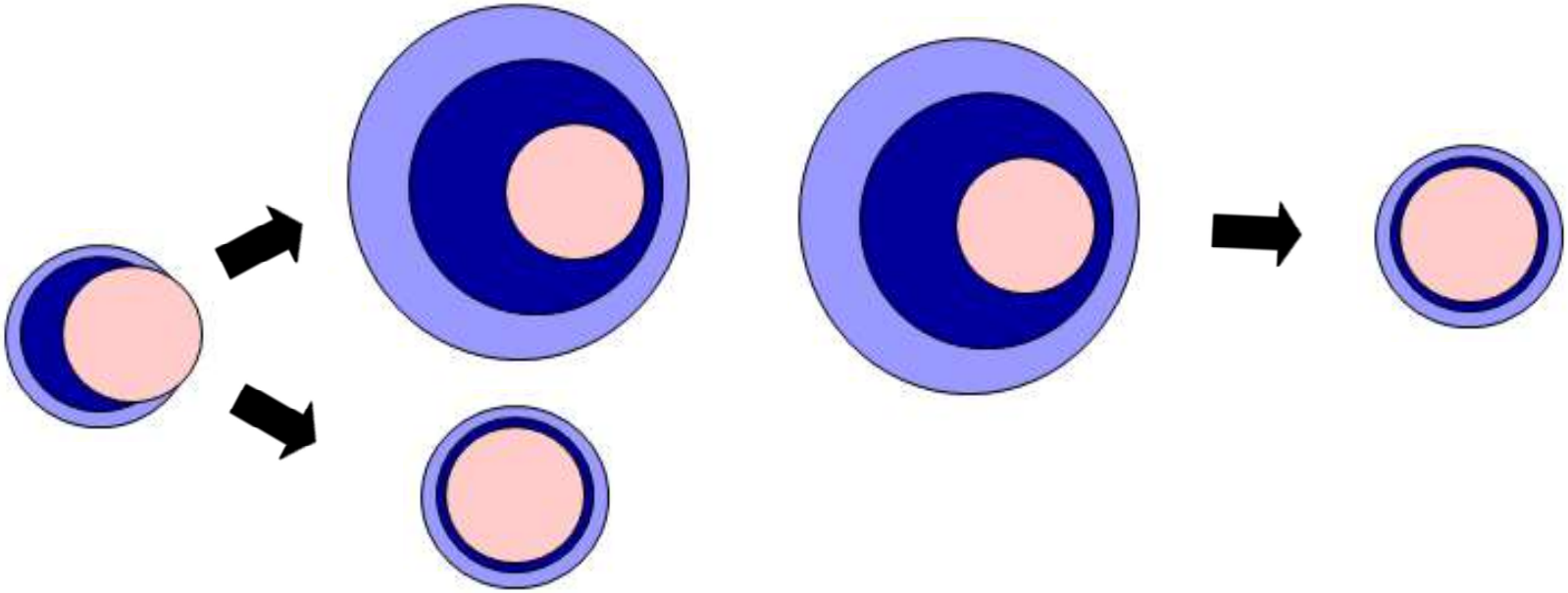
How much volume needs to be irradiated?

Tumor

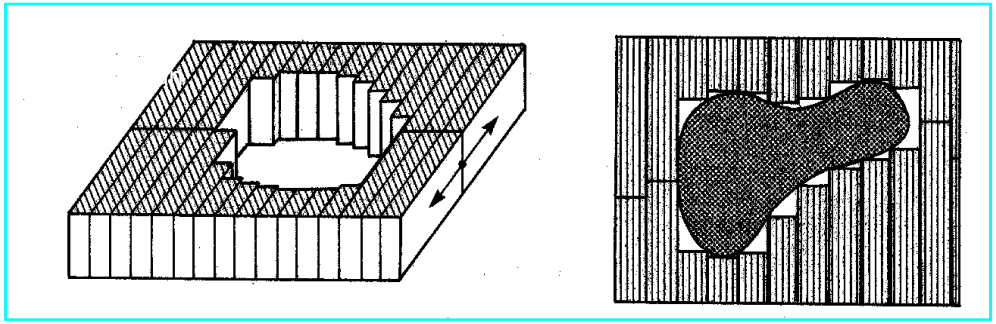
- Highest dose possible
- Hitting the target volume

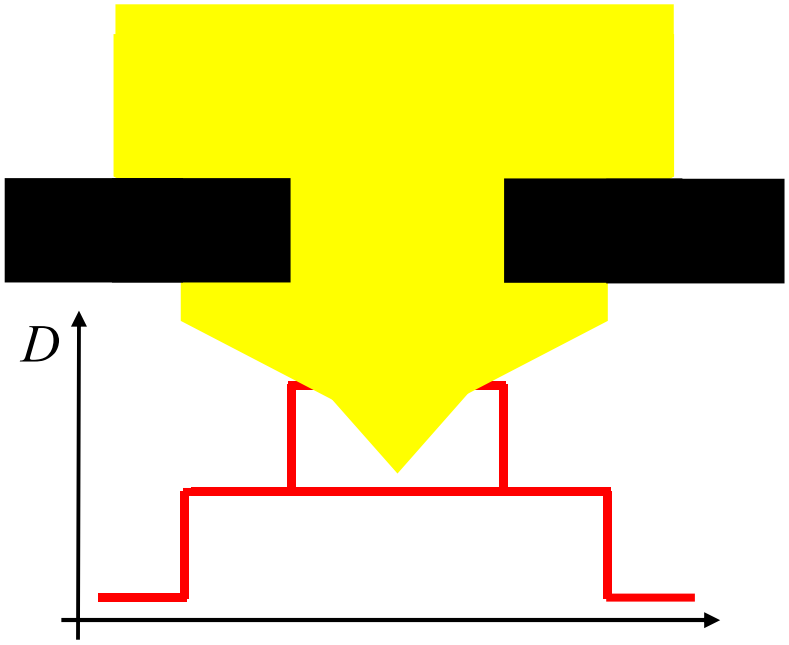
Normal tissues

- Lowest dose possible
- Smallest volume possible



Photon irradiation with LINAC





Krieger: Strahlenphysik, Dosimetrie und Strahlenschutz, Band 1: Grundlagen, Teubner, 1998

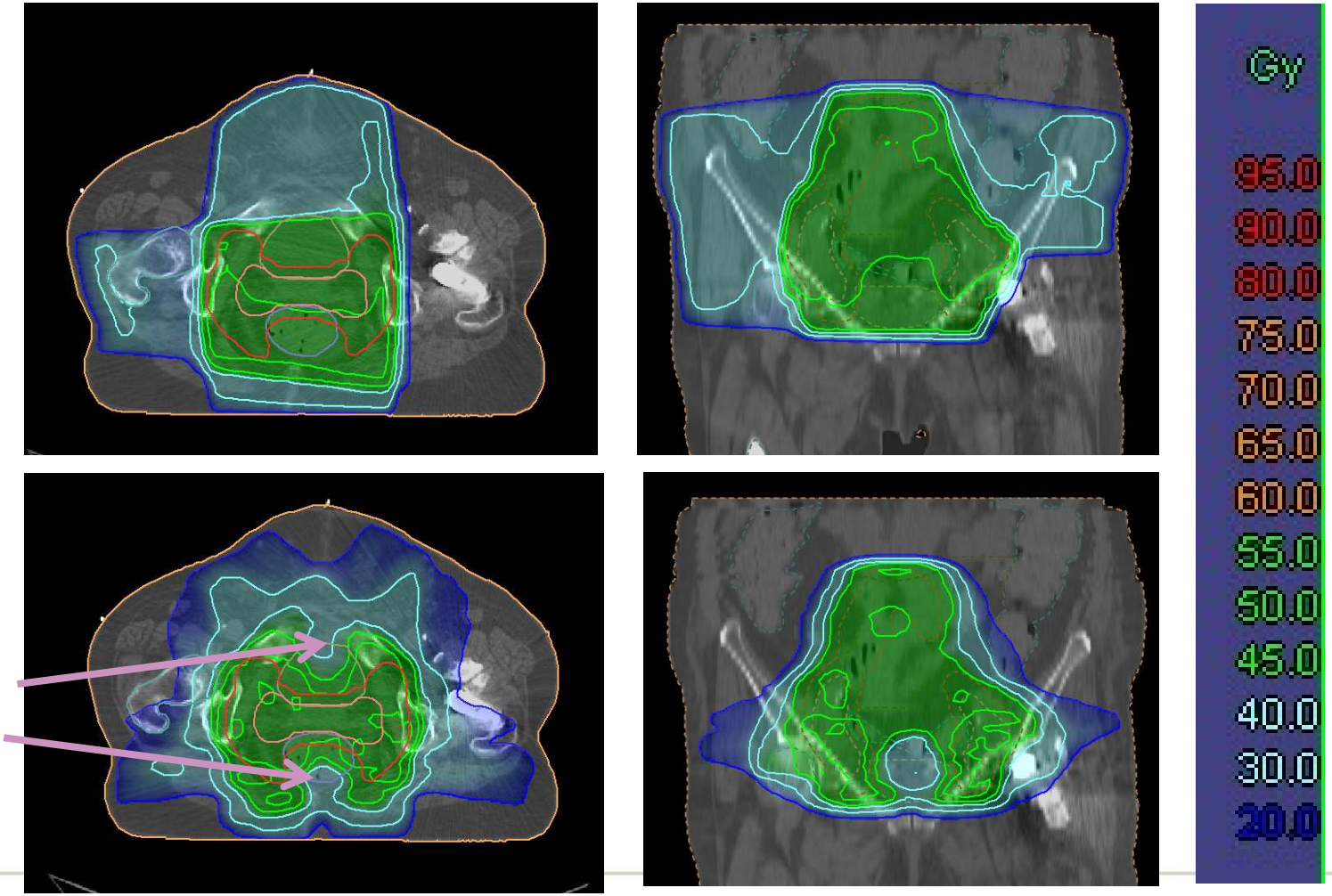
IMRT enables superior normal tissue sparing

Carcinoma of the uterine cervix, 50 Gy

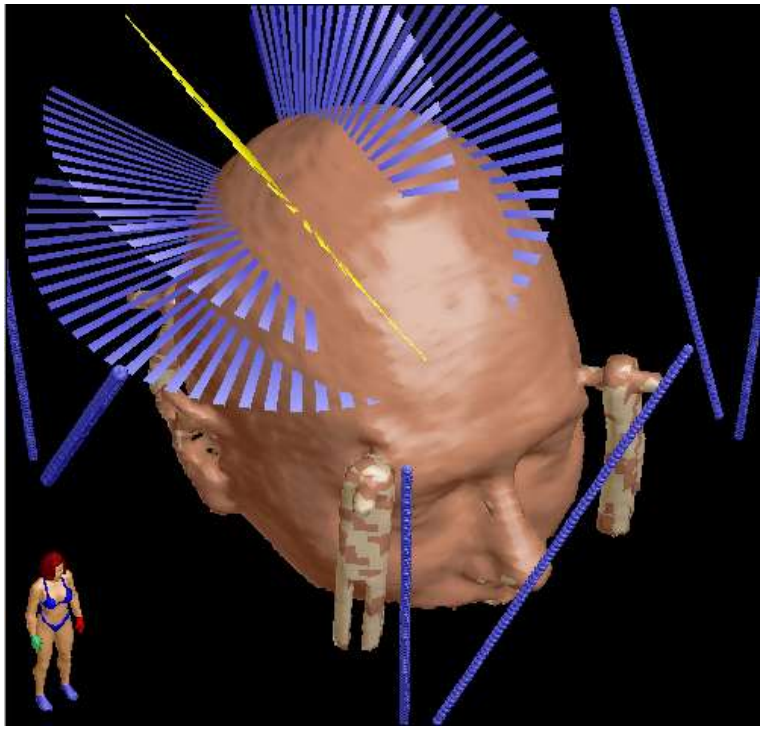
3-D conformal RT (Hip prosthesis L)

IMRT

Improved sparing of OARs



Stereotactic irradiation



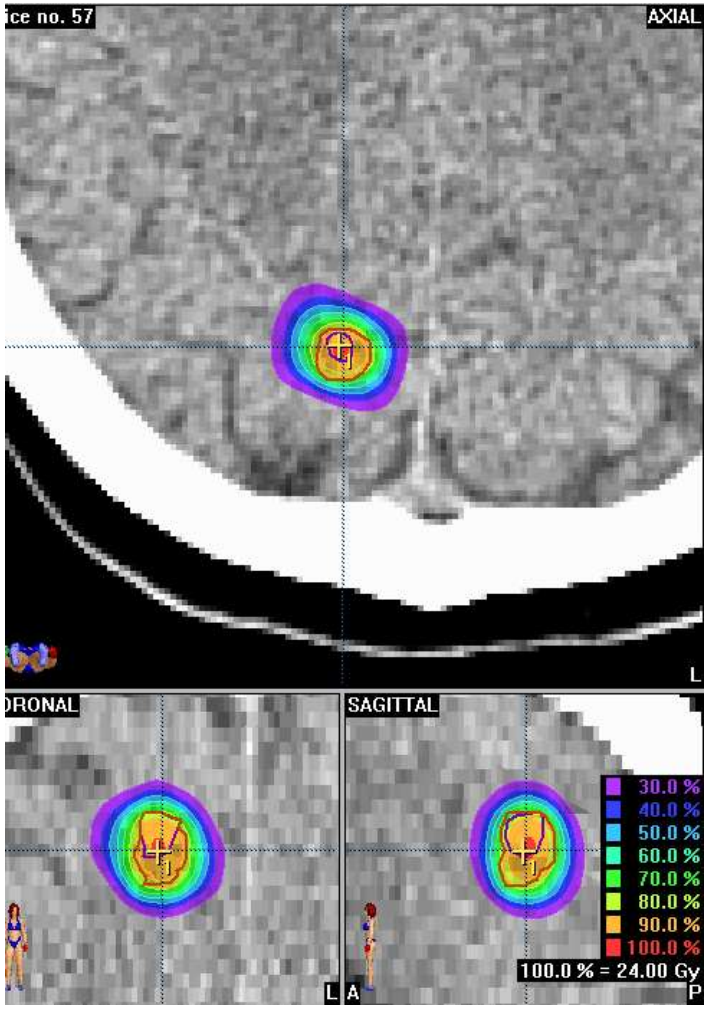
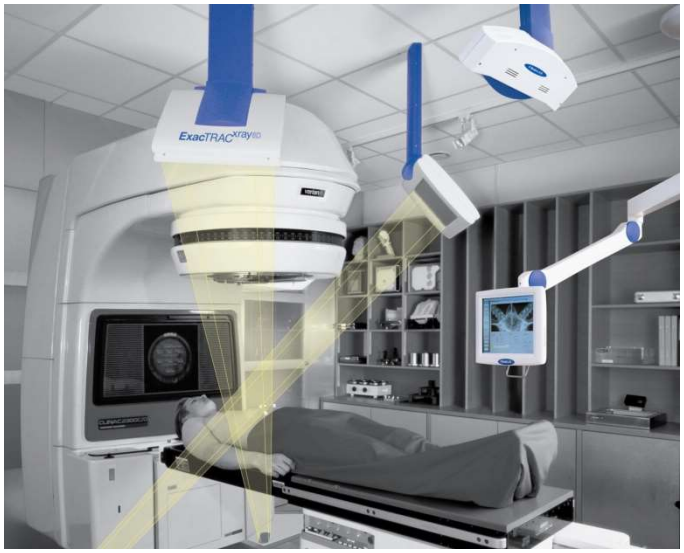
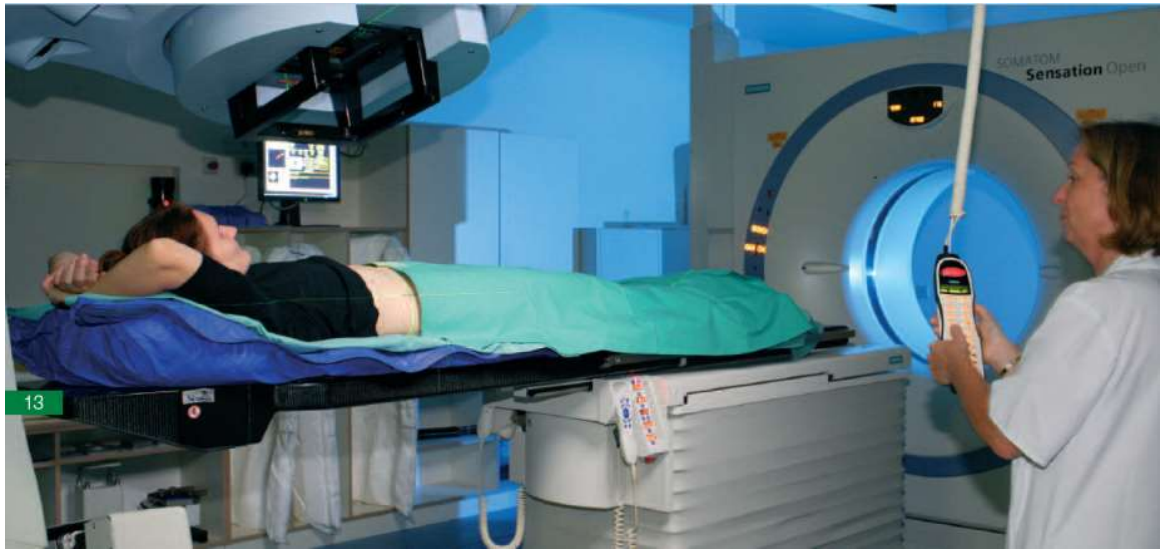
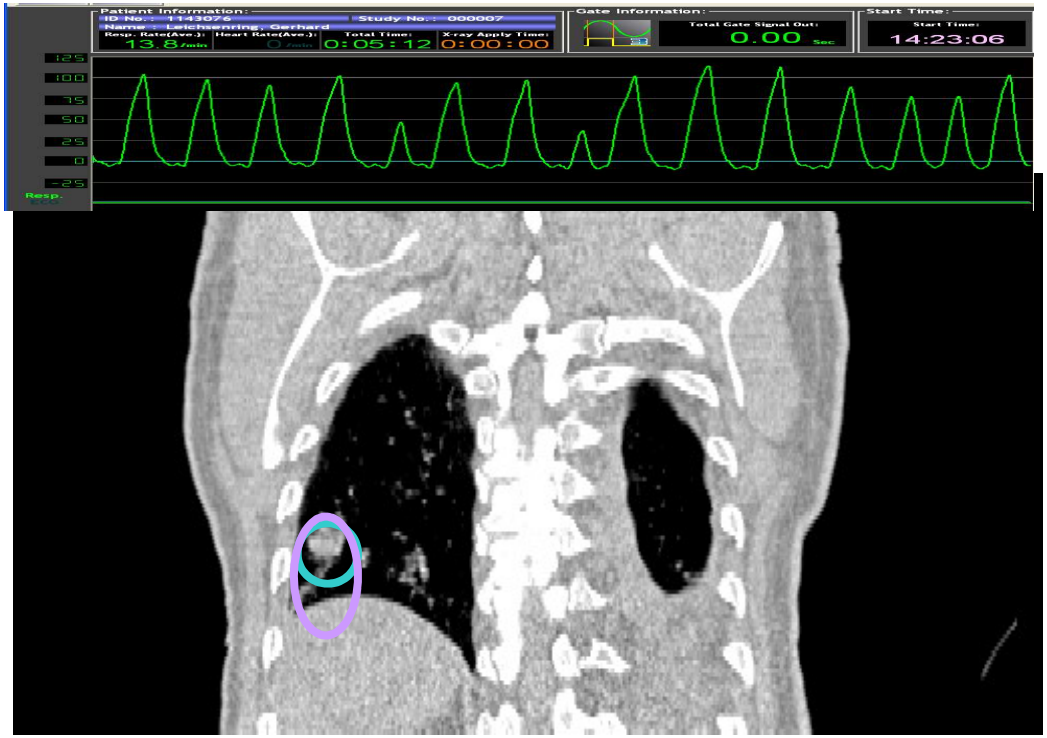


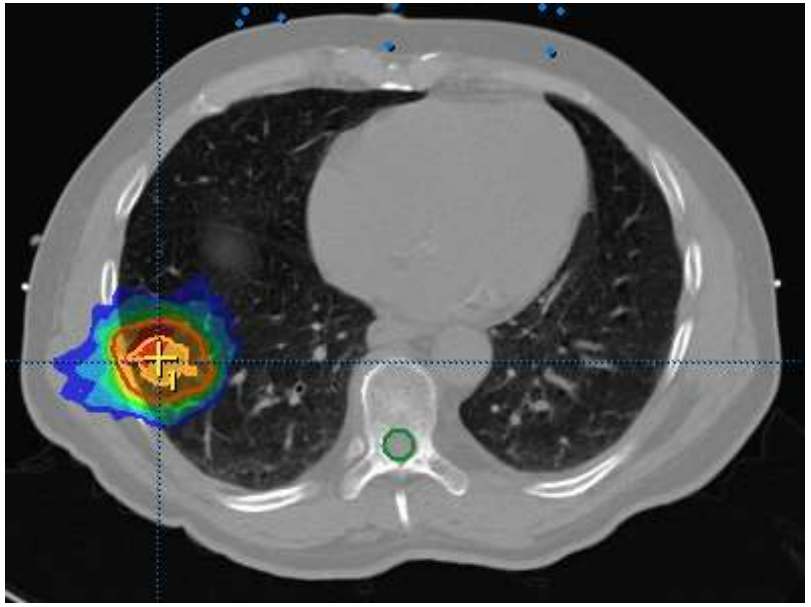
Image-guided radiotherapy

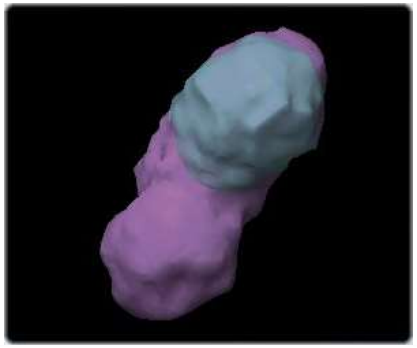




4D-radiotherapy, gating



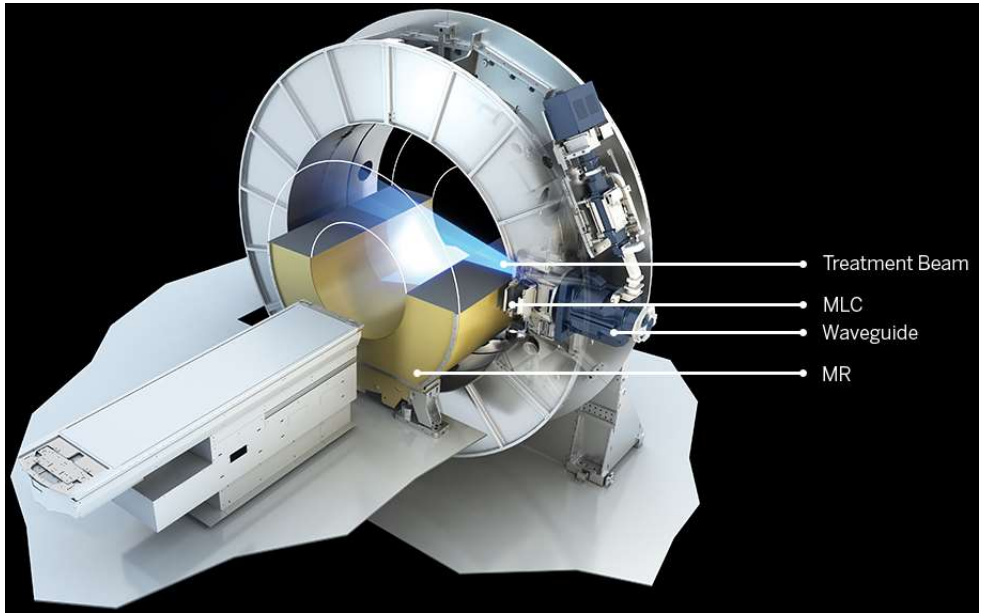


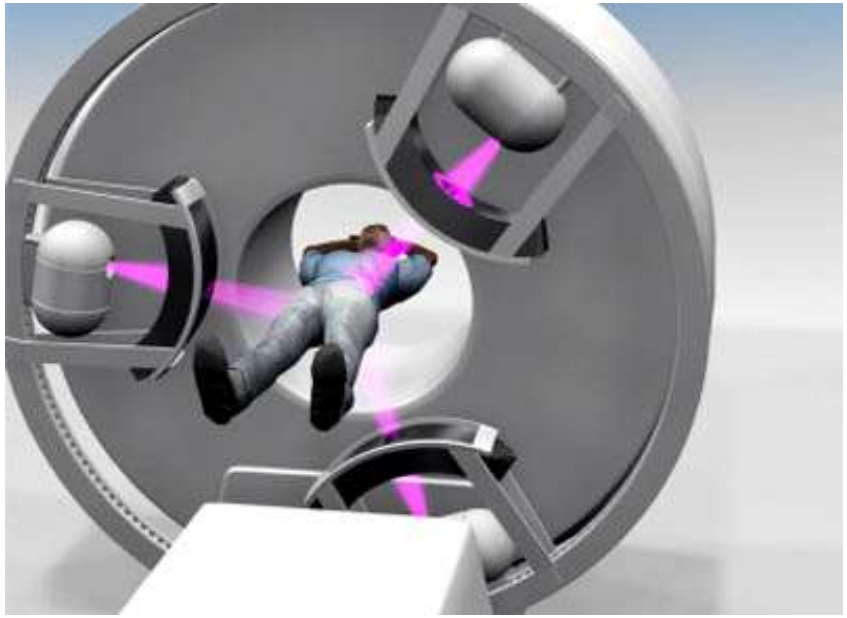


Target volume; entire breathing cycle

Target volume; exspiration

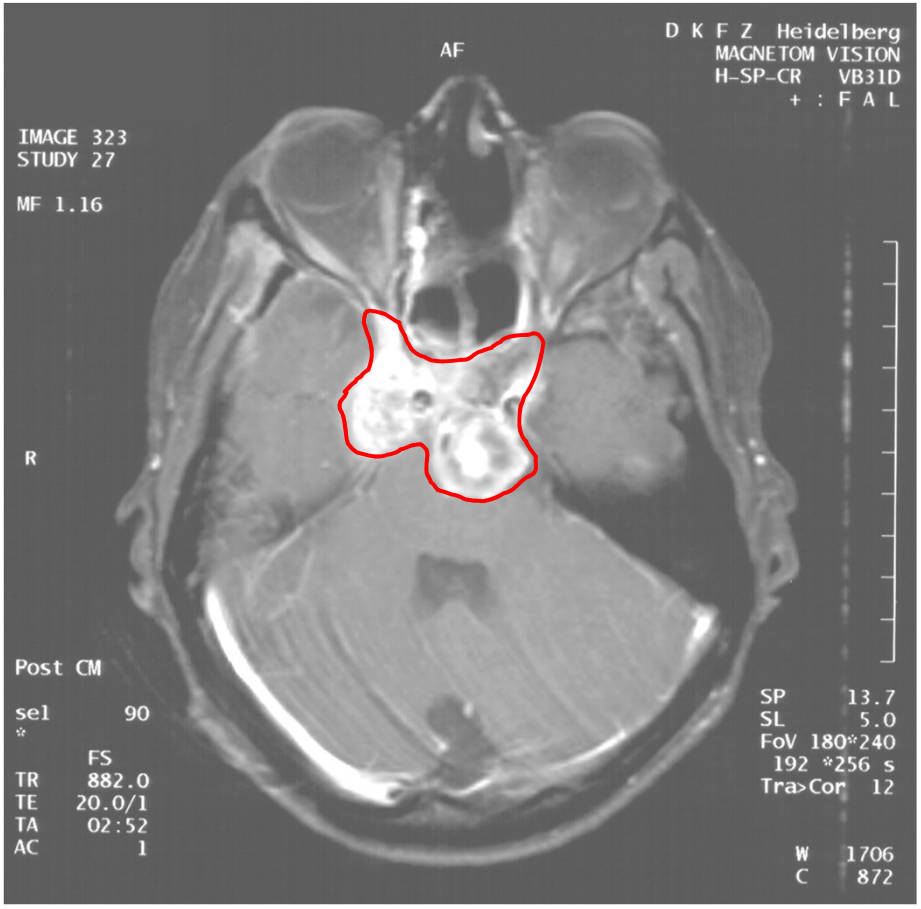
MR-LINAC

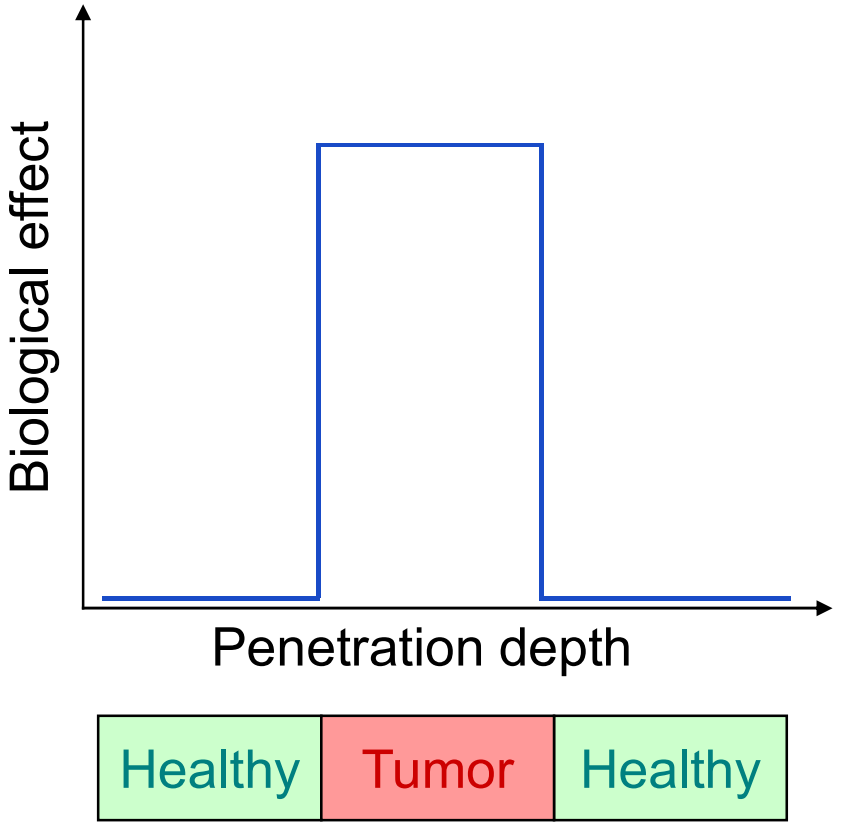




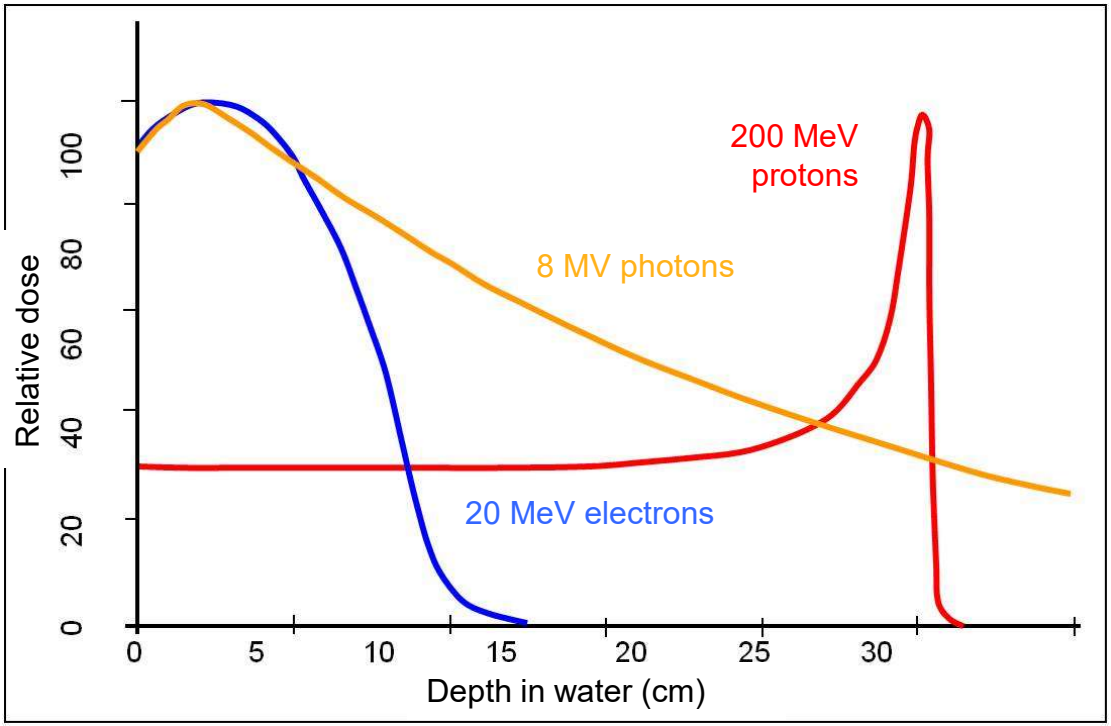
Philips; ViewRay

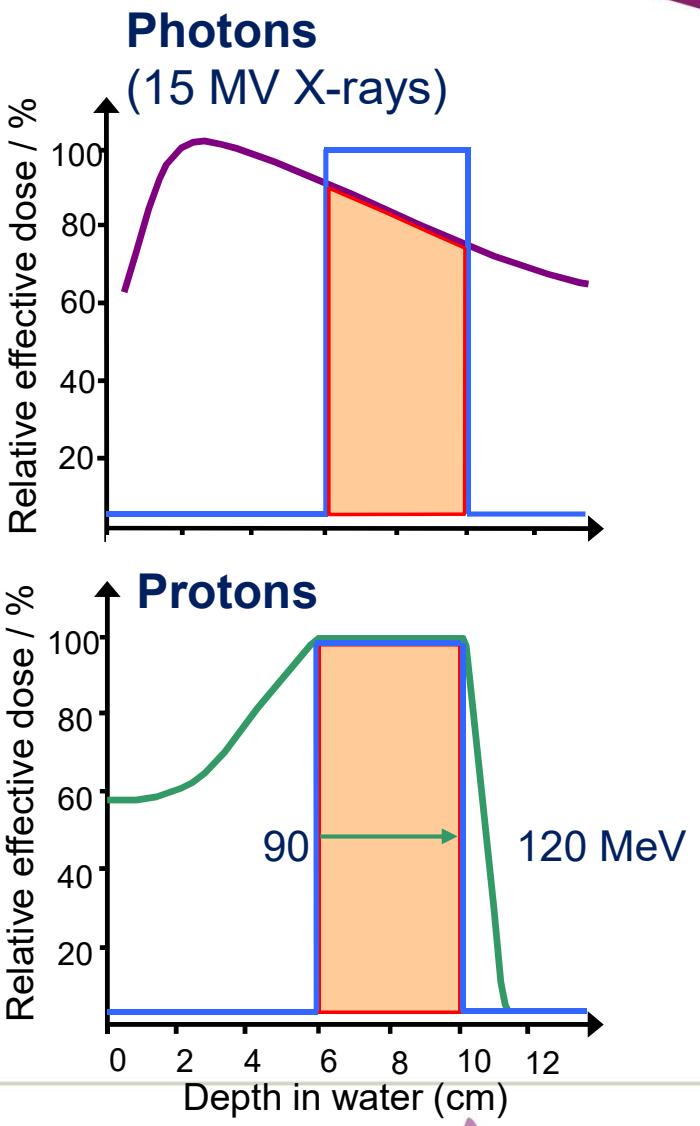
The ideal radiation beam



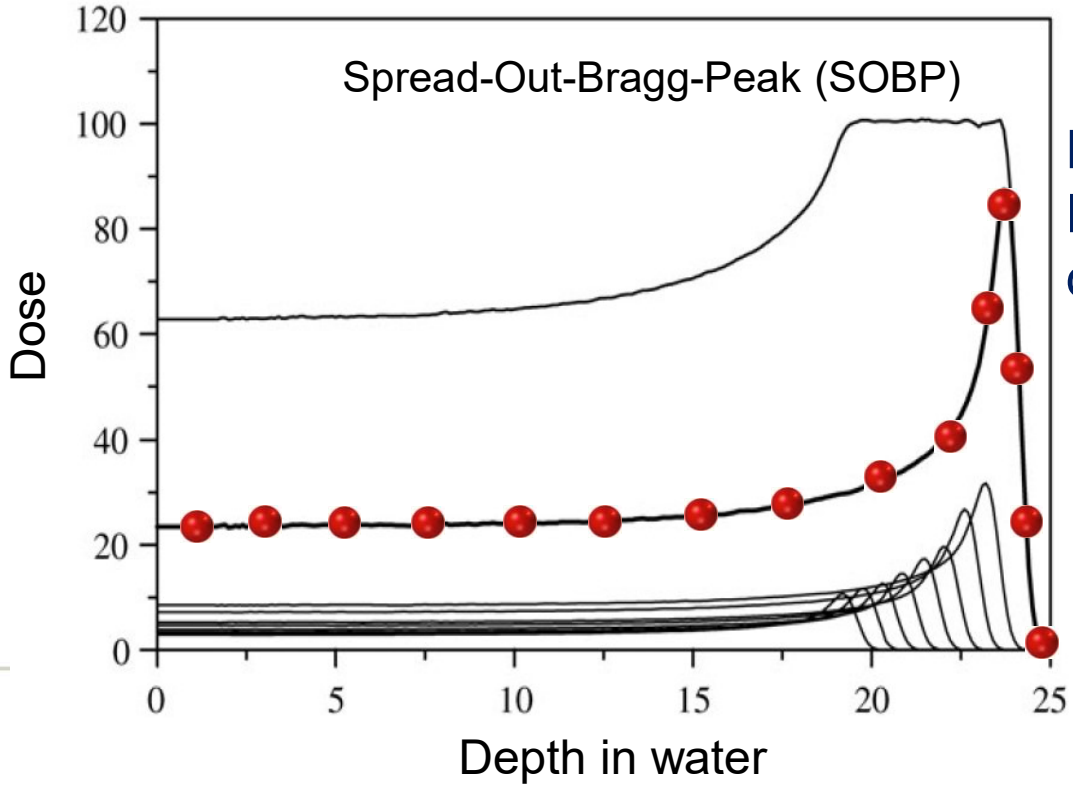


Protons: basic physics





Depth dose profile of protons



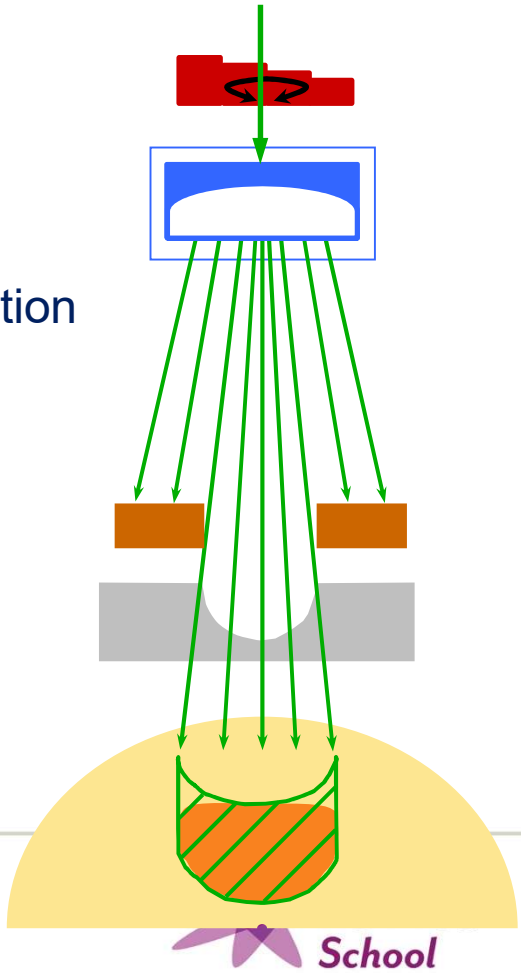
Bragg-Peak,
Depth is energy dependent

Proton therapy techniques

Universal Nozzle

1. Double Scattering (in clinical use since 12.12.14)

- 3D-adaptation of the monoenergetic, small proton beam in accordance to the tumor shape
- **Range-Modulator**
  ⇨ Broadening of beam direction in beam
- **Scatter system**
  ⇨ 2D lateral broadening
- **Apertur**
  ⇨ Lateral collimation
- **Compensator**
  ⇨ Distal adaptation



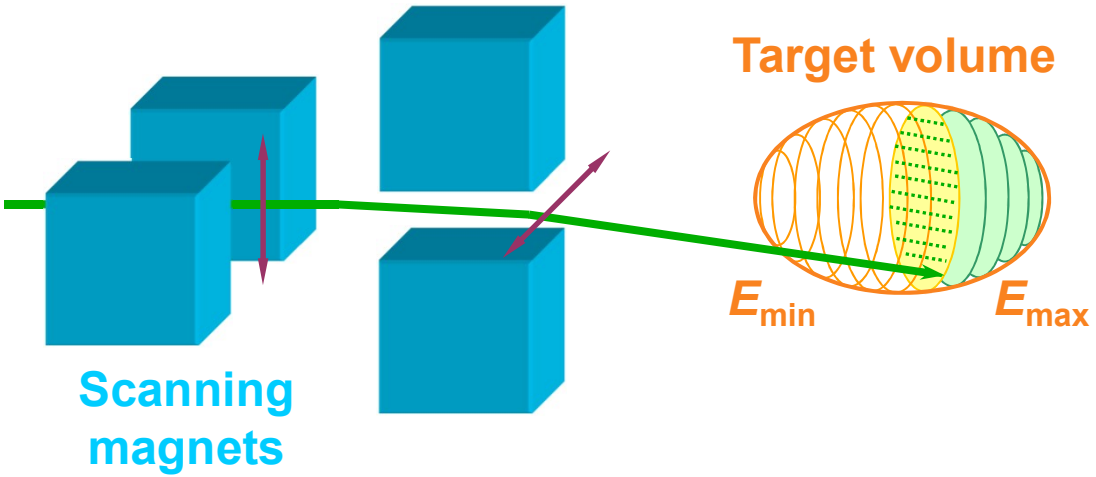
Courtesy: D. Kunath

Proton therapy techniques

Universal Nozzle

2. Pencil Beam Scanning

- Separation of the target volume:
  - In beam direction: monoenergetic layers
  - In lateral direction: in raster points
- 2D guidance of the monoenergetic, small proton beam using a magnetic system

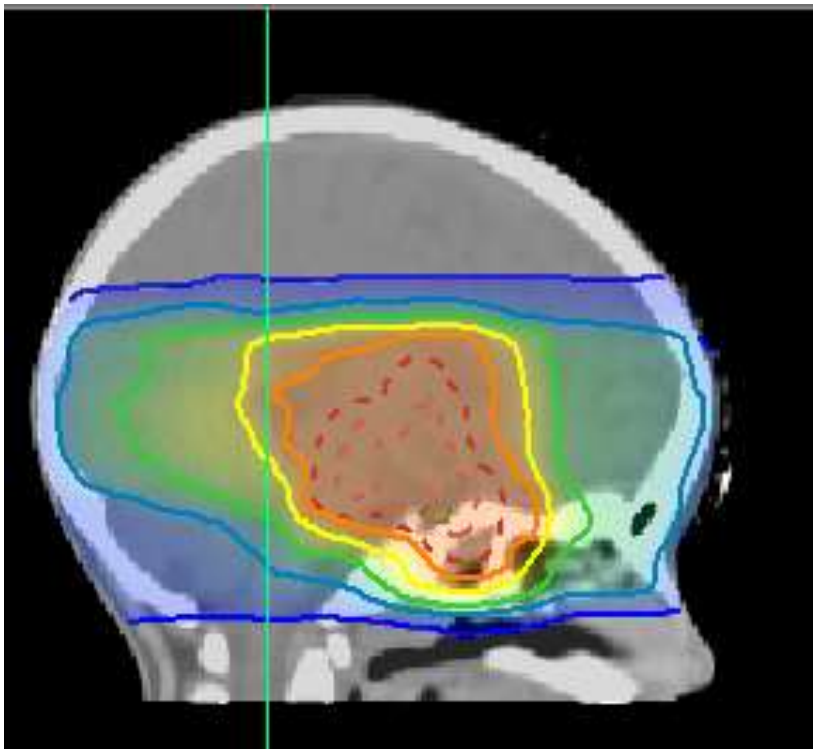


Courtesy: D. Kunath

Comparison of dose distributions

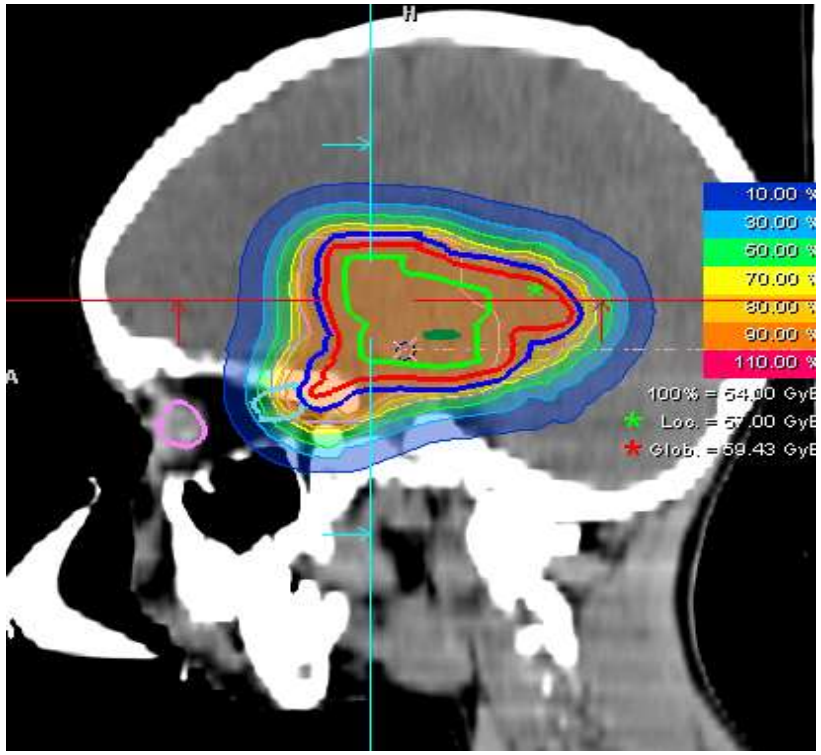
5-year old child with brain tumor

Photon-IMRT



University Proton Therapy Dresden

Protons

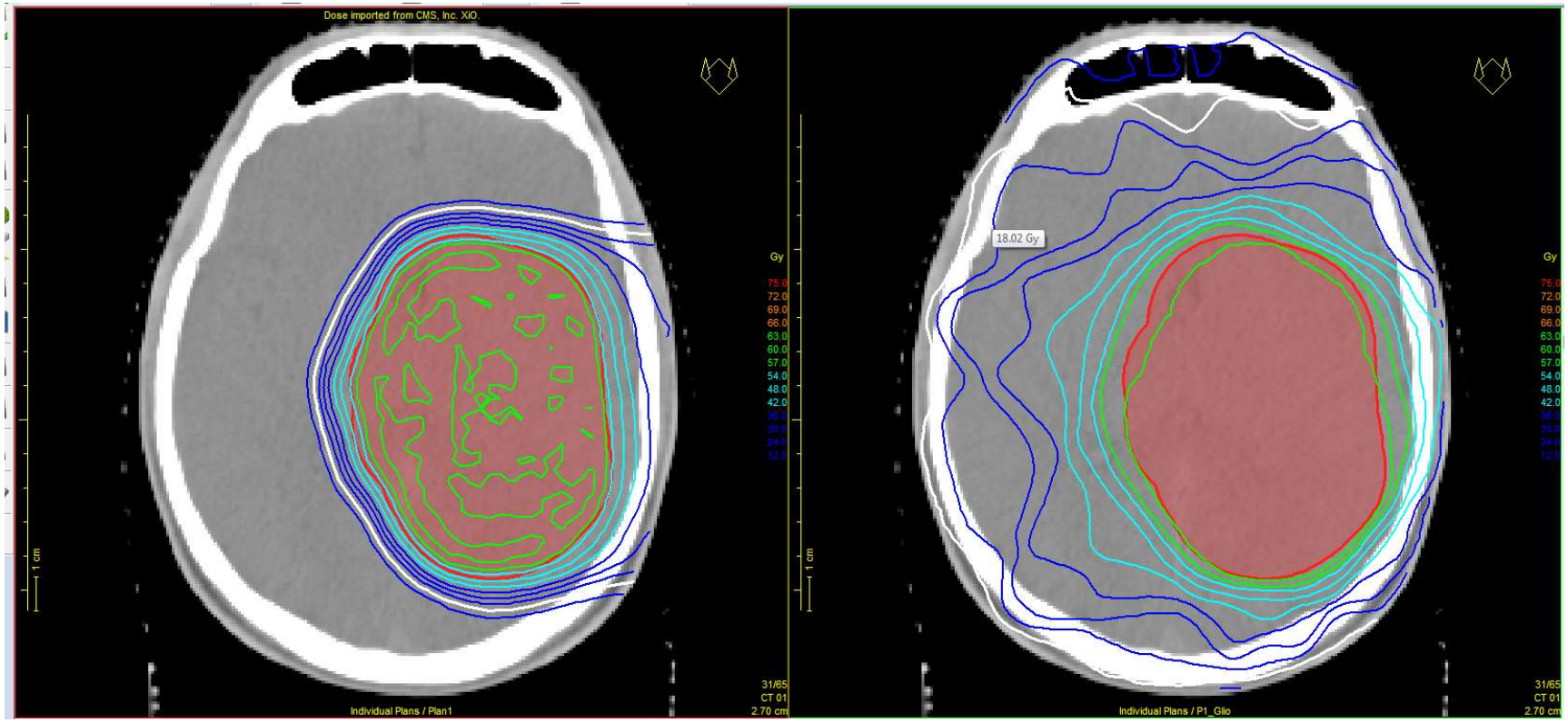


HIT, Heidelberg

Comparison of dose distributions

Protons (2 scattered beams)

Photons (7 fields)



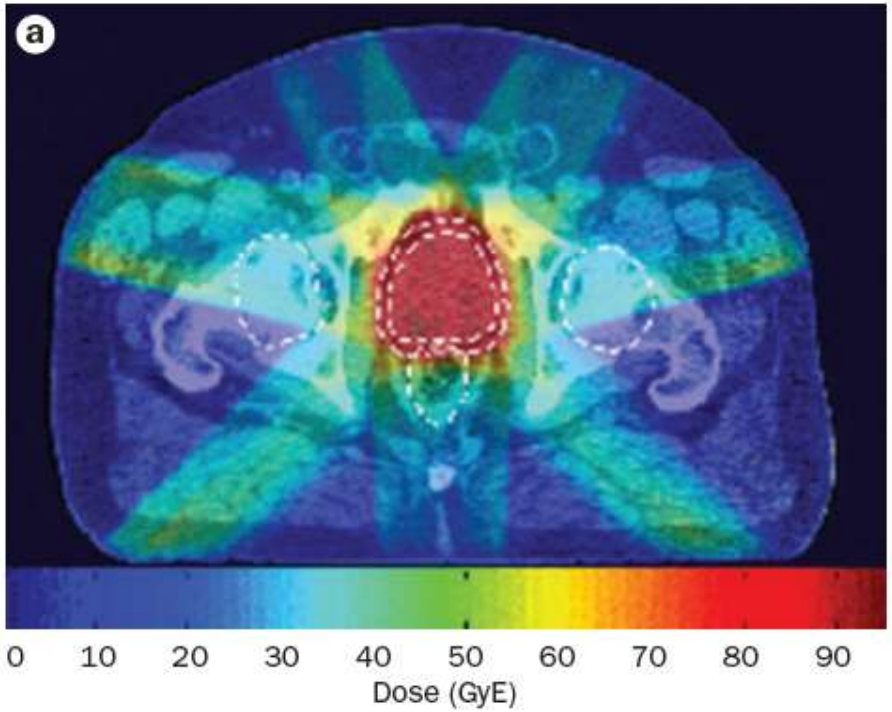
D [Gy]

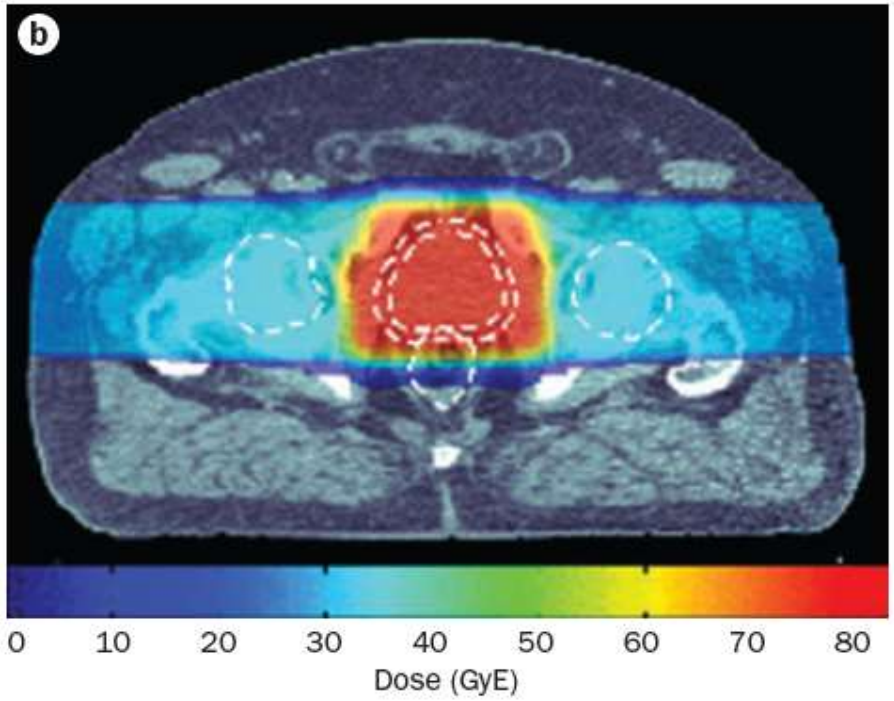
Glioblastoma in 17-year old patient, prescribed dose 60 Gy

Advantage Protons: no low-dose bath to entire brain

Courtesy: D. Kunath

Comparison in prostate patients





7-field IMRT photons

2 scattered proton beams

Prostate carcinoma: no evidence of benefit of proton beam therapy, but...

Coen, J. J. & Zietman, A. L. Nat. Rev. Urol. 6, 324–330 (2009)
Zietman et al., various publications

Eye tumors

Largest tumor diameter lr-p-value 0.001	**time**	**Freedom from local failure**
<10mm (10/244)	5ys	98%
	10ys	98%
	15ys	95%
10-15mm (20/1051)	5ys	96%
	10ys	95%
	15ys	95%
15.1-20mm (31/1208)	5ys	97%
	10ys	96%
	15ys	93%
> 20mm (22/490)	5ys	94%
	10ys	92%
	15ys	92%

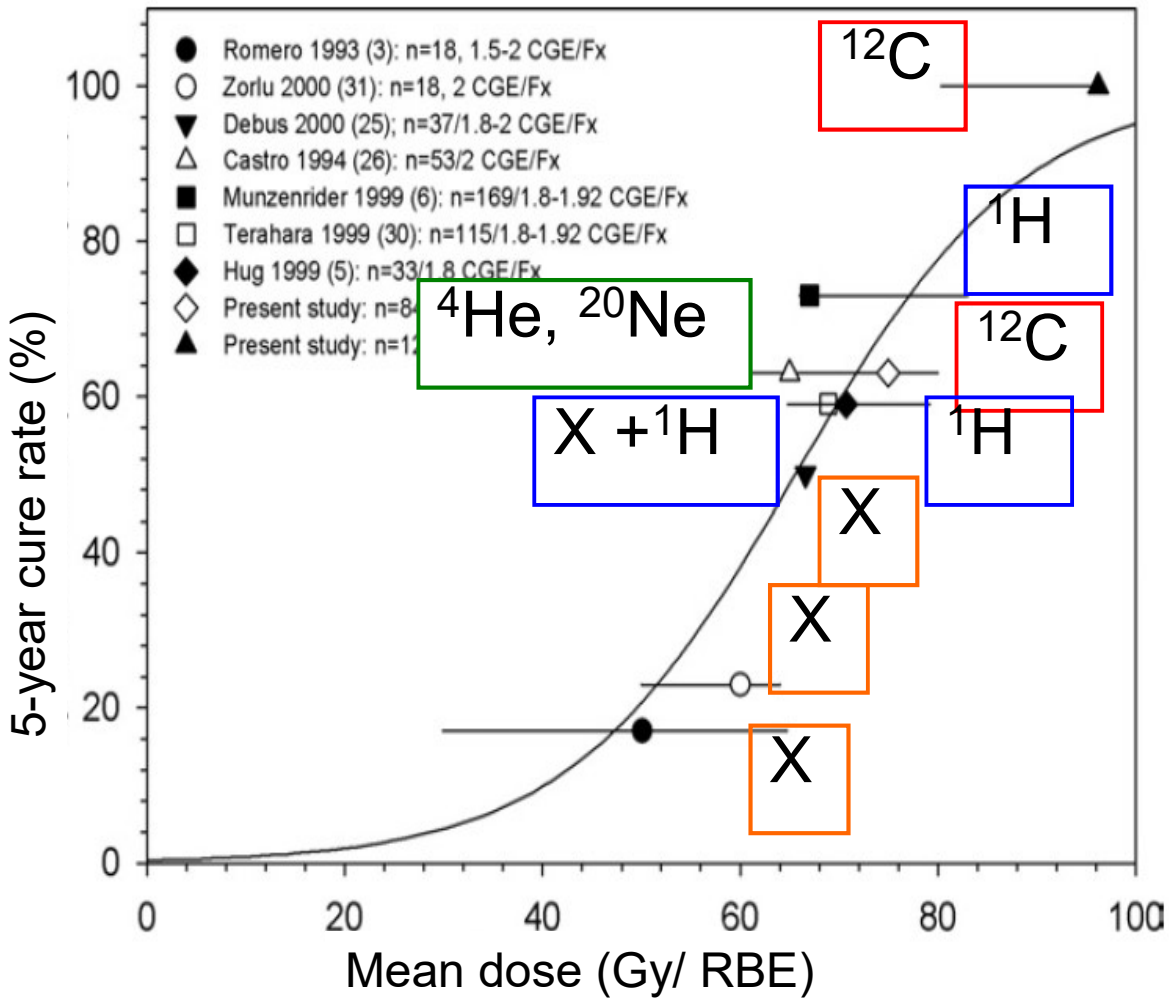
20.000 documented irradiations, less side-effects compared with photons

In small tumors at the back of the eye, protons are not superior to brachytherapy (contact therapy with radioactive sources)

In larger (thicker) tumors, protons have a superior dose distribution and are therefore the treatment of choice

This applies to various eye tumors, however, most evidence exists for ocular melanoma

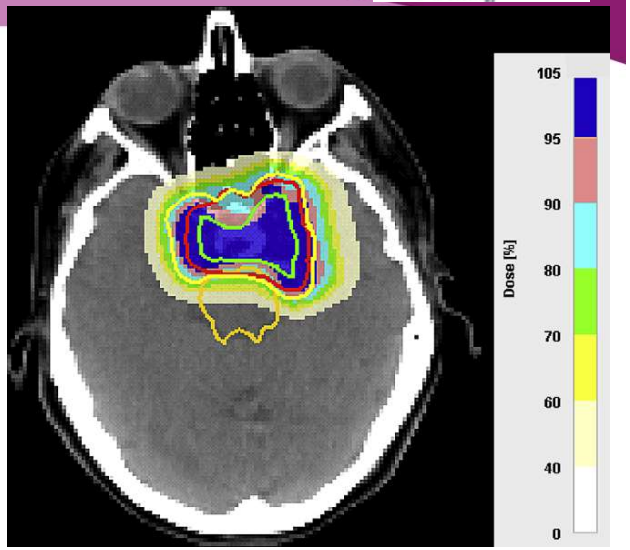
Advantage in chordoma

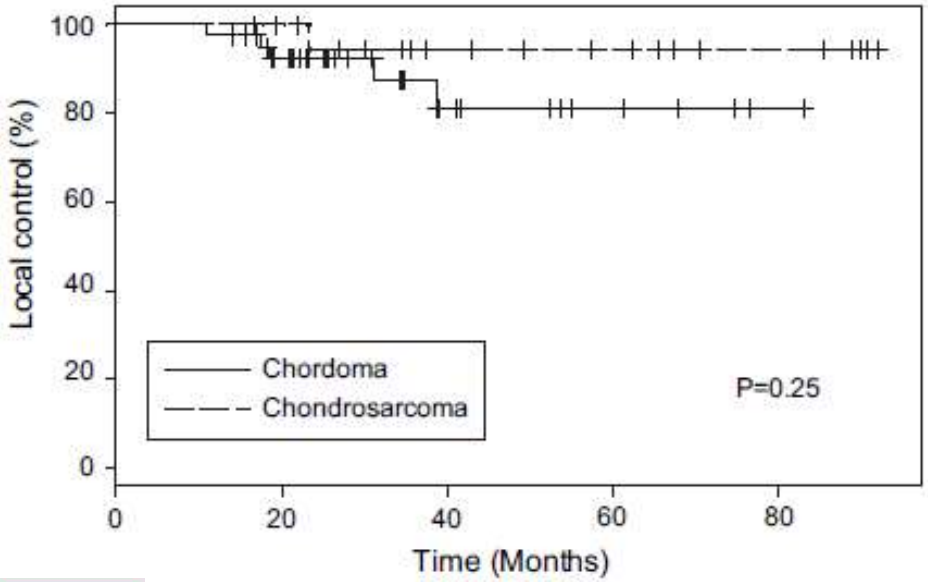


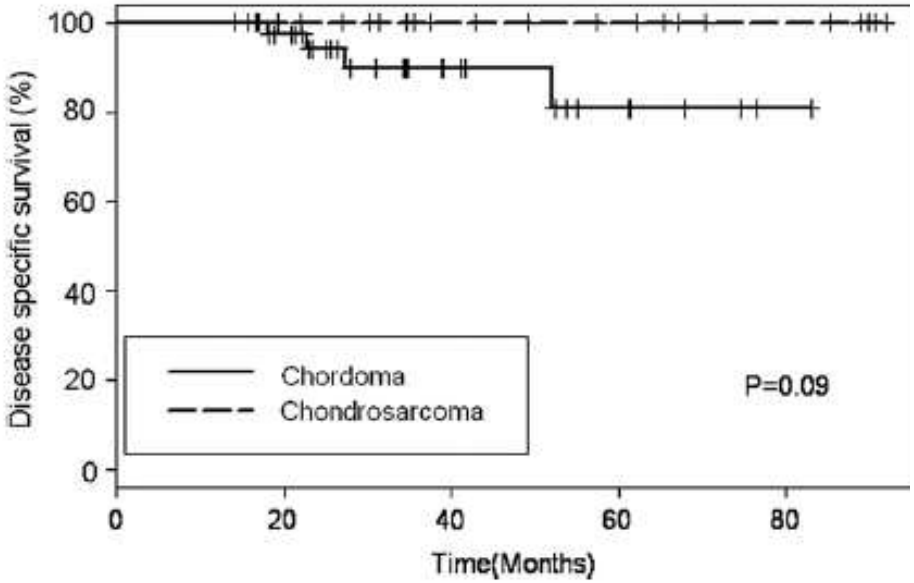
Base of skull tumors

- n=64, 1998-2005 PSI, Switserland
- Adjuvant proton therapy after primary surgery or for recurrent disease
- Chordoma: 3y-, 5y- local control 87%, 81%
- Chondrosarcoma: 3y-, 5y- local control 94%

- Comparison to surgery only: 10y-local control 31%;

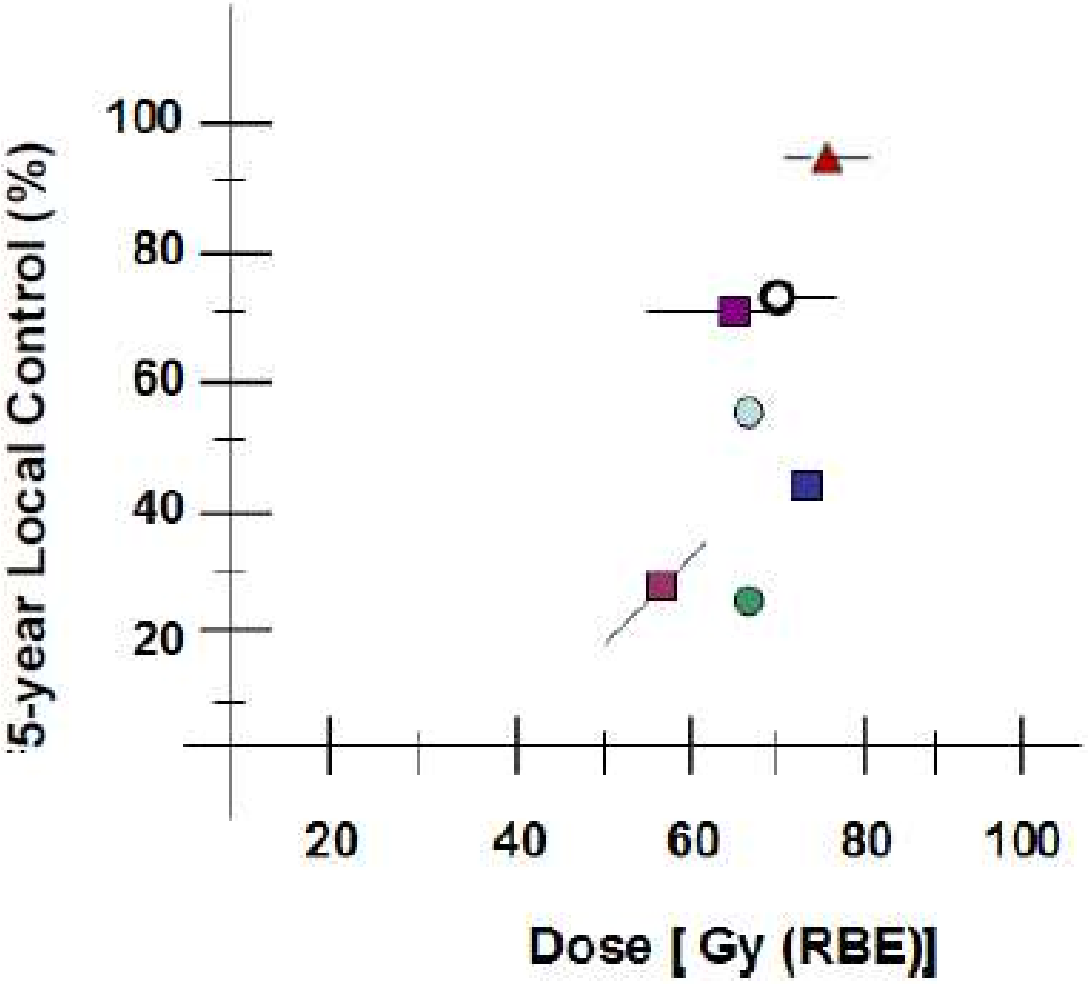






Ares et al., IJROBP 75, 1111-18, 2009

Base of skull: adenoid cystic carcinoma

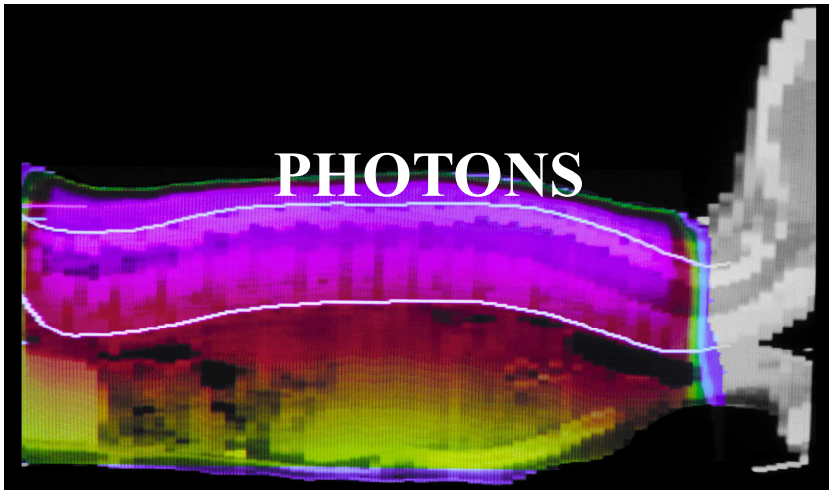


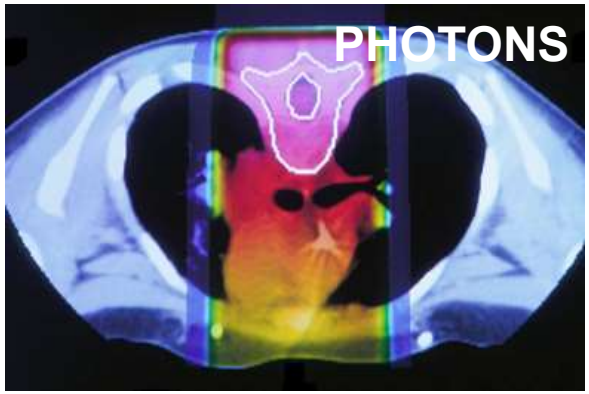
▲ Protons:

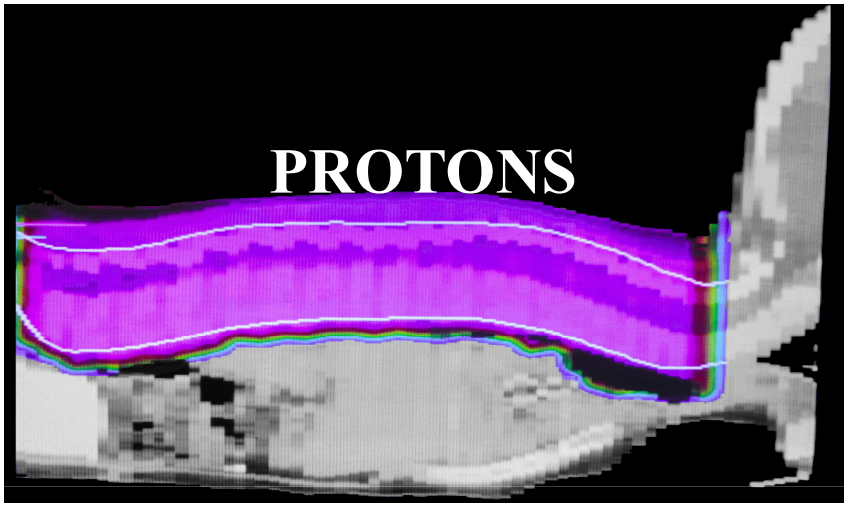
Pommier et al.
MGH,
Acta Otolayng Head Neck Surg
2006;132(11):1242
Median F/U > 5 y
93% 5–y LC

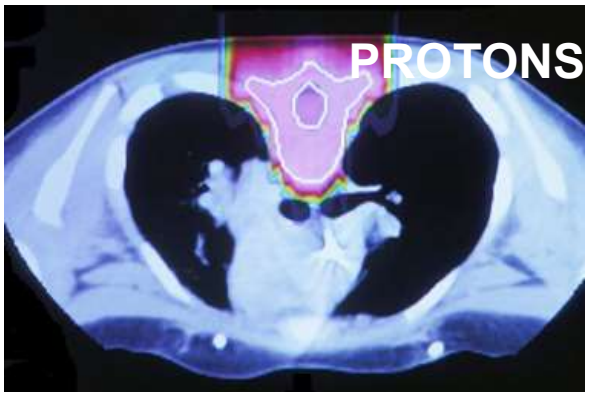
Courtesy of: Carmen Ares, PSI

Medulloblastoma in children: standard indication outside clinical studies



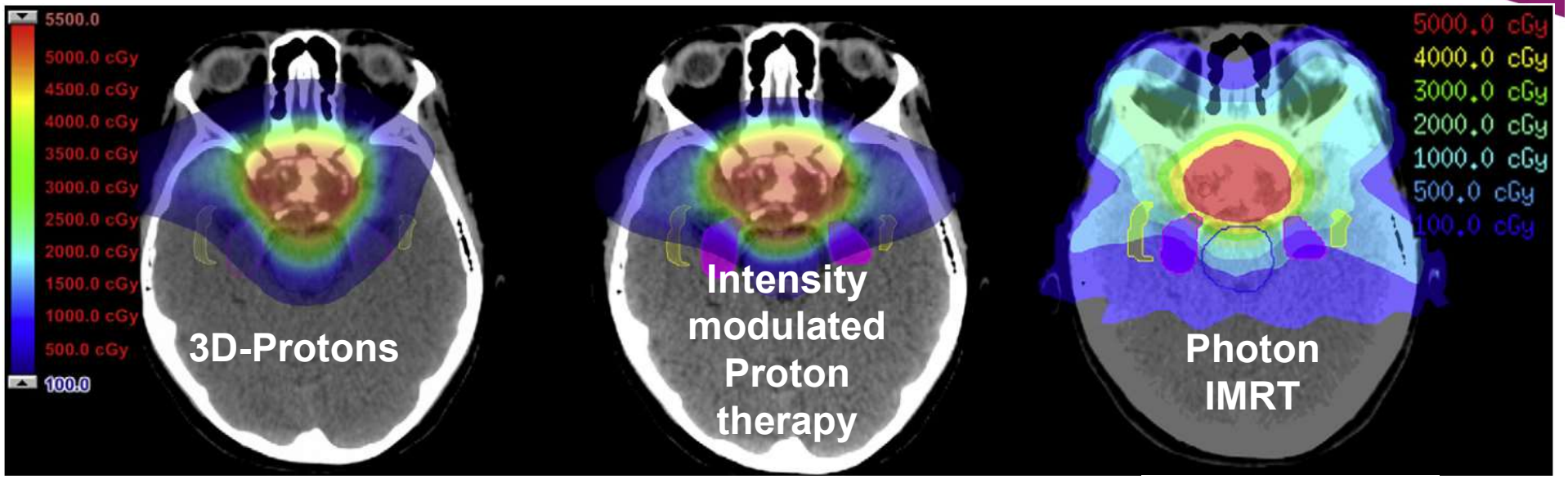




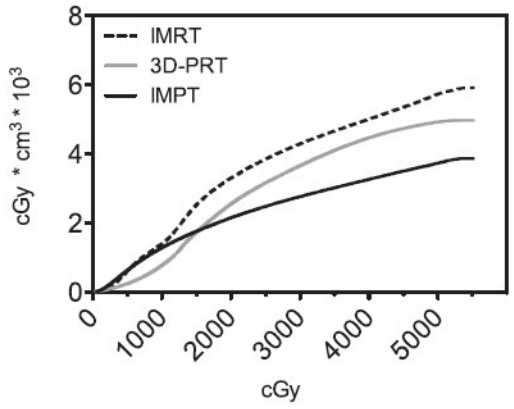


Supplied by A. Zietman

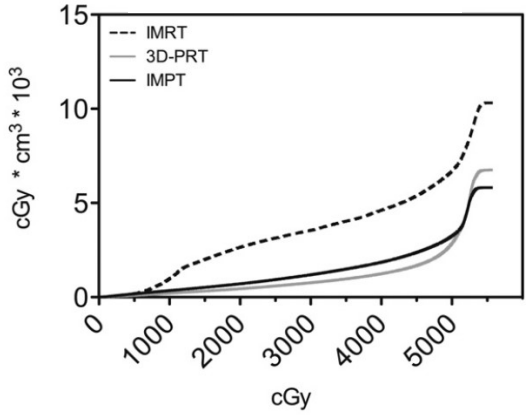
Comparison in pediatric tumors



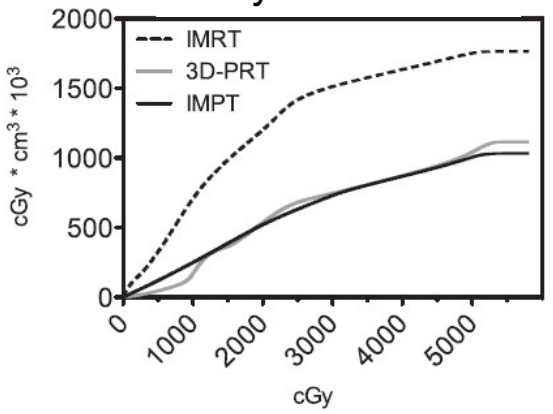
Hippocampus



Carotid arteries



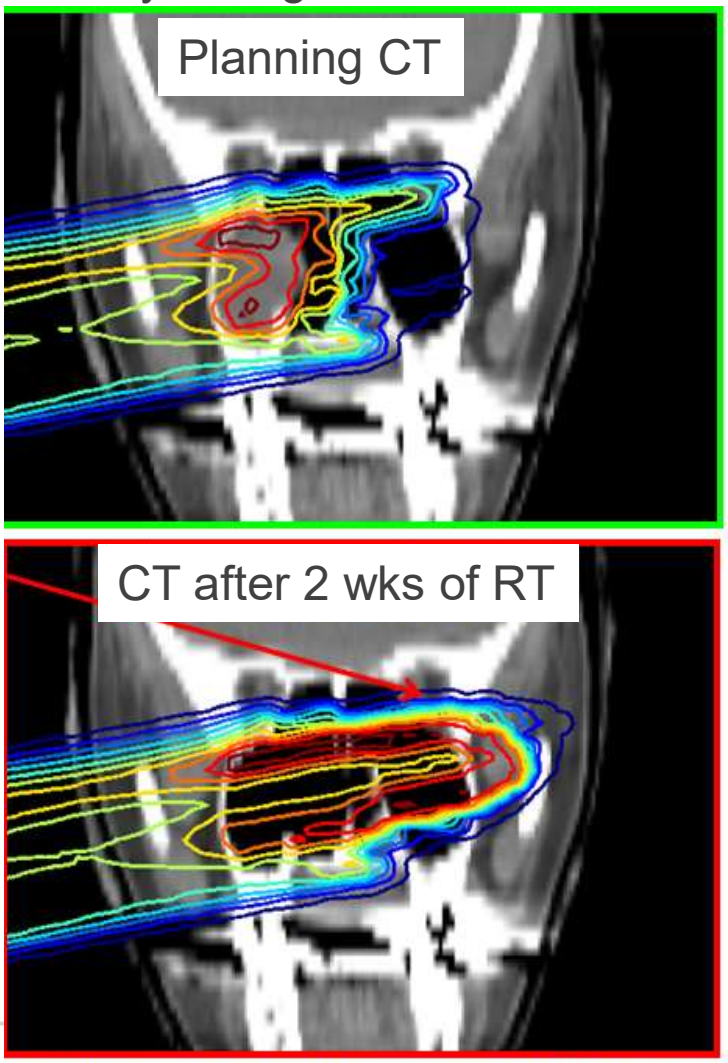
Body dose - PTV



Boehling et al., IJROBP 82, 643-52, 2012

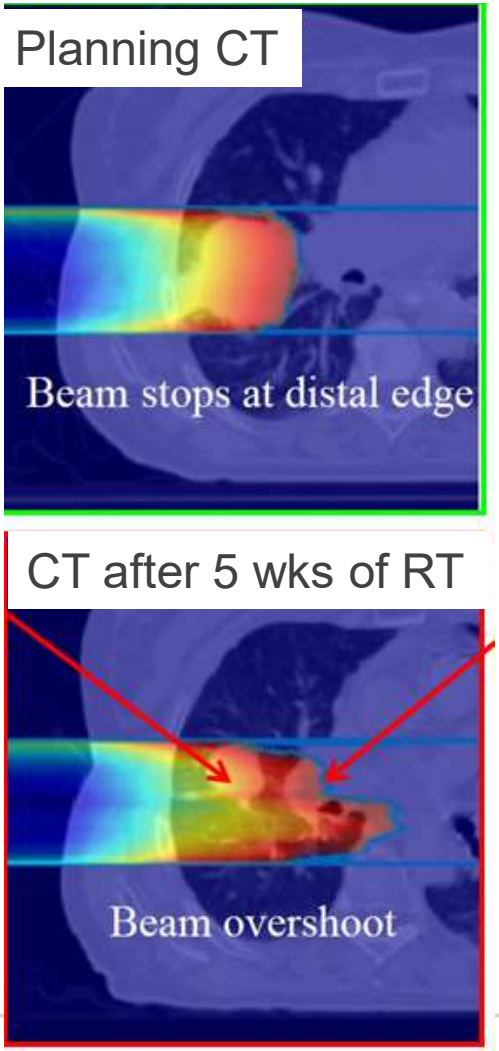
Specific challenges in proton therapy

Density changes



W. Enghardt et al.: Radiother. Oncol 73 (2004) S96

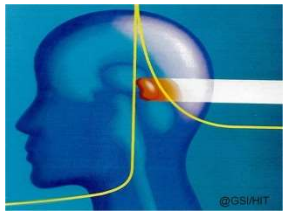
Movement or tumor volume shrinkage



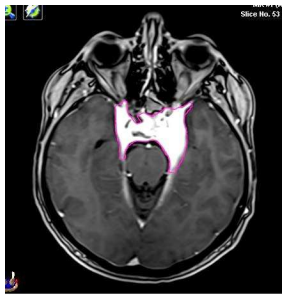
T. Bortfeld, MGH, AAPM 2009

Guidelines for proton therapy: ESTRO/ASTRO

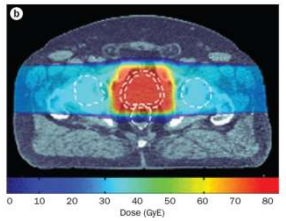
- **Proven benefit:** large ocular melanoma, chordoma/ chondrosarcoma, adenoid cystic carcinoma



- **Approved applications:** brain tumors (and other tumors in) children, tumors in proximity to the spinal cord, some re-irradiations, tumors in which a clear advantage is expected after plan comparison (Dutch model-based approach)



- **Moreover:** Patients with tumors of unclear indication may be treated in the context of prospective clinical trials

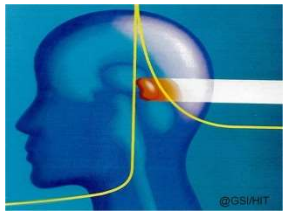


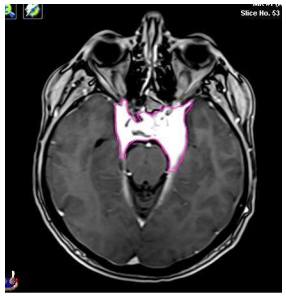
De Ruysscher et al. *Radiother Oncol* 103 : 5, 2012; Allan et al. *Radiother Oncol* 103 : 8, 2012; DEGRO website

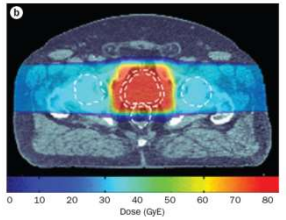
Guidelines for proton therapy: ESTRO/ASTRO

- **No clear evidence:** lymphoma, non-sm
  cancer, head-and-neck cancer, rect
  cancer

Proton beam therapy may be relevant for 15-20% of the patients currently undergoing photon irradiation?!

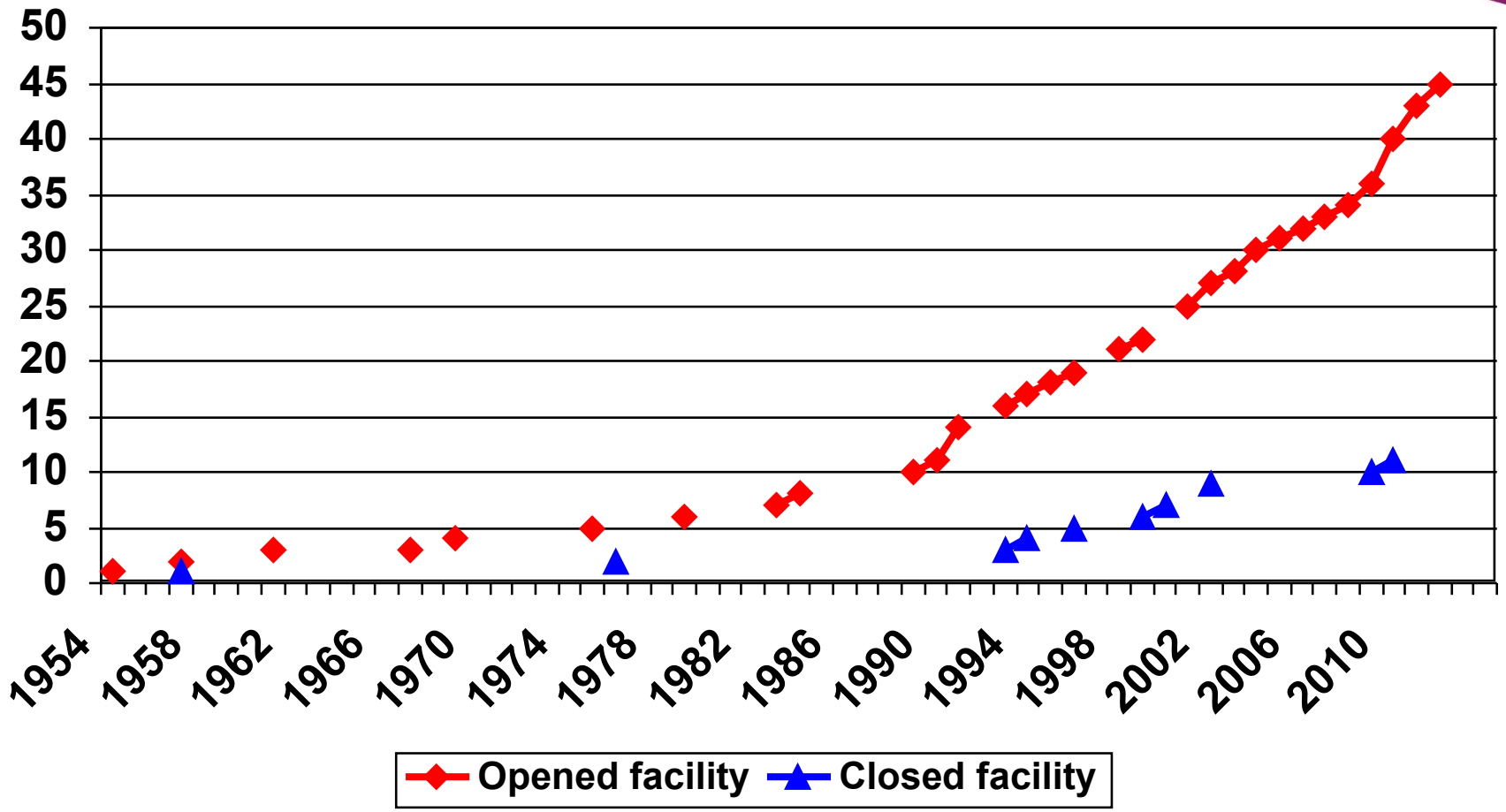






De Ruysscher et al. *Radiother Oncol* 103 : 5, 2012; Allan et al. *Radiother Oncol* 103 : 8, 2012; DEGRO website

Particle therapy treatment sites

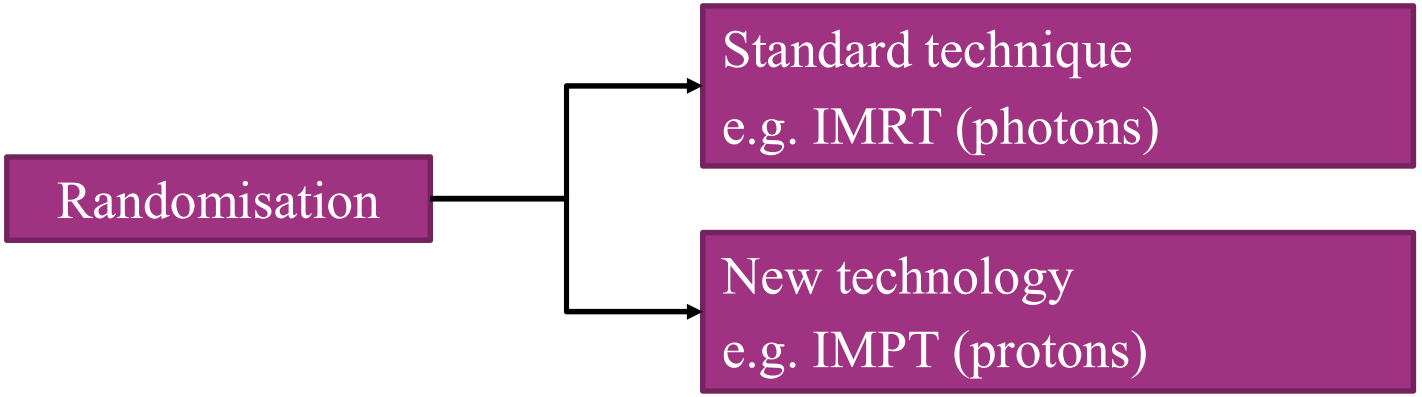


- Currently approx. 50 running facilities worldwide
- >150.000 irradiated patients, mostly with protons (>130.000)

http://ptcog.web.psi.ch/Archive/pat_statistics.pdf

Evidence-based medicine: gold standard

RCT (**R**andomised **C**ontrolled **T**rial)



True if main purpose is to **improve efficacy** (local control and survival)

Reduction of radiation-induced side effects?

Model-based approach

Selection

STEP 1: NTCP model

Multivariable NTCP-models

STEP 2: Individual dose comparison

Dose reduction (**ΔDose**): relevant DVH parameters?

STEP 3: Estimate NTCP reduction (ΔNTCP)

Translate **ΔDose** to **ΔNTCP**

Validation

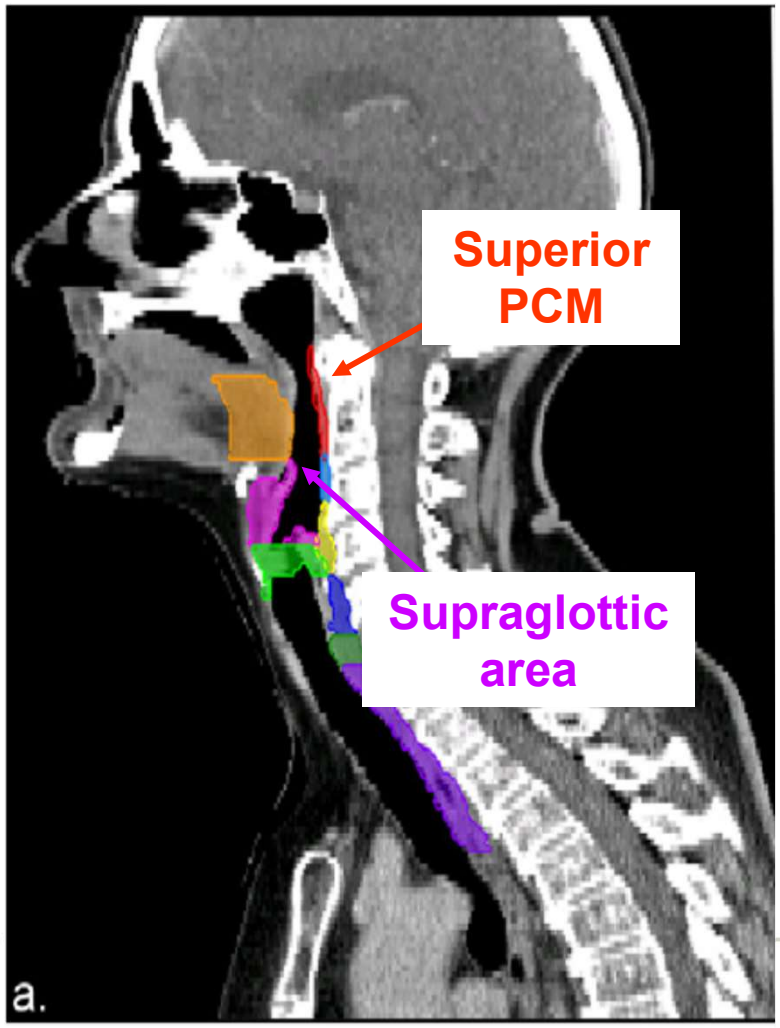
STEP 4: Validation

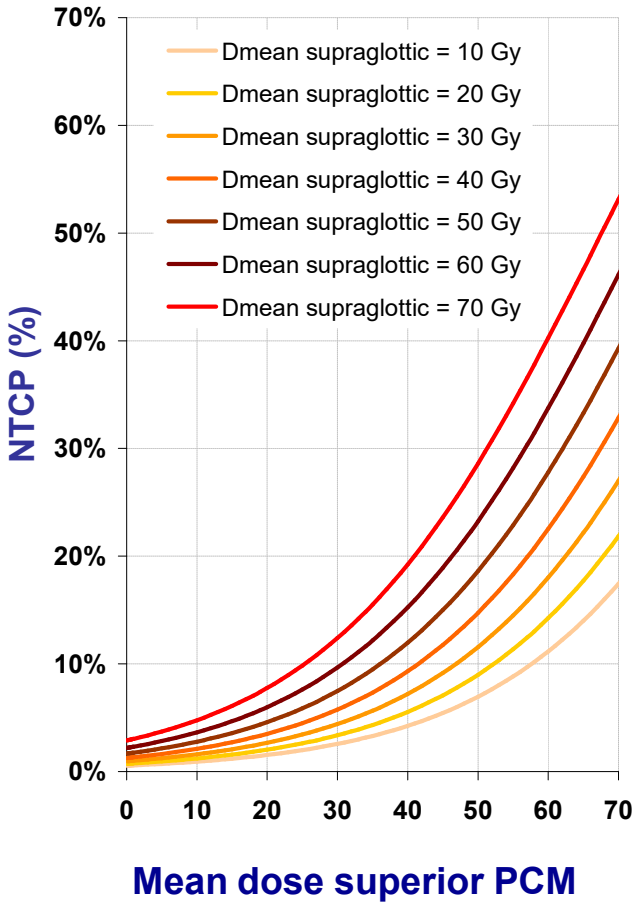
External validation NTCP-model with new technology

Langendijk, *et al*. Radiother Oncol 2013; Courtesy of Hans Langendijk, UMC Groningen

Step 1: NTCP-model

Endpoint: Grade II-IV late dysphagia at 6 months





Christianen, *et al*. Radiother Oncol 2011

Step 2: Planning comparison

Estimation of dose difference (Δdose)

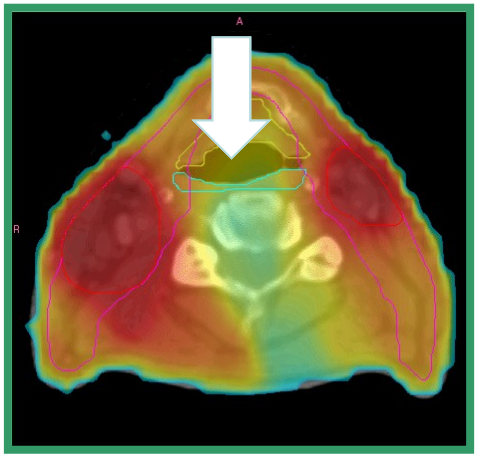
Standard IMRT:

Dose reduction parotid glands

No dose constraints for SWOARs

D_{mean} superior PCM = 64 Gy

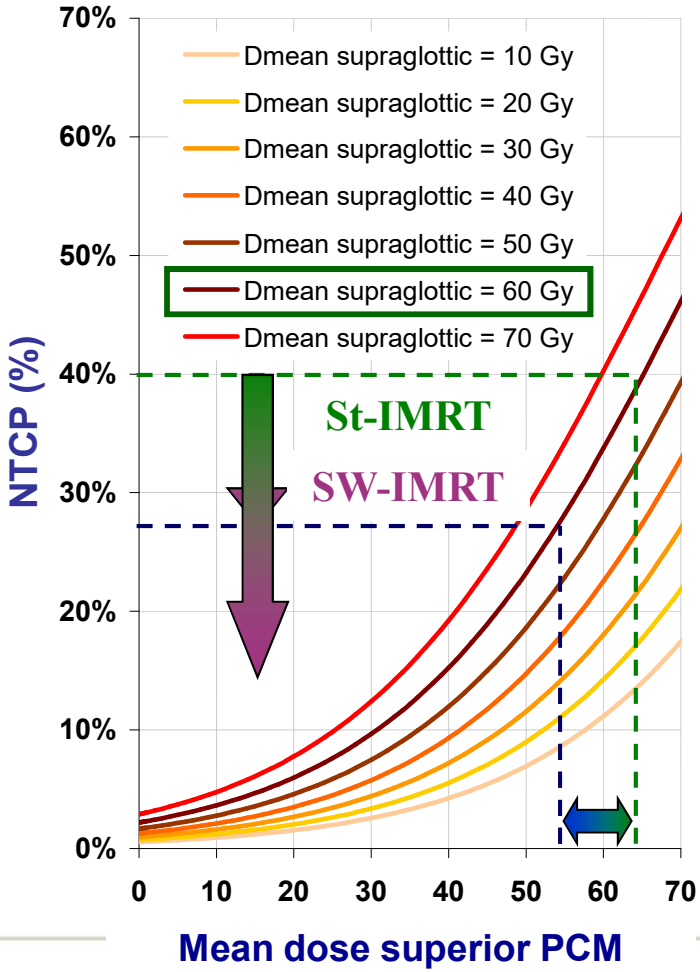
D_{mean} supraglottis = 60 Gy

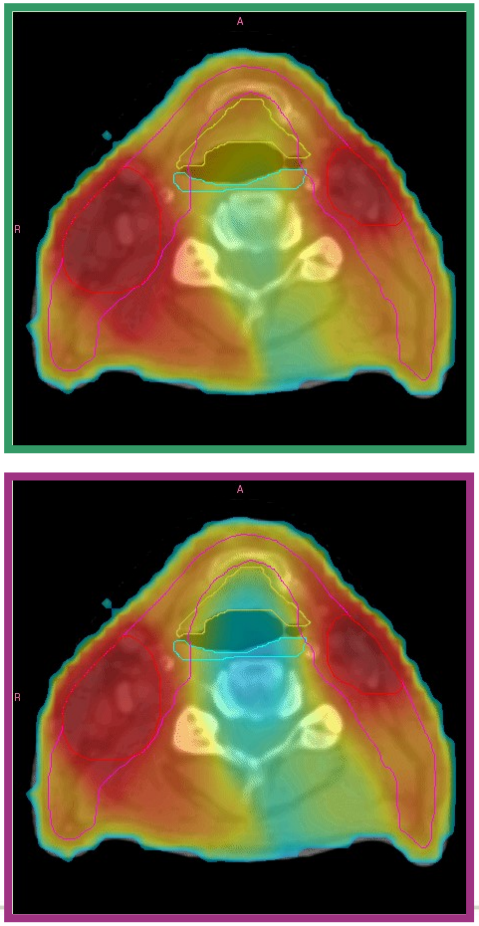


Van der Laan, *et al*. Radiother Oncol 2013

STEP 3: Integration step 1 and 2

Translate Δdose ➔ ΔNTCP



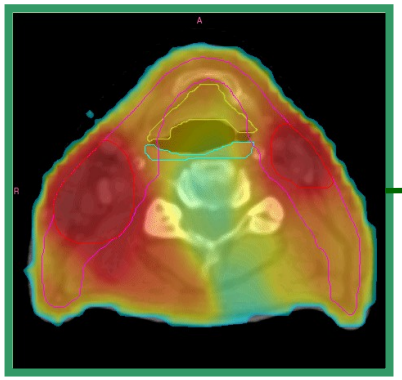


Langendijk, *et al*. Radiother Oncol 2013

Step 4: Clinical validation study

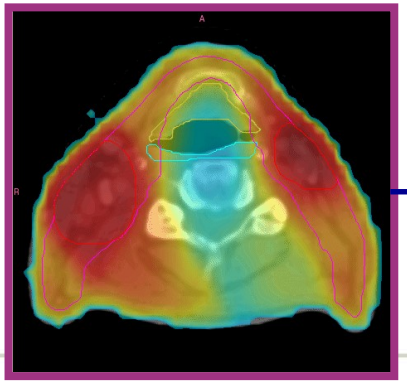
Study design

Standard IMRT plan



1. Spare parotid glands
2. NO dose constraints for SWOARs
3. Estimate NTCP for grade II-IV Dysphagia = $\mathbf{NTCP_{standard\ IMRT}}$
4. Save and store **(BACK UP plan)**

SW-IMRT plan



1. Similar dose to parotid glands
2. Spare SWOARs
3. Estimate NTCP for grade II-IV Dysphagia = $\mathbf{NTCP_{SW\text{-}IMRT}}$

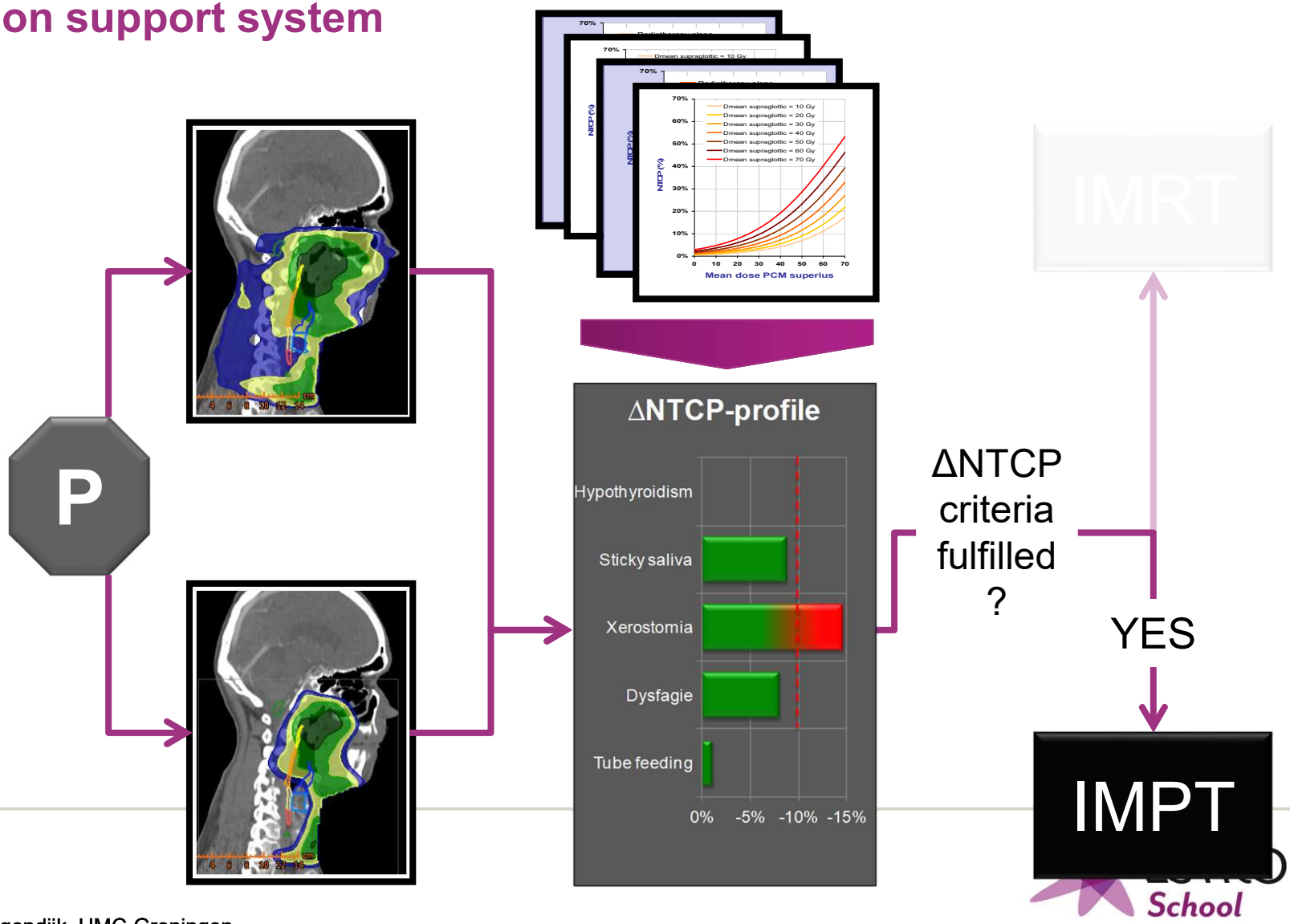
4. Calculate expected **ΔNTCP** = $\mathbf{NTCP_{standard\ IMRT} - NTCP_{SW\text{-}IMRT}}$

Treat with SW-IMRT

Courtesy of Hans Langendijk, UMC Groningen

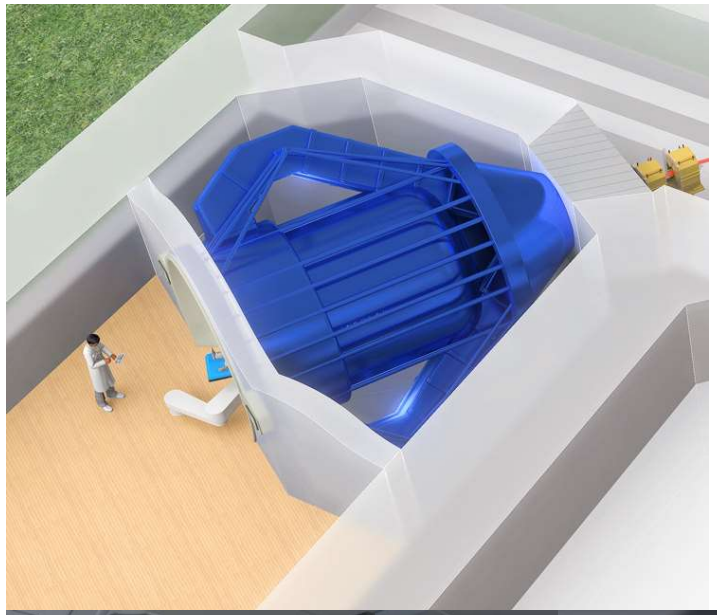
Model-based selection

Decision support system



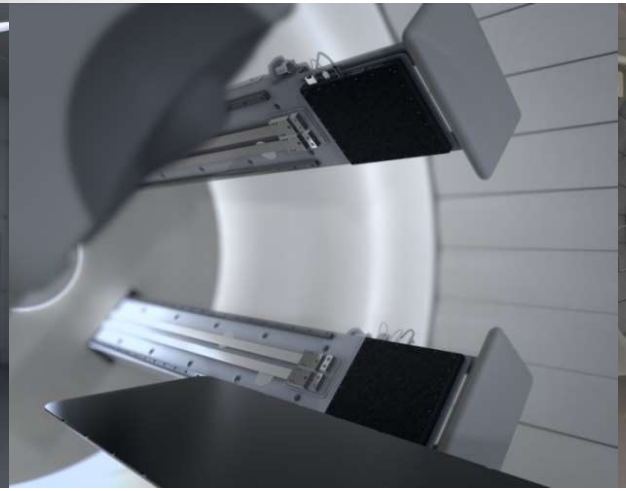
Courtesy of Hans Langendijk, UMC Groningen

Proton site in Dresden



Treatment room

- Isocentric gantry
- Patient couch on robotic arm
- planar X-ray (BEV and orthogonal)
- CT-on-Rails



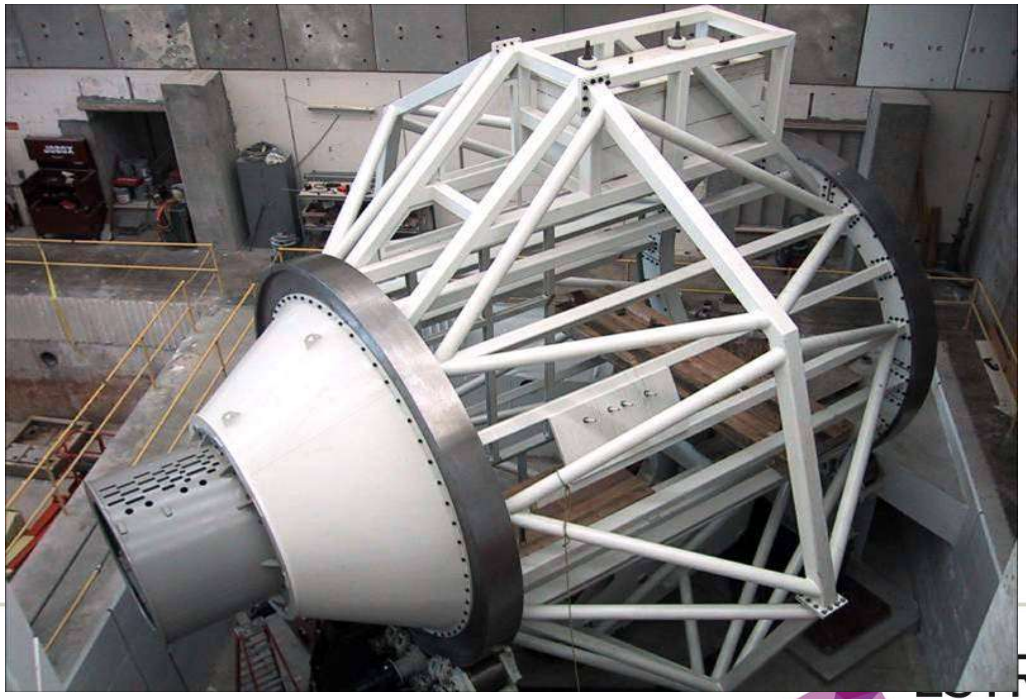
Courtesy: D. Kunath

Proton site in Dresden

Courtesy: D. Kunath

Gantry

- Weight = 120 t
- Diameter = 10 m
- Rotation = ± 185°



Thank you for your attention

Commissioning and QA/QC of equipment and software

Milan TOMSEJ

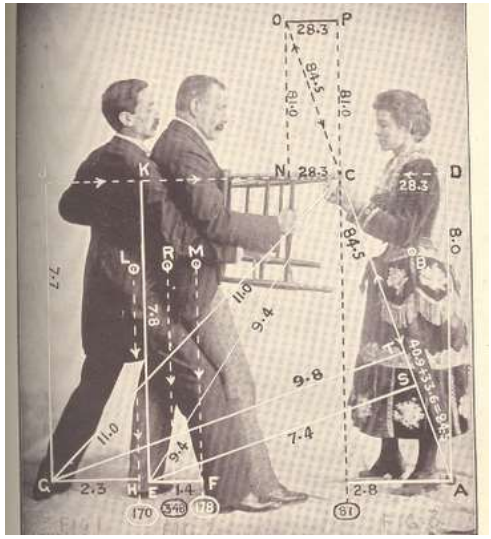
CHU A. Vésale

Charleroi

BELGIUM

ESTRO School

Contents



COMMISSIONING AND ACCEPTANCE

Acceptance and Commissioning Phase

- **Acceptance phase**
  - Performance of equipment meets the minimum requirements (manufacturer's guidelines)
- **Commissioning phase**
  - Is the process through which all the possible machine characteristics relevant to clinical use are investigated, measured, and recorded (medical physicist's guidelines)
  - Data is the standard for clinical use and should be verified periodically

Vendor provided data could only be used as a reference but it should never be used as a substitute for the commissioned data!

Commissioning of a Linear (Medical) Accelerator

Accelerator beam data commissioning equipment and procedures: Report of the TG-106 of the Therapy Physics Committee of the AAPM

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(Received 4 February 2008; revised 18 July 2008; accepted for publication 18 July 2008; published 22 August 2008)

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Delivery of dose within ±5%

- **Sources of uncertainty**
  - Treatment planning (estimated uncertainty of the order of ± 2%)
  - Machine performance on the day (± 2%)
  - Patient set-up and movement (± 3%)

  - Absolute dosimetry/calibration
  - Relative dosimetry (%depth dose, profiles, output factors)

Not much room for error in dosimetry ...

What to Measure?

- Beam data for monitor unit (MU) calculations
- Beam data input for the treatment planning system (TPS)

- Much larger range of measurements
  - To test the accuracy of the TPS
  - To understand the influence of beam modifiers
  - To understand for example skin sparing and use of bolus material

  - **To measure test sets as reference for future QA**

What to Measure?

- At a minimum, the following data should be collected during commissioning:
  - **For photon beams**
    - Percent depth dose (PDD) and profiles
      - In-plane and/or cross-plane at various depths for open and wedge fields
    - Data related to multileaf collimator (MLC) such as inter- and intraleaf leakage, penumbra, tongue and groove effect, etc.
    - Head collimator scatter, total scatter, tray, and wedge factors
  - **For electron beams**
    - PDD, profiles, cone factors, insert factors, and virtual source positions

Absolute and Relative Dose Measurements

- It is convenient to make a distinction between **absolute** and **relative** dose measurements

- **Absolute dose**
  - Determined in reference conditions
  - Use published codes of practice!
- **Relative dose**
  - Measure dose for a wide range of conditions
  - Representative for clinical use

Estimated Time for Commissioning

- **It takes 30 hours for**
  - One PDD and five depth profiles for 15 field sizes for each of five beam modifiers (one open and four physical wedges) for a dual energy accelerator
- 1.5 week for photon beam scanning
  - Equipment setup, change in machine parameters, machine faults, …
- 1 week for point dose collection
- 1-2 weeks for electron beams
- 1-2 weeks analysis and report writing

4-6 weeks for commissioning (excluding acceptance)

Full Image-Guided IMRT System

- **Full commissioning takes twelve weeks at Erasmus MC**
  - Commissioning Cone beam CT scanner
  - Commissioning Electronic Portal Imaging Device
  - Commissioning Automatic Treatment Coach
  - IMRT measurements
  - End-to-end testing
  - R&V system testing
  - …

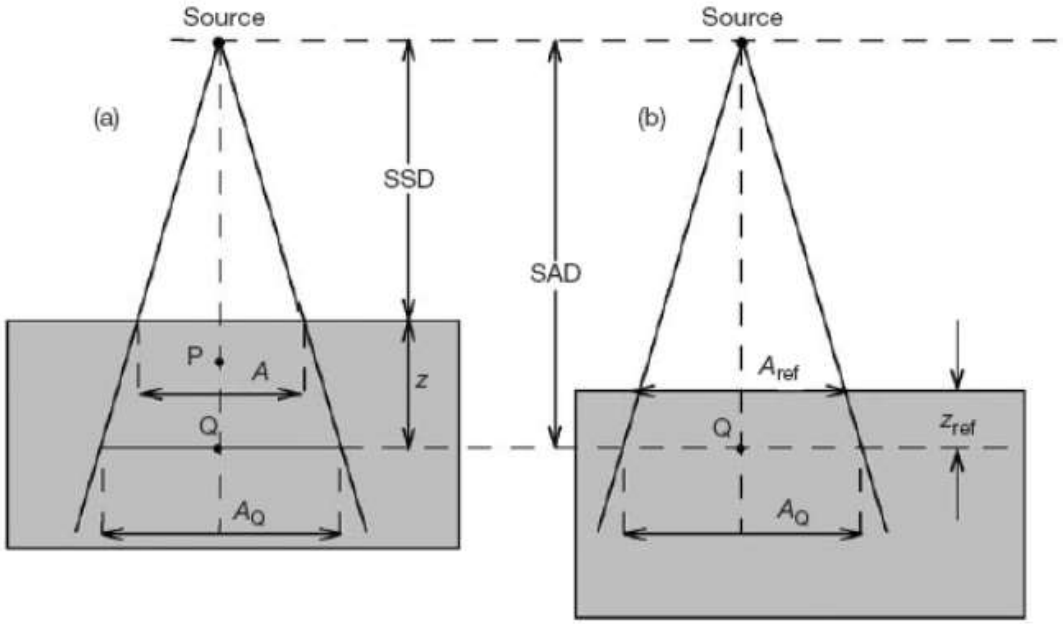
Pre-Measurement Preparation

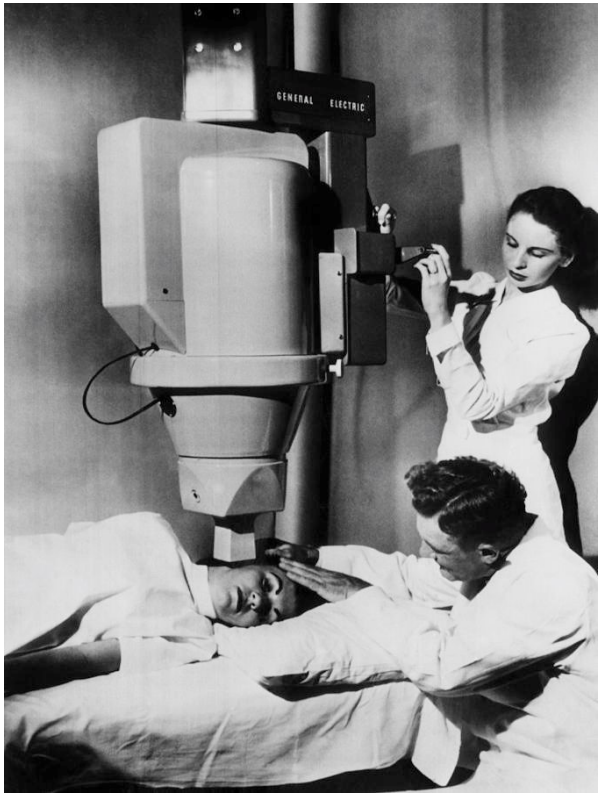
- Sometimes it is the only time that physicists can **extensively** measure radiation beams and beam modifiers

- All in-house dosimetry equipment should be checked for calibration, accuracy, and availability
  - Mechanical motion of water tank
  - Noise and leakage of ionization chambers and diodes
  - Phantom check

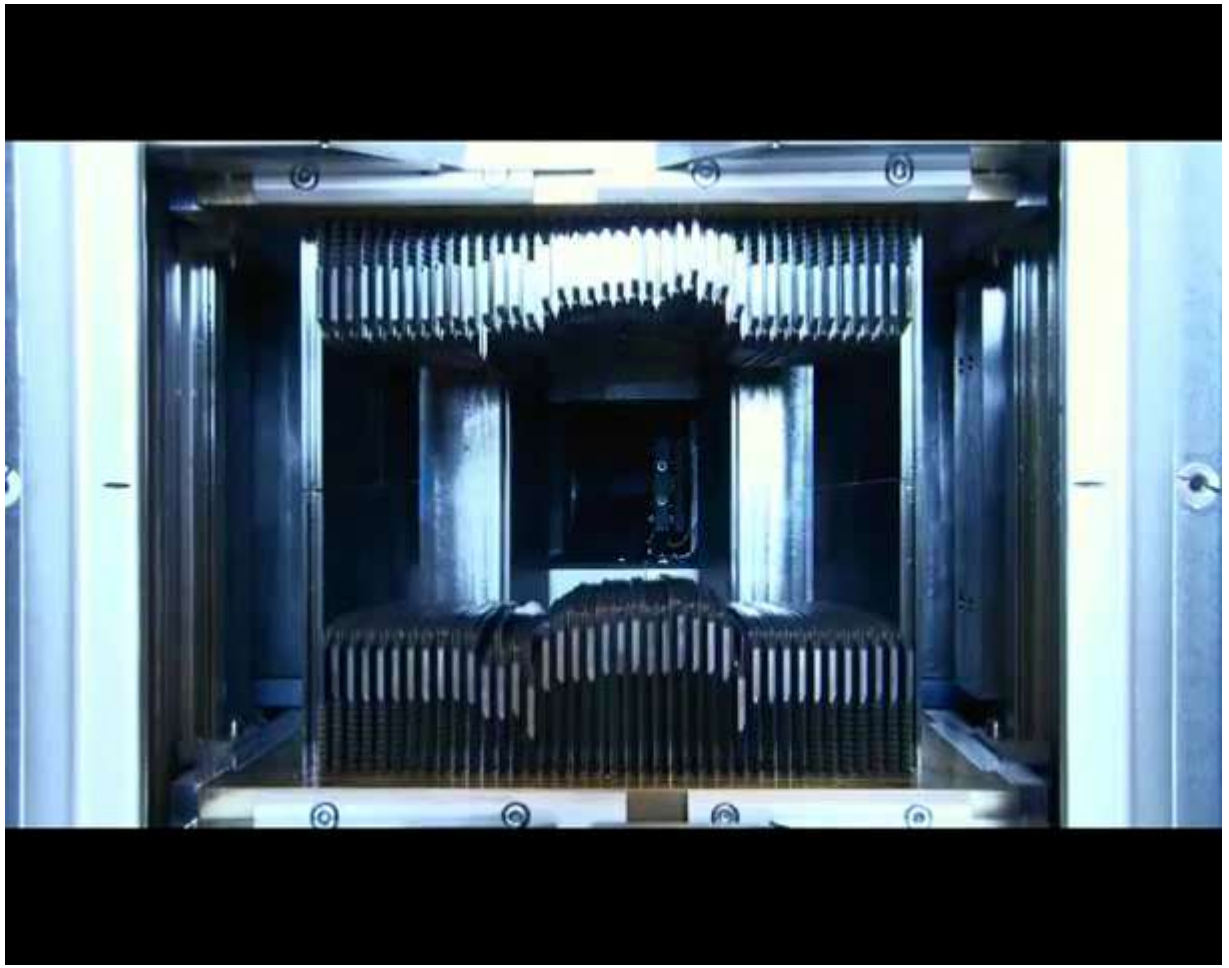
- **Errors in these phases may affect many patients!**
- **BUT DON'T FORGET PATIENT-SPECIFIC QA**

Reference Conditions





Current Technology



Pre-measurement Preparation: Phantom Materials

- **Scanned data**
  - Scanning water phantom

- **Point dose data (non-scanned)**
  - Scanning water phantom
  - Solid phantom
    - For consistency in measurements
    - Plastic materials that mimic water
      - Correction factors required
    - Solid water
    - Detector should fit tightly in drilled cavity

Pre-measurement Preparation: Water Phantom

- At least a 40x40 cm^2 field and a scanning depth of 40 cm
  - $\rightarrow$ Full scatter conditions
- Scanning in both cross- and in-planes (*x and y directions)*
- Position detector with a precision of 1 mm
- Programmable scans

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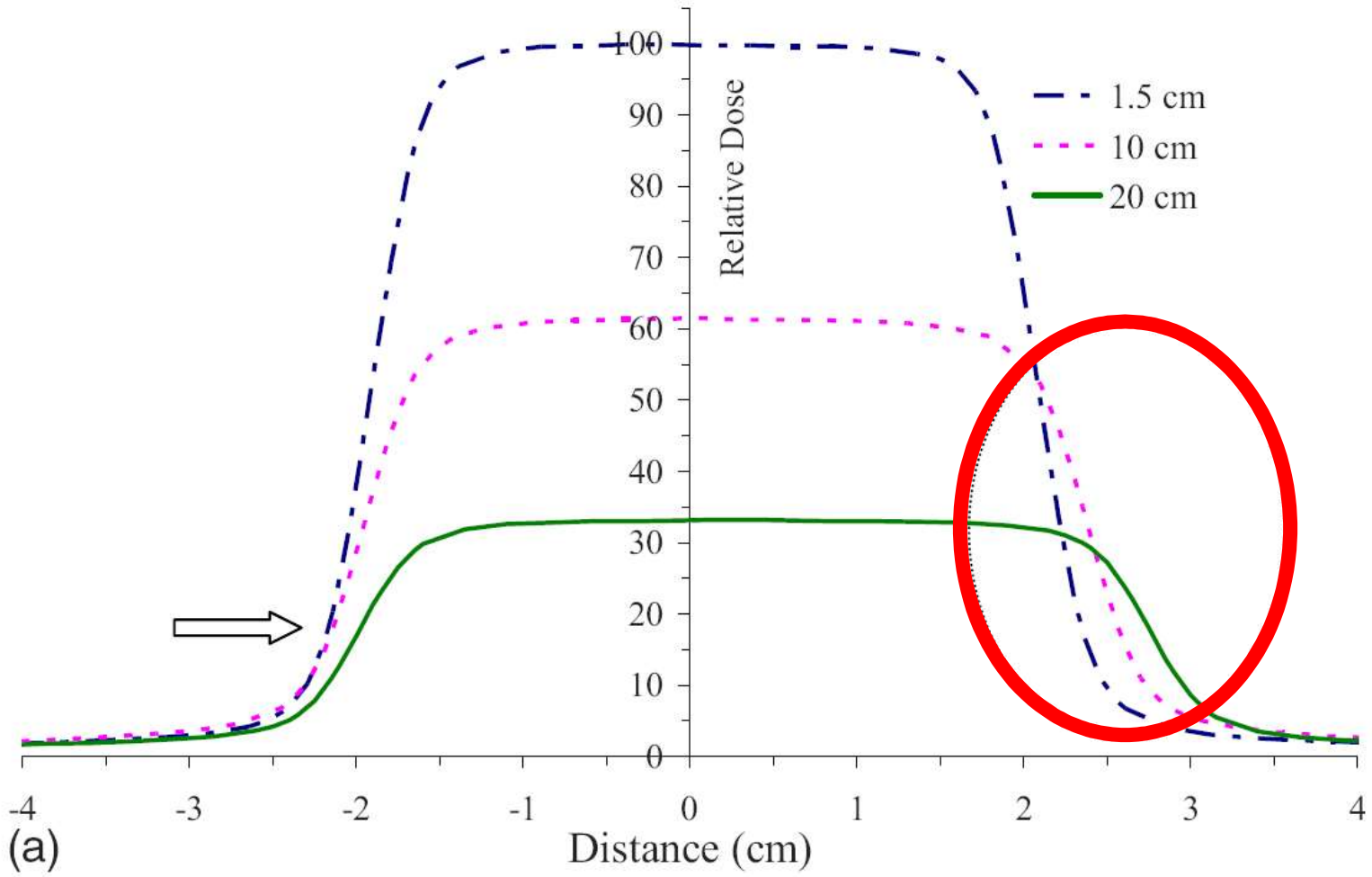
Pre-measurement Preparation: Water Phantom

- **Some important checks**
  - Detector moves parallel to the central axis of the beam
  - Detector moves parallel to the water surface
  - The origin of the scanning coordinate system is correct
  - Orientation of the detector is appropriate relative to the direction of scanning
  - The reference detector does not perturb the measured dose distribution
  - Source-to-surface distance is correct and does not change in time
  - …

Effect of Scanning Arm Tilt



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Pre-measurement Preparation: Choice of Detectors

- **Standard chamber 10^{-1} cm^3**
  - The active volume for a standard Farmer-type ionization chamber is on average 0.6 cm^3
- **Minichamber 10^{-2} cm^3**
  - The active volume is on average 0.05 cm^3
- **Microchamber 10^{-3} cm^3**
  - The active volume is on average 0.007 cm^3 and ideally suited for small field dosimetry such as radiosurgery, gamma knife, CyberKnife, and IMRT

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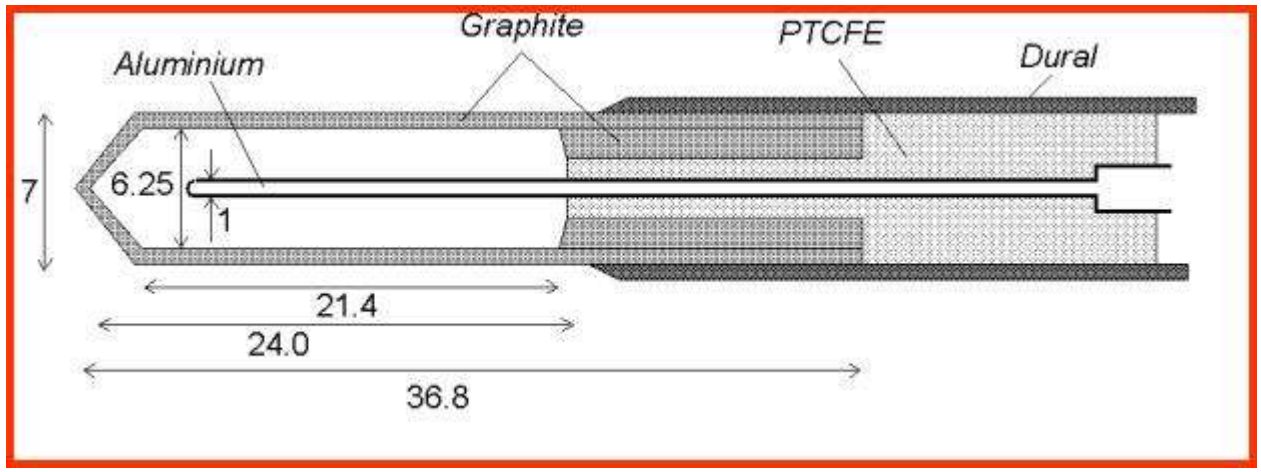
Ion Chamber

- The work horse in dosimetry
  - Small variation in response to energy, dose rate, and reproducibility
- Cylindrical, spherical, and parallel plate
- Standard, mini, and micro



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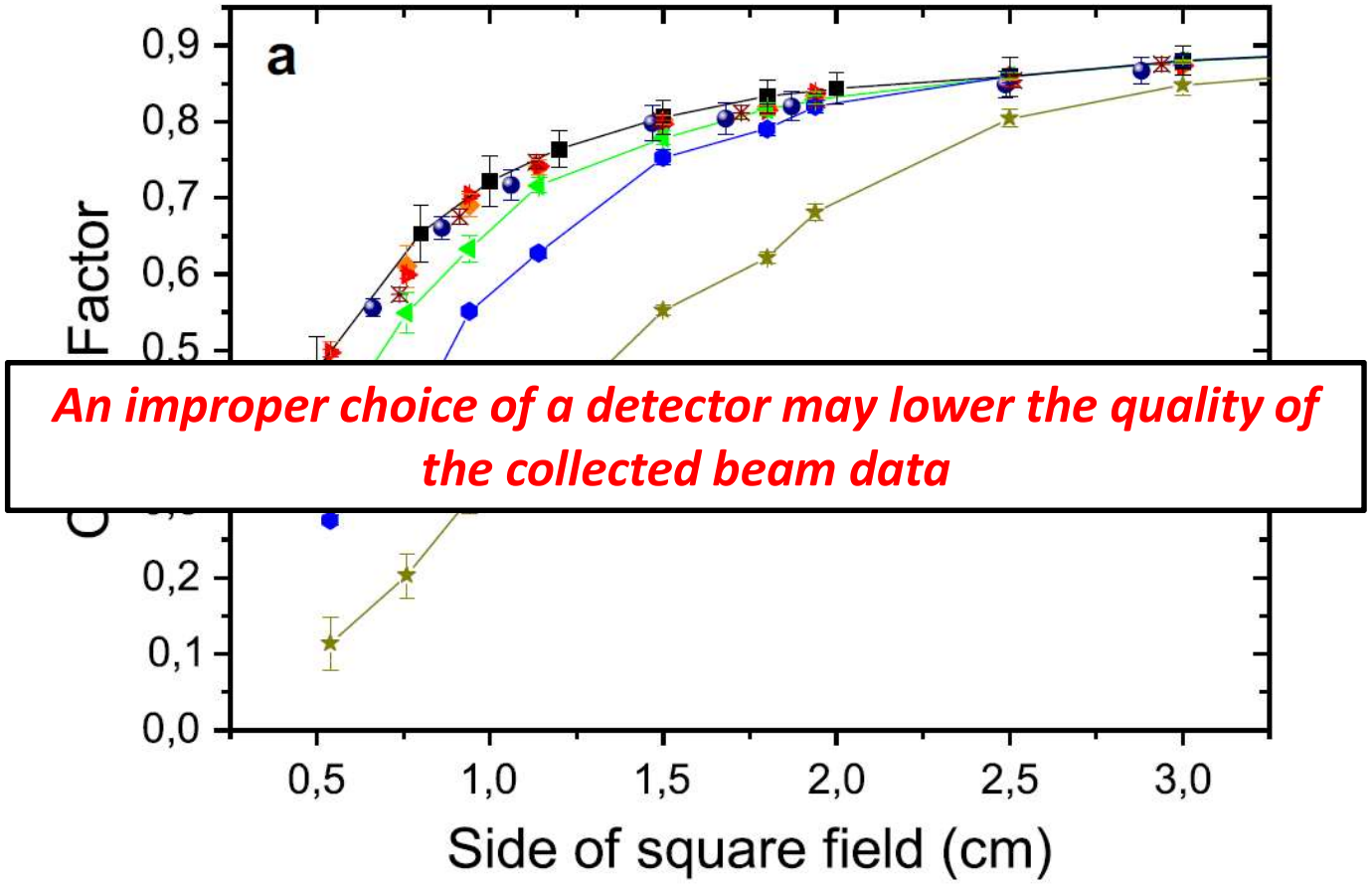
Output Factor for Various Detectors



An improper choice of a detector may lower the quality of the collected beam data

Sánchez-Doblado F, Hartmann GH, Pena J, Roselló JV, Russiello G, Gonzalez-Castaño DM. Phys Med. 2007 Jun;23(2):58-66. Epub 2007 May 2.

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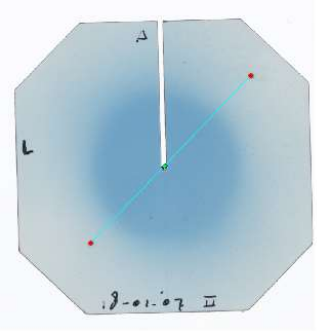
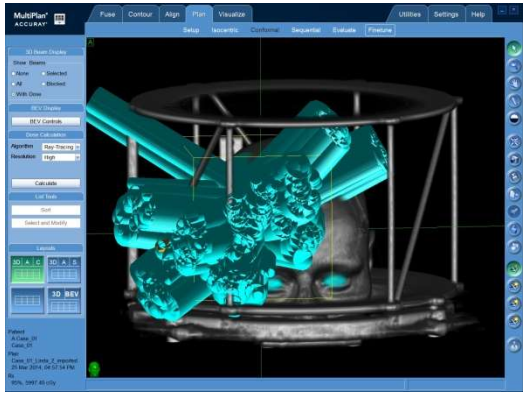
Diodes

- Widely used
- Quick response
- Excellent spatial resolution (small fields)
- Specific types: electron diode and photon diode
- Response is dose rate dependent (SSD or wedge), energy, angular dependence
- Aging effects
- Check with ion chamber

Other Detectors

- Detector arrays
  - Array of ion chamber or diodes
- Diamond detector
  - Solid state detector, expensive
- Thermoluminescent dosimetry
  - Point dose measurement, in-vivo dosimetry
- Gafchromic Film
  - Spatial resolution but not as accurate as ion chambers





TPS COMMISSIONING AND ACCEPTANCE

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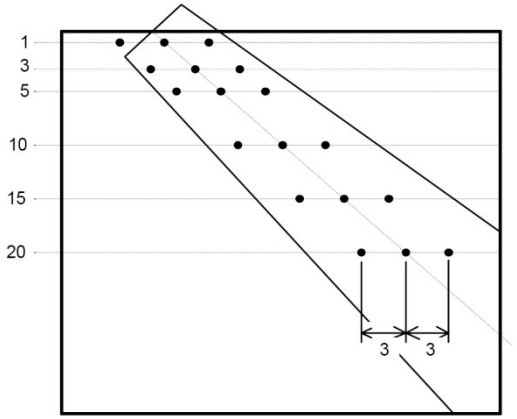
Report on TPS Acceptance and Commissioning

- Quality assurance of 3-D treatment planning systems for external photon and electron beams
  - Practical guidelines for initial verification and periodic quality control of radiation therapy treatment planning systems
  - The Netherlands Commission on Radiation Dosimetry

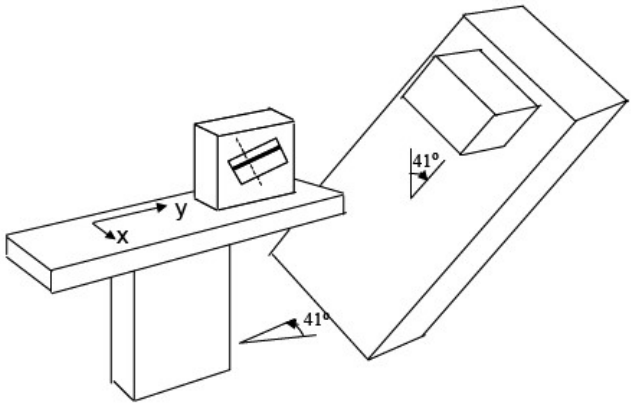
- Other reports:
  - American Association of Physicists in Medicine Radiation Therapy Committee Task Group 53: Quality assurance for clinical radiotherapy treatment planning

Many Tests

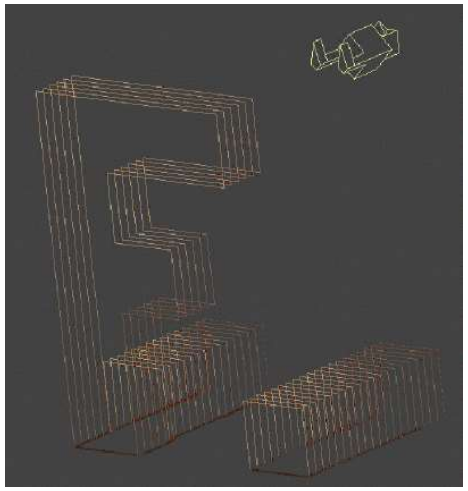
Beam Data Display



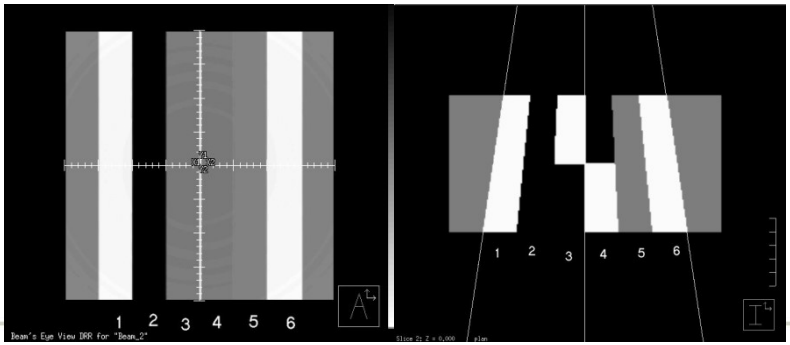
Machine Orientation



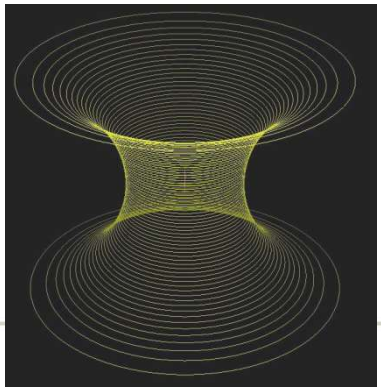
Patient Orientation



DRR Generation



Margin Check



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Margins

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

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- "Second, In retrospect it turned out that the planning system is unable to handle CC margins that are not a multiple of the planning CT slice thickness (2 mm); therefore the real CC margin was not the requested 5 mm but was 4 mm instead."

DOSIMETRY AUDITS

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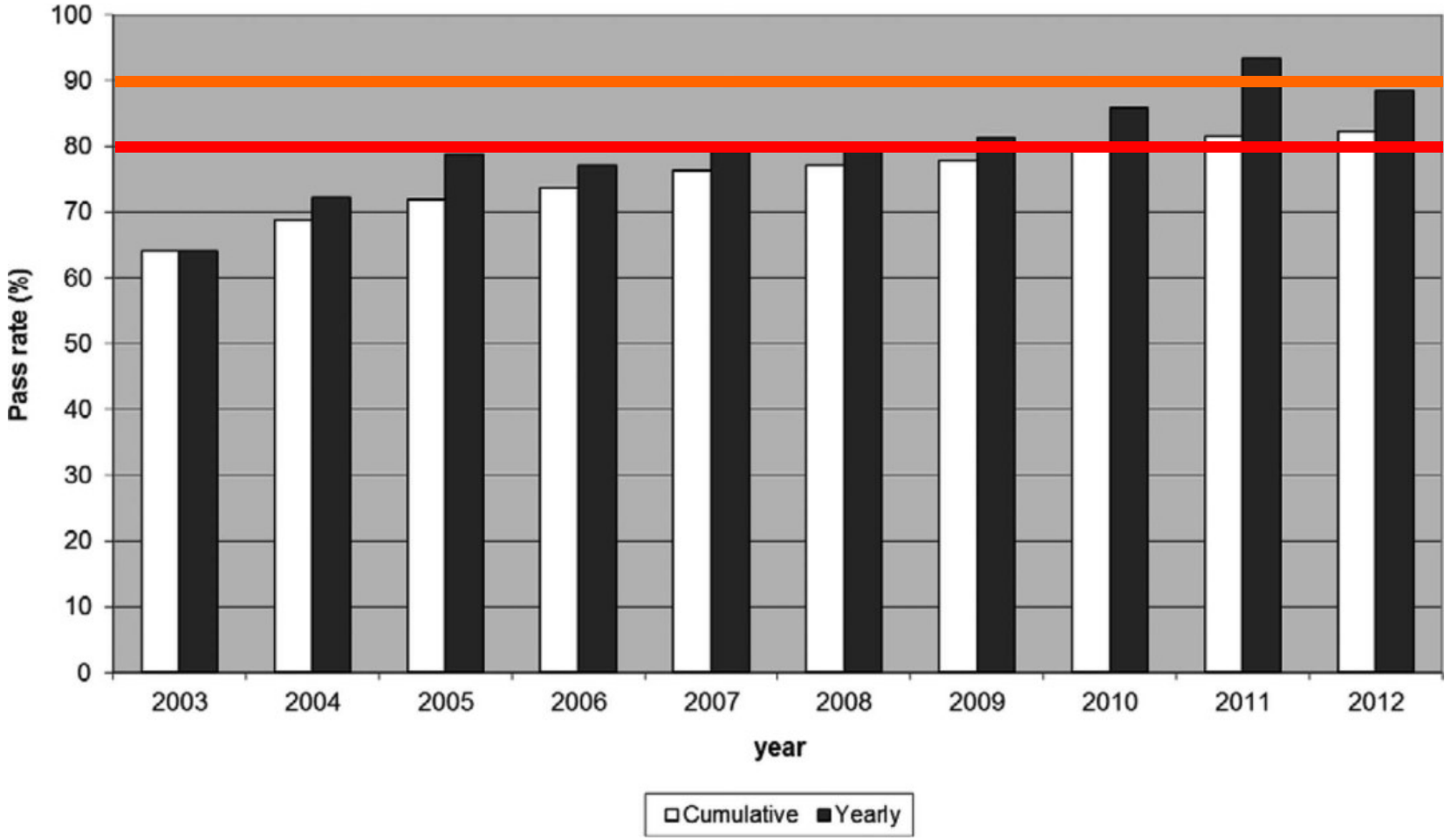
Dosimetry Audits

- No one is infallible …
- Dosimetry may be a difficult and complex task
- A fresh look from outside can verify dosimetry

- **Radiological Physics Center (RPC) TLD service**
  - To verify, on a periodic basis, that an institution is within acceptable limits in beam output for photons and electrons
  - To identify institutions with potential problems and flag them for additional review

Dosimetry Audits: Fail rate is still high!

Fail Rate in IMRT Audits of RPC



From: Andrea Molineu, Nadia Hernandez, Trang Nguyen, Geoffrey Ibbott, and David Followill, Med. Phys. 40 (2), February 2013

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QUALITY ASSURANCE AND QUALITY CHECKS

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Quality Assurance and Quality Checks

Task Group 142 report: Quality assurance of medical accelerators[a)]

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(Received 24 February 2009; revised 8 July 2009; accepted for publication 8 July 2009; published 17 August 2009)

The task group (TG) for quality assurance of medical accelerators was constituted by the American Association of Physicists in Medicine's Science Council under the direction of the Radiation Therapy Committee and the Quality Assurance and Outcome Improvement Subcommittee. The task group (TG-142) had two main charges. First to update, as needed, recommendations of Table II of the AAPM TG-40 report on quality assurance and second, to add recommendations for asymmetric jaws, multileaf collimation (MLC), and dynamic/virtual wedges. The TG accomplished the update to TG-40, specifying new test and tolerances, and has added recommendations for not only the new ancillary delivery technologies but also for imaging devices that are part of the linear accelerator. The imaging devices include x-ray imaging, photon portal imaging, and cone-beam CT. The TG report was designed to account for the types of treatments delivered with the particular machine. For example, machines that are used for radiosurgery treatments or intensity-modulated radiotherapy (IMRT) require different tests and/or tolerances. There are specific recommendations for MLC quality assurance for machines performing IMRT. The report also gives recommendations as to action levels for the physicists to implement particular actions, whether they are inspection, scheduled action, or immediate and corrective action. The report is geared to be flexible for the physicist to customize the QA program depending on clinical utility. There are specific tables according to daily, monthly, and annual reviews, along with unique tables for wedge systems, MLC, and imaging checks. The report also gives specific recommendations regarding setup of a QA program by the physicist in regards to building a QA team, establishing procedures, training of personnel, documentation, and end-to-end system checks. The tabulated items of this report have

- The goal of a QA program for linear accelerators is to assure that the machine characteristics do not deviate significantly from their baseline values acquired at the time of acceptance and commissioning*

*Task Group 142 report

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Daily Checks

TABLE I. Daily.

Procedure	Machine-type tolerance		
	Non-IMRT	IMRT	SRS/SBRT
Dosimetry			
X-ray output constancy (all energies)	3%		
Electron output constancy (weekly, except for machines with unique e-monitoring requiring daily)			
Mechanical			
Laser localization	2 mm	1.5 mm	1 mm
Distance indicator (ODI) @ iso	2 mm	2 mm	2 mm
Collimator size indicator	2 mm	2 mm	1 mm
Safety			
Door interlock (beam off)		Functional	
Door closing safety		Functional	
Audiovisual monitor(s)		Functional	
Stereotactic interlocks (lockout)	NA	NA	Functional
Radiation area monitor (if used)		Functional	
Beam on indicator		Functional	

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Monthly Checks

TABLE II. Monthly.

Procedure	Machine-type tolerance		
	Non-IMRT	IMRT	SRS/SBRT
Dosimetry			
X-ray output constancy			
Electron output constancy		2%	
Backup monitor chamber constancy			
Typical dose rate[a] output constancy	NA	2% (@ IMRT dose rate)	2% (@ stereo dose rate, MU)
Photon beam profile constancy		1%	
Electron beam profile constancy		1%	
Electron beam energy constancy		2%/2 mm	
Mechanical			
Light/radiation field coincidence[b]		2 mm or 1% on a side	
Light/radiation field coincidence[b] (asymmetric)		1 mm or 1% on a side	
Distance check device for lasers compared with front pointer		1mm	
Gantry/collimator angle indicators (@ cardinal angles) (digital only)		1.0°	
Accessory trays (i.e., port film graticle tray)		2 mm	
Jaw position indicators (symmetric)[c]		2 mm	
Jaw position indicators (asymmetric)[d]		1 mm	
Cross-hair centering (walkout)		1 mm	
Treatment couch position indicators[e]	2 mm/1°	2 mm/1°	1 mm/0.5°
Wedge placement accuracy		2 mm	
Compensator placement accuracy[f]		1 mm	
Latching of wedges, blocking tray[g]		Functional	
Localizing lasers	±2 mm	±1 mm	< ±1 mm
Safety			
Laser guard-interlock test		Functional	

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Annual Checks

TABLE III. Annual.

Procedure	Machine-type tolerance		
	Non-IMRT	IMRT	SRS/SBRT
Dosimetry			
X-ray flatness change from baseline		1%	
X-ray symmetry change from baseline		±1%	
Electron flatness change from baseline		1%	
Electron symmetry change from baseline		±1%	
SRS arc rotation mode (range: 0.5–10 MU/deg)	NA	NA	Monitor units set vs delivered: 1.0 MU or 2% (whichever is greater) Gantry arc set vs delivered: 1.0° or 2% (whichever is greater)
X-ray/electron output calibration (TG-51)		±1% (absolute)	
Spot check of field size dependent output factors for x ray (two or more FSs)		2% for field size $<4\times4$ cm^2, 1% $\geq4\times4$ cm^2	
Output factors for electron applicators (spot check of one applicator/energy)		±2% from baseline	
X-ray beam quality (PDD_{10} or TMR_{10}^{20})		±1% from baseline	
Electron beam quality (R_{50})		±1 mm	
Physical wedge transmission factor constancy		±2%	
X-ray monitor unit linearity (output constancy)	±2% ≥5 MU	±5% (2–4 MU), ±2% ≥5 MU	±5% (2–4 MU), ±2% ≥5 MU

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Three Levels of Action

- **Level 1: Inspection Action**
  - A sudden and significant deviation from the expected value not exceeding a tolerance level
  - Thresholds evolve from the QA data
- **Level 2: Scheduled Action**
  - Deviations slightly exceeding tolerance
  - Clinical impact over the course of a few days not significant
  - Action should be scheduled within one or two working days
- **Level 3: Immediate Action**
  - Exceeding tolerance has direct clinical impact
  - Stop treatment

ACCIDENTS IN RADIOTHERAPY

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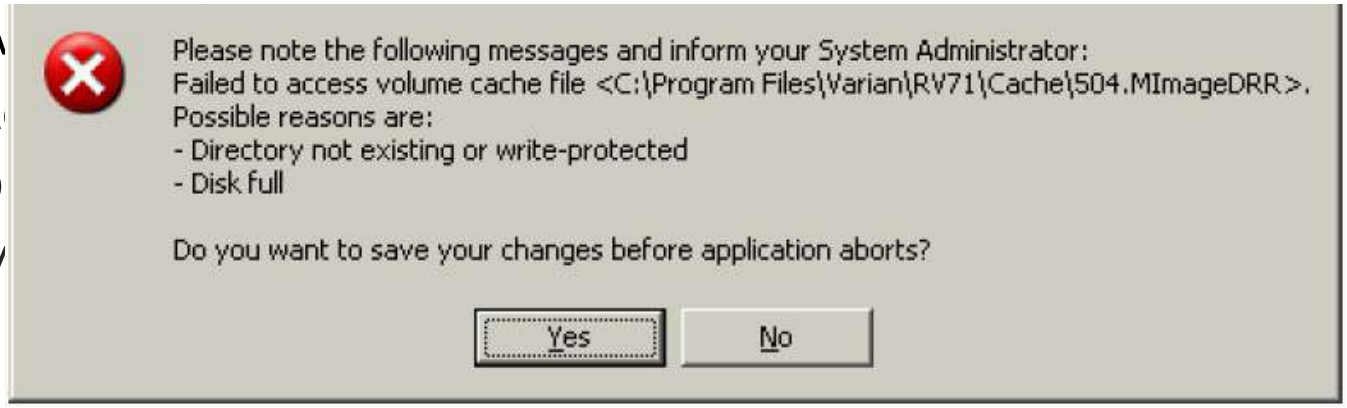
Mistreatment IMRT H&N (2005)

- IMRT of Oropharyngeal cancer
- Initial IMRT plan was verified with an EPID
- Patient treated correctly for the first 4 fractions
- Position verification by kV imaging

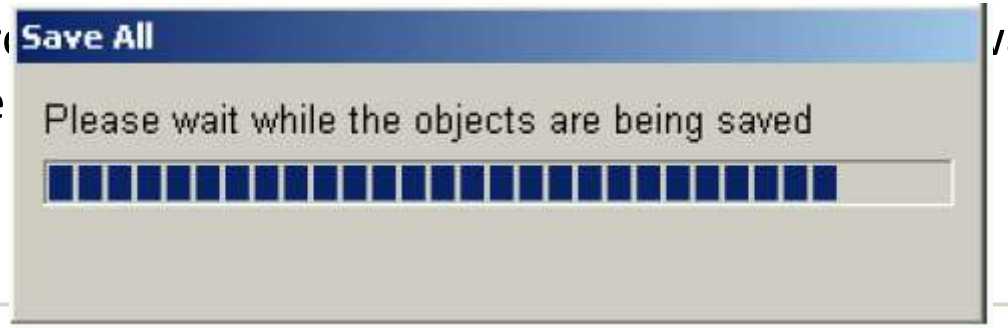
- After several fractions, the physician reviewed the plan and wanted a revised treatment plan with reduced dose to the teeth

Mistreatment IMRT H&N (2005)

- New plan was created and “save all” button was clicked
- Prior to writing the data, data was temporarily held until all the data was receiv
  - A
  - D
  - M



- Problem with software (not responding program)
- The case was reopened
- No MLC contr as re-opened; MLC fields we



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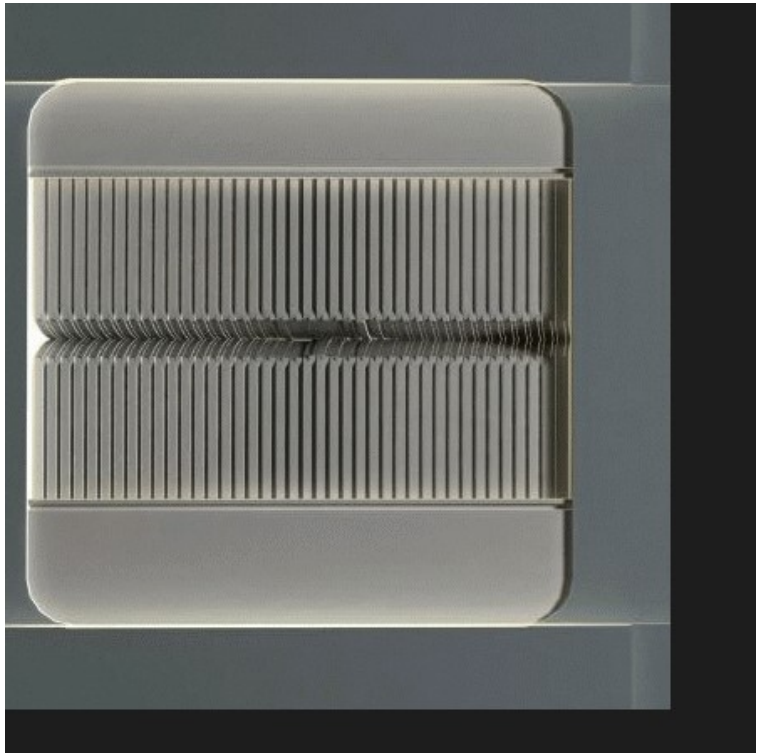
Mistreatment IMRT H&N (2005)

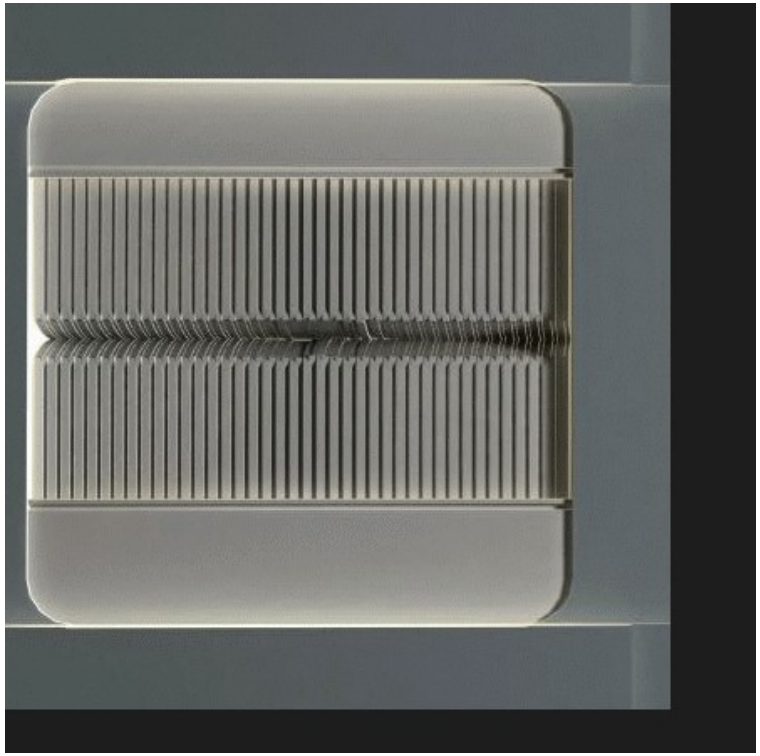
Dynamic IMRT



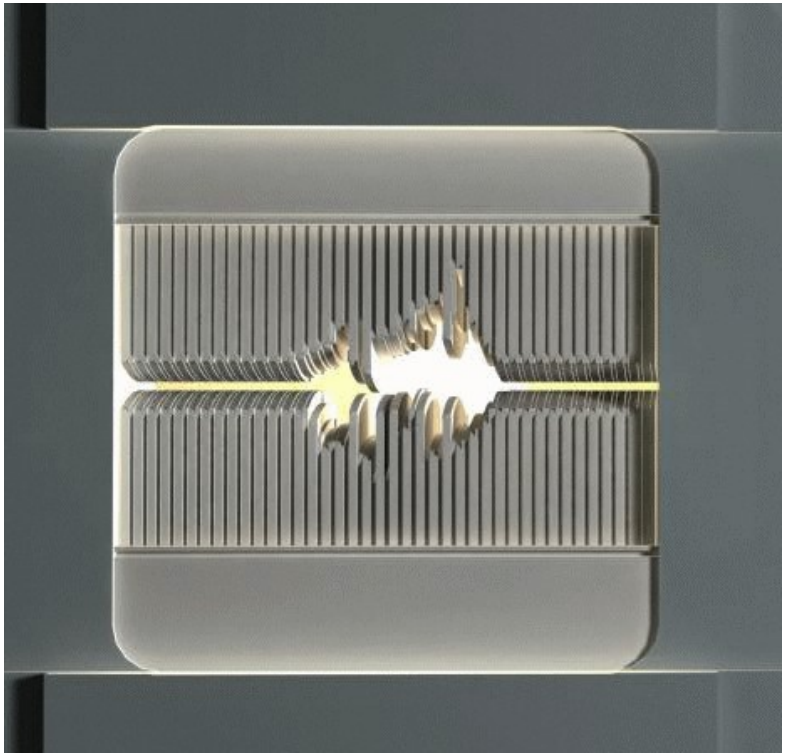
New York Times

Mistreatment IMRT H&N (2005)

Dynamic IMRT



Open Field



New York Times

Mistreatment IMRT H&N (2005)

- Monitor units from IMRT MLC field were used for the open field
- Patient was treated with incorrect plan for 3 fractions
- The console screen would have indicated that MLC was not being used during treatment.
- After 3 fractions, QA was run for the new treatment plan. Operator noticed lack of MLC shapes and modulation

- **Double Trouble**
  - Open fields instead of conformal fields
  - MUs of IMRT
  - **Patient received 13 Gy per fraction**

Mistreatment IMRT H&N (2005)

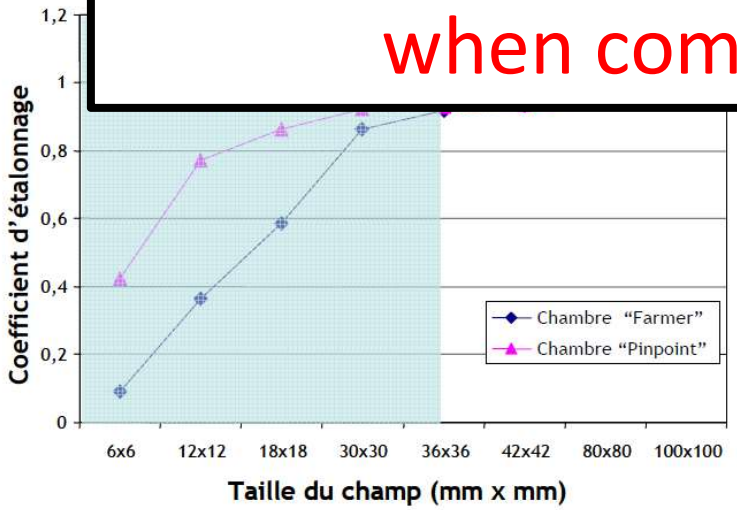
- **Modern RT department**
  - State-of-the-art machines
  - Application of IMRT
  - 3D Image verification protocol
  - Patient-specific QA protocol

- **Lessons learned**
  - Pre-treatment IMRT QA is required
  - Visual inspection of the treatment plan prior to treatment
  - Measurement or calculation check: use the actual treatment files

Measurement for dosimetric data input in TPS

- France 2006-2007
- 145 patients
- Non-adequate detector for small beams measurements
- Detected by the company 1 year after
- Neu

Importance of the choice of detectors when commissioning !



IRSN: Note de synthese sur les surexpositions au Centre Hospitalier Universitaire de Toulouse

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Other Accidents

- **Bad interpretation of physical units (Costa Rica, 1996)**
  - 115 patients, 17 died
  - Bad interpretation of unit of time
  - 0.3 minute: 30 seconds?
  - Observation of non-usual severe reactions (skin burnt, abdominal pain, diarrhea, etc)
- **Bad calculation of MUs for wedged beams**
  - France 2004-2005
  - Several hundreds of patients (+8%), 23 over-irradiated severely (+20 à 30%), 5 died
  - Misunderstanding between 2 wedge techniques (hard and dynamic wedge)

CLINICAL RATIONAL OF QA

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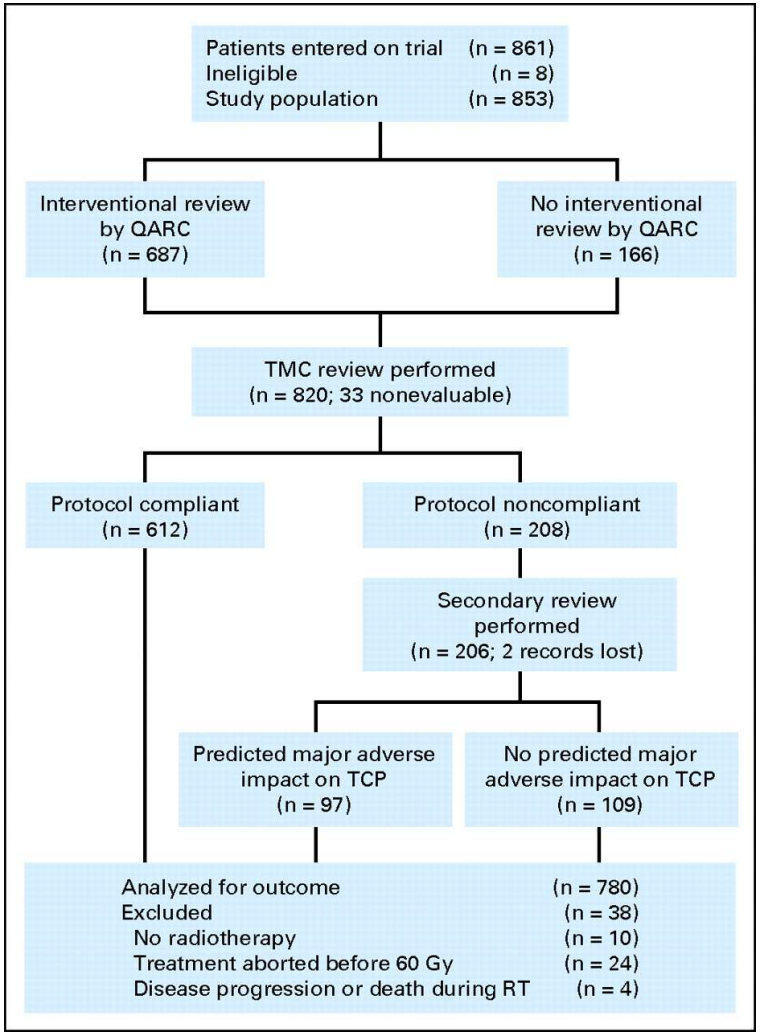
Trial Design

- This trial was undertaken to test the benefit of adding the hypoxic cell cytotoxin tirapazamine (TPZ) to cisplatin (CIS) -based chemoradiotherapy in patients with locoregionally advanced squamous cell carcinoma of the head and neck
- **Radiotherapy**
  - RT in both arms
    - 70 Gy in 35 fractions in 7 weeks to gross disease
    - 50 Gy in 25 fractions in 5 weeks to electively treated areas
- **Chemotherapy**
  - Arm A: Cisplatin
  - Arm B: Cisplatin + Tirapazamine
- Powered at 90% to detect 10% improvement in survival at two years

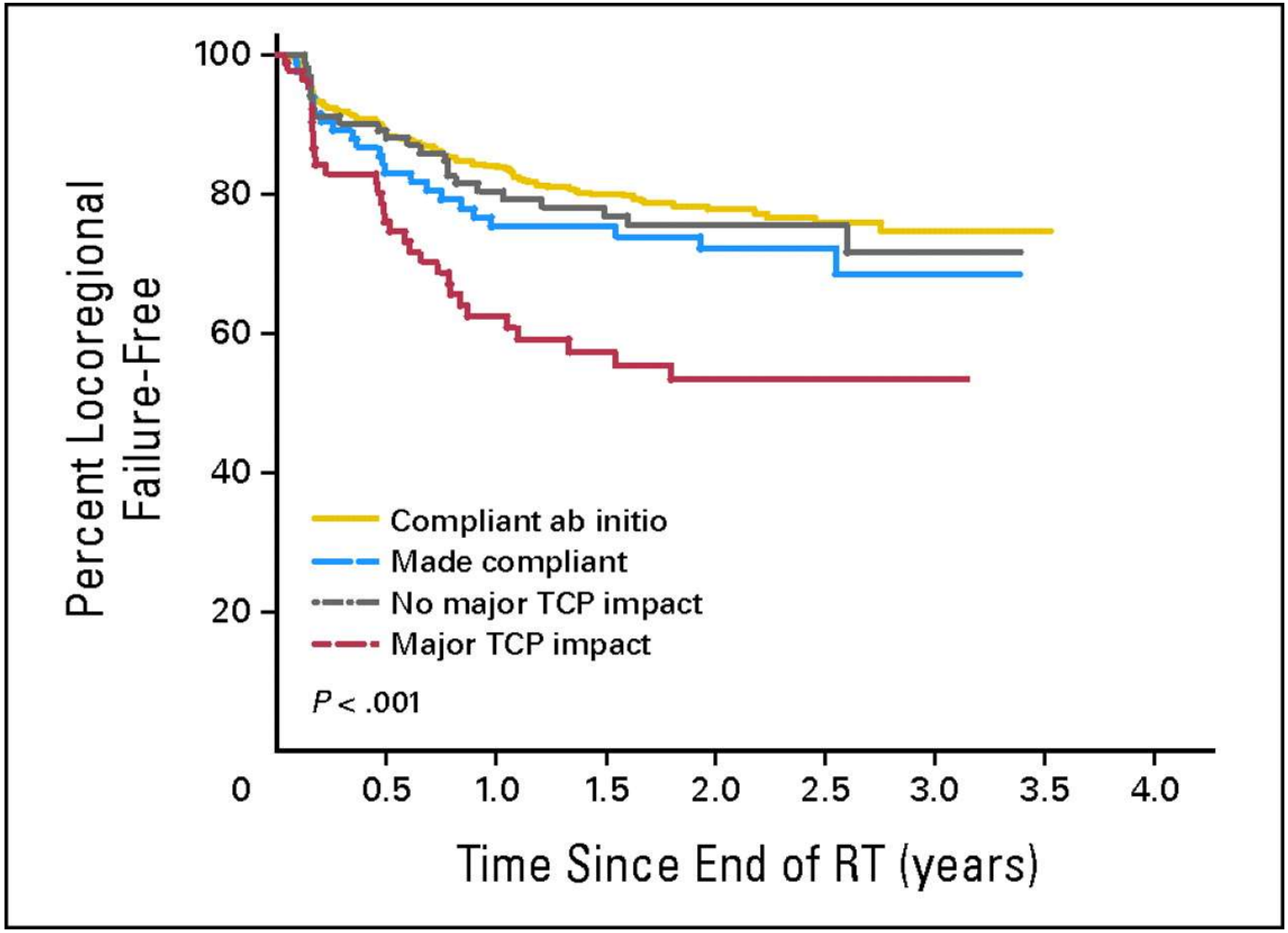
Lester J. Peters, Brian O'Sullivan, Jordi Giralt, Thomas J. Fitzgerald, Andy Trotti, Jacques Bernier, Jean Bourhis, Kally Yuen, Richard Fisher and Danny Rischin. JCO 2010;28:2996-3001.

CONSORT flow chart of reviews and analyses



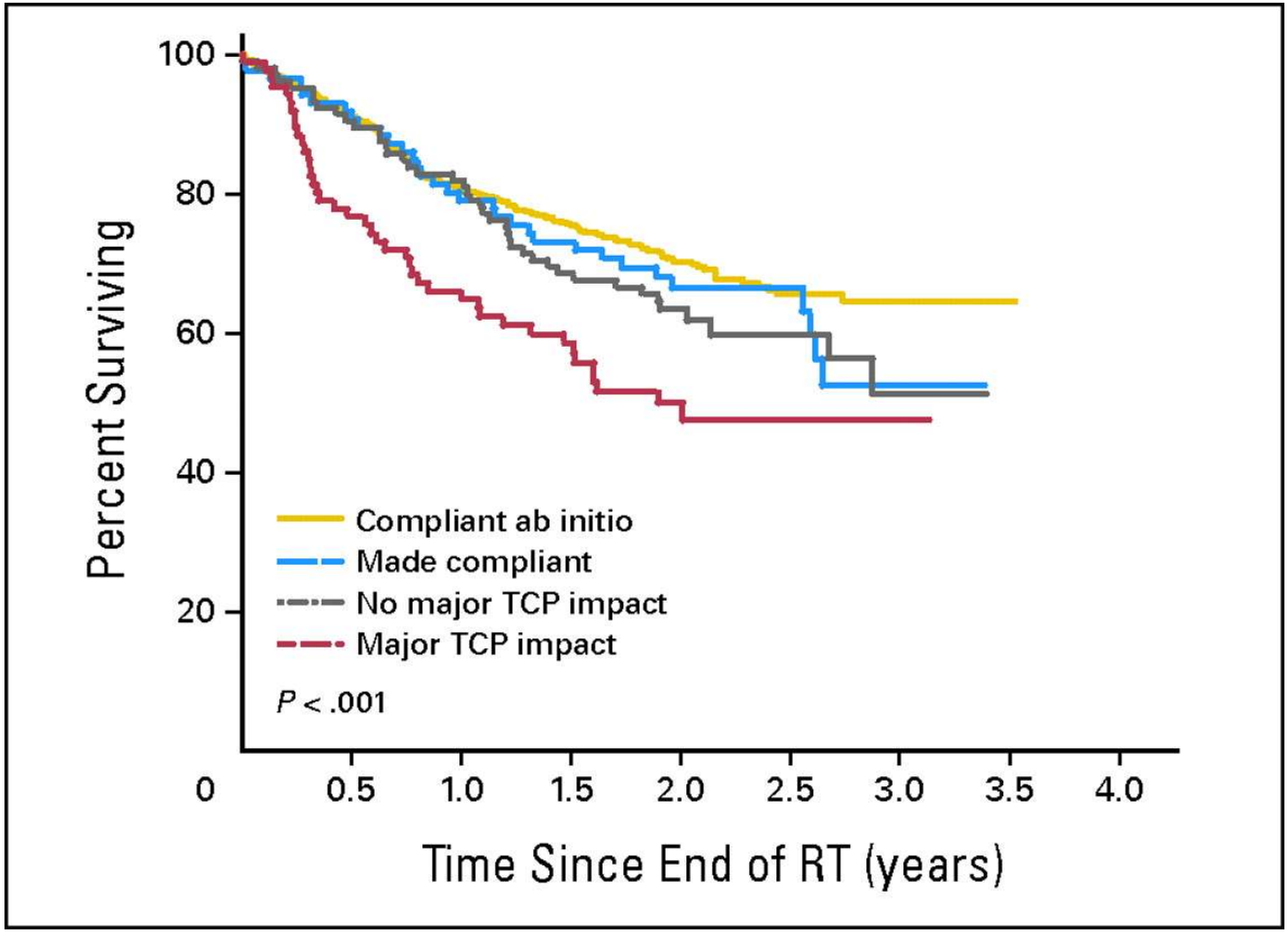
Peters L J et al. JCO 2010;28:2996-3001

Time to locoregional failure by deviation status



Peters L J et al. JCO 2010;28:2996-3001

Overall survival by deviation status



Peters L J et al. JCO 2010;28:2996-3001

CONCLUSIONS

Conclusions

- In radiotherapy a high dose is delivered to the tumor
  - Carries risk of severe complications
  - Must be delivered safely and accurately
  - Dose should be delivered within ±5% of the prescribed dose
  - Considering other uncertainties this leaves ±3% for dosimetry

  - QA can improve survival

RISK ANALYSIS

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Why Use Prospective Analysis?

- **HFMEA: H**ealthcare **F**ailure **M**ode and **E**ffect **A**nalysis

- Aimed at prevention of adverse events
- Doesn’t require previous bad experience (patient harm)
- Makes system more robust

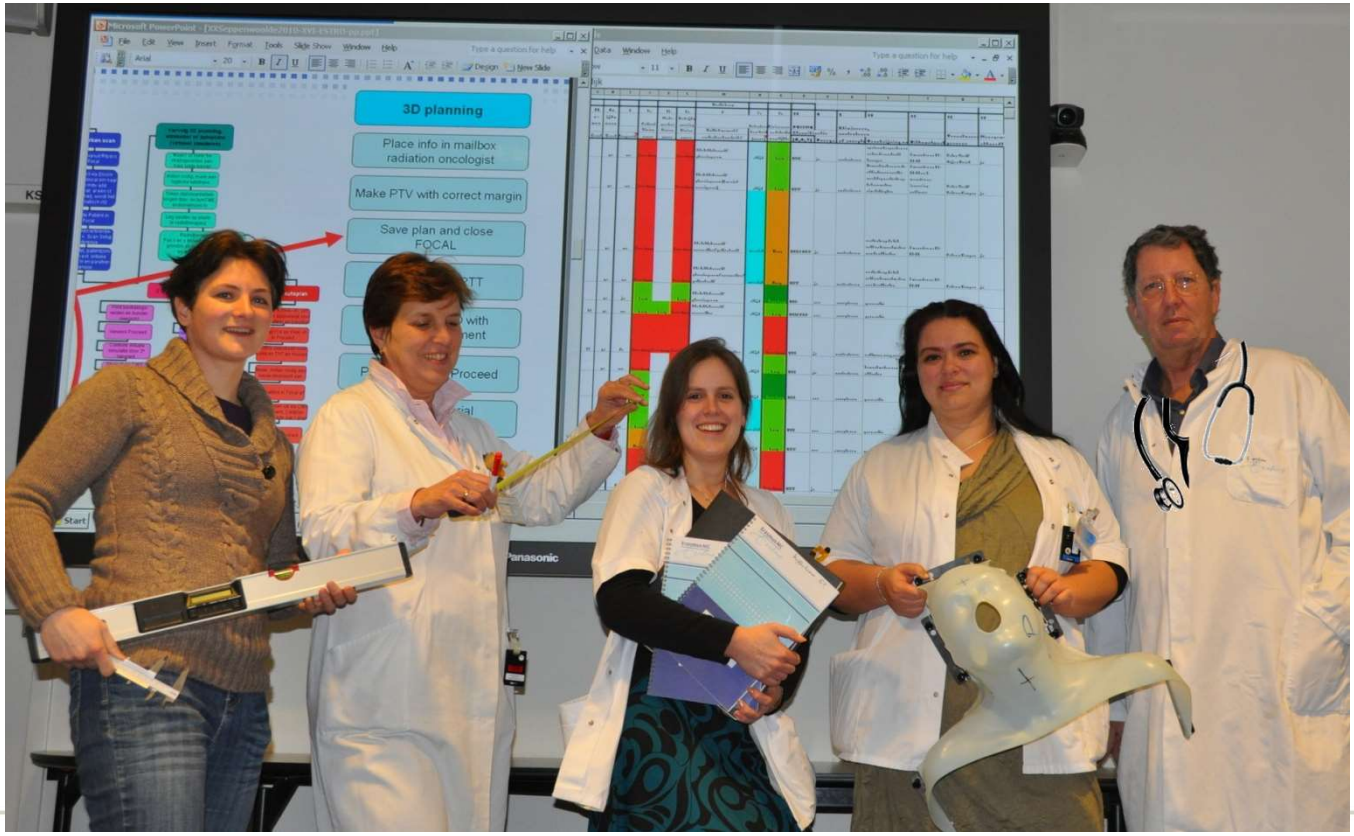
- Identify and prioritize high-risk processes
- Identify potential “failure modes”
- For each “failure mode,” identify the possible effects
- For the most critical effects, conduct a root cause analysis

Healthcare Failure Mode Effect Analysis Process

1. Define the topic
2. Assemble the team
3. Graphically describe the process
4. Conduct the analysis
5. Identify actions and outcome measures

The team

- A multidisciplinary **team has to be assembled** including subject matter experts and an advisor



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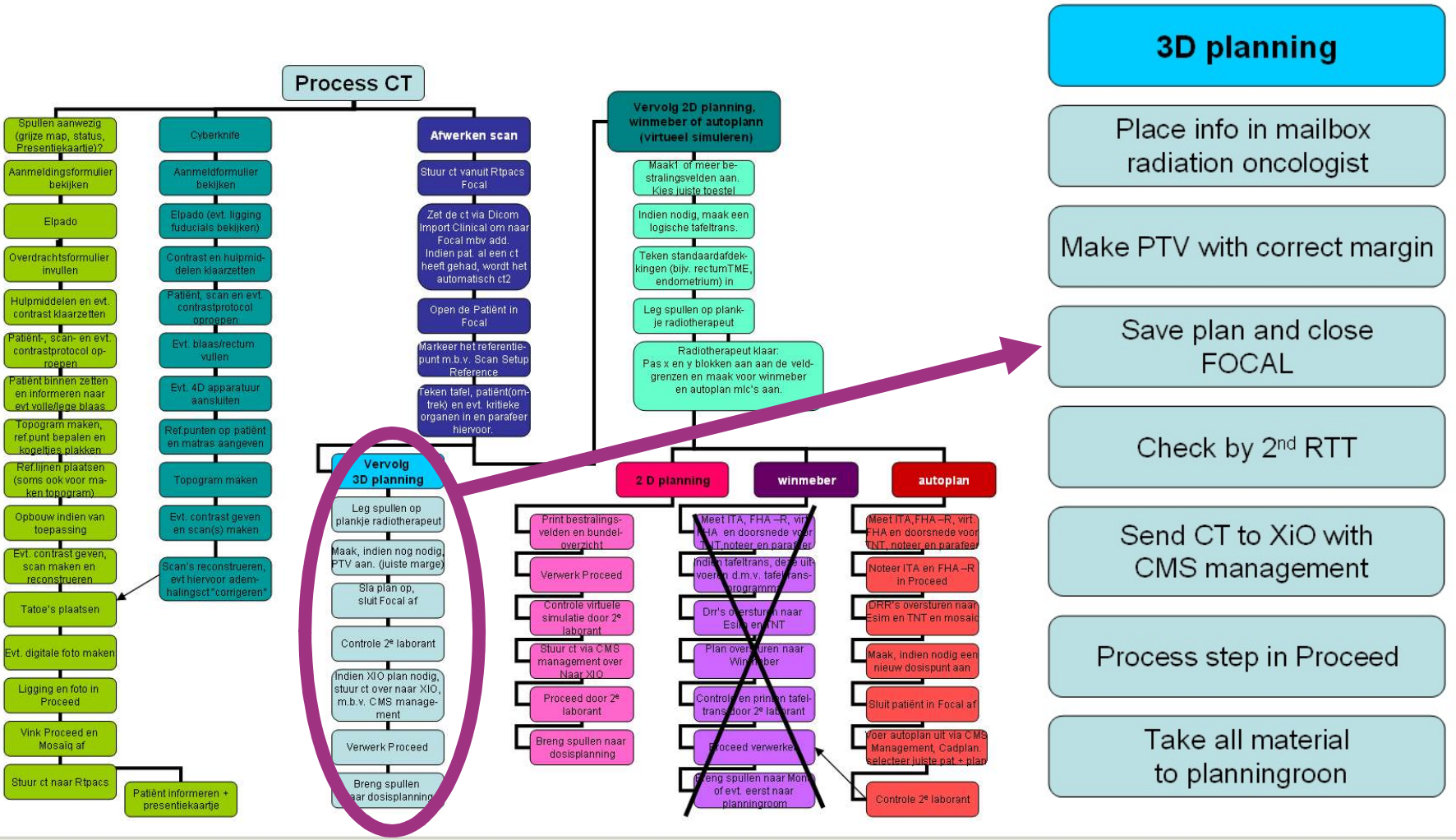
Graphically Describe the Process



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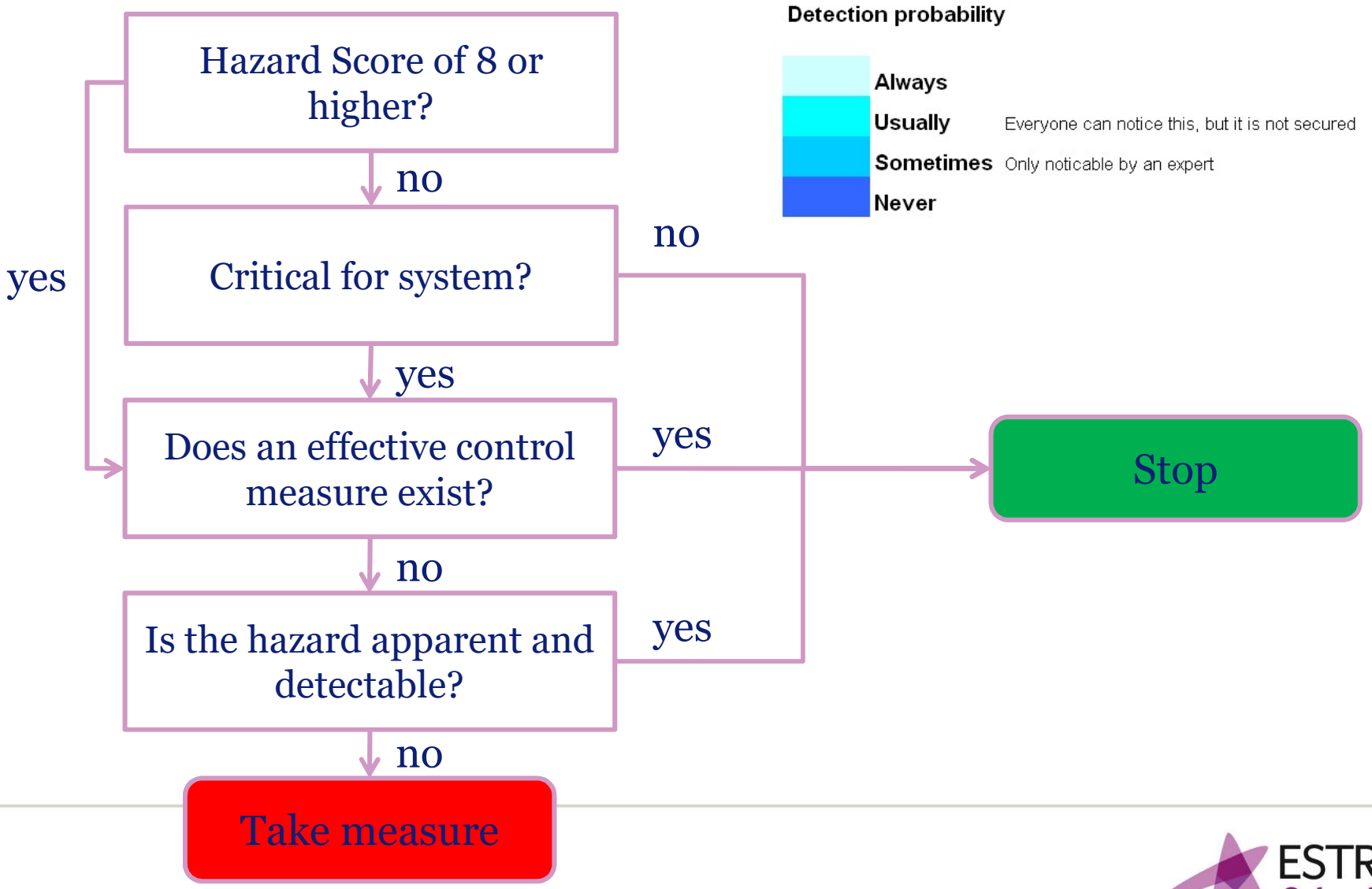
HFMEATM Hazard Scoring Matrix

Probability	Severity			
	Catastrophic	Major	Moderate	Minor
Frequent	16	12	8	4
Occasional	12	9	6	3
Uncommon	8	6	4	2
Remote	4	3	2	1

HFMEA Decision Tree



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  - Procedure for performing a failure mode effect and criticality analysis, November 9, 1949, United States Military Procedure, MIL-P-1629

Thank you!

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In-vivo Dosimetry

by Vibeke Nordmark Hansen

Royal Marsden NHS Trust, UK and

Tom Depuydt

University Hospital of Brussels Vrije University, Belgium

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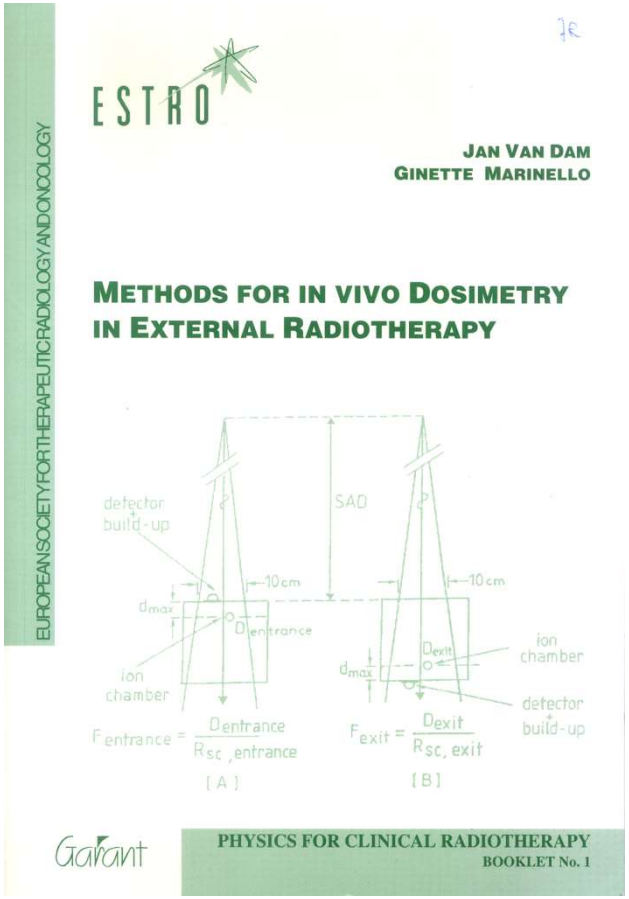
The philosophy .....



"In vivo dosimetry is the methodology of choice in verifying whether a correct dose is actually being delivered to the patient, and is as such a crucial tool in quality assurance of the treatment of the individual patient."

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The philosophy …..

Deviations in dose delivery for an individual patient may arise due to the influence of:

patient contours
patient mobility
inhomogeneities
internal organ motion
transferring treatment data from the treatment planning system or simulator
the treatment machine settings and calibration
positioning the patient and beam modifiers
…….

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The philosophy …..

I*n vivo* dosimetry is:

- The ultimate check at the patient level

recommended by several national and international organizations (AAPM, ICRU and NACP) UK: “Towards safer Radiotherapy”

- Incorporated in some counties legislation

able to detect systematic errors in dose delivery

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SYSTEM AND MEASUREMENT CONFIGURATION

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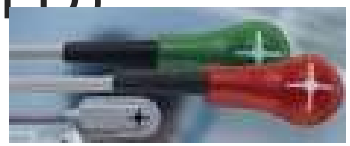
System & measurement configuration

- Radiation detectors
  - Semiconductors (diodes)
  - Thermo Luminescent Dosimeters (TLD)
  - …..



- Dose registration system
  - Electrometers for diodes
  - TLD readers

- EPID dosimetry
- Measurement
  - Tolerance /Action level protocols

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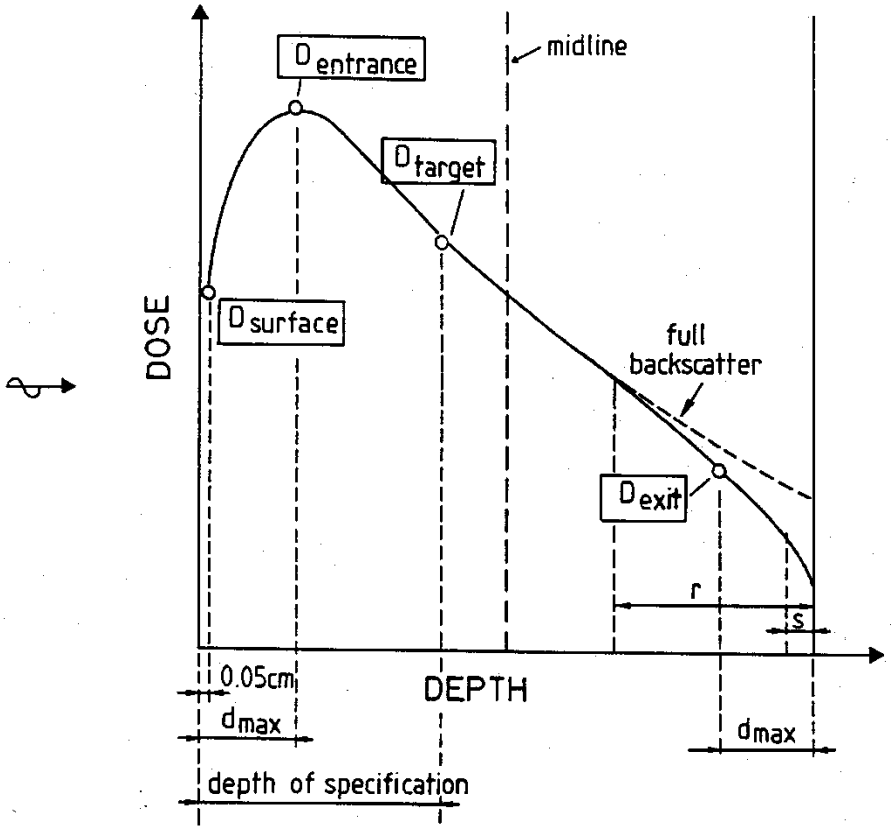
System & measurement configuration



Measurement of the entrance and exit dose, $D_{ent.}$ and D_{exit}, provide information about whether:

- Calculated out-put dose is correct according to pts. anatomy

- Target volume will receive the intended dose

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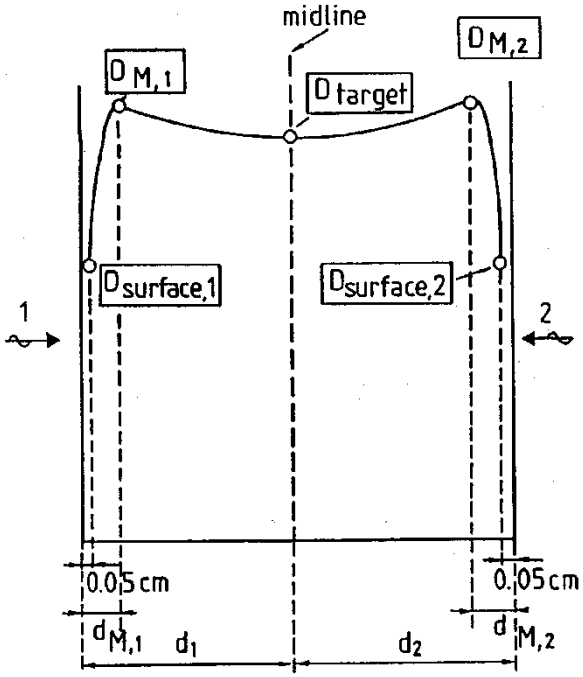
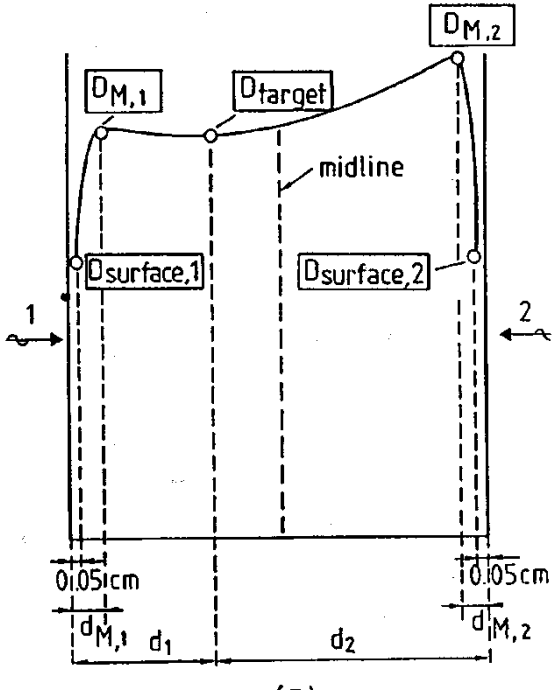
System & measurement configuration



Based on the measurements of the entrance and exit dose, $D_{ent.}$ and D_{exit}, actual mid plane or target dose can be found.



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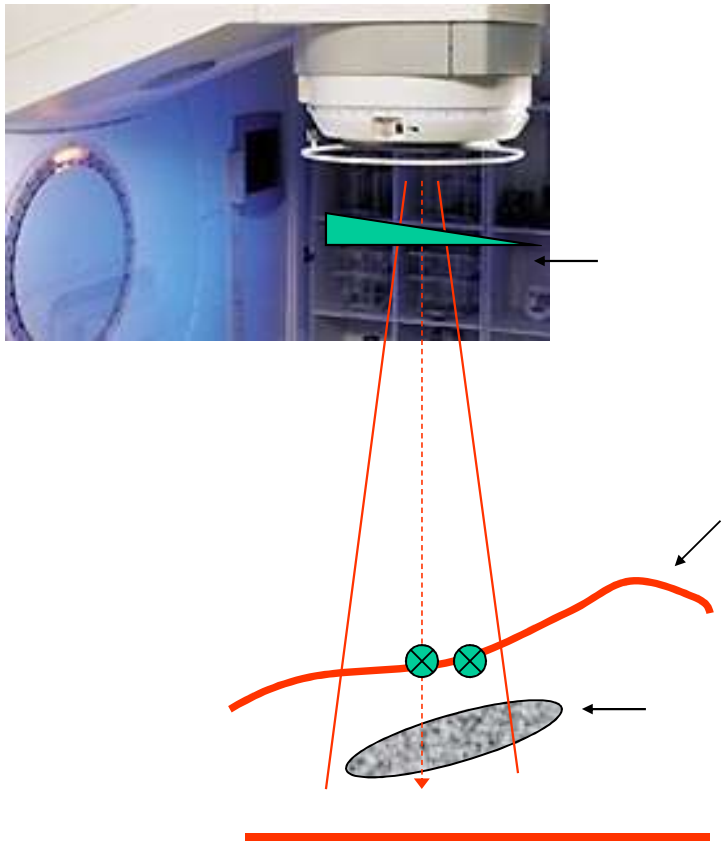
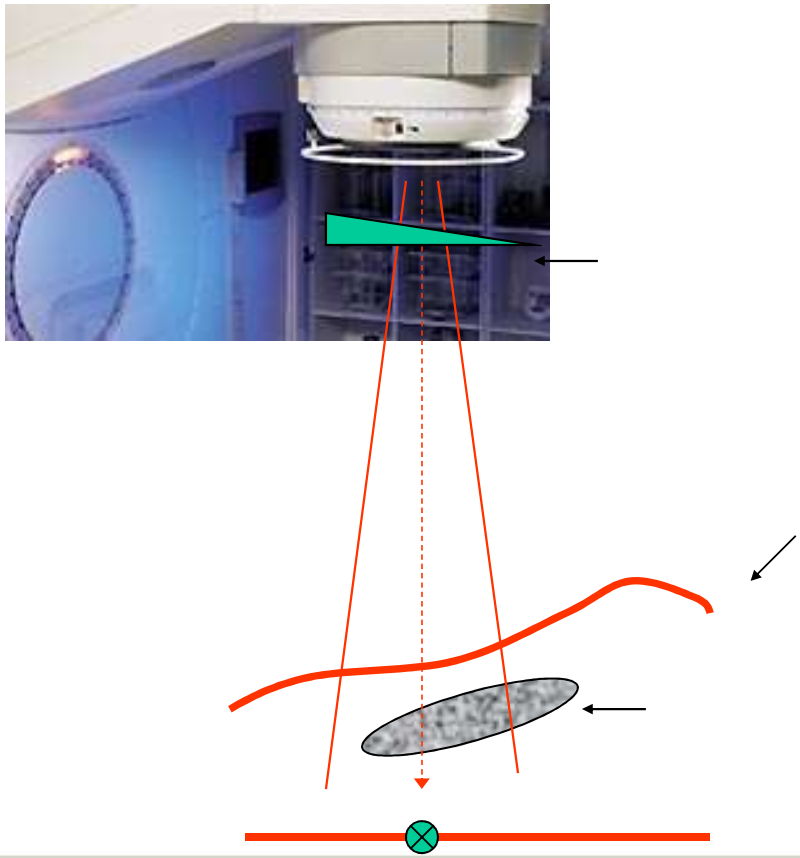
System & measurement configuration

- Entrance dose measurements, on axis, will verify correct out-put and correct SSD.
- Entrance dose measurements, off axis, will verify appropriate use of wedge according to anatomy



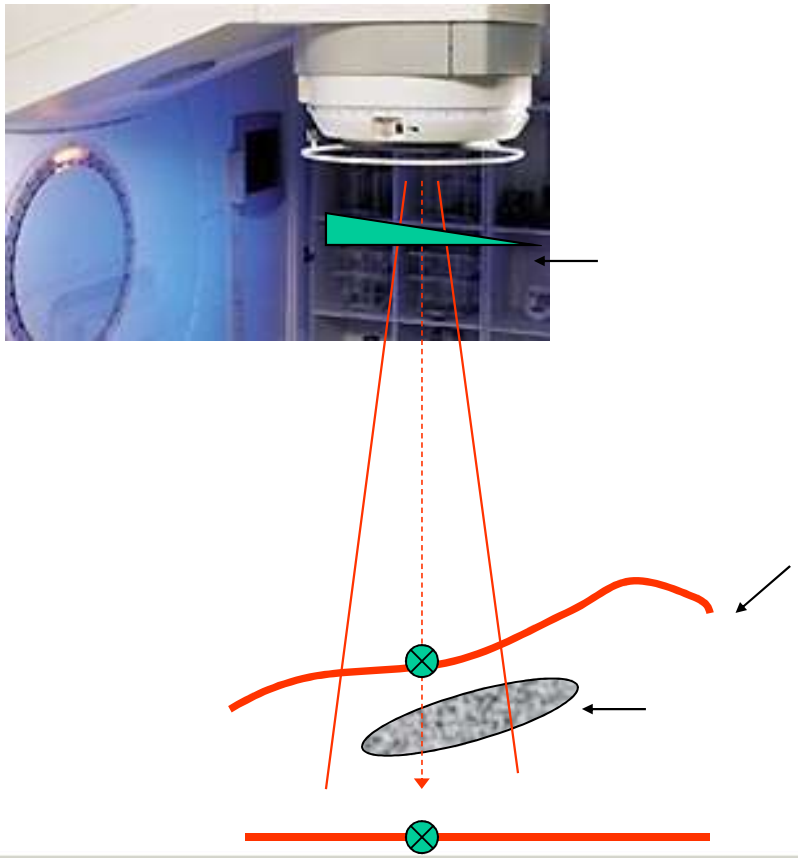
System & measurement configuration

- Exit dose measurements, on axis, will verify whether calculated monitor units are correct according to thickness and tissue density.



System & measurement configuration

- Combined exit and entrance measurement can provide information about mid plan dose

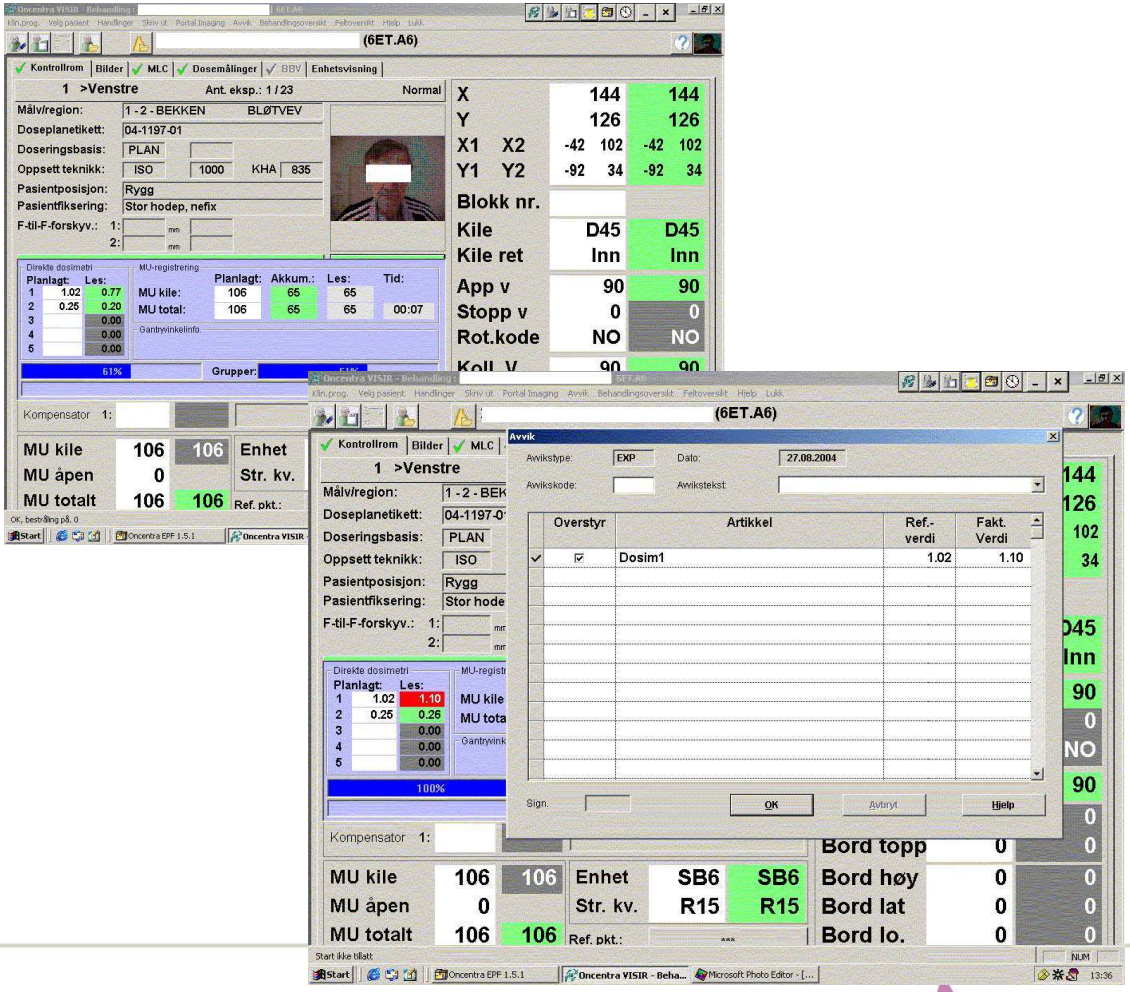


System & measurement configuration

In vivo measurements

Dose registration and automatic comparison with expected values

Action suggested and taken according to predefined protocol



DETECTORS

DETECTORS

- Semiconductors (diodes, MOSFET)
- Thermo Luminescent Dosimeters (TLD)
- Electronic portal device (EPID)
- ….

Diodes

- The diodes in use for *in vivo* dosimetry are silicon detectors.

- The response of the diods depend on:
  - accumulated dose,
  - dose rate,
  - temperature
  - beam energy

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Diodes

- Radiation produces electrons (-) and ’holes’ (+)
- These are attracted to the positive and negative side
- A current in the circuit is thus induced

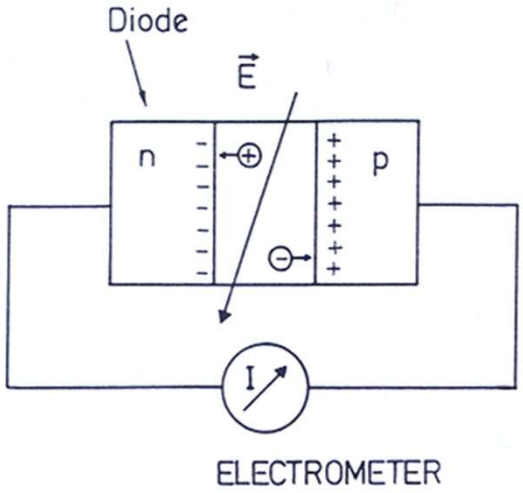
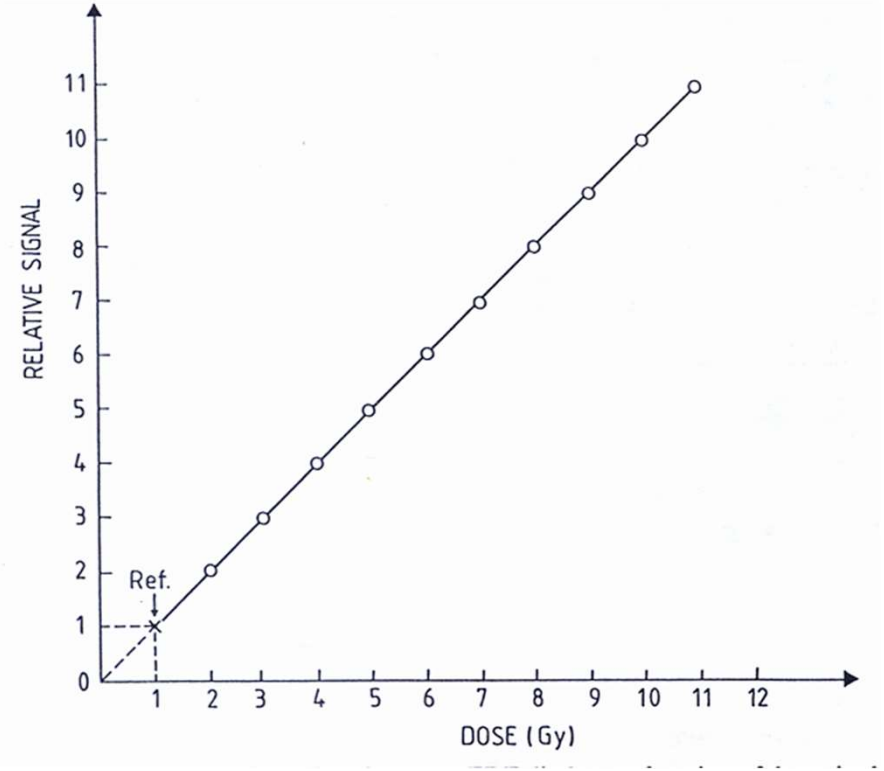


Illustration of a diode detector circuit.

Diodes

Dose response relationship for a given detector:

- a linear response is preferable.
- otherwise correction factors have to be introduced.



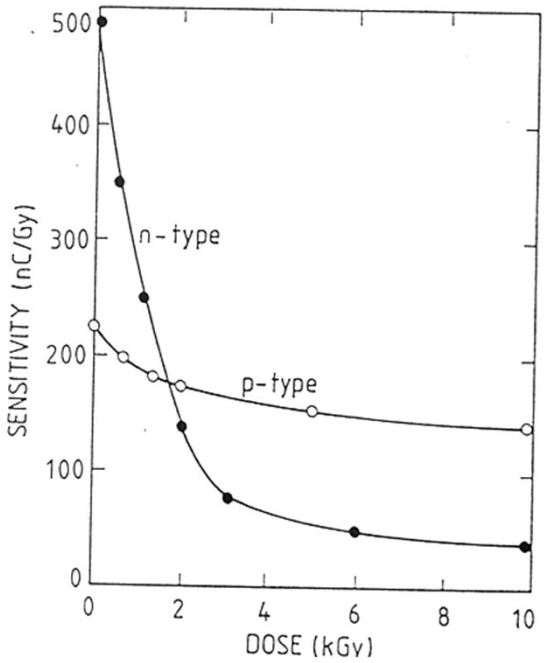
Diodes

Sensitivity of the diode decreases with accumulated dose:

- Pre-irradiation reduces the change in response

(Detectors can be pre-irradiated up to 20kGy all n-type diodes are pre-irradiated)

- Regularly calibration is required



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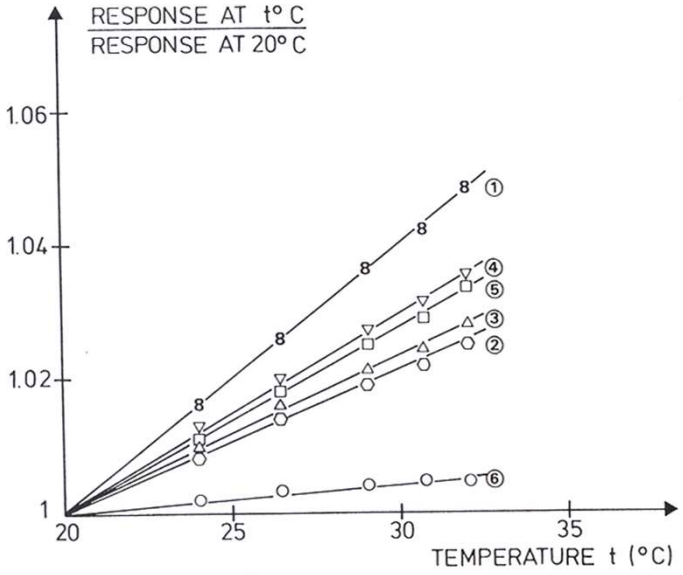
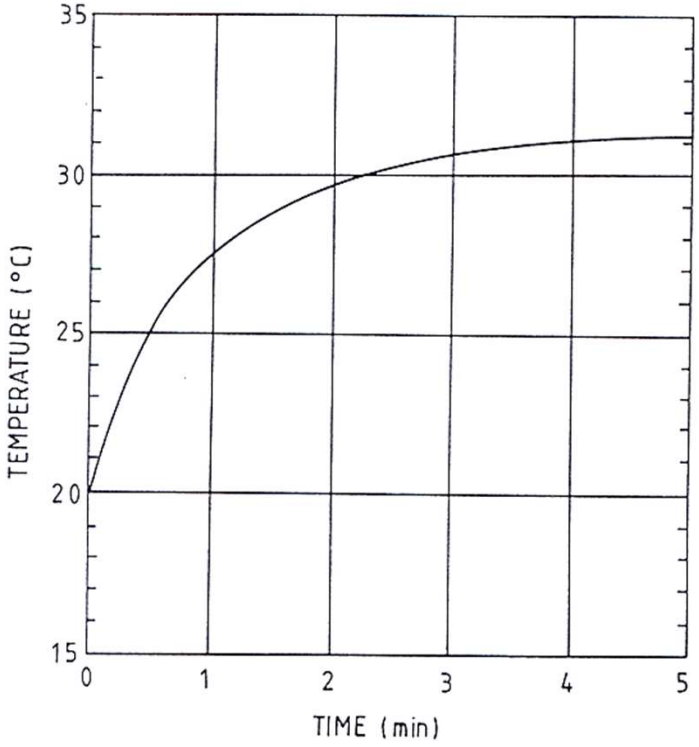
Diodes

Response of the detector is dependent on the temperature



"The temperature dependence of the diode is probably the characteristic which is the most difficult to master in the clinic"



Detector temperature after taping onto the patient.

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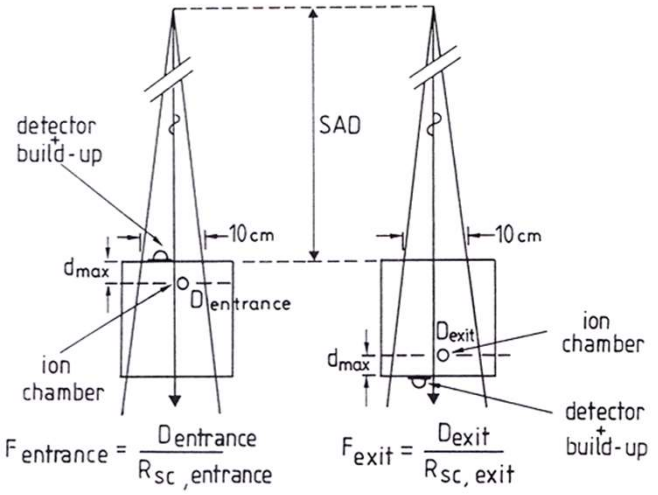
Diodes

Calibration factors for both exit and entrance measurements is required as the response have been shown to differ.



$$F_{exit} = \frac{D_{exit}}{R_{sc,exit}} \qquad F_{entrance} = \frac{D_{entrance}}{R_{sc,entrance}}$$

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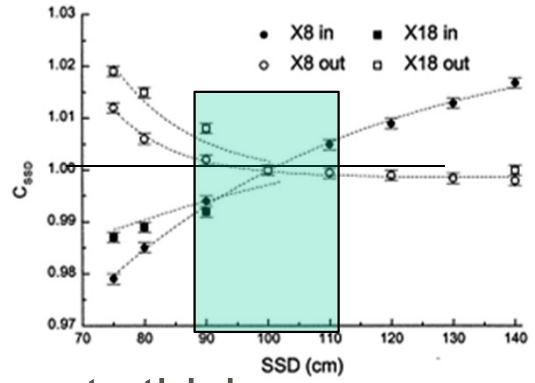
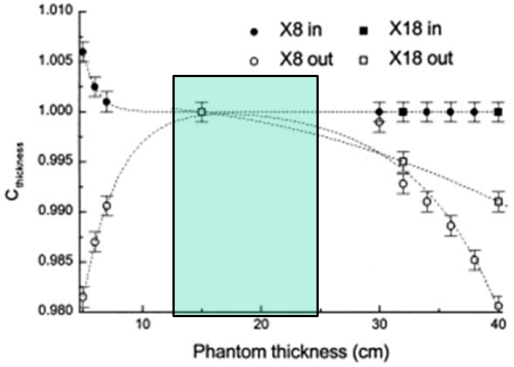
Diodes

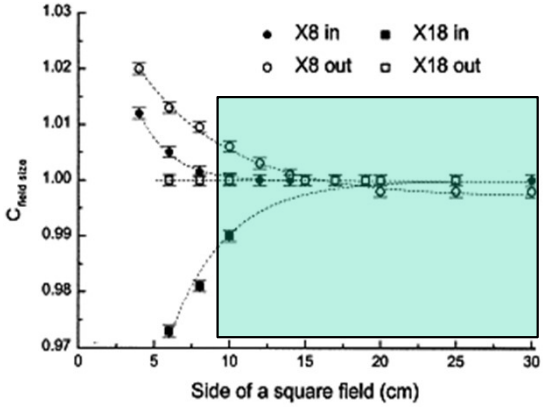
SSD



pts.thickness



field size



Although an appropriate calibration factor N_D is established for each beam energy, correction factors are required for a diode reading R_{diode}:

$$D_{diode} = R_{diode} \cdot N_D \cdot C_{SSD} \cdot C_{pts.thikness} \cdot C_{field\ size}$$

May be acceptable with no correction

Meijer GJ, et.al. Int J Radiat Oncol Biol Phys. 49:1409-18, 2001.

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TLD

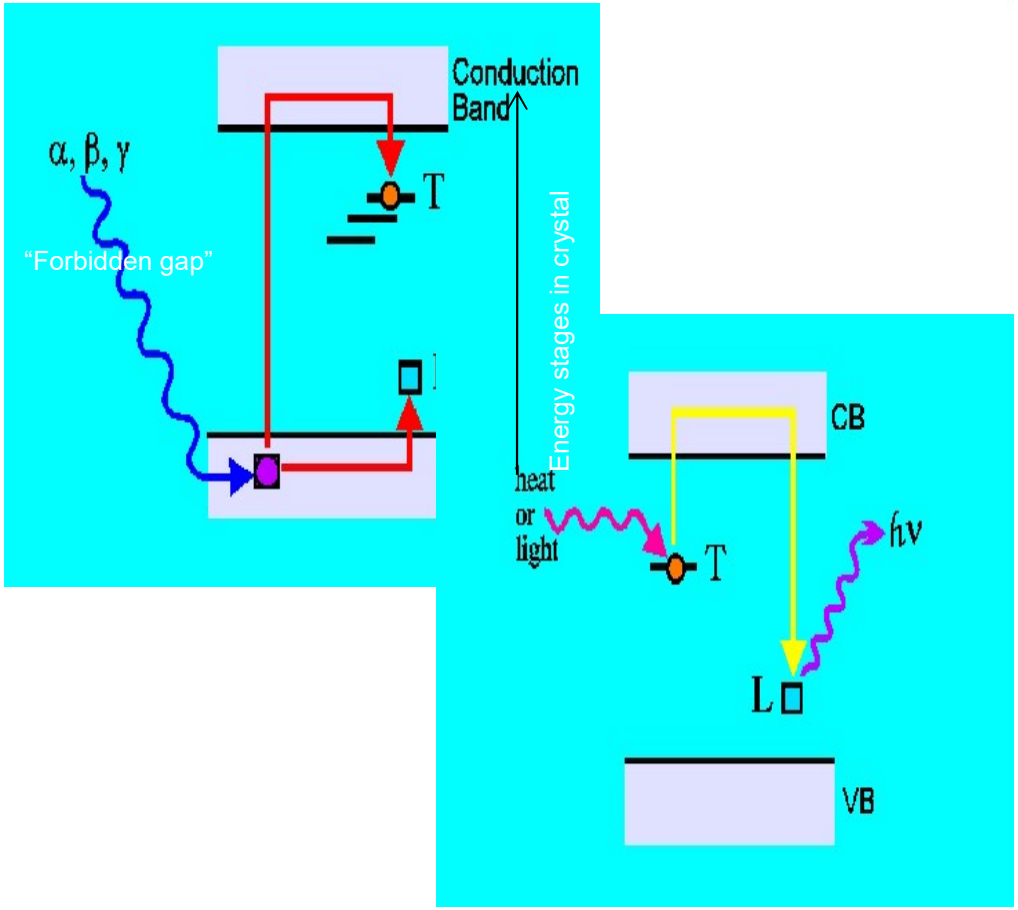
The most common types of TLDs are phosphors such as lithium fluoride (LiF), lithium borate (Li2 B4 07), calcium sulphate (CaSO4) and calcium fluoride (CaF2) doped with impurities called activators

Li based TLD are mainly used for soft tissue equivalent, and Ca based for bone

Soft tissue or lung	Bone
LiF (Mg, Ti)	CaSO4 : Mn
LiF (Mg, Ti, Na)	CaSO4 : Dy
Li2 B4 07 : Mn	CaF2 : Mn
Li2 B4 07 : Cu	CaF2 : Dy

TLD

- Free electrons and holes are formed and trapped at defects in the crystalline structure.
- When heated the electrons return to the conduction band while emitting energy



Schematic illustration of the TLDs response to radiation

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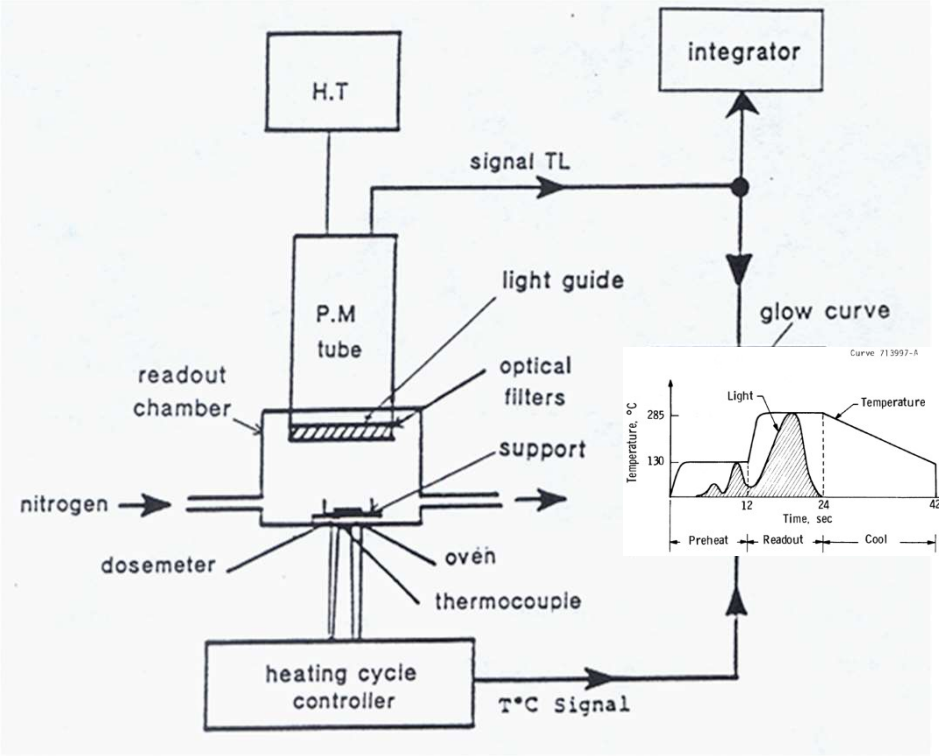
TLD

- The light is detected by a photomultiplier and is a measure of the absorbed dose.
- After annealing, (i.e. “baking”) the TLD can be used again.



Schematic illustration of a TLD reader

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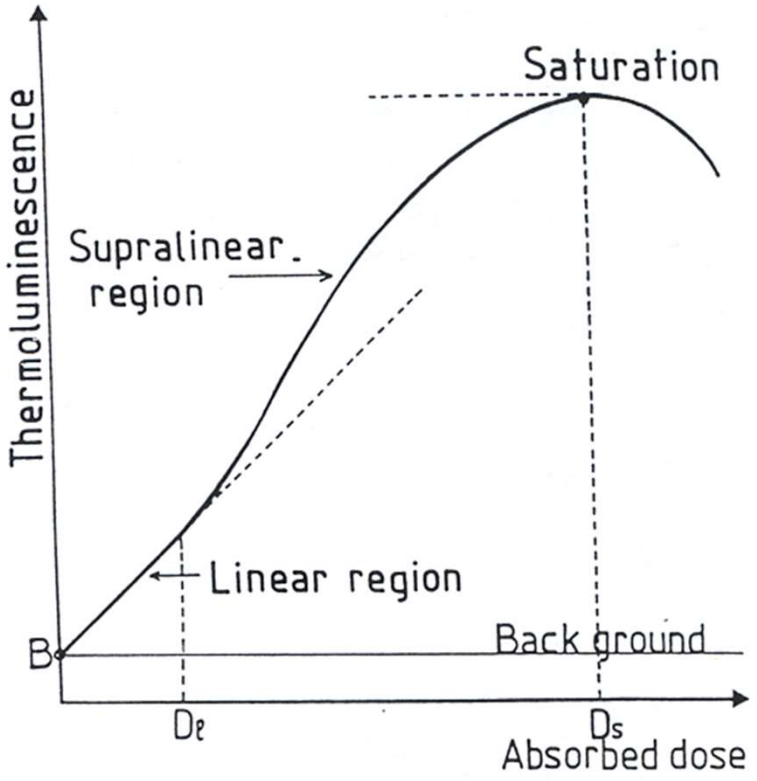
TLD

Dose response relationship:

- a linear response is preferable.
- if used out side the linear region, correction factors must be applied.



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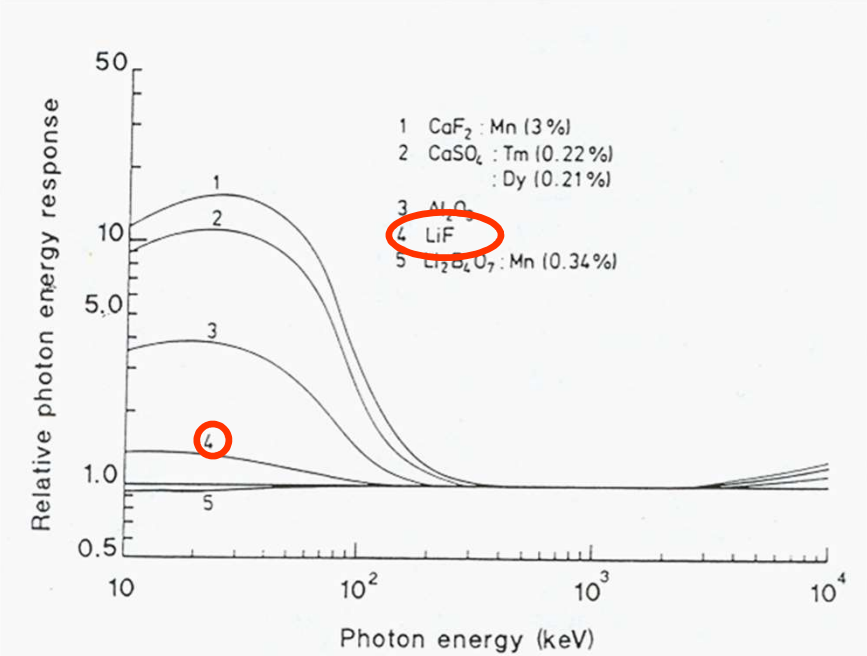
TLD

The response is energy-dependent, but varies between different TL materials.



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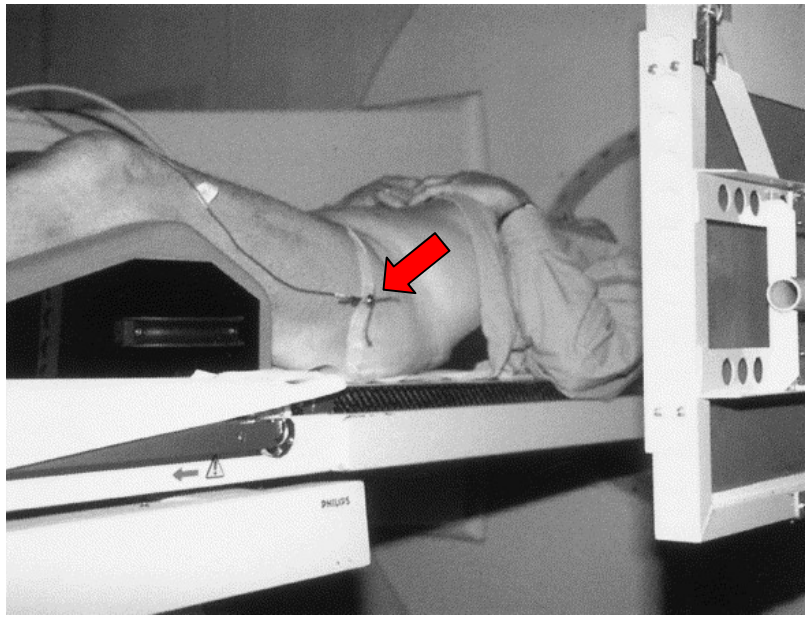
Summary of point dose detectors

Dosimeter	Advantages	Disadvantages
Diode	High intrinsic precision High sensitivity Real time dose information Simple read-out	Energy dependant Temperature dependant Corrections for SSD, Field size, Wedge etc
(micro) MOSFET	Small sensitive volume Small physical size Real time dose information Neglectible beam perturbations Energy independent	Limited life-time Limited intrinsic precision
TLD	Small volume Cheap Long life-time Neglectible beam perturbations	No real time dose information Limited intrinsic precision Signal erased during read-out Easy to lose Accurate result require care

Adapted from thesis of E.Bloemen- van Gurp: “In vivo dosimetry using MOSFET detectors in radiotherapy

Clinical example

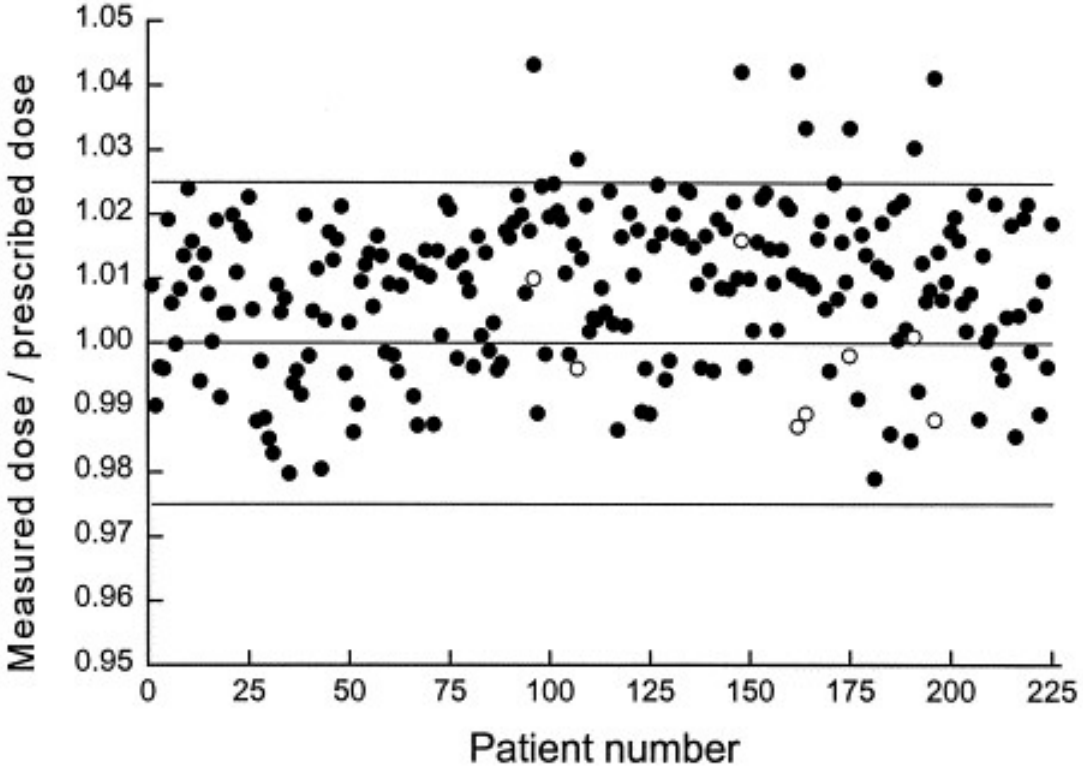


Patient with an EDP-20 diode with extra build-up cap.

The diode is slightly shifted with respect to the central beam axis, to avoid shielding by the entrance diode.

The electronic portal imaging device (EPID) on the right is used to verify the correct diode position

Clinical example



In vivo dosimetry results of 225 prostate patients. The open circles correspond to the IVD results after correction.

Meijer GJ, et.al. Int J Radiat Oncol Biol Phys. 49:1409-18, 2001.

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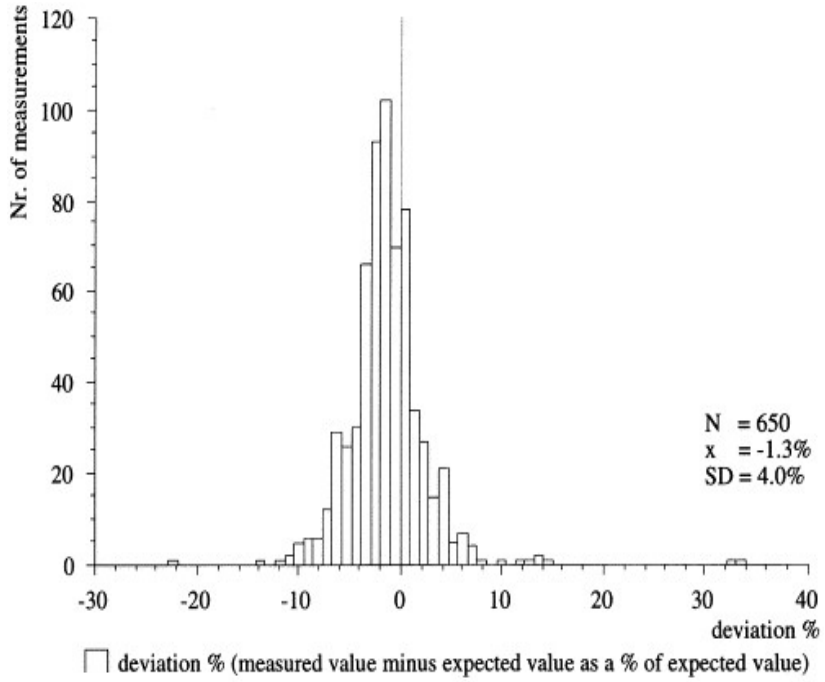
Clinical example



Entrance dose measurements: overall results.

650 entrance dose measurements for lung, H&N, breast and pelvic irradiation.

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EPI dosimetry

M. Essers, et al. Int J Radiat Oncol Biol Phys 34:931-41, 1996.

EPID can determine transmission dose in the entire irradiation field, and thus, the exit or midline dose in a plane can be obtained.

Using this information, the dose homogeity in the e.g. target volume can be assessed.


CLINAC

Use the EPID for in-vivo dosimetry

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EPID dose back projection

i The dose-response of the EPID;

ii The lateral scatter within the EPID;

iii The scatter from the phantom or patient to the

EPID;

iv The attenuation of the beam by the phantom or patient;

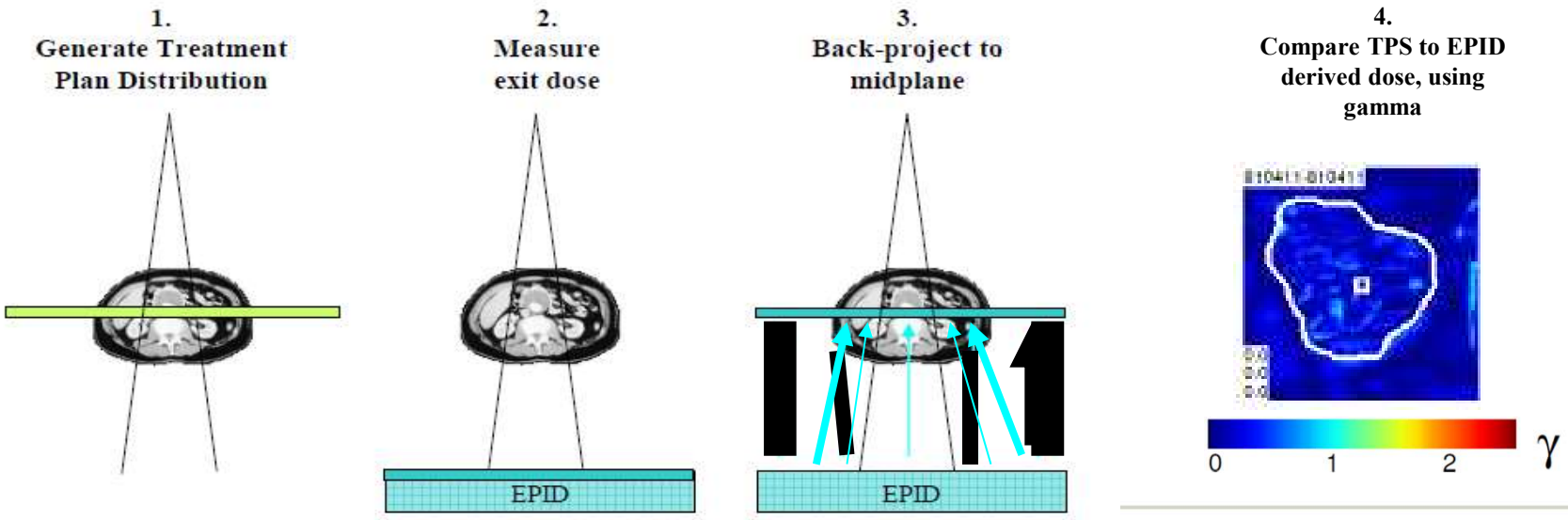
v The distance from the radiation source to the EPID

Wendling *et al.*: Back-projection EPID dosimetry Medical Physics, Vol. 33, No. 2, February

EPID based in-vivo dosimetry program developed by the Netherlands Cancer Institute (NKI)

Has been installed at the Royal Marsden since 2008

Allows 2D in-vivo dosimetry measurement and fast IMRT verification



[1] Wendling M et. al. Accurate two-dimsensional IMRT verification using a back-projected EPID dosimetry method, Medical Physics, 2006: 33: 259-272.

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PC

EPID dosimetry software

DICOM database

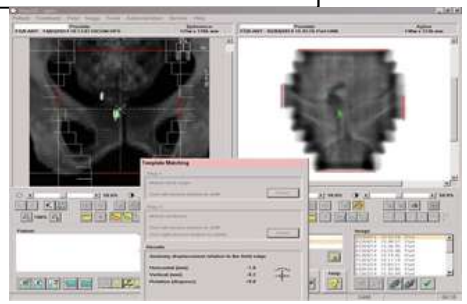
CT

RTPlan

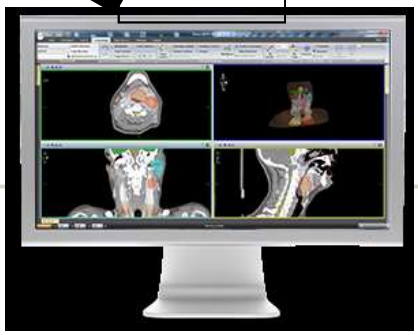
RTStructure

RTDose

EPID database



TPS



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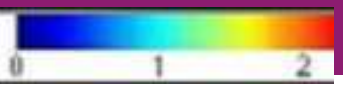
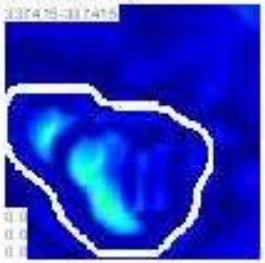
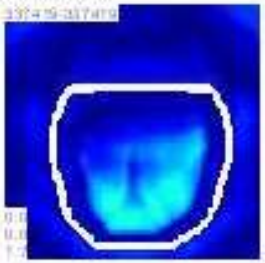
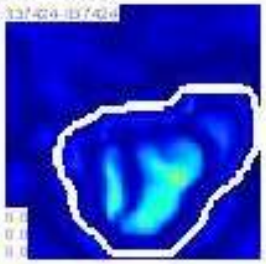
EPID DOSIMETRY REPORT



EPID date: 12-11-2008 | Analyzed by: vnh on 02-12-2008 11:05 | Gamma crit: 3.0%, 3.0 mm
Output/EPID factor: no/no | Dose model: 3D | Linac: EPID JU / planJU

Field name:

G,C,T,#S,E:	270,0,0,3,15	0,0,0,2,15	90,0,0,3,15	
				
mean γ	0.34	0.42	0.37	
γ 1%	1.17	1.12	1.22	
% γ <= 1	94.2	92.0	92.0	
isoc dose (cGy):				
Plan	53.8	94.1	51.7	Total: 199.6
EPID	53.8	95.4	51.7	201.0 (0.7%)

mean γ 0.34
γ 1% 1.17
% γ <= 1 94.2
isoc dose (cGy):
Plan 53.8
EPID 53.8

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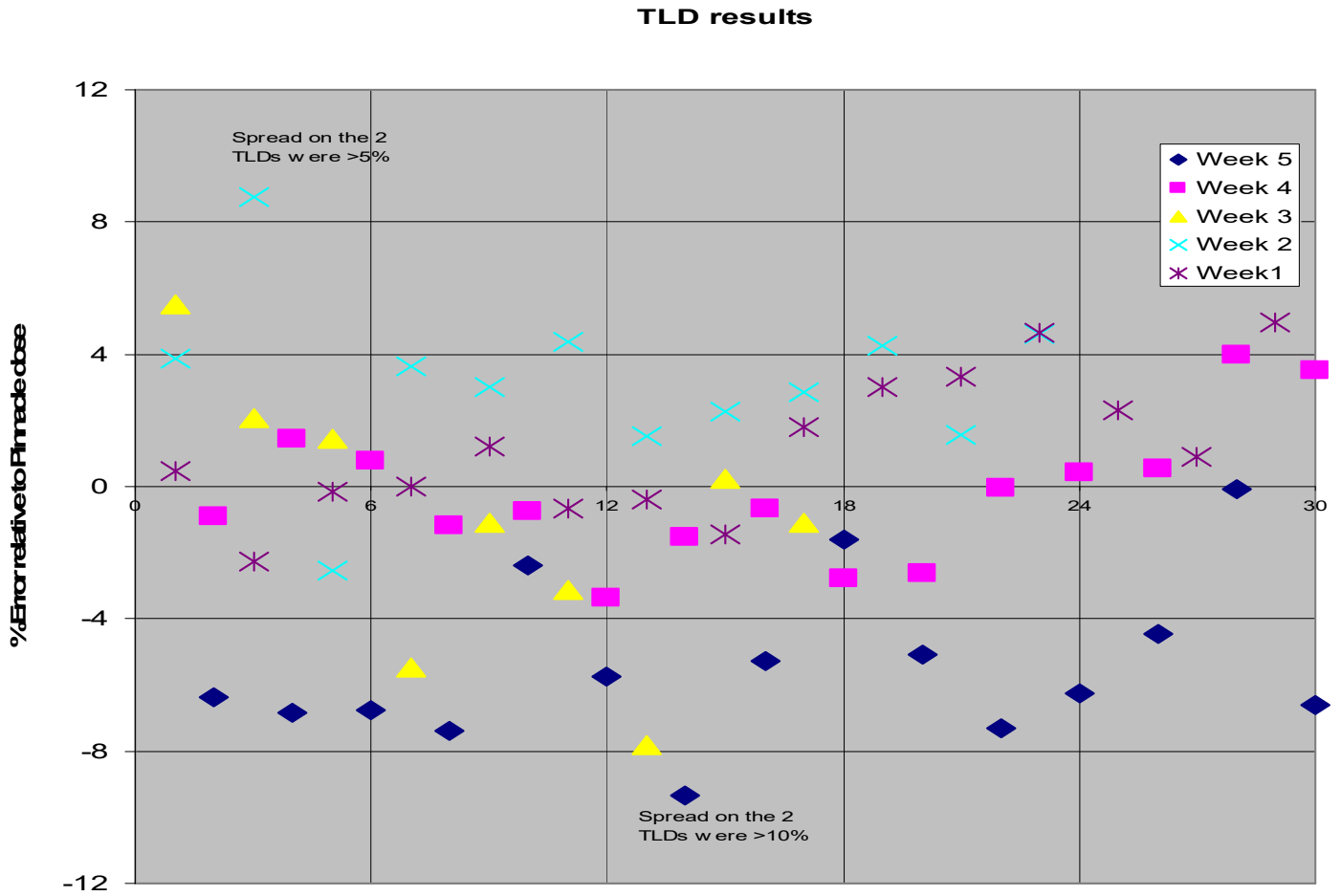
To introduce EPID dosimetry into the clinic a small TLD vs EPID dosimetry study:

Daily in-vivo dosimetry on 5 prostate patients were done

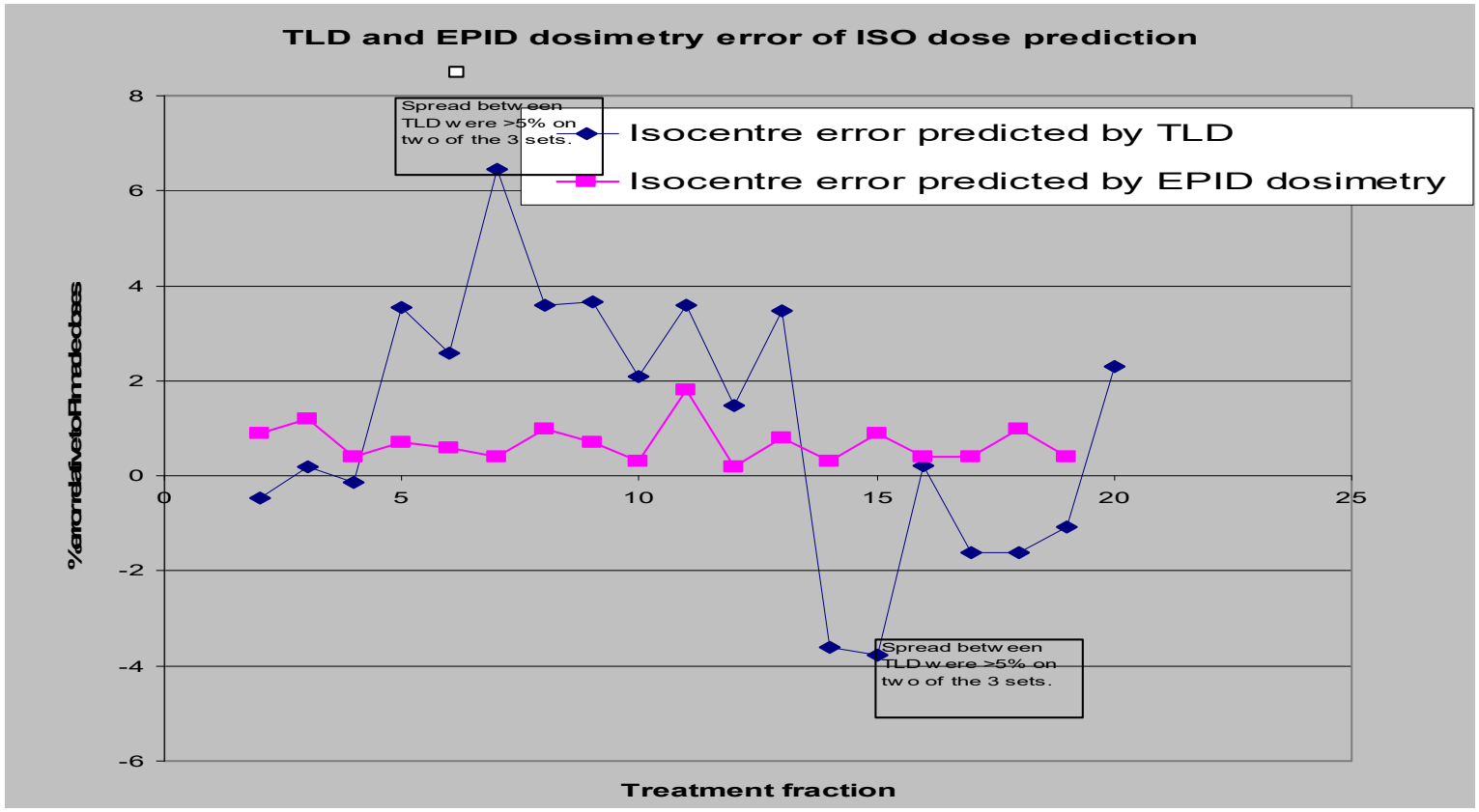
Results TLD


TLD results
12
8
4
0
-4
-8
-12
0
6
12
18
24
30
Spread on the 2 TLDs were >5%
Spread on the 2 TLDs were >10%
Week 5
Week 4
Week 3
Week 2
Week1

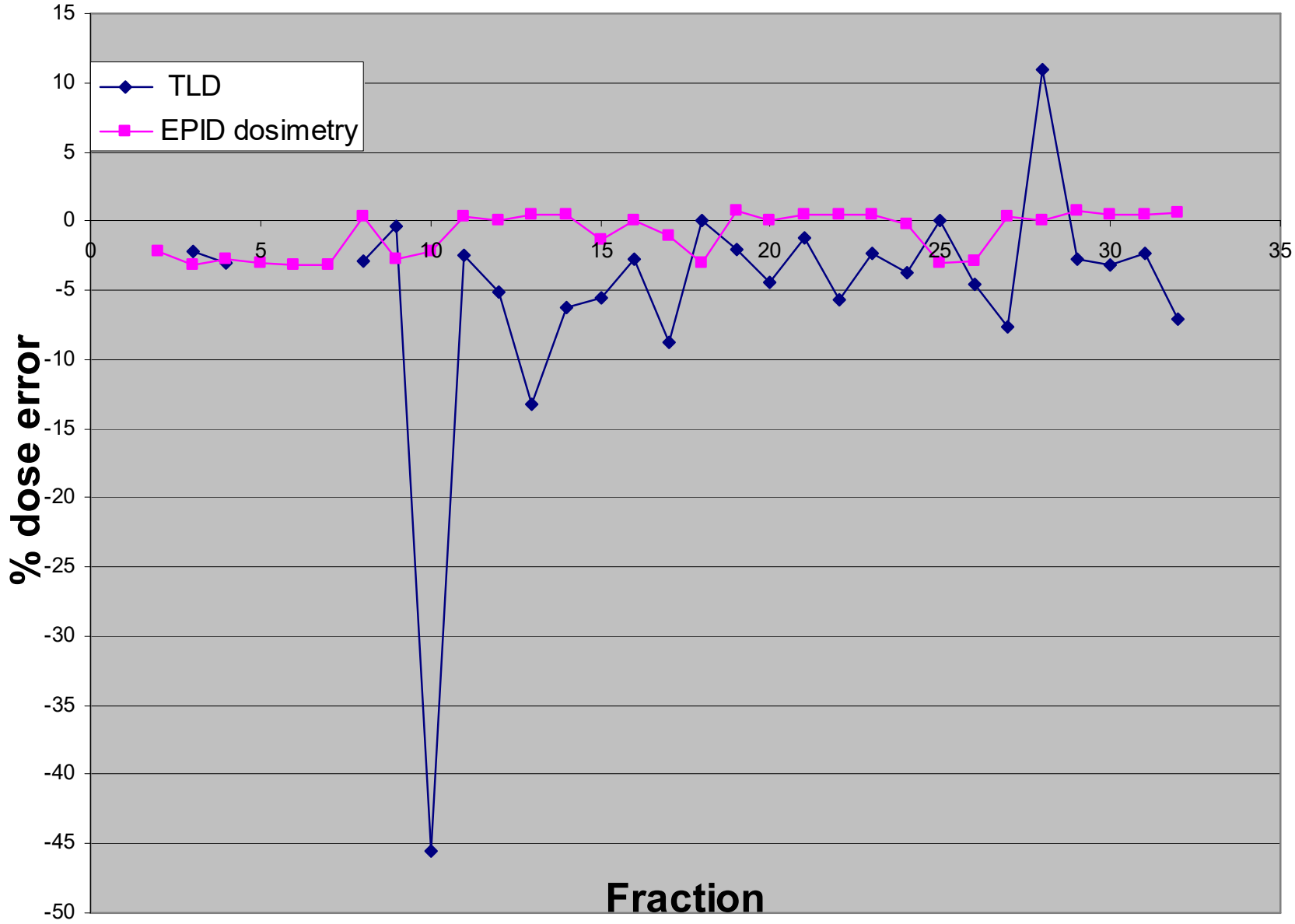
ISOcentre dose error

$$ISO_{error} = \sum_{Ant,Rlat,Llat} Dose \quad weight * TLD_{error}$$

Results EPID dosimetry vs TLD



Isocentre dose error measured by TLD and EPID dosimetry Patient 4



EPID vs TLD study conclusion

EPID dosimetry gave very reproducible results and errors were traceable.

Unlike the TLD errors

At the time of treatment

- TLD required extra time to position detectors
- EPID had no time penalty

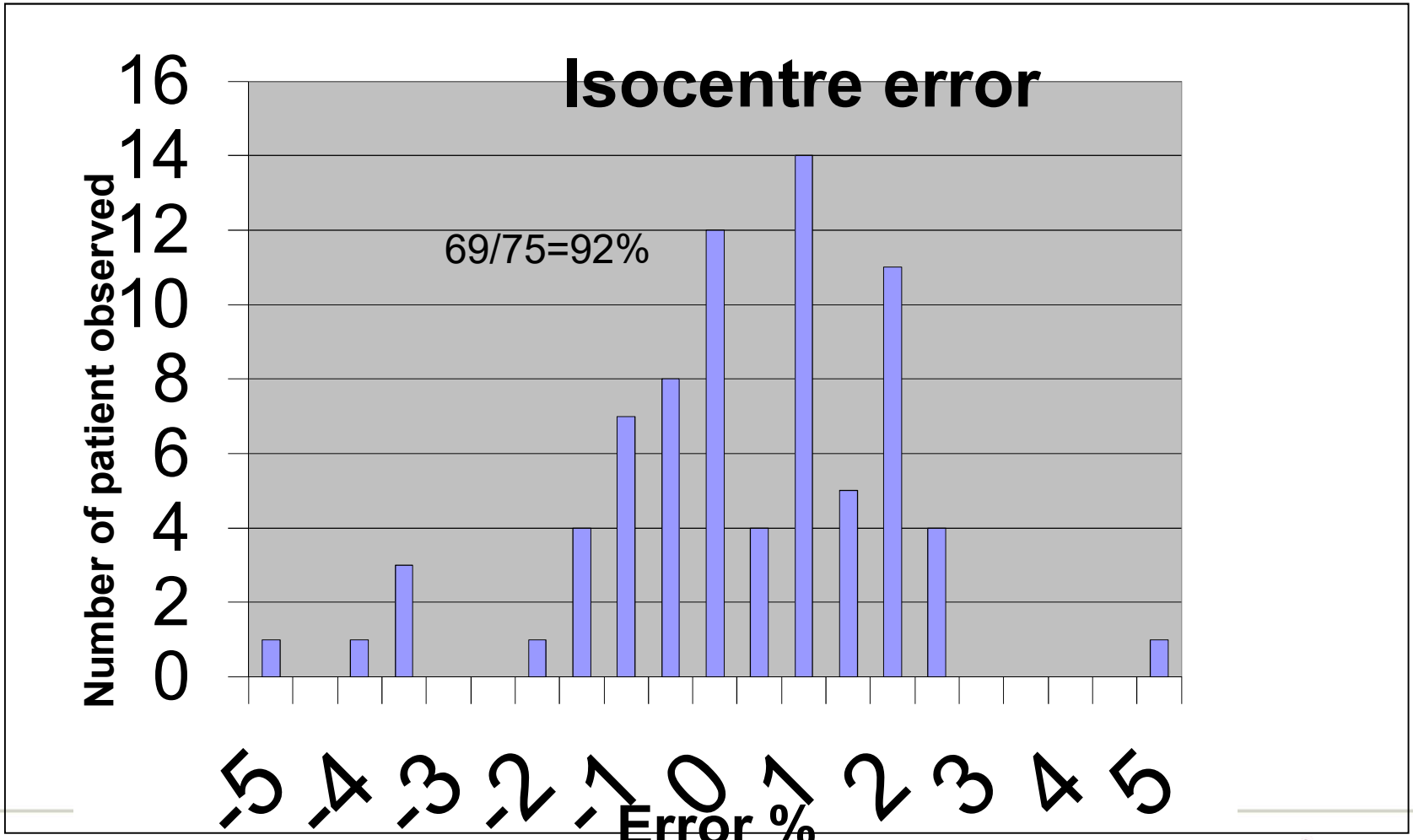
1st year ~75 Prostate Chhip style

Isodose mean = 0.18 % error

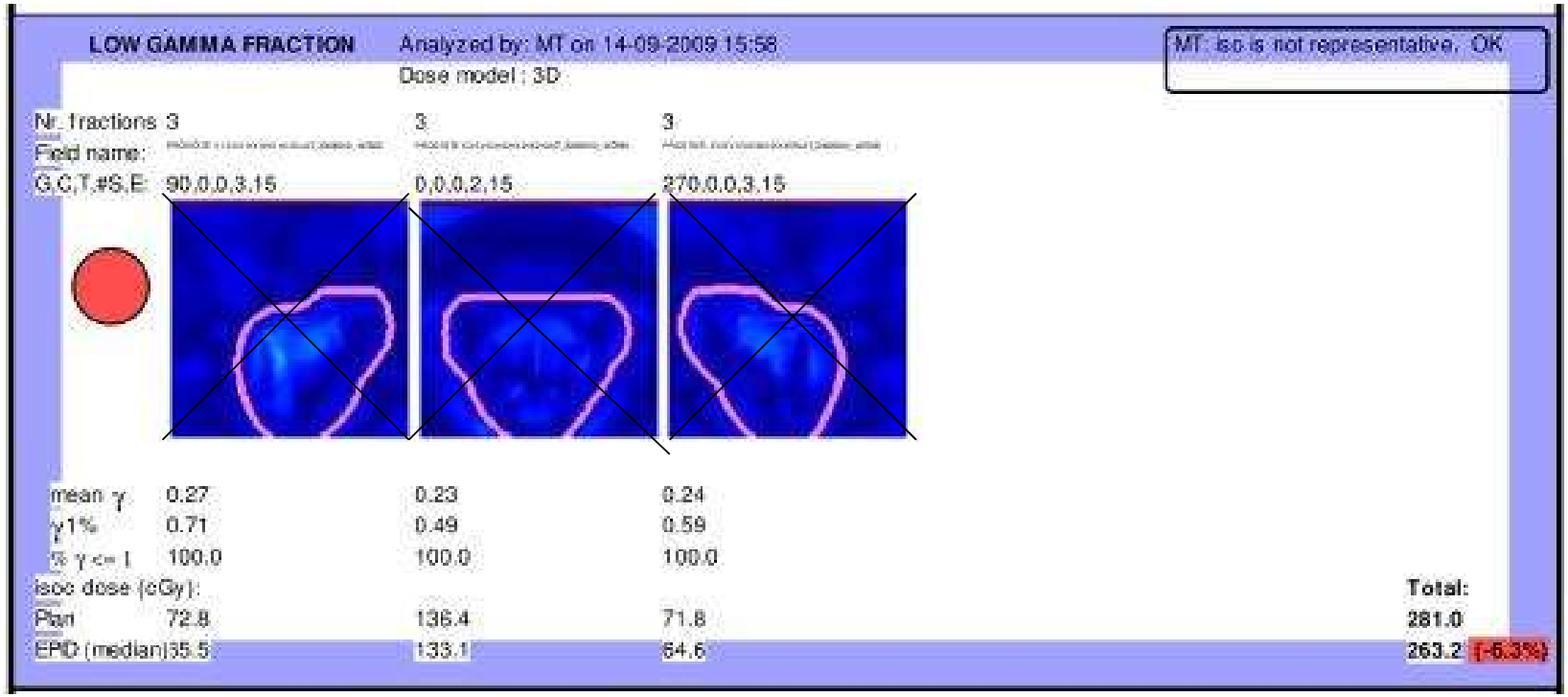
Standard deviation =1.69%

1 patient had artificial hip

5 patients had the isocentre near the edge of the field



Poor isocentre position



Dose error -11.1% 2.4% -11.1%

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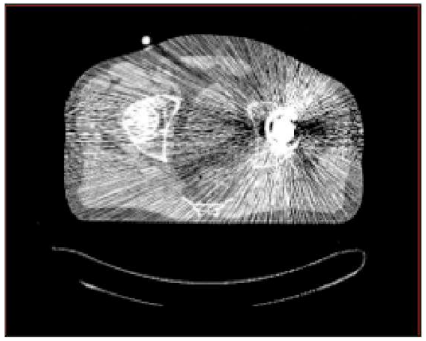
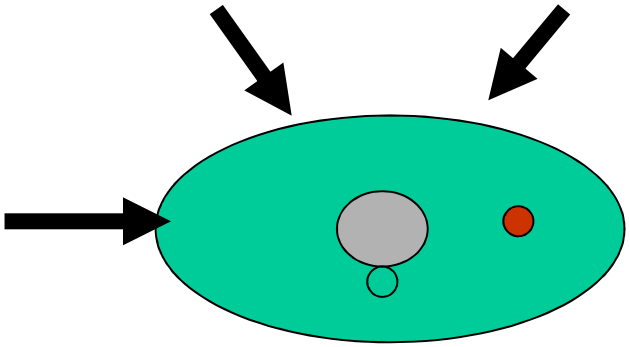
Hip-replacement





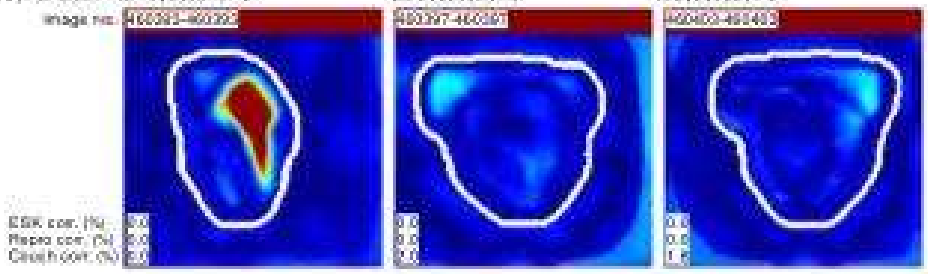
EPID date: 19-08-2009
Output/EPID factor: no/no

Analyzed by: MT on 21-08-2009 18:27
Dose model : 3D

Gamma crit: 3.0%, 3.0 mm
Linac: EPID JU / plan JU

MT: fraction treated on Juniper

Field name:
G,C,T,#S,E: 270,0,0,4,15 328,0,0,2,15 23,0,0,3,15



mean γ	0.78	0.28	0.27
γ1%	4.79	1.00	0.99
% γ <= 1	79.1	99.0	99.1
Isoc dose (cGy):			
Plan	75.4	124.1	95.6
EPID	63.2	124.8	96.2

Total:
295.1
284.2 (-3.7%)

error -19.3% 0.6% -0.4%

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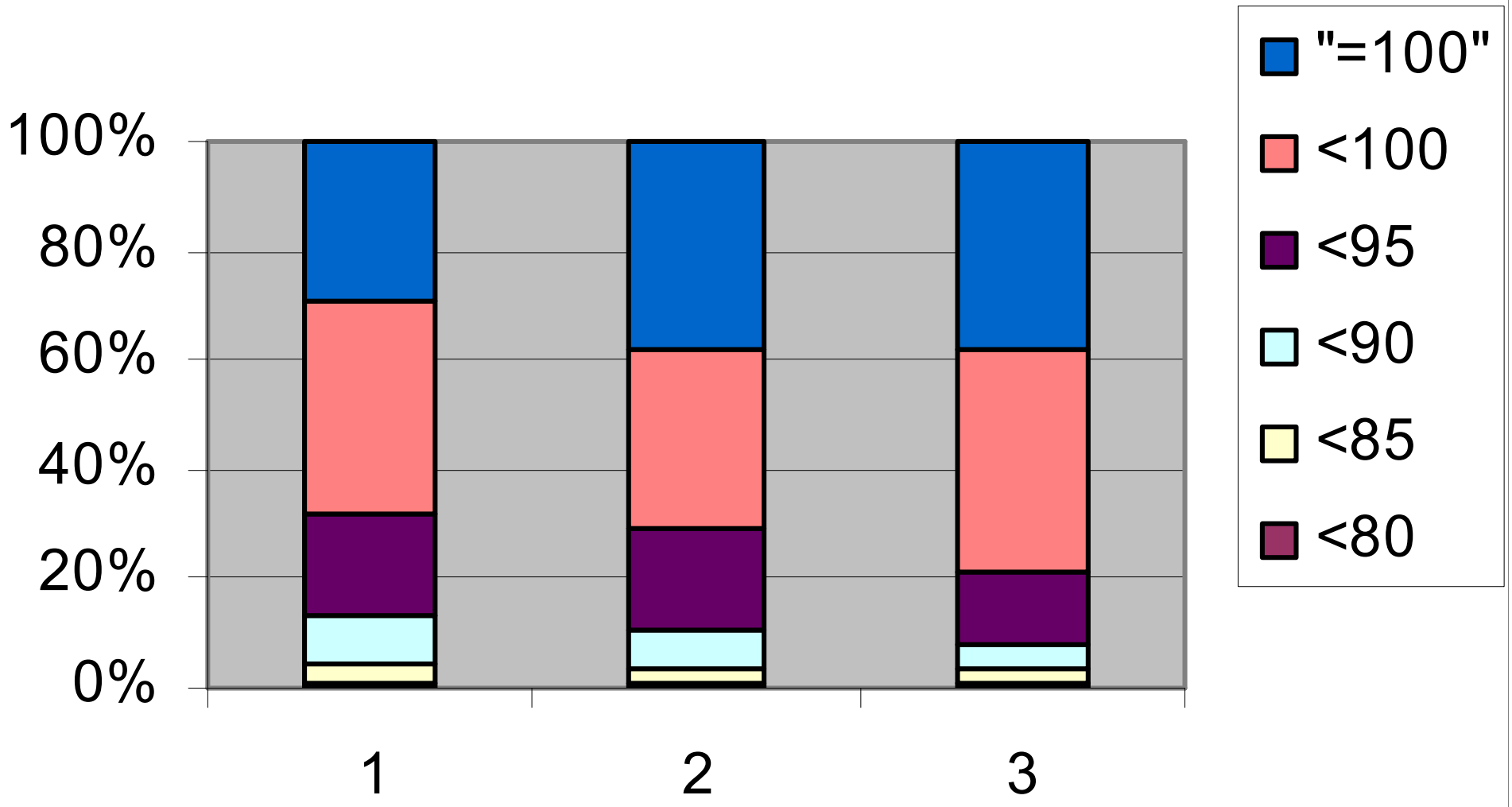
Gamma maps



EPID dosimetry is not only for 2D beam by beam verification.

Wendling M, McDermott LN, Mans A, Sonke J-J, van Herk M, Mijnheer B. A simple back-projection algorithm for 3D EPID dosimetry of IMRT treatments. Med Phys 2009;36:3310–21.

Contents lists available at ScienceDirect

Radiotherapy and Oncology

Vol 94 pp 181-187, 2010

Original article

3D Dosimetric verification of volumetric-modulated arc therapy by portal dosimetry

Anton Mans *, Peter Remeijer, Igor Olaciregui-Ruiz, Markus Wendling [1], Jan-Jakob Sonke, Ben Mijnheer, Marcel van Herk, Joep C. Stroom

Department of Radiation Oncology, The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

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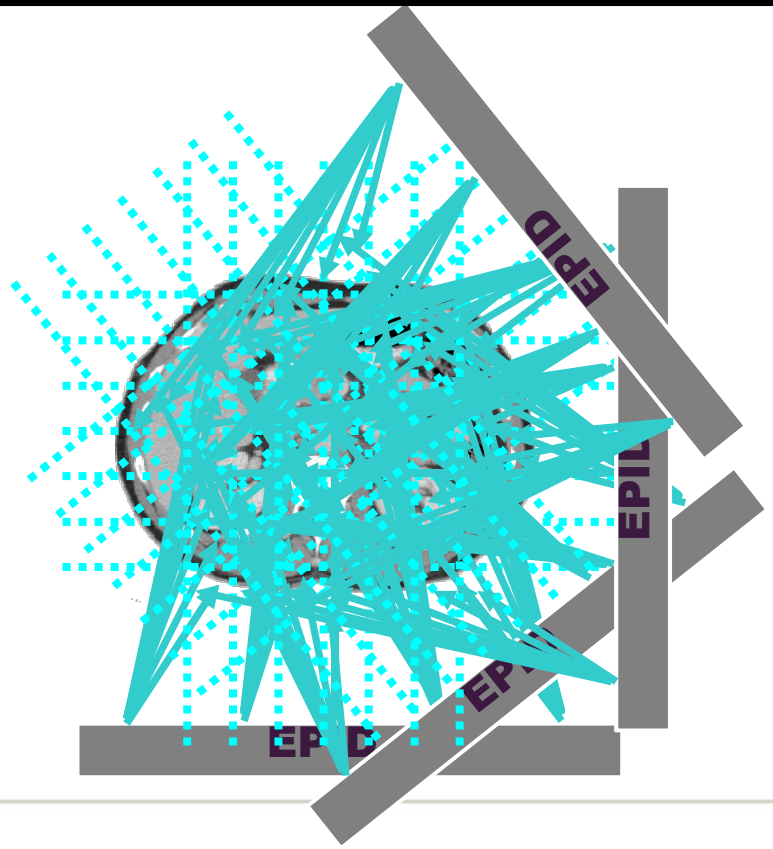
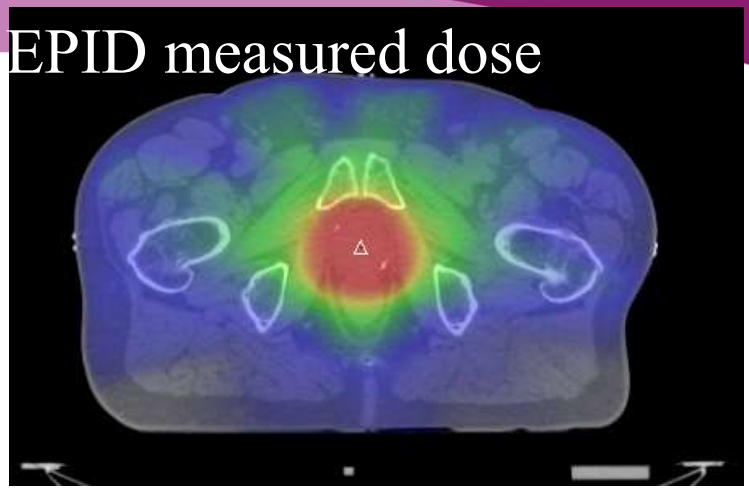
How it works 3D - VMAT

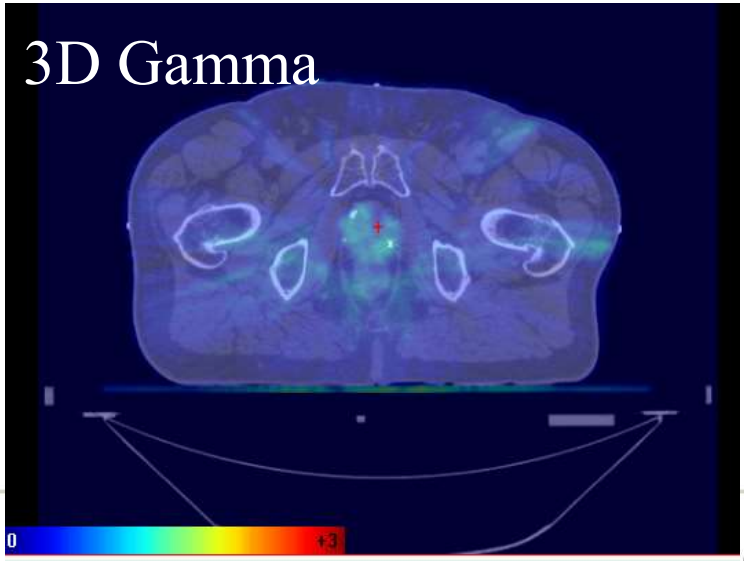
No open images

Mans A et. al. 3D dosimetric verification of volumetric-modulated arc therapy by portal dosimetry,
Rad. Oncol. J. Eur. Soc. Ther. Rad. Onc. 2010: 94: 181-187.





Compare to TPS



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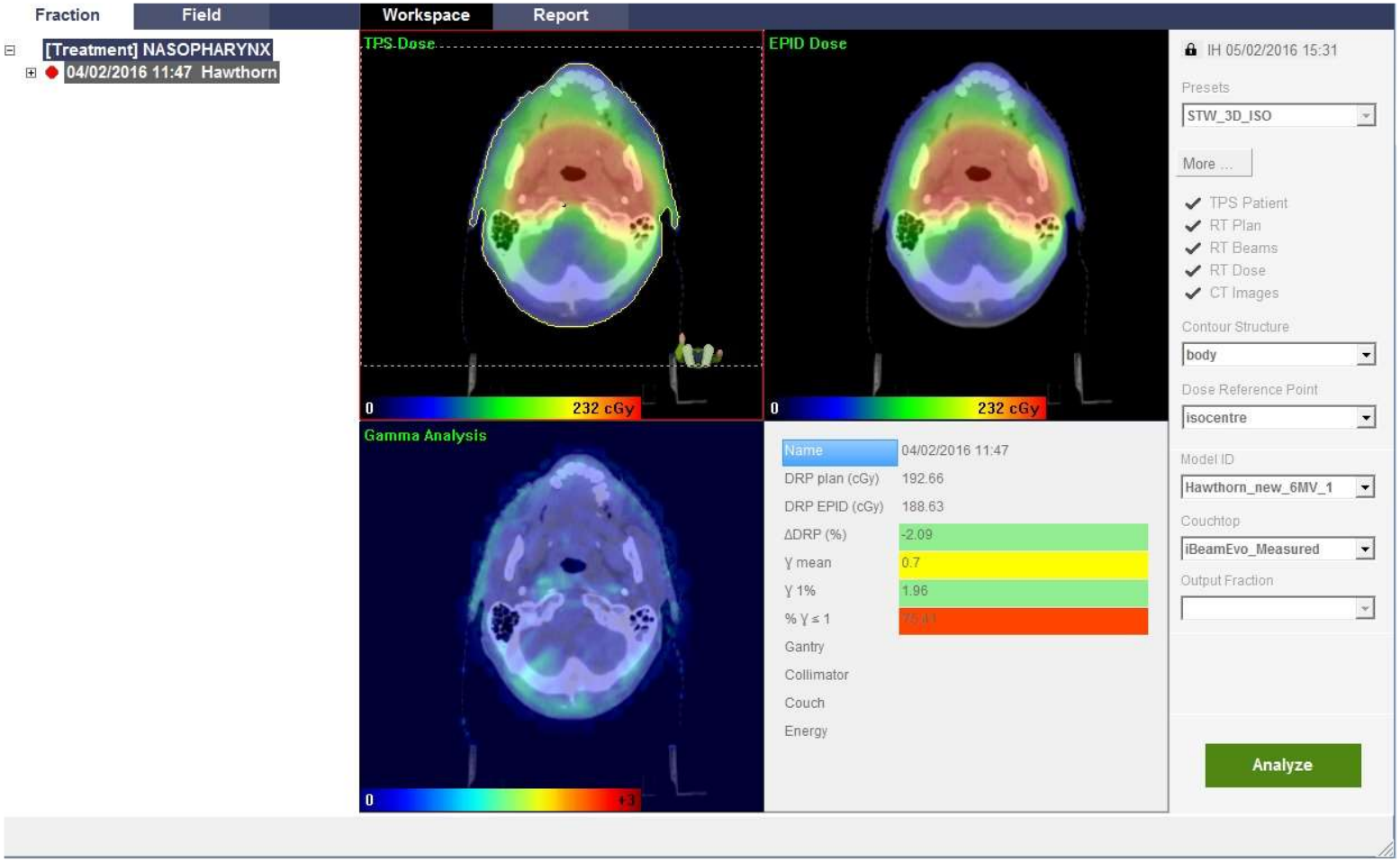
VMAT, 306 movie frames, re-binned to match the 179 control points from the TPS



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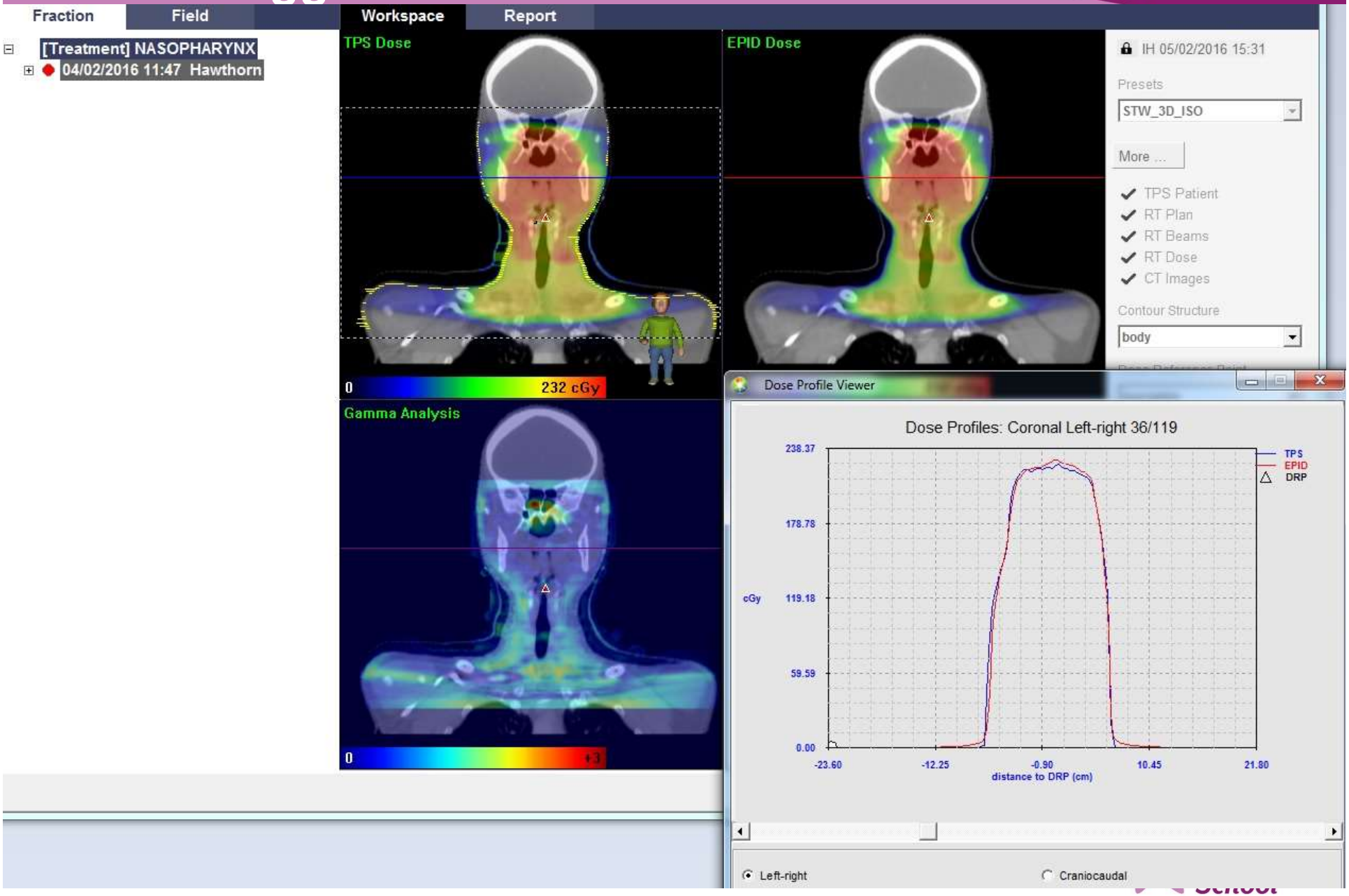
IMRT saggital and coronal view



Final VMAT iViewDose Report

Fraction | Field | Workspace | Report

[Treatment] NASOPHARYNX
04/02/2016 11:47 Hawthorn

γ 0 1 2 3 **iViewDose Report**

Patient Name	
Patient ID	
Treatment Site	NASOPHARYNX
Plan Name	1Plan_3
Preset	STW_3D_ISO γ 3.0%, 3.0mm, > 50% isodose [3D per Fraction]
DRP	isocentre
External	body
In Aqua	No

No. RT Beams 1

RT Beams Ignored	Fields (iViewGT™) Ignored
None	None

Fraction 04/02/2016 11:47 **Linac** Hawthorn **Couch** iBeamEvo_Measured

NASOPHARYNX

Analysis Date	05/02/2016 15:34
No. EPID Fields	1/1

Planned Dose (cGy)	EPID Dose (cGy)	γ	Dose Difference
192.7	188.6	0.55	-2.1%

Model ID	Hawthorn_new_6MV_1
γ Mean	0.70
γ 1%	1.96
% γ ≤ 1	75.4

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Measurement and action protocol

EPID dosimetry results from NKI* based on 5547 patients
(16986 fractions)

%Isocentre difference <5%

Gamma <1 >70%

NKI experience is ~90% of patients will be within criteria

ICRU 83:

5 % was the original ICRU requirement for accuracy of delivery at the ICRU Reference Point (ICRU, 1993).

For high-gradient (>20 %/cm) regions, the accuracy of DTA should be 3.5 mm

In the future, the recommended accuracy criteria might be made more stringent

*Reference: I Olaciregui_Ruiz et all Radiotherapy and Oncology 2011

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Practical Radiation Oncology (2015) 5, e679-e687

practical radiation oncology
pro
www.practicalradonc.org

Original Report

Overview of 3-year experience with large-scale electronic portal imaging device–based 3-dimensional transit dosimetry

Ben J. Mijnheer PhD*, Patrick González PhD, Igor Olaciregui-Ruiz MSc, Roel A. Rozendaal MSc, Marcel van Herk PhD, Anton Mans PhD

Department of Radiation Oncology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

Received 2 March 2015; revised 23 May 2015; accepted 2 July 2015

Table 1 Current clinical alert criteria for the dose difference at the DRP and for the 3D γ evaluation (3%/3 mm) within the 50% isodose surface

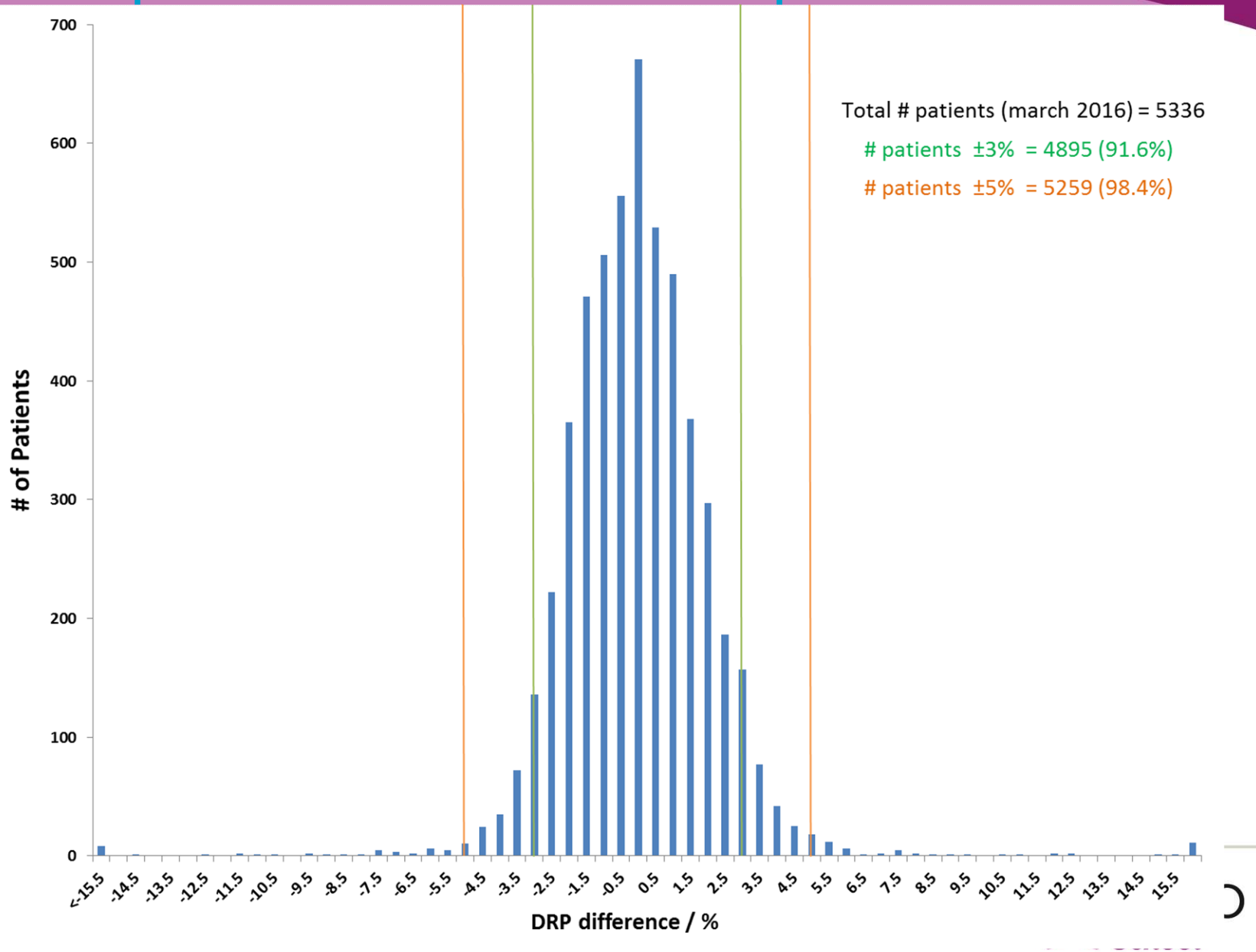
Treatment site	DRP dose difference (%)	Mean γ	γ pass rate (%)	1% γ
Most	3.0	0.5	85	2.0
Head and neck/rectum/gynecology	4.0	0.7	80	2.5
Breast	3.0	1.4	50	5.0

Alerts and causes for different sites:

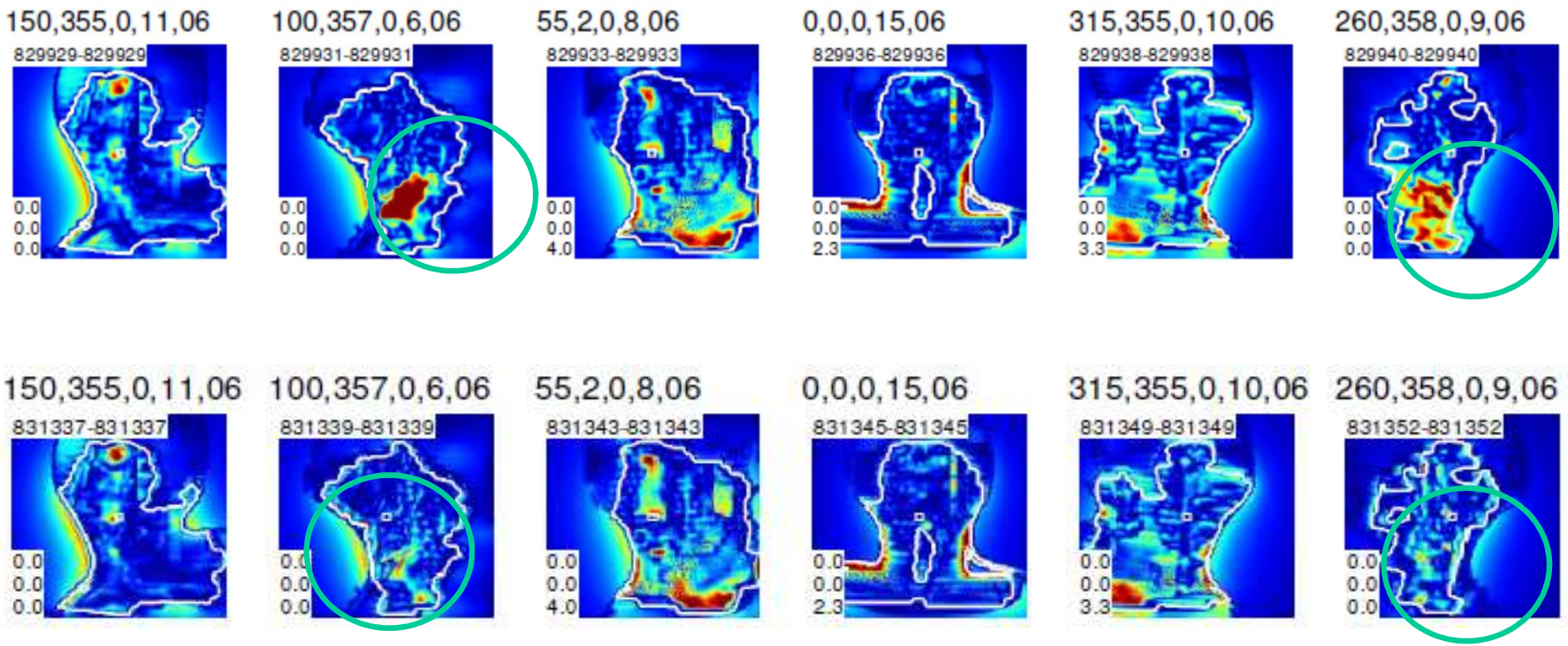
Table 3 Number of plans verified in 2013 by means of 3D transit dosimetry and the classification of the alerted plans

Treatment site	No. of verified plans	No. of alerted plans	% alerted plans	Unknown	External	Patient	Model
Bone metastasis	991	100	10	20	44	24	30
Brain:							
Total	268	87	32	21	12	1	62
Hypofractionated	131	32	27	12	0	0	24
Conventional fractionation	137	55	47	9	12	1	38
Breast (including thoracic wall)	1188	442	37	15	226	217	386
Gastroenterology (excluding rectum and esophagus)	73	17	23	2	4	11	2
Gynaecology	121	32	26		11	13	12
Head and neck	437	183	42	29 <7%	98	57	53
Lung:							
Total	570	203	36	35	2	112	71
Hypofractionated	160	58	36	10	0	31	17
Conventional fractionation	410	145	35	25	2	81	54
Lymphoma	103	29	28	5	6	12	17
Esophagus	69	25	36	5	0	17	6
Other	355	88	25	13	17	41	32
Prostate	379	99	26	16	51	39	9
Rectum:							
Total	180	31	17	4	3	11	16
Hypofractionated	96	17	19	2	2	6	9
Conventional fractionation	84	14	15	2	1	5	7
Sarcoma	51	29	57	5	10	11	12
Urology (excluding prostate)	94	23	24	1	5	13	7
Total	4879	1388	28	171	489	579	715

Reference point dose Results – all plans



AUDIT: Head & Neck – Shoulder position



Slide courtesy of Ian Hanson

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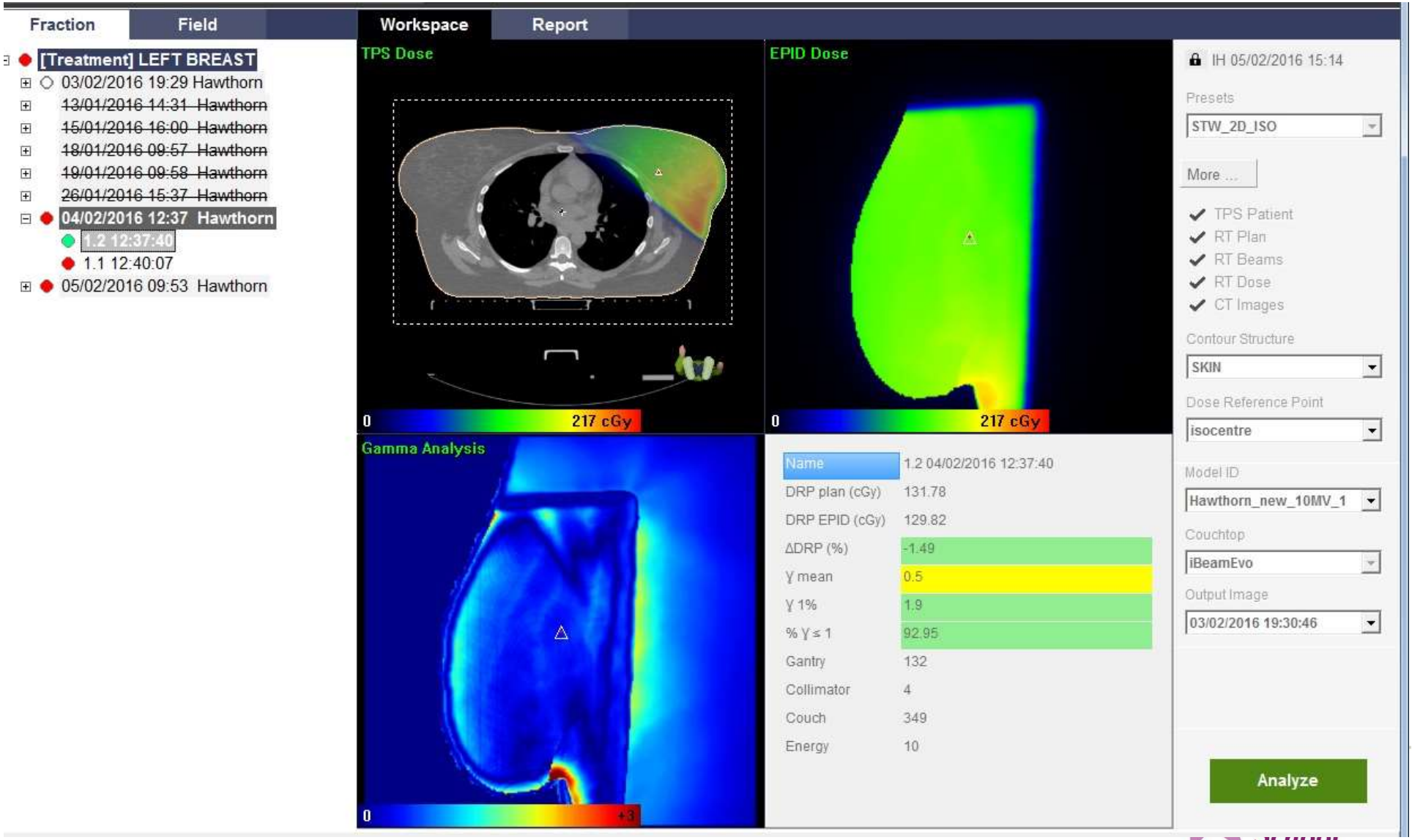
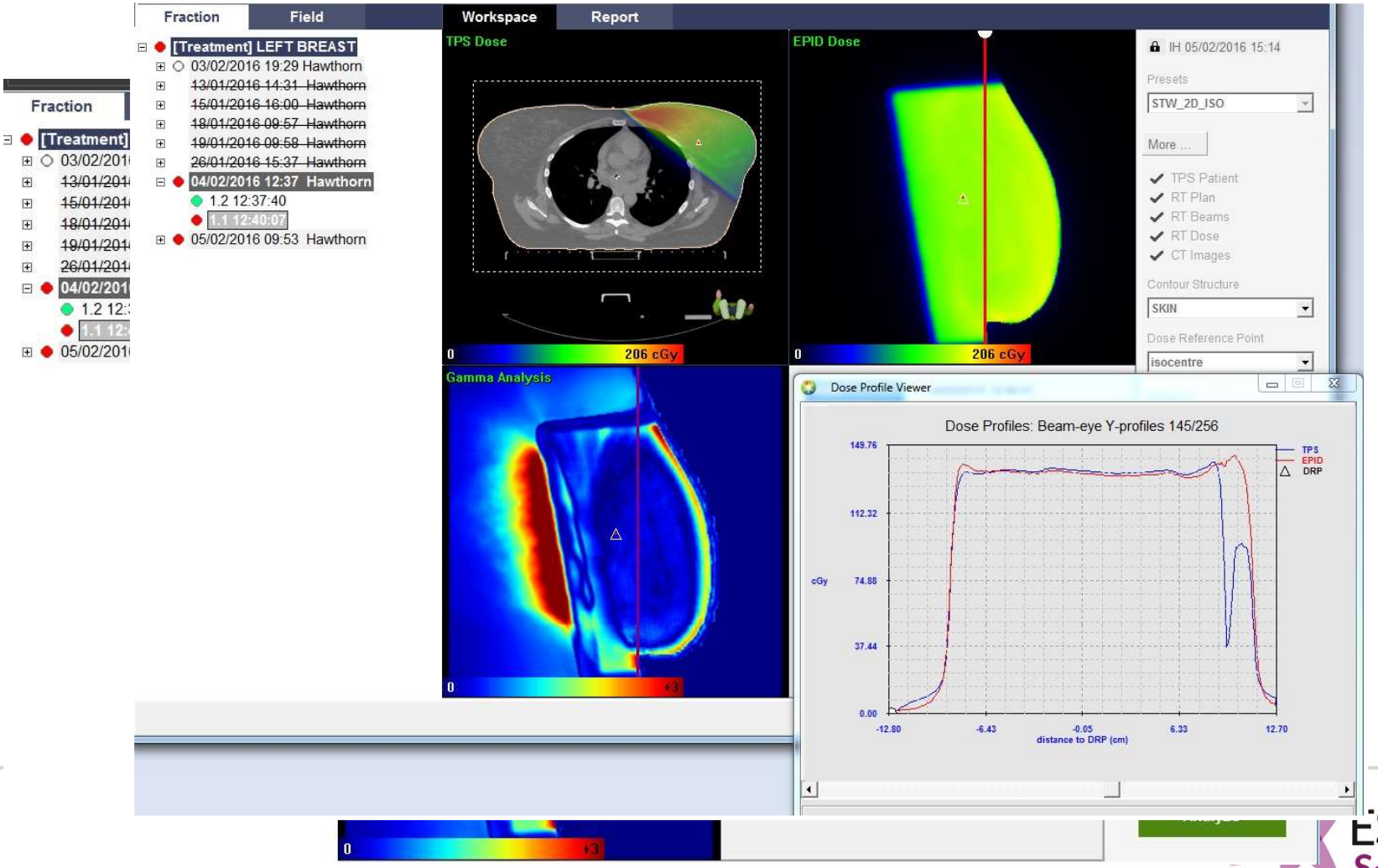
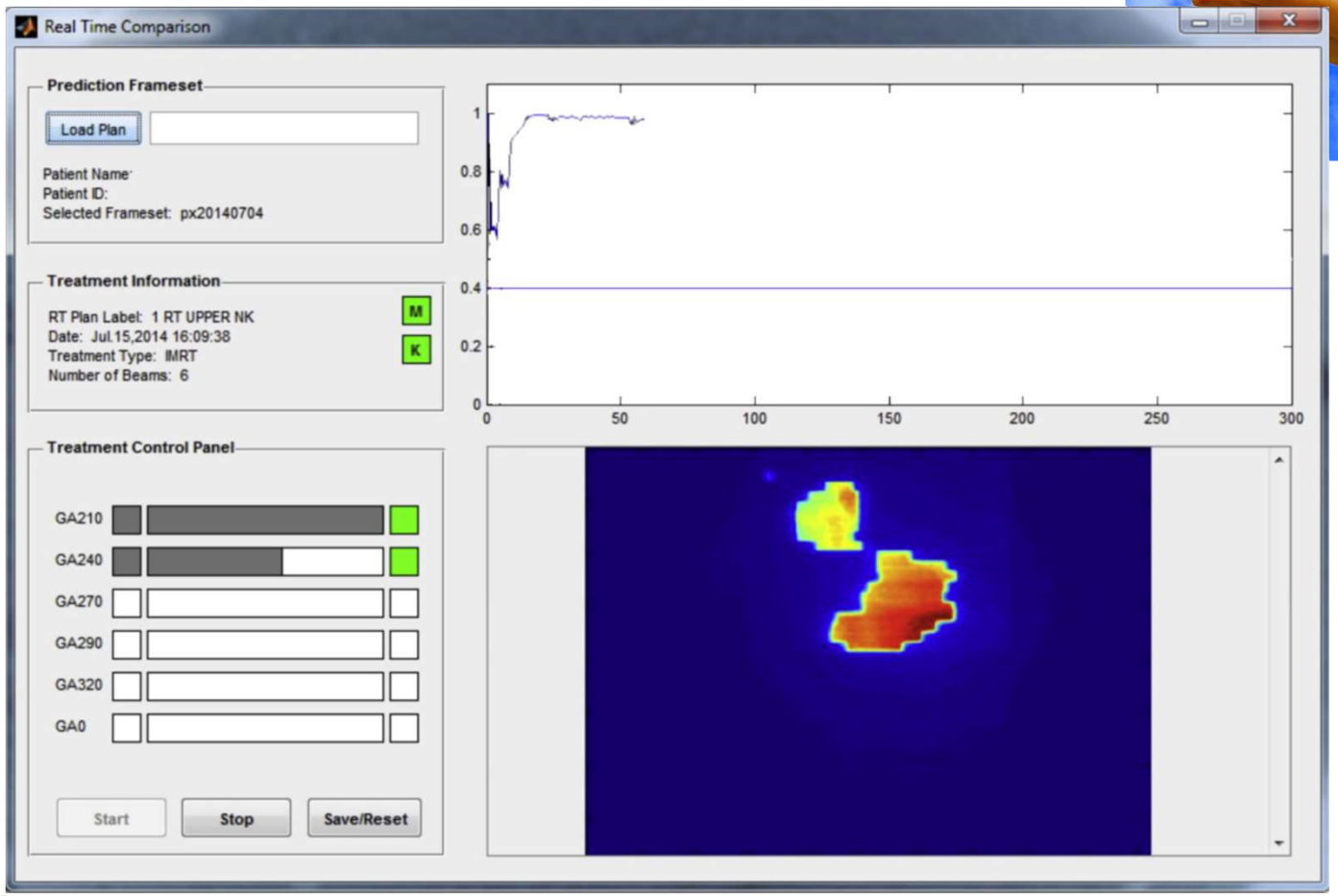
Simple breast, dose results



Breast with minor shape changes



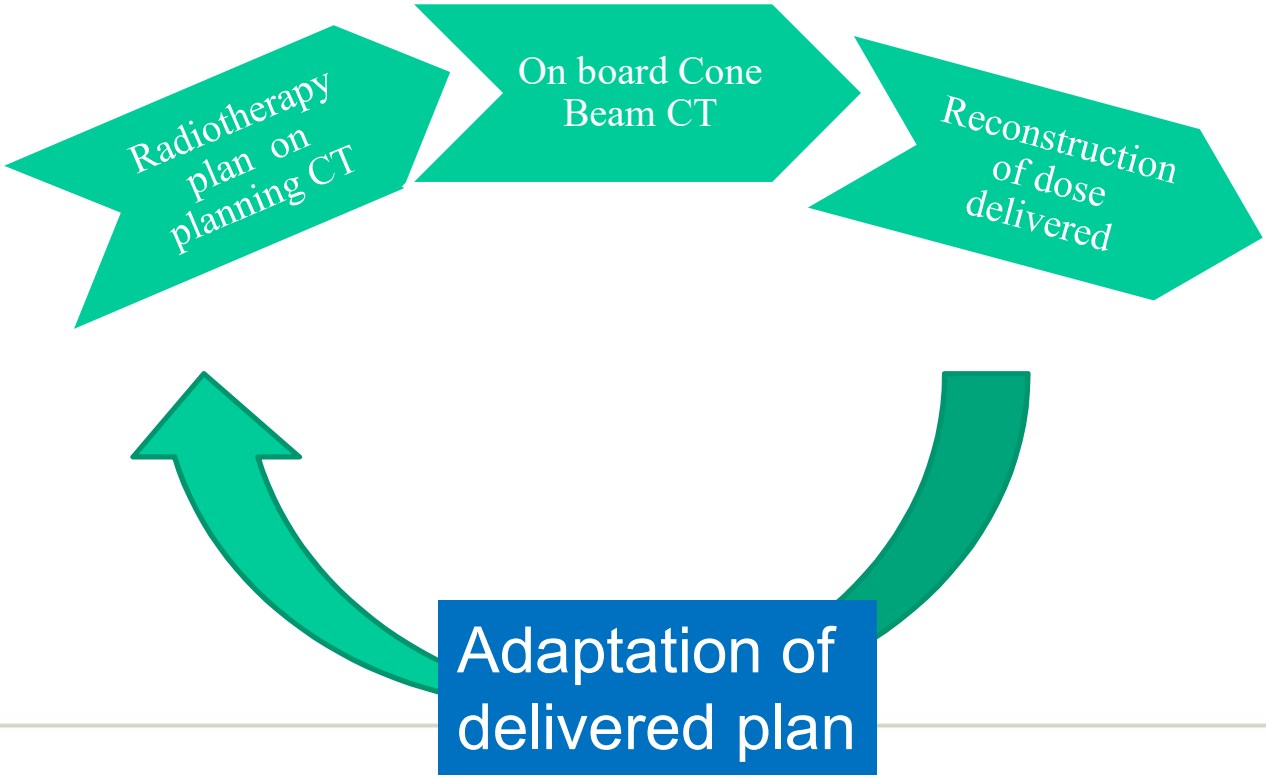
The Future????? Watchdog:



First Experience With Real-Time **EPID**-Based Delivery Verification During IMRT and VMAT Sessions.
Woodruff HC, Fuangrod T, Van Uytven E, McCurdy BM, van Beek T, Bhatia S, Greer PB.
Int J Radiat Oncol Biol Phys. 2015 Nov 1;93(3):516

Future developments

The ultimate in-vivo patient specific dosimetry is dose-of-the-day reconstruction on the anatomy-of-the-day and a close day-to-day follow up.



Conclusions

In vivo dosimetry....

....it's worth while doing !

It is the final real check of dose delivery to your patient.

It may be the only comprehensive check of an IMRT plan.

BUT it is extra work and you do get errors, which you have to study

Thank you for your attention

Any questions

Adaptive Radiotherapy

Shaista Hafeez MRCP, FRCR, PhD
Clinician Scientist Precision Radiotherapy, Radiation Oncologist, London. UK
shaista.hafeez@icr.ac.uk

Physics for Modern Radiotherapy, Bucharest, 2017

Overview

Adaptive radiotherapy

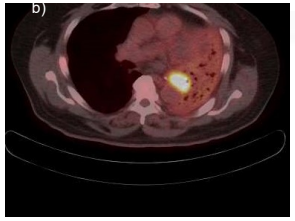
- Definition
- Models of adaption
- Site specific adaption solutions
- The future

Current radiotherapy planning

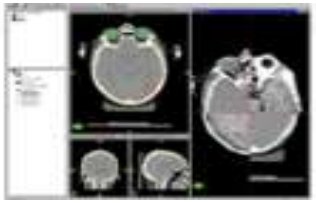
The evolution of radiotherapy

First Linac

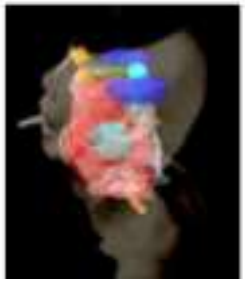
Image fusion



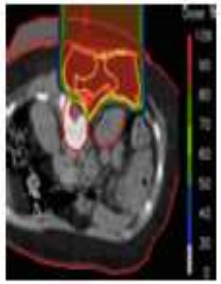
Computer based CT planning



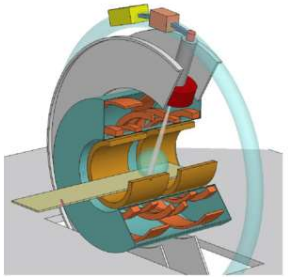
IMRT



Particles



MRI-Linac



1960 1970 1980 1990 2000 2010

Standard collimation

Multi-leaf collimation

CBCT

Volumetric arc therapy

SBRT

Aim to increase conformity and reduce toxicity through anatomical accuracy
i.e. dose to the target avoiding critical structures

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Image guidance

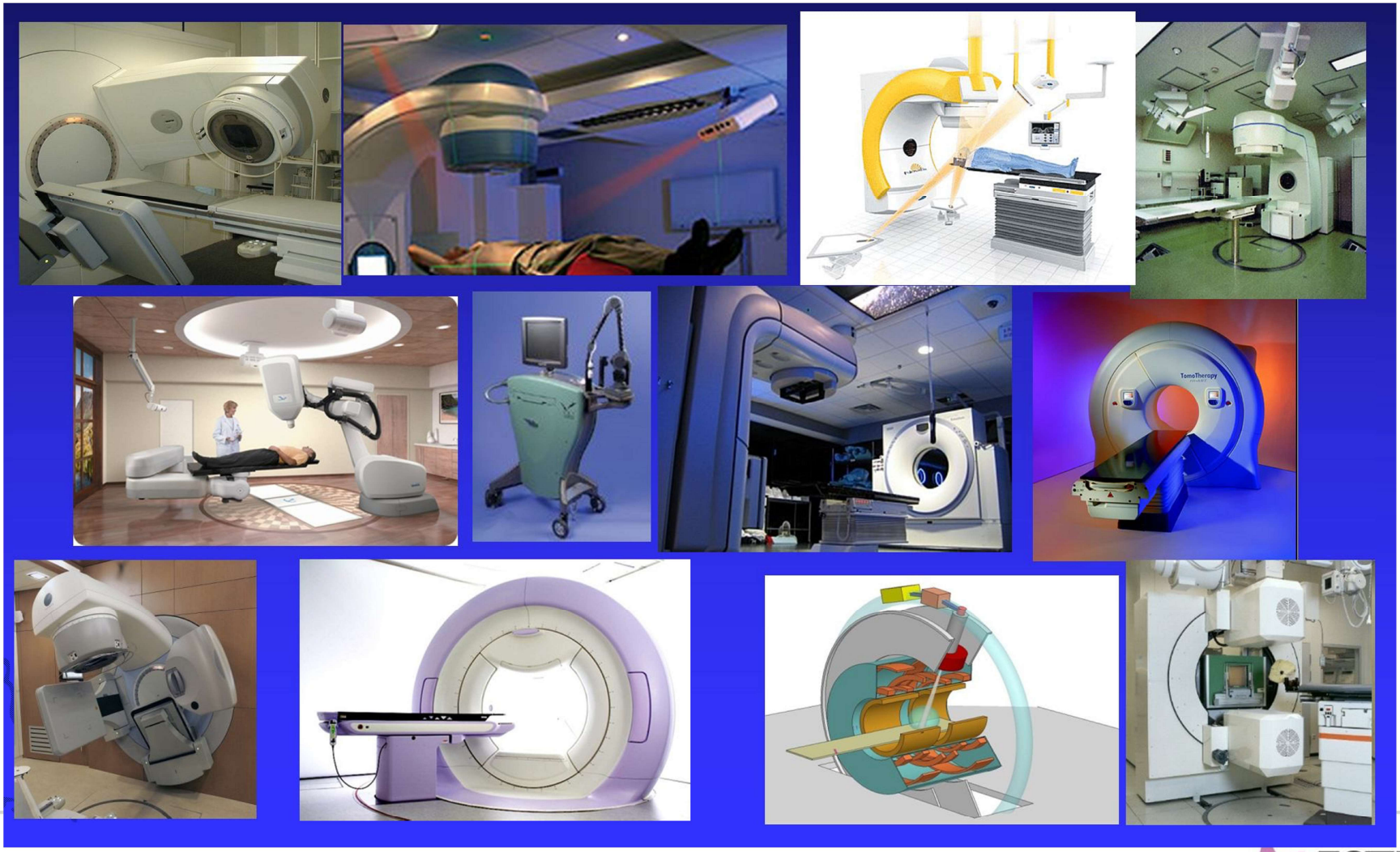

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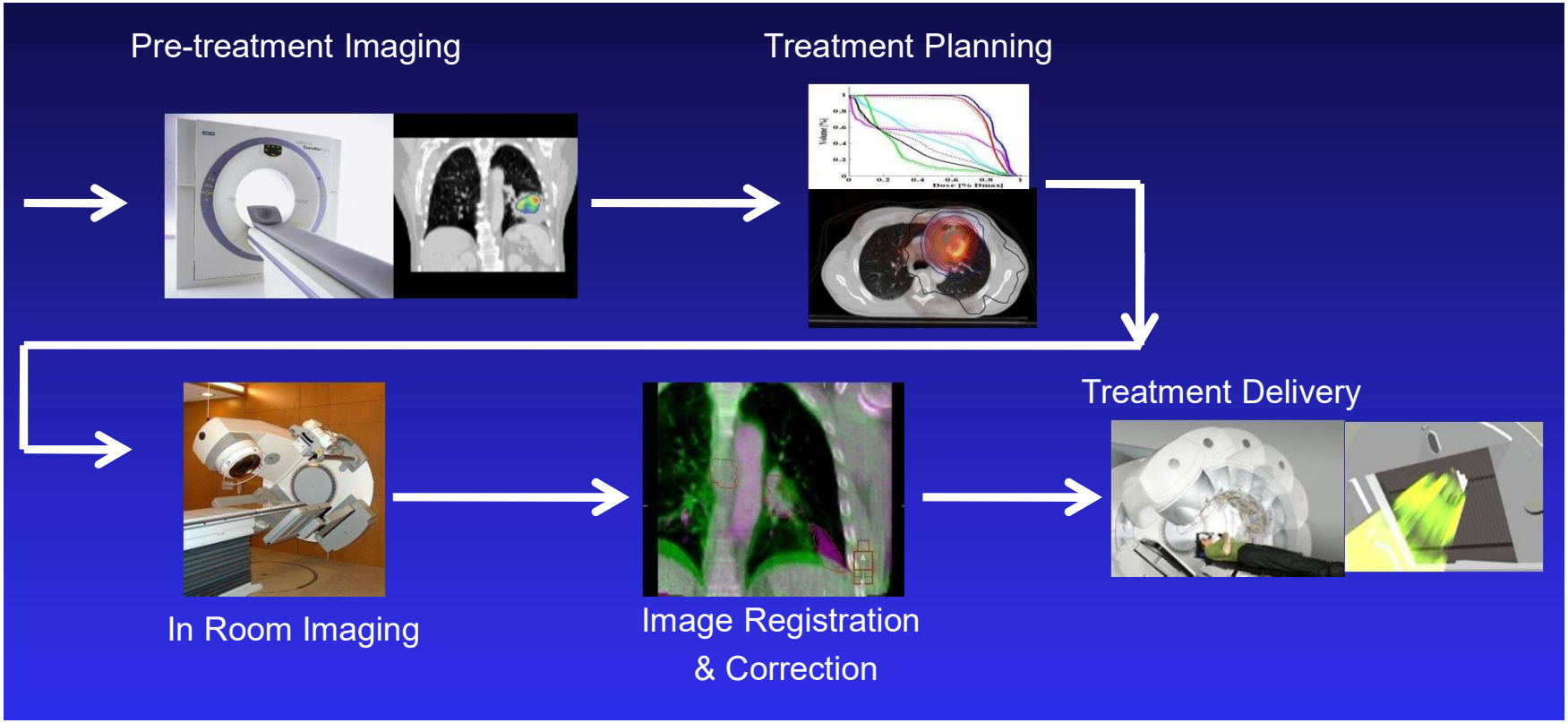
Image guidance

In room imaging- ‘knowledge of change’
Field light
X-rays
Cone Beam CT (CBCT)
In room MRI
Functional imaging

Established need for image guidance

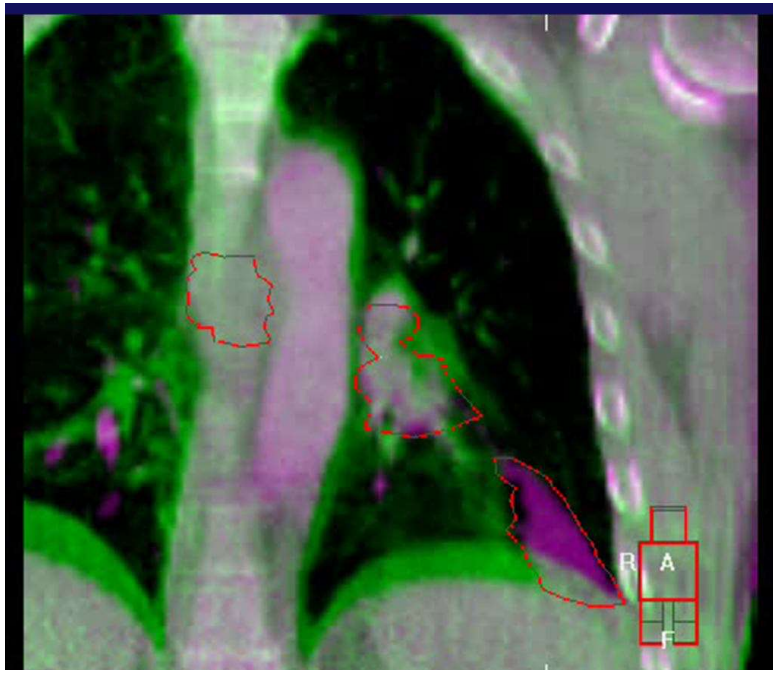
- Image tumour and OARs (or their surrogates just prior to or during treatment
- Assess change in position relative to treatment plan
- Adapt treatment plan (couch shift to account for changes), increase treatment precision

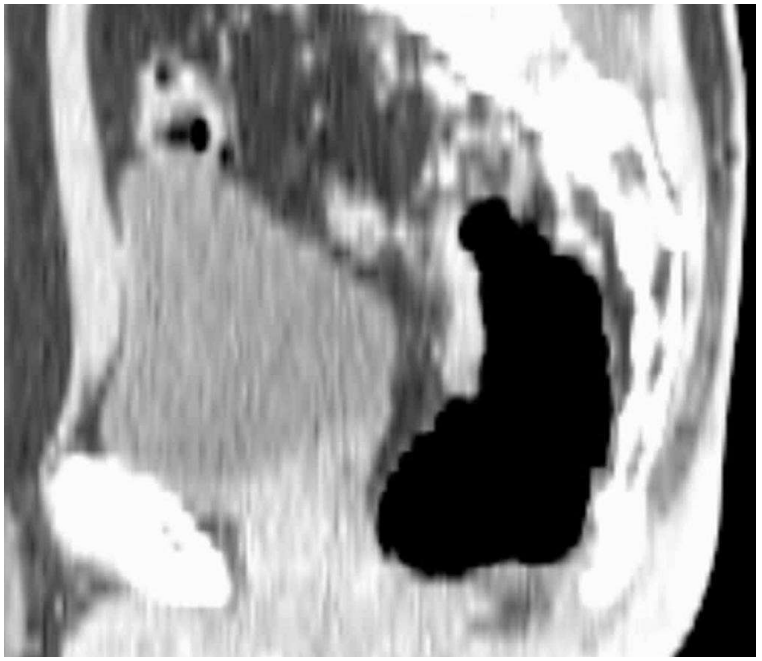
Image guidance



Limitations

No couch correction can address these problems





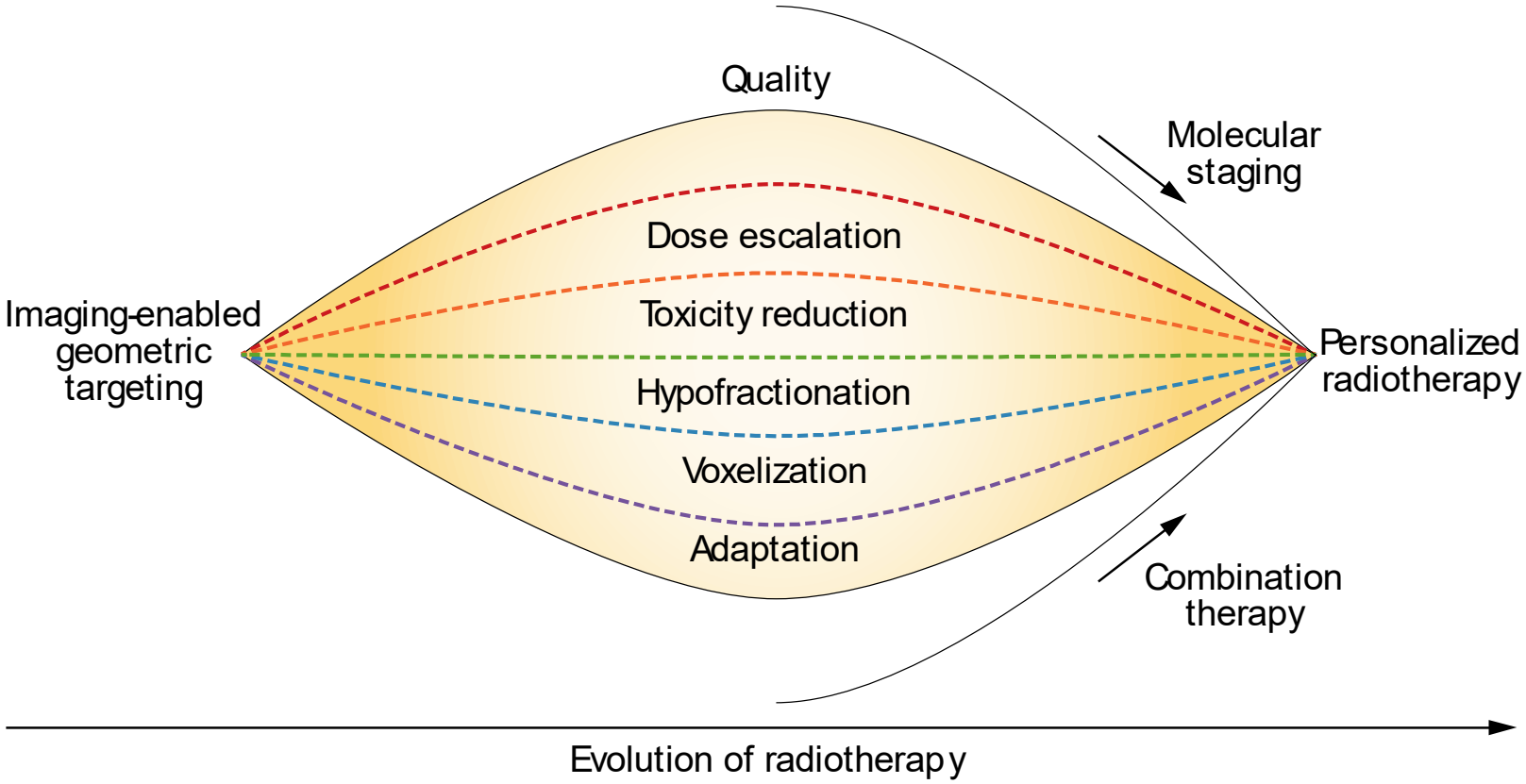
What is adaptive radiotherapy?

Adaptive radiation planning

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.

Yan D, Vicini F, Wong J, Martinez A: Adaptive radiation therapy. Phys Med Biol 1997, 42(1):123-132.

The evolution of radiotherapy



Jaffray DA: Image-guided radiotherapy: from current concept to future perspectives. *Nat Rev Clin Oncol* 2012, 9(12):688-699.

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Image guidance versus adaptive planning

Image guidance

- process of repositioning without modification of the original plan

Adaptive radiotherapy

- Modification of the initial plan, including changing beam apertures or intensity patterns

Are commonly used together

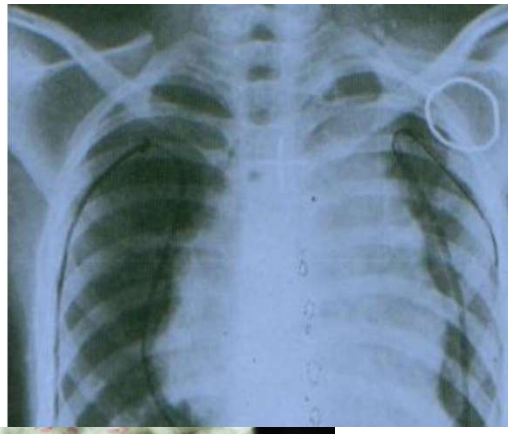
Adaptive radiation planning

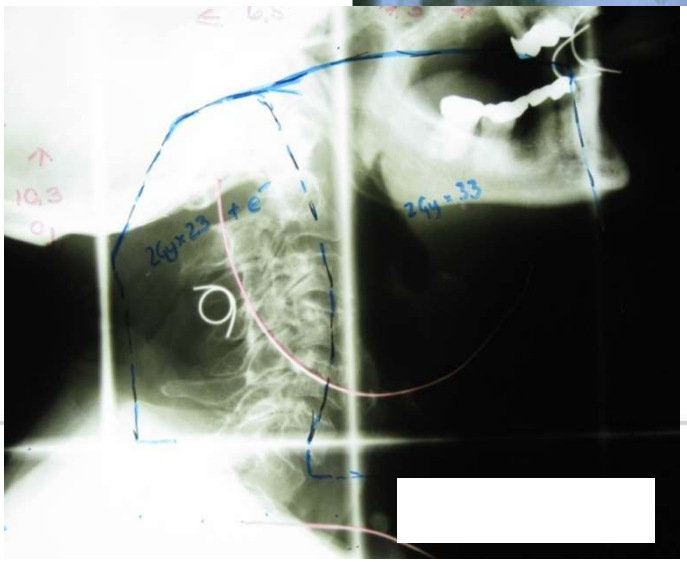
- We are all doing some adaptive treatment for our patients
- Volumetric IGRT more common, the more you look the more you see
- Greater integrated care, dosimetric consequence of shape changes (weight loss) = reactive

X-rays and change of strategy

Reduction in target at boost planning – Head and Neck metastases/lymphoma

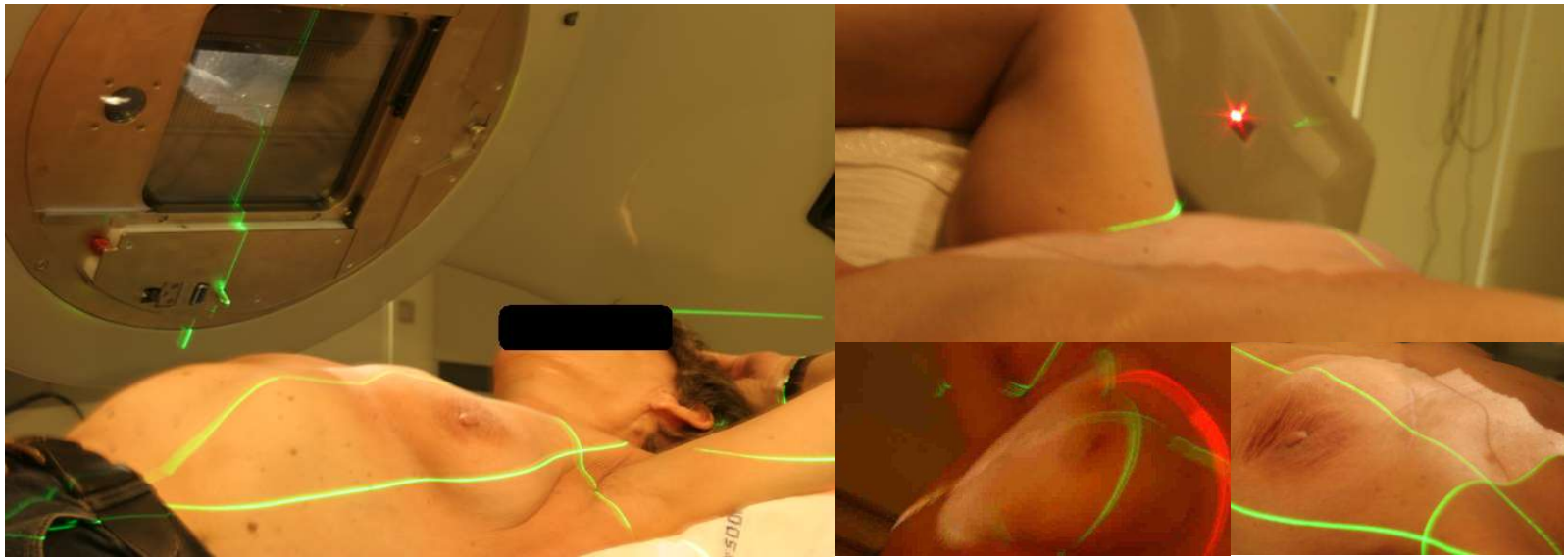
2D: X-ray Sim, individual blocks
Hodgkin´s Disease
Boost Head and neck





Field light and Daily

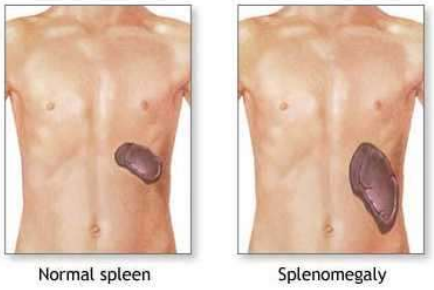
- Breast oedema during treatment
  - Treatment staff check field light every day

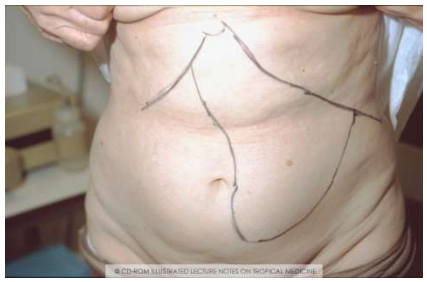


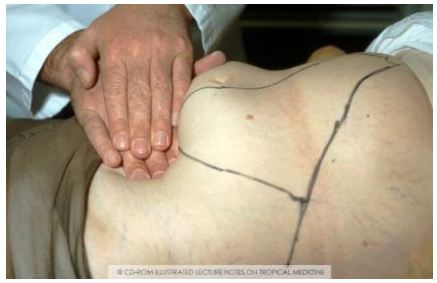
  - If the visible breast not within field light – ‘open one or two caudal MLCs’

Field light or CBCT and planned interval

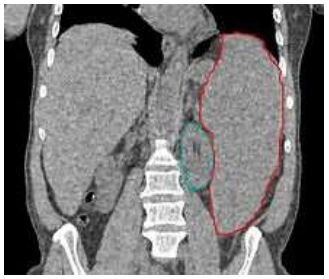
- Spleen size – palliative radiotherapy splenomegaly (0.5 Gy x 20)







  - Doctor palpate abdomen every week and compare 'size of day' with field light. If size reduction – 'close one or two caudal MLCs'



  - or in present era CBCT – and re-plan once a week

Adaptive radiotherapy models

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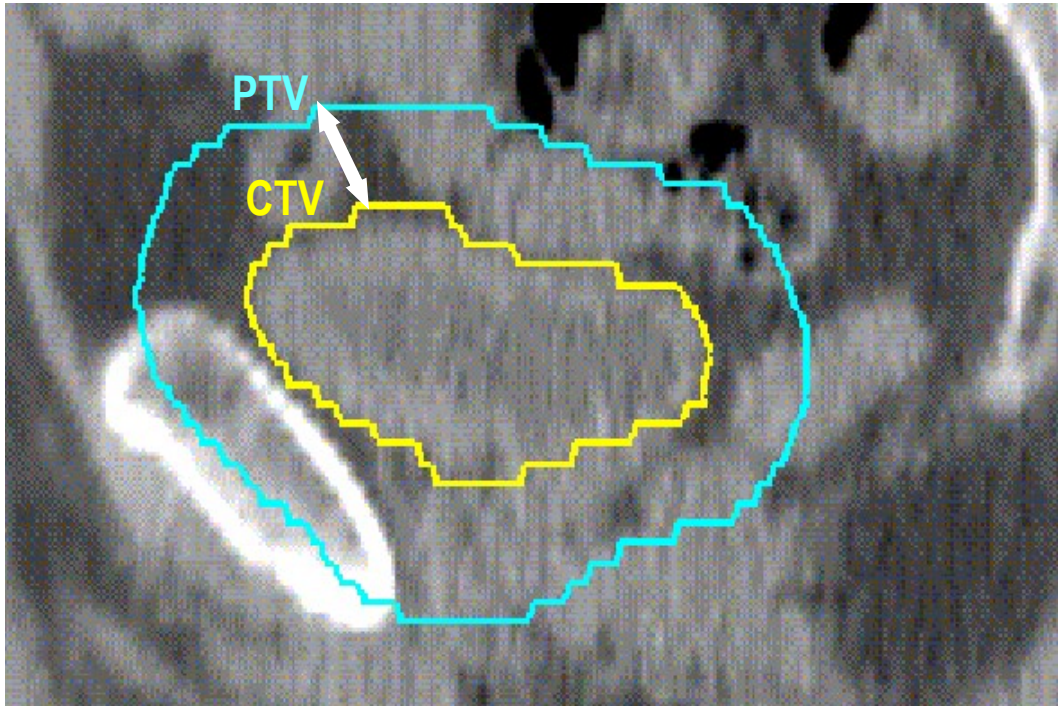
Established need for radiotherapy image guidance and adaptation

Conventional population based margin

- isotropic 1.5-3cm
- ~40% fractions incur geographical miss

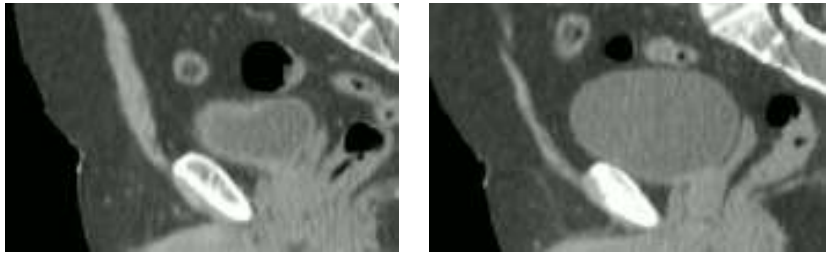


Isotropic margin (1.5–3 cm)

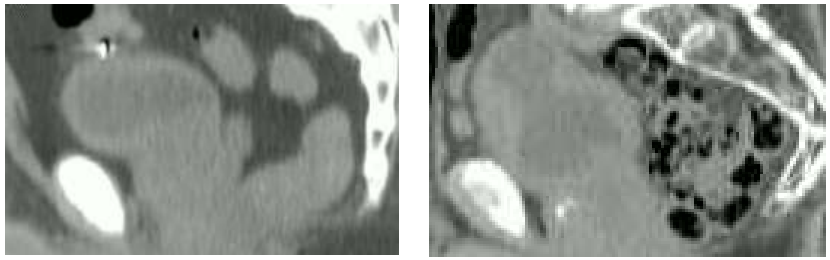
Established need for radiotherapy image guidance and adaptation (pelvic tumours)

Conventional population based margin

- isotropic 1.5-3cm
- ~40% fractions incur geographical miss



Presumed empty bladder on two different occasions

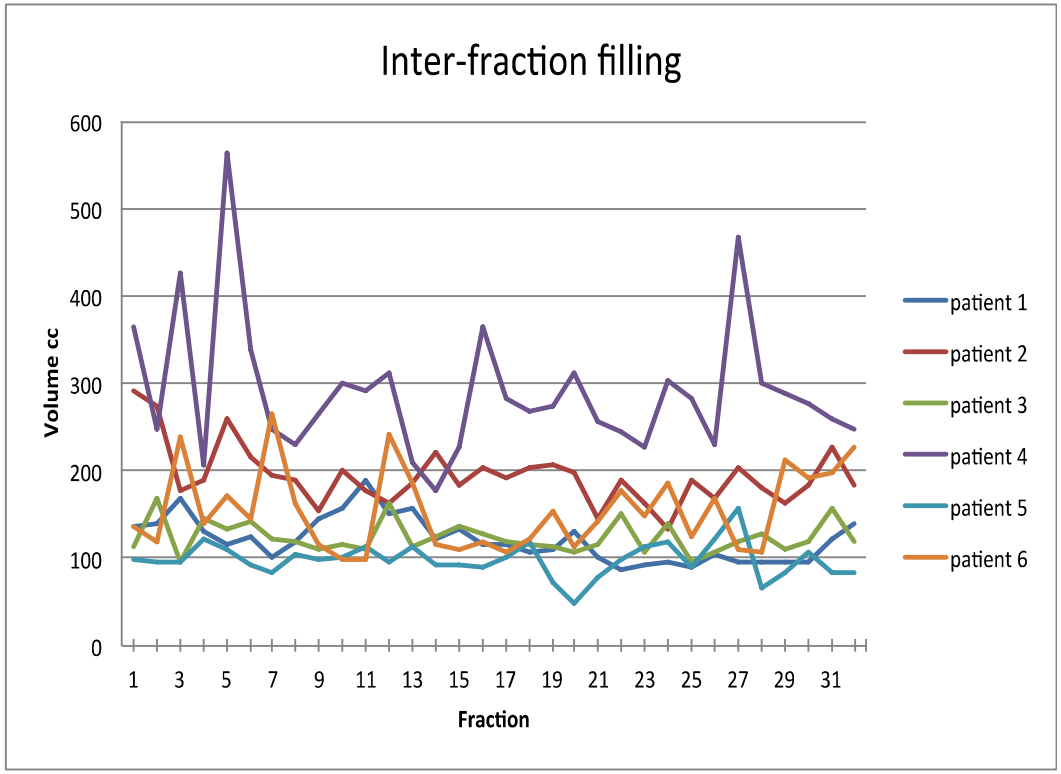


Influence of rectal filling

Established need for radiotherapy image guidance and adaptation

Conventional population based margin

- isotropic 1.5-3cm
- ~40% fractions incur geographical miss



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Limitations of margin recipes

According to ‘margin recipe’ bladder tumour at the dome
[Van Herk equation 2.5 $\sum$ + 0.7 σ] = 4cm margin

Oversimplification

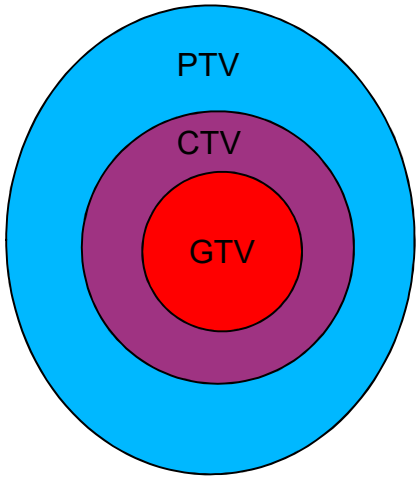
- ?applicability to bladder if derived from solid organ
- comparison with direct empirical approaches up 9mm difference

Muren LP, Smaaland R, Dahl O: Organ motion, set-up variation and treatment margins in radical radiotherapy of urinary bladder cancer. Radiother Oncol 2003, 69(3):291-304.

Influence of margin on volume

- Third-power relationship between radius of a sphere and volume ($4/3\pi r^3$)
- Small reduction in margin (5mm) yields a 50% reduction in volume
- The volume of the outer layer equals the volume of the core of the orange

- GTV, 2 cm diameter, volume 4.2 cm^3
  - Add 1 cm to
- CTV, 4 cm diameter, volume 33.5 cm^3
  - Add 1 cm to
- PTV, 6 cm diameter, volume 113 cm^3



Verellen D, Ridder MD, Linthout N, Tournel K, Soete G, Storme G: Innovations in image-guided radiotherapy. Nat Rev Cancer 2007, 7(12):949-960.

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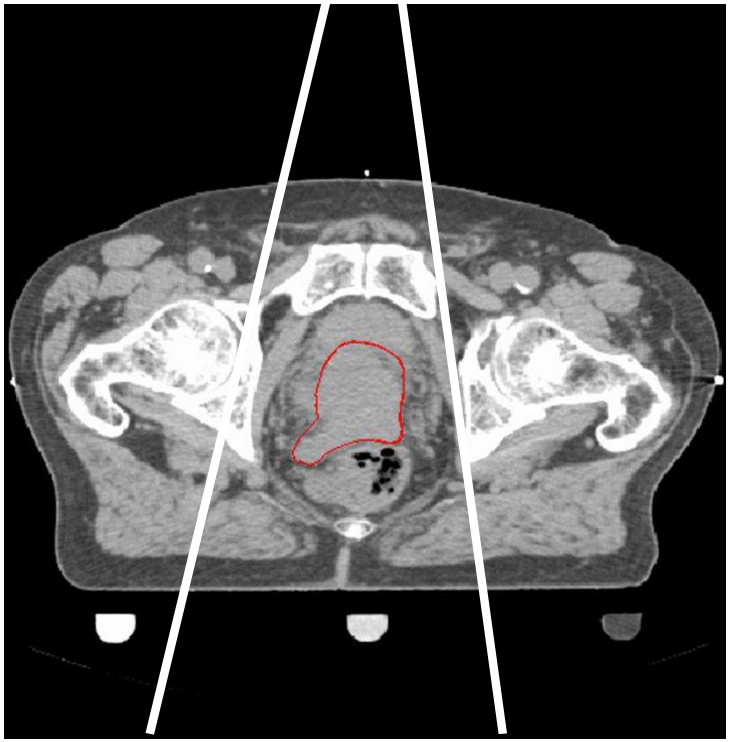
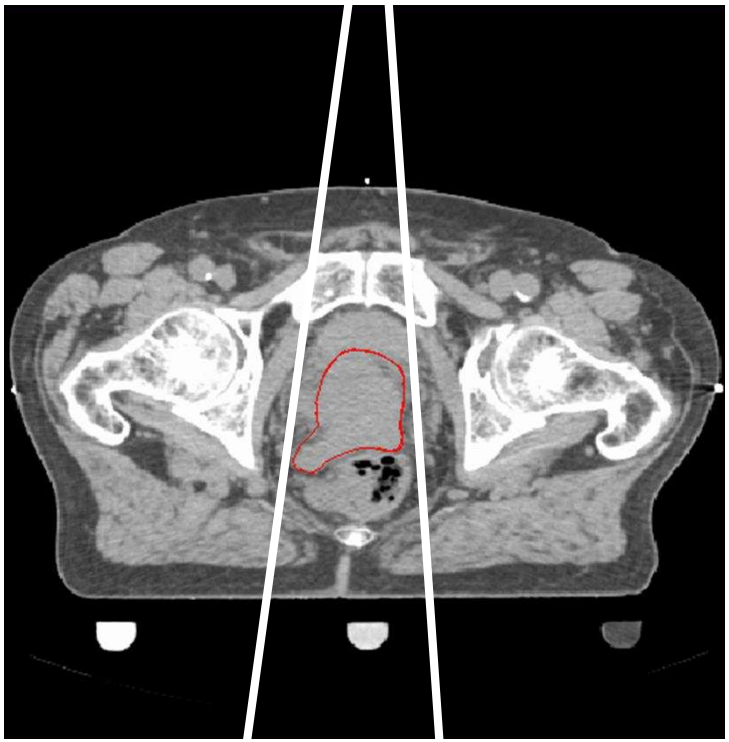
Off-line observational studies

Study (year)	n	Imaging technique	Margins applied to bladder (CTV)					Number of patients in whom bladder excursions were encompassed by target volume used
			Ant	Post	Sup	Inf	Lat	
Sur et al., (1993)	90	Planning CT, repeated halfway through treatment	1.0-2.0 isotropic					80%
Turner et al., (1997)	30	Planning CT, repeated weekly through treatment	1.5-2.0 isotropic					67% (33% had at least one incidence of wall movement >15 mm)
Harris et al., (1998)	20	Planning CT, repeated halfway through and end of treatment	1.0-2.0 isotropic					80%
Pos et al., (2003)	17	Planning CT, repeated weekly through treatment	1.5-2.0 isotropic					35% (71%, GTV received at least 95% of dose on weekly scans)
Muren et al., (2003)	20	Planning CT, weekly CT (and EPI)	2.0	1.4	2.0	1.0	1.1 (L) 0.8 (R)	84%

Fokdal et al., (2004)	15	Five serial planning CTs, with varied filling of urinary catheter and rectal balloon; planning CT scan at 20 fractions	2.4	1.1	3.5	0.5	1.3	87%
Manger et al., (2007)	9	Cine-MRI over 20mins pre-RT, repeated after week 4	1.5 isotropic					89% (78%, 95% confidence interval maximum displacement <1.5 cm)
McBain et al., (2009)	15	Cine-MRI over 28mins at staging, 2-3 weeks later prior to RT	1.5-2.0 isotropic					50% at 14mins with 1.5cm margin
Lalondrelle et al., (2011)	15	Planning CT 0 (CT0), 15, 30mins, pre-RT CBCT (CTVcb), post RT CBCT,	1.5 (CTV0), 0.5 (CTVcb)					49% of fractions (51% of pre-RT outside CT0)
Gronberg et al., (2015)	9	Planning CT, pre-RT CBCT, weekly post RT CBCT, MRI scan pre-treatment, weekly at 0, 2, 4, 6, 8,10mins						63% with population based margin (3 out of 8 patients did not have bladder encompassed by PTV; bladder volume coverage in these patients was 98.1%-99.9%)

How can we solve this problem





1. Use a large margin, irradiates excessive normal tissues

2. Use a small margin, risk target misses

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Established need for image guidance

Retrospective analysis of 27 patients having daily CBCT

To determine CTV to PTV margin required to achieve coverage of bladder when using skin, bone or soft tissue matching

% of patients where expanded CTV covered 95% of wall displacements

	CTV+0.5	CTV+1.0	CTV+1.5	CTV+2.0	CTV+2.5
Skin	0	19	56	93	96
Bone	0	41	63	89	96
Soft tissue	52	89	96	100	100

Foroudi et al. Bladder cancer radiotherapy margins: a comparison of daily alignment using skin, bone or soft tissue 2012 Clin Oncol 24 673-681

How can we use this pre-treatment information to change (adapt) treatment?

Adaptive radiotherapy

Can occur at three different timescales

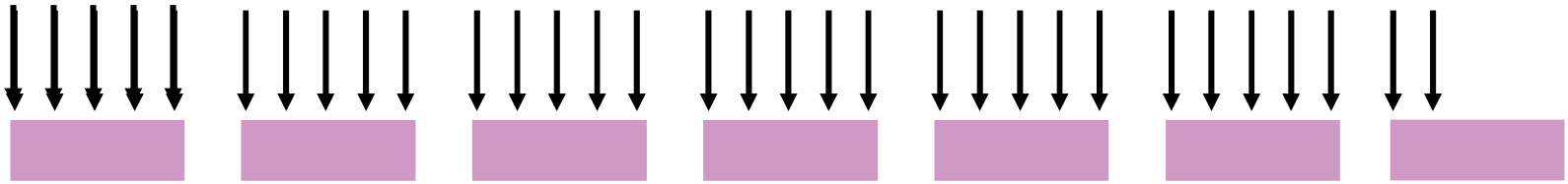
1. **Offline between fractions**

1. Online immediately prior to a fraction

1. In real time during a fraction

Radiotherapy schedules

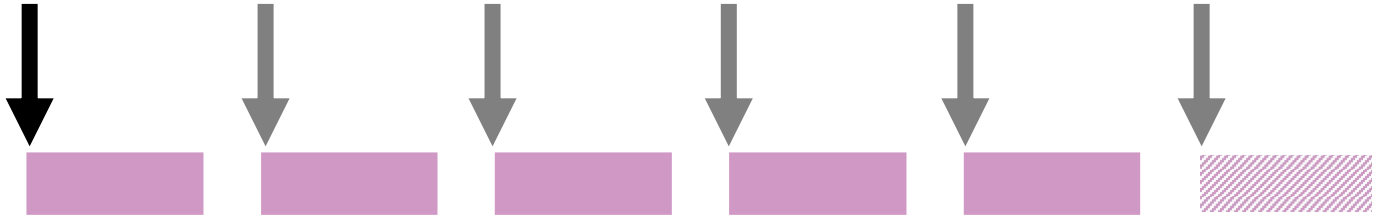
Radical



64Gy in 32# over 6.5 weeks

55Gy in 20# over 4 weeks

High dose palliative



30-36Gy in 5-6# over 5-6 weeks

James ND et al: Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med 2012, 366(16):1477-1488.
Hoskin PJ et al., Radiotherapy with concurrent carbogen and nicotinamide in bladder carcinoma. J Clin Oncol 2010, 28(33):4912-4918. Duchesne GM et al., A randomized trial of hypofractionated schedules of palliative radiotherapy in the management of bladder carcinoma: results of medical research council trial BA09. Int J Radiat Oncol Biol Phys 2000, 47(2):379-388

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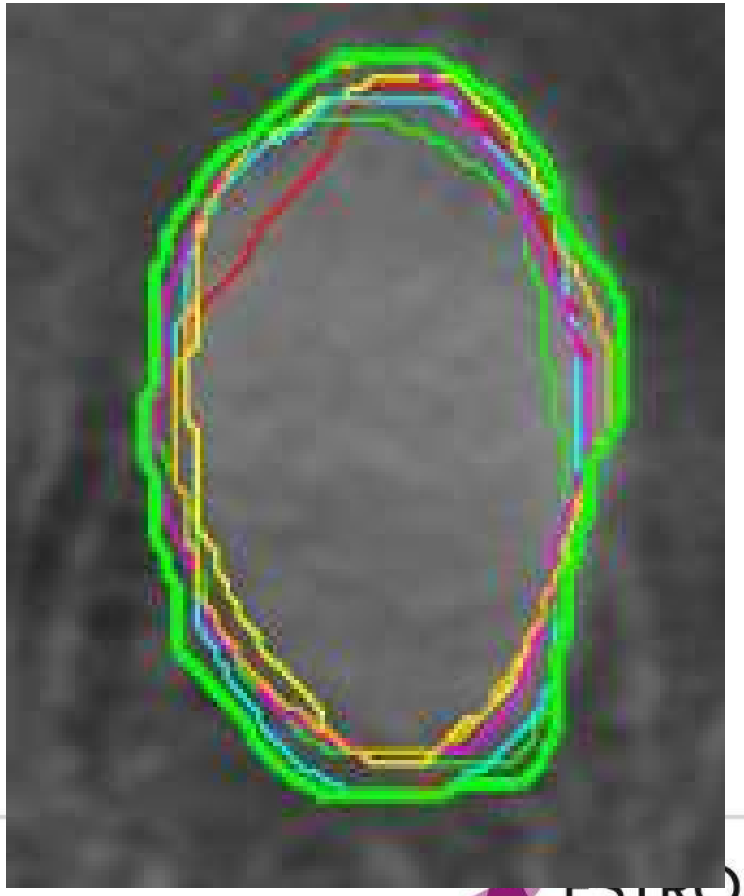
Adaptive planning solutions

Composite volume

CBCTS acquired from D1-5 fused with planning CT

Determine maximum excursion of bladder

Smaller CTV-PTV margin added to account for set up error and intra fraction motion

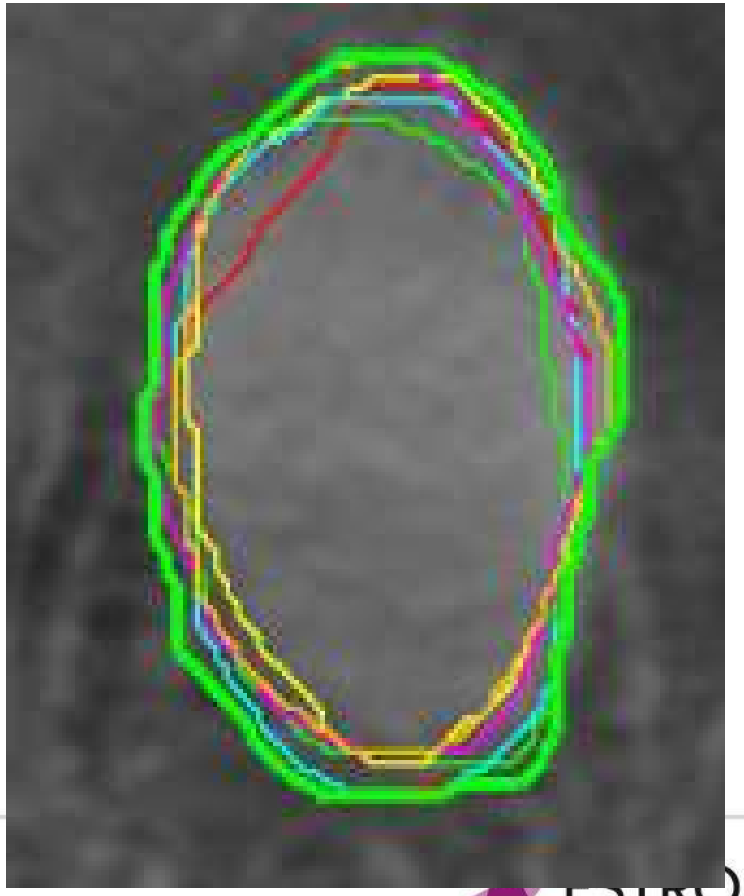


Adaptive planning solutions

Composite volume

Advantages

PTV reduced by 40% when compared to isotropic PTV (1.5cm)



Challenges

Additional resources for replanning

Use only following 2nd week RT

Applicability for hypofractionated (weekly) RT

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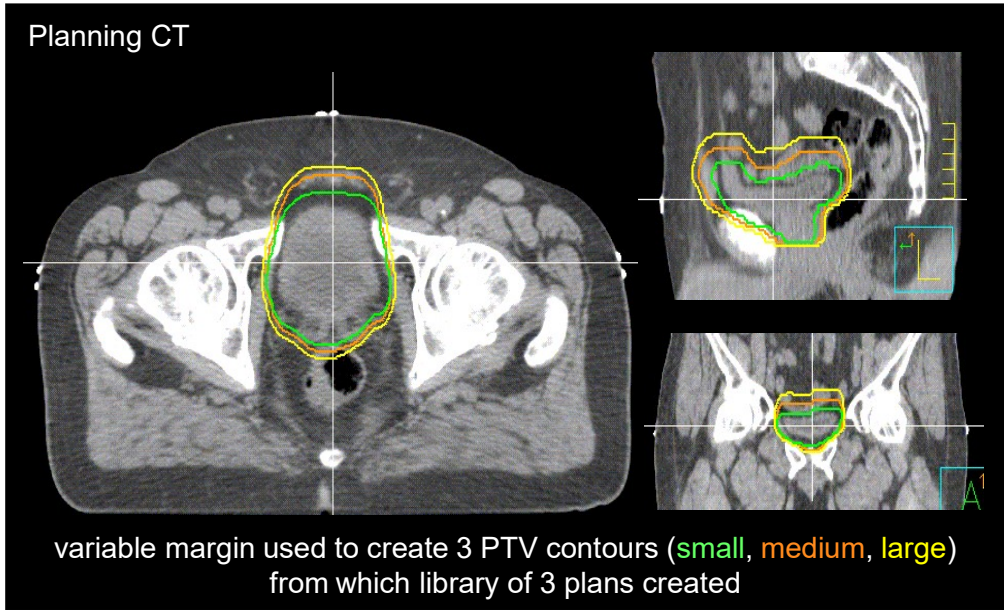
Adaptive planning solutions

Plan of the day

Library of plans based on

i)Variable margins around empty bladder

i)Patient's own bladder filling (and variable margins)



variable margin used to create 3 PTV contours (small, medium, large) from which library of 3 plans created

Hafeez S et al: Prospective Study Delivering Simultaneous Integrated High-dose Tumor Boost (≤70 Gy) With Image Guided Adaptive Radiation Therapy for Radical Treatment of Localized Muscle-Invasive Bladder Cancer. International Journal of Radiation Oncology*Biology*Physics 2016, 94(5):1022-1030.

Lalondrelle S, et al. Adaptive-predictive organ localization using cone-beam computed tomography for improved accuracy in external beam radiotherapy for bladder cancer. Int J Radiat Oncol Biol Phys 2011, 79(3):705-712.

McDonald F et al: Clinical implementation of adaptive hypofractionated bladder radiotherapy for improvement in normal tissue irradiation. Clin Oncol (R Coll Radiol) 2013, 25(9):549-556

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Adaptive planning solutions

Plan of the day/adaptive predictive organ localisation

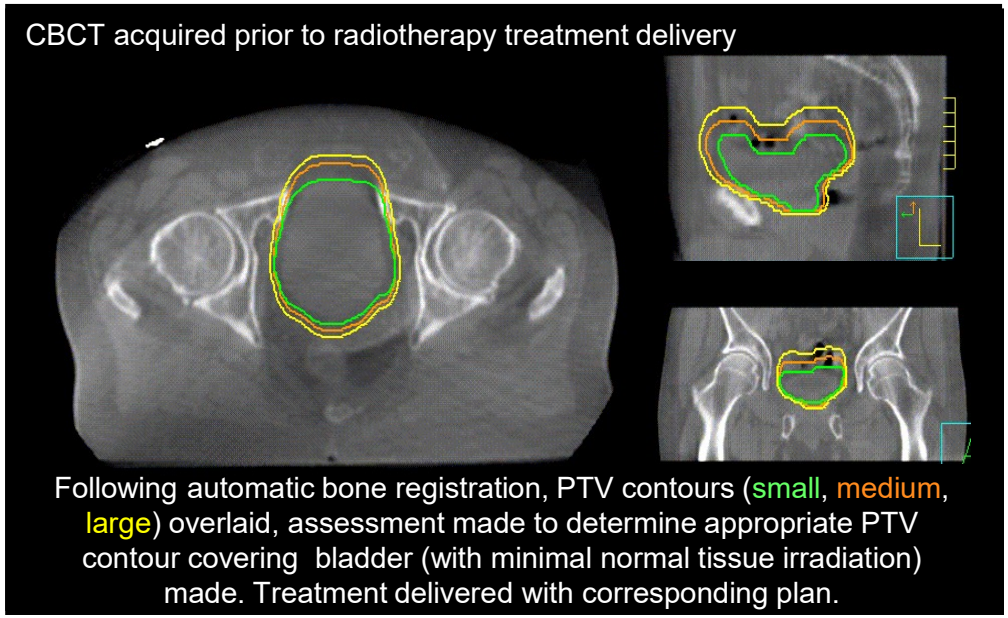
CTV → PTV (cm)	Small PTV	Medium PTV	Large PTV	
			Based on CT30	Based on CT0
Anterior	0.5	1.5	1.5	2.0
Posterior	0.5	1.0	1.0	1.2
Lateral	0.5	0.5	0.5	0.75
Superior	0.5	1.5	1.5	2.5
Inferior	0.5	0.5	0.5	0.75

Adaptive planning solutions

Plan of the day

CBCT assess bladder in relation to planning CT

Choose best fit plan.



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Adaptive planning solutions

Plan of the day

Advantages

Reduction in PTV of 40% when compared to isotropic PTV (1.5cm)

Challenges

Additional training

Ensuring concordance of plan selections

Increased work load (vs single plan)

Library size vs conformity of plan selection

Impact of training- to improve plan selection

Period	Year evaluated	No. of images evaluated	Concordance achieved	Reference
Pre-training	2010	20	73%	
Post training				[1] Taylor H et al.,
Round 1	2010	20	66%	[2] McNair H et al.,
Round 2	2010	20	76%	
Clinical implementation (From 2011)	2013	139	91%	[3] McDonald F et al.,
	2014	125	92%	[4] Hafeez S et al.,
	2015	734	94%	[5] Hafeez S et al.,

[1] Taylor H Lalondrelle S, McDonald F, McNair H, Huddart R.: Developing advanced competencies in CBCT for the implementation of adaptive radiotherapy. Radiotherapy and Oncology 2010(96):S27.
[2] McNair HA, Hafeez S, Taylor H, Lalondrelle S, McDonald F, Hansen VN, Huddart R: Radiographer-led plan selection for bladder cancer radiotherapy: initiating a training programme and maintaining competency. Br J Radiol 2015, 88(1048):20140690.
[3] McDonald F, Lalondrelle S, Taylor H, Warren-Oseni K, Khoo V, McNair HA, Harris V, Hafeez S, Hansen VN, Thomas K et al: Clinical implementation of adaptive hypofractionated bladder radiotherapy for improvement in normal tissue irradiation. Clin Oncol (R Coll Radiol) 2013, 25(9):549-556
[4] Hafeez S, McNair H, Warren-Oseni K, Hansen V, Huddart R: Audit of Radiographer Led Plan Selection in Imaged Guided Adaptive Radiotherapy (IGART) for Bladder Cancer. Clinical Oncology 2014, 6(26):S7–S8.
[5] Hafeez S, Warren-Oseni K, McNair H, Hansen V, Jones K, Tan M, Khan A, Harris V, McDonald F, Lalondrelle S, Mohammed K, Thomas K, Thompson A, Kumar P, Dearnaley D, Horwich A, Huddart R: Prospective study delivering simultaneous integrated high dose tumour boost (up to 70Gy) with image guided adaptive radiotherapy (IGART) for the radical treatment of localized muscle invasive bladder cancer. GU ASCO 2015

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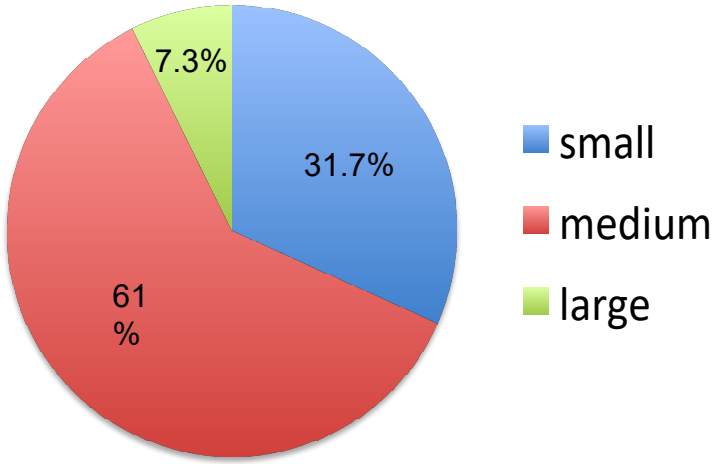
Non-concordant plan selection

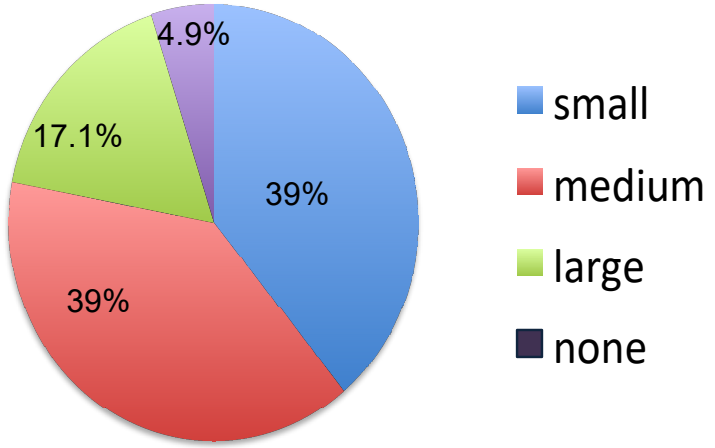
40/638 plan selections were non-concordant

the on-line choice was smaller than off-line selection on 21 occasions,
and larger than off-line selection on 17 occasions,
on 2 occasions no plan was deemed optimal for treatment

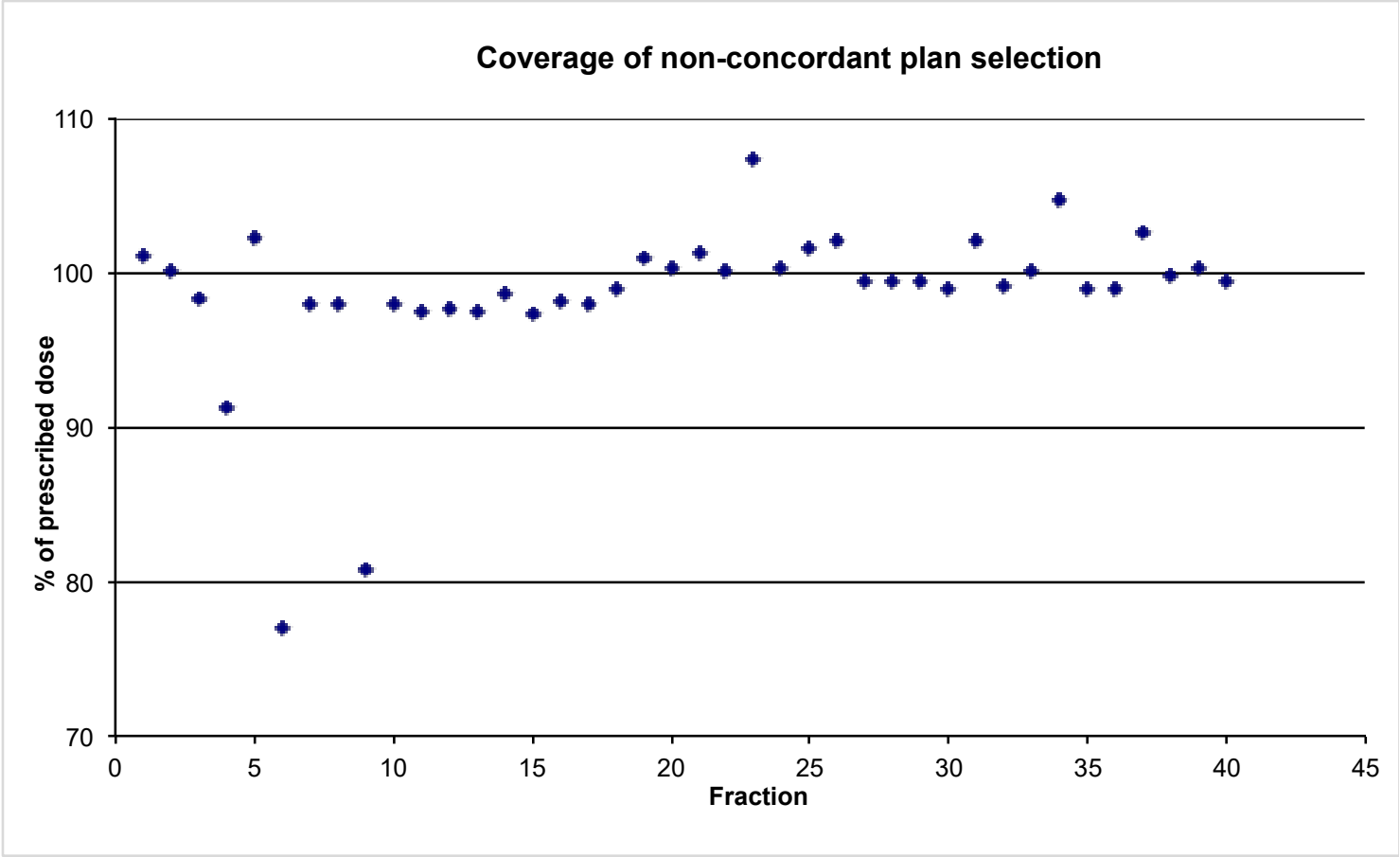
On line plan selection (radiographer)



Off line plan selection (clinician)



Non-concordant plan selection



Mean D98 of bladder with non-concordant plan selection

98.6%

(SD 5.1, range 77.0-107.3)

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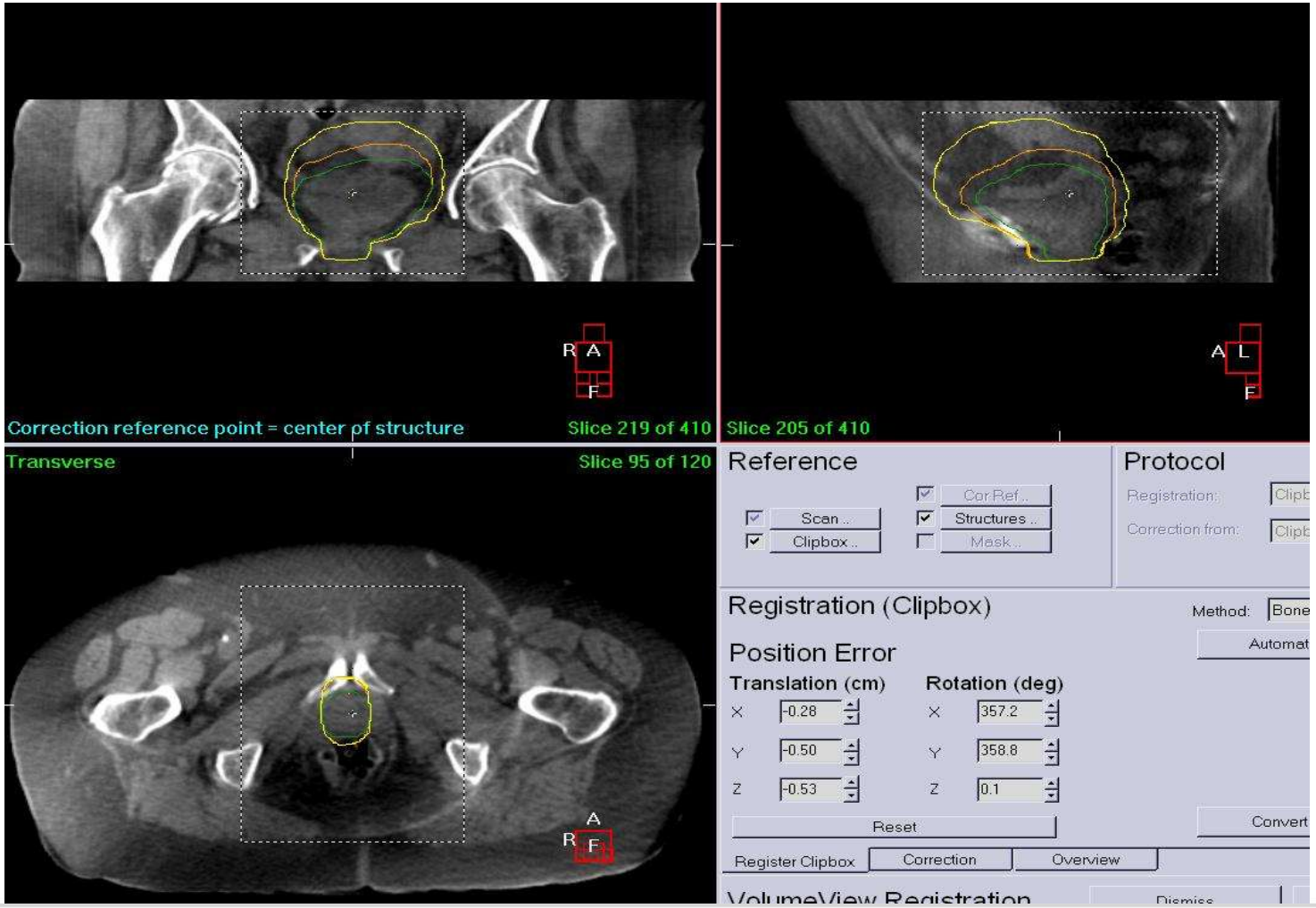
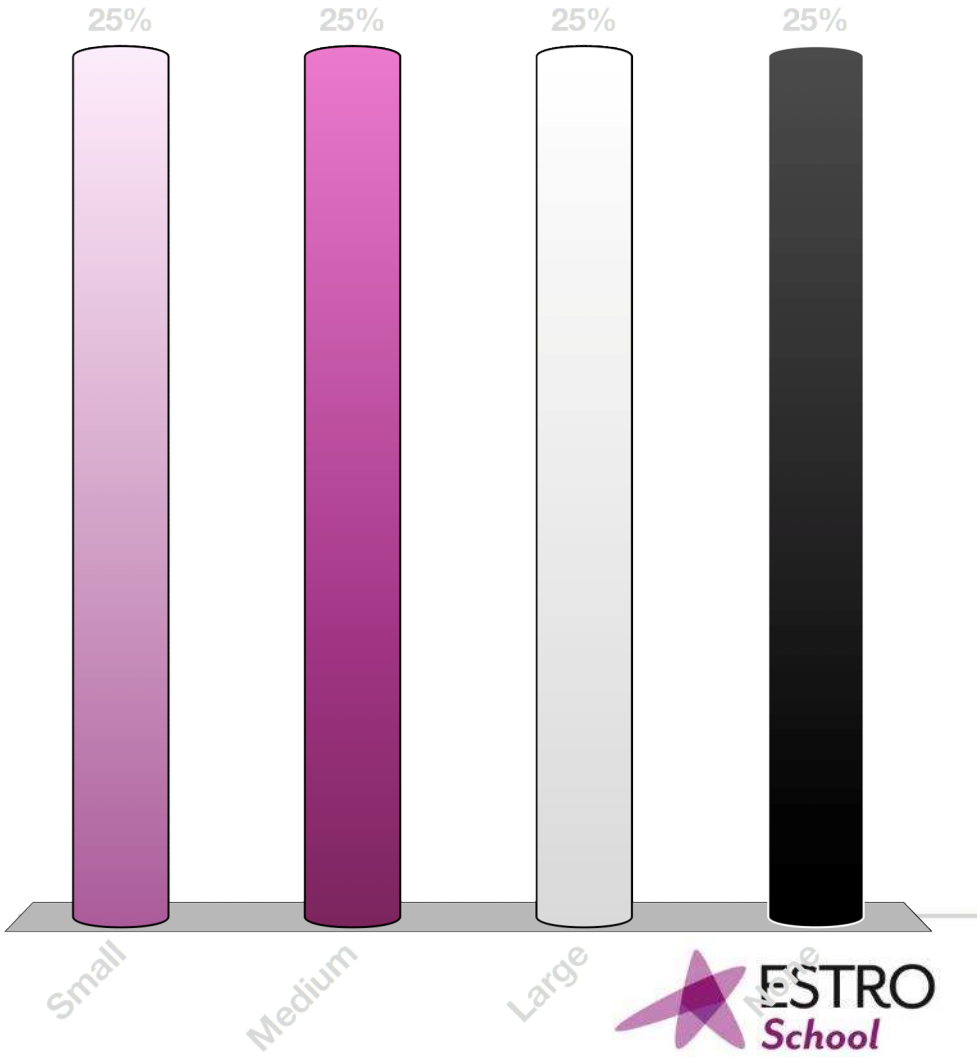
CBCT examples



CBCT examples

A. Small
B. Medium
C. Large
D. None



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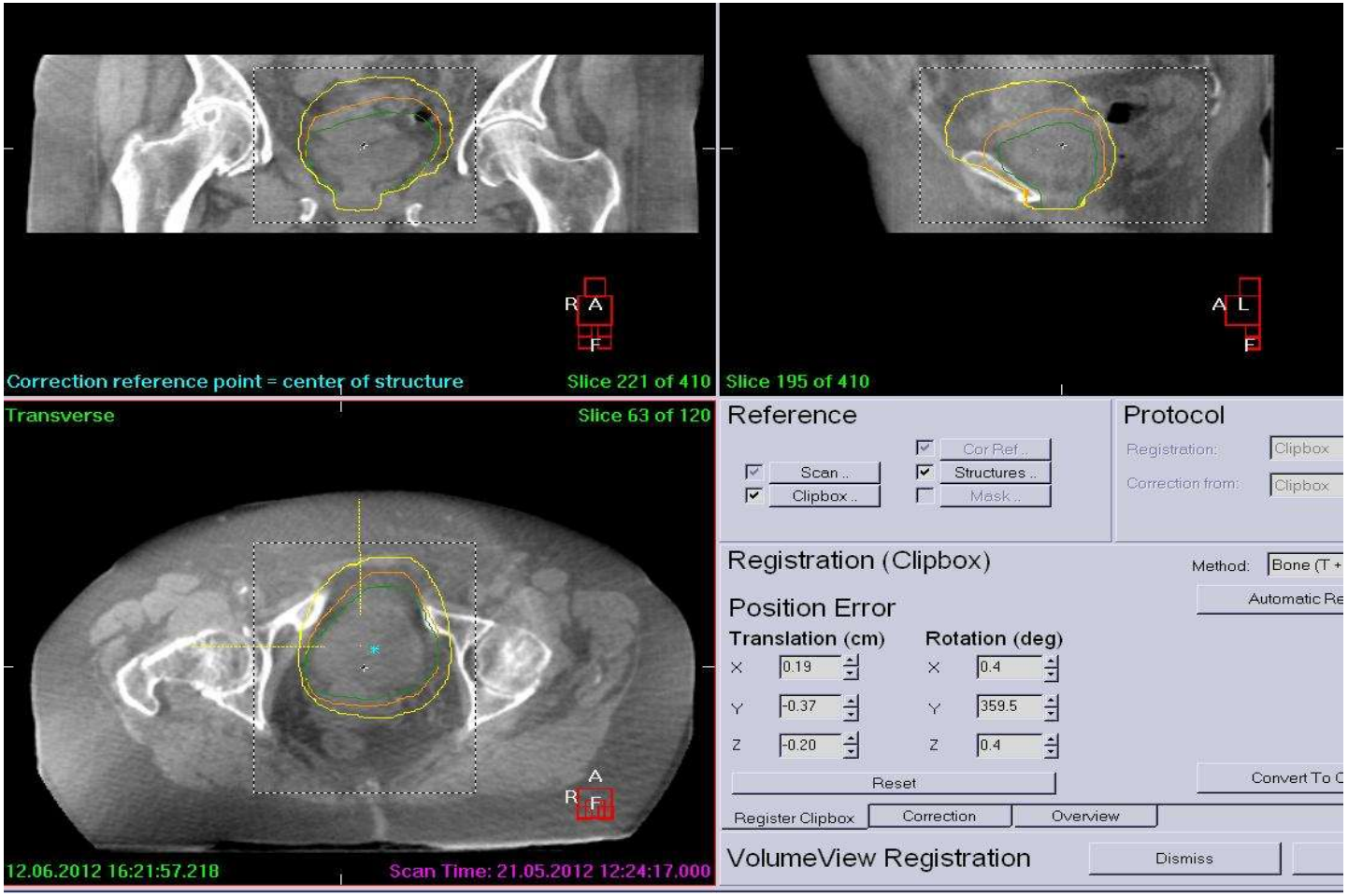
CBCT examples



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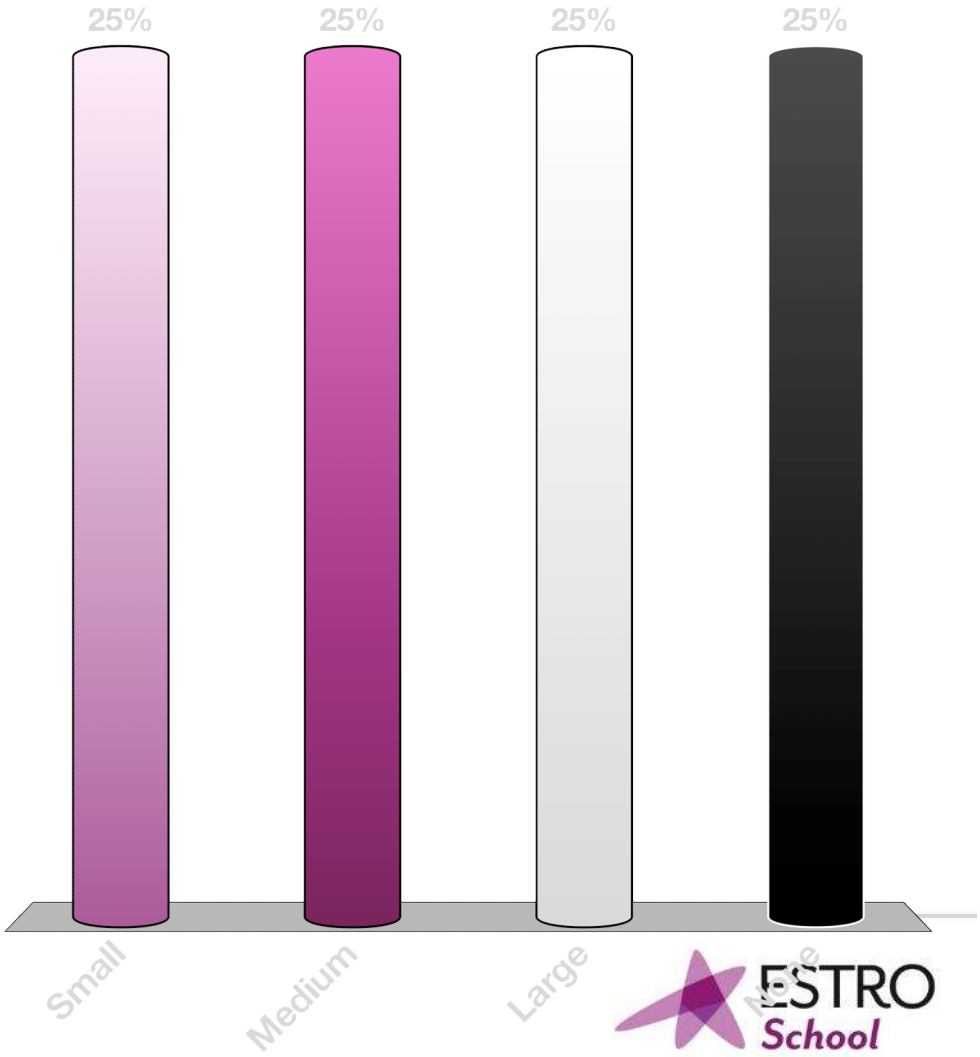
CBCT examples

A. Small
B. Medium
C. Large
D. None



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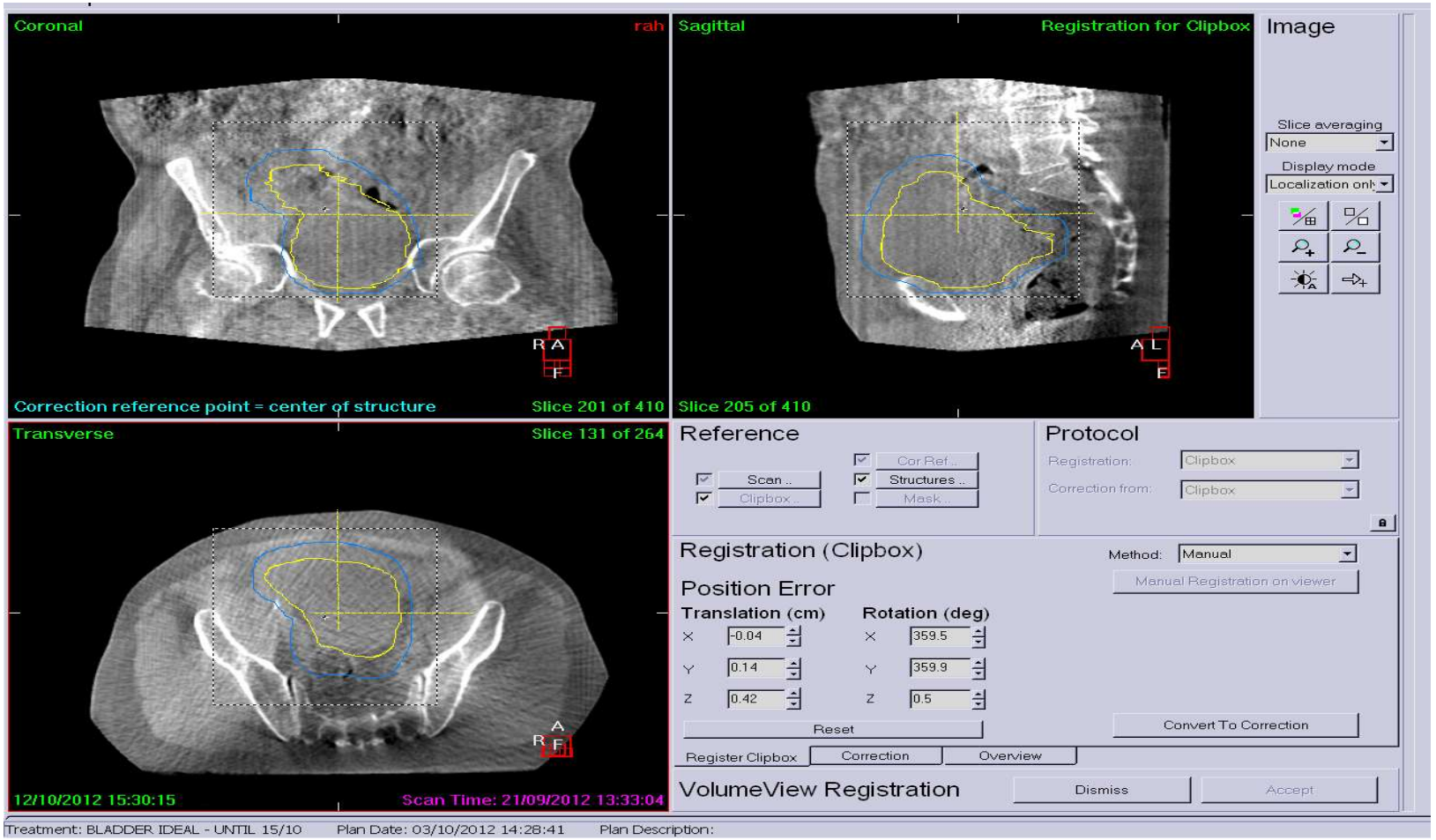
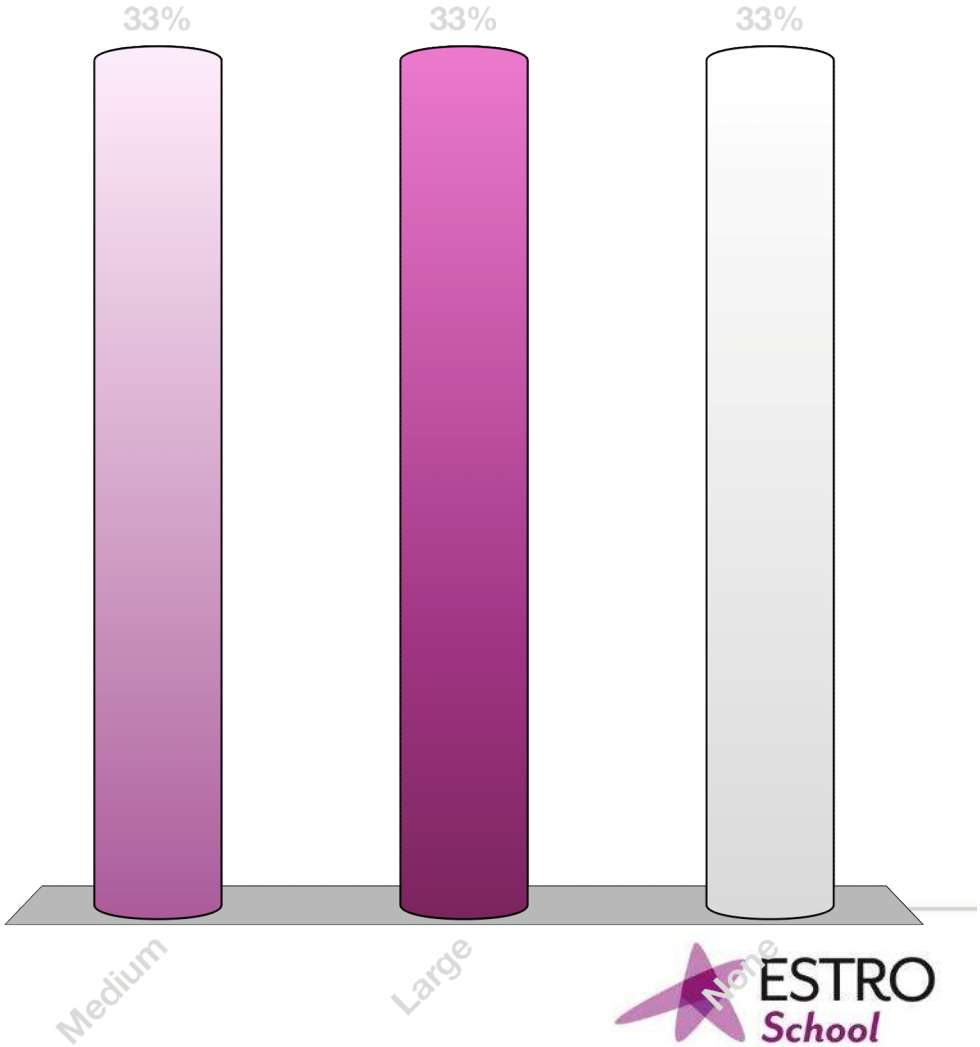
CBCT examples



CBCT examples

A. Medium
B. Large
C. None



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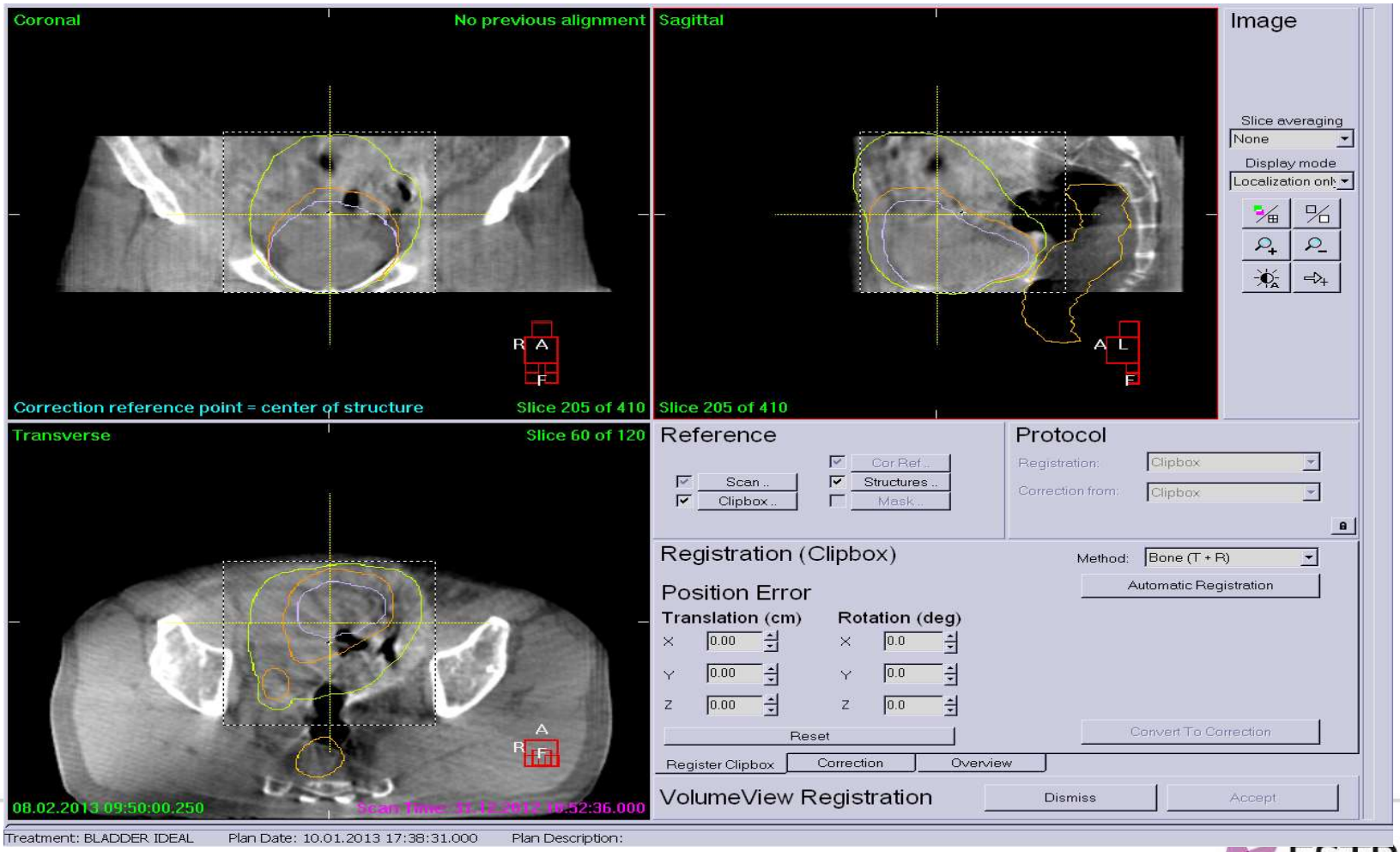
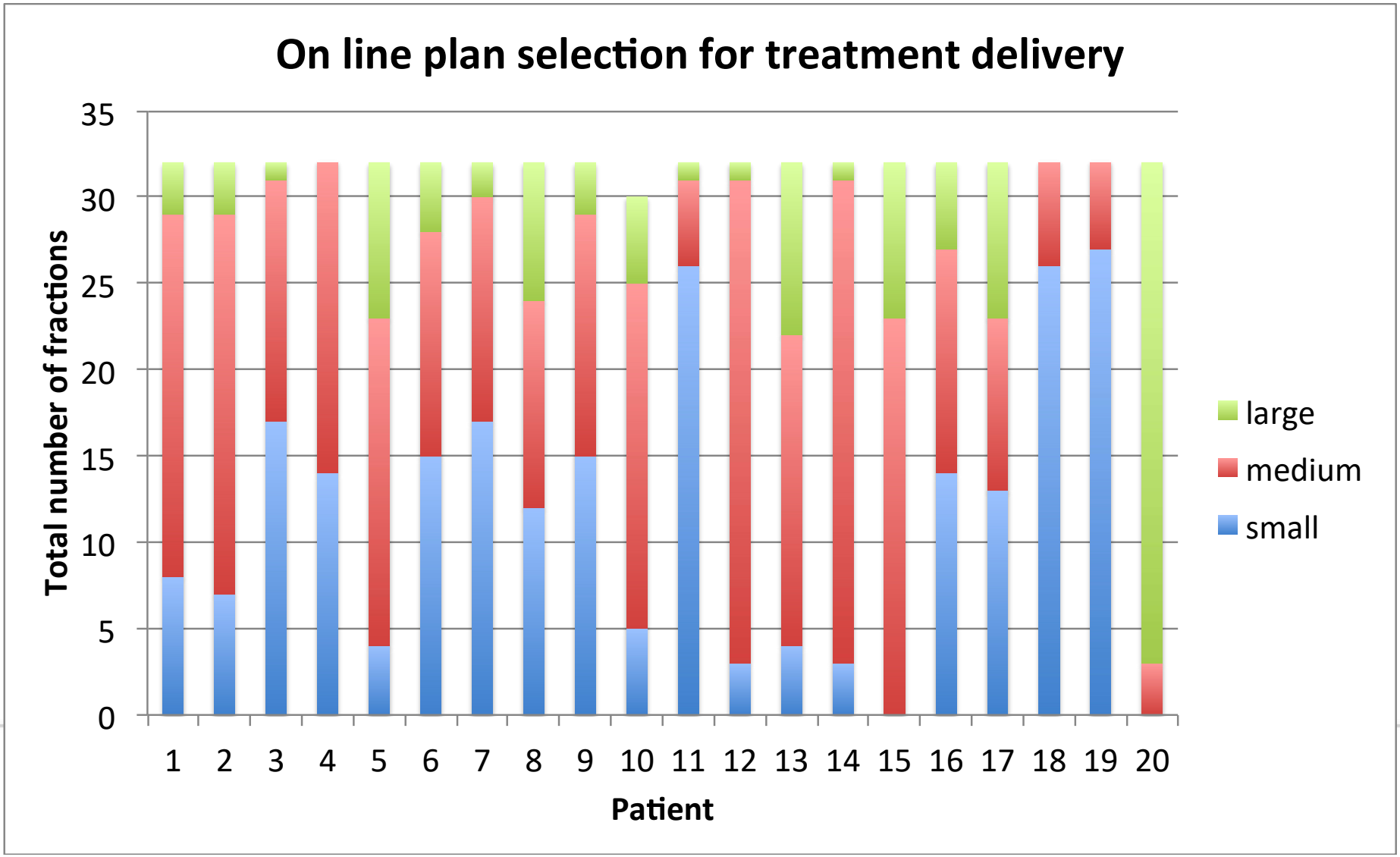
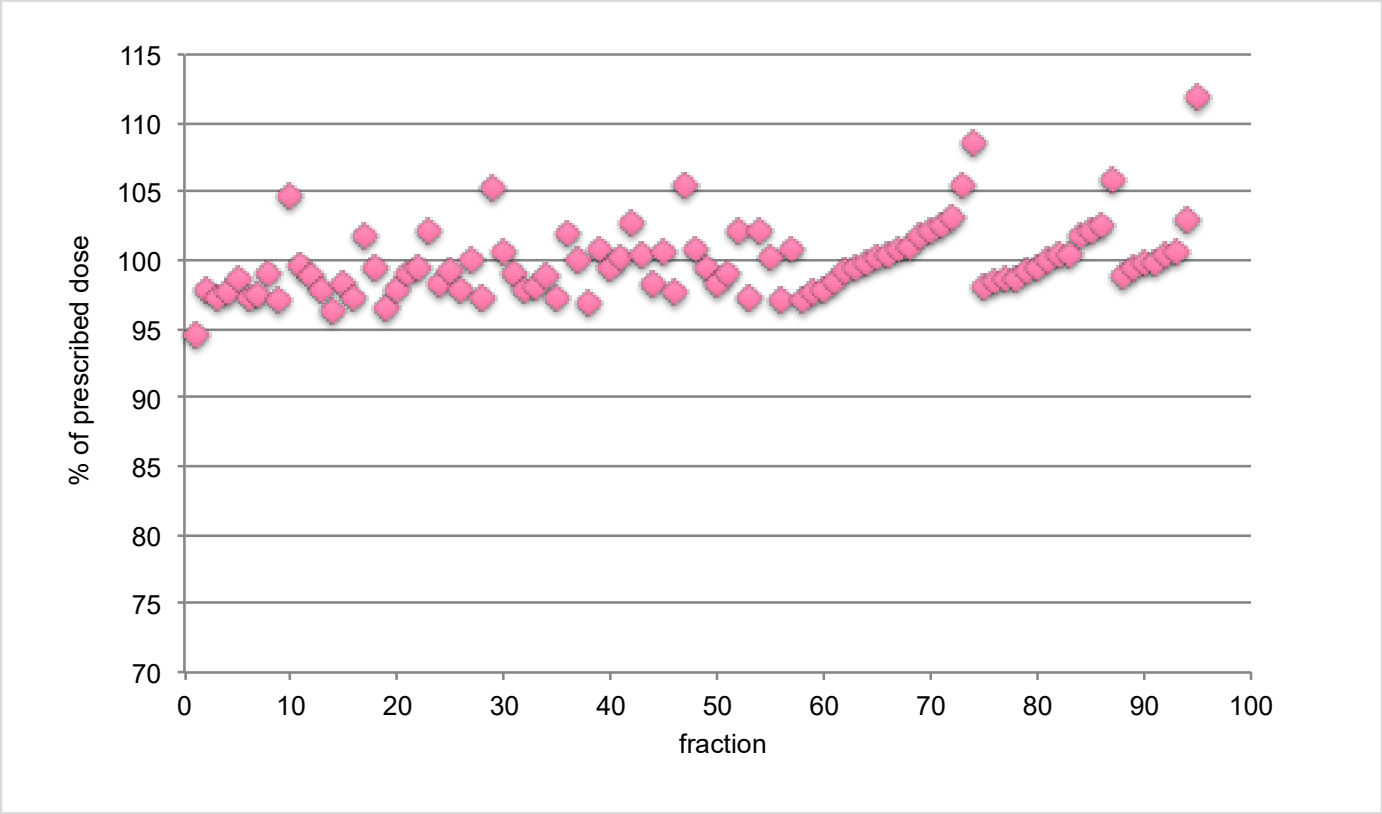
Too Small Bladder



Results


On line plan selection for treatment delivery
Total number of fractions
35
30
25
20
15
10
5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Patient
large
medium
small

Impact of filling on target coverage



Mean D98 of bladder as assessed on post treatment CBCT with on line plan selection 99.97% (SD 2.62, range 96.4-112.0)

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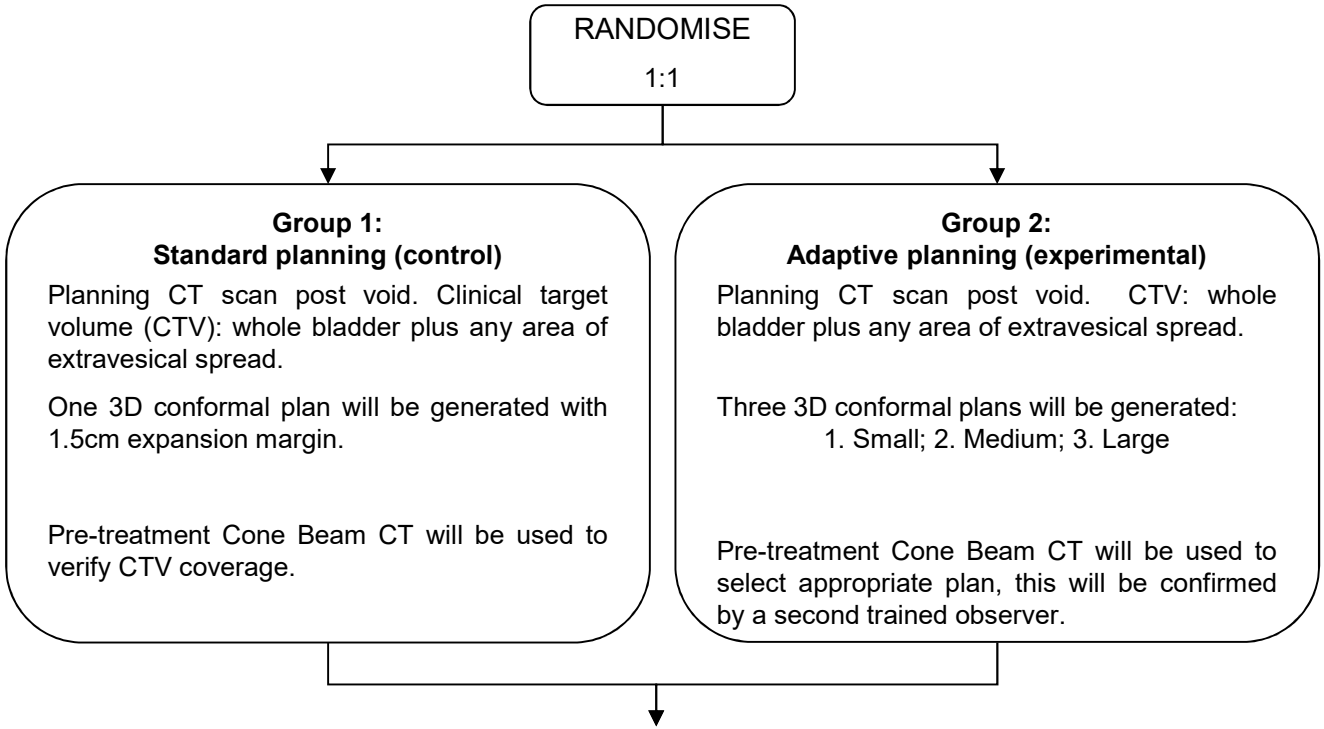
Clinical studies

Study (year)	n	Dose	Adaptive strategy	Target coverage	Normal tissue sparing
Pos et al., (2006)	21	55Gy in 20f (bladder) (40Gy in 20f pelvis) or 60Gy in 25f (tumour, 6 patients)	3DCRT composite from week 3, for 10-25f	5% repeat CT scan GTV not covered by PTV	40% reduction in PTV
Huddart et al., (2011)	26	64-68Gy in 32-34f (tumour) 50Gy in 25f (bladder)	3DCRT 3 phase sequential delivery (adaptive phase 3 plan of the day or composite)	*V95 98% (plan of the day), 91% (composite)	185cm^3 high dose volume reduction (plan of the day) and 220cm^3 (composite) compared to conventional margin approach
Tuomikoski et al., (2011)	5	45-50.4 Gy in 25-28f (bladder) followed by 10-20Gy in 5-10f (tumour)	IMRT 2 phase sequential delivery Plan of the day, phase 1, 3-4 plans; phase 2, 2-4 plans	V95<100% 3% (4/121 fractions)	Bowel V45Gy improved by 155cm^3 compared to conventional margin
McDonald et al., (2011)	25	36Gy in 6f (bladder)	3DCRT Plan of the day, 3 plans	*V95 99%	210cm^3 volume reduction in tissue receiving 95% dose compared to conventional margin approach

Foroudi et al., (2011)	27	64Gy in 32f (bladder)	3DCRT, Plan of the day, 3 plans for 8-32f	V95< 99% in 2.7%	29% reduction in tissue receiving >45Gy compared to conventional approach
Meijer et al., (2012)	20	59.8Gy in 23f (tumour) 46Gy in 23f (bladder)	IMRT Plan of the day, 6 plans	>95% appropriately fractions covered	
Foroudi et al., (2014)	54	64Gy in 32f (bladder)	3DCRT Plan of the day, 3 plans for 8-32f	18.4% patients target at least once (5.5% f) outside PTV as assessed on post RT CBCT	
Vestergaard et al., (2014)	20	60Gy in 30f (bladder) 48Gy in 30f to (pelvic LN)	IMRT (VMAT) Plan of the day, 3 plans for 6-30f		30% (185cm^3) reduction in adaptive PTV, bowel V45Gy improved by 100cm^3 and rectal V30 improved by 10% compared to non-adaptive approach
Murthy et al., (2016)	44	68Gy in 32f (tumour) 64Gy in 32f (bladder) 55Gy in 32f (pelvic LN)	IMRT (tomotherapy) Plan of the day, 3 or 6 plans		
Hafeez et al., (2016)	20	70Gy in 32f (tumour) 52Gy in 32f (bladder)	IMRT Plan of the day, 3 plans	D98 > 97% (post treatment CBCT)	

HYBRID study of hypofractionated Bladder Radiotherapy with or without Image guided aDaptive planning

A multicentre randomised phase II study



CANCER RESEARCH UK

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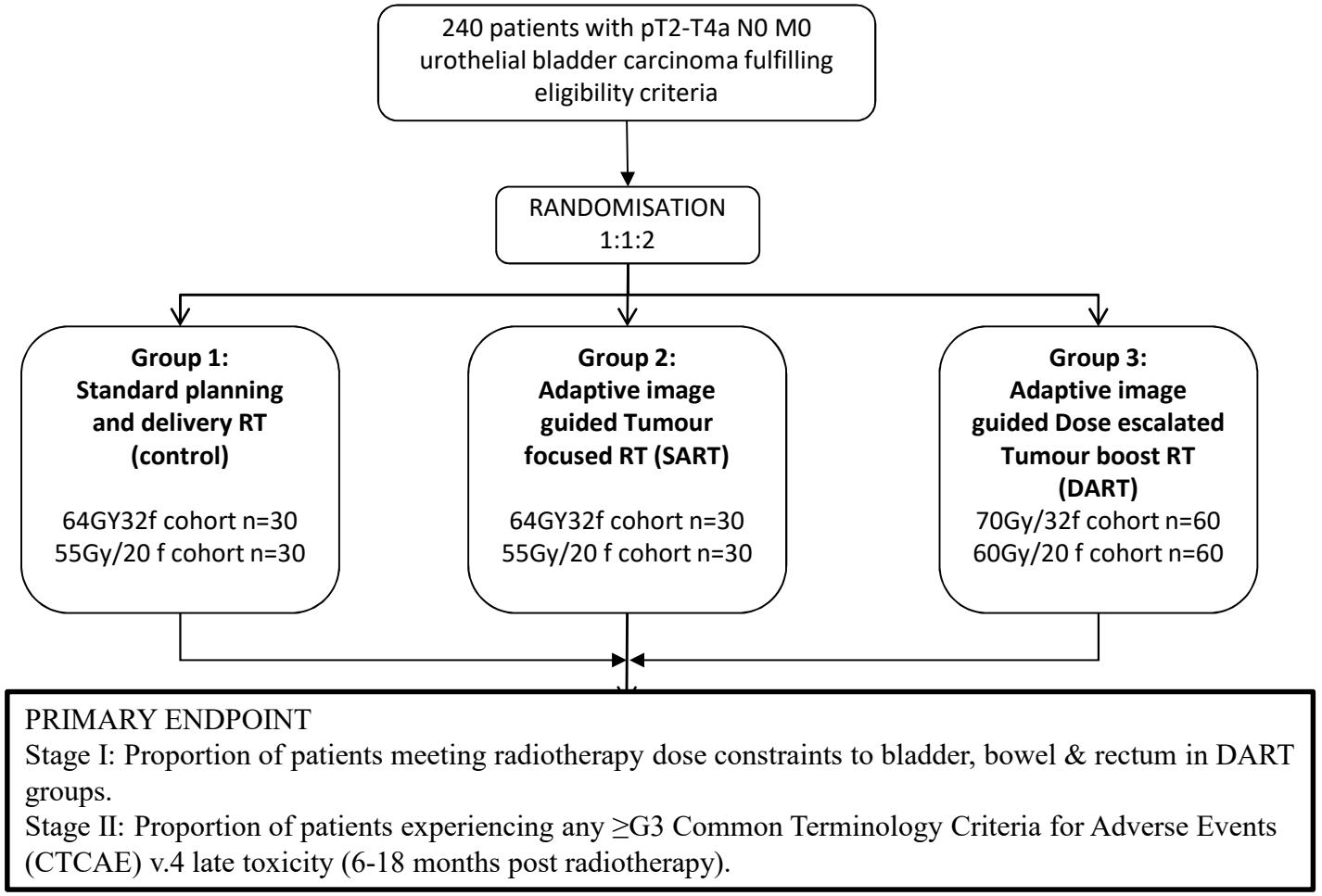
RAIDER- **R**andomised phase II trial of **A**daptive **I**mage guided standard or **D**ose **E**scalated tumour boost **R**adiotherapy in the treatment of transitional cell carcinoma of the bladder



CANCER RESEARCH UK

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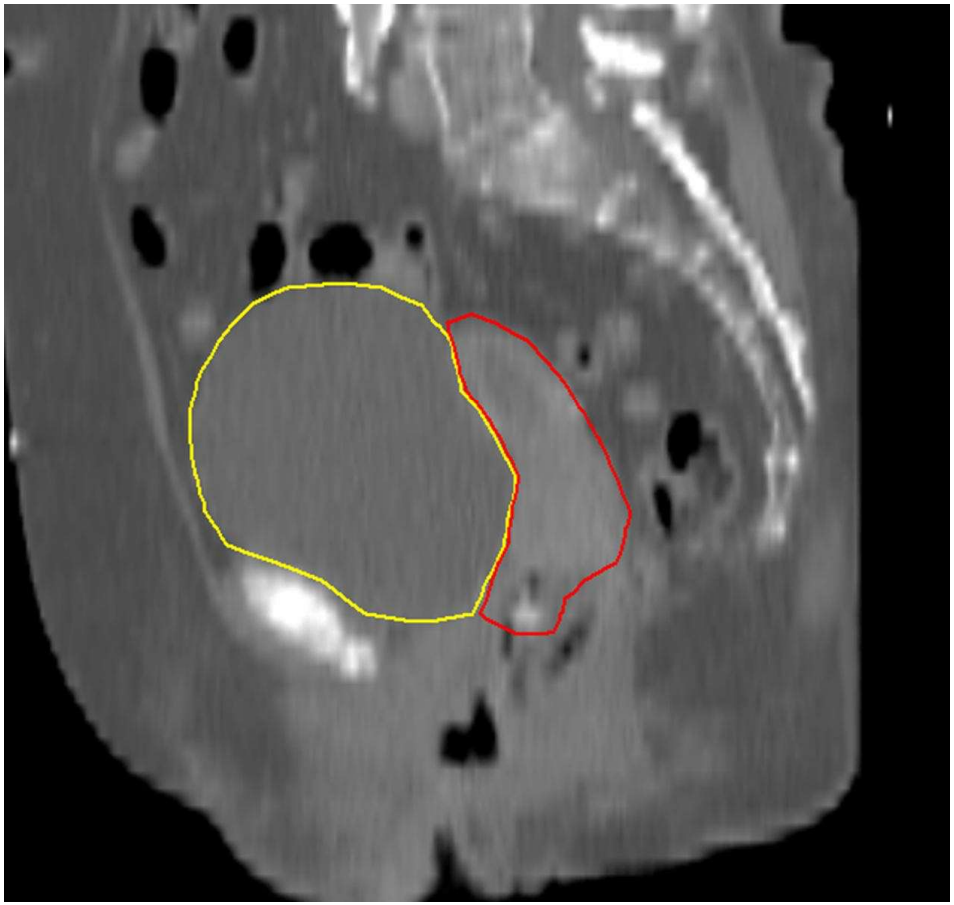
Adaptive planning- cervix model



Bondar ML, Hoogeman MS, Mens JW, Quint S, Ahmad R, Dhawtal G, Heijmen BJ: Individualized nonadaptive and online-adaptive intensity-modulated radiotherapy treatment strategies for cervical cancer patients based on pretreatment acquired variable bladder filling computed tomography scans. *Int J Radiat Oncol Biol Phys* 2012, 83(5):1617-1623.

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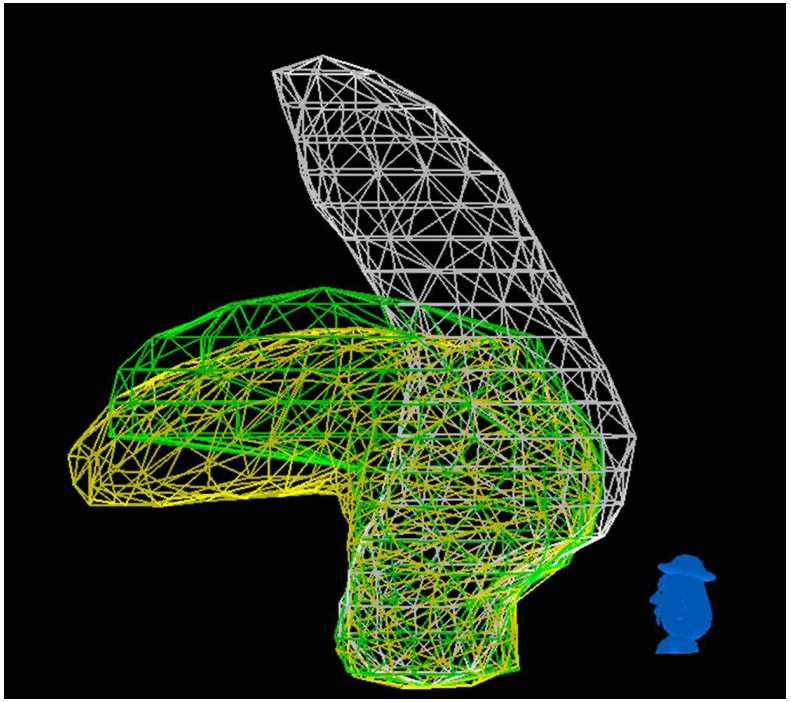
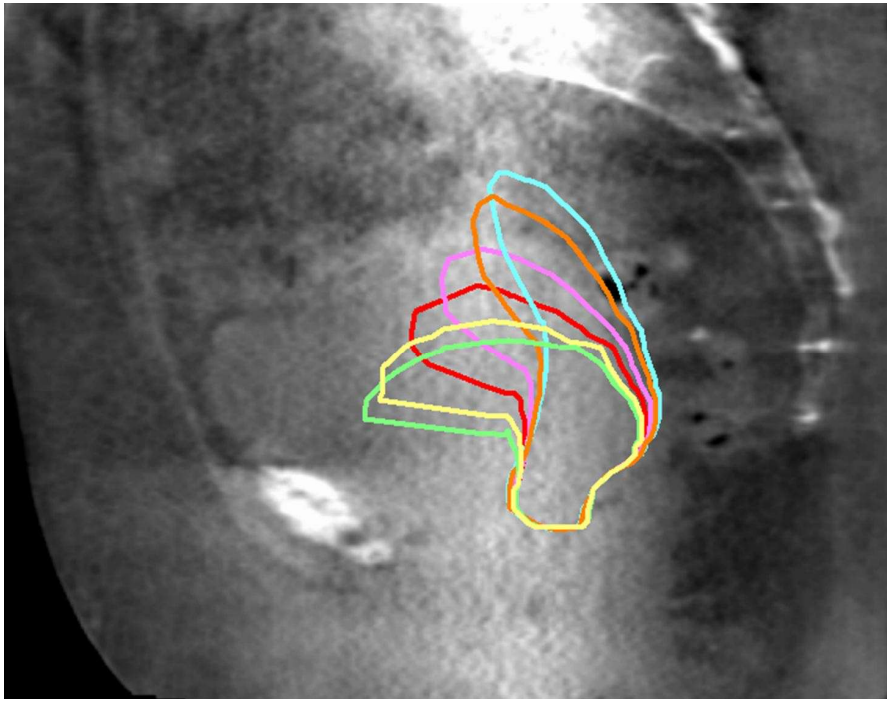
Adaptive planning- Gynae model



Uterine position based on bladder filling.



Plan selection on CBCT position

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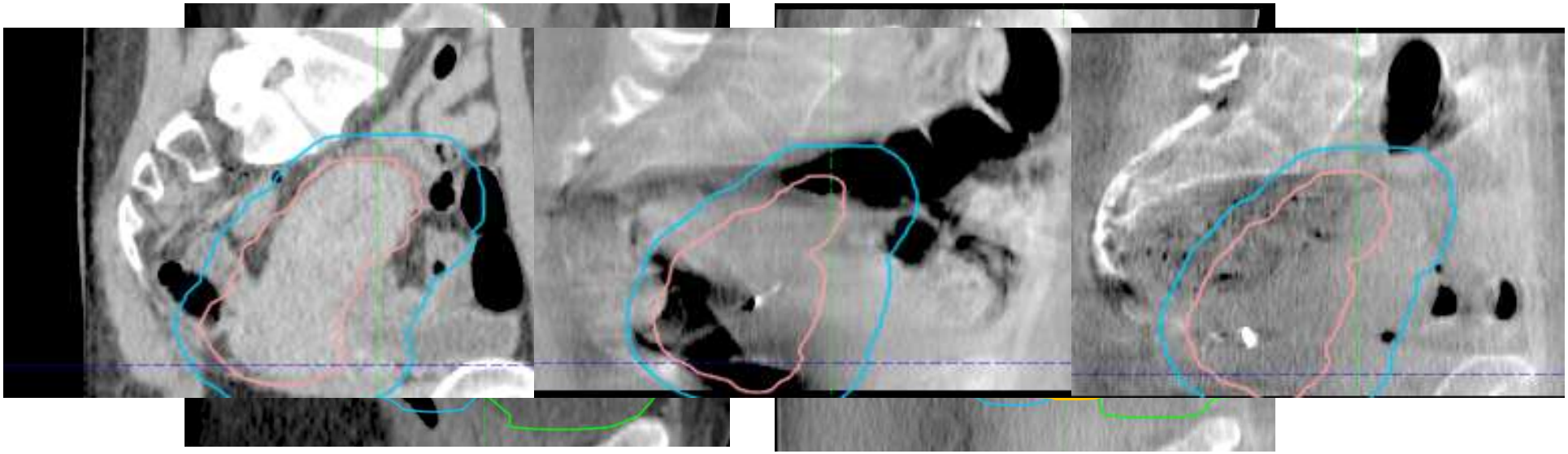
Multiple initial imaging and daily CBCT

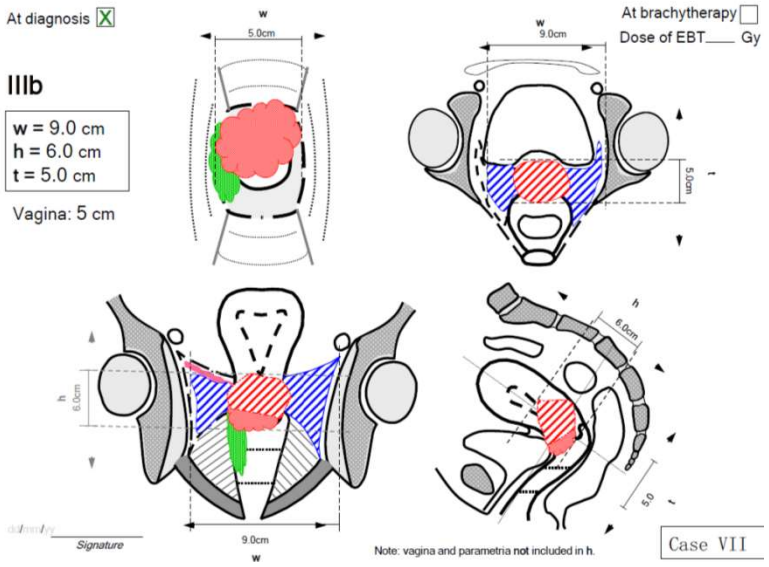
Sometimes the recto-sigmoid filling is the bigger problem

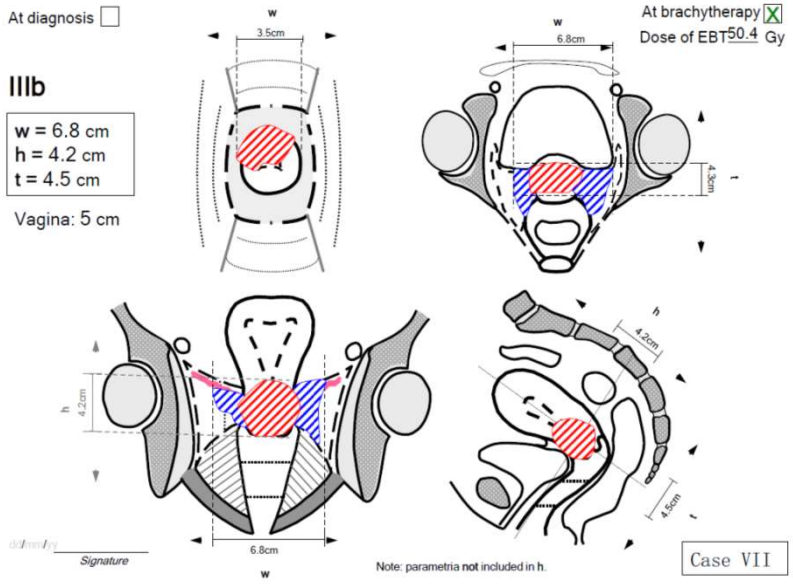


Change of strategy and Re-planning

Brachytherapy for Cervix cancer: ‘Adapt geometric variations of GTV, CVT and OARs’

Physical examination and drawing a sketch





Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Haie-Meder C: Radiother Oncol. 2005Mar;**74**(3):235-45.

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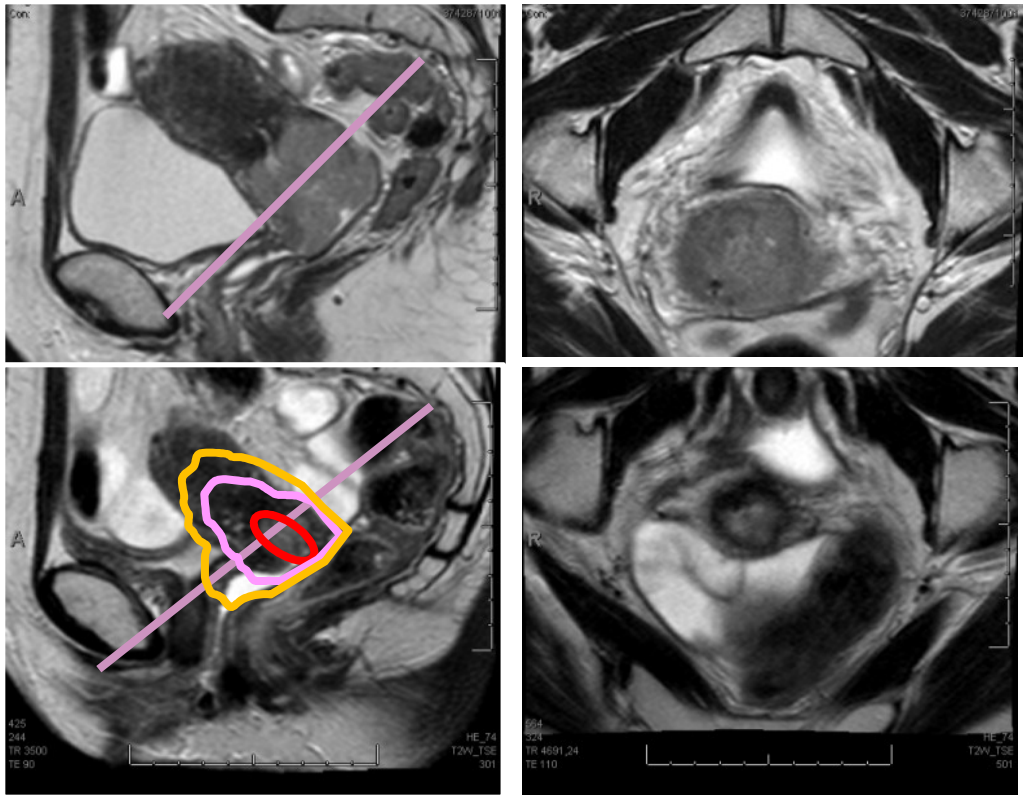
Change of strategy and Re-planning

Standard imaging protocol at initial planning and at brachytherapy planning



External Beam Planning

- GTV-D, CTV-THighRiskInitial, CTV-TIntermediateRiskInitial, CTV-ULowRiskInitial

Brachytherapy Planning

- GTV-B, HighRisk- CTV, IntermediateRisk-CTV

Adaptive planning-rectal model

Radiotherapy and Oncology 103 (2012) 353–359

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Adaptive radiotherapy in rectal cancer

Adaptive radiotherapy for long course neo-adjuvant treatment of rectal cancer

Jasper Nijkamp [a], Corrie Marijnen [b], Marcel van Herk [a], Baukelien van Triest [a], Jan-Jakob Sonke [a,*]

[a] Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam; [b] Department of Clinical Oncology, Leiden University Medical Center, The Netherlands

-28 patients
-Repeat CT scans were taken daily during 1st week f/b once weekly
-Substantial systematic and random shape variation demanded for a PTV margin up to 2.4 cm at the upper-anterior part of the CTV. Plan adaptation after fraction 4 resulted in a maximum 0.7 cm margin reduction and a significant PTV reduction from **1185 to 1023 cc**

Nijkamp J, Marijnen C, van Herk M, van Triest B, Sonke JJ: Adaptive radiotherapy for long course neo-adjuvant treatment of rectal cancer. *Radiother Oncol* 2012, 103(3):353-359.

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Adaptive planning- rectal model

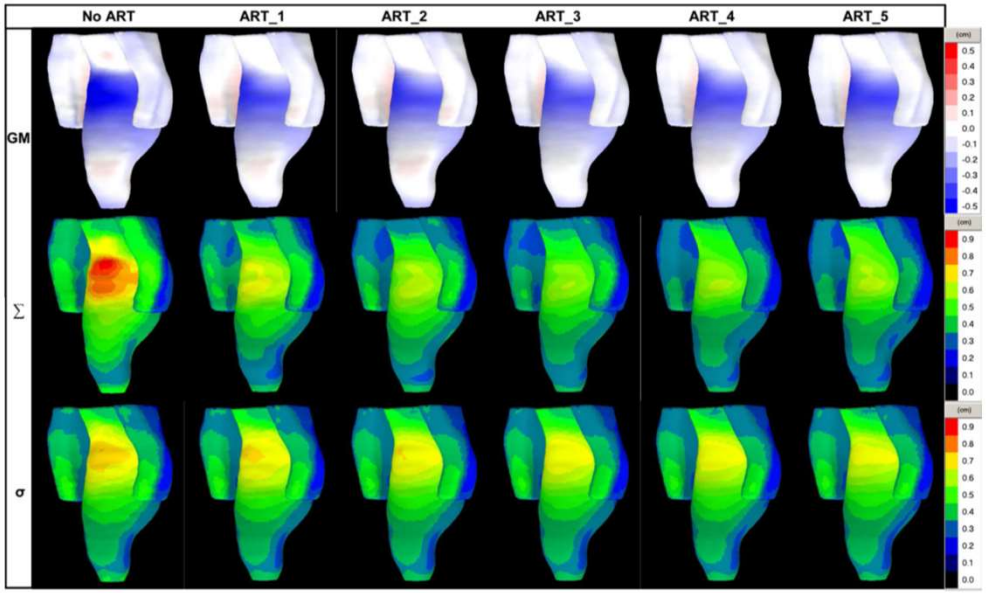

Fig. 1. Left anterior view of the GM (top), $\sum$ (middle) and σ (bottom) errors without ART (left) and the residual errors after the five tested adaptive RT procedures ART_1, ART_2, ART_3, ART_4, and ART_5.

Dosimetric parameters for comparison of the four treatment plans. The *p*-values were calculated using a paired 2-sided students *t*-test.

	PTV (1SD)	PTV_ART (1SD)	Statistical difference
Bladder Dmean (Gy)	26.3 (2.4)	23.6 (3.1)	$p < 0.0001$
Bowel area V15 (cc)	372 (199)	358 (199)	$p = 0.0077$
Bowel area V45 (cc)	92 (70)	73 (59)	$p < 0.0001$
Bowel area V50 (cc)	44 (36)	27 (24)	$p < 0.0001$
	PTV_clin (1SD)	PTV_clin_ART (1SD)	Statistical difference
Bladder Dmean (Gy)	27.4 (3.7)	24.9 (2.4)	$p < 0.0001$
Bowel area V15 (cc)	436 (206)	402 (200)	$p < 0.0001$
Bowel area V45 (cc)	111 (76)	81 (60)	$p < 0.0001$
Bowel area V50 (cc)	49 (39)	29 (25)	$p < 0.0001$

Nijkamp J, Marijnen C, van Herk M, van Triest B, Sonke JJ: Adaptive radiotherapy for long course neo-adjuvant treatment of rectal cancer. *Radiother Oncol* 2012, 103(3):353-359.

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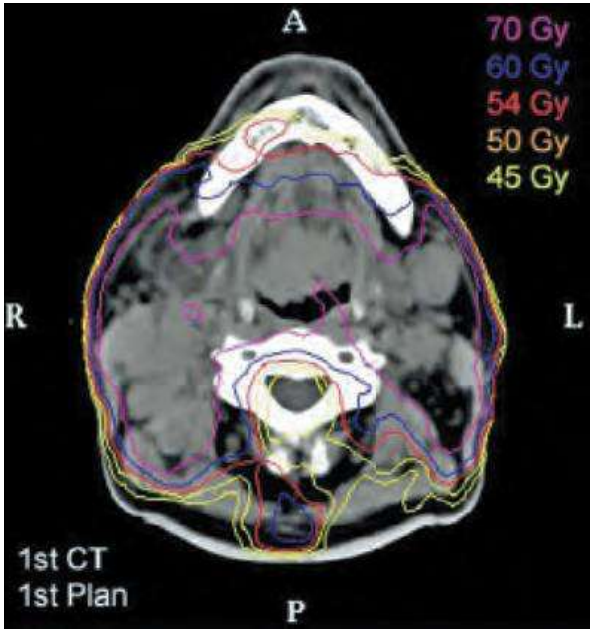
Adaptive planning- head and neck model

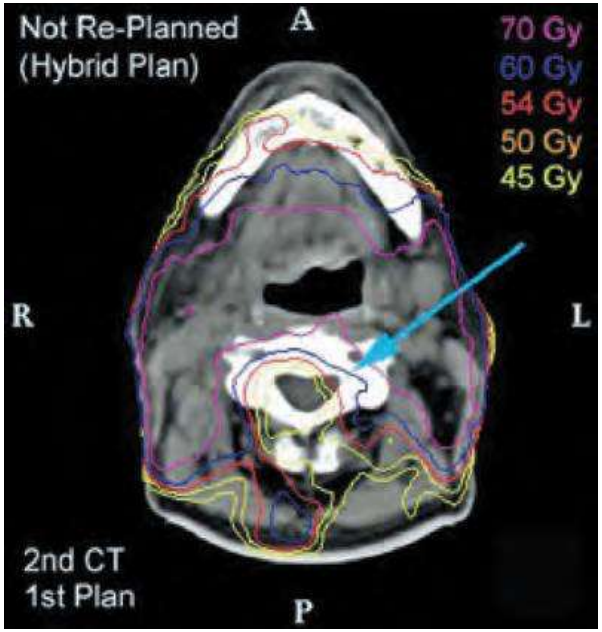
- We usually adapt to **changes in morphology of tumor and OAR's.**
- Provoking factors**: weight loss, tumor response, progression of disease**

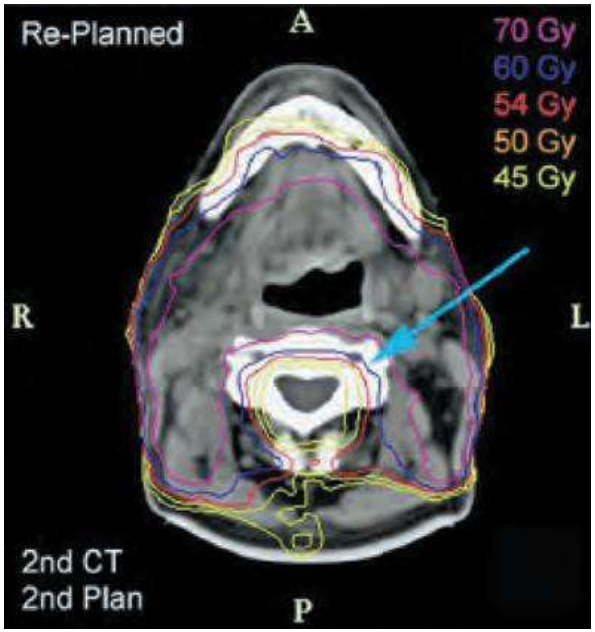
Hansen et al.

- evaluated the impact of replanning in a cohort of **13 HNC patients** with either significant weight loss or tumor response during IMRT.
- Compared to **replanning**, ***not*** **replanning** significantly decreased dose to the target volume and increased doses to normal tissues (spinal cord and brainstem). The **doses to 95% of the PTV-GTV and the PTV-CTV decreased by up to 6.3 Gy and 7.4 Gy, respectively.**

Adaptive planning- head and neck model







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Adaptive planning- head and neck model

Radiotherapy and Oncology 115 (2015) 285–294

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

Identifying patients who may benefit from adaptive radiotherapy: Does the literature on anatomic and dosimetric changes in head and neck organs at risk during radiotherapy provide information to help?

Charlotte L. Brouwer, Roel J.H.M. Steenbakkers, Johannes A. Langendijk, Nanna M. Sijtsema *

University of Groningen, University Medical Center Groningen, Department of Radiation Oncology, The Netherlands

Adaptive planning- head and neck model

- Weight loss >5% and/or decrease of neck diameter >10% was associated with higher xerostomia.
- Chen et al. - In less than 20% of all head and neck patients replanning was needed because of target underdosage or OAR overdosage, usually during the first three weeks of treatment

Adaptive planning- head and neck model

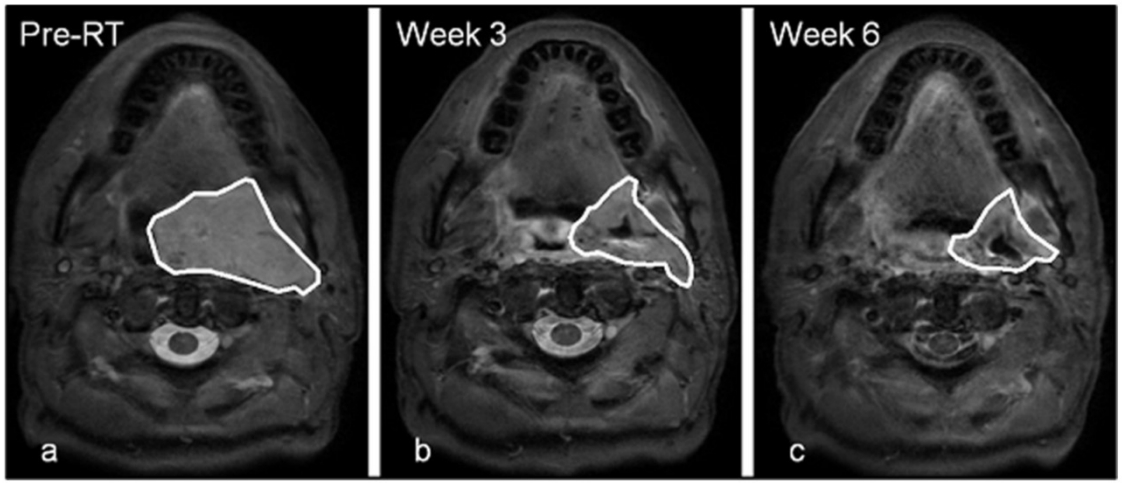

Fig. 1. GTV delineations in patient 6 on MRI pre-treatment (a), in week 3 of treatment (b) and in week 6 of treatment (c).

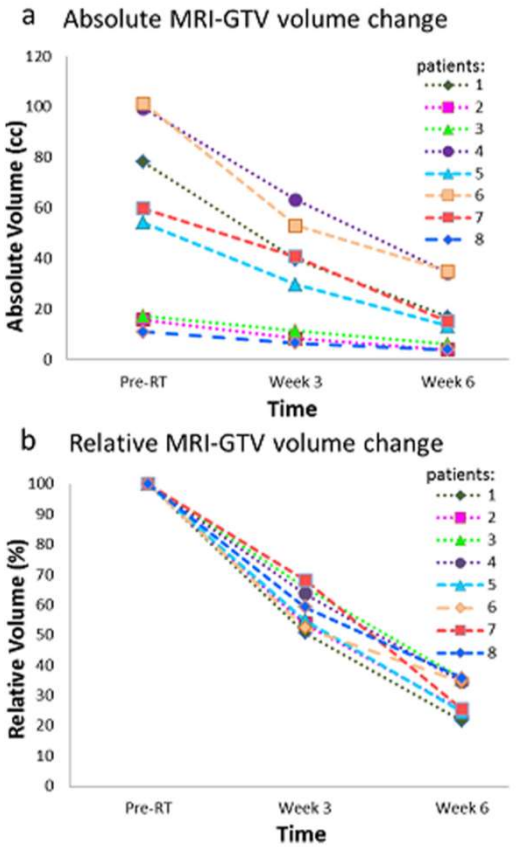

Fig. 2. Absolute (a) and relative (b) GTV volume change on MRI for all patients comparing weeks 3 and 6 during treatment with pre-treatment.

Brouwer CL, Steenbakkers RJ, Langendijk JA, Sijtsema NM: Identifying patients who may benefit from adaptive radiotherapy: Does the literature on anatomic and dosimetric changes in head and neck organs at risk during radiotherapy provide information to help? *Radiother Oncol* 2015, 115(3):285-294.

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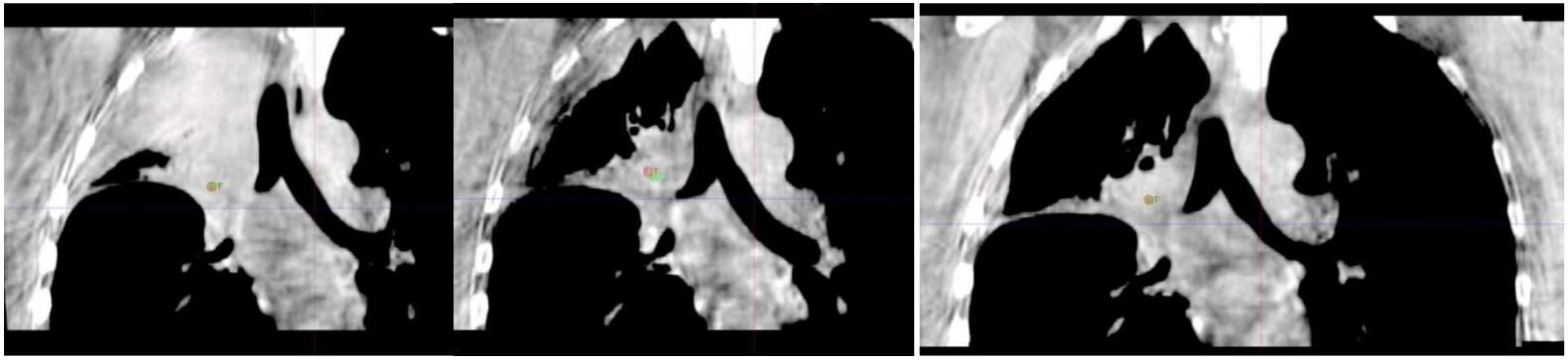
Adaptive Strategies-Lung cancer

Lung cancer irradiation, the problems numerous!

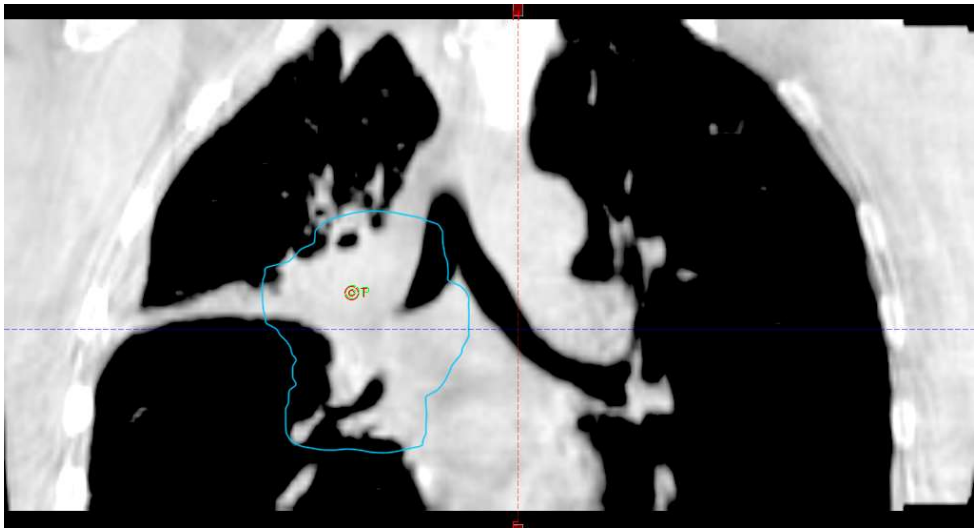
- At planning
  - Boost volume based on functional imaging
  - Breathing influences sub-volumes differently
    - Upper vs. lower lobe tumours
    - Tumours vs. lymph nodes
    - Target vs. OAR (spinal cord)
- Online imaging and matching
  - Bone vs. soft tissue/tumour
- Interfraction variations
  - Atelectasis (and lung density changes)
  - Tumour shrinkage
  - Pleural effusion

Adaptive Strategies-Lung cancer

(change in density)



D2 D6 D7



Moller DS, Khalil AA, Knap MM, Hoffmann L: Adaptive radiotherapy of lung cancer patients with pleural effusion or atelectasis. *Radiother Oncol* 2014, 110(3):517-522.

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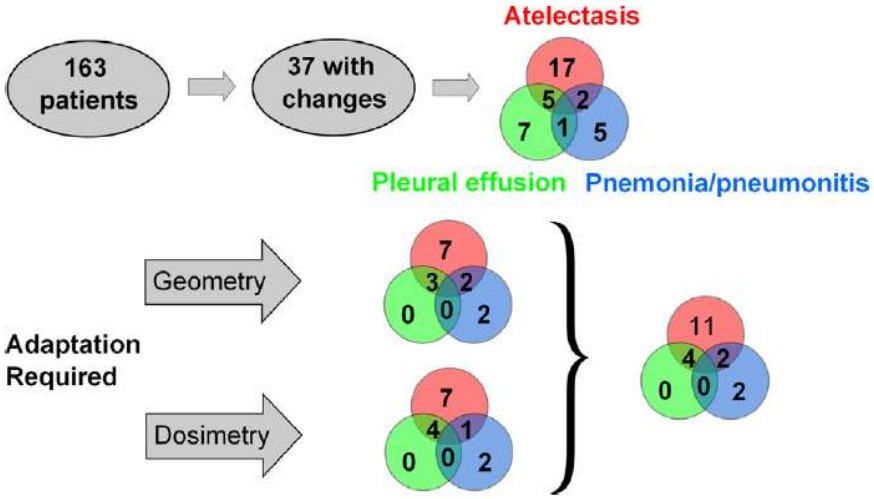
With planned intervals – CBCT

Quantification of need for adaptive strategy

- CBCT at fraction 1, 6, 11, 16, 21, 26 and 31
- Dosimetric evaluation- deemed insufficient if when compared to planning CT
  - V_{95}PTV decreased more than 3%.
  - PTV_{mean} decreased more than 1%.
  - V_{107}body increased more than 5 cm^3.



Moller DS, Khalil AA, Knap MM, Hoffmann L: Adaptive radiotherapy of lung cancer patients with pleural effusion or atelectasis. *Radiother Oncol* 2014, 110(3):517-522.

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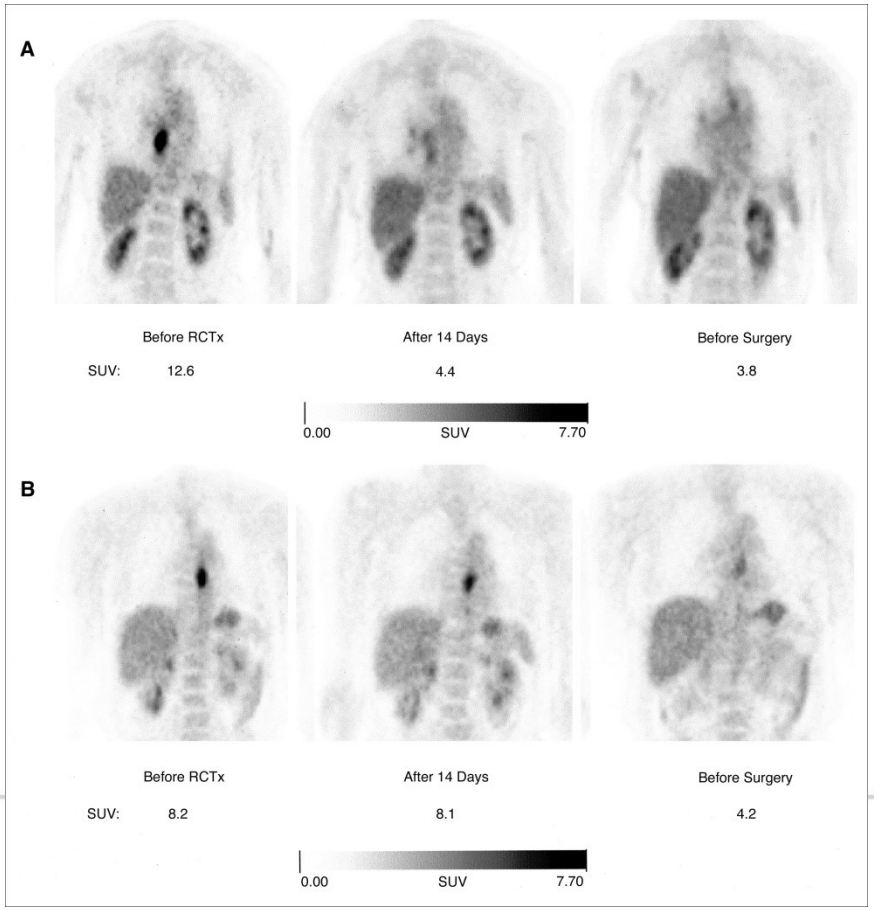
Functional Imaging – during treatment

Imaging during treatment – re-plan based on functional data

- Changes in metabolic activity are significantly correlated with tumour response and patient survival.



Wieder et al. JCO, 2004

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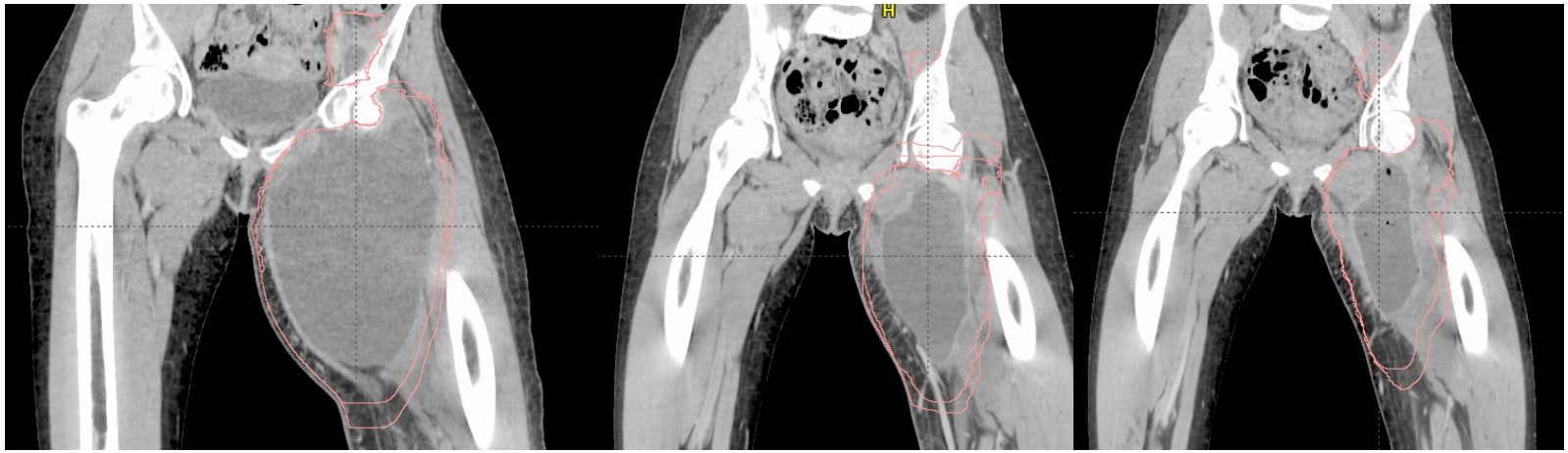
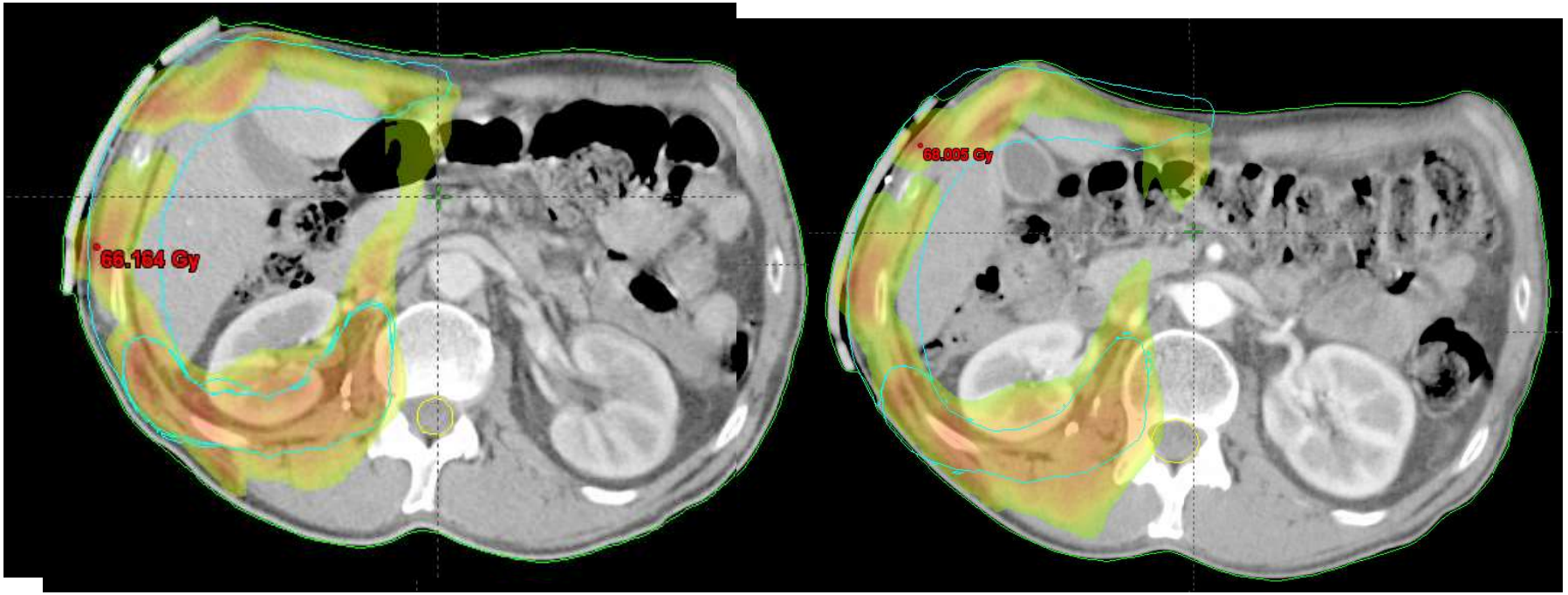
No strategy – post operative sarcoma



At planning	At first fraction	At 16th fraction

No strategy – weight loss



Benefits of on-line adaptation

- Correct for non-rigid anatomical changes beyond image guidance
- Improve conformity of delivered plan
  - Reduce margin requirements for IGRT
  - Reduce normal tissue dose
  - Dose guided, instead of anatomy based
  - Correction for acute biological changes

Requirements for on-line planning

- Fast imaging
- Fast target and normal tissue delineation (auto segmentation)
- Auto planning
- Fast QA and real time beam variation
- Intra-fractional management

Summary

Scoring sheet

Problem	IGRT	Off-line ART	Online ART
Daily target position			
Systematic target shape change			
Systematic OAR shape change			
Daily target shape change			
Daily OAR shape change			

Summary

Scoring sheet

Problem	IGRT	Off-line ART	Online ART
Daily target position	✓		
Systematic target shape change	X		
Systematic OAR shape change	X		
Daily target shape change	X		
Daily OAR shape change	X		

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Summary

Scoring sheet

Problem	IGRT	Off-line ART	Online ART
Daily target position	✓	✓	
Systematic target shape change	X	✓	
Systematic OAR shape change	X	✓	
Daily target shape change	X	X	
Daily OAR shape change	X	X	

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Summary

Scoring sheet

Problem	IGRT	Off-line ART	Online ART
Daily target position	✓	✓	✓
Systematic target shape change	X	✓	✓
Systematic OAR shape change	X	✓	✓
Daily target shape change	X	X	✓
Daily OAR shape change	X	X	✓

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References

- Adaptive radiation therapy. Yan D: Phys. Med. Biol. **42** (1997) 123–132
- Seminars in Radiation Oncology, Volume **20**, Number 2
- Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Haie-Meder C: Radiother Oncol. 2005 Mar;**74**(3):235-45.
- Clinical implementation of an online adaptive plan-of-the-day protocol for nonrigid motion management in locally advanced cervical cancer IMRT. Heijkoop et al. IJROBP 2014 Nov 1;90(3):673-9
- Adaptive radiotherapy of lung cancer patients with pleural effusion or atelectasis. Møller et al: RadOnc110 (2014) 517–522
- Normal tissue sparing in a phase II trial on daily adaptive plan selection in radiotherapy for urinary bladder cancer. Vestergaard et al. Acta Oncol 2014; 53: 997-1004
- Adaptive radiotherapy strategies for pelvic tumors - a systematic review of clinical implementations. Thörnqvist, Acta Oncologica (2016) vol 55, no 8, 943–958

Physical Issues in Advanced Radiotherapy

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Physics for Modern Radiotherapy
Bucharest, Romania - 4 - 8 June 2017

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Contents

Uncertainties in advanced RT techniques

→Delineation
→Planning
→Delivery
→Prescription (particle therapy)

Physics problem in RT

Improved dose focusing

3DCRT → IMRT
Passive → Active
SFUD → IMPT

More sensitive to **errors**

Higher precision in target localization (in space and time)	Uncertainties management Robustness analysis	Advanced QA

Matching between imaging, planning and delivery is a key factor

Uncertainties

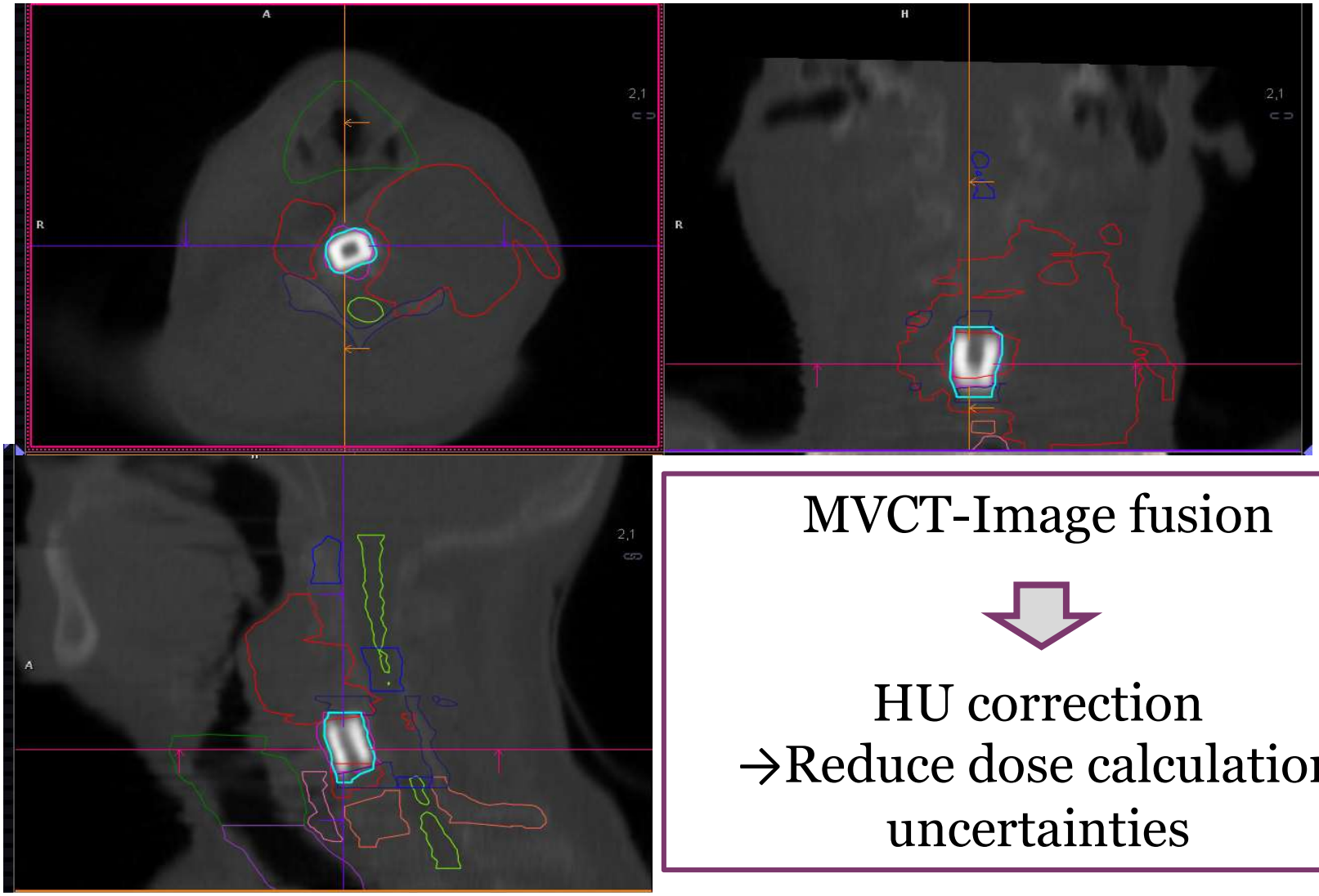
- IMRT/PT are generally more vulnerable to uncertainties mainly because of the steeper dose gradient and highly inhomogeneous in field fluence distribution.
- Many sources of uncertainty need to be taken into account in treatment planning and delivery:
  - → Patient positioning uncertainties
  - → TPS Dose calculation algorithm approximations
  - → Segmentation of tumor and critical structures based on medical images
  - → Anatomical changes (and motion) during imaging and treatment (inter-fraction and intra-fraction).
  - → Machine technical delivery uncertainties
- RBE-weighted dose definition (only particle therapy)

Contents

1) Segmentation of tumor and critical structures based on medical images

→Delineation
→Planning
→Delivery
→Prescription

HU → CT Artefacts – Metal implants



MVCT-Image fusion

HU correction
→Reduce dose calculation uncertainties

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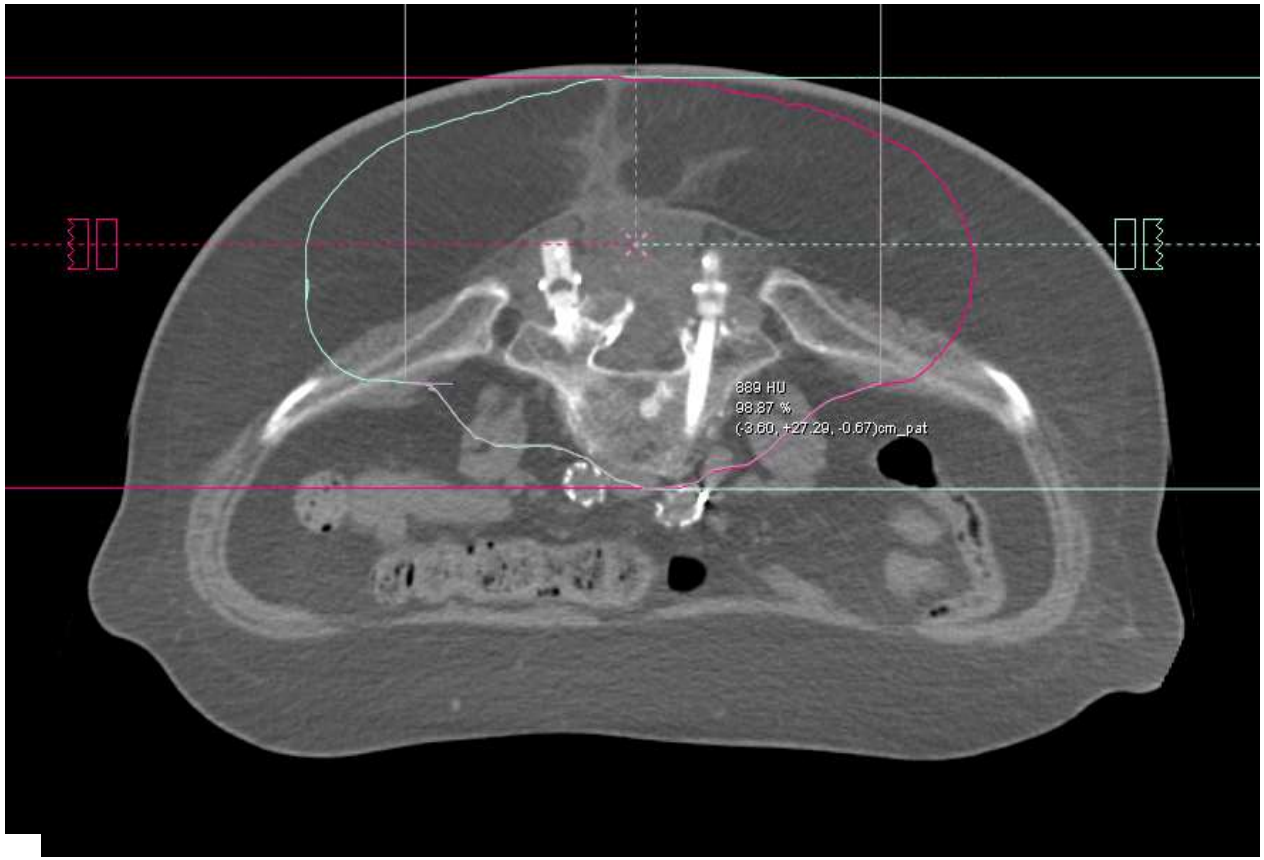
CT artifacts – HU uncertainties

Carbon fiber
Correct HU value

NO artifacts
<< dose calculation errors



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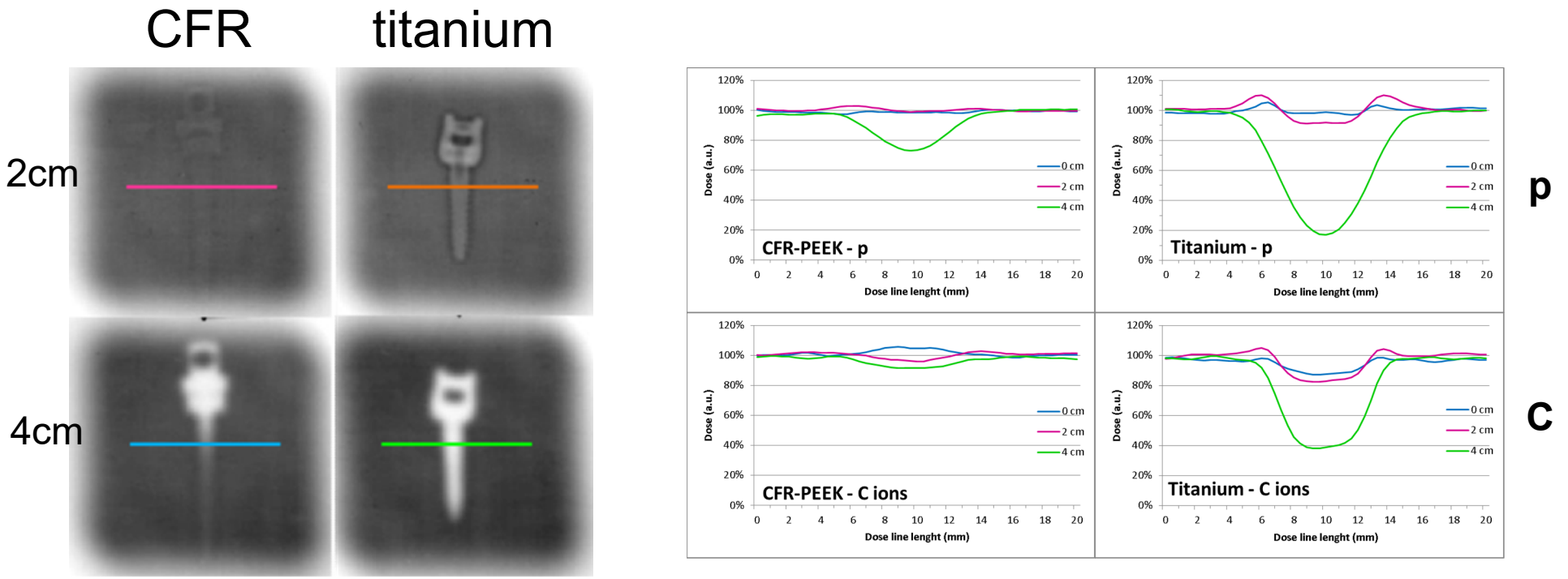
Carbon fiber screw vs titanium implants



Digitized EBT3 films irradiated at depth of 2 cm (top panel) and of 4 cm (bottom panel) in a SOBP (On the left: CFR-PEEK screw - On the right: titanium screw) and corresponding dose profiles

Credits to E Mastella, CNAO

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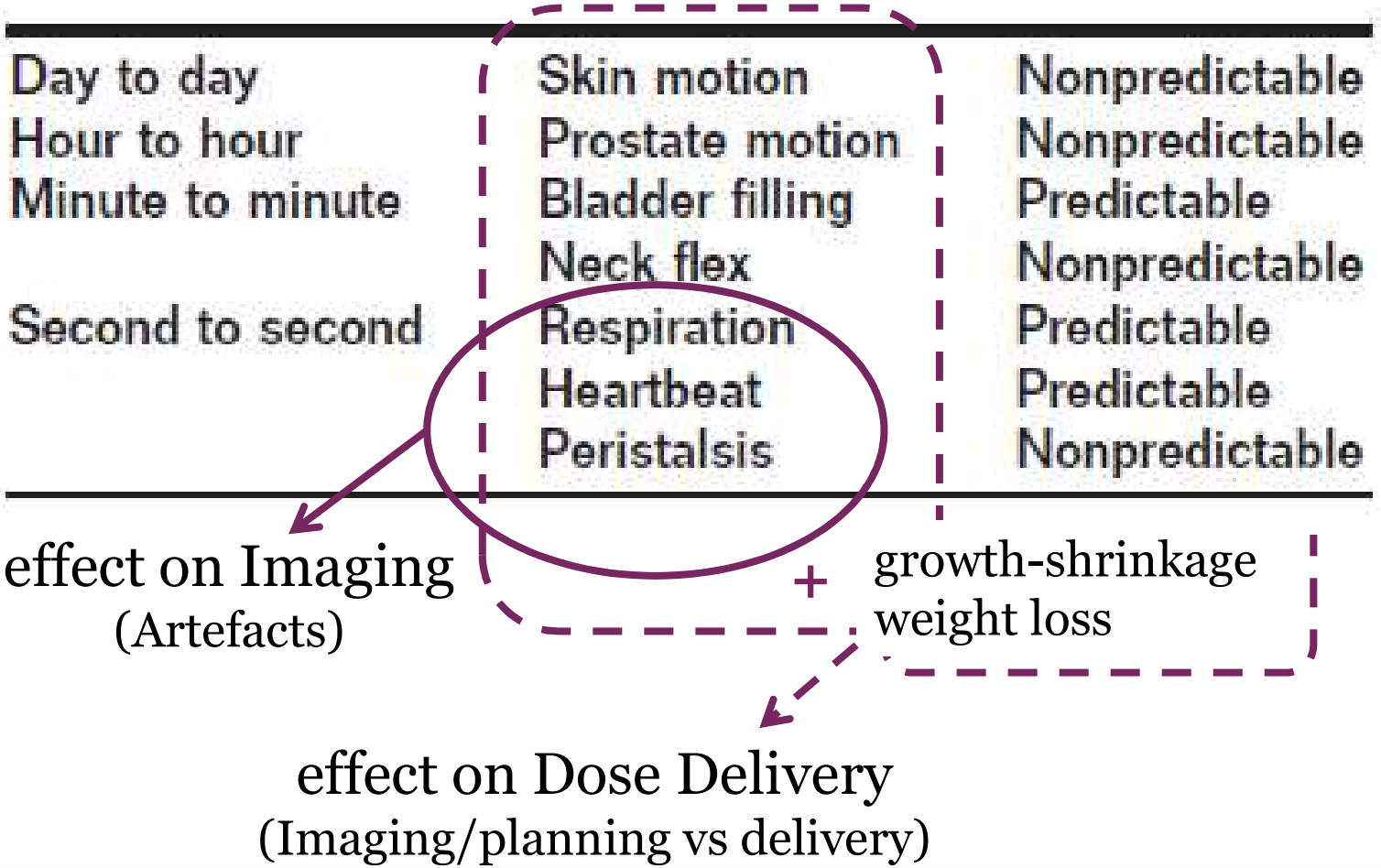
Anatomical changes and time scale



Van Herk, Sem Rad Oncol (17) 2007

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Contents

2) Anatomical changes (motion) during imaging

→Delineation
→Planning
→Delivery
→Prescription

Motion effect on Imaging - CT Artefacts (Lung)

Image blurring
contours overlapping
and organ smearing

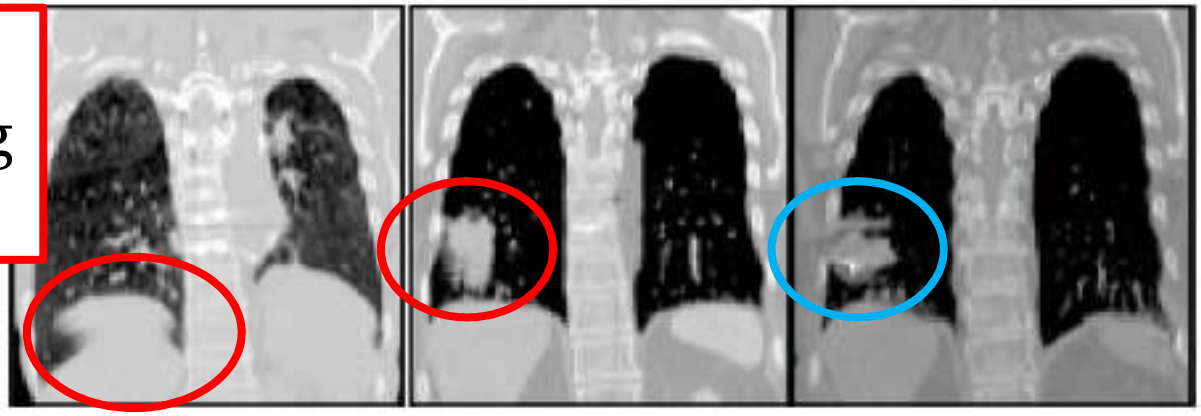


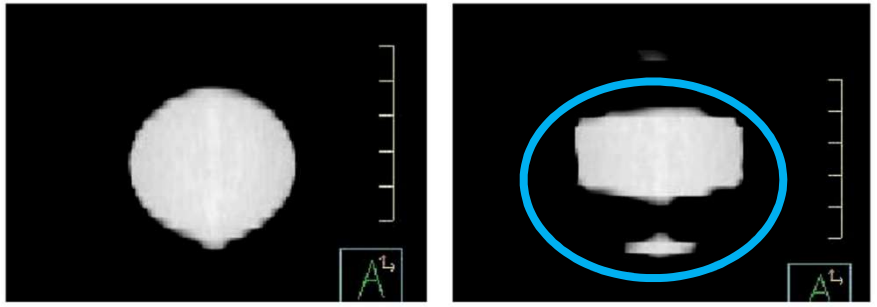
Figure 3. Examples of breathing induced image artifacts in coronal 3DCT images: overlapping contours and smearing of the right diaphragmatic dome (left). Overlapping structures and smearing of the caudal part of the tumor in the right lung (middle). Duplicate structures are seen in the tumor in the right lung (right). (Reprinted with permission from Persson (2011).)

Korreman S PMB (57) 2012

Partial projection effect

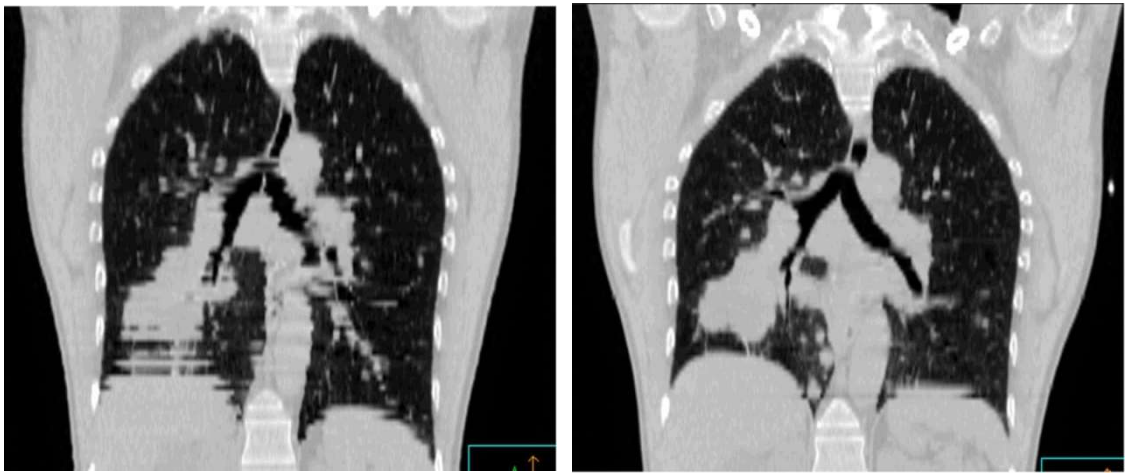
→ interference between moving structure and patient movement in the scanner

→ adjacent slices in the scan show non-adjacent parts of the moving structure



Coronal views of CT scans of a static sphere (a) and a sinusoidally moving sphere (b) (2-cm range of motion and a 4-second period).
Vedam et al. PMB (48) 2003

Motion effect on Imaging – 4DCT



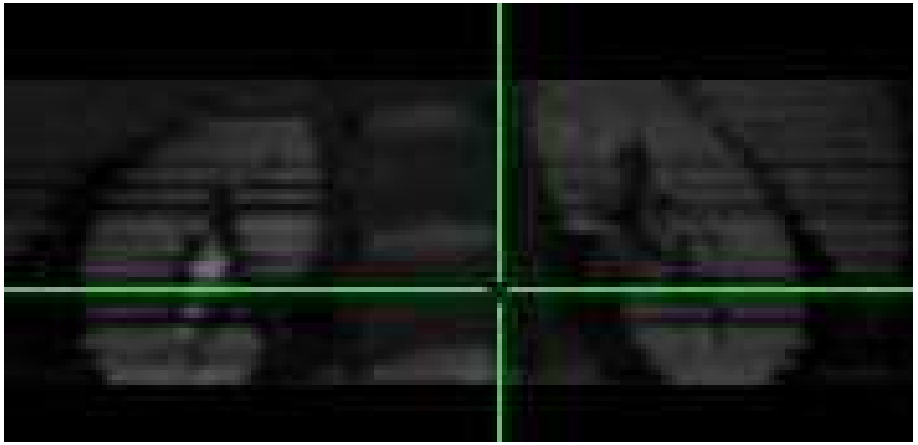
Coronal views of CT scans of the same patient taken during free breathing (FB) (a) and with respiratory-gated scanning at exhale (b)
Keall et al. Australas Phys Eng Sci Med 25 (1), 2002.

CT acquisition synchronized with respiration
→ Very high quality
→ Still non zero, but few artefacts
→ NB: it's a movie snapshot of the motion during few cycles
→ Irregularities in breathing cycles cannot be seen

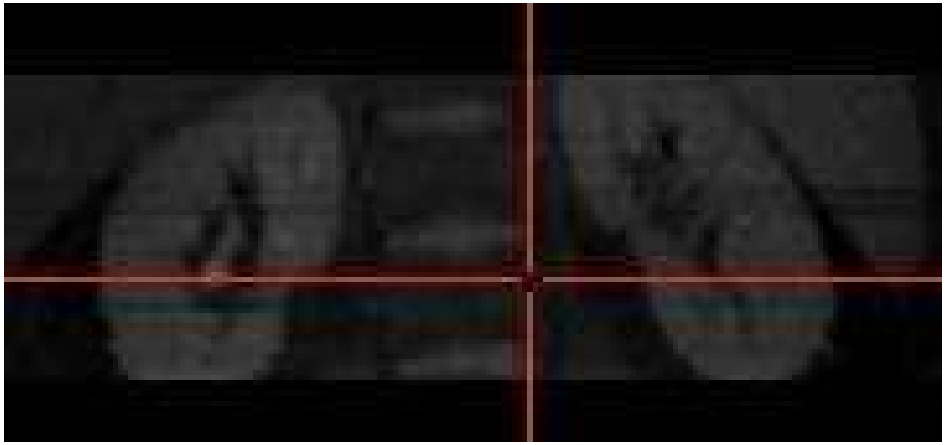
Motion effect on Imaging - MR Artefacts (Abdomen)

MR acquisition sequence: Haste T2
TA/slice ≈ 386 ms (slow)

Free breathing
3D MRI



Espirio 4D MRI
retrospective reconstruction
6 breathing phases



Contents

3) Anatomical changes (and motion) during treatment (inter-fraction and intra-fraction)

→ Delineation
→ Planning
→ Delivery
→ Prescription

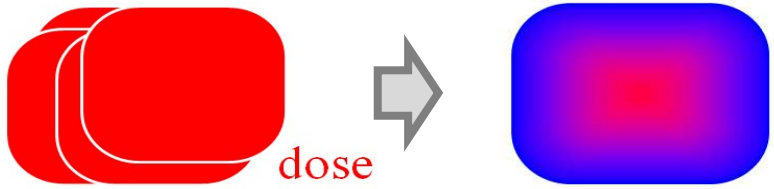
Anatomical changes effect on Delivery

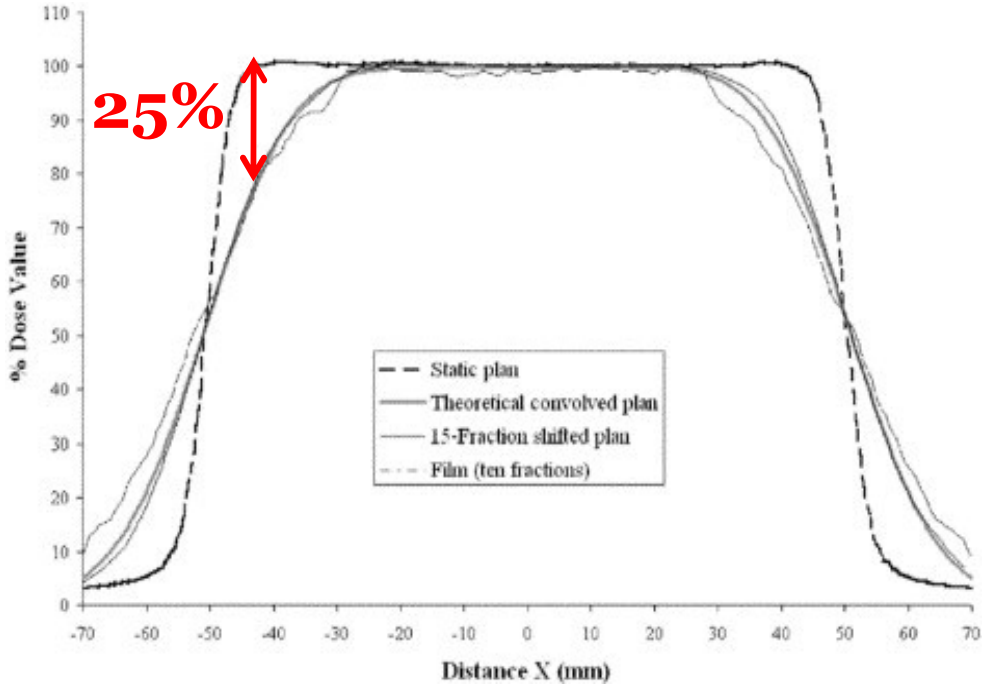
- Blurring of dose gradients (all techiques – field edges)
- Dose deformation/interface effects (all techniques - interfaces)
  → Radiological path length variation (particles)
- Interplay effect (dynamic techniques)

the importance of the effect depends on the delivery technique

Blurring → 'unsharpened' dose distribution

- Averaging or smearing of the dose distribution near beam edges → increased beam penumbra → loss in dose homogeneity and conformity
- The amount of blurring depends on the amplitude and the characteristics of the motion and on the "sharpness" (inhomogeneity) of the static dose distribution
- Worst for IMR/PT → margin reduction





McCarter&Beckam, PMB (45) 2001

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Dose deformation - photons

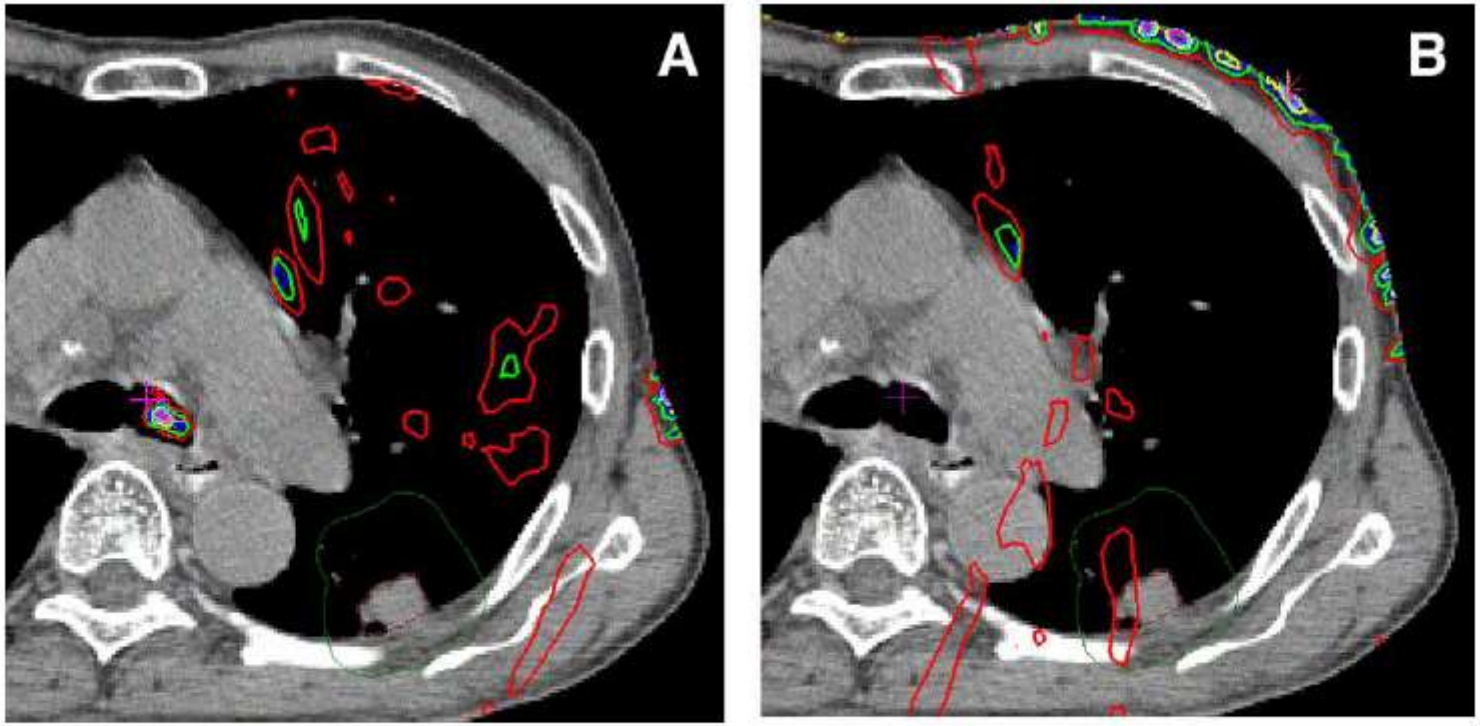

Figure 9. Relative isolevels of the differences between dose distributions calculated with the same treatment plan for breathing phases close to inhale and close to exhale. Plotted are the positive differences for the dose subtractions of breathing phases close to inhale and exhale, (A) inhale-exhale and (B) exhale-inhale. The differences are normalized to the doses calculated based on the CT-data set close to inhale: red 1%, green 2%, dark blue 3%, yellow 4%, light blue 5%, and magenta 6%. The CT data sets were acquired under the current 4DCT protocol at Massachusetts General Hospital.

The deposited dose changes within 3% because of the patient's respiratory motion. Within the CTV 1% - 5-field plan.

Bortfeld et al. Semin Rad Oncol (14) 2004

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Influence on the radiological pathlength

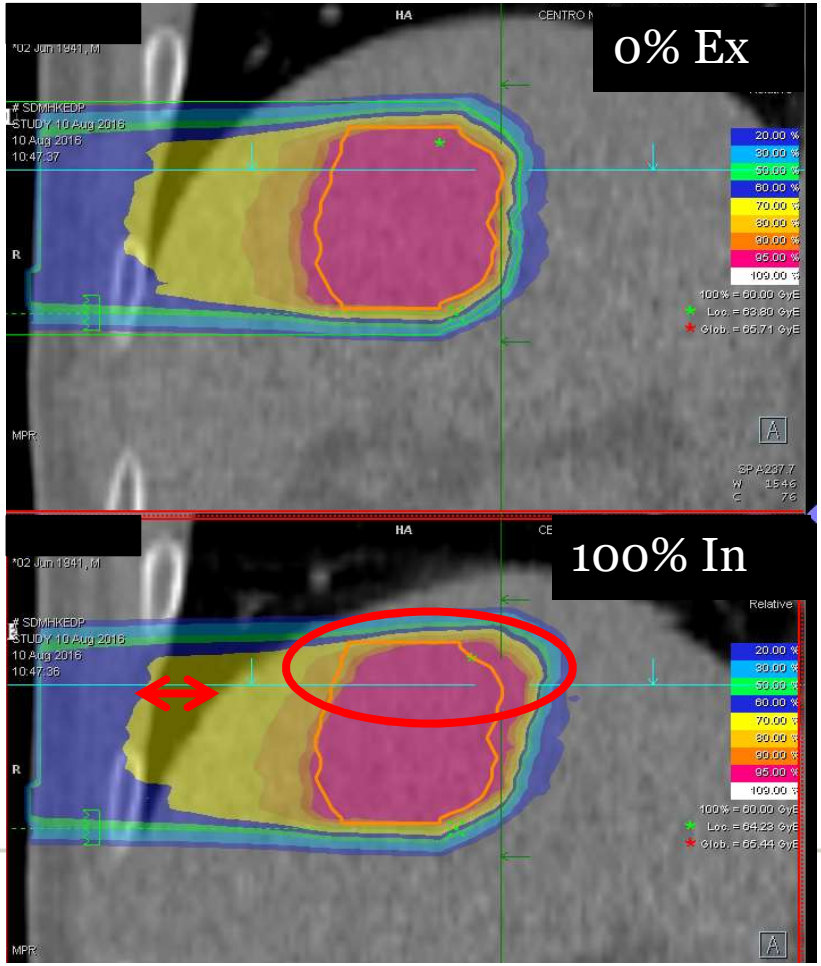
Moving anatomical districts with strong inhomogeneities may cause variation in BP deposition → Particles stop before/beyond the expected position.

→ Uncorrect Dose Distribution

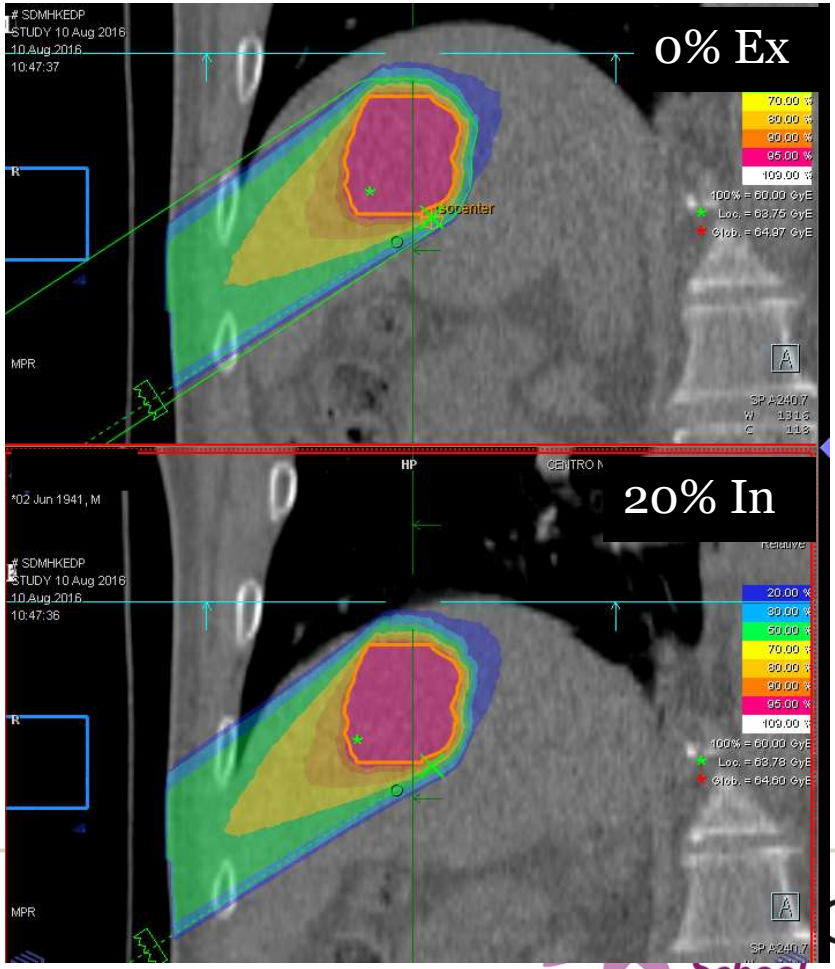
Particle Therapy → high sensitivity of the dose distribution to density variation in the entrance channel → any concept to compensate for the uncertainties due to organ motion/variation needs to incorporate also the influence on the beam's range on **dose DEFORMATION**

Intra-fraction - Breathing

No robustness and/or motion mitigation strategies

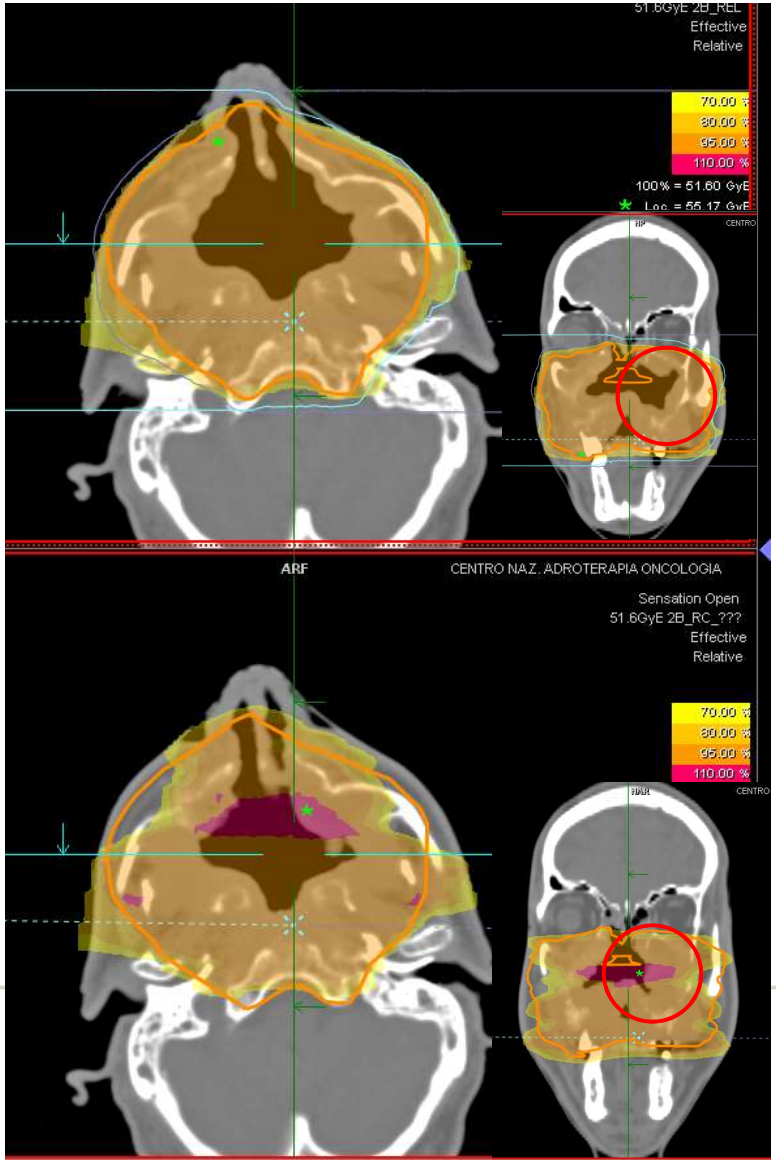


‘Home-made’ robust approach
&
Gating

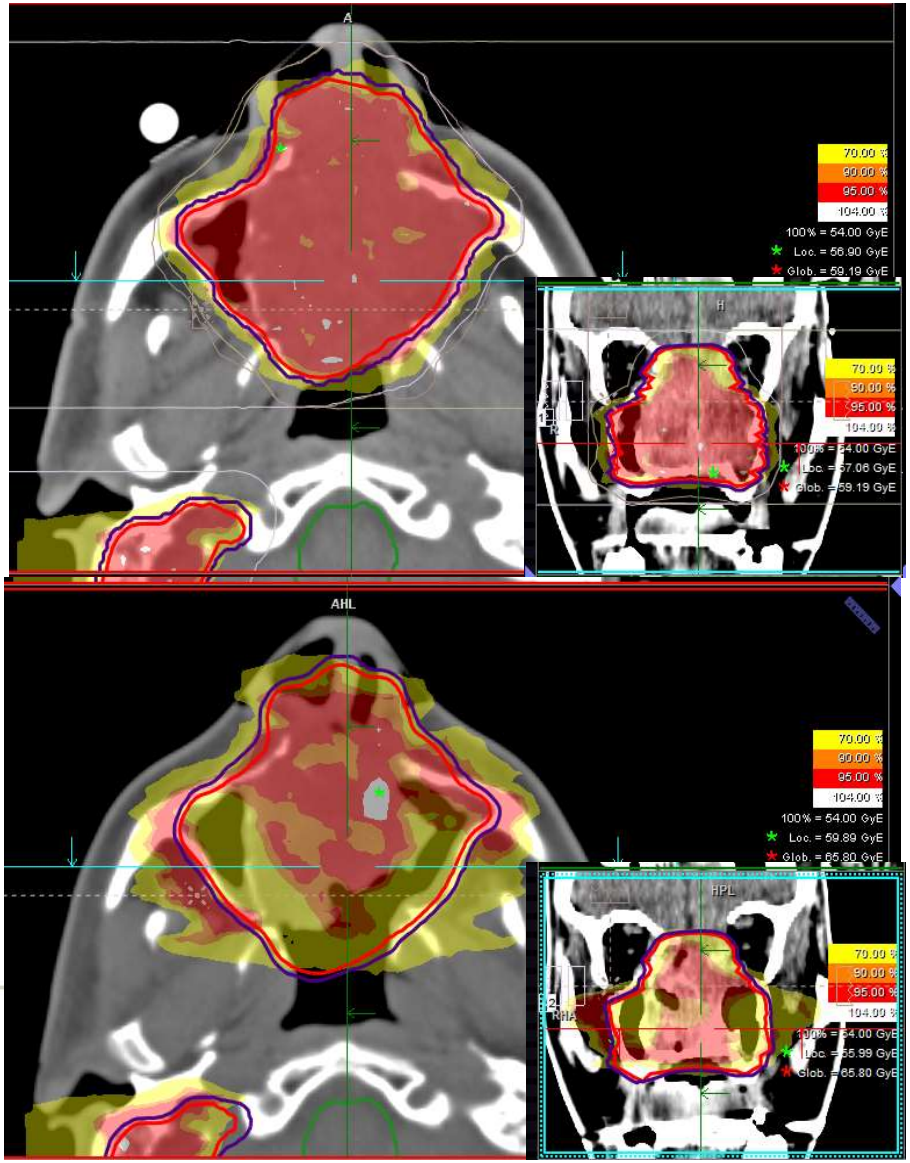


Inter-fraction – Tumor volume variation

Tumor growth



Tumor shrinkage



Interplay - Dynamic techniques

Problem: planning for IMRT, dynamic arc treatment or active scanning particle therapy on a moving target

→ the motion of the target may **interfere constructively or destructively** with the motion of the MLC leaves, the beam opening, the gantry rotation, the beam scan path and/or other dynamic parameters during treatment delivery.

→ The effect of such interferences is that the dose to sub-volumes in the patient may be significantly different from the planned dose, since **interferences are not modeled** in the treatment planning system.

Interplay - Dynamic IMRT

Time scale of dynamic dose delivery (fluence pattern) comparable to time scale of organ motion

Interplay effect

between organ motion and the movement (or 'sequencing') of the MLC

a volume element in the tumor may not receive primary radiation at all because it is always hidden behind a leaf of the MLC

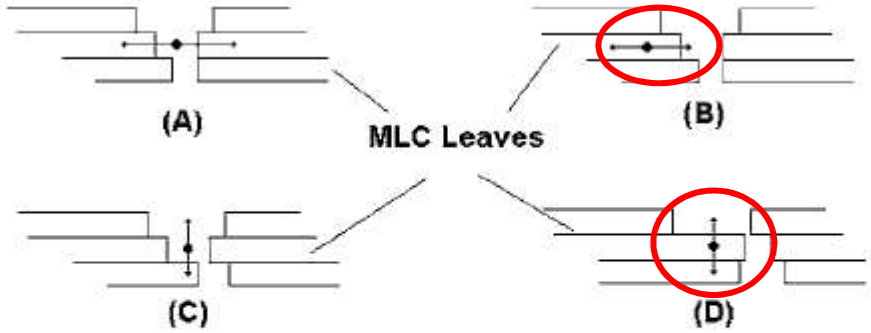


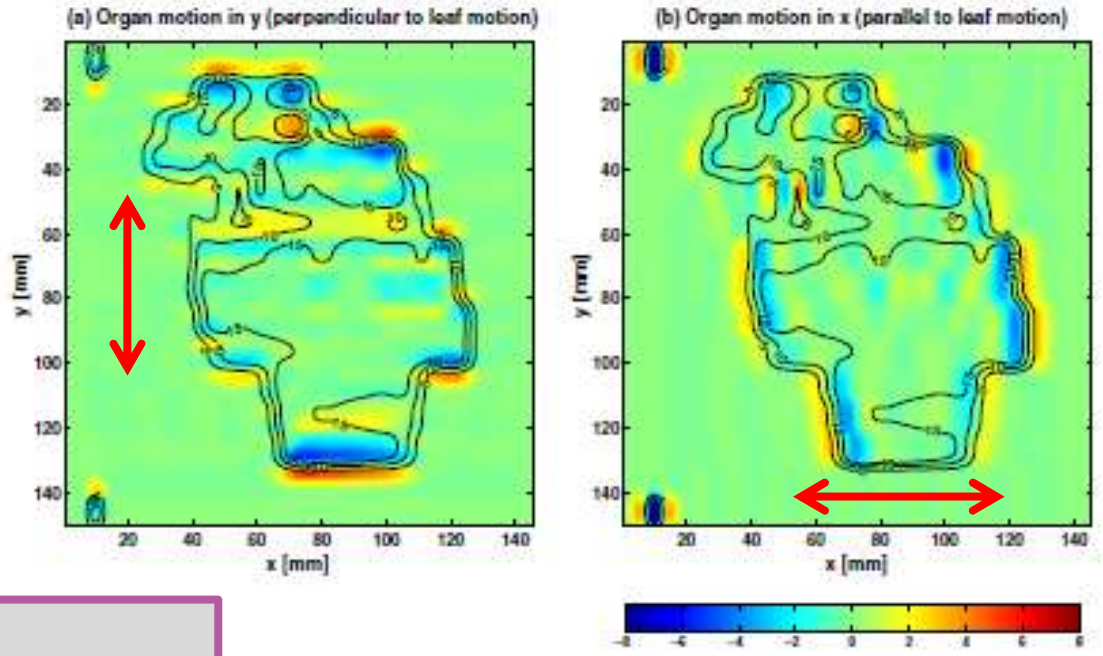
FIG. 1. Examples of interplay effects between IMRT delivery and tumor motion. Organ motion may occur parallel to the leaf motion such as represented in (a) and (b), and motion may occur perpendicular to the leaf motion such as represented in (c) and (d).

Seco et al. Med Phys(34) 2007

Interplay - Dynamic IMRT

→ If motion mitigation is not applied during IMRT to a moving target

CTV under/over-dosage



Bortfeld PMB (47) 2002

- Fractionation
1fx → 20% dose variation
30fx → <2% dose variation
Bortfeld PMB (47) 2002 - Jiang PMB (48) 2003 - ...

- Multiple fields → statistical averaging over the beam reduces the overall dose error

- Avoid low MU segments (few s delivery)
Seco et al. Med Phys(34) 2007

→ Delivery time comparable to breathing period
→ Segment size comparable to breathing amplitude

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Interplay – VMAT (+ FFF)

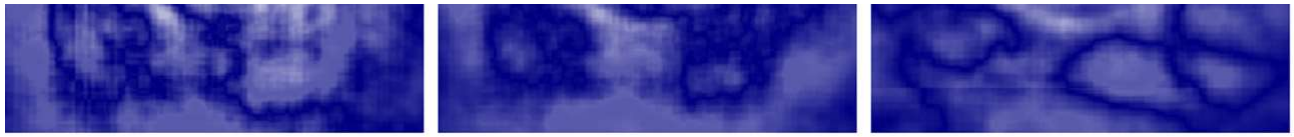
2400MU/min - reduce treatment times – < **breathing cycles**
fast IMRT of a mobile target under free breathing conditions

↓

interplay effect (no averaging)

↓

Over/Underdosage within the target region
during a single fraction, mitigated by using 2 to 3 fractions and 2 arcs per fraction



CW 400 MU/min | Sum 400 MU/min | 3 Fractions 2400 MU/min

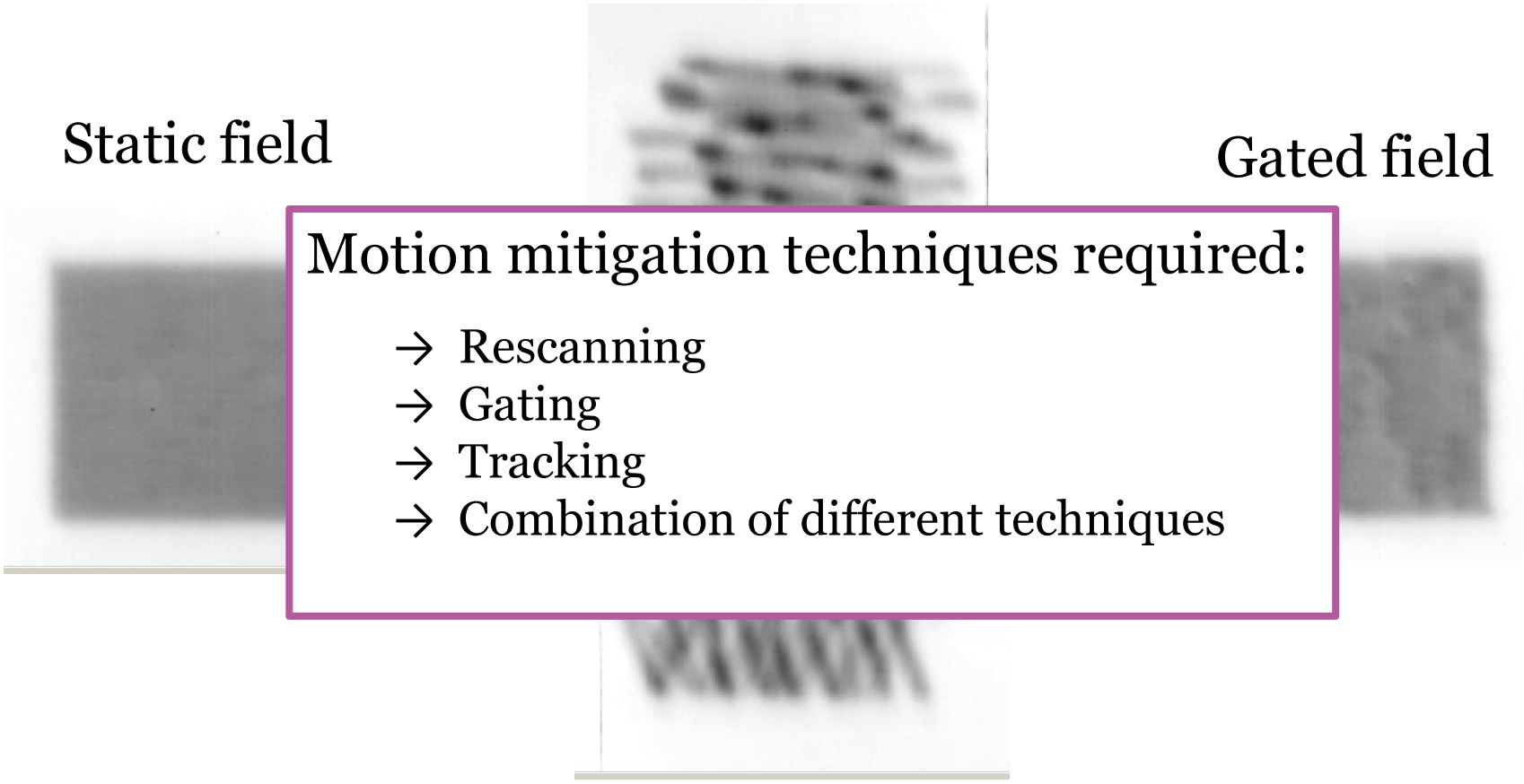
Ong CL et al, Int J Radiat Oncol Biol Phys. 2013 Jul 15;86(4):743-8

Interplay – Particle therapy - Active scanning

Motion - scan direction

Static field

Gated field



Motion mitigation techniques required:

- → Rescanning
- → Gating
- → Tracking
- → Combination of different techniques

Interplay – Active scanning

- Interference effects of target motion and scanned beam can further cause severe under/over-dosage of the target volume despite using margins to account for the radiological depth (WEPL based geometry).
- The dose uniformity is very dependent on the motion amplitude and the relative direction of beam motion and target motion.
- Multiple irradiations of the volume decrease the sensitivity to these interference effects → rescanning (statistical averaging of local over and under-dosage due to interplay effect)
- SFUD planning, multiple fields and fractionation are a type of re-scanning.

Contents

3) Machine technical delivery uncertainties

→Delineation
→Planning
→Delivery
→Prescription

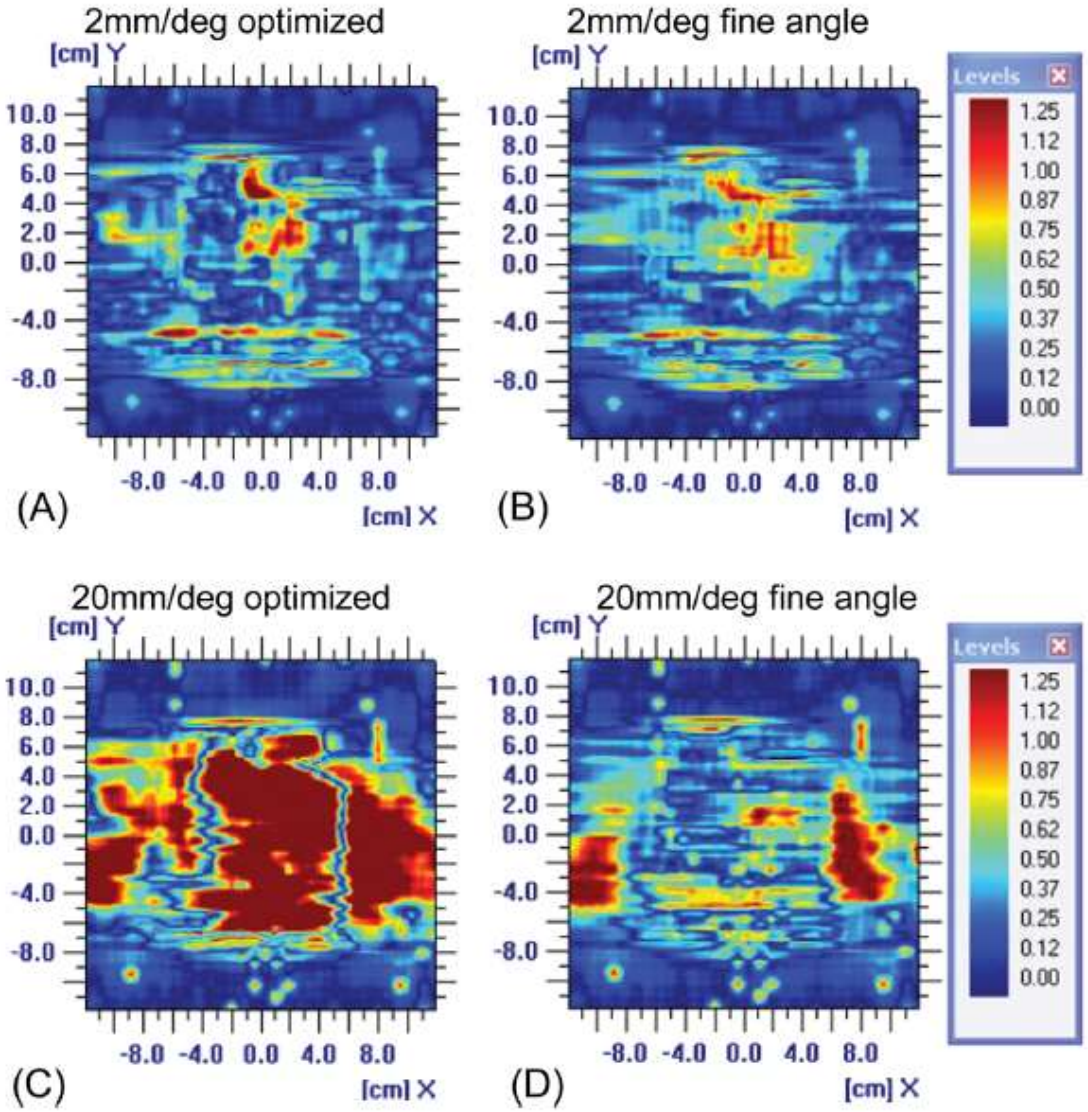
Plan quality vs Delivery accuracy - VMAT

Leaf motion constraint

- max distance a MLC leaf can travel between adjacent control points
- ensures the deliverability of the optimized plan, but it also impacts the plan quality, delivery accuracy and efficiency
- a less restrictive leaf motion constraint (> 5 mm/deg) results in > plan quality but < accurate dose distribution
- γ-analysis passing rate from 98% to 80% when the allowable leaf motion increased from 3 to 20 mm/deg.

Chen F et al. Med Phys (38) 2011

Gamma-analysis



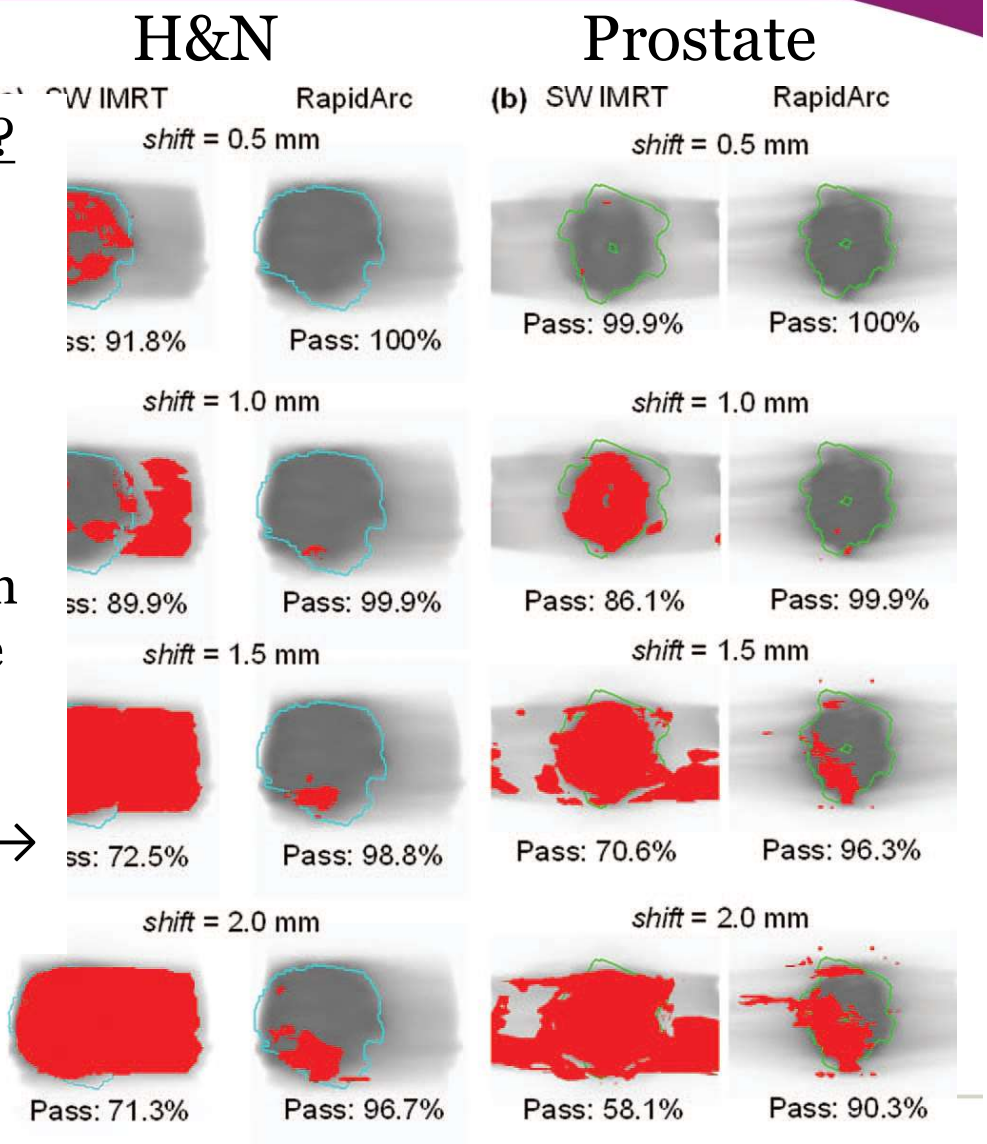
Delivery uncertainties - IMRT

how intensity modulation is achieved?

- sliding window → larger number of overlapping segments and MU
- RapidArc → rotation → larger apertures and less MU

The susceptibility to MLC leaf position errors is inversely proportional to the mean leaf gap width

Geometric errors in smaller apertures → larger impact on dosimetric errors.



2%-2 mm γ for systematic MLC leaf bank shifts of 0.5, 1, 1.5, and 2 mm. Points that failed in red.

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Betzel GT et al, Med Phys 39(10) 2012

Delivery uncertainties proton therapy

Hp Pencil beam scanning proton therapy requires the delivery of many thousand beams, each modulated for position, energy and monitor units, to provide a highly conformal patient treatment.

How

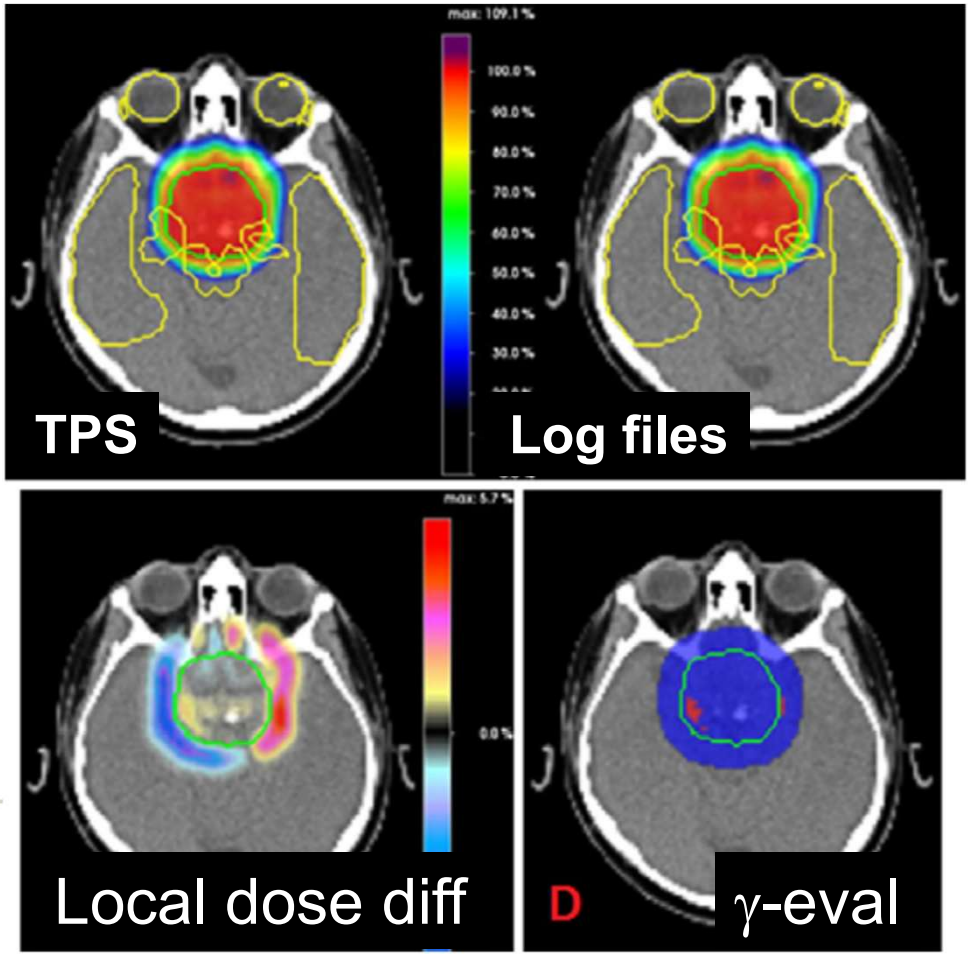
treatment log files (record of the machine parameters) to investigate the integrity of treatment delivery compared to the nominal planned dose.

Results

→ the integrity of treatment delivery is dependent on daily machine performance and is highly correlated with the accuracy of beam position.

→ Increased robustness gained by using multiple fields per series

→ Extra patient specific QA benefit!



Scandurra D, PMB (61) 2016

Robust control

- A prerequisite of high precision dose delivery is high precision of targeting.
- If (all) involved uncertainties are not taken into account → reduced benefit of highly conformal techniques.
- Margins are a robust strategy for target coverage with a clear price (healthy tissues irradiation) … but in some cases are not enough.
- To fully exploit the potential of IMRT/PT in complex cases with considerable organ motion, real time image guidance is necessary.
- In the absence of accurate prognostic factors an adaptive approach (repeat imaging – calculation – planning) is recommended in PT.
- A plan is robust if treatment goals are met despite uncertainties in the patient model and the plan remains acceptable over a range of likely variations.
- Optimal dose distribution → dose conformity, healthy tissue sparing and robustness towards uncertainties.

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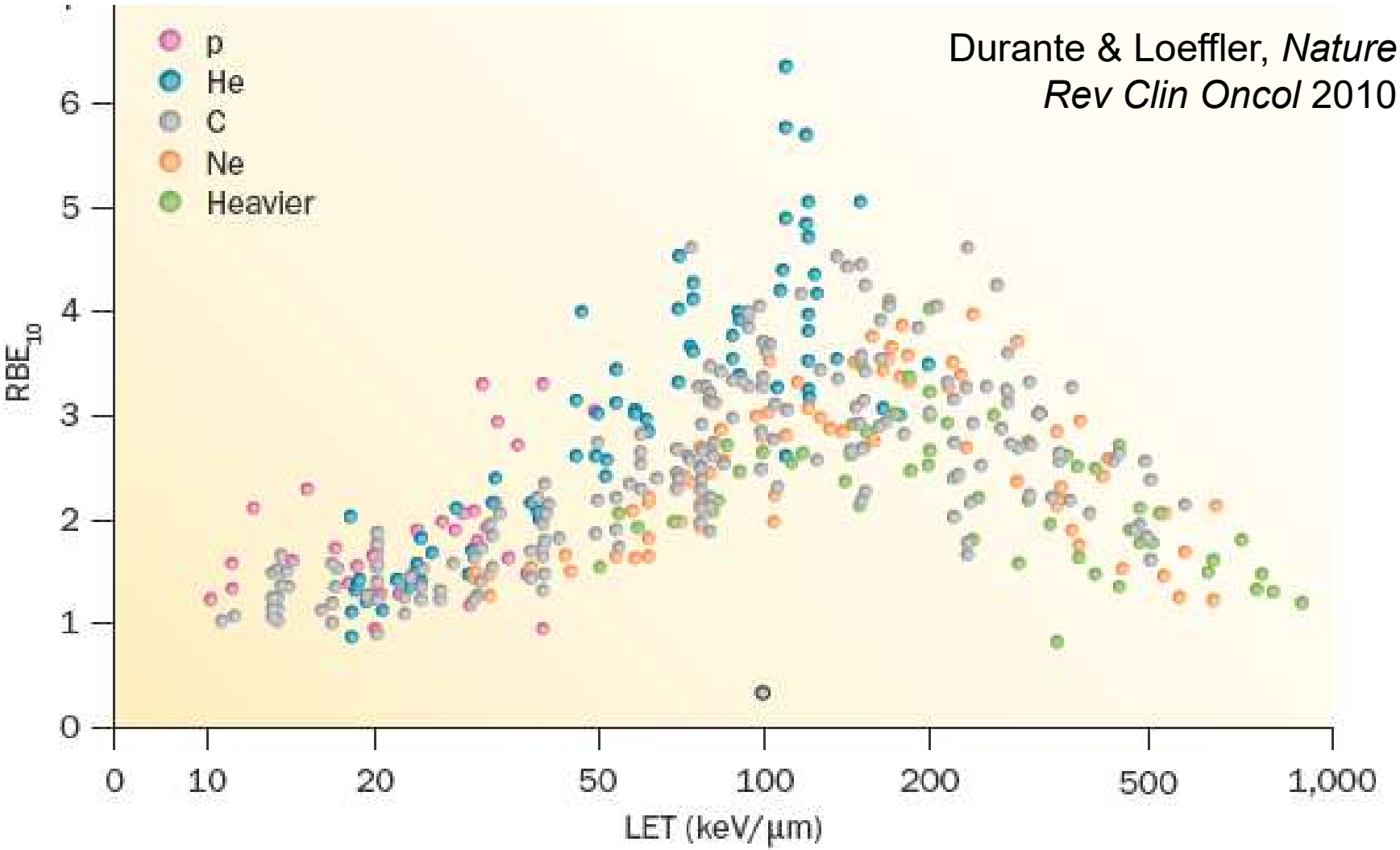
Contents

3) RBE-weighted dose definition

→Delineation
→Planning
→Delivery
→Prescription

RBE for various particles



Durante & Loeffler, *Nature Rev Clin Oncol* 2010

RBE is a function of LET, Z, cell type, dose, endpoint

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Proton RBE

ICRU 78 - 2007

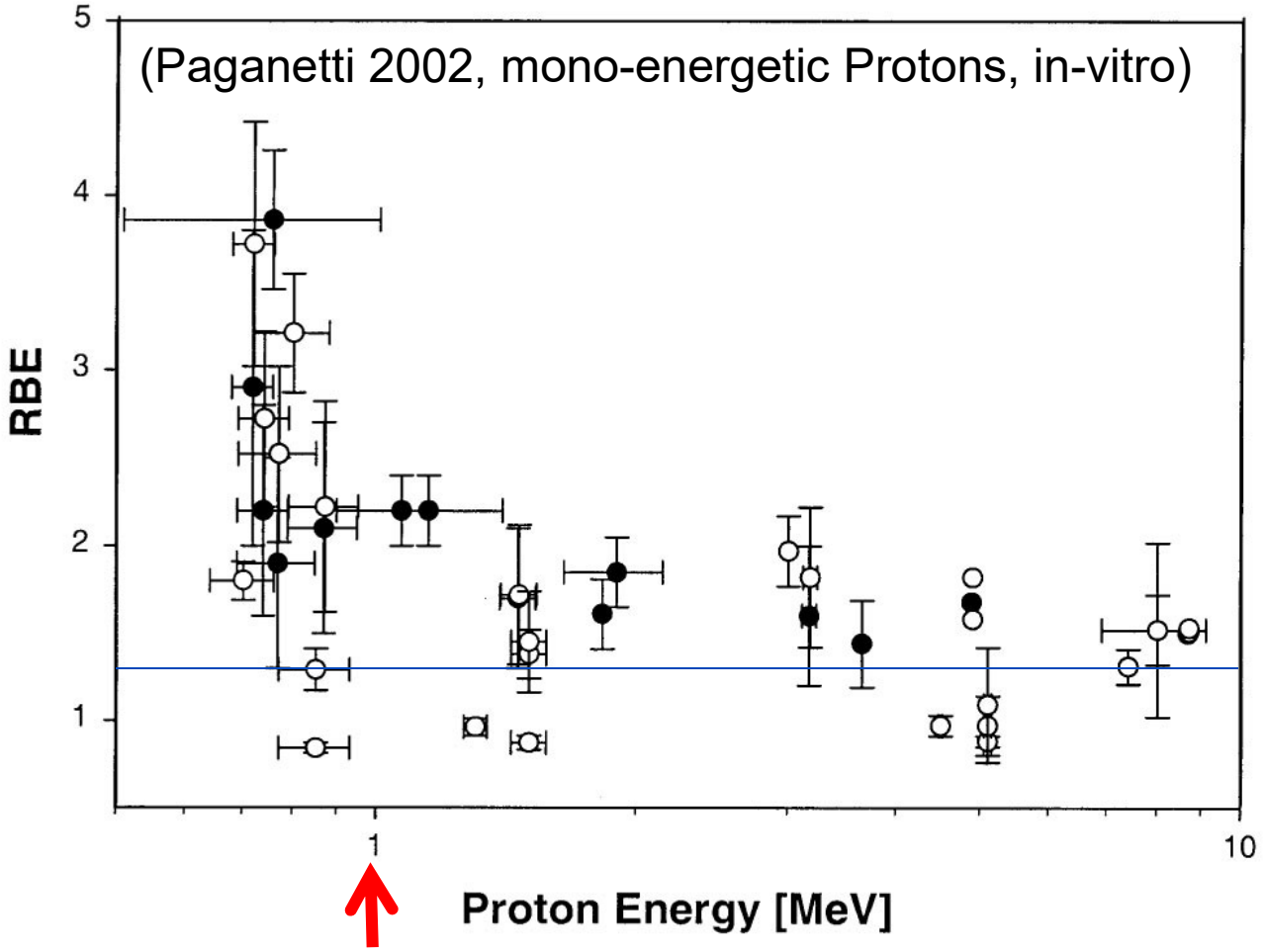
All protons are equal

→ the RBE of protons is **1.1**

(independent on LET, dose, end point, α/β)…

RBE for protons

Some protons are more equal than others



Residual range: ~25 μm → Bragg peak position

Carbon ions Gy (RBE) – Radiobiological Model

Same absorbed dose

⇩

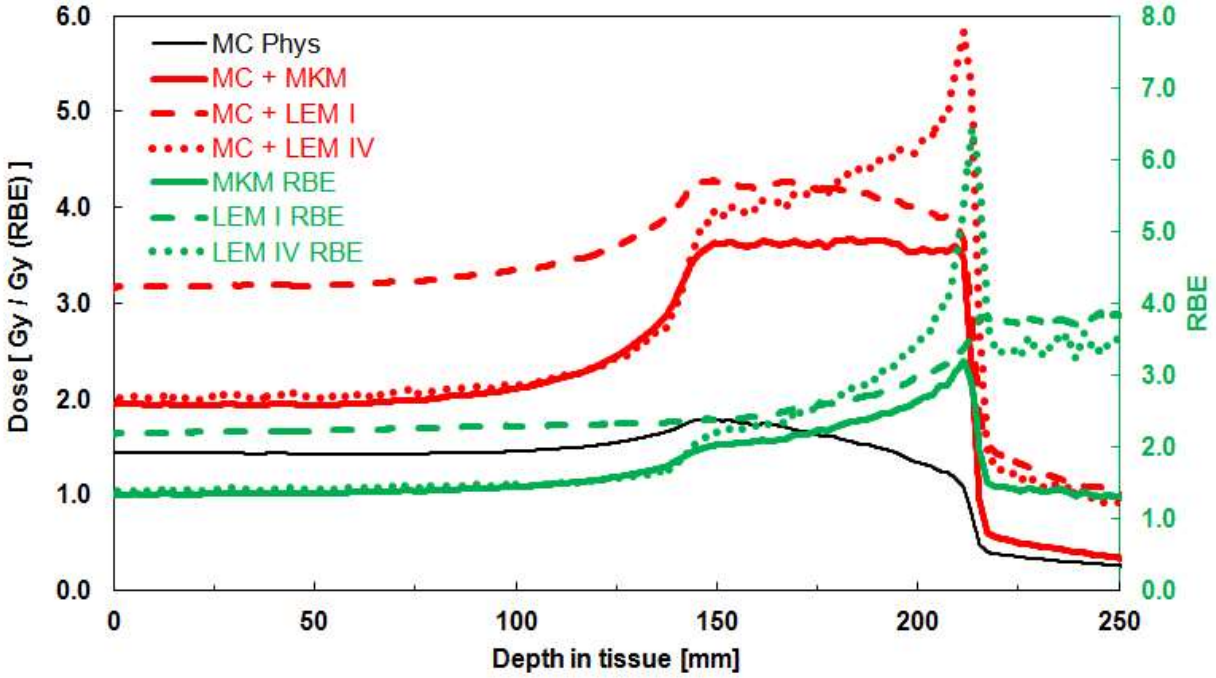
Different RBE model

- Kanai model
- MKM
- LEM I/IV

⇩

Different
RBE-weighted dose

MC simulation of a prostate treatment field



Magro G – to be submitted

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Carbon ions Gy (RBE) – Radiobiological Model

Same effective dose prescribed

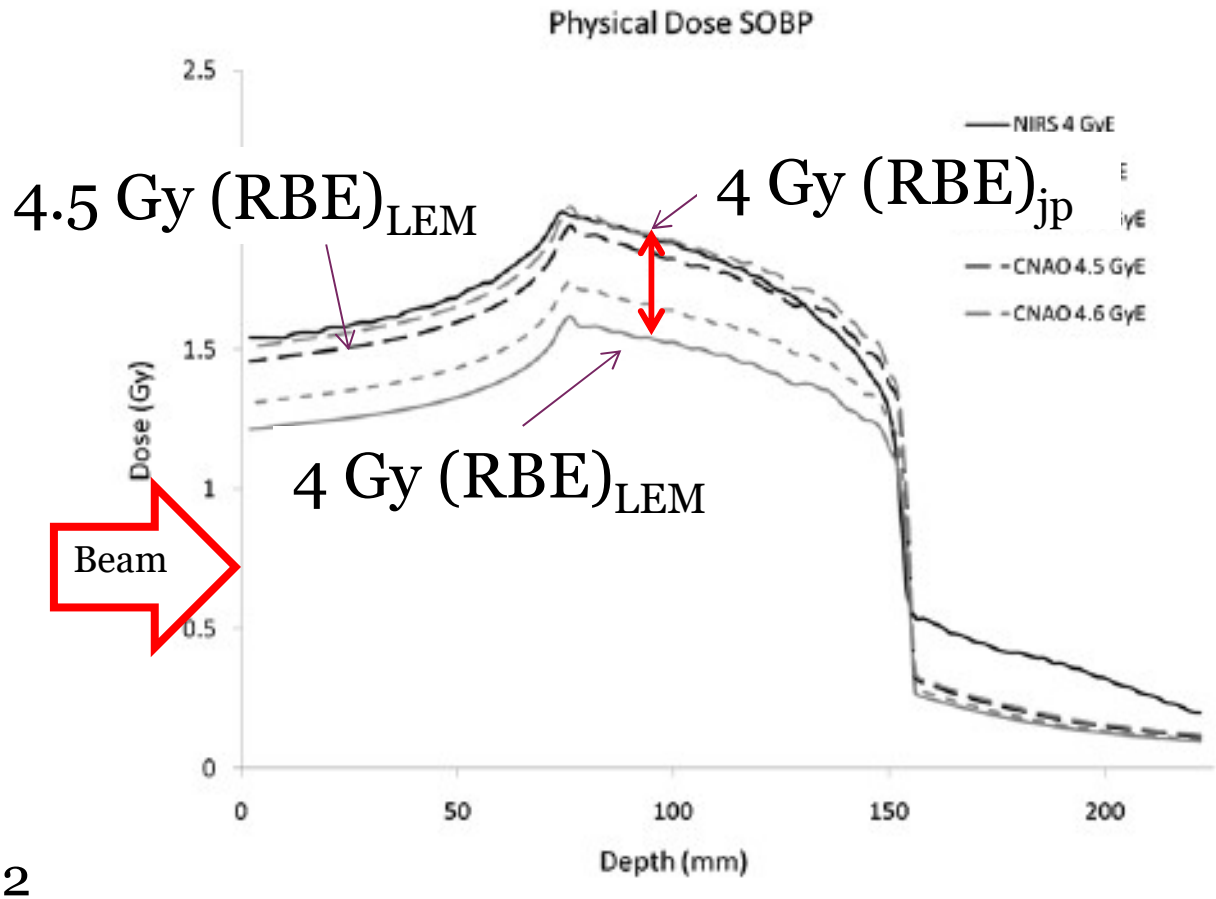
⇩

Different absorbed dose delivered

⇩

Can we change the prescription dose?

Physical dose profiles corresponding to different prescription doses according to different RBE models

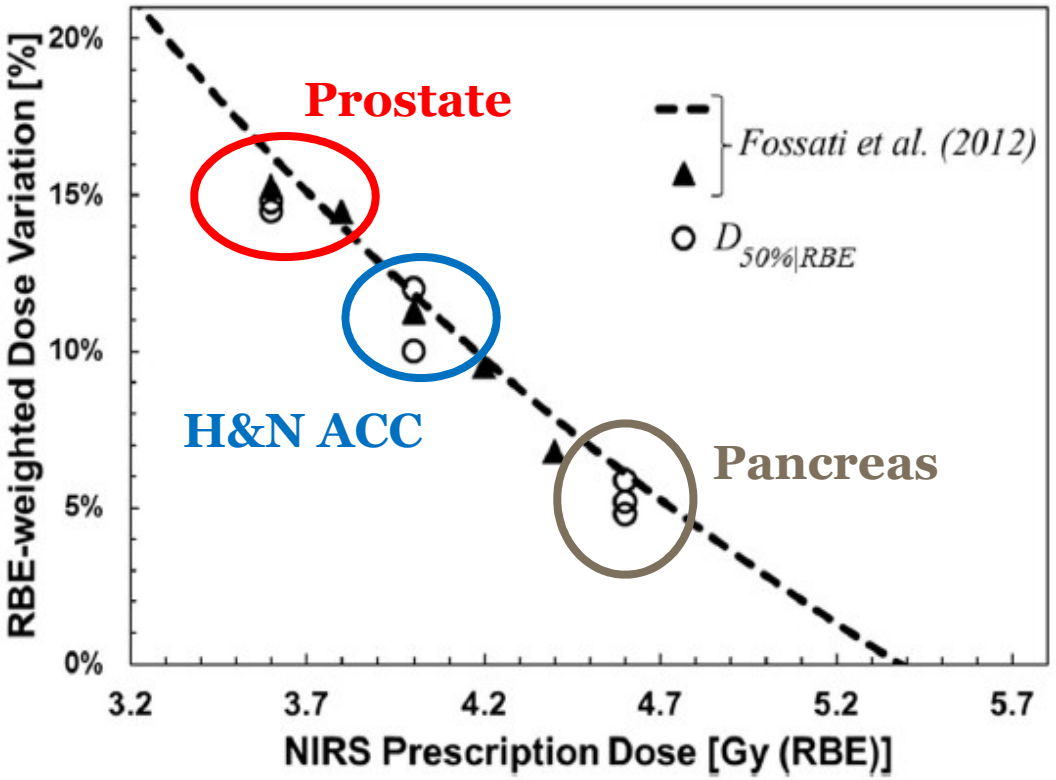


Fossati P et al. PMB (57) 2012

Carbon ions Gy (RBE) – 3D Radiobiological Model

To deliver the same physical median dose to the target volume a possible approach is to prescribe corrected RBE-weighted dose values

Target median RBE-weighted dose difference Japanese vs European RBE adopted models



Molinelli et al. R&O 2016

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The Uncertainty of RBE (by Oliver Jakel - HIT)

Relative Uncertainty in the SOBP:

Variation of the RBE as a function of various parameters (depth, dose, beam energy, fractionation, tumor type, etc.)

Precision probably around 10%

Absolute uncertainty:

"Correct doses" have to be evaluated in clinical studies

Accuracy of RBE(C12) probably around 20% - 30%

Comparison:

Clinical Proton-RBE: ~10-20%

RBE for Brachytherapy (^{125}I and ^{103}Pd): ~1.5 (+-20%)

Changes of fractionation schemes (using α/β): ~15%

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Sources and References

- **IAEA**

Radiation protection of Patients
http://rpop.iaea.org/RPOP/RPoP/Content/
Radiation Oncology physics handbook
http://www-naweb.iaea.org/nahu/dmrp/

- **The Physics of Radiation Therapy**

Faiz M Khan (Lippincott Williams & Wilkins)

- **The physical principles of medical imaging**

http://www.sprawls.org/resources

Reference Dosimetry

(external beam photon therapy with linacs)

Ben Heijmen

Erasmus MC
University Medical Center Rotterdam

ESTRO - Physics for Modern Radiotherapy
Bucharest 2017

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Reference dosimetry

- about absolute dose measurement (Gy) in ***reference*** conditions in water: 10x10 cm^2, d_{ref}, 100 cm, …

- most important application: calibration of Monitor Unit (MU) chambers in linear accelerators: 1 MU = 1 cGy

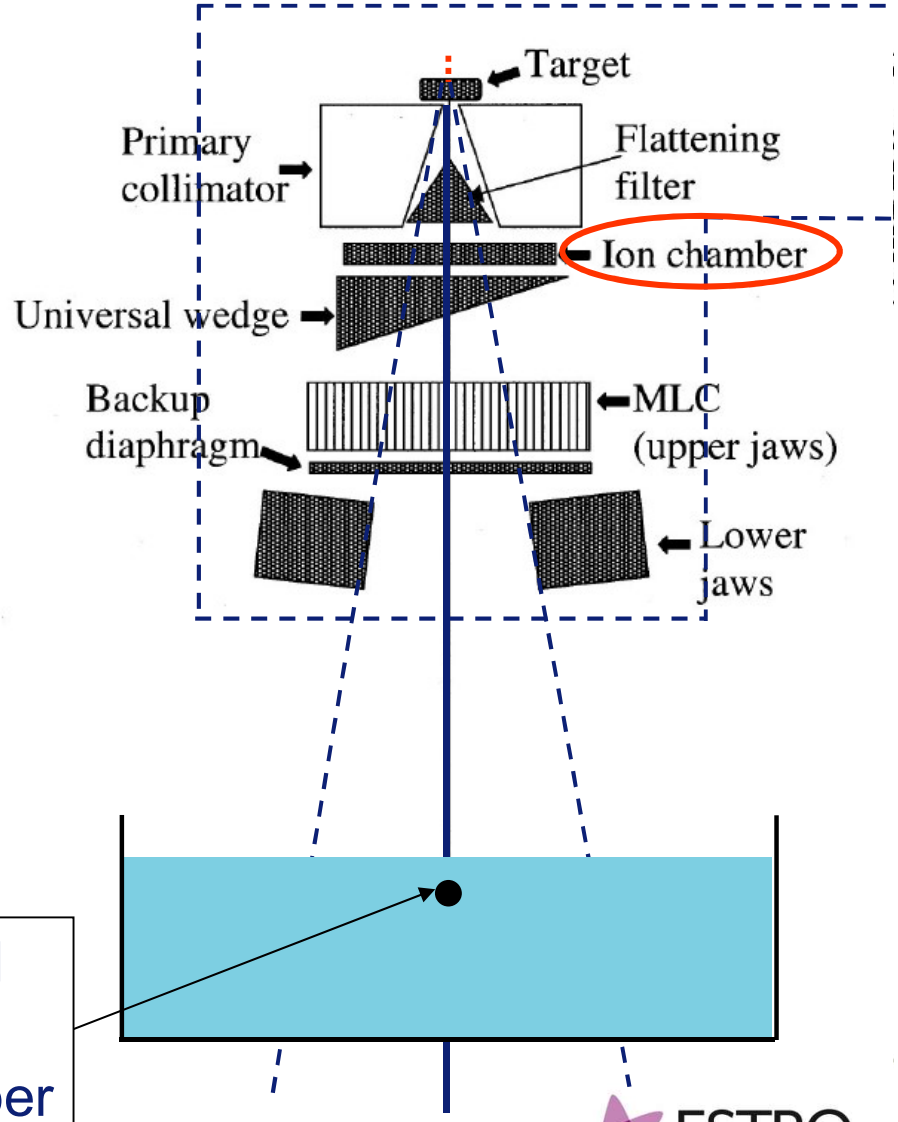
Calibration of MU-chamber

MU-chamber

- is a transmission ionization chamber
- electronics generates 'counts' (MUs) after a pre-set charge Q_{MU} measured

Calibration of MU-chamber:

electronics is tuned such that
1MU corresponds with
a dose of 1 cGy in H_20
in *reference* conditions



dose measured
with *calibrated*
ionization chamber

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What accuracy in delivered dose is required?

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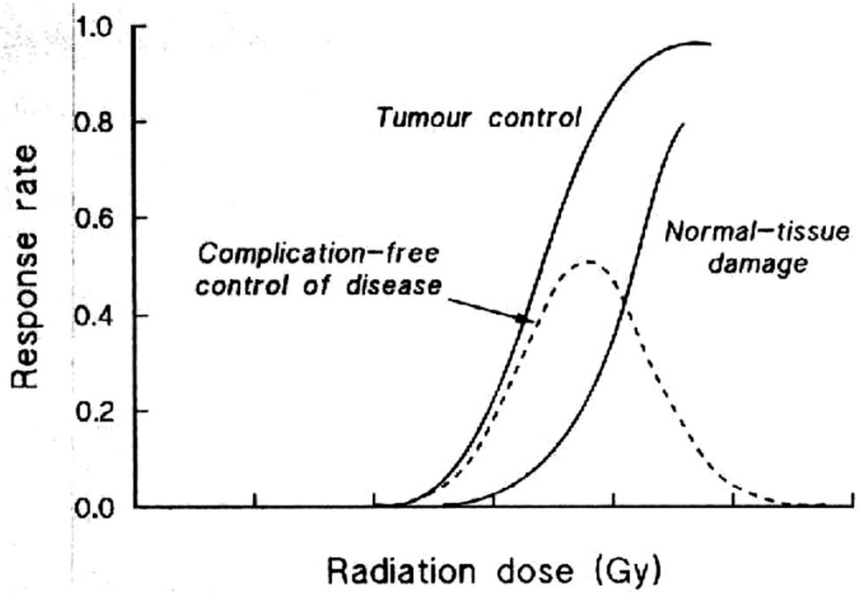
Delivered dose is main treatment related predictor for radiotherapy outcome:

➔ local control and toxicity



- MU calibration is one of the principal responsibilities of the medical physicist.
- If wrong, dose is too low or too high for all patients.

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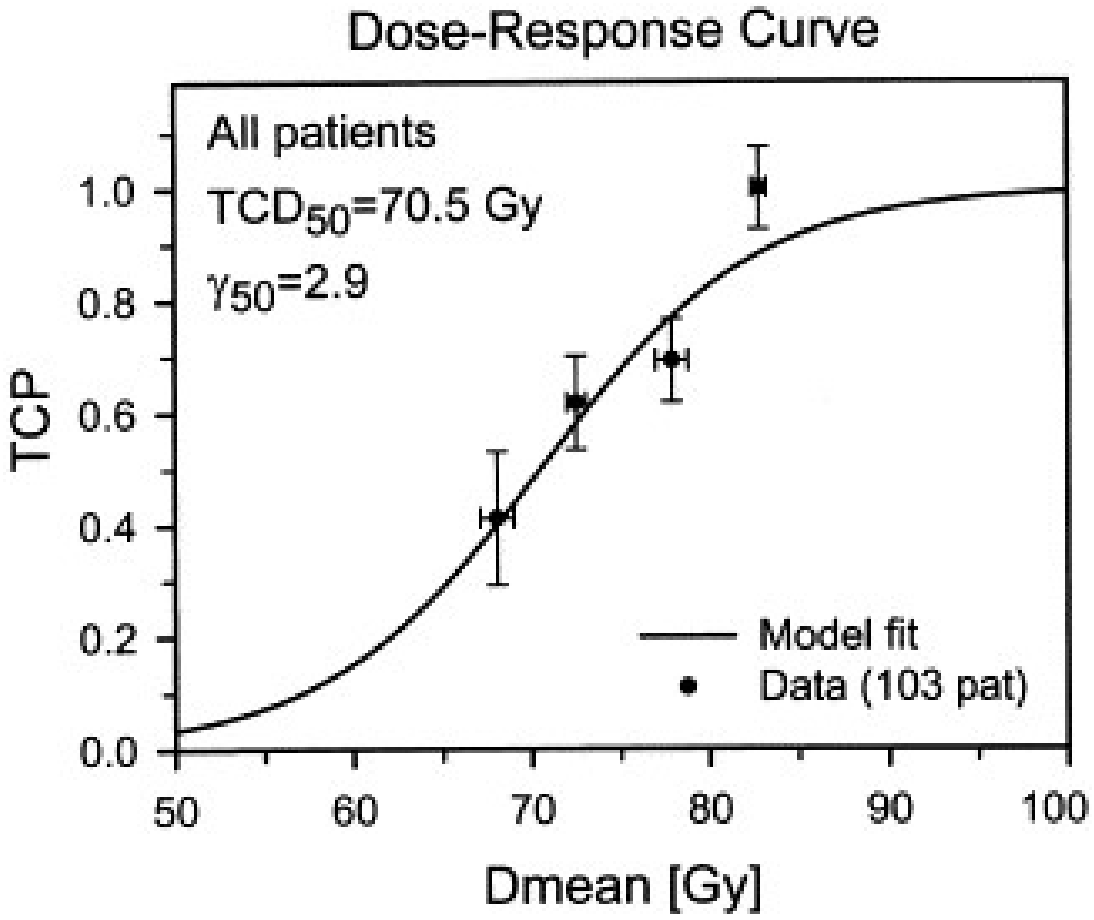
What accuracy in delivered dose is required?

Prostate cancer



(Levegrun, IJROBP 2002)

$$\Delta TCP = \gamma \times \frac{\Delta D}{D}$$

1% change in dose results in
γ % change in TCP

γ=3
5% change in dose results in
15 % change in TCP

(50%➔35%)

$$\frac{\Delta D}{D} < 1\% ?$$

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What accuracy in delivered dose is required?

Table 1

Clinically observed normalized dose response gradients for malignant tissues

Site	γ_c	References
Nasopharynx		
T1/2	2.8	METZ et coll. (25)
T3	1.0	
Squamous cell carcinoma	3.5	PATTERSON (27)
Squamous cell carcinoma	5.9	HLINIAK et coll. (15)
Glottic carcinoma T2	4.6	HARWOOD (12)
Larynx		
T3	4.0	STEWART & JACKSON (33)
T3/4	8.0	MACIEJEWSKI et coll. (24)
T2/3	3.5	SHUKOVSKY (31)
Larynx	3.0	KIM et coll. (22)
Larynx	2.4	ARISTIZABAL & CALDWELL (1)
Glossopalatine sulcus	3.7	SHUKOVSKY et coll. (32)
Hodgkin's disease	0.4	KAPLAN (19)
Melanoma metastasis	4.0	TROTT et coll. (36)

Often, γ-values for organs at risk are even higher

A. Brahme
Acta Radiologica Oncology
1984

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What is needed to perform reference dosimetry in a hospital?

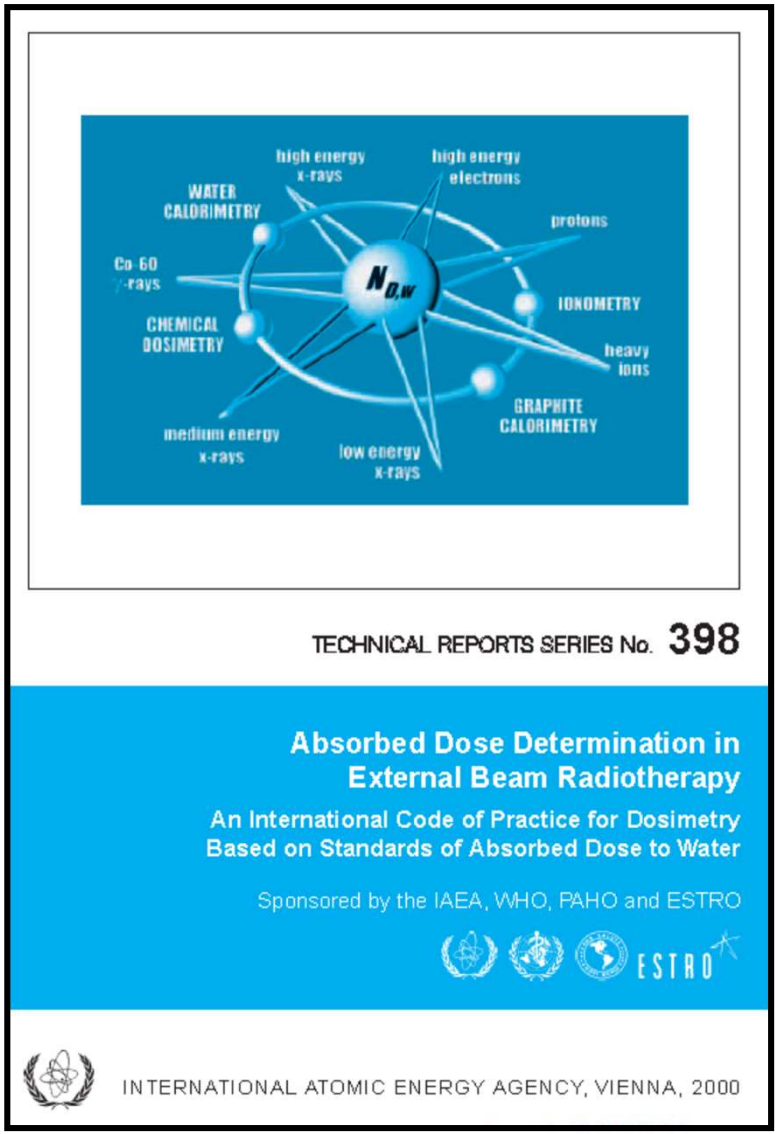
Needed by hospital:

1. calibrated ionization chamber (i.c.):
   $N_{D,w,Co}$ (dose in H_2O in ^{60}Co / charge)
2. protocol to use calibrated i.c.
   in a therapeutic beam

Choose i.c. recommended by protocol

IAEA-report TRS 398

free download IAEA website



Reference Dosimetry

for high energy, external beam photon beam therapy

Outline

1. Global workflow in a hospital
2. Introduction to primary dosimetry standards and standard laboratories (needed for calibration of i.c.)
3. Detailed example of reference dosimetry in the hospital
4. Details and physics of ***primary*** standards of absorbed dose to water

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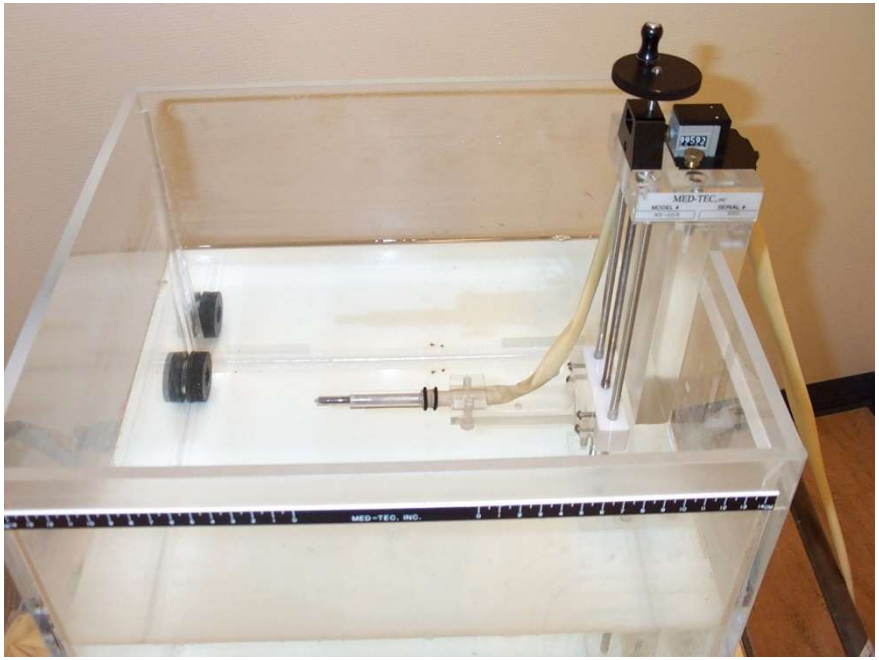
Global workflow for reference dosimetry in a hospital

1. Hospital buys i.c. recommended by TRS 398
2. Hospital's i.c. + electrometer to a standard laboratory for calibration ➔ $N_{D,w,Co}$: dose in water in ^{60}Co /reading
3. Absolute water dose measurements in the hospital for MU-chamber calibration, using:
   - the calibrated i.c.
   - TRS398 protocol



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What are dosimetry standards and standard laboratories:

Classification of instruments	Standards laboratories
Primary standard An instrument of the highest metrological quality that permits determination of the unit of a quantity from its definition, the accuracy of which has been verified by comparison with the comparable standards of other institutions at the same level.	**Primary Standard Dosimetry Laboratory (PSDL)** A national standardizing laboratory designated by the government for the purpose of developing, maintaining and improving primary standards in radiation dosimetry. **(~20 PSDL world wide)**
Secondary standard An instrument calibrated by comparison with a primary standard	**Secondary Standard Dosimetry Laboratory (SSDL)** A dosimetry laboratory designated by the competent authorities to provide calibration services, and which is equipped with at least one secondary standard that has been calibrated against a primary standard.
National standard A standard recognized by an official national decision as the basis for fixing the value in a country of all other standards of the given quantity.	

At present only

- calorimetry
- chemical dosimetry (Fricke)
- ionization dosimetry

are sufficiently accurate to form the basis of primary standards

Procedure in the standard laboratory for calibration of your ionization chamber

your i.c. in water in reference conditions in ^{60}Co beam ➔ M_{Co}

their primary or secondary standard in water in ^{60}Co ➔ $D_{w,Co}$

$$N_{D,w,Co} = D_{w,Co} / M_{Co}$$

your calibration factor

= dose/reading in ^{60}Co beam

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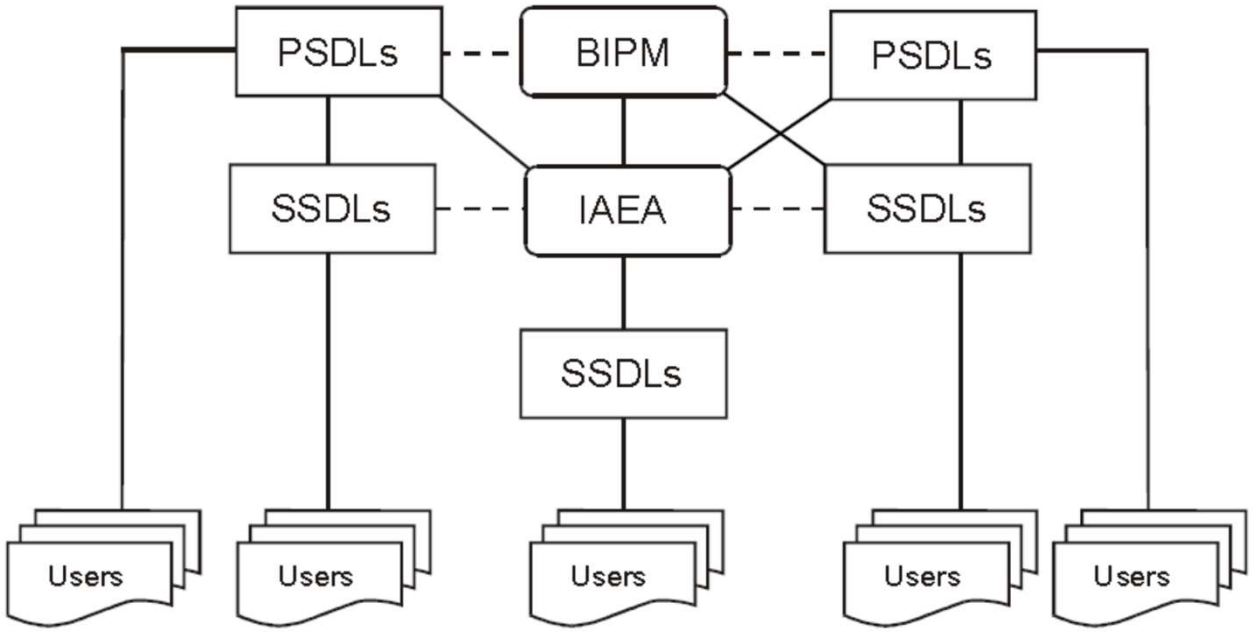
International Measurement System (IMS) for radiation metrology



BIPM (Bureau International des Poids et Mesures):

- set up by the Metre Convention (originally signed in 1875)
- serves as the international centre for metrology, laboratory and offices in Sèvres (France)
- aim: ensuring worldwide uniformity in matters relating to metrology.

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How to measure absorbed dose in water:

- put ionisation chamber in H_2O in reference conditions
- irradiate with photon beam ➔ reading M_Q (Q = quality of your beam)

calculate dose to H_2O in absence chamber:

$$D_{w,Q} = M_Q \cdot N_{D,w,Co} \cdot k_{Q,Co} \cdot \Pi k_i$$

$N_{D,w,Co}$: chamber calibration factor, delivered by standards laboratory ($N_{D,w,Co}$ specific for each individual chamber)

$k_{Q,Co}$: correction of $N_{D,w,Co}$ for use in quality Q instead of Co (depends on chamber type and beam quality Q)

$\Pi_i k_i$: corrections for deviations from reference conditions other than Q, e.g. temperature, air pressure, recombination, etc.

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$\prod_i k_i$:

$$k_{TP} = \frac{(273.2 + T)}{(273.2 + T_o)} \frac{P_o}{P}$$

(open chambers are recommended)

Practical example:

MU-chamber calibration with NE 2571 chamber
(one of the recommended chambers)

How to measure $D_{w,Q}$ according to TRS 398?

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$D_{w,Q} = M_Q \cdot N_{D,w,Co} \cdot k_{Q,Co} \cdot \Pi k_i$

1. Determine (once) $k_{Q,Co}$, dependent on chamber ***type*** and Q
    1. determine Q: $TPR_{20,10}$ ($\propto$ effective beam attenuation coefficient)
    2. determine $k_{Q,Co}$: look-up table TRS 398 for NE2571 and $TPR_{20,10}$

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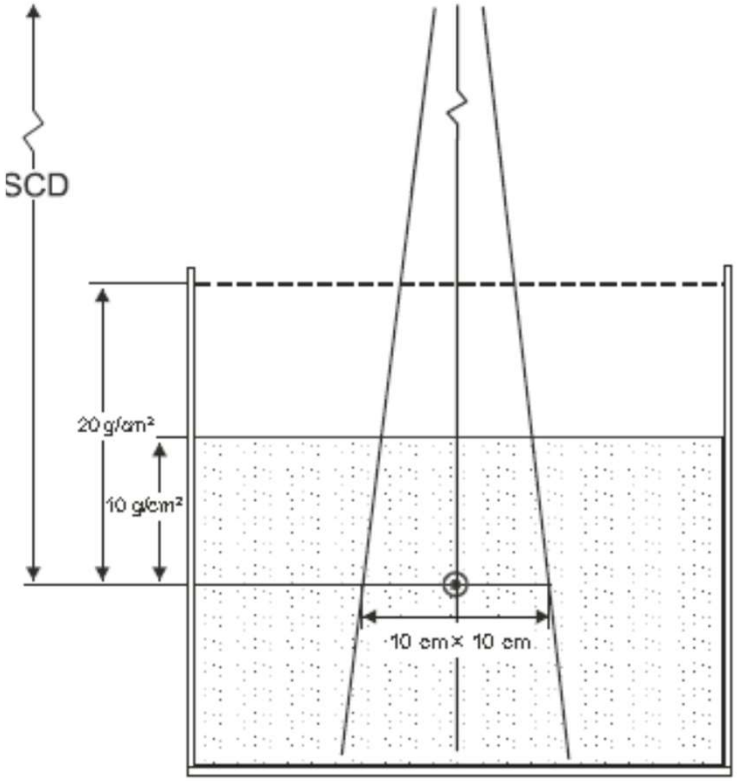
To determine $k_{Q,Co}$: determine $TPR_{20,10}(Q)$

$$TPR_{20,10}(Q)=D(d=20)/D(d=10)$$

TABLE 12. REFERENCE CONDITIONS FOR THE DETERMINATION OF PHOTON BEAM QUALITY ($TPR_{20,10}$)

Influence quantity	Reference value or reference characteristics
Phantom material	Water
Chamber type	Cylindrical or plane parallel
Measurement depths	20 g/cm^2 and 10 g/cm^2
Reference point of the chamber	For cylindrical chambers, on the central axis at the centre of the cavity volume. For plane-parallel chambers, on the inner surface of the window at its centre
Position of the reference point of the chamber	For cylindrical and plane-parallel chambers, at the measurement depths
SCD	100 cm
Field size at SCD	10 cm × 10 cm[a]

[a] The field size is defined at the plane of the reference point of the detector, placed at the recommended depths in the water phantom.



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To determine $k_{Q,Co}$: use lookup Table in TRS938

TABLE 14. CALCULATED VALUES OF k_Q FOR HIGH ENERGY PHOTON BEAMS FOR VARIOUS CYLINDRICAL IONIZATION CHAMBERS AS A FUNCTION OF BEAM QUALITY $TPR_{20,10}$ *(adapted from Andreo [20])*

Ionization chamber type[a]	Beam quality $TPR_{20,10}$														
	0.50	0.53	0.56	0.59	0.62	0.65	0.68	0.70	0.72	0.74	0.76	0.78	0.80	0.82	0.84
Capintec PR-05P mini	1.004	1.003	1.002	1.001	1.000	0.998	0.996	0.994	0.991	0.987	0.983	0.975	0.968	0.960	0.949
Capintec PR-05 mini	1.004	1.003	1.002	1.001	1.000	0.998	0.996	0.994	0.991	0.987	0.983	0.975	0.968	0.960	0.949
Capintec PR-06C/G Farmer	1.001	1.001	1.000	0.998	0.998	0.995	0.992	0.990	0.988	0.984	0.980	0.972	0.965	0.956	0.944
Exradin A2 Spokas	1.001	1.001	1.001	1.000	0.999	0.997	0.996	0.994	0.992	0.989	0.986	0.979	0.971	0.962	0.949
Exradin T2 Spokas	1.002	1.001	0.999	0.996	0.993	0.988	0.984	0.980	0.977	0.973	0.969	0.962	0.954	0.946	0.934
Exradin A1 mini Shonka	1.002	1.002	1.001	1.000	1.000	0.998	0.996	0.994	0.991	0.986	0.982	0.974	0.966	0.957	0.945
Exradin T1 mini Shonka	1.003	1.001	0.999	0.996	0.993	0.988	0.984	0.980	0.975	0.970	0.965	0.957	0.949	0.942	0.930
NE 2505/3, 3A Farmer	1.005	1.004	1.002	1.000	0.998	0.995	0.993	0.991	0.989	0.986	0.982	0.975	0.969	0.961	0.949
NE 2505/3, 3B Farmer	1.006	1.004	1.001	0.999	0.996	0.991	0.987	0.984	0.980	0.976	0.971	0.964	0.957	0.950	0.938
NE 2571 Farmer	1.005	1.004	1.002	1.000	0.998	0.995	0.993	0.991	0.989	0.986	0.982	0.975	0.969	0.961	0.949
NE 2581 Farmer	1.005	1.003	1.001	0.998	0.995	0.991	0.986	0.983	0.980	0.975	0.970	0.963	0.956	0.949	0.937

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$D_{w,Q} = M_Q \cdot N_{D,w,Co} \cdot k_{Q,Co} \cdot \Pi k_i$

1. Determine (once) $k_{Q,Co}$, dependent on chamber ***type*** and Q
   1. determine Q: $TPR_{20,10}$ ($\propto$ effective attenuation coefficient)
   2. determine $k_{Q,Co}$: look-up table TRS 398 for NE2571 and $TPR_{20,10}$
2. Establish (once) part of k_i in treatment beam (k_{rec}, k_{pol})

3. Perform measurement in beam Q in reference conditions ➔ M_Q
4. Correct with $k_{p,T}$
5. $D_{w,Q} = M_Q \cdot N_{D,w,Co} \cdot k_{Q,Co} \cdot \Pi k_i$

estimated accuracy of dose measurement in high energy photon beams (TRS 398)

TABLE 15. ESTIMATED RELATIVE STANDARD UNCERTAINTY [a] OF $D_{w,Q}$ AT THE REFERENCE DEPTH IN WATER AND FOR A HIGH ENERGY PHOTON BEAM, BASED ON A CHAMBER CALIBRATION IN ^{60}Co GAMMA RADIATION

Physical quantity or procedure	Relative standard uncertainty (%)
Step 1: Standards laboratory[b]	
$N_{D,w}$ calibration of secondary standard at PSDL	0.5
Long term stability of secondary standard	0.1
$N_{D,w}$ calibration of the user dosimeter at the standard laboratory	0.4
Combined uncertainty of step 1	*0.6*
Step 2: User high energy photon beam	
Long term stability of user dosimeter	0.3
Establishment of reference conditions	0.4
Dosimeter reading M_Q relative to beam monitor	0.6
Correction for influence quantities k_i	0.4
Beam quality correction k_Q (calculated values)	1.0[c]
Combined uncertainty of step 2	*1.4*
Combined standard uncertainty of $D_{w,Q}$ (steps 1 + 2)	**1.5**

[a] See the ISO Guide for the expression of uncertainty [32], or Appendix IV. The estimates given in the table should be considered typical values; these may vary depending on the uncertainty quoted by standards laboratories for calibration factors and on the experimental uncertainty at the user's institution.

[b] If the calibration of the user dosimeter is performed at a PSDL, then the combined standard uncertainty in step 1 is lower. The combined standard uncertainty in D_w should be adjusted accordingly.

[c] If k_Q is measured at a PSDL for the user chamber, this uncertainty is approximately of the order of 0.7%.

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Reference Dosimetry

for high energy, external beam photon beam therapy

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Only 3 methods for are suited for absolute dose measurement in a primary standard in a standard laboratory:

- calorimetry
- ionization dosimetry
- chemical dosimetry (Fricke)

Calorimetric standard

- core material: graphite or water
- principle:
  - $D_{c,Co} = E/m$, E=energy deposited in core, m= mass core
  - $E \propto \Delta T_{core}$ (E almost fully converted into heat)
    - ➔ $D_{c,Co} = k \cdot \Delta T_{core}$
- ΔT_{core} is measured with thermistor

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Calorimetric standard

- $D_{c,Co} = k \cdot \Delta T_{core}$

  core = water ➔

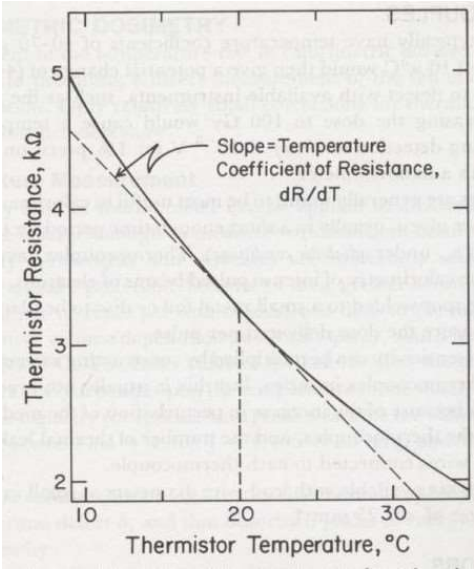
- $D_{w,Co} = c_w \cdot \Delta T_{water} \cdot 1/(1-h) \cdot \Pi c_i$

  - c_w= specific heat capacity of water = 4181 $Jkg^{-1}{}^{o}C^{-1}$ (1 cal $kg^{-1}{}^{o}C^{-1}$)
  - h = thermal defect: part of absorbed energy not leading to ΔT_{water} (chemical reactions, heat leakage, ..)
  - Πc_i = other "technical" factors derived from measurements or calculations

thermistor: $\Delta R/R \approx 3.7\%$ / ºC

$\Delta T_{water} \approx 0.00024$ ºC / Gy

thermistor: $\Delta R/R = 0.0009\%$ / Gy



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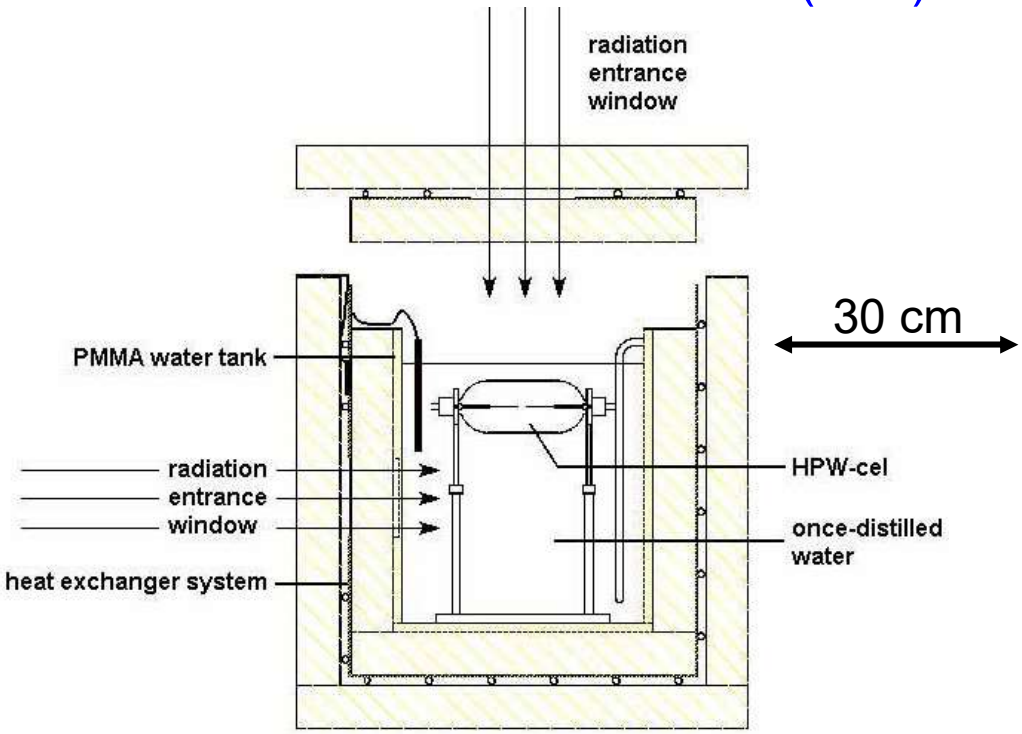
Calorimetric standard

water calorimeter in dutch PSDL (NMi)



- 2 thermistors in glass vessel
- calorimeter both in horizontal and vertical beams
- apart from ^{60}Co, also applicable in linac beams

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Chemical standard (Fricke)

- dose determined by measuring chemical change in an irradiated medium
- Fricke dosimetry: dosimeter consists of Fe^{2+} in water (solution highly water equivalent)
- due to ionizing radiation $Fe^{2+} \rightarrow Fe^{3+}$
- $D = \Delta M / (\rho \cdot G(Fe^{3+}))$
  - ΔM = mole Fe^{3+}/liter
  - ρ = 1.024 kg/liter for standard Fricke solution
  - $G(Fe^{3+}) = 1.607 \cdot 10^{-6}$ mole Fe^{3+}/J, for ^{60}Co

➔ dosimetry: determine concentration of Fe^{3+} in Mole/liter

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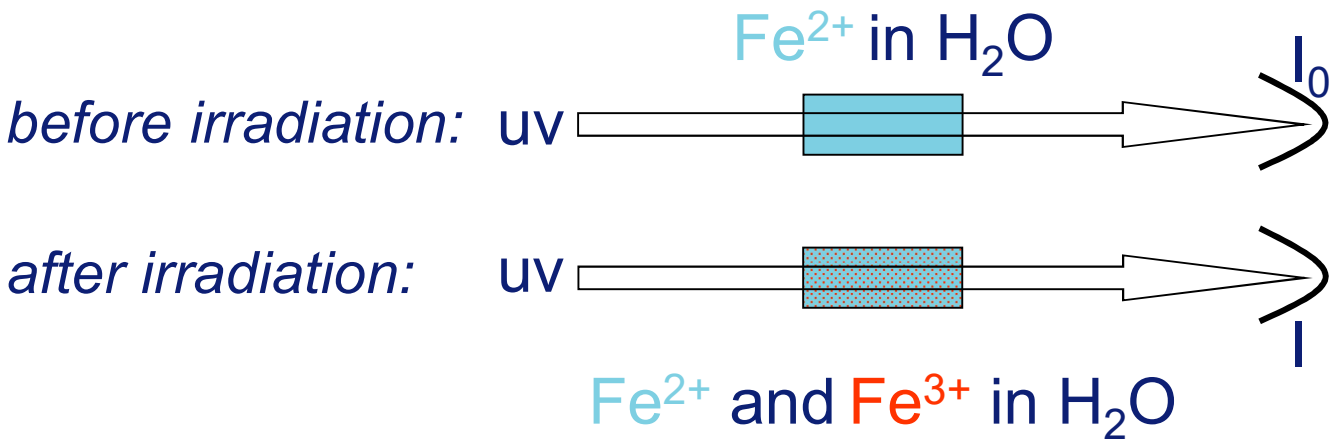
Chemical standard (Fricke)

Determine ΔM = mole Fe^{3+}/liter

- Fe^{3+} strong absorption peak at λ = 304 nm, Fe^{2+} not

- measure UV transmissions through Fricke samples:



$$\Delta M = \frac{\log(I_0/I)}{\varepsilon \cdot L} \qquad \varepsilon = 2187 \text{ liter mole}^{-1} \text{ cm}^{-1}$$

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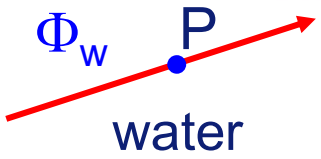
Intermezzo to introduce ionometric standards (I)

Dose in a point P in water:

$D_w = \Phi_w \cdot (S/\rho)_{c,w}$



Φ_w = secondary electron fluence [electrons / m^2]

$S_{c,w}$ = restricted collision stopping power
= dE/dx, energy loss electrons per meter travelled (excl.δ-rays, and brehmstrahlung)

- known as function of electron energy, medium (calculations, measurements)

ρ_w = density of water [kg/m^3]

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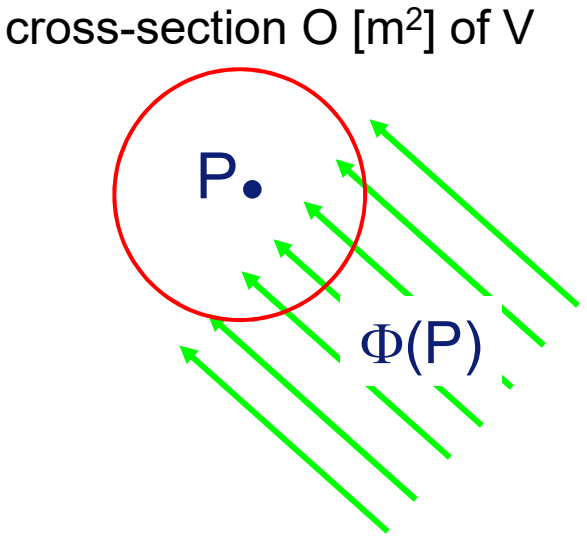
Intermezzo to introduce ionometric standards (II)

$$D(P) = \frac{\#\,\text{electrons passing V} \times \text{mean energy loss in V per passing electron}}{\text{mass of medium in V}}$$

Consider parallel beam from certain direction
(without loss of generality)



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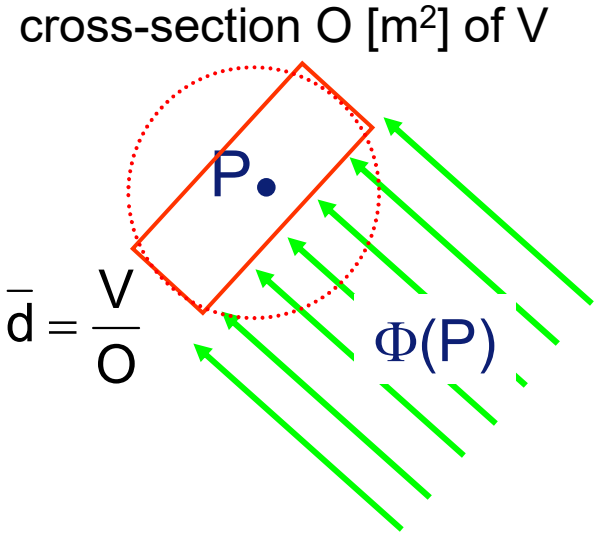
Intermezzo to introduce ionometric standards (III)

$$D(P) = \frac{\#\,\text{electrons passing V} \times \text{mean energy loss in V per passing electron}}{\text{mass of medium in V}}$$

Consider parallel beam from certain direction
(without loss of generality)

$$D(P) = \frac{\Phi(P) \cdot \cancel{O} \times \frac{dE_c}{dx} \cdot \cancel{\bar{d}}}{\rho \cdot \cancel{V}}$$

$$D(P) = \frac{\Phi(P)\frac{dE_c}{dx}}{\rho} = \Phi(P) \cdot (S/\rho)_c$$



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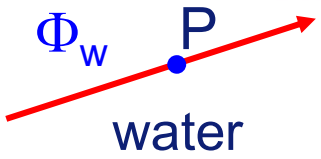
Ionometric standard

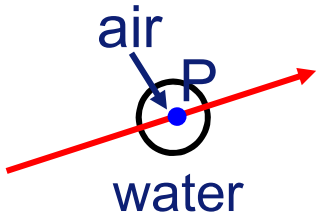
Dose in a point P in water:

$D_w = \Phi_w \cdot (S/\rho)_{c,w}$



measurement in water with air-filled i.c.

$D_{air} = \Phi_{air} \cdot (S/\rho)_{c,air}$



Bragg-Gray cavity theory: $\Phi_{air} = \Phi_w$

valid if:

- dimensions of *air* are small enough to not disturb charged particle fluence Φ_w
- charged particles are only generated in w

$D_w = D_{air} \cdot (S/\rho)_{c,w} / (S/\rho)_{c,air}$

$$D_w = D_{air} \cdot s_{w,air}$$

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Ionometric standard

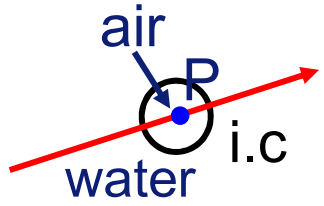
standard dosimetry: dose measurement with i.c. in ^{60}Co:

$D_{w,Co} = D_{air,Co} \cdot (s_{w,air})_{Co}$

$D_{air,Co} = E_{air,Co}/m$, $E_{air,Co}$ is energy deposited in air by electrons

$D_{air,Co} = (Q \cdot W_{air,Co})/m$

- Q = charge formed in air cavity (measured with electrometer)
- $W_{air,Co}$ = average energy expended in air per coulomb
- m = mass of air in cavity



$D_{w,Co} = ((Q \cdot W_{air,Co})/m) \cdot (s_{w,air})_{Co}$

TRS398:

- $W_{air,Co}$ = 33.97 J/C
- $(s_{w,air})_{Co}$ = 1.134

Refinements needed e.g. to correct for deviations Bragg-Gray (in TRS398)

used in standard laboratory to assess dose with their ionometric standard:

$D_{w,Co} = ((Q \cdot W_{air,Co})/m) \cdot (s_{w,air})_{Co} \cdot \Pi f_i$

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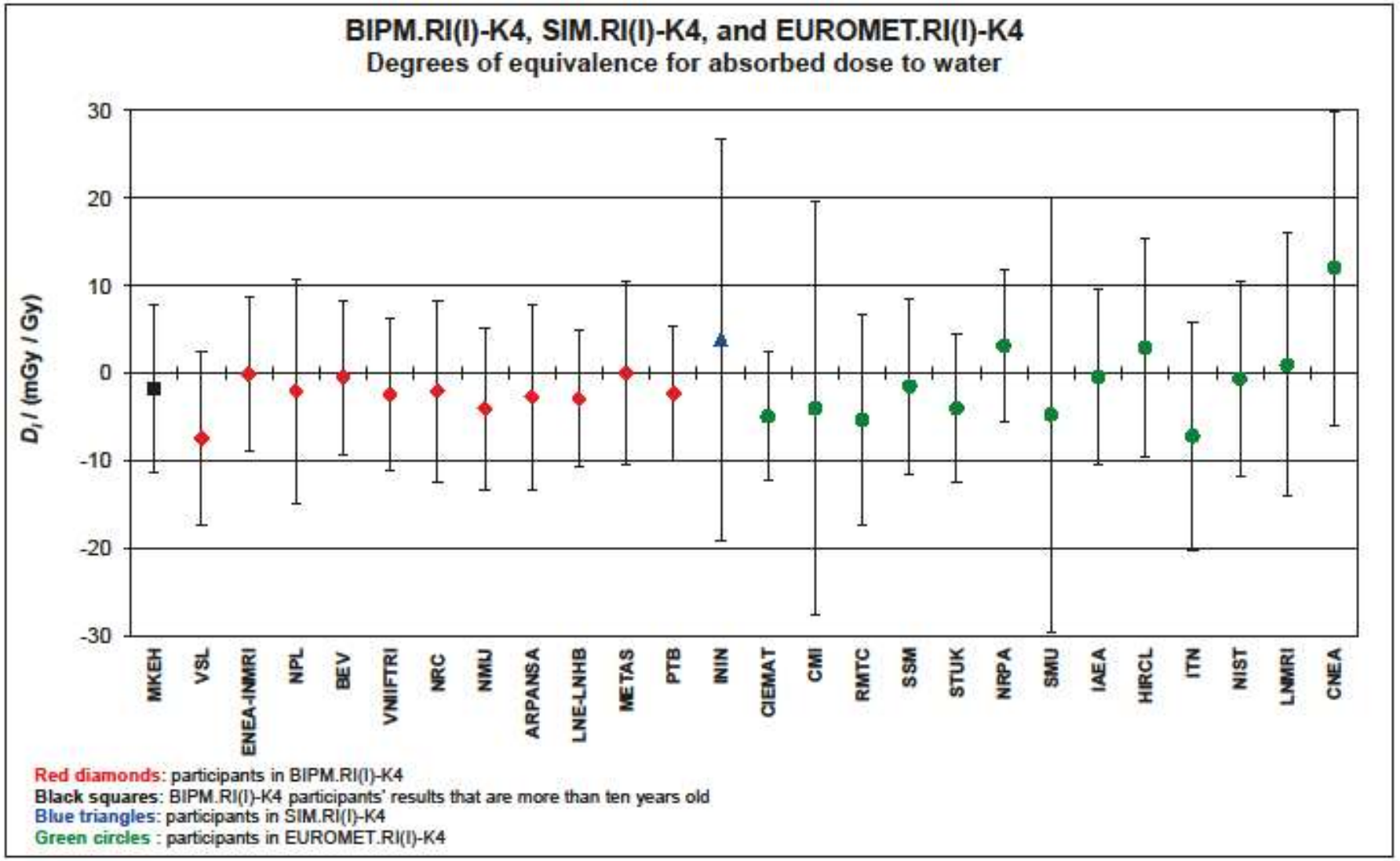
Comparison of standards

TABLE 2. PRIMARY STANDARDS USED IN THE COMPARISONS OF ABSORBED DOSE TO WATER AT THE BIPM

PSDL	Primary standard	PSDL	Primary standard
BIPM	Ionization chamber	NIST (USA)	Sealed water calorimeter
ARPANSA (Australia)	Graphite calorimeter	NPL (UK)	Graphite calorimeter
BEV (Austria)	Graphite calorimeter	NRC (Canada)	Sealed water calorimeter
ENEA (Italy)	Graphite calorimeter	PTB (Germany)	Fricke dosimeter
LPRI (France)	Graphite calorimeter		

BIPM: Bureau International des Poids et Mesures (Paris)

Comparison of standards



Further reading:

- Absorbed Dose Determination in External Beam Radiotherapy – An International Code of Practice for Dosimetry Based on Standards of Absorbed Dose to Water IAEA, technical report series No. 398, Vienna, 2000 (free download IAEA website)
- Code of Practice for the Absorbed Dose Determination in High energy Photon and Electron Beams, Report 18 of the Netherlands Commission on Radiation Dosimetry, 2008 (free download; http://www.ncs-dos.org/)
- Radiation Oncology Physics: A Handbook for Teachers and Students, editor E.B. Podgorsak, IAEA (free download IAEA website)
- Introduction to radiological physics and radiation dosimetry, Frank H. Attix, ISBN 0471011460
- Dosimetric precision requirements in radiation therapy, A. Brahme, Acta Radiol Oncol.1984; 23(5): 379-91.
- ICRU Report 24, Determination of Absorbed Dose in a Patient Irradiated by Beams of X or Gamma Rays in Radiotherapy Procedures, 1976
- ICRU Report 60: Key data for ionizing-radiation dosimetry: measurement standards and applications

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Basic Dose Calculation Principles

Dr Vibeke Nordmark Hansen
and and
Dr Tom Depuydt
with slides from Dr Rune Dag Olson

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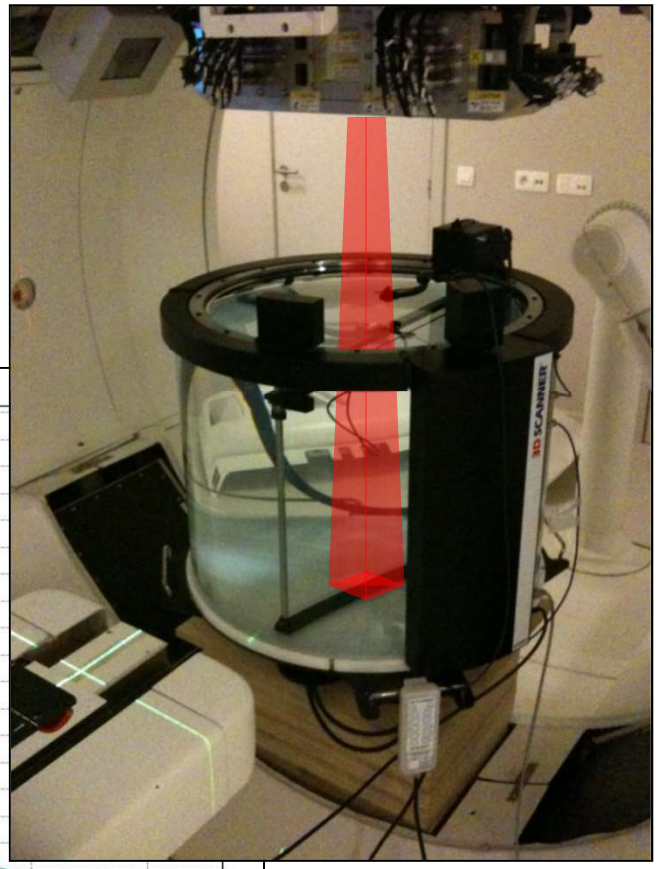
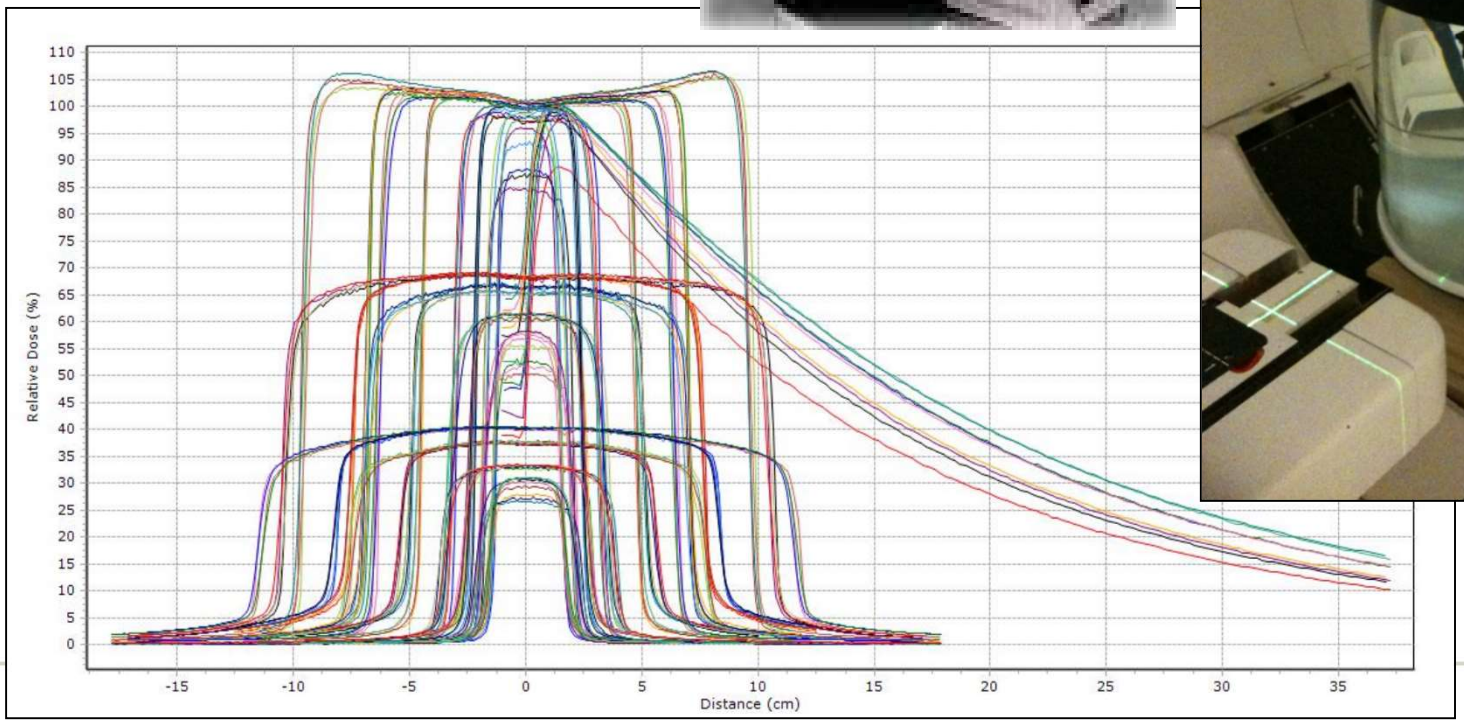
Basic dose calculations

- **Using dose measurements from water tanks and translate it to dose delivered to a patient.**

Basic Dose Calculation Principles

Linac 6MV beam data, measured





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Basic dose measurements

- Percentage Depth Dose (PDD)
- Profile data (Off axis)
- Output factors

All above are relative measurements

Absolute Calibration

Reference condition:

(this can differ from institute to institute)

- 10*10 cm field at Isocentre
- 100cm SSD delivers
- 1 Gy (100cGy) per 100 MU at d_{max}

Other reference conditions:

- 10*10 cm field at isocentre
- 100cm- d_{max} SSD delivers
- 1Gy per 100 MU at d_{max}

- 10*10 cm field at isocentre
- 90cm SSD delivers
- 1Gy per 100 MU at d_{10cm}

NOTE:

1 MU at your centre

may not be the same dose as

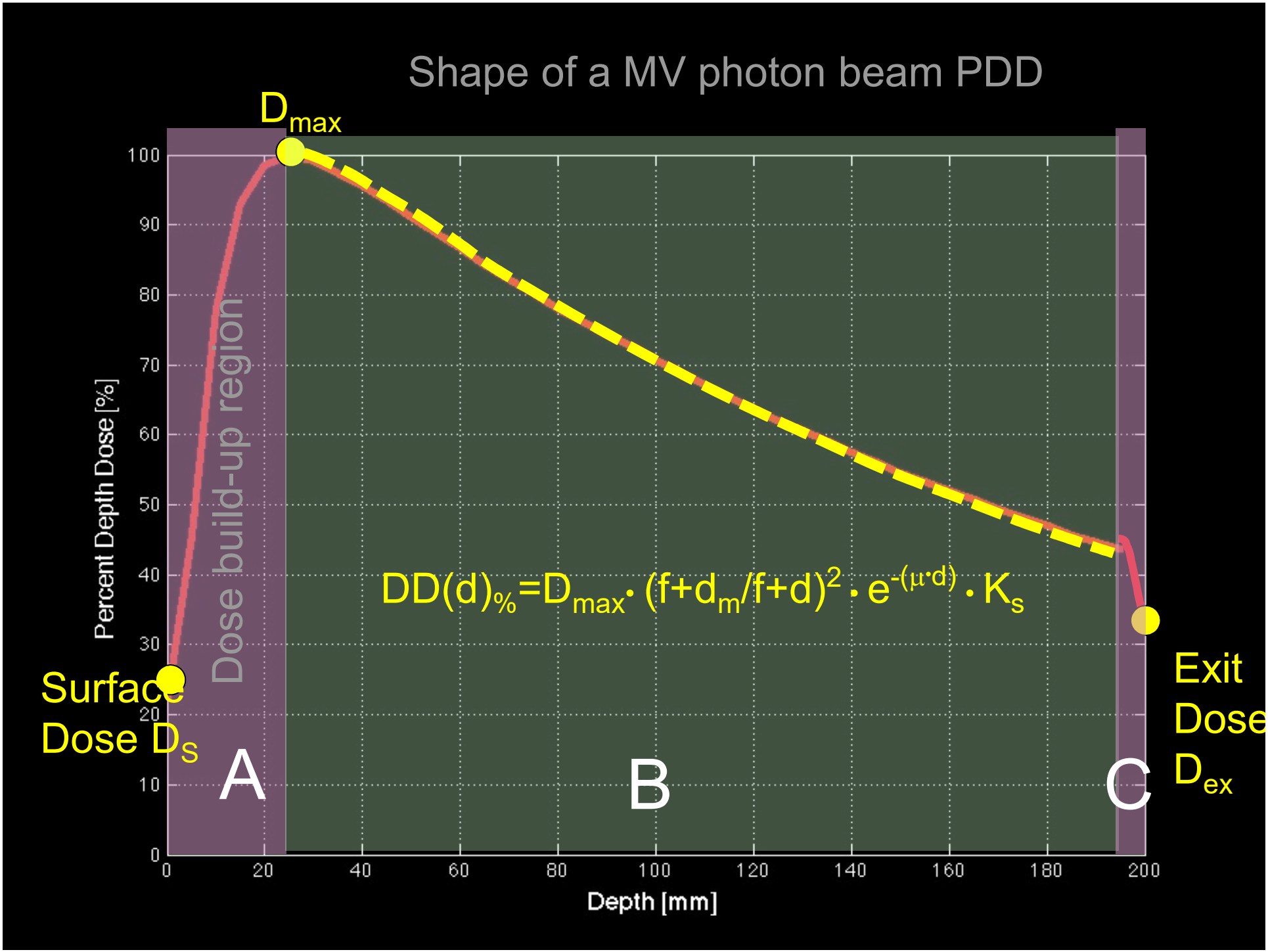
1 MU at “my” centre.

BUT:

1 Gy at your centre

is calibrated to give the same dose as

1Gy at “my” centre!


Shape of a MV photon beam PDD
D_{max}
Dose build-up region
Percent Depth Dose [%]
Depth [mm]
$DD(d)_{\%}=D_{max}\cdot(f+d_m/f+d)^2\cdot e^{-(\mu\cdot d)}\cdot K_s$
Surface Dose D_s
Exit Dose D_{ex}
A
B
C
0
10
20
30
40
50
60
70
80
90
100
0
20
40
60
80
100
120
140
160
180
200

Basic Dose Calculation Principles

Simplified depth dose formalism, beoynd d_m

$$DD(d)_{\%} = D_{max} \cdot (f+d_m/f+d)^2 \cdot e^{-(\mu \cdot d)} \cdot K_s$$

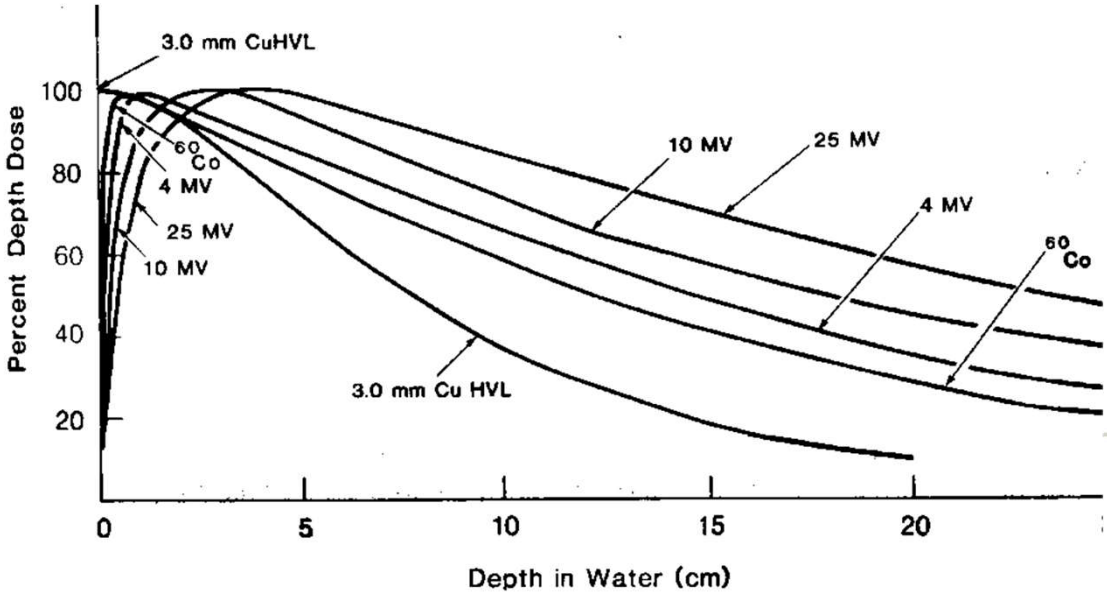
distance attenuation scatter

f distance from source to surface

$\mathbf{d_m}$ or depth to $\mathbf{D_{max}}$

d is depth in tissue

$\mathbf{K_s}$ is the scatter



Basic Dose Calculation Principles

Simplified depth dose formalism

$$DD(d)_{\%} = D_{max} \cdot \left(\frac{f+d_m}{f+d}\right)^2 \cdot e^{-(\mu \cdot d)} \cdot K_s$$

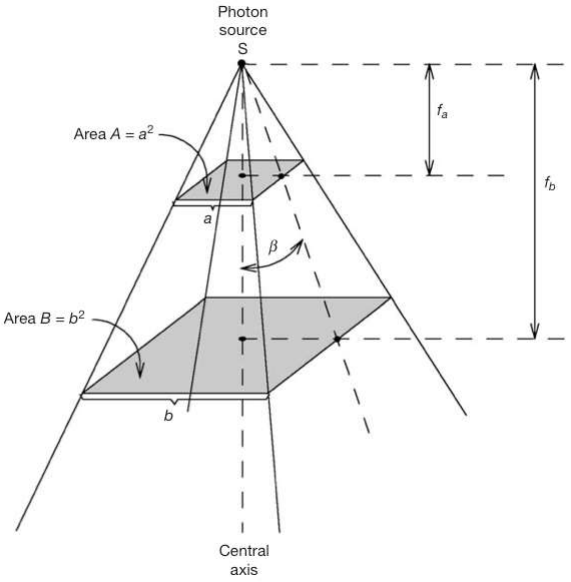
distance

f distance from source to surface

$\mathbf{d_m}$ or depth to $\mathbf{D_{max}}$

d is depth in tissue

$\mathbf{K_s}$ is the scatter



Total fluence at A is same as at B:

$$A\phi_A = B\phi_B$$

$$\frac{\phi_A}{\phi_B} = \frac{B}{A} = \frac{b^2}{a^2} = \frac{f_b^2}{f_a^2}$$

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Basic Dose Calculation Principles

Simplified depth dose formalism

$$DD(d)_{\%} = D_{max} \cdot (f + d_m / f + d)^2 \cdot e^{-(\mu \cdot d)} \cdot K_s$$

attenuation

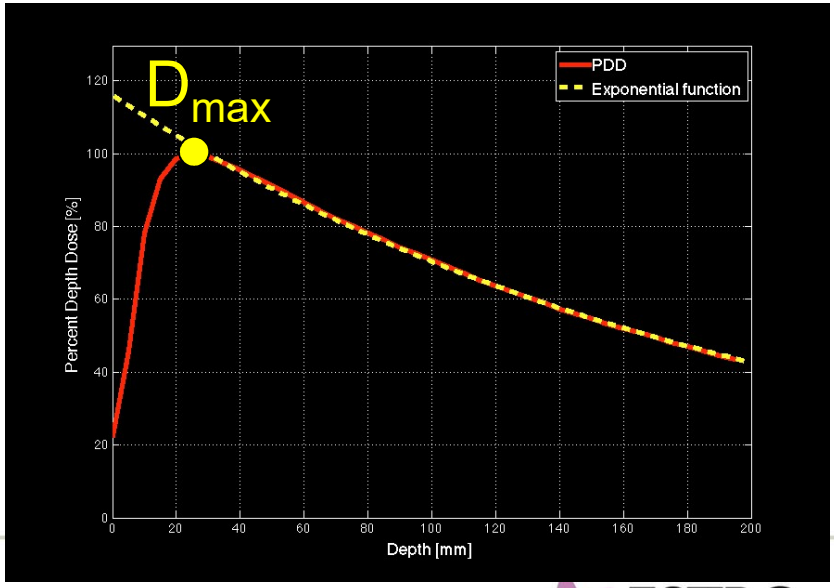
f distance from source to surface

$\mathbf{d_m}$ or depth to $\mathbf{D_{max}}$

d is depth in tissue

μ is energy dependent attenuation coefficient

$\mathbf{K_s}$ is the scatter



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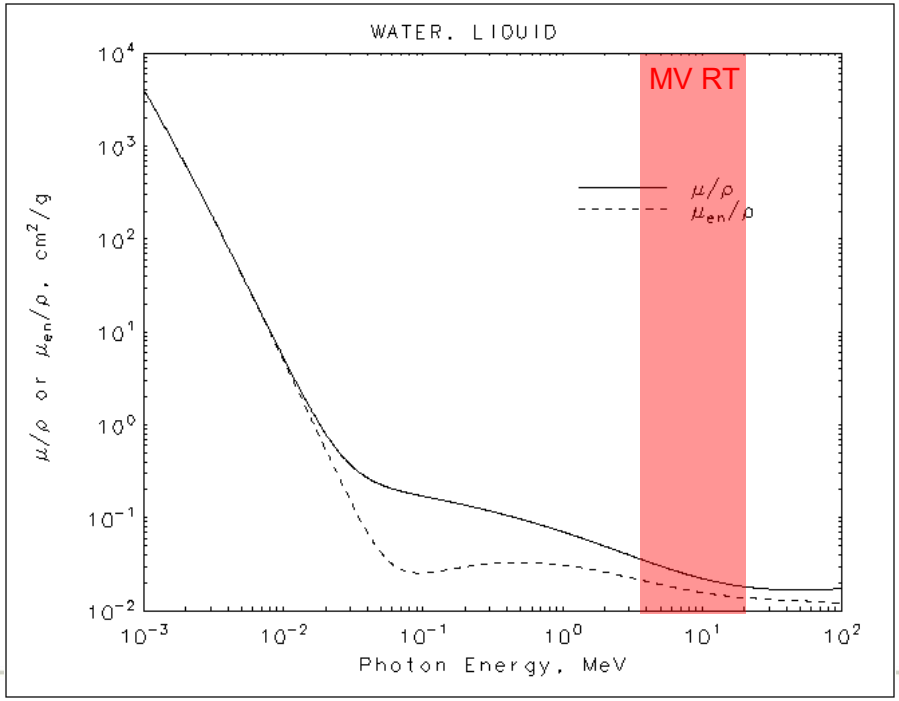
Basic Dose Calculation Principles

Simplified depth dose formalism

$$DD(d)_{\%} = D_{max} \cdot (f+d_m/f+d)^2 \cdot e^{-(\mu \cdot d)} \cdot K_s$$

attenuation



X-ray Mass Attenuation Coefficient

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Basic Dose Calculation Principles

Simplified depth dose formalism

$$DD(d)_{\%} = D_{max} \cdot (f+d_m/f+d)^2 \cdot e^{-(\mu \cdot d)} \cdot K_s$$

primary component

scatter

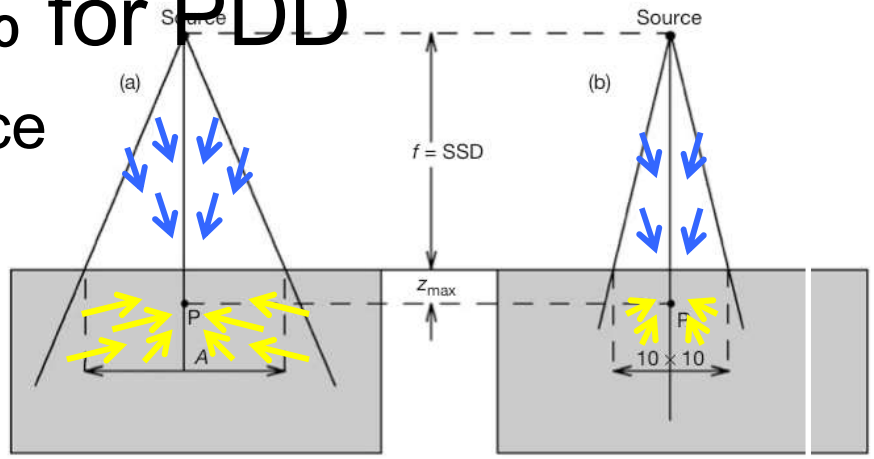
D_{max} max dose,ie 100% for PDD

f distance from source to surface

$\mathbf{d_m}$ or depth to $\mathbf{D_{max}}$

d is depth in tissue

$\mathbf{K_s}$ is the scatter



"For a given photon beam at a given SSD, the dose rate at point P depends on the field size A; the larger the field size, the larger the dose. "

IAEA Handbook Chapter 6

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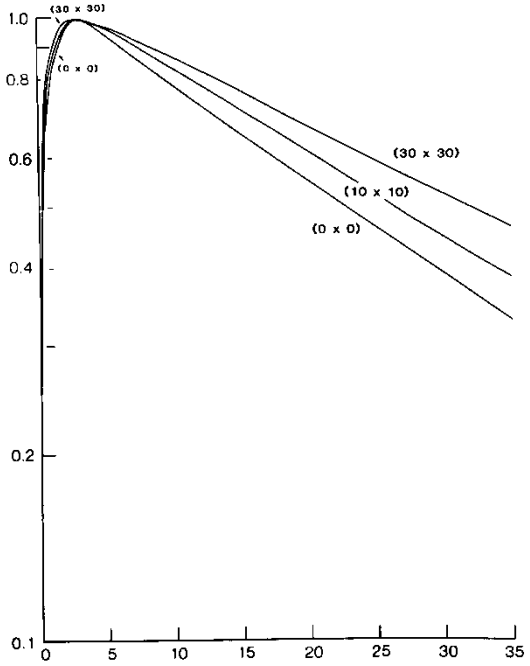
Basic Dose Calculation Principles

$$DD(d)_{\%} = D_{max} \cdot (f+d_m/f+d)^2 \cdot T(d),$$

$$T(d) = e^{-(\mu \cdot d)} \cdot K_s$$

Different approaches for omitting the distance effect

- TAR - tissue air ratio
- TMR – tissue maximume ratio
- TPR – tissue phantom ratio



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Basic Dose Calculation Principles

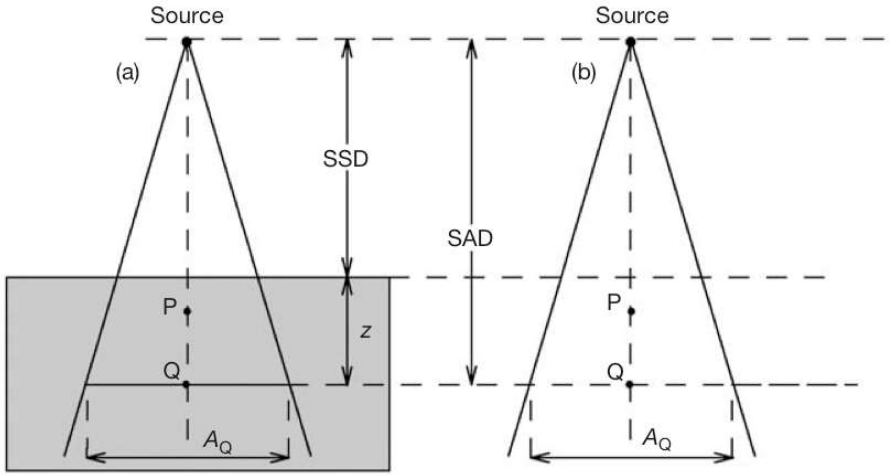
TAR and TMR/TPR measurement setup

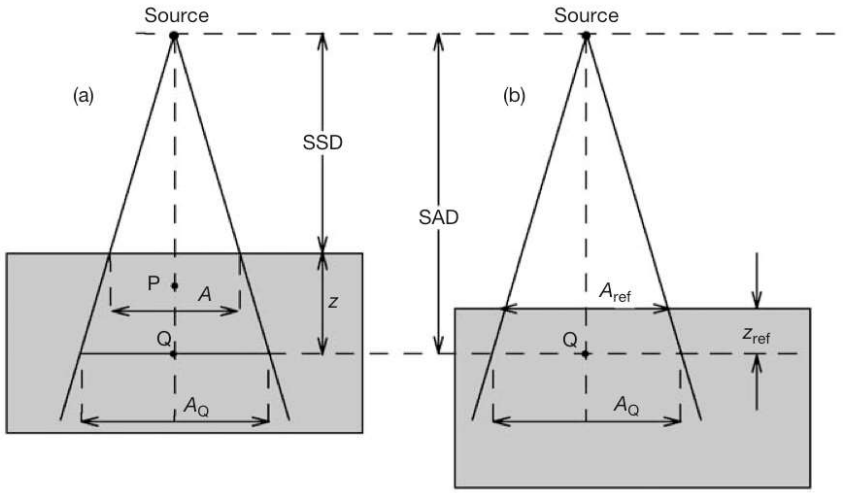
Note: Depth is z on this slide
NOT d!

$$\mathrm{TAR}(z, A_Q, h\nu) = \frac{D_Q}{D'_Q} = \frac{\dot{D}_Q}{\dot{D}'_Q}$$

$$\mathrm{TPR}(z, A_Q, h\nu) = \frac{D_Q}{D_{Qref}} = \frac{\dot{D}_Q}{\dot{D}_{Qref}}$$

$$\mathrm{TMR}(z, A_Q, h\nu) = \frac{D_Q}{D_{Qmax}} = \frac{\dot{D}_Q}{\dot{D}_{Qmax}}$$





TAR, TMR or TPR essential in isocentric treatments

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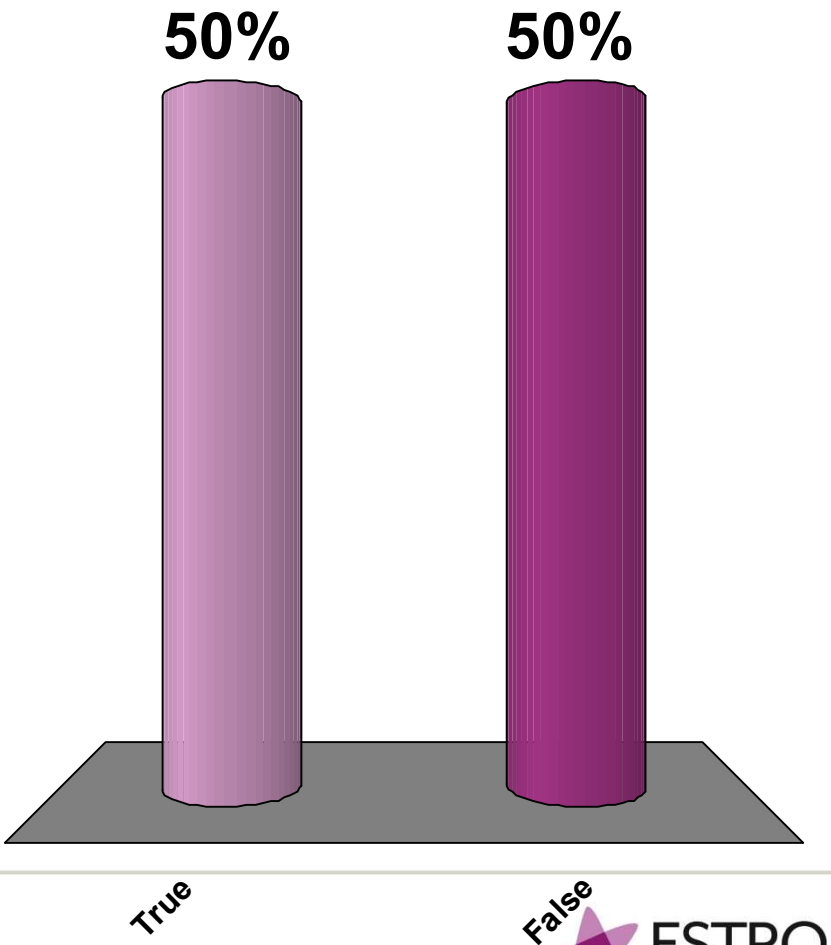
For equal number of MU : Dose increase with energy (beyond d_{max})

A. True

B. False



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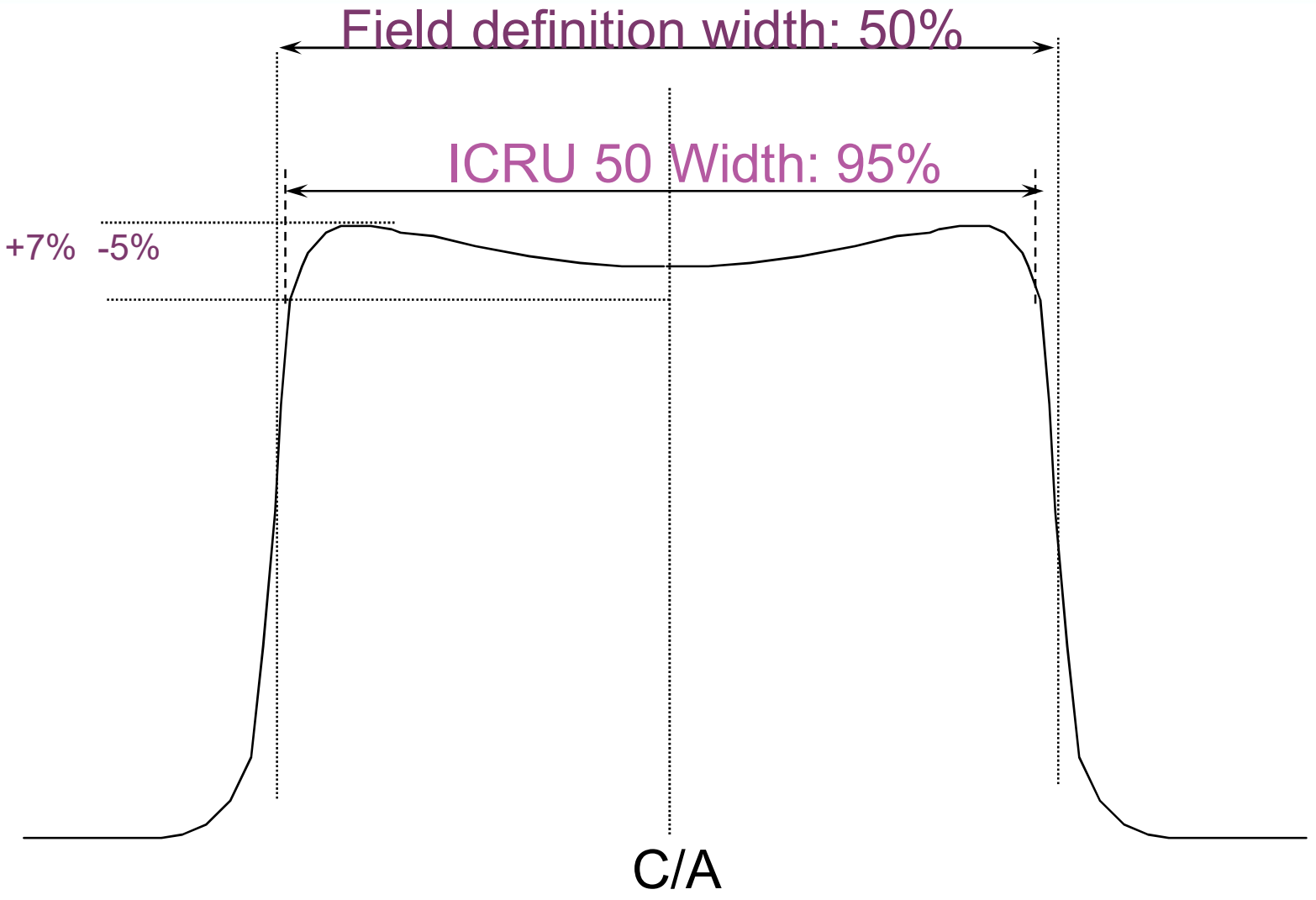
Profile data for “standard” beam with Flattening Filter



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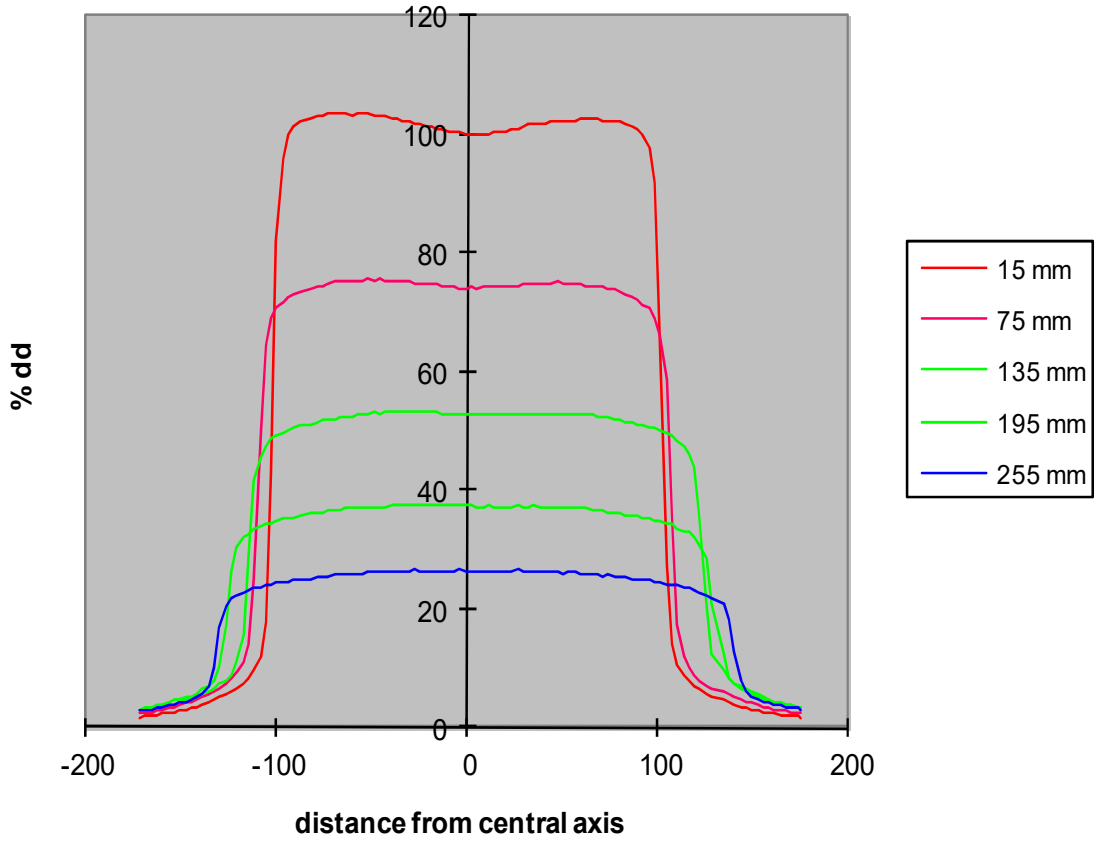
Off-axis factors
More pronounced “sholders” at Dmax than at depth.



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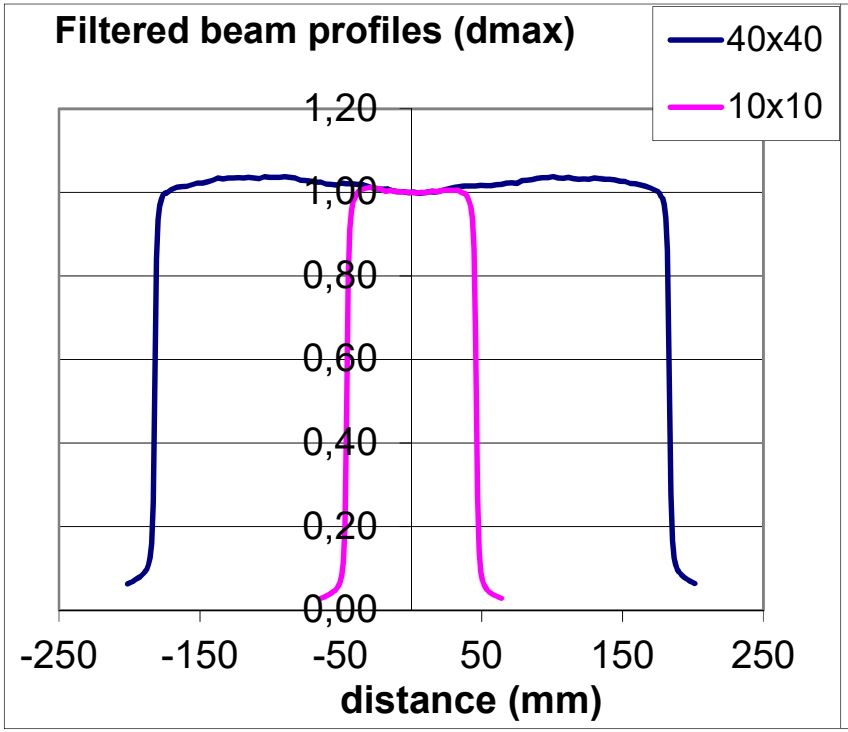
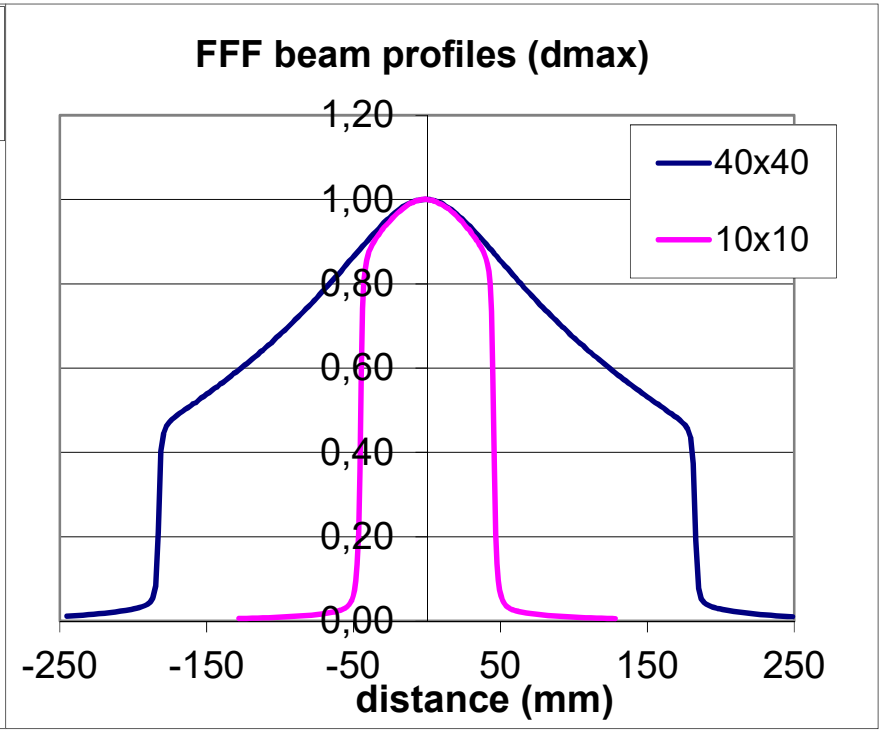
Beam profiles with and without flattening filters.

Why do we have flattening filters?





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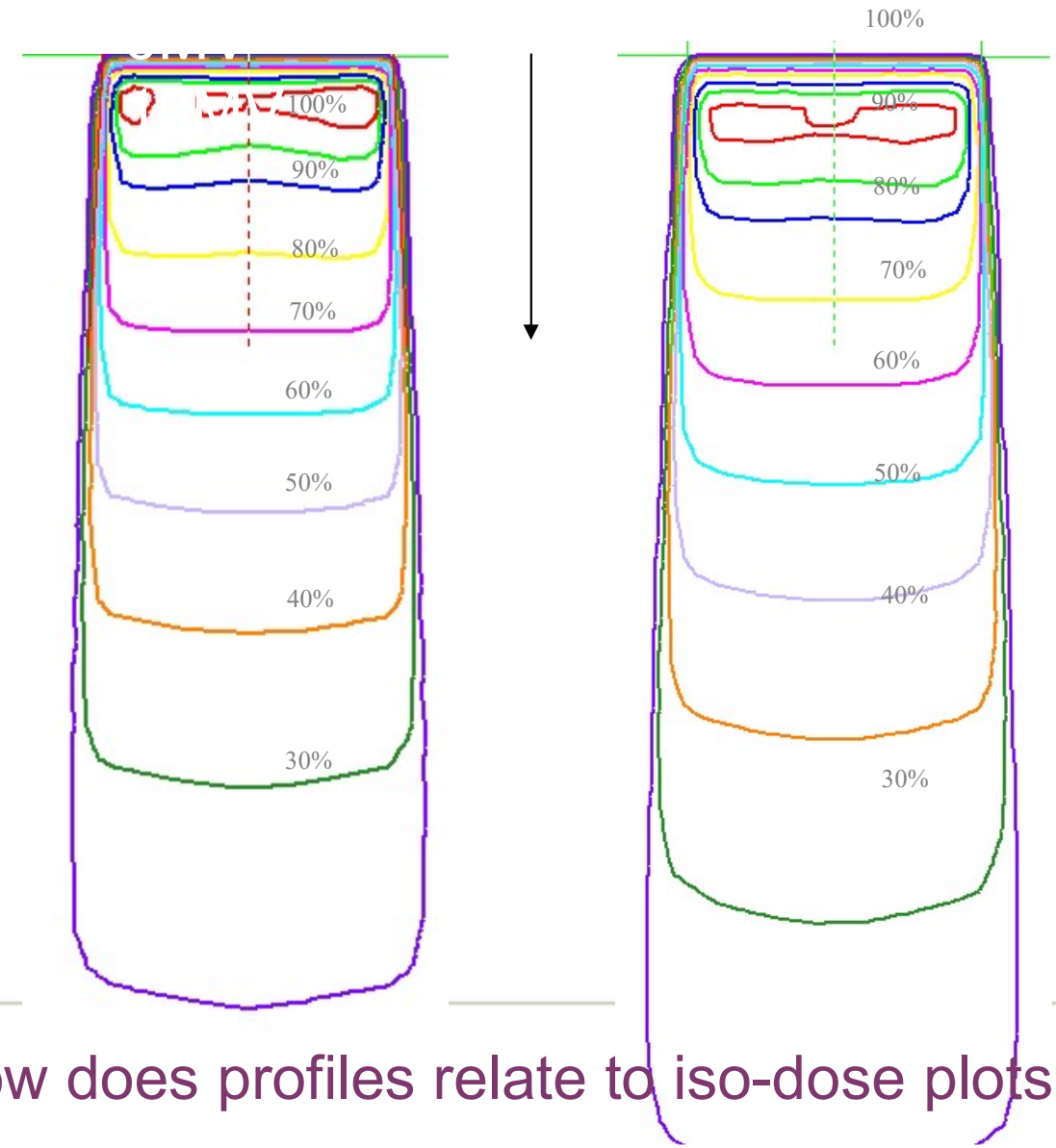
Isodose distributions in water



How does profiles relate to iso-dose plots ?

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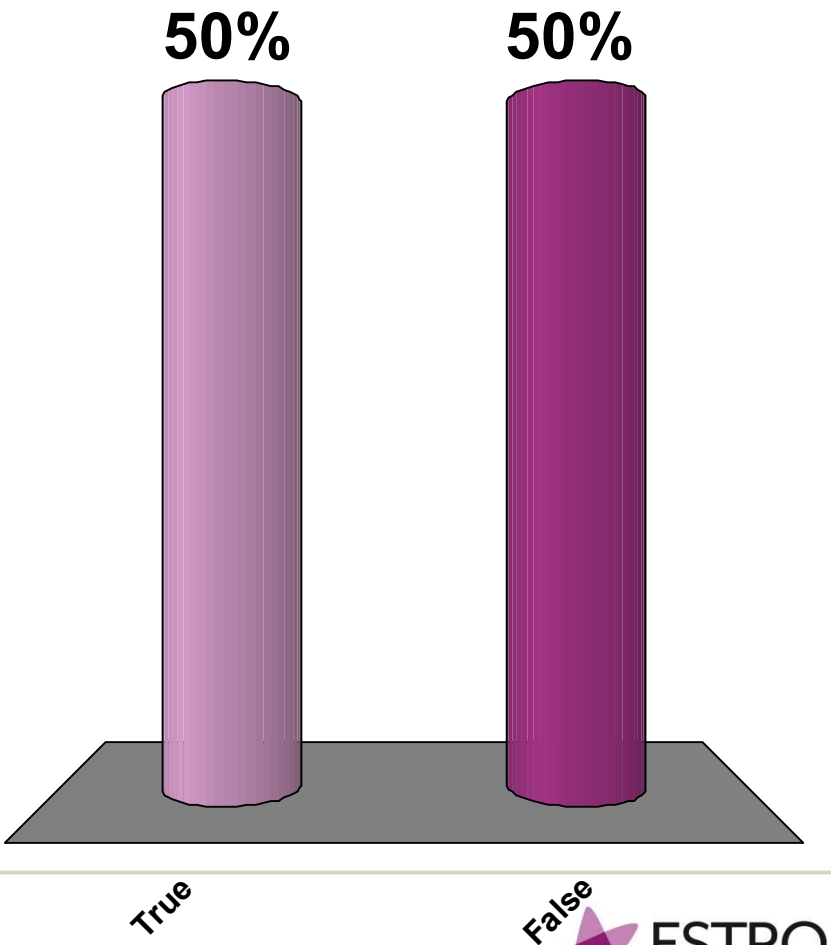
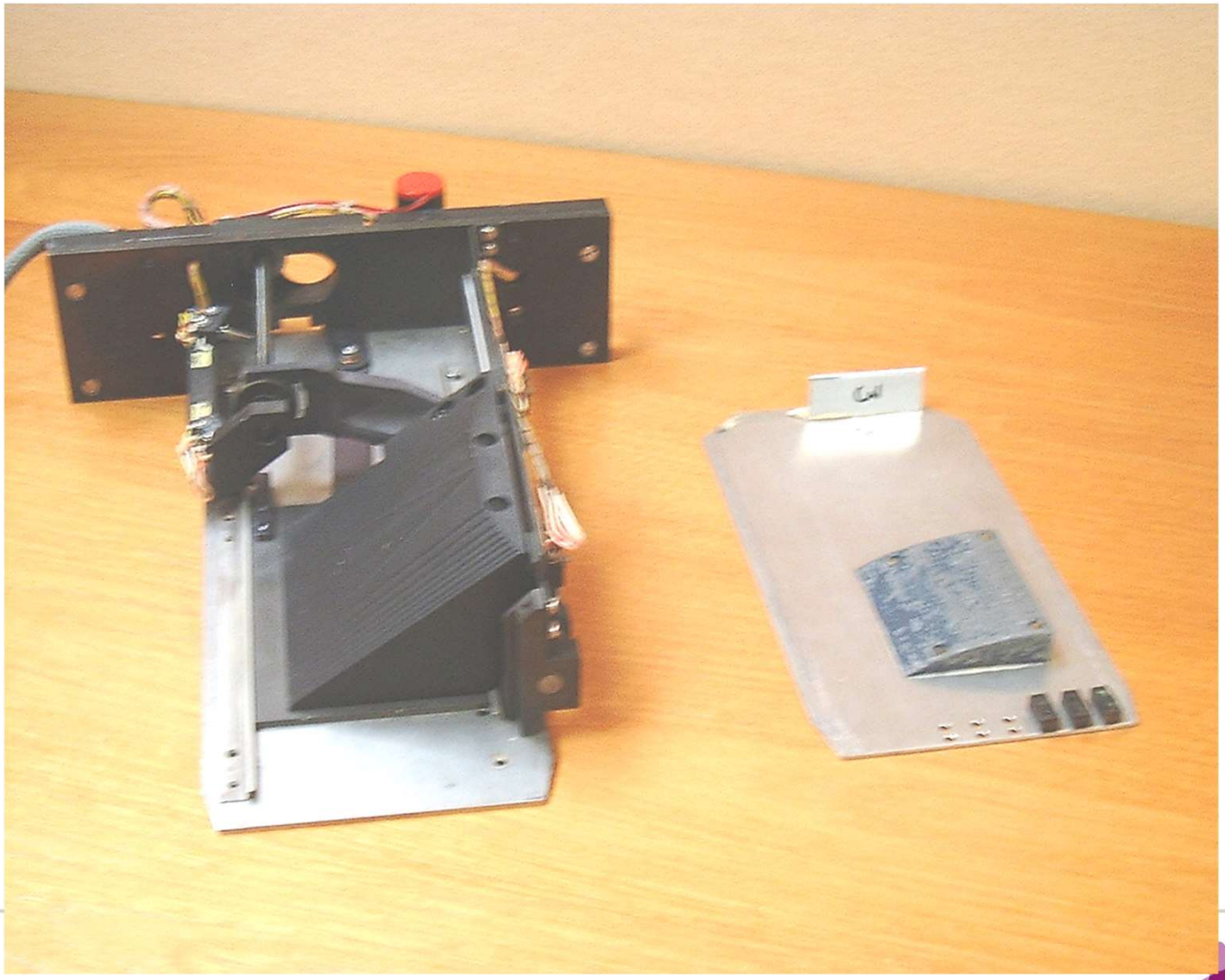
For equal number of MU : Dose increase with depth (beyond d_{max})

A. True

B. False



Elekta motor wedge and fixed wedge



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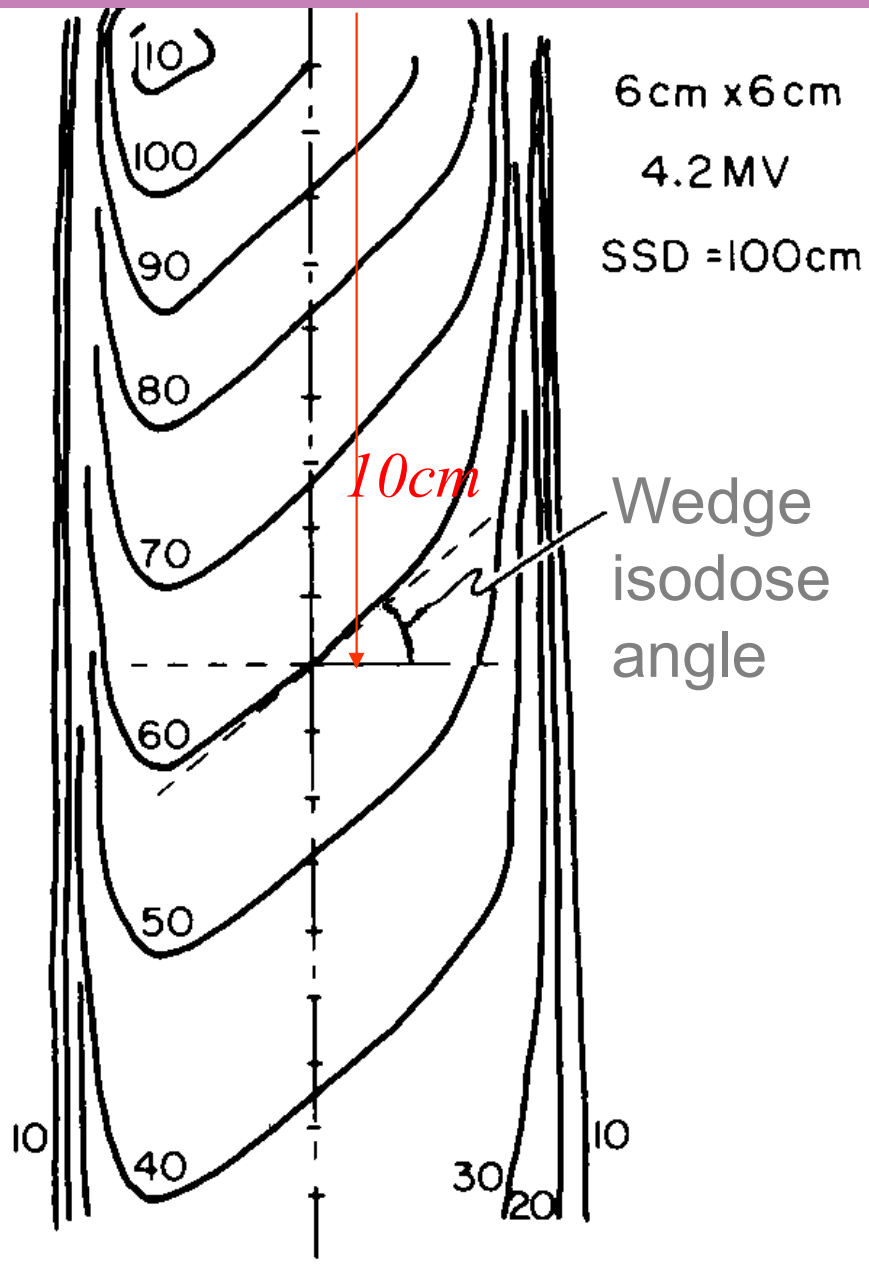

Wedged beam

isodose distribution

showing ICRU's wedge angle definition from ICRU Report no 24

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Wedges

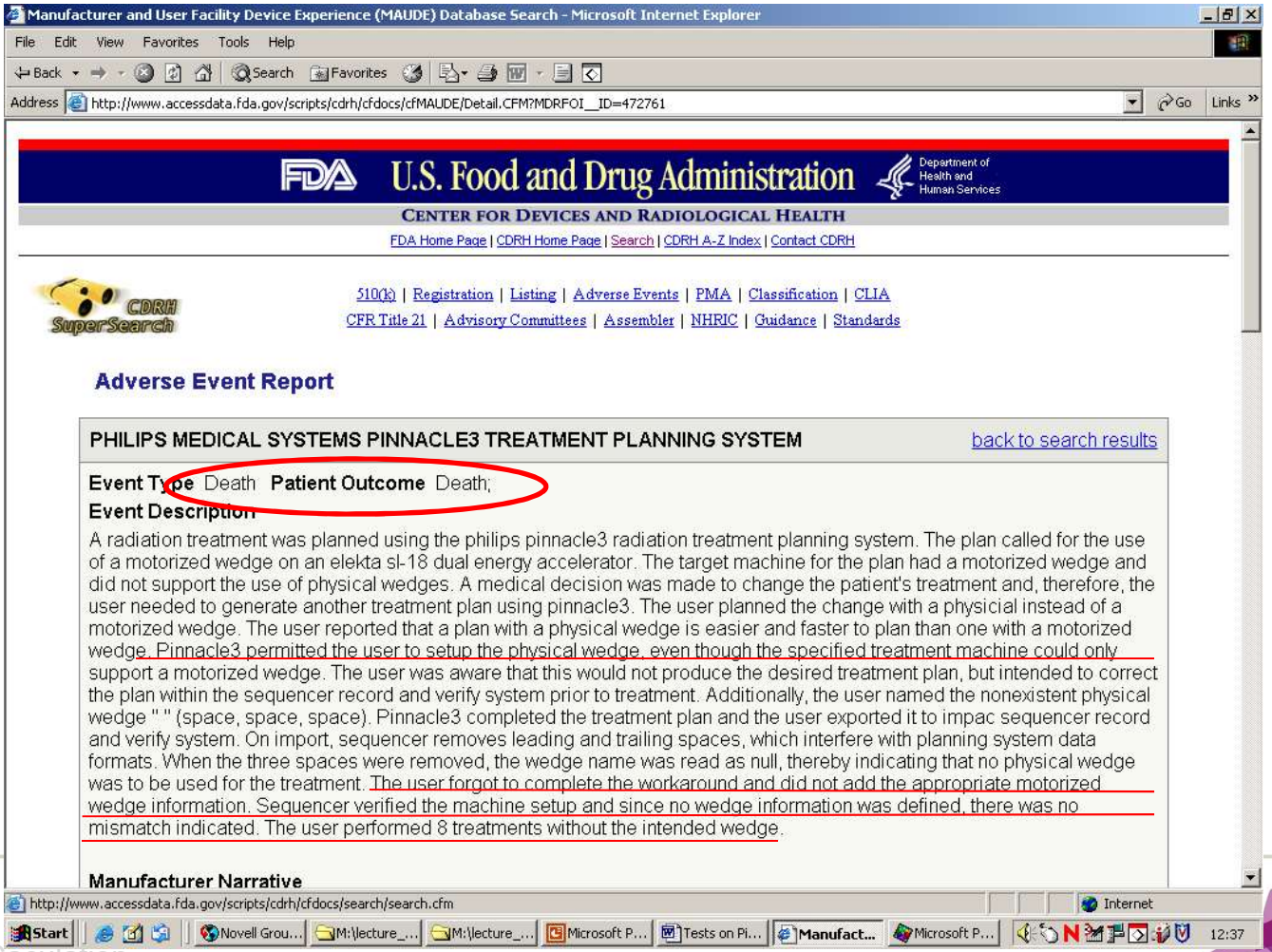
Wedge factor is energy dependent

$$WF(E) = \frac{D(d_m, cxc, SSD_{100cm}, +Wedge)}{D(d_m, cxc, SSD_{100cm}, -Wedge)}$$

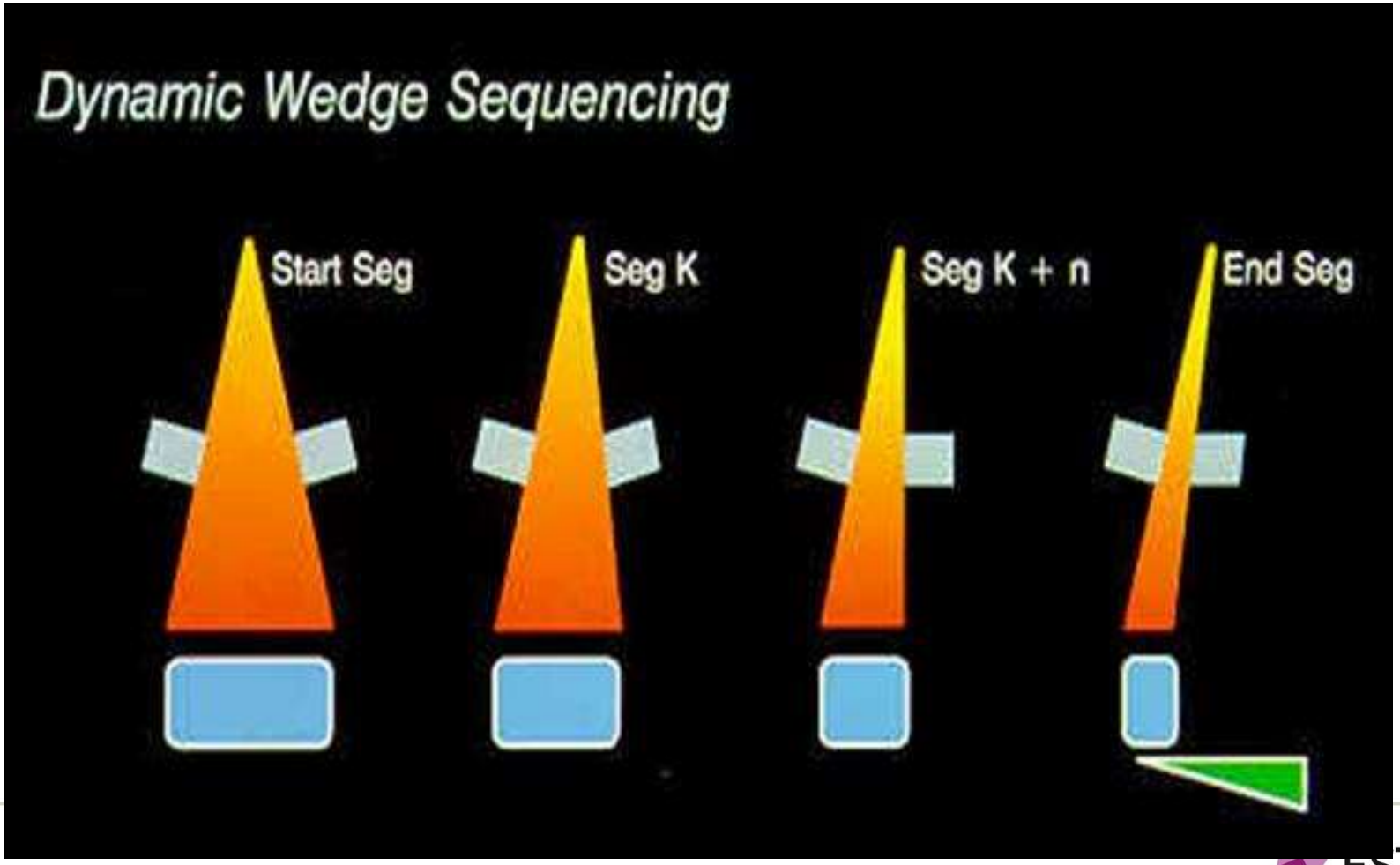
For the 60 degree Elekta wedge the wedge factor is ~0.25 for 6mv and ~0.29 for 10mv

Warning!

Incorrect use of wedge factor can lead to disaster



Wedge profile can also be created by a “dynamic wedge”



Advantages of Dynamic wedge:

Will always use fewer MU, ie shorter treatment time

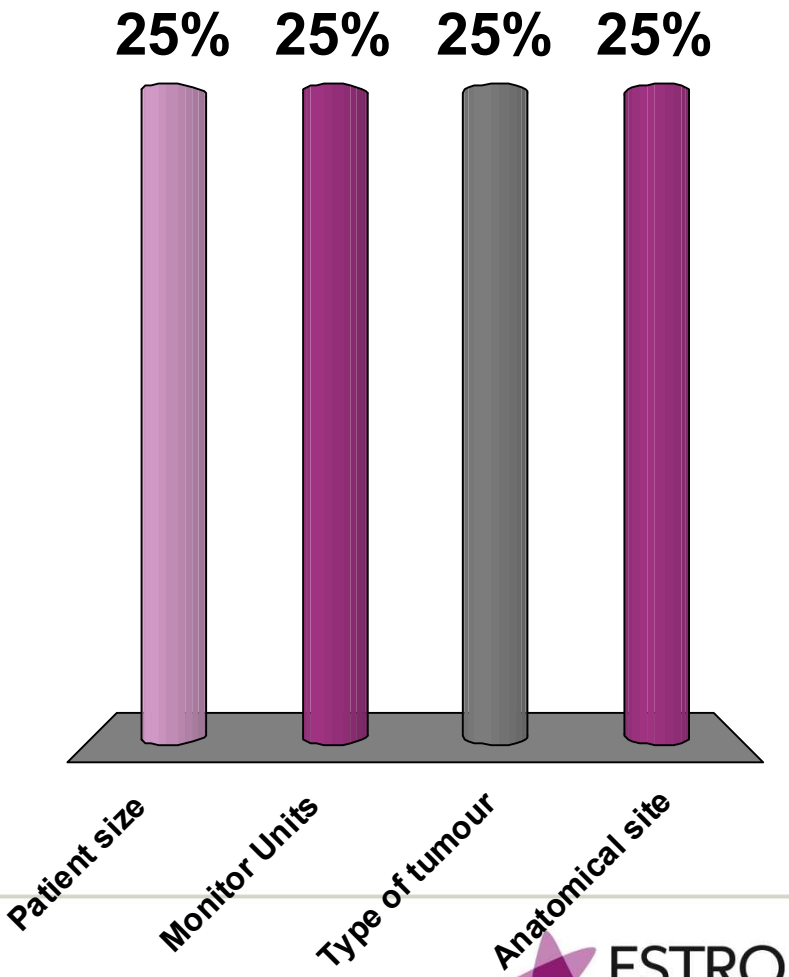
- Less leakage – ie unwanted dose

No extra scatter material in the treatment head

- Less head scatter per MU – ie less unwanted dose

What do we need to know to deliver the prescribed dose?

A. Patient size
B. Monitor Units
C. Type of tumour
D. Anatomical site



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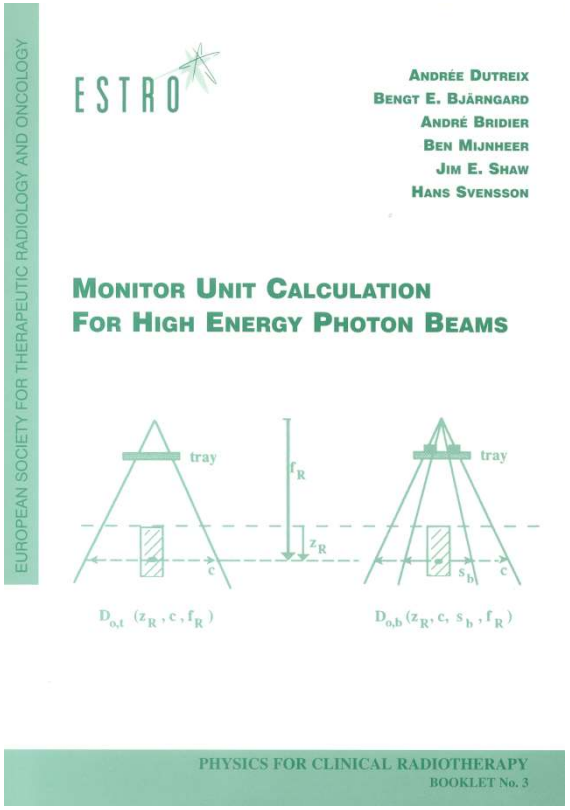
MONITOR UNIT (MU) CALCULATIONS



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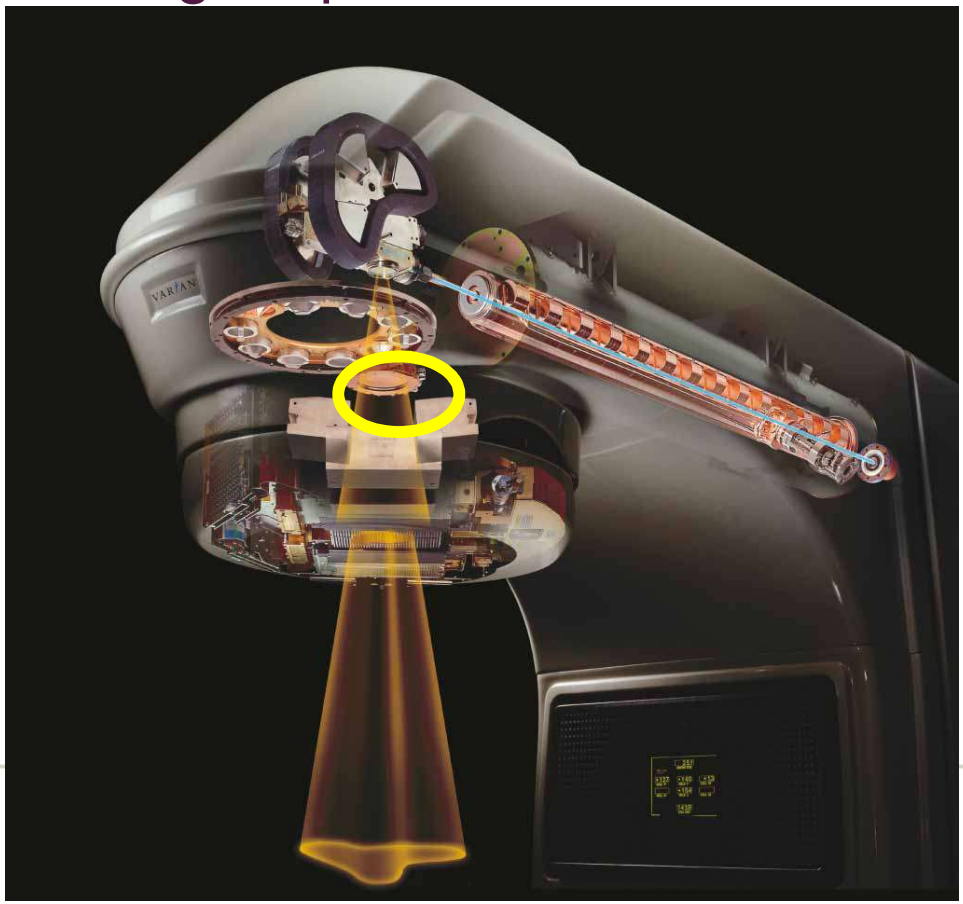
What is a monitor?

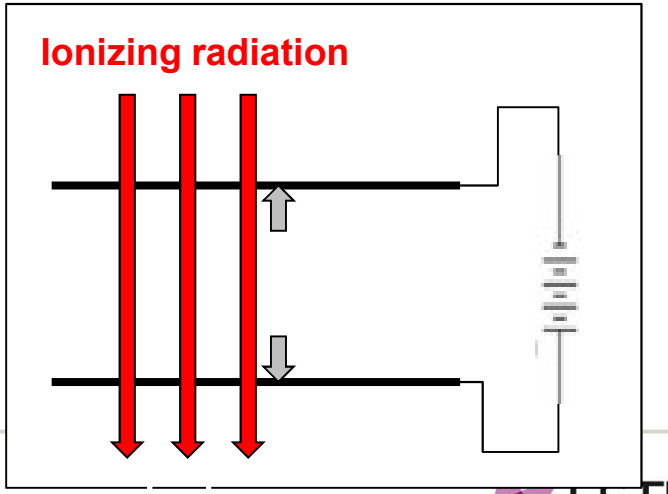
A monitor is:

-a part of a linac's beam line

-a plane parallel transmission ionization chamber

Detecting output of the linac





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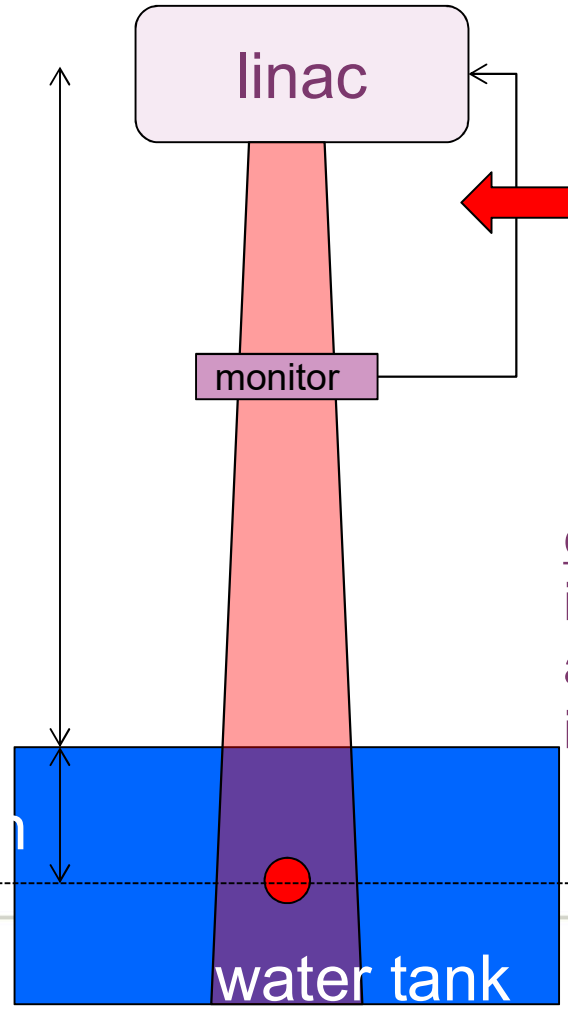
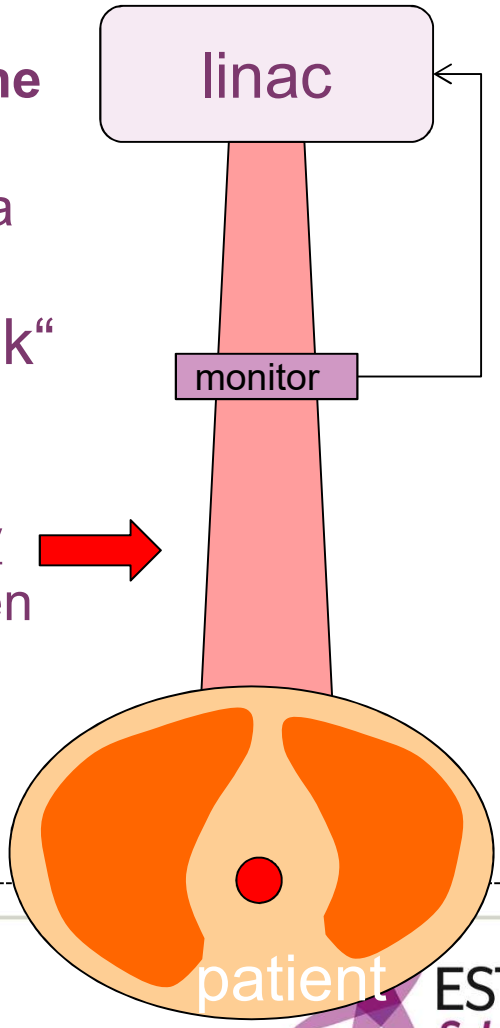
What is a monitor unit (MU)?



"**1 MU = signal of the monitor** when delivering **1 cGy** to a certain **reference point** in a water tank"

1 MU will not correspond to 1 cGy in the same point when a **different geometry** is considered"



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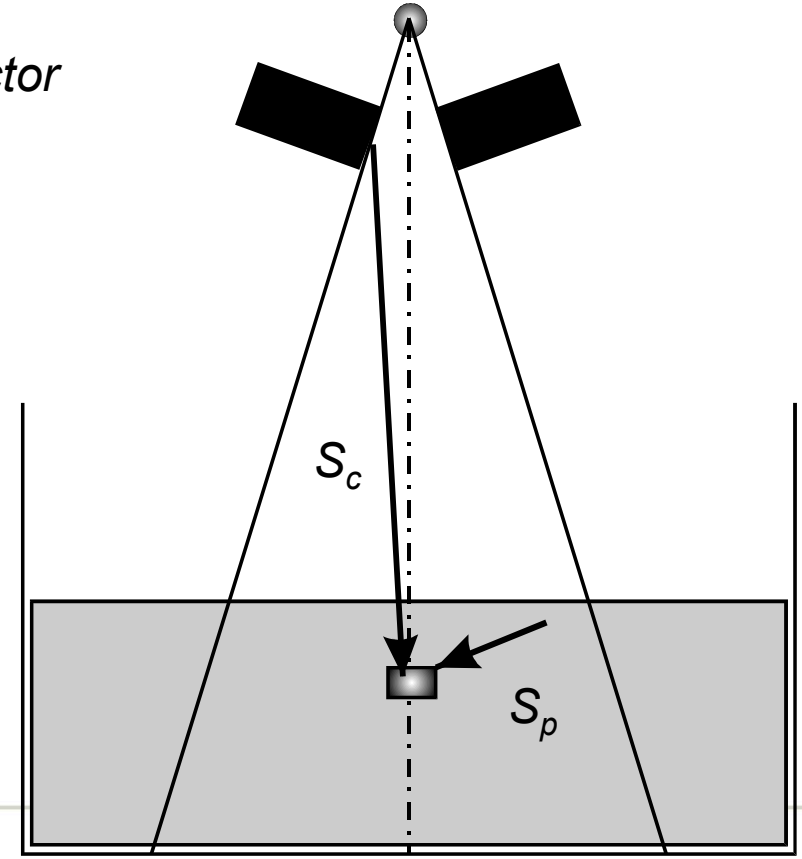
Correction for Field Size

Also called output factor (OF),
and of course depending on Field Size

Total scatter correction factor

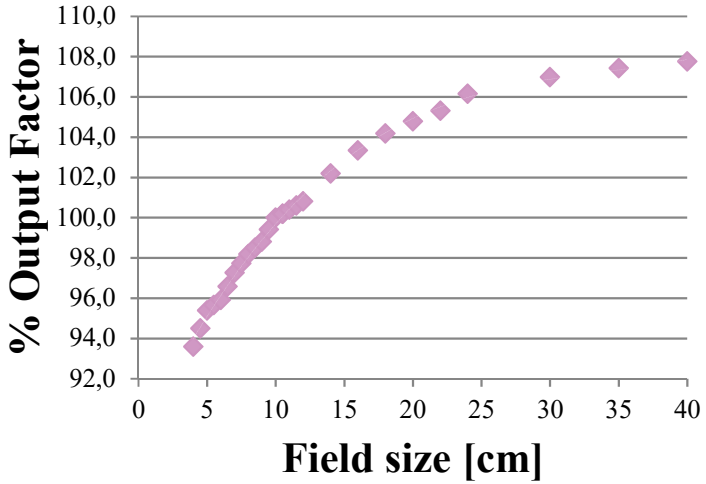
$$S_{c,p} = S_c \times S_p$$



ESTRO School

Correction for Field Size

$$OF(Fs,E) = \frac{D(d_m, F_s, SSD, E)}{D(d_m, F_{s\,ref}, SSD, E)}$$



$F_{s\,ref}$= 10*10

$$MU = \frac{Prescription\ Dose}{PDD(d,Fs,E) * Output(Fs,E)} * 100$$

"The larger the scatter contribution, less MU need to be given"

Careful: PDD and TMR also change with field size!

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When may manual calculations be required?

- Non CT Patient calculations

  (Mainly palliative patient)

- Checking of TPS calculations

- Understanding non standard conditions

Calculate dose in simple set-up

Patient is set up at standard SSD
(often 100cm, where your PDD was acquired)

$$MU = \frac{\text{Prescription dose}}{PDD(d, Fs, E) * Output(Fs, E)} * 100$$

d: Depth of calculation point

Fs : Field size

E: Energy

Example

Palliative case treating a field of 8*8 cm to 20Gy in 4#

Prescription point 5cm depth.

Patient to be treated at 100SSD

$$MU = \frac{500cGy}{84.5 *} * 100$$

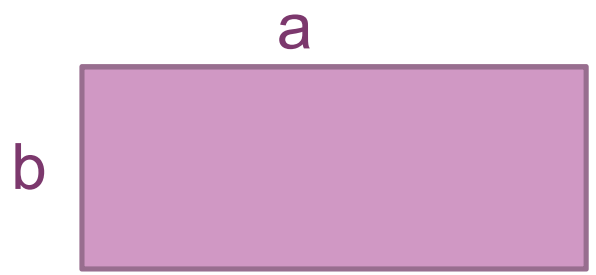
$$=591.7$$

"Willow" 6MV PDD* Output

Depth (cm)	Equivalent Square Field Size (cm)												
	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10
Dmax (1.5)	93.6	94.5	95.4	95.7	95.9	96.6	97.3	97.7	98.2	98.5	98.8	99.4	100.0
2.0	92.7	93.7	94.7	94.8	94.8	95.5	96.1	96.6	97.1	97.4	97.7	98.3	99.0
2.5	90.5	91.5	92.6	92.8	93.0	93.5	94.1	94.6	95.1	95.4	95.8	96.3	96.9
3.0	88.0	89.1	90.1	90.4	90.7	91.2	91.8	92.3	92.8	93.2	93.6	94.3	95.0
3.5	85.8	86.9	88.0	88.3	88.7	89.2	89.8	90.3	90.8	91.2	91.6	92.1	92.6
4.0	83.7	84.7	85.7	86.0	86.3	87.0	87.7	88.2	88.6	89.1	89.5	90.2	90.8
4.5	81.3	82.2	83.1	83.6	84.2	84.9	85.6	86.1	86.5	87.0	87.4	88.0	88.6
5.0	79.1	80.0	80.8	81.5	82.2	82.8	83.4	84.0	84.5	84.9	85.4	86.0	86.7
5.5	76.7	77.9	79.0	79.3	79.6	80.5	81.3	81.9	82.4	82.8	83.3	84.0	84.7
6.0	74.7	75.6	76.5	77.2	77.8	78.5	79.1	79.7	80.3	80.9	81.6	82.1	82.5
6.5	72.5	73.6	74.7	75.2	75.7	76.6	77.4	77.9	78.4	78.8	79.2	79.9	80.5
7.0	70.5	71.5	72.5	73.1	73.7	74.4	75.1	75.8	76.4	76.9	77.3	77.8	78.4
7.5	68.3	69.5	70.7	71.2	71.6	72.4	73.2	73.8	74.3	74.8	75.3	76.1	76.8
8.0	66.4	67.5	68.5	69.2	69.8	70.5	71.2	71.9	72.6	72.9	73.3	74.1	74.8
8.5	64.5	65.6	66.6	67.3	67.9	68.6	69.3	70.0	70.7	71.1	71.5	72.2	72.9
9.0	62.5	63.6	64.8	65.4	66.1	66.7	67.4	68.1	68.7	69.1	69.5	70.3	71.1
9.5	60.8	61.9	63.0	63.5	64.1	64.8	65.5	66.2	66.9	67.5	68.0	68.6	69.2
10.0	58.8	59.9	61.1	61.7	62.3	63.1	63.8	64.5	65.1	65.6	66.1	66.8	67.5
10.5	57.1	58.3	59.5	60.0	60.4	61.2	62.1	62.7	63.2	63.8	64.4	65.0	65.6
11.0	55.5	56.6	57.7	58.2	58.7	59.5	60.4	61.0	61.6	62.2	62.8	63.4	64.0
11.5	53.9	55.0	56.0	56.5	57.1	57.9	58.8	59.4	60.1	60.6	61.1	61.6	62.2
12.0	52.3	53.4	54.4	55.0	55.6	56.3	57.1	57.7	58.4	58.9	59.4	60.1	60.8

Treatment fields are not always square fields

Rectangular fields



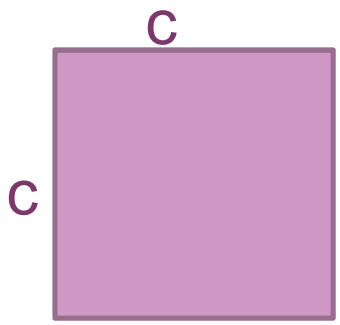
Equivalent square fields (EQS) is equivalent surface to circumference ratio

Note this is an approximation

$$\frac{c * c}{4 * c} = \frac{a * b}{2(a + b)}$$

$$\Updownarrow$$

$$c = \frac{2(a * b)}{a + b}$$



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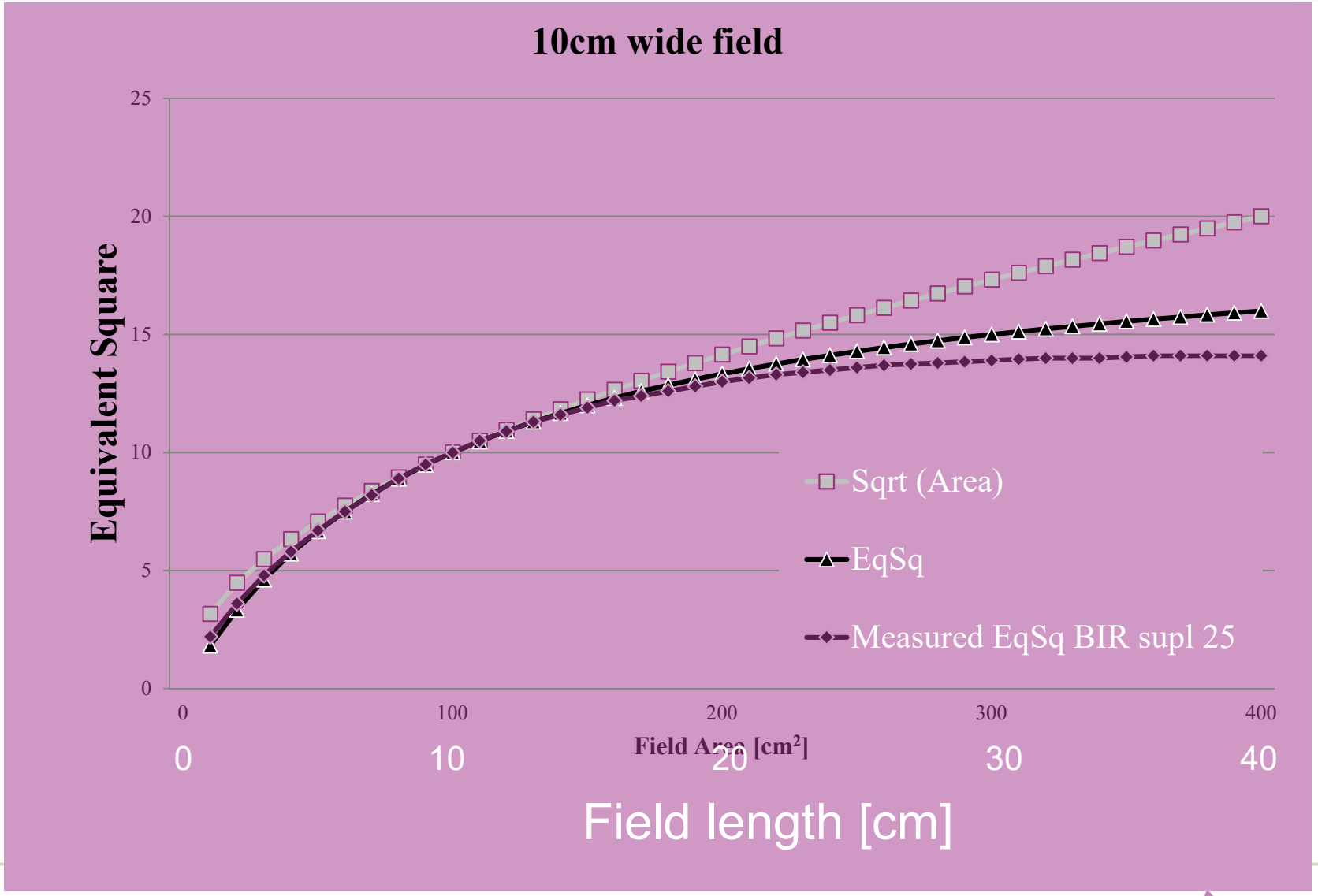

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Example

100cm SSD spine field 8cm*15cm,

Prescription single fraction 8Gy, prescribed to 7cm depth.

Calculated EqSq $= \frac{2 * 8 * 15}{8 + 15} = \frac{240}{23} = 10.4cm$

Look up in BIR supl 25: 10.3cm

$$MU = \frac{800cGy}{78.7} * 100$$

=1016.5

Max dose in many clinical settings for a single beam is 1000MU

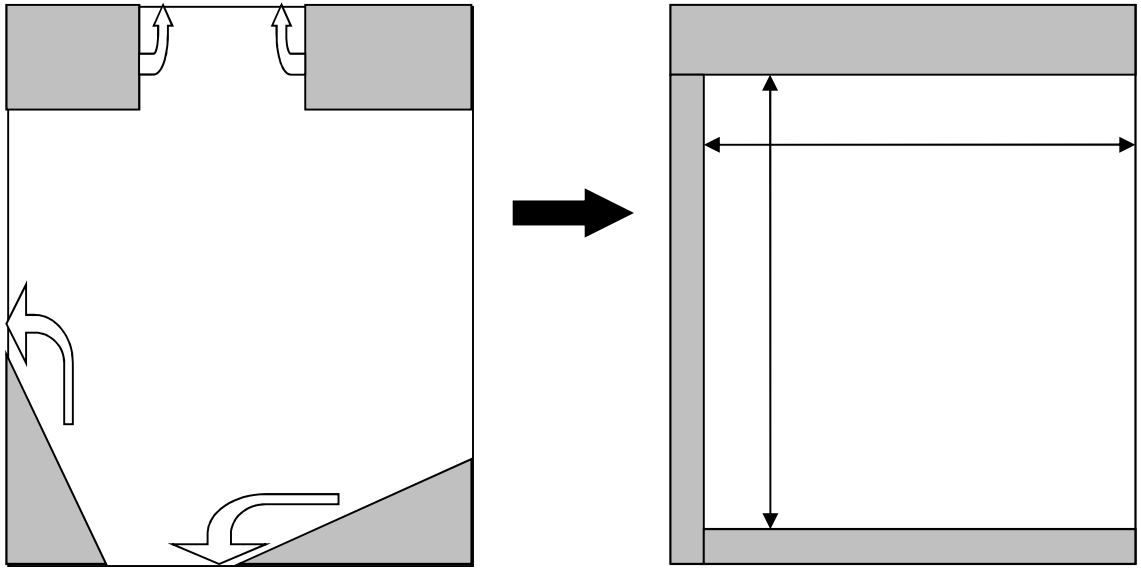
What do we do?

"Willow" 6MV PDD* Output

Depth (cm)	Equivalent Square Field Size (cm)													
	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10	10.5
Dmax (1.5)	93.6	94.5	95.4	95.7	95.9	96.6	97.3	97.7	98.2	98.5	98.8	99.4	100.0	100.2
2.0	92.7	93.7	94.7	94.8	94.8	95.5	96.1	96.6	97.1	97.4	97.7	98.3	99.0	99.1
2.5	90.5	91.5	92.6	92.8	93.0	93.5	94.1	94.6	95.1	95.4	95.8	96.3	96.9	97.1
3.0	88.0	89.1	90.1	90.4	90.7	91.2	91.8	92.3	92.8	93.2	93.6	94.3	95.0	95.2
3.5	85.8	86.9	88.0	88.3	88.7	89.2	89.8	90.3	90.8	91.2	91.6	92.1	92.6	93.0
4.0	83.7	84.7	85.7	86.0	86.3	87.0	87.7	88.2	88.6	89.1	89.5	90.2	90.8	91.1
4.5	81.3	82.2	83.1	83.6	84.2	84.9	85.6	86.1	86.5	87.0	87.4	88.0	88.6	89.0
5.0	79.1	80.0	80.8	81.5	82.2	82.8	83.4	84.0	84.5	84.9	85.4	86.0	86.7	87.0
5.5	76.7	77.9	79.0	79.3	79.6	80.5	81.3	81.9	82.4	82.8	83.3	84.0	84.7	84.9
6.0	74.7	75.6	76.5	77.2	77.8	78.5	79.1	79.7	80.3	80.9	81.6	82.1	82.5	82.8
6.5	72.5	73.6	74.7	75.2	75.7	76.6	77.4	77.9	78.4	78.8	79.2	79.9	80.5	80.8
7.0	70.5	71.5	72.5	73.1	73.7	74.4	75.1	75.8	76.4	76.9	77.3	77.8	78.4	78.8
7.5	68.3	69.5	70.7	71.2	71.6	72.4	73.2	73.8	74.3	74.8	75.3	76.1	76.8	77.1
8.0	66.4	67.5	68.5	69.2	69.8	70.5	71.2	71.9	72.6	72.9	73.3	74.1	74.8	75.1
8.5	64.5	65.6	66.6	67.3	67.9	68.6	69.3	70.0	70.7	71.1	71.5	72.2	72.9	73.2
9.0	62.5	63.6	64.8	65.4	66.1	66.7	67.4	68.1	68.7	69.1	69.5	70.3	71.1	71.4
9.5	60.8	61.9	63.0	63.5	64.1	64.8	65.5	66.2	66.9	67.5	68.0	68.6	69.2	69.5
10.0	58.8	59.9	61.1	61.7	62.3	63.1	63.8	64.5	65.1	65.6	66.1	66.8	67.5	67.9
10.5	57.1	58.3	59.5	60.0	60.4	61.2	62.1	62.7	63.2	63.8	64.4	65.0	65.6	65.9
11.0	55.5	56.6	57.7	58.2	58.7	59.5	60.4	61.0	61.6	62.2	62.8	63.4	64.0	64.4
11.5	53.9	55.0	56.0	56.5	57.1	57.9	58.8	59.4	60.1	60.6	61.2	61.8	62.2	62.7
12.0	52.3	53.4	54.4	55.0	55.6	56.3	57.1	57.7	58.4	58.9	59.4	60.1	60.8	61.2

Fields can have even more complex shapes by MLC or blocks

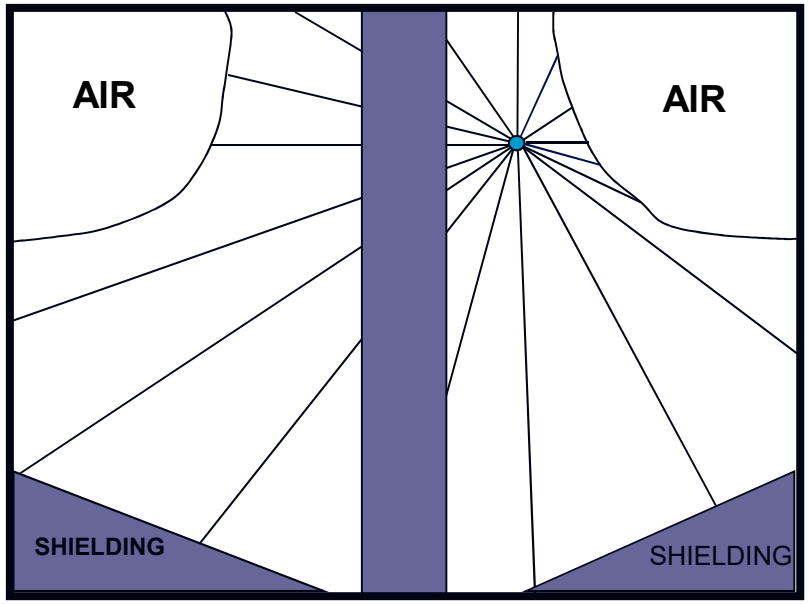
Simple method for estimating equivalent square of an irregular field



Use Field Output Factor of equivalent square field to calculate MUs

Clarkson Integration of scatter dose mainly used in "simple computer point dose calculations"

The field is sub-divided into equal sectors of an arc, and the scatter contribution from each sector is taken into account to determine the EqSq.



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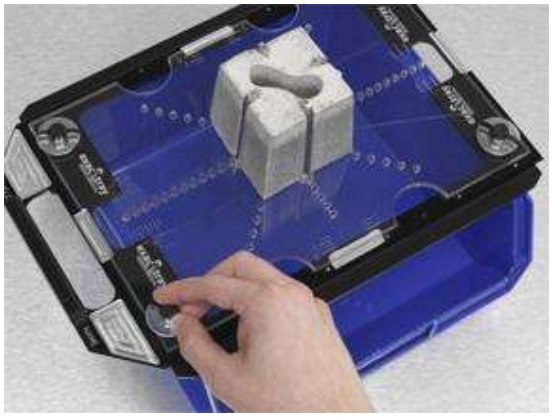
Shadow blocks



Transmission factor, TF, for the shadow tray:

$$TF(E) = \frac{D(d_m, F_{s\,ref}, SSD + tray, E)}{D(d_m, F_{s\,ref}, SSD\ no\ tray, E)}$$

$$MU = \frac{Prescription\ Dose}{PDD(d, Fs, E) * Output(Fs, E) * TF(E)} * 100$$

The size of TF depend of thickness and material of the shadow tray but will generally be 0.9-0.97

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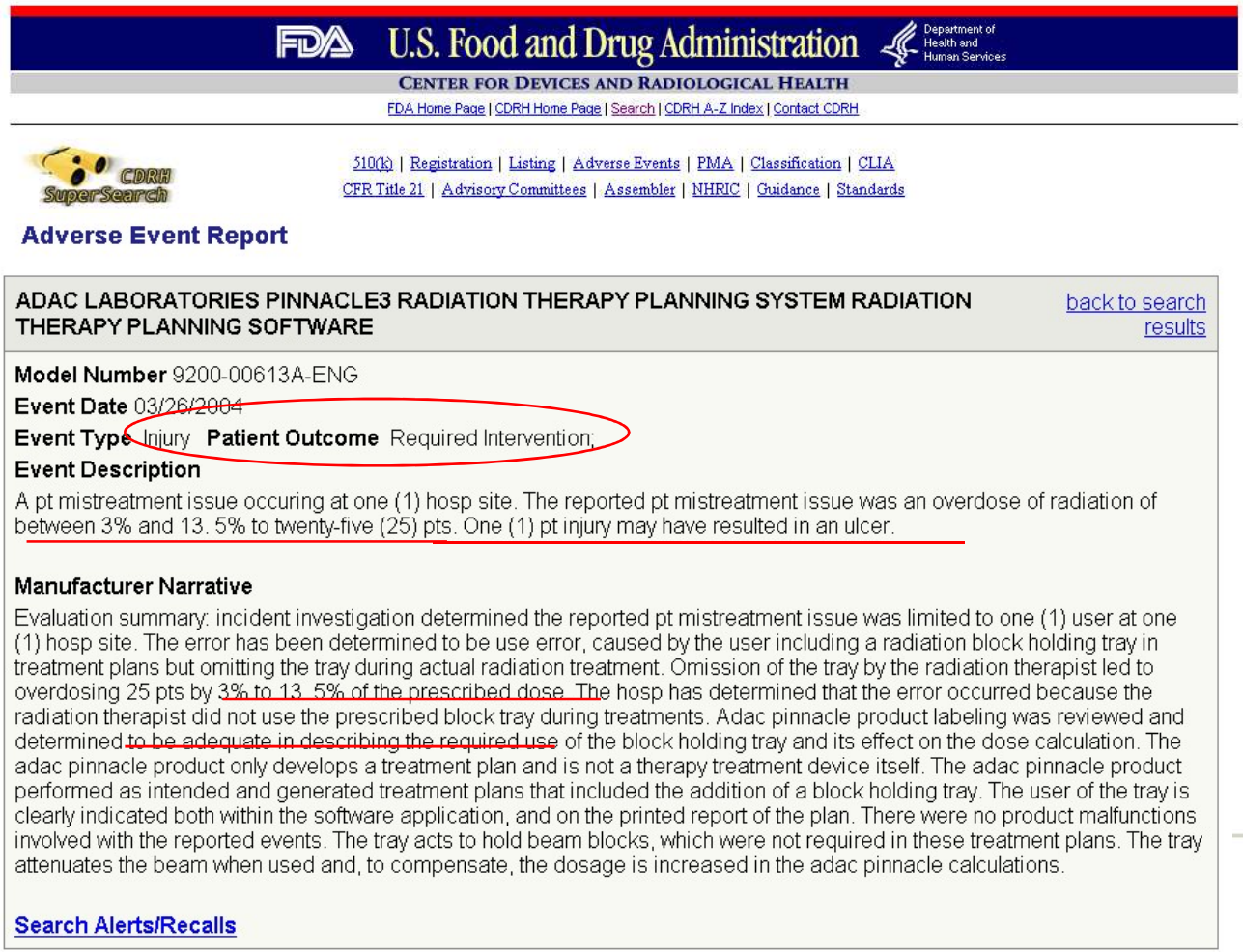
Warning: transmission factors are ONLY used for physical blocks. NOT for MLC.



FDA U.S. Food and Drug Administration — Department of Health and Human Services

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Adverse Event Report

ADAC LABORATORIES PINNACLE3 RADIATION THERAPY PLANNING SYSTEM RADIATION THERAPY PLANNING SOFTWARE

back to search results

Model Number 9200-00613A-ENG

Event Date 03/26/2004

Event Type Injury **Patient Outcome** Required Intervention;

Event Description

A pt mistreatment issue occuring at one (1) hosp site. The reported pt mistreatment issue was an overdose of radiation of between 3% and 13. 5% to twenty-five (25) pts. One (1) pt injury may have resulted in an ulcer.

Manufacturer Narrative

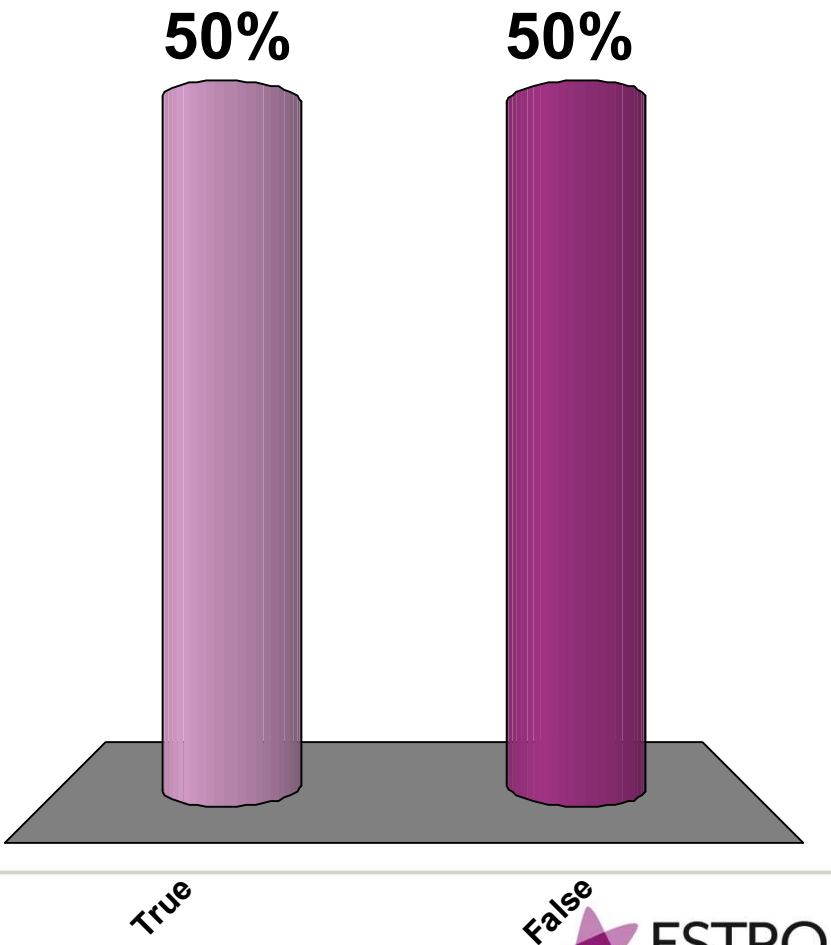
Evaluation summary: incident investigation determined the reported pt mistreatment issue was limited to one (1) user at one (1) hosp site. The error has been determined to be use error, caused by the user including a radiation block holding tray in treatment plans but omitting the tray during actual radiation treatment. Omission of the tray by the radiation therapist led to overdosing 25 pts by 3% to 13. 5% of the prescribed dose. The hosp has determined that the error occurred because the radiation therapist did not use the prescribed block tray during treatments. Adac pinnacle product labeling was reviewed and determined to be adequate in describing the required use of the block holding tray and its effect on the dose calculation. The adac pinnacle product only develops a treatment plan and is not a therapy treatment device itself. The adac pinnacle product performed as intended and generated treatment plans that included the addition of a block holding tray. The user of the tray is clearly indicated both within the software application, and on the printed report of the plan. There were no product malfunctions involved with the reported events. The tray acts to hold beam blocks, which were not required in these treatment plans. The tray attenuates the beam when used and, to compensate, the dosage is increased in the adac pinnacle calculations.

Search Alerts/Recalls

For equal number of MU :
Dose increase with larger field sizes

A. True

B. False



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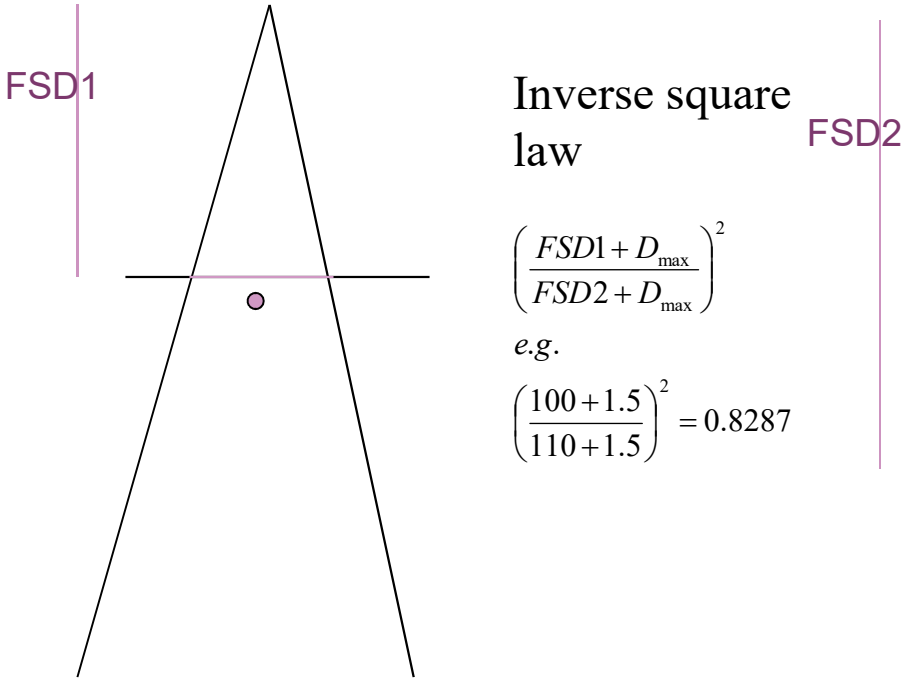
Treatment at different SSD

We may want to do that to extend the maximum field size (extended FSD for e.g. CNS treatments)

For isocentric treatments, so we only set-up the patient once and treat around the common isocentre.

Extended FSD
Note Change in divergence

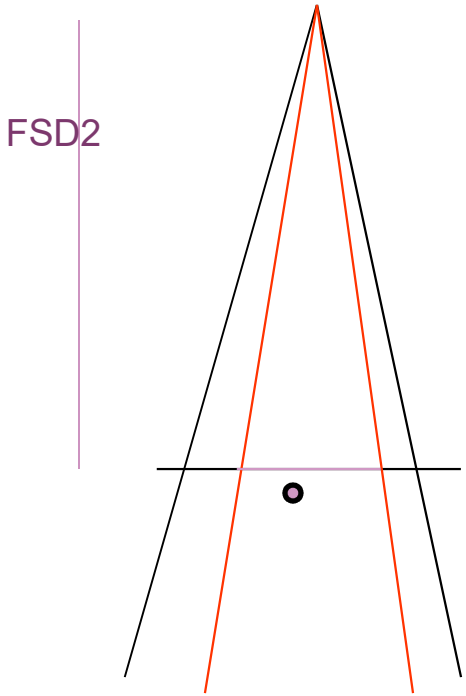


Inverse square law

$$\left(\frac{FSD1 + D_{max}}{FSD2 + D_{max}}\right)^2$$

e.g.

$$\left(\frac{100 + 1.5}{110 + 1.5}\right)^2 = 0.8287$$



Pure use of the inverse square law with PDDs should only happen within +/- 10cm

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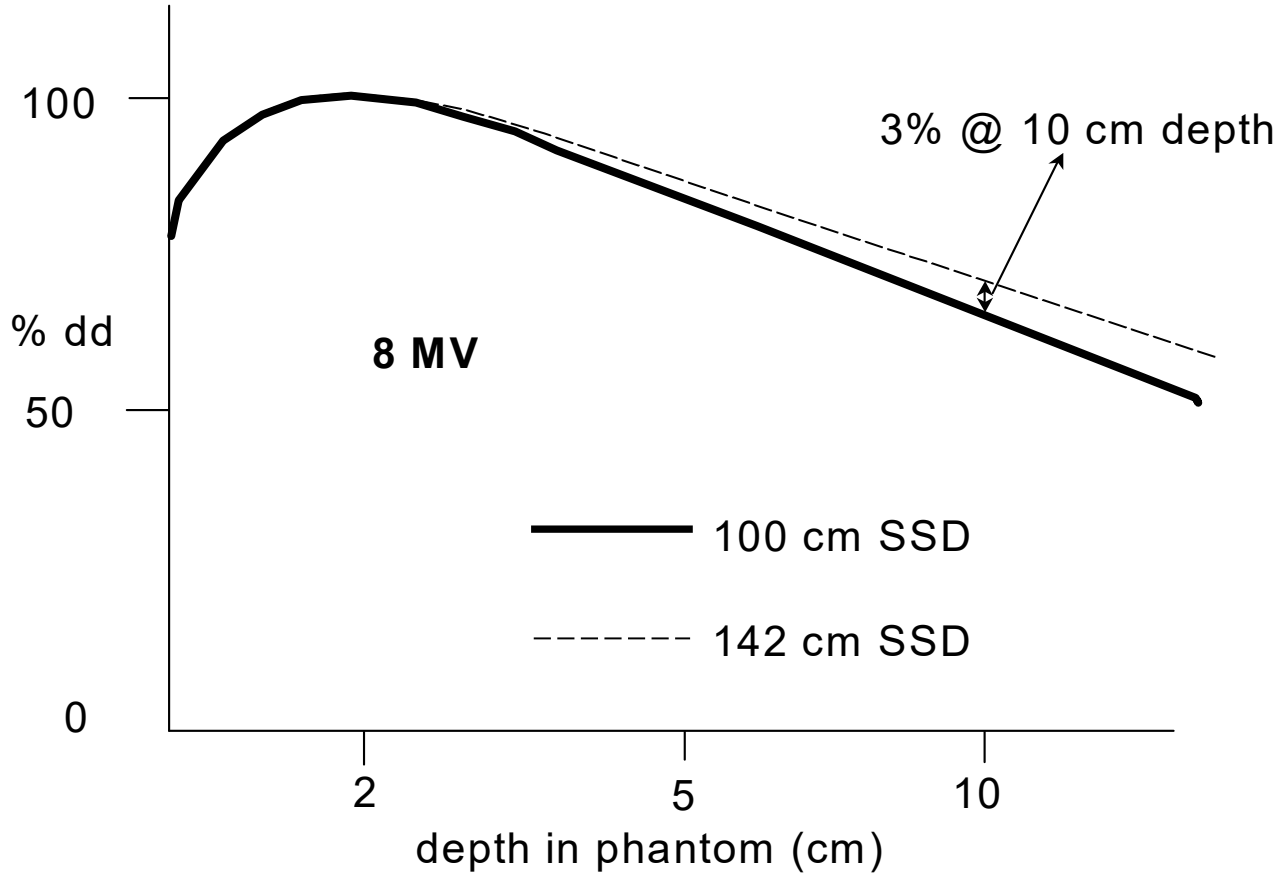
Comparison of central axis depth doses at two source- surface distances (Philips SL75/10)

The inverse square law is only "fully compensated at D_{max}"

The scatter differ due to different divergence



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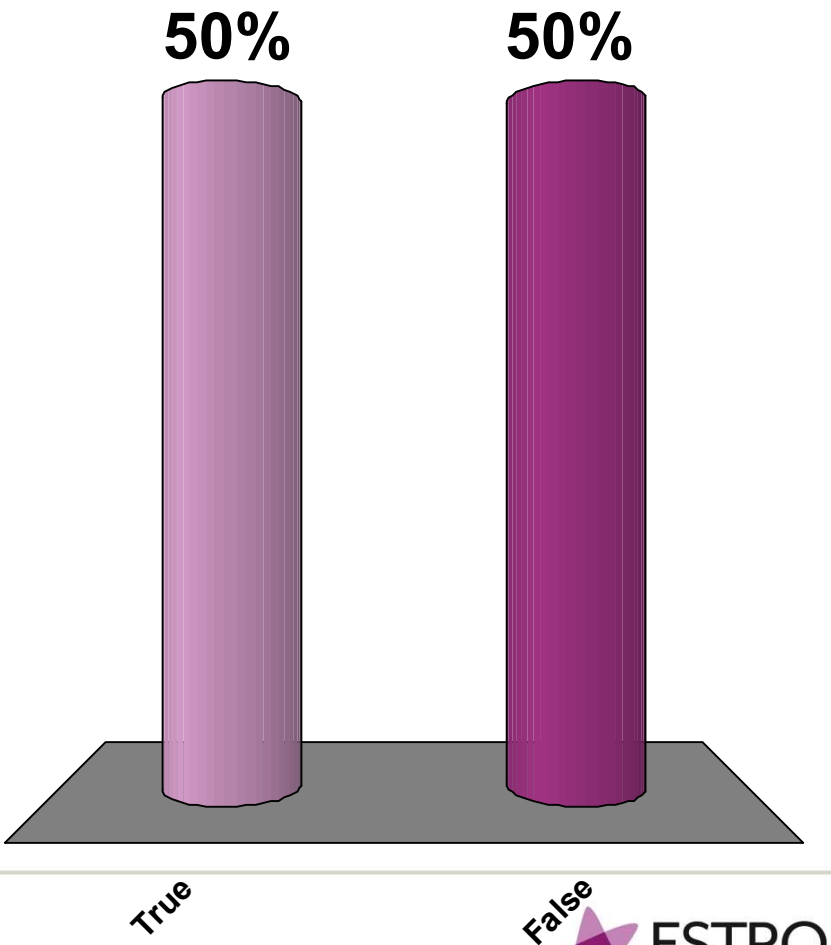
For equal number of MU : Dose decrease with larger SSD

A. True

B. False



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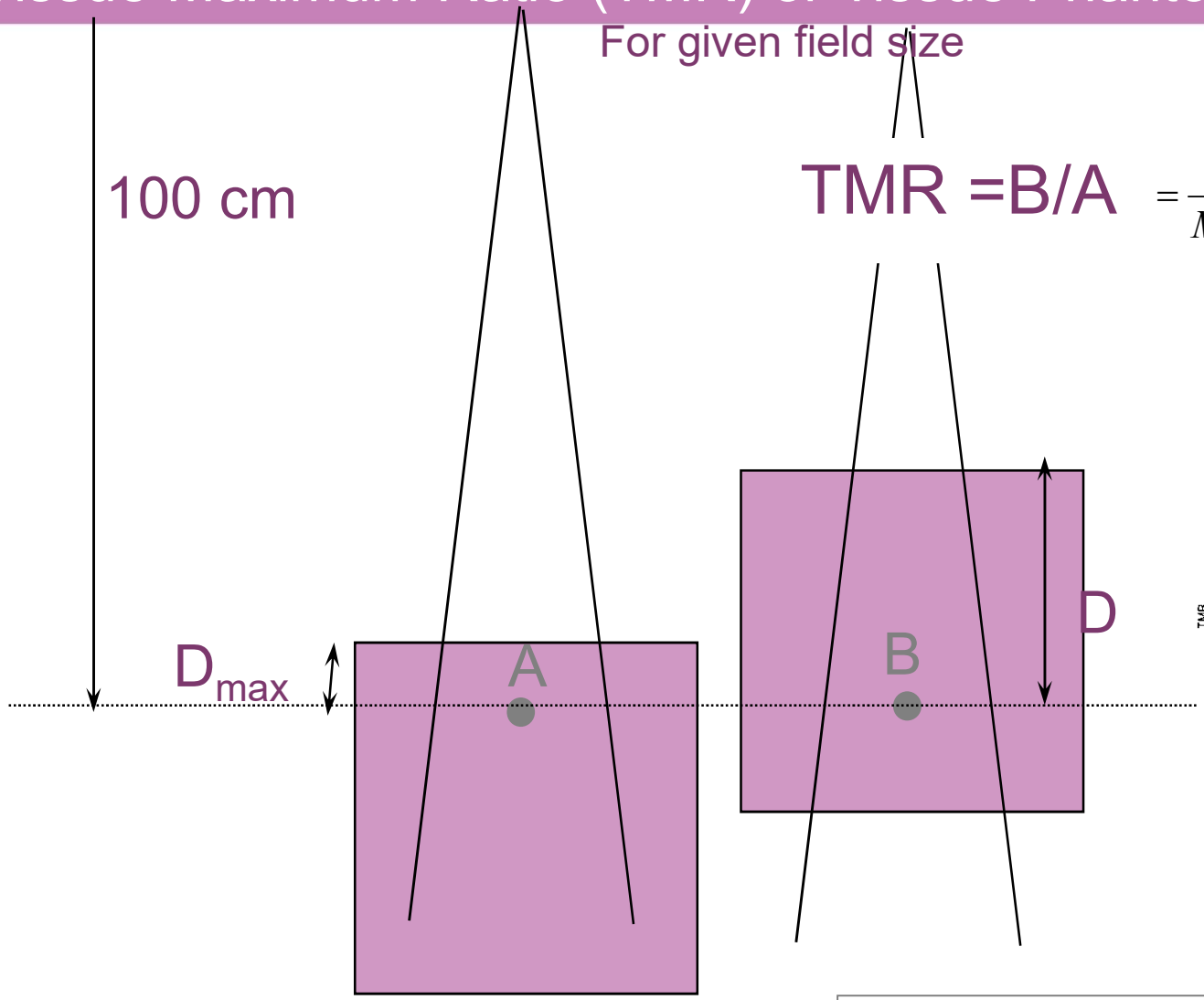
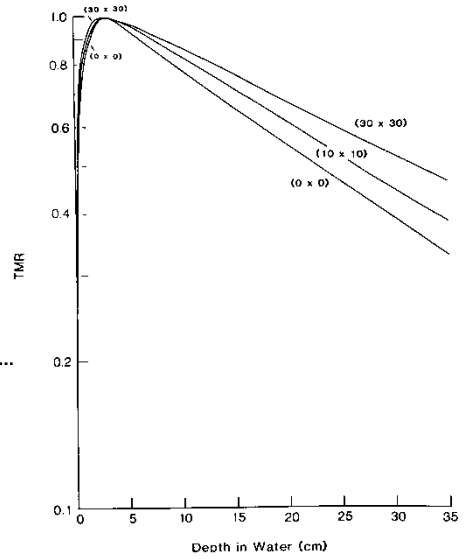
Tissue Maximum Ratio (TMR) or Tissue Phantom Ratio (TPR)

For given field size



$$TMR = B/A = \frac{M(D, SAD - D)}{M(D_{max}, SAD - D_{max})}$$



SAD = source to Axis Distance

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Multiple fields

Parallel opposed fields

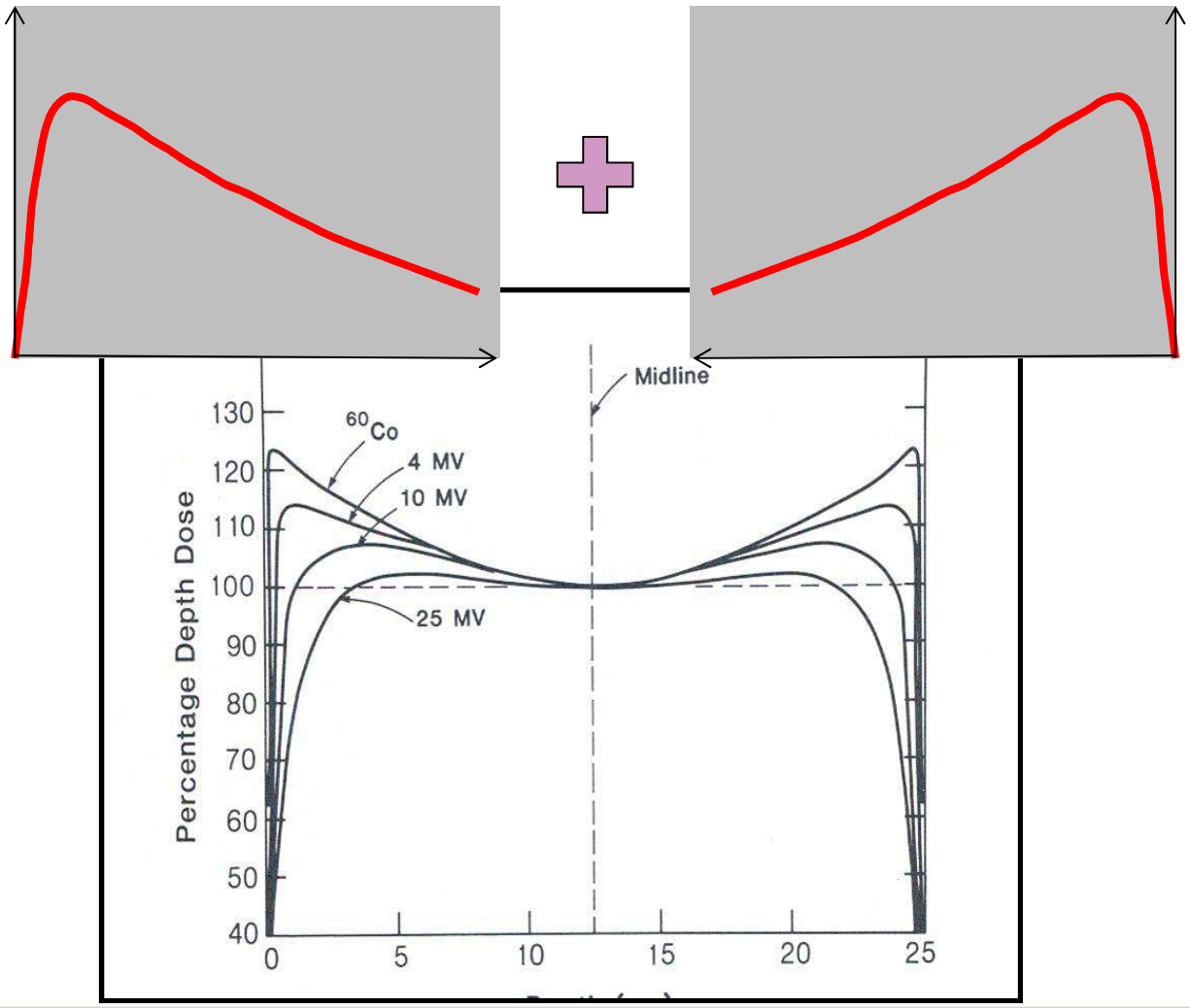
Beam weights

Two-field planning (non parallel opposed)

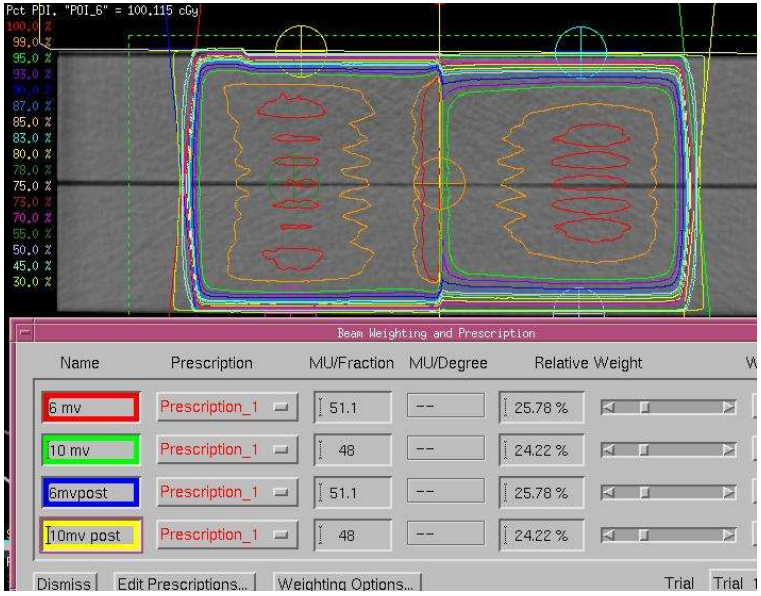
Wedges

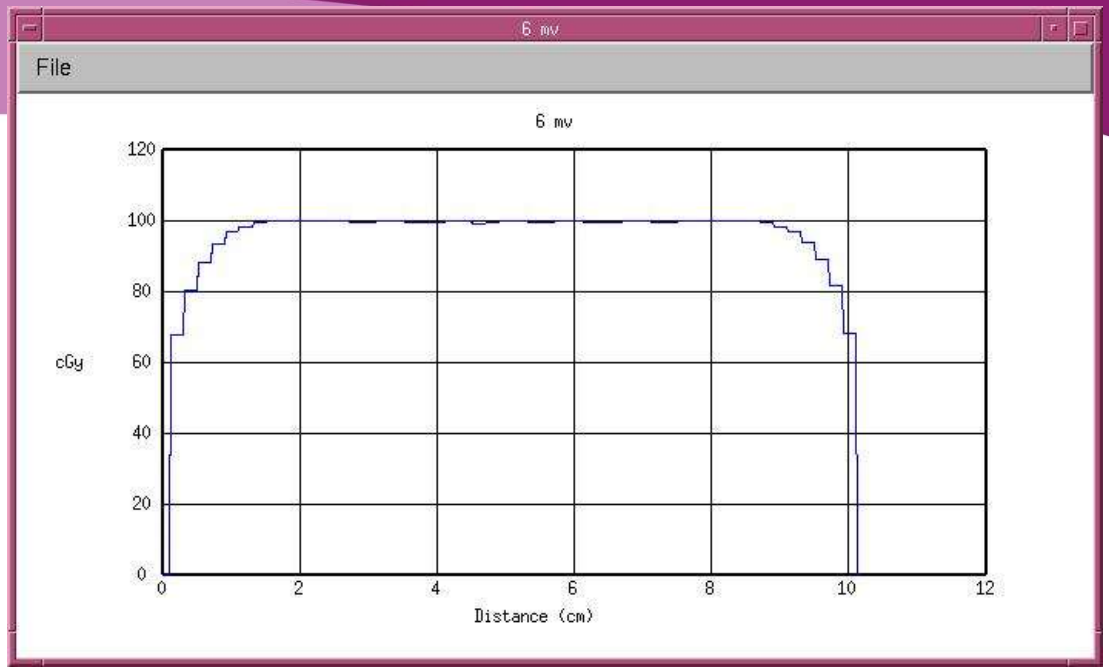
Three- and four-field techniques

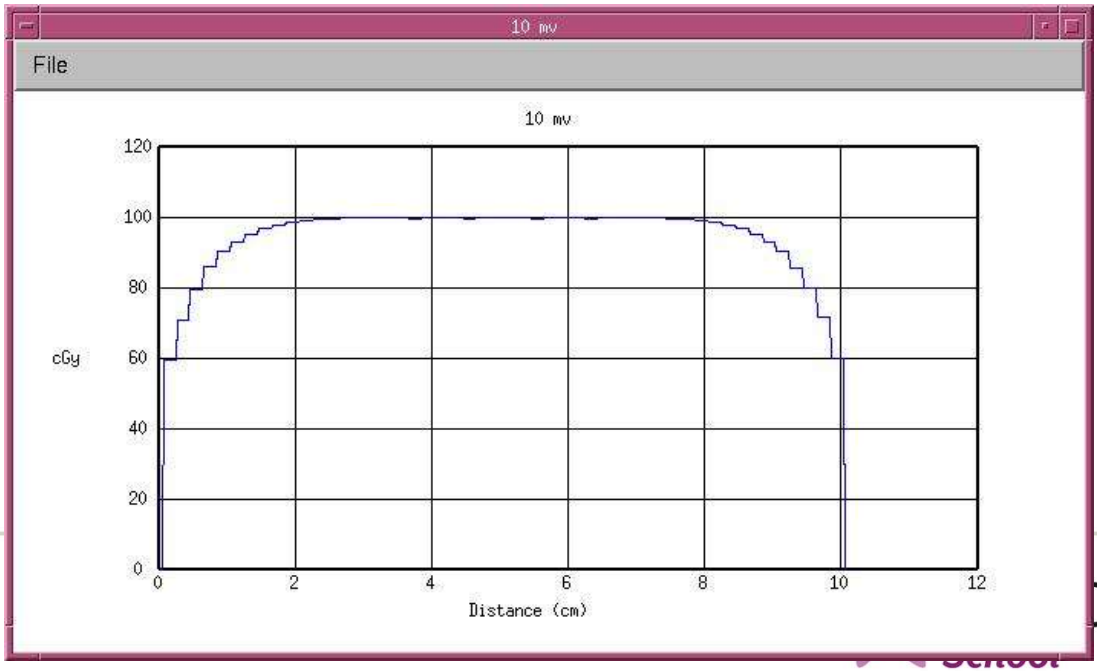
Parallel opposed



10cm blocks

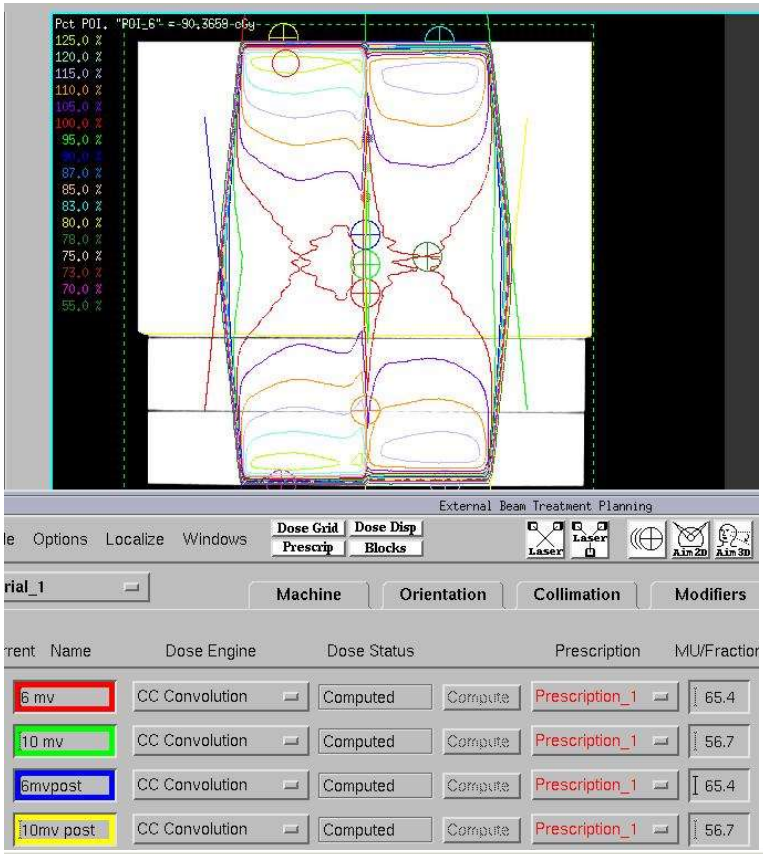

Pct POI, "POI_6" = 100.115 cGy
Beam Weighting and Prescription
Name
Prescription
MU/Fraction
MU/Degree
Relative Weight
6 mv
Prescription_1
51.1
--
25.78 %
10 mv
Prescription_1
48
--
24.22 %
6mvpost
Prescription_1
51.1
--
25.78 %
10mv post
Prescription_1
48
--
24.22 %
Dismiss
Edit Prescriptions...
Weighting Options...
Trial
Trial


6 mv
File
6 mv
cGy
Distance (cm)

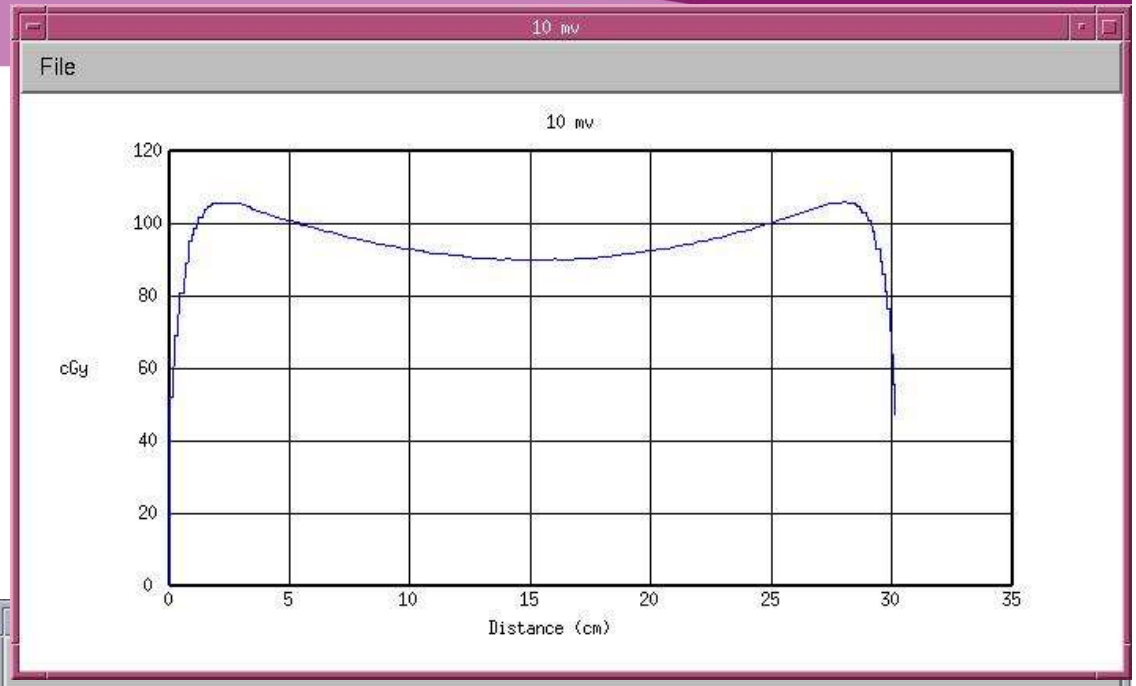

10 mv
File
10 mv
cGy
Distance (cm)

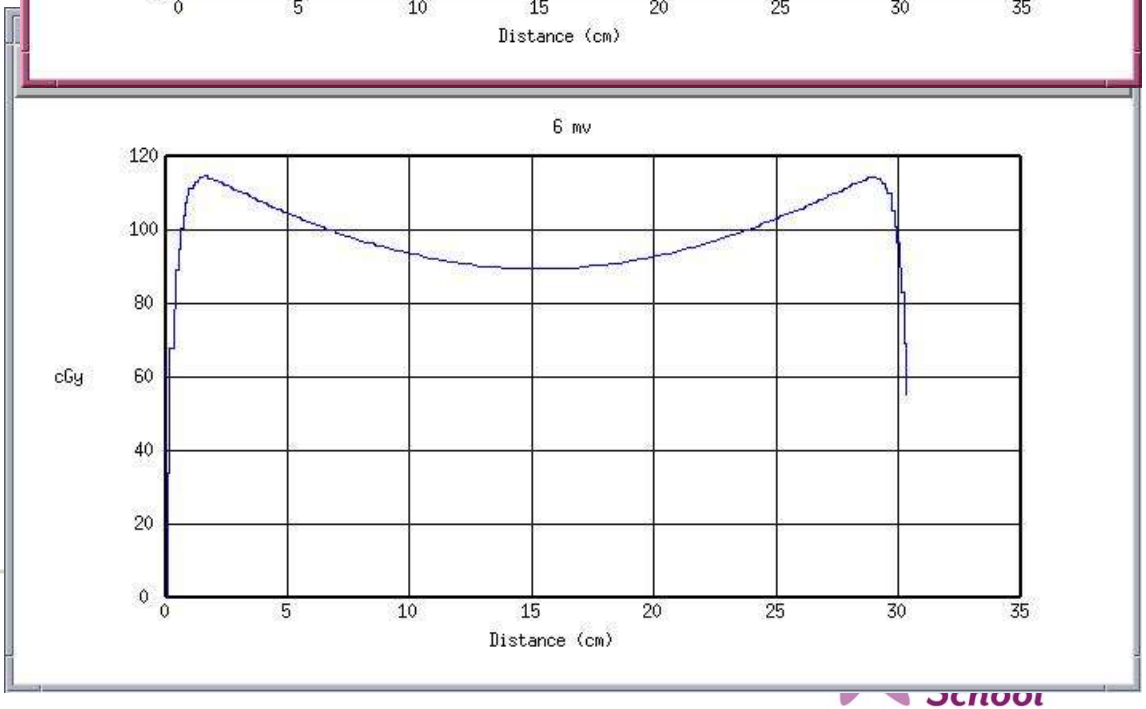
30 cm blocks

Dmax/Dca = 105/90
= 117%

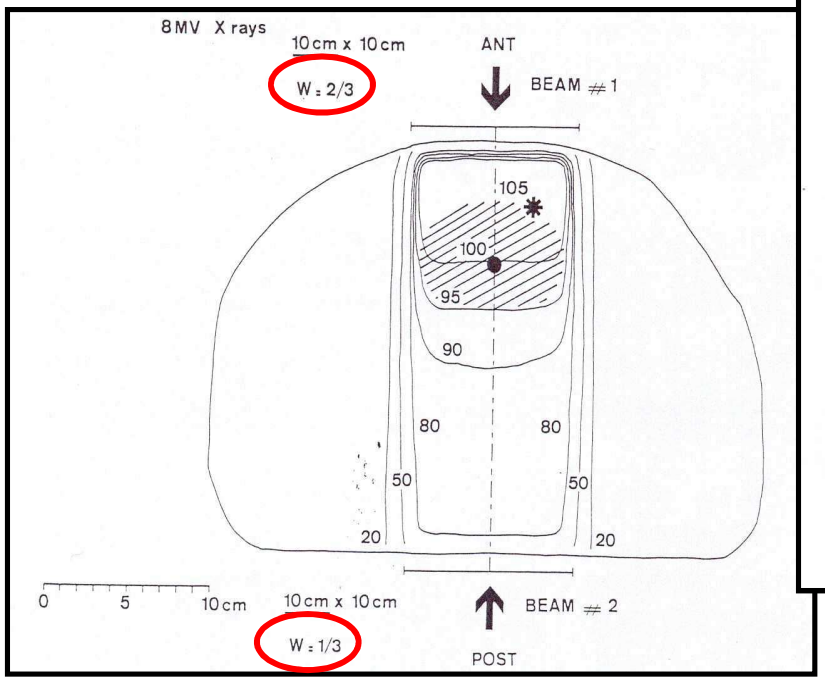


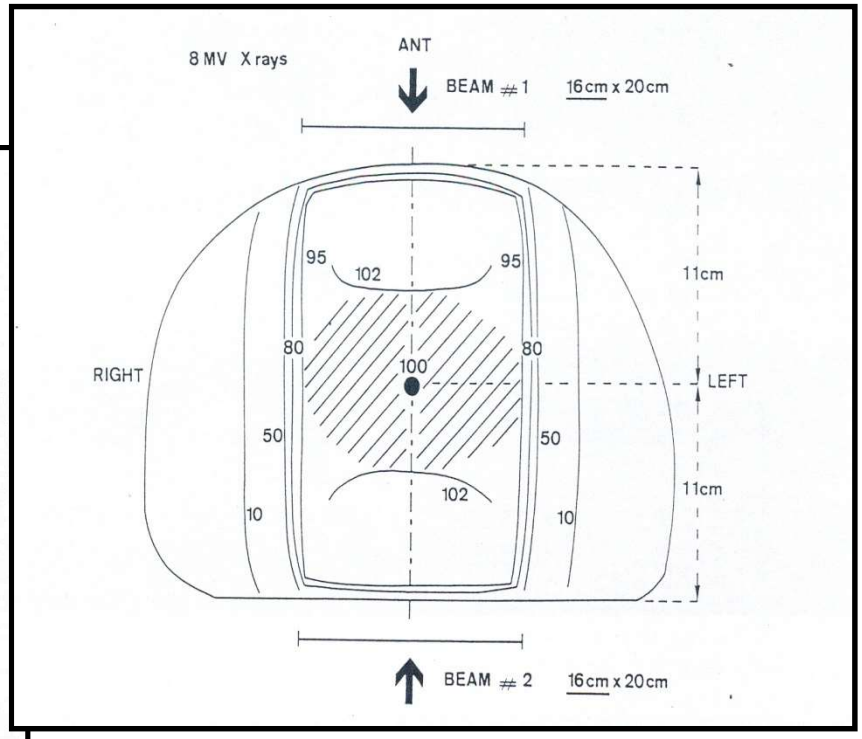
Dmax/Dca = 112/90
= 124.4%

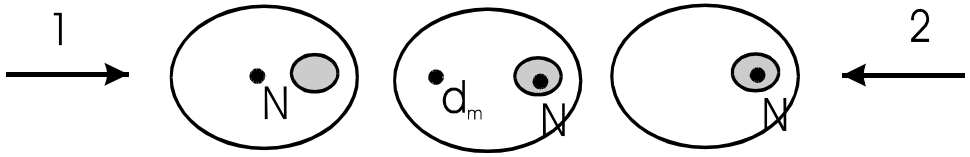




Beam weights







50% - 50%
$\#MU_1 = \#MU_2$

50% - 50%
$\#MU_1 > \#MU_2$

30% - 70%
$\#MU_1 \sim \#MU_2$

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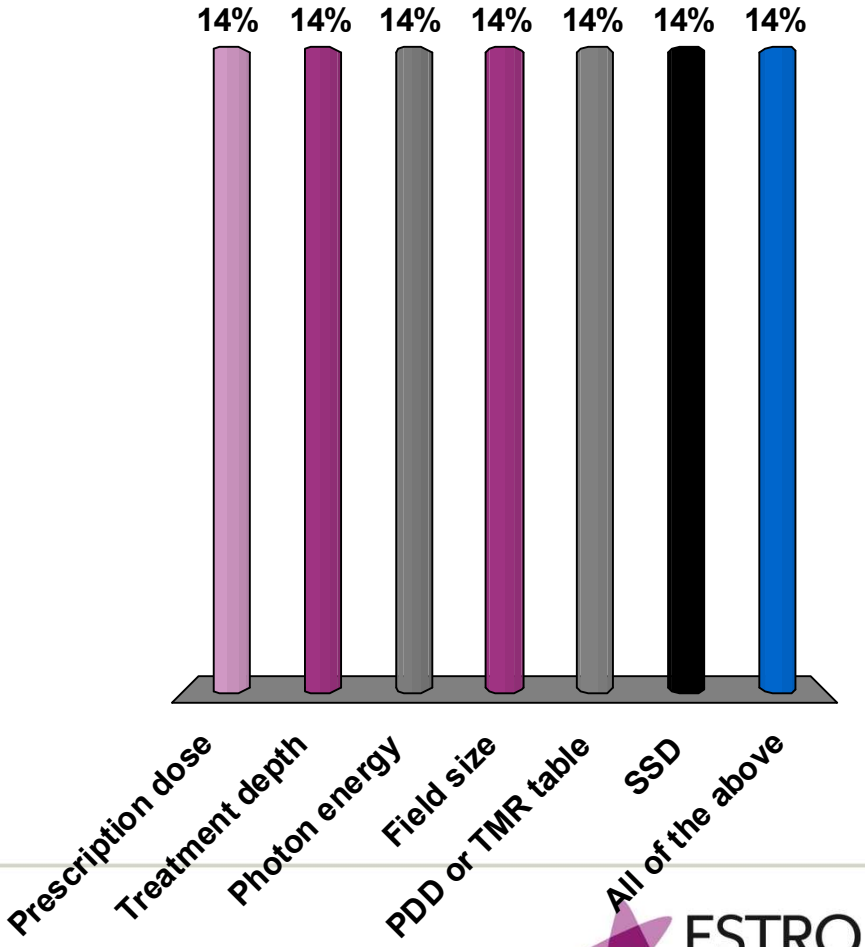
To calculate MU for a treatment beam, what are the minimum information you need?

A. Prescription dose
B. Treatment depth
C. Photon energy
D. Field size
E. PDD or TMR table
F. SSD
G. All of the above



MU examples

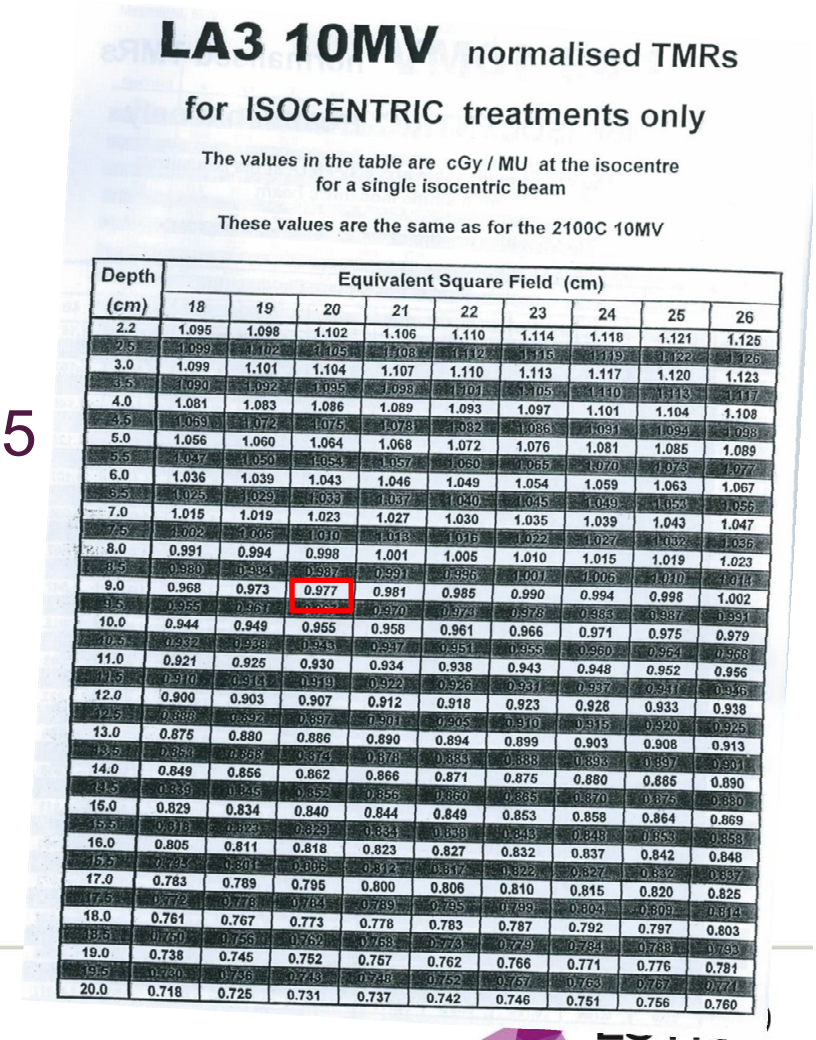
- Treat 2 GY to the centre of a volume – use parallel opposed beams
- The Field size is 20*20cm^2
- Patient separation is 18 cm
- Treat with SSD= 91 cm, 10 MV

Example:

TMR table :

TMR(9 cm, 20)=0.977cGy/MU
Dose from each field is 1 Gy
To deliver 1Gy :
100cGy/0.977cGy/MU = 102.35

MU ie 102 MU
from each beam



LA3 10MV normalised TMRs

for ISOCENTRIC treatments only

The values in the table are cGy / MU at the isocentre for a single isocentric beam

These values are the same as for the 2100C 10MV

Depth (cm)	Equivalent Square Field (cm)								
	18	19	20	21	22	23	24	25	26
2.2	1.095	1.098	1.102	1.106	1.110	1.114	1.118	1.121	1.125
2.5	1.099	1.102	1.105	1.108	1.112	1.115	1.119	1.122	1.126
3.0	1.099	1.101	1.104	1.107	1.110	1.113	1.117	1.120	1.123
3.5	1.090	1.092	1.095	1.098	1.101	1.105	1.110	1.113	1.117
4.0	1.081	1.083	1.086	1.089	1.093	1.097	1.101	1.104	1.108
4.5	1.069	1.072	1.075	1.078	1.082	1.086	1.091	1.094	1.098
5.0	1.056	1.060	1.064	1.068	1.072	1.076	1.081	1.085	1.089
5.5	1.047	1.050	1.054	1.057	1.060	1.065	1.070	1.073	1.077
6.0	1.036	1.039	1.043	1.046	1.049	1.054	1.059	1.063	1.067
6.5	1.025	1.029	1.033	1.037	1.040	1.045	1.049	1.053	1.056
7.0	1.015	1.019	1.023	1.027	1.030	1.035	1.039	1.043	1.047
7.5	1.002	1.006	1.010	1.013	1.016	1.022	1.027	1.032	1.036
8.0	0.991	0.994	0.998	1.001	1.005	1.010	1.015	1.019	1.023
8.5	0.980	0.984	0.987	0.991	0.995	1.001	1.005	1.010	1.014
9.0	0.968	0.973	0.977	0.981	0.985	0.990	0.994	0.998	1.002
9.5	0.955	0.961	0.967	0.970	0.973	0.978	0.983	0.987	0.991
10.0	0.944	0.949	0.955	0.958	0.961	0.966	0.971	0.975	0.979
10.5	0.932	0.938	0.943	0.947	0.951	0.955	0.960	0.964	0.968
11.0	0.921	0.925	0.930	0.934	0.938	0.943	0.948	0.952	0.956
11.5	0.910	0.914	0.919	0.922	0.926	0.931	0.937	0.941	0.946
12.0	0.900	0.903	0.907	0.912	0.918	0.923	0.928	0.933	0.938
12.5	0.888	0.892	0.897	0.901	0.905	0.910	0.915	0.920	0.925
13.0	0.875	0.880	0.886	0.890	0.894	0.899	0.903	0.908	0.913
13.5	0.868	0.868	0.874	0.878	0.883	0.888	0.893	0.897	0.901
14.0	0.849	0.856	0.862	0.866	0.871	0.875	0.880	0.885	0.890
14.5	0.839	0.845	0.852	0.856	0.860	0.865	0.870	0.875	0.880
15.0	0.829	0.834	0.840	0.844	0.849	0.853	0.858	0.864	0.869
15.5	0.818	0.823	0.829	0.834	0.838	0.843	0.848	0.853	0.858
16.0	0.805	0.811	0.818	0.823	0.827	0.832	0.837	0.842	0.848
16.5	0.794	0.801	0.806	0.812	0.817	0.822	0.827	0.832	0.837
17.0	0.783	0.789	0.795	0.800	0.806	0.810	0.815	0.820	0.825
17.5	0.772	0.778	0.784	0.789	0.795	0.799	0.804	0.809	0.814
18.0	0.761	0.767	0.773	0.778	0.783	0.787	0.792	0.797	0.803
18.5	0.750	0.756	0.762	0.768	0.773	0.779	0.784	0.788	0.793
19.0	0.738	0.745	0.752	0.757	0.762	0.766	0.771	0.776	0.781
19.5	0.730	0.736	0.743	0.748	0.752	0.757	0.763	0.767	0.771
20.0	0.718	0.725	0.731	0.737	0.742	0.746	0.751	0.756	0.760

MU examples

Treat 2 GY to the centre of a volume ||pair

The Field size is 20*20cm^2

Patient separation is 18 cm

Treat with SSD= 100 cm, 10 MV

Use the Depth dose chart:

PDD*output(9 cm, 20)=80.9cGy/100MU

Dose from each field is 1 Gy

$$= \frac{\text{Prescription dose}}{\text{PDD}(d, Fs, E) * \text{Output}(Fs, E)} * 100$$

To deliver 1Gy : 100cGy/80.9(cGy/100MU)*100 = 123.6 MU ie 124 MU

from each beam

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Summary
Basic Dose Calculation Principles

For equal number of MU :

Dose decrease with depth (beyond d_{max})

- Dose absorption and inverse square law

Dose increase with larger field sizes

- More scatter to contribute to dose (Output factors)

Dose decrease with larger SSD

- inverse square law

Dose increase with energy (beyond d_{max})

- less attenuation for higher energies

Dose increase off central axis – most at d_{max} less at depth.

- Flattening filter, Beam spectrum is “softer” off axis (off axis factors)

Limitations of “basic calculations” Patients are NOT water phantoms

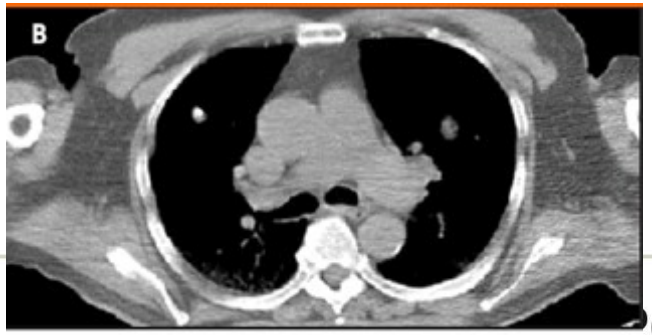
Patient contour:

- beam may be obliquely incident onto the patient
- patient surface may be curved or of irregular shape

- **Heterogeneities:**
- tissues, such as lung and bone, have densities that differ considerably from that of water.

Limitations will be looked at in

“Calculation of dose distributions in TPS”



Thank you for your attention

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QA for Advanced Delivery Techniques

Milan TOMSEJ

CHU A. Vésale

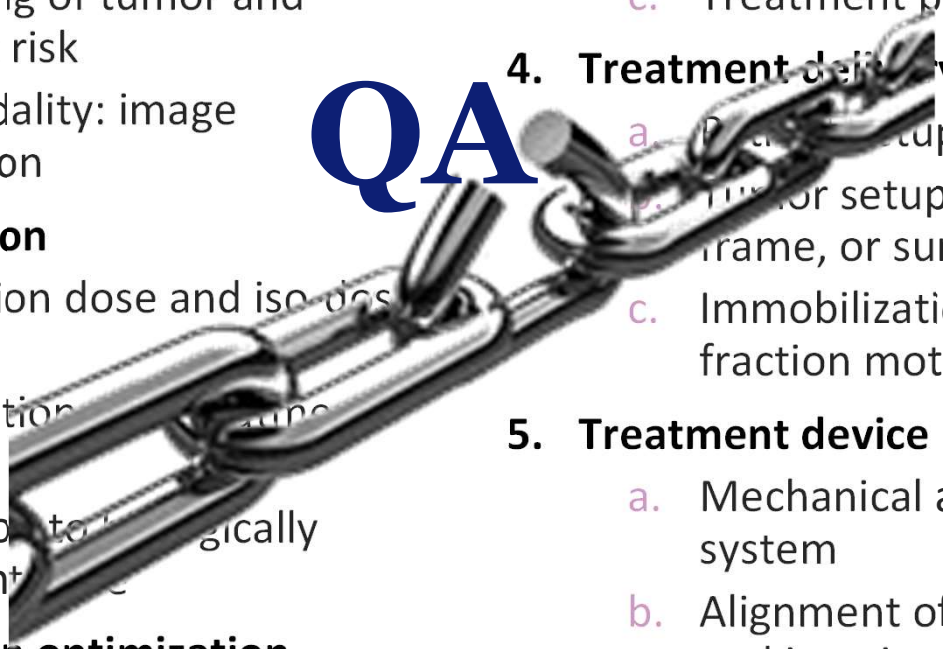
Charleroi

BELGIUM

ESTRO School

Radiotherapy Treatment Chain

1. **Localization**
   a. Contouring of tumor and organs at risk
   b. Multimodality: image registration
2. **Dose prescription**
   a. Prescription dose and iso-dose line
   b. Fractionation [illegible] duration
   c. Conversion to biologically equivalent dose
3. **Treatment plan optimization**
   a. Dose commissioning
   b. Dose calculation
   c. Treatment planning
4. **Treatment delivery**
   a. Patient setup
   b. Tumor setup (by imaging, frame, or surrogate)
   c. Immobilization and intra-fraction motion
5. **Treatment device**
   a. Mechanical accuracy of the system
   b. Alignment of treatment beam and imaging or localization system



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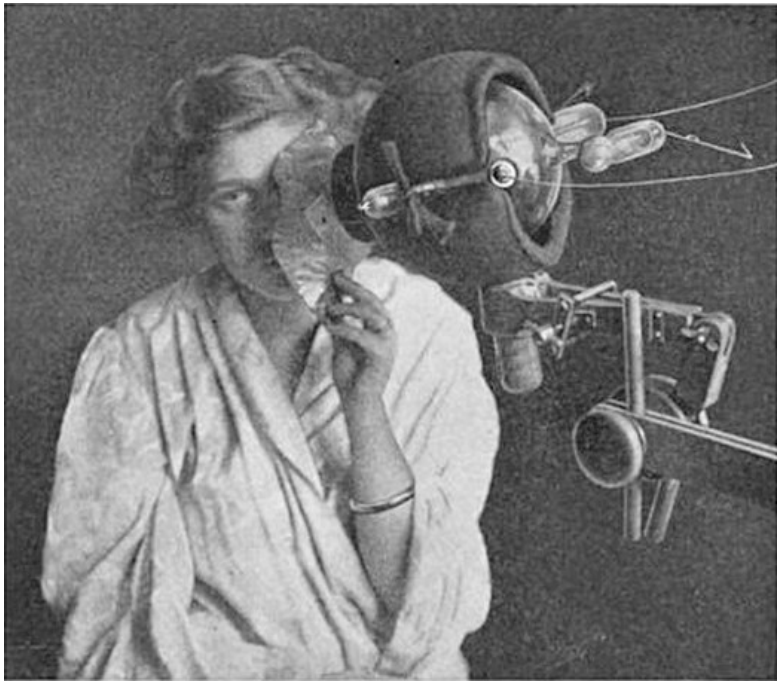
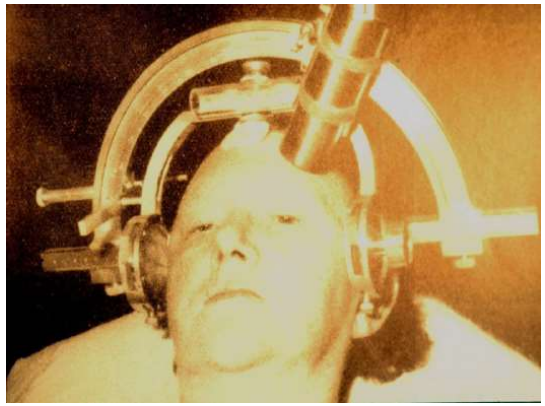
From Simple to Complex



Complexity (number of degrees of freedom) increased by two to three orders of magnitude

Vendors' Claims for Advanced Delivery Systems

- "… system capable of delivering high doses of radiation with sub-millimeter accuracy anywhere in the body …"
- "… doctors are able to focus radiation directly, and very precisely, on the target in the brain …"
- "… It combines imaging, beam delivery and sophisticated technology to accurately and precisely target tumors …"
- " … designed for precision …"



Contents

QA OF IMRT, VMAT, RAPIDARC, AND TOMOTHERAPY

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IMRT: What are the Potential Weak Links?

- **Many (small) field segments are made by the MLC for building a dose distribution**
  - Leaf positioning and travelling becomes important
  - Dose calculations are more complex due to leaf rounding effects, tongue and groove effects, leaf transmission …
  - Small-field dosimetry (output factor and beam profiles) becomes important
- **Beam stability (segmented IMRT)**
  - Low MU fields lead to short beam-on times
  - Check output, flatness, and symmetry stability at start up and steady state of the dose delivery
  - For > 2 MU dose output and beam profile stability should be within ±2% (1 SD)

Ezzell G, Galvin JM, Low D, Palta JR, Rosen I, Sharpe MB, Xia P, Xiao Y, Xing L and Yu CX. Guidance document on delivery, treatment planning, and clinical implementation of IMRT: Report of the IMRT subcommittee of the AAPM Radiation Therapy Committee. Med. Phys. 30: 2090 – 2115, 2003

IMRT: What are the Potential Weak Links?

- **MU-dose relationship is not intuitive**
  - Simple point dose verification calculations do not cover the properties of the whole dose distribution
- **Inverse Treatment Planning**
  - The multiple constraints, (competing) objectives, and the numerous degrees of freedom make plan optimization a large scale multi-criteria, non-convex, combinatorial, and discrete problem and thereby not straightforward to solve.
- **Mechanical accuracy of the linear accelerator**
  - Gantry, collimator, table iso-center (typically < 1 mm)

Ezzell G, Galvin JM, Low D, Palta JR, Rosen I, Sharpe MB, Xia P, Xiao Y, Xing L and Yu CX. Guidance document on delivery, treatment planning, and clinical implementation of IMRT: Report of the IMRT subcommittee of the AAPM Radiation Therapy Committee. Med. Phys. 30: 2090 – 2115, 2003

QA STRATEGIES

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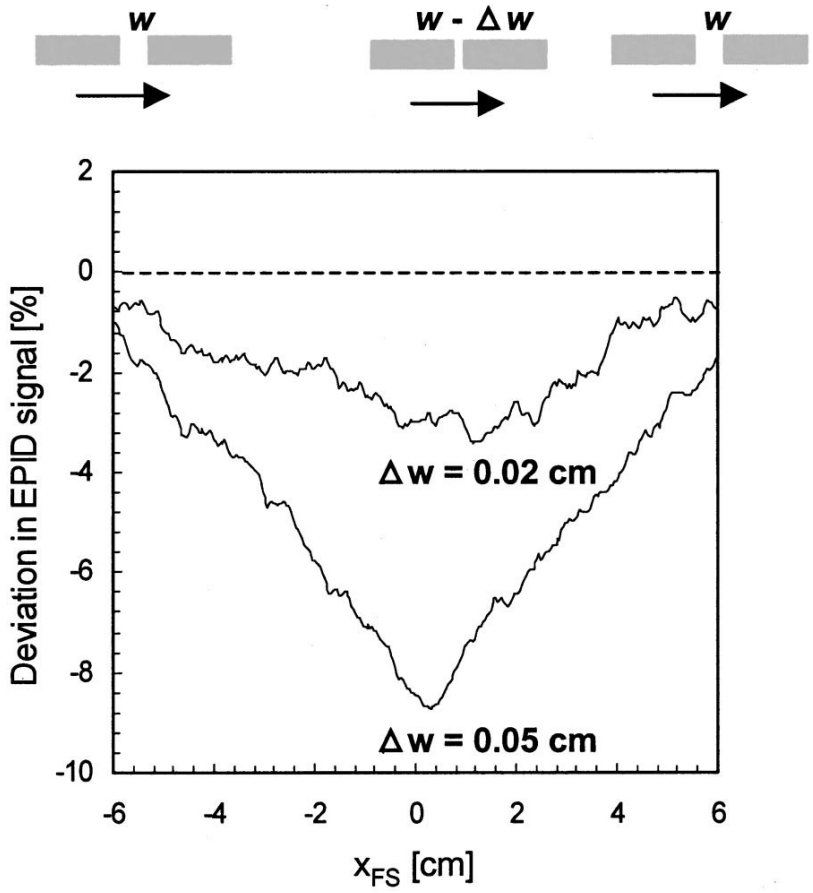
QA of IMRT

- **Acceptance testing**
  - Check whether specifications meet requirements for accurate IMRTand VMAT delivery
- **Commissioning**
  - Acquisition of the input parameters for the treatment planning system
  - Testing of the dose calculation algorithm
  - E2E testing of the complete treatment chain
- **Routine MLC QA**
  - E.g. stability of MLC and machine output characteristics
- **Patient specific QA**
  - Pretreatment measurements and in-vivo dosimetry
  - 3D Redundant dose calculation

Leaf Positioning

- For 3DCRT the accuracy of the leaf positioning affects the borders of the radiation field. Typically, errors of 1 mm are accepted and can be accounted for in a CTV-to-PTV margin
- **For IMRT leaf positioning errors can also impact the dose inside the target**
  - E.g. a 1 mm gap error can introduce a dose error of 5%.
  - Overlapping or underlapping of abutting fields lead to hot and cold spots up to 17%/mm



Sandra C. Vieira,a) Maarten L. P. Dirkx, Kasper L. Pasma, and Ben J. M. Heijmen Fast and accurate leaf verification for dynamic multileaf collimation using an electronic portal imaging device. Med. Phys. 29 (9), September 2002

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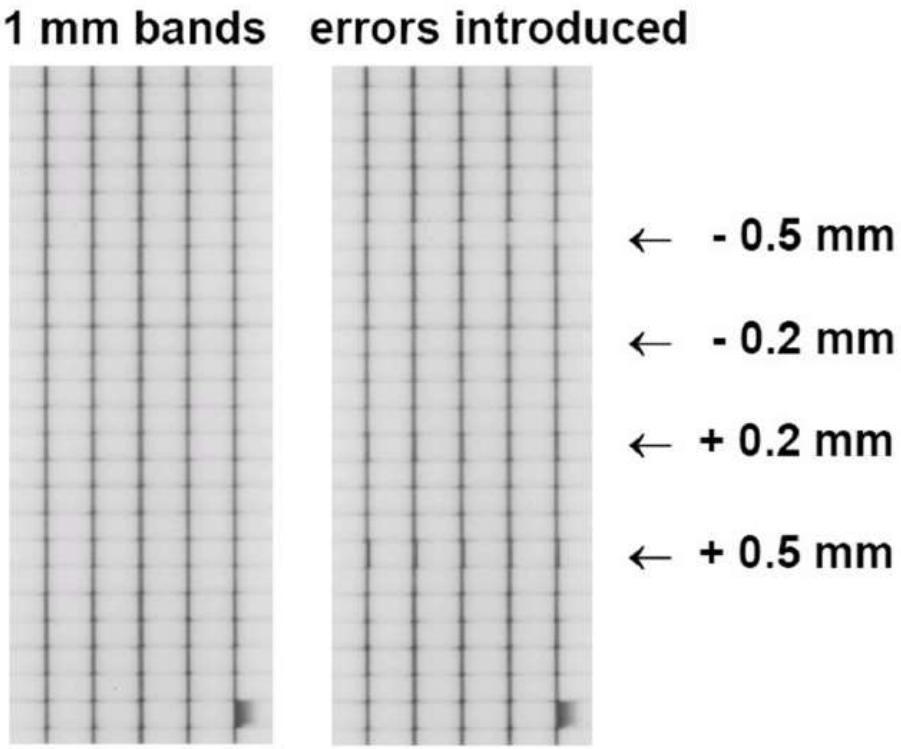
Picket Fence Test

- Checks the position of each MLC leaf relative to the alignment of the other leaves



Thomas J. Losasso "IMRT Delivery System QA", AAPM Medical Physics Monograph No. 29, Intensity-Modulated Radiation Therapy, The State of the Art, Jatinder R. Palta and T. Rockwell Mackie, Editors, Medical Physics Publishing, Madison, WI, USA, 2003

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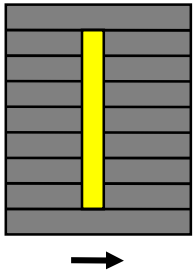
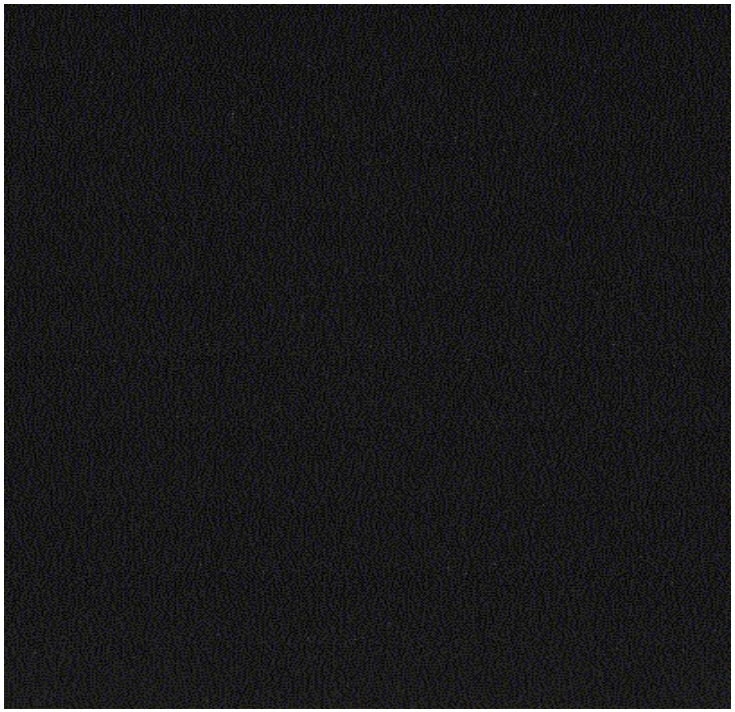
QA of Leaf Travel With an EPID





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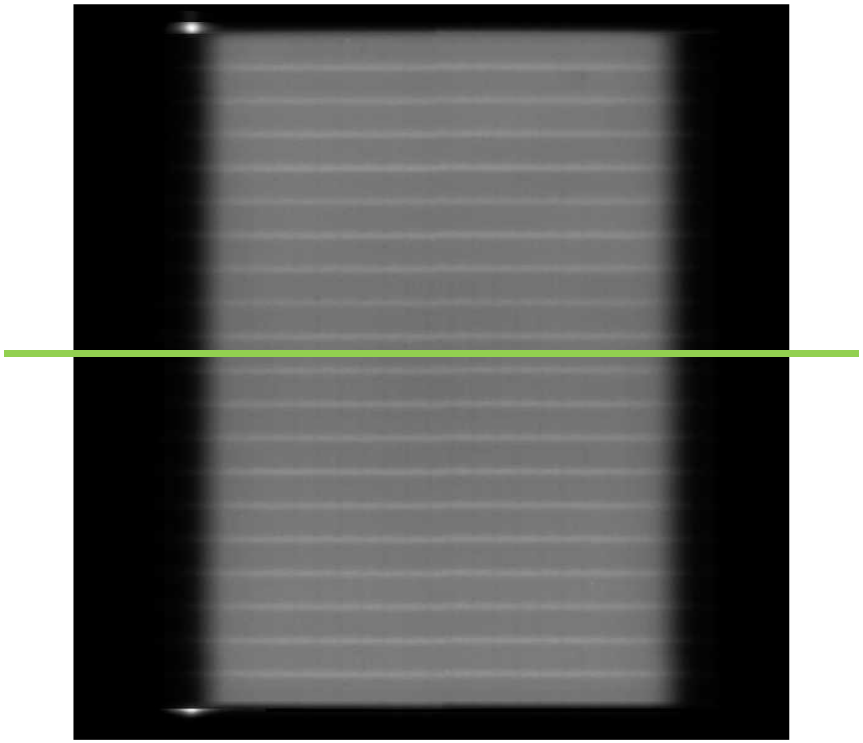
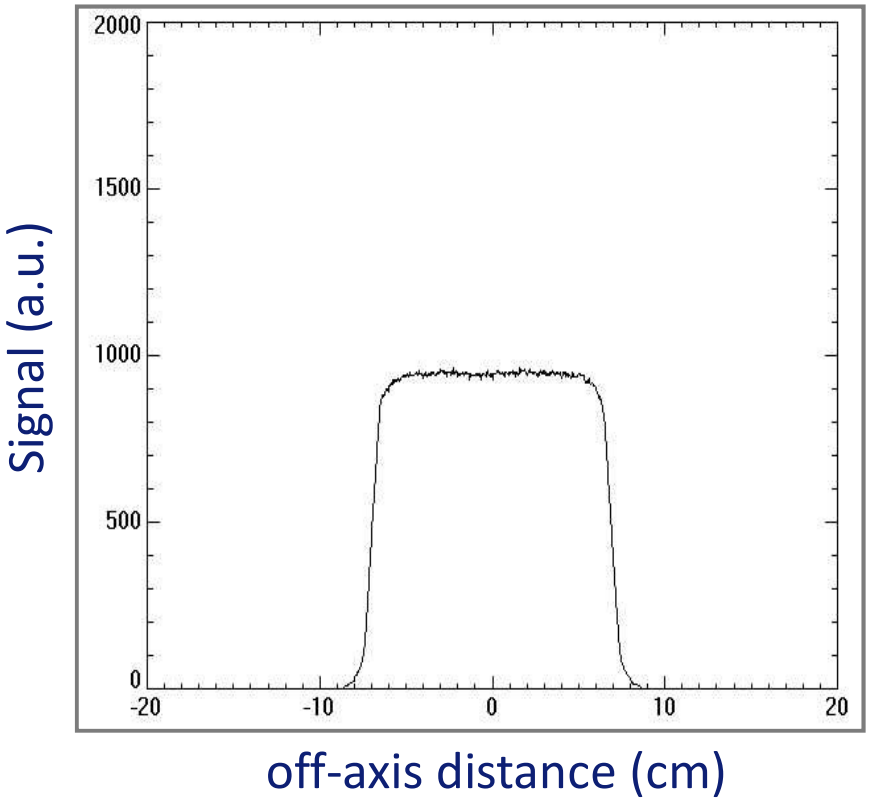
QA of Leaf Travel With an EPID: Processed Image

EPID Images





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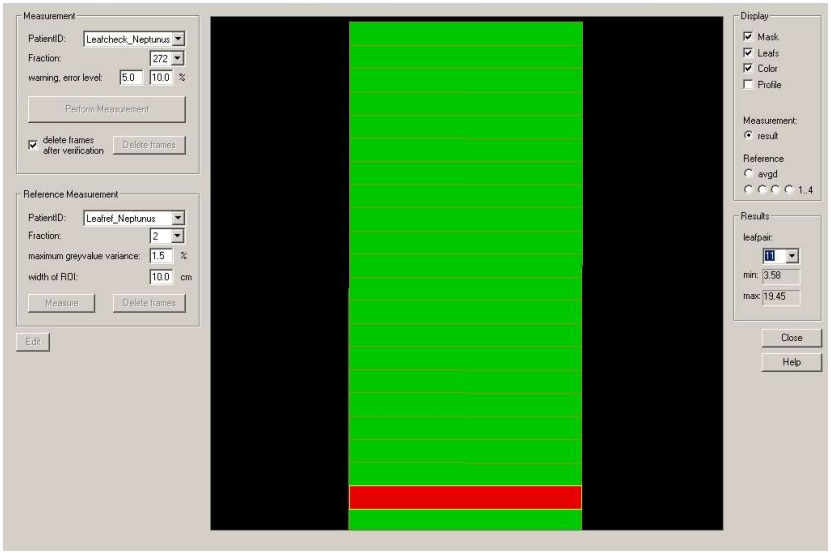
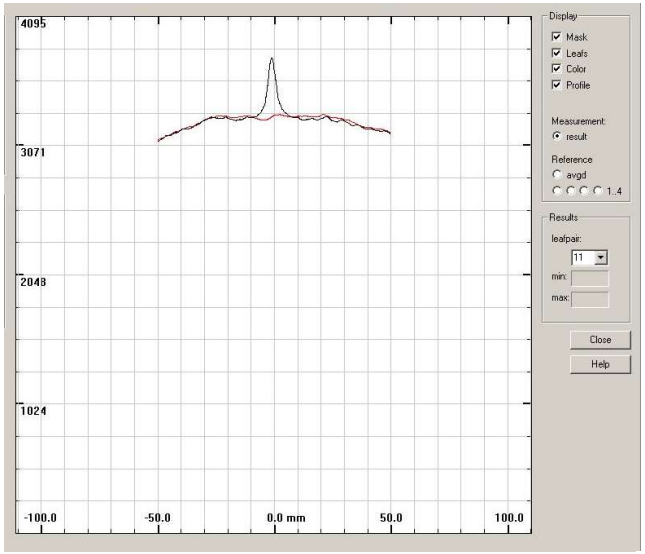
Example of Malfunctioning Leaf





Daily (low cost) test of MLC

Sandra C. Vieira,a) Maarten L. P. Dirkx, Kasper L. Pasma, and Ben J. M. Heijmen Fast and accurate leaf verification for dynamic multileaf collimation using an electronic portal imaging device. Med. Phys. 29 (9), September 2002

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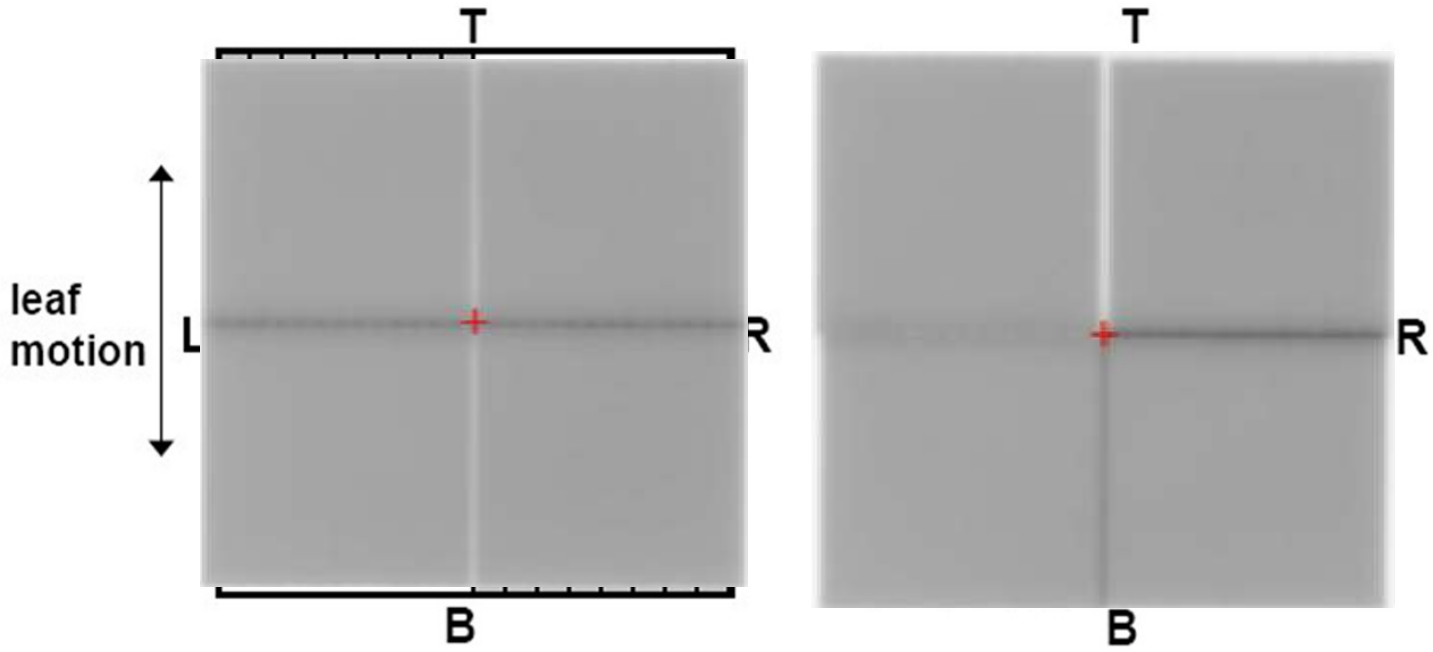
MLC Alignment Tests



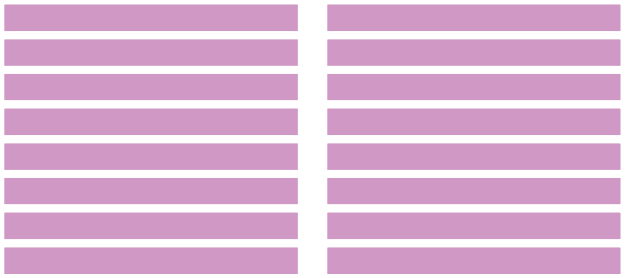
Collimator = 90°

Thomas J. Losasso “IMRT Delivery System QA”, AAPM Medical Physics Monograph No. 29, Intensity-Modulated Radiation Therapy, The State of the Art, Jatinder R. Palta and T. Rockwell Mackie, Editors, Medical Physics Publishing, Madison, WI, USA, 2003

VMAT and RapidArc

- VMAT and RapidArc adds more degrees of freedom to the treatment plan
  - Simultaneous gantry rotation and irradiation
    - Variable gantry speed
    - Variable dose rate

- **Test 1: MLC movement during gantry rotation**
  - Leaf gap 1 mm
  - Continuous gantry rotation
  - MLC moves 2 cm and stops



C. Clifton Ling, Pengpeng Zhang, Yves Archambault, Jiri Bocanek, Grace Tang, M. Phil, and Thomas Losasso, Commissioning And Quality Assurance Of Rapidarc Radiotherapy Delivery System Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 2, Pp. 575–581, 2008

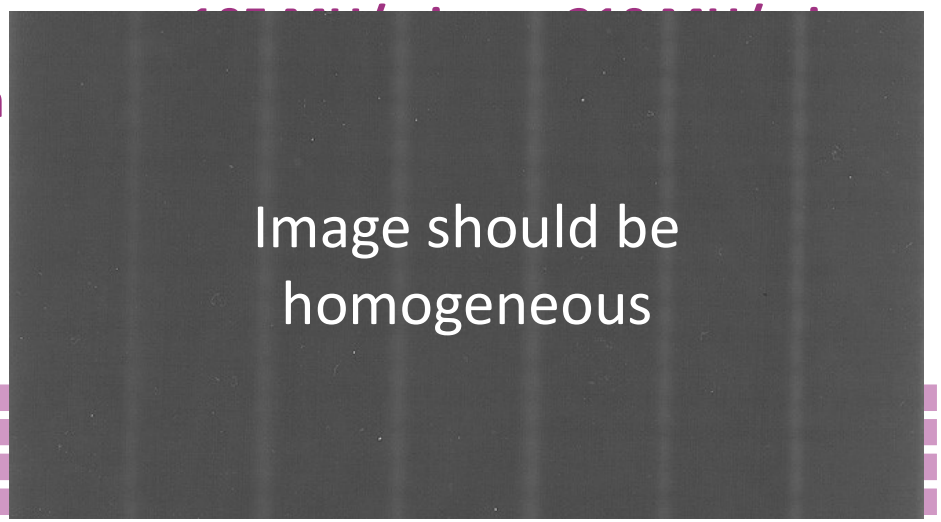
Test 2: Dose rate and gantry speed

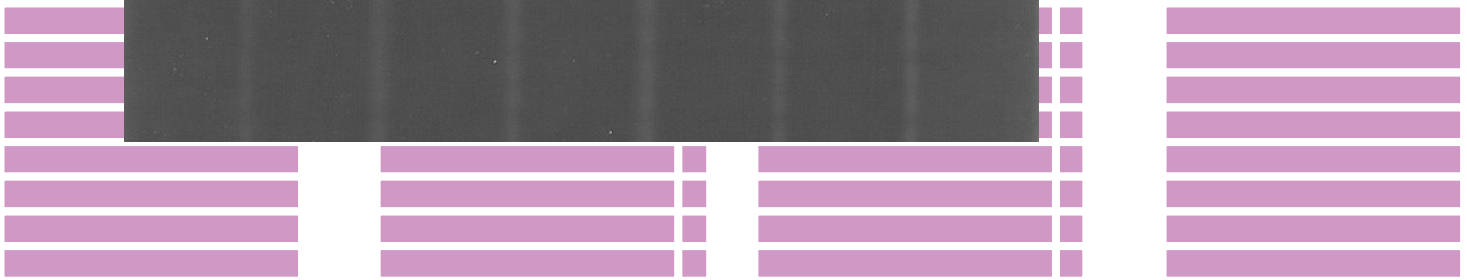
- Dose [MU] = dose rate [MU/min] *arc length [^{o}] *(1 / gantry speed) [s/^{o}] * 1/60 [min/s]

- **Dose rate** **600MU/min**
- **Arc length** **13.3^o**
- **G speed** **4.4^o/s**

1/60 min/s

- **Dose** **= 30 MU**





C. Clifton Ling, Pengpeng Zhang, Yves Archambault, Jiri Bocanek, Grace Tang, M. Phil, and Thomas Losasso, Commissioning And Quality Assurance Of Rapidarc Radiotherapy Delivery System Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 2, Pp. 575–581, 2008

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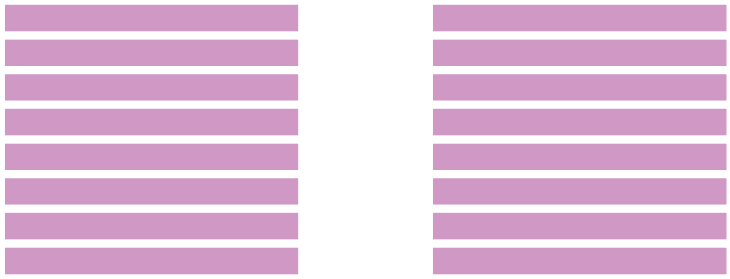
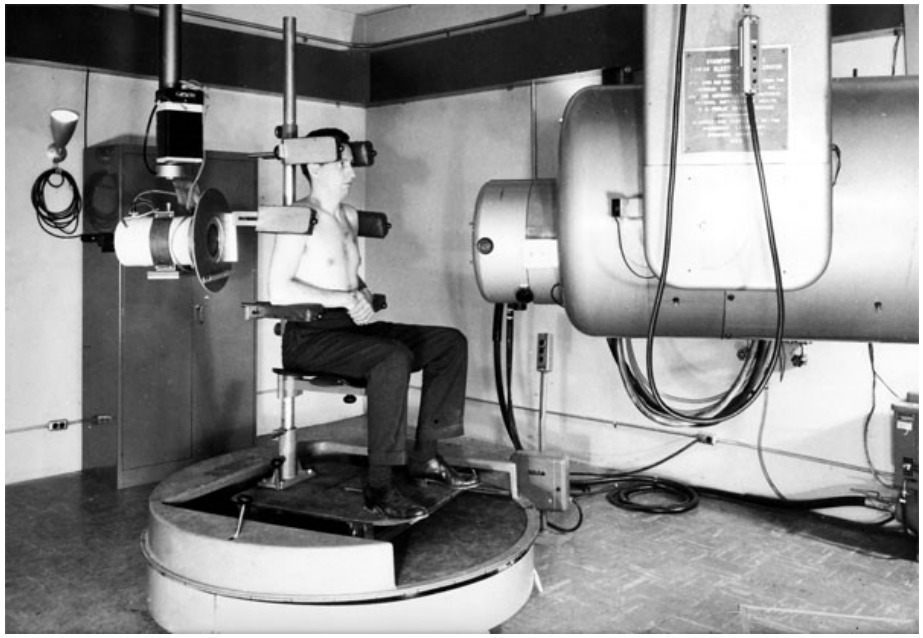
Test 3: Dose Rate and MLC Speed

- Dose [MU] = dose rate [MU/min] *path leafs [cm]*(1/ speed leafs) [s/cm] * 1/60 [min/s]

Dose rate	480 MU/min	240 MU/min
Leaf speed	0.4 cm/s	0.8 cm/s
Dose	15 MU	15 MU

Image should be homogeneous



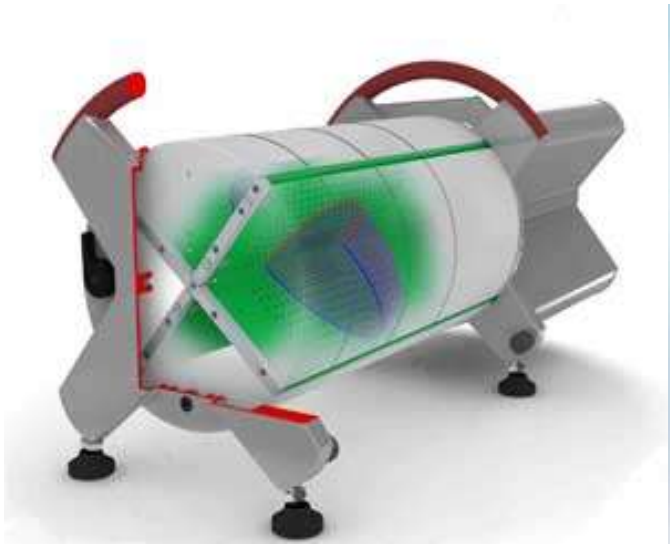


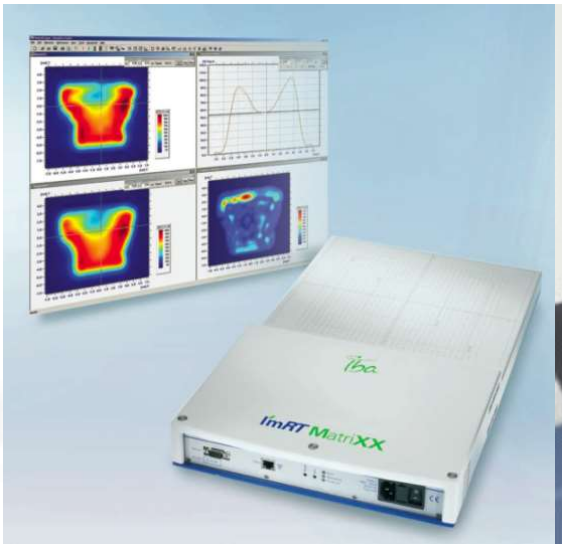
TOWARD CLINICAL REALITY

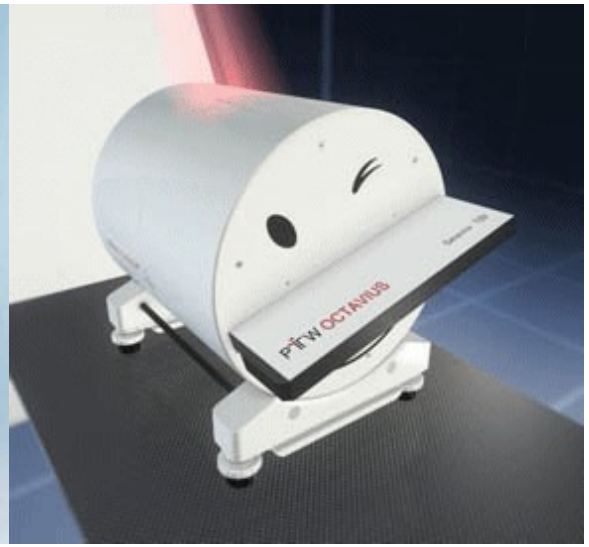
Patient Specific Pretreatment QA

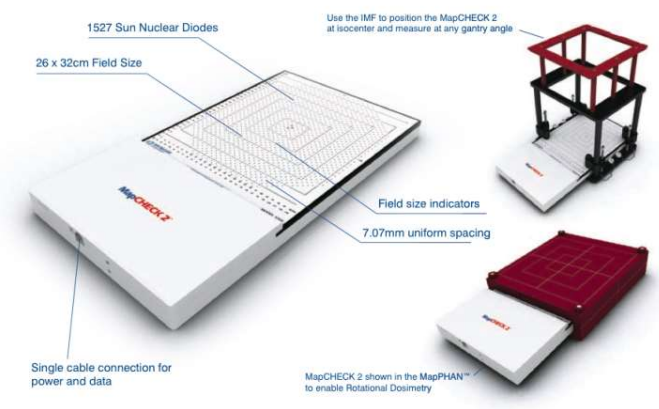
1. **IMRT or VMAT plan is approved by Radiation Oncologist**
2. **Redundant dose calculation**
   - Single point or full 3D dose distribution
   - Based on treatment planning output or machine control settings
3. **Pretreatment QA**
   1. Plan is copied to measurement device
   2. Dose is recalculated on measurement device
      - Convert all fields to 0-gantry, 0-collimator, 0-table rotation (analyze results on a field-by-field basis)
   3. Export calculated dose (at the plan of the detector)

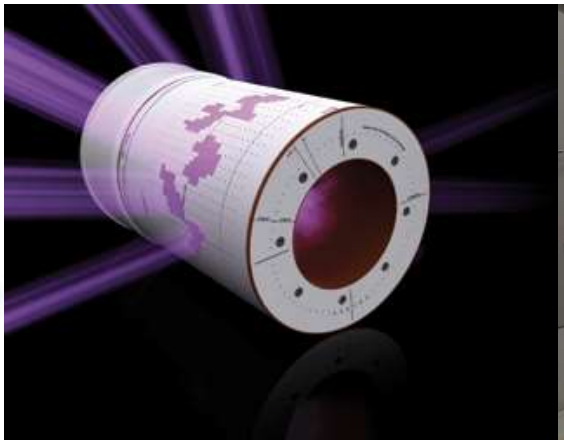
2D Arrays of Ionization Chambers and Diodes

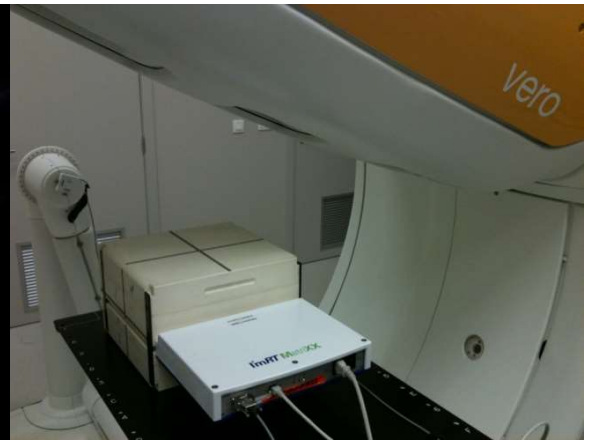












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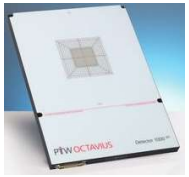
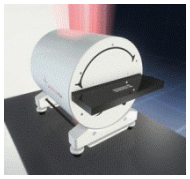
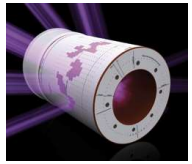
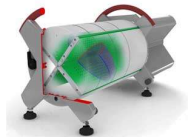
What is Important?

- **Detectors**
  - Ionization chambers (absolute dose)
  - Liquid ionization chambers (cross calibration)
  - Diodes (cross calibration)
- **Directional dependence**
  - Various solutions: correction lookup table or compensation by phantom geometry
- **Energy dependence**
  - ICs better than diodes
- **Detector size**
  - Volume effects
- **Detector resolution**

Suppliers and Model Types

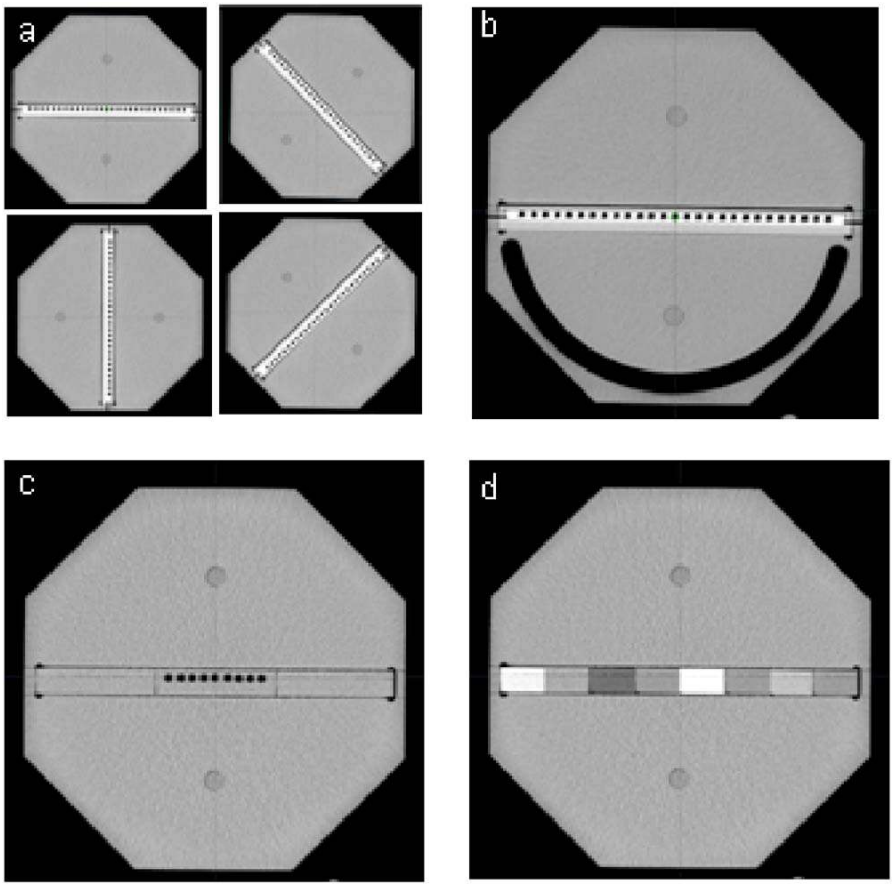


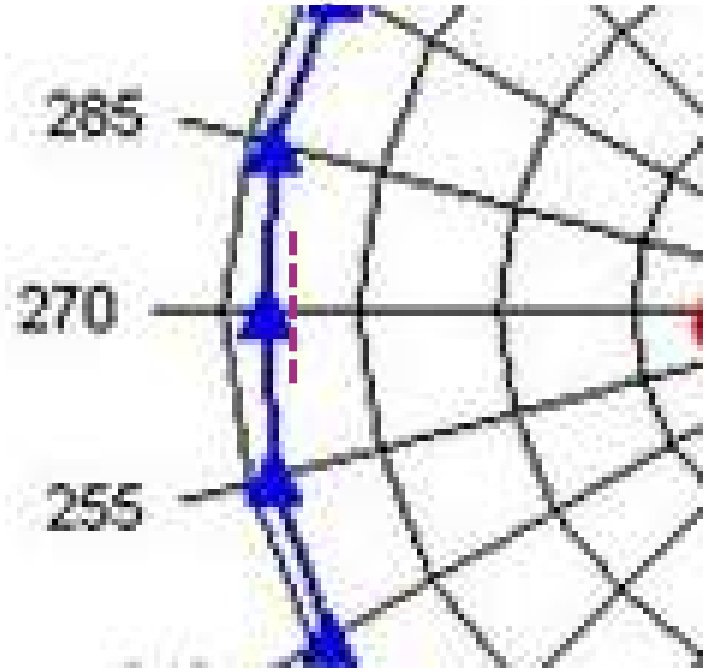



	Sun Nuclear	PTW	PTW	PTW	IBA	Sun Nuclear	ScandiDos
	MapCheck 2	Octavius II	Octavius 1000 SRS	Octavius 4D	MatriXX	ArcCHECK	Delta4
Array		Seven29	1000SRS	Seven29 1000SRS			
Resolution (mm)	7.1	10	2.5-5	10/2.5-5	7.6	1.0	5-10
Detector	Diode	IC	Liquid IC		IC	Diode	Diode
Application	IMRT, Arc, FFF	IMRT, Arc, FFF	SRS/SBRT, IMRT, Arc, FFF	IMRT, Arc, FFF	IMRT, FFF*, Arc with MultiCube	IMRT, Arc, FFF, SRS/SBRT	IMRT, Arc, FFF
2D/3D	2D	2D	2D	2D and 3D	2D and 3D	2D and 3D	2D and 3D

Octavius and Angular Dependence





From PTW website: right: NKI-AVL and ieft: Van Esch A, Clermont C, Devillers M, Iori M, Huyskens DP. On-line quality assurance of rotational radiotherapy treatment delivery by means of a 2D ion chamber array and the Octavius phantom. Med Phys. 2007 Oct;34(10):3825-37.

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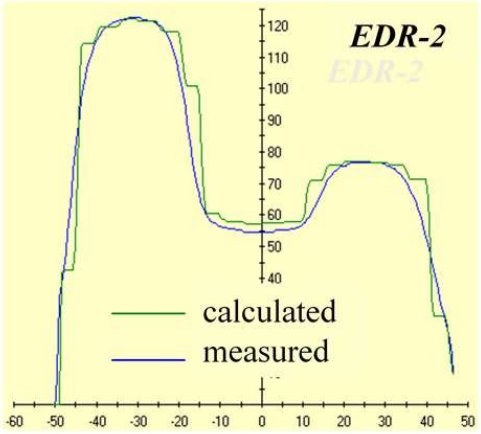
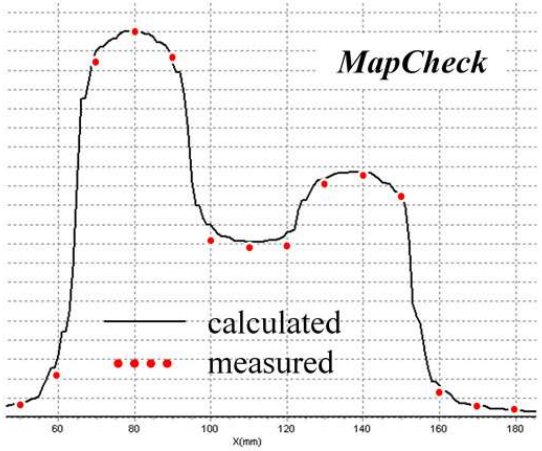
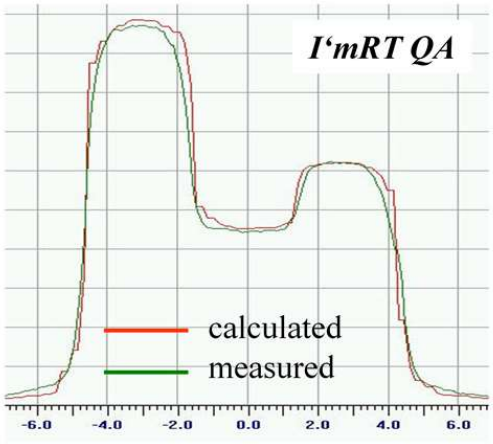
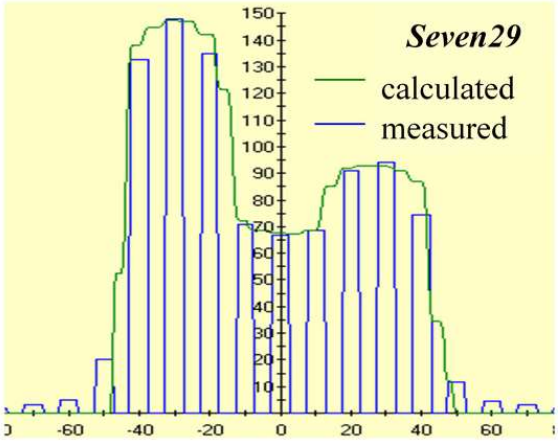
Consider Resolution of Detector System









From Wiezorek T, Banz N, Schwedas M, Scheithauer M, Salz H, Georg D, Wendt TG. Dosimetric quality assurance for intensity-modulated radiotherapy feasibility study for a filmless approach. Strahlenther Onkol. 2005 Jul;181(7):468-74.

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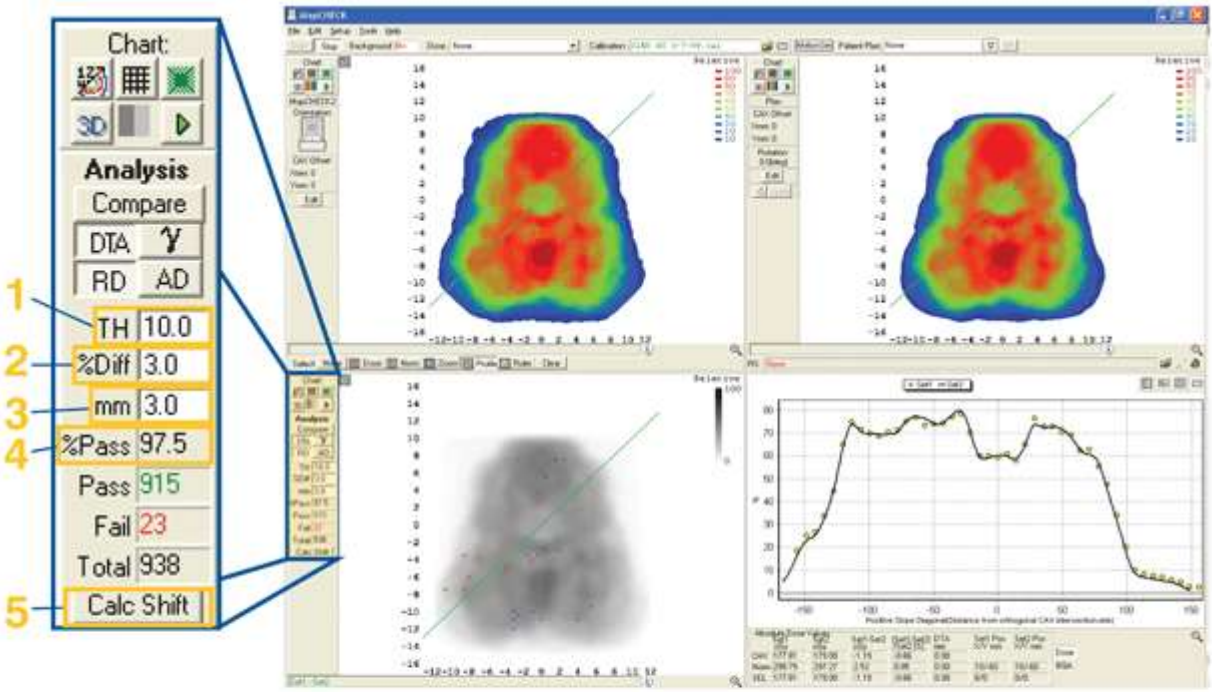
2D Analysis



1 **TH:** Isodose percentage line that defines the dose area to evaluate.

2 **% Diff:** Percent acceptance criterion between Set 1 and Set 2 dose values.

3 **mm:** Distance-to-agreement criterion

4 **% Pass:** Percentage of detector points that passed within the defined threshold with a pass/fail indication

5 **Calc Shift:** Determines if there is a misalignment between the measured & planned dose maps and automatically corrects for the misalignment if accepted by the user

From: Sun Nuclear website

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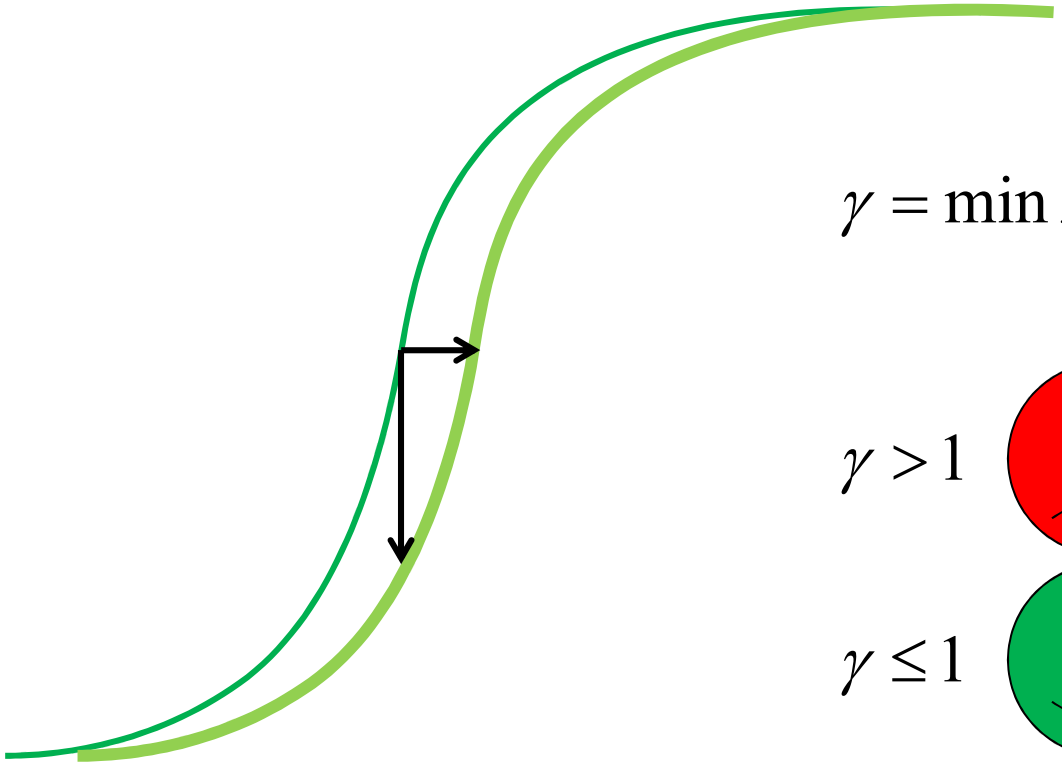
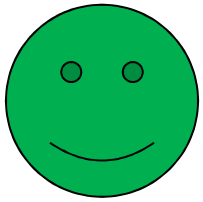
Gamma Analysis



$$\gamma = \min \sqrt{\left(\frac{d}{DD}\right)^2 + \left(\frac{r}{DTA}\right)^2}$$

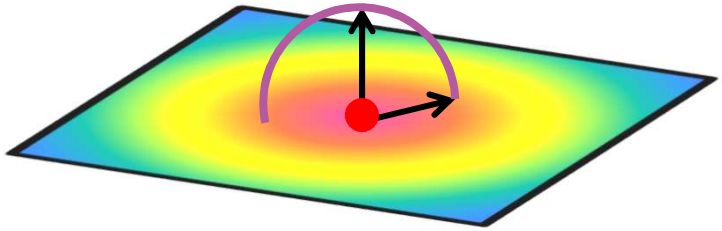
$\gamma > 1$

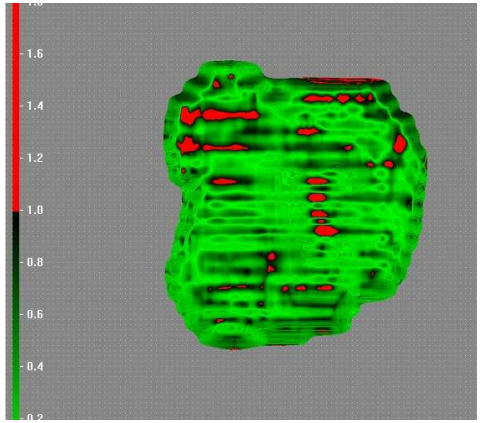
$\gamma \leq 1$



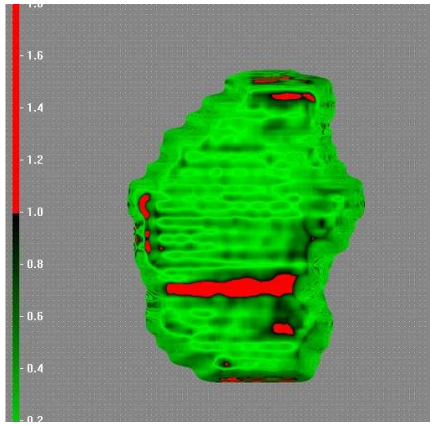
Interpretation of Gamma Statistics

- DD = 2% and DTA = 2 mm?
- Local or global dose?
- Threshold for passing?
- 2D or pseudo 3D?





N_{reject}= 3.8% γ_{mean}= 0.41



N_{reject}= 4.9% γ_{mean}= 0.36

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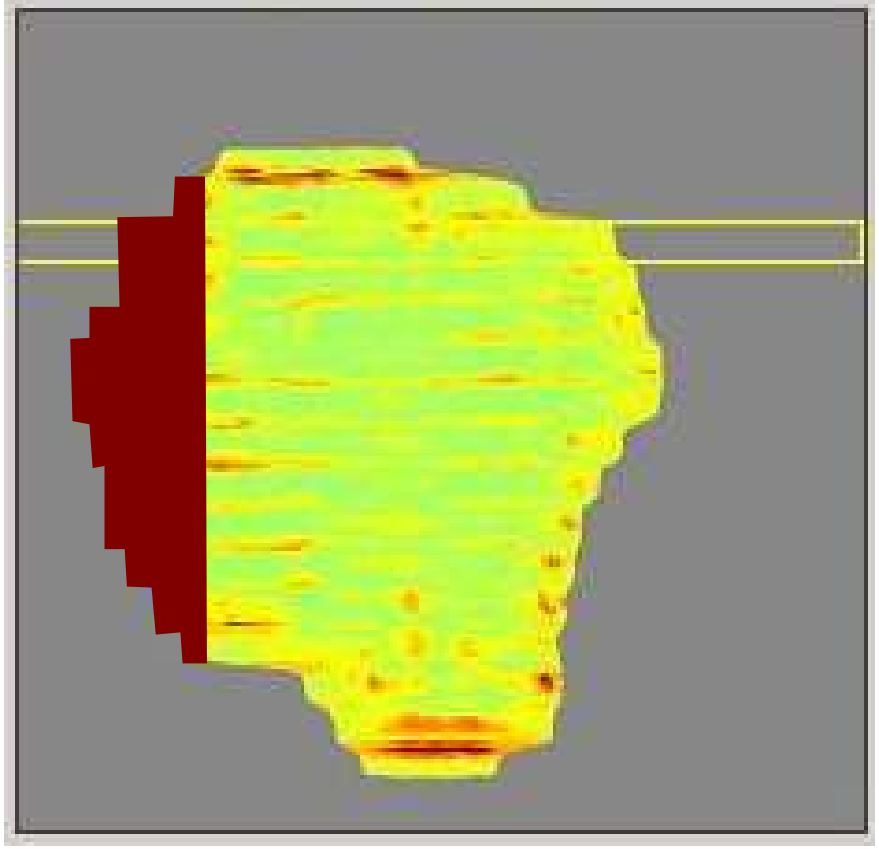
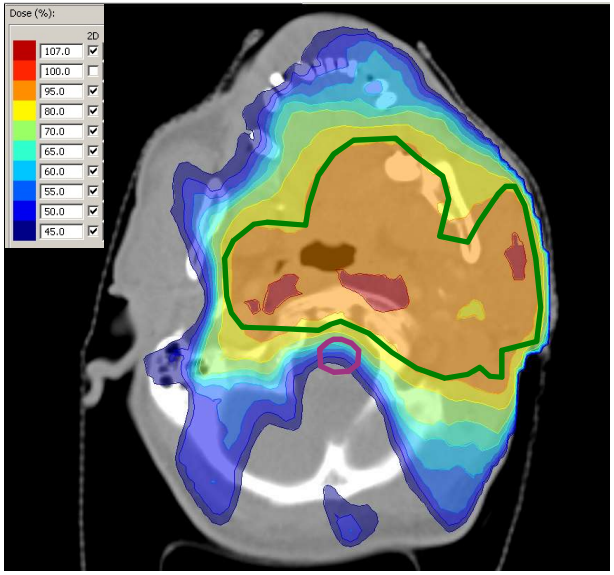
Detected Errors During Pretreatment Verification

Field shape changed in R&V system



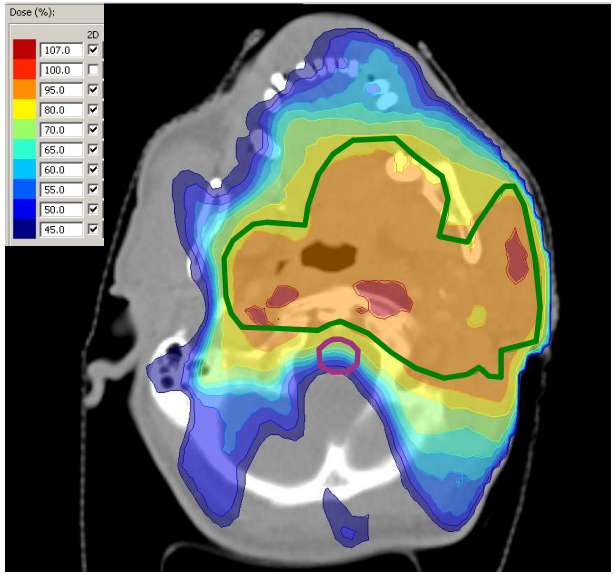
Limitation of Gamma Analysis: DTA



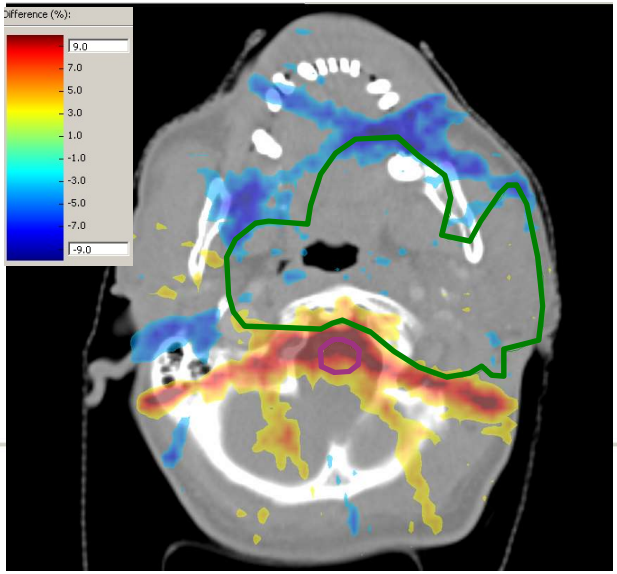
planned dose distribution

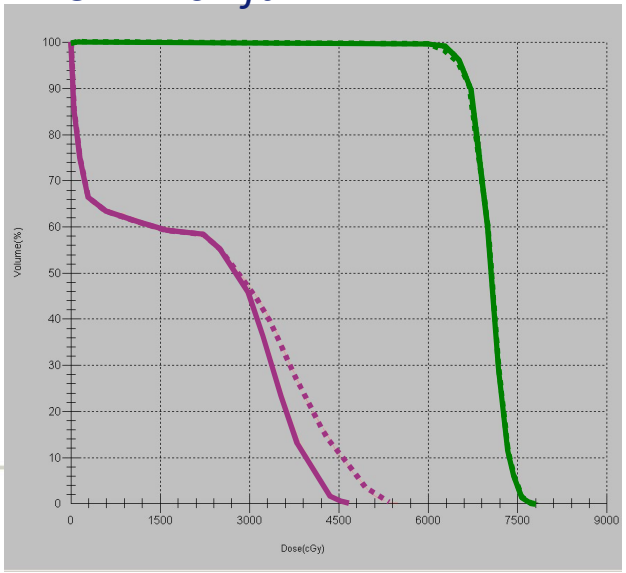
PTV

cord

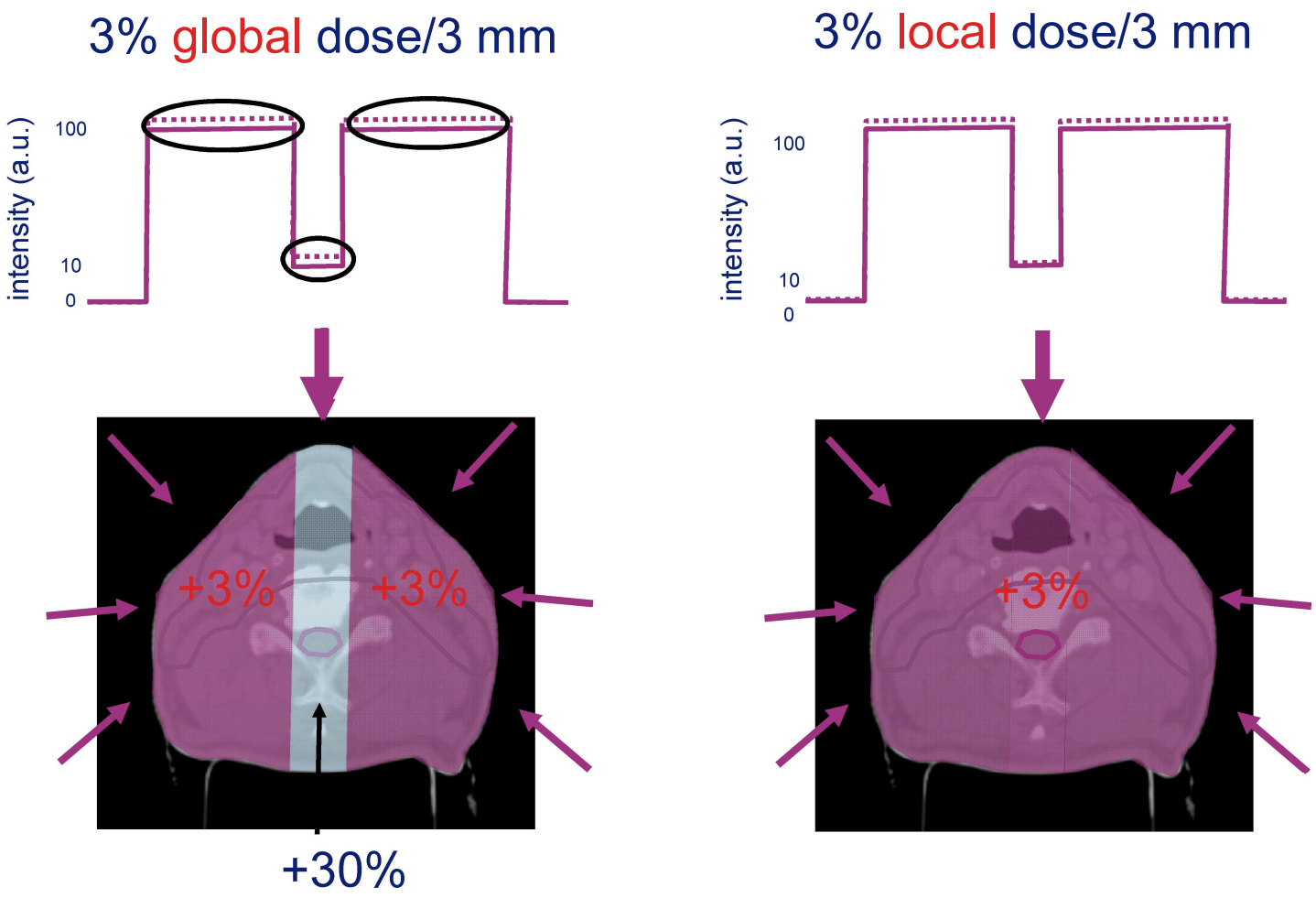


3 mm shift





2D Gamma Evaluation: Reference Criteria



From: M.L.P Dirkx

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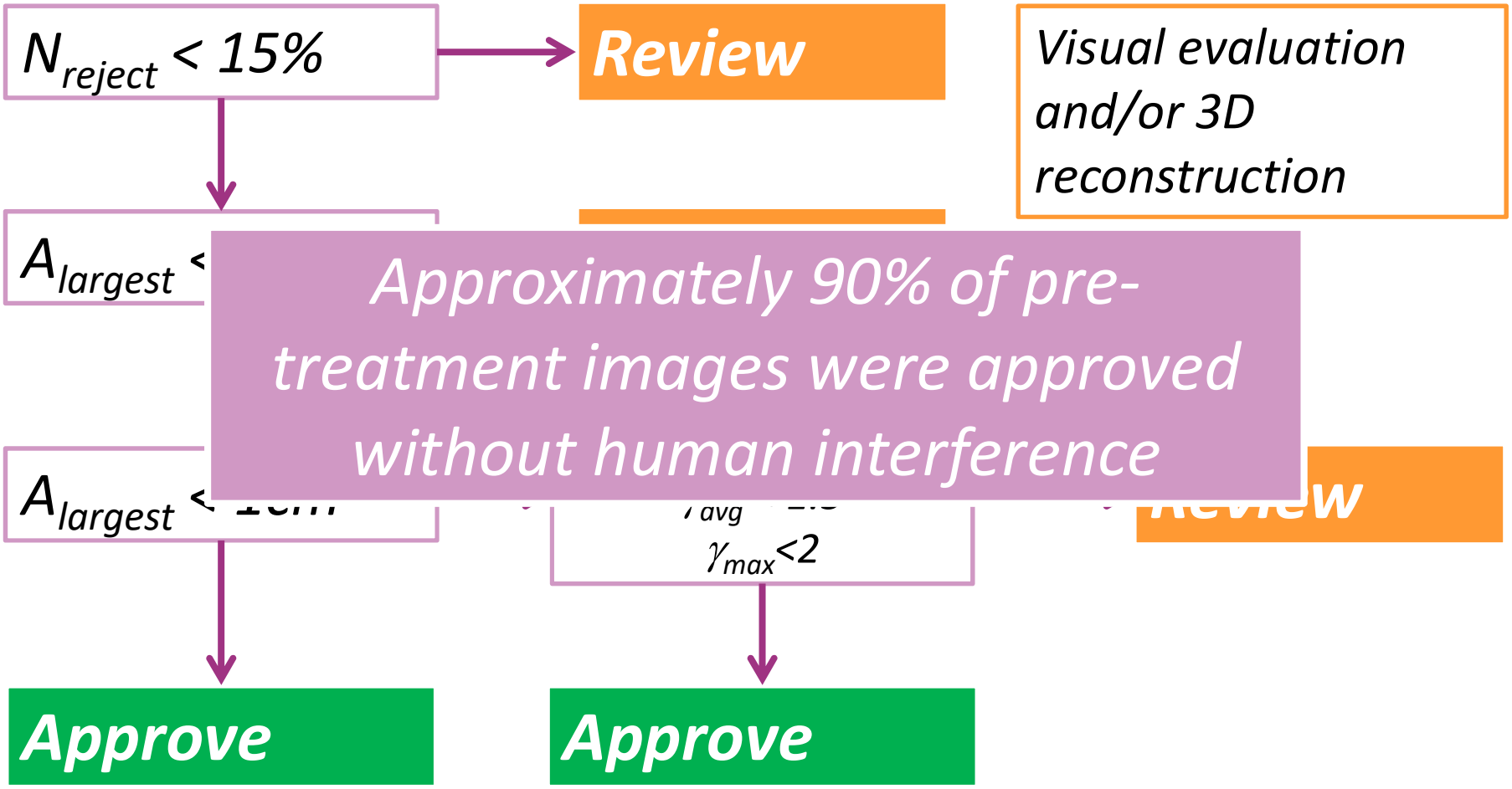
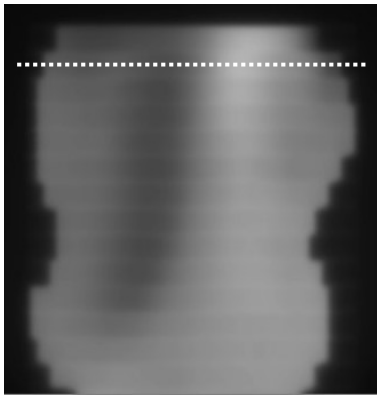
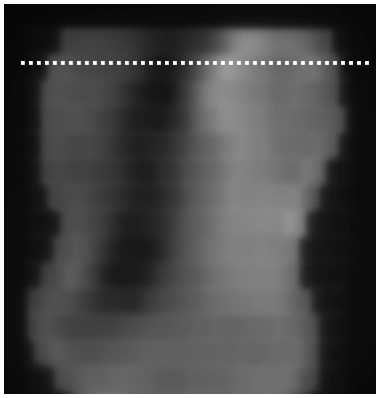
Semi-automatic Evaluation Scheme



Wrong Plan in R&V System

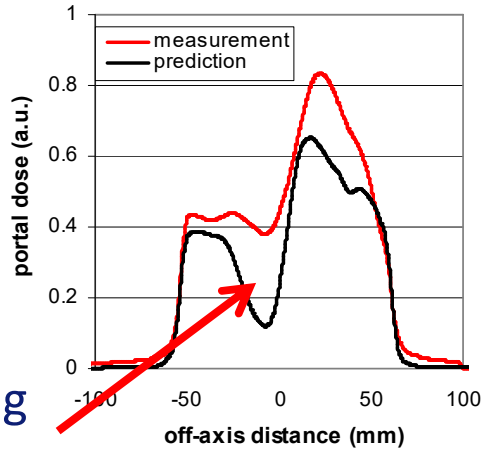


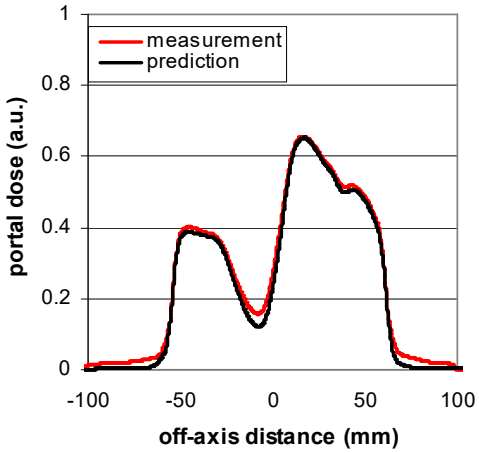
measured PDI



predicted PDI

shielding cord





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From 2D to 3D Dose-Volume Analysis

- "There is a lack of correlation between conventional IMRT QA performance metrics (Gamma passing rates) and dose errors in anatomic regions-of-interest. The most common acceptance criteria and published actions levels therefore have insufficient, or at least unproven, predictive power for per-patient IMRT QA."*

- **To 3D using 2D measurements**
  - Mathematically perturb the dose in the patient
  - Reconstruct the dose in the phantom
  - Recalculate dose in the patient based on the reconstructed fluence

*Nelms BE, Zhen H, Tomé WA. Per-beam, planar IMRT QA passing rates do not predict clinically relevant patient dose errors. Med Phys. 2011 Feb;38(2):1037-44.

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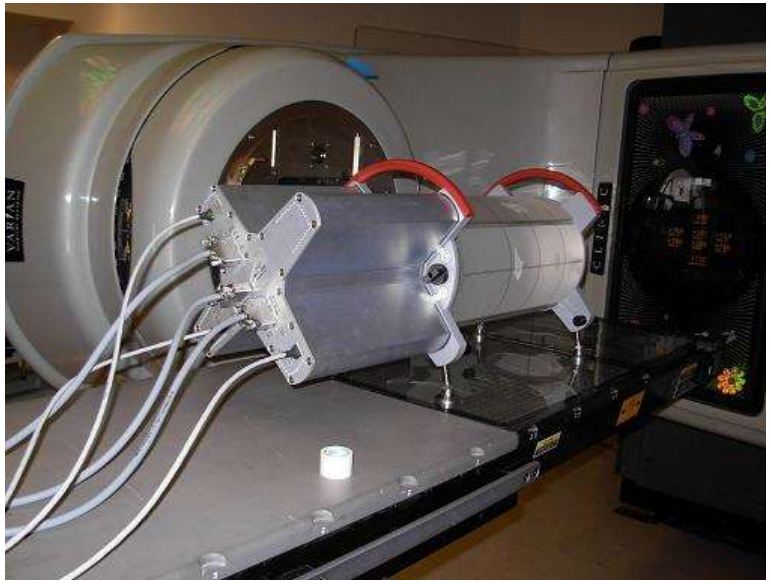
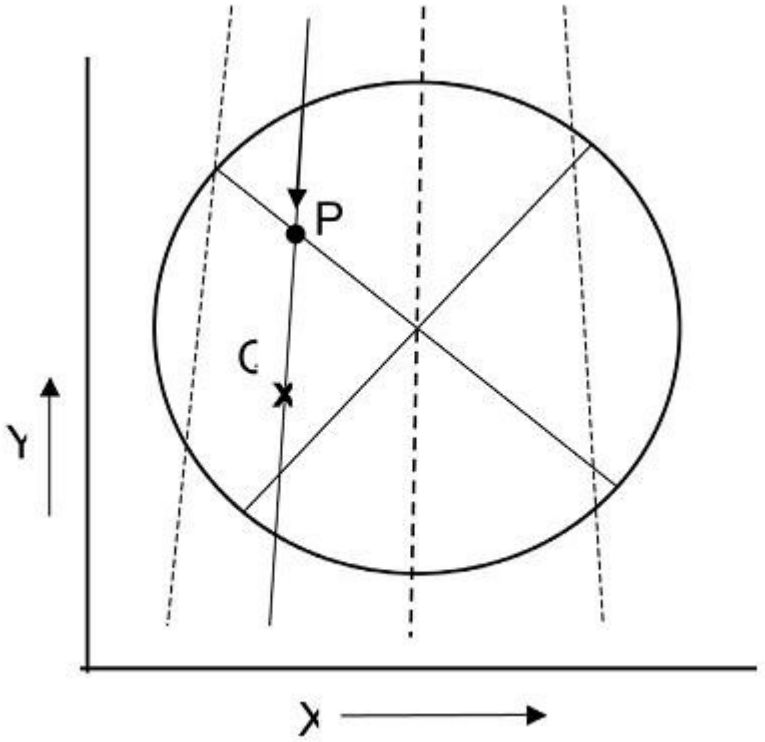
Delta4 System: Dose Perturbation





$$D_{SM}(Q) = D_M(P) * D_C(Q) / D_C(P)$$

Sadagopan R, Bencomo JA, Martin RL, Nilsson G, Matzen T, Balter PA. Characterization and clinical evaluation of a novel IMRT quality assurance system. J Appl Clin Med Phys. 2009 May 7;10(2):2928. PubMed PMID: 19458595.

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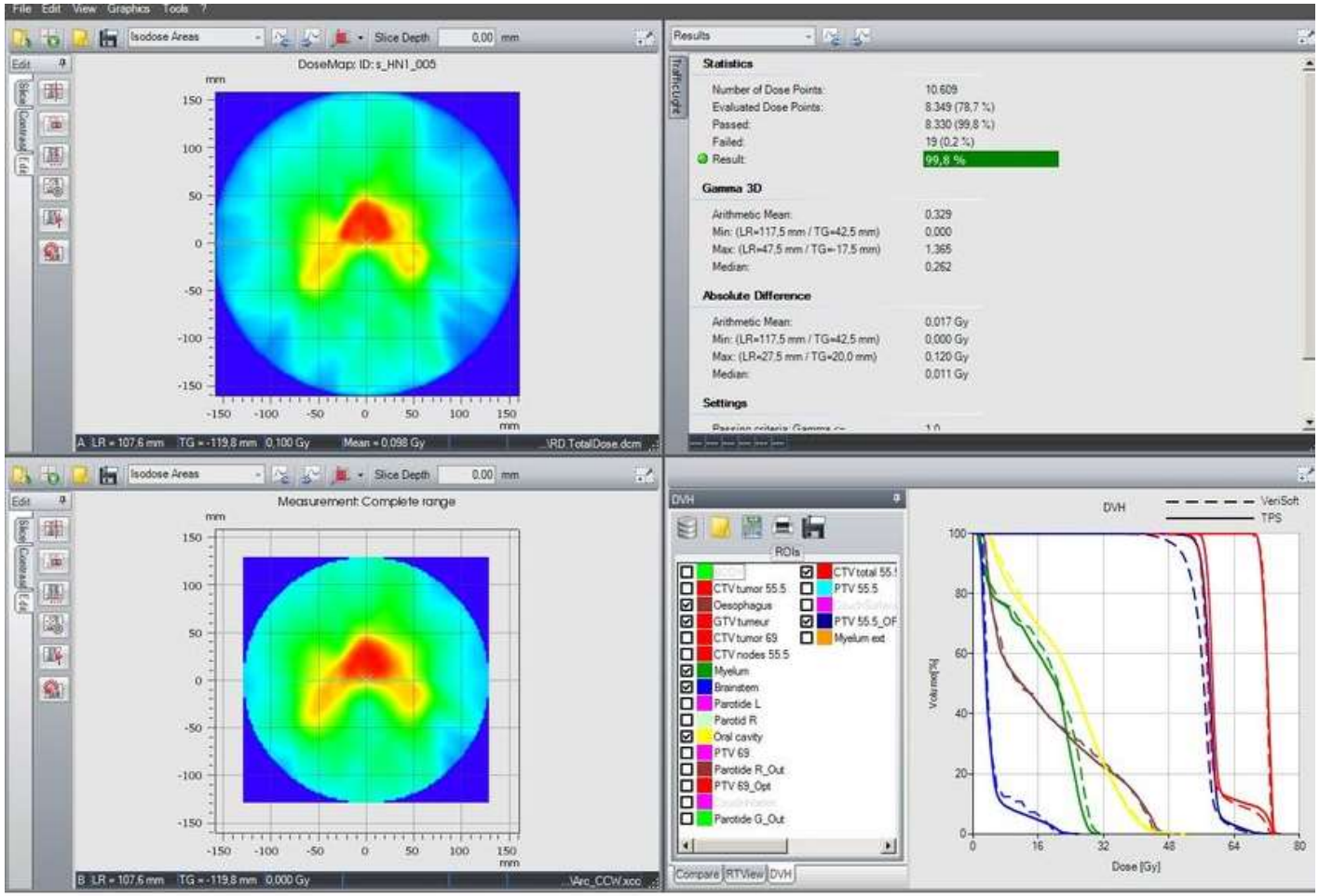
3D Volume Analysis



From: PTW website

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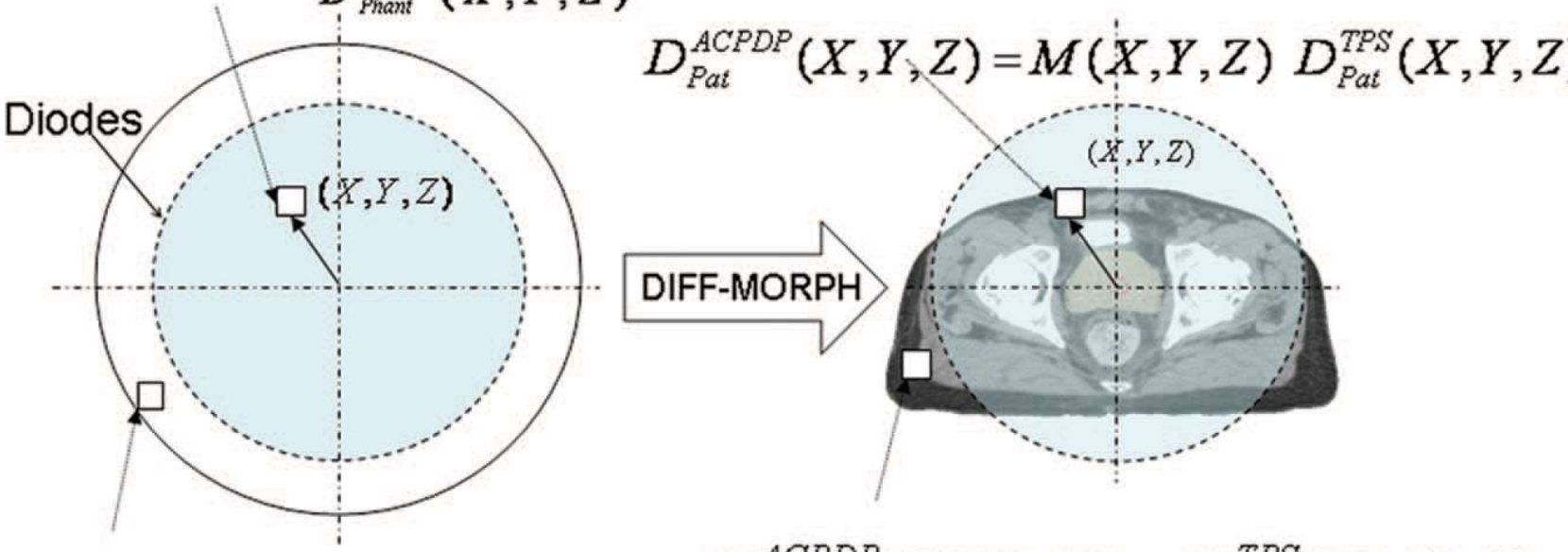
From Phantom to Patient

$$VCF\ (X,Y,Z) = \frac{D^{ACPDP}_{Phant}\ (X,Y,Z)}{D^{TPS}_{Phant}\ (X,Y,Z)}$$



$$D^{ACPDP}_{Pat}(X,Y,Z) = M(X,Y,Z)\ D^{TPS}_{Pat}(X,Y,Z)$$

$$VCF(X,Y,Z) = 1.0$$

$$D^{ACPDP}_{Pat}(X,Y,Z) = D^{TPS}_{Pat}(X,Y,Z)$$

From: elms BE, Opp D, Robinson J, Wolf TK, Zhang G, Moros E, Feygelman V. VMAT QA: measurement-guided 4D dose reconstruction on a patient. Med Phys. 2012 Jul;39(7):4228-38. doi: 10.1118/1.4729709.

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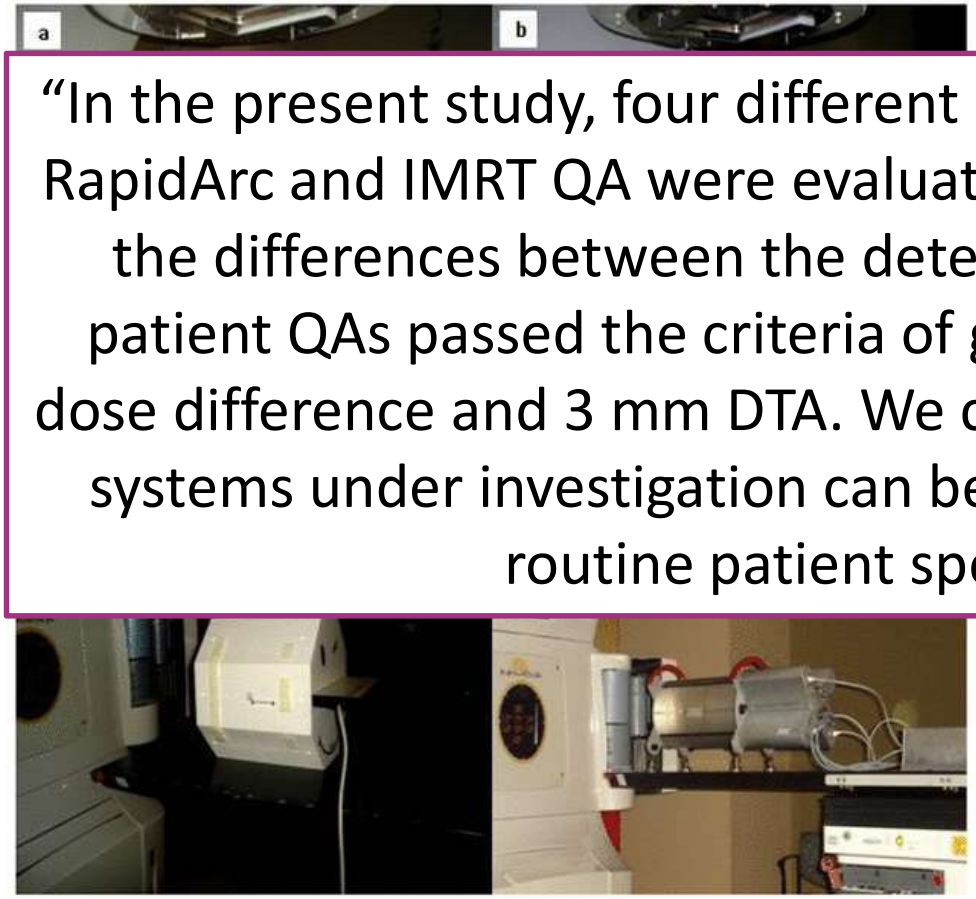
Compass by IBA: Recalculation Based on Fluence

Inter-Device Comparison



"In the present study, four different methods for patient specific RapidArc and IMRT QA were evaluated. The results showed that the differences between the detectors are insignificant. All patient QAs passed the criteria of gamma index values of 3% dose difference and 3 mm DTA. We conclude that the dosimetric systems under investigation can be used interchangeably for routine patient specific QA."

From: CHANDRARAJ, Varatharaj et al. Comparison of four commercial devices for RapidArc and sliding window IMRT QA.Journal of Applied Clinical Medical Physics, [S.l.], v. 12, n. 2, apr. 2011

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DOSIMETRY AUDITS AND E2E TESTING

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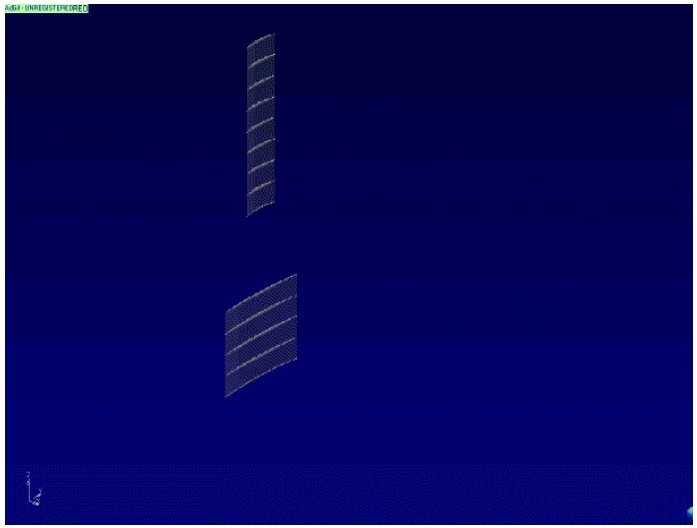
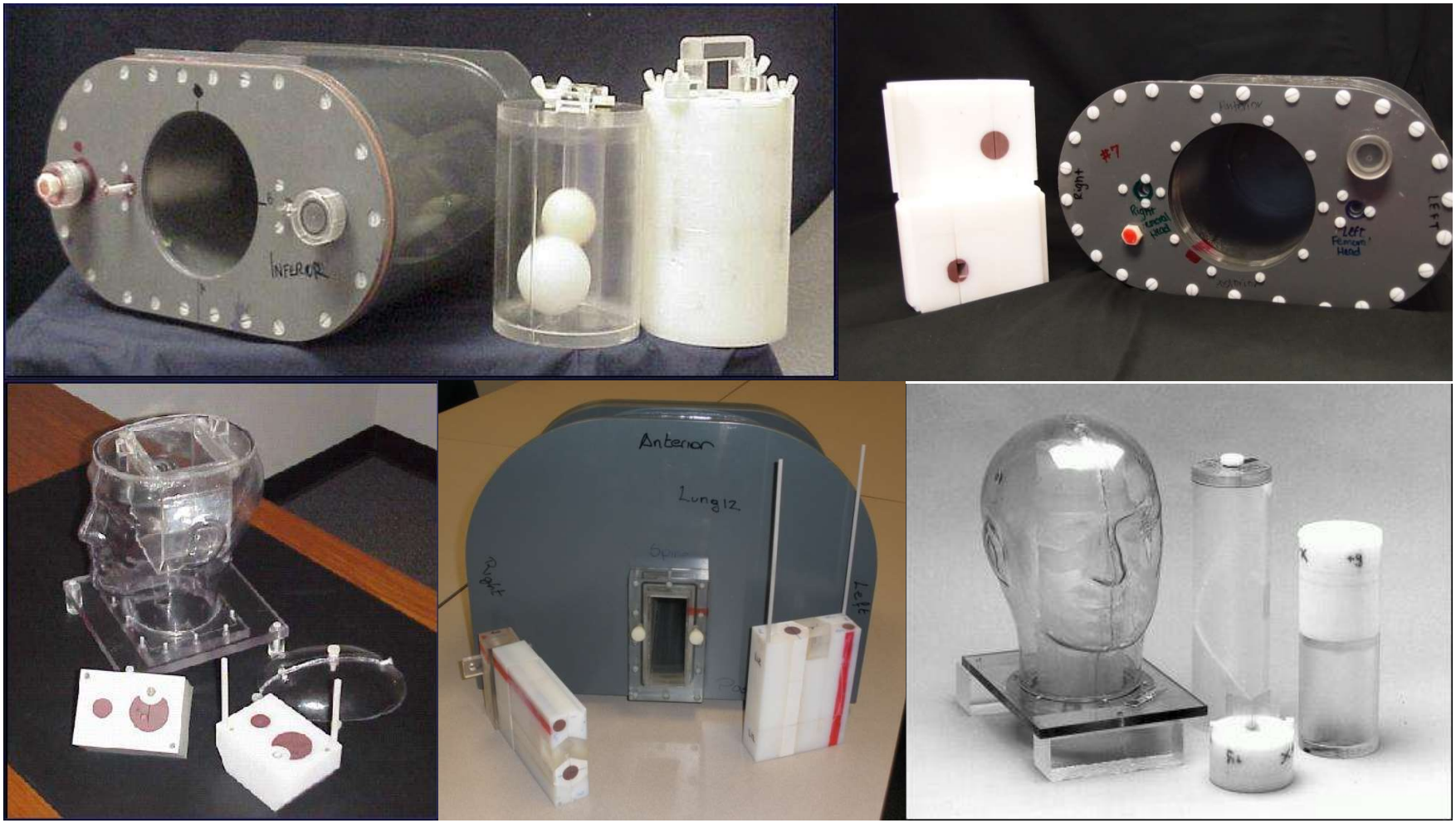
End-to-End Testing

- No one is infallible … and treatment chains are complex
- “End-to-end testing involves ensuring that that integrated components of an application function as expected. The entire application is tested in a real-world scenario such as communicating with the database, network, hardware and other applications” (Techopedia)



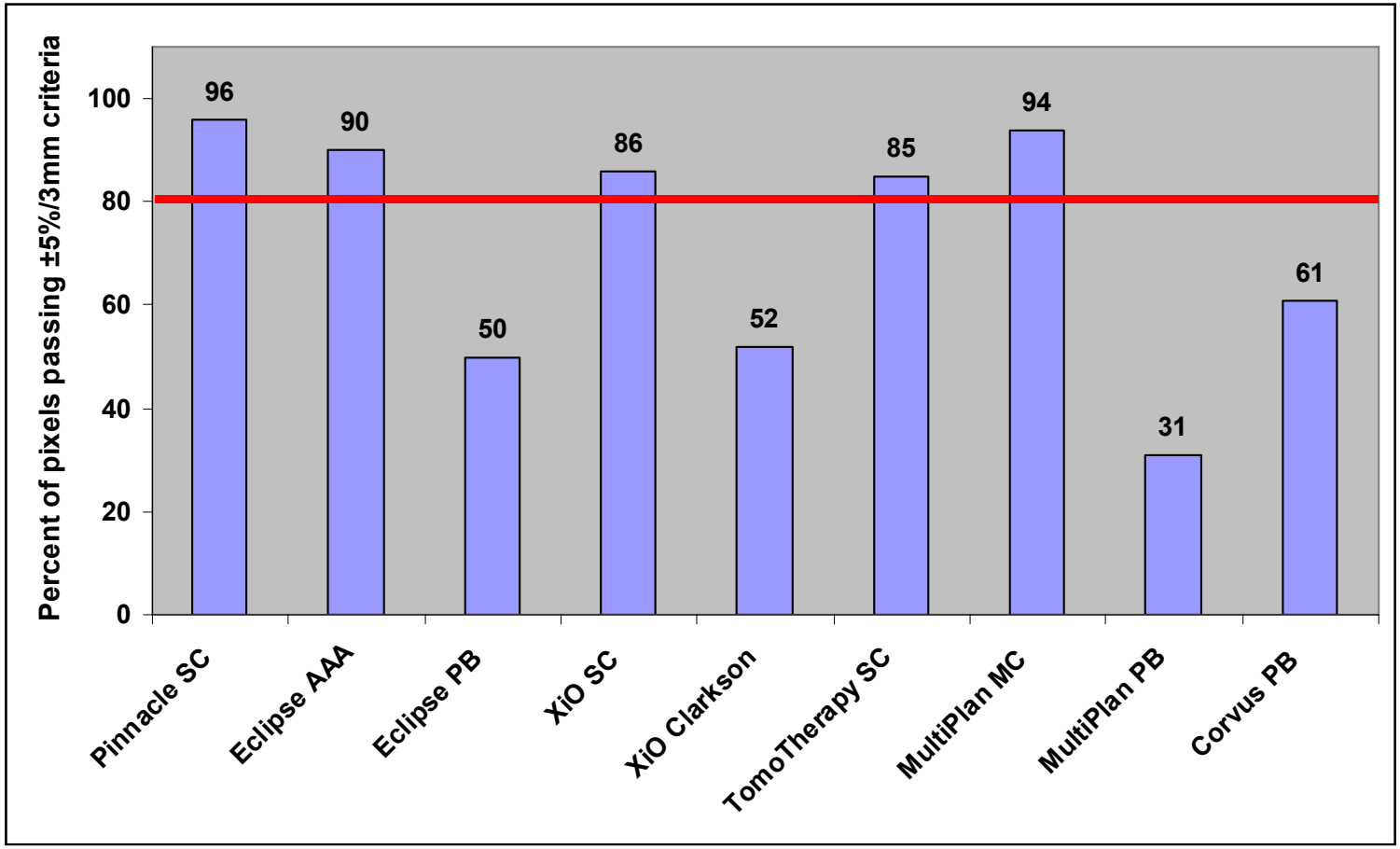
Movie from: © fantôme GORTEC PIGG, M. Tomsej & V. Marchesi

Radiological Physics Center (RPC) Services



From: RPC website

Heterogeneous Dose Calculation Credentialing



From: MD Anderson RPC website; David Followill, Ph.D. and RPC Staff

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IMAGE-GUIDED AND TRACKING SYSTEMS

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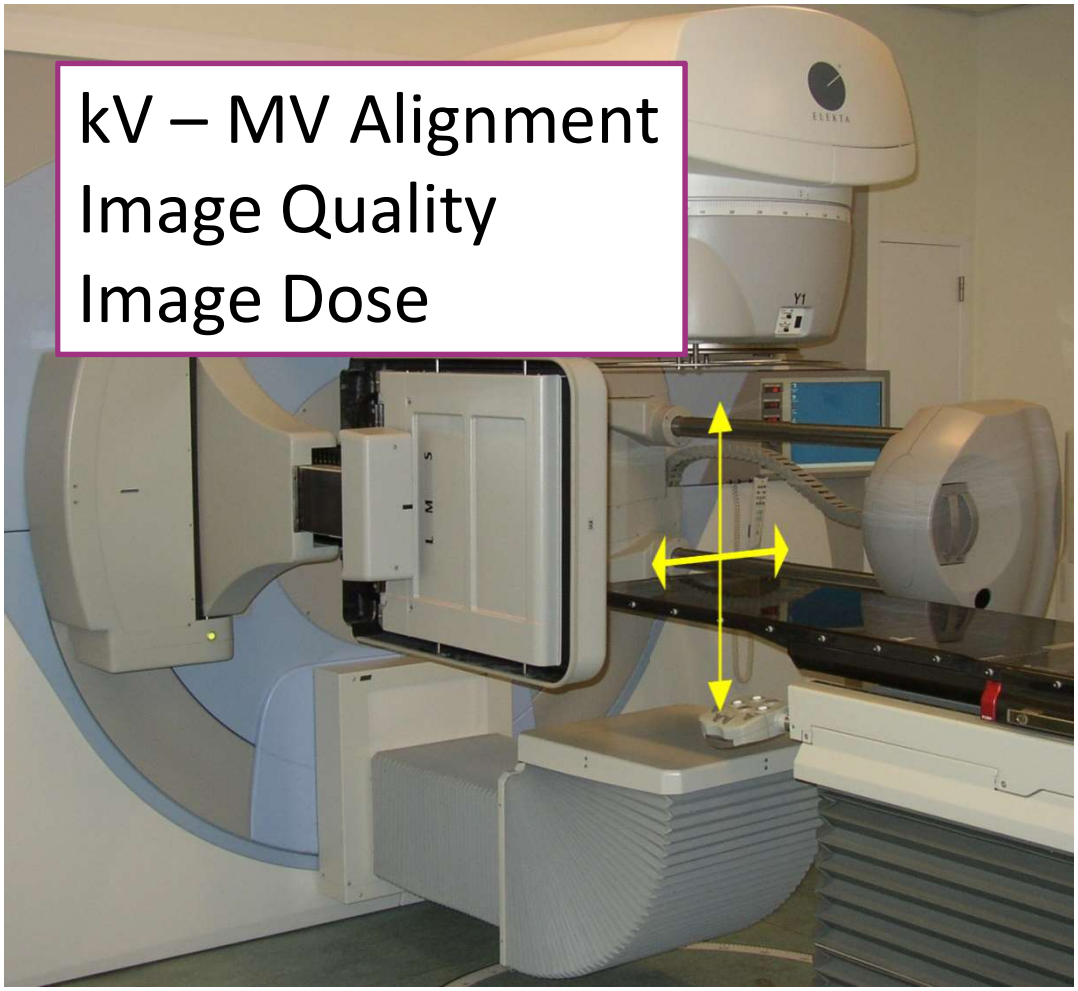
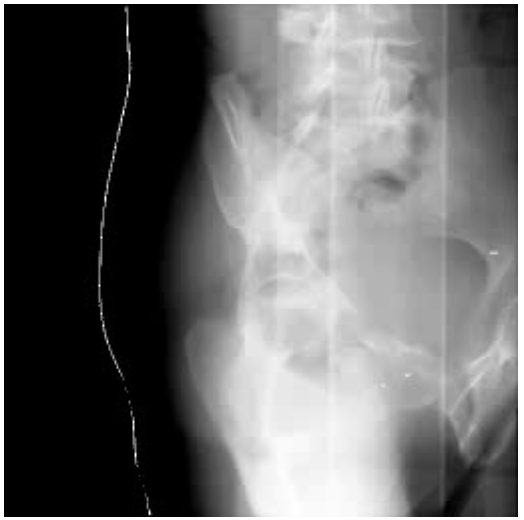
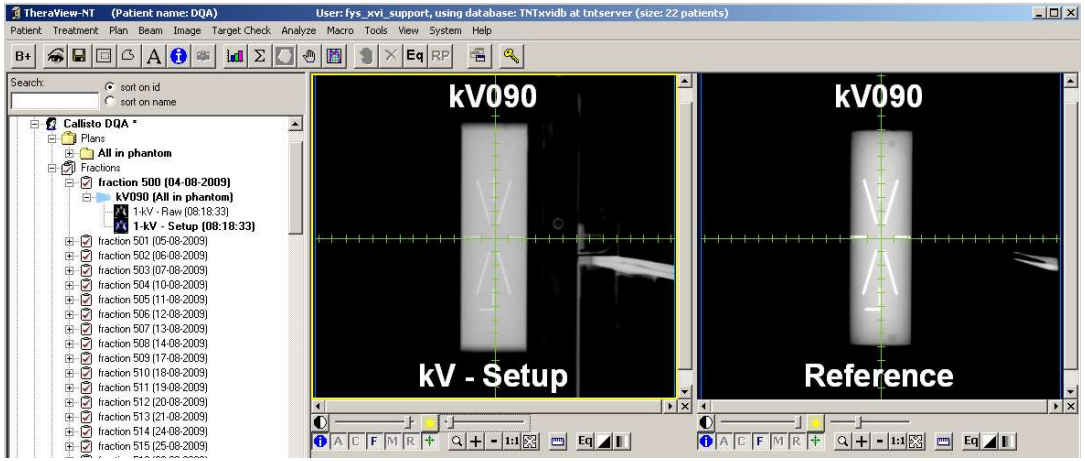
QA of On-Board Imaging Systems





Daily QA Phantom



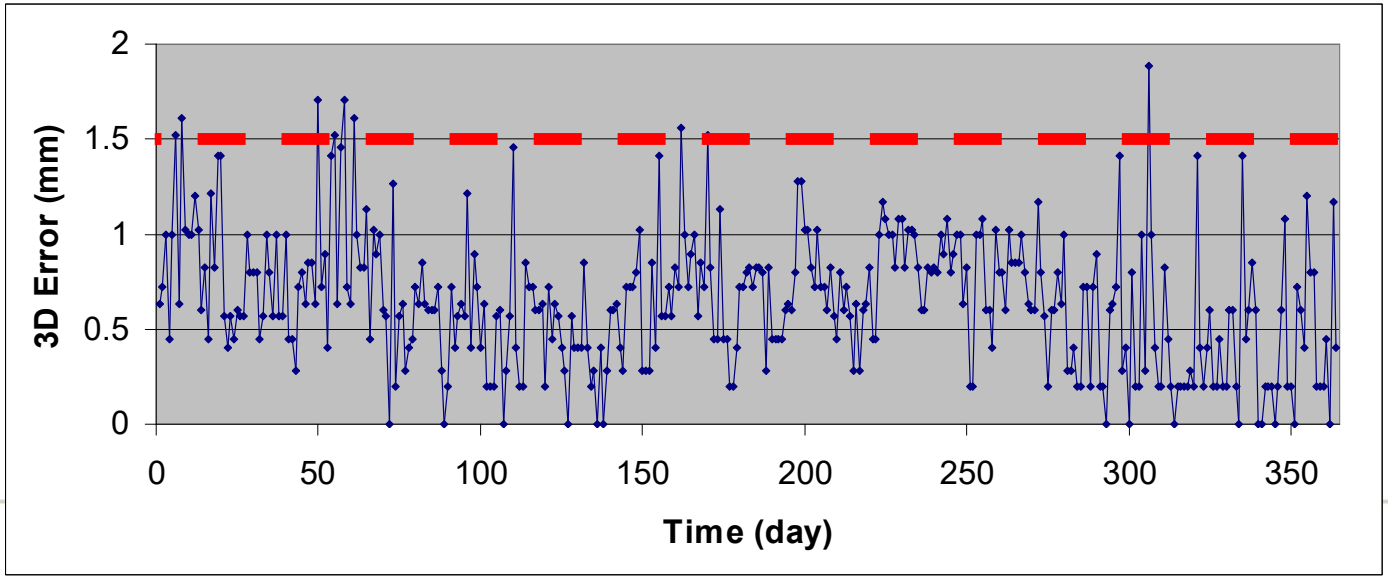


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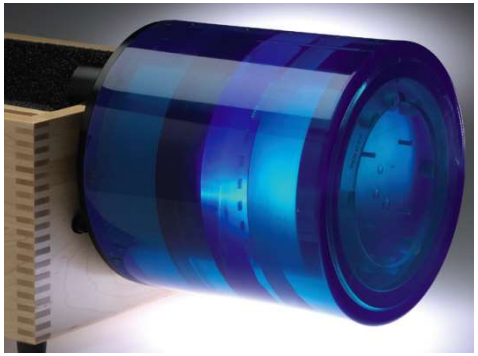
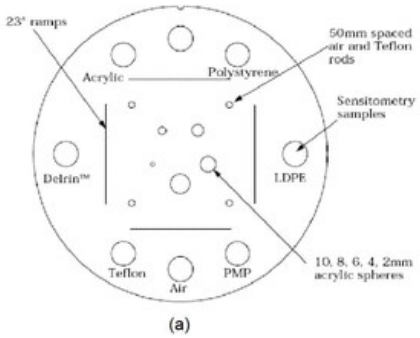
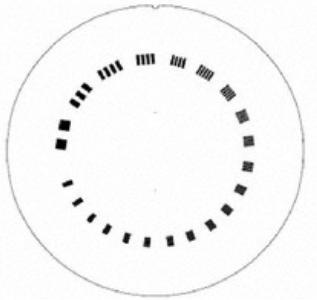
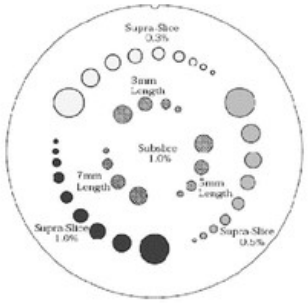
Image Quality: Catphan Phantom



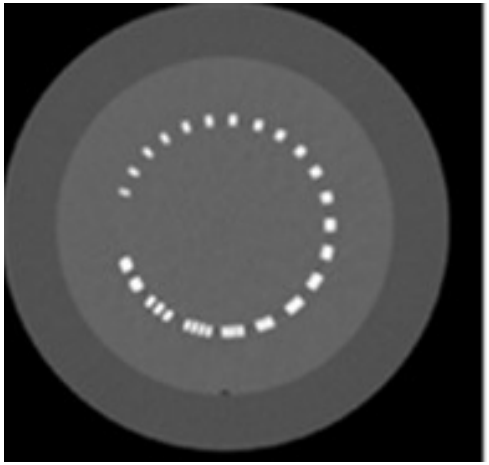


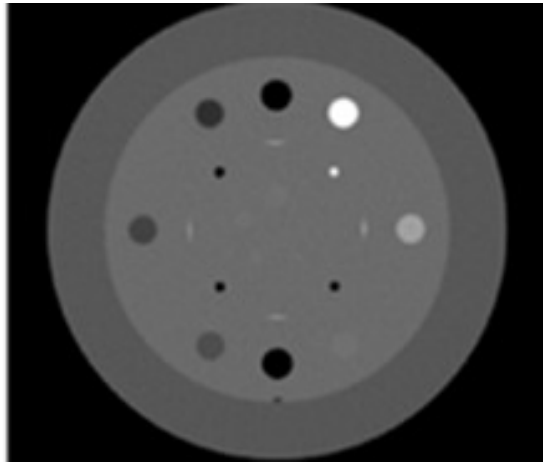
(a)

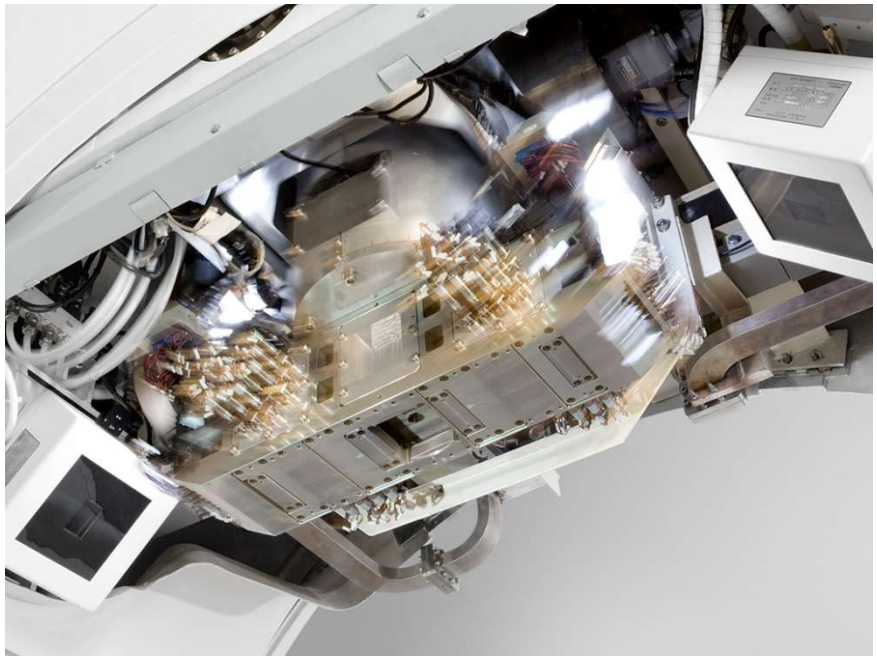

(b)



(c)

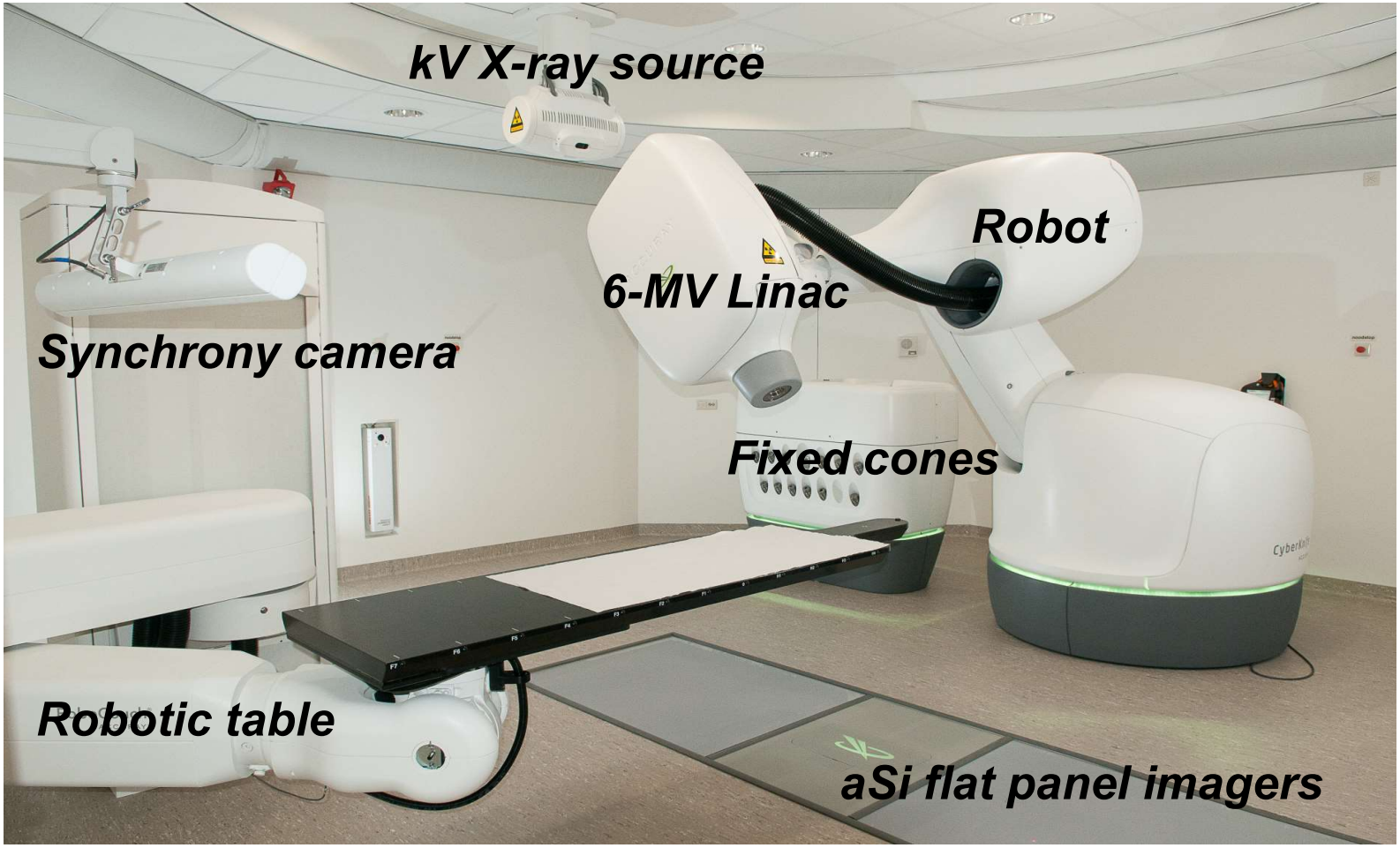




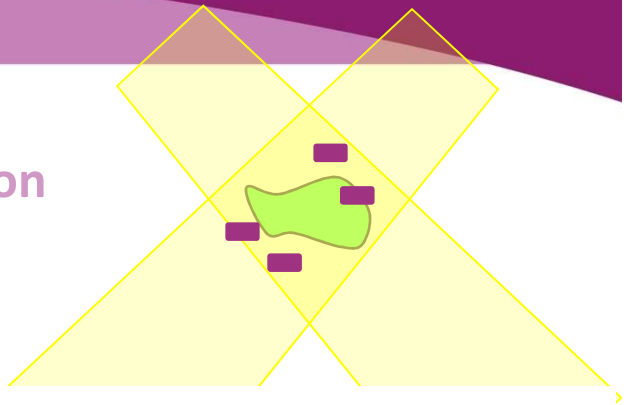


DYNAMIC TUMOR TRACKING

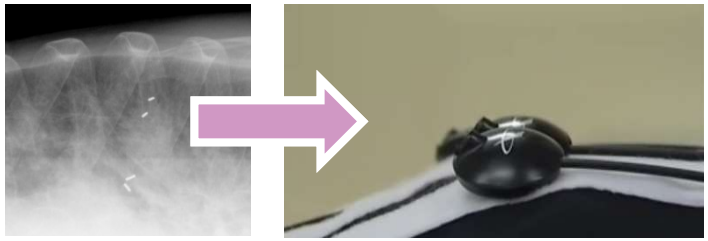
CyberKnife System Components



Real-time Respiratory Motion Tracking

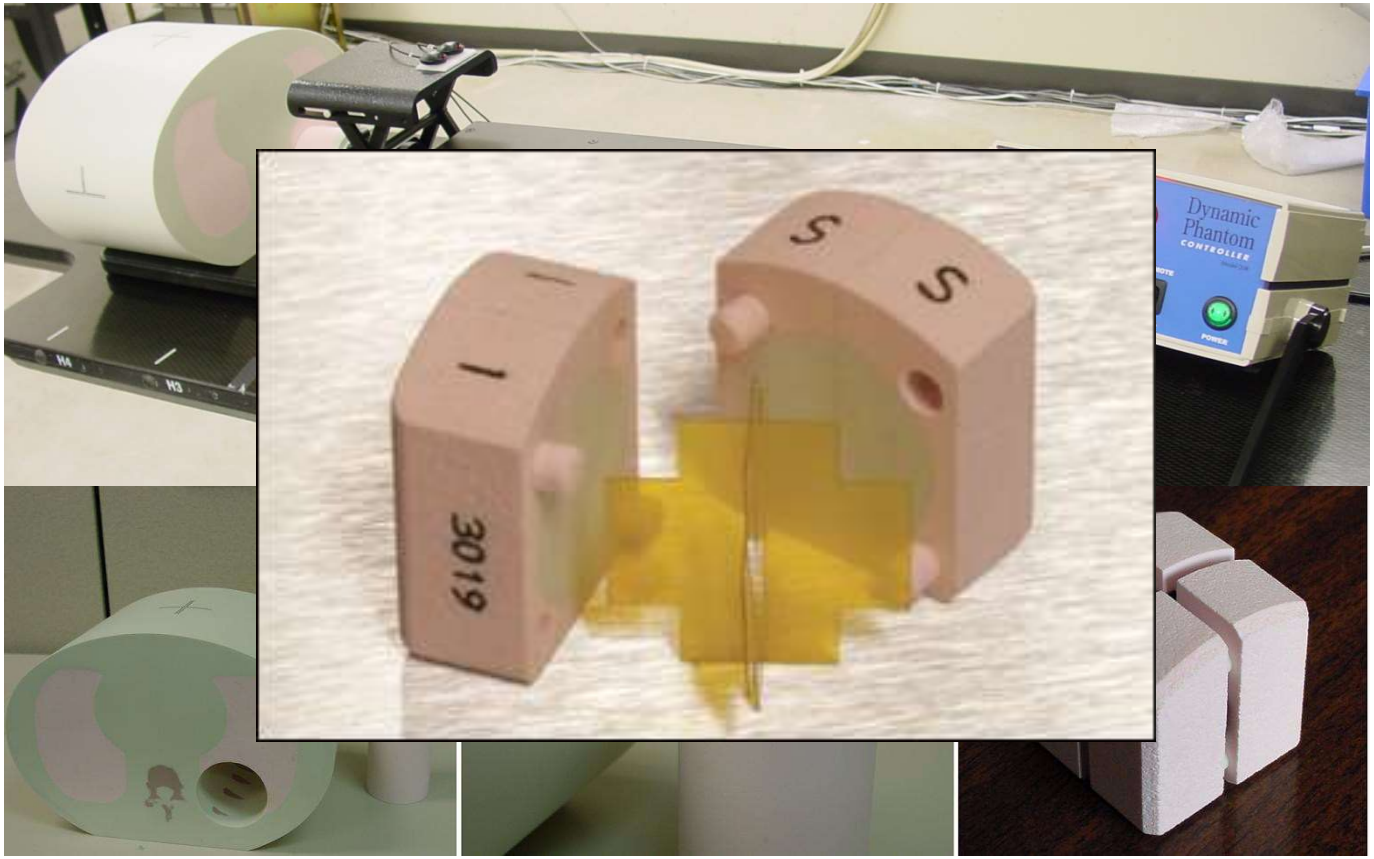


1. Correlation model relating tumor and chest motion



2. Prediction model forecasting motion to compensate system lag

E2E Tests: Direct Target Localization (Xsight Lung Tracking)



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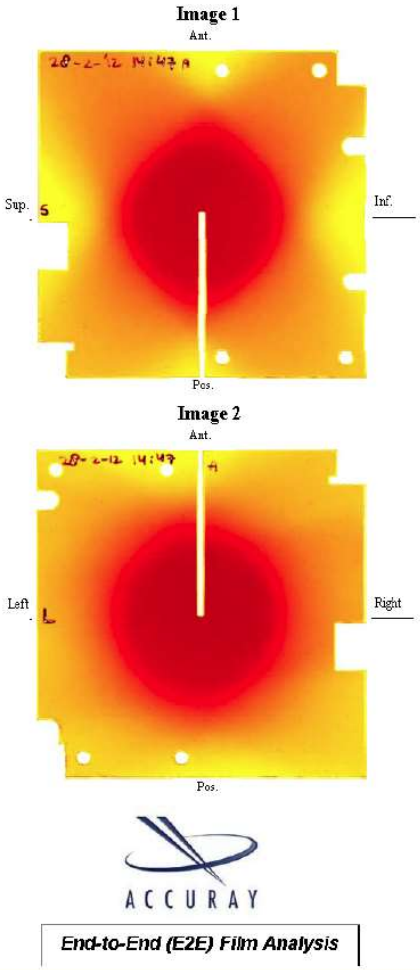
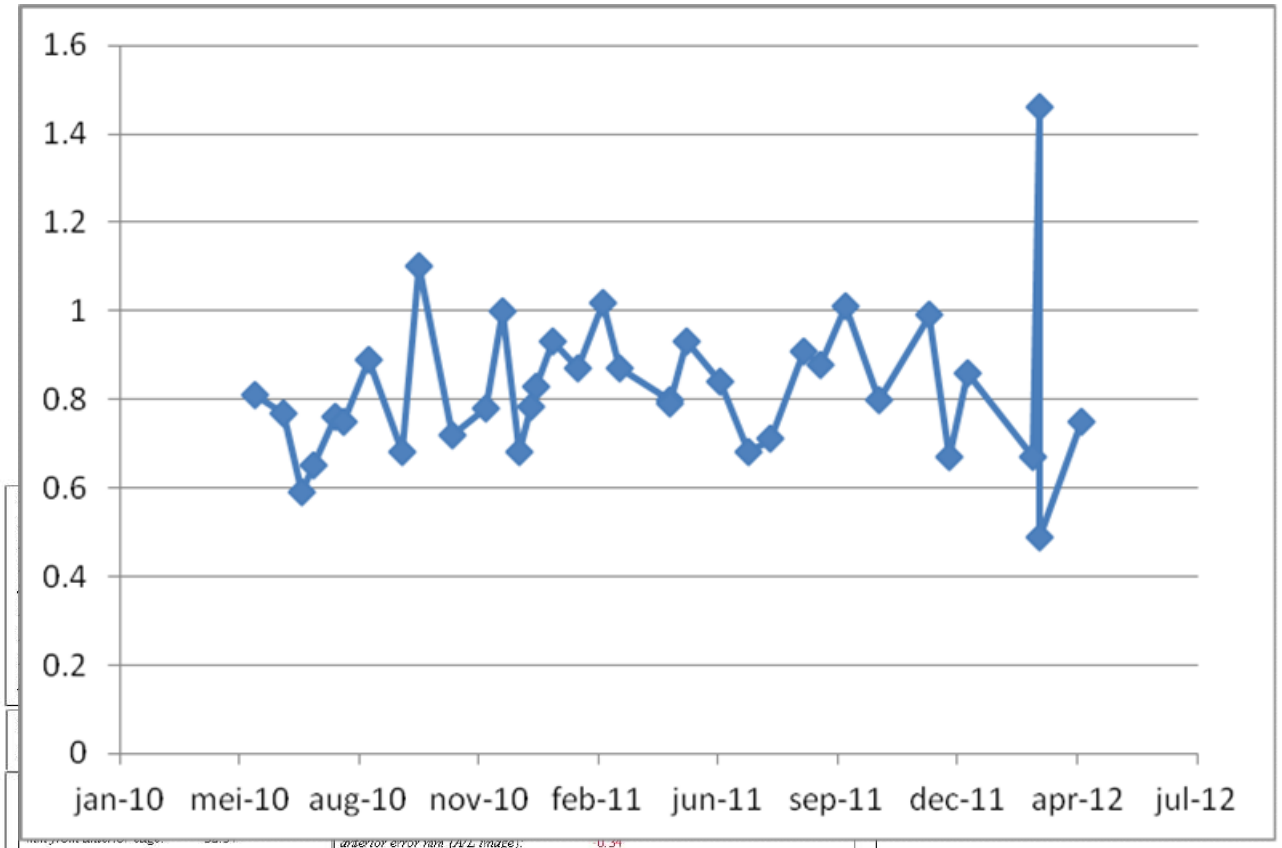
Treatment Delivery

Analysis of Tracking Error





contour area/ball area:	1.02

Image 2 (A/L Image)	
mm from left edge:	31.23
mm from anterior edge:	32.09
contour area/ball area:	1.15

superior error mm:	0.11
anterior error mm (A/S image):	-0.59
average anterior error mm:	-0.47
TOTAL TARGETING ERROR mm:	0.7

70% Contour Level

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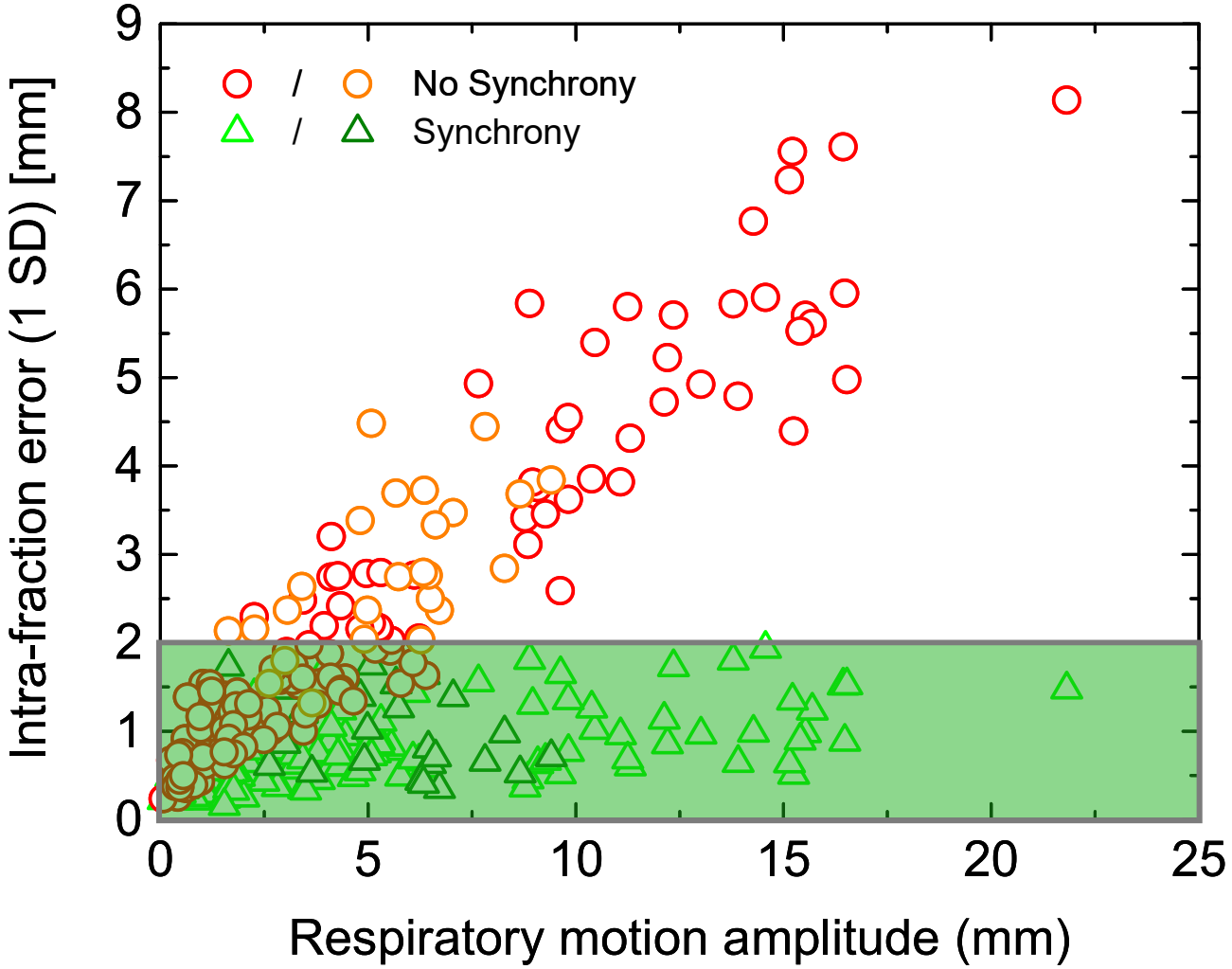
Correlation Model Error (167 treatment fractions)



Hoogeman M, Prévost JB, Nuyttens J, Pöll J, Levendag P, Heijmen B, Clinical accuracy of the respiratory tumor tracking system of the cyberknife: assessment by analysis of log files. Int J Radiat Oncol Biol Phys. 2009 May 1;74(1):297-303.

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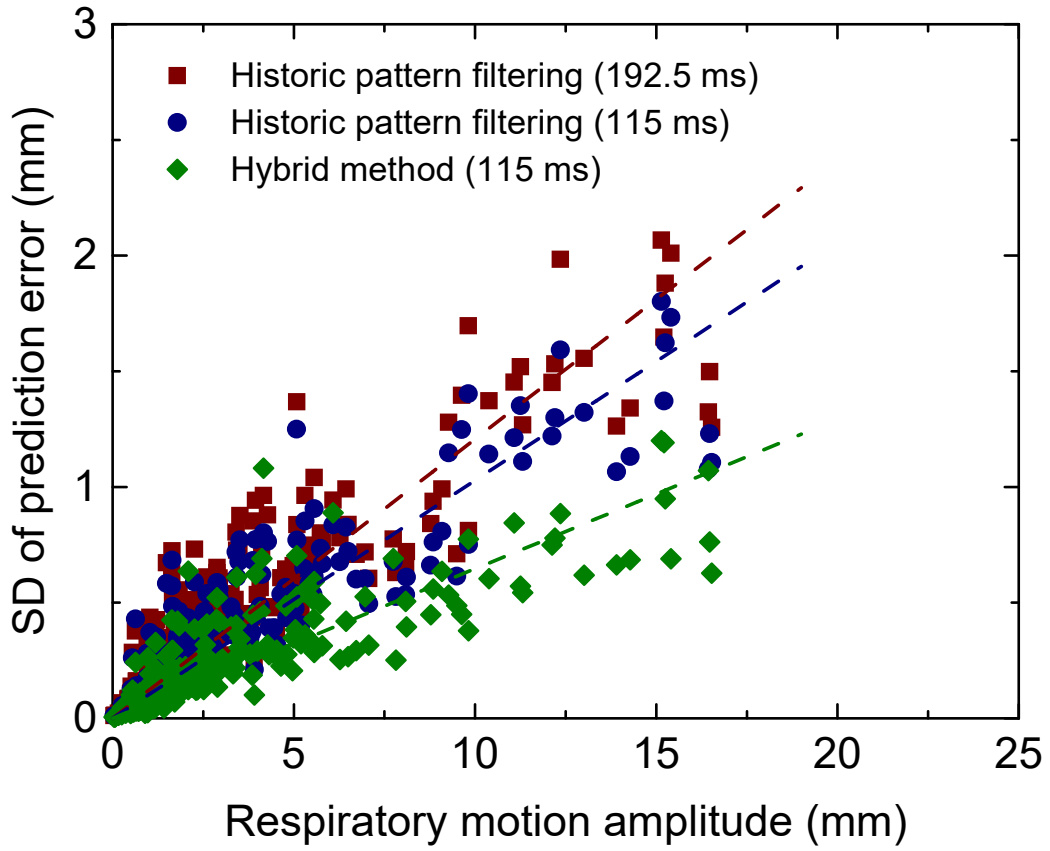
Prediction Error vs. Motion Amplitude



Hoogeman M, Prévost JB, Nuyttens J, Pöll J, Levendag P, Heijmen B, Clinical accuracy of the respiratory tumor tracking system of the cyberknife: assessment by analysis of log files. Int J Radiat Oncol Biol Phys. 2009 May 1;74(1):297-303.

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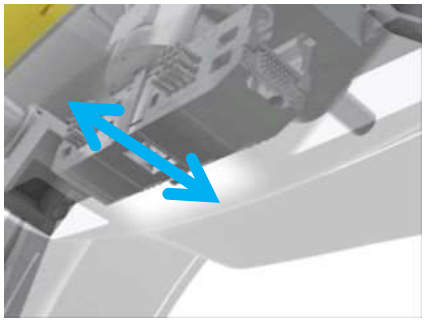
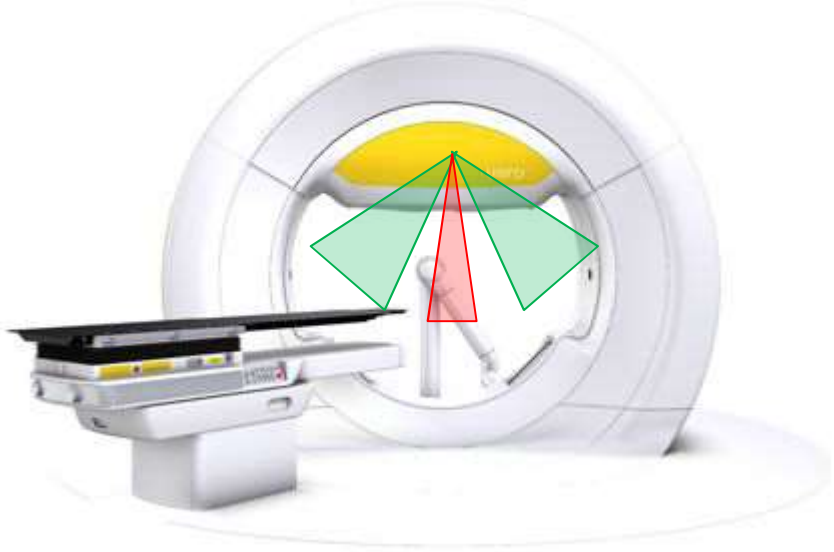
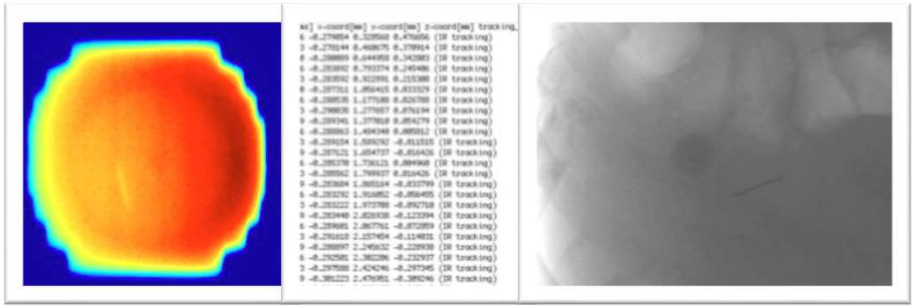
Vero System and 4D Quasar







From: Dirk Verellen

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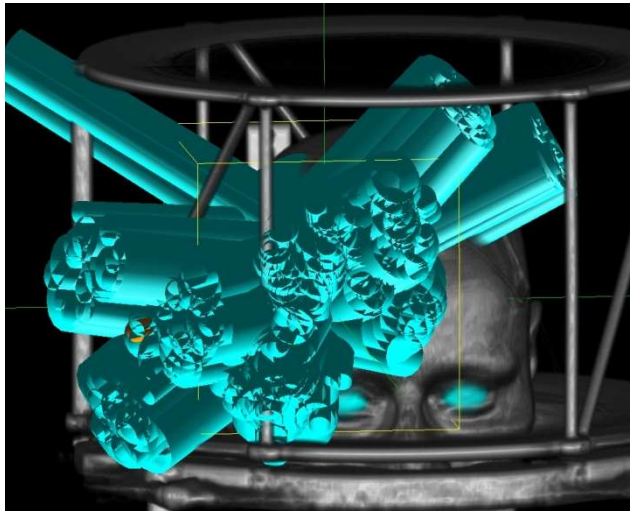

TREATMENT PLANNING QA

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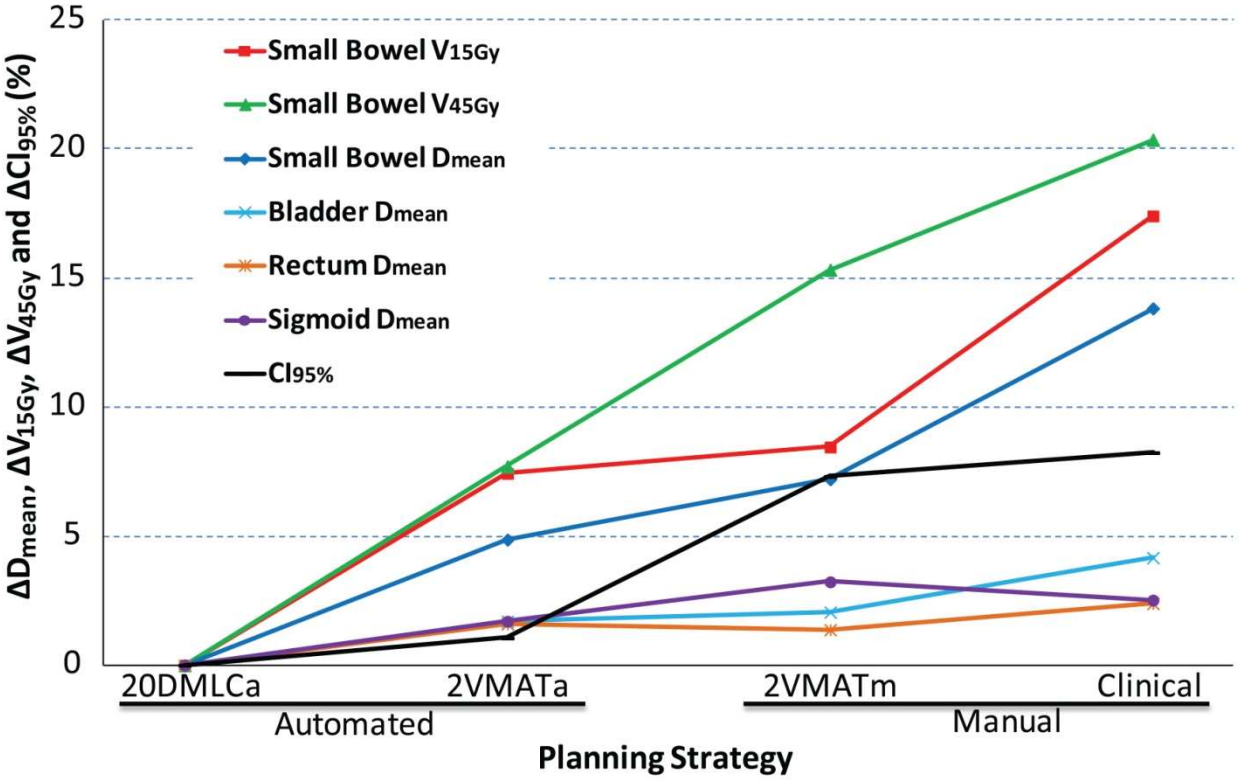
Automated vs. Manual Planning for Cervix VMAT



Sharfo et al.; Erasmus-iCyce: Breedveld S, Storchi PR, Voet PW, Heijmen BJ. iCycle: Integrated, multicriterial beam angle, and profile optimization for generation of coplanar and noncoplanar IMRT plans. Med Phys. 2012 Feb;39(2):951-63.

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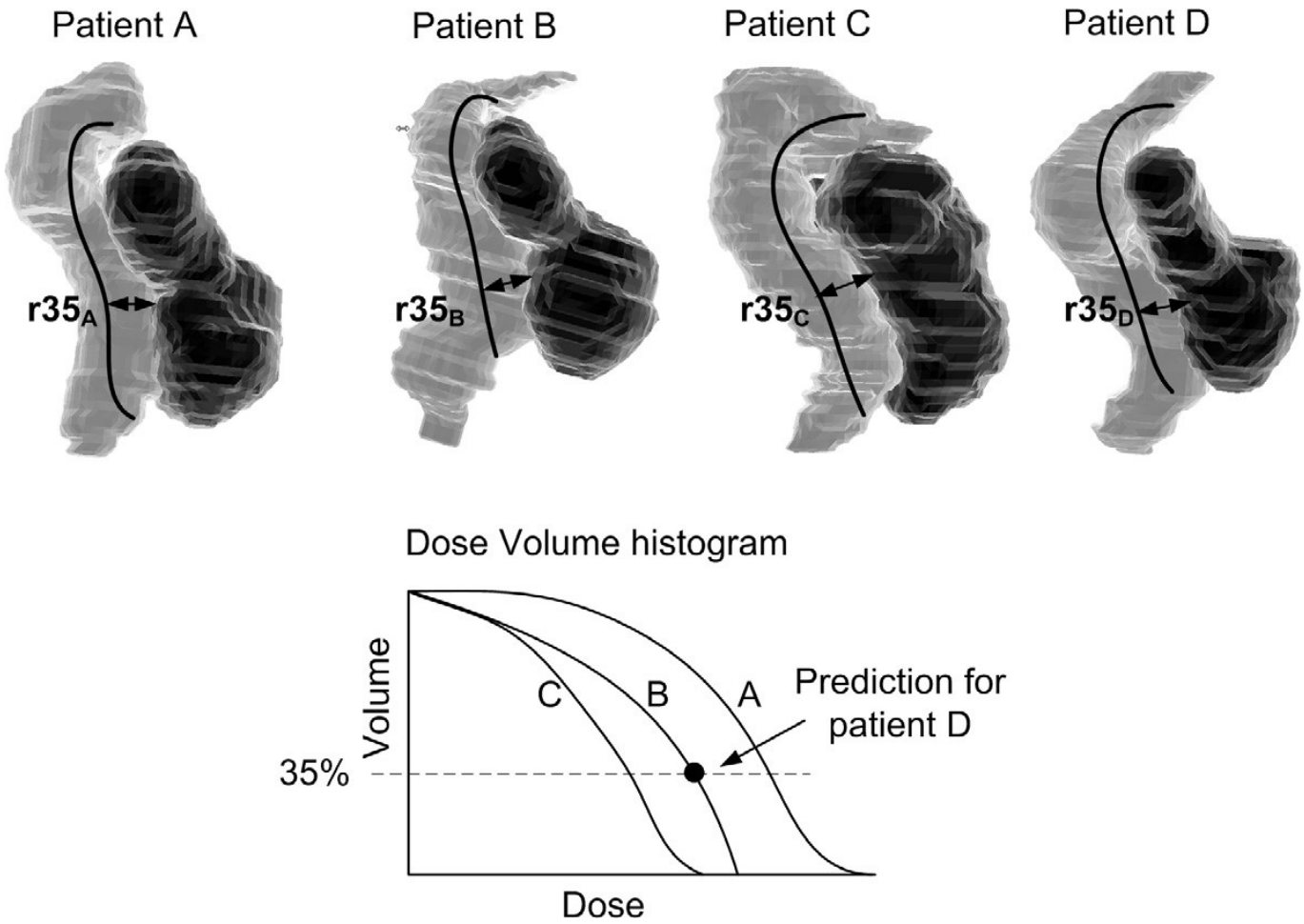
Plan QA by Overlap Histograms



From: Wang Y, Zolnay A, Incrocci L, Joosten H, McNutt T, Heijmen B, Petit S. A quality control model that uses PTV-rectal distances to predict the lowest achievable rectum dose, improves IMRT planning for patients with prostate cancer. Radiother Oncol. 2013 Jun;107(3):352-7.

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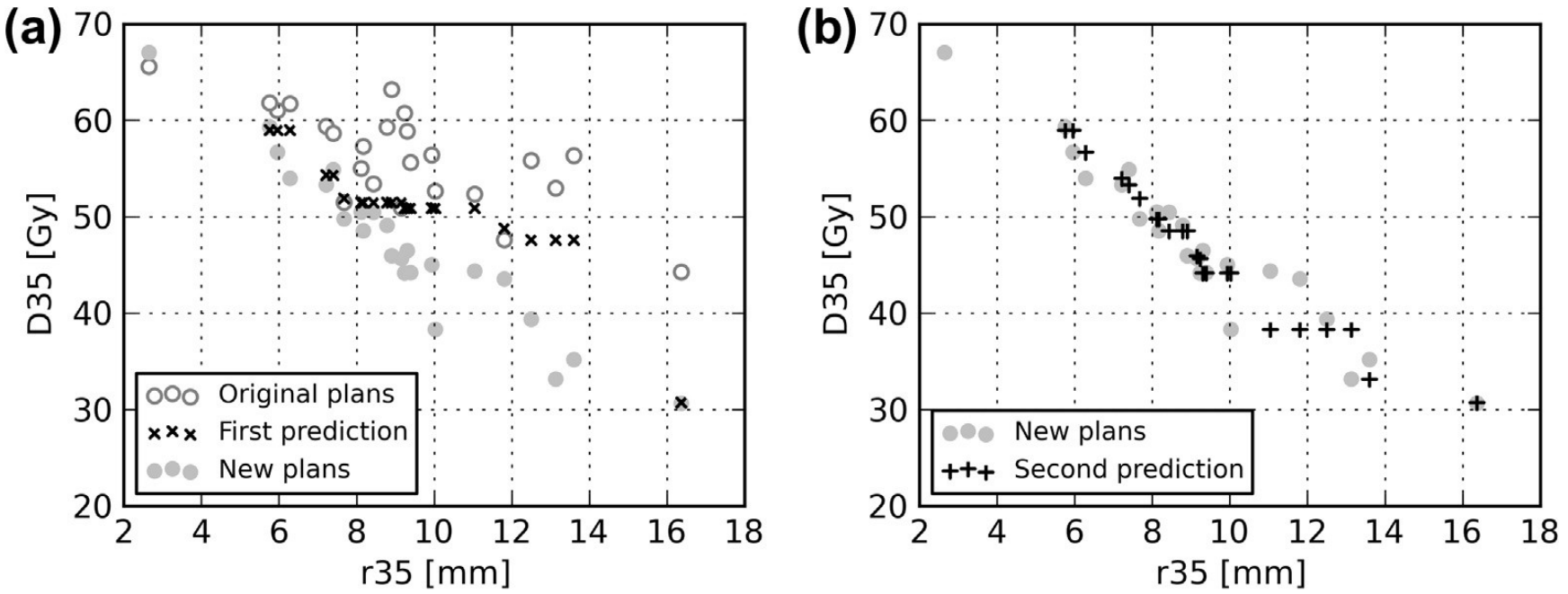
Plan Improvements by Benchmarking with Database



From: Wang Y, Zolnay A, Incrocci L, Joosten H, McNutt T, Heijmen B, Petit S. A quality control model that uses PTV-rectal distances to predict the lowest achievable rectum dose, improves IMRT planning for patients with prostate cancer. Radiother Oncol. 2013 Jun;107(3):352-7.

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Conclusions

- Advanced delivery systems are complex and non-intuitive and are challenging QA
- Gamma index is useful to monitor e.g. machine consistency and major failures, but it correlates poorly with clinically relevant parameters
- 3D dose reconstruction and DVH analysis for patient specific QA provides better clinically interpretable results, but careful consideration of the method used for dose reconstruction is required
- Image QA of on-board imaging devices is not well established in radiotherapy
- E2E testing of advanced treatments should be mandatory before the first patient treatment
- QA of treatment planning is often undervalued

- Thank you!

Calculation of dose in the TPS

Vibeke Nordmark Hansen

Royal Marsden NHS Trust, UK

and

Tom Depuydt

University Hospital of Brussels Vrije University, Belgium

(based partly on material from Professor Dag Rune Olsen, University Bergen)

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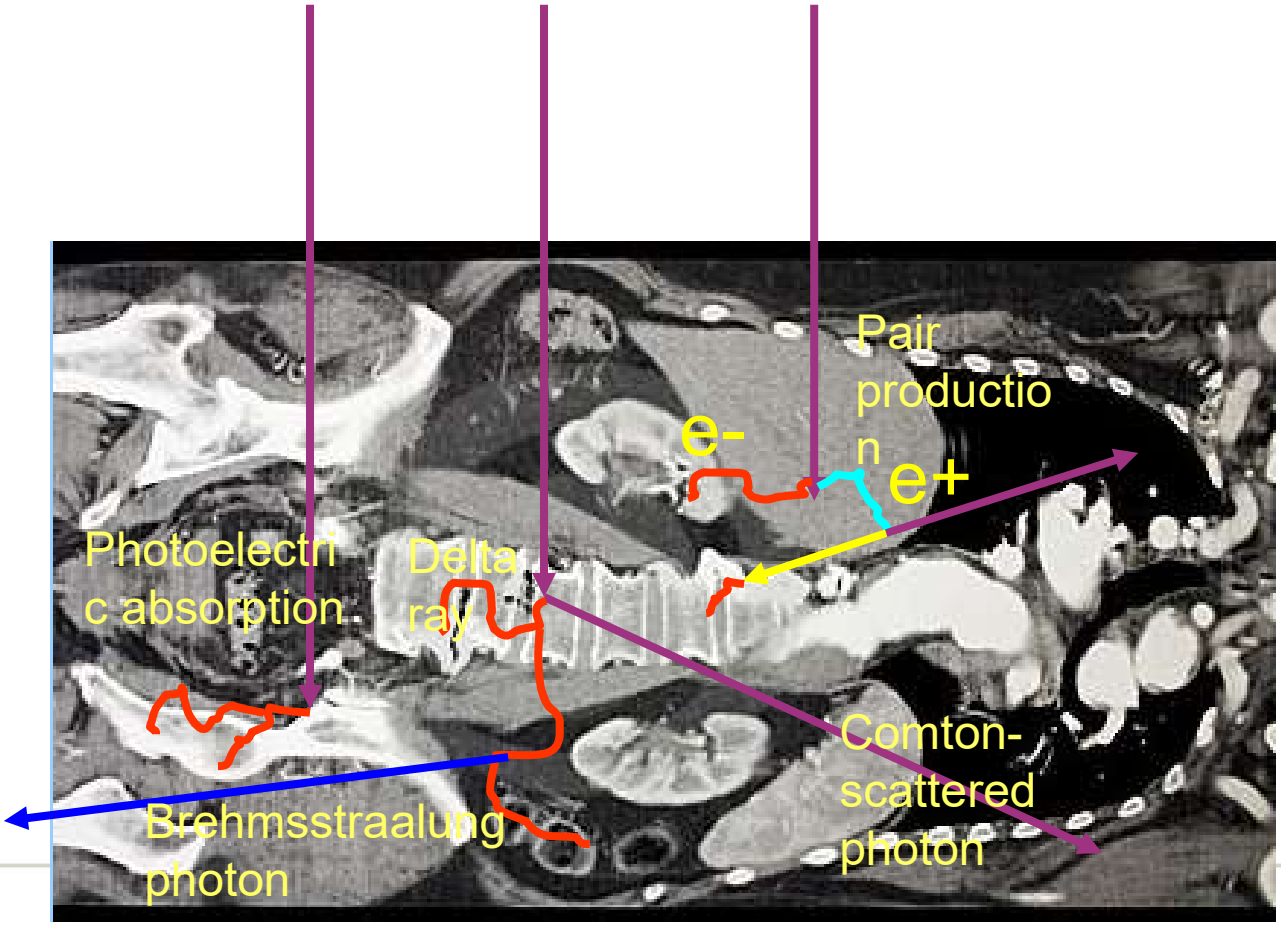
Photon beam dose calculations

modeling of complex physical processes



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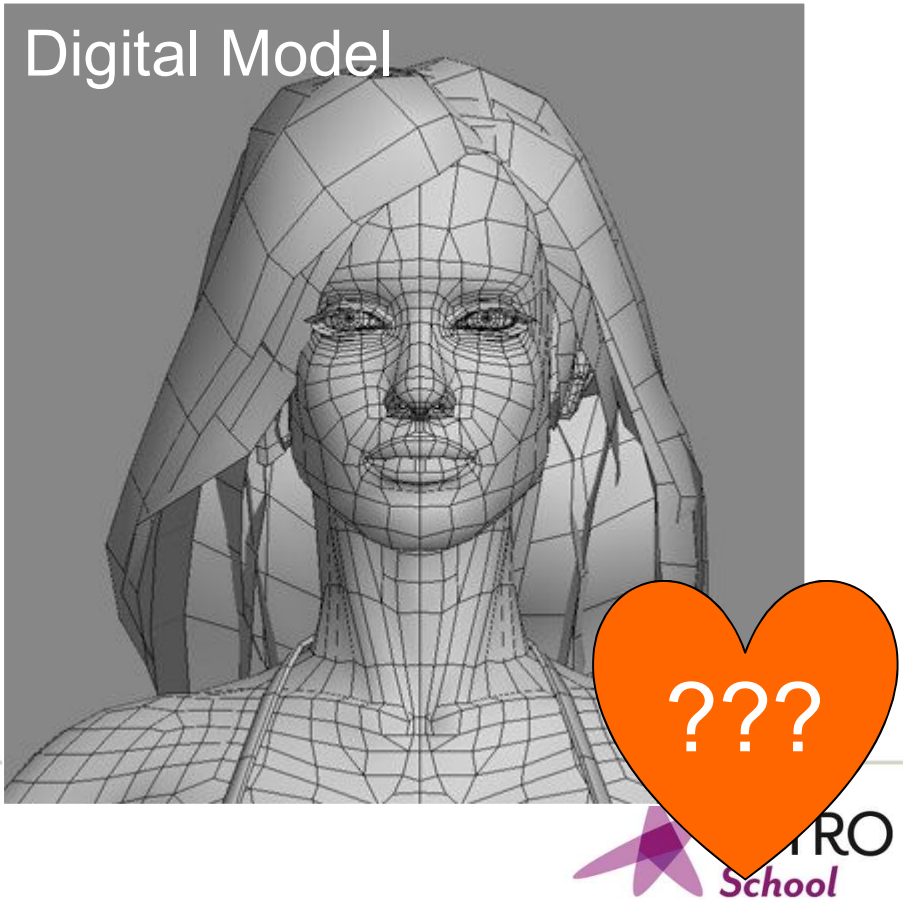
Computer approximation

"A computer calculates a simulation based on a digital model. The results is only as good as the model allows it to be"



TYPES OF DOSE CALCULATION

- Central axis models
  - PDD, TMR, PSF etc.

→ Can be hand calculations for point doses

- Semi-empirical models
  - Based on tables of measured beam data
  - Bentley-Milan algorithm

→ Used on all 2D planning systems. Often used for dose checking

- Pencil-beam algorithms **Model based**
  - 2D convolution

→ Popular for IMRT optimisation

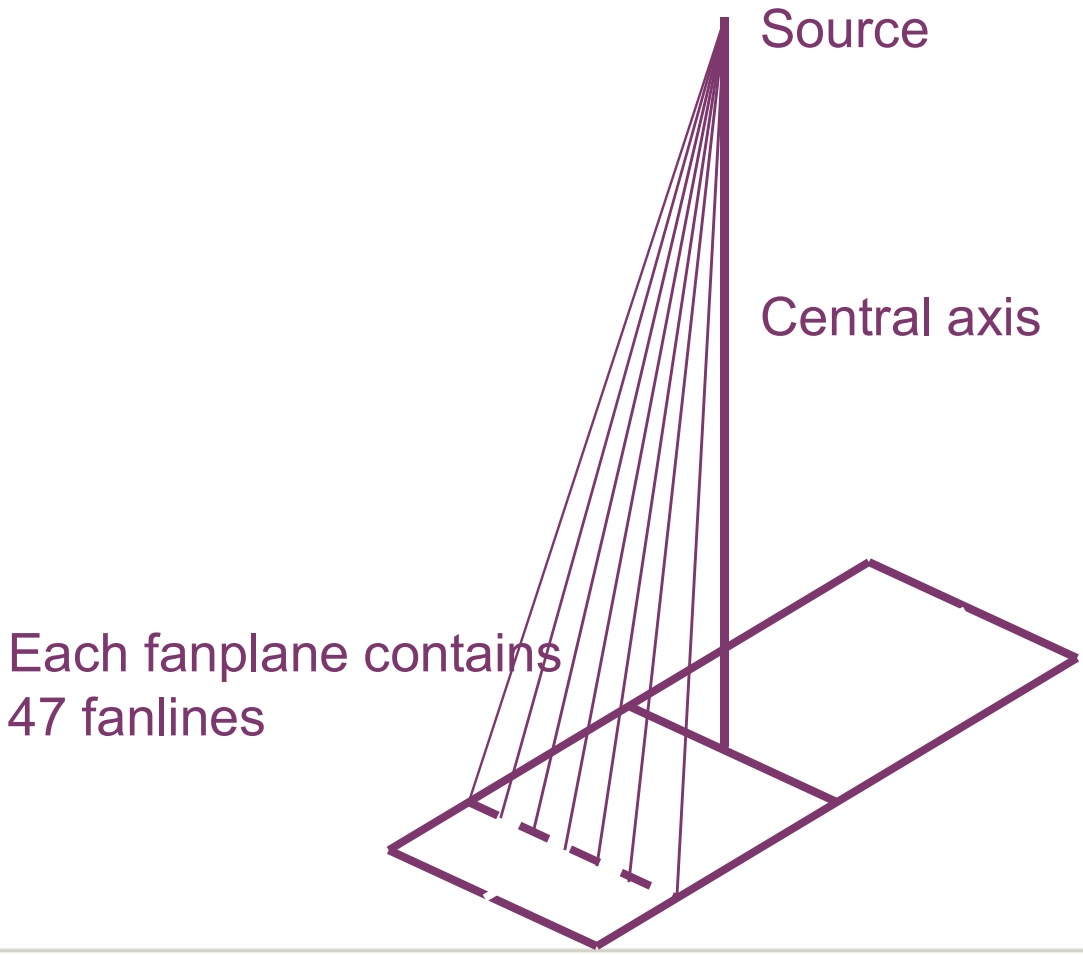
- Convolution algorithms **Model based**
  - 3D convolution

→ Main algorithm today

- Monte Carlo simulation
  - Limitations in accuracy vs speed

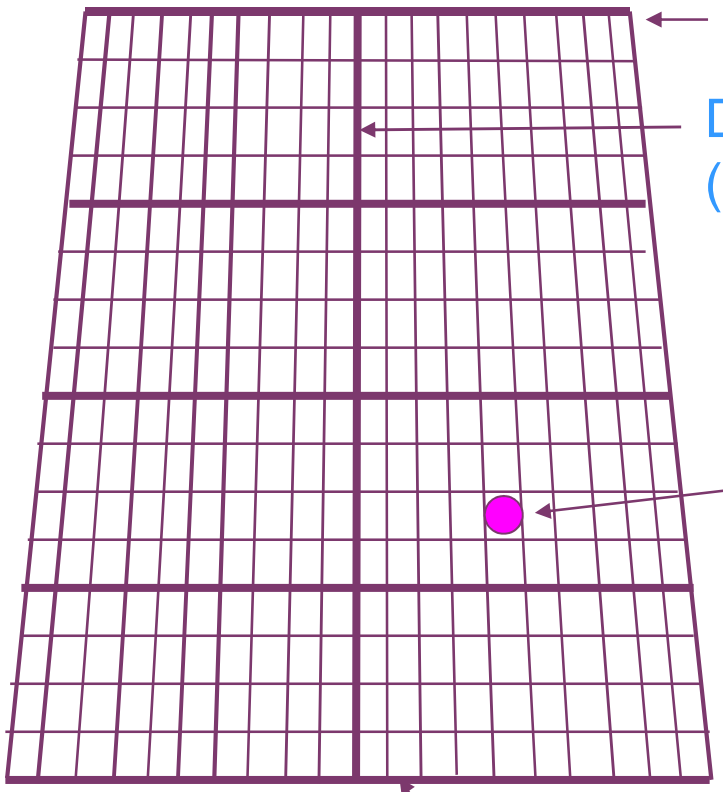
Boltzmann transport equation

BENTLEY-MILAN ALGORITHM



BEAM DATA

Data are typically collected for open and wedged square fields



$$\text{Dose} = \text{PDD} \times \text{OAR}$$

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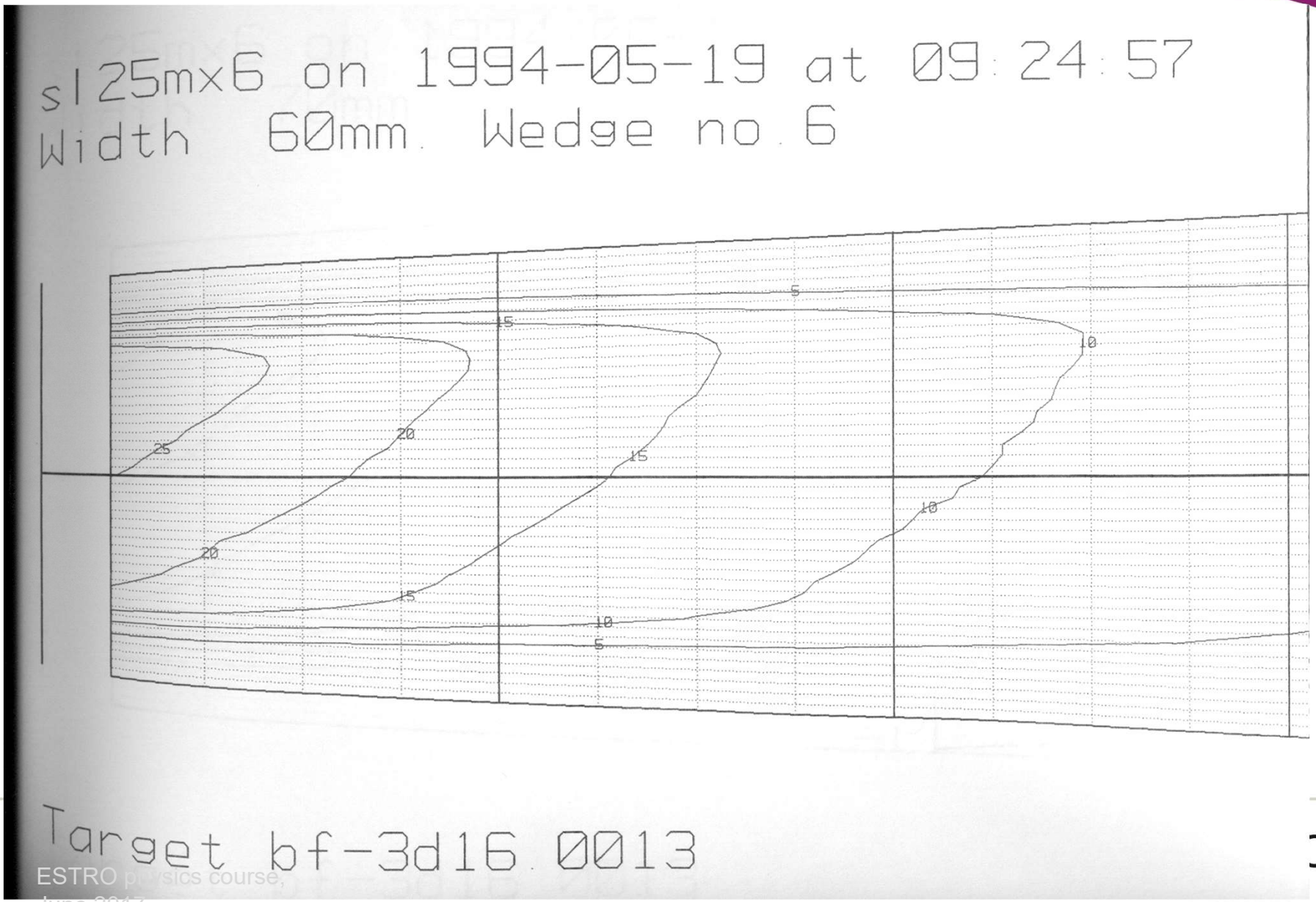
BEAM DATA


s125mx6 on 1994-05-19 at 09:24:57
Width 60mm Wedge no 6
25
20
15
10
5
20
15
10
5
Target bf-3d16 0013

OFF-AXIS RATIOS

$$OAR = OAR_x \times OAR_y$$

- Multiply orthogonal factors
- Interpolate
  - Between depths
  - Between field sizes
- Radial non-flatness is over-accentuated
  - Non-flatness due to
    - Scatter
    - Deliberate effect to compensate for beam softening at depth
- Apply radial correction

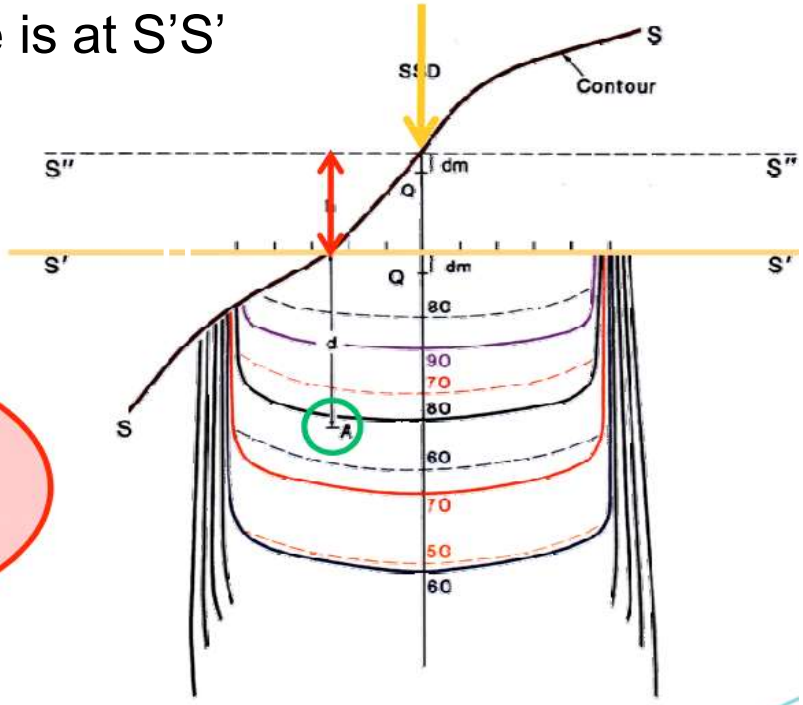
Irregular contours and oblique beams

Effective SSD method

Represents an inverse square correction factor. The parameter h is the thickness of missing tissue while the parameter –h represents the thickness of excess tissue

- Shift isodose chart so that its surface line is at S'S'
- Correct by the inverse square law factor

$$P_{corr} = P\left(\frac{SDD + d_m}{SDD + h + d_m}\right)^2$$



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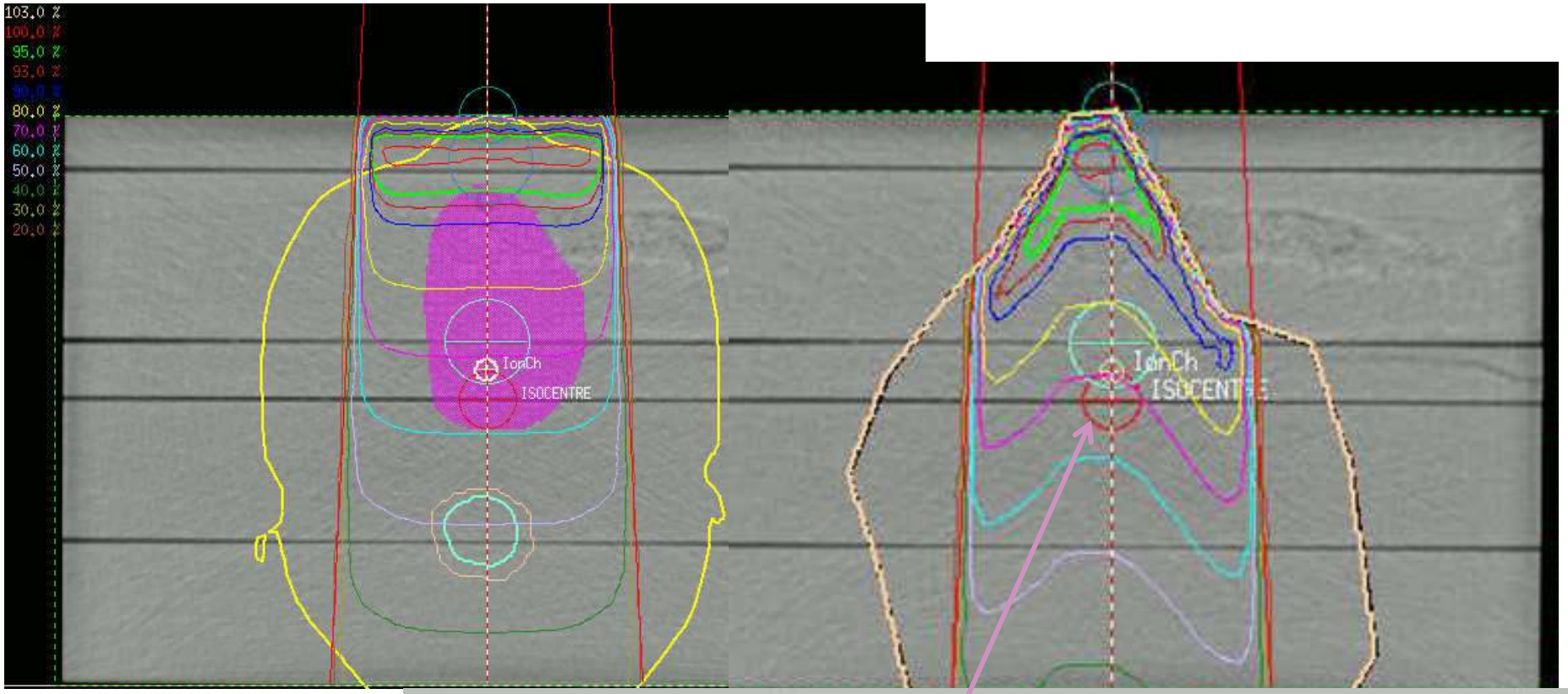
Example of oblique distribution



Name	Override Sequence	Override Density	Load Voxels	Density
Newbody	5	Yes	Outside ROI	0

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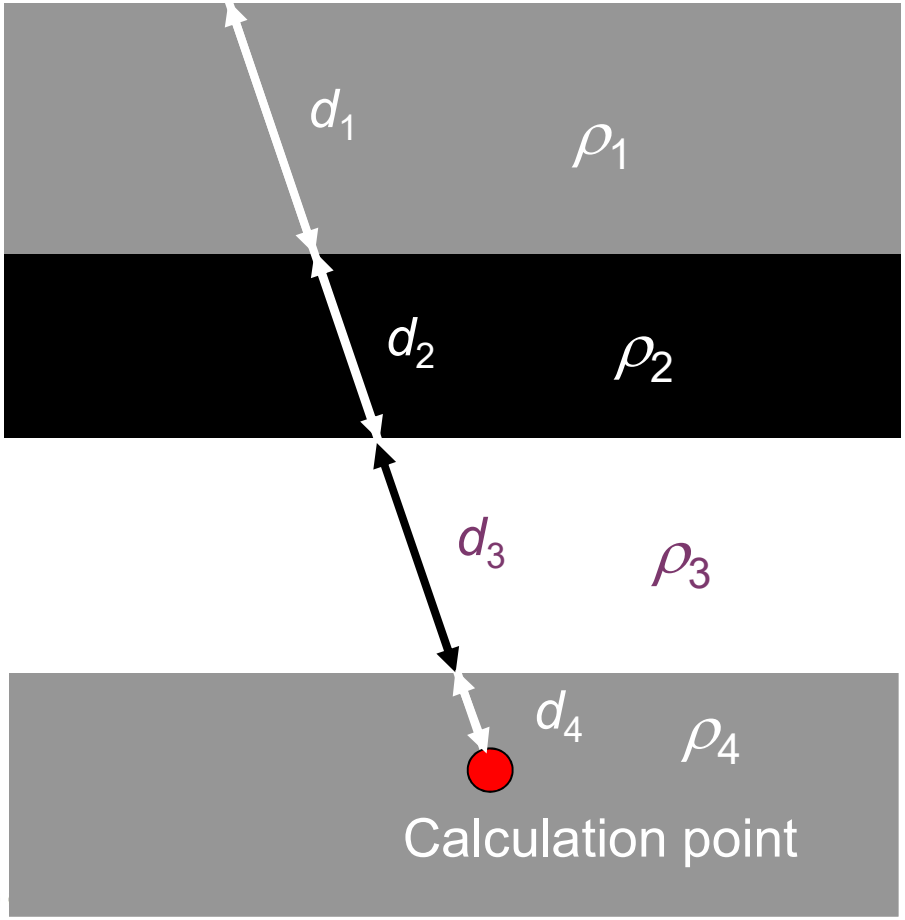
HETEROGENEITY CORRECTIONS

- Bulk density equivalent path length
- Pixel-by-pixel equivalent path length
- Power law method (Batho)
- ETAR method

EQUIVALENT PATH LENGTH



$$EPL = \rho_1 d_1 + \rho_2 d_2 + \rho_3 d_3 + \rho_4 d_4$$

$$\exp(-\mu_1 d_1)\exp(-\mu_2 d_2)... = \exp(-(\mu_1 d_1 + \mu_2 d_2 + ...))$$

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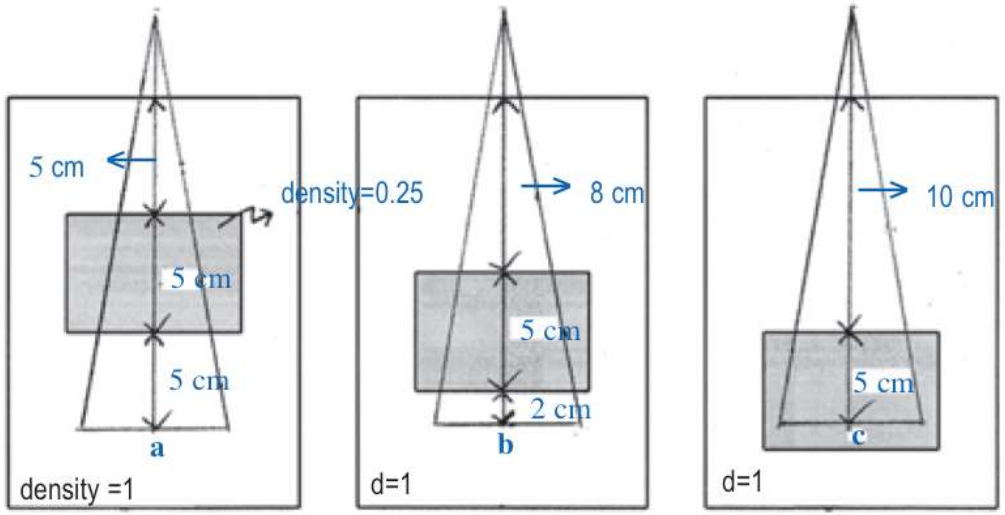
Corrections for inhomogeneities



	point a	point b	point c
Equivalent path	0.62	0.62	0.62
TAR ratio	0.66	0.66	0.66
Batho- **Power law**	0.65	0.63	0.58

Principles and Practice of Clinical Physics and Dosimetry
Michael L.F. Lim, CMD, ACT

EFFECTIVE PENUMBRA

$$\text{Penumbra factor} = \frac{\cos(180r/e)+1}{2} \times (1-T)+T$$

r = distance away from edge of block
s = effective source diameter
T = transmission factor

"Simple" measurement based dose algorithms become complicated when we need to correct for:

- Obliquity
- Blocks
- Heterogeneity
- Penumbra

However, these algorithms are still used in many checking computers, so their limitations needs to be known

In the planning system

What should be characterised at commissioning

Individual dose calculation based on the patient CT and the beam geometry, gantry angle, jaw and MLC settings

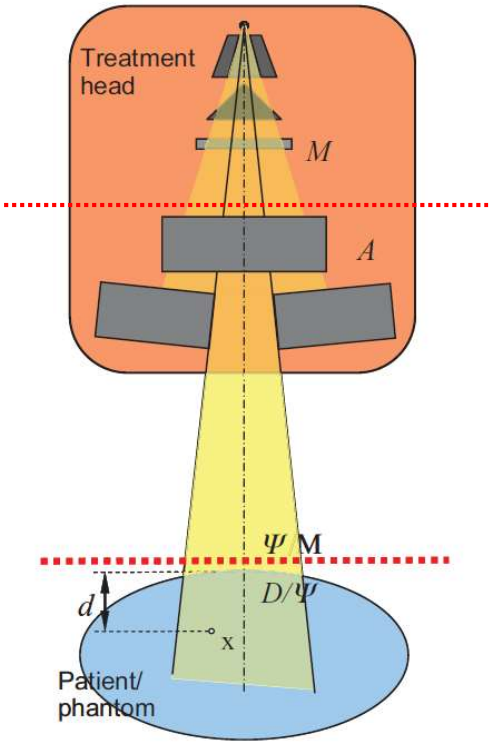


Figure 5.1. Schematic illustration of the separation (red dotted line) in equation (5.1) between energy fluence modelling, associated with the treatment head, and the subsequent formation of dose inside the irradiated patient/phantom.

Booklet 10 - Independent Dose Calculations - Concepts and Models
http://www.estro-education.org/publications/Pages/ESTROPhysicsBooklets.aspx

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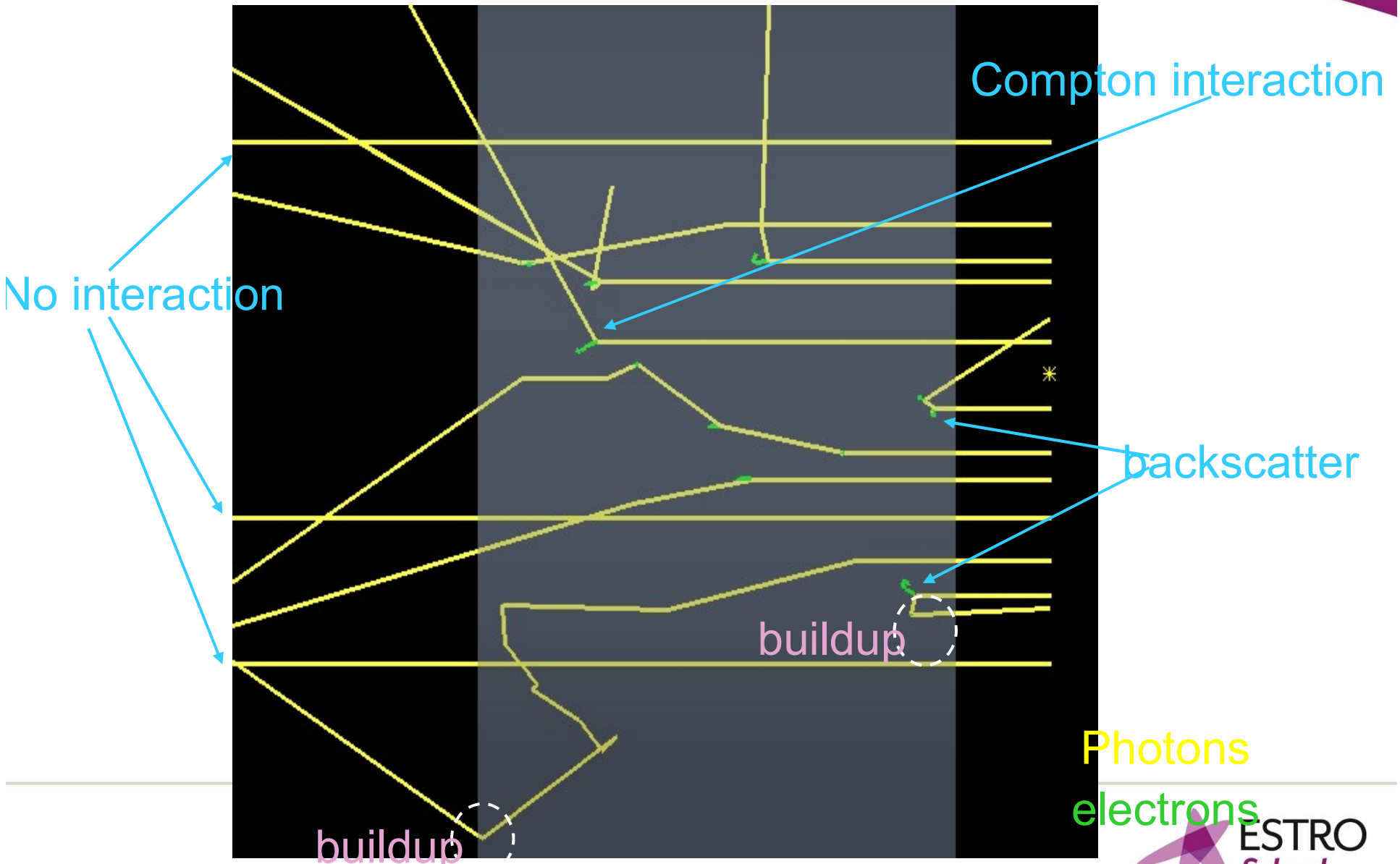
Monte Carlo

Ideal simulations are tracking Photon Histories

- Track individual photons in medium
- Using Monte Carlo simulation techniques
- Based on probabilities of interactions and probabilities of outcome.

6 MeV photons in 50 cm water … a few photons



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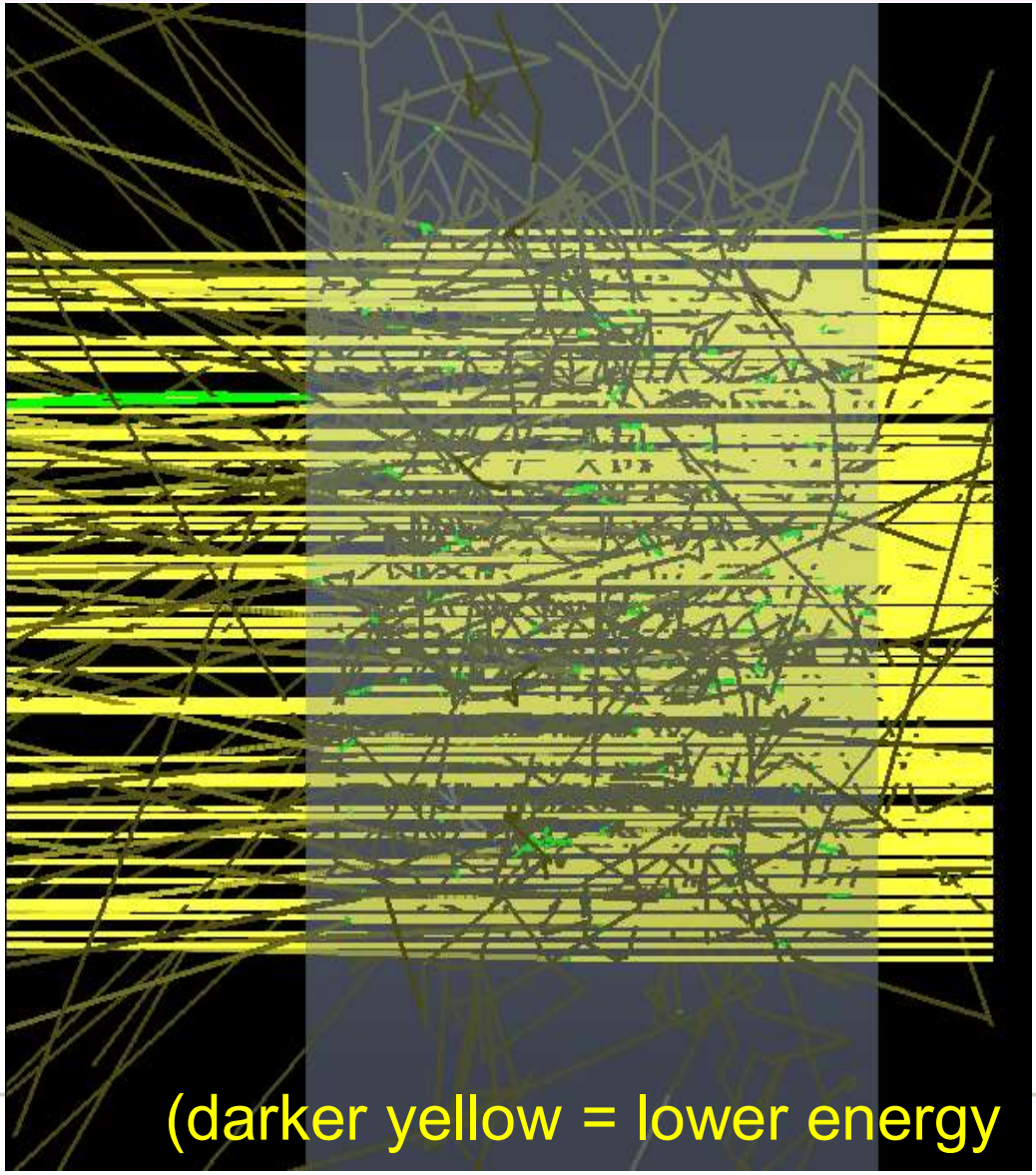
6 MeV photons in 50 cm water … many photons



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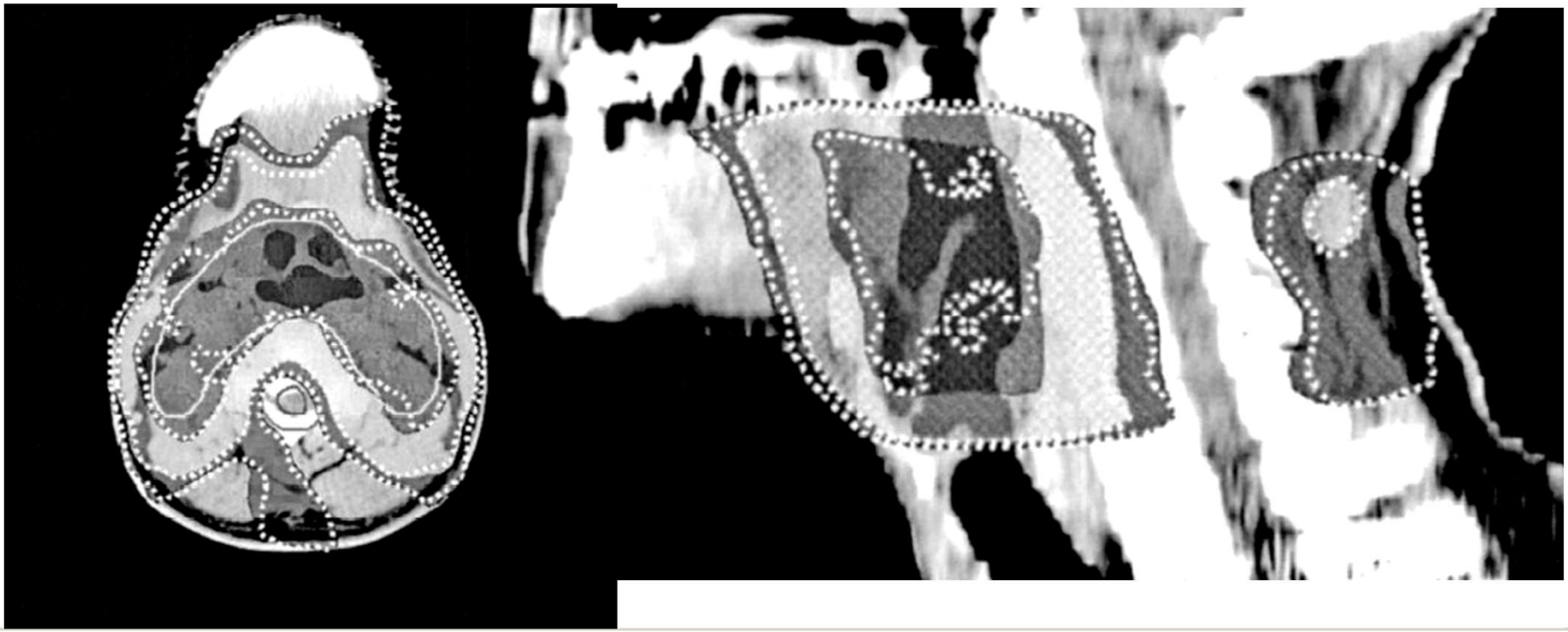
MONTE CARLO SIMULATION

- MC is in planning systems like Monaco
- Currently being used for IMRT verification
- Use BEAM to generate output from accelerator
- Use DOSXYZ to apply this to the patient

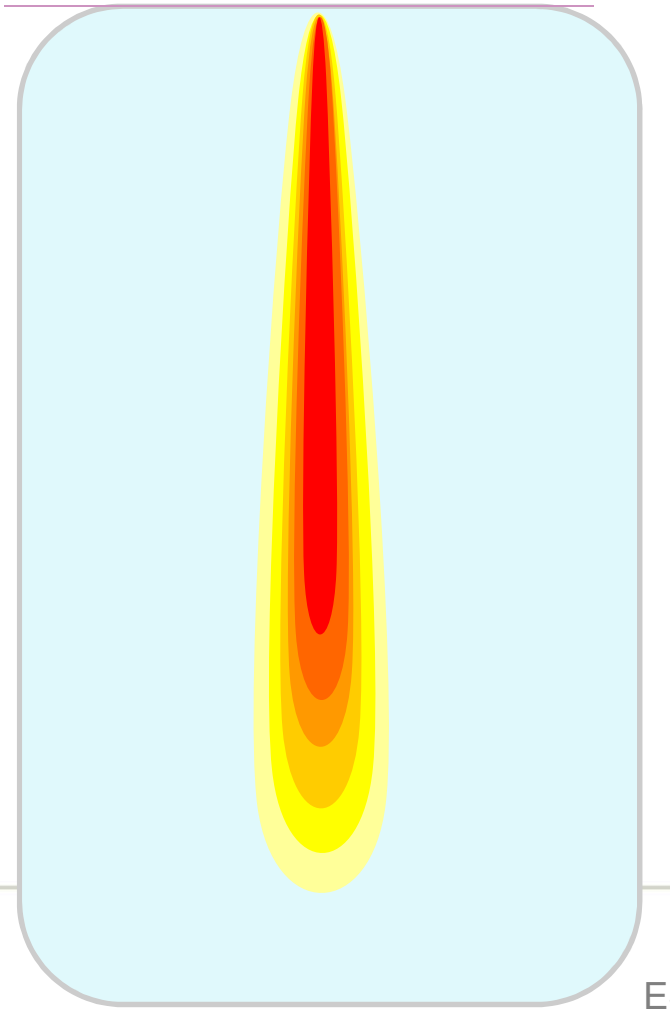


Francescon et al. Dose verification of an IMRT treatment planning system with the BEAM EGS4-based Monte Carlo code. Med. Phys. 30:144-157 (2003).

PENCIL BEAM ALGORITHM

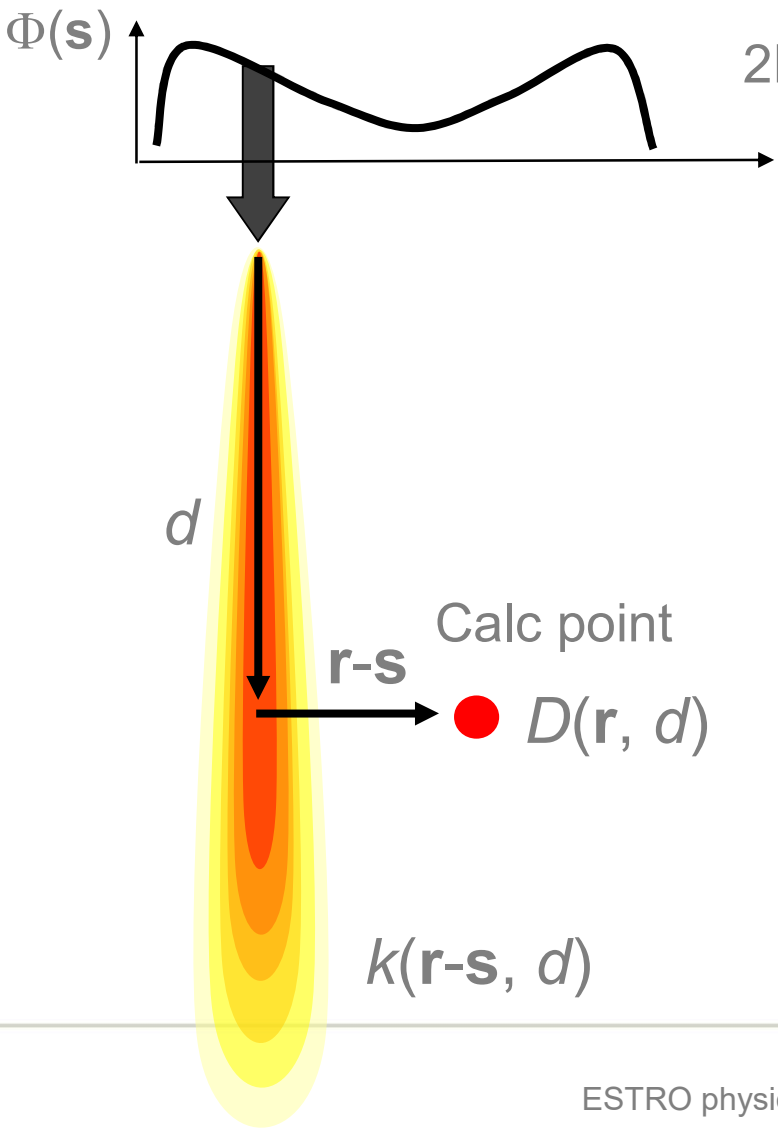
- Introduced to provide more accurate handling of irregular fields
- More suitable for conformal radiotherapy
- Often used in IMRT inverse planning algorithms
- Still subject to some inaccuracy in very inhomogeneous situations

PENCIL BEAM KERNEL



- A *pencil beam kernel* describes the energy deposition in a semi-infinite medium from a point monodirectional beam
- Generated by Monte Carlo as the experimental determination is difficult (deconvolution)

PENCIL BEAM ALGORITHM

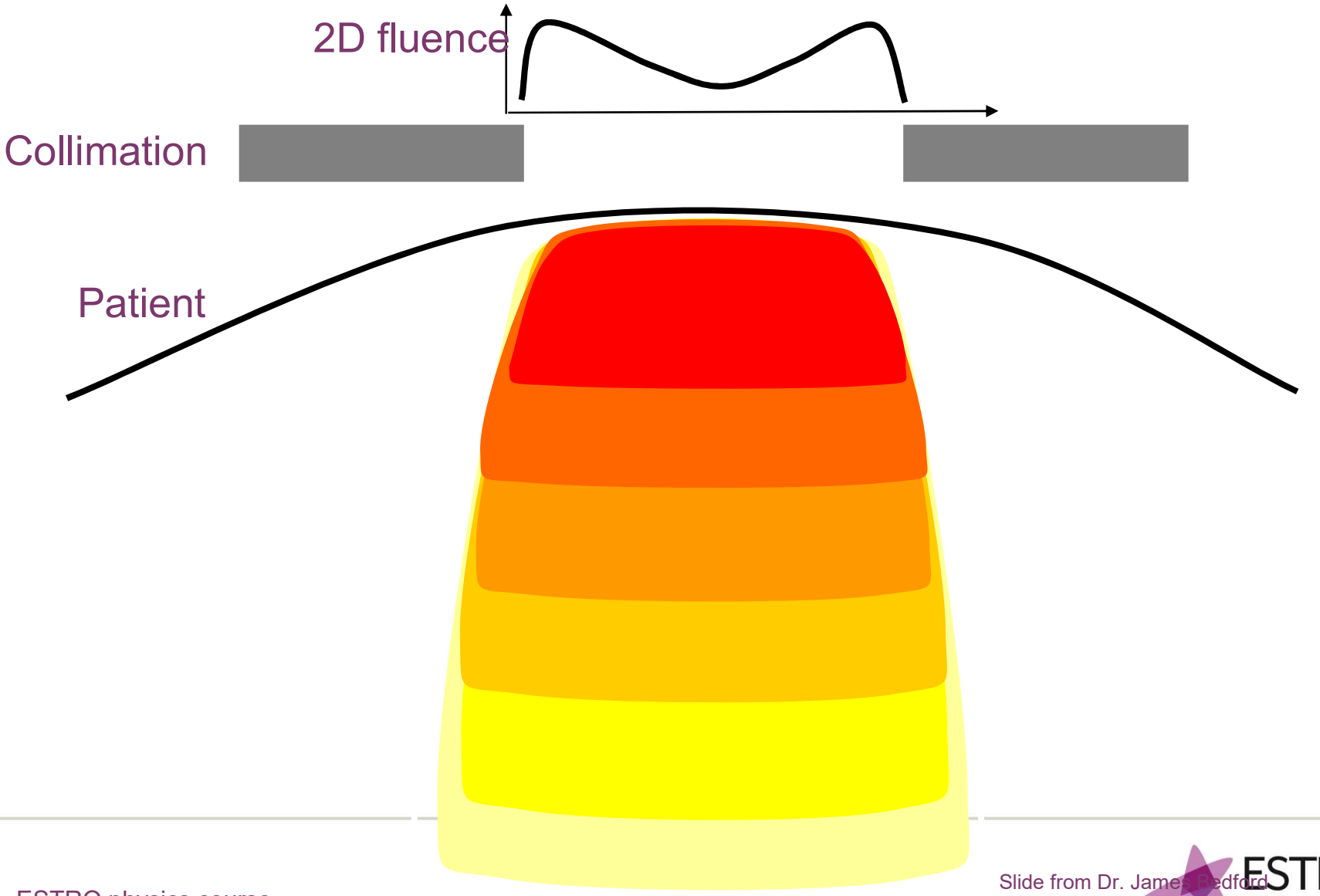


$$D(\mathbf{r},d)=\iint_A \Phi(\mathbf{s})k(\mathbf{r}-\mathbf{s},d)d^2s$$

Slide from Dr. James Bedford

ESTRO School

2D CONVOLUTION



Slide from Dr. James Bedford

PENCIL BEAM ALGORITHM

Summation over energy according to calculated Beam spectrum

$$D(\mathbf{r},d)=\int_E \iint_A \Phi_E(\mathbf{s})k(E,\mathbf{r}-\mathbf{s},d)d^2s \; dE$$

from Dr. James Bedford

PENCIL BEAM STEPS

- Beforehand
  - Calculate pencil beam kernels from Monte Carlo
    - Kernel for each energy
  - Fit energy spectrum to measured depth dose curves using Monte Carlo
  - Generate polyenergetic pencil beam kernel

- At time of calculation
  - Ray trace through accelerator head components and patient
    - Take into account energy spectrum and off-axis spectral changes
  - Convolve with source distribution
  - Convolve with polyenergetic pencil beams at 8-10 depths
  - Calculate dose by interpolation between convolutions

Slide from Dr. James Bedford

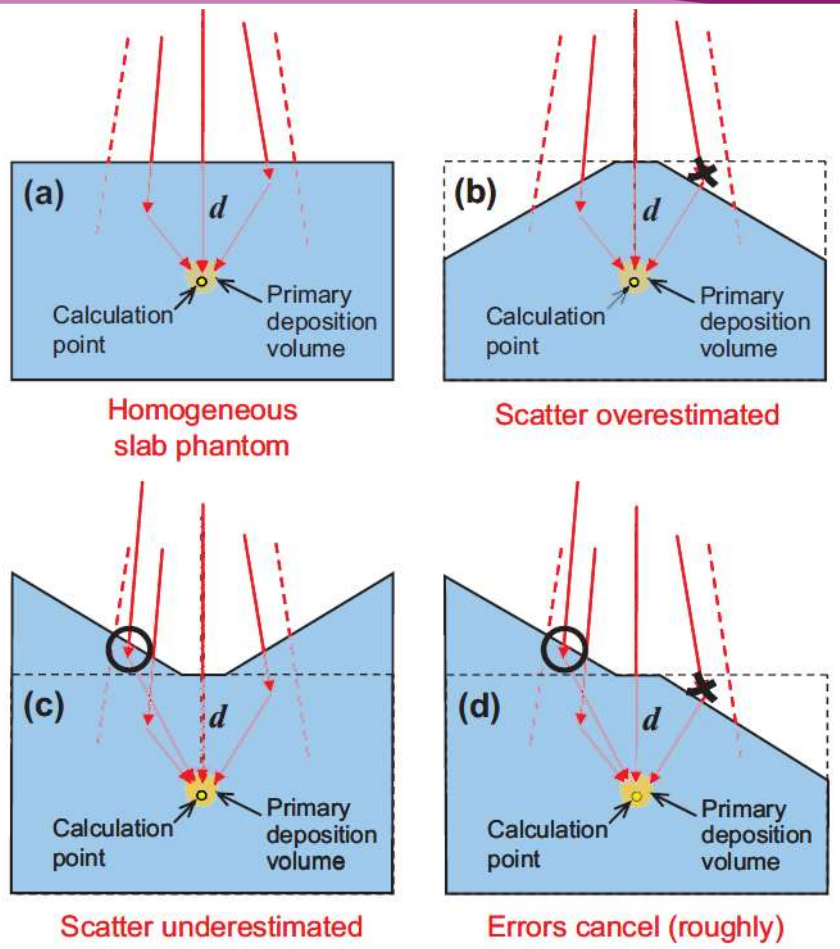


Figure 5.11. During pencil kernel integration a laterally constant depth, i.e. a slab phantom geometry, is generally assumed (a). Laterally varying depths, illustrated in (b), (c), and (d), may therefore yield over- or underestimated scatter contributions, depending on the exact geometry.

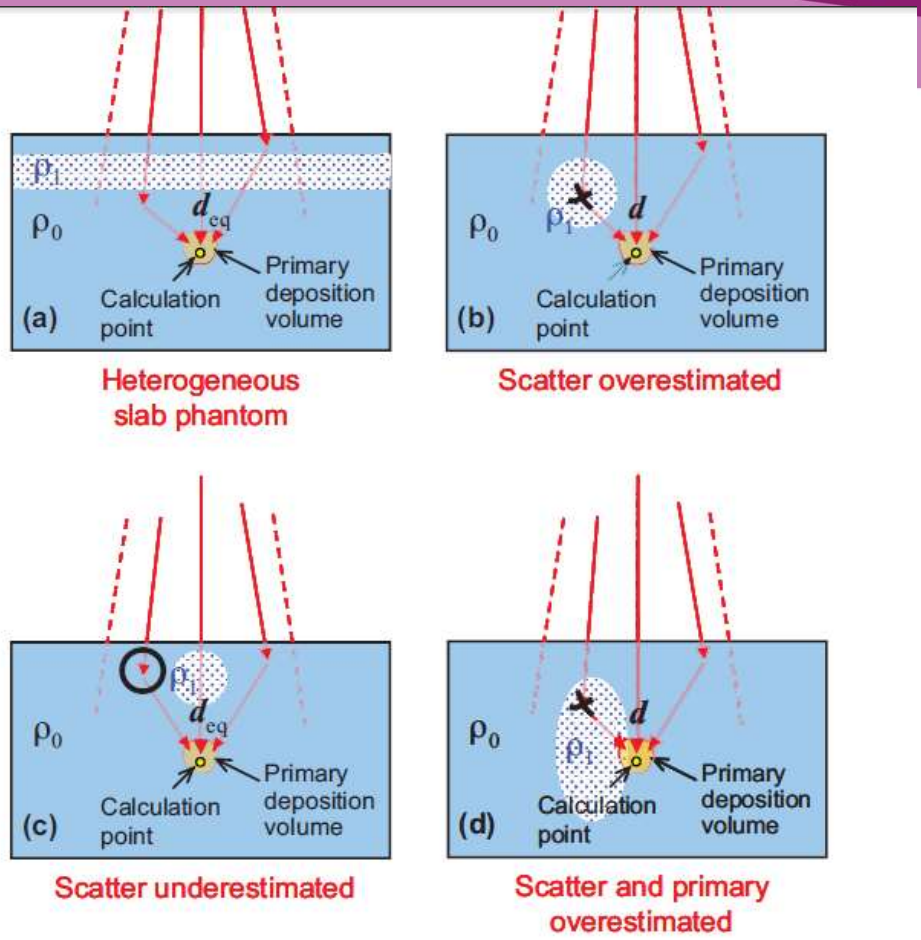
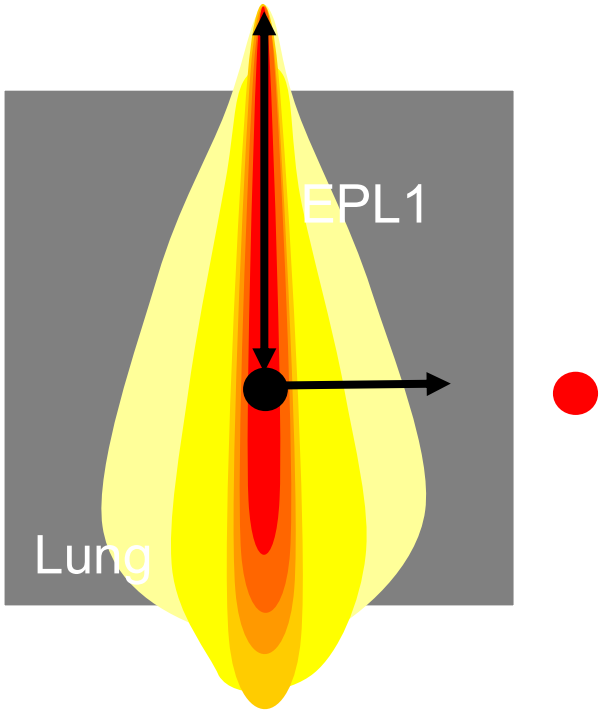
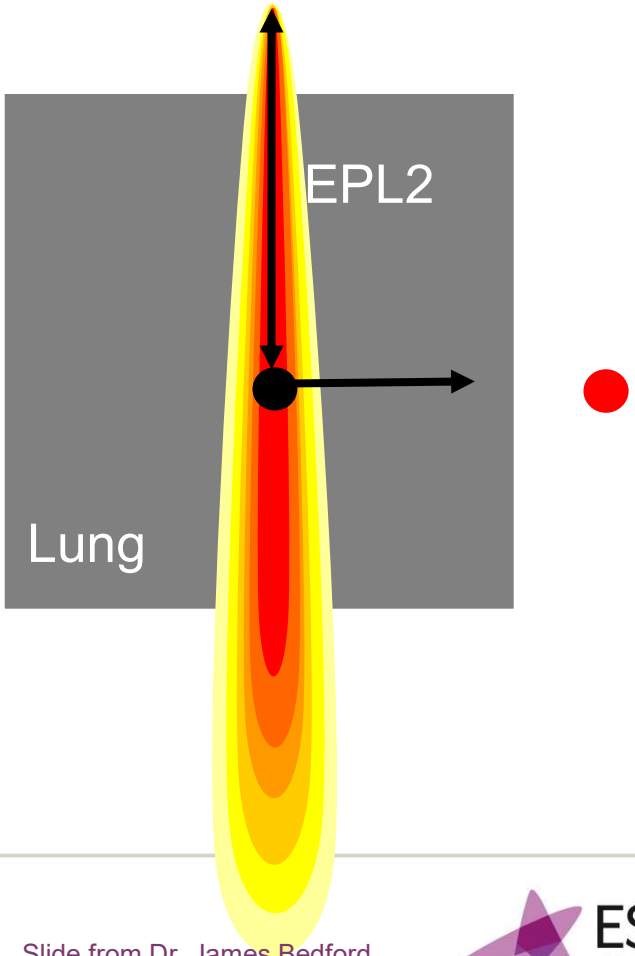


Figure 5.12. If the density variations (heterogeneities) fit the slab phantom geometry (a) pencil kernel models can yield fairly correct dose calculations through the use of an equivalent depth, here denoted d_{eq}. However, scatter effects associated with heterogeneities that are smaller than the lateral beam dimensions, illustrated by a low-density volume ρ_1 in (b), (c), and (d), can not be adequately modelled. In addition, the primary dose deposition is generally not scaled laterally, which means that it will be incorrectly modelled in cases of lateral charged particle disequilibrium (d).

PENCIL BEAM LIMITATIONS





1. Increased primary
2. Lack of scattering material
3. Modified kernel

Slide from Dr. James Bedford

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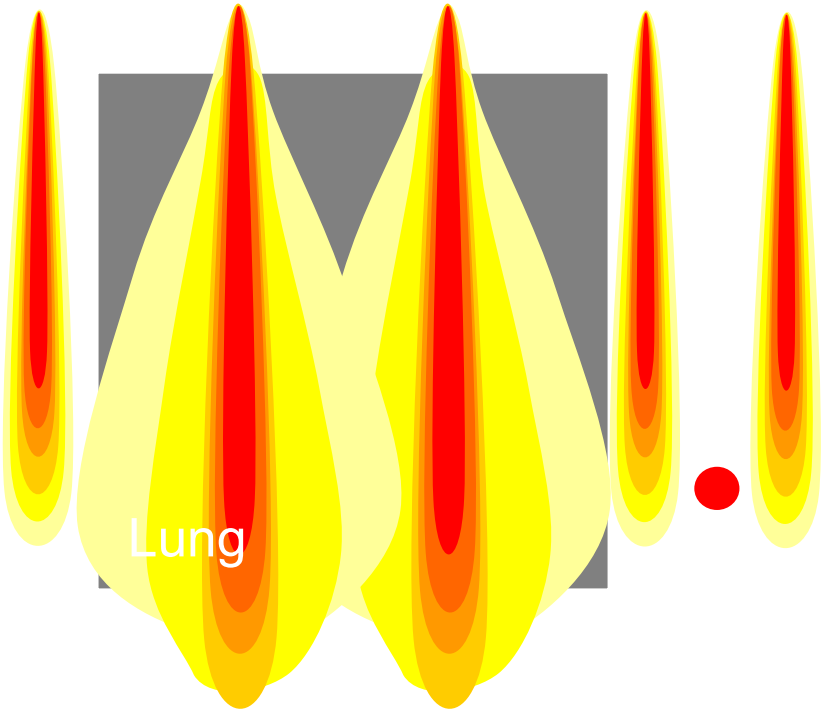
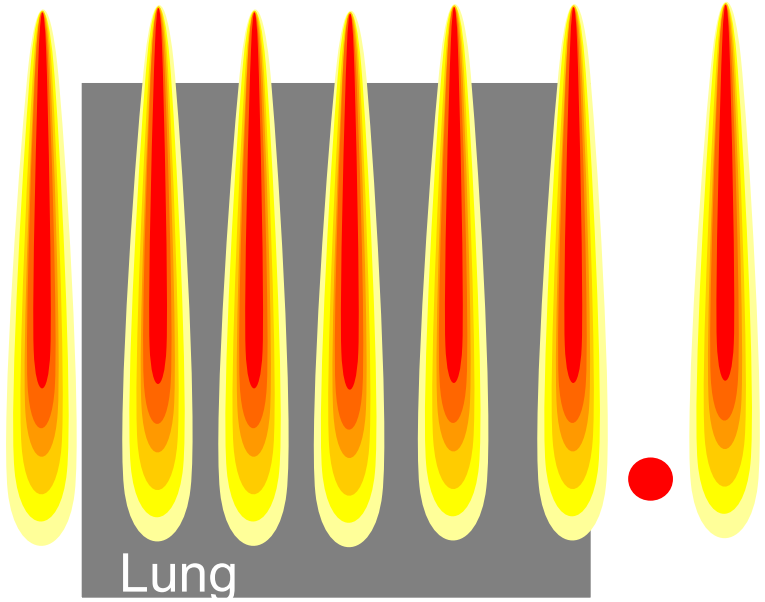
PENCIL BEAM LIMITATIONS

Actual situation



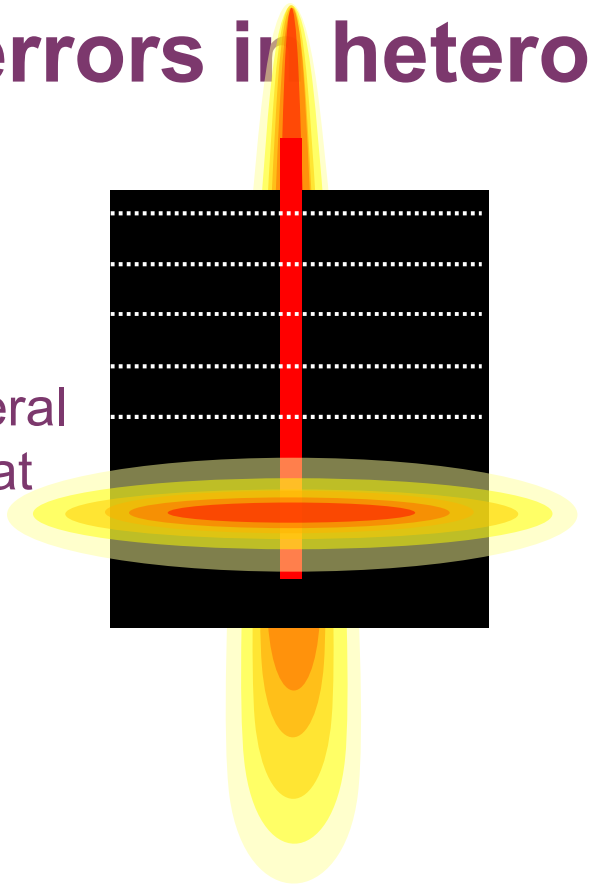
Pencil beam model situation



AAA Analytical Anisotropic Algorithm

Expansion of the pencil beam to reduce errors in heterogeneous media

1. Obtain depth component $k_d(d)$ by lateral integration at each depth



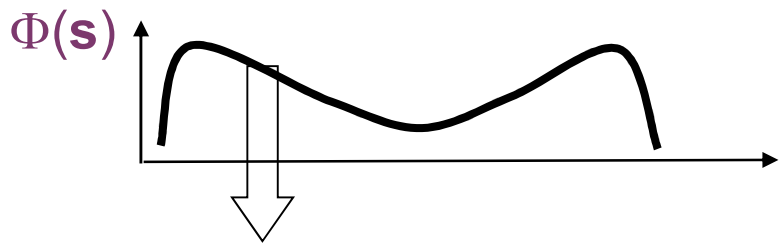
2. Apply lateral component using sum of exponentials

$$k_r(d,r) = \sum_{i=1}^{6} c_i \frac{1}{\mu_i} e^{-\mu_i r}$$

$$k(d,r) = k_d(d) \cdot k_r(d,r)$$

Van Esch et al. Testing of the analytical anisotropic algorithm for photon dose calculation. Med. Phys. 33:4130-4148 (2006)

AAA



´now individually calculated for each pencil beam, according to equivalent path length

$k(d, |\mathbf{r}-\mathbf{s}|)$

$D(\mathbf{r}, d)$

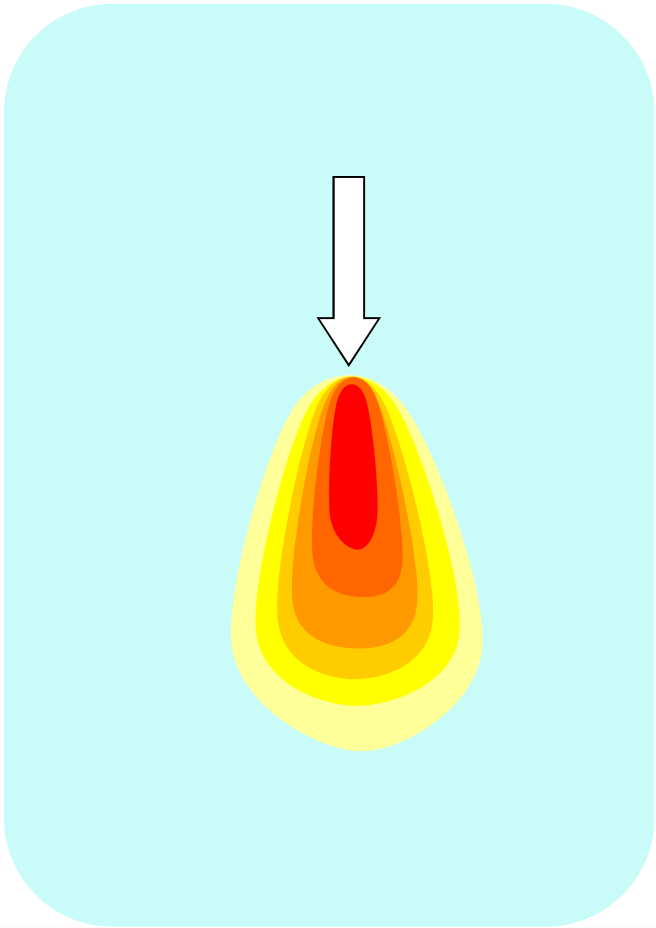
$$D(\mathbf{r},d)=\iint_A \Phi(\mathbf{s})k_d(d')k_r\left(d',|\mathbf{r}-\mathbf{s}|'\right)\rho(\mathbf{s},d)d^2s$$

CONVOLUTION ALGORITHM

- Usually collapsed cone convolution
- Convolution -superposition
- Can handle inhomogeneities properly

CONVOLUTION KERNEL

(Point-spread function)



Dose distribution
due to interactions
at a single point in
an infinite medium

from Dr. James Bedford

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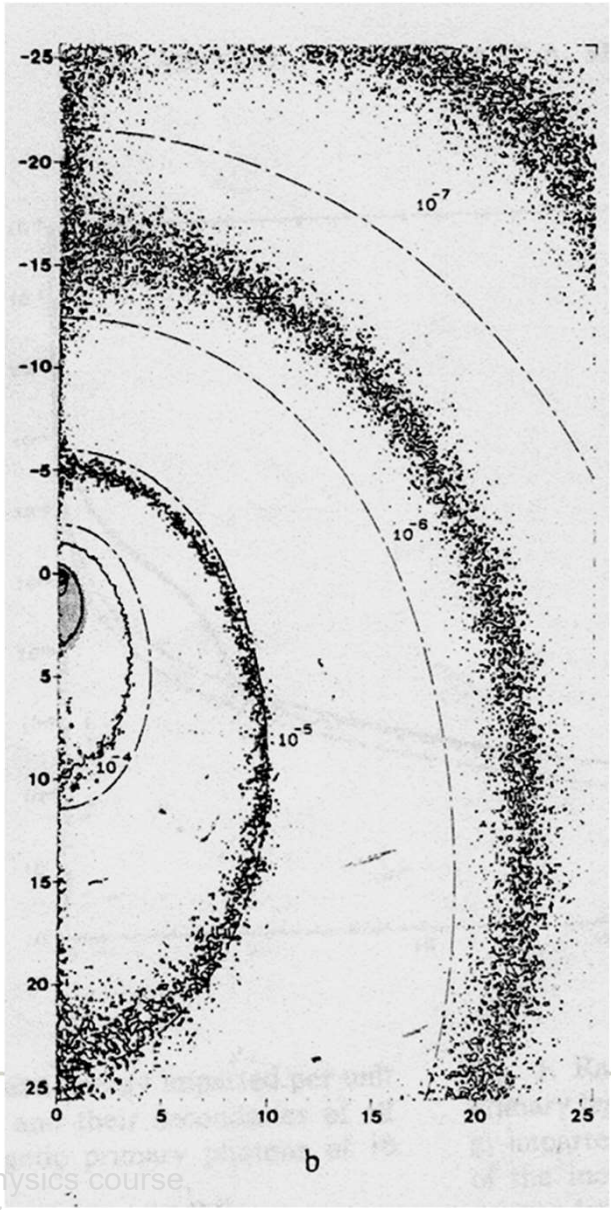
CONVOLUTION KERNEL



Ahnesjö et al. Calculation and application of point spread functions for treatment planning with high energy photon beams. Acta Oncol. 26:49-56 (1987).

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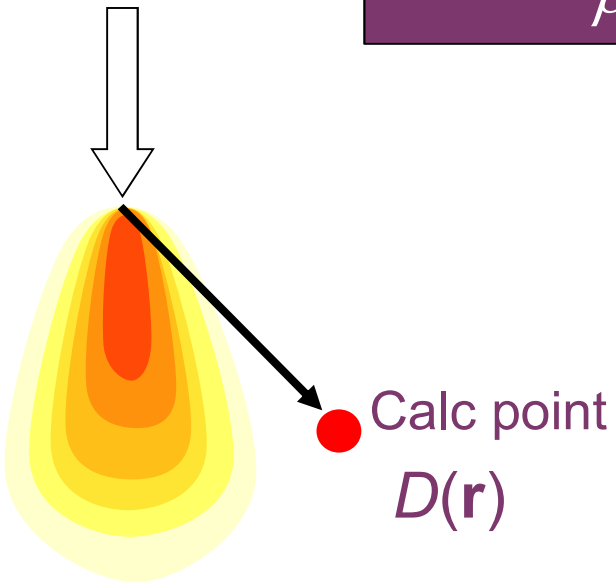
CONVOLUTION ALGORITHM

Homogeneous media

3D Terma distribution $T_E(\mathbf{r}) = \frac{\mu}{\rho}(E,\mathbf{r})\Psi_E(\mathbf{r})$



$$D(\mathbf{r}) = \iiint_V T(\mathbf{s})k(\mathbf{r}-\mathbf{s})d^3\mathbf{s}$$

Slide from Dr. James Bedford

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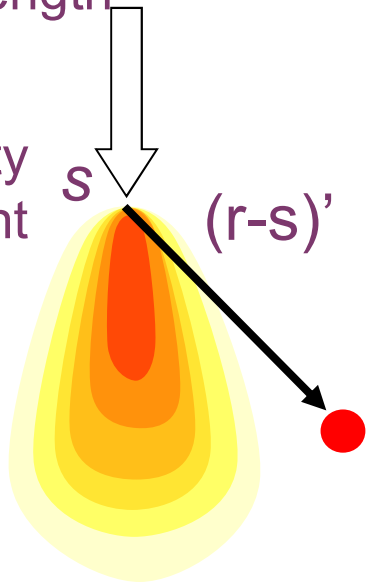
CONVOLUTION - SUPERPOSITION

Inhomogeneous media

3D Terma distribution calculated using equivalent path length

Multiply by density at interaction point



Use equivalent path length for kernel lookup

$$D(\mathbf{r}) = \iiint_V T(\mathbf{s}')\rho(\mathbf{s})k\left((\mathbf{r}-\mathbf{s})'\right)d^3\mathbf{s}$$

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The basics of point kernel convolution models

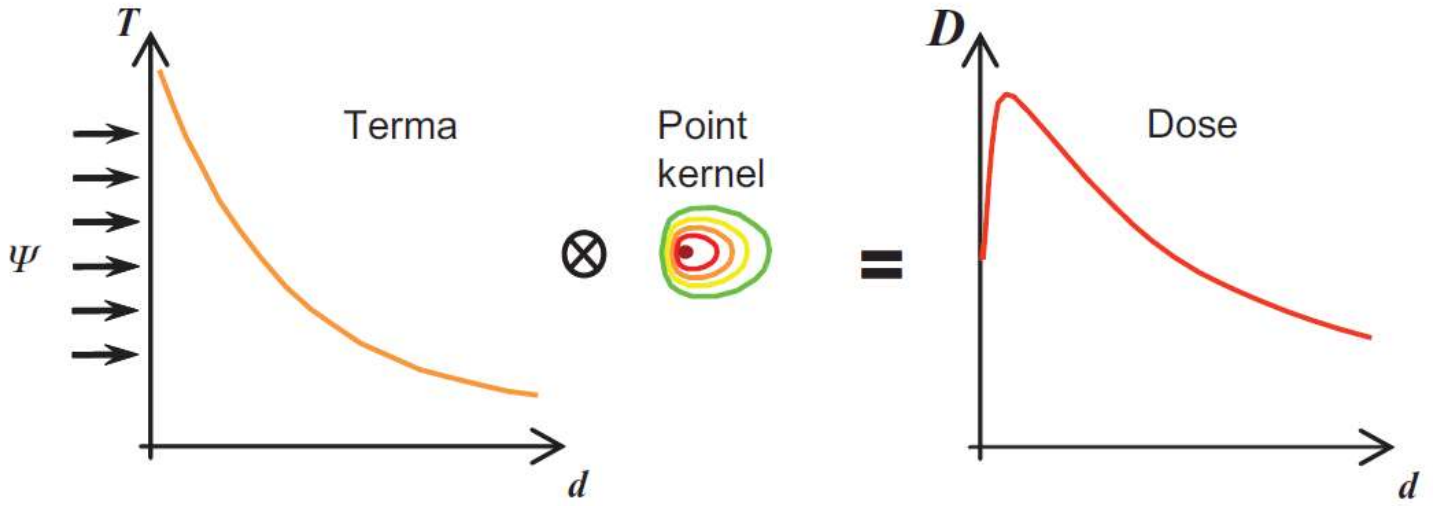
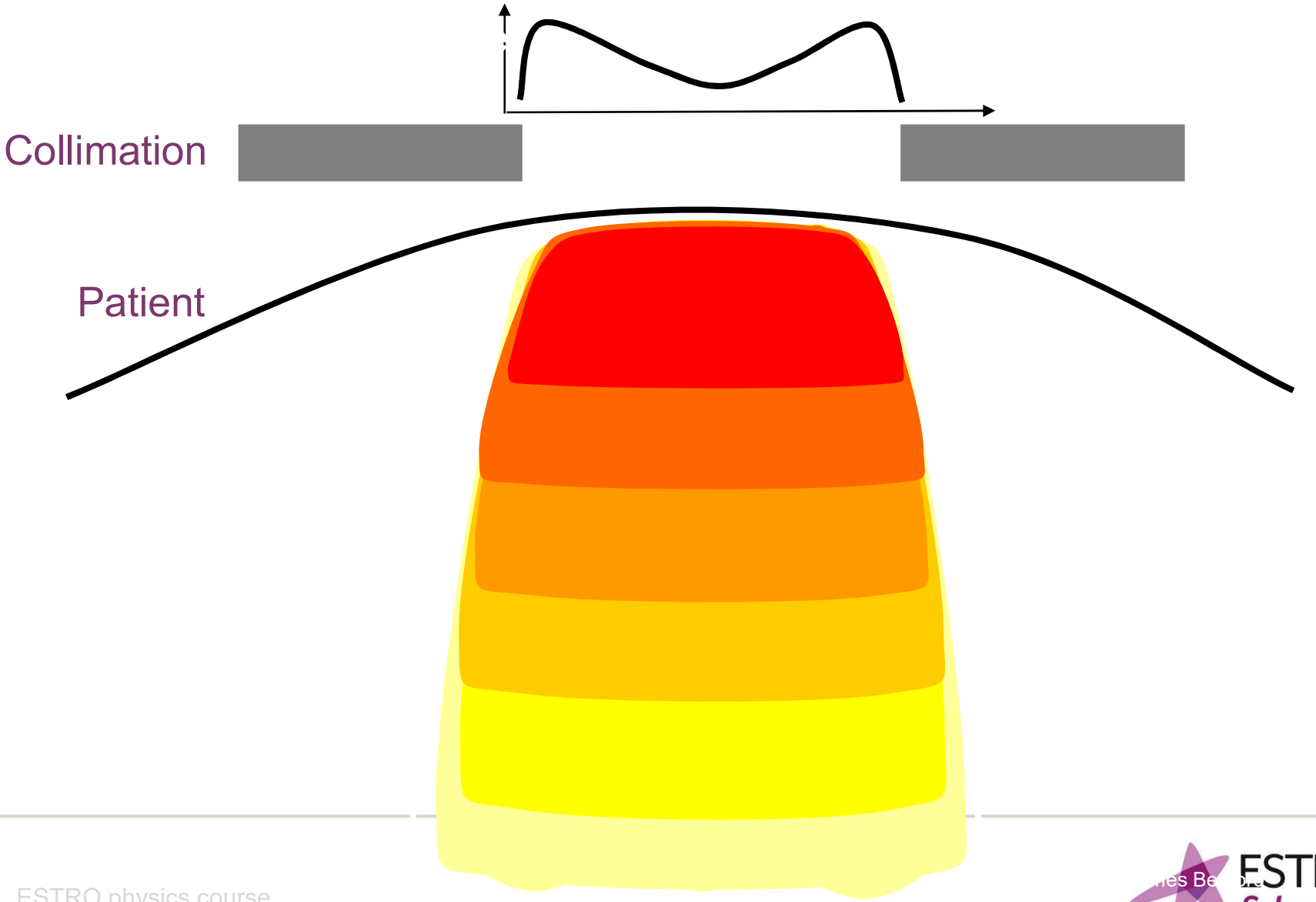


Figure 5.13. In a point kernel (convolution/superposition) model the resulting dose distribution is calculated by convolving the *terma* (total energy released per unit mass) with one or a few point kernels, here illustrated along the depth dimension.

3D CONVOLUTION



CONVOLUTION ALGORITHM

Summation over energy according to calculated Beam spectrum

$$D(\mathbf{r}) = \int_E \iiint_V T_E(\mathbf{s})\, k(E, \mathbf{r}-\mathbf{s})\, d^3\mathbf{s}\; dE$$

Collapsed cone approximation

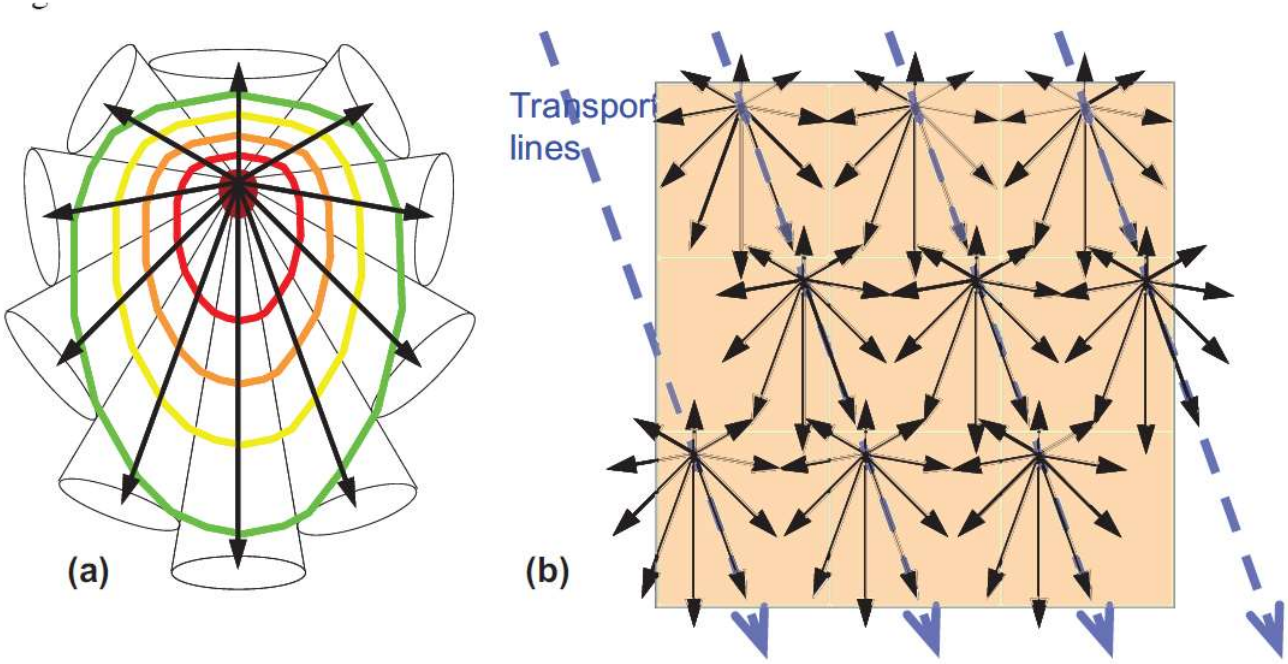
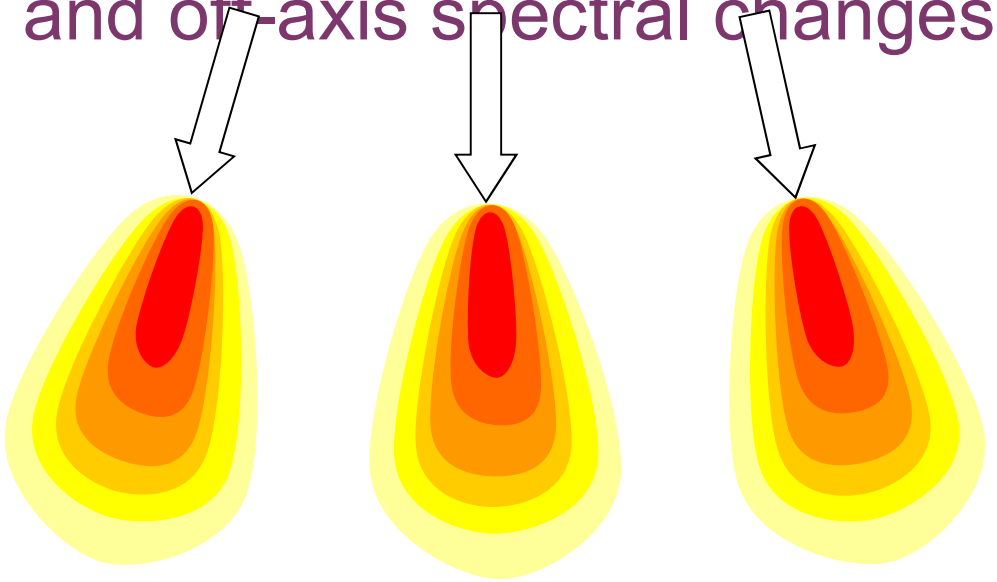


Figure 5.14. The *collapsed cone* approximation employs discretized point kernels where the full solid angle is divided into a number of conical sectors, each 'collapsed' onto a single transport direction along the cone axis (a). The dose distribution is determined by following the fixed transport lines while collecting and depositing energy in each intersected voxel (b).

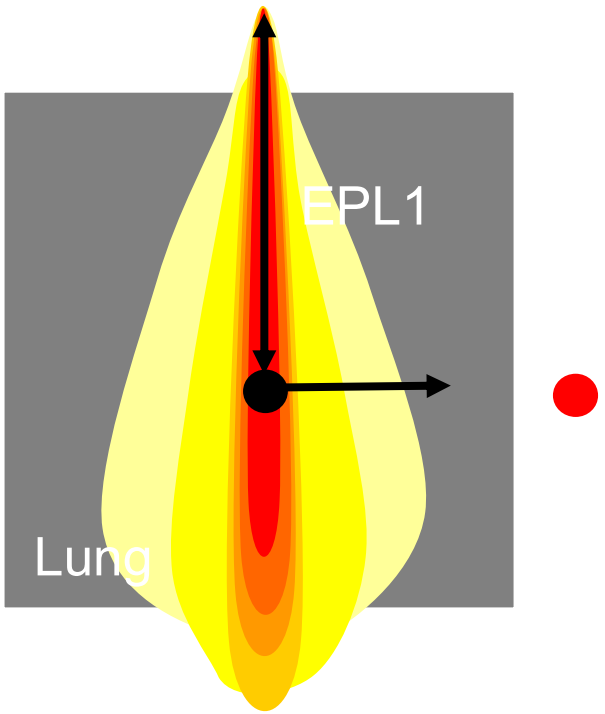
Collapsed cone !!

- Both pencil beam and convolution algorithms
- Divergence
- Depth and off-axis spectral changes

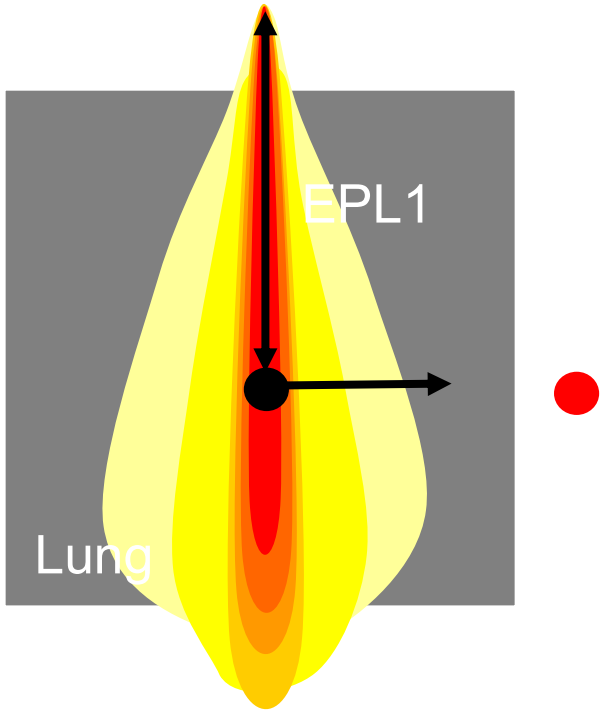


CONVOLUTION STRENGTHS

Actual situation



Convolution situation



1. Increased primary
2. Lack of scattering material
3. Modified kernel

Slide from Dr. James Bedford

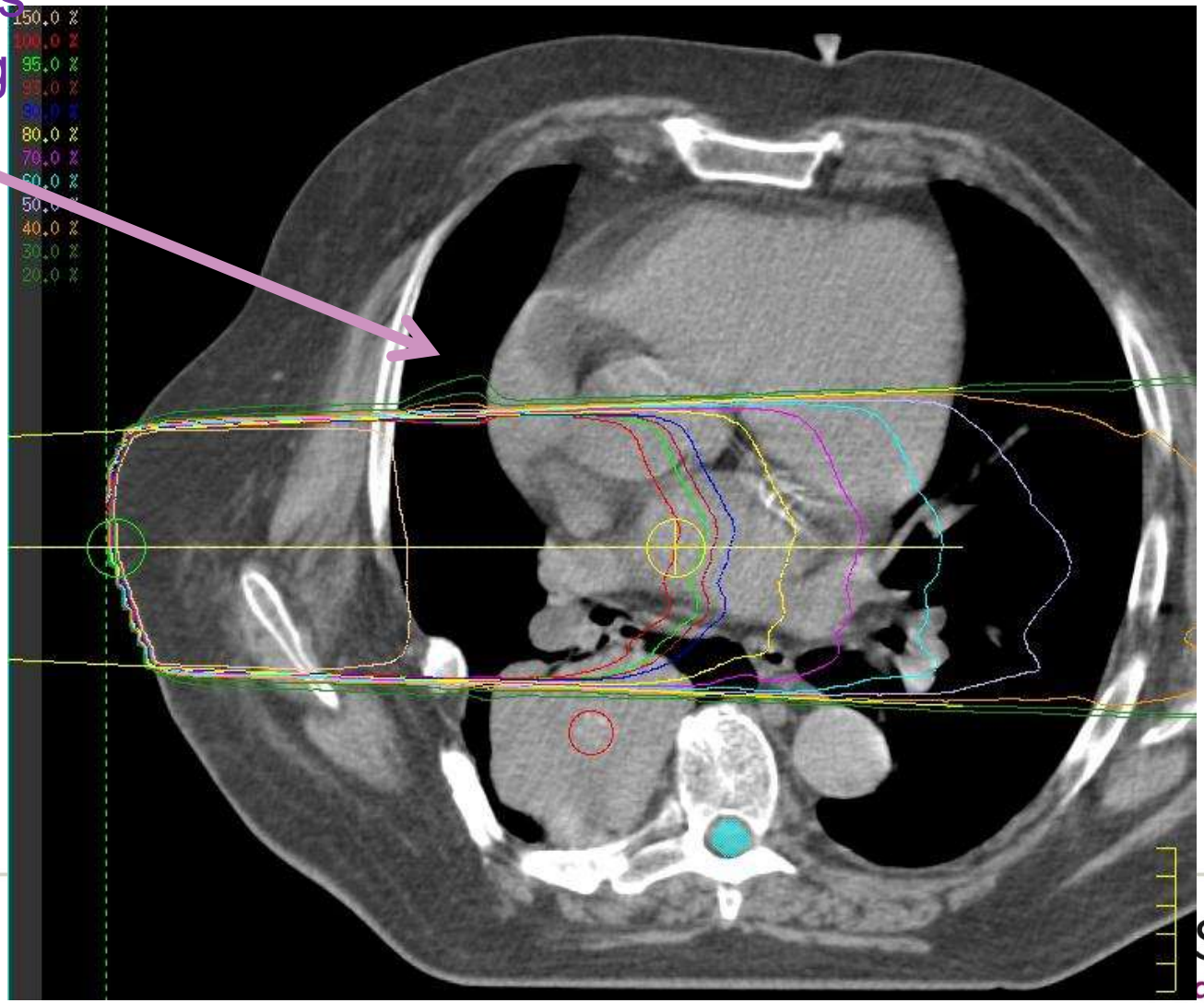
CONVOLUTION STEPS

- Beforehand
  - Calculate scatter kernels from Monte Carlo
    - Kernel for each energy
  - Fit energy spectrum to measured depth dose curves using Monte Carlo
  - Combine kernels into polyenergetic kernel

- At time of calculation
  - Ray trace through accelerator head components and patient
    - Take into account energy spectrum and off-axis spectral changes
  - Convolve with source distribution
  - Convolve with polyenergetic scatter kernels

Example of effects you may see with CC algorithm

Scatter travels further in lung tissue



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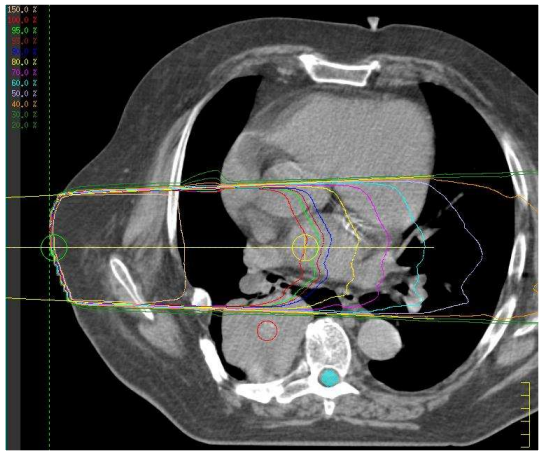
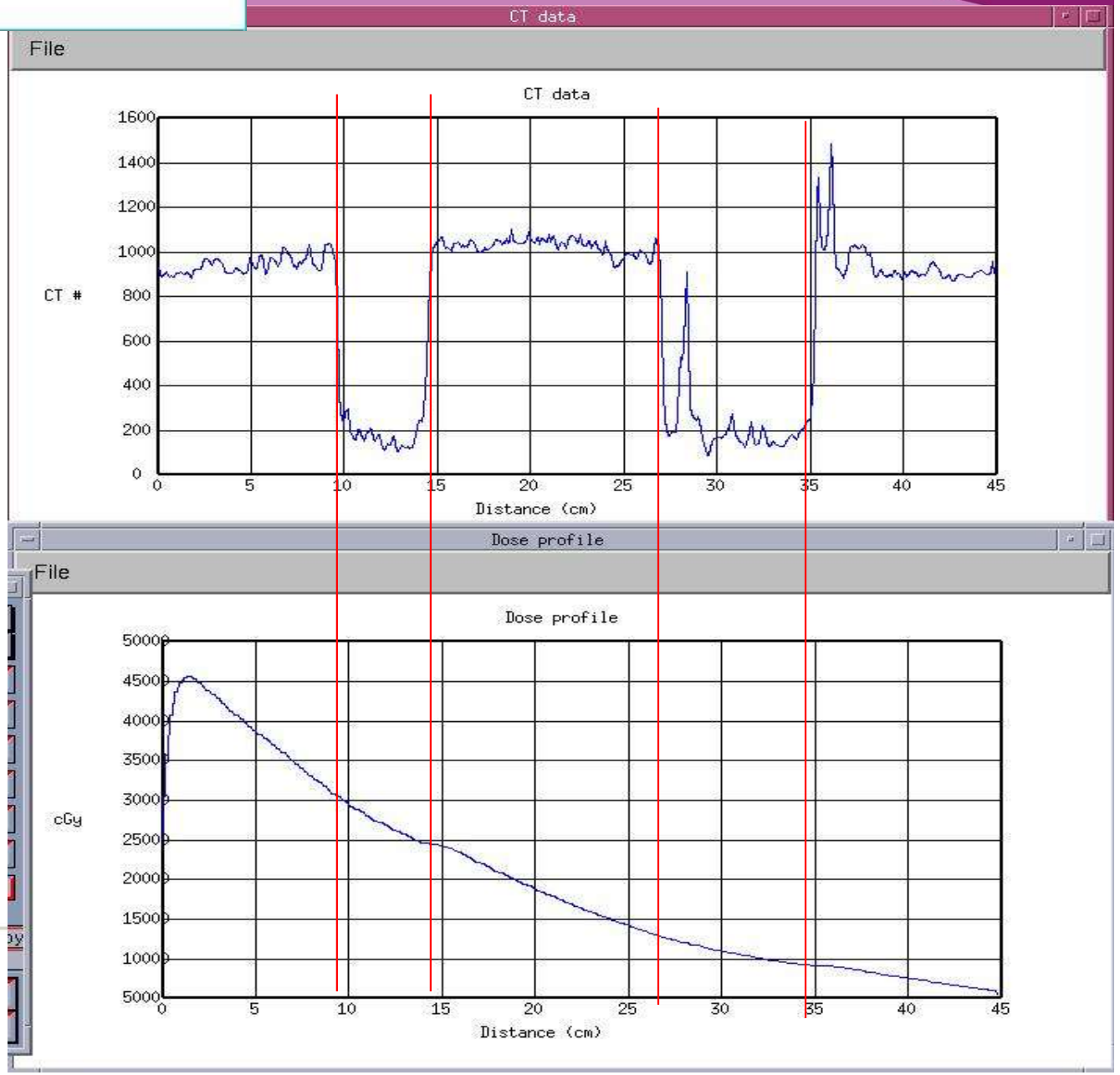
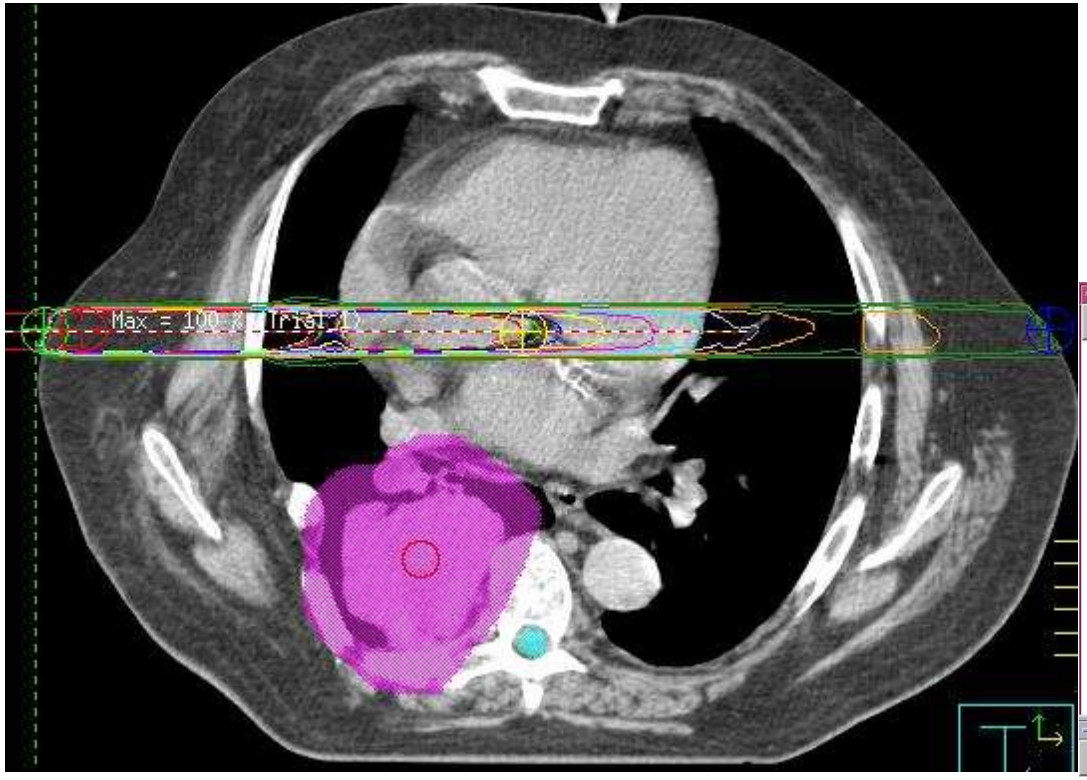
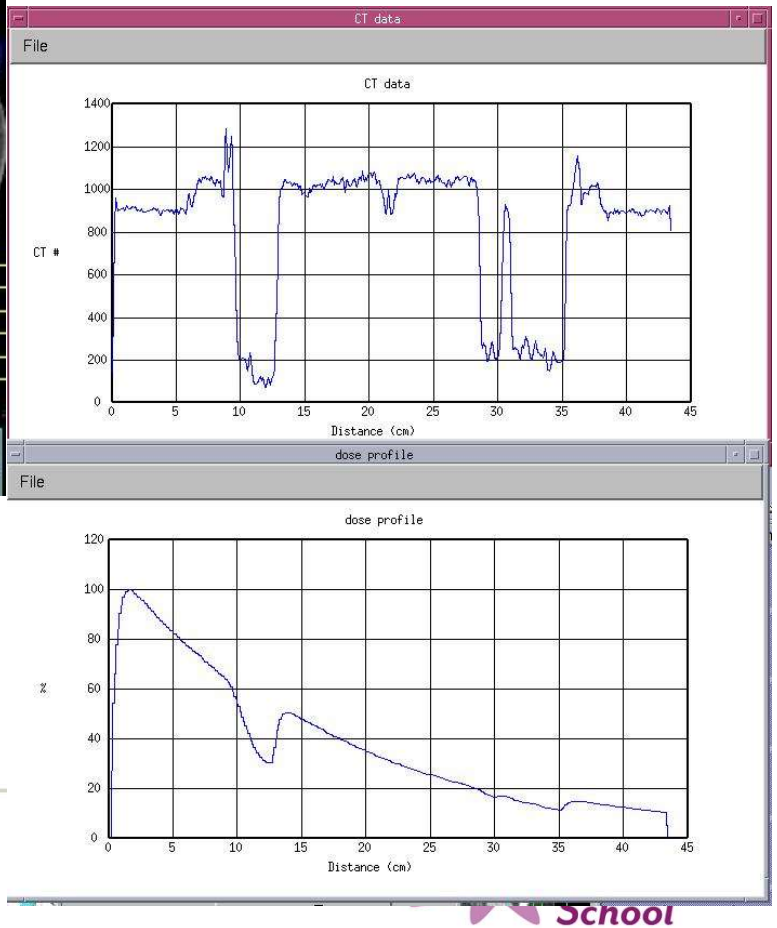
chool

$$CT\,number = \frac{\mu_{tissue} - \mu_{water}}{\mu_{water}} \times 1000 + 1000$$





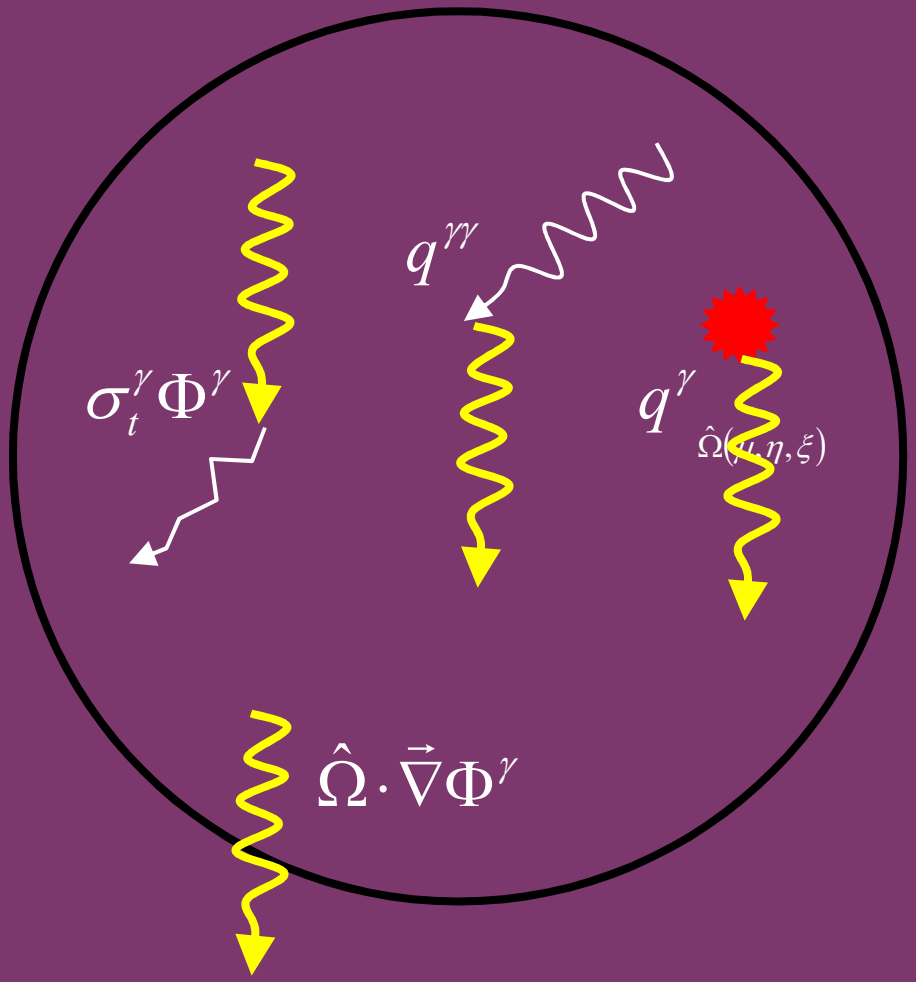




More pronounced effect on small fields.
Note also the re-build-up

ACUROS XB ALGORITHM

Linear Boltzmann transport equations (photons)



Direction
Energy *E*

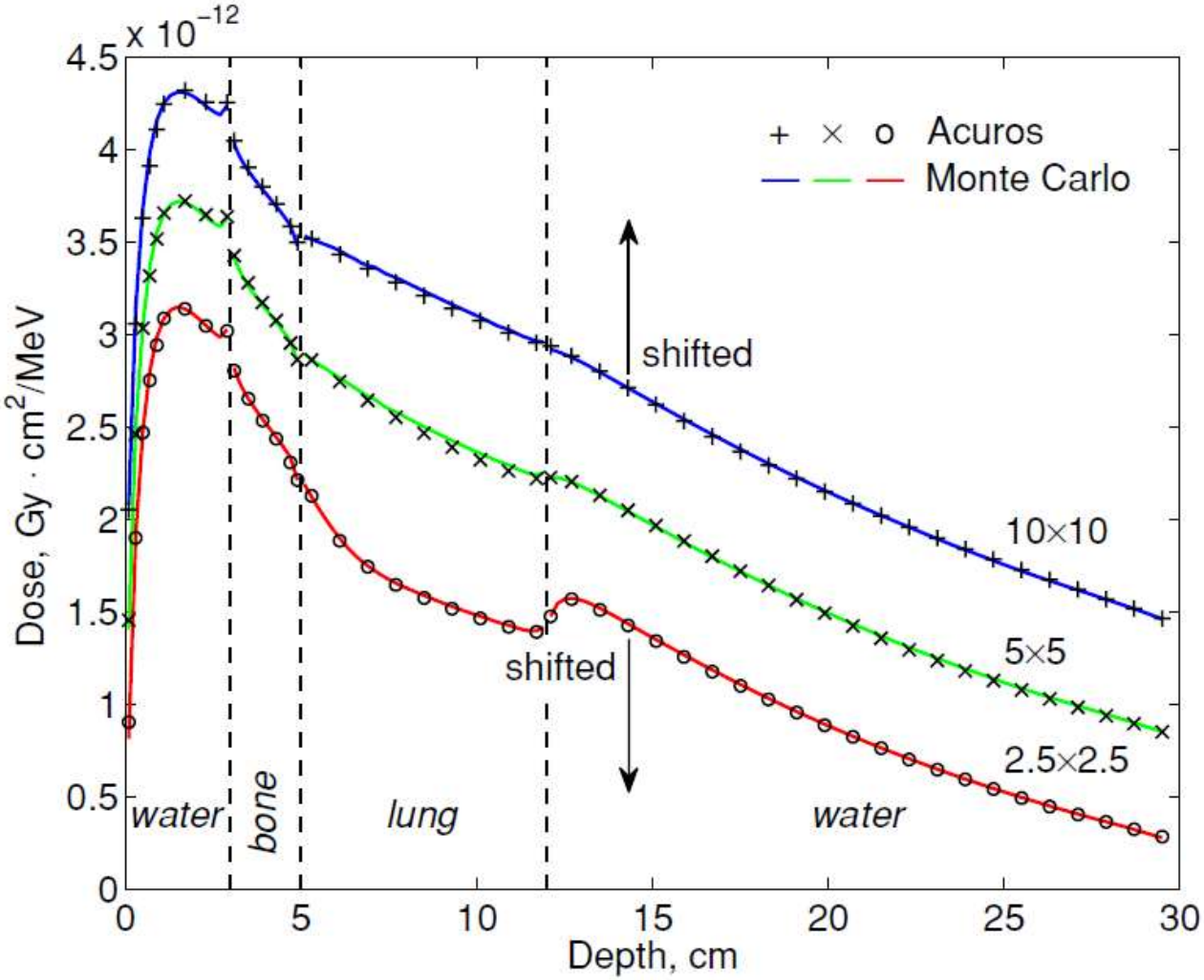
ACUROS XB ALGORITHM

Linear Boltzmann transport equations

Photons: $\hat{\Omega}\cdot\vec{\nabla}\Phi^{\gamma}+\sigma_t^{\gamma}\Phi^{\gamma}=q^{\gamma\gamma}+q^{\gamma}$

Electrons: $\hat{\Omega}\cdot\vec{\nabla}\Phi^{e}+\sigma_t^{e}\Phi^{e}-\frac{\partial}{\partial E}\left(S_R\Phi^{e}\right)=q^{ee}+q^{\gamma e}+q^{e}$

$\hat{\Omega}(\mu,\eta,\xi)$	unit direction vector
$\Phi^{\gamma,e}(\vec{r},E,\hat{\Omega})$	photon/electron angular fluence
$\vec{r}(x,y,z)$	position vector
E	energy
σ_t	total cross-section
q	particle sources
$S_R(\vec{r},E)$	stopping power



Vassiliev et al. Validation of a new grid-based Boltzmann equation solver for dose calculation in radiotherapy with photon beams. Phys. Med. Biol. 55:581-598 (2010)

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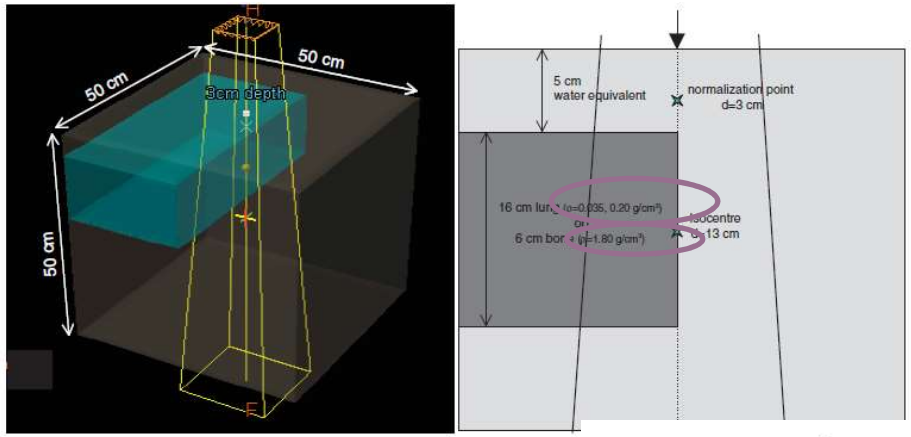
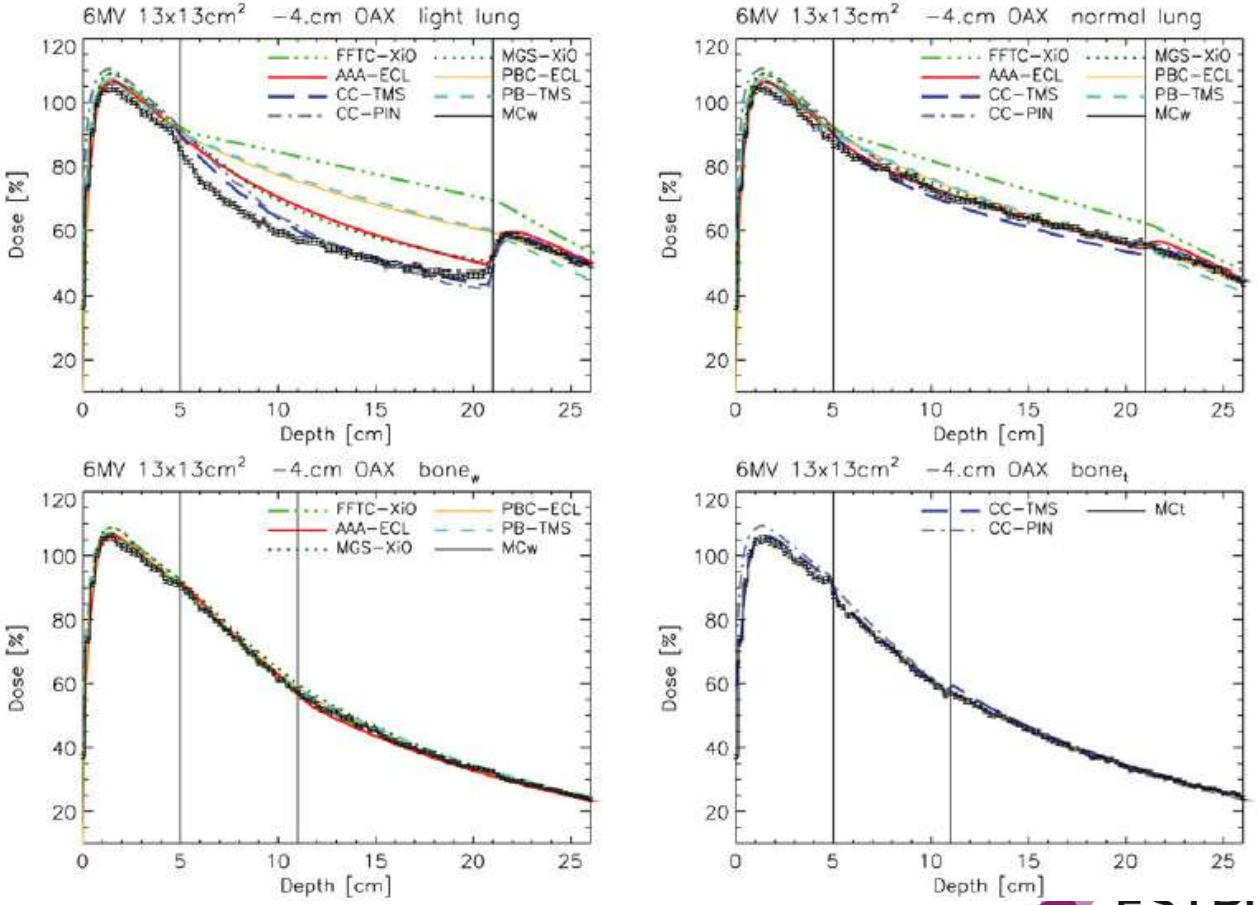
Phantom comparisons of dose algorithms

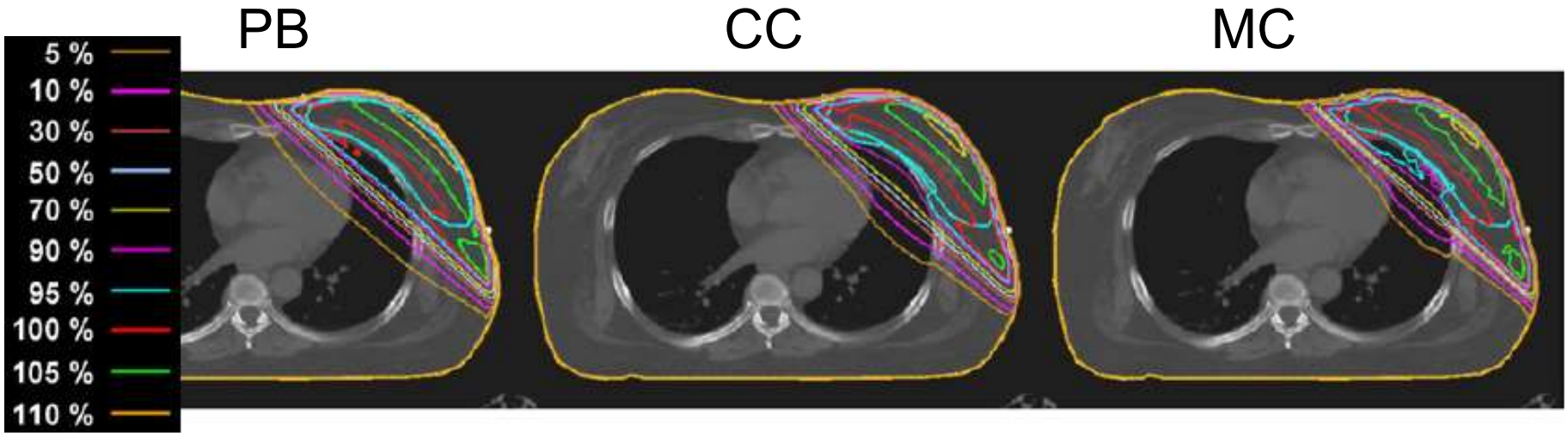




Fogliata et al,
Phys. Med. Biol. **52**
(2007) 1363–1385

Tangential Breast plan

6 mv breast plan,



Knöös et al. Phys. Med. Biol. **51 (2006) 5785–5807**
Comparison of dose calculation algorithms for treatment planning in external photon beam therapy for clinical situations

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Breast plan, DVH for the PTV and the Lung

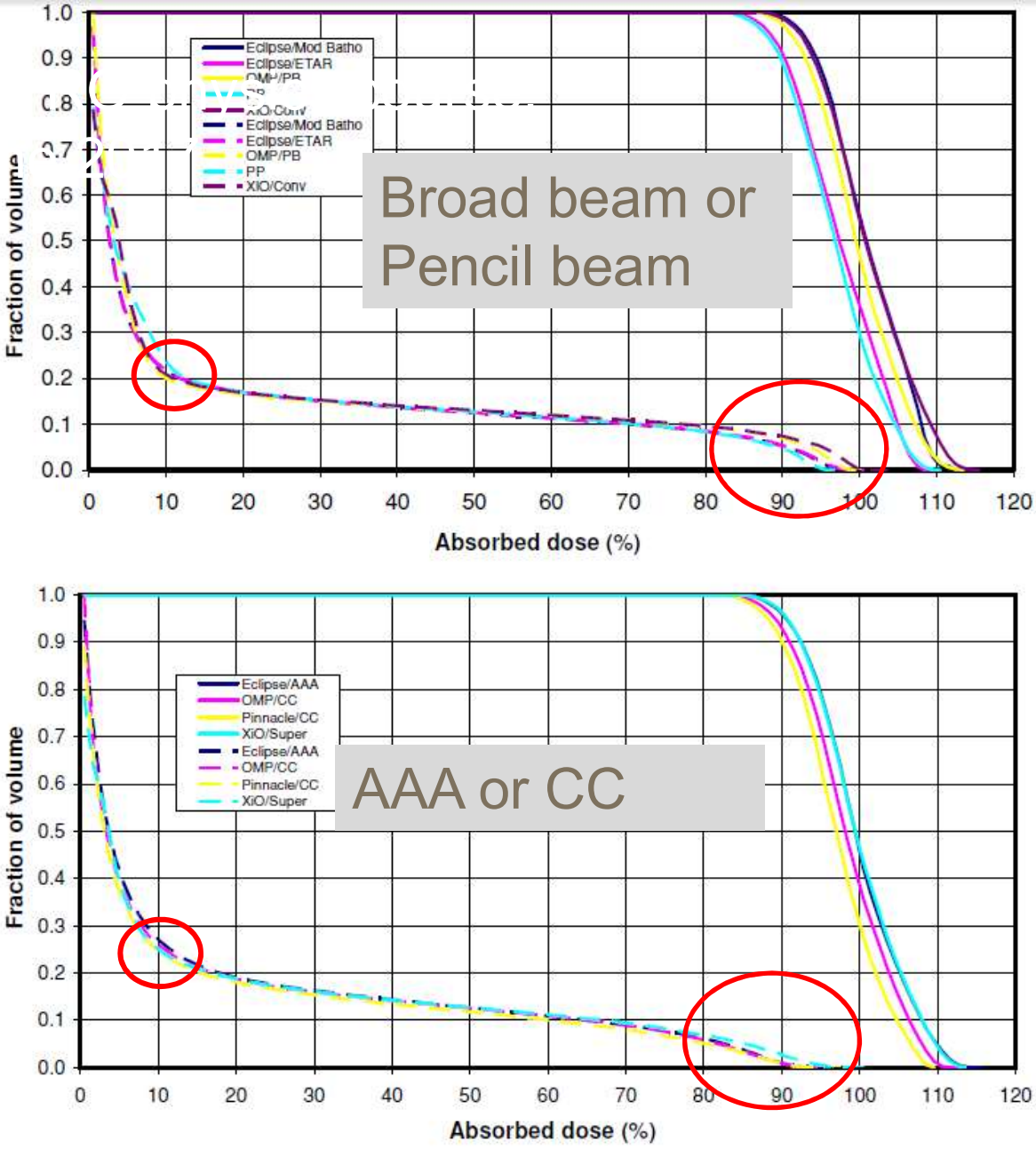
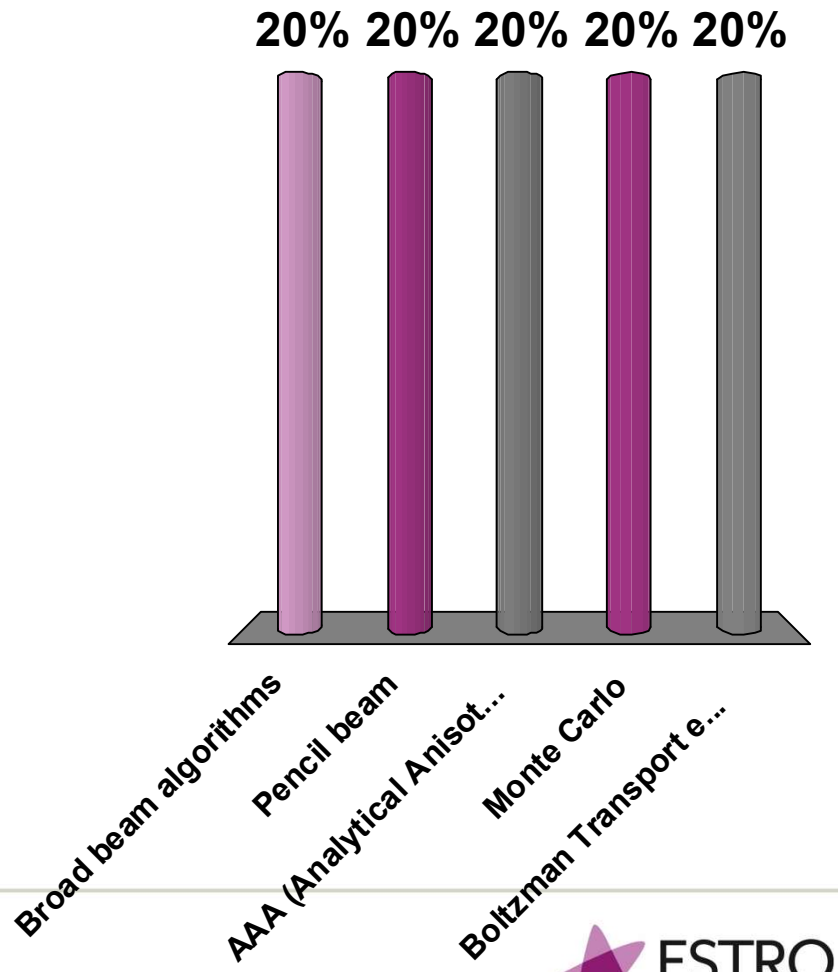


Figure 1. DVH for the PTV and the adjacent lung for the 6 MV tangential treatment of the breast calculated with *type a* (upper panel) and *type b* (lower panel) models. Solid lines are the PTV and the dashed lines are for the lung.

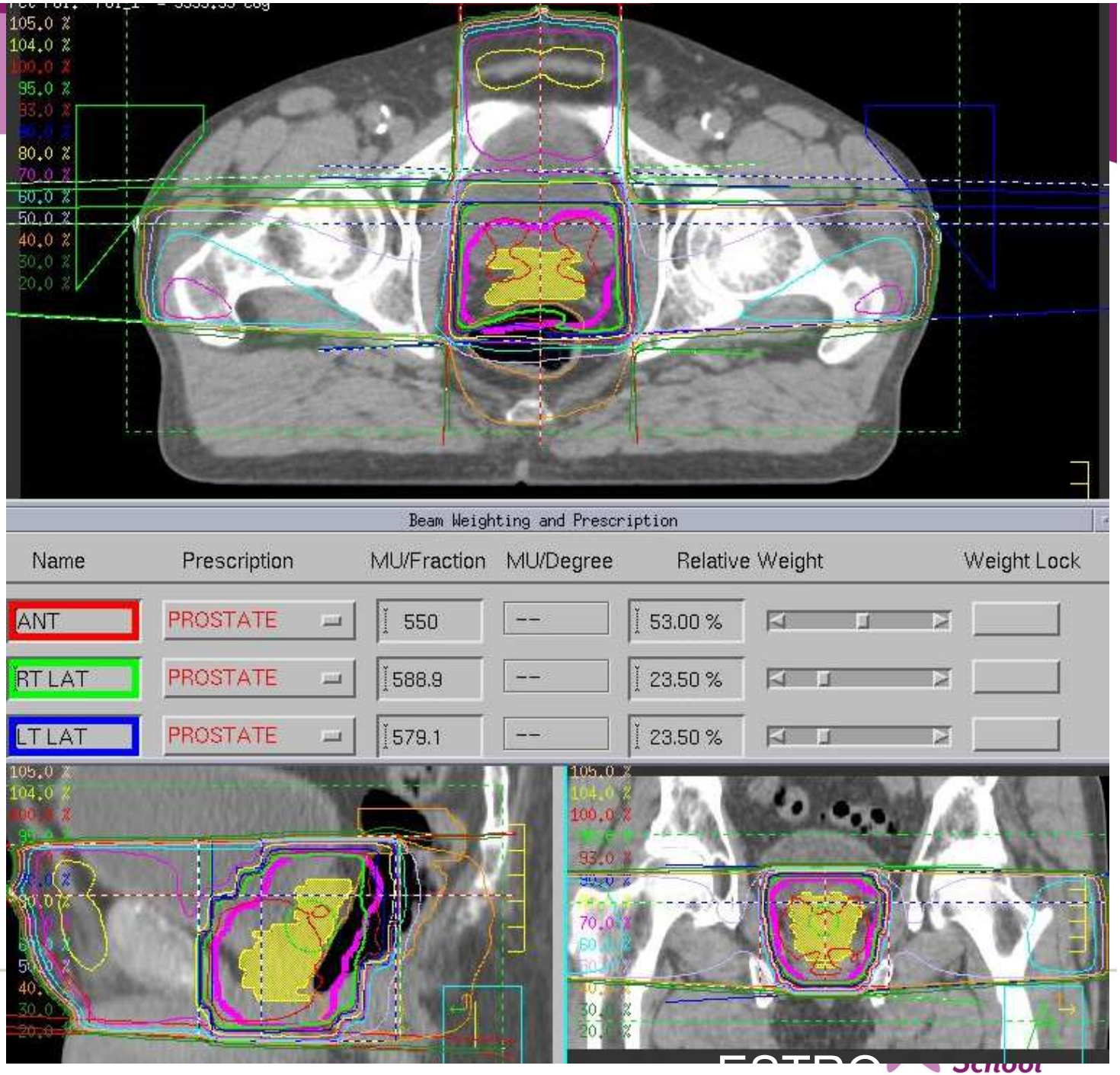
Which algorithm will allow you to see increased scatter in lung?

A. Broad beam algorithms
B. Pencil beam
C. AAA (Analytical Anisotropic Algorythm)
D. Monte Carlo
E. Boltzman Transport equation (Acuros)



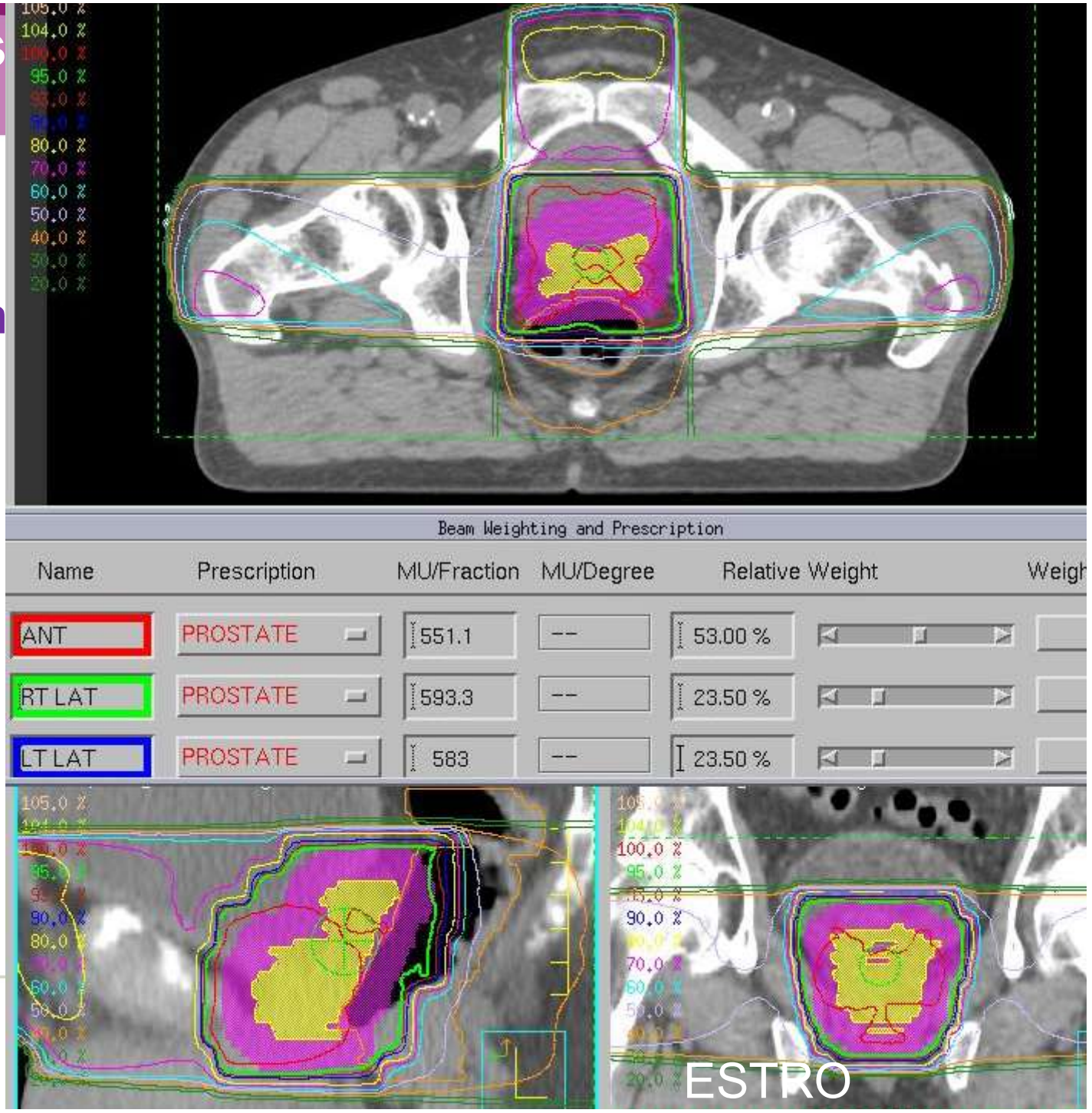
Full scatter

Collapsed cone beam algorithm



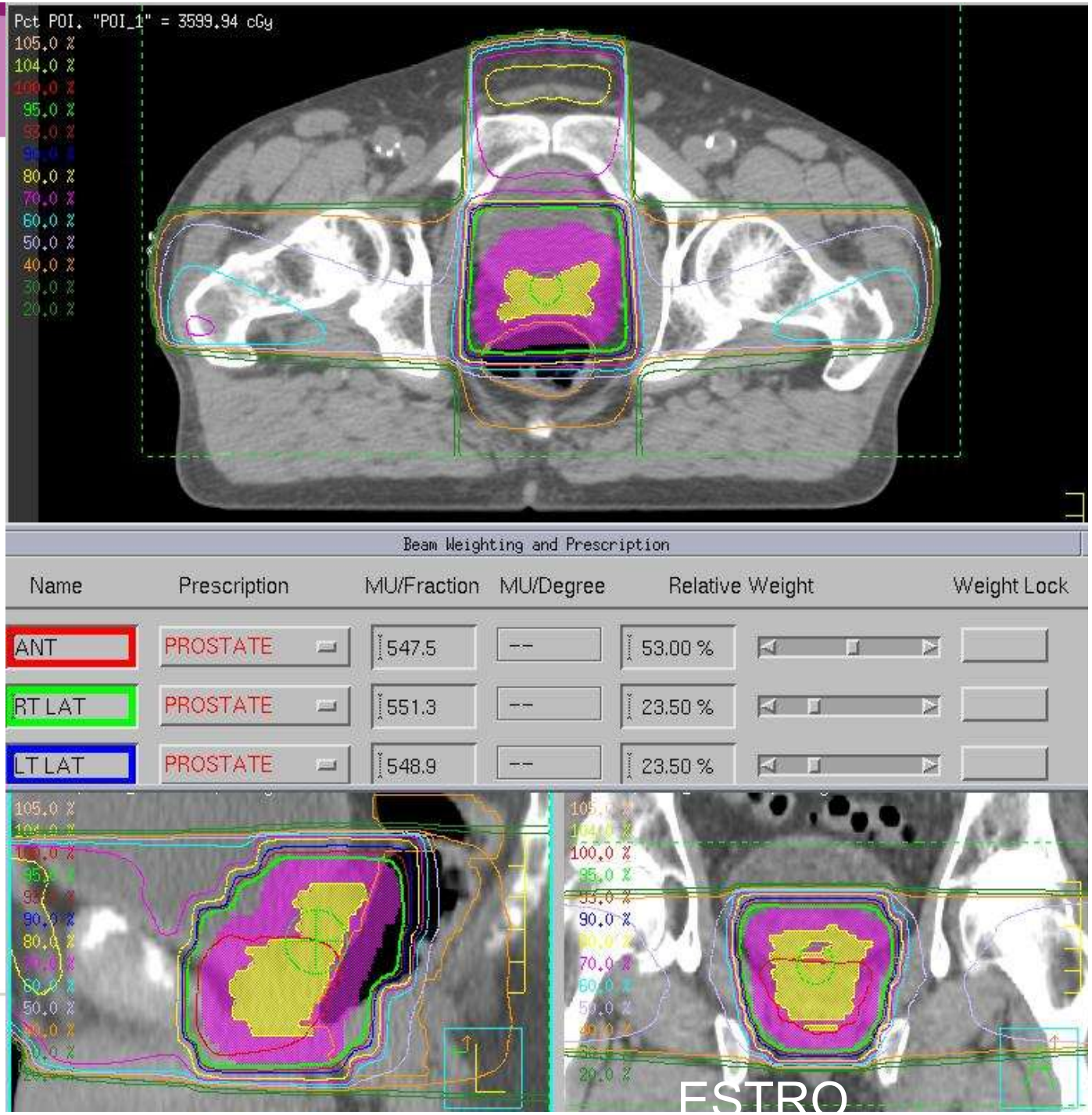
Homogenous Scatter

Like Pencil beam algorithm



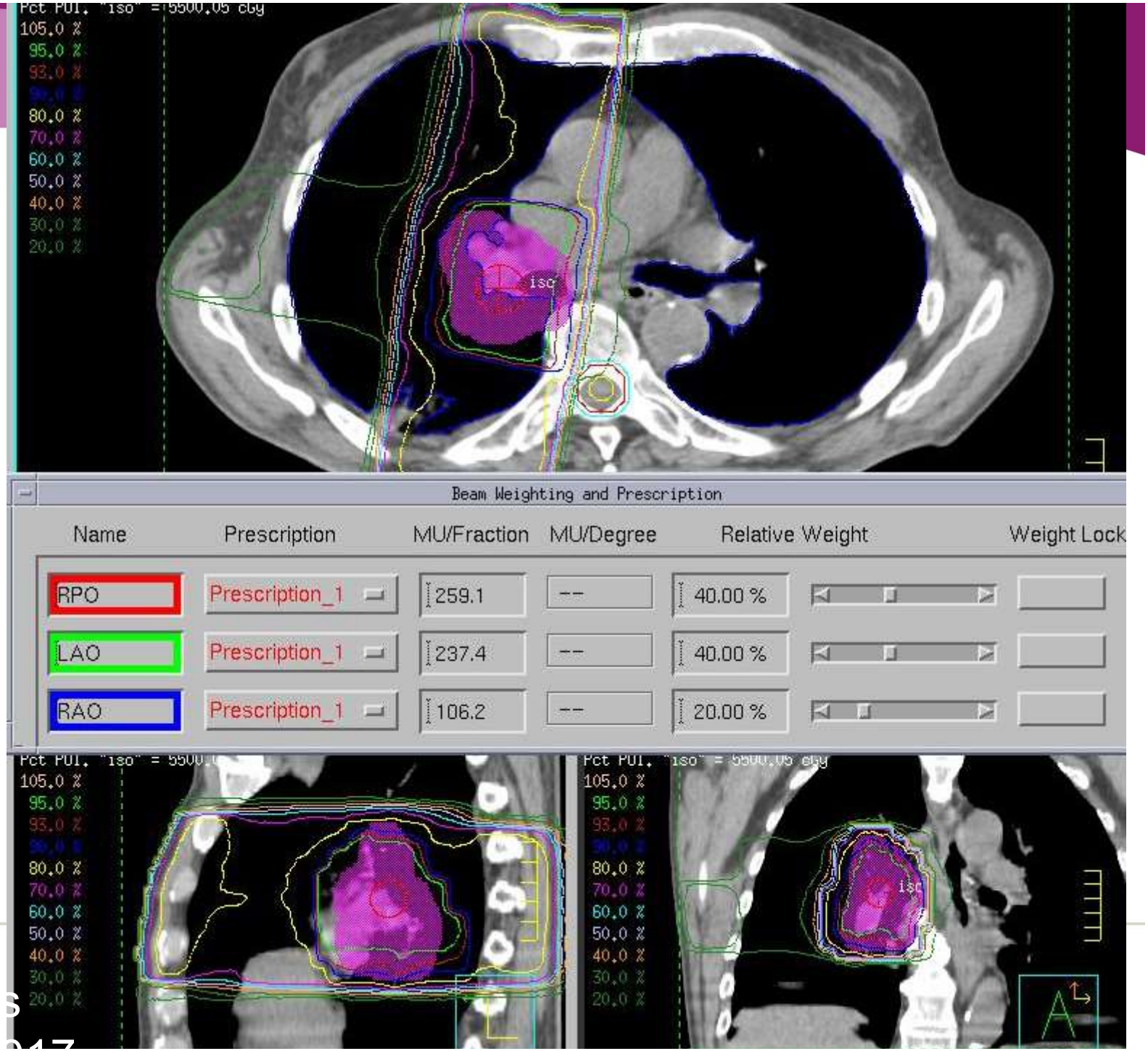
Homogenous

No CT correction for tissue



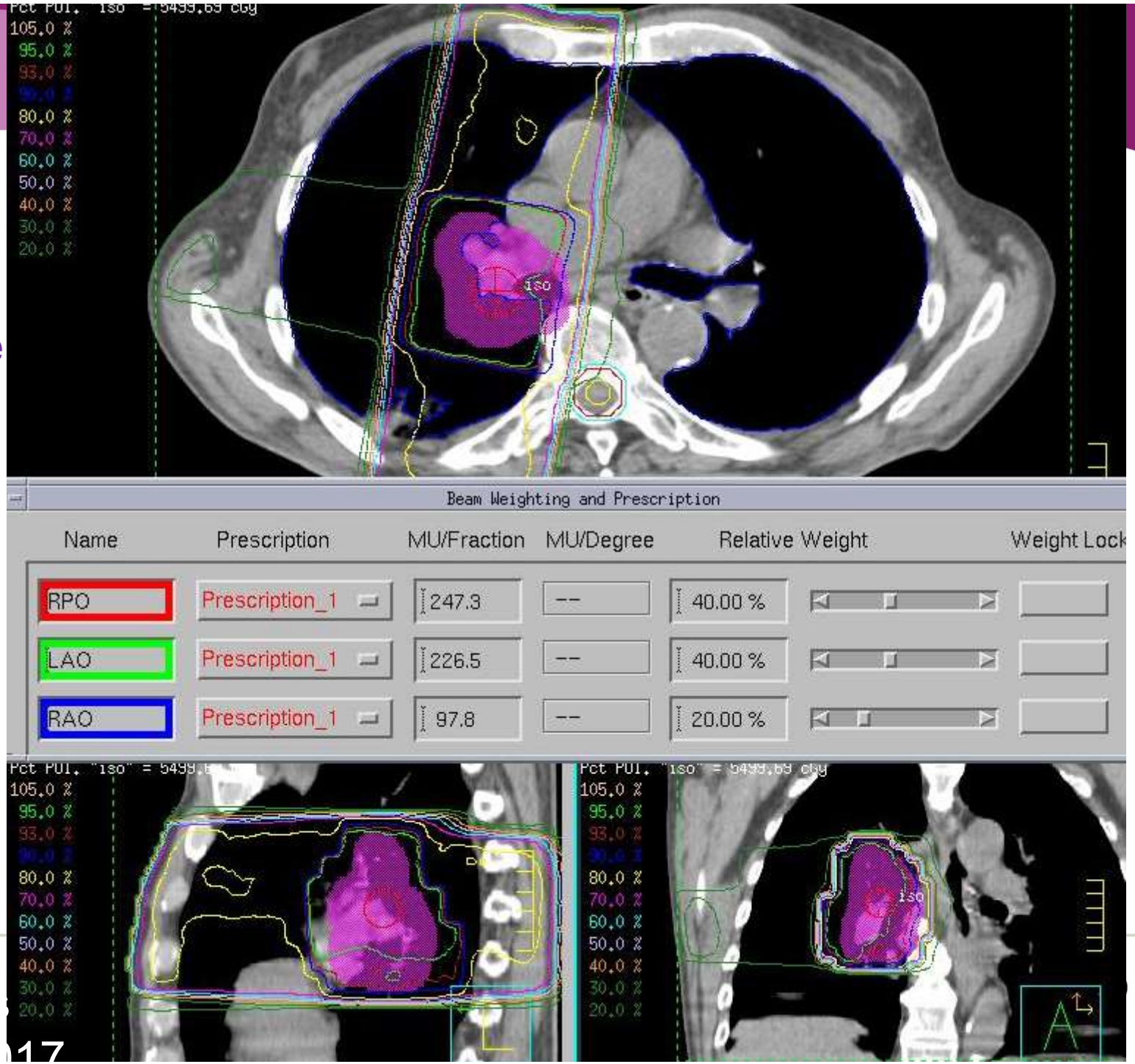
	Full Scatter	Hom. Scatter	Hom. Primary
ANT	550.0	551.1	547.5
RT LAT	588.9	593.3	551.3
LT LAT	579.1	583	548.9
Average error on this pt.		+0.5%	-4.1%

Full scatter

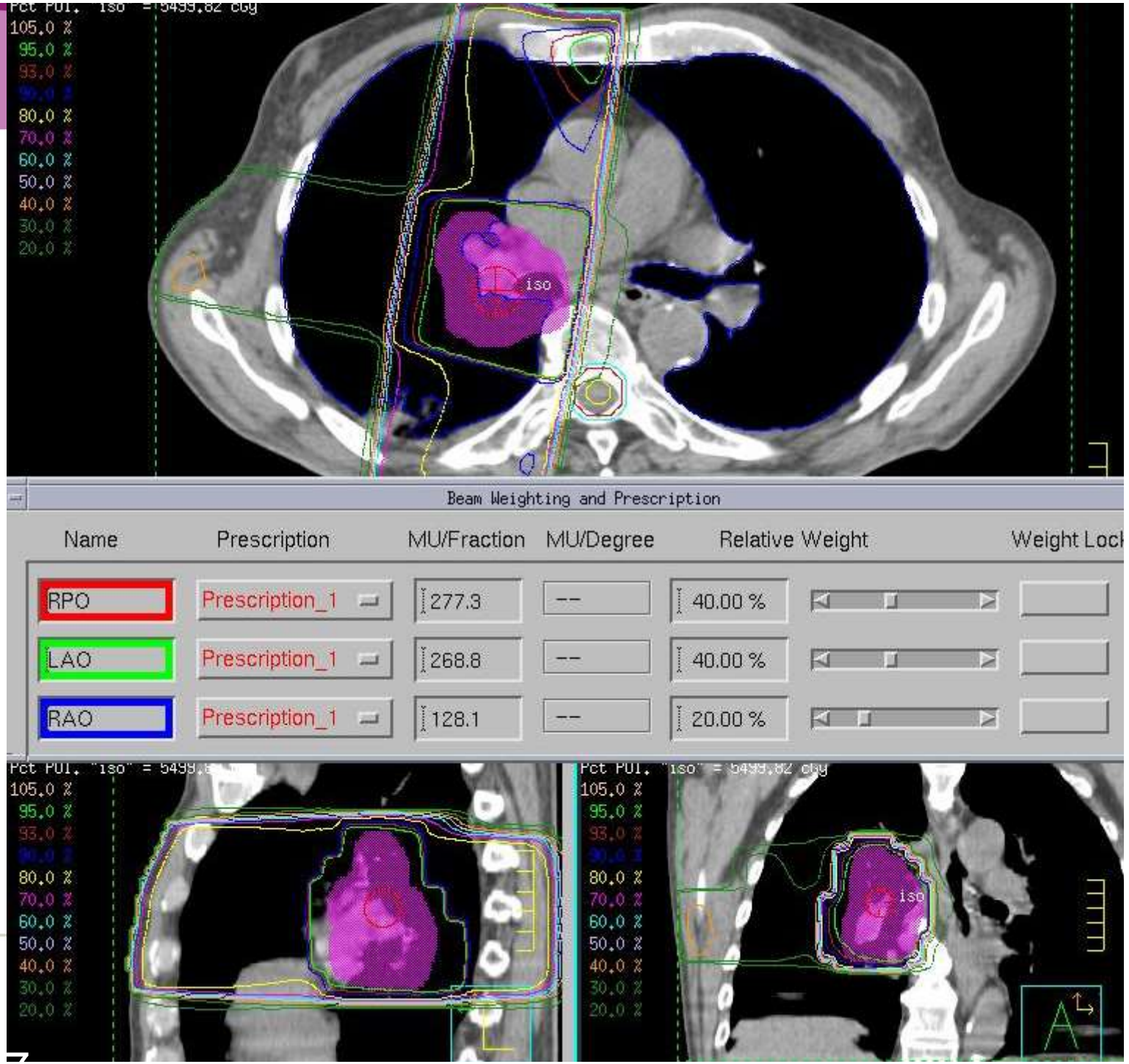


Homogene

Scatter



Homo Primary



	Full Scatter	Hom. Scatter	Hom. Primary
RPO	259.1	247.3	277.3
LAO	237.4	226.5	268.8
RAO	106.2	97.8	128.1
Average error on this pt.		- 5.2%	+ 11.86%

CONCLUSION

- Broadbeam methods
- Accurate ONLY for simple fields, homogeneous volumes.
- Pencil beam algorithm
- Used to overcome limitations with irregular fields, only AAA takes lateral scatter into account
- Convolution algorithms
- Provide high accuracy with inhomogeneities
- Monte Carlo
- Solution of the Boltzman transport equation
- Please get to know your planning system's dose algorithm and it's limitations

REFERENCES

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  - Milan and Bentley Br. J. Radiol. 47:115-121 (1974)
  - Sontag and Cunningham Radiology 129:787-794 (1978)
- **Pencil beam algorithms**
  - Mohan and Chui Med. Phys. 14:70-77 (1987)
  - Bortfeld et al. Med. Phys. 20:311-318 (1993)
- **Convolution algorithms**
  - Ahnesjö Med. Phys. 16:577-592 (1989)
  - Zhu and Boyer Phys. Med. Biol. 35:351-368 (1990)
  - **Monte Carlo**
- "Monte Carlo Techniques in Radiotherapy" Edited by Seco and Verhaegen
  - **Boltzmann transport equation**
  - Phys. Med. Biol. 55:581-598 (2010)
- **Useful texts**
  - Johns and Cunningham
  - Khan
- **Review**
  - Ahnesjö and Aspradakis Phys. Med. Biol. 44:R99-R155 (1999)
- **Your planning system manual!**

Thank you for your attention

QUESTIONS ?

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non-Reference Dosimetry

Ben Heijmen

Erasmus MC
University Medical Center Rotterdam

ESTRO - Physics for modern radiotherapy
Bucharest, 2017

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reference dosimetry: absolute dose measurement in water in reference conditions, mainly calibration of MU-chambers

Examples of ***non***-reference dosimetry:

- measurement of input for TPS (PDDs, profiles, ..)
- verification of dose calculation algorithms (in phantoms)
- verification of complex/new treatment techniques by measurements in anthropomorphic phantoms
- pre-treatment dosimetric verification of IMRT/VMAT (e.g. with EPID, delta 4, ArcCHECK)
- in-vivo dosimetry
- …..

Dosimeters recommended for reference dosimetry are in many cases ***not*** useful:

- large sensitive volume (0.1-1 cm^3) ➔ volume averaging (build-up, penumbra, IMRT gradients, output small fields)
- single point ➔ long measurement times
- bulky ➔ difficult in solid anthropomorphic phantoms

but, there are many useful alternatives.

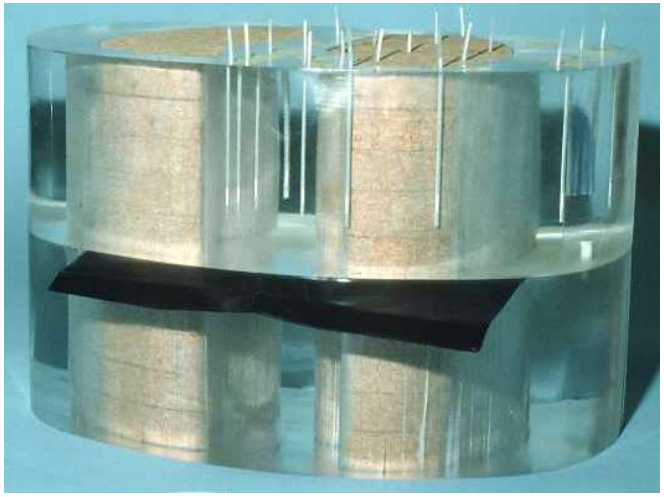
- radiochromic/radiographic film
- semiconductors (diodes)
- TLD (thermo-luminescent dosimetry)
- micro chambers
- synthetic diamond
- organic scintillators
- OSL (optically stimulated luminescence)
- extrapolation chambers (build-up region)
- gel dosimetry (3D - MRI or optical)
- alanine
- MOSFET
- 1D or 2D detector arrays (diodes, ionization chambers)
- EPID
- …..

Also alternatives have limitations:

- for no alternative: **reading = C·dose,** with fixed C in all situations (non-linearity, energy-dependence, dose-rate dependence, …)
- deviations from ideal not always known or easily predictable

Nevertheless:

- detectors are applied a lot and they are indispensable in RT
- often combination of detector types: check for consistency, gather complimentary data.



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non-Reference Dosimetry, outline:

- **radiochromic/radiographic film**
- **semiconductors (diodes)**
- **TLD (thermo-luminescent dosimetry)**
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- …..

small field dosimetry

γ-index for comparison of dose distributions

examples of non-reference dosimetry

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small field dosimetry

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examples of non-reference dosimetry

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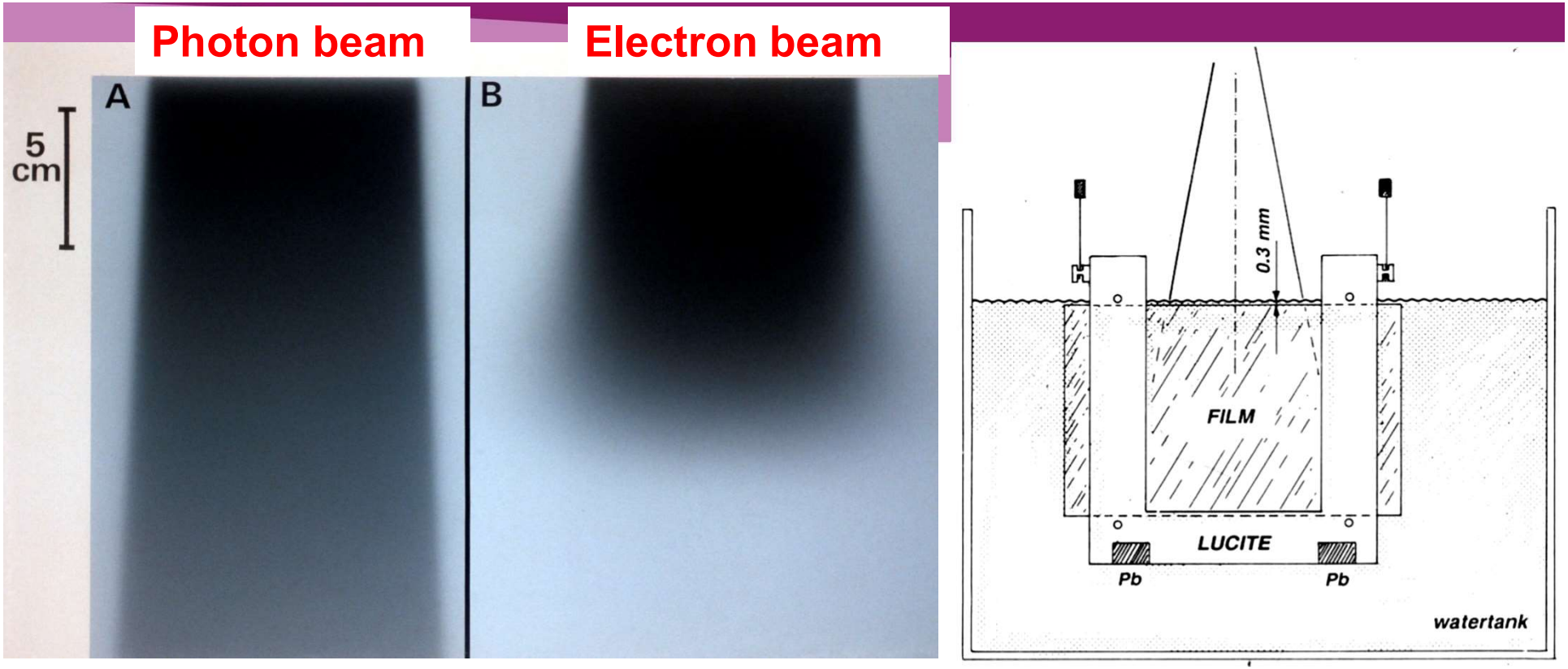

The more ‘black’, the higher the dose deposited ***in film***

Determine dose $D_w(i)$ ***in water***:

1. measure I(i) and $I_0(i)$ with densitometer
2. Transmission $T(i)=I(i)/I_0(i)$
3. calculate OD_{net}: $OD(i)={}^{10}\log T(i) - OD_{fog}$

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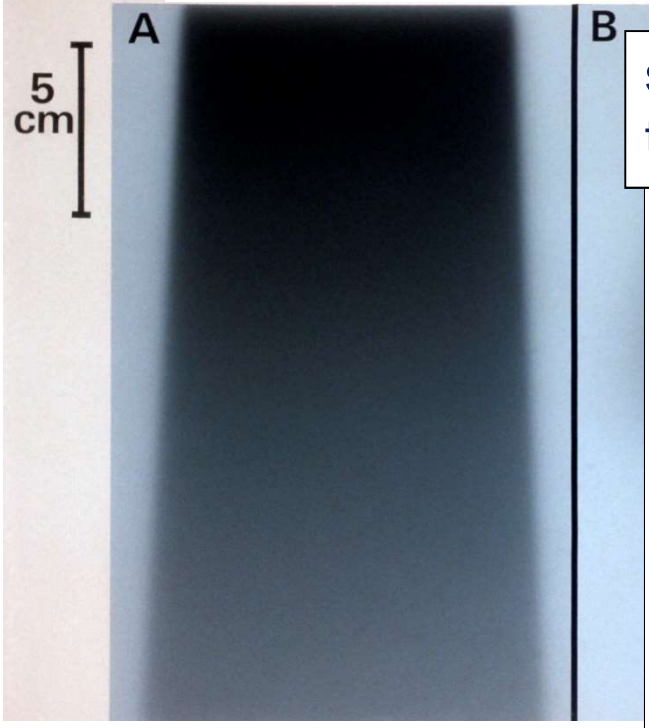
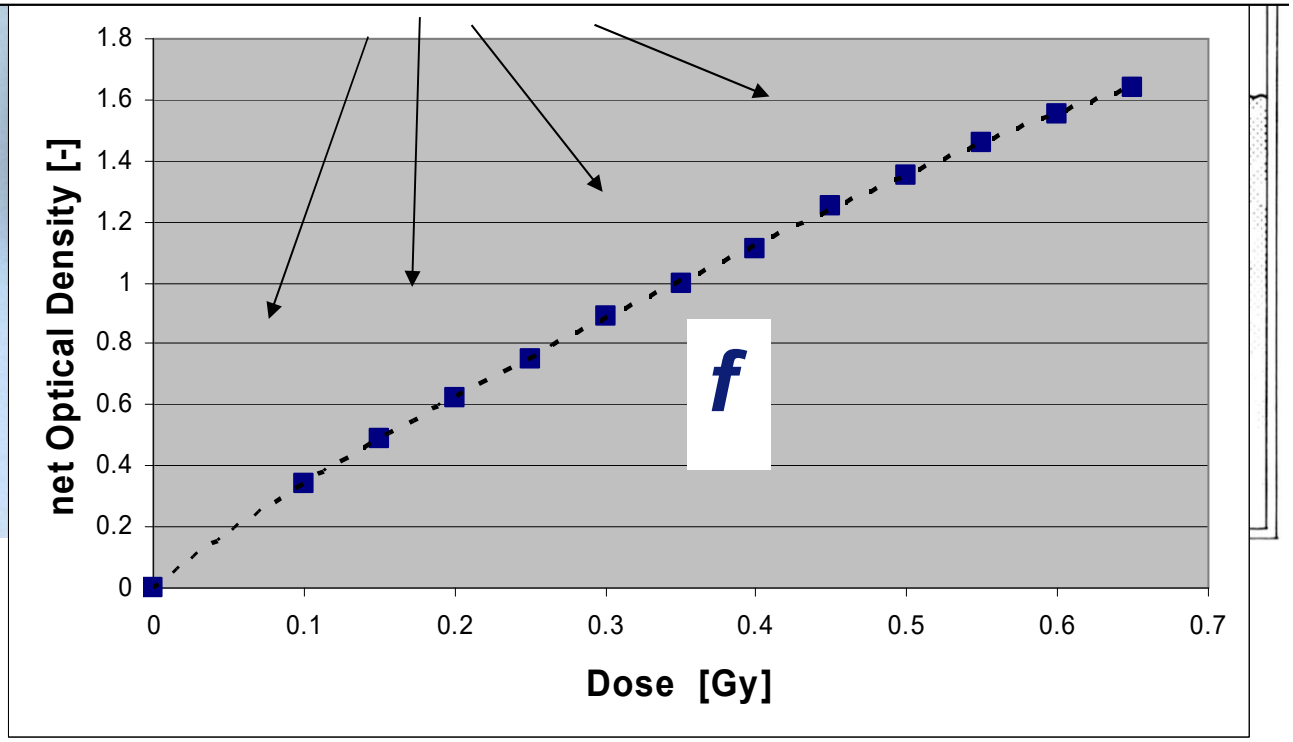
Photon beam **Electron beam**



small pieces of film irradiated with various doses in the same conditions



Determine dose $D_w(i)$ ***in water***:

4. $D_w(i) = f^{-1}(OD(i))$

f is determined experimentally

- f is 'sensitometric curve'

- corrects for film non-linearity

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Film types

RadioGraphic

- radiation + developer: **AgBr** crystals that received dose are converted into Ag-grains
- AgBr: large over-response for low energy photons (**photo-electric effect**)

  ➔ **huge over-response in large fields and at large depths**
- sensitive to light (sealing)

Examples: Kodak XV-2, EDR

RadioChromic

- radiation: **transparant monomers**

  ➔ opaque polymers
- "Dry" film, "self developing"
- **monomers close to water equivalent ➔ little energy dependence in megavolt beams**
- applicable in "daylight"
- applicable in water

Examples: **EBT-XD, EBT3, EBT2,** EBT, HS, MD55

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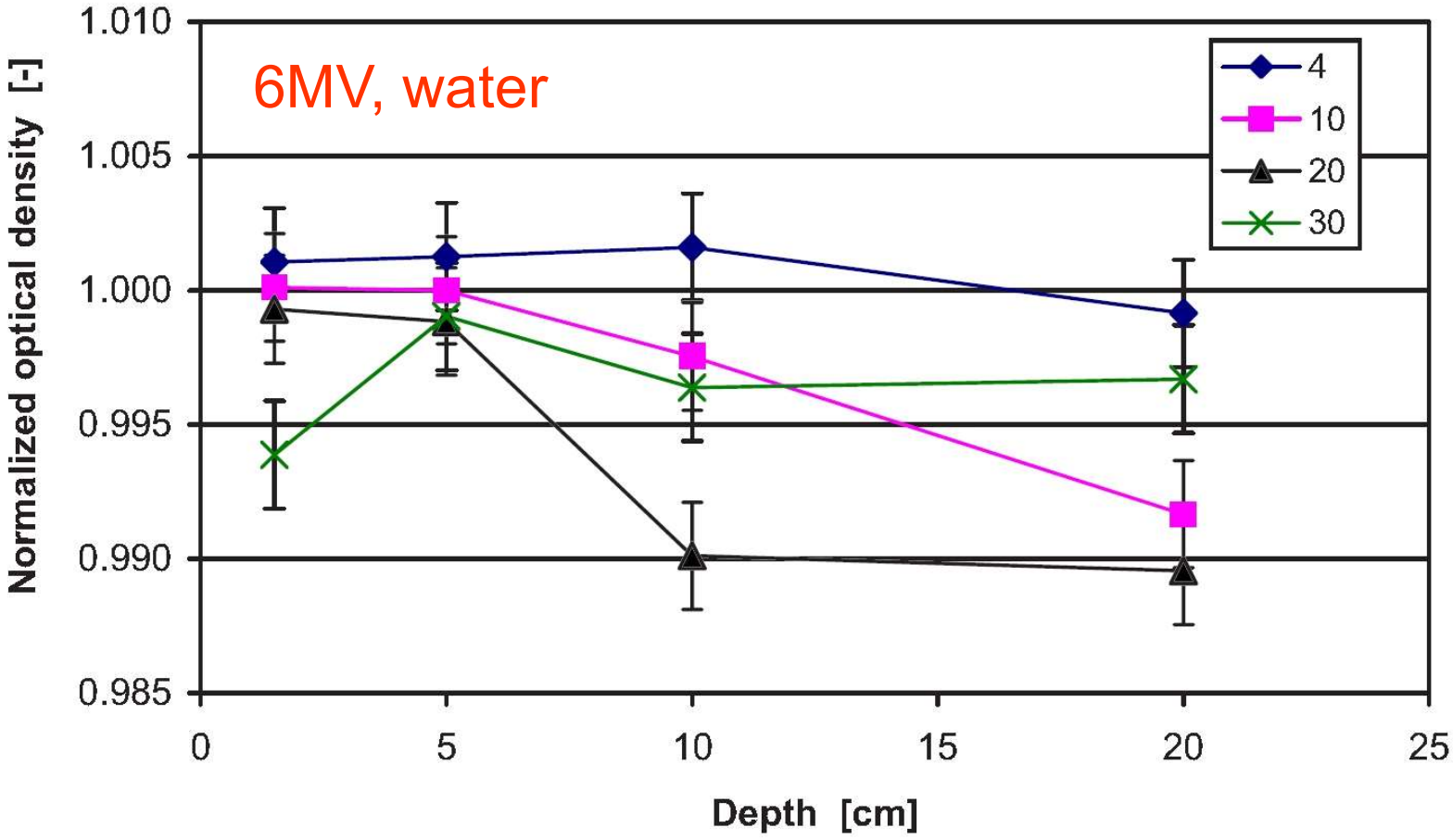
Low energy dependence of radiochromic film



Accurate dosimetry with GafChromic™ EBT film of a 6 MV photon beam in water: What level is achievable?, LJ van Battum, D Hoffmans, H Piersma, and S Heukelom, Med. Phys. 2008; 35(2): 704-716

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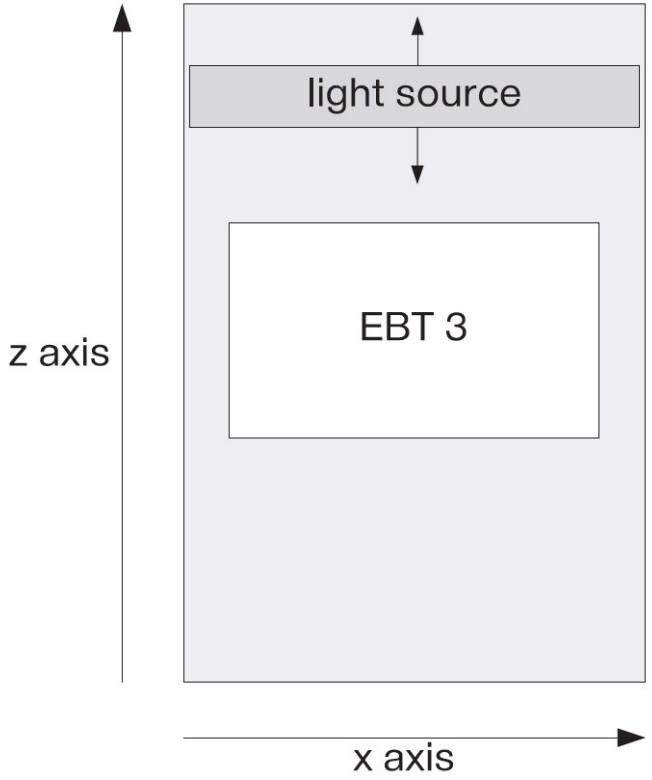
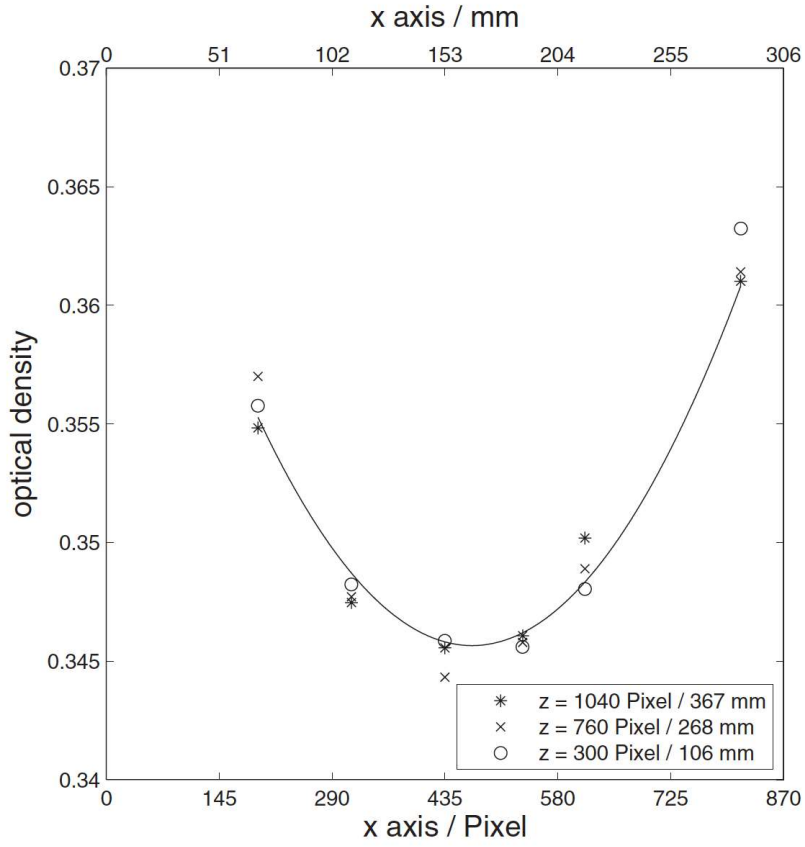
However,

- also radiochromic film has pitfalls and challenges (inhomogeneity of sensitive layer, parabola effect flatbed scanner, ….)





- can be tackled with appropriate approaches, making it extremely useful for dosimetry, e.g small field dosimetry

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Comparison of Gafchromic EBT2 and EBT3 films for clinical photon and proton beams S. Reinhardt, M. Hillbrand, J. J. Wilkens, and W. Assmann Med. Phys. 2012, 39: 5257

Dosimetric characterization and use of GAFCHROMIC EBT3 film for IMRT dose verification Valeria Casanova Borca, Massimo Pasquino,a Giuliana Russo, Pierangelo Grosso, Domenico Cante, Piera Sciacero, Giuseppe Girelli, Maria Rosa La Porta, Santi Tofani JACMP 2013, 14(2): 158

Evaluation of Gafchromic EBT3 films characteristics in therapy photon, electron and proton beams J. Sorriaux, A. Kacperek, S. Rossomme, J.A. Lee, D. Bertrand, S. Vynckier, E. Sterpin Physica Medica 2013, 29: 599-606

- can be tackled with appropriate approaches, making it extremely useful for dosimetry, e.g small field dosimetry

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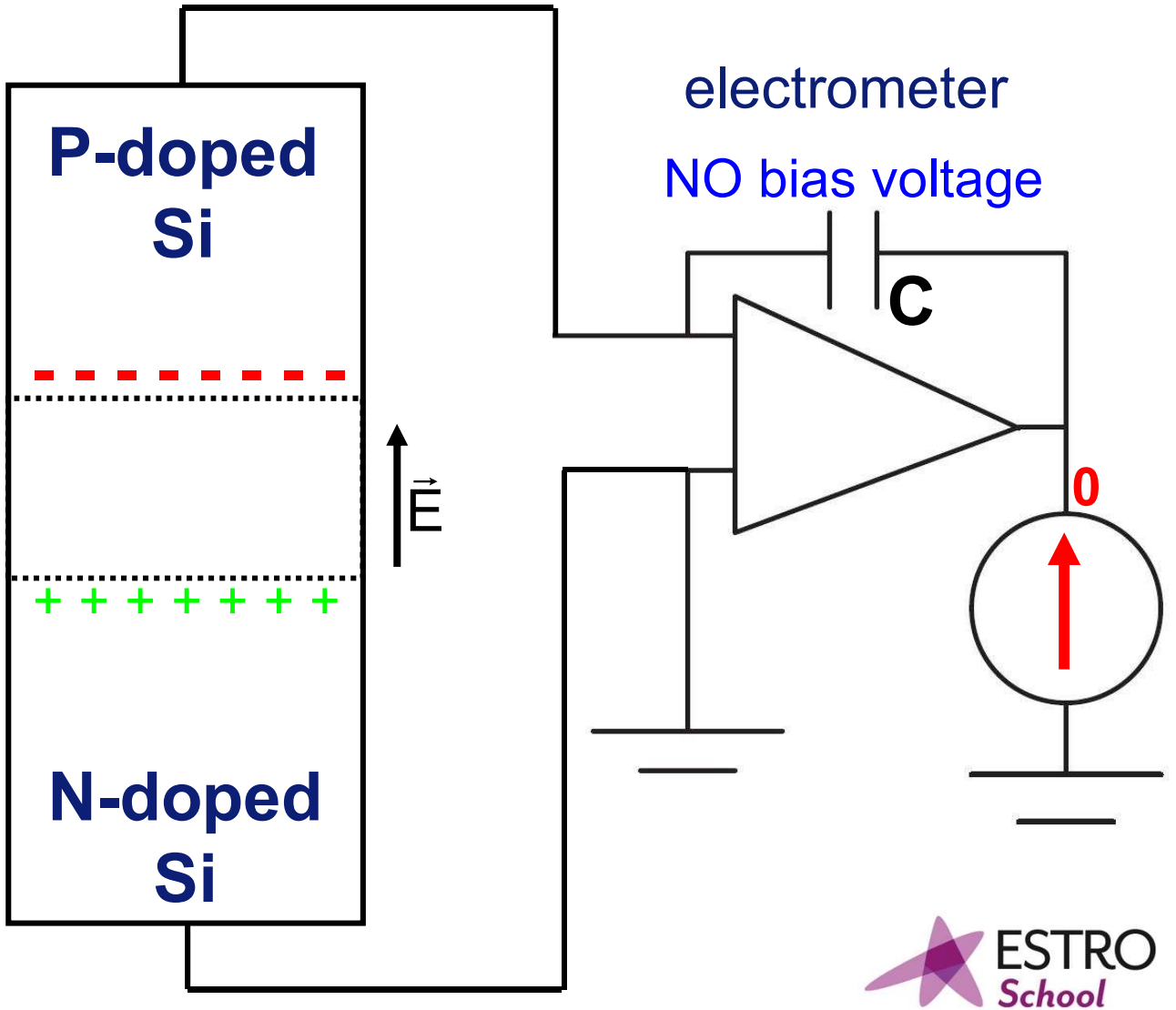
Semiconductor/diode dosimetry

NO radiation – steady state

PN-junction:
- depletion layer, i.e. no charge carriers
- electric field



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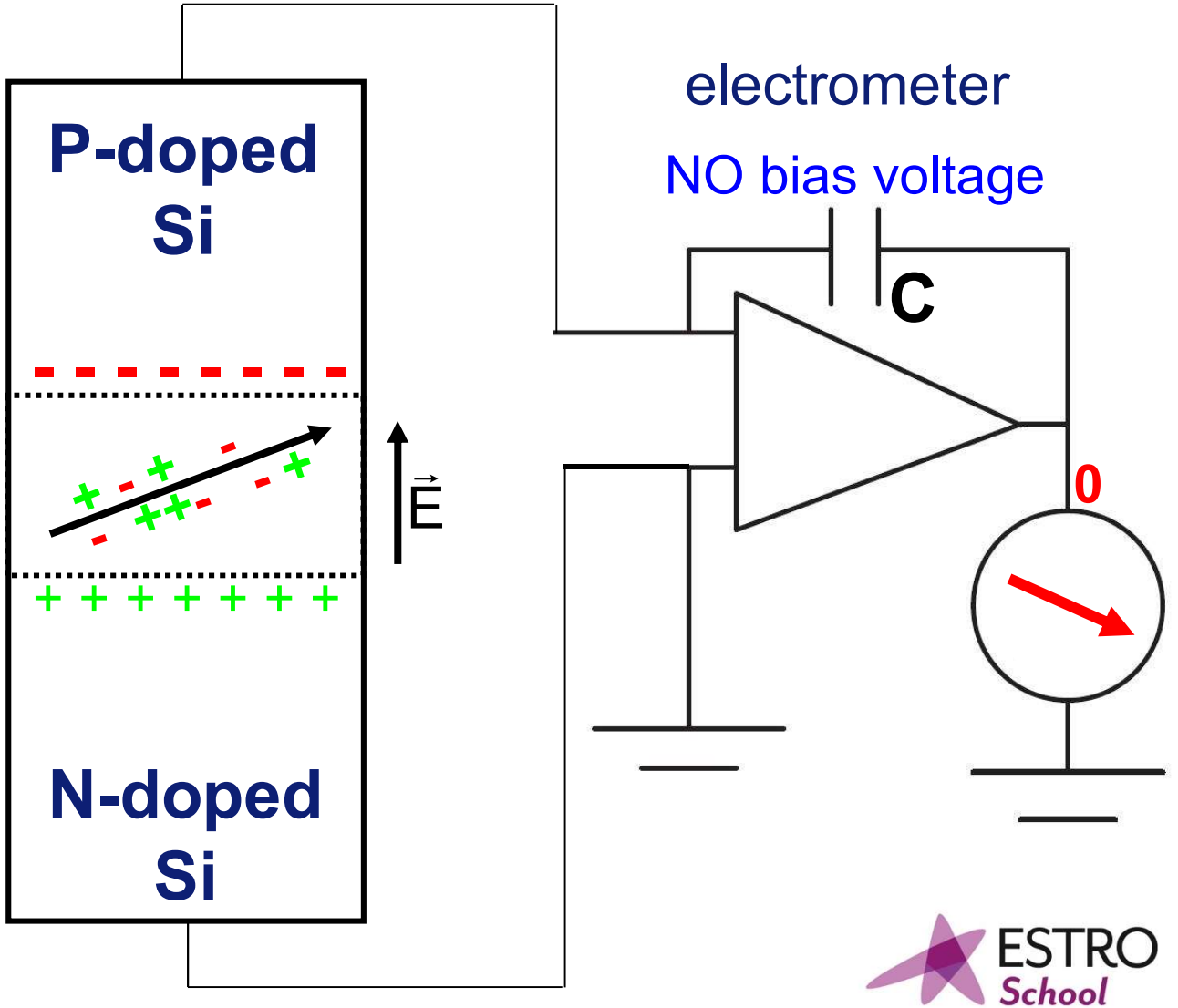
Semiconductor/diode dosimetry

Beam ON

PN-junction:
- depletion layer, i.e. no charge carriers
- electric field



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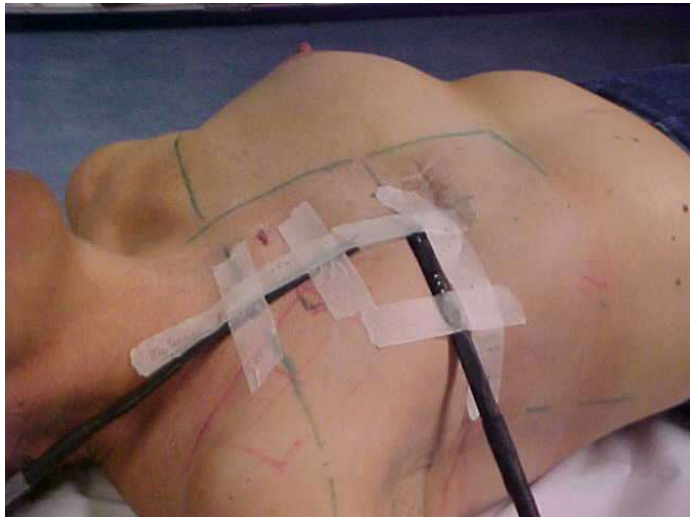
pro's and con's of semiconductor/diode dosimetry

pro's

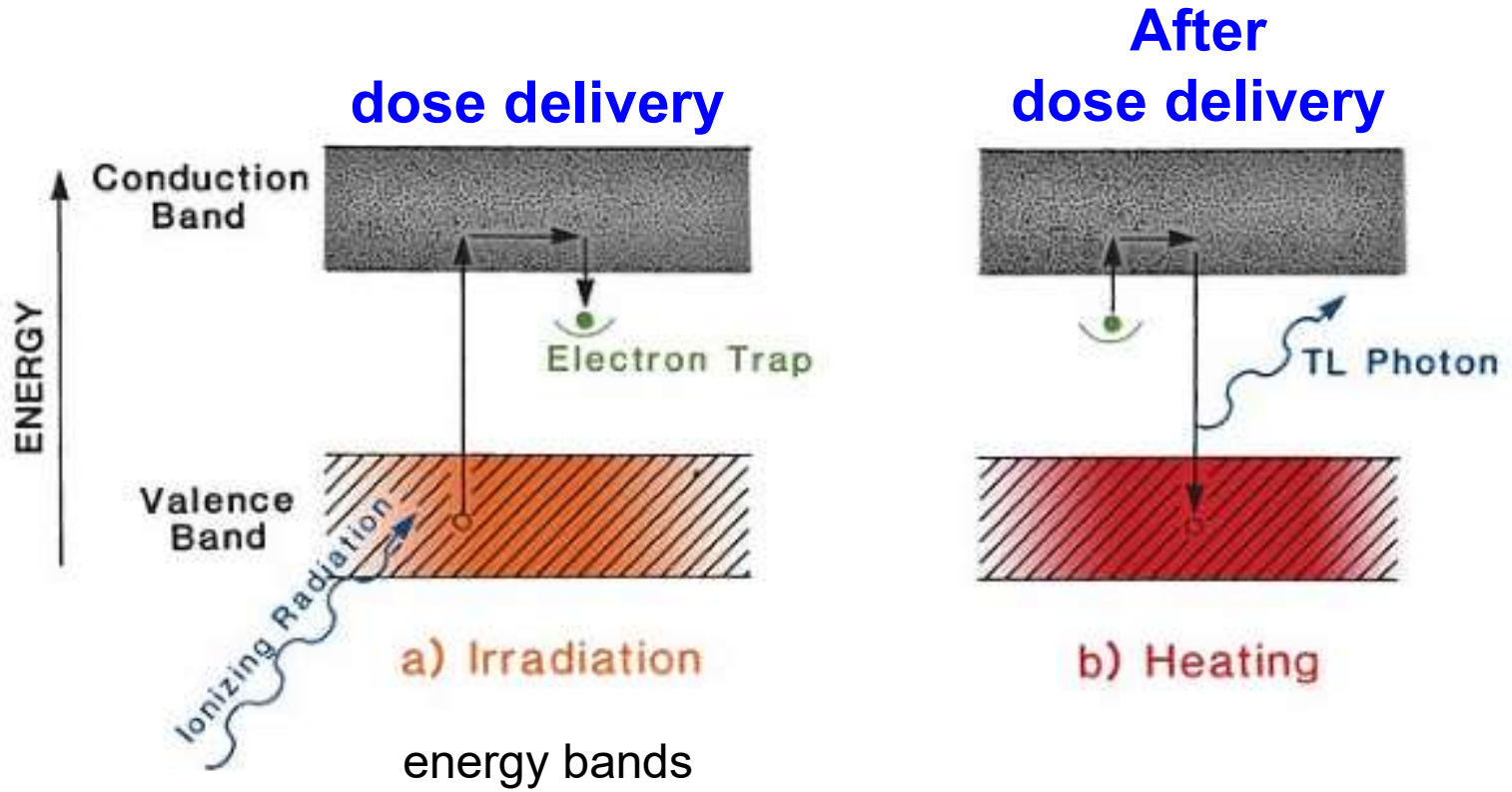
- small dimensions (~ mm)
  - little volume averaging
  - suited for OF stereotactic fields
- reading immediately avaliable
- linear dose response
- PDDs in electron beams: R∝dose (in contrast to ionization chambers)
- suited for dose-rate measurement

con's

- energy dependence, Si ➔ over-response for low photon energies
- temperature dependence (in-vivo)
- dose-rate dependent response (SSD)
- beam directional dependence
- single point
- radiation damage ➔ gradual decrease in response



ThermoLuminescence Dosimetry (TLD)
mainly LiF as phospor



energy bands
of phosphor

Khan 2010

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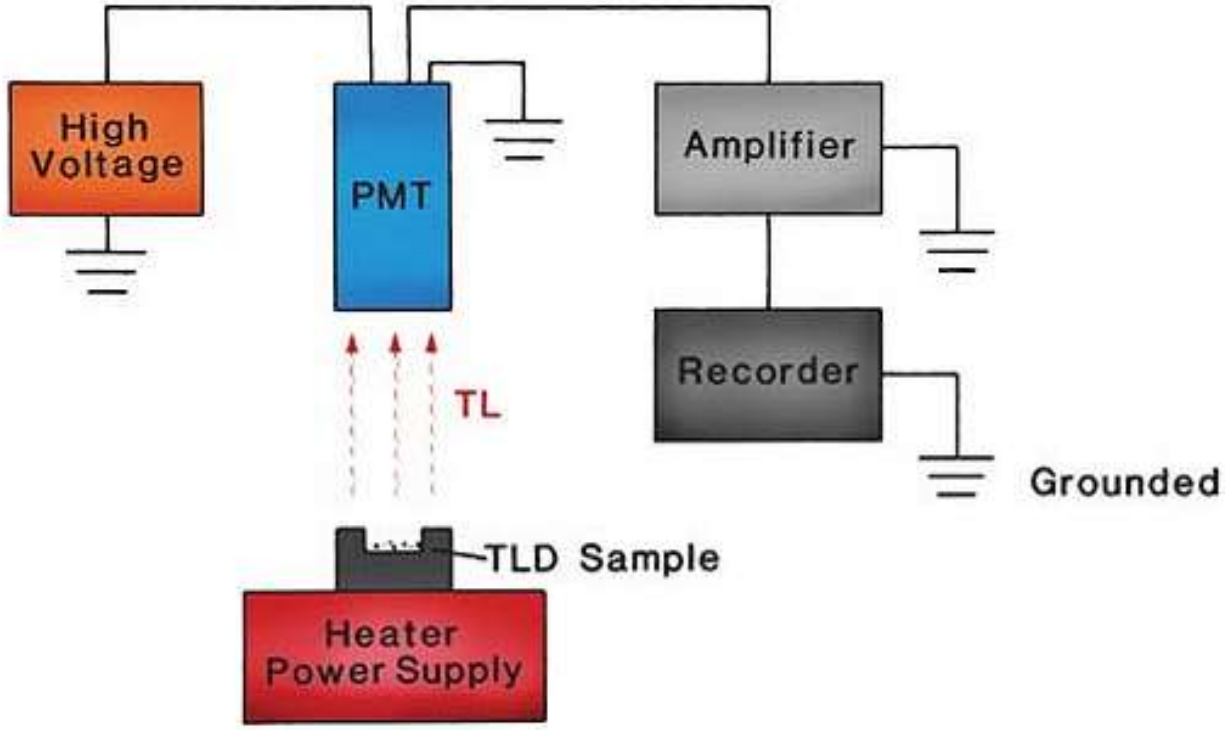
ThermoLuminescence Dosimetry (TLD)
mainly LiF as phospor



Schematic diagram showing apparatus for measuring thermoluminescence (TL). PMT, photomultiplier tube; TLD, thermoluminescent dosimeter.

Khan 2010

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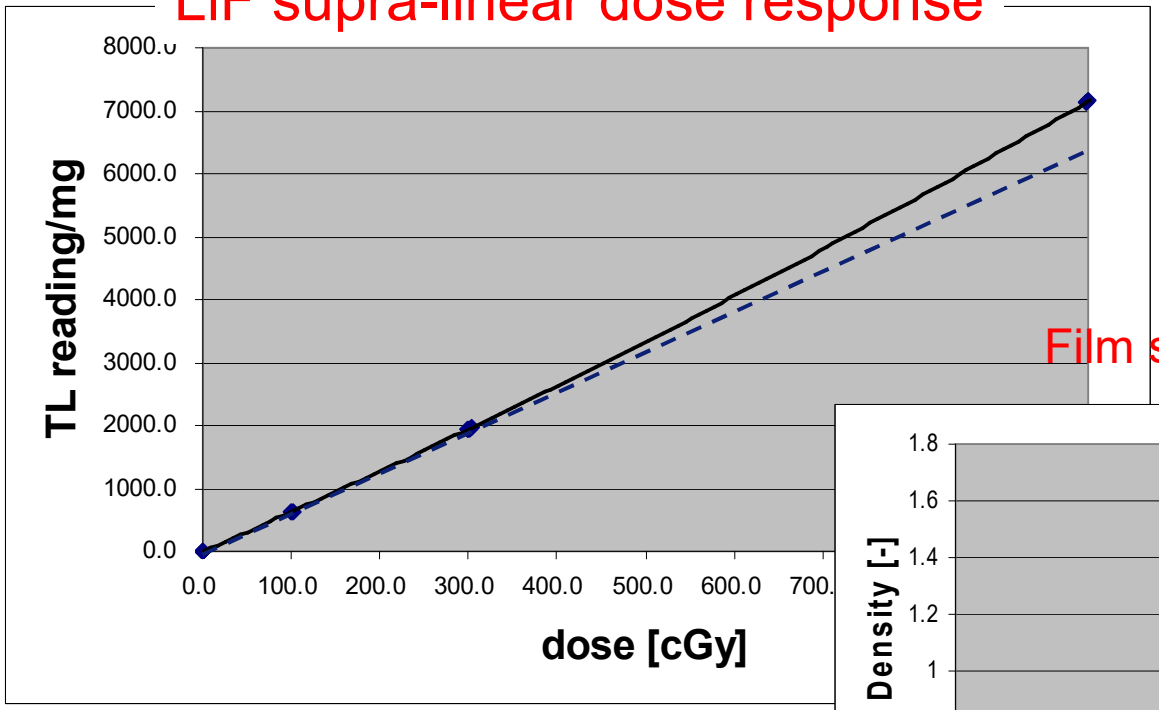
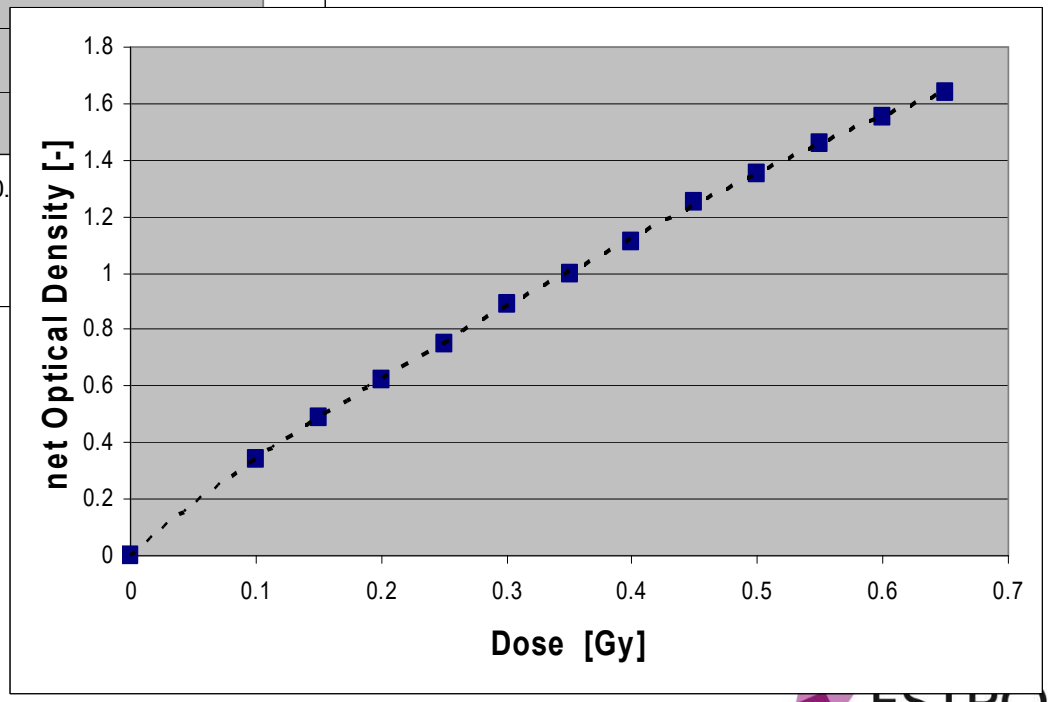
ThermoLuminescence Dosimetry (TLD)
mainly LiF as phospor

LiF supra-linear dose response



Film sensitometric curve



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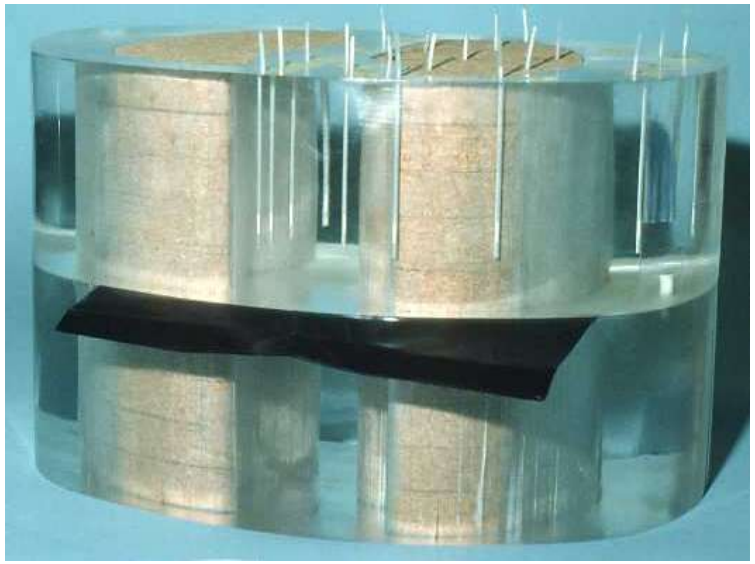
pro's and con's of ThermoLuminescence Dosimetry (TLD)
with LiF as phospor

pro's
- small dimensions
  - little volume averaging
  - suited for anthropomorphic phantoms
- powder/thin films: measurements in build-up or transition regions
- LiF: small energy dependence in MV range
- large dose range: < mGy → > kGy
- dose-rate independent
- re-usable (in contrast to film)



con's
- high accuracy (1-2%) requires careful procedure and skilled operator
- single point
- batch of chips: distribution of sensitivities
- fading
- reading not directly available
- labor/reading
- no record (in contrast to film)

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non-Reference Dosimetry, outline:

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- EPID
- …..

small field dosimetry

γ-index for comparison of dose distributions

examples of non-reference dosimetry

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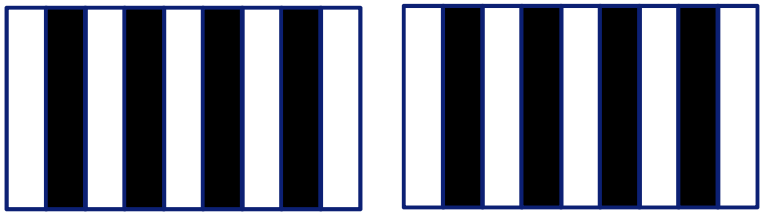
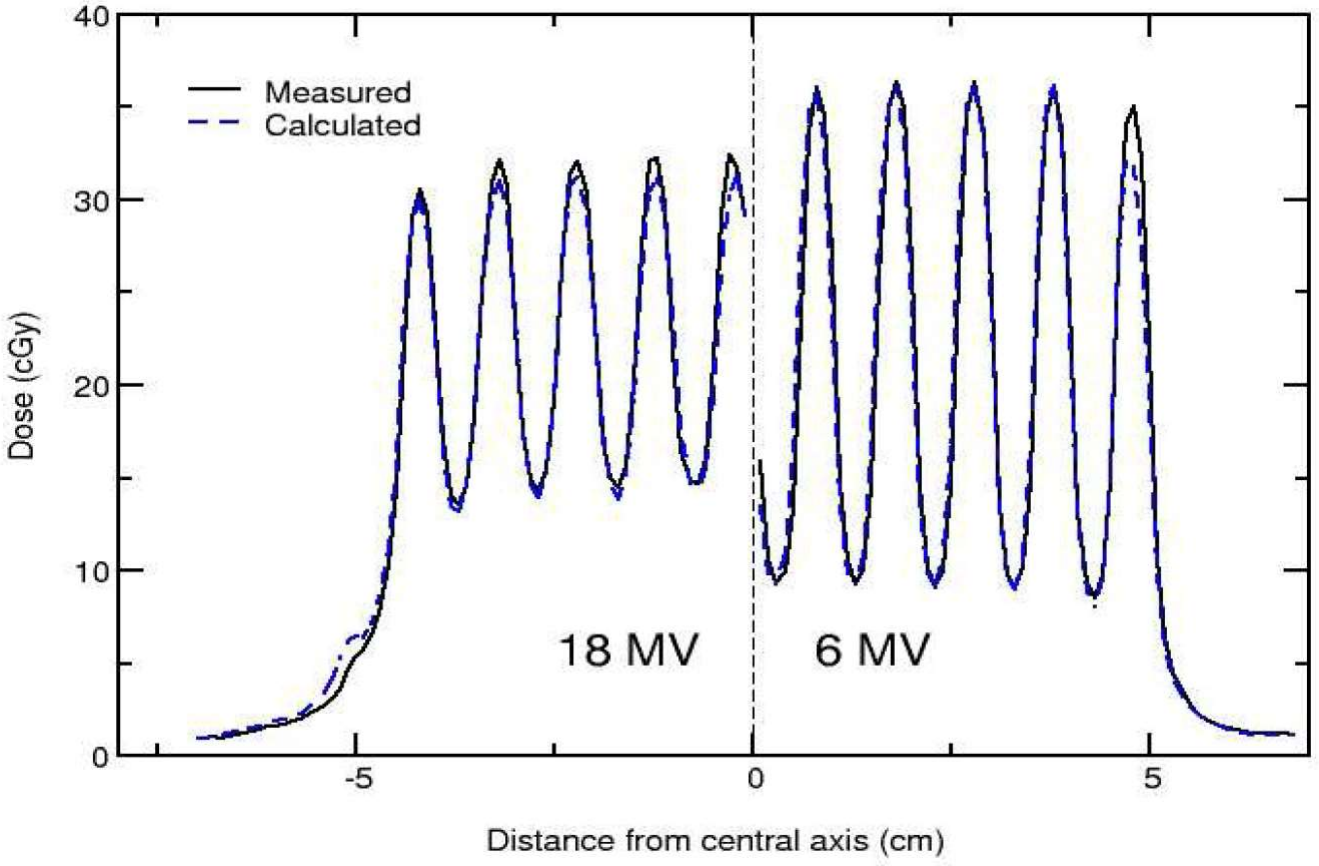
Why increased attention for small field dosimetry?

- Increased use in RT
- Stereotactic Radiotherapy (SRT)
- Stereotactic Body Radiotherapy (SBRT)
- Intensity Modulated Radiation Therapy (IMRT)
- Involves regular linacs with high resolution MLCs, TomoTherapy, CyberKnife, GammaKnife

Example showing complexity

0.5 cm leaves





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Why complexity of small field dosimetry

$$D_w = C(w, Q, \dots) \cdot R$$

$$\frac{\partial C}{\partial w}, \frac{\partial C}{\partial Q}, \dots \textit{ very large for small } w$$

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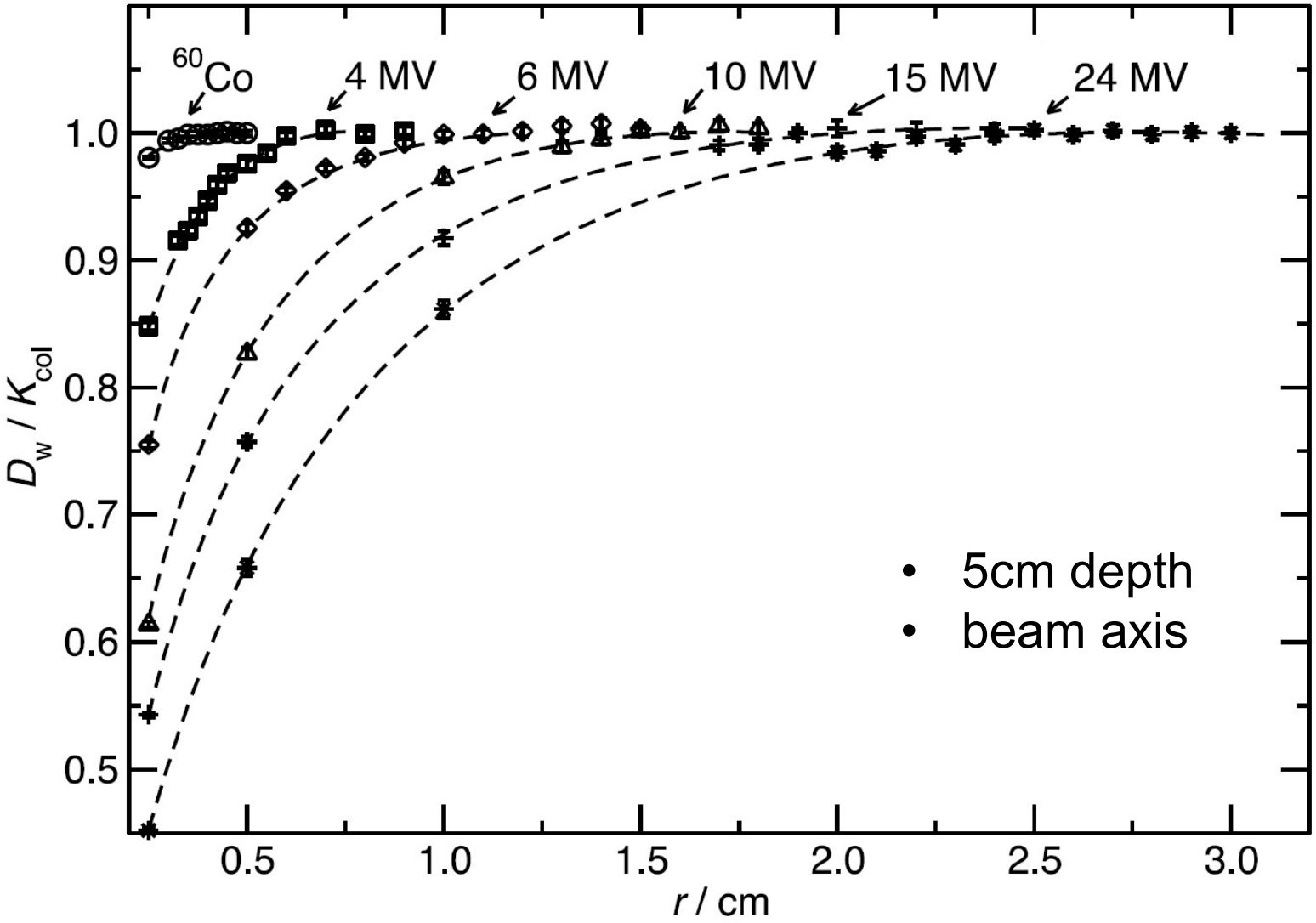
Definition of small field

- loss of lateral charged particle equilibrium on beam axis
- partial occlusion of primary photon source by collimating devices on beam axis
- size of detector is similar or large compared to the beam dimensions

All three conditions result in overlap between the field penumbrae and the detector volume.

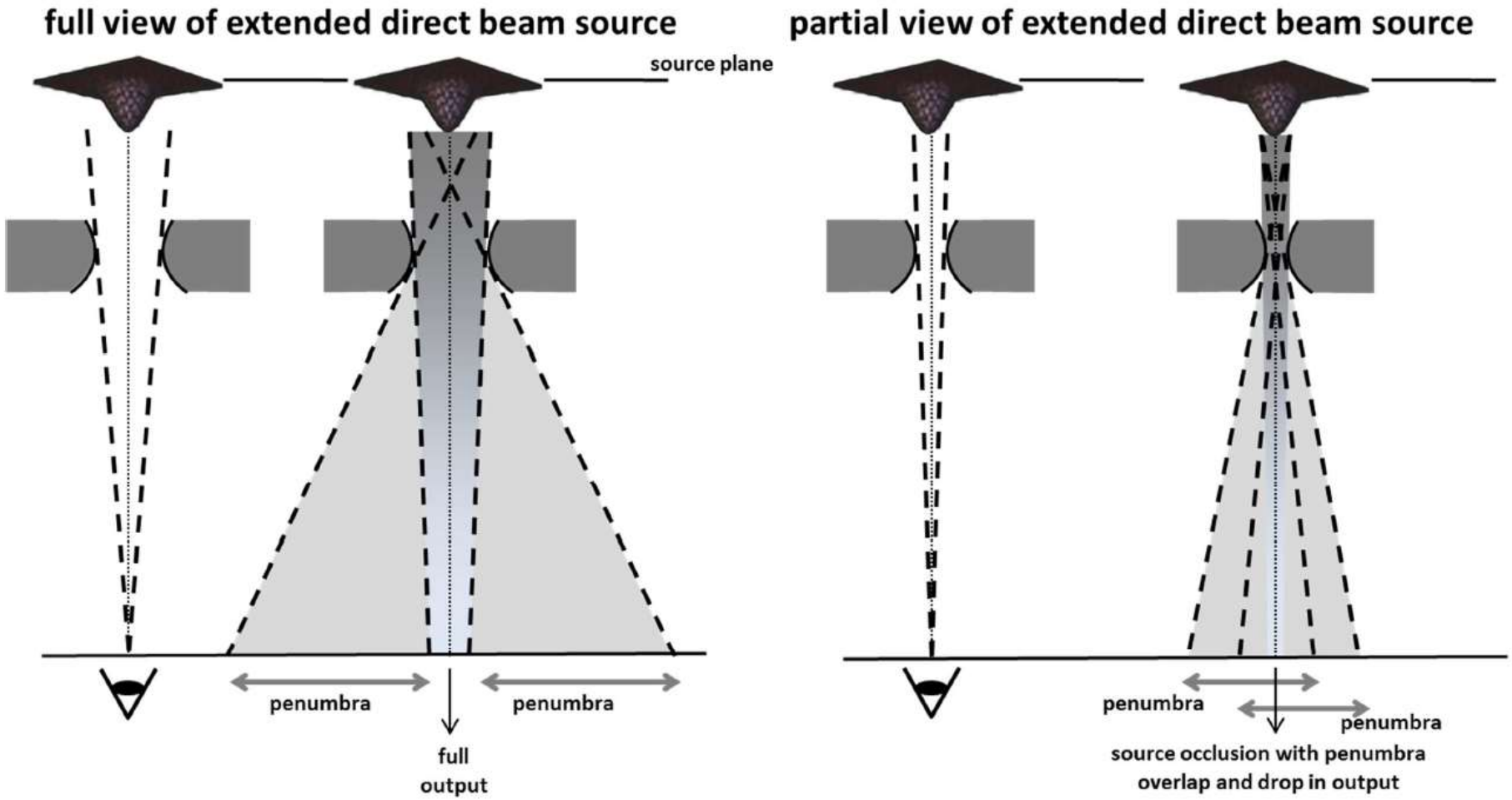
loss of lateral charged particle equilibrium

Dose-to-water / water-collision Kerma



Li X.A. et al. Med Phys 22:1167-1170 (1995)

partial occlusion of primary photon source



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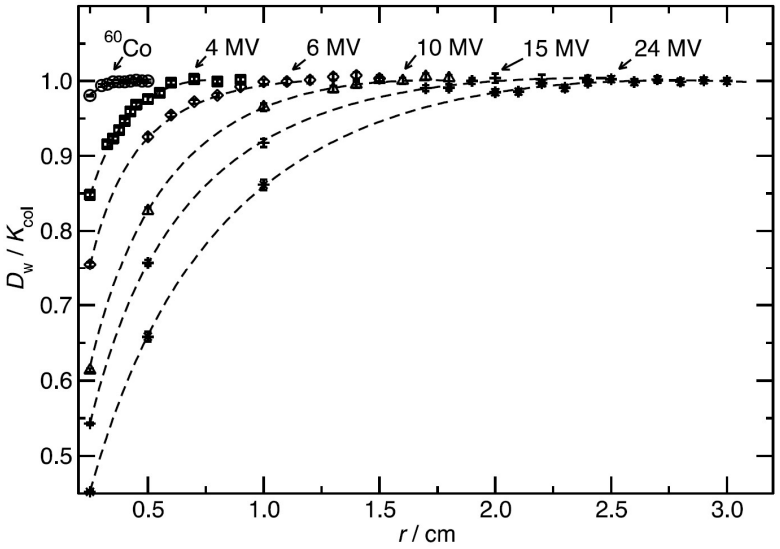

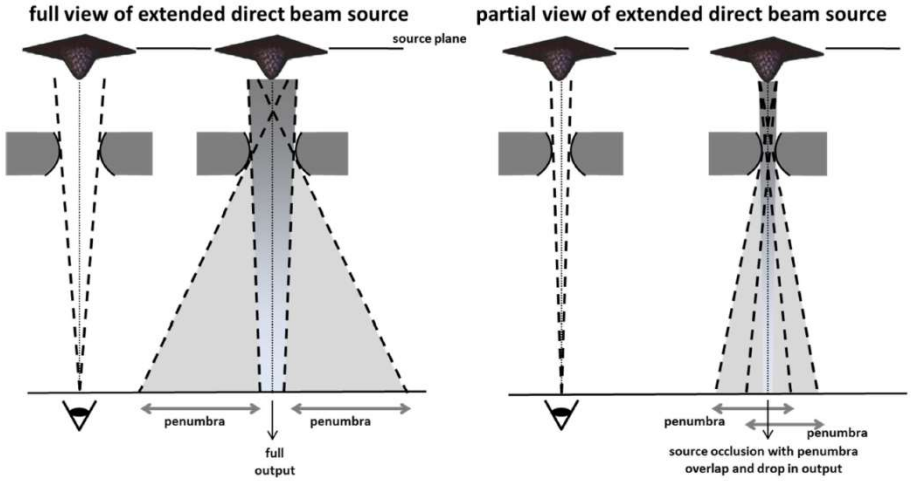

- loss of LCPE and photon source occlusion:
  - impact on beam spectrum
  - responsible for sharp drop in beam output with decreasing field size.
- drop more pronounced when photon beam energy increases or the density of medium decreases

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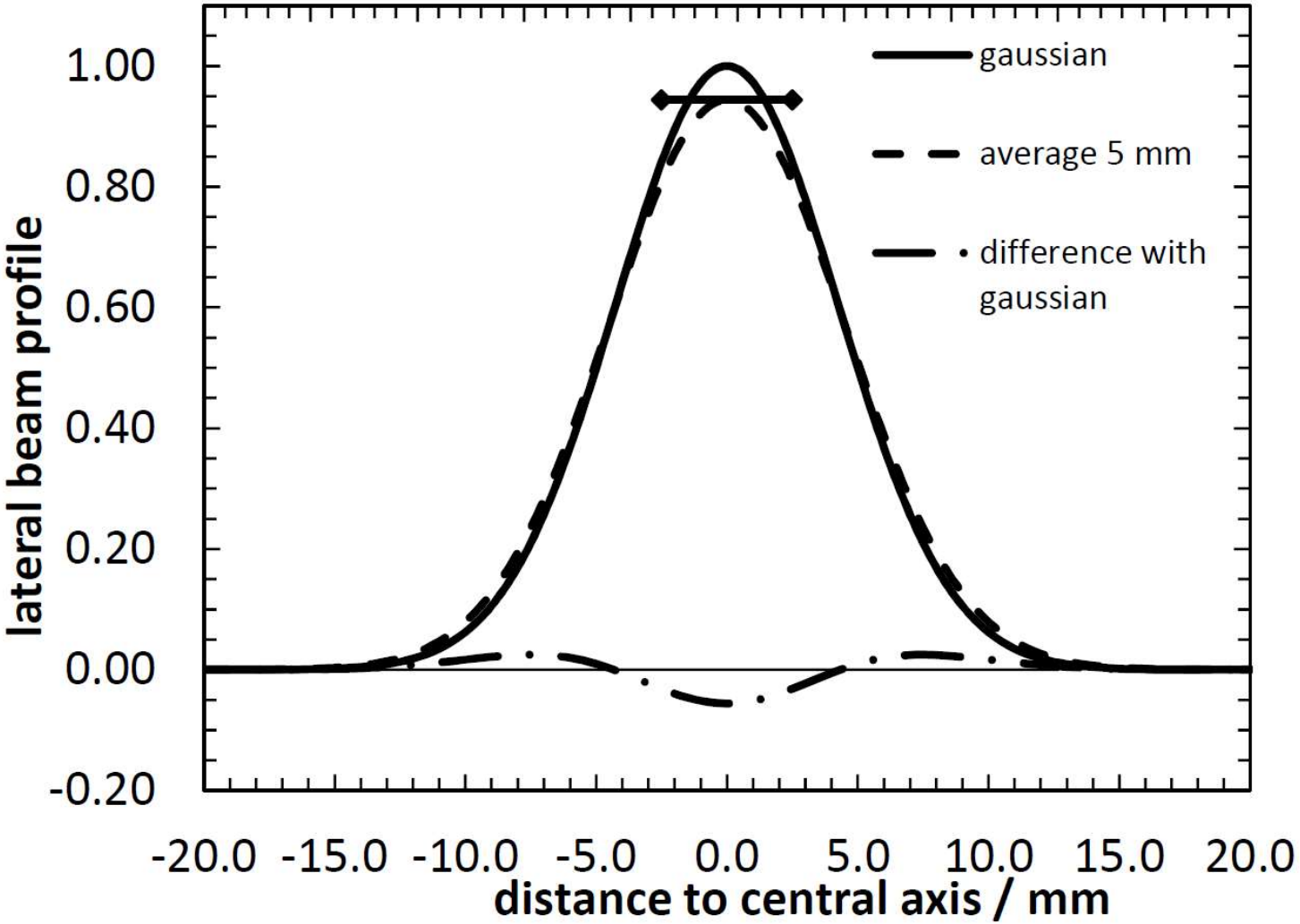
detector size similar or large compared to the beam

Volume averaging effect



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How deal with small fields?

- IPEM 103 - Small Field MV Photon Dosimetry
- Dosimetry of Small Static Fields Used in External Beam Radiotherapy -
  an IAEA – AAPM International Code of Practice for Reference and Relative Dose Determination

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non-Reference Dosimetry, outline:

- **radiochromic/radiographic film**
- **semiconductors (diodes)**
- **TLD (thermo-luminescent dosimetry)**
- micro chambers
- synthetic diamond
- organic scintillators
- OSL (optically stimulated luminescence)
- extrapolation chambers (build-up region)
- gel dosimetry (3D - MRI or optical)
- alanine
- MOSFET
- 1D or 2D detector arrays (diodes, ionization chambers)
- EPID
- …..

small field dosimetry

γ-index for comparison of dose distributions

examples of non-reference dosimetry

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A technique for the quantitative evaluation of dose distributions

Daniel A. Low,[a] William B. Harms, Sasa Mutic, and James A. Purdy
Mallinckrodt Institute of Radiology, Division of Radiation Oncology, 510 South Kingshighway Blvd., St. Louis, Missouri 63110

Med Phys. 1998; 25(5): 656-61

γ-index method: comparison of 2D/3D dose distributions
e.g. measurement vs. calculation

basic idea: in area with high dose gradients,
larger dose differences are acceptable

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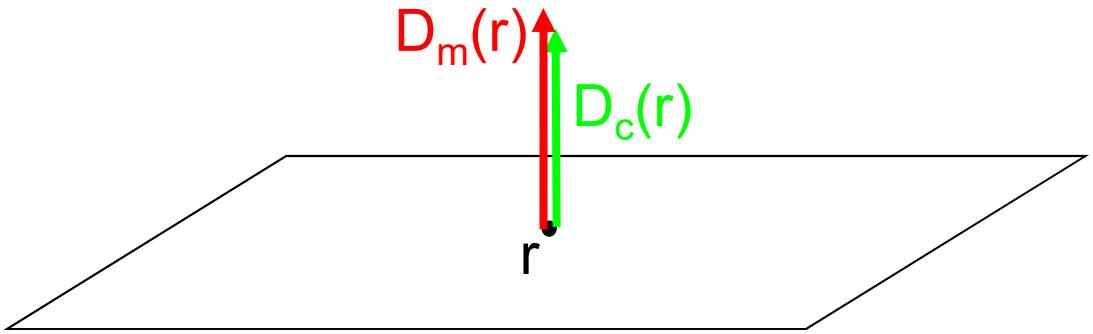
The γ-index method for comparison of measured and calculated dose distributions

Explanation of method for 2D dose distributions,
e.g. comparison measured film dose vs. TPS dose



each point r in plane has a measured and a calculated dose

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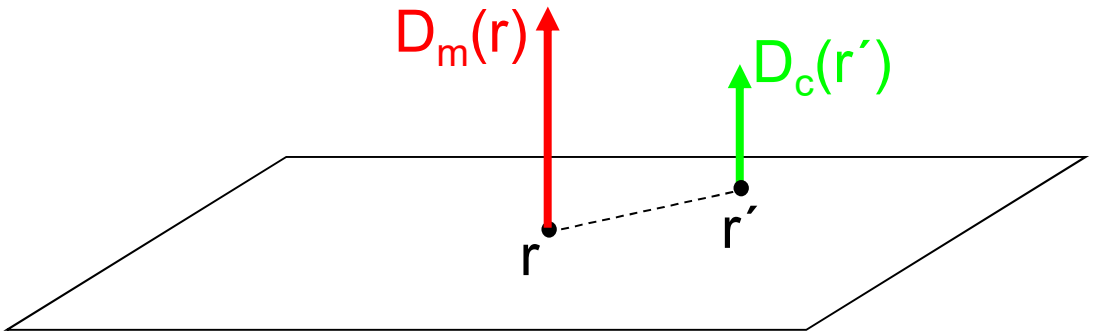
The γ-index method for comparison of measured and calculated dose distributions



Determine γ(r), the γ-index of r:

1. Determine for all r′: $\Gamma(r') = \sqrt{\left(\frac{|r-r'|}{\Delta d}\right)^2 + \left(\frac{(D_m(r) - D_c(r')}{\Delta D}\right)^2}$

2. $\gamma(r) = \min(\Gamma(r'))$

Δd = 3mm ΔD = 3%

- γ-test: pixel r passes if γ(r)≤1
- for Γ(r′) to be ≤1: |r-r′|≤ 3 mm AND $D_m(r)$-$D_c(r')$ ≤3%

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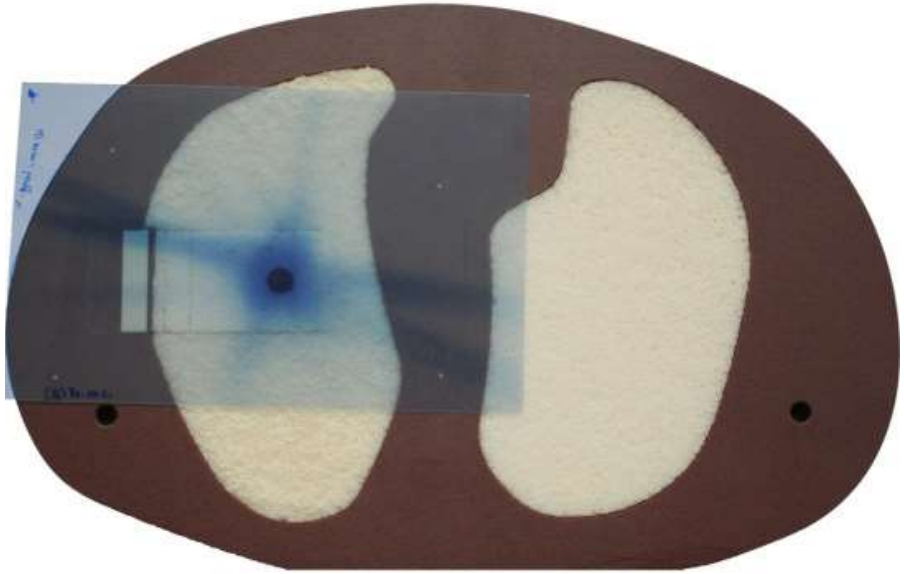
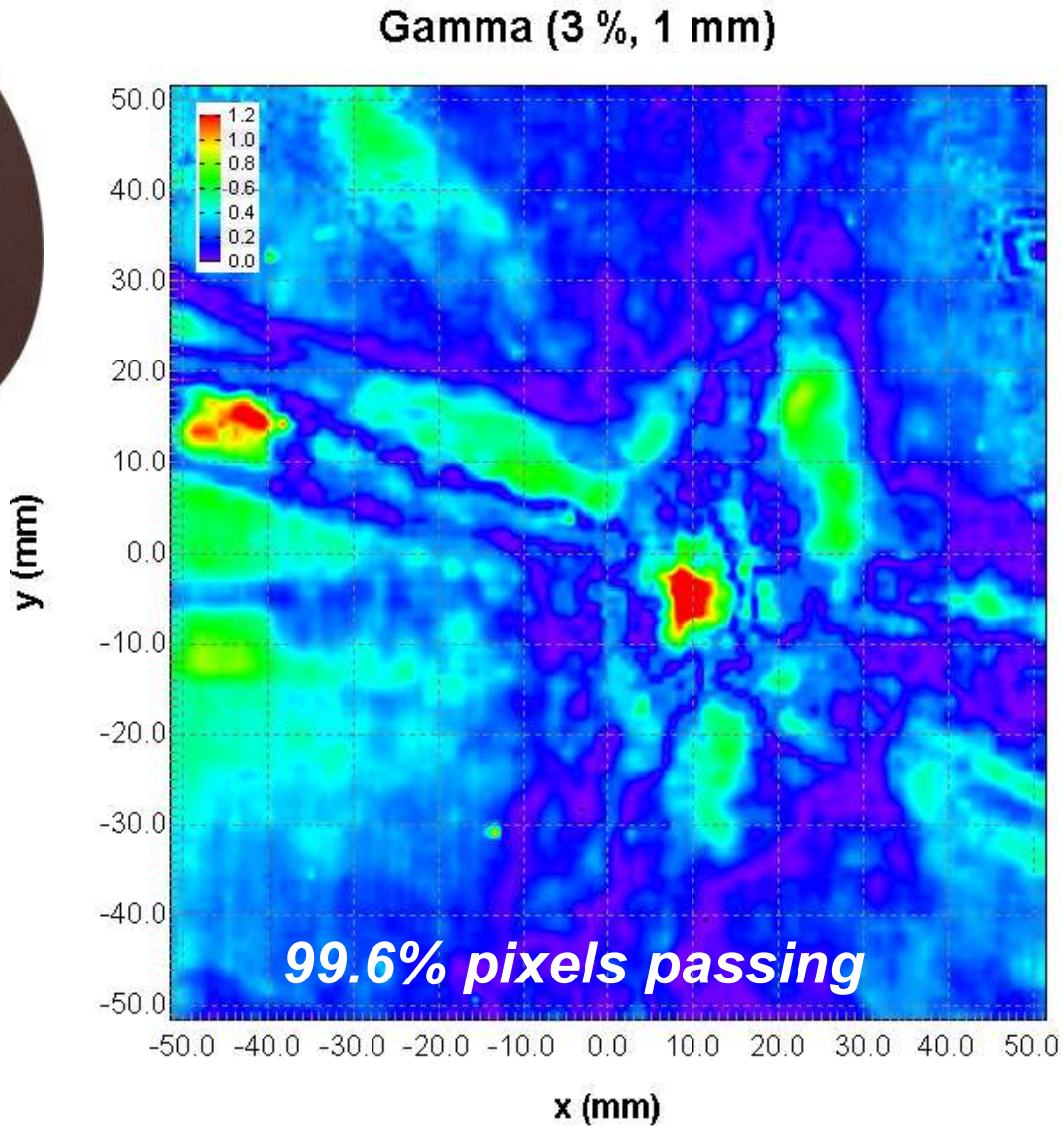
Example of γ-comparison: film vs. Monte Carlo dose calculation

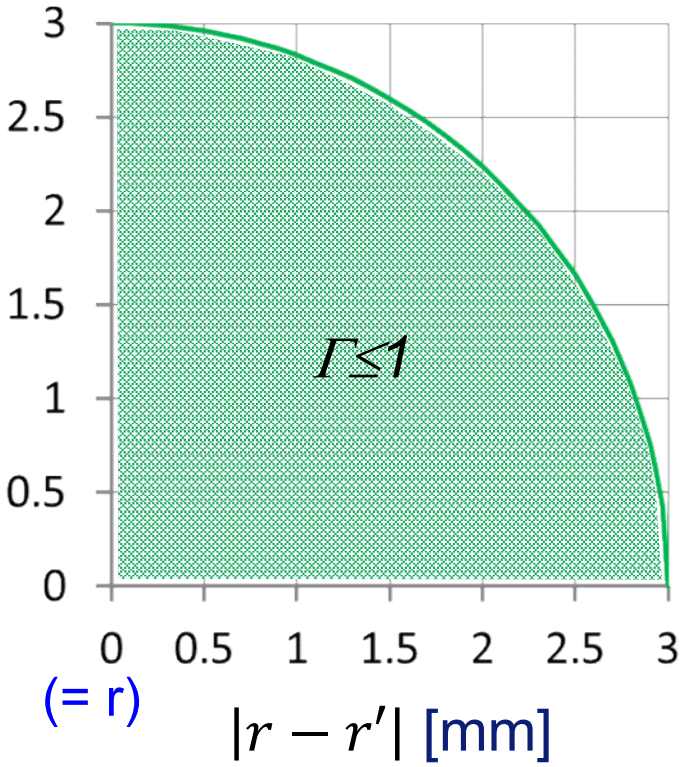


γ-distribution: film vs Monte Carlo



The γ-index method for comparison of measured and calculated dose distributions

$(D_m(r) - D_c(r')$ [%]



$$\Gamma(r') = \sqrt{\left(\frac{|r - r'|}{\Delta d}\right)^2 + \left(\frac{(D_m(r) - D_c(r')}{\Delta D}\right)^2}$$

$\Gamma(r') \leq 1$

Δd: 3mm

ΔD: 3%

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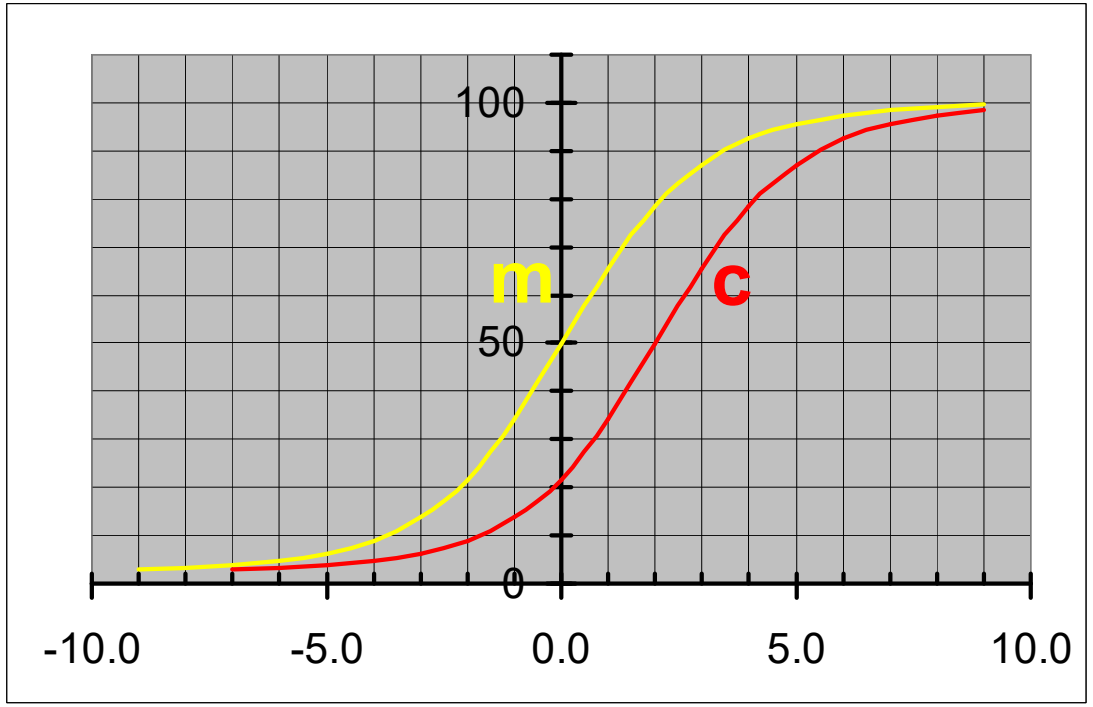
γ-comparison in penumbra region



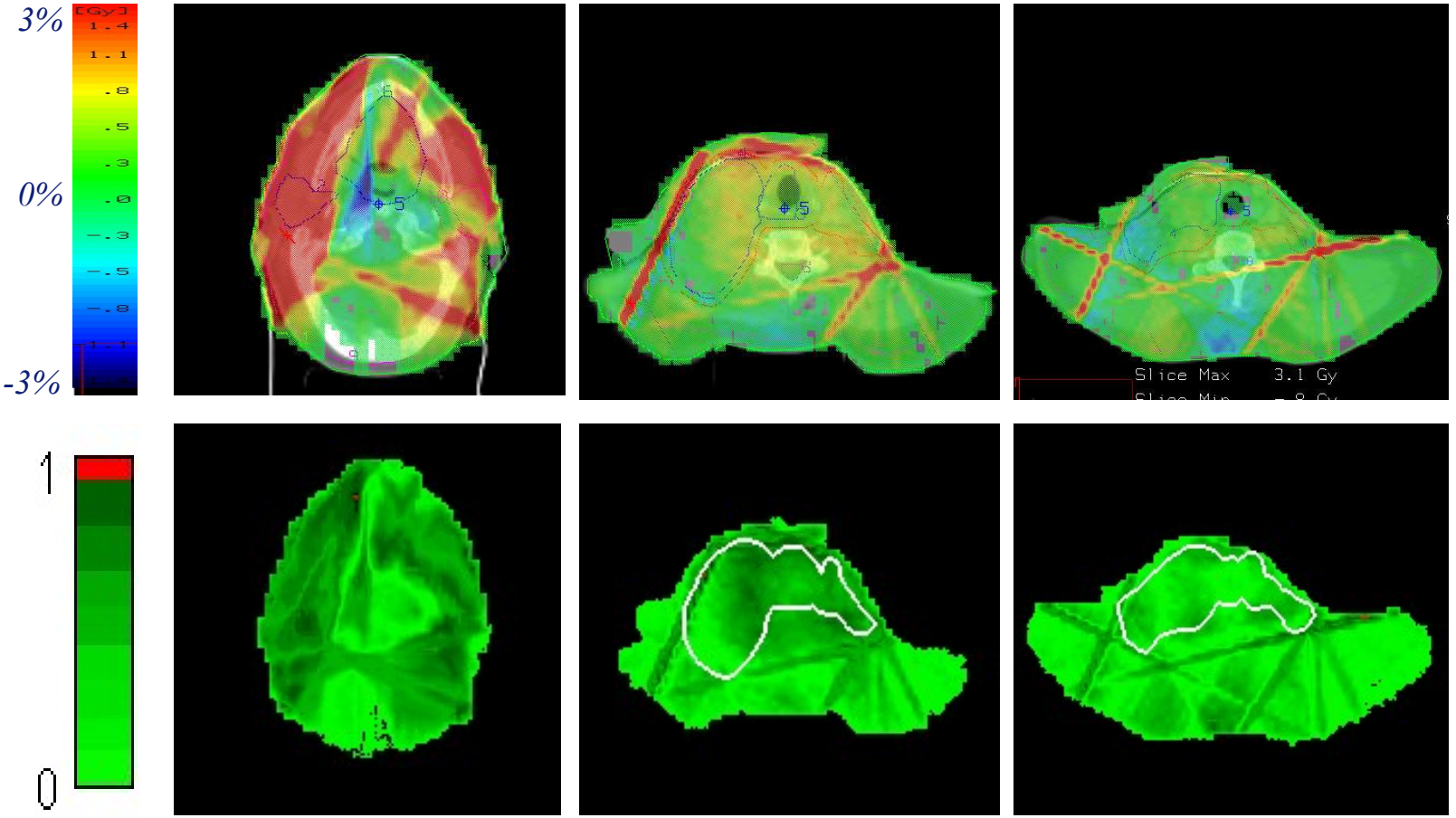
Local dose difference at x = 0: 28%

$$\Gamma(x'=2)=\sqrt{\left(\frac{2}{\Delta d=3\,mm}\right)^2+\left(\frac{0}{\Delta D=3\%}\right)^2}=0.67$$ ➔ x = 0 passed γ-test

Only small shift between D_m and D_c results in perfect agreement in dose

H&N cancer patient: TPS vs. EPID back-projected dose

Dose difference



3D γ analysis 3%/ 2 mm

Van Zijtveld, Dirkx, Heijmen, et al., 2007

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small field dosimetry

γ-index for comparison of dose distributions

examples of non-reference dosimetry

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PHYSICS CONTRIBUTION

CHEST WALL IRRADIATION WITH MLC-SHAPED PHOTON AND ELECTRON FIELDS

MARION ESSERS, PH.D.,* MARCEL EGGEN,† DIRK BINNEKAMP,* CARIEN L. CREUTZBERG, M.D., PH.D.,† AND BEN J. M. HEIJMEN, PH.D.*

*Division of Clinical Physics, and †Department of Radiation Oncology, University Hospital Rotterdam-Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

film dosimetry aspects

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Chestwall irradiation - technique

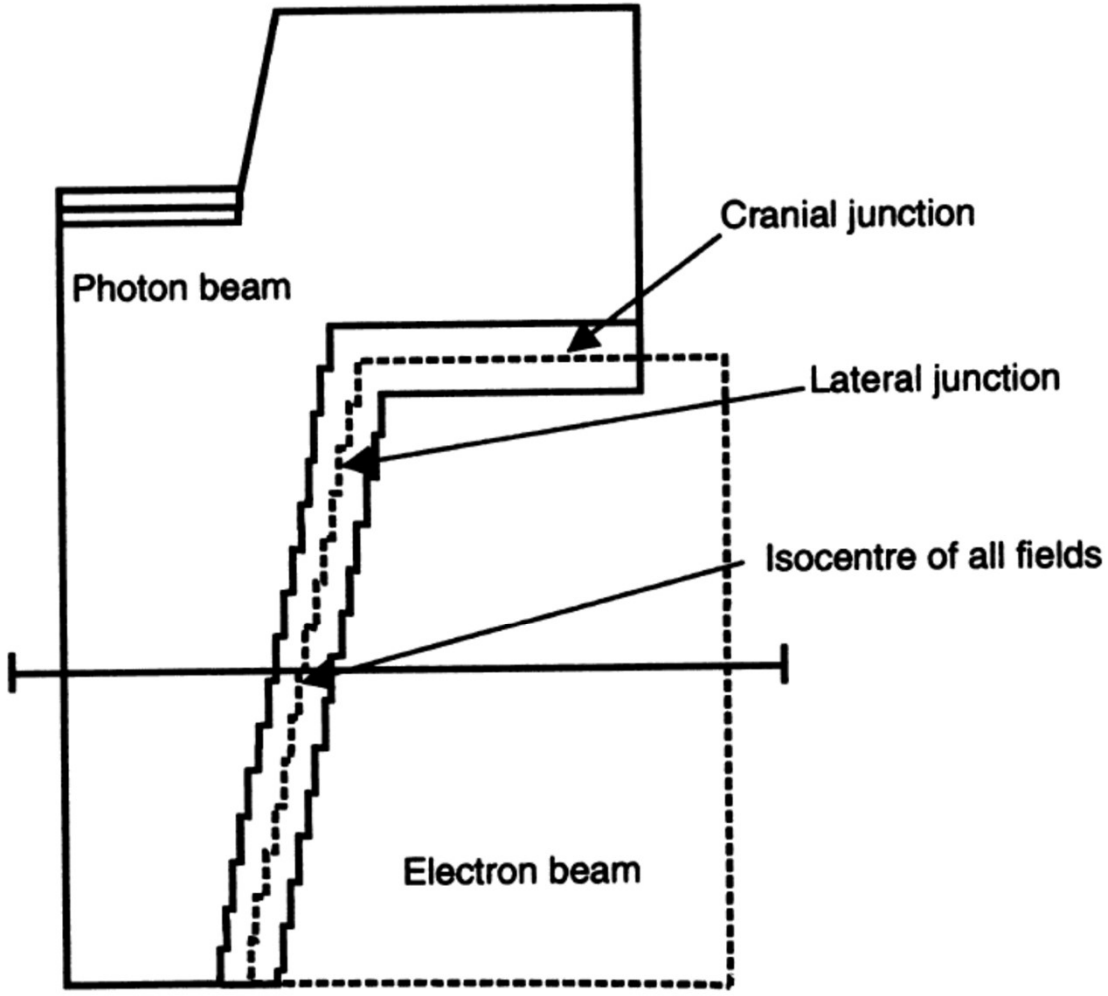

Fig. 2. The optimized treatment technique on the MM50 Racetrack Microtron. Both electron and photon fields are shaped with the MLC. The photon field consists of three segments, having a gap or an overlap of 9 mm with the electron field, or a perfect match.

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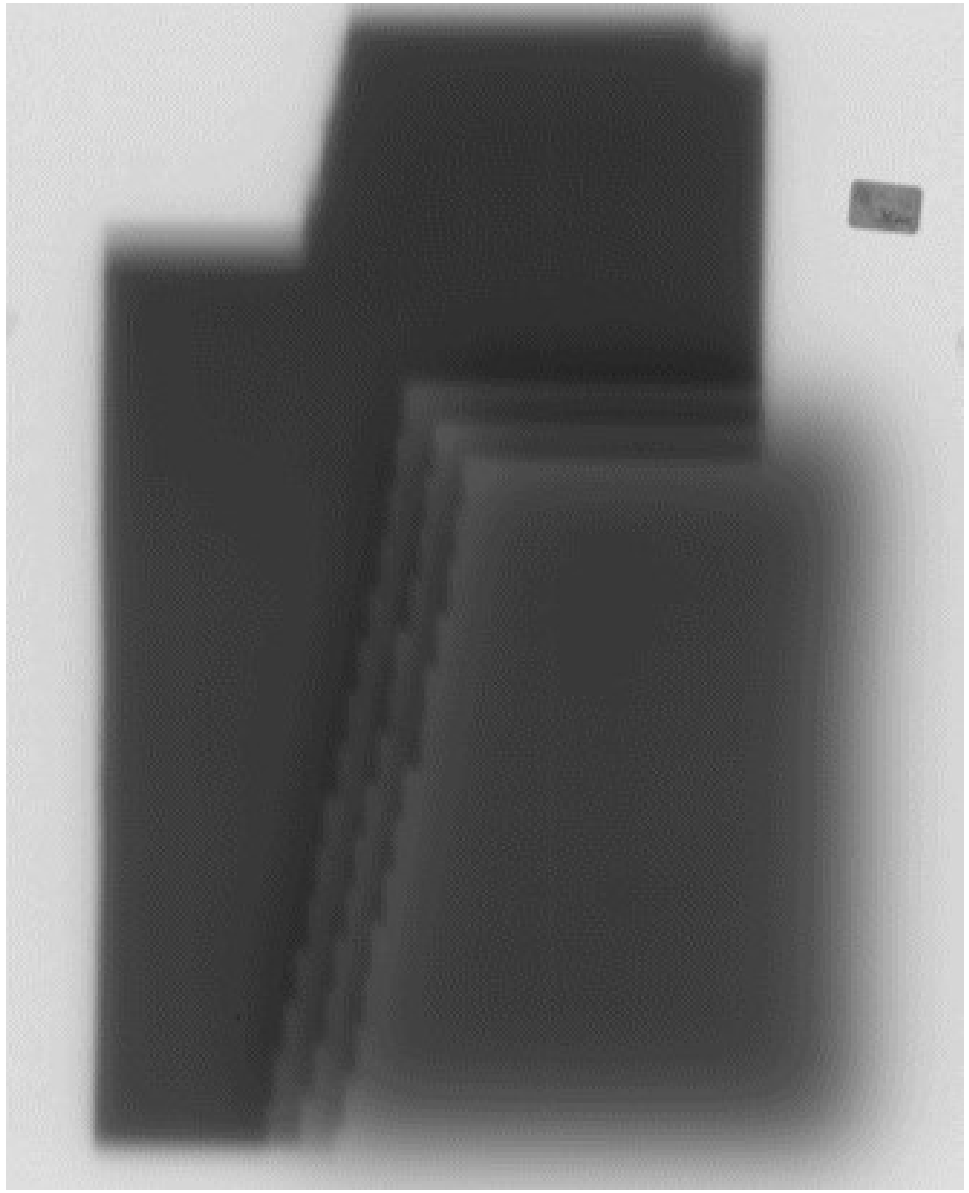
10 MV X-rays and 10 MeV electrons



depth = 3 cm

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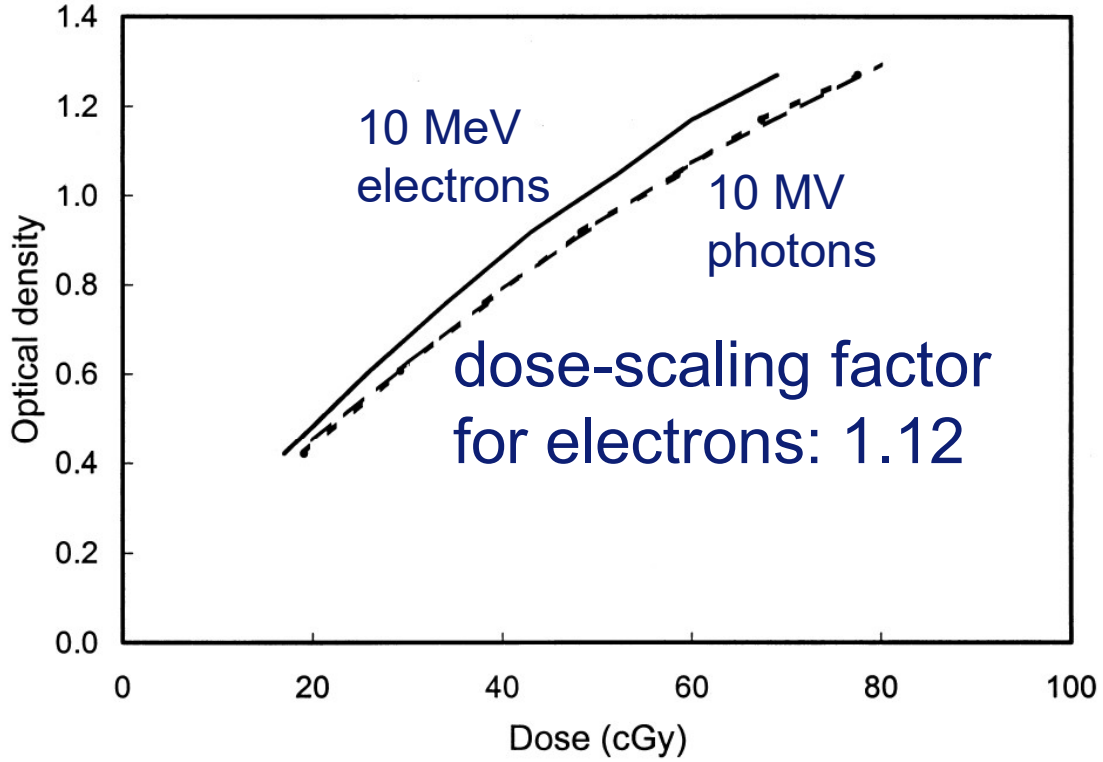
10 MV X-rays and 10 MeV electrons



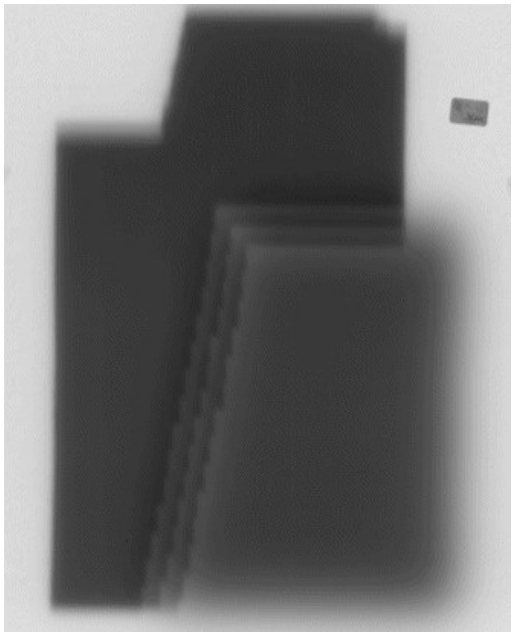


Fig. 3. Sensitometric curves for the 10-MeV electron beam (straight line), and the 10-MV photon beam (dashed line). The dotted line is the rescaled curve for the 10-MeV electron beam (see text).

1. Irradiate film with electron and photons, use for electrons 1/1.12 * (prescribed dose)
2. Analyze film with sensitometric curve of photons

➔ Reliable relative dose distribution

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I. J. Radiation Oncology ● Biology ● Physics Volume 48, Number 4, 2000

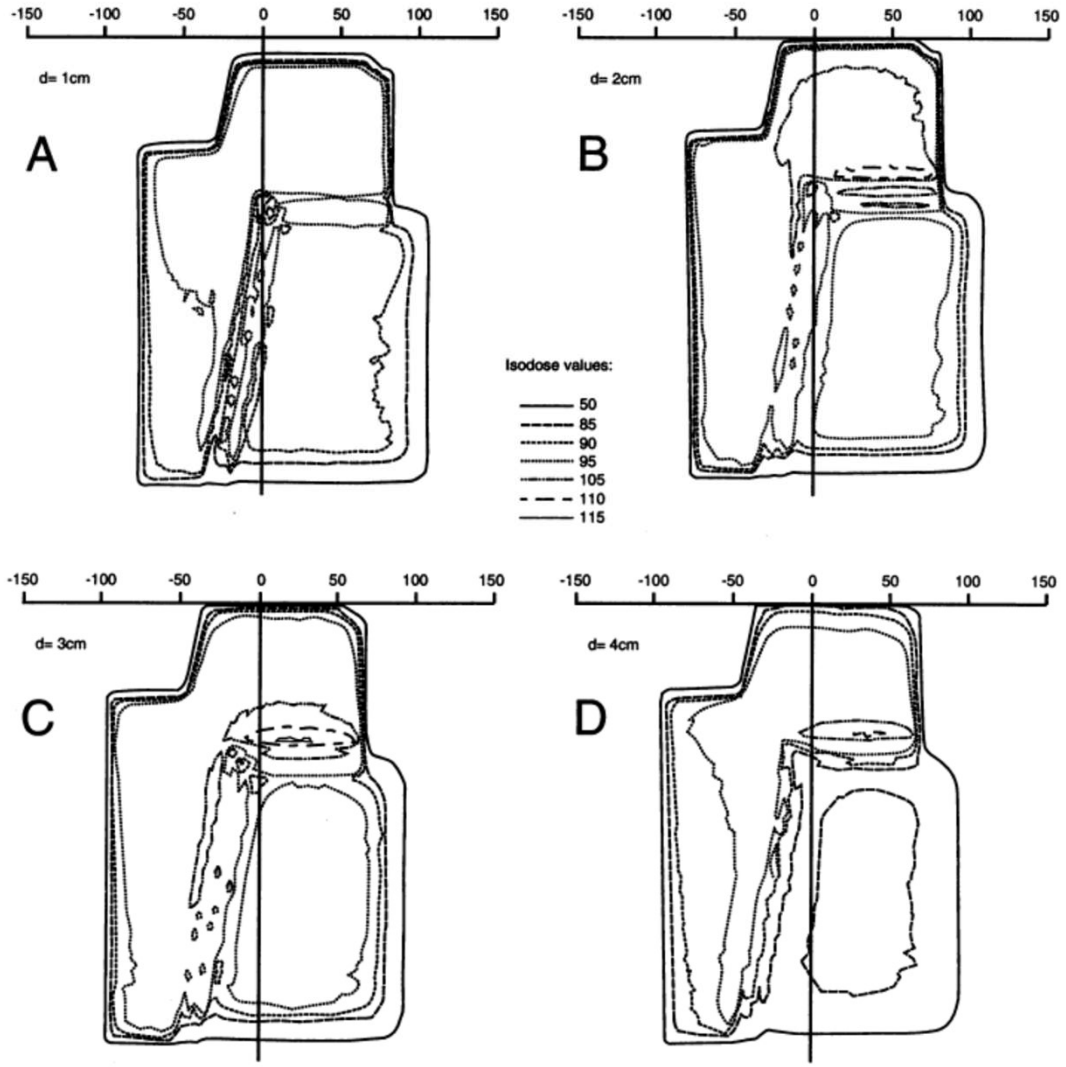

Fig. 8. Isodose distributions for a 10-MV photon beam produced with three photon beam segments matched to a 12.5-MeV electron beam, at depths of (A) 1 cm, (B) 2 cm, (C) 3 cm, and (D) 4 cm. The dose is normalized at a depth of 3 cm. At 4-cm depth, the dose has dropped in the electron beam area due to the PDD of the 12.5-MeV electron beam.

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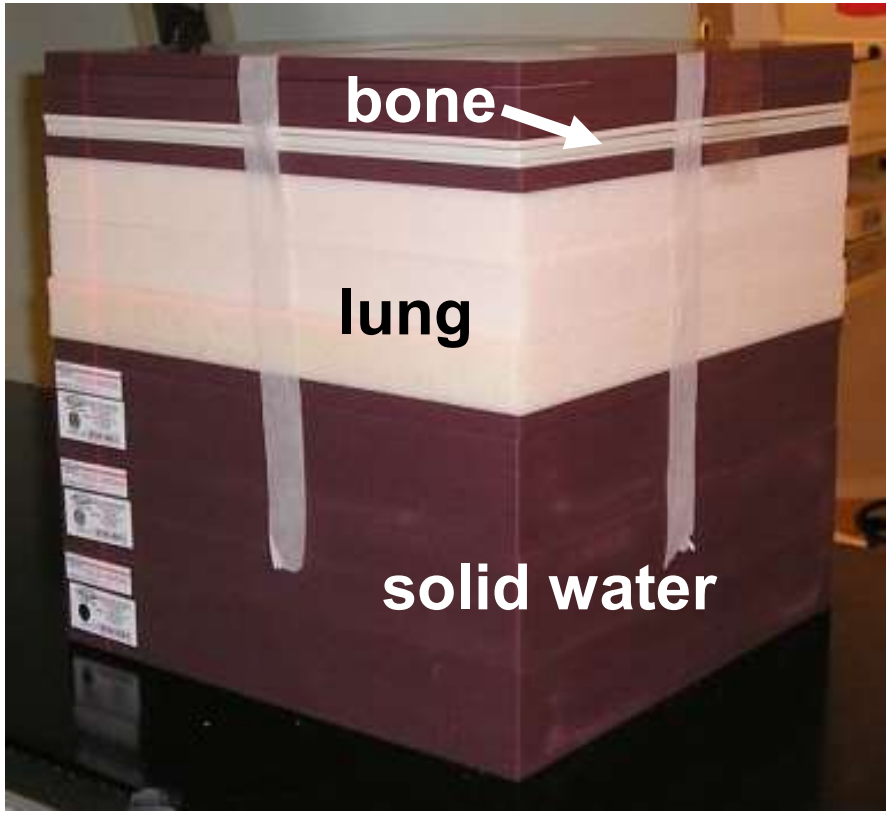
Very fast Monte Carlo dose calculations for the Cyberknife

Accuracy ?



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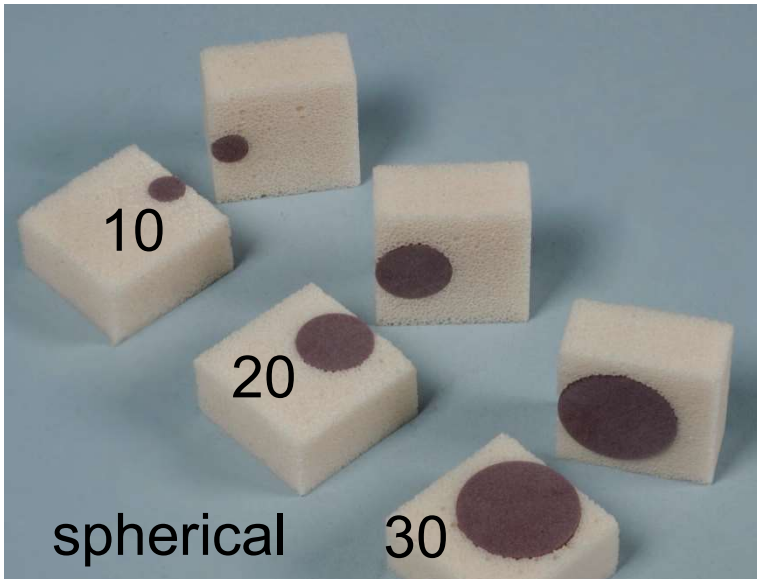
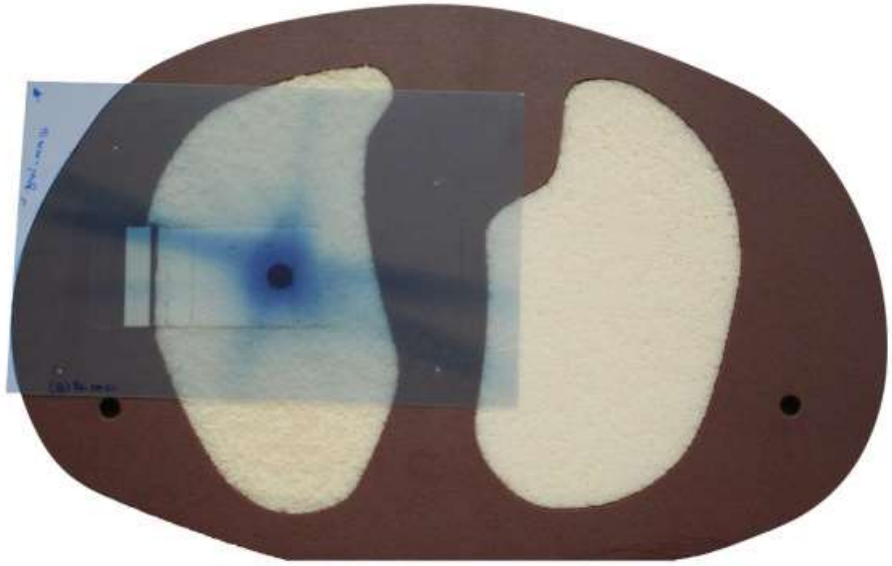
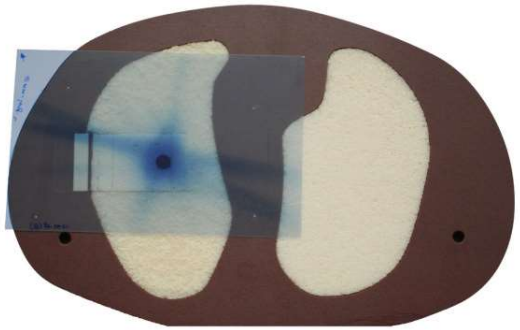
Very fast Monte Carlo dose calculations for the Cyberknife





Very fast Monte Carlo dose calculations for the Cyberknife

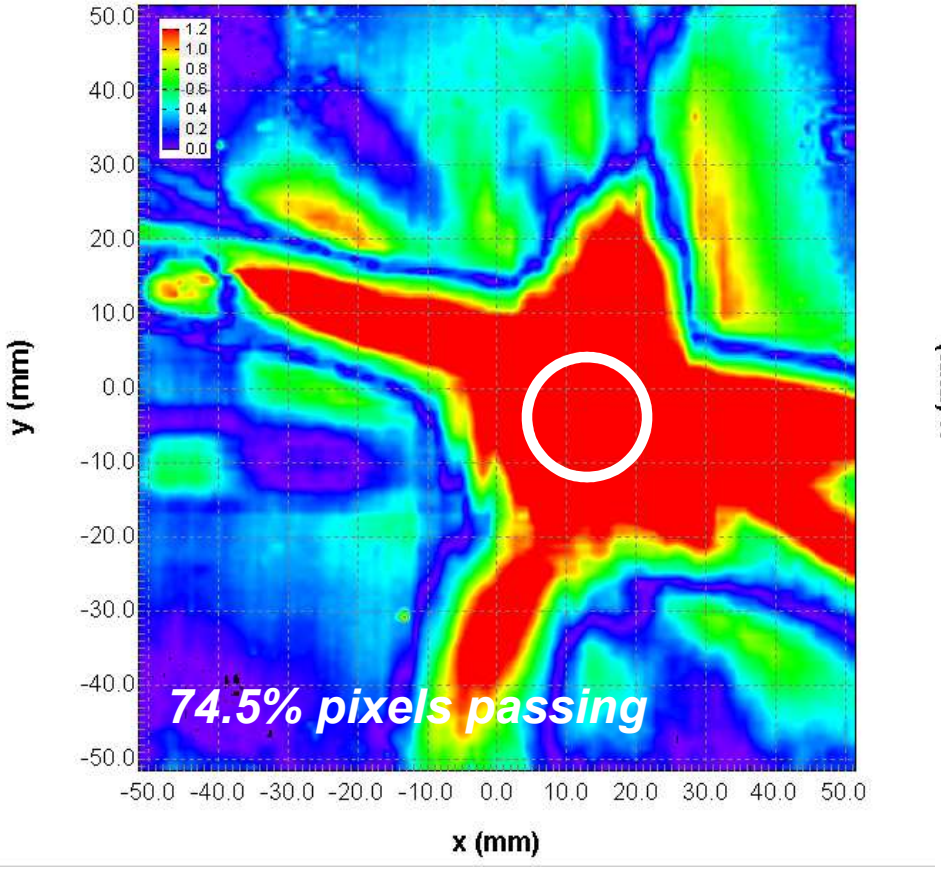
Very fast Monte Carlo dose calculations for the Cyberknife



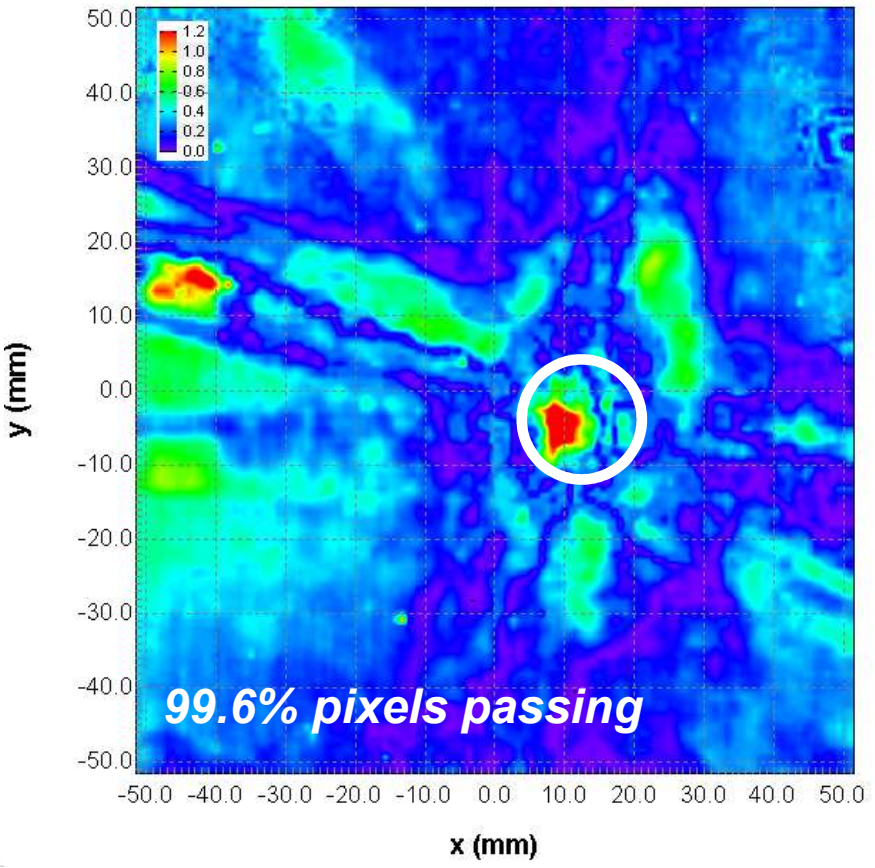
Case 1: central 10-mm tumor

γ (3%,1mm), absolute dose

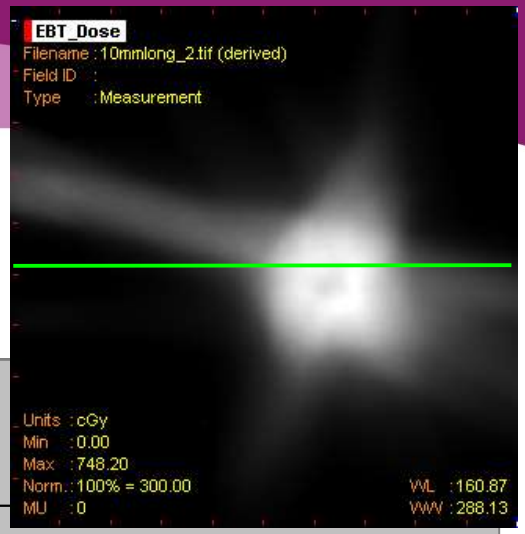
Film vs Ray Tracing

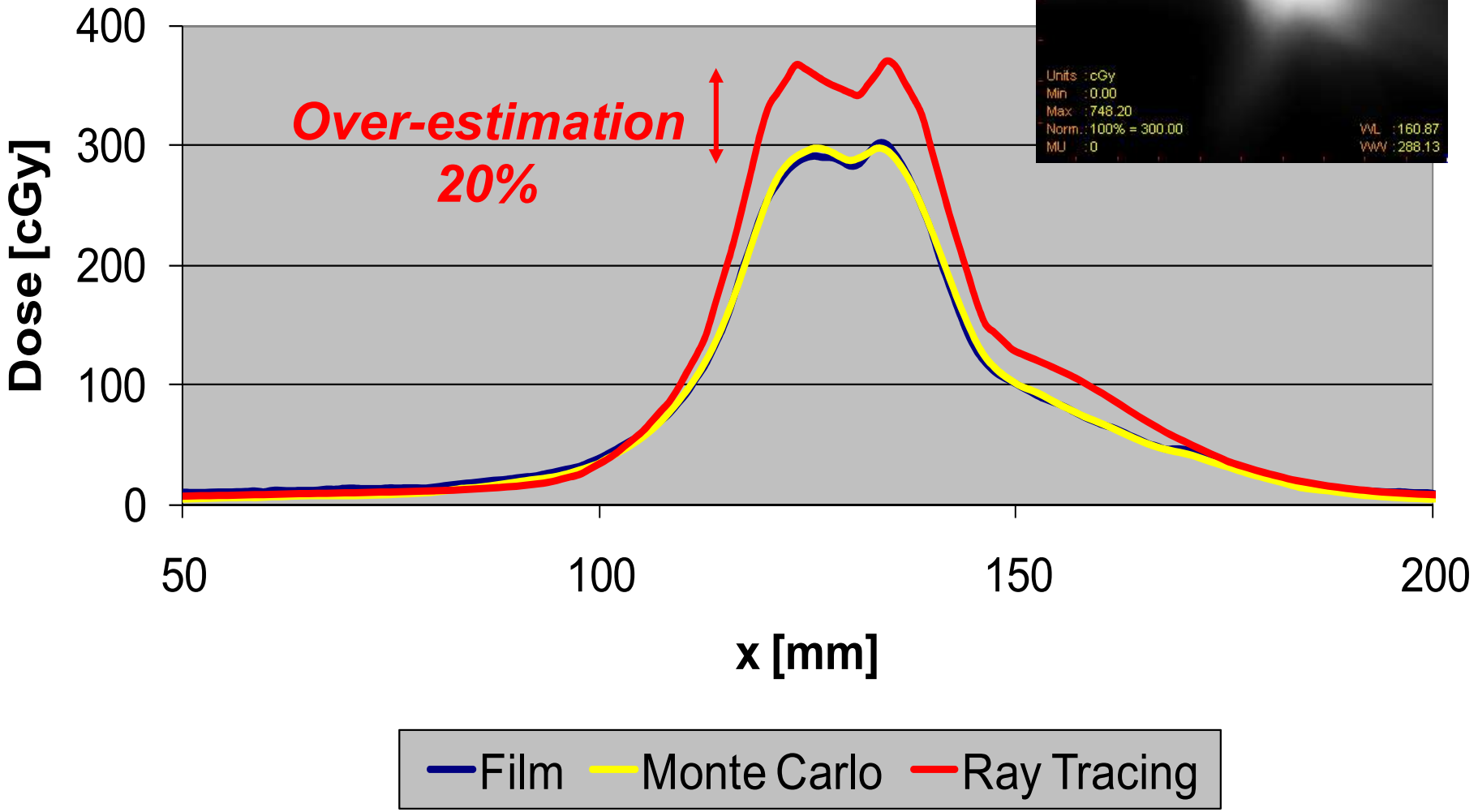


Film vs Monte Carlo



Case 1: central 10-mm tumor





Real-time tumor-tracking to correct for respiratory tumor motion

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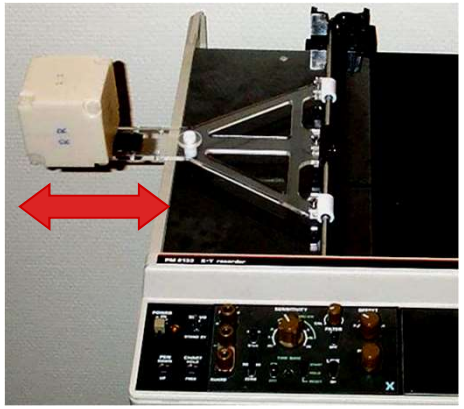
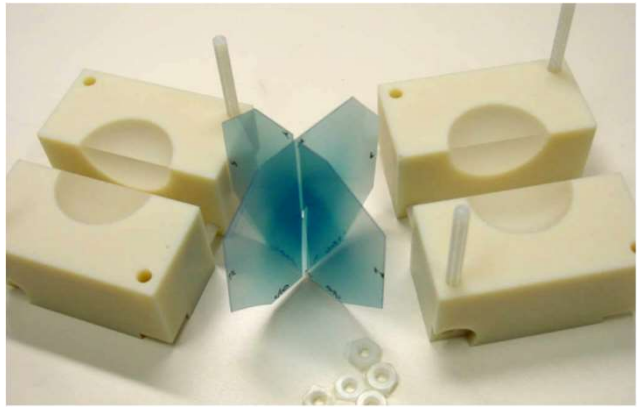
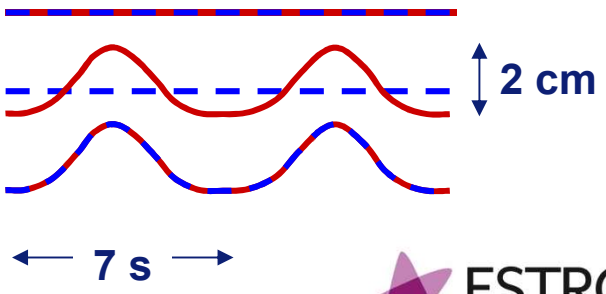
Dosimetric verification

With a programmable motion table, the effect of tumor tracking on the dose distribution was investigated with Gafchromic® film in a phantom





	Motion	Synchrony compensation
Static irradiation	---	No
"Breathing"	$2 \cdot \sin^4(\pi t/7)$	No
"Breathing"	$2 \cdot \sin^4(\pi t/7)$	Yes



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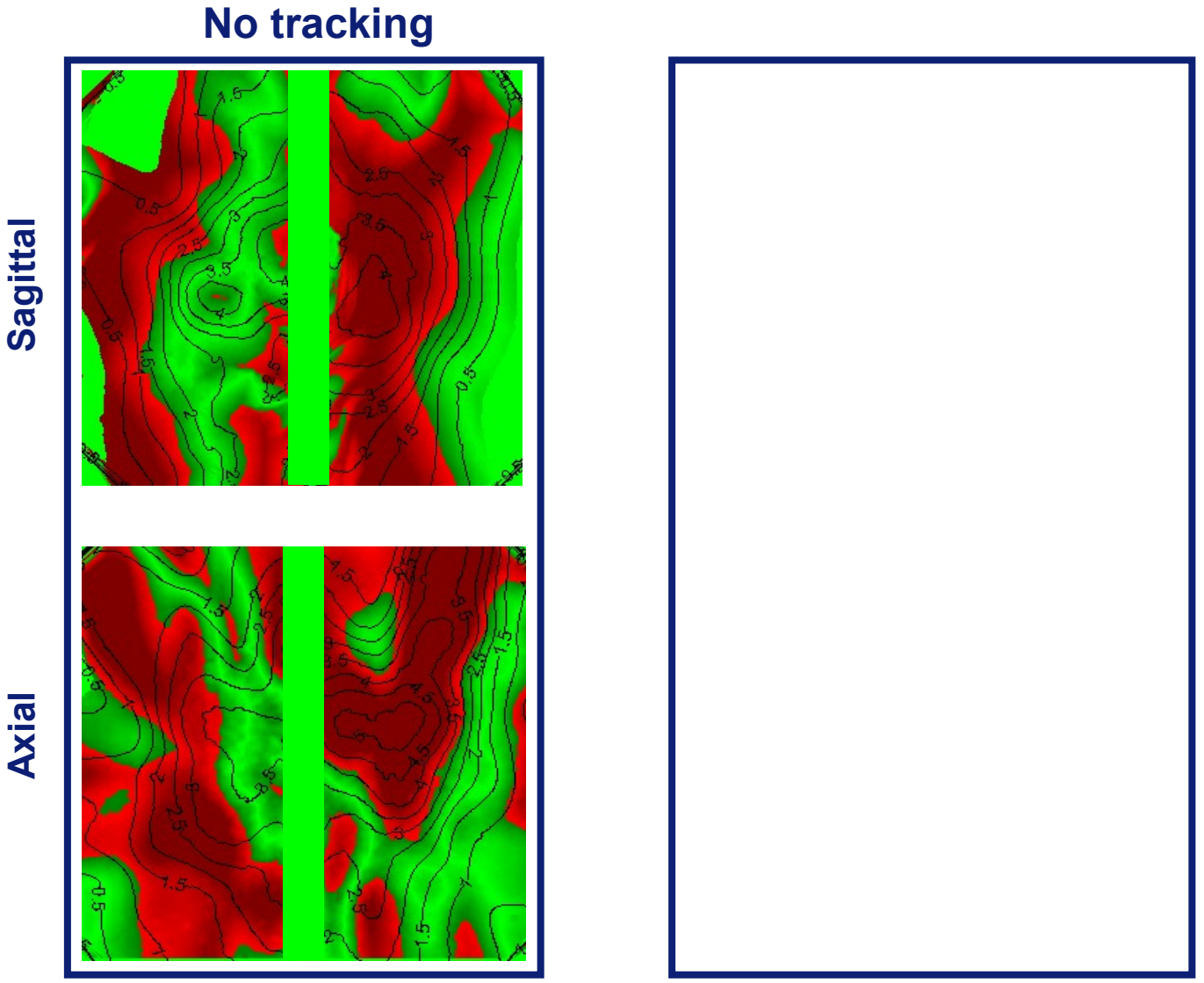
Results 3% dose - 1 mm distance Gamma analysis



Black isodose lines = static irradiation

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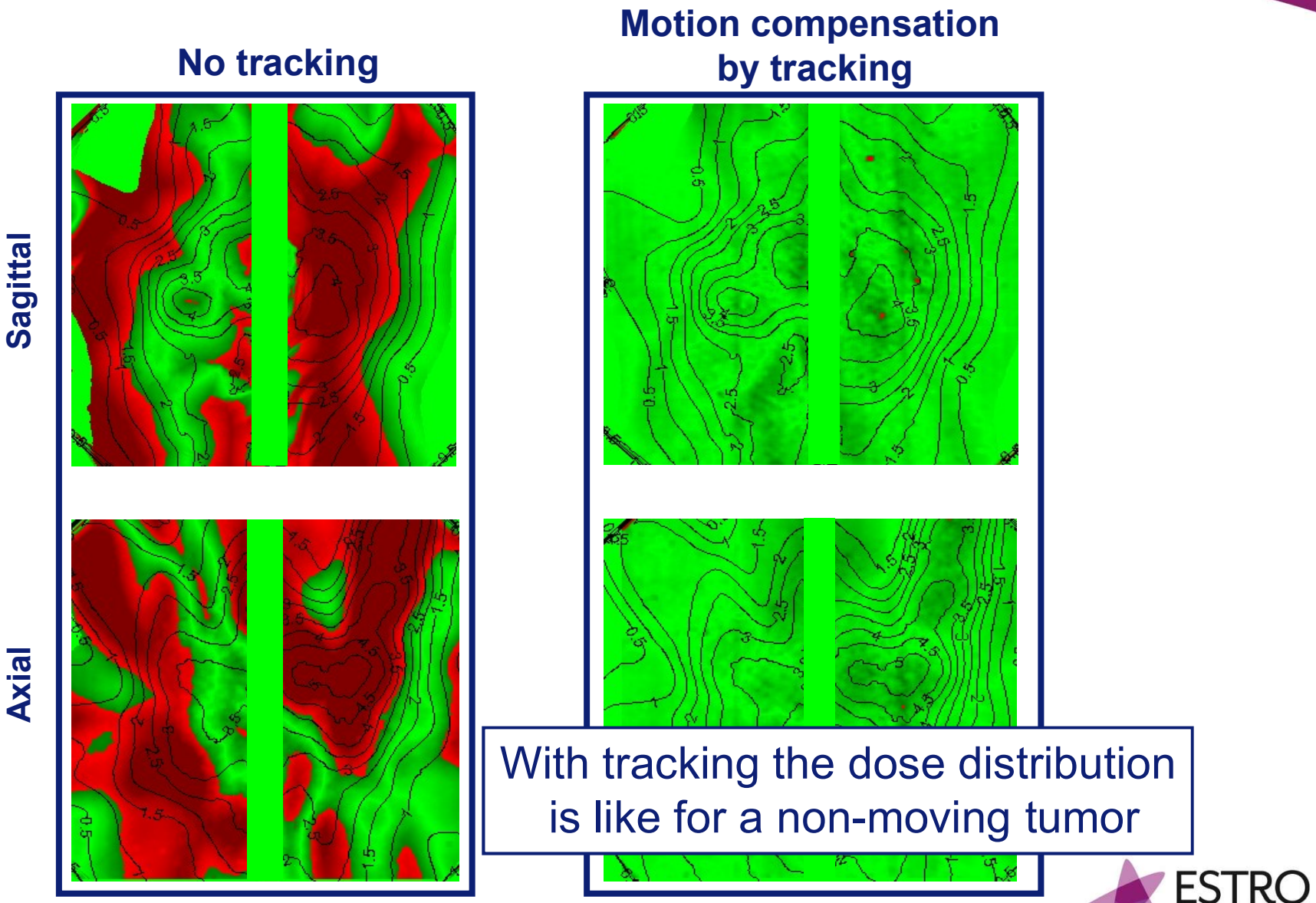
Results 3% dose - 1 mm distance Gamma analysis



Black isodose lines = static irradiation

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Further reading:

- Radiation Oncology Physics: A Handbook for Teachers and Students, editor E.B. Podgorsak, IAEA (http://www-naweb.iaea.org/nahu/dmrp/publication.asp)
- Introduction to radiological physics and radiation dosimetry, Frank H. Attix, ISBN 0471011460
- Influence of phantom material and phantom size on radiographic film response in therapy photon beams, A. Palm and T. LoSasso, Med. Phys. 2005 Aug; 32(8): 2434-42
- Characteristics of sensitometric curves of radiographic films, XR Zhu et al., Med Phys. 2003; 30(5): 912-9
- Film dosimetry in water in a 23 MV therapeutic photon beam, LJ van Battum and BJM Heijmen, Radiother Oncol. 1995; 34(2): 152-9
- Accurate dosimetry with GafChromic™ EBT film of a 6 MV photon beam in water: What level is achievable?, LJ van Battum, D Hoffmans, H Piersma, and S Heukelom, Med. Phys. 2008; 35(2); 704-716
- A technique for the quantitative evaluation of dose distributions. Low DA, Harms WB, Mutic S, Purdy JA, Med Phys. 1998; 25(5): 656-61
- Accuracy of tumor motion compensation algorithm from a robotic respiratory tracking system: a simulation study, Y Seppenwoolde, RI Berbeco, S Nishioka, H Shirato, BJM Heijmen, Med Phys. 2007; 34(7): 2774-84
- Investigation of energy dependence of EBT and EBT-2 Gafchromic film. Patricia Lindsay, Alexandra Rink, Mark Ruschin, and David Jaffray. Med. Phys. 2010; 37(2): 571-576
- Energy dependence and dose response of Gafchromic EBT2 film over a wide range of photon, electron, and proton beam energies. Bijan Arjomandy, Ramesh Tailor, Aman Anand, Narayan Sahoo, Michael Gillin, Karl Prado, and Milos Vicic, Med. Phys. 2010; 37(5): 1942-1947
- The Physics of Radiation Therapy, Faiz M. Khan, 4th Edition, 2010
- Review on the characteristics of radiation detectors for dosimetry and imaging, SECO, J., CLASIE, B., PARTRIDGE, M., Phys. Med. Biol., 59, R303-R347, 2014.
- Dosimetry of ionising radiation in modern radiation oncology, T. Kron, J. Lehmann, and P.B. Greer, Phys. Med. Biol. 61 (2016) R167–205.

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Brachytherapy

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Leeds Cancer Centre and University of Leeds, UK.

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The Use of Small Sealed Radionuclides in Radiotherapy

Brachytherapy

Use of radioactive sources at short distances to treat various tumours

Surface moulds | Interstitial | Intracavitary

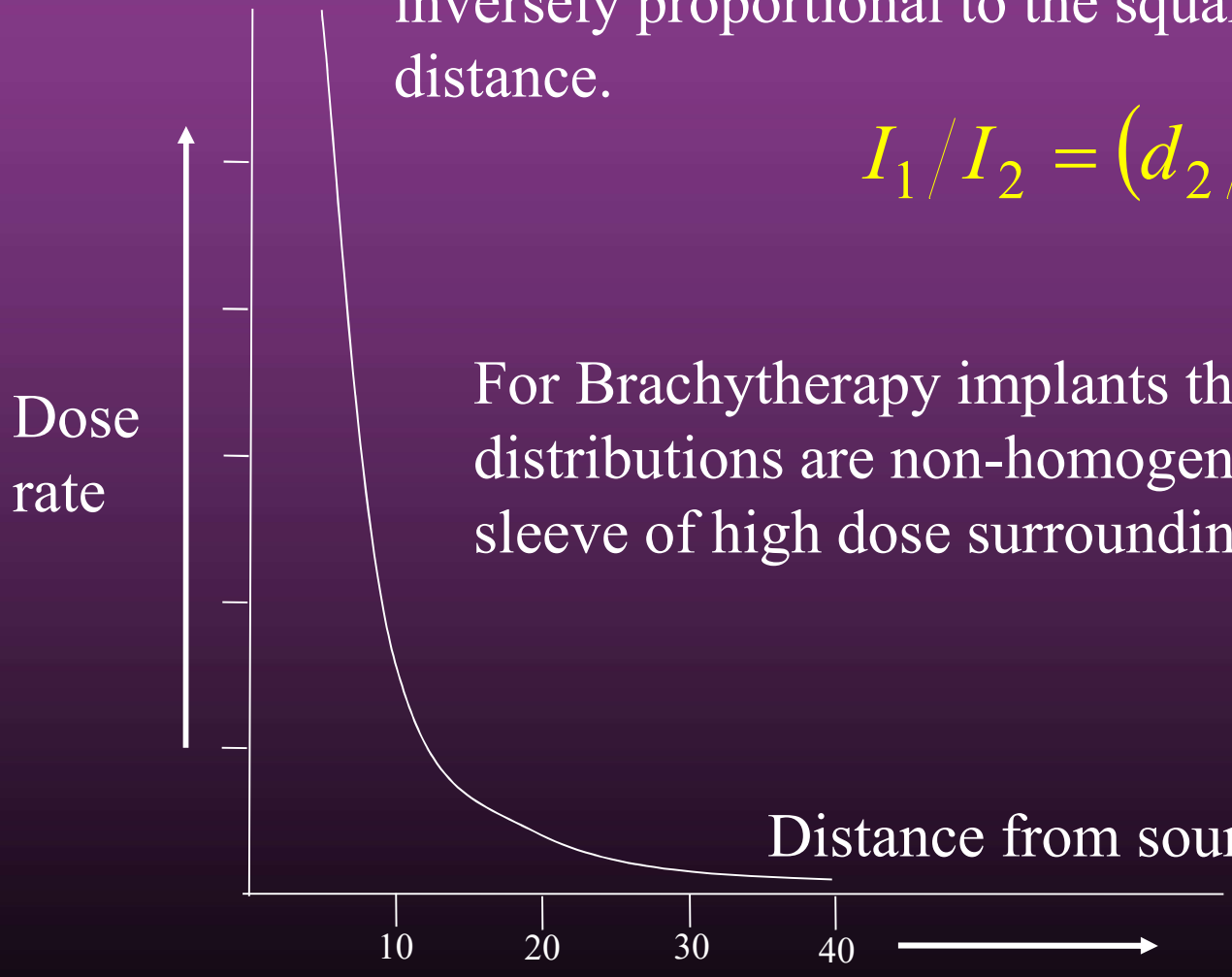
Why brachytherapy?

Its main advantage is that it is a localised treatment giving a high dose near to the radioactive sources with a rapid fall off further away.

Inverse Square Law

The intensity of electromagnetic radiation is inversely proportional to the square of the distance.

$$I_1 / I_2 = \left(d_2 / d_1\right)^2$$



For Brachytherapy implants this means the dose distributions are non-homogenous and there is a sleeve of high dose surrounding each source

Advantages of Brachytherapy

- Brachytherapy allows dose escalation beyond that achievable by any form of external beam (improved local control)
- Allows greater conformity and sparing of surrounding tissues (minimises toxicity)
- In prostate cancer RCTs demonstrate brachytherapy dose escalation improves prostate cancer control
- In locally advanced cervix cancer IGBT results in improved local control and reduced toxicity

Types of sources

Source	Form	Production	Half life	γ-ray energies	Yield (Ci per mg)
Ra^{226}	Cylindrical	Naturally occurring	1620yr	0.86 MeV	
Cs^{137}	Cylindrical or spherical	Fission product	30yr	0.66MeV	0.0865
Co^{60}	Cylindrical	n, γ	5.26yr	1.17,1.34MeV	1.13
Au^{198}	2.5mm grains 14 in magazine	n, γ	2.7 days	~0.4 MeV	243.9
Ir^{192}	Wire, pins, hairpins	n, γ	74 days	Many γ's about 0.3MeV	9.17
Pd^{103}	4.5mm seeds graphite pellets with radiographic marker	n, γ	17 days	21 keV effective	
I^{125}	4.5mm seeds	Decay product of Xe^{125}	59.6 days	27.4,35.3 keV	

Dose Rate Definitions

Definitions vary across organisation (ICRU and AAPM) but generally:

LDR 0.5 to 1 Gy per hour

MDR 1 to 12 Gy per hour

HDR > 12 Gy per hour but is usually as high as 2 to 5 Gy per minute

Pulsed dose rate delivers large number of fractions with short intervals between and aims to have similar effect as LDR

Afterloading systems

Applicators positioned in a patient and radioactive sources introduced later

Introduced for Radiation Protection reasons

Reduction in staff exposure doses

Improved geometry

MANUAL AFTERLOADING

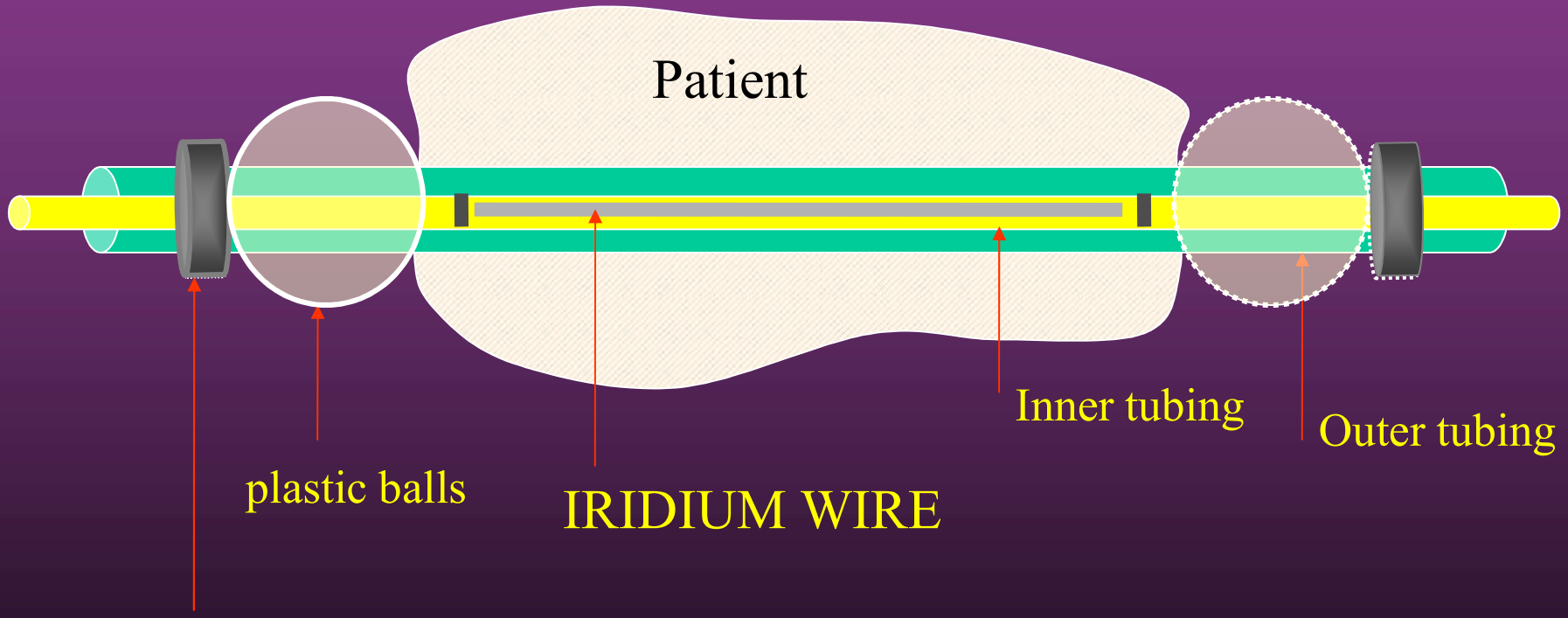
Cervix applicators

Iridium wire system

REMOTE AFTERLOADING

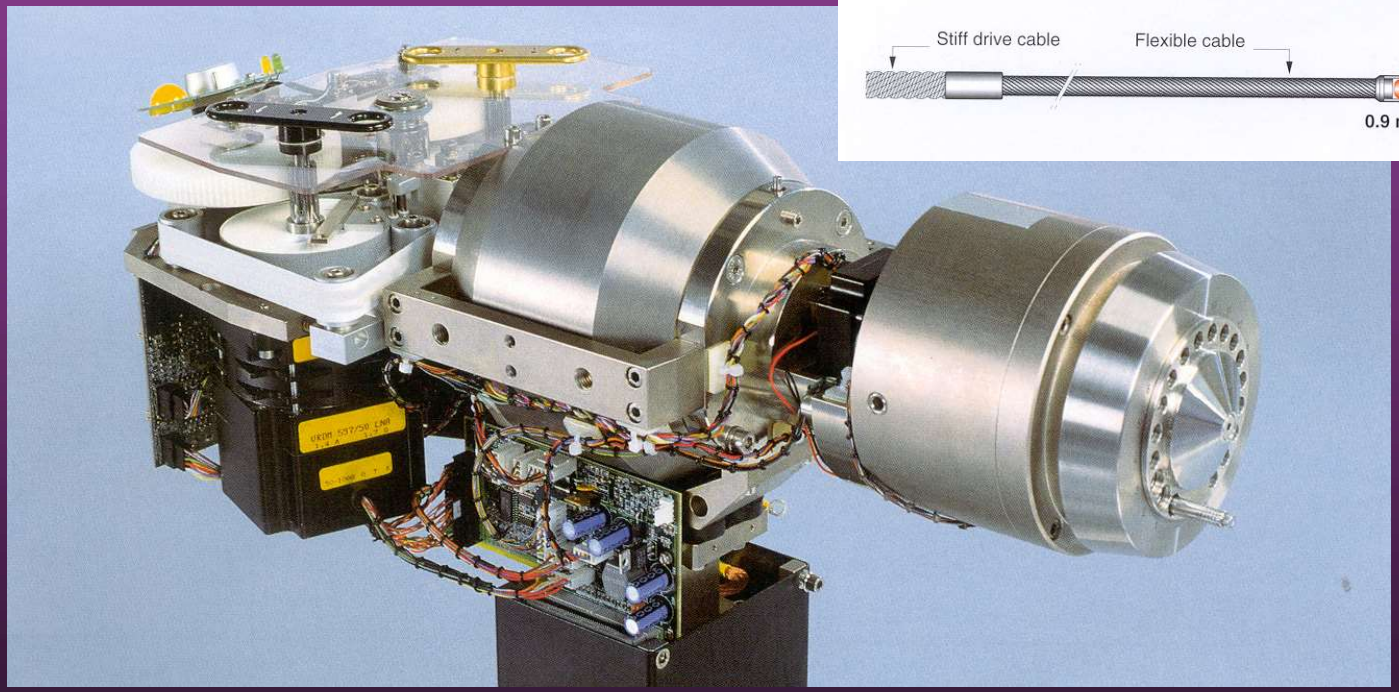
Various PDR and HDR systems

Manual afterloading : Iridium wire



Single source stepper afterloader Iridium-192

Nucletron micro-Selectron

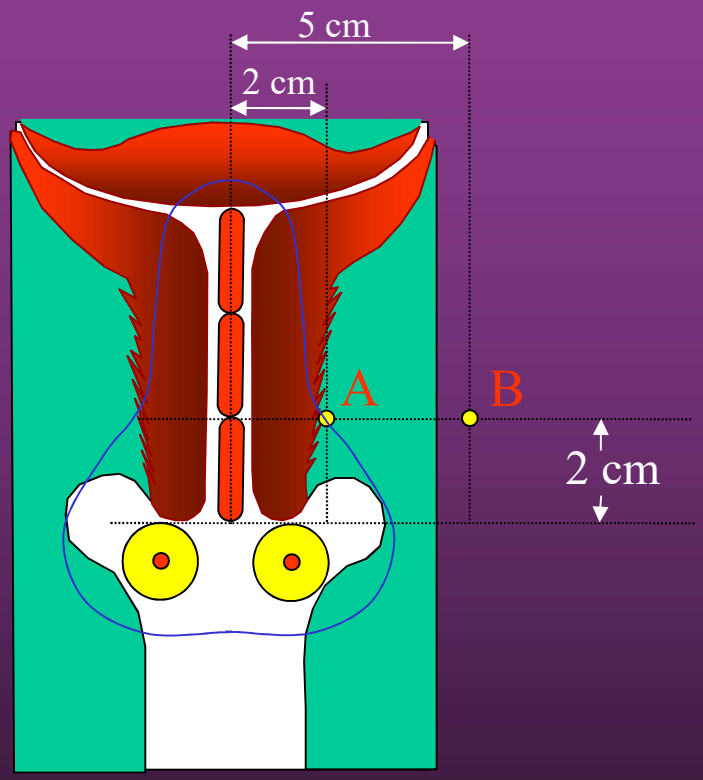


Each machine contains Ir-192 source welded to a drive cable. Multiple channels and dwell positions/times.

Clinical indications and outcomes

- Gynaecological cancer
  - Used for cervix, endometrial, vaginal and vulva cancers
  - Move from 2D to 3/4 D IGBT
- Prostate cancer
  - As both monotherapy and boost with EBRT
- Breast cancer
  - Accelerated Partial Breast Irradiation (APBI) and boost
- Head and neck cancers
  - As primary treatment and salvage after previous EBRT

2D Gynaecological brachytherapy



Point A and B: reference points from orthogonal X-rays

An "ideal" geometric arrangement, producing the desired pear-shape dose distribution.

A standard system for a standard patient producing

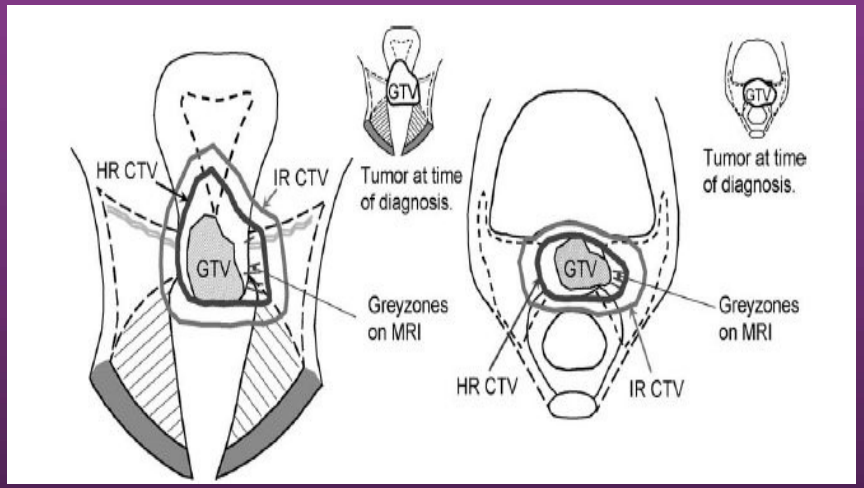
NO ANATOMICAL DOSES FOR INDIVIDUAL PATIENTS

Moving from 2D to 3D/ 4D IGBT

- Geometric errors in target coverage of 40% (SD) with cancer in parametrium often under-dosed in bulky cancers
- Information about OAR doses unreliable (20% SD)
- All resulted in variable practice and sub-optimal outcomes
- GEC ESTRO Guidelines published 2005-6
  - Concepts and terms for use with 3D MRI
  - DVH parameters, aspects of anatomy/physics/radiobiology
- Implemented over last 15 years driven by EMBRACE trial

GEC ESTRO recommendations

- Overview
  - Outlining and 3D dose parameters
  - Dose for 2Gy equivalent: best approximation
  - GTV/CTV: HR and IR volumes
  - $\alpha/\beta=10$ for GTV and CTV: D90
  - $\alpha/\beta=3$ for OAR:D2cc, D1cc, D0.1cc, V100, V5.4Gy



RO (2005) 74 :235-45

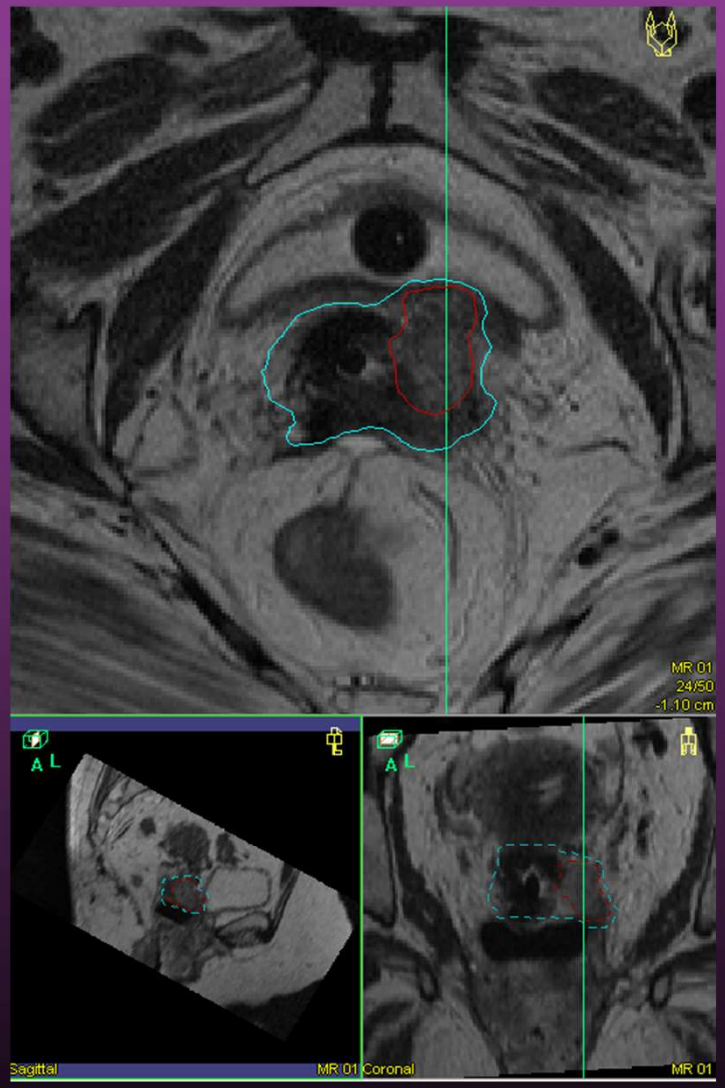
and

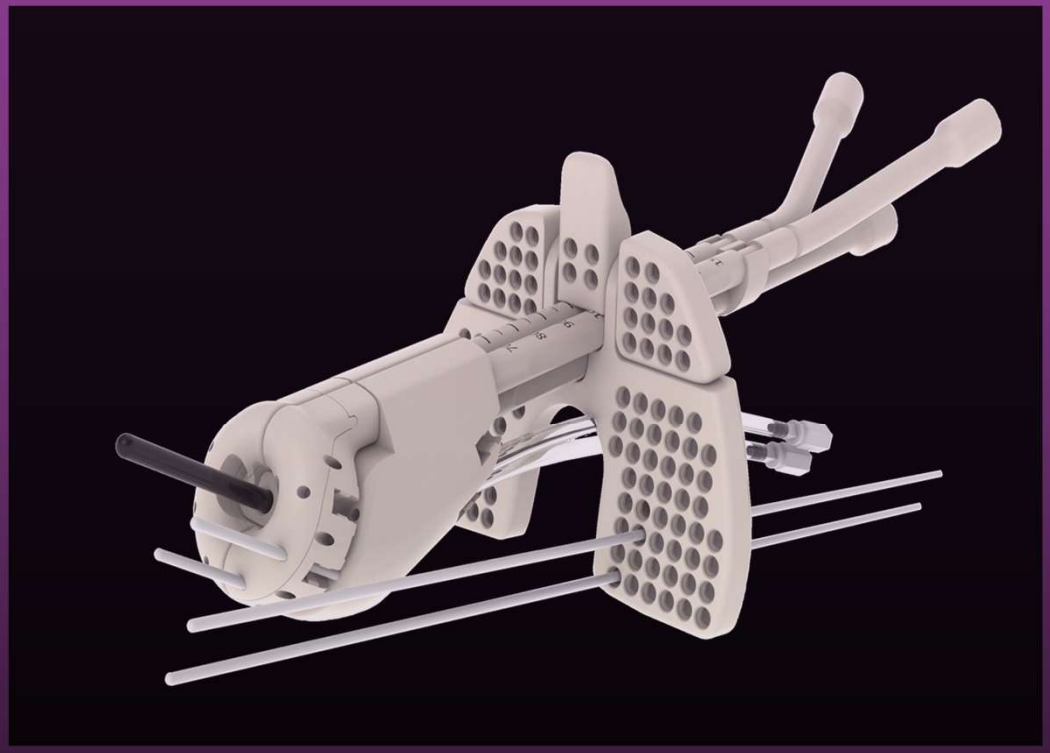
RO (2006) 78: 67-77

EMbrace clinical trial

- European study on MRI-guided brachytherapy in locally advanced cervical cancer
- Multi-centre observational study to introduce MRI based 3D brachytherapy planning in 27 centres
- Collect data on outcomes and develop prognostic / predictive markers with > 1200 patients recruited end 2014
- EMBRACE II opening with many more centres aiming to participate
- ICRU 89: New recommendations for gynaecological brachytherapy published 2016
  - Higher dose to HR CTV improves control >85Gy
  - Need to use interstitial needles in larger tumours
  - Lower doses in smaller tumours

Interstitial needles for IGBT



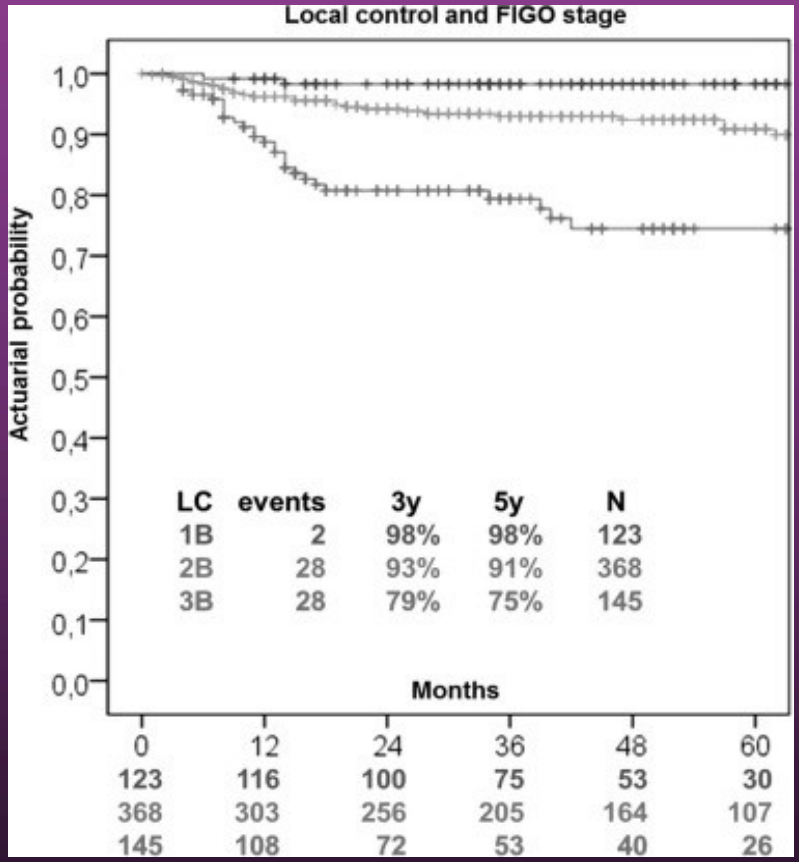


™Venezia advanced gynaecological applicator Elekta

Requires use of MR

Retro-EMBRACE results

- Outcomes from 12 centers with N=731
- Procedure
  - 80% IGBT using MR for at least 1 intervention
  - 23% combined intracavity-interstitial intervention
- Increased pelvic control and OS by 10% compared to historical series
- Effect larger in more advanced
- G3+ toxicity 5-7%



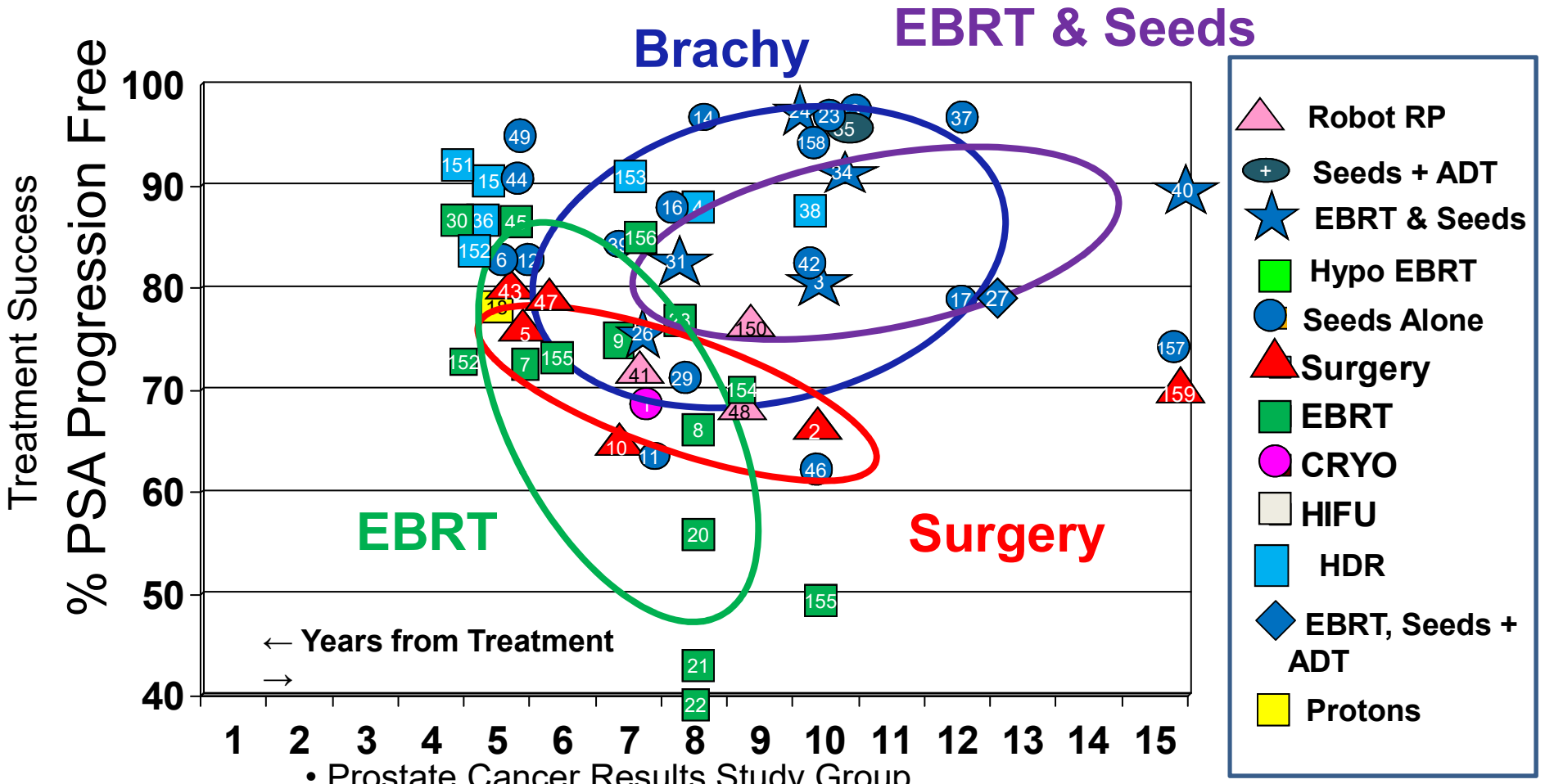
Sturdza et al. Radiotherapy and Oncology (2016) .

Prostate Brachytherapy

- Low Dose Rate (LDR)
  - Permanent radioactive seed implantation
  - Iodine^{125} (most commonly used) or Palladium^{103} or Caesium^{131}
  - Loose or stranded seeds
  - Sole treatment or boost with EBRT
- High Dose Rate (HDR)
  - Generally temporary Iridium^{192} implantation
  - Boost with EBRT or sole treatment (in clinical trials)
  - Increasingly used

INTERMEDIATE RISK RESULTS

Weighted



- Prostate Cancer Results Study Group
- Numbers within symbols refer to references

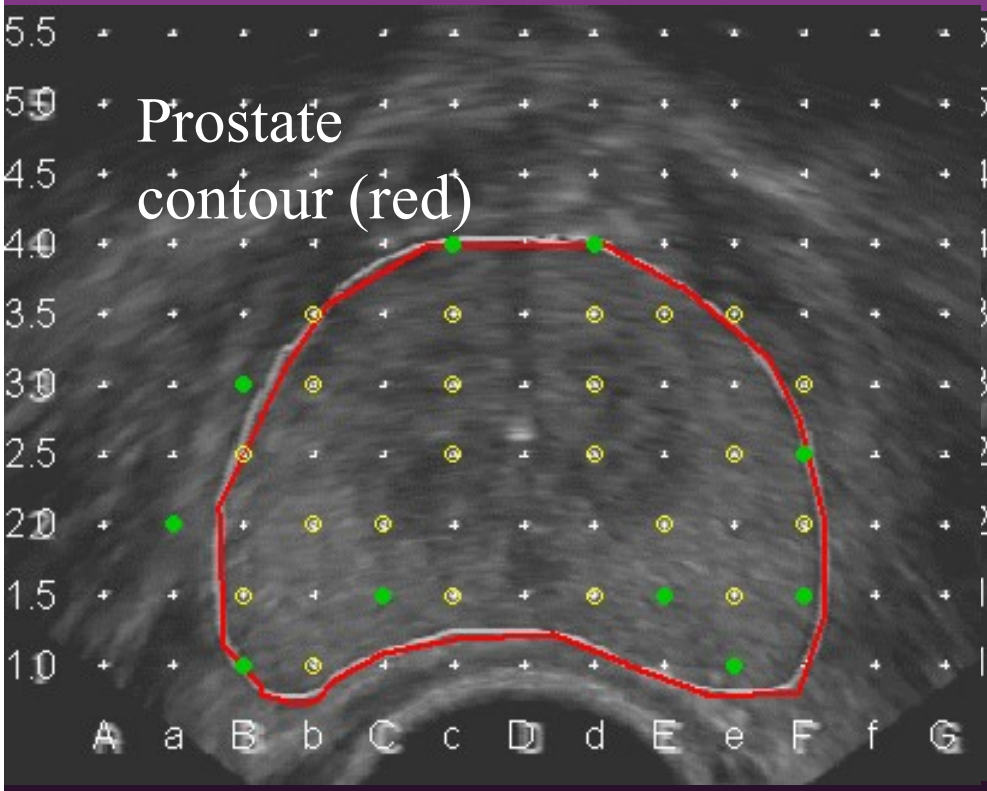
I-125 permanent prostate brachytherapy selection criteria

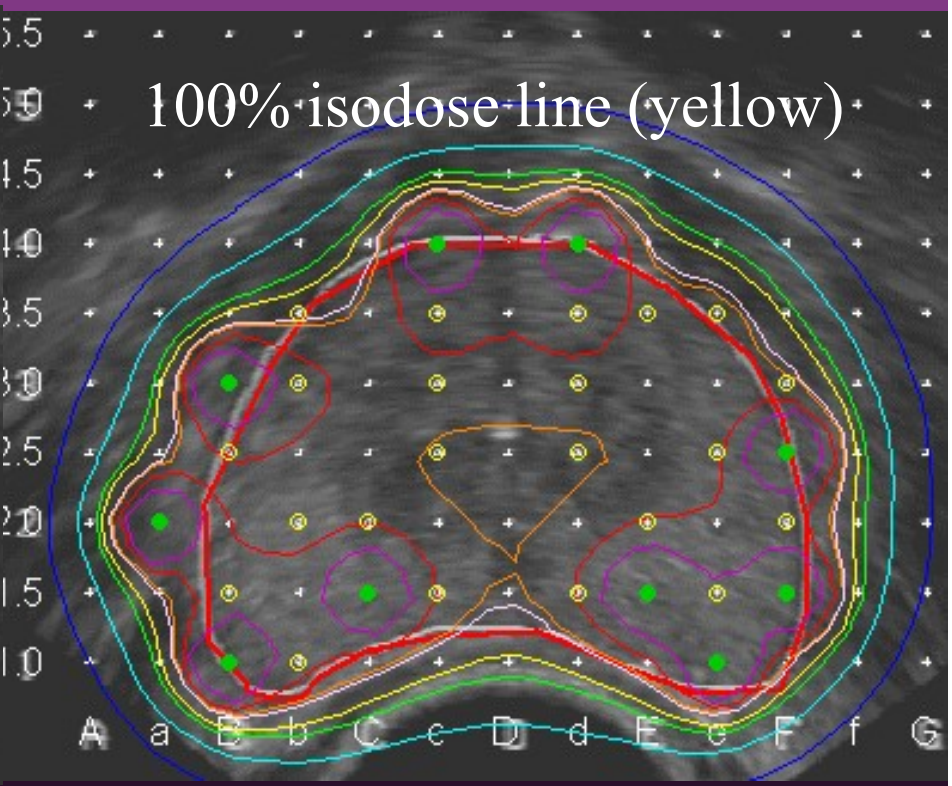
- Low or selected intermediate risk localised disease
- Life expectancy > 10 years
- Prostate volume < 50mls, if larger may need hormone treatment prior to brachytherapy to shrink prostate
- Excluded

  - if significant obstructive urinary symptoms (urine peak flow rate < 10mls per sec or large post-micturition residual volume) as at high risk of catheterisation

  - previous Trans-Urethral Resection of Prostate (TURP) resulting in large prostate defect

Higher PSA and Gleason score are associated with an increased risk of extra-capsular extension of prostate cancer





In I-125 brachytherapy the dose (145Gy) is prescribed to the 100% isodose which should encompass the prostate with a 3mm margin. Any extra-capsular spread beyond the prostate will not be encompassed and risks treatment failure so I-125 alone is not recommended with higher PSA or Gleason scores

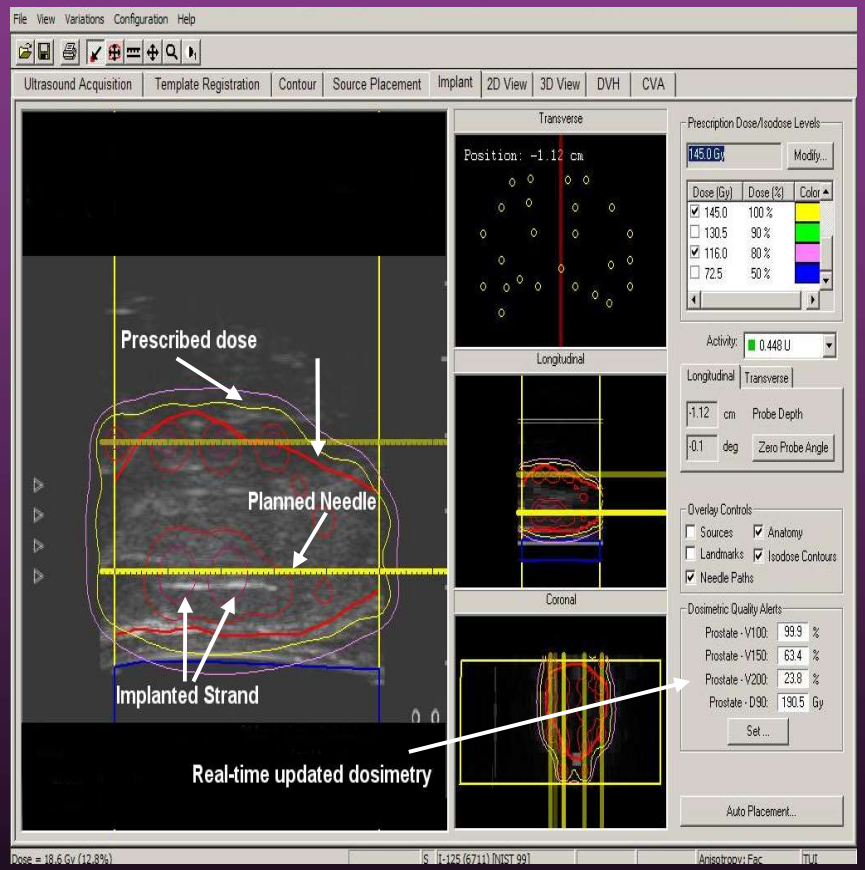
Pre-plan generated using TRUS dataset

- CTV = prostate + 3mm margin constrained by rectum posteriorly (CTV=PTV)
- Typical planning objectives and constraints for I-125
  - minimum peripheral dose of 145 Gy to CTV
  - $V_{CTV}100$ (CTV covered by 100% of the prescription dose) $\geq$ 95%
  - D90 (dose to 90% of the CTV) > 100%
  - $V_{CTV}150$ (CTV covered by 150% of the prescription dose) < 50%
  - Rectal mucosal volume which receives 100% (Vr100) of the dose of less than 2 cc
  - $D_{urethra}10 < 150\%$ and $D_{urethra}30 < 130\%$

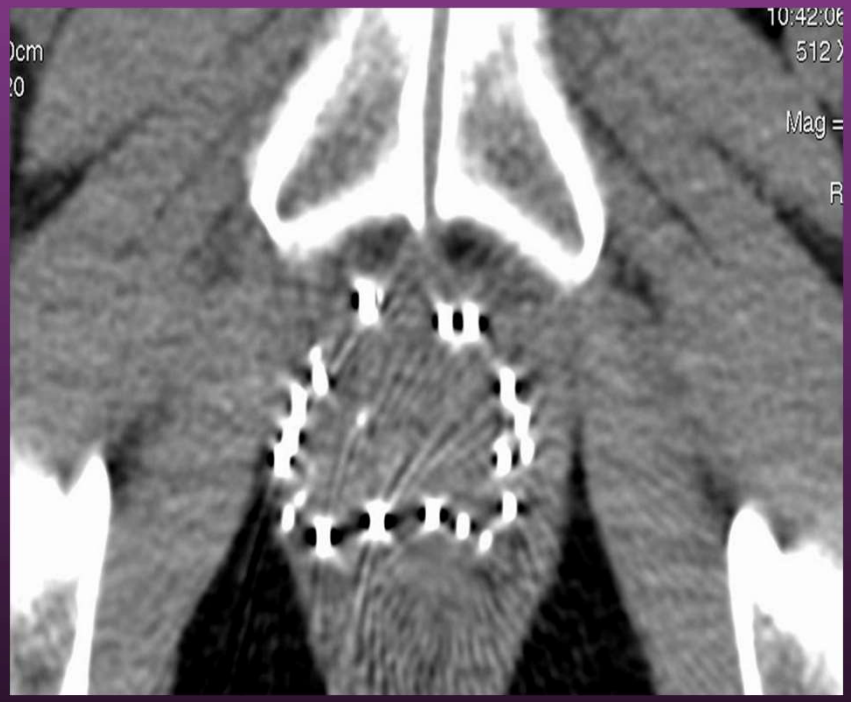
From: Tumour and target volumes in permanent prostate brachytherapy: A supplement to the ESTRO/EAU/EORTC recommendations on prostate brachytherapy. Salembier et al. RO 83(2007):3-10.

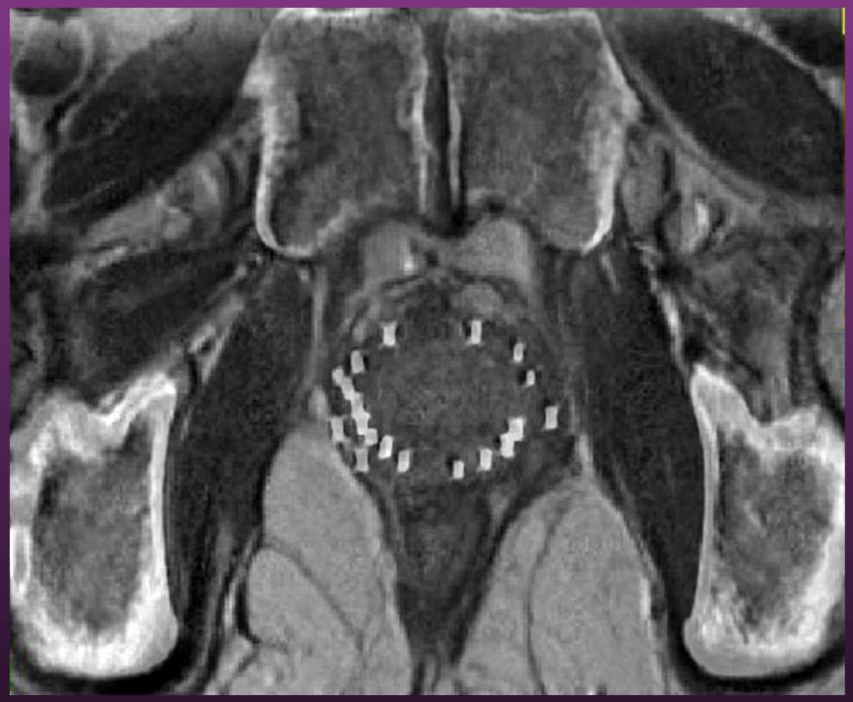
Interactive implantation

- As each needle or strand of seeds is implanted, actual position is tracked, fed back into TPS and dosimetry updated in real-time
- May improve the quality of the implant and also avoids the ‘learning curve’ seen when starting a new brachytherapy programme
- Disadvantage: Can take longer to do



Quality Assurance: Post Implant Imaging with CT +/- MRI





Expected toxicity

- Urinary symptoms peaking at 2-3 weeks but persisting for 2-3 months
- 10-15 % risk of temporary catheterisation. Risk of permanent incontinence < 1%
- Impotence in 33% (if no hormones) with response to medication in 85%
- Side effects relate to $T_{1/2}$ of isotope (I_{125}=60 days, Pd_{103}=17 days), so settle earlier with shorter $T_{1/2}$

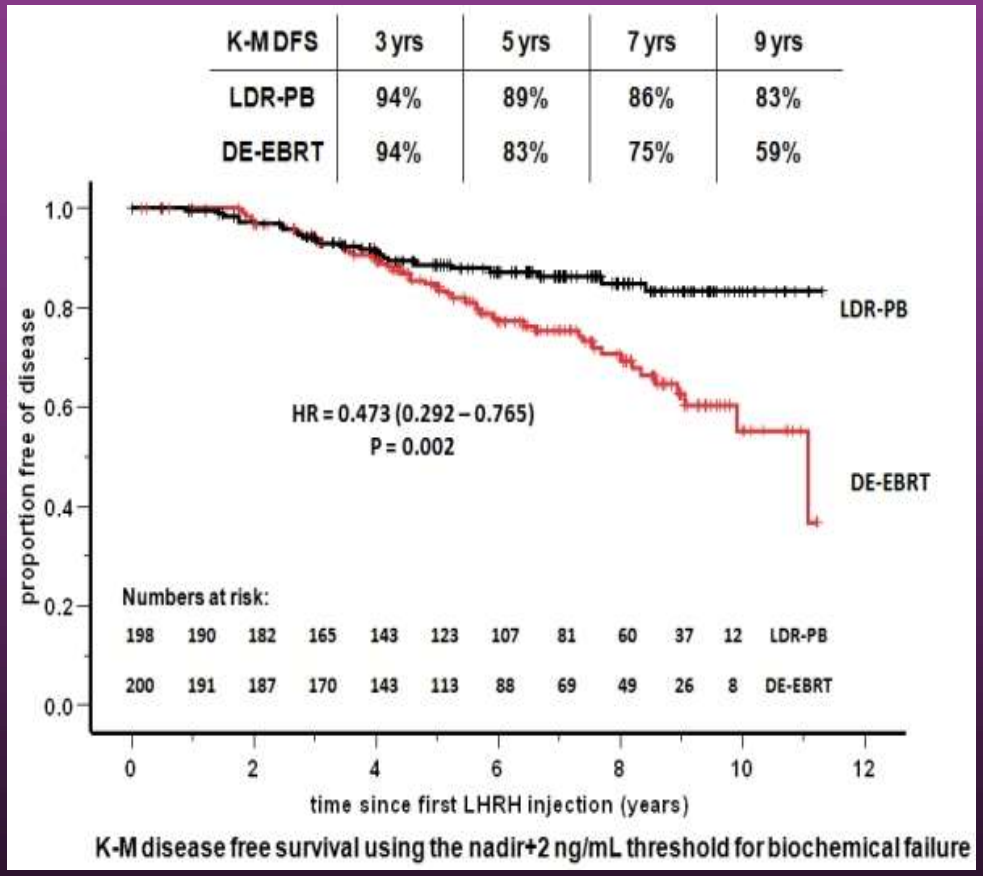
Brachytherapy boost with EBRT as means of dose escalation

- Either LDR or HDR treatments can be used in patients with extra-capsular spread or high risk disease
- Randomised trials available using both LDR and HDR boosts
- Brachytherapy allows dose escalation without issues of organ motion

Prostate Cancer Level I (RCT) evidence: EBRT +/- BT boost

	Hoskin 2007 (UK)	Morris 2015 (Canada)
No. patients	218	398
Mean age yrs	68.9	68
Technique	HDR (8.5Gyx2)	LDR (115Gy)
Risk groups	Low 4% Inter 42% High 54%	 Inter 31% High 69%
Outcomes	At 7.1 yrs 31% reduction in recurrence	50% reduction in PSA recurrence ↑ late GU toxicity
Criticism	EBRT comparator only 55Gy/20	EBRT comparator 76Gy but not IMRT/IGRT

ASCENDE- RT trial



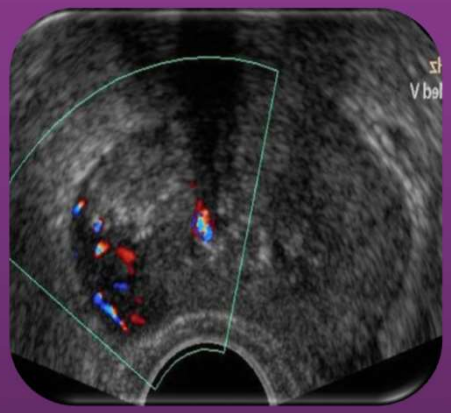
BUT higher late G3+ GU (*18% in BT boost arm vs. 8% in EBRT alone*)

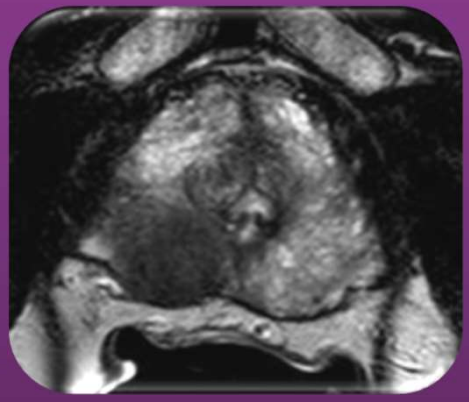
Most strictures and urinary incontinence

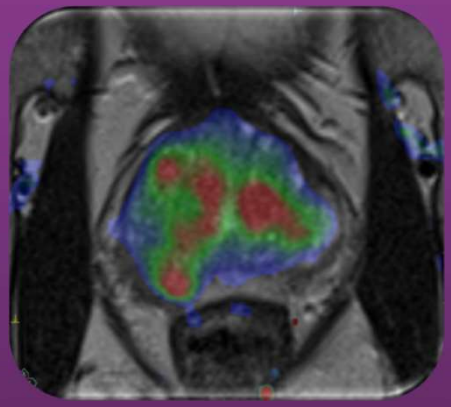
Recommended boost dose reduced to 110Gy

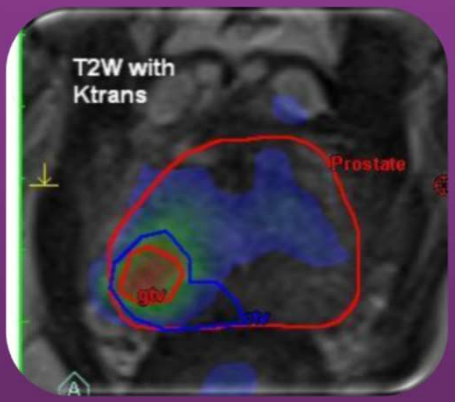
Morris WJ, et al. ASCENDE-RT: A multicenter, randomized trial of dose-escalated external beam radiiation therapy (EBRT-B) versus low-dose-rate brachytherapy (LDR-B) for men with unfavorable-riisk localized prostate cancer. JCO 2015;33 (suppl 7) abstr 3.

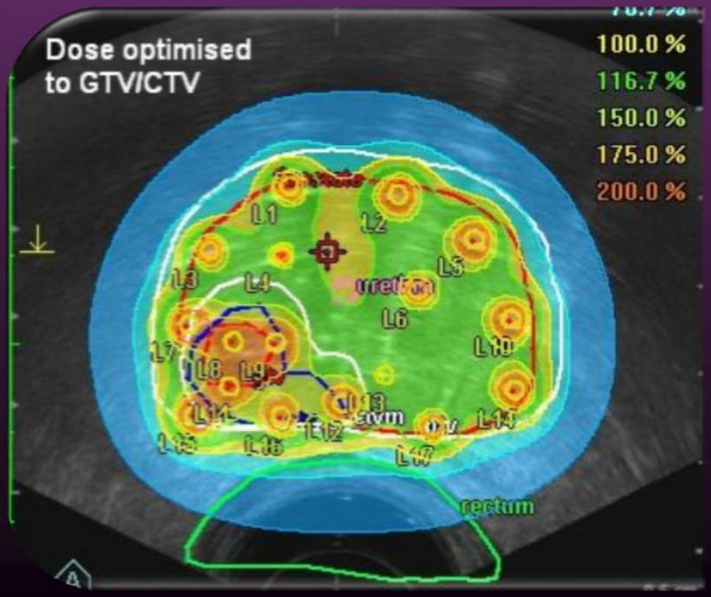
Mp-MRI
for brachytherapy sub-volume boosting



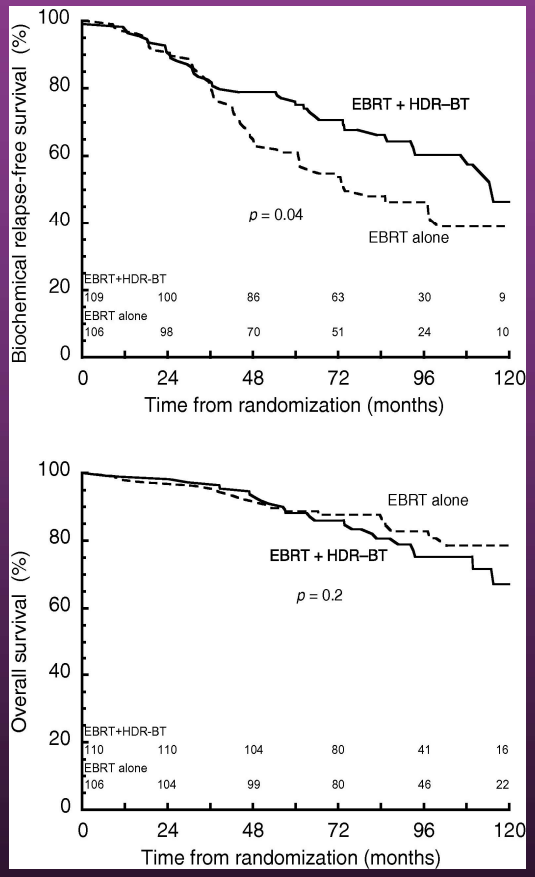








HDR vs. LDR in prostate cancer



Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer Peter J. Hoskin et al. RO 2012; 103(2):217-22.

May be radiobiological advantage of HDR over LDR if prostate α/β ratio is low

HDR Equipment already available in most departments and less costly

HDR may have fewer issues with QA: mis-placement of LDR seeds results in poor quality implants

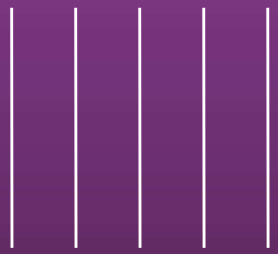
Toxicity profile may be more favourable (shorter duration)

Interstitial brachytherapy dosimetry: Paris system

- Developed for Iridium wire or hairpins
- System defines permissible geometry
- System defines method of calculating dosimetry

Implant rules

1. Sources should be straight and parallel



No crossing sources

2. Sources should be of equal length

3. Equal separation between sources. Separation may be between 5mm and 20mm.

Implant rules (cont.)

4. In cross section, sources should follow the following patterns.

Single plane

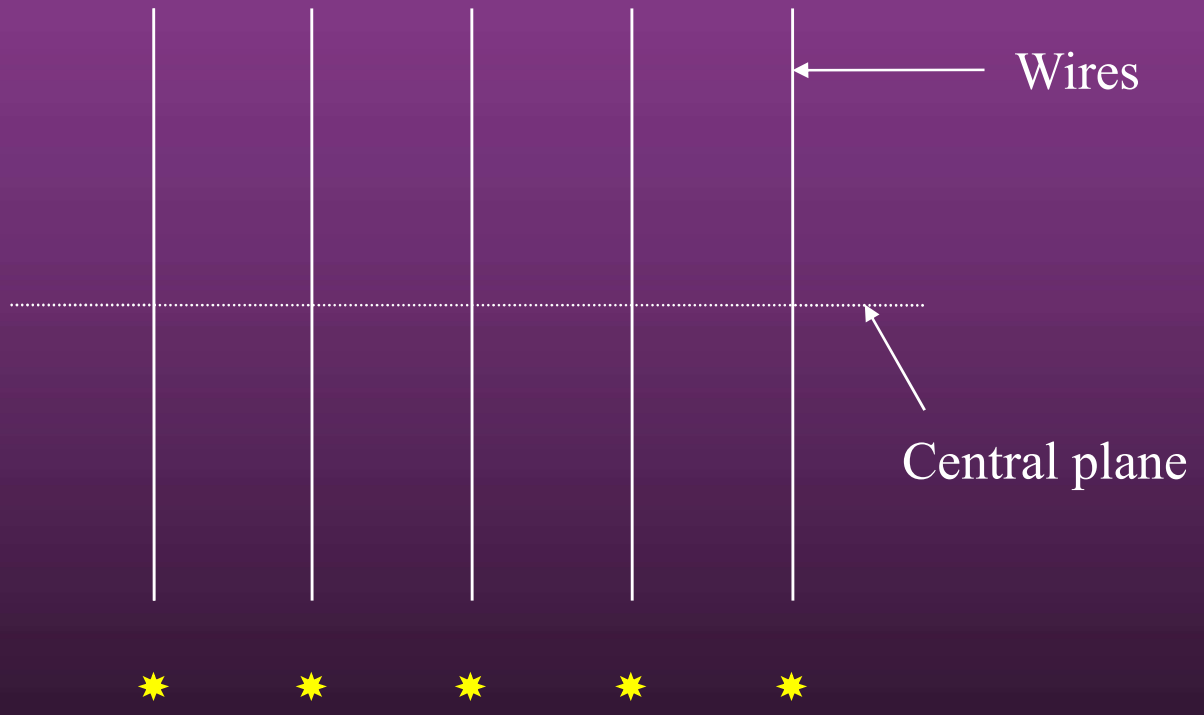
Double plane

Triangles

Squares

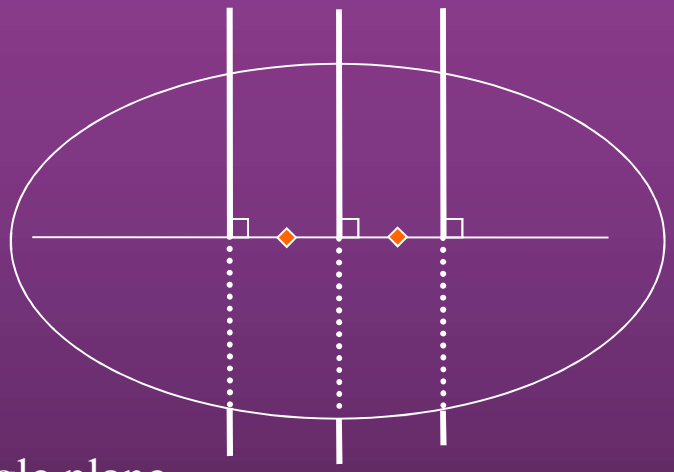
Paris system calculation

1. Dosimetry is calculated on the central plane

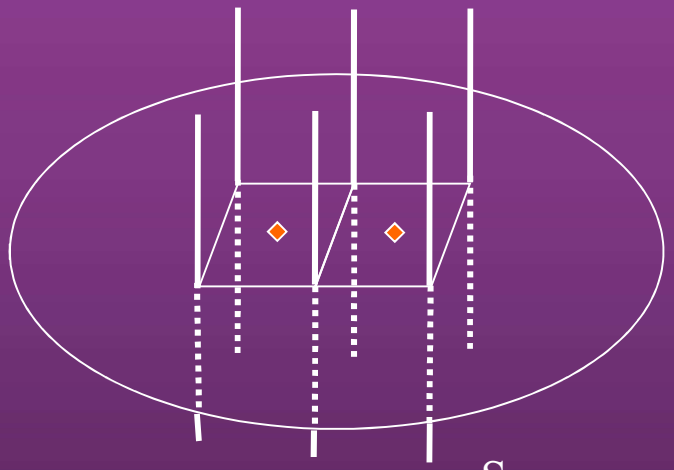


2. We define a set of dose points (Basal Points) on the Central plane.

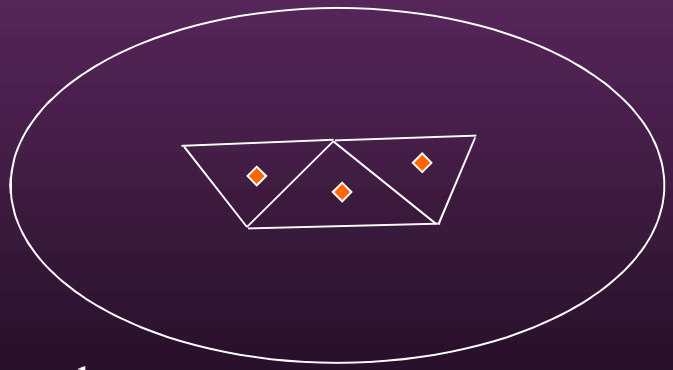
Geometry of Paris implants and basal dose points.



Single plane



Square plane



Triangular plane

◆ Basal dose points

Paris system calculation (cont.)

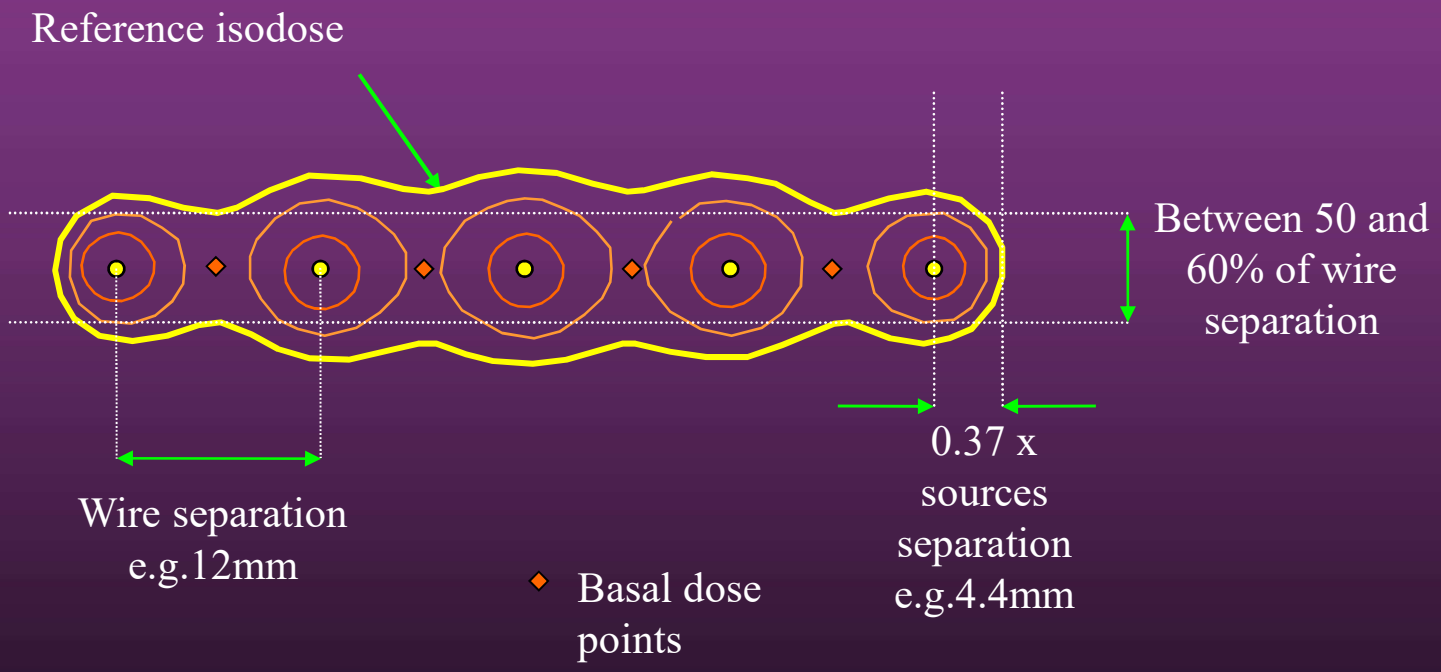
3. Calculate the doserate at each Basal Point

4. Calculate the mean of the individual Basal Point Doserates (known as the Basal Doserate)

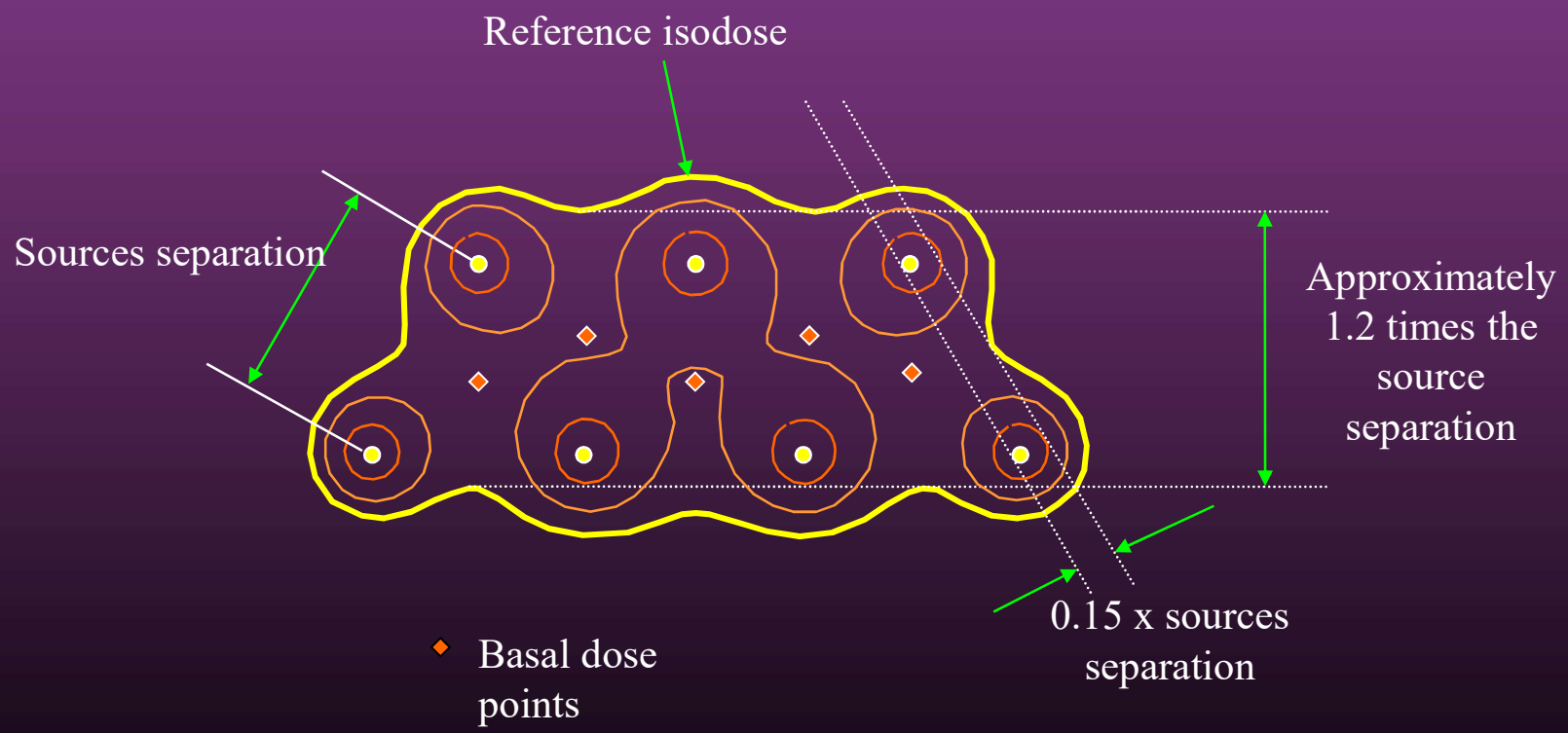
5. Calculate 85% of the Basal Doserate (known as the Reference Doserate). This isodose was chosen for clinical reasons – best compromise between good coverage and keeping hotspots small

6. Calculate the treatment time based on the Reference Doserate and the dose required

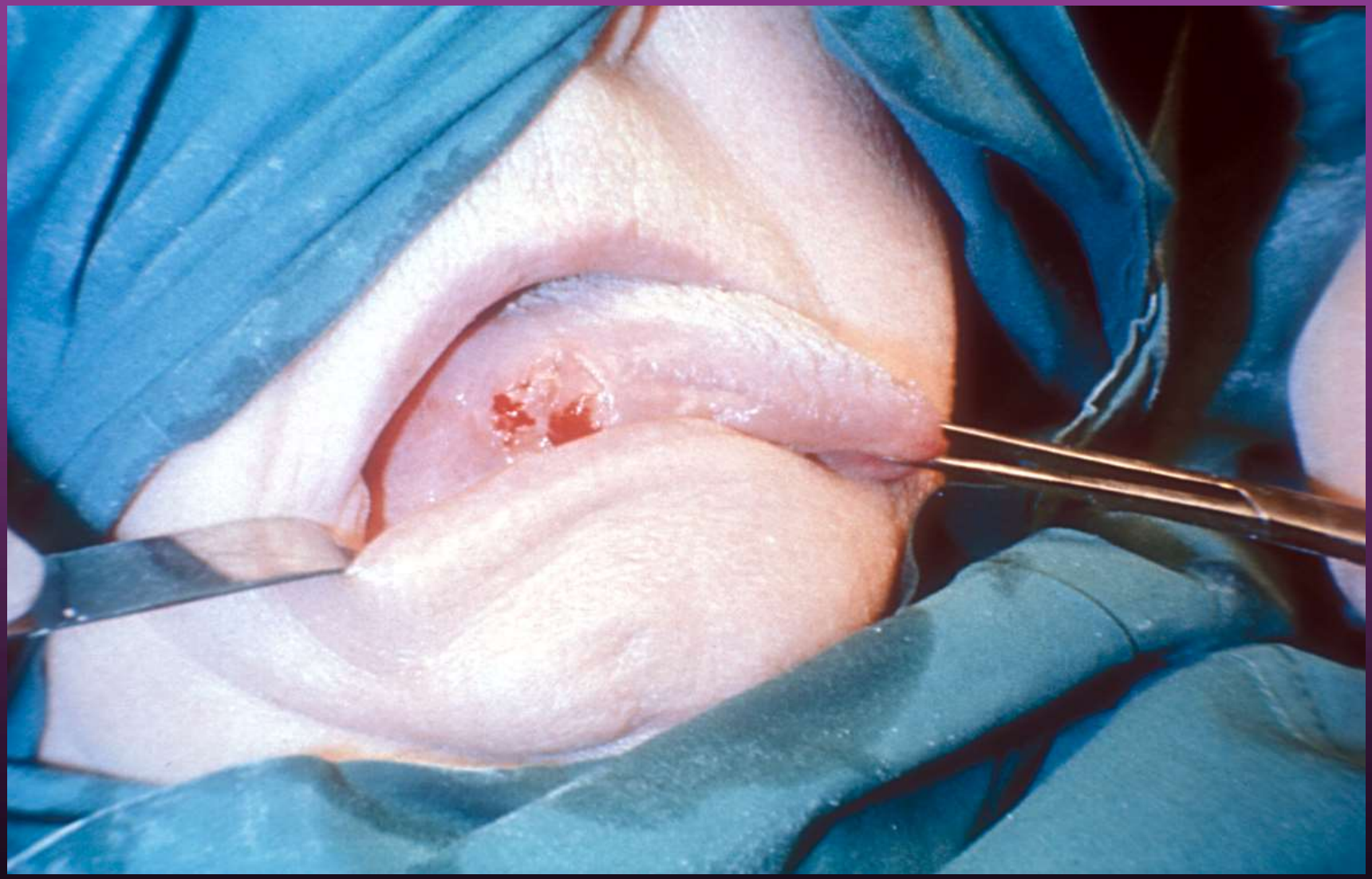
The dimensions of the treated volume and margins for a single plane implant



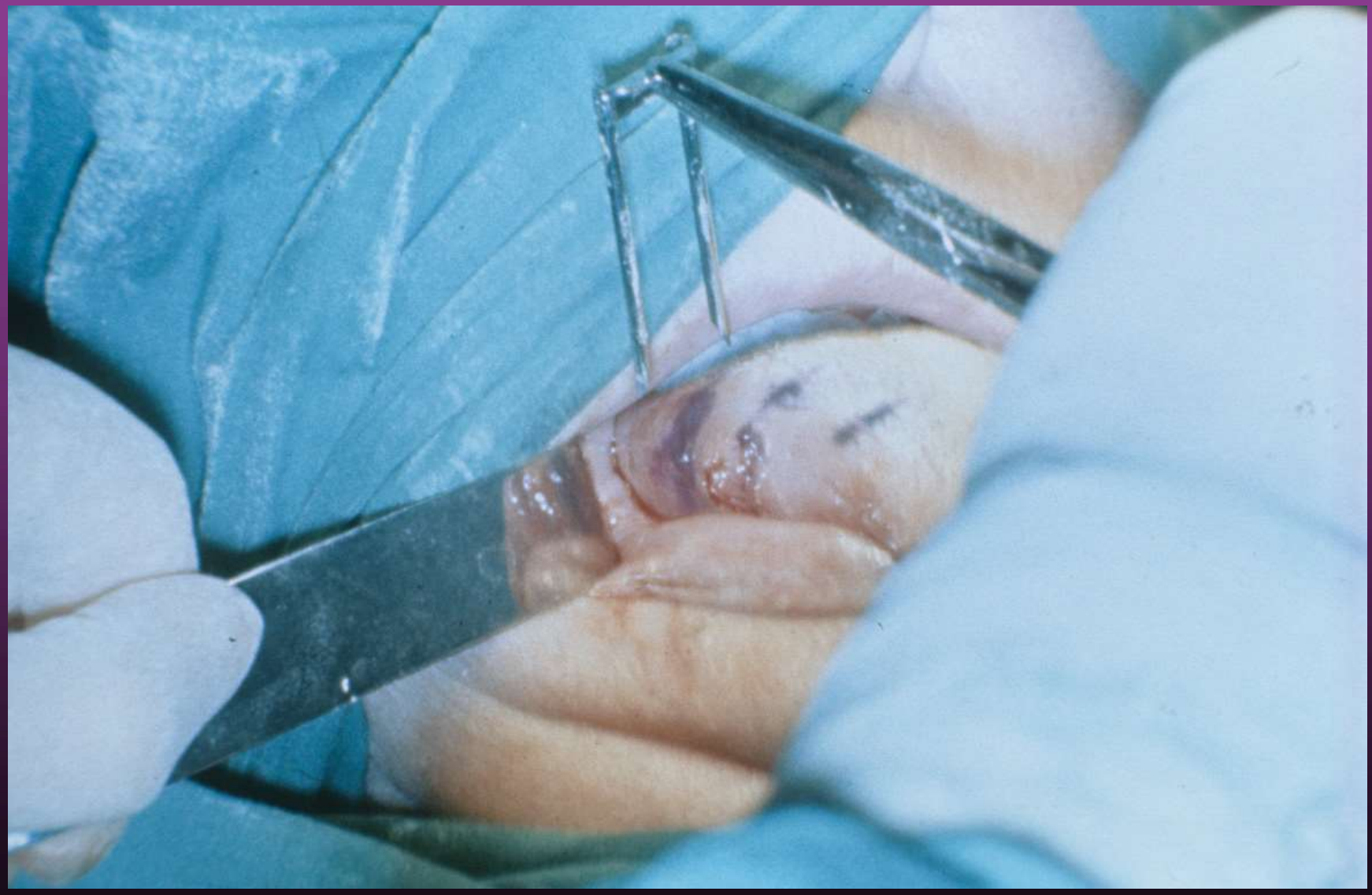
The dimensions of the treated volume and margins for a triangular implant



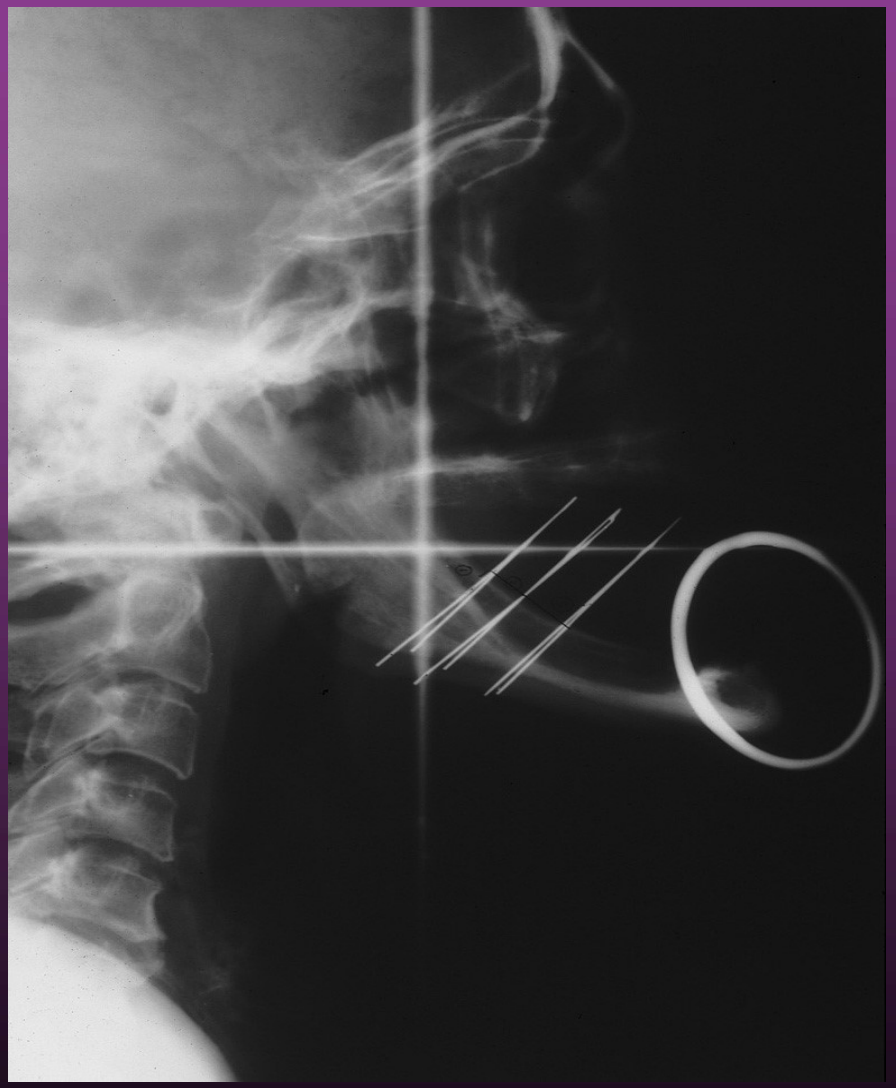
Squamous cell cancer of the lateral border of the tongue



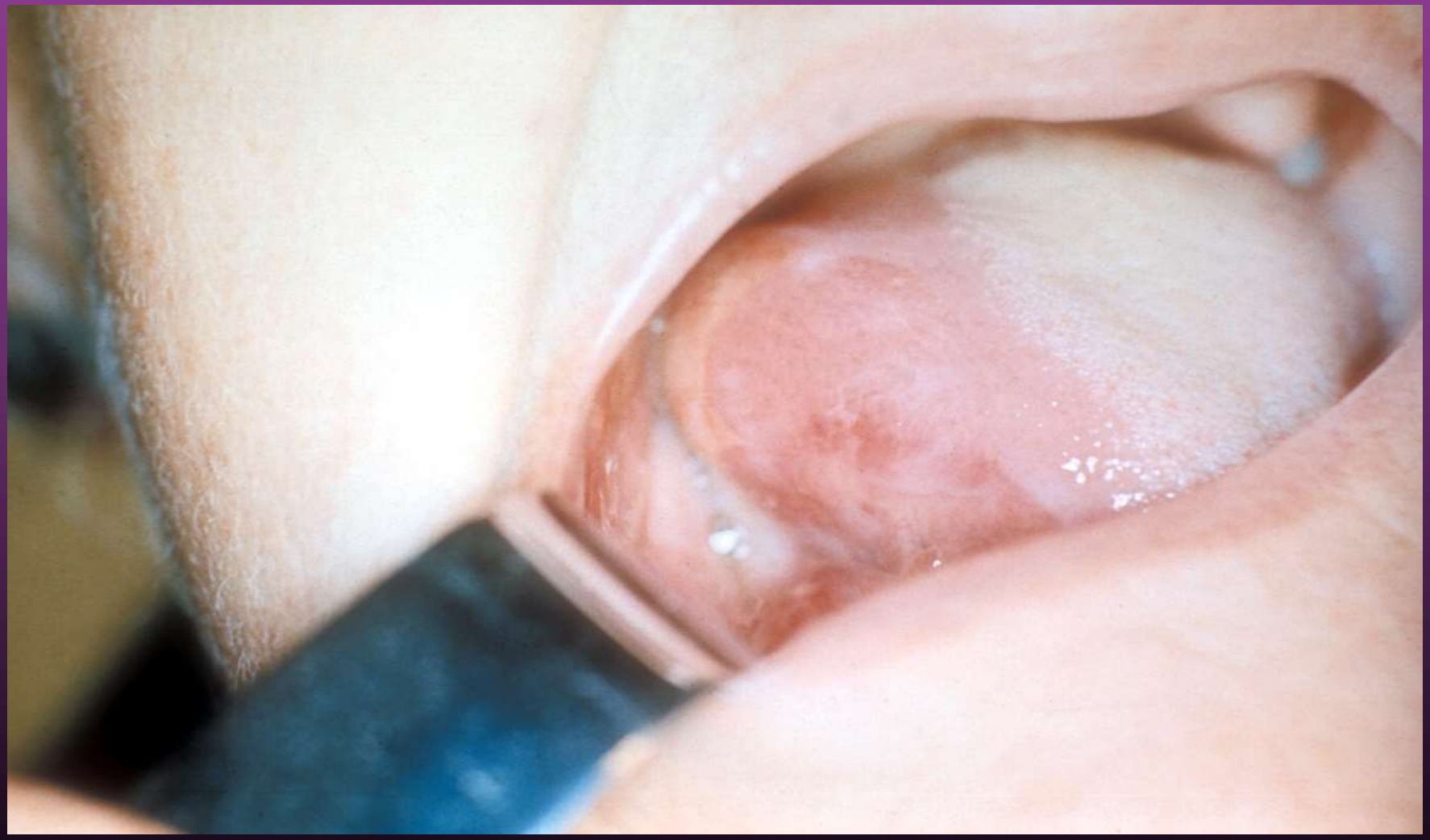
Hairpin gutters inserted into the tumour



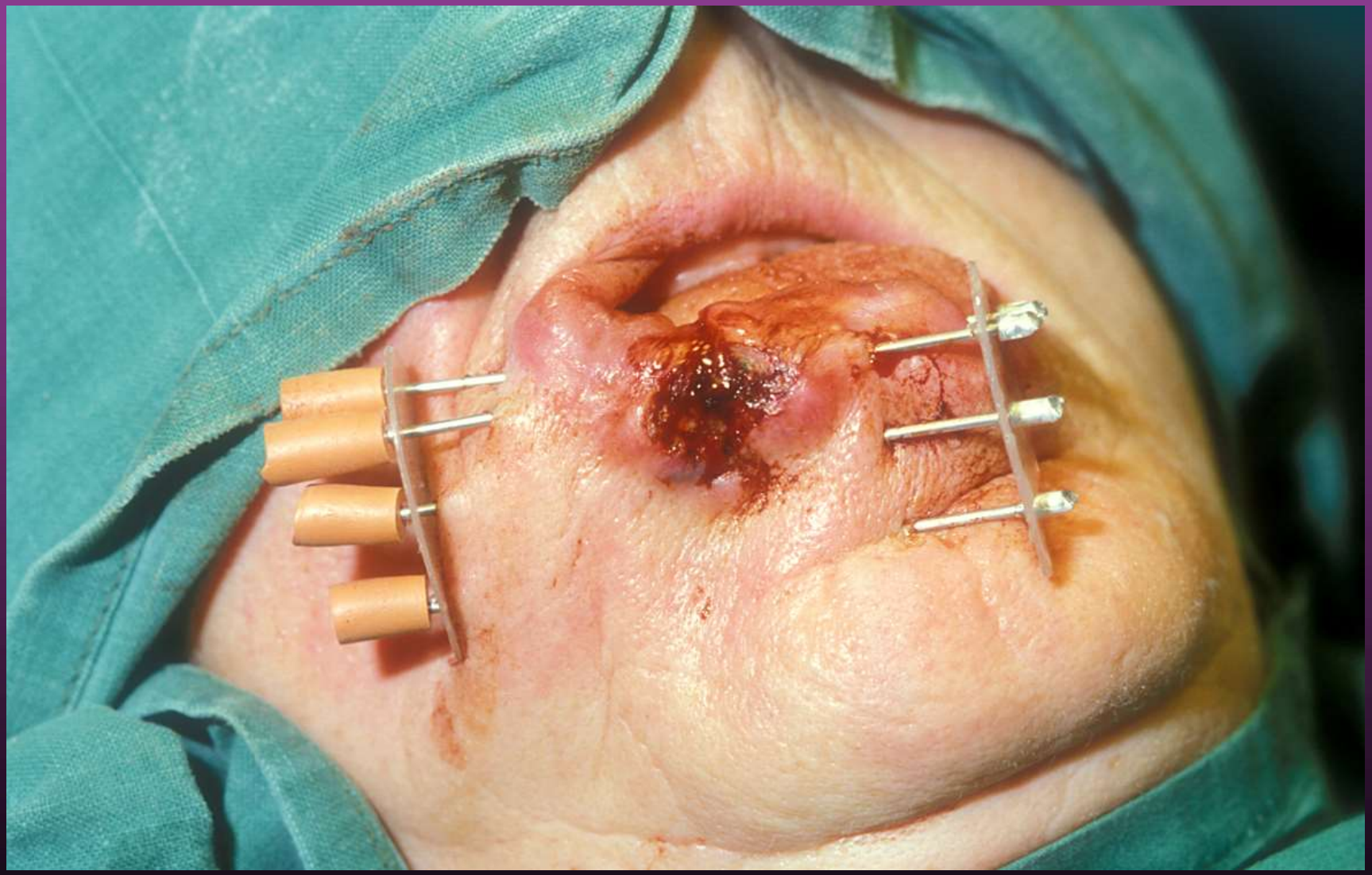
X-ray taken to check actual hairpin position matches that planned



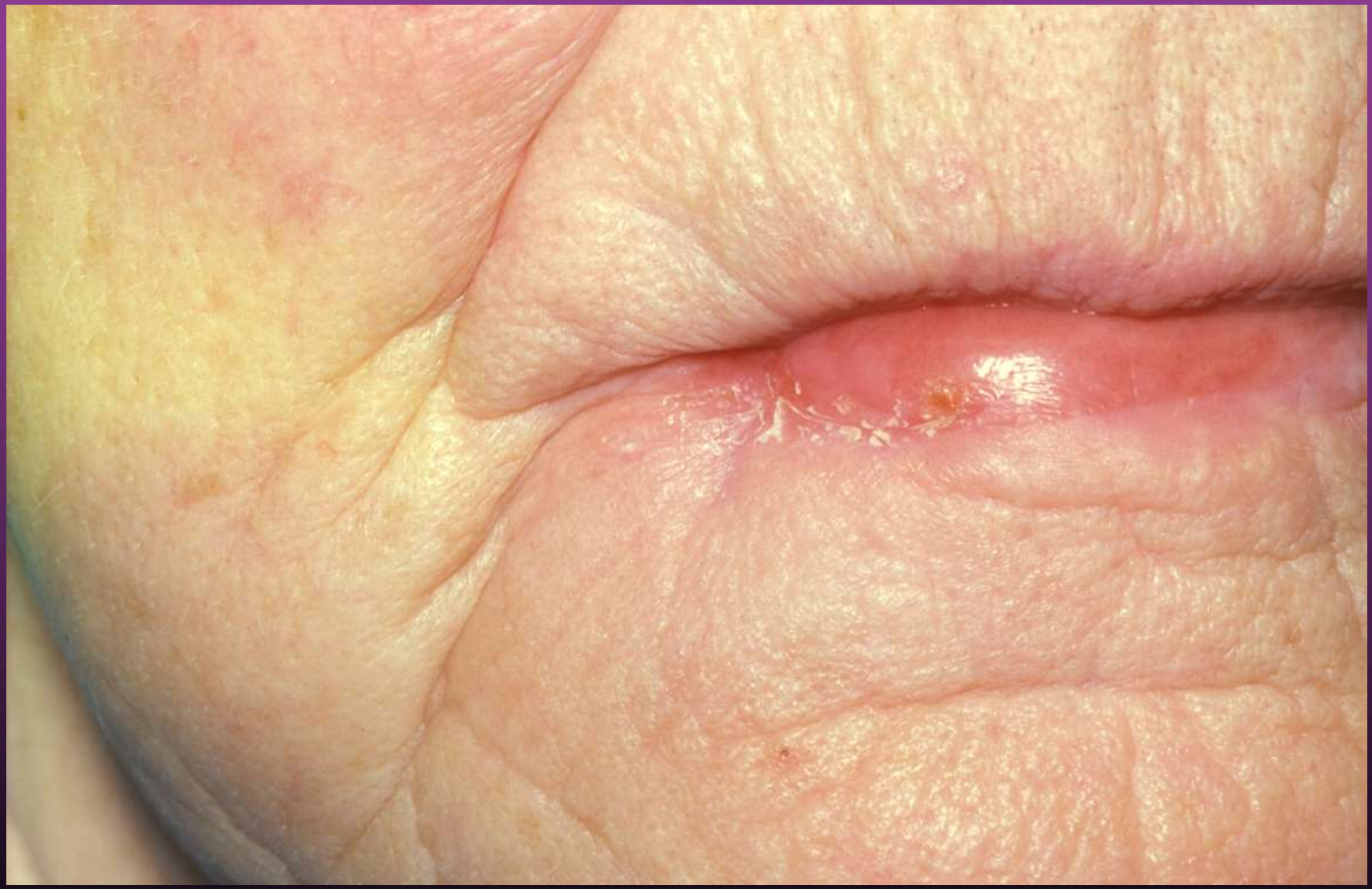
Long-term result: complete tumour response with preservation of tongue



Cancer of lip with metal needles containing ^{192}Ir wire in situ



Long term tumour control with excellent cosmesis



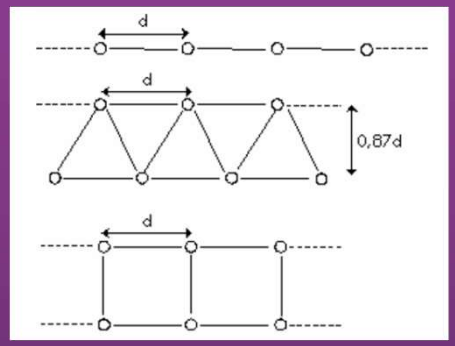
Partial Breast Irradiation: BrachytherapyTechniques

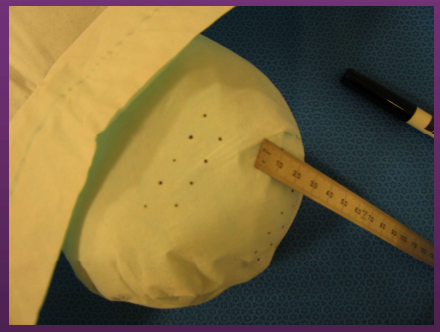
- Interstitial brachytherapy
  - LDR/ PDR/ HDR
- Intra-operative radiotherapy (IORT)
  - INTRABEAM TARGIT
  - ELIOT (Electron intra-operative therapy)
  - Balloon system: MammoSite

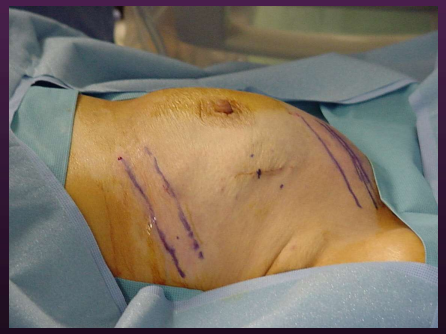
Breast Interstitial Brachytherapy

- Depending on the volume to be covered, 1, 2 or 3 planes are drawn on the patient's skin, laterally and medially to the area to be implanted

- Planes are separated by a ~ 1.5 cm- 2 cm distance (Based on the Paris system) planned site of needle insertion is drawn, with an average distance of 1.5 cm in between markings, using a triangular pattern.





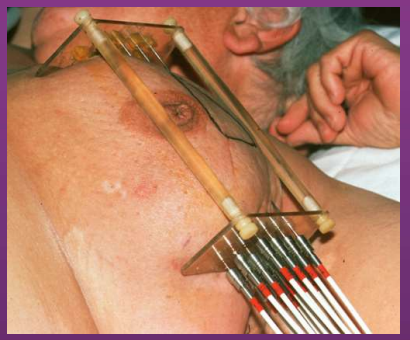


Courtesy Dr.Arthur

Breast Interstitial Procedure

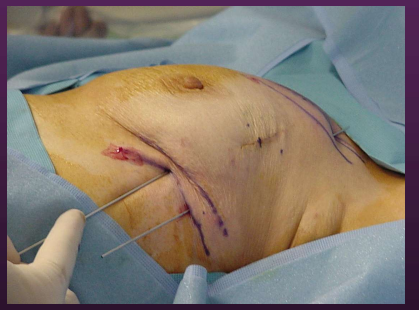
Insertion of trocars under U/S guidance

- Technique
  - Template-guided
  - Free hand technique
- Trocars are inserted in an orderly fashion
  - Beginning with the deepest plane and then proceeding towards the more superficial planes
- Particular care has to be taken with deep-seated needles in order not to puncture the thoracic wall/pleura
  - Latero-medial orientation is preferred



Template-guided Technique

Courtesy Dr.Arthur



Free hand Technique

Courtesy Dr.Arthur

Is multi-catheter interstitial brachytherapy optimal technique for APBI?

- Last decade increased interest in Accelerated Partial Breast Irradiation (APBI)
- In low risk patients treating the tumour bed alone may reduce SE without increasing local recurrence
- Fewer treatments and shorter overall treatment times
- Studies using EBRT have shown increased local recurrence

GEC-ESTRO APBI interstitial brachytherapy RCT

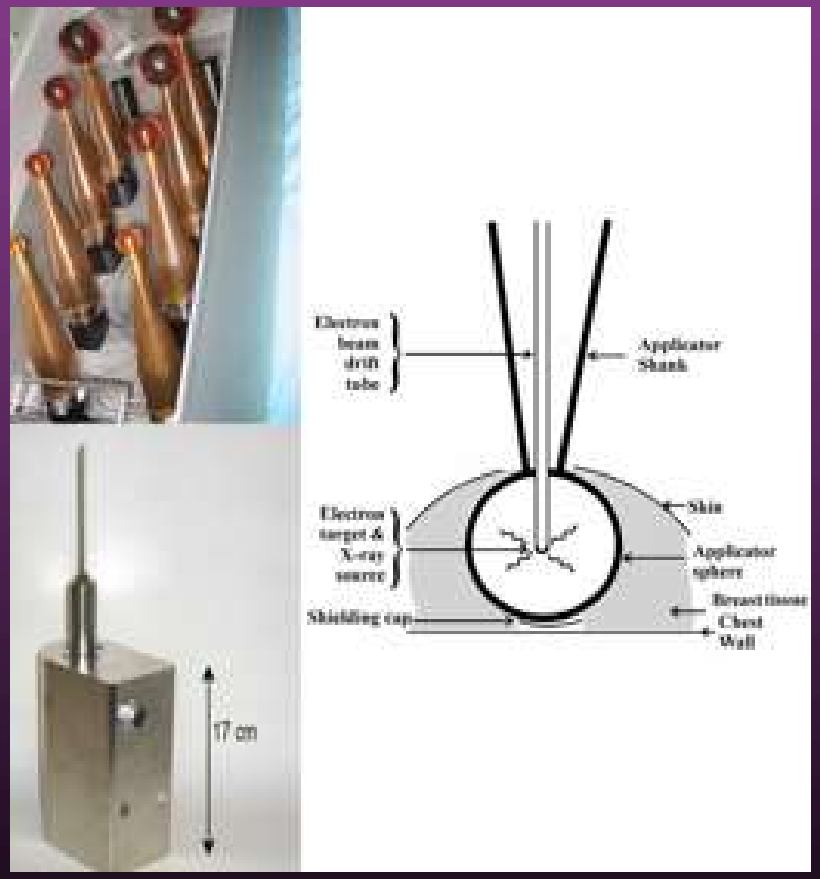
- Phase III RCT involving 16 European centres
- 1184 patients with low risk invasive or DCIS
  - randomised to whole breast or APBI using interstitial multi-catheter techniques delivered in 4-5 days post-op
- 5 year local recurrence rates
  - APBI 1.44% (95% CI 0.51-2.38)
  - Whole breast 0.92% (95% CI 0.12-1.73)
- No significant difference in 5 year late toxicity
- Brachytherapy non-inferior to whole breast EBRT

- *Strnad V et al. Lancet 2016:387 (10015):229-38.*

Intra-operative electrons: ELIOT trial

- ELIOT system : single dose 21Gy intra-operative electrons immediately post-operatively pioneered in Milan
- RCT of breast EBRT vs. ELIOT shows higher local cancer recurrence with ELIOT
  - EBRT 5 year recurrence 0.4%
  - ELIOT 5 year recurrence 4.4%
- Only recommended in clinical trials with small tumours
- Veronesi et al. Lancet Oncology (2013) 14: 1269

Intra-operative KV: Intrabeam TARGIT



- Developed in UCL
- Minature mobile X-ray source (Max 50kV)
- Spherical applicator with an isotropic distribution
- Closed cavity
- Eliot system not isotropic and needs open dissection of cavity

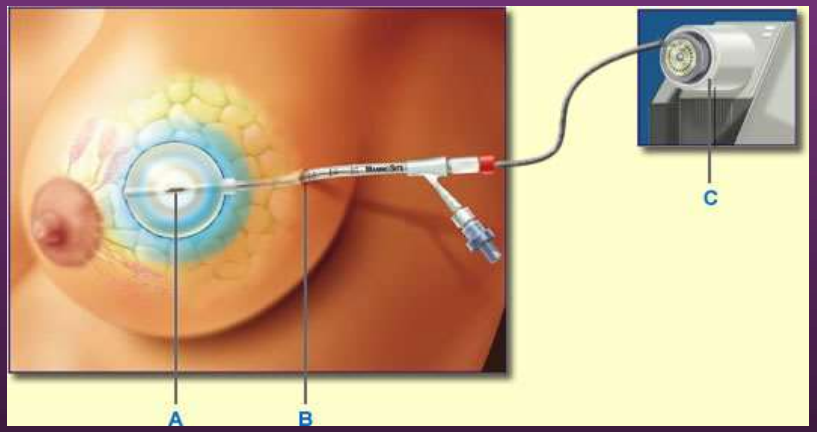
TARGIT clinical trials

- Phase 3 RCT compared single 20Gy TARGIT with whole breast irradiation
- Over 3,500 patients recruited from 33 centres
- Entry if > 45 years and solitary cancer < 3.5cm diameter
- Additional EBRT given in 1 in 5 if histology more adverse (risk stratified approach)
- Recurrence 3.3% TARGIT vs. 1.3% EBRT
- Controversy about statistical analysis and interpretation

Vaidya et al. Lancet (2014) 383: 603-13

Breast treatments using Mammosite™

- Single balloon (round or oval) catheter inserted into the tumour cavity at op or under US guidance post-op
- Inflated to fill cavity
- Attached to after-loader to deliver treatment
- CTV tumour bed +1cm
- 34Gy/10# over 5 days
- Newer applicators with 5-11 catheters and vacuum ports



A: Balloon catheter

B: Applicator shaft

C: After-loader with ^{192}Ir source

Features of modern brachytherapy

- Excellent dose conformality to tumour with avoidance of OAR allows dose escalation beyond that achieved with EBRT alone
- Image Guided Brachytherapy (IGBT) using MR is gold standard in cervical cancer
- Increasing evidence from clinical trials that IGBT in addition to EBRT improves patient outcomes in locally advanced cervix and prostate cancer
- IGBT now being used for cancers of vagina and vulva

Acknowledgements

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- Carolyn Richardson
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- Rachel Cooper

Radiation Protection

Silvia Molinelli
Medical Physics Unit, CNAO - Pavia, Italy

Physics for Modern Radiotherapy
Bucharest, Romania - 4 - 8 June 2017

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Contents

- Radiation Effects
- RP system → Radiation Exposure
- Risk mitigation → Proactive Methods
- RP Strategies → Shielding calculation
- Measurement and quantification

Radiation Effects (ICRP60 – 1991)

• **Somatic:** they affect the health of the irradiated person. Mainly different kinds of cancer (leukemia is the most common, with a delay period of 2-5 years, but also colon, lung, stomach cancer…).

• **Hereditary:** (genetic) affect the health of the offspring of the irradiated person. Mainly mutations that cause malformation of any kind.

• **Antenatal:** somatic and hereditary; expressed in the foetus (more sensitive than the adult), in the live born or descendants. The type of effect depends on the time of irradiation and development: abortion-mental retardation-malformation → threshold dose. Cancer risk similar to that following irradiation in early childhood. (ICRP 103)

Radiation Effects: Time-Dose (ICRP60 – 1991)

- **Deterministic:** threshold for effect → below, no effect; above, certainty, and severity increases with dose. Acute and late effects, clinically attributable in the exposed individual.

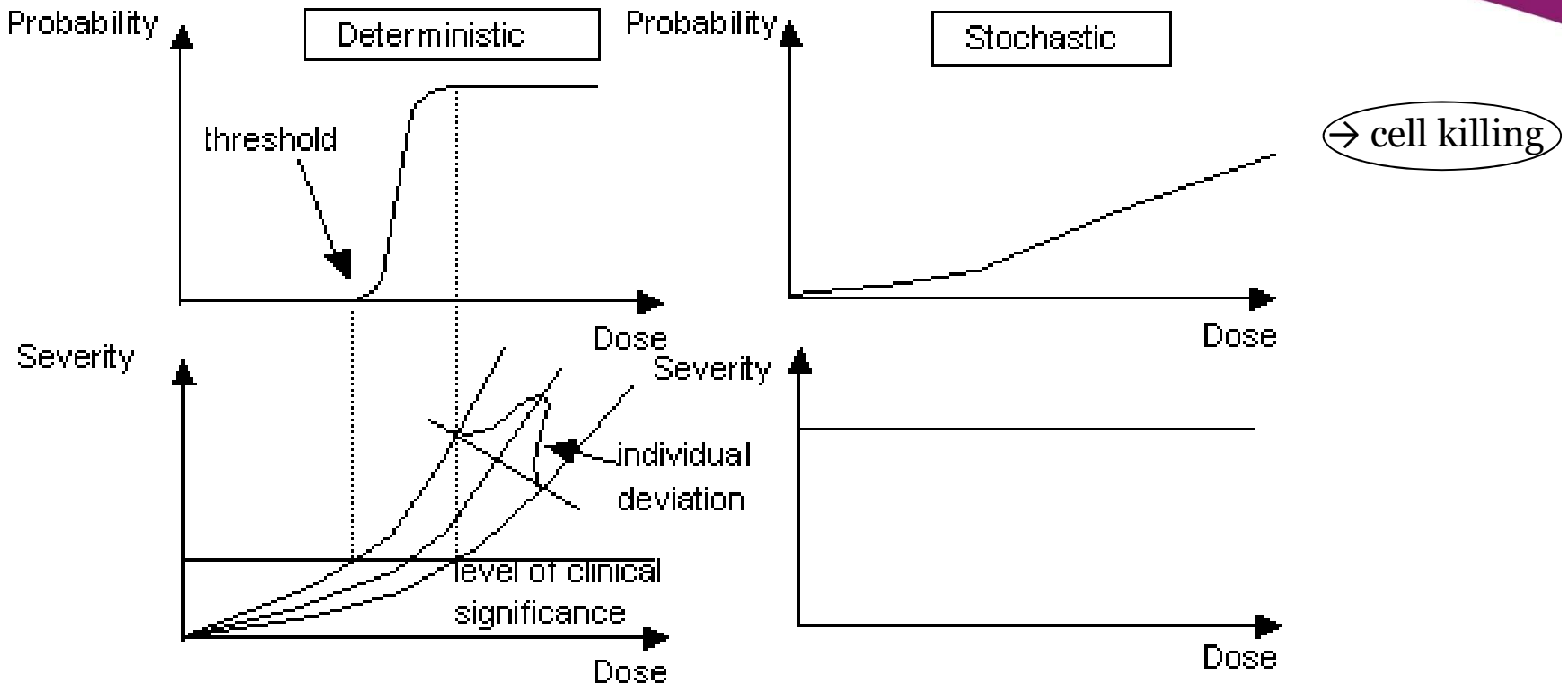
- **Stochastic:** probability of effect related to dose, down to zero (?) dose. Expressed after a latency period, epidemiologically attributable in large populations.

Two objectives ICRP reports 73 and 86

Radiotherapy: deliberately uses radiation on patients to produce **deterministic effects** (tumor cell kill) - in this context some deterministic effects and stochastic effects are accepted (= ***side effects***)

Radiation protection: to manage and control exposures to ionizing radiation to: 1) prevent and minimize the risk of **deterministic effects** which are NOT intended: accidental medical exposure and 'unacceptable' radiation effects to the patient (= ***complications***) due to mistakes or suboptimal irradiation practice; 2) minimize the risk of **detrimental effect** to others; 3) reduce the probability of **stochastic effects** to the extent reasonably achievable

Deterministic Stochastic



- Mainly due to cell killing
- Have a dose threshold (Gy)
- Specific to particular tissues
- Severity of harm is dose dependent

- Due to cell changes (DNA) and proliferation towards a malignant disease
- Severity independent of the dose
- No dose threshold
- Probability of effect increases with dose

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Deterministic effects → Tissue reactions (ICRP 2007 – 2012)

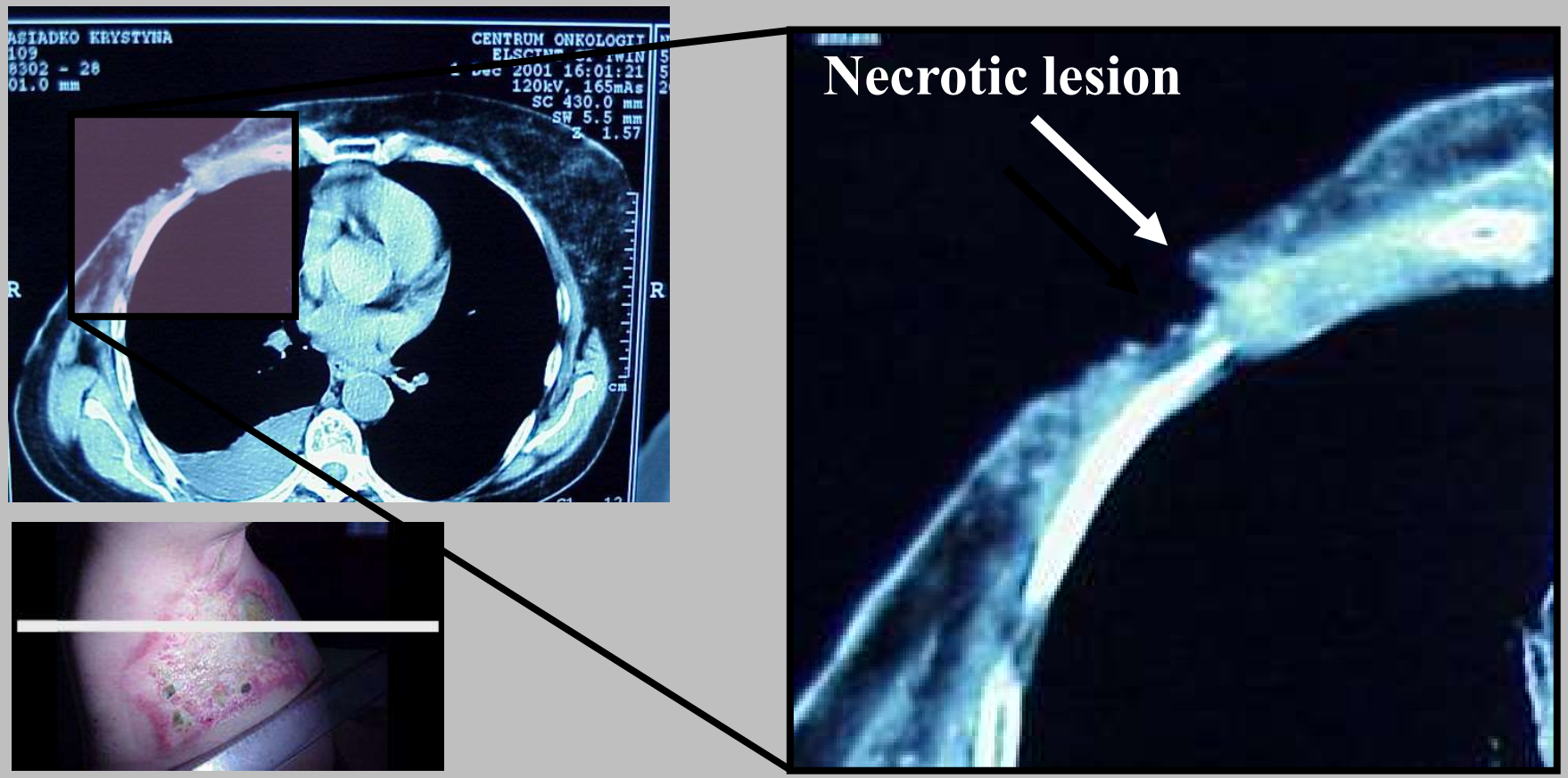
• **ICRP 60 – 1991** → Deterministic: casually determined by preceding events.

• **ICRP 103 - 2007** → They are not necessarly PREdetermined and can be modified after irradiation by the use of various biological response modifier. Stochastic are presumed to be unicellular in origin while **Tissue /Organ reactions** are due to injury in a population of cells.

• **ICRP 60 – 1991** → the emphasis was on radiation-induced cell killing in relation to tissue damage.

• **ICRP 118 - 2012** → 1) the cytotoxic effects of radiation cannot explain all tissue reactions (especially late effects - fibrosis); 2) non-lethal effects of radiation on cells and tissues, with the resultant disturbances in molecular cell signalling, also play a crucial role in determining tissue response to radiation; 3) more information has become available regarding the effect of biological response modifiers in mitigating tissue reactions, which has the effect of modifying threshold doses.

Tissue reactions (Skin) ICRP 118 - 2012



Over-exposure due to accelerator interlock failure, Poland 2001

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Radiation Effects

cell survives
lesion
complexity

stochastic effects
long latency time

Tissue reactions
short occurrence time
relevant to radiotherapy
effects on embrio-fetus

Somatic → cancer induction

Germ line → hereditary effects

Foetal → developmental effects

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Timing of events

TIME (sec)

10^{-15}		Energy deposition	PHYSICAL INTERACTIONS
		Excitation/ionization	
10^{-12}		Initial particle tracks	
10^{-9}		Radical formation	PHYSICO-CHEMICAL INTERACTIONS
		Diffusion, chemical reactions	
10^{-6}		Initial DNA damage	
10^{-3}	1 ms	DNA breaks / base damage	
10^{0}	1 second	Repair processes	BIOLOGICAL RESPONSE
		Damage fixation	
10^{3}	1 hour	Cell killing	
	1 day	Mutations/transformations/aberrations	
10^{6}		Proliferation of "damaged" cells	MEDICAL EFFECTS
	1 year	Promotion/completion	
10^{9}		Teratogenesis	
		Cancer	
	100 years	Hereditary defects	

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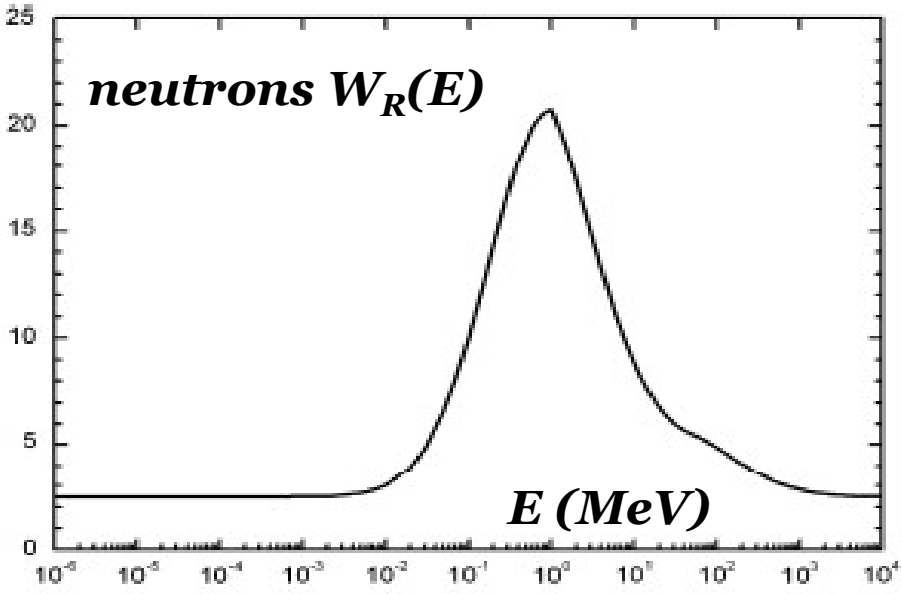
Equivalent Dose H = D x w_R Sievert (Sv); (rem = 0.01 Sv)

Radiation Weighting Factors (**ICRP 60 ->103-116**)

Type of Radiation	W_R
beta	1
protons	2
Alpha-fission frag-heavy ions	20
X Rays	1
gamma rays	1
neutrons <10 keV	5
neutrons (10 keV – 100 keV)	10
neutrons (100 keV – 2 MeV)	20
neutrons (2 meV – 20 MeV)	10
neutrons >2 MeV	5



$$w_R = \begin{cases} 2{,}5 + 18{,}2\, e^{-[\ln(E_n)]^2/6}, & E_n < 1\,MeV \\ 5{,}0 + 17{,}0\, e^{-[\ln(2E_n)]^2/6}, & 1\,MeV \le E_n \le 50\,MeV \\ 2{,}5 + 3{,}25\, e^{-[\ln(0{,}04E_n)]^2/6}, & E_n > 50\,MeV \end{cases}$$

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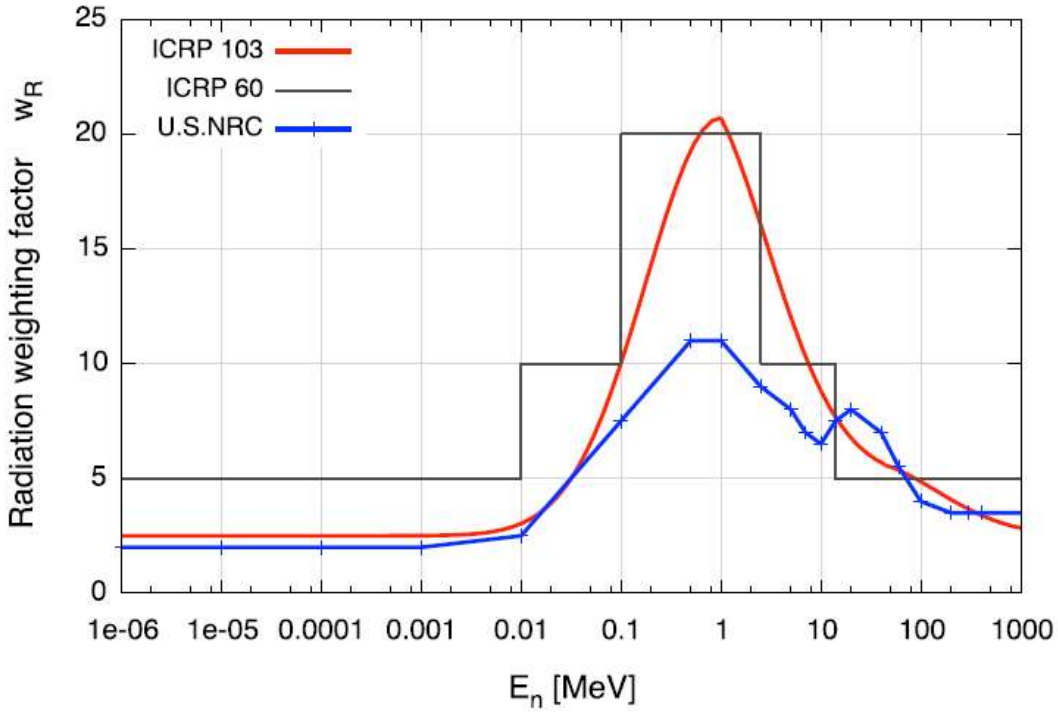
Neutrons w_R

- Radiation quality factors established based on epidemiological studies and radiobiological measurements

- Values change based on standard considered, but a common maximum for 1MeV



ICRP103 w_R in funzione di E_n

$$w_r = \begin{cases} 2,5 + 18,2 \cdot e^{\frac{-[ln(E_n)]^2}{6}} & E_n < 1 \\ 5 + 17,0 \cdot e^{\frac{-[ln(2E_n)]^2}{6}} & 1 \le E_n \le 50 \\ 2,5 + 3,25 \cdot e^{\frac{-[ln(0,04E_n)]^2}{6}} & E_n > 50 \end{cases}$$

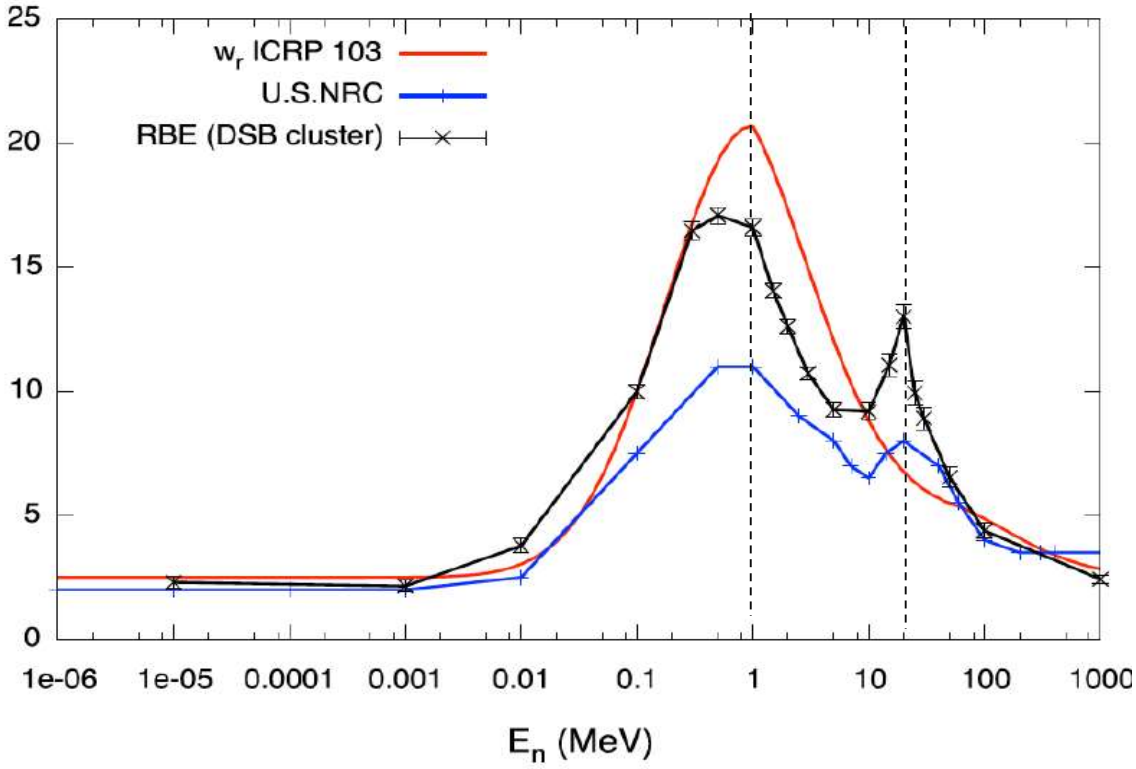
U.S.NRC] NRC Regulations Title 10, Code of Federal Regulations: 10 CFR. §20.1004

Neutrons w_R

• Changing the neutron energy, the accelerated products and how they induce the biological damage change
• The balance between these two factors (particle spectrum and LET) is the origin of the effectiveness variation of neutrons (E)

• 1 MeV neutrons mainly accelerate protons which deposits energy close to their max LET

• Contribute of heavier nuclei accelerated by neutrons increases with energy with a maximum around 20 MeV



The origin of neutron biological effectiveness as a function of energy
G. Baiocco *et al* 2016, *submitted*

Effective Dose $E = \Sigma_{\text{all organs}} (w_T H) = \Sigma_{\text{all organs}} (w_T w_R D)$

Tissue Weighting Factors (**ICRP 60 -> 103 - 116**)

	Tissue weighting factor (w_T)	Σw_T
Bone marrow (red), colon, lung, stomach, breast, remainder tissues*	0.12	0.72
Gonads	0.08	0.08
Bladder, oesophagus, liver, thyroid	0.04	0.16
Bone surface, brain, salivary glands, skin	0.01	0.04
	Total	1.00

* Remainder tissues: adrenals, extrathoracic region, gallbladder, heart, kidneys, lymphatic nodes, muscles, oral mucosa, pancreas, prostate, small intestine, spleen, thymus, and uterus/cervix.

- Tissue weighted sum of equivalent doses in all specified organs and tissues of the body
- $\mathbf{w_T}$ is the tissue weighting factor by which the equivalent dose in an organ or tissue T is weighted to represent the age- and sex-averaged relative contribution of T to overall radiation detriment from stochastic effects (ICRP, 1991)
- Effective dose is a quantification of risk for **stochastic** effects

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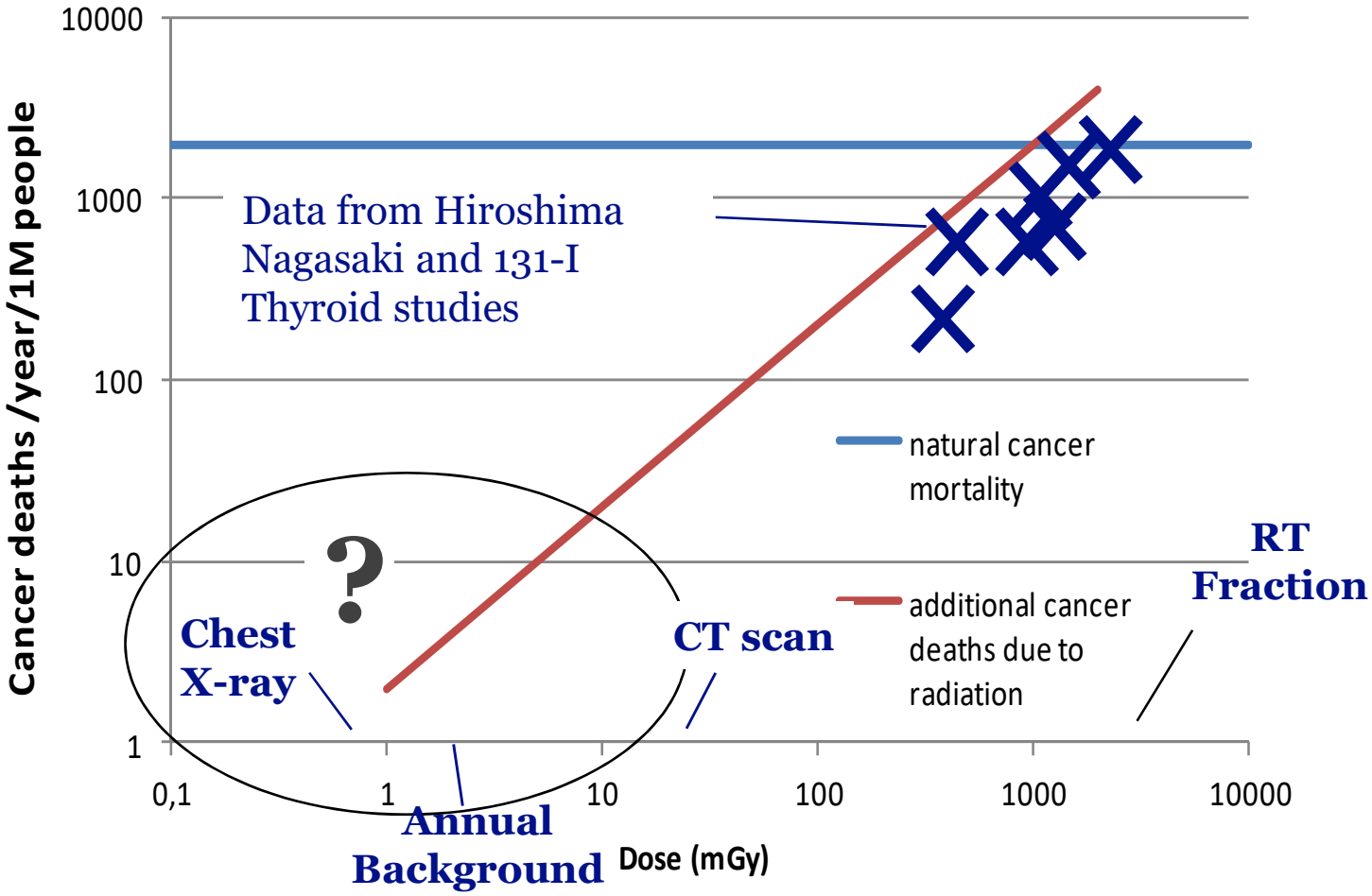
Epidemiology of Cancer Risks



LIFE SPAN STUDY

Only ~5% of 7800 deaths from cancer or leukaemia due to radiation

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Linear No Threshold (LNT) hypothesis

It is generally assumed that even very small doses of ionizing radiation can potentially be harmful

Persons must be protected from ionizing radiation at all dose levels

How?

ICRP publication (60 – 1991 → 103 - 2007)

- Weighs all existing data to arrive at quantitative recommendations for risk, detriment, dose and dose rate weighting factors
- Considers exposure to humans only (→ environmental protection?)
- Considers exposure in three categories:
  occupational, medical, public

- Practice (Intervention): any human activity that introduces or extends (reduces) sources of exposure or exposure pathways (→ exposure situations: planned, emergency, existing situations)

ICRP publication 26 - 1977

The recommended system of radiation protection is based upon 3 principles:

- Benefit of a decision that alters the radiation exposure situation must offset the radiation detriment (**Justification)**
- Exposures (number of people and magnitude of doses) and likelihood of exposure should be kept as low as reasonably achievable (ALARA), technical, economic and social factors being taken into account (**Optimization of protection and safety**)
- Dose limits should be set to ensure that no individual faces an unacceptable risk in normal circumstances from planned exposure situations other than medical (**Limitation of doses**[*])

[*]No dose limitation applies to medical exposure - however, both justification and optimization are essential. Limits need to be applied for public and occupational exposures.

Justification

Hp

- All, even the smallest exposures are potentially harmful
- No use of ionizing radiation is justified if there is no benefit

Exposure situations should not be authorized unless the benefits are greater than the detriments, taking account of social, economic and other factors

IGRT

Critical organs → < tissue side effects

Critical organs → > **radio-carcinogenic risk factors**

Optimization in the context of RT

- Optimization of the treatment: therapeutic ratio
- Optimization of the diagnosis: Diagnostic Reference Levels- (DRL) → image quality
- Optimization of protection
  - of the staff
  - of the patient
  - of the public

} **Accident prevention**

- Must take into account the resources available - this includes economic circumstances
- Harmonization of the Dose Management System (Standardized procedures)

Major documented accidents in RT 2004 - 2007

Country	approx. dates	patients affected	probable cause
UK	Jan 2006	1	Incorrect manual parameter transfer (+67% MU)
USA	Oct 2007	1	Reversal of images (HFS → FFS)
France	2006 - 2007	145	Inappropriate measuring device for small fields dosimetry 6 pts >5% OAR volume overdose
France	2004 –2005	23	Erroneous calculation of soft wedges 5 deaths – 10 severe complications
USA	March 2005	1	Incorrect IMRT planning (MLC control points not saved →3 frs of 13 Gy)

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Dose limits recommended in ICRP 60

Exposure	Limits on effective dose	Limits on annual equivalent doses
Occupational exposure	20 mSv per year averaged over defined 5 years (max 50 mSv over one year)	The lens of the eye: 150 mSv The skin: 500 mSv The hands and feet: 500 mSv

- A dose of 0.5 Gy (new threshold) could readily be exceeded on the basis of the current equivalent dose limit for the lens of the eye of 150 mSv per year.
- **ICRP 2011-2012** recommend a dose limit to the lens of the eye of **20 mSv per year averaged over defined 5 years (max 50 mSv over one year)** for Occupational exposure.
- No new limit has been recommended for **public exposures** to the lens of the eye (**1 mSv/year** was judged adequately protective).

a) No limits are applicable in case of life saving activities.

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Prospective Risk analysis and management

- QM guidelines → monitoring functional performance of RT equipment by measurable parameters (tolerances set at strict but achievable values). **Device focused**
- > complexity of modern RT techniques → dramatic increase in number and sophistication of possible tests and measurements.
- Suitable QA approach that balances patient safety and quality versus resources available based on estimates of clinical outcome, risk assessment, and failure modes. **Process focused**

A method for evaluating quality assurance needs in radiation therapy
AAPM TG-100, Huq et al. 2008 IJROBP 71 (1)

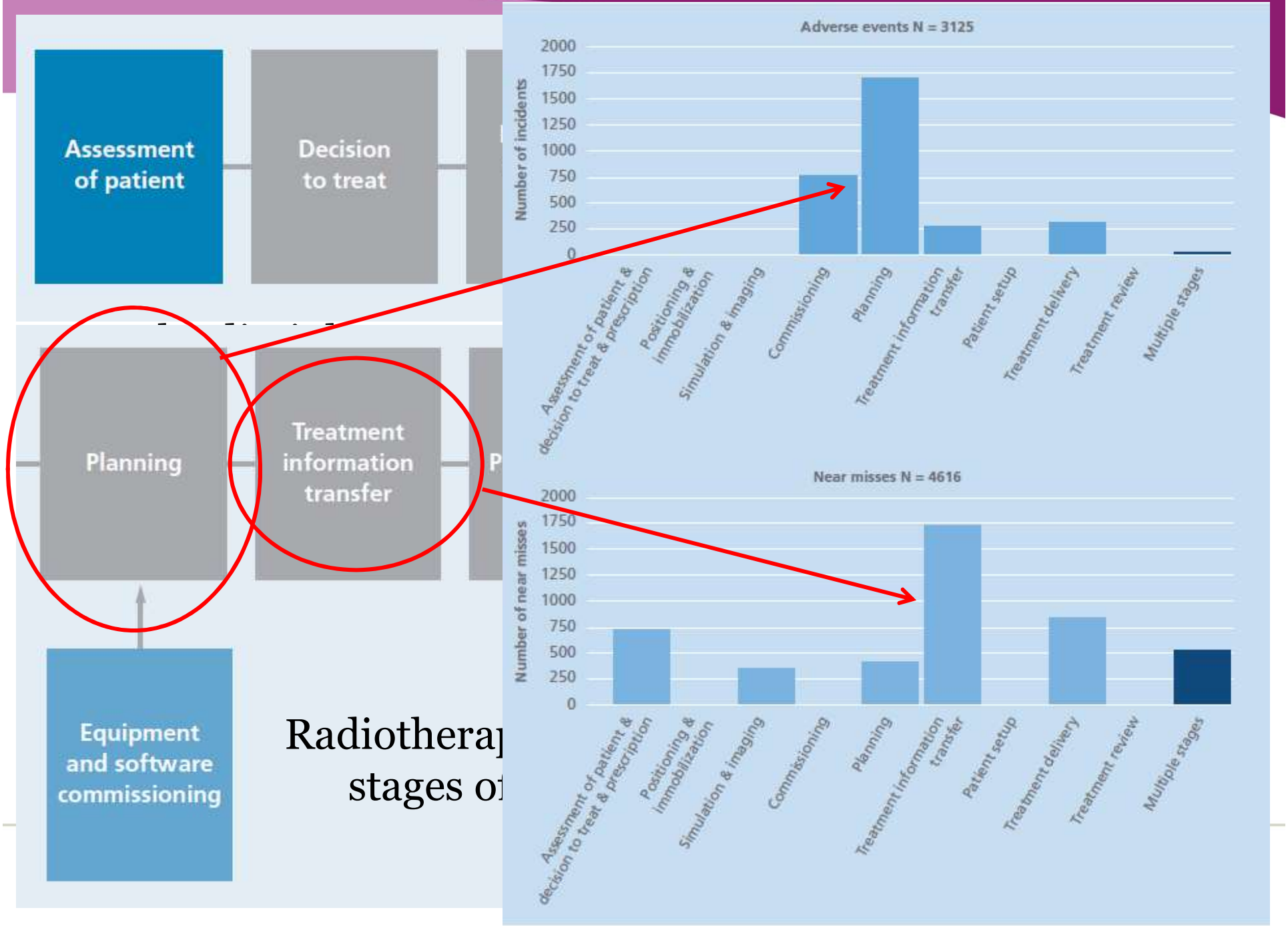
Proactive methods adapted to RT

→ Identification of a list of potential failure events in every step of the radiation therapy process

→ Risk evaluation

→ Provide a risk-informed and rational choice of safety provisions

- Failure mode and effect analysis (FMEA)
- Risk matrix approach
- Probabilistic safety assessment (PSA)



Radiotherap
stages o

FMEA methodology

- Identification of Failure modes→ fault tree → Cause & Effects (Worst case scenario)
- Process control strategies in operation → Prevent causes, detect failures, mitigate severity of the effects
- Judge the effectiveness of the current process control
- Failure modes sorting based on 3 indexes (ordinal scales):
  - Occurrence (O)
  - Severity (S)
  - Detectability (D)
- 1 = low probability, low severity, high detectability
- 10 = high probability, high severity, low detectability

FMEA methodology

Ordinal scales should not be subject to arithmetic operations

- Risk probability number (RPN) = O x S x D
- Risk acceptance threshold RPN < 125
- RPN > 125 and high S value → additional safety measures required with a priority based on
  - expected RPN reduction
  - Feasibility (costs, resources, routine implementation)
  - Define deadlines!
- Check the effect!

Table 2 Application of failure mode and effects analysis for the treatment planning stage in proton beam radiotherapy

Sub-process	N	Potential failure mode	Potential causes of failure	Potential effects of failure	O	S	D	RPN
(I) Selection of the reference CT scan for planning	1	Error in selecting the CT scan (e.g. incorrect patient set up, outdated representation of the anatomy) in case of multiple CT scans	Human error, failure in the communication between operators	Wrong dose distribution/ wrong dose delivery	3	8	4	96
	2	Outdated representation of the anatomy (single CT scan)	Anatomical changes (related to time delay)	Wrong dose distribution/ wrong dose delivery	3	8	8	192
(III) Manual correction of external contour	3	Incorrect external contour definition (body or patient mask countour underestimation, i.e. not fully included in the external contour)	Human error	Wrong dose distribution / wrong dose delivery	4	5	4	80
	4	Failure of object/region identification	Human error	Wrong dose distribution	3	8	4	96
(IV) Delineation of CT artefacts, altered structures, metal implants and manual assignment of specific HU numbers	5	Inaccurate delineation	Human error	Wrong dose distribution	4	6	6	144
	6	Incorrect HU number manual assignment	Human error or lack of documentation from the referring clinicians (e.g. surgeons)	Wrong dose distribution	4	7	7	196
	7	Lack of couch origin of coordinates definition	Human error	Unintended normal tissue irradiated and CTV missing	3	10	3	90

FMEA FFF delivery

TABLE 3. Example FMEA analysis of beam delivery unique to FFF. Per TG-100, a 1–10 scale is used, where Occurrence (O) ranges from 1 (almost impossible) to 10 (almost inevitable), Severity (S) ranges from 1 (minor annoyance) to 10 (lethal), and Detectability (D) ranges from 1 (highly detectable) through 10 (almost impossible to detect until it causes patient harm). The product of O, S, and D denotes the relative risk of that failure mode. Values presented in the table are suggestions only, pooled from authors on this report.

Failure Mode	*O*	*S*	*D*	*Risk Probability Number (product)*
Inaccurate calibration (e.g., error in P_{ion})	2	5	6	60
Failure to account for excessive skin dose	5	6	4	120
Dose problems from low MU segments	3	4	4	48
Inaccuracy of QA devices	4	5	4	80
Wrong beam type selection due to confusing user interface in planning	3	4	4	48
Wrong beam type selection due to confusing user interface in delivery	2	6	3	36
Wrong beam type selection due to incorrect transfer from TPS and/or R&V	2	6	2	24
Use of wedges or other devices for which FFF wasn't commissioned	2	6	4	48
Failure to catch problem during treatment due to fast delivery	3	5	5	75
Calibration error due to chamber placement off-axis	2	5	6	60

Xiao et al. JAMP (16) 2015

FMEA methodology

- Understanding the care process under evaluation and have a semi-quantitative risk estimation and prioritize QA procedures.
- Identification and management of new risks that emerge with the implementation of new tools and technologies.
- Easy to implement, but still needs validity assessment.
- Main problem → use of numerical values to subjectively rank potential failures.
- Errors propagation between different steps not considered.
- Healthcare organization should not solely depend on their FMEA results to prioritize patient safety issues.
- Workers training and procedures.
- A Quality Assurance program is a key element in prevention of accidental exposures.

Shielding NCRP 49-151

- **Aim:** to limit radiation exposure to acceptable levels and optimize protection of staff, patients, visitors and the public
- It is a **3D** problem → wall and ceiling materials and thicknesses - critical areas close: radiology, nuclear medicine
- Different considerations are required for: superficial/orthovoltage X Ray units, simulators, CT, cobalt 60 units, linear accelerators (TBI-IMRT-SRT), Brachytherapy, Hadrontherapy
- 3 steps procedure: i) establishing a design value for the effective dose in the occupied area, ii) estimating the radiation field in the area if there were no shielding, iii) obtaining the **attenuation factor** required to go from ii) to i)

Information required

- **Equipment type**
  - Type, manufacturer, serial number,…
  - Source isotope, activity (date of calibration), air KERMA, ...
  - Radiation quality, Dose rate, Field size
  - Extras: *e.g.* MLC, IMRT, EPID, ...
- **Workload (W)** (Gy/time)
- **Target dose** the dose typically applied to the target in the treatment
- **Use factor** and direction of primary beam **(U)**
- **Distance** to the area of interest **(d)**
- **Occupancy** of area to be shielded: Fraction of time a particular place is occupied by staff, patients or public. Has to be conservative. Ranges from 1 for all offices and work areas to 0.05 for toilets or 0.025 for unattended car parks (NCRP 151) **(T)**
- **Limit value** in area to be shielded **(L)** (Sv/time)

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Workload

- A measure of the radiation output
  - mA-minutes for X Ray units
  - Gy for treatment units
- Should consider ALL uses (*e.g.* include QA measurements)

Example for workload on linac

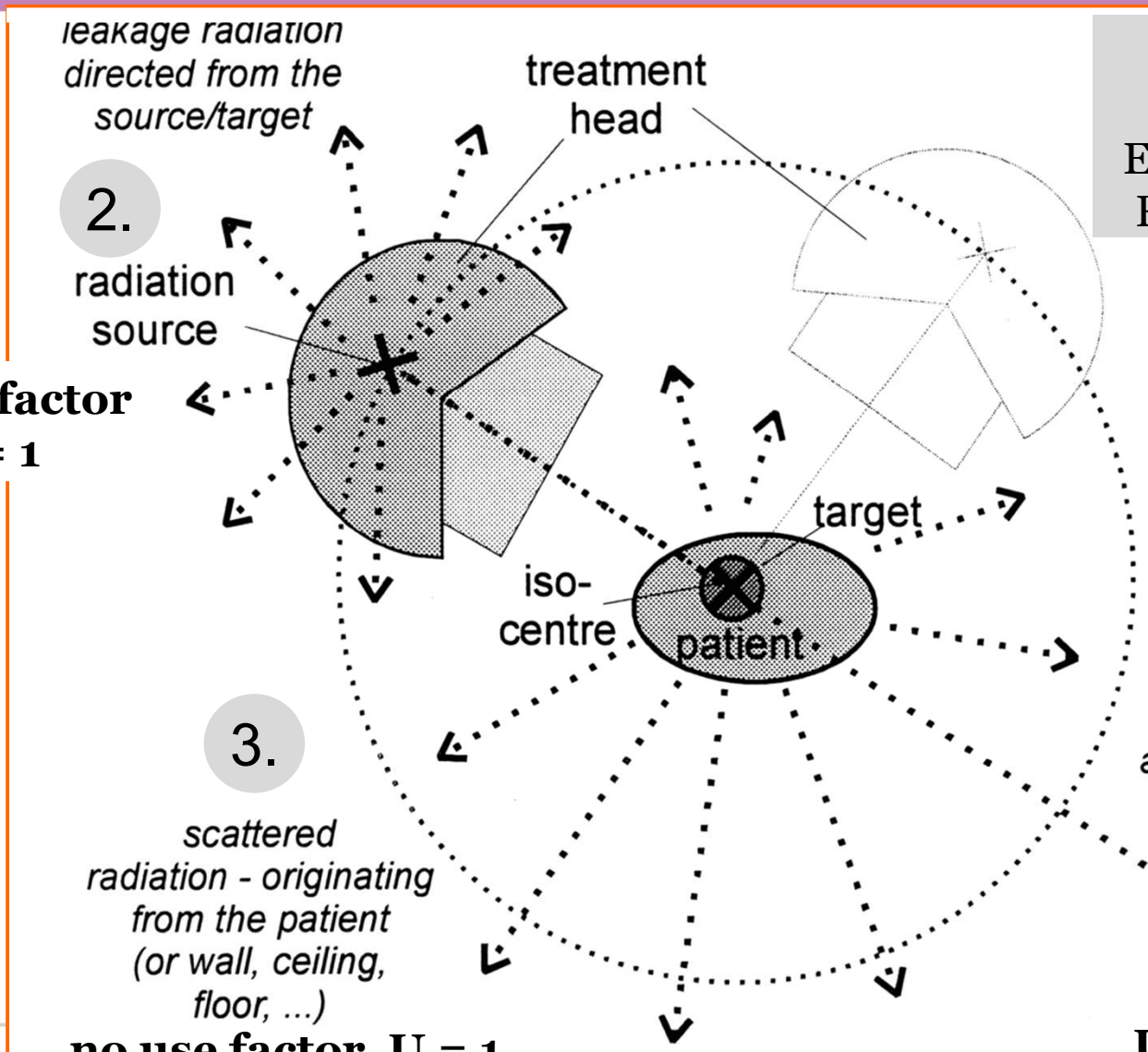
Hp D = 2.5Gy at isocentre, 50 patients treated per day on 250 working days/y

W = 50 x 250 x 2.5 = 31250 Gy/year

allow for other uses such as physics, blood irradiation, …

Total : 40000Gy per year at isocentre

Primary and secondary shielding



"Sources" of radiation in External Beam Radiotherapy

no use factor
U = 1

no use factor U = 1

1 ↓
U = 0.5 ↑
0.25 ↔

Secondary Sources in External Beam RT

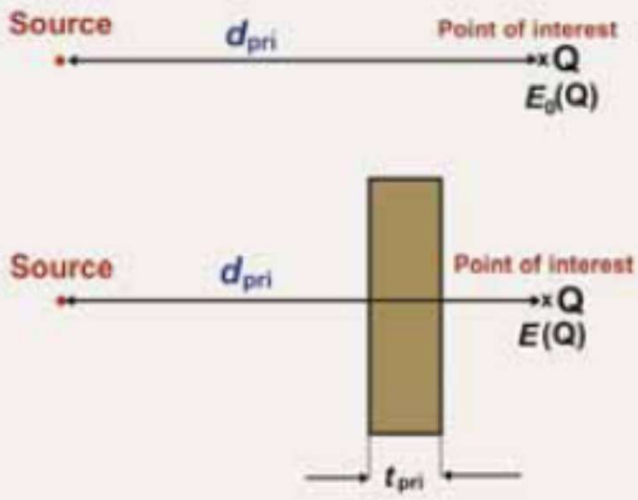
Secondary barriers are designed to protect individuals beyond the treatment room from:

Leakage: dependent on design, typically limited to 0.1 to 0.2% of the primary beam originates from target - not necessarily via the isocentre. IMRT -> the leakage radiation can be significantly increased (a factor of 10 is often assumed).

Scatter: assumed to come from the patient and room walls. Difficult to calculate - use largest field size for measurements the lower the radiation energy, the more of a concern for photon beams.

Primary shielding (NCRP 151)

Primary barrier transmission factor B_{pri}



$$E_0 = WUT\left(\frac{d_0}{d_{pri}}\right)^2$$

$$E(t) = E_0 e^{-\mu t} = WUT\left(\frac{d_0}{d_{pri}}\right)^2 e^{-\mu t}$$

$$B_{pri} = \frac{E}{E_0} = e^{-\mu t_{pri}} = e^{-\left(\frac{\ln 10}{TVL}\right)t_{pri}} = 10^{-\frac{t_{pri}}{TVL}} = 10^{-n} \Rightarrow n = -\log B_{pri} = \frac{t_{pri}}{TVL}$$

n is the number of order of magnitude you want to reduce your beam exposure with the shielding material

Example for primary beam

Waiting room adjacent to a linac bunker

Equipment type = linac,
FAD = 1m, 6MV

W = 40000Gy/year

D = 2.5Gy

U = 0.25 (lateral approach)

d = 6m

T = 0.25 (waiting room)

E = 0.001Gy/year (limit value in the area to be shielded

d_o as the distance from source to reference point (e.g. isocentre)

$E_o = WUT\ (d_{ref}/d)^2 = 69.444$

$n = -\log(E/E_o) = 5$

Need to know the TVL (tenth value layer or thickness required to attenuate the beam by a factor of 10) of concrete in a 6MV beam -> TVL ≈ 30cm

Required barrier thickness:

$$t_{pri} = nTVL = ???\ m$$

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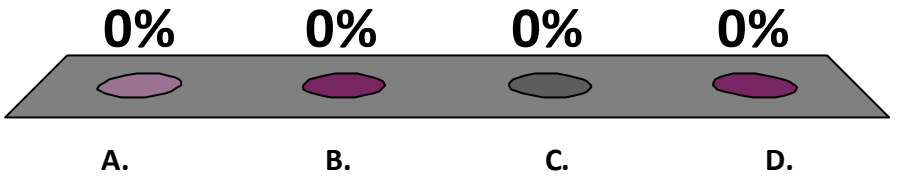
The required concrete barrier thickness is:

A. 1 m

B. 30 cm

C. 1.5 m

D. 5 m



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IAEA

Radiation protection of Patients
Radiation Oncology physics handbook

http://rpop.iaea.org/RPOP/RPoP/Content/
http://www-naweb.iaea.org/nahu/dmrp/

ICRP – NCRP - IAEA

• ICRP. Protection against ionising radiation from external sources used in medicine, ICRP report 33. Oxford: Pergamon Press; 1982.

• ICRP. Protection of the patient in radiotherapy, ICRP report 44. Oxford: Pergamon Press; 1985.

• ICRP 60: 1990 recommendations of the International Commission on Radiological Protection, 60

• ICRP. Radiological Protection and Safety in Medicine, ICRP report 73. Oxford: Pergamon Press; 1996.

• ICRP. Protection from potential exposures: application to selected radiation sources, ICRP report 76. Oxford: Pergamon Press; 1997.

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• Annals of the ICRP. Publication 103. The 2007 Recommendations of the International Commission on Radiological Protection

• ICRP, 2010. Conversion Coefficients for Radiological Protection Quantities for External Radiation Exposures. ICRP Publication 116, Ann. ICRP 40(2–5).

• ICRP, 2012. ICRP Statement on Tissue Reactions / Early and Late Effects of Radiation in Normal Tissues and Organs – Threshold Doses for Tissue Reactions in a Radiation Protection Context. ICRP Publication 118. Ann. ICRP 41(1/2)

• International Basic Safety Standards (BSS) for Protection against Ionizing Radiation and for the Safety of Radiation Sources, IAEA Safety Series No 115, Vienna 1996 (IAEA, FAO, ILO, OECD/NEA, PAHO and WHO)

• NCRP 49: Structural Shielding Design for Medical use of X Rays and Gamma Rays of Energies up to 10 MeV, September 15, 1976.

• NCRP 147: Structural Shielding Design for Medical X-ray Imaging Facilities, November 19, 2004.

• NCRP 151: Structural Shielding Design and Evaluation for Megavoltage X- and Gamma-Ray Radiotherapy Facilities, 2005

ESTRO Teaching Course on Physics for Clinical Radiotherapy, Bucharest 2017

Radiotherapy dose & induction of secondary tumors

Stéphanie Peeters

ESTRO School

Overview

- Introduction
- Tumor induction by peripheral dose (dose outside collimated beams)
- Definition equivalent dose for neutrons present in high energy photon beams
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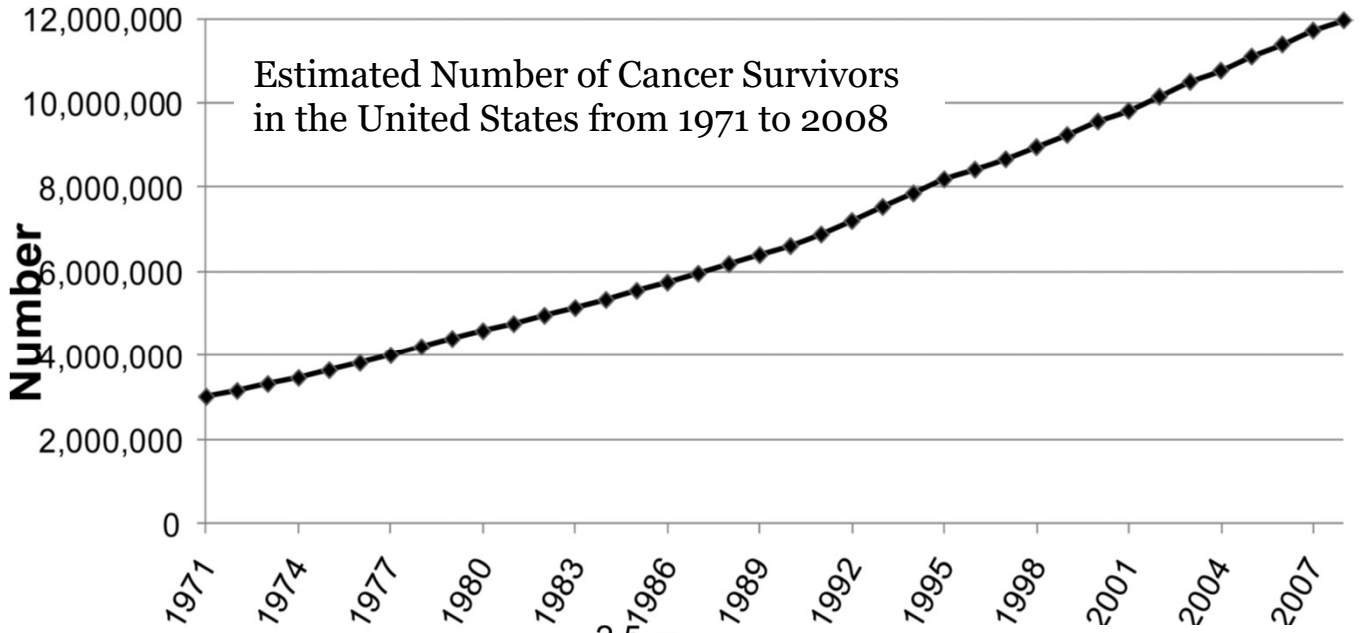
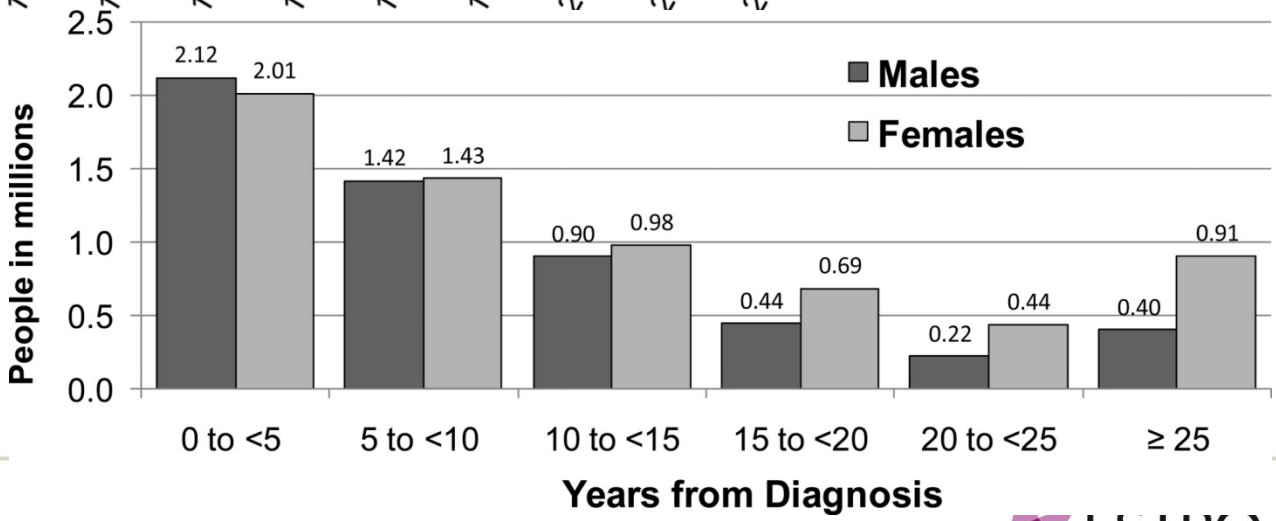
- (Bibliography)

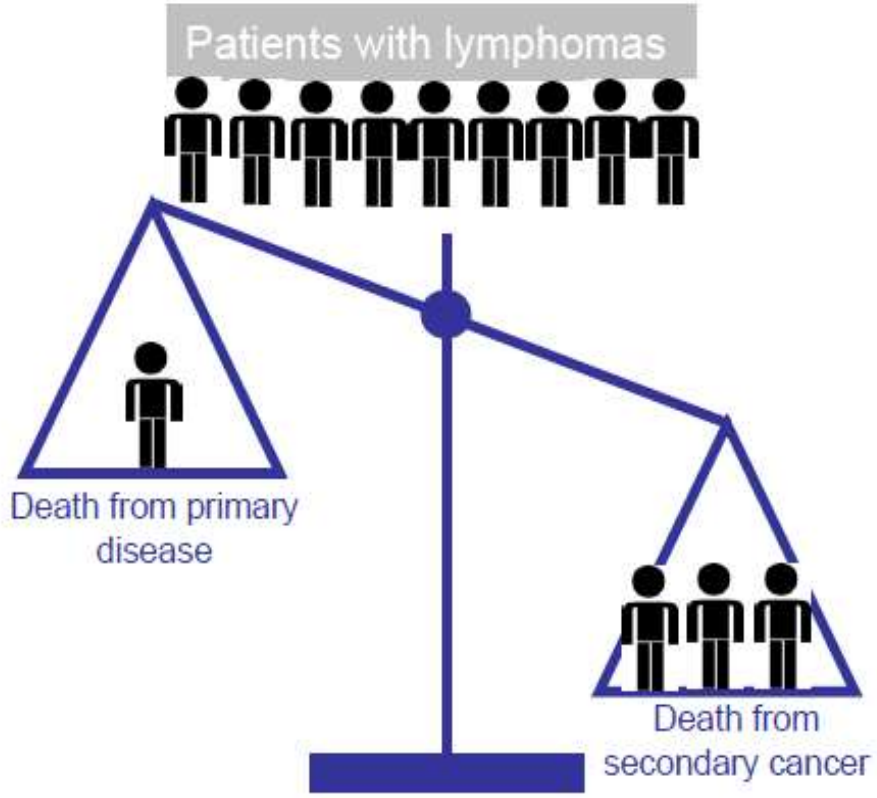
Introduction: surviving cancer





Parry 2011 Cancer Epidemiol Biomarkers Prev.

Surviving cancer



Secondary cancers can be a significant cause of death
In extreme situations (some cancer forms) – higher death rate from secondary malignancies

Tubiana M. Radiother Oncol 2009

Risk of second cancer by primary site

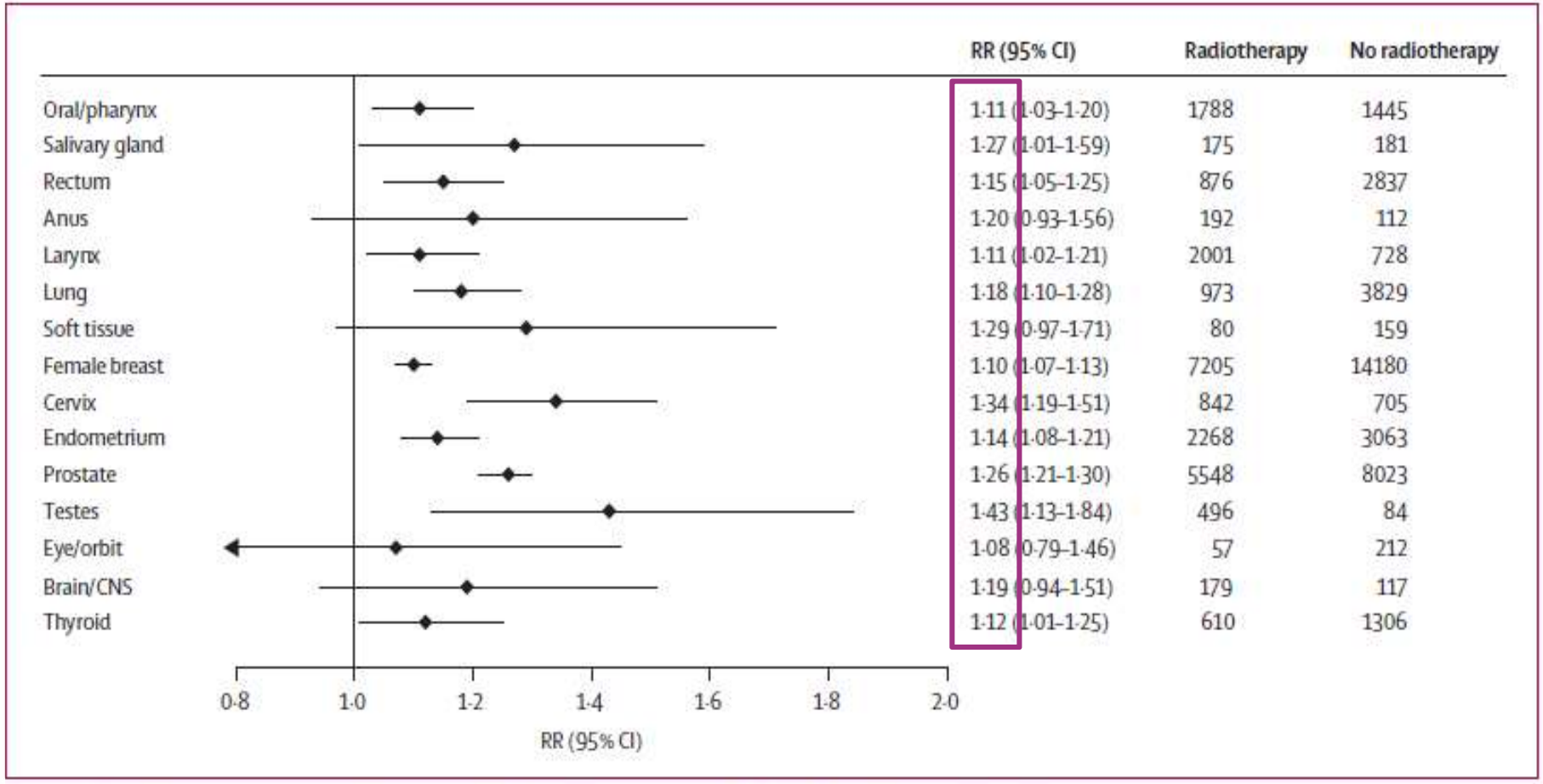


Figure 1: **Relative risk of second solid cancer for radiotherapy versus no radiotherapy by site of first cancer**
Relative risk (RR) adjusted for sex, attained age, and attained year through the use of external rates and additionally adjusted for stage, age at diagnosis, and year of diagnosis through stratification. For salivary gland, cervix, endometrial, prostate, and thyroid cancers second cancers of the same site were excluded because standard treatment usually involves surgical removal of the affected organ or because of second cancer coding rules (prostate).

Berrington et al. Lancet Oncol. 2011

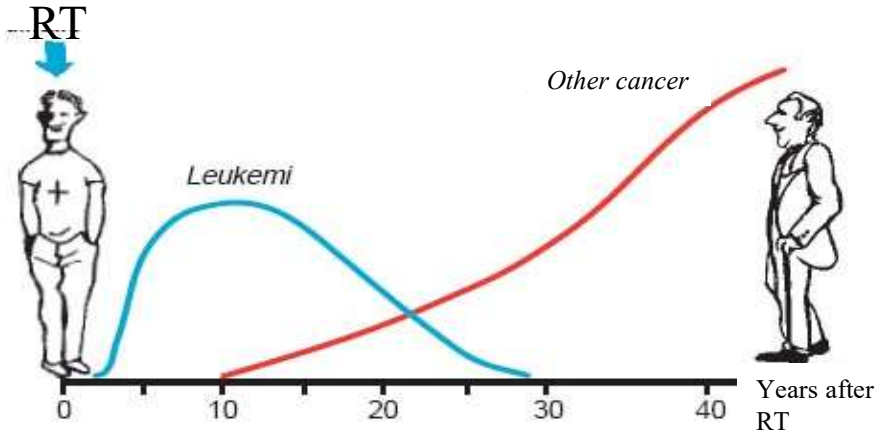
Definition

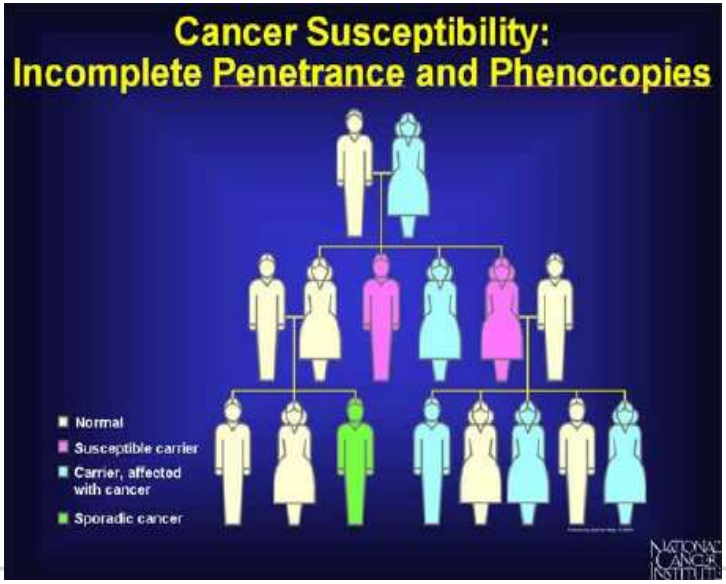
What is a secondary cancer?

A tumor caused by dose given in connection to radiotherapy/imaging.

A tumor with a histology which is different than the primary disease.

A tumor that occurs after a latency period from the treatment of the primary disease.





What is NOT a secondary cancer?

Recurrent cancer.

Sporadic cancer.

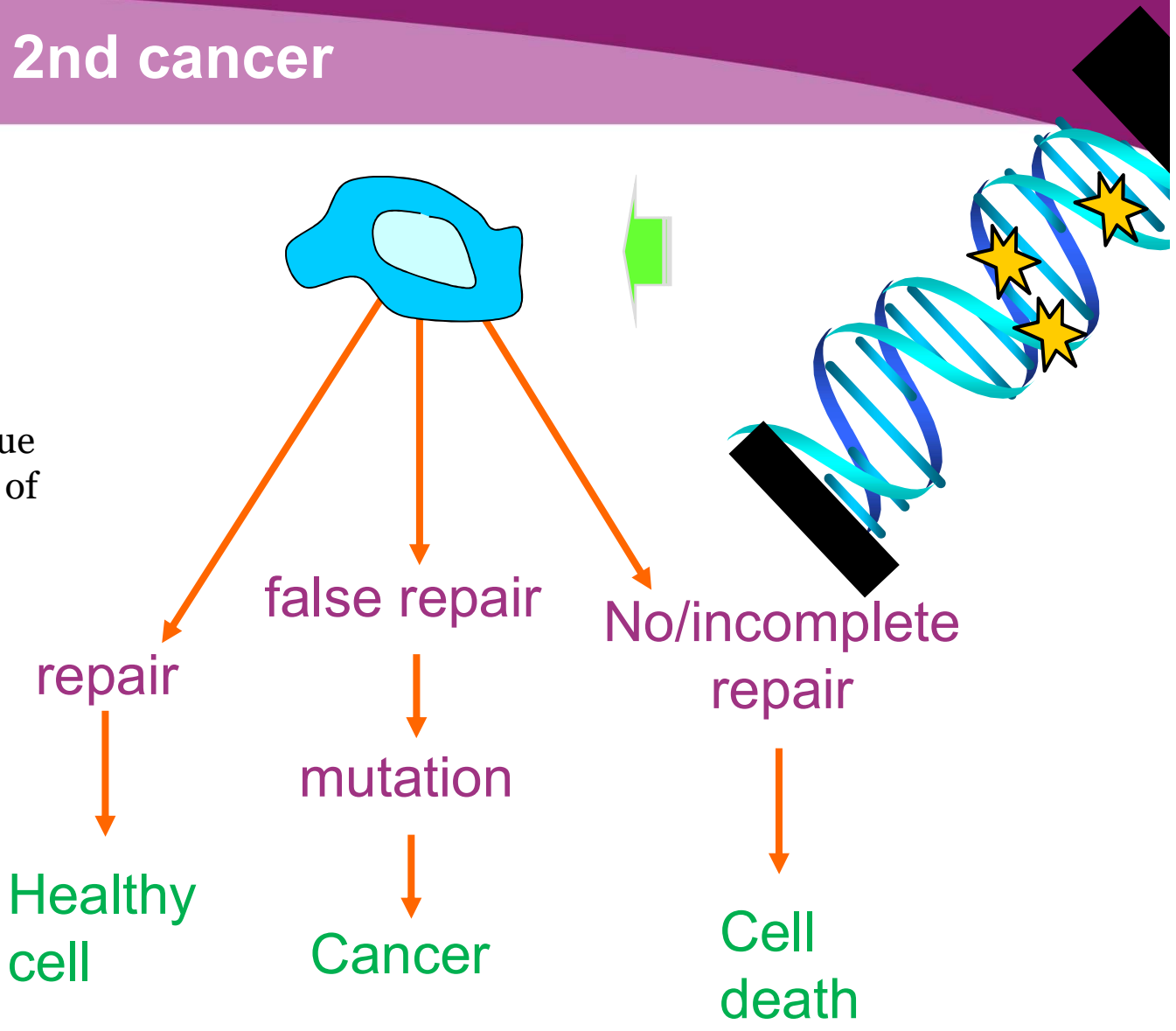
Cancer connected to genetic factors.

Exogenous factors (smoking, diet etc.) causing the first cancer can also cause the next.

Mechanism of 2nd cancer

Ionizing radiation causes

- DNA damage and mutations
- Cell kill in normal tissue that alters proliferation of mutated cells
- Chronic inflammation



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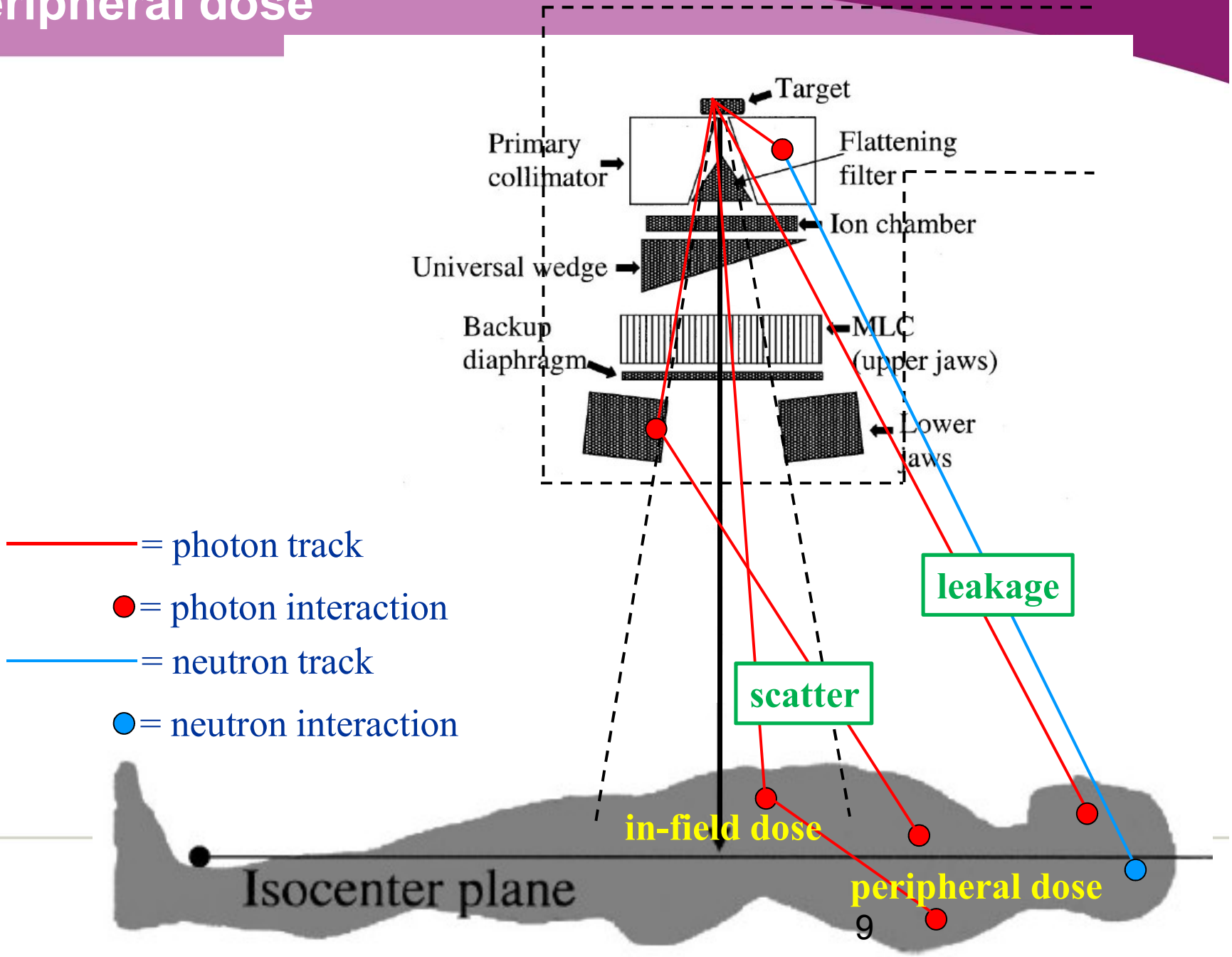
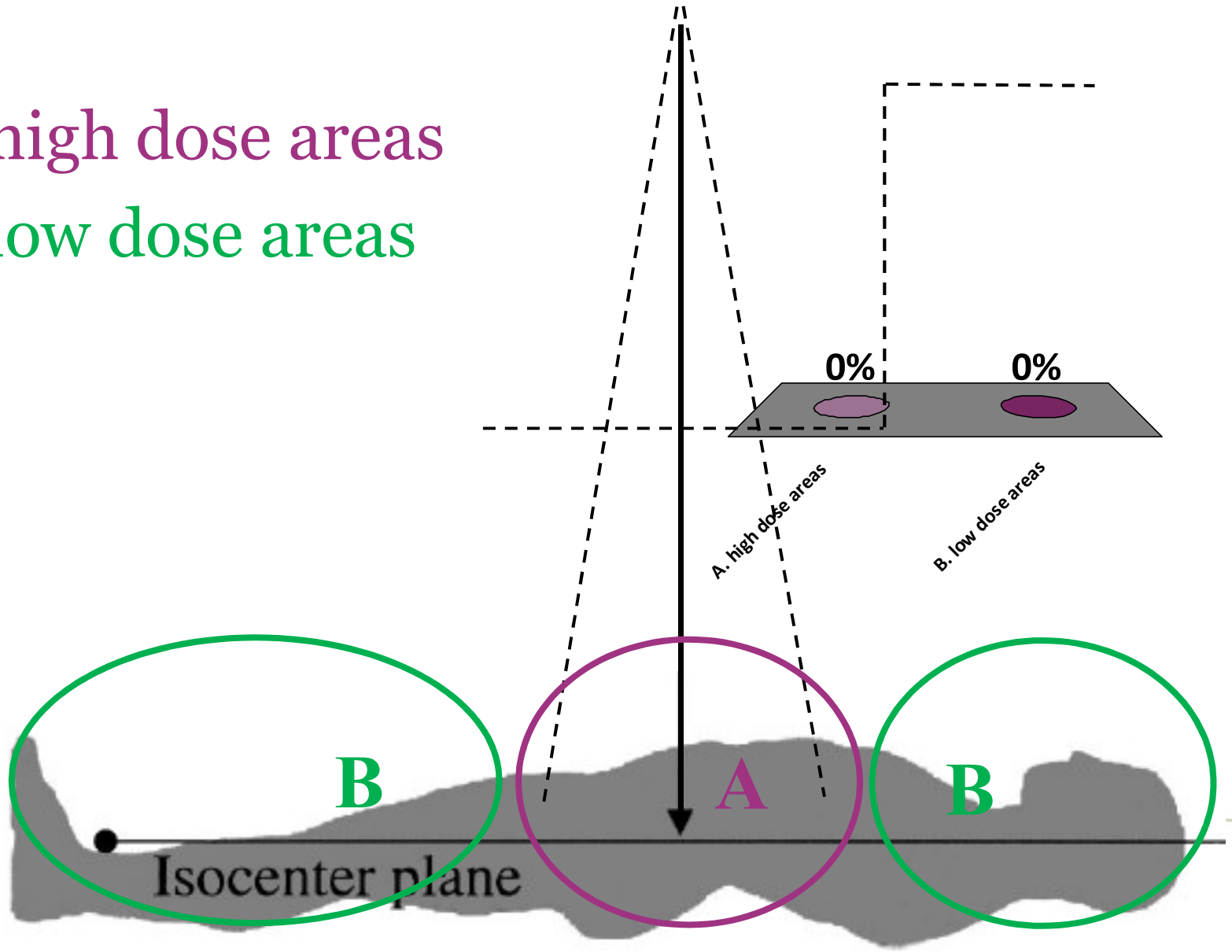
Peripheral dose



Secondary cancers appear most frequently in...

A. A. high dose areas

B. B. low dose areas



Peripheral dose

Peripheral dose in a 6 MV beam determined with Monte Carlo calculations

Peripheral dose	
6 MV, 3.75 cm depth, 10x10 cm^2	
distance from field edge	Dose [% of isocenter dose]
5 cm	1.5 %
10 cm	0.5 %
20 cm	0.3 %
40 cm	0.05 %

Bednarz and Xu, 2009

Concept of Equivalent Dose

Background

- both **photons** and **neutrons** can induce tumors
- biological effect of **neutrons** is higher than of **photons** ➔
  - for the same physical dose D [Gy=J/kg], more tumors with **neutrons**
  - biologically, 1 Gy in a **photon** beam ≠ 1 Gy in a **neutron** beam

use $\mathbf{D_{equivalent}}$ instead of physical dose D

- unit of $D_{equivalent}$ is Sievert (Sv)
- 1 Sv has the same tumor induction in all types of beams

How to calculate $D_{equivalent}$

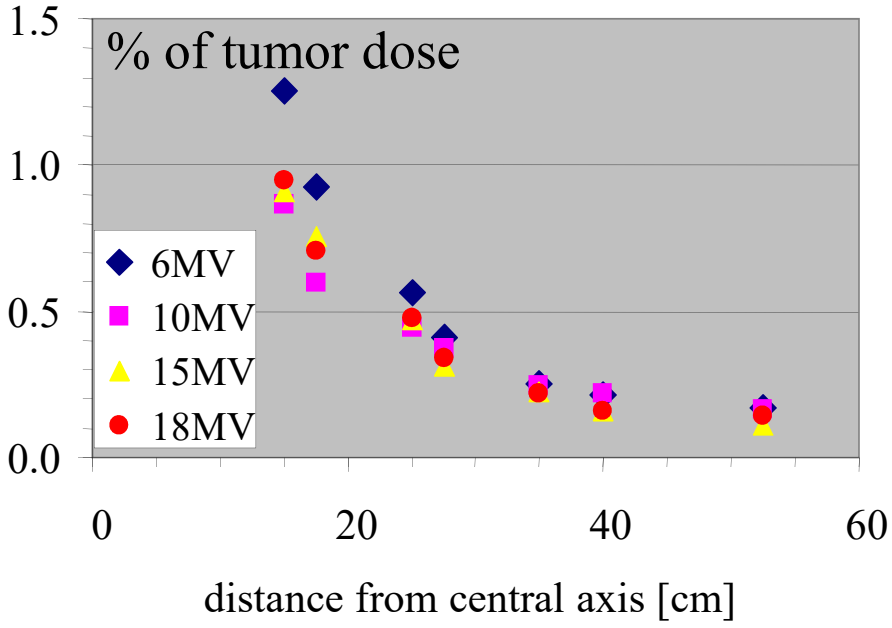
Photon beam	$D_{equivalent}\ [Sv] = D\ [Gy]$
Neutron beam	$D_{equivalent}\ [Sv] = w_N \times D\ [Gy]$
Mixed beam	$D_{equivalent}\ [Sv] = D_{photons}\ [Gy] + w_N \times D_{neutrons}\ [Gy]$

w_N = 5-20, dependant on energy

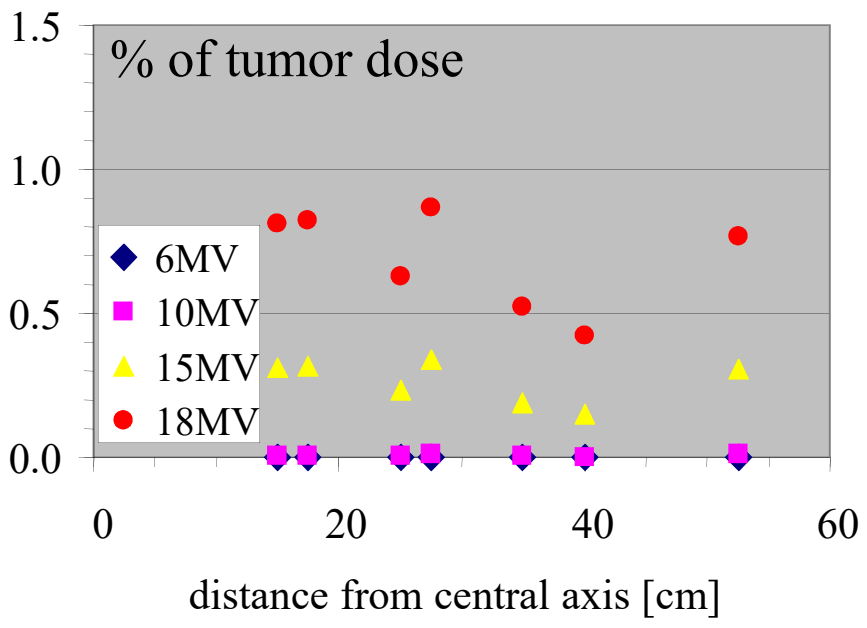
Measured peripheral photon and neutron equivalent doses

Prostate IMRT plans

Peripheral equivalent dose: **photons**



Peripheral equivalent dose: **neutrons**



Equivalent dose

Neutrons: important for energies > 10 MV

For 18 MV, **neutrons** are more important than **photons** for large distances

Kry et al 2005

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Quantities expressing risk for tumor induction

Excess Absolute Risk

EAR = fraction of irradiated patients that get a radiation-induced tumor

often applied units: %/Sv or PY·Gy

Relative Risk

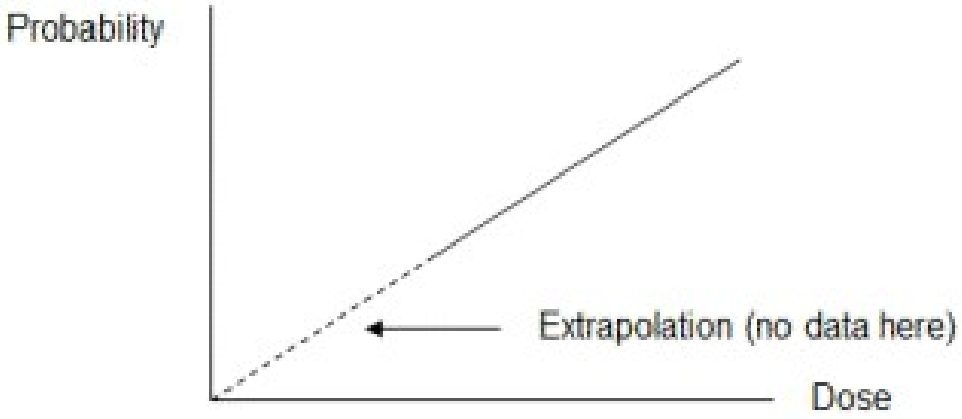
$$\mathbf{RR} = \frac{\text{baseline tumors + radiation-induced tumors}}{\text{baseline tumors}}$$ (by definition, RR >1)

Excess Relative Risk

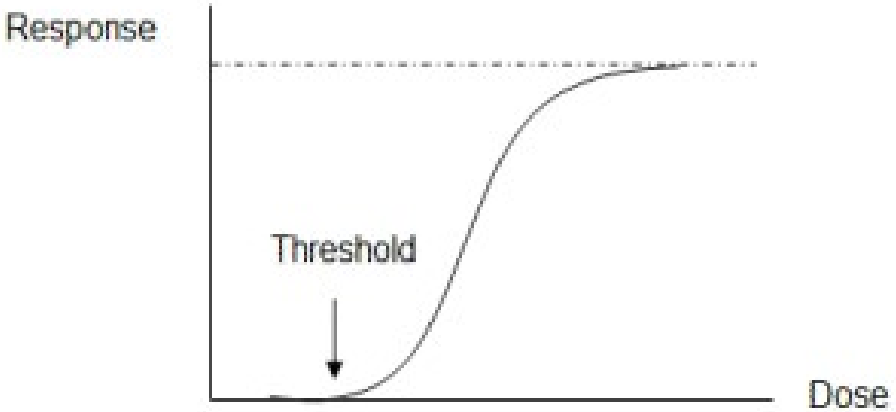
$$\mathbf{ERR} = \frac{\text{radiation-induced}}{\text{baseline}}$$ (ERR = RR-1)

If ERR is X% ➔ due to radiation, total numbers of tumors increases by X%

Clinical data



Stochastic effects. As the dose increases, so does the probability of occurrence of a stochastic effect (e.g. cancer)



Deterministic effects. As the dose increases, so does the severity of a deterministic effect, e.g. skin reddening. Note the threshold dose for deterministic effects.

*BEIR VII, phase II, DDREF=1.5

Clinical data

Epidemiological data on radiation induced cancers after radiotherapy treatment

- large bulk of literature
- only few studies give insight in dose – response relationship
- use of chemotherapy becomes often a confounding factor
- data from selected groups of diagnoses
  - Hodgkin's lymphoma
  - Prostate cancer
  - Breast cancer
  - Seminoma

2nd tumors in patients treated for BREAST CANCER

Close to irradiated tumor

Exces cancer risk due to radiotherapy	INCIDENCE	
	ERR	2p
contralateral breast cancer	18%	0,002
lung cancer	61%	0,0007
oesophagus cancer	106%	0,05
leukemia	71%	0,04
soft-tissue carcinoma	134%	0,03

Lancet 2005; 366: 2087–2106

- meta analysis of 78 randomized trials
- 32.800 patients in studies evaluating addition of RT (50% irradiated)

2nd tumors in patients treated for BREAST CANCER

Second tumor: contralateral breast cancer (CBC)

- **40-50%** of all secondary tumors are in the contralateral breast.
- **At 15y, 10-13%** of patients have developed contralateral tumor (2- to 5-fold higher than general female population).
- High risk for CBC is mostly unrelated to RT (**pre-disposition**).
- **Conflicting data** on contribution of RT: Some large studies show increased risk for CBC due to RT, others only for young patients, others don't show any enhanced risk
- Hormonal treatment with **tamoxifen reduces risk** for CBC by 30-40%

2nd tumors in patients treated for BREAST CANCER

Second tumor: Lung cancer

- **Increased lung cancer risk** in breast cancer patients is largely attributed to RT
- Association between RT and subsequent lung cancer was found stronger for the **ipsilateral** lung
- **Postmastectomy** RT (often including supraclavicular, axillary, or internal mammary nodal region): **2 to 3-fold increased risk** after 10+ years
- RT after **breast conserving surgery** (less often including regional lymph node irradiation): impact RT is **less certain**

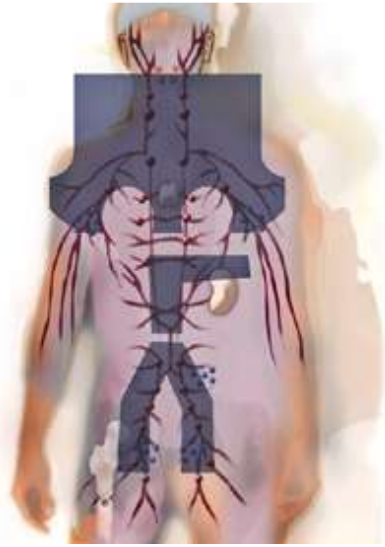
2nd tumors in patients treated for BREAST CANCER

Second tumor: Soft tissue sarcoma

- **15y incidence** of soft tissue sarcoma after RT **<0.5%**, but **ERR=600%** relative to general population
- *Rubino et al, 2005*: all soft tissue and bone sarcomas in irradiated women, were located in irradiated fields or upper ipsilateral arm (**high dose areas**)

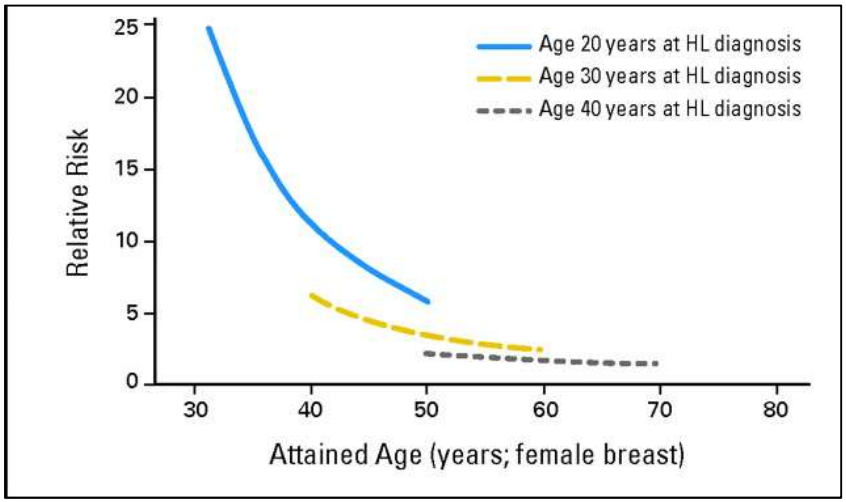
2nd tumors in patients treated for M. HODGKIN

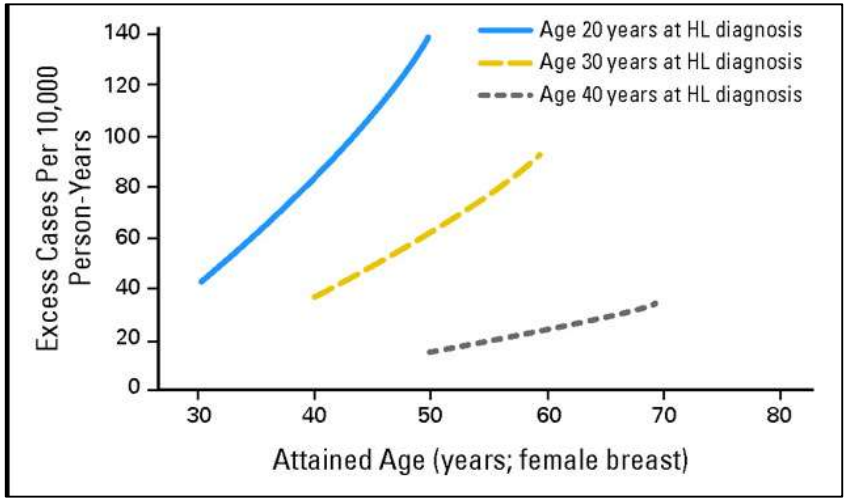
- **a lot of data** for HD: young age, high curability, long follow-up
- death due to second cancer is the **most common cause of mortality** among long-term survivors
- solid tumors are most frequent (75-80%), mainly **lung** and **breast cancer**
- both for lung and breast cancer: **higher dose ➔ higher incidence**
- most data for large field RT, **nowadays smaller fields ➔** reduction in second tumors expected



2nd tumors in patients treated for M. HODGKIN

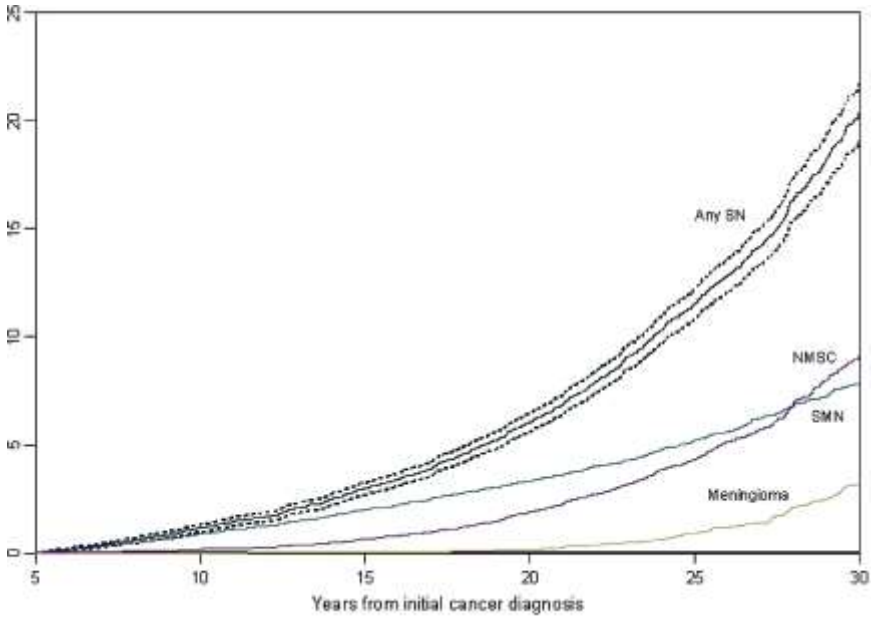
Relative risk (RR) and excess absolute risk (EAR) for breast cancer according to **age at diagnosis** of HL and **attained age**

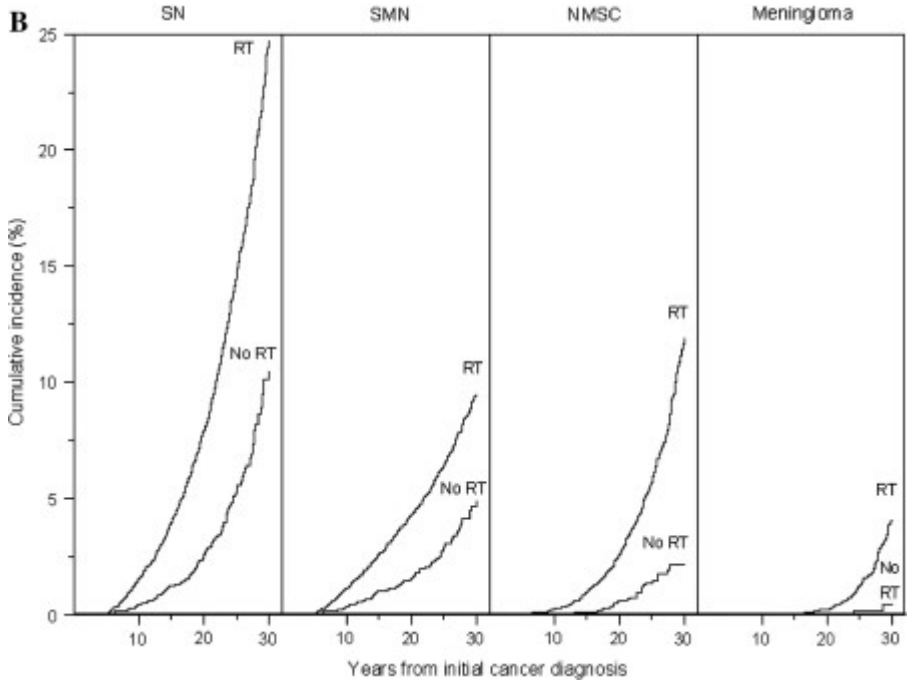




Hodgson et al. JCO 2007

2nd tumors in patients treated for M. HODGKIN





Friedman J Natl Cancer Inst 2010

Age at exposure

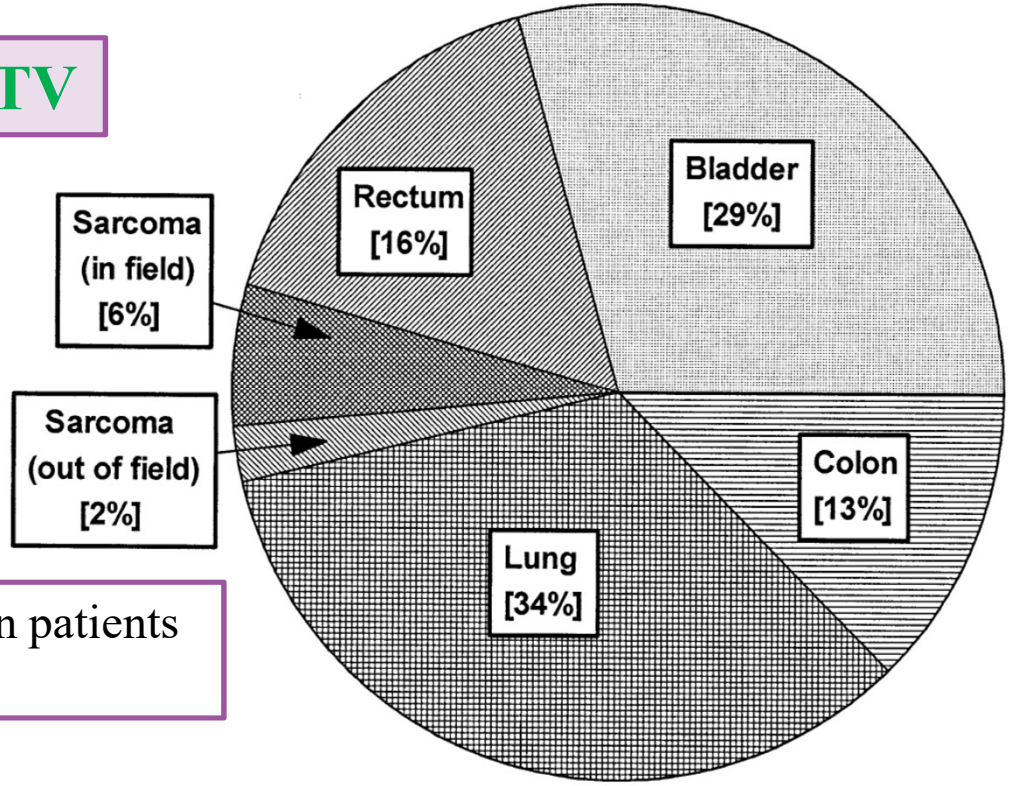
Matured A-bomb survivors data

- 5% per Sv for the risk of radiation-induced fatal cancer (an average for all ages)
- the risk is closer to 15% per Sv for a young female
- about 1% per Sv for mature individuals 60 years of age and older

2nd tumors in patients treated for PROSTATE CANCER

- 1 in 70 patients with 10+ years survival had secondary tumor related to RT
- all years: 1 in 290

most 2nd tumors close to PTV



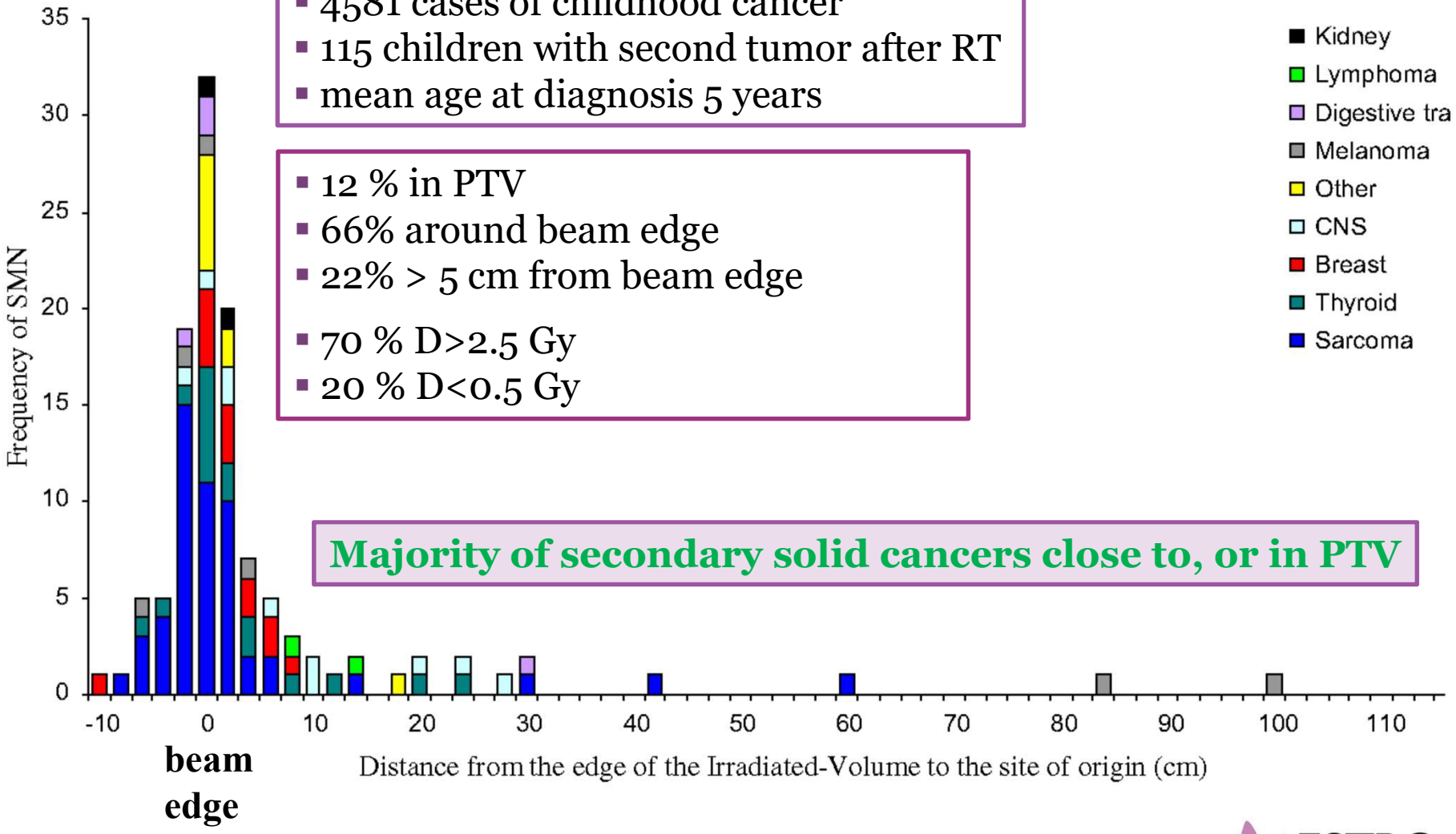
Radiation-associated solid cancers in patients surviving 10+ years (p>0.05)

Brenner et al, 2000: 51.584 pts treated with RT, 70.539 only surgery

Position of RT induced 2nd tumors relative to HIGH DOSE AREA

- 4581 cases of childhood cancer
- 115 children with second tumor after RT
- mean age at diagnosis 5 years

- 12 % in PTV
- 66% around beam edge
- 22% > 5 cm from beam edge
- 70 % D>2.5 Gy
- 20 % D<0.5 Gy



Majority of secondary solid cancers close to, or in PTV

Diallo et al, IJROBP 2009

Position of RT induced 2nd tumors relative to HIGH DOSE AREA

Various primary tumors:

- **Prostate**: increased risk relative to surgery, for ≥ 10 y fu: bladder (ERR=77%), rectum (105%), in-field sarcomas (217%), and lung (42%) *(Brenner et al. 2000)*

- **Breast**: compared to no RT: contralateral breast (ERR=18%), soft-tissue sarcoma (134%), lung (61%), oesophagus (106%), leukemia (71%) *(EBCTCG, Lancet 2005)*

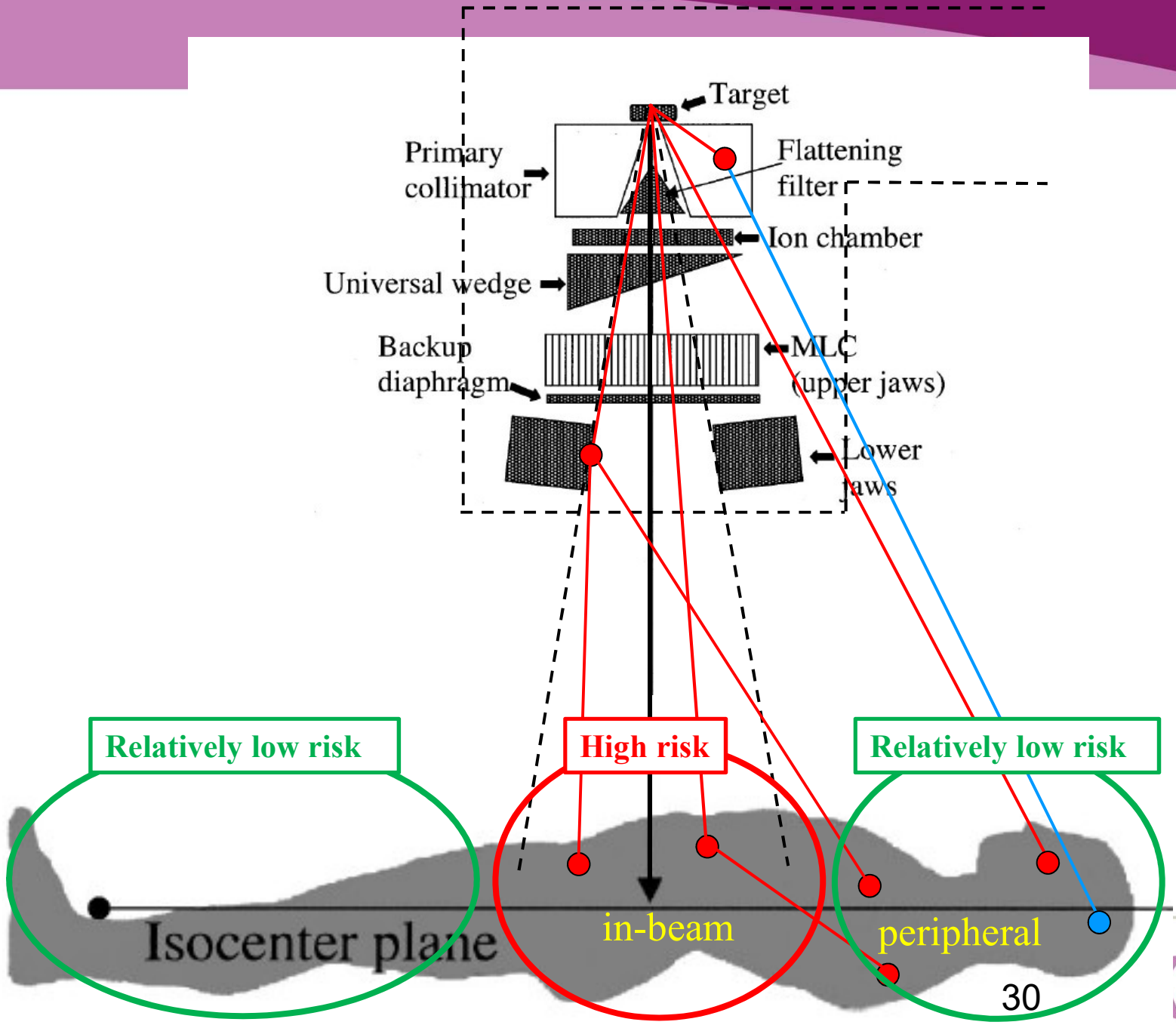
- **Breast**: compared to no RT: ERR= 45% for sites with D>1Gy (lung, oesophagus, pleura, bone, soft tissue), ERR=9% for contralateral breast ca (D≈1Gy), no evidence for enhanced risk for D<1 Gy *(Berrington de Gonzalez et al. 2010)*

- **Cervix**: compared to general population: for all latency periods ERR(D>3Gy) > ERR(1Gy<D<3Gy) > ERR(D<1Gy). 10-19y: 53%, 22%, 12% *(Chaturvedi, Travis, et al, 2007)*

- **Several sites**: 85%: D≥3 Gy *(Dörr and Herrmann, 2002)*

Relatively few secondary solid cancers for very low doses

Clinical data

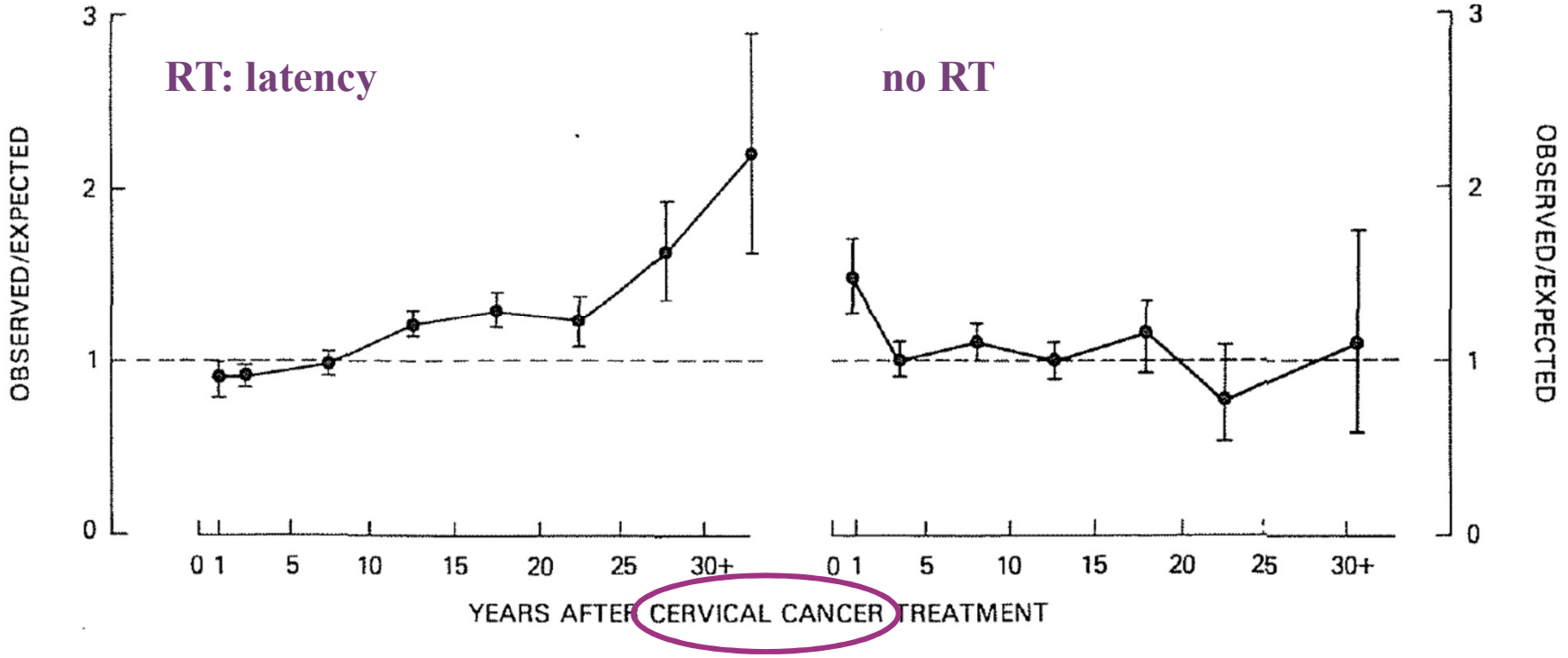

Target
Primary collimator
Flattening filter
Ion chamber
Universal wedge
Backup diaphragm
MLC (upper jaws)
Lower jaws
Relatively low risk
High risk
Relatively low risk
Isocenter plane
in-beam
peripheral

Latency in appearance of radiation-induced tumors

Clinical data

Challenge in epidemiological studies

Latency: (increased) secondary tumor appearance **up to 30-40 years after RT**



Boice et al. 1985

ESTRO School

Latency in appearance of radiation-induced tumors

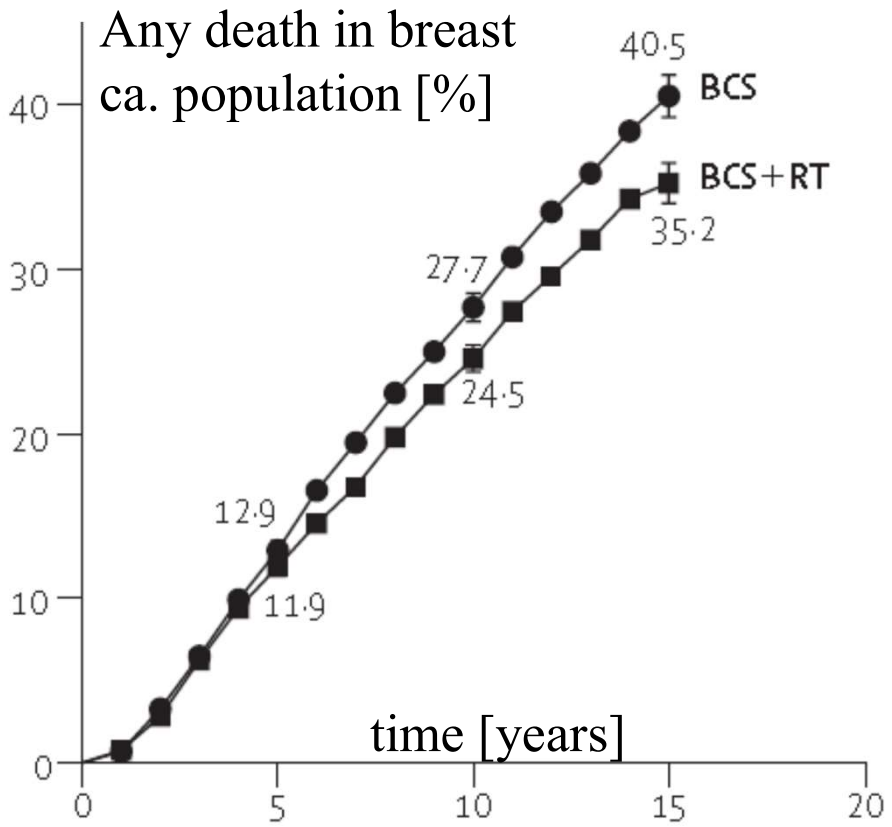
Challenge in epidemiological studies

- many (known and unknown) reasons why people get a cancer.
- most second tumors are **not** induced by RT
  - *Boice 1985*: 68.730 irradiated cervical cancer patients with > 1 year follow-up, 3.324 (4.8%) second cancers, 162 (4.9 %) could be attributed to RT (162 = 0.24% of total number).

    ➔ detect small number of RT-induced tumors on top of large unknown baseline of non RT-induced tumors

tion of existing treatments that have proven and established efficacy, however, should not be conducted outside the setting of clinical trials. Moreover, it is important to keep in mind that second malignancies, although serious sequelae, are not seen unless a patient survives a cancer diagnosis. The survival benefits provided by many cancer treatments thus greatly outweigh the risk for developing a second primary cancer.

Lois B. Travis



Lancet 2005; 366: 2087–2106

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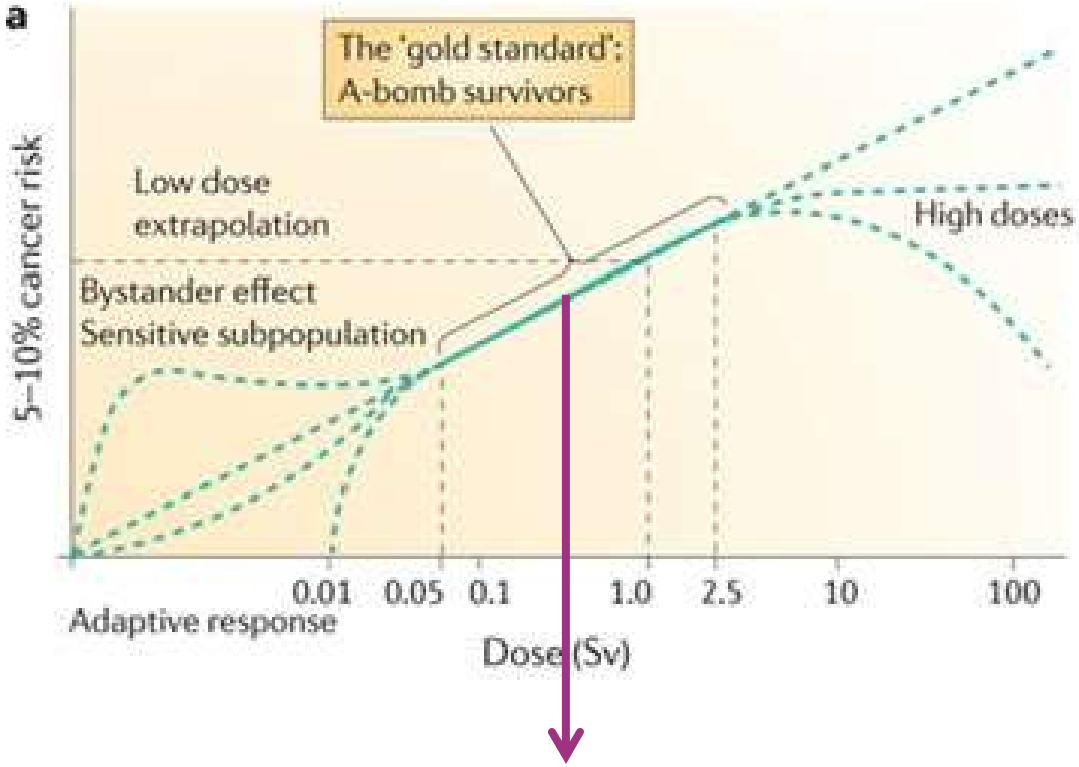
Dose-effect relationship for tumor induction at high doses?

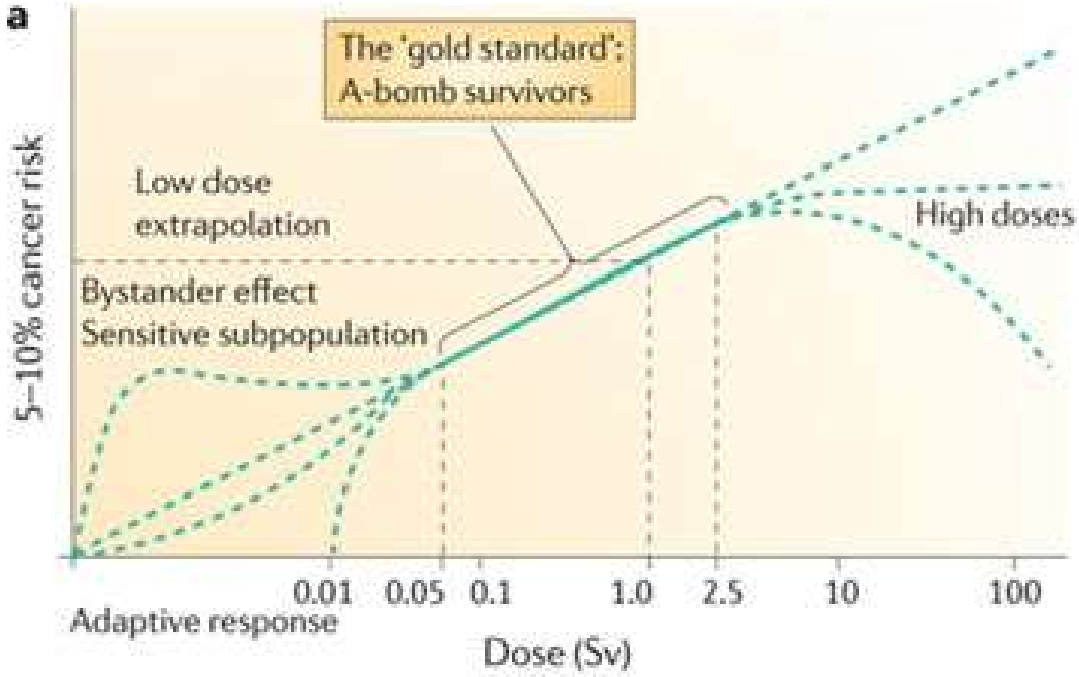


Linear at dose range 0,05-2,5 Gy

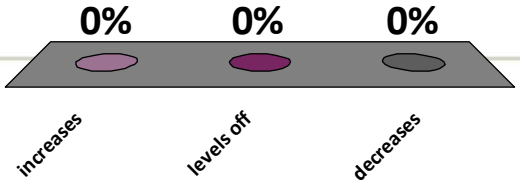
Hall 2006

At high doses the risk of secondary cancers…

A. increases
B. levels off
C. decreases



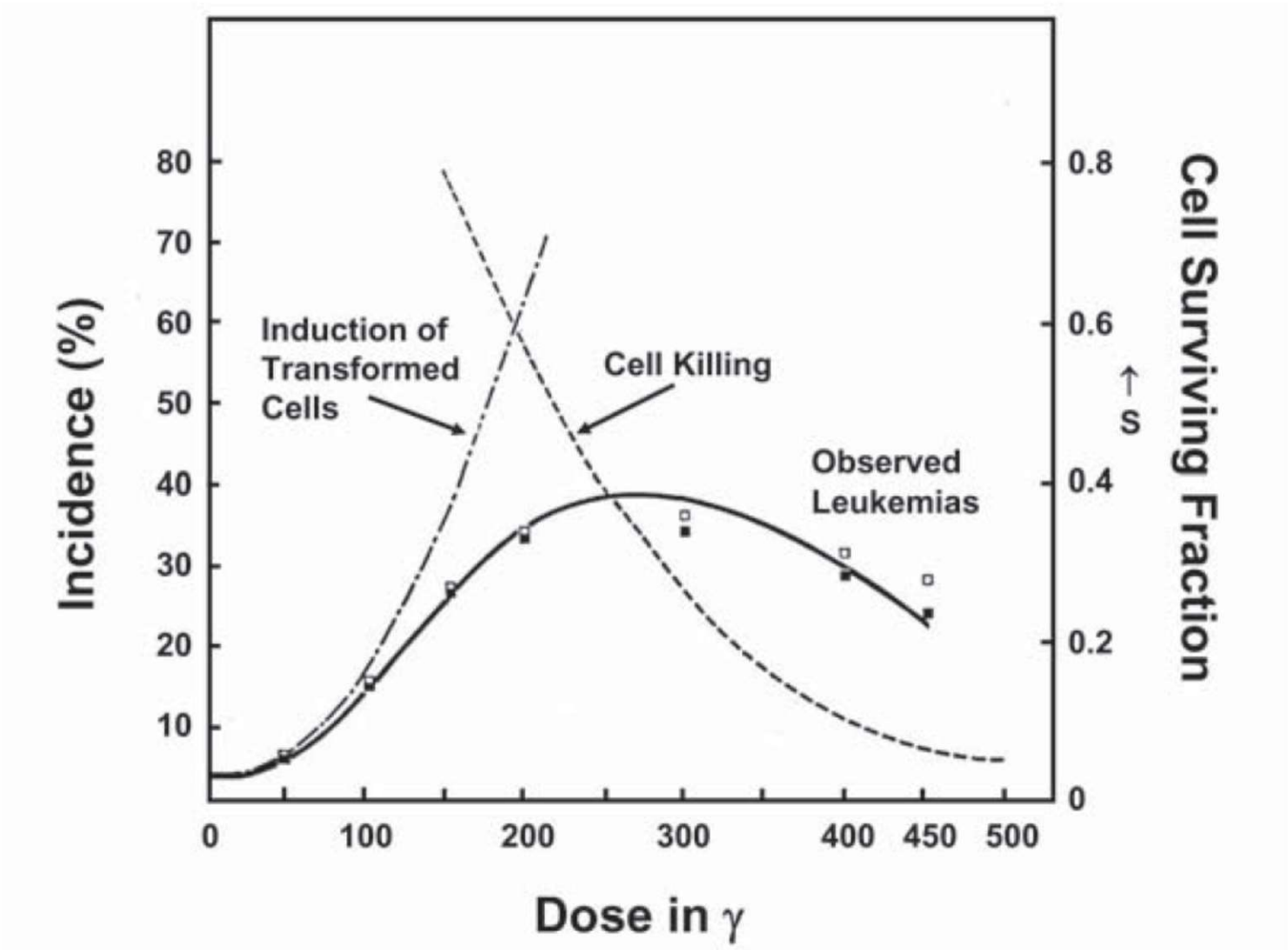
A.
B.
C.



ESTRO School

Dose-effect relationship

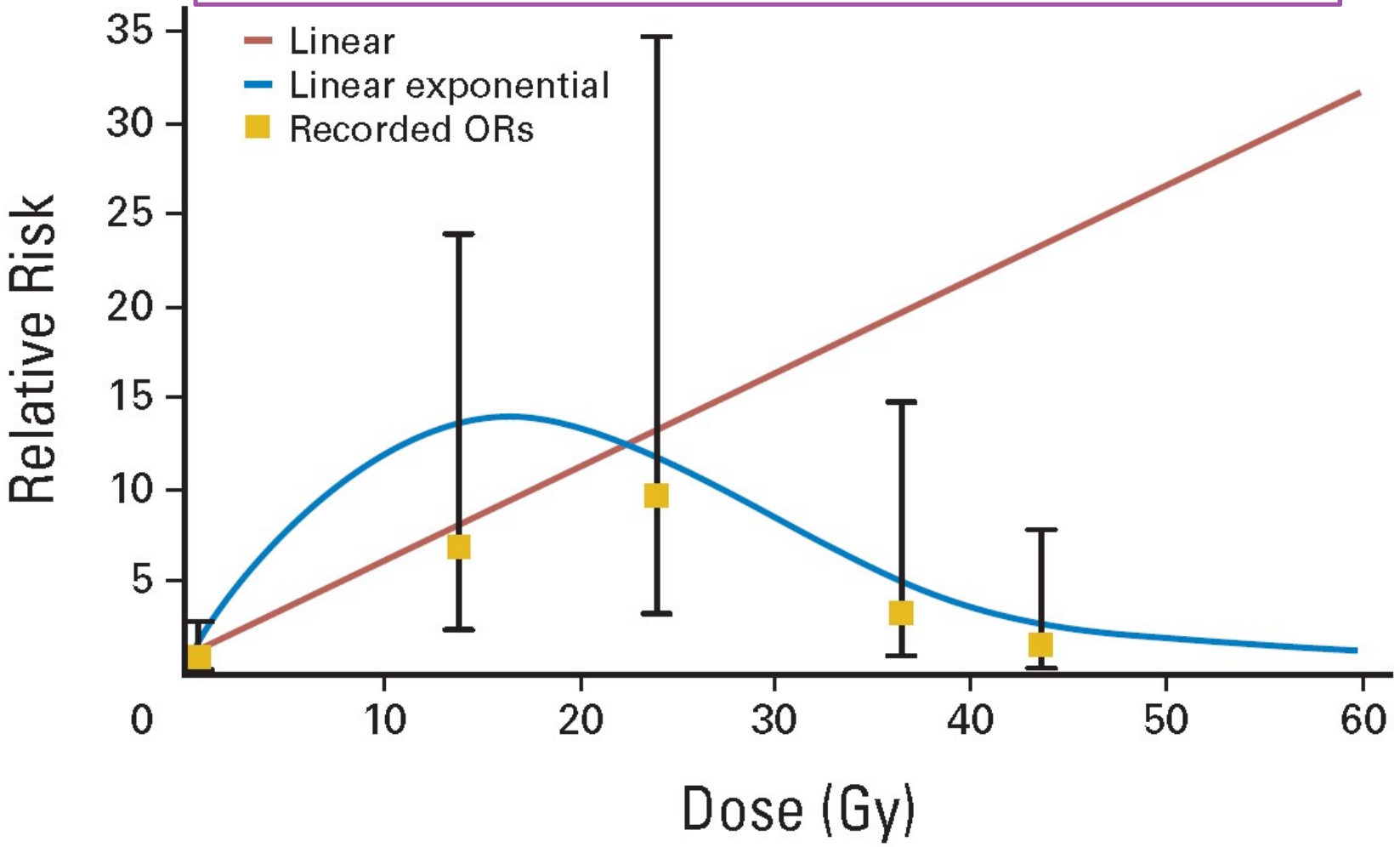
Leukemia from Whole Body Irradiation of Mice (Gray, 1957)



Hall 2006

Dose-effect relationship

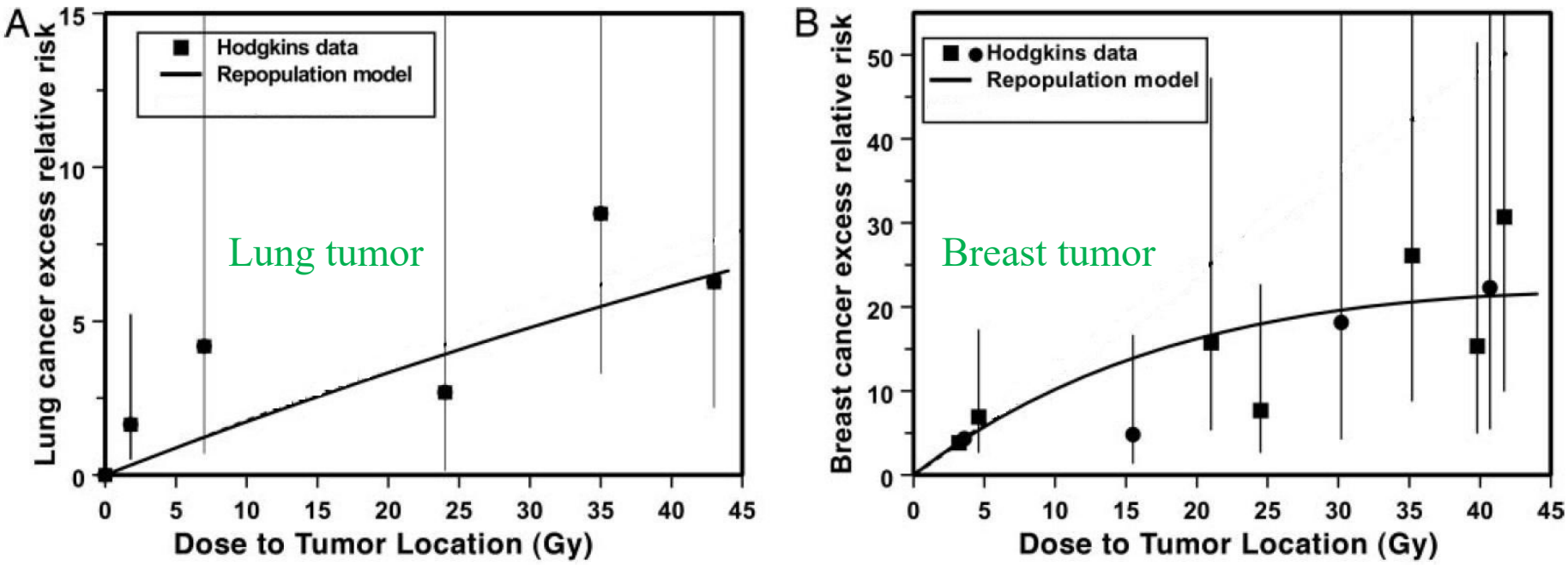
Induction of thyroid cancer in 14.358 survivors of childhood cancer



Meadows JCO 2009

Dose-effect relationship

Hodgkins disease – dose dependence lung and breast cancer induction

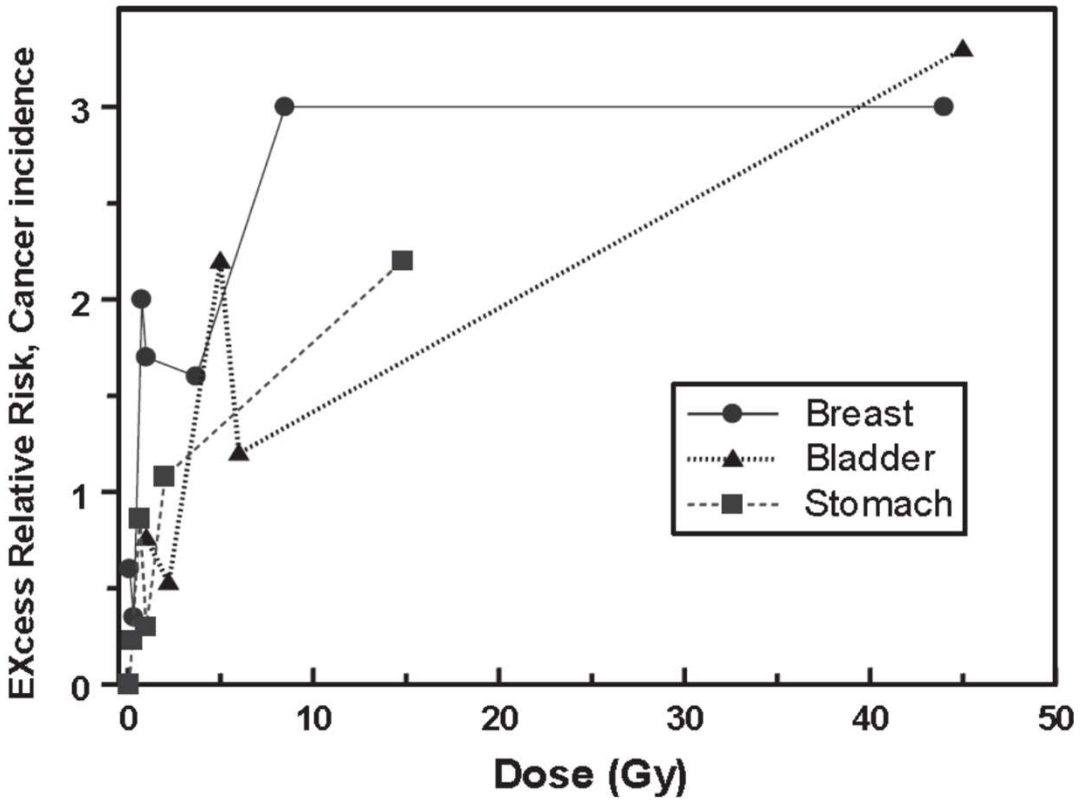


Fitted curves based on a model considering
1) cancer induction, 2) cell kill, 3) tumor cell repopulation

Brenner 2005

Dose-effect relationship for tumor induction at high doses?

Dose Response for Carcinogenesis at High Radiation Doses



Hall 2006

Overview

- Introduction
- Tumor induction by peripheral dose (dose outside collimated beams)
- Definition equivalent dose for neutrons present in high energy photon beams
- Epidemiologic observations of tumor induction by radiation
- Dose-effect relationships
- Prediction of tumor induction risk
- Clinical lessons – discussion
- (Bibliography)

Why prediction of tumor induction risk?

1. Include in treatment plan optimization
2. Compare treatment techniques, e.g. 3DCRT vs. IMRT vs. protons
3. Compare beam energies, 6 MV or 18 MV
4. Compare linac types: Varian vs. Elekta
5. Assess impact of kV/MV image guidance procedures on tumor induction
6. Information for patients: quantification of risk

Problems: Data are incomplete and conflicting, models are simple

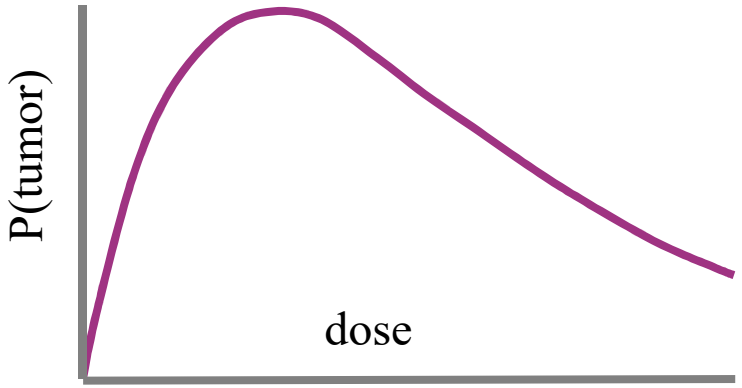
IMRT and prediction of tumor induction

1st problem with IMRT:

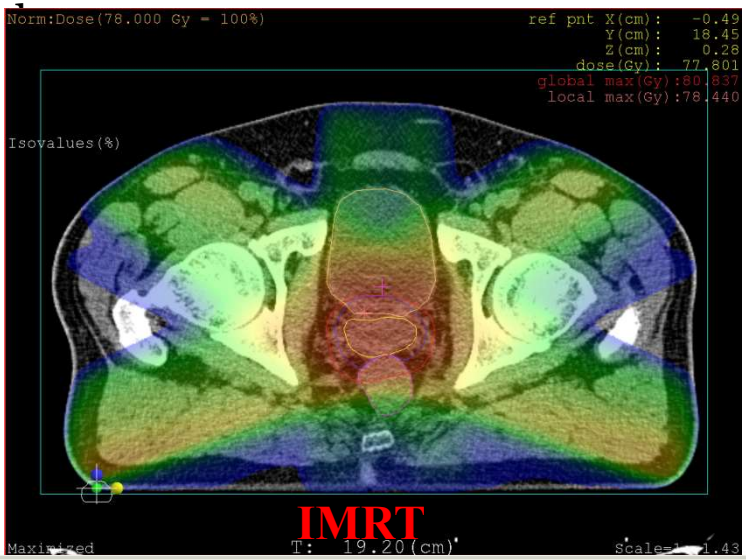
more beams than 3DCRT

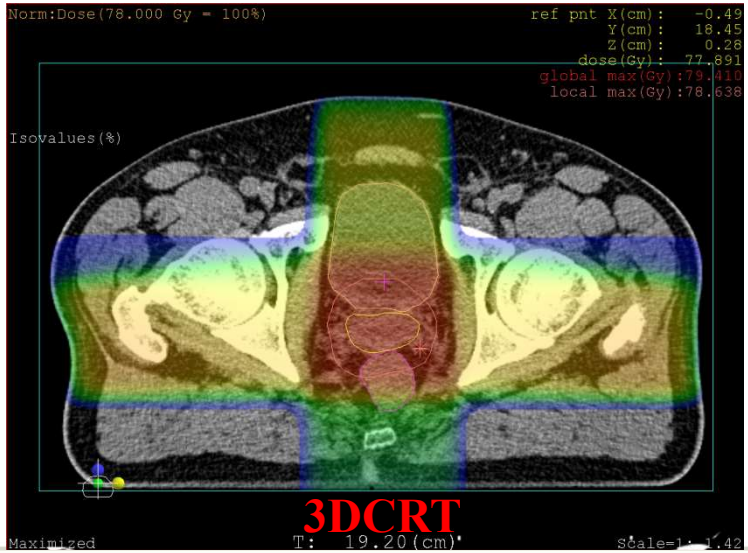
➔ larger patient volume covered with beams

➔ depending on dose-effect relation, higher risk



2 plans for the same prostate patient, total dose 78 Gy IMRT 5 beams, 3DCRT 3





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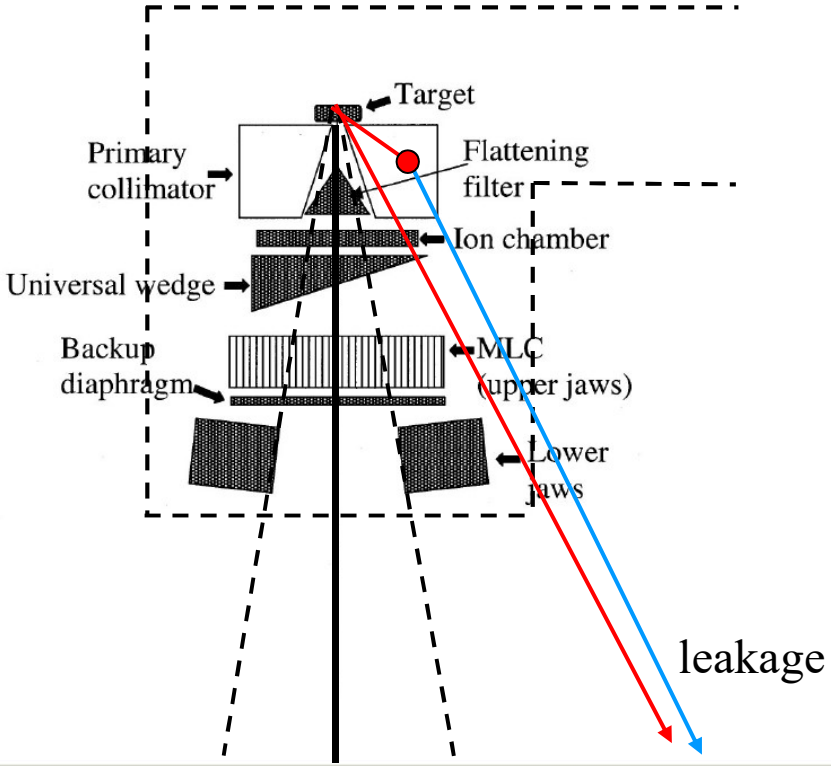
IMRT and prediction of tumor induction

2nd problem with IMRT:

small subfields ➔ **more MU** to treat the whole tumor to 2 Gy
➔ higher peripheral dose from **leakage**



ESTRO School

IMRT and prediction of tumor induction

2nd problem with IMRT:

small subfields ➔ **more MU** to treat the whole tumor to 2 Gy
➔ higher peripheral dose from **leakage**

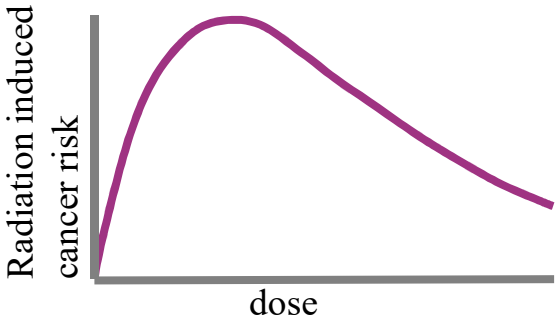
MUs for 10 prostate patients

Table 2. Mean and maximal MU requirements per fraction for each treatment approach*

Treatment type, energy, and accelerator	MUs per fraction: Mean (SD of the mean) (SD)	MUs per fraction: Maximal†
Conventional		
18 MV	233 (2) (7)	254
IMRT		
6 MV		
Varian	986 (24) (75)	1211
Siemens	1147 (35) (110)	1477
10 MV		
Varian	808 (20) (64)	1001
15 MV		
Varian	830 (25) (78)	1064
Siemens	1049 (30) (96)	1337

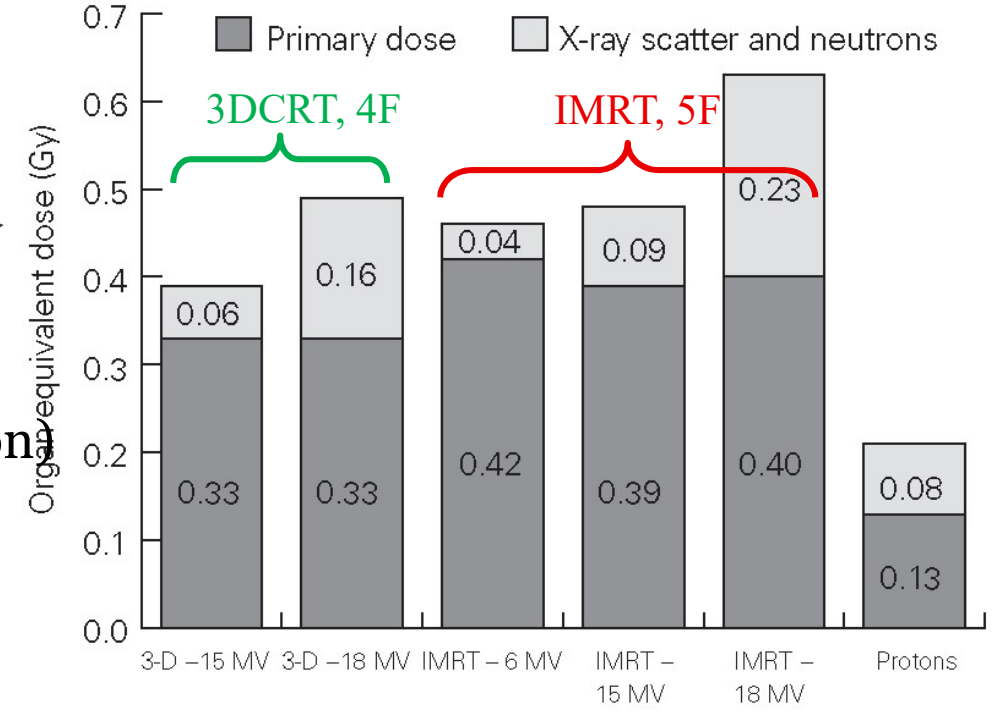
Kry 2005

IMRT and prediction of tumor induction



proportional to P(cancer induction)

Calculations for prostate cancer



Schneider et al. 2006

RT for Hodgkin: prediction of BREAST and LUNG cancer incidence

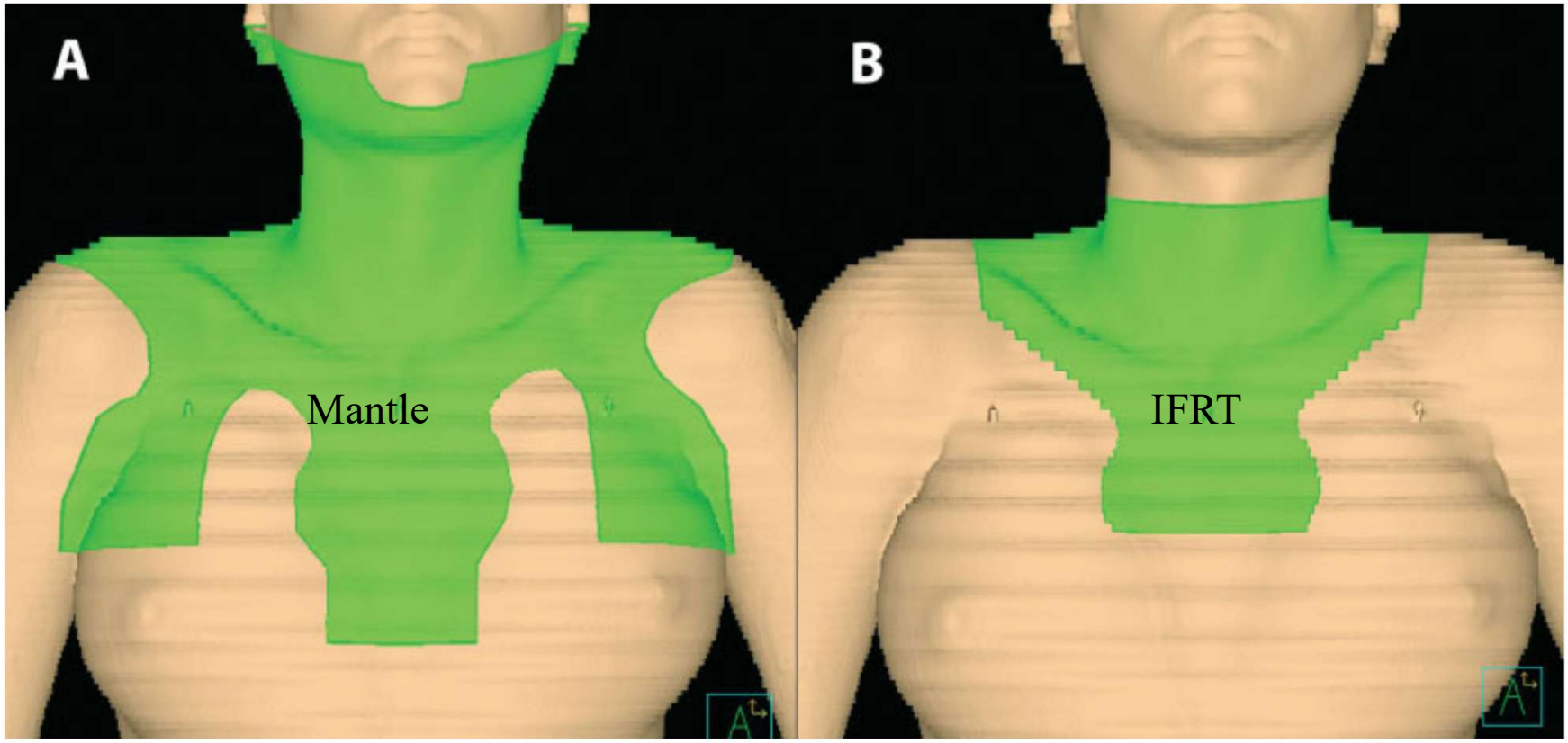
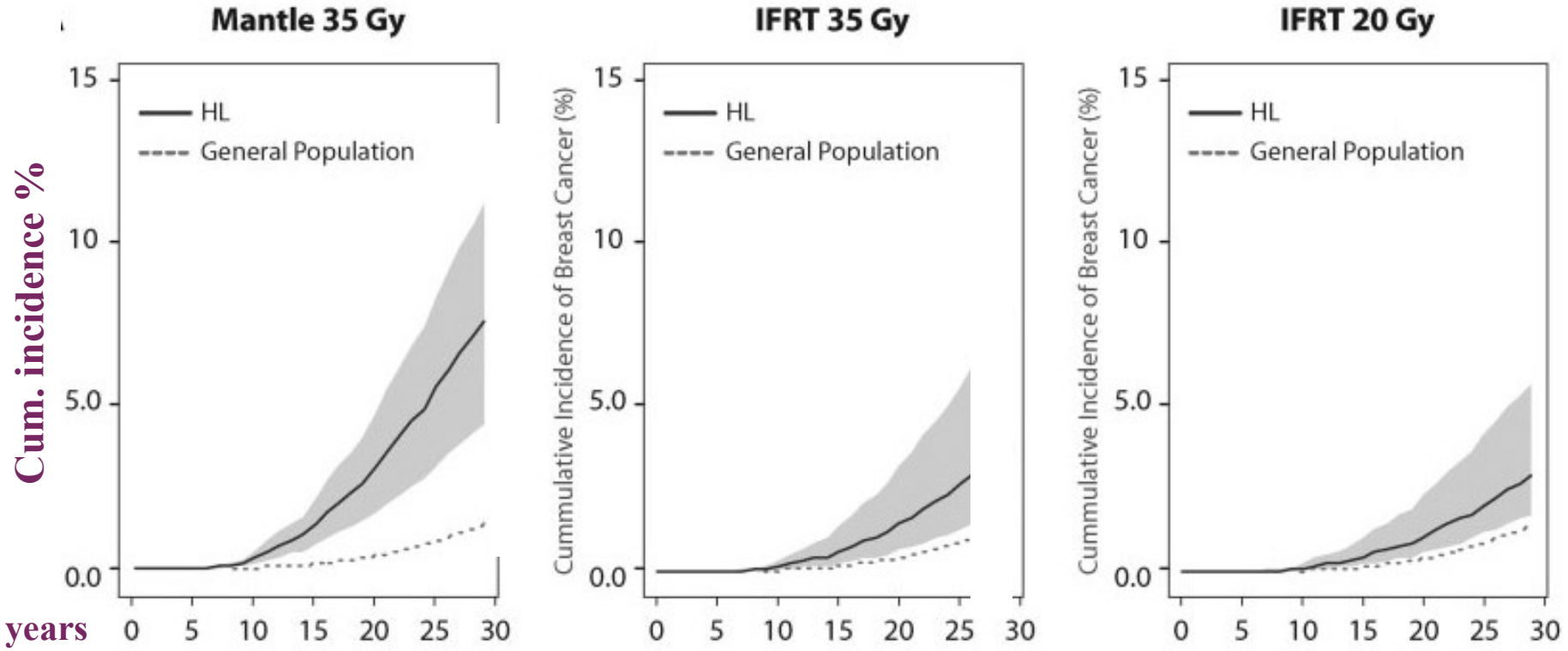


FIGURE 1. Digitally reconstructed CT planning images demonstrate surface projection of (A) anterior beam of mantle RT field, (B) mediastinal involved field RT (IFRT). Substantial reduction in breast tissue exposure can be seen with the omission of the axillae from IFRT fields.

Hodgson et al, 2007

RT for Hodgkin: prediction of BREAST and LUNG cancer incidence



grey areas: spread in 37 patients

Hodgson, Brenner et al, 2007

Clinical lessons - Discussion

- Generally, the **benefits** of RT greatly **outweigh risks** for tumor induction! (improvements are needed, increased survival).
- Second tumor incidence far from **high dose areas** is often relatively low (non-IMRT).
- Depending on **tissue/primary tumor**,… the risk may increase, level off, or decrease at high dose.
- If probability of tumor induction levels off, or decreases for higher doses, tumor induction **may increase for IMRT and rotational therapy**.
- High energy **photon beams (>10 MV)** may result in enhanced tumor induction due to neutron peripheral dose.
- **Uncertainty in epidemiological data**: even studies based on large databases of cancer registries (~100.000 patients) may have conflicting outcome on second cancer incidence. More/better data is needed, e.g. to predict the impact of new techniques such as IMRT or VMAT.

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