ESTRO School

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From frame-based stereotactic radiosurgery to frameless image-guidance:

a historical overview

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DV is involved in an on-going scientific collaboration with RaySearch, Sun Nuclear, ORFIT

Learning objectives

- To learn the historical background and development of cranial radiosurgery (SRS) and stereotactic body radiotherapy (SBRT)
- To discuss the practice of frame-less image-guided versus frame-based stereotactic cranial radiosurgery.
- Be able to compare frame-based and IGRT-frameless intracranial stereotactic radiosurgery (SRS).
- Understand the uncertainties involved in target localization and patient positioning in intracranial SRS.

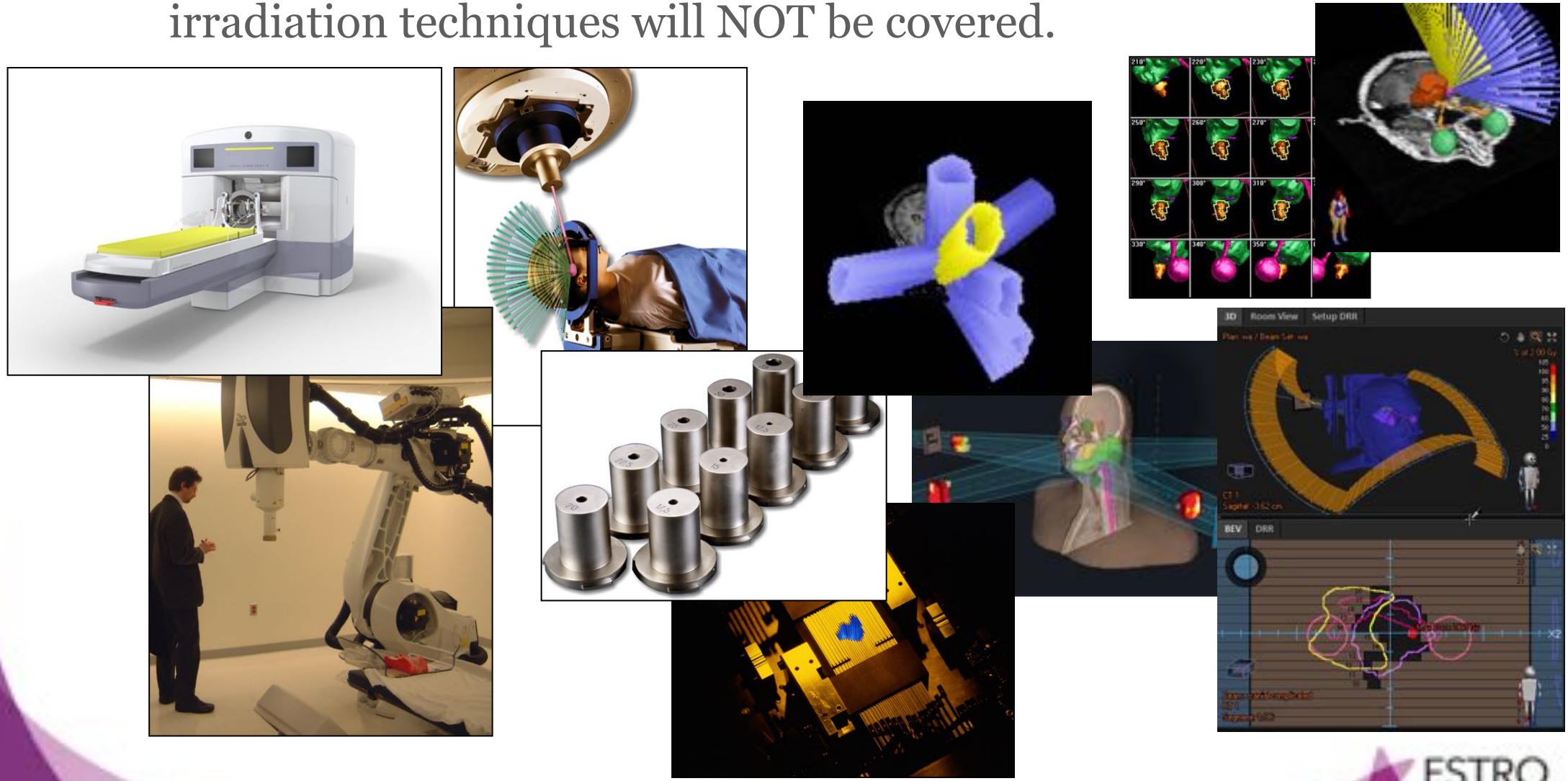
Disclaimer

- The perfect tool does not exist ... it's how you use it
- A fool with a tool is still a fool!

- Basically, it's a team effort really!

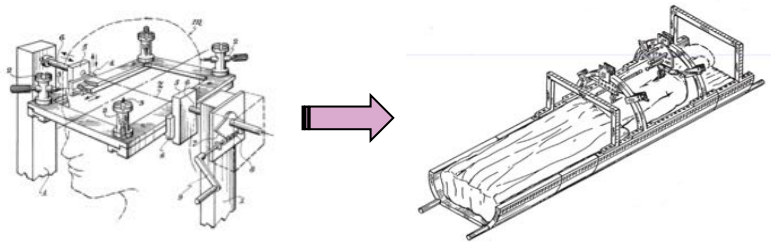
Comment

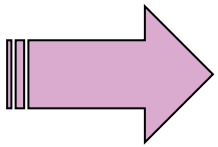
- The main focus of this presentation is on target localization, irradiation techniques will NOT be covered.

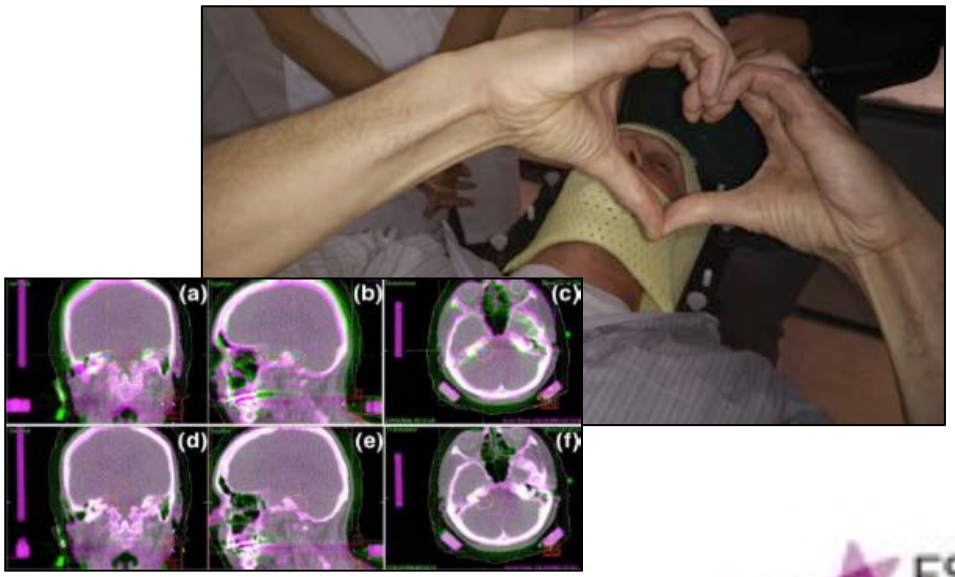


To frame or not to frame …

- Why evolving towards frameless intracranial SRS?
- Historical evolution:
  - SRS with frame to SBRT with frame
  - SBRT from frame (SBF) to IGRT
  - SRS following the IGRT evolution in SBRT
  - Accuracy of frameless SRS

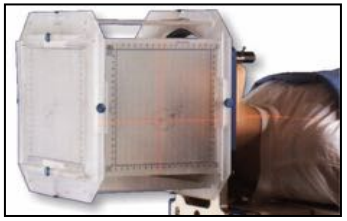




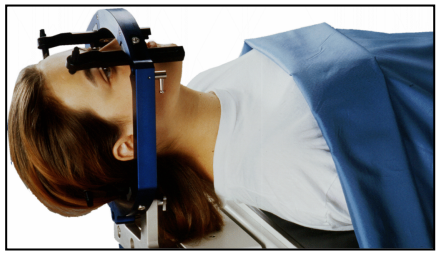
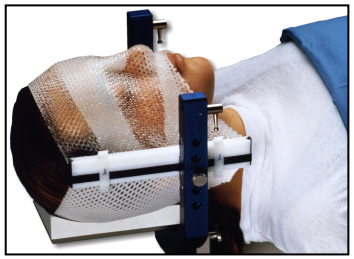


Some definitions

- Frame-based versus Frameless
  - Whether a stereotactic system of external coordinates is used for localization and positioning or anatomy and ‘real-time’ in-room imaging

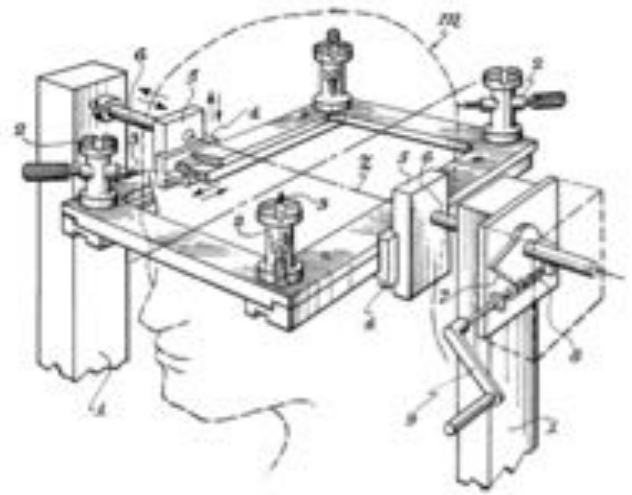


- Invasive versus non-invasive
  - Whether the patient is rigidly fixed to the stereotactic system using invasive techniques or a ‘patient friendly’ immobilization system is used allowing multiple fractions

A short history of intracranial SRS

- The stereotactic frame was essential for ~ 100 year
- Stereotactic:
  - **stereos**: rigid, fixed
  - **taxis**: ordering
  - Rigid relationship between an external system of coordinates and the internal anatomy of the brain



Derechinski *et al.*

- Invasive fixation of the stereotactic frame to the bony skull was considered to ensure sub-millimeter accuracy for surgery and radiotherapy

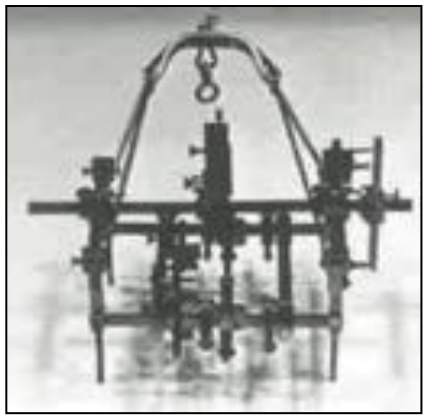
A short history of intracranial SRS

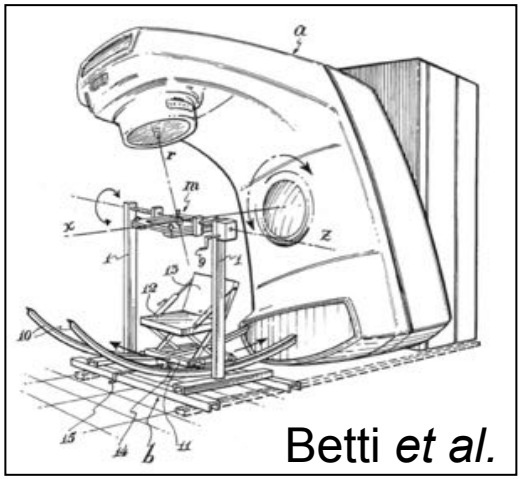
- **1908:**
  - **Robert Henry Clarke and Victory Horsley:** Stereotactic technique based on the reproducibility of the relationships between landmarks on the skull (external auditory canals, midline) and anatomical structures within the brain
- **1950s:**
  - **Lars Leksell:**

    Experiments with 250 kV rotating X-ray source (1951) and stereotactic proton therapy (1955)
- **1967:**
  - **Lars Leksell:**

    Gamma-knife radiosurgery using ^{60}Co-sources for treatment of functional disorders
- **1980s:**
  - **Oswaldo Betti and Frederico Colombo:**

    CT-localization and linac-based SRS





Mechanical accuracy, in phantom!

	Mechanical accuracy	Overall treatment accuracy
Gamma Knife Perfexion♮	**0.30 mm**	**0.93 mm**
Dedicated Linac: Novalis°	**0.31 mm**	**0.50 – 1.5 mm**
Cyberknife*	**0.50 mm**	**0.85 mm**

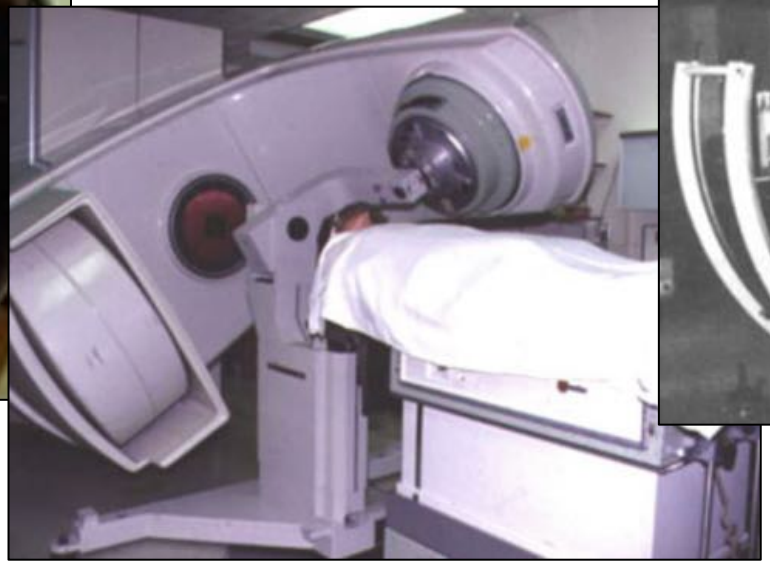
* Hoogeman 2008 & Murphy 2009
♮ Wu & Maitz & Massagier 2007
° Verellen 2003

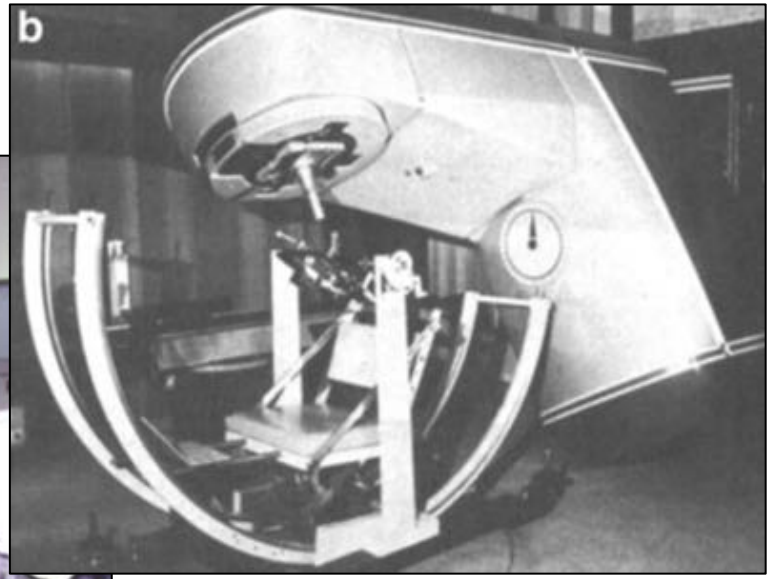
Frame-based SRS

- Frame makes sense in a setup with a physical-rigid connection between patient and radiation source

Leksell *et al.*

Bova-Friedman *et al.*





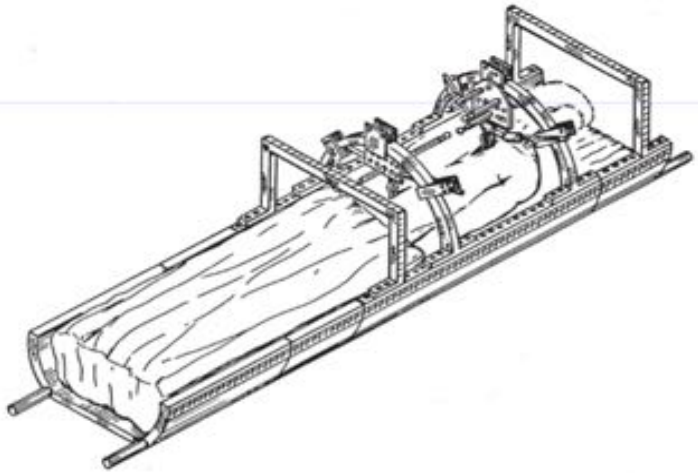
Betti *et al.*

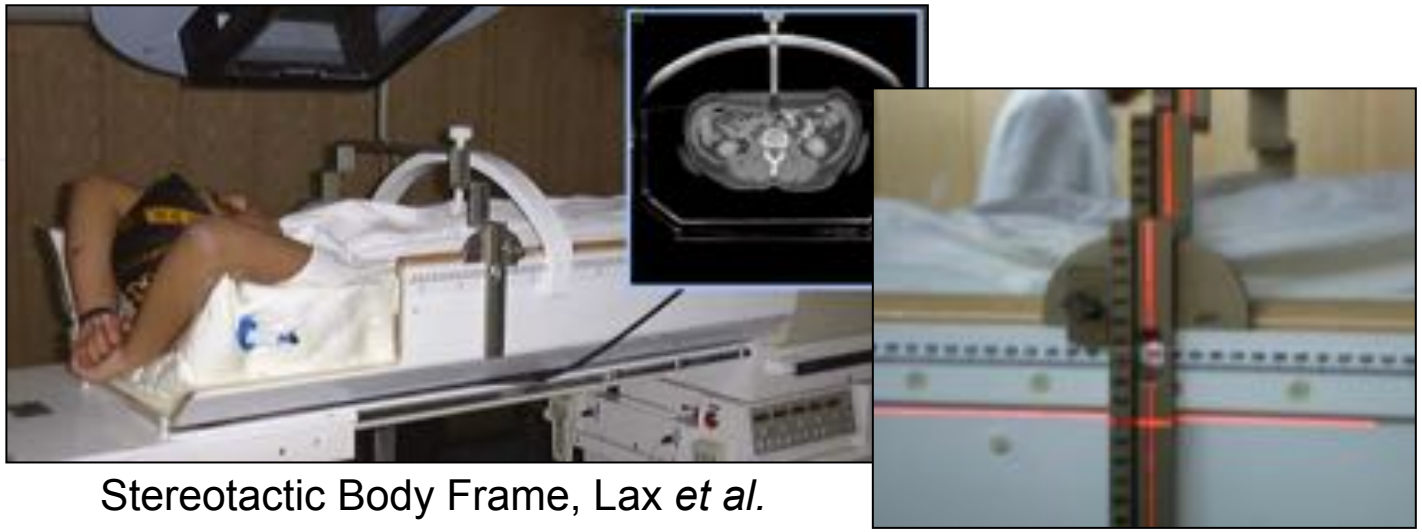
Frame-based SRS

- Frame makes sense in a setup with a physical-rigid connection between patient and radiation source …
- The treatment couch is probably the weakest link

Towards extracranial SRS: body frames

- Challenge:
  - ➢ Creating a rigid external frame that will provide a repeatable reference for sites in the body



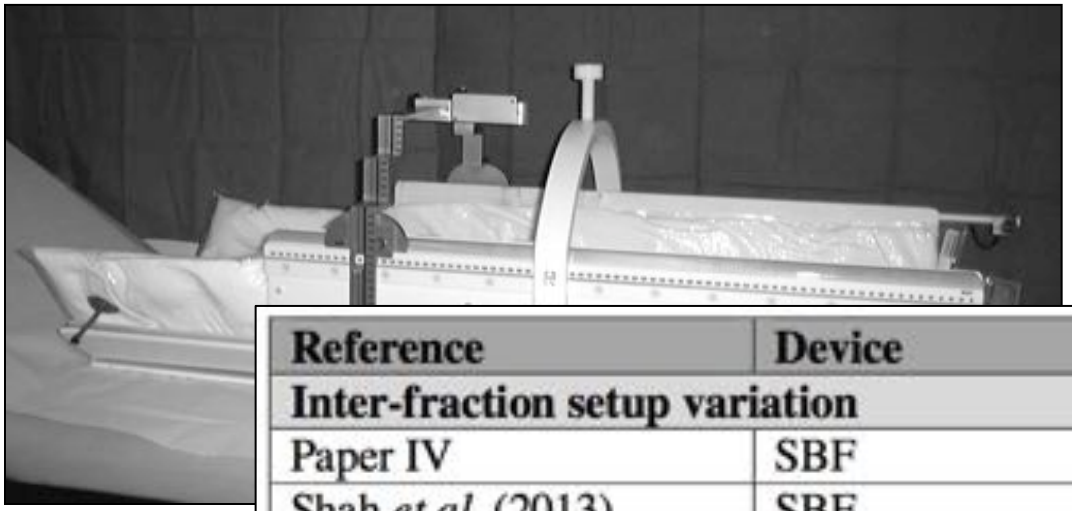


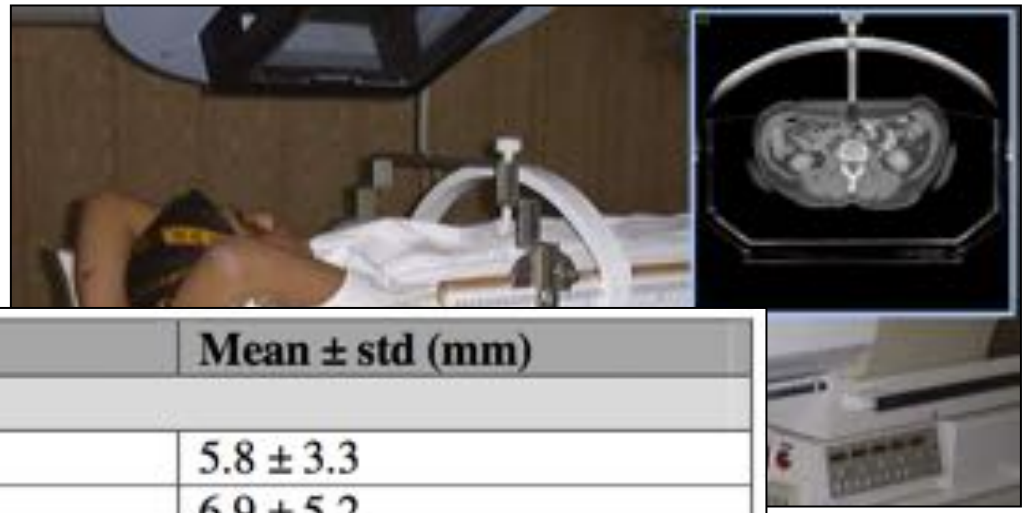
Stereotactic Body Frame, Lax *et al.*

'Introduced' for both **immobilization** as well as **target localization** ("stereotactic reference frame"), cf. stereotactic radiosurgery

!Pioneers in SBRT!

Towards extracranial SRS: body frames





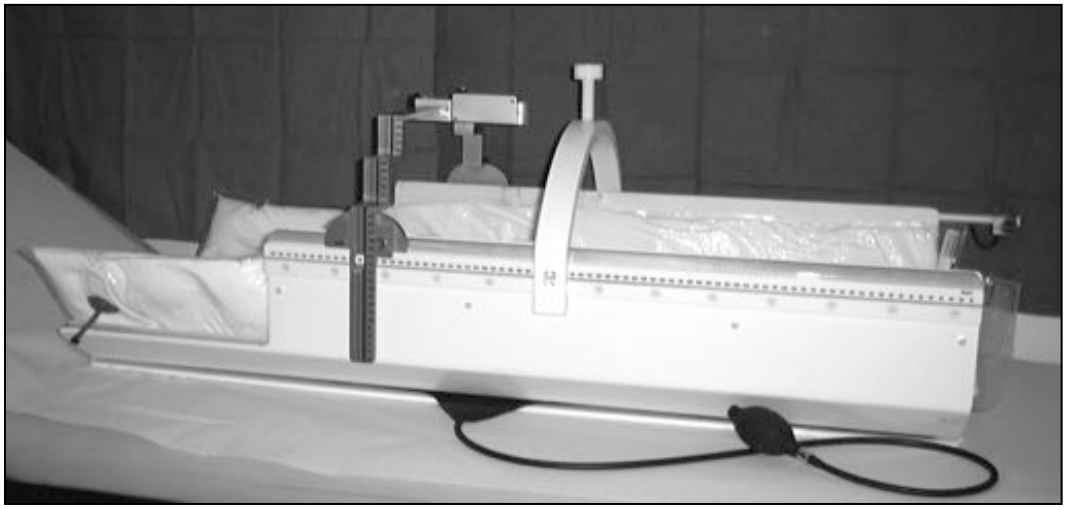
Reference	Device	Mean ± std (mm)
Inter-fraction setup variation		
Paper IV	SBF	5.8 ± 3.3
Shah *et al.* (2013)	SBF	6.9 ± 5.2
Foster *et al.* (2013)	SBF without compression	7.4 ± 4.0
Foster *et al.* (2013)	SBF with compression	7.3 ± 4.1
Shah *et al.* (2013)	Hybrid device	12.6 ± 10.2
Intra-fraction tumour position variation		
Shah *et al.* (2013)	SBF	2.3 ± 1.4
Foster *et al.* (2013)	SBF without compression	1.3 ± 1.5
Foster *et al.* (2013)	SBF with compression	1.7 ± 2.0
Shah *et al.* (2013)	Wing board	3.3 ± 1.7
Shah *et al.* (2013)	No device	3.3 ± 2.2

std = standard deviation, SBF = stereotactic body frame

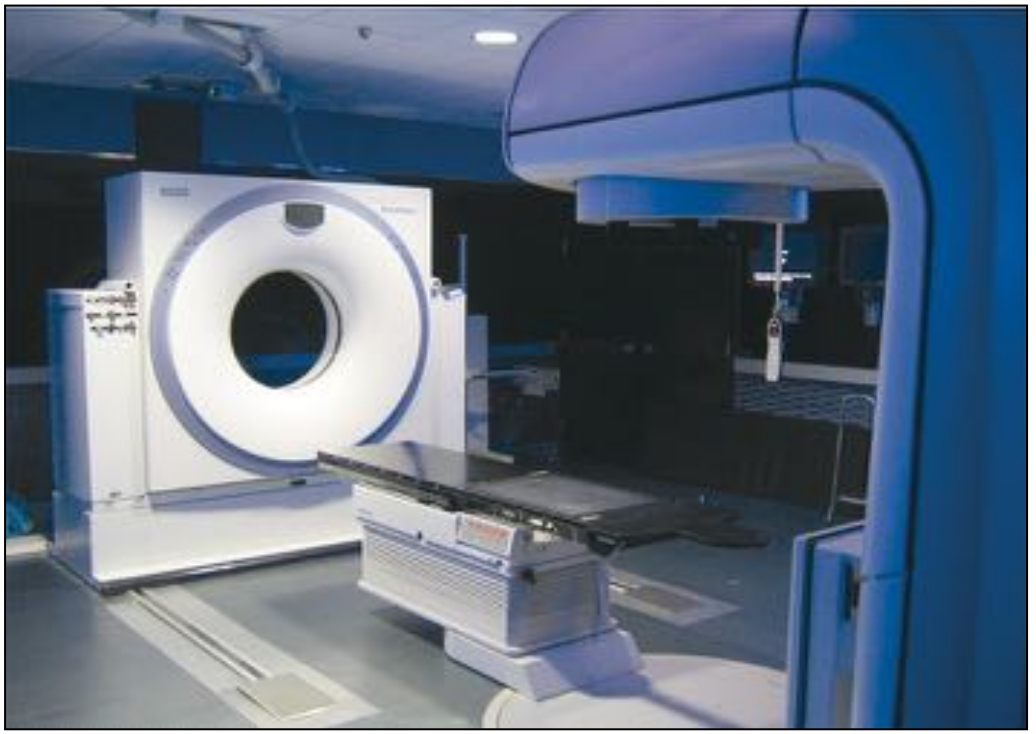
K. Karlsson, PhD thesis, 2016

Towards extracranial SRS: body frames

… still requires IGRT



Stereotactic Body Frame, Lax *et al.*



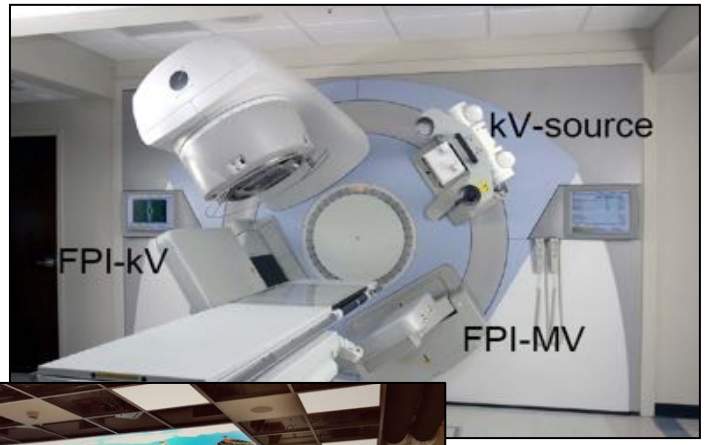
- AAPM TG 101 recommendation:
  - "Body frames and fiducial systems are OK for immobilization and coarse localization"
  - "They shall **NOT** be used as sole localization technique"

Lax *et al.* Acta Oncol 1994

Benedict *et al.* Med Phys 2010

Evolution of IG-SBRT

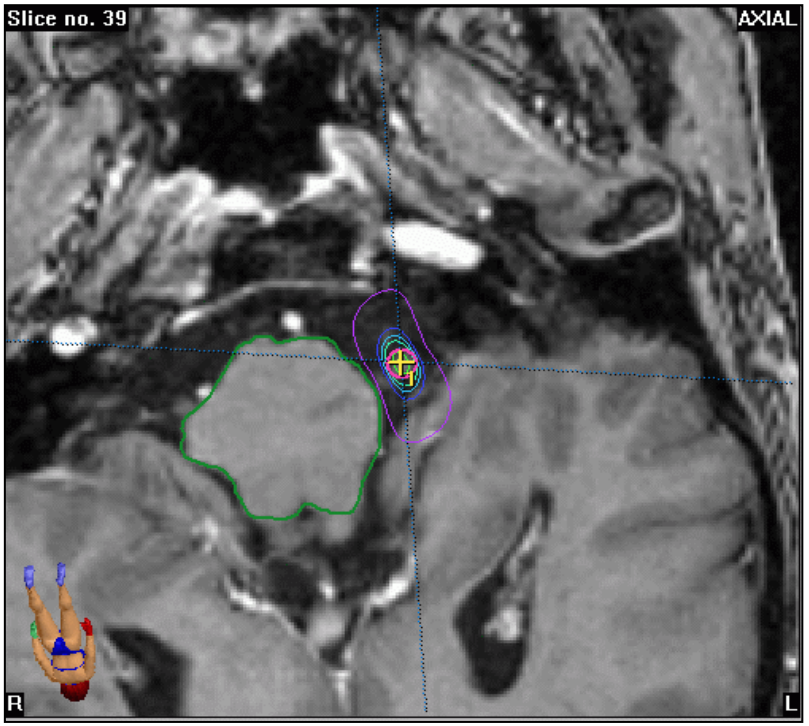
- SBRT and motion management



- … well, you'll see plenty of this during the course

Frameless SRS

- High precision “frameless” stereotactic radiosurgery:

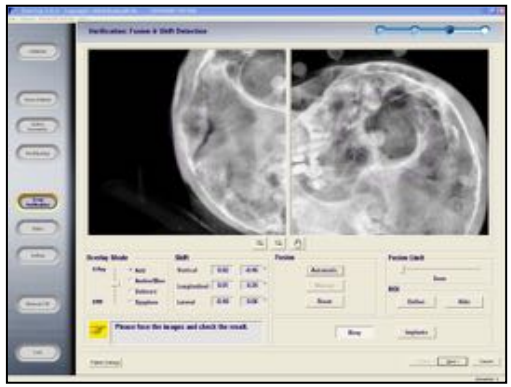


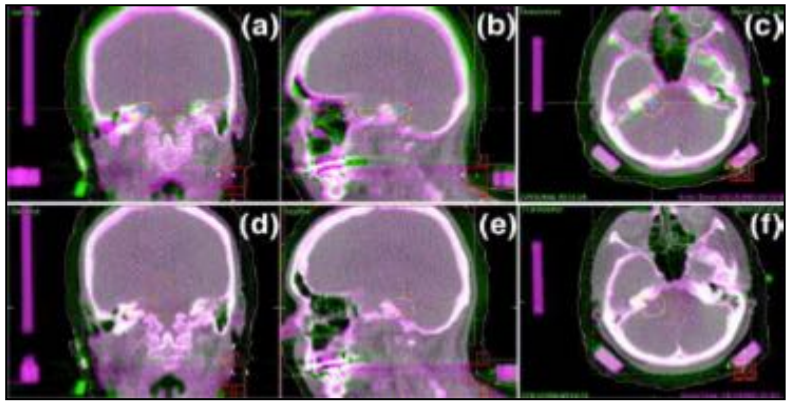
- … **also** requires implementation of image guidance systems for target localization and positioning on the linac!

Image-guided frameless SRS

- Image-guided “frameless” stereotactic radiosurgery:

  - Replacement of the stereotactic devices with external co-ordinate and reference systems for patient positioning, by **direct imaging** before and during treatment with **on-line correction**

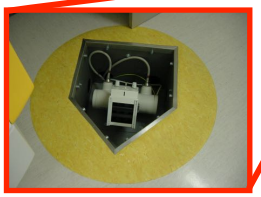


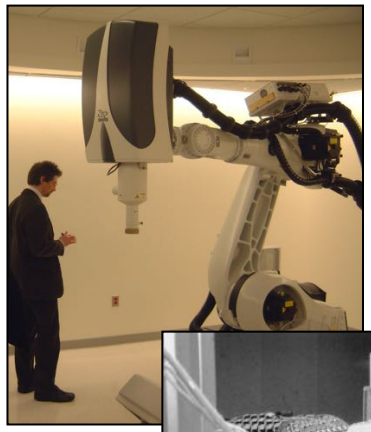


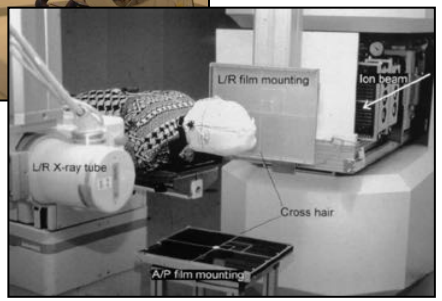
  - Making use of **internal anatomy rather than external landmarks** to localize target, position patient, and avoid geographic miss during treatment.

Image-guided frameless SRS

- 2D/3D, planar imaging







- 3D, volumetric imaging

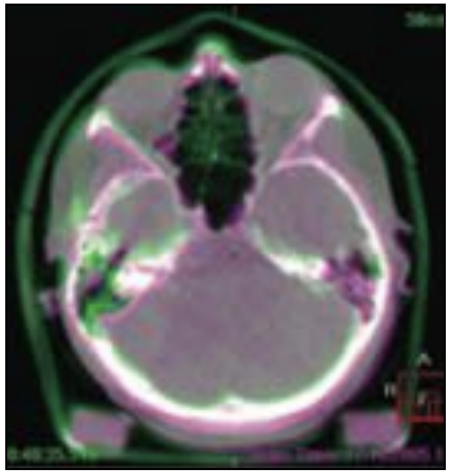


Image-guided frameless SRS

- Also LGK is introducing image-guided non-invasive frame-based and frameless SRS.

Courtesy K. Dieckmann

Image-guided frameless radiosurgery
A typical workflow

- Non-invasive immobilization

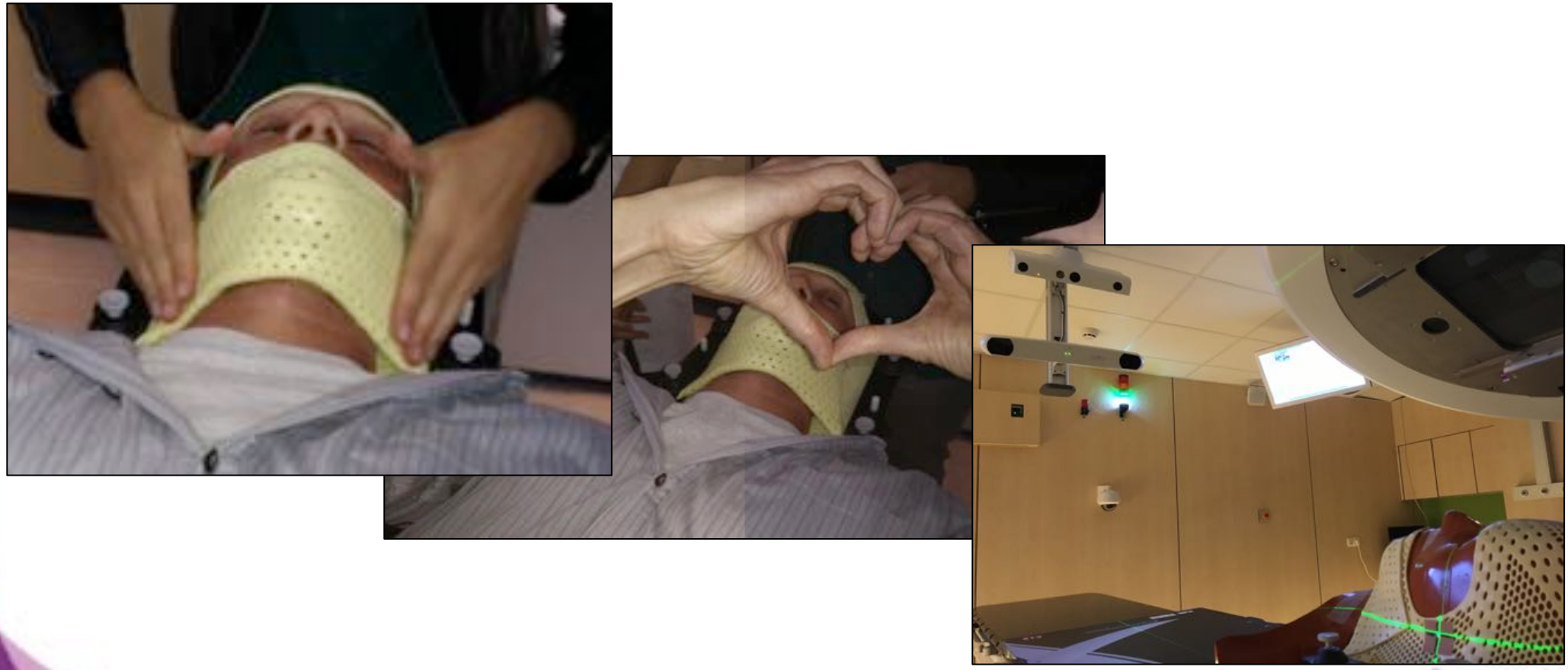


Image-guided frameless radiosurgery
A typical workflow

- Image-guided, automated positioning

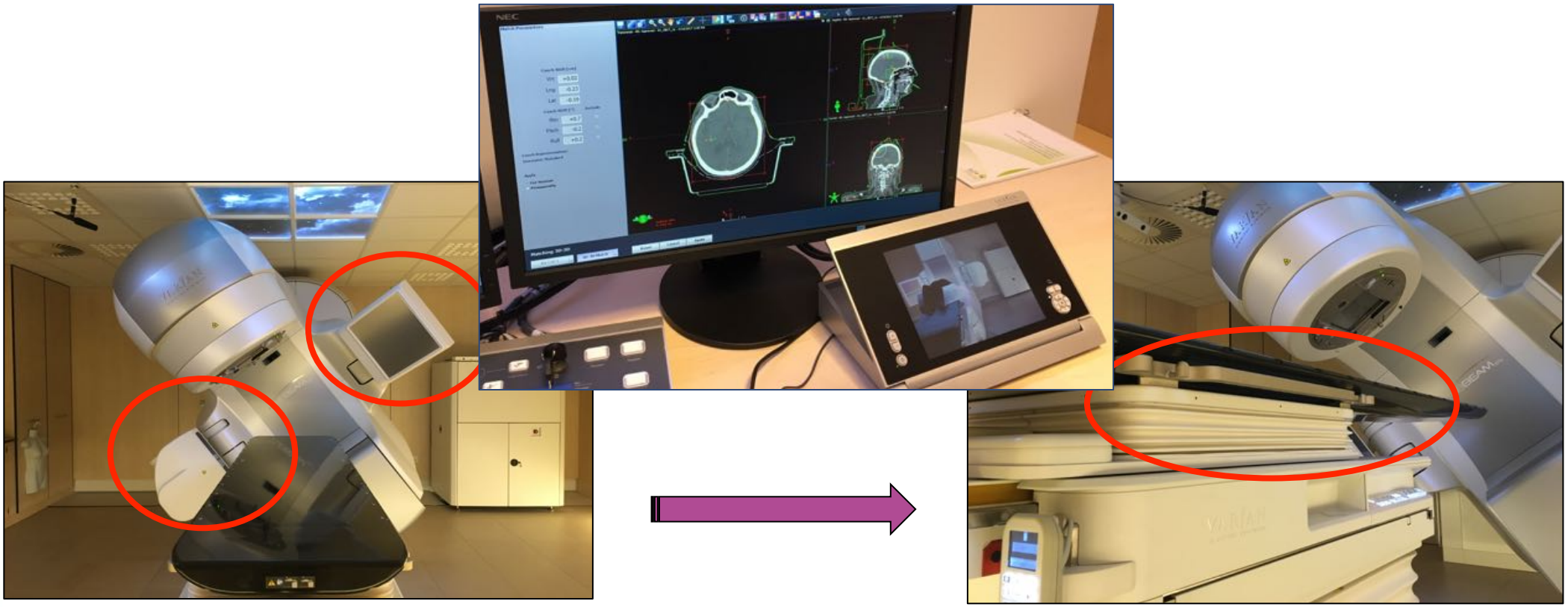


Image-guided frameless radiosurgery
A typical workflow

- Constant and real-time monitoring of motion

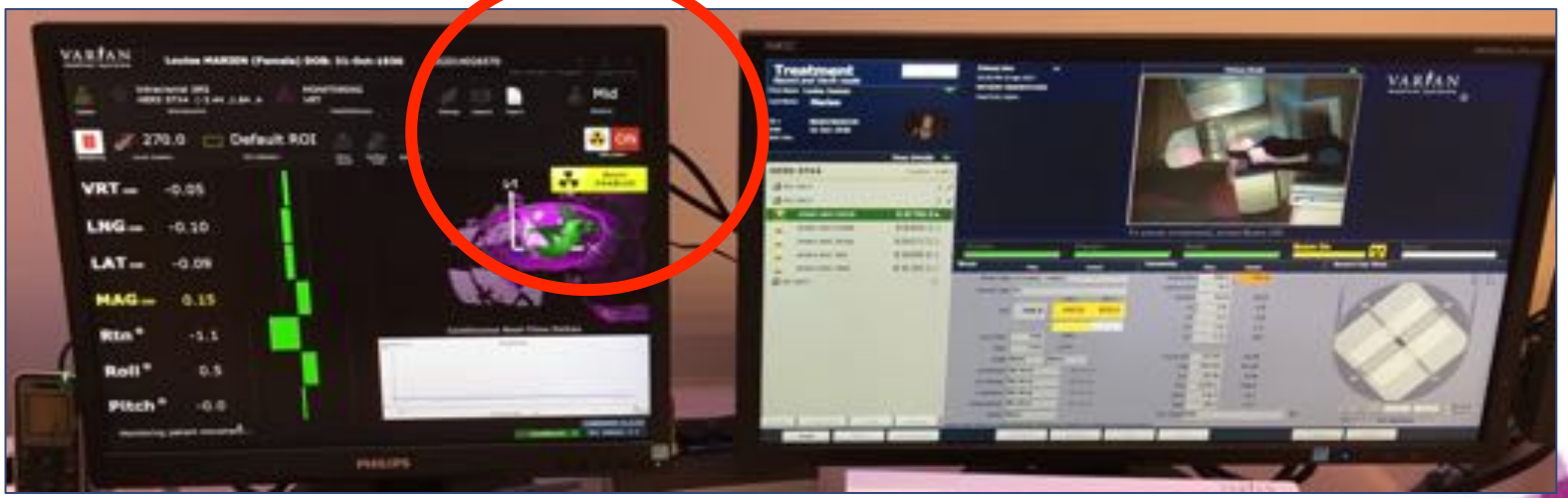
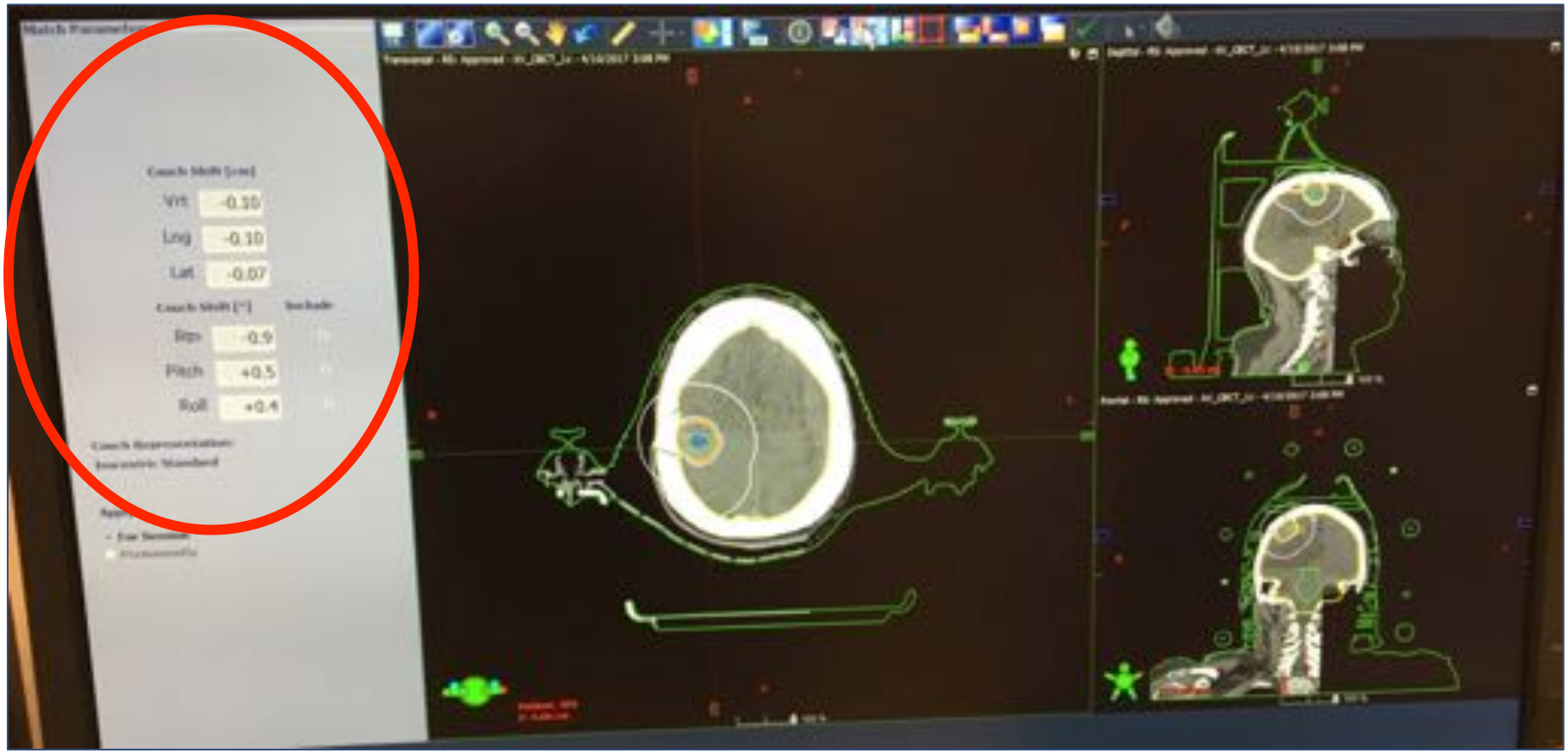


Image-guided frameless radiosurgery
A typical workflow

- Final verification with volumetric 3D CBCT



Outline

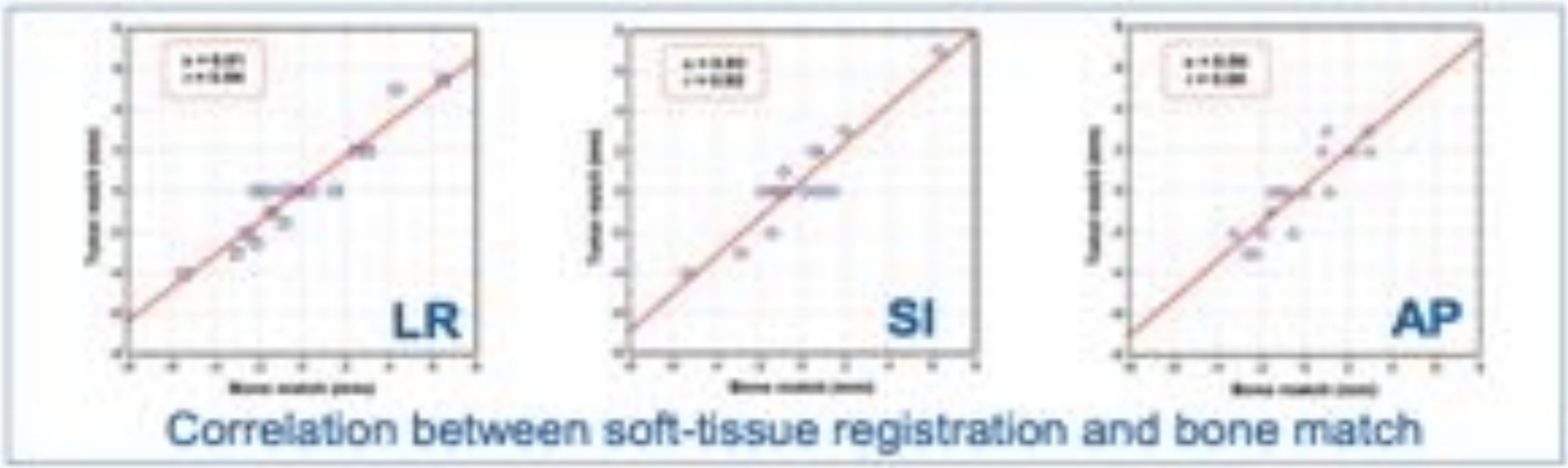
- Can we use bony structures for target localization?
- What accuracy can be achieved?
  - In phantom
  - Clinical validation
- Frame versus frameless
- Some words of caution
- Conclusions and food for thought

Is the skull a suitable reference?

- If visualization of the target is not possible, one has to use the bony skull as a surrogate for the actual intra-cranial target in IGRT

- However, internal „motion“ of intra-cerebral tumor could be caused by:
  - Tumor progression
  - Tumor shrinkage
  - Changes of peritumoral oedema
  - **This is the same for invasive frame-based techniques**

Is the skull a suitable reference?



Correlation between soft-tissue registration and bone match

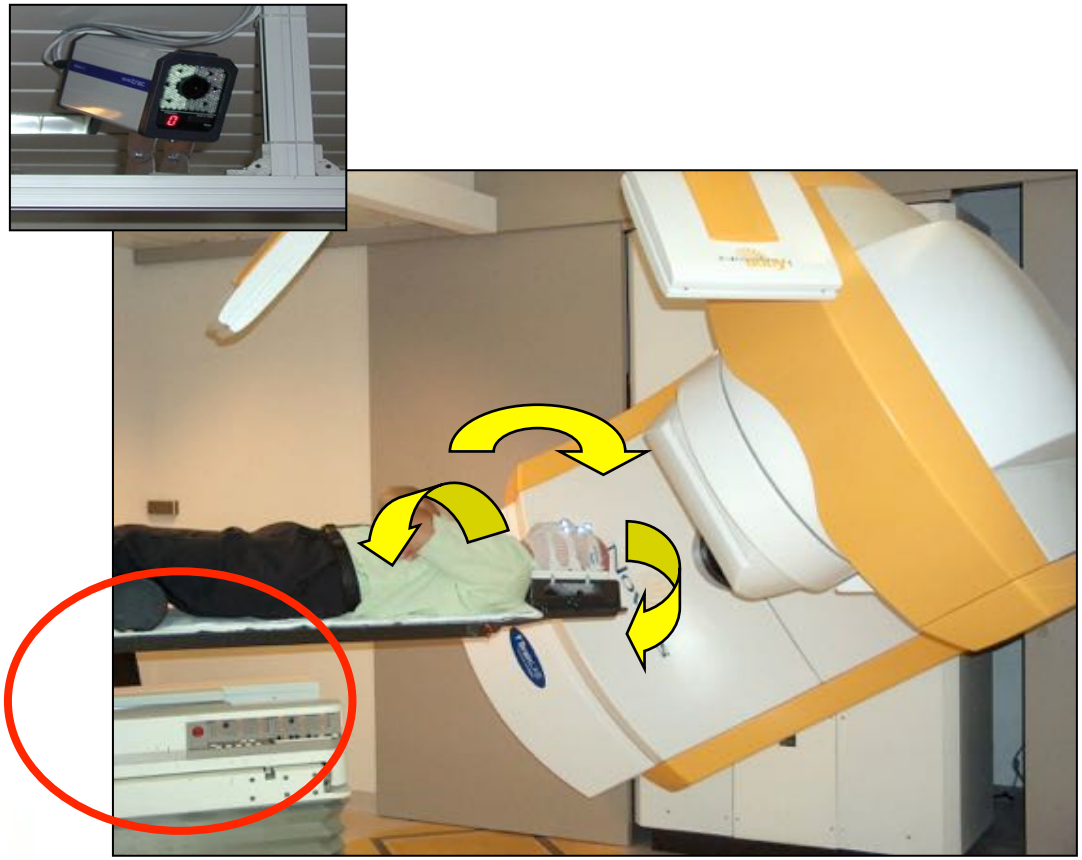
	Differences between bone and tumor match (mm)			
	LR	SI	AP	3D
Mean ± SD	-0.6 ± 1.0	0.0 ± 1.1	-0.2 ± 1.0	1.7 ± 0.7
Maximum	1.8	2.3	2	2.8

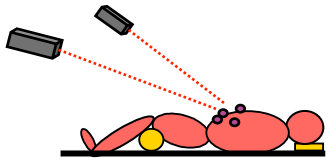
Stable tumor position relative to the skull for one week interval between planning and treatment

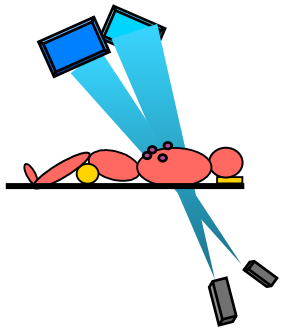
No influence of pre-treatment steroids

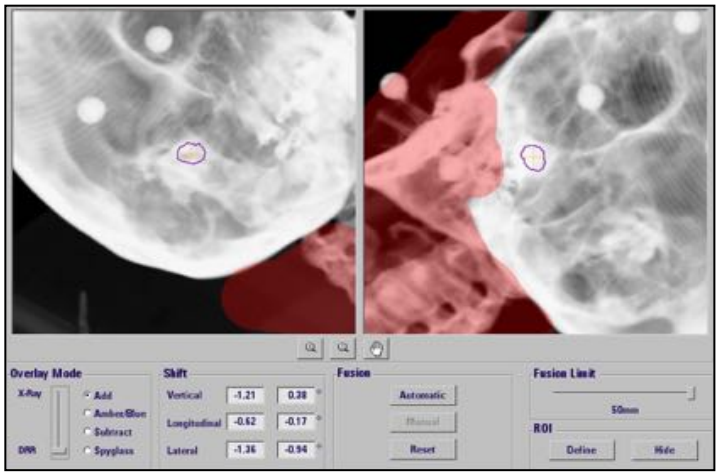
M. Guckenberger *et al.* IJROBP 2007

Is the skull a suitable reference?



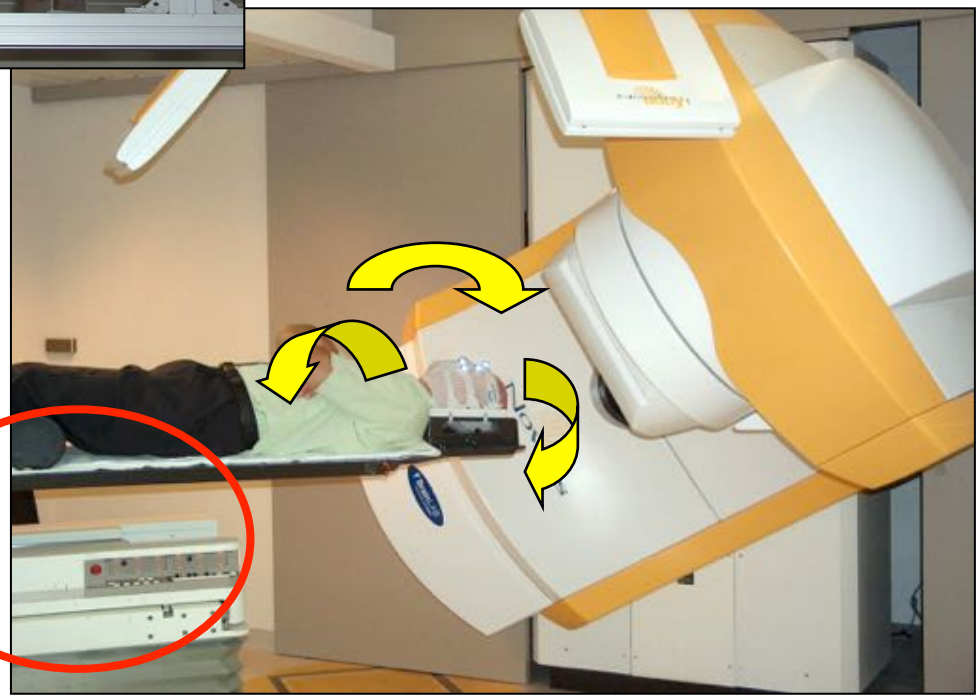


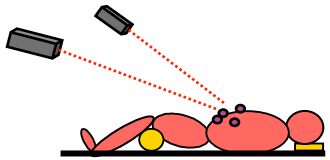


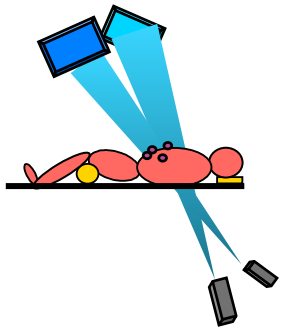


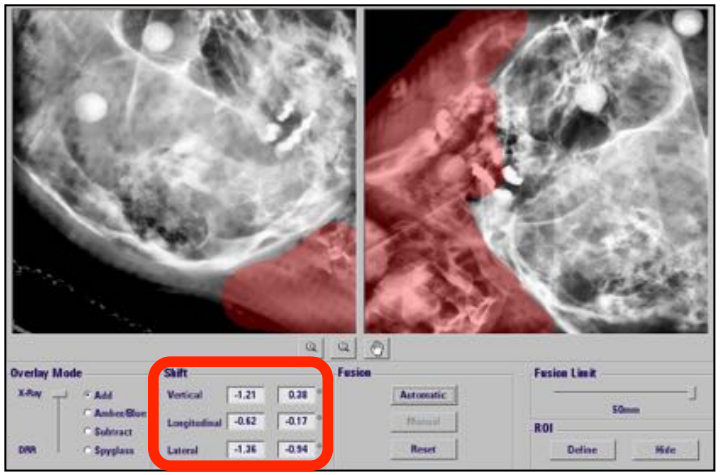
Full 6 DOF automated patient set-up

Is the skull a suitable reference?





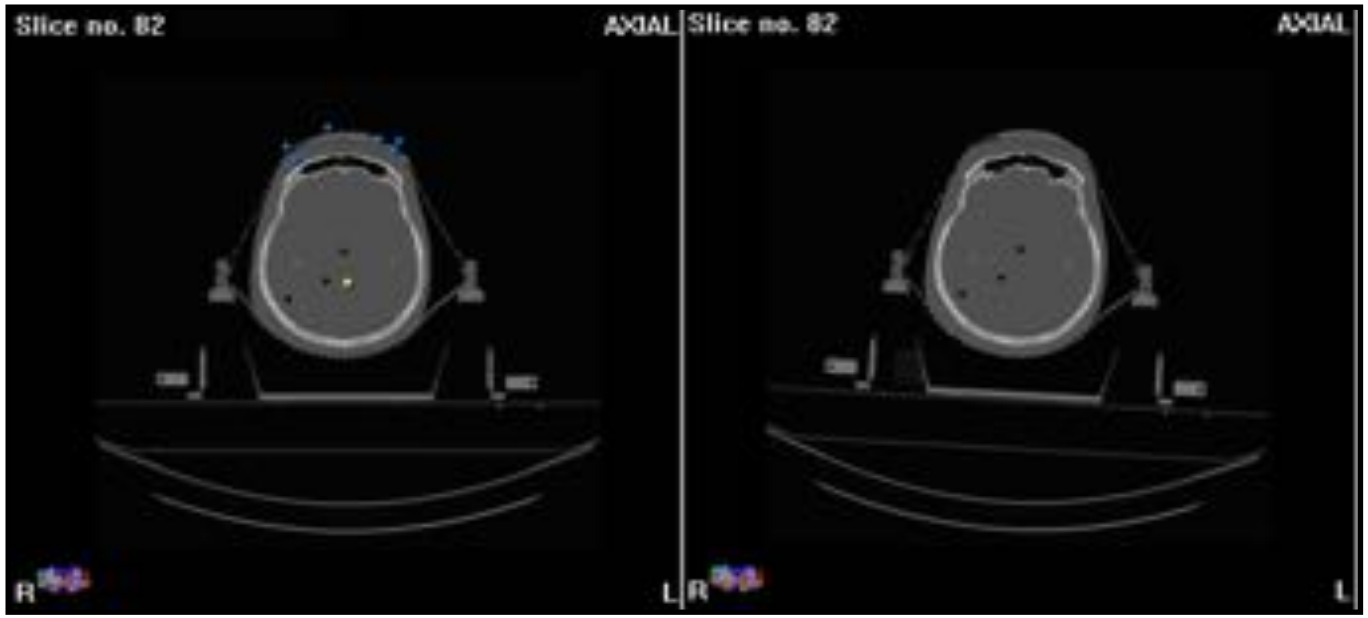


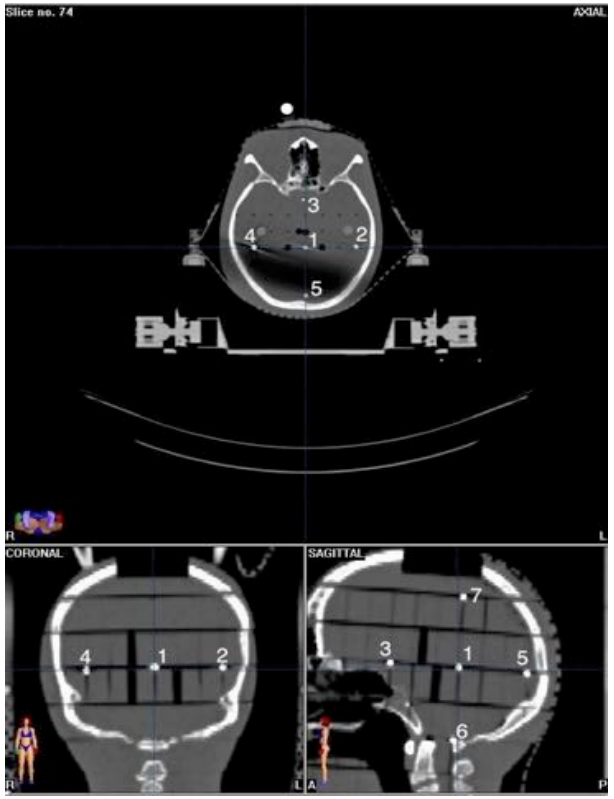


Full 6 DOF automated patient set-up

Is the skull a suitable reference?

- **A phantom study**
- Reference CT dataset rotated with center of rotation at the center of the image data set
- Positioning assessed by IR, water level, ExacTrac X-ray, portal films and implanted markers

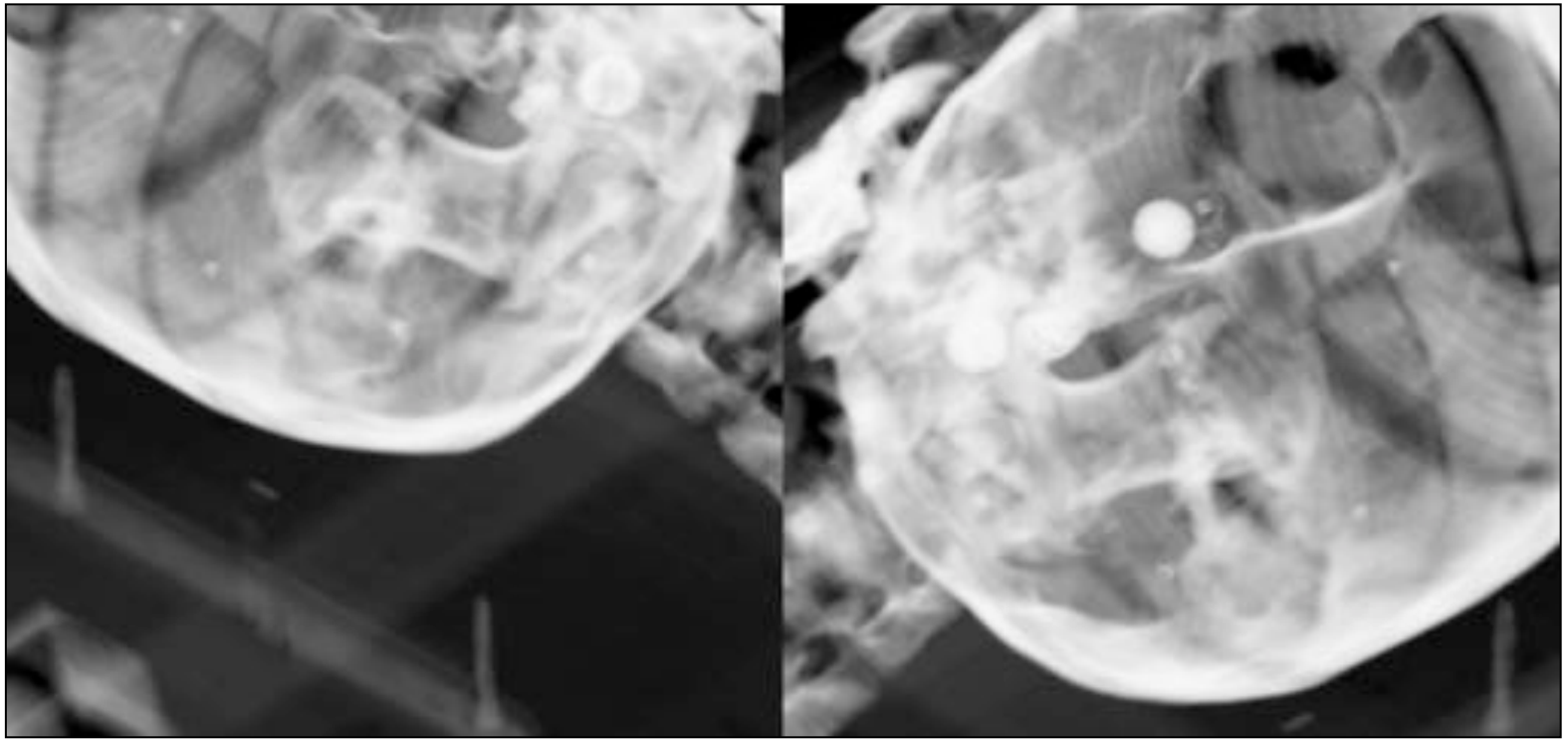




Gevaert *et al.* Int J Radiat Oncol Biol Phys 2012

Is the skull a suitable reference?

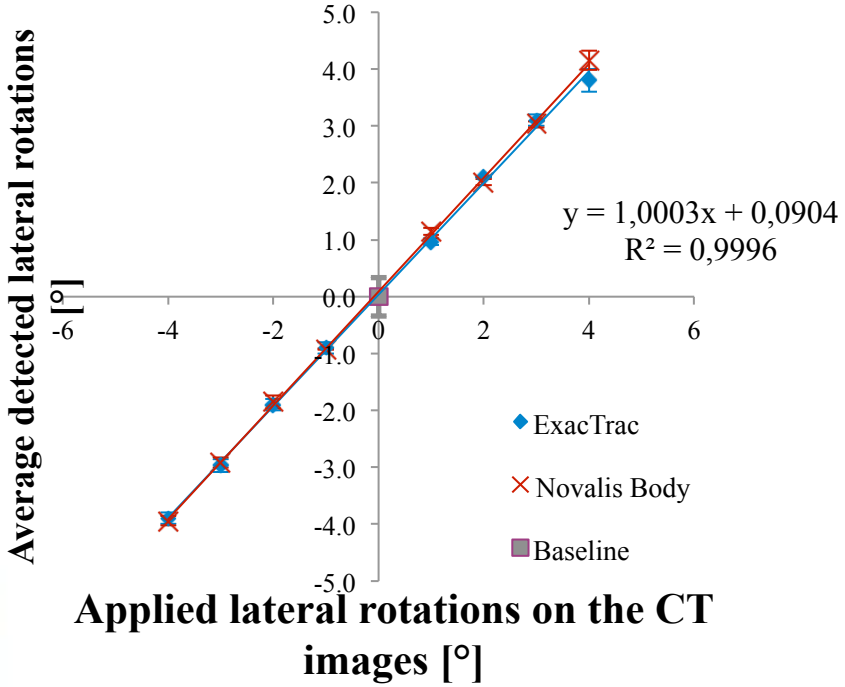
- Different locations were chosen to investigate the sensitivity of the registration algorithm on presence/absence of bony fiducials

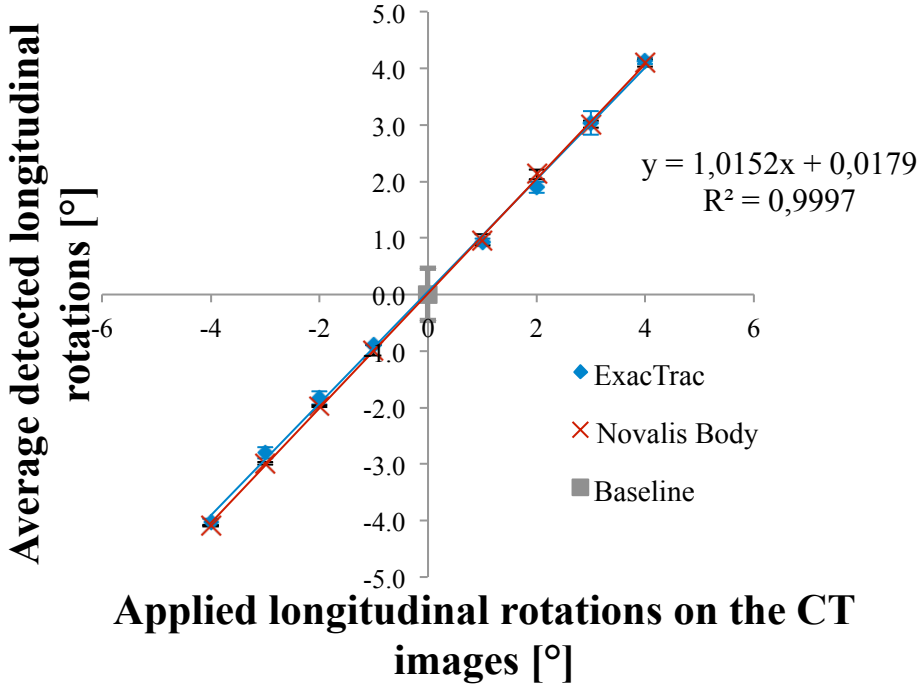


Gevaert *et al.* Int J Radiat Oncol Biol Phys 2012

Is the skull a suitable reference?

- Detection accuracy

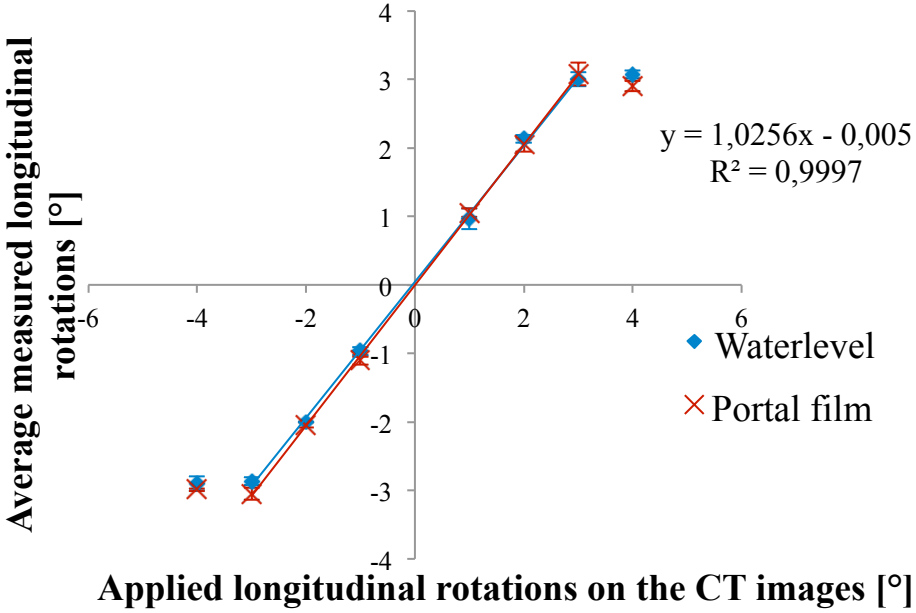


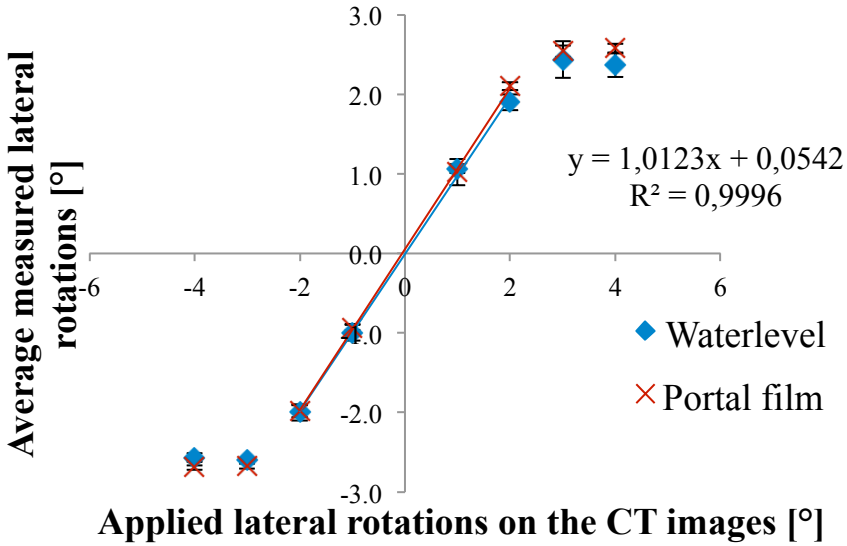


Gevaert *et al.* Int J Radiat Oncol Biol Phys 2012

Is the skull a suitable reference?

- Positioning accuracy (6DOF robotic couch)

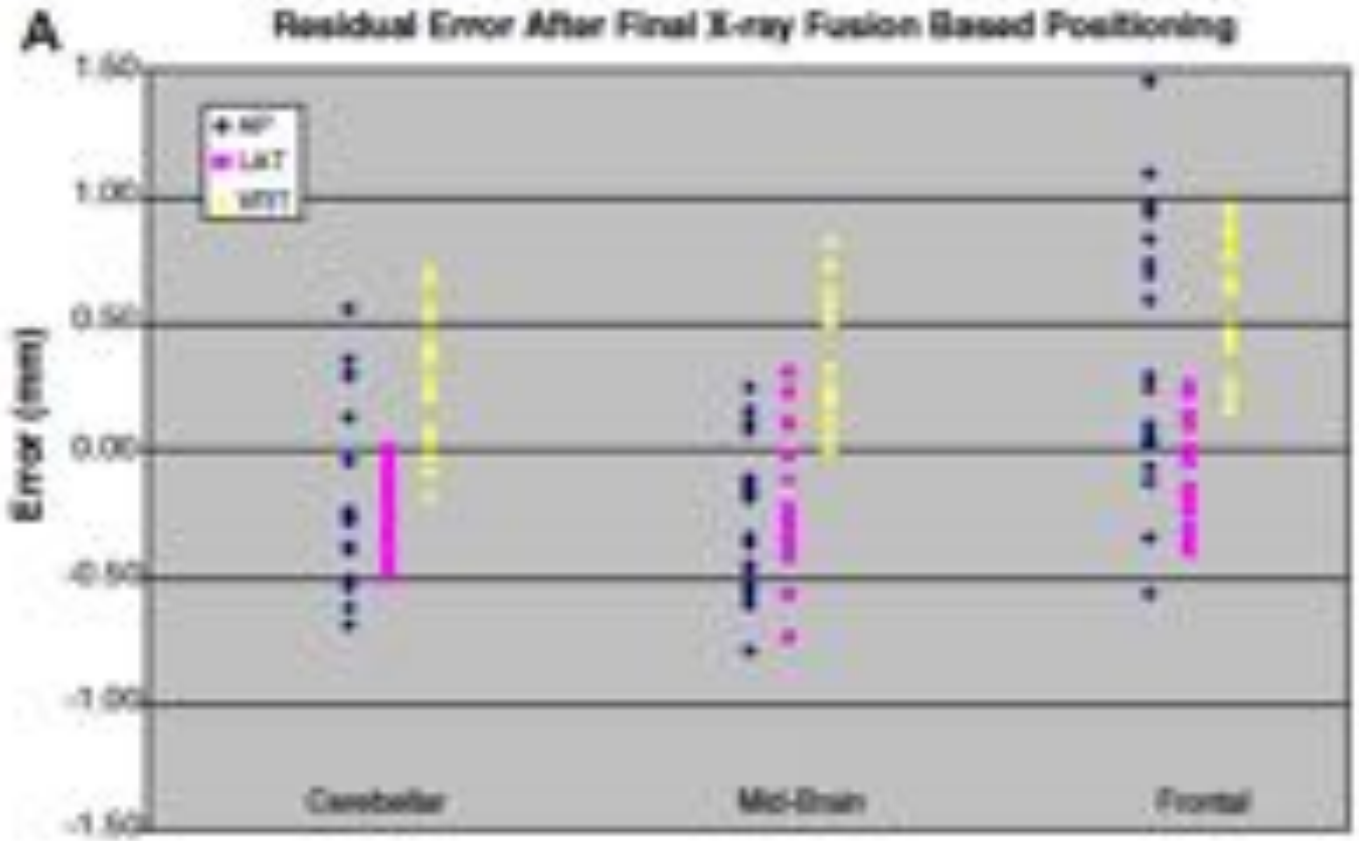




Gevaert *et al.* Int J Radiat Oncol Biol Phys 2012

Accuracy of IGRT/frameless SRS

- Hidden target Test
- 157 phantom set-ups, ≠ locations
- Residual error < 1.6mm (mean total error 0.7mm (1SD: 0.3mm)



Ramakrishna *et al.* Radiother Oncol 2010

Accuracy of IGRT/frameless SRS

Table 5. Summarized repositioning errors resulting from multiple translations and multiple rotations

	Bone		Gray value	
	Translational errors [mm] (x,y,z)	Rotational errors [°] (u,v,w)	Translational errors [mm] (x,y,z)	Rotational errors [°] (u,v,w)
Mean	0.04	0.01	0.08	−0.05
SD	0.13	0.40	0.10	0.16
Max ABS	0.30	0.90	0.20	0.30
Accuracy	0.11	0.29	0.11	0.12

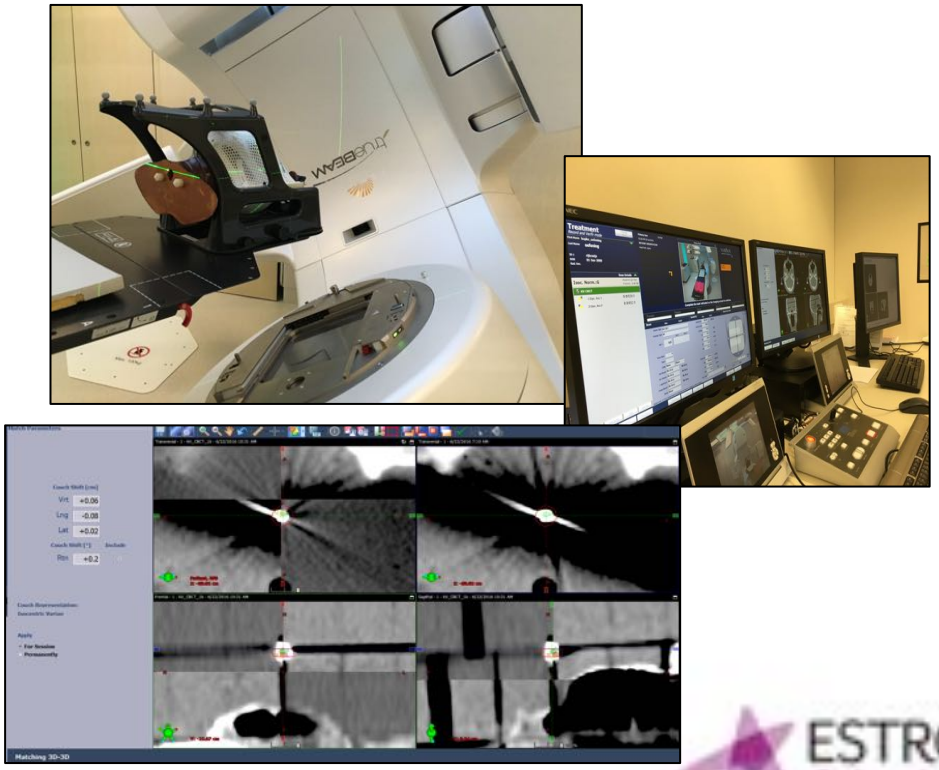
- IGRT work-flow with CBCT imaging and robotic correction of set-up errors achieves sub-millimeter accuracy **in phantom studies**

Meyer *et al.* IJROBP 2008

Accuracy of IGRT/frameless SRS

- Today's treatment machines achieve sub-millimeter geometric accuracy (with phantoms).
  - Sub-millimeter treatment and imaging isocentre accuracy

  - Sub-millimeter accuracy E2E "in phantom" testing (performed by RTT's)



IGRT/frameless: Clinical validation

Intra-fractional accuracy of the frame-less system

autor	Fixation system	x	y	z	Imaging device
Tryggestadt	1	0.06±0.7	0.02±	-0.12±0.8	CBCT
	2	0.26±0.7	0.10±	-0.26±0.5	CBCT
	3	0.06±0.5	-0.23±	0.04±0.4	CBCT
	4	0.03±0.3	-0.29±	-0.14±0.4	CBCT

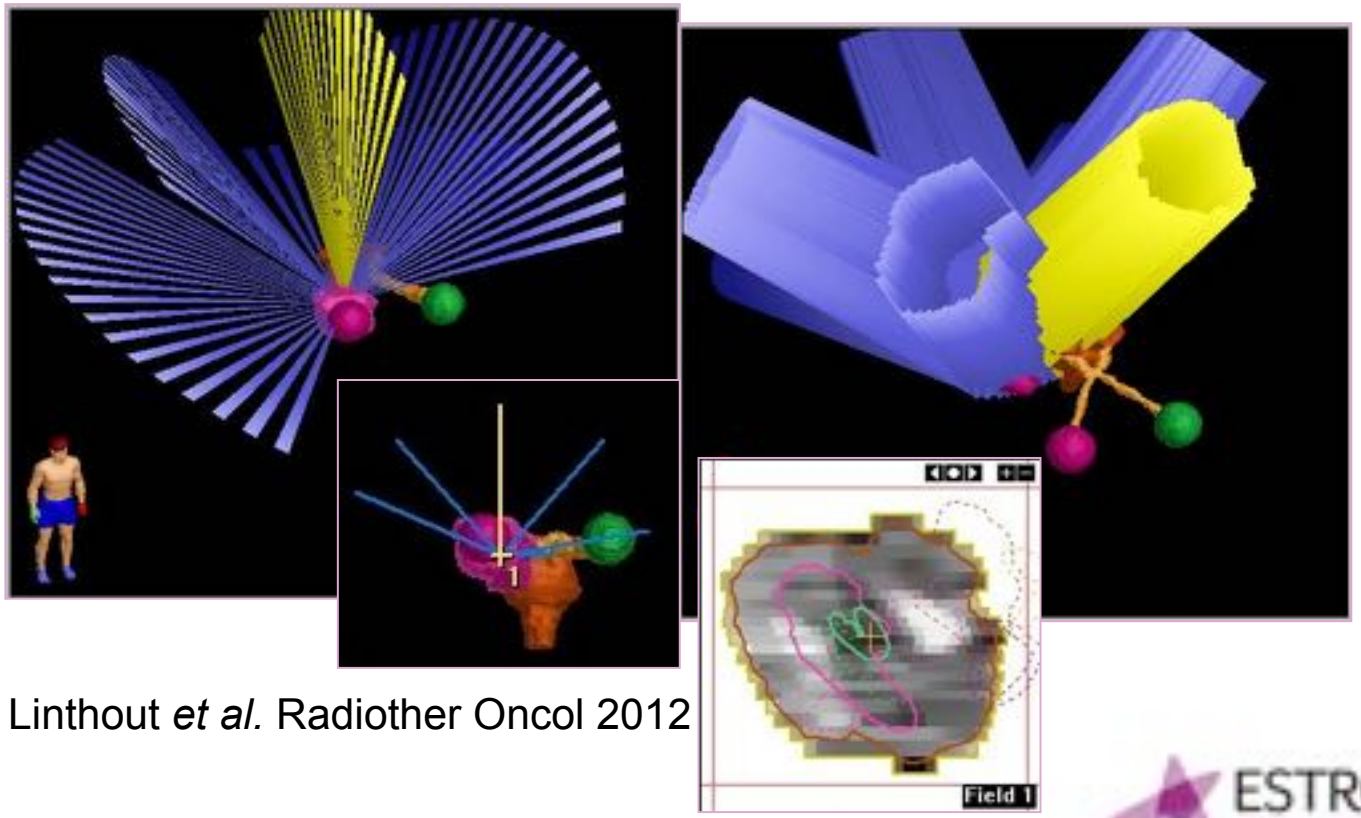
IGRT/frameless: Clinical validation

autors	Lateral x	AP y	CC z	Positioning error	Imaging modality
Miniti 2012	0.12mm±0.35	0.2mm±0.4	0.4mm±0.6		CT
Ingrosso 2012	0.5 mm±1.6	0.4mm±2.7	0.4mm±1.9	3.1mm±2.1	CBCT
Masi 2008	0.5mm±1.3	0.2mm±2.4	0.0mm±1.7	3.2mm±1.5	CBCT
Guckenberger 2007	0.7mm±2.7	0.0mm±2.4	-0.1mm±2.0	3.0mm±1.7	CBCT
Baumert 2005	0.04 mm±1.4	-0.1mm±0.8	0.6mm±1.8	3.7mm±1.5	CT

Mask system with and without bite block and dental fixation systems were analysed

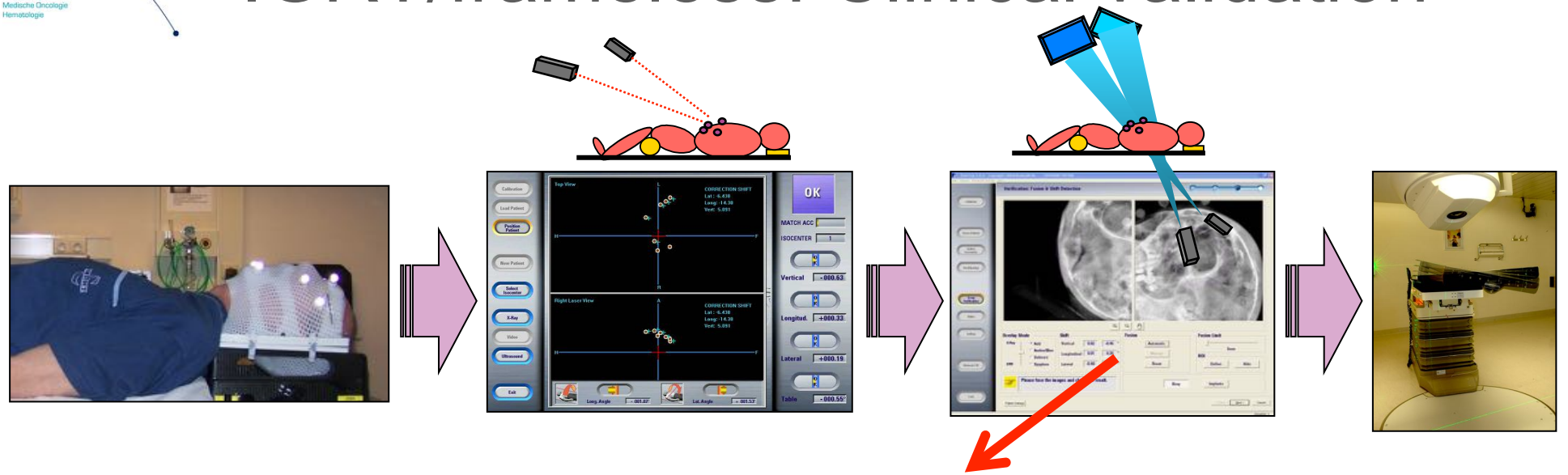
IGRT/frameless: Clinical validation

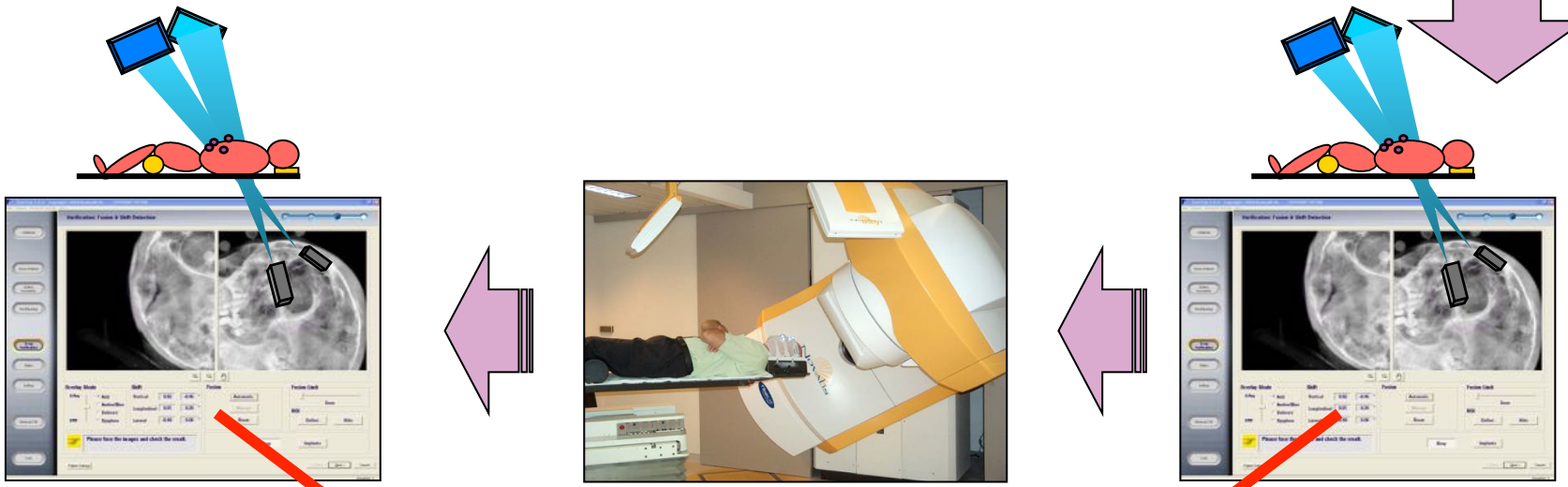
- 140 patients evaluated (Feb ’07 – Mar ’09)
  - Age 6y – 89y (mean 57y) ; 63 male / 76 female
  - 2861 fractions
- Non-coplanar dynamic conformal arc or non-coplanar IMRT
  - Average treatment time 14.6 min (**5.0 – 34.0 min**); SD 3.9 min



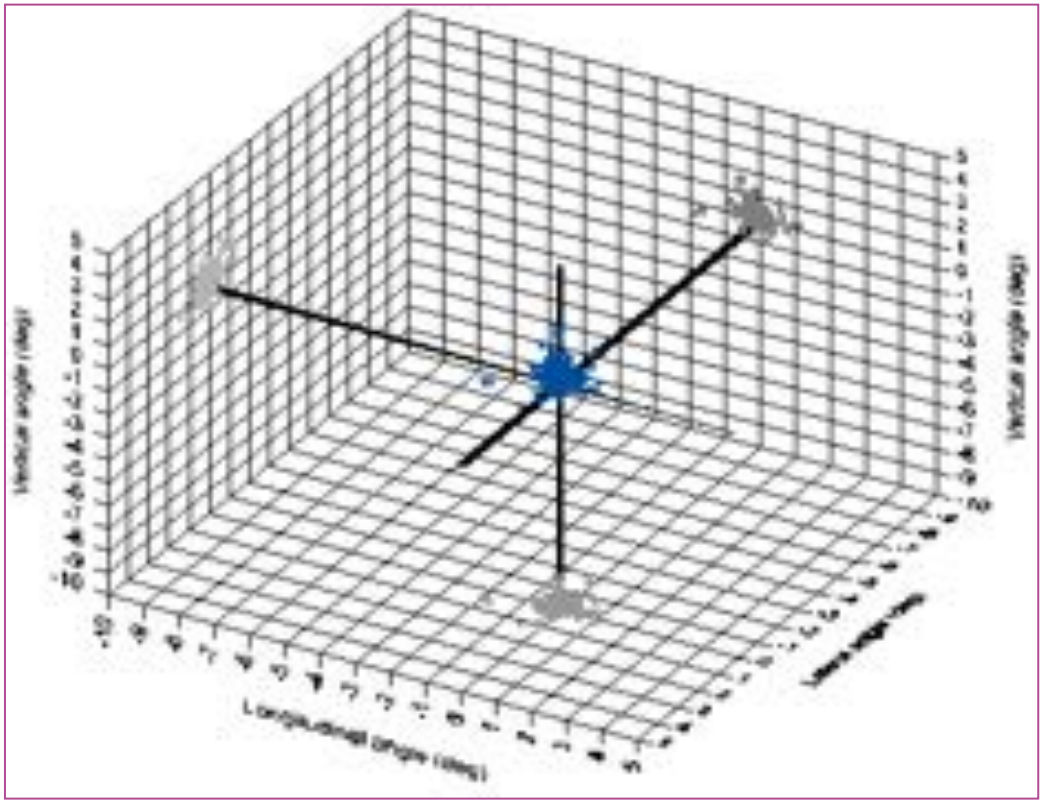
Linthout *et al.* Radiother Oncol 2012

IGRT/frameless: Clinical validation





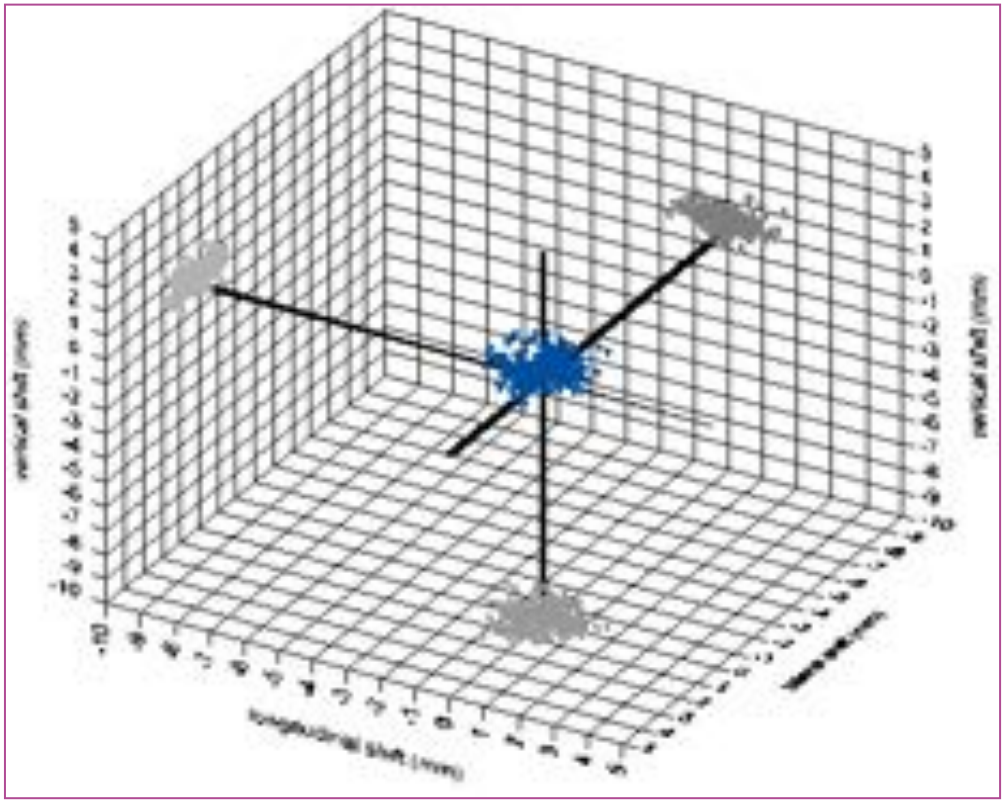
Results: X-ray residual rotations



- Lateral
  - Mean: 0.05°, SD: 0.30°
  - **-1.49° - 1.33°**
- Longitudinal
  - Mean: 0.00°, SD: 0.29°
  - **-1.83° - 1.21°**
- Vertical
  - Mean: 0.02°, SD: 0.31°
  - **-1.21° - 1.37°**

Linthout *et al.* Radiother Oncol 2012

Results: X-ray residual shifts



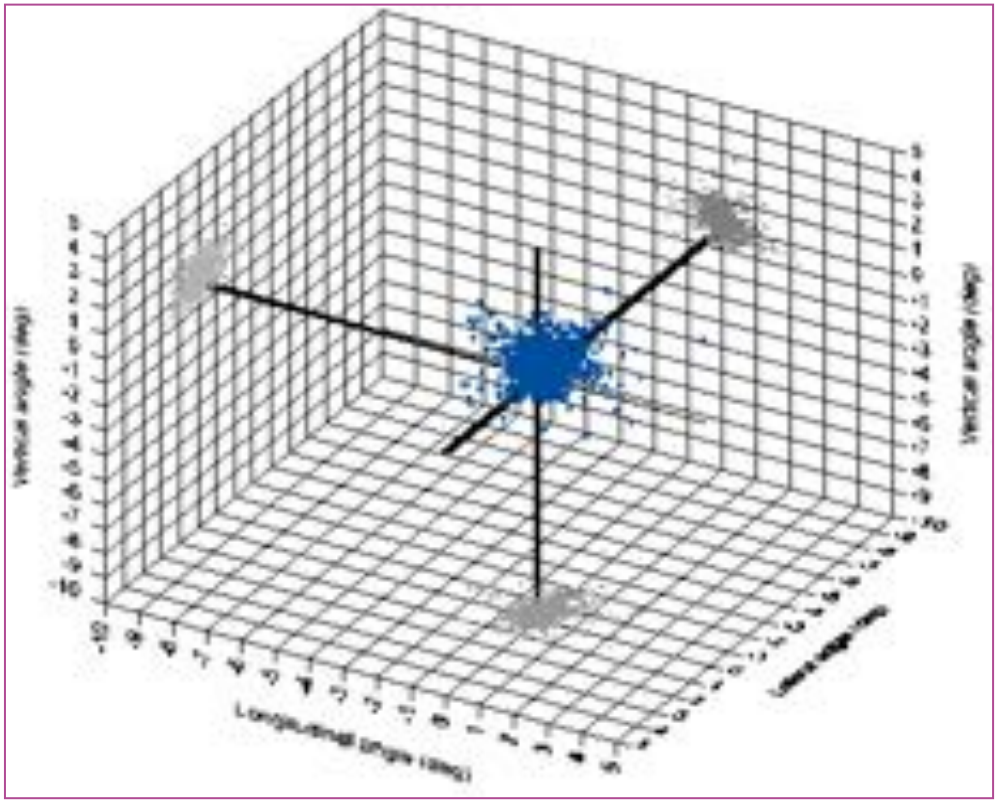
- Lateral
  - Mean: 0.02mm, SD: 0.66mm
  - **-1.59mm – 1.66mm**
- Longitudinal
  - Mean: 0.04mm, SD: 0.53mm
  - **-1.67mm – 1.67mm**
- Vertical
  - Mean: 0.04mm, SD: 0.32mm
  - **-1.11mm – 1.22mm**

Van Herk formula ($2.5\sum+0.7\sigma$)

- Lateral **1.29mm**; longitudinal **1.27mm**; vertical **0.67mm**

Linthout *et al.* Radiother Oncol 2012

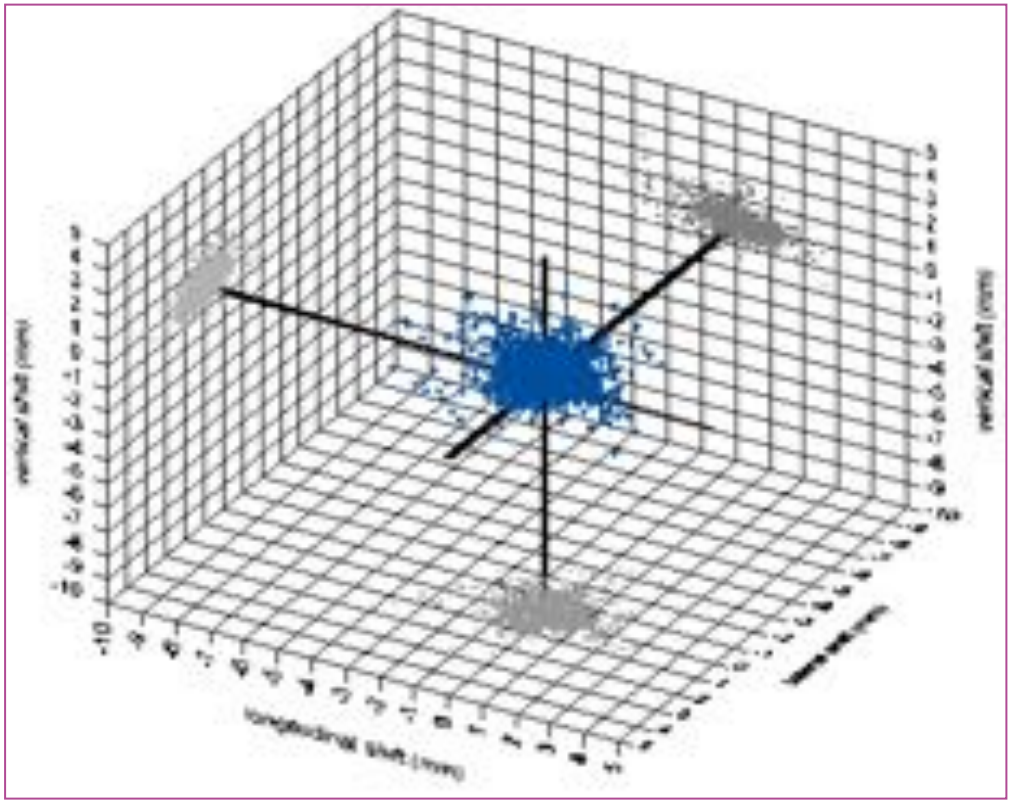
Results: Intrafraction rotations



- Lateral
  - Mean: -0.15°, SD: 0.50°
  - **-4.96° - 3.09°**
- Longitudinal
  - Mean: 0.02°, SD: 0.37°
  - **-2.19° - 3.50°**
- Vertical
  - Mean: 0.02°, SD: 0.41°
  - **-2.64° - 2.56°**

Linthout *et al.* Radiother Oncol 2012

Results: Intrafraction shifts



- Lateral
  - Mean: -0.11 mm, SD: 0.65 mm
  - **-3.52mm – 2.87mm**
- Longitudinal
  - Mean: 0.13 mm, SD: 0.78 mm
  - **-4.01mm – 2.99mm**
- Vertical
  - Mean: -0.11 mm, SD: 0.48 mm
  - **-3.08mm – 1.51mm**

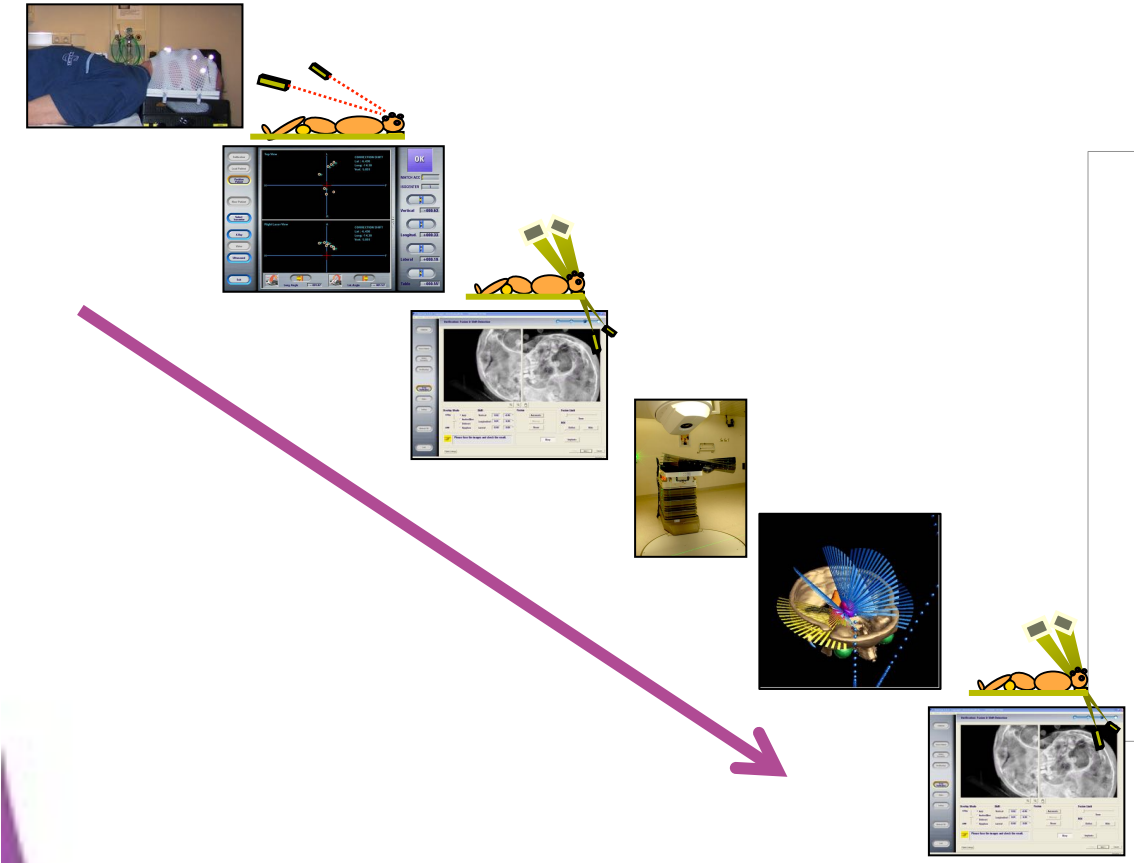
Van Herk formula ($2.5\sum+0.7\sigma$)

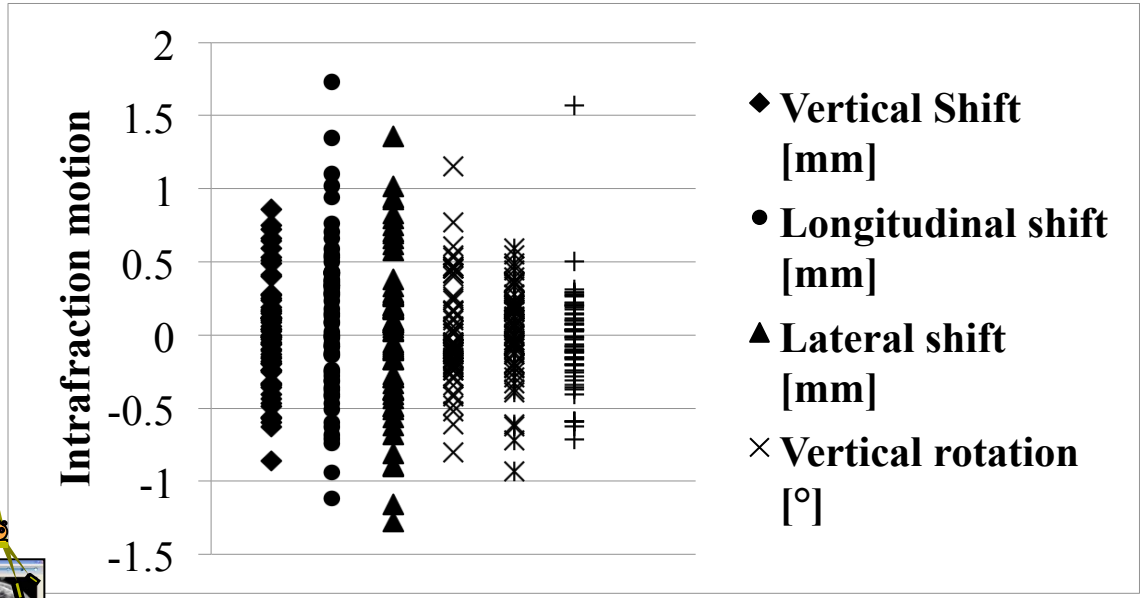
- Lateral **1.37mm**; longitudinal **1.85mm**; vertical **1.00mm**

Linthout *et al.* Radiother Oncol 2012

IGRT/frameless: Intrafraction motion

- 40 patients (66 brain metastases)
- Immobilized with Brainlab frameless mask, ExacTrac 6DOF set-up





- Intrafraction motion: **mean 3D of 0.58 mm (SD: 0.42 mm)**

Gevaert *et al*, 2012

IGRT/frameless: Intrafraction motion

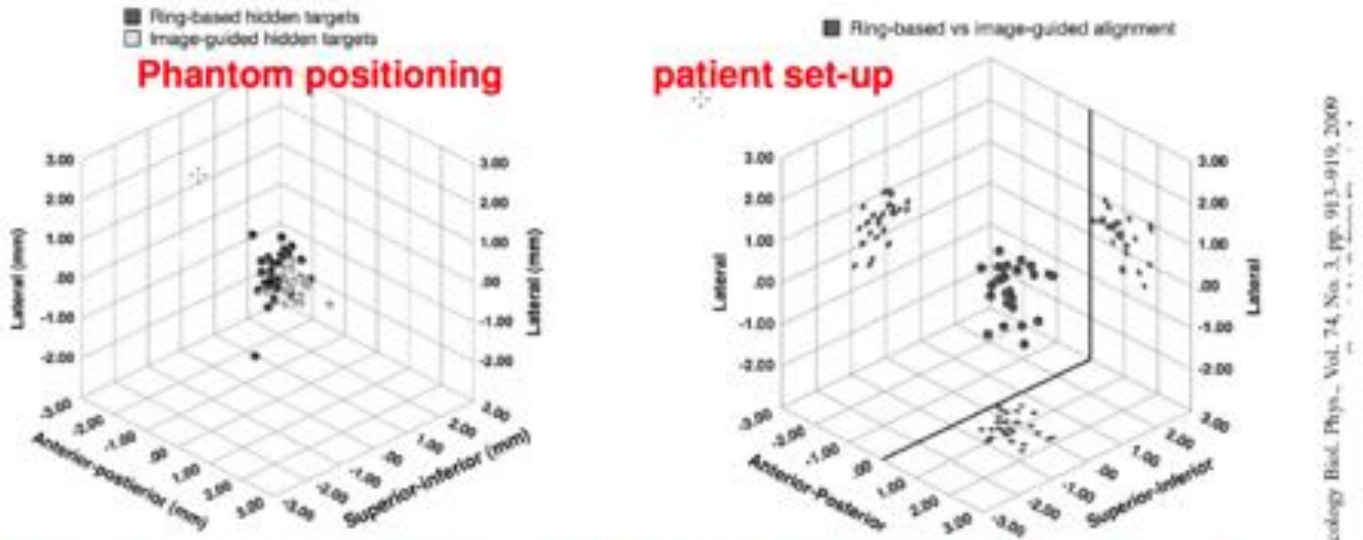
Study	Immobilization system	Imaging modality	Intrafractional error 3D vector
Boda-Heggemann 2006	Thermoplastic masks Scotch cast mask	Cone-beam CT	**1.8mm ± 0.7mm** **1.3mm ± 1.4mm**
Masi 2008	Thermoplastic mask & Bite block Bite-block	Cone-beam CT	**< 1mm** **< 1mm**
Lamda 2009	BrainLab mask	Orthogonal x-rays	**0.5mm ± 0.3mm**
Ramakrishna 2010	BrainLab mask	Orthogonal x-rays	**0.7mm ± 0.5mm**
Guckenberger 2010	Scotch cast mask Thermoplastic masks	Cone-beam CT	**0.8mm ± 0.4mm** **0.8mm ± 0.5mm**

IGRT/frameless: Intrafraction motion

EVALUATION OF IMAGE-GUIDED POSITIONING FOR FRAMELESS INTRACRANIAL RADIOSURGERY

MICHAEL LAMBA, PH.D.,* JOHN C. BRENEMAN, M.D.,* AND RONALD E. WARNICK, M.D.†

BrainLAB Novalis System

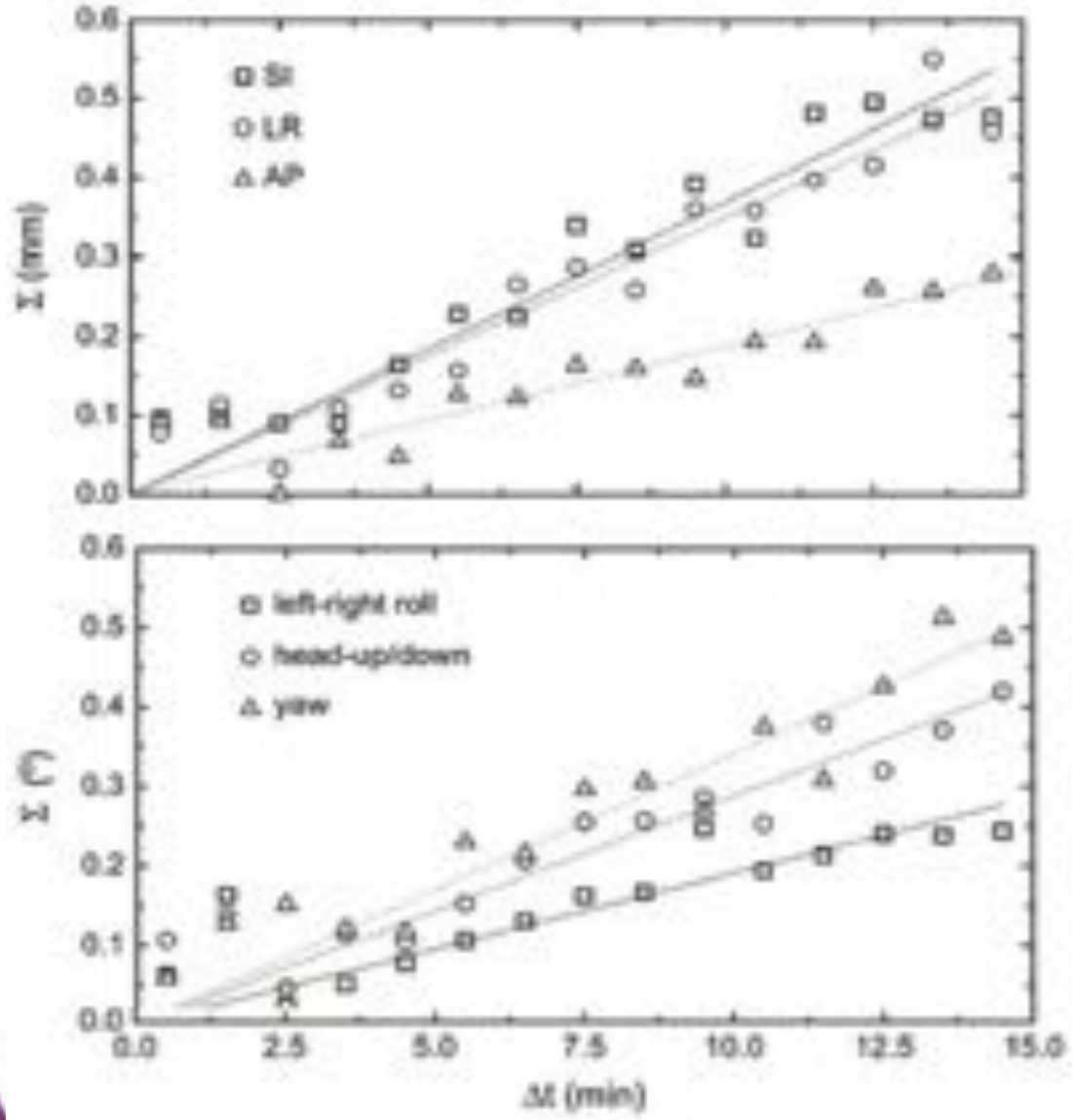


Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 3, pp. 913–919, 2009

Two groups of patients with stereotactic localizer and immobilisation mask

Difference in alignment 0.9±0.5mm antero-posterior
0.2±0.4mm superior-inferior
0.3±0.5mm lateral

IGRT/frameless: Intrafraction motion



- Immobilization in conventional thermoplastic head masks:
  - Time dependence of intra- fractional patient motion
- Keep total treatment time as short as possible !!!

Hoogeman *et al.* IJROBP 2008

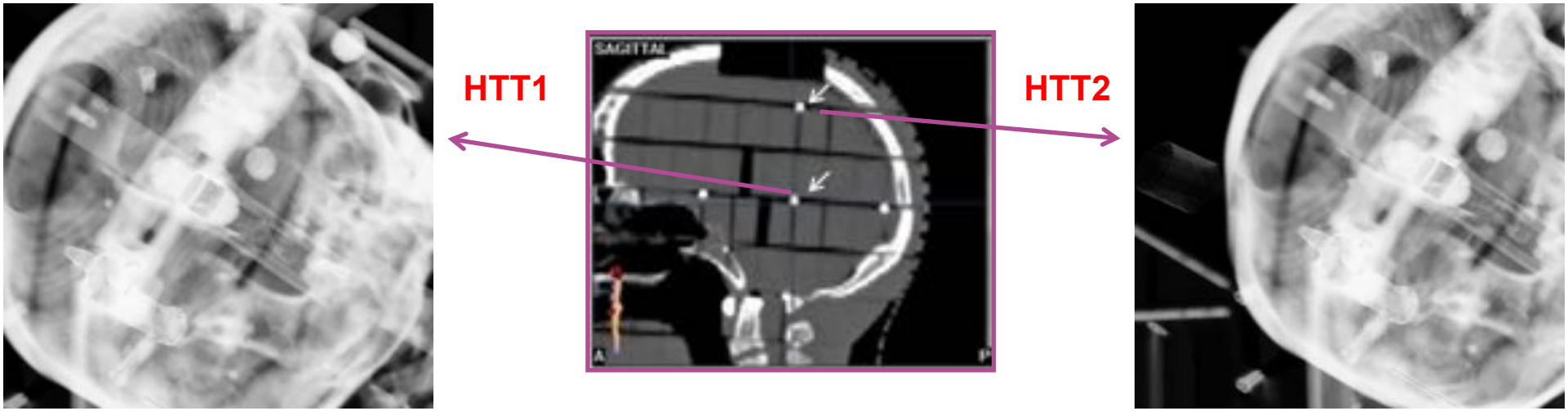
Accuracy: Frame-based versus IGRT-frameless

- Invasive SRS is NOT without uncertainties
- Factors most influencing accuracy:
  - CT image slice thickness
  - Tension / distorsion of ring due to patient weight
  - MRI distorsion
  - CT, MRI, PET image registration
  - Target definition
  - Target localization

Maciunas *et al.* Neurosurgery 1994

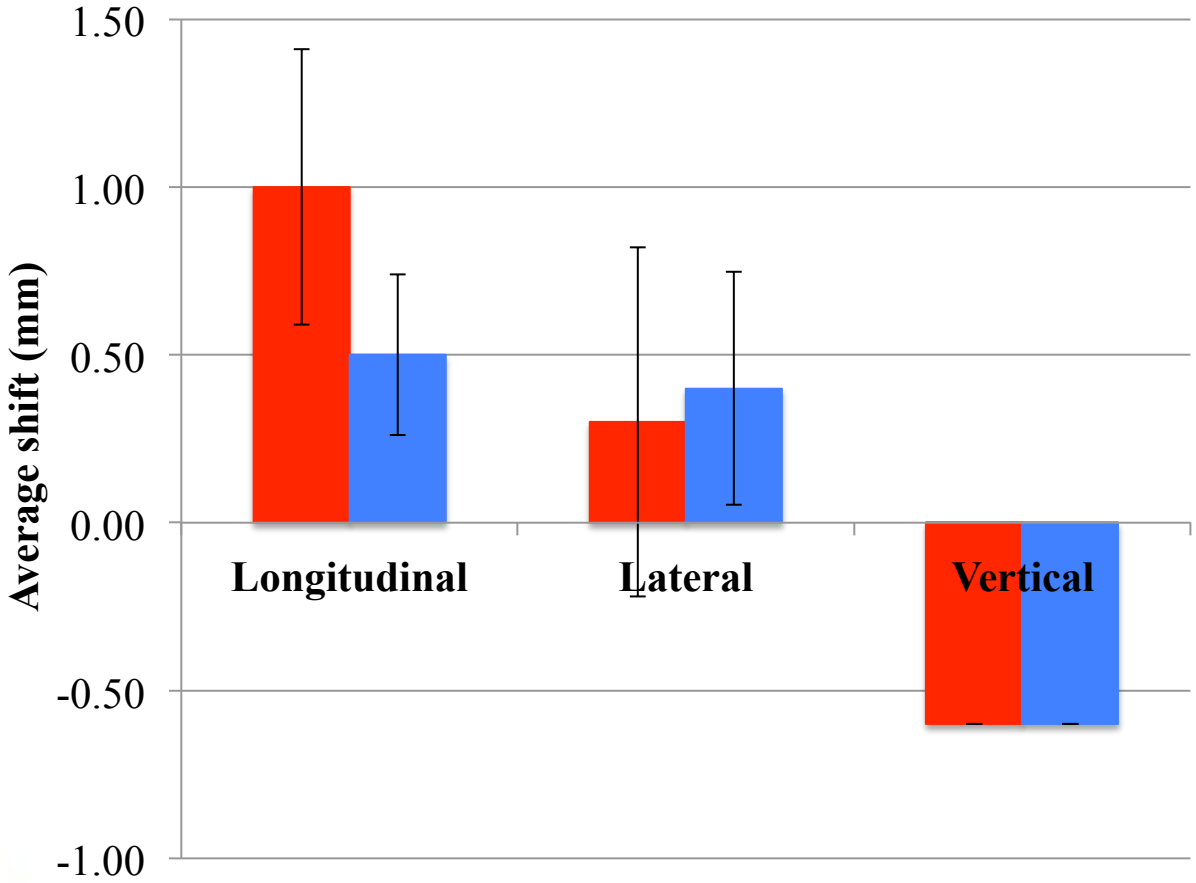
CT Slice Thickness (mm)	Measurement	Leksell (mm)
1	Mean ± 3 SE_M	1.7 ± 0.10
	99% CI for the mean	1.60 to 1.80
1 canted	Mean ± 3 SE_M	N/A
	99% CI for the mean	N/A
4	Mean ± 3 SE_M	2.6 ± 0.14
	99% CI for the mean	2.46 to 2.74
8	Mean ± 3 SE_M	5.4 ± 0.24
	99% CI for the mean	5.16 to 5.64

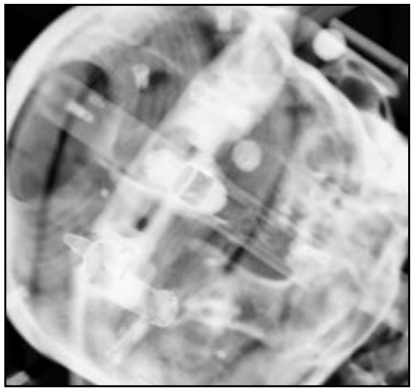
Accuracy:
Frame-based versus IGRT-frameless



Gevaert *et al.* Int J Radiat Oncol Biol Phys 2012

Accuracy: Frame-based versus IGRT-frameless

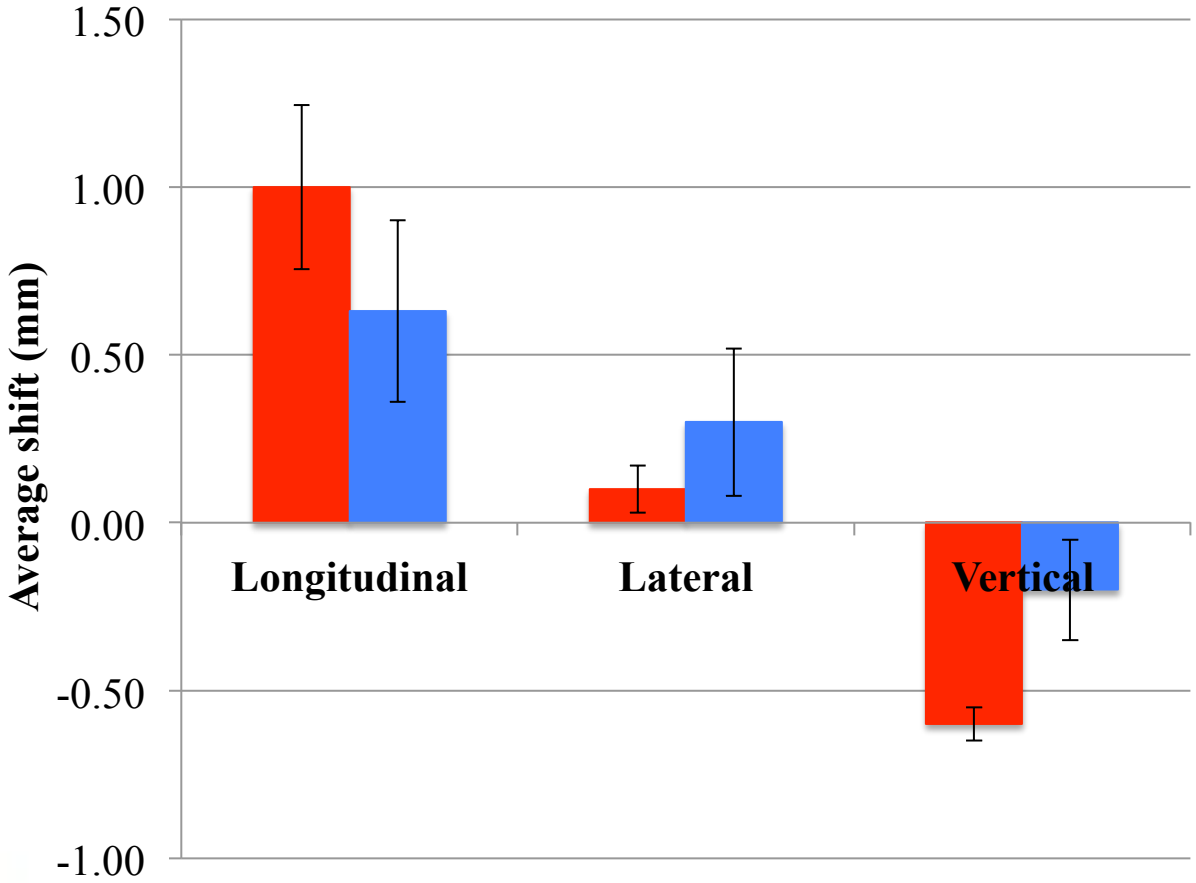


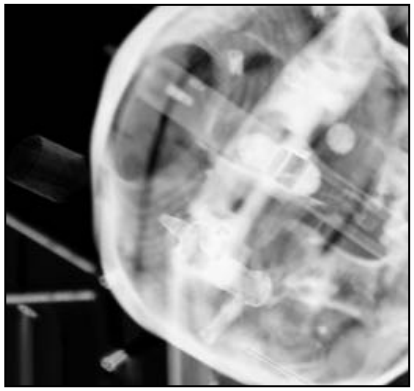


Overall 3D accuracy: 1.20 mm SD 0.66 mm (frame-based)
0.88 mm SD 0.42 mm (frameless)

Gevaert *et al.* Int J Radiat Oncol Biol Phys 2012

Accuracy: Frame-based versus IGRT-frameless



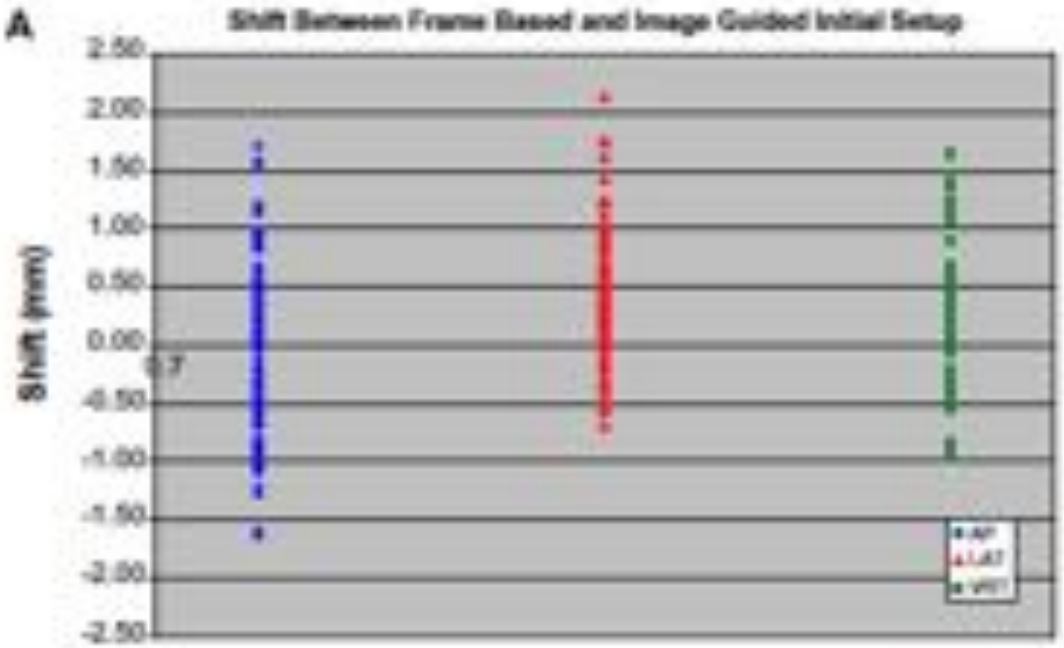


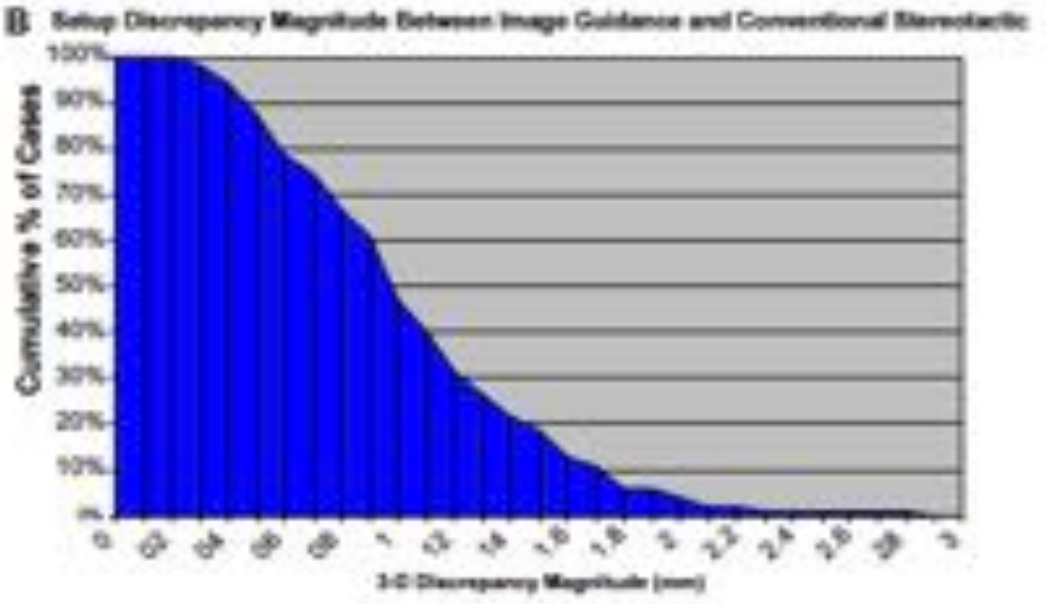
Overall 3D accuracy: 1.17 mm SD 0.24 mm (frame-based)
0.85 mm SD 0.52 mm (frameless)

Gevaert *et al.* Int J Radiat Oncol Biol Phys 2012

Accuracy: Frame-based versus IGRT-frameless

- Passive Image-Guided **monitoring of frame-based** SRS (GTC-head-ring, BRW frame)
- 102 **patient** set-ups

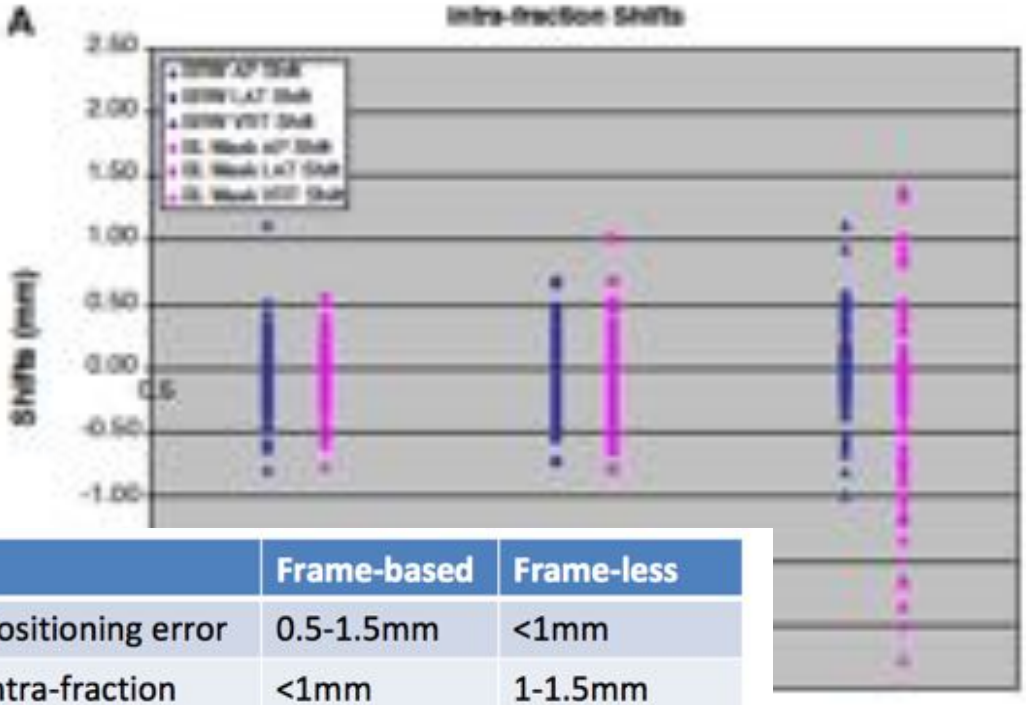


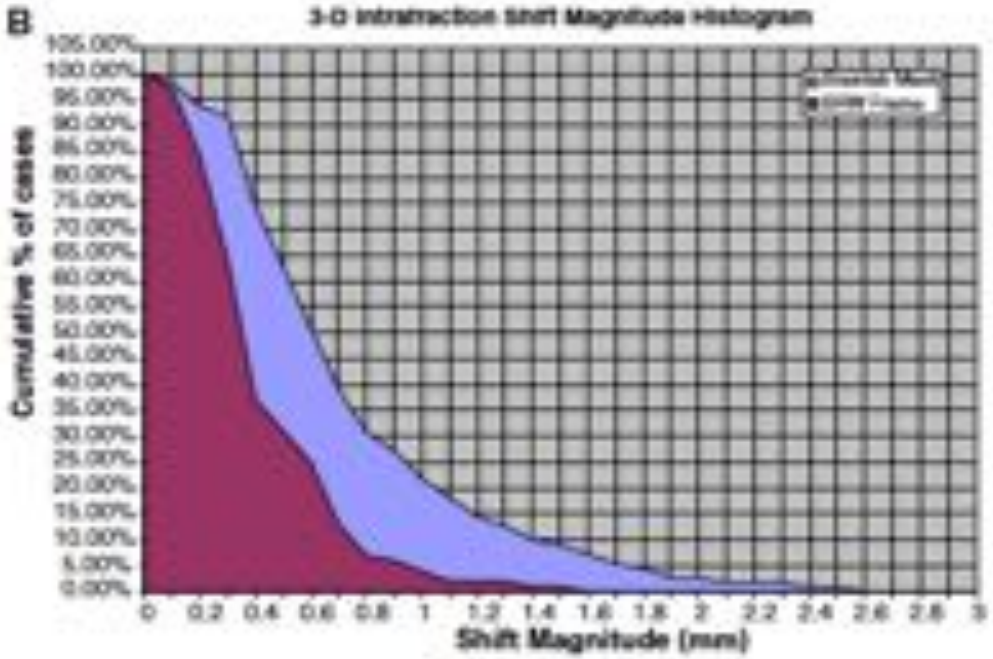


Ramakrishna *et al.* Radiother Oncol 2010

Accuracy: Frame-based versus IGRT-frameless

- Intrafraction motion monitored with frame-based (BRW) and frameless SRS: **clinical validation**.
  - **Frame-based** (N=102): 0.4mm (1SD: 0.3mm)
  - **Frameless** (N=110): 0.7mm (1SD: 0.5mm)





	Frame-based	Frame-less
Positioning error	0.5-1.5mm	<1mm
Intra-fraction motion	<1mm	1-1.5mm

Ramakrishna *et al.* Radiother Oncol 2010

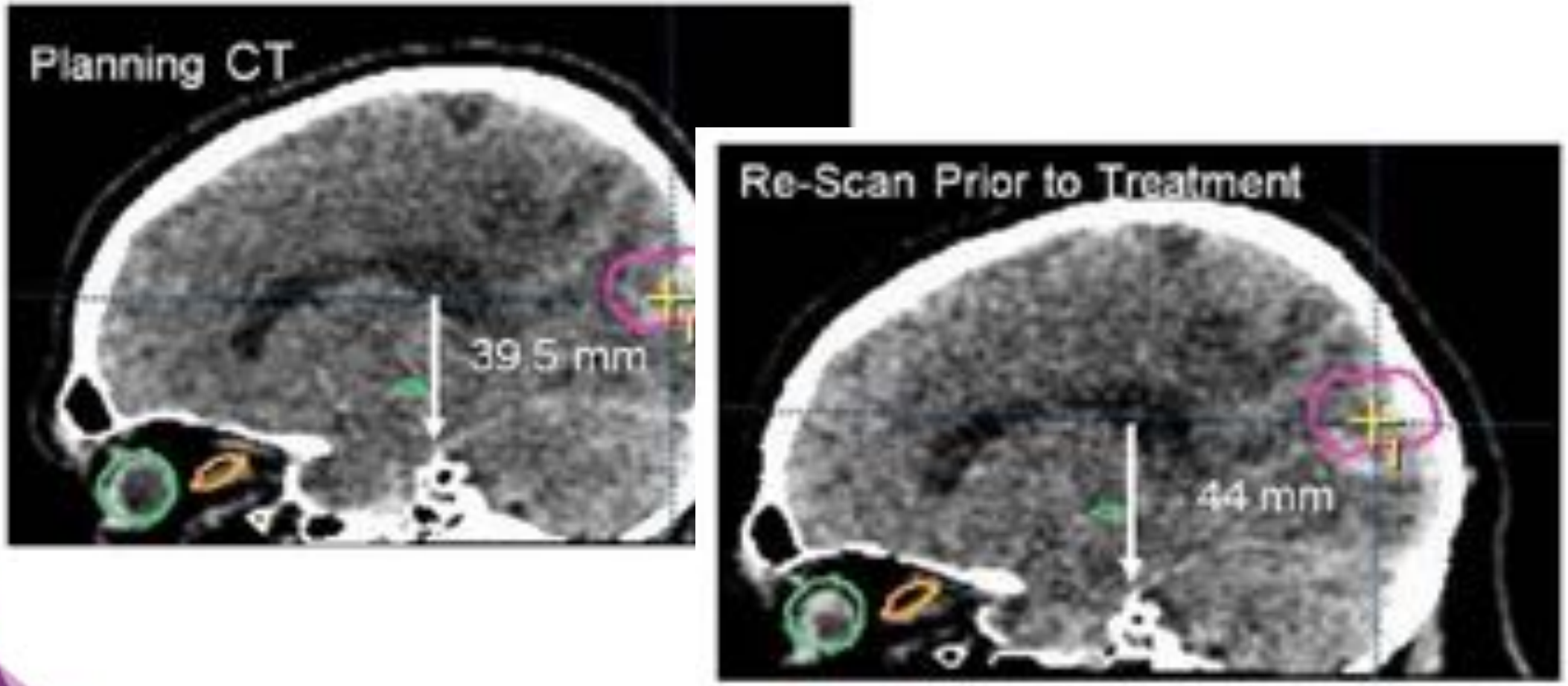
Margins: Frame-based versus IGRT-frameless

- Combs *et al.* (IJROBP 2009), the DKFZ experience comparing fractionated stereotactic radiotherapy (FSRT) using a relocatable frame-based mask system and stereotactic radiosurgery (SRS) using an invasive frame for treatment of Vestibular Schwannoma (N=202):
  - Comparable local control rates 96% at 5 years
  - The PTV was defined after a fusion of CT/MR images as the area of contrast enhancement on T1-weighted MRI images, with the addition **of a 1-2 mm safety margin, both for FSRT and SRS**!
- Meijer *et al.* (IJROBP 2003), the VUMC experience for Vestibular Schwannoma (N=129):
  - 2 Groups: dentate patients – FSRT, edentated patients SRS
  - Again, comparable results, with small difference in trigeminal nerve preservation rate in favor of FSRT.
  - A **minimum safety margin of 1mm was used in both groups**!

Some words of caution

SRS Frame-based: frame slippage

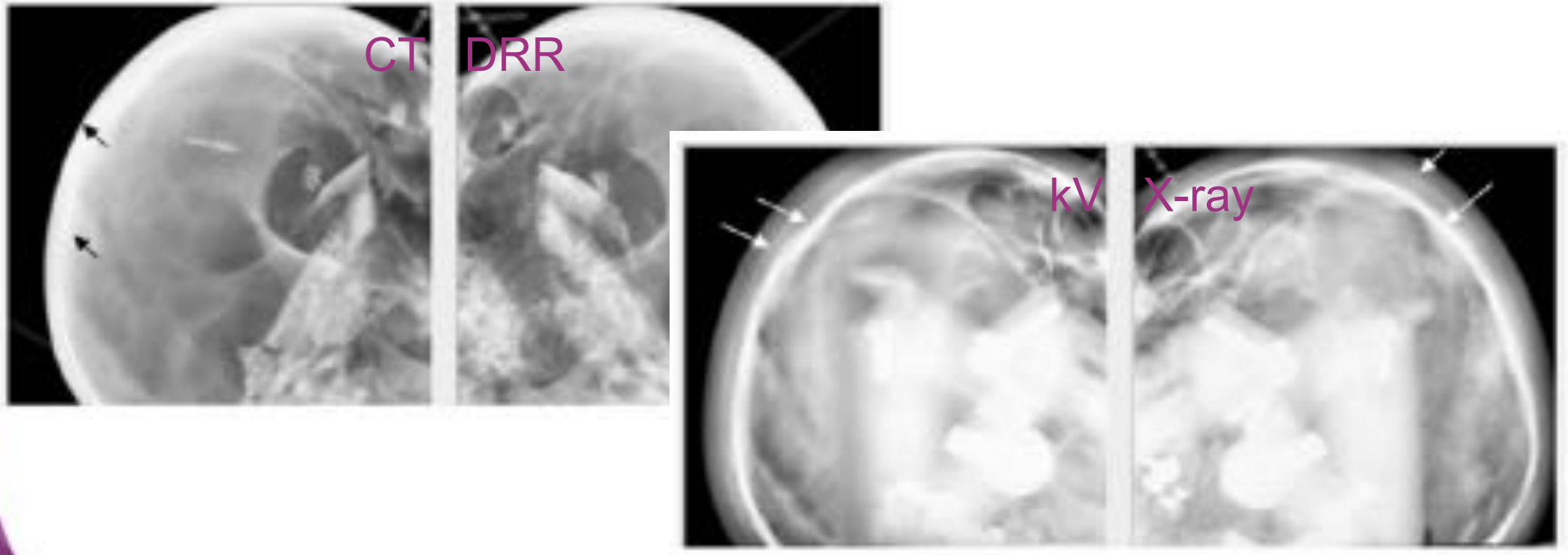
- Frame slippage (4.23 mm) observed with image-guided monitoring of frame-based SRS, confirmed with CT-scan.



Ramakrishna *et al.* Radiother Oncol 2010

IGRT/Frameless: Automated co-registration

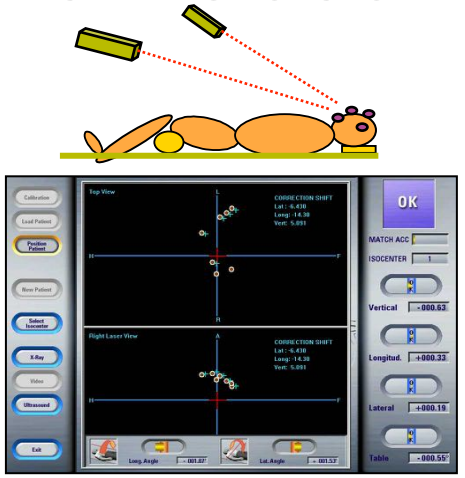
- kV X-ray images might display difference in skull density contours relative to CT-DRR, resulting in erroneous image co-registration.



Ramakrishna *et al.* Radiother Oncol 2010

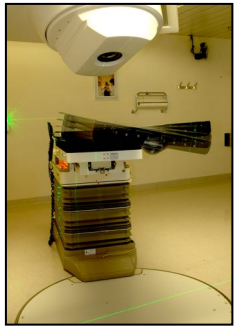
How about table rotations?

Phantom 0°



IR pre-positioning

6DOF registration



6DOF positioning

HTT

Phantom 90°

HTT

Phantom 270°

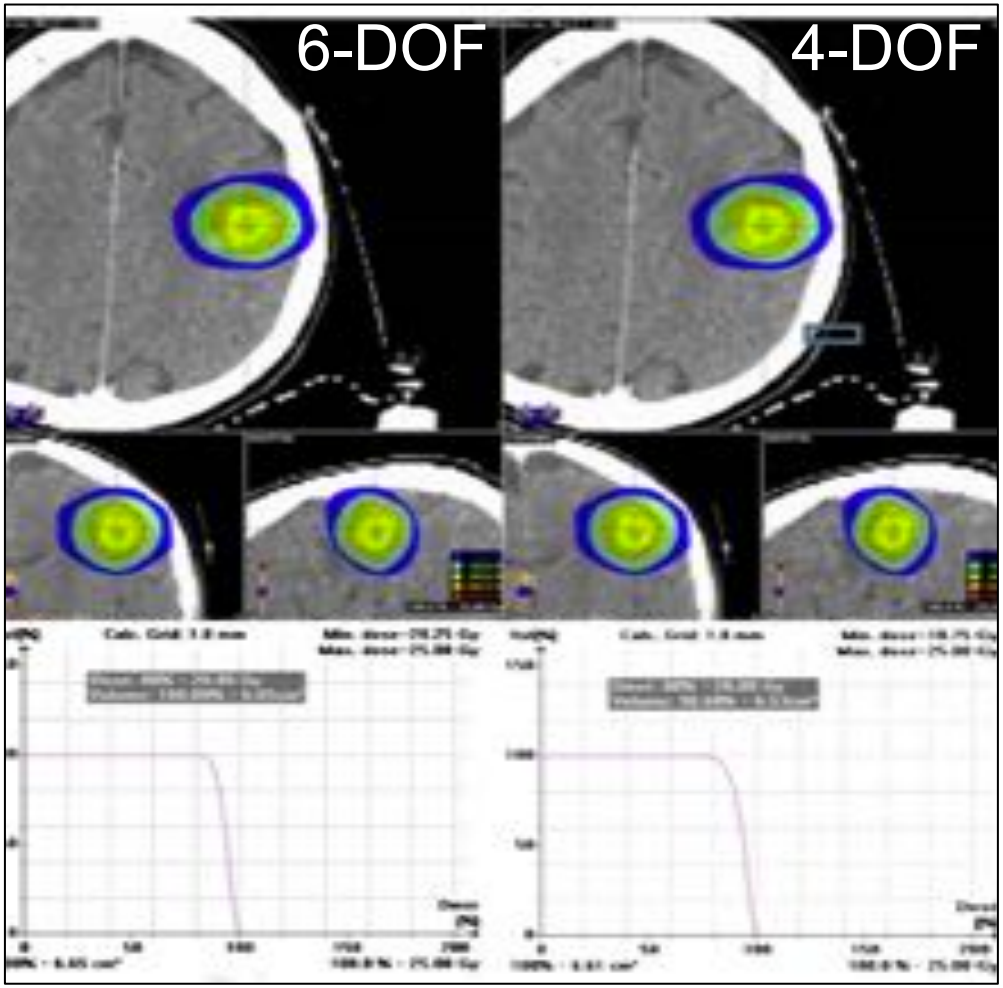
HTT

How about table rotations?

	Not corrected for table positions		Reference	Corrected for table positions	
Table positions	**90°**	**270°**	**0°**	**90°**	**270°**
	Average shifts				
	mm	**mm**	**mm**	**mm**	**mm**
Vertical	0,79 ± 0,5	0,77 ± 0,31	0,47 ± 0,15	0,55 ± 0,26	0,52 ± 0,12
Longitudinal	0,94 ± 0,76	0,79 ± 0,32	0,47 ± 0,21	0,30 ± 0,11	0,49 ± 0,17
Lateral	0,83 ± 0,12	0,64 ± 0,31	0,30 ± 0,09	0,41 ± 0,33	0,30 ± 0,07
3D vector	**1,48 ± 0,34**	**1,28 ± 0,16**	**0,73 ± 0,11**	**0,75 ± 0,32**	**0,77 ± 0,14**

Gevaert *et al.* Radiother Oncol 2012

IGRT/Frameless: rotational correction



- 40 patients, 66 Brain metastases
- Treatment with **6-DOF** robotic couch correction based on ET/NB IGRT
- Retrospective simulation of **4-DOF** by manipulation of CT-dataset in TPS, omitting rotational correction

- Paddick Conformity Index reduces from **0.68 to 0.59**
(6-DOF versus 4-DOF correction)

$$\frac{TV_{PI}}{PI} \times \frac{TV_{PI}}{TV}$$

- **Loss of 5%** in prescription isodose **coverage** (80%).

Gevaert *et al.* Int J Radiat Oncol Biol Phys 2012

How about table rotations?

- 16 patients: Trigeminal Neuralgia
- Frameless IGRT
  - BrainLAB mask
  - 6DOF ExacTrac for patient set-up and verification

- Verification images after each table rotation, prior to each treatment beam/arc.

Gevaert *et al.* Radiother Oncol 2012

How about table rotations?

- Relation between table rotation and overall 3D accuracy, if NOT corrected in between table positions:

Couch rotation	Overall 3D accuracy
10	0,46 ± 0,11
15	0,49 ± 0,15
20	0,57 ± 0,13
60	1,10 ± 0,33
70	1,15 ± 0,42
80	1,21 ± 0,22
90	1,24 ± 0,19

Gevaert *et al.* Radiother Oncol 2012

How about table rotations?

- Patient intrafraction motion and uncertainties, with IGRT corrections in between couch rotations:
  - Mean shifts:
    - Vertical: -0.01 mm (SD 0.39 mm)
    - Longitudinal: -0.05 mm (SD 0.47 mm)
    - Lateral: 0.16 mm (SD 0.44 mm)

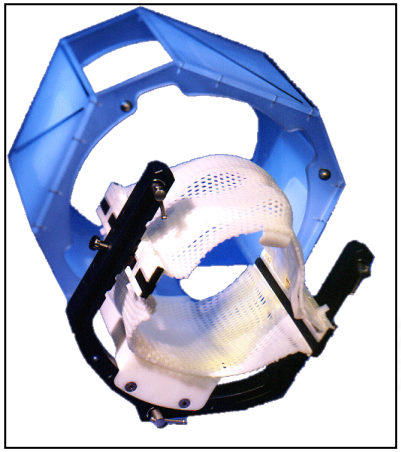
    Mean 3D of 0.89 mm (SD 0.35 mm)
  - Mean rotations:
    - Vertical: -0.08°(SD 0.25°)
    - Longitudinal: 0.09°(SD 0.29°)
    - Lateral: -0.05°(SD 0.20°)

Gevaert *et al.* Radiother Oncol 2012

Non-invasive, frame-based???

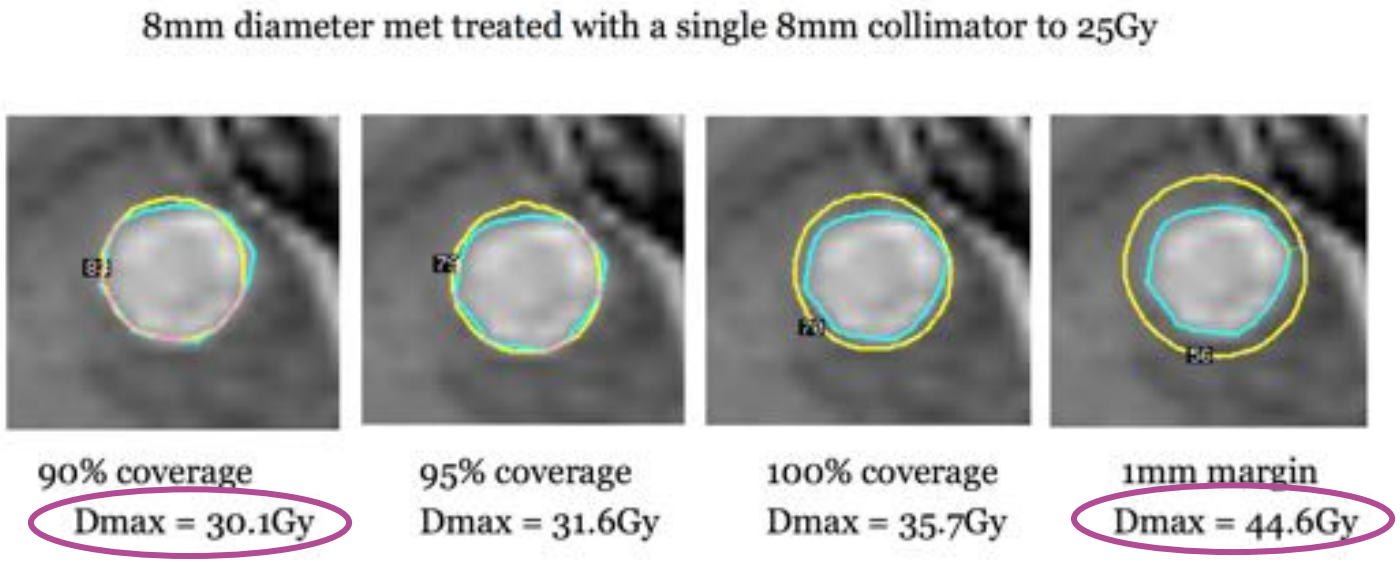
Study	SRT positioning system	Imaging modality	Positioning error
	2D-2D image registration for verification of set-up		
Rosenthal 1995	Dental fixation	Orthogonal radiographs	2.3mm ± 1.6mm
Sweeney 2001	Vogele Bale Hohner head holder	Portal imaging	1.9mm ± 1.2mm
Kumar 2005	Gill-Thomas-Cosman	Portal imaging	1.8mm ± 0.8mm
Georg 2006	Brain Lab Mask	Portal imaging	1.3mm ± 0.9mm
	3D-3D image registration for verification of set-up		
Baumert 2005	Stereotactic mask	CT	3.7mm ± 0.8mm
Boda-Heggemann 2006	Scotch cast mask	Cone-beam CT	3.1mm ± 1.5mm
Guckenberger 2007	Scotch cast mask	Cone-beam CT	3.0mm ± 1.7mm

- Significant uncertainties in patient (re-) positioning despite stereotactic technique
- Positioning a “box” and less correlation with patient’s anatomy
- **“Worst” of both worlds**



Reporting dose

- Dose prescription and margins in SRS
- 2 lesions, treated to **25Gy covering 97%** of the target
  - 8mm ϕ lesion, **8mm collimator**, **25Gy @ 80%**:
    - **D_{max} = 31.3 Gy** / D_{mean} = 27.5Gy
  - 11mm ϕ lesion, **8mm collimator**, **25Gy @ 50%**:
    - **D_{max} = 50.0 Gy** / D_{mean} = 35.0Gy
- Same lesion, same dose prescription, variable isodose:



I. Paddick *et al.*

Take home messages

- Why evolving to **non-invasive frameless IGRT** treatment:

- For single fraction SRS
  - Patient comfort (no risk of bleeding nor infection)
  - More time for multi-modality, complex treatment planning
  - Possibility for in-treatment verification, reducing intrafractional motion
  - No difference in accuracy compared to frame-based

- For fractionated SRT
  - Improved accuracy
  - Efficient work-flow

Conclusions

- The most important thing to a patient is not the availability of some hight technology device, rather it is the ability of a team of physicians, physicists, dosimetrists and therapists to use a technology with skill for the benefit of the patient.
  - Dr. Marc Edwards

- The true challenge is to develop the wisdom to know when to select which [treatment modality] in the clinic.
  - Dr. Steve Webb

Food for thought

- Traditionally, we haven't been using **margins** with the frame-based SRS!
  - ➢ It was (is) assumed to be 'perfect'
- Whilst we might should have used margins!
  - ➢ There are always uncertainties
- Should we omit margins in frameless SRS, based on clinical experience with frame-based SRS (the dose distribution covers it)?

- The concept of "**frame**" comes from the LGK, where the patient is mechanically fixed to the frame, which in turn is mechanically fixed to the delivery machine
- This concept is **NO LONGER VALID** for linac-based or Cyberknife systems, where a direct coupling between treatment machine and patient is absent! IGRT is the only safe way to go!!!

Acknowledgements

Many thanks to all Friends and Colleagues
for their nice slides!!!

Case example I:
Stage I small cell lung cancer

Morten Høyer professor, medical director
Danish Center for Particle Therapy
Aarhus University Hospital
Denmark
hoyer@aarhus.rm.dk

Case example I: Stage 1 NSCLC

- 66 year old male; smoker (20 cigarettes for 50 years)
- Moderate COPD, acute exacerbation over 4 weeks
- Chest X-ray: infiltration in left lung
- CT: infiltration in upper left lobe, 28 mm
- FEV1: 38%; FVC: 80%

A
IEC 61217
Head First-Supine
P

Case example I: Stage 1 NSCLC

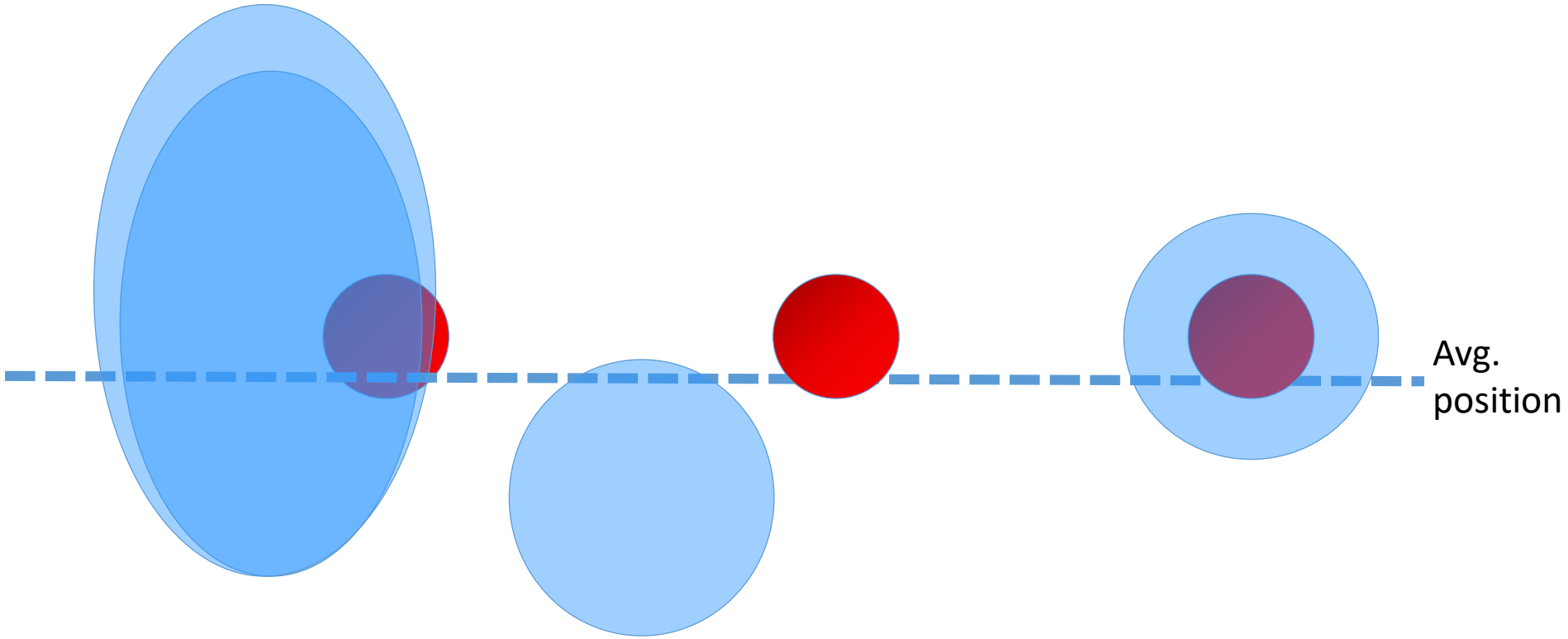
- 66 year old male; smoker (20 cigarettes for 50 years)
- Moderate COPD, acute exacerbation over 4 weeks
- Chest X-ray: infiltration in left lung
- CT: infiltration in upper left lobe, 28 mm
- FEV1: 38%; FVC: 80%
- FNA: adenocarcinoma
- FDG PET/CT: solitary lung nodule
- Conclusion: NSCLC T1N0M0

General concepts in motion management

1) Mid-ventilation or
2) ITV approaches

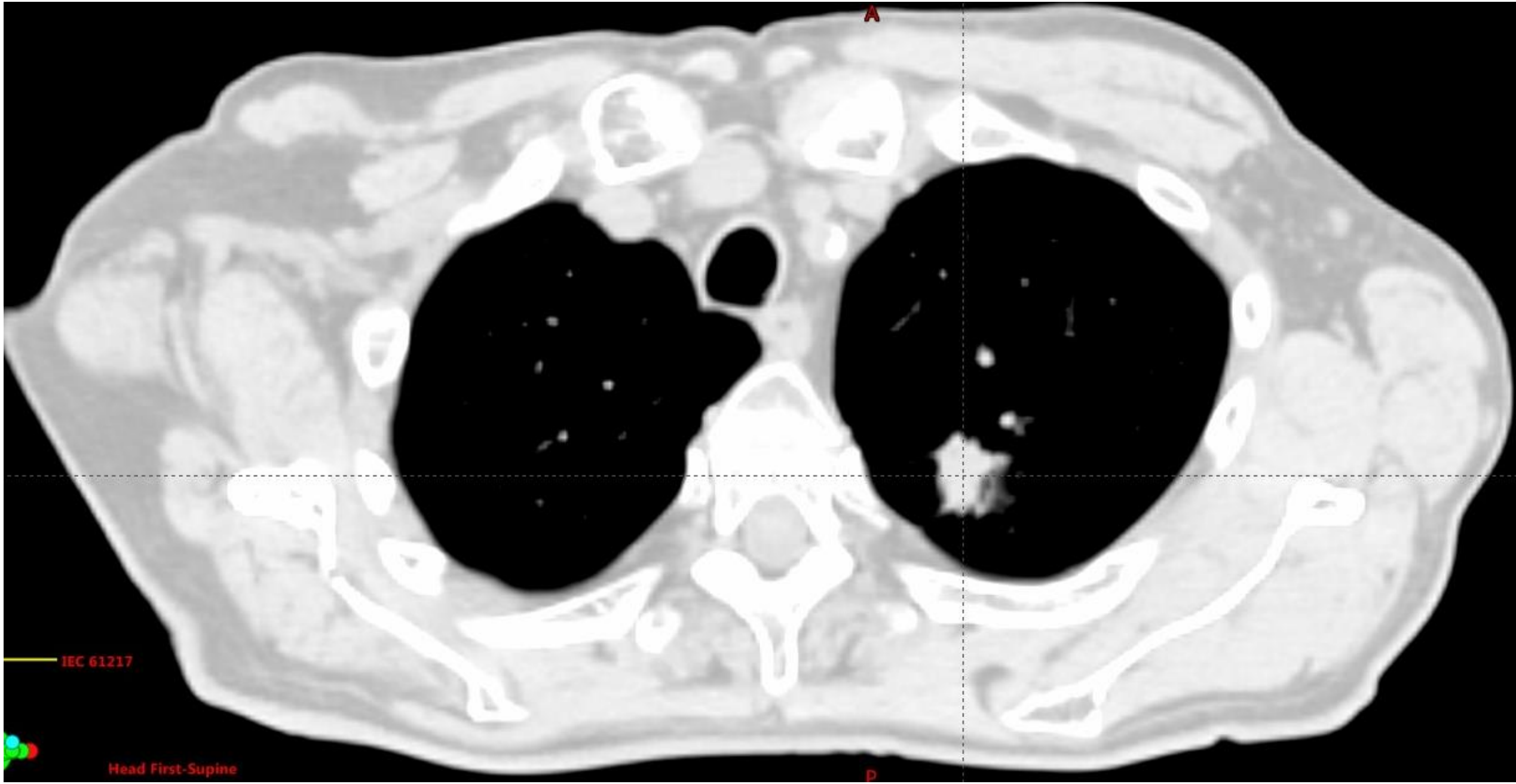
3) Gating

4) Tracking



Concept of the present case

- Fixation: Vac-loc system
- 4DCT
- Treatment planning in mid-vent phase
- Step-and-shoot 3D-CRT
- Delivery of treatment under free-breathing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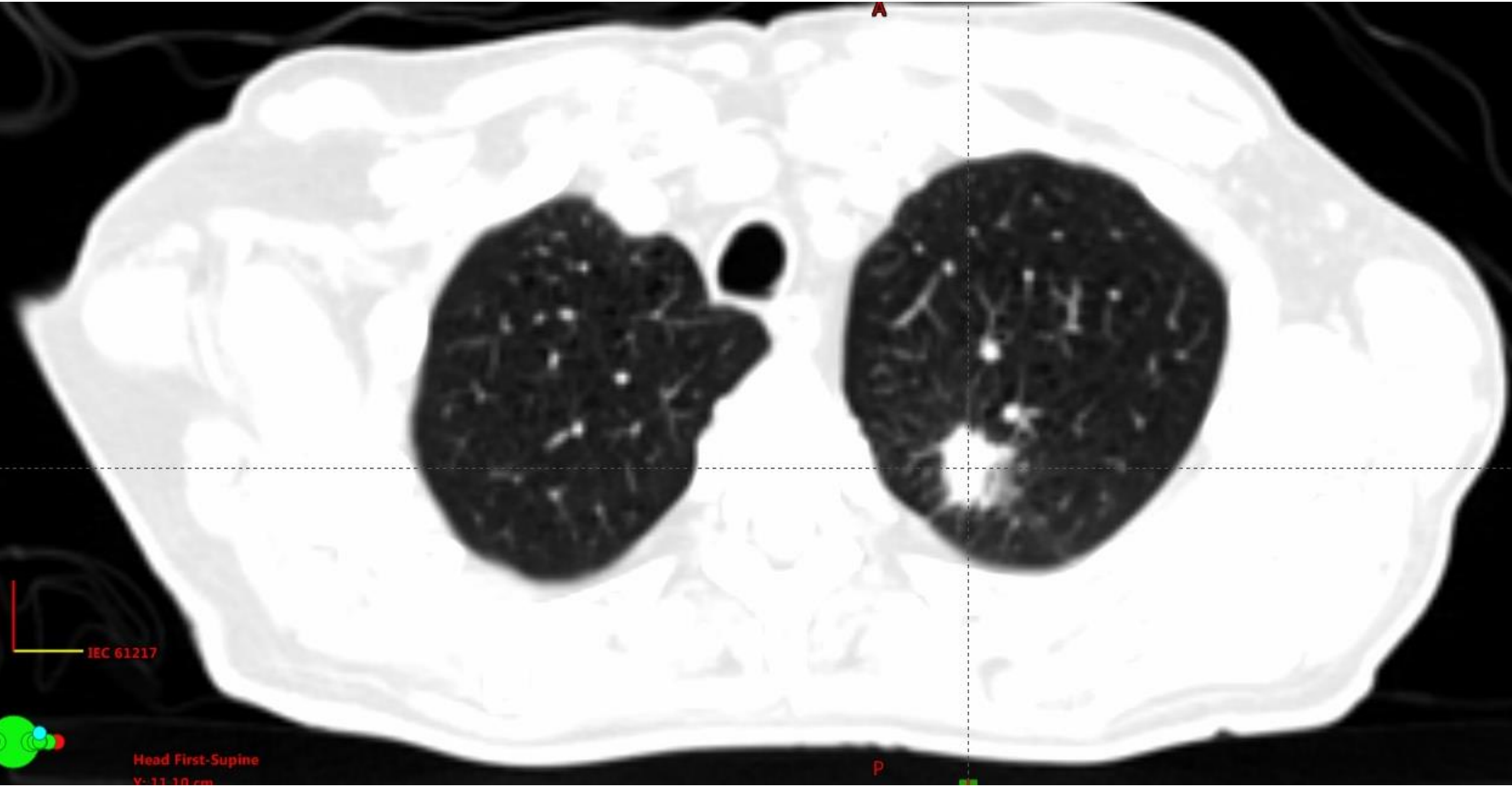
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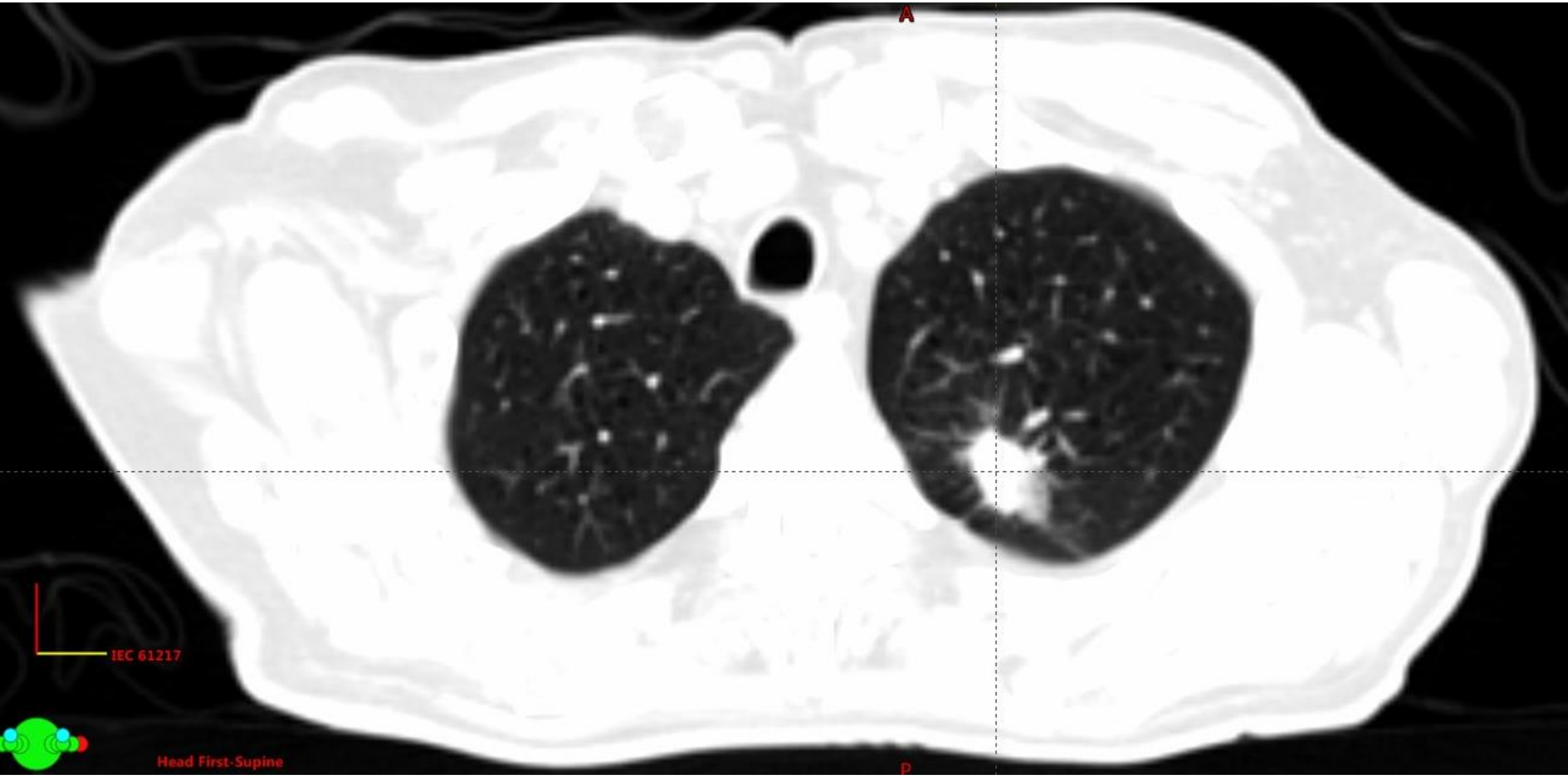
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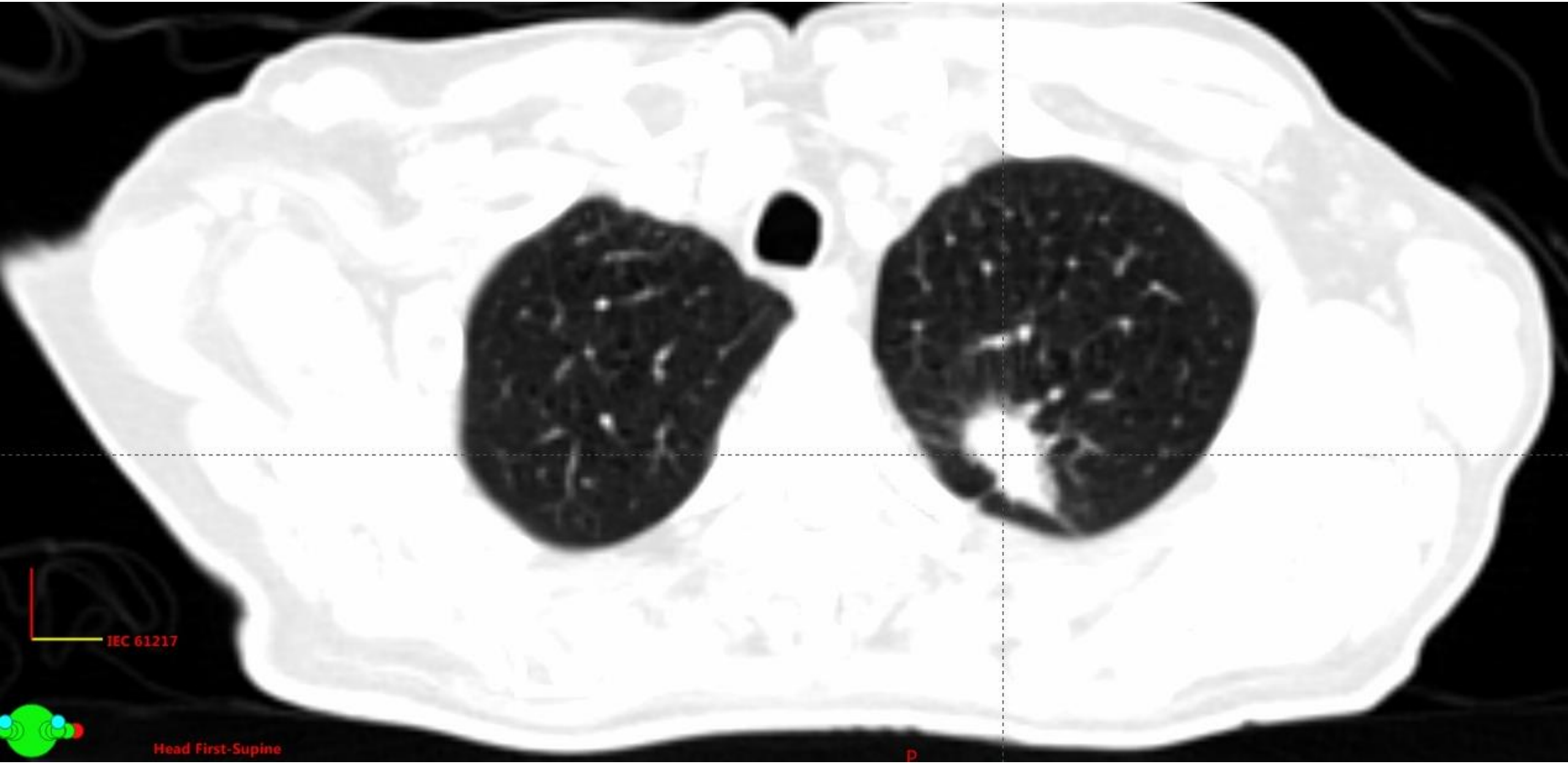
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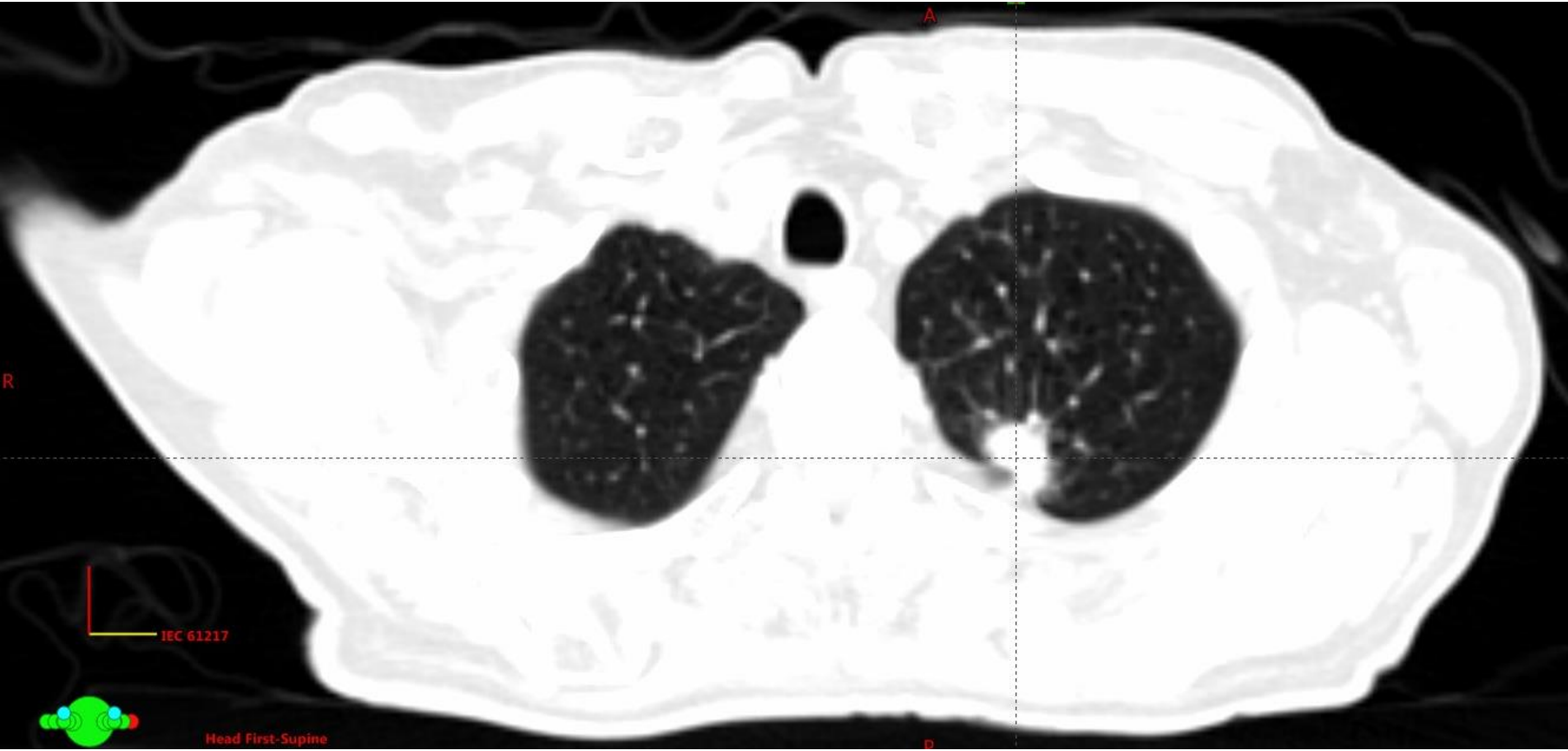
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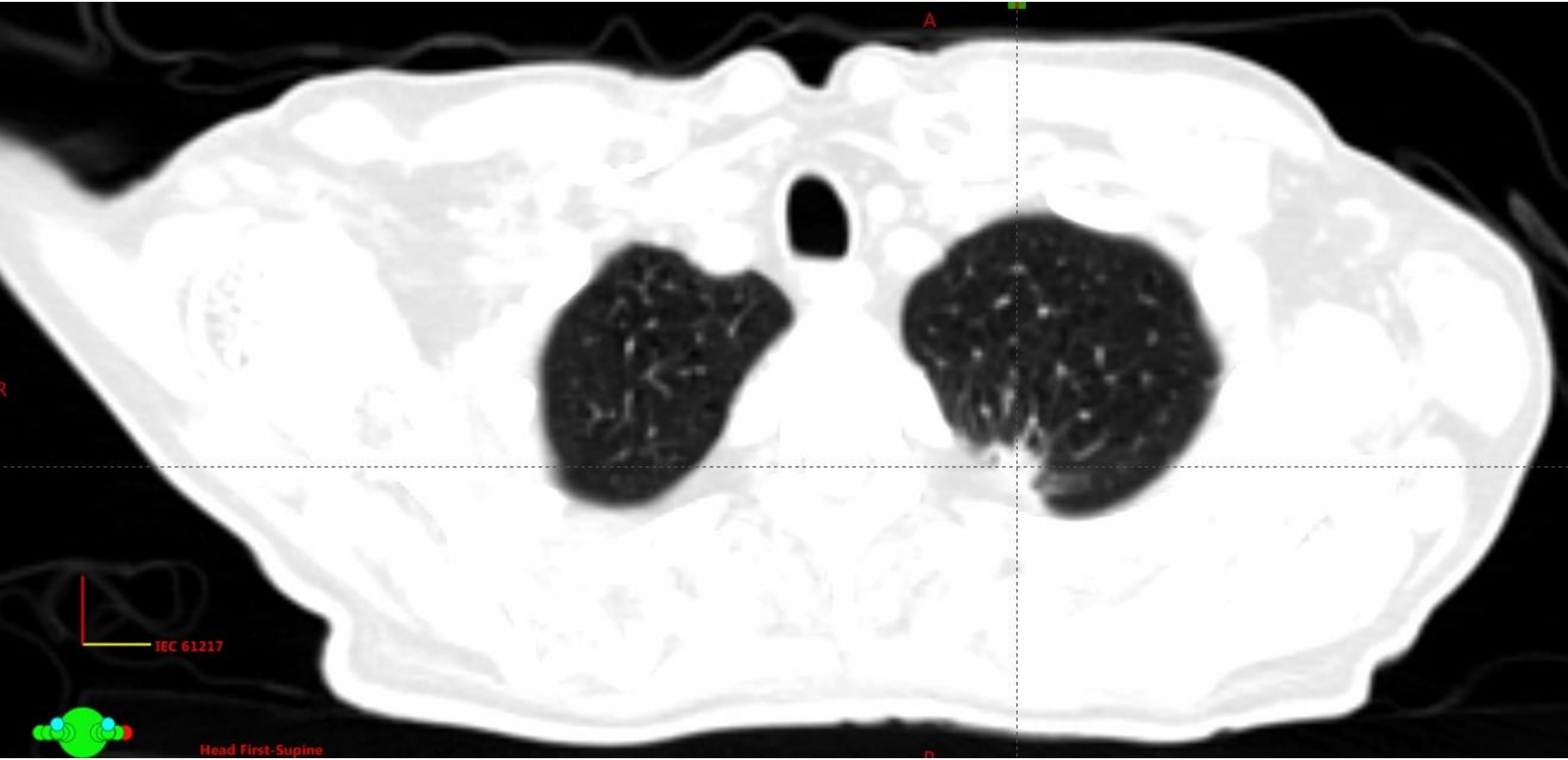
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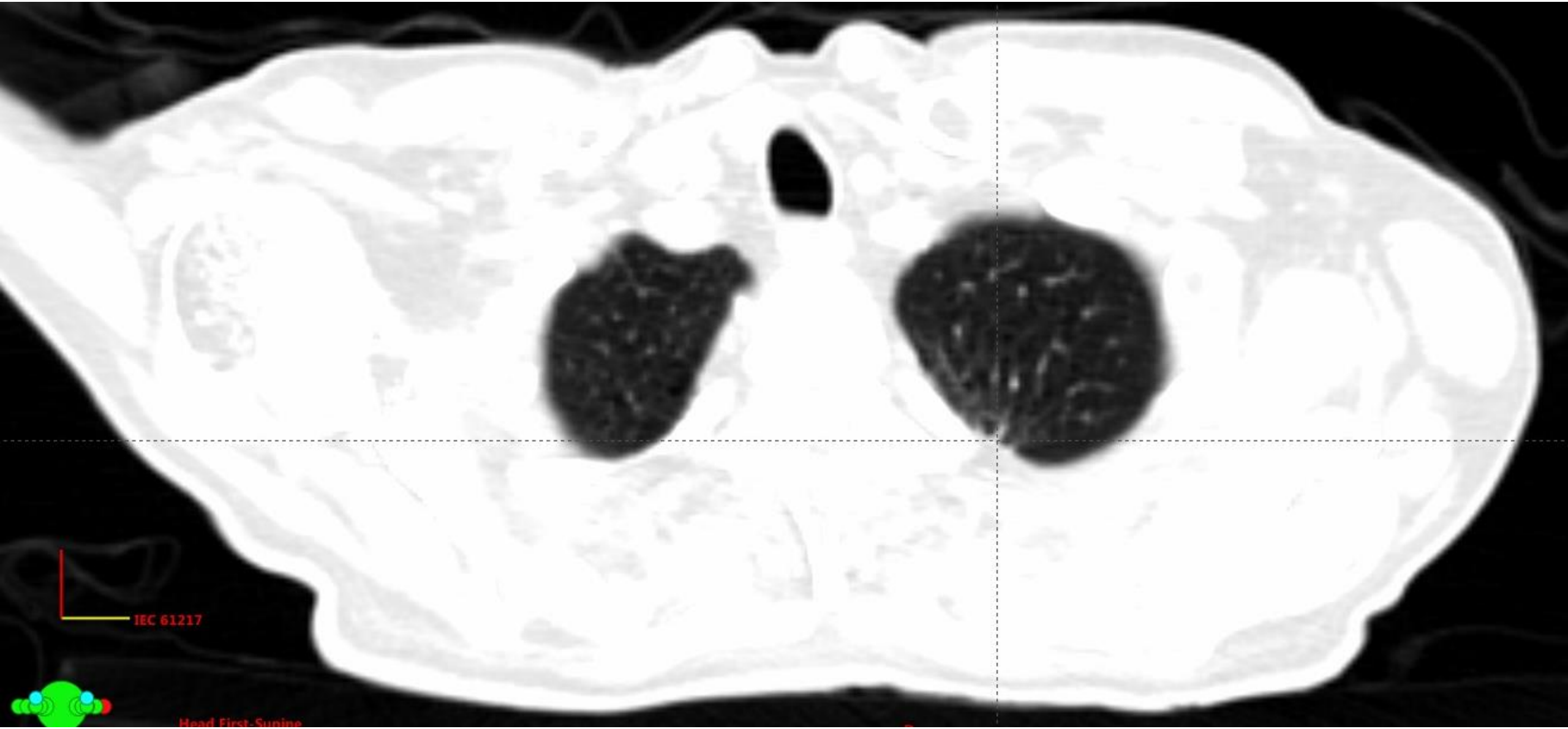
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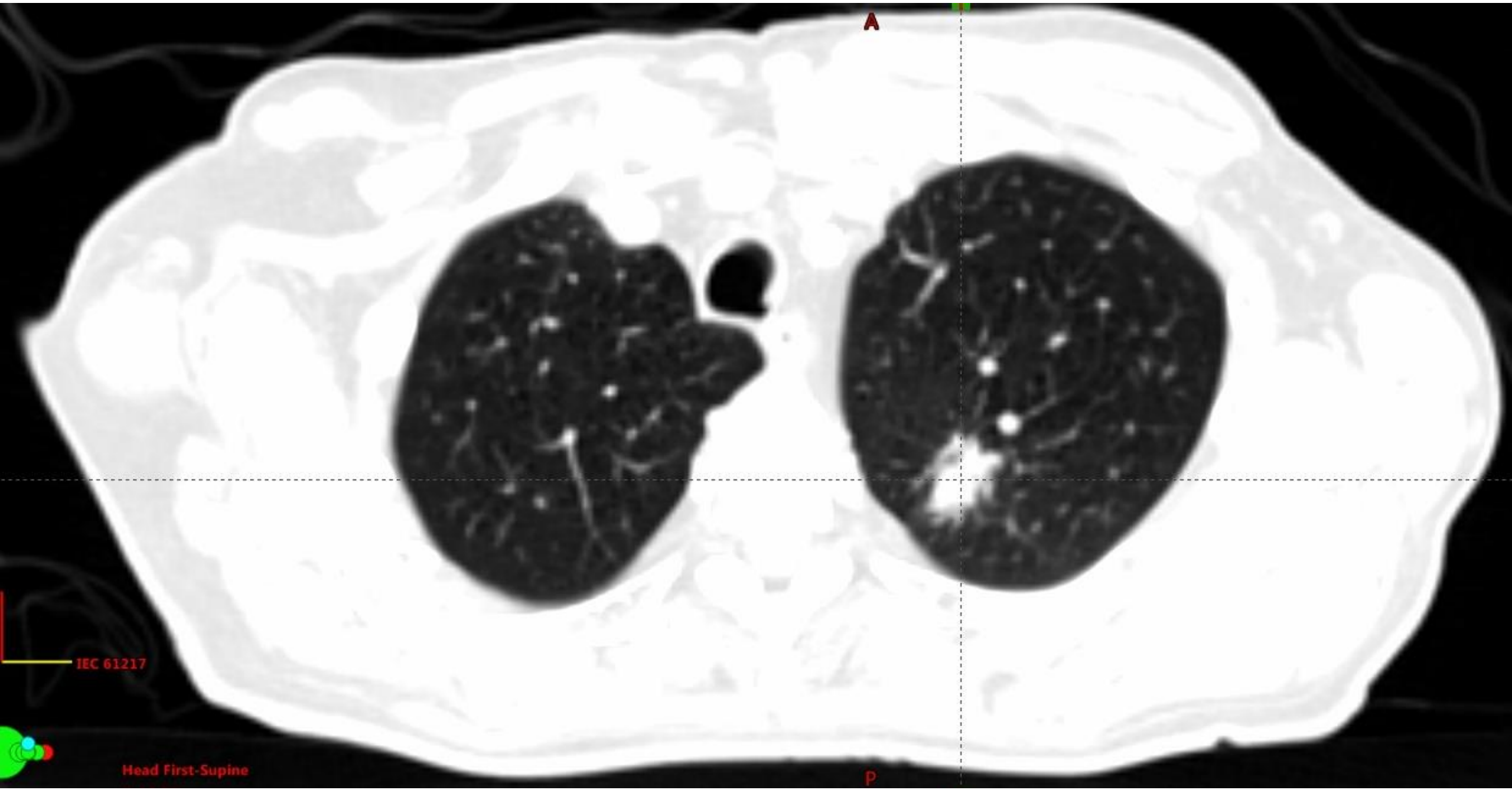
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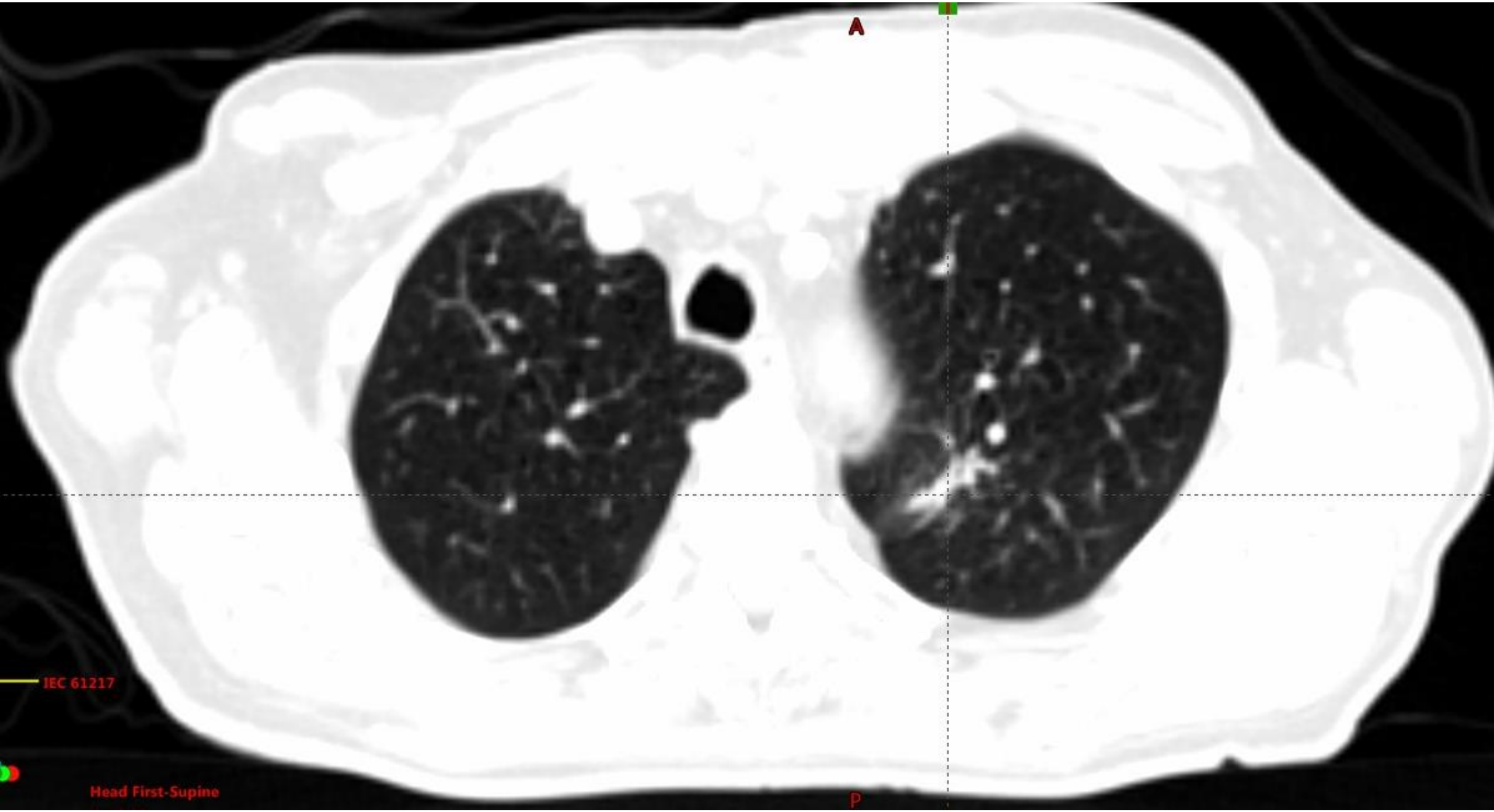
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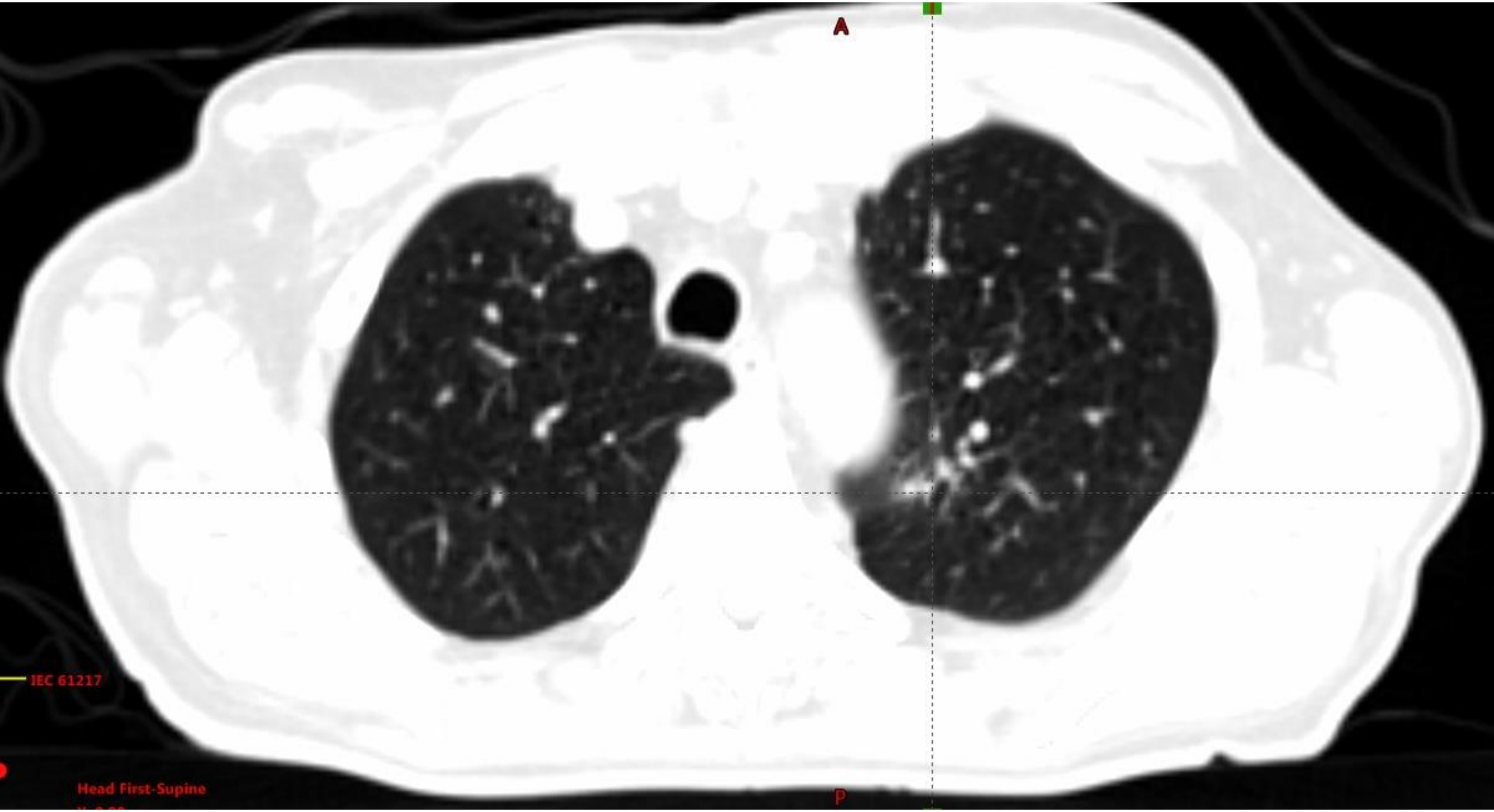
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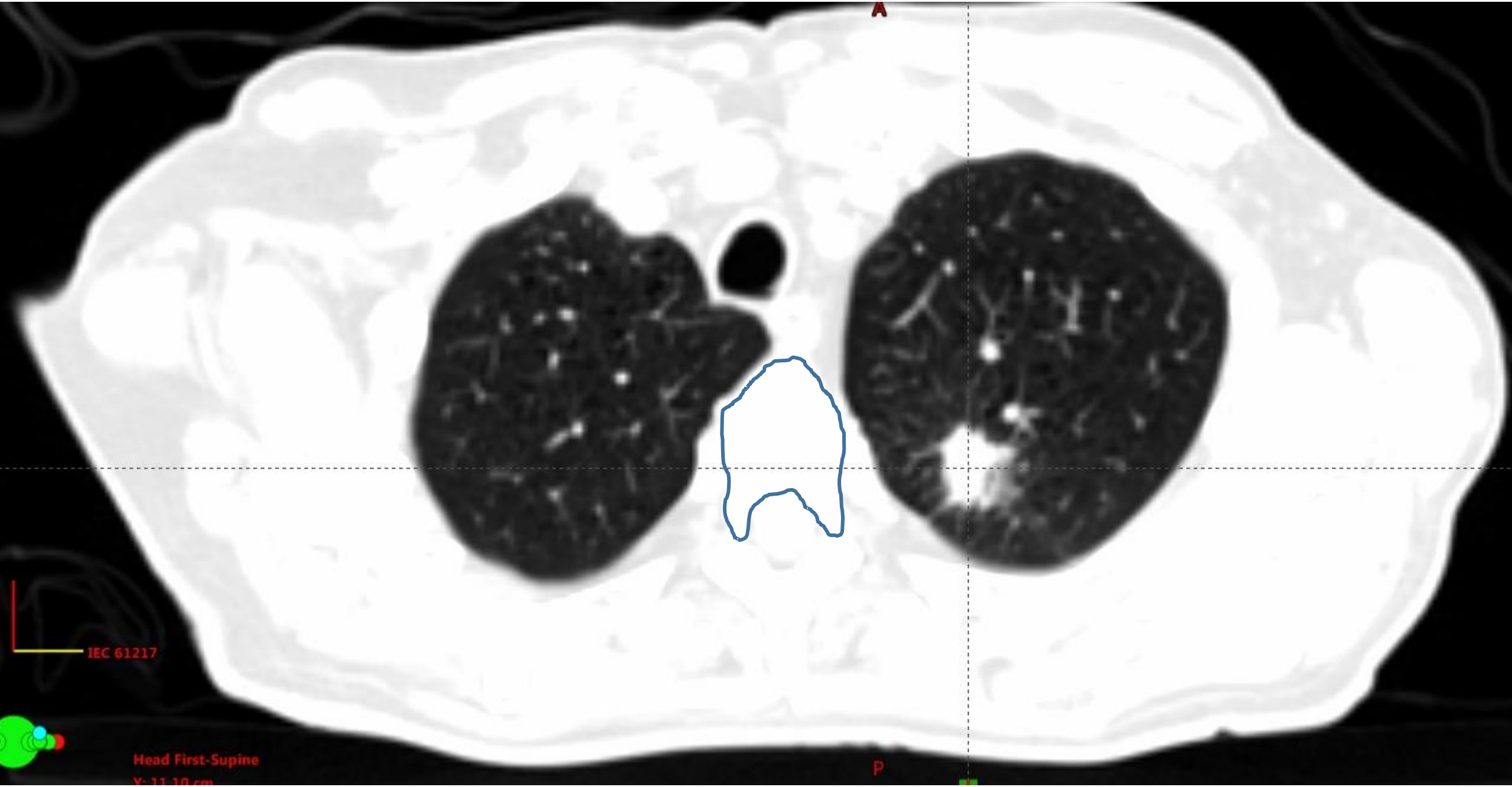
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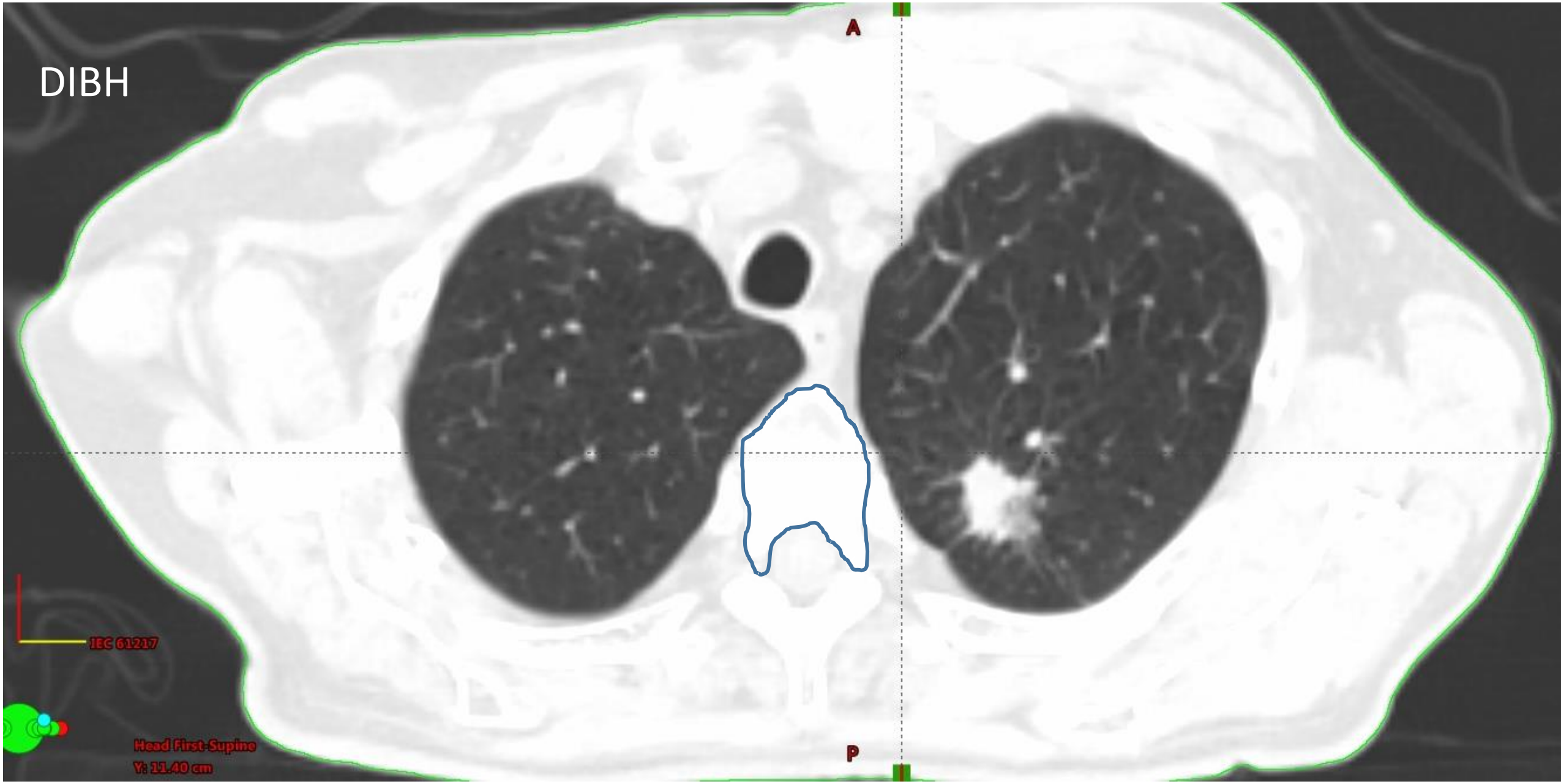
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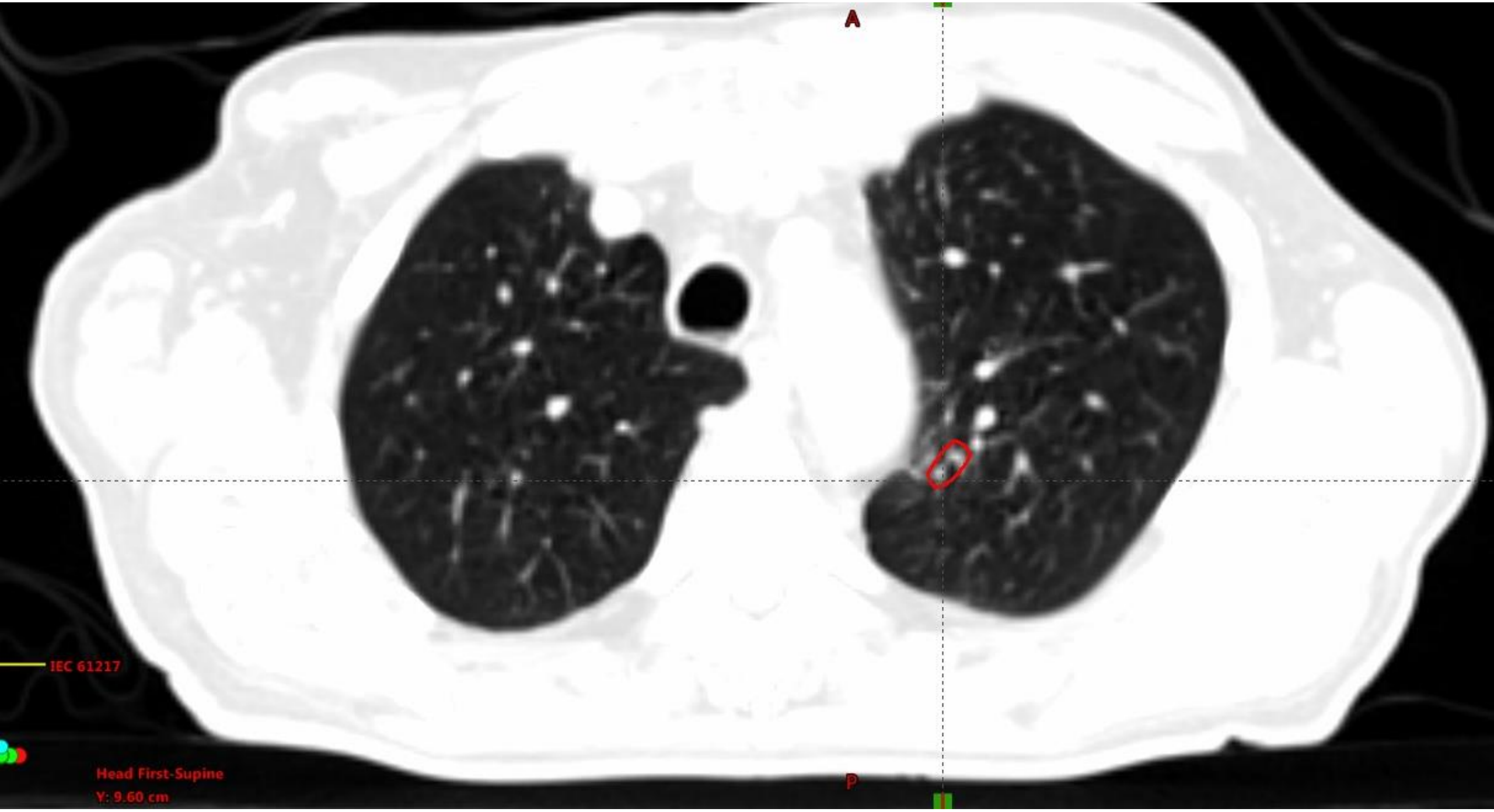
Head First-Supine
Y: 11.40 cm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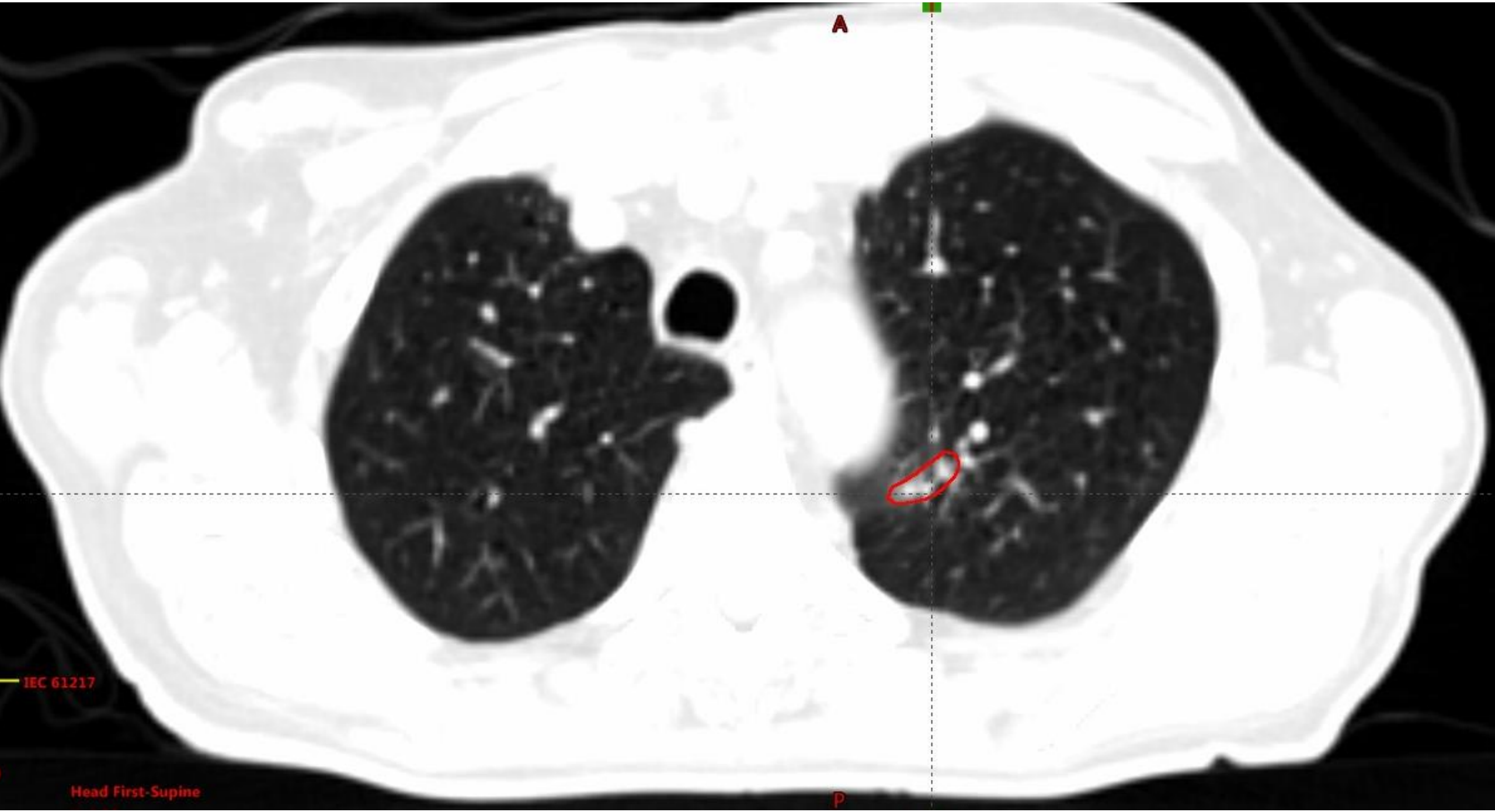
Head First-Supine
Y: 9.60 cm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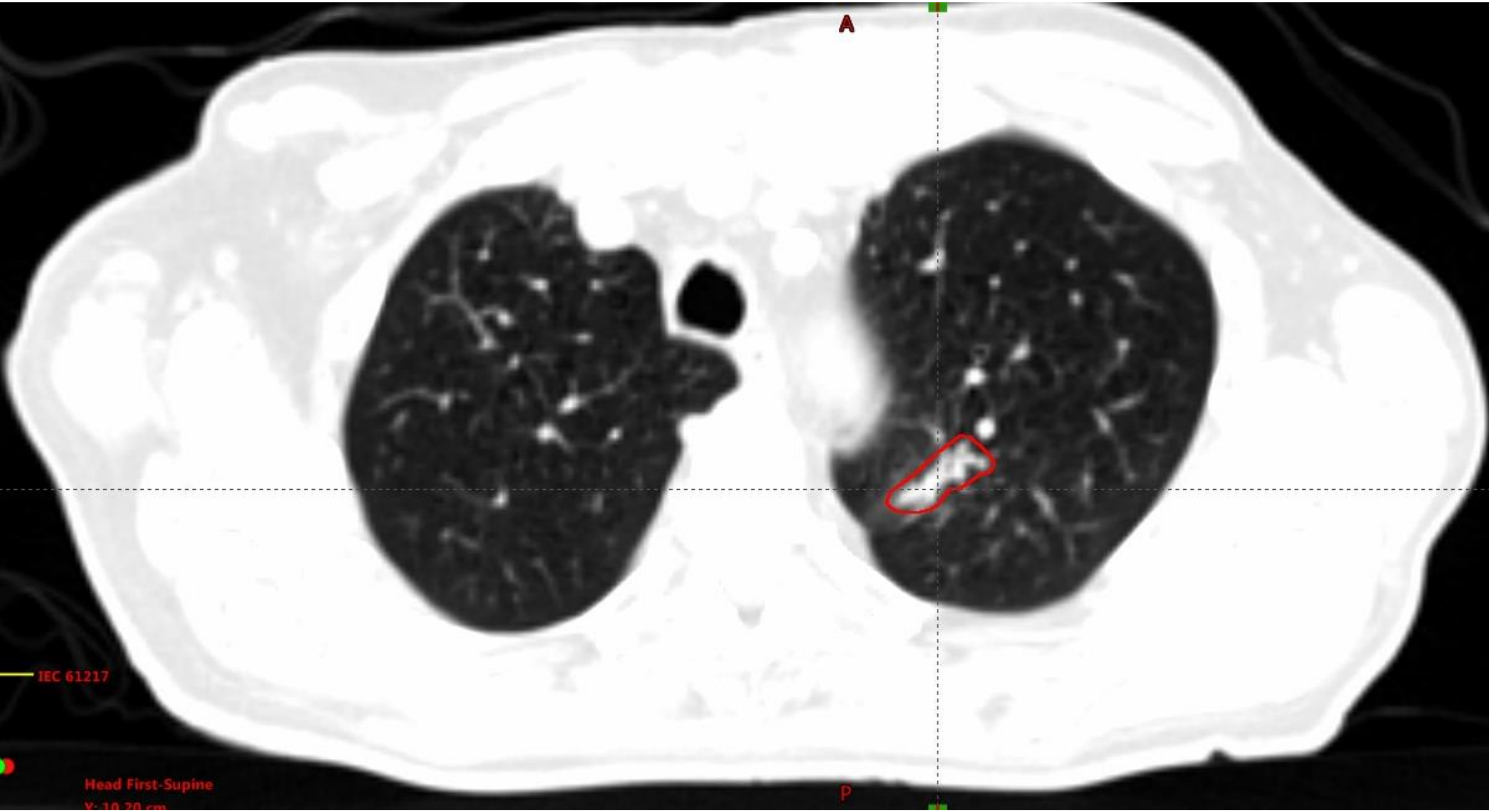
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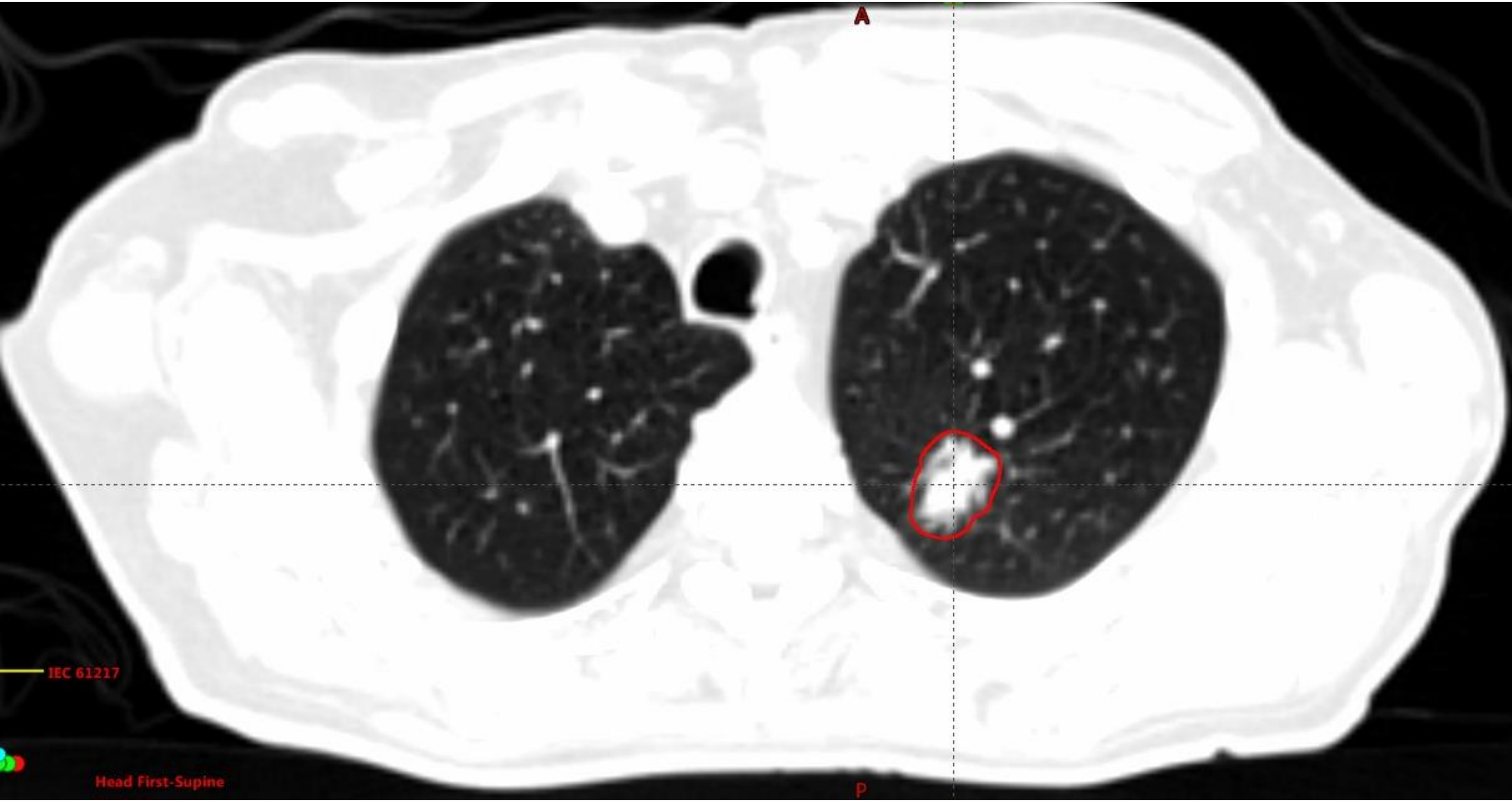
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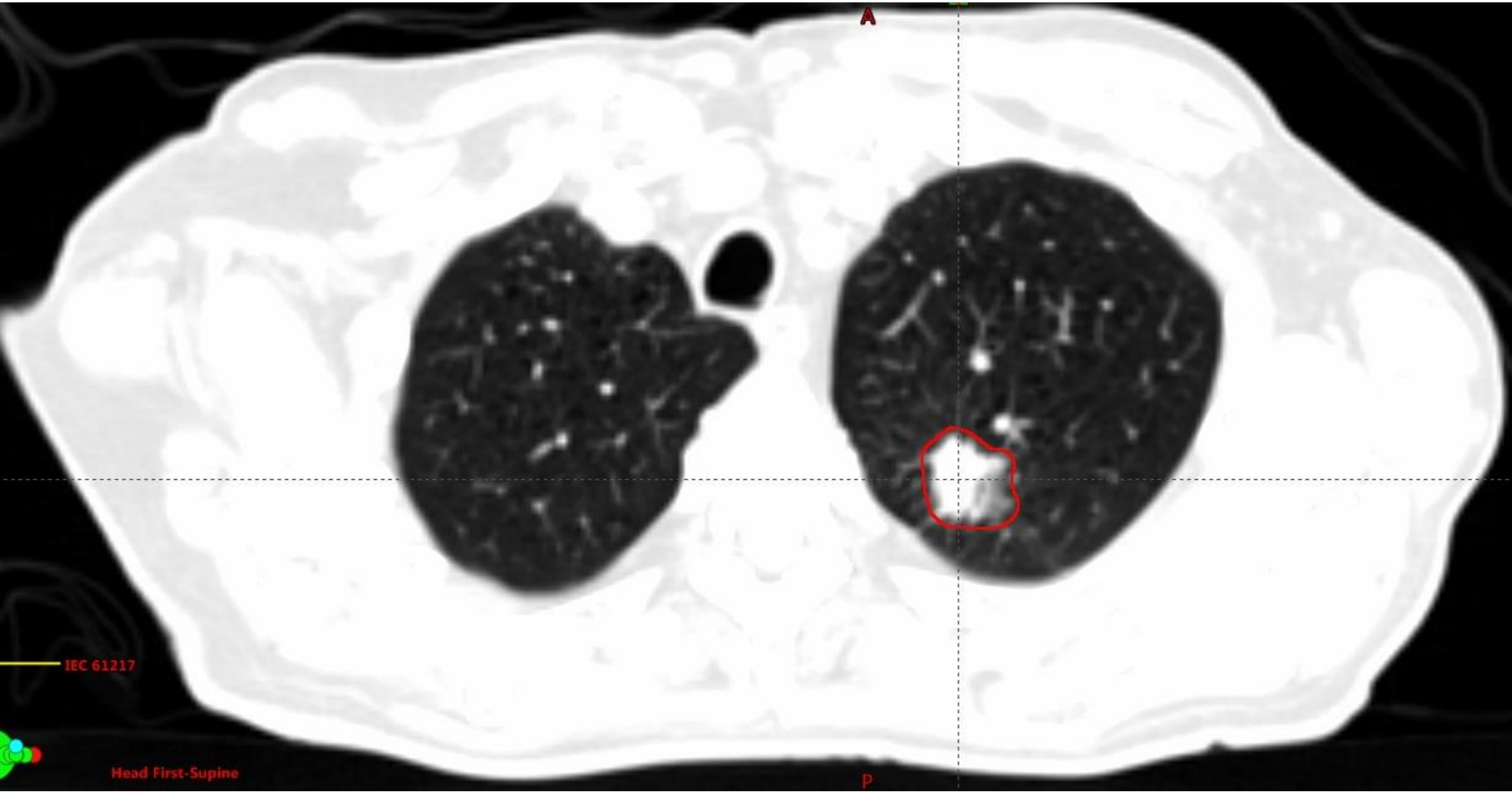
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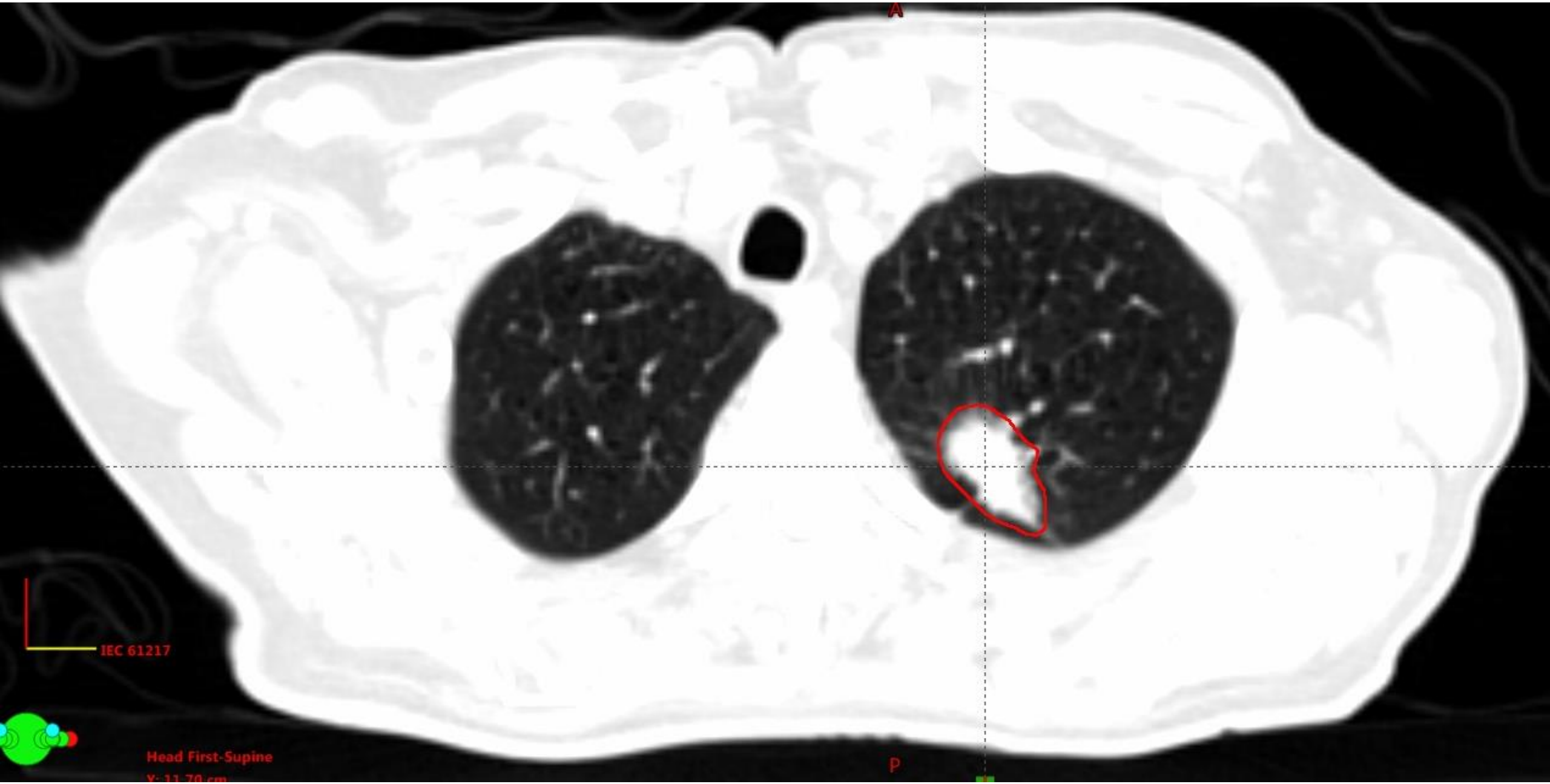
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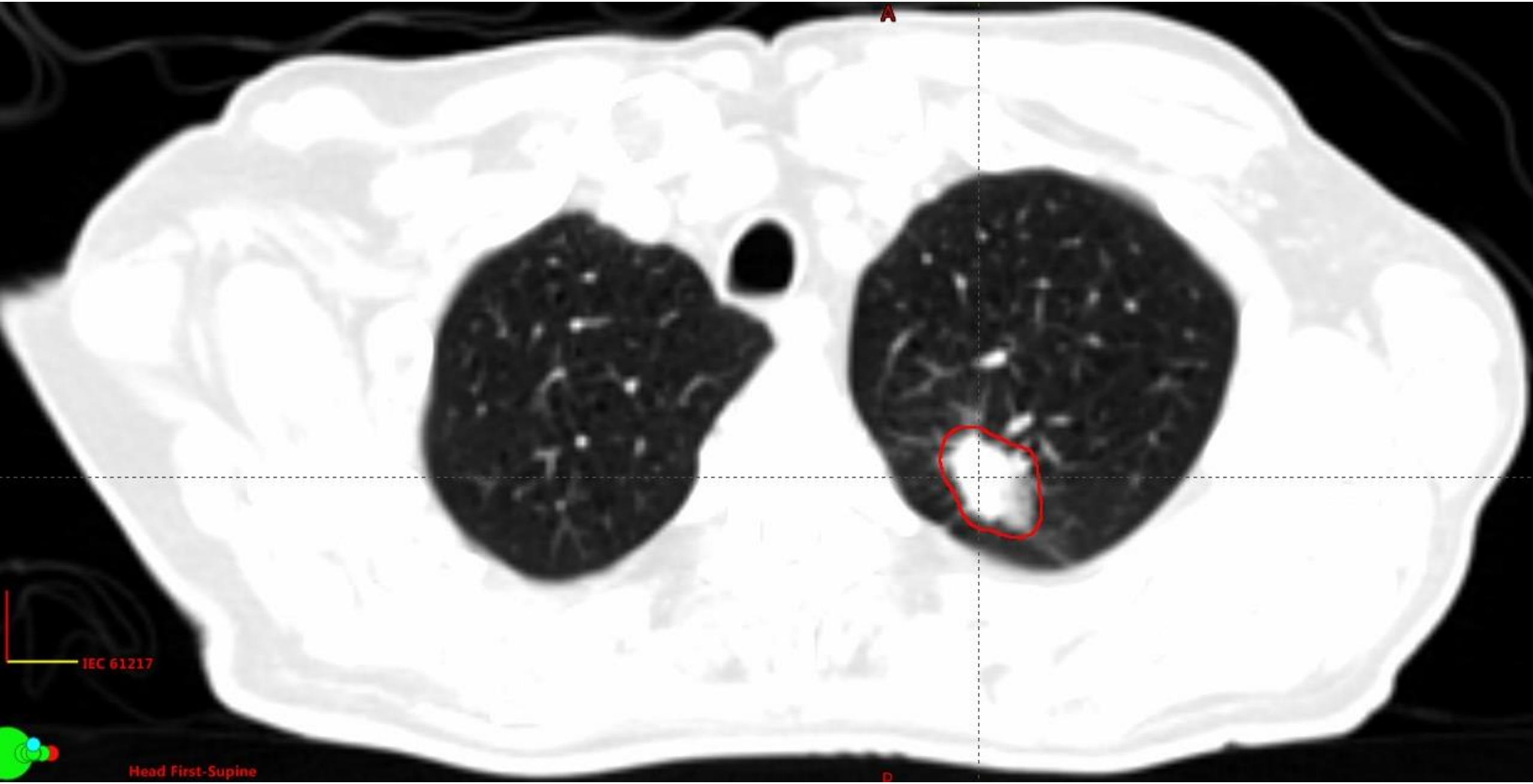
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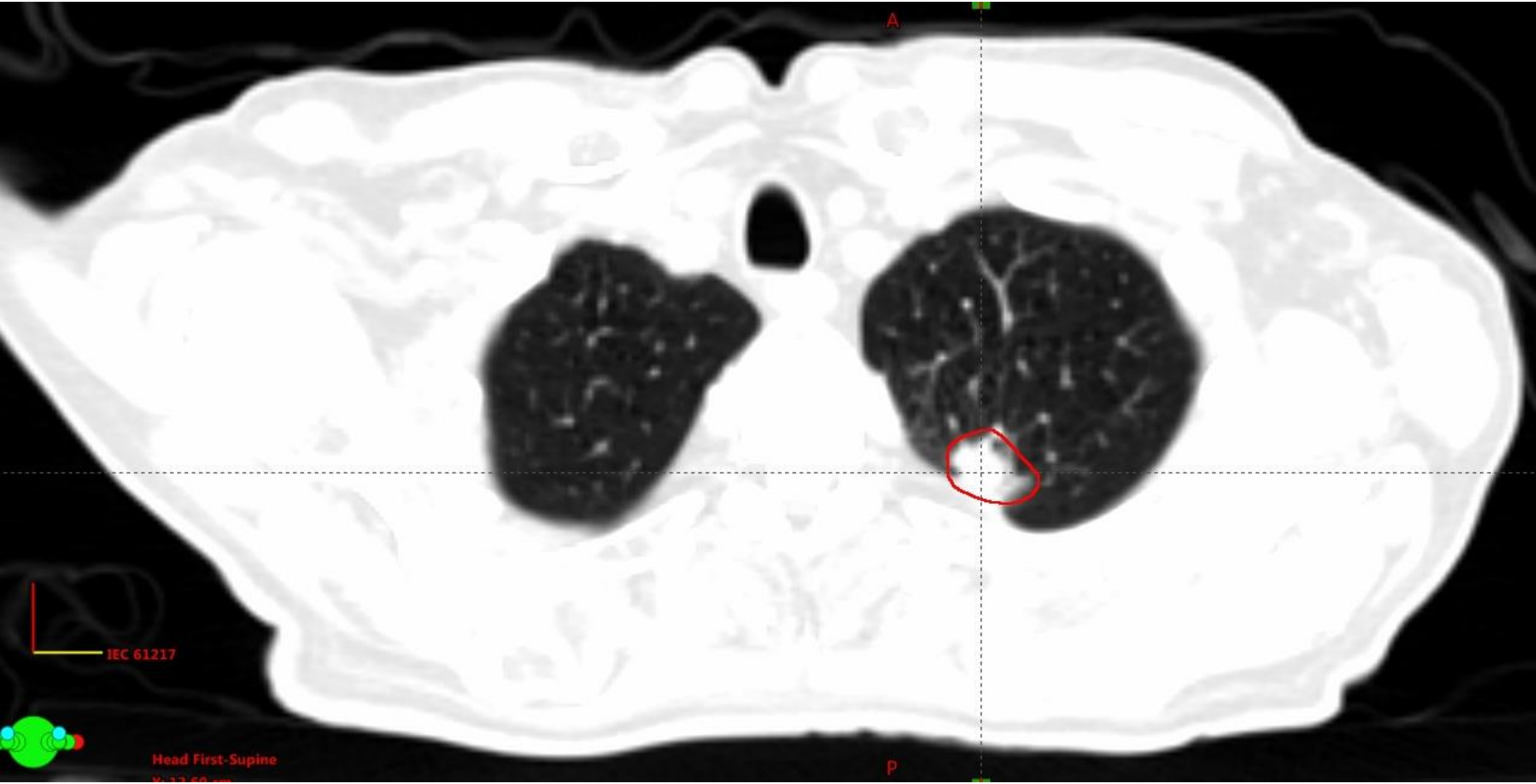
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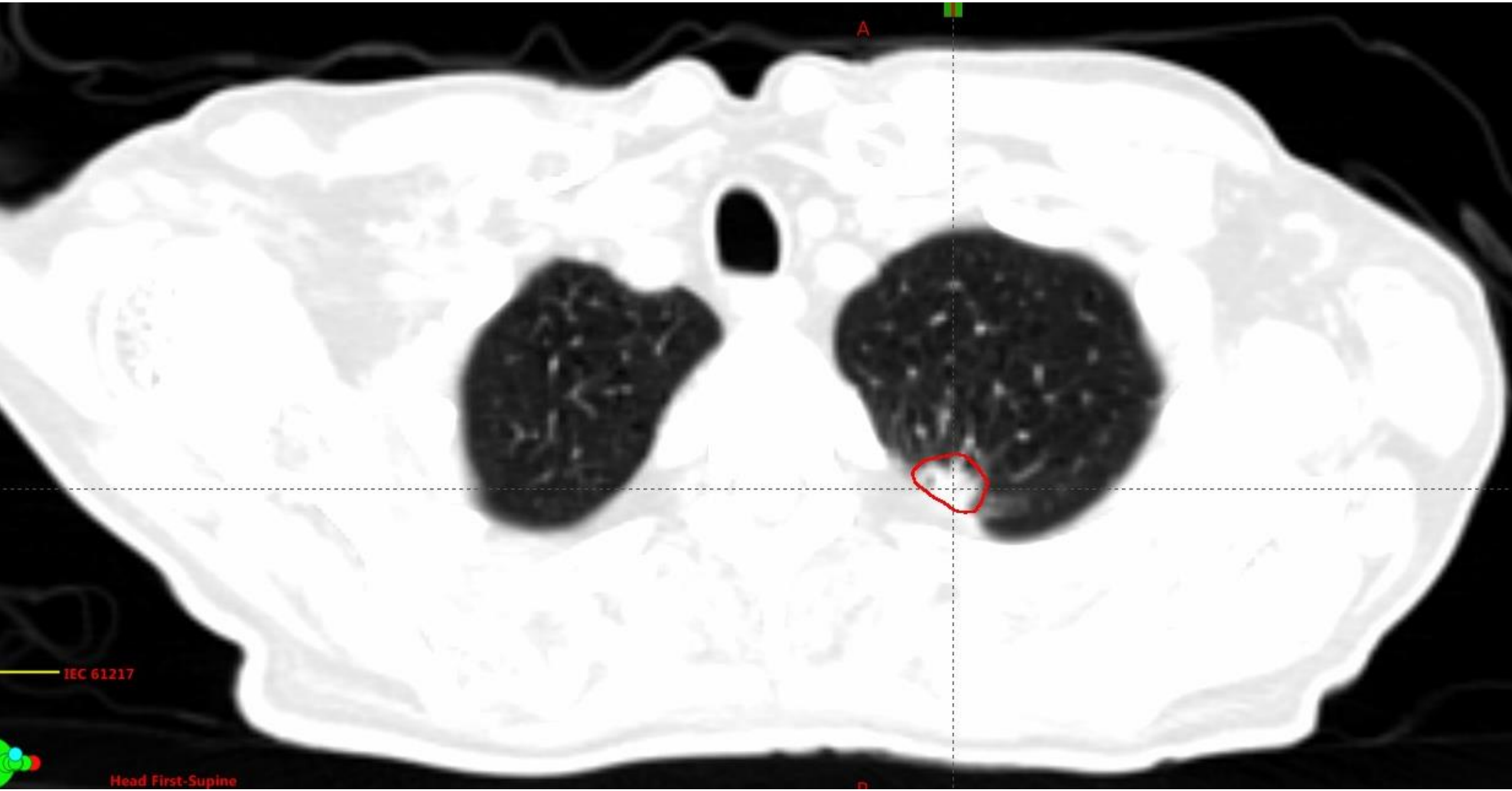
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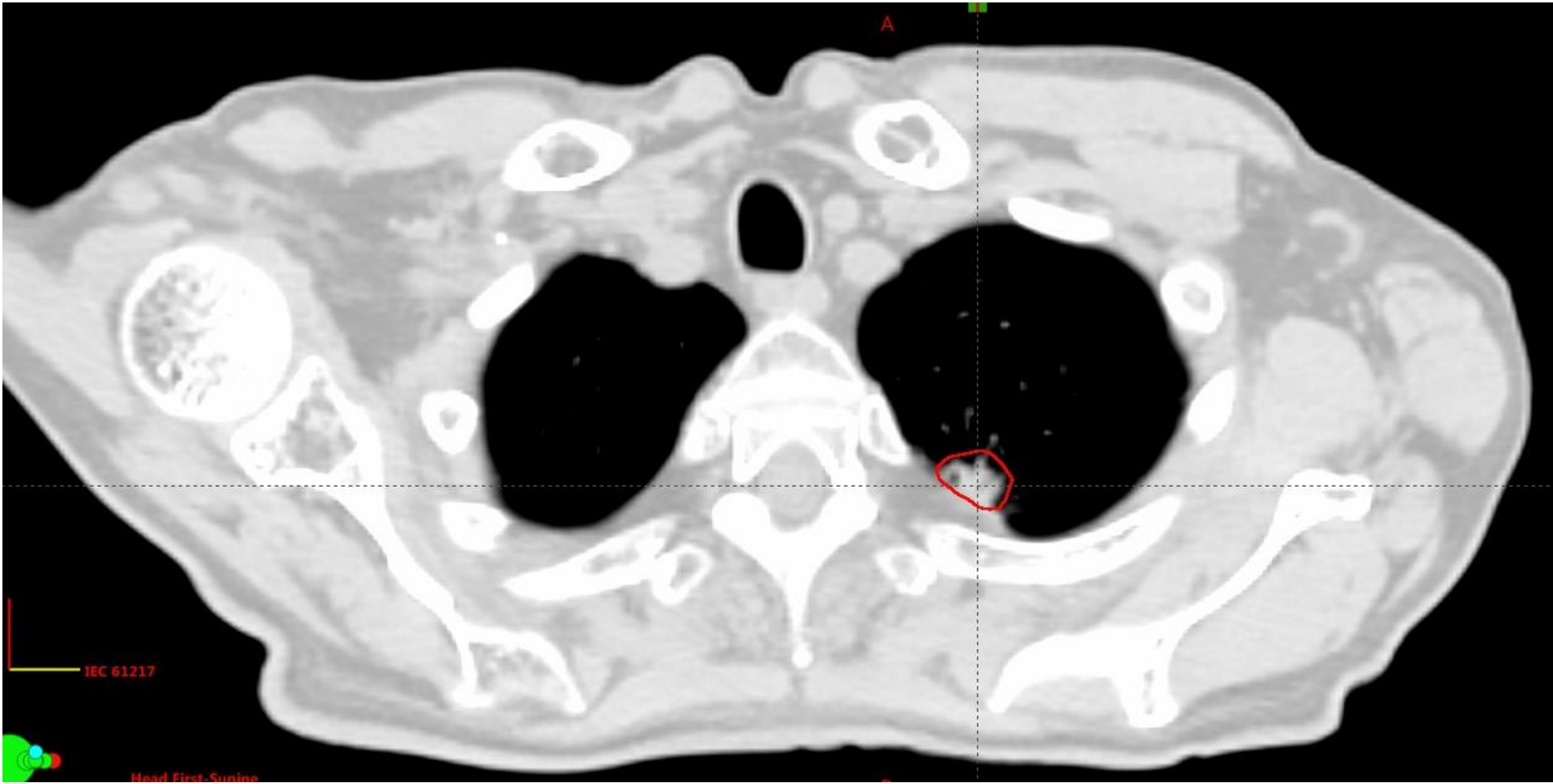
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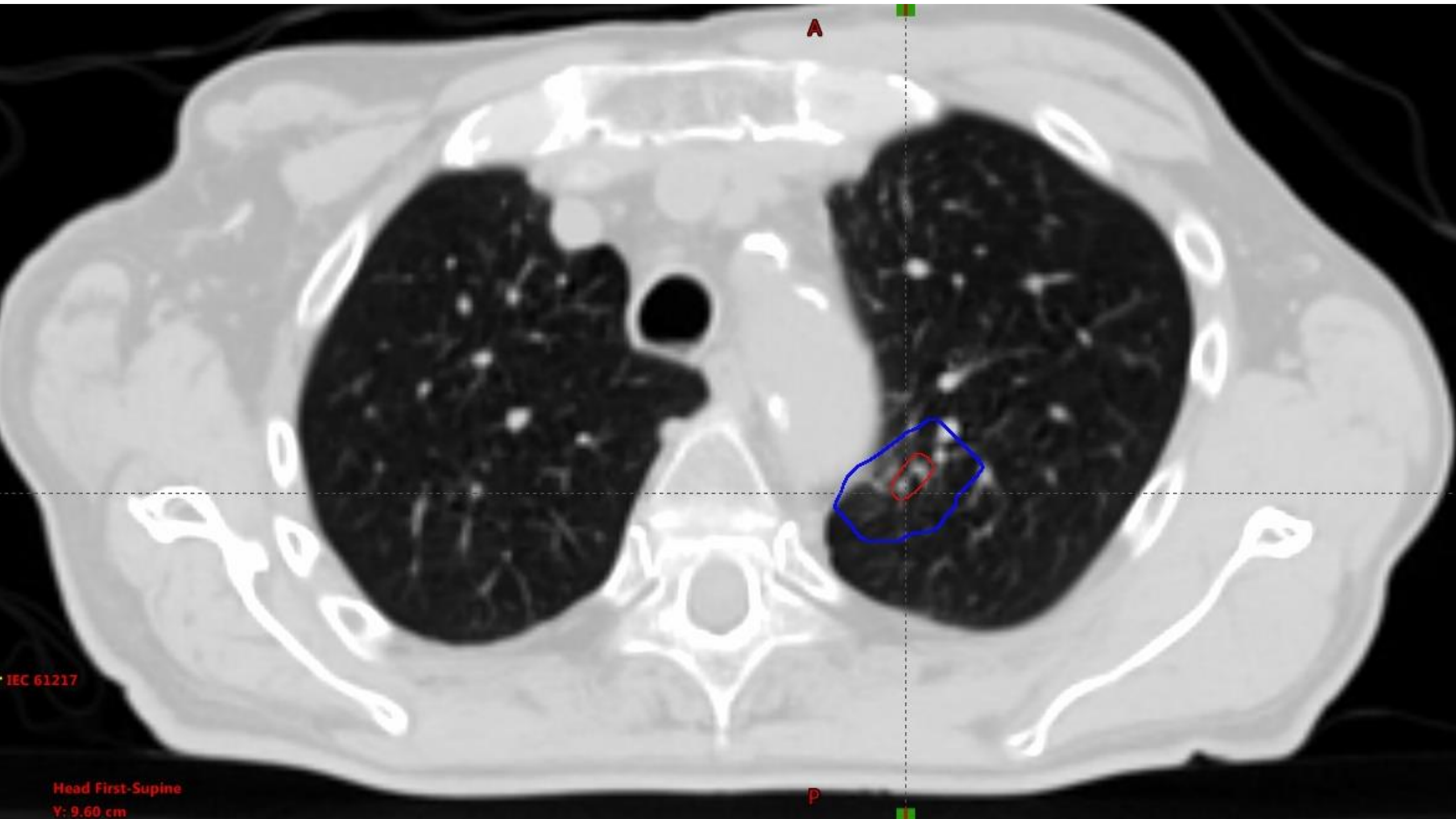
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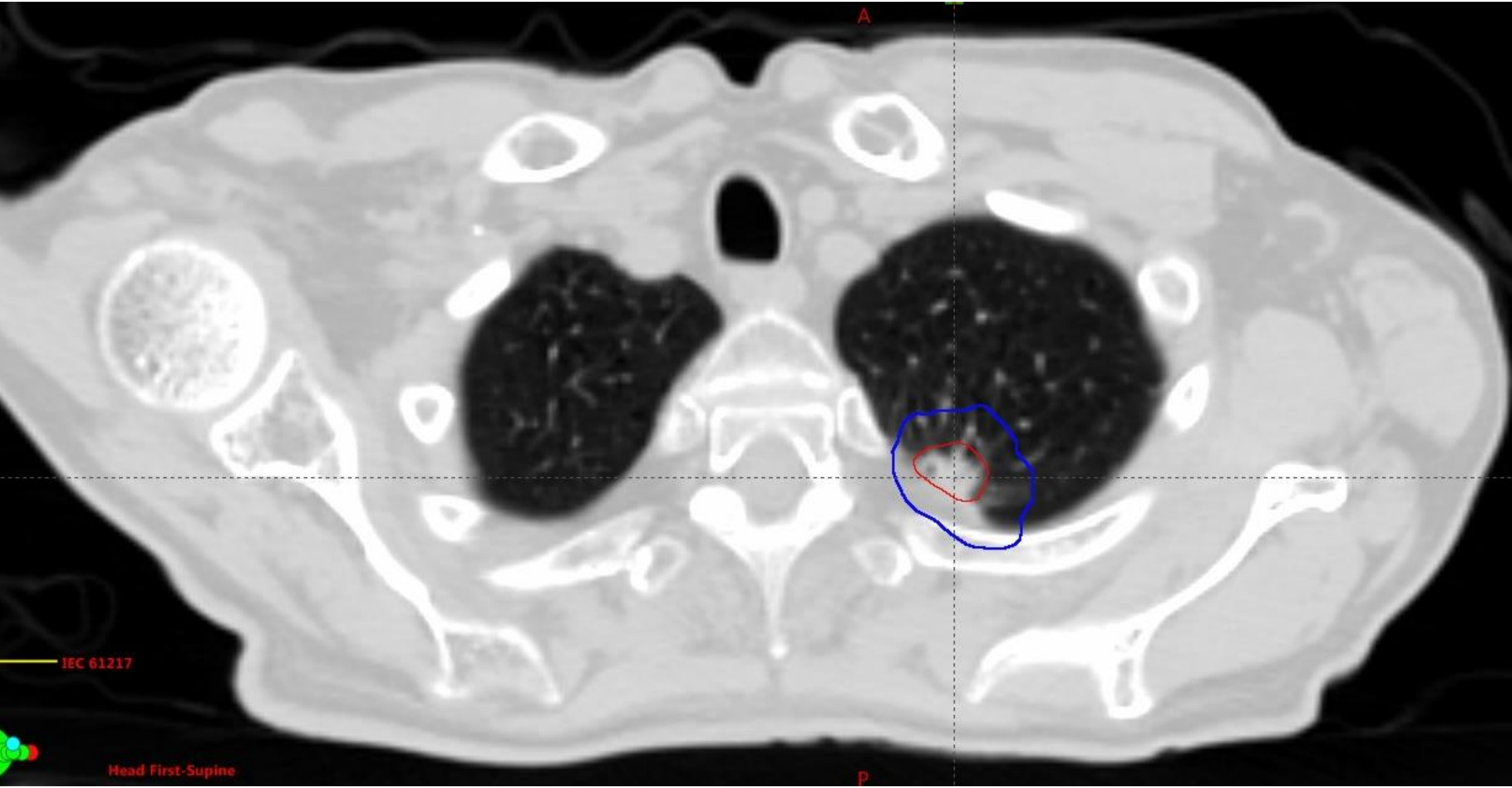
Head First-Supine
Y: 9.60 cm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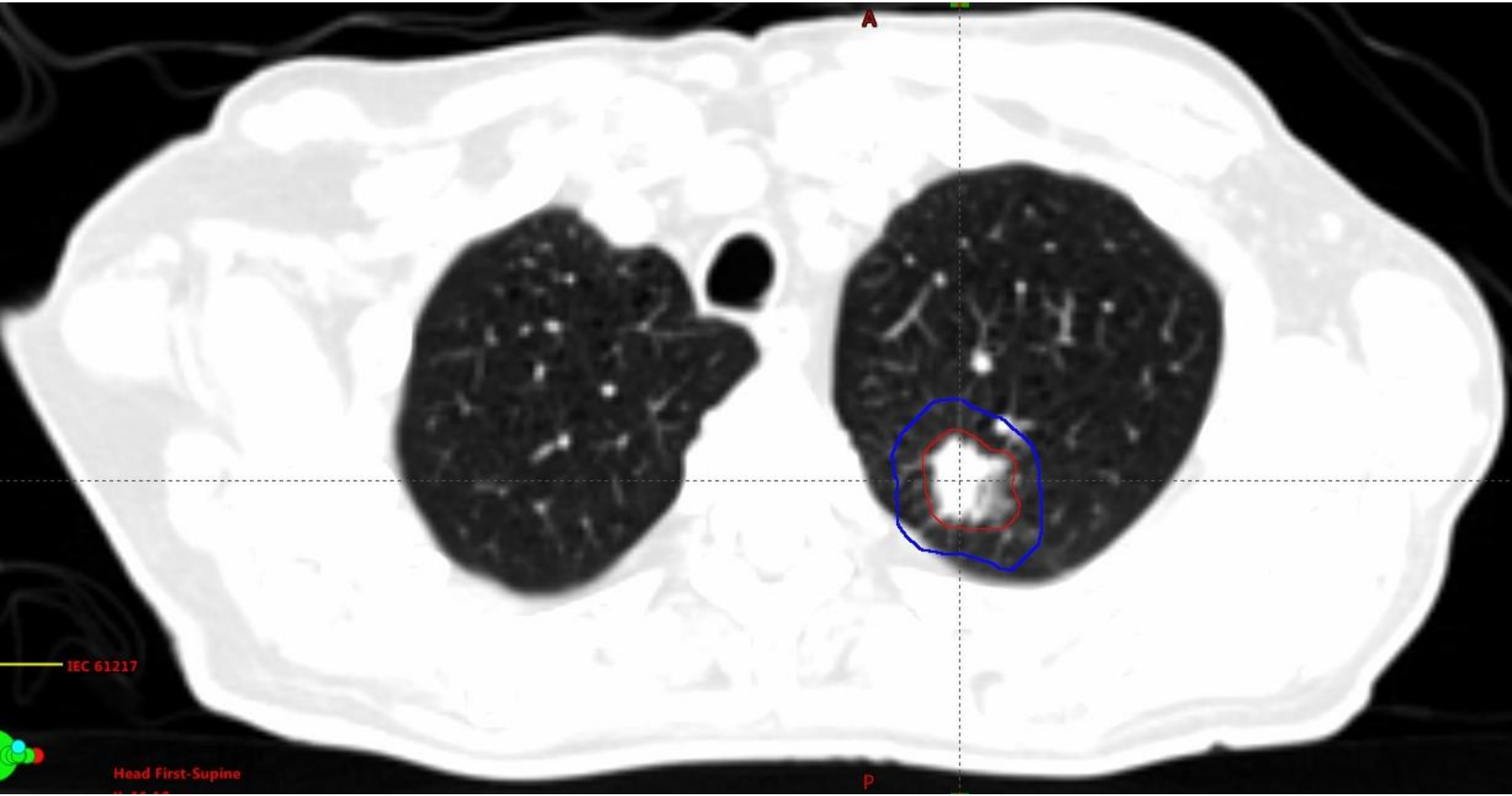
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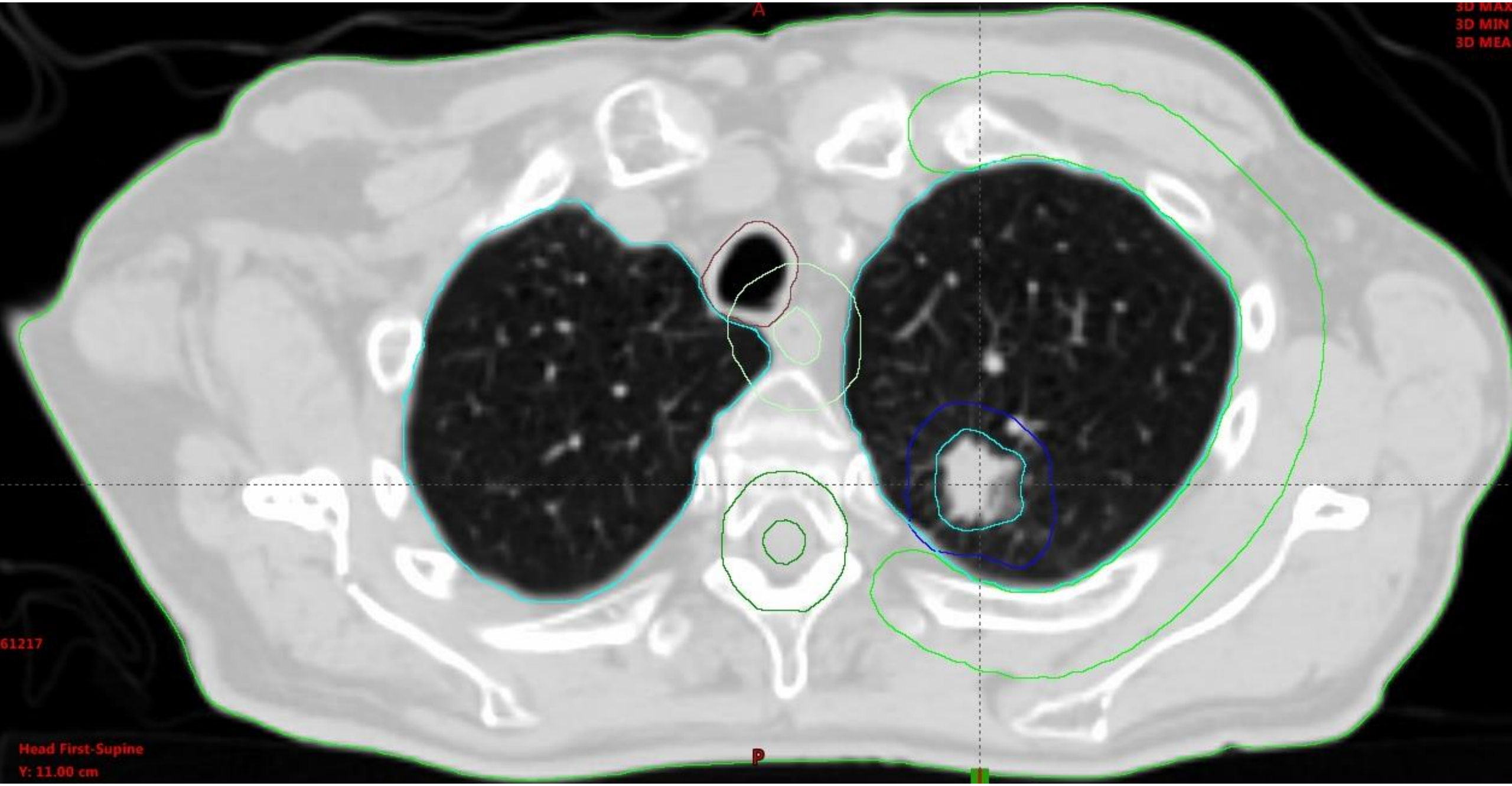
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3D MAX
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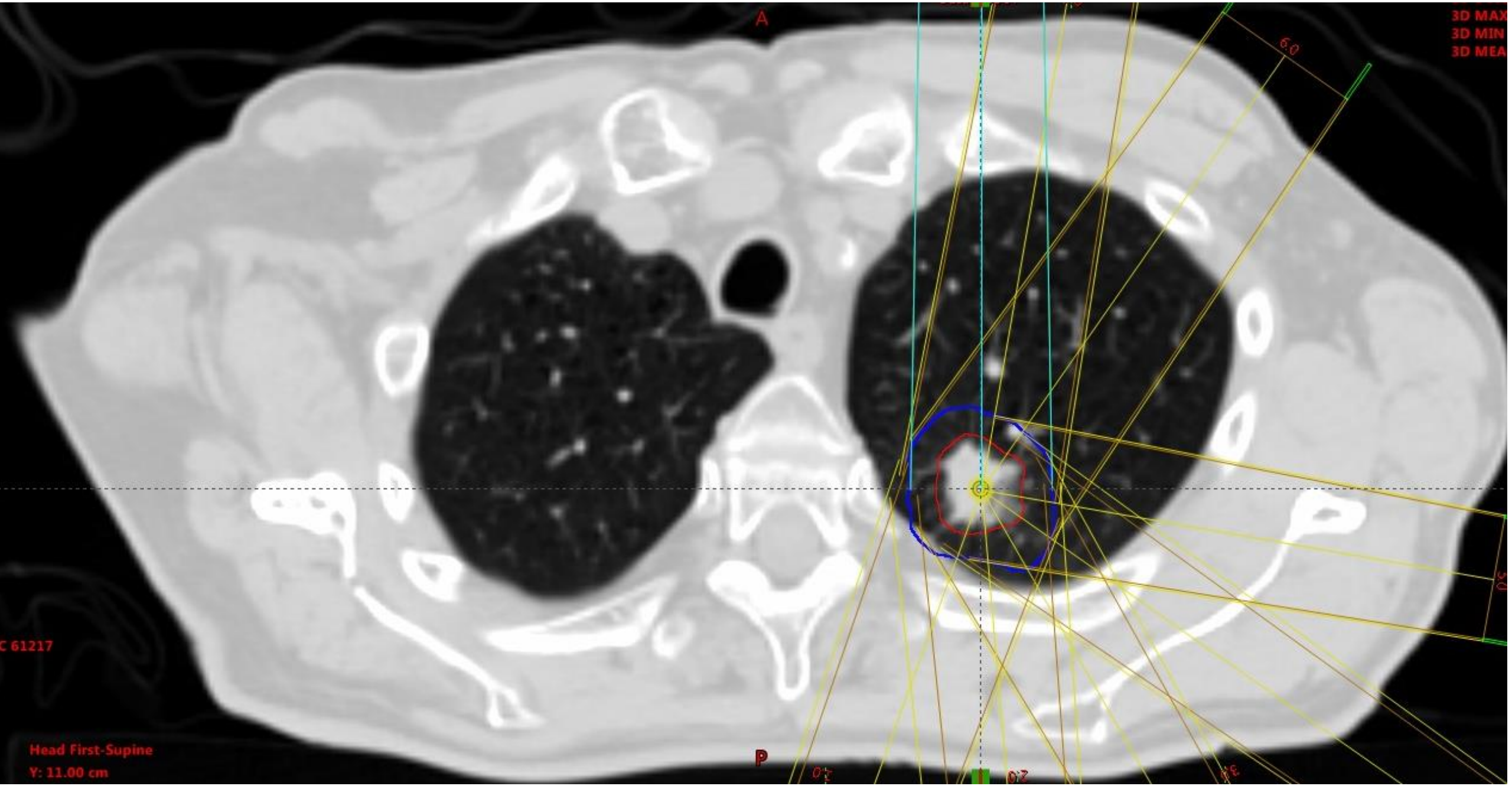
Head First-Supine
Y: 11.00 cm
P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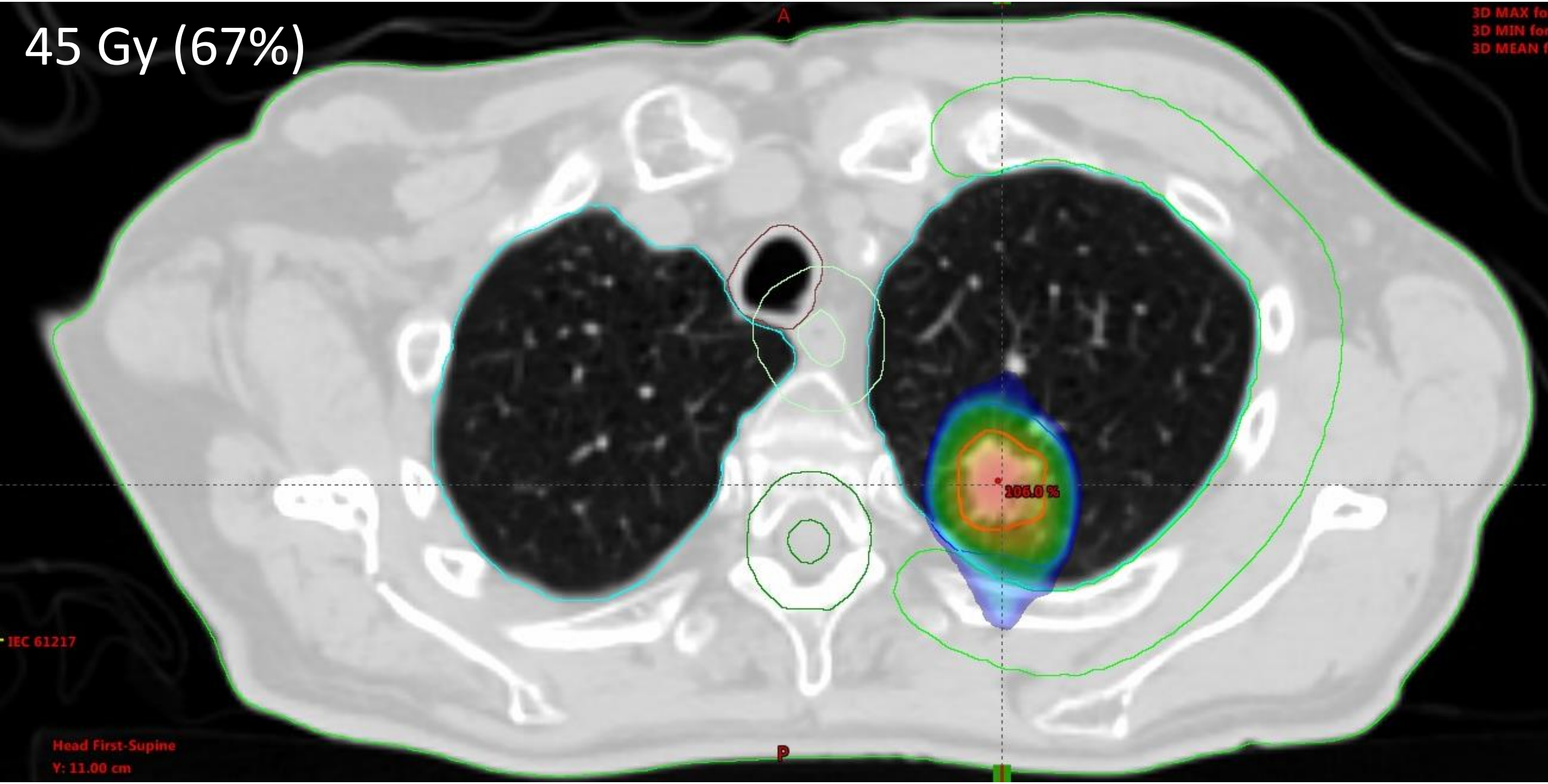
3D MAX
3D MIN
3D MEA
6.0
C 61217
Head First-Supine
Y: 11.00 cm


45 Gy (67%)
A
P
106.0 %
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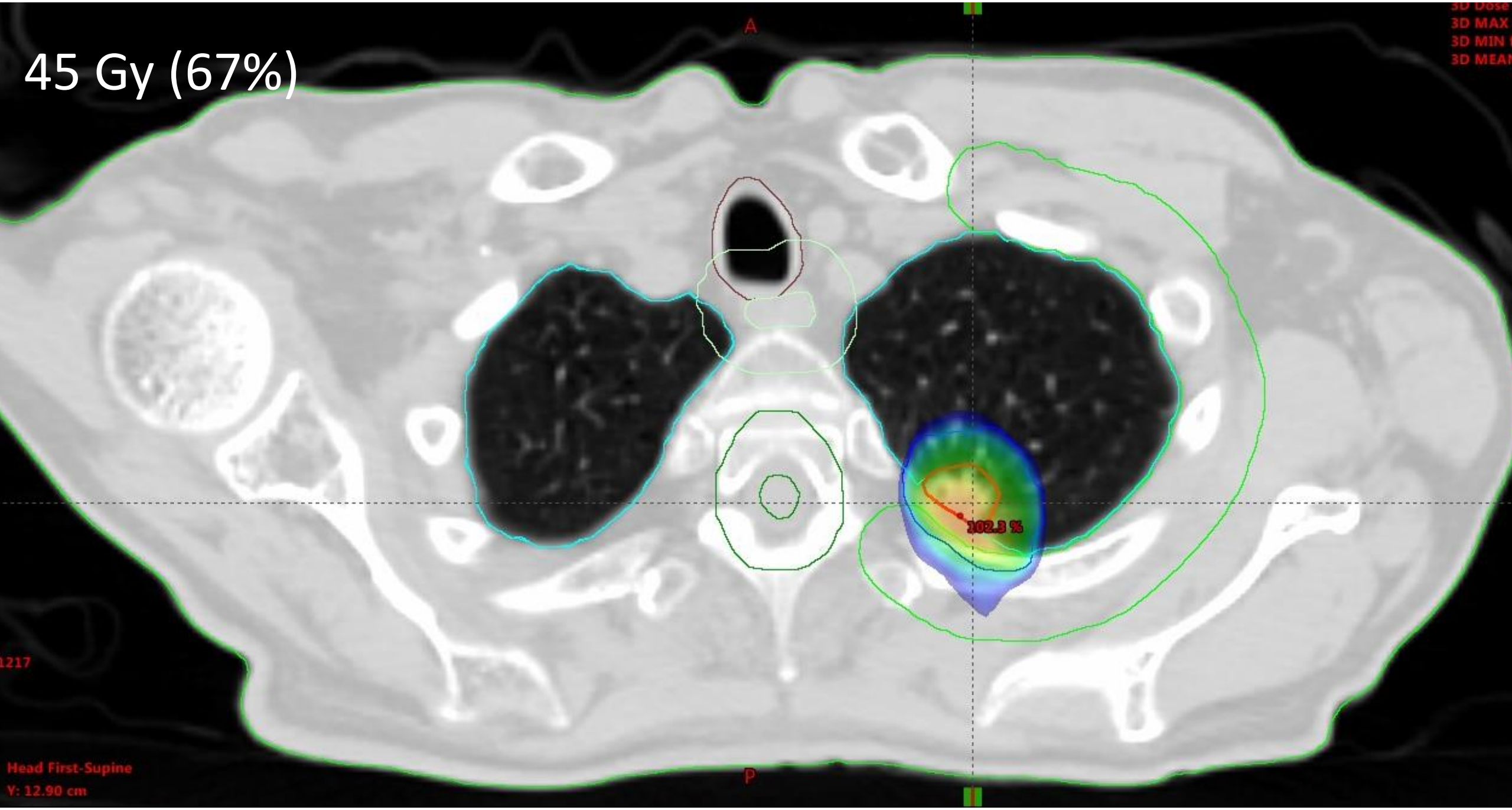
Head First-Supine
Y: 11.00 cm


45 Gy (67%)
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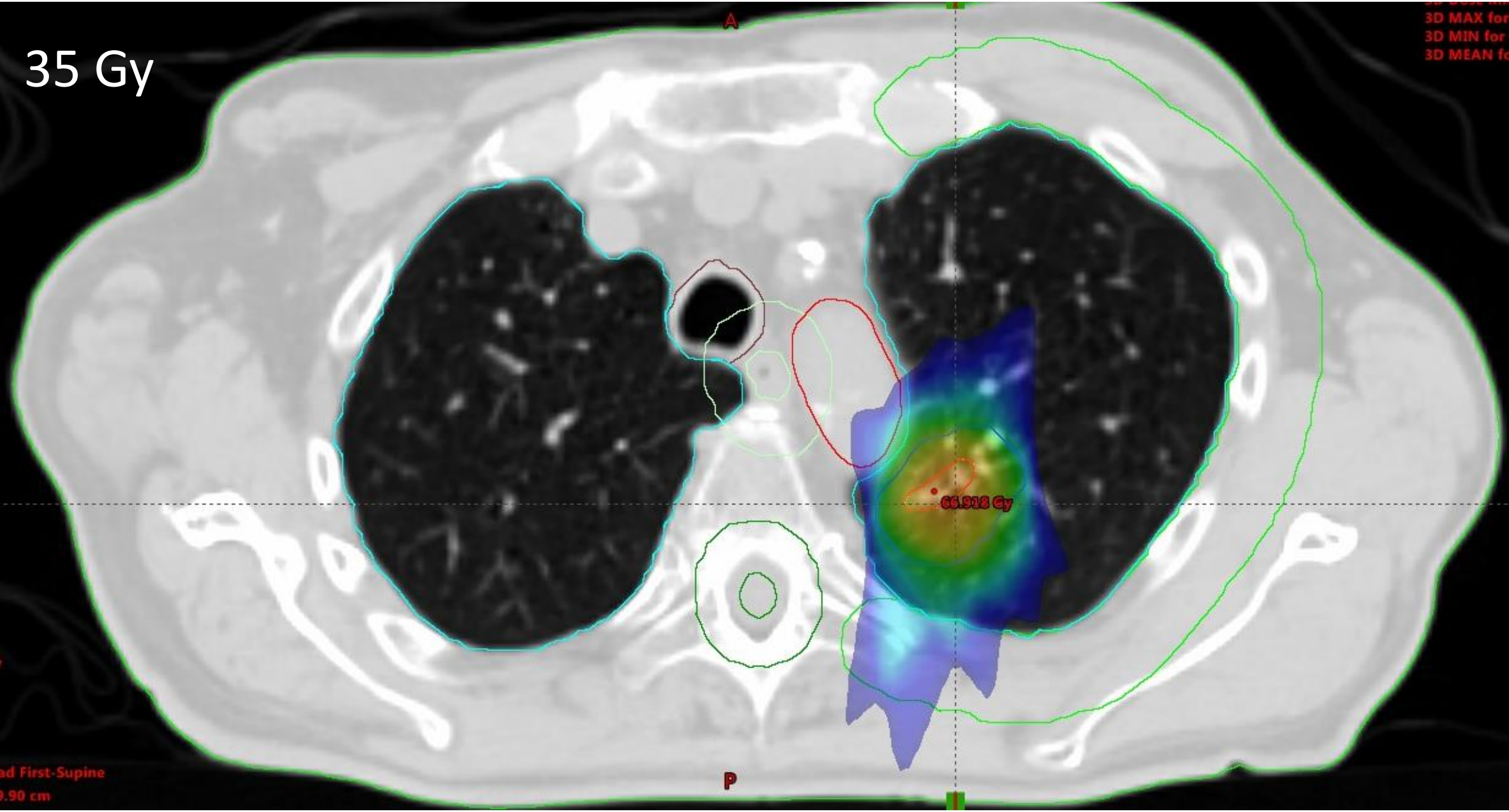
P
102.3 %
Head First-Supine
Y: 12.90 cm


35 Gy
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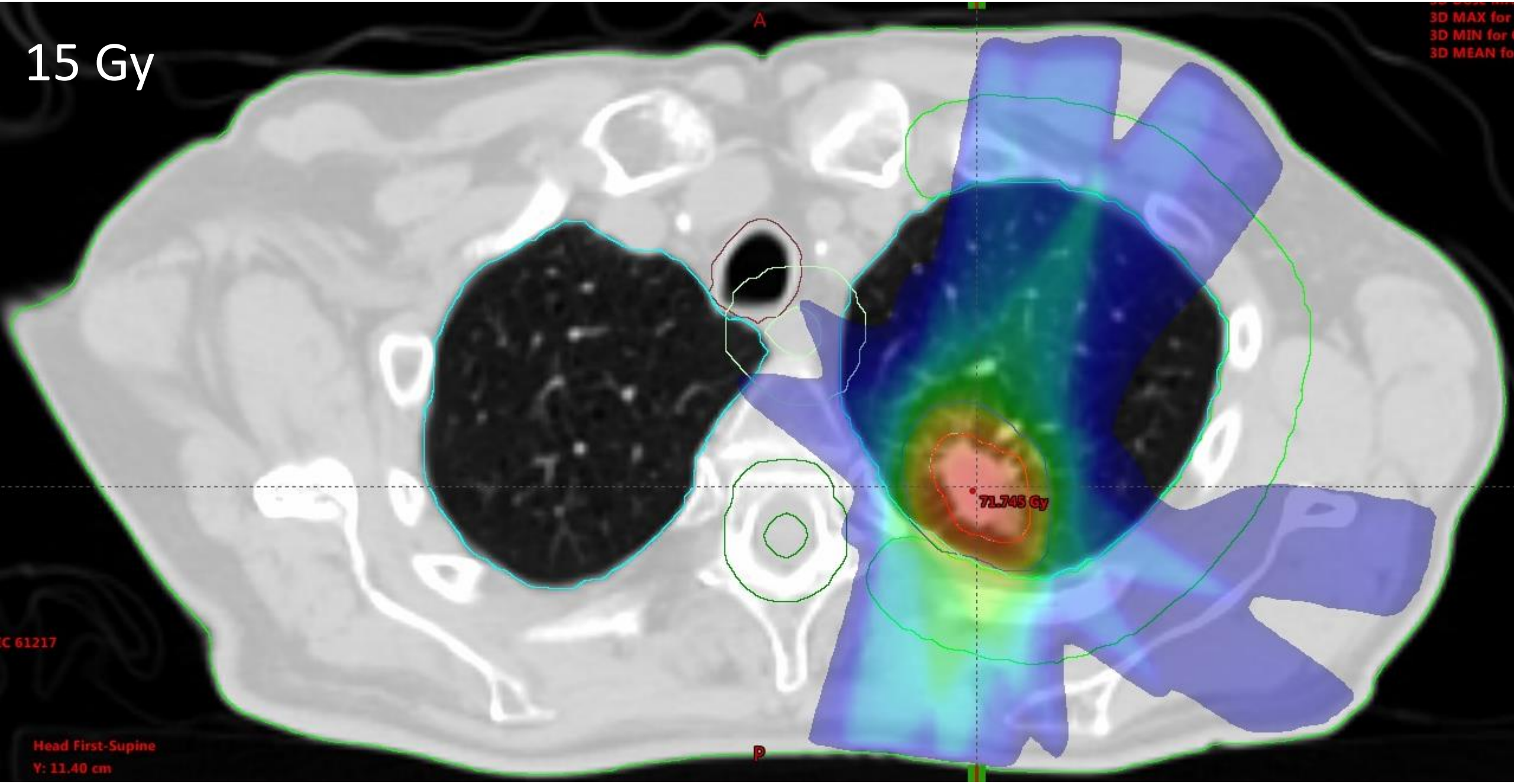
66.918 Gy


15 Gy
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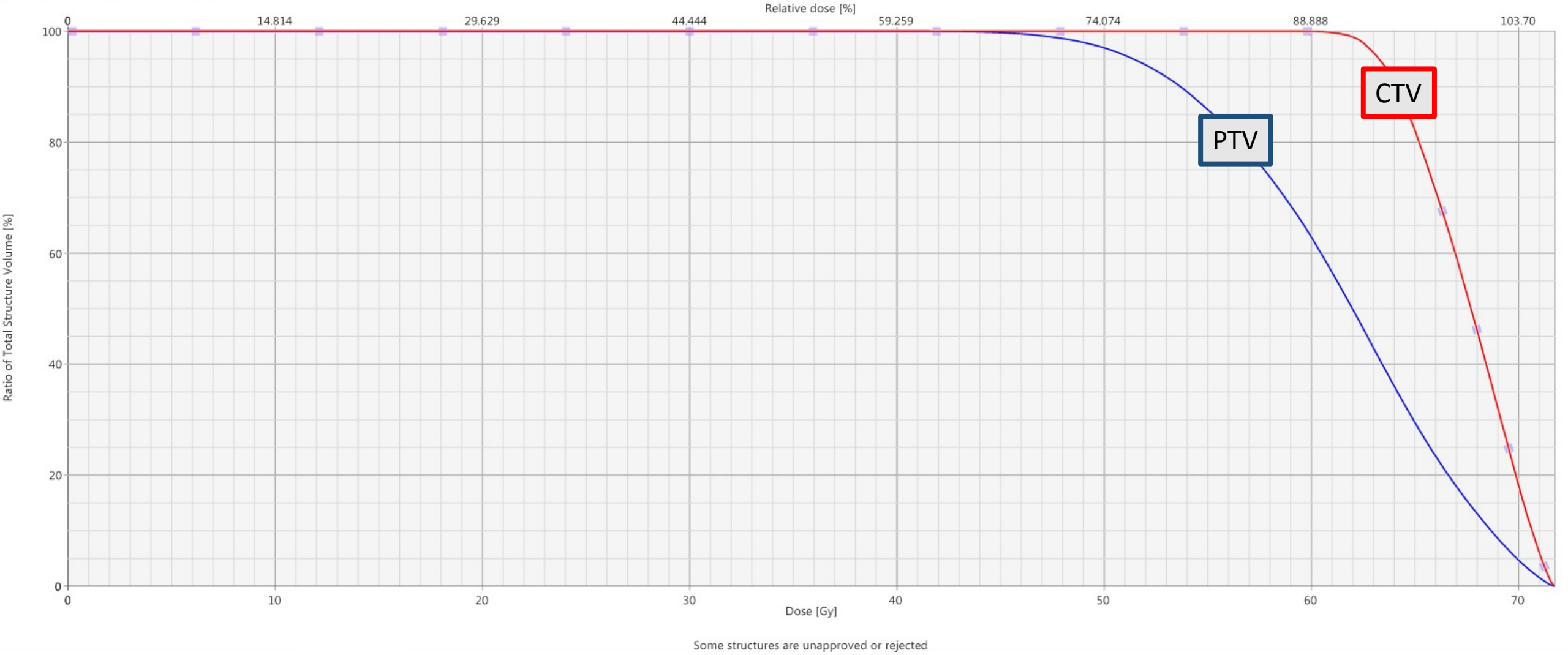
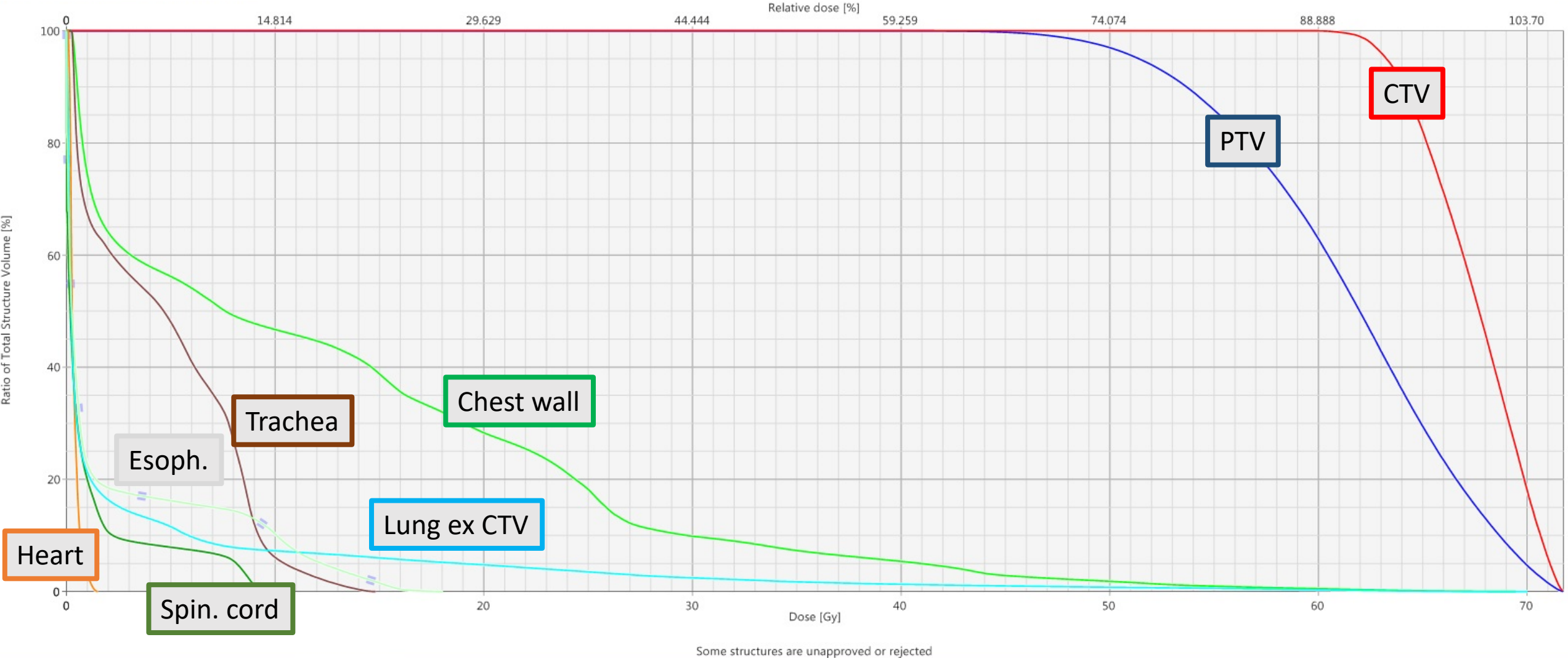
71.745 Gy
Head First-Supine
Y: 11.40 cm


Relative dose [%]
0
14.814
29.629
44.444
59.259
74.074
88.888
103.70
100
80
60
40
20
0
Ratio of Total Structure Volume [%]
0
10
20
30
40
50
60
70
Dose [Gy]
CTV
PTV
Some structures are unapproved or rejected


Relative dose [%]
0
14.814
29.629
44.444
59.259
74.074
88.888
103.70
100
80
60
40
20
0
Ratio of Total Structure Volume [%]
0
20
30
40
50
60
70
Dose [Gy]
CTV
PTV
Chest wall
Trachea
Esoph.
Lung ex CTV
Heart
Spin. cord
Some structures are unapproved or rejected

Department of Radiation Oncology
Chairman: Prof. Dr. Matthias Guckenberger

SBRT in synchronous metastatic NSCLC

Matthias Guckenberger

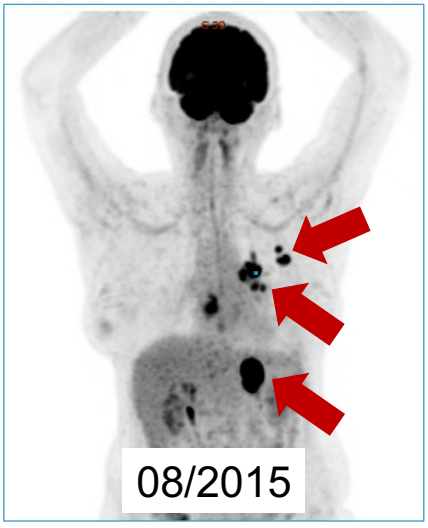
UniversityHospital Zurich

ESTRO

Patient presentation

- 65 year old female
- Performance status 90%
- Comorbidities:
  - No relevant until diagnosis of cancer
- Paraneoplastic syndroms:
  - Anemia
- Depression after diagnosis of cancer

Initial staging & histopathology



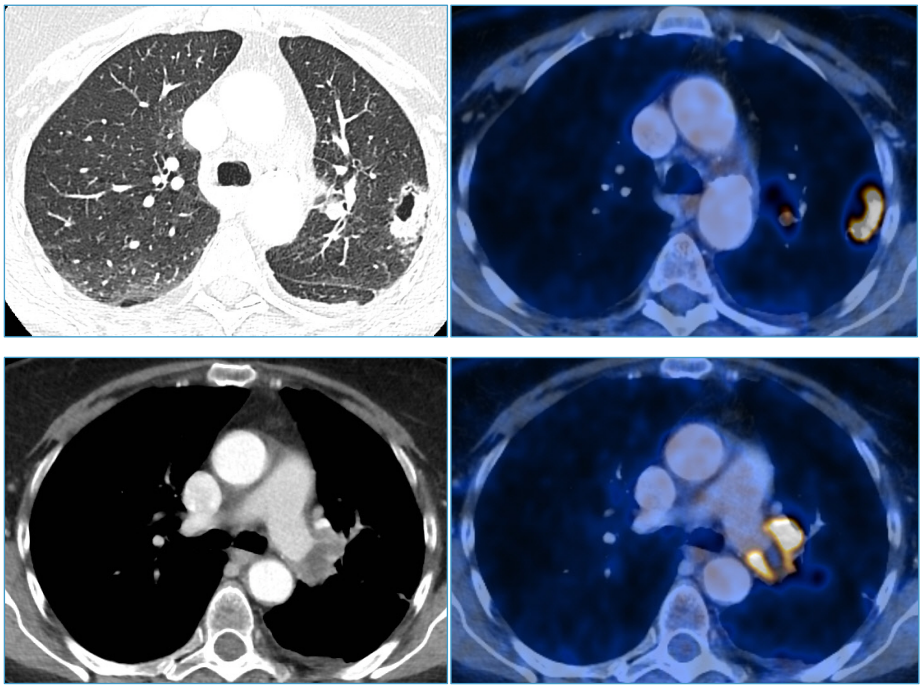
Primary

Hilar LN

Adrenal

- NSCLC cT2 cN1 cM1 (adrenal), Adeno Carcinoma
- Synchronous oligo-metastatic stage IV NSCLC
- EGFR, BRAF, KRAS, ERBB2, ALK, ROS1 negative

Initial staging & histopathology



Treatment strategy

Multidisciplinary tumor board

- Curative approch because of oligometastatic state of disease
  - Induction chemotherapy
  - followed by curative intent surgery for primary
  - and SBRT for adrenal metastasis

- 10 / 2015 induction chemotherapy with 2 cycles of Cisplatin / Pemetrexed

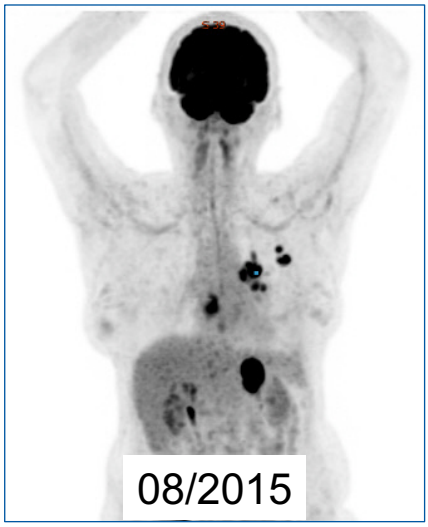
Initial staging & histopathology

Paraneoplastic and / or chemotherapy complications:

- 09/2015: Renal vein thrombosis
- 11/2015: Hypertensive left venticular decompensation
- 12/2015: Insult cerebellum with severe ataxia and vertigo

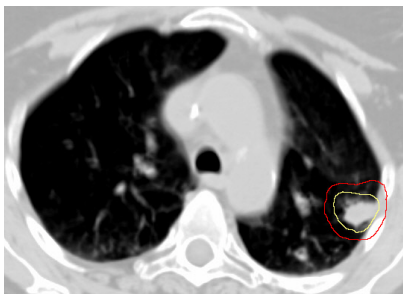
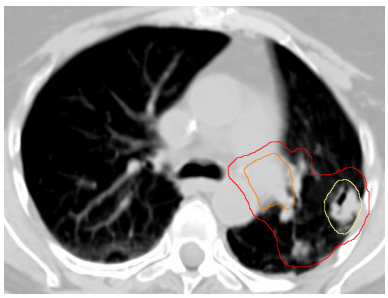
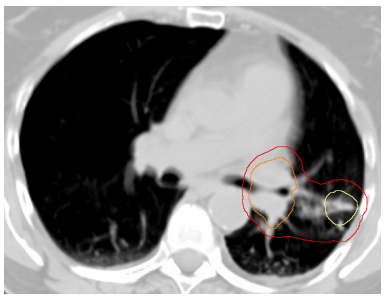
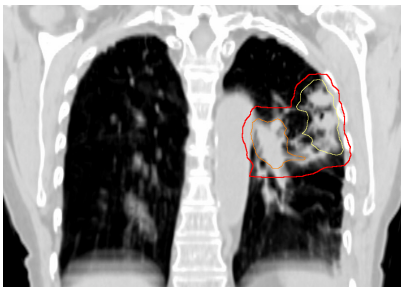
- ➢ Cancer therapy stopped until 12 / 2015
- ➢ Restaging – no systemic progression of disease
- ➢ Curative intent radiotherapy instead of surgery

Restaging prior to radiotherapy



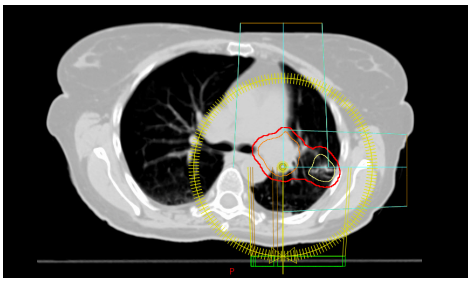
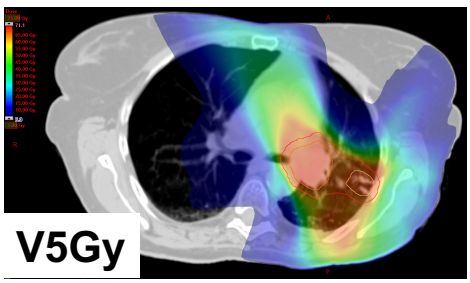
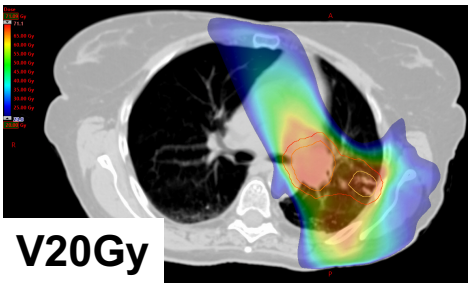
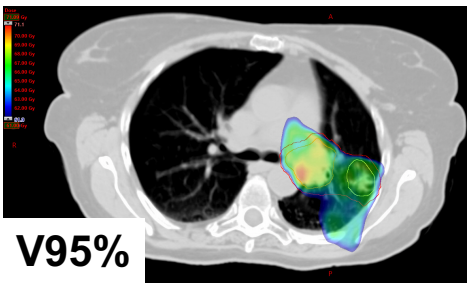
- ➢ Partial response

Radiotherapy planning - primary

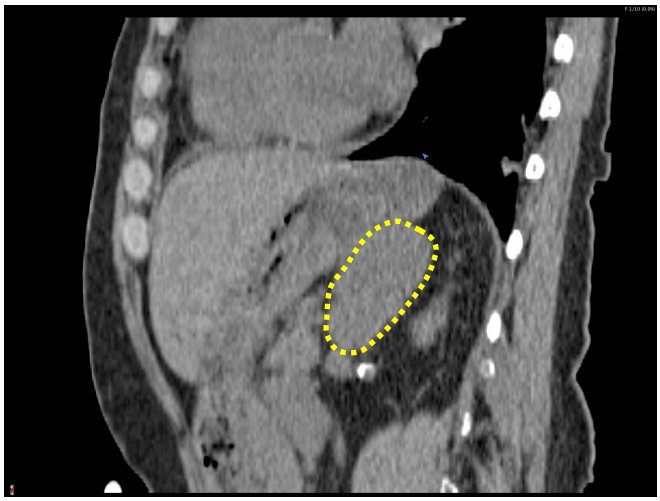
- Involved-field target volume concept
- 4D CT
- ITV motion compensation
- 10mm ITV to PTV margins

Radiotherapy planning - primary



V5Gy

V20Gy

V95%

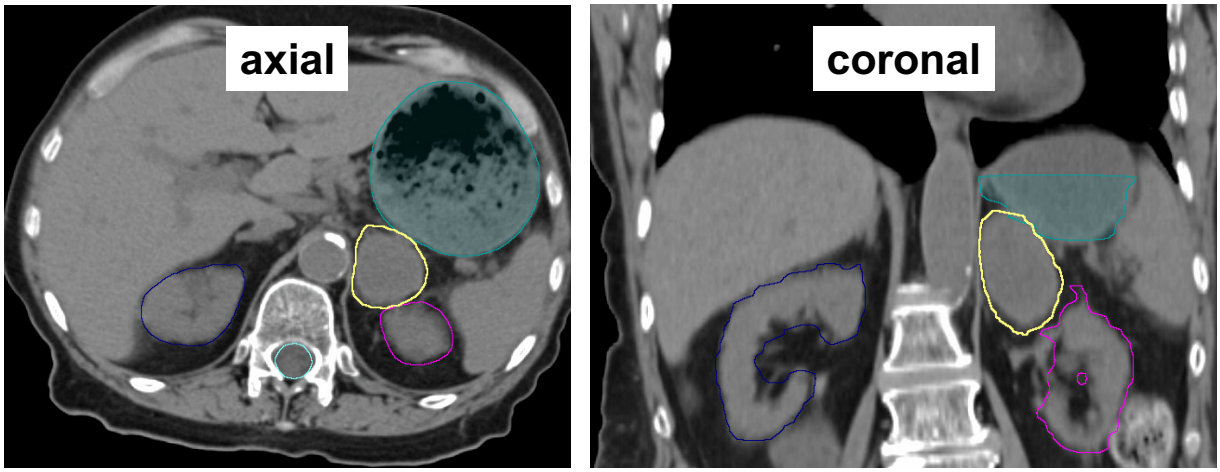
- RapidArc planning
- Fractionation: 24 x 2.75Gy

Radiotherapy planning - adrenal



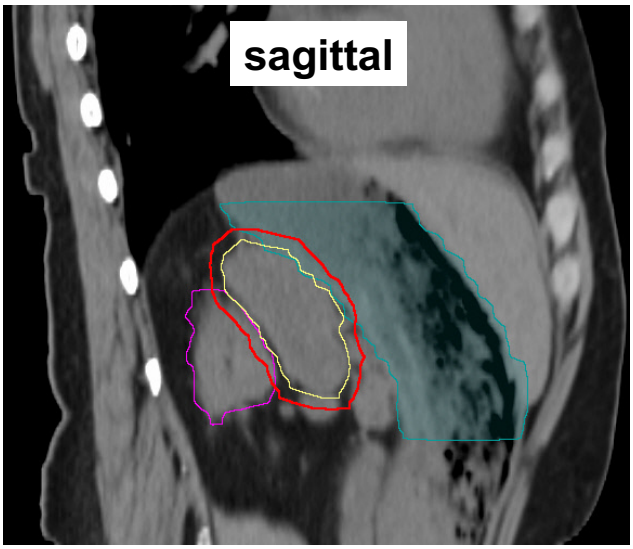
- Respiration correlated 4D-CT
- More deformation than motion

Radiotherapy planning - adrenal



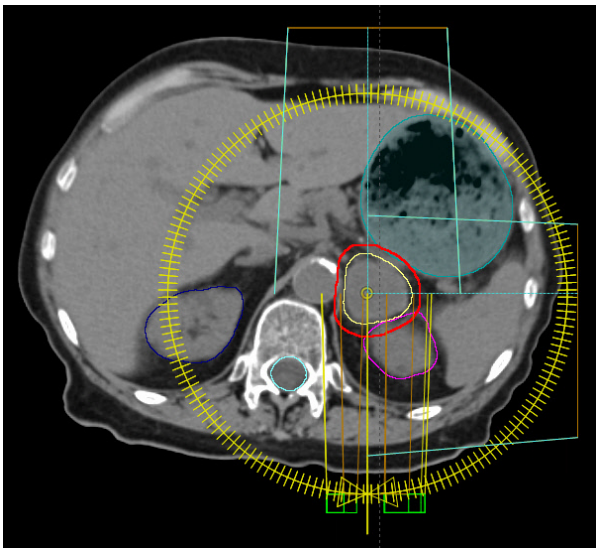
- Tumor broadly abutting stomach and left kidney
- ITV concept with 5mm ITV-to-PTV margin

Radiotherapy planning - adrenal



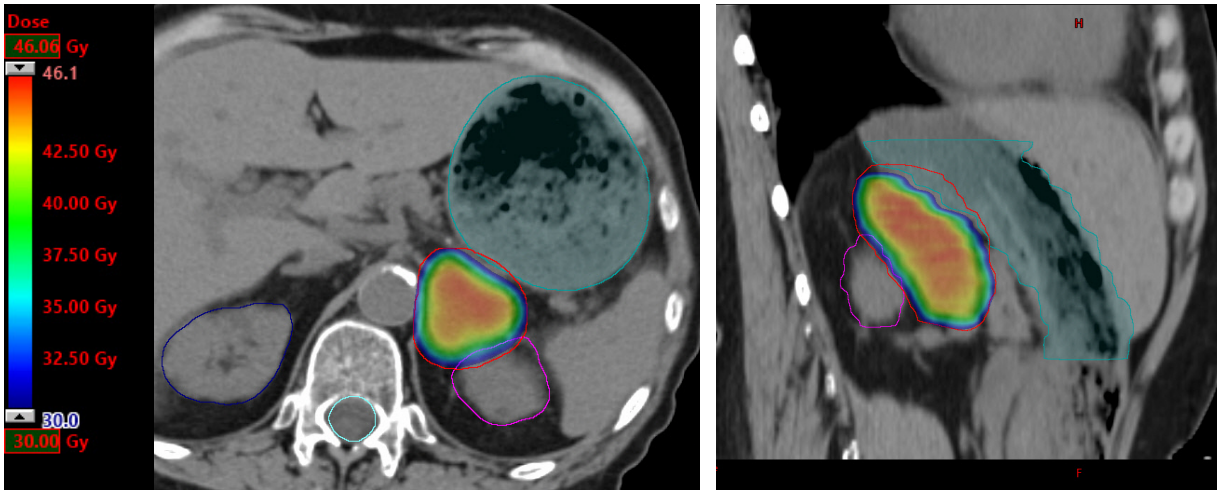
- Broad overlap between PTV, stomach and kidney

Radiotherapy planning - adrenal



- VMAT (RaidArc) planning
- 3 arcs

Radiotherapy planning - adrenal

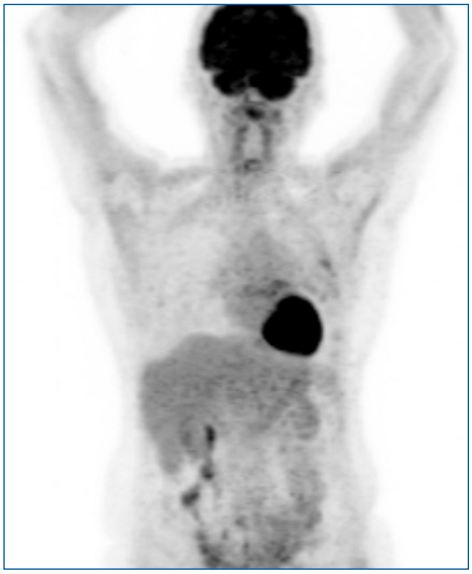


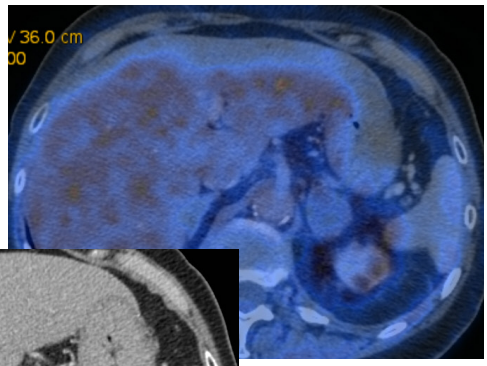
- 5 fractions of 7 Gy prescribed to 65%

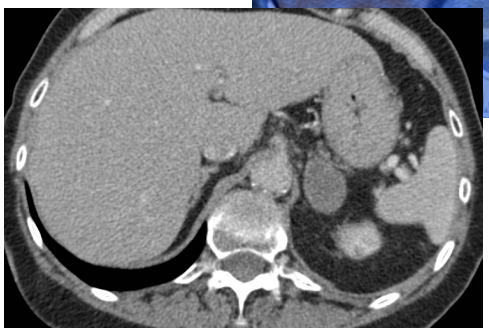
Radiotherapy planning - adrenal

- Median GTV dose 43Gy in 5 fractions
- Stomach: maximum dose 28Gy

Follow-up 3 months after Tx







- Metabolic complete response
- No systemic progression

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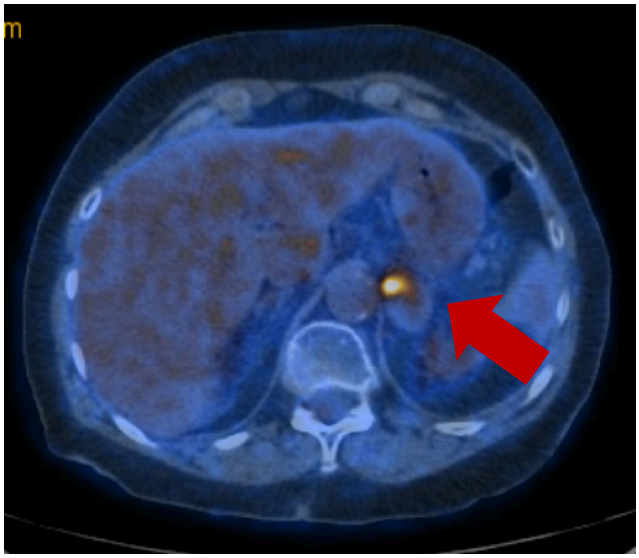
Follow-up 12 months after Tx



- Isolated recurrence of adrenal metastases
- Laparoscopic resection

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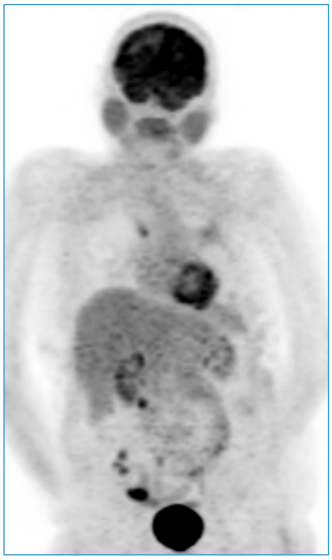
Follow-up 16 months



- Reduced performance status
- Confused and desoriented
- Hemiparesis

- Cranial – 3 cystic brain metastases
- Extracranial - metabolic complete response

Brain metastases

- Neurosurgical resection not possible due to coagulation disorder
- Whole brain irradiation
- Palliative care
- Slow and continuous deterioration of neurological status

- Patient died 19 months after PD

ESTRO ACROP

Practice Guideline for peripherally located early stage NSCLC

Dirk Verellen, Matthias Guckenberger

UniversityHospital Zurich

ESTRO

Your questions – ESTRO SBRT 2017

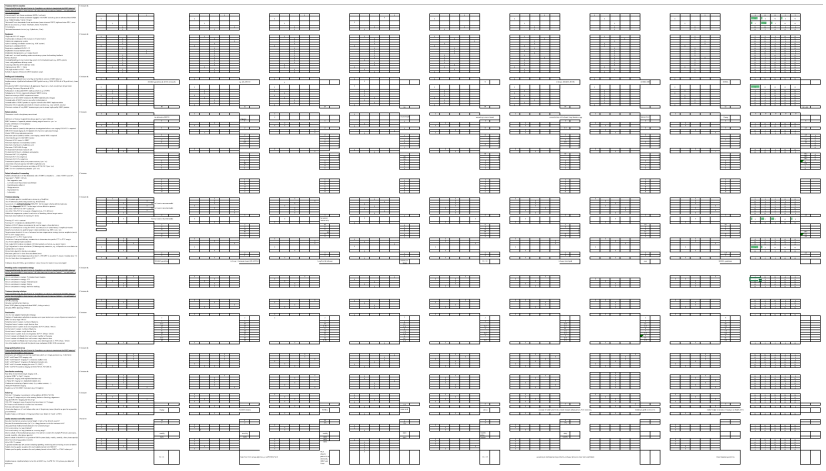
OAR constraints
- Which is the best protocol to follow regarding the OAR in SBRT?
- How to find specific dose constraints for organs at risk.

Patient positioning / fixation
- Recommandations for patient positioning fixation for SBRT in thorax

Recommended target size?
- Large size tumor SBRT
- Can we recommend SBRT with large tumors (>5~10cm) at multidisciplinary treatment planning?

Planning
- Is it possible to plan a SBRT plan with VMAT? If no what are the disadvantages?

ESTRO ACROP guideline development

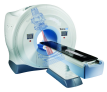


- Questionnaire of 140 items
- **Consensus** of 11 experts from the ESTRO SBRT teaching course and their **8 institutions**

ESTRO ACROP guideline development

Category	Definition:
Mandatory	**Minimum** equipment and methodology required to achieve clinical **outcome in agreement to published prospective clinical trials**.
Recommended	Equipment and methodology achieving **potentially best clinical outcome and best accuracy** currently achievable.
Optional	Equipment and methodology that **might improve clinical outcome and accuracy of SBRT without clinical evidence** available, yet.
Insufficient	Equipment and methodology resulting in **potentially worse clinical outcome** compared to published prospective clinical trials.
Discouraged	Equipment and methodology resulting in no improvement in accuracy or clinical outcome and in **no other obvious advantage**.

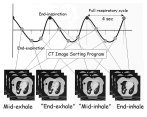
Radiotherapy delivery device

	Device	Mandatory	Recommended	Optional	Insufficient	Discouraged
	Conventional C-arm linac	1	0	0	5	2
	Conventional C-arm linac with IGRT technology	6	1	0	1	0
	Dedicated C-arm stereotactic linac	1	5	1	0	0
	Tomotherapy	0	0	6	1	1
	Dedicated stereotactic device	0	2	6	0	0

- Mandatory: C-arm linac with CBCT
- Recommended: “Stereotactic” C-arm linac

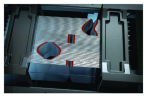
Additional technologies

Mandatory



	Mandatory	Recommended	Optional
Respiration correlated 4D-CT	**5**	3	0

Recommended



	Mandatory	Recommended	Optional
High-resolution MLC < 10mm	2	**6**	0

- Mandatory: 4D-CT
- Recommended: HR-MLC (5-9mm)

Additional technologies

	Mandatory	Recommended	Optional
Fluoroscopy at simulation for evaluation of tumor motion	0	0	**6**
Abdominal compression system	0	0	**5**
Active breathing coordinator system (e.g. ABC system)	0	2	**5**
Respiration correlated 4D-PET-CT	0	0	**8**
Implantable fiducial marker system	0	1	**6**
Implantable transponders e.g. Calypso System	0	0	**7**
Audio and / or visual breathing motion monitoring system for breathing feedback	0	2	**6**
Surface Scanner	0	1	**5**
External breathing motion monitoring system in the treatment room (e.g. RPM system)	0	3	**5**
Linac with gated beam delivery mode	0	2	**6**
Flattening filter free (FFF) delivery mode	0	2	**6**
Very high resolution MLC < 5mm	0	2	**6**
Robotic 6 degrees of freedom (DOF) treatment couch	1	2	**5**

- Most additional technologies optional

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Staffing and Credentialing

	Mandatory
Written departmental protocol covering all mandatory aspects of SBRT practice	8
Site-specific SBRT implementation & application based on **a multi-disciplinary project team** involving Clinicians, Physicists & RTTs	8
Structured follow-up and assessment of clinical outcomes (e.g. local control, toxicity)	8

- Mandatory: Protocols, multi-professional team & structured follow-up

UniversityHospital Zurich ESTRO

Staffing and Credentialing

	Mandatory	Recommended	Optional
Participation in dedicated SBRT teaching course (e.g. **ESTRO SBRT course**)	1	7	0
Particpation in **Vendor**-organized dedicated SBRT training	2	6	0
Supervision of first SBRT treatments by SBRT-experienced colleague	2	5	1
Hands-on training at SBRT-experienced center	3	5	0
External audit of SBRT practice **once** after implementation	0	4	4
External audits of SBRT practice in **regular** intervalls after SBRT implementation	0	4	4

- Recommended: investment in training and teaching instead of technology

Patient selection for SBRT

Relevant!

• Minimum ECOG status	2 - 3
• Minimum expected life expectancy (years)	1

Not relevant!

• Upper patient age limit for SBRT (years)	8
• Maximum Charlston Co-morbidity score	6
• Maximum COPD GOLD stage	6
• Minimum FEF1 (%) eligibility	6
• Minimum DLCO (%) eligibility	6
• Minimum FeFV (%) eligibility	4

- SBRT should be offered to all patients with sufficient PS and OS expectancy

Patient selection for SBRT: Procedures

Mandatory

	Mandatory	Recommended
Discussion in multi-disciplinary tumor board	**8**	0
FDG-PET staging	**5**	4
Pre-treatment Pulmonary function test	**4**	2

Recommended

	Mandatory	Recommended
Biopsy confirmation of malignancy	1	**6**
Cranial MRI for asymptomatic patients	1	3

Patient selection for SBRT: Tumor characteristics

SBRT for central tumor location accroding to RTOG 0813	**7**
SBRT for two simultaneous primaries	**8**
SBRT after contralateral pneumonectomy	**8**

- HOWEVER: Higher risk patients should only be treated at experienced centres

Patient selection for SBRT: Tumor characteristics

Maximum target size

5 cm	6 cm	7cm	8cm	10 cm	No specific cut-off
3	1	1	1	1	1

- Maximum GTV diameter should by < 5cm despite SBRT of larger lesions is possible in principle

Treatment planning

Mandatory

	Mandatory	Recommended
Typ B algorithm for dose calculation	**7**	1
Evaluation of setup and delivery uncertainties to determine **site specific CTV to PTV margin**	**4**	2
Planning CT in **respiration correlated 4D-CT** mode	**4**	4

Treatment planning: Planning technique

	Mandatory	Recommended	Optional
3D CRT planning	**6**	2	0
Dynamic conformal arc planning	2	1	4
Static IMRT planning	0	0	5
Dynamic IMRT planning	0	**5**	3

- Mandatory: 3D-CRT
- Recommended: VMAT

Treatment planning

Optional

- **Monte Carlo** algorithm for dose calculation
- Planning CT with **iv contrast**
- Use of the **FDG-PET** for **GTV** definition
- Use of **non-coplanar** beam directions
- Use of **stereotactic positioning system** (e.g. BodyFrame)
- Use of patient-specific **immobilization device** (e.g. BodyFix)
- **Abdominal compression** system for reduction of breathing induced target motion

- Most additional technologies optional

Breathing motion compensation

	Mandatory	Recommended	Optional	Insufficient
Population-based margins	1	0	0	**4**
ITV	**7**	1	2	0
Midventilation	0	**4**	4	0
Gating	0	2	**6**	0
Real-time tracking	0	1	**7**	0

- Mandatory: ITV
- Recommended: Mid-ventilation

Treatment planning

Planning CT

	Median
Maximum slice thickness of planning CT	3mm
Maximum gird size for dose dose calculation	2mm

Safety margins

	Median
GTV - CTV margin	0mm
Minimum CTV - PTV margin	5mm

Treatment planning: Dose prescription

- PTV encompassing isodose line 3/8
- Volumetric prescription to PTV D99%-D95% 4/8
- Median GTV dose 1/8

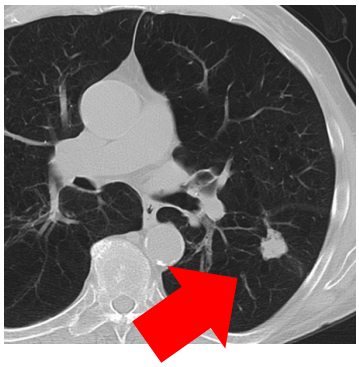
- Volumetric prescription to D98 – D95 of PTV
- Inhomogeneous dose with Dmax 125 – 150%

Treatment planning: Fractionation

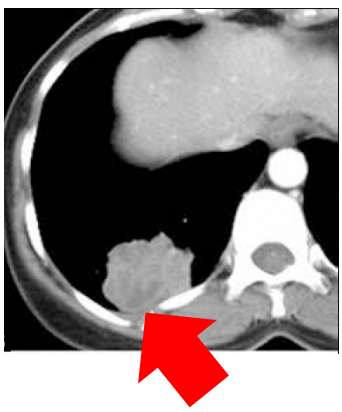
Mandatory:

Risk adapted fractionation 7

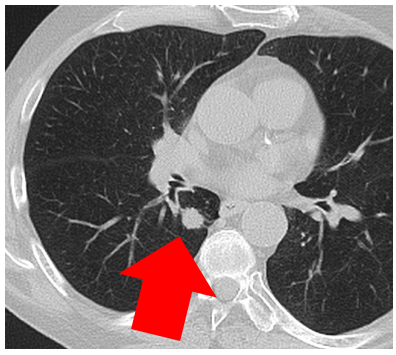
Peripheral



Chest wall



Central



Treatment planning: Fractionation

	Institutional specific fractionations	Consensus fractionation	BED10 of consensus fractionation
Peripheral	3 x 13.5Gy (n=2) 3 x 15Gy (n=1) 3 x 17Gy (n=1) 3 x 18Gy (n=2) 4 x 12 Gy (n=1)	**3 x 15Gy**	**113Gy BED10**
Broad chest wall contact	3 x 13.5Gy (n=1) 3 x 15Gy (n=1) 3 x 17Gy (n=1) 4 x 12Gy (n=1) 5 x 9Gy (n=1) 5 x 11Gy (n=2)	**4 x 12Gy**	**107 Gy BED10**
Central	5 x 11Gy (n=1) 8 x 6 Gy (n=1) 8 x 7 Gy (n=1) 8 x 7.5 Gy (n=3) 11 x 5Gy (n=1)	**8 x 7.5Gy**	**105 Gy BED10**

- Consensus for inoperable stage I NSCLC
- Operable patients: MTD of 3 x 18Gy

Image guidance

	Mandatory	Recommended	Optional	Insufficient / discouraged
Stereotactic set-up based on external coordinate system	0	0	2	6
IGRT with Planar EPID imaging only	0	0	0	8
IGRT with Planar kV imaging w/o implanted markers only	1	0	0	7
IGRT with Planar kV imaging with implanted markers only	1	0	**6**	0
IGRT with Volumetric imaging	**6**	1	1	0
IGRT with 4D Volumetric imaging	0	**7**	2	0

- Mandatory: in-room 3D IGRT
- Recommended: in-room 4D IGRT

Follow-up

Mandatory

	Mandatory	Recommended
• Periodic CT imaging in accordance with guidelines (ESMO, NCCN)	6	2
• FDG-PET imaging in case of suspect local recurrence in CT images	5	2

- Periodic CT-based imaging and FDG-PET in case of suspect local recurrence

Quality assurance

ALL mandatory or recommended

	Mandatory	Recommended
Dedicated small field dosimetry detectors for commissioning?	**7**	0
QA of in-room imag-guidance systems	**7**	0
QA of 4D CT scanner	**6**	1
A general radiotherapy QA system including reporting, monitoring and correcting process deviations	**6**	1
End to end testing in a lung phantom?	**5**	2
End to end testing in a lung phantom on a moving stage?	1	**6**

- Again, investment into human resources of utmost importance

OVERALL

- Good consensus between teachers despite the use of various technologies:
  - >50% agreement in 72% of the items
- **Technology:**
  - 8 / 57 mandatory
  - 6 / 57 recommended
  - 32 / 55 optional
- **Quality assurance**
  - 12 / 24 mandatory
  - 9 / 24 recommended

Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline

Gregory M.M. Videtic MD, CM, FRCPC, FACR [a,*], Jessica Donington MD [b], Meredith Giuliani MBBS [c], John Heinzerling MD [d], Tomer Z. Karas MD [e], Chris R. Kelsey MD [f], Brian E. Lally MD [g], Karen Latzka [h], Simon S. Lo MB, ChB, FACR [i], Drew Moghanaki MD, MPH [j], Benjamin Movsas MD [k], Andreas Rimner MD [l], Michael Roach MD [m], George Rodrigues MD, PhD, FRCPC [n], Shervin M. Shirvani MD, MPH [o], Charles B. Simone II MD [p], Robert Timmerman MD [q], Megan E. Daly MD [r]

Pract Radiat Oncol. 2017 Jun 5

When is SBRT appropriate for patients with T1-2, N0 NSCLC who are medically operable?

Statement	Consensus
Any patient should be evaluated by a thoracic surgeon, preferably in a multidisciplinary setting.	100%
For patients with “standard operative risk” (ie, with anticipated operative mortality of <1.5%) and stage I NSCLC, SBRT is not recommended as an alternative to surgery outside of a clinical trial. Discussions about SBRT are appropriate, with the disclosure that long-term outcomes with SBRT N3 years are not well established.	94%
For patients with “high operative risk” (ie, those who cannot tolerate lobectomy, but are candidates for sublobar resection) stage I NSCLC, discussions about SBRT as a potential alternative to surgery are encouraged.	94%

When is SBRT appropriate for medically inoperable patients with T1-2, N0 NSCLC

Statement	Consensus
Central location: ➢ Unique and significant risk ➢ 3-fraction regimens should be avoided ➢ 4-5 fractions recommended ➢ Adherence to DVH constraints	94%
> 5cm diameter: ➢ SBRT appropriate option	89%
Lack of tissue confirmation: ➢ Obtaing tissue confirmation highly recommended ➢ SBRT possible if biopsy impossible	100%

When is SBRT appropriate for medically inoperable patients with T1-2, N0 NSCLC

Statement	Consensus
Multiple primaries: ➢ Evaluate in a MD team ➢ FDG-PET and cMRI recommended ➢ Synchronous primaries: SBRT may be considered ➢ Metachronous primaries: SBRT recommended	94%
Second primary after pneumonectomy: ➢ SBRT may be considered	94%

Technical challenges in "high-risk" clinical scenarios

Statement	Consensus
Close to proximal bronchial tree: ➢ 4-5 fractions recommended ➢ Adherence to DVH constraints of prospective trials	83%
Close to esophagus: ➢ Adherence to DVH constraints of prospective trials	94%
Close to heart & pericardium: ➢ 4-5 fractions recommended ➢ Adherence to DVH constraints of prospective trials	83%
Abutting or invading chest wall: ➢ SBRT appropriate	94%

SBRT in the salvage situation

Primary radical Tx	SBRT use	Consensus
CF-RT	May be offered to selected patients	100%
SBRT	Highly individual process	94%
Sublocar resection	Highly individual process	94%

Your questions – ESTRO SBRT 2017

OAR constraints
- Which is the best protocol to follow regarding the OAR in SBRT?
- How to find specific dose constraints for organs at risk.

Patient positioning / fixation
- Recommandations for patient positioning fixation for SBRT in thorax

Recommended target size?
- Large size tumor SBRT
- Can we recommend SBRT with large tumors (>5~10cm) at multidisciplinary treatment planning?

Planning
- Is it possible to plan a SBRT plan with VMAT? If no what are the disadvantages?

Radiobiology of SBRT

Morten Høyer Professor, MD, PhD
Danish Center for Particle Therapy
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Denmark

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AARHUS UNIVERSITET
Aarhus Universitetshospital
CIRRO
ESTRO School

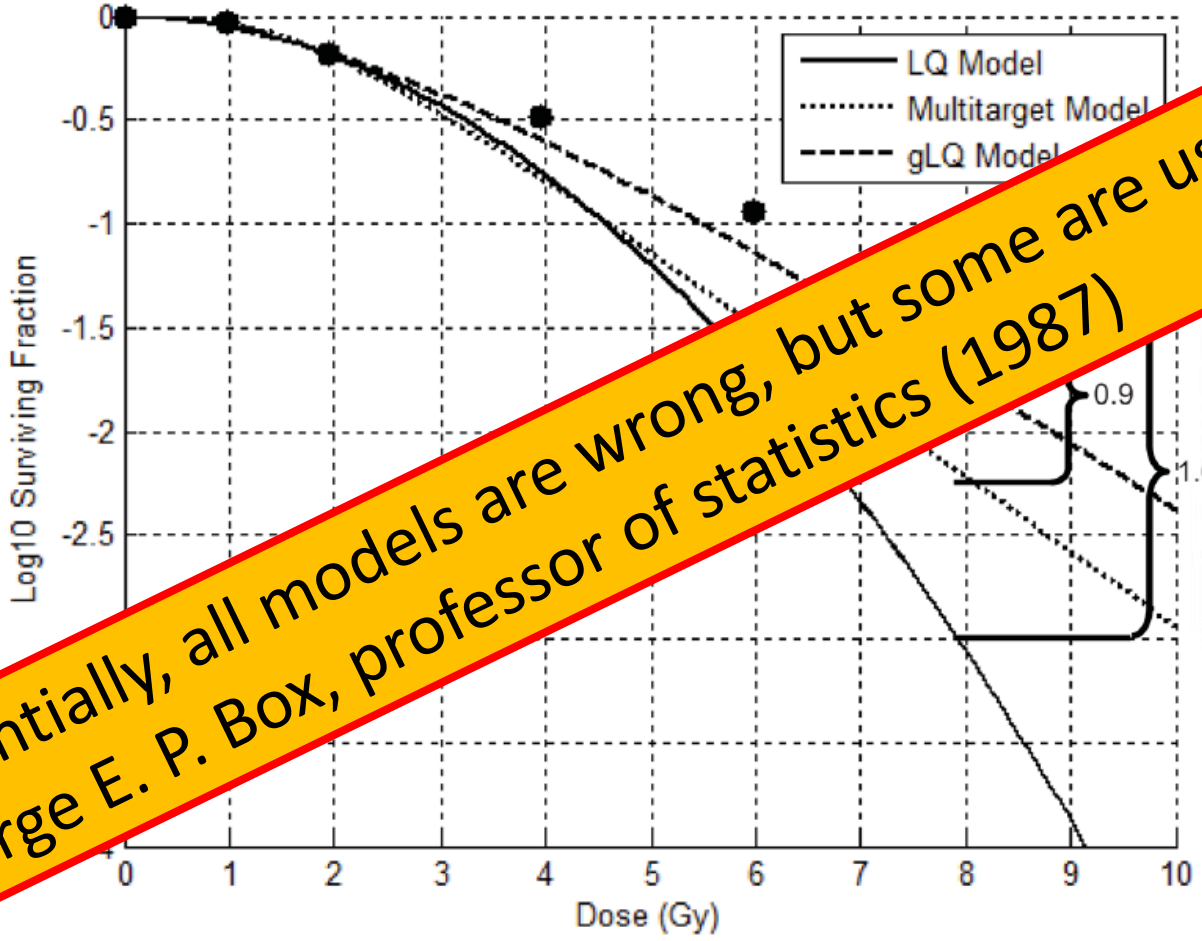
Questions from the participants

1. SBRT combined with immunotherapy in melanoma
2. SBRT Radiobiology
    - Bystander effect
    - Abscopal effect

In a moment he will say that the LQ-model

Modeling survival after radiation therapy

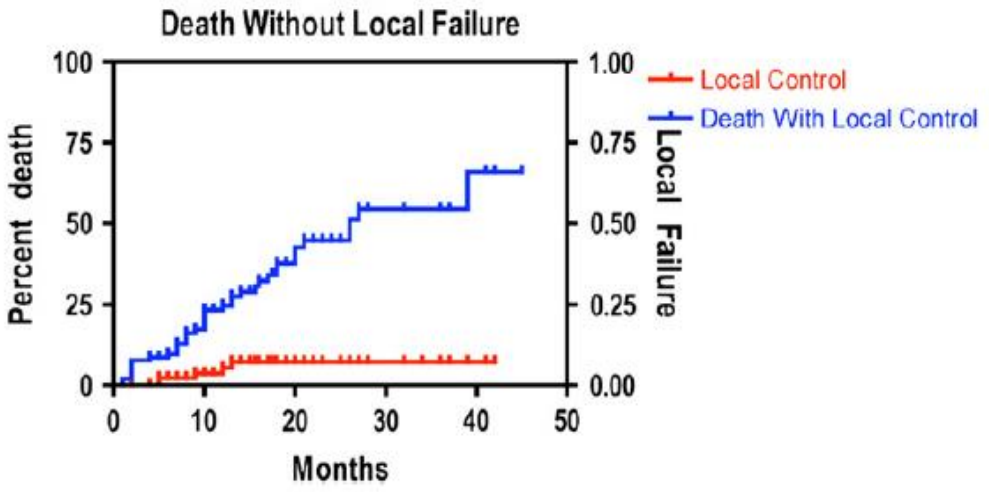
Linear-quadratic-, multitarget- and generalized linear-quadratic models

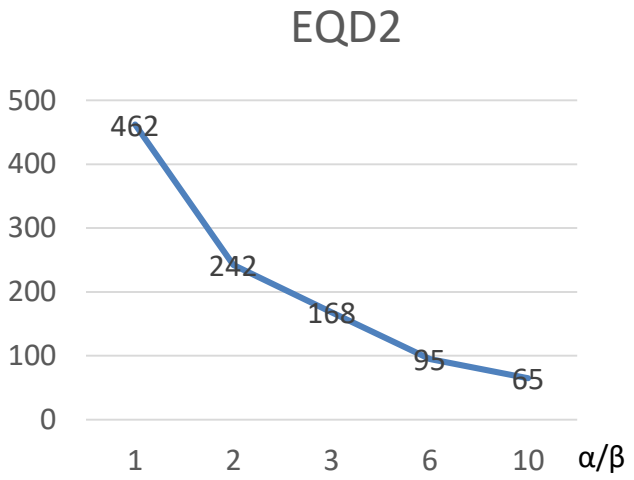


"Essentially, all models are wrong, but some are useful."
George E. P. Box, professor of statistics (1987)

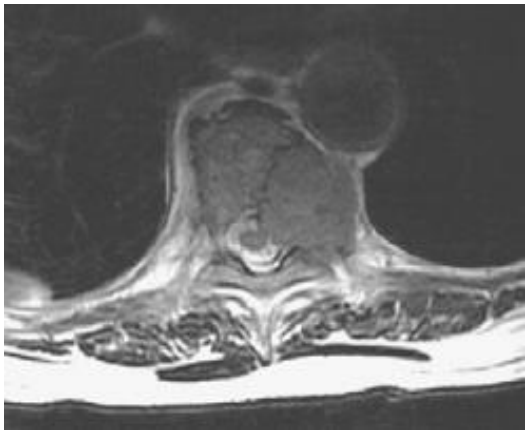
Ohri et al: IJROBP 2012; 83 (1): 385

The success of SBRT

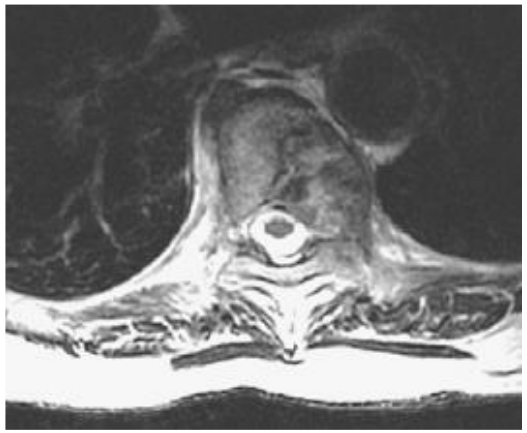




Pre-SBRT



3 months post-SBRT (1 x 21 Gy)



Yamada et al IJROBP 2008; 71(2): 484

The 4 Rs in CRT and SBRT

Are there specific biological responses to SBRT?

	CRT	SBRT
Repair	+	(↓)
Redistribution	+	(↓)
Repopulation	+	(↓)
Reoxygenation	+	↓↓

Are there additional factors?

Vascular effects	?	?
Immune responses	?	?

Stereotactic body radiation therapy (SBRT)

Martin Brown, Stanford University (editorial):

> It seems, therefore, that high-dose single-fraction radiotherapy is achieving higher local control than could be expected given what we know about radiation killing of cancer cells in a tumor.

> It is therefore possible that the antitumor effects of high single doses of radiation are not only because of direct radiation-killing of the tumor cells but also because the vascular endothelium rapidly degenerates in the tumor, thereby killing more tumor cell by a secondary response.

Brown et al. IJROBP 2008; 71(2): 324

Vascular effects

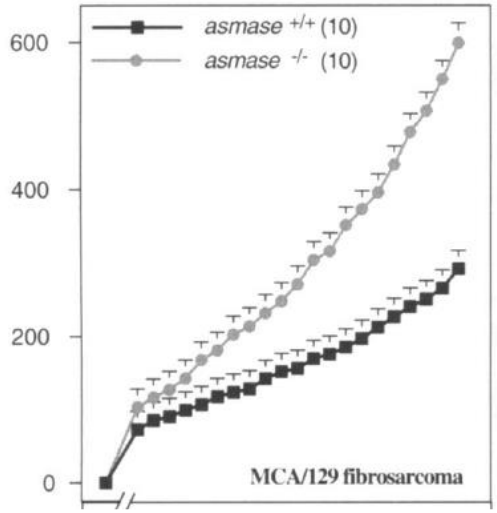
Endothelial response to high RT doses

Tumor Response to Radiotherapy Regulated by Endothelial Cell Apoptosis

Monica Garcia-Barros,[1] Francois Paris,[1] Carlos Cordon-Cardo,[2] David Lyden,[3] Shahin Rafii,[5] Adriana Haimovitz-Friedman,[4] Zvi Fuks,[4]* Richard Kolesnick[1]*†

MCA 129 fibrosarcoma and B16F1 melanoma grown in apoptosis resistant acid sphingomyelinase (asmase)-deficient or Bax-deficient mice

Reduced tumor endothelial apoptosis in asmase -/- mice. Tumors grew 2-4 x faster than in the wild-type.



Science 300: 1155; 2003

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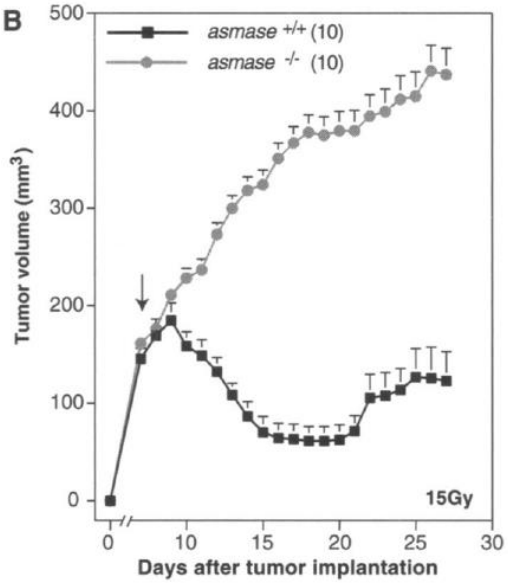
Tumors with apoptosis-resistent vascular endothelium were resistant to radiation



Science 300: 1155; 2003

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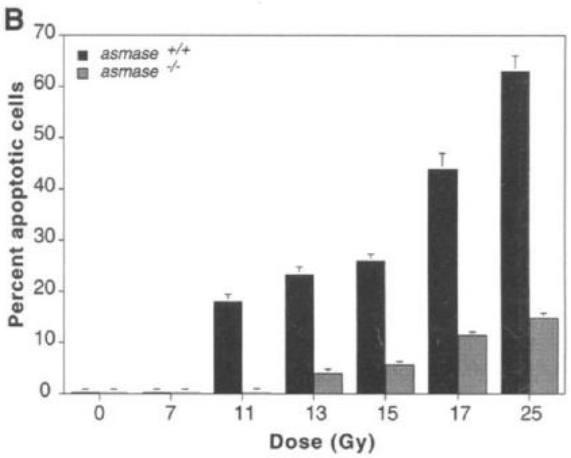
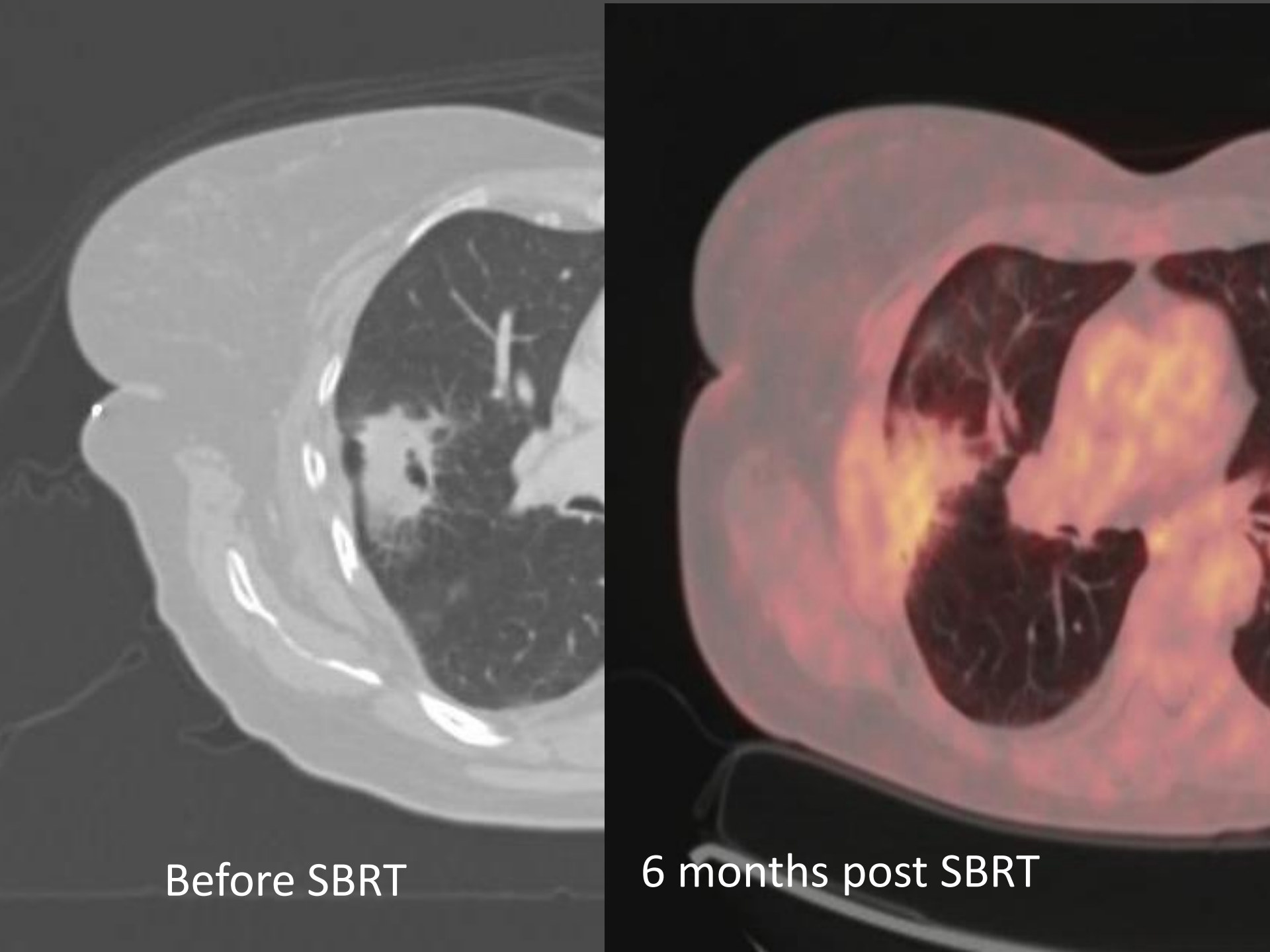
Tumors with apoptosis-resistent vascular endothelium Were resistant to radiation

Endothelial apoptosis was observed with doses >8 Gy in wild-type endothelium.



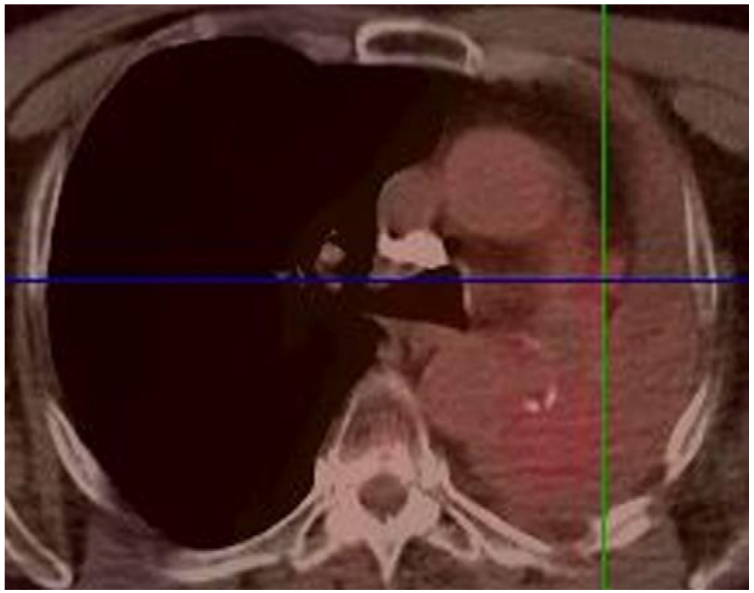
Science 300: 1155; 2003

Immune effects


Before SBRT
6 months post SBRT

FDG-PET response following SBRT

23 months post-SBRT



SUV = 5.87

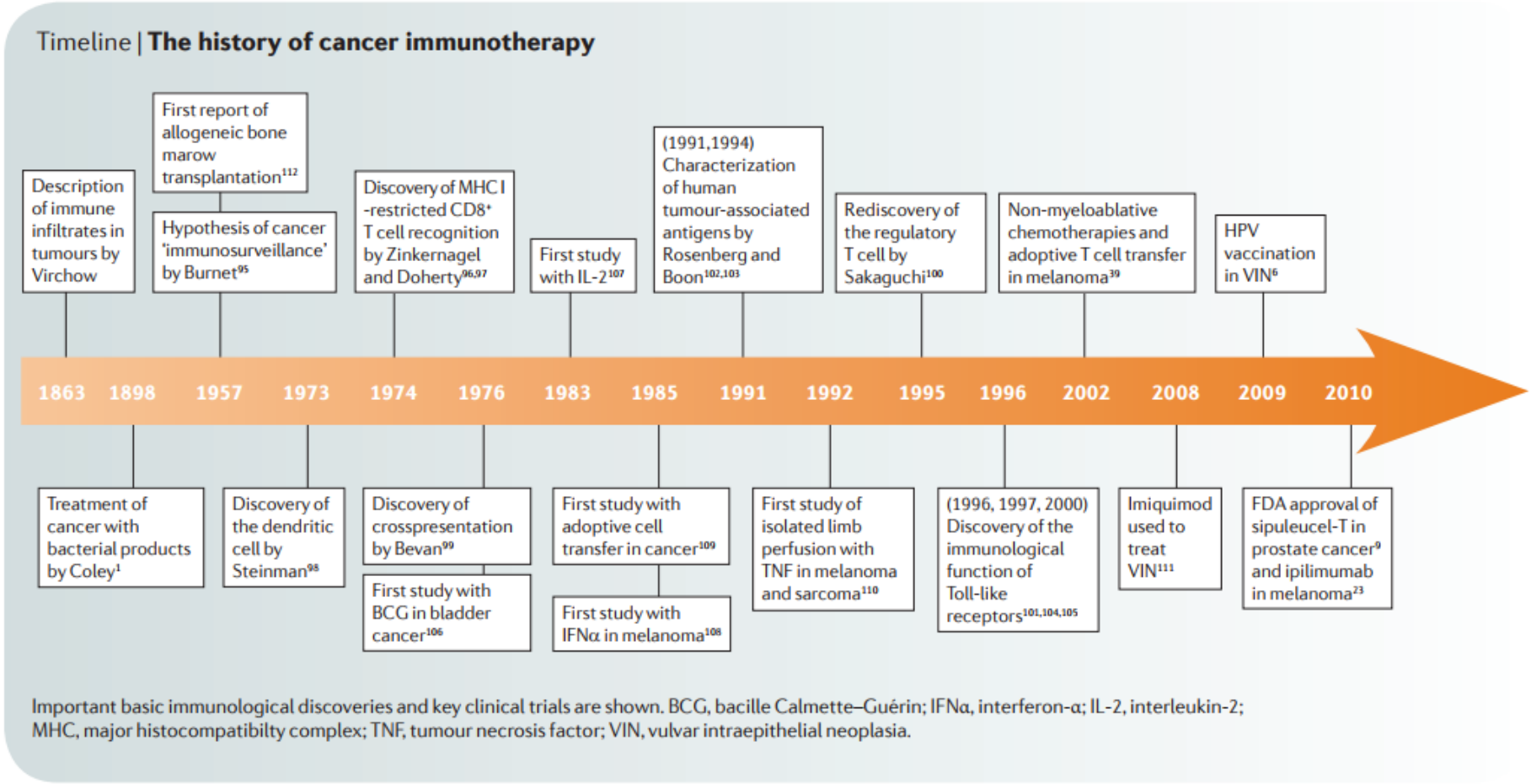
39 months post-SBRT

Table 4 Patients with concerning SUVs without evidence of failure

Pre-SBRT SUV	Total dose in three fractions	Interval to post-SBRT PET	Post-SBRT PET SUV	Interval to most recent follow-up	Clinical status and imaging
18.10	6600 cGy	23 months	5.87	44 months	Alive, PET-CT shows no disease (max SUV 1.37)
18.50	6600 cGy	26 months	5.07	47 months	Alive, CT shows no evidence of disease
Unavailable	6000 cGy	22 months	3.10	42 months	Alive, CT shows no evidence of disease
Unavailable	4800 cGy	23 months	2.48	49 months	Alive, chest X-ray shows no evidence of disease

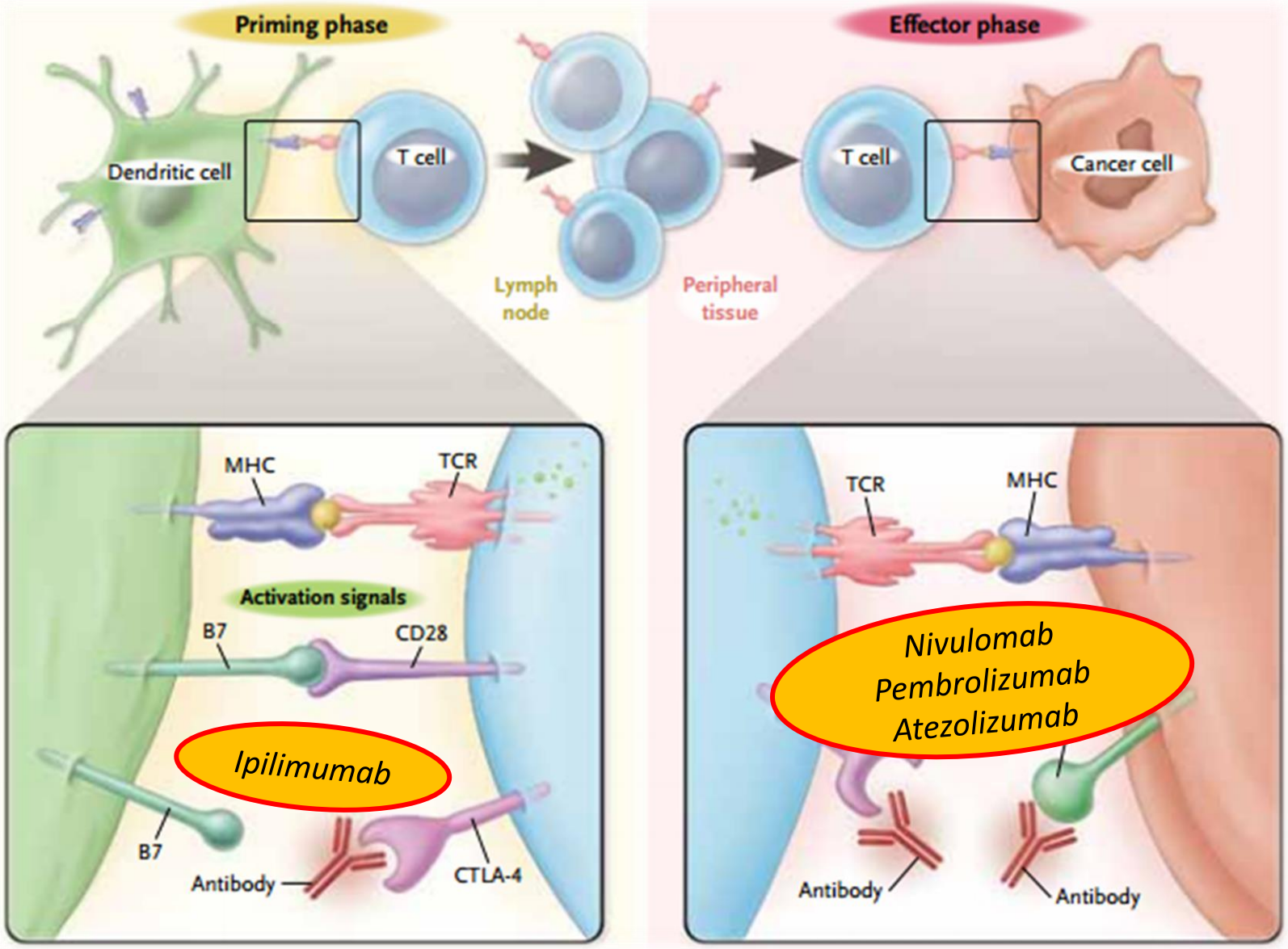
Hopes et al. Lung Cancer 2007; 56(2): 229

Long history of immune therapies



Lesterhuis et al. Nat Rev Drug Discov 2011; 10(8): 591

Immune check-point inhibitors



Ribas A: N Engl J Med 2012366;26

RT changes the diversity of T-cell receptors

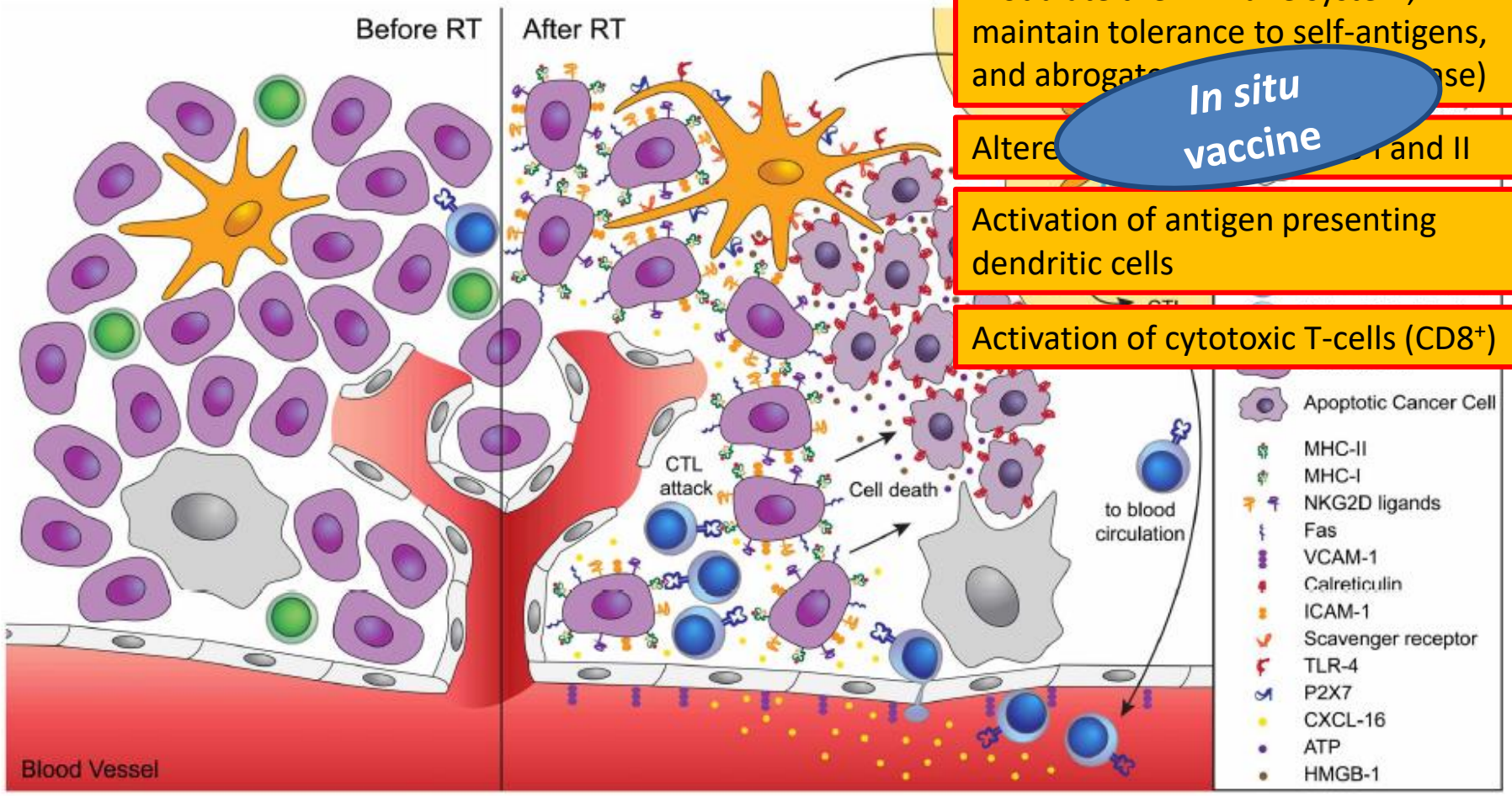
Depletion of Treg (T cells which modulate the immune system, maintain tolerance to self-antigens, and abrogat… …se)

Altere… …I and II

In situ vaccine

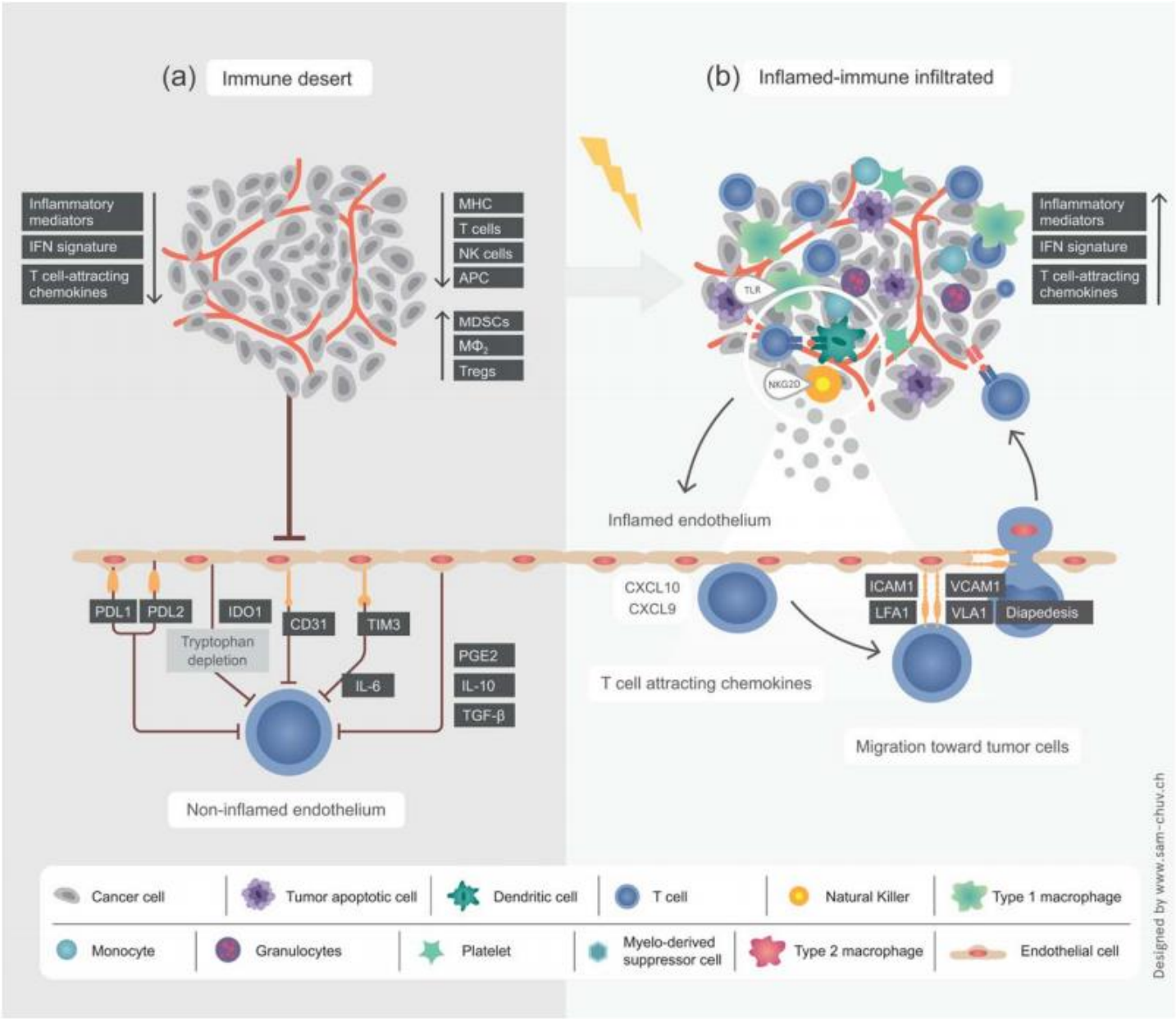
Activation of antigen presenting dendritic cells

Activation of cytotoxic T-cells ($CD8^+$)



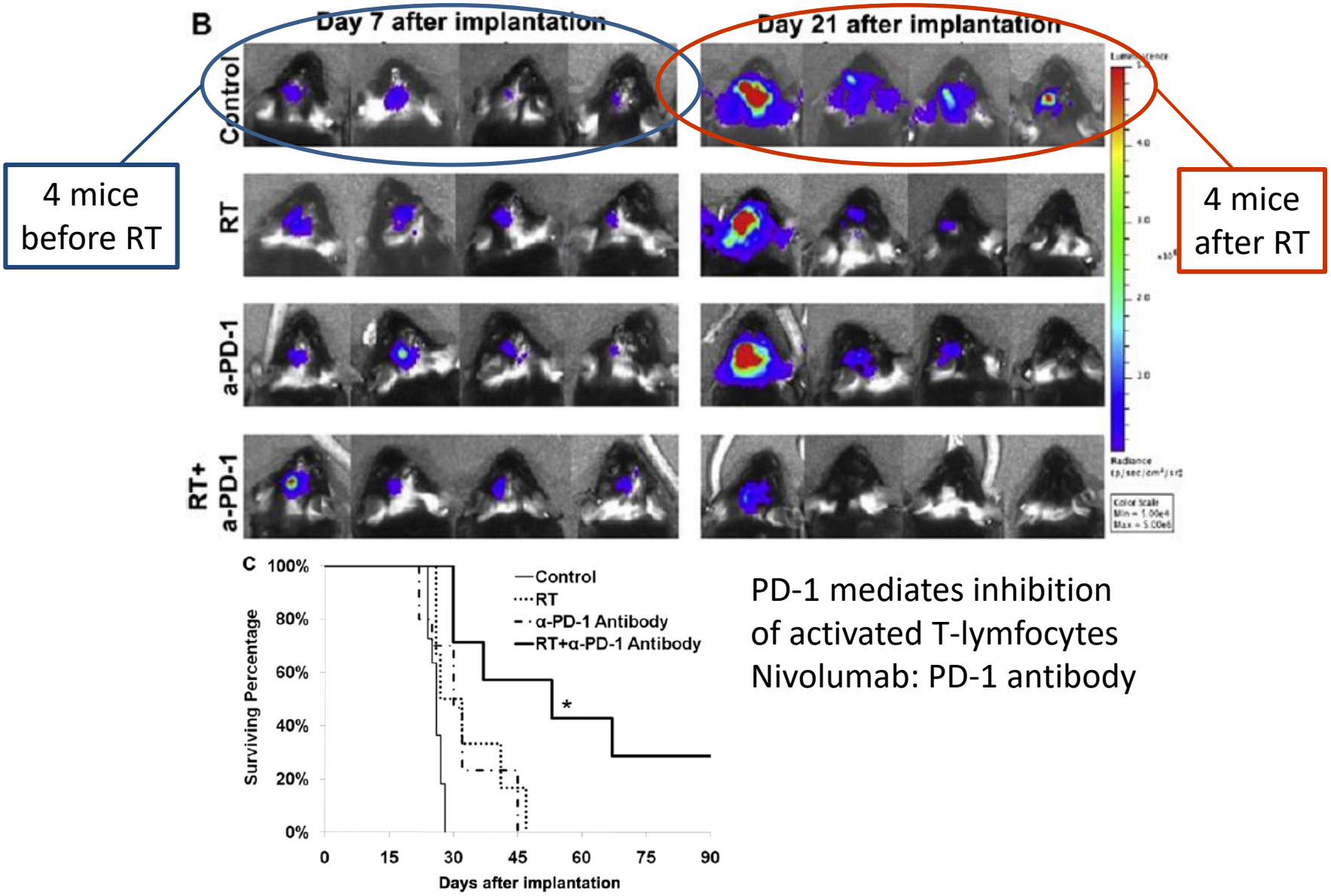
Demaria et al. Front Oncol 2012; 2: 1-7

RT induced immune reaction



Herrera t al. CA Cancer J Clin 2017;67:65

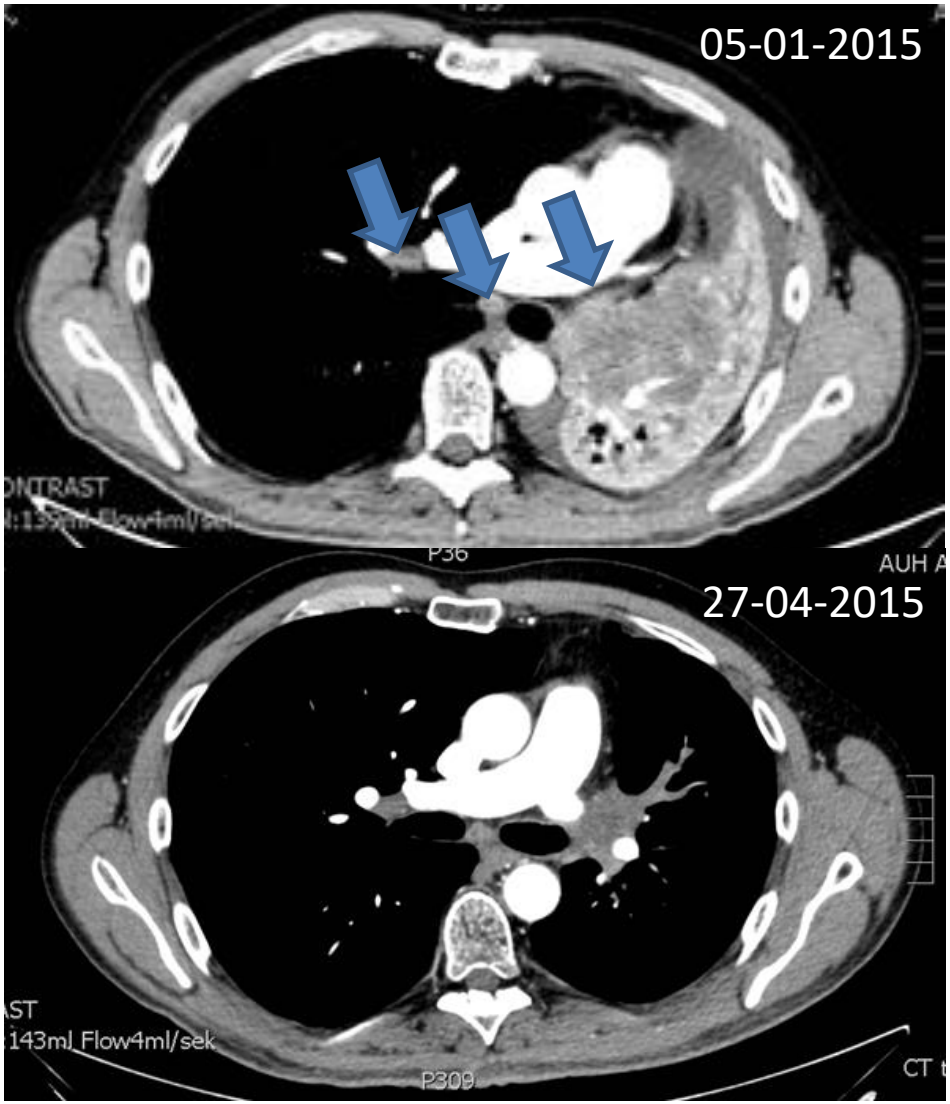
PD-1 antibody and RT for exp. glioma



PD-1 mediates inhibition
of activated T-lymfocytes
Nivolumab: PD-1 antibody

Zeng et al. IJROBP 2012; 86(2): 343

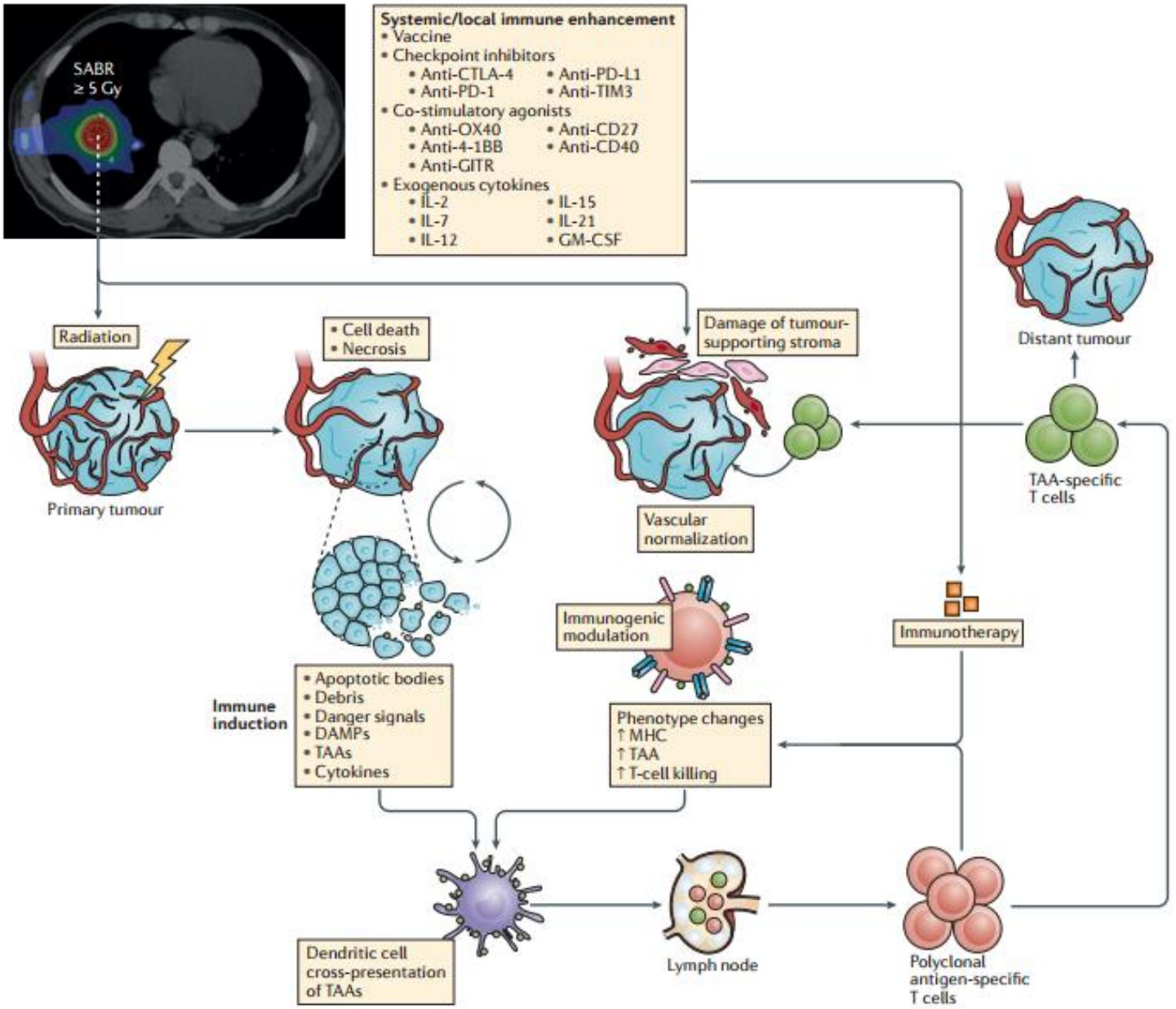
A recent case from AUH



56-year old male with metastatic melanoma

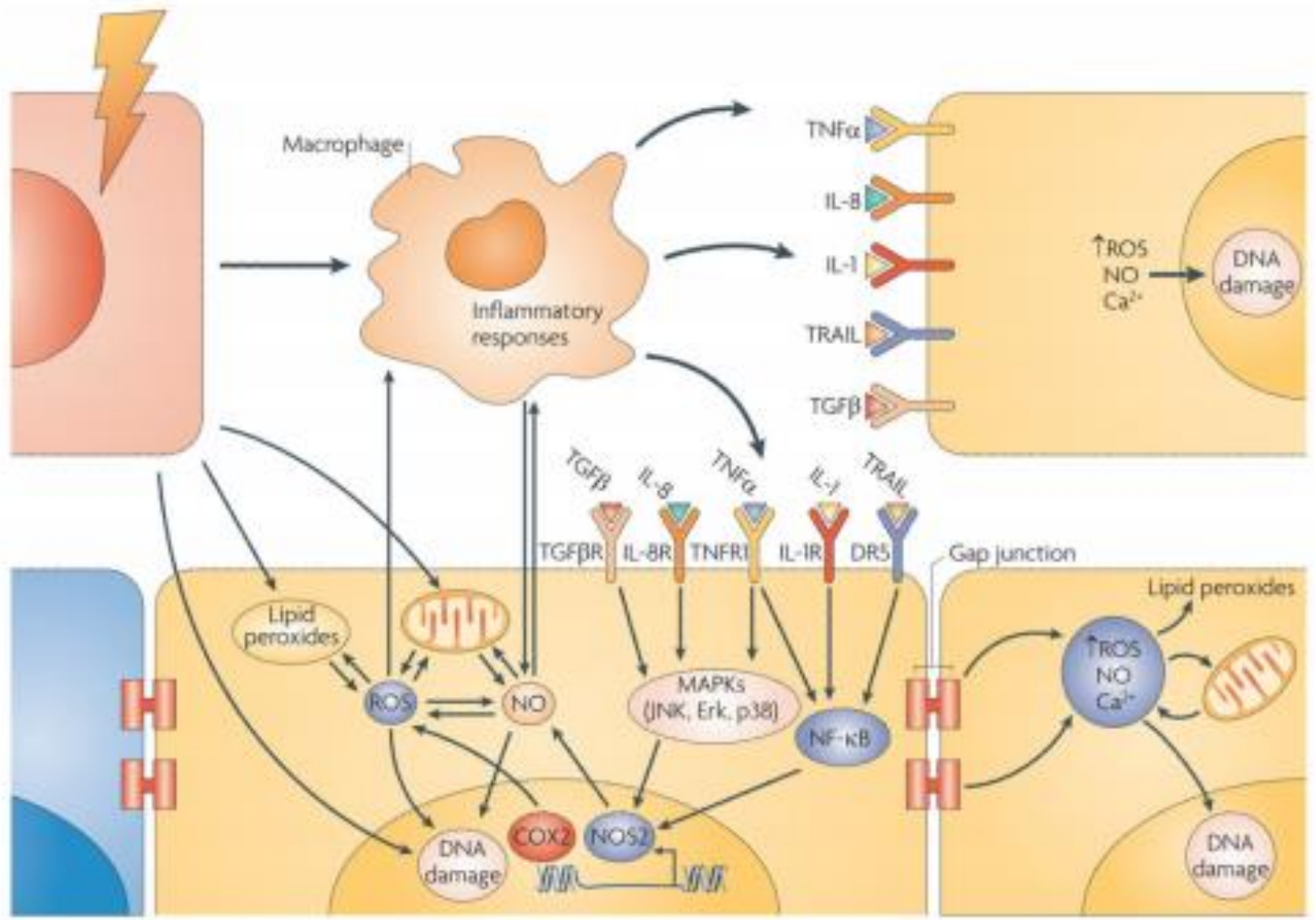
- IL-2
- Ipilumimab
- Re-induction Ipilimumab
- Temodal
- Activated T-cells
- January 2-6, 2015: Palliative RT 20 Gy/4 frx
- January 20, 2015 Pembrolizumab
- Still without progression

Abscopal immune response



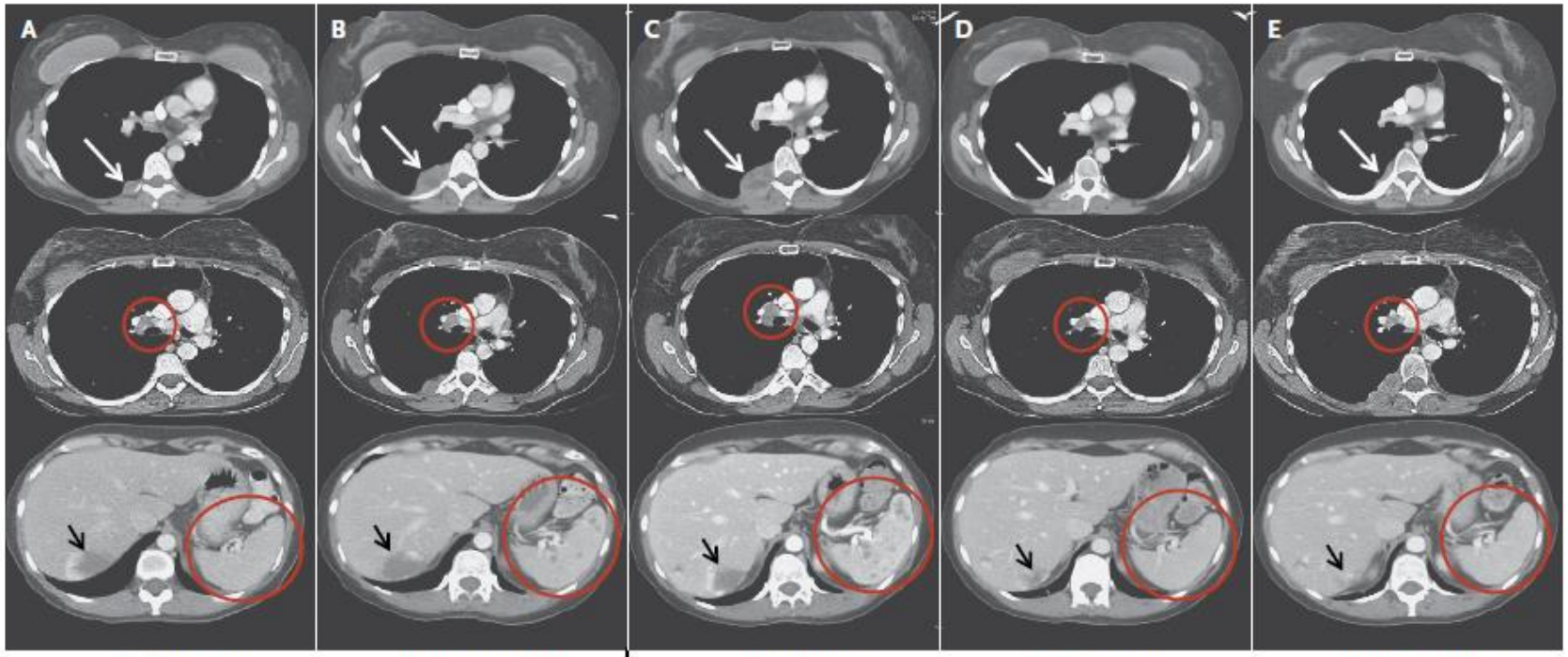
Bernstein et al. Nat. Rev Clin Oncol *e-pub 2016*

Bystander effects

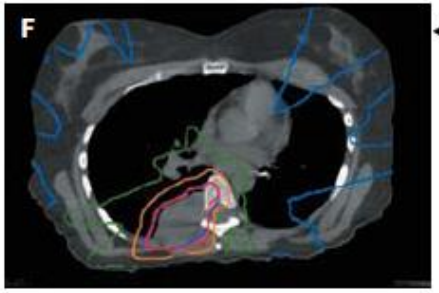


Prise et al. Nat Rev Cancer. 2009; 9(5): 351

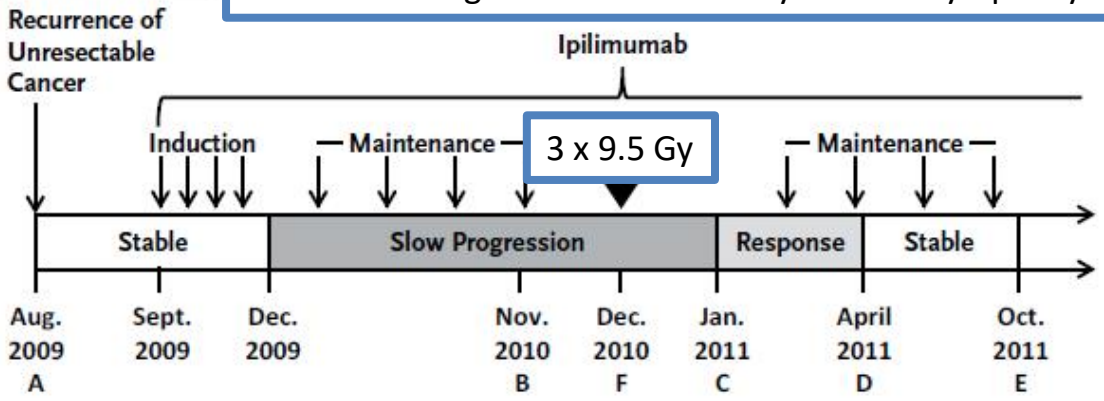
Abscopal immune response



Ipilumimab is an antibody aginst the T-cell CLTA4 receptor.
Inhibits the negative feed-back of cytotoxic T-lymphocytes



December 2010



Postow et al:
NEJM 2012;366:925

Publications on abscopal effects

W/o immune stimulating agents

Table 1
Reported clinical cases of abscopal effects with conventional radiation in non-haematological malignancies; patient characteristics and treatment strategy and patient outcomes.

Author	Year	Sex	Age	Histology	Primary site	Primary treated? (Y/N)	RT dose/fraction	Biological equivalent dose (BED)	Areas of abscopal regression	Time interval	Duration of response	Patient Outcome
Ehlers [9]	1973	F	35	Papillary adenocarcinoma	Unknown	N, unknown primary	40 Gy/20fx/5	48	Mediastinal mass	Not described	Not described	Not described
Kingsley [10]	1975	M	28	Melanoma	Skin	Y, excision	14.40 Gy in 12fx fast neutrons*	56.7	Para-aortic nodes	3 months	17 months	Death without disease
Fairlamb [11]	1981	F	73	Renal cell carcinoma	Kidney	Y, nephrectomy	40 Gy/15fx/5	51.4	Lung metastases	Less than 12 months	39 months	Alive without disease
Rees [12]	1983	M	49	Adenocarcinoma	Oesophagus	Y, radiation	40 Gy/20fx/5	48	Lung metastases	6 months	13 months	Death related to disease
Rees [12]	1983	M	56	Adenocarcinoma	Lung	Y, radiation	35 Gy/10fx/5	47.3	Cutaneous metastases	During radiation	3 months	Death related to disease
MacManus [8]	1994	M	58	Renal cell carcinoma	Kidney	Y, radiation	20 Gy/10fx/5	24	Lung metastases + mediastinal nodes	6 months	11 months	Death related to disease
Ohba [13]	1998	M	76	Hepatocellular carcinoma	Liver	Y, hepatectomy, arterial chemo-embolization	36 Gy total dose	Unknown	Hepatic metastases	10 months	29 months	Alive with minimal disease
Takaya [14]	2007	F	69	Cervical carcinoma	Cervix	Y, radiation and brachytherapy	50.8 Gy/ 27fx + intracavitary brachytherapy 24 Gy/4	61.1	Para-aortic nodes	Not described	Not described	Alive without disease
Okuma [15]	2011	M	63	Hepatocellular carcinoma	Liver	Y, hepatectomy	60.75/27fx/4	72.5 Gy	Lung metastases	Not described	54 months	Alive without disease
Cotter [16]	2011	M	70	Merkel Cell Carcinoma	Skin	Y, excision and adjuvant RT	12 Gy/2fx/2	19.2	Distant cutaneous metastases	Several weeks	25 months	Visceral metastases

* The equivalent dose/fractionation schedule when related to photon therapy is approximately 12 Gy × 3.5 Gy [25].

W immune stimulating agents

Table 2
Reported clinical cases of abscopal effects in melanoma when combined with immunotherapy.

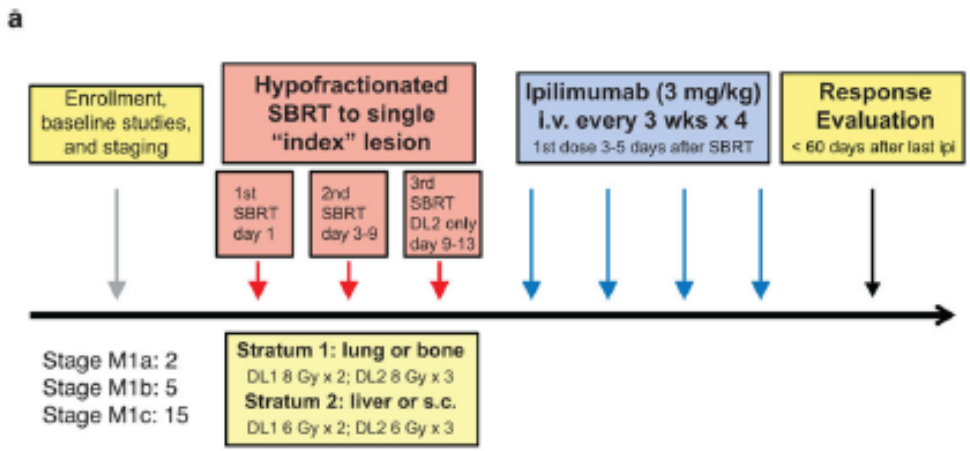
Author	Year	Sex	Age	Site of RT	RT dose/ fractionation	Biological equivalent Dose (BED)	Immunological agent	Areas of abscopal regression	Time interval	Duration of response	Patient out come	Overall survival
Postow [122]	2012	F	33	Paraspinal mass	28.5 Gy/3/3	55.6 Gy	Ipilumimab	R hilar lymph nodes, spleen	6 months	>10 months	Alive with disease	>24 mo
Stamell [123]	2013	M	67	Scalp	24 Gy/3/3	43.2 Gy	Ipilumumab	Skin in-transit metastases	8 months	36 months	Alive without disease	>7 y
Okwan-Duodu [124]*	2013	F	50	Brain	30 Gy/10/ 5 + SRS 21 Gy/1 and 18 Gy/1	39.0 Gy, 65.1 Gy, 50.4 Gy	IL2	Pulmonary, retroperitoneal and mesenteric lymph nodes	6 months	7 months	Alive with disease	>3 y

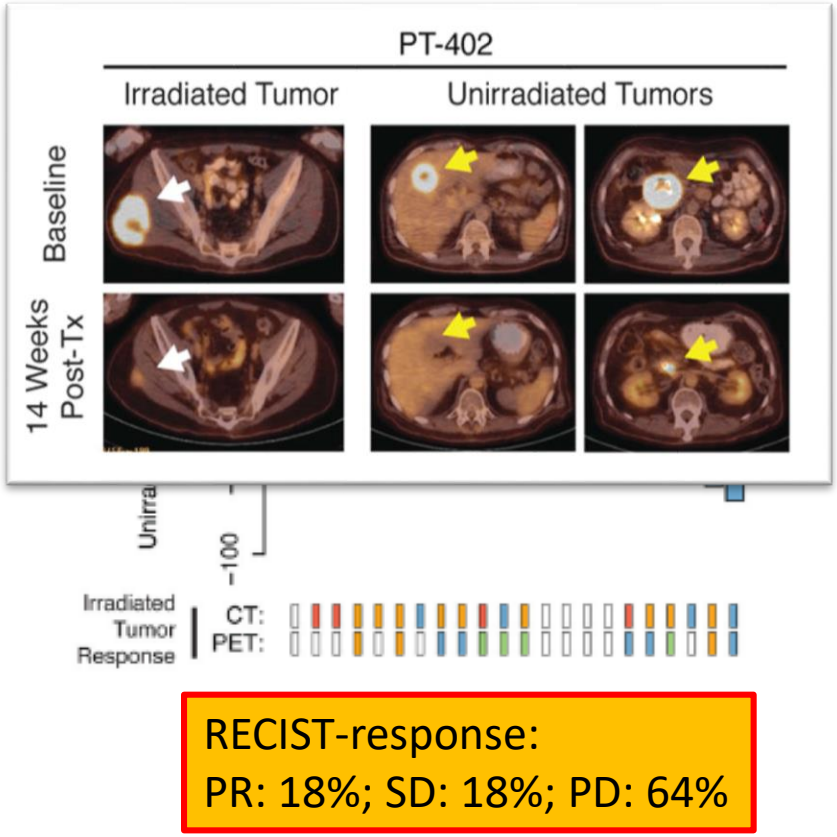
* Personal communication.

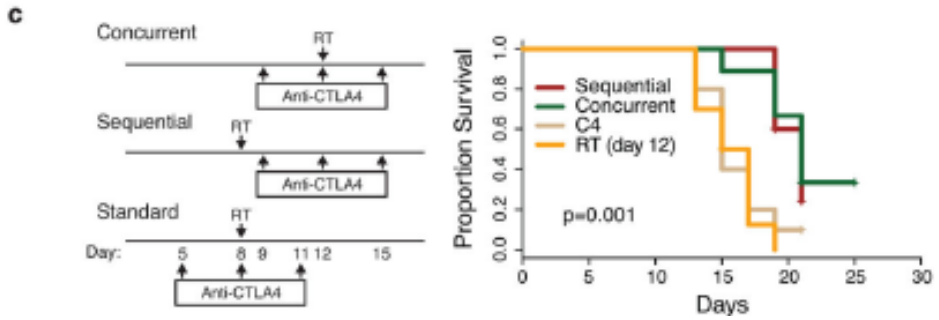
Siva et al. Cancer letters 2015; 356: 82

Abscopal effects in metatatic melanoma

Clinical results: Phase I study





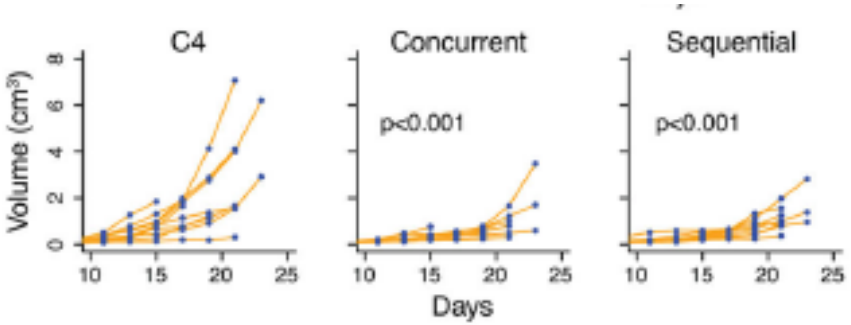


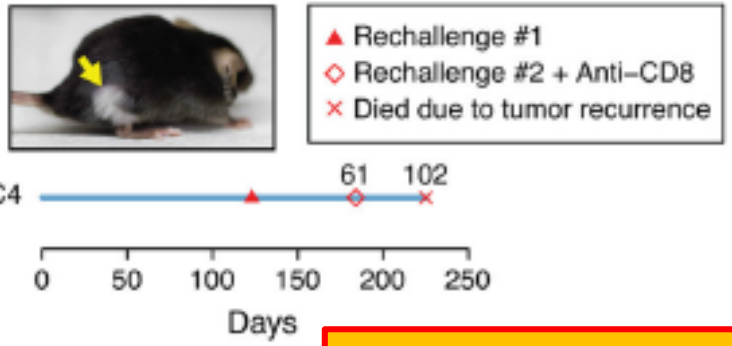
RECIST-response:
PR: 18%; SD: 18%; PD: 64%

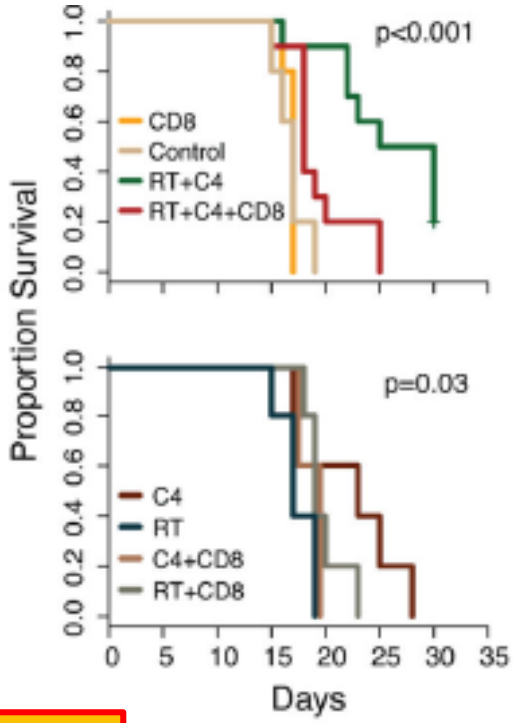
Twyman-Saint Victor et al. Nature 2015; 520(7547): 373

Abscopal effects in metastatic melanoma

Experimental data







Resistance depends on:

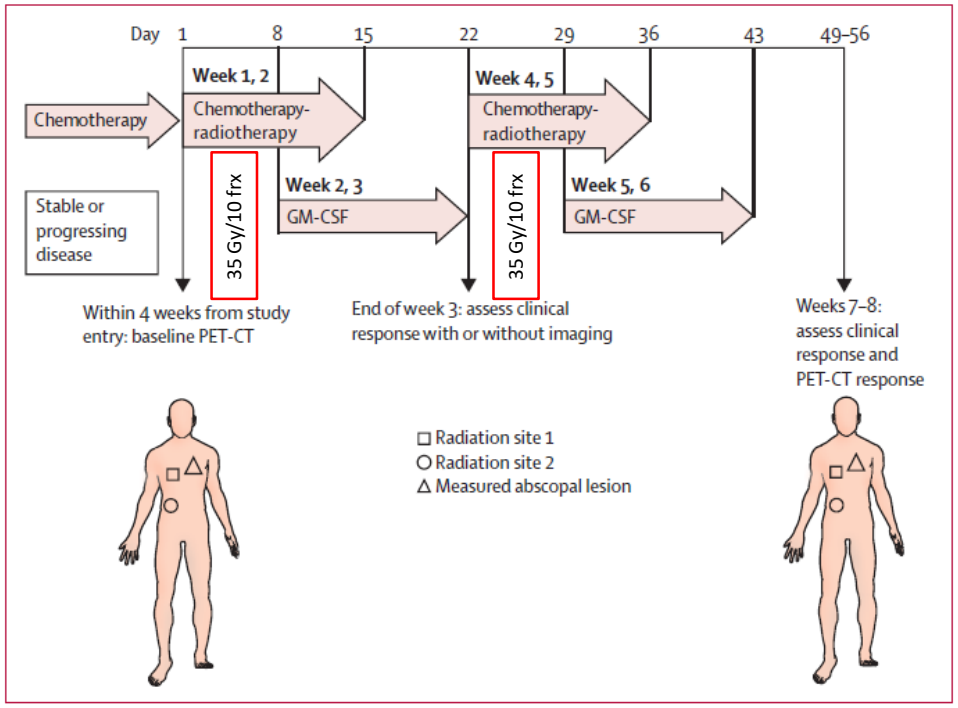
- PD-L1 upregulation on melanoma cells
- T-cell exhaustion (low tumor CD8 count)

Twyman-Saint Victor et al. Nature 2015; 520(7547): 373

Abscopal effects with GM-CSF

Phase I data

GM-CSF: A potent stimulator of dendritic cell maturation



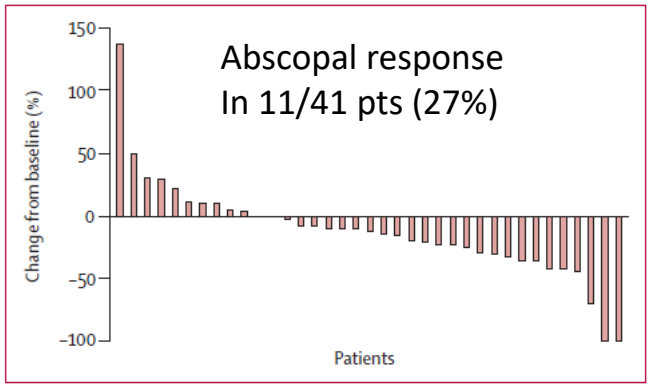


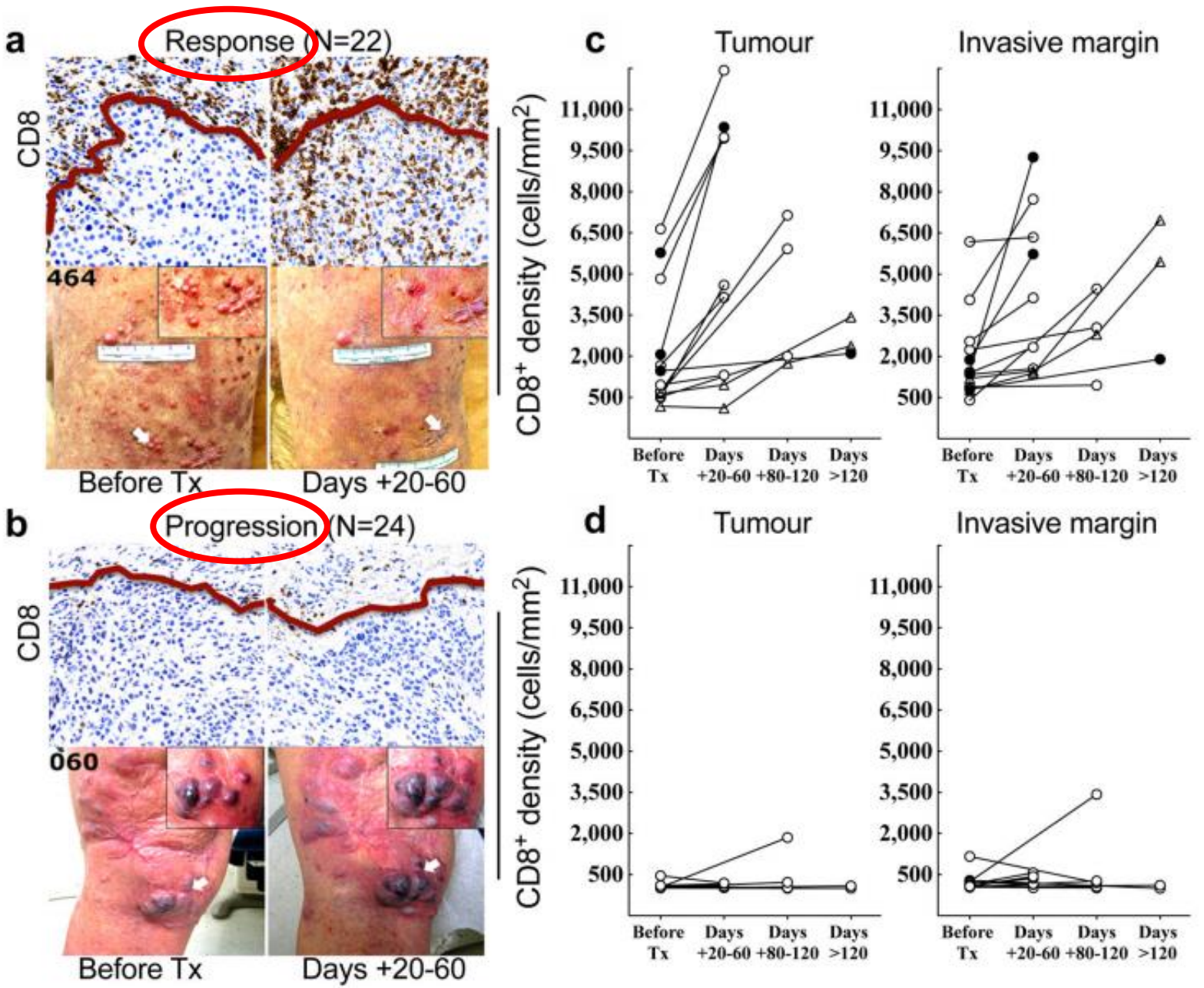
Figure 2: **Waterfall plot of best abscopal responses**

Responders:
NSCLC: 4/18 (2 CR)
Breast: 5/14
Thymic: 2/2

Patients with stable or progressing metastatic solid tumours, on single-agent chemotherapy or hormonal therapy, with at least three distinct measurable sites of disease

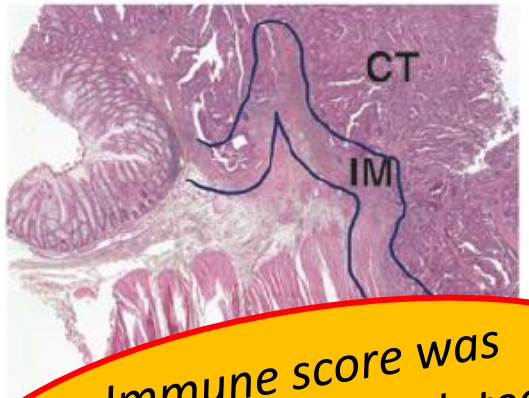
Golden et al. Lancet Oncol 2015; 16: 795

CD8 T-lymphocytes as a response to Pembro

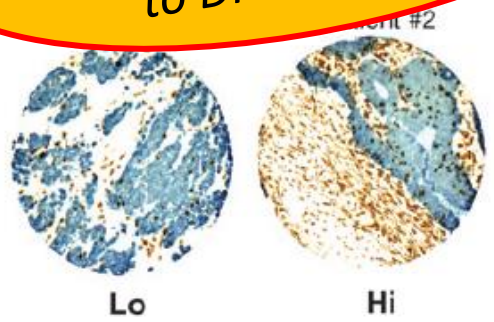


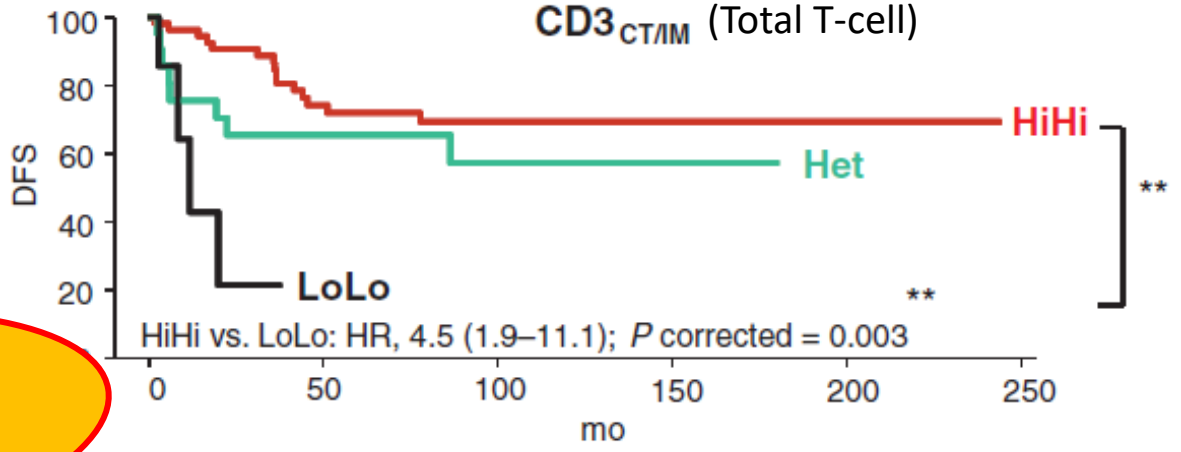
Tumeh et al. Nature 2014; 515(7528): 568

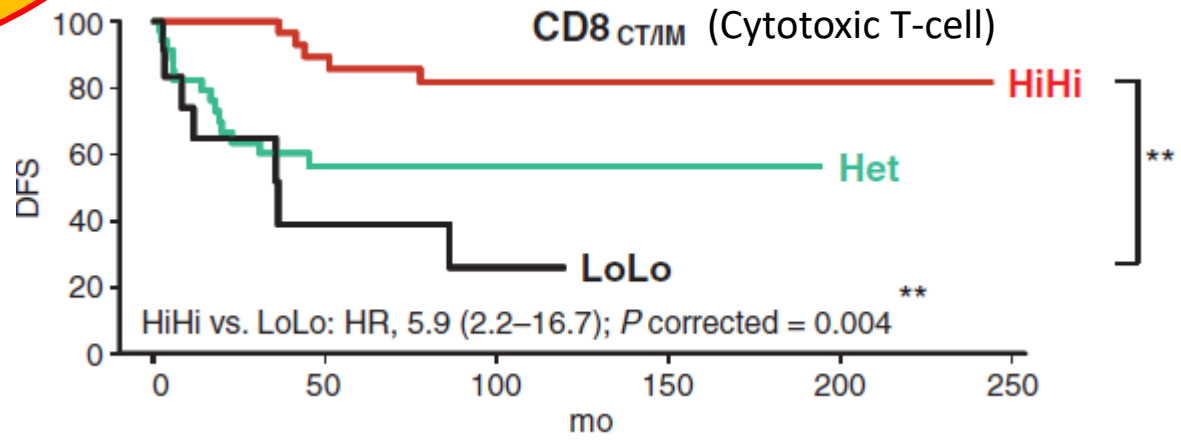
Effect on tumor infiltrating T-cells on PFS after preop chemo-RT for rectal cancer



Immune score was independently related to DFS and OS



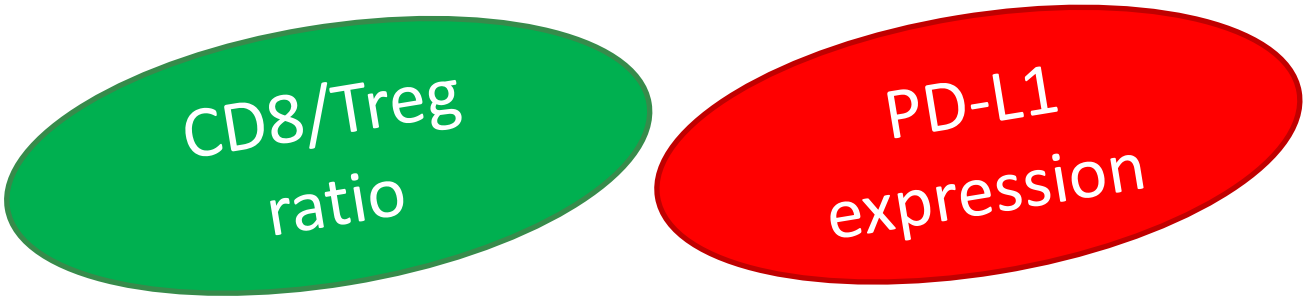




Anitei et al Clin Cancer Res 2014; 20(7): 1892

Biomarkers related to abscopal response

- RT enhances the diversity of the T cell receptor repertoire of intratumoral T cells
- High PD-L1 expression on tumor cells related to progression
- CD8 (cytotoxic) T-cells are related to response
- Treg T-cells are related to progression



Somatic mutations affects the immunogenic response

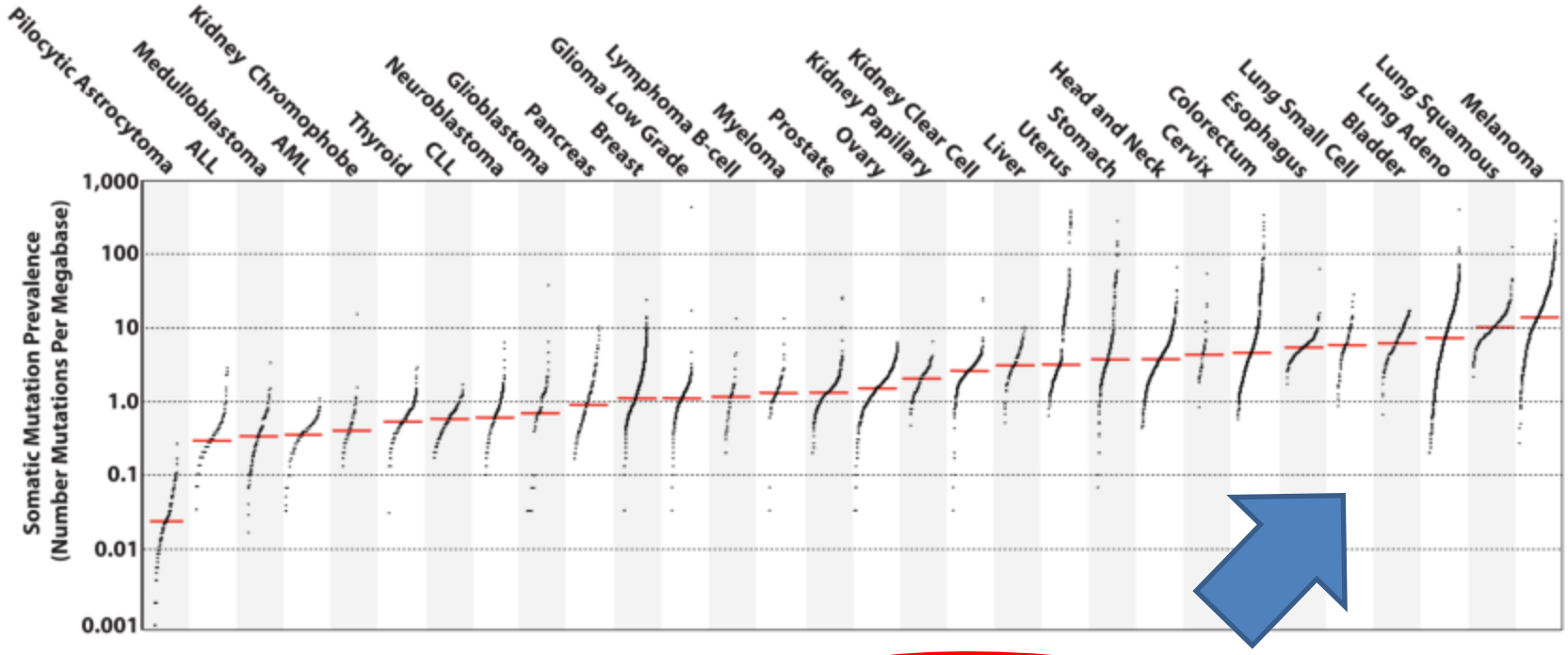
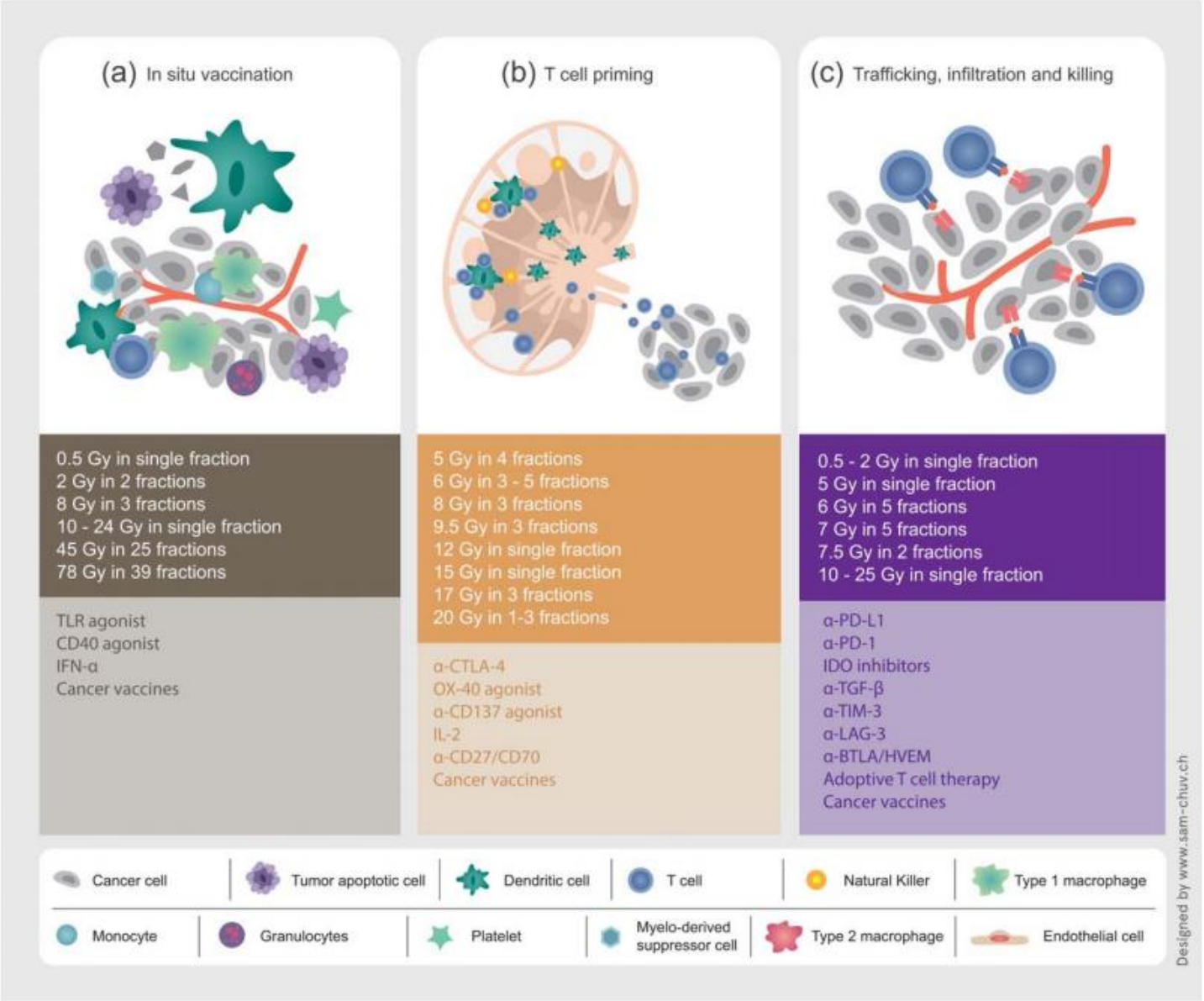


Figure 1. The prevalence of somatic mutation

High frequency of somatic mutations is related to a high chance of imunogenic response

Alexandrov et al. Nature 2013; 500(7463): 415

Combinations, timing and doses



Herrera et al. CA Cancer J Clin 2017;67:65

Ongoing studies on iSBRT in the US

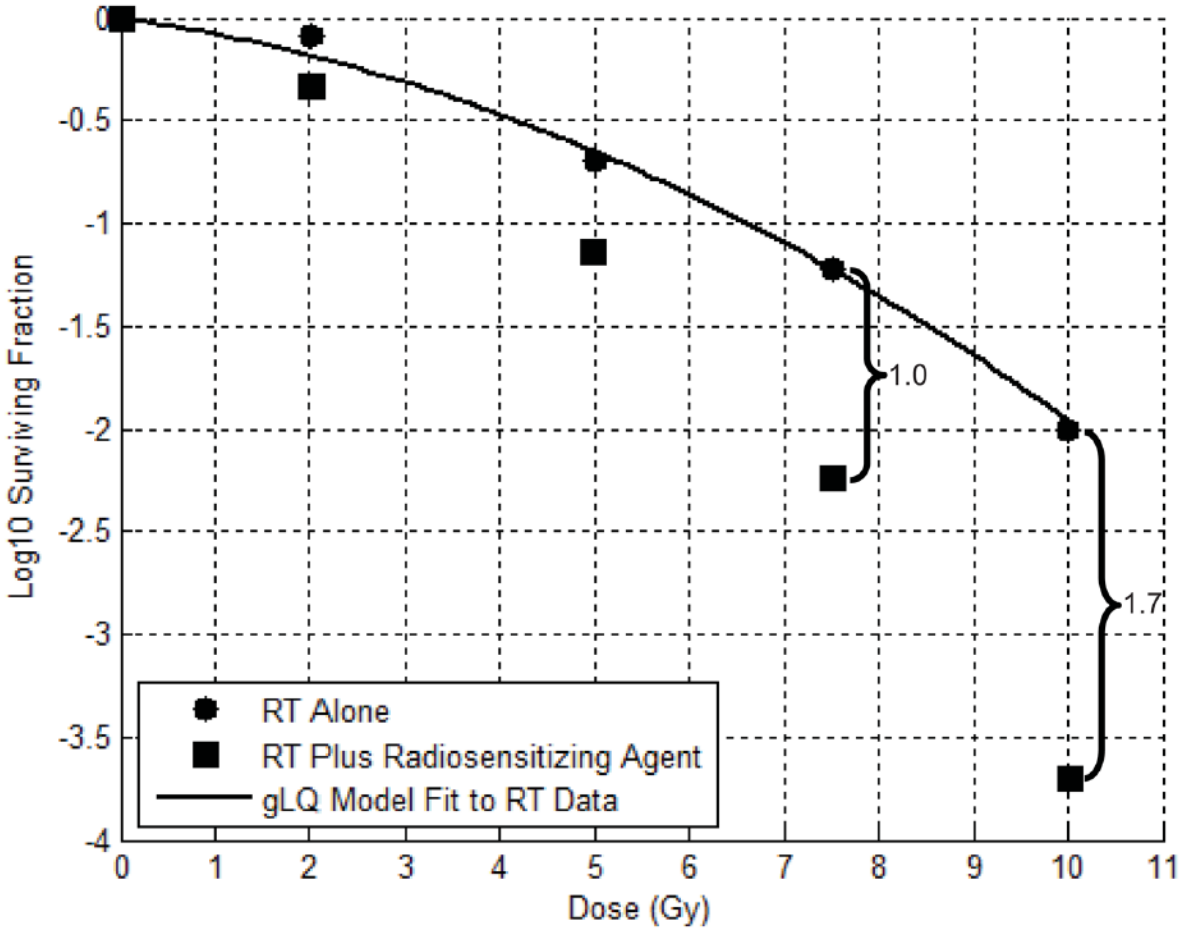
Table 2 | **Selected ongoing clinical trials investigating the efficacy of ISABR**

Institution and study details	SABR dose (Gy)/fraction	SABR Target	Immunotherapy agent	Sequence of treatments	Phase
Johns Hopkins University, NCT01950195 (REF. 45)	NS	Brain, spine	Ipilimumab	Immunotherapy, then SABR, then immunotherapy	I
University of Pennsylvania, NCT01497808 (RADVAX)[46]	NS	NS	Ipilimumab	SABR then immunotherapy	I/II
MD Anderson Cancer Center, NCT02239900 (REF. 47)	• 50/4 • 60/10	Liver, lung, adrenal	Ipilimumab	Concurrent; or immunotherpy then SABR	I/II
Chiles Research Institute, NCT01862900 (REF. 68)	• 15/1 • 20/1	Lung, liver	Anti-OX40	Concurrent	I/II
Stanford University, NCT01769222 (REF. 69)	20/2	Any	Ipilimumab	Concurrent	I/II
New York University, NCT01401062 (REF. 70)	22.5/3	Any	Fresolimumab	Concurrent	I/II
NIH/NCI, NCT02298946 (REF. 71)	• 8/1 • 24/3	Liver	PD-1 inhibitor	SABR then immunotherapy	I
Thomas Jefferson University, NCT01703507 (REF. 72)	• 24/1 • 21/1 • 18/1 • 15/1	Brain	Ipilimumab	Concurrent	I
MD Anderson Cancer Center, NCT02444741 (REF. 73)	50/4	Lung, liver	PD-1 inhibitor	Concurrent	I/II

ISABR; Immunotherapy and stereotactic ablative radiotherapy; NCI, National Cancer Institute; NS, not specified; PD-1, programmed cell death protein 1; SABR, stereotactic ablative radiotherapy.

Concomitant chemotherapy

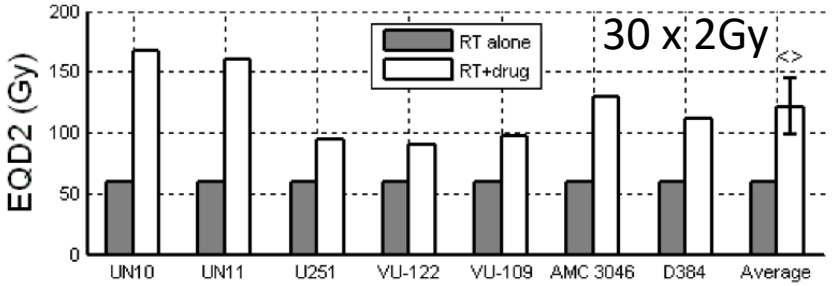
Radiosensitizing chemotherapy

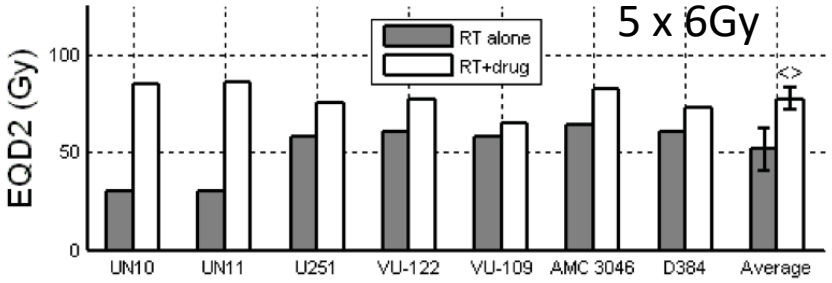


Ohri et al: IJROBP 2012; 83 (1): 385

Radiosensitizing chemotherapy

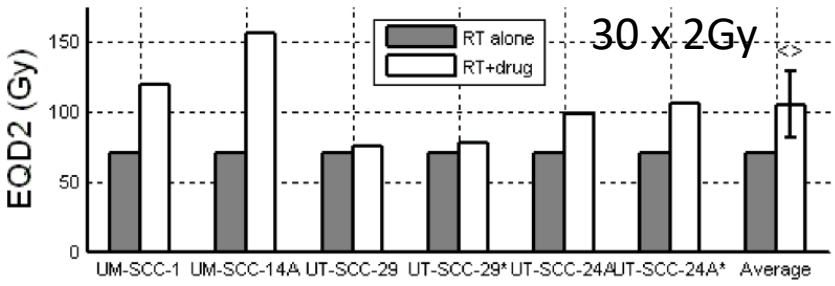
GBM

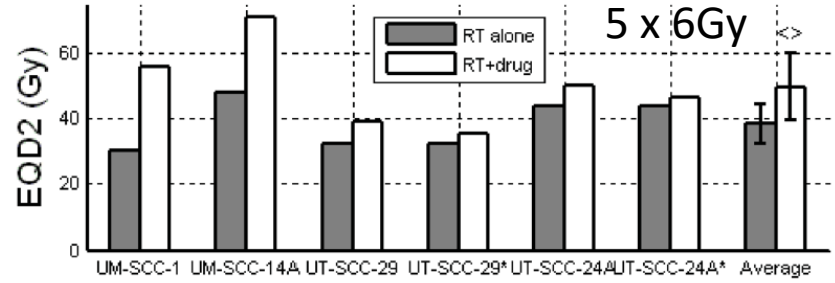




RT +/- concurrent temozolomide

HNC

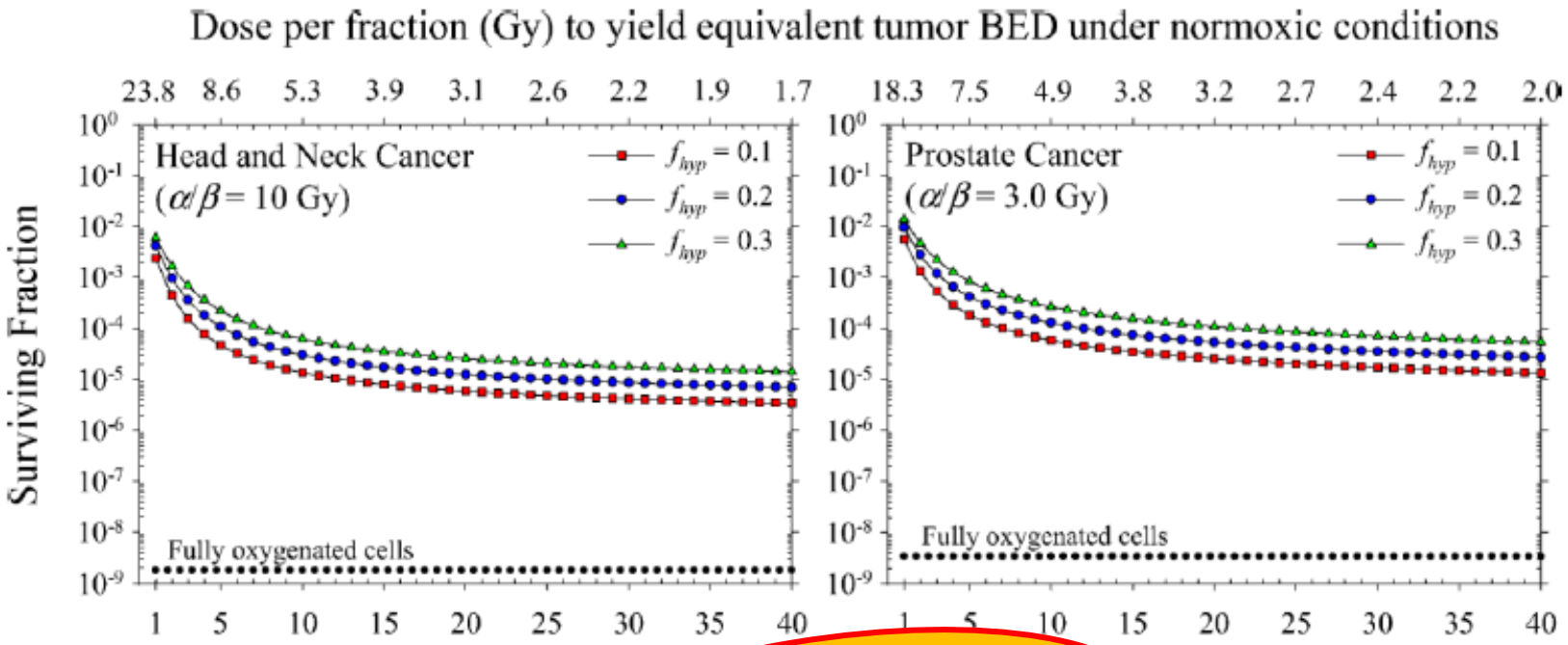




RT +/- concurrent cisplatin

Ohri et al: IJROBP 2012; 83 (1): 385

The effect of hypoxia is dependent of the number of fractions



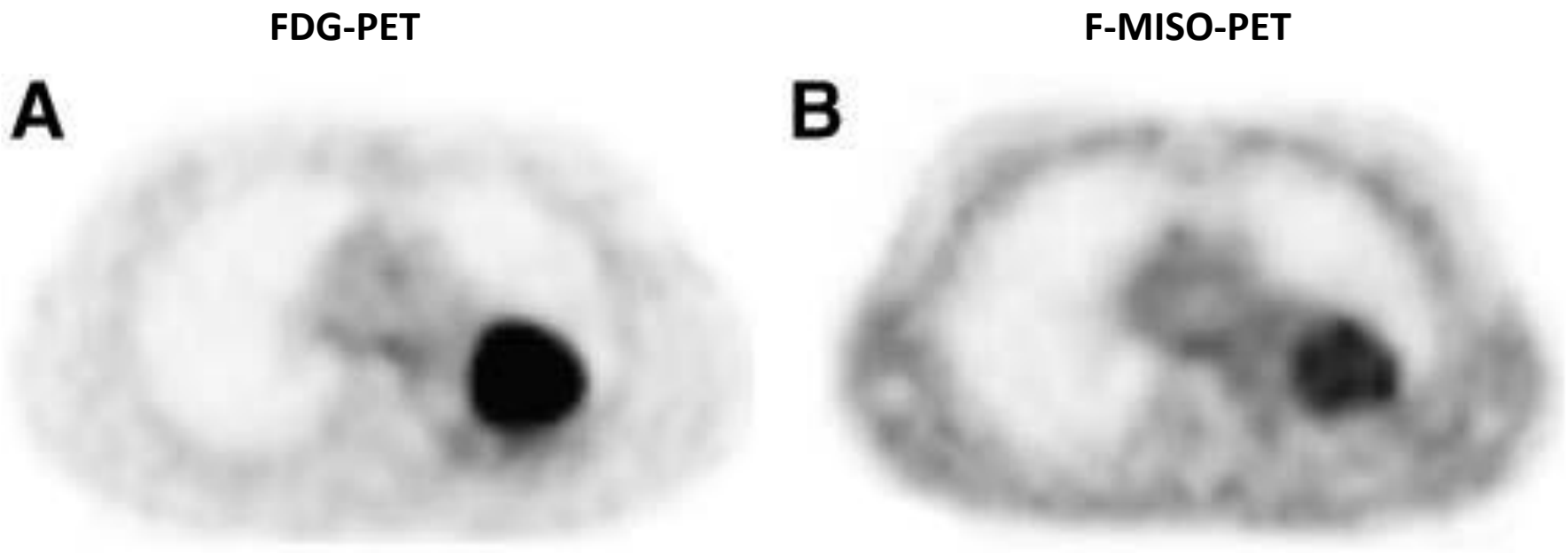
….so, why don't we add nimorazole to SBRT?

Carlson et al. IJROBP 2011; 79: 1188

FAZA-PET in lung cancer

Hypoxia

11/17 patients with hypoxic tumors



Trinkaus et al. J Med Imaging Radiat Oncol 2013; 57(4): 475

Conclusions

Based on experimental observations:

- Traditional models for cell survival after radiation may overestimate the cell kill (especially with high dose per fraction)
- In addition to direct radiation cell kill, there may be indirect cell kill related to
  - (Vascular effects and)
  - Immune effects
- Chemotherapy may enhance SBRT induced cell kill
- Hypoxia should not be ignored; why not add nimorazole?

AARHUS UNIVERSITY

CIRRO

Questions from the participants

1. SBRT combined with immunotherapy in melanoma
2. SBRT Radiobiology
    - Bystander effect
    - Abscopal effect

Department of Radiation Oncology
Chairman: Prof. Dr. Matthias Guckenberger

SBRT – What we know about dose & fractionation

Matthias Guckenberger

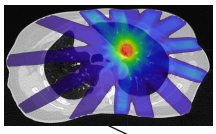
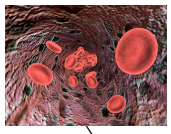
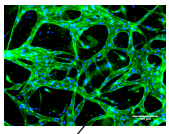
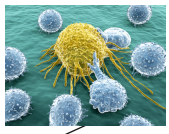
UniversityHospital Zurich

ESTRO

Technology meets Biology

Biology of Stereotactic Body radiotherapy

Ablative RT dose	Endothelial damage	Anti-vascular effect	Immune effect

Local tumor control rates:
Consistently **> 90%**

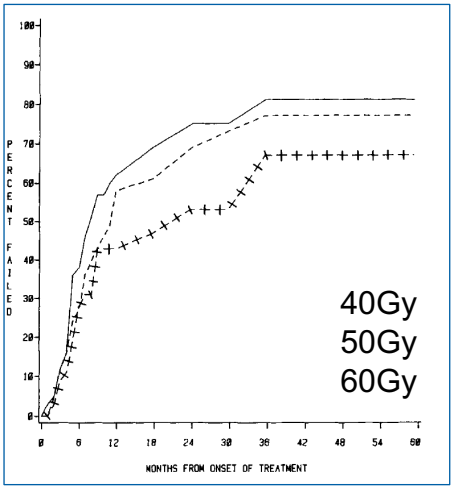
DOSE in SBRT

30 x 2Gy = **60Gy**

3 x 20Gy = **60Gy**

- Despite physical doses identical, biological doses are certainly not
- Need to compare !

Dose effect relationship in NSCLC



Perez Cancer 1987

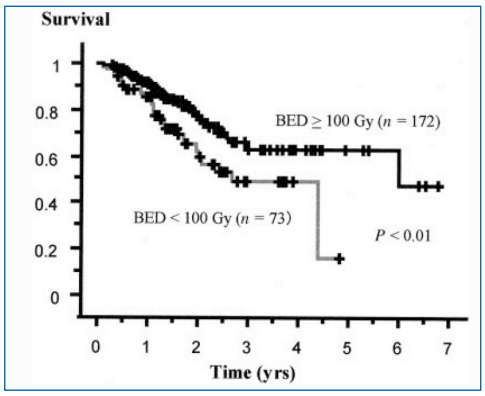
Isocenter dose	Estimated LPFS (%) at:		
	12 months	24 months	30 months
>70 Gy group, mean = 75 Gy (%)	81	61	38
<70 Gy group, mean = 65 Gy (%)	53	26	26
Dose at 50% LPFS (Gy)	64	72	84.5

Martel Lung Cancer 1999

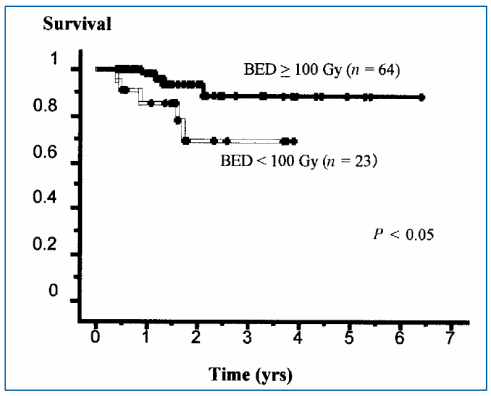
- High irradiation doses required for local tumor control
- Effect on OS limited due to competing risk of systemic progression

Dose effect relationship in SBRT for NSCLC

Onishi Cancer 2004



All patients

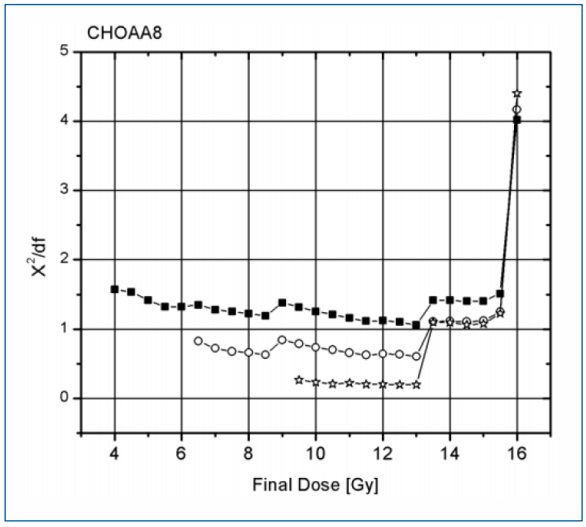


Medically operable patients

- Dose effect relationship in SBRT
- Local tumor control and OS
- LQ model for adjustment of variable dose per fraction

Applicability of LQ model in SBRT

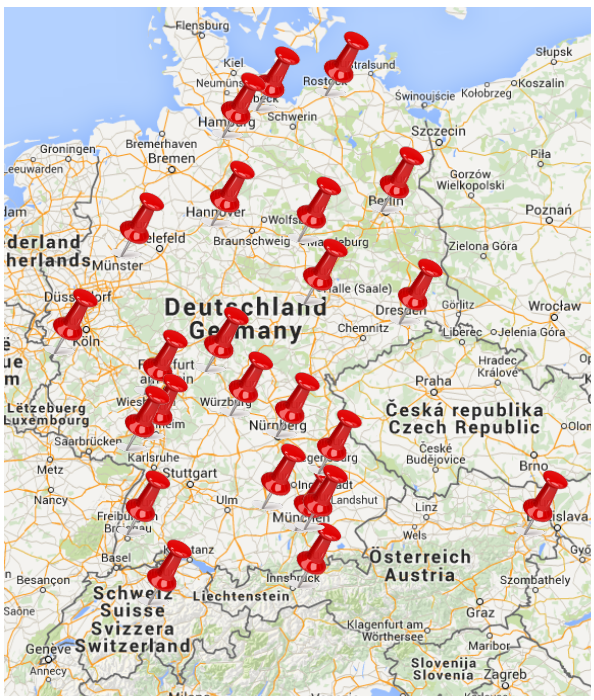
Garcia Phys Med Biol 2006



In cell lines (*fibroblasts, glioblastoma, prostate cancer*)

➢ LQ accurate up to single fraction doses of ~15Gy

Applicability of LQ model in SBRT

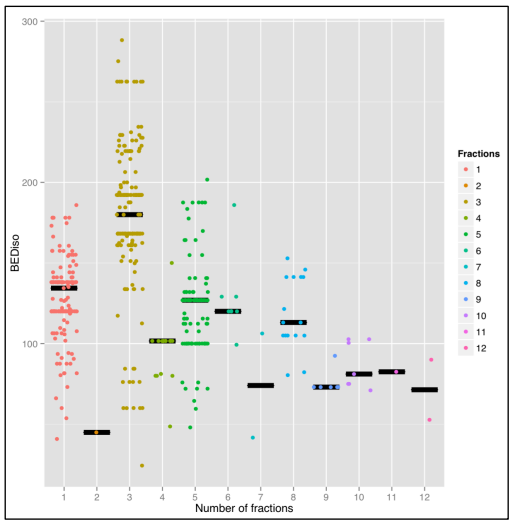


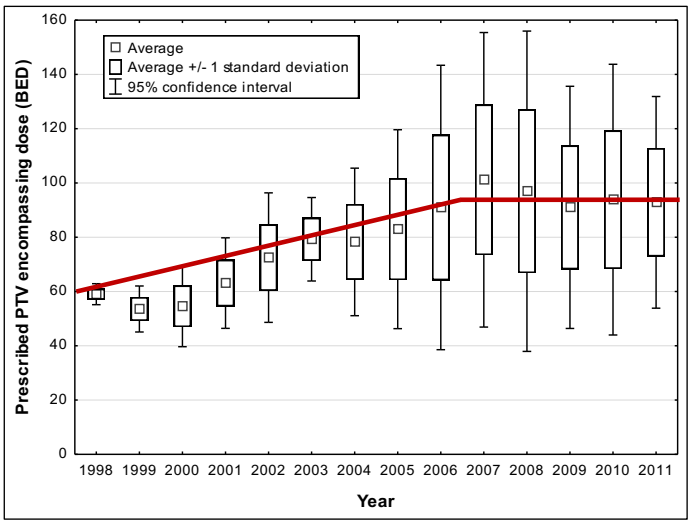
Study Design

- Multi-institutional & multi-national retrospective database of lung SBRT
  - Stage I NSCLC n=582
  - Lung metastases n=964

DEGRO AG Stereotactic Radiotherapy

Variability in treatment doses





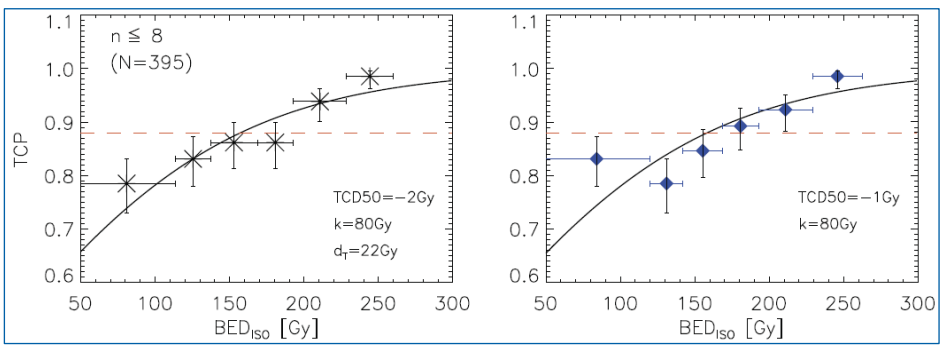
Guckenberger JTO 2013

- Huge variability in irradiation doses
- Learning curve with escalation of prescription dose

UniversityHospital Zurich ESTRO

Applicability of LQ model in SBRT: TCP of local tumor control

LQ model LQ-L model



Guckenberger Radiother Oncol 2013

- Clear dose effect relationship in fractionated SBRT
- LQL-model **not** statistically superior to LQ model

UniversityHospital Zurich ESTRO

LQ model versus “extended” biological models

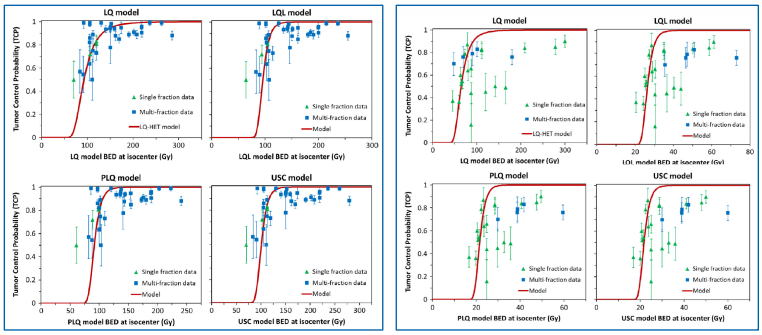
SBRT - stage I NSCLC **SRS & SRT - brain mets**

Linear quadratic model

Linear quadratic linear model

Universal Survival Curve

Pade Linear Quadratic



Shuryak Radiother Oncol 2015

- LQ model sufficient for description of clinical data

LQ model versus “extended” biological models

Linear quadratic model

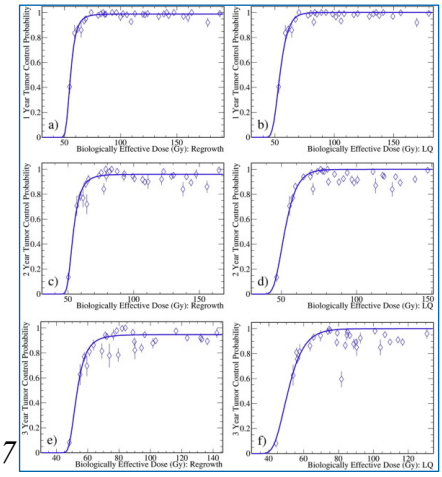
Linear quadratic linear model

Universal Survival Curve

Modified Linear quadratic model

Modified Linear quadratic linear model

Regrowth model

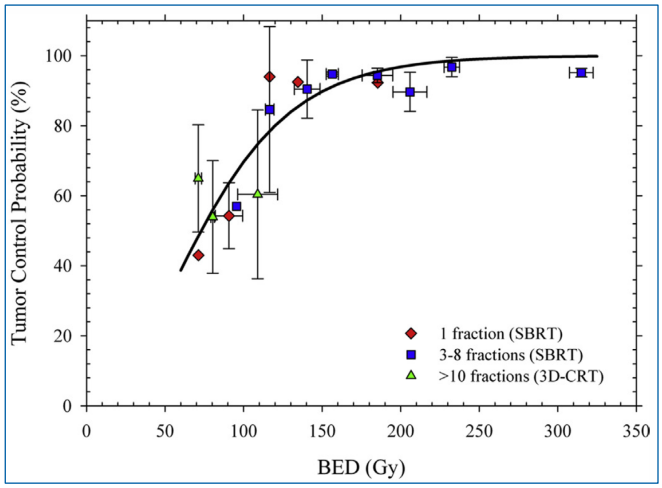


Liu Radiother Oncol 2017

- Significant fit of all models
- Alpha / Beta ratio of 20Gy, > 10Gy *Klement Radiother Oncol 2017*
- Best fit of regrowth model

TCP modeling considering different fractionations

Brown IJROBP 2013

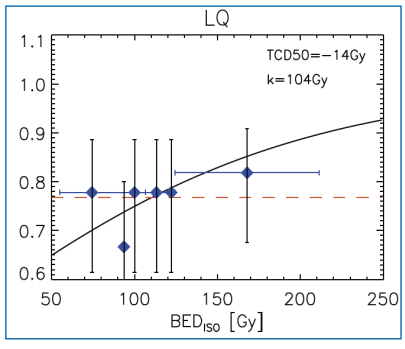


- One TCP model describing outcome of various fractionations

Single fraction SRS versus fractionated stereotactic radiotherapy

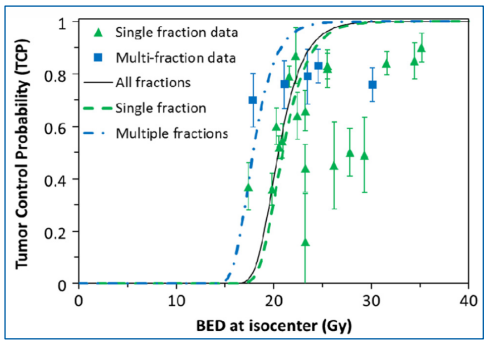
SBRT for stage I NSCLC

Guckenberger Radiother Oncol 2013



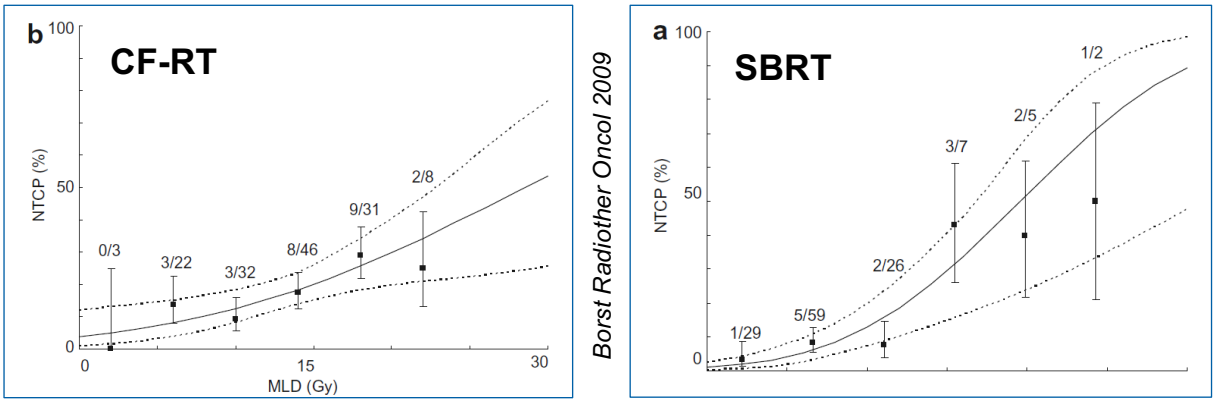
SRS for brain metastases

Shuryak Radiother Oncol 2015



- ***Stage I NSCLC***: No dose effect relationship for 15-33Gy
- ***Brain metastases***: Higher efficacy of SRT vs SRS

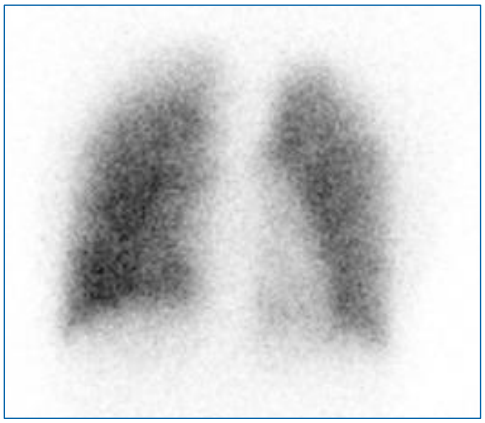
Applicability of LQ model in SBRT: NTCP of pneumonitis

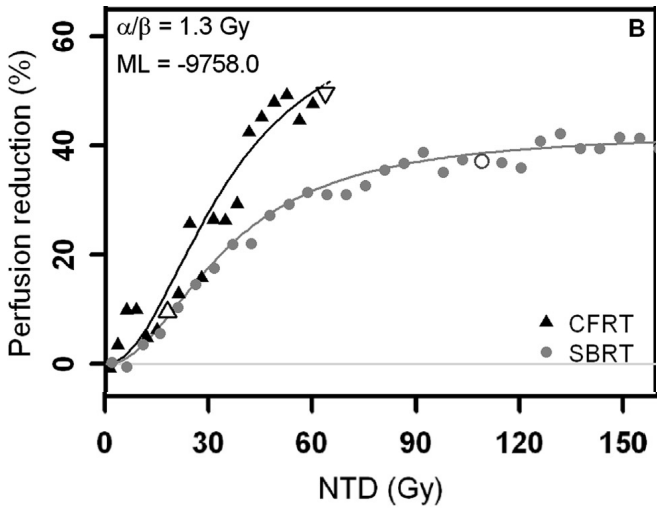


After correction for differences in SFD using the LQ model:

- One NTCP model describing outcome of CF-RT & SBRT

Applicability of LQ model in SBRT: NTCP of lung perfusion



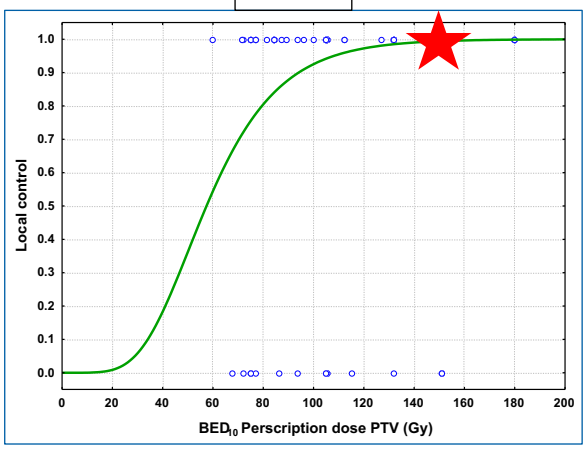


After correction for differences in SFD using the LQ model:

- One NTCP model describing outcome of CF-RT & SBRT

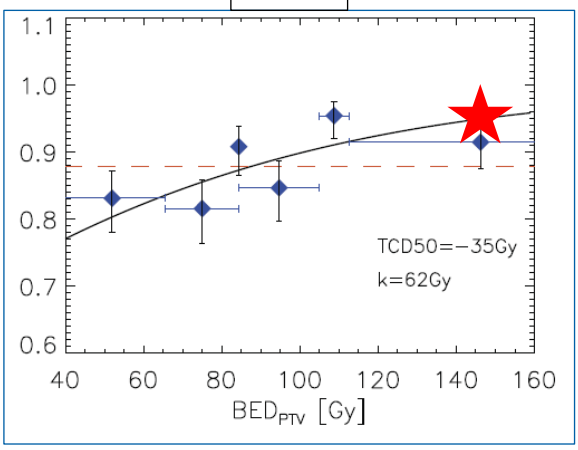
What dose is now actually required?

n=505



Grills JTO 2010; Ohiri IJROBP 2012

n=395



Guckenberger Radiother Oncol 2013

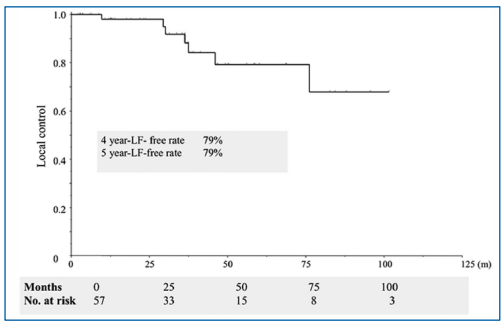
★ = 3 x 18Gy

➢ Very limited gain in TCP for doses >100Gy BED

Late recurrences in stage I NSCLC

Swedish phase II trial:
N=57

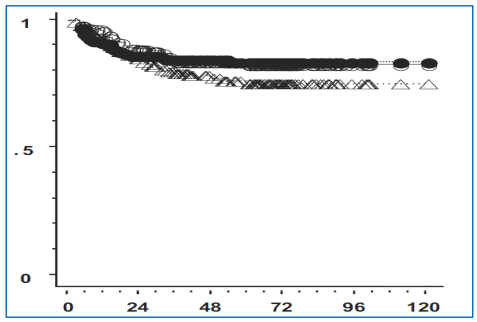
Lindberg Acta Oncol 2015



Median FU 41.5 months
3 x 15Gy @ 67%

Japanese prospective study:
N=180

Shibamoto JTO 2015



Median FU 52.5 months
4 x 11-13 Gy @ isocenter

- Very few recurrences after 3 – 5 years

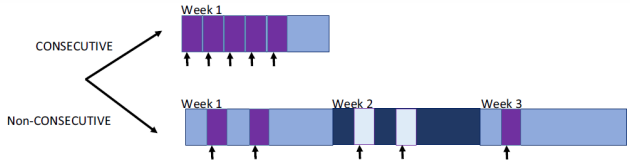
➢ Validity of TCP modelling

Fractionation

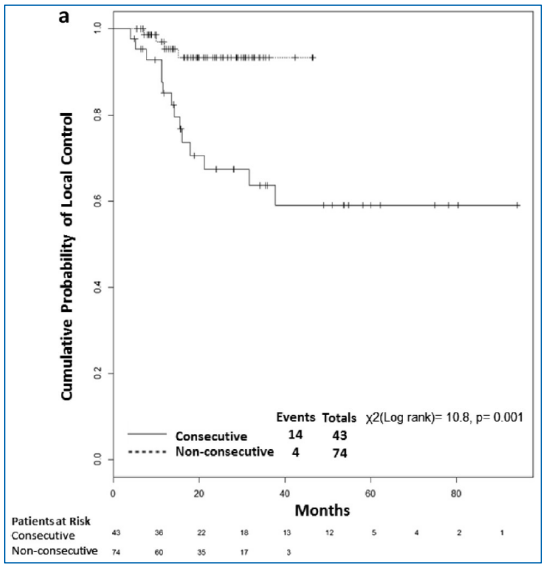
107 patients with stage I NSCLC

SBRT 50 – 60 Gy in 5 Fx:

- 5 fractions on consecutive days
- 5 fractions over 3 weeks

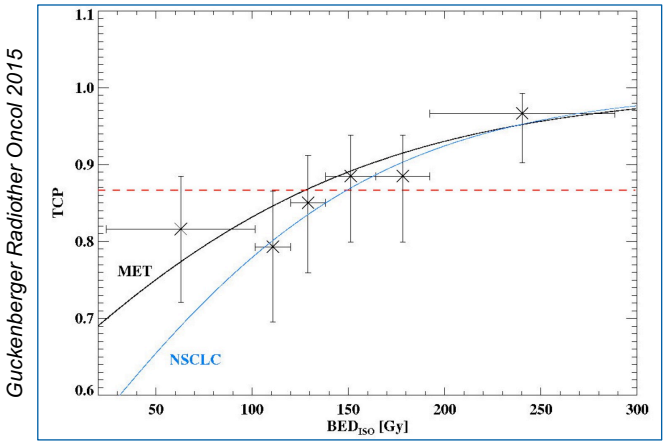


Alite Radiother Oncol 2017



- Significantly improved LC for SBRT delivered on non-consecutive days

Primary NSCLC & lung metastases



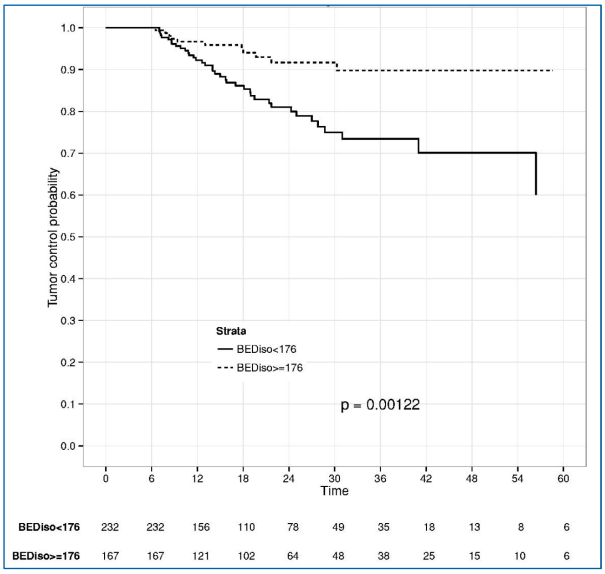
NSCLC: n=525

Lung mets: n=399

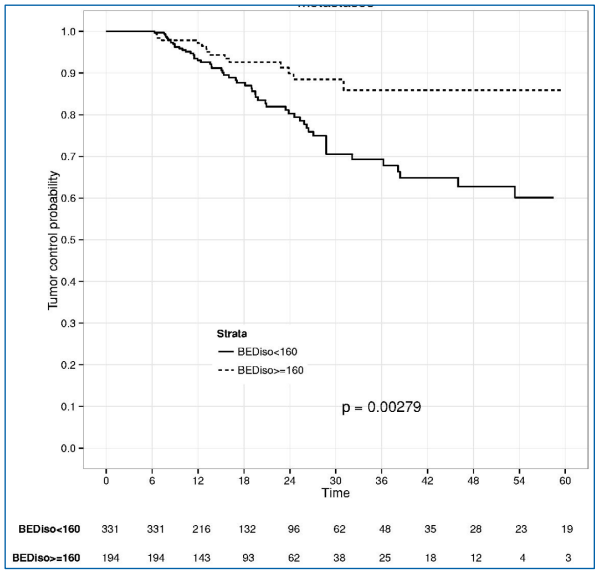
Dose effect relationship not significantly different between
- Primary NSCLC
- Lung metastases of various primary tumor sites

Primary NSCLC & lung metastases

Primary stage I NSCLC

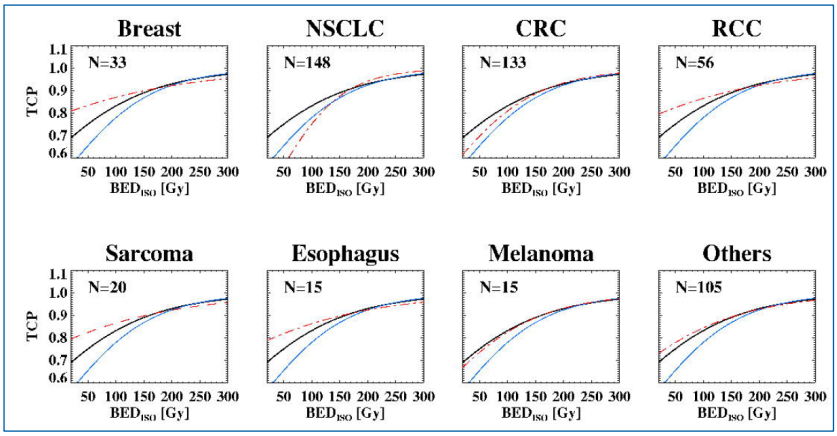


Pulmonary metastases



Guckenberger Radiother Oncol 2015

Lung mets of various primary tumor sites



	n	TCD90 (BED Iso)
NSCLC	148	**167 Gy**
CRC	133	**162 Gy**
RCC	56	**151 Gy**

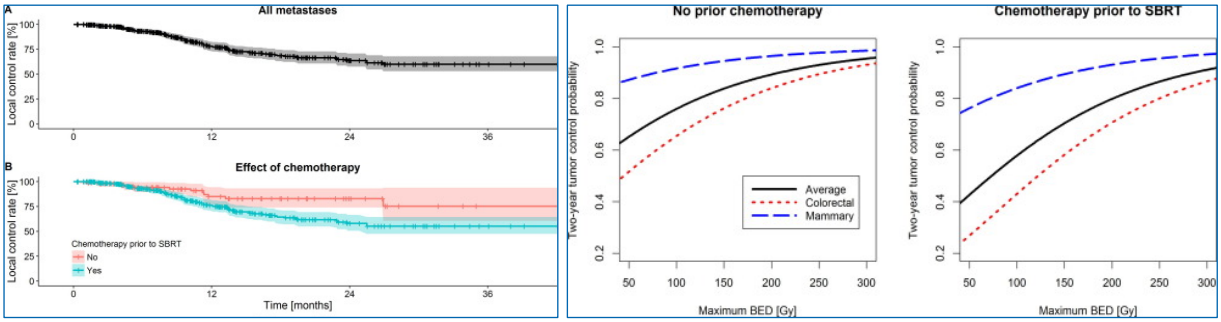
Guckenberger Radiother Oncol 2015

- TCP models very similar
- TCD90 not significantly different
- Results do not exclude differences in the low-dose region

Liver mets of various primary tumor sites

DEGRO cohort of oligo-metastatic liver disease

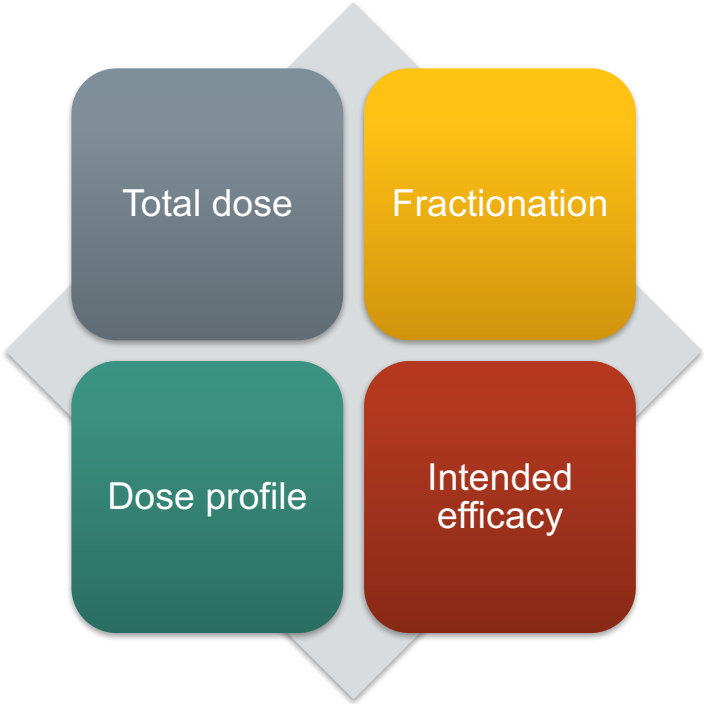
- 452 SBRT treatments in 363 patients



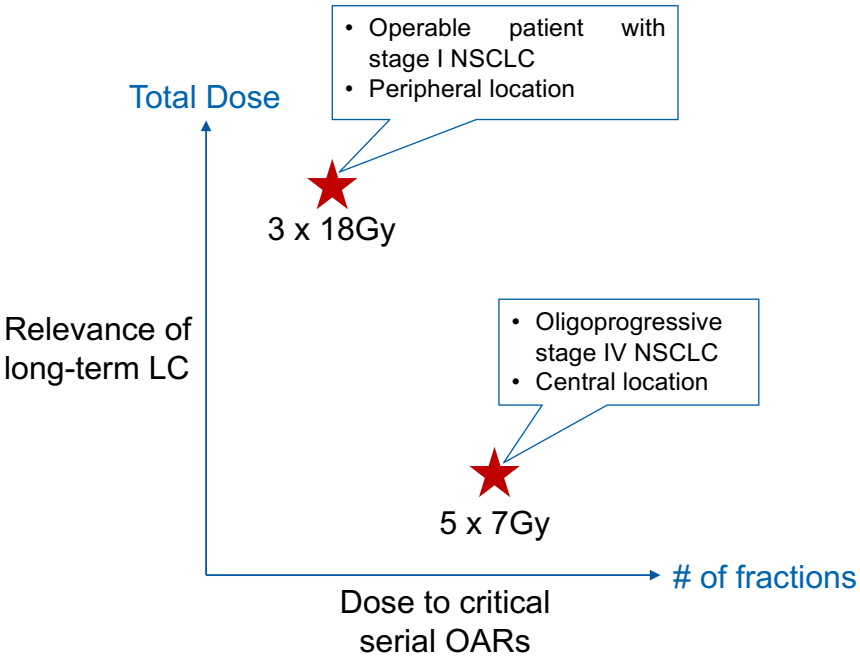
Klement Radiother Oncol 2017

- Worse LC in liver mets compared to lung mets
- Significant influence of histology
- Pre-SBRT chemotherapy affecting LC

Degrees of freedom in SBRT

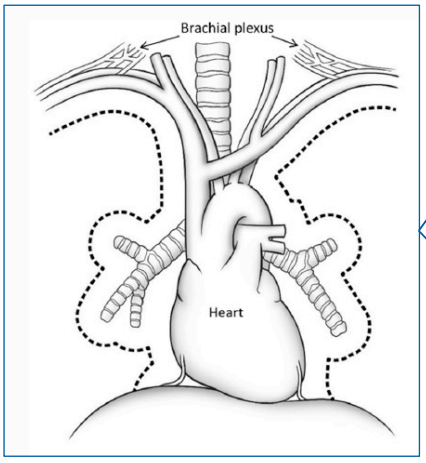


Risk adapted fractionation



Risk adapted fractionation – tumor location

Central location



Chang JTO 2015

3 x 20 – 22Gy

~ 50% severe toxicity @ 2 years

Timmerman JCO 2006

5 x 10 – 12Gy

5 x 10-11Gy: 2 in 34 G3-5 Tox
5 x 11.5-12Gy: 13 in 86 G3-5 Tox

Bezjak IJROBP Supp 2015

- SBRT for central location - standard practice
- Optimal dose and definition of “too” central lacking

Risk adapted fractionation – Clinical Situation

Prospective Phase II trial ***Iyenger JCO 2014***

- Maximum 5 Platin-resistant sites based on FDG-PET
- SBRT to all progressive sites,
- Switch to concurrent Erlotinib
- 24 patients with 52 sites

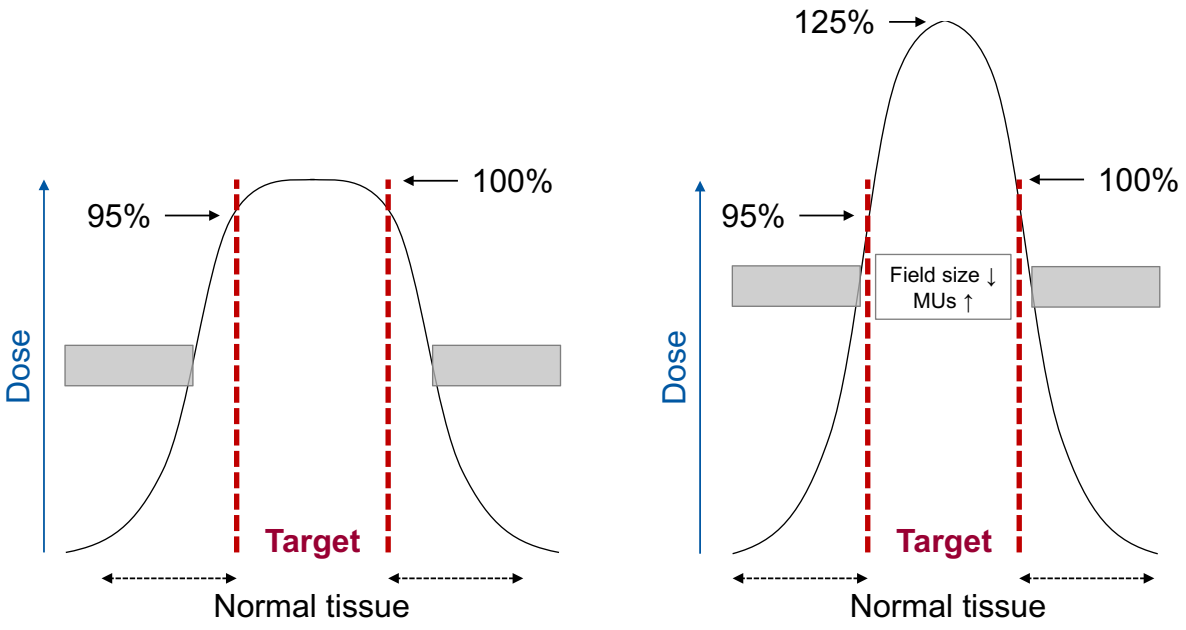
In-field failure	**3 / 21**
Out-field failure	**10 / 21**
No failure	**10 / 21**

	1 Fx	3 Fx	5 Fx
Physical dose	19 – 24Gy	27 – 33Gy	35 – 40Gy
Max BED	82Gy	70Gy	72Gy

➢ Excellent OS AND local tumor control lower SBRT doses

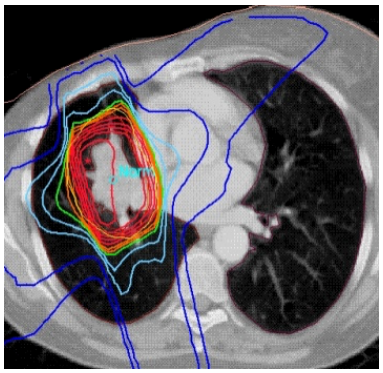
Dose in SBRT – dose prescription

Conventional radiotherapy ***Stereotactic radiotherapy***



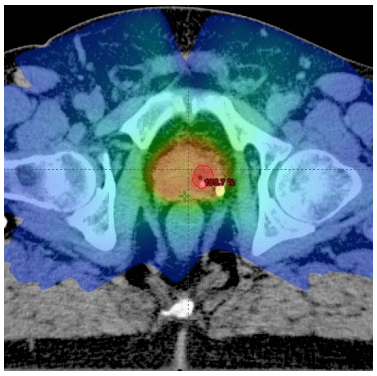
Dose escalation WITHIN the PTV

Central location



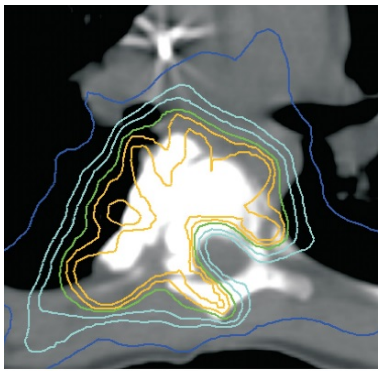
Bronchi
- Stenosis

Prostate



Urethra
- Scricture

Spine



Bone
- Fracture

- Adaptation of dose profile **within** the PTV

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C O N C L U S I O N S

- Dose explains high rates of local tumor control
- LQ model describes reasonably well what we observe in clinical practice
- Dose-response not different between primary NSCLC and pulmonary metastases
- PTV encompassing dose >100Gy BED achieves >90% TCP
- Total dose adapted to competing risk of death / distant progression
- Fractionation adapted to risk of OAR toxicity

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Department of Radiation Oncology
Chairman: Prof. Dr. Matthias Guckenberger

SBRT in the context of current developments in oncology

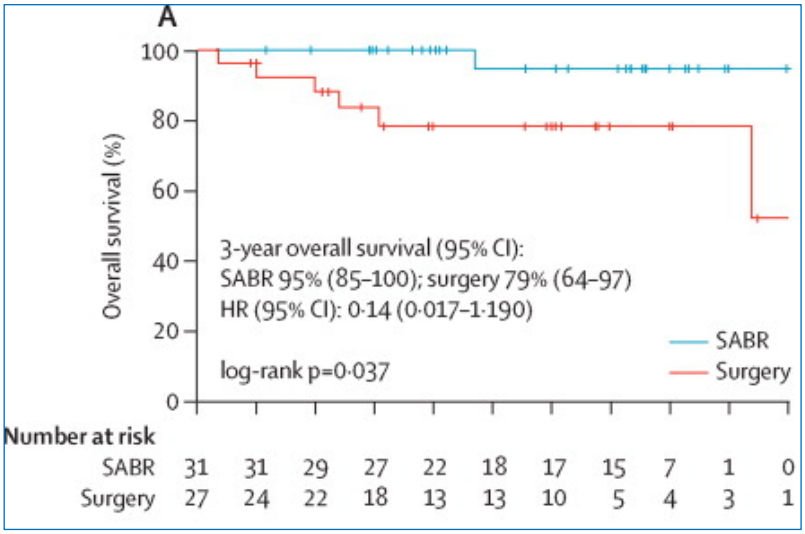
Matthias Guckenberger

UniversityHospital Zurich

ESTRO

SBRT for stage I NSCLC

Chang Lancet Oncology 2015



- SBRT equivalent to surgery
- Change of the perception of radiotherapy

Question

If all patients with inoperable stage I NSCLC would be referred to your department

What is the **proportion** of the **overall patient load**?

1) About 5 %
2) About 2.5 %
3) About 1 %
4) About 0.25%

SBRT for stage I NSCLC

100%		All cancer
13%	(13%)	Lung cancer
10.4%	(80%)	NSCLC
2.1%	(20%)	Early stage NSCLC
0.23%	(11%)	Inoperable stage I NSCLC

- Stage I NSCLC = RARE DISEASE
- Majority of our patient will NOT benefit from SBRT
- **Proof of principle**

„Mega“ trends & challenges in Oncology

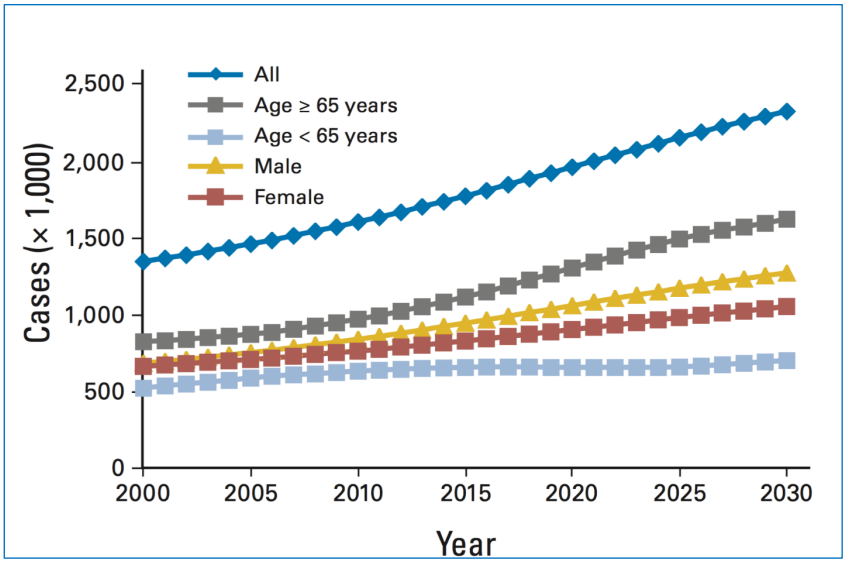
- Aging population / increased comorbidities
- Precision medicine / cancer as a chronic disease
- Tighter financial resources

➢How does SBRT fit into this picture ?

„Mega“ trends & challenges in Oncology

- Aging population / increased comorbidities
- Precision medicine / cancer as a chronic disease
- Tighter financial resources

Development of cancer incidence rates



- Strong increase of new cancer cases
- Almost exclusively in patients > 65 years old

Life expectancy

	At birth	At the age of 80
Men	+ 81	+ 9
Woman	+ 85	+ 10

Switzerland - Bundesamt für Statistik

- Definition of elderly > 65 years not true anymore

Recent randomized studies in Radation Oncology

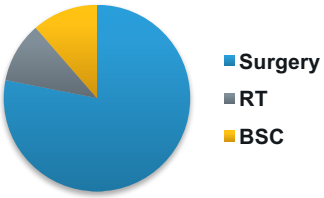
Study characteristic published in 2015				Median age at diagnosis (SEER)
Tumor entity	**Study question**	**Median age**	**Maximum age**	
Breast	RT of mammaria interna	**54 years**	**75 years**	**61 years**
Breast	RT of mammaria interna	**54 years**	**84 years**	**61 years**
NSCLC	Dose escalation Cetuximab	**64 years**	**83 years**	**70 years**
Rectal	Adjuvant CT after neoadjuvent RCHT	**62 years**	**68 years**	**68 years**
Prostate	**Duration AHT**	**72 years**	**85 years**	**66 years**
Prostate	**Hypofractionation of RT**	**71 years**	**75 years**	**66 years**

➢ Lack of evidence covering elderly patients

Treatment given to patients with curable stage I NSCLC

Overall population

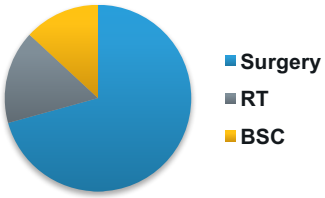
11%



Raz Chest 2007

SEER > 65 years

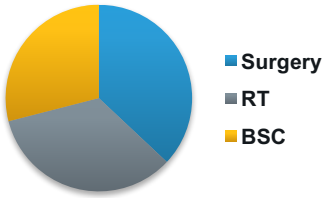
13%



Shirvani IJROBP 2012

Netherlands >75a

29%



Haasbeek Ann Oncol 2012

➢ 1/3 of all patients >75 old remain untreated

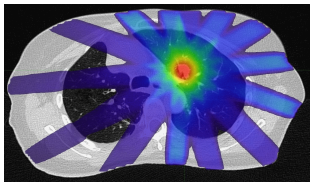
Safety & efficacy in elderly patients

	Patients	Median Age	Grade V death	Grade III - IV
Takeda 2013	109	83	n=1	n=4
Sandhu 2013	24	85	n=0	n=0
Haasebeek 2010	193	79	n=0	n=4

- Low mortality and morbidity despite very old age

➢ Excellent safety profile

SBRT in the context of an aging and comorbid patient population



➢ Few fractions

➢ Outpatient procedure

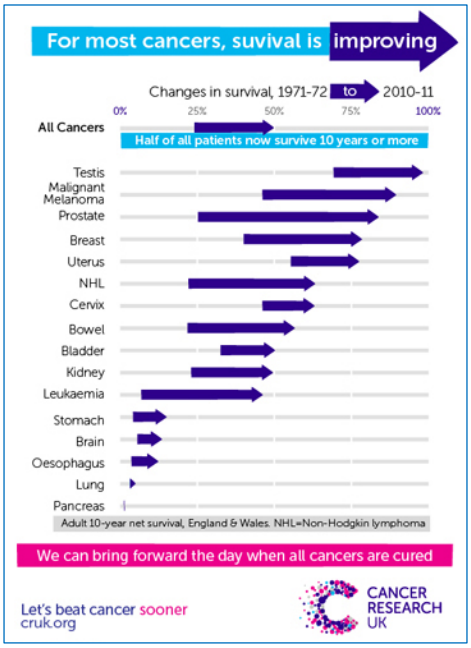
➢ Non-invasive not requiring anaesthesia

➢ Low toxicity in small tumor distant to serial critical OARs

„Mega“ trends & challenges in Oncology

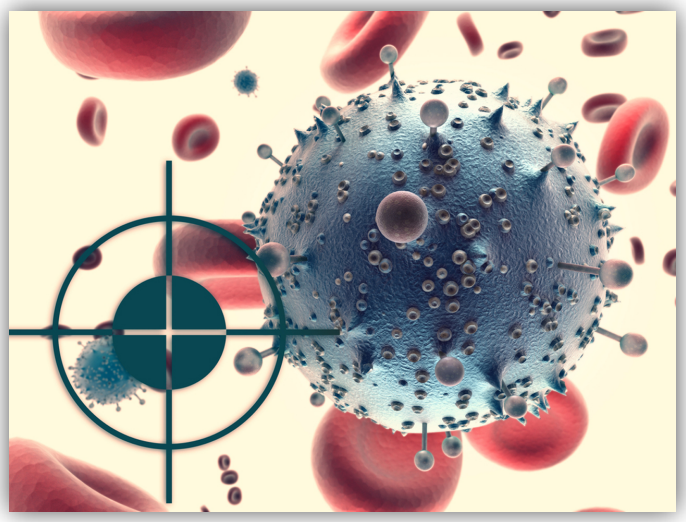
- Aging population / increased comorbidities
- Precision medicine / cancer as a chronic disease
- Tighter financial resources

Overall survival in cancer patients



- ➢ Early detection of cancer
- ➢ More effective radical Tx
- ➢ More effective systemic Tx

Precision medicine becoming reality



Oncology - Radiotherapy

- High – speed train -> Oncology
- Lady missing the train -> Radiotherapy

Approved targeted drugs

Medical Oncology		Radio-Oncology	
Cetuximab	Colorectal	Cetuximab	Head & Neck
Panatimumab	Breast		
Erlotinib	Pancreas		
Trastuzumab	NSCLC		
Lapatinib	Glioblastoma		
Bevacizumab	Kidney		
Axatinib	GIST		
Sorafenib	Thyroid		
Sunitinib	Head & Neck		
Pazopanib			
Ipilimumab			
Vandetanib			

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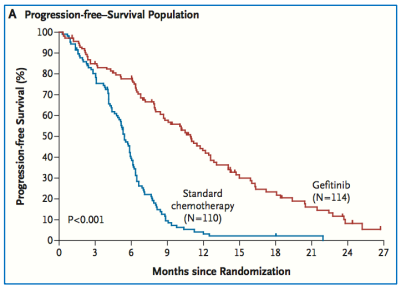
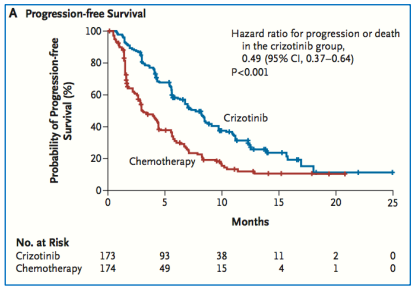
Progression under targeted systemic

Gefitinib
in mutant EGFR



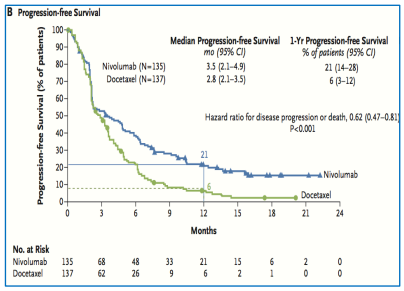
Maemondo NEJM 2010

Crizotinib
in ALK positive



Shaw NEJM 2013

Nivolumab
in unselected patients



Brahmer NEJM 2015

- Substantial and clinically relevant improvement
- Still: 60 – 80% develop progressive disease after 12 months

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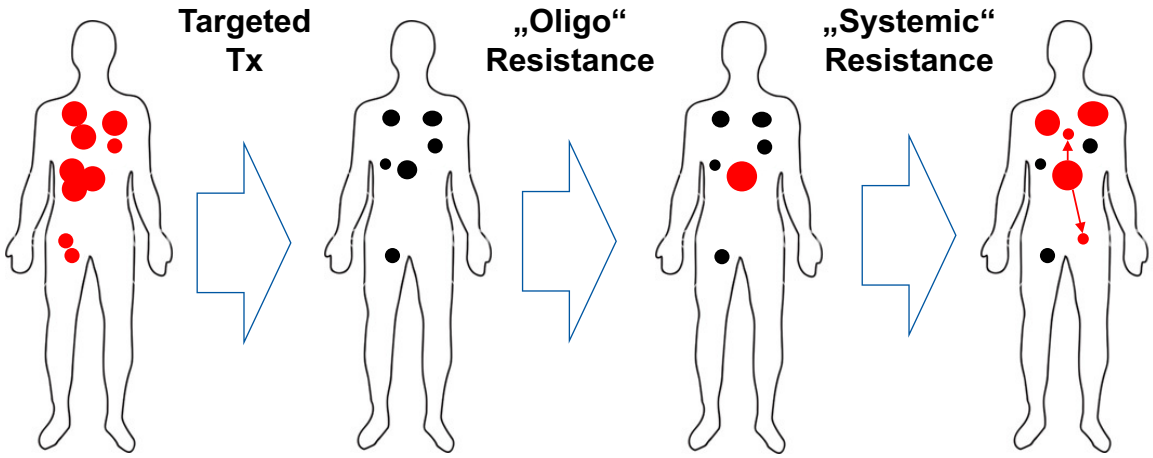
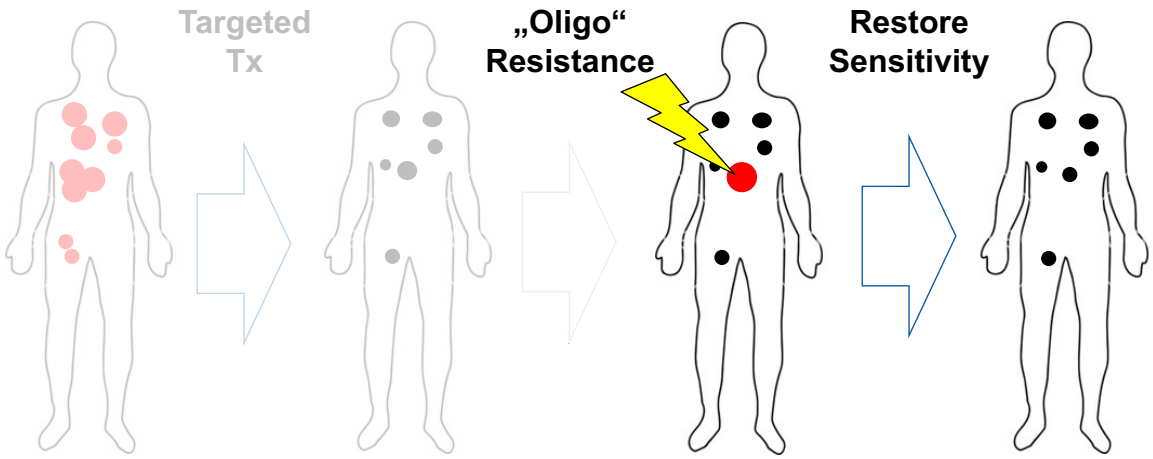
Acquisition of resistance



- Development of acquired resistance unlikely a systemically parallel process but a cascade of sequential events

Acquisition of resistance:
A potential role for targeted radiotherapy



- Local eradication of the oligo-resistant tumor site(s) to keep the patient in a sensitive state

Evidence of combining SBRT & targeted drugs

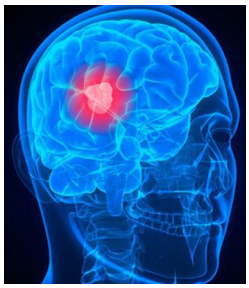
Agent	Patients	Studies	Primary Tumor	SRT Location
Antibodies				
Bevacizumab	202	11	Glioma, NSCLC, CRC	Brain
Cetuximab	251	6	SCCHNC	Head-and-neck
Trastuzumab	7	1	Mamma	Brain
Ipilimumab	121	8	Melanoma, Adenocarcinoma Lung	Brain, Liver
Nivolumab	27	2	Melanoma	Brain
TKIs				
Sorafenib	142	3	RCC, HCC, CRC	Brain, Spine, Abdomen
Sunitinib	15	2	RCC, Lung, Breast, Melanoma,	Brain, Abdomen
Gefitinib	47	3	NSCLC, Glioma	Brain, Lung
Erlotinib	24	1	NSCLC	Abdomen, Lung, Bone
Crizitonib	39	2	NSCLC	Brain, Lung, Abdomen, Bone
Vemurafenib	75	6	Melanoma	Brain, Spine
Dabrafenib	56	4	Melanoma	Brain
Trametinib	6	1	Melanoma	Brain

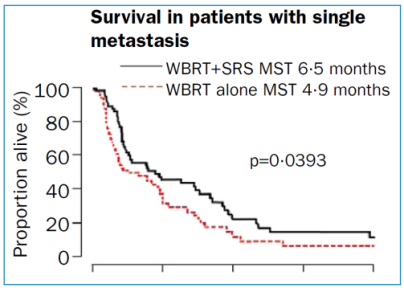
- Very little data available: 1042 patients in 50 studies

Brain metastases

Low tech
Whole brain irradiation

High tech
Radiosurgery





Andrews Lancet 2004

- High tech in palliative setting in good prognosis patients
- ➢ Aim: prolongation of OS

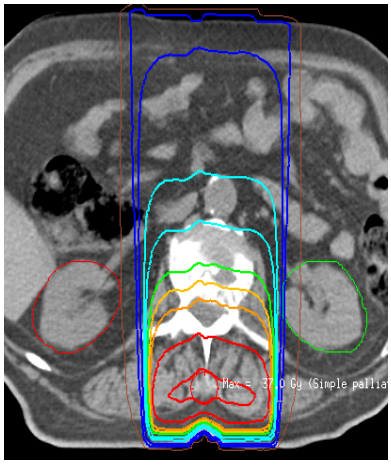
Brain metastases

NCCTG N0574 (Alliance): A phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases *Brown ASCO 2015*

Cognitive function deterioration @ 3 months	SRS	SRS + WBI
immediate recall	8%	31%
delayed recall	20%	51%
verbal fluency	2%	19%

➢ Adverse effect of WBI on neurocognitive fraction already after 3 months

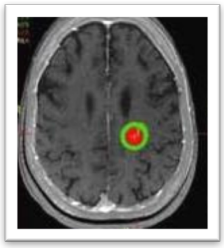
Painful bone / vertebral metastases

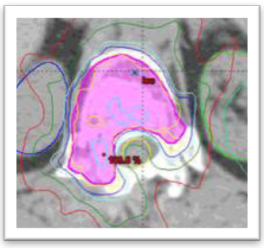


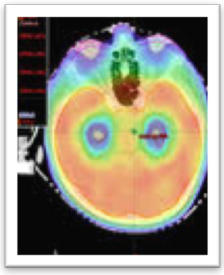
	Palliative RT	Pain response	Duration
Prince 1986	1 x 8Gy 10 x 3Gy	73% 64%	**59% @ 3 mo** **50% @ 3 mo**
Gaze 1997	1 x 10Gy 5 x 4.5Gy	84% 89%	**Median 3.5 mo** **Median 3.5 mo**
Steenland 1999	1 x 8Gy 6 x 4Gy	72% 69%	**Median 5 mo** **Median 6 mo**
Roos 2005	1 x 8Gy 5 x 4Gy	61% 53%	**Median 3.5mo** **Median 5.5 mo**

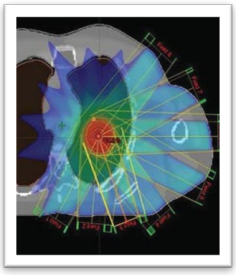
• Conventional radiotherapy = Short term palliation
➢ Patients with better OS will develop pain recurrence

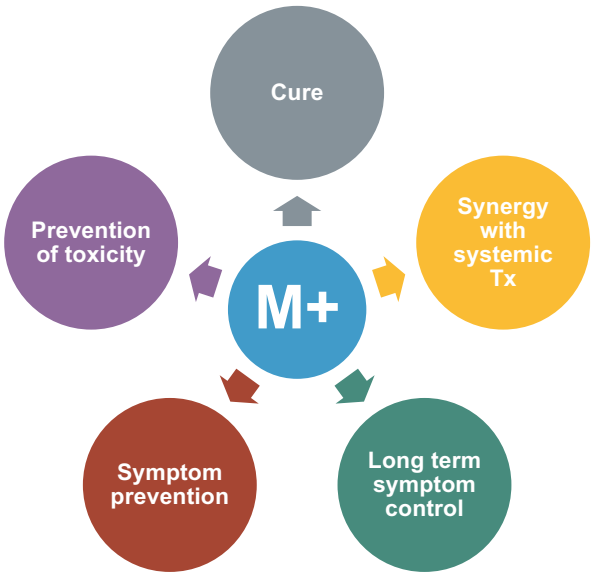
Goals of high-tech RT in the metastatic setting









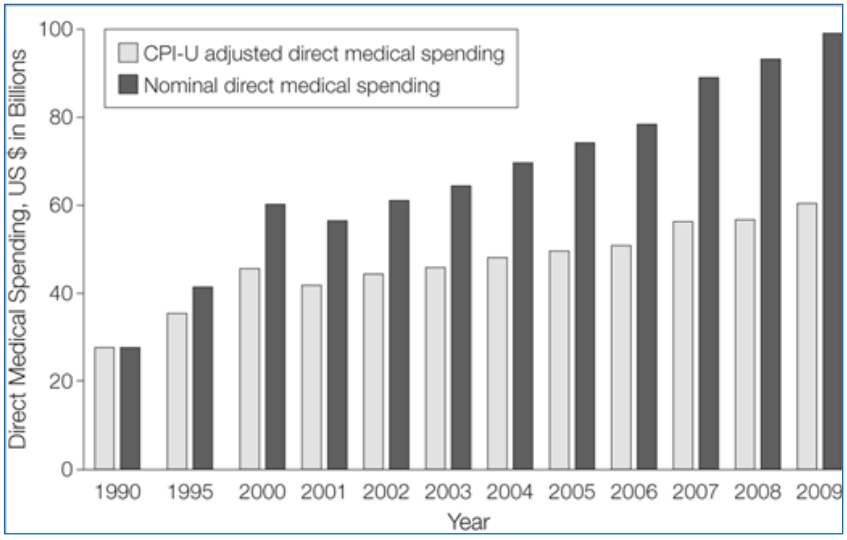


„Mega“ trends & challenges in Oncology

- Aging population / increased comorbidities
- Precision medicine / cancer as a chronic disease
- Tighter financial resources

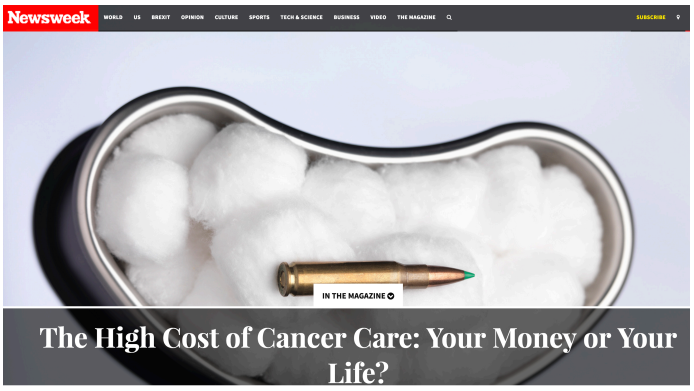
Health care spending on cancer care

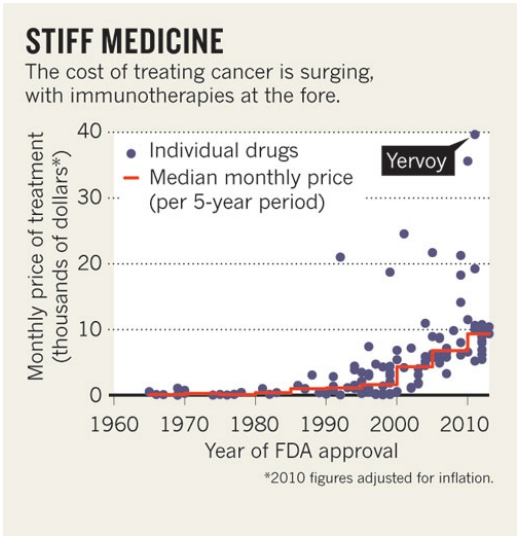
Elkin JAMA 2010



- Continuous and above-inflation increase of cancer care costs

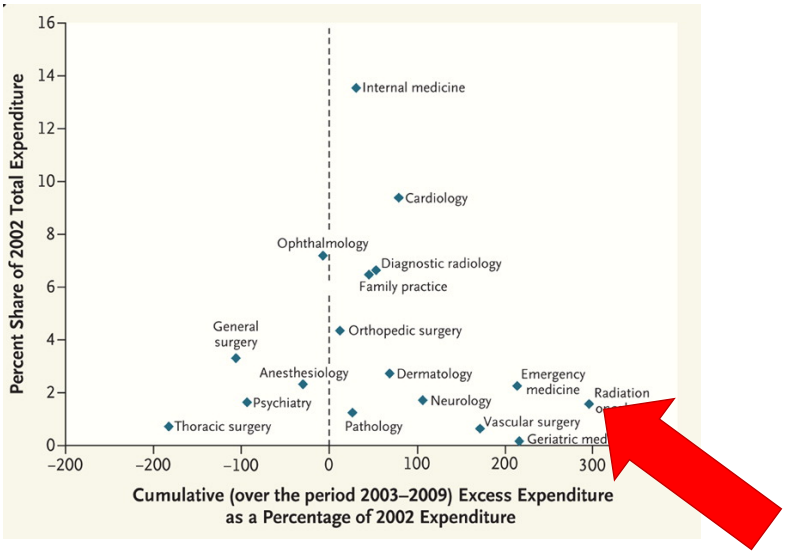
Health care spending on cancer care





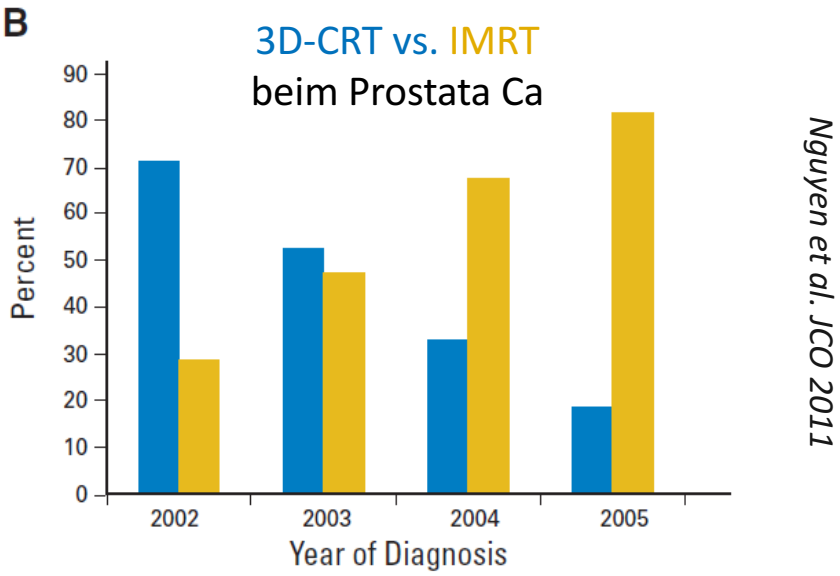
- Excessive prices for modern cancer drugs

Increase in costs caused by discipline



- Radiation Oncology as **#1 cost** driver in US medicine

The IMRT and prostate story ...



- IMRT: Additional costs of 282.000.000 $ in 2005
- Still „limited comparative effectiveness research“

Protons

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BUSINESS

Big Bets on Proton Therapy Face Uncertain Future

Insurers balk at expensive radiation treatment; can smaller machines turn the tide?

New and costly proton-radiation therapy centers are scheduled to open in the U.S. in the next few years, entering a market where most insurers have stopped covering it for prostate cancer. *PHOTO: HOWARD LIPIN/U-T SAN DIEGO/ZUMA PRESS*

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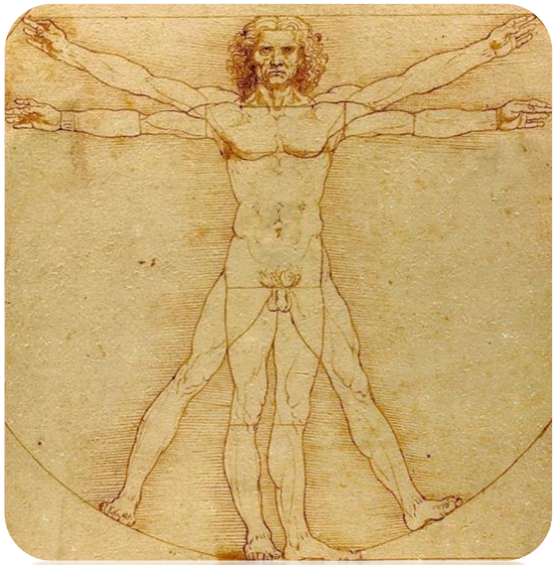
Potential application of SBRT

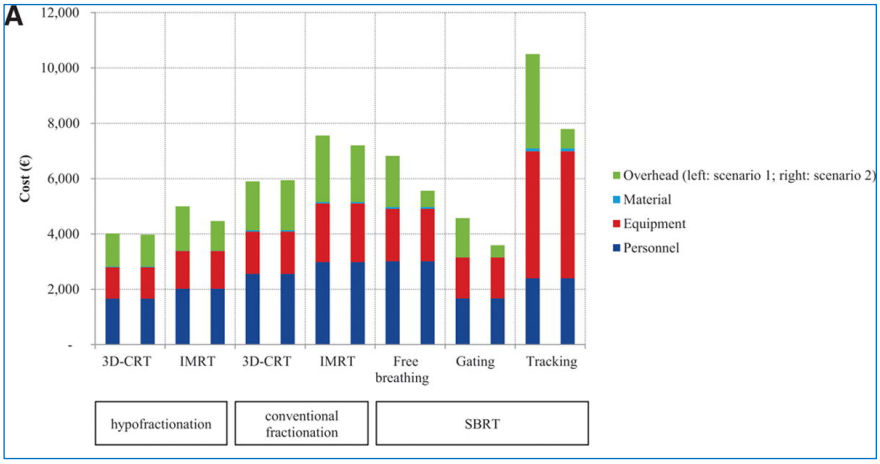


- Brain metastases
- Primary brain tumors
- Recurrent head & neck
- Breast Cancer
- Primary lung cancer
- SBRT for locally advanced NSCLC
- Lung metastases
- Spine SBRT
- Primary liver cancer
- Liver metastases
- Pancreatic cancer
- Lymph node metastases
- Prostate cancer
- Cervical cancer
- ...

Costs (not reimbursement) of SBRT

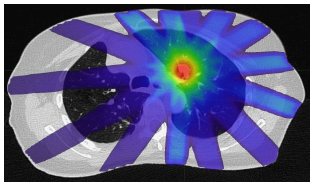
- Time-driven activity-based costing model
- 10 Belgian radiotherapy centers

Lievens *JTO 2015*



➢ Considerable variation in cost mostly depending on technology and staff resources
➢ Potential of being a highly-cost effective technology

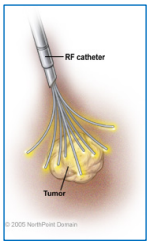
SBRT in the context of decreasing resources

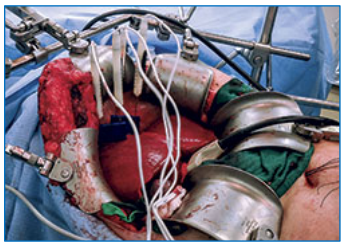


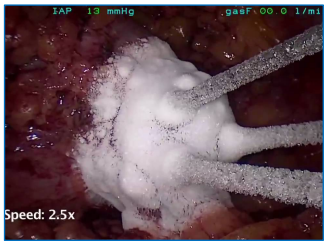
- Costs for radiotherapy / new technologies have increased substantially
- Costs of SBRT are highly dependent on
  - Technology
  - Staffing

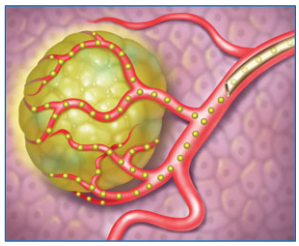
➢ Potential to achieve LOWER costs than conventional radiotherapy

Minimally invasive, ablative technologies









- No question, there is (huge) competition
- Substantial differences: biology, ablation zone, local efficacy, invasiveness, logistical efforts, costs
- Consider them as a “toolkit”

C O N C L U S I O N S

- Substantial changes and progress in current oncology
- Pressure on Radiation Oncology to participate and adapt
- Multiple opportunities especially for SBRT

Erasmus MC
Universitair Medisch Centrum Rotterdam

Cancer Institute

SBRT in the Context of Future (Technology) Developments in Oncology

Mischa Hoogeman

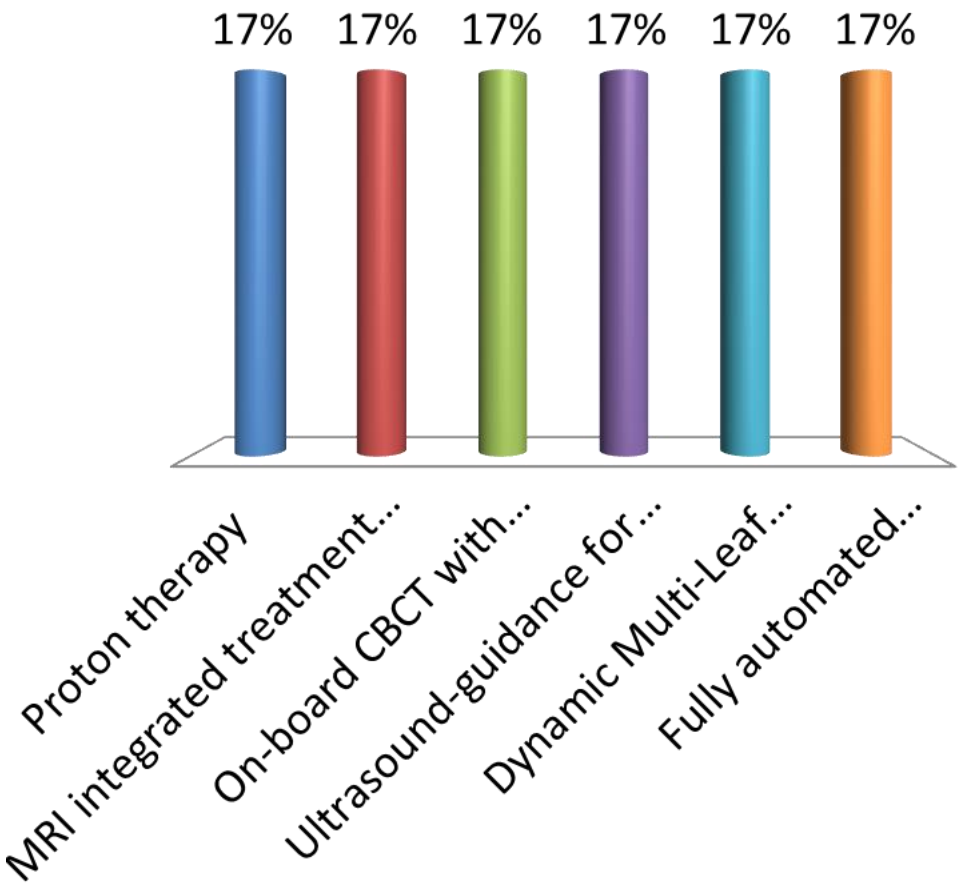
Outline

- Technology for improved image-guidance and correction
- Proton therapy
- Evidence and justification
- Automation in SBRT

- POLL

Which technology do you consider to have the greatest impact on SBRT in clinical practice in the coming 5-10 years?

A. Proton therapy
B. MRI integrated treatment units
C. On-board CBCT with diagnostic image-quality
D. Ultrasound-guidance for cost-effective radiation therapy
E. Dynamic Multi-Leaf Collimator
F. Fully automated workflows (single push button treatments, one stop shops)



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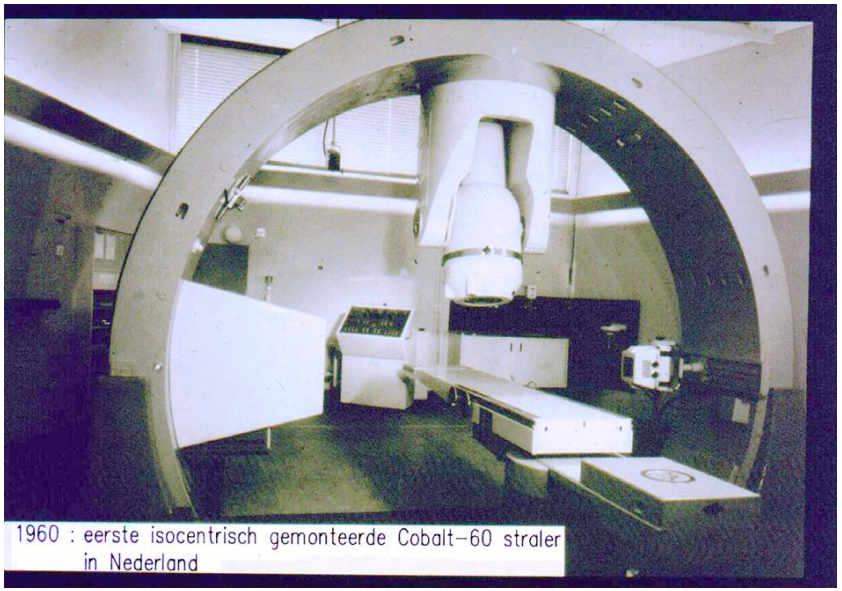

IMPROVED IMAGE-GUIDANCE AND CORRECTION FOR PHOTON RT

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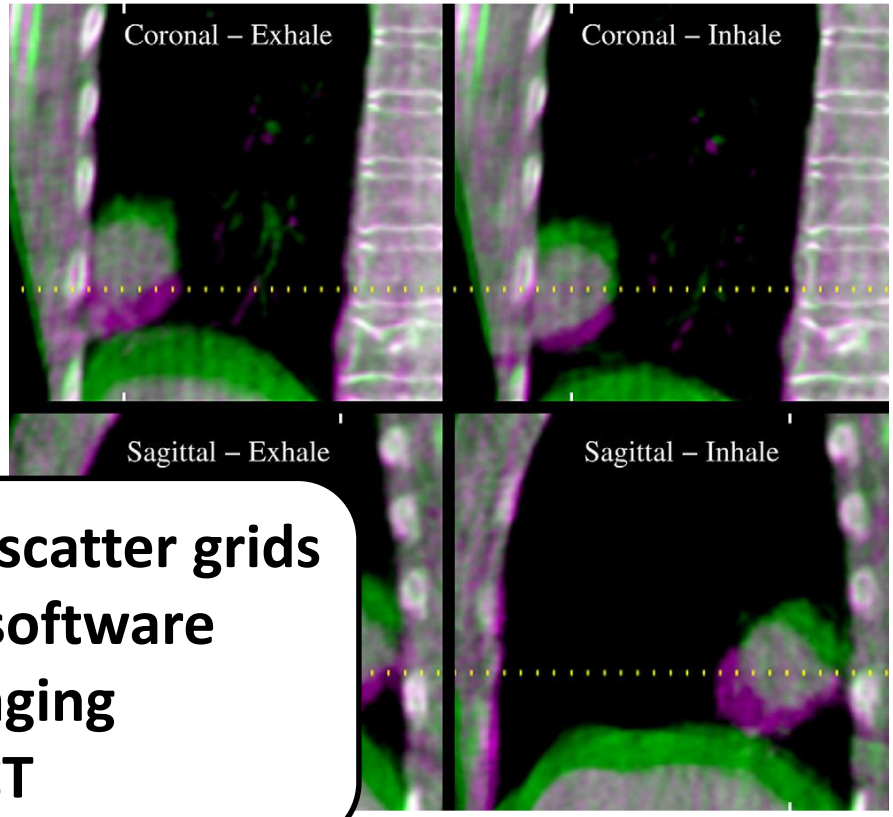
Ease of Use: Frameless Lung SBRT and SRS

- AAPM TG 179: "Perhaps, the most important application of **CBCT has been the simplification of hypofractionated SBRT**"



- **Improving contrast by anti-scatter grids and scatter correction software**
- **Real-time CBCT imaging**
- **Dual Energy CBCT**

From: Sonke JJ, Lebesque J, van Herk M. Variability of four-dimensional computed tomography patient models. Int J Radiat Oncol Biol Phys. 2008 Feb 1;70(2):590-8.

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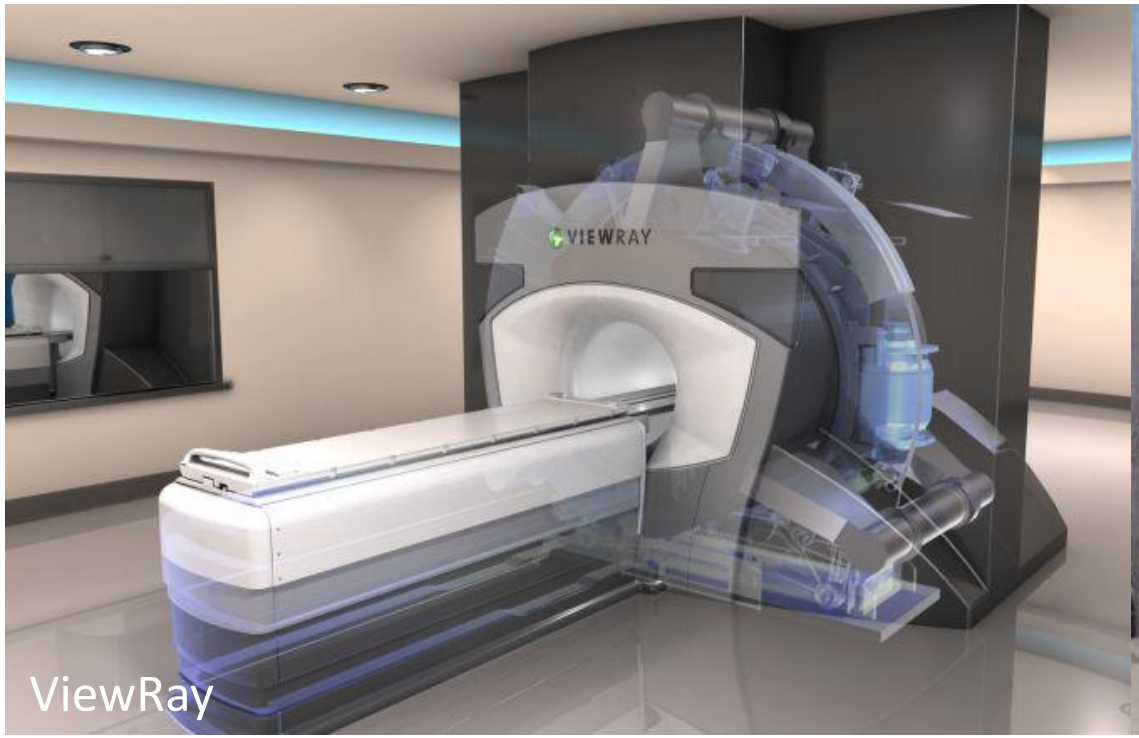
MRI-Integrated Radiotherapy Systems



ViewRay

Elekta-Philips Utrecht

Nature Reviews Clinical Oncology 9, 688-699 (December 2012) |
doi:10.1038/nrclinonc.2012.194

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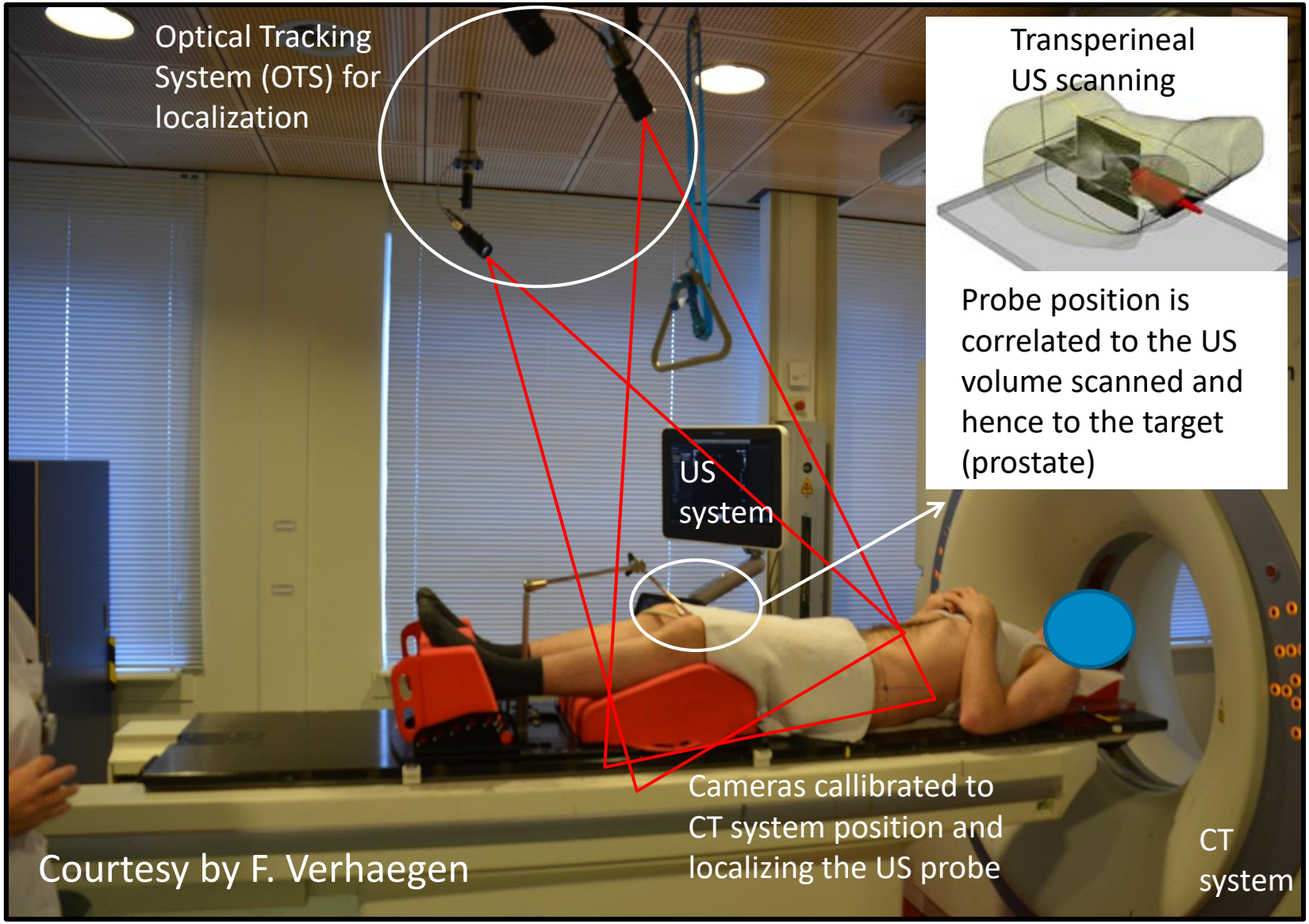
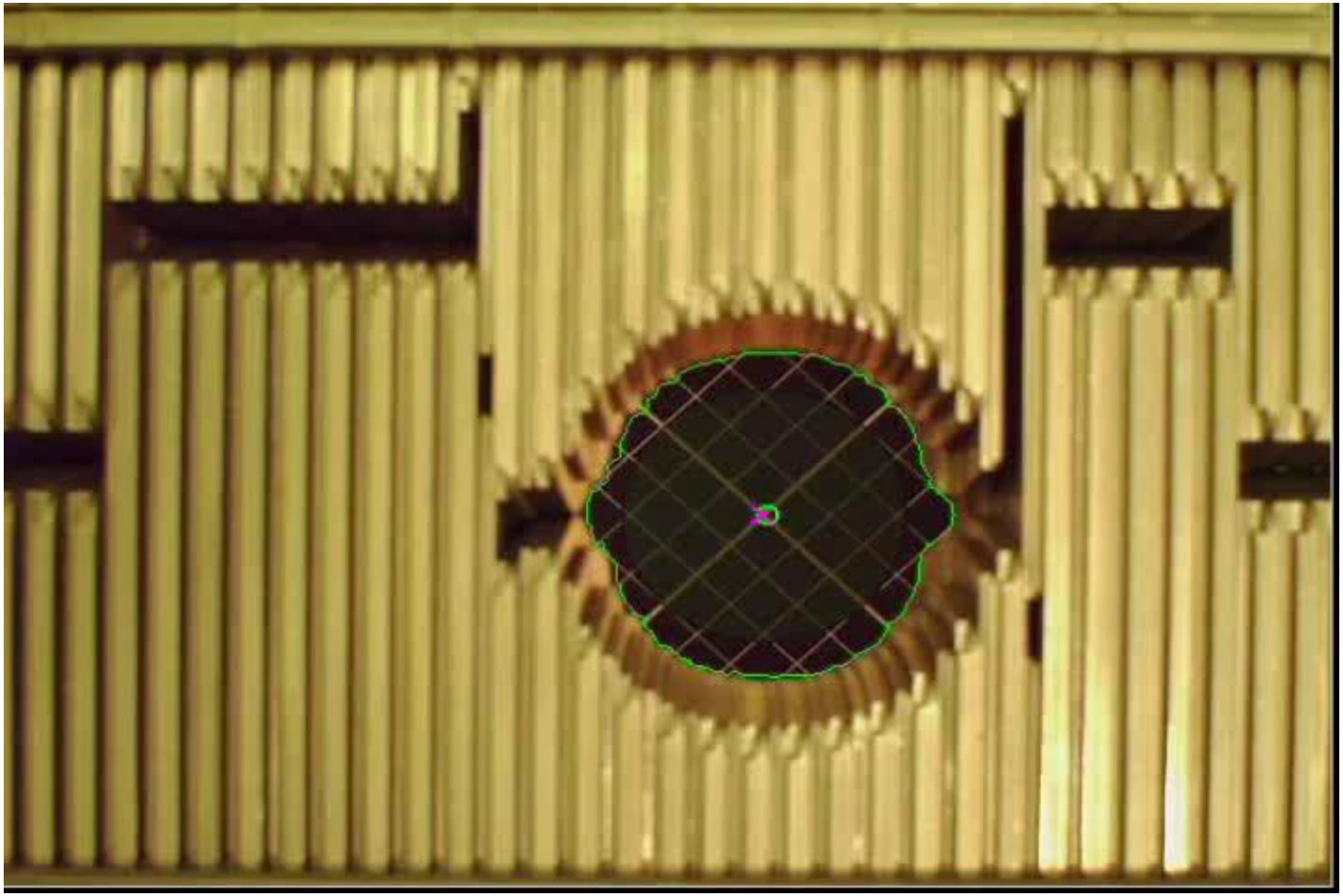
Soft-Tissue Contrast: CT on Rails



Research 4DUS system at MAASTRO Clinic (Maastricht, Netherlands)

Dynamic Multileaf Collimator Tracking by Paul Keall (2007)



https://www.youtube.com/watch?v=LOETSm_HliU

How Much Technology Do We Need for SBRT?

Challenges	IGRT	Offline Adaptive RT	Online Adaptive RT
Change in daily target position	Yes		
Systematic target shape change	No	Yes	
Systematic OAR shape change	No	Yes	
Daily target shape change	No	No	Yes
Daily OAR shape change	No	No	Yes

Sparing of organs at risk by online adaptation

- Important for dose-limited treatments

Adapted from Lei Dong

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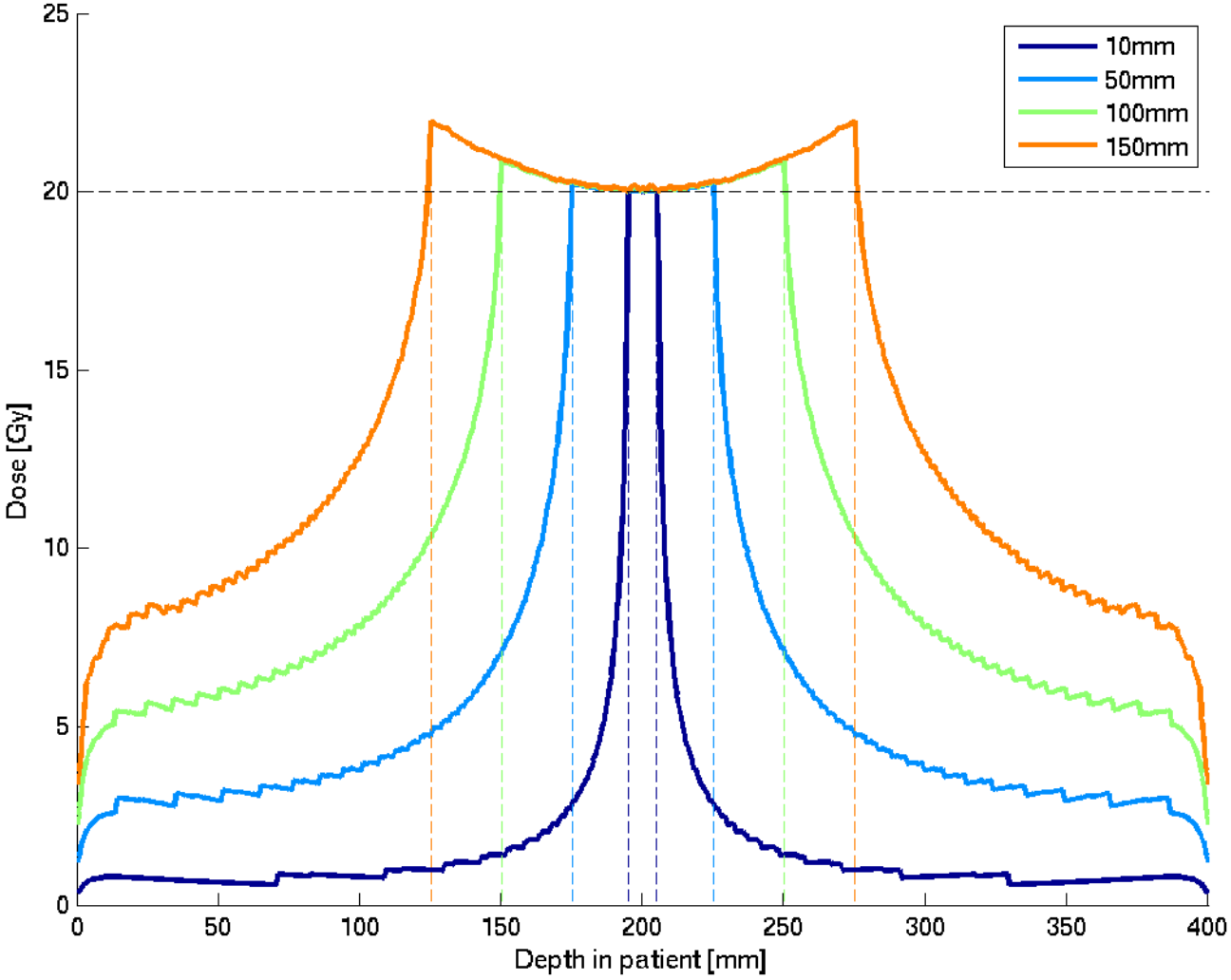
Target-Size Effect



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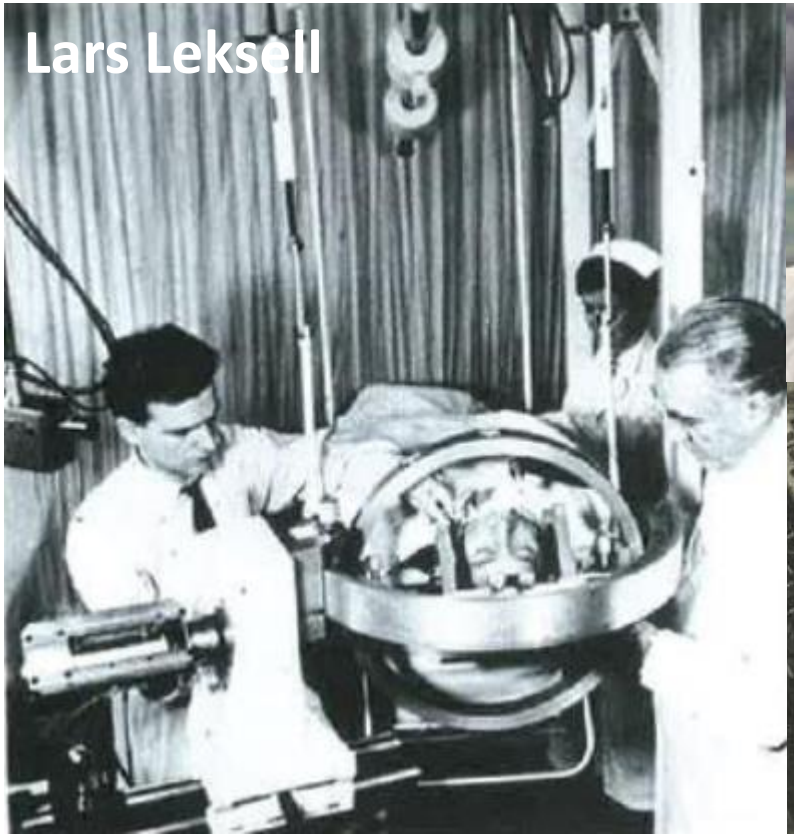

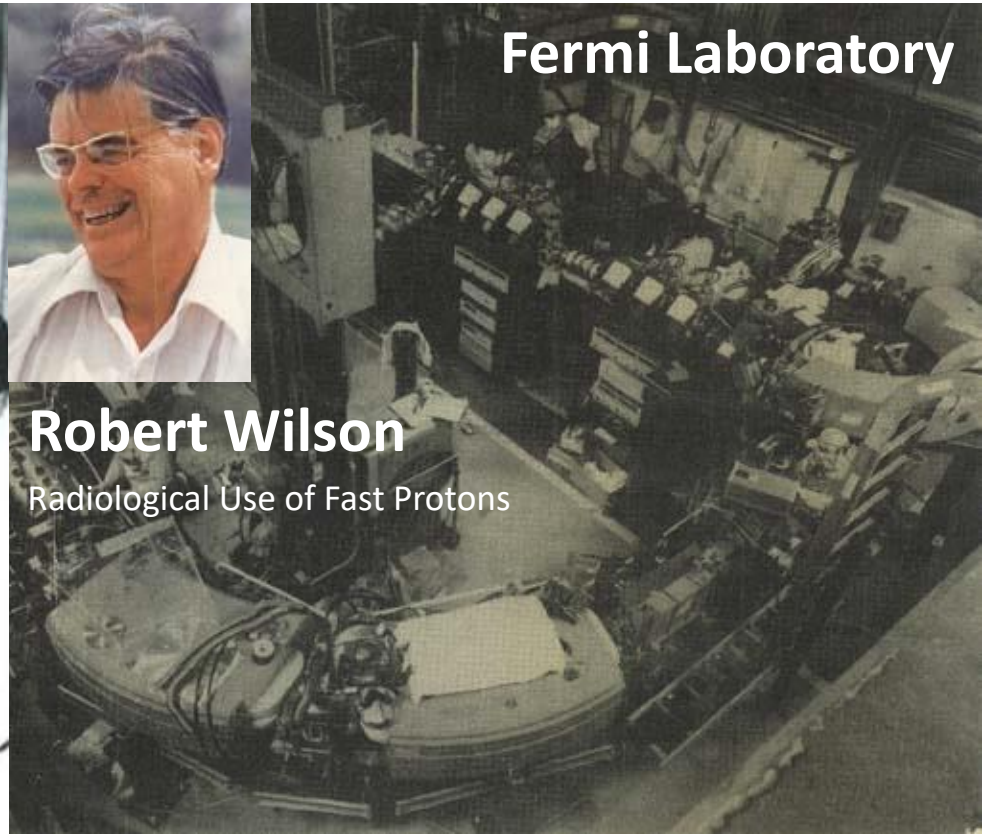

PROTON THERAPY

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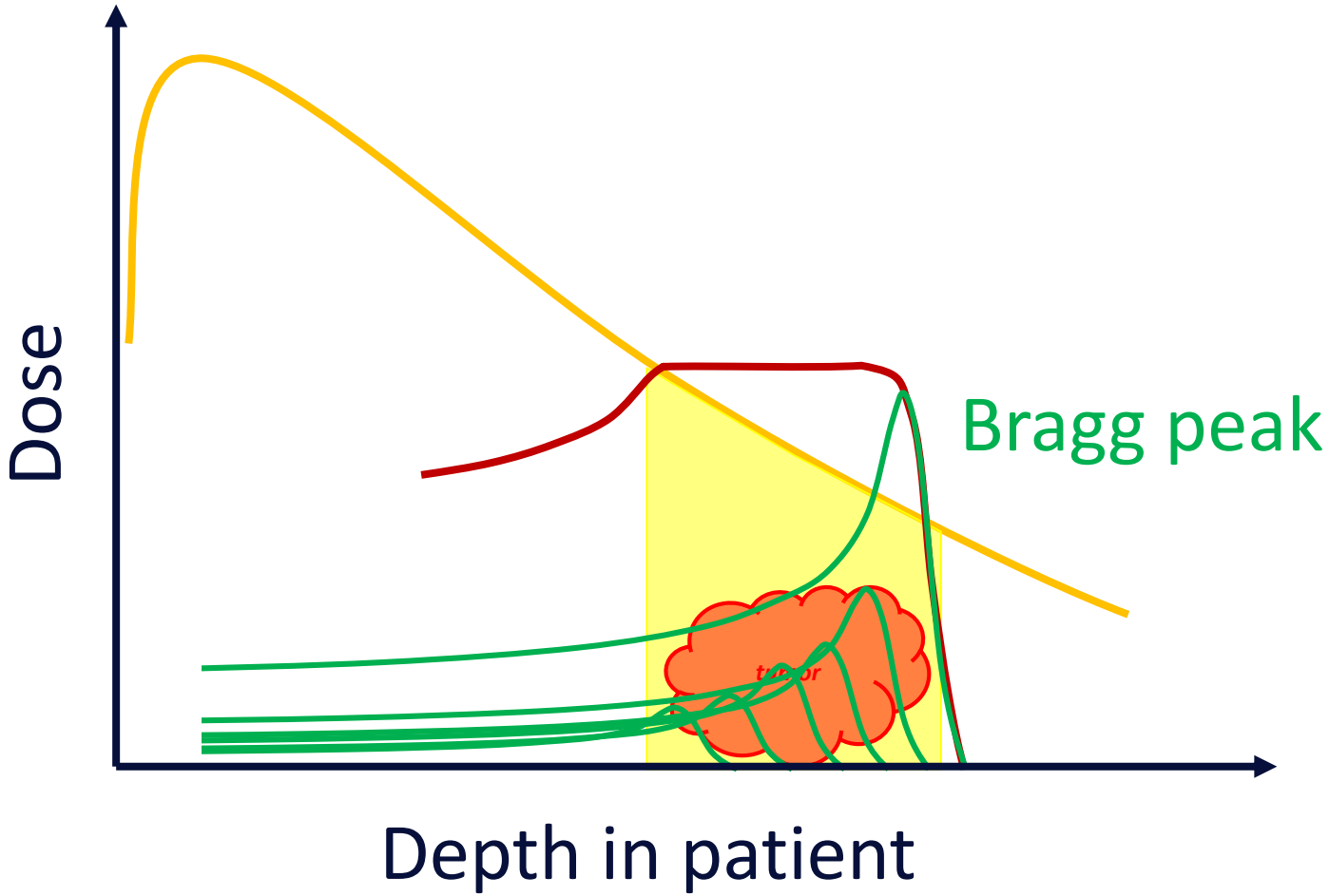
How to Improve Selectivity?



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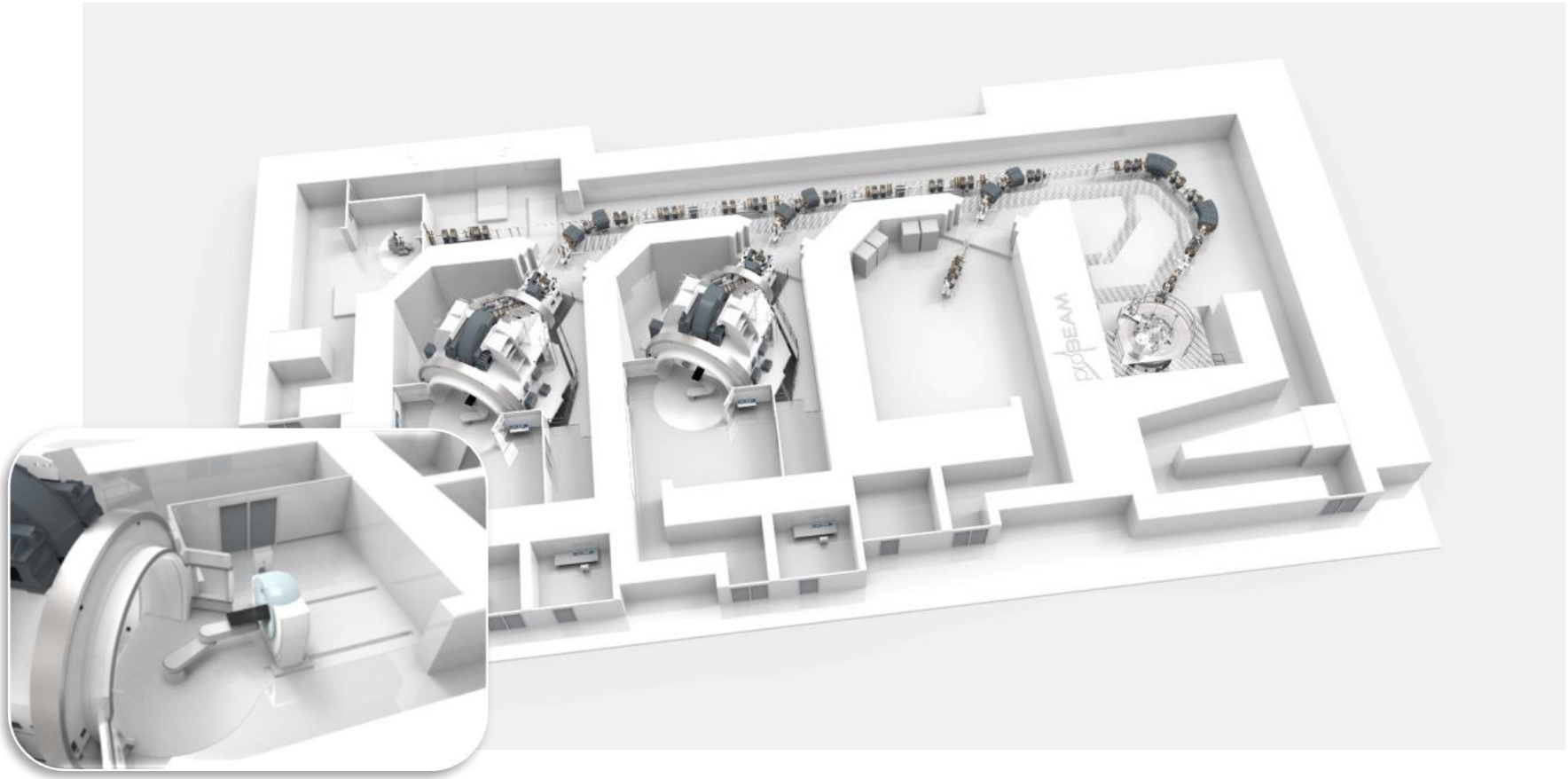
Proton Therapy



medical delta

LUMC
Leids Universitair Medisch Centrum

TU Delft

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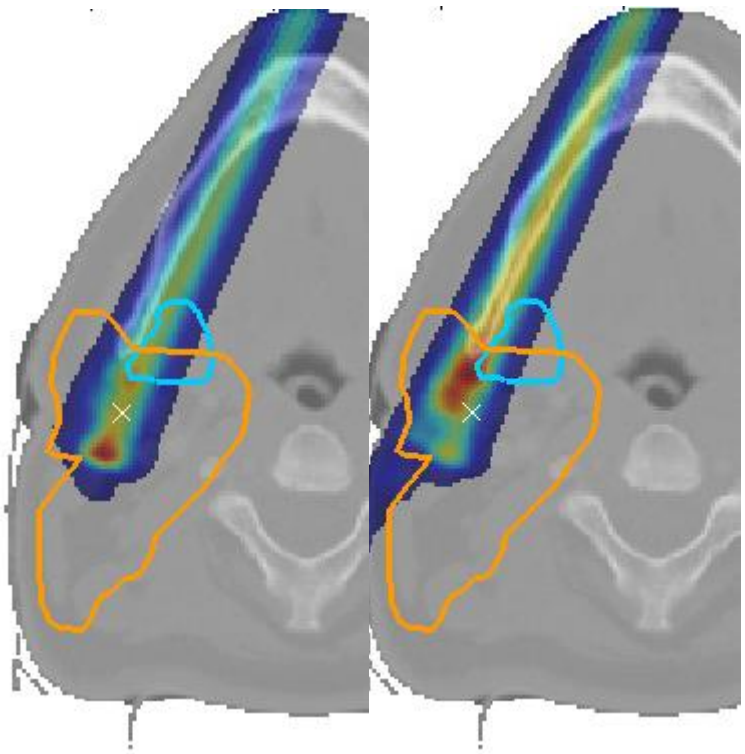
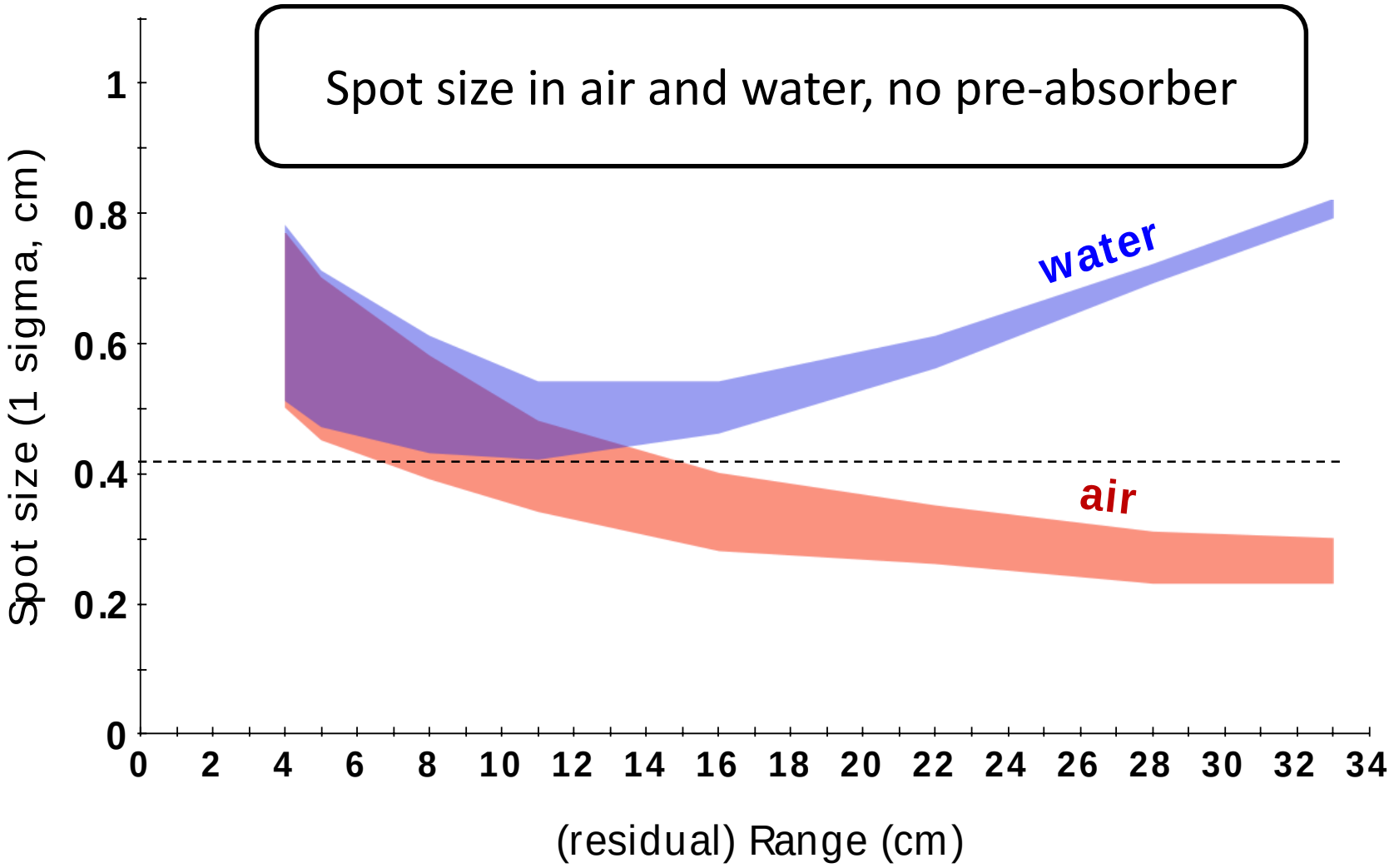
Treatment Uncertainties

- Proton therapy is relatively sensitive for uncertainties in proton range:
  - Patient setup
  - Dose calculation
  - Patient anatomy
  - …

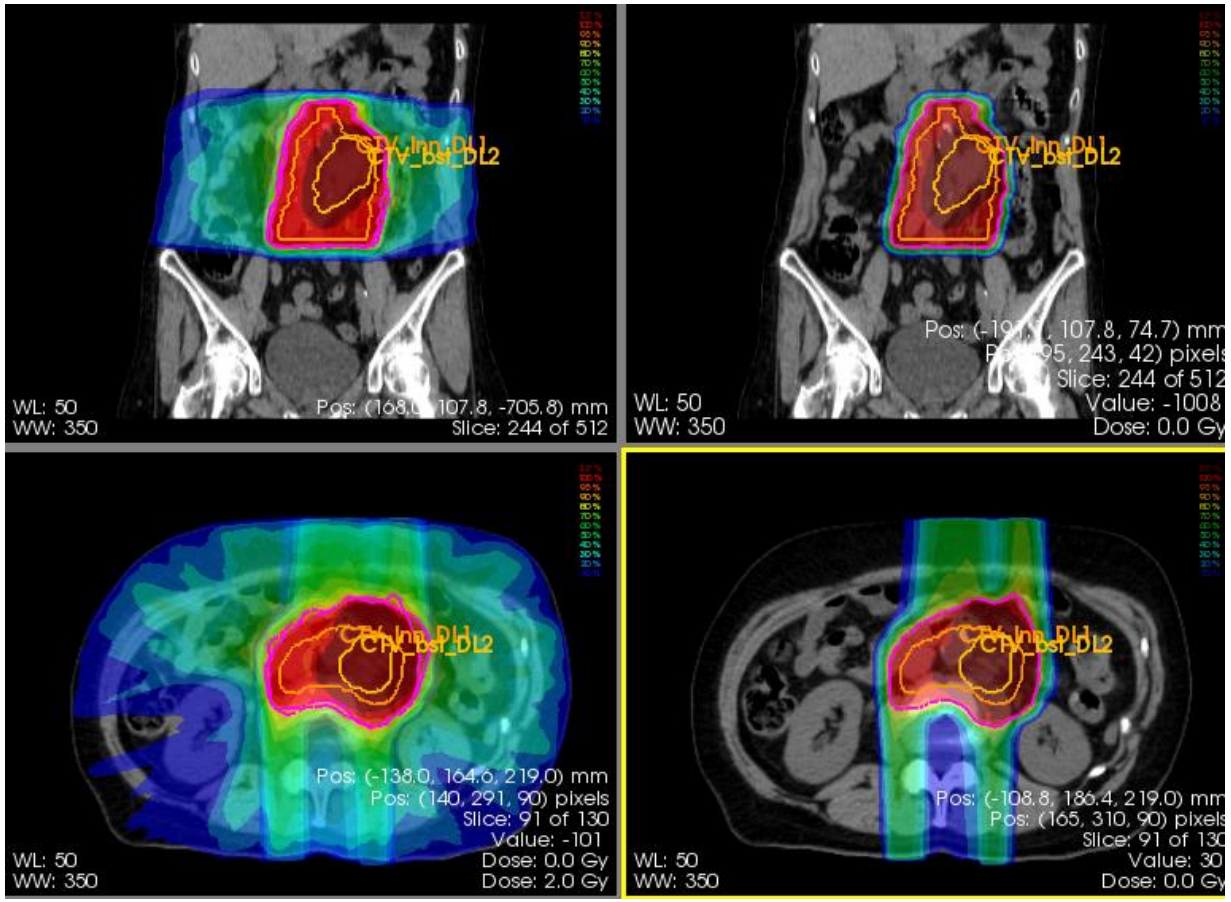


Typical Spot Sizes



Courtesy by M. Engelsman

Photon vs. Proton Radiation Tx



M van de Sande, C Creutzberg, M Hoogeman et al.

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Benefits of Proton Therapy in SRT or SBRT setting

- Large tumors in the liver
- HCC type liver tumors
- Larger early stage tumor in the lung
- Oligo-metastatic disease when integral dose is limiting
- …
- Benign meningioma
- Low grade glioma
- …
- Base of skull tumors
- Ocular melanoma

EVIDENCE AND JUSTIFICATION

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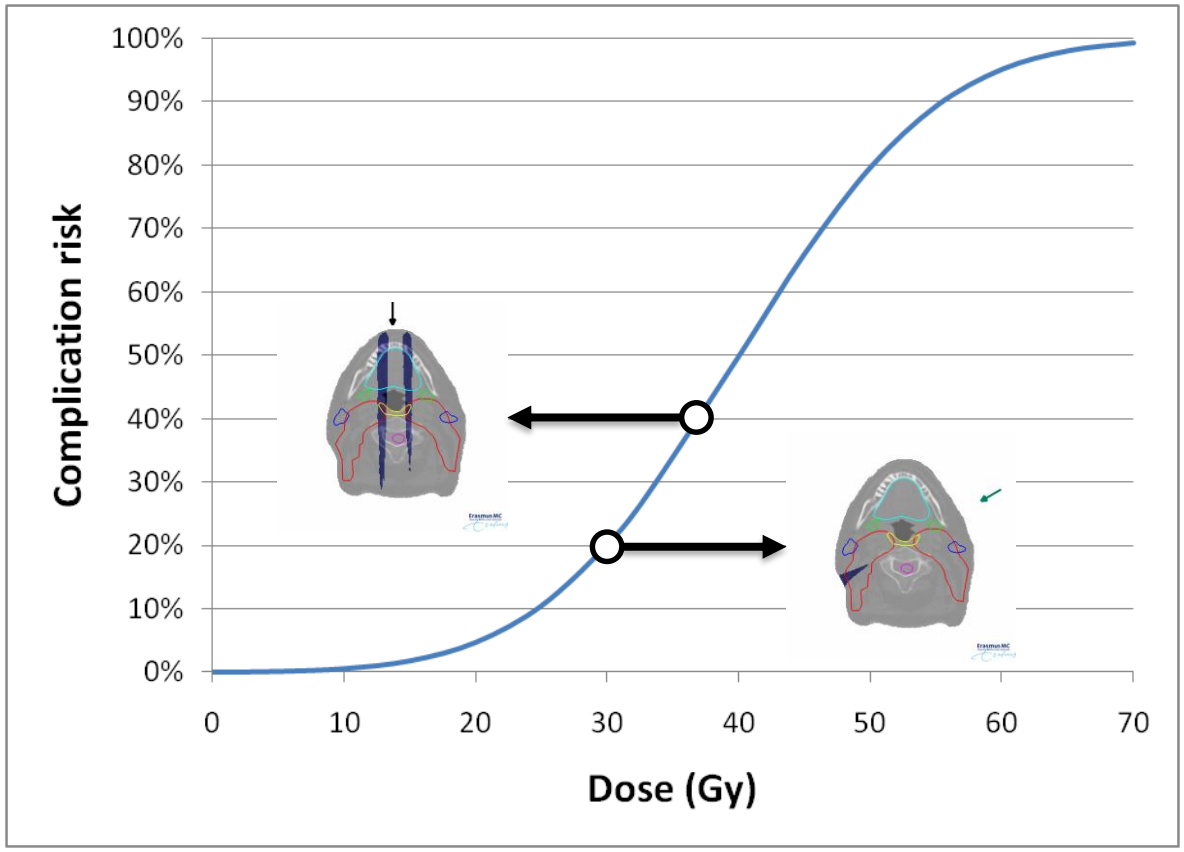
How to Prove the Benefit of Protons or Other Technology?

- Randomized Controlled Trials (RCTs) are the golden standard to proof benefit of competitive treatments
    1. Technology evolves fast and when the outcomes are published the technique has already been outdated
    2. Events are rare or delayed (secondary tumors, cardiac morbidity)
    3. Equipoise is missing if the “experimental” technique is only meant to reduce side effects or the induction of secondary tumors (ALARA: less is better)

ΔNTCP Based Patient Selection



ΔNTCP>10%

Widder J, van der Schaaf A, Lambin P, et al. The Quest for Evidence for Proton Therapy: Model-Based Approach and Precision Medicine. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):30-6.

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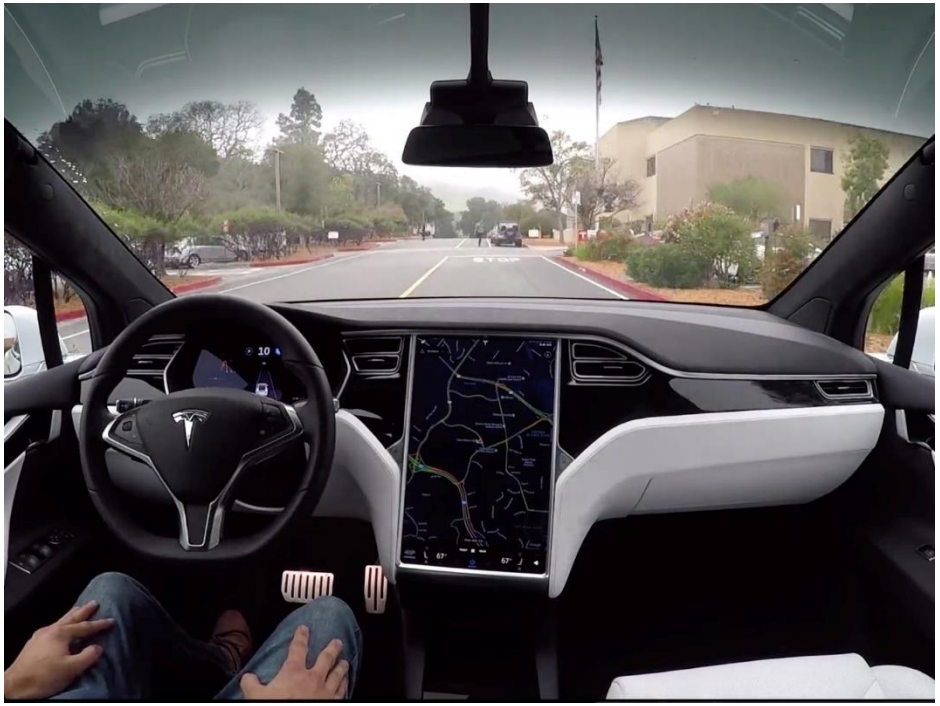

AUTOMATION

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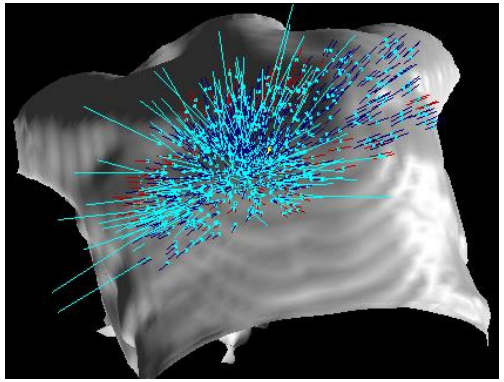
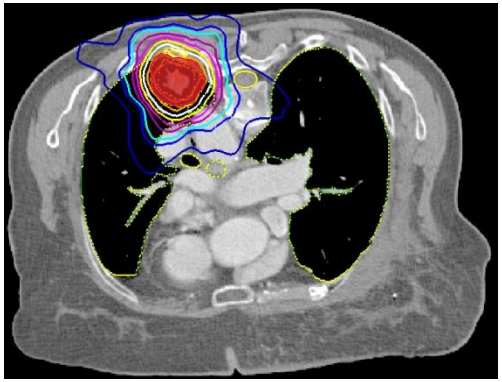
Radiotherapy Workflow





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Automation, Why Not?

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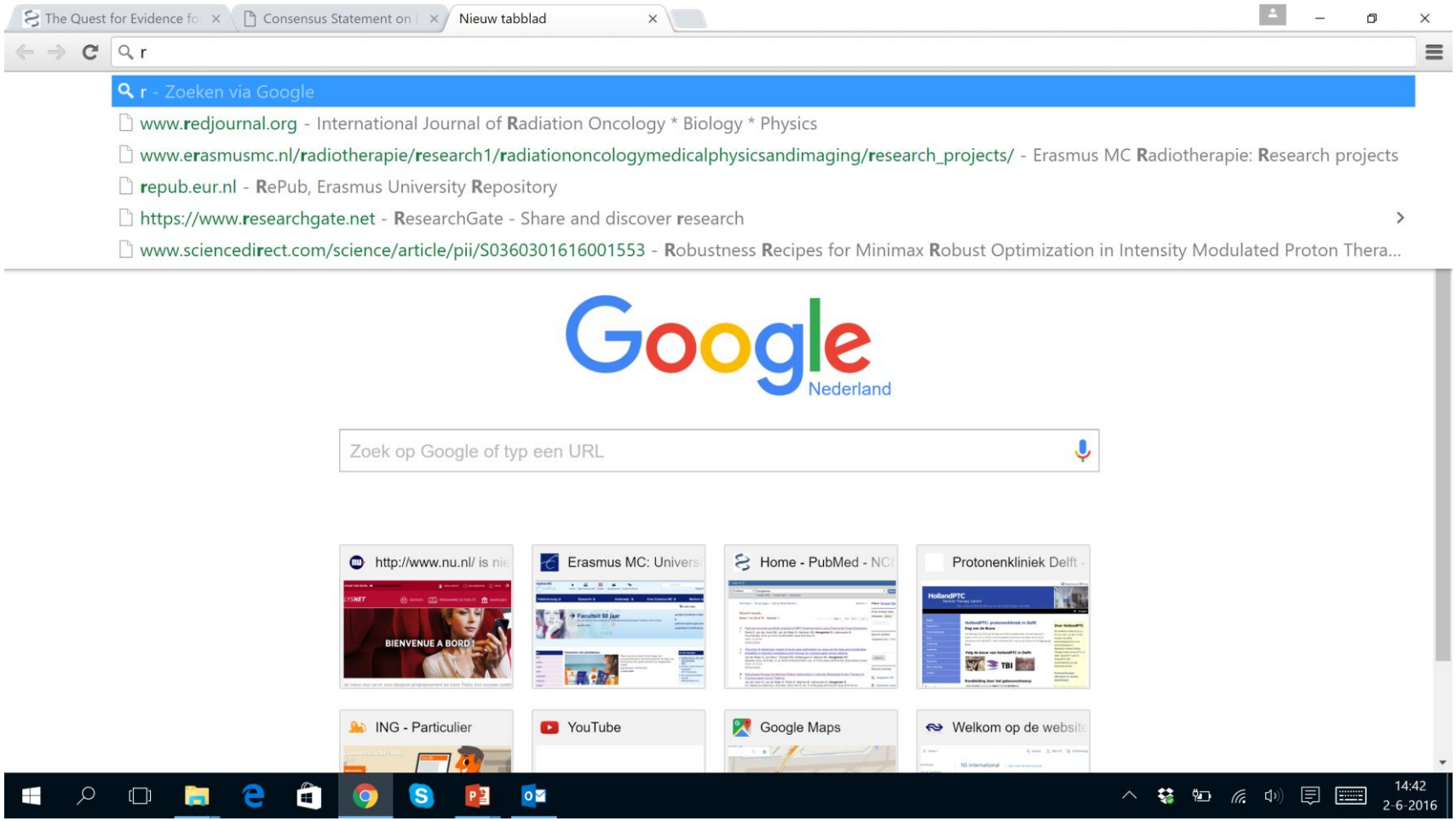
Knowledge-based Automation, Big-data, Machine Learning …



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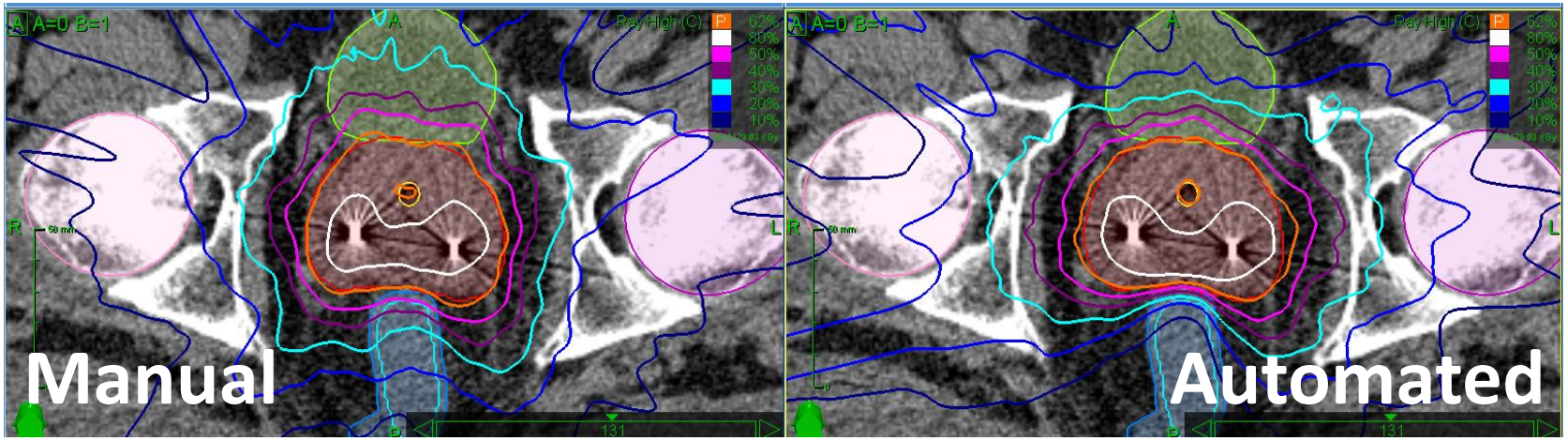
Knowledge Based Automated Treatments

- Knowledge based dose prescription
- Knowledge based auto-segmentation
- Knowledge based automated treatment plan generation
- …

Widen therapeutic window

Lower costs

Does both



Courtesy by Linda Rossi

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Conclusions

- Keep it simple!

- Technology should make life easier, e.g. by simplifying and highly automating treatment workflows
- Radiation therapy should not price itself out of the market

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University Medical Center Rotterdam

Daniel den Hoed
Cancer Center

Errors and Uncertainties in SBRT

Mischa Hoogeman

Learning Objectives

- **To give an overview of errors and uncertainties in stereotactic body radiotherapy**
  - Details on the various errors and uncertainties will be covered in separate lectures

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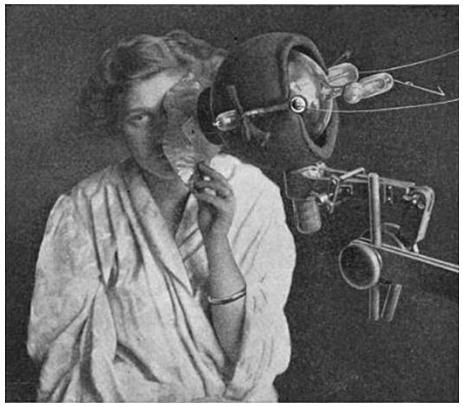
Vendors' Claims of Stereotactic Devices

- "… 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 …"



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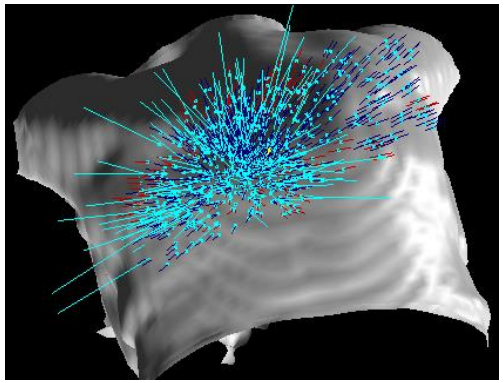
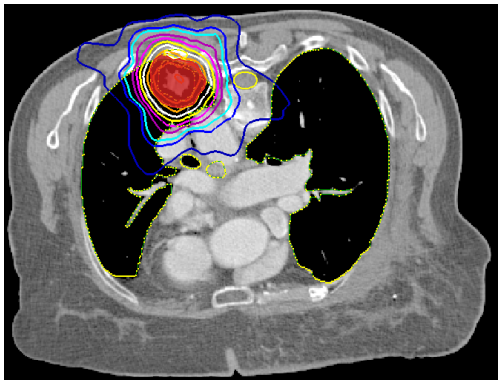
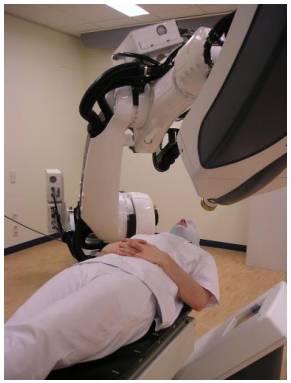
SBRT process

- **Tumor** is being irradiated to a lethal dose
- **Health tissue** is being spared to minimize treatment related damage







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SRT/SBRT 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 and treatment 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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LOCALIZATION

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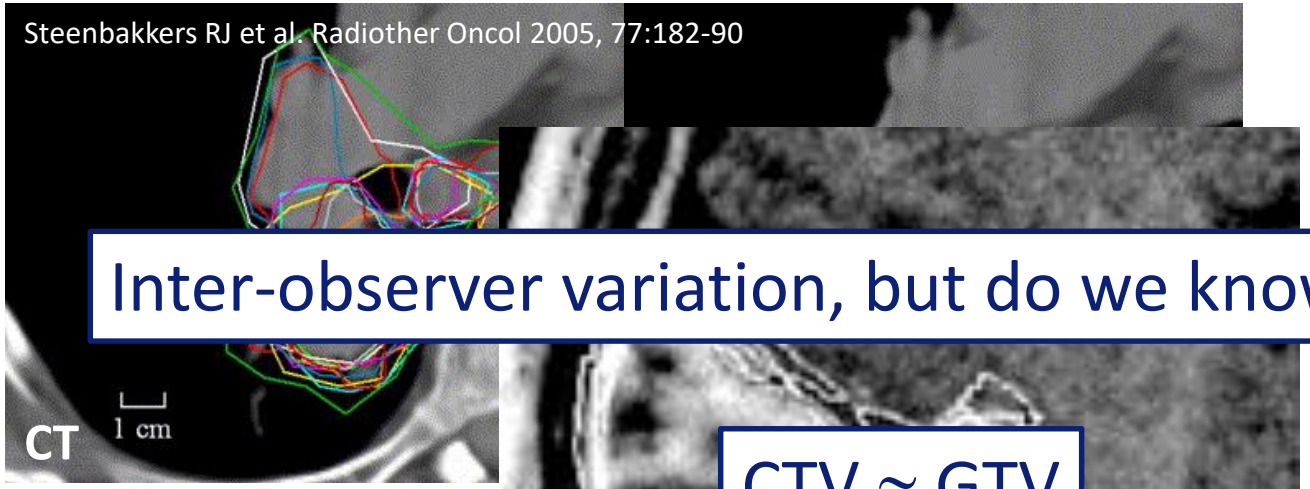
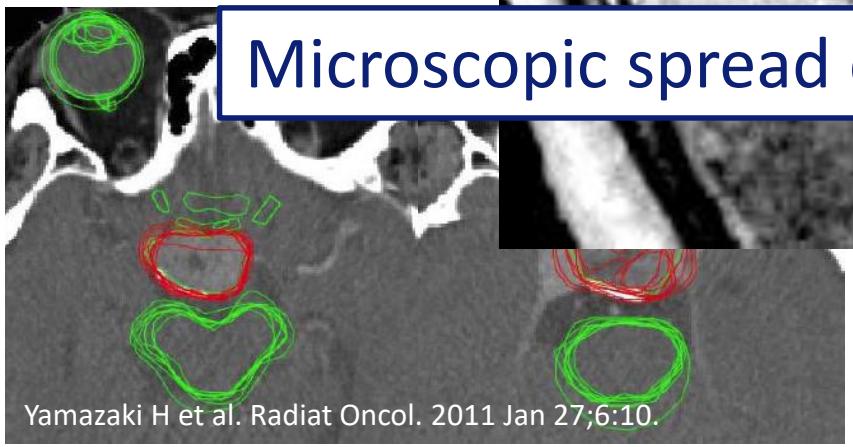
Contouring the Tumor

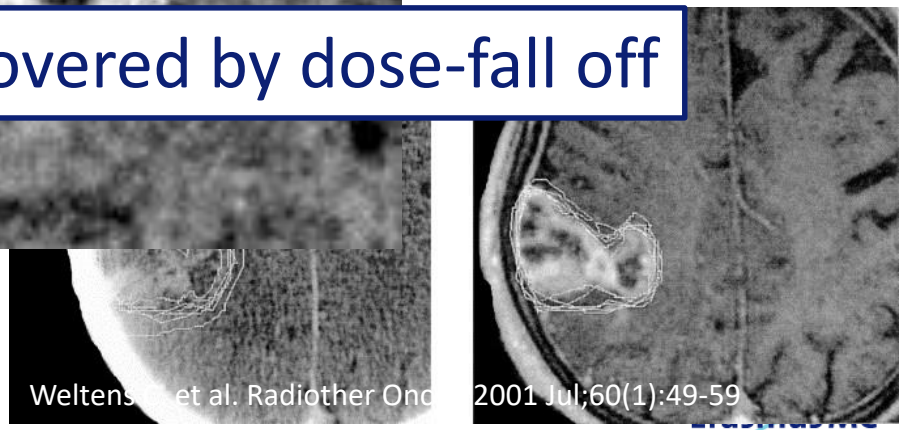


Inter-observer variation, but do we know the truth?

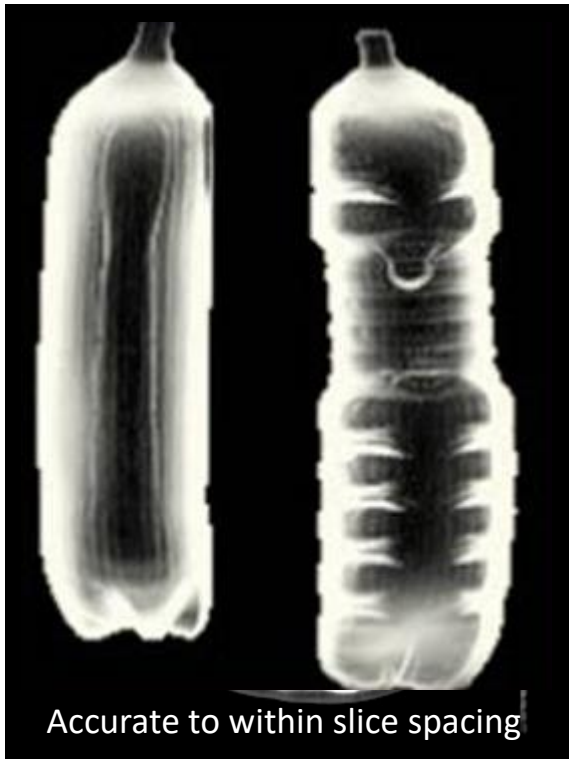
CTV ≈ GTV

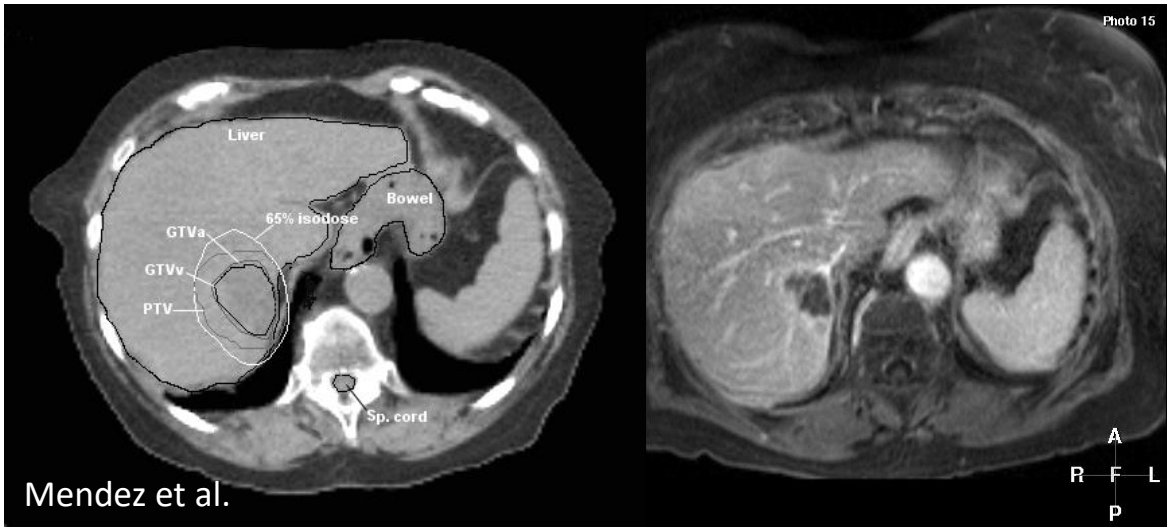


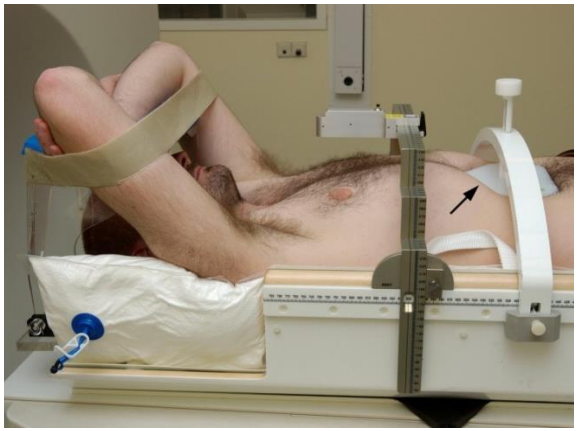
Microscopic spread covered by dose-fall off



Multimodality Imaging and Registration







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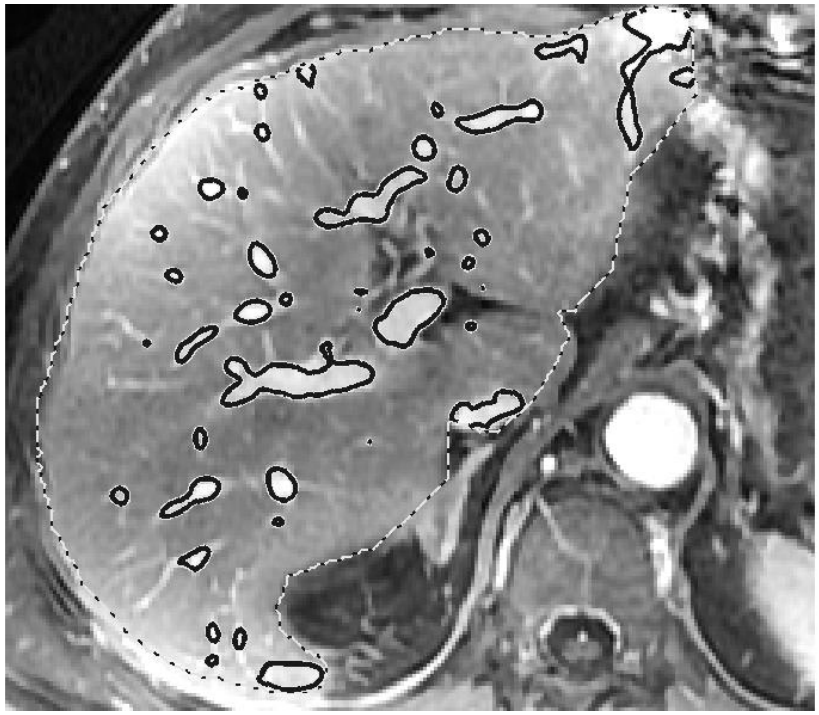
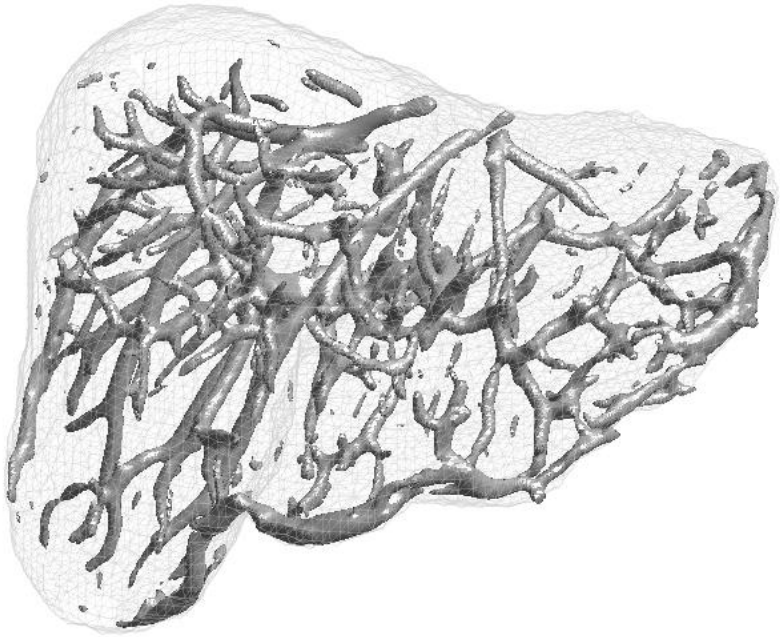
Non-rigid Matching by Vessel Segmentation





Vasquez Osorio E et al. Med Phys. 2012 May;39(5):2463-77

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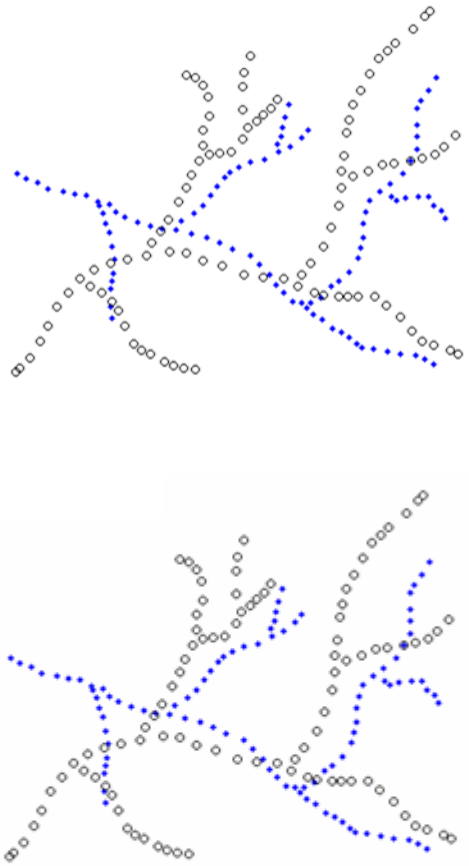
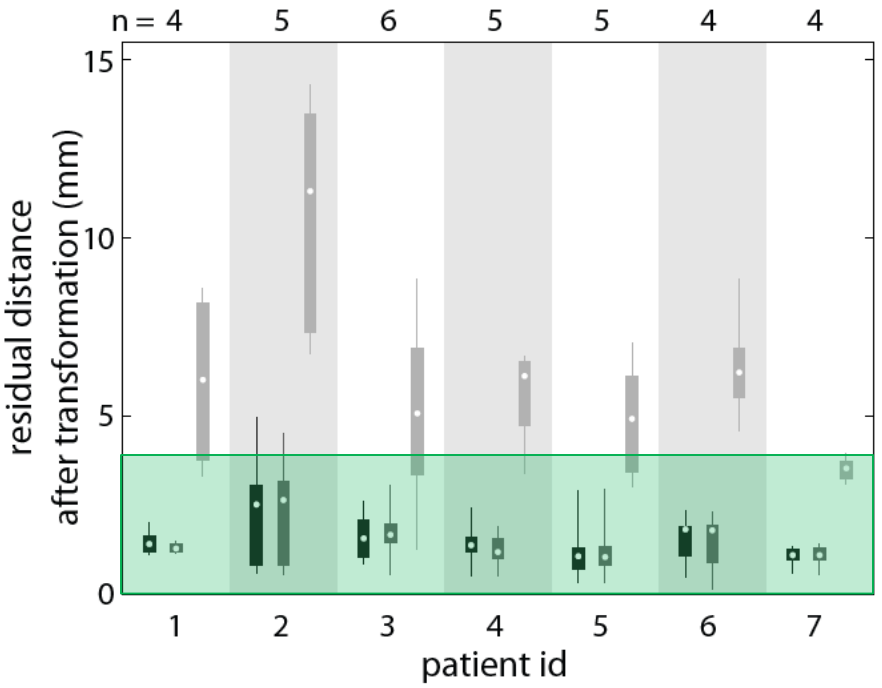
Transformation Error and Anatomical Validation



Anatomical landmarks



Vasquez Osorio E et al. Med Phys. 2012 May;39(5):2463-77

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A Multi-institution Deformable Registration Accuracy Study

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 2, pp. 583–596, 2010
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0360-3016/10/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.06.031

PHYSICS CONTRIBUTION

RESULTS OF A MULTI-INSTITUTION DEFORMABLE REGISTRATION ACCURACY STUDY (MIDRAS)

KRISTY K. BROCK, PH.D., ON BEHALF OF THE DEFORMABLE REGISTRATION ACCURACY CONSORTIUM

Princess Margaret Hospital, University Health Network, Departments of Radiation Oncology and Medical Biophysics, University of Toronto, Toronto, Ontario, Canada

"The range of average absolute error for … and the repeat prostate MRI prostate datasets was 0.5–6.2 mm (LR), 3.1–3.7 mm (AP), and 0.4–2.0 mm (SI)."

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DOSE PRESCRIPTION

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Radiobiology

- SBRT involves the application of high fractional doses in a range not studied in prior decades
  - Conversion of physical dose to biologically equivalent dose (e.g. in 2-Gy fractions)
  - Derived from linear-quadratic model which may not describe all tissue effects
  - Uncertainty in α/β parameter:
    - Prostate: 4 x 9.5 Gy (α/β = 2 ± 1 Gy) => 109 (95 – 133) Gy
  - Uncertainty in normal tissue tolerance (small volumes; high doses)
  - Wide variation on fraction duration, overall treatment time, prescription isodose line: **50-80%** (high dose regions inside tumor)

Stereotactic body radiation therapy: The report of AAPM Task Group 101

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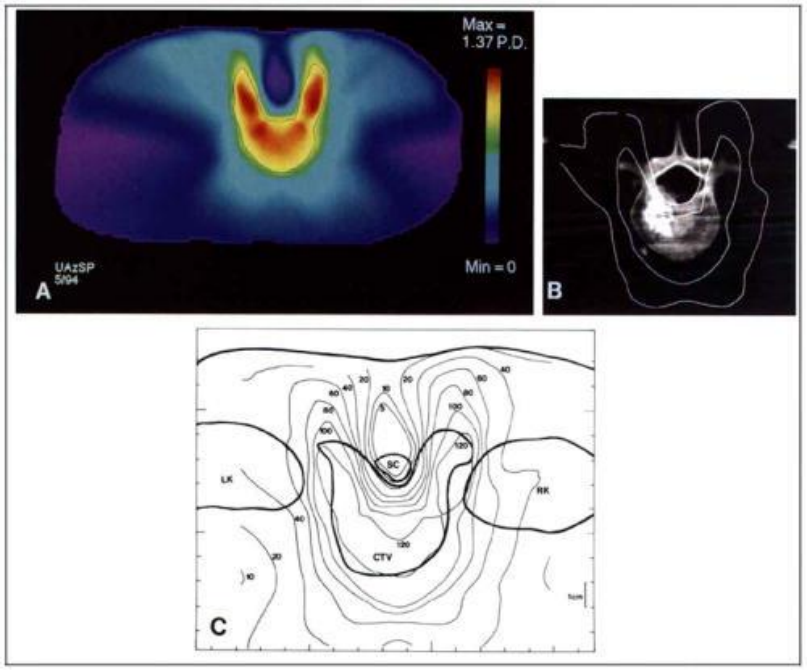
Preliminary Clinical Experience with Linear Accelerator-based Spinal Stereotactic Radiosurgery
Hamilton, Allan J. M.D.; Lulu, Bruce A. Ph.D.; Fosmire, Helen M.D.; Stea, Baldassarre M.D., Ph.D.; Cassady, J. Robert M.D. Volume 36(2), February 1995, p 311–319.



TREATMENT PLANNING

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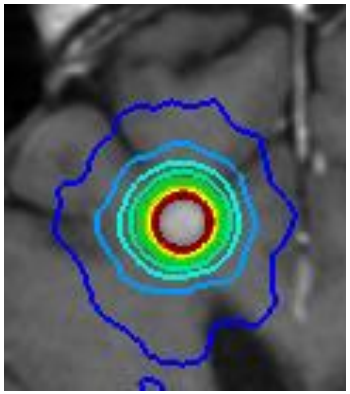
Dose Calculation

- SBRT commonly includes extremely high-dose gradients near the boundary of the target
- AAPM 101 recommendation on calculation grid size:
  - Use an isotropic grid size of 2 mm or finer
  - The use of grid sizes greater than 3 mm is discouraged for SBRT



- **Also commission**
  - Dose-Volume Histogram calculation => segmentation of volume
  - Margin generation algorithm

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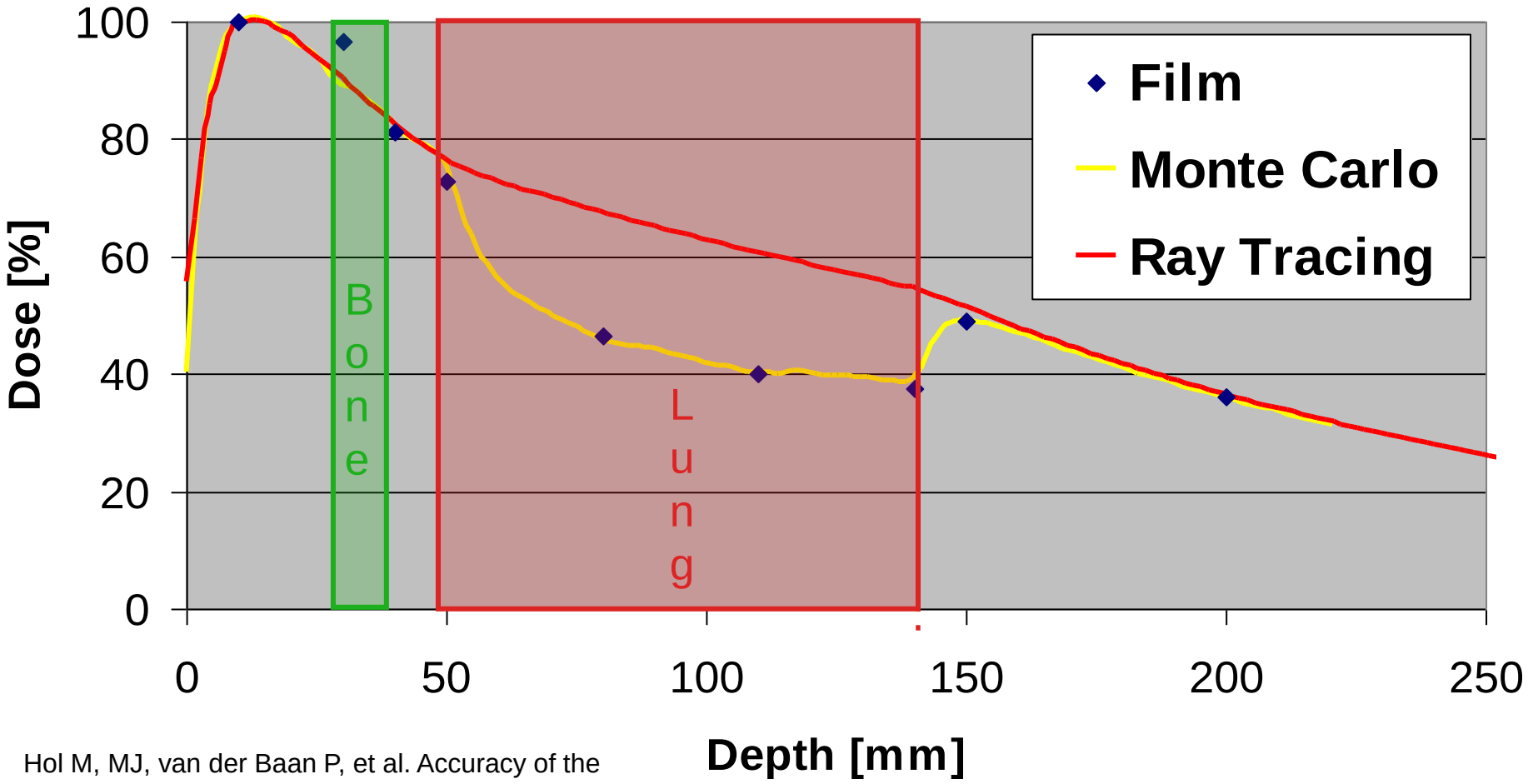
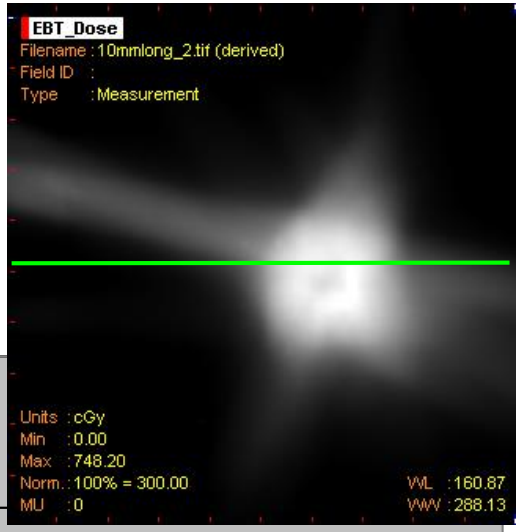
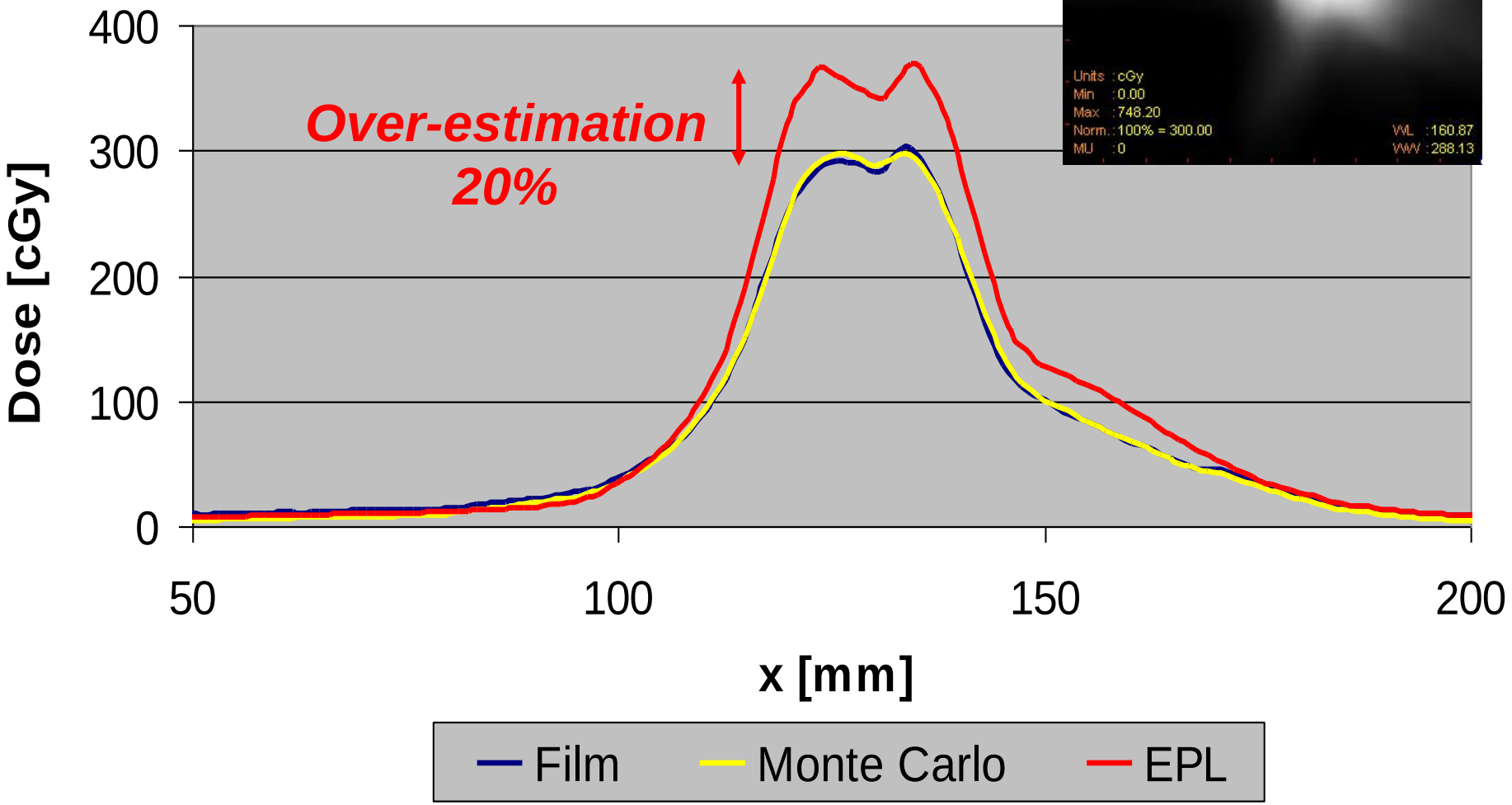
Dose Calculation Algorithm



Hol M, MJ, van der Baan P, et al. Accuracy of the Monte Carlo Dose Calculation Algorithm for Cyberknife Treatment of Small Lung Lesions. Med Phys 2008;35:2953

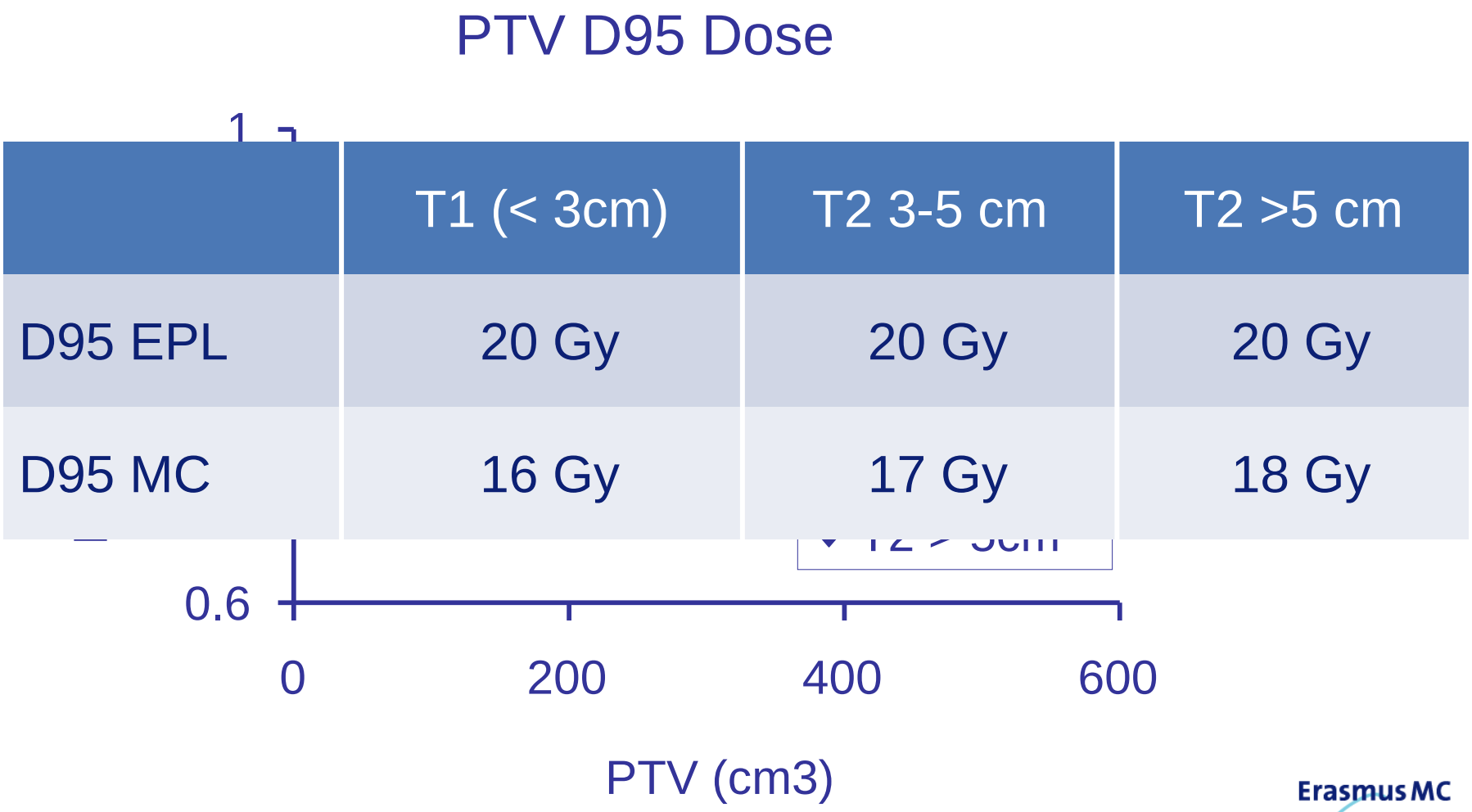
Peripheral 10-mm tumor





Prescription MC/EPL as a Function of PTV

	T1 (< 3cm)	T2 3-5 cm	T2 >5 cm
D95 EPL	20 Gy	20 Gy	20 Gy
D95 MC	16 Gy	17 Gy	18 Gy



van der Voort van Zyp NC et al. Radiother Oncol. 2010 Jul;96(1):55-60. Epub 2010 Apr 27

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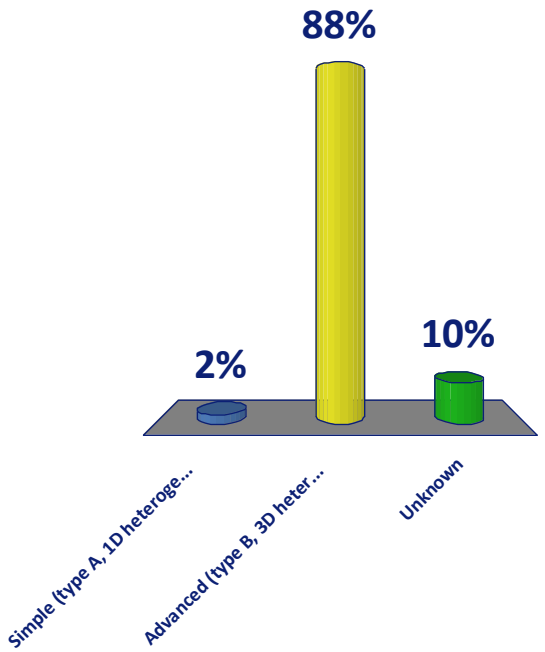
Which dose algorithm will you use (are using) for lung SBRT?

A. **Simple** (type A, 1D heterogeneity correction, e.g. ray tracing, EPL)

B. **Advanced** (type B, 3D heterogeneity correction, e.g. collapsed cone, MC)

C. **Unknown**



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Dosimetry of Small Fields

- Measurement of small photon beams is complicated by
  - loss of lateral electronic equilibrium,
  - volume averaging,
  - detector-interface artifacts,
  - collimator effects,
  - and detector position-orientation effects

- Recommendation: use an appropriate dosimeter with a spatial resolution of approximately 1 mm or better (stereotactic detectors)
- Collimator with a diameter of 5 mm => dose falloff over a radius of 2.5 mm
  - Thickness of 1 euro coin is 2.3 mm!

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Output Factor Correction

- Even with stereotactic detectors, careful detector phantom setup, and detailed dose corrections, one might still find more than 10% discrepancies

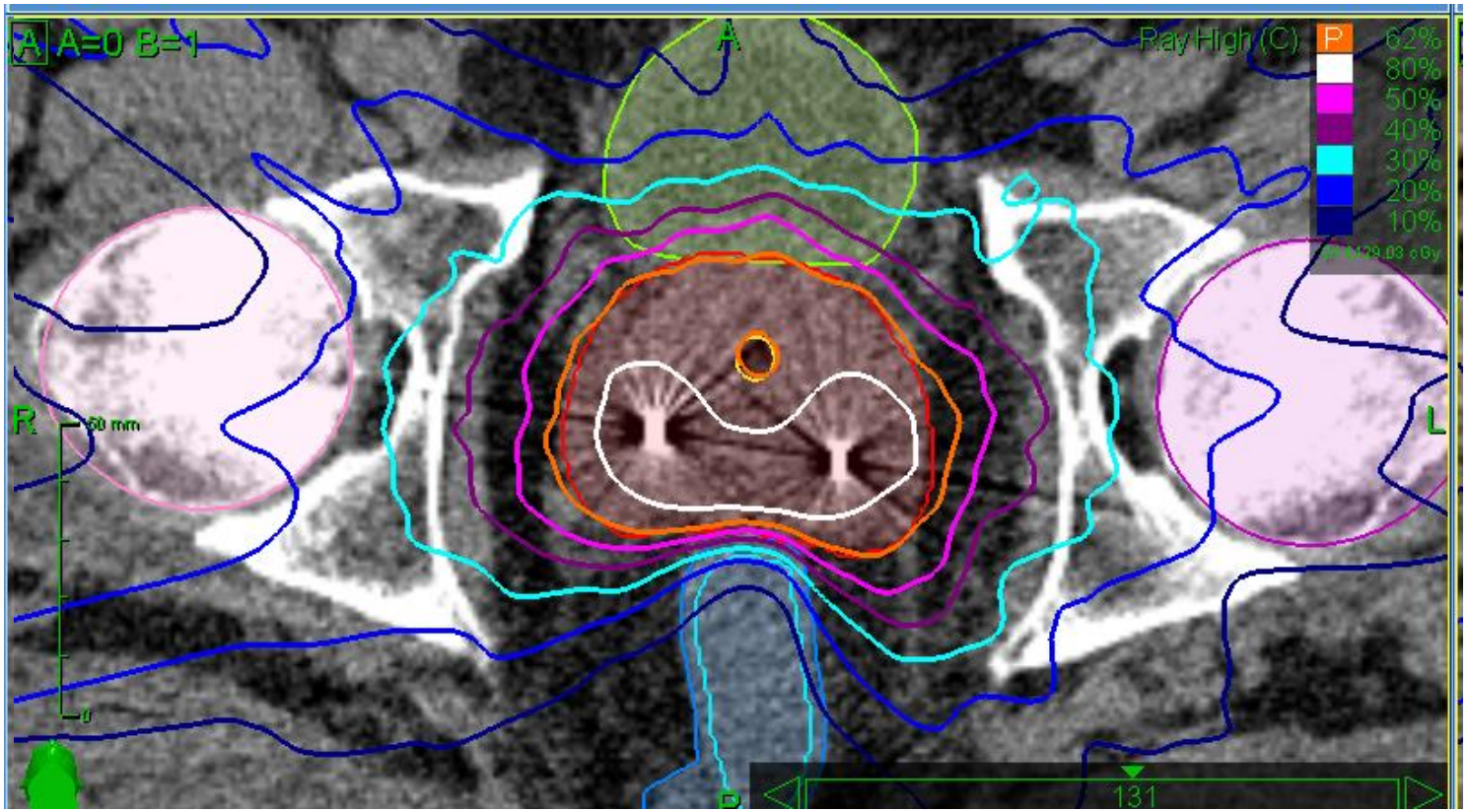
	5 mm	
	Raw $s_{c,p}$	$s^{*}_{c,p}$
A16	0.615	0.675
PinPoint	0.613	0.679
Diode	0.710	0.679
Diamond	0.613	0.677
Mean $s_{c,p}$	0.638	0.677
$\pm 2\sigma$	0.096	0.004

Francescon et al. Med Phys. 2008 Feb;35(2):504-13

Francescon P, Kilby W, Satariano N, Cora S. Monte Carlo simulated correction factors for machine specific reference field dose calibration and output factor measurement using fixed and iris collimators on the CyberKnife system. Phys Med Biol. 2012 Jun 21;57(12):3741-58.

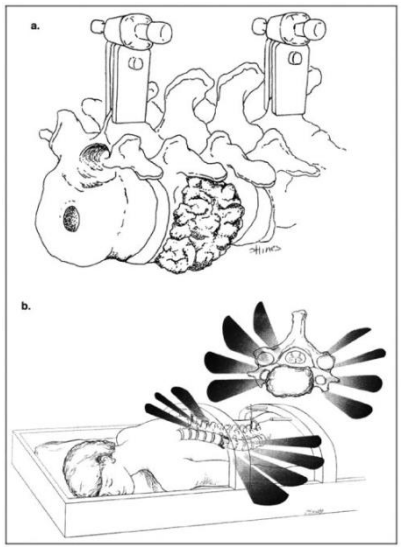
Francescon P, Cora S, Satariano N. Calculation of k(Q(clin),Q(msr)) (f(clin),f(msr)) for several small detectors and for two linear accelerators using Monte Carlo simulations. Med Phys. 2011 Dec;38(12):6513-27

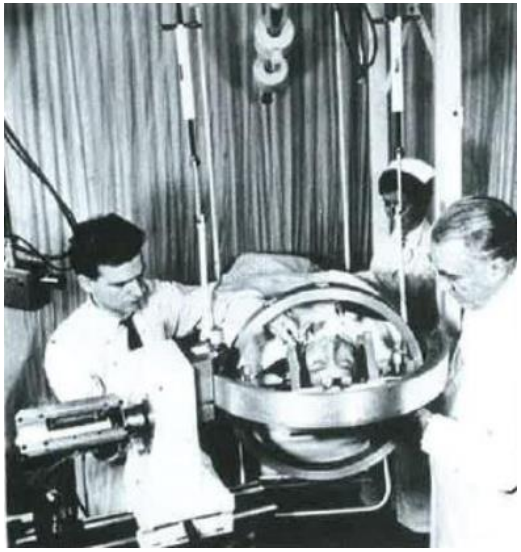
Treatment Plan Quality



Courtesy of Linda Rossi

Erasmus MC





PATIENT SETUP, IMMOBILIZATION, TARGET LOCALIZATION, AND DELIVERY

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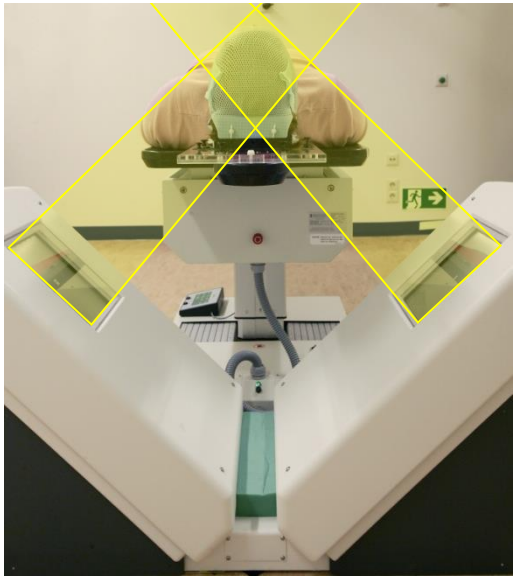
From CT to LINAC: Image-based Alignments (Frameless)

3D to 3D



2D to 3D

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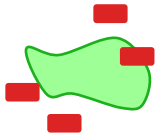

MARKERS AS SURROGATE

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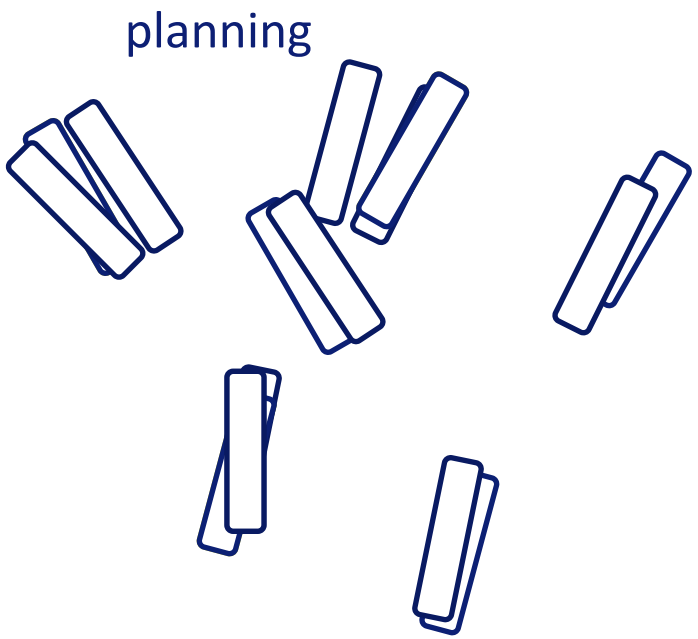
Deformation in Marker Configuration



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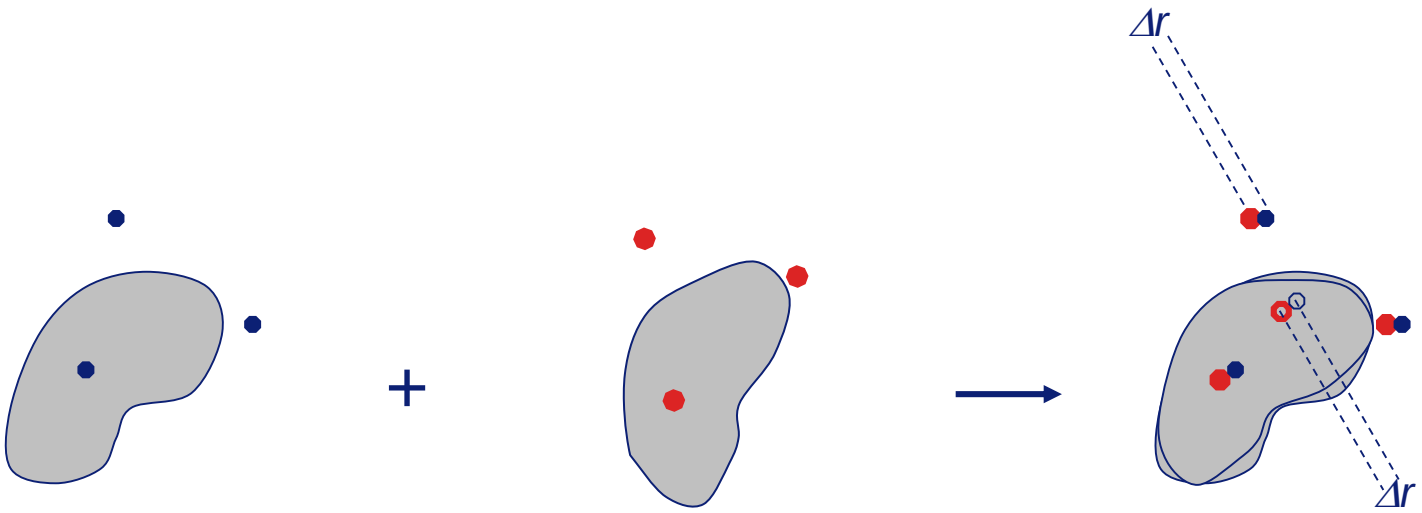
Assessing Marker Stability



Planning CT-scan Repeat CT-scan Registered CT-scans

→ Distance between the COM of marker configurations

→ Change in distance between pairs of markers

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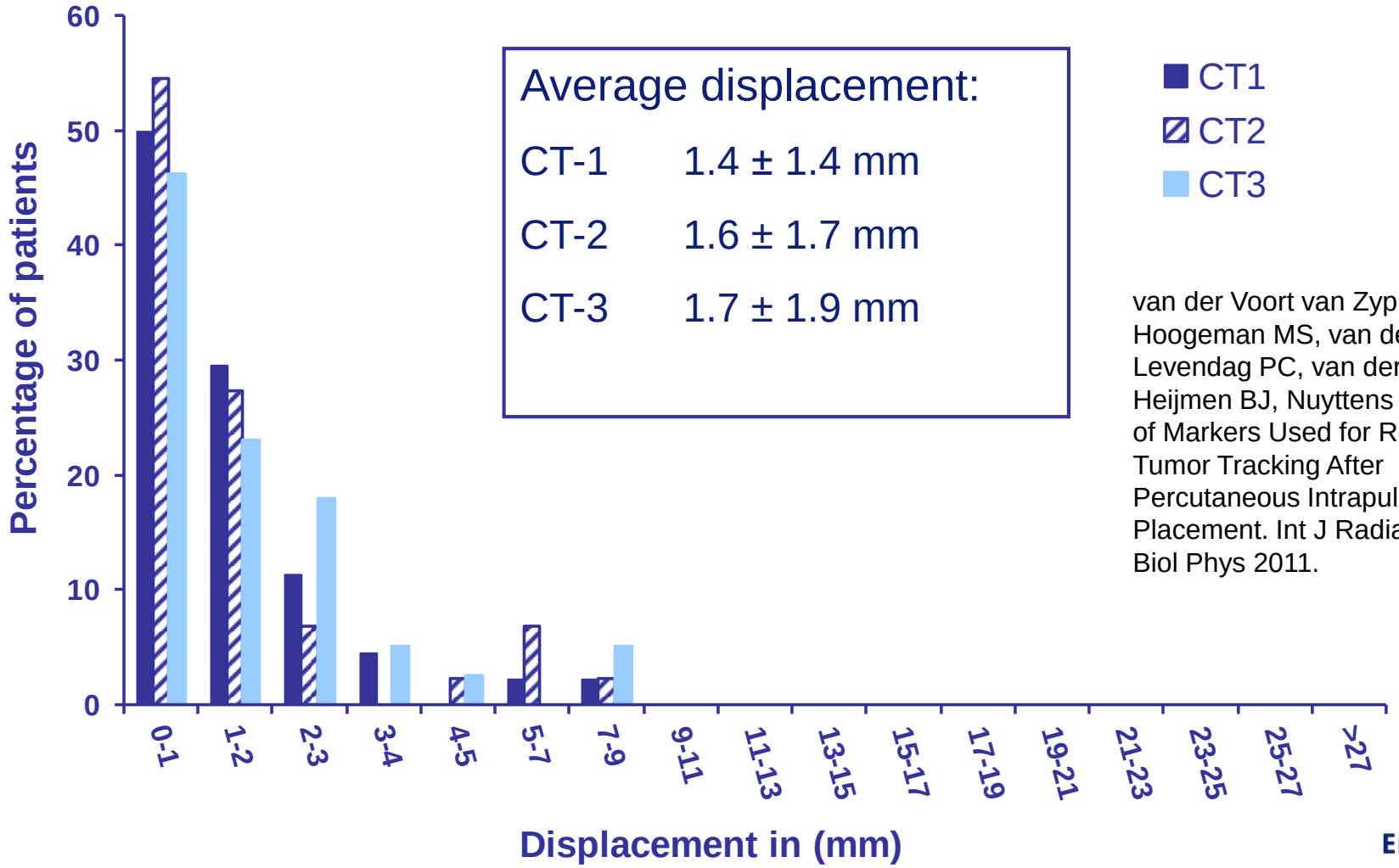
Displacement of the COM of Marker Configurations



Average displacement:

CT-1	1.4 ± 1.4 mm
CT-2	1.6 ± 1.7 mm
CT-3	1.7 ± 1.9 mm

van der Voort van Zyp NC, Hoogeman MS, van de Water S, Levendag PC, van der Holt B, Heijmen BJ, Nuyttens JJ. Stability of Markers Used for Real-Time Tumor Tracking After Percutaneous Intrapulmonary Placement. Int J Radiat Oncol Biol Phys 2011.

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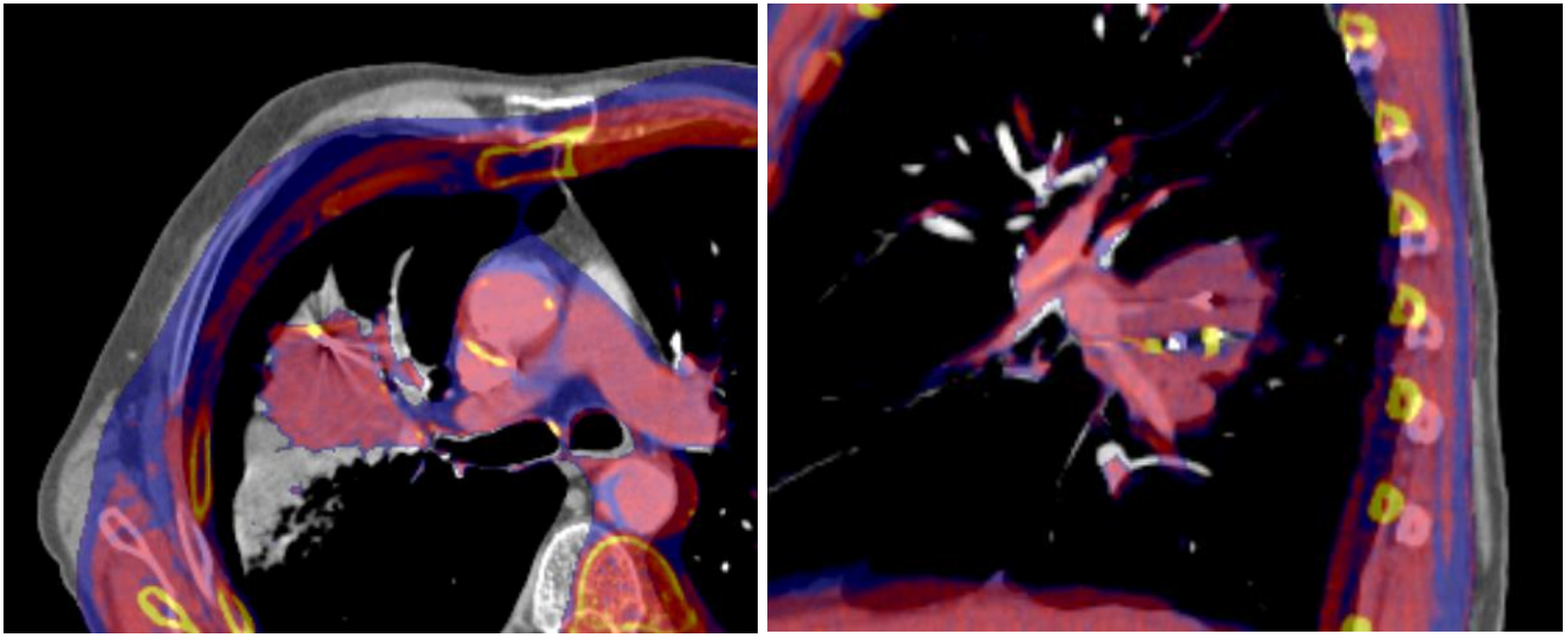
Examples of displacements in COM ≥ 3 mm



Evident migration in 1 patient

Insert 3 markers

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Non-Synchronous Motion Between Markers and Tumor

- Accurate tumor tracking requires a 4D CT scan to select markers moving synchronous to the tumor

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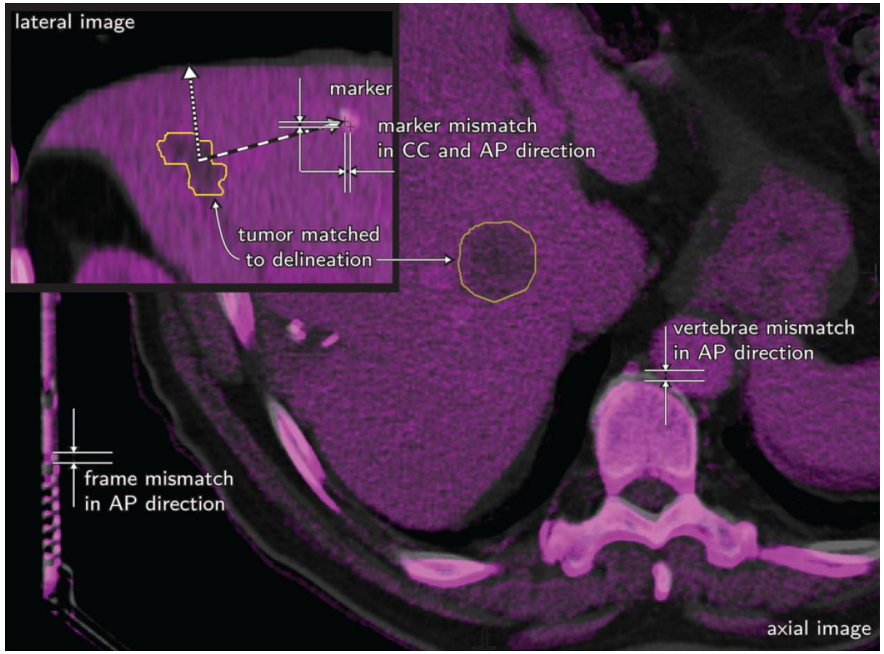
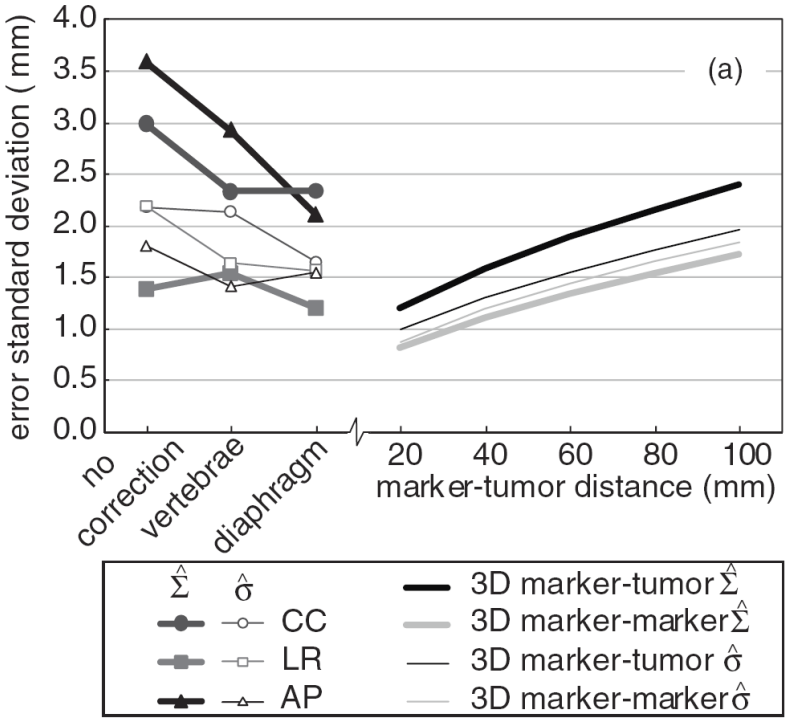
Liver Tumor Surrogates





Seppenwoolde Y, Wunderink W et al. Phys. Med. Biol. **56 (2011) 5445–5468**

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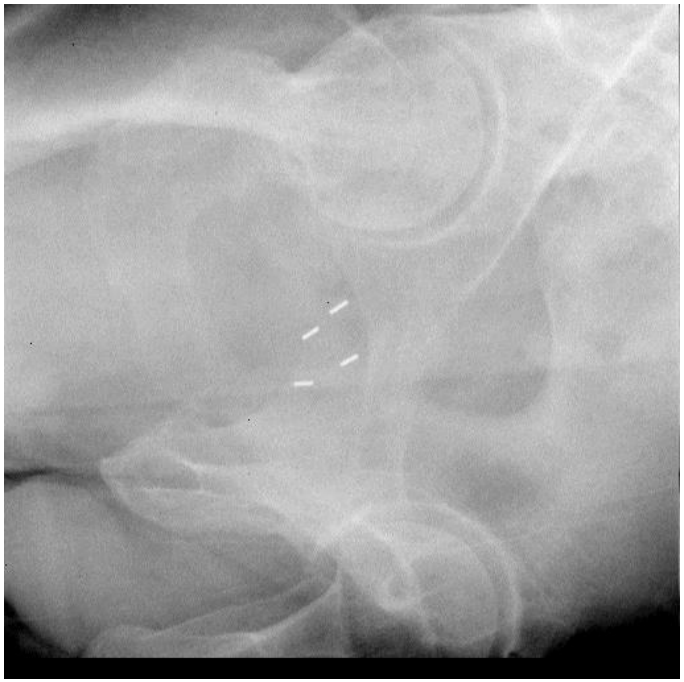
Inter-Fraction and Intra-Fraction Errors

- Inter-fraction: daily tumor alignment
- Intra-fraction: tumor alignment during fraction



Hoogeman et al. Radiother Oncol. 2005; 74:177-85

=> Monday morning talks

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TREATMENT DEVICES

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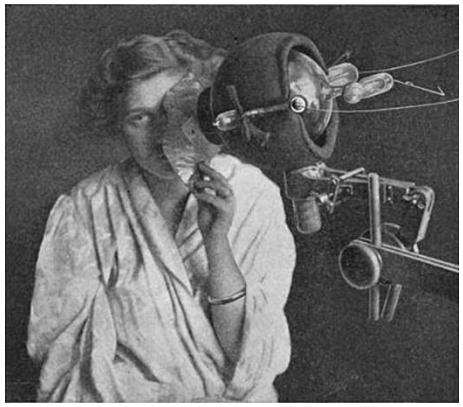
Vendors' Claims of Stereotactic Devices

- "… 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 …"



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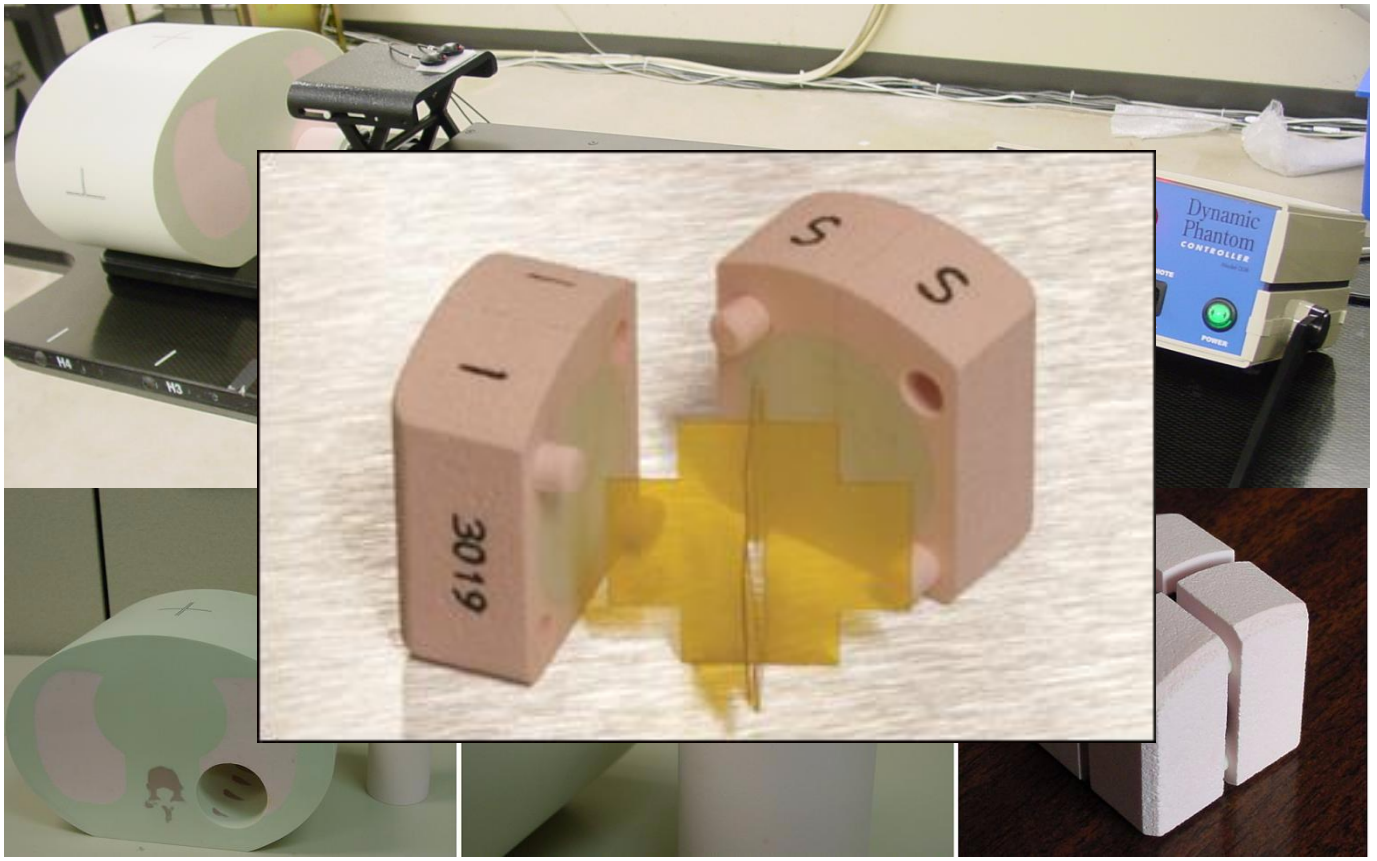
E2E Tests: Direct Target Localization (Xsight Lung Tracking)



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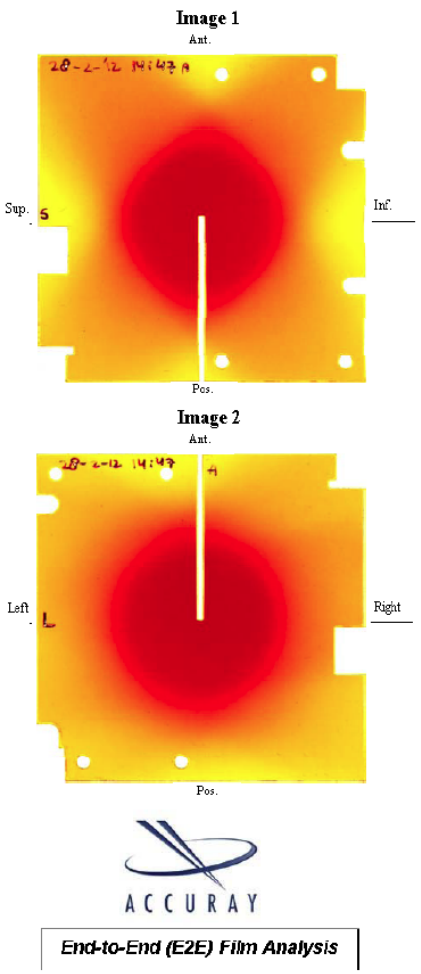
Analysis of Tracking Error



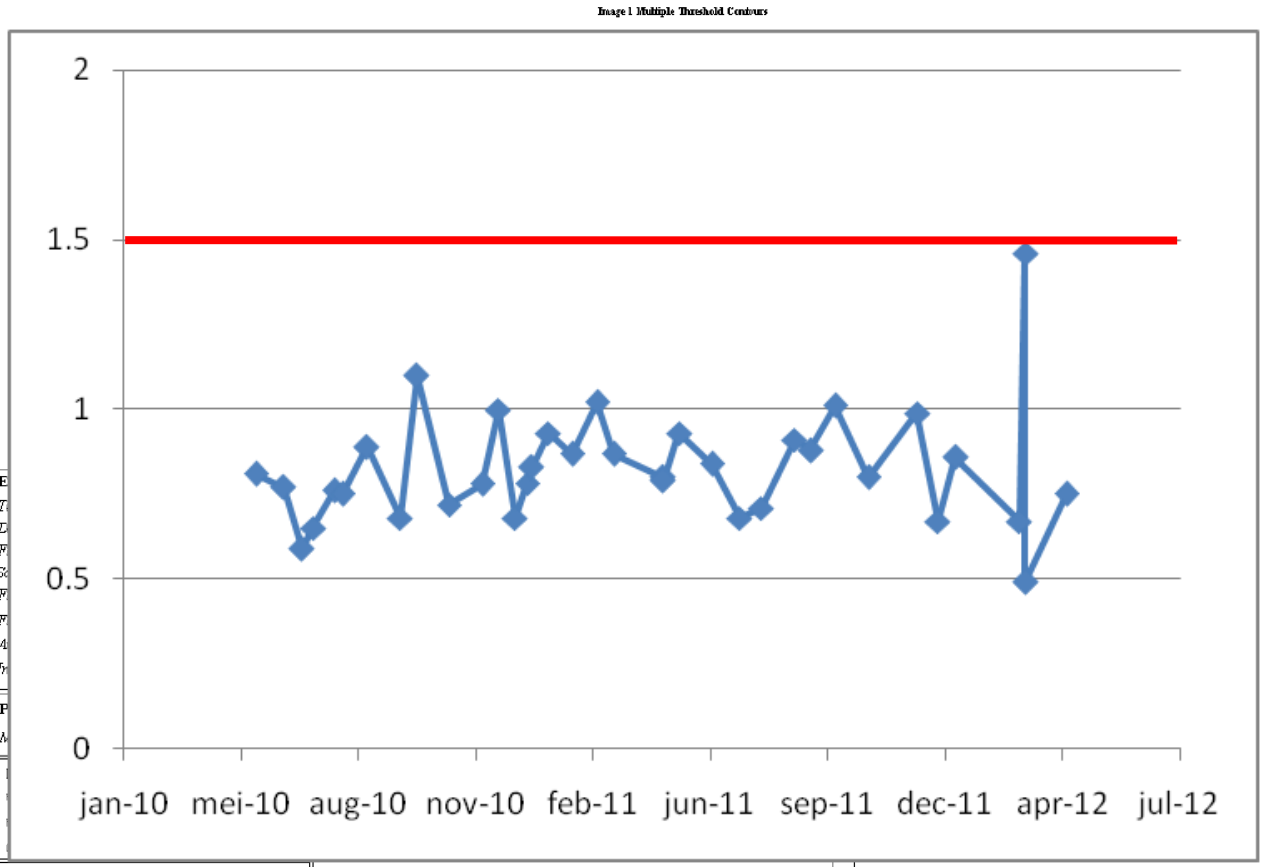


Image 2 (A/L Image)	
mm from left edge:	31.23
mm from anterior edge:	32.09
contour area/ball area:	1.15

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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CONCLUSIONS

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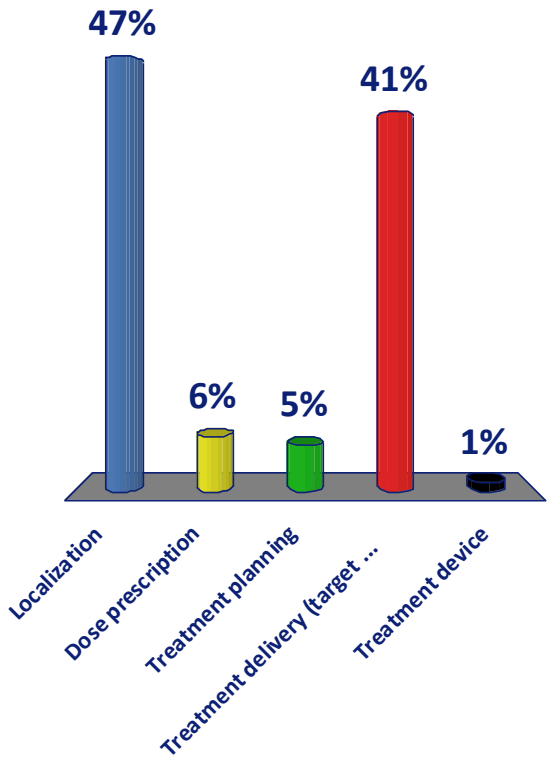
Which type of error is clinically most significant?

A. Localization
B. Dose prescription
C. Treatment planning
D. Treatment delivery (target motion …)
E. Treatment device



Erasmus MC

Erasmus MC
University Medical Center Rotterdam

Daniel den Hoed
Cancer Center

Margins in SBRT

Mischa Hoogeman

Learning Objectives

- **To give an overview of margin concepts**
  - Why do we use or need margins?
  - To provide a qualitative understanding of a margin recipe
  - To provide an overview of assumptions being made in the derivations of the van Herk margin recipe
- **To discuss applicability of "conventional" margin concepts in hypo-fractionated / single fraction SBRT**
  - To discuss the effect of a limited number of fractions on random error
    - Explain why a random error for hypofractionated treatments results in a systematic error
    - Explain how to calculate margins for single fraction and hypofractionated treatment and provide some practical examples
    - How to add errors?
- **To discuss margins for tumors that move with respiration**
- **To give suggestions for further reading**

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MARGIN CONCEPTS

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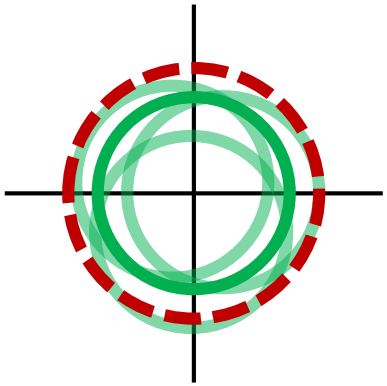
Why do we use margins?

- **Target / tumor**
  - To **a-priori** compensate for deviations between the intended target position and the real target position during dose delivery
  - Deviations are **estimated** from population-based measurements of geometrical errors (can be patient specific, e.g. respiratory motion)



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How large should the margin be?

- **What is the incentive?**
  - 99% of the target volume receives 95% of the prescribed dose or more (coverage probability) - **Stroom et al.**
  - 90% of patients in the population receives a minimum cumulative CTV dose of at least 95% of the prescribed dose - **van Herk et al.**

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PII S0360-3016(98)00468-4

PHYSICS CONTRIBUTION

INCLUSION OF GEOMETRICAL UNCERTAINTIES IN RADIOTHERAPY TREATMENT PLANNING BY MEANS OF COVERAGE PROBABILITY

Joep C. Stroom, M.Sc.,* Hans C. J. de Boer, M.Sc.,* Henk Huizenga, Ph.D.,† and Andries G. Visser, Ph.D.*

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Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 4, pp. 1121–1135, 2000
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0360-3016/00/$–see front matter

PII S0360-3016(00)00518-6

PHYSICS CONTRIBUTIONS

THE PROBABILITY OF CORRECT TARGET DOSAGE: DOSE-POPULATION HISTOGRAMS FOR DERIVING TREATMENT MARGINS IN RADIOTHERAPY

Marcel van Herk, Ph.D., Peter Remeijer, Ph.D., Coen Rasch, M.D, and Joos V. Lebesque, M.D., Ph.D.

Erasmus MC

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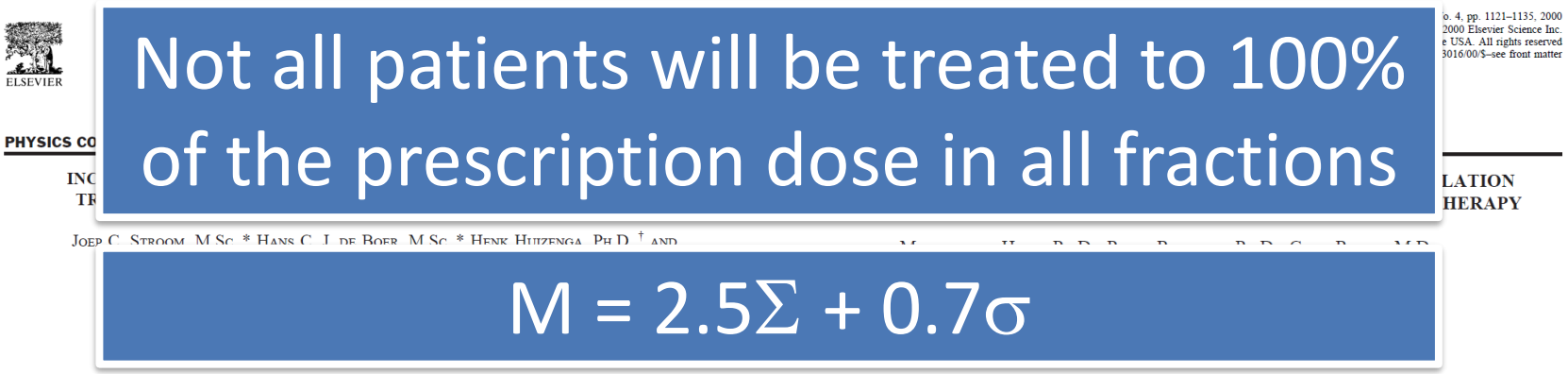

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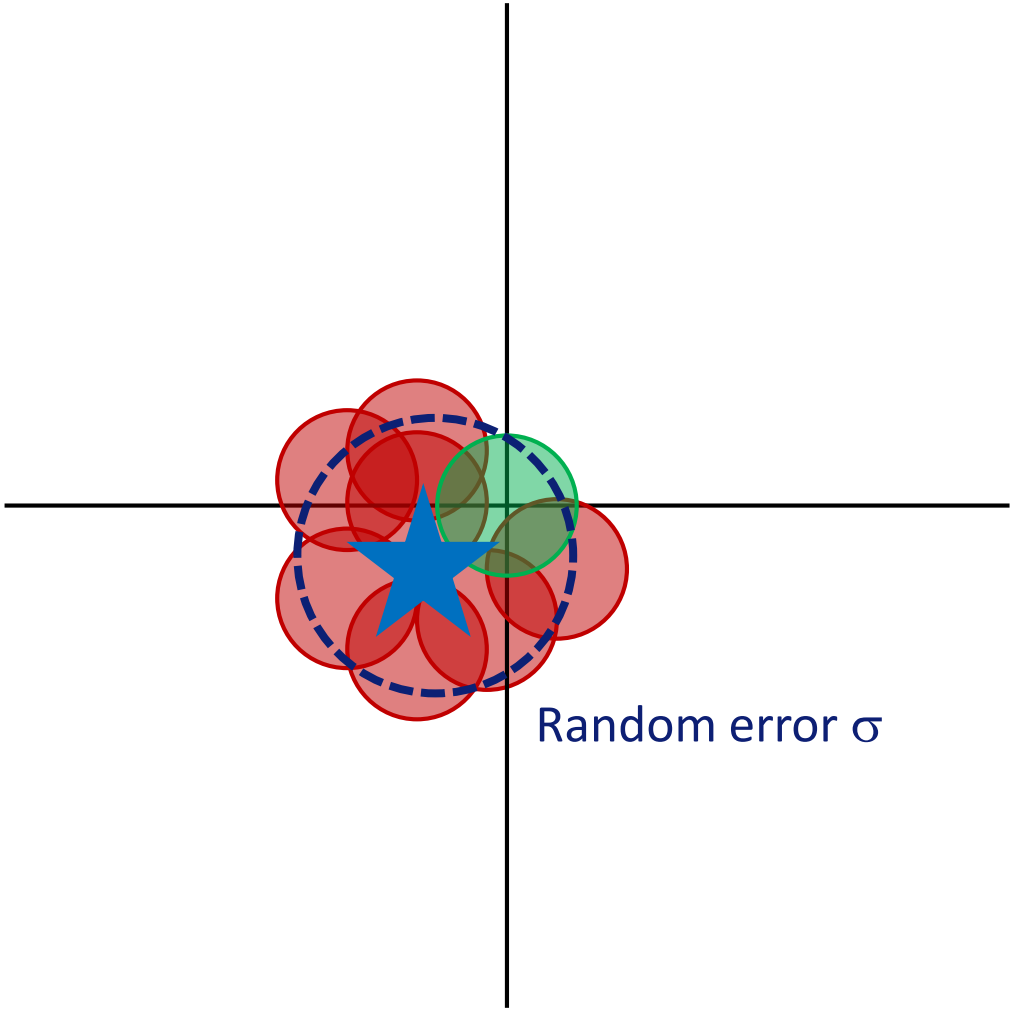
Categorization of Errors: a 2D Example



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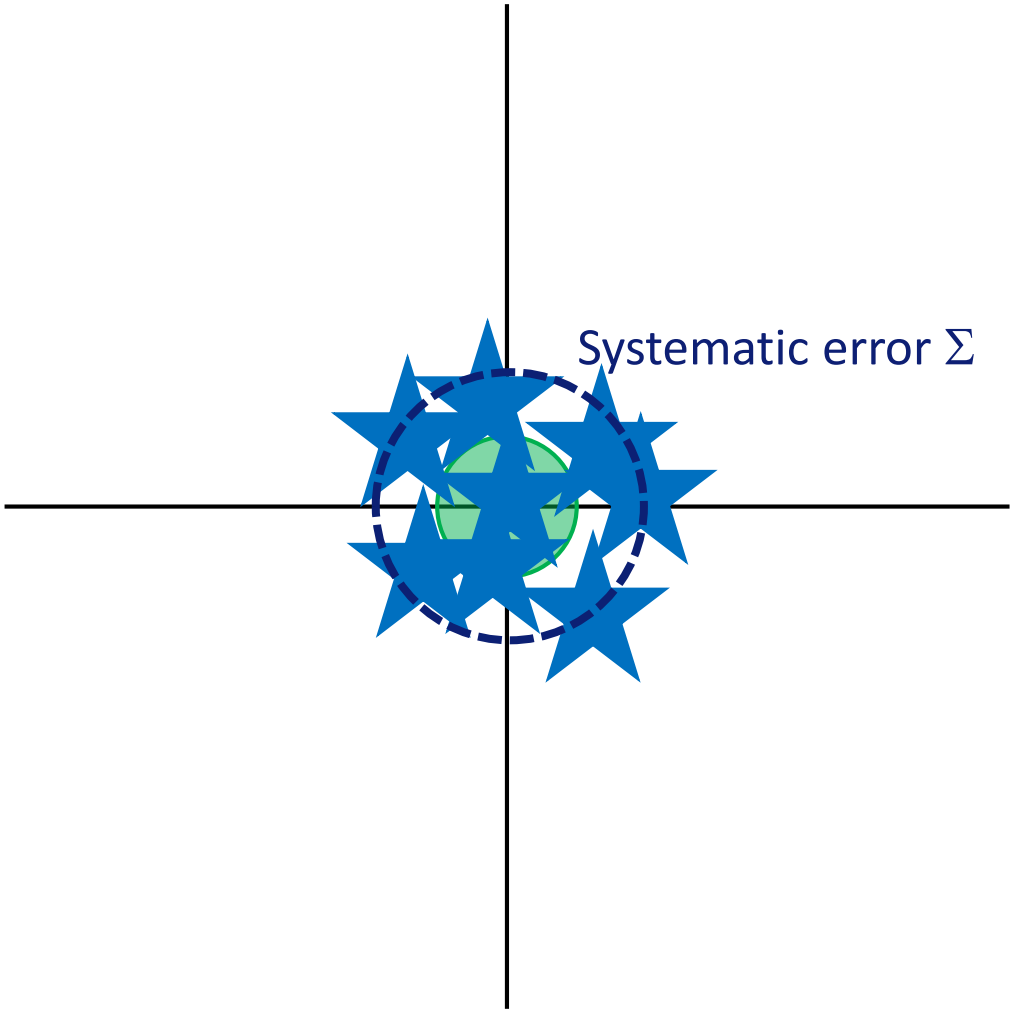

Erasmus MC

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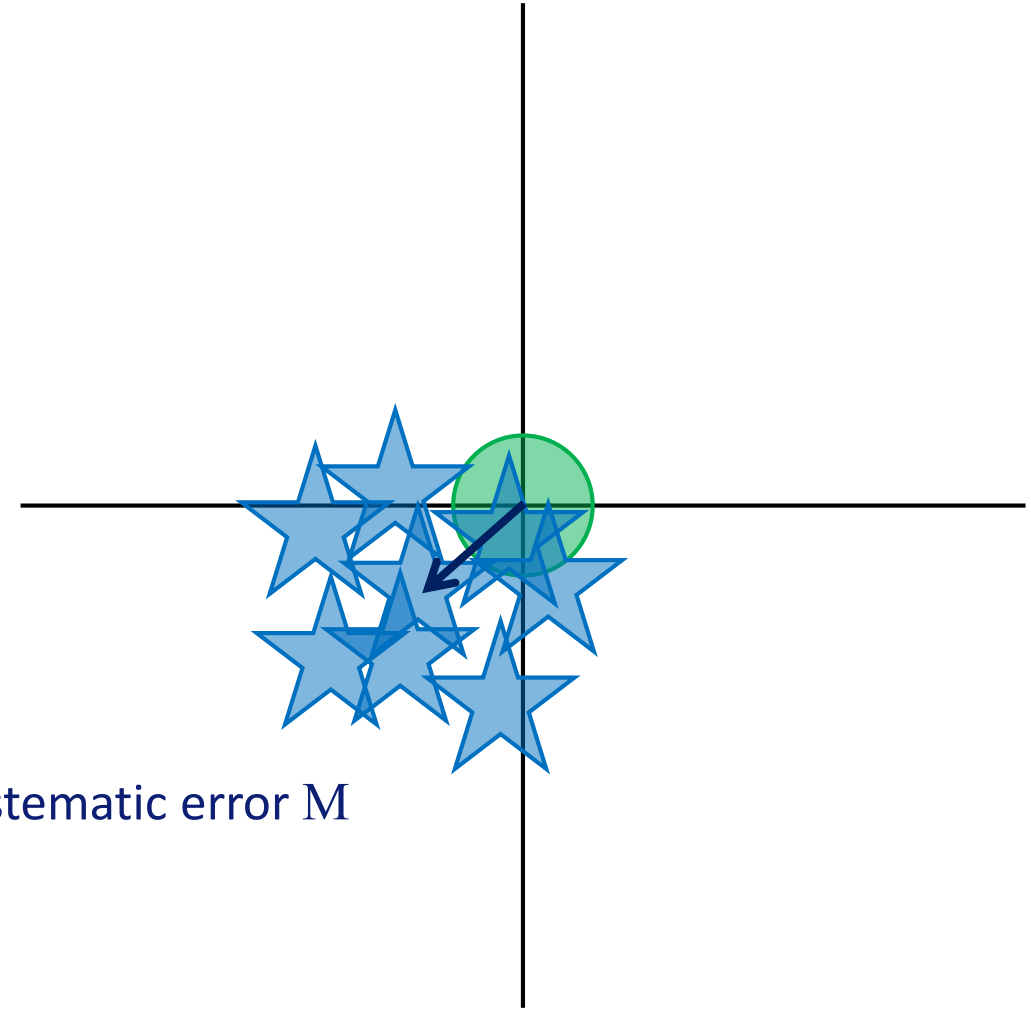

Systematic error M

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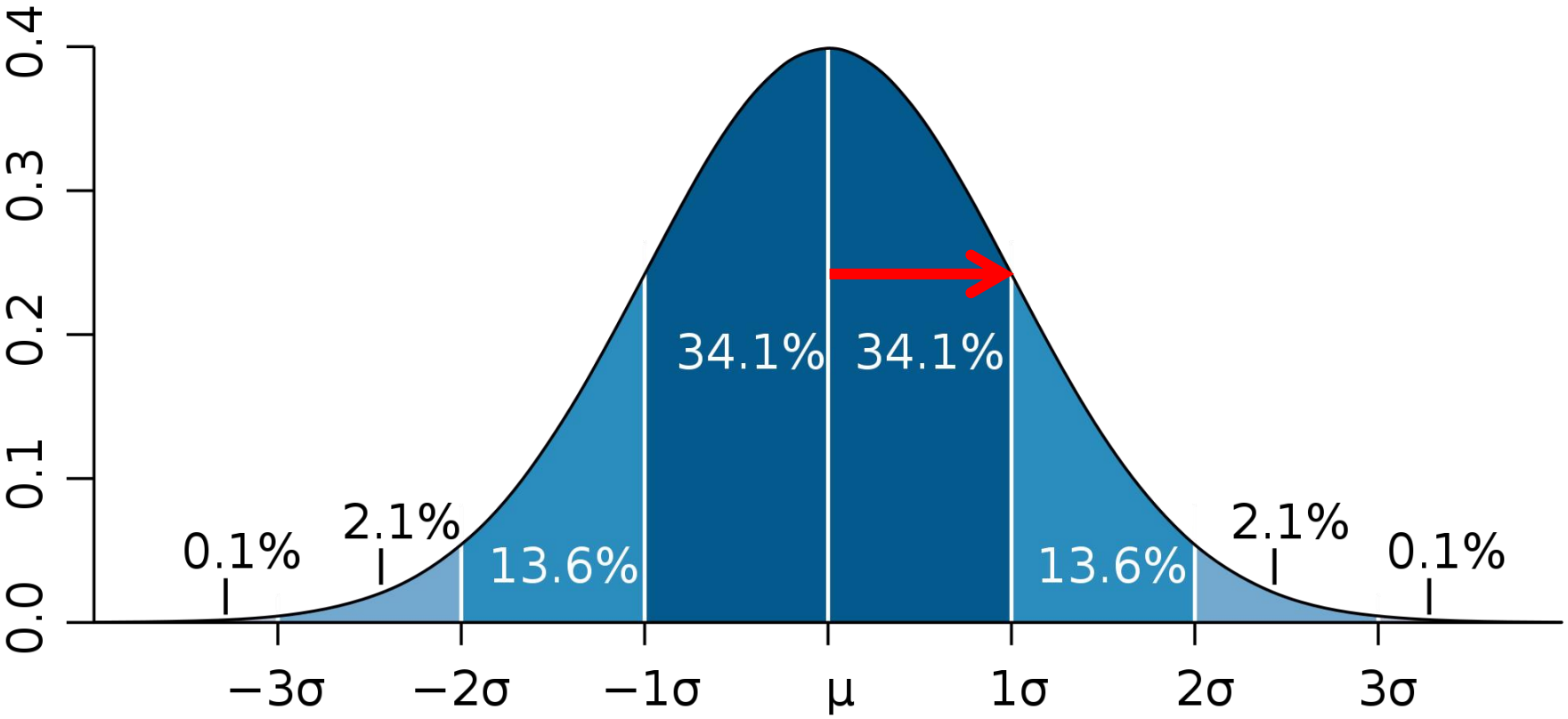
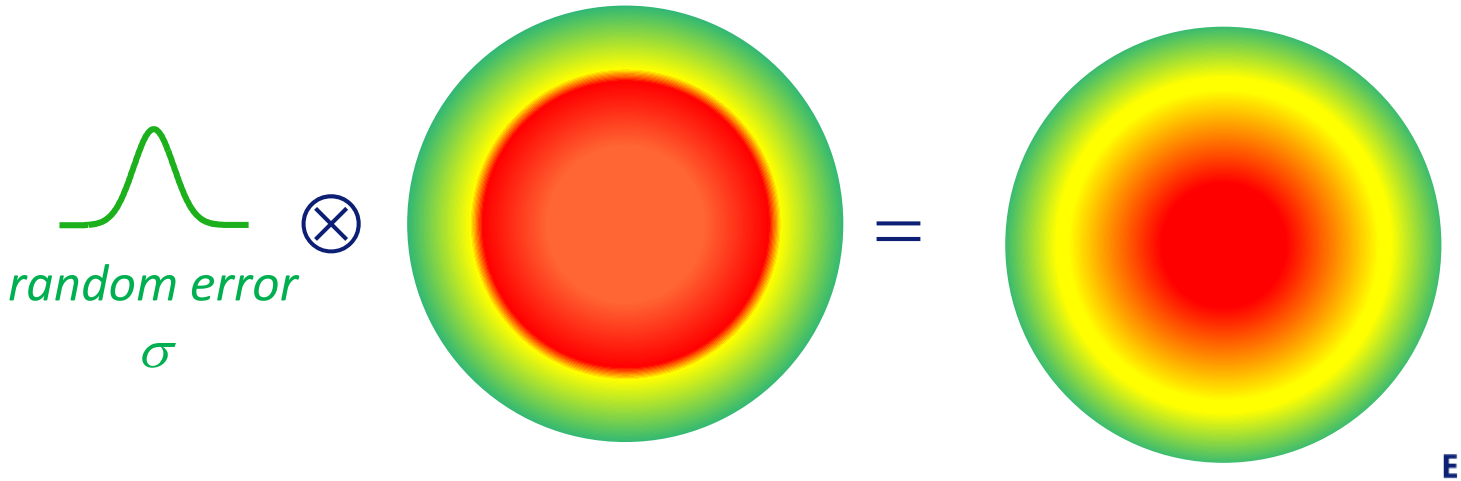
Probability Density Function: Normal Distribution



Erasmus MC

Random Errors Only: $M_{rand}=0.7\sigma$

- The CTV experiences daily shifts of the dose distribution due to daily random variations in the position of the CTV
- If we add the daily shifted dose distributions the dose distribution appeares to be blurred (motion blurring)
- The effect of the random error can be calculated by convolving the random error distribution with the dose distribution => blurred dose distribution



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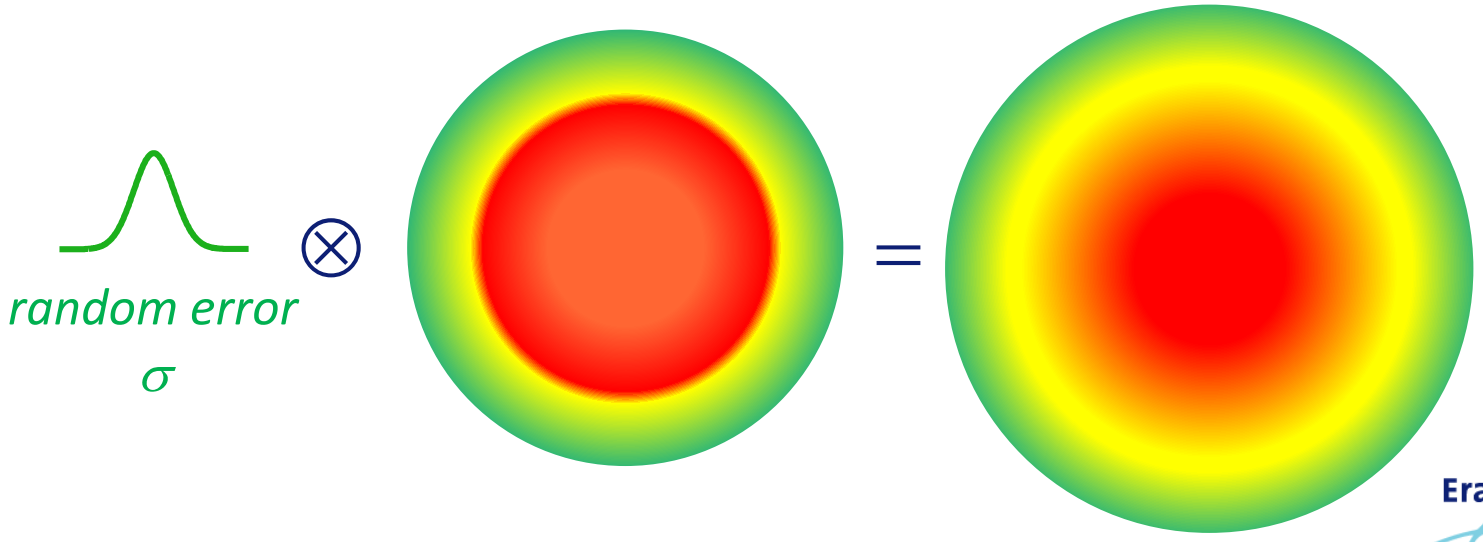
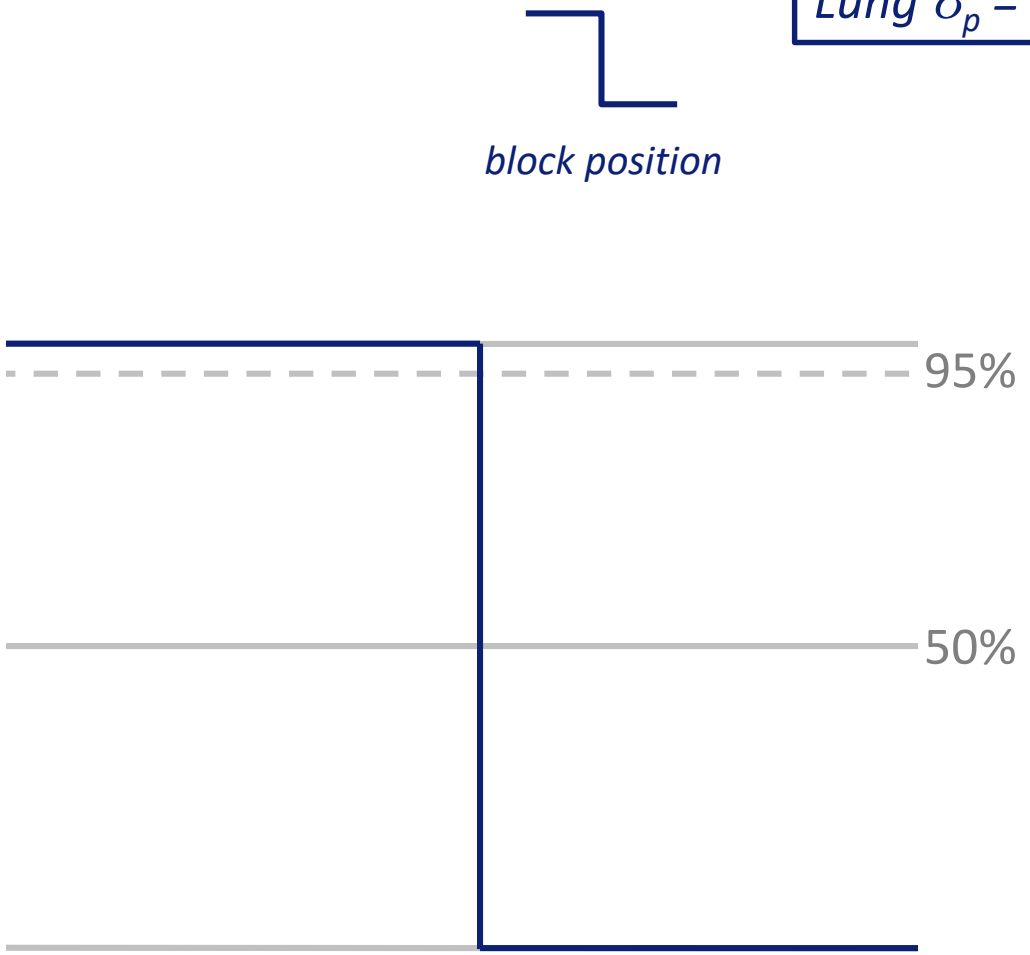


Erasmus MC

Margin Recipe for Random Error

Water σ_p= 3.2 mm
Lung σ_p = 6.4 mm



Erasmus MC

Margin Recipe for Random Error

Water σ_p= 3.2 mm
Lung σ_p = 6.4 mm

penumbra σ_p *block position*

Erasmus MC

Margin Recipe for Random Error

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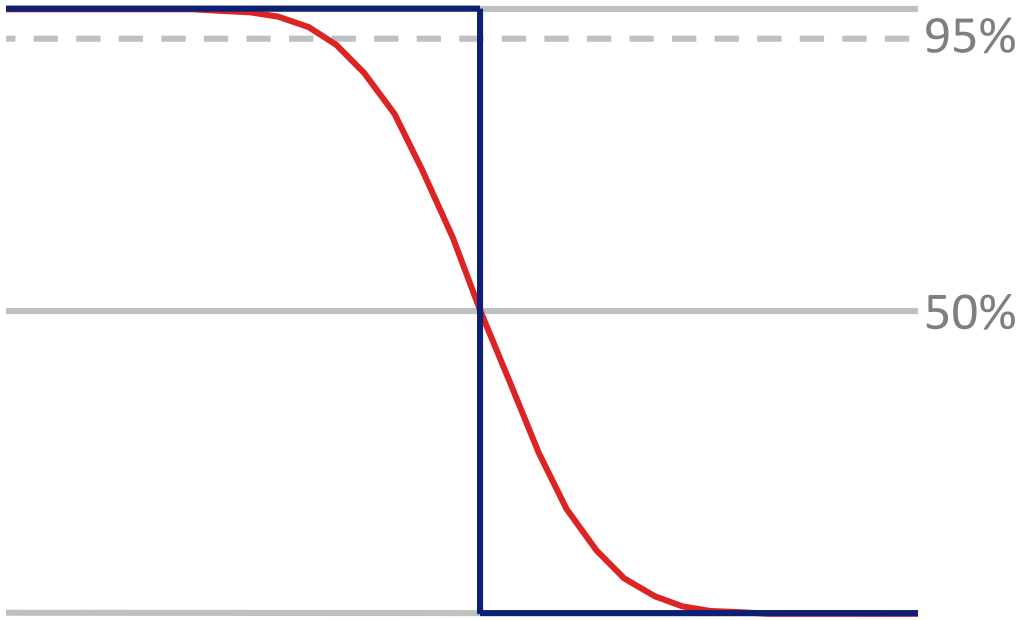

Erasmus MC

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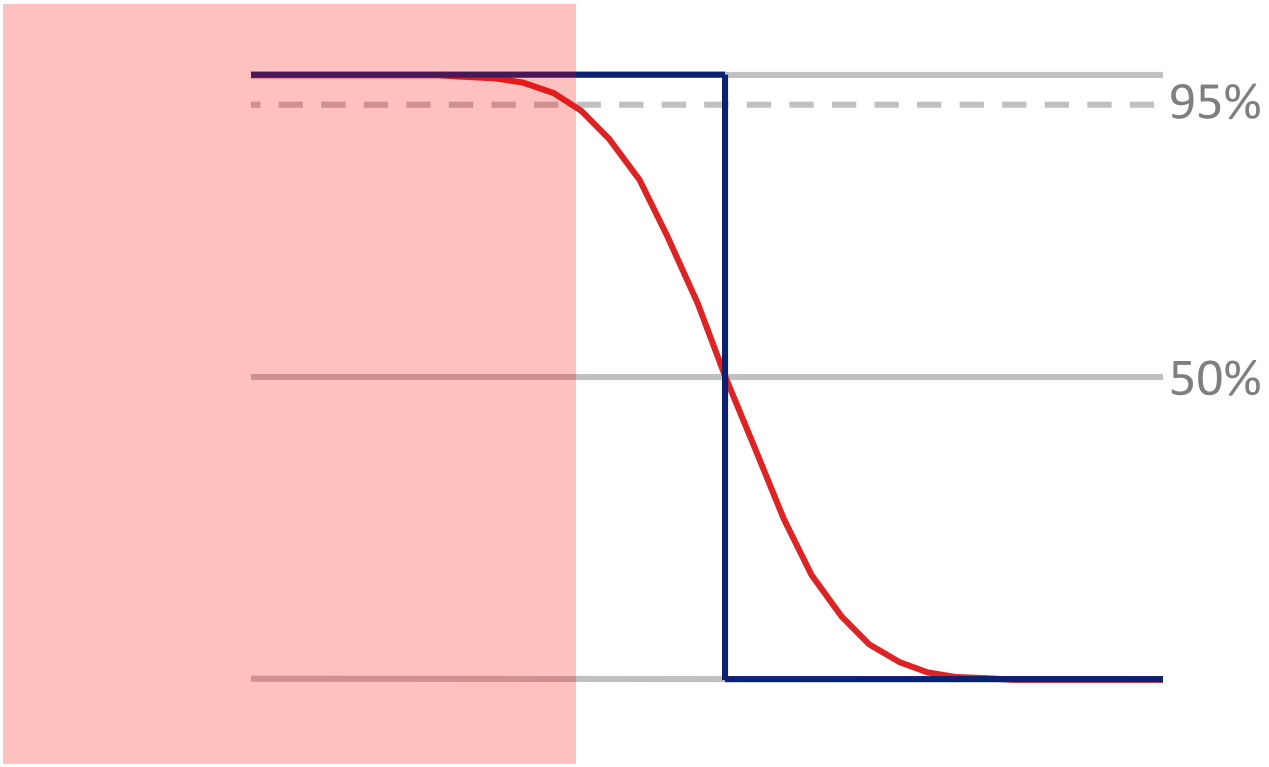

Erasmus MC

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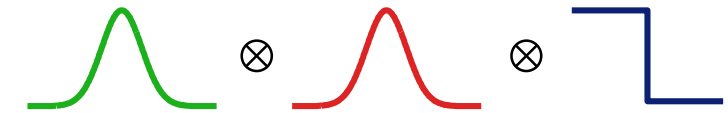
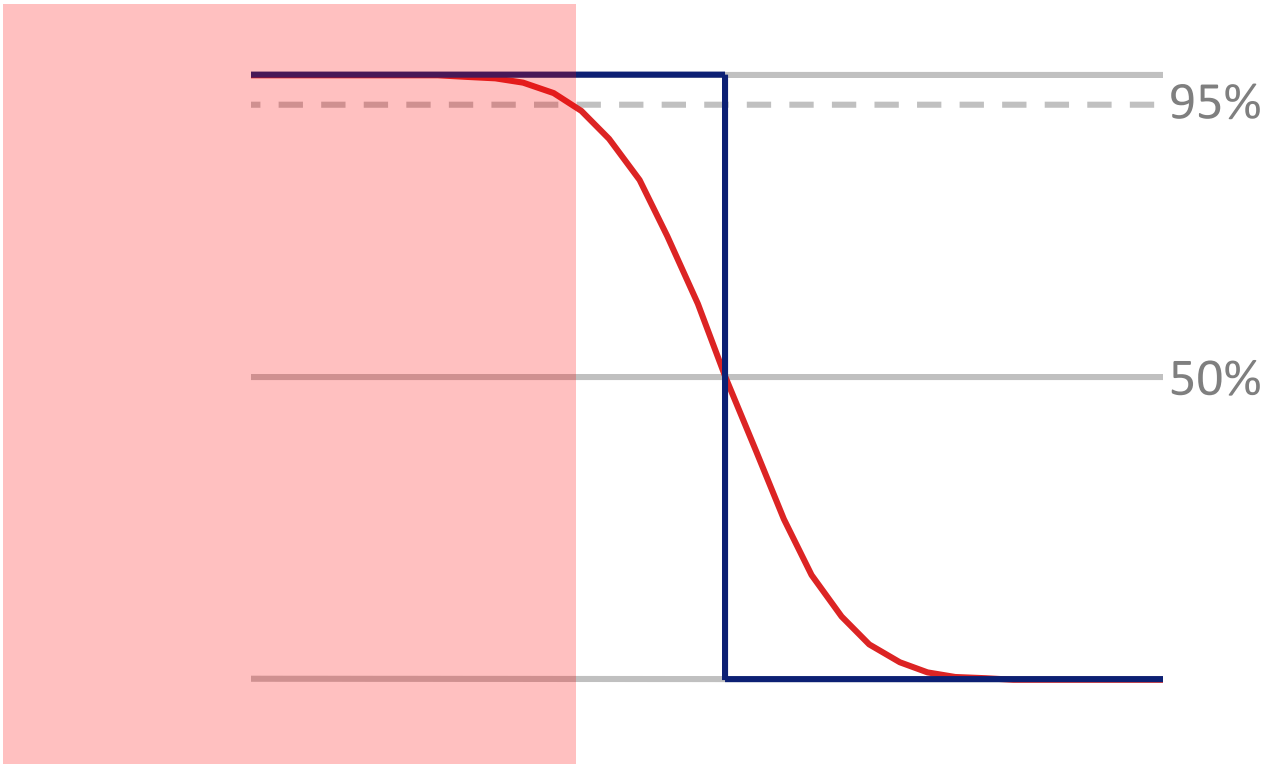


random error σ ⊗ *penumbra* σ_p ⊗ *block position*



Erasmus MC

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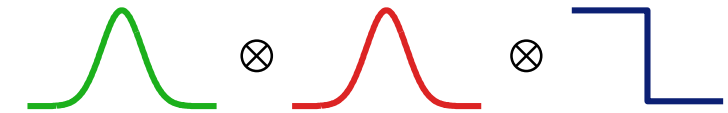
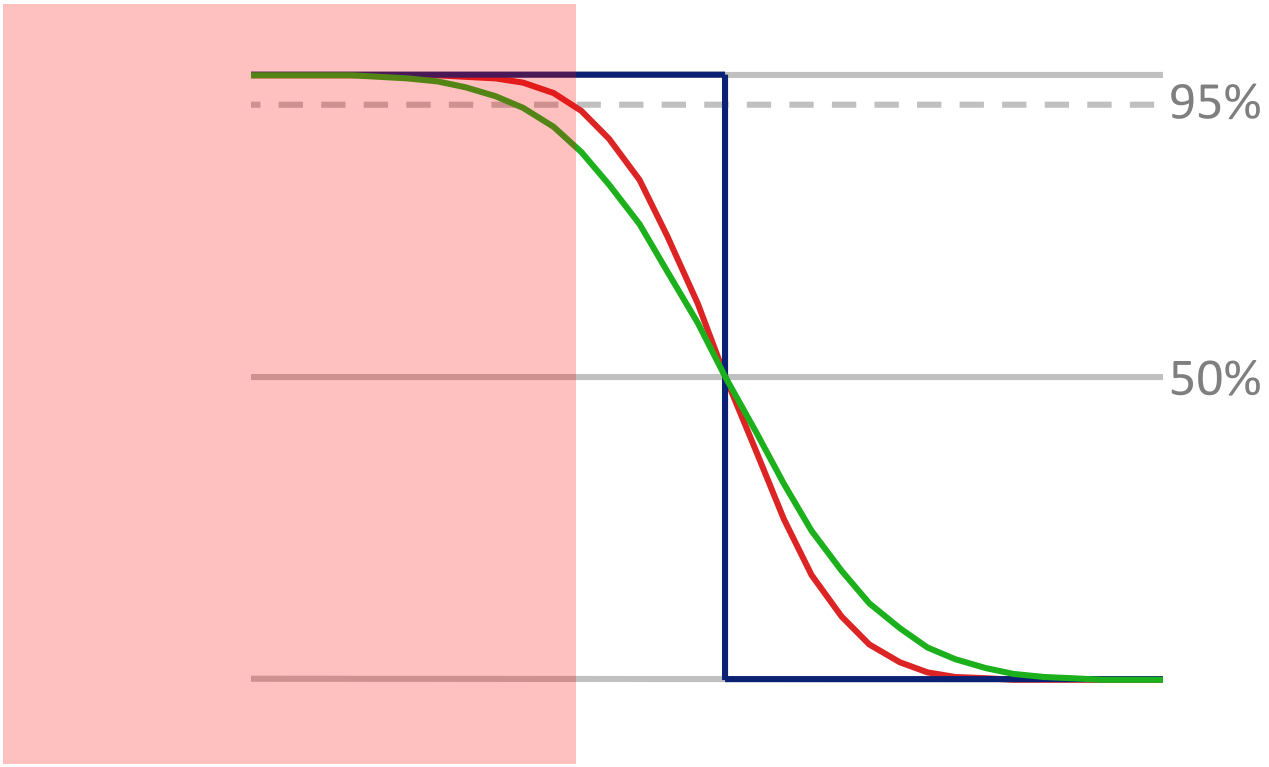
Lung σ_p = 6.4 mm



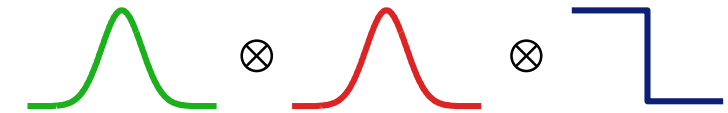
random error σ ⊗ *penumbra* σ_p ⊗ *block position*



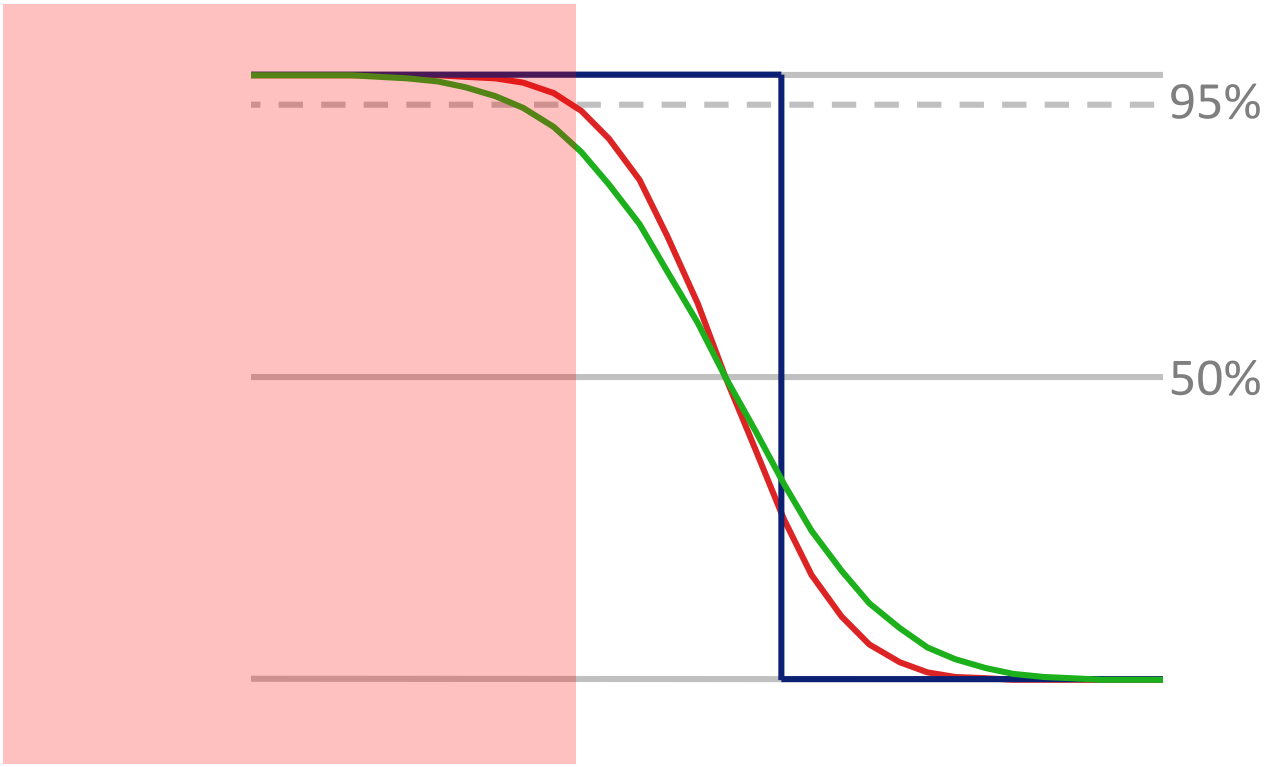
Erasmus MC

Margin Recipe for Random Error

Water σ_p= 3.2 mm
Lung σ_p = 6.4 mm



random error σ ⊗ *penumbra* σ_p ⊗ *block position*



Erasmus MC

Margin Recipe for Random Error

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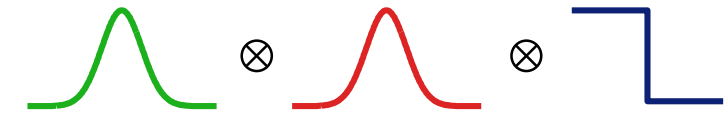
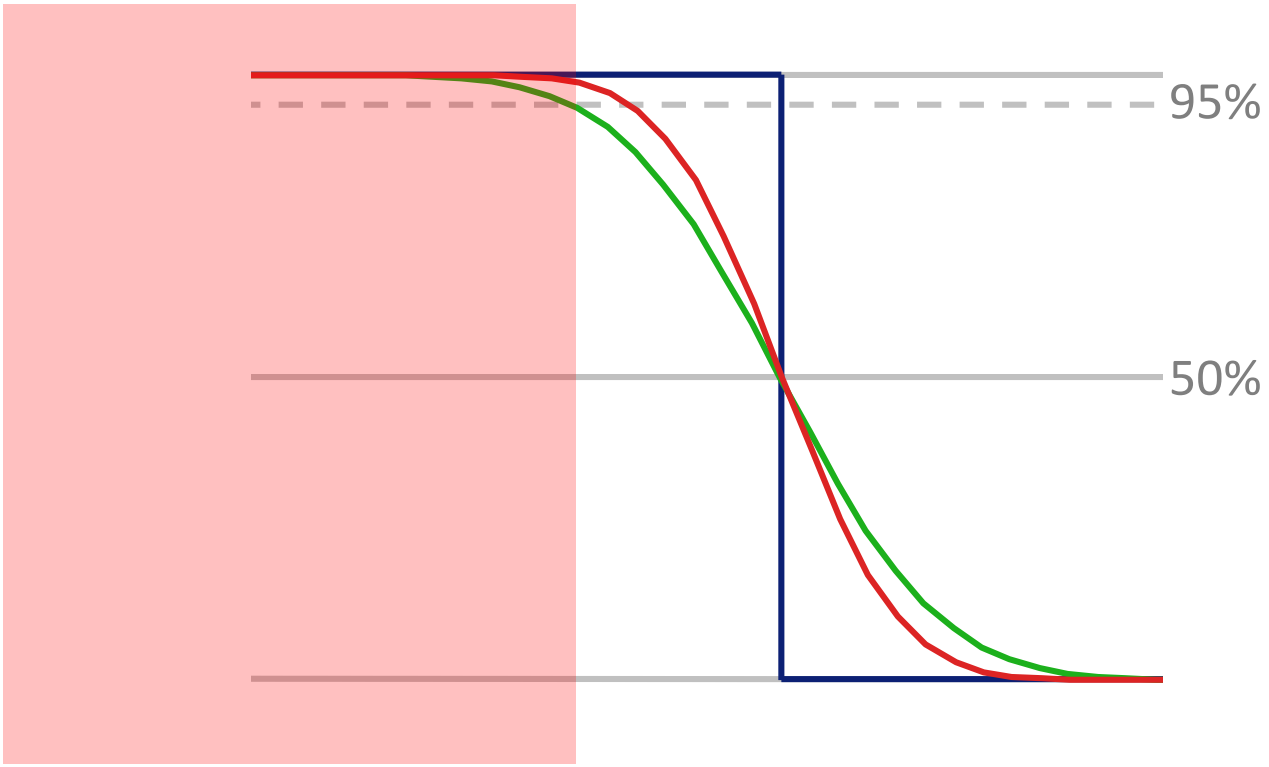


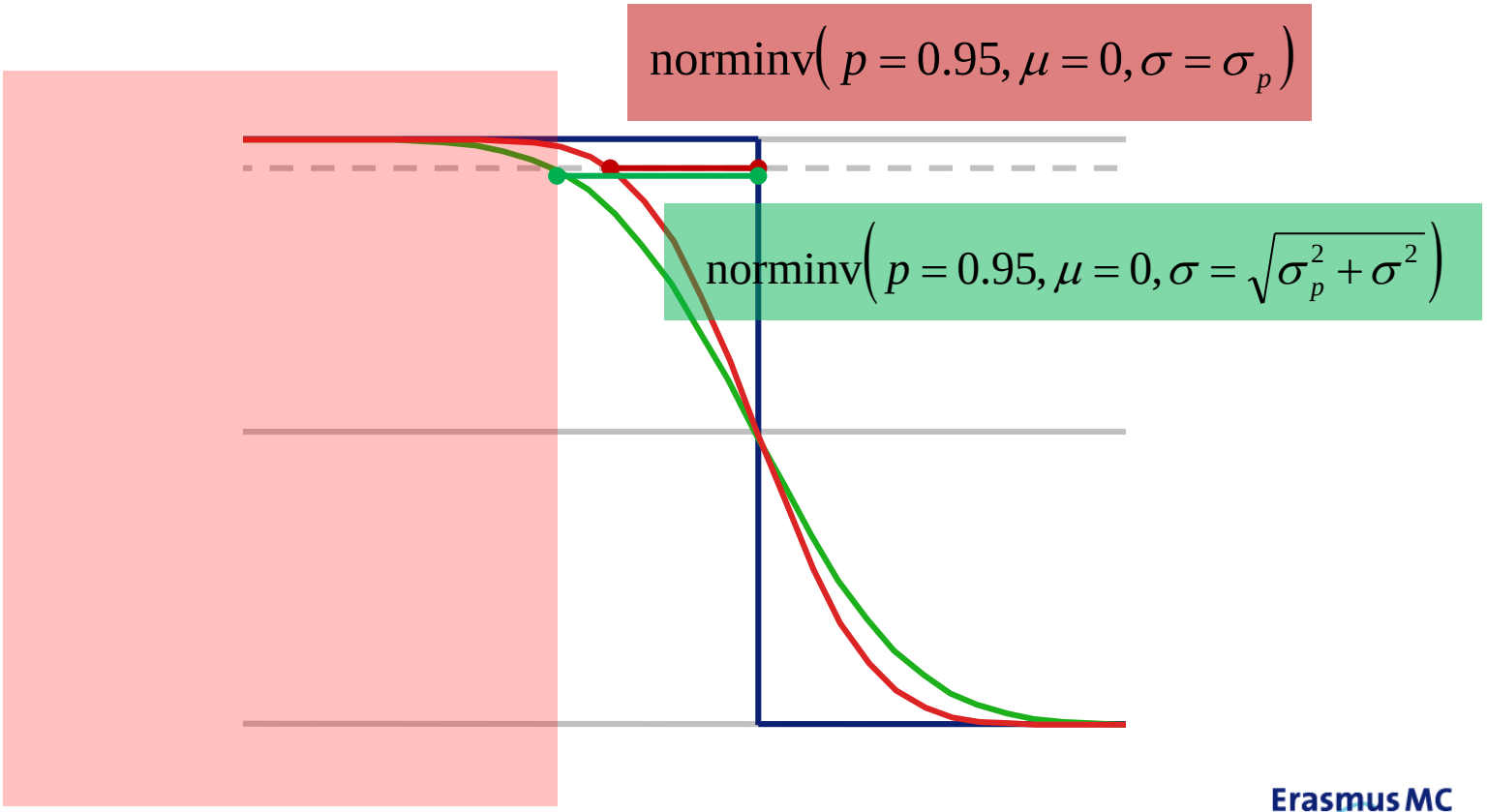
random error σ ⊗ *penumbra* σ_p ⊗ *block position*



Erasmus MC

Margin Calculation: Random Component

- The margin that would be needed to ensure a coverage of at least 95%



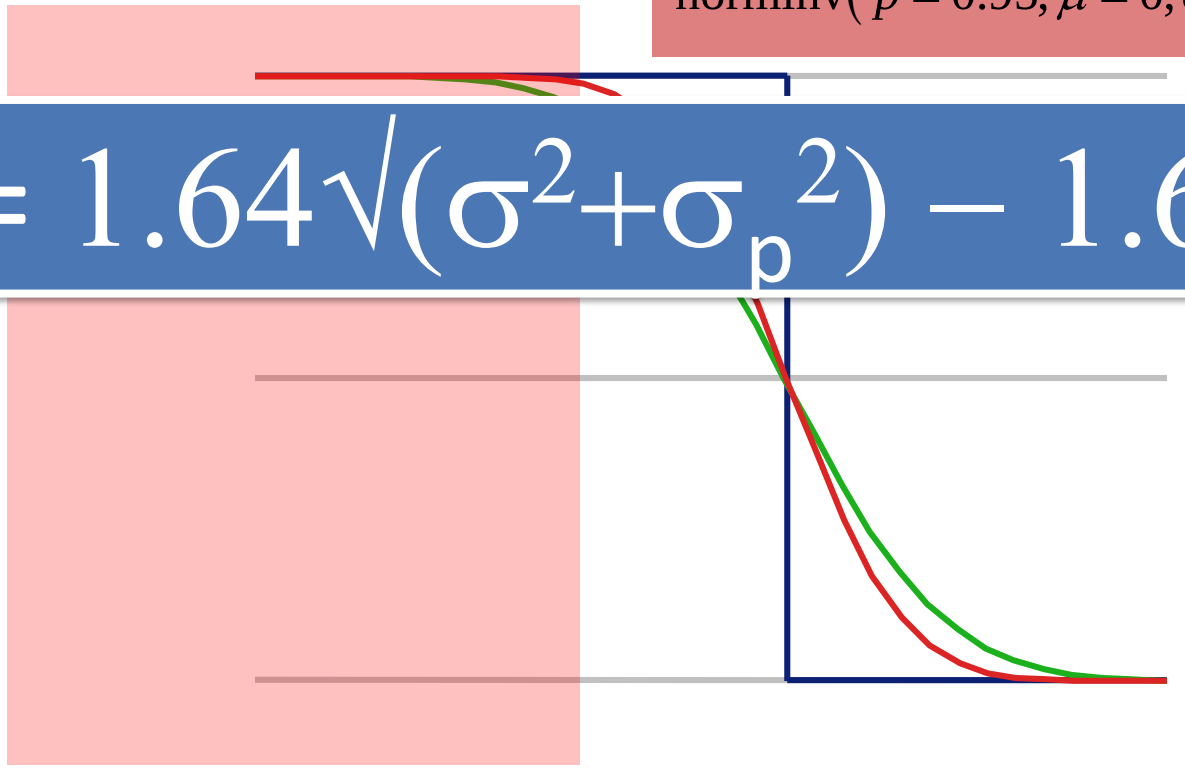
Erasmus MC

Margin Calculation: Random Component

- The margin that would be needed to ensure a coverage of at least 95%

$$\text{norminv}\left(p = 0.95, \mu = 0, \sigma = \sigma_p\right)$$

$$M = 1.64\sqrt{(\sigma^2 + \sigma_p{}^2)} - 1.64\sigma_p$$



Erasmus MC

Margin Calculation: Random Component

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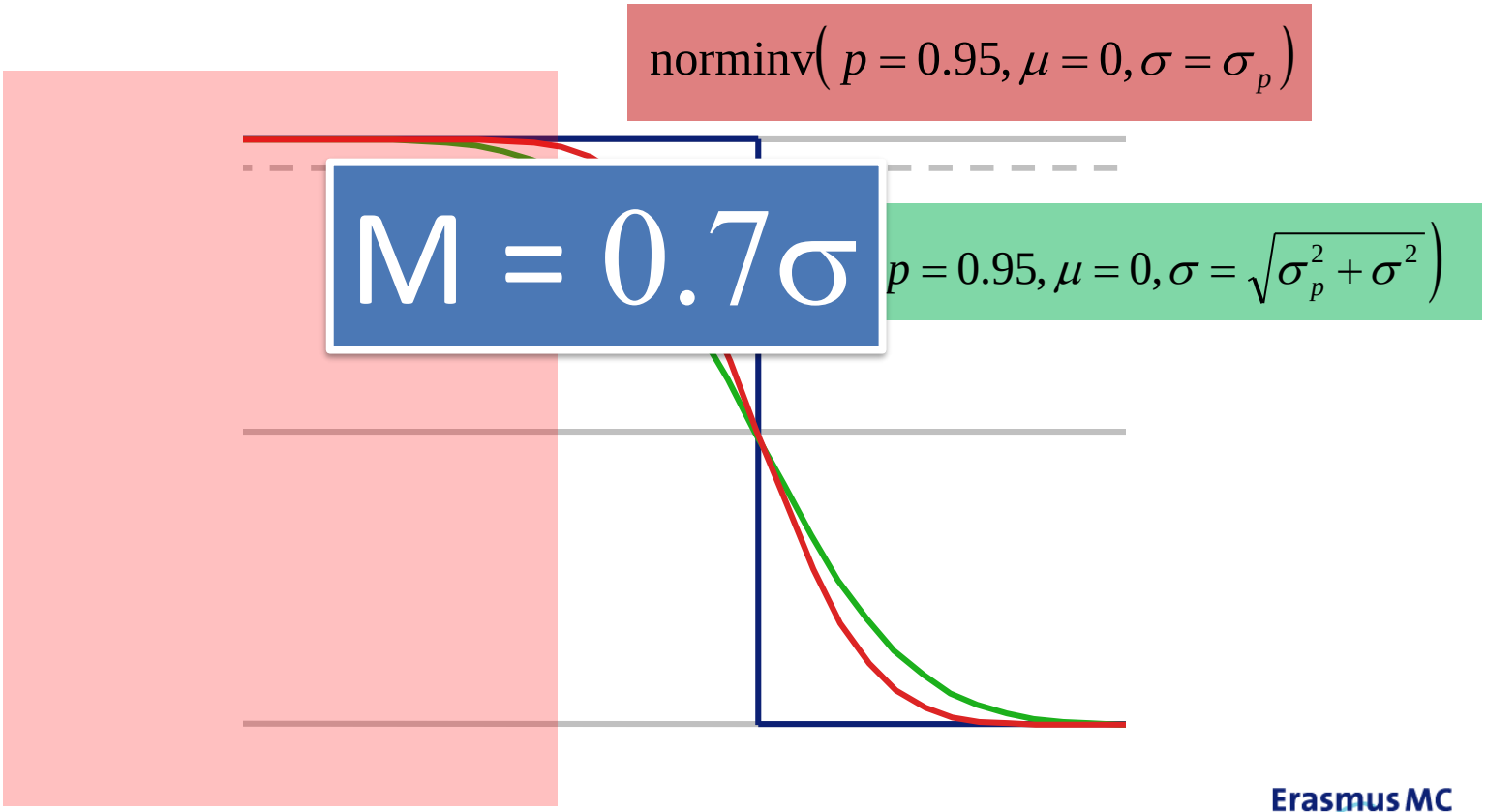
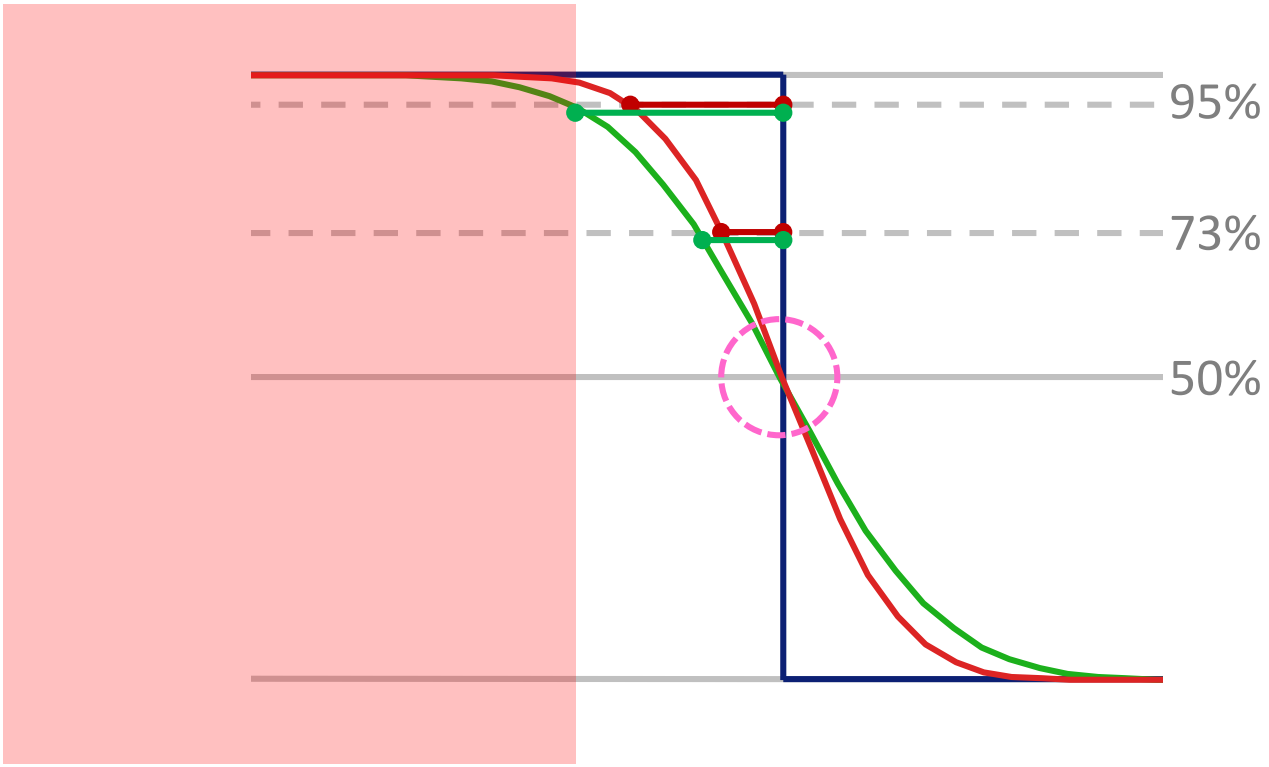


Erasmus MC

Random Error and Minimum Dose Requirement

- The margin for random decreases with decreasing prescription isodose line / minimum dose requirement

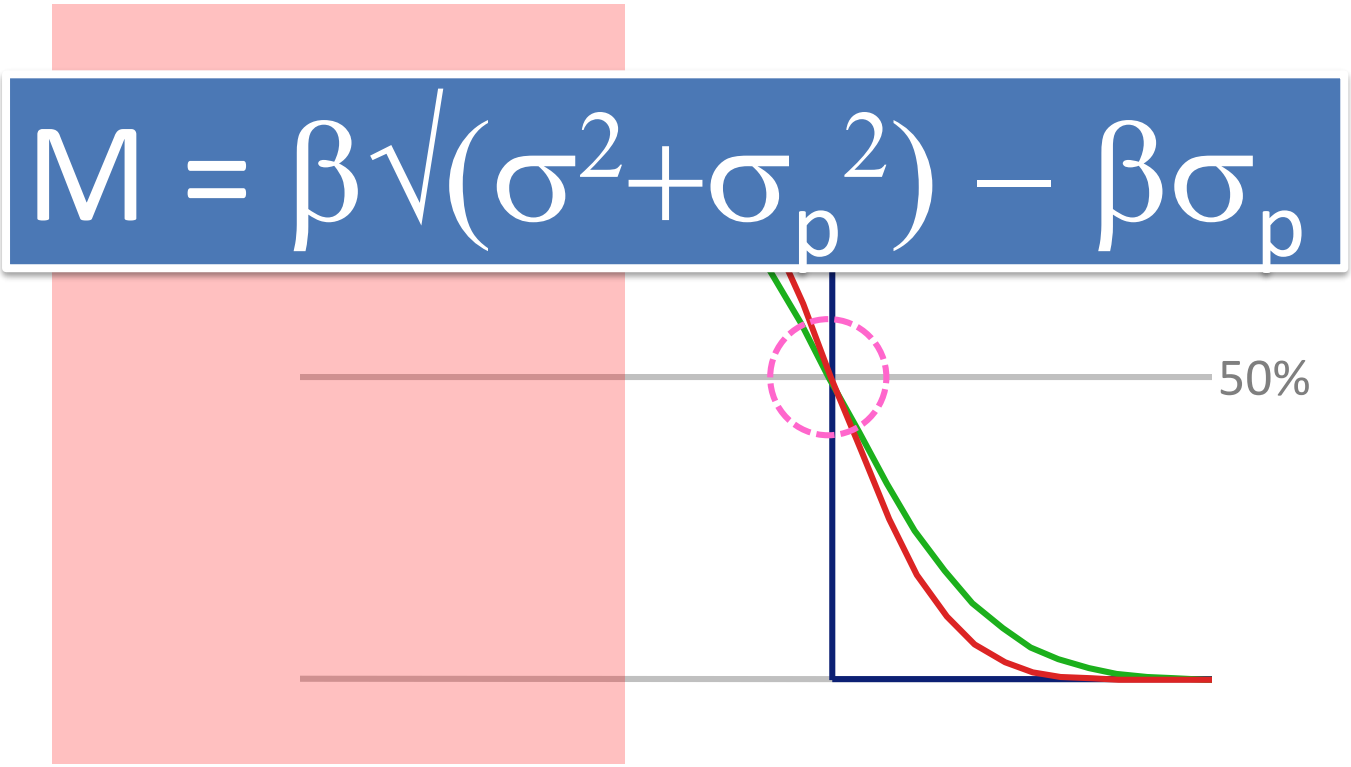


Erasmus MC

Random Error and Minimum Dose Requirement

- The margin for random decreases with decreasing prescription isodose line / minimum dose requirement

$$M = \beta\sqrt{(\sigma^2+\sigma_p{}^2)} - \beta\sigma_p$$



Erasmus MC

Random Error and Minimum Dose Requirement

- The margin for random decreases with decreasing prescription isodose line / minimum dose requirement

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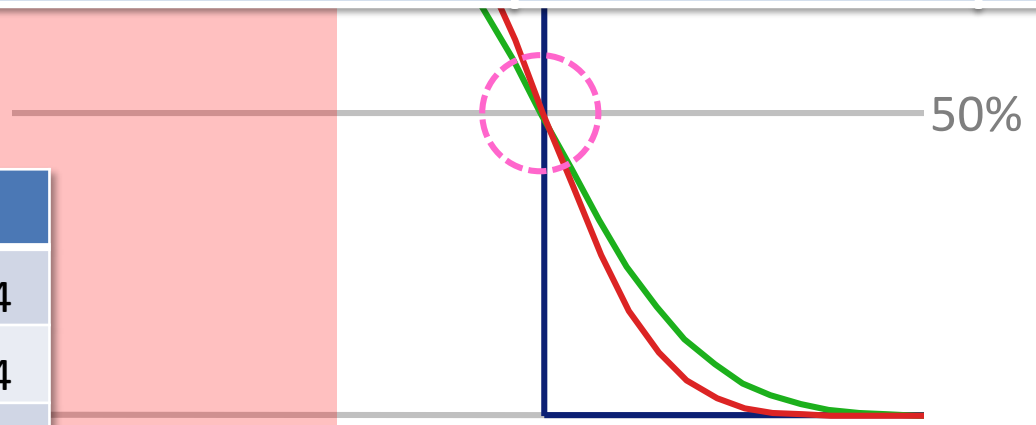

Prescription level	β
95%	1.64
80%	0.84
70%	0.52
60%	0.25

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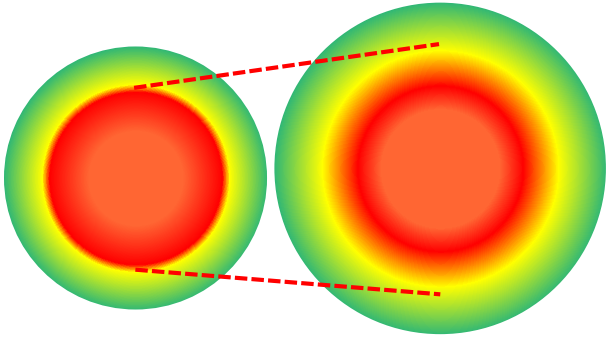
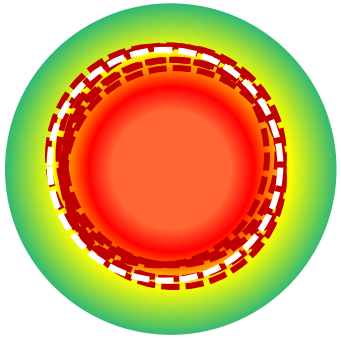
Margin Recipe: Systematic Error and Random Errors



Cumulative minimum dose ≥ 95%

$$M_r = \beta\sqrt{(\sigma^2+\sigma_p^2)} - \beta\sigma_p$$

- Systematic errors are assumed to have an independent effect on the blurred dose distribution



≥ 90% of population receives a cumulative CTV dose of ≥ 95%

$$M = 2.5\Sigma + M_r$$

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How to Add Various Error Contributions?

- For a simple criteria as a probability level of the minimum dose the **systematic error and random error are added linearly**

- For various systematic errors and various random errors the errors (SDs) should be **added in quadrature**:

$$\Sigma = \sqrt{\Sigma_a^2 + \Sigma_b^2 + \Sigma_c^2}$$

$$\Sigma = \sqrt{10^2 + 3^2 + 3^2} = 10.9(10)$$

Emphasis on large errors!

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APPLICATION TO SRT AND SBRT

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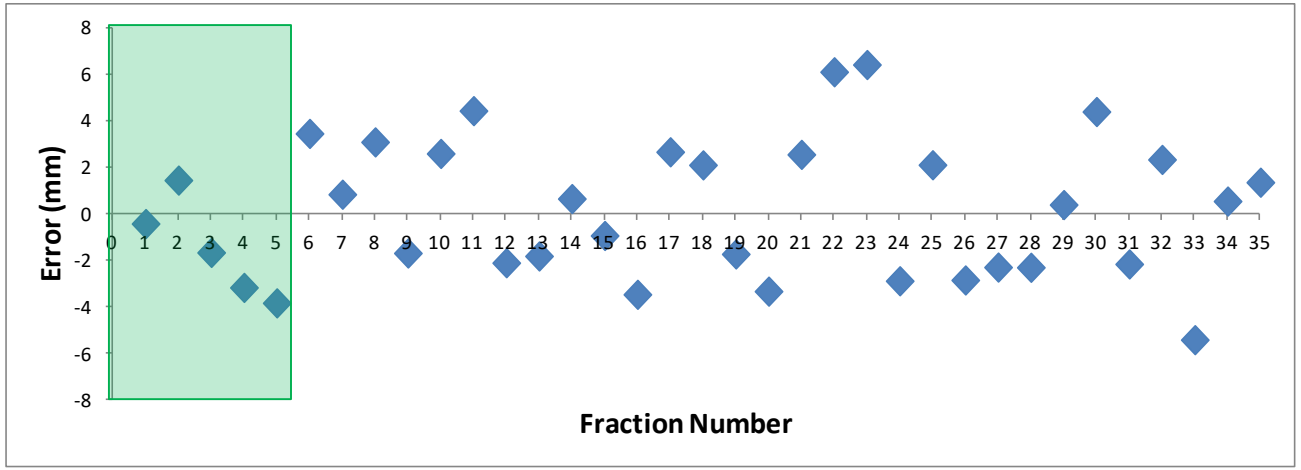
Number of Fractions and Residual Systematic Error

- Limited number of fractions results in a residual shift of the dose distribution



- Residual error
  - Error after 35 fractions = 0.1 mm
  - Error after 5 fractions = -1.6 mm

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Effective Standard Deviation of the Errors

- Effective Systematic Error

Error in estimating the average

$$\Sigma_{effective} = \sqrt{\Sigma^2 + \frac{1}{N}\sigma^2}$$

- Effective Random Error

$$\sigma_{effective} = \sqrt{\left(1 - \frac{1}{N}\right)\sigma^2}$$

de Boer H C and Heijmen B J 2001 A protocol for the reduction of systematic patient setup errors with minimal portal imaging workload Int. J. Radiat. Oncol. Biol. Phys. ***50 1350–65***

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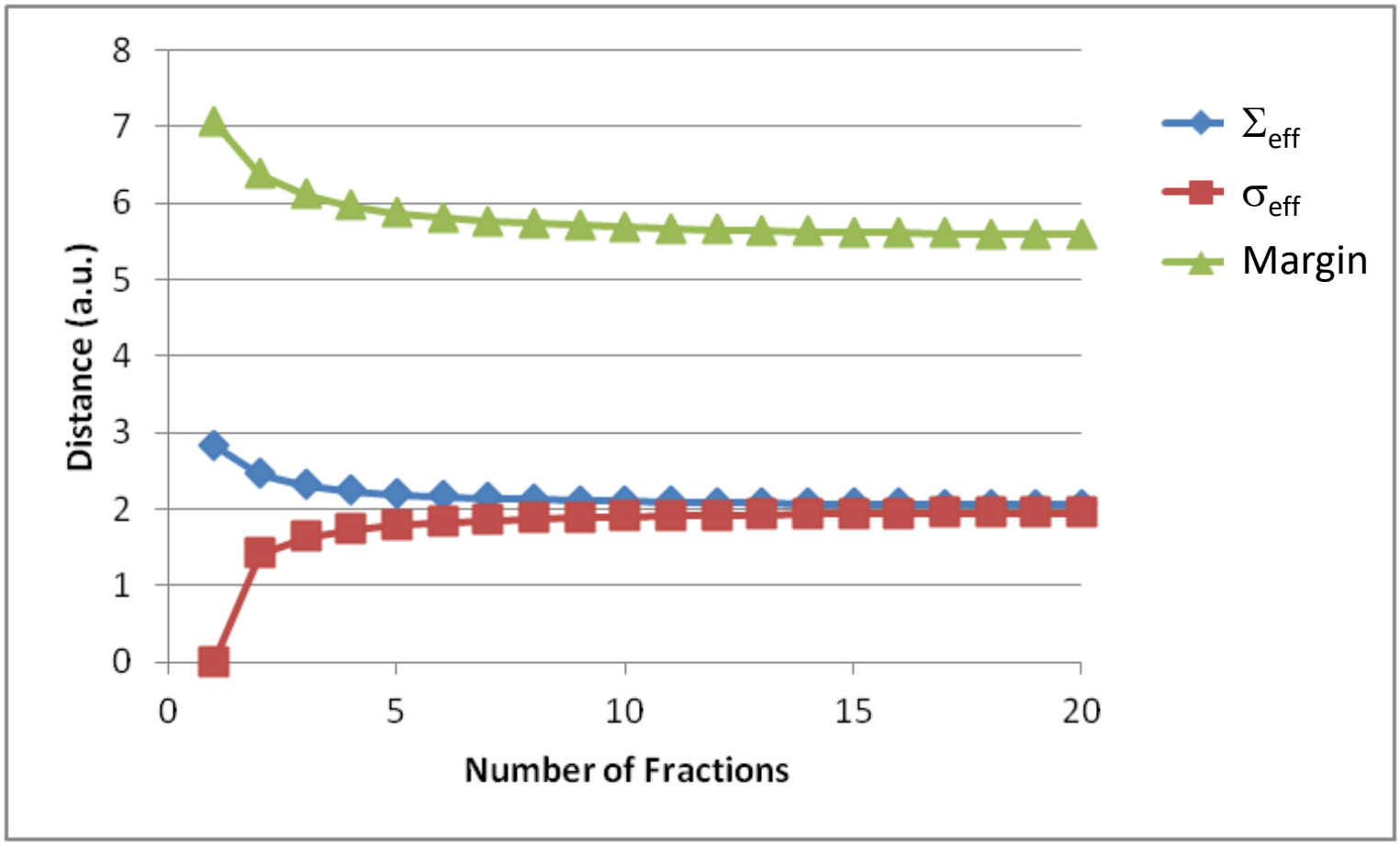
Margin and Number of Fractions



Σ = 2 mm, σ = 2 mm, P=80%

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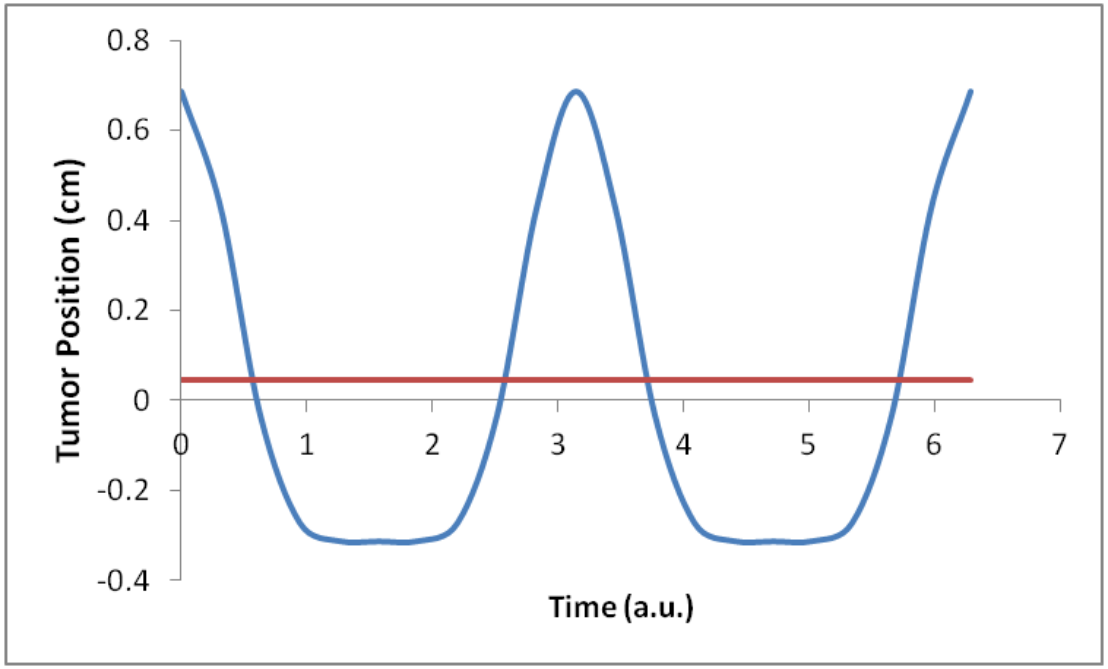
Including Error due to Respiratory Motion

- Respiratory motion modeled as $\sin^6 t$



- The respiratory motion can be described as a standard deviation for a given amplitude
  - $\sigma = 0.358A$

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PRACTICAL EXAMPLES

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A Practical Example: SRT Case

- Intracranial lesion: 3 x 8 Gy @ 80%
- SD of the penumbra is 3.2 mm
- E2E test device error (1 SD) = 0.4 mm (measured over a long period)
- Localization (delineation) error = 1.0 mm (1 SD)
- Systematic error = 0.5 mm (1 SD) [measured from 30-fraction treatments]
- Random error = 0.5 mm (1 SD) [measured from 30-fraction treatments]
- Intra-fraction error = 0.5 mm (1 SD) [measured from 30-fraction treatments at end of treatment]

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Which margin would you use for this treatment?

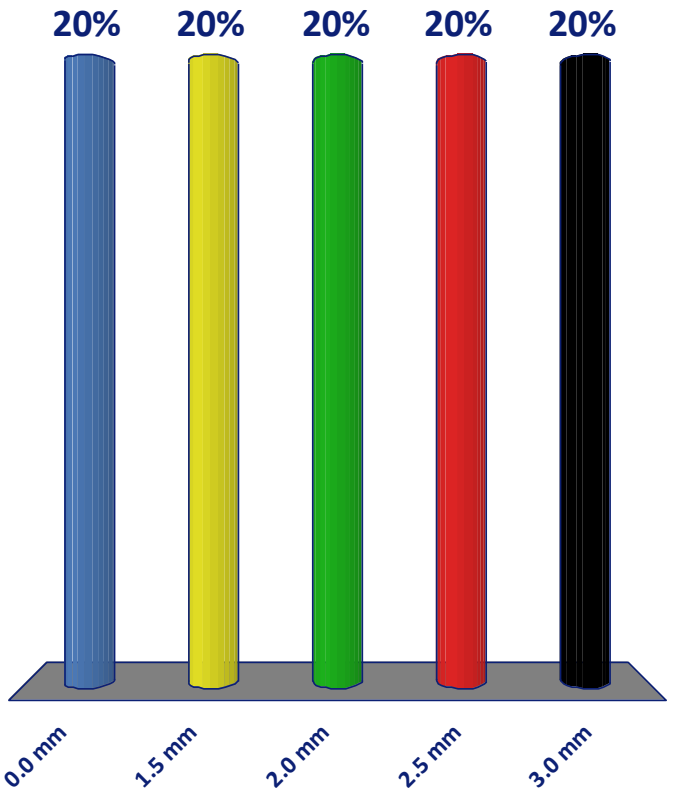
A. 0.0 mm

B. 1.5 mm

C. 2.0 mm

D. 2.5 mm

E. 3.0 mm



A Practical Example: SRT Case

- Intracranial lesion: 3 x 8 Gy @ 80% **N=3, β=0.84**
- SD of the penumbra is 3.2 mm **σ_{pen}=3.2 mm**
- E2E test device error (Σ) = 0.4 mm **Σ_1=0.4 mm**
- Localization (delineation) error = 1.0 mm (1 SD) **Σ_2=1.0 mm**
- Systematic error = 0.5 mm (1 SD) **Σ_{eff}=0.58 mm**
- Random error = 0.5 mm (1 SD) **σ_{eff}=0.41 mm**
- Intra-fraction error = 0.5 mm (1 SD) **σ_{eff}=0.20 mm**

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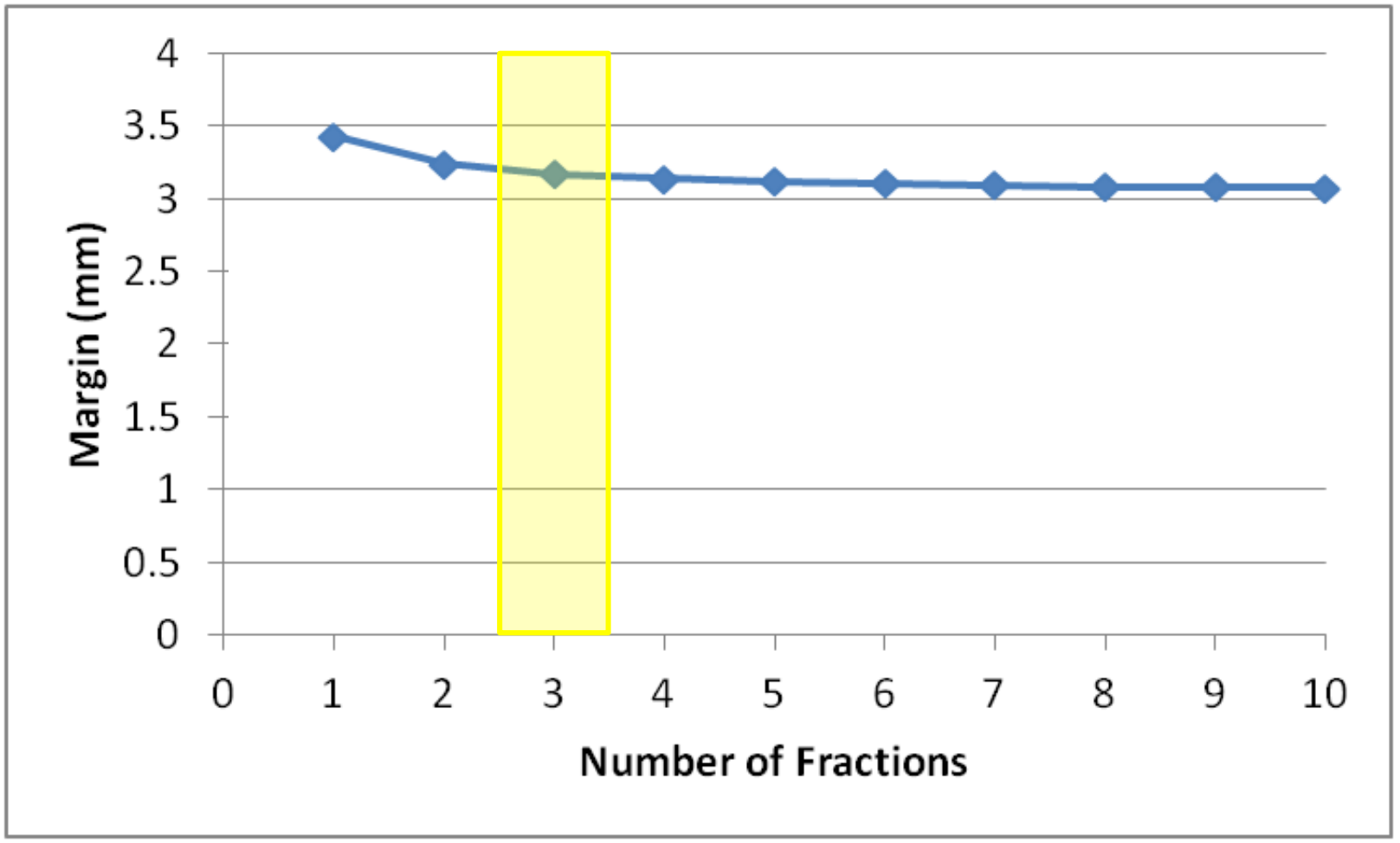
Results SRT Example



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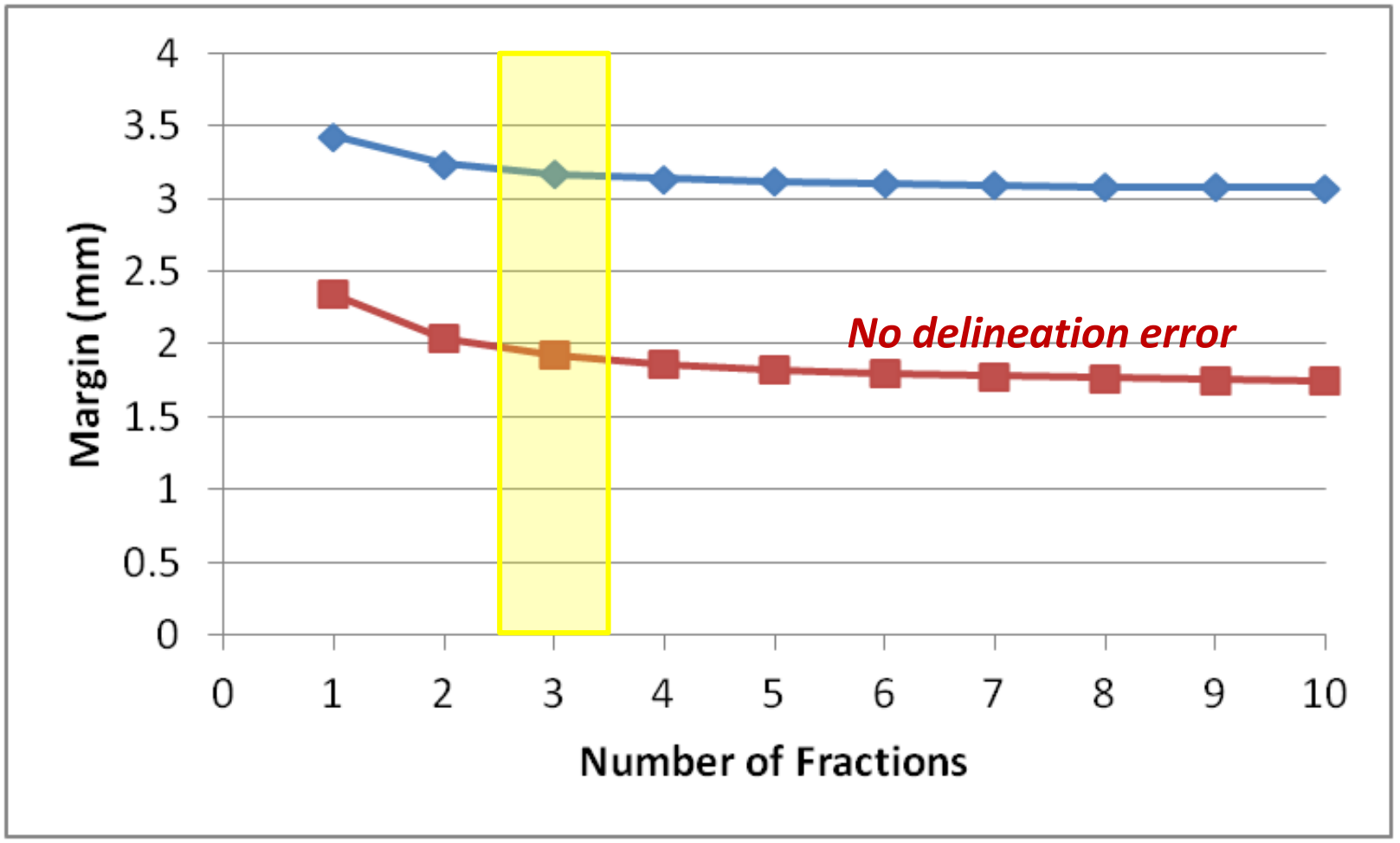
Results SRT Example



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A Practical Example: SBRT Lung Case

- T1 primary lung lesion: 3 x 18 Gy @ 80%
- Alignment on time-averaged tumor position by CBCT
- Tumor in lung tissue
- E2E test device error (1 SD) = 0.4 mm (measured over a long period)
- Localization (delineation) error = 2.0 mm (1 SD)
- Systematic error = 1.0 mm (1 SD) [measured from 3-fraction treatments]
- Random error = 1.0 mm (1 SD) [measured from 3-fraction treatments]
- Intra-fraction amplitude = 1 – 25 mm

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A Practical Example: SBRT Lung Case

- T1 primary lung lesion: 3 x 18 Gy @ 80% **N = 3, β = 0.84**
- Alignment on time-averaged tumor position by CBCT
- SD of the penumbra is 6.4 mm **σ_{pen} = 6.4 mm**
- E2E test device error (Σ) = 0.4 mm **Σ_1 = 0.4 mm**
- Localization (delineation) error = 2.0 mm (1 SD) **Σ_2 = 2.0 mm**
- Systematic error = 1.0 mm (1 SD) **Σ_{eff} = 1.0 mm**
- Random error = 1.0 mm (1 SD) **σ_{eff} = 1.0 mm**
- Intra-fraction amplitude = 1 – 25 mm **σ_r = 0.4 – 9.0 mm**

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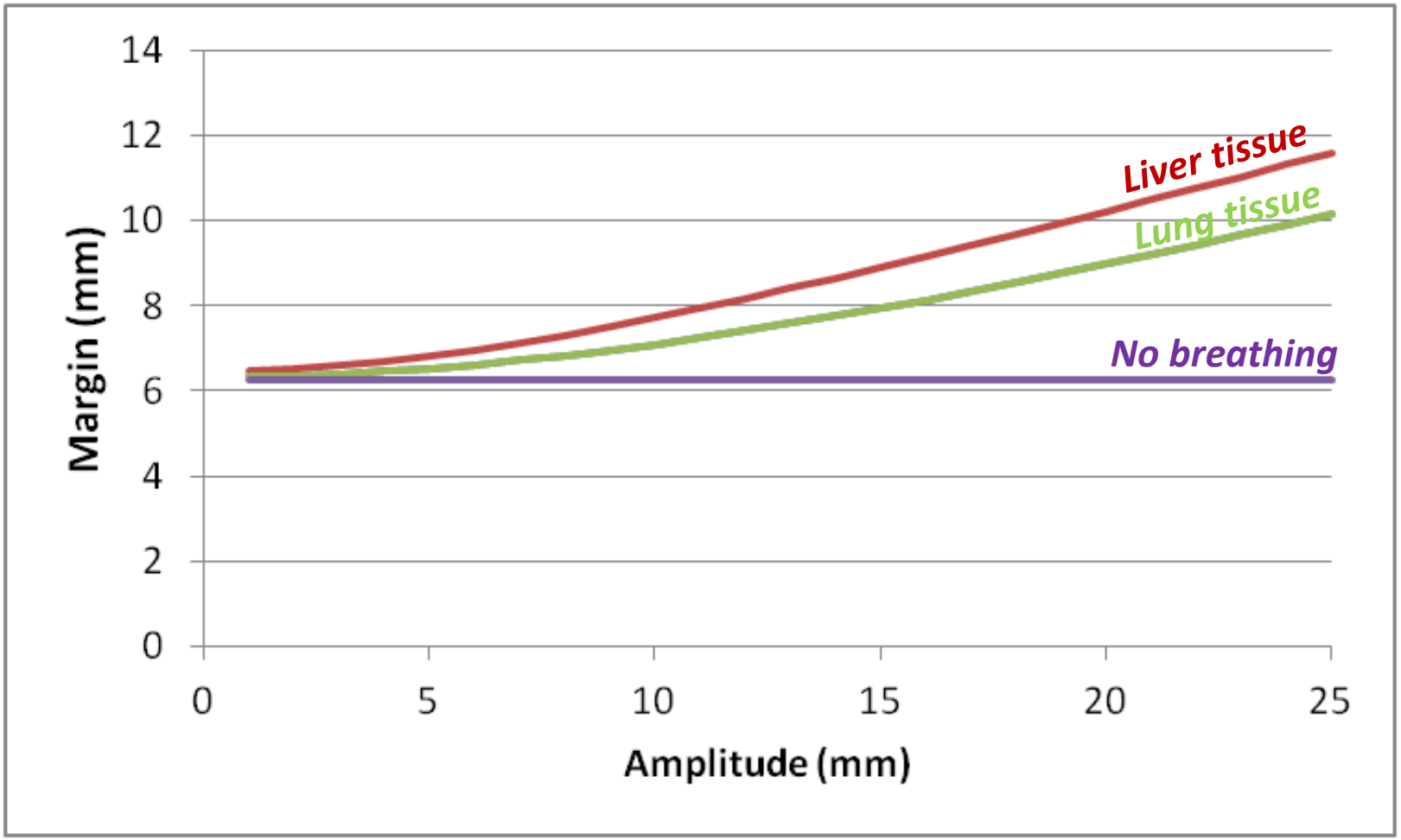
Margins SBRT Lung Case



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INTERNAL TARGET VOLUME

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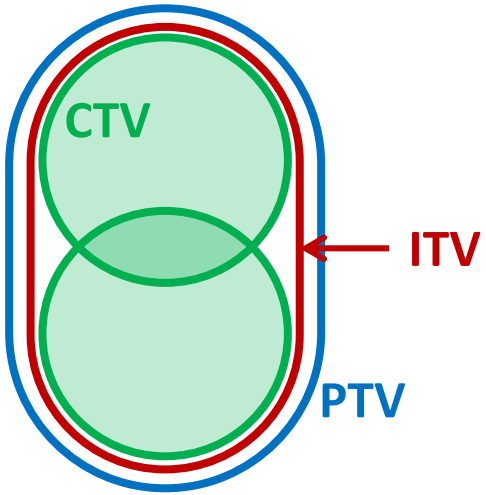
ITV Concept in ICRU-62 Report

- PTV margin should be derived from
  - Internal Margin (IM) or Internal Target Volume (ITV)
  - Setup Margin
- IM or ITV should compensate for physiological movements and variations in size, shape, and position of the CTV in relation to an internal reference point

- ITV often applied in lung SBRT where it encloses the full CTV in all respiratory phases



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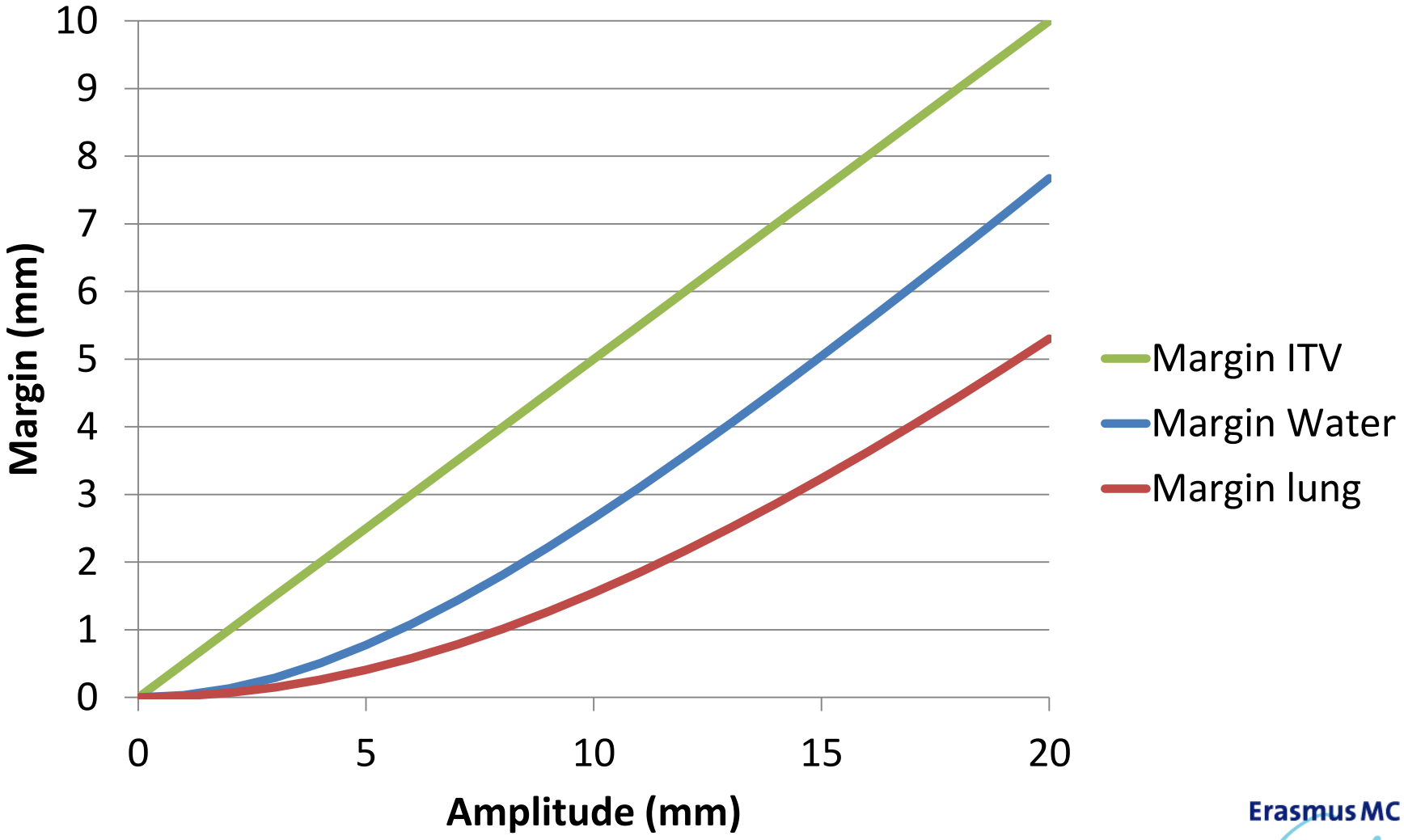
Margin vs ITV for Perfect Inter-fraction Alignment



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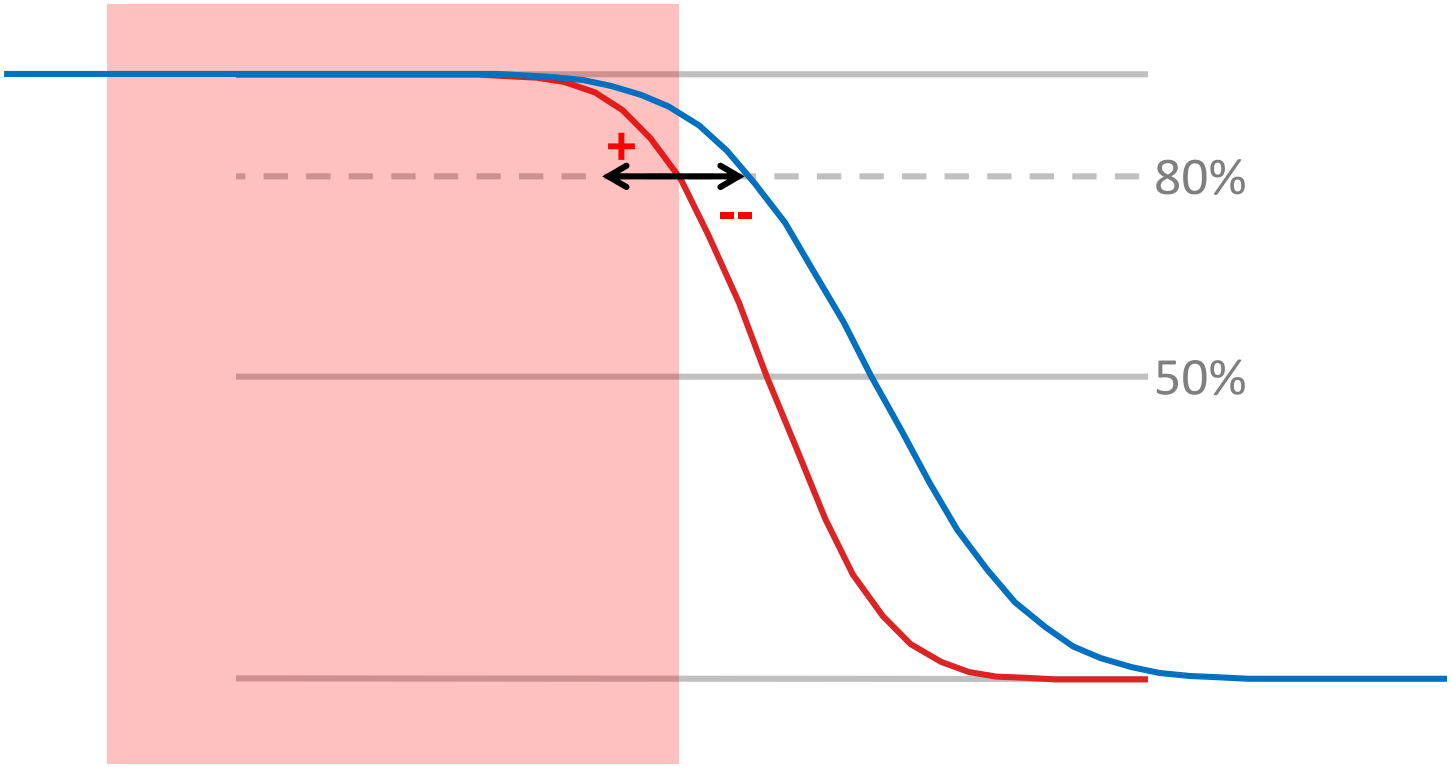
Margin Recipe for Random Error



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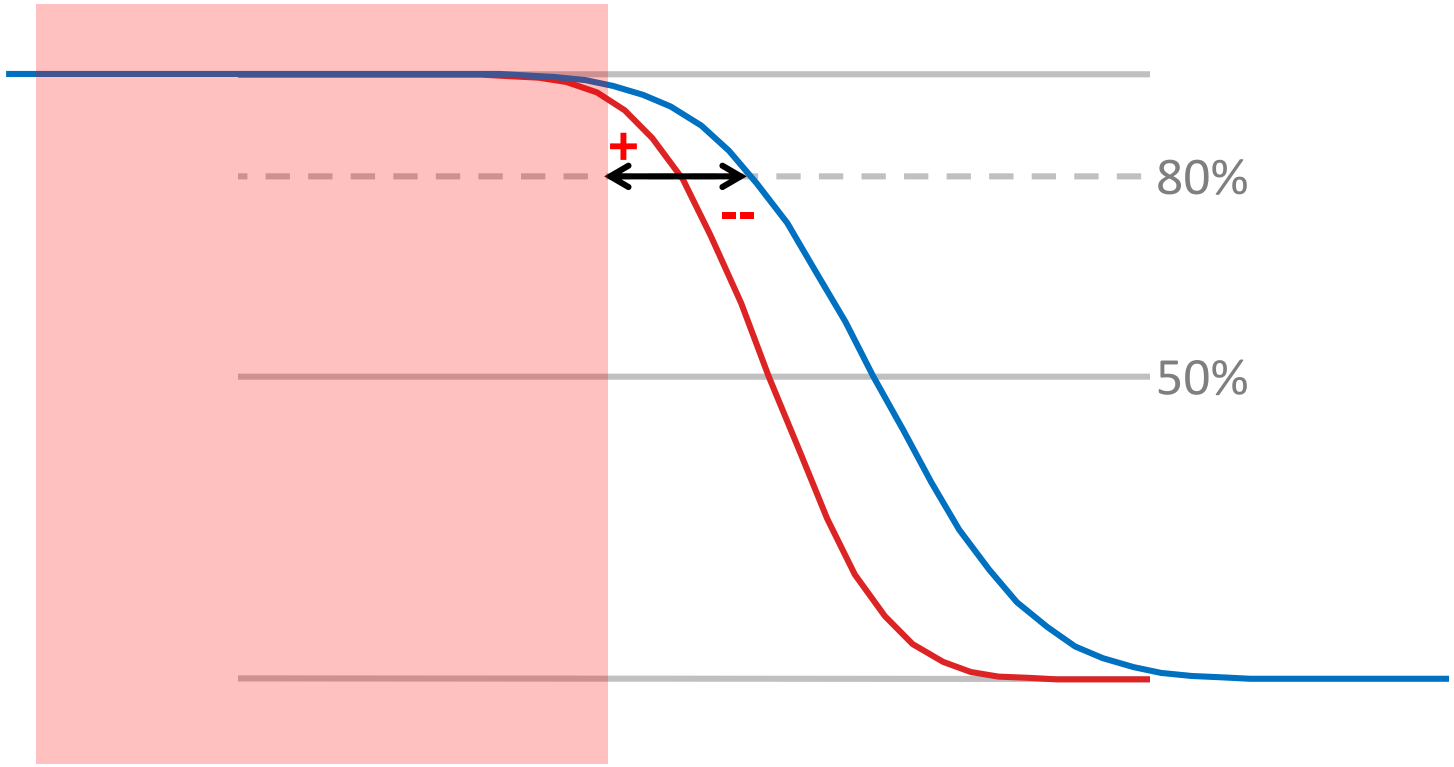
Margin Recipe for Random Error



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Some Concluding Remarks

- **In radiosurgery often 0-mm margins are being advocated**
  - There will always be residual geometrical uncertainties
    - Target definition
    - Errors in image-guidance systems
    - Indirect measures of tumor position

- **Always verify the margin algorithm used in the Treatment Planning System**
  - 3D margin algorithm (and not 2D)
  - What is the resolution of the margin algorithm (e.g. CT resolution?)
    - Verify that margin are not truncated to voxel positions, especially in the superior-inferior direction

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References for Further Reading

- Stroom JC, de Boer HC, Huizenga H, Visser AG. Inclusion of geometrical uncertainties in radiotherapy treatment planning by means of coverage probability. Int J Radiat Oncol Biol Phys. 1999 Mar 1;43(4):905-19.
- Van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: Dose population histograms for deriving margins in radiotherapy. Int J Radiat Oncol Biol Phys. 2000;47:1121-1135.
- van Herk M, Remeijer P, Lebesque JV. Inclusion of geometric uncertainties in treatment plan evaluation. Int J Radiat Oncol Biol Phys. 2002 Apr 1;52(5):1407-22.
- Witte MG, van der Geer J, Schneider C, Lebesque JV, van Herk M. The effects of target size and tissue density on the minimum margin required for random errors. Med Phys. 2004 Nov;31(11):3068-79
- International Commission on Radiation Units and Measurements. Prescribing, recording and reporting photon beam therapy. ICRU Report 50. Bethesda; 1993.
- International Commission on Radiation Units and Measurements. Prescribing, recording and reporting photon beam therapy (Supplement to ICRU Report 50). ICRU Report 62 Bethesda; 1999.
- International Commission on Radiation Units and Measurements. Prescribing, recording and reporting Photon Beam Intensity-Modulated Radiation Therapy (IMRT). ICRU Report 83; 2010.
- Wolthaus JW, Sonke J-J, van Herk M, et al. Comparison of different strategies to use four-dimensional computed tomography in treatment planning for lung cancer patients. Int J Radiat Oncol Biol Phys 2008;70:1229–1238.
- van Herk M, Witte M, van der Geer J, Schneider C, Lebesque JV Int. J. Radiation Oncology Biol. Phys., Vol. 57, No. 5, pp. 1460–1471, 2003.
- Wunderink W PhD Thesis Erasmus University, Rotterdam, The Netherlands http://hdl.handle.net/1765/23257.
- Gordon JJ, Siebers JV. Convolution method and CTV-to-PTV margins for finite fractions and small systematic errors. Phys Med Biol. 2007 Apr 7;52(7):1967-90.

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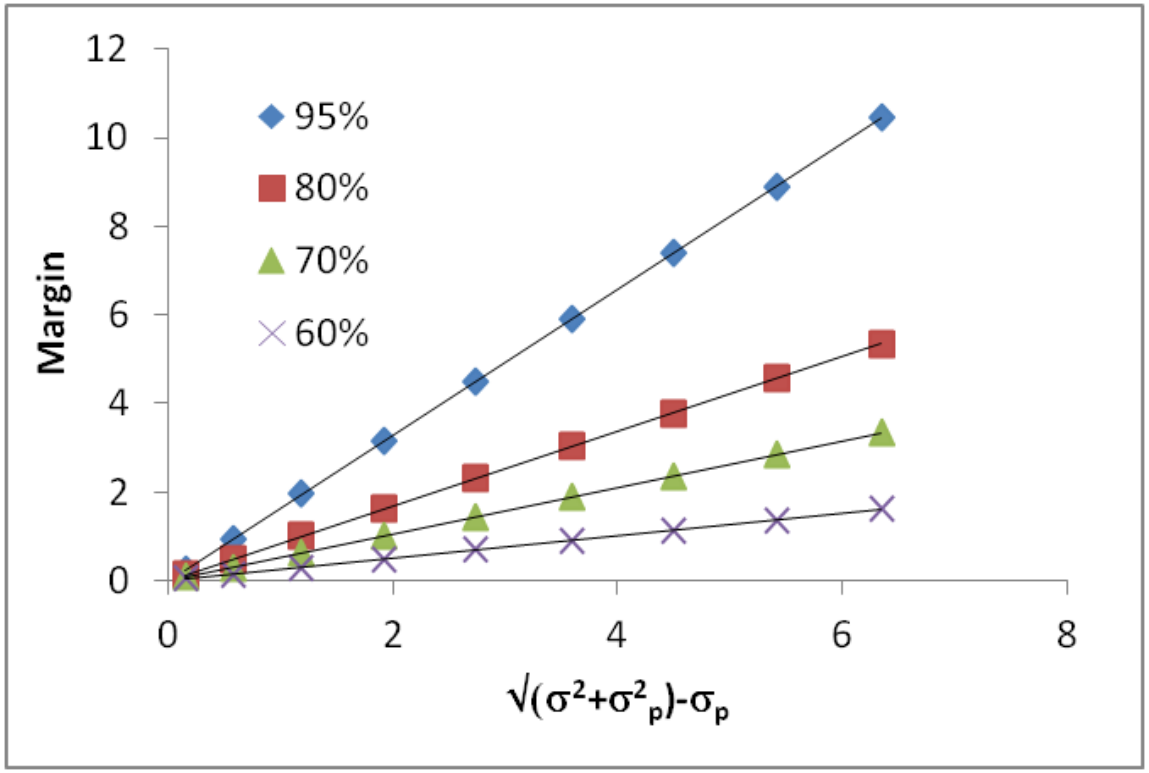
Random Margin and Prescription Level



Prescription level	β
95%	1.64
80%	0.84
70%	0.52
60%	0.25

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Management of targets w/o respiration induced motion

Prostate

Stephanie Tanadini-Lang

University Hospital Zürich

UniversityHospital Zurich

Universität Zürich[UZH]

ESTRO School

Outline

- Delineation uncertainty
  - Definition of the prostate
  - Definition of the tumor lesion
- Management of interfractional motion
  - Image guidance
- Management of intrafractional motion
  - Patient fixation
  - Rectal balloons
  - Patient instructions
  - Active motion compensation

Questions

Prostate SBRT

Which is the best choice for an optimal rectal preparation for prostate SBRT?

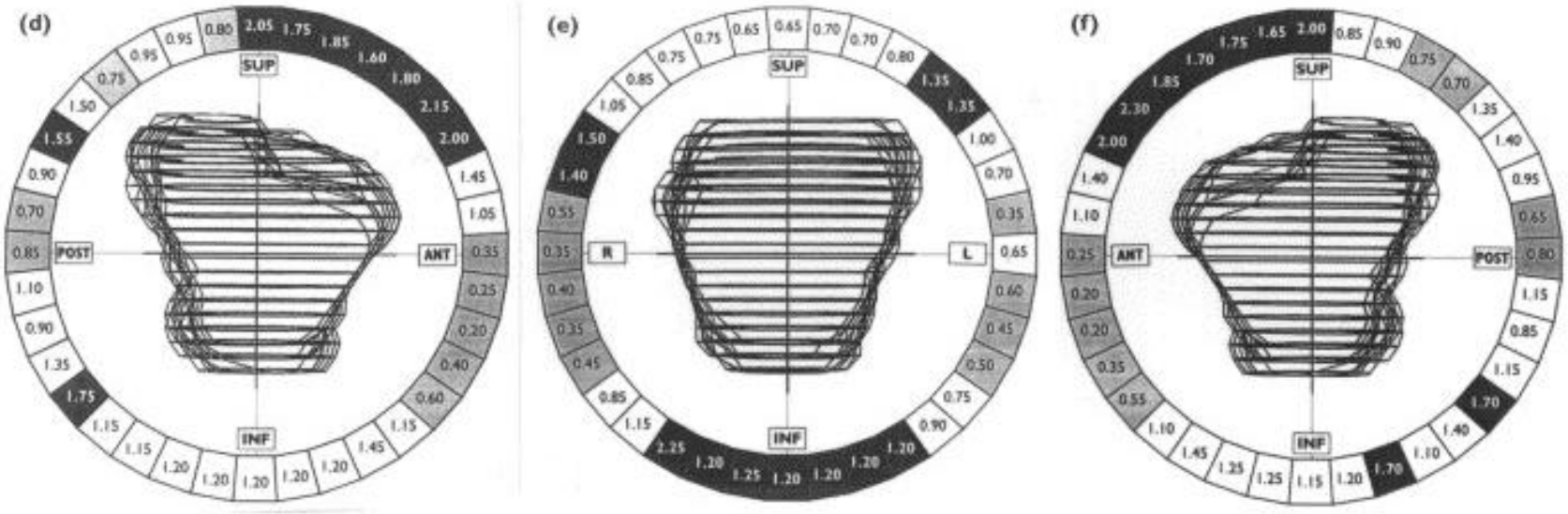
Patient positioning / fixation

Recommandations for patient positioning fixation for SBRT

In treatment imaging

What is the optimal time interval imaging during treatment for brain metastasis, spine, begnin brain diseases, lung, prostate... ?

Delineation uncertainty

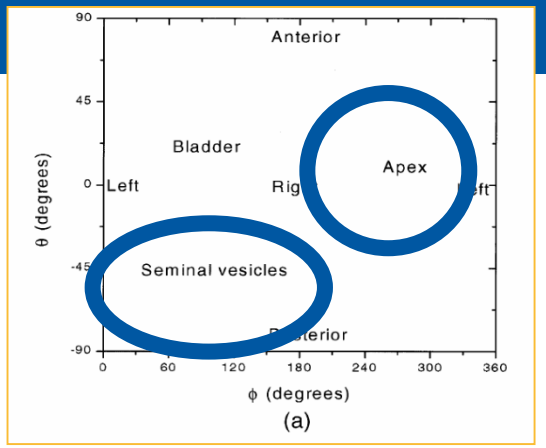


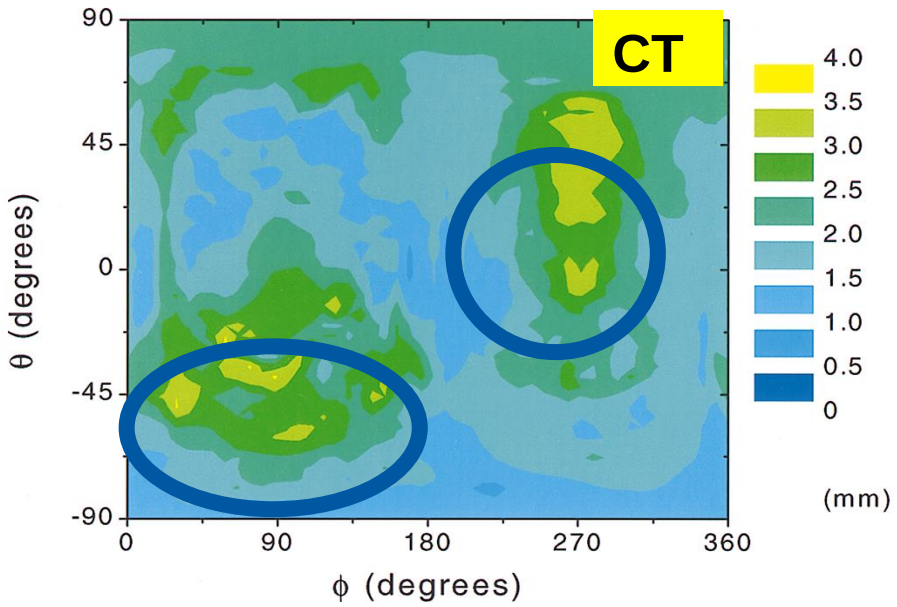
Seddon et al, Radiother Oncol, 2000; 56(1); 73–83

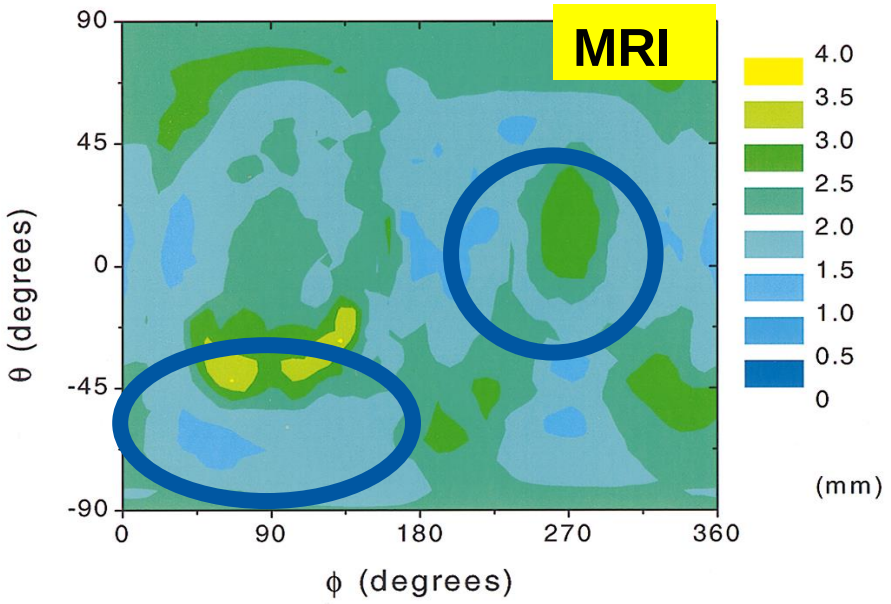
Large interobserver differences in delineation of the prostate.

Delineation uncertainty

Inter-observer variations – MRI vs CT







Reduced inter-observer variations using MRI.

Rasch et al, IJROBP 1999

UniversitätsSpital Zürich

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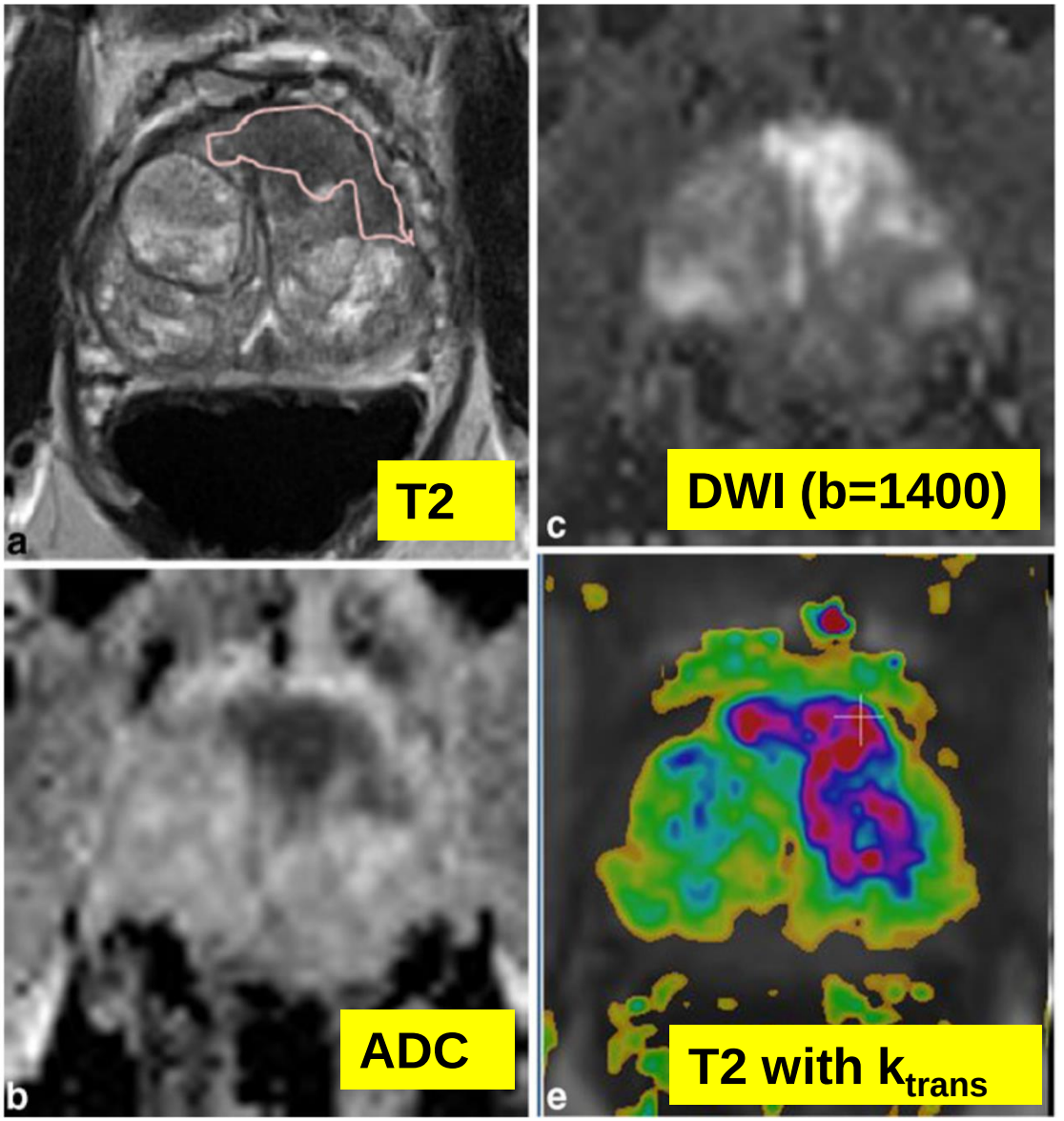
Definition of the tumor lesion

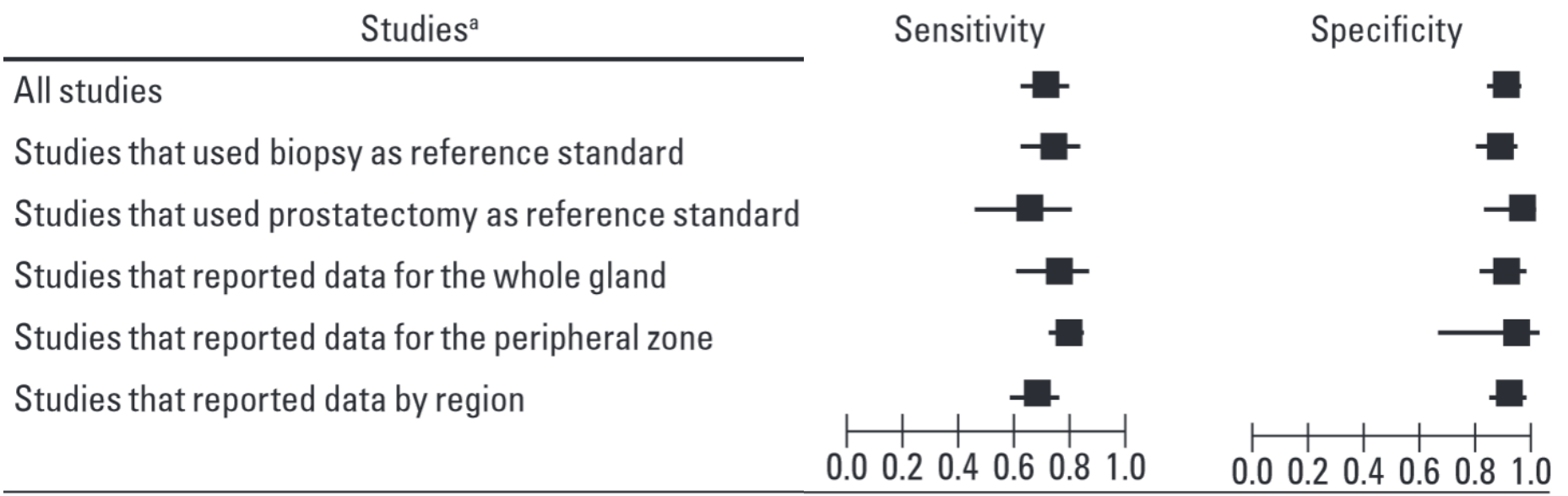
Multiparametric MRI imaging



Barenetst, Eur Radiol (2012), ESUR guidlines

UniversitätsSpital Zürich

Definition of the tumor lesion



de Rooij et al, AJR 202.2 (2014): 343-351.

Sensitivity and specificity not large enough to irradadiate the tumor lesion alone.

MRI to CT Registration

Keep patient positioning the same for MRI and CT scanning

- Flat table top
- Similar bladder filling and rectum filling instructions (also for treatment)
- No rectal coil!!!!

Markers are poorly visible on standard MRI sequences that are used to visualize the tumor

- Use additional sequence to visualize markers in order to facilitate MRI-to-CT registration

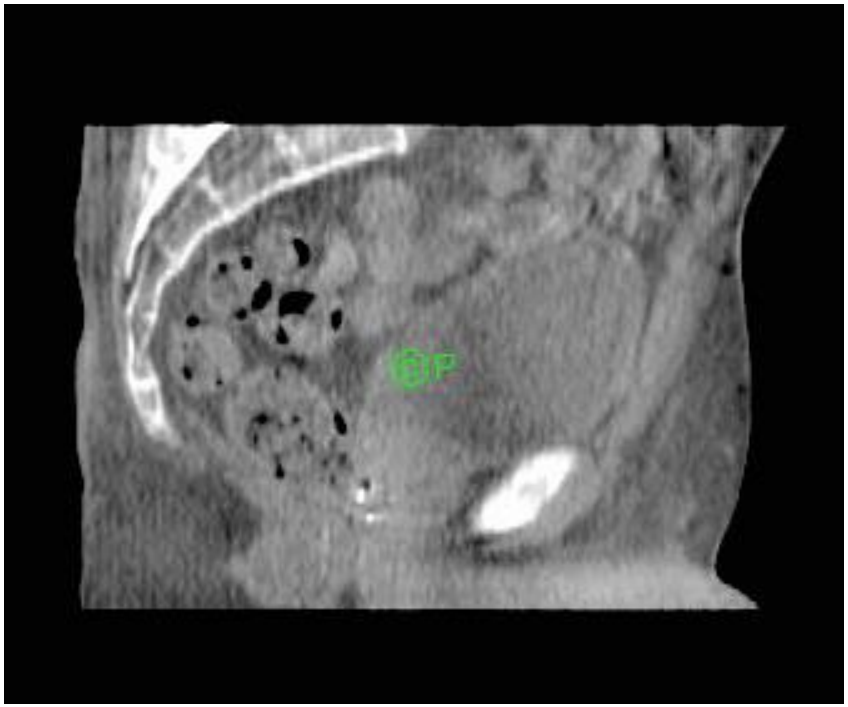
Calypso markers give large artefact in MRI

- Do MRI before implantation of markers

Discuss with the radiologist the MRI settings and sequences

- A MRI for radiotherapy has other requirements as for radiology purposes (e.g. slice thickness)

Interfractional motion



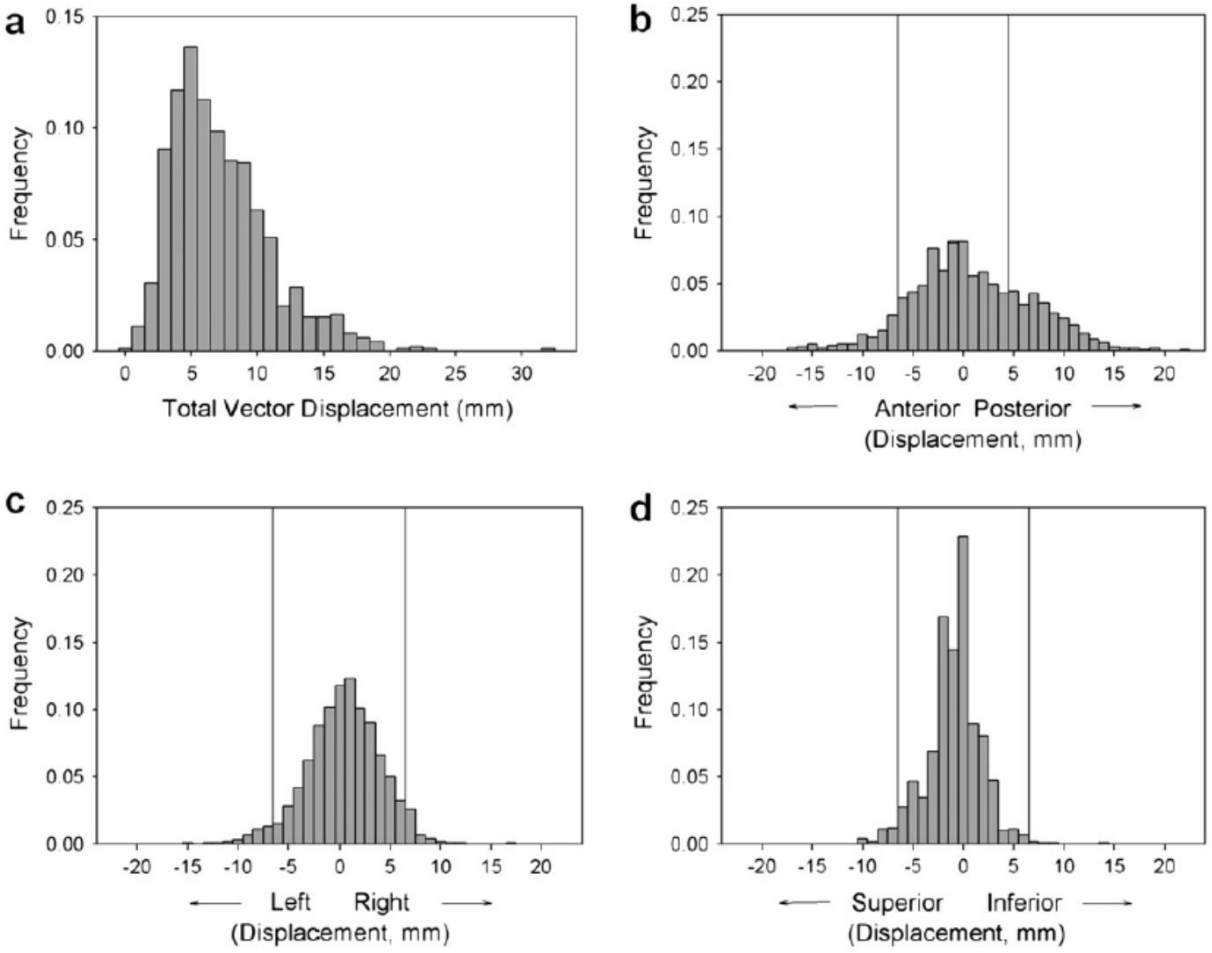
Different bladder filling

Different rectal filling

Different patient positioning

Anatomical changes of the patient

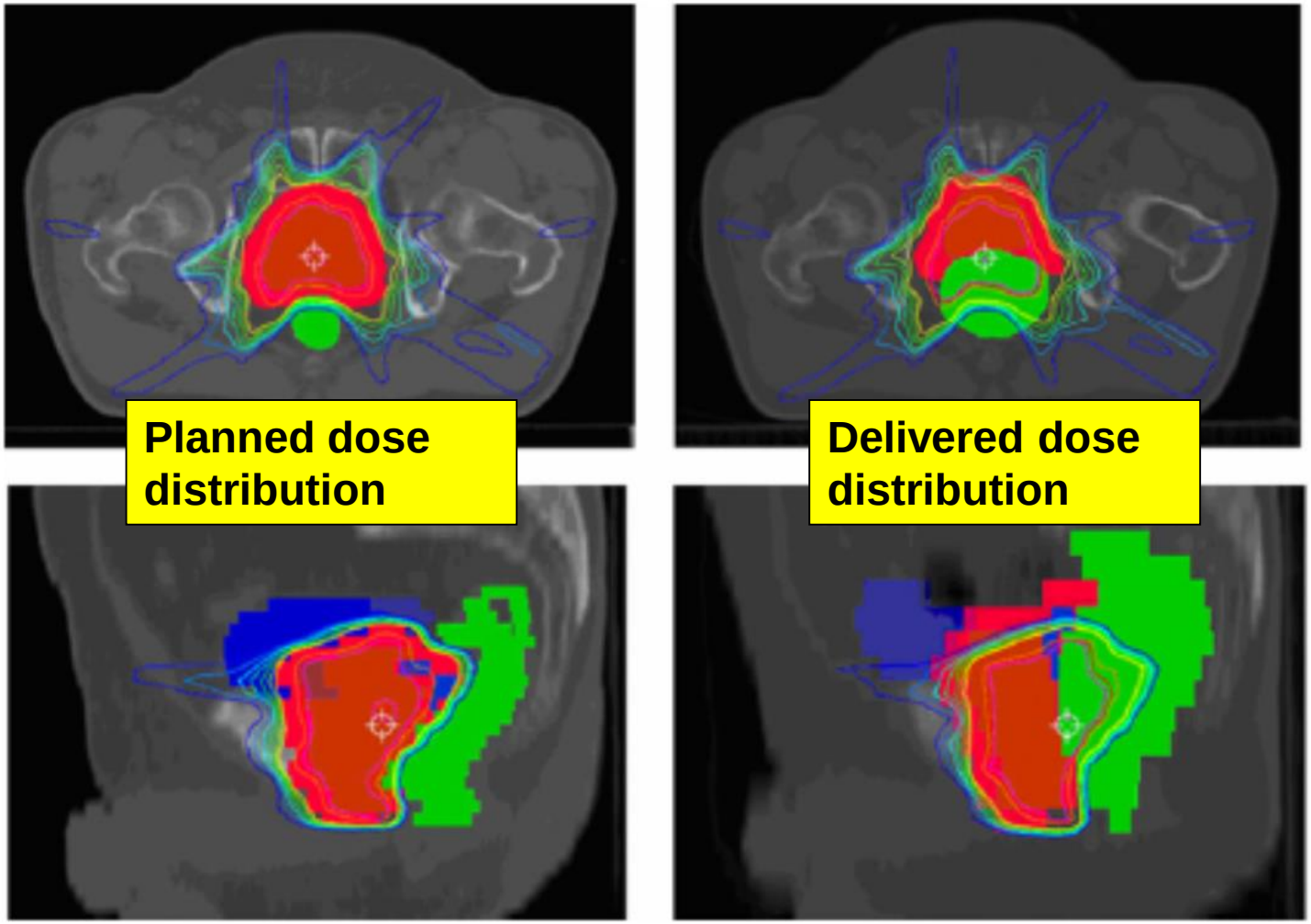
Interfractional motion



→ Up to 3 cm interfractional motion.

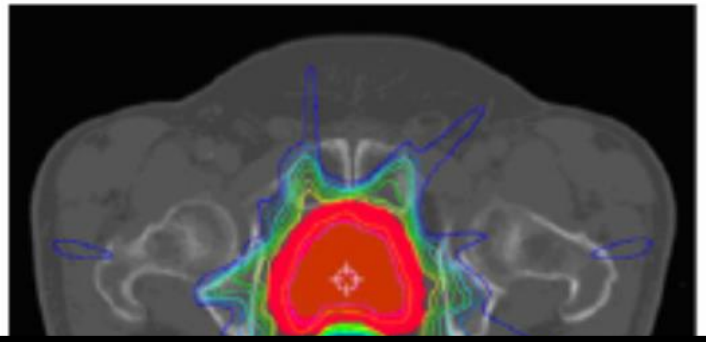
Bylund et al, IJROBP 2008

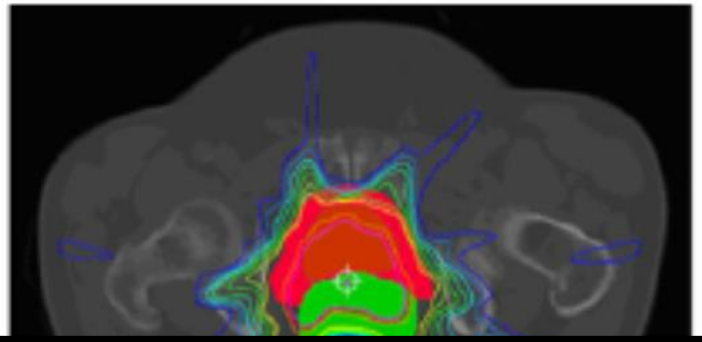
Interfractional motion – Dosimetric impact



Wertz et al, 2007, Phys Med Biol

Interfractional motion – Dosimetric impact



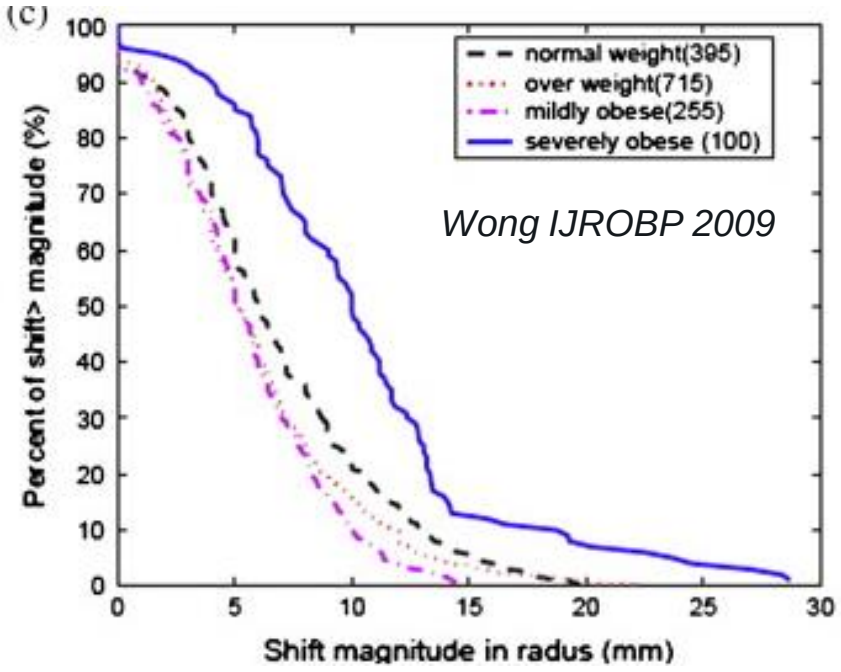


Volume covered by 95% dose	Reference plan [%] mean ± SD	Value deviations uncorrected plan [%-p] mean (min to max)
Prostate	84.5 ± 4.7	−13.3 (−23.6 to −2.1)
Seminal vesicles	67.4 ± 8.7	3.9 (−27.7 to 26.9)

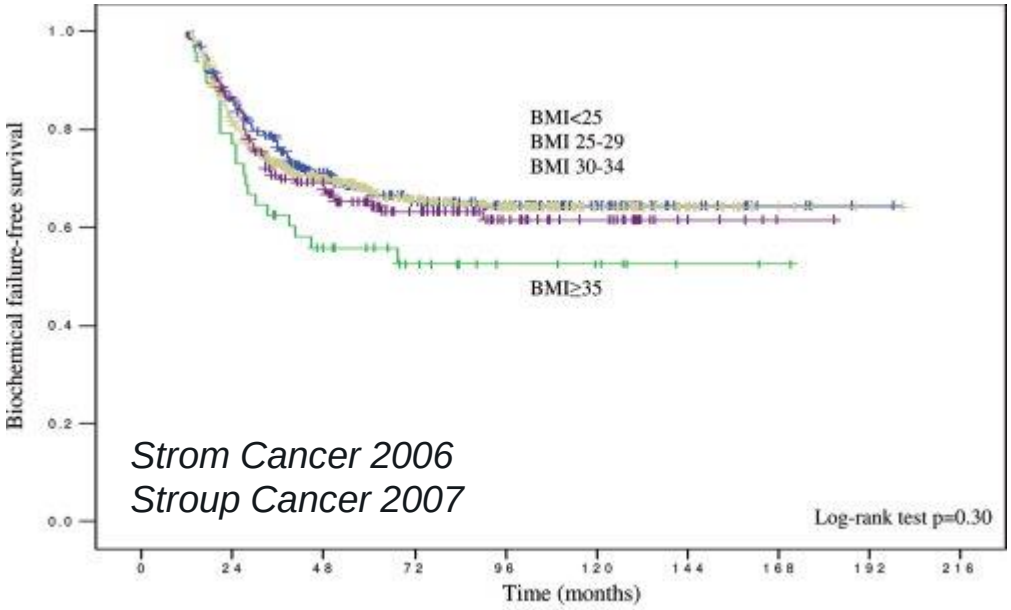
Wertz et al, 2007, Phys Med Biol

Interfractional motion – Impact on outcome

Set-up errors in relationship to the patients` BMI



Wong IJROBP 2009



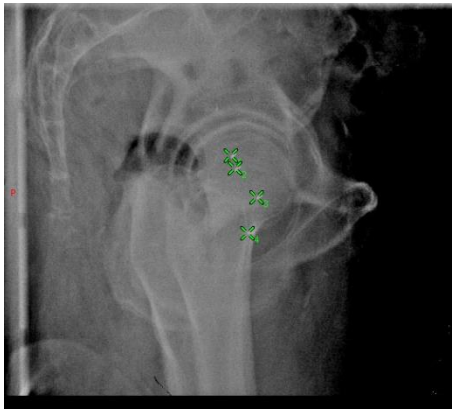
Strom Cancer 2006
Stroup Cancer 2007

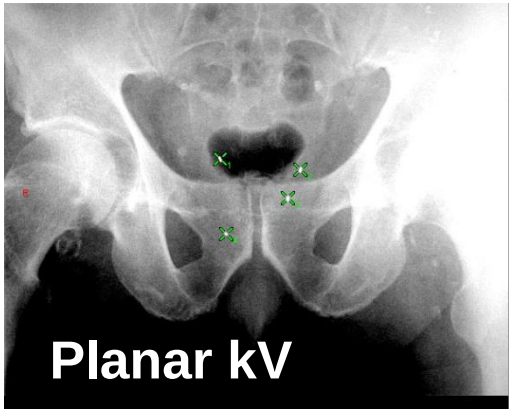
Log-rank test: BMI 25-29 vs. < 25 (P = 0.76); 30-34 vs. < 25 (P = 0.52); ≥ 35 vs. < 25 (P = 0.06)

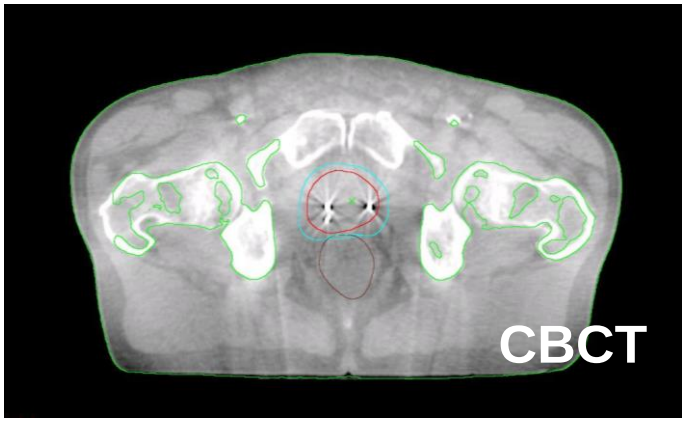
Inaccurate set-up could explain inferior PSA control in obese patients
➢Need for image – guidance

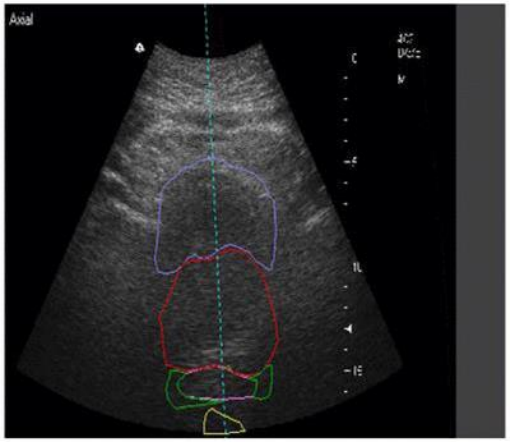
Management of interfraction motion

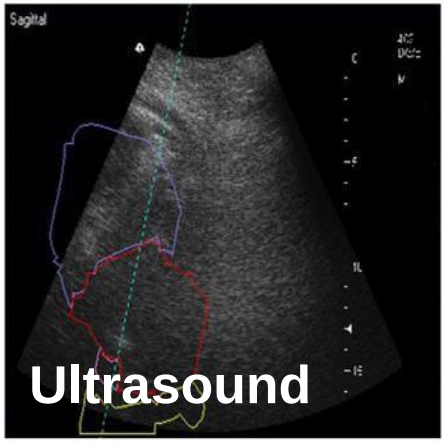
Image guidance

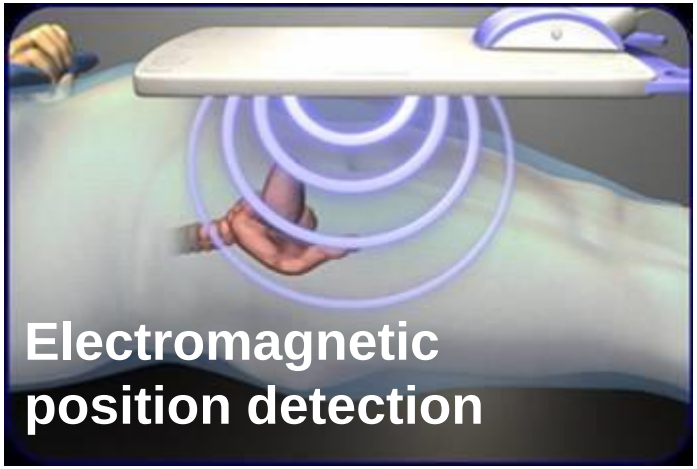












Management of interfraction motion

Image guidance – reduction of margins

Scenarios	Image Guidance Frequency (%)	Margins (mm)		
		Anterior/ Posterior	Lateral	Superior/ Inferior
1. No imaging	0	12	10	10
2. Initial fraction only	3	14	14	7
3. Mean of initial 3 fractions	10	10	9	5
4. Mean of initial 5 fractions	16	9	8	5
5. Mean of initial 7 fractions	23	8	7	5
6. Weekly imaging, 3-mm threshold	21	8	8	6
7. First 5 fractions + weekly imaging, patient-specific threshold	32	7	8	5
8. Imaging every other fraction, running mean	49	7	7	4

Kupelian et al, Semin Radiat Oncol, 2008

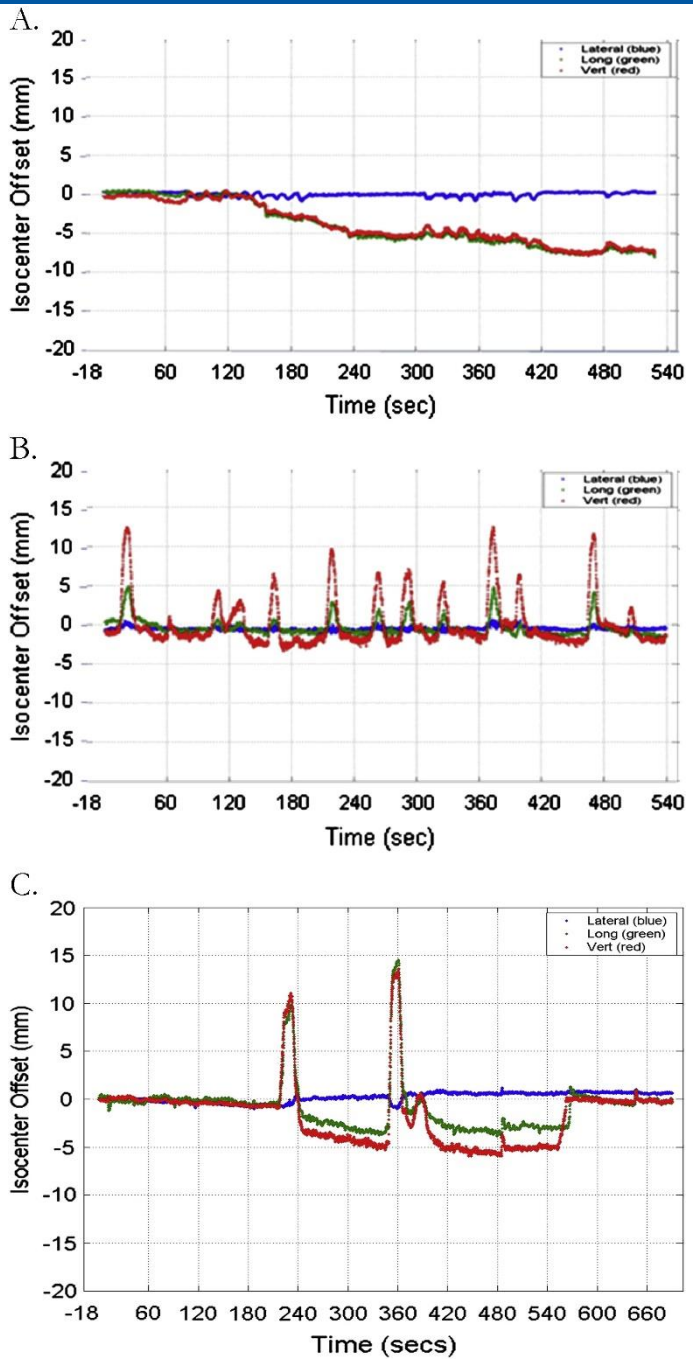
Intrafractional motion

2 TYPES OF MOTION:

A: Slow drift motion
→Mainly posterioly and inferiorly
→Can reach large extends over long time periods
→Probably due to pelvic musculature relaxation or/and
→Gradually Moving rectal content

B: Erractic motion
→Sudden and transient
→Often significant extend
→Probably related due to peristaltic motion

C: Combination of A and B



Langen et al, IJROBP, Volume 71, Issue 4, 15 July 2008

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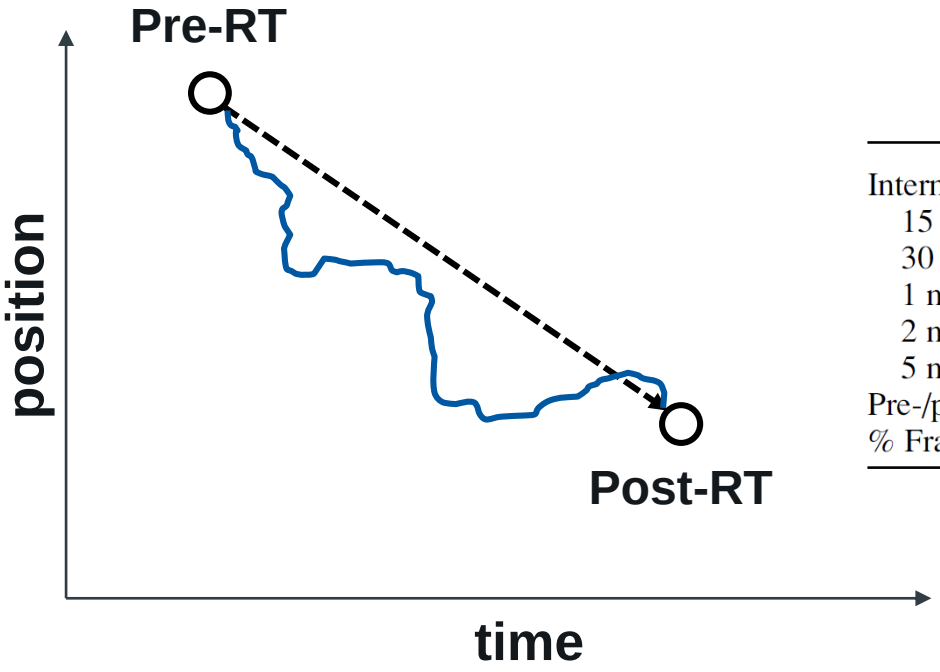
Intrafractional motion



Model	Displacement 3 mm	5 mm	7 mm
Intermittent imaging sensitivity (%)			
15 s	96	94	88
30 s	92	89	85
1 min	85	81	73
2 min	77	71	63
5 min	57	60	46
Pre-/post-treatment imaging sensitivity (%)	53	49	39
% Fractions exceeding displacement	37	15	7

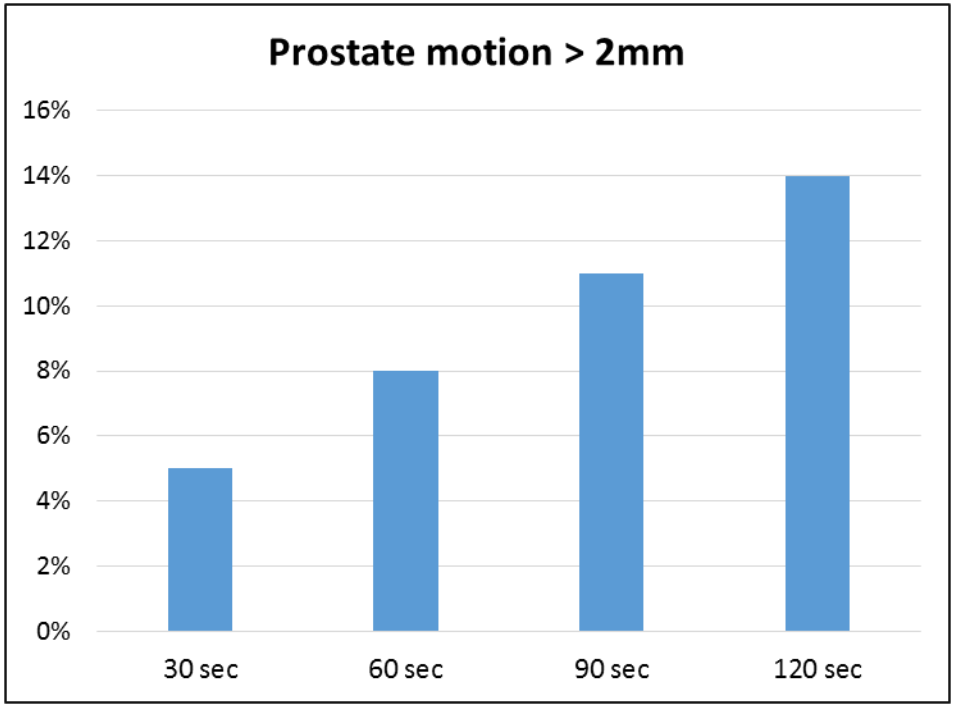
30 sec

Noel IJROBP 2009

Pre and Post RT imaging does not accuratly describe intra-fractional motion.

Intrafractional motion

- 21 patients
- 427 data sets
- Stereostopic x-ray



Xie IJROBP 2008

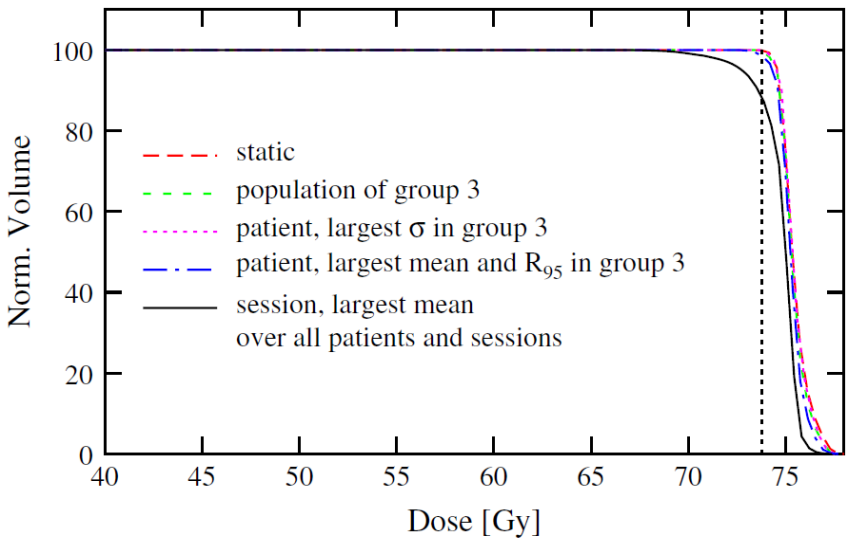
- **Intra-fractional prostate motion „usually“ within 2mm**
- **Intrafractional motion increases with time.**

Dosimetric impact of prostate motion

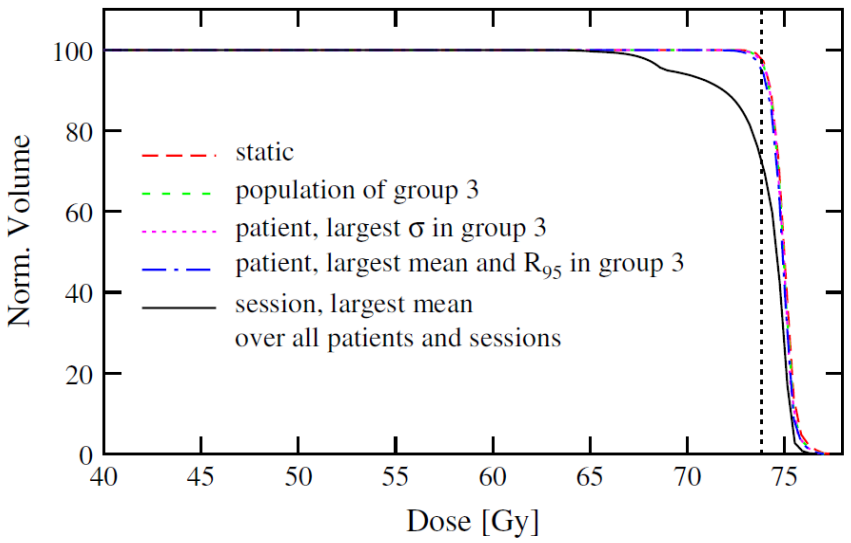
Conventionally fractionated radiotherapy:

Haisen IJROBP 2008

5mm margin



2mm margin



- **Relevant loss of target coverage in individual fractions**
- **No impact in conventionally fractionated RT.**

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Dosimetric impact of prostate motion

Stereotactic Body Radiation Therapy:

- Longer treatment fractions with ↑ motion
- Less „smearing“ effect
- Smaller margins

Van de Water IJROBP 2014

3mm SM 4 Fx	% Px with 98% coverage
w/o tracking	**61 %**
15 sec imaging interval	91%
60 sec imaging interval	96%

- **Increased relevance of prostate motion in SBRT**
- **Increased imaging frequency does not necessarily improve accuracy**

Management of intrafraction motion

Patient positioning – prone versus supine

Boyley et al, 2004:

- → Prone positioning versus supine positioning
- → 28 patients
- → Replanning after half of the fractions with changed patient position
- → anterior - posterior prostate motion was much smaller in supine position

Management of intrafraction motion

Patient positioning - fixation

Roswell et al, 2008:

→ Standard Vaclok versus BodyFix with abdominal compression

→ no difference in intra-fractional motion

It is recommended to treat patients in supine position with ankle and knee support.

Management of intrafraction motion

Patient instructions

Smitsmans et al, 2009:

→ Evaluation of a dietry protocol in combination with magnesiumoxide

→ Reduced feces, gas and moving gas

→ However no reduction in intrafractional motion

Libs et al, 2011, McNair el al, 2011, Nichol et al, 2011, Abdollah et al 2012:

→ No reduction of intrafrational motion due to dietry protocols and/or magnesiumoxide

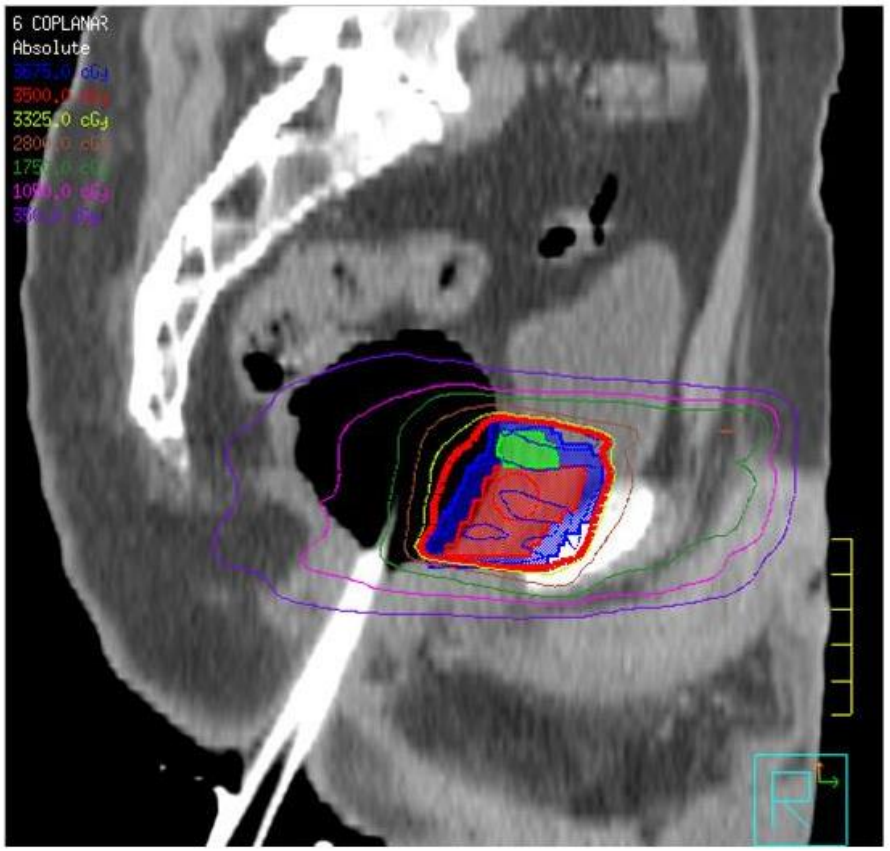
Dietry protocols or magnesiumoxides are not recommended for routine clinical practice.

Management of intrafraction motion

Rectal balloons

Aims:

- Reduce intrafractional motion
- Reduce dose to the anterior rectal wall (re-build up effect at the air-tissue interface)
- Move the posterior rectal wall away from the target



Teh et al, Disc Med 2010

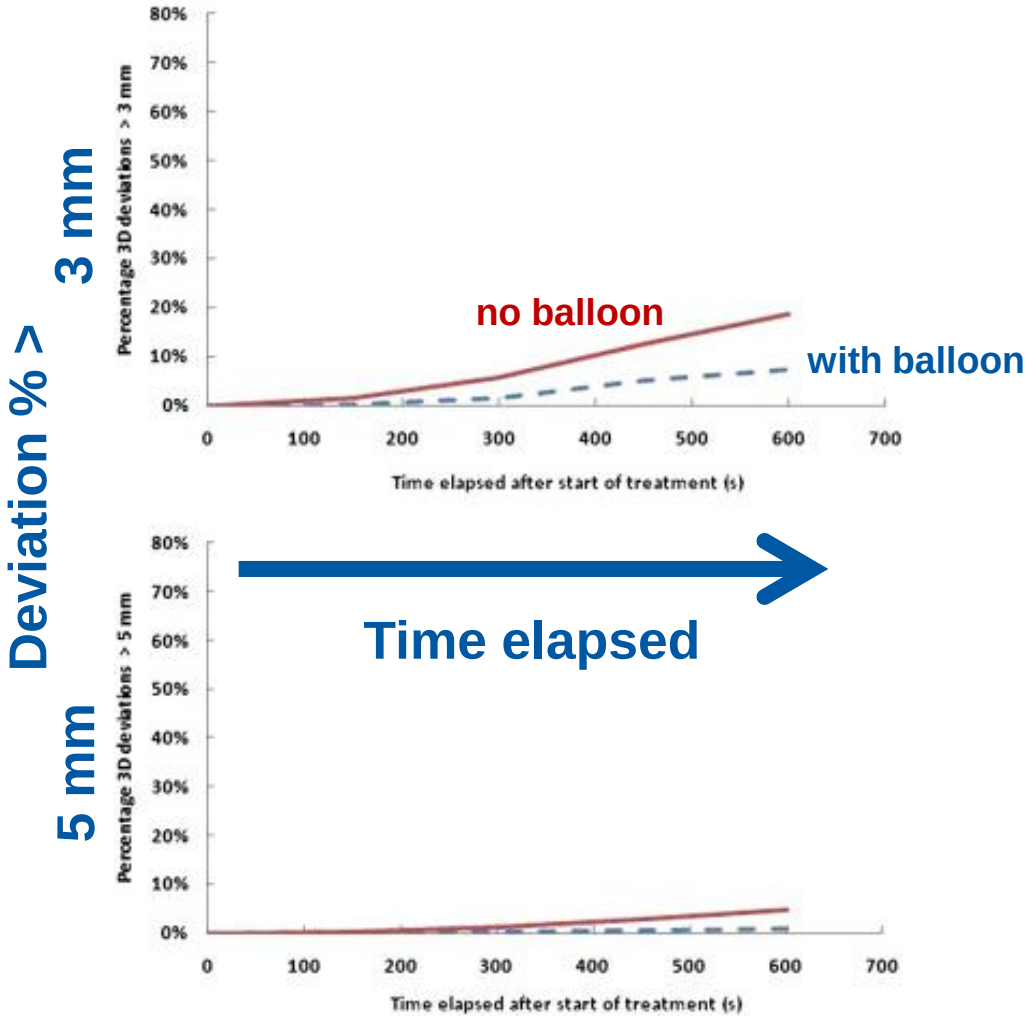
Management of intrafraction motion

Rectal balloons

30 patients:
15 treated with balloon
15 treated without

Monitoring of implanted electromagnetic transponders

ERB significantly reduces intrafraction prostate motion, and may in particular be beneficial for treatment sessions longer than 150 s.



Smeenk IJROBP 2012

Management of intrafraction motion

Rectal balloons disadvantages

Dosimetric gain is mostly for 3D CRT (i.e. 4-field box)

Irritation of the anal canal (hemorroids) Cho KJMS 2009

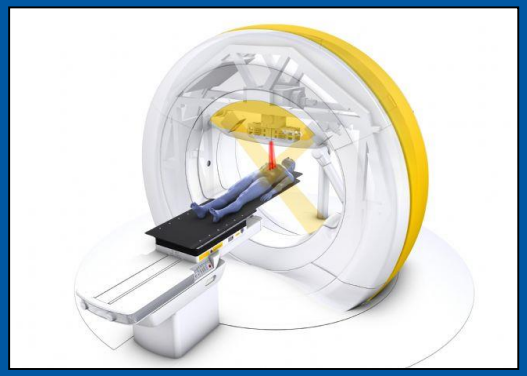
Complex procedure: may require frequent adjustments to avoid systematic errors or deformations (Jones Med Phys 2012, Miralbell IJROBP 2010)

Increases treatment time

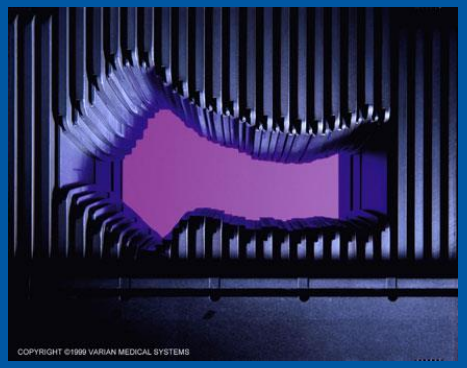
Mixed experience, complex and invasive procedure with questionable benefit.

Tracking – Adaption to the motion

‘Special machines’



‘Add-ons’ Conventional Linacs



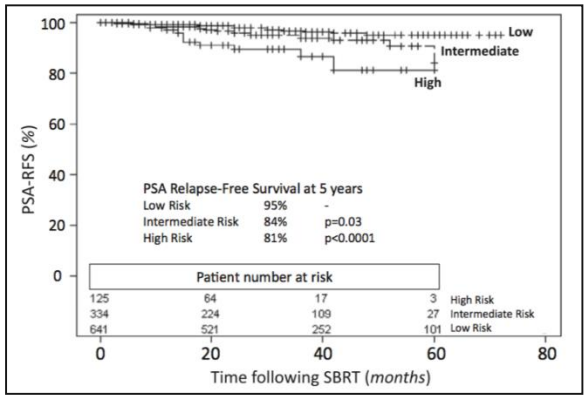
MLC and couch tracking can be performed on conventional linear accelerators, whereas for linac tracking dedicated machines are needed.

Tracking – Adaption to the motion

Cyberknife

King 2013

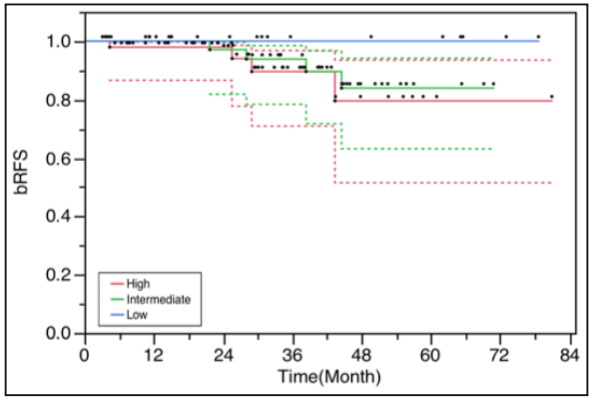
- 1100 patients
- 5 Fx SBRT



Couch tracking

Shimizu 2014

- 110 patients
- 30 Fx



MLC tracking

Keall 2014

- 10 patients
- 30 Fx

Questions

Prostate SBRT

Which is the best choice for an optimal rectal preparation for prostate SBRT?

Patient positioning / fixation

Recommandations for patient positioning fixation for SBRT

In treatment imaging

What is the optimal time interval imaging during treatment for brain metastasis, spine, begnin brain diseases, lung, prostate... ?

Recommeded Literature

Kupelian, Patrick, and John L. Meyer. "Prostate cancer: image guidance and adaptive therapy." (2007): 289-314.

Guckenberger, Matthias. "Value of Patient Immobilization in External Beam Radiotherapy for Prostate Cancer." *Radiotherapy in Prostate Cancer*. Springer Berlin Heidelberg, 2015. 41-44.

Villeirs, Geert M., et al. "Interobserver Delineation Variation Using CT versus Combined CT+ MRI in Intensity–Modulated Radiotherapy for Prostate Cancer." *Strahlentherapie und Onkologie* 181.7 (2005): 424-430.

van de Water, Steven, et al. "Intrafraction prostate translations and rotations during hypofractionated robotic radiation surgery: Dosimetric impact of correction strategies and margins." *International Journal of Radiation Oncology* Biology* Physics* 88.5 (2014): 1154-1160.

Thank you for providing me with some slides:
Marianne Aznar
Mischa Hoogeman

Thank you for your attention.

Questions?

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Management of brain and spine SBRT: Positioning

Coen Hurkmans, clinical physicist

Catharina Hospital, The Netherlands

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Content

- The treatment chain
- End-to-end tests and set-up accuracy
- intrafraction motion brain treatment
- intrafraction motion spine treatment
- Brain SBRT: End-to-end accuracy at CZE

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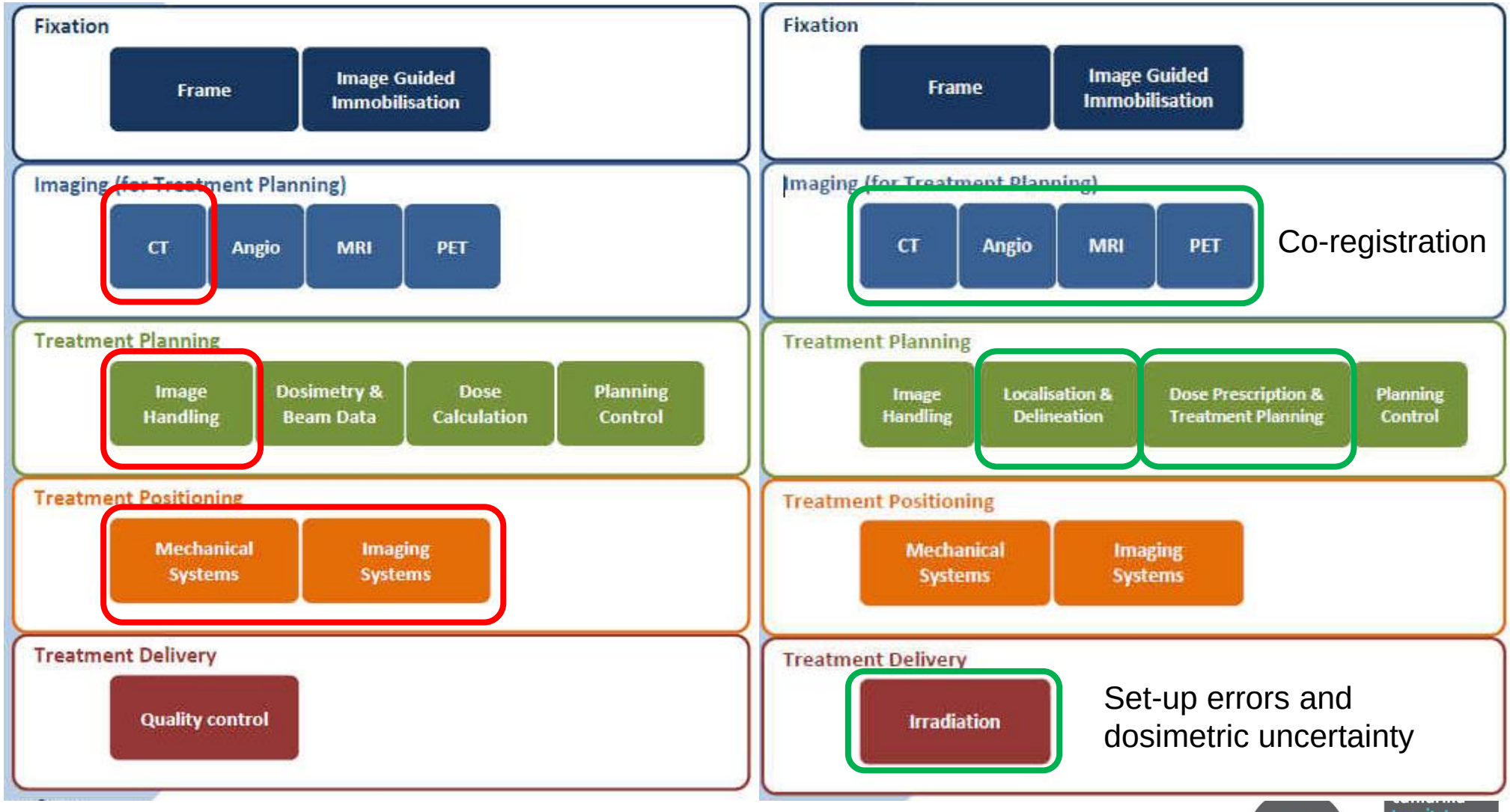
SBRT QA: the treatment chain

End-to-end test



From NCS report 25 (2015): QA of brain SBRT

SBRT QA: AAPM TG 101 (2010) end-to-end tests

TABLE V. Summary of published QA recommendations for SBRT and SBRT-related techniques.

Source	Purpose	Proposed test	Reported achievable tolerance	Proposed frequency
Ryu *et al.*, 2001[a]	End-to-end localization accuracy	Stereo x ray/DRR fusion	1.0 to 1.2 mm root mean square	Initial commissioning and annually thereafter
Ryu *et al.*, 2001[a]	Intrafraction targeting variability	Stereo x ray/DRR fusion	0.2 mm average, 1.5 mm maximum	Daily (during treatment)
Verellen *et al.*, 2003[b]	End-to-end localization accuracy	Hidden target (using stereo x ray/DRR fusion)	0.41 ± 0.92 mm	Initial commissioning and annually thereafter
Verellen *et al.*, 2003[b]	End-to-end localization accuracy	Hidden target (using implanted fiducials)	0.28 ± 0.36 mm	Initial commissioning and annually thereafter
Yu *et al.*, 2004[c]	End-to-end localization accuracy	Dosimetric assessment of hidden target (using implanted fiducials)	0.68 ± 0.29 mm	Initial commissioning and annually thereafter
Sharpe *et al.*, 2006[d]	CBCT mechanical stability	Constancy comparison to MV imaging isocenter (using hidden targets)	0.50 ± 0.5 mm	Baseline at commissioning and monthly thereafter
Galvin *et al.*, 2008[e]	Overall positioning accuracy, including image registration (frame-based systems)	Winston–Lutz test modified to make use of the in-room imaging systems	≤ 2 mm for multiple couch angles	Initial commissioning and monthly thereafter
Palta *et al.*, 2008[f]	MLC accuracy	Light field, radiographic film, or EPID	<0.5 mm (especially for IMRT delivery)	Annually
Solberg *et al.*, 2008[g]	End-to-end localization accuracy	Hidden target in anthropomorphic phantom	1.10 ± 0.42 mm	Initial commissioning and annually thereafter
Jiang *et al.*, 2008[h]	Respiratory motion tracking and gating in 4D CT	Phantoms with cyclical motion	N/A	N/A
Bissonnette *et al.*, 2008[i]	CBCT geometric accuracy	Portal image vs CBCT image isocenter coincidence	± 2 mm	daily

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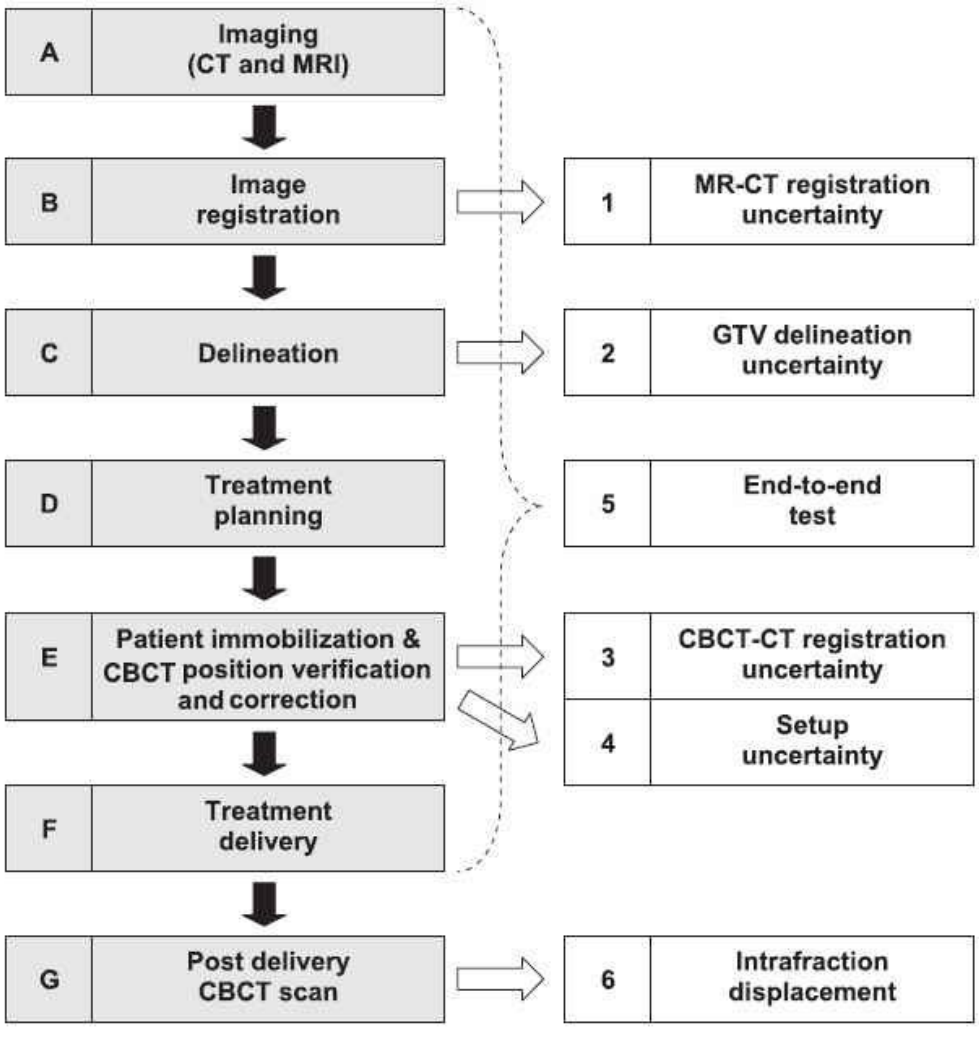
The treatment chain: Measured uncertainties



Error Source	Data based on # patients	# lesions	Direction AP	CC	LR
1) MR-CT registration	10	–			
M [mm]			n.a.	n.a.	n.a.
Σ [mm]			0.32	0.57	0.33
σ [mm]			n.a.	n.a.	n.a.
2) GTV delineation	12	16			
M [mm]			n.a.	n.a.	n.a.
Σ [mm]			0.30	0.29	0.28
σ [mm]			n.a.	n.a.	n.a.
3) CBCT-CT registration (not included in total errors[a])	10	12			
M [mm]			n.a.	n.a.	n.a.
Σ [mm]			0.21	0.17	0.07
σ [mm]			n.a.	n.a.	n.a.
4) Setup variation (not included in total errors[b])	52[c]	69[c]			
M [mm]			0.51	−0.51	−0.06
Σ [mm]			1.35	1.98	1.32
σ [mm]			0.80	1.17	1.23
5) End-to-end test Including CBCT-CT registration	–	2			
M [mm]			0.93	0.50	0.12
Σ [mm]			0.57	0.21	0.68
σ [mm]			0.32	0.66	0.60
6) Intrafraction displacement (= CBCT2–CBCT1) i.e. intrafraction motion + residual couch shift error	52[c]	59[c]			
M [mm]			0.16	0.12	−0.02
Σ [mm]			0.38	0.72	0.56
σ [mm]			0.40	0.55	0.39
Total SRT treatment chain (1 + 2 + 5 + 6)					
Σ_T [mm]			0.82	0.98	0.98
σ_T [mm]			0.51	0.86	0.72
Required GTV-PTV margin [mm] (margin = 2.5 Σ_T + 0.7 σ_T)			2.4	3.1	3.0

Seravalli et al, R&O 116(1)p131 2015

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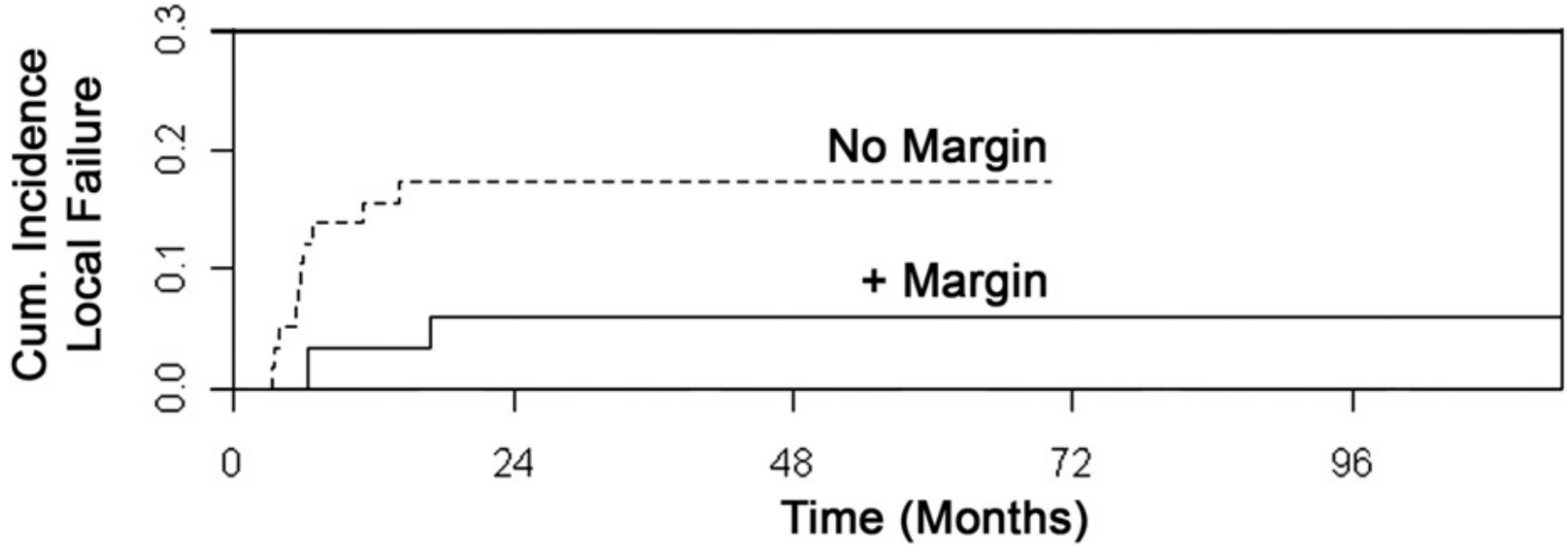
Brain SBRT: required accuracy



The 12-month cumulative incidence rates of LF with and without margin were 3% and 16%, respectively (P=0.042). The 12-month toxicity rates with and without margin were 3% and 8%, respectively (P=0.27).

2 mm margin, Aquaplast mask, Cyberknife treatment, 112 pats

median marginal dose of 20 Gy (range, 12-30 Gy) in 1-5 fractions, prescribed to the median 79% isodose line (range, 60%-90%)

Choi IJROBP 2012, 84 p336

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Intrafraction motion

- AccuForm head cushion (Civco) and BlueBag indexed body immobilization system (Medical Intelligence) and Precise Bite mouthpiece (Civco), 121 pats
- Mean 3D intrafraction motion (mm, °):
  immob 1: 1.1 (± 1.2) and 0.54°
  immob 2: 1.1 (± 1.1) and 0.48°
  immob 3: 0.7 (± 0.9) and 0.47°
  immob 4: 0.7 (± 0.8) and 0.41°
- Rotations: 1° to 1.4° (1D, 1 SD)
- **Intra fraction: 3 and 4 better than 1 and 2**

Tryggestad, IJROBP 80, 2011 P281

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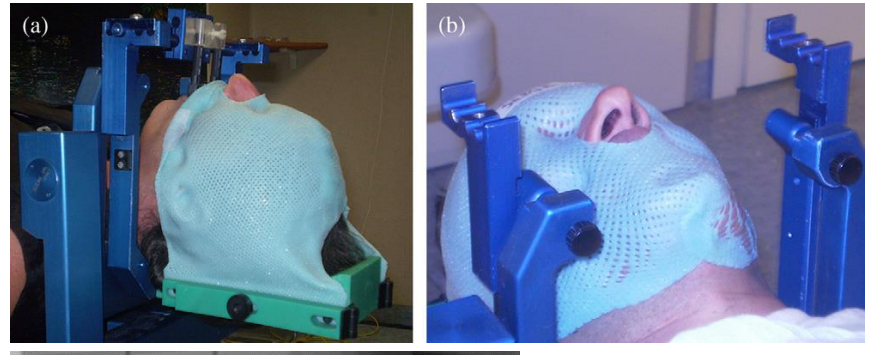
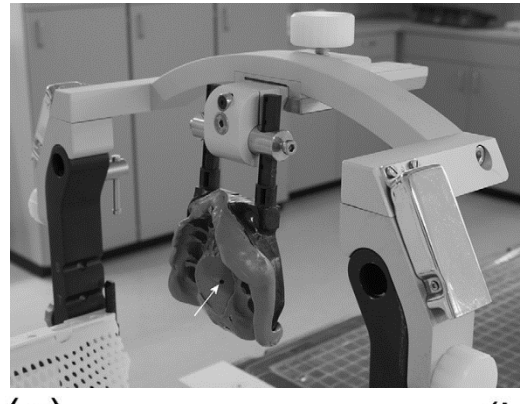
Intrafraction motion with bite blocks

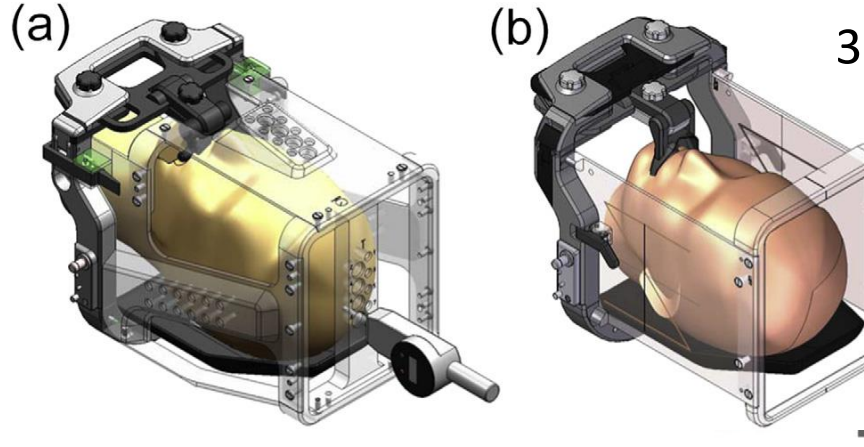
1. Masi, IJROBP 71, 2008 p926 (Novastereo, Novater) (**with bite block, ns**)
   X:-0.2±0.6 Y:0.1±0.6 Z:0.3±0.6
   and rotations:
   -1.0° ±1.6, -0.8° ±1.0° , -0.1° ±1.2°
   trend towards higher intrafraction error with longer treatment time (15 min). Use of bite-block reduced.
2. Santvoort IJROBP 72, 2008 p261, Brainlab
   Mask: 3D: 0.7 ±0.6 mm
   AP:-0.01±**0.10** CC:0.05±**0.28** LR:-0.11±0.20
   Table: 0.02±0.22 CC:-0.02±0.23 LR:-0.05±**0.31**
   With bite block: 3D: 0.4 ± 0.4mm,
   AP:-0.03±**0.06** CC:-0.13±**0.13** LR:-0.11±0.16
   Table: 0.06±0.17 CC:-0.02±0.15 LR:-0.02±**0.11**
   Intrafraction errors for vertical and longitudinal translations and for rotations were smaller with bite block.
3. Ruschin IJROBP 79, 2010 p306 Gamma-Knife bite block accuracy: 3D: 0.4 mm ±0.3 mm



1



2



3

Intrafraction motion: match region

pub	fixation	Result (3D)
Li (2016)	nose tip: Target region:	0.41±0.36 mm (CBCT) 0.56±0.51 mm (IR tracking) 0.34±0.25 mm (CBCT) max 1.5 mm
Guckenberger (2007)	Bone: Δ bone-target:	0.9±0.6mm 1.7 ± 0.7 mm, maximum 2.8 mm (tumour shrinkage)
Ruschin (2010)	Bone: Repositioning tool:	0.4 mm ±0.3 mm (CBCT) 0.7 mm ±0.5 mm (CBCT)

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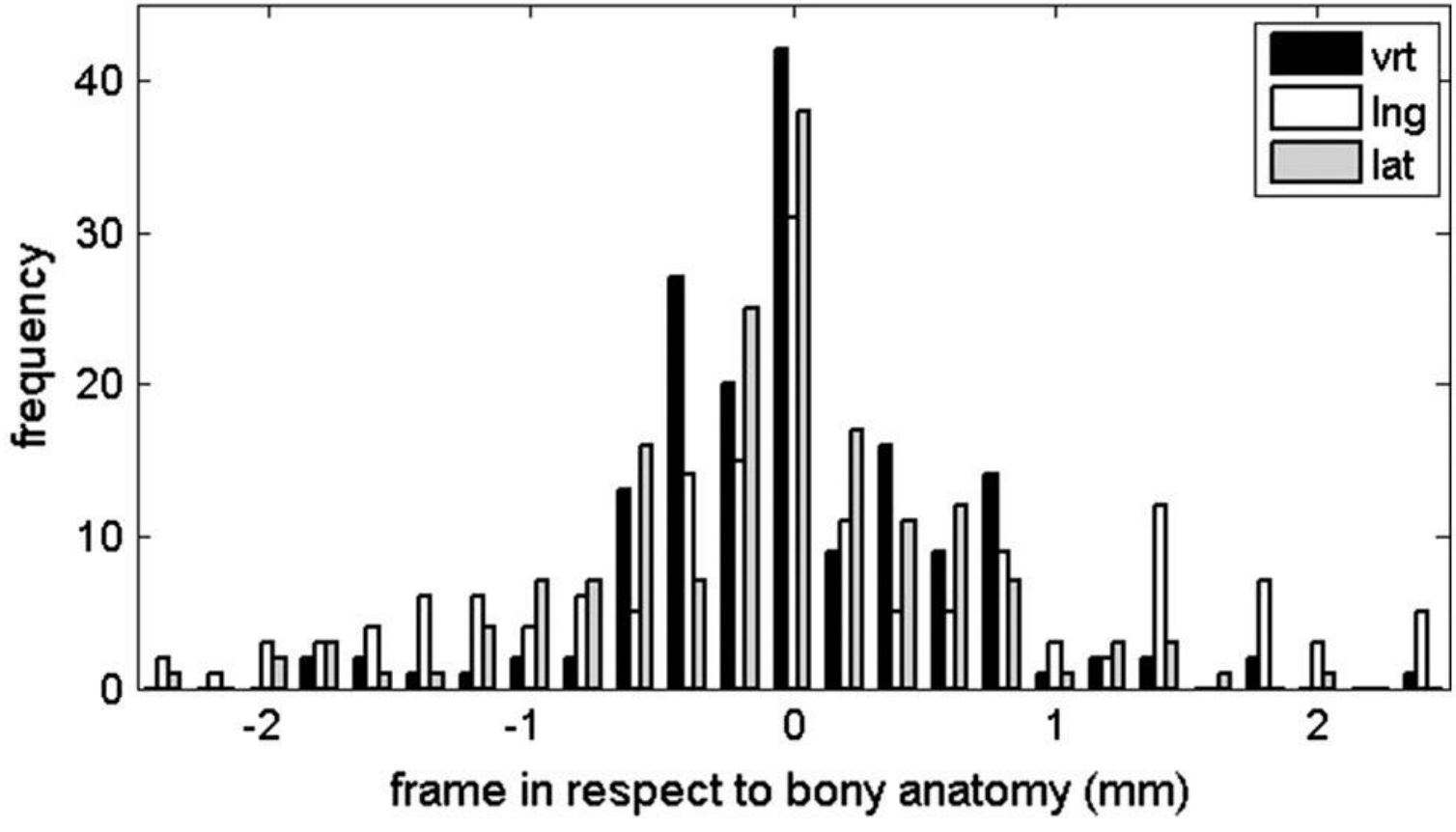
Intra fraction motion: match structure



Lang et al PRO, 2015

73 patients with trUpoint masks on truebeam

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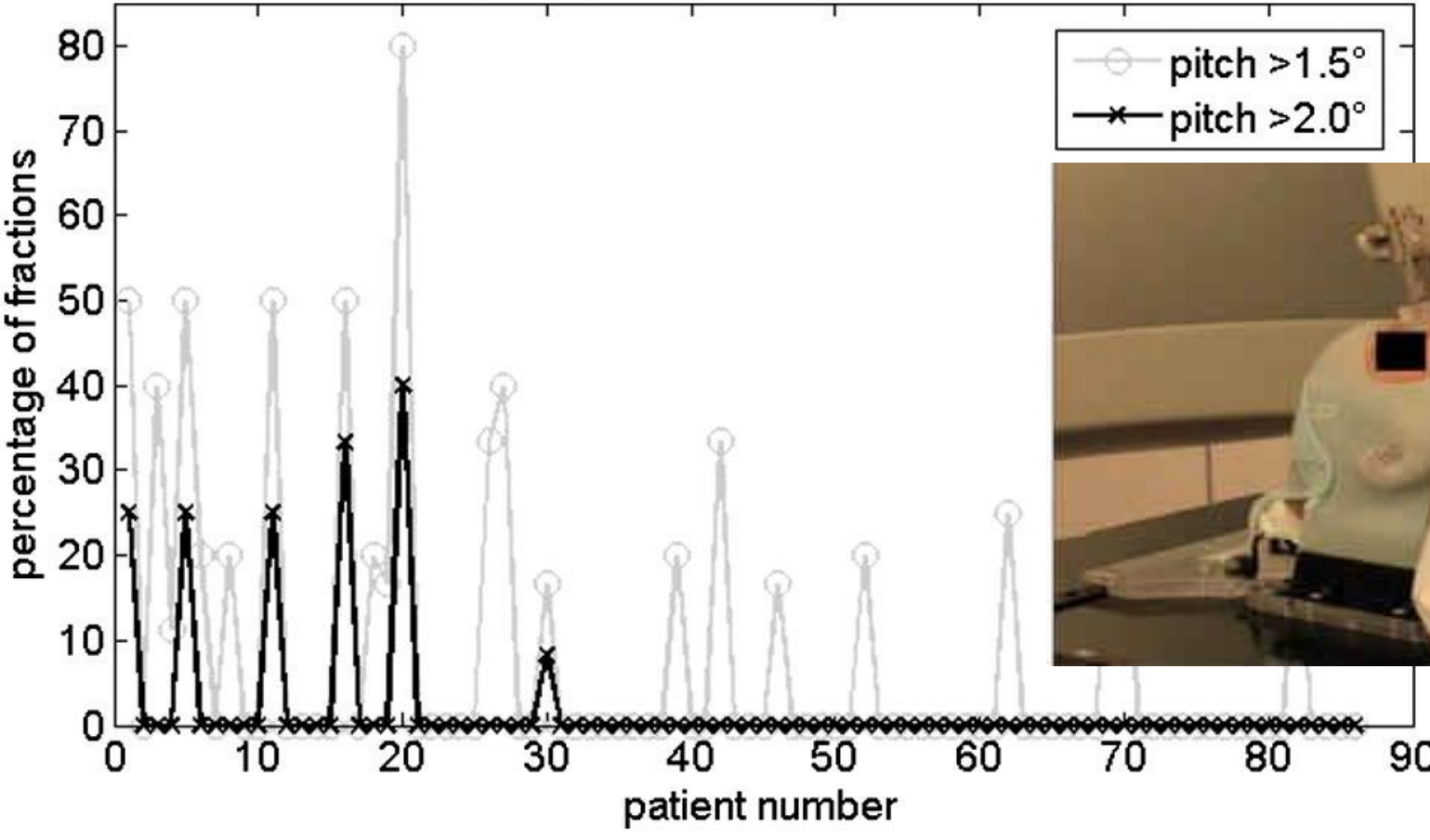
Mask QA: experience with a new system



Lang et al PRO, 2015

73 patients with trUpoint masks on truebeam

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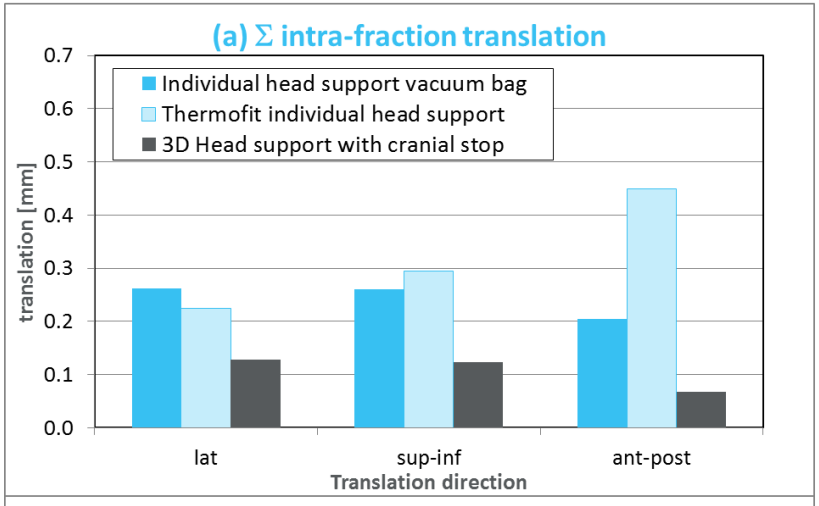
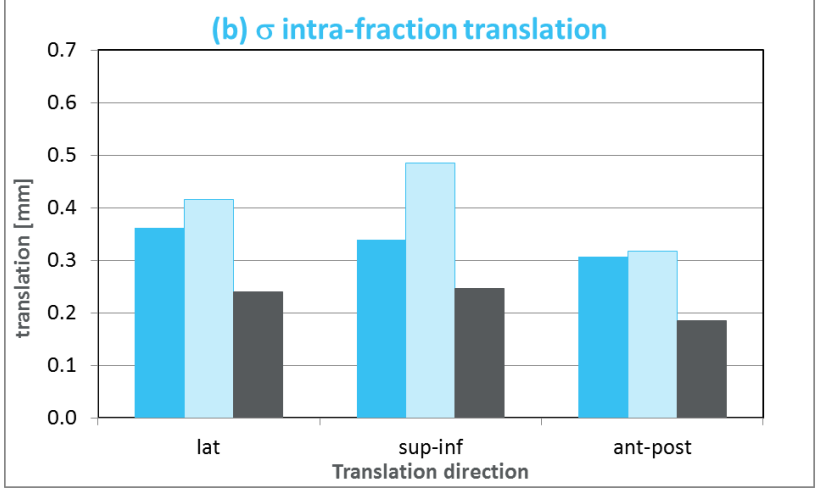
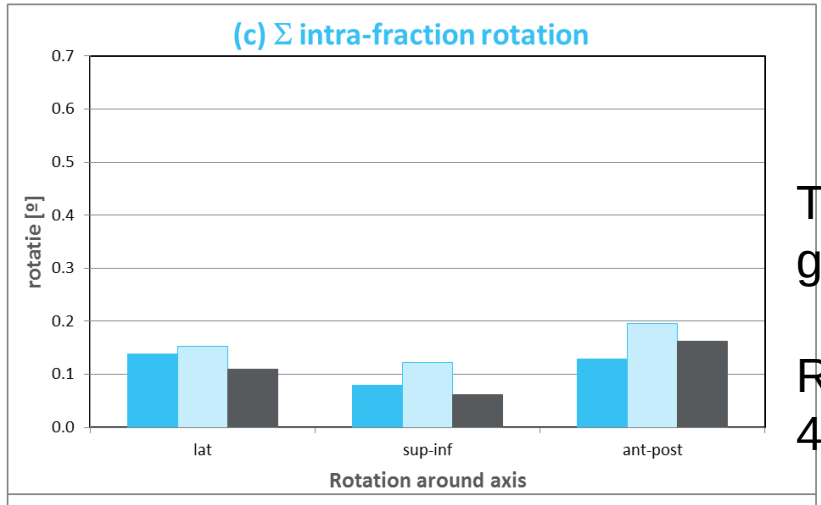
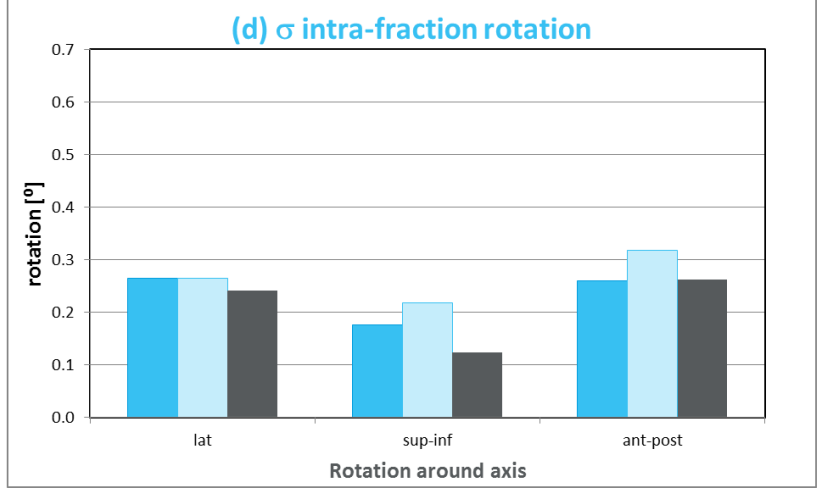
Practical implementation at CZE







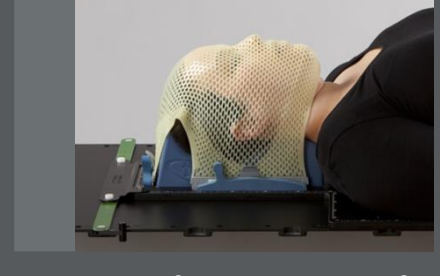


Translations generally < 1mm,

Rotations up to 4° observed

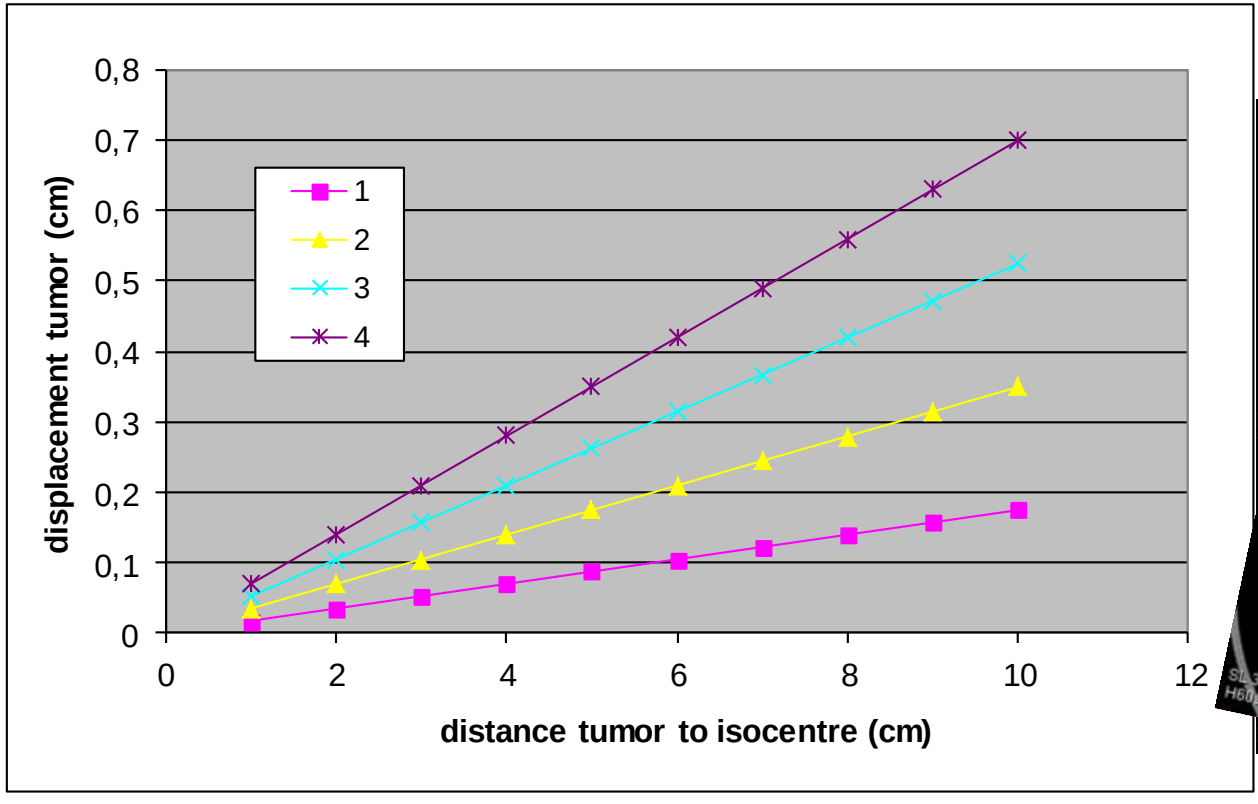
Individual head

Thermofit individual



3D Head support with cranial stop

Rotations in single isocentre treatments with multiple lesions



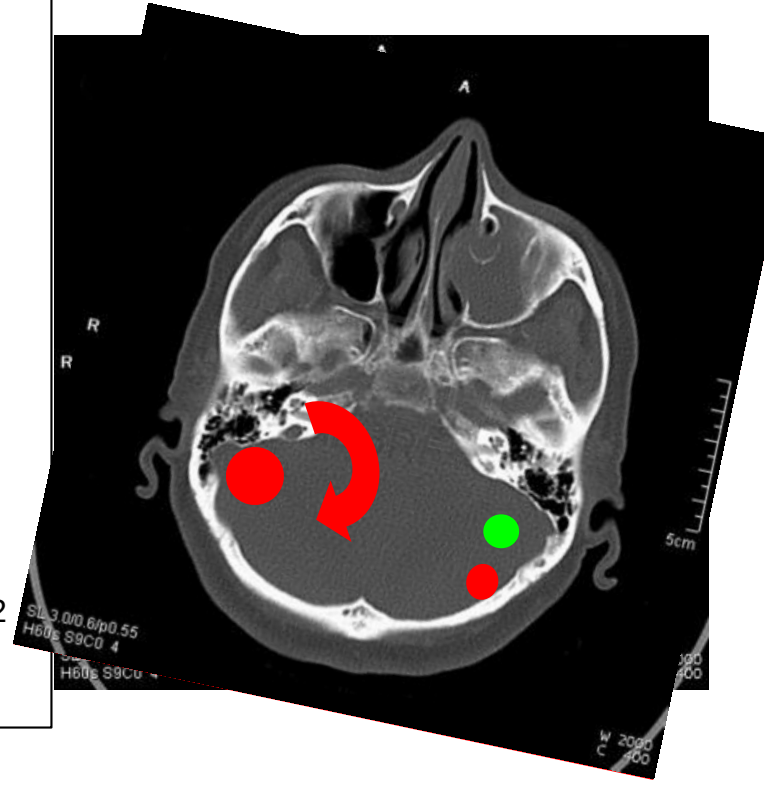
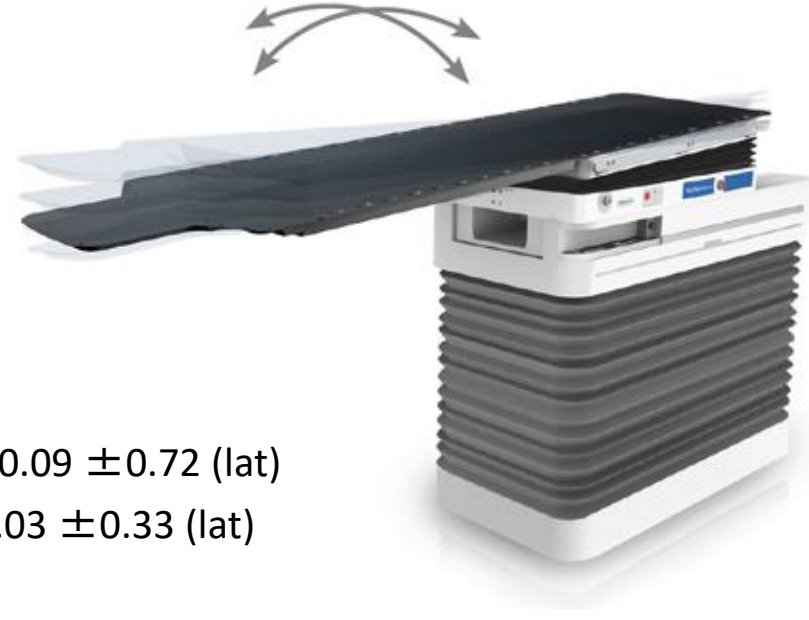


Table assisted rotation correction



• Gevaert (and verellen) IJROBP 83, 2012 p467:

Using Brainlab mask system, 40 pats

Before and after IGRT on Novalis couch:

Mean 3D:

Before: M=1.91 mm ± 1.25 mm and
after: M=0.58 mm ± 0.42 mm.

Mean rotational errors:

Before: -0.10 ±1.03 (vert), 0.23 ±0.82 (long) and -0.09 ±0.72 (lat)

After: 0.01 ±0.35 (vert),0.03 ±0.31 (long) and 0.03 ±0.33 (lat)

(intrafraction, after approx 15 min)

• Ohtakara R&O 102, 2012 p198: Brainlab vs standard mask:
Both are suitable for 6DOF brain SBRT set-up, with standard mask requiring 0.5 mm larger margin

• Further reading: Winey et al JACMP 15(3)p122 2014

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Intra fraction motion: treatment time

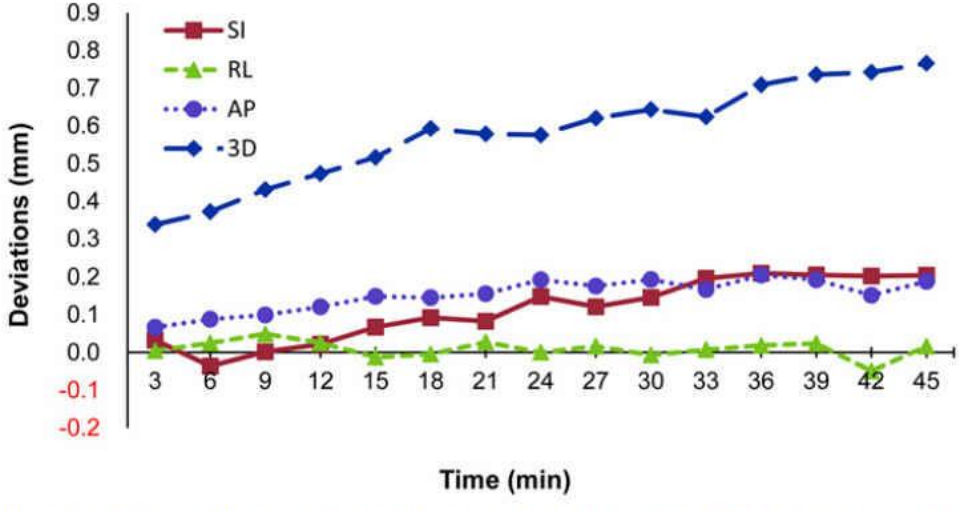
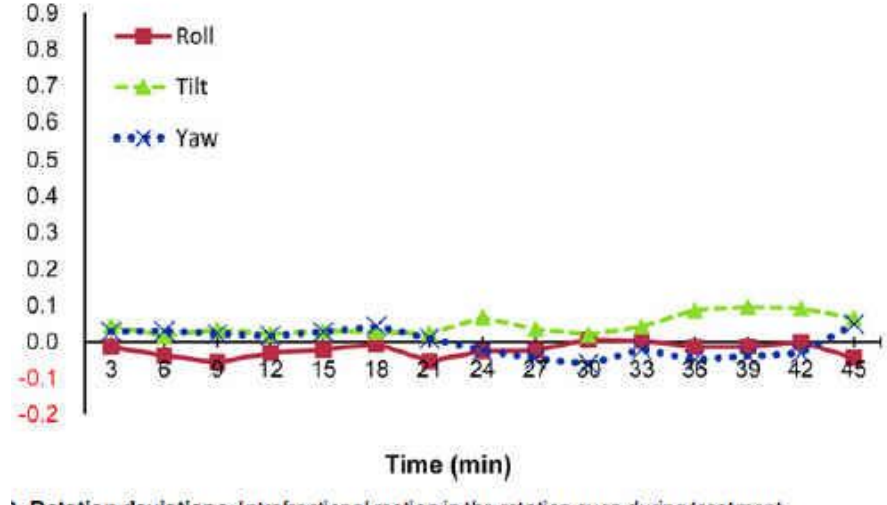


Fig 2. Translational deviations. Intrafractional motion in the translational axes during treatment.



. Rotation deviations. Intrafractional motion in the rotation axes during treatment.

50 patients with masks on cyberknife

Wang et al Plos-one 10(4) 2015

See also: Hoogeman et al, IJROBP 70(2) 2008

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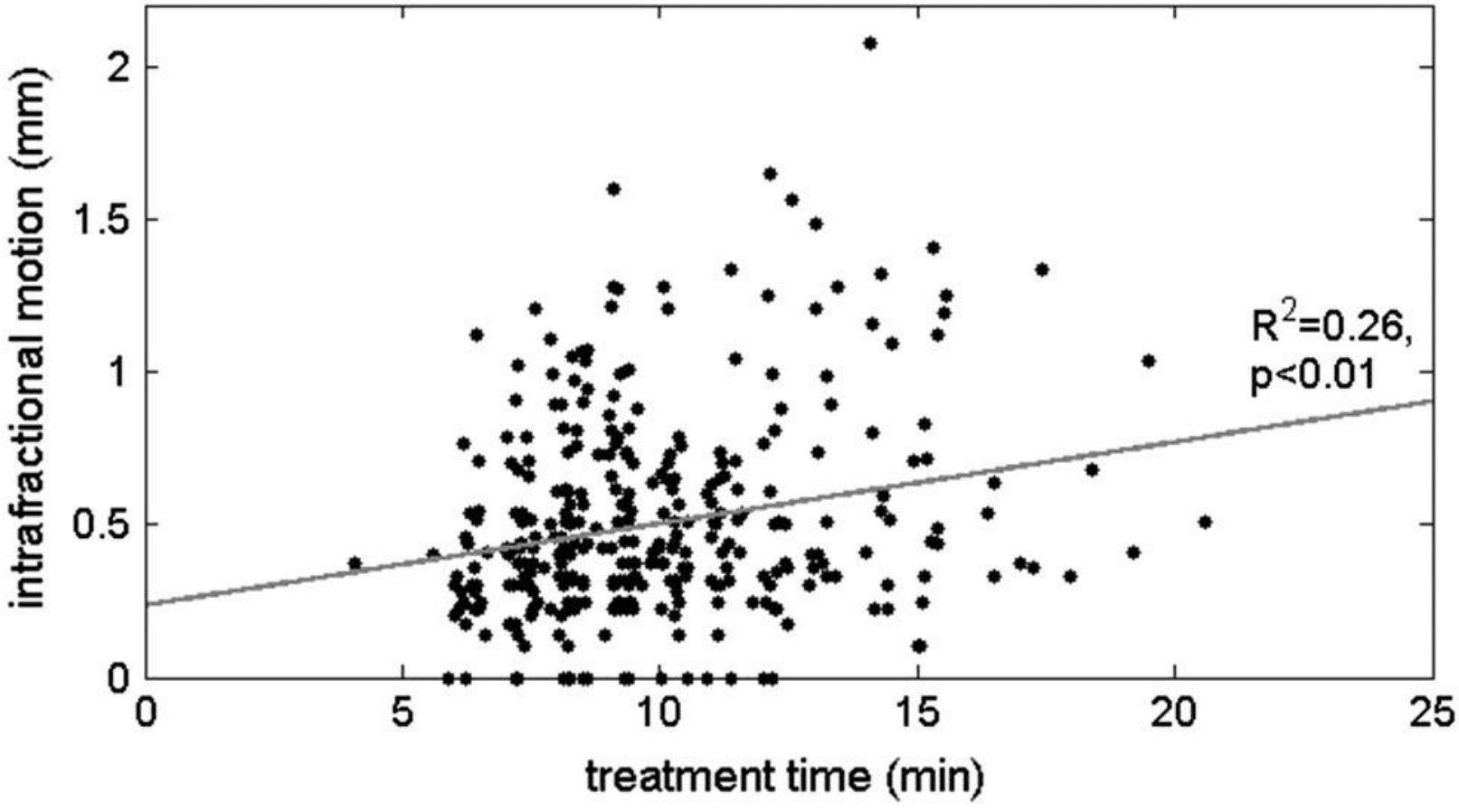
Intra fraction motion: treatment time



Lang et al PRO, 2015

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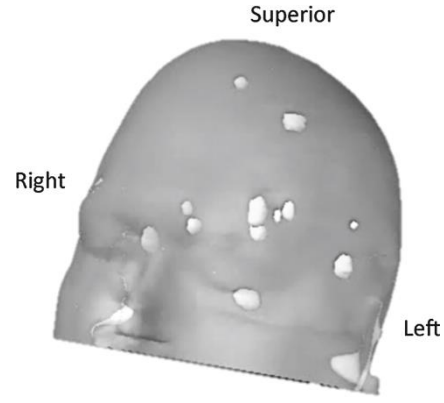
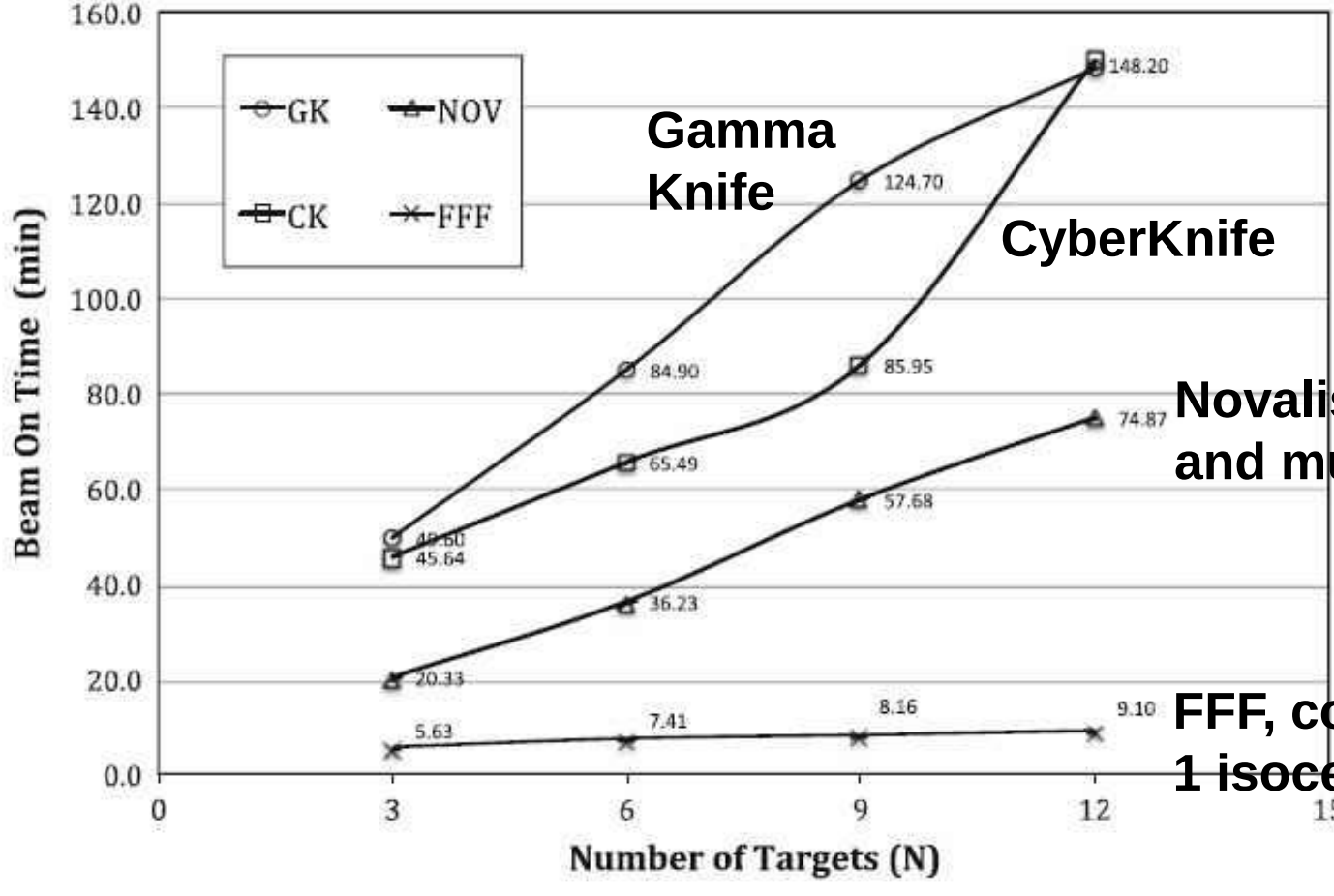
Treatment time





Gamma Knife

CyberKnife

Novalis, noncoplanar and multi-isocenter

FFF, coplanar and 1 isocenter

Ma et al Int J CARS, p1079 2014

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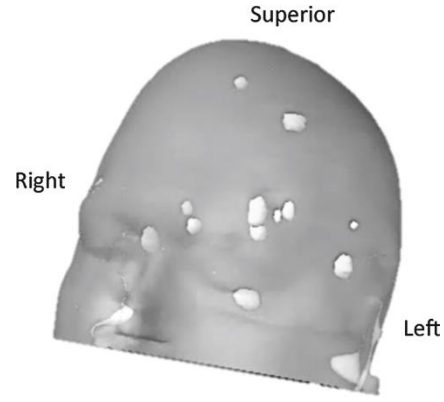
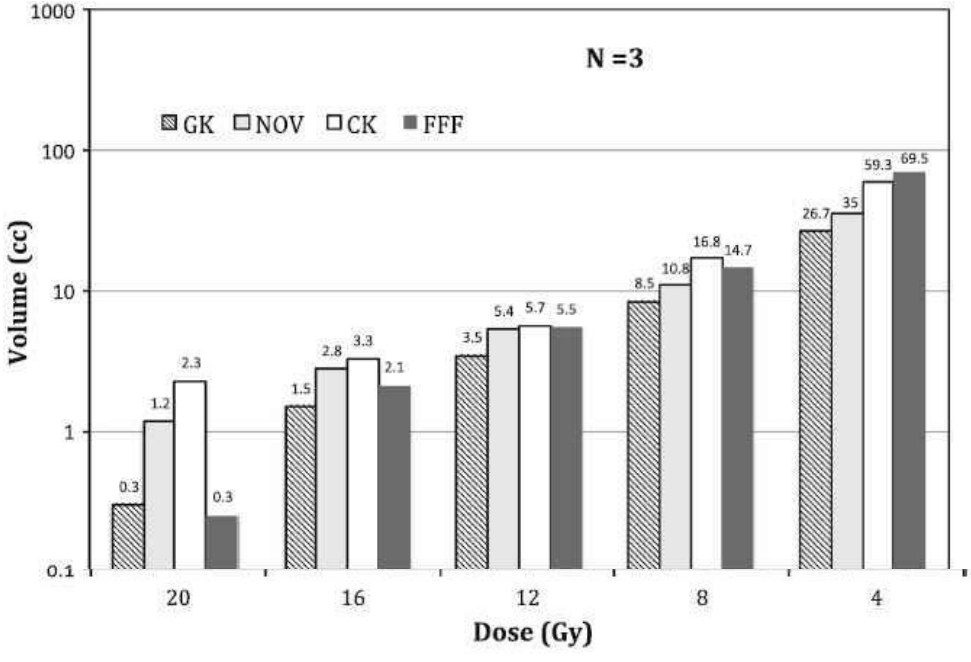
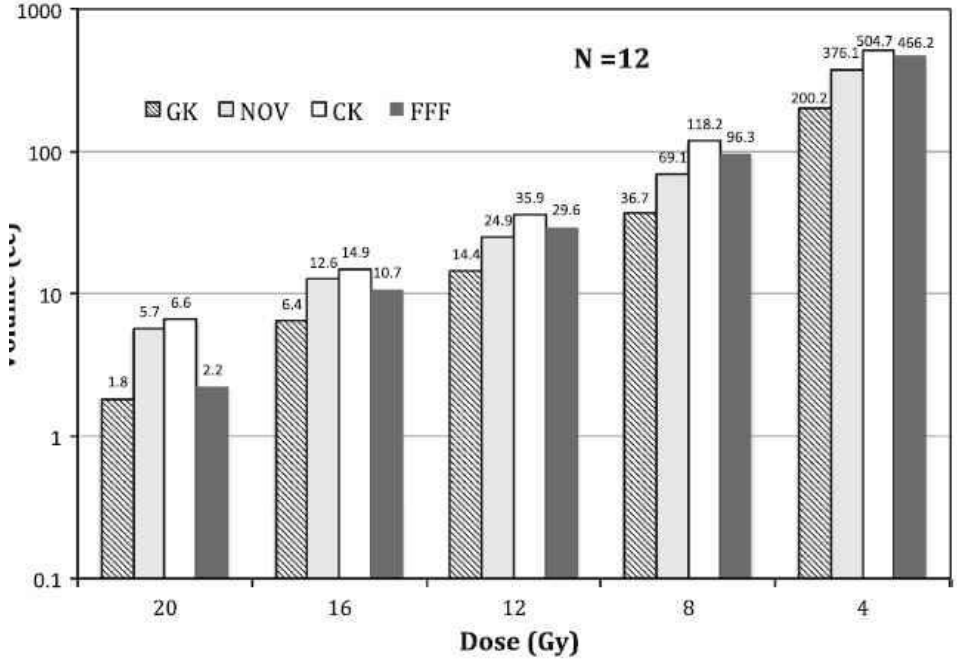
Treatment time



Normal brain dose





Gamma Knife results in lower normal brain dose

Margins?

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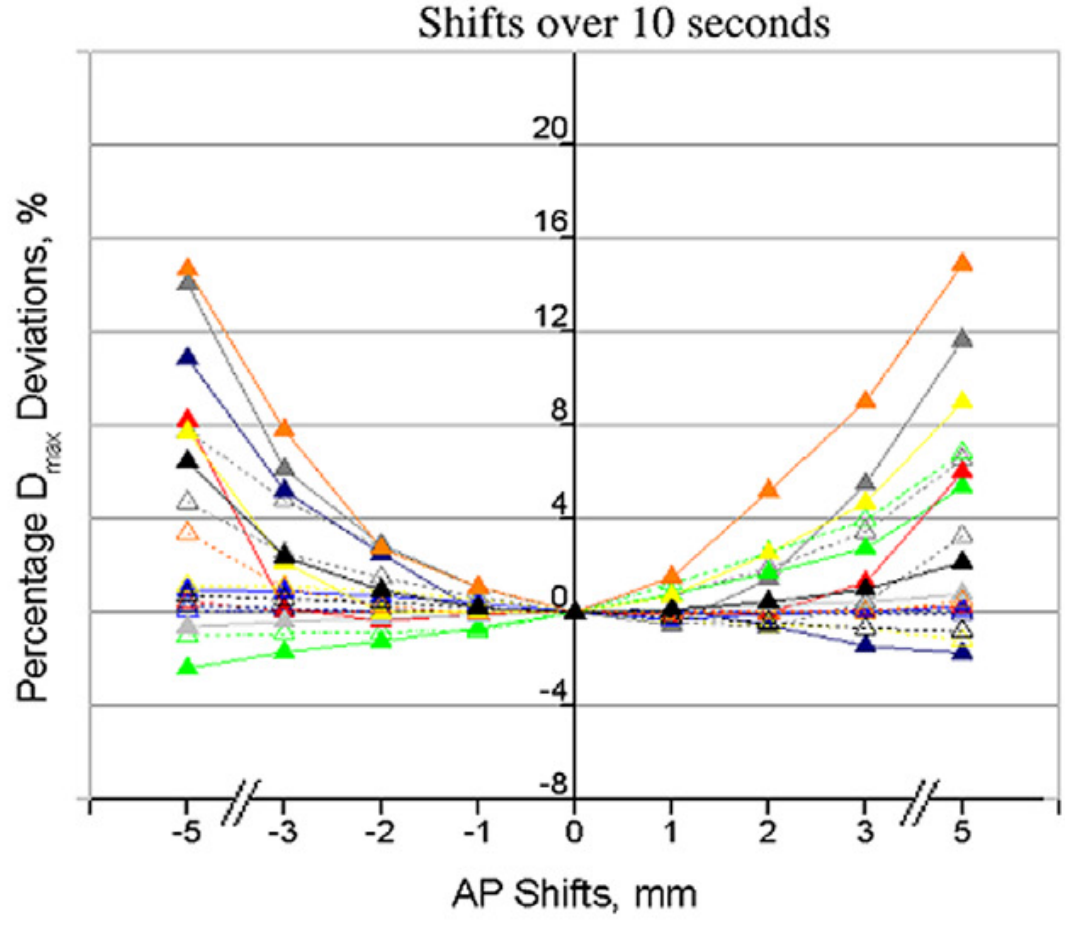
Spine SBRT: Required accuracy

Increase in spinal cord dose due to shifts can be significant!

More pronounced for FFF than for standard beams due to short treatment time



FFF beams (solid line, filled triangle) and standard beams (dashed line, empty triangle).

Ong IJROBP 86 2013 p420

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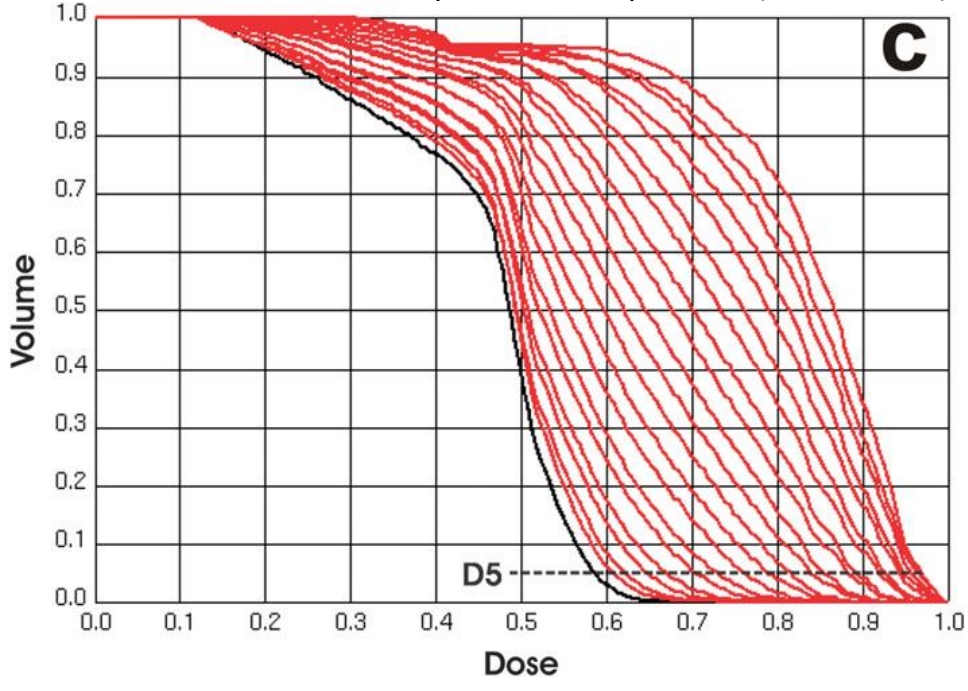
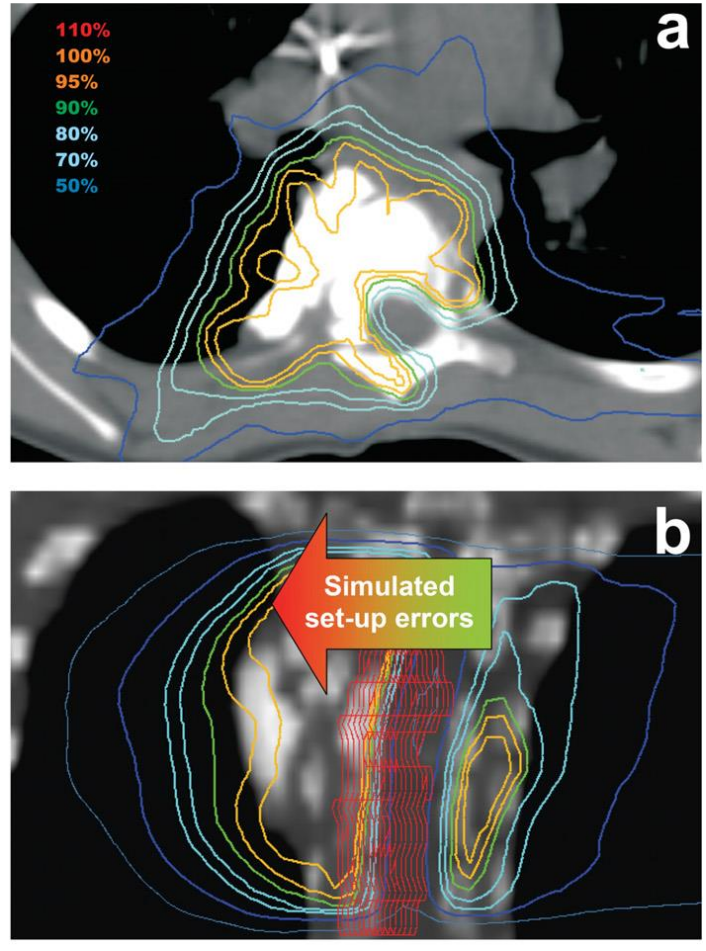
Spine SBRT: Required accuracy

Simulated transversal patient set-up errors (0.5–10 mm)





maximum tolerable errors on average :

1 mm (transversal plane)

4 mm (SI direction)

3.5˚

(spinal cord dose within ±5% of prescribed dose)

Guckenberger R&O 84, 2007 p56

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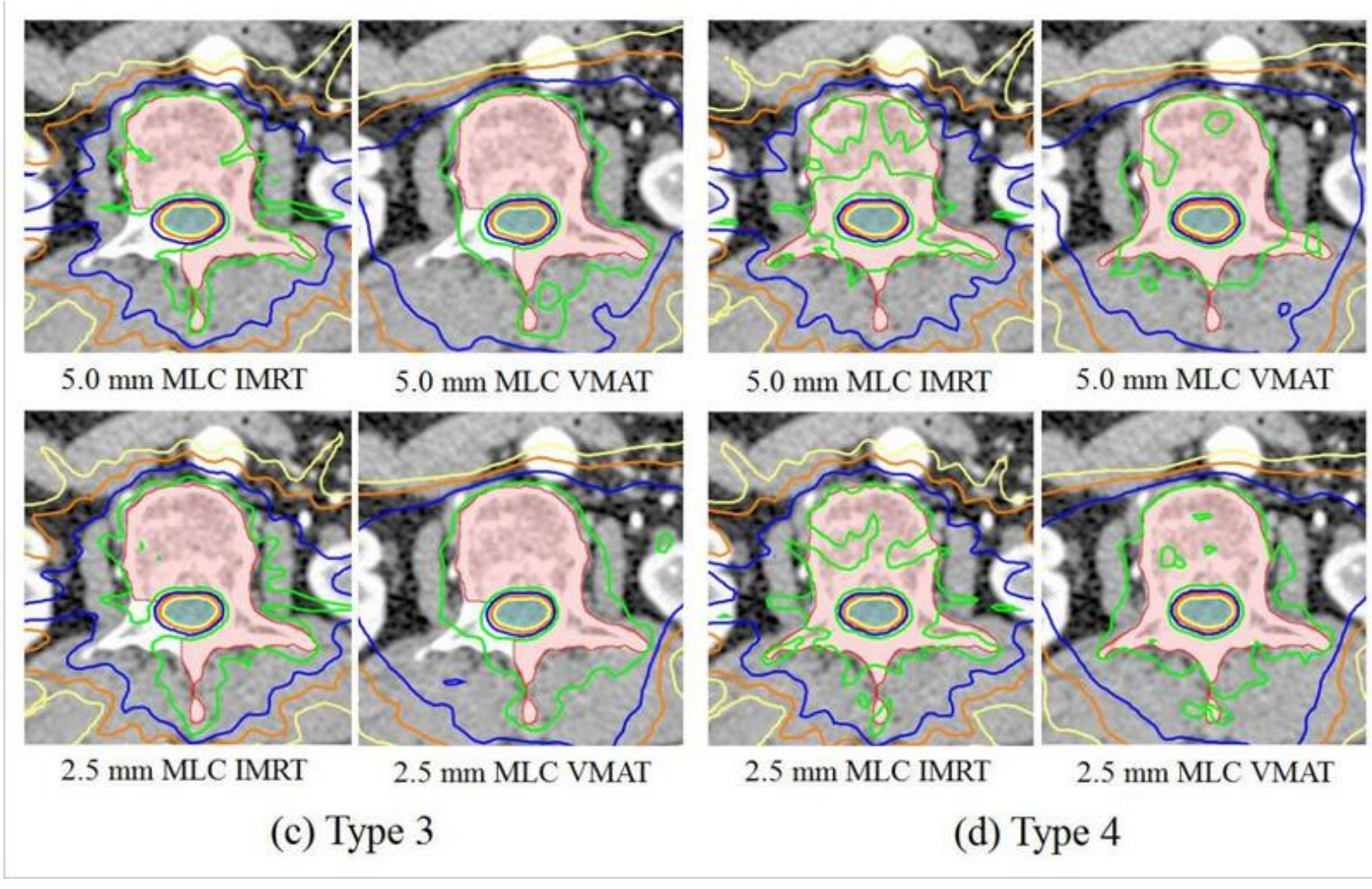
Spine SBRT: Required accuracy MLC



Chae, Radiat Oncol. 2014 Mar 8;9:72

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Spine SBRT: Required accuracy MLC

		2.5-mm MLC	5-mm MLC	Improvement ratio (%)	*p* value
IMRT	TVC	88.40 ± 15.62	83.55 ± 20.24	8.38 ± 13.66	0.042
	CI	2.03 ± 0.67	2.24 ± 1.06	−4.86 ± 13.00	0.119
	GI	9.30 ± 2.06	10.98 ± 3.34	−13.79 ± 7.38	0.003
VMAT	TVC	95.26 ± 3.12	92.65 ± 5.48	2.97 ± 3.10	0.005
	CI	1.85 ± 0.34	1.88 ± 0.41	0.02 ± 11.48	0.689
	GI	10.68 ± 2.04	10.80 ± 2.30	1.27 ± 23.74	0.871

Chae, Radiat Oncol. 2014 Mar 8;9:72

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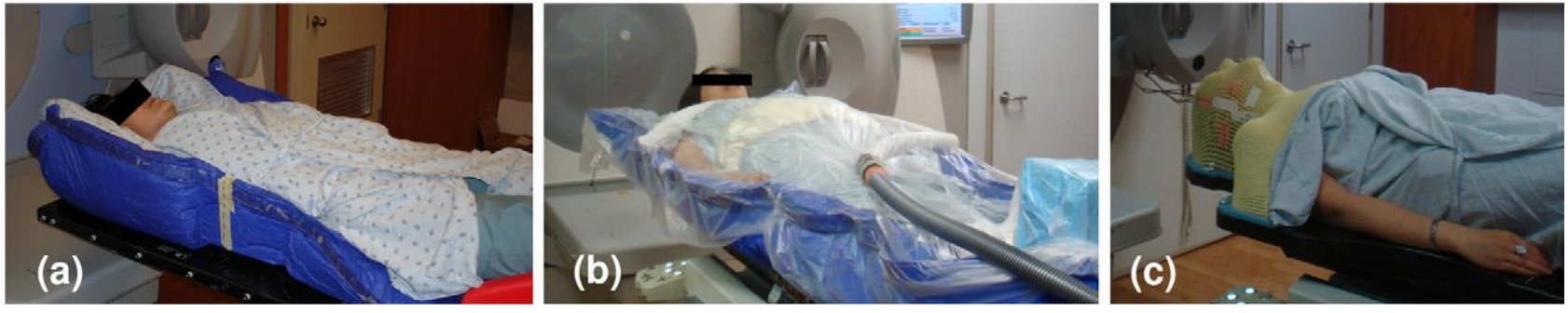
Positioning for spine SBRT

Before IGRT: (a) M:-0.4 to 1.5, SD of 2-3 mm

(b) and (c) M: of -6.2 to 0.8, SD of 4-7 mm



After IGRT: SD of 0.6 to 0.9 mm and 0.9° to 1.6°

Thus: IGRT resolves initial differences in set-up accuracy

However: Mean localisation to post treatment CBCT time 34±7 min

6% of all fractions were within the tolerance (2mm) on localization CBCTs.

97% directly after IGRT

93% at mid-treatment,

82% at post-treatment. **Try to reduce treatment time!**

Li IJROBP 84, 2012 p520

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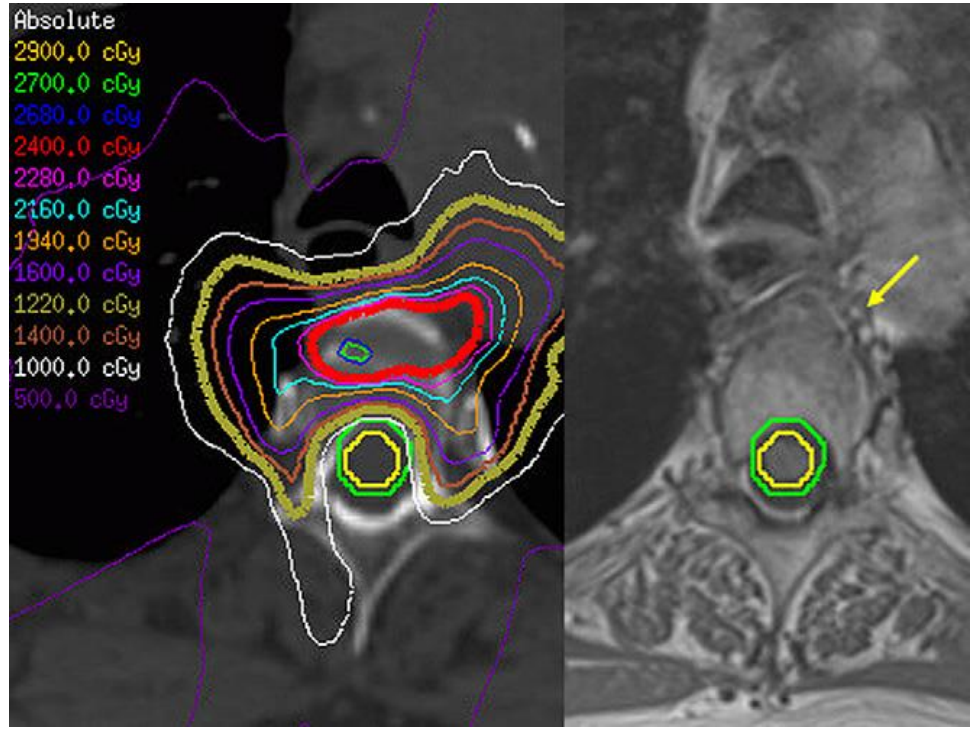
Positioning for spine SBRT

BodyFIX and Hexapod 6DOF table, Elekta CBCT. (42 spine patients)

Small positioning errors after the initial CBCT setup were observed, with 90% within 1 mm and 97% within 1° (after 10±3 min.).

Only half of patients within tolerance (1 mm and 1°) for the entire treatment (63± 4 min).

With intra-fraction IGRT every 15-20 min and using a 1-mm and 1 correction threshold, the target was localized to within 1.2 mm and 0.9° with 95% confidence.



intrafractional imaging and corrections needed approximately every 15 to 20 min.

Hyde IJROBP 82, 2012 e555

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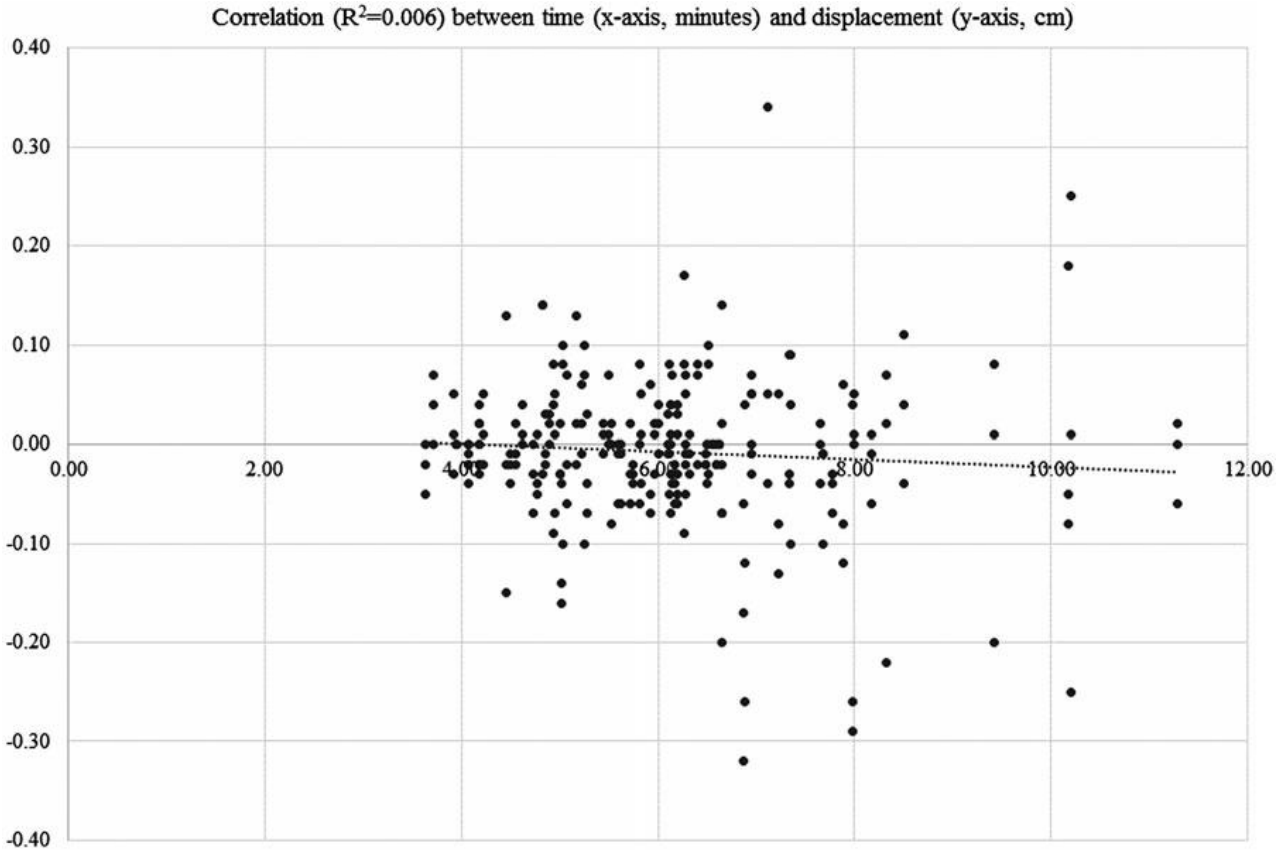
Positioning for spine SBRT



Mean 18.3 min (6.6 min)
From start imaging to end arcs
FFF, 2400 MU/min,
7-10 Gy/fraction

Figure 1. The relationship between translational displacements (n=249) measured between arcs 1 and 2, and time (x-axis, minutes), where time represents the interval between the start of the CBCT performed before arc 1 and the start of the first CBCT scan after completion of arc 1.

Dahele M et al, Acta Oncologica, 2016

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Accuracy of current IGRT systems (from ICRU 91, 2017)

Table 5.1. Geometric residual errors of current commercial IGRT systems

IGRT system	IGRT geometric residual errors on phantom tests
Novalis ExacTrac	Total residual average error: $\leq$ 1.5 mm $\pm$ 0.7 mm (Hacker *et al.*, 2006) 0.56 mm $\pm$ 0.7 mm (Jin *et al.*, 2008b) 0.6 mm $\pm$ 0.9 mm (Verellen *et al.*, 2003)
CyberKnife	Maximum error: 0.56 mm $\pm$ 0.7 mm (Antypas and Pantelis, 2008) 0.8 mm $\pm$ 0.05 mm (Desai *et al.*, 2006) 0.4 mm $\pm$ 0.1 mm Skull tracking; 0.5 mm $\pm$ 0.2 mm Spine tracking; 0.3 mm $\pm$ 0.1 mm Fiducial tracking; (Kilby *et al.*, 2010).
CBCT	<1.4 mm translations and < 0.7° rotations at 95 % confidence interval level (Hyde *et al.*, 2012) 1–1.5 mm 95 % confidence interval level (Sharpe *et al.*, 2006)
TomoTherapy	$\pm$1 mm (Fenwick *et al.*, 2004) 1 mm (Boswell *et al.*, 2006)
VERO	0.54 mm $\pm$ 0.2 mm (Depuydt *et al.*, 2011)

P91 of ICRU “The tolerance specification of the spatial calibration is within ±2mm for kV-CBCT (AAPM TG 179), which is considered acceptable also for SRT.”

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Take home message

- One should perform **complete end-to-end tests, including patient delineation and setup data** to establish the complete treatment chain accuracy and implement the appropriate CTV-PTV margins accordingly.

- A set-up accuracy of approximately 2 mm/1° for brain and 1 mm/1 ° for spine irradiations (1 SD) has been associated with clinically relevant parameters.

- **All** current immobilisation systems for brain or spine SBRT can be used **if** properly combined with **on-line** IGRT.

- Immobilisation systems associated with larger rotational errors **are not preferred or** should be combined with a 6DOF couch correction or in combination with multiple isocenters.

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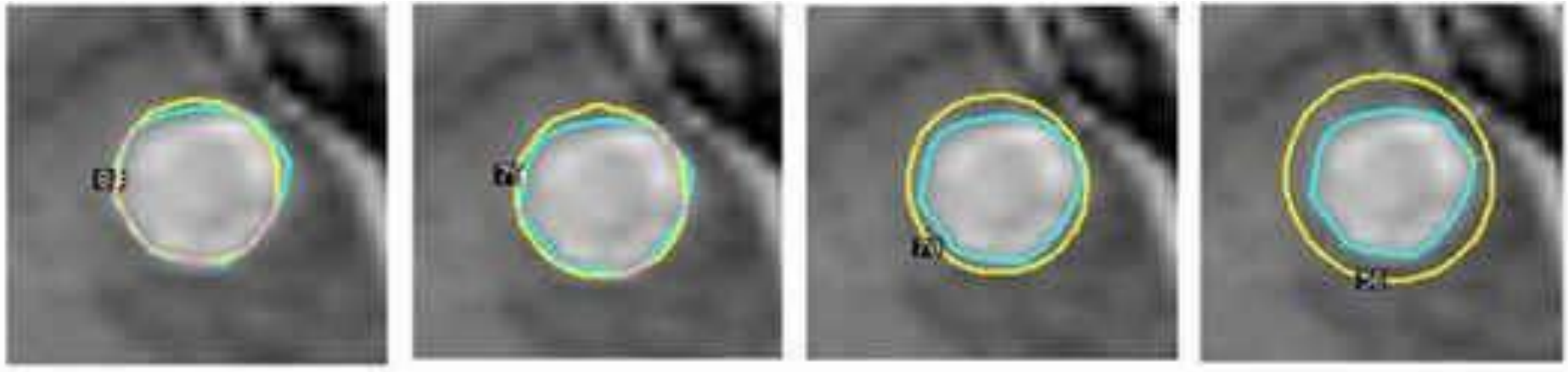
Dose prescription

“I am giving 1 fraction of 25 Gy….”



Isodose line:

83%	79%	70%	56%

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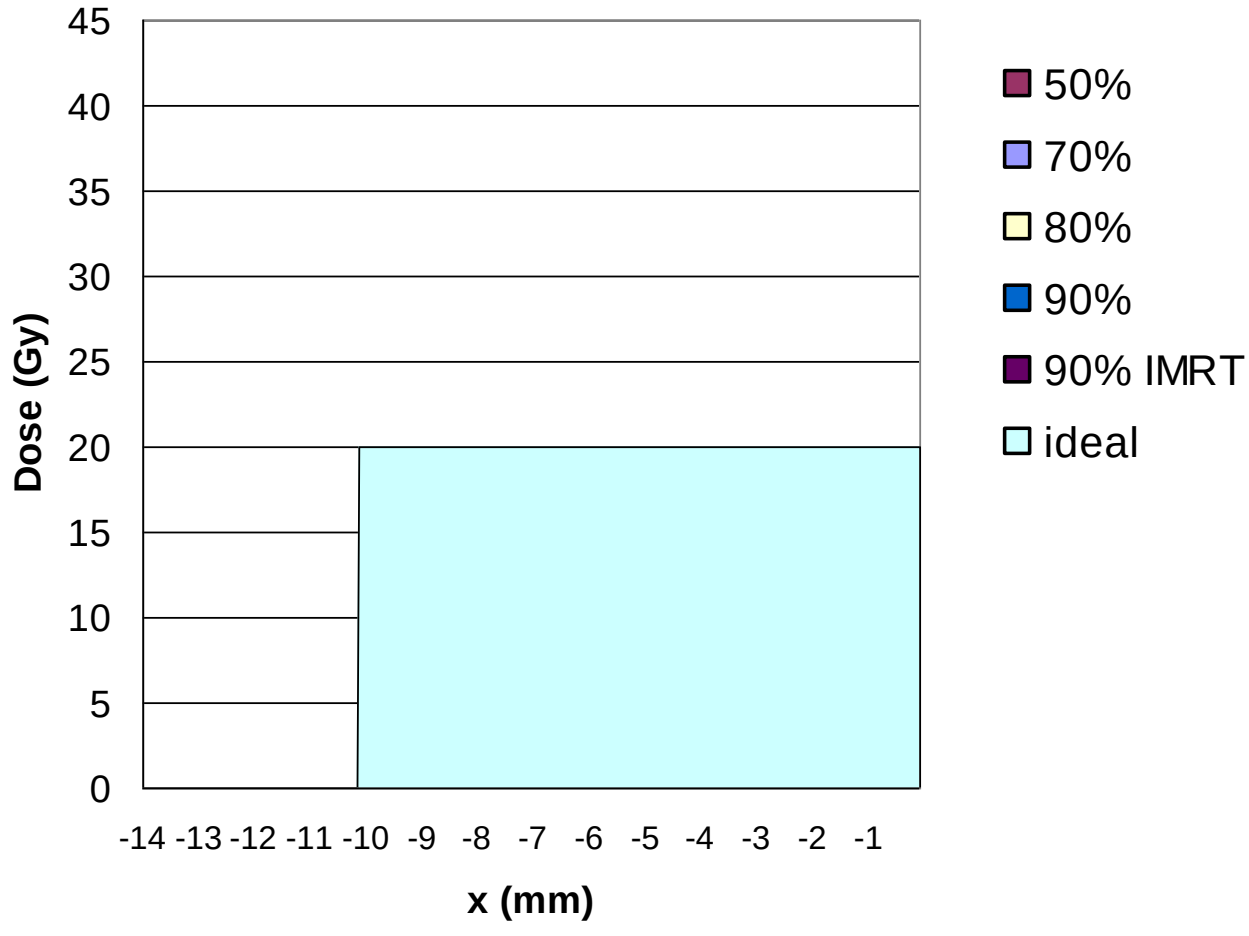
Prescription isodose vs modern linac RT



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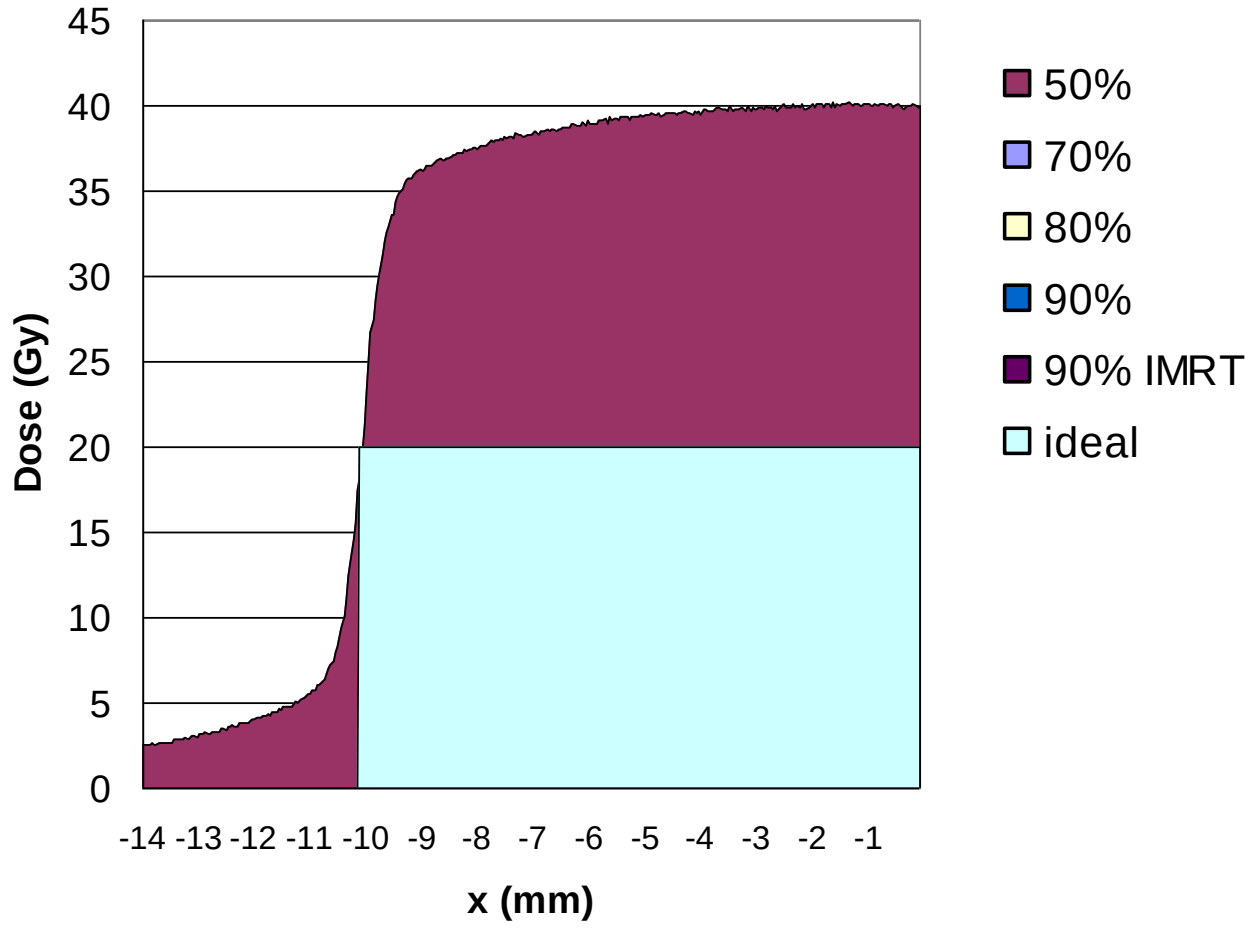
Prescription isodose vs modern linac RT



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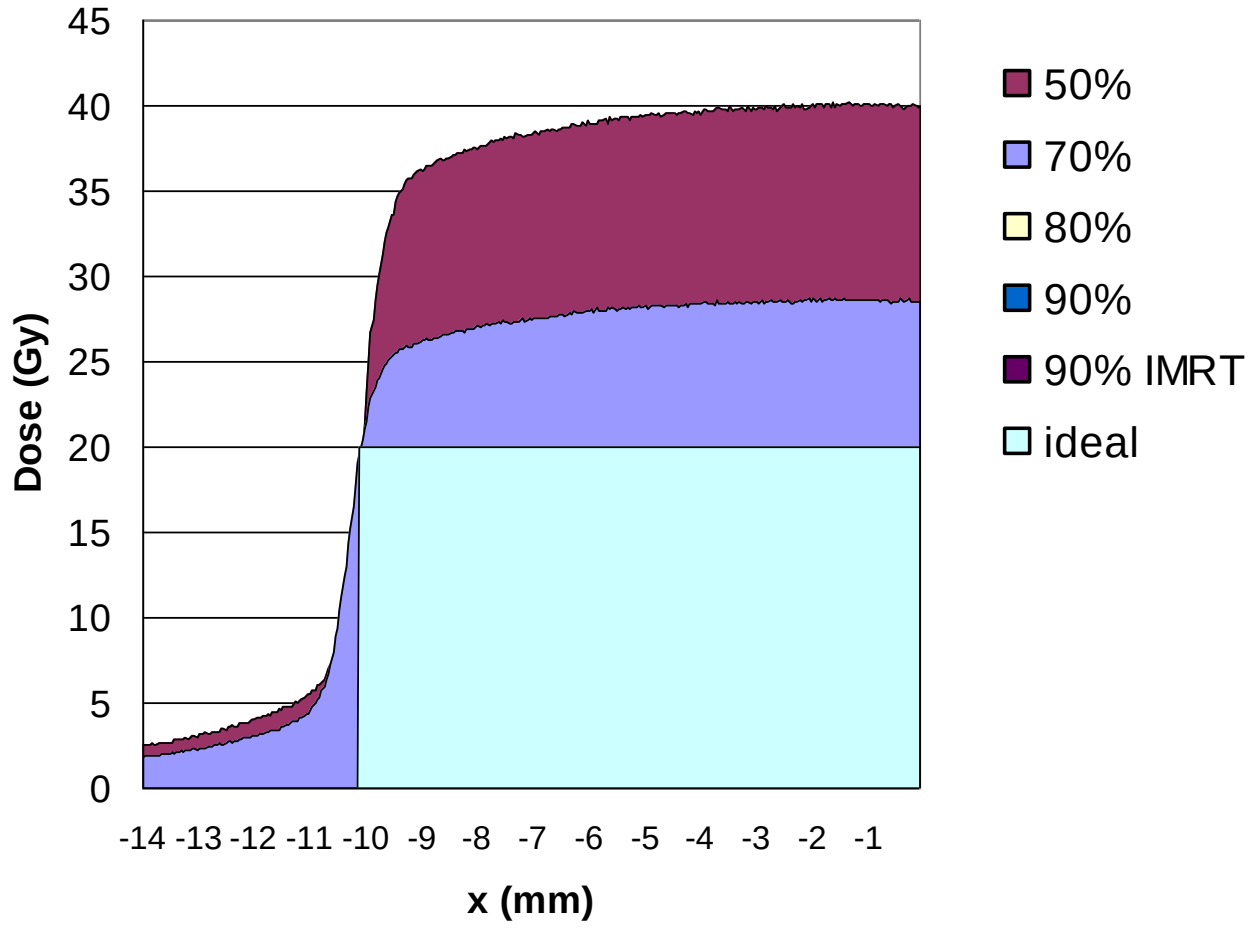
Prescription isodose vs modern linac RT



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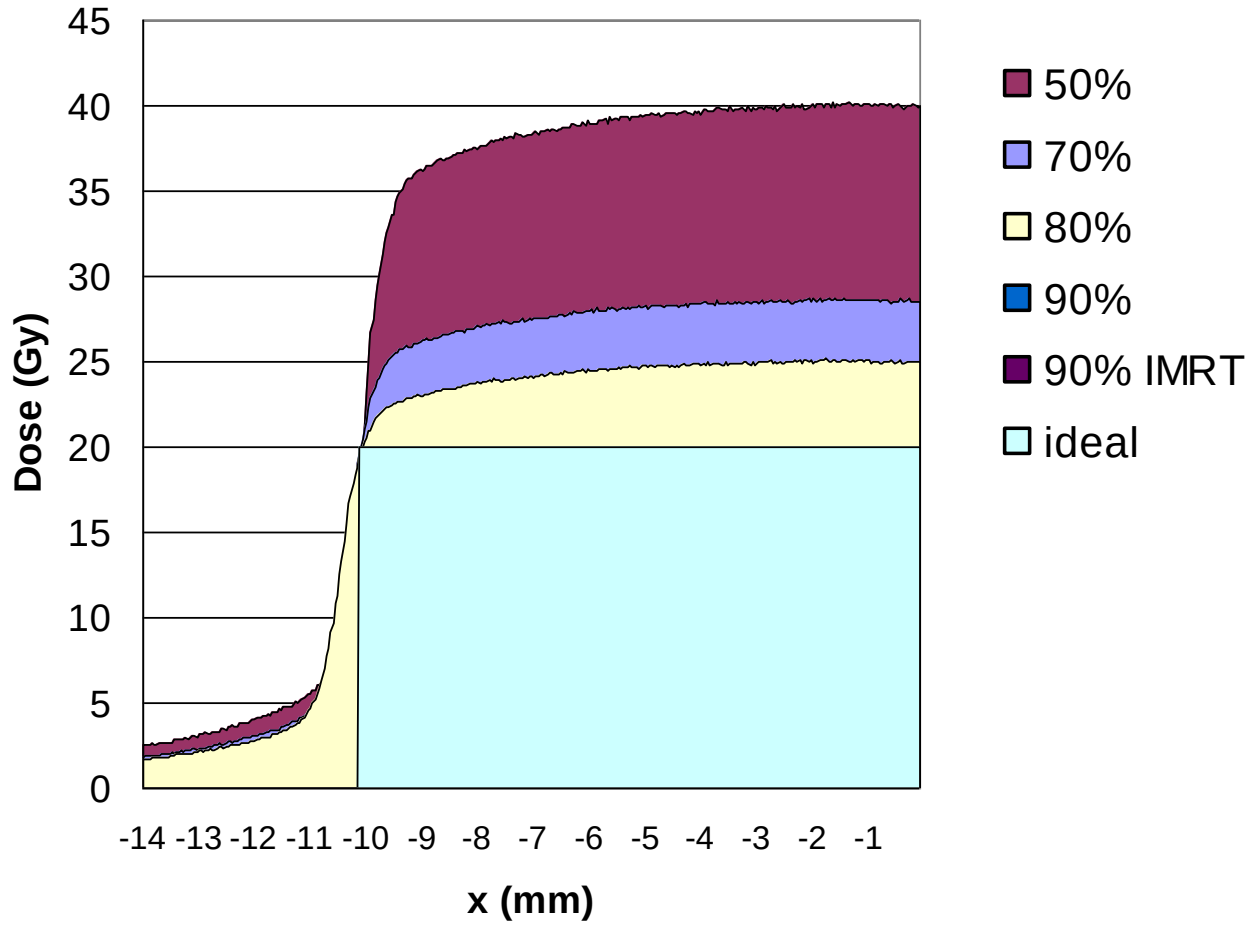
Prescription isodose vs modern linac RT



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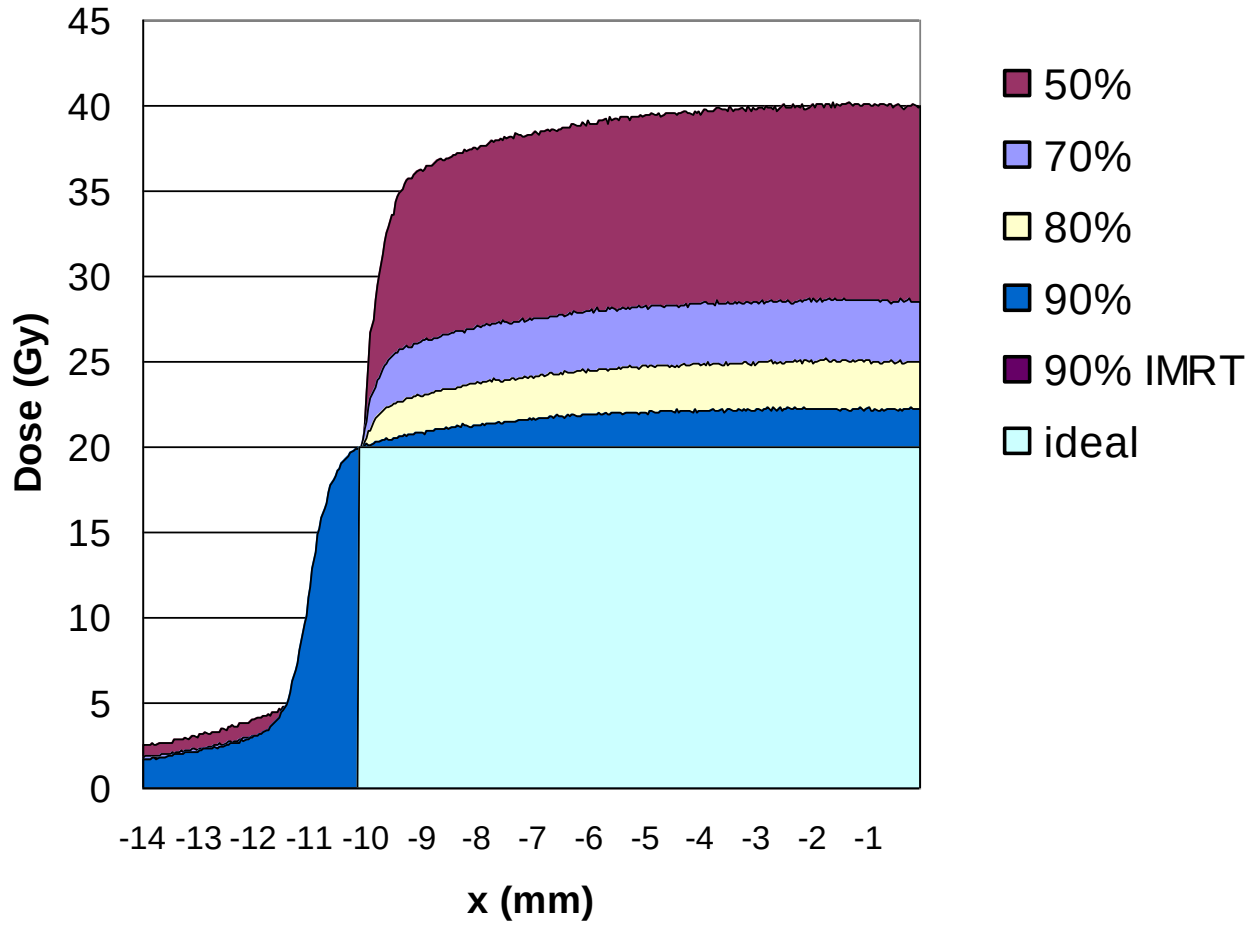
Prescription isodose vs modern linac RT



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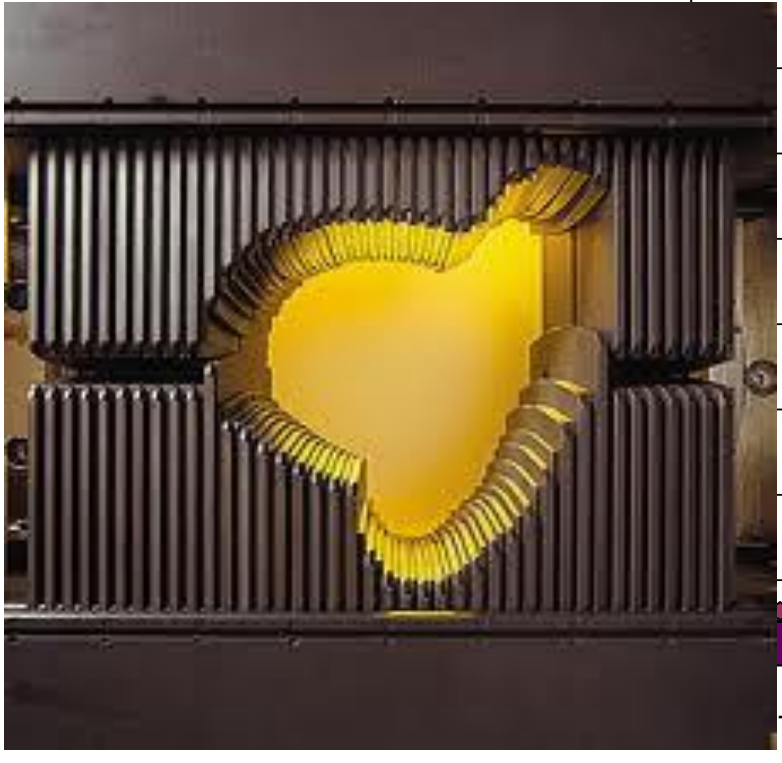
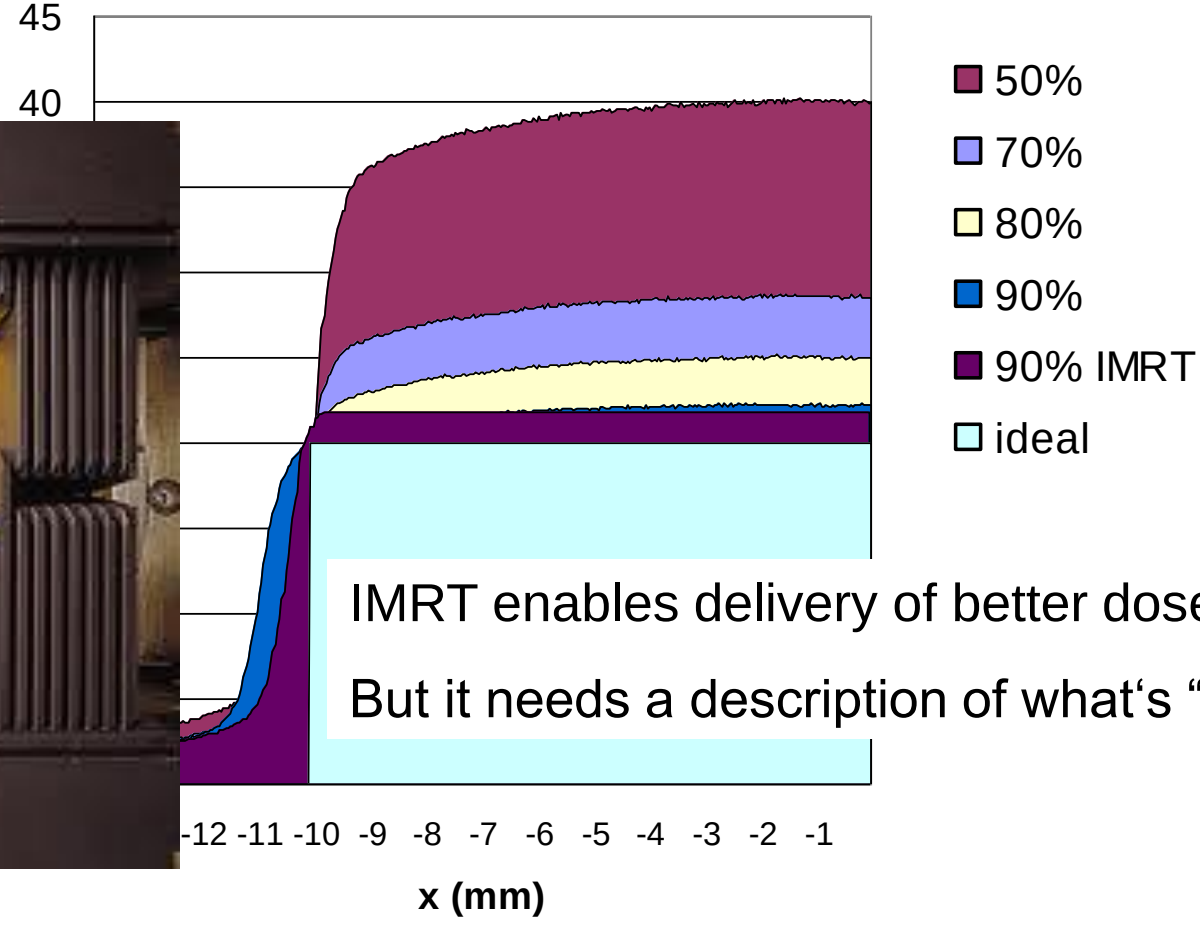
Prescription isodose vs modern linac RT





IMRT enables delivery of better dose profiles

But it needs a description of what‘s “better”

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The bridge to Linac based RT: Dose

"I think you'll agree that this comparison, though unpopular, has some real merit."

Prescription dose to % of PTV

+ Mean / Median dose and Dose to Organs at risk

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Conclusion

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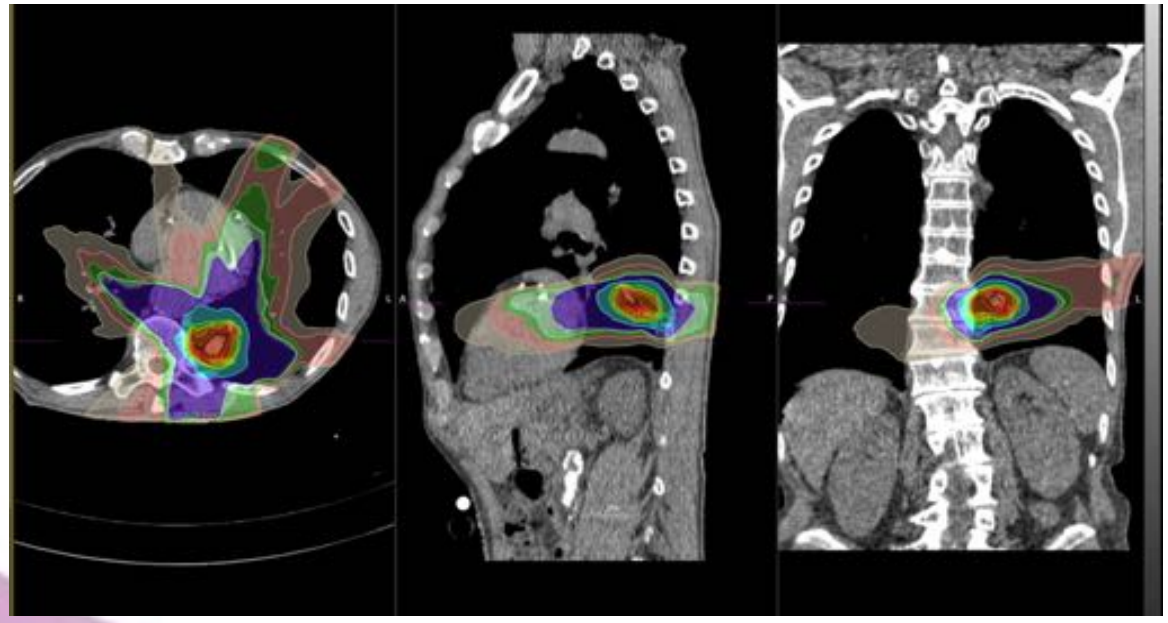
iridium kankernetwerk
Radiotherapie
Medische Oncologie
Hematologie

VUB VRIJE UNIVERSITEIT BRUSSEL

Management of targets with respiration induced motion: part II



Mischa Hoogeman & Dirk Verellen

DV is involved in an on-going scientific collaboration with RaySearch, Sun Nuclear and ORFIT

ESTRO School

Learning objectives

- To give an overview of the magnitude of intra-fractional position errors for patients
- To demonstrate the dosimetric and clinical relevance of these errors
- Sites of interest
  - Intra-cranial
  - Head and neck
  - Spine (supine vs. prone)
  - Prostate
  - Lung
  - Liver

- **To give an overview of 4D pre-planning imaging in relation to the chosen treatment strategy**
- **To give an overview of current technologies and correction strategies managing intra-fractional respiration induced motion**
  - Breath-hold
  - Mid-ventilation
  - Gating
  - Tracking
- **To show some of the pitfalls related to these strategies**

Questions from the audience

- Some questions related to motion management

  - 4DCT: QA, what phantoms, what controls, what periodicity?

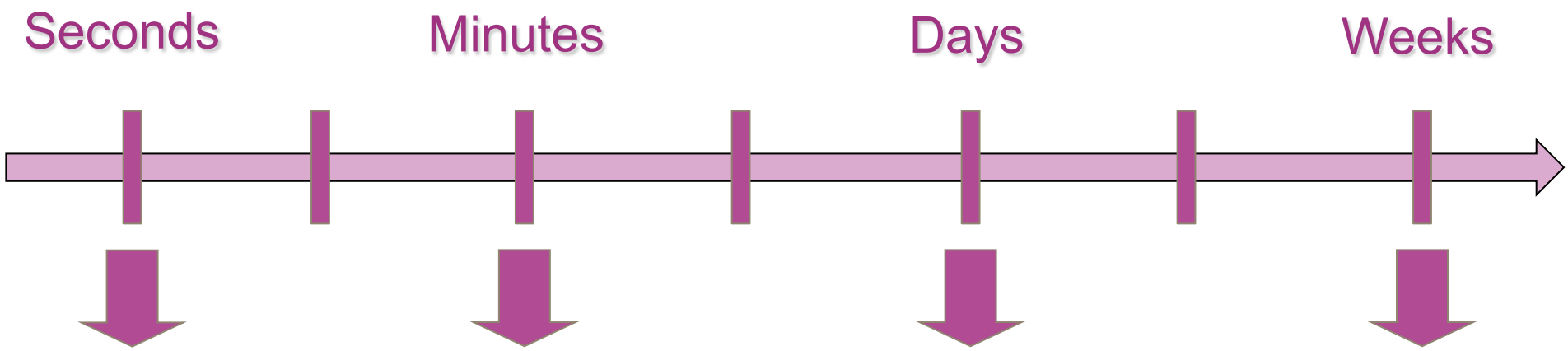
  - Use 3DCRT, IMRT or VMAT for lung SABR?
  - Are there reliable planning/measurement studies quantifying breathing-MLC interplay effects?
  - VMAT for lung SBRT: evidence for/against, what to watch out for, comparison with DCAT

  - Techniques for SBRT in solitary abdominal mets (gating, tracking, or abdominal compression?)
  - For tracking what kind of control do we have to implement?

Outline

- 4D imaging for treatment preparation
- Motion management during treatment
  - ➢ “**Passive**” versus “**Active**”
- Real-time motion management, what are the options?
- Pitfalls

Motion management: the variables

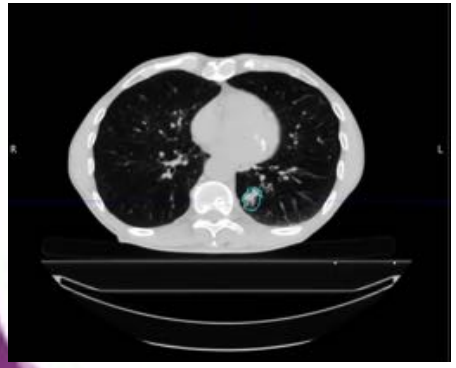


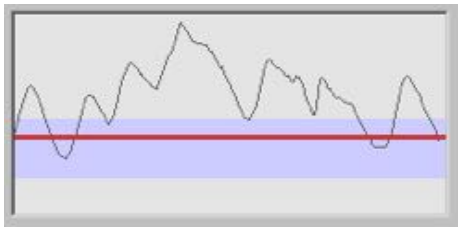
- Breathing
- Peristaltic
- Heart Beat

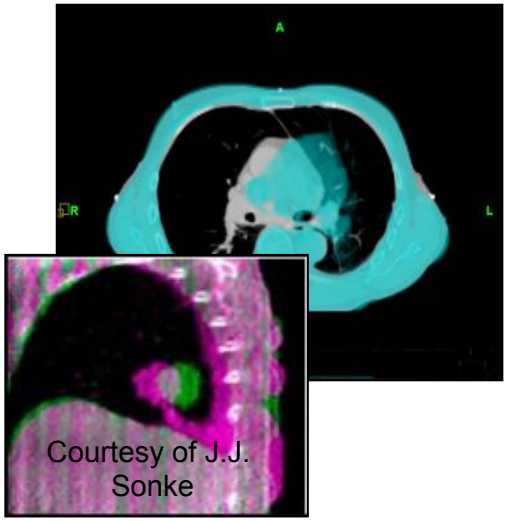
- Patient motion
- Tumor drifts

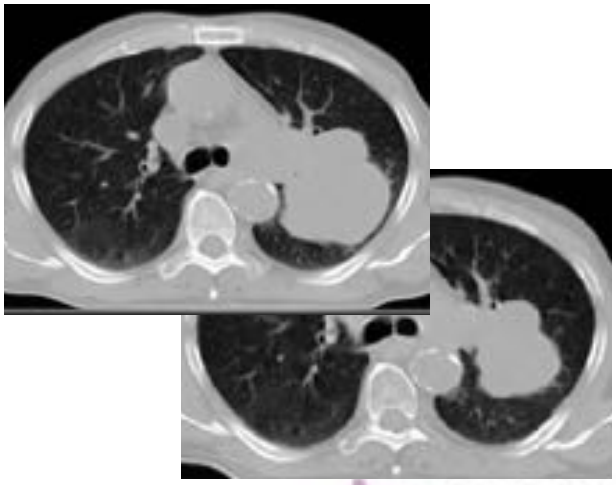
- Breathing pattern
- Baseline shifts
- Patient position

- Shrinkage
- Progression
- Weight loss



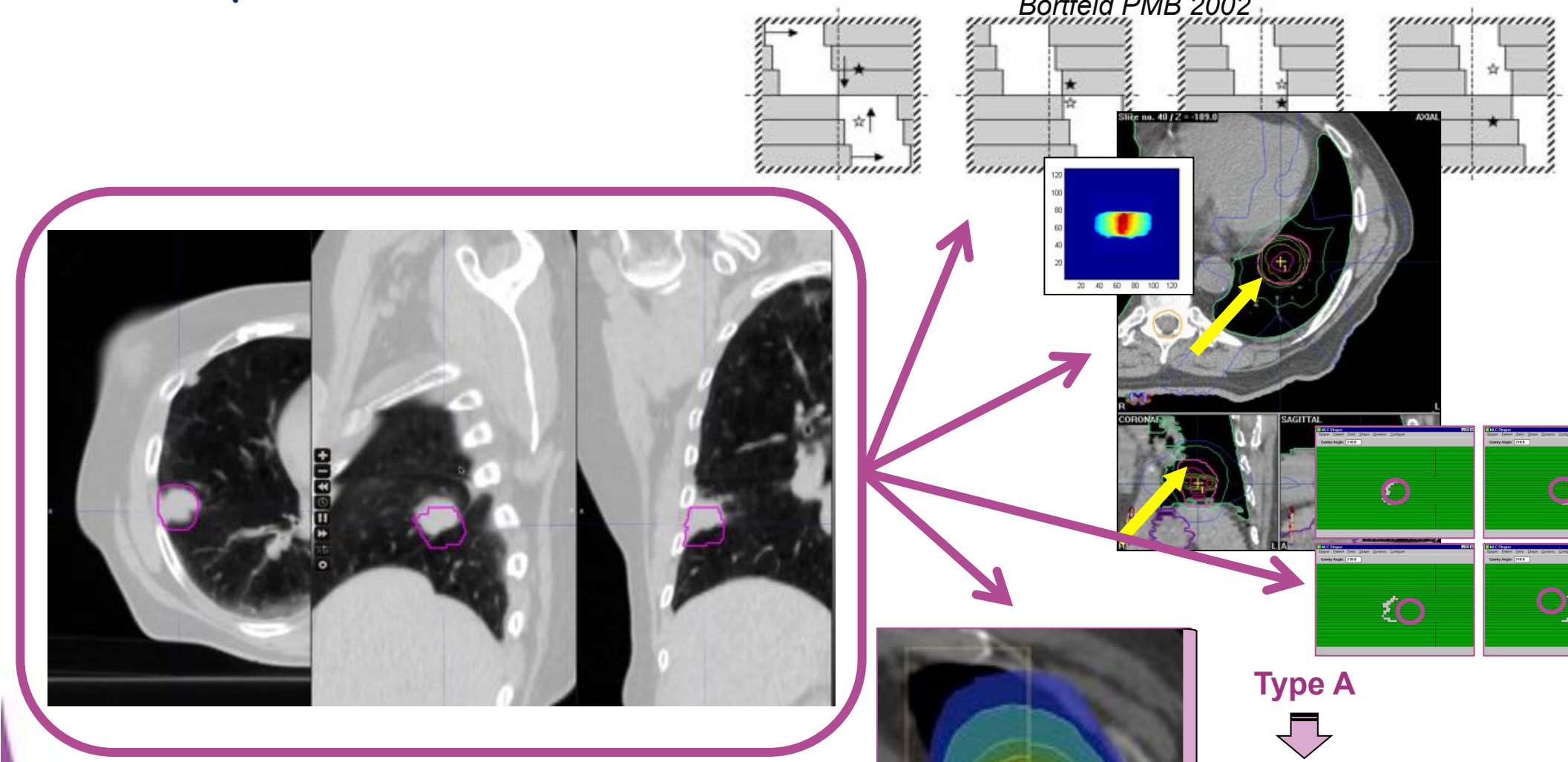






Why motion management?

Bortfeld PMB 2002



Type A

Type B

Inverse optimization

Motion management

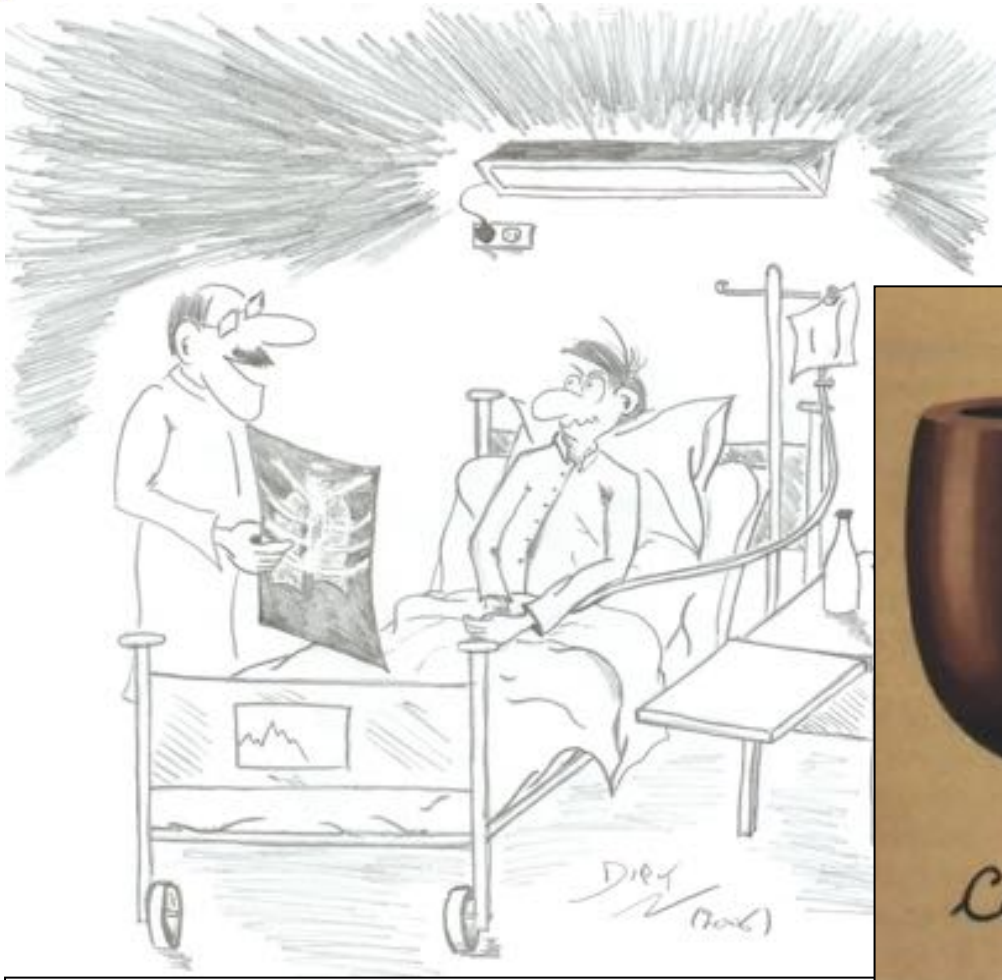
- "Passive":
  - Realizing motion exist, try to quantify it and adapt the treatment strategy accordingly … **prior** to delivery.

- "Active":
  - Monitor motion in real-time and adapt **during** treatment delivery accordingly.
  - '*Breathing Synchronized Irradiation Techniques*'

Disclaimer

- There is no 1 perfect solution, it's how you use it …

So, what's the 1st problem?



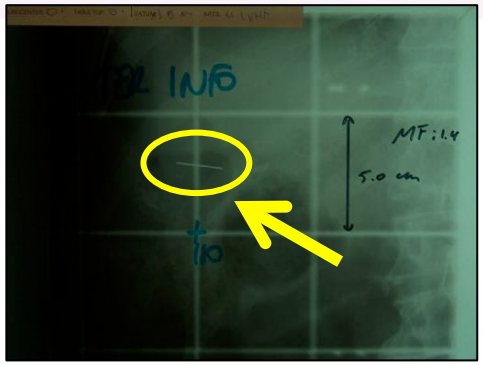
"We discovered a lung tumour,

but we fixed it with Photo-Shop"

Imaging for target definition

- Fluoroscopic imaging

Pros	Cons
"Widely" available (simulator)	No volume information
Imaging for longer duration	Limited soft-tissue contrast
Tool for selecting strategy	Markers associated with a risk of pneumothorax
	Difficult integration into TPS



Imaging for target definition

- PET

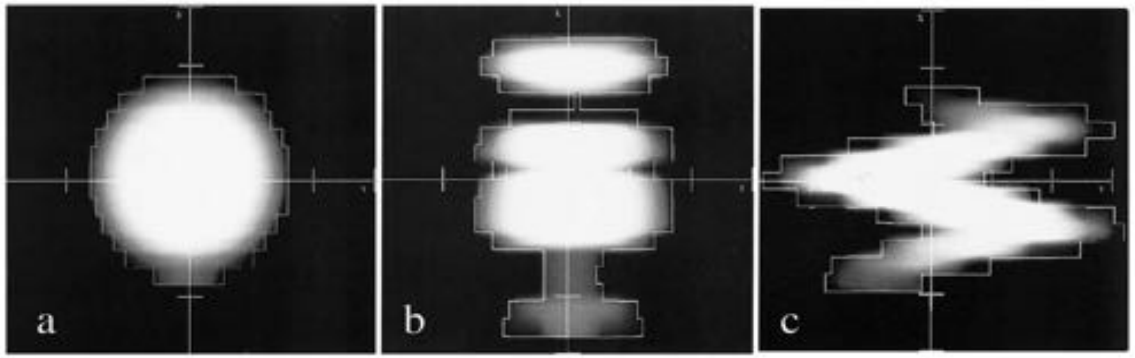


Fig. 3. AP DRRs of a 3.2-cm-diameter sphere generated from spiral CT acquisitions while (a) stationary, and moving 25 mm in the (b) longitudinal and (c) transaxial directions. The period was 4 s. The graphical overlay displays the region localized using a threshold of −875 HU. These images show some of the possible distortions that can result in the 3D representations of moving objects acquired using fast, spiral CT.

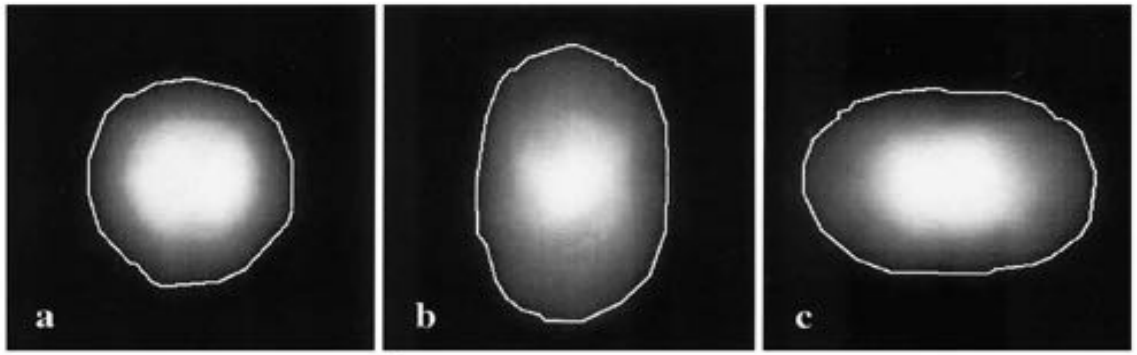
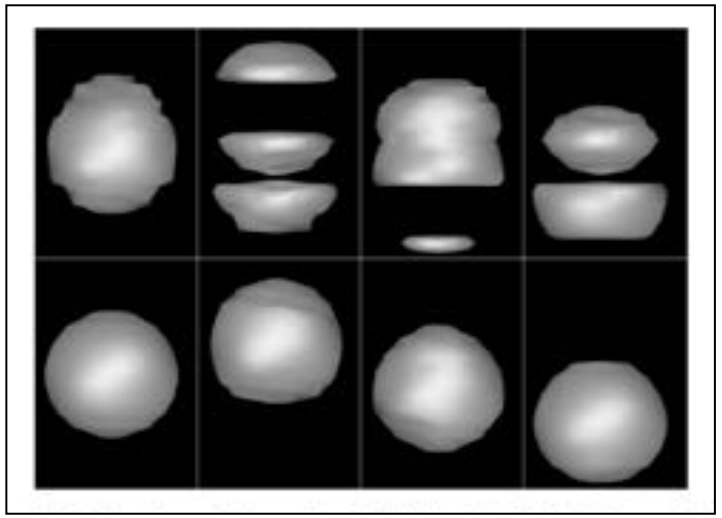


Fig. 4. AP maximum pixel ray trace ^{22}Na-PET images of the same sphere while (a) stationary and moving 25 mm in the (b) longitudinal and (c) transaxial directions. The period was 4 s, and the images were acquired over 20 min. The graphical overlay represents the region localized using a threshold defined by 15% of the maximum voxel value. These images illustrate that the time-averaged, capsule-shaped geometry that the moving sphere traces is better represented by PET compared with spiral CT.

Caldwell *et al.*, IJROBP, 2003

"PET imaging can provide a more accurate representation of the 3D volume encompassing motion of tumors and has potential to provide patient-specific motion volumes for an individualized Internal Target Volume (ITV)"



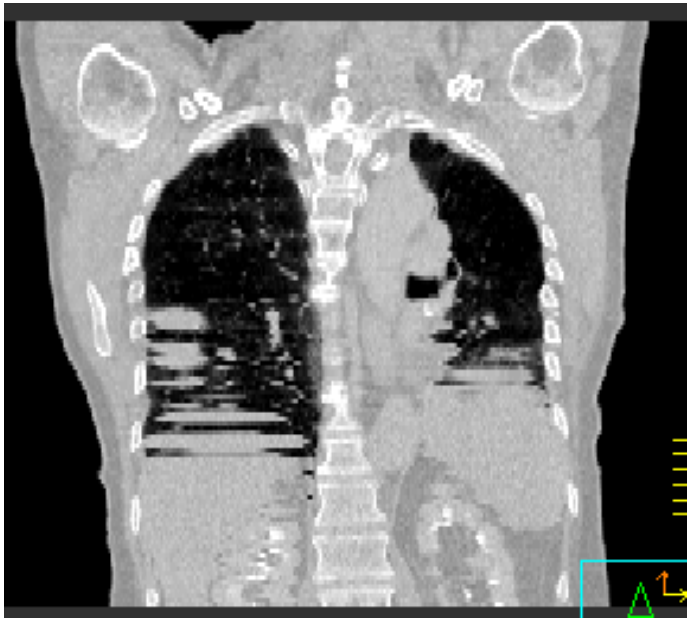
Rietzel *et al.*, Med Phys

… but, quantitative information is blurred

… strong influence by widowing

Imaging for target definition

- Slow 3D-CT

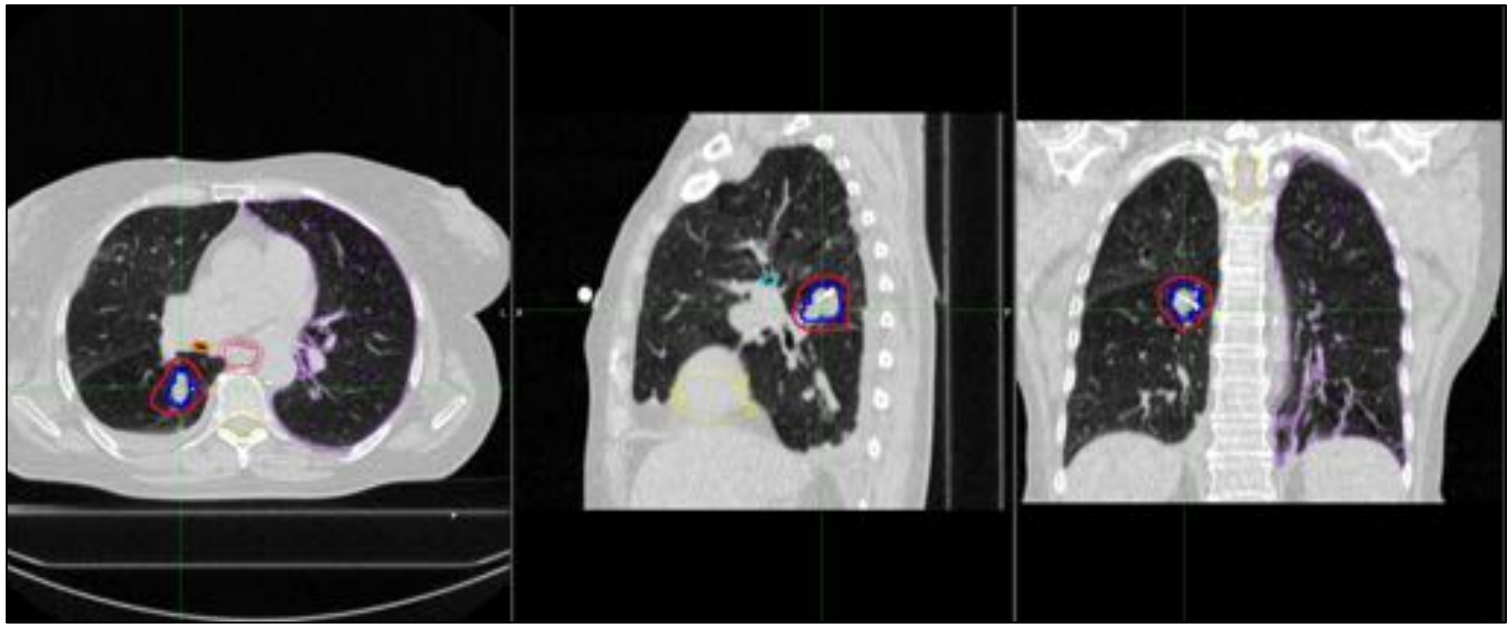


4D-CT image artifact reduction

- Images acquired in breathhold are **NOT** representative for treatment!
- Images acquired in free breathing are associated with multiple uncertainties:
  - Size and shape of the target?
  - Target position / organs at risk?
  - Motion range and trajectory of target and organs at risk?

Imaging for target definition

- Fast 3D-CT

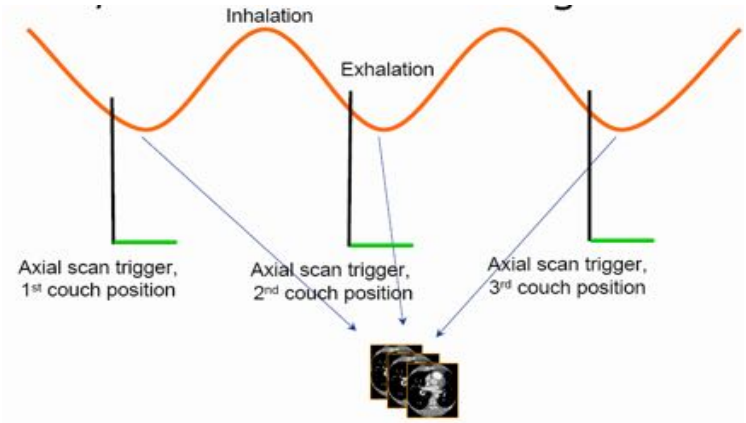


➢ **Snapshot in time** representing 1 specific target position, again associated with multiple uncertainties:

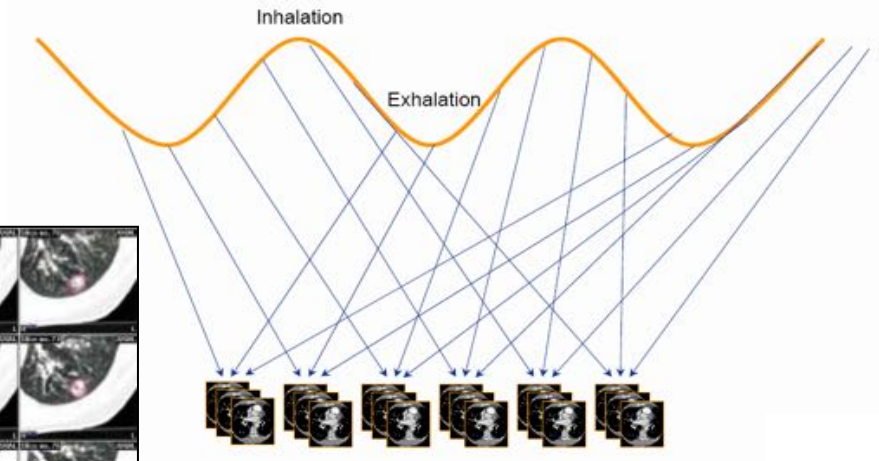
- Target position?
- Target motion?
- Target trajectory?
- Baseline?
- Motion of OAR with respect to target?

Imaging for target definition

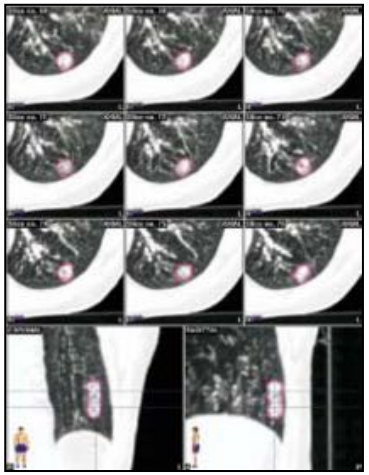
- 4D-CT
  - Gated / breathhold 4D-CT



  - Respiration correlated (RC 4D-CT)



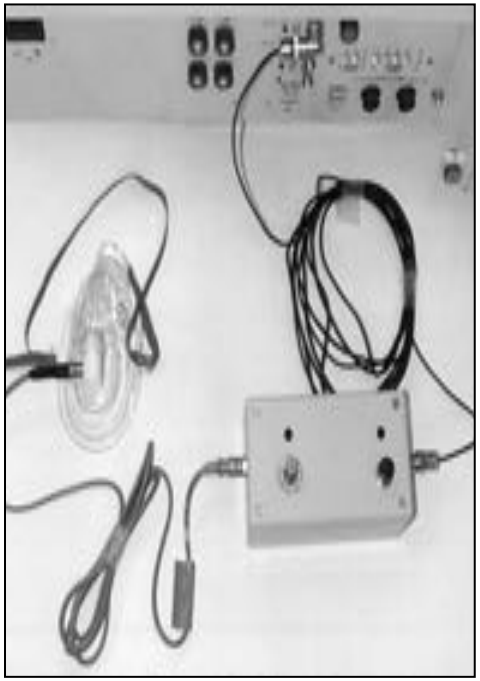
  - Maximum Intensity Profile



Imaging for target definition: RC-CT

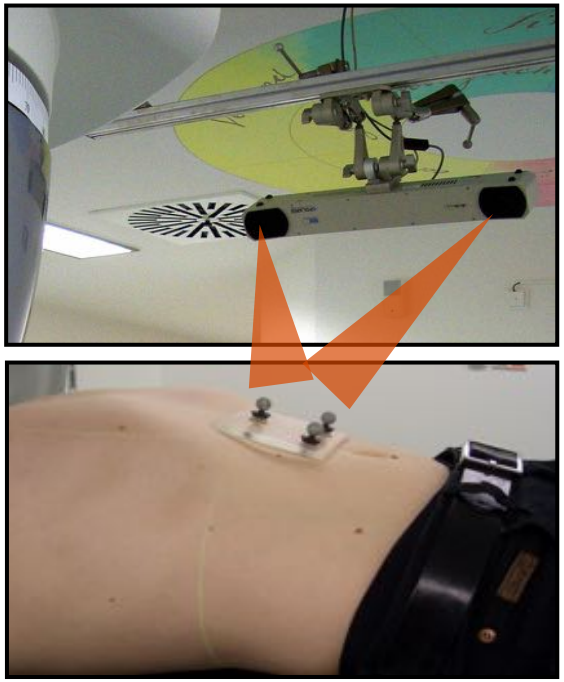
- External surrogate for acquiring respiration signal needed for image triggering or binning/sorting.

Spirometer



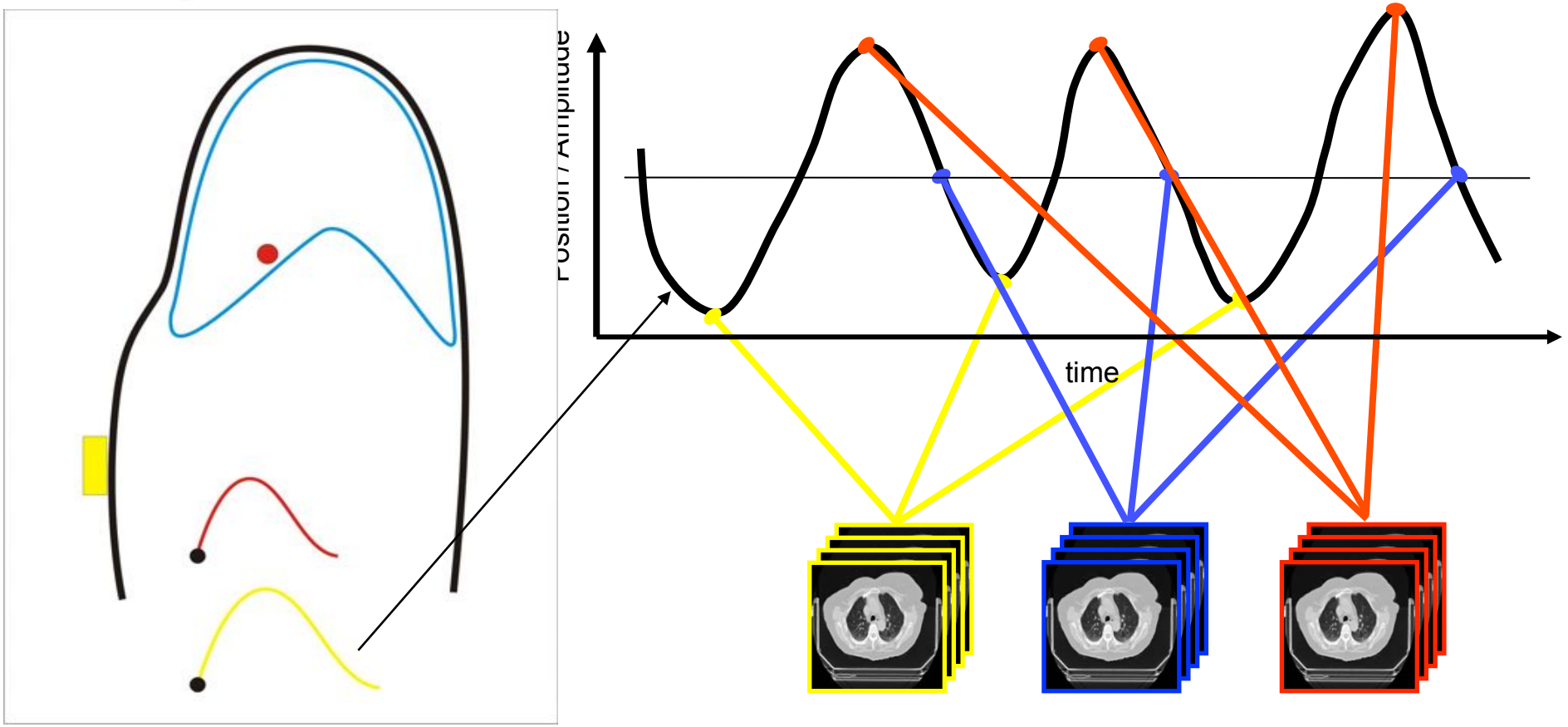
Nasal temperature

Abdominal pressure sensor



Infrared sensor

Imaging for target definition: RC-CT



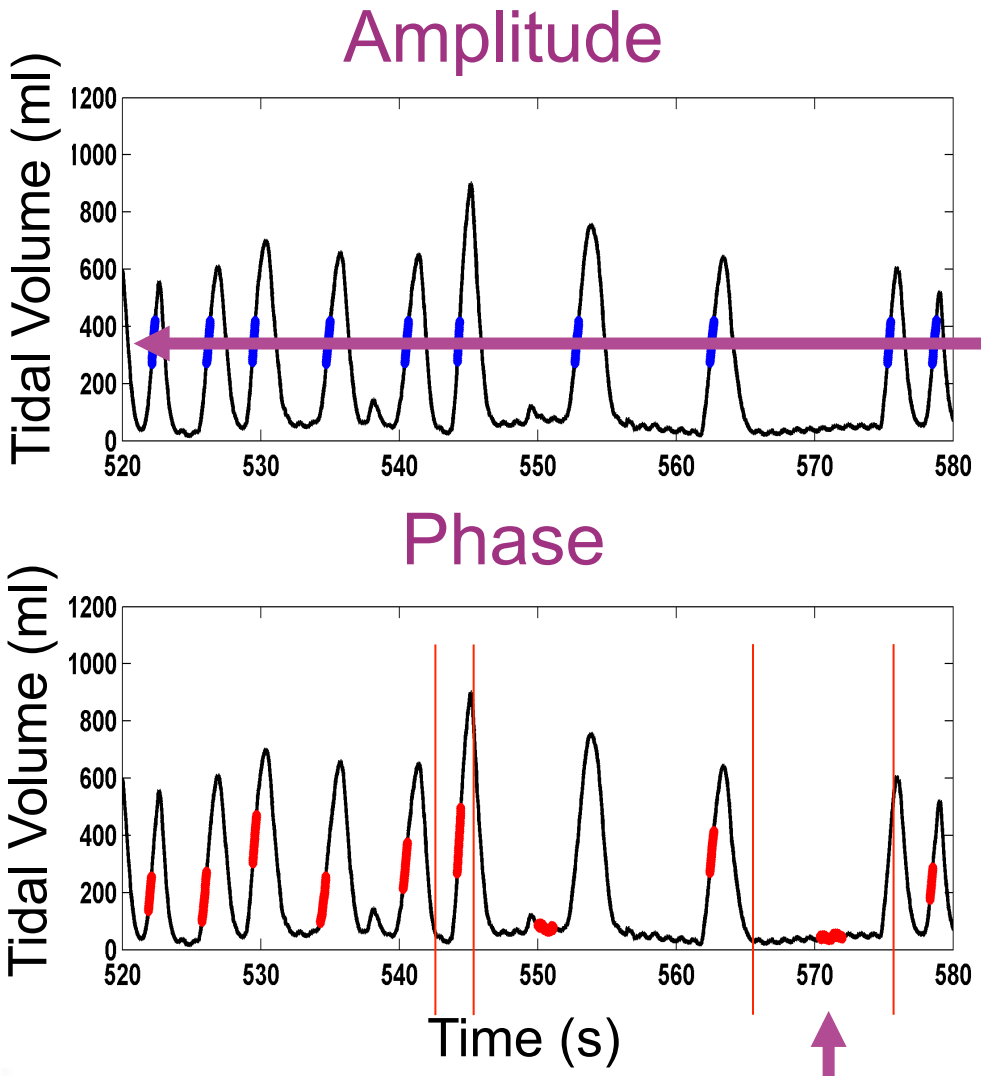
Respiration Correlated CT (4D RC-CT):

- Assumes stable correlation between internal and external motion
- Images are tagged with a time stamp and binned

Courtesy Guckenberger *et al*

Imaging for target definition: RC-CT

- **AMPLITUDE**-based versus **PHASE**-based binning



Mid-inspiration differs based on selection method

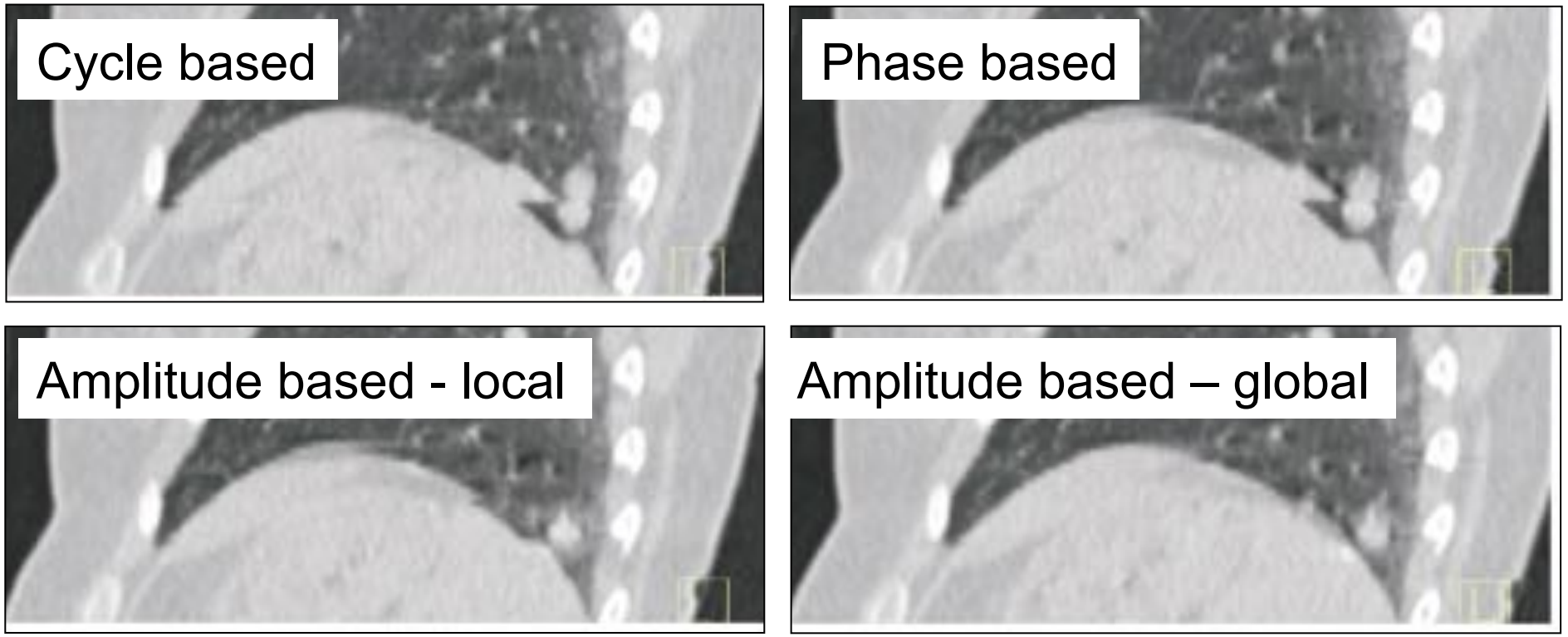
Mid-inspiration defined by percentile tidal volumes

Mid-inspiration defined by time between exhalation and inhalation peaks

Lu *et al*, Med Phys, 2006

Imaging for target definition: RC-CT

- Amplitude-based sorting of projections:
  - ➢ Improved image quality
    (motion artifacts and reproducibility of tumor motion)
  - ➢ Limitations for reconstruction of peaks (deep breaths ...)

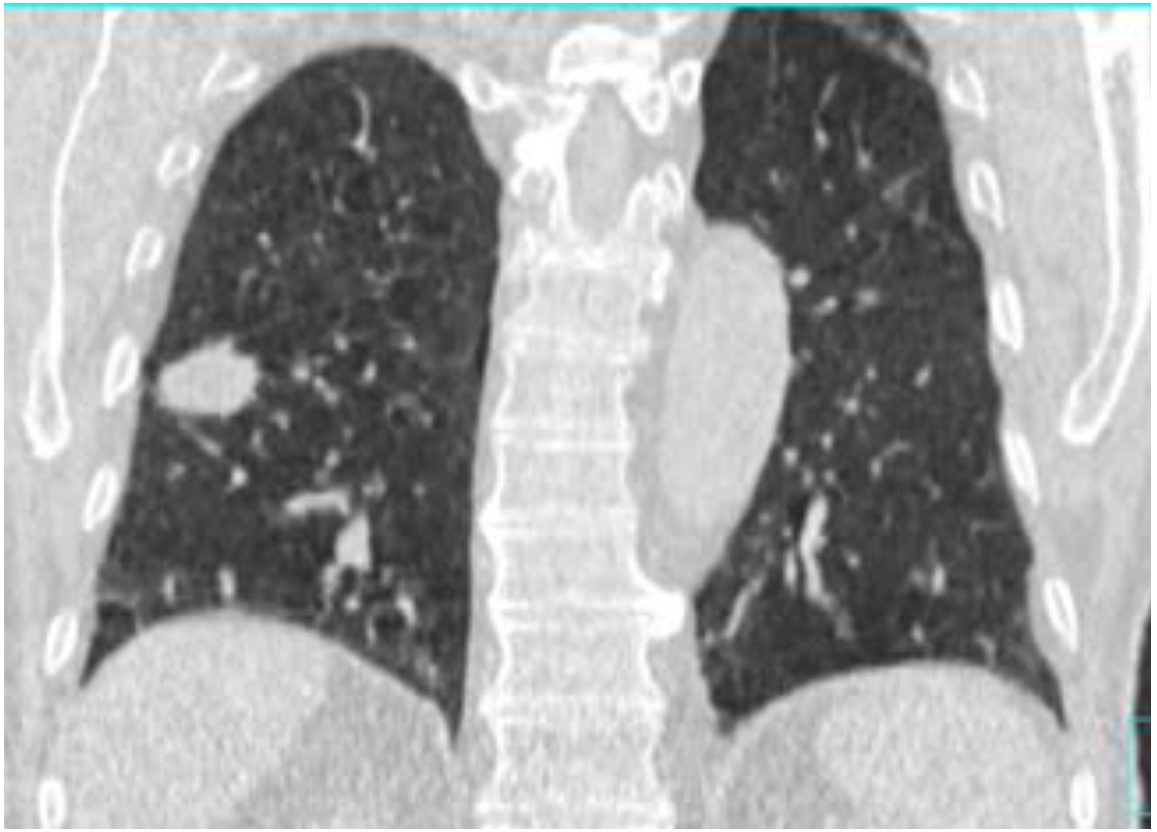


Lu *et al*, Med Phys, 2006 – Guckenberger *et al* Radiother Oncol 2007

Imaging for target definition: RC-CT

Conventional 3D CT

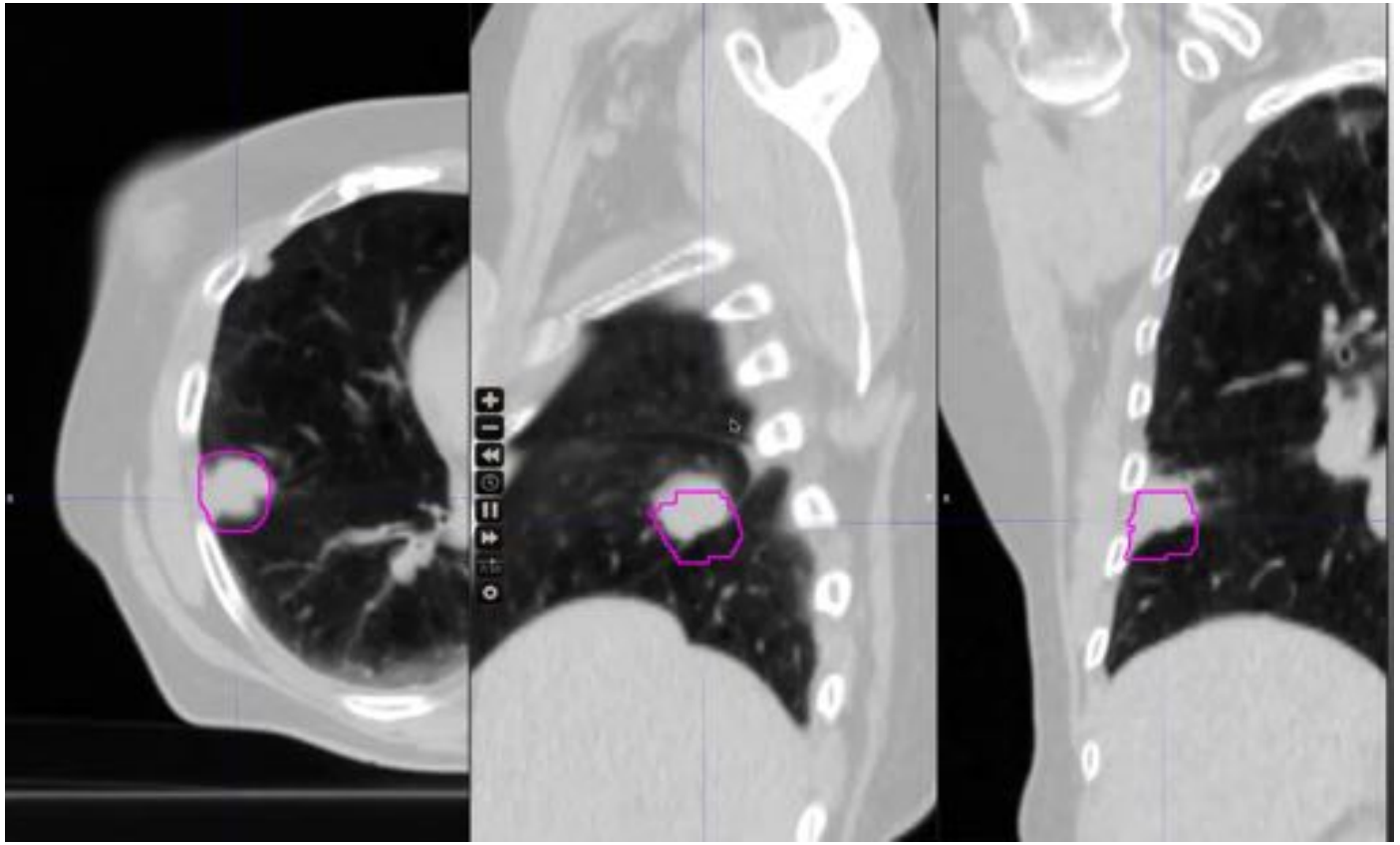
Respiration correlated 4D-CT



Courtesy Guckenberger *et al*

So, what's the problem?

Imaging for target definition: RC-CT



IT'S JUST A MOVIE LOOP!

Imaging for target definition: RC-CT

- Is 1 respiration correlated 4D-CT representative for the actual treatment?

Repeated 4D-CTs **before** treatment planning

Four 4D-CTs in ten minutes intervals:

- No systematic changes of motion pattern
- Increased variability for lower lobe tumors

Guckenberger IJROBP 2007

Two successive 4D-CTs:

- Volume of the PTV not systematically different
- Motion range variability <2mm in 81%
- Coverage not compromised

van der Geld Radiat Oncol. 2006

No benefit of repeated 4D-CT imaging in 1 session

Imaging for target definition: RC-CT

- Is 1 respiration correlated 4D-CT representative for the actual treatment?

Repeated 4D-CTs **during** the treatment course

Second 4D-CT after > 2 fractions (median 6 days):

Haasbeck IJROBP 2007

- No systematic changes of motion pattern and target volume
- Target coverage compromised in one patient (atelectasis)

Repeated 4D CBCT scans (median 9) during RT:

Sonke IJROBP 2008

- Stable trajectory with variability (1SD) less than 1mm
- Significant base-line shifts

Continuous tumor tracking in EPID images:

Richter IJROBP 2010

- Stable tumor trajectory, both intra-fractional and inter-fractional

No benefit of replanning because of motion variability

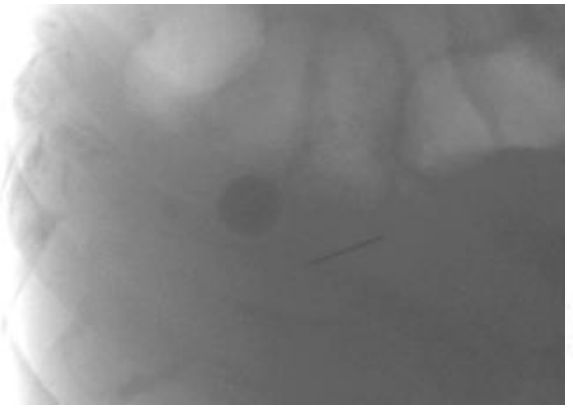
Imaging for target definition: RC-CT

- Correlation of motion amplitude in planning 4D-CT and average motion observed during treatment (X-ray fluoroscopy)

Table 1
Patient information, length of kV X-ray sequence, measure of breathing rate and breathing motion ranges from X-ray data and from 4D CT data, in both cases calculated from the center-of-mass positions of the implanted fiducial marker.

Session	Site	X-ray seq. duration [s]	Breathing rate [bpm]	X-ray marker motion CC [mm]	X-ray marker motion AP [mm]	X-ray marker motion LAT [mm]	4D CT marker motion CC [mm]	4D CT marker motion AP [mm]	4D CT marker motion LAT [mm]
Patient 1 (1)	Liver (segm. 4b), HCC	20	17.4	10.3	5.4	1.5	7.9	1.7	0.9
Patient 1 (2)	Liver (segm. 4b), HCC	20	16.4	8.4	3.8	0.7	7.9	1.7	0.9
Patient 2	Liver (segm. 5), metastasis	20	14.8	[illegible]	6.3	1.6	[illegible]	5.6	1.3
Patient 3	Liver (segm. 8), metastasis	40	17.1	11.3	1.5	2.5	5.5	1.0	0.8
Patient 4	Lung (right upper lobe)	30	23.5	[illegible]	2.0	1.3	[illegible]	1.7	0.8
Patient 5 (1)	Lung (right lower lobe)	20	14.1	10.6	4.2	1.8	10.0	4.0	1.2
Patient 5 (2)	Lung (right lower lobe)	20	14.1	10.6	4.2	1.8	10.0	4.0	1.2
Mean			16.8	9.6	3.9	1.6	7.9	2.8	1.0

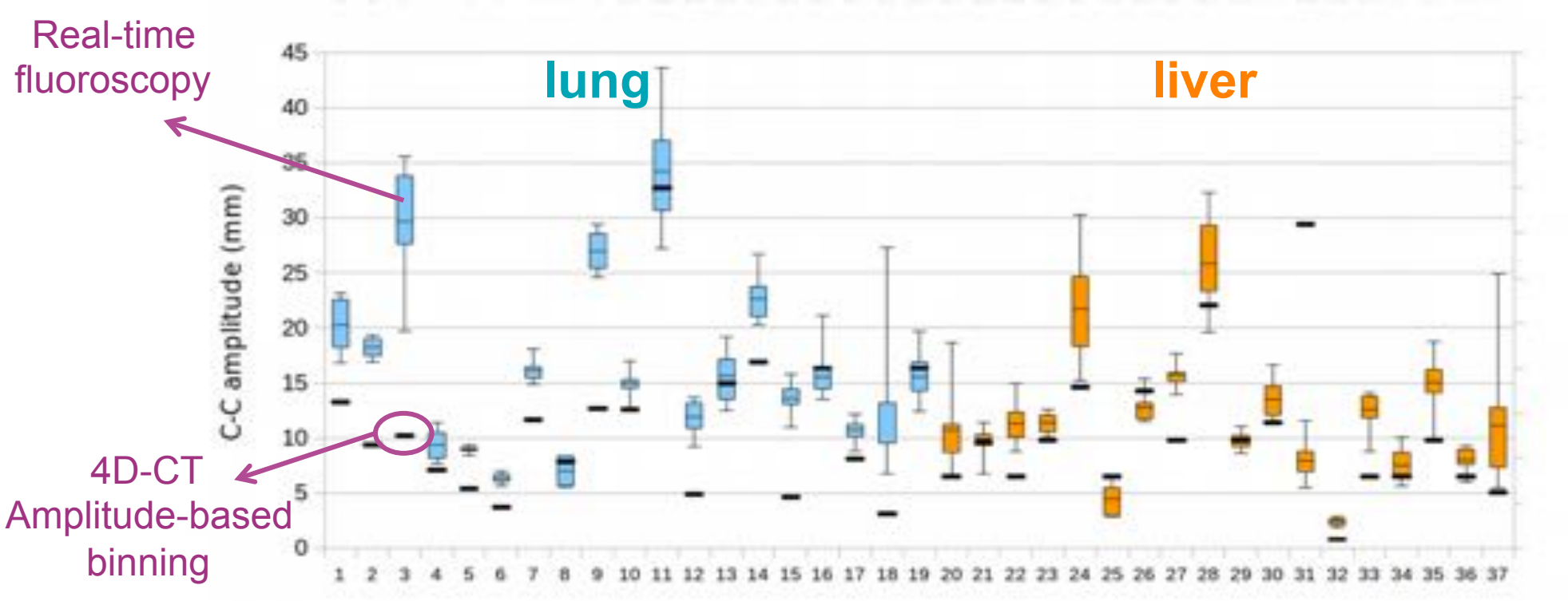
- On average the motion range observed in 4DCT was **22%** lower than that observed with X-ray fluoroscopy on the treatment couch



Depuydt *et al.* Radiother Oncol 2012

Imaging for target definition: RC-CT

- The so-called 4D CT is nothing but a **continuous movie-loop** and might NOT be representative for the breathing pattern at the time of treatment!!!!



Dhont J., Verellen D. (Radiother Oncol, 2017, In Press)

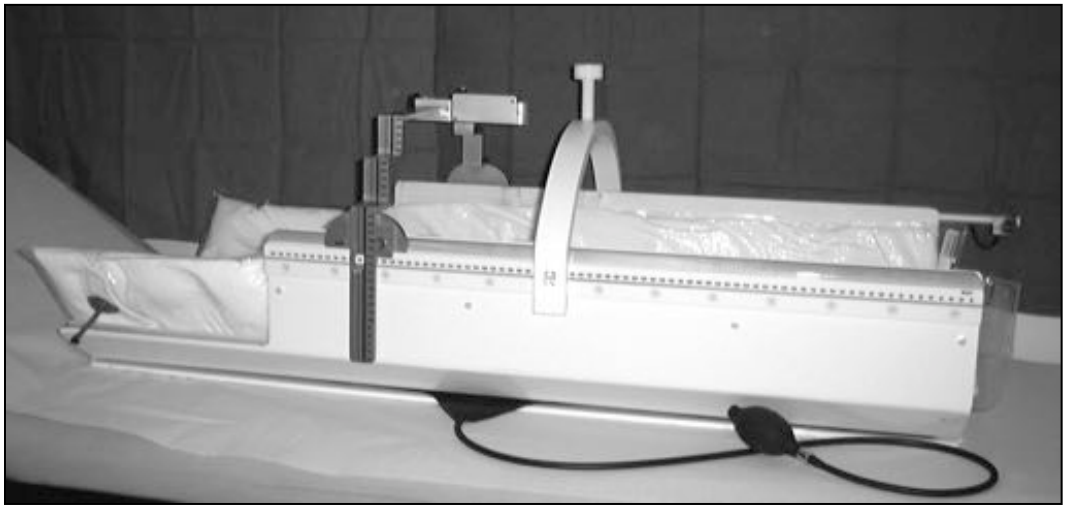
Take home message

- Fluoroscopy could be used for:
  - Selection of tumors that might require motion management during treatment, or strategy selection.
- FDG-PET should be used for
  - Exclusion of stage IV metastatic disease
  - Staging of nodal status
  - Differentiation of tumor - atelectasis
- Respiration correlated 4D-CT should be used for:
  - Elimination of motion artifacts in delineation
  - Evaluation of target motion (… and OARs)

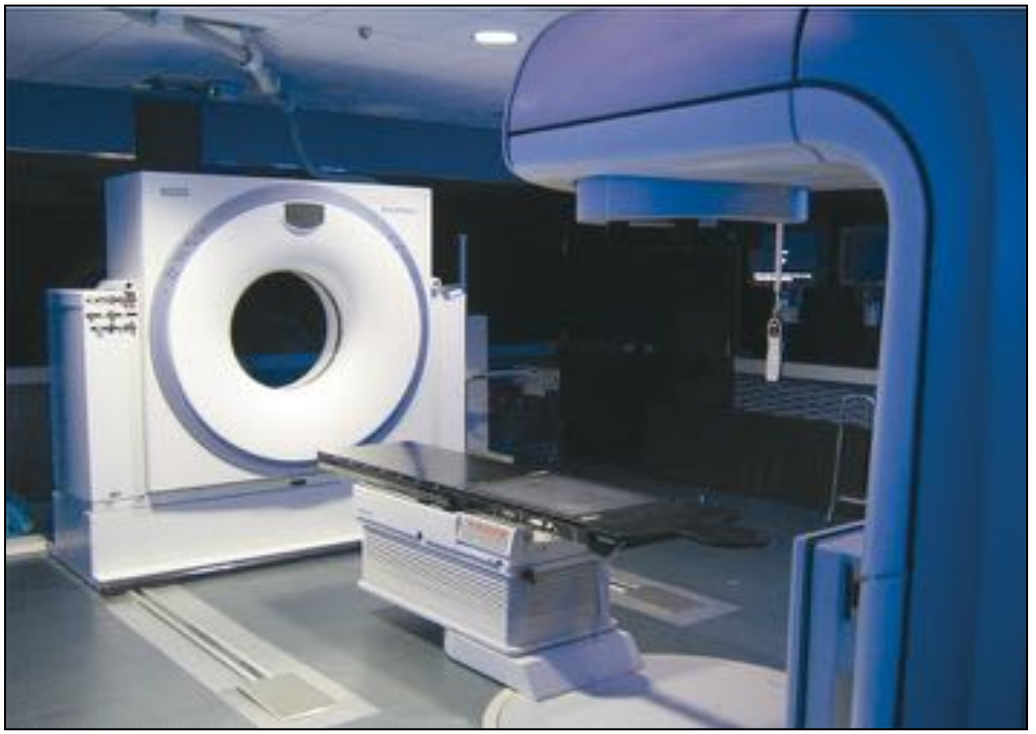
Motion management: Passive

Forced shallow breathing: body frames

… still requires IGRT



Stereotactic Body Frame, Lax *et al.*



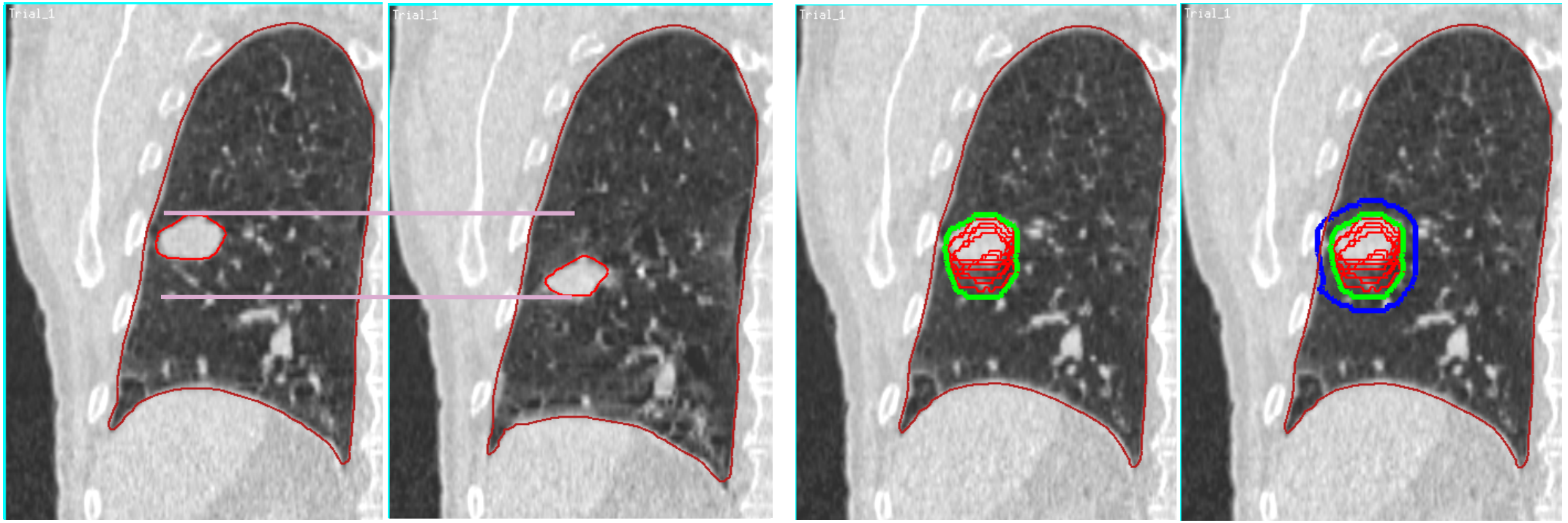
- AAPM TG 101 recommendation:
  - "Body frames and fiducial systems are OK for immobilization and coarse localization"
  - "They shall **NOT** be used as sole localization technique"

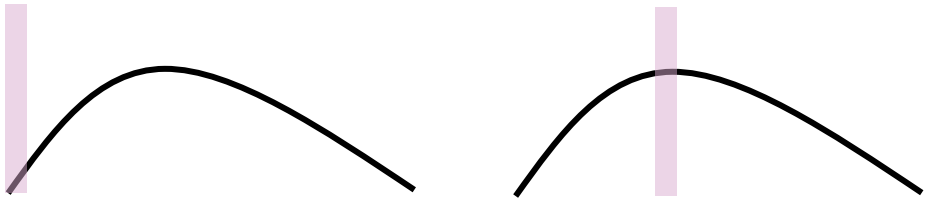
Lax *et al.* Acta Oncol 1994

Benedict *et al.* Med Phys 2010

Motion compensation techniques

- The concept of Internal Target Volume (ITV)





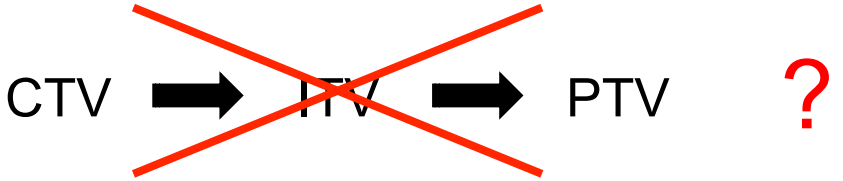
ITV → PTV

Courtesy Guckenberger *et al*

Motion compensation techniques

- The concept of **ITV** does not mix very well with the definition of **PTV**.

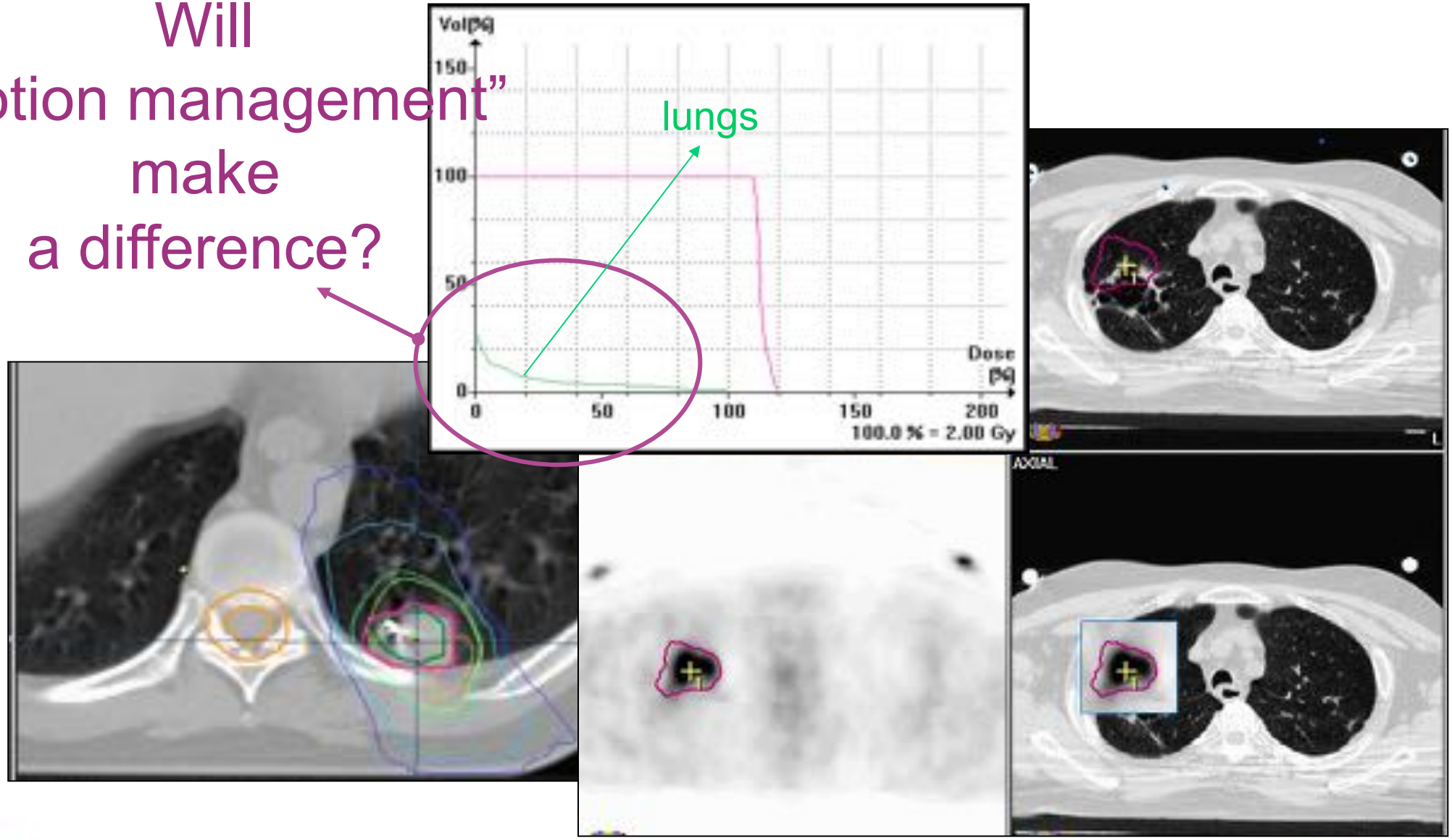
$$M_r = \alpha\sqrt{\Sigma^2} + \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$



- Target volumes are too large
- BUT:
  - Target coverage is ensured
  - Motion amplitude <10mm in majority of patients
  - Clinical data with ITV and SBRT is excellent
  - It is the most practical 4D solution

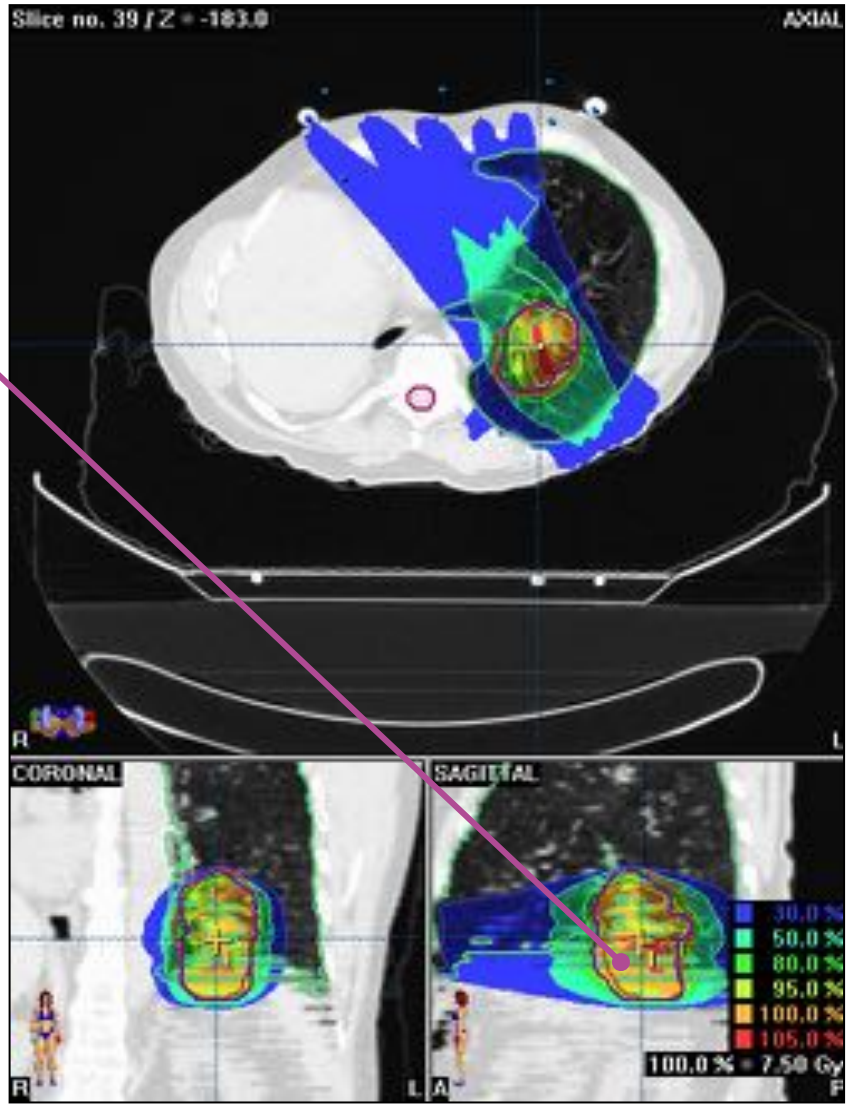
Motion encompassing techniques

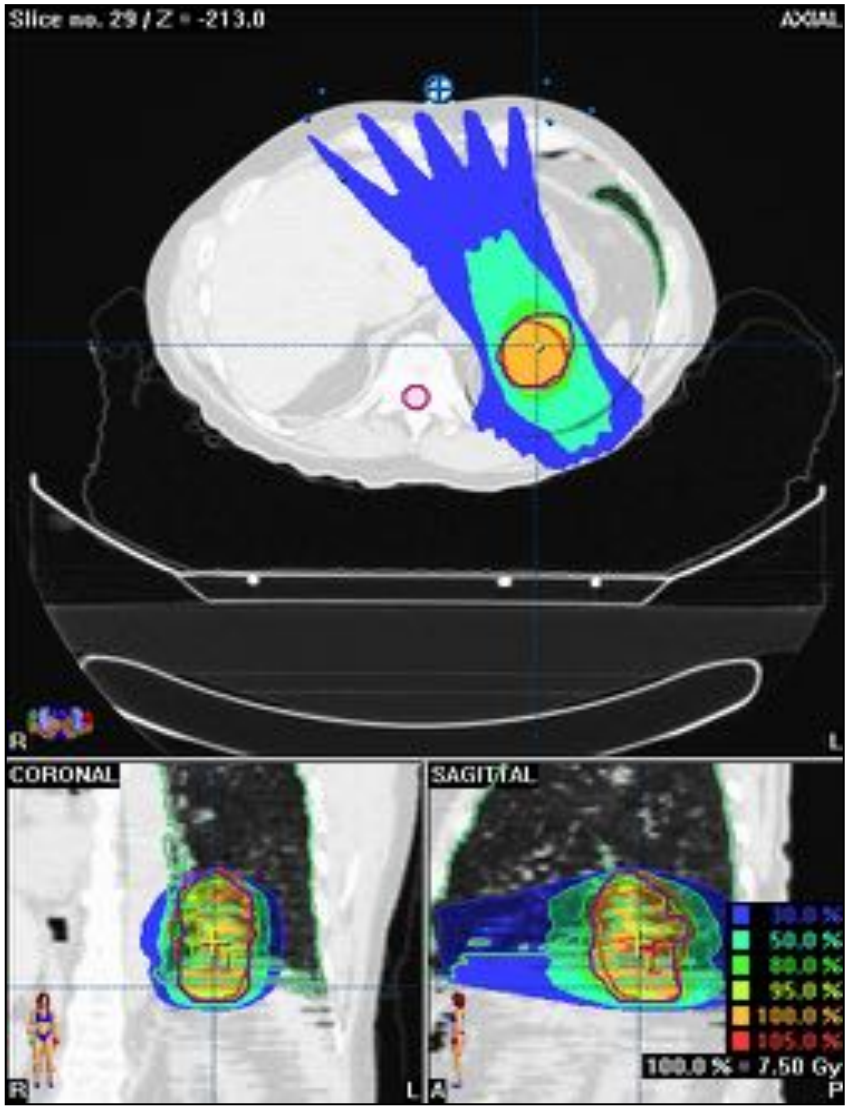
Will
"motion management"
make
a difference?



Motion encompassing techniques

Maybe …

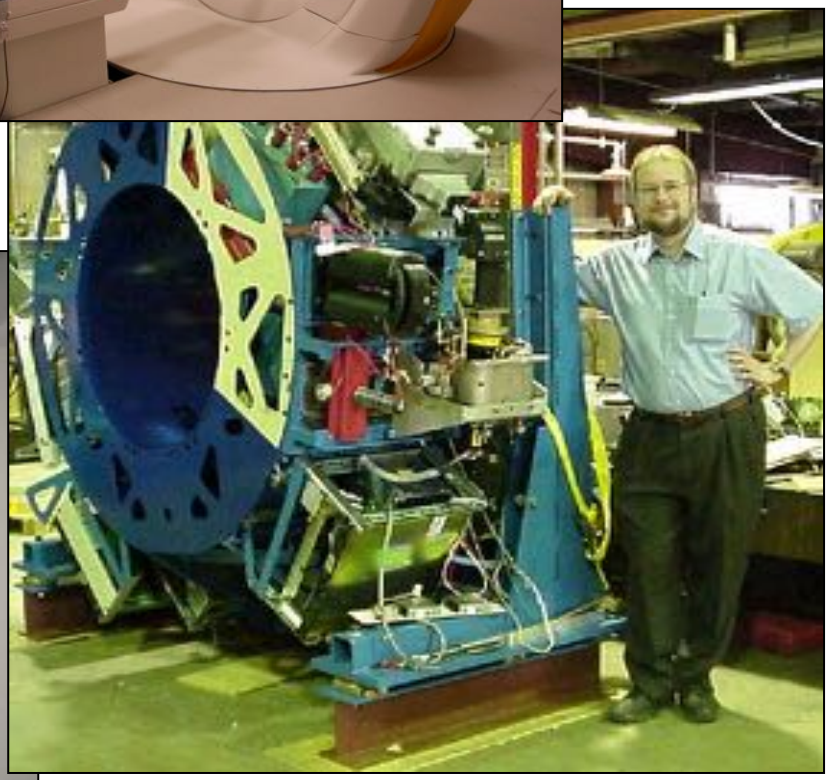


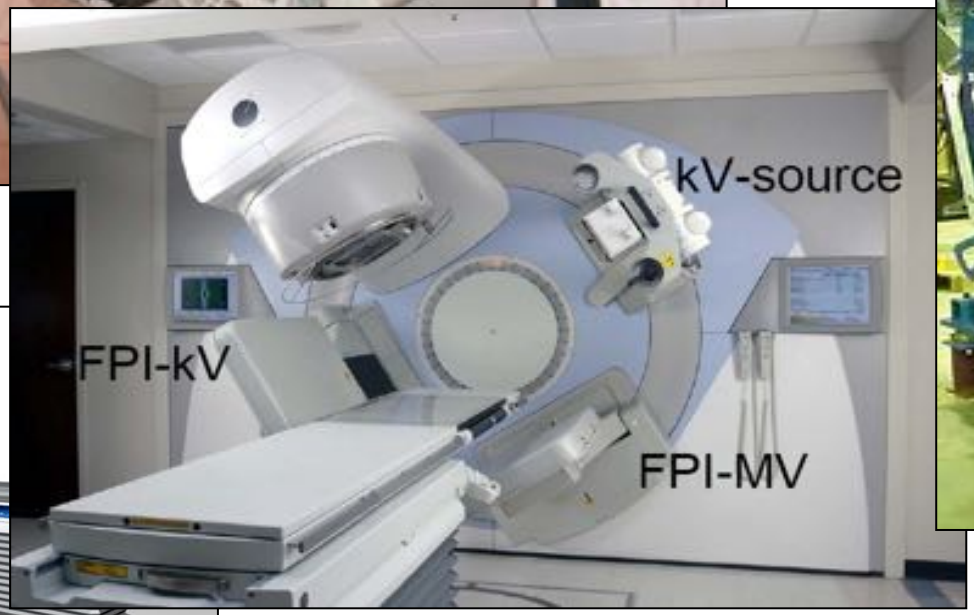


On board volumetric imaging

- So, what can we do with volumetric imaging?

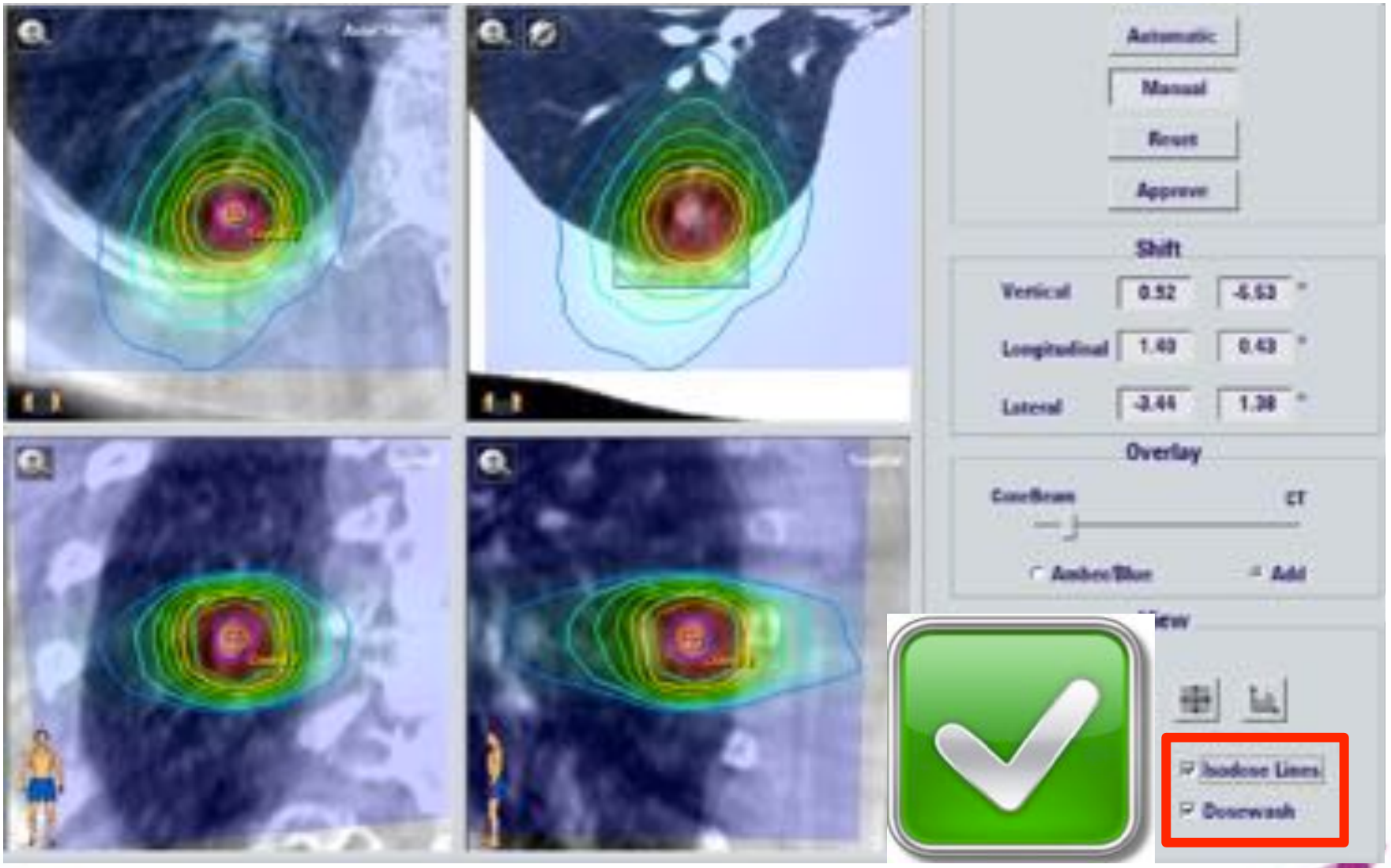
On board volumetric imaging



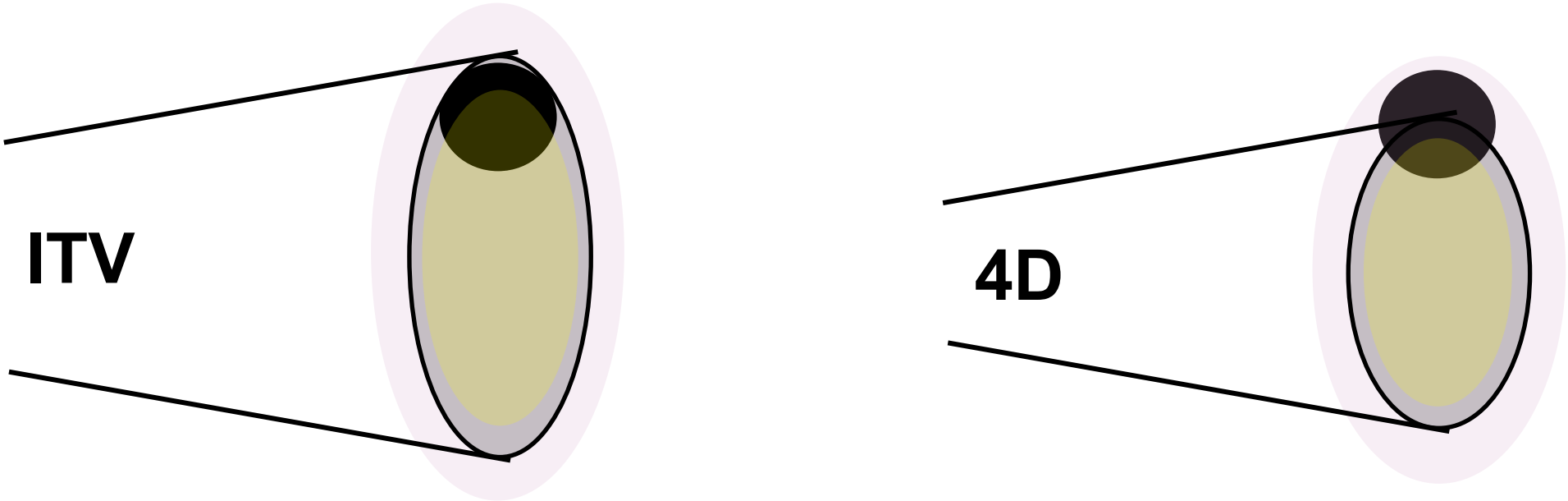


Motion compensation techniques

- Registration of blurred target from CBCT with ITV/PTV

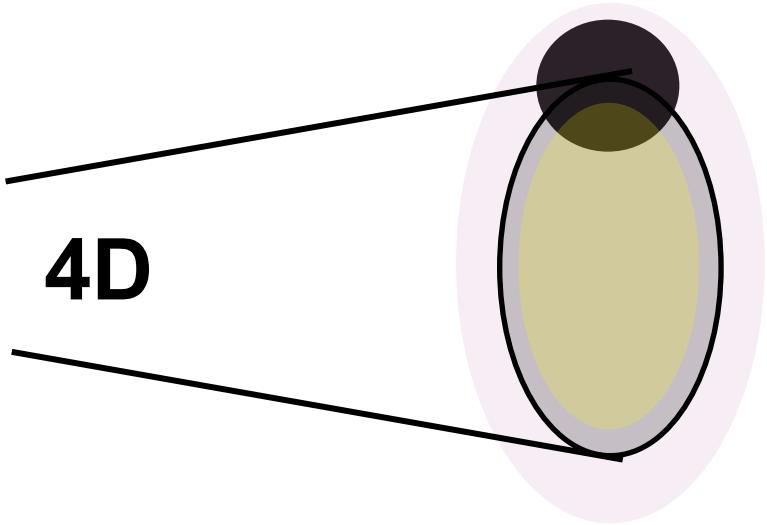


Motion compensation techniques



Courtesy Guckenberger *et al*

Motion compensation techniques



- ➔ The tumour is ~10% of the time at 50% of the dose
- ➔ This only accounts for about 5% underdose
- ➔ Even with large amplitudes, the margin needs not to be large.
- ➔ Mid-ventilation or Mid-position approach

- The radiation beam does not necessarily need encompass the complete breathing amplitude
  - ➢ Broad beam penumbra in the lung tissue
  - ➢ Time spend at edges of “ITV” is short
  - ➢ **Dose loss at edges can be compensated for by higher doses at the centre**

Motion compensation techniques

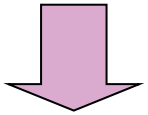
Treatment planning:
Reference Image

Treatment delivery:
Verification Image

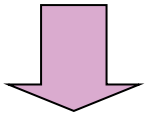
Courtesy Guckenberger *et al*

Motion compensation techniques

Knowledge on organ motion
(clinical studies, multiple CT scans, 4D CT, ...)

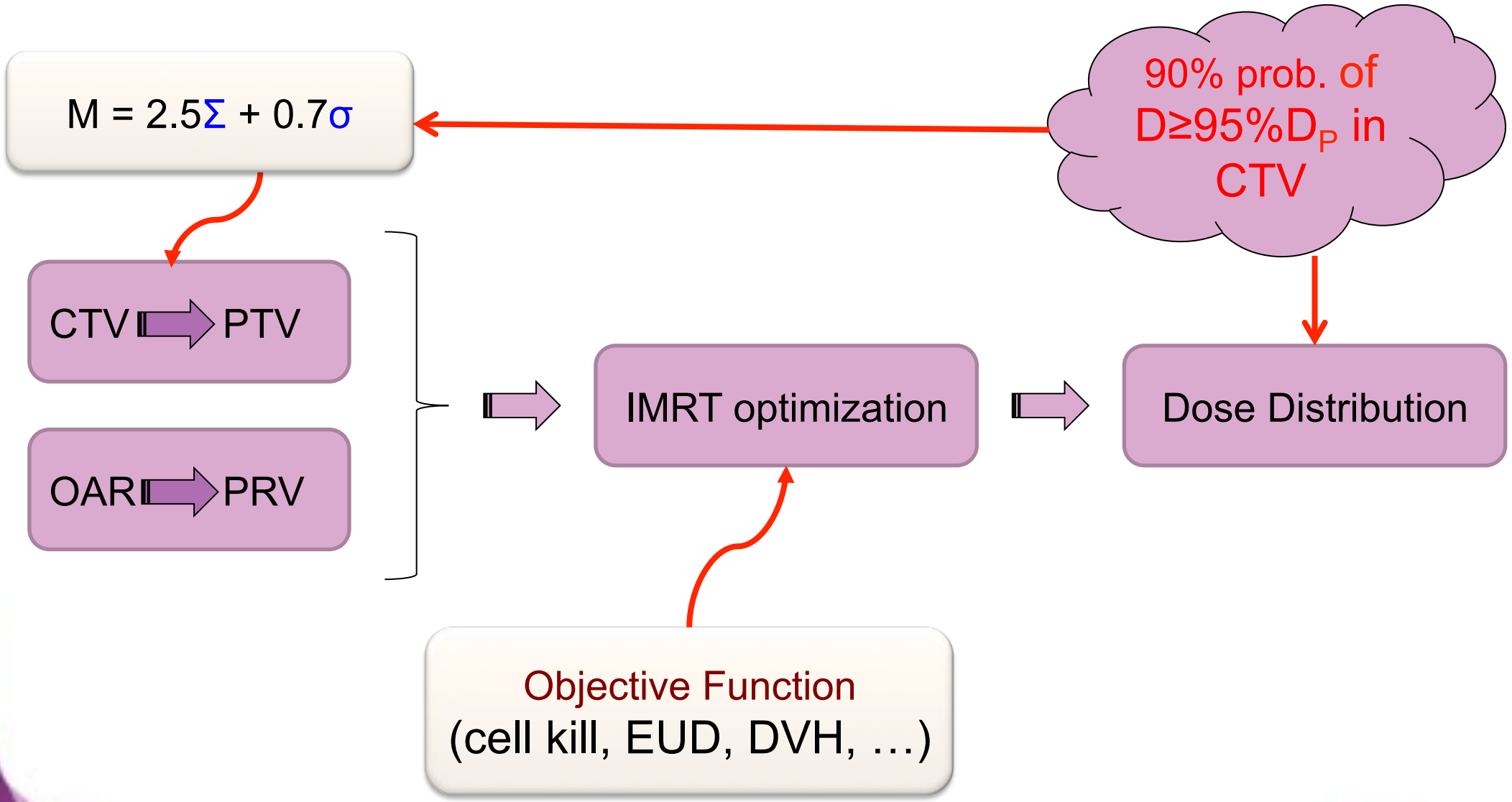


Mathematical model to describe organ motion induced geometric changes
Probability distribution of patient geometries

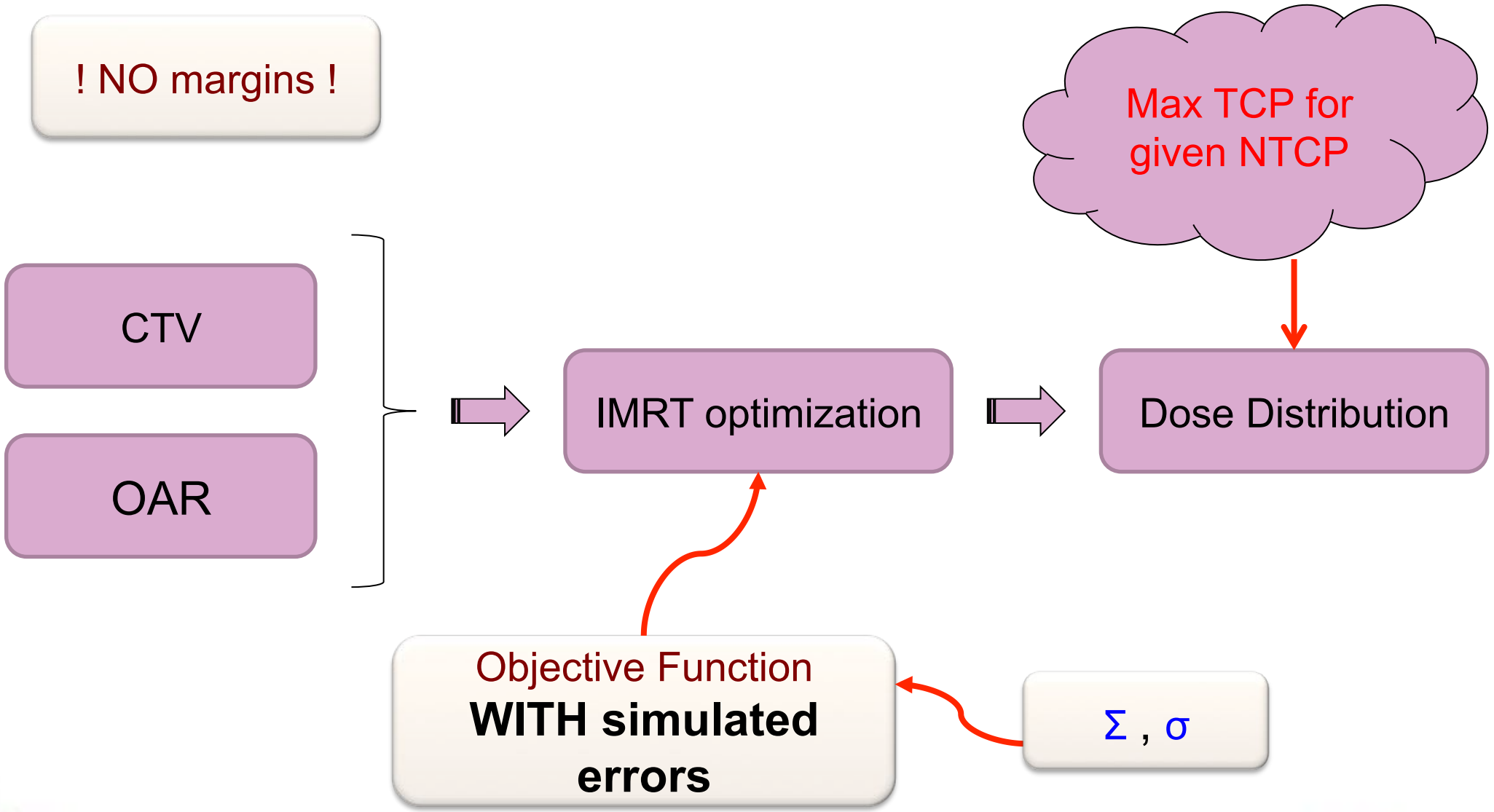


Probabilistic IMRT optimization

“Conventional” IMRT planning

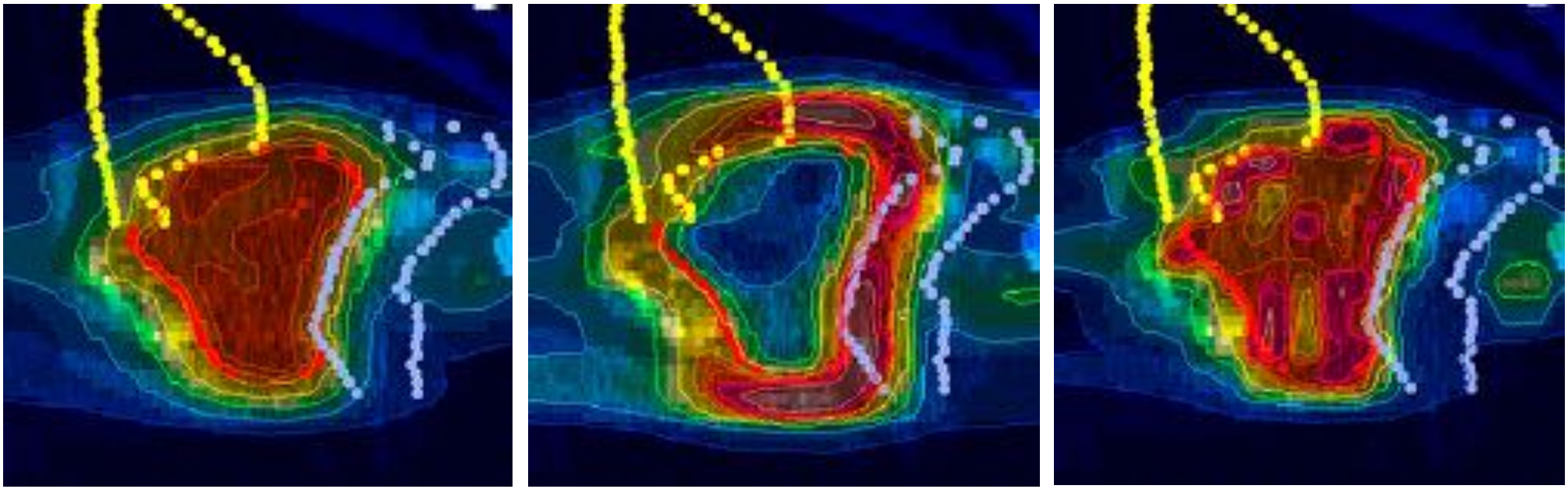


“Probabilistic” IMRT planning



“Probabilistic” IMRT planning

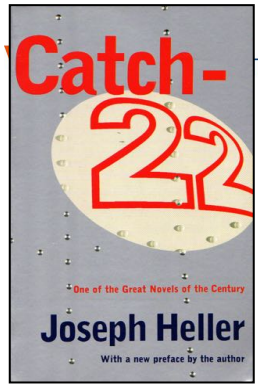
Expectation value | Dose variance per voxel | Risk, ‘static’ dose



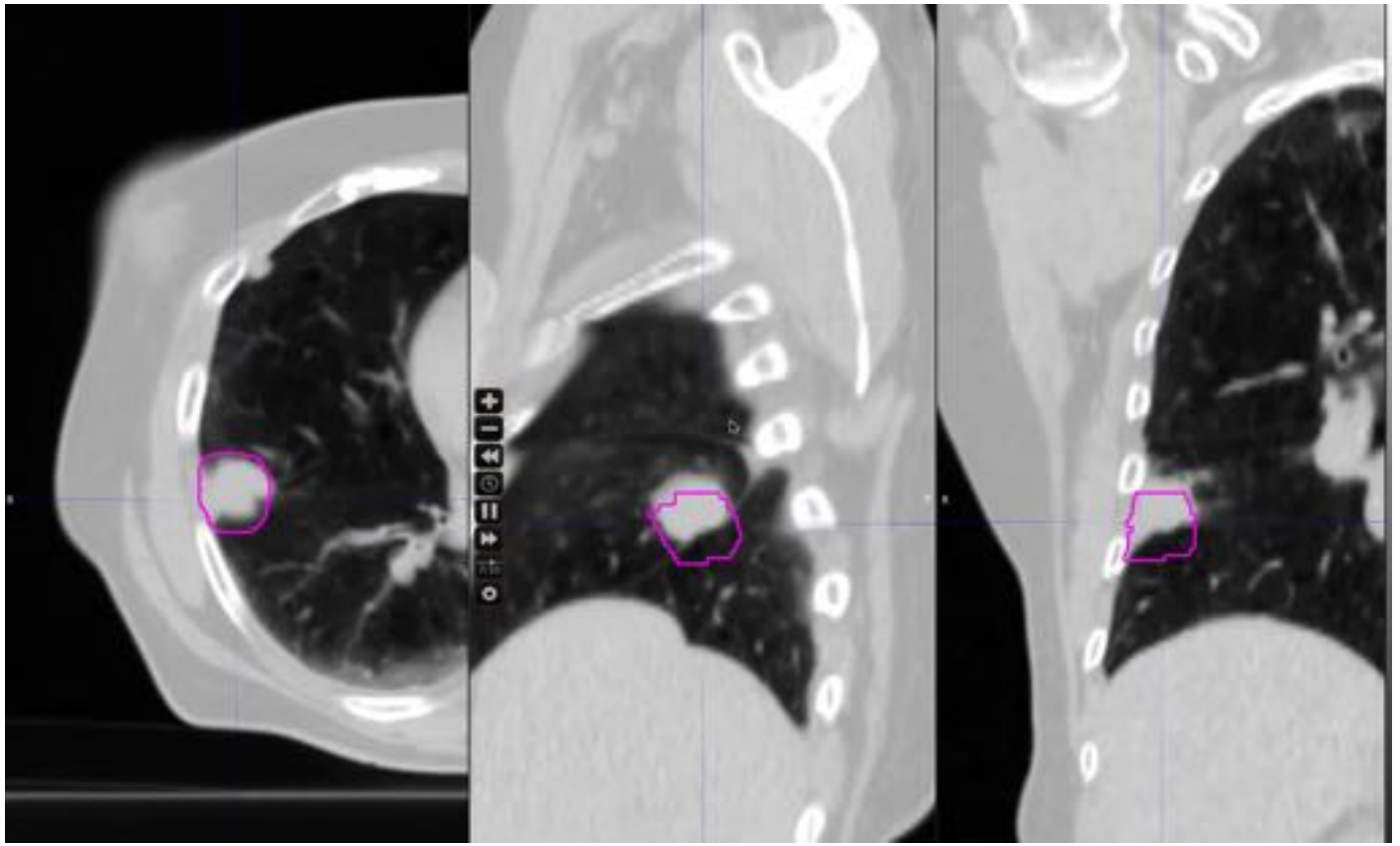
Courtesy U. Oelfke

- These “passive” approaches, require some prior knowledge of tumor motion and assume a ‘reasonable’ reproducible, predictive breathing pattern

Where's the catch?

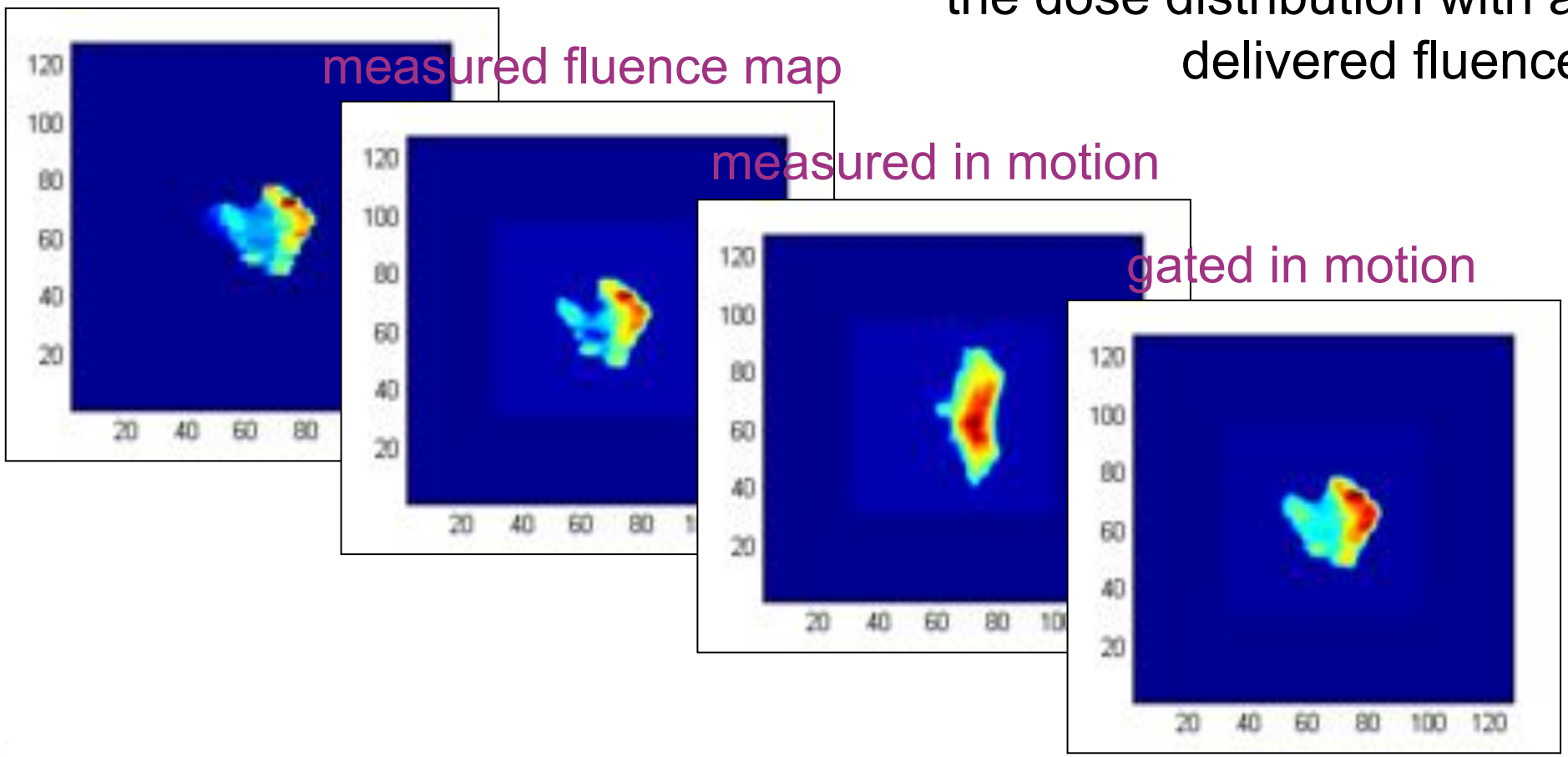


- The so-called 4D CT is nothing but a **continuous movie-loop** and might NOT be representative for the breathing pattern at the time of treatment!!!!



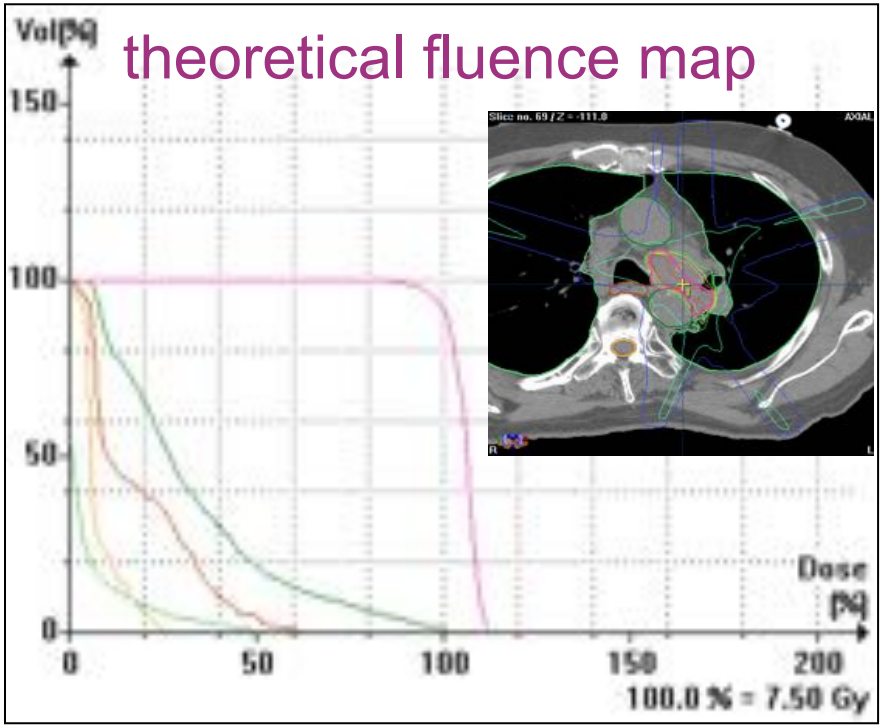
Why motion management in IMRT?

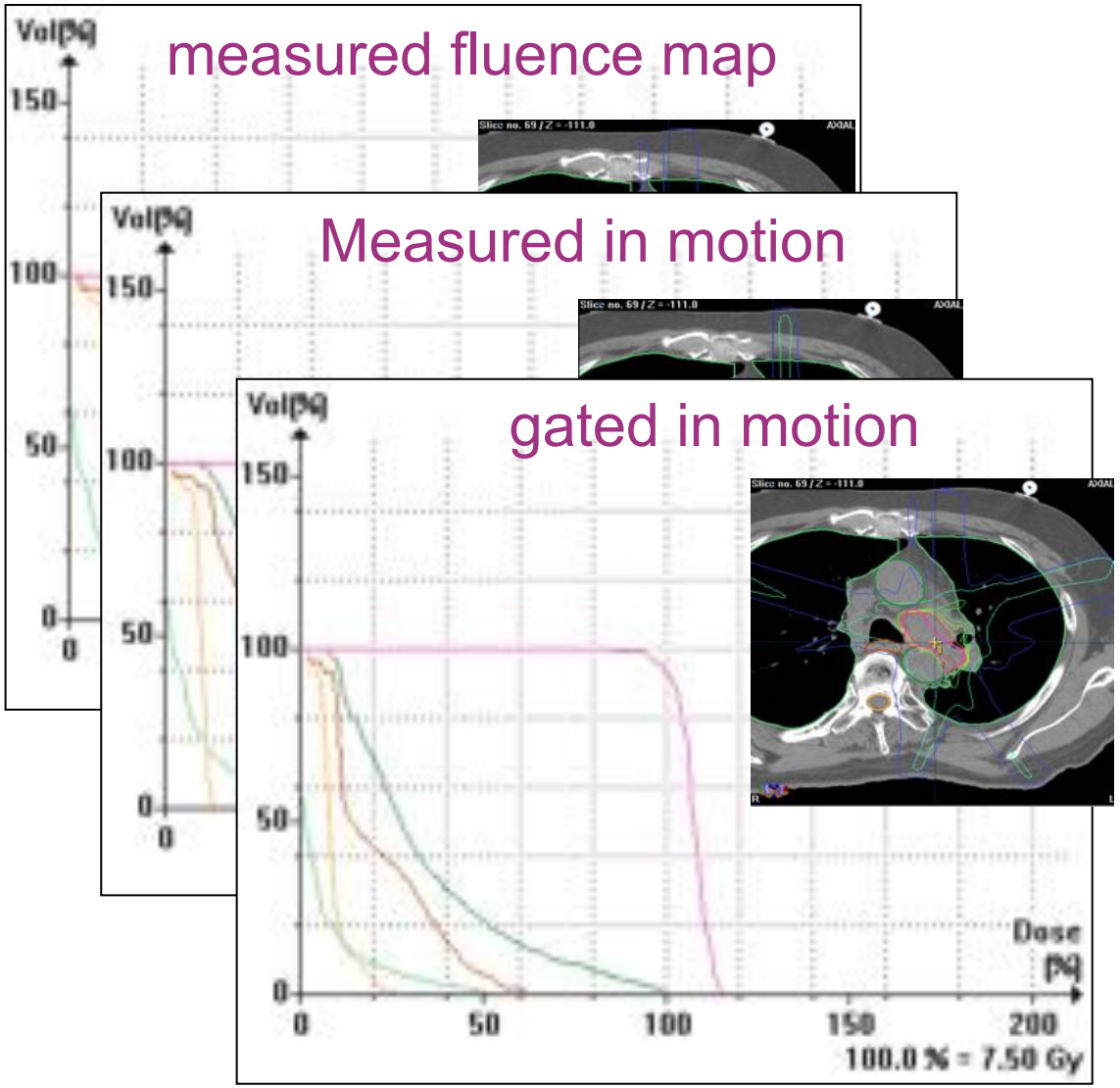
Importing theoretical and measured fluence maps into Treatment Planning System to re-calculate the dose distribution with actually delivered fluence maps



Verellen *et al* Radiother Oncol 2006

Why motion management in IMRT?

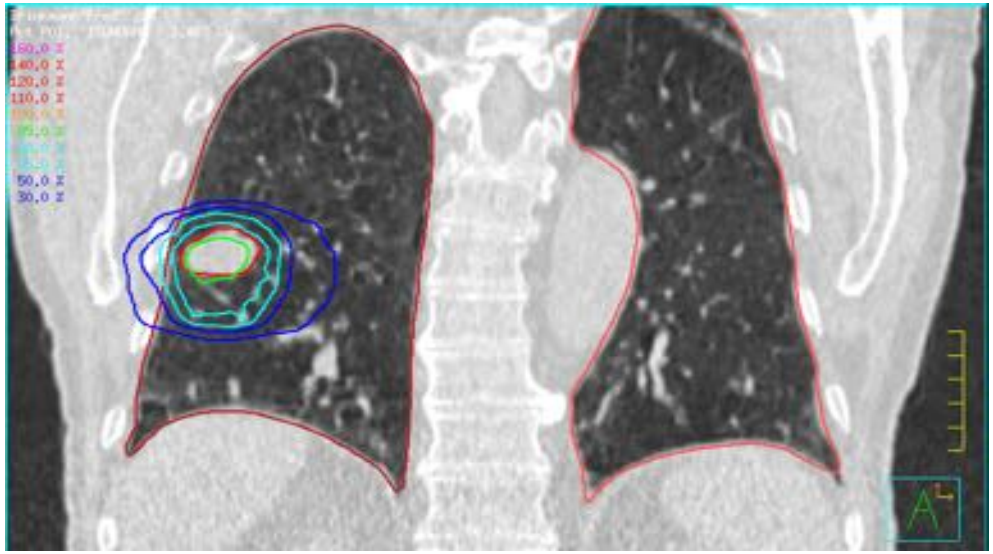




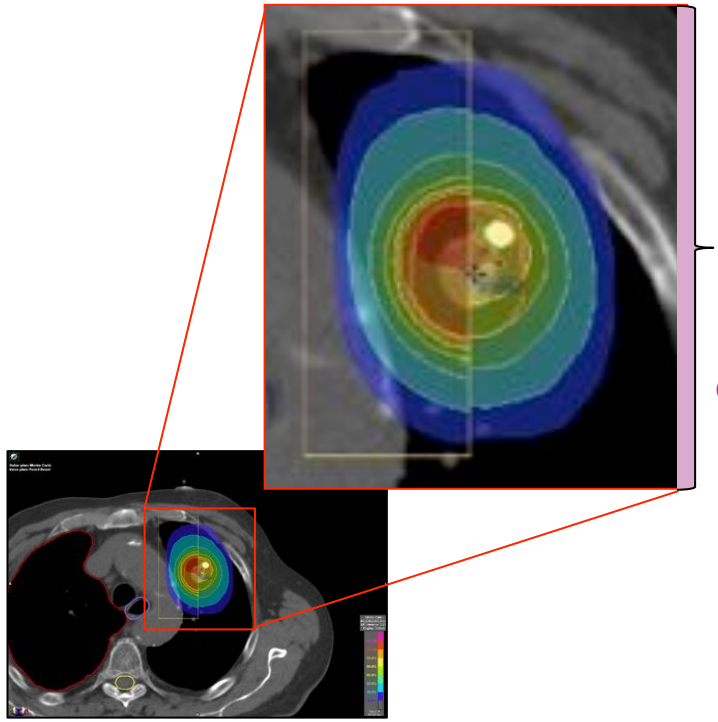
Verellen *et al* Radiother Oncol 2006

Why motion management in IMRT?

- "Open" beams:
  - "Advantage" of photons: dose deposition "tracks" soft tissue surrounded by lung tissue.



Courtesy M. Guckenberger

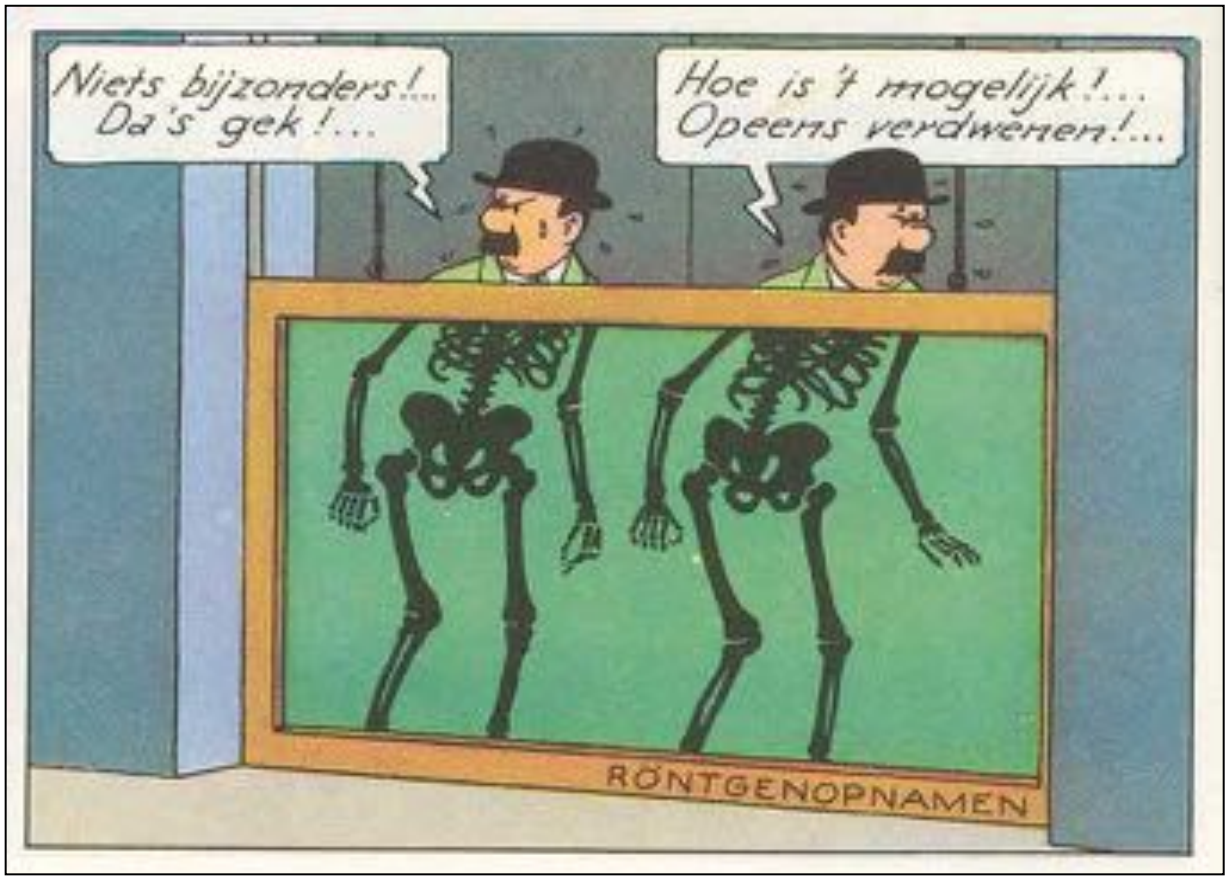


- Volumetric Modulated Arc Therapy:
  - Boost fluence in lung tissue inside PTV
  - What if healthy tisue or GTV moves in boosted fluence?

Motion management: Active

Planar imaging

- So, what can we do with planar imaging?

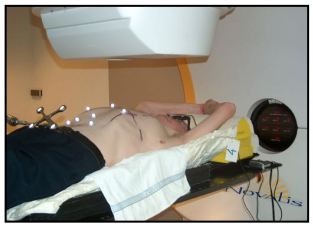


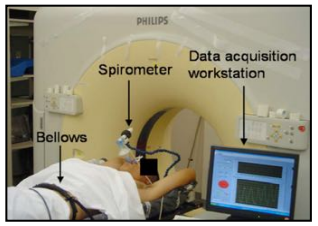
Motion management: Active

Courtesy Guckenberger *et al*

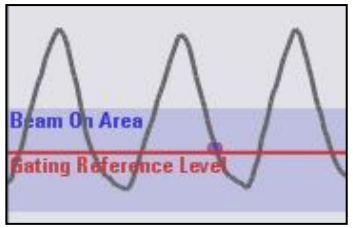
Breathing synchronization: Anticipating unpredictable motion …

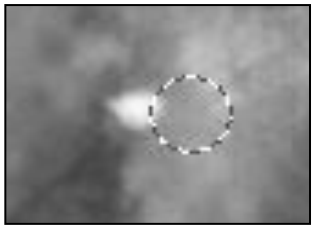
- Monitoring respiration:
  - Requires …



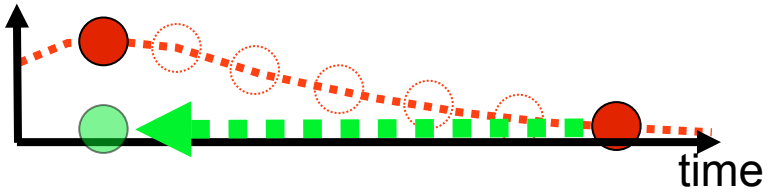


- Correlation model:
  - Requires "stable" correlation between internal and external motion

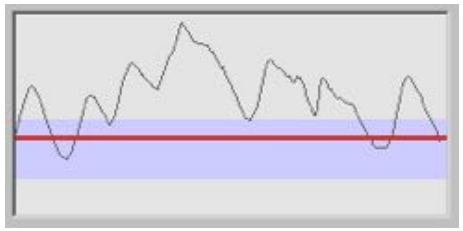




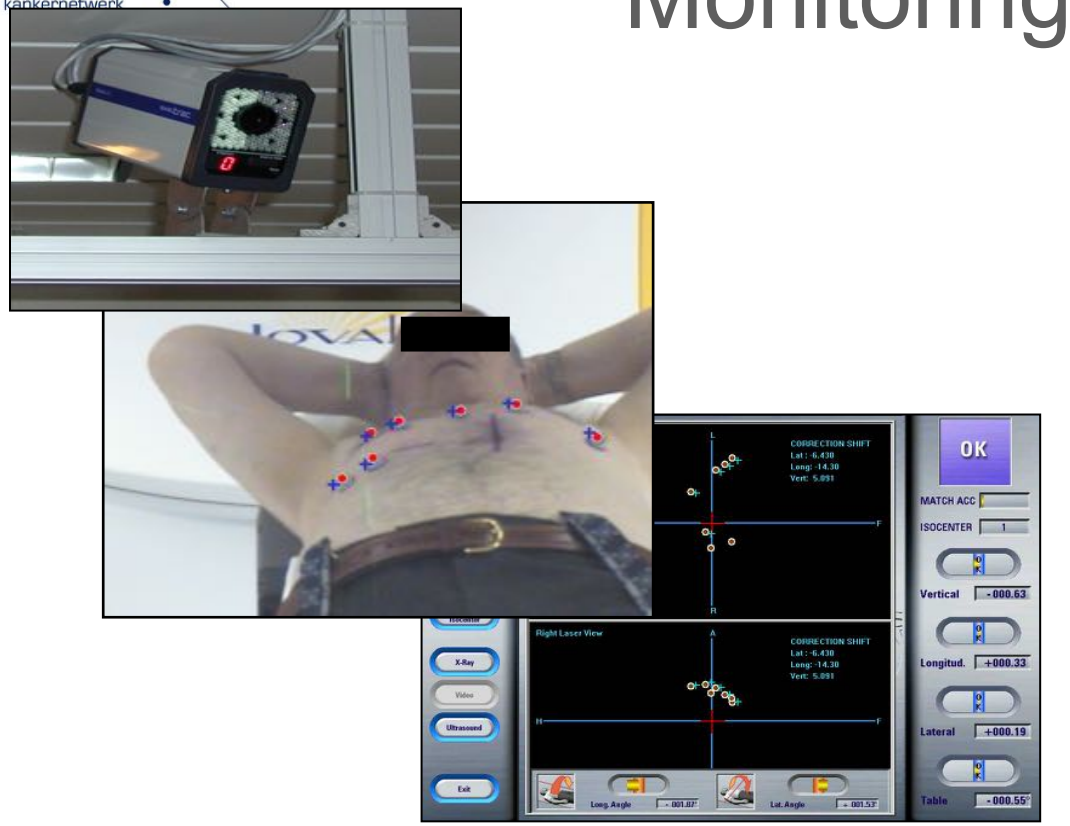
- Prediction model to compensate for system latency:
  - Requires "predictive" (i.e. periodic) motion

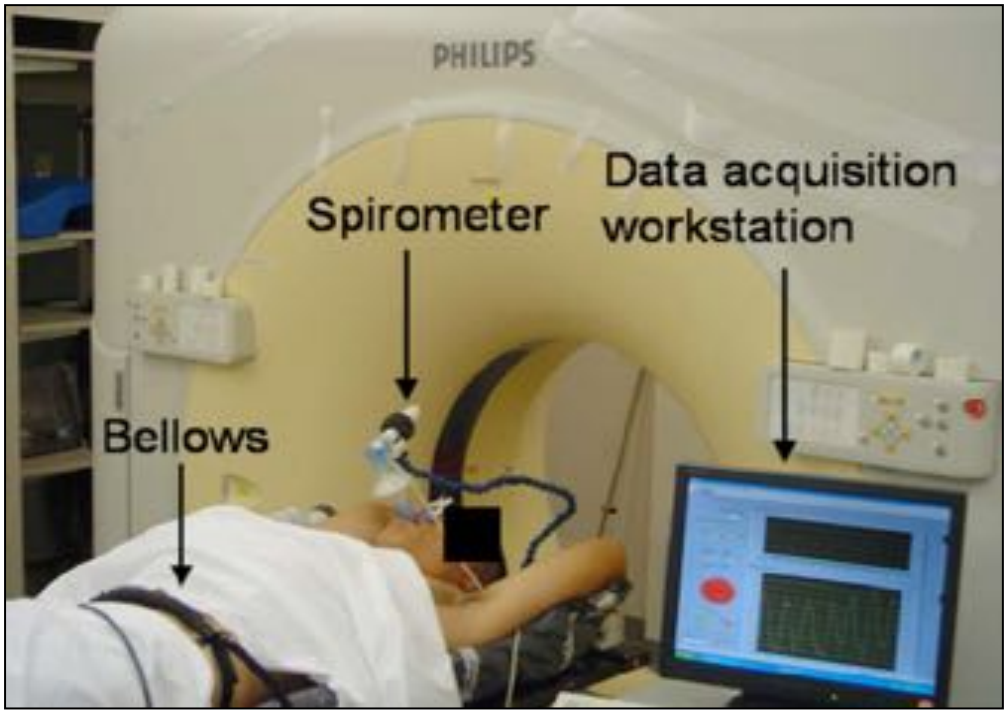


- Interface between machine and man …
  - By definition "unpredictable"?

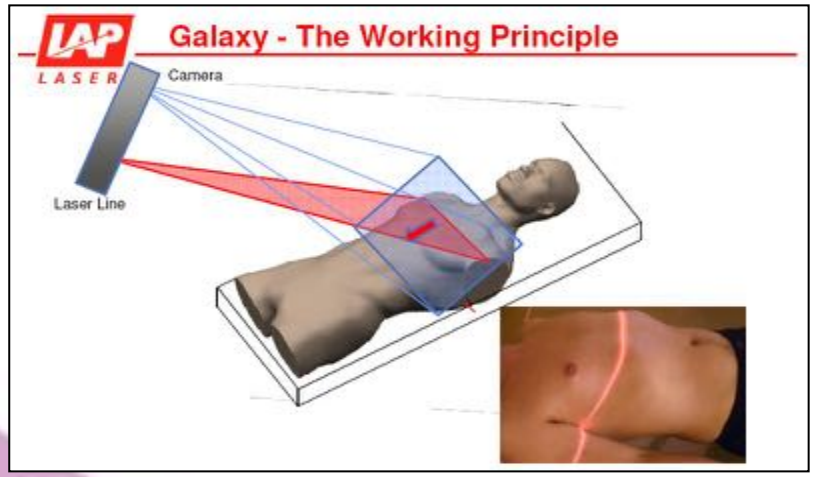


Monitoring respiration





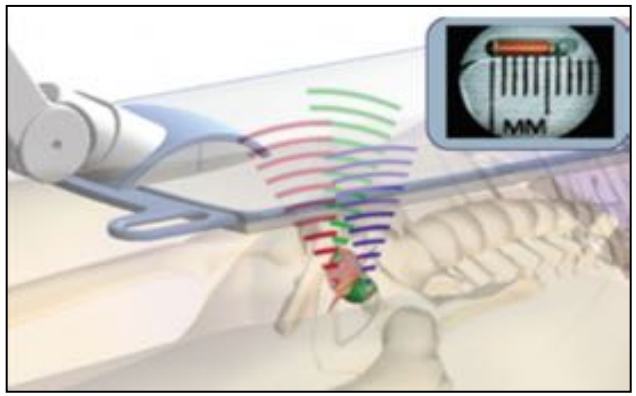
Low *et al.*



Keall *et al.*

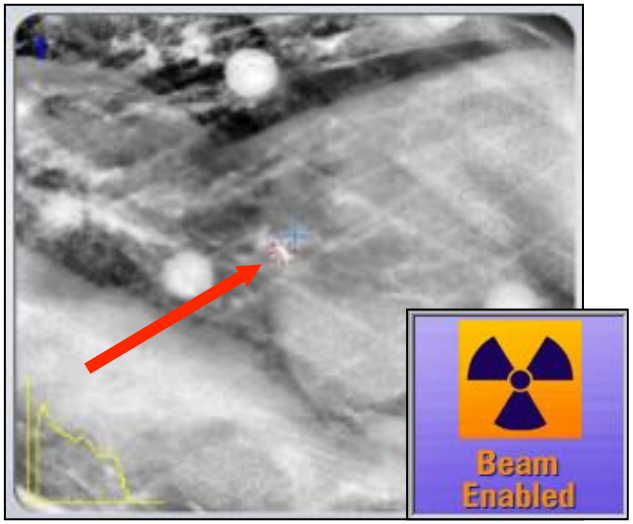
Correlating internal/external motion

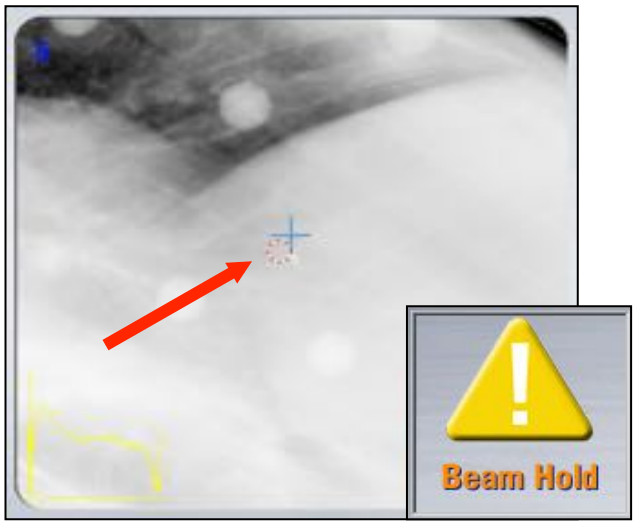
- Real-time tracking of internal marker or direct visualization of tumour



Courtesy Calypso Medical Technologies

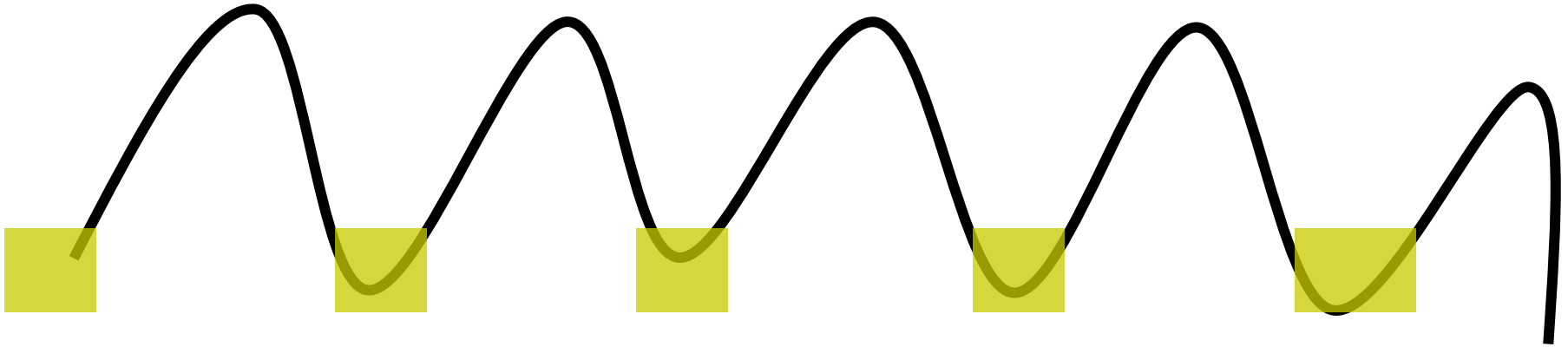
- Correlating external breathing signal with internal tumour motion
  - ➢ Using surrogates (implanted marker, diaphragm, …)



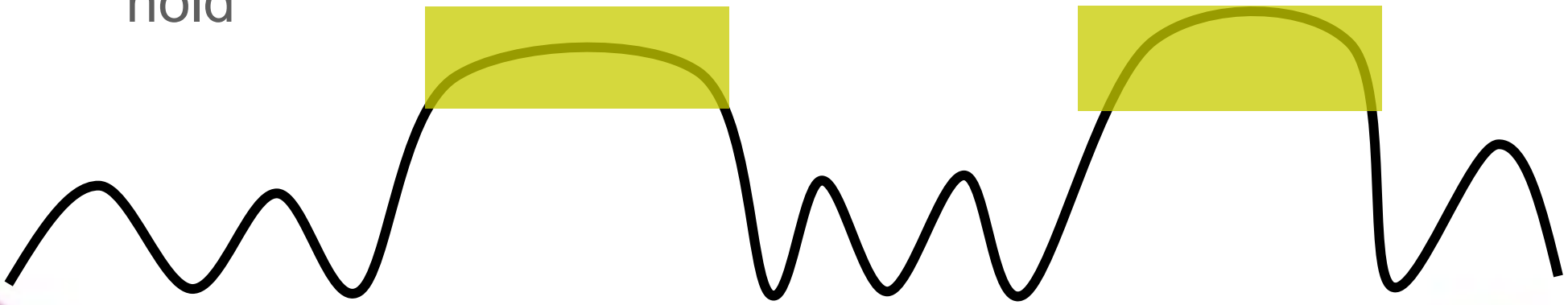


Gating: free breathing / breath hold

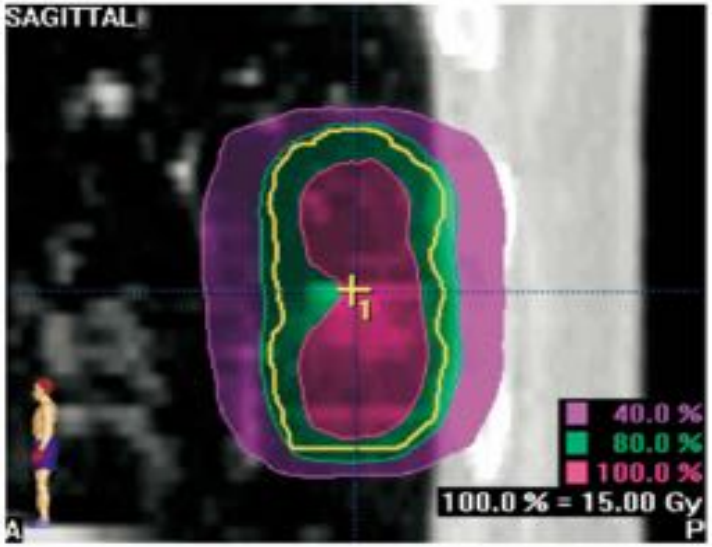
- Free breathing: Beam is switched on during 1 fraction of the breathing cycle

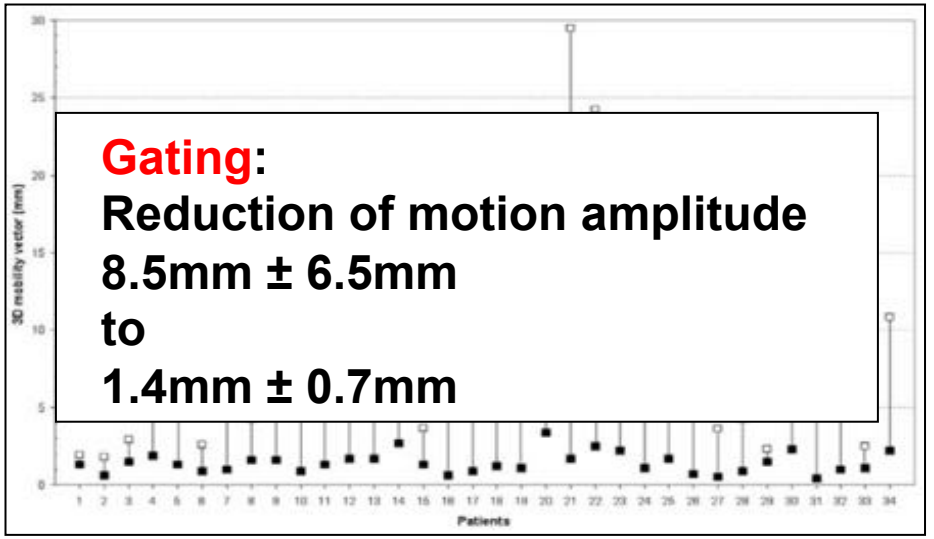


- Breath hold: Beam is switched on only during breath hold



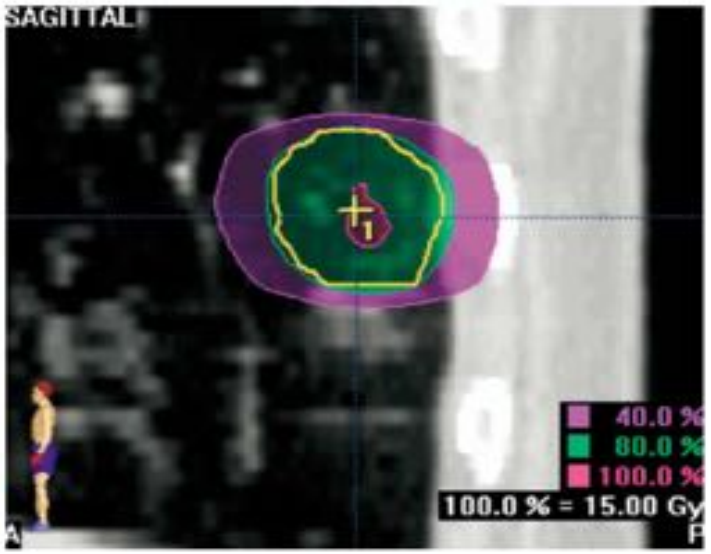
Gating: free breathing / breath hold

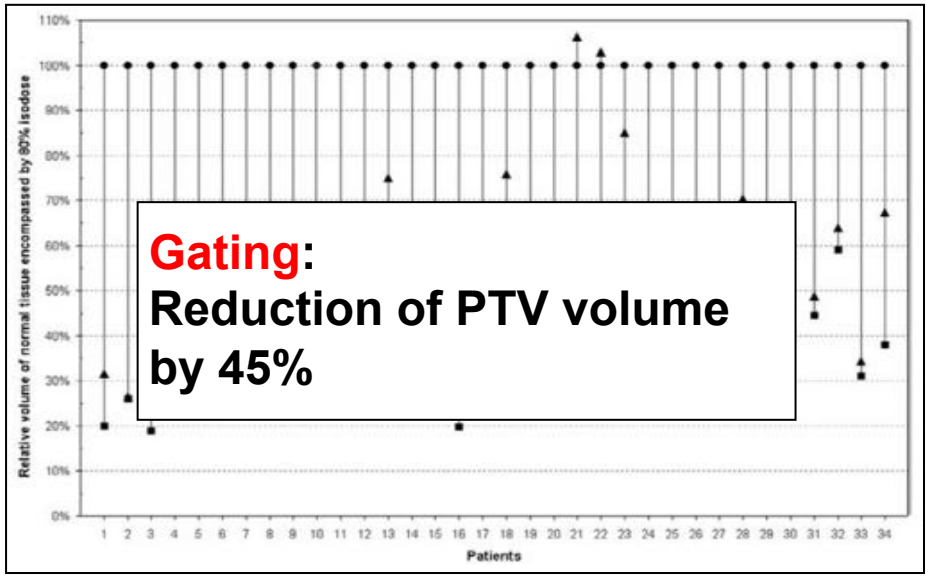




Gating:
Reduction of motion amplitude
8.5mm ± 6.5mm
to
1.4mm ± 0.7mm

Motion amplitude





Gating:
Reduction of PTV volume
by 45%

PTV volume

Duty cycle
30 % !

Underberg *et al* IJROBP 2005

1st and 2nd generation RTRT system

- RTRT system @ Hokkaido University

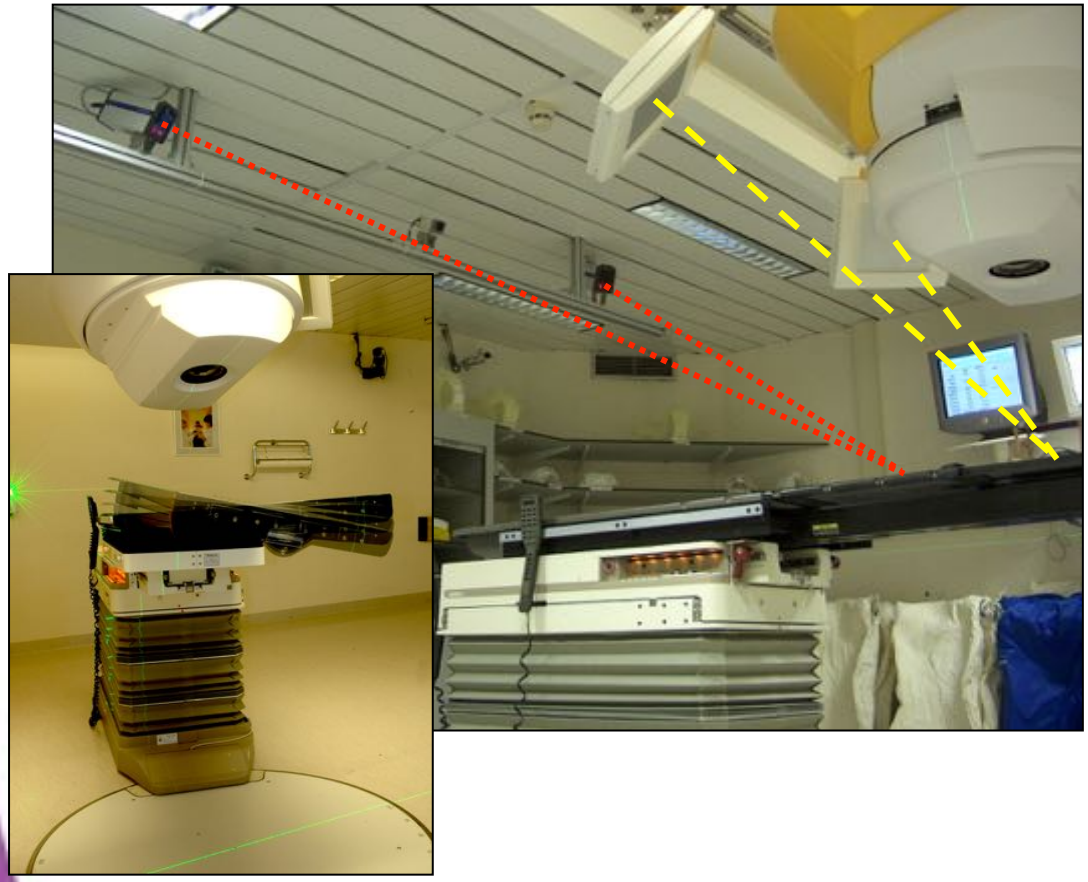
Shirato *et al.*

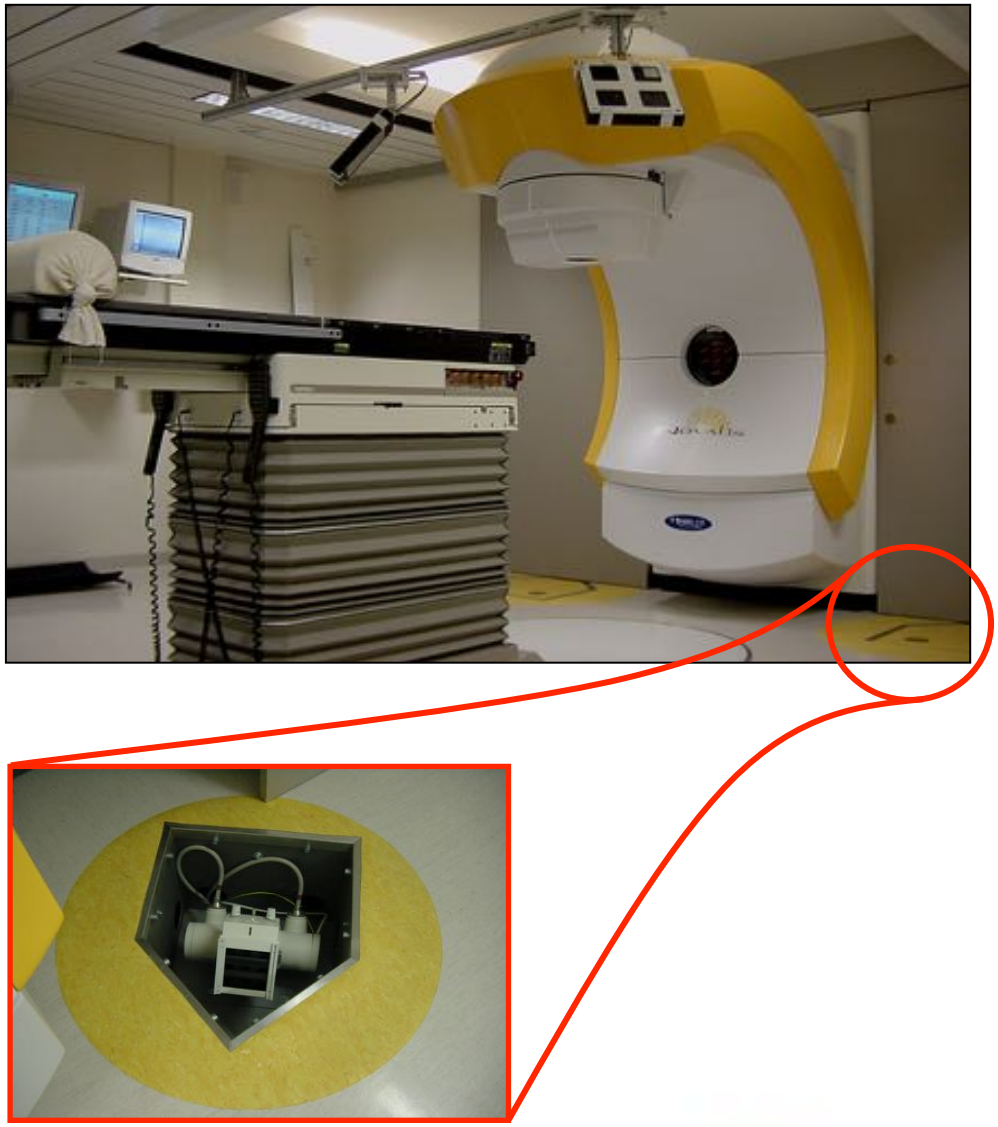
1st Gen: 1999 ~ 2010

2nd Gen: 2004 ~

Gating: An example

- The NOVALIS System



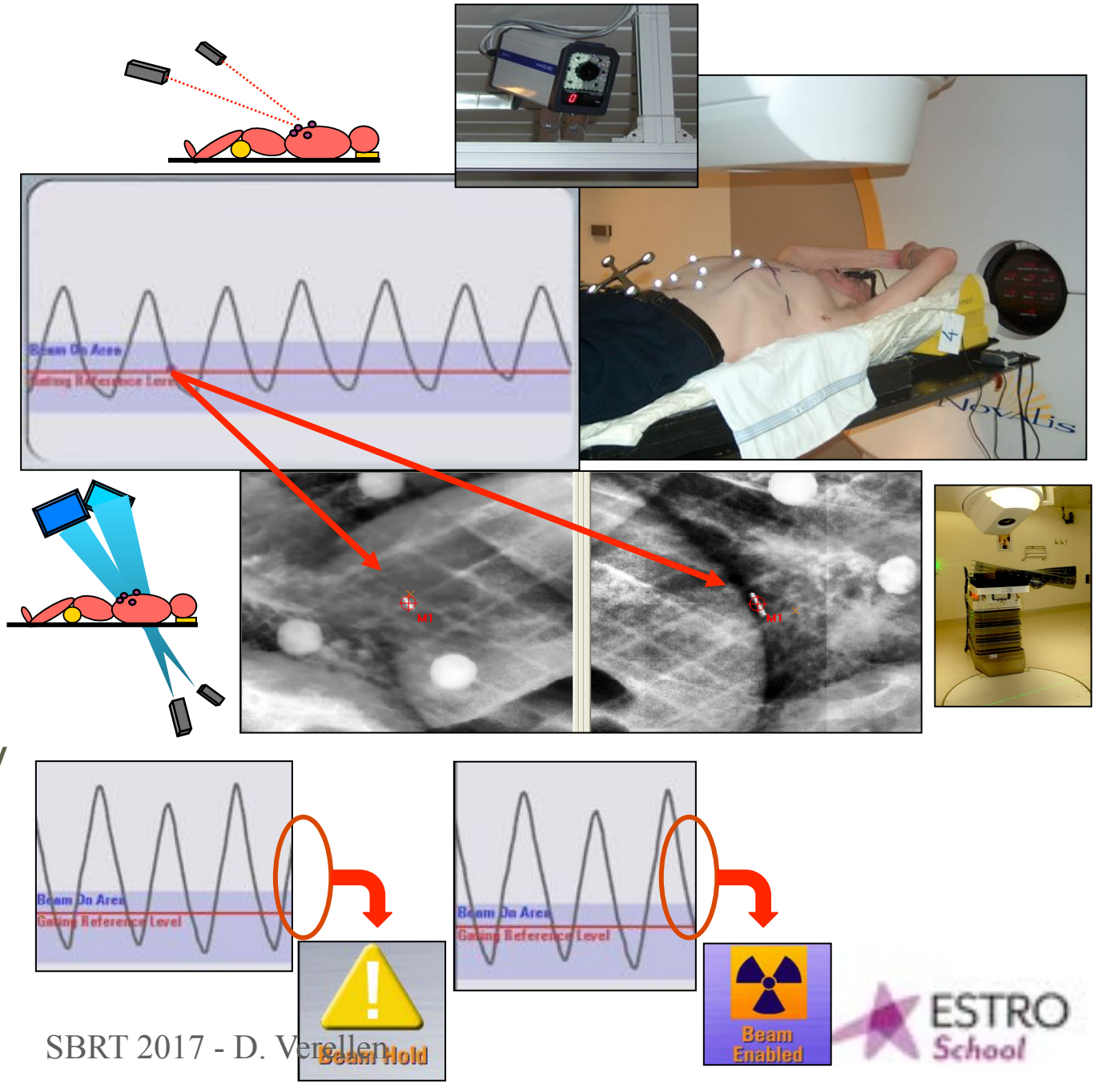


Gating: An example

Breathing is monitored during free breathing by IR reflecting markers

Correlation of internal marker location and external breathing signal

Linac triggered to irradiate only when target is aligned with linac's isocenter

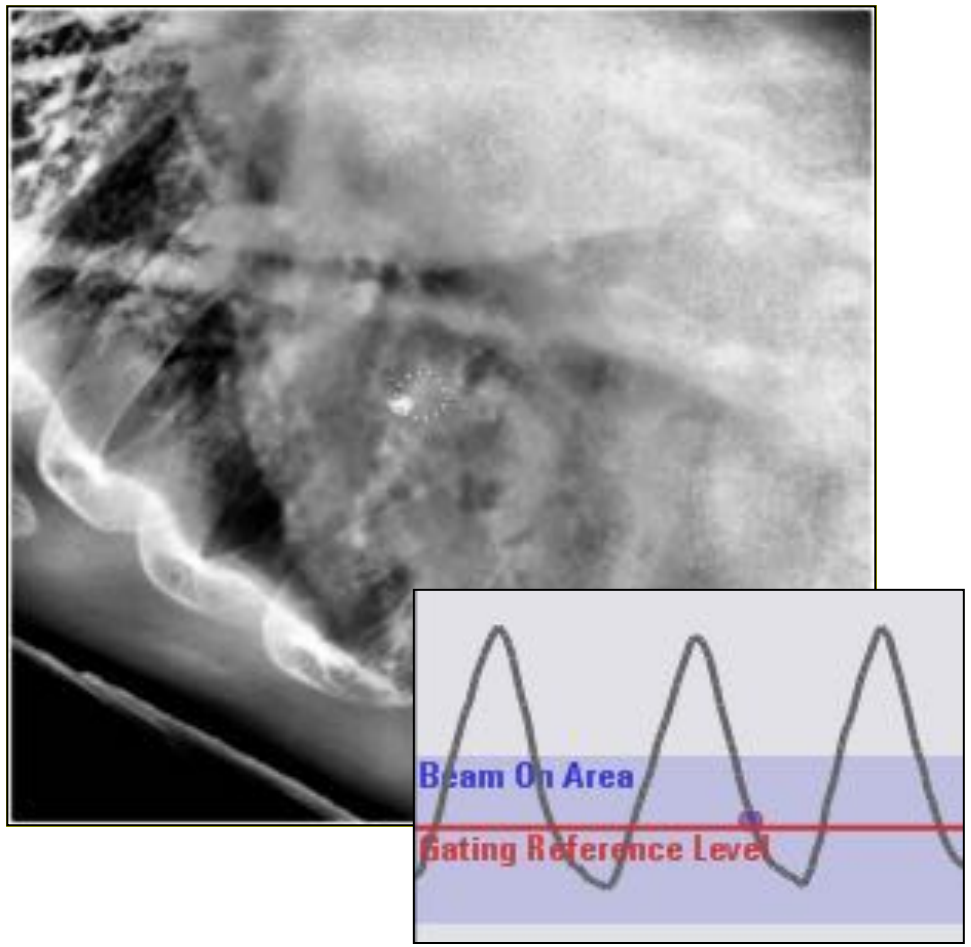


Gating: continuous verification

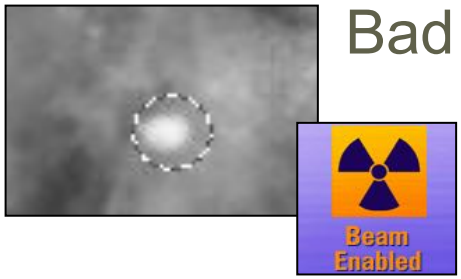
- Target localization verified with repeated on-line verification images
  - 516 verification images
  - Deviation between expected and actual position of internal marker at reference level:

mean 0.8 mm

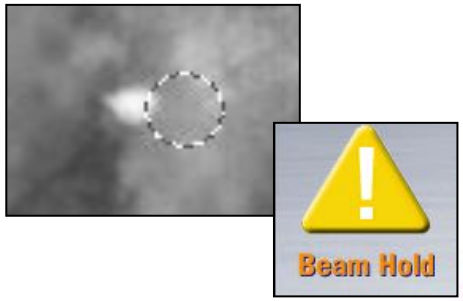
(SD 0.4 mm; max 2.6 mm)



Good correlation



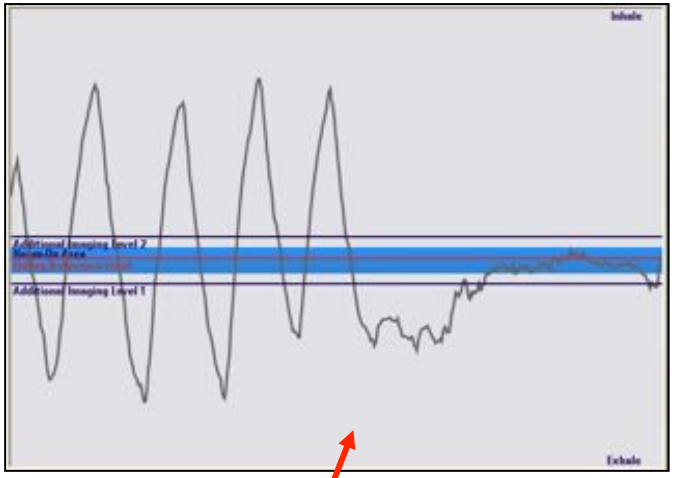
Bad correlation

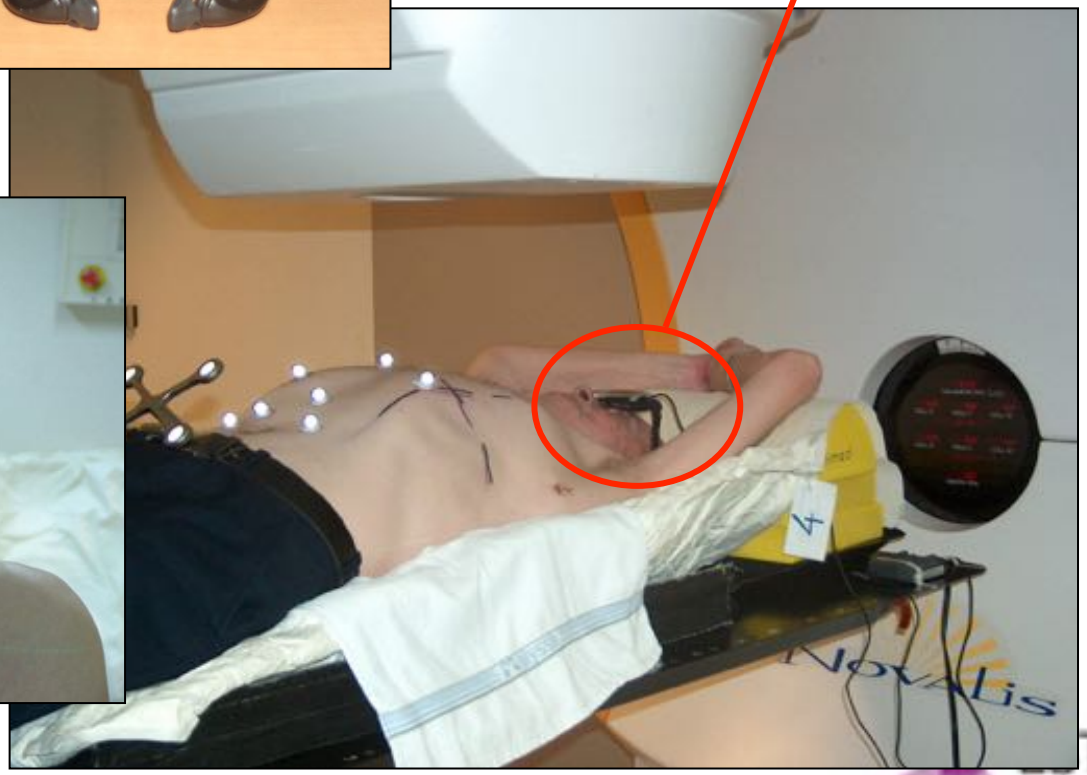


Visually guided voluntary breath-hold

1st patient (Dec 2006):

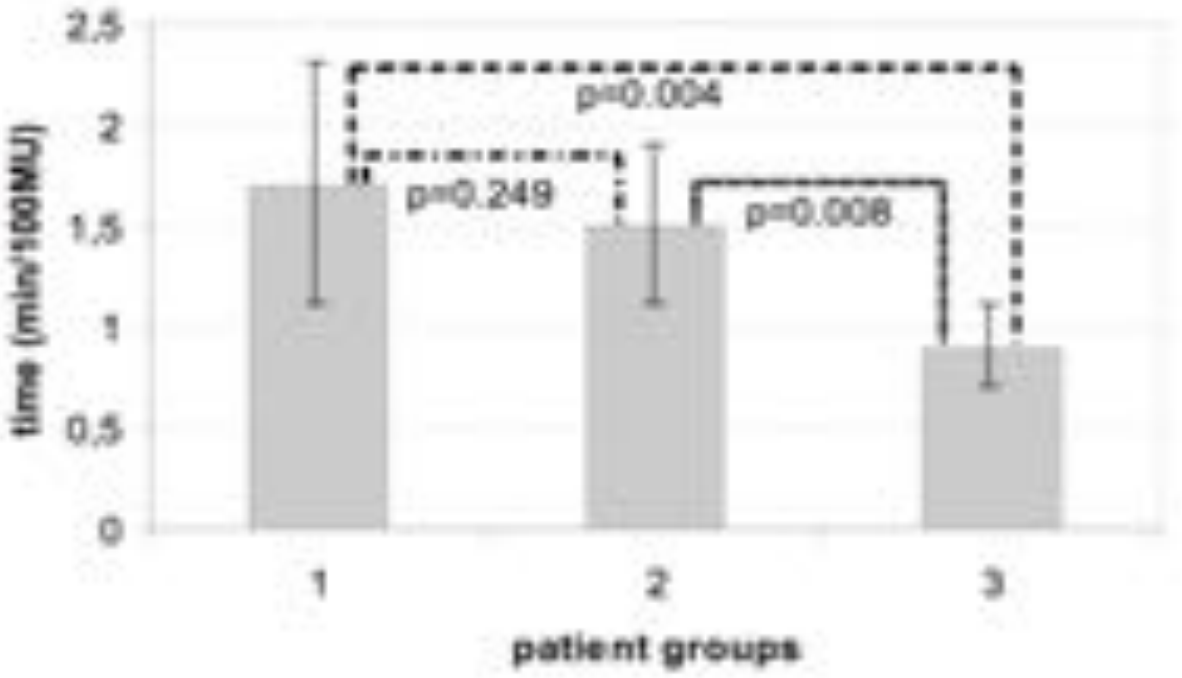
- 80 year old
- NSCLC left lower lobe
- 8 x 7,5Gy

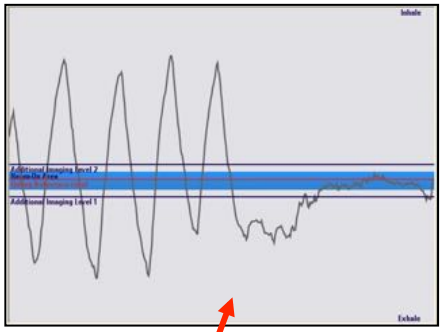




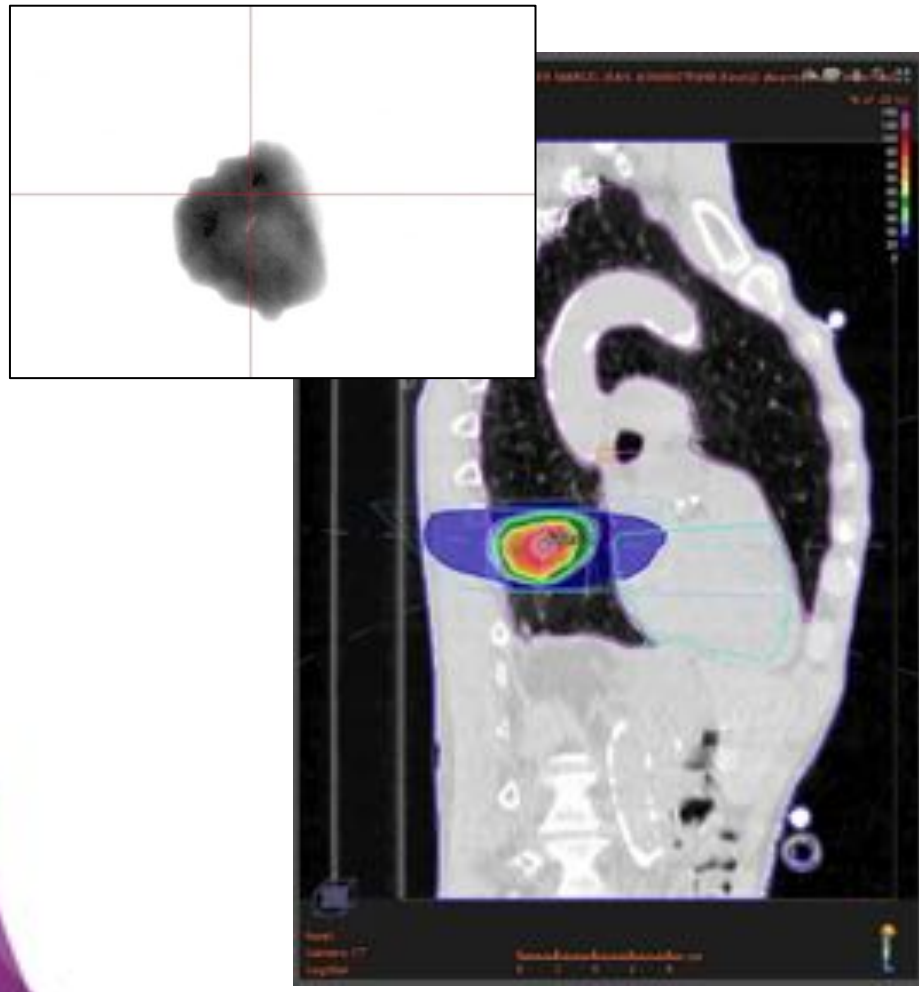
Gating: An example

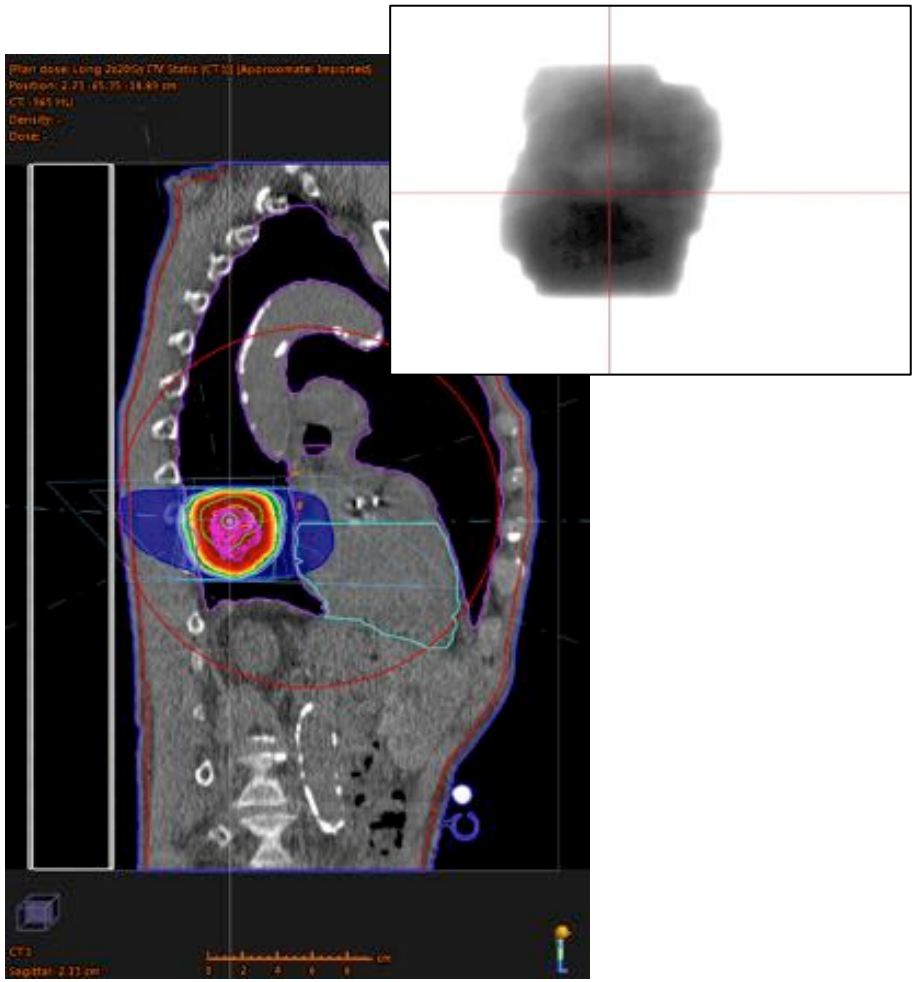
- Group 1: gated treatment in free breathing
- Group 2: gated treatment with visual feedback during treatment
- Group 3: gated treatment with audio-visual feedback during treatment





Tracking: “sticky” dose

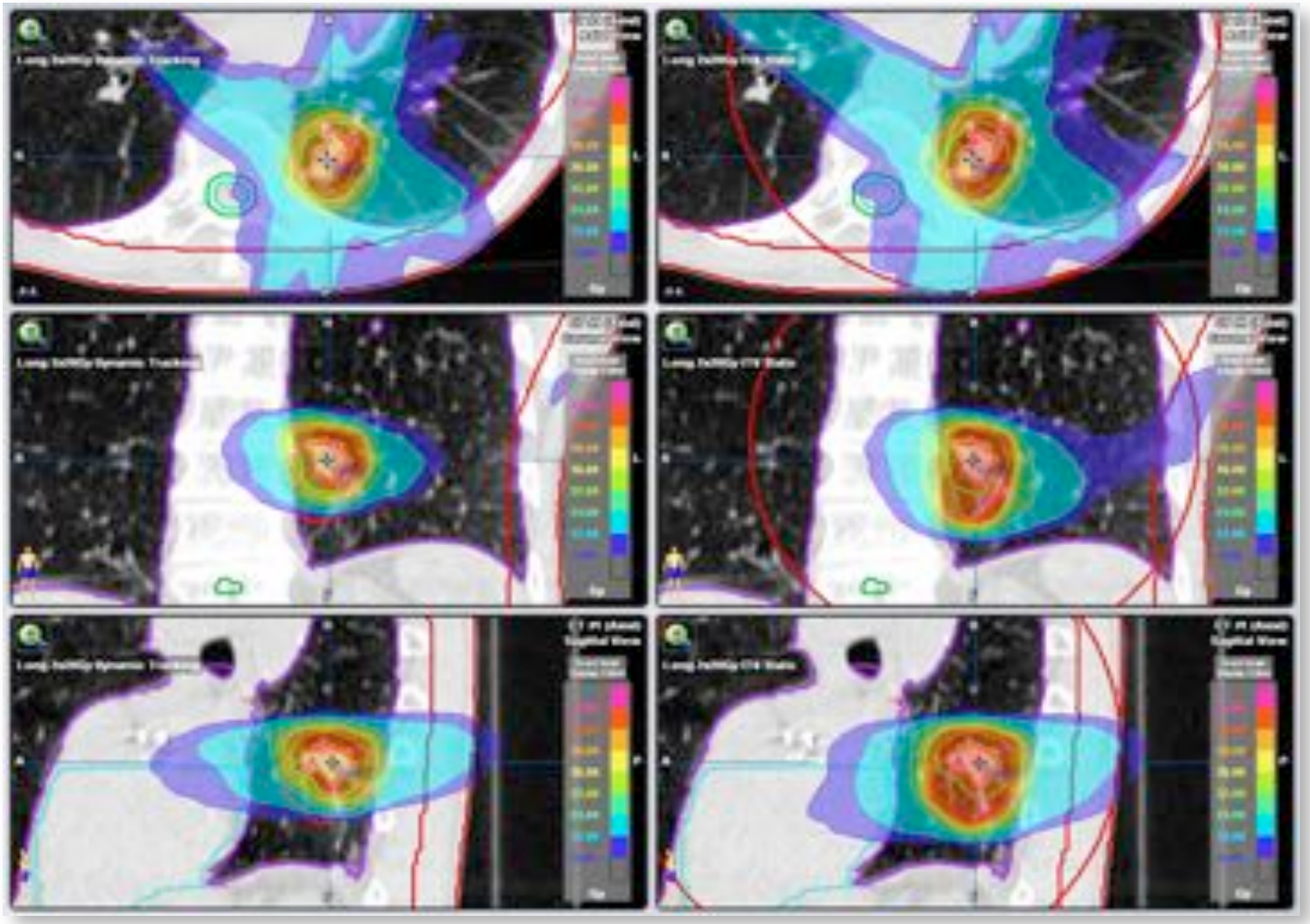




PTV volume reduction

	Site	PTV volume reduction [%]
Patient 1	lung	-39,50
Patient 2	lung	-37,59
Patient 3	liver	-16,21
Patient 4	liver	-46,00
Patient 5	liver	-37,75
Patient 6	lung	-52,72
Patient 7	lung	-44,37
Patient 8	lung	-29,47
Average		**-38,0**

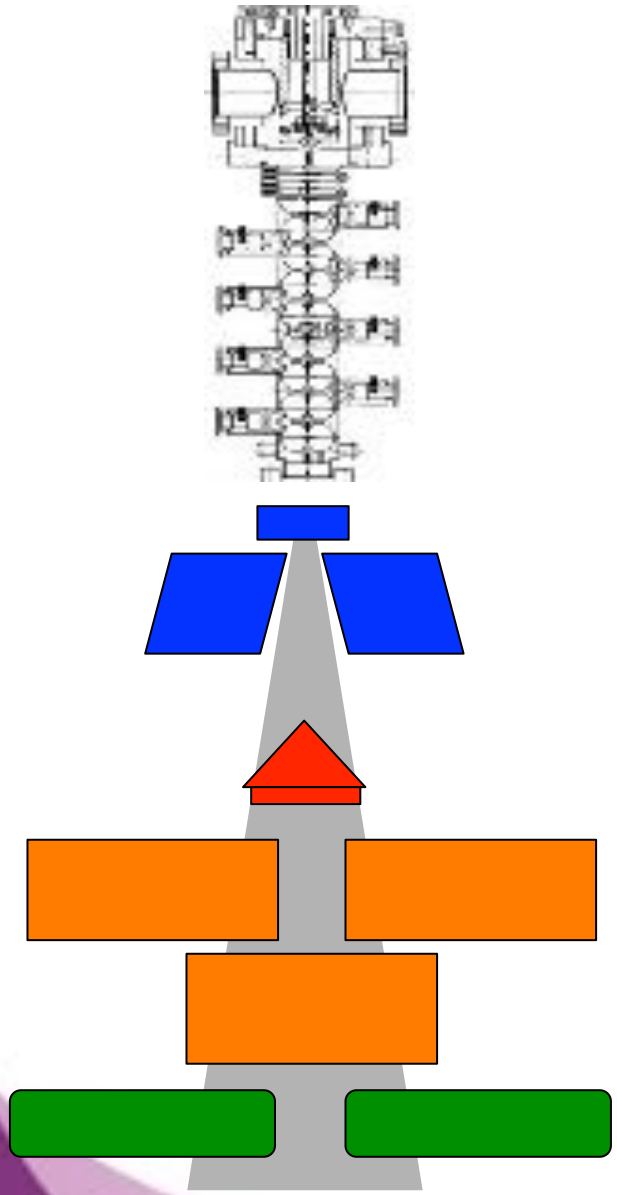
DT ITV



Dynamic tracking patients @ UZ Brussel (2012-2013)

Tumor tracking

Medical linac full beam line



“What parts of the beam line should move to create a moving beam?”

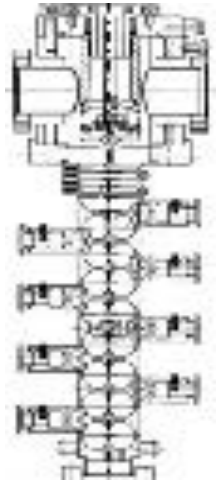
Dynamics of breathing/tracking:
-Frequencies up to 30 Hz
-Amplitudes of a few centimeters
-Sub-millimeter accuracy

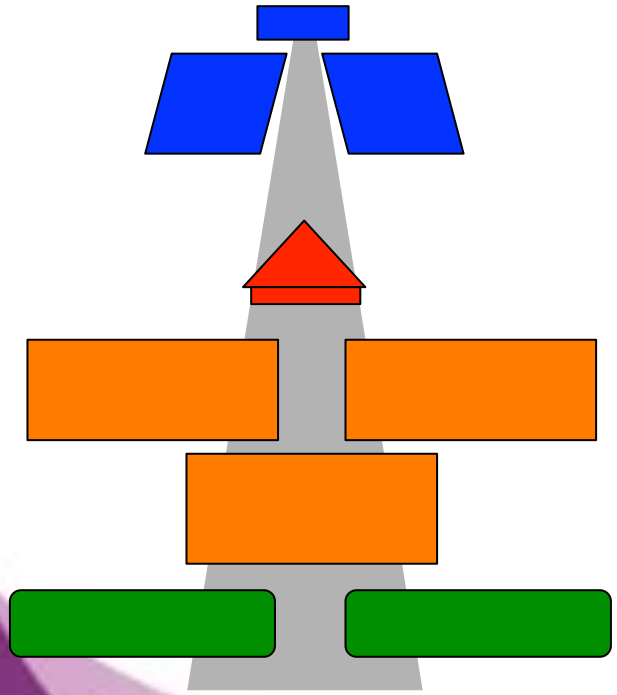
Too heavy !!! (>>1000kg)

“Move only certain parts of the beam line?”
“Loose some of that weight?”

Tumor tracking

Medical linac full beam line





Electron Gun

Accelerator

Target

Primary collimator

Flattening filter

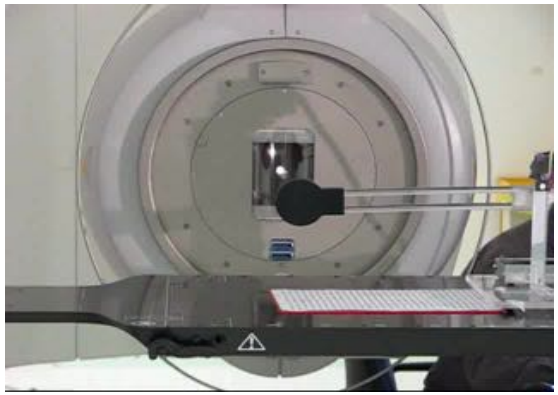
Jaws (X,Y)

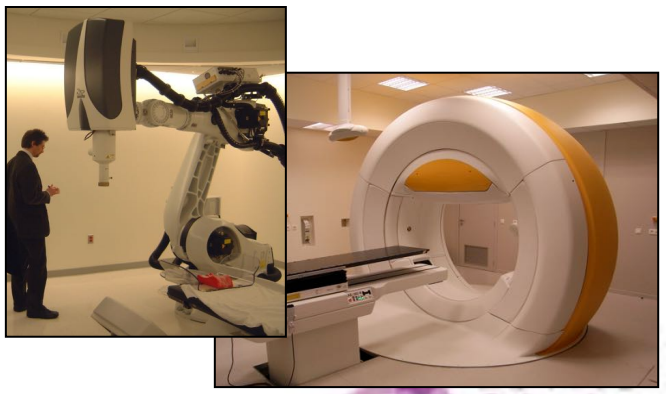
MLC

MLC tracking

Dynamic couch

Beam line

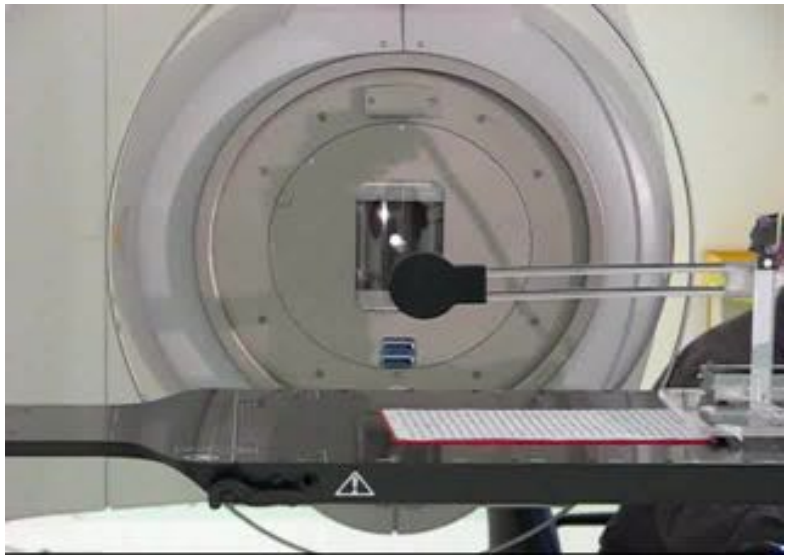




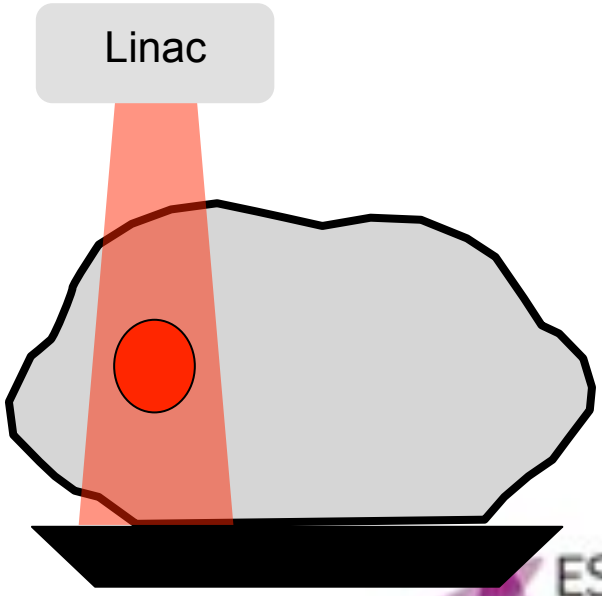
Tumor tracking: couch compensation

Dynamic couch compensation

"Keeping **the tumor position fixed in space** by **counteracting motions** of the treatment couch and irradiate with **a static beam"**



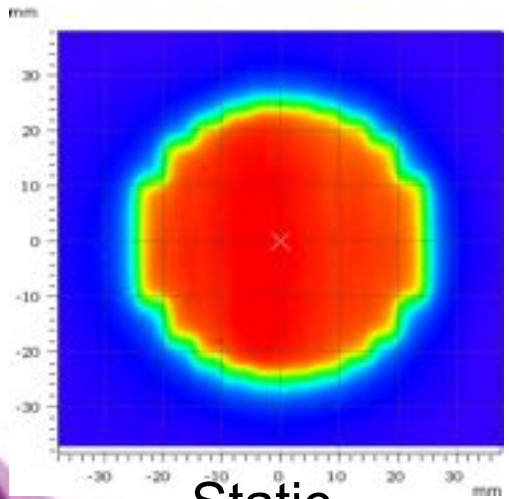
- **Advantages**:
  - Free breathing
  - Linac can operate as in a static situation
- **Drawbacks**:
  - Dynamic behavior of the couch (weight distr.)
  - Complex feedback control system for couch motion
  - Discomfort patient? Relaxing?
  - Impact on tumor motion, patient positioning?
  - Changing position of beam with respect to patient anatomy



Courtesy O. Haas

Tumor tracking: DMLC

- **Advantages**:
  - Using the available dynamic MLC mode for tumor pursuit
  - Use of full field size
  - Little compromises for other classic treatments
- **Drawbacks**:
  - Only useable with a flattened beam, what with FFF?
  - Tracking and DMLC intensity modulation are coupled: coupled constraints and increased complexity with higher modulation and higher velocities
  - Tracking perpendicular to MLC leaf tracks?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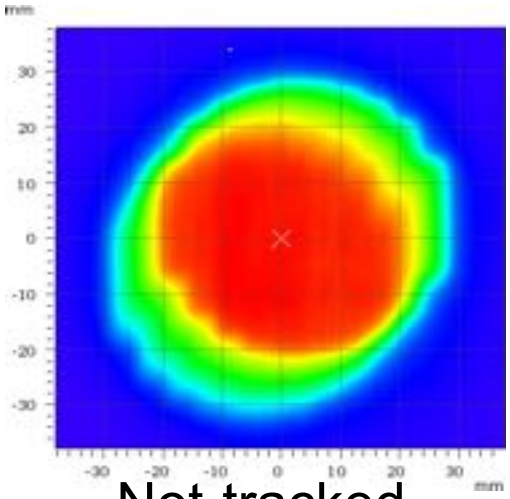
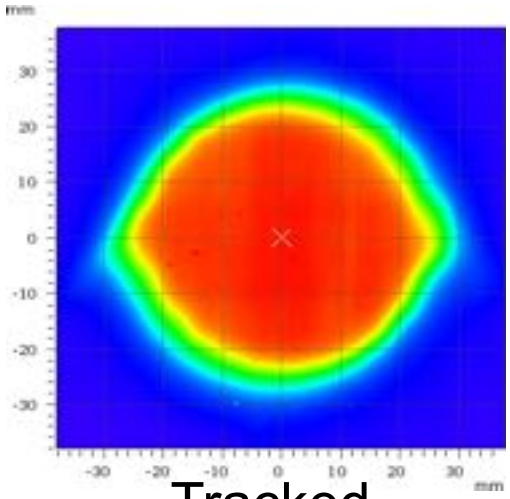
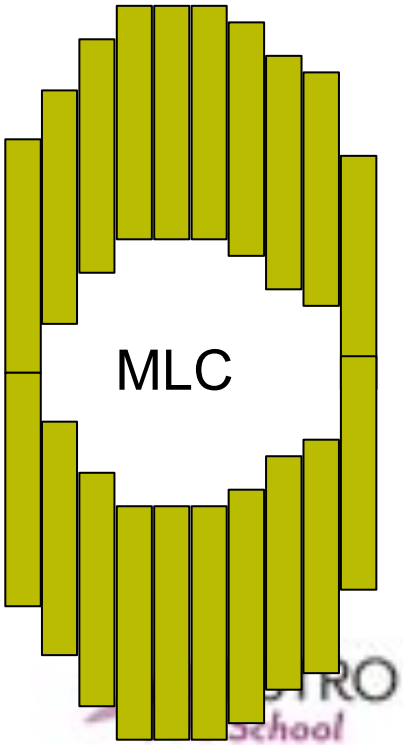
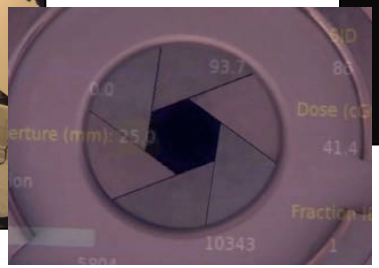
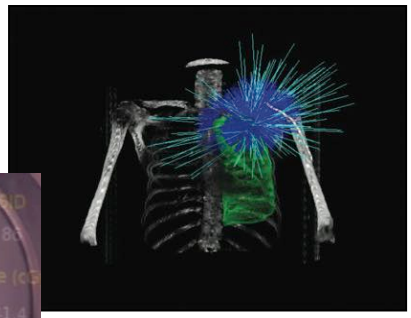

Not-tracked


Tracked



Tumor tracking: Cyberknife





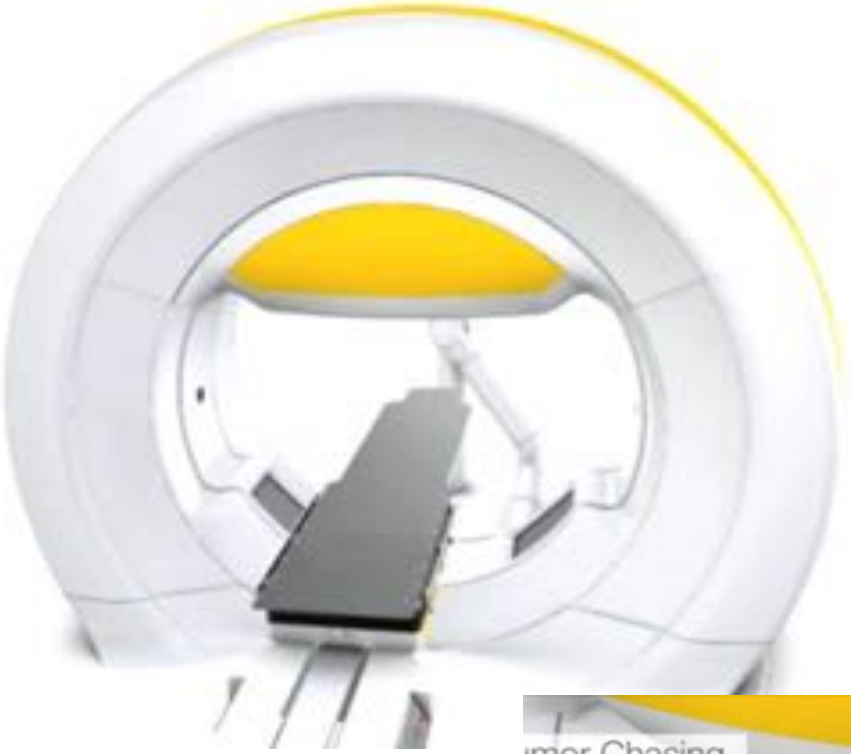
- **Advantages**:
  - High dynamic and geometric accuracy
  - Markerless tracking available for specific cases
- **Drawbacks**:
  - Small circular field sizes (new version comes with MLC)
  - Long treatment times
  - Posterior beams not possible
  - Volumetric imaging not supported
  - Direct verification of beam not supported.

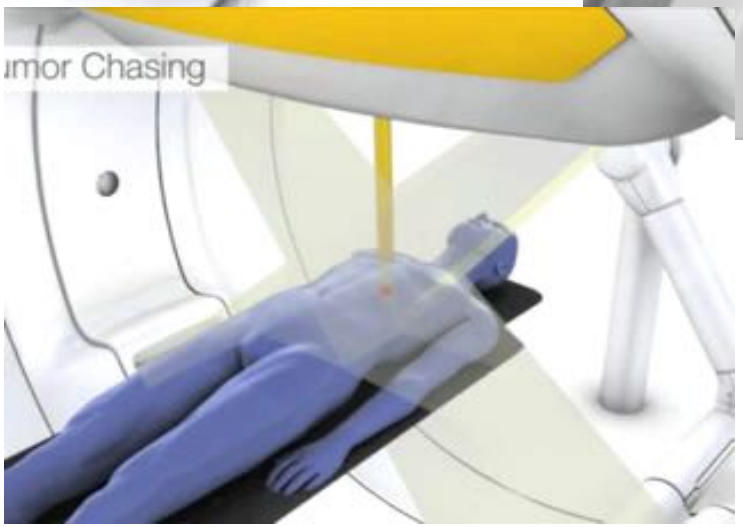
-Light and compact linac (< 300kg)

-Mounted on a robot

Tumor tracking: VERO

… limited edition

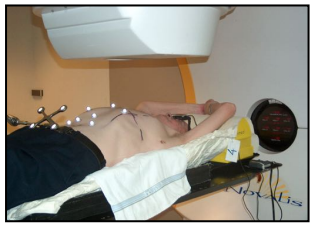


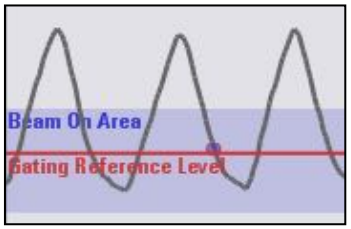


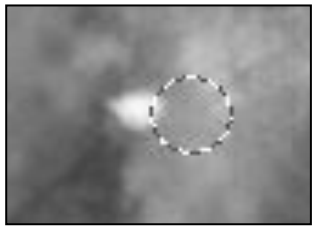
Challenge: patient vs. machine

Anticipating unpredictable motion …

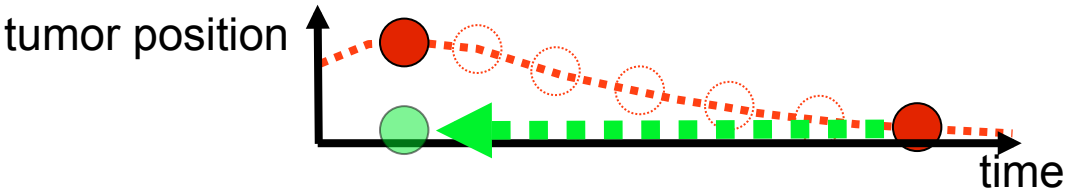
- Correlation model:
  - Requires “stable” correlation between internal and external motion



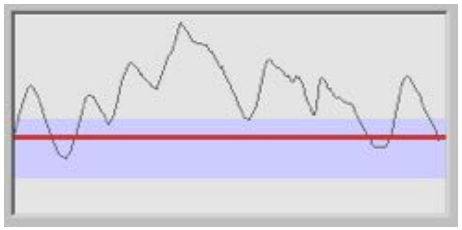




- Prediction model:
  - Requires “predictive” (i.e. periodic) motion



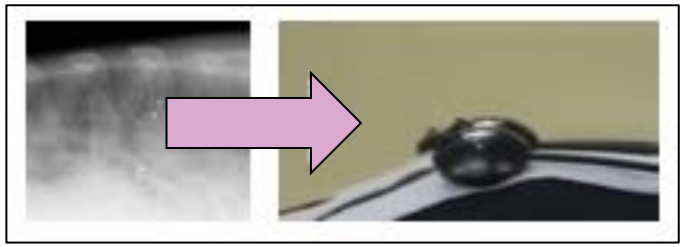
- Interface between machine and man …
  - By definition “unpredictable”?



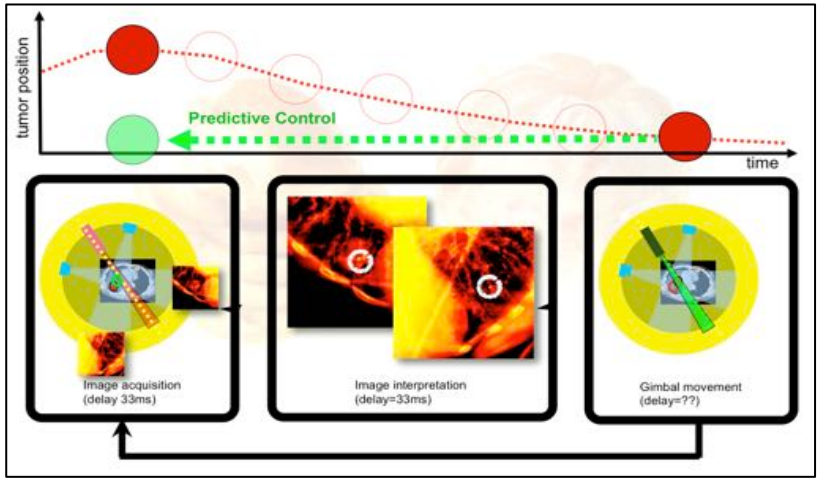
Tracking: error analysis

- Tumor localization:
  - Fiducial markers: stability, how many needed, migration, …
  - Direct visualization: real-time requires planar imaging, only limited number of cases practically possible

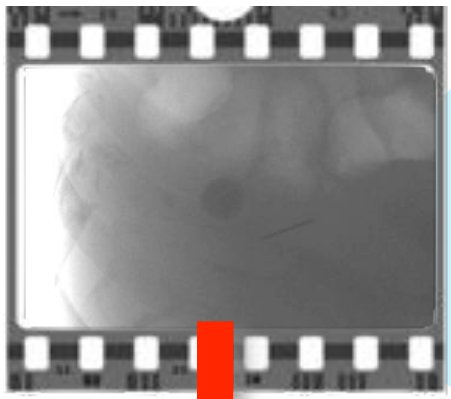
- Correlation model between external markers (chest motion …) and internal tumor motion.

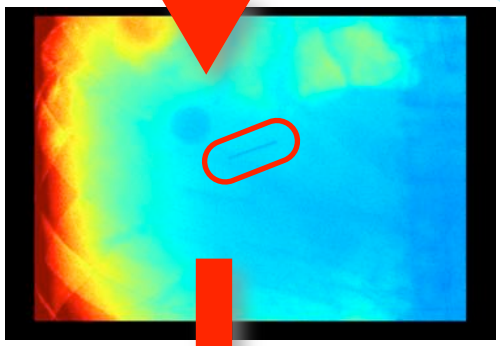


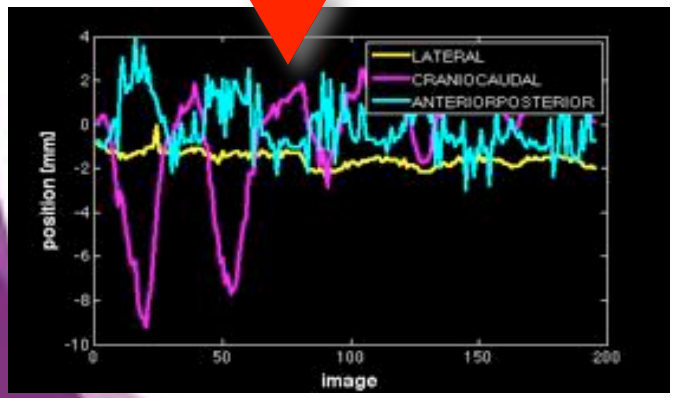
- Prediction model forecasting tumor position to compensate for system latency:
  - Cyberknife: ± 115 ms (Hoogeman *et al.*)
  - MLC: ± 140 ms (Poulsen *et al.*)
  - Vero: ± 50 ms (Depuydt *et al.*)



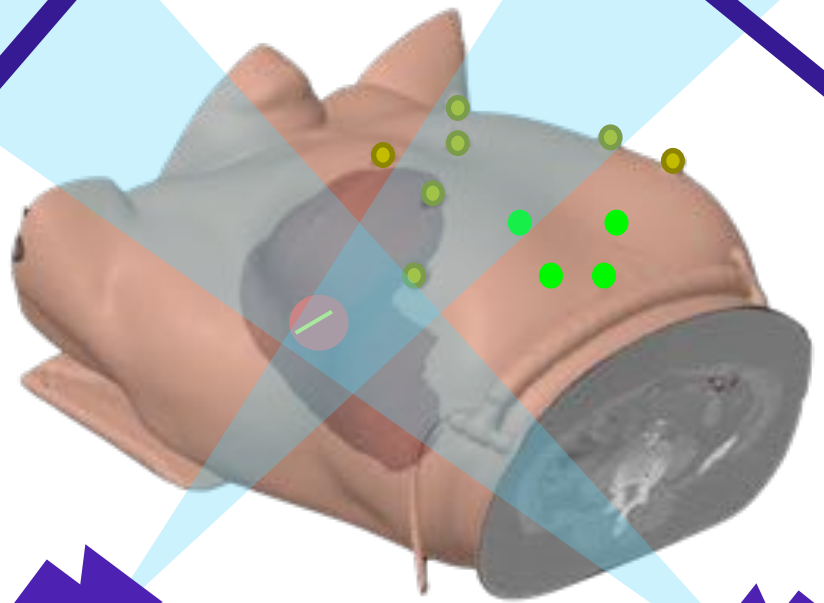
Tracking: Correlation models

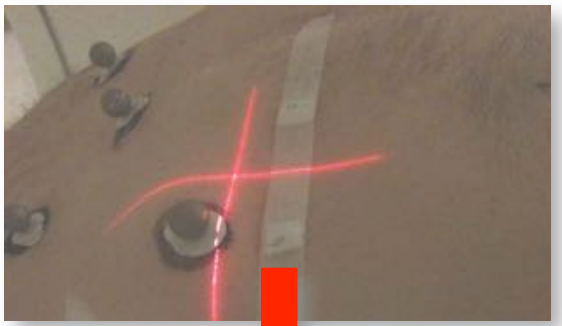


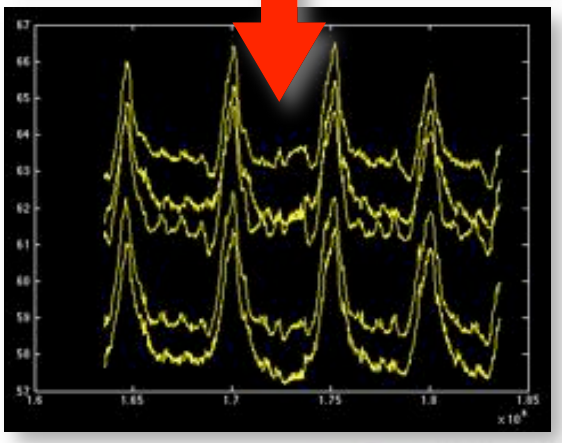




Acquisition of kV fluoro sequence and IR marker motion





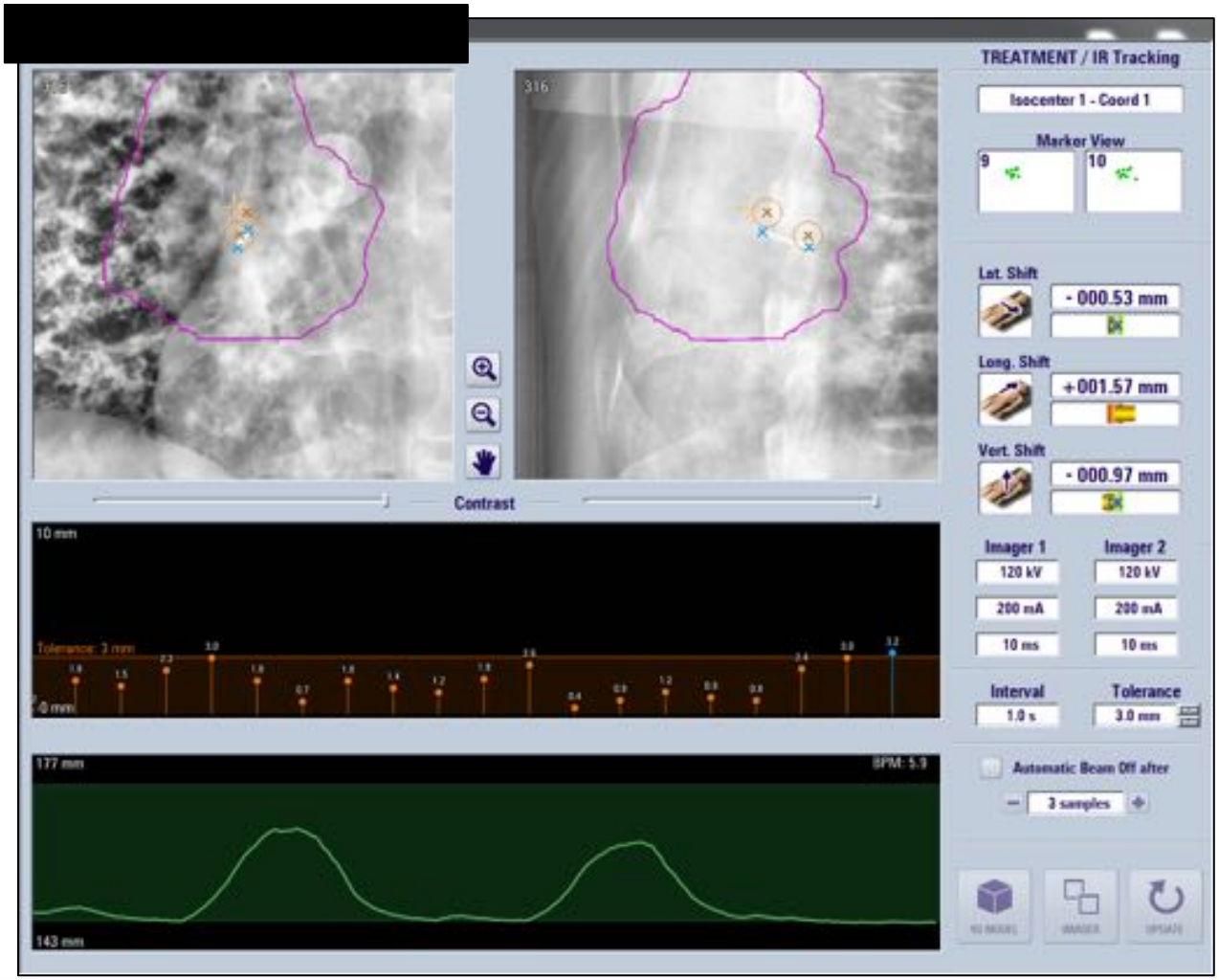


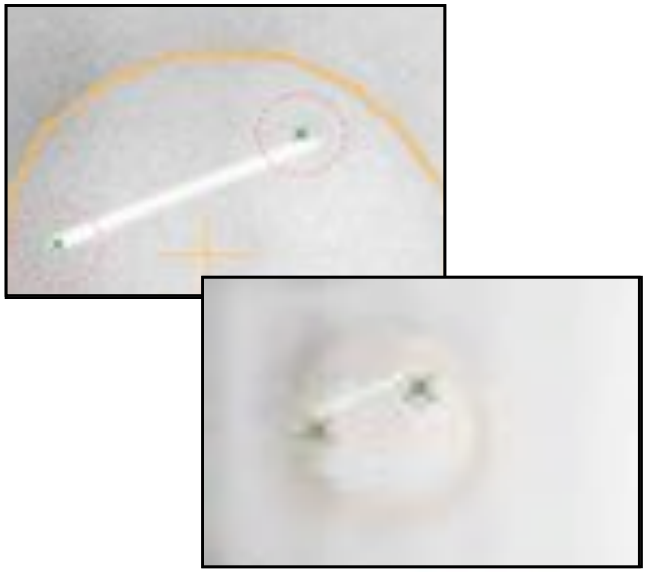
Detection Visicoil and Building correlation model (IR vs internal motion)

- "stable" IR markers
- "moving" IR markers
- tumor and implanted Visicoil

Tracking: verifying corr. model

Monitoring imaging during tracking:





Challenges / pitfalls

High precision RT and IGRT

This does **NOT** mean that margins can converge to zero!!!!!!!!

margin recipes are still a necessity

Engels B, Soete G, Verellen D, Storme G.

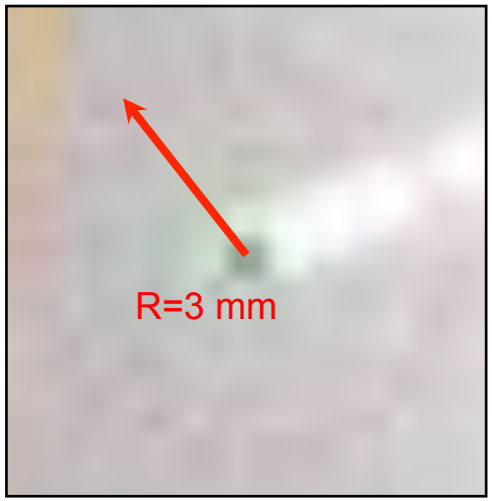
Conformal arc radiotherapy for prostate cancer: increased biochemical failure in patients with distened rectum on the planning CT in spite of image guidance by implanted markers.

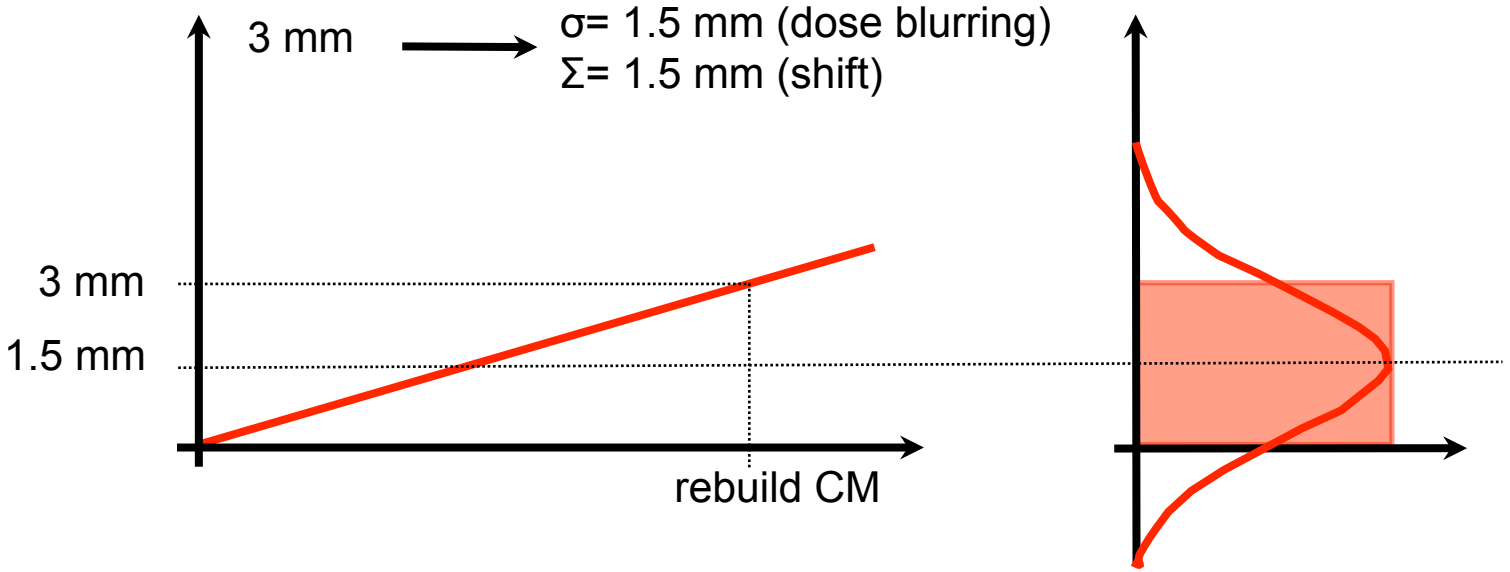
Int J Radiat Oncol Biol Phys 2008; (In Press).

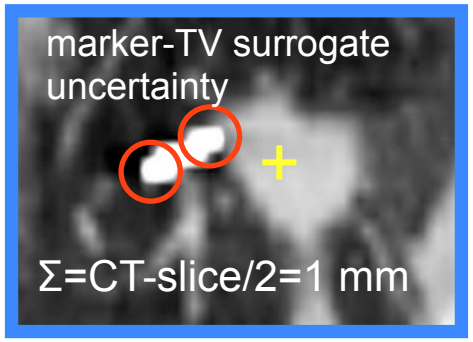
See Mischa's presentation earlier this morning!!

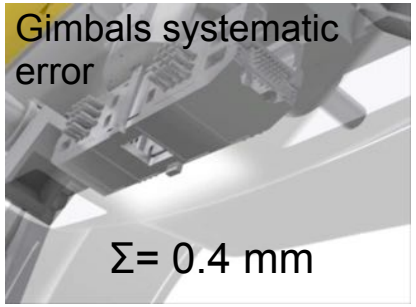
Margin definition DT patients

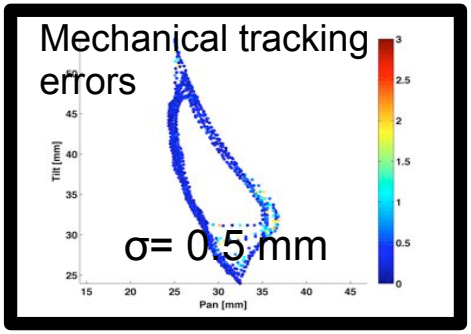
Prediction error tolerance level of 3 mm











Penumbra:
σ_p=4.05mm
β=0.73
(for 95% isodose)

$$M=2.5*\sqrt{((1mm)^2+(1.5mm)^2+(0.4mm)^2)}+0.73*\sqrt{((1.5mm)^2+(\mathbf{0.5mm})^2+(1mm)^2+(4.05mm)^2)}-0.73*4.05mm$$

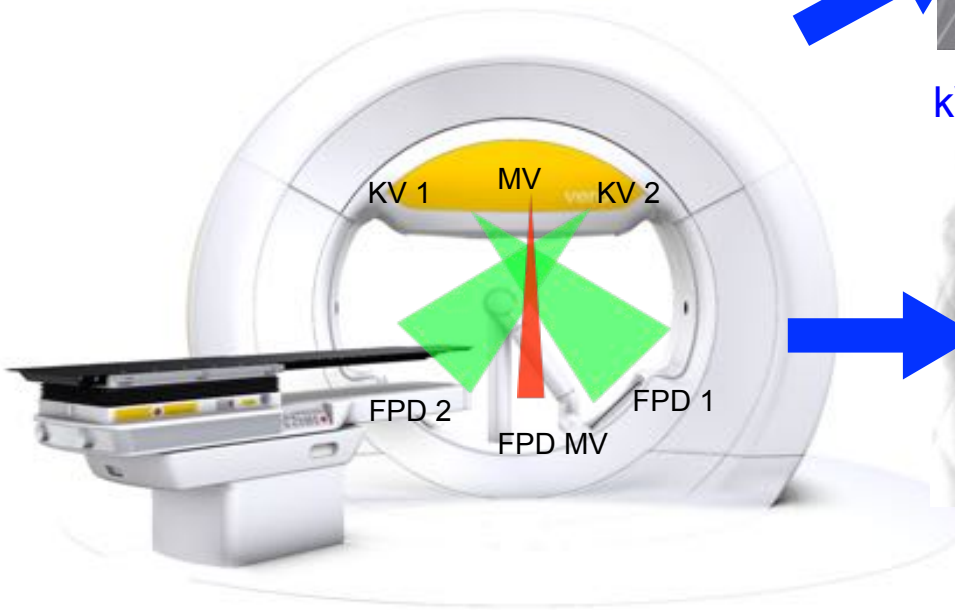
=4.9 mm => 5 mm

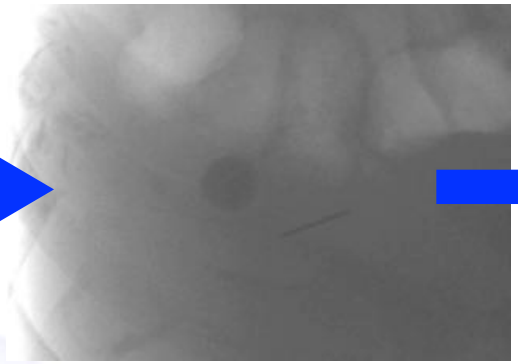
-surrogate vs TV relative rotation in "relative ITV"
-no patient specific tracking error yet

Tumour Tracking Verification

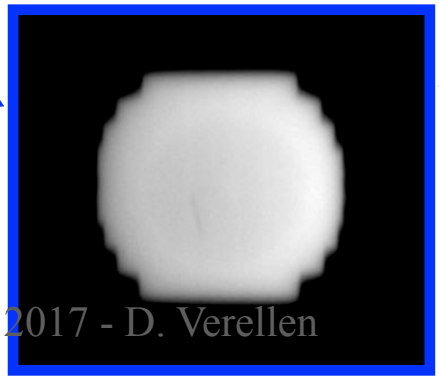
Gimbals position logging

kV Monitoring Imaging

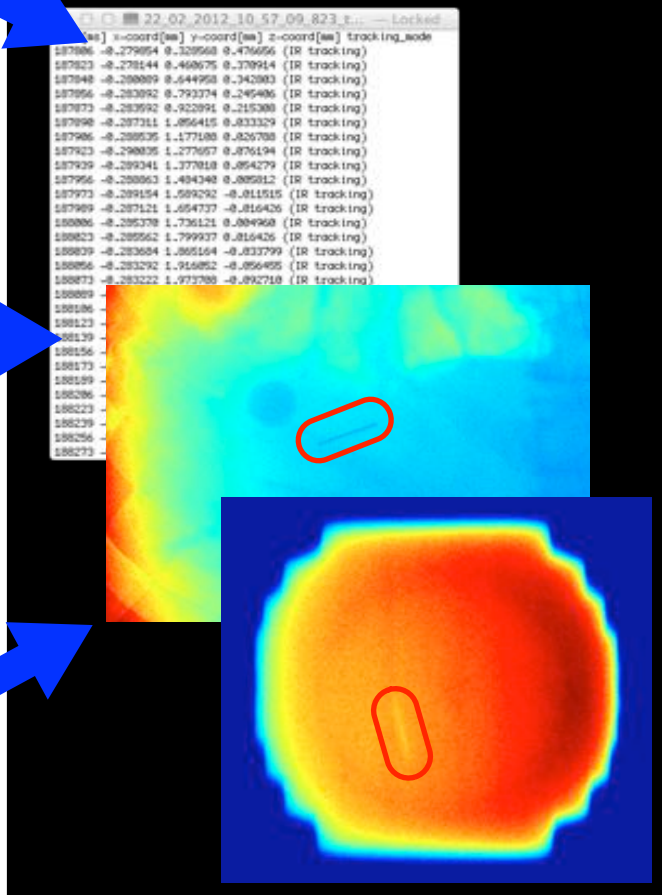




EPID MV Imaging



Per fraction QA through combination of different information sources



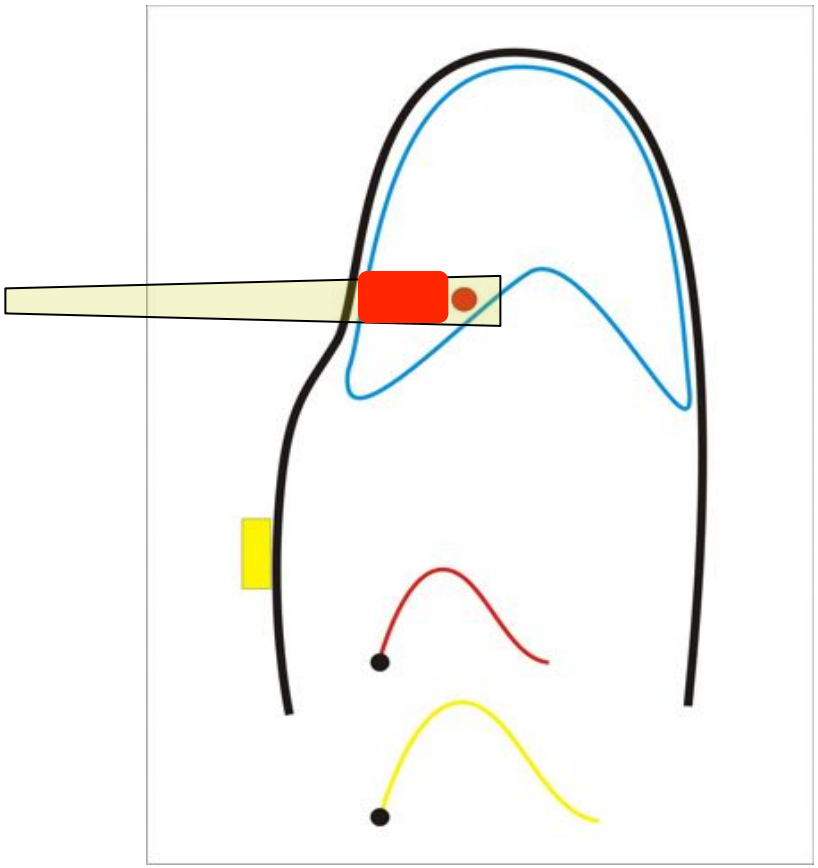
Margin definition DT patients

Patient	EPID TE (mm)	XRLog TE (mm)	D (mm)
DTP001	3.3	3.4	+0.2
DTP002	7.0	6.0	-1.0
DTP003	3.5	4.0	+0.5
DTP004	4.5	4.7	+0.2
DTP005	4.6	5.1	+0.5

- Obviously, ***population-based*** or ***process-based*** *treatment margins* are **not** the way to go!!!
- We need individualized approaches, with real-time adaptation.

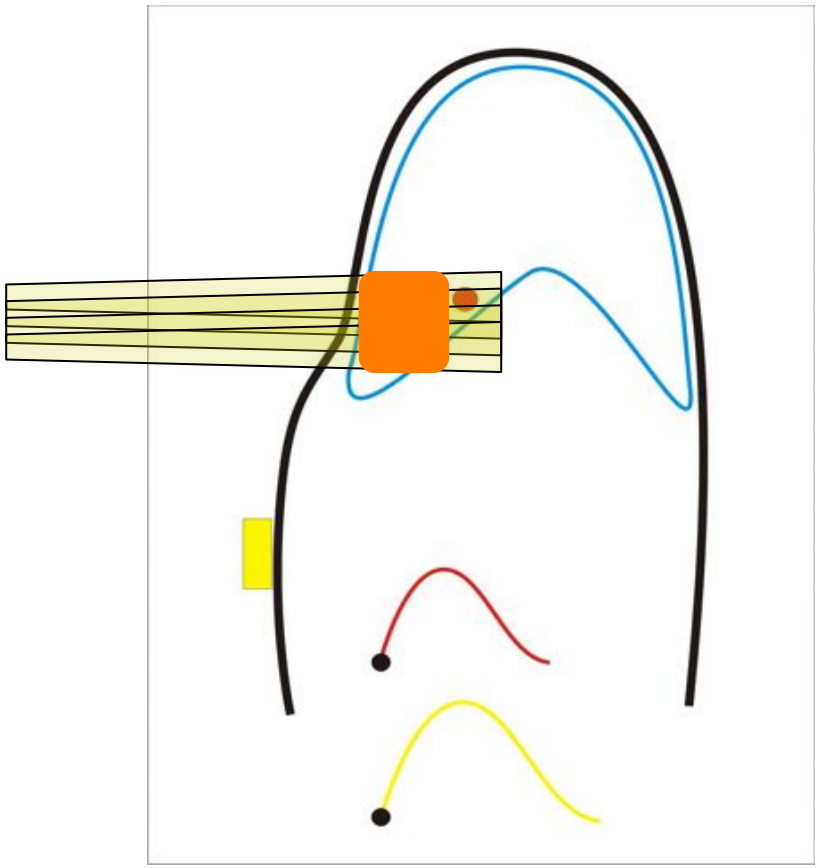
Tracking versus gating

- Gating



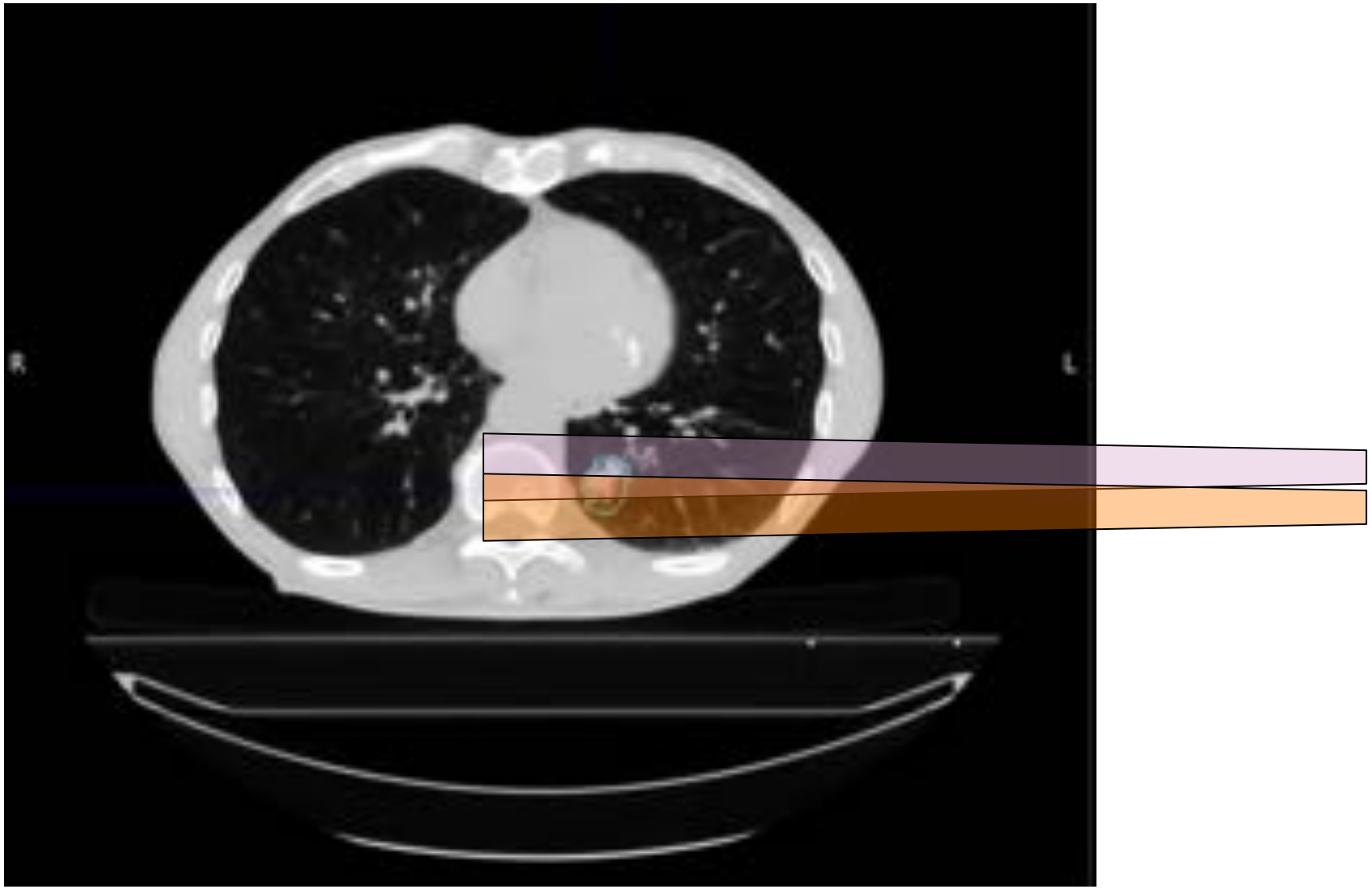
➢ Higher dose, concentrated

- Tracking



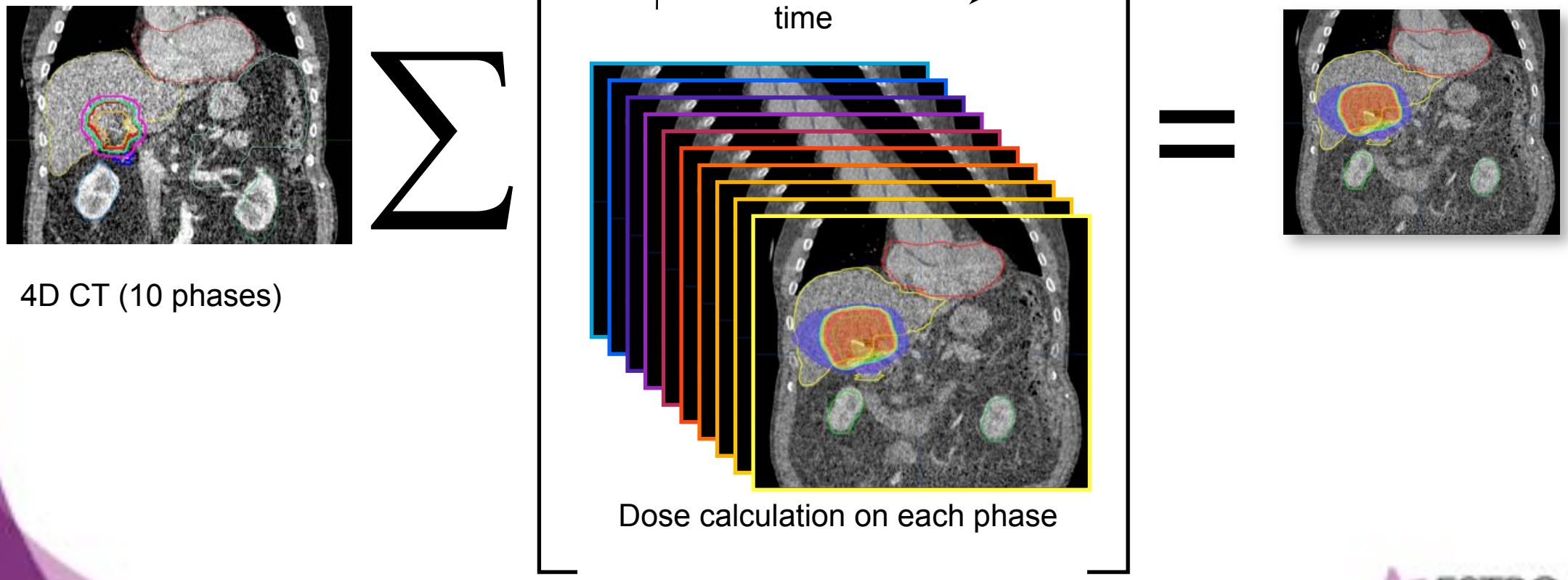
➢ Lower dose, larger volume

Challenges



Challenges

- 4D-CT dose accumulation



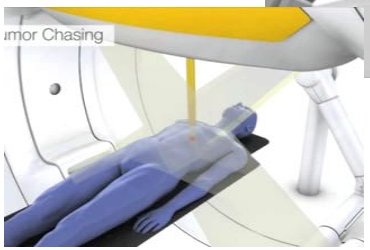
Marker placement

- Oops …

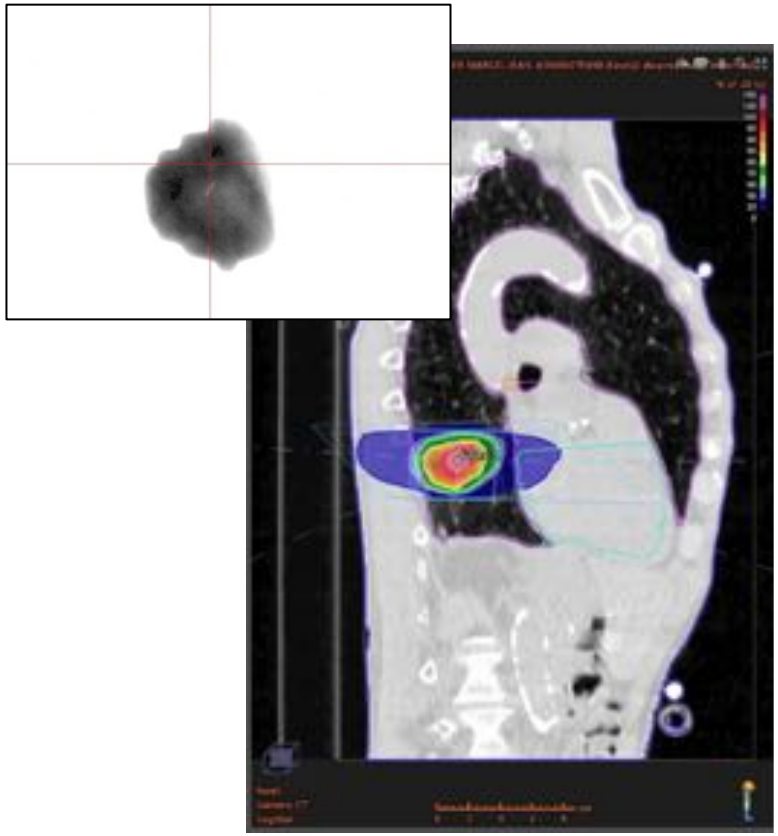
➢ Yes … relative high risk for pneumothorax

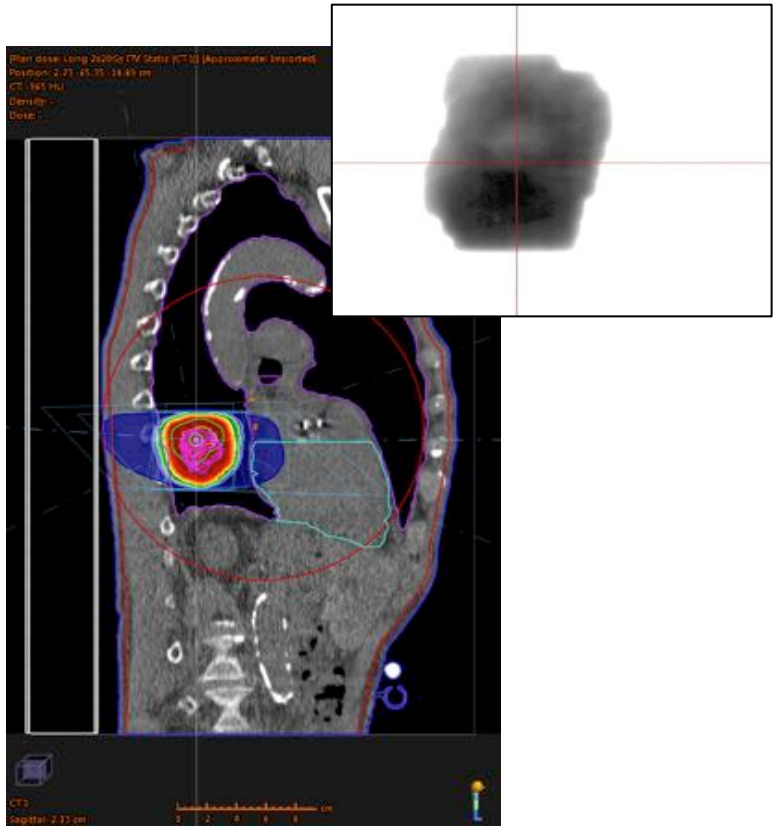
So … will we make a difference?

Motion management

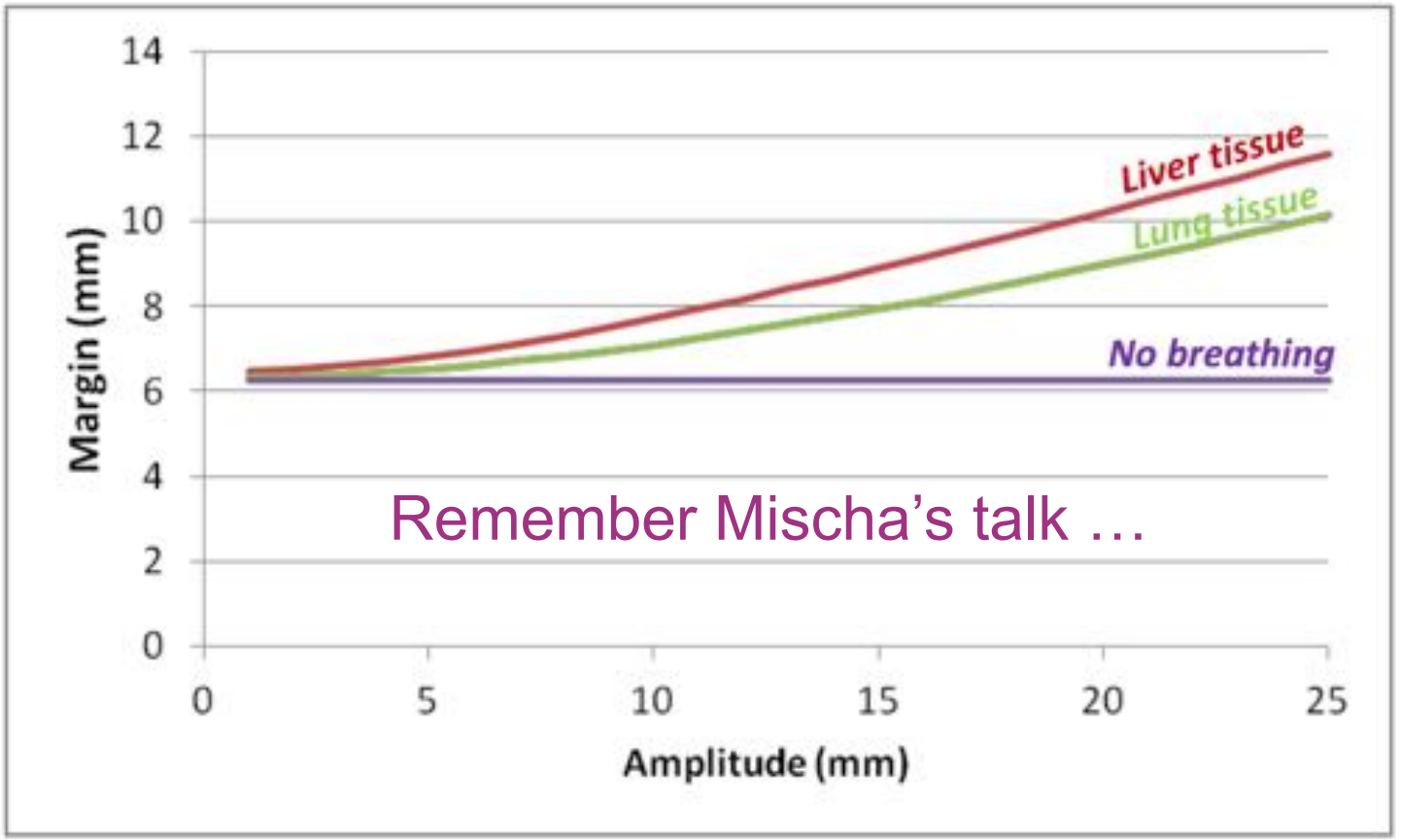


- SBRT:
  - Real-time tumour tracking **for a few**
  - Versus TV/Mid-Vent/Mid-Pos **for many**





Motion management



"I thought I was on to something but I can't figure out how to move it."

- Limited benefit for gated beam delivery or tracking for tumor motion < 15 mm

Motion management

Courtesy, M. Brada

Questions from the audience

- Some questions related to motion management

  - 4DCT: QA, what phantoms, what controls, what periodicity?

  - Use 3DCRT, IMRT or VMAT for lung SABR?
  - Are there reliable planning/measurement studies quantifying breathing-MLC interplay effects?
  - VMAT for lung SBRT: evidence for/against, what to watch out for, comparison with DCAT.

  - Techniques for SBRT in solitary abdominal mets (gating, tracking, or abdominal compression?)
  - For tracking what kind of control do we have to implement?

Take home messages

- Motion encompassing **ITV** is a reasonable 4D method, but overestimates the required margin.
- **4D-CBCT / 4D-CT registration** (e.g. mid-ventilation technique) allows for smaller margins.
- **Gated** irradiation (free breathing / breath hold) requires patient compliance and increases treatment time.
- **Tracking** technically challenging and requires building and verification of robust correlation/prediction models.
- **Tracking and gating** only beneficial for relative large tumor motions (i.e. > 10-15 mm)
- **Tracking or Gating?** Clinically probably equivalent, the difference is dose per beam spread out over region of motion versus somewhat larger dose concentrated at same location in lung (different penumbras?).

Conclusions

- The most important thing to a patient is not the availability of some high technology device, rather it is the ability of a team of physicians, physicists, dosimetrists and therapists to use a technology with skill for the benefit of the patient.
  - Dr. Marc Edwards

- The true challenge is to develop the wisdom to know when to select which [treatment modality] in the clinic.
  - Dr. Steve Webb

Acknowledgements

Many thanks to all Friends and Colleagues
for their nice slides!!!

Erasmus MC
University Medical Center Rotterdam

Daniel den Hoed
Cancer Center

Management of targets with respiration induced motion: lung, liver, abdomen

Mischa Hoogeman
Dirk Verellen

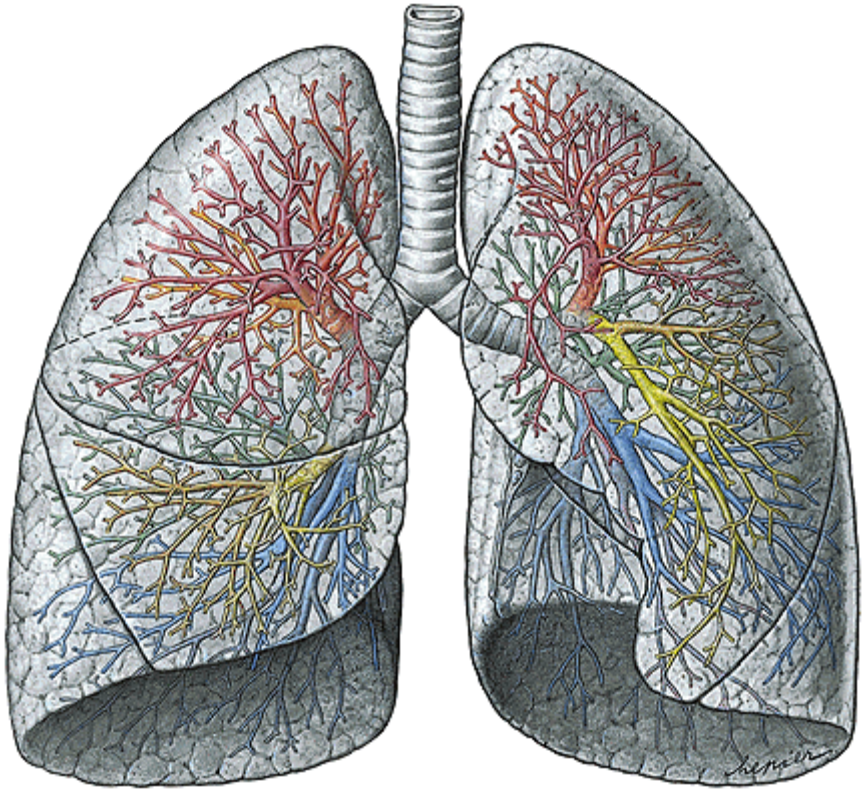
Learning Objectives

- **To give an overview of the magnitude of respiratory-induced inter-fractional and intra-fractional position errors**
- **To demonstrate the dosimetric and clinical relevance of these errors**
- **Sites of interest**
  - Lung
  - Liver
  - Pancreas

- **To give an overview of current technologies and correction strategies (Gating, Breath hold, mid-ventilation, tracking)**
- **To show pitfalls of these technologies**

Erasmus MC

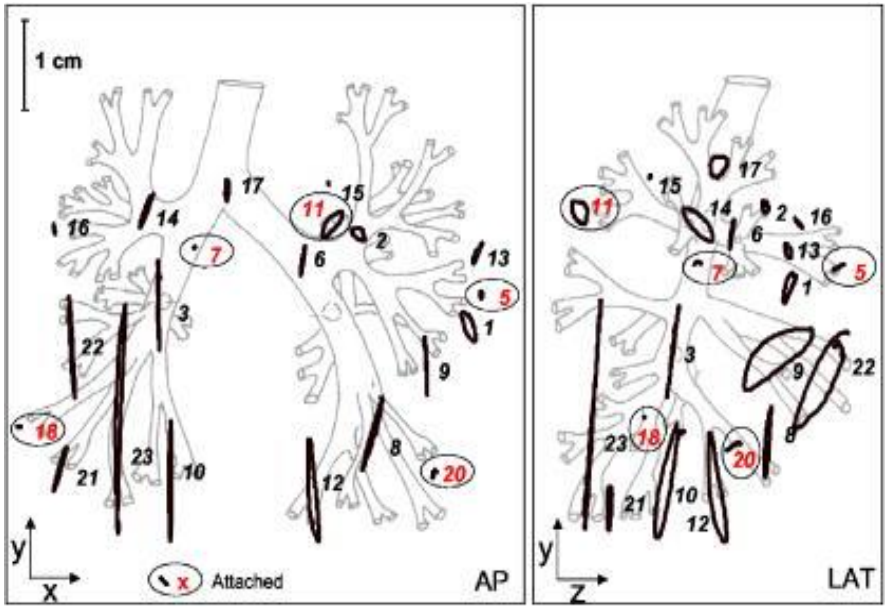
LUNG



Erasmus MC

Observation of Motion

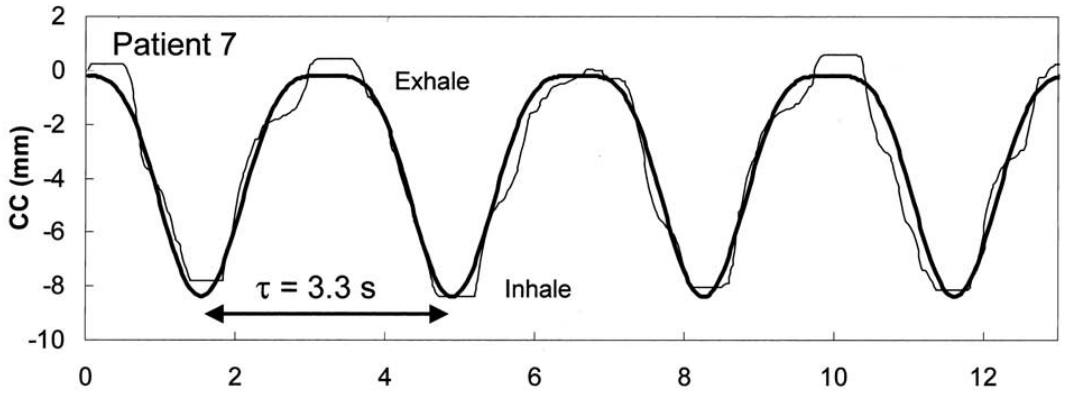
- Fluoroscopy



Seppenwoolde et al. IJROBP 53 (2002)

Observation of Motion

- Tumor motion varies widely (0-50 mm)
  - 12 mm on average in CC direction
  - 2 mm on average in AP and LR direction
- The tumor position in the exhale phase is more stable than the tumor position in the inhale phase



$$y = y_0 - A\cos^{2n}\left(\frac{\pi t}{\tau} - \phi\right)$$

Seppenwoolde et al. Int. J. Radiation Oncology Biol. Phys., Vol. 53, No. 4, pp. 822–834, 2002

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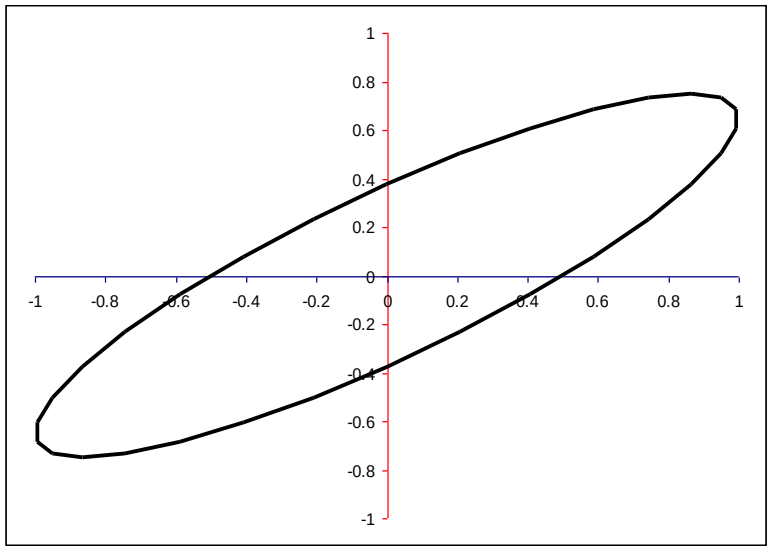
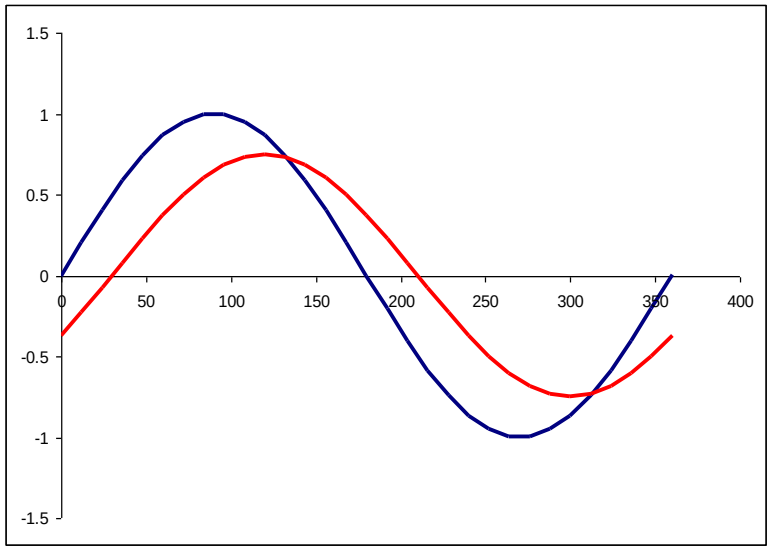
Observation of Motion



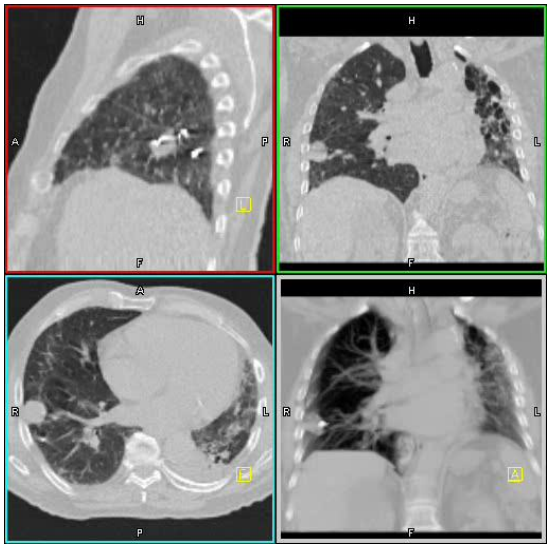


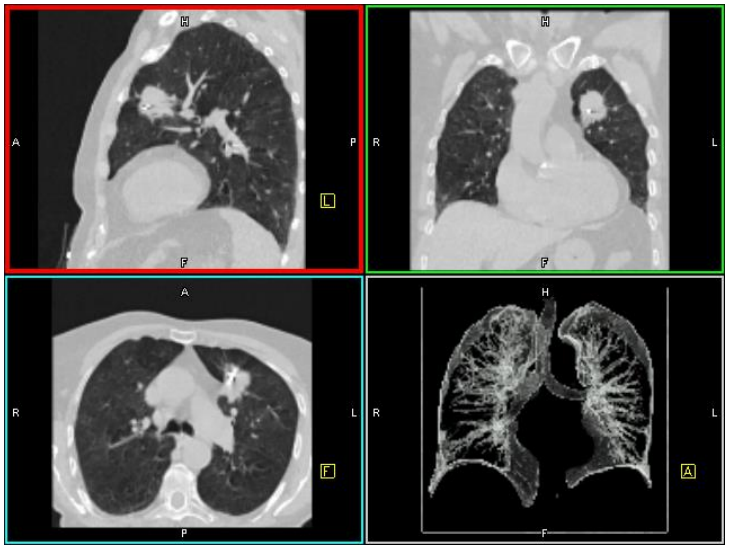
- Hysteresis in half of the patients (1-5 mm separation of trajectories)
- The extent of hysteresis and the amplitude of the tumor motion remains fairly constant during the entire treatment
- However, in many patients, shifts in the exhale tumor position were observed intra- and interfractionally

Erasmus MC

Observation of Motion

- **Respiratory correlated CT or 4D CT scan**
  - Sort projections according to breathing phase and apply CT reconstruction
  - CT data set typically containing ~8 breathing phases
  - Detailed 3D information, but limited time resolution (8 phases, 1 averaged cycle)





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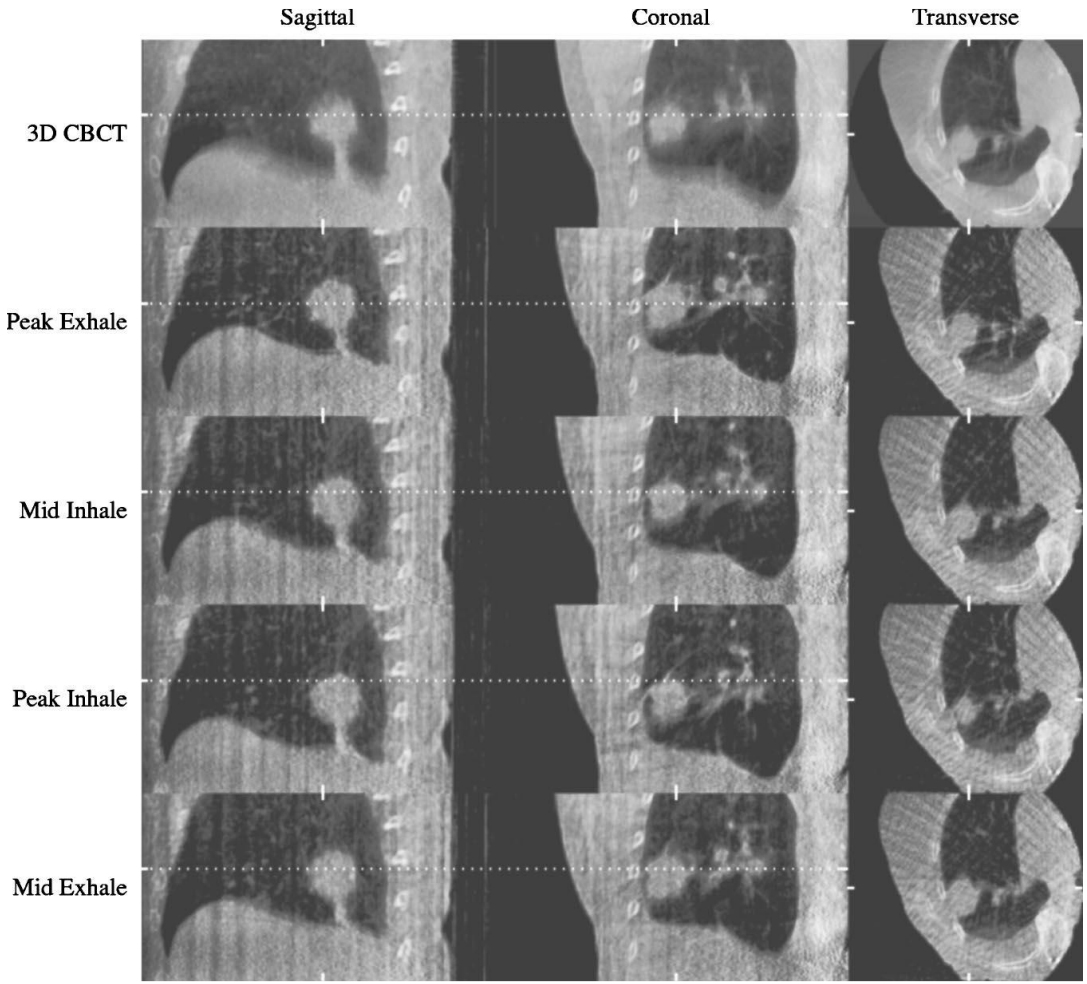
Respiratory Correlated Cone Beam CT Scanning



Sonke JJ et al. Medical Physics, Vol. 32, No. 4, April 2005

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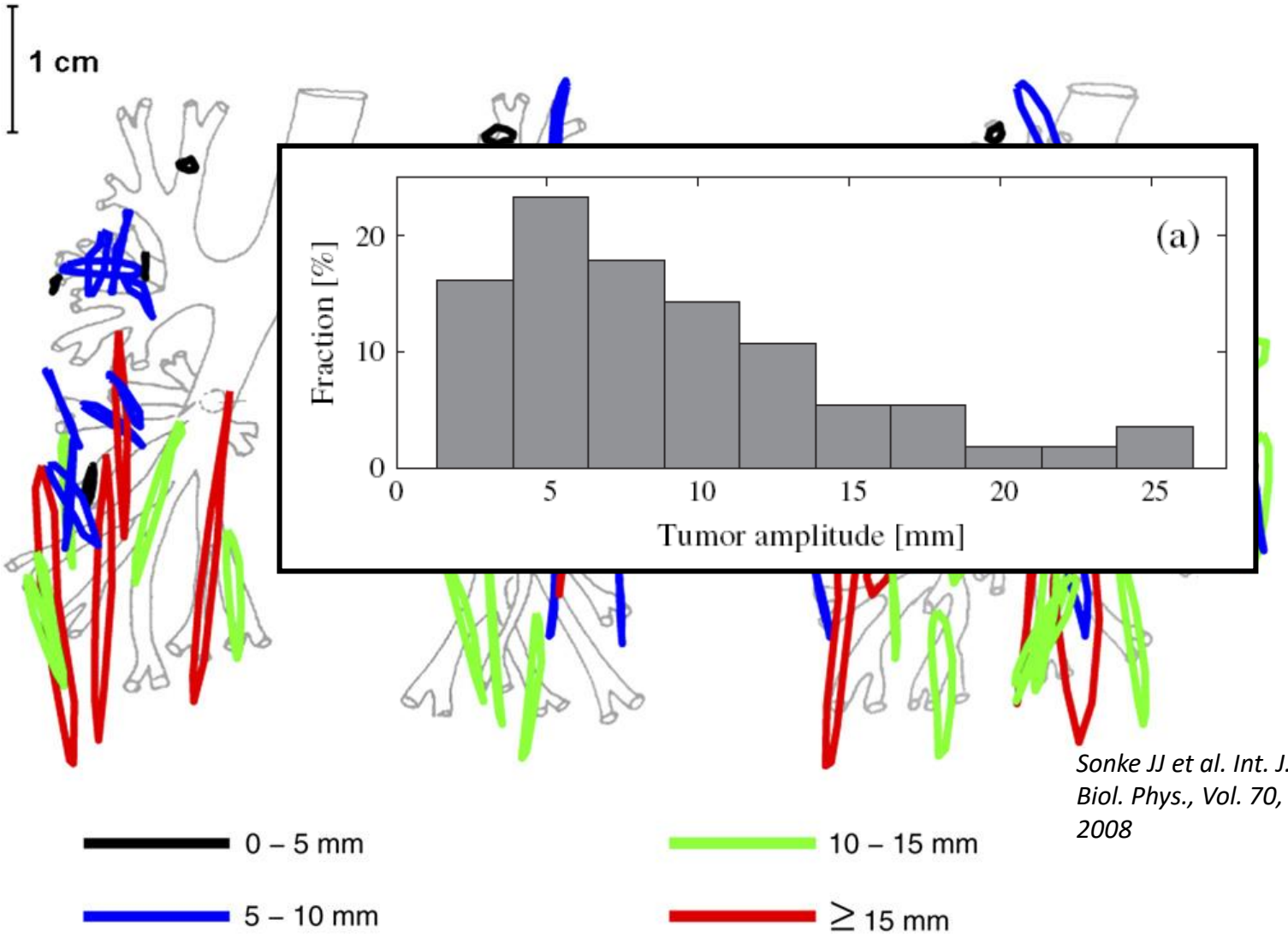
Motion Observations



Sonke JJ et al. Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 2, pp. 590–598, 2008

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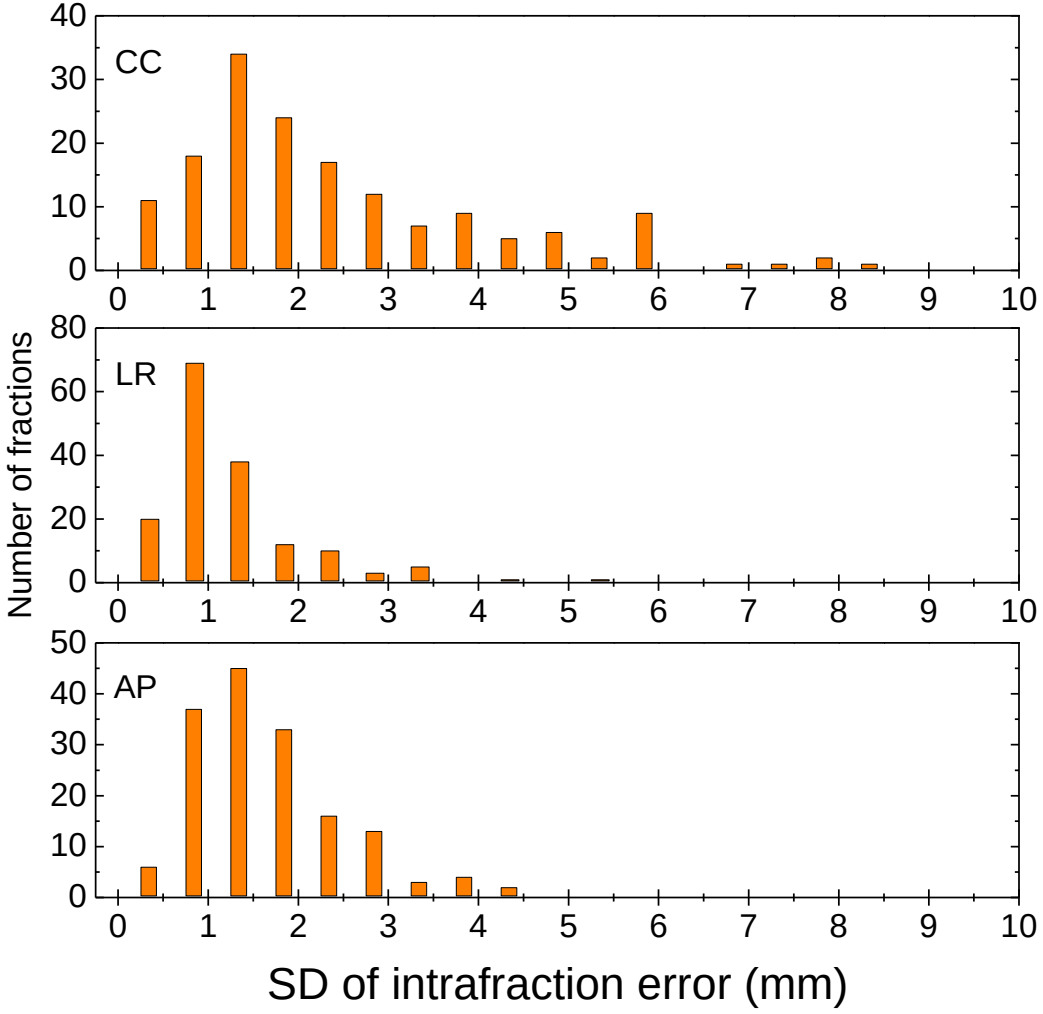
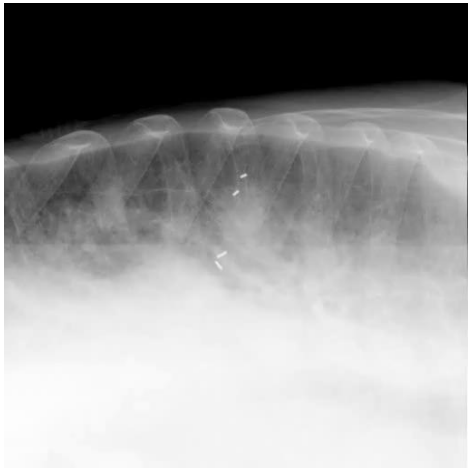
Distribution of Intra-fractional Respiratory Motion (1 SD)



Hoogeman M, et al. IJROBP 2009 May 1;74(1):297-303.



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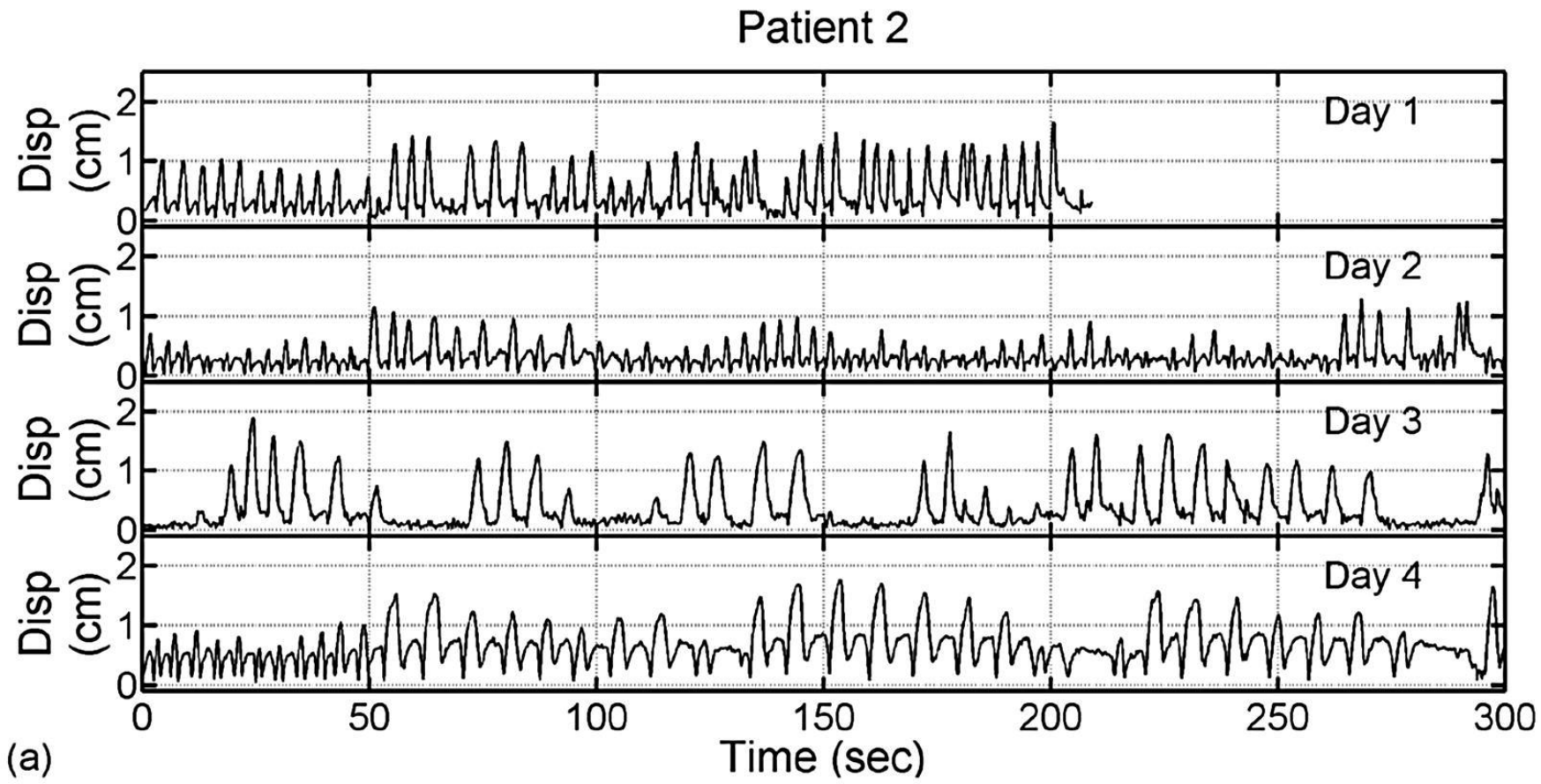
Day-to-Day Variation in Lung Tumor Motion



Shah AP, Kupelian PA, Waghorn BJ, Willoughby TR, Rineer JM, Mañon RR, Vollenweider MA, Meeks SL. Real-time tumor tracking in the lung using an electromagnetic tracking system. Int J Radiat Oncol Biol Phys. 2013 Jul1;86(3):47783.

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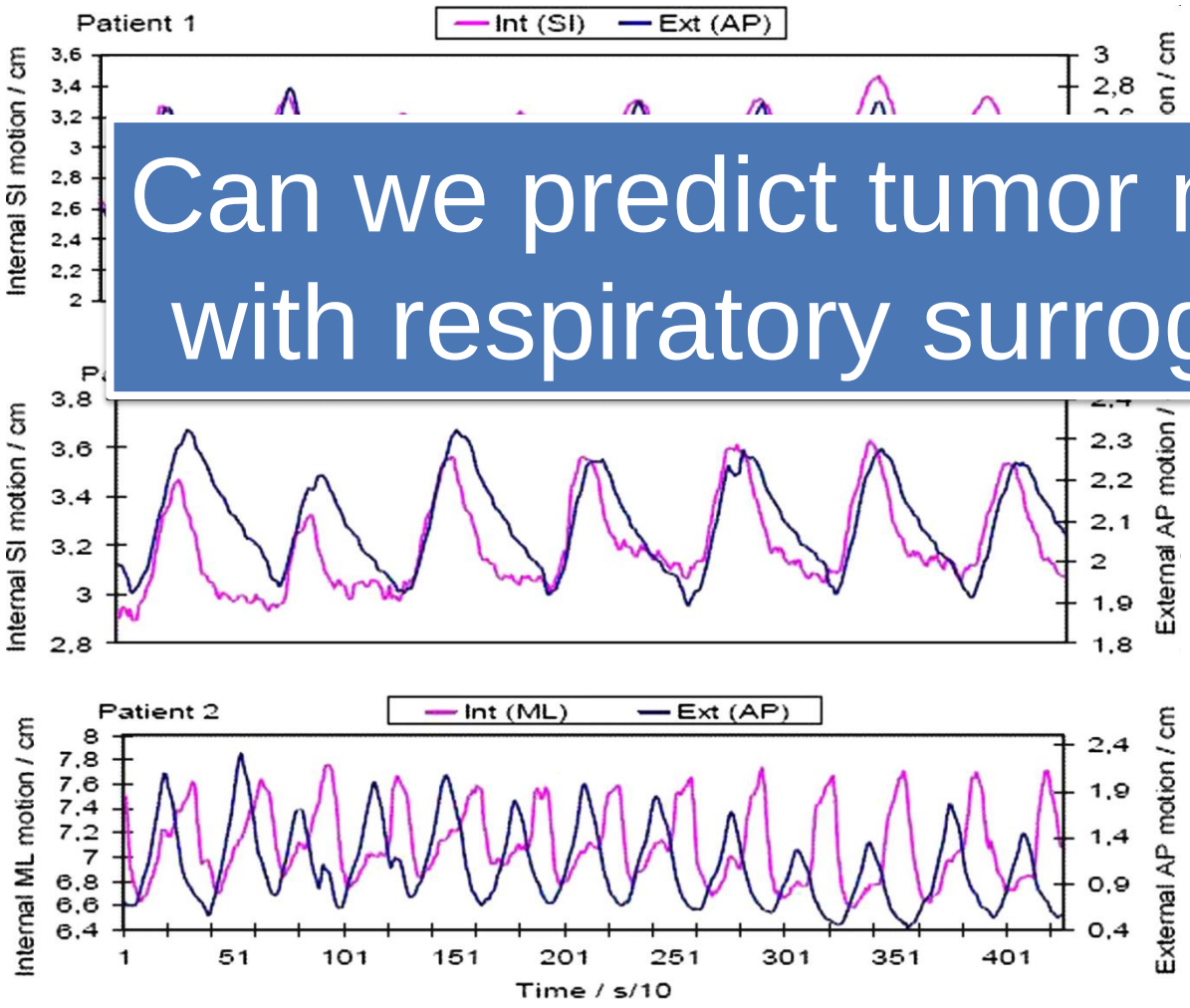
Bad Correlation Internal and External Signal

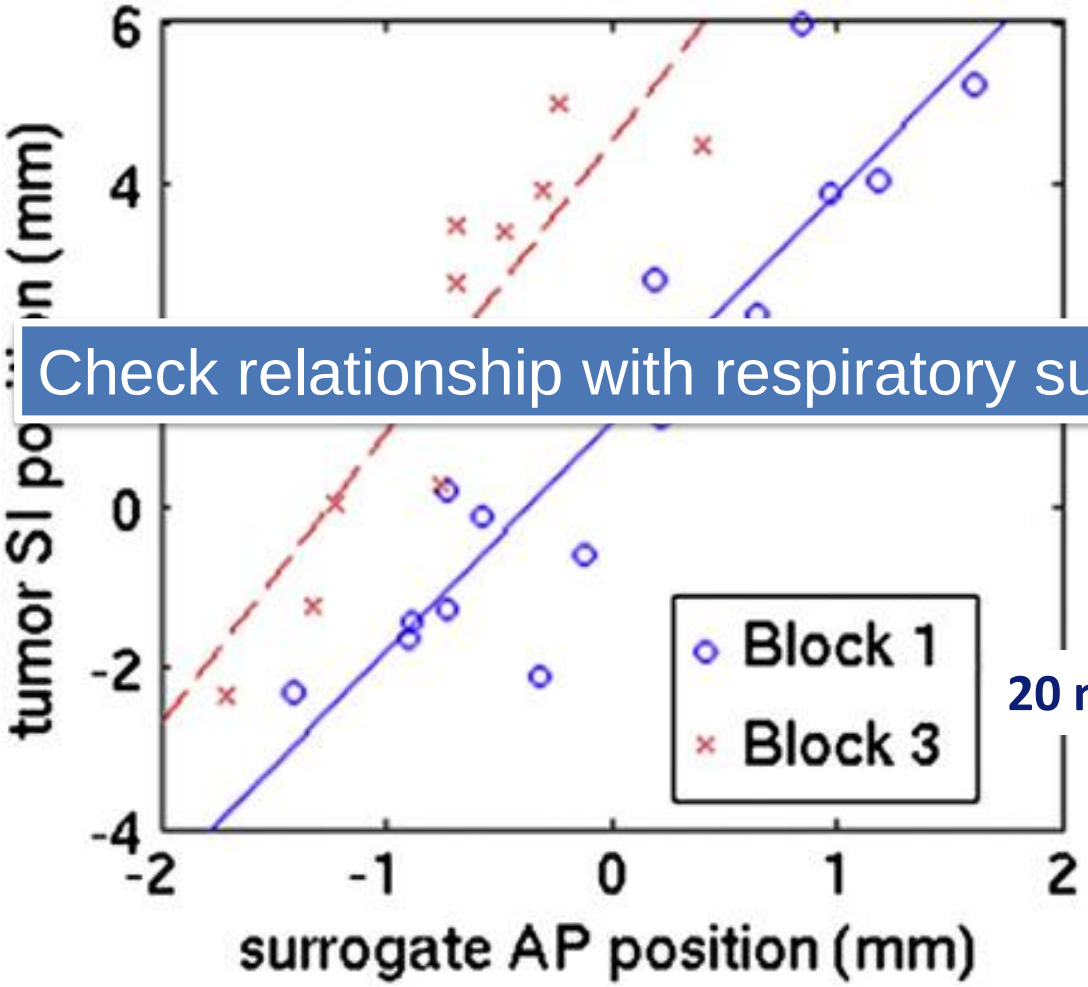


Can we predict tumor motion with respiratory surrogates?

Korreman et al. R&O 2008

Erasmus MC

Changes in Relationship with Respiratory Surrogate



Malinowski K et al. Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 5, pp. 1665–1673, 2012

Check relationship with respiratory surrogate after 10 min

20 min difference (+2 mm margin)

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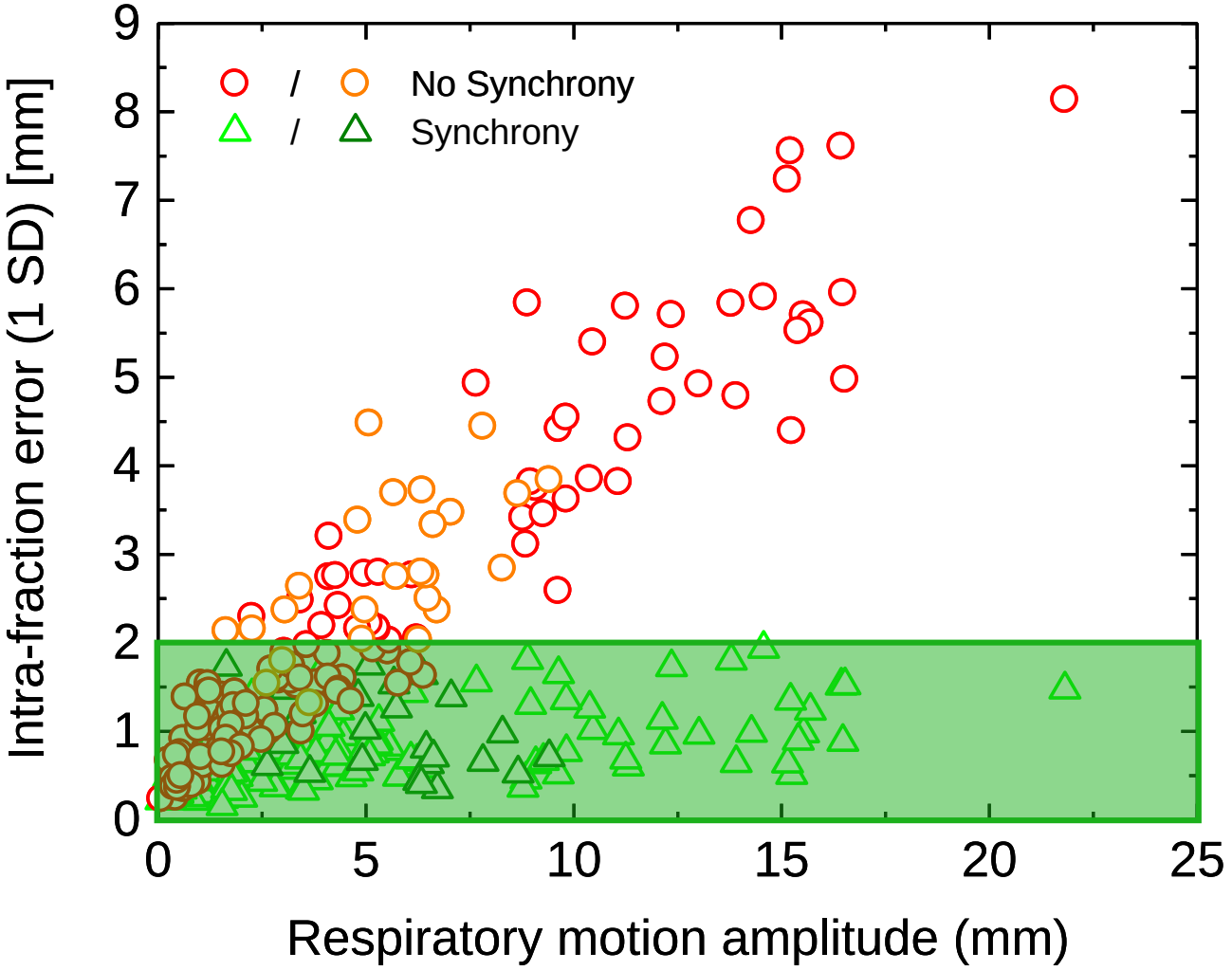
Intra-Fraction Error (167 treatment fractions)



Hoogeman M et al. Int J Radiat Oncol Biol Phys. 2009 May 1;74(1):297-303.

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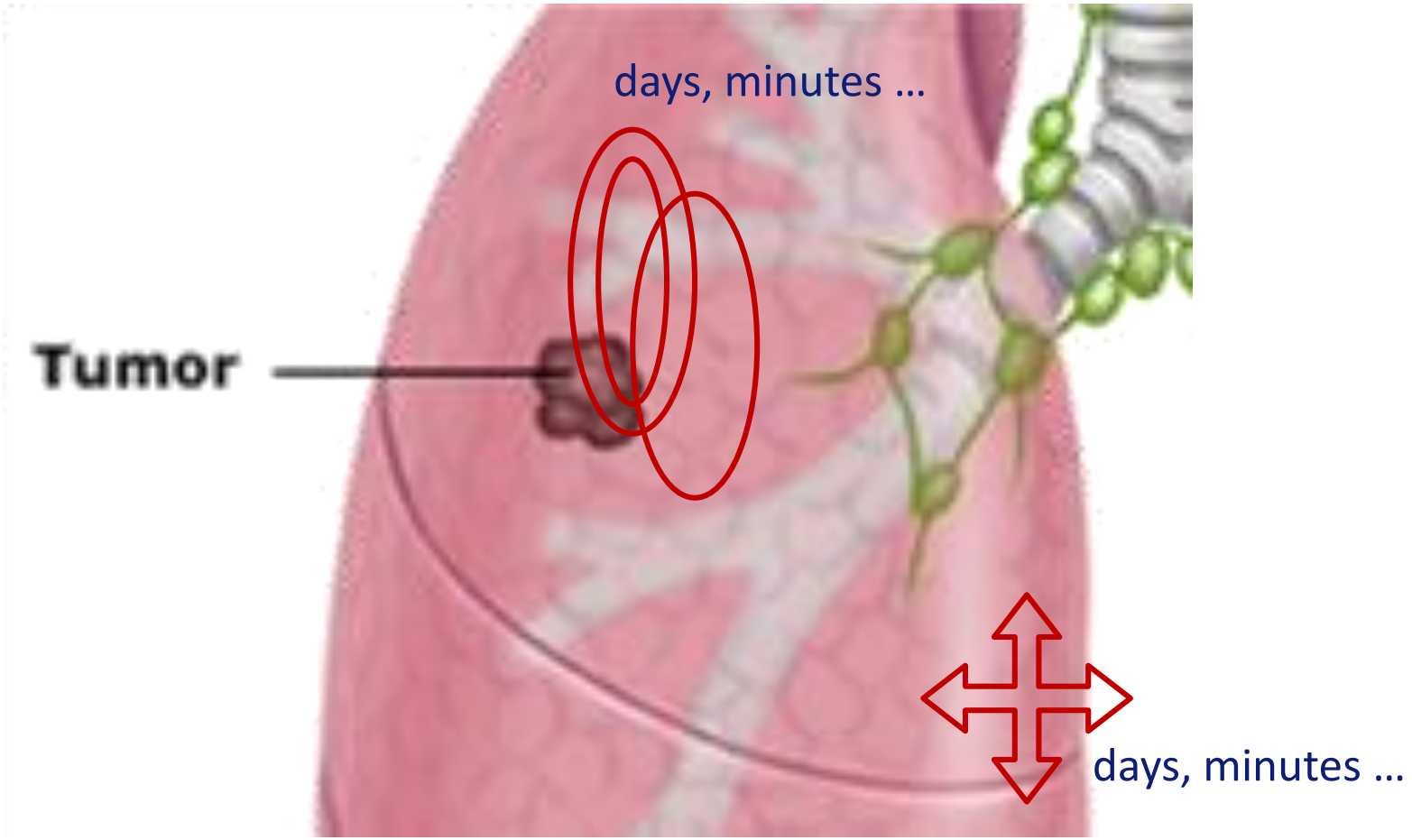
Various Types of Motion



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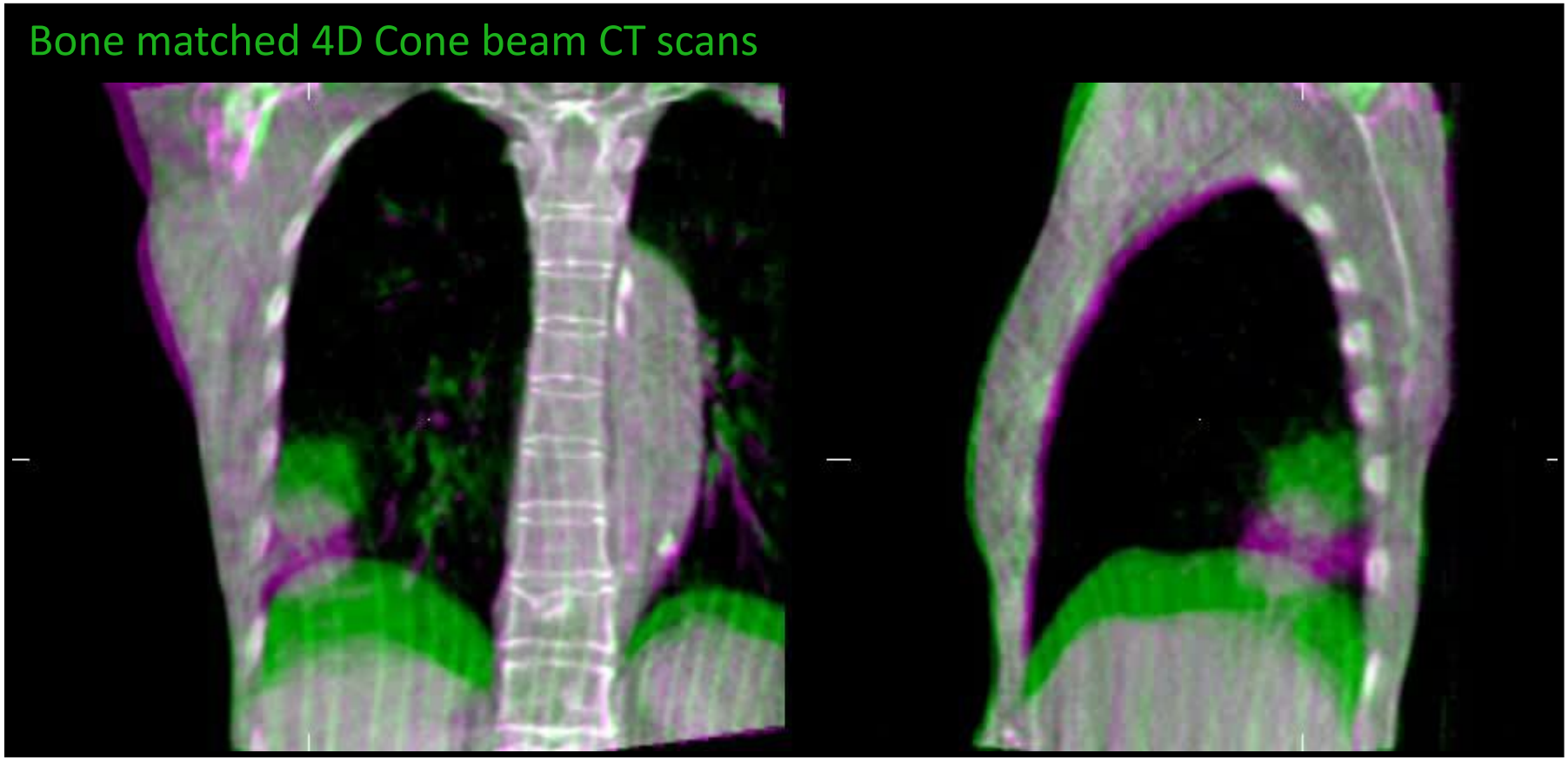
Systematic error and baseline shift



Courtesy of J.J. Sonke et al. NKI-AVL
Sonke et al. IJROBP 2007 Nov 23, Epub

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Interfraction Variability of Tumor Motion (Day)

Table 2. Interfraction baseline variation (tumor–bony anatomy) in terms of group mean (GM), systematic error (Σ), and random error (σ)

	Left-right (mm)	Craniocaudal (mm)	Anteroposterior (mm)
GM	0.3	0.1	−2.2
Σ	1.8	2.9	3.0
σ	1.1	1.5	2.0

Sonke et al. IJROBP 2007 Nov 23, Epub

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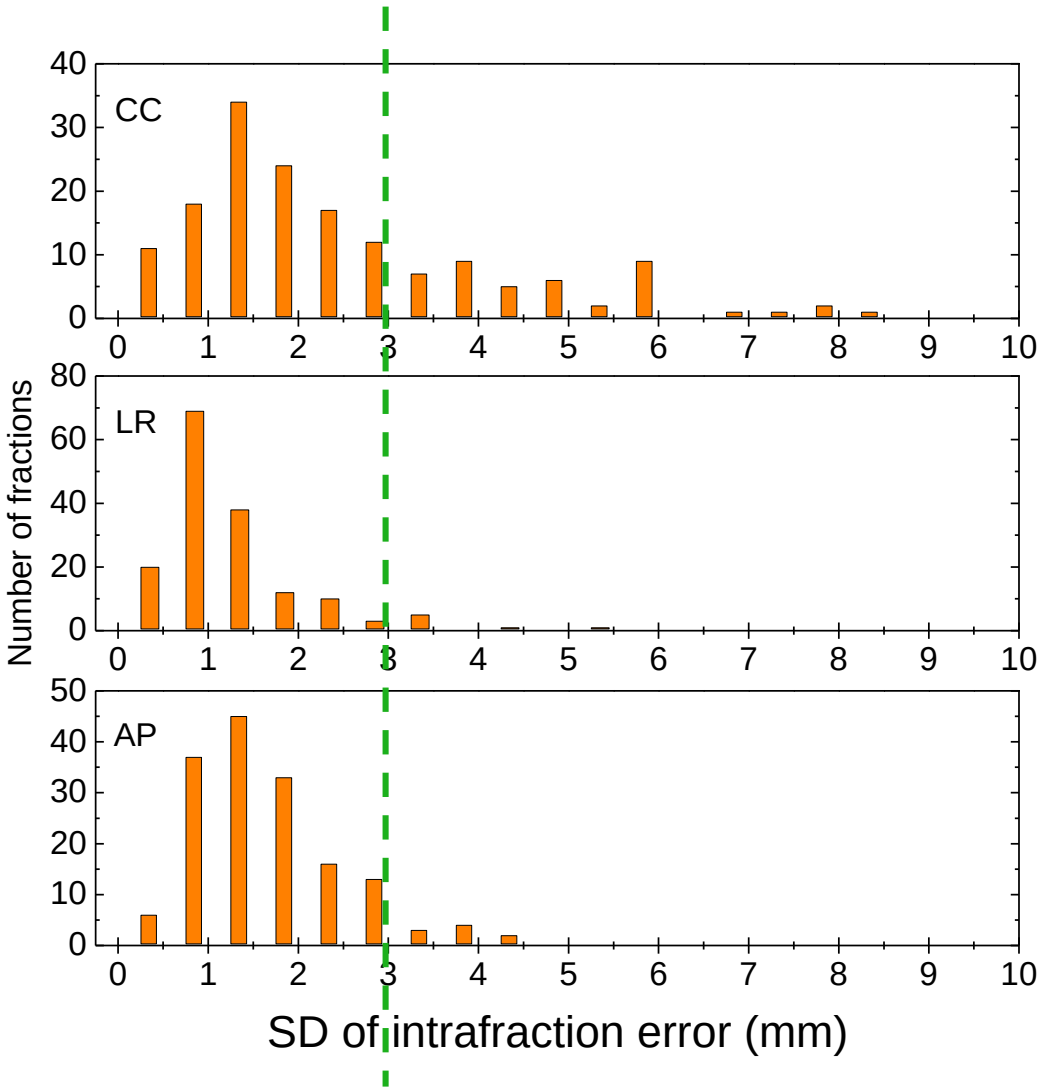
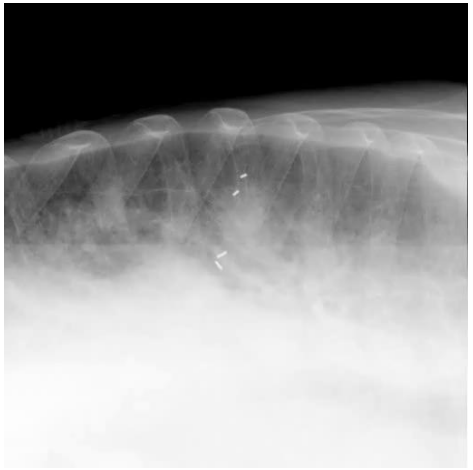
Distribution of Intra-fractional Respiratory Motion (1 SD)



Hoogeman M, et al. IJROBP 2009 May 1;74(1):297-303.



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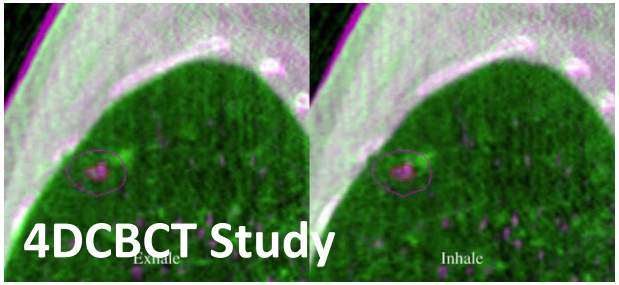
Intra-fraction Variability of Tumor, Bone, and Baseline (Minutes)



Average beam on time 28 ± 5 min

Table 3. Intrafraction variability of tumor, bony anatomy, and baseline in terms of group mean (GM), systematic error (Σ), and random error (σ)

	Left-right (mm)	Craniocaudal (mm)	Anteroposterior (mm)
Tumor			
GM	0.0	1.0	−0.9
Σ	1.2	1.2	1.8
σ	1.3	1.5	1.8
Bone			
GM	0.0	0.4	−0.3
Σ	1.0	0.8	1.1
σ	1.3	1.0	1.1
Baseline			
GM	0.0	0.6	−0.6
Σ	0.6	1.0	1.4
σ	0.7	1.1	1.5

Sonke JJ et al. Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 2, pp. 567–574, 2009

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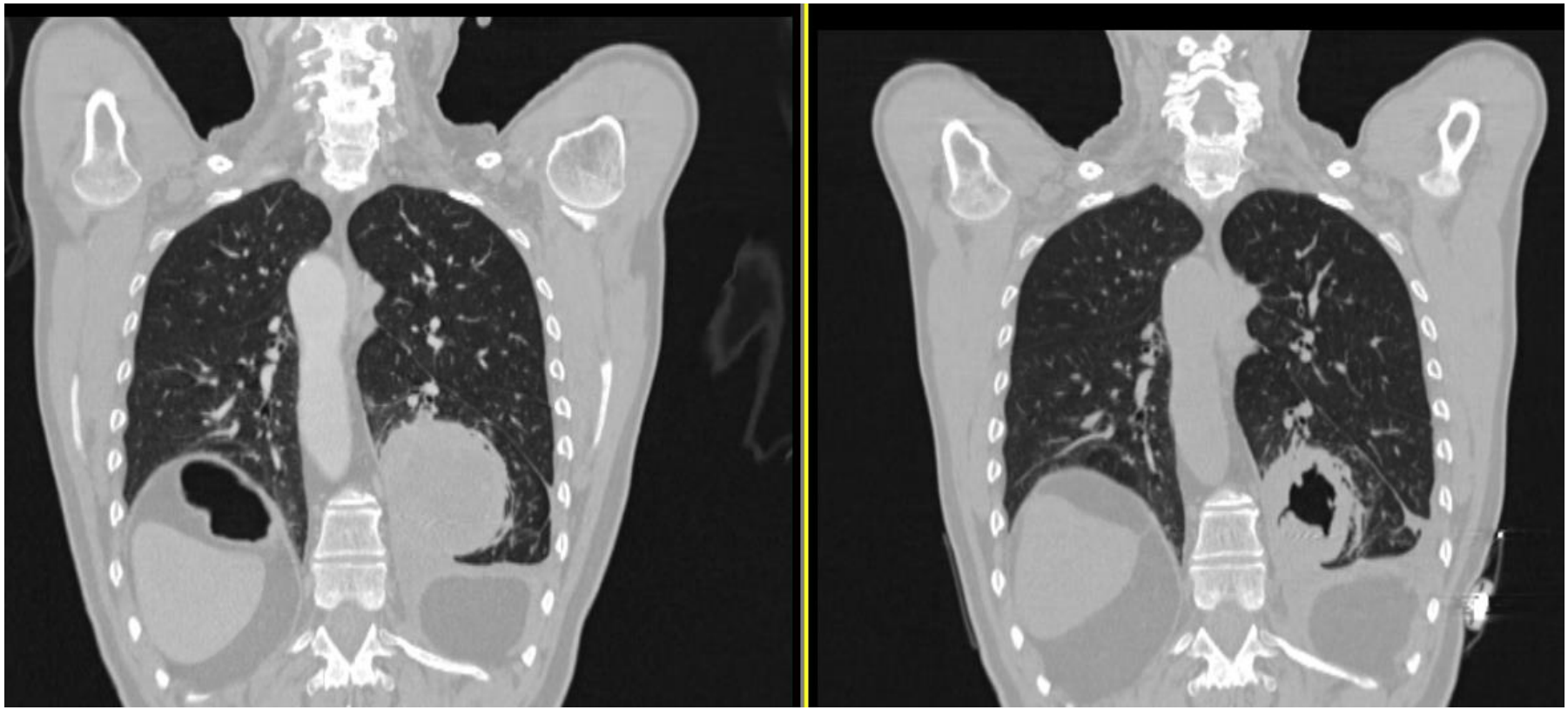
Changes in Volume and Shape



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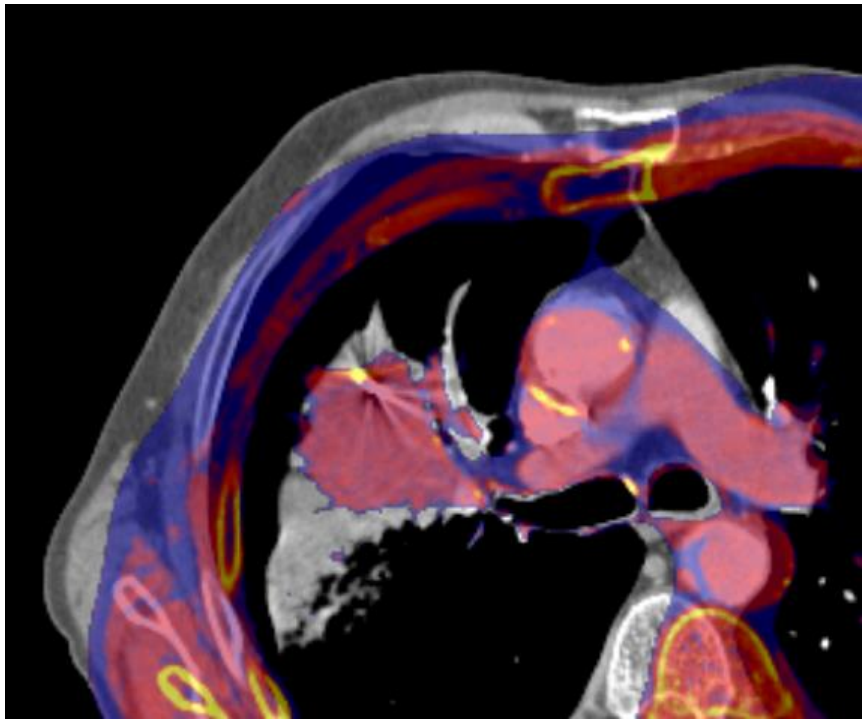
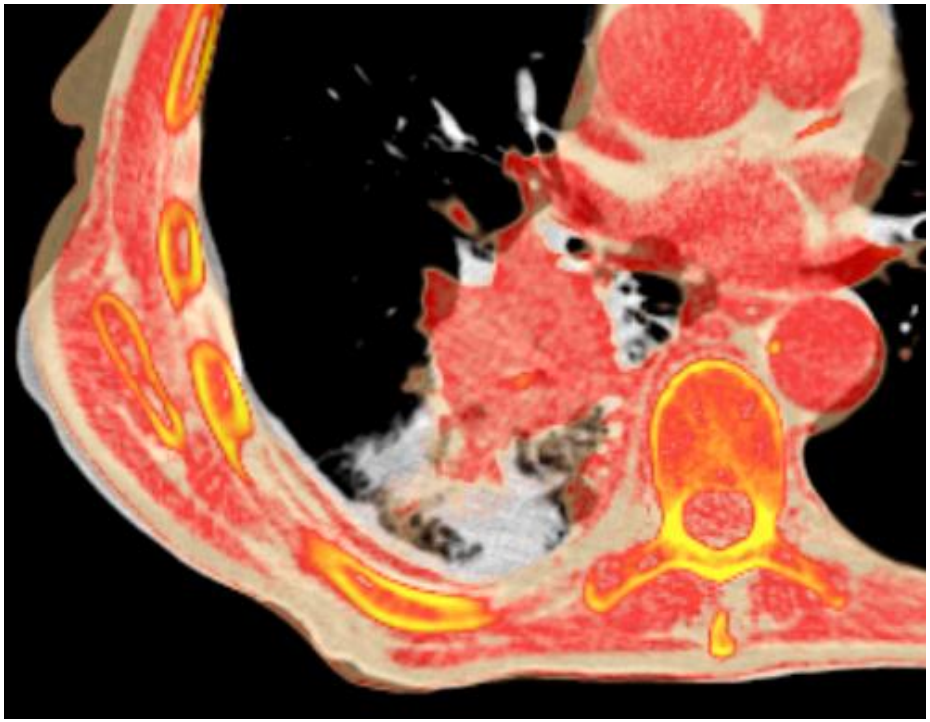
Tumor Changes in Volume and Shape





- In 4/44 (42 patients) tumors changes in volume and shape were observed

van der Voort van Zyp NC et al. Int J Radiat Oncol Biol Phys. 2011 Nov 1;81(3):e75-81

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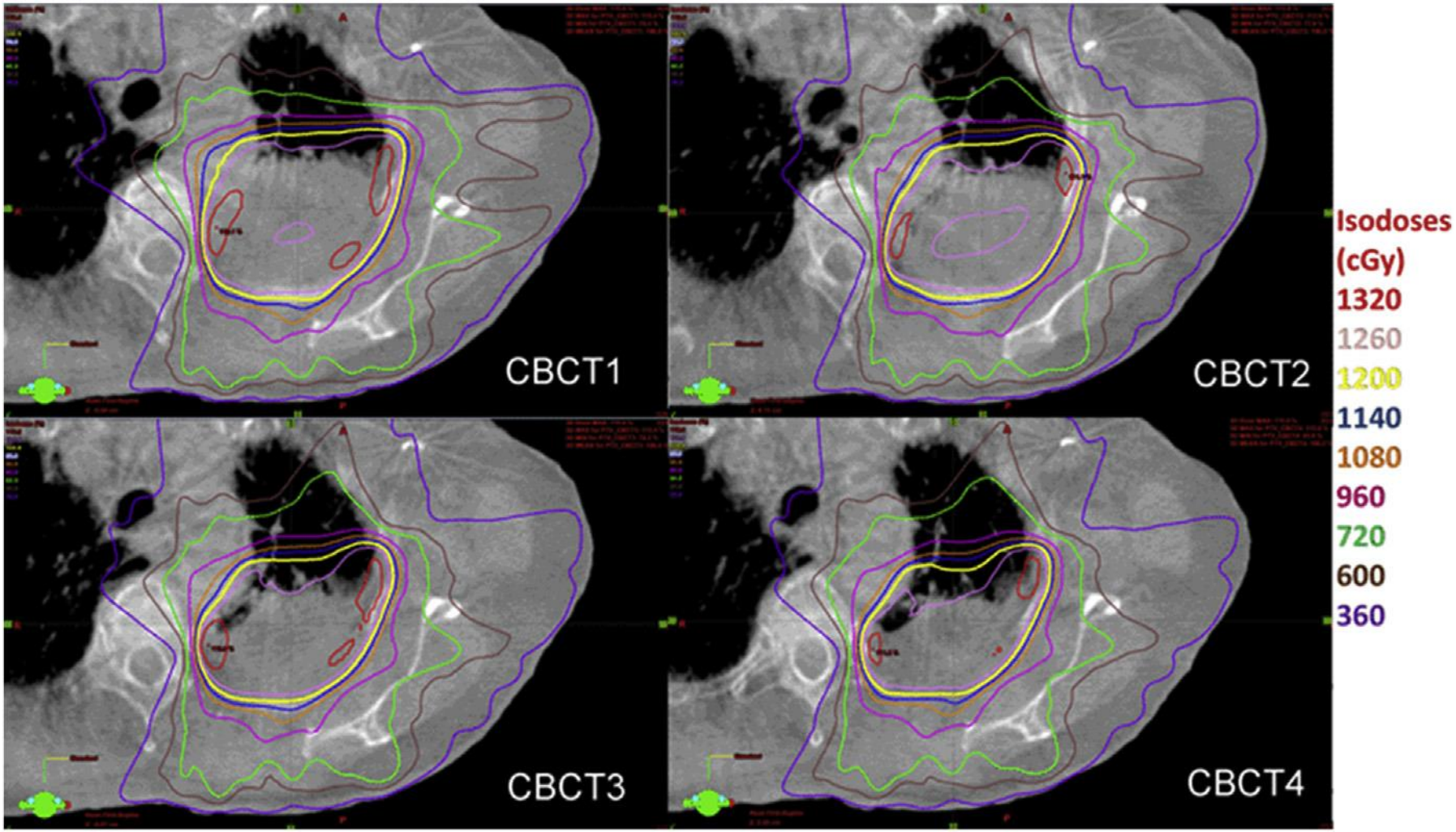
Replanning Example



Yujiao Qin et al. Int J Radiat Oncol Biol Phys. 2013 Jun 19. pii: S0360-3016(13)00537-3

Discussion: Clinical Relevance

- **Replanning … when and on what volume?**
  - Target size change and tumor-to-OAR distances should be considered when deciding whether a lung SBRT patient would benefit from adaptive treatment (Yujiao Qin et al.)
  - Do not start with replanning when implementing lung SBRT
- **Safety issues**
  - The relation between fiducial markers and tumor may have changed
  - Check tumor position with respect to the organs at risk and adapt the plan if organs at risk constraints are violated

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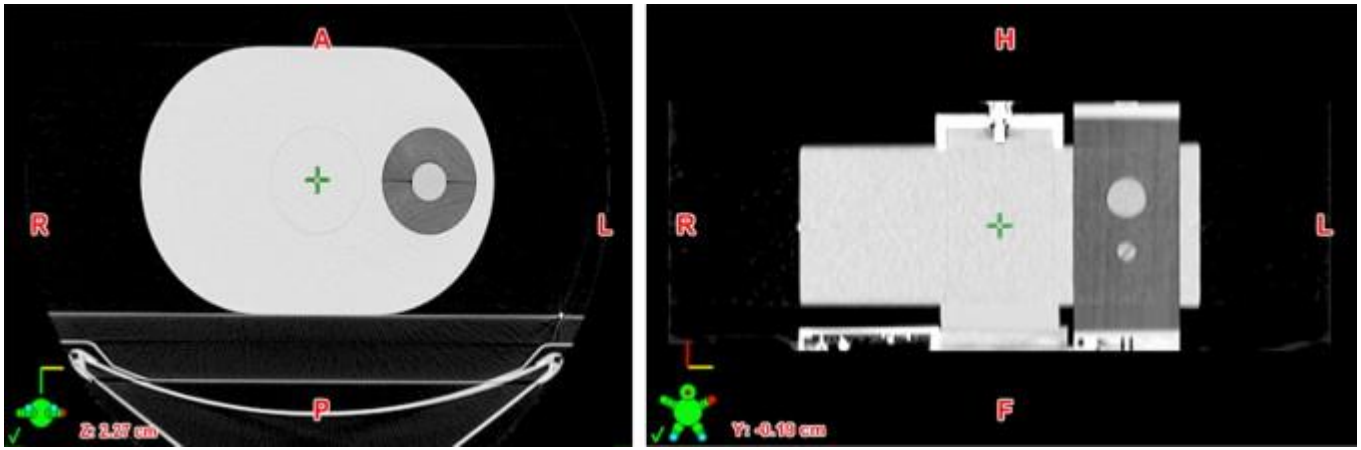
Volumetric Modulated Arc Therapy



- Interplay between leaves and tumor motion is not significant for single-fraction treatments when RapidArc is delivered with two different arcs
- Under phantom conditions, single-arc and single-fraction 2400 MU/min FFF RapidArc lung stereotactic body radiation therapy is susceptible to interplay. **Two arcs and ≥2 fractions reduced the effect to a level that appeared unlikely to be clinically significant**

Ong et al. Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 1, pp. 305–311, 2011
Ong et al. Int J Radiation Oncol Biol Phys, Vol. 86, No. 4, pp. 743e748, 2013

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Discussion: Clinical Relevance

- **Should we measure intra-fraction motion?**
  - Yes, at planning in order to individualize the safety margin (and to determine the time-averaged mean position)
- **Should we correct for intra-fraction motion?**
  - Amplitude seems to have a minor effect on the margin. However,
    - for central lesions and lesions close to the thoracic wall the penumbra will be sharper
    - Take care of small lesions and large amplitudes
- **Should we correct for inter-fraction motion?**
  - **YES!**
- **Dosimetrical effects?**
  - Be cautious for fast and single-fraction treatments

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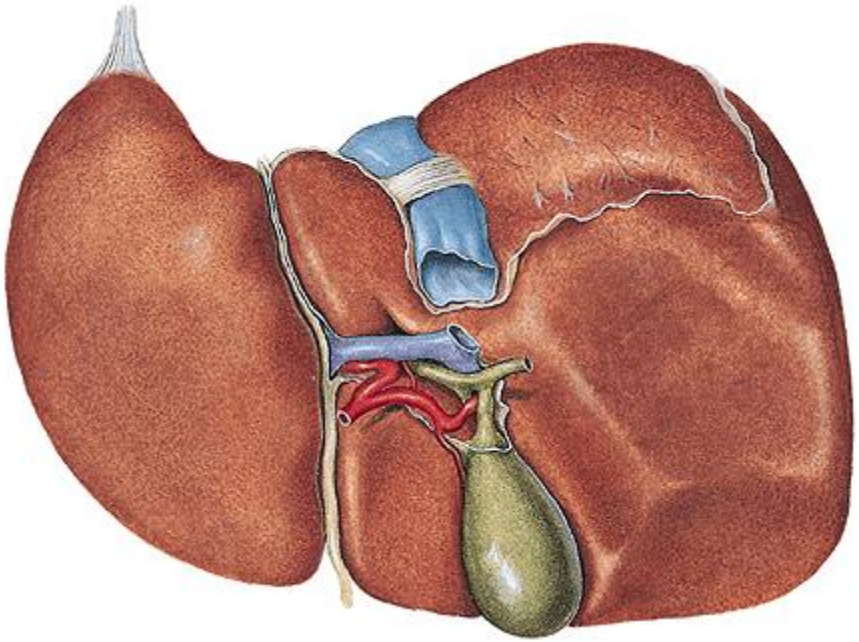
LIVER



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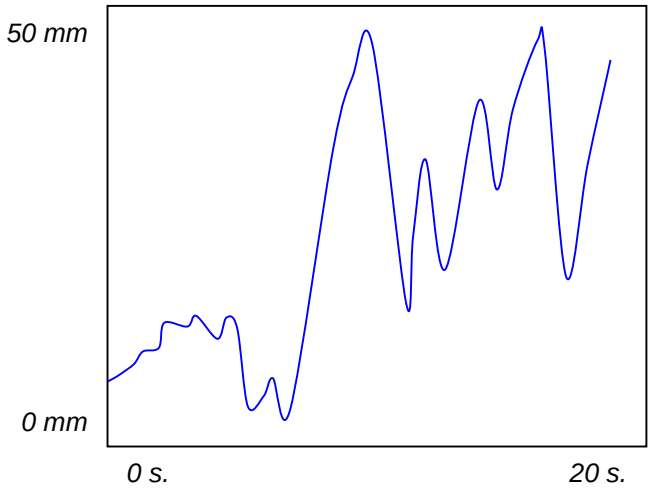
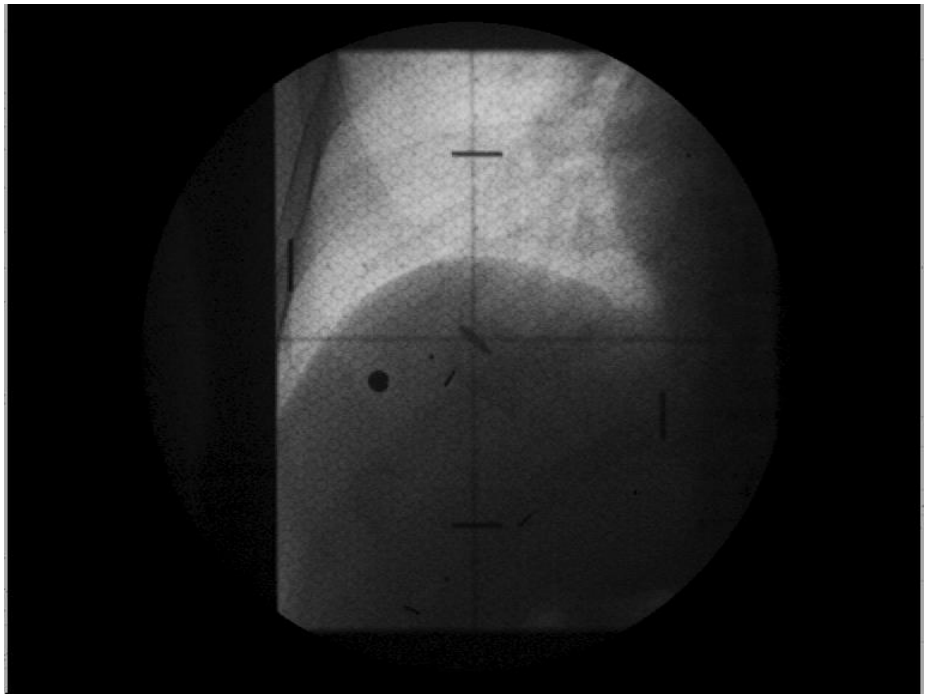
Observation of Motion

- Tumors in the liver are not or poorly visible on CT scans or CBCT scans
- => MRI, ultrasound, and implanted fiducial markers are used to assess tumor motion in the liver





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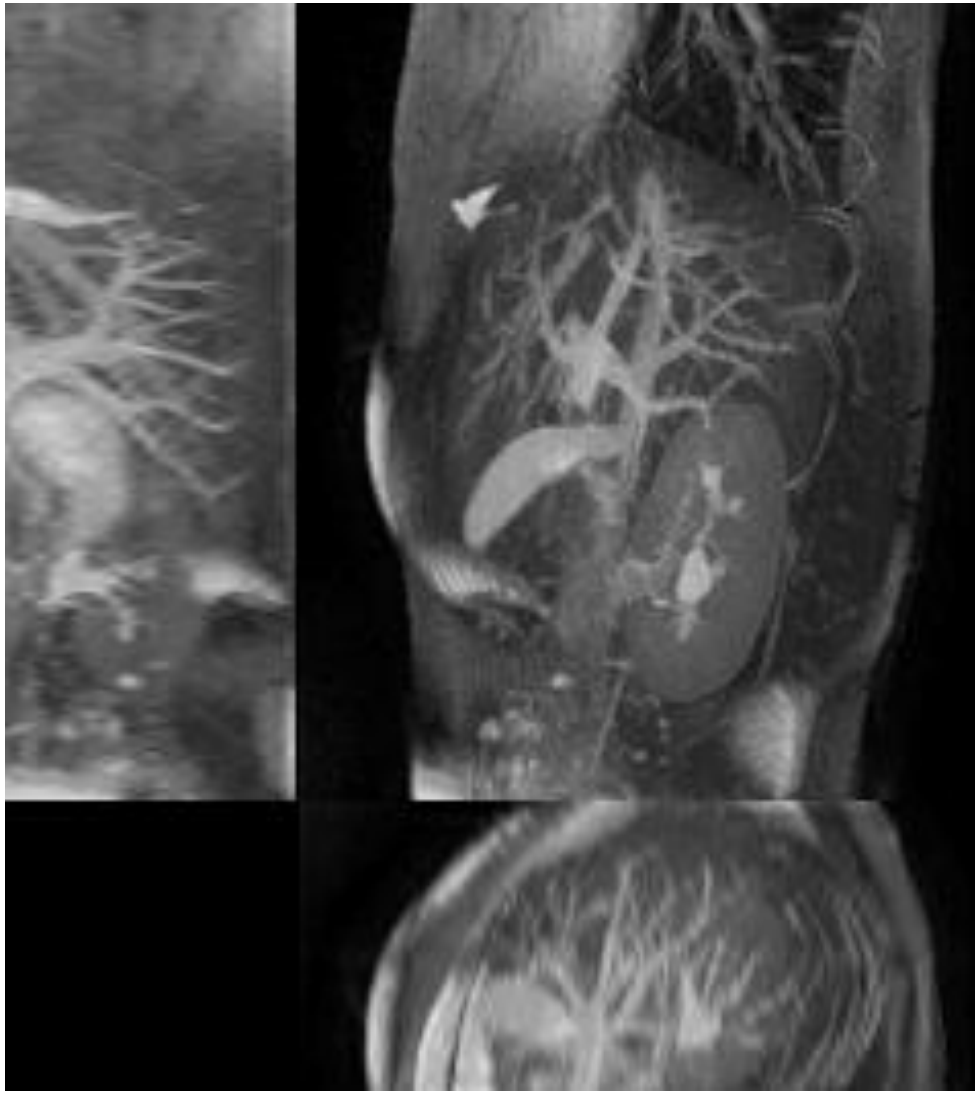
4D MRI Data of Liver



www.vision.ethz.ch/4dmri
von Siebenthal, M., Székely, G., Lomax, A. and Cattin, Ph. : 2007, "Systematic Errors in Respiratory Gating due to Intrafraction Deformations of the Liver“ Med. Phys. 34(9), 3620-3629

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Respiratory Motion Amplitudes

Free breathing liver motion, average + range (mm):

Publication	CC	AP	LR	Px	Method
Suramo 1984	25 [10 – 40] Deep: 55 [30 – 80]			50	Ultrasound
Davies 1994	10 [5 – 17] Deep: 37 [25 – 57]	< 2	< 2	9	Ultrasound
Kitamura 2003	9 [2 – 19]	5 [2 – 12]	4 [1 – 12]	20	Fluoroscopy + markers
Dawson 2005	16 [7 – 35]	10 [4 – 21]	8 [4 – 16]	32	MRI
Wunderink 2008	11 [4 – 39]	4 [1 – 12]	2 [1 – 4]	9	Fluoroscopy + markers

Slide courtesy of W. Wunderink

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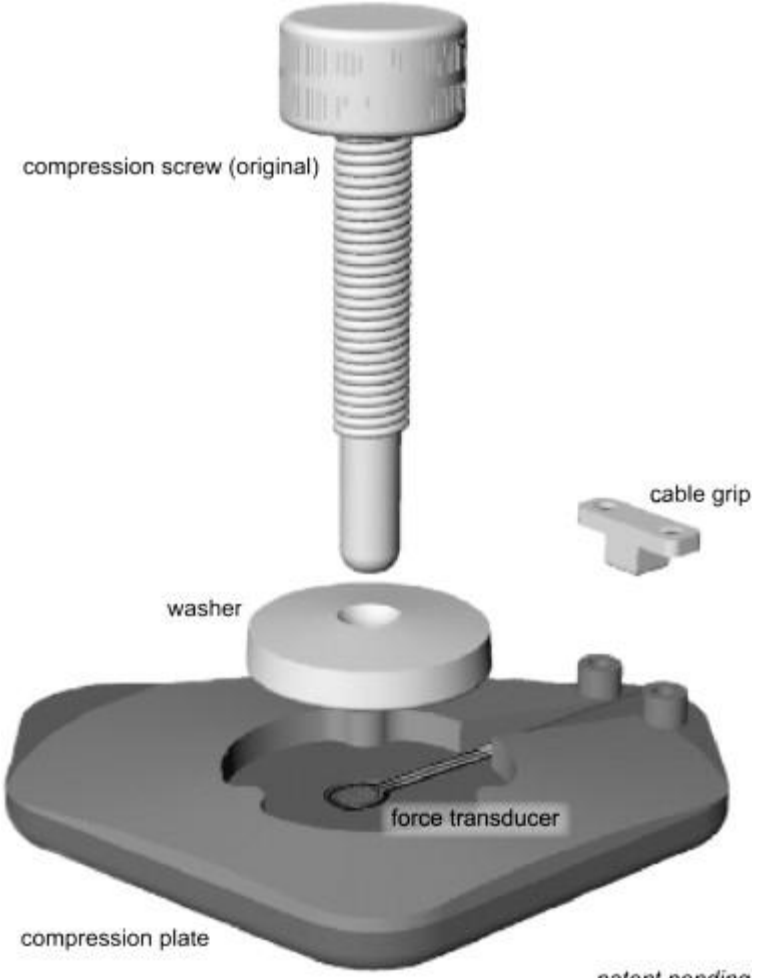
W. Wunderink, A. Méndez Romero et al.

Abdominal Compression



patent pending

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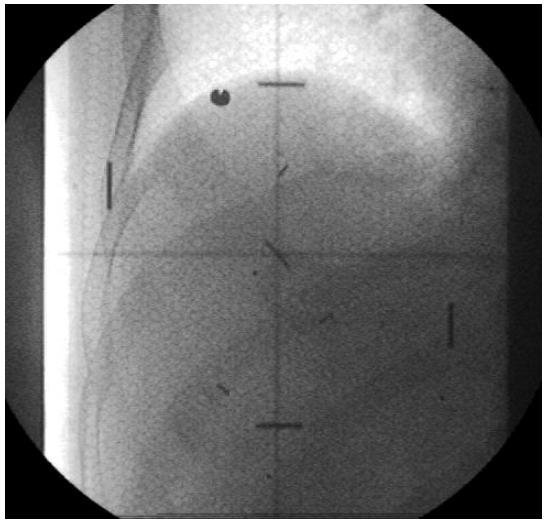
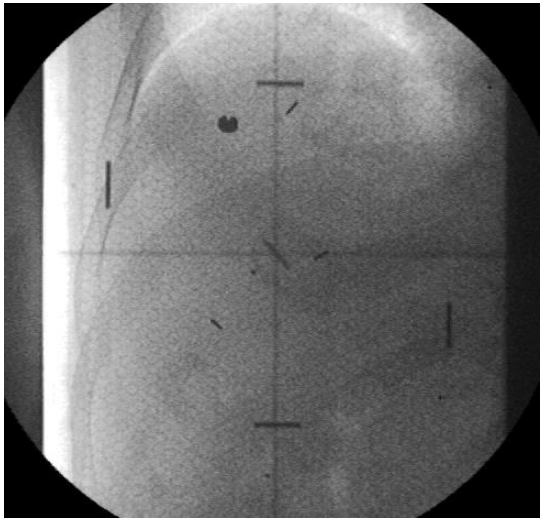
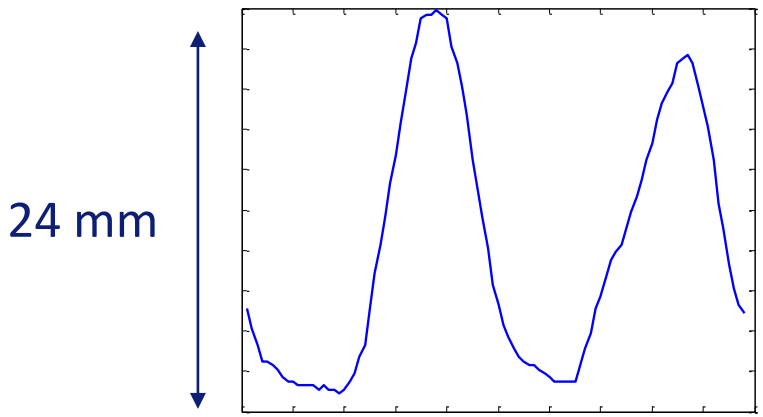
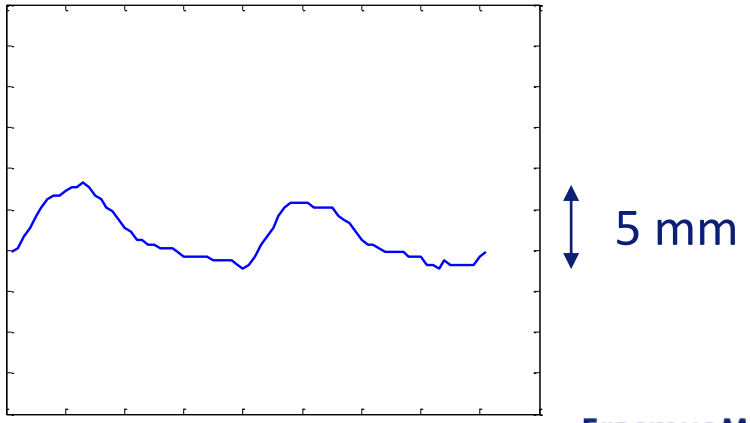
W. Wunderink, A. Méndez Romero et al.

Fluoroscopy









no compression

with compression

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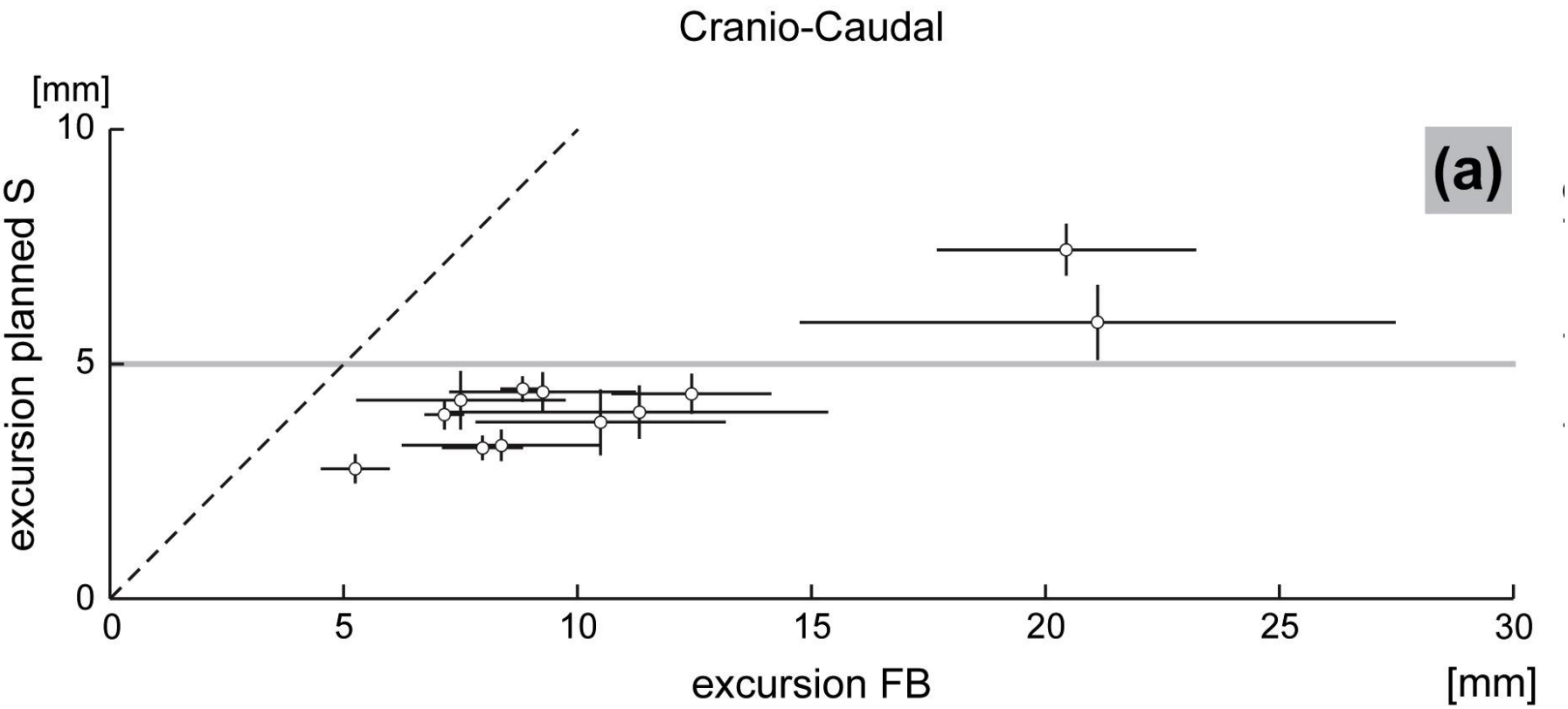
Amplitude Reduction by Abdominal Compression



Wunderink et al. Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 3, pp. 907–915, 2008

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Inter-fraction and Intra-fraction Liver Position Change

Table 1. Grouped mean, systematic, and random change in exhale baseline liver position

	Intrafraction (mm)			Interfraction (mm)		
Variable	ML	CC	AP	ML	CC	AP
Free-breathing patients (n = 158 CBCT scans)						
ΔM	−0.2	0.5	−0.02	1.0	1.0	−1.0
Σ	1.2	1.4	1.0	1.5	3.1	1.6
σ	2.2	3.0	1.9	1.8	3.6	2.7
Patients with abdominal compression (n = 156 CBCT scans)						
ΔM	0.03	0.4	0.3	0.8	0.3	−0.9
Σ	0.6	0.8	1.2	1.5	2.8	1.9
σ	1.4	1.6	1.8	1.8	2.6	2.2

Case R et al. Int. J. Radiation Oncology Biol. Phys., Vol. 75, No. 1, pp. 302–308, 2009

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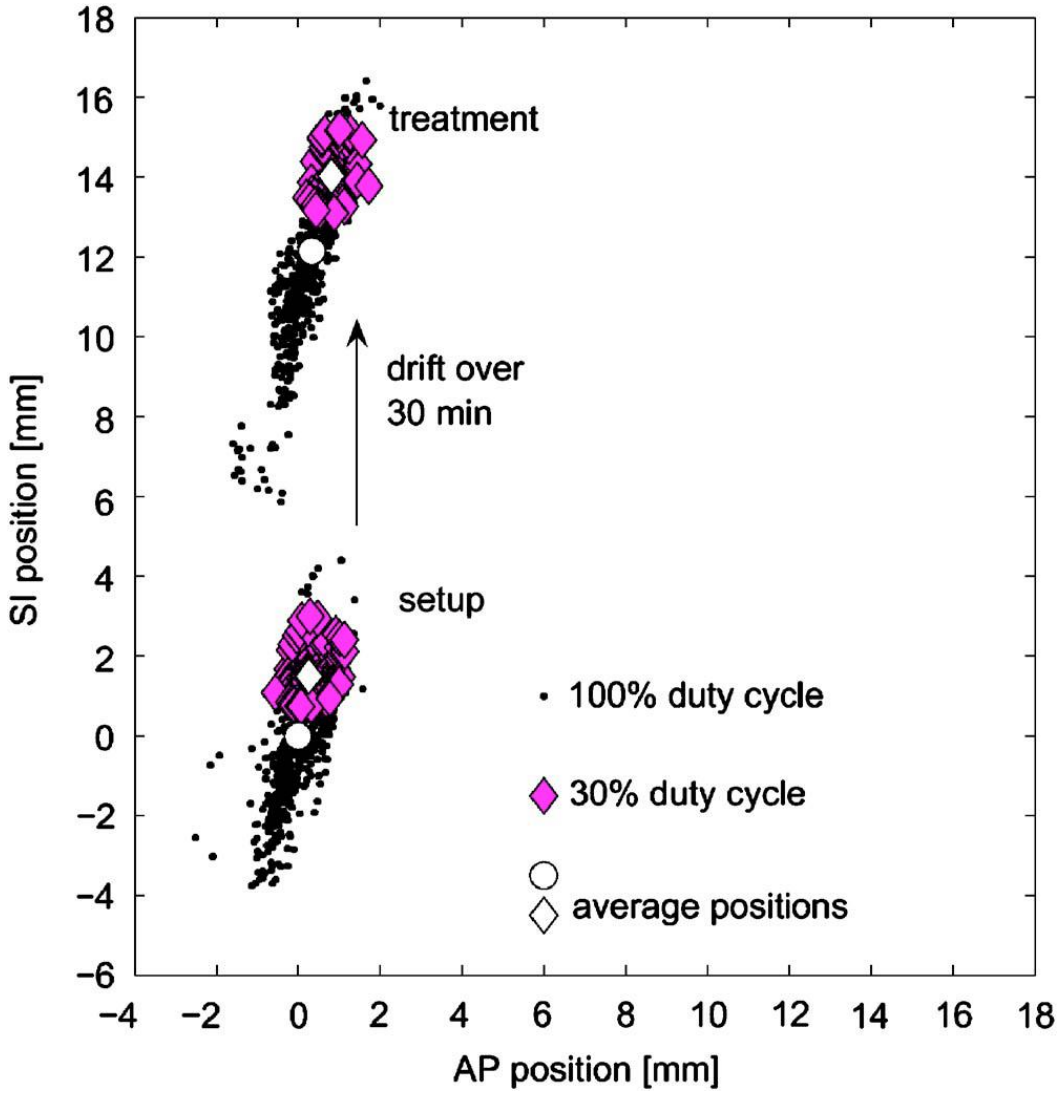
Drift During a Hypothetical 30-min Treatment



von Siebenthal, M., Székely, G., Lomax, A. and Cattin, Ph. : 2007, "Systematic Errors in Respiratory Gating due to Intrafraction Deformations of the Liver“ Med. Phys. 34(9), 3620-3629

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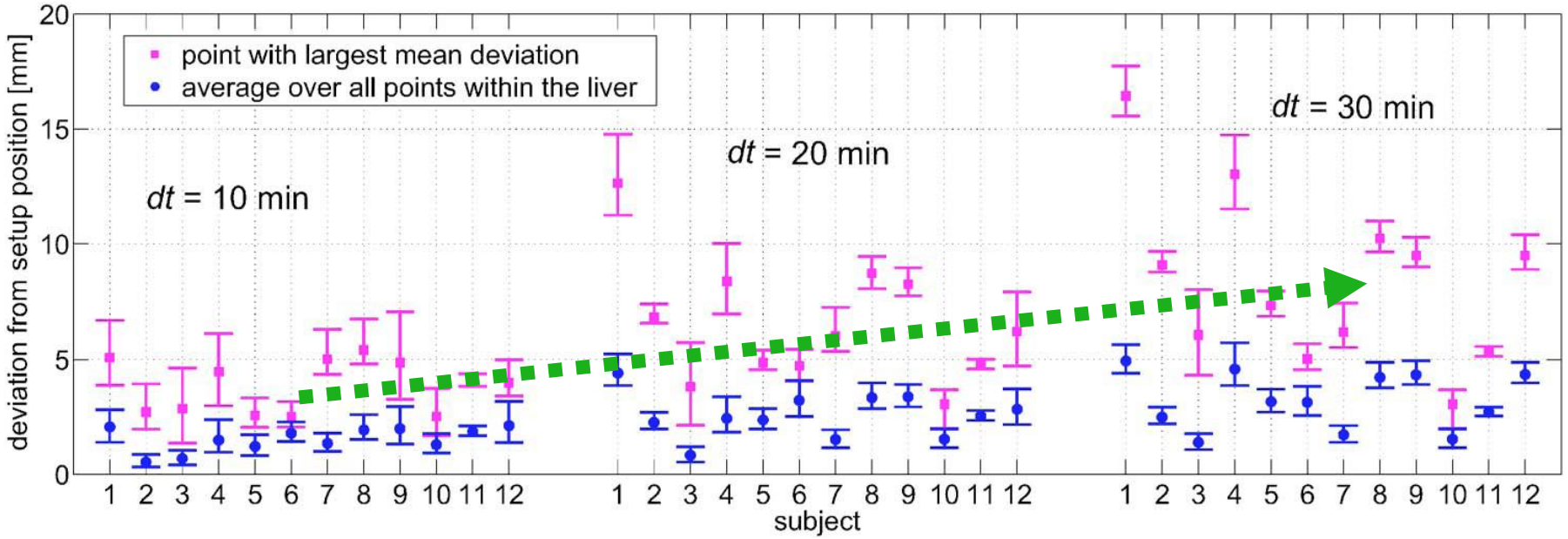
Deviation as a Function of Treatment Time



von Siebenthal, M., Székely, G., Lomax, A. and Cattin, Ph. : 2007, "Systematic Errors in Respiratory Gating due to Intrafraction Deformations of the Liver“ Med. Phys. 34(9), 3620-3629

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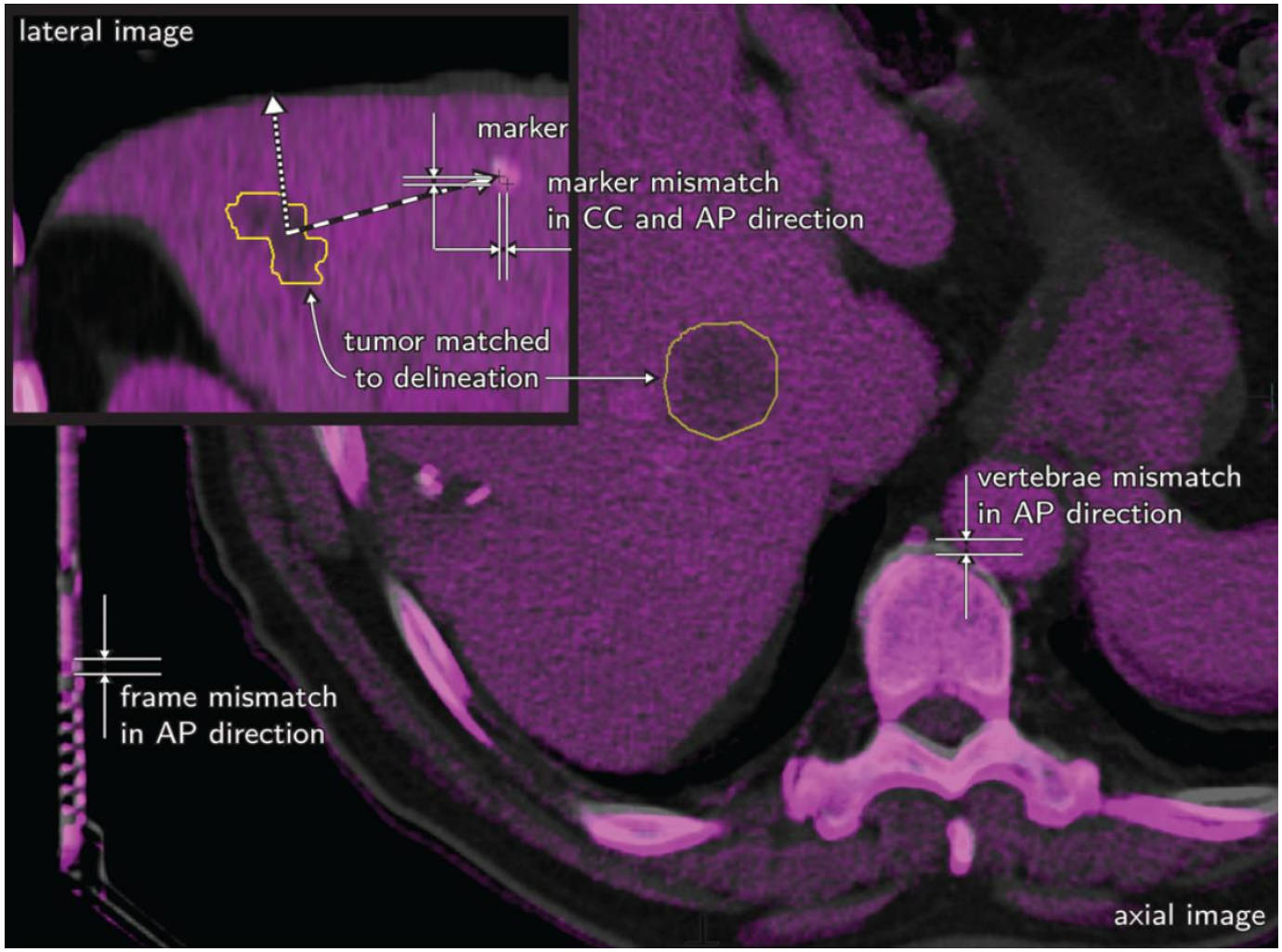
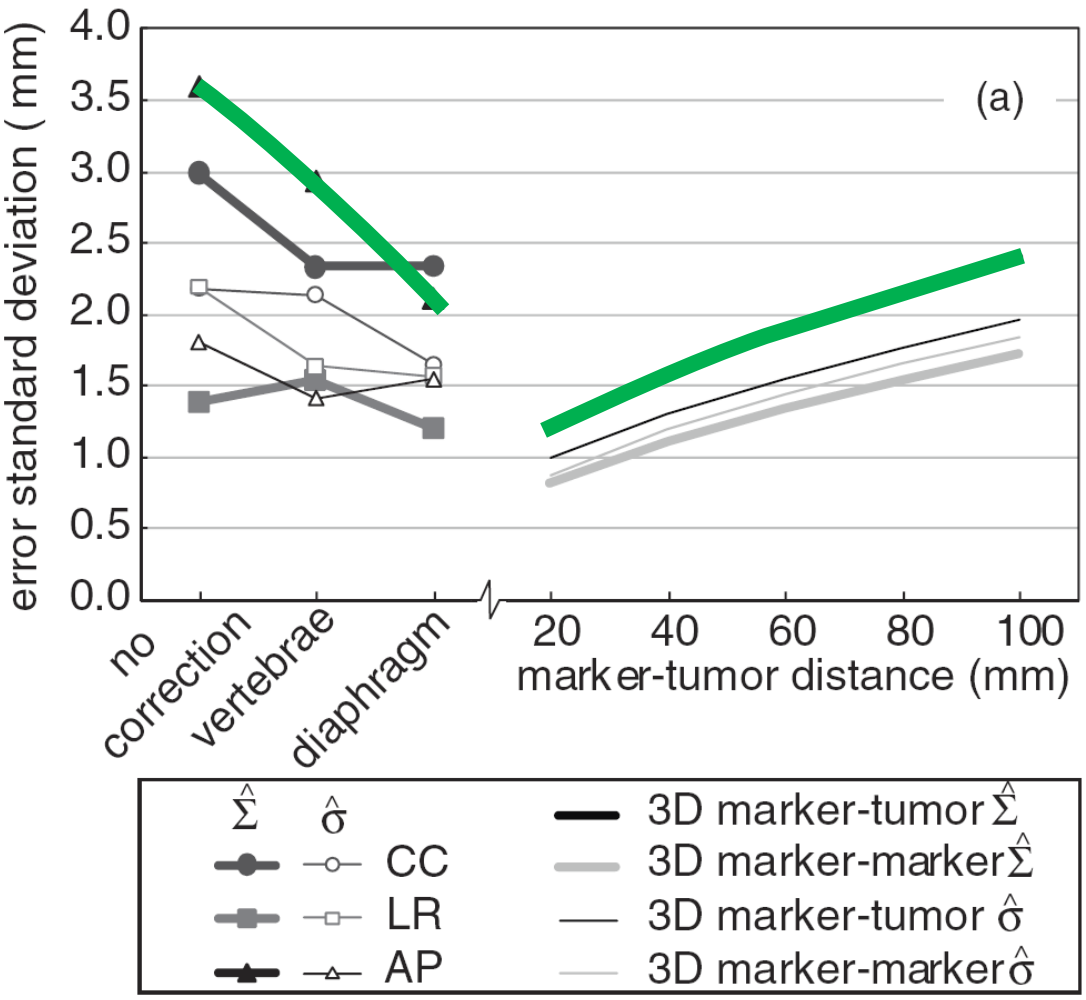
Liver Tumor Surrogates

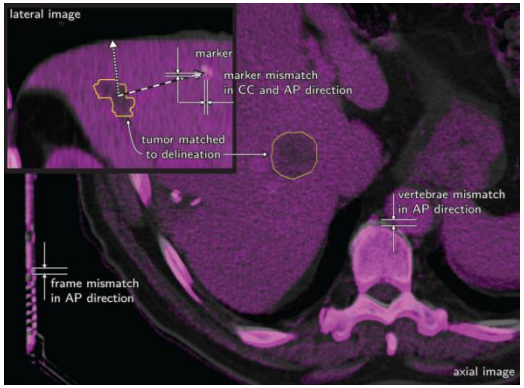


Seppenwoolde Y, Wunderink W et al. Phys. Med. Biol. **56 (2011) 5445–5468**

Erasmus MC

Liver Tumor Surrogates

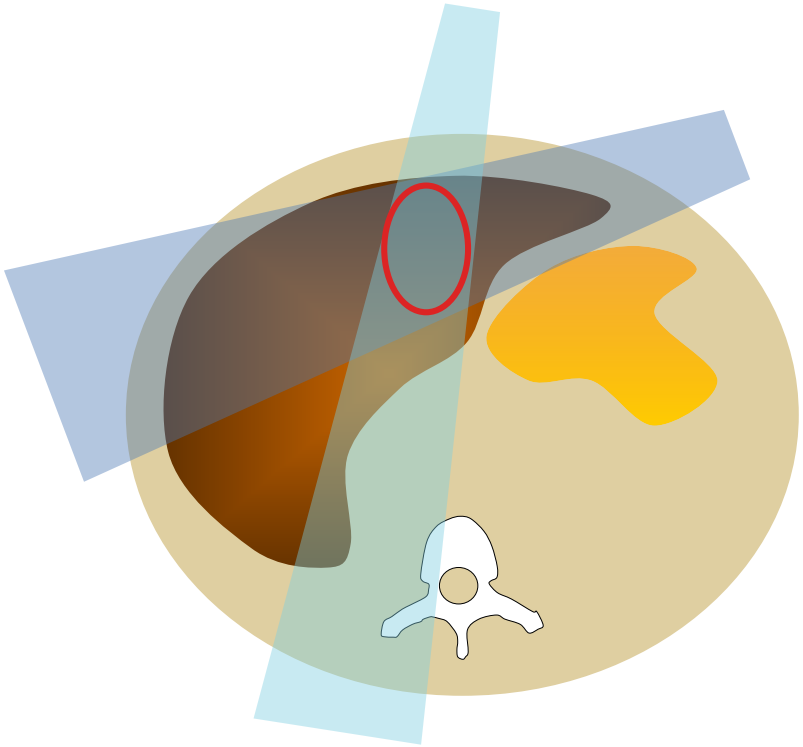




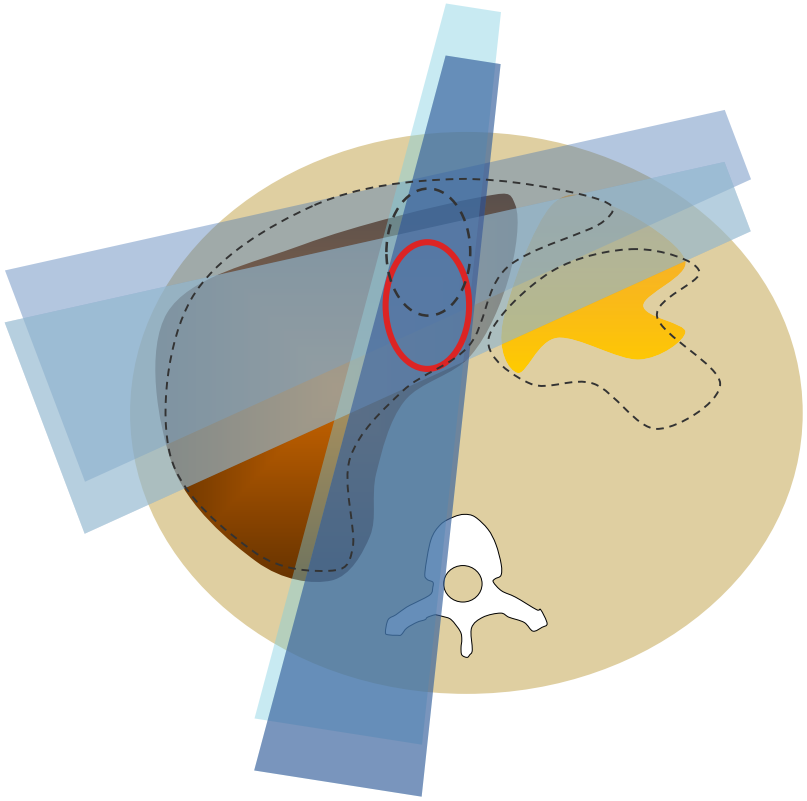
Seppenwoolde Y, Wunderink W et al. Phys. Med. Biol. **56 (2011) 5445–5468**

Erasmus MC

Online Adaptive RT for Liver?



Planning

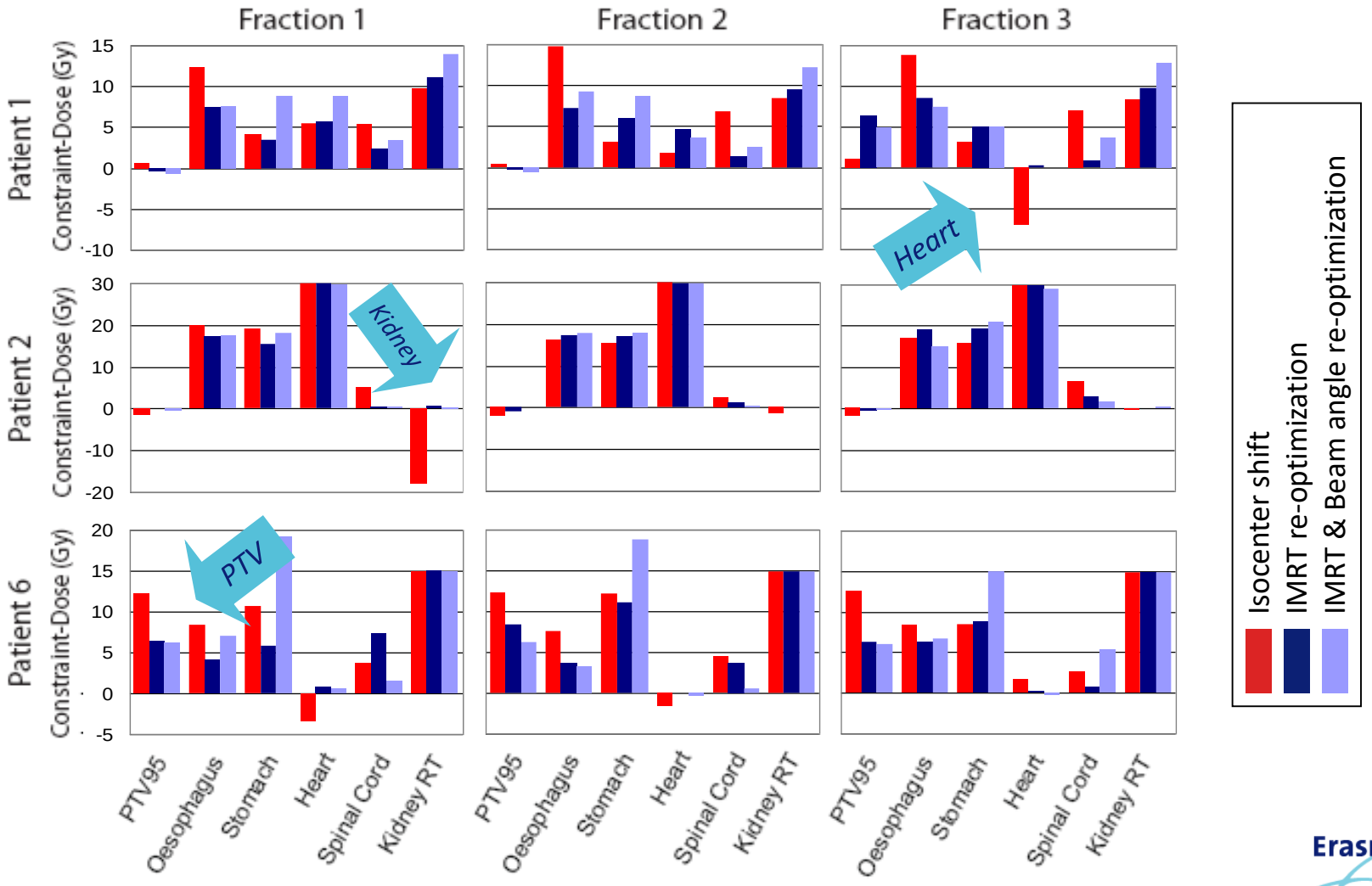


Treatment

Suzanne Leinders IJROBP 2014; slides courtesy of Seppenwoolde

Erasmus MC

Online Adaptive RT for Liver

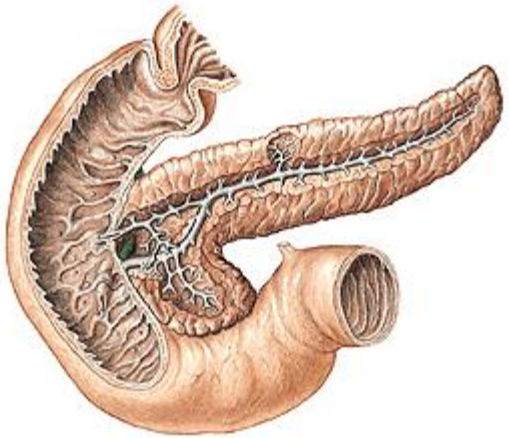


Erasmus MC

Discussion: Clinical Relevance

- **Should we measure intra-fraction motion?**
  - Yes, at planning in order to individualize the safety margin
  - And if necessary to reduce the motion amplitude with compression
- **Should we correct for intra-fraction motion?**
  - The penumbra is more sharp in liver than in lung
  - Amplitude has an effect on the margin
  - Still systematic uncertainties dominate the required margin
- **Should we correct for inter-fraction motion?**
  - **YES!**
- **Should we adapt the treatment plan?**
  - First solve issues mentioned above

Erasmus MC



PANCREAS

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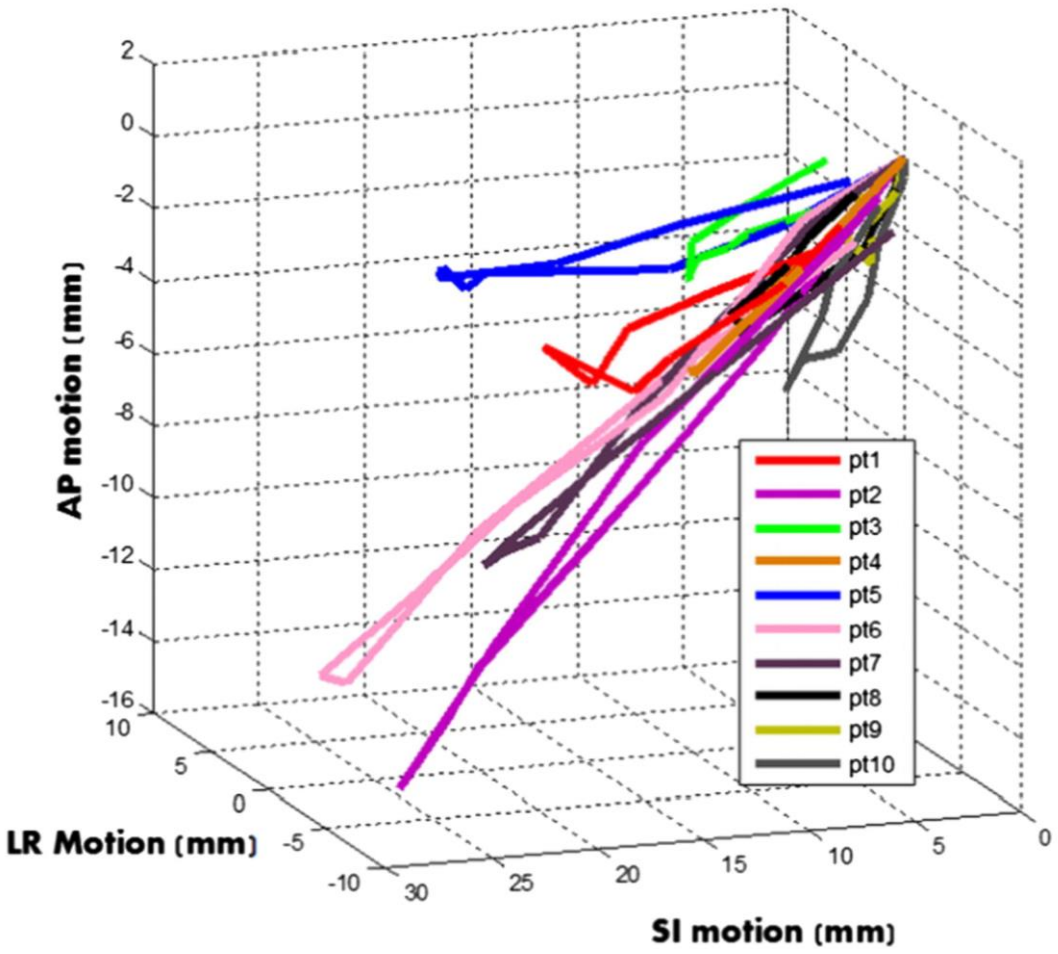
Pancreas Motion Assessed With 4D CT Scanning



Jiajia Ge at al., Int J Radiation Oncol Biol Phys, Vol. 85, No. 4, pp. 999e1005, 2013

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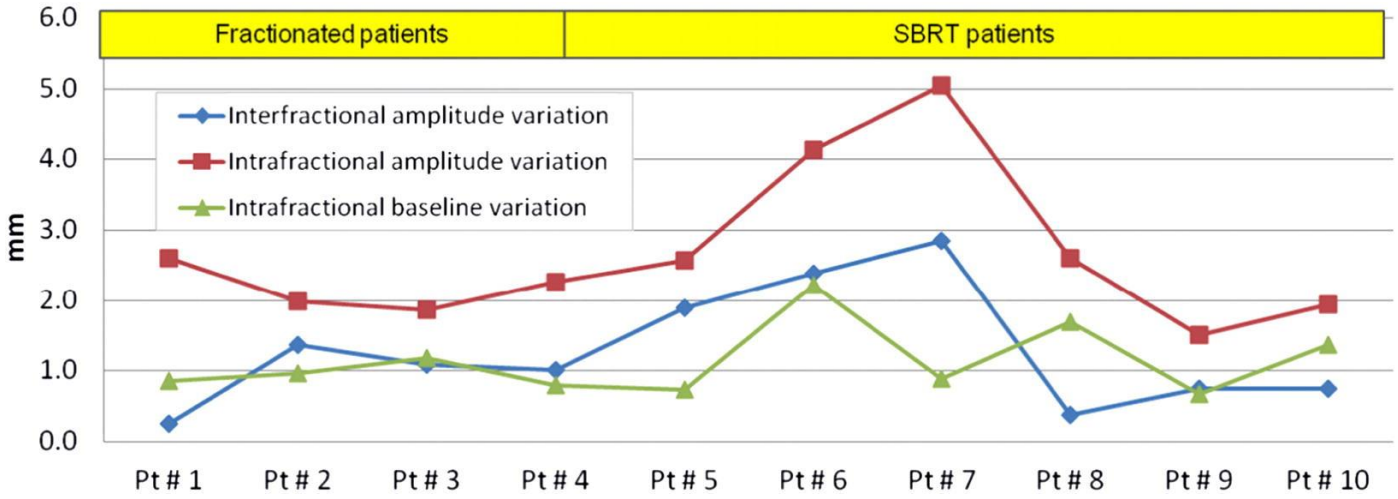
Uncertainty in Motion

- A single pre-treatment 4DCT is often not representative for the magnitude of motion during the treatment delivery
- Substantial tumor motion during breath-holding



- Jiajia Ge at al., Int J Radiation Oncol Biol Phys, Vol. 85, No. 4, pp. 999e1005, 2013
- Lens E, van der Horst A, Versteijne E, Bel A, van Tienhoven G. Considerable pancreatic tumor motion during breath-holding. Acta Oncol. 2016 Nov;55(11):1360-1368.
- Lens E, van der Horst A, Kroon PS, van Hooft JE, Dávila Fajardo R, Fockens P, van Tienhoven G, Bel A. Differences in respiratory-induced pancreatic tumor motion between 4D treatment planning CT and daily cone beam CT, measured using intratumoral fiducials. Acta Oncol. 2014 Sep;53(9):1257-64.

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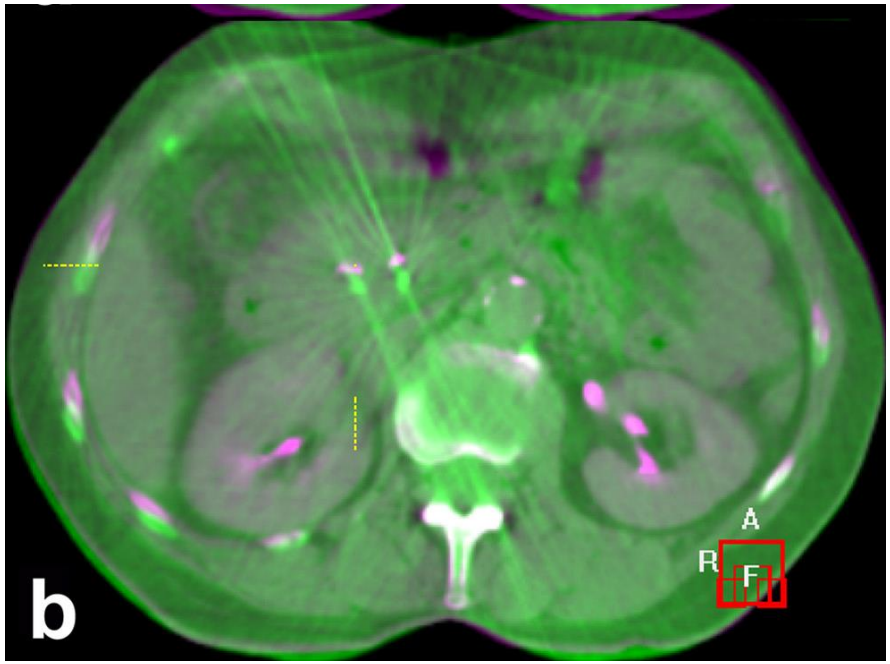
Inter-fraction Variation: Implanted Markers and CBCTs

- Systematic errors of 3.5 to 6.6 mm depending on the direction
- Random errors of 2.5 to 4.7 mm depending on the direction



Horst van der A, Int J Radiation Oncol Biol Phys, Vol. 87, No. 1, pp. 202e208, 2013

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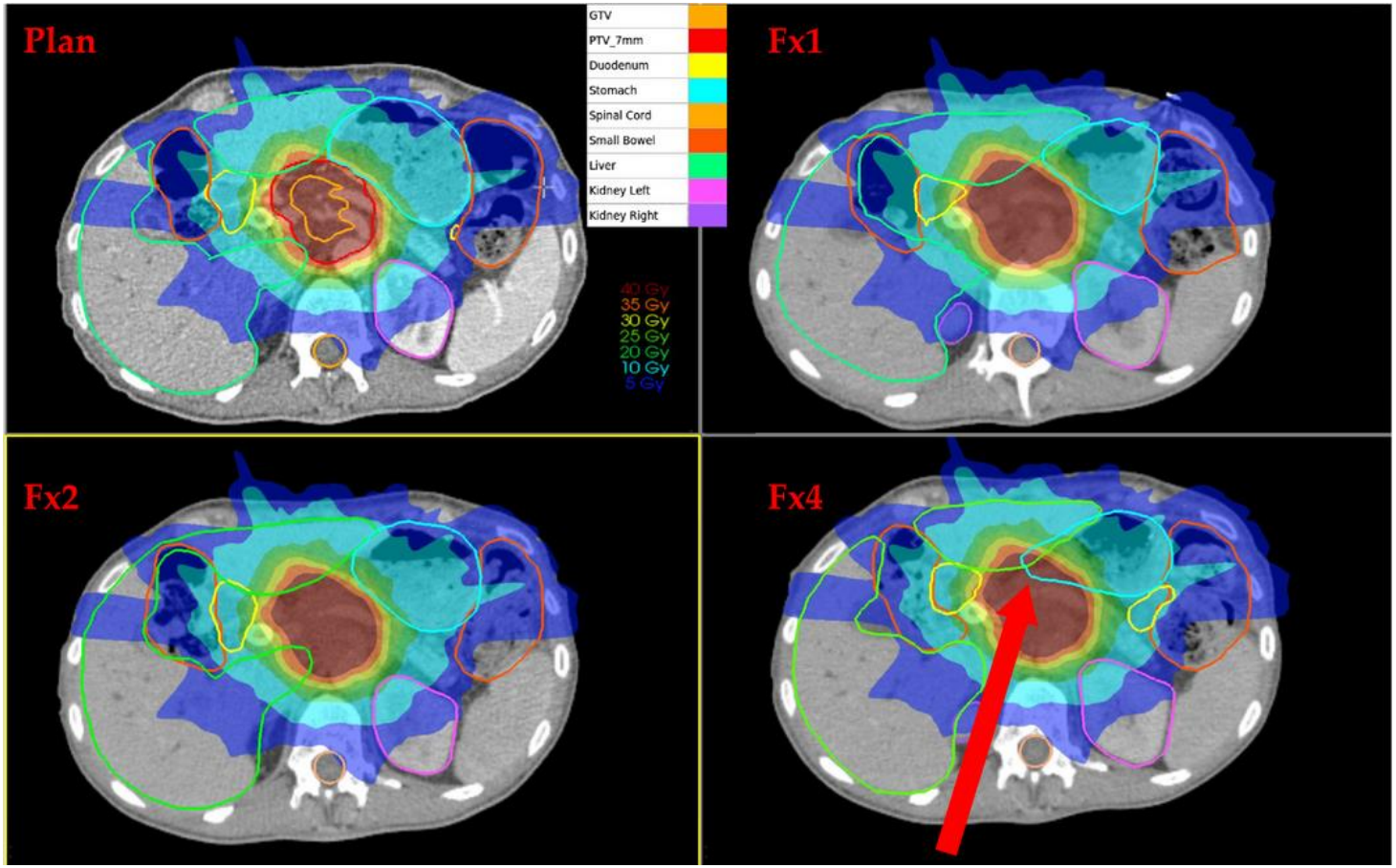
Daily Dose Variations in Organs at Risk



Papalazarou C, Klop GJ, Milder MTW, Marijnissen JPA, Gupta V, Heijmen BJM, Nuyttens JJME, Hoogeman MS. CyberKnife with integrated CT-on-rails: System description and first clinical application for pancreas SBRT. Med Phys. 2017 Jun 28.

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Discussion: Clinical Relevance

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  - And if necessary to reduce the motion amplitude with compression
- **Should we correct for intra-fraction motion?**
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- **Should we correct for inter-fraction motion?**
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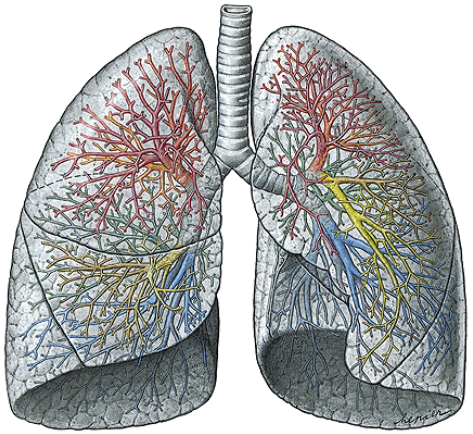
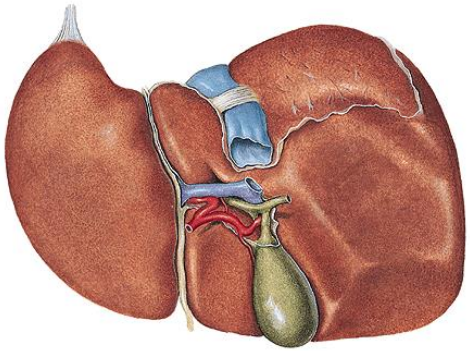
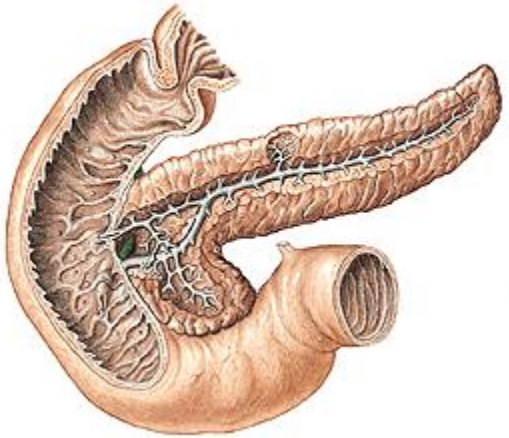
Summary







Treatment planning and evaluation

Coen Hurkmans, clinical physicist

Catharina Hospital, The Netherlands

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First a tough one..

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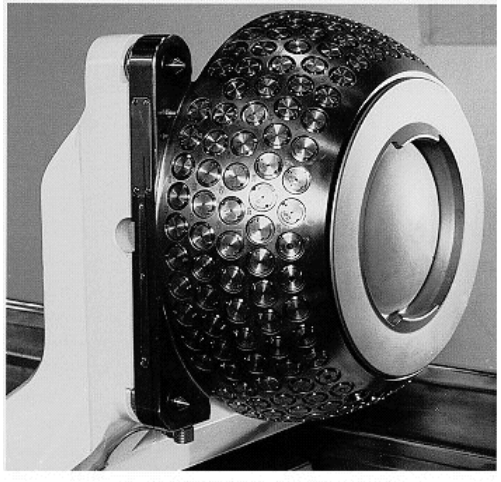
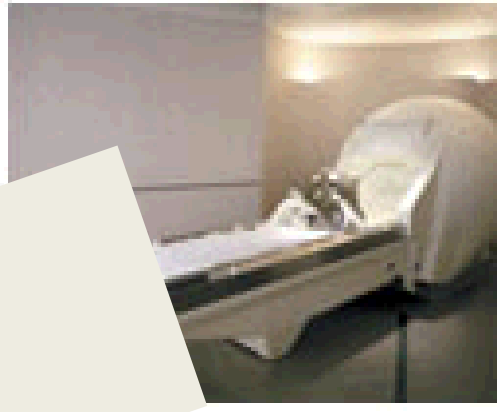
First SBRT: Gammaknife



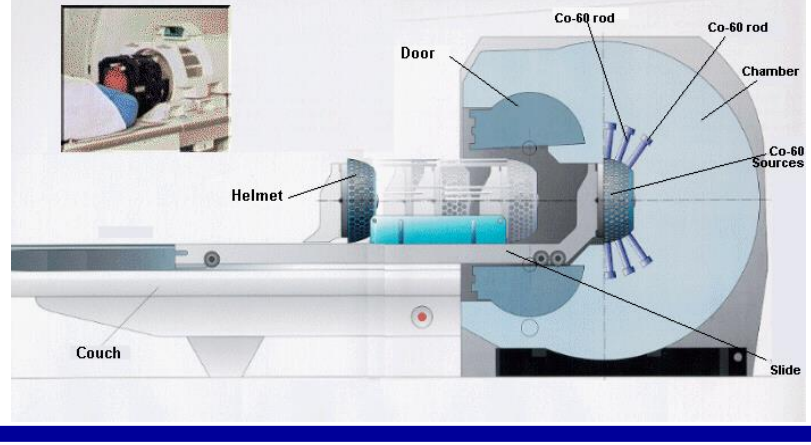
Gamma Knife Radiation Helmet



Isocenter dose = 100%

1st patient treate

Start at t ska, Stockholm, Sweden



1968 1969

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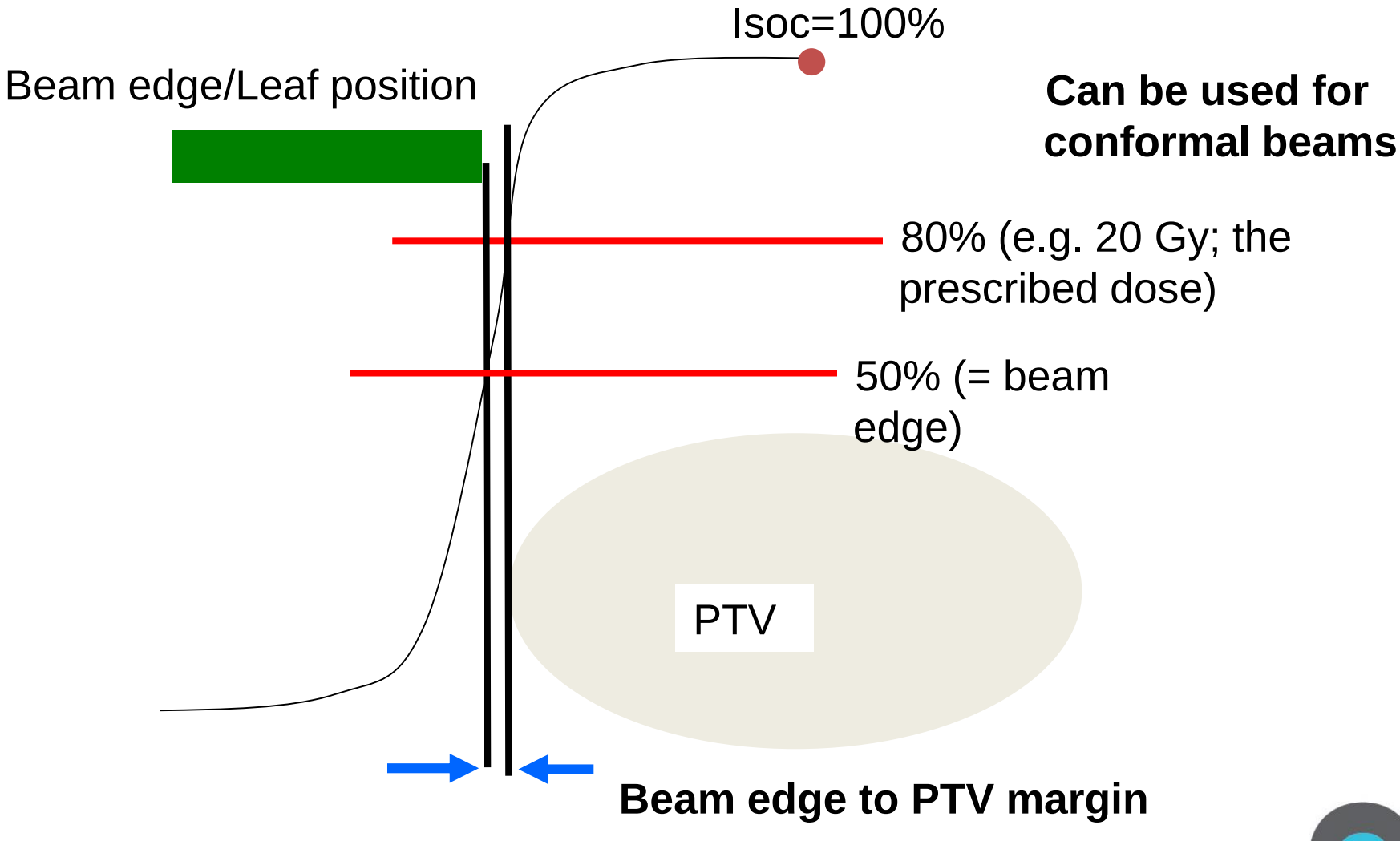
Historical dose prescription: on the xx% isodose



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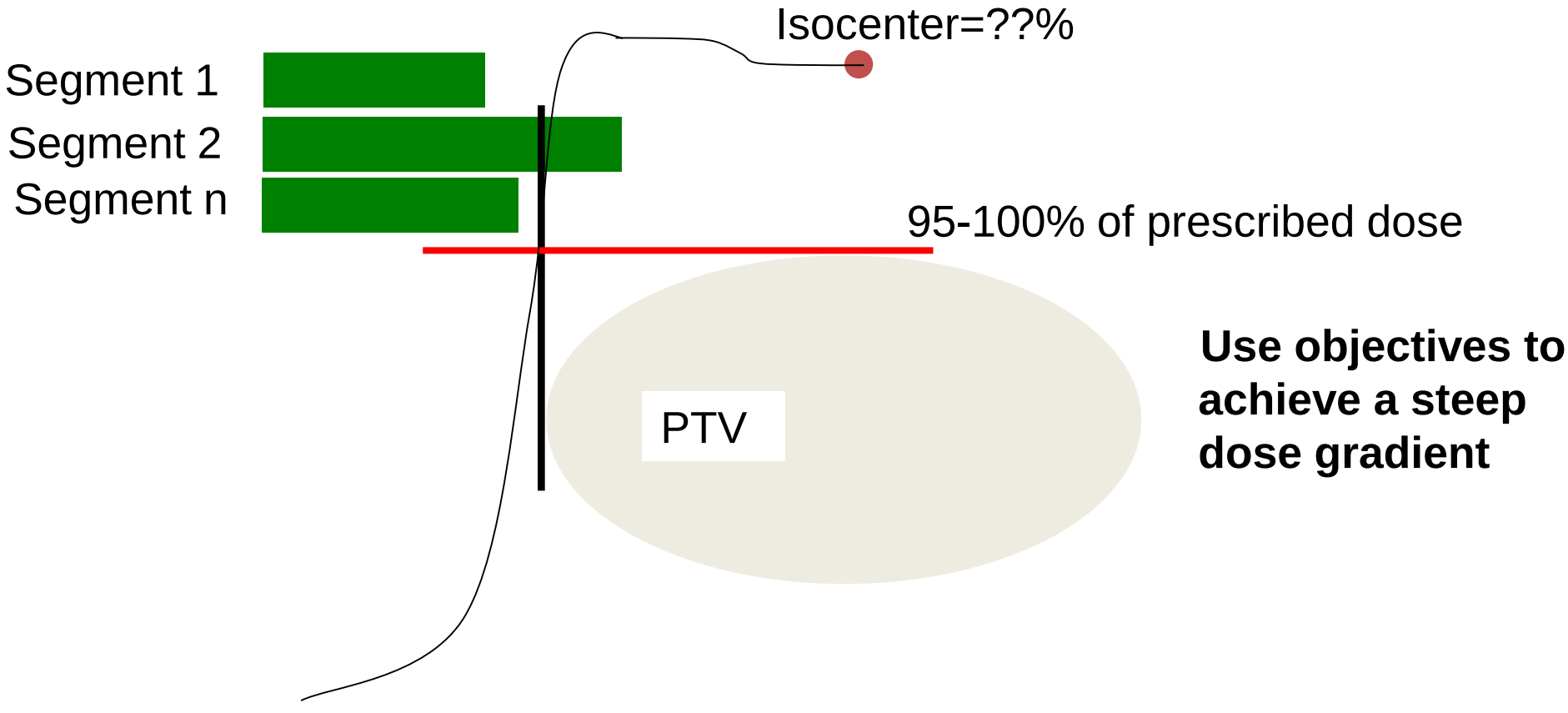
Dose prescription beyond conformal:ICRU



Use objectives to achieve a steep dose gradient

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Historical vs ICRU vs SBRT

- **Historical (on the xx% isodose)**
  - High central dose is ok
  - Maximal dose gradient outside PTV
  - Plan optimization through variation of beam edge to PTV distance
- **ICRU 50 and 62 and 83**
  - Homogeneous dose in PTV; high dose **NOT** ok
- **SBRT**
  - High central dose is ok
  - Maximal dose gradient outside PTV
  - Plan optimization through use of objectives
  - IMRT/VMAT/FFF etc possible

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Be careful clinicians – physicists don't know what they do!

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Be careful physicists – clinicians also don’t know!

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Harmonisation of dose prescription and dose reporting nomenclature is needed!
Dose in relation to volume

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ICRU 91 2017: prescribe

- The planning aims, also known as the treatment goals, must be described and defined.
- Usually, the planning aims are specified by the treating physician.
- An optimization process of the (complex) beam delivery.
- **A complete set of finally accepted values, which becomes the "prescription"** and, together with the required "technical data" represents the "accepted treatment plan."

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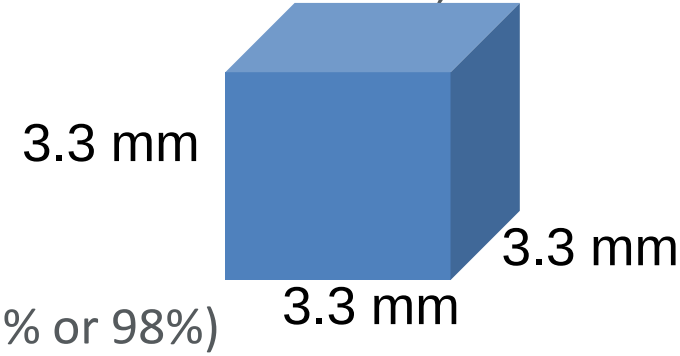
ICRU 91 2017: reporting

- PTV median absorbed dose, D50%
- Dnear-max (and near-min) For PTV larger than or equal to 2 cm^3, the volume nearmax represents 2 % of the PTV, as recommended in ICRU Report 83 (D2%). For PTV V of less than 2 cm^3, near-max is an absolute volume of 35mm^3, in which case *D*35mm^3 is reported.



- Both CTV and PTV DVH
- No recommendation for Dv for prescription (e.g. 95% or 98%)
- OAR near min and max, and recommend to report always 2 levels. If it is not clearly a parallel or serial structure than 3 levels should be reported
- Paddick CI, also to GTV
- For brain, also Dose gradient GI may be considered = PIVhalf/PIV

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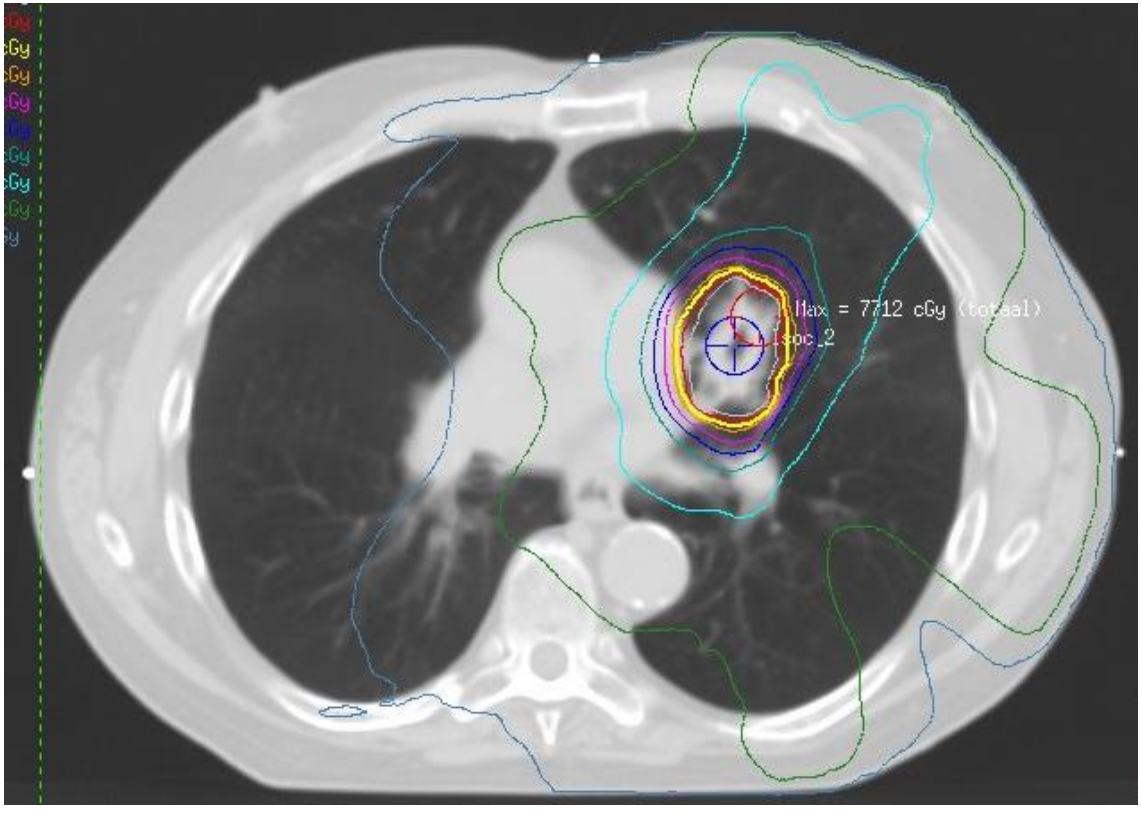
Dose in relation to volume: Target



EORTC Lungtech trial guidelines:

- D95% of PTV ≥ 60 Gy AND
- D99% of PTV ≥ 54 Gy

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Dose in relation to volume: OARs

OAR	αβ in Gy	D_{max} in Gy	EqD2 in Gy	Acceptable variation in Gy	Unacceptable variation in Gy	Unacceptable variation EqD2 in Gy
Trachea/ MainBronchus	3	8*5.5= 44	74.8	<8*5.81=46.68	≥8*5.81=46.68	≥81.9
Heart*	3	**8*5.5= 44**	**74.8**	**<8*6=48**	**≥8*6=48**	**≥86.4**
GreatVessels*	3	**8*5.5= 44**	**74.8**	**<8*6=48**	**≥8*6=48**	**≥86.4**
Esophagus	3	8*5 = 40	64	<8*5.44=43.52	≥8*5.44=43.52	≥73.6
SpinalCord&	2	8*4= 32	48		>8*4=32	≥48
BrachialPlexus&	3	8*4.75=38	58.9	<8*5.17=41.36	≥8*5.17=41.36	≥ 67.7
External-PTV &	3	8*7.5= 60	126	<8*7.785=62.28	≥8*7.785=62.28	≥134.2
Lungs-CTV*	3	**V20Gy<6%**		**V20<10%**	**V20Gy≥10%**	
ChestWall§	3	**8*8.25=66**	**148.5**		**≥8*9=72**	**≥172.8**

& for <0.5 cc

§ no restrictions are provided but recording of DVH data for toxicity evaluation is required

Catharina Cancer Centre guidelines

Adebahr S et al. BJR 2015, EORTC Lungtech trial

* Following Mangona, IJROBP 91(1) p124-132 2015, William Beaumont Hospital

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Dose in relation to volume: OARs

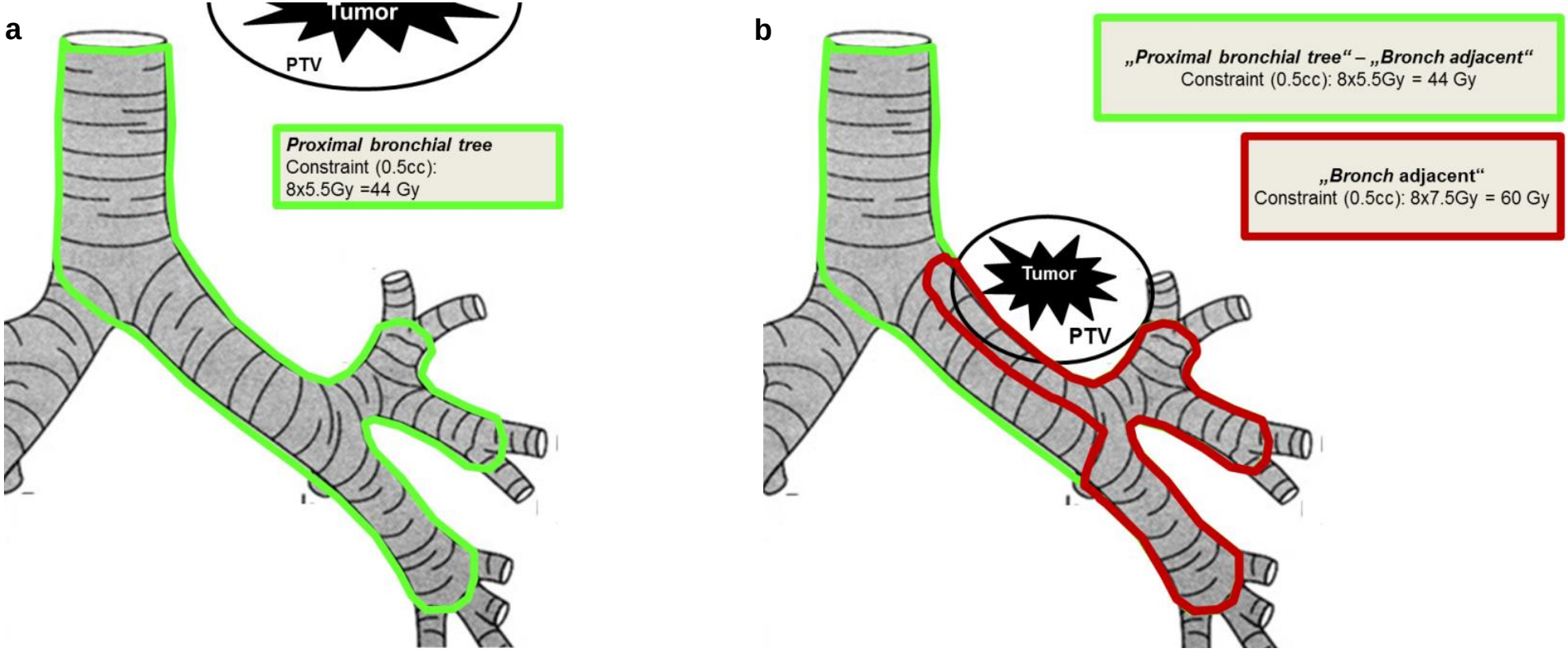

Figure: Dose constraints for the proximal bronchial tree
a) The general dose constraint for the whole structure “proxBT” (green) is 44Gy (<0.5cc) in 8 fractions. For PTVs near or abutting the main bronchus (b) a subvolume “Bronch adjacent” has to be generated (red). The dose constraint for this volume (<0.5cc) is 60Gy/8fractions, while the constraint for the rest of the “proxBT” (green) remains 44Gy/8fractions.

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Dose in relation to volume: OARs

TABLE 2. Dosimetric Characteristics of Organs at Risk

	Dmax (Gy)	Dmax 0.5 ml (Gy)	Dmax 1.0 ml (Gy)	V25 (ml)	V50 (ml) (*n*)
	Median (Range)	Median (Range)	Median (Range)	Median (Range)	Median (Range)
Aorta (*n* = 72)	44.7 (25.9–77.8)	43.8 (19.9–66.0)	42.5 (18.2–60.6)	9.90 (0.01–53.10)	2.48 (0.01–8.31) (*n* = 24)
Vena cava (*n* = 33)	41.0 (25.9–60.7)	32.0 (21.6–54.1)	28.0 (18.1–52.1)	1.26 (0.02–14.01)	0.50 (0.01–1.54) (*n* = 8)
Pulmonary artery (*n* = 73)					
No toxicity (*n* = 70)	42.2 (25.5–64.2)	30.6 (16.5–60.1)	25.6 (12.3–56.0)	1.35 (0.01–17.62)	0.42 (0.01–1.79) (*n* = 13)
Hemoptysis grade 5 (*n* = 2)	60.2, 62.4	59.2, 61.3	58.4, 60.5	5.32, 9.79	3.58, 3.77
Hemoptysis grade 3 (*n* = 1)	53.2	39.5	30.3	1.34	0.05
Pulmonary vein (*n* = 60)	41.5 (26.4–63.3)	29.1 (15.8–53.8)	23.4 (12.2–43.7)	0.80 (0.01–3.76)	0.07 (0.01–0.62) (*n* = 13)
Bronchus (*n* = 55)					
No toxicity (*n* = 50)	39.4 (26.1–62.2)	27.4 (16.4–59.2)	23.2 (12.9–50.4)	0.83 (0.01–7.09)	0.13 (0.01–1.04) (*n* = 8)
Hemoptysis grade 5 (*n* = 2)	58.0, 61.4	54.4, 59.6	52.0. 58.5	3.97, 6.41	1.37, 2.45
Hemoptysis grade 3 (*n* = 1)	39.2	24.9	21.8	0.49	NA
Obstructive pneumonia (*n* = 2)	49.2, 49.8	41.5, 47.7	36.3, 46.3	2.37, 3.99	NA
Trachea (*n* = 13)	33.3 (25.3–58.8)	28.7 (19.7–49.8)	26.4 (17.9–45.4)	1.46 (0.01–7.94)	0.476 (*n* = 1)
Heart (*n* = 69)	45.3 (25.9–72.8)	41.1 (22.7–65.8)	37.8 (19.4–62.1)	8.48 (0.05–59.16)	0.94 (0.01–7.55) (*n* = 2)
Esophagus (*n* = 23)	28.4 (25.6–40.8)	21.7 (15.7–32.0)	19.5 (13.3–29.9)	0.06 (0.01–3.16)	NA

Dmax = maximum dose; DXml = minimum doses delivered to X ml of the most irradiated OAR volumes; VX = absolute volumes receiving >X Gy; NA = not available; OAR, organs at risk.

n.b. 1 ml = 1 cm^3 = 1000 mm^3 !!

Nishimura et al. (Ofuna Chuo Hospital Japan) JTO 9-9 p 1370 2014

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Chest wall /Ribs dose effects

TABLE 2. Chest Wall Pain Grading System

Grade	Definition According to CTCAE	Corresponding Pain Medication
1	Mild pain	No pain medication needed
2	Moderate pain, limiting instrumental daily activities	Use of nonopioid pain medication
3	Severe pain, limiting self-care	Use of opioids

No grades 4–5 are defined in CTCAE version 4.03.
CTCAE, Common Terminology Criteria for Adverse Events.

Bongers et al. JTO 2011 6(12):2052-7

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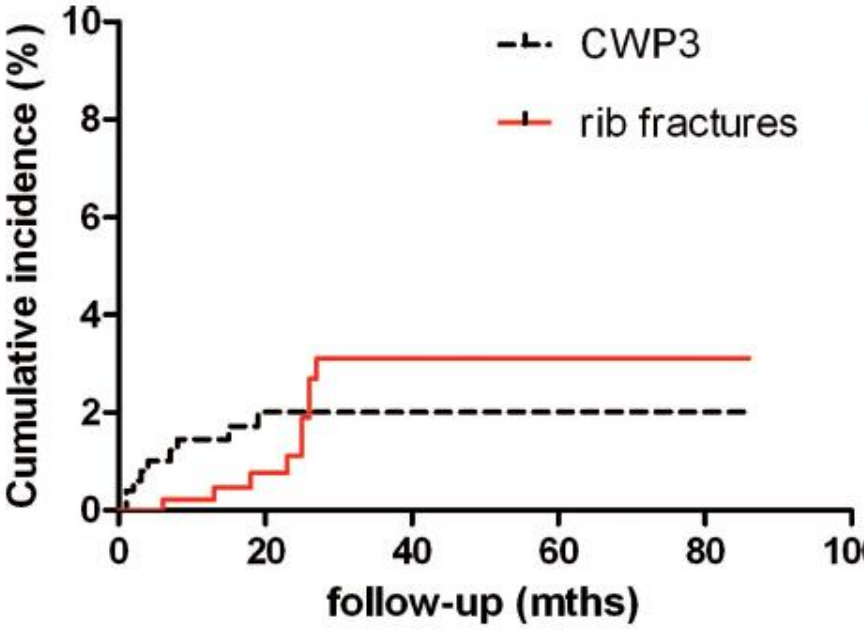
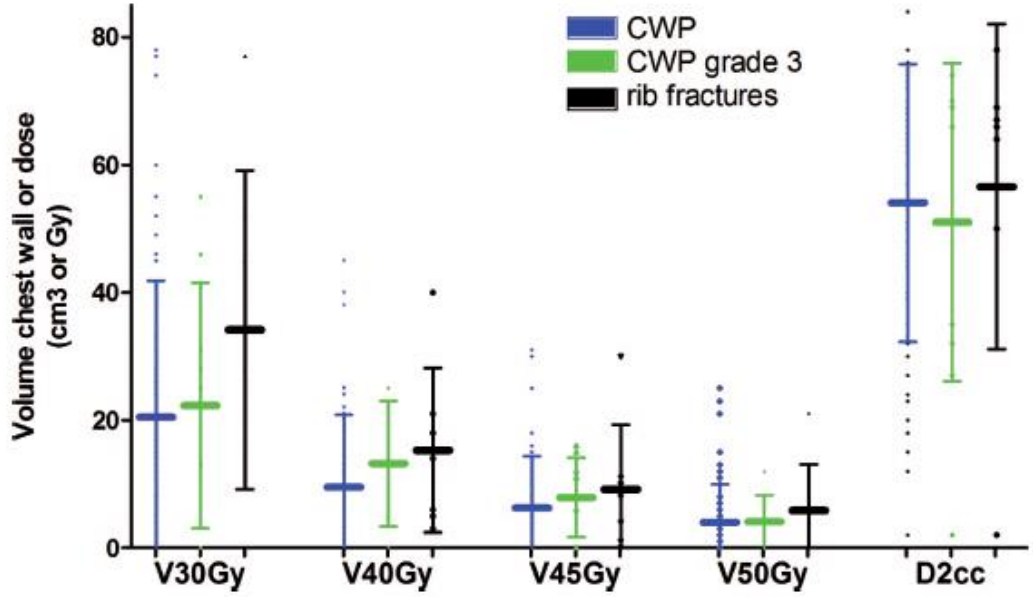
Chest wall /Ribs dose effects





Bongers et al. JTO 2011 6(12):2052-7

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Chest wall /Ribs dose effects

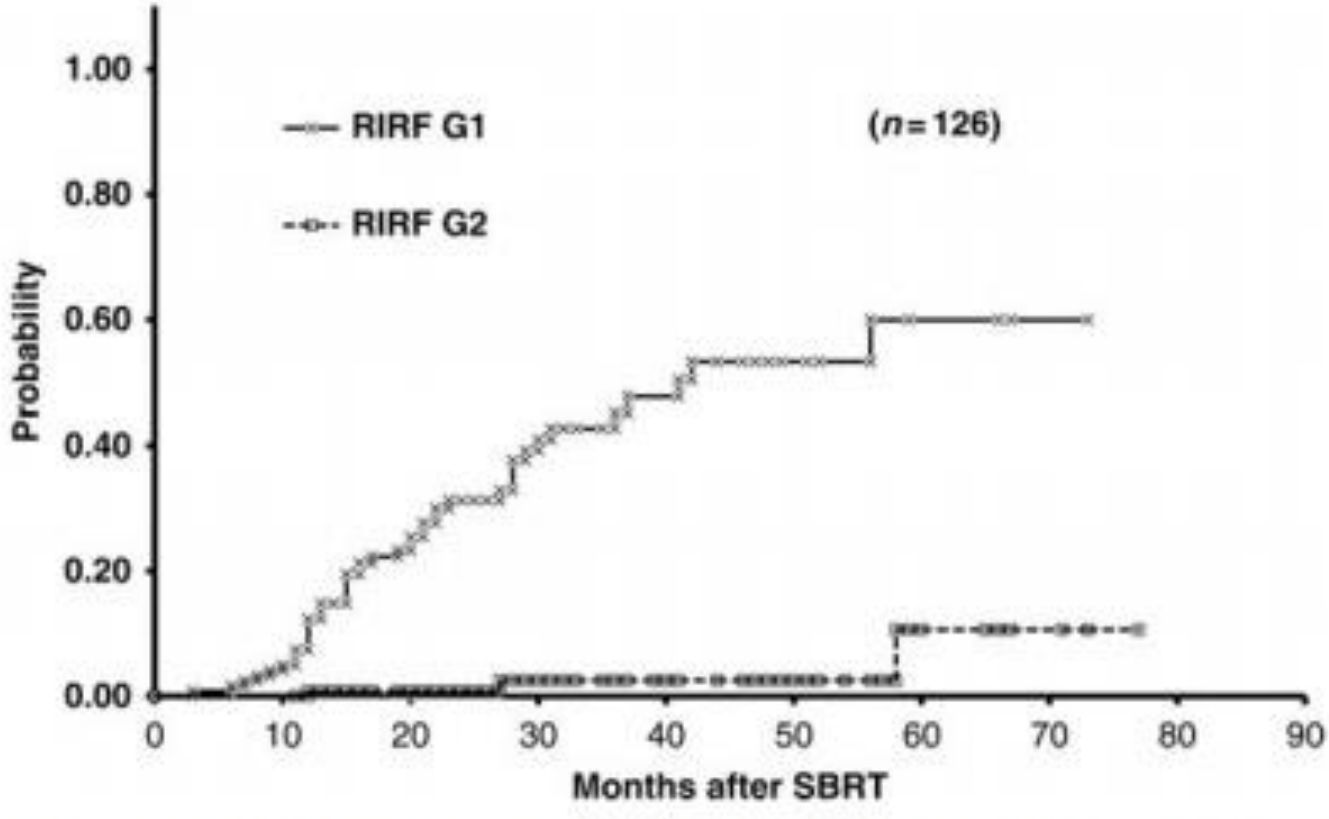

Fig. 2. Cumulative probability of RIRFs after SBRT by symptom grade (NCI–CTCAE). The 3-year cumulative probabilities were 45% and 3% for Grade 1 and 2 RIRFs, respectively.

Miura et al. J rad. Research 2015 (56):332

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Chest wall /Ribs dose effects

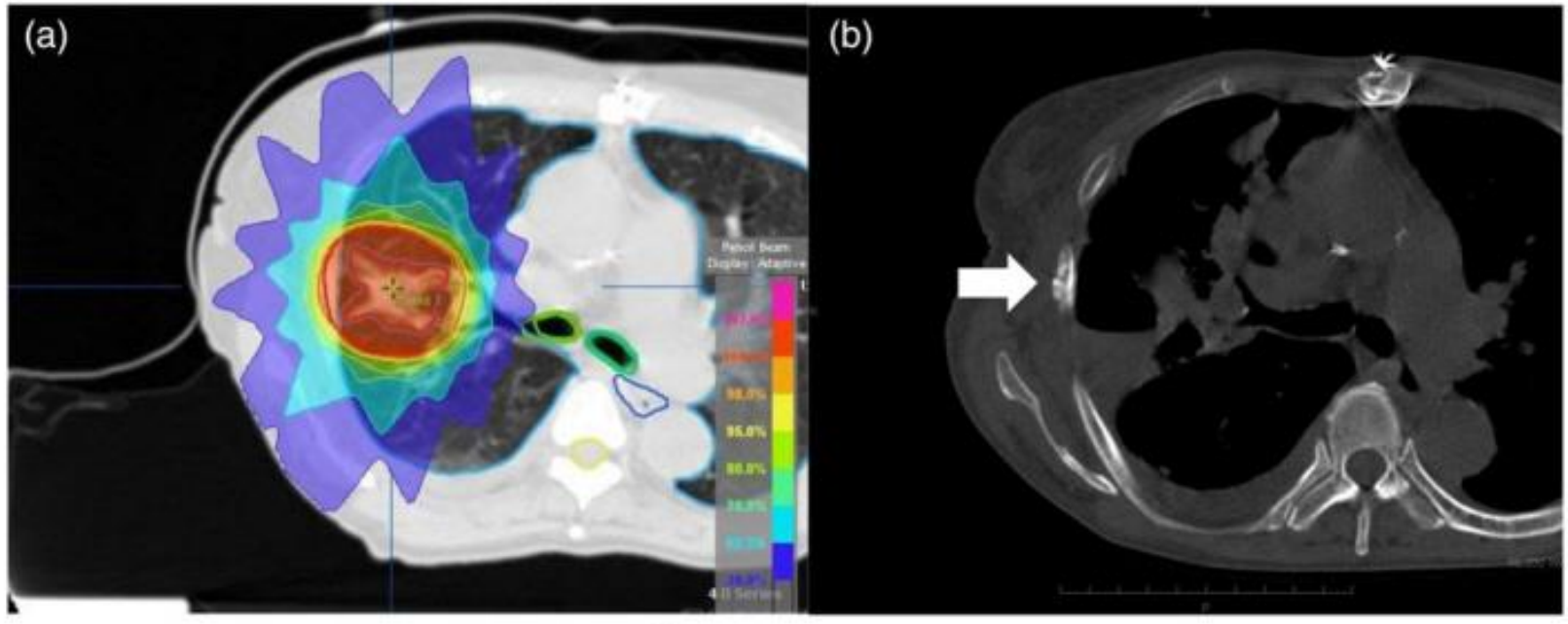

Fig. 1. (**a**) Dose distribution image shows the D (0.5 cm^3) prescribed dose to the rib as 49.6 Gy, with a BED3 of 254.6 Gy. (**b**) Bone window image shows a rib fracture (white arrow) 21 months after completion of SBRT.

Multivariate analysis showed that tumor location was a statistically significant risk factor for the development of Grade 1 RIRFs. Of the 77 RIRFs, 71 (92%) developed in the true ribs (ribs 1–7), and the remaining six developed in the false ribs (ribs 8–12).
The D(0.5 cm3) BED3 associated with 10% and 50% probabilities of RIRF were 55 and 210 Gy to the true ribs and 240 and 260 Gy to the false ribs. We conclude that RIRFs develop more frequently in true ribs than in false ribs.

Miura et al. J rad. Research 2015 (56):332

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Treatment planning

- Irradiation technique:
  - ITV/ MidVent / Gating / Tracking
- Planning technique
  - number of beams / coplanar/non-coplanar
  - Vmat, rapidarc
  - FFF / Treatment time

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SBRT lung in The Netherlands 2008

Institute	CT, Period adapted?	Plan	Algorithm	Beams	Treat time (min)
1	10, time, j	Mid-vent	B	9, coplanair	20
2	10, time, ?	MIP	B	3-5 arcs	15
3	8, ampl., n	Mid-vent	A	8-12 non-co	15-20
4	6, ampl., j	MIP	A	Arcs	15
5	7 x 3D	MIP	A	7-10 non-co	30
6	10, time, j	Mid-vent	B	12-17 non-co	20

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SBRT lung in The Netherlands 2013

Institute	CT	Plan	Beams	time (min)
1	10, time, j	Mid-vent	2 (half) arcs	<5
2	10, time, j	ITV	2 arcs	2.5
3	10, time, ?	ITV	2 arcs	15
4	6, ampl., n	ITV	3-5 arcs	20-25 (slot)
5	7 3D-CTs	ITV	7 co-planair	10
6	10, time, j	Mid-vent	2 arcs	5
7	10, time, ?	ITV	6-8, coplanair	30 (slot)
8	10, time	ITV	10-12 non-co	50 (slot)
9	5, ampl., j	ITV	2 Arcs	<10
10	10, amp,?	ITV	2 arcs	10-15 (slot)
11	10, time, ?	Mid-vent	1 arc	10-20 (slot)
12	?	ITV	2 arcs	10
13	10, time, j	ITV	1 arc	5
14	?	?	Tomo	?
15	8, ampl, n	ITV	2 (half) arcs	10-15
16	8, time, j	GTVexhale	cyberknife	60

* Might not be complete

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SBRT central lung lesions in 2017

Institution	# beams/type	MU	TPS	Linac	leave width (mm)
1	1/tomo	13.5 Min.	TOMO	Tomotherapy HD	
2	2/full arcs	1803	ARIA 11.0.47	Varian 2100C/D	5
3	14/static	1016	Iplan 4.5.3	Varian Novalis Tx	2.5
4	2/full arcs	1912	ARIA 13.5.37	Varian TrueBeam	2.5
5	3/230 degree arcs	2930	ARIA 13.5.37	Varian 2100C/D	5
6	11/static	833	Pinnacle 9.8	Elekta Agility	5
7	1/210 degree arc	1049	Iplan 4.5.4	Varian Truebeam STx Novalis	2.5
8	1/full arc	1160	Hyperion 2.4.4	Elekta	
9	2/full arcs	2669	ARIA 11.0.42	Varian TrueBeam EDGE	2.5
10	1/full arc	1990	Monaco 5.10.02	Elekta Agility	5
11	1/full arc	2336	Monaco 5.00.04	Elekta Synergy	5
12	3/arc	1907	ARIA 11.0.47	Varian Novalis TB	2.5
13	13/static	1155	Iplan 4.5.1	Varian Novalis	2.5
14	2/200 degree arcs	2584	ARIA 11.0.47	Varian	
15	2/full arcs	1651	ARIA 10.0.42	Varian 2100C/D	5

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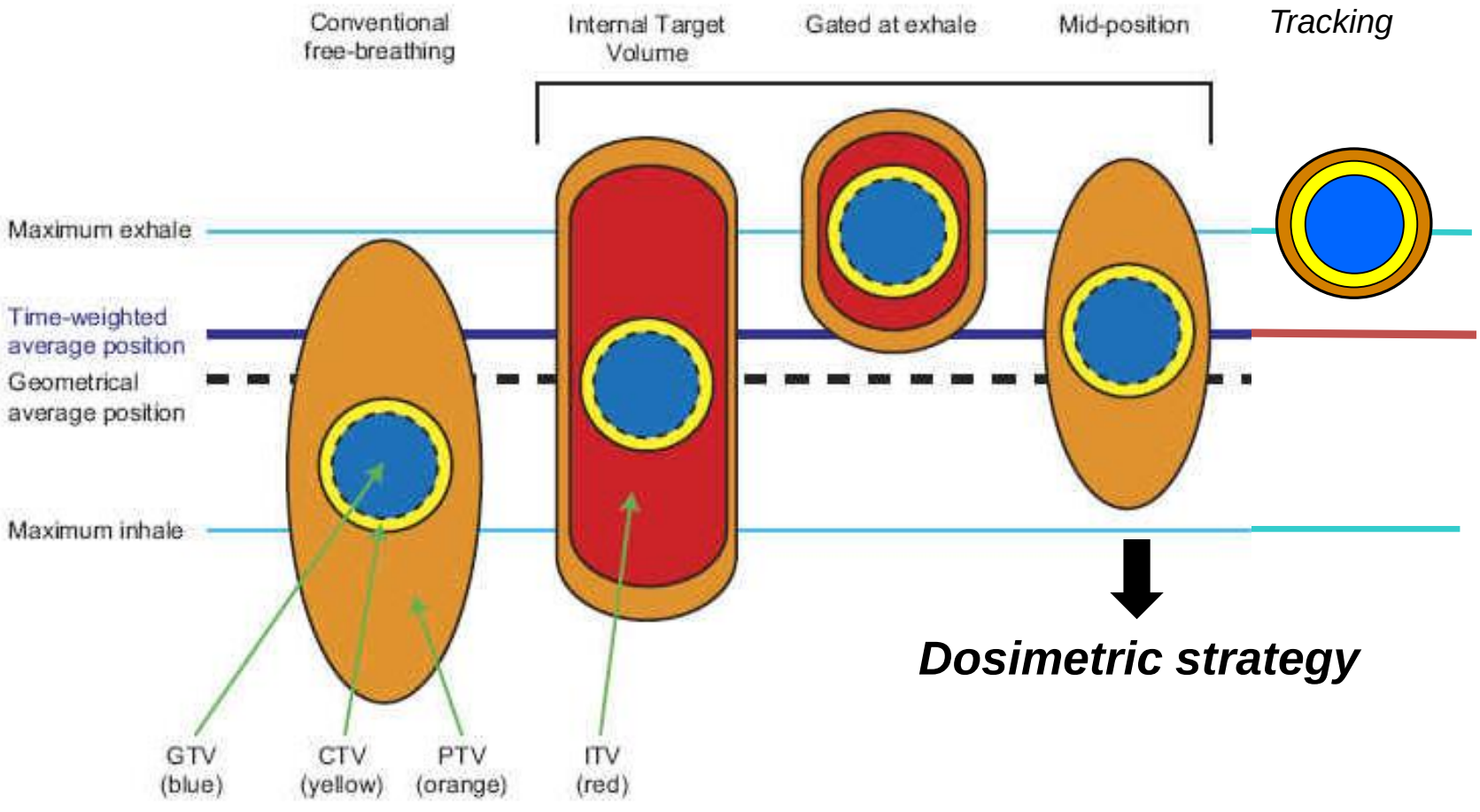
Technique flavours



Wolthaus, IJROBP 70 (2008) p1229

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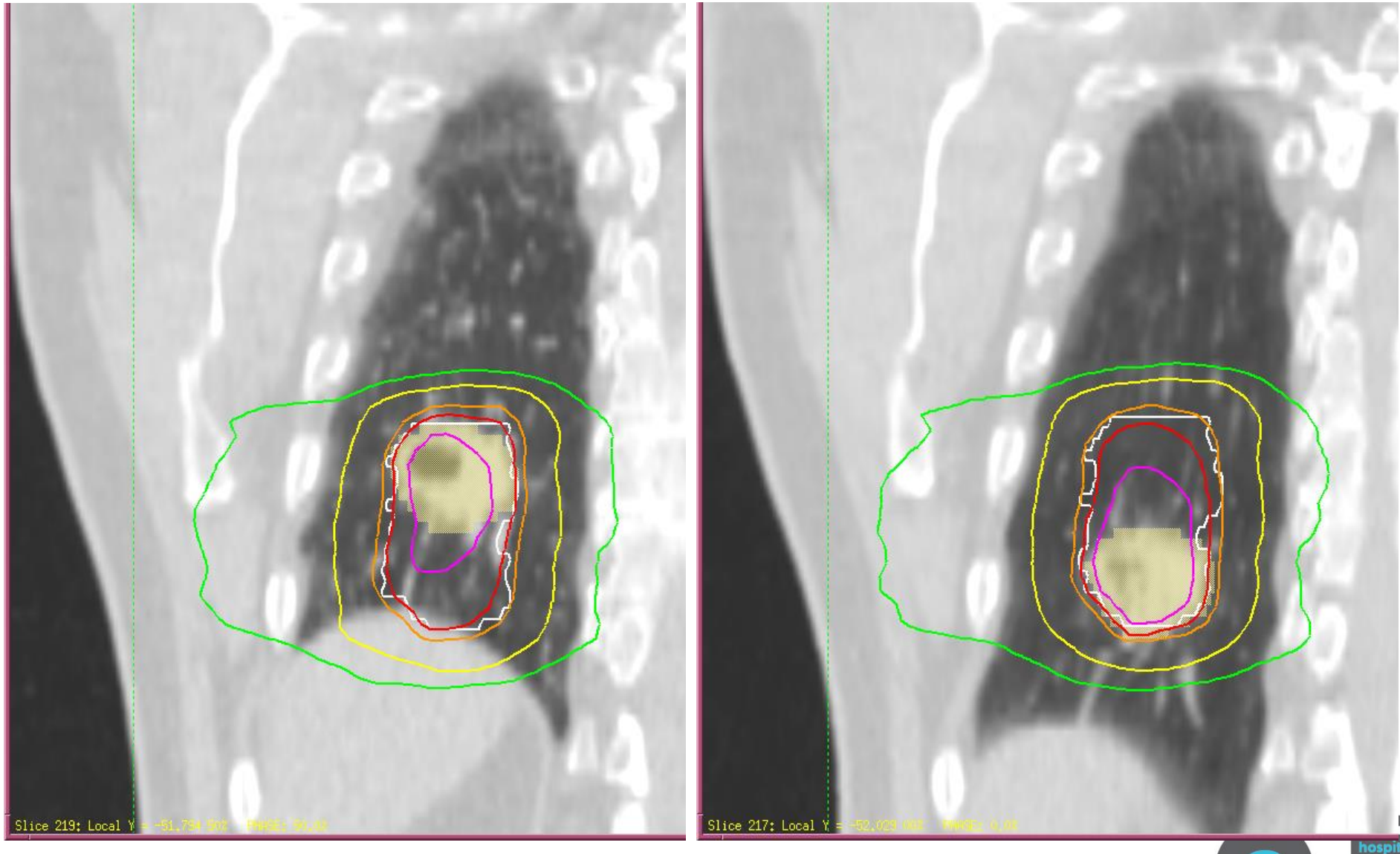
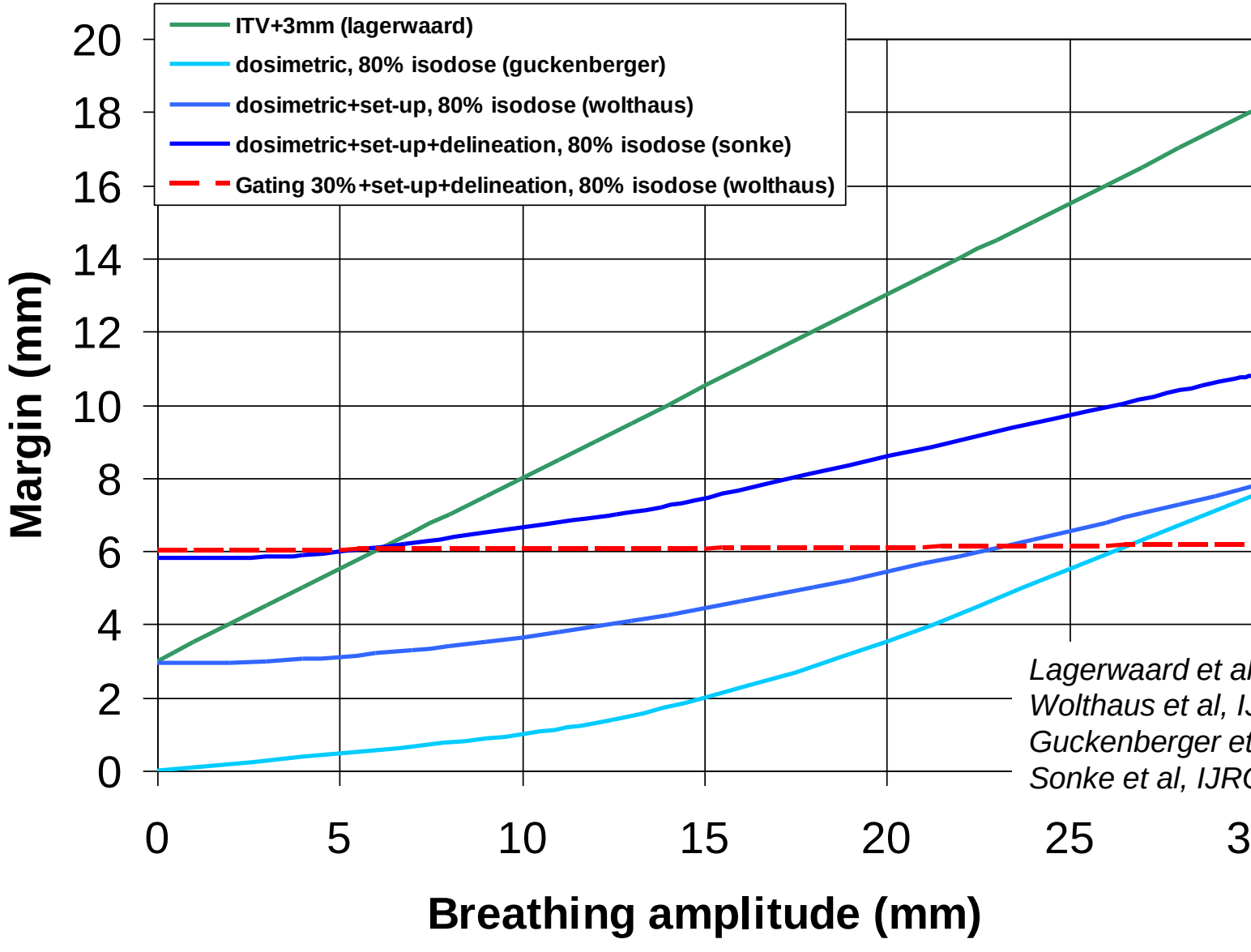
Why it works best in lung



Admiraal et al, Radiother Oncol 86 (2008) 55

Breathing margins: margin recipe



Lagerwaard et al, IJROBP (2008) p685
Wolthaus et al, IJROBP (2008) p1229
Guckenberger et al, R&O 91(2009) p288
Sonke et al, IJROBP (2009) p567

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ITV vs Gating

reduced lung dose

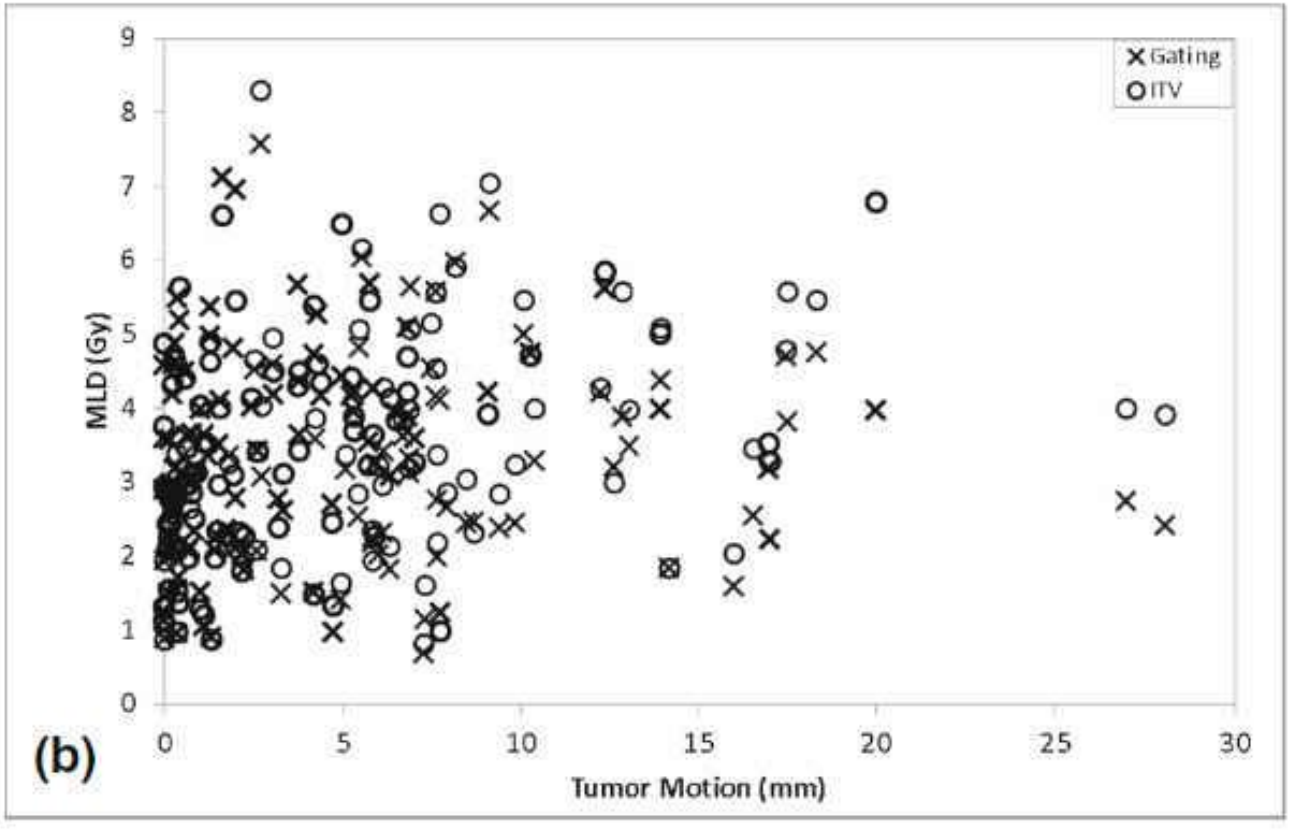

Fig. 3 MLD vs. motion for 3 × 18 Gy regimen. Plot of difference in MLD between gating and ITV-based margins versus tumor motion for the **a** 3 × 18 Gy fractionation regimen. Data organized by lower

- 150 consecutive patients
- 5 mm PTV margin
- No clinically significant reduction
- Small benefits for motion > 2 cm

Kim et al Rad Oncol 11 2016

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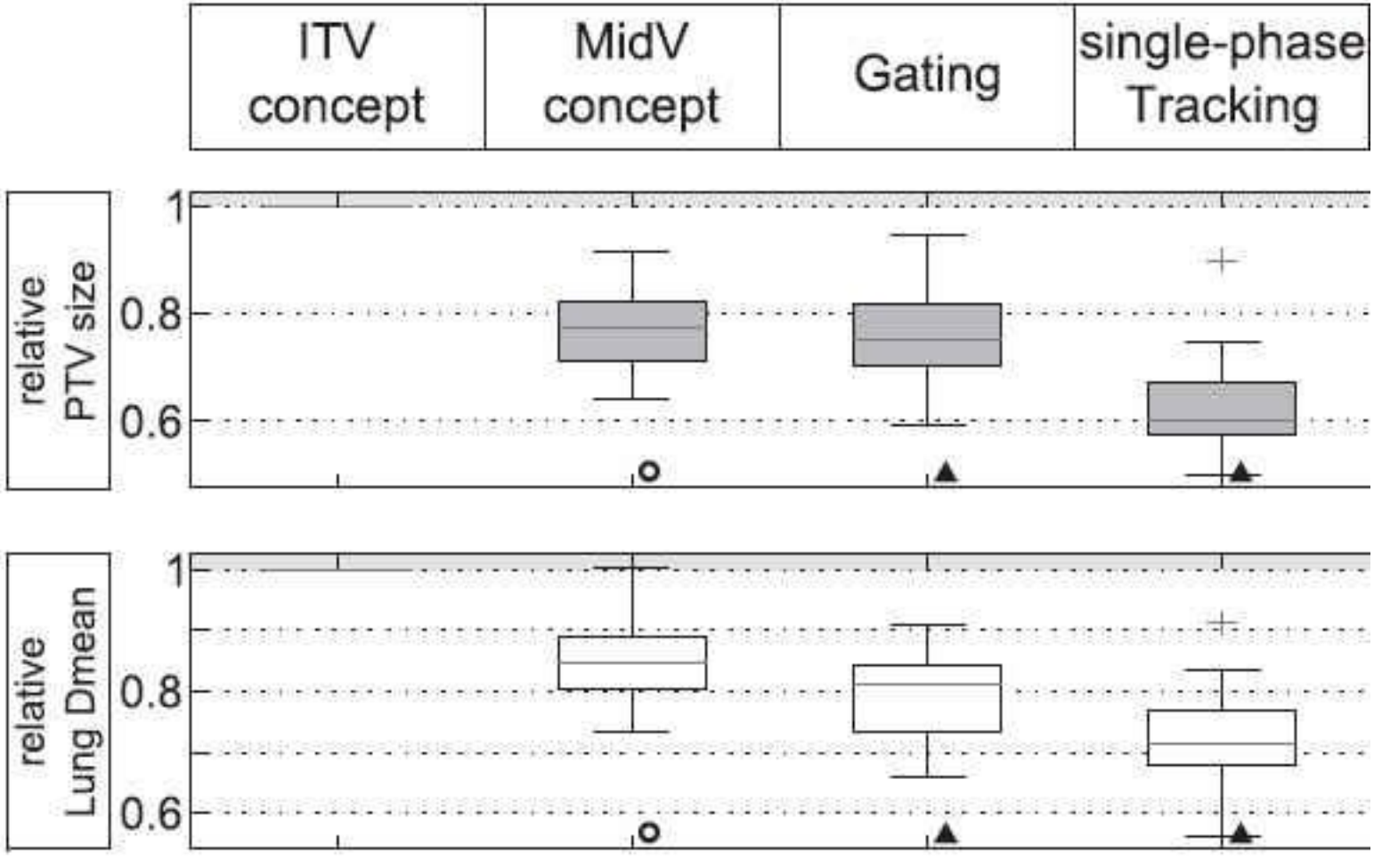
ITV vs MidV vs Gating vs Tracking

reduced ipsilateral lung dose

- 20 selected patients
- Motion 5-29 mm, median 12.5 mm



Ehrbar et al R&O 124 p80 2017

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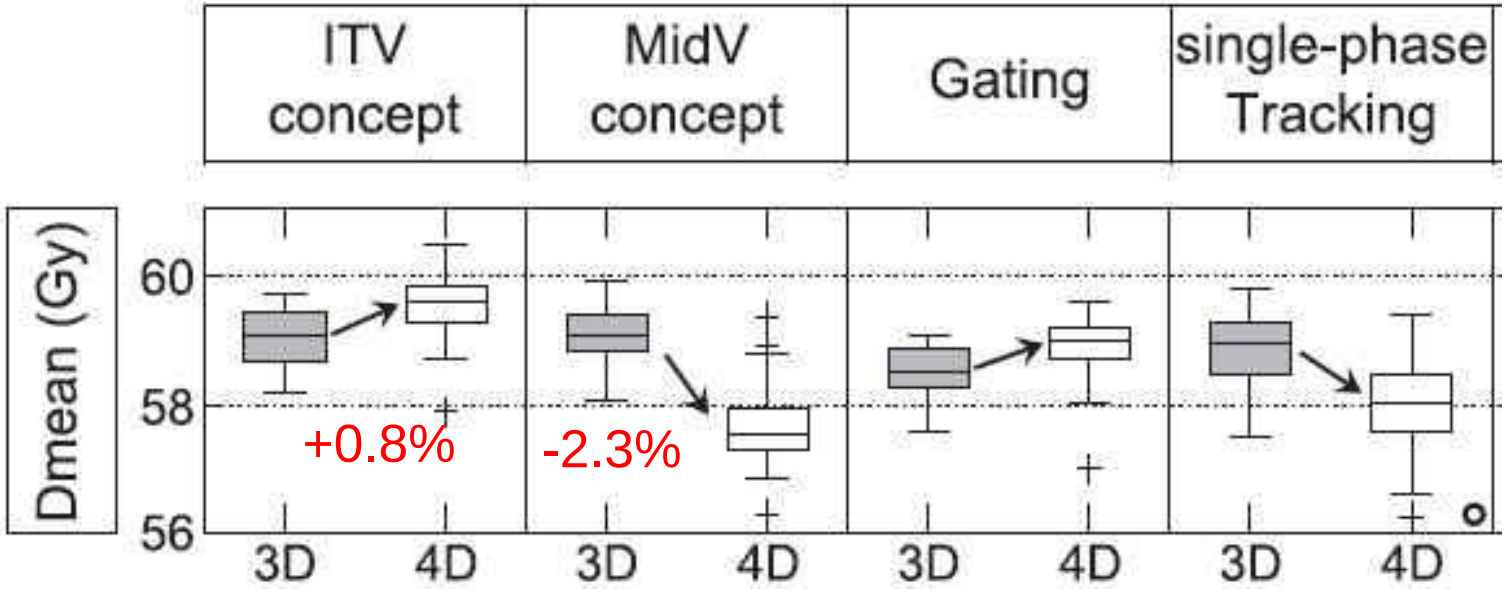
ITV vs MidV vs Gating vs Tracking

Dose to GTV – 4D calculations



Ehrbar et al R&O 124 p80 2017

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Dose calculation accuracy

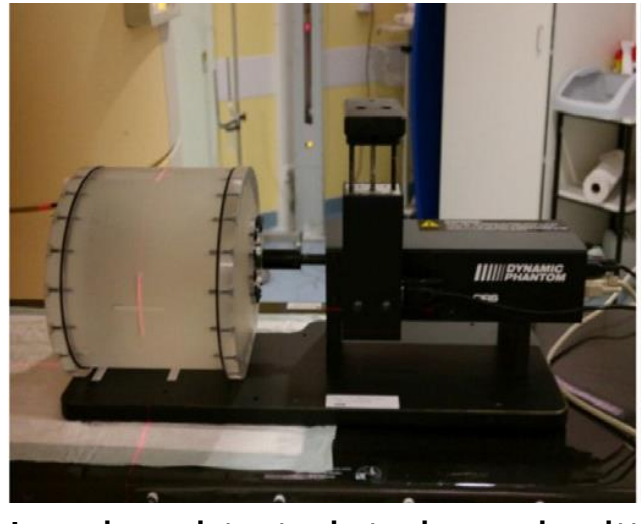
Static phantom

Algorithm	N	Mean
AAA	417	0.962
S/C	360	0.968
MC	89	0.982
Acuros	63	0.991

Clark et al. Phys Med 2017

Dynamic phantom

	1.5cm sphere	2.5cm sphere
Static plan	**98.9%** ***+/- 1.3%*** ***Max 6%***	***99.9%*** ***+/-2.8%***
Dynamic plan 1.5cm/3s	***98.6%*** ***+/-0.86%*** ***max 15%***	



Lambrecht et al. to be submitted

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Warning: Old dose calculation algorithms

- Type A models (the VUmc model falls into this category): Models primarily based on electronic path length (EPL) scaling for inhomogeneity corrections. Changes in lateral transport of electrons are not modelled. The algorithms in this group are e.g. Eclipse/ModBatho and Eclipse/ETAR, OMP/PB, PrecisePLAN, Plato ETAR, Brainscan, I-plan Dose/PB and XiO/Convolution.

- Type B models: Models that in an approximate way consider changes in lateral electron transport. The models in this group are e.g. Pinnacle/CC, Eclipse/AAA, OMP/CC, I-Plan-dose with Monte-Carlo algorithm and XiO/Superposition.

Knöös, PMB 51 (2006) 5785

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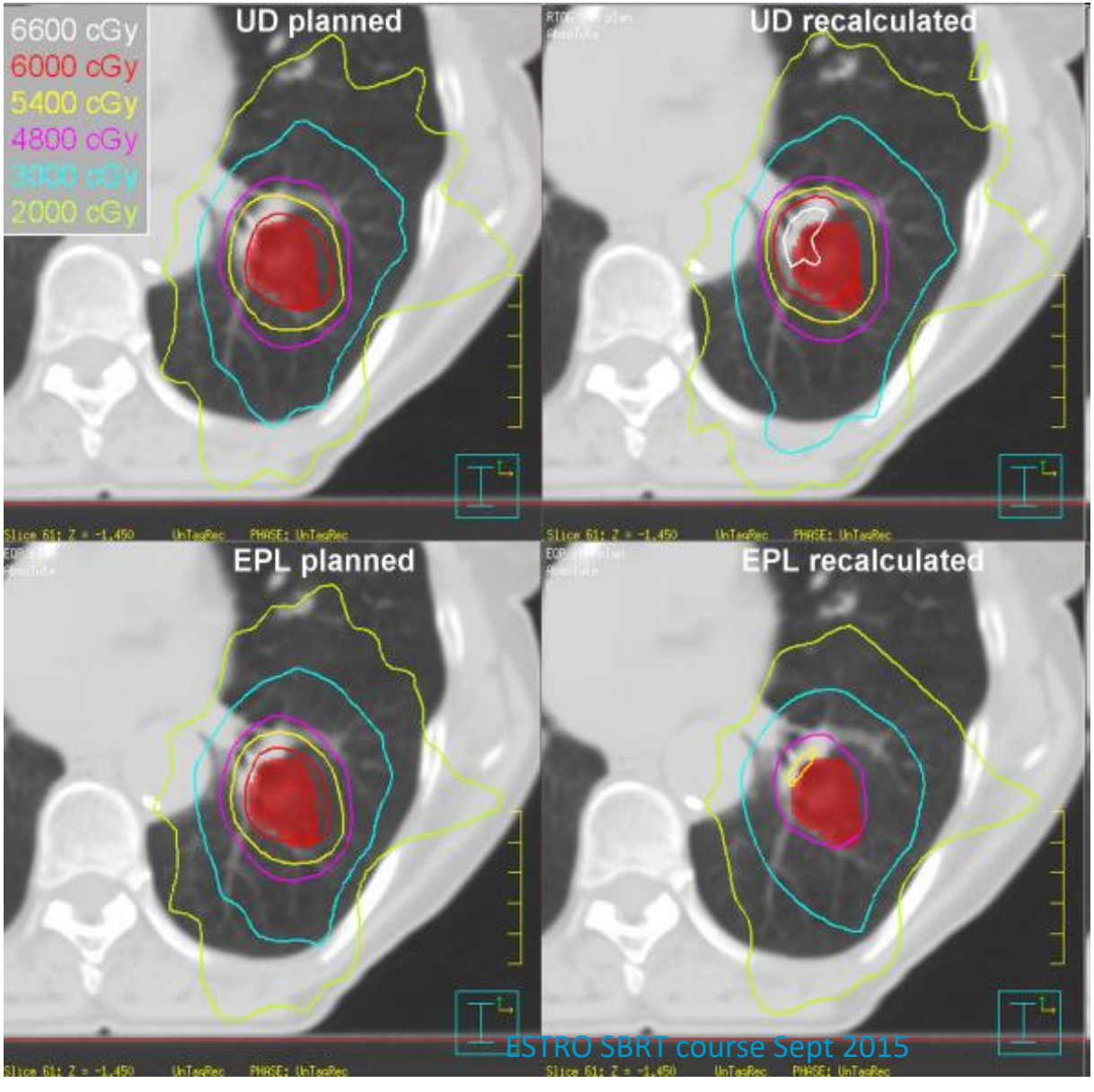
Influence on dose distribution



- Changes in
  - target dose
  - conformity
  - dose to organs at risk

Study:

- Optimised with 3 algorithms and criteria determined
- Recalculated

Schuring and Hurkmans, Rad Onc (2008)

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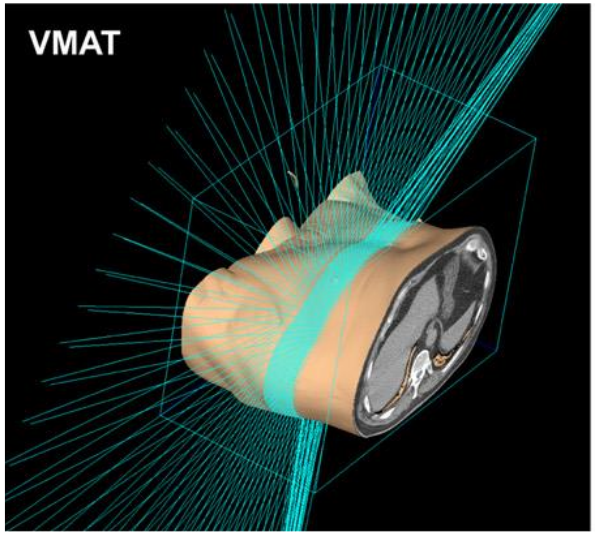
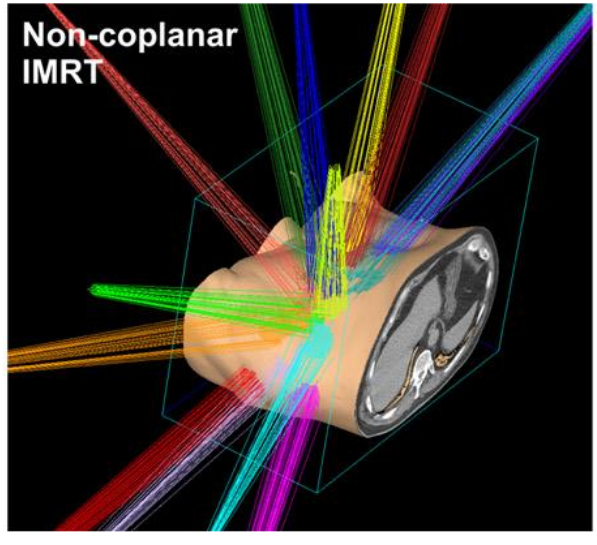
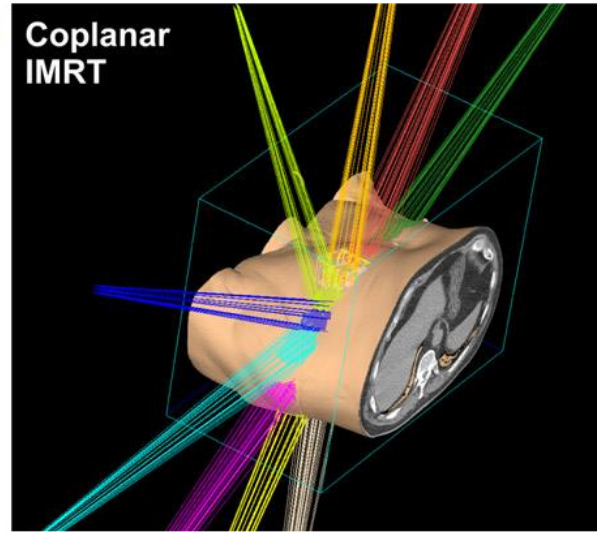
Planning technique







Planning technique

PHYSICS CONTRIBUTION

VOLUMETRIC-MODULATED ARC THERAPY FOR STEREOTACTIC BODY RADIOTHERAPY OF LUNG TUMORS: A COMPARISON WITH INTENSITY-MODULATED RADIOTHERAPY TECHNIQUES

ANDREA HOLT, PH.D.,* CORINE VAN VLIET-VROEGINDEWEIJ, PH.D.,* ANTON MANS, PH.D.,* JOSÉ S. BELDERBOS, M.D., PH.D.,* AND EUGÈNE M. F. DAMEN, PH.D.*

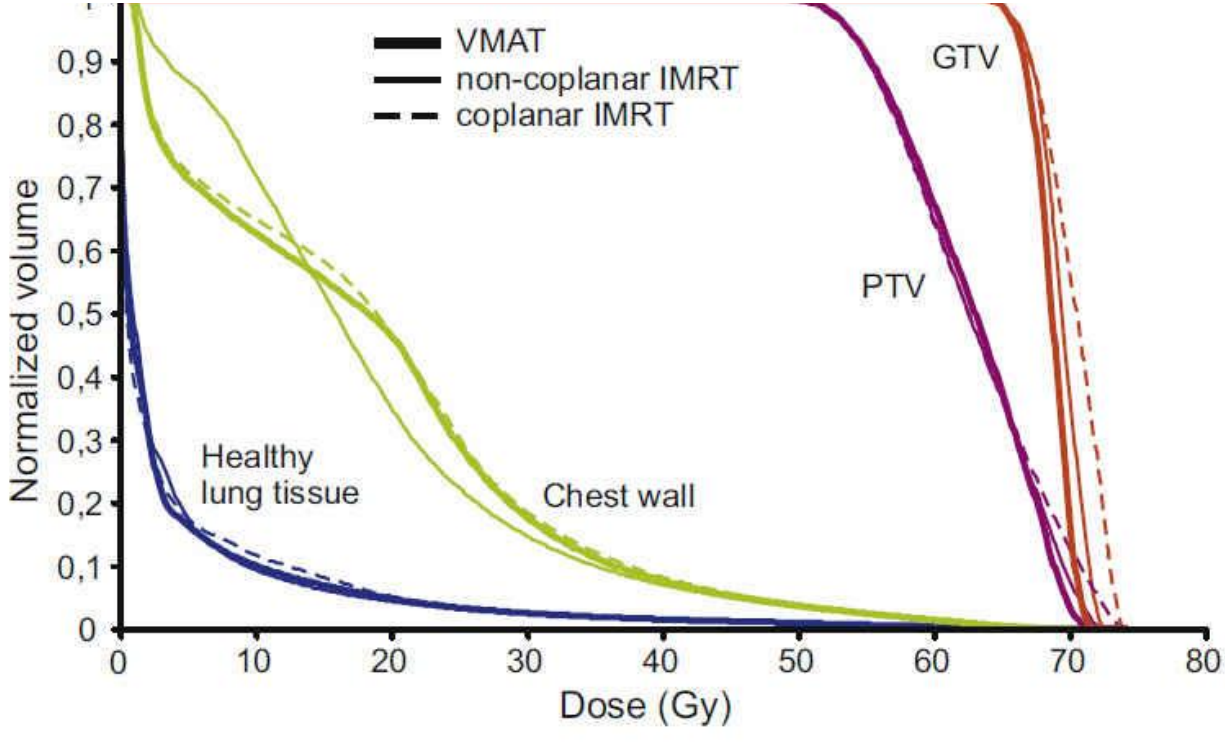


Fig. 3. Dose–volume histograms for example case shown in Fig. 2.

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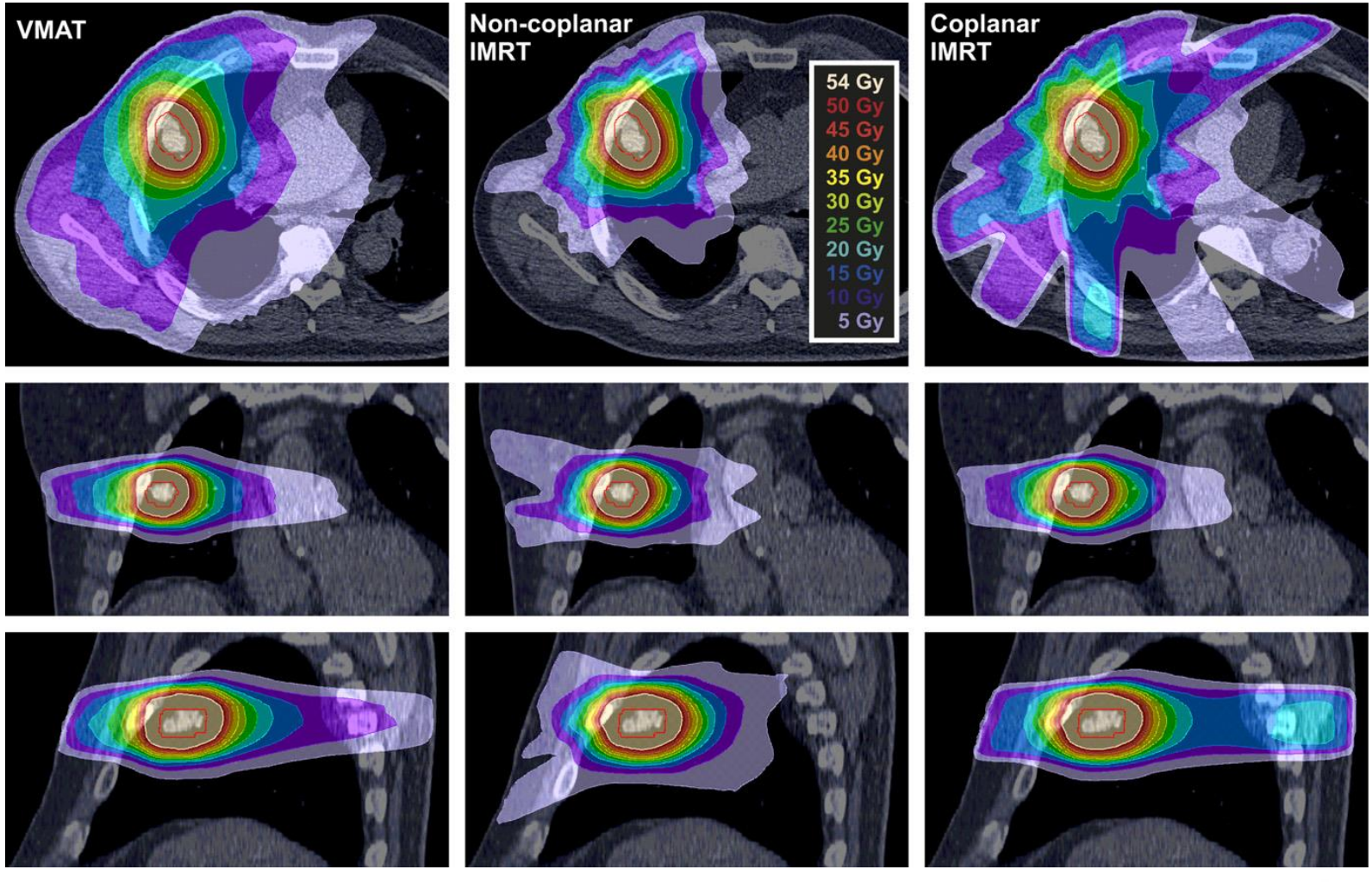
Planning technique



Delivery time

Table 4. Differences in plan parameters between different treatment techniques

		VMAT and IMRT NCP		VMAT and IMRT CP		IMRT NCP and IMRT CP	
	Dose type	Mean (range)	p^*	Mean (range)	p^*	Mean (range)	p^*
Delivery time (min)	NA	-17.1 (-34.2–-9.0)	.000	-10.8 (-19.5–-5.7)	.000	6 (-2–21)	.000

Non-coplanar IMRT delivery time : 22.7 beam delivery, 30-45 min total

Vmat : 6.6 min beam delivery, 20-25 min total

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Delivery time - FFF

Table 1 Summary of dosimetric metrics for FF and FFF plans

Sites	Metric	Unit	FF 6 MV	FFF 10 MV	*p*
Lung	3 × 18 Gy (n = 4)		4.8 ± 0.4	2.6 ± 0.1	–
	5 × 11 Gy (n = 3)		3.2 ± 0.2	2.5 ± 0.1	–
	8 × 7.5 Gy (n = 3)		2.5 ± 0.1	2.5 ± 0.1	–
Spine	1 × 16 Gy (n = 3)		9.9 ± 1.6	3.4 ± 0.4	–
	2 × 10 Gy (n = 3)		6.8 ± 1.8	2.7 ± 0.2	–
	3 × 9 Gy (n = 4)		4.3 ± 0.7	2.5 ± 0.1	–

Abbreviations: FF = flattened beam; FFF = flattening filter–free; PVT = planning target volume; ITV = internal target volume; PRV = planning at risk volume.
Values are mean ± SD.

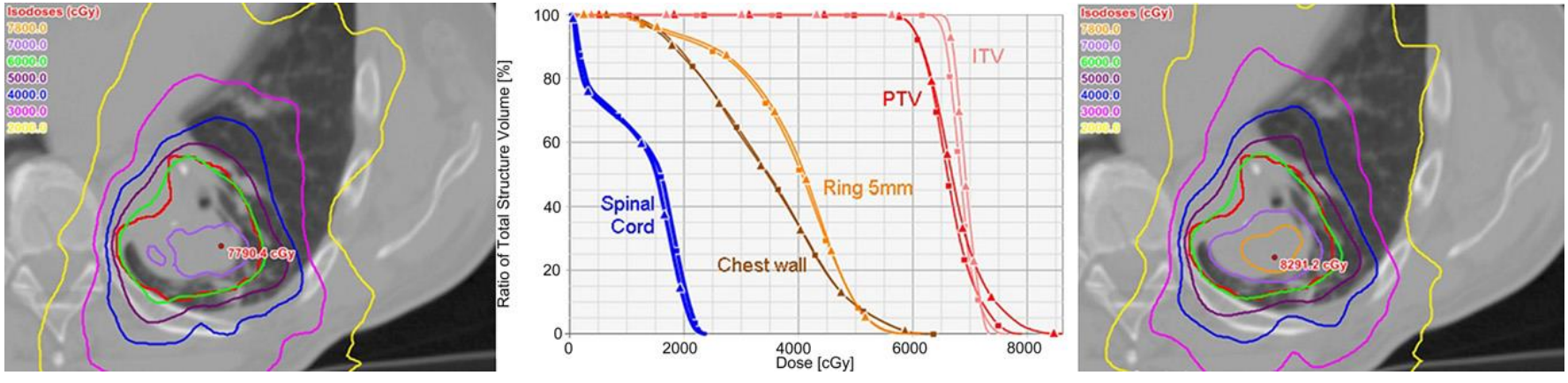

Fig. 2. Comparison of dose distributions in transverse planes for lung flattened beam plan (left) and flattening filterfree plan (right), with planning target volume outlined in red. The dosevolume histogram shows similar planning target volume coverage and organ at risk sparing between 6-MV flattened beam plan (squares) and 10-MV flattening filterfree plan (triangles).

Ong et al, IJROBP 83(1) e137-e143, 2012

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Conclusions (1)

- Precisely define the dose you want to give to the target volume.
- Use OAR objectives that have clinical merits.
- Define acceptable variations.
- Use type B algoritms. type B or Monte Carlo based are strongly recommended
- Various treatment techniques may lead to adequate dose distributions.
- Co-planar VMAT techniques with FFF beams lead to shortest treatment times.

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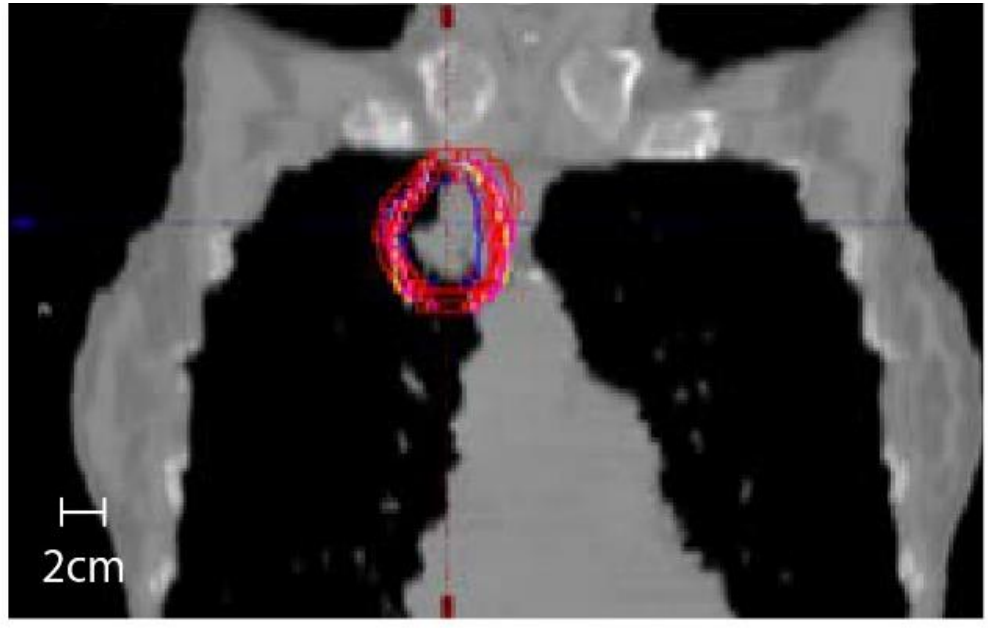
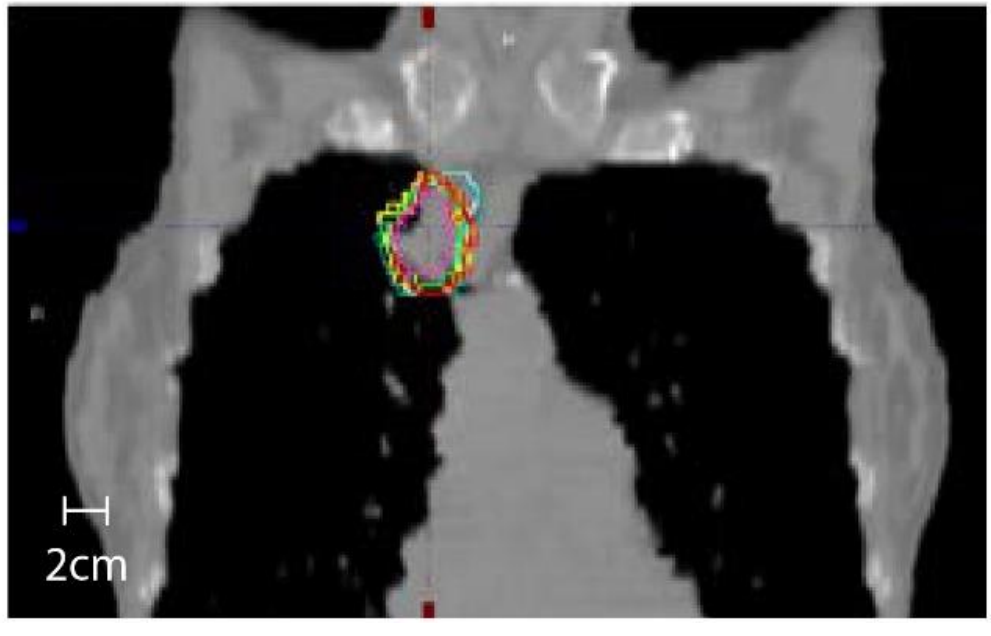
EORTC Lungtech trial delineations

PTV



ITV



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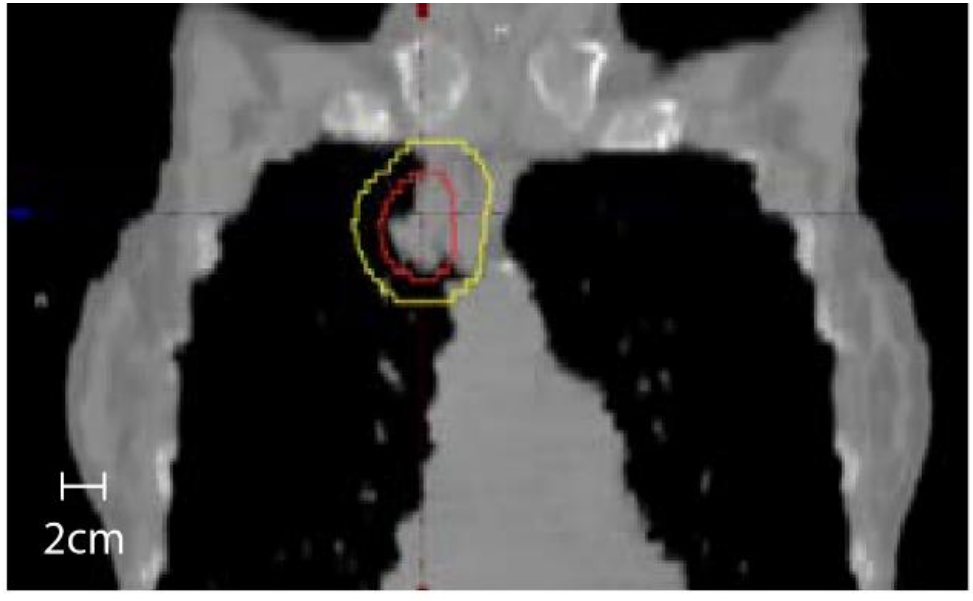
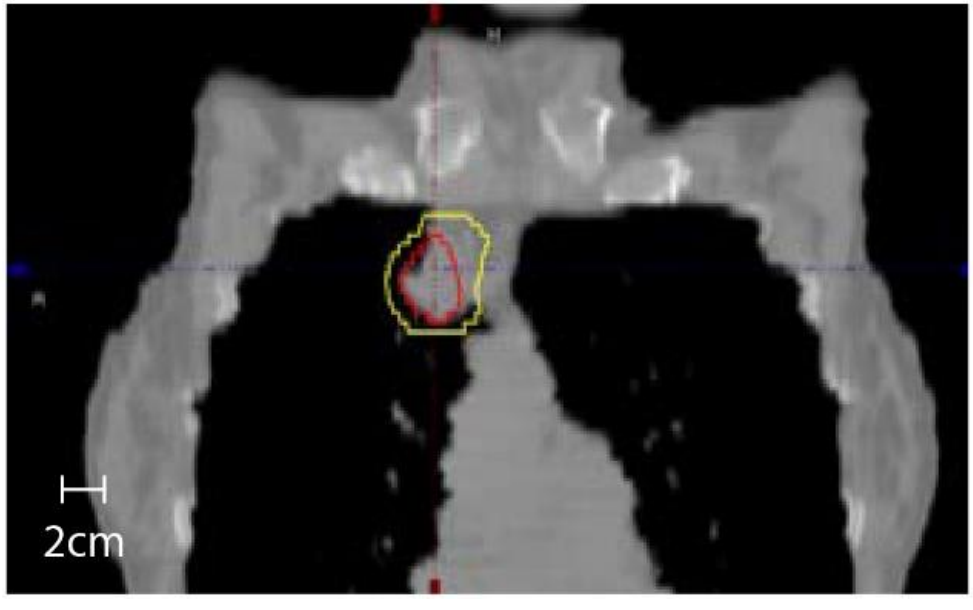
EORTC Lungtech trial delineations

PTV

ITV





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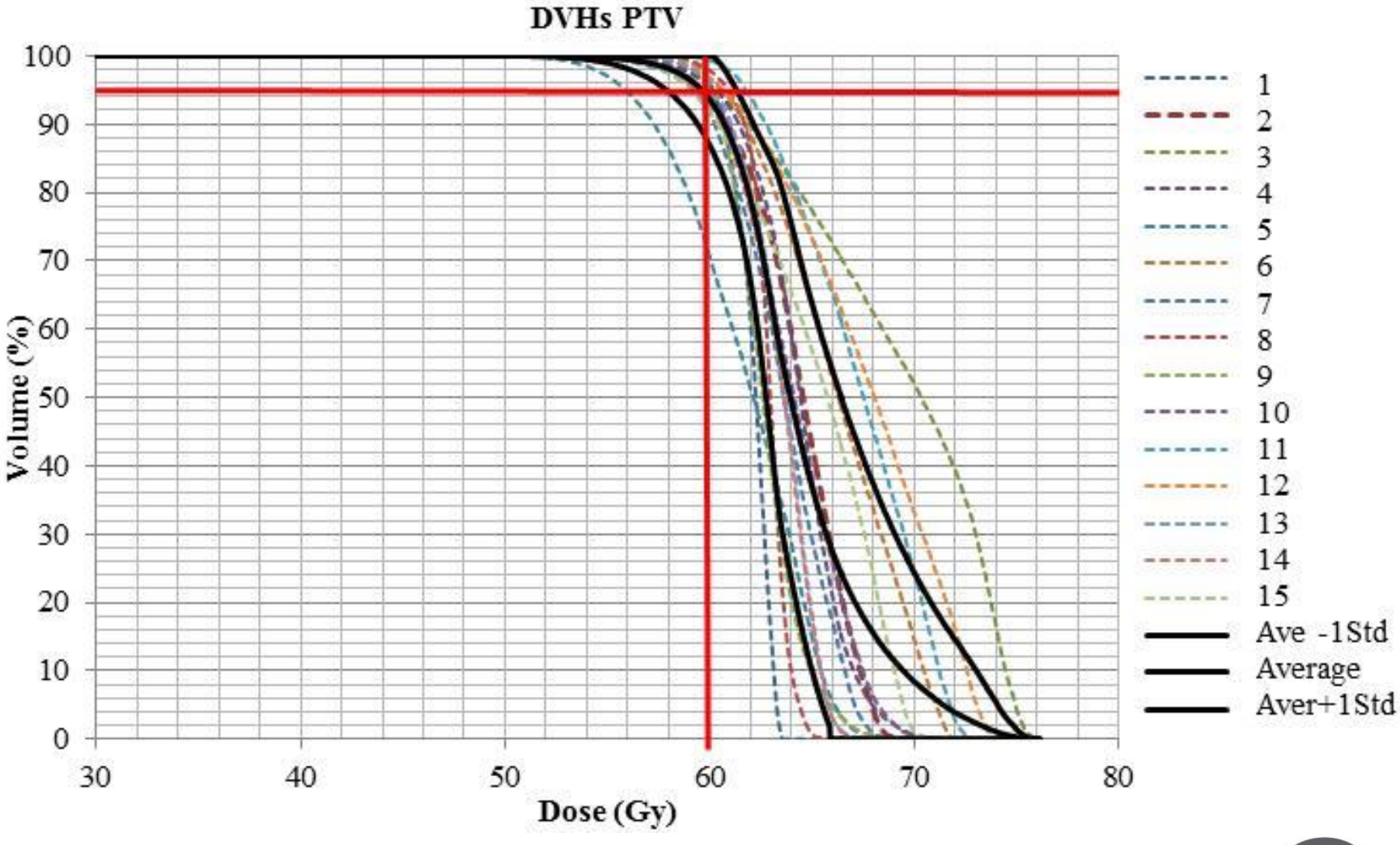
Lungtech approved benchmarks



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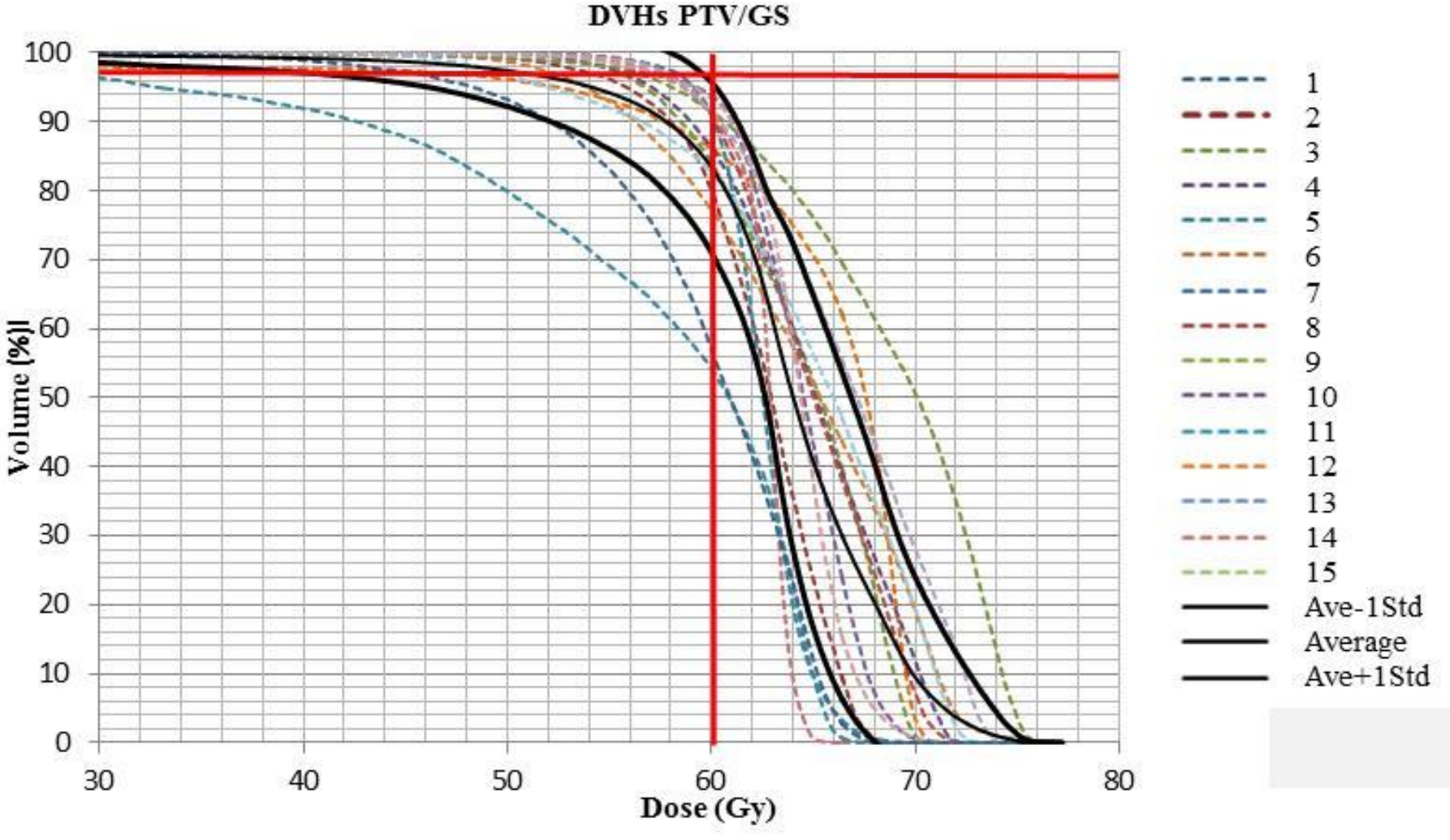
Lungtech benchmarks on gold standard



Conclusions (2)

Realise that small changes in delineation may lead to large changes in dose coverage

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Further reading

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

European Organization for Research and Treatment of Cancer (EORTC) recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer

Dirk De Ruysscher [a,b,*], Corinne Faivre-Finn [c], Ditte Moeller [d], Ursula Nestle [e,f], Coen W. Hurkmans [g], Cécile Le Péchoux [h], José Belderbos [i], Matthias Guckenberger [j], Suresh Senan [k], on behalf of theLung Group and the Radiation Oncology Group of the European Organization for Research and Treatment of Cancer (EORTC)

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer

Matthias Guckenberger [a,*], Nicolaus Andratschke [b], Karin Dieckmann [c], Mischa S. Hoogeman [d], Morten Hoyer [e], Coen Hurkmans [f], Stephanie Lang [b], Eric Lartigau [g], Alejandra Méndez Romero [d], Suresh Senan [h], Dirk Verellen [i]

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SBRT treatment planning
Liver, Spine and Prostate

Stephanie Lang

University Hospital Zürich

UniversityHospital Zurich

Universität Zürich[UZH]

ESTRO School

Outline

- SBRT treatment planning for Liver cancer
- SBRT treatment planning for spine
- SBRT treatment planning for prostate cancer
- 4π treatments – a benefit for SBRT?
- FFF beams - a benefit for SBRT treatments?

Questions

How can I reach the optimal SBRT plan?

VMAT without/with FFF in moving targets?

SBRT treatment planning Basic rules and tricks

Most clinical data is based on type B algorithm. When type C algorithm is used, what will be the optimal prescription dose?

Is it possible to plan a SBRT plan with VMAT? If no what are the disadvantages?

SBRT liver treatment planning

On which CT should we calculate dose?

What do we have available?

- 8-10 phases of 4DCT
- 3DCT with contrast
- MidVent phase
- Average CT

On which CT should we calculate dose?

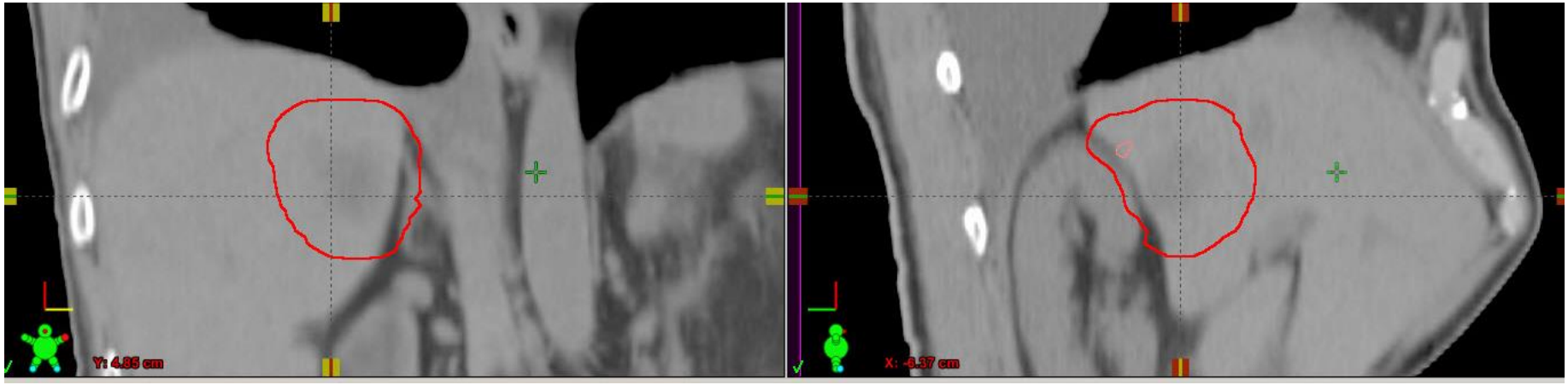
What do we have available?

- 8-10 phases of 4DCT
- 3DCT with contrast
- MidVent phase
- Average CT

→ Overestimates Liver volume, underestimated dose to the liver

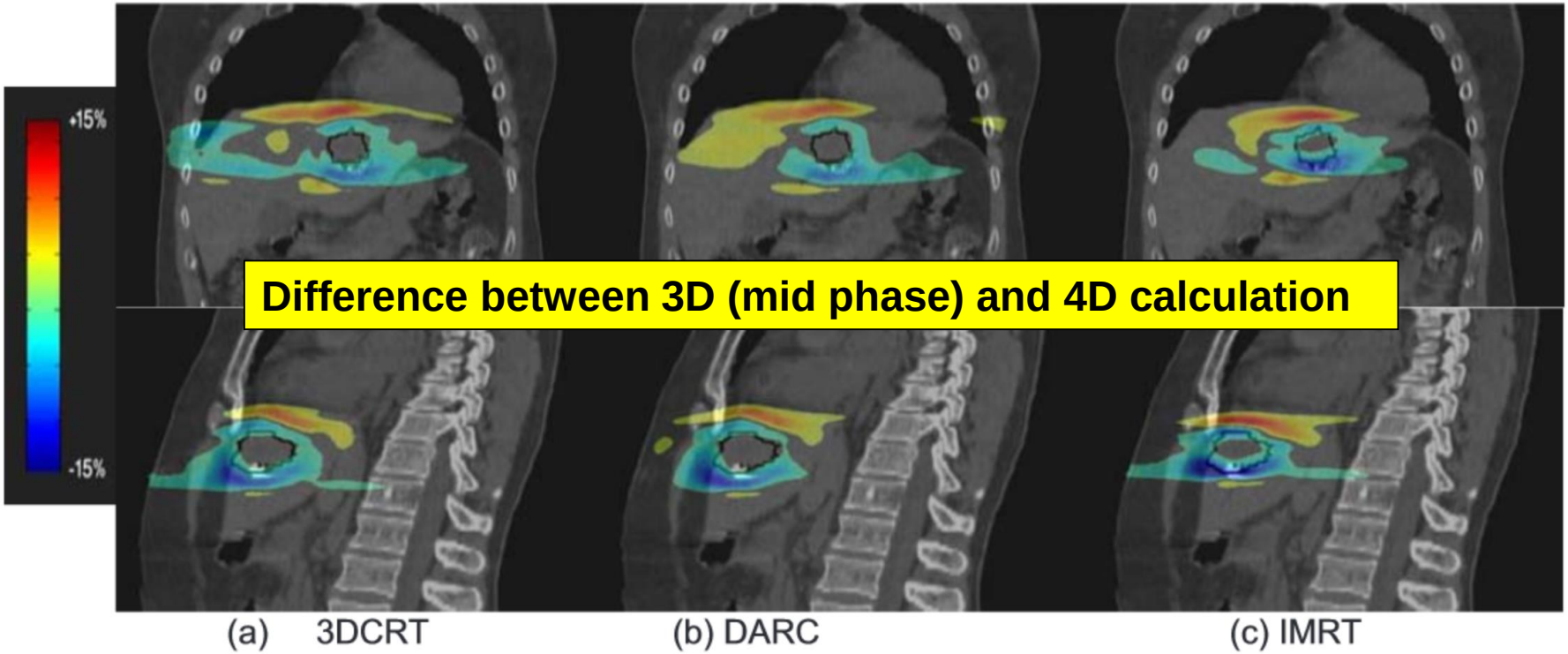
On which CT should we calculate dose?

Tumors in the middle of the liver?



On which CT should we calculate dose?

Tumors in the middle of the liver?

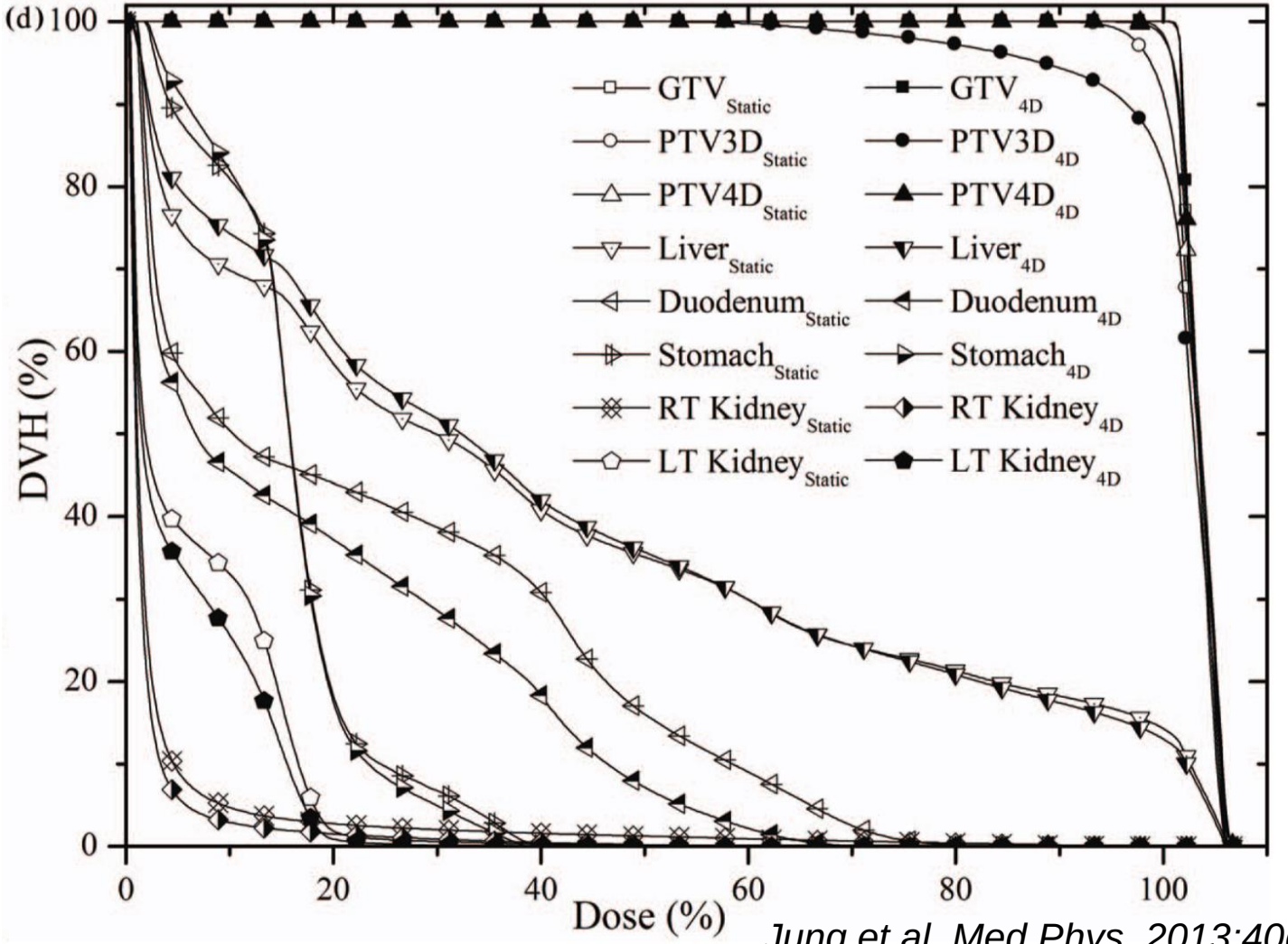


Wu et al, Med Phys,2008;35(4)

Small differences in the dose to the GTV.

On which CT should we calculate dose?

Tumors in the middle of the liver?



Jung et al, Med Phys, 2013;40(1)

Small differences in the dose to the GTV and PTV.

→ It is recommended to calculate the dose on the midPhase CT or the exhale CT

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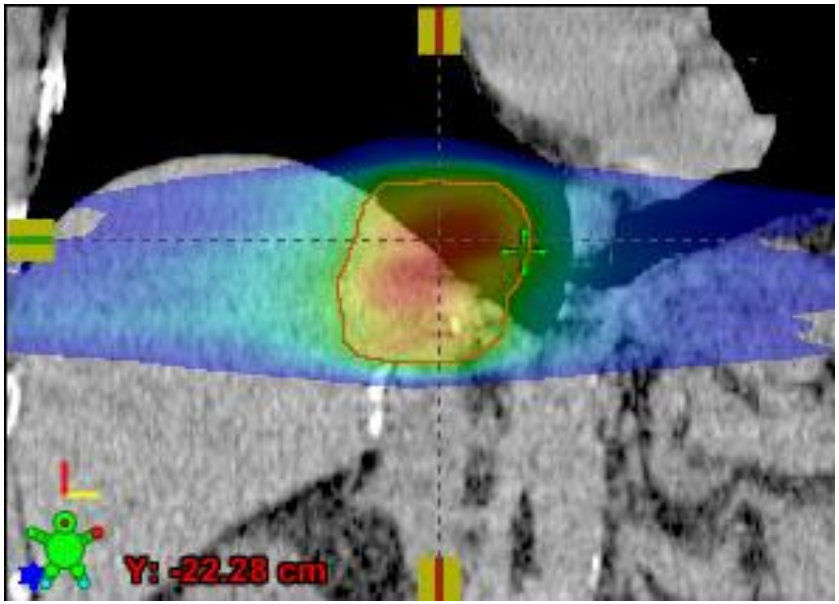
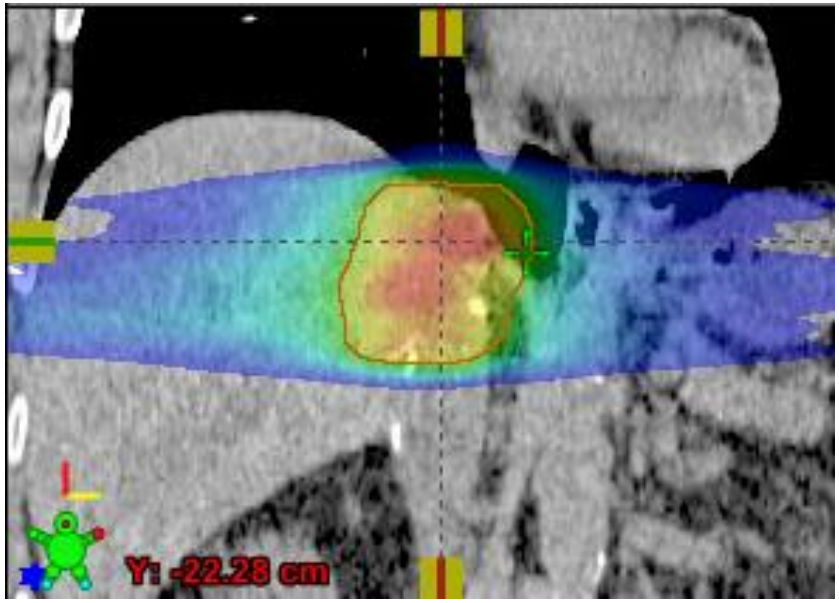
On which CT should we calculate dose?

Tumors on the boundary liver - lung?

On which CT should we calculate dose?

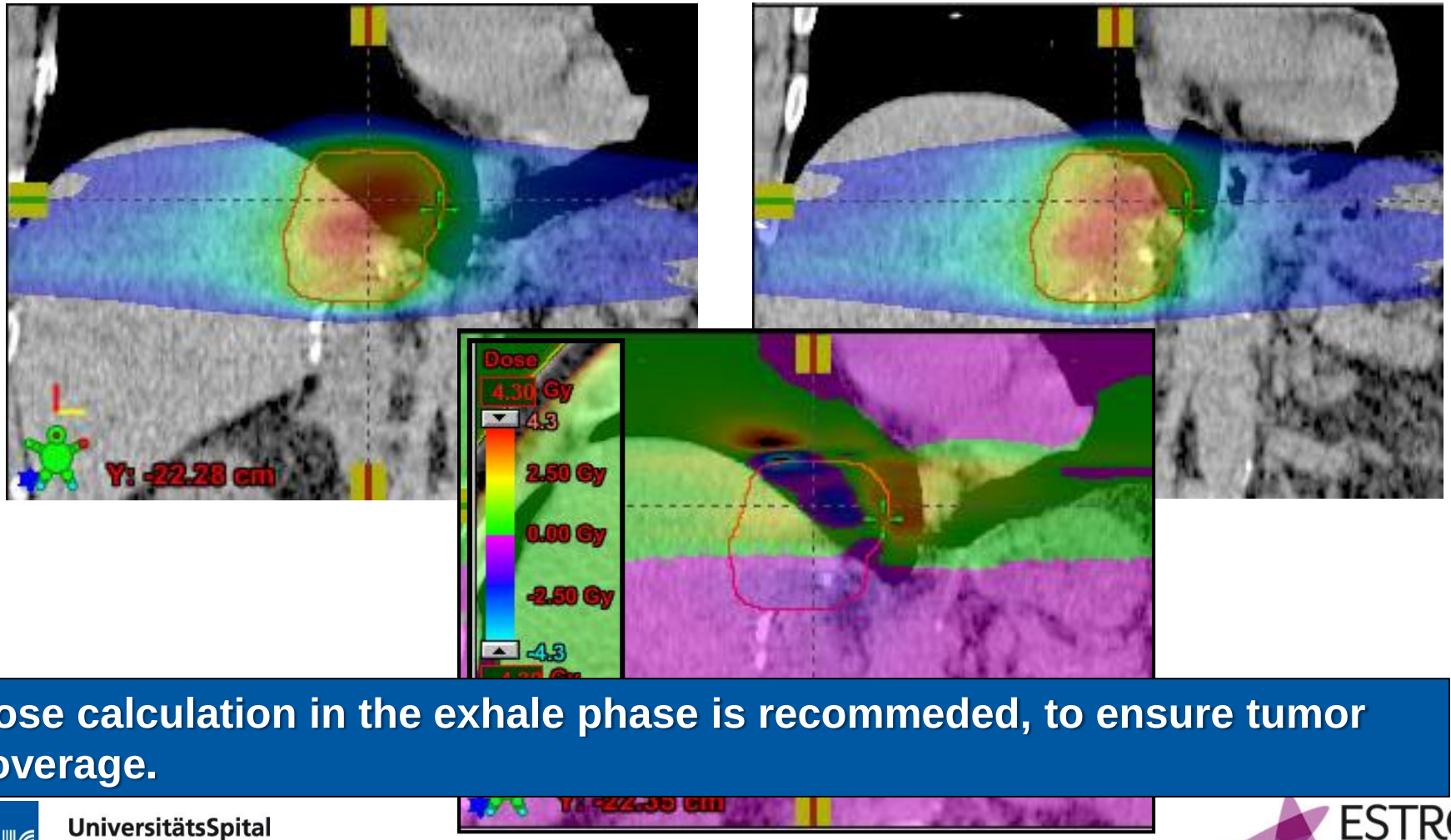
Tumors on the boundary liver - lung?





On which CT should we calculate dose?

Tumors on the boundary liver - lung?



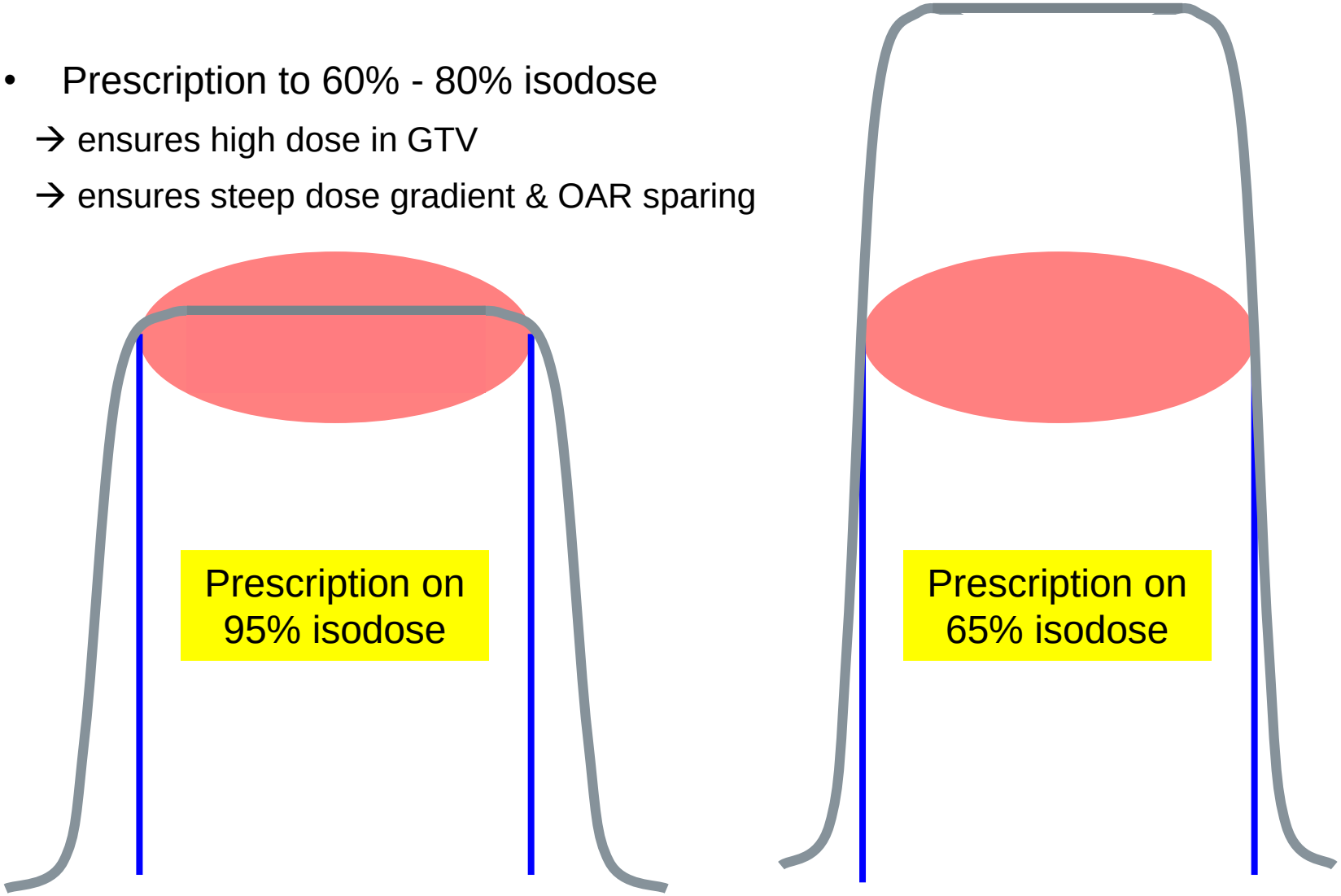
Dose calculation in the exhale phase is recommeded, to ensure tumor coverage.

Treatment planning for liver cancer

- Prescription to 60% - 80% isodose

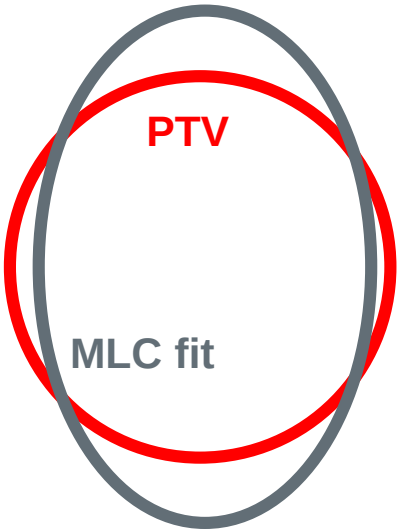
→ ensures high dose in GTV

→ ensures steep dose gradient & OAR sparing



3D conformal treatment planning

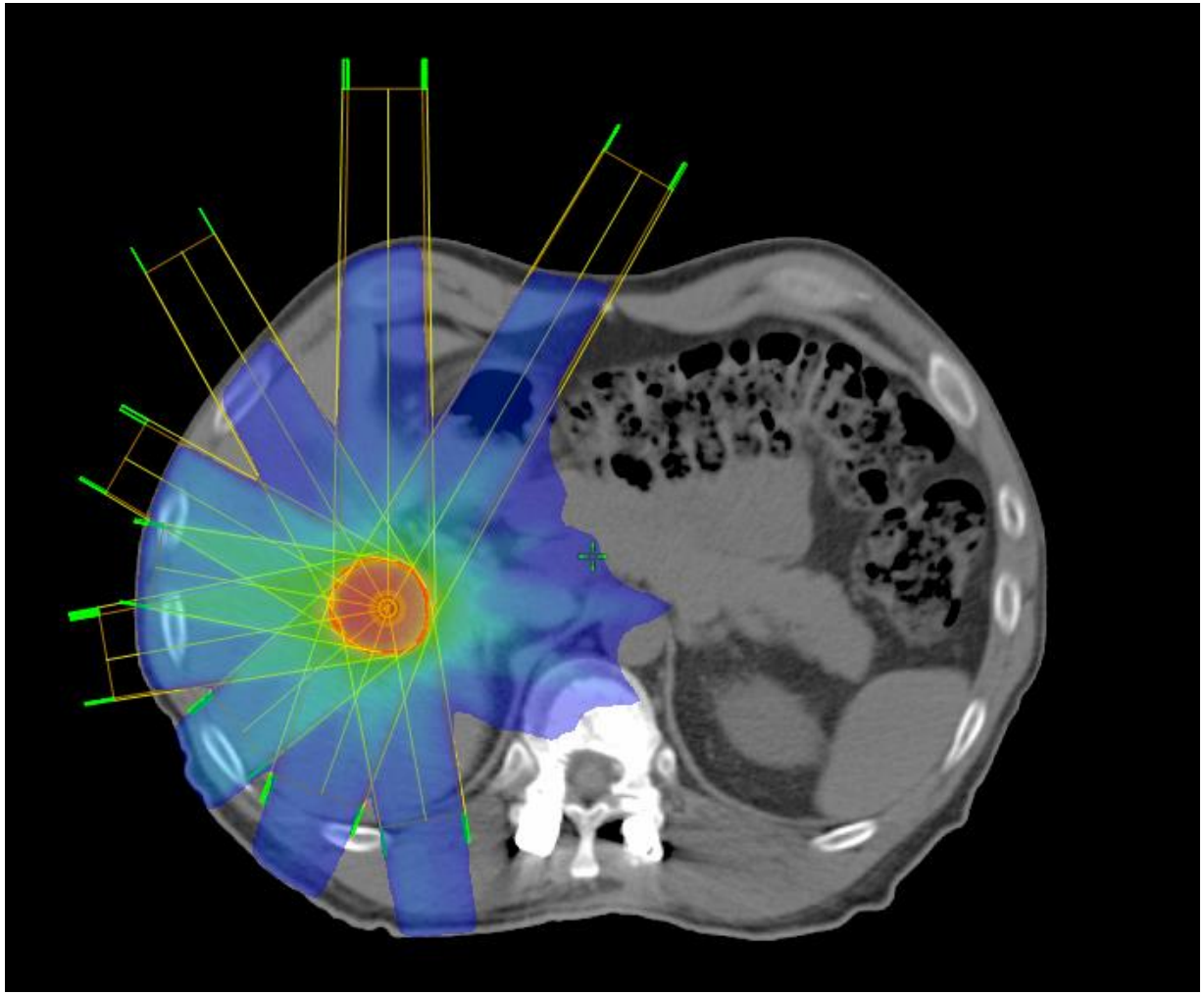
- Isocenter placed in target
- 7-11 fields spread as much as possible
- Avoid directly opposing fields
- Avoid entering a OAR (spinal cod, duodenum, bowel, kidneys).
- Fit MLC to help structure

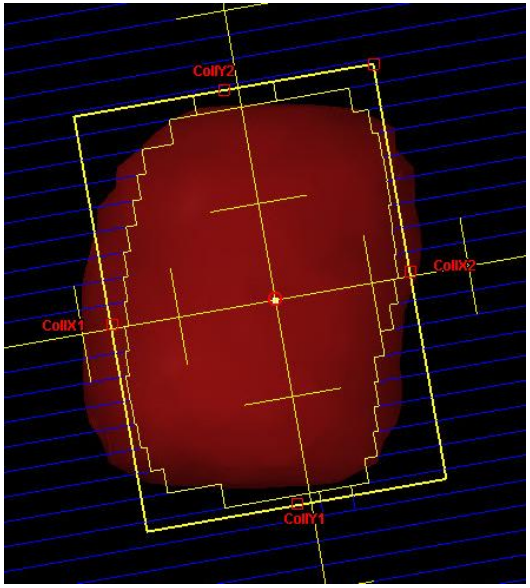


• MLC fit is 2mm longer (sup-inf) and 3 mm tighter (lat and AP) than the PTV

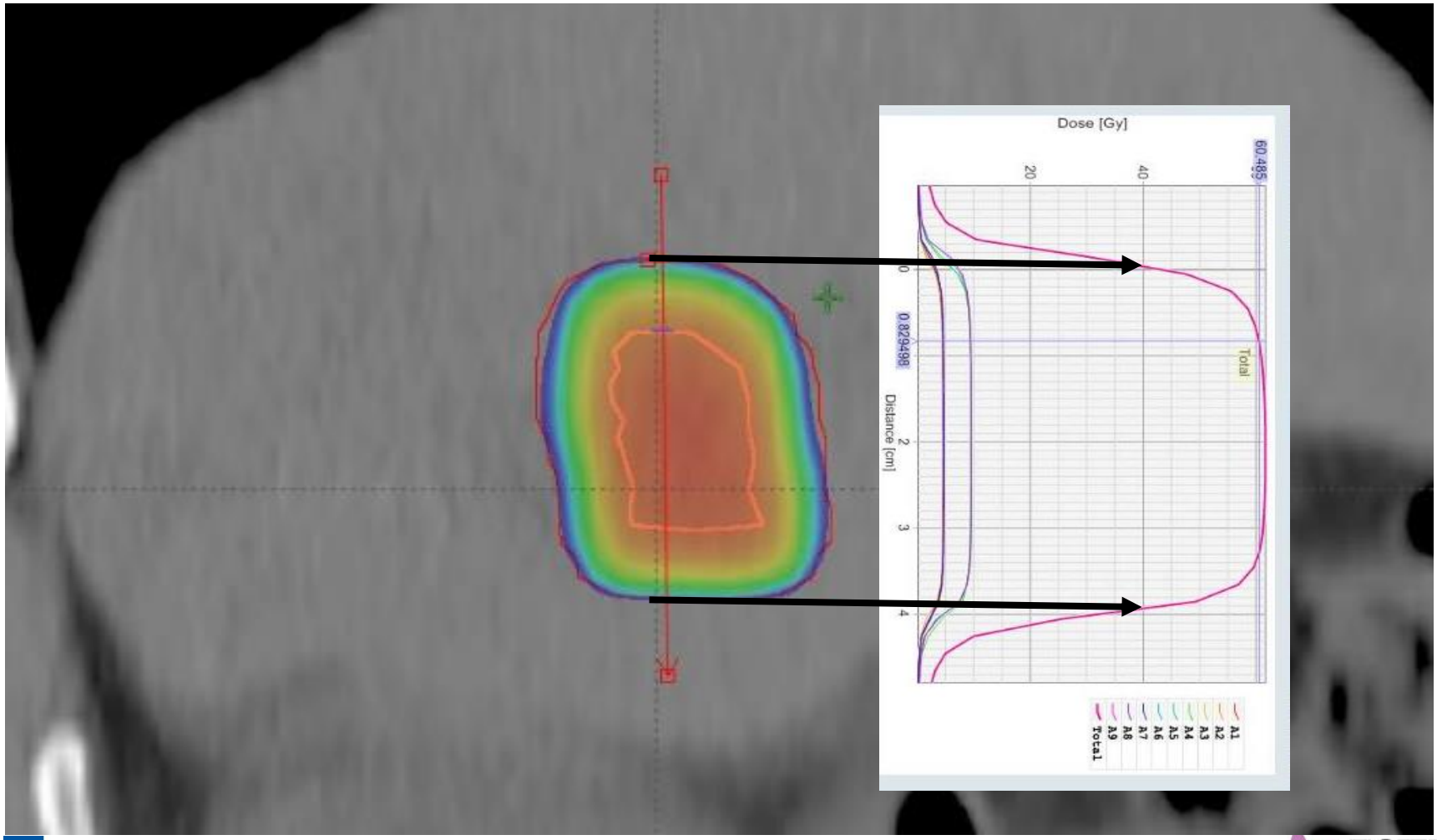
• Manual adjustements may be necessary, for example to sprare thoracic wall better

3D conformal treatment planning

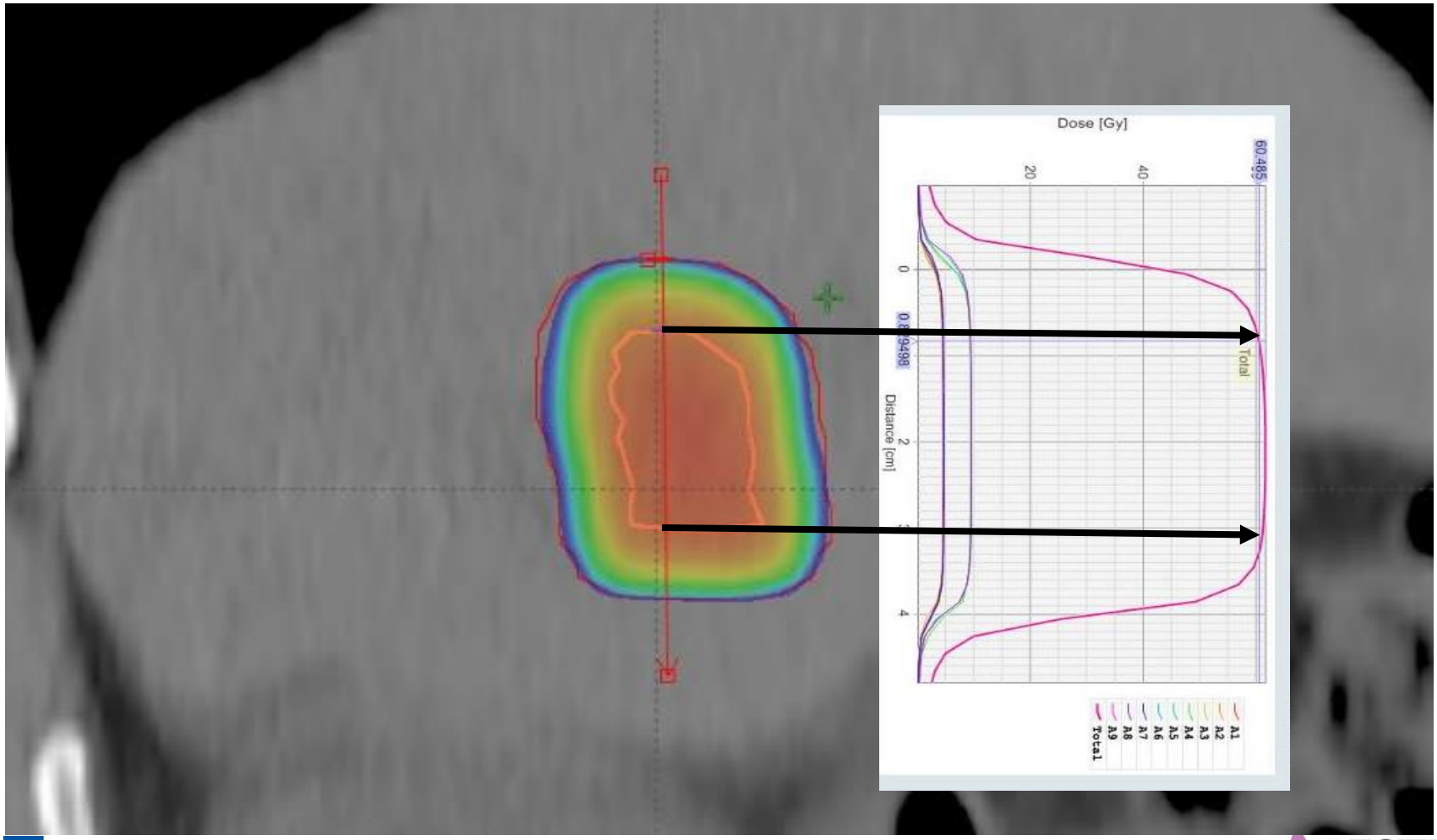




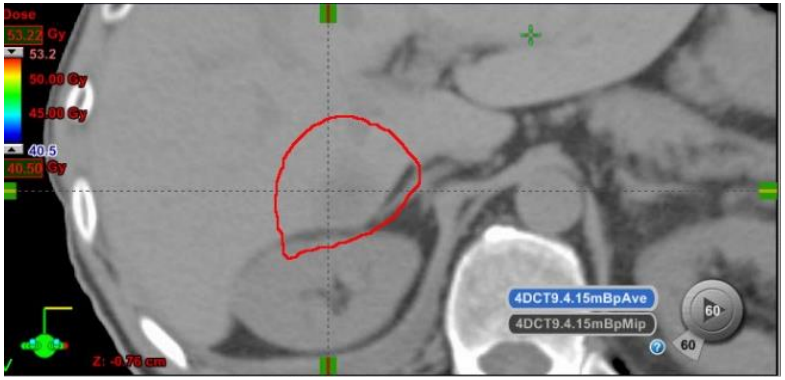
3D conformal treatment planning

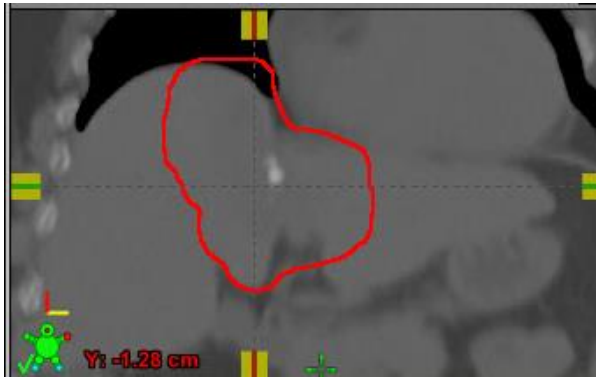


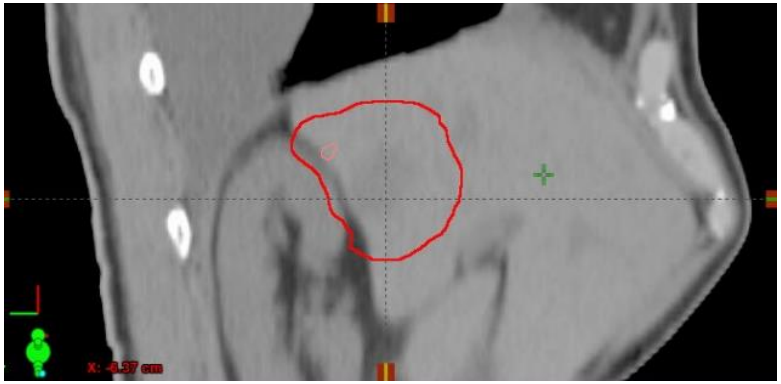
3D conformal treatment planning

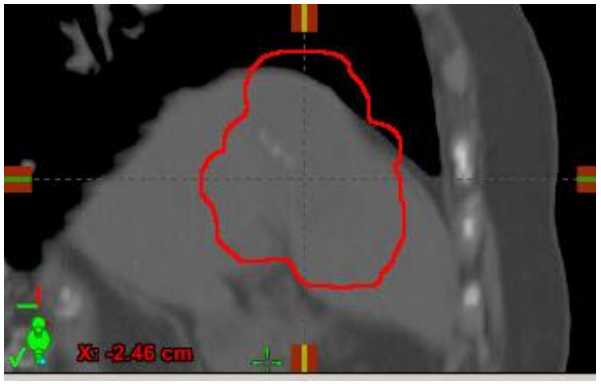


Do we need VMAT?





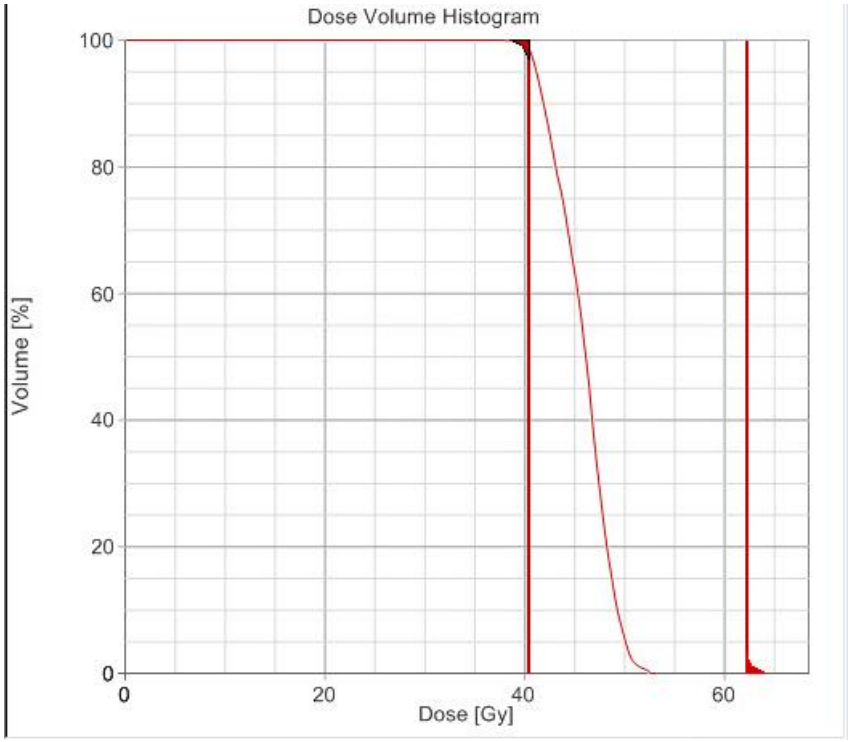


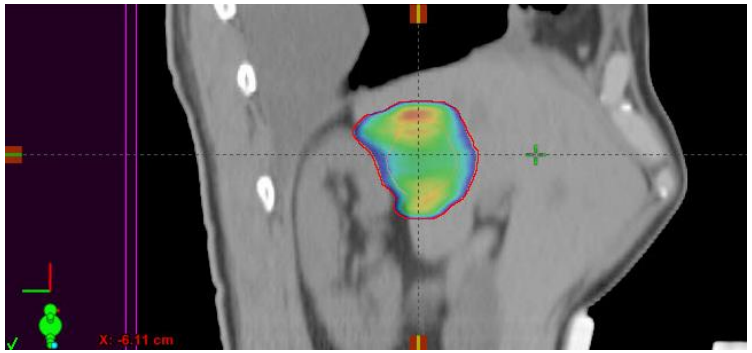


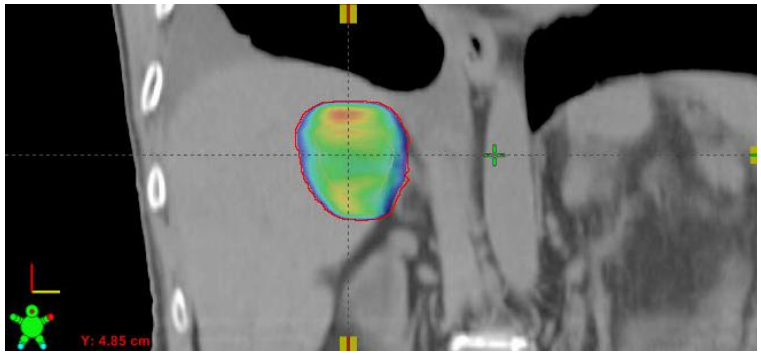
VMAT has advantages when the target volume has a complex shape or an organ at risk is close to the PTV.

VMAT optimisation

How to get the inhomogeneity?

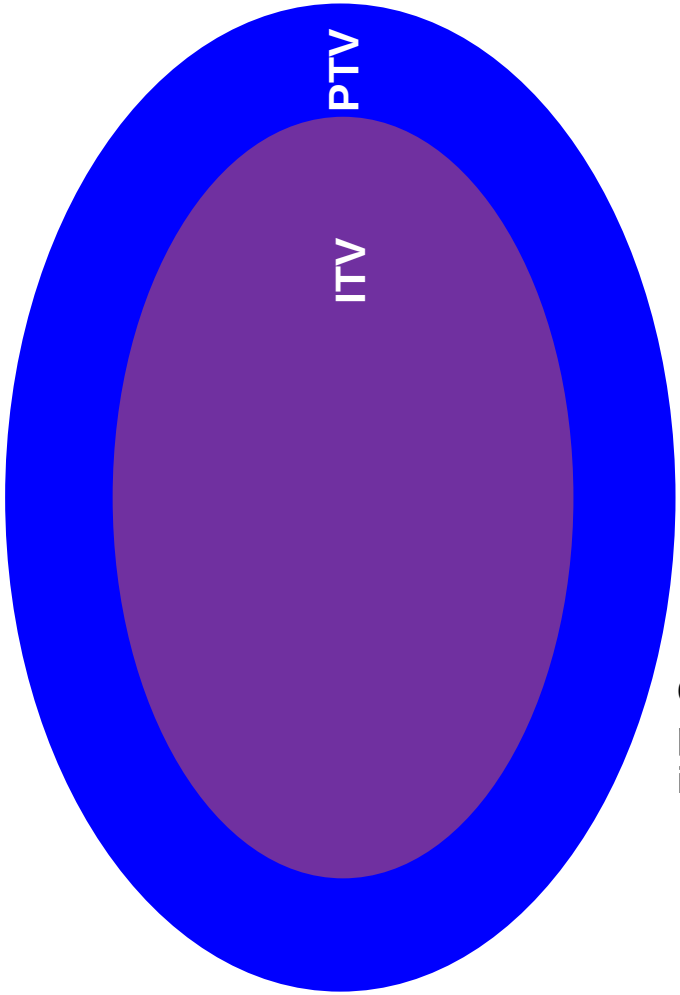






Just an upper and lower constraint lead to an inhomogeneity of about 80% and a hotspot, which is normally not located in the center.

VMAT – how to achieve the inhomogeneity



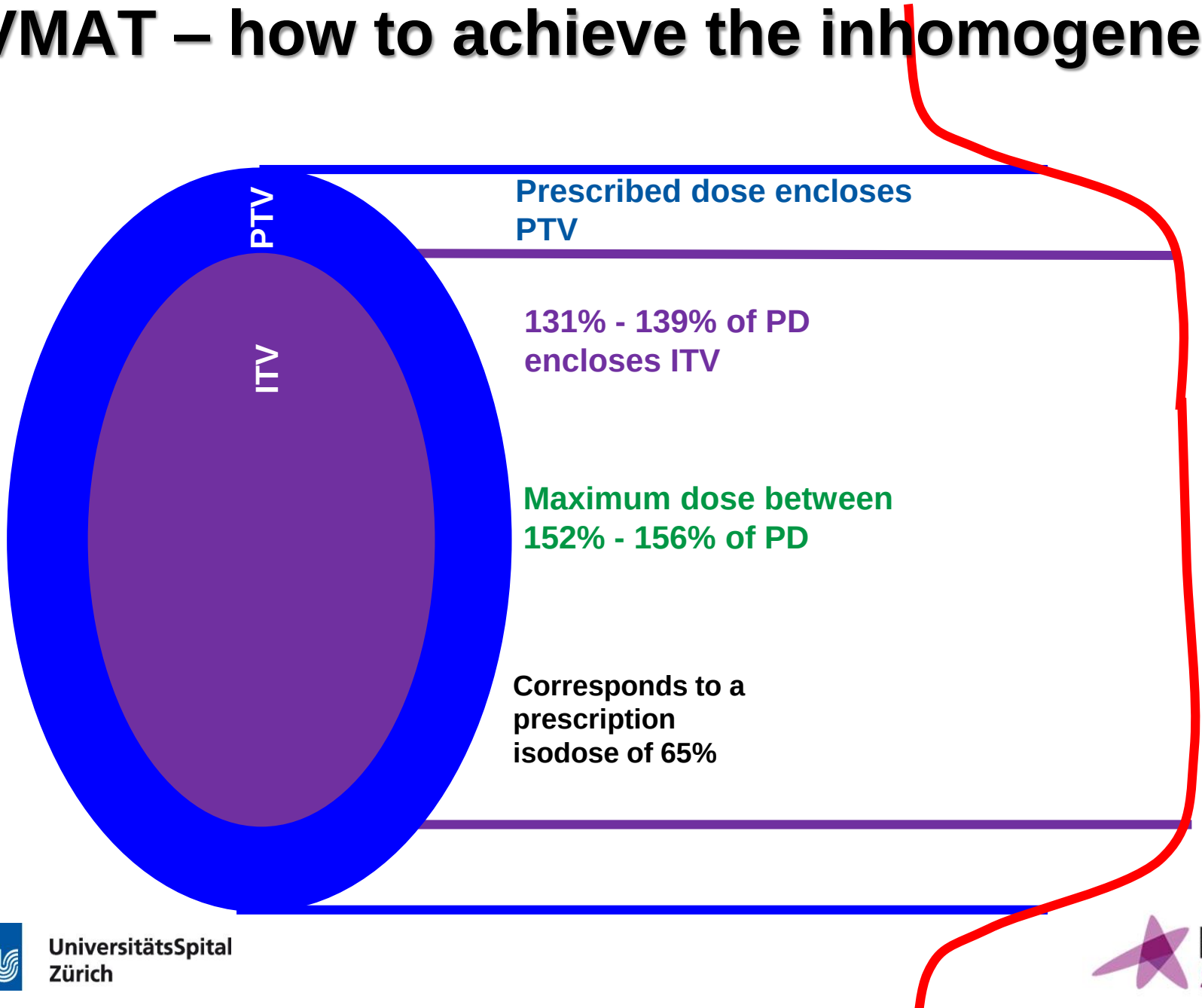
Prescribed dose encloses PTV

131% - 139% of PD encloses ITV

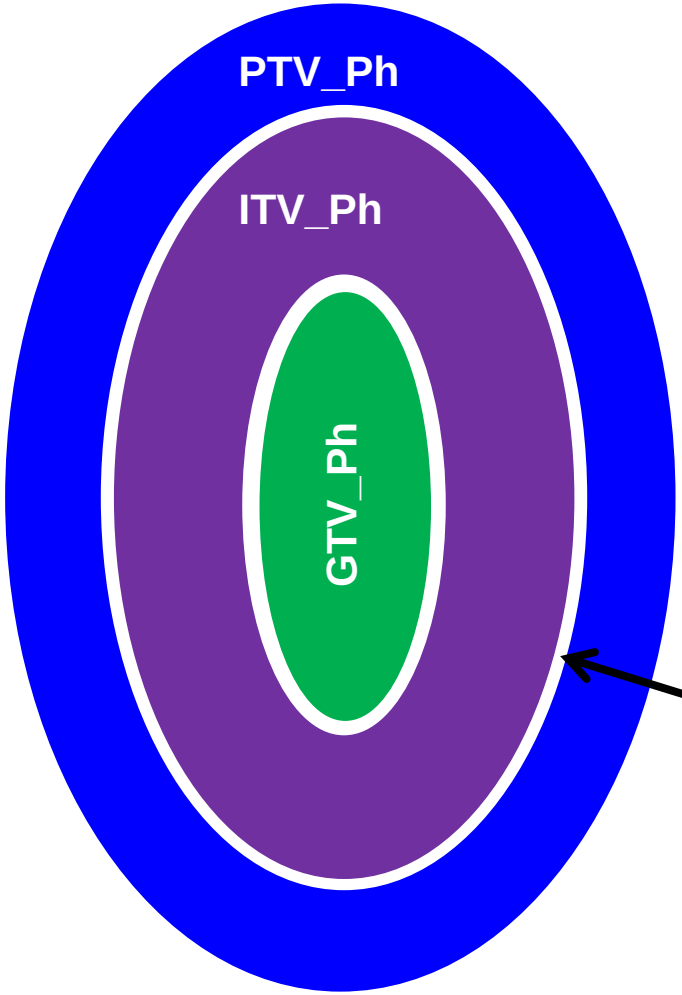
Maximum dose between 152% - 156% of PD

Corresponds to a prescription isodose of 65%

VMAT – how to achieve the inhomogeneity



VMAT - Optimisation help structures



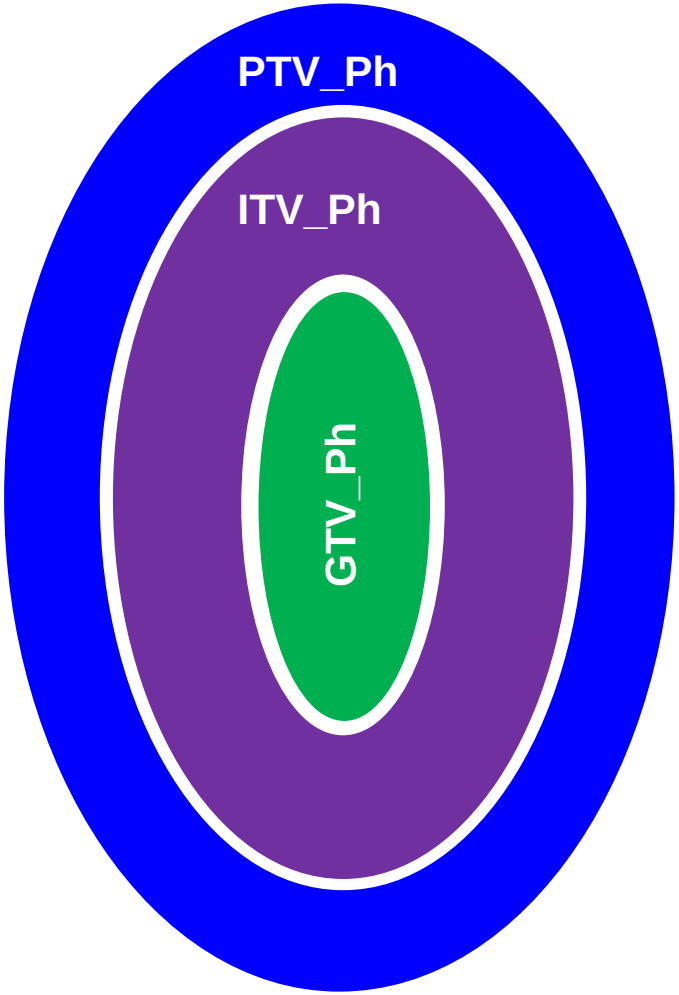
Prescribed dose encloses PTV

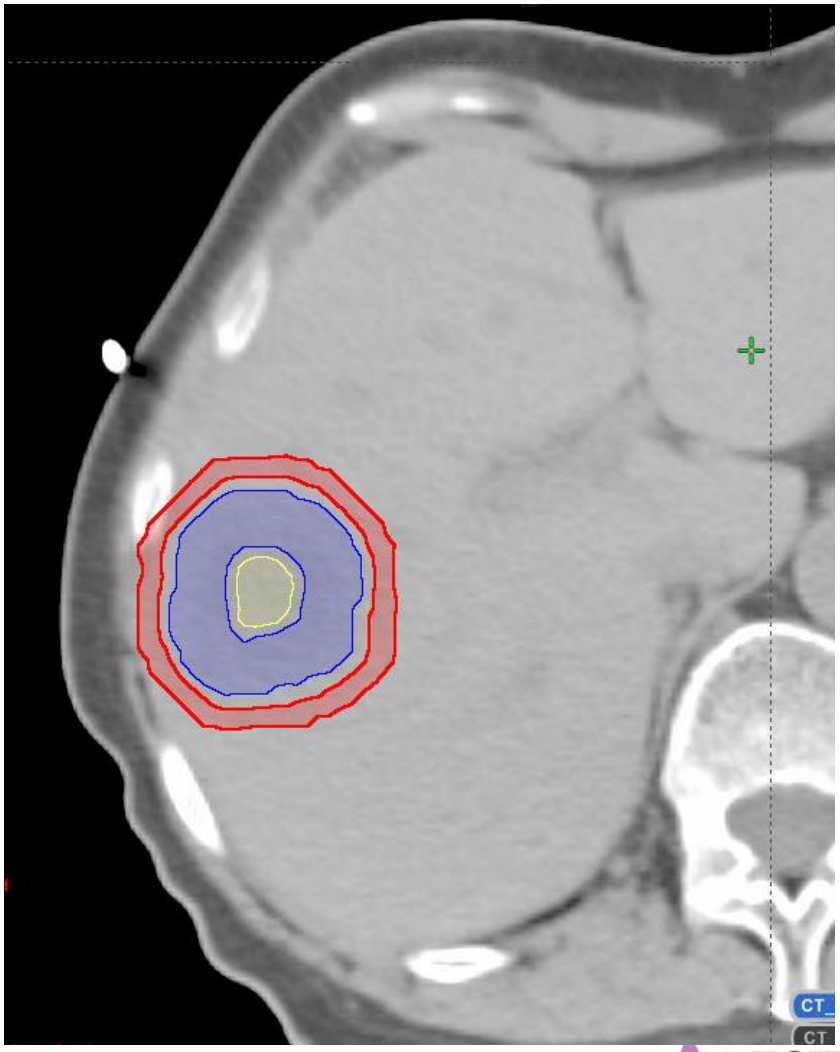
131% - 139% of PD encloses ITV

Maximum dose between 152% - 156% of PD

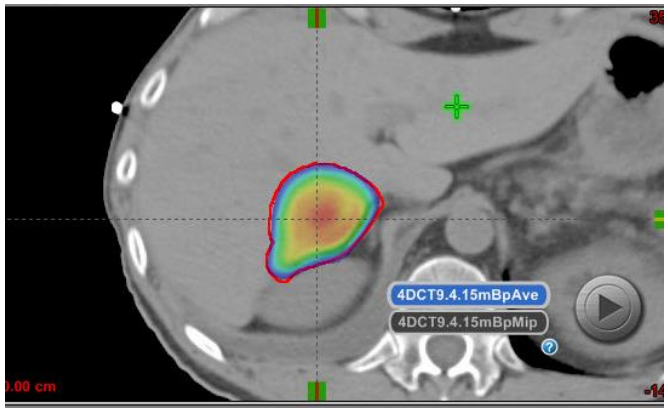
2mm distance

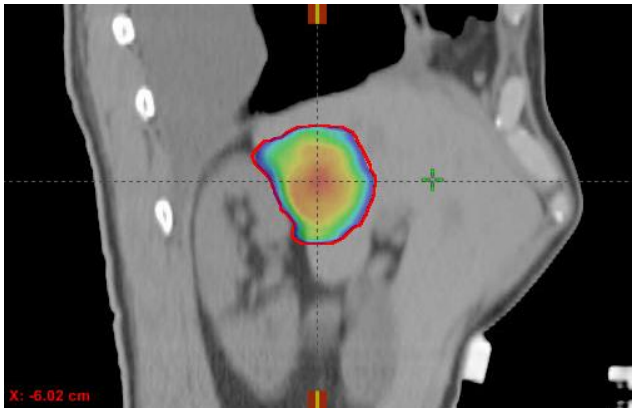
VMAT - Optimisation help structures

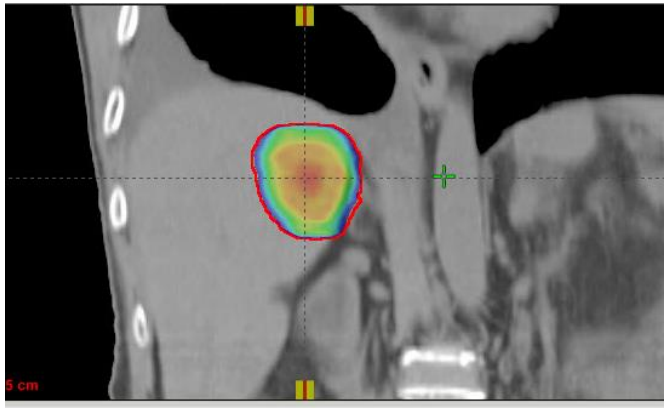




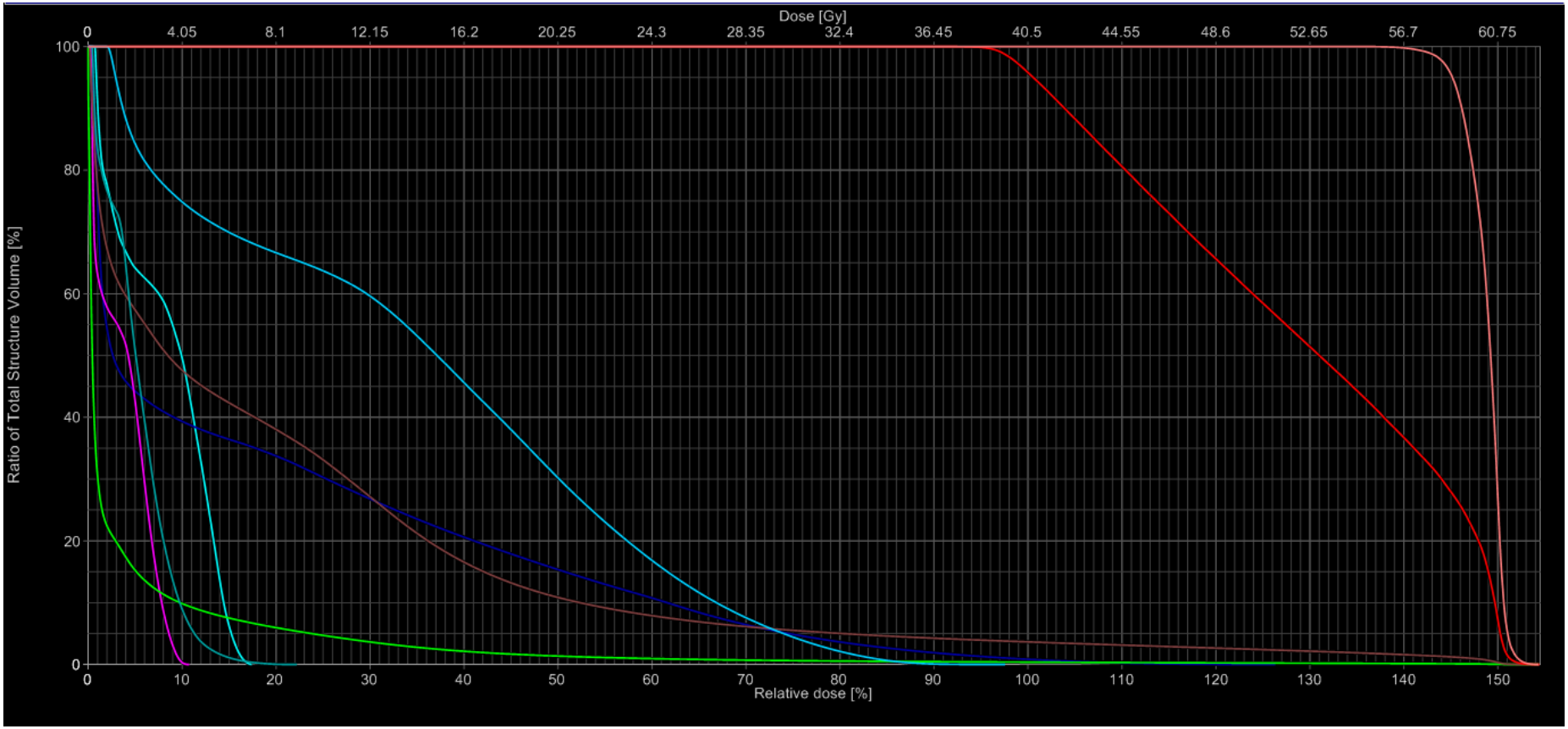
VMAT – dose distribution



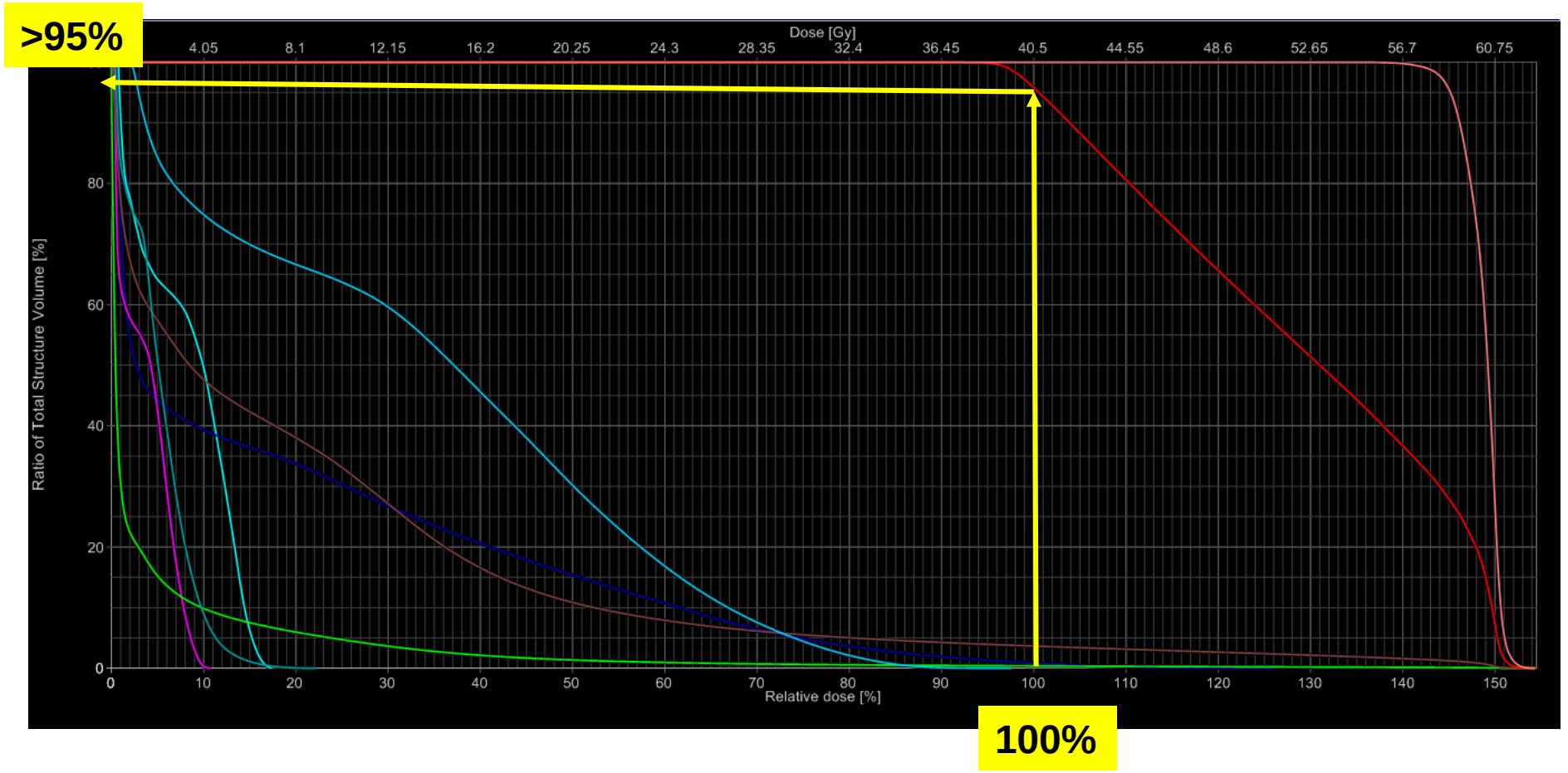




VMAT – dose distribution

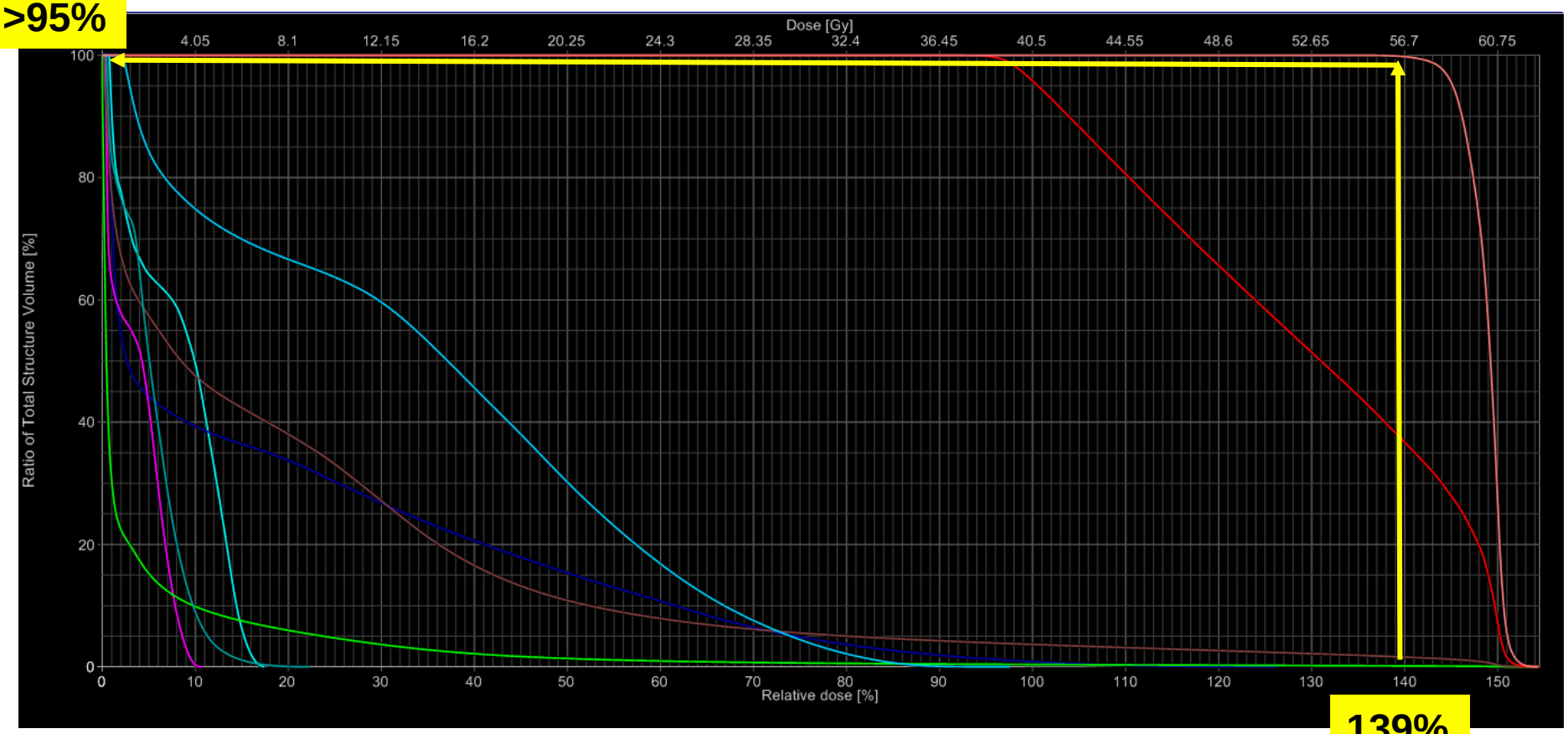


Plan evaluation



More than 95% of PTV should receive 100% of prescribed dose.

Plan evaluation



More than 95% of GTV should receive 139% of prescribed dose (derived frome 3D conformal planning)

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SBRT spine treatment planning

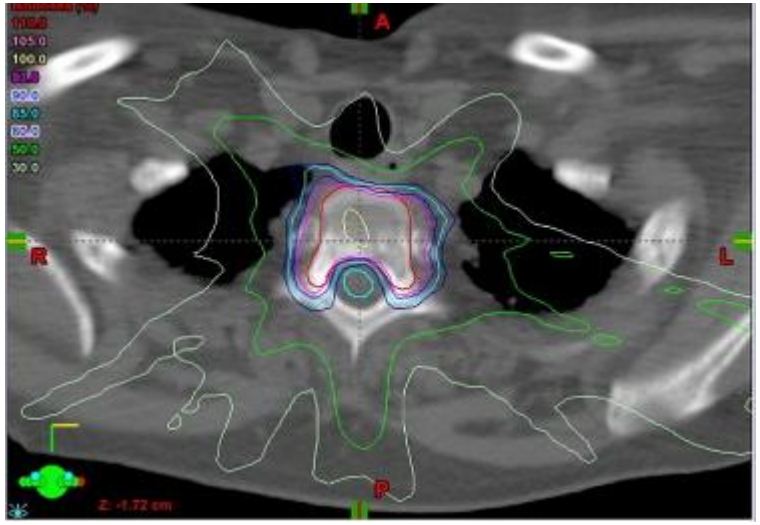
Different concepts

Treatment of the tumor lesion:

1 x 12.5Gy – 25Gy @ 80-95%

3-5 x 7Gy-9Gy @80-95%

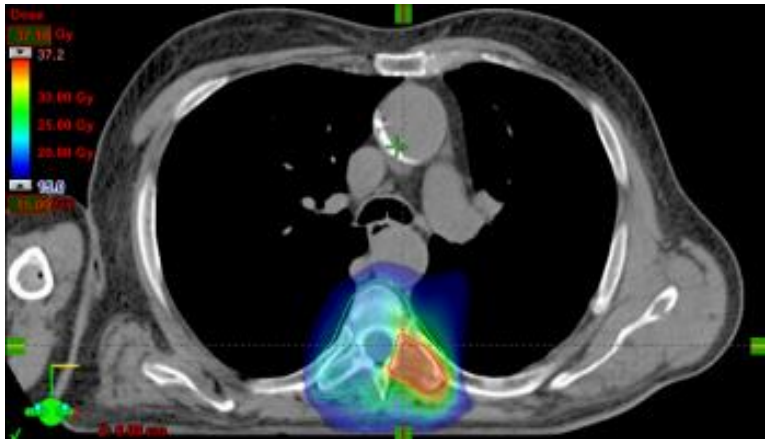
Distance between GTV and spinal cord > 3mm



Integrated boost concept:

5 x 7Gy @ target lesion
5 x 4Gy @ whole vertebra body
Homogeneous prescription

10 x 4.75Gy 7Gy @ target lesion
10 x 3Gy @ whole vertebra body
Homogeneous prescription

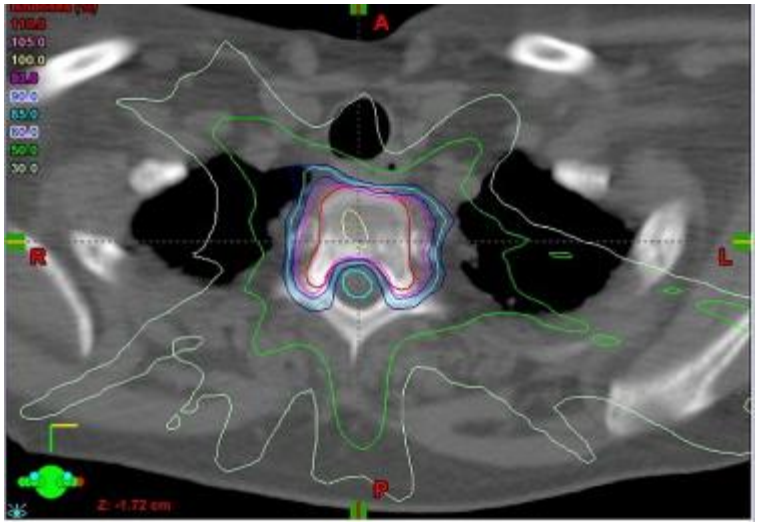


SBRT of spine tumors

Treatment technique:

Concave shaped volumes
→ Use an **intensity modulated techique:**

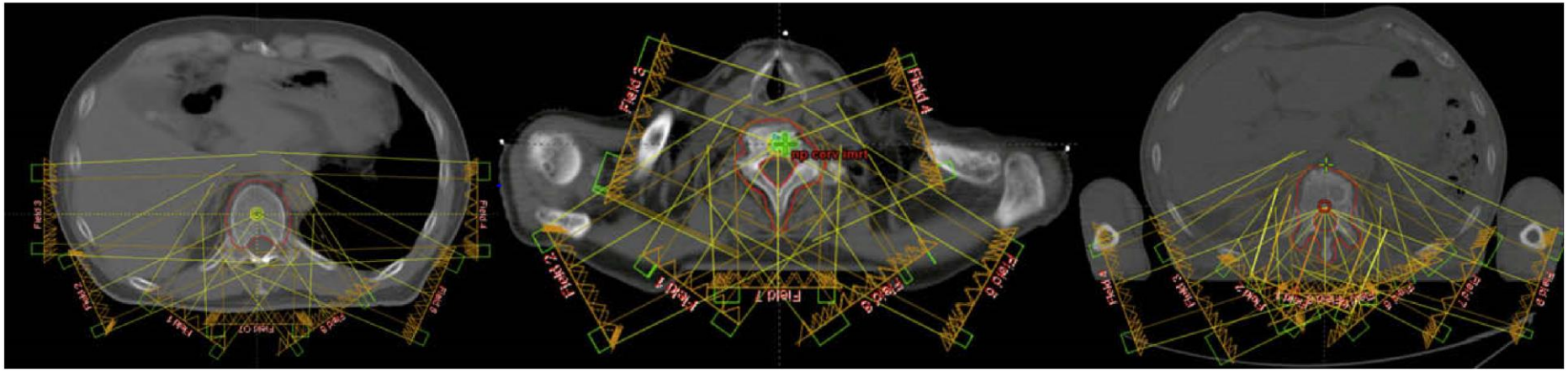
- to shape the dose around the target and
- better spare the spinal cord



SBRT of spine tumors

Treatment technique IMRT:

9-11 fields using 6MV beam
Sliding window IMRT
Collimator angle between 0° and 55°
Adapted beam setup according to the spinal level

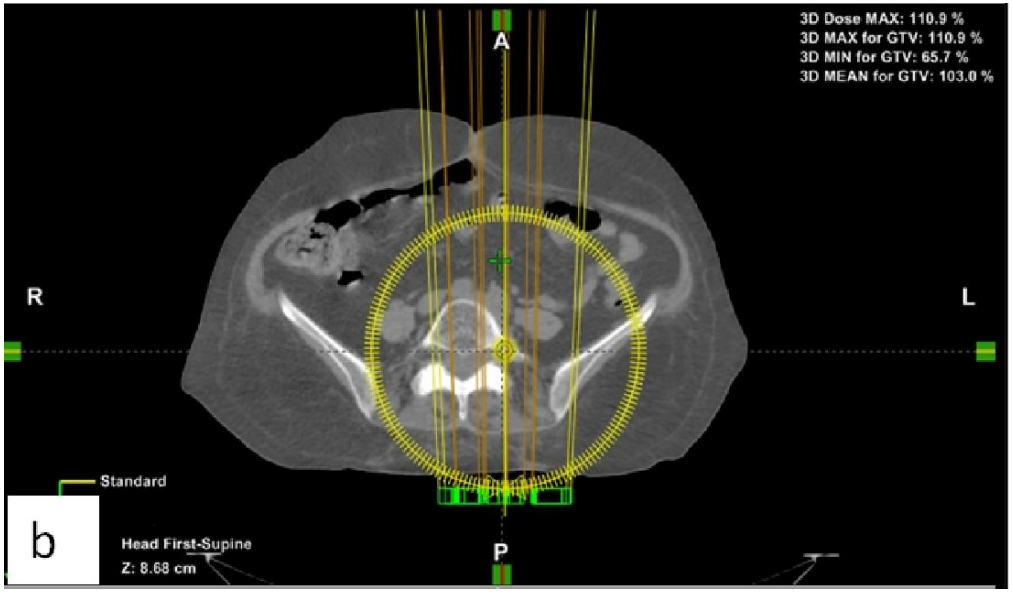


Kuijpers et al, RO, 2010

SBRT of spine tumors

Treatment technique VMAT:

Kuijpers et al, 2010, Amoush et al, 2015, Oh et al, 2013:
1-2 arcs using 6MV beam
Collimator angle between 20° and 90°
Avoidance sectors to spare organs at risk



SBRT of spine tumors

Treatment technique VMAT versus IMRT:

Kuijpers et al, 2010
→ Comparable plan quality and treatment delivery time

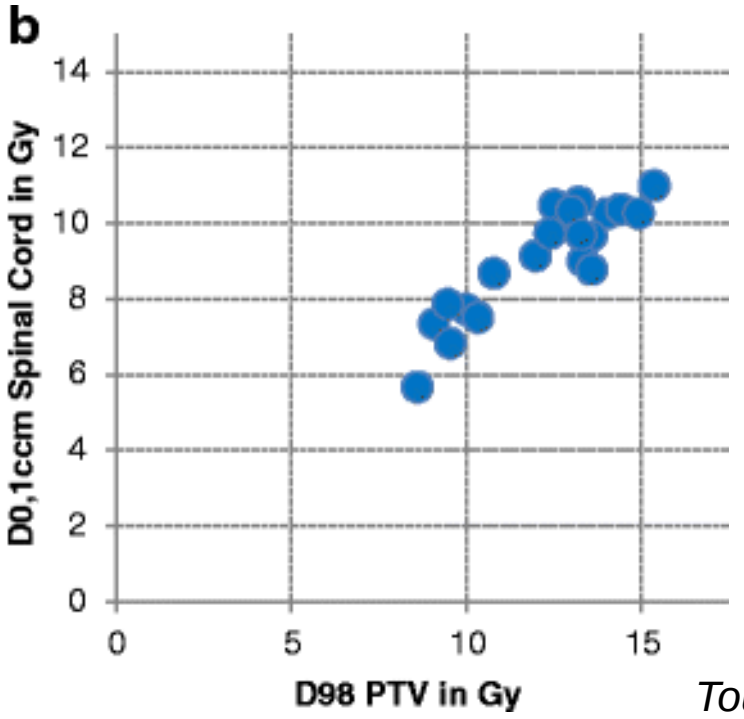
Oh et al, 2013
→Comparable plan quality

Amoush et al, 2015
→ Comparable plan quality
→ Smaller treatment time using VMAT

No difference between VMAT and IMRT in plan quality, however reduced treatment time with VMAT.

SBRT of spine tumors

Dose to the spinal cord:



Treatment plans of:

- 4 SBRT spine cases
- Each planned at 5 different centers

Toussaint et al, Radiation Oncology 11.1 (2016): 1

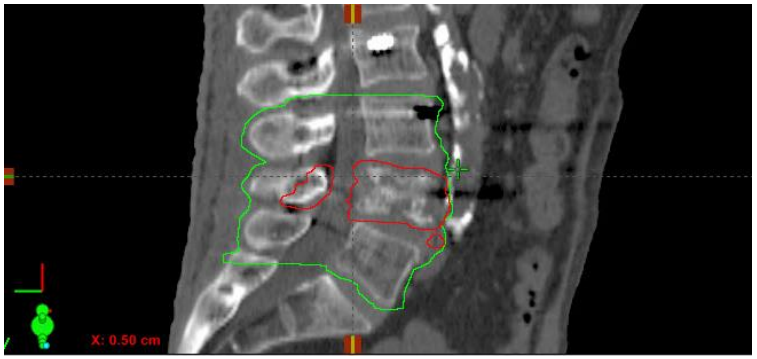
Don't expect miracles: The smaller the dose to the spinal cord the worse the coverage of the PTV.

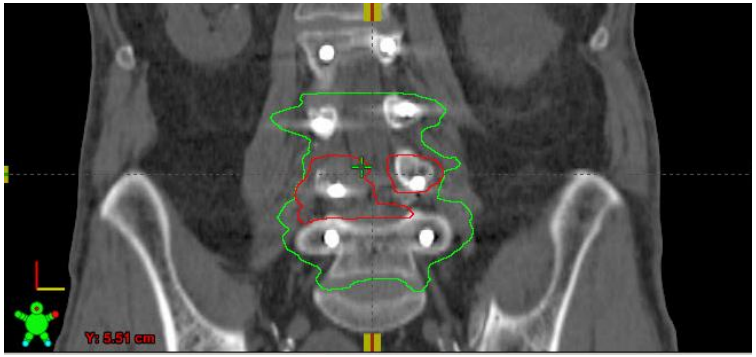
SBRT spine – integrated boost concept

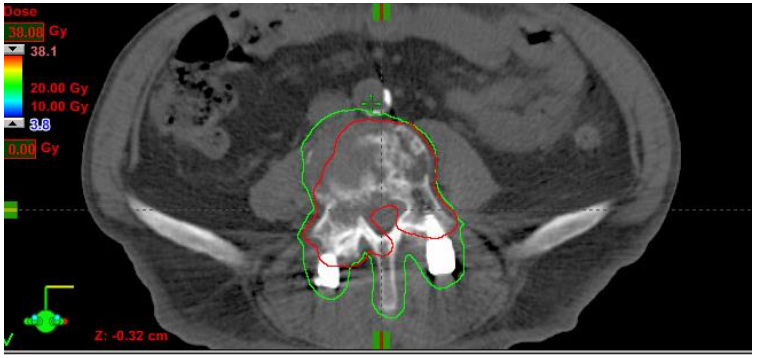
Integrated boost concept:

5 x 7Gy @ target lesion
5 x 4Gy @ whole vertebra body
Homogeneous prescription

10 x 4.75Gy @ target lesion
10 x 3Gy @ whole vertebra body
Homogeneous prescription







Guckenberger et al, BMC cancer 12.1 (2012): 530.

SBRT spine – integrated boost concept

Integrated boost concept: Motivation

- **Single fraction limited by tolerance to the cord**
- **Many single fractions protocols are only for target >3mm away from the cord (example RTOG 0613)**

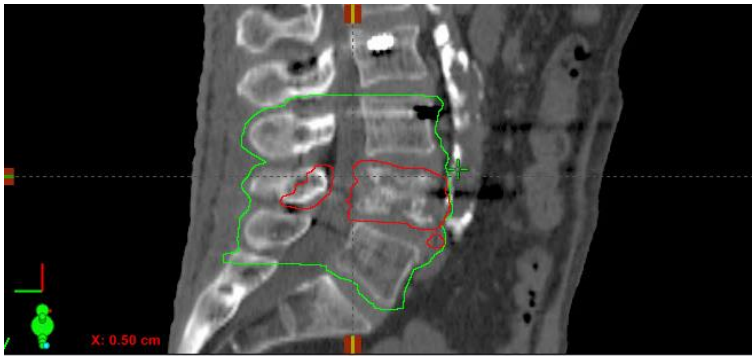
→ Fractionated approach

- **Most local failures after SBRT are in the epidural space or in the untreated vertebral elements (Nguyen 2010, Nelson 2008)**

→ Integrated boost concept

- **10-20% vertebral compression fractures in single fraction SBRT (Boehling, 2012, Sahgal 2013)**

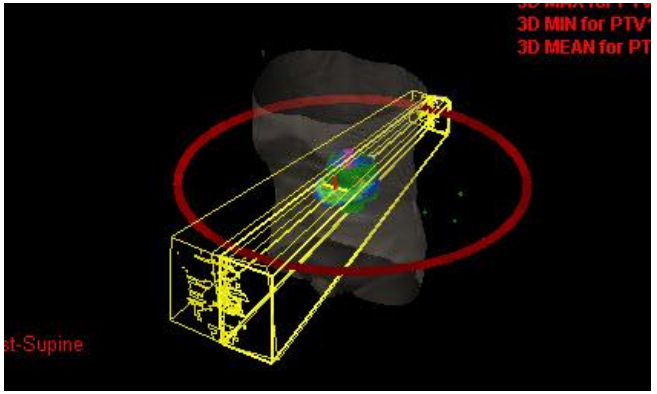
→ Homogeneous prescription

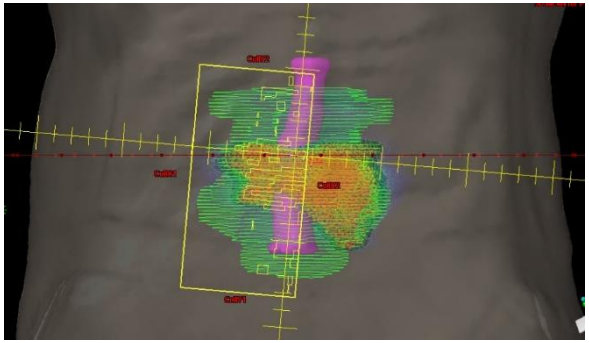


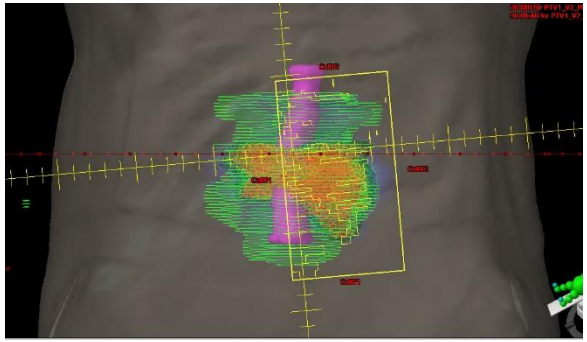
SBRT spine – integrated boost concept

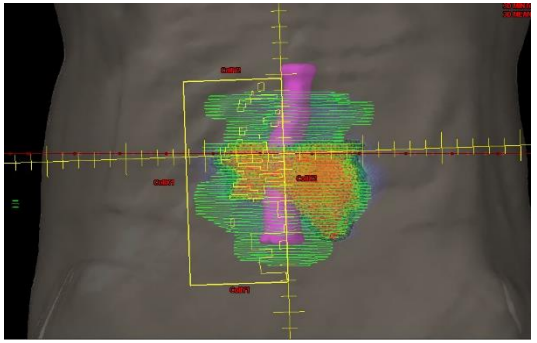
Planning technique:

- VMAT
- 2-4 arcs
- Collimator angle between +/- 10°
- Fields **cover PTV only partially** to better spare the spinal cord



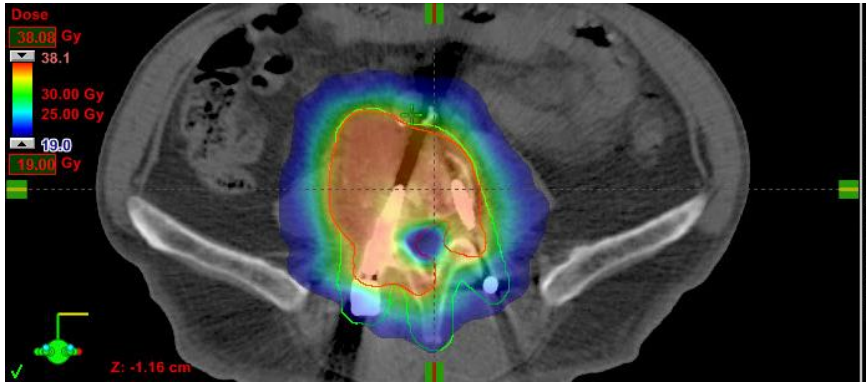


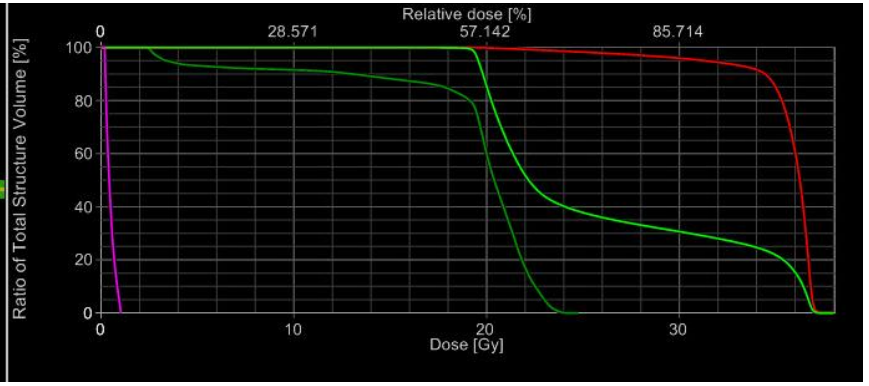


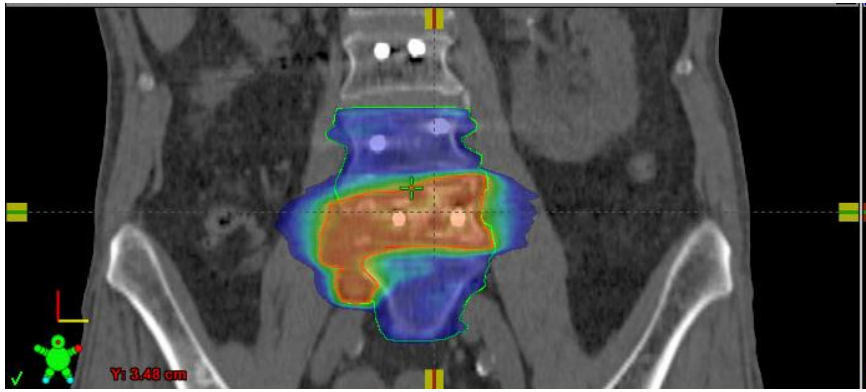


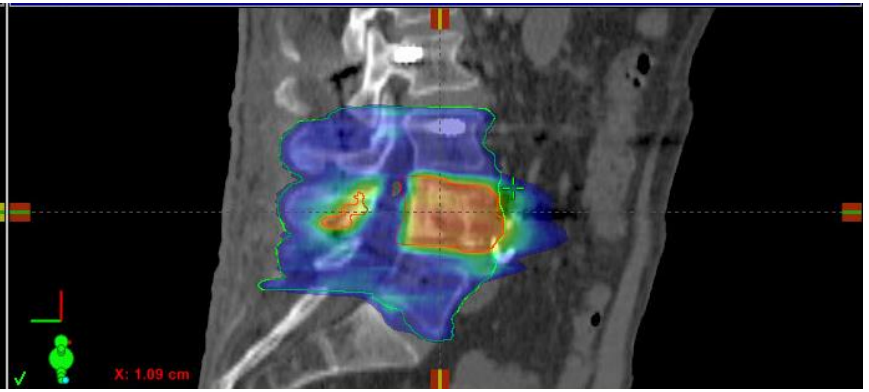
SBRT spine – integrated boost concept

Dose distribution





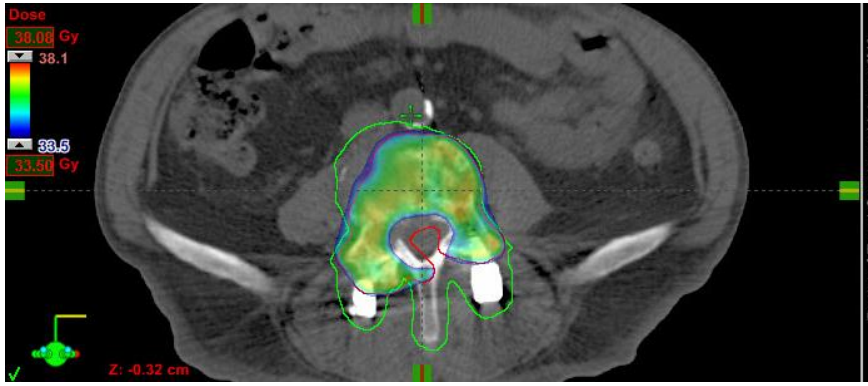


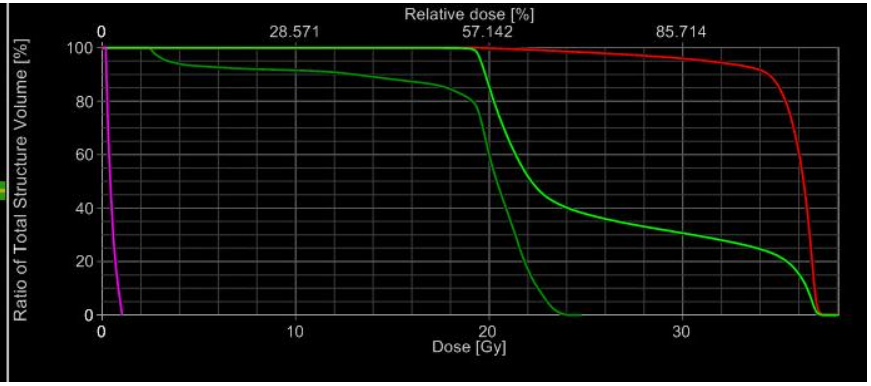


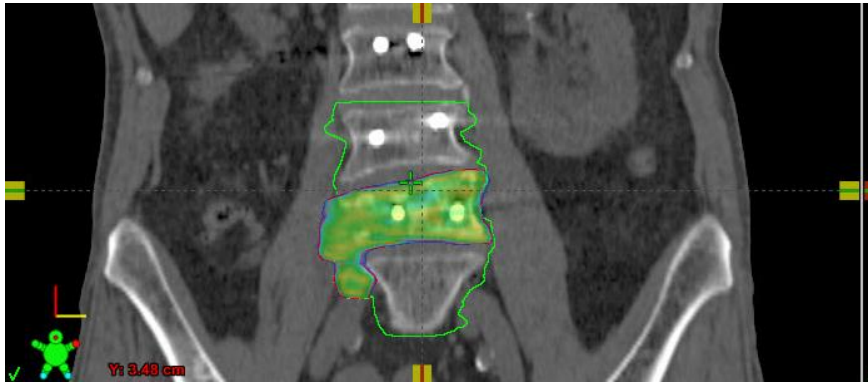
SBRT spine – integrated boost concept

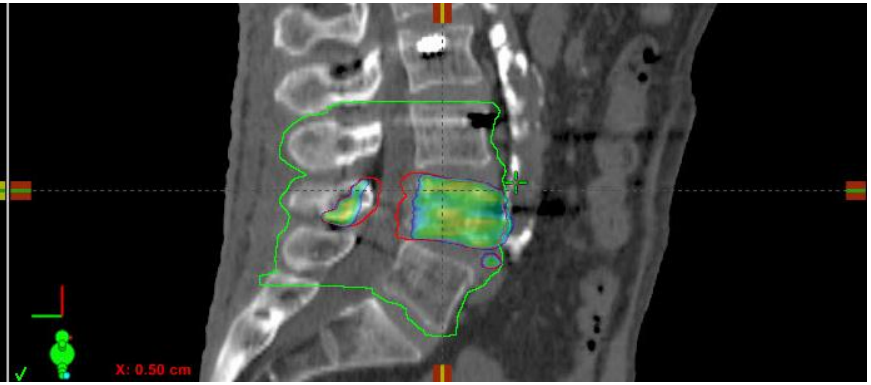
Spinal cord tolerance:

spinal cord max 23.75 Gy → compromise PTV coverage

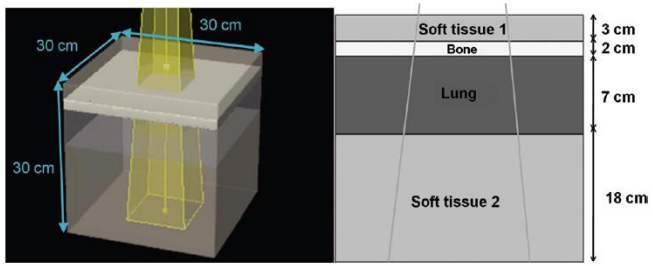


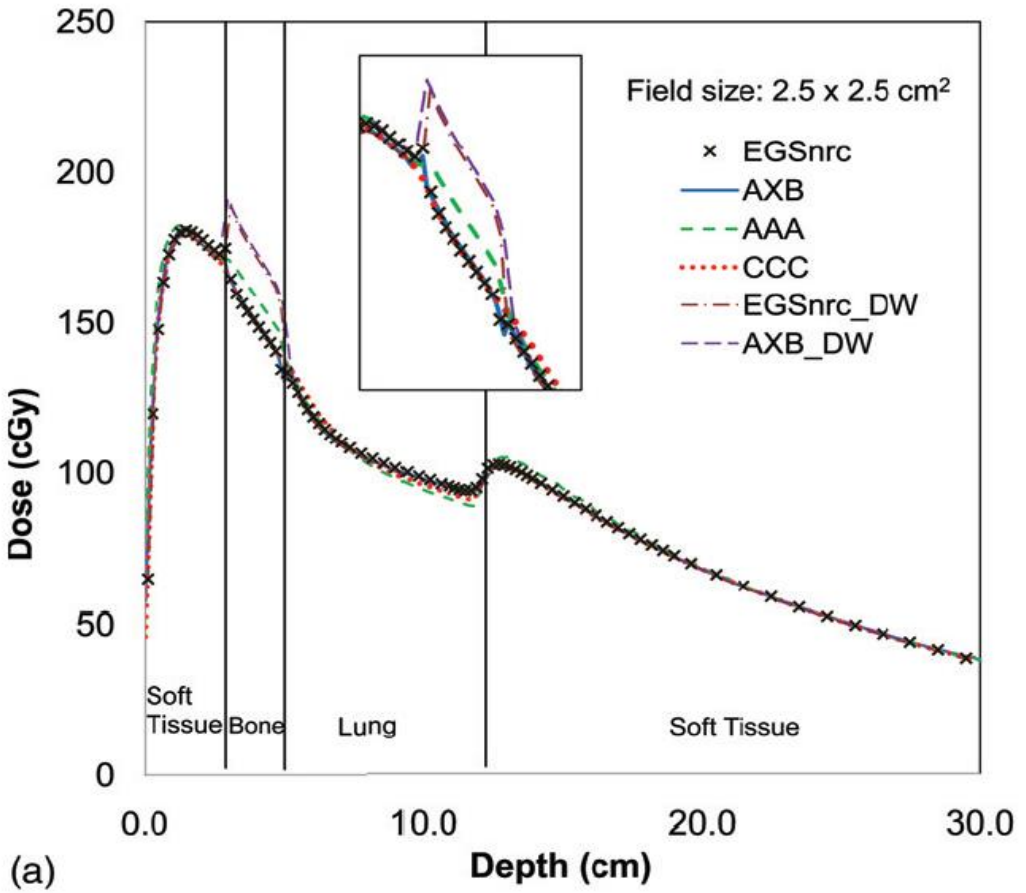






SBRT spine – Is a type C agorithm needed?





No deviations in soft tissue, small deviations in lung and largest deviations in bone!

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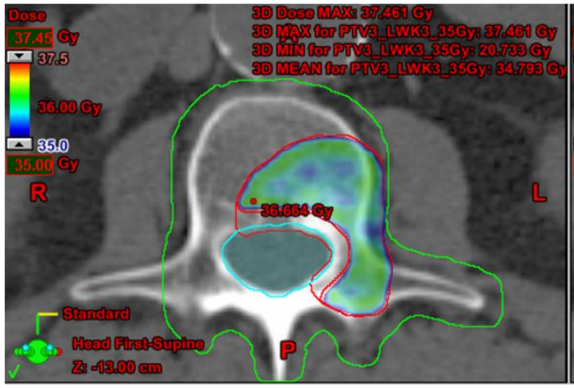
Han et al, Med. Phys. 38 (5),2011

SBRT spine – Is a type C agorithm needed?

AAA



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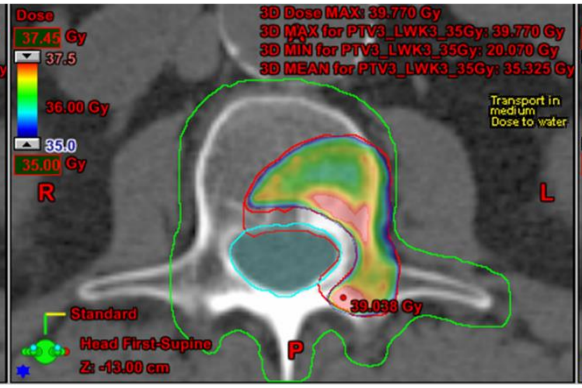

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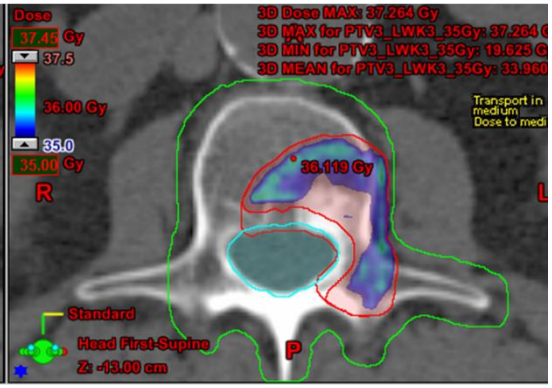
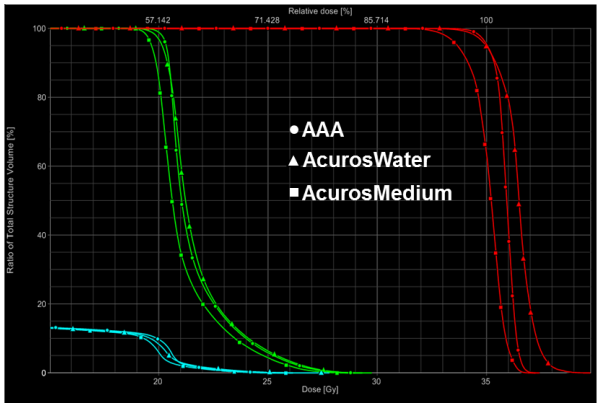
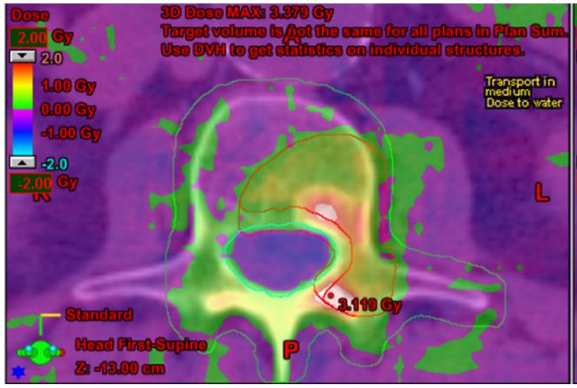




Dw-AAA



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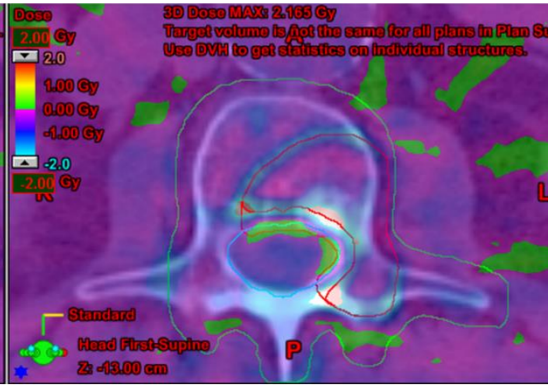

No deviations in soft tissue, small deviations in lung and largest deviations in bone!

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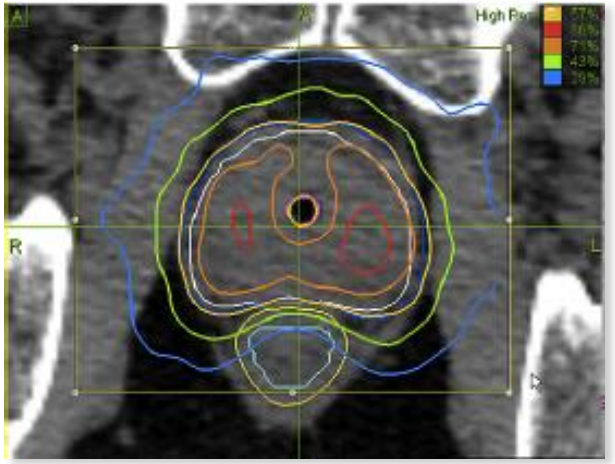
SBRT prostate treatment planning

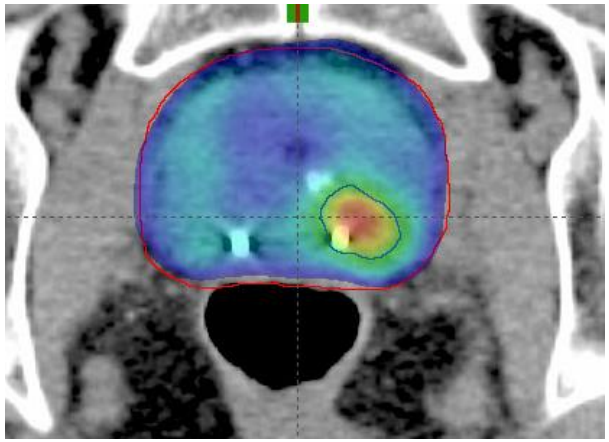
Different concepts

Treatment of the whole prostate:
5 x 6.6 Gy -10 Gy
Inhomogeneous prescription on 60-80% isodose line
‘peripheral loading’



Integrated boost concept:

5 x 7Gy @ prostate
5 x 8Gy @ index lesion
Homogeneous prescription



SBRT Prostate

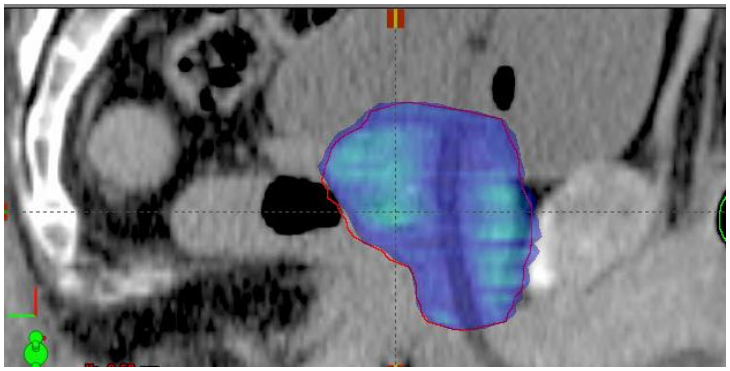
Planning technique:

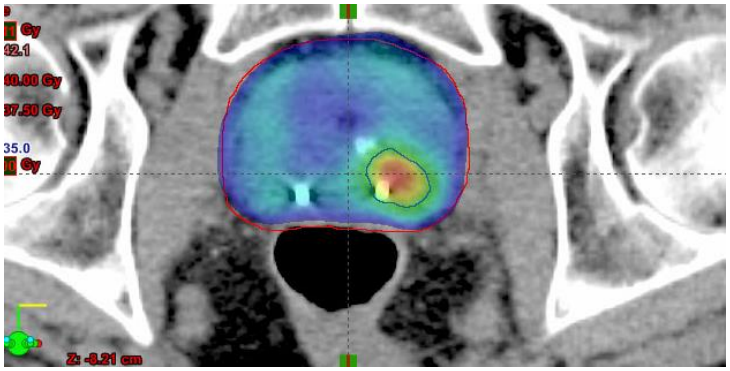
- Same field setup as in conventional fractionated RT of the prostate
- IMRT or VMAT should be used to better spare the rectum and to avoid hotspotts in the urethra

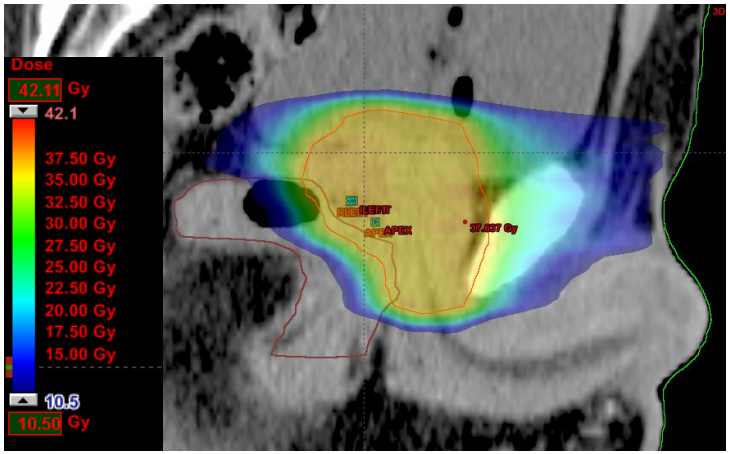
SBRT Prostate - OAR

Avoid hotspots in the urethra and in the overlapp between urethra and rectum

The anterior part of the rectum should receive less than 30% of the prescribed dose







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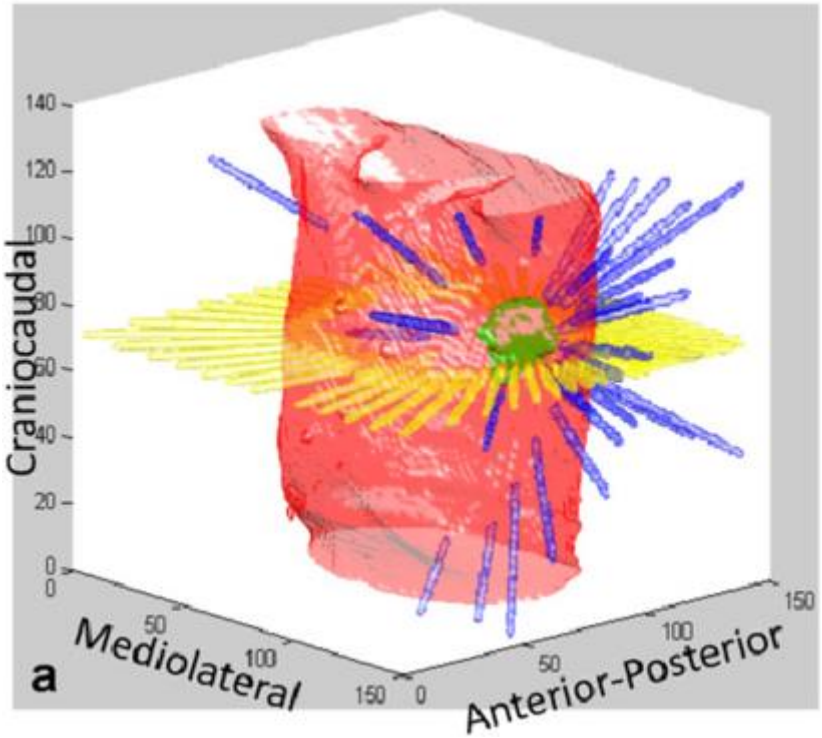
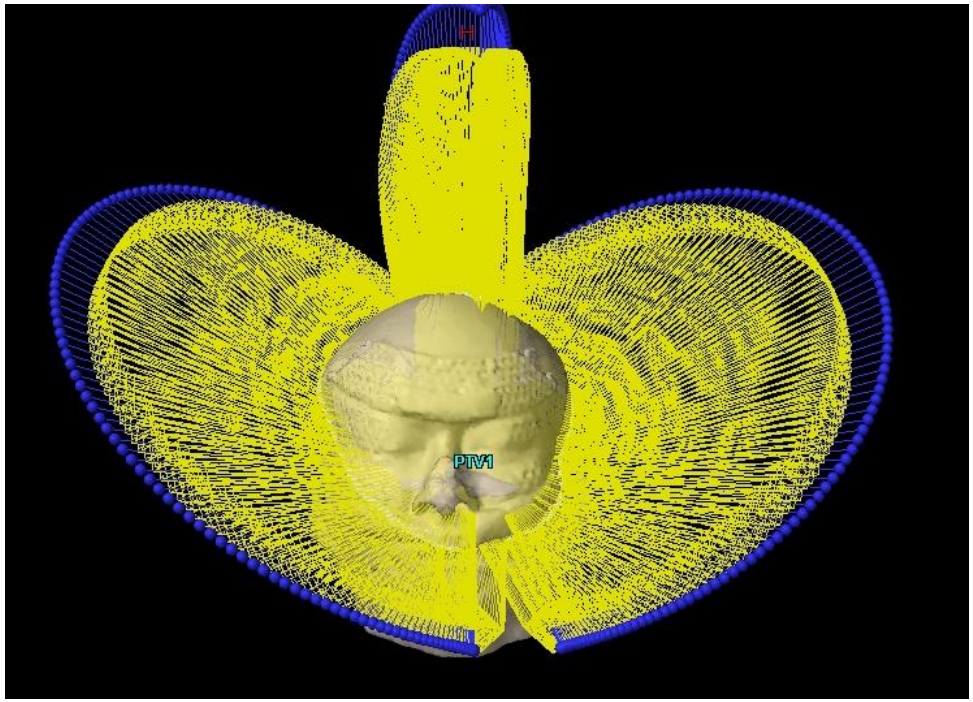
4π – any advantage?

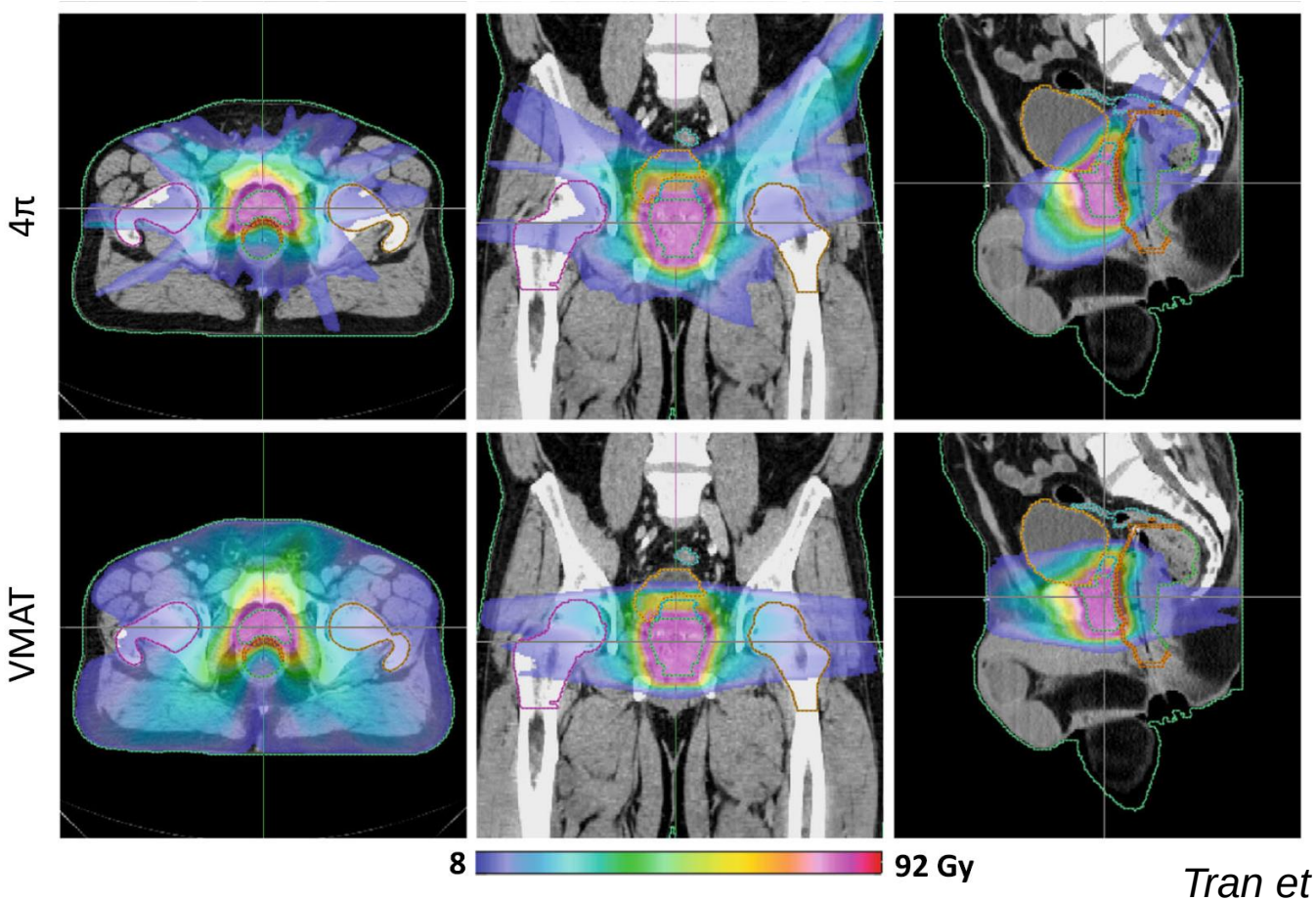
4π – What is it?





4π is a technique which tries to optimize the beam directions not only planar but also co-planar.

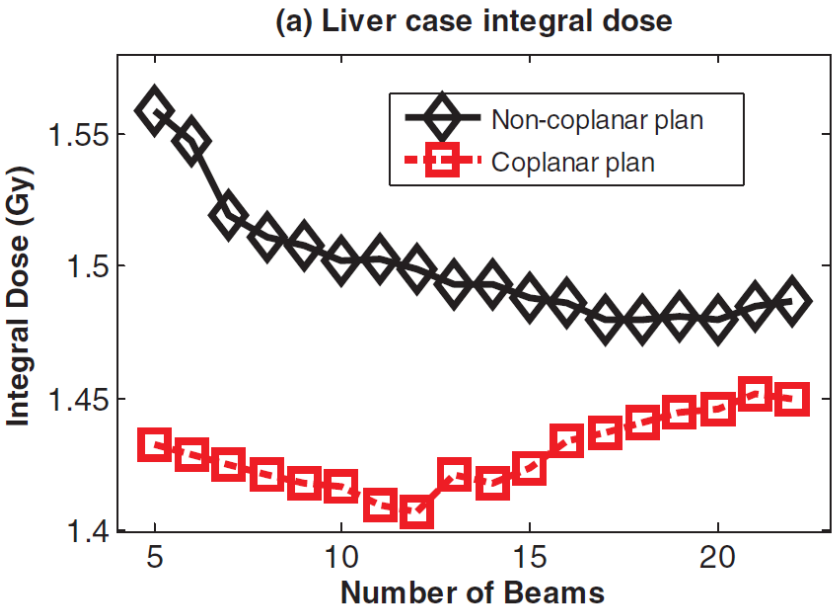
Coplanar versus non-coplanar

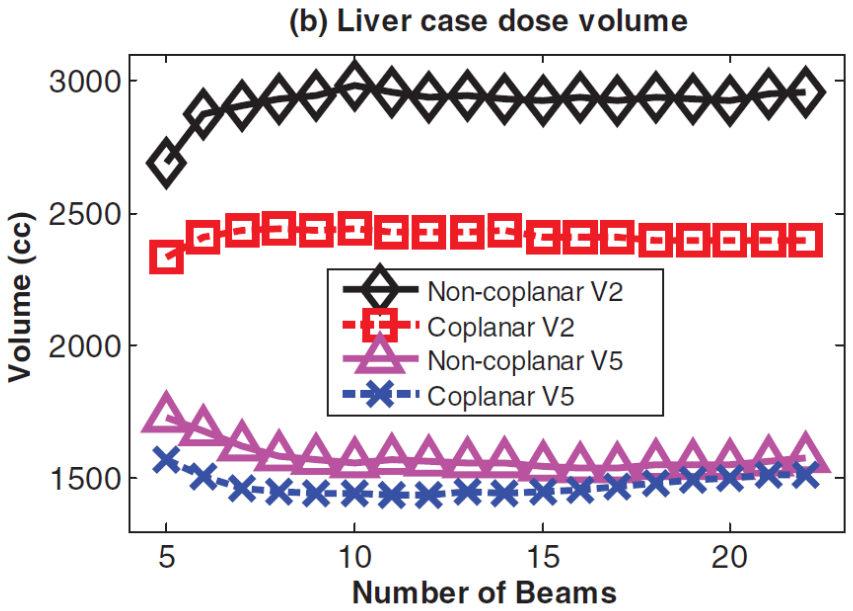


Tran et al, Rad. Onc. 2017

Increased low dose bath using non-coplanar beams.
Reduced volume of high doses.

Coplanar versus non-coplanar

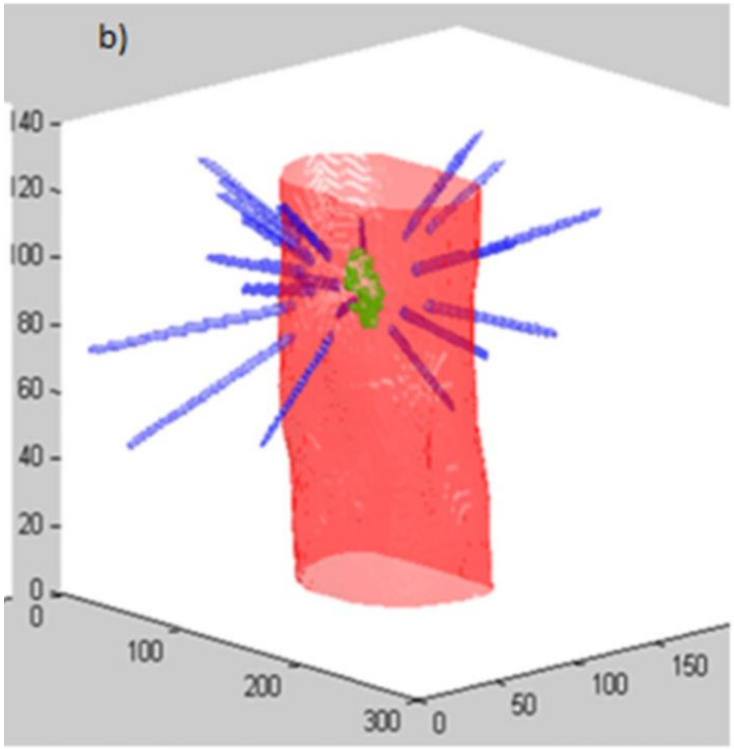




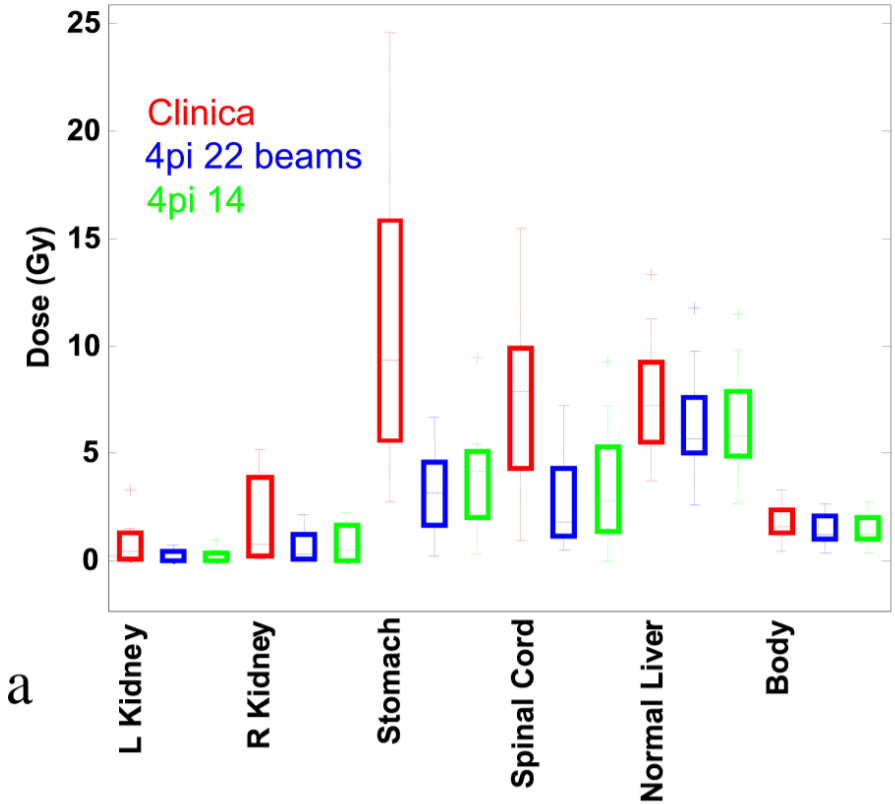
Nguyen et al, Med. Phys. 2014

Increased low dose bath using non-coplanar beams.

Coplanar versus non-coplanar



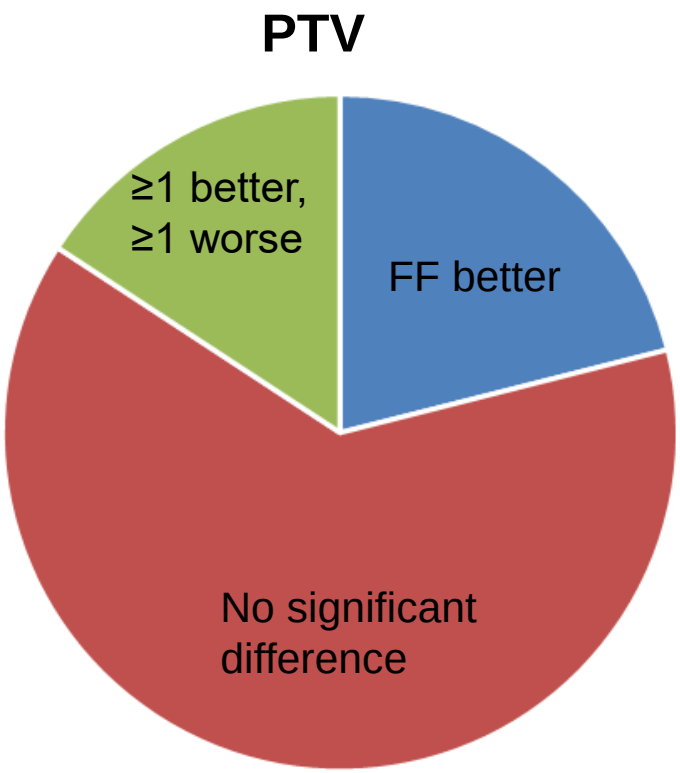
Dong et al, IJROBP 2012

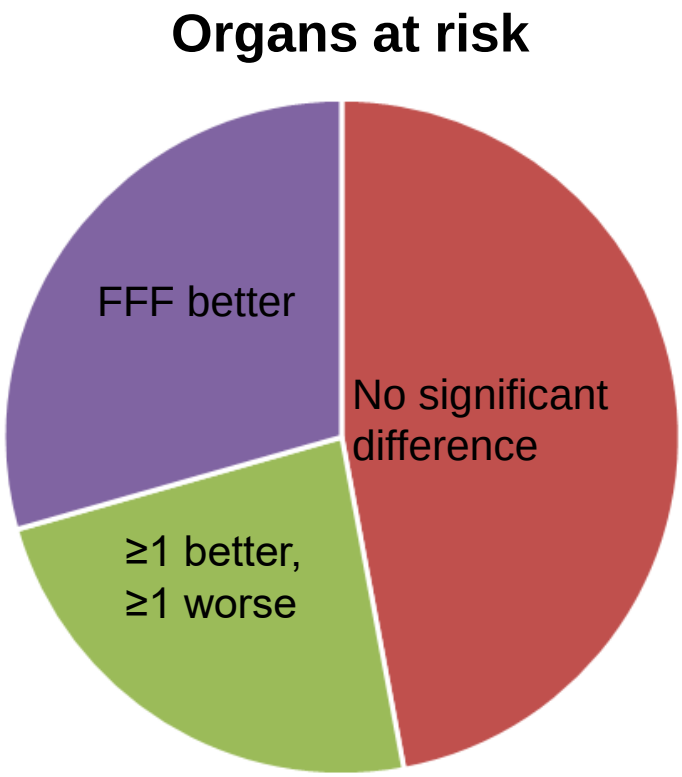


Improved sparing of organs at risk using non-coplanar fields.

FFF beams – any advantage?

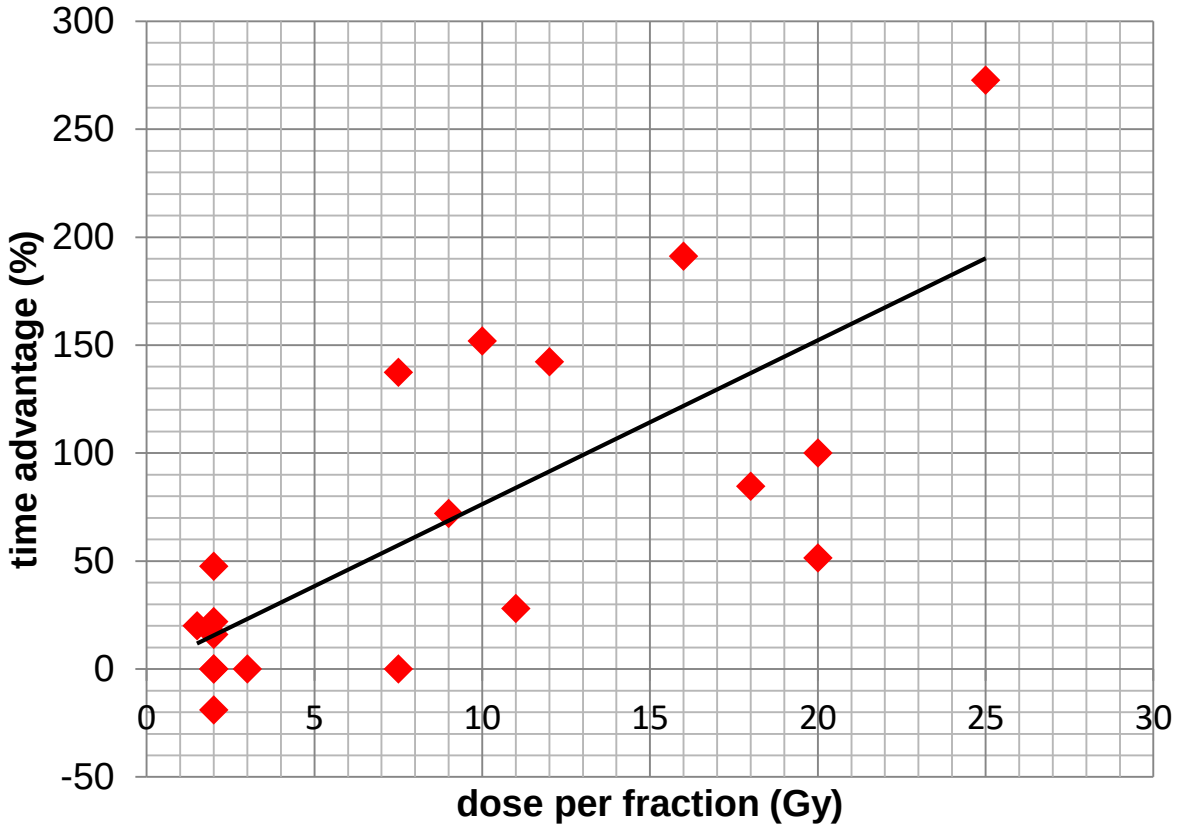
FFF beams – any dosimetric benefit?





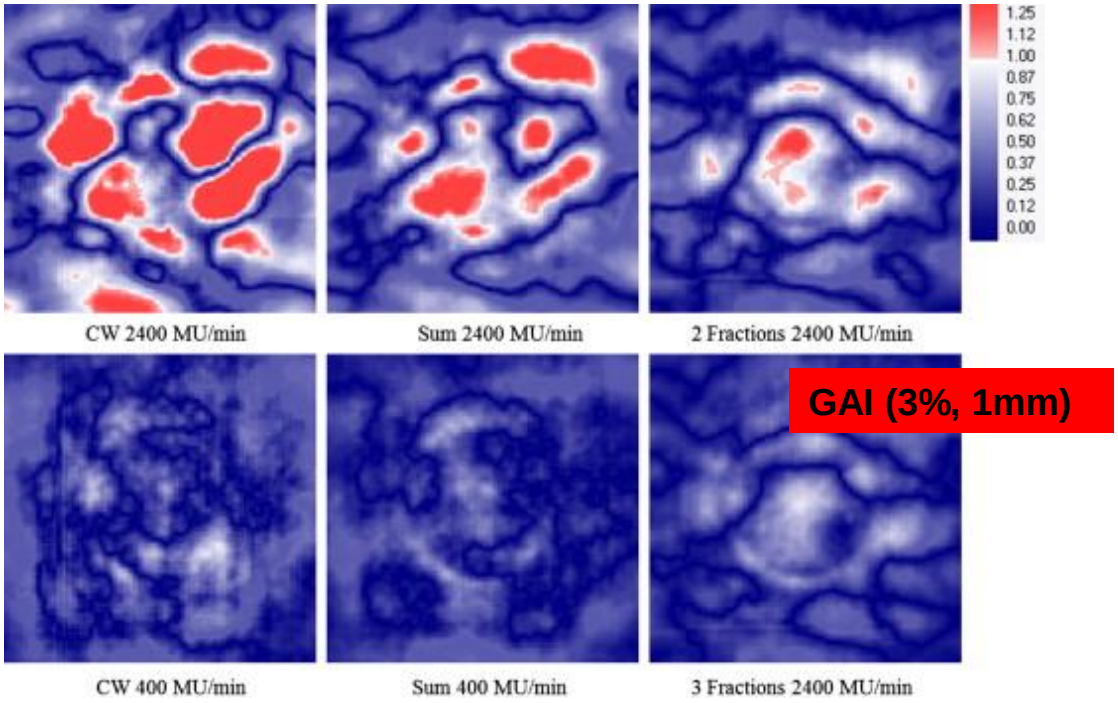
20 studies comparing FFF versus FF:
Lang et al, Ong et al, Reggiori et al, Lechner et al, Alongi et al, Nicolini et al, Lechner et al, Dzierma et al, Kretschmer et al, Lai et al, Wang et al, Stieler et al, Zhuang et al, Hrbacek et al, Shi et al, Gasic et al, Fu et al, Hansen et al, Pruijt et al

FFF beams – faster treatments?



11 studies comparing FFF and FF:
Lang et al,
Ong et al,
Reggiori et al,
Lechner et al,
Alongi et al,
Nicolini et al,
Dzierma et al,
Lai et al,
Wang et al,
Stieler et al,
Zhuang et al,
Hrbacek et al

FFF – increased interplay effect



Ong et al, IJRO, 2012

For treatments with few fractions two arcs should be used for treatment planning.

Questions

How can I reach the optimal SBRT plan?

VMAT without/with FFF in moving targets?

SBRT treatment planning Basic rules and tricks

Most clinical data is based on type B algorithm. When type C algorithm is used, what will be the optimal prescription dose?

Is it possible to plan a SBRT plan with VMAT? If no what are the disadvantages?

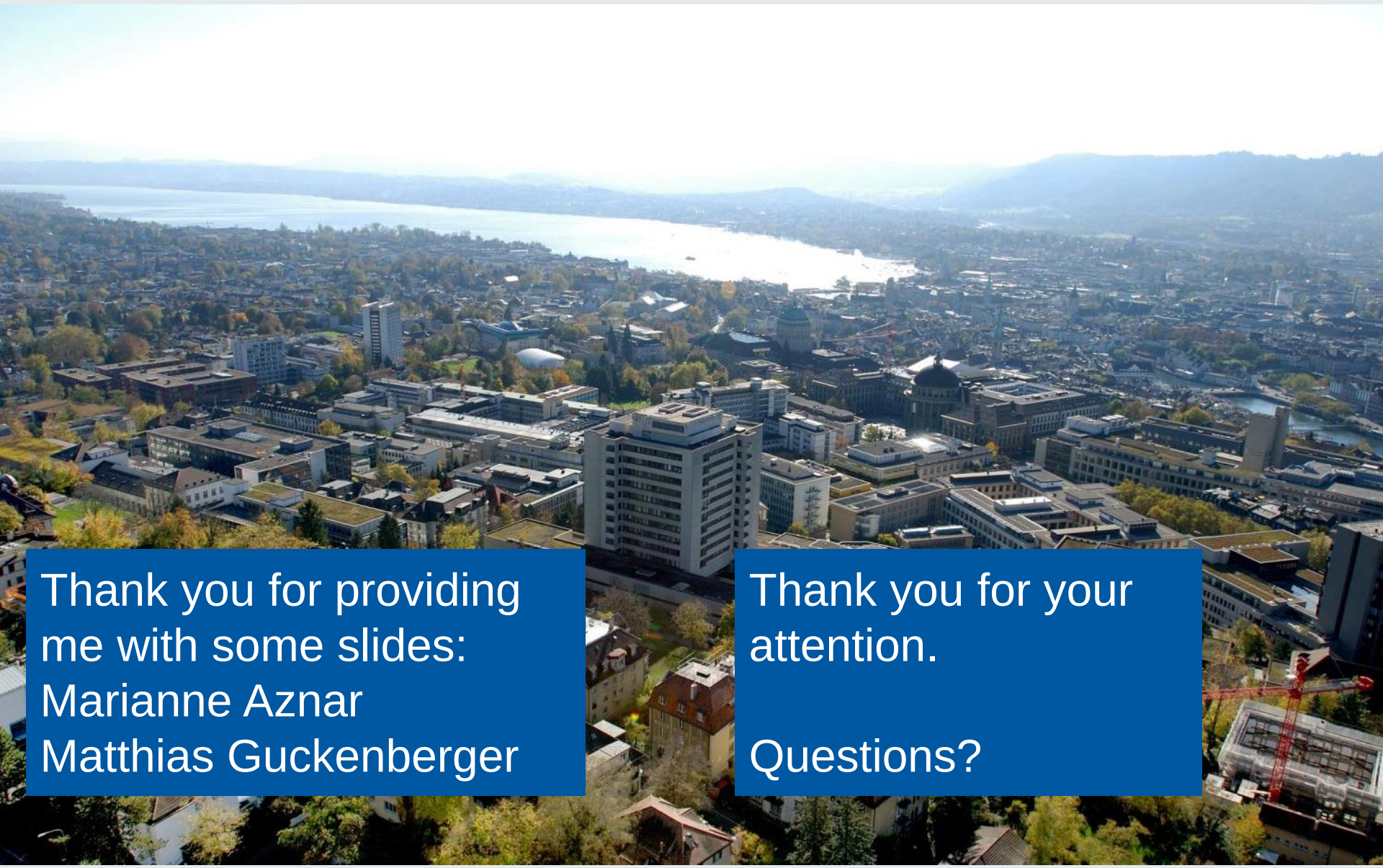
References

Jung, S. H., Yoon, S. M., Park, S. H., Cho, B., Park, J. W., Jung, J., ... & Do Ahn, S. (2013). Four-dimensional dose evaluation using deformable image registration in radiotherapy for liver cancer. *Medical physics*, *40*(1), 011706.

Ong, C., Verbakel, W. F., Cuijpers, J. P., Slotman, B. J., & Senan, S. (2011). Dosimetric impact of interplay effect on RapidArc lung stereotactic treatment delivery. *International Journal of Radiation Oncology* Biology* Physics*, *79*(1), 305-311.

Guckenberger, M., Hawkins, M., Flentje, M., & Sweeney, R. A. (2012). Fractionated radiosurgery for painful spinal metastases: DOSIS-a phase II trial. *BMC cancer*, *12*(1), 530.

Amoush, Ahmad, et al. "Volumetric modulated arc therapy for spine SBRT patients to reduce treatment time and intrafractional motion." *International Journal of Cancer Therapy and Oncology* 3.2 (2015).



Thank you for providing me with some slides:
Marianne Aznar
Matthias Guckenberger

Thank you for your attention.

Questions?

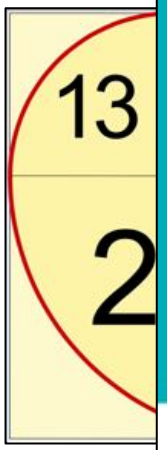
UniversitätsSpital Zürich

ESTRO School

WWW.ESTRO.ORG/SCHOOL

Mathematical series and physics

- What is the ne
  - 1 – 4 – 9 –
- Everyone knov
  - 1 – 1 – 2 –



- What about thi
  - 50 – 62 –

iridium kankernetwerk
Radiotherapie
Medische Oncologie
Hematologie

VUB VRIJE UNIVERSITEIT BRUSSEL

Understanding dose prescription in SRS and SBRT

Dirk Verellen

DV is involved in an on-going scientific collaboration with RaySearch, Sun Nuclear, ORFIT

ESTRO School

Learning objectives

- To understand the historical background, evolution and purpose of ICRU reports 50, 62, 83, 91...
- To understand the influence of PTV margins, tissue heterogeneity and motion on dose prescription and reporting in SRS en SBRT.
- To understand the variety on dose reporting and how it might influence clinical implementation of SBRT programs.
- To provide a summary of the ICRU 91 report on prescribing, recording, and reporting of stereotactic treatments with small photon beams.

Questions from the audience

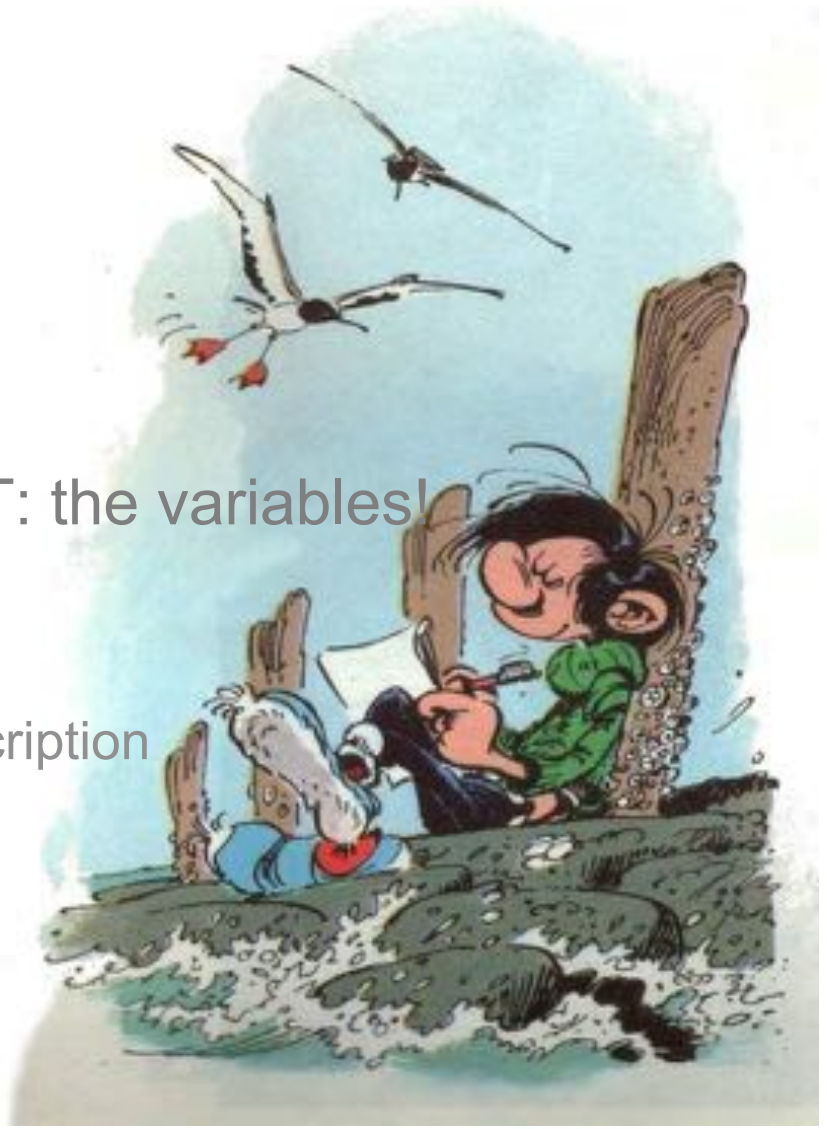
- Some questions related to the ICRU 91 report
  - GTV to CTV margin: yes or no?
  - SRS/SRT/SBRT what is the difference
  - Prescribing to an enveloping isodose line is fine, but what isodose should we use? Isodose compared to what normalization point?

Outline

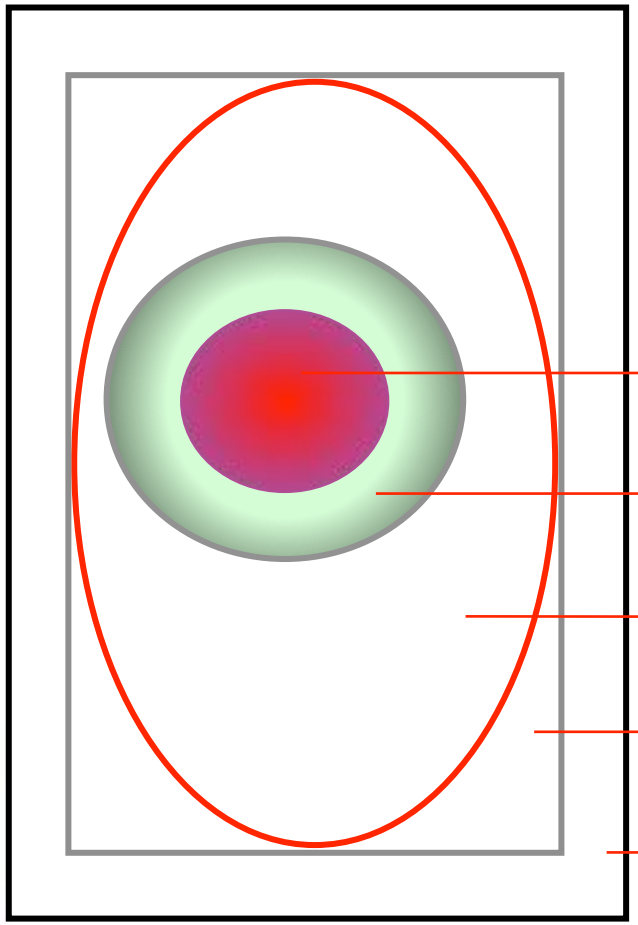
- Let's start with the definition of the PTV:
  - Evolution of ICRU reports in fast forward
  - PTV and SRS / SBRT

- Dose prescription and reporting in SBRT: the variables!
  - PTV & dose prescription
  - Tissue heterogeneity & dose prescription
  - PTV & tissue heterogeneity % dose prescription
  - Motion & dose prescription

- What about the ICRU 91?



Let's start with the definitions



GTV

CTV

Clinically determined

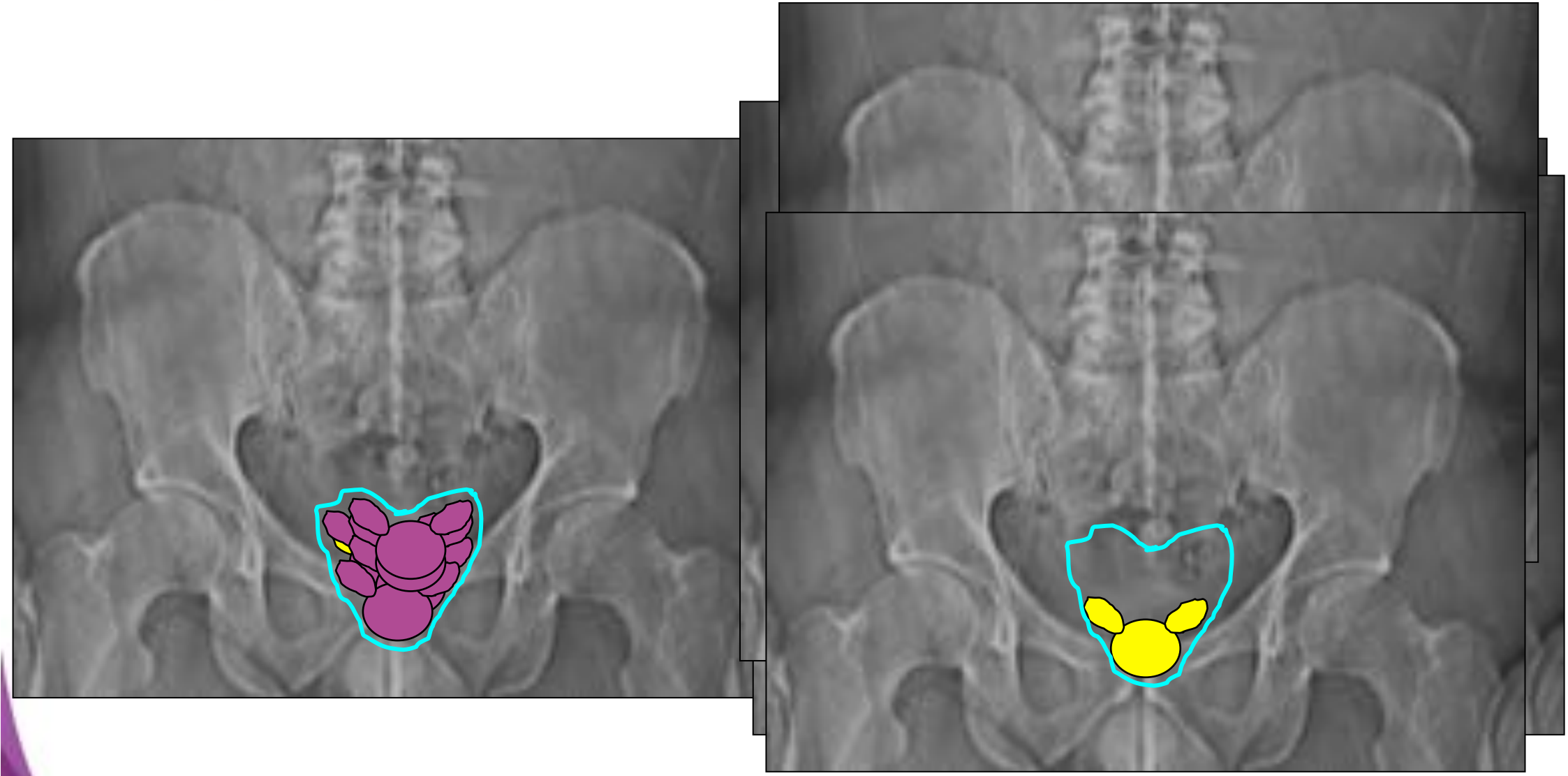
PTV

"statistical box" representing a volume with a high probability of containing the CTV

TV

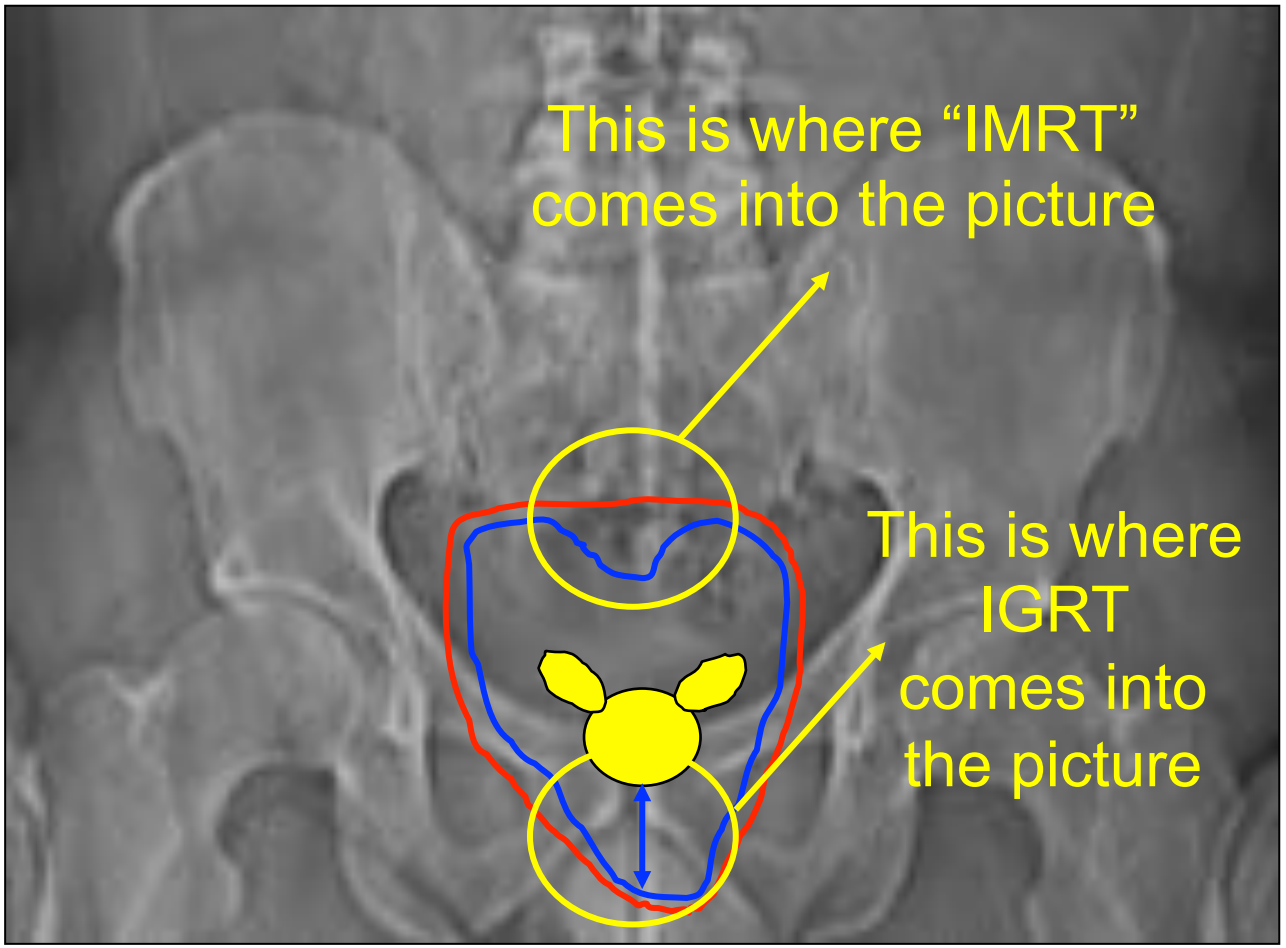
IV

Let's start with the definitions



"The dancing prostate"

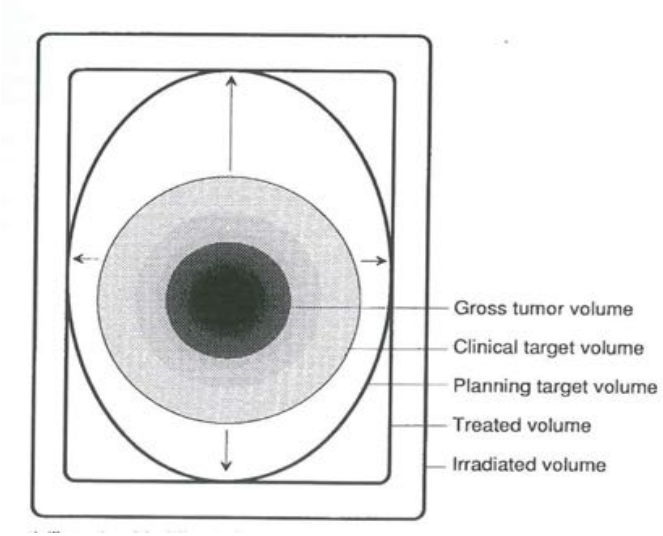
Let's start with the definitions



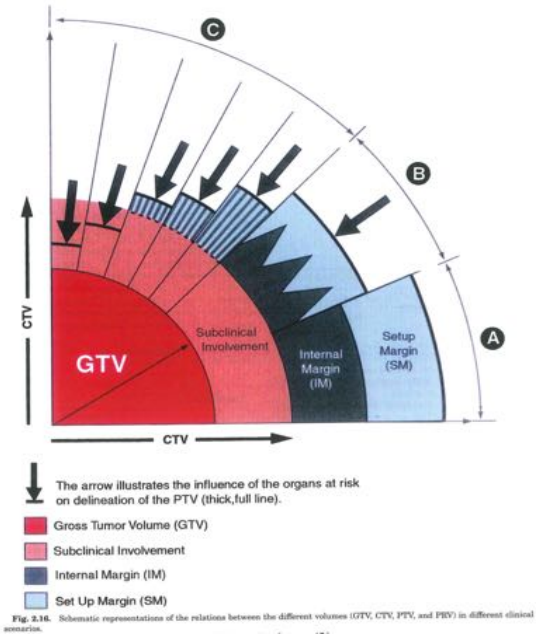
"The dancing prostate"

Let's start with the definitions

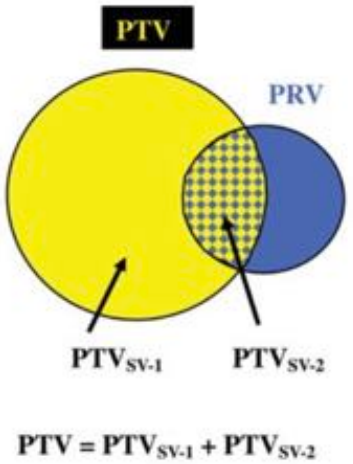
- ICRU 50



- ICRU 62



- ICRU 83



Let's start with the definitions

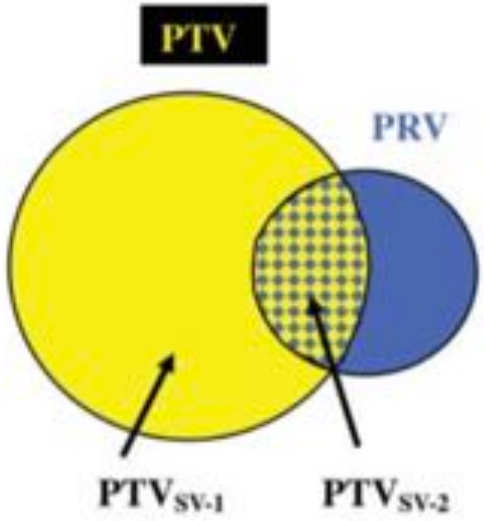
- ICRU 83:
  - The PTV is **A GEOMETRICAL CONCEPT** introduced for treatment planning and evaluation. **It is the recommended tool to shape absorbed-dose distributions to ensure that the prescribed absorbed dose will actually be delivered to all parts of the CTV with a clinically acceptable probability**, despite geometrical uncertainties such as organ motion and setup variations
  - It surrounds the representation of the CTV with a margin such that the planned absorbed dose is delivered to the CTV
  - This margin takes into account both the **internal** and the **setup** uncertainties
  - **Although the delineation of the GTV and the CTV is independent of the irradiation technique, the delineation of the PTV is dependent on the technique and is part of the treatment prescription**.
  - A margin must be added to the CTV taking into account uncertainties and variations in (1) position, size, and shape of the CTV (internal variations), and (2) patient and beam positioning (external variations)

Let's start with the definitions

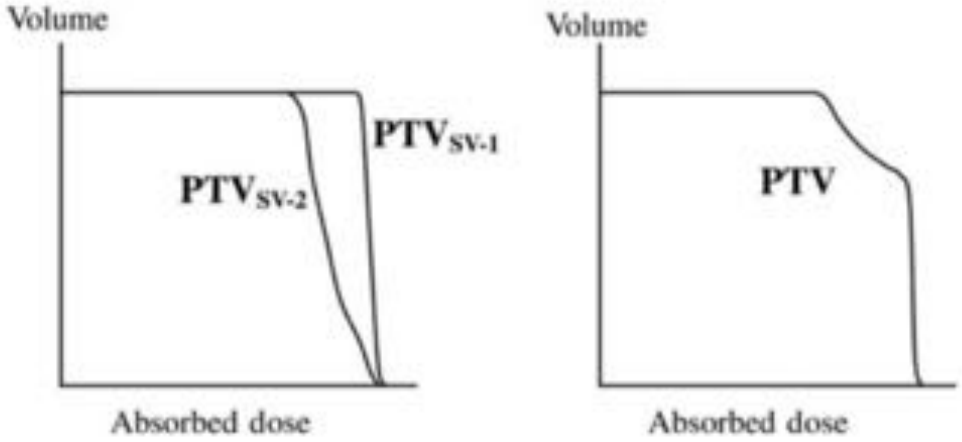
- ICRU 83:
  - In earlier ICRU documents, the possibility of **compromising the margins of the PTV** if they encroached on **OAR** was suggested (ICRU, 1999; 2004; 2007), but is **no longer recommended**. To reduce the CTV-to-PTV margin has always been a temptation. As an example, the CTV-to-PTV margin between the prostate and rectum is often 1 cm, except in the anterior – posterior direction for which it is reduced to spare the rectum
  - To ensure accurate reporting of absorbed dose to the PTV in cases for which the PTV encroaches or overlaps another PTV, OAR, or PRV, it is now recommended that **the delineation of the primary PTV margins should not be compromised**. Developments in treatment-planning software now make it possible to achieve sufficient dose sparing of the OAR by **using priority rules in optimizer** planning systems. Alternatively, subdivision of the PTV into regions with different prescribed absorbed doses (so-called **PTV-subvolumes**, PTV_{SV}) may be used.

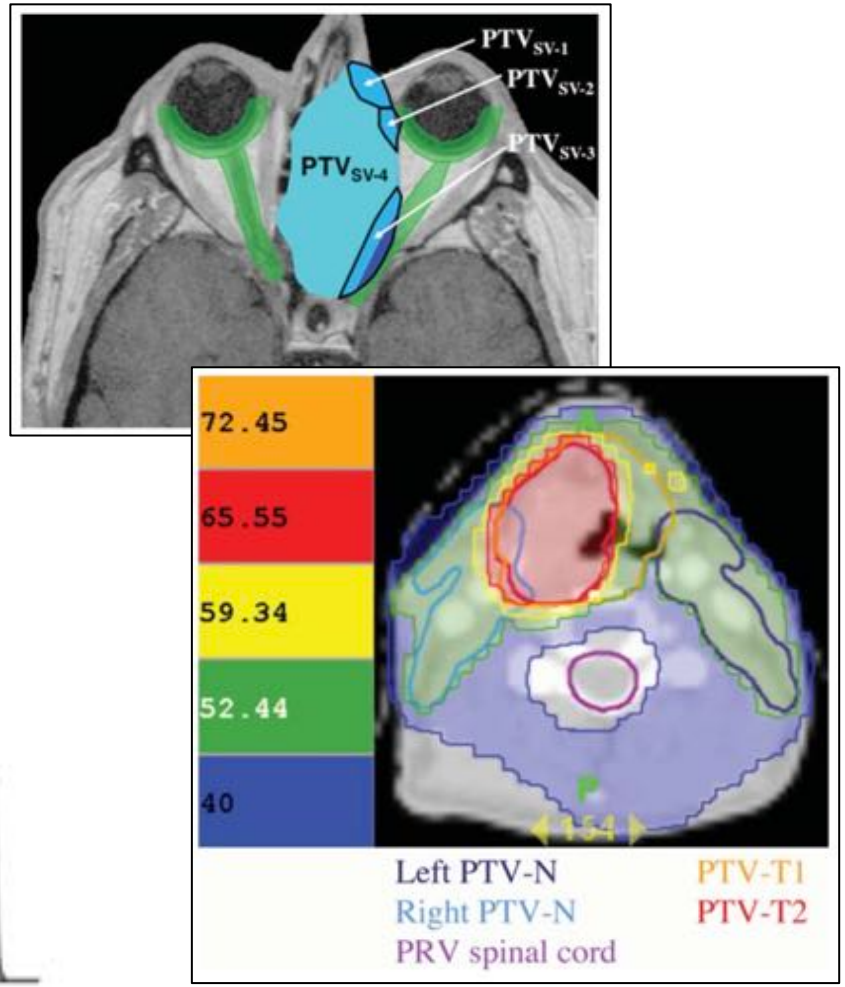
Let's start with the definitions

- ICRU 83:



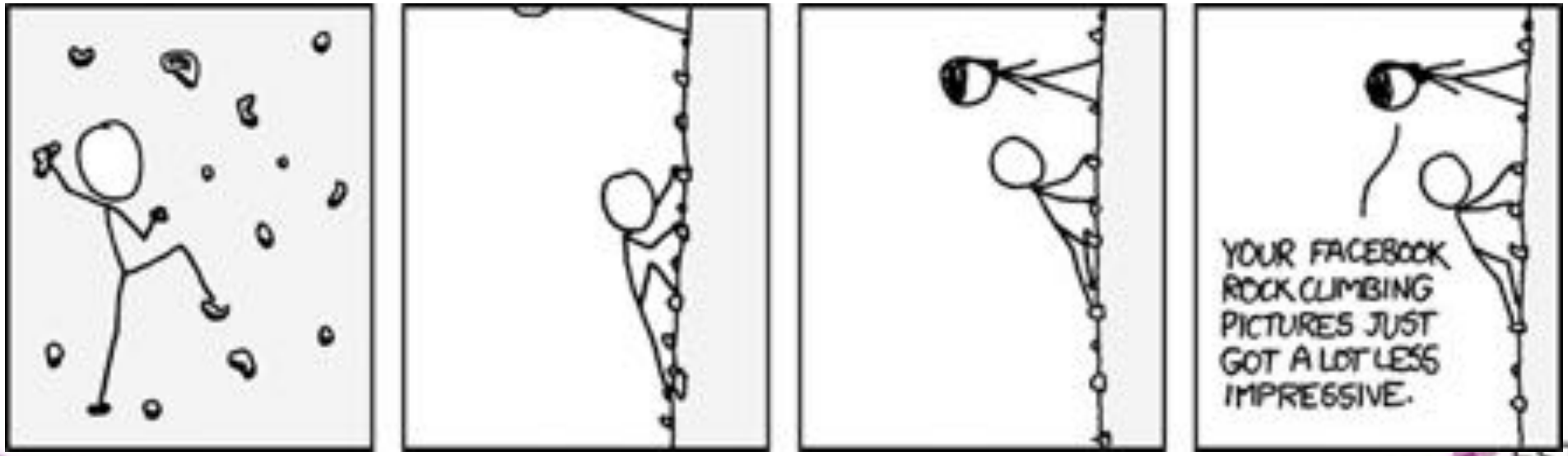
$$PTV = PTV_{SV-1} + PTV_{SV-2}$$





That was easy …

- What about clinical practice?
  - Requiring 100 % confidence for adequately treating the CTV would result in unreasonably large margins.
  - To quote ICRU 83, case number B3. Adenocarcinoma of the Prostate: "*The PTV-T was defined by adding an anisotropic margin to the CTV. This margin was 7 mm posteriorly, and 10 mm in all other directions* …"
- **But where does the 7 mm come from**??????



Margins and the “van Herk recipe”

- Don’t use ...

Simplified PTV margin recipe for dose - probability

To cover the CTV for 90% of the patients with the 95% isodose (analytical solution) :

PTV margin = 2.5 Σ + 0.7 σ

Σ = quadratic sum of SD of all preparation (systematic) errors
σ = quadratic sum of SD of all execution (random) errors

(van Herk et al, IJROBP 47: 1121-1135, 2000)

*For a big CTV with smooth shape, penumbra 5 mm

- ... without knowing what it’s about
- Mischa made that clear in his presentation!

Margins and the “van Herk recipe”

- A short refreshment on the “philosophy”
  - “**BLUR**” the planned dose distribution using ***all execution (random) errors*** (i.e. set-up, inter/intra fraction motion, penumbra, …) to estimate the cumulative dose distribution: **σ**
  - **SHIFT** the blurred dose with the ***preparation*** error (***systematic error***): **Σ**
  - Use a probability distribution of preparation errors to compute the fraction of patients that receive a certain dose to the CTV. For a given dose level:
    - Find the region of space where the cumulative dose exceeds the given dose level.
    - Compute the ***probability*** that the CTV is in that region
  - … this gives you the required margin.

$$M_{ptv} = \alpha\sqrt{(\Sigma^2_i + \Sigma^2_e)} + \beta\sqrt{(\sigma^2_i + \sigma^2_e + \sigma^2_p)} - \beta\sigma_p, \quad (13)$$

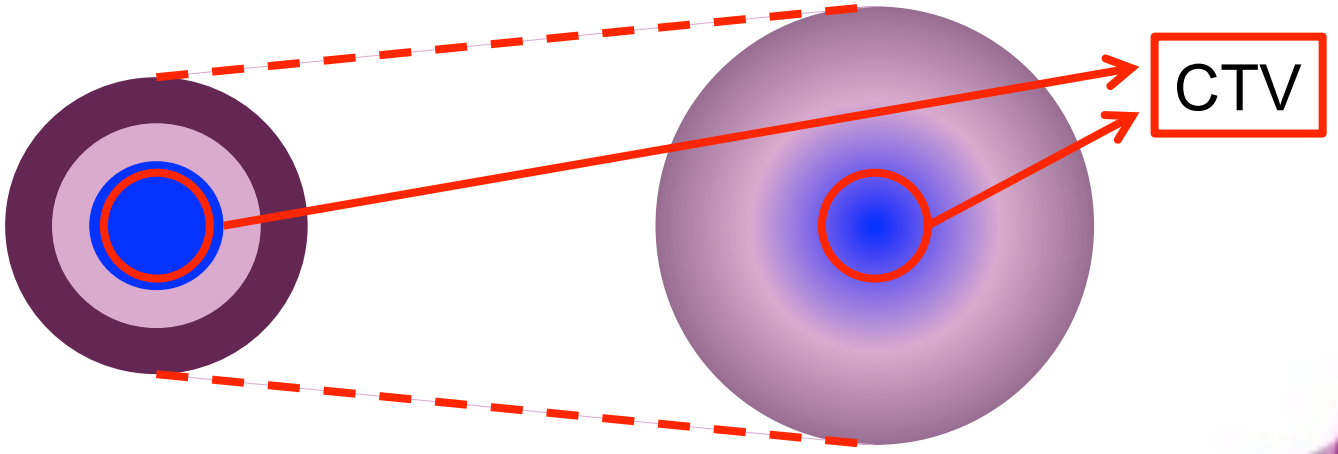
The “blurring” part: random

- Cumulative minimum dose to CTV ≥ 95% of prescription dose

	σ_p
Water	3.2
Lung	6.4

$$M_r = \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

% of D_{norm}	β
95%	1.64
80%	0.84
70%	0.52
60%	0.25



The “blurring” part: random

- Cumulative minimum dose to CTV ≥ 95% of prescription dose

	σ_p
Water	3.2
Lung	6.4

But, what about:
IMRT, VMAT,
Helical TomoTherapy?

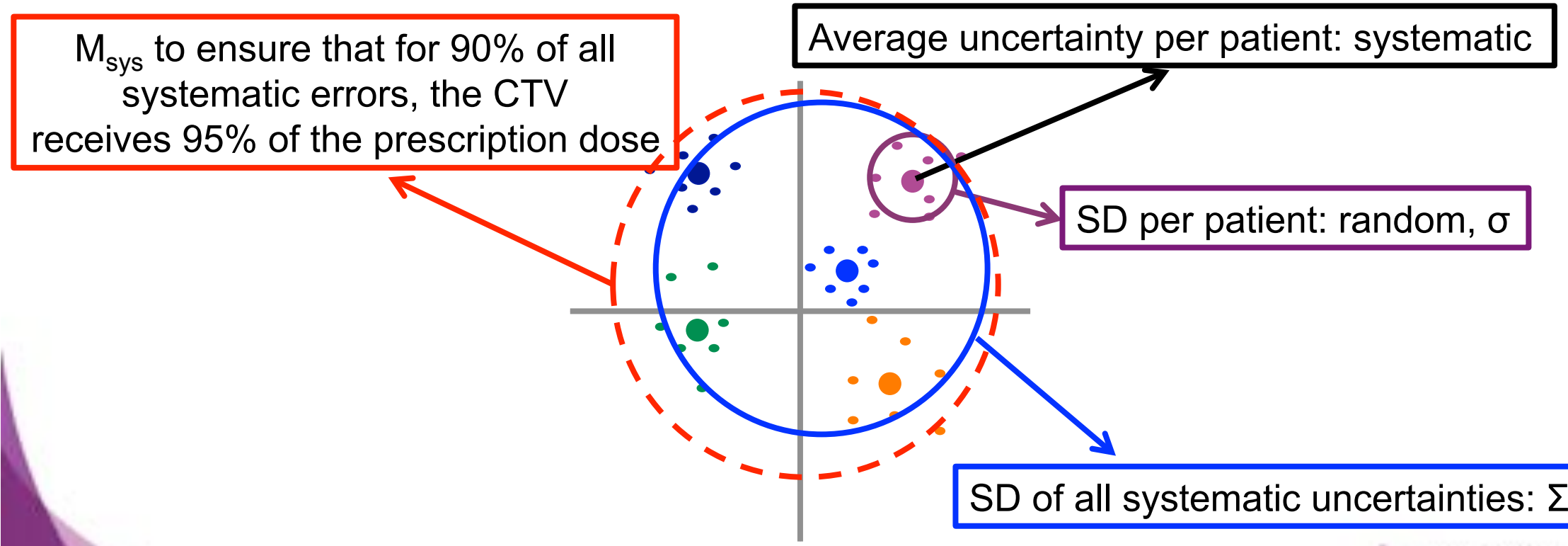
$$M_r = \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

% of D_{norm}	β
95%	1.64
80%	0.84
70%	0.52
60%	0.25

This is where things get complicated in SRS/SBRT

The “shift” part: systematic

- Systematic uncertainties (typically preparation errors) cause a **shift** of the (blurred) dose distribution.
- Again, we assume the systematic uncertainties within a certain population of patients to be described by a normal distribution



The “shift” part: systematic

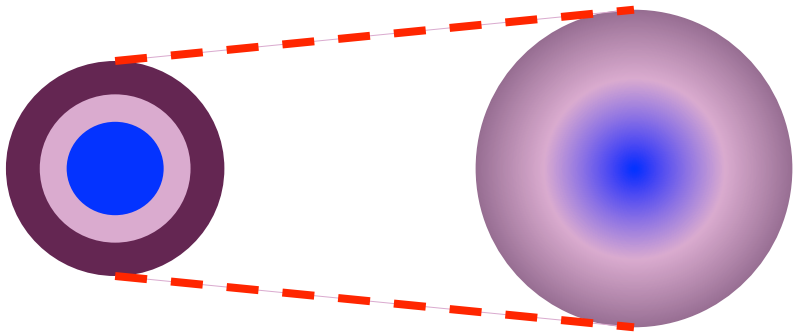
- Assuming a “spherical” target

$$\int_0^{M_{sys}} p(\Sigma)\,dr = 0.9 \quad \Rightarrow \quad M_{sys} = 2.5\Sigma$$

confidence	α
80%	2.16
90%	2.50
95%	2.79
99%	3.36

Margins and the “van Herk recipe”

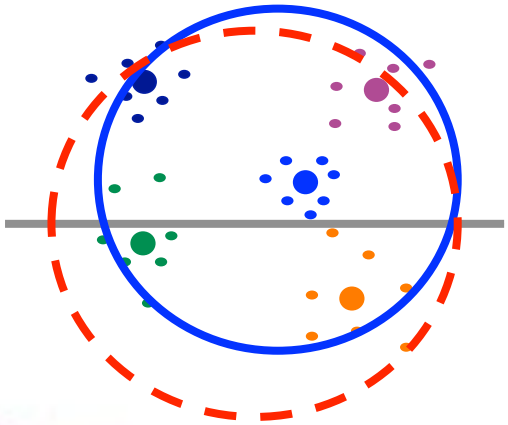
- “Blurring” part: cumulative minimum dose ≥ 95% of D_p



$$M_r = \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

$$\beta = 1.64$$

- “Shifting part: ≥90% of population receives a cumulative CTV dose ≥ 95% of D_p



$$M = \alpha\Sigma + M_r$$

$$\alpha = 2.5$$

Margins and number of fractions

- If the number of fractions decreases (eg HYPOFRACTIONATION) the “random” component becomes more “systematic” (ie a “shift”)

- Effective systematic uncertainty (shift)

$$\Sigma_{eff} = \sqrt{\Sigma^2 + \frac{1}{N}\sigma^2}$$

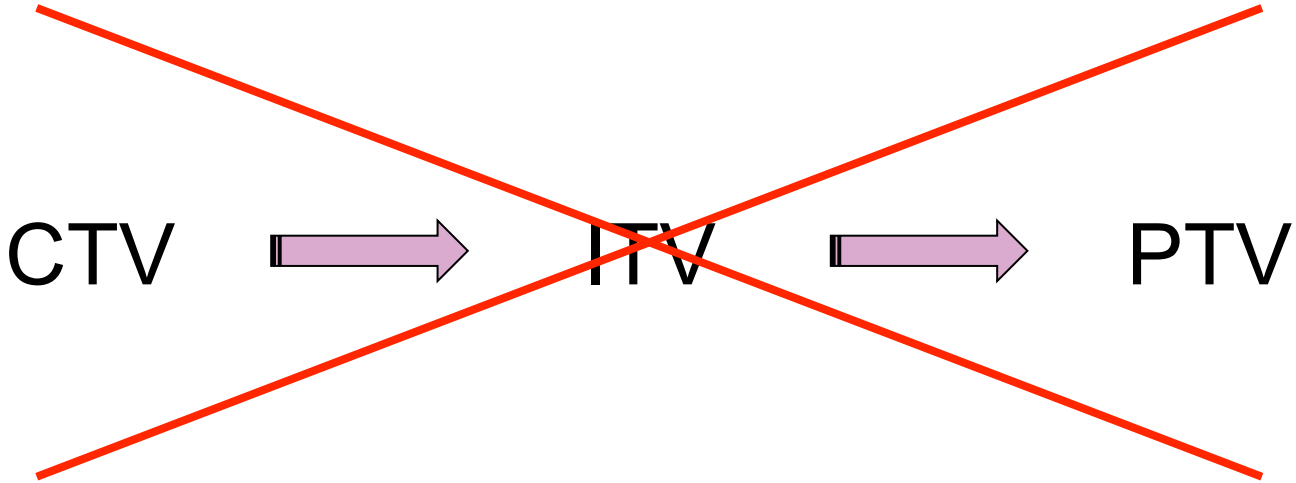
- Effective random uncertainty (blur)

$$\sigma_{eff} = \sqrt{\left(1 - \frac{1}{N}\right)\sigma^2}$$

$$N \to 1$$

… and motion management

- Based on the previous, it is obvious that



$$\mathbf{M}_{ptv} = \alpha\sqrt{(\boldsymbol{\Sigma}^2{}_i + \boldsymbol{\Sigma}^2{}_e)} + \beta\sqrt{(\boldsymbol{\sigma}^2{}_i + \boldsymbol{\sigma}^2{}_e + \boldsymbol{\sigma}^2{}_p)} - \beta\boldsymbol{\sigma}_p, \quad (13)$$

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- Let's start with the definition of the PTV:
  - Evolution of ICRU reports in fast forward
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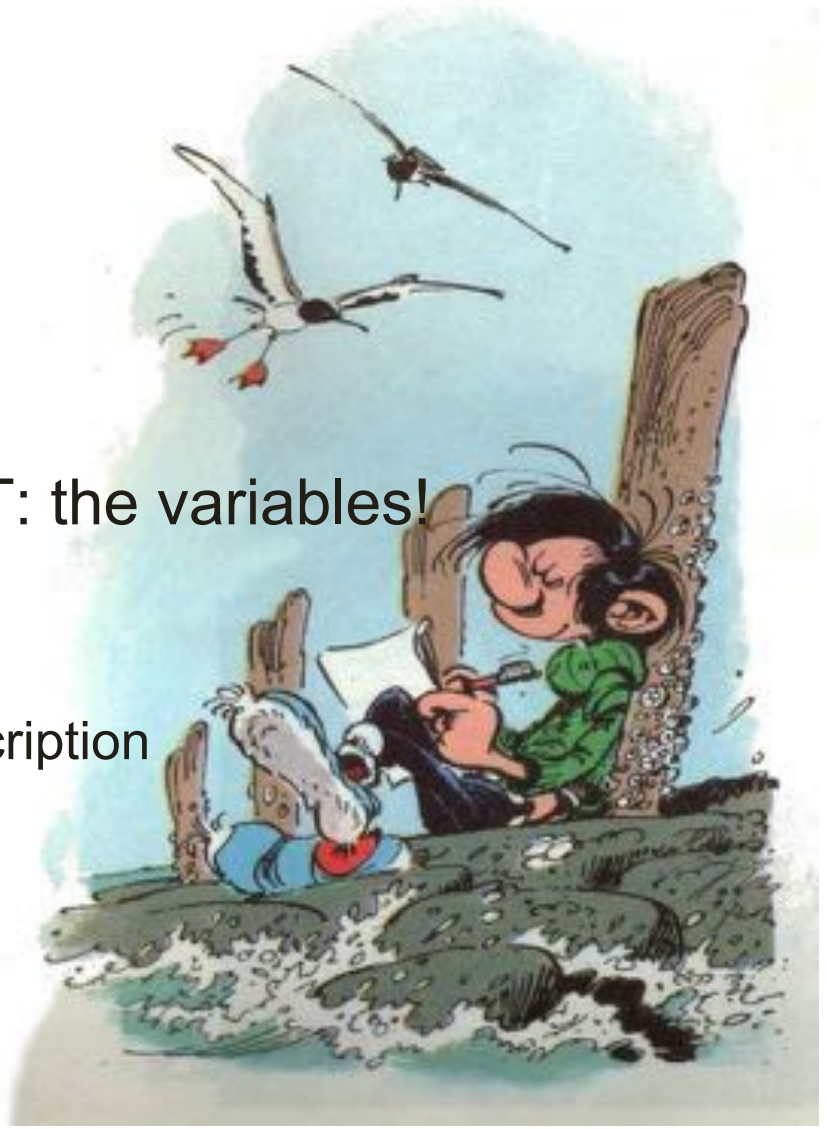
- Dose prescription and reporting in SBRT: the variables!
  - PTV & dose prescription
  - Tissue heterogeneity & dose prescription
  - PTV & tissue heterogeneity % dose prescription
  - Motion & dose prescription

- What about the ICRU 91?



PTV & dose prescription

- So, don't use ...

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Σ = quadratic sum of SD of all preparation (systematic) errors
σ = quadratic sum of SD of all execution (random) errors

(van Herk et al, IJROBP 47: 1121-1135, 2000)

*For a big CTV with smooth shape, penumbra 5 mm

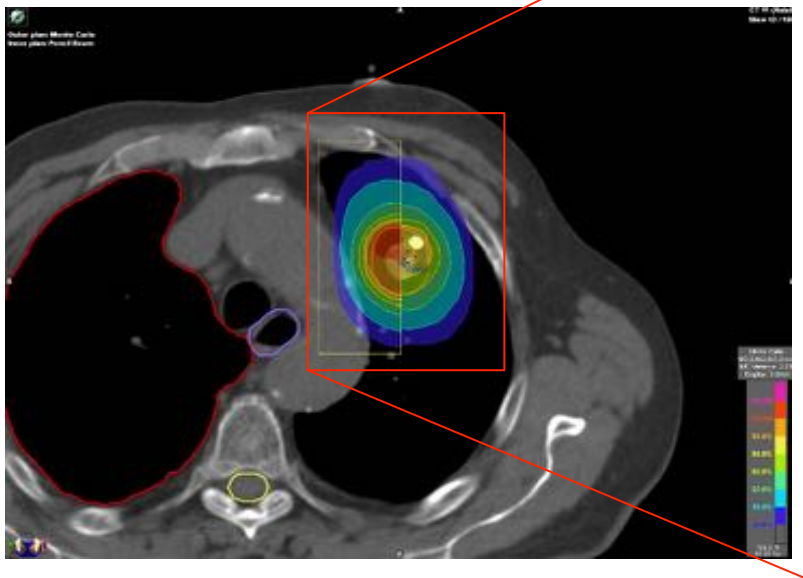
- ... without knowing what it's about

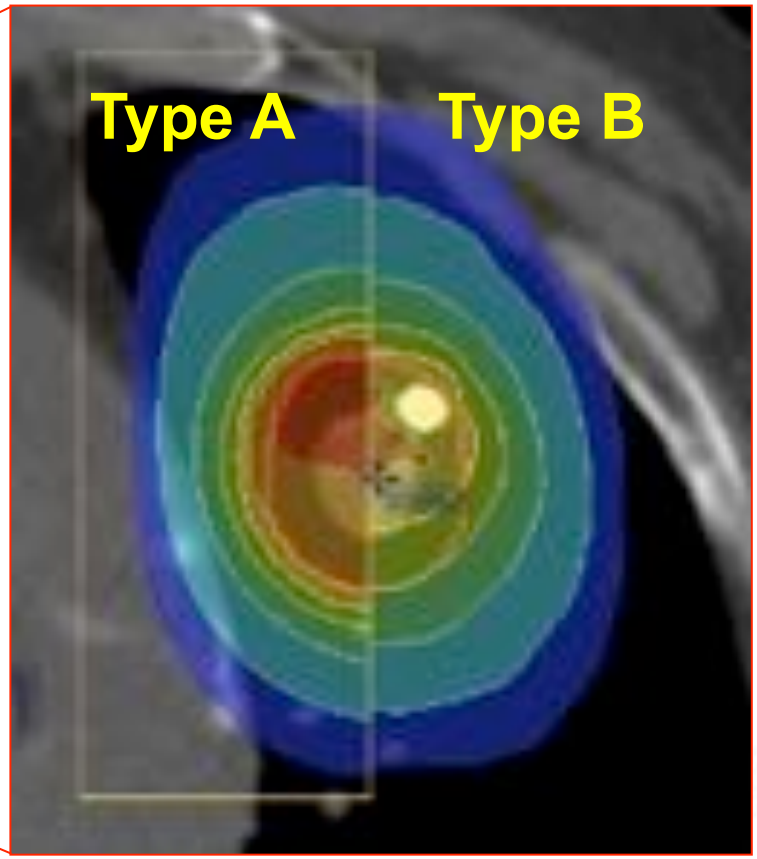
Tissue heterogeneity & dose prescription

- The problem is that with the evolution of more accurate or different dose calculations, the reported doses using one system are not always comparable to doses obtained with another (**SBRT lung as a case in point!!**).

- e.g. recent protocol for a randomized trial: hypofractionated SBRT versus surgery for IA NSCLC: **ROSEL DOSE PRESCRIPTION**
(Hurkmans *et al.*, Radiat Oncol 2008)

For type A dose calculation models: 3 x 20 Gy
For type B dose calculation models: 3 x 18 Gy





Tissue heterogeneity & dose prescription

Type A models (standard algorithms).

$R_{100\%}$		$R_{50\%}$		D_{2cm} (%)		V_{20Gy} (%)		PTV (cc)
Deviation		Deviation		Deviation		Deviation		
None	Minor	None	Minor	None	Minor	None	Minor	
<1.15	1.15-1.25	<10	8-10	<55	55-60	<4	4-6	0-20
<1.15	1.15-1.25	<8	7-8	<65	65-70	<6	6-8	20-40
<1.10	1.10-1.20	<6.5	6-6.5	<65	65-75	<8	8-10	>40

Type B models (more advanced algorithms).

$R_{100\%}$		$R_{50\%}$		D_{2cm} (%)		V_{20Gy} (%)		PTV (cc)
Deviation		Deviation		Deviation		Deviation		
None	Minor	None	Minor	None	Minor	None	Minor	
<1.25	1.25-1.40	<12	12-14	<65	65-75	<5	5-8	0-20
<1.15	1.15-1.25	<9	9-11	<70	70-80	<6	6-10	20-40
<1.10	1.10-1.20	<6	6-8	<70	70-80	<10	10-15	>40

$R_{x\%}$ = volume of x% of D_p isodose volume / PTV

Hurkmans *et al.*, Radiat Oncol 2008

Tissue heterogeneity & dose prescription

Table 2. Dose constraints for organs at risk.

		Deviation given as cumulative absolute dose (Gy)			
		3 fraction scheme		5 fraction scheme	
Organ	Volume (cc)	None	Minor	None	Minor
Spinal Cord	Any point	18	> 18 to 22	25	> 25 to 28
Oesophagus	1	24	> 24 to 27	27	> 27 to 28.5
Ipsilateral Brachial Plexus	1	24	> 24 to 26	27	> 27 to 29
Heart	1	24	> 24 to 26	27	> 27 to 29
Trachea and main stem bronchus	1	30	> 30 to 32	32	> 32 to 35

Hurkmans *et al.*, Radiat Oncol 2008

Tissue heterogeneity & dose prescription

- "It is clear that using a **type B** algorithm, it is more difficult to conform the planned dose to the PTV than using a **type A** algorithm, especially for a small PTV."

- This is caused by the increased influence of lateral scatter disequilibrium for smaller PTV, which is modeled better using a type B algorithm.

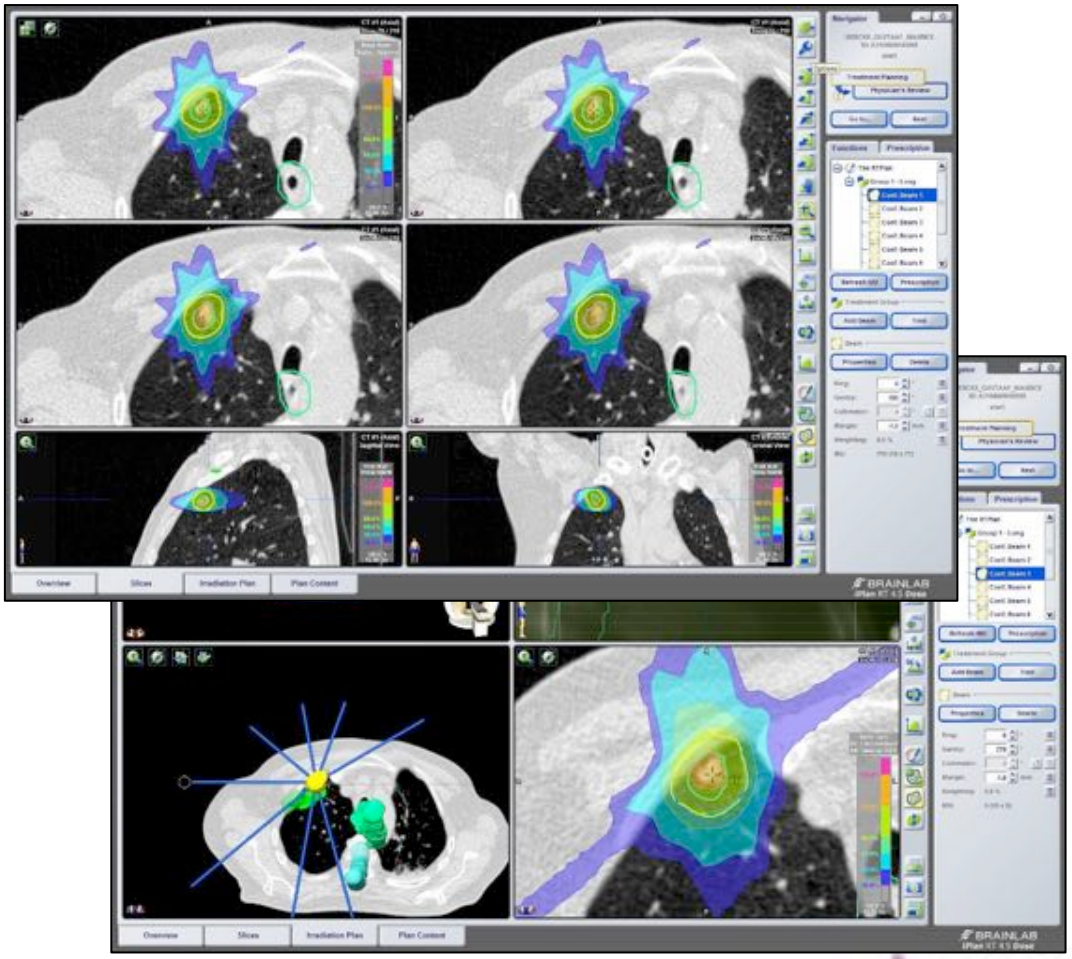
- Thus, **a less strict conformity requirement is formulated for type B**.

PTV & tissue heterogeneity & dose prescription

- Vero conformal beams @ UZ Brussel as an example

  - Create conformal dose distribution with **type A** calculation algorithm (PB)

  - Switch on **type B** calculation algorithm (MC) and tune beam shapes and weights to
    - Comply to dose prescription
    - Comply to dose constraints



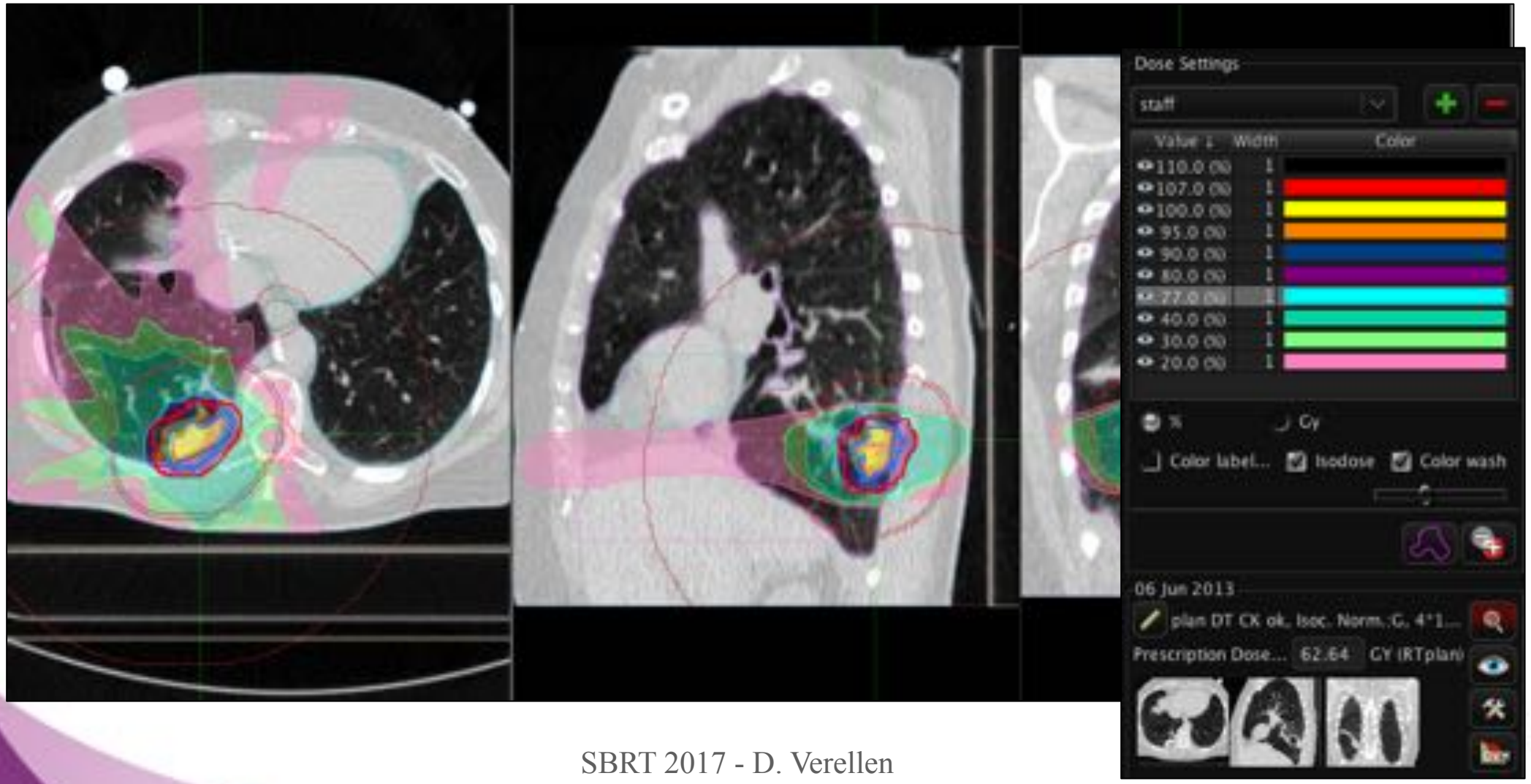
PTV & tissue heterogeneity & dose prescription

- Type B dose calculation algorithm: XVMC
- Treatment constraints:
  - PTV = GTV + 5mm
  - Dose prescription
    - Centrally located lesions
    - Lesions < 1cm from thoracic wall
    - Peripheral lesions

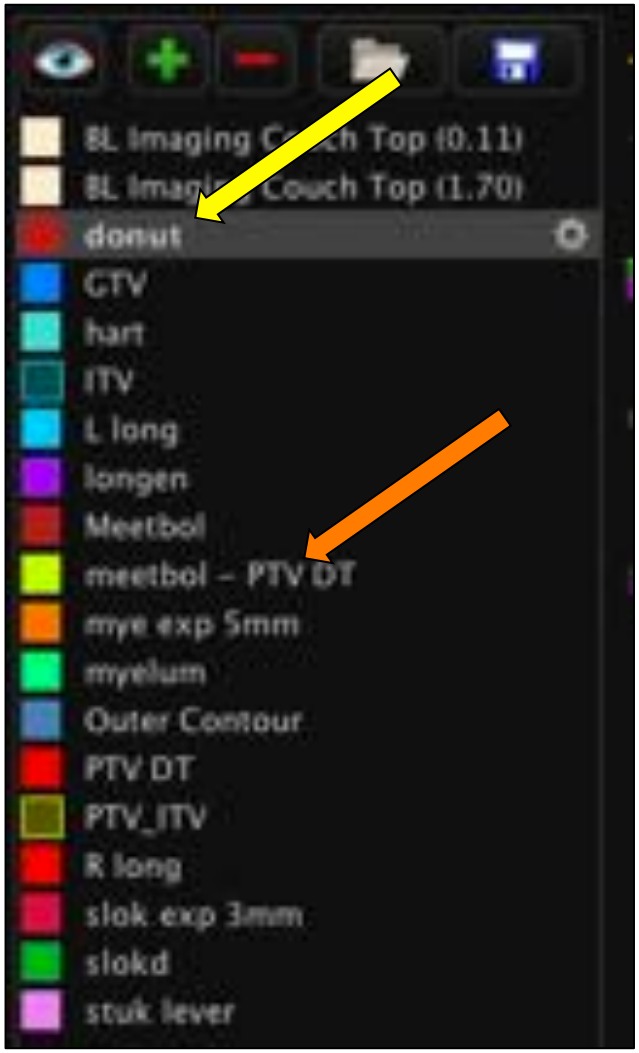
    ⇒ **4 x 12 Gy (Monte Carlo)**

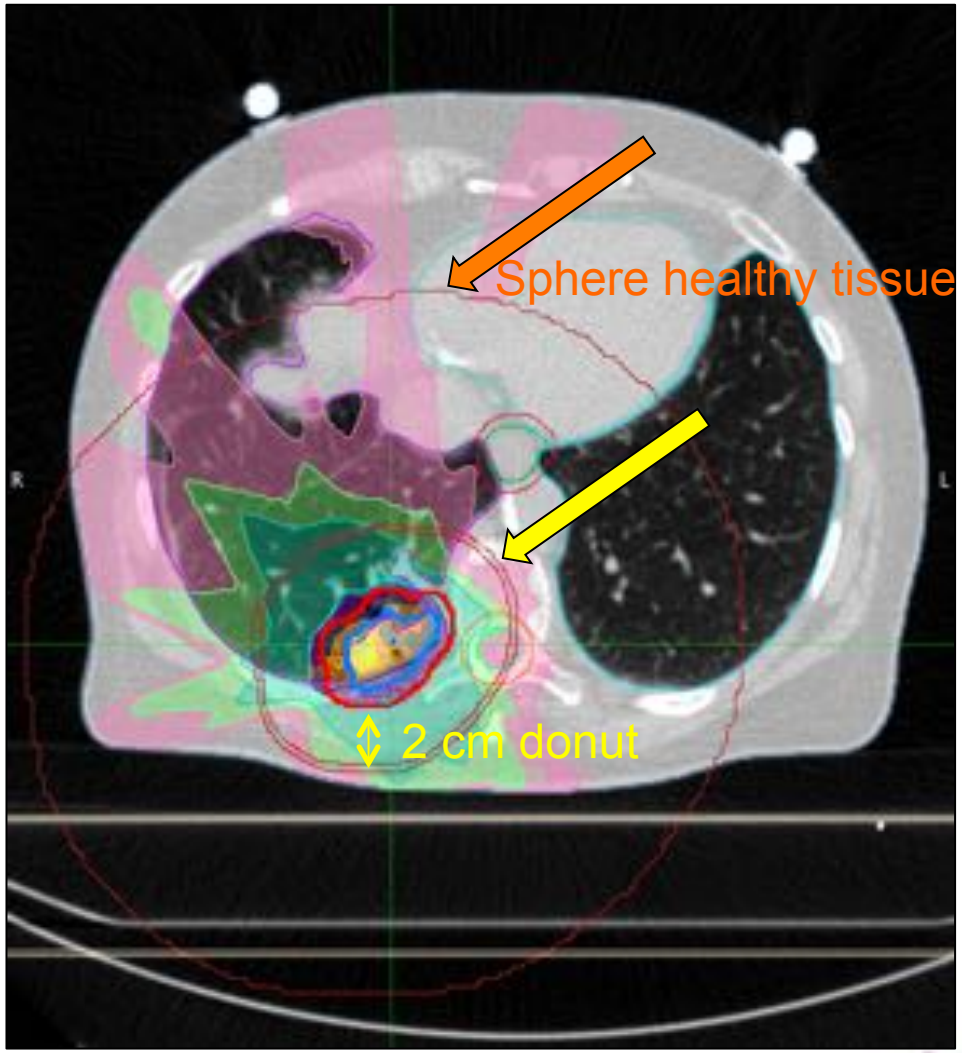
    ⇒ **3 x 17 Gy (Monte Carlo)**
  - Dose prescription
    - Normalization: 100% @ **isocentre**, $D_{2\%}$ < 105%
    - 95% of PTV covered by **prescription isodose** surface (i.e. 12 or 17Gy)
    - 99% of PTV covered by 90% of **prescription isodose** surface
  - Dose constraints:
    - Conformity, low and high dose spillage …
    - Normal tissues …

PTV & tissue heterogeneity & dose prescription



PTV & tissue heterogeneity & dose prescription





PTV & tissue heterogeneity & dose prescription

- Target dose and coverage:

➢ Prescription isodose (**PD**):	48.0 Gy – 77%	
➢ Isocentre Dose (**ID**):	62.6 Gy – 100%	
➢ PTV volume:	39.8 cm^3	
➢ % PTV covered by 77% (100% of **PD**):	97%	(> 95%)
➢ % PTV covered by 69.3% (90% of **PD**):	100%	(> 99%)
➢ $D_{2\%}$:	64.5 Gy – 103%	(< 105%)
➢ D_{mean}:	56.8 Gy – 91%	

PTV & tissue heterogeneity & dose prescription

- Conformity:
  - Ratio of volume receiving **PD** over volume PTV

$$\frac{Volume(sphere, 100\%PD)}{Volume(PTV)} = \frac{Volume(sphere, 48Gy)}{Volume(PTV)} = \frac{49.8cm^3}{39.8cm^3} = 1.25 \quad (< 1.2\ [1.2 - 1.5])$$

PTV & tissue heterogeneity & dose prescription

- High dose spillage:
  - Any dose > 105% of **PD** should be concentrated inside PTV
  - Volume (tissue outside PTV receiving > 105% **PD**) < 15% of PTV volume

$$\left.\begin{array}{l}\dfrac{Volume(sphere-PTV,>105\%PD)}{Volume(PTV)}\\[2ex]\dfrac{Volume(sphere-PTV,>50.4Gy)}{Volume(PTV)}\end{array}\right\} = \frac{5.97cm^3}{39.8cm^3} = 0.15 \quad (< 15\%)$$

PTV & tissue heterogeneity & dose prescription

- Low dose spillage:
  - Maximal dose at 2cm from PTV must be between 50-77% of **ID**

$$D_{\max}\left(donut\left[PTV+2.2cm\right]-\left[PTV+2cm\right]\right)=32.6Gy=52\%(ID) \quad (50\text{-}77\%)$$

- Volume low dose spillage:
  - Ratio of volume receiving 50% of **PD** over PTV volume must between 5.9 and 2.9

$$\frac{Volume\left(sphere,50\%PD\right)}{VolumePTV}=\frac{Volume\left(24Gy\right)}{Volume\left(PTV\right)}=\frac{191.7cm^3}{39.8cm^3}=4.8 \qquad (2.9\text{-}5.9)$$

PTV & tissue heterogeneity & dose prescription

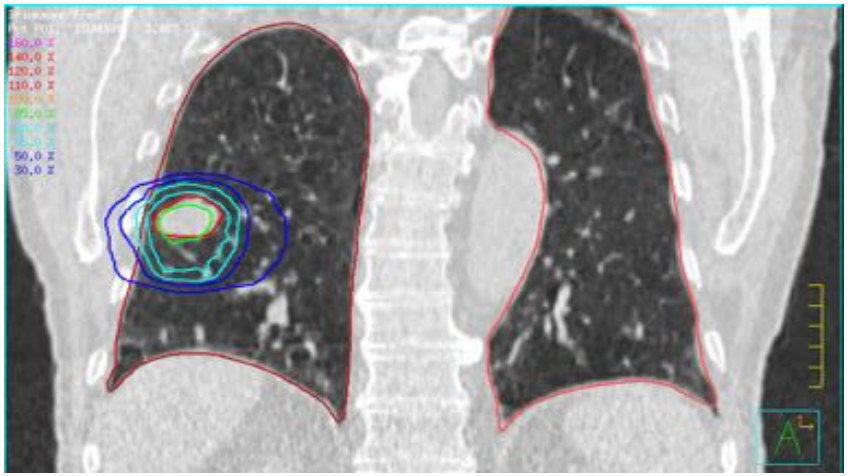
- Some more statistics and constraints:

  - $D_{2\%}$(esophagus): 12 Gy
  - $D_{2\%}$(heart): 15 Gy
  - $D_{2\%}$(spinal cord, exp): 33 Gy
  - $D_{2\%}$(skin): 24 Gy

  - V_{20}: 3.4%
  - MLD: 2.9 Gy
  - V_5(contra lateral lung): 4.6%

PTV & tissue heterogeneity & dose prescription

- With open beams (non-IMRT), things are “reasonably” simple
  - The high dose more or less follows the dense tissue



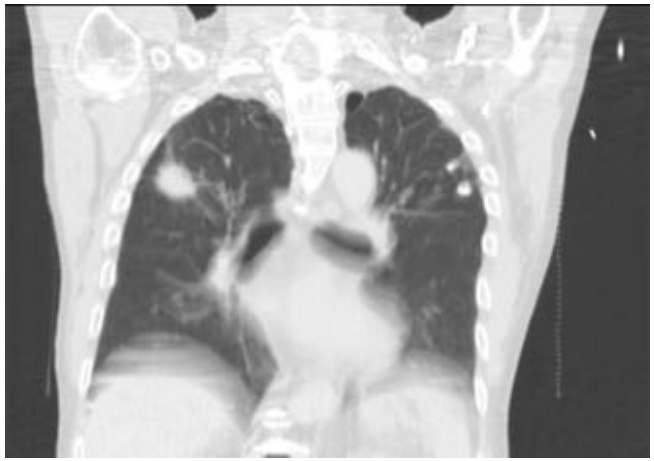
Courtesy M. Guckenberger

- But what about IMRT, VMAT?
  - If a homogeneous coverage of the PTV is prescribed, the IMRT optimization will artificially boost the fluence to the air inside the PTV
  - What if GTV and OAR move inside these area’s?

PTV & tissue heterogeneity & dose prescription

- VUMC strategy with average density CT (Ong *et al.*, PhD thesis)

Free breathing fast 3D-CT



Average intensity

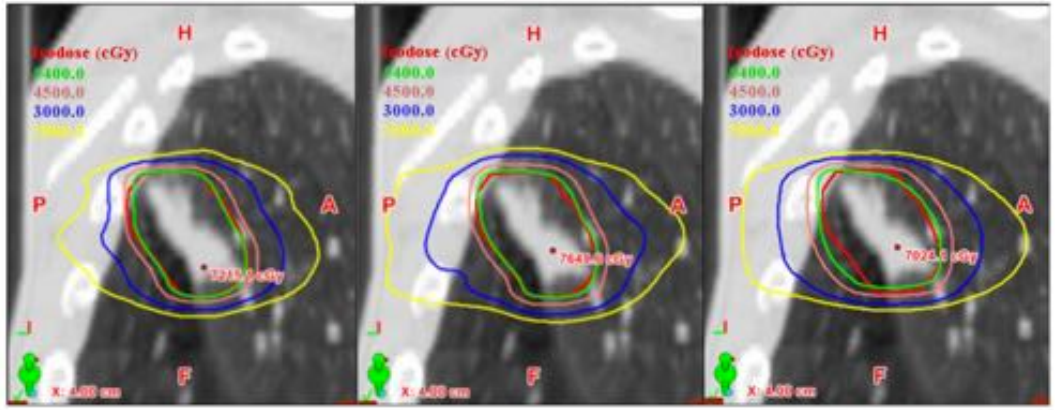
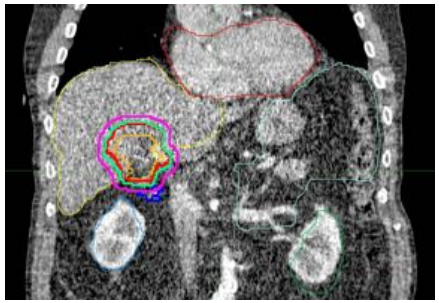


Fig. 2. Case 11. Comparison of dose distribution in sagital planes. (a) RapidArc, (b) 10 beams conf-SBRT, (c) Dynamic Conformal Arc. The volume of the chest wall encompassed by the 30 Gy isodose was least for the RapidArc plan.

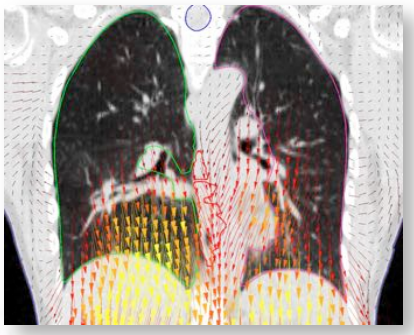
- Risk for underestimating dose to the real GTV (which has higher densities).
- Risk for modulating fluence to non-existing tissues.

Motion & dose prescription

- 4D planning to assess influence of motion

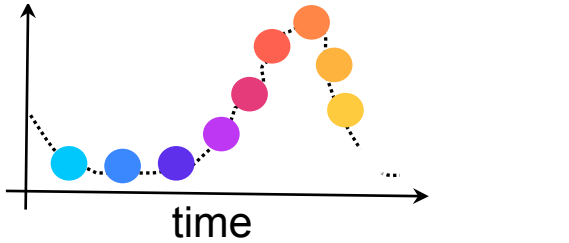


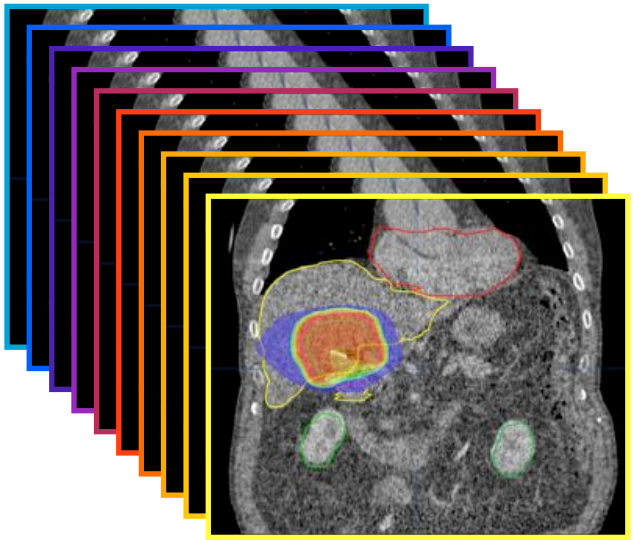
4D CT (10 phases), XVMC dose calculation



Deformable registration to reference phase

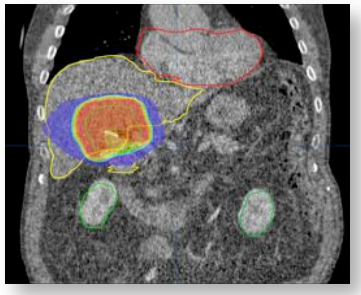
$\sum$



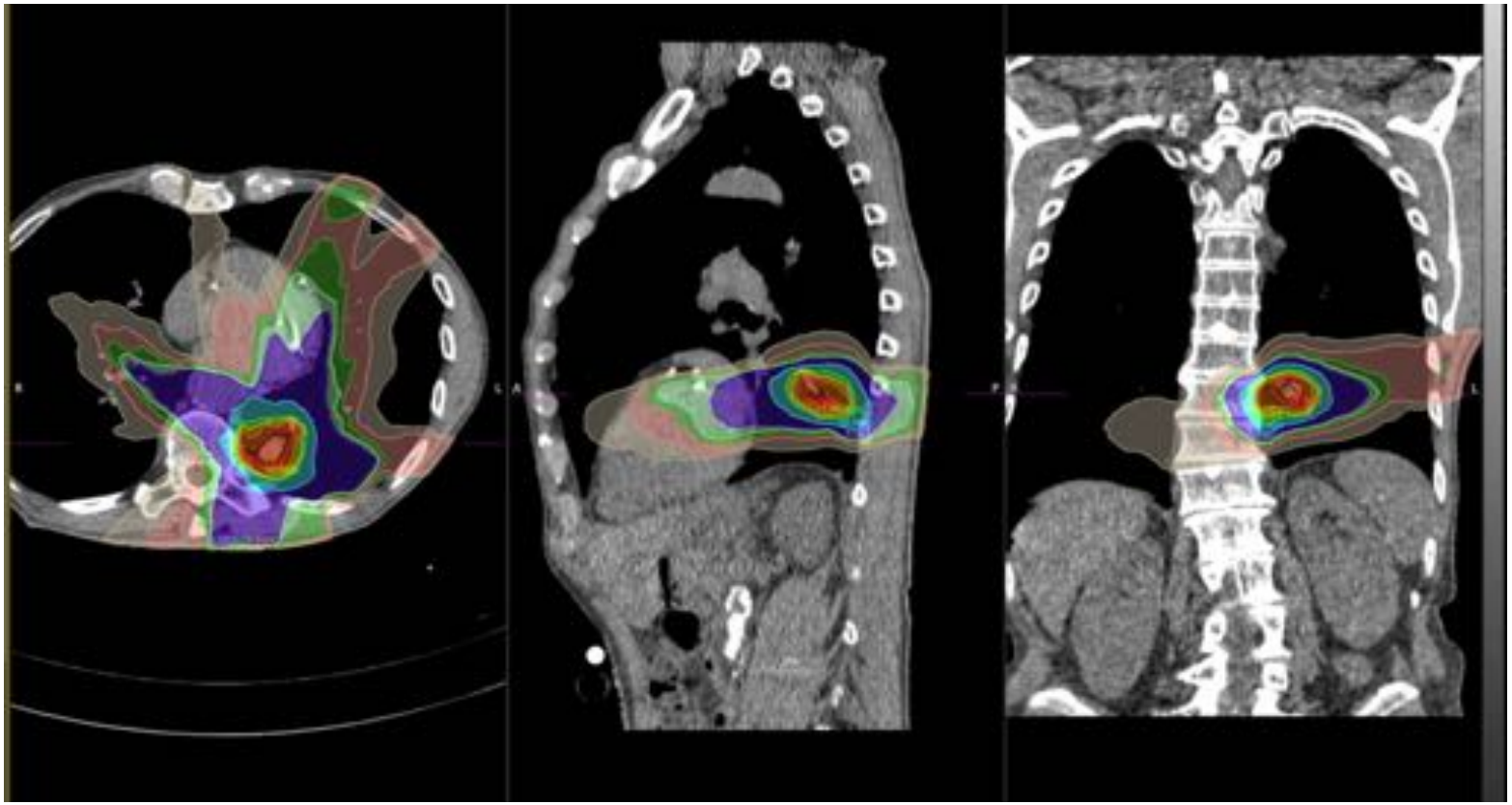


Dose calculation on each phase

=



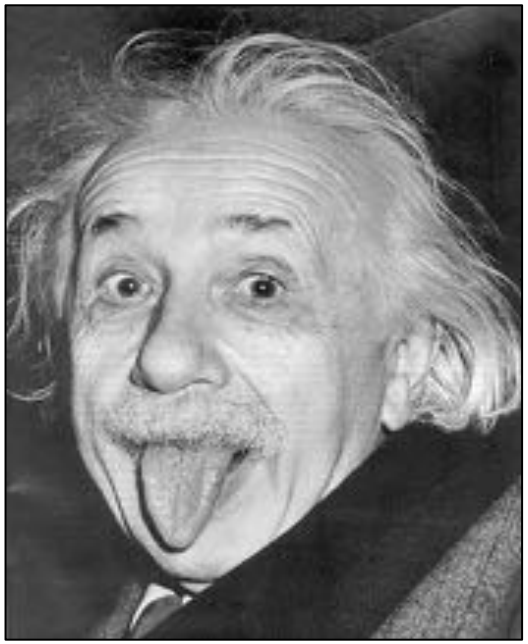
Motion & dose prescription

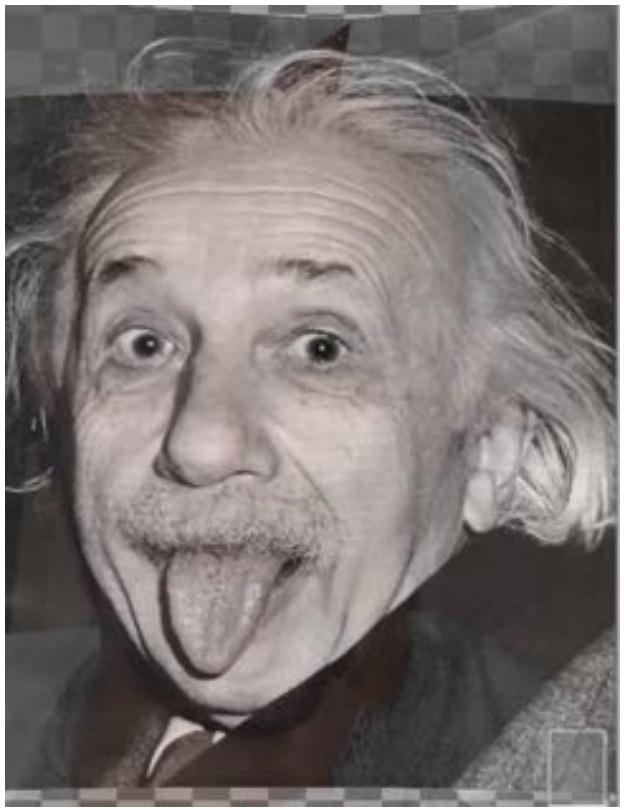


- Real-time tumor tracking dose reconstructed on 4D CT and transferred to 1 phase

Motion & dose prescription

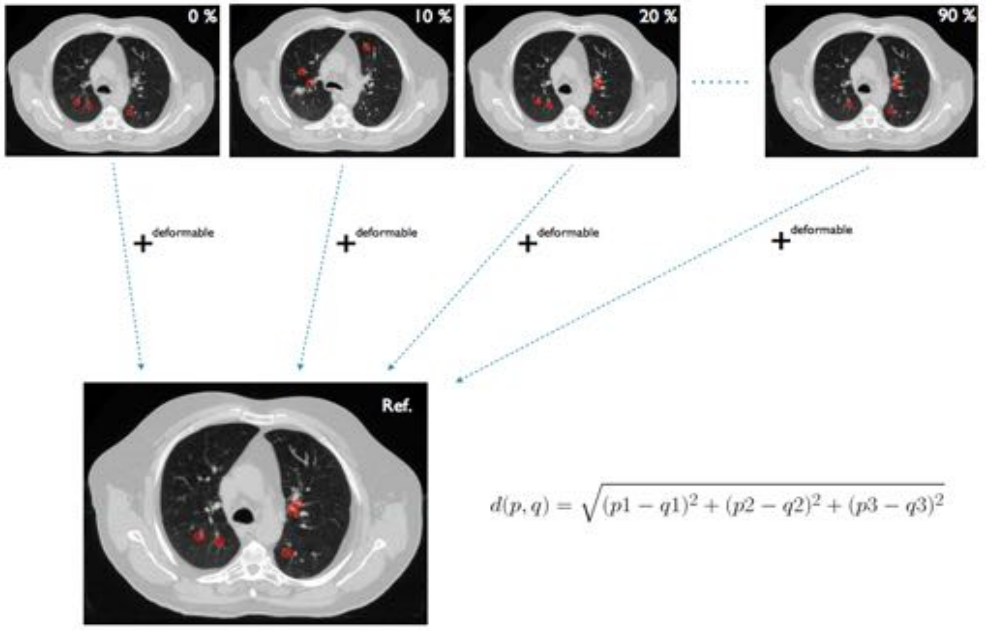
- Deformable image registration ...
  - Descriptive: OK for segmentation
  - Quantitative: **NEEDED** for dose calculation
  - *Not yet clinically available*



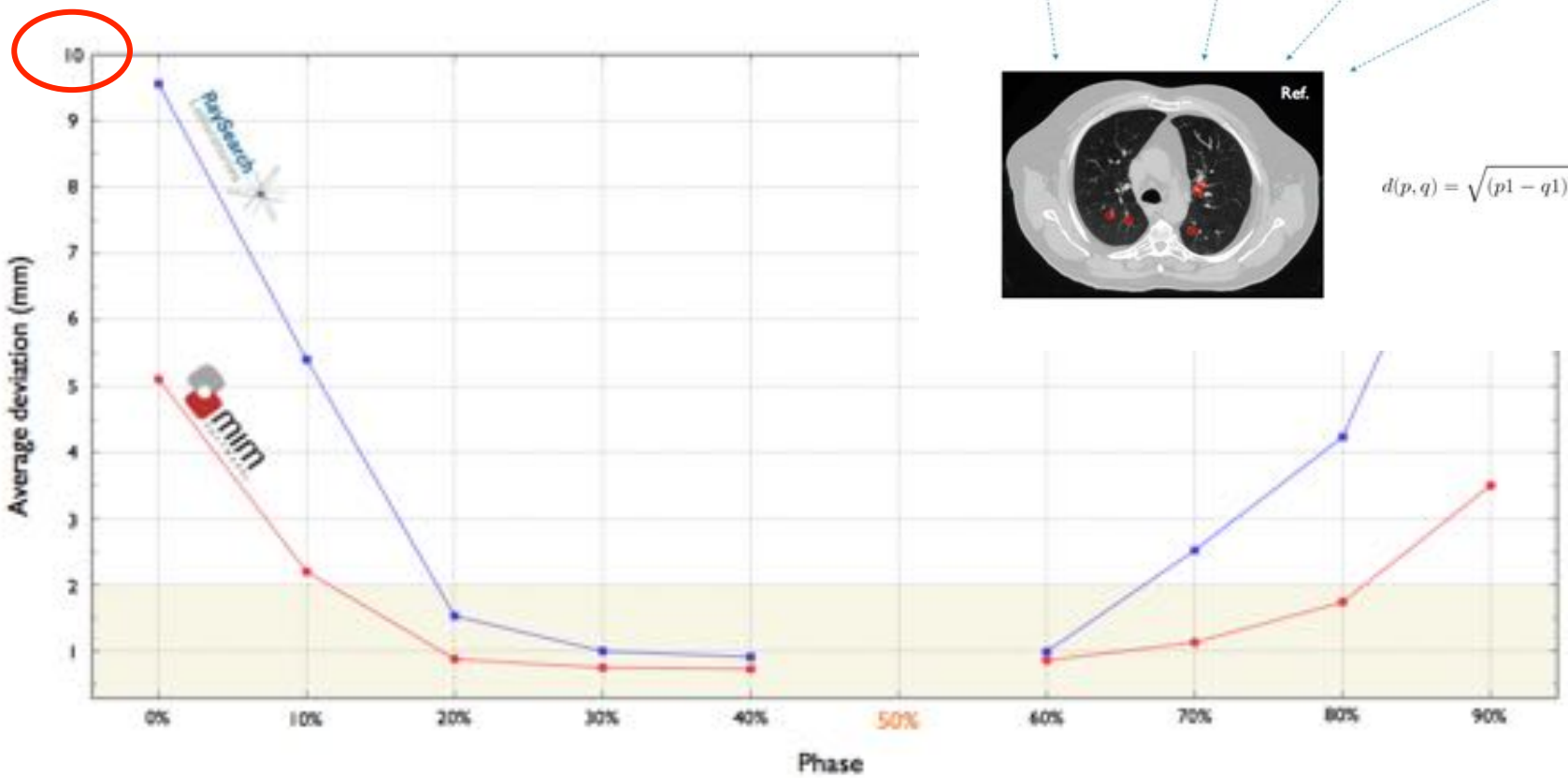


Motion & dose prescription

- http://www.creatis.insa-lyon.fr/rio/popi-model
- 4D-CT datasets, with 100 POIs on vessel and bronchial bifurcations

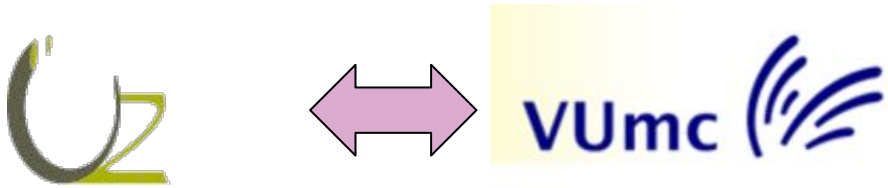


$$d(p,q) = \sqrt{(p1-q1)^2 + (p2-q2)^2 + (p3-q3)^2}$$

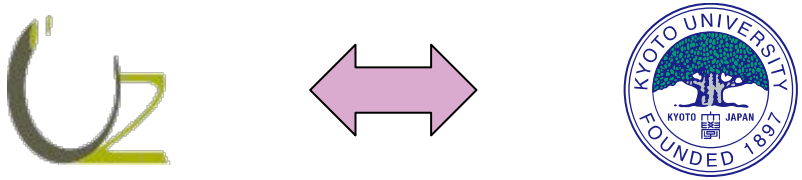


Reporting dose

- Normalization, prescribing and reporting dose in SBRT!
  - 3 x 20 Gy in UZ Brussel ≠ 3 x 20 Gy in VUmc Amsterdam
  - VERO RTTT open beams versus Elekta CBCT and VMAT



  - 3 x 20 Gy in UZ Brussel ≠ 3 x 20 Gy in Kyoto
  - VERO RTTT versus VERO RTTT



Reporting dose

- Consequences for dose prescription when transferring from type A to type B dose calculation algorithms:

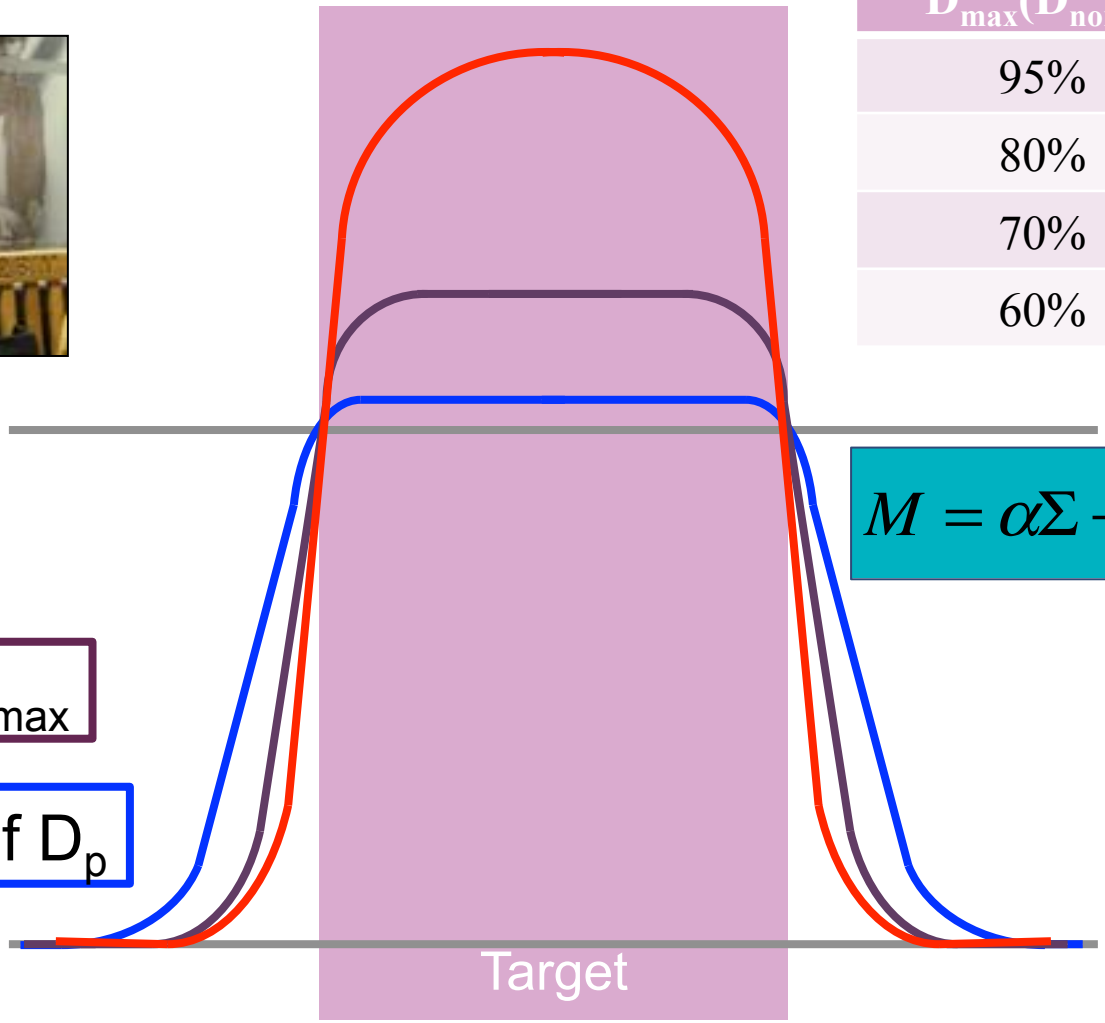
- <u>UZ Brussel (VERO)</u>
  - Dose prescription on D_{95}
  - **MU(typeA) < MU(typeB)**

- <u>Kyoto University (VERO)</u>
  - Dose prescription at isocentre
  - **PTV>: MU(typeA) ≅ MU(typeB)**
  - **PTV<: MU(typeA) < MU(typeB)**

Reporting dose

- Dose prescription and margins ...

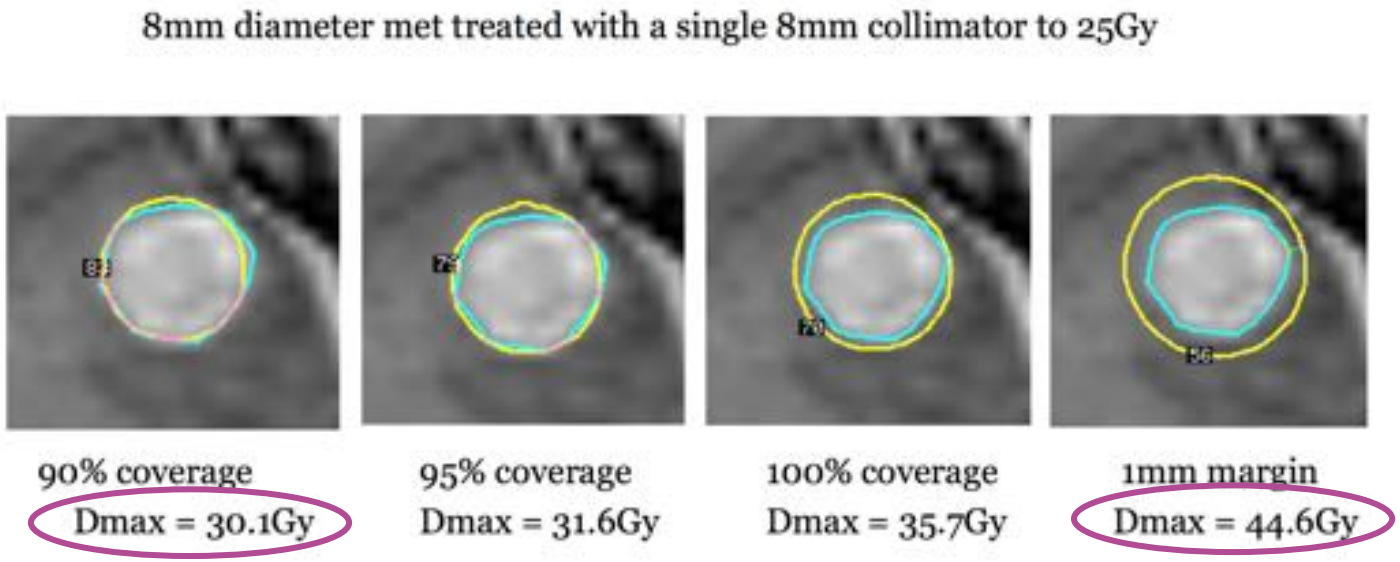
% of $D_{max}(D_{norm})$	β
95%	1.64
80%	0.84
70%	0.52
60%	0.25



$$M = \alpha\Sigma + \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

Reporting dose

- Dose prescription and margins in SRS
- 2 lesions, treated to **25Gy covering 97%** of the target
  - 8mm ϕ lesion, **8mm collimator**, **25Gy @ 80%**:
    - **D_{max} = 31.3 Gy** / D_{mean} = 27.5Gy
  - 11mm ϕ lesion, **8mm collimator**, **25Gy @ 50%**:
    - **D_{max} = 50.0 Gy** / D_{mean} = 35.0Gy
- Same lesion, same dose prescription, variable isodose:



I. Paddick *et al.*

Reporting dose

- Lax et al. 1993:
  - "Normalizing to the 65%-isodose leads to a 50% increase of dose in the target center without substantial increase of dose outside the PTV in comparison to dose loads for a homogenous dose distribution"

- This is all very nice, but how do we know what exactly was reported in literature? To quote ICRU 91:
  - "Despite the long clinical history of SRT for intracranial lesions, at the time of writing of this report, around **14 000 clinical manuscripts** on stereotactic radiotherapy have been reported in PubMed with Phase III studies only in brain metastases. **Prescribing, reporting, and recording are performed in different ways at different institutions which emphasizes the need for the present Report to standardize the process**."

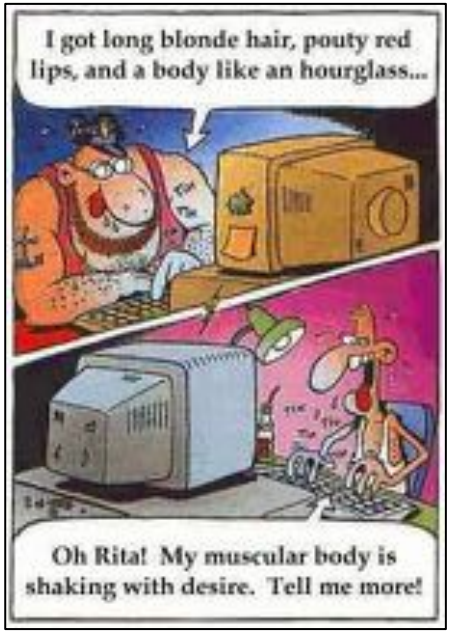
Reporting dose

T. Lacornerie, COL

- PTV or ITV $D_{95\%}$ does not predict the minimum dose to the GTV, because the PTV/ITV margin consists mostly of low-density region.
  Therefore, it makes more sense to **report the GTV dose**!
  - ➢ the PTV prescription does not predict the dose to the GTV.
- Moreover, GTV dose seems to be a more **robust parameter** for reporting (independent of delivery method).
- By the way, usually the PTV margin is in lung tissue, where the accurate dose calculation is most uncertain, **prescribing and reporting** dose to this margin seems highly inaccurate!!!

Reporting dose

- **What you see is NOT (always) what you get**



- **Garbage in – garbage out**

The QUANTEC Report 2010

I. J. Radiation Oncology ● Biology ● Physics Volume 76, Number 3, Supplement, 2010

Introductory Papers
History/Overview/Scientific Issues
Application of QUANTEC metrics/models into clinical practice

Organ-Specific Papers

1. **Brain**
2. **Optic Nerve/Chiasm**
3. **Brain Stem**
4. **Spinal Cord**
5. **Ear**
6. **Parotid**
7. **Larynx/Pharynx**
8. **Lung**
9. **Heart**
10. **Esophagus**
11. **Liver**
12. **Stomach/Small Bowel**
13. **Kidney**
14. **Bladder**
15. **Rectum**
16. **Penile Bulb**

Vision Papers
True Dose
Imaging
Biomarkers
Data Sharing
Lessons of QUANTEC

Each with 10 sections

1. **Clinical Significance**- Describes the clinical situations where the organ is irradiated, and the incidence/significance of organ injury.
2. **Endpoints**- Describes the different endpoints often considered when assessing injury, the impact of endpoint-selection on the reported injury rates, the challenges/utilities of different endpoints, and the time course of organ injury.
3. **Challenges Defining Volumes**- Describes how the organ is typically defined (or segmented) on treatment planning images. Includes a discussion of uncertainties/challenges in organ definition (e.g. changes in organ volume/shape during therapy), and the associated impact on DVH's and dose/volume/outcome analyses.
4. **Review of Dose/Volume Data**- A comprehensive summary of reported 3D dose/volume data for clinically-relevant outcomes.
5. **Factors Affecting Risk**- Other clinical factors affecting the risk of injury are noted (e.g. age, combined modality therapy, dose fractionation).
6. **Mathematical/Biological Models**- Models that have been used to relate 3D dose/volume data to clinical outcomes are summarized, along with associated model parameters, limitations and uncertainties.
7. **Special Situations**- Most of the data discussed relates to conventional fractionation. This section describes situations were the presented data/models may not apply (e.g. hypo-fractionation).
8. **Recommended Dose/Volume Limits**- The available information is condensed into meaningful dose/volume limits, with associated risk rates, to apply clinically.
9. **Future Toxicity Studies**- Describes areas in need of future study.
10. **Toxicity Scoring**- Recommendations on how to score organ injury.

Fig. 1. Outline of the issue: the first section consists of Introductory Papers; the second section consists of Organ-Specific Papers, each containing 10 topic sections; and the third section consists of Vision Papers.

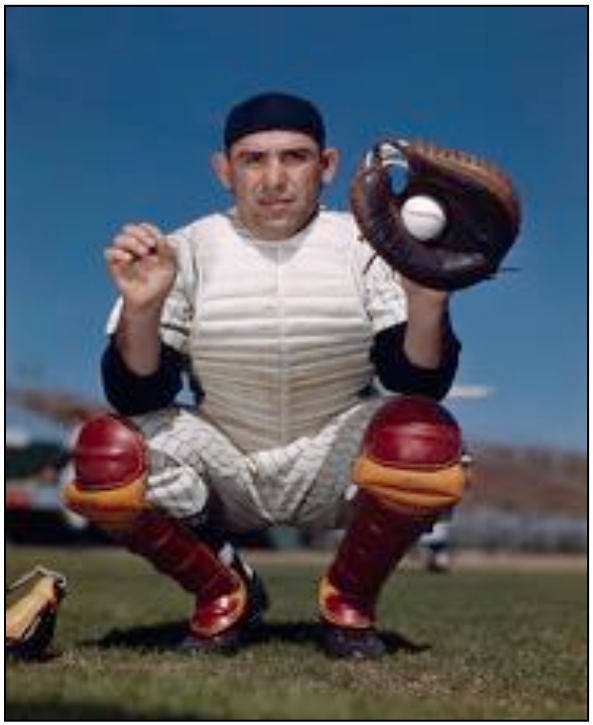
- Useful guidelines for normal tissue tolerances in the **primary** situation for conventional fractionation
- Limited data for **hypofractionation**
- Very limited information concerning **re-irradiation**

Let’s start with some Yogi wisdom …

- Quoting the famous Yogi Berra:
  - “If you don't know where you're going, you might not get there.”

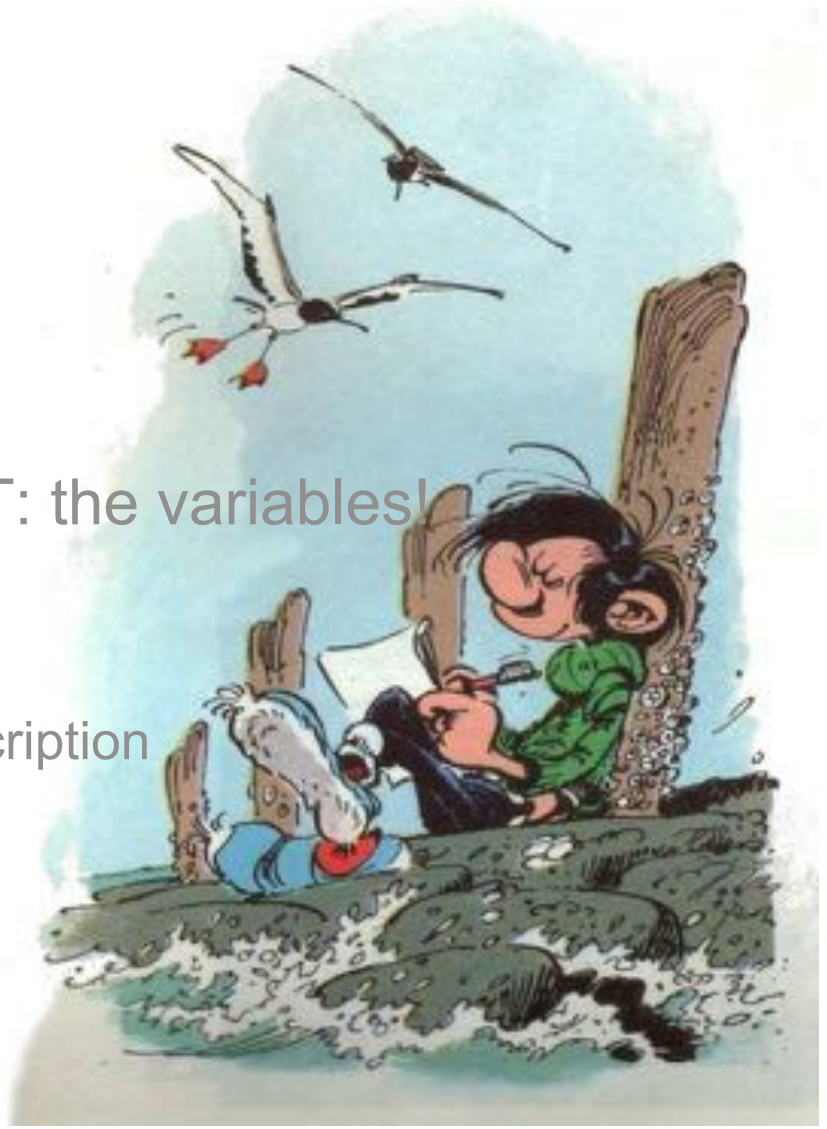
Let's start with some Yogi wisdom …

- … he also said:
  - "I knew the record would stand until it was broken."
- … free translated for SRS/SBRT:
  - "**I knew the PTV would remain in use until it became useless.**"



Outline

- Let's start with the definition of the PTV:
  - Evolution of ICRU reports in fast forward
  - PTV and SRS / SBRT
- Dose prescription and reporting in SBRT: the variables!
  - PTV & dose prescription
  - Tissue heterogeneity & dose prescription
  - PTV & tissue heterogeneity % dose prescription
  - Motion & dose prescription
- What about the ICRU 91?



ICRU 91
Executive Summary

50 – 62 – 83 – 91

- The median absorbed dose, $D_{50\%}$, should be as close as possible to the near-minimum dose, $D_{98\%}$.
- **Emphasis on dose homogeneity**

- Steep dose gradients, dose fall-off, and small lesions.
- **accept dose heterogeneity** to obtain optimal conformity and steep gradients

Recommendation for prescription

- 1) Planning aims (treatment goals) must be described:
  - Delineated volumes
  - Desired absorbed dose levels
- 2) The optimization process of the beam delivery.
- 3) The accepted treatment plan”
  - A complete set of finally accepted values: the “prescription”
  - The required “technical data”

Volumes

- The good news: the concept of volumes hasn't changed much

- GTV, CTV, PTV
- OAR, PRV, RVR

- RVR: Remaining Volume at Risk
  - The imaged volume within the patient, excluding any delineated OAR and the CTV's.
  - Is of importance in evaluating plans as there can be unsuspected regions of high absorbed dose within the patient that would otherwise not be reported.
  - Might be useful in estimating the risk of certain late effects.

Recommendation for reporting

- In order to have a common language and ability to compare clinical reports, reporting rules are recommended in ICRU 91.

- SRS, SRT, SBRT reporting should only be done at Level 2 or 3.

  - Level 2: State-of-the-art radiation therapy techniques
  - Level 3: Research an developmental procedures

Recommendation for reporting

- Level 2 reporting should include:
  - Brief clinical history including description of the clinical examination, location, diagnostic technique used, histopathological evaluation if any, staging, prior treatment, performance status.
  - Treatment intent (i.e., palliative, curative)
  - **Patient simulation** (i.e., immobilization devices, accessories, planning image acquisition, and protocols)
  - Target volumes and OAR selection and delineation (**GTV, CTV, ITV, PTV; OAR, PRV, RVR**; in cm^3)
  - **Planning aims and dose–volume constraints**
  - **Description of treatment planning system** (i.e., algorithm, voxel size, calculation dose grid, type-A uncertainty for MC-based systems)
  - Prescription
  - **Patient-specific QA**
  - Delivery (i.e., treatment unit and energy, image verification device, and data set)
  - **DOSE REPORTING**

Recommendation for reporting

- **Dose reporting**
  - Dose in PTV and, if applicable in CTV and/or GTV (see infra)
  - Dose in OAR and PRV (cf ICRU 83)

Recommendation for reporting

- **Dose reporting**
  - Dose in PTV and, if applicable in CTV and/or GTV (see infra)
  - Dose in OAR and PRV (cf ICRU 83)

- Let's start with the PTV:

  - **PTV median absorbed dose: $D_{50\%}$**

  - $D_{50\%}$ **can also** be reported for the CTV

Recommendation for reporting

- **PTV median absorbed dose: $D_{50\%}$**
  - $D_{50\%}$ **can also** be reported for the CTV

- **HOWEVER**:
  - In the specific case of **peripheral lung lesions**, where the dose distribution is strongly affected by tissue density variations, a dose to a target, which does *not include uninvolved* lung parenchyma **$D_{50\%}$ (GTV/CTV), SHOULD BE SYSTEMATICALLY REPORTED**.
    - The median dose, $D_{50\%}$, is likely to be a good measure for a typical dose in a relatively homogeneously irradiated tumor.
    - The original rationale for reporting the dose at the ICRU reference point and reporting of $D_{50\%}$ are very similar.
    - If it were possible to obtain the "true" DVH for the CTV, where motion and setup uncertainties were accounted for in detail, it would typically be contained within the DVHs of the CTV and PTV
    - Wherever the CTV lies within the PTV envelope, the CTV median dose is almost constant.

Recommendation for reporting

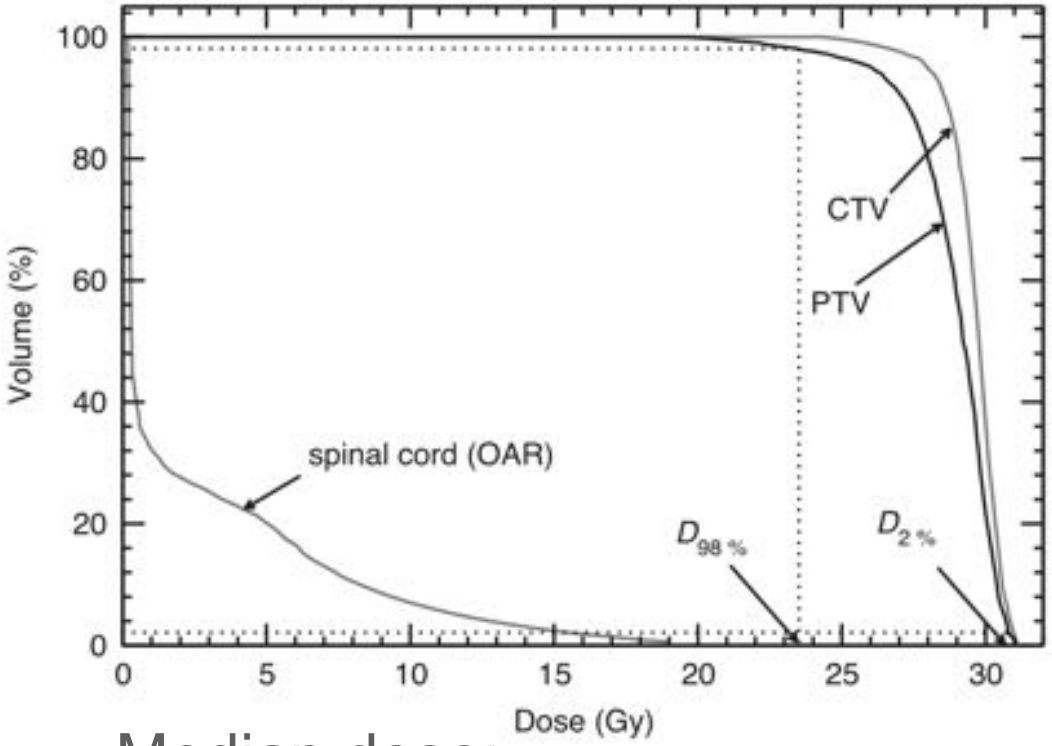
- **SRT near-maximum dose** to the PTV
  - Case 1: **PTV ≥ 2 cm^3**
  - **$D_{near\text{-}max} = D_{2\%}$** (cf ICRU 83)
  - Case 2: **PTV < 2 cm^3**
  - **$D_{near\text{-}max} = D_{35mm3}$** (Dose to an absolute volume of 35 mm^3)
- **SRT near-minimum dose** to the PTV
  - Case 1: **PTV ≥ 2 cm^3**
  - **$D_{near\text{-}min} = D_{98\%}$** (cf ICRU 83)
  - Case 2: **PTV < 2 cm^3**
  - **$D_{near\text{-}min} = D_{V\text{-}35mm3}$** (Dose to an absolute volume of 35 mm^3)

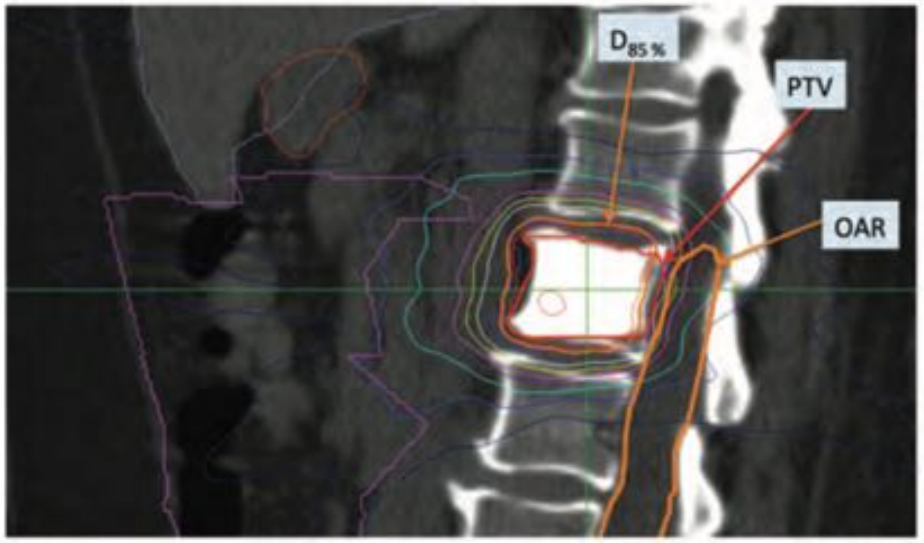
Recommendation for reporting

- Rationale for **SRT near-maximum** and **near-minimum dose**:
  - **ICRU 83** introduced **$D_{2\%}$** and **$D_{98\%}$**
  - An absorbed dose is reported that is NOT DEPENDING on a single computation point and suffers less from sampling errors and calculation uncertainties.
  - **ICRU 91**, for small PTV, SRT near-maximum dose is **D_V, where V represents a minimal absolute volume element within which the absorbed dose can be calculated to sufficient accuracy**.
  - This volume element needs to be chosen taking into account the calculation grid size and considerations related to dose-calculation accuracies in a single voxel.
  - Turns out that absolute volumes of **30-35 mm^3** seem adequate (Benedict 2010, Roberge 2015).

Recommendation for reporting

- An example using DVH for SRT of a spine metastasis:





- Median dose:
  - $D_{50\%}$ CTV = 29.7 Gy / $D_{50\%}$ PTV = 29.2 Gy
- SRT near-maximum dose, **PTV > 2 cm^3** ⇨ : $D_{2\%}$ = 30.8 Gy

Recommendation for reporting

- The clinical relevance of the **lowest PTV dose points** may depend on their **position within the PTV**.

- The **location** of low-dose regions within the GTV, CTV, and PTV boundaries may be of concern but **the DVH will not provide that information**. Such regions might, however, be identifiable using isodose contours.

- Hence, **it is important that the radiation oncologist not rely solely on the DVH for treatment evaluation but also carefully inspect the dose distributions slice-by-slice** (or in three dimensions) to make sure that the PTV is being adequately irradiated and that any regions of low dose are those required to avoid complications.

Recommendation for reporting

- **What about OARs?**

Typical parallel structures

- Volume V_D of tissue receiving a clinically relevant dose D depending on the type of organ or clinical situation

Typical parallel structures

- D_{mean} and/or D_{median} depending on the type of organ or clinical situation.

- SRT near-maximum dose $D_{2\%}$ or D_{35mm3}.

Typical serial structures

Recommendation for reporting

- Dose homogeneity:
  - Characteristically low in SRS/SBRT
  - Suggested to report the **Mean Dose to the PTV and its standard deviation**
- Conformity:
  - Characterizes to which degree the high dose region conforms to the **target volume**.
  - Paddick Conformity Index:

Clearly define GTV or PTV!

$$\frac{TV_{PIV}}{PIV} \times \frac{TV_{PIV}}{TV}$$

TV_{PIV}: Target Volume (TV) within Prescription Isodose Volume (PIV)

Healthy tissue receiving dose > PIV

Quality of target coverage

  - The inverse PCI is recommended: $\frac{TV \times PIV}{TV_{PIV}^2}$
- Gradient Index: $\frac{PIV_{half}}{PIV}$ (“dose fall off”)

Recommendation for reporting

- Integral dose
  - The concept of integral dose in radiation therapy has gained interest in the context of second cancer induction or complication as a result of the irradiation of large body volumes and the extensive exposure at the time of diagnostic/planning and image guidance.
  - In SRT, the treated volumes are typically small and the number of fractions limited. Nevertheless**, strong consideration should be given to the recording of integral dose especially for patient treated for benign lesions**.
- Treatment planning and delivery
  - Dose calculation algorithm
  - Grid size
  - Heterogeneity correction
  - Dose to water – dose to tissue

Recommendation for reporting

- Confidence levels

  - Rather than simply reporting $D_{50\%}$ for an individual or the average $D_{50\%}$ for patients in a trial, **the confidence intervals** for these values should be reported.
  - If **QA measurements** were conducted to verify doses delivered to patients in a trial, the population-averaged deviaton of these measurements from the planned dose would be a useful measure as would the confidence interval of the deviation

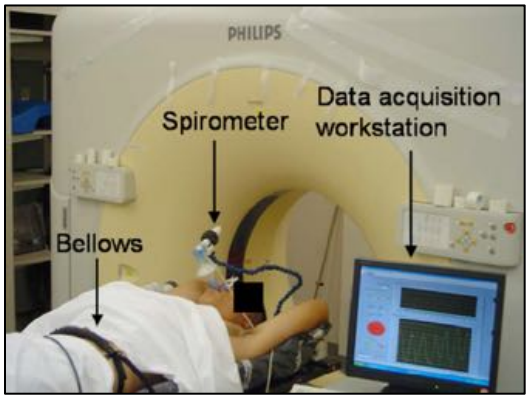
An example

- Patient History
  - A 79 year old male presented with increased shortness of breath and mass on a chest x-ray in February 2015. The mass was located in the left middle lobe and had a diameter of 12 mm on a CT- scan.
  - Bronchoscopy revealed a squamous cell carcinoma and the PET(CT) scan showed a solitary PET-positive nodule in the lung.
  - The patient had a history of COPD GOLD class III with a FEV1 (forced expiratory volume) of 1130 ml (46 % of the predicted value) and a history of cerebrovascular accidents and transient ischemic attack.
  - The ventilation/perfusion scan showed that the right lung contributed 48% of the ventilation/perfusion capacity while the left lung contributed 42 %.
  - As the patient had mediocre lung function, he was considered inoperable.
  - This patient was referred for curative stereotactic treatment with the CyberKnife.

An example

- Treatment intent
  - The intent of the treatment was to cure the patient.

- Simulation
  - The patient assumed the prone treatment position on a vacuum mattress used for the planning CT-scan.
  - The treatment planning CT scan was made with intravenous contrast during exhalation with our wide-bore multi-slice CT simulator. The patient was scanned from the teeth to the middle of his abdomen. The trans-axial imaging had a slice thickness of 1.5 mm.



An example

- Target volume and OAR selection and delineation
  - The planning CT was transferred to the treatment planning system (Accuray, Sunnyvale, CA). The tumor and organs at risk (OAR) were then contoured. The gross tumor volume (GTV, 1.5 cm3) was contoured using the lung window. The planning target volume (PTV, 6.7 cm3) was obtained by adding a 5mm margin to the GTV. The OARs were the lungs, the heart, the esophagus and the spinal cord.
- Planning aims and DVH constraints
  - The total dose was prescribed to the outer border of the PTV, and 95% of the volume of the PTV had to receive the prescription dose. The dose constraints for the organs at risk for a peripheral lung tumor are shown in Table A.1

Table A.1. Dose constraints for a peripheral tumor, treated with 51 Gy in 3 fractions

Organ	D_{max} (Gy)
Spinal Cord	18 Gy
Esophagus	21 Gy
Trachea and main bronchus	33 Gy
Plexus brachialis	21 Gy
Liver*	17 Gy
Organ	**Volume & dose**
Lung minus GTV	<31 % should receive 13 Gy

An example

- Description of the treatment planning system
  - The treatment planning was made with Multiplan version 2.2.0, the treatment planning system of the Cyberknife (Accuray, Sunnyvale, CA). Multiplan has implemented both equivalent path length (EPL) and Monte Carlo (MC) dose calculation algorithms. The MC dose calculation algorithm was validated (Grofsmid et al., 2010). The treatment plans in Multiplan were first recalculated with EPL, and then with MC. This was done to eliminate subtle differences between the OnTarget and Multiplan treatment planning systems. A high-resolution grid (256 × 256) was used for the EPL and MC calculations and the type-A uncertainty in the MC calculation was set to 2 %. MC computation time was approximately 5–10 minutes

An example

- Prescription
  - The PTV (outer border) was treated with a dose of 51 Gy in 3 fractions and the dose was prescribed to the 74 % isodose line.

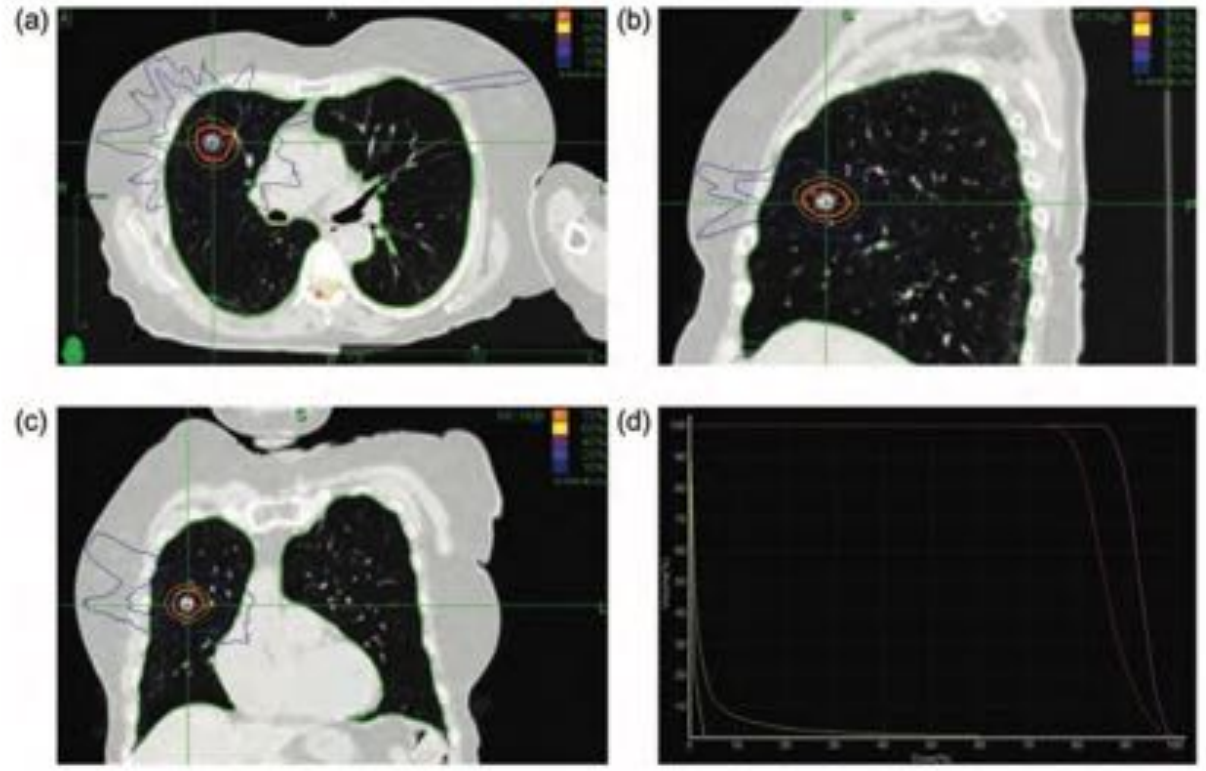
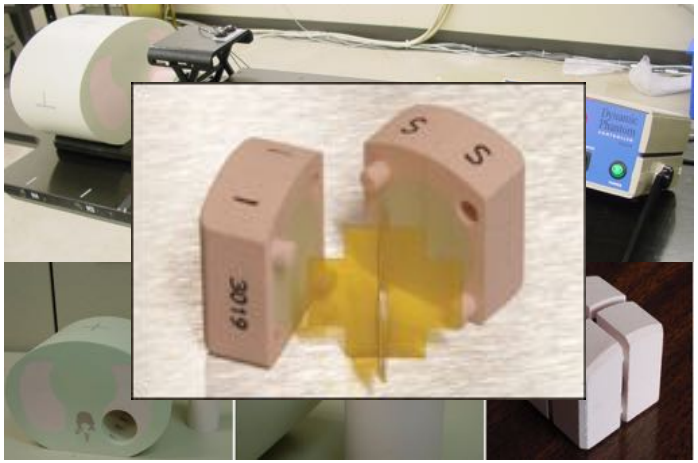


Figure A.1. Lung cancer SBRT treatment with Cyberknife. The dose distribution is in the axial (a), sagittal (b) and coronal (c) planes and the dose volume histogram is shown in (d). The PTV is shown in red, the GTV in purple, the "lungs minus GTV" in green and the spinal cord in yellow. The dose is prescribed to the 78 % isodose line (blue).

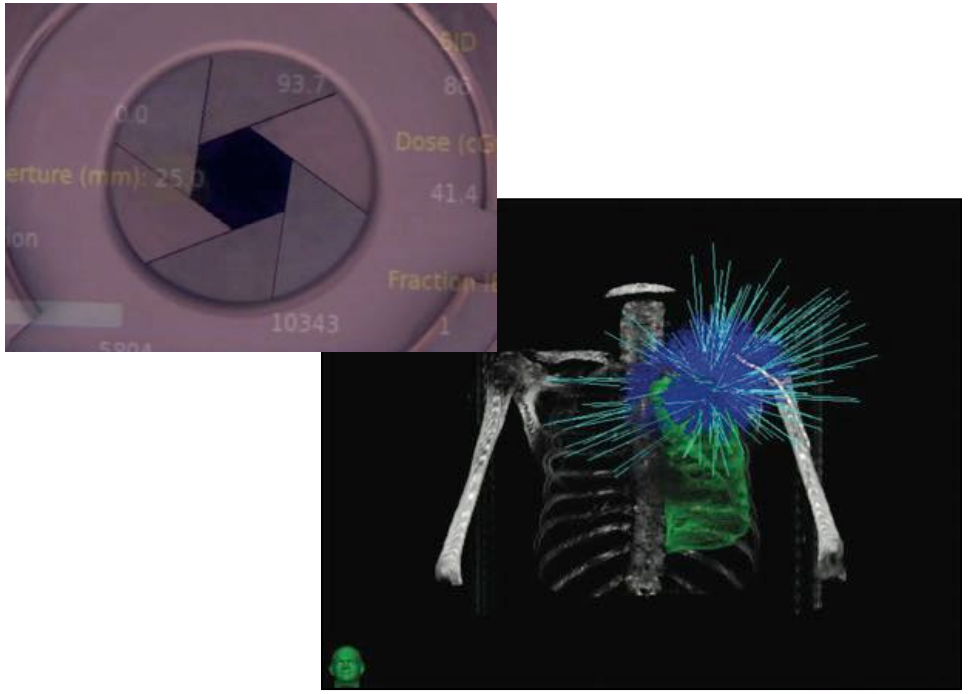
An example

- Patient specific QA
  - QA of stereotactic lung treatments is part of an overall QA program for this stereotactic unit. The QA is performed weekly. The end-to-end tests are performed alternating such that the end-to-end test for Xsight lung tracking occurs every 8 weeks. The end-to-end test for fiducial tracking is performed every 4 weeks.
  - Patient-specific QA did not include pre-treatment QA; instead, it consists of a semi-automated check of the treatment plan according to a check list.
  - These checks include treatment parameters, tracking alignment, plan details, Monte Carlo checks and an independent MU calculation.



An example

- Delivery
  - The dose was delivered with the CyberKnife using an iris collimator. In total, 97 non-coplanar beams were used with a total of 11302 monitor units per fraction. The tumor was treated with the fiducial tracking system of the CyberKnife.



An example

- Dose reporting
  - The PTV was 6.7 cm3. The median absorbed dose to the PTV ($D_{50\%}$) was 56.0 Gy, the near minimum dose $D_{98\%}$ was 50.4 Gy and the near maximum dose was $D_{2\%}$ = 63.4 Gy. The median absorbed dose to the GTV ($D_{50\%}$ was 60.6 Gy, the near minimum dose $D_{98\%}$ was 56.6 Gy and the near maximum dose was $D_{2\%}$ = 64.5 Gy.
  - Doses to normal tissues (lungs, heart, spinal cord, etc.) were within the constraints (see Table A.1).

Table A.1. Dose constraints for a peripheral tumor, treated with 51 Gy in 3 fractions

Organ	D_{max} (Gy)
Spinal Cord	18 Gy
Esophagus	21 Gy
Trachea and main bronchus	33 Gy
Plexus brachialis	21 Gy
Liver*	17 Gy
Organ	**Volume & dose**
Lung minus GTV	<31 % should receive 13 Gy

Take home message

- ... just read the new ICRU report, it's actually a good refreshment:

  - History of SRS and SRT
  - Overview of small-field radiation therapy equipment
  - Similarities & differences between 3D-CRT, IMRT, SRT
  - Clinical experience with small field radiation therapy
  - Small field dosimetry
  - Definition of volumes
  - Treatment planning algorithms
  - Image-guided beam delivery
  - Quality assurance
  - Prescribing, recording, and reporting
  - Clinical examples

Questions from the audience

- Some careful considerations, some answers ...

  - SRS/SRT/SBRT what is the difference
    - A better definition would be “high-dose-per-fraction-high-precision-techniques”, in any case the label “stereo” is outdated ... but it sticks (reimbursement?).

  - GTV to CTV margin: yes or no?
    - For benign lesions or functional intracranial SRS, GTV = CTV
    - Extracranial there might be situations where GTV and CTV represent identical volumes. When this is the case, **the CTV should still be defined**.
    - Even if it can be assumed that the penumbra (dose fall-off) will be sufficient to eradicate microscopic infiltrates. **Instead of assuming that the penumbra will cover the undefined CTV, it is recommended to formally assess the dose to the CTV**.
    - **Moreover, physicians are pushing physicists to reduce the fall-off, be careful what you ask for, we will get there**!

Questions from the audience

- Some careful considerations, some answers ...

  - Prescribing to an enveloping isodose line is fine, but what isodose should we use? Isodose compared to what normalization point?

    - Isodose compared to isocentre dose or $D_{near\text{-}max}$?
    - Which isodose 60%-80%, 95%?
    - Unfortunately ICRU only says “an enveloping isodose” must be used, so: “yes it is still confusing”.
    - Fortunately, with what should be reported ($D_{50\%}$ to PTV and GTV, and $D_{near\text{-}max}$ and $D_{near\text{-}min}$), you should be able to translate a published result to your prescrition method.
      - eg, if you use 15 Gy to 60% of isocentre dose, it will become difficult to compare that to a study reporting $D_{50\%}$ = 15Gy, $D_{near\text{-}max}$ = 17Gy ...

  - Very confusing in the ICRU 91 is the concept in that the accepted plan becomes the “prescription” for reporting, this is contradicting daily practice ...

Acknowledgements

Many thanks to all Friends and Colleagues
for their nice slides!!!

Stereotactic ablative radiotherapy (SABR) for early-stage NSCLC

Professor Suresh Senan
VU University Medical Center

Disclosures:

Research grant: Varian Medical Systems, ViewRay Inc

Advisory boards – Eli Lilly, AstraZeneca, Merck

Questions from participants

Definitions

- Definition of SBRT - some authors mentioned 6~10F treatment as SBRT. is that right

Patient selection

- Is there some radiobiologic difference between large tumor, small tumor SBRT?
- Can we recommend SBRT with large tumors (>5~10cm) at MDT's?
- Recommended target size for NSCLC SBRT?

- Use of SBRT in previously irradiated sites
- Re-irradiation for metachronous st I NSCLC: different dose- constraints for OAR

Questions from participants

Planning and delivery

- Recommendations for patient positioning fixation for SBRT in thorax

- OAR constraints
- What constraints could be used for brachial plexus in lung SBRT?
- What dose constraints for the thoracic aorta in treating lung tumors with SBRT?
- Which is the best protocol to follow regarding the OAR in SBRT?

- When to recommend gated treatment for SBRT lung
- What is the optimal time for interval imaging during treatment for lung tumors

Follow-up

- Advise to the ideal response evaluation criteria for local control in Lung SBRT

Learning aims

- Implementing SABR for peripheral lung tumors
- Conduct post-SABR follow-up (toxicity, relapses, 2nd tumors)
- Approach to complex SABR cases (central, tumors >5 cm)
- Areas of ongoing clinical research

SABR for stage I NSCLC

- SABR (or SBRT) is a technique for delivering high-dose radiotherapy with high precision, to an extra-cranial target

- **ESMO Guidelines** [Vansteenkiste J, 2014]: Preferred treatment in patients with a peripheral early-stage NSCLC who are unfit for surgery, or who refuse it.
- Minimal delivered radiation dose BED_{10} ≥100 Gy

- **NCCN Guidelines** [version 7.2015]

- **ASTRO guidelines** [PRO 2017]

How did SABR become the standard of care?

"There are three types of people in this world:

those who make things happen,

those who watch things happen,

and those who wonder what happened"

Mary K. Ash 1918-2001

SABR - Recurrence patterns in stage I NSCLC

Recurrences	Local	Regional	Distant
VU University Med Ctr 676 patients; median follow-up of 33 months	**10.5%**	**12.7%**	**20%**
MD Anderson Hospital 912 patients; median follow-up of 59 months	**11%**	**12%**	**21%**

[1] Senthi S, Lancet Oncol 2012

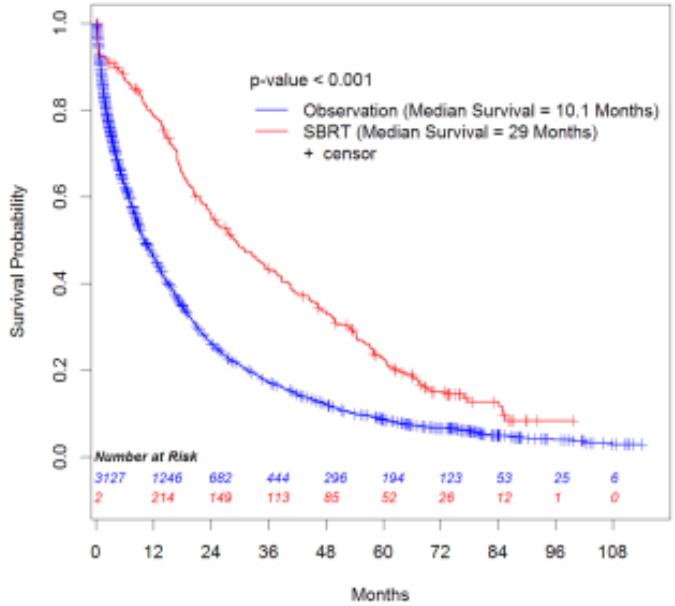
[2] Brooks E, IJROBP 2017 and update at ASCO (Abstr 8501)

SBRT vs no treatment (NCDB)

3147 pathology-proven patients >70 years (2003-2006)

No treatment = 2889 patients (92%); SBRT = 258 patients (8%)

No significant differences in Charlson/Deyo comorbidity index scores



US National Cancer Database **(NCDB)**

Median survival (MS) with only observation was **10.1 months**

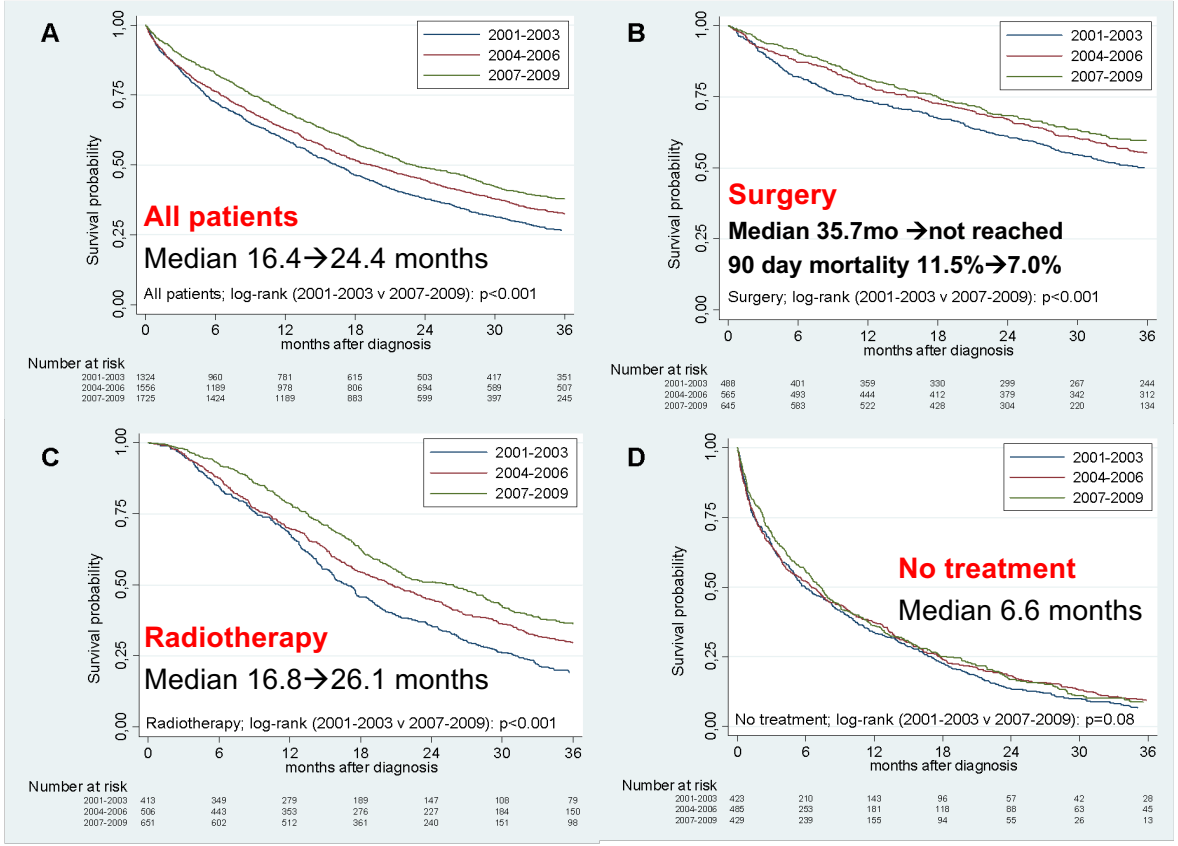
MS with SABR was **29 months**

Nanda RH, Cancer 2015

Dutch population outcomes (2001-2009)

Survival in 4605 patients aged ≥75 years

Haasbeek CJA,2012



Haasbeek C, Ann Oncol 2012

Is SABR superior to conventional RT?

- **SPACE trial** (NTC01920789)
- **CHISEL - TROG 09.02** (NCT01014130)
- Canadian SBRT vs hypofractionated RT (NCT01014130)

SPACE trial [Nyman J, Radioth Oncol 2016]

102 patients were randomized (2007-2011)

Primary endpoint: progression free survival at 3 years

Local control: SABR - 86% vs conventional - 86%

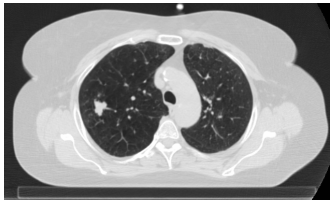
HRQL evaluation (EORTC QLQ 30, LC14 modules): 3DCRT patients had **worse dyspnea** (p = 0.01), **chest pain** (p = 0.02) and **cough** (>10 points difference)

Which patients to accept into your SABR program?

- Availability of pathology
- Extent of nodal staging

Treatment without pathology

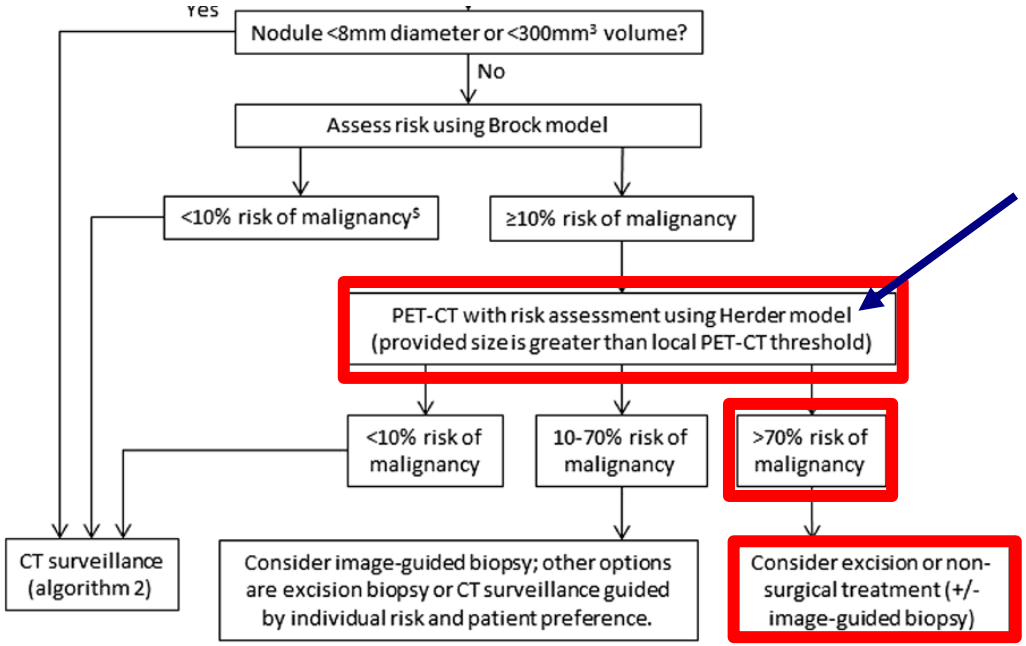
- “pre-treatment pathological diagnosis strongly recommended in all patients before **any curative treatment**, unless a multidisciplinary tumour board (MDT) is of the opinion that the risk-benefit ratio of the procedure is unacceptable.



- Expert MDT’s best placed to assess likelihood of benign disease in their populations including, where available, **algorithms** validated for the population in question. In case of the latter, a **likelihood of malignancy exceeding 85%** may be preferred”.

ESMO Guidelines [Vansteenkiste J, Ann Oncol 2014]

British Thoracic Society guidelines



UK population use of a 70% threshold leads to a “small increase” in risk of benign disease, but reduces treatment delays

Callister MEJ, Thorax 2015

ASTRO Evidence-Based Guideline

SBRT can be delivered in patients who **refuse a biopsy**, have undergone **non-diagnostic biopsy**, or who are thought to be at **prohibitive risk of biopsy**. Prior to SBRT in patients lacking tissue confirmation of malignancy, patients are recommended to be discussed in a **multidisciplinary** manner with a consensus that the lesion is radiographically and clinically consistent with a malignant lung lesion based on tumor, patient, and environmental factors

- **Recommendation strength:** Strong
- **Quality of evidence:** Moderate
- **Consensus:** 100%

Videtic GMM, PRO 2017

Asian clinical practice consensus

- High prevalence of granulomatous disease and other infectious causes of pulmonary nodules
- Diagnosis risk calculators developed in non-Asian patients may not be applicable
- Tuberculosis in Asia favors (i) lesser reliance on PET scanning, and (ii) greater use of non-surgical biopsy over surgical diagnosis or surveillance

Bai C, Chest 2016

Nodal staging before SABR in stage I NSCLC

Systematic review on nodal recurrence after SABR

No evidence that inoperable clinical stage I patients without evidence for pathological lymph nodes on PET-CT, will benefit from more invasive lymph node staging prior to SABR [1]

Wink K, Cancer Treat Reviews 2017[1]

Mediastinal staging before SABR

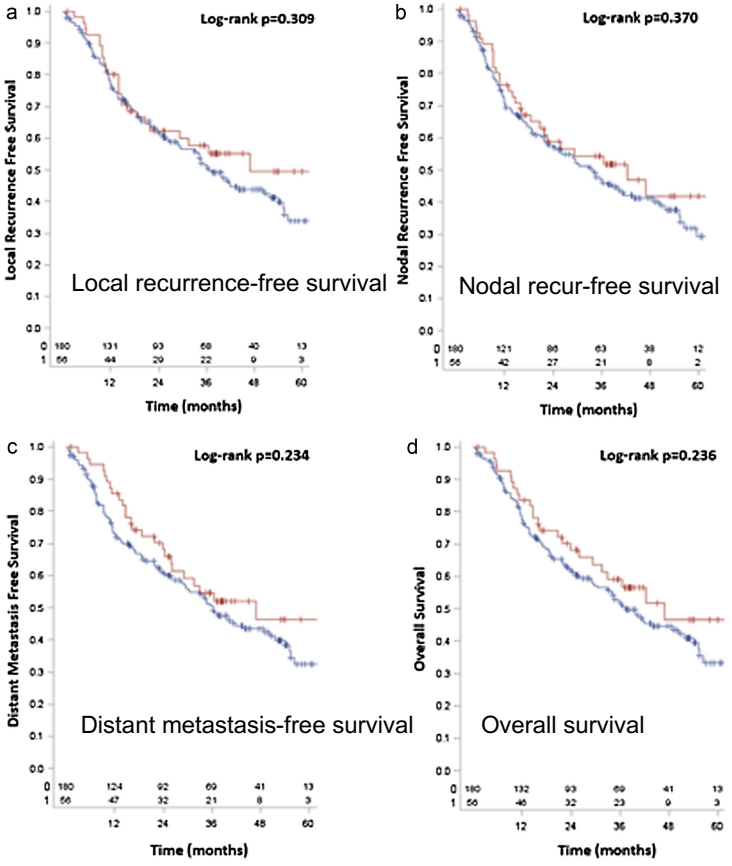
180 patients (199 lesions) staged with PET/CT alone vs. 56 patients (58 lesions) after additional IMNS

IMNS group: 52 (93%) EBUS and 4 (7%) mediastinoscopy

Median follow-up of 33.5 months

IMNS – invasive mediastinal nodal staging

Blue curve corresponds to patients undergoing PET/CT staging alone; ed curve corresponds to patients additionally undergoing IMNS



Schoenewolf CA, Lung Cancer 2017

SABR and occult nodal metastases

- 284 patients with PET-CT-staged clinical T1-2N0 disease
- Occult N2 metastases detected on either mediastinoscopy or endobronchial ultrasound (EBUS) in 7.0%
- 18% occult N2 metastases in tumors located within inner 1/3 of lung fields
- Occult N1 disease seen in 3% of patients with T1 disease, and 14% with T2 disease ($P < 0.001$)

Gao SJ, Lung Cancer 2017

SABR and occult nodal metastases

STAGE study (NCT02997449)

- Prospective international study in patients with CT-PET imaging showing: centrally located or a T2 peripheral located tumour or with suspicion of N1 or N2/3 nodal disease

- Complete endosonographic nodal staging (EBUS-EUS) of lung cancer in patients eligible for SABR

Crombag L, ERS oral presentation, 10 September 2017

SABR practice at VUMC – typical approach

Radiation Oncology

BioMed Central

Study protocol

Open Access

Recommendations for implementing stereotactic radiotherapy in peripheral stage IA non-small cell lung cancer: report from the Quality Assurance Working Party of the randomised phase III ROSEL study

Coen W Hurkmans*[1], Johan P Cuijpers[2], Frank J Lagerwaard[2], Joachim Widder[3], Uulke A van der Heide[4], Danny Schuring[1] and Suresh Senan[2]

METRICS

- Article accesses: 18553
- Citations: 138 more information

SABR practice at VUMC – typical approach

Radiotherapy and Oncology 124 (2017) 11–17

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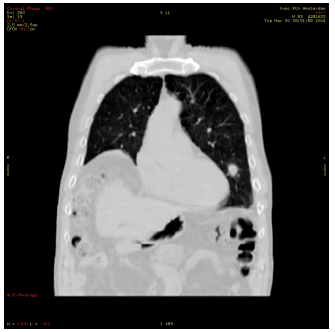
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

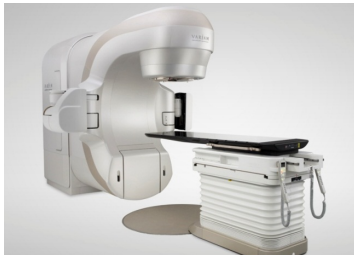
ESTRO-ACROP consensus guideline

ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer

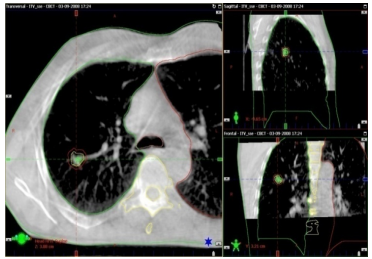
Matthias Guckenberger [a,*], Nicolaus Andratschke [a], Karin Dieckmann [b], Mischa S. Hoogeman [c], Morten Hoyer [d], Coen Hurkmans [e], Stephanie Tanadini-Lang [a], Eric Lartigau [f], Alejandra Méndez Romero [c], Suresh Senan [g], Dirk Verellen [h]



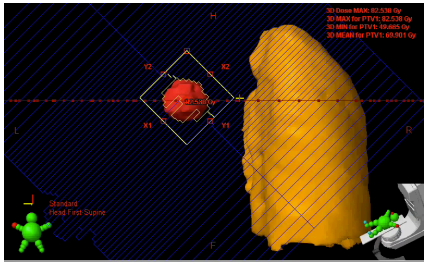
4-Dimensional CT scan



Linear accelerator (linac)



Cone-beam CT scan at linac



Delivery using VMAT (FFF mode) in less than 4 mins

Institutional prtactice at VUMC

Tumor characteristics	Fractionation	Year implemented	BED_{10} (Gy)	Overall treatment time
Tumor <3 cm	3 fractions of 18 Gy	2003	151 Gy	2 weeks
Tumor <3 cm and broad contact with chest wall	5 fractions of 11 Gy	2003	116 Gy	2 weeks
Tumor >3 cm, but <7 cm	5 fractions of 11 Gy	2003	116 Gy	2 weeks
Central tumor adjacent to and/or minimal overlap with plexus, hilus, stomach, pericardium, or mediastinum	8 fractions of 7.5 Gy	2003	105 Gy	2.5 weeks
Tumor >7 cm and/or Central tumor with a substantial overlap with mediastinal structures and/or Pathological ipsilateral mediastinal nodes	12 fractions of 5 Gy	2010	90 Gy	3 weeks

Dose constraints in SBRT trials

Table 1
Dose constraints used in major trials of SBRT

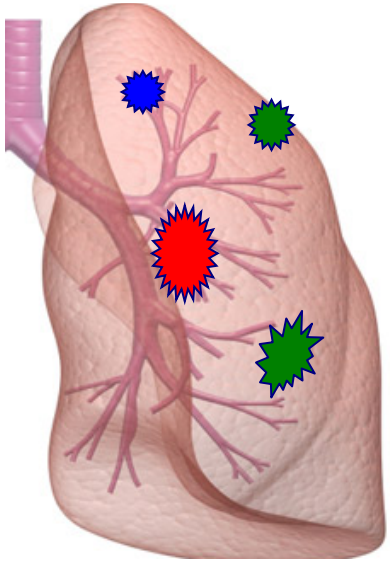
Organ	RTOG 0618 (3 Fractions)	Dutch ROSEL[a] Trial (3 Fractions)	Dutch ROSEL Trial (5 Fractions)	International STARS[b] Trial (4 Fractions)	JCOG 0403
Spinal cord	≤18 Gy	≤18 Gy	≤25 Gy	20 Gy ≤1 mL 15 Gy ≤10 mL	≤25 Gy
Esophagus	≤27 Gy	≤24 Gy	≤27 Gy	35 Gy ≤1 mL 30 Gy ≤10 mL	40 Gy ≤1 mL 35 Gy ≤10 mL
Lung	V20 ≤10%	V20 ≤5%–10%	V20 ≤5%–10%	V20 ≤20% V10 ≤30% V5 ≤50%	V15 ≤25% 40 Gy ≤100 mL MLD ≤18 mL
Brachial plexus	≤24 Gy	≤24 Gy	≤27 Gy	Point ≤40 Gy 35 Gy ≤1 mL 30 Gy ≤10 mL	Not limited
Heart	≤30 Gy	≤24 Gy	≤27 Gy	40 Gy ≤1 mL 35 Gy ≤10 mL	48 Gy ≤1 mL 40 Gy ≤10 mL
Trachea	≤30 Gy	≤30 Gy	≤32 Gy	35 Gy ≤1 mL 30 Gy ≤10 mL	40 Gy ≤10 mL
Bronchi	≤30 Gy	≤30 Gy	≤32 Gy	40 Gy ≤1 mL 35 Gy ≤10 mL	40 Gy ≤10 mL
Skin	≤24 Gy	Not limited	Not limited	40 Gy ≤1 mL 35 Gy ≤10 mL	Not limited

Doses represent limits at any point in the organ at risk unless otherwise specified.
Abbreviations: JCOG, Japanese Clinical Oncology Group; MLD, Mean Lung Dose.
[a] Randomized clinical trial of surgery versus radiosurgery in patients with stage IA NSCLC who are fit to undergo primary resection.
[b] Randomized study of lobectomy versus CyberKnife (Accuray, Sunnyvale, CA, USA) for operable lung cancer.

Shervani S, Thorac Surg Clin 2013

‘Risk-adapted’ SABR fractionation

Dutch fractionation schedules [Hurkmans C, Rad Onc 2009]



- **3 fractions of 18Gy**: T1 lesions, not adjacent to chest wall
- **5 fractions of 11Gy**: T1 lesions with broad chest wall contact, and T2 lesions
- **8 fractions of 7.5Gy**: central lesions with limited overlap with mediastinum

Learning aims

- Implementing SABR for peripheral lung tumors
- Conduct post-SABR follow-up (toxicity, relapses, 2nd tumors)
- Approach to complex SABR cases (central, tumors >5 cm)
- Areas of ongoing clinical research

SABR toxicity

- Chest wall toxicity (rib, soft tissues, pleural)
- Radiation pneumonitis
- Bronchial toxicity
- Less common: plexus injury, esophageal perforation, pericarditis, arrythmia

SABR – Toxicity in peripheral tumors

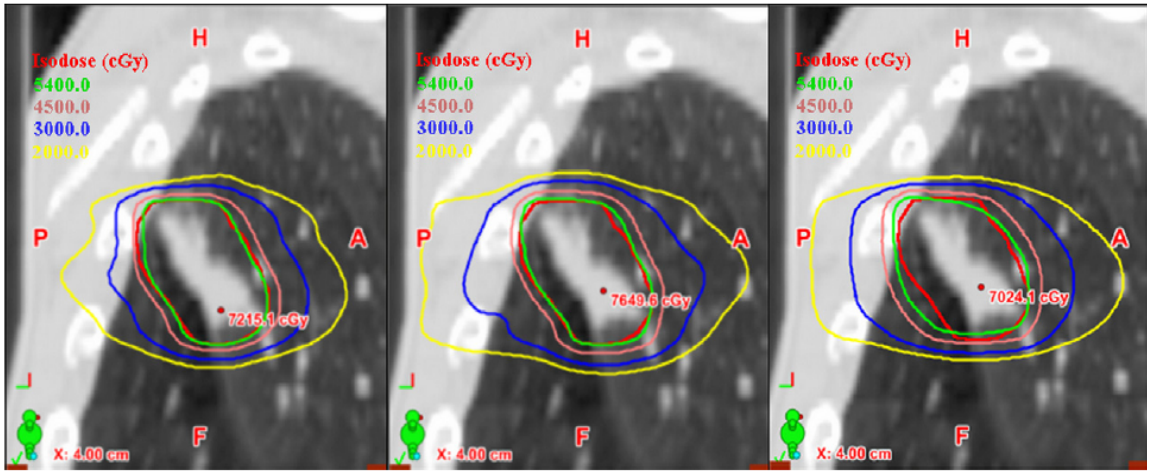
- No decreases in quality of life: Systematic review of 9 prospective studies [1]
- Chest wall pain of CTCAE Grades II or higher in 1-19 % of patients; fractures in between 2-39 % [2]
- SABR-related **mortality** of approximately **16%** in patients with preexisting interstitial lung disease: Systematic review [3]

[1] Chen H, Clin Lung Cancer 2016;
[2] Shaik T, Cancer Treat Rev 2014;
[3] Chen H, Int J Rad Onc Biol Phys 2017

SABR delivery - Limit chest wall doses

EORTC recommendations [De Ruysscher D, JCO 2010]:
Chest wall doses preferably to <30 Gy in 3-5 fractions, to a volume of <30 mL

RapidArc™ | 10 beam conformal | Dynamic conformal arc

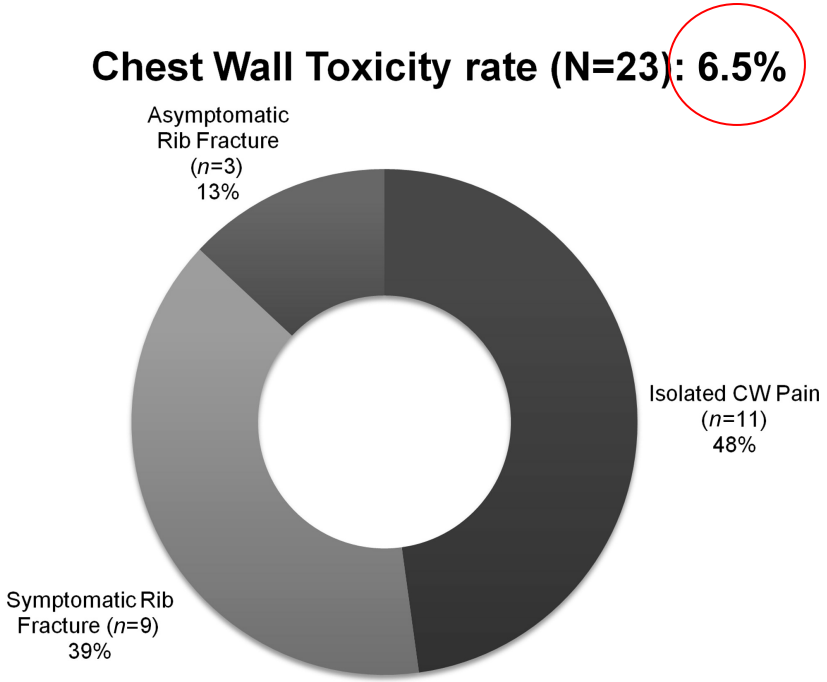


30 Gy isodose

Ong CL, Radioth Oncol 2010

SABR toxicity: Chest wall (CW)

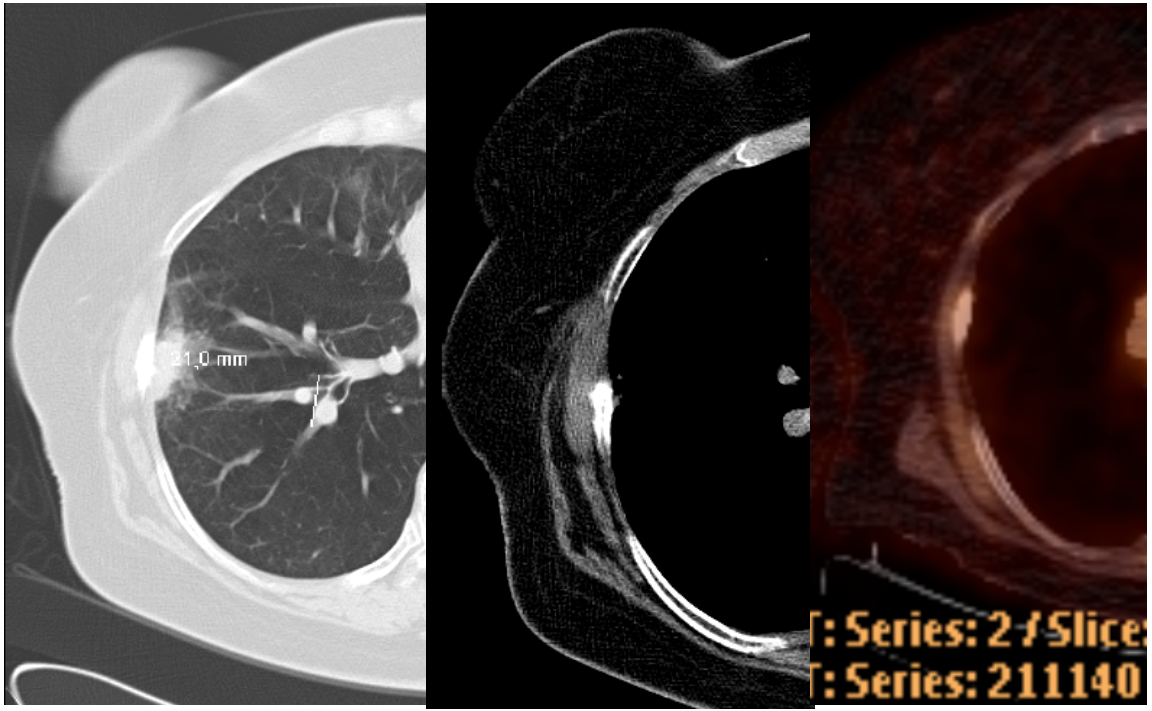
- N = 361 lesions in 356 patients
- CW structure using a 3-cm expansion of the lung. Median PTV dose 60 Gy.
- SABR in 3 fractions for patients with CW $V_{30} < 30\ cm^3$
- If CW $V_{30} > 30\ cm^3$, 5 fractions used and dose optimized based on CW V_{37} (biol equivalent to V_{30} of 3-fraction plans)



Jumeau R, BJR 2017

SABR – Toxicity in peripheral tumors

Chest-wall and fracture 2 years post-SABR
Pain decreased and resolved 3 months later



Tumors abutting or invading chest wall

SBRT is an appropriate option for treatment and should be offered for **T1-2 tumors** that abut the chest wall. Grades 1-2 chest wall toxicity is a common occurrence post SBRT that usually resolves with conservative management.

- **Recommendation strength:** Strong
- **Quality of evidence:** High
- **Consensus:** 94%

SBRT may be utilized in patients with **cT3 disease** due to chest wall invasion without clear evidence of reduced efficacy or increased toxicity compared to tumors abutting the chest wall.

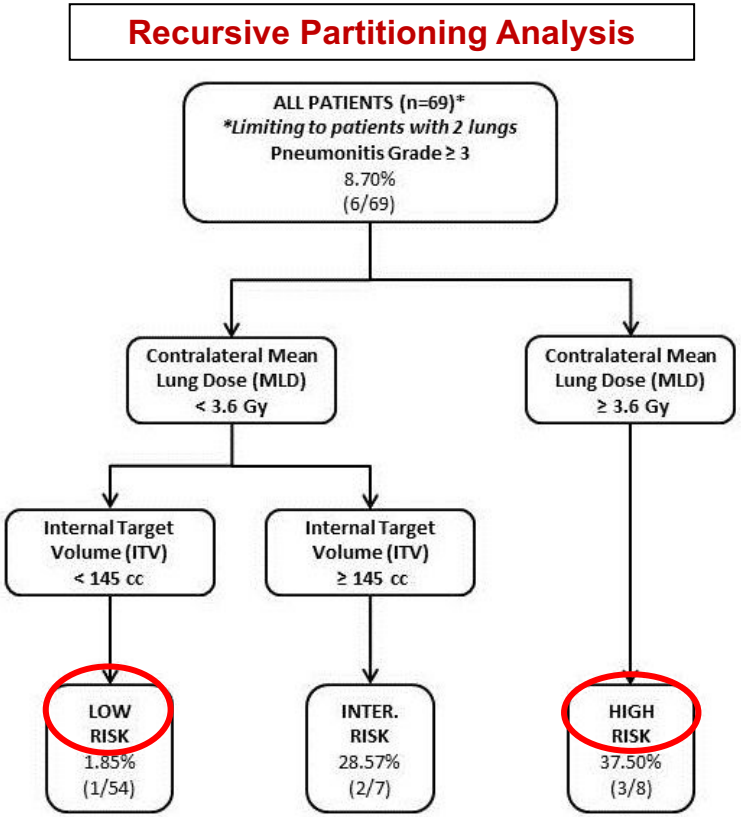
- **Recommendation strength:** Conditional
- **Quality of evidence:** Low
- **Consensus:** 88%

ASTRO evidence-based guideline, Videtic GMM, PRO 2017

SABR toxicity

- Chest wall toxicity (rib, soft tissues, pleural)
- Radiation pneumonitis
- Bronchial toxicity
- Less common: plexus injury, esophageal perforation, pericarditis, arrythmia

Predictors of G3 radiation pneumonitis



79 consecutive patients treated with VMAT for either a PTV >100 cm^3 (n=69), or a previous pneumonectomy or bi-lobectomy (n=13)

Bongers E, Radioth Oncol 2013

Radiation pneumonitis with SABR

Interstitial lung disease (ILD)

Bahig H, Prac Rad Oncol 2016

- 504 SABR patients (6% preexisting ILD Disease)
- Grade ≥ 3RP of 4% in entire cohort
- Grade ≥ 3 RP in 2% of patients without ILD

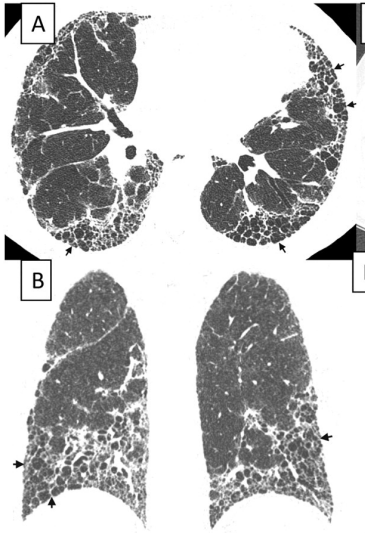
- Grade ≥ 3 RP in 32% of patients with ILD
- Grade 5 RP in 21% of patients with ILD

Chen H, IJROBP 2017

- Systematic review - SABR-related mortality rate is 16% in patients with co-existing ILD

Idiopathic pulmonary fibrosis (IPF, ILD)

- A severe, progressive and debilitating disease with a median survival time of 3-5 years after diagnosis
- Median age at diagnosis – 66 yrs. Prevalence in United States between 14 - 43 per 100,000 persons
- Estimated prevalence of lung cancer in IPF higher in Asian reports (20-23%), than in US and UK (3–4%)
- Diagnosis requires multidisciplinary discussion between experienced pulmonologists, radiologists, and pathologists



Raghu G, AJRCCM 2011; Raghu G, ERJ 2016

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

TABLE 4. HIGH-RESOLUTION COMPUTED TOMOGRAPHY CRITERIA FOR UIP PATTERN

UIP Pattern (All Four Features)	Possible UIP Pattern (All Three Features)	Inconsistent with UIP Pattern (Any of the Seven Features)
• Subpleural, basal predominance • Reticular abnormality • Honeycombing with or without traction bronchiectasis • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• Subpleural, basal predominance • Reticular abnormality • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• Upper or mid-lung predominance • Peribronchovascular predominance • Extensive ground glass abnormality (extent > reticular abnormality) • Profuse micronodules (bilateral, predominantly upper lobes) • Discrete cysts (multiple, bilateral, away from areas of honeycombing) • Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes) • Consolidation in bronchopulmonary segment(s)/lobe(s)

Definition of abbreviation: UIP = usual interstitial pneumonia.

Raghu G, AJRCCM 2011

Usual interstitial pneumonitis (UIP)

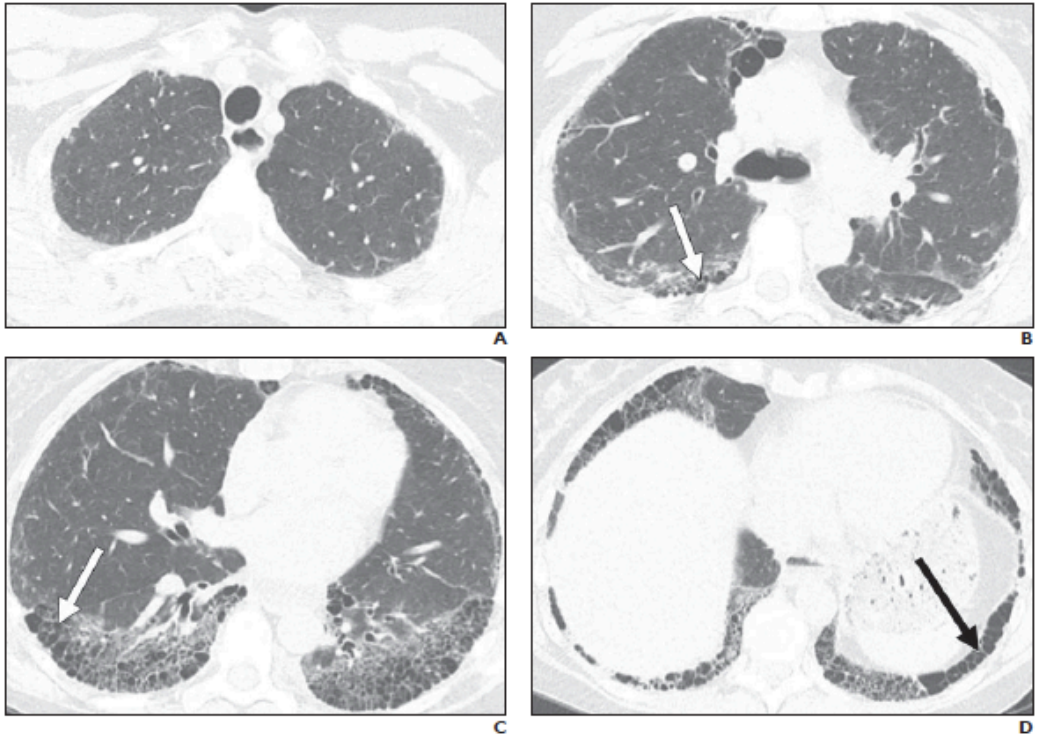


Fig. 1—71-year-old man with shortness of breath and crackles on auscultation.
A–D, Axial high-resolution CT images show peripheral and basilar-predominant pulmonary fibrosis and clustered honeycombing (*arrows*, B–D) in subpleural lung in this patient with usual interstitial pneumonitis pattern of pulmonary fibrosis.

Chung JH, AJR 2016

Limited fibrosis on CT scan

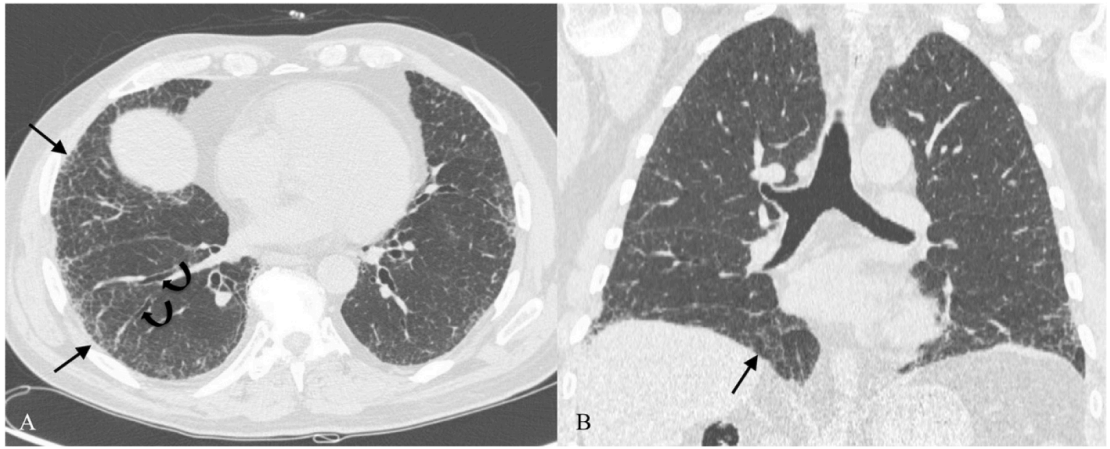


Fig. 6 "Possible UIP" pattern in a 77-year-old man. The possible UIP pattern includes: (1) reticular pattern (black arrows), with or without bronchiectasis (curved black arrows); (2) the presence of a typical subpleural location (black arrows); (3) no features listed as inconsistent with the UIP pattern

Example from Palmucci S, Insights Imaging 2014

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

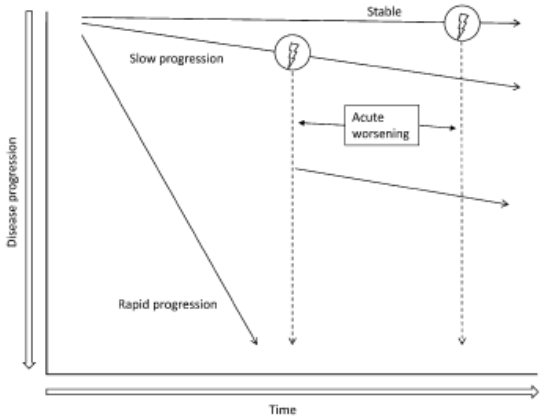


Figure 4. Natural history of IPF. There appear to be several possible natural histories for patients with IPF. The majority of patients experience a slow but steady worsening of their disease ("Slow progression"). Some patients remain stable ("Stable"), while others have an accelerated decline ("Rapid progression"). A minority of patients may experience unpredictable acute worsening of their disease (lightning bolt), either from a secondary complication such as pneumonia, or for unrecognized reasons. This event may be fatal or may leave patients with substantially worsened disease. The relative frequency of each of these natural histories is unknown.

Natural history of IPF can be unpredictable, with the majority of patients demonstrating a slow, gradual progression over many years.

<u>Policy adopted at VUMC</u>

A wait-and-see policy to exclude those with an accelerated decline in IPF, is often not feasible. Seek advice from **specialist IPF panels**

Raghu AJRCCM 2011

Learning aims

- Implementing SABR for peripheral lung tumors
- **Conduct post-SABR follow-up** (toxicity, relapses, 2nd tumors)
- Approach to complex SABR cases (central, tumors >5 cm)
- Areas of ongoing clinical research

Post SABR radiological follow-up

- Recognize ‘expected’ patterns of fibrosis (avoid patient anxiety, risky interventions)
- Toxicity (rib fractures, atelactases)
- Identify high-risk radiological features
- Detect and treat second tumors
- Smoking cessation

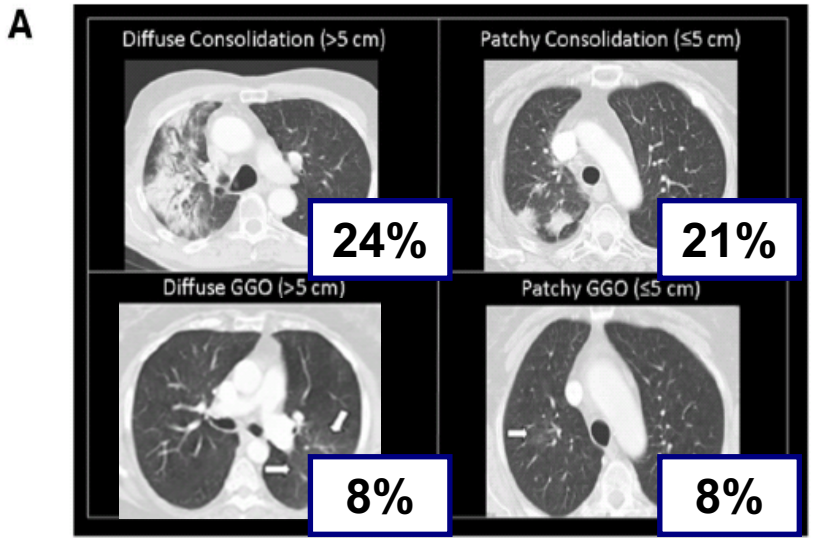
Post SABR radiological follow-up

- Surveillance 6 monthly for 2 years with preferably contrast-enhanced chest CT scan **at least at 12** and **24 months** recommended.
- Thereafter, an **annual visit** including history, physical examination and chest CT scan in order to detect second primary tumours [III, B]
- Due to a high number of false-positive findings on PET, patients suitable for salvage therapy should undergo a biopsy, whenever possible [III, B]

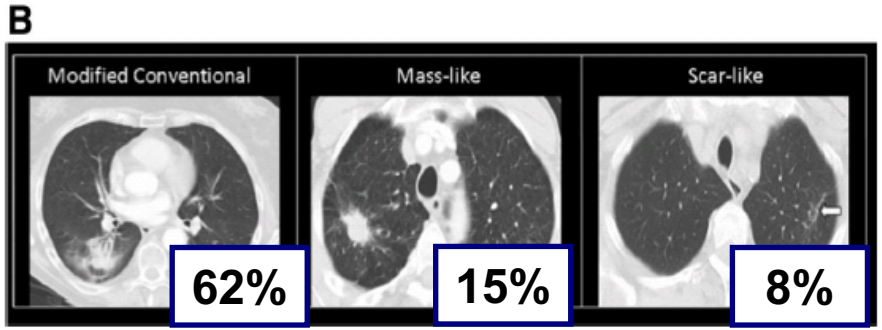
ESMO recomendations (Postmus PE, Ann Oncol 2017)

Post-SABR lung fibrosis

Acute:
≤6 months



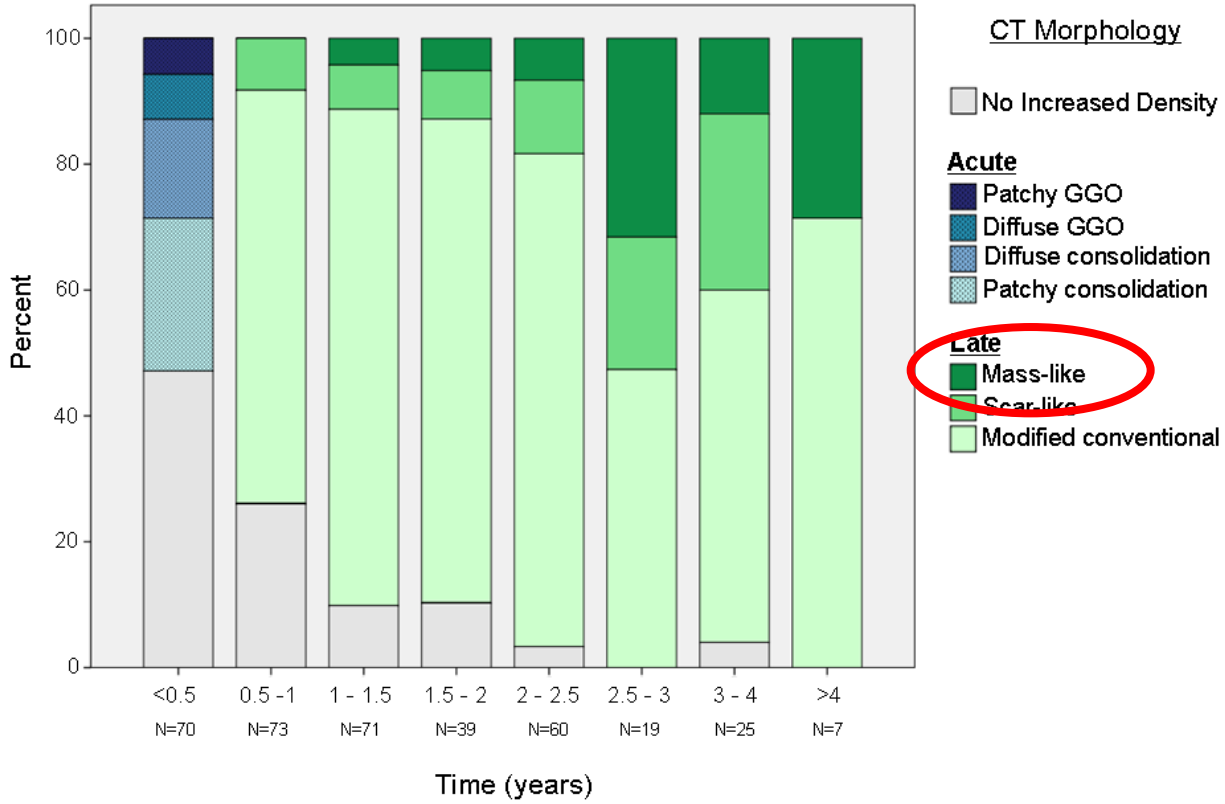
Late:
>6 months



Dahele M, JTO 2011

Post-SABR radiological changes

- All but



Dahele M, JTO 2011

Post-SABR radiological changes

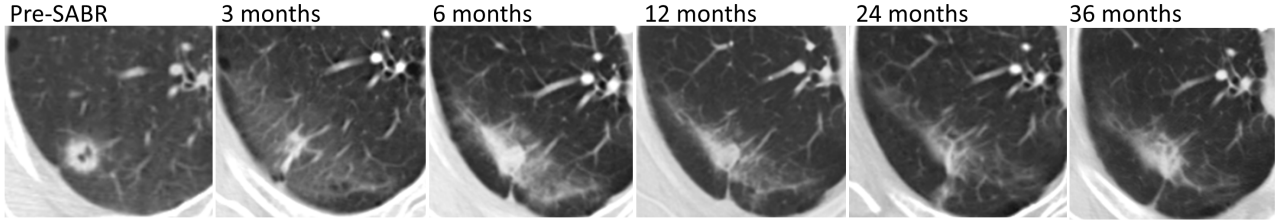
High-Risk Features
Enlarging Opacity
Sequential Enlargement
Enlargement after 12 months
Bulging Margin
Linear Margin Disappearance
Loss of Air Bronchogram
Cranio-Caudal Growth

Huang K, Radioth Oncol 2012, 2013

Fibrosis or recurrence after SABR?

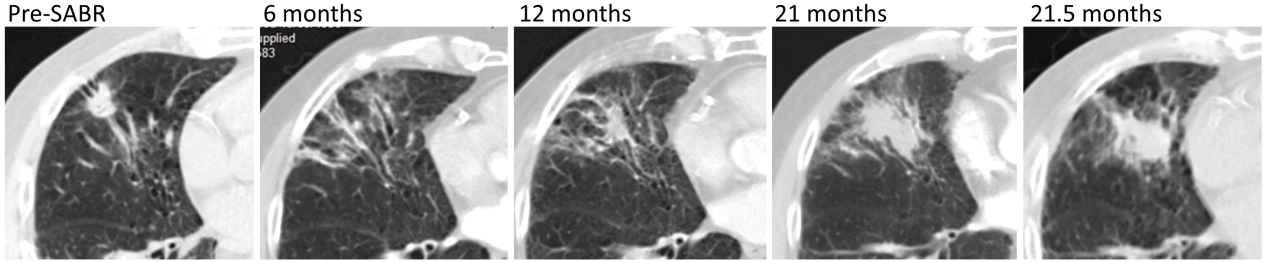
Blinded scoring of 12 path. proven recurrences matched with 24 non-reccurences

A. No Recurrence



HRF: Enlarging Opacity

B. Recurrence



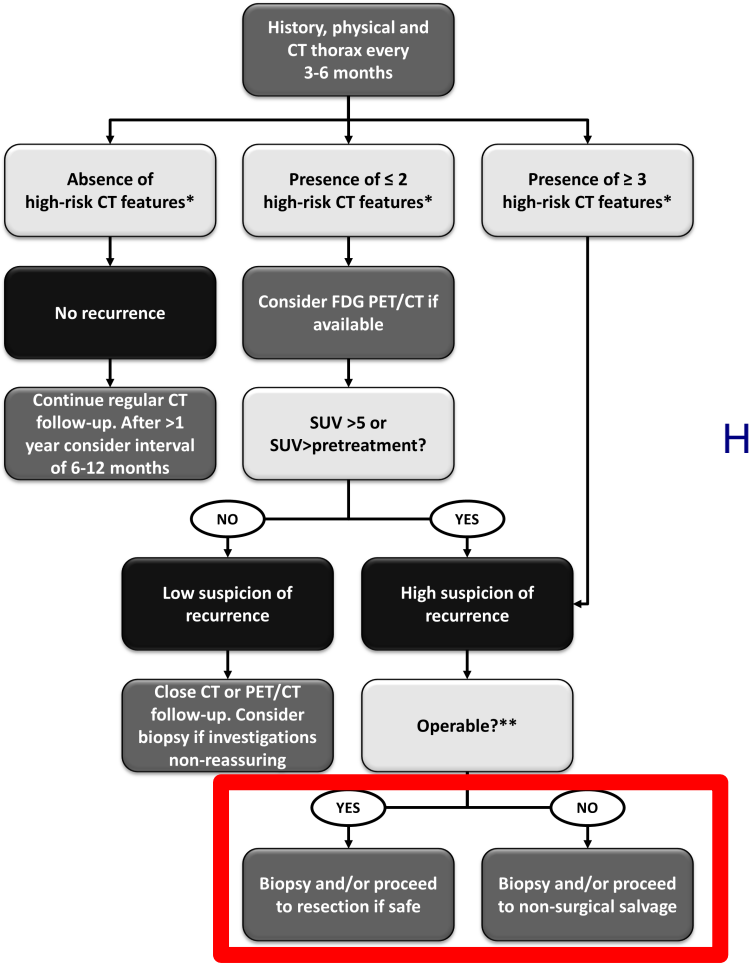
HRFs: Enlarging Opacity
Craniocaudal Growth

Sequential Enlargement
Enlargement after 12 months
Linear Margin Disappearance
Bulging Margin

Loss of Air Bronchogram

Huang K, Radioth Oncol 2013

Fibrosis or recurrence after SABR?



Huang K, Radioth Oncol 2013

Incidence of HRF in patients with no recurrence

HRF = high risk factors

- Eligible patients: follow-up CT scans for ≧2 years post-VMAT SABR, and no local recurrences

- 5 clinicians blinded to outcomes in **88 patients** (747 CT scans)

- Most frequent HRF's recorded by ≥ 3 clinicians on ≥ 1 follow-up scan were Enlarging Opacity (64.8%), Enlarging Opacity after 12 mo (50.0%) and sequential enlargement (13.6%)

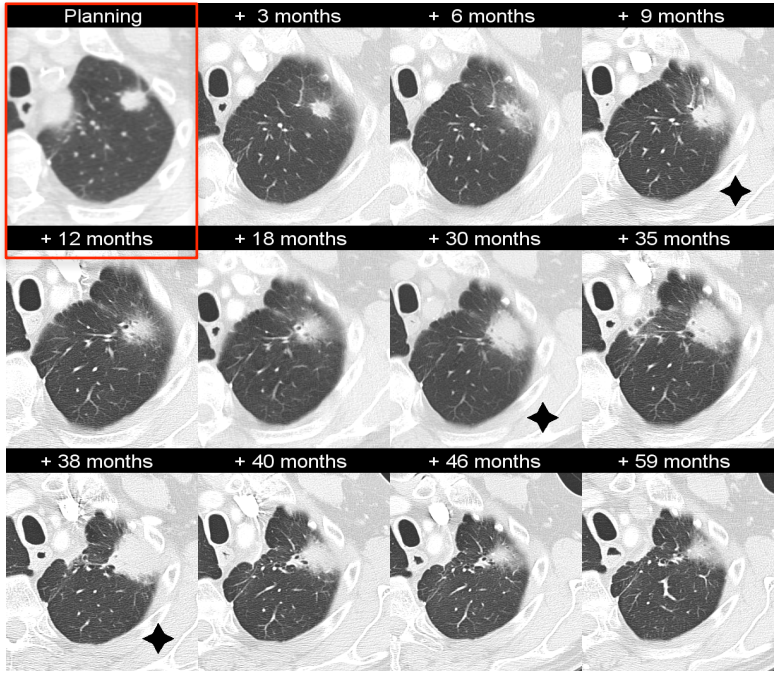
- **56 patients** developed enlarging opacity (EO) in year 1, and 46 of them also developed subsequent EO (EO12).

- ≥ 3 HRF's were observed in 23% of patients

Ronden M, *under review*

HRF in patients without recurrence

Serial images in a patient without recurrence



Ronden M, *under review*

Salvage surgery possible post-SABR

- Chen F, J Thoracic Oncology, 2010
- Neri S, J Thoracic Oncology, 2010
- Hamamoto Y, Japan J Radiology 2012
- Allibhai Z, Eur Resp Journal, 2012
- Hamaji M, J Thoracic Oncology, 2015
- Verstegen N, Radioth Oncol 2016
- Antonoff MB, JTCVS 2017

Salvage SABR is possible after SABR

Clinical outcomes reported by selected studies.

Author publication year [references]	Follow-up (after salvage treatment, months)	Local control	Overall survival	Severe acute and late toxicity rates
Coon et al. (2008) [23]	12	1-Year: 92%	1-Year: 81%	NA
Kelly et al. (2010) [24]	15	2-Years: 92%	2-Years: 59%	G3 pneumonitis: 28% G3 Esophagitis: 4% Chest wall pain: 31%:
Seung et al. (2011) [25]	18	At 18 months: 86%	At 18 months: 87.5%	None
Peulen et al. (2011) [26]	12	1-Year: 52% 2-Years: 43%	1-Year: 59%	G3 pneumonitis: 30% G4–5: 13% (central lesion)
Trakul et al. (2012) [27]	15	1-Year: 65%	1-Year: 80%	None
Liu et al. (2012) [28]	16	1-Year: 95%	2-Years: 74%	G3 pneumonitis: 19% 1 pt: G5 pneumonitis
Valakh et al. (2013) [29]	22	2-Years: 75%	2-Years: 69%	Late G3 pneumonitis: 22% Late G3 chest wall pain: 11%
Meijneke et al. (2013) [30]	12	1-Years: 75% 2-Years: 50%	1-Years: 67% 2-Years: 33%	None
Reyngold et al. (2013) [31]	12	1-Year: 77% 2-Years: 64%	22 months (median)	G3 pneumonitis: 5% G4 skin:25%
Trovò et al. (2014) [32]	18	1-Year: 86%	1-Year: 59% 2-Years: 29%	G3 pneumonitis: 17% −1 pt: G5 pneumonitis −1 pt: G5 bleeding
Hearn et al. (2014) [33]	14	Not specified*	Four patients presented a local failure at a median of 9.9 months.	No G3–5 toxicity
Kilburn et al. (2014) [34]	11	2-Years: 67%	21 months (median)	Late G3 pneumonitis: 3% 1 pt: G5 aorto-esophageal fistula

Abbreviations: fx = fractions; NA = Not Available.

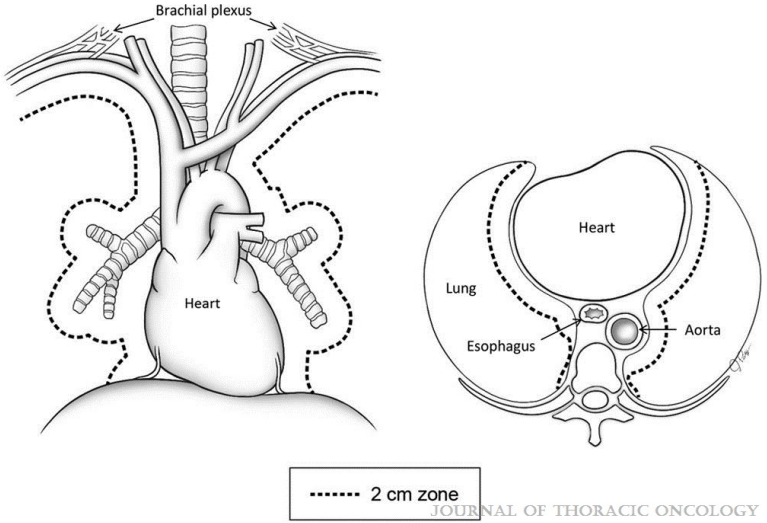
* In this study, authors report a description of the outcomes of the patients. Since salvage SBRT, 3 patients are alive and without evidence of disease, with follow-up of 11.7, 13.0, and 43.5 months. A fourth patient had no evidence of disease and died of medical comorbidities 13.0 months after salvage SBRT. Two patients developed distant disease despite local control at 5.1 and 15.6 months.

De Bari B, Cancer Trt Rev 2015

Learning aims

- Implementing SABR for peripheral lung tumors
- Conduct post-SABR follow-up (toxicity, relapses, 2nd tumors)
- Approach to complex SABR cases (central, tumors >5 cm)
- Areas of ongoing clinical research

Defining central lung tumors: IASLC



A tumor within 2 cm in all directions of any mediastinal critical structure, including bronchial tree, esophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve, and recurrent laryngeal nerve.

Chang JY, JTO 2015

Use of SABR for central tumors

- Dahele M, Acta Oncol 2015
  23 of 30 European centers treat centrally located tumors (defined as within 2cm of central mediastinal structures)

- ESTRO ACROP guidelines, Guckenberger, Radioth Oncol 2017
  SBRT of centrally located tumors practiced routinely by most faculty (agreement 87.5%)

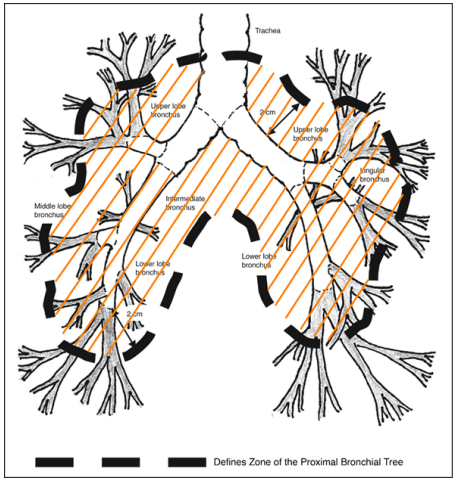
- ASTRO guidelines. Videtic GM PRO 2017

Statement KQ 2B: SBRT directed at central lung tumors should be delivered in 4 or 5 fractions. Adherence to volumetric and maximum dose constraints may optimize the safety profile of this treatment. For central tumors for which SBRT is deemed too high risk, hypofractionated radiation therapy utilizing 6 to 15 fractions can be considered.

Recommendation strength: Conditional
Quality of evidence: Moderate
Consensus: 94%

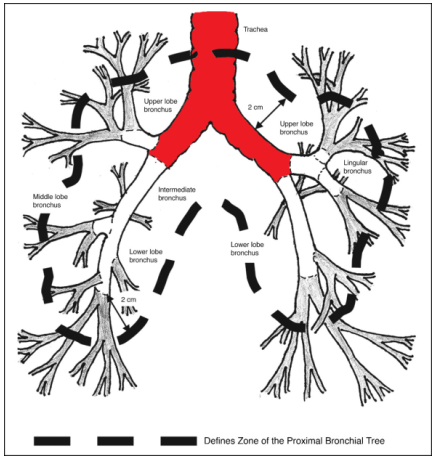
Moderately central vs ‘ultracentral’ tumors

Moderately central tumors



Use of SABR is feasible ASTRO guidelines [Videtic GMM, Prac Rad Onc 2017]

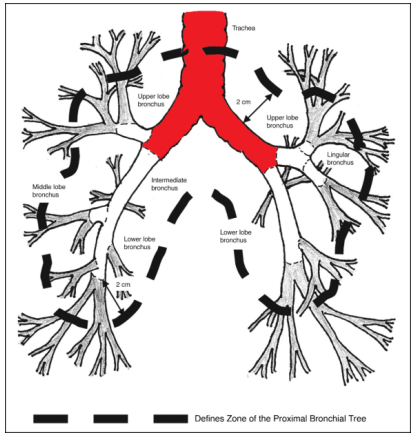
Ultracentral tumors



Higher toxicity with high-dose radiation [MSKCC, Tekatli H, JTO 2016; HILUS-Lindberg K, WCLC 2016]

‘Ultracentral’ tumors: definitions

Ultracentral tumors



GTV directly **abutting** the central airway [Chaudhuri AA, Lung Cancer 2015]

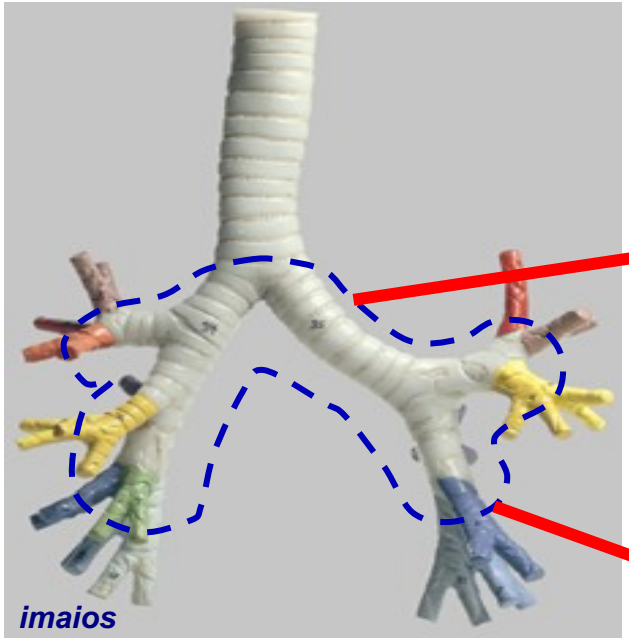
GTV **close to or abutting** the proximal bronchial tree [Haseltine JM, PRO 2016]

When PTV **overlaps** the trachea or main bronchi [Tekatli H, JTO 2016]

Moderately central vs ‘ultracentral’ tumors

Nordic - HILUS study
8 x 7 Gy prescribed to 65-70% isodose line

A: close to a main bronchus
B: close to a lobar bronchus



Group A (n=42)
CTV-bronchus : 1 mm (0-13)
Size : 25mm (9-50)

Group B (n=31)
CTV-bronchus : 1 mm (0-10)
Size : 20 mm (10-48)

Lindberg K, WCLC 2016

Moderately central vs ‘ultracentral’ tumors

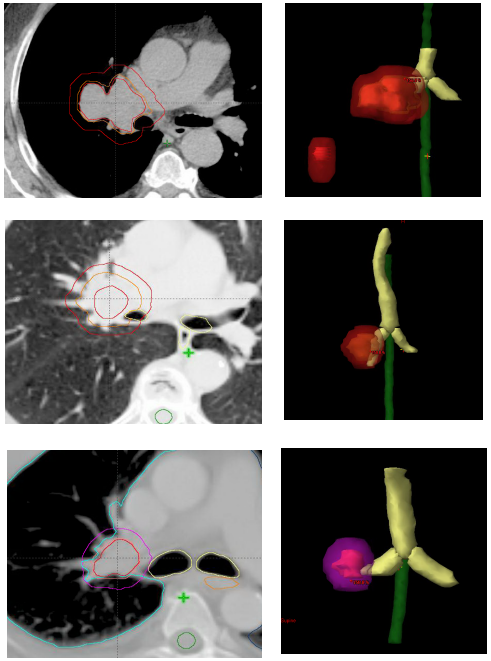
Nordic - HILUS study
8 x 7 Gy prescribed to 65-70% isodose line

A: close to a main bronchus
B: close to a lobar bronchus

74 patients (42 in arm A, 31 in arm B)

21 patients (28%) experienced grade 3-5 side effects (*atrioventricular block, bleeding, dyspnea, empyema, fatigue, fever, fistula, lung infection, pain, pneumonitis, pneumothorax and ventricular arrhythmia*)

7 patients experienced G5 toxicity (6 in group A)
6 patients experienced G5 hemoptysis
G4-5 side effects occurred more frequently in group A than in group B (19% vs 3%)



Lindberg K, WCLC 2016

Ultra-central tumors: non-SABR

ORIGINAL ARTICLE

Outcomes of Hypofractionated High-Dose Radiotherapy in Poor-Risk Patients with "Ultracentral" Non–Small Cell Lung Cancer

12 fractions of 5Gy (BED_{10} = 90Gy, heterogeneous dose distribution)

All patients were unfit for surgery / conventional chemo-radiotherapy

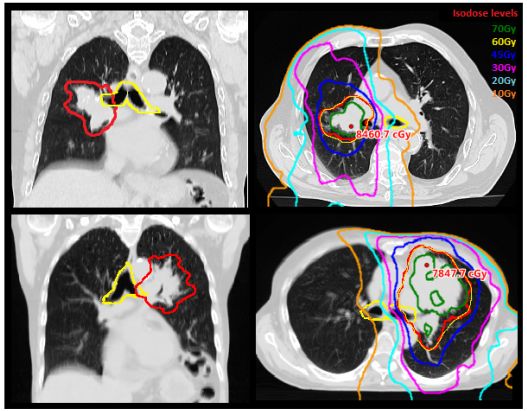
Tekatli, H, JTO 2016

‘Ultracentral’ tumors: non-SABR results

47 consecutive cases of NSCLC (2010-2015)

Median age: 77.5 yrs; WHO PS ≥2 in 49%

Median OS 15.9 months, 3-year survival 20.1%
No isolated local recurrences

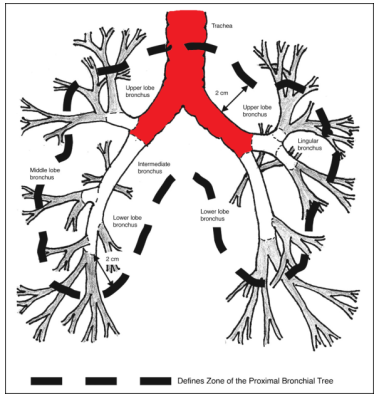


21% **“*possible*” (n=2)** or **“*likely*” (n=8)** treatment-related deaths. Fatal pulmonary hemorrhage in 15%

Tekatli, H, JTO 2016

Moderately central vs ‘ultracentral’ tumors

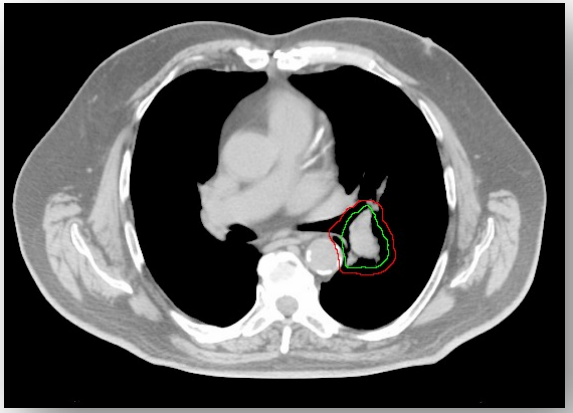
Ultracentral tumors

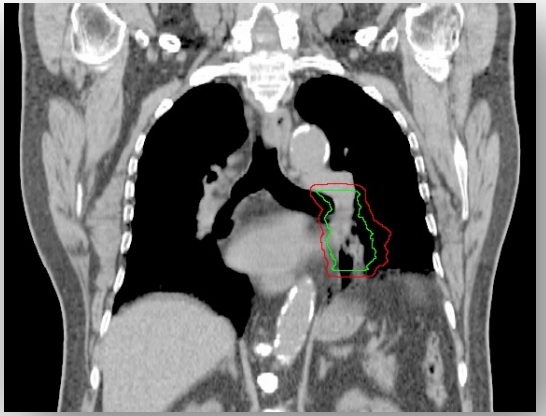


Do we need to standardize the definition of ultracentral tumors,

Or should identification of more reliable dose constraints for central airways be a priority?

Bronchial toxicity

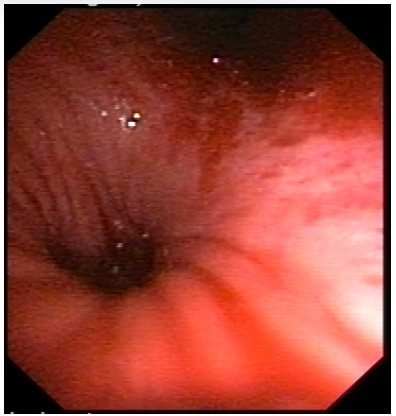




78 year-old - extensive cardiovascular morbidity
Pathology: squamous carcinoma, T2aN0M0

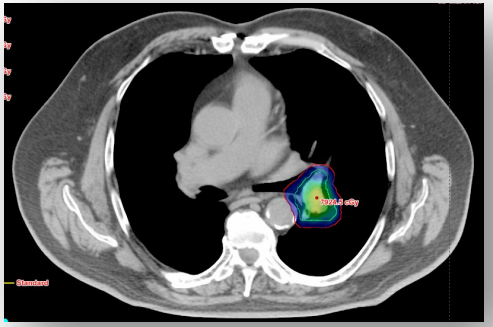
Tumor board: unfit to undergo pneumonectomy

SABR in 8 fractions

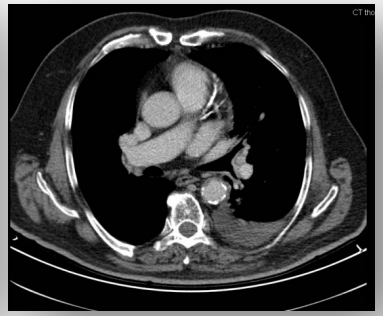


Senthi S, J Thorac Oncol 2013

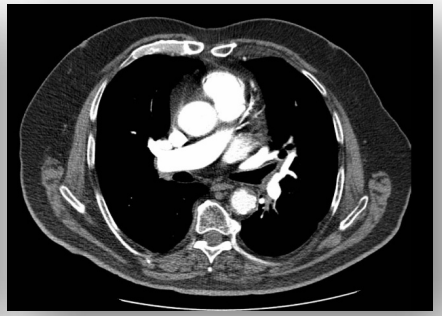
Bronchial toxicity



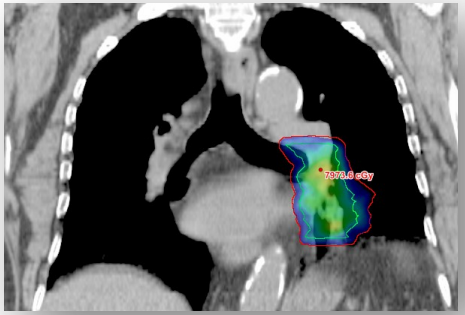
2009: SABR 60Gy (8 frac)



3 months



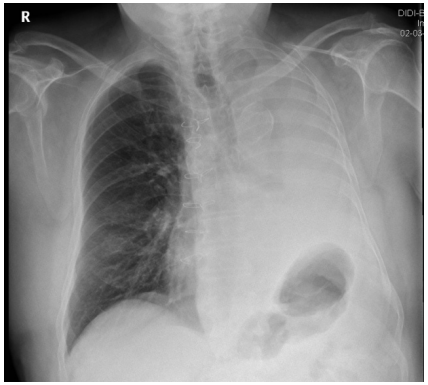
6 months



Senthi S, J Thorac Oncol 2013

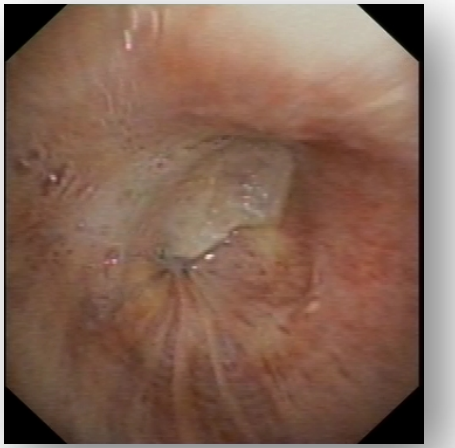
Bronchial toxicity

12 months: shortness of breath



Bronchoscopy with 8 biopsies & pleural cytology: No malignancy

FDG-PET: No recurrence



Senthi S, J Thorac Oncol 2013

Post-SABR bronchial assesment

- Necrotic tissue in central airways should only be biopsied with caution as it may cause injury to exposed blood vessels or worsen the necrosis. Avoid also a bronchial brushing procedure in the first instance.

- Review contrast-enhanced diagnostic CT scan for information on the area behind the necrosis (bulky tumor, no big vessels in proximity).

- Commence with saline lavage and suctioning. If this results in removal of mucus or necrosis and if exophytic tumor is visualized, a biopsy could be considered in cases where the diagnostic CT suggests that it could be safe.

- If endobronchial appearance remains unchanged after saline lavage and suctioning (*appearance of necrosis, unidentified tissue*), the bronchoscopy procedure should stop, and clinical or PET-CT follow-up performed as appropriate.

Personal communication, Dr. J.M.A. Daniels, interventional pulmonologist, VU University Medical Center Amsterdam

SABR outcomes in tumors measuring >5 cm

Author, year	Patient selection	Fractionation (fx) schemes	Number of patients	Median FU	G3 or higher toxicity	Survival	Disease control
Woody, 2015 IJROBP	NSCLC ≥5 cm 2003-2014 (single institution)	5x10Gy, 8x7.5Gy, 10x5Gy, or other	N = 40	10.8 mo	N = 3 (7.5%) → lobar collapse, pleural effusion, pneumonitis. – G5 tox: 3%	Median OS: 19.9 mo 18 mo survival 60%	Local failure: 7.5% Locoreg control @18 mo: 64.4% Distant failure: 32.5% Median DFS: 14.4 mo
Verma, 2016 Cancer	NSCLC ≥5 cm 2004-2016 (multi-institutional)	3x18Gy, 4x12Gy, 5x10Gy, or other ≤5 fx schemes	N = 92	12.0 mo	N = 6 (6.5%) G3: n= 5 G4: n = 0 G5: n = 1	Median OS: 21.4 mo 2 yr survival: 46%	Local failure: n = 15% Local control 1 yr: 95.7% Distant failure: 21% Median DFS: 32.4 mo
Verma, 2016 IJROBP	NSCLC ≥5 cm 2004-2012 (NCDB)	48, 50, 54, or 60 Gy in ≤10 fx	SABR: 171 SABR-chemo: 30	41.1 mo	Not reported	Median OS: 25.1 mo 3 yr survival: 33%	Not reported
Peterson, 2016 Clinical Lung Cancer	Node-negative NSCLC > 5cm (single institution)	Median radiation dose/fraction: 50Gy in 5 fractions	N = 41	15.2 mo	G3: n = 2 (4.8%) Shortness of breath Pneumonitis G4/G5: n =0	Median OS: 17.5 mo 2 yr survival: 34%	Local failure: 4.8% Distant failure: 31%
Tekatli, JTO 2017	NSCLC ≥5 cm 2003-2014 (single institution)	5x11Gy, 5x12Gy, or 8x7.5Gy	N = 63	54.7 mo	N= 19 (30%) – Pneumonitis most common – G5 tox: 19%	Median OS: 28.3 mo 3 yr survival: 42%	Local failure: 6% Regional failure: 6% Distant failure: 19% DFS at 2 years: 82.1%

Tekatli H, JTO 2017

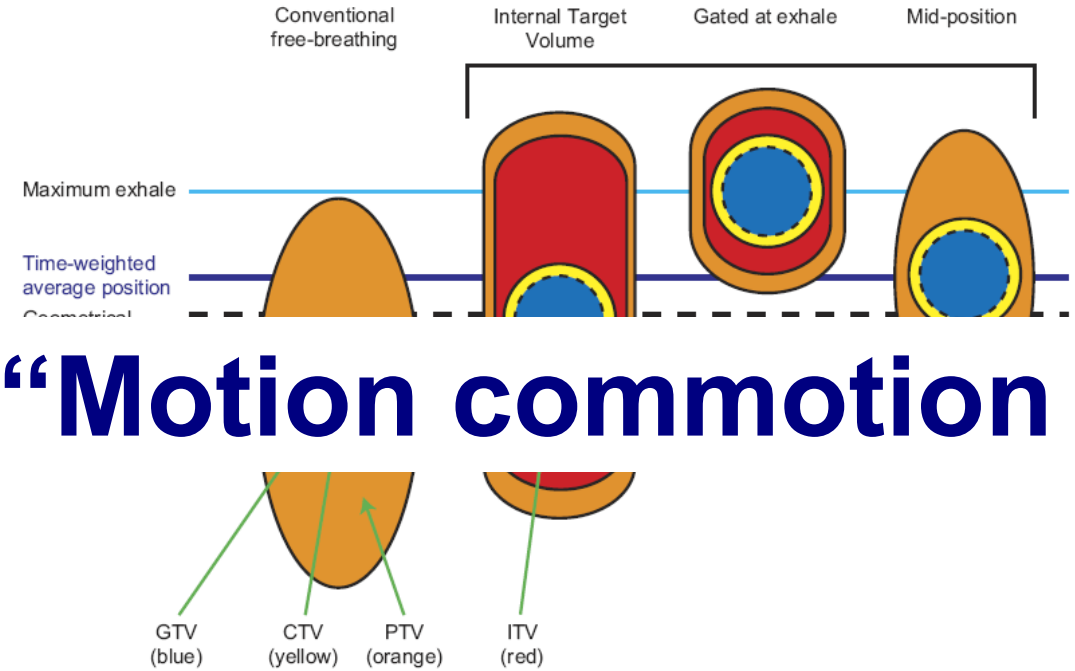
Learning aims

- Implementing SABR for peripheral lung tumors
- Conduct post-SABR follow-up (toxicity, relapses, 2nd tumors)
- Approach to complex SABR cases (central, tumors >5 cm)
- Areas of ongoing clinical research

Areas of ongoing clinical research

- Gating and tracking
- Adaptive radiotherapy
- Operable patients
- Unrecognized toxicity
- Immune effects of therapy

Defining target volumes



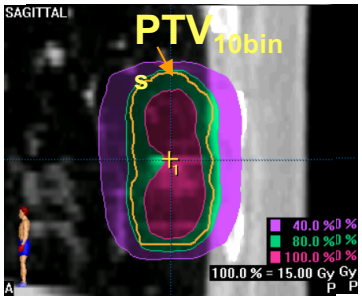
“Motion commotion !!”

Fig. 1. Schematic overview of different treatment-planning concepts: conventional free-breathing, internal target volume (ITV), gating (at exhale), and mid-position. GTV = gross tumor volume; CTV = clinical target volume; PTV = planning target volume.

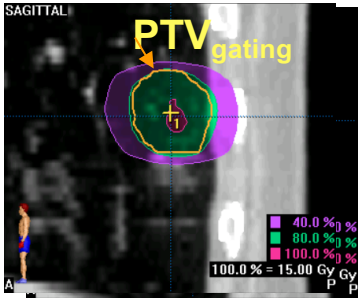
Wolthaus J, IJROBP 2008

Gated SABR: 4DCT planning study

Non-gated PTV



Gated PTV



Lack of positional verification during delivery

Underberg R, 2005

Electromagnetic-guided MLC tracking

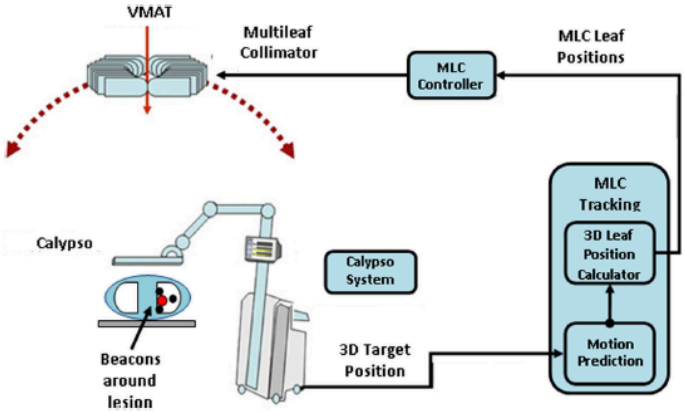


Fig. 1. Schematic of the MLC tracking control system used for the clinical trial. Electromagnetic transponders send real-time localisation to the MLC tracking system which updates the MLC pattern and sends these new leaf positions to the MLC controller for treatment at the linac.

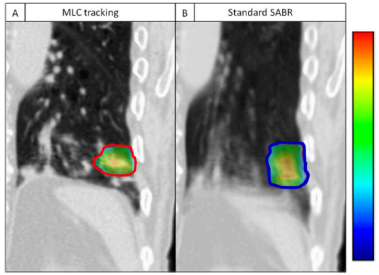


Fig. 2. Comparison of Planning Target Volumes shows a significant reduction (41%) in the volume with MLC tracking delivery (A) compared to standard ITV-based planning (B). The red contour indicates the PTV on end exhale phase of 4DCT used for MLC tracking and the blue contour indicates the PTV on mean of 4DCT used for the ITV-based plan. Coronal view.

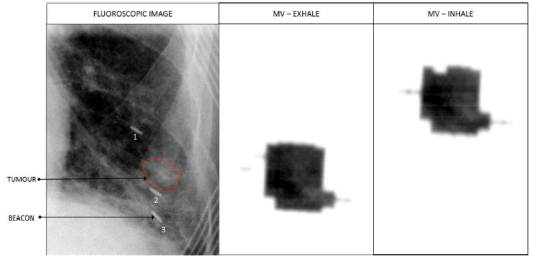


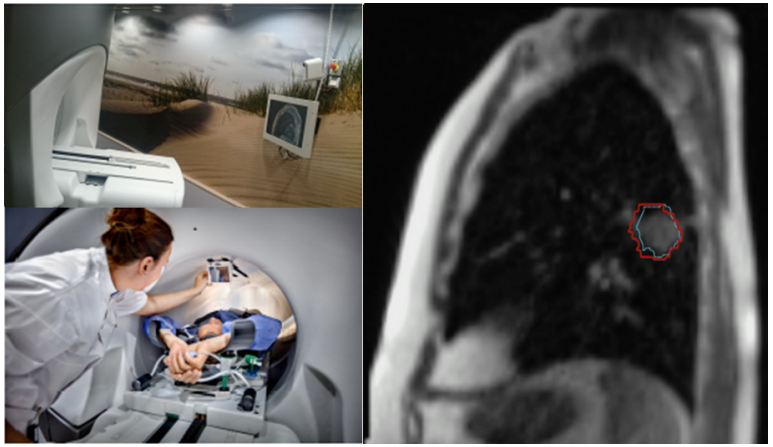
Fig. 4. Fluoroscopic image (left) showing three electromagnetic transponders and the tumour contour, and corresponding MV treatment images at inhale and exhale (right). A movie of the kV and MV images acquired during the treatment delivery is attached as supplementary material.

Booth JT, Radioth Oncol 2017

MRI-guided adaptive SABR

VUmc

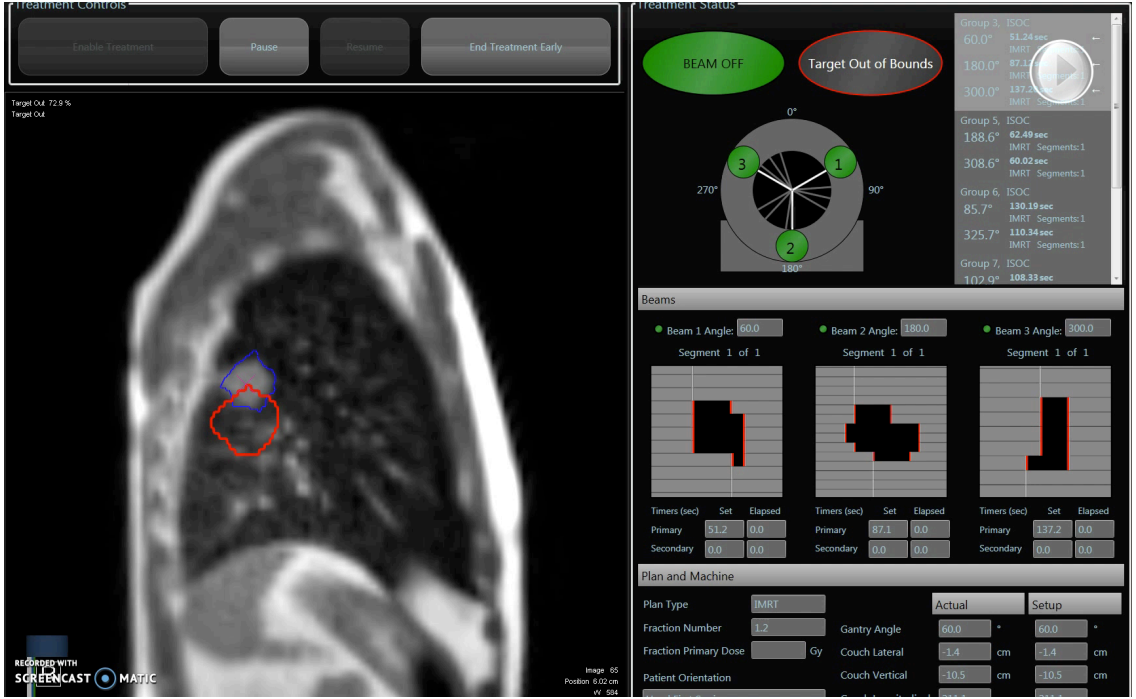
MR-guided tumor setup	Adaptive planning	Online guidance	Gated delivery (markerless)



- High-risk cases: central, re-irradiation, IPF, mobile tumors [Senan S, Proc ASTRO 2017]
- On-table adaptive planning procedure [Bohoudi O, Radioth Oncol 2017]

MRI-guided Adaptive SABR

MR-guided tumor setup	Adaptive planning	Online guidance	Gated delivery (markerless)



Senan S, Proc ASTRO 2017

SABR for operable patients

ASTRO guidelines PRO 2017

For patients with “standard operative risk” (i.e. **with anticipated operative mortality of <1.5%**) and stage I NSCLC, SABR is not recommended as an alternative to surgery outside of a clinical trial.

*American Society for Radiation Oncology (**ASTRO**) Guidelines 2017*

Endorsed by the European Society for Radiotherapy & Oncology, the Royal Australian and New Zealand College of Radiologists, and the International Association for the Study of Lung Cancer

30- and 90-day mortality after surgery

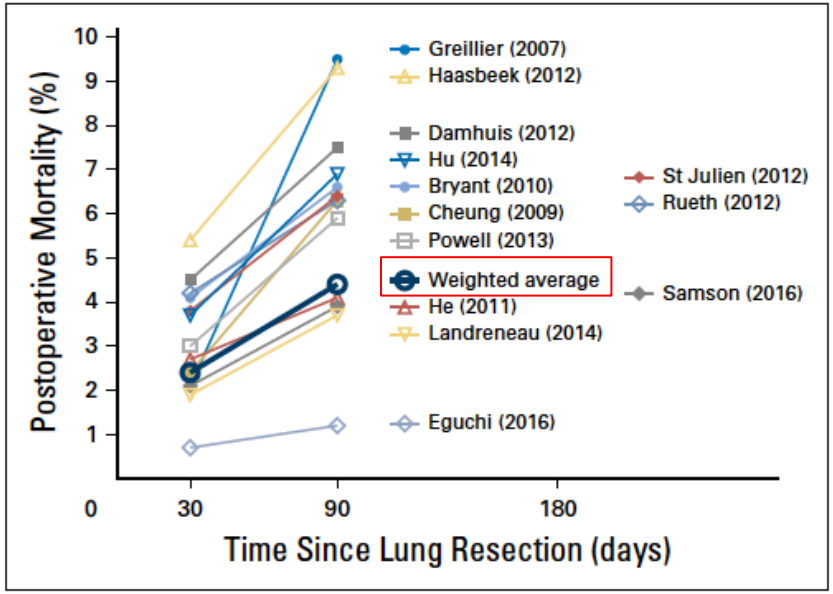


Fig 1. Thirty-day and 90-day postoperative mortality for lung cancer resection in contemporary series. Weighted average calculated from the sum of individual mortality events in all studies/total patient numbers in all studies. Only series from unique data sets are included, with the exception of Rueth et al[2] and Hu et al,[3] which report SEER-Medicare data from nonoverlapping years. Data sets for other series displayed include Bryant et al (University of Alabama at Birmingham),[4] Greillier et al[5] (Hopitaux de Marseille), Cheung et al[6] (Florida State Registries), He et al[7] (Guangzhou), Haasbeek et al[8] (Netherlands Registry), St Julien et al[9] (Veterans Affairs), Damhuis et al[10] (Rotterdam Registry), Powell et al[11] (English Registry), Landreneau et al[12] (University of Pittsburgh), and Samson et al[13] (National Cancer Database).

Rusthoven CG, JCO 2017

Surgery versus SABR in operable patients

4 unsuccessful attempts at performing prospective randomized trials

ROSEL	**NCT00687986**
STARS	**NCT00840749**
ACOSOG-4099/RTOG1021	**NCT01336894**
Mayo Clinic	**NCT01622621**

Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials Lancet Oncol 2015

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

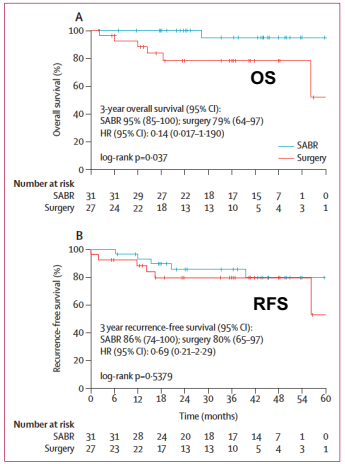


Figure 2: **Overall survival (A) and recurrence-free survival (B)**
One patient died and five had recurrence in the SABR group compared with six and six patients, respectively, in the surgery group. SABR=stereotactic ablative radiotherapy. HR=hazard ratio.

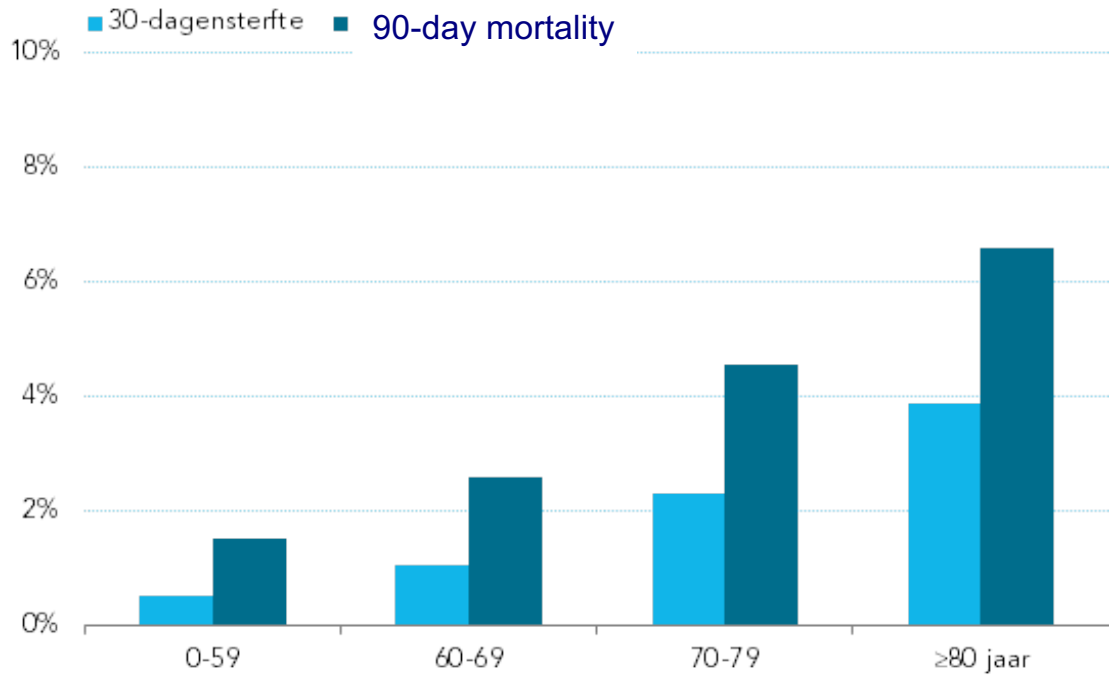
SABR vs surgery: New randomised trials

	VALOR (USA)	POSTILV (China)	SABRTooth (UK)	STABLE-MATES (USA)
Eligibility criteria	Tumor ≤5cm (peripheral and central)	Tumor ≤3 cm, fit for lobectomy or pneumonectomy	**High-risk** operable, peripheral tumors ≤5cm,	**High-risk** operable, patients pre-randomized
Primary End-point	5-year overall survival	2-year local-regional control	Average recruitment rate of 3 pts/month for a 15 month period	3-year overall survival
Secondary end-points	QoL, patterns of failure, cause of death	OS, DFS, site-specific failure, Time to LR failure and DM		PFS, failure patterns, toxicity, and 5-year overall survival
Planned accrual	670	76	54 (feasibilty phase)	258

Late toxicity, 2nd tumors, overall survival

Data on early deaths, toxicity, QoL

Surgical mortality after lobectomy
Netherlands Cancer Registry



https://shop.iknl.nl/shop/kankerzorg-in-beeld-de-oudere-patiënt-(2016)/123187

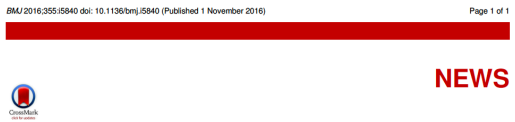
Population trends in early-stage NSCLC

Netherlands Cancer Registry: Treatment utilization by diagnosis year
(n = 21,032 patients)

	Diagnosis year 1997-1999	Diagnosis year 2009-2011
Surgery	62%	60%
Radiation	19%	28%
Palliative therapy	19%	13%

Louie AV, Lung Cancer 2016

UK Supreme court ruling: Montgomery versus Lanarkshire Health Board



BMJ 2016;355:i5840 doi: 10.1136/bmj.i5840 (Published 1 November 2016) Page 1 of 1

NEWS

Trusts risk litigation payouts by not adopting full consent process, warns college

The Cambridge Law Journal

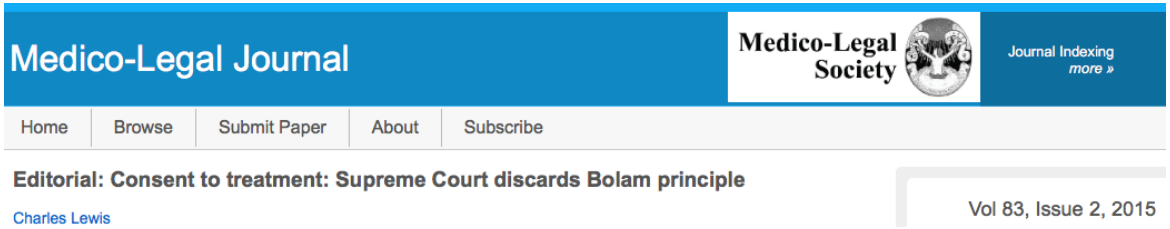
Article Metrics

Volume 74, Issue 2 July 2015 , pp. 211-214

"TRUST ME, I'M A PATIENT …": DISCLOSURE STANDARDS AND THE PATIENT'S RIGHT TO DECIDE

C.P. McGrath

DOI: https://doi.org/10.1017/S0008197315000537 Published online: 03 July 2015



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Editorial: Consent to treatment: Supreme Court discards Bolam principle

Charles Lewis

Vol 83, Issue 2, 2015

Doctors must now ask themselves three questions:

- Does the patient know about the material risks of the treatment I am proposing?
- Does the patient know about reasonable alternatives to this treatment?
- Have I taken reasonable care to ensure that the patient actually knows this?

Cardiac mortality in lung cancer

COPD is present in 40–70% of patients with lung cancer[1]

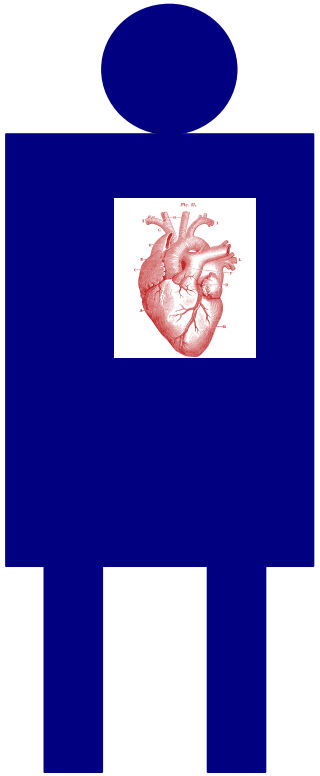
COPD patients have 2-5 fold higher risk of ischaemic heart disease, cardiac dysrhythmia, heart failure [2]

Sub-groups of COPD have 5-8 fold higher risks of cardiovascular mortality [3]

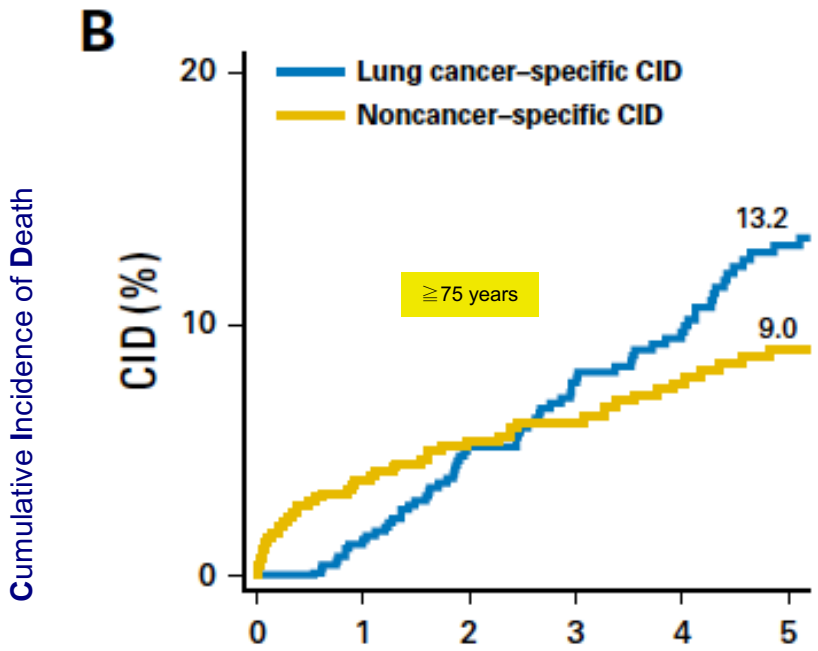
COPD patients have a 34% higher risk for sudden cardiac death [4]

[1]Congleton J, Resp Med 2005; [2] Chen W, Lancet Resp Med 2015; [3] Lange P, AJRCCM 2012; [4] Lahousse L, Eur H J 2015

Radiation doses to upper heart regions significantly associated with non-cancer deaths [Stam B, Radioth Oncol 2017]

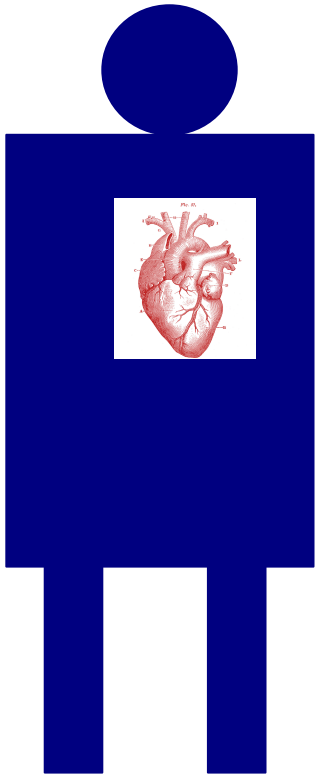


Non-cancer deaths in survivors of early NSCLC

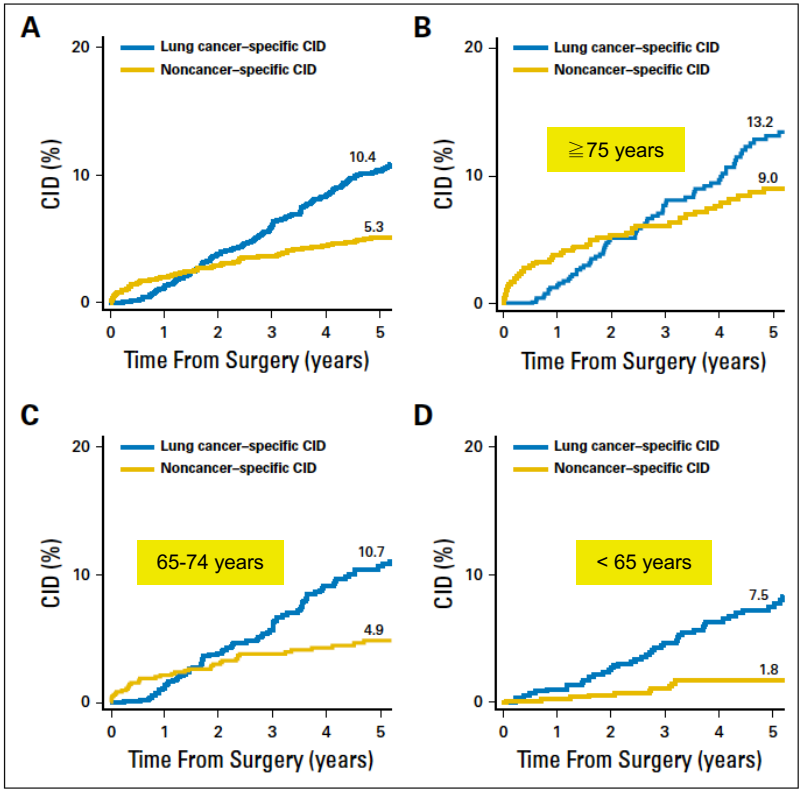


Deaths after local treatment for early-stage NSCLC

Resected stage I NSCLC at MSKCC [Eguchi T, JCO 2017]



Lung cancer–specific and noncancer-specific 5-year cumulative incidence of death (CID) by age-group



5,371 consecutive patients (2000-2011)

Fig 2. Lung cancer–specific and noncancer-specific 5-year cumulative incidence of death (CID) by age-group. (A) Up to approximately 1.5 years after surgery, noncancer-specific CID was higher than lung cancer–specific CID. After 1.5 years, lung cancer–specific CID surpassed noncancer-specific CID (N = 2,186). (B) The higher noncancer-specific CID observed in the early postoperative phase increased in patients ≥ 75 years of age, in whom noncancer-specific mortality was higher than lung cancer–specific mortality until approximately 2.5 years postsurgery (n = 638). (C) In patients 65 to 74 years of age, the difference between curves was similar to that for the total cohort (n = 894). (D) In patients < 65 years of age, lung cancer–specific mortality was higher than noncancer-specific mortality during most of the postoperative period (n = 654).

Eguchi T, JCO 2017

SABR and the immune system

REVIEWS

NATURE REVIEWS | CLINICAL ONCOLOGY

Radiotherapy and immunotherapy: a beneficial liaison?

Ralph R. Weichselbaum[1], Hua Liang[1], Liufu Deng[1] and Yang-Xin Fu[2]

SCIENTIFIC REPORTS

OPEN

Hypofractionated stereotactic radiation therapy activates the peripheral immune response in operable stage I non-small-cell lung cancer

Received: 17 November 2016
Accepted: 23 May 2017
Published online: 07 July 2017

Ting Zhang[1,4], Haifeng Yu[2], Chao Ni[3], Tao Zhang[4], Luying Liu[4], Qinghua Lv[4], Zhigang Zhang[4], Zhen Wang[4], Dang Wu[1,4], Pin Wu[4], Guodi Chen[2], Liancong Wang[1], Qichun Wei[2], Jian Huang[4] & Xiaojian Wang[5]

American Journal of Respiratory and Critical Care Medicine/AJRCCM

ATS

STEREOTACTIC ABLATIVE RADIOTHERAPY INDUCES PERIPHERAL T-CELL ACTIVATION IN EARLY STAGE LUNG CANCER PATIENTS

Authors:
Pauline L. de Goeje[1], Egbert F. Smit[2], Cynthia Waasdorp[1*], Merel T.B. Schram[1,3], Margaretha E.H. Kaijen-Lambers[1], Koen Bezemer[1], Mark de Mol[1,3], Koen J. Hartemink[4], Joost J.M.E. Nuyttens[5], Alexander P.W.M. Maat[6], Joost P.J.J. Hegmans[1], Rudi W. Hendriks[1], Suresh Senan[7], Joachim G.J.V. Aerts[1,3]

SBRT for primary liver cancer

Morten Høyer
Danish Center for Particle Therapy
Aarhus University Hospital, Denmark

CIRRO AARHUS UNIVERSITET

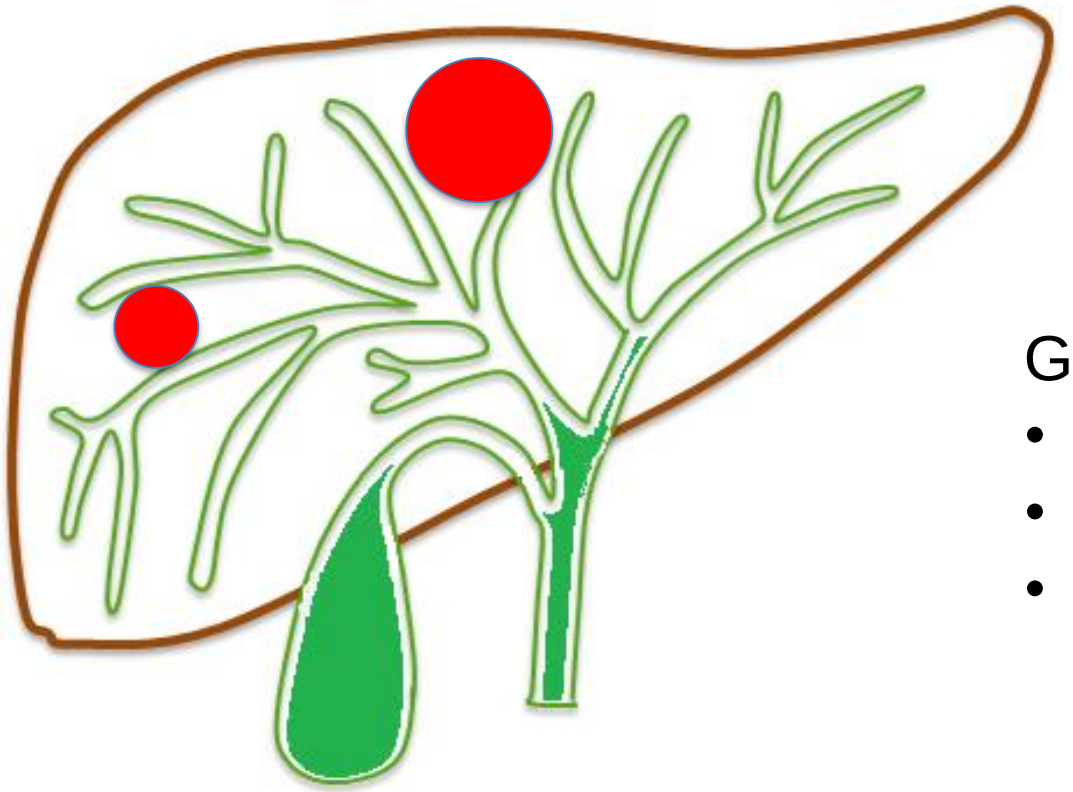
Questions from the participants

- In Europe, HCC radiotherapy is seemed to be overwhelmed by others (such as internal radiotherapy).
- How is the trend of HCC radiotherapy in Europe? For example, what do you prefer as primary local treatment for HCC PVT? (SIRT, EBRT, TACE?)

Primary liver cancer

Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma



Growth pattern

- Focal (massive)
- Multifocal (nodular)
- Diffuse

Aetiology of hepatocellular carcinoma

- Risk factors
  - Alcoholic cirrhosis in the western world
  - Hepatitis B (HBV) and C (HCV) in Asia and Africa
  - Haemochromatosis, Wilson's disease and other congenital diseases
  - Aflatoxin (*Aspergillus*)
  - Obesity; non-alcoholic steatohepatitis (NASH) – in the western world

    70-90% of all HCC cases are based on chronic liver disease or cirrhosis
- Protective factors
  - Reduce/eliminate alcohol consumption
  - Antiviral therapy
  - Healthy lifestyle

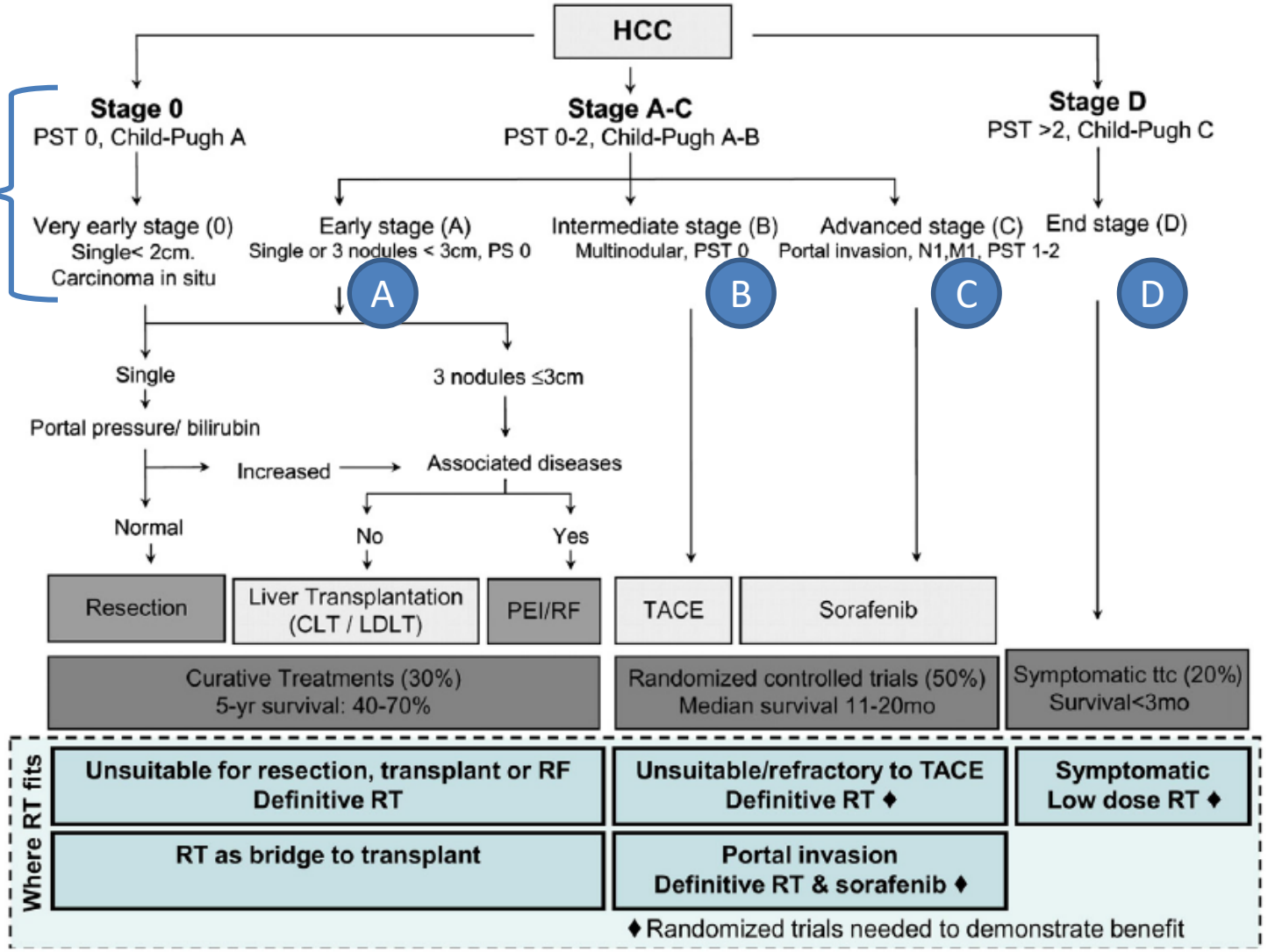
Child-Pugh Classification

Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3

Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)
Class A = 5 to 6 points (least severe liver disease)
Class B = 7 to 9 points (moderately severe liver disease)
Class C = 10 to 15 points (most severe liver disease)

The Barcelona Clinic Liver Cancer Group (BCLCG) staging system

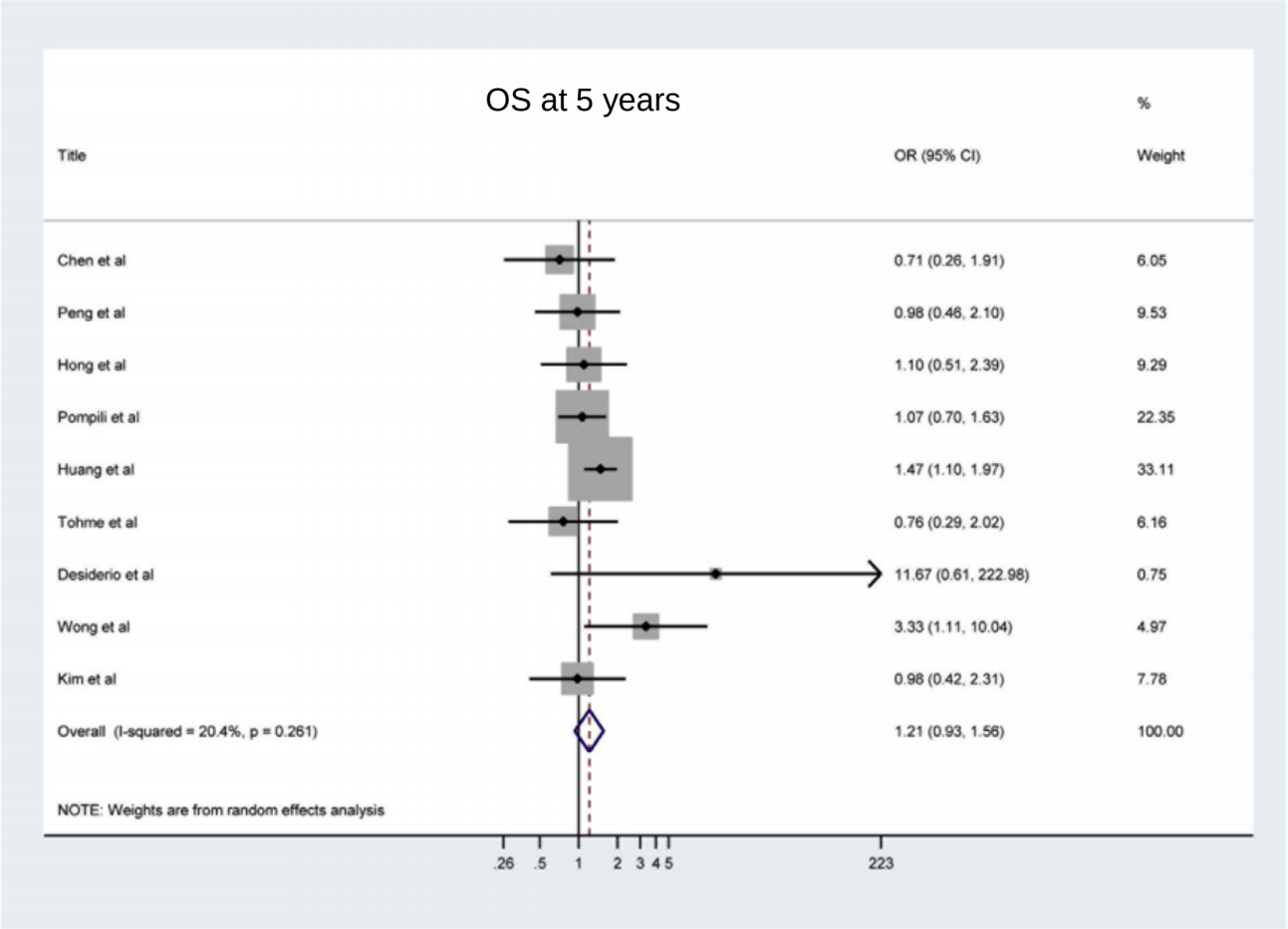
PS
C-P
Number
Size



Modified Klein & Lawson IJROBP 2013; 87(1): e22

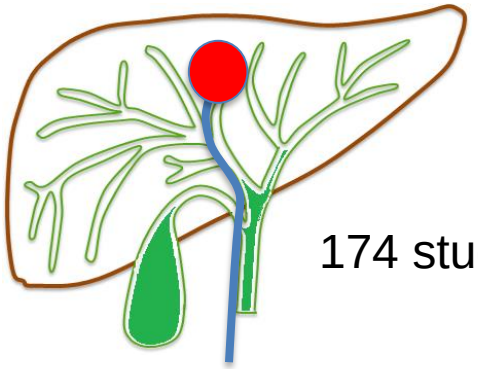
RFA versus surgical resection for HCC (<3 cm)

15 studies 3627 patients



Jia et al Clinical Radiol in press 2017

SIRT (TARE) versus TACE for HCC



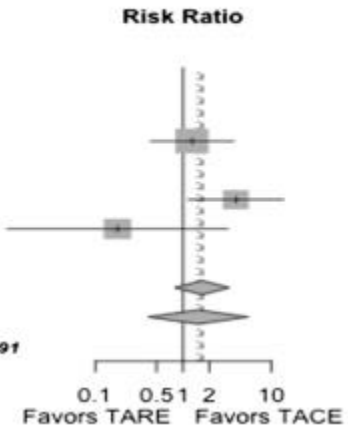
Selective internal radiation therapy (Yttrium-90)

174 studies; 284 underwent TACE and 269 TARE

Survival at 4 year (RR= 1.64, 95% CI 0.80-3.34, p=0.17)

Study	TARE Events	TARE Total	TACE Events	TACE Total	RR	95%-CI	W(fixed)	W(random)
Akinwande 2015	0	20	0	28			0.0%	0.0%
Morano _Luna 2013	7	61	5	55	1.26	[0.43; 3.75]	44.9%	44.1%
Lance 2011	0	38	0	35			0.0%	0.0%
Salem 2011	12	123	3	122	3.97	[1.15; 13.71]	25.7%	40.4%
Kooby 2010	0	27	4	44	0.18	[0.01; 3.21]	29.4%	15.5%
Fixed effect model		**269**		**284**	**1.64**	**[0.80; 3.34]**	**100%**	--
Random effects model					**1.48**	**[0.40; 5.47]**	--	**100%**

Heterogeneity: I-squared=54.9%, tau-squared=0.7011, p=0.1091



Lobo et al. Cardiovasc Intervent Radiol (2016) 39:1580

AIMS OF THE SARAH TRIAL

- Prospective open-label, phase 3, multi-center, investigator-based RCT
  - Locally advanced HCC and inoperable HCC who failed after 2 rounds of TACE
  - Comparison of selective internal radiation therapy (SIRT) to sorafenib

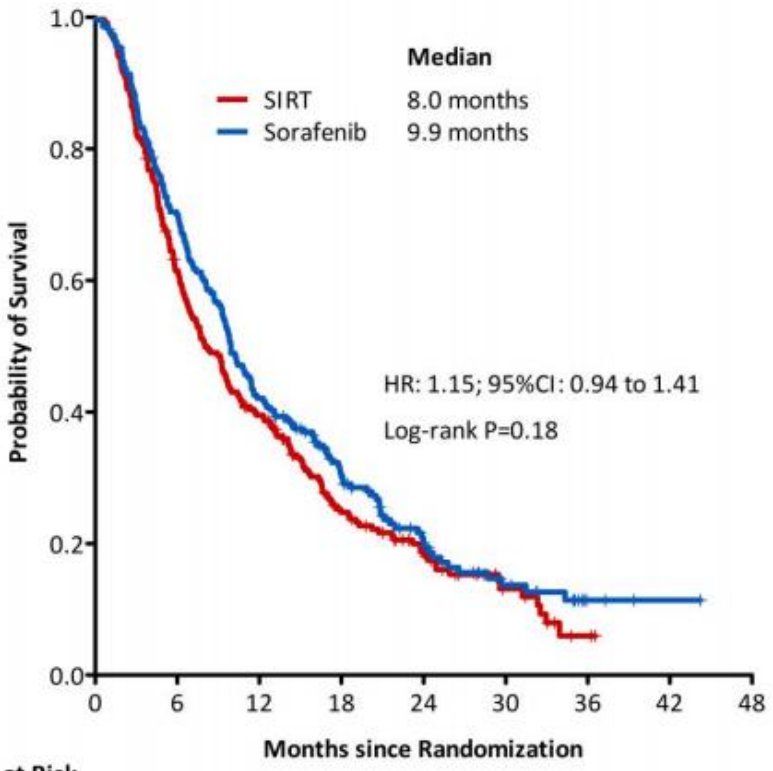
- **Primary objective**
  - Overall survival (OS)
- **Secondary objectives**
  - Progression-free survival
  - Incidence of progression in the liver / outside the liver
  - Tumor response rate
  - Tolerance, Quality of Life

TACE = transcatheter arterial chemoembolization

OVERALL SURVIVAL

HCC connect
POWERED BY COR2ED

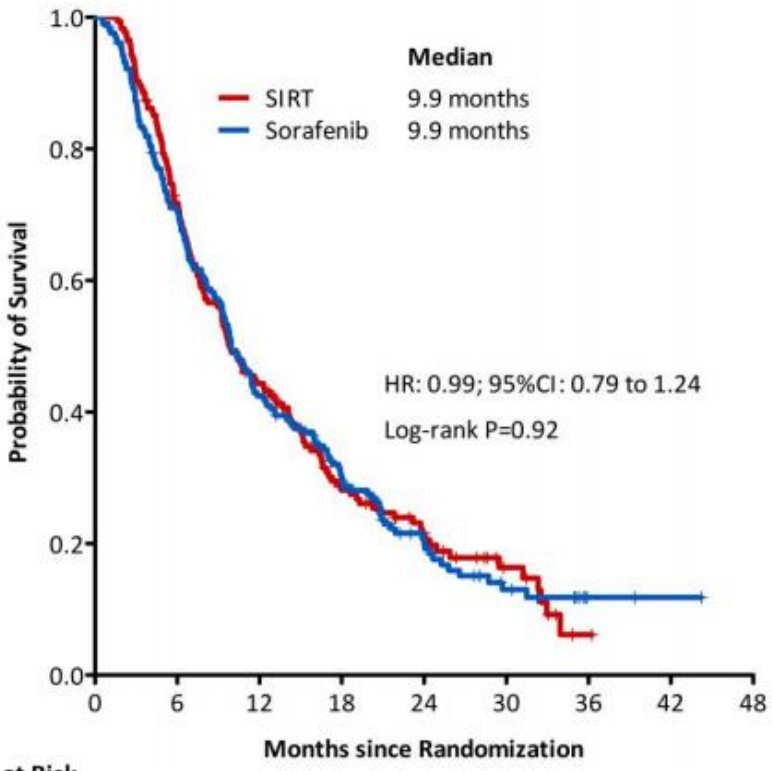
Intention to treat population
N=459



No. at Risk

SIRT	237	143	90	49	30	11	2	0	
Sorafenib	222	153	92	57	28	14	3	1	0

Per-protocol population
N=380



No. at Risk

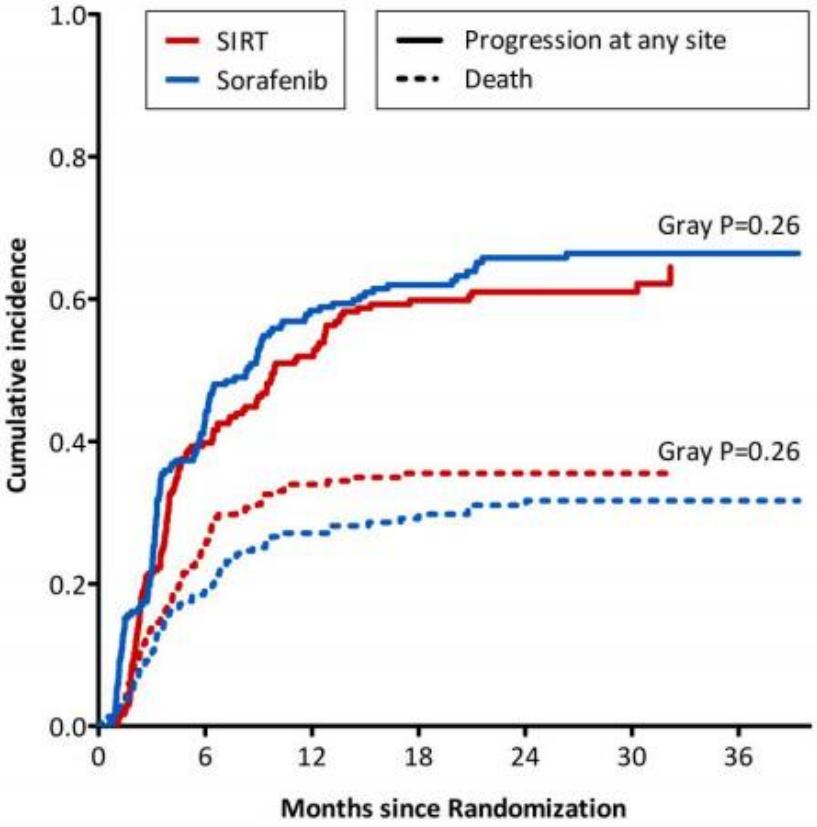
SIRT	174	123	75	41	26	10	1	0	
Sorafenib	206	143	86	54	26	12	2	1	0

No difference in overall survival between groups

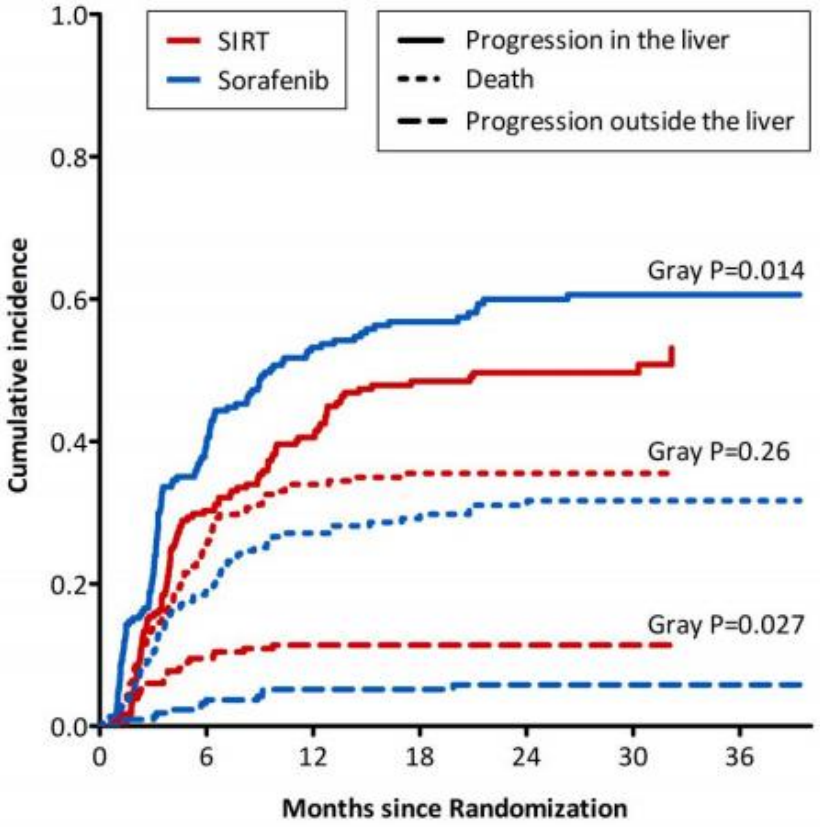
RADIOLOGIC PROGRESSION

HCC connect
POWERED BY COR2ED

ITT: Progression at any site



ITT: Progression in the liver as first site



Progression in the liver as first site was lower in the SIRT group

TOLERANCE AND SAFETY

Treatment-related AEs	SIRT	Sorafenib
All	1297	2837
⩾ Grade 3	230	411

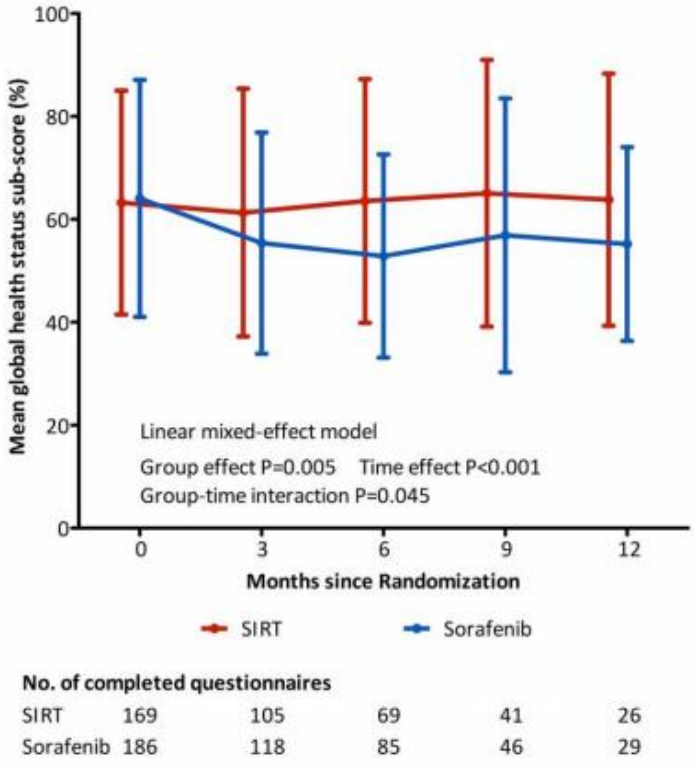
Treatment related AEs were lower in the SIRT group

Treatment-related AES	SIRT Nb of patients (⩾G 3)	Sorafenib Nb of patients (⩾G 3)
Fatigue	94 (20)	140 (41)
Weight loss	14 (0)	46 (6)
Alopecia	0 (0)	35 (0)
Hand foot skin reaction	1(1)	45 (12)
Pruritus	7 (1)	19 (1)
Diarrhea	29 (3)	146 (30)
Abdominal pain	46 (6)	63 (14)
Hypertension	6 (0)	28 (5)

QUALITY OF LIFE (QoL)

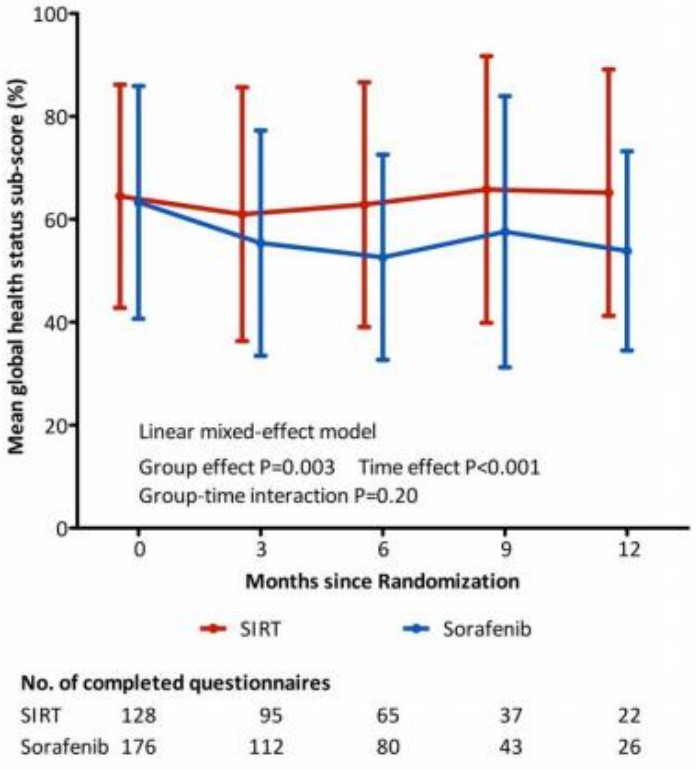
HCC connect
POWERED BY COR2ED

Intention to treat population
N=459



No. of completed questionnaires					
SIRT	169	105	69	41	26
Sorafenib	186	118	85	46	29

Per-protocol population
N=380



No. of completed questionnaires					
SIRT	128	95	65	37	22
Sorafenib	176	112	80	43	26

Global health subscore EORTC QLQ 30

QoL was better in the SIRT group than sorafenib over time

Morbidity in two prospective SBRT trials on HCC

Phase I (n=50) Cardenes et al Clin Transl Oncol 2010; 12:218
Phase II (n=52) Tse et al JCO 2008; 26: 3911

} N=102

All pts C-P 6 treated with NTCP-based dose-prescription (≤10% RILD)

- No classic RILD
- Decline in C-P class by 2 points in 29% at 3 mts and 6% at 12 mts
- Liver failure (gr 5) in 5 pts 5%
- Cholangitis (gr 5) 1 pt
- Duodenal bleed (gr 5) 1 pt

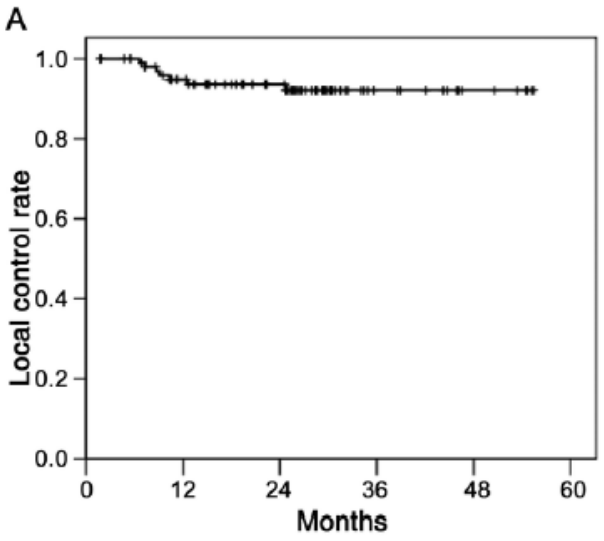
Median $D_{liver-CTV}$
- Failure 18.1 Gy
- No failure 14.4 Gy

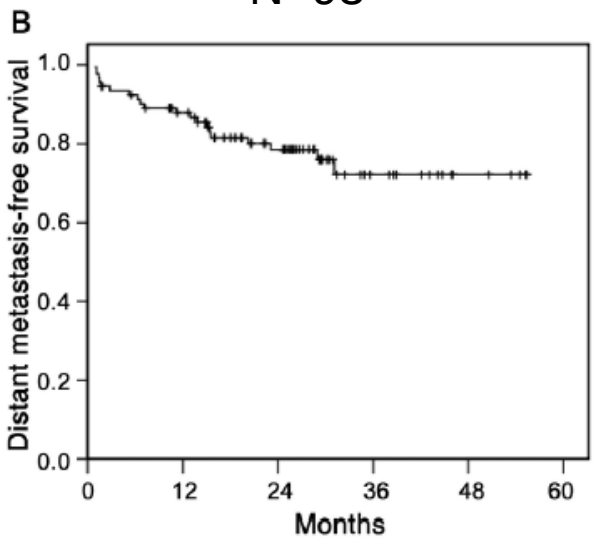
Classic RILD
(without underlying liver disease)
- Fatigue
- Abdominal pain
- Increased abdominal girth
- Hepatomegaly
- Anicteric ascites
- Isolated elevation of alkaline phosphatase

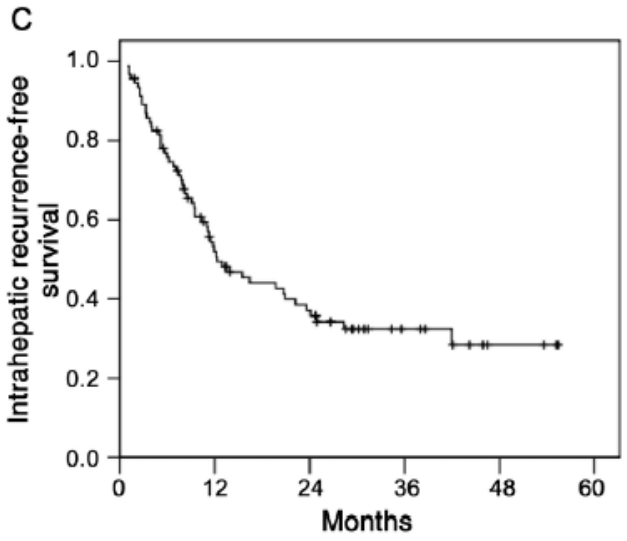
Non-classic RILD
(with underlying liver disease)
- Jaundice
- Markedly elevated serum transaminase

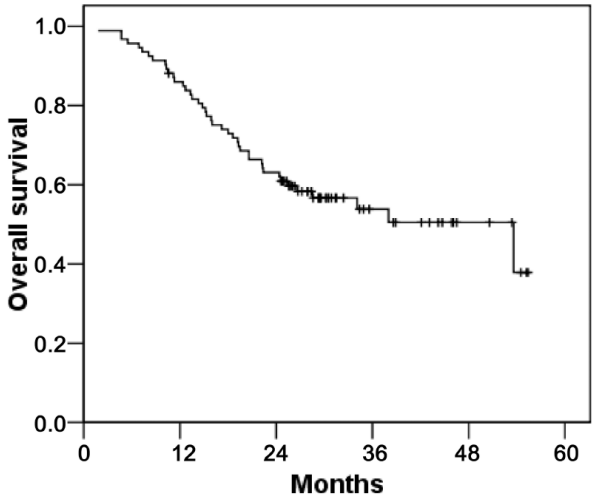
Korean registry study

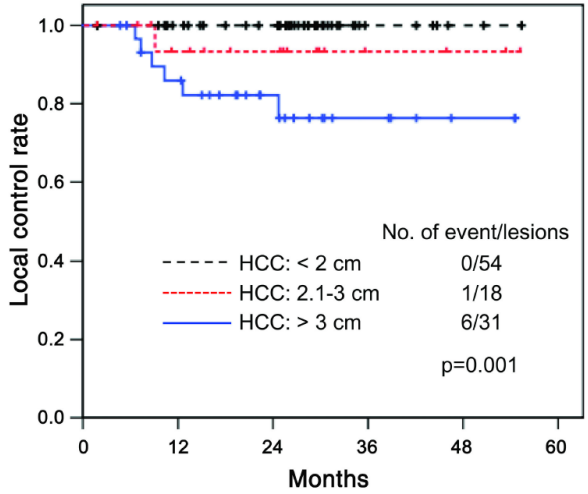
N=93







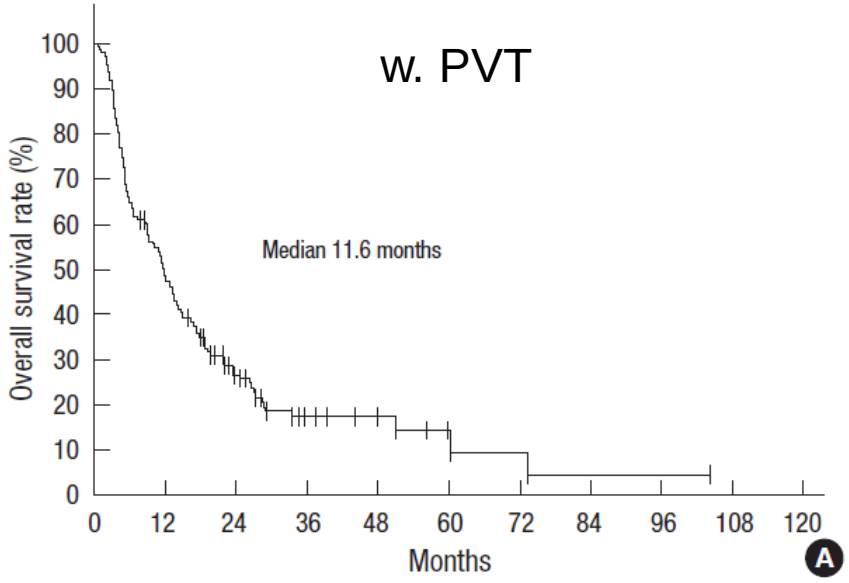


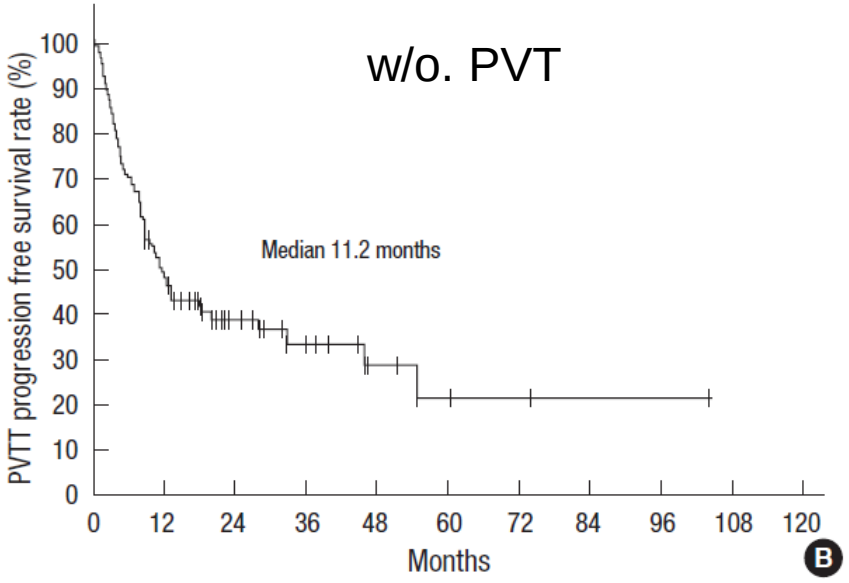


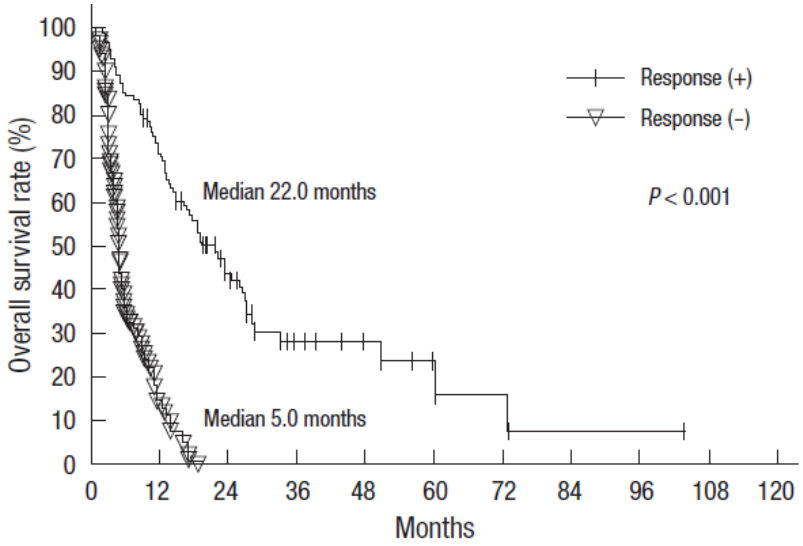
- Favorable local control
- 65% wo. extrahepatic progression
- Patients fail with a new intrahepatic lesions
- Local control dependent on lesion size

Yoon et al PLoS ONE 8(11): e79854

Portal vein (tumor-)thrombosis

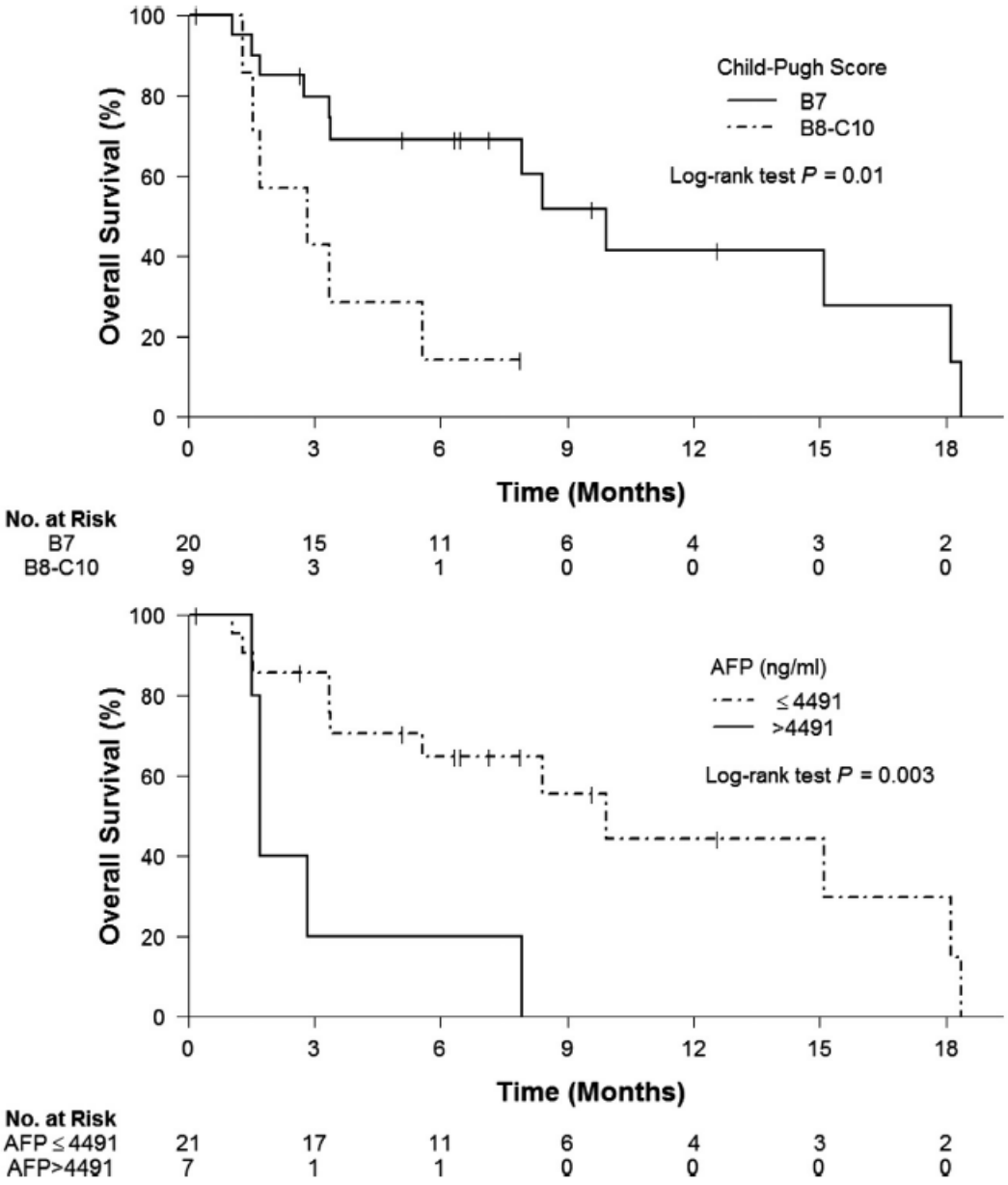






Yu et al. J Korean Med Sci 2011; 26: 1014

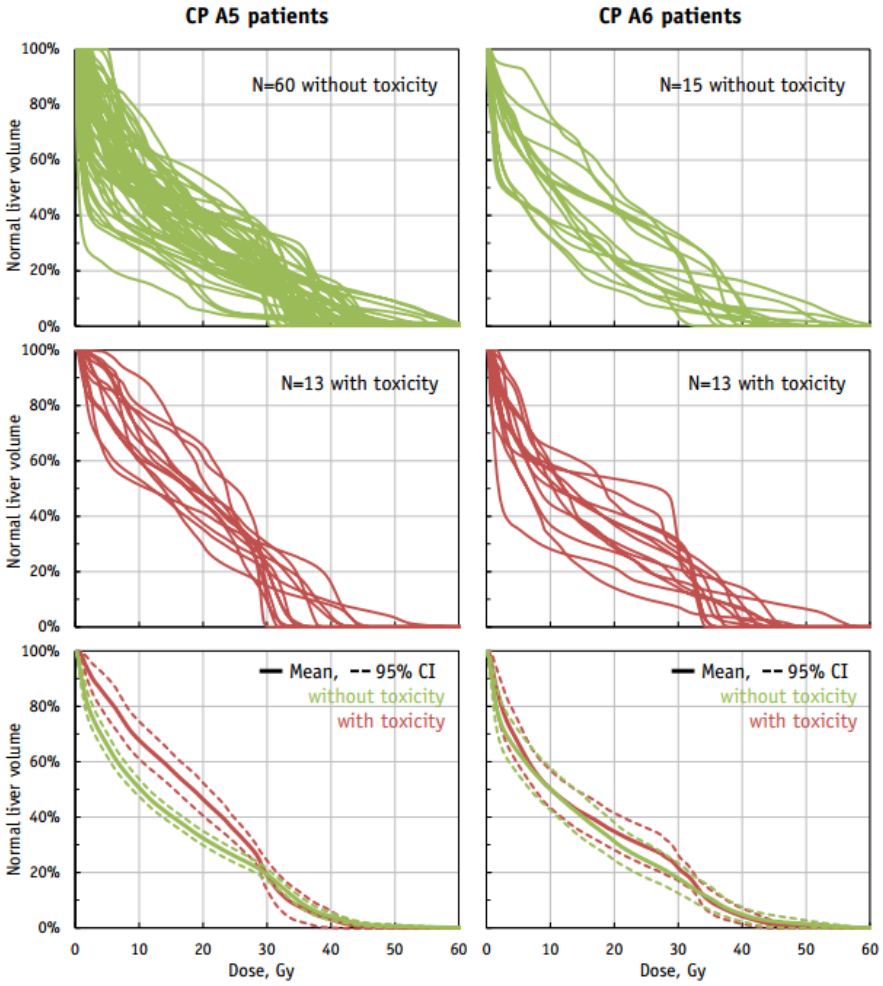
Prognostic factors in SBRT for HCC

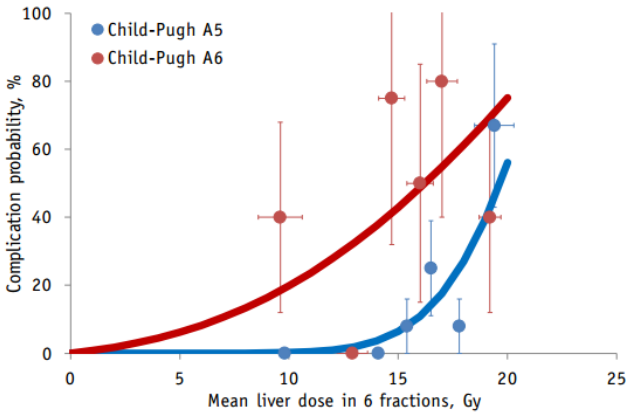


Culleton et al. Radiother Oncol 2014; 111: 412

Prediction of liver toxicity

Increase in C-P score ≥2 at 3 months; 6 fractions





A5		Mean Liver Dose (Gy)						
		≤ 15	≤ 16	≤ 17	≤ 18	≤ 19	≤ 20	≤ 21
D800cc (Gy)	≤ 5	0% (0/17)	0% (0/22)	0% (0/25)	3% (1/29)	6% (2/31)	6% (2/31)	6% (2/32)
	≤ 10	0 % (0/22)	0% (0/30)	0% (0/36)	5% (2/43)	7% (3/45)	7% (3/45)	7% (3/45)
	≤ 15	0% (0/24)	3% (1/34)	2% (1/41)	6% (3/51)	7% (4/56)	7% (4/57)	7% (4/57)
	≤ 20	0% (0/24)	3% (1/35)	5% (2/43)	8% (4/53)	10% (6/60)	11% (7/62)	13% (8/63)
	≤ 25	0% (0/24)	3% (1/35)	7% (3/45)	9% (5/55)	11% (7/63)	12% (8/65)	16% (11/68)
	≤ 30	0% (0/24)	3% (1/35)	7% (3/45)	9% (5/55)	11% (7/64)	13% (9/67)	18% (13/71)

Velec et al. IJOBP 2017; 97(5): 939

SBRT and sorafenib for HCC

- Phase I study; 16 Child-Pugh class A patients
- Low Veff (<30%) n=4 and high Veff (30-60%) n=
- Sorafenib escalation 100 mg >
- Results:

CONCLUSIONS:
Significant toxicity was observed in the high Veff stratum, and concurrent SBRT with sorafenib is not recommended outside a clinical trial.

grade 3 "tumor rupture"
Veff had worsening of Child-Pugh class

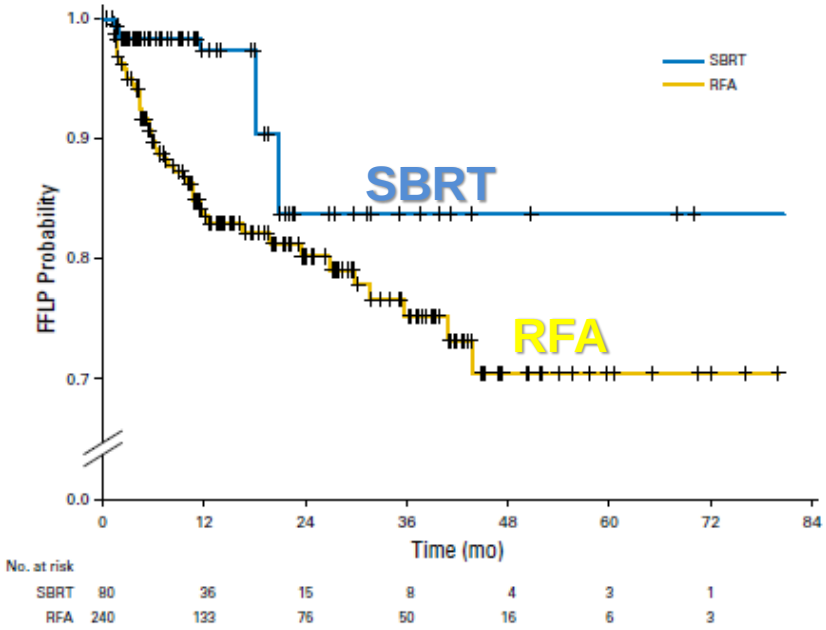
Brade et al. IJROBP 2016; 94(3):580-7

Comparizon: SBRT versus other modalities

- SBRT versus RFA
- SBRT versus TACE (ongoing)
- TACE versus TACE+SBRT (ongoing)
- SBRT versus TACE versus RFA in *Bridge to transplant*

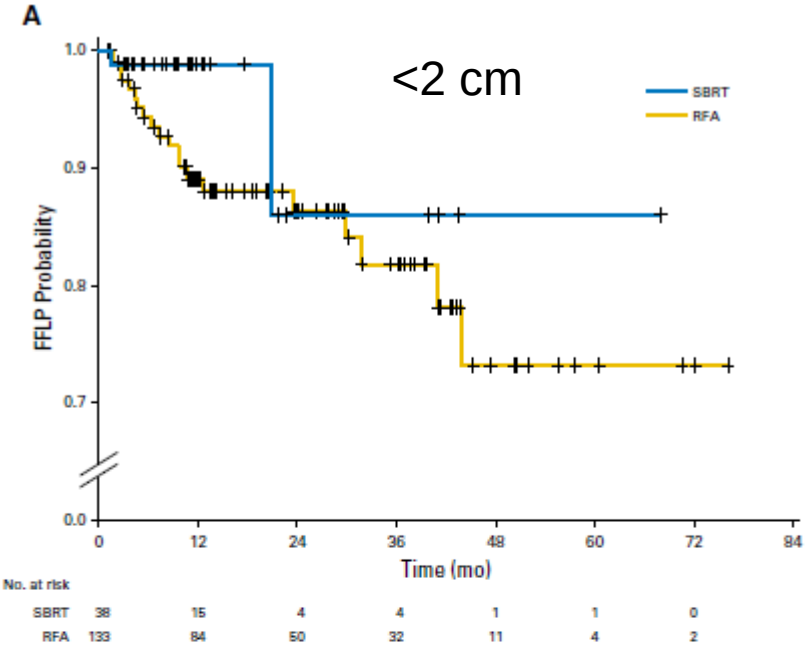
SBRT versus RFA

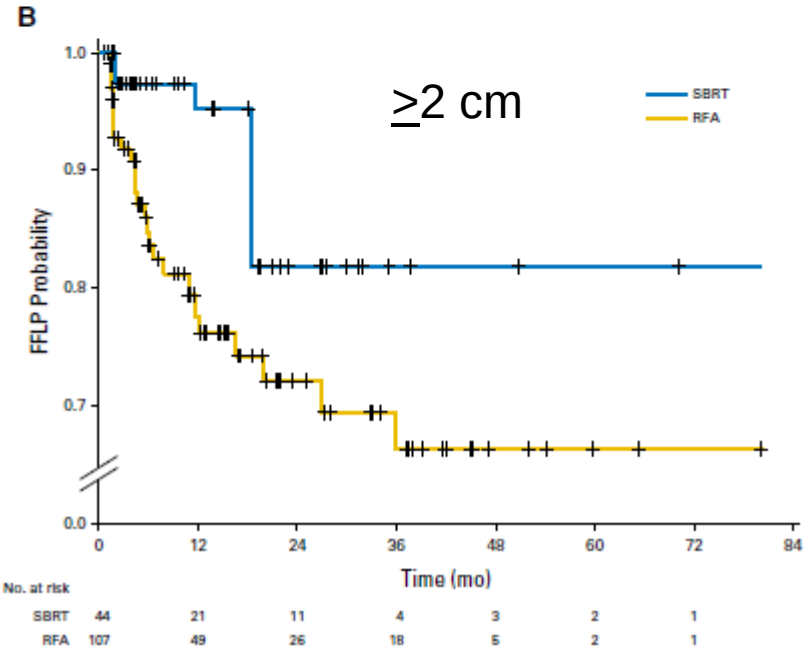
Inoperable HCC wo. PVT



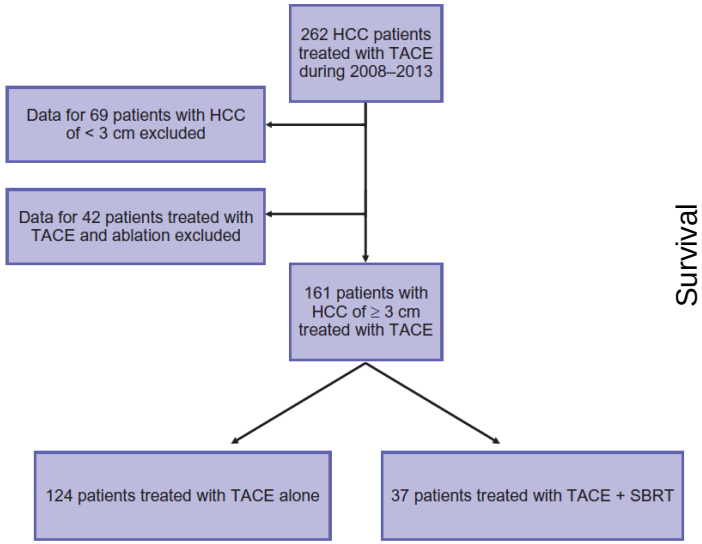
	SBRT	RFA
FFLP (1-yr)	97%	84%
OS (1-yr)	84%	80%
Gr 3+ tox	5%	11%

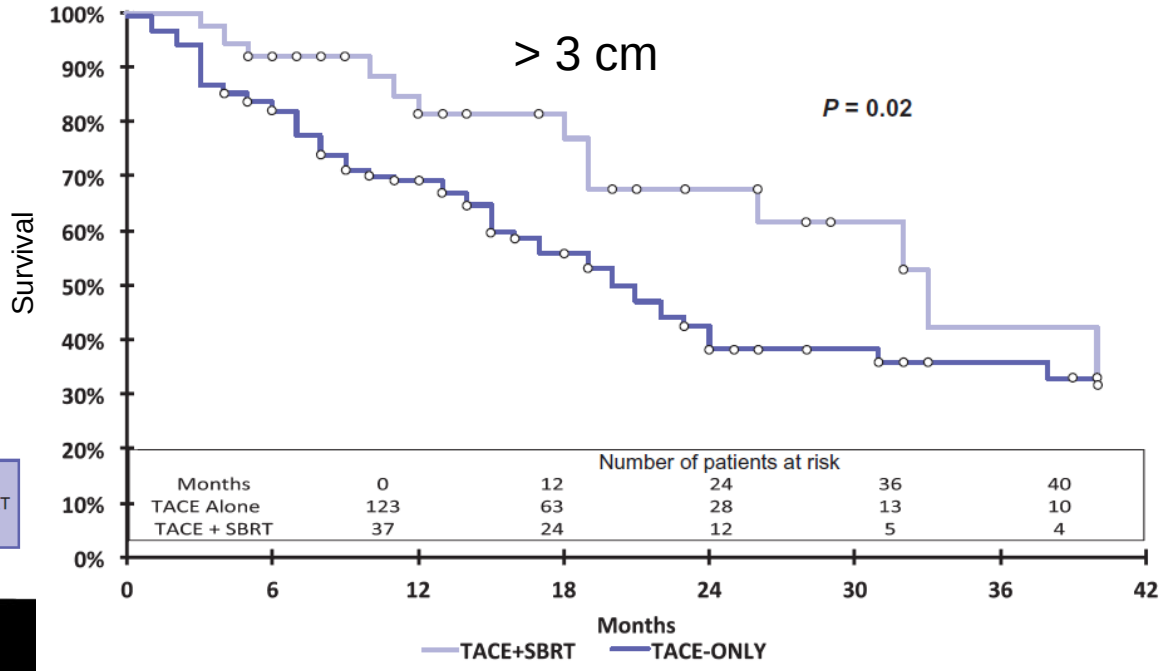
Wahl et al JCO 2016; 34(5): 452

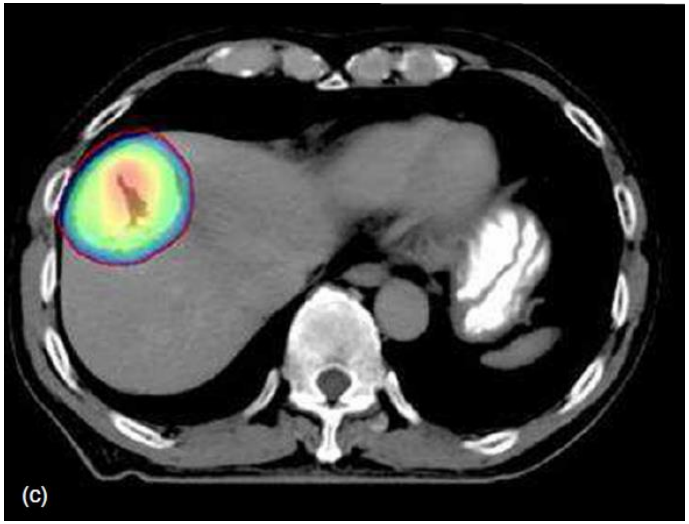




TACE versus TACE+SBRT for large HCC



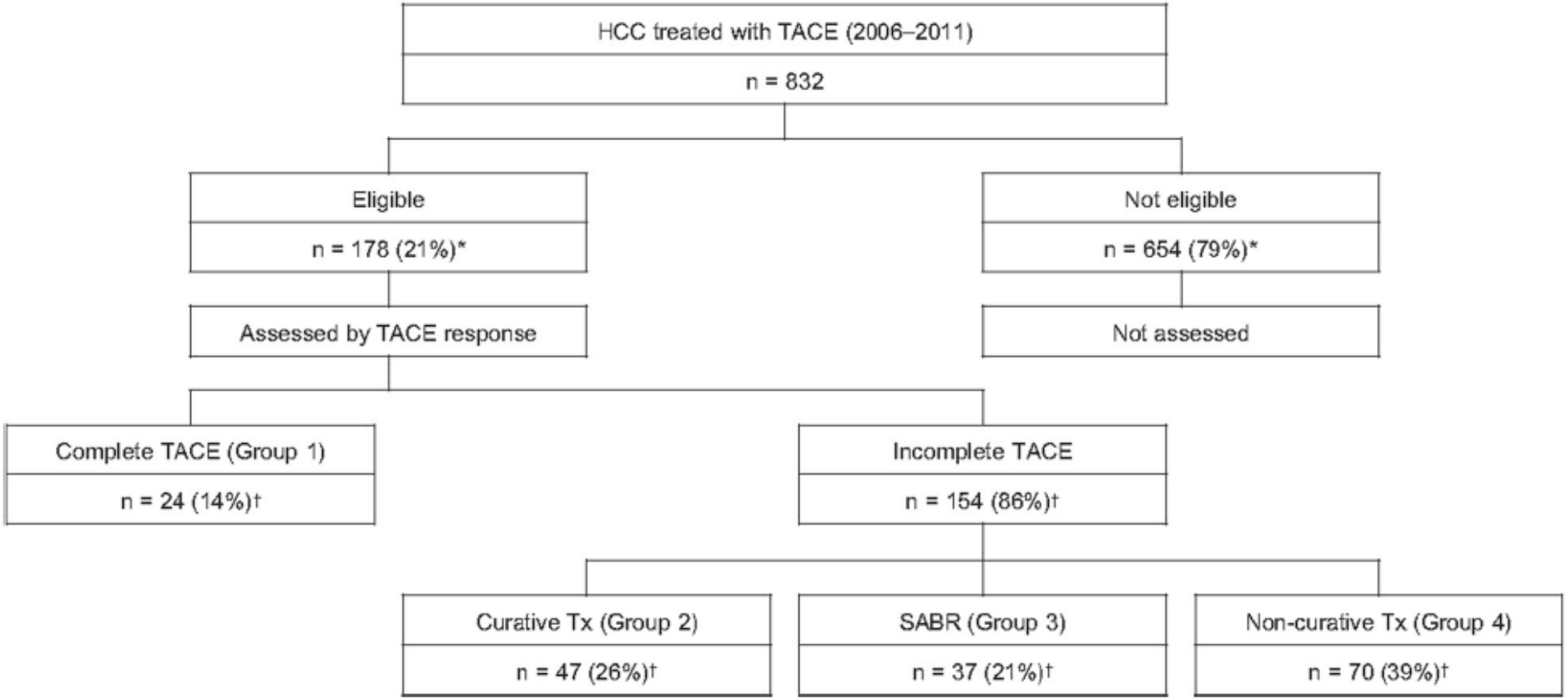




TACE n=124; LF: 26%
TACE+SBRT n=37; LF: 11%

Jacob et al HPB 2015, 17, 140

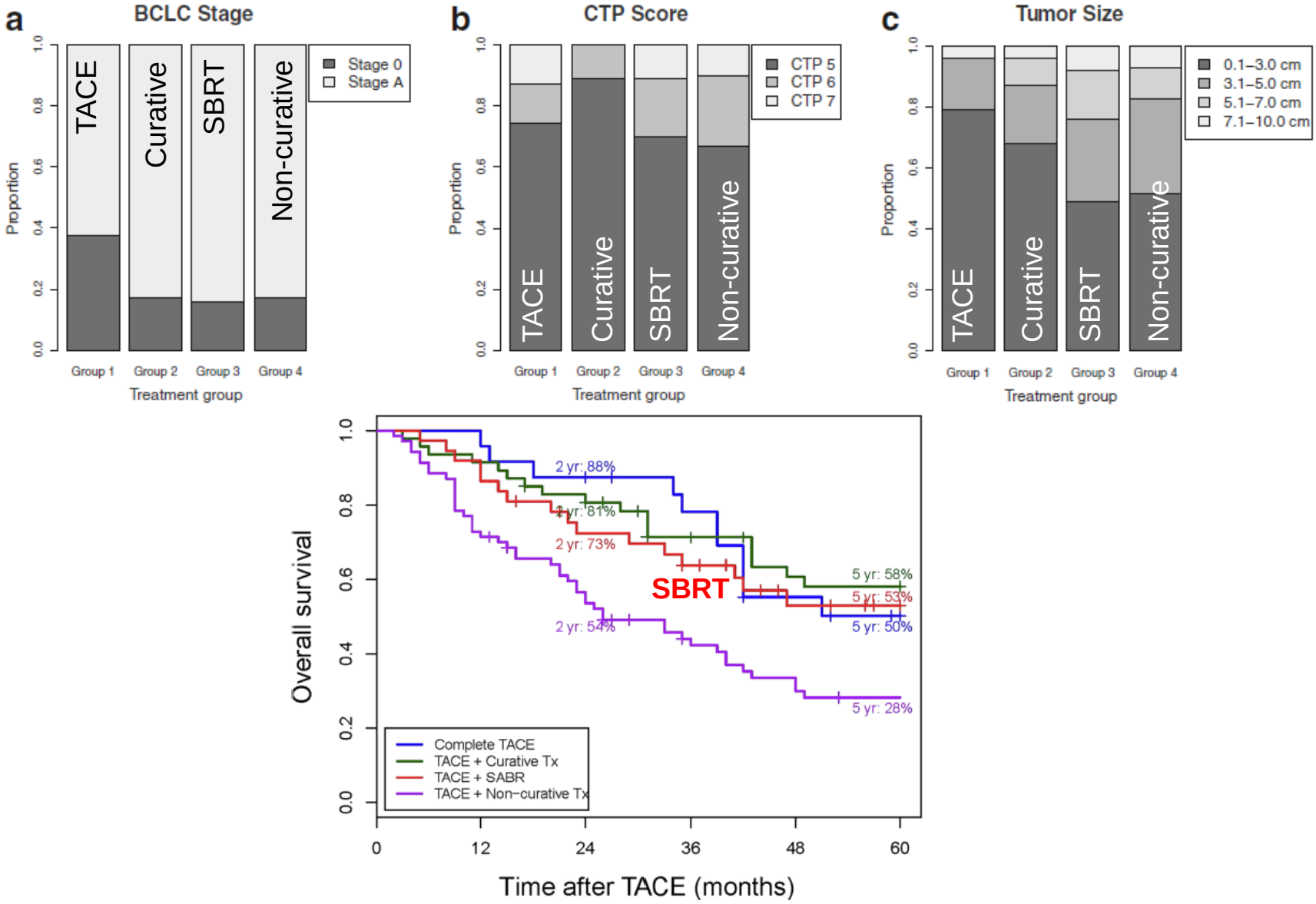
SBRT to incompletely treated TACE



Resection
RFA
PEI

Paik et al. Radiat Oncol 2016; 11:22

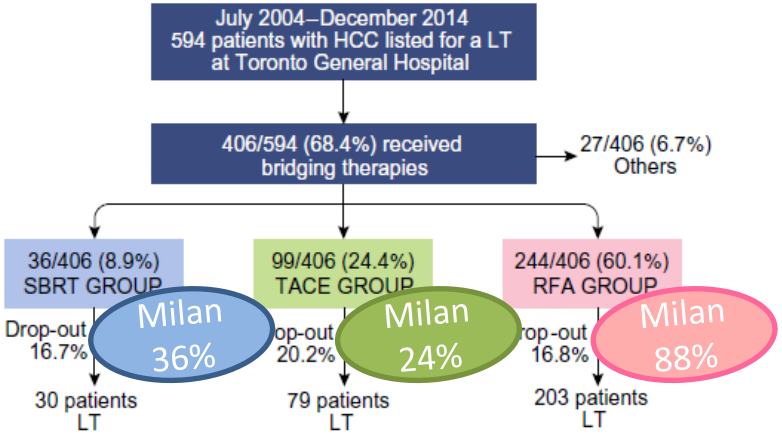
SBRT to incompletely TACE treated HCC

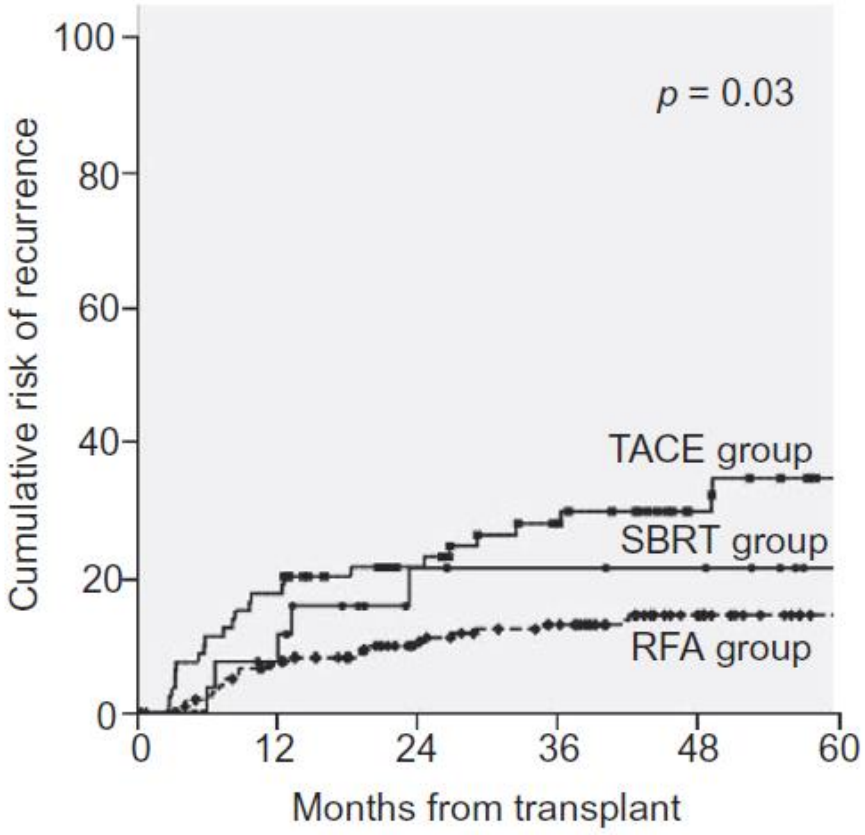


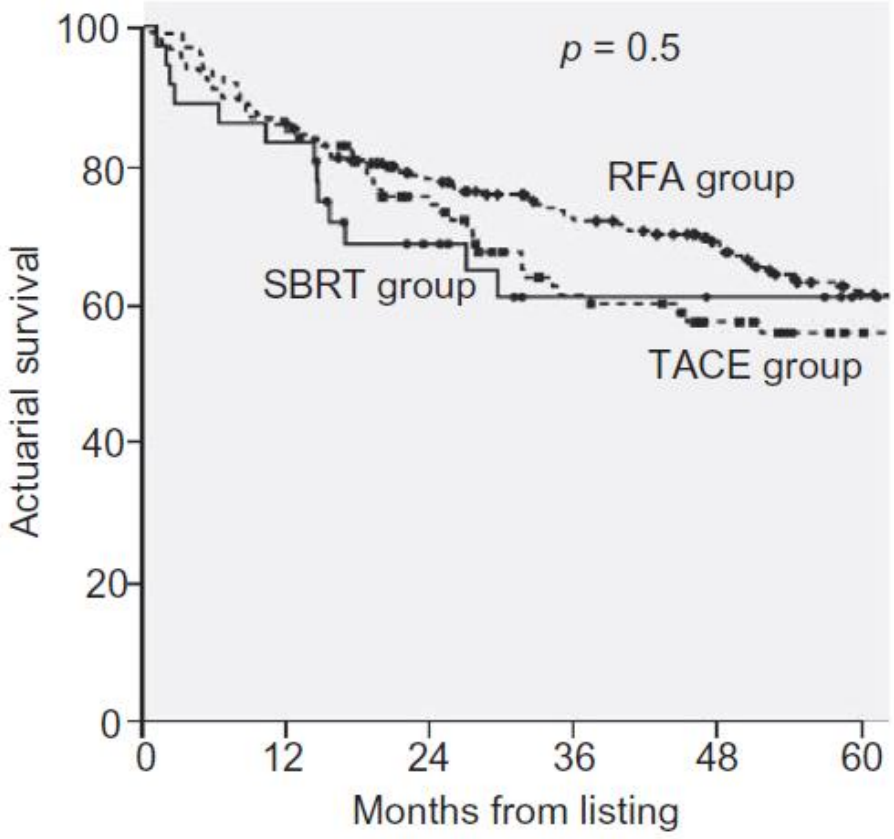
Paik et al. Radiat Oncol 2016; 11:22

Bridge to transplant

PMH - Toronto

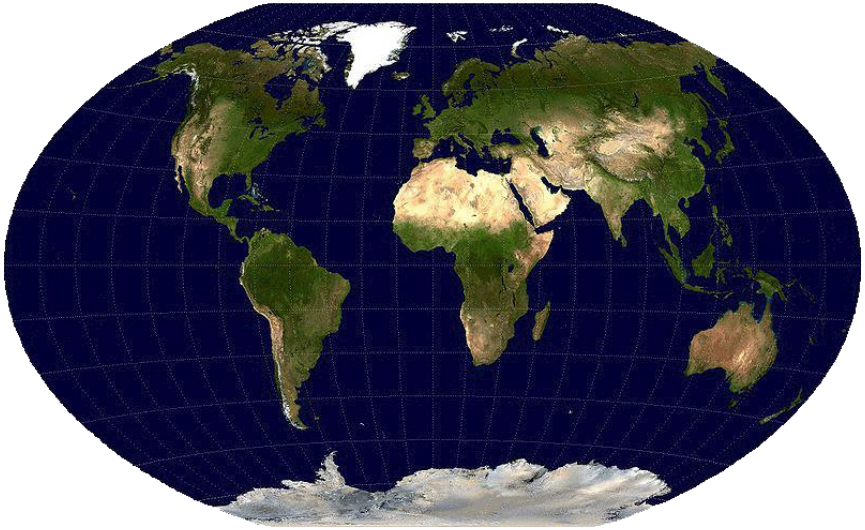


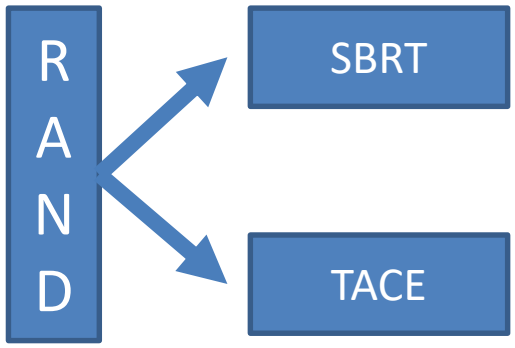




Sapitochin et al. J Hepatol *in press*

IAEA randomized trial on HCC

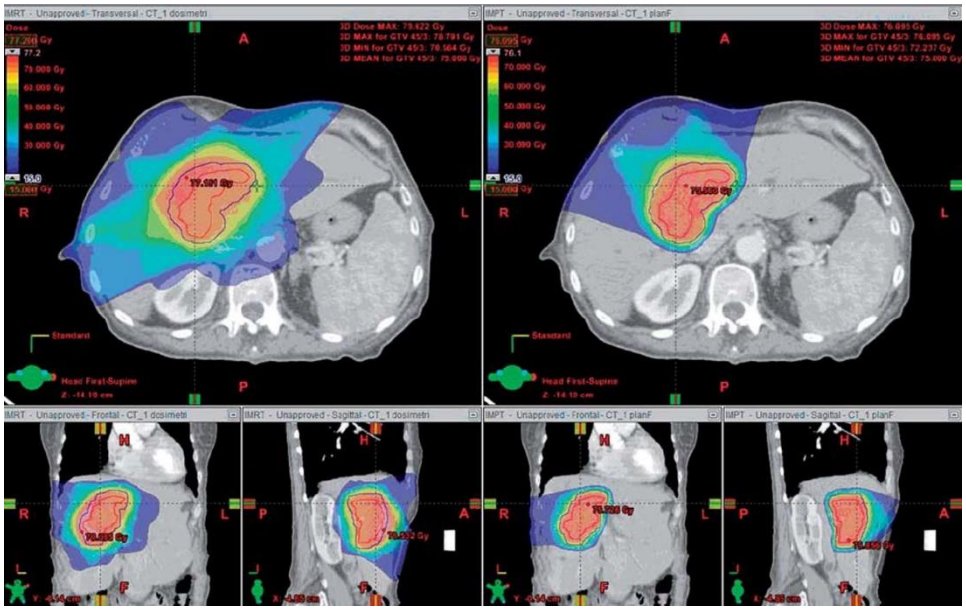


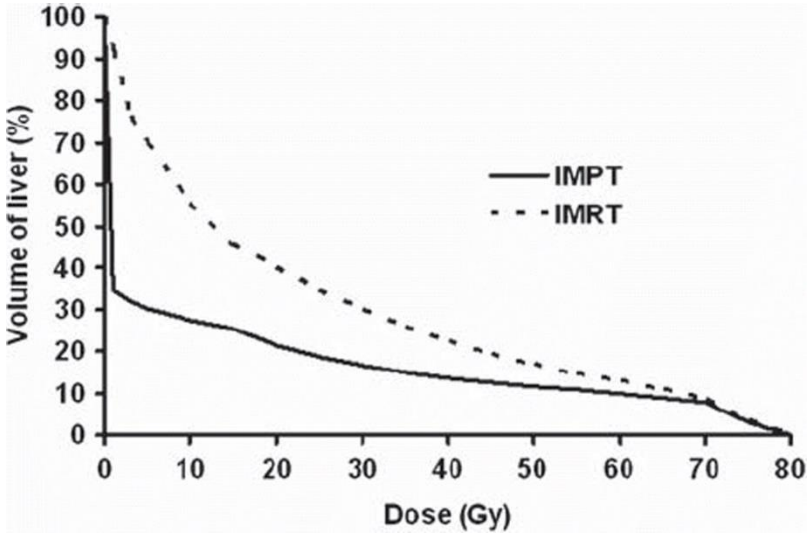


Inclusion criteria

- Hepatocellular carcinoma
- Σ 10 cm
- Max. 3 tumors
- Child-Pugh class A-B7
- BCLC A or B

SBRT or proton therapy to the liver



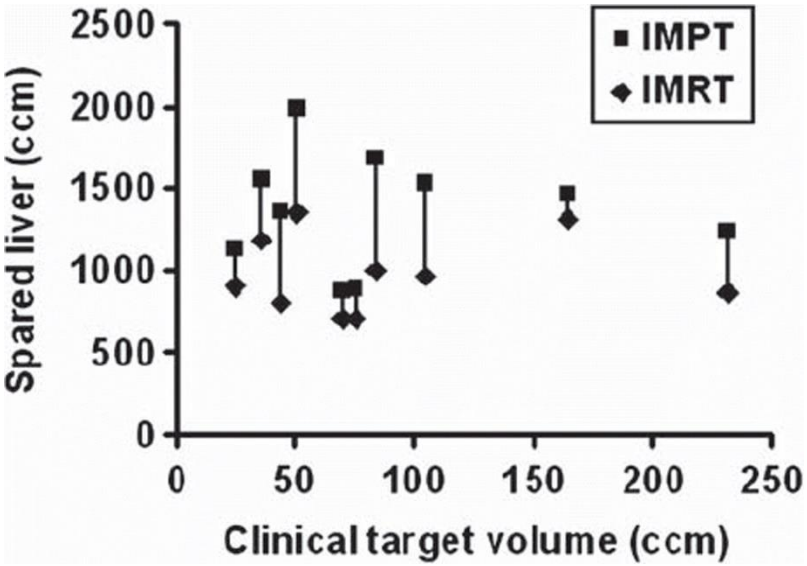


Petersen et al
Acta Oncol
2011; 50(6): 823

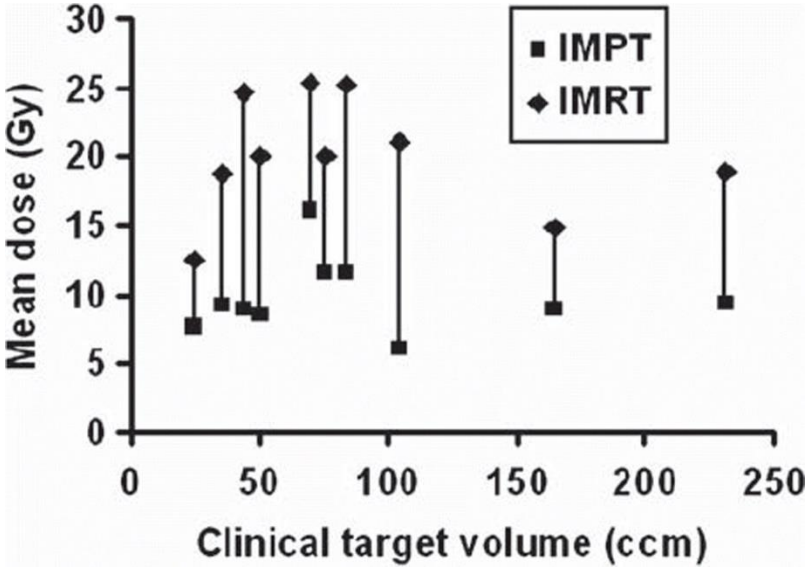
SBRT or proton therapy to the liver

Treatment plan comparison of liver cancer

$V_{<15\ Gy}$

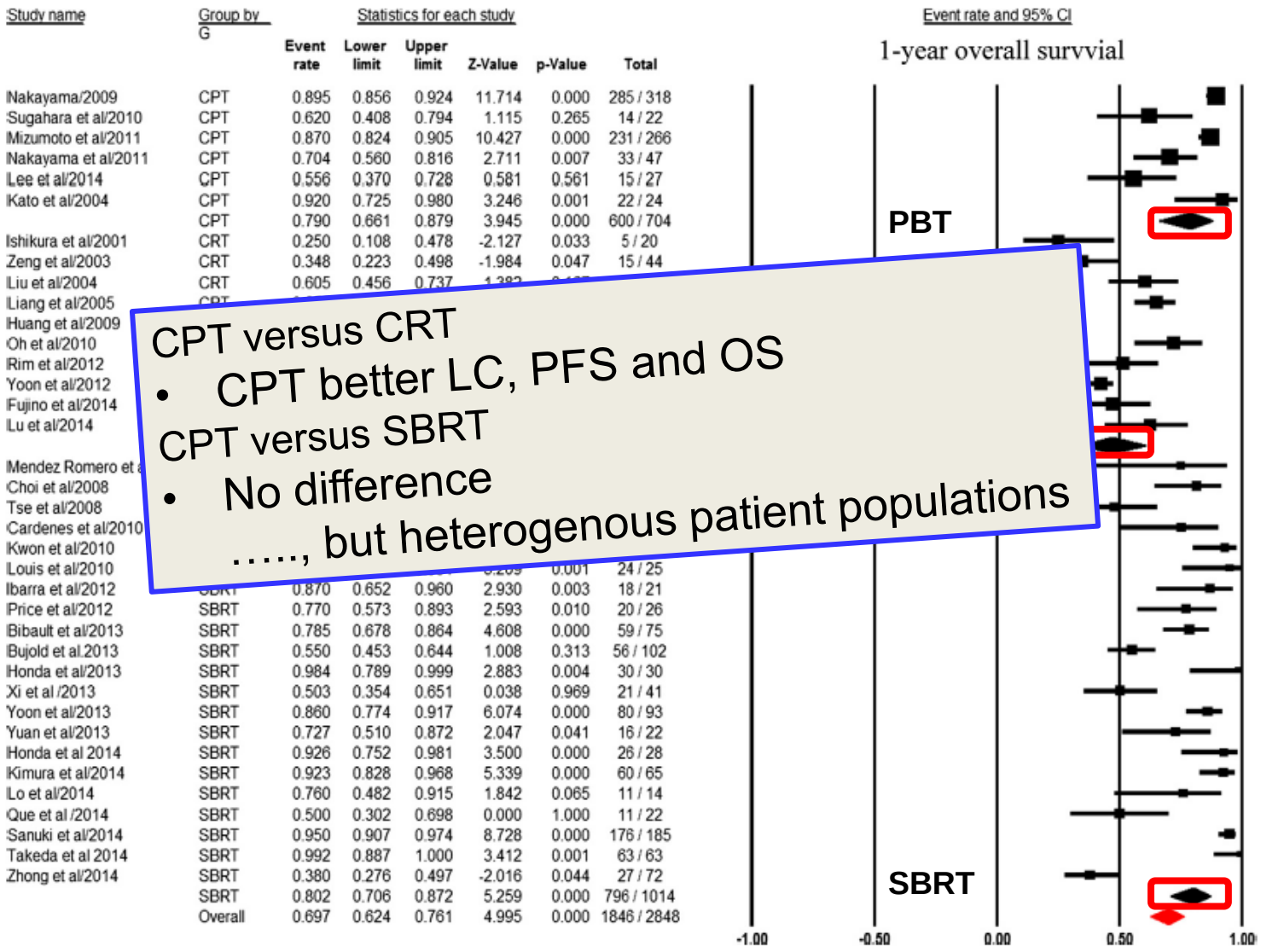


D_{mean}



Petersen et al. Acta Oncol 2011; 50(6): 823

Meta-analysis of proton treatment of HCC



CPT versus CRT
- CPT better LC, PFS and OS

CPT versus SBRT
- No difference

….., but heterogenous patient populations

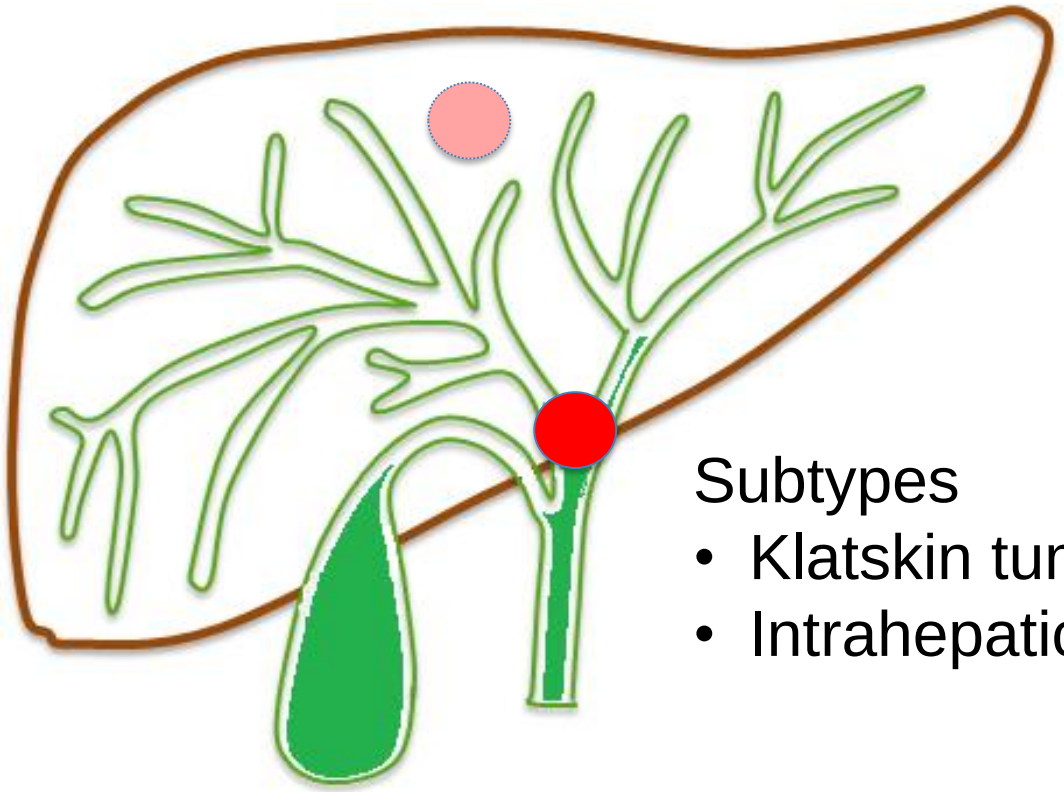
Review and metaanalysis of 5204 patients
Qi et al. Radiother Oncol 2015; 114:289

Fig. 2. Forest plot for meta-analysis of 1-year overall survival in patients with HCC.

Primary liver cancer

Cholangiocarcinoma

Cholangiocarcinoma



Subtypes

- Klatskin tumour
- Intrahepatic cholangiocarcinoma

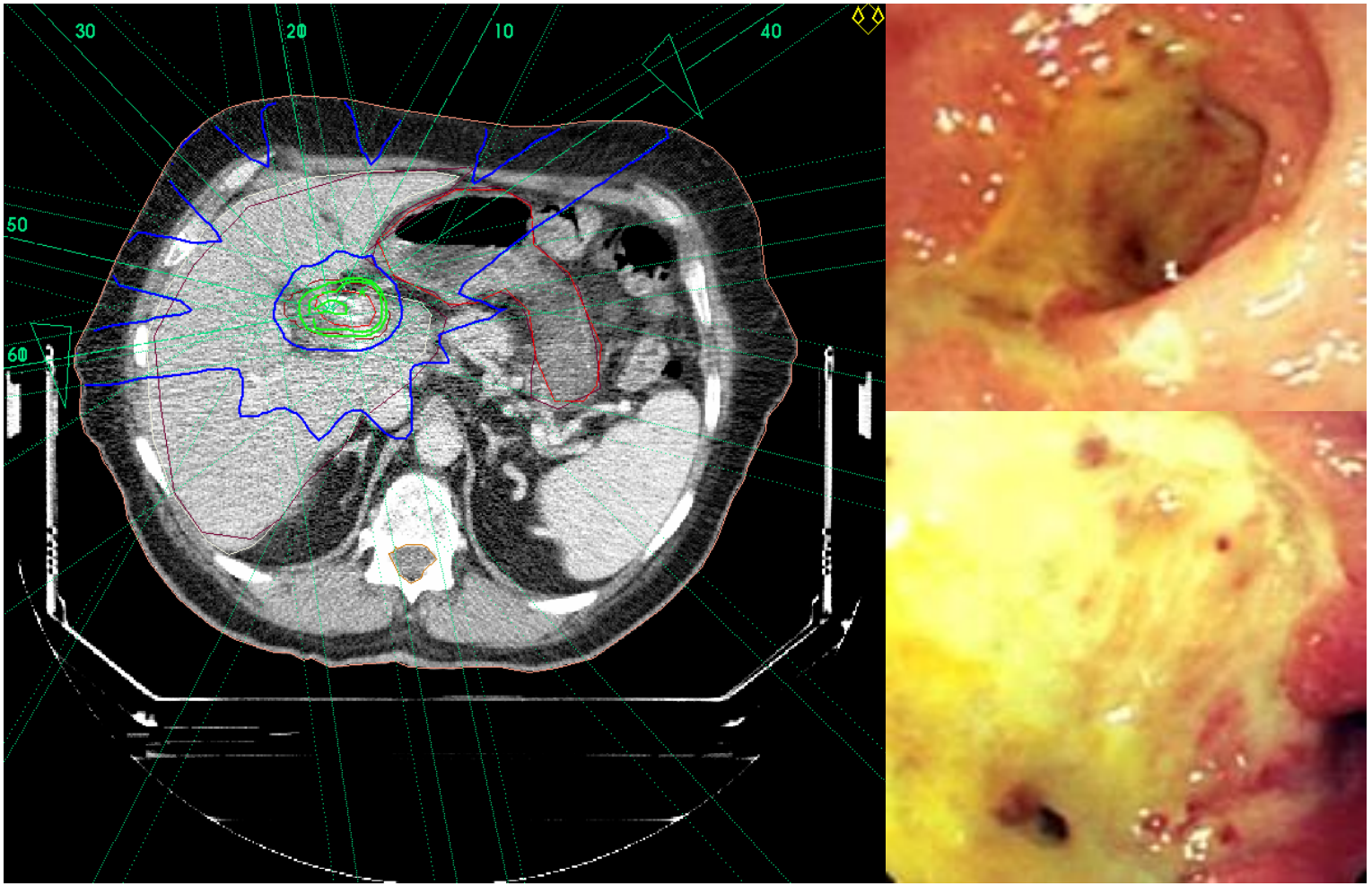
Aetiology of cholangiocarcinoma

- Risk factors
  - Primary sclerosing cholangitis (long-standing ulcerative colitis)
  - Parasites/flatworms (*Clonorchis sinensis* and *Opisthorchis viverrini)*
  - Chemical exposure (aircraft, rubber, and wood-finishing industries)

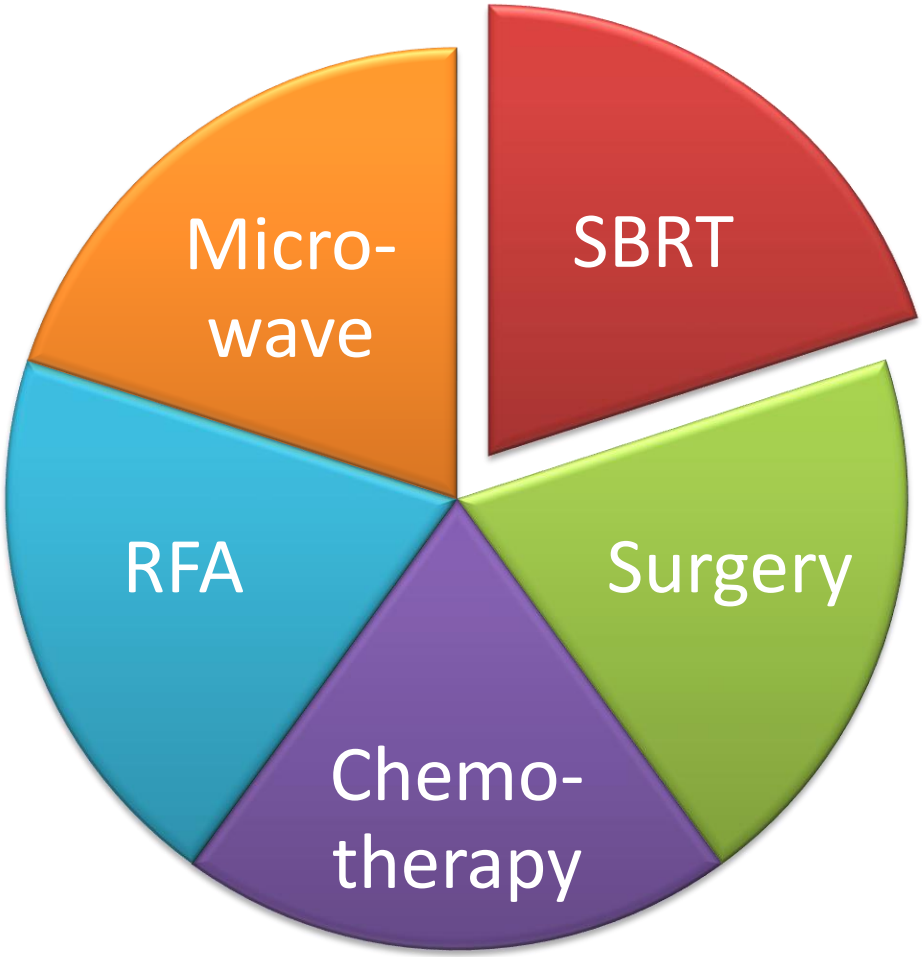
SBRT for cholangiocarcinoma

Author	Patients Prim//mets	Dose-fractionation (prescript. isodose)	Median follow-up (m)	TTP Median (m)	Survival (%) 1 year
Tse 2008	10 IHC	6 x 6-9 Gy (100%)	18	-	60
Kopek 2010	27 26 KT/1 IHC	3 x 15Gy (67%)	64	7	45
Polistina 2011	10 KT	3 x 10 Gy (80%) + weekly gemcitabine	36	30	80
Ibarra 2012	11 IHC	3 x 7.5-11.5	8	-	75

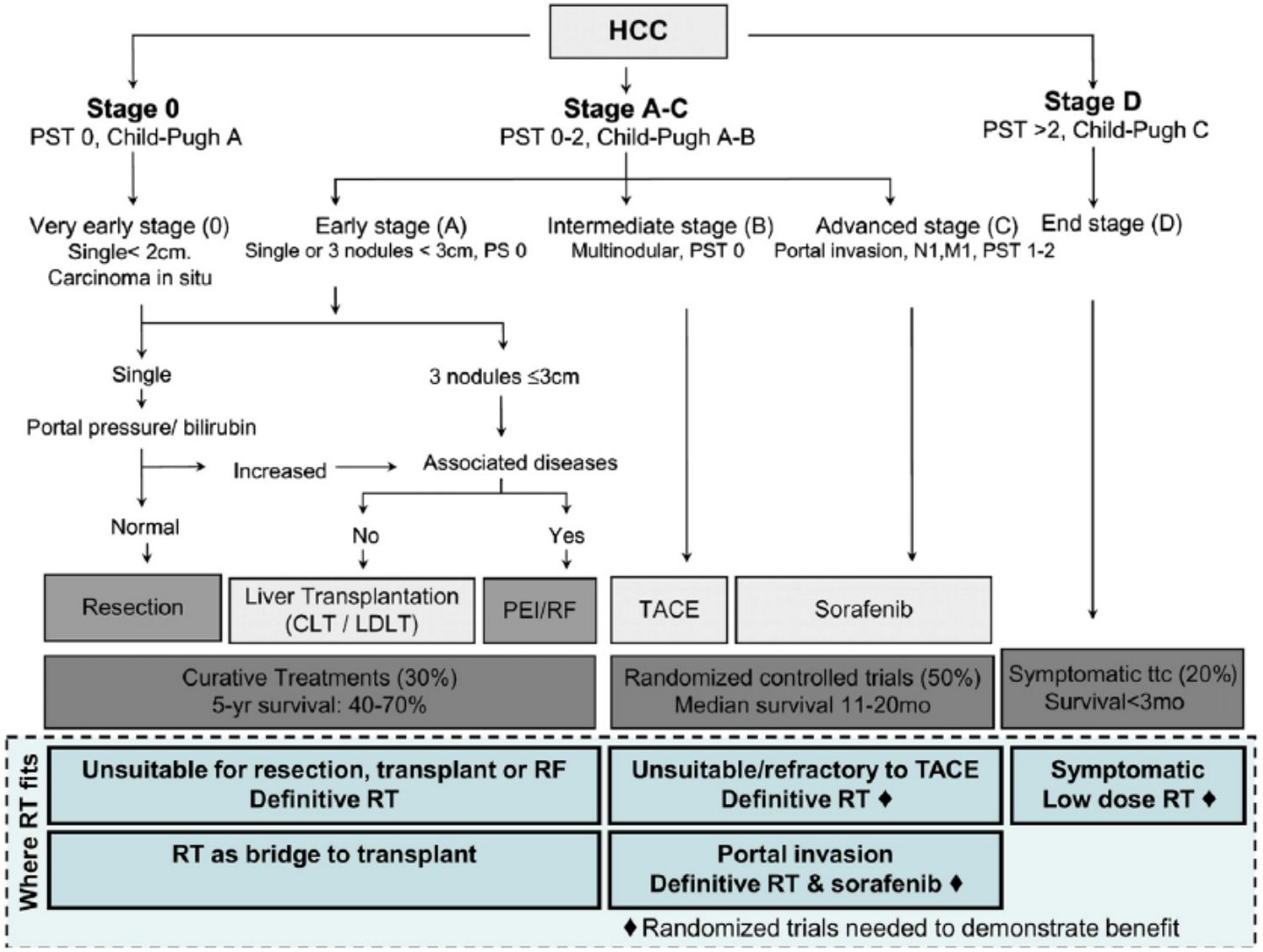
Morbidity following SBRT of CAC



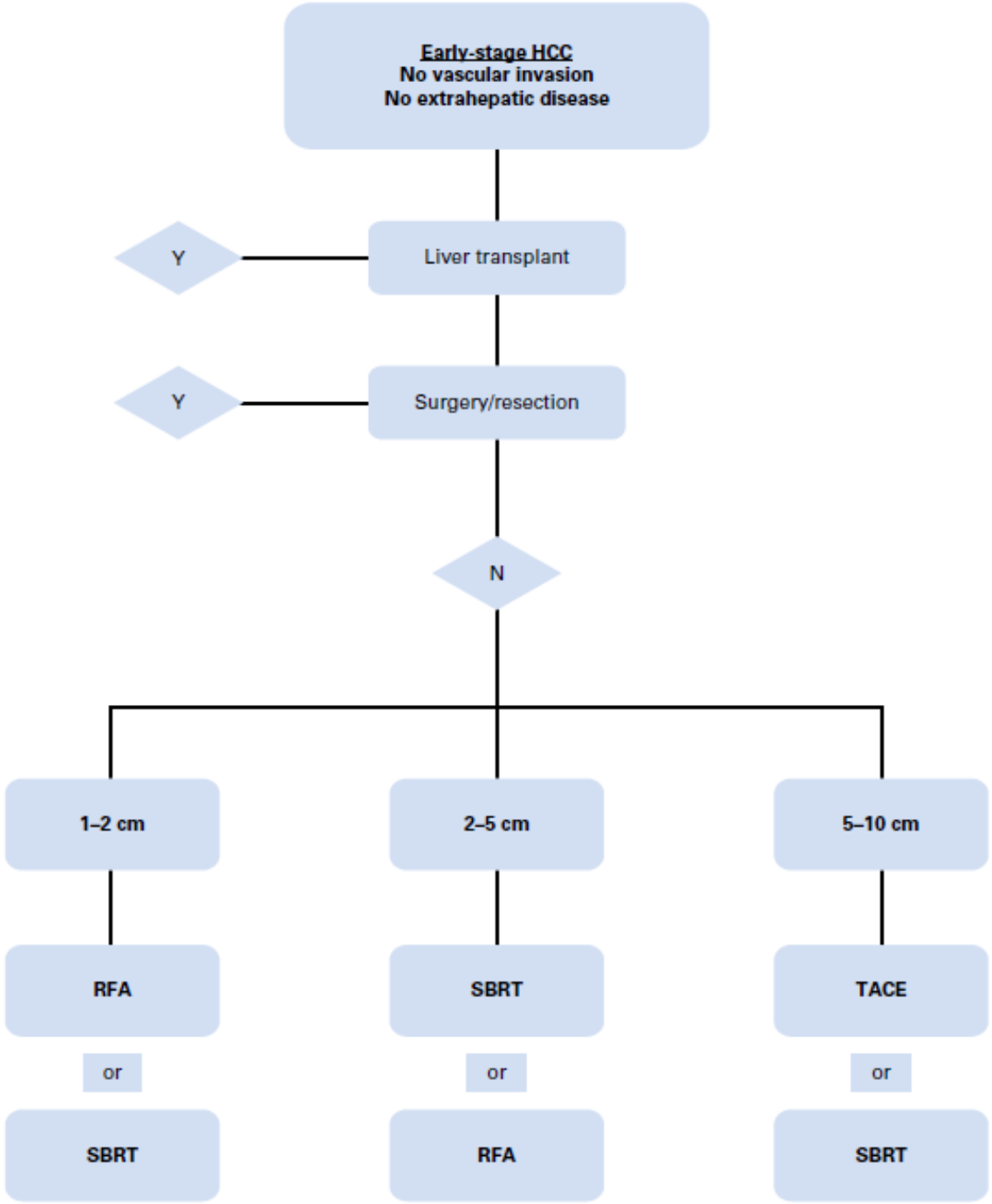
Treatment of liver cancer in a Multidisciplinary Team



The Barcelona Clinic Liver Cancer Group (BCLCG) staging system



Modified Klein & Lawson IJROBP 2013; 87(1): e22



Berry et al. JCO 2016; 34(5):404

Conclusions – SBRT of primary liver cancer

- SBRT competitive to RFA and SIRT in inoperable HCC
- Prognostic factors
  - C-P Score, tumor size, s-AFP and PVT
- Risk of liver failure in C-P B (low) and C-P C (high) HCC patients

Questions from the participants

- In Europe, HCC radiotherapy is seemed to be overwhelmed by others (such as internal radiotherapy).
- How is the trend of HCC radiotherapy in Europe? For example, what do you prefer as primary local treatment for HCC PVT? (SIRT, EBRT, TACE?)

Clinical practice of liver SBRT

Morten Hoyer
Aarhus University Hospital
hoyer@aarhus.rm.dk

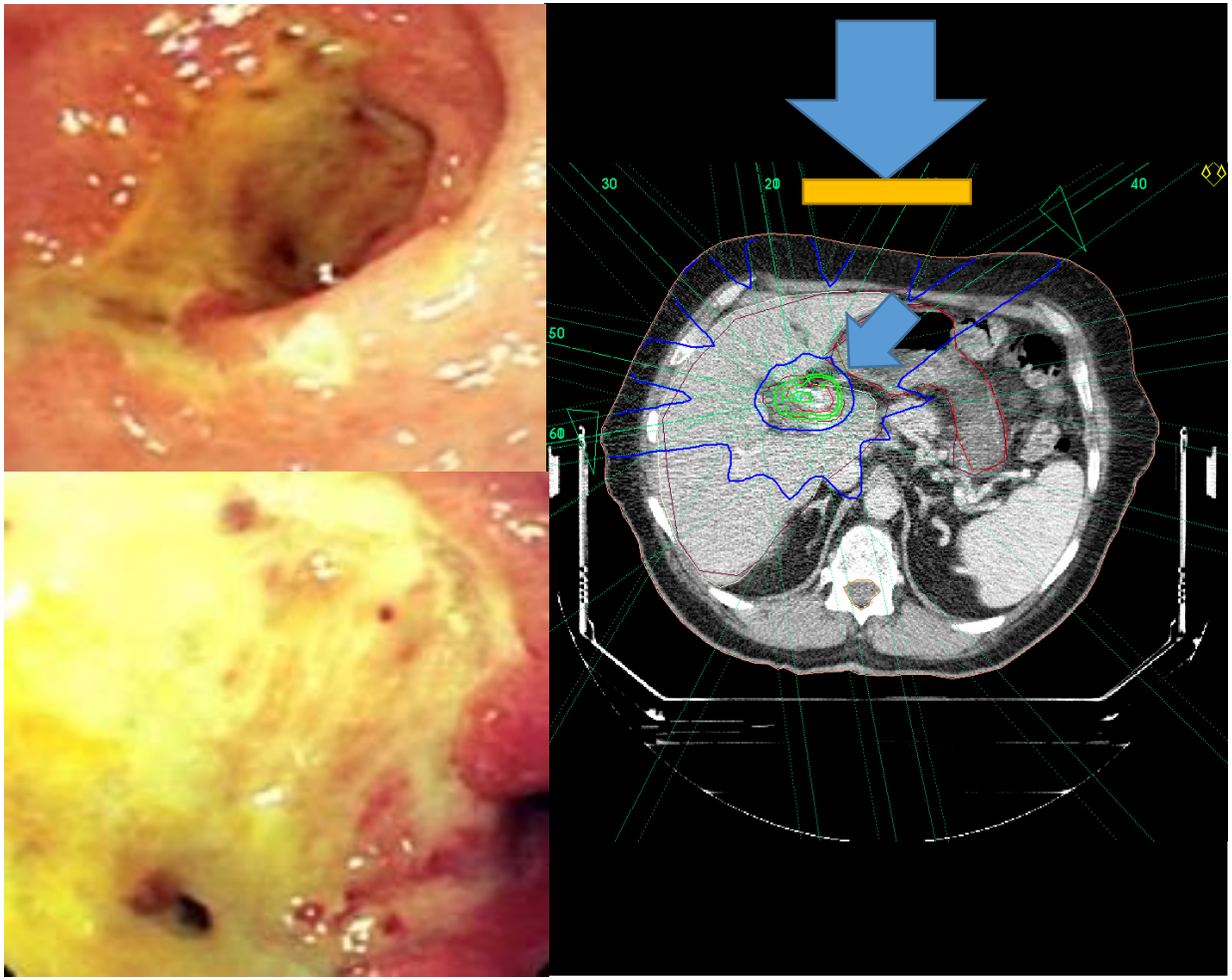
- Fractionation and planning procedure for locations like adrenals, **liver**, skeleton etc
- Optimal SBRT fractionation in different organs and dose constraints for OAR
- How to select patients suitable for liver SBRT

Challenges in liver SBRT

- Limited imaging in the treatment position
  - Match on markers (surrogates)
  - Match on liver/diaphragm/skeleton
- Internal motion
- Risk of morbidity
  - Liver (liver cirrhosis, heptitis-carriers)
  - Intestinal structures

Immobilization (abdominal compression)

Abdominal compression



Fiducial markers

Controversies

- SBRT is non-invasive
- ……,but fiducial markers i… …cy

Implantation of fiducial markers should be with the lowest possible risk of complication

Fiducial markers

High Z-factor

Gold fiducials x 3

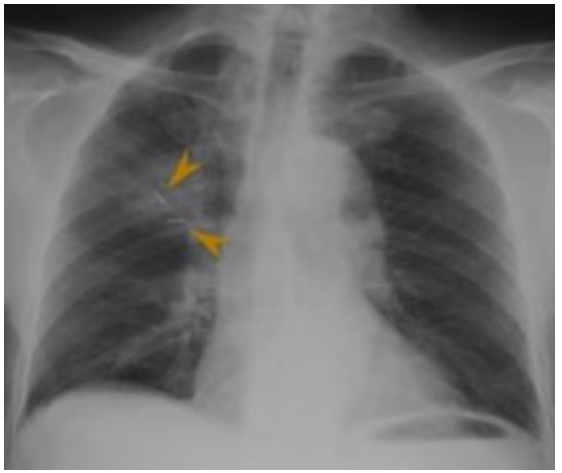
- 1 mm x 3 mm implanted into the liver with a 18 Gauge needle (outer diameter = 1.3 mm)

Calypso x 3 transponders

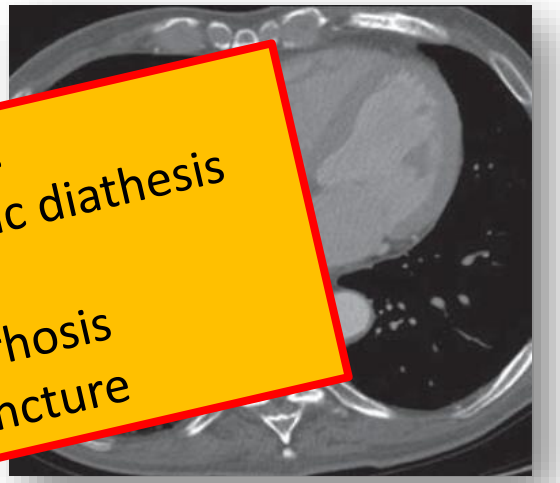
- 1.8 mm x 8.5 mm implanted with a 14 Gauge needle (outer diameter = 2.1 mm)
- New Calypso 50% size, implanted with 17 Gauge needle

Other

- BioXmark (Nanovi) biodegradable liquid fiducial marker
- Visicoil markers
- Gold anchor



Risks of complications

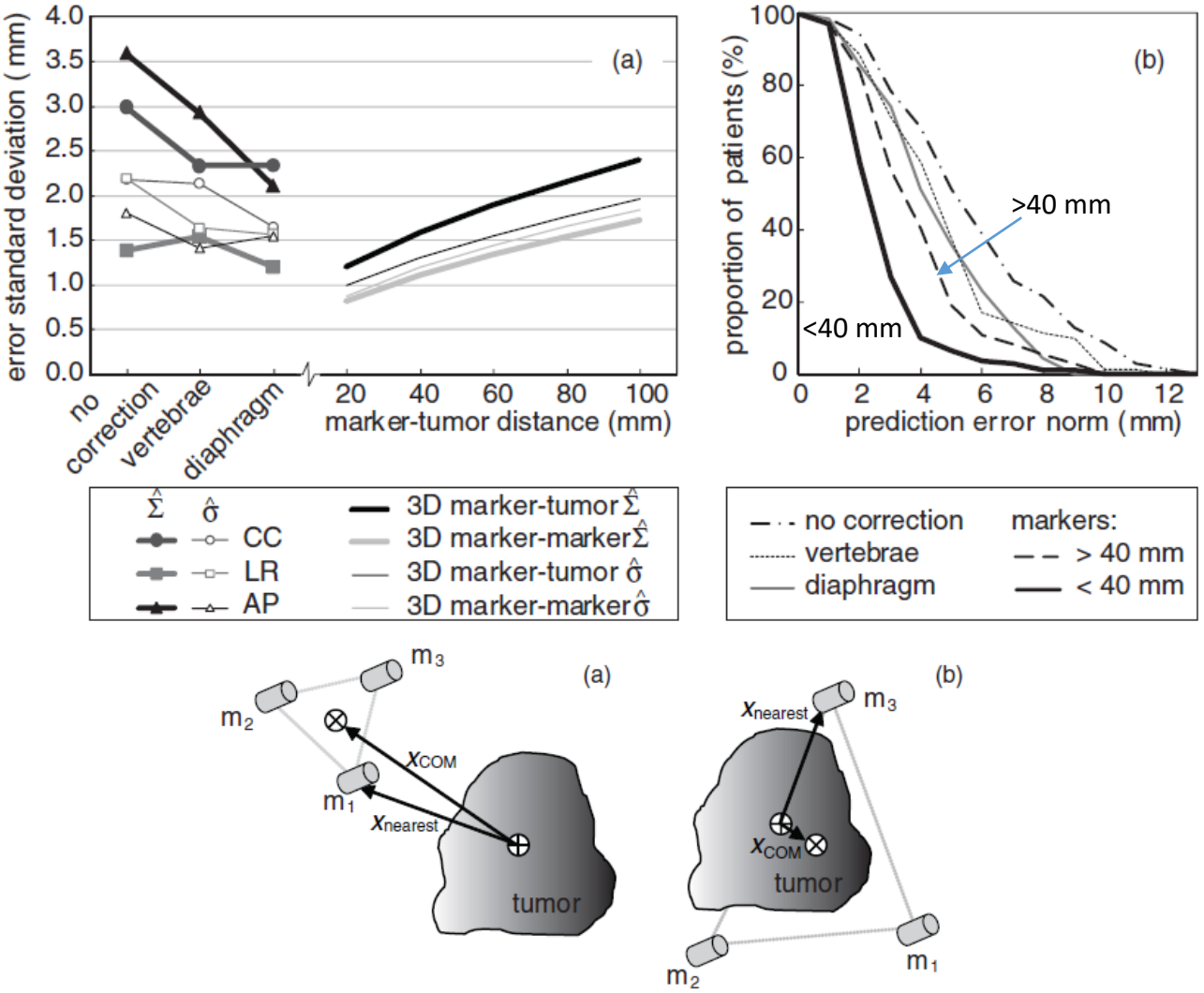


Core needle biopsies

- Mortality 0.1% (fatal bleed
- Complications
  - Bleeding/hematoma, pneumothorax, infection
    - Major (Requiring therapeutic intervention) 0.5%
    - Minor (No therapeutic intervention) 0.7%

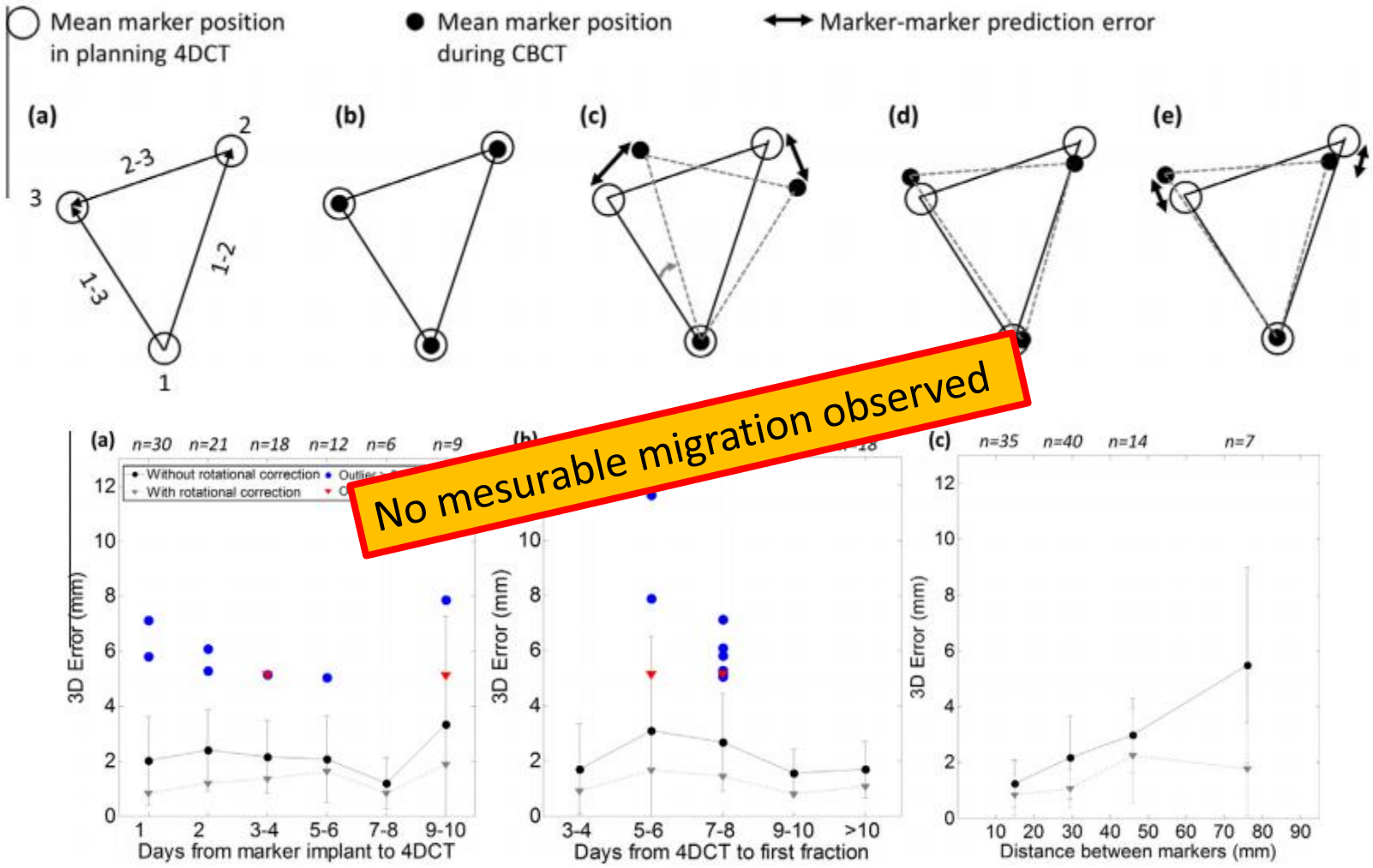
      (Mueller et al. BMC Gastroenterol 2012;12:173)
  - Risk depending on Quick-test and PTT, not platelet count
  - Consider risk of complications 1% → 2% with Calypso (in a metaanalysis of liver biopsies from the UK, needle size was not related to risk of complication (Howlett et al Radiology 2013; 266(1): 226)

Fiducial markers



Seppenwoolde et al Med Phys Biol 2011; 56: 5445

Marker migration of cylindric fiducials

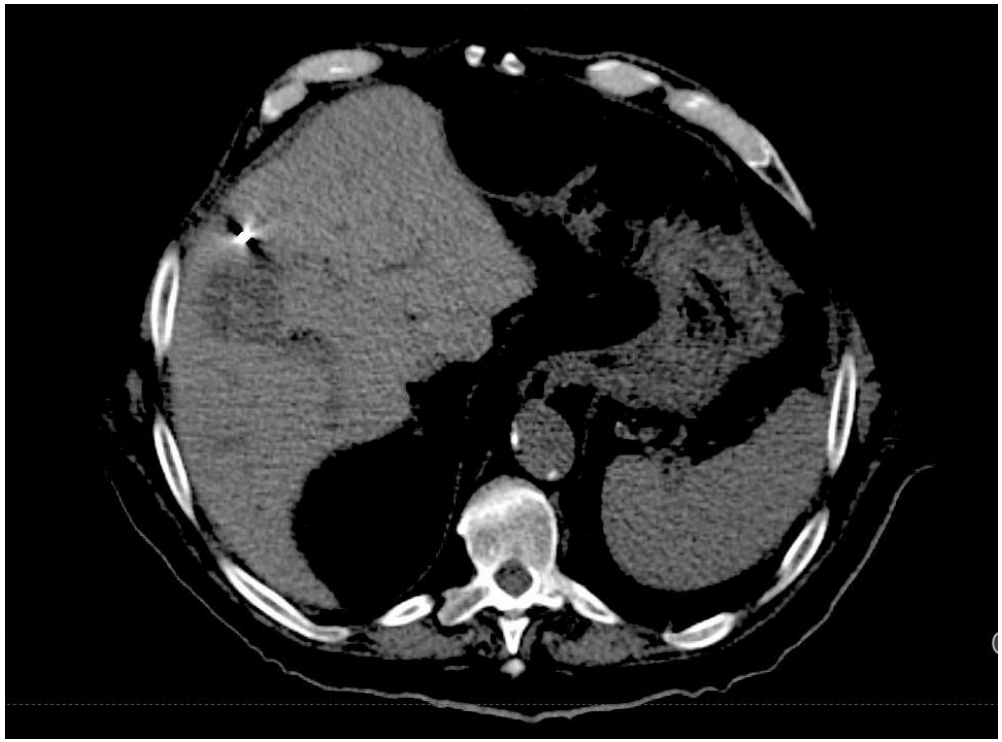


Worm et al. Radiother Oncol 2016; 121:75

CIRRO

AARHUS UNIVERSITY

Strategy for implantation



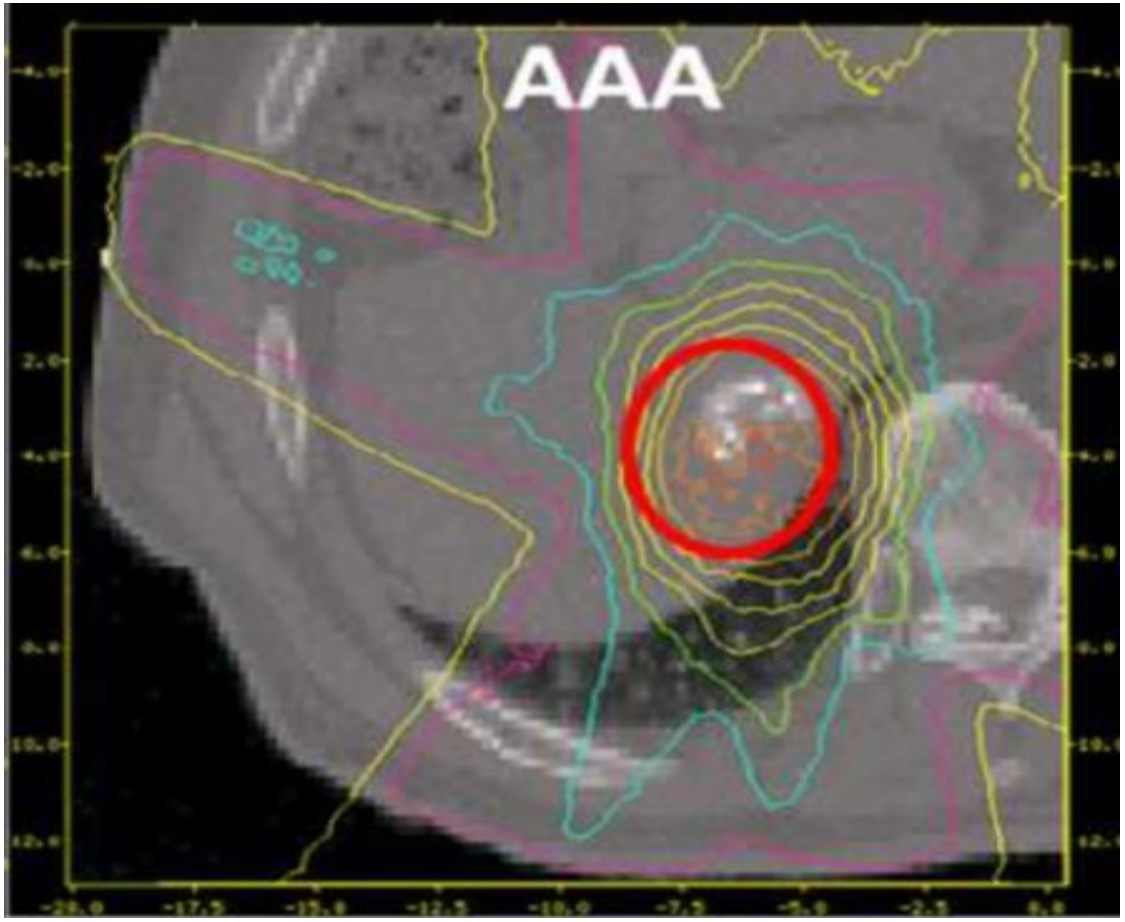
Strategy

- Dedicated interventional radiologist
- Trained together for two years
- Marked the diagnostic CT-scan
- Implantation guided by ultrasonography

Objectives

- In a triangle
- Cranial and caudal to target
- One met: max 4 cm marker-tumor center
- Multiple mets: max 6 cm marker-
- Min 3 cm inter-marker distance

Lipiodol as an alternative to fiducial markers



Kawahara et al. Med. Phys. 2017; 44 (1): 342

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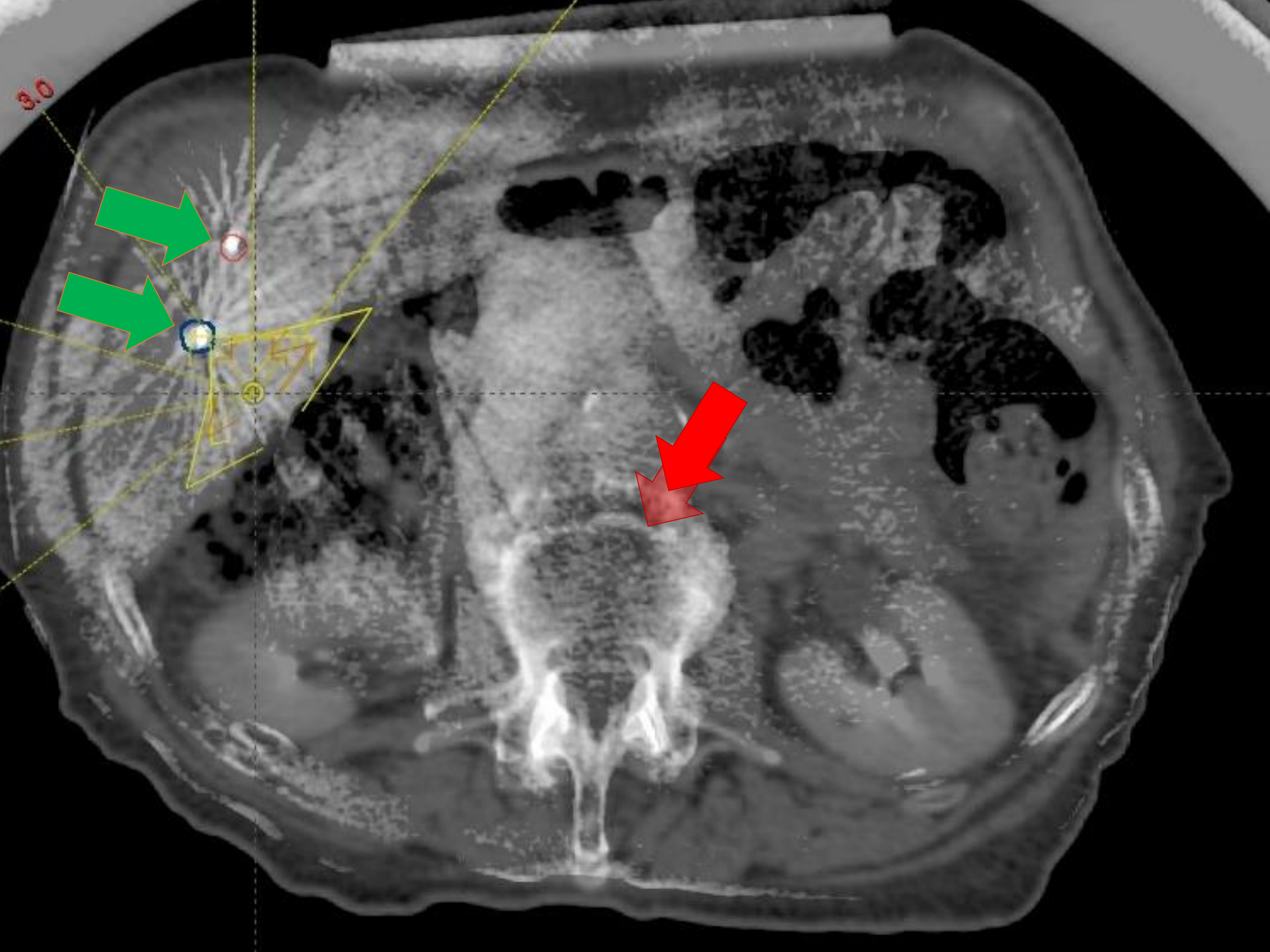
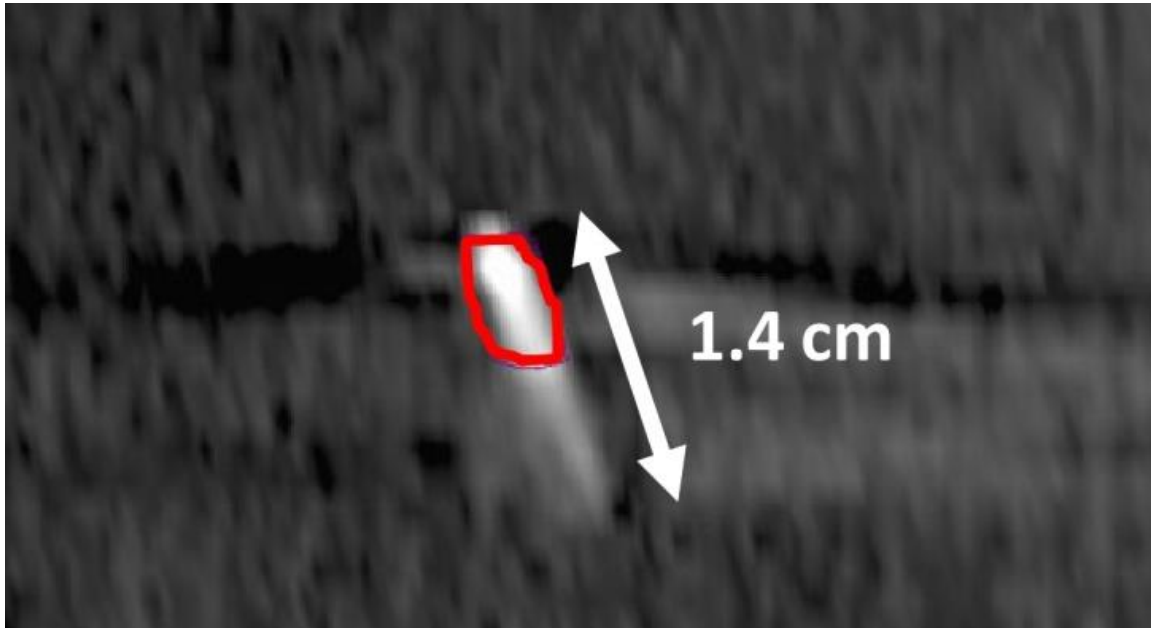

3.0

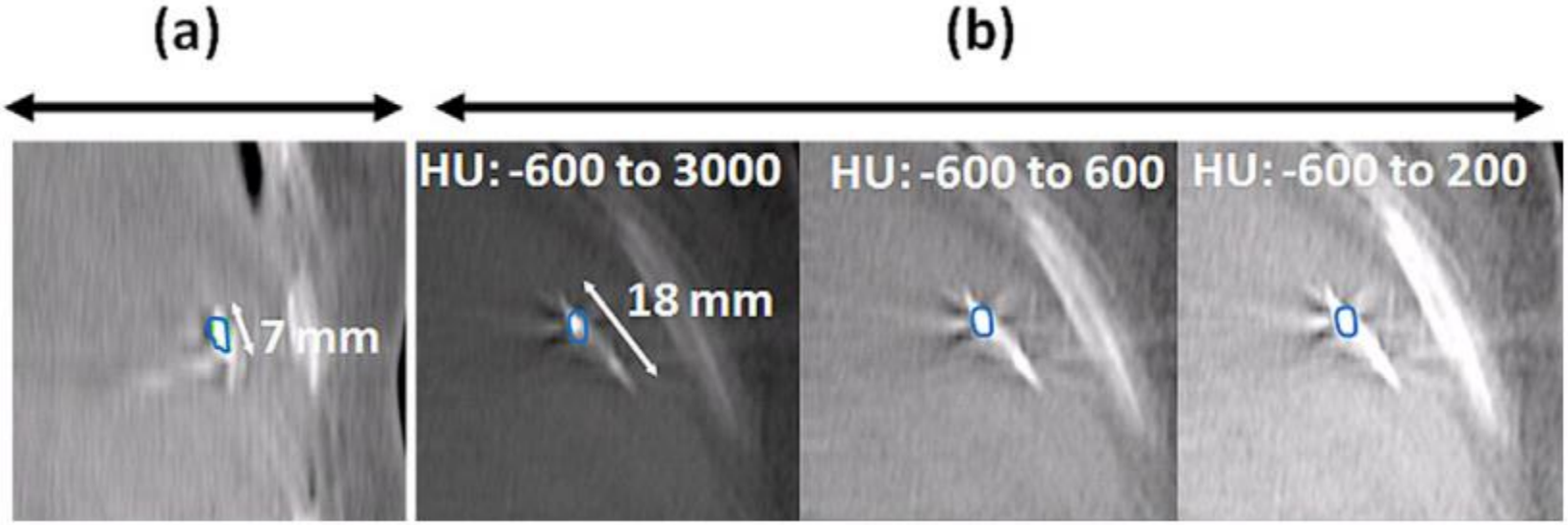
CBCT of fiducial markers



Motion blurring of marker in CBCT scan

Worm et al Aarhus University Hospital

Cone-beam CT and fiducial marker match



Worm et al. Int J Radiation Oncol Biol Phys 83(1): e145

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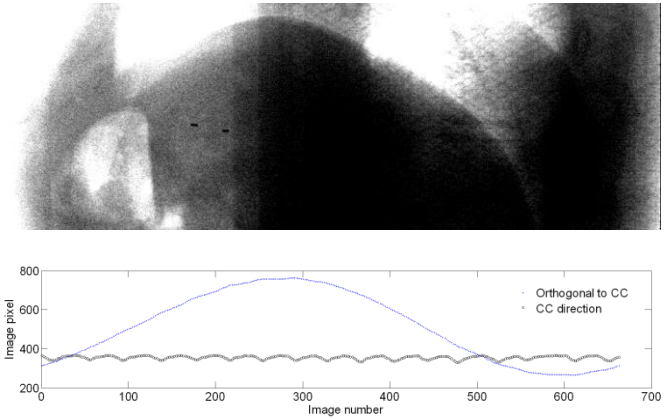
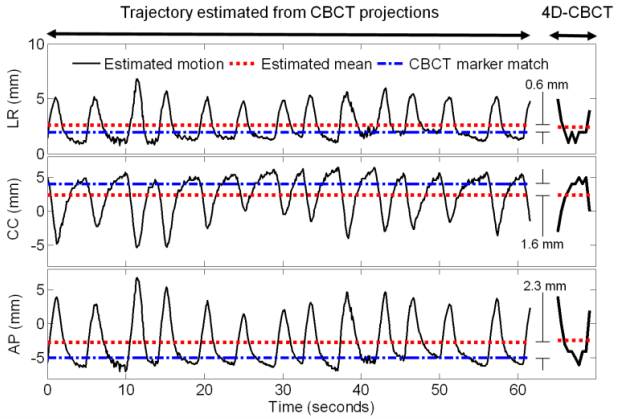
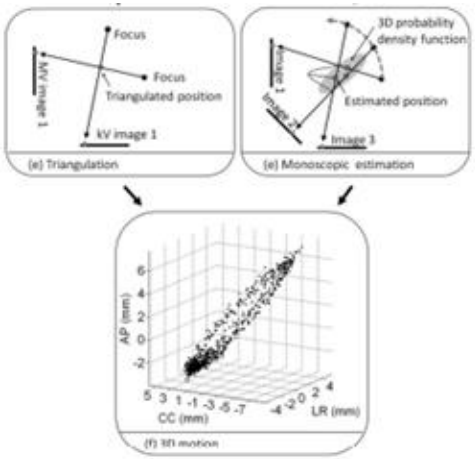
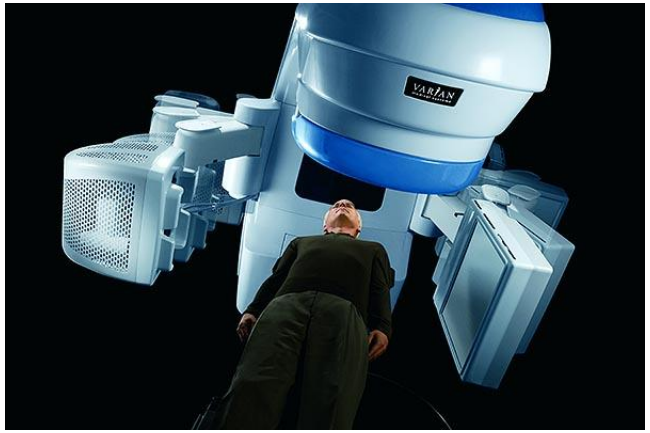
Set-up based on 3D marker trajectory estimation from cone-beam CT



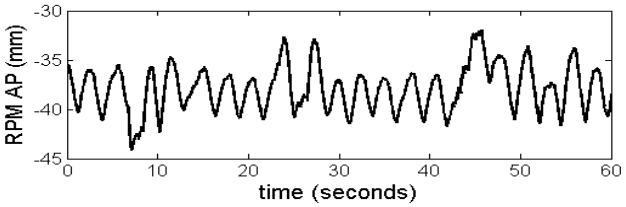


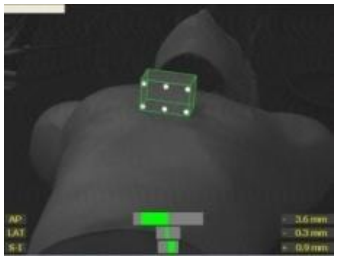
Probability density function





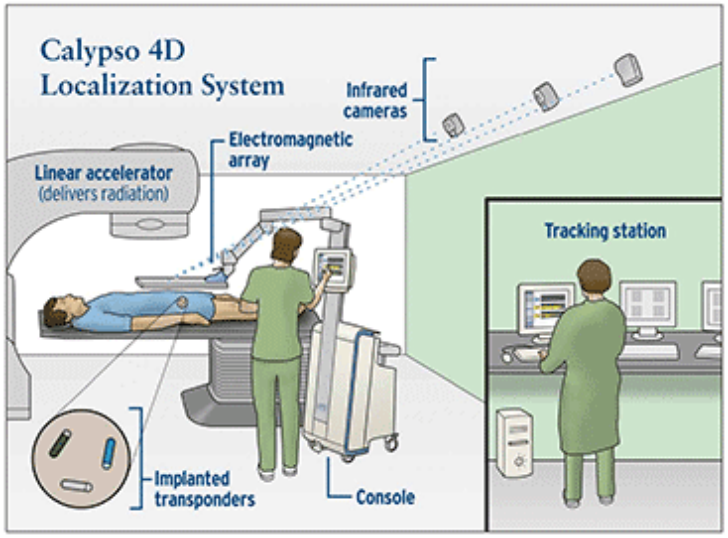
Correlation model: ext - int

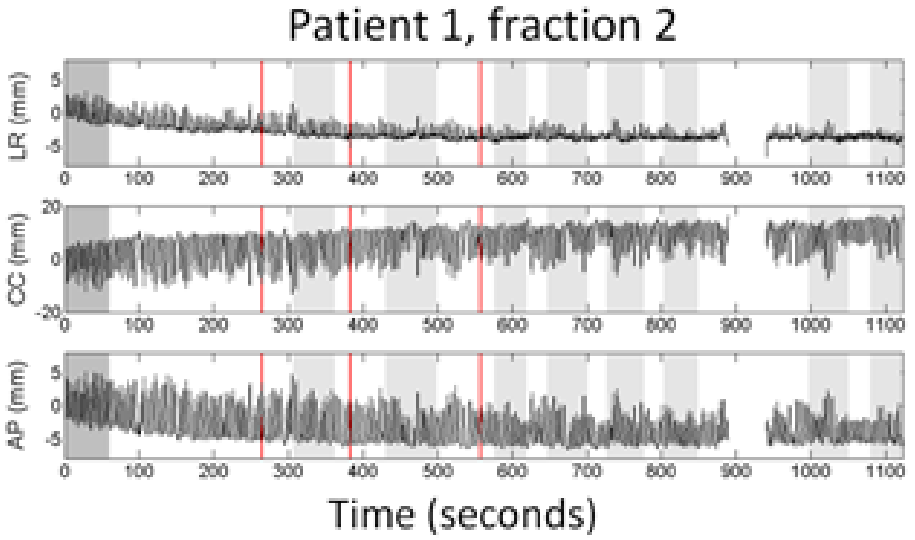


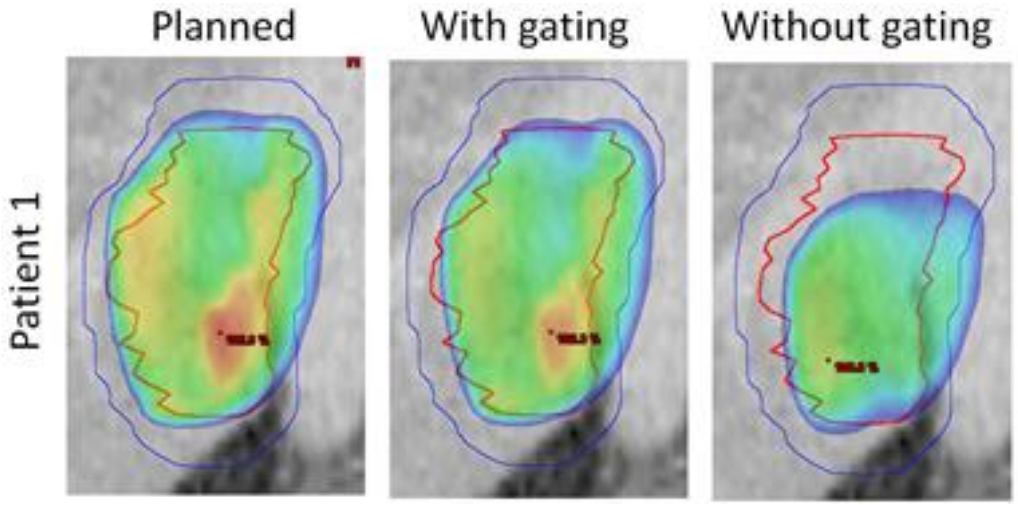


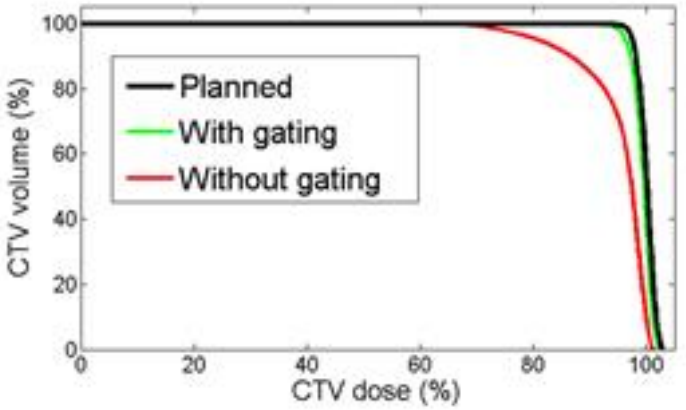
Poulsen et al. Phys Med Biol 2008; 53(16):4331
Esben Worm IJROBP 2012; 83(1): e145

Electromagnetic transponder based respiratory gating in SBRT for liver tumors



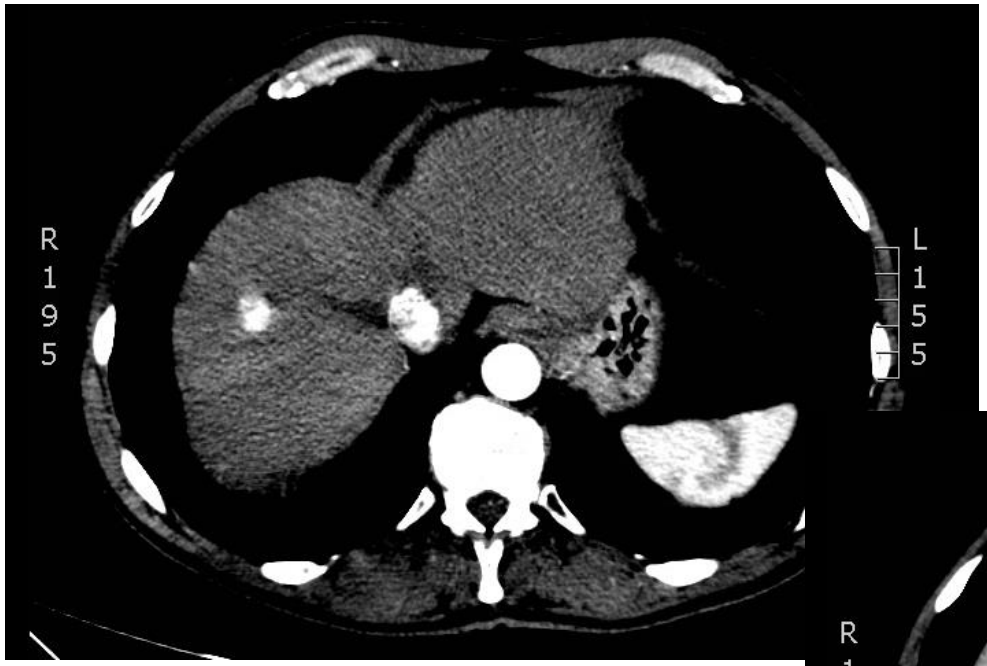




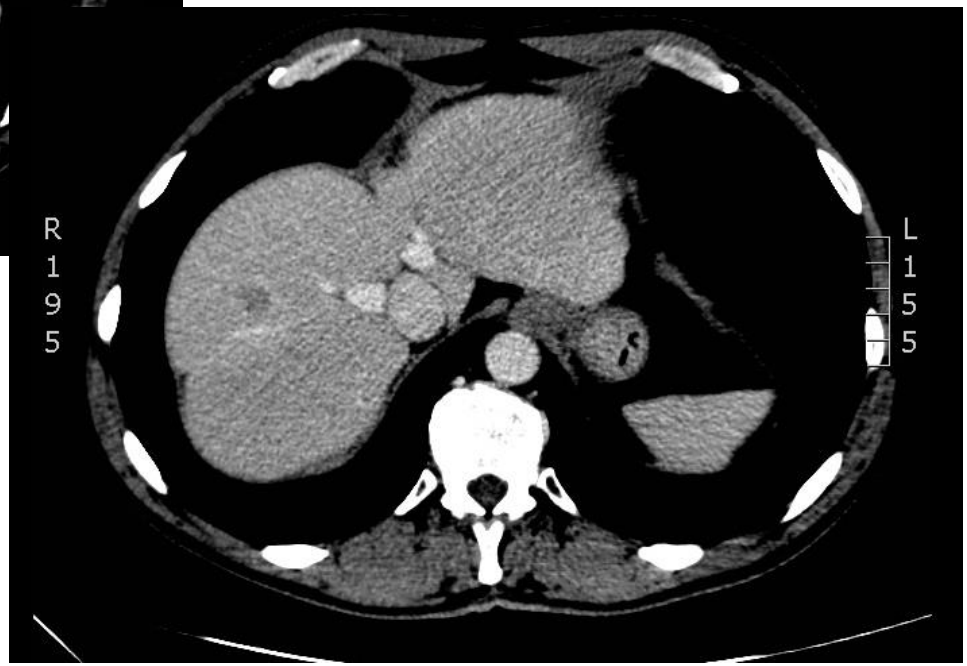


Per R. Poulsen et al; Acta Oncol 2016

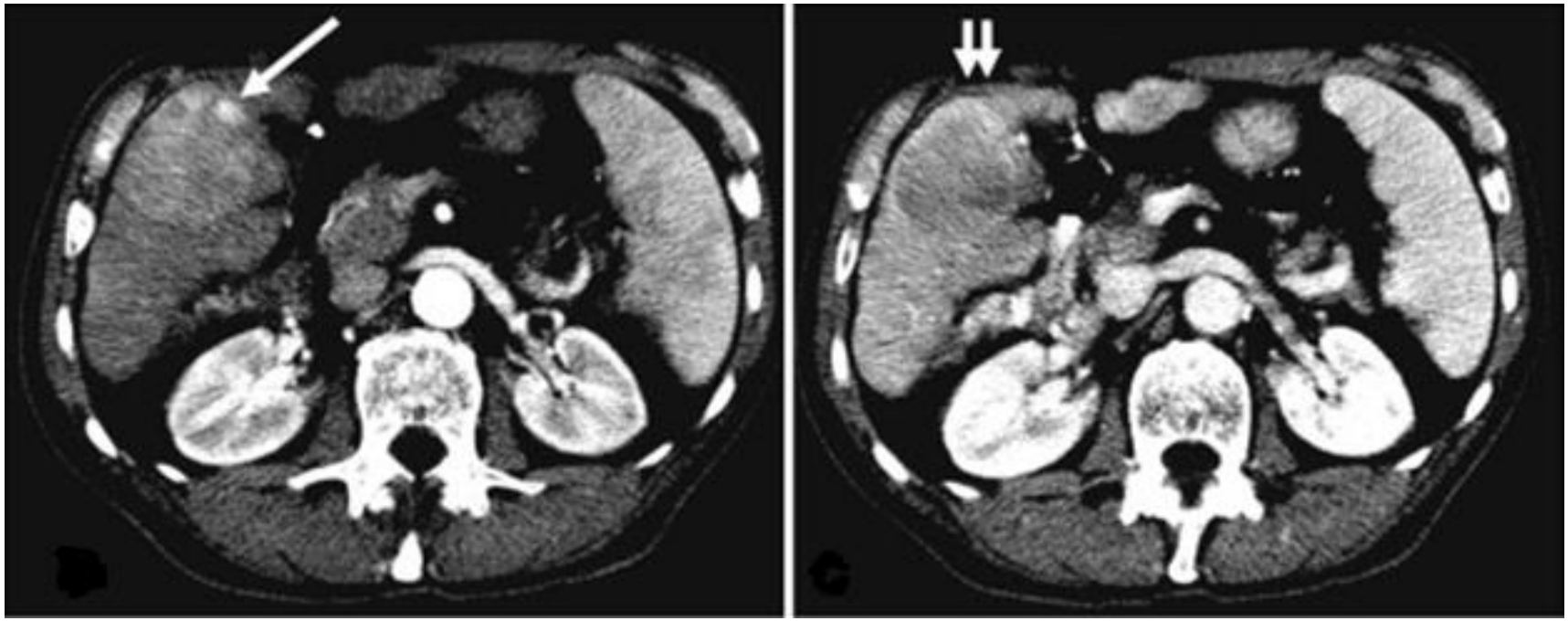
Contrast enhanced CT scan



HCC on contrast enhancement in arterial phase. Wash-out in porta-venous phase

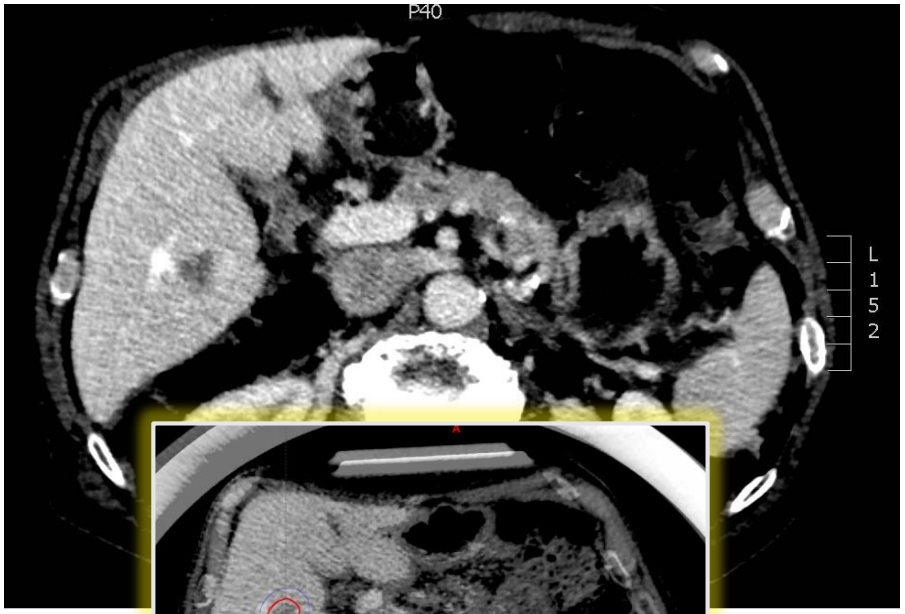


Use both arterial and porta-venous phases!

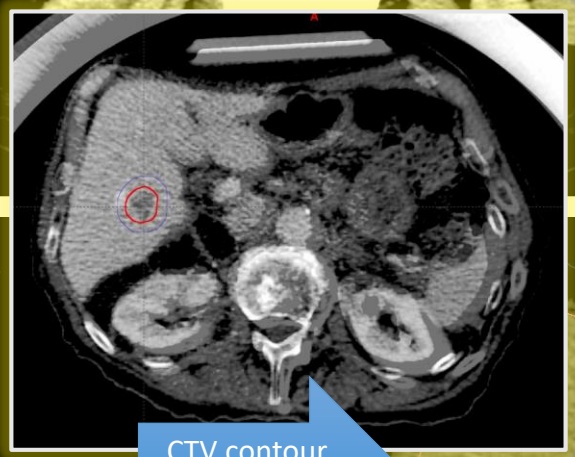


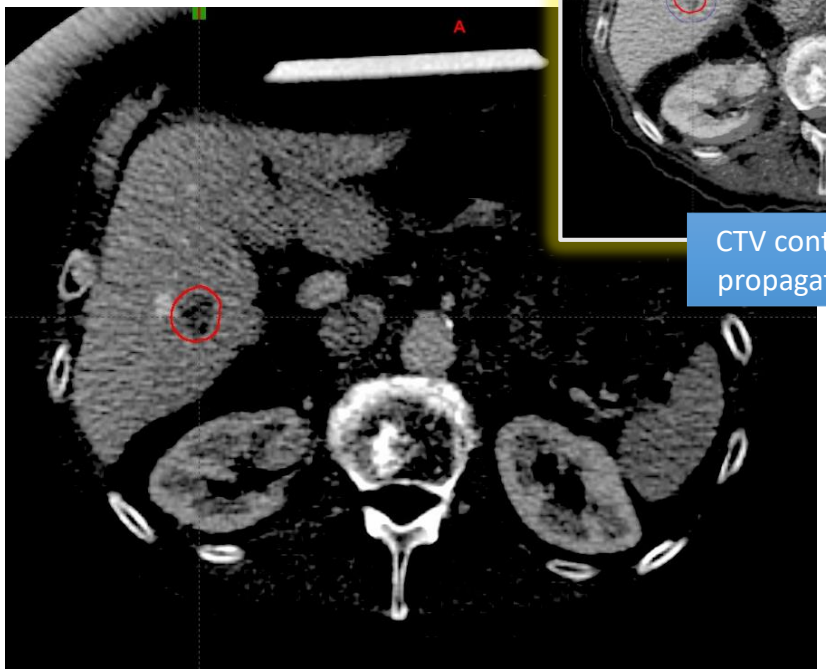
HCC in cirrhotic liver

Colorectal liver metastases on contrast enhanced CT scan in porta-venous phase.
Two window-settings.

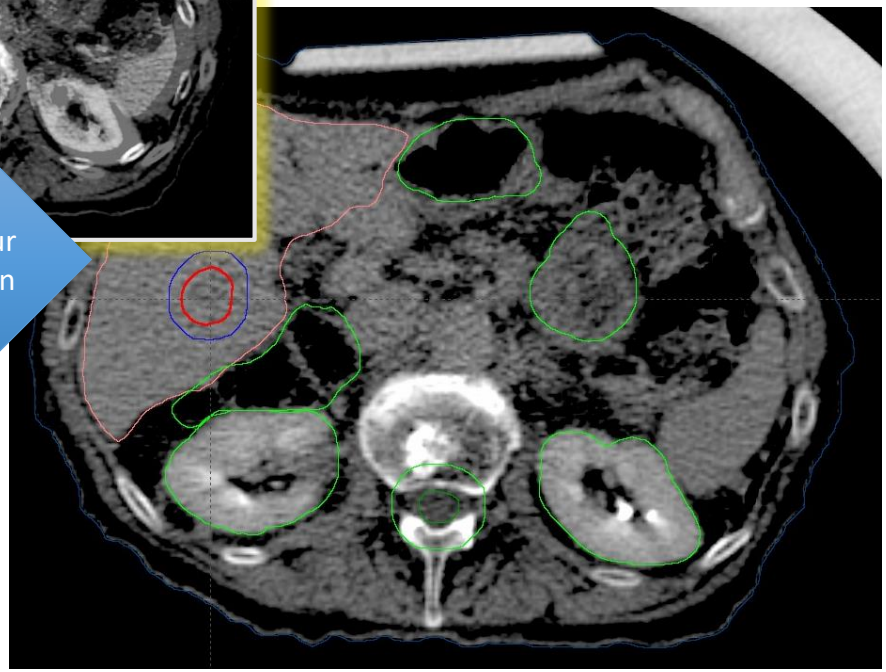


Diagnostic
CT scan





CTV contour
propagation

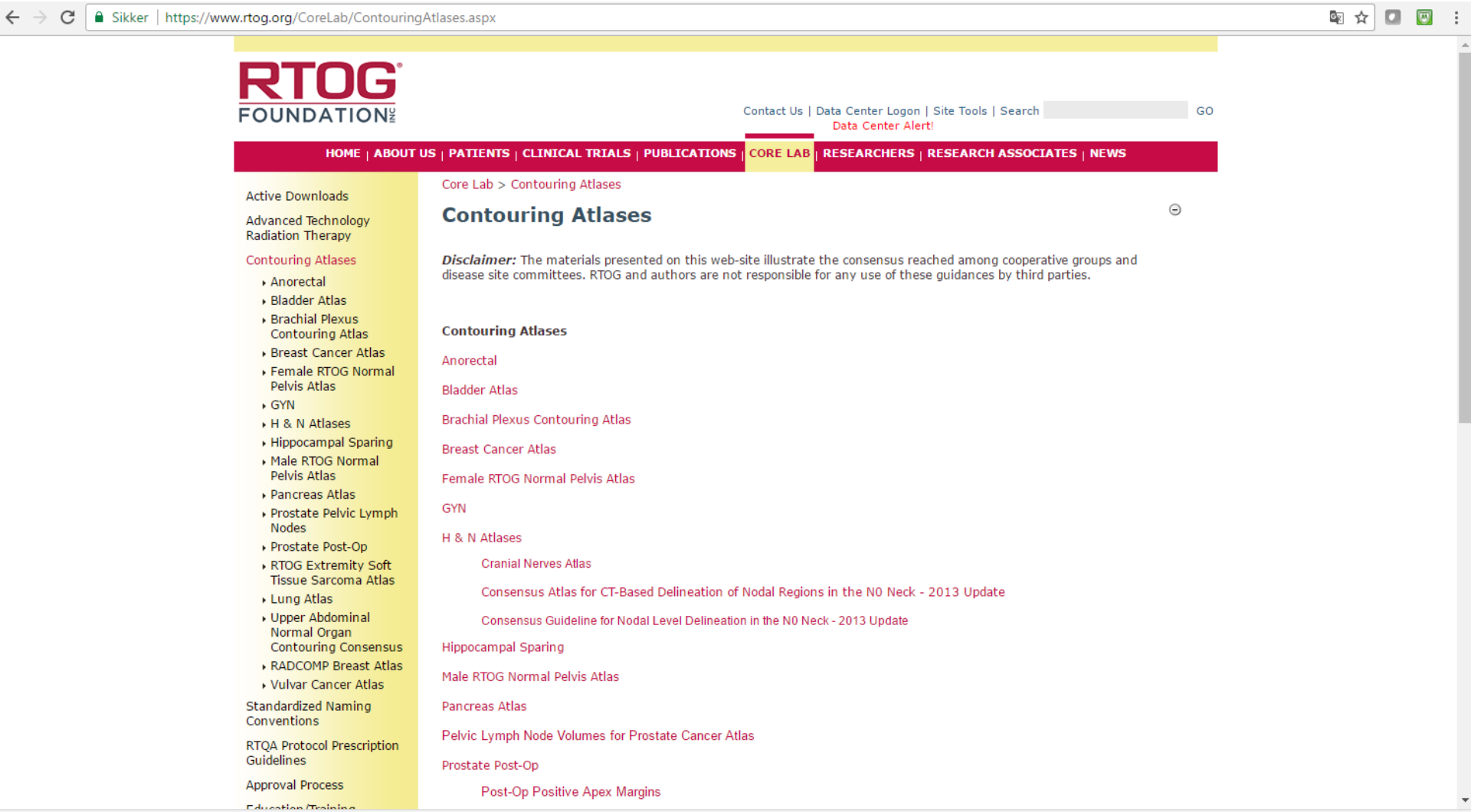


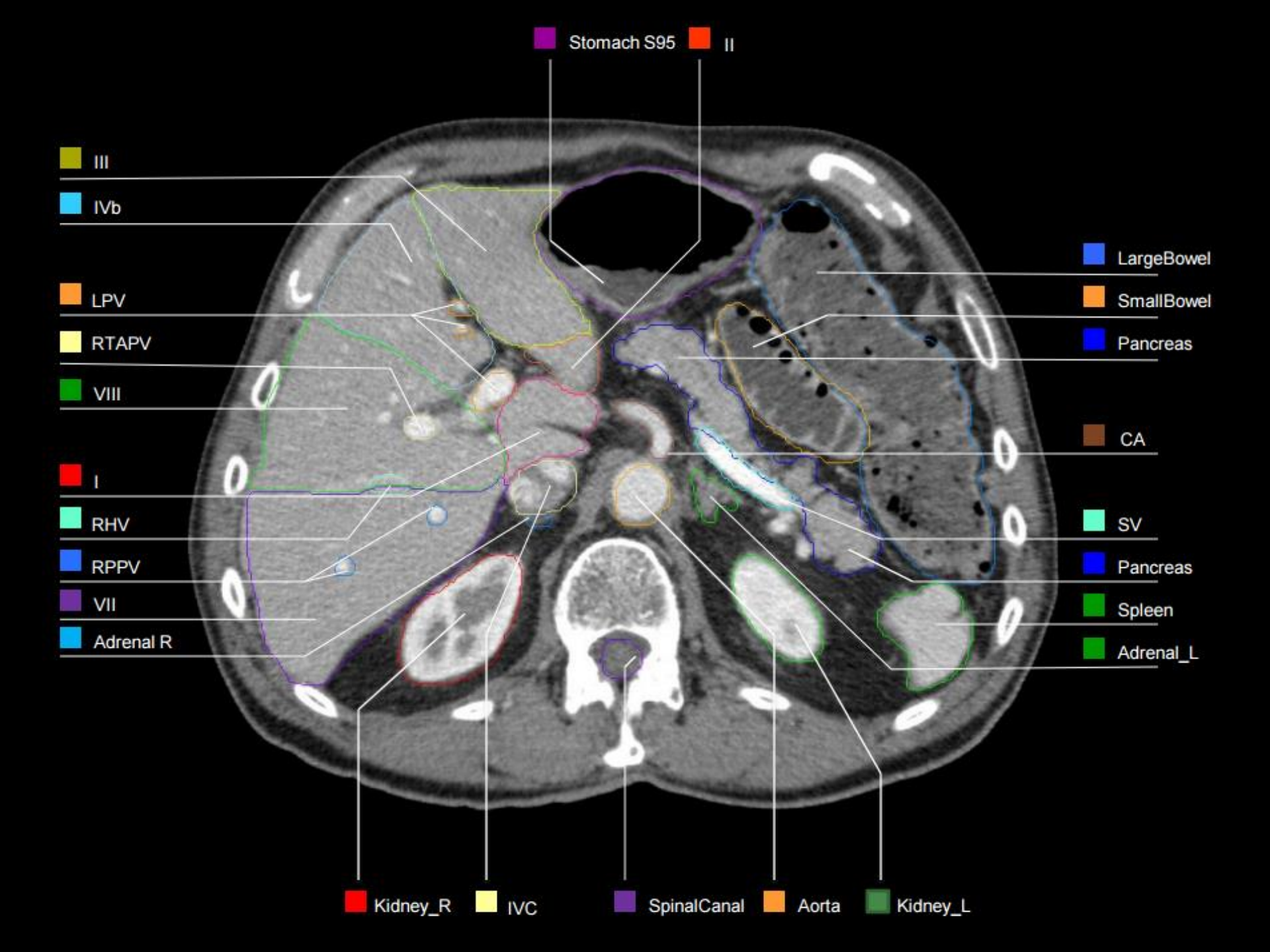
Treatment plan CT scan (breath-hold w. contrast enhancement)

Treatment plan CT scan (mid-vent bin)

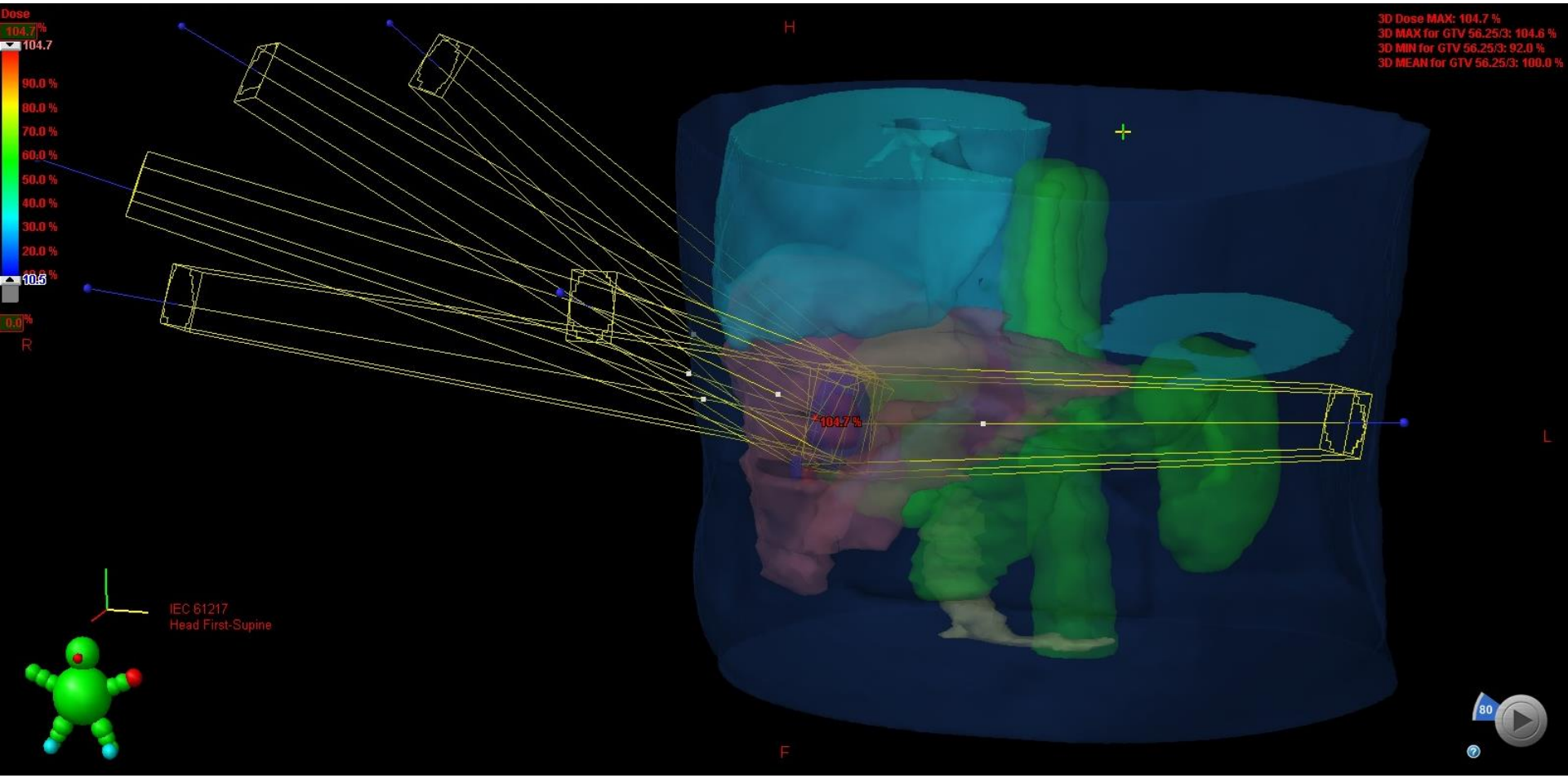
RTOG contouring atlas

https://www.rtog.org/CoreLab/ContouringAtlases.aspx

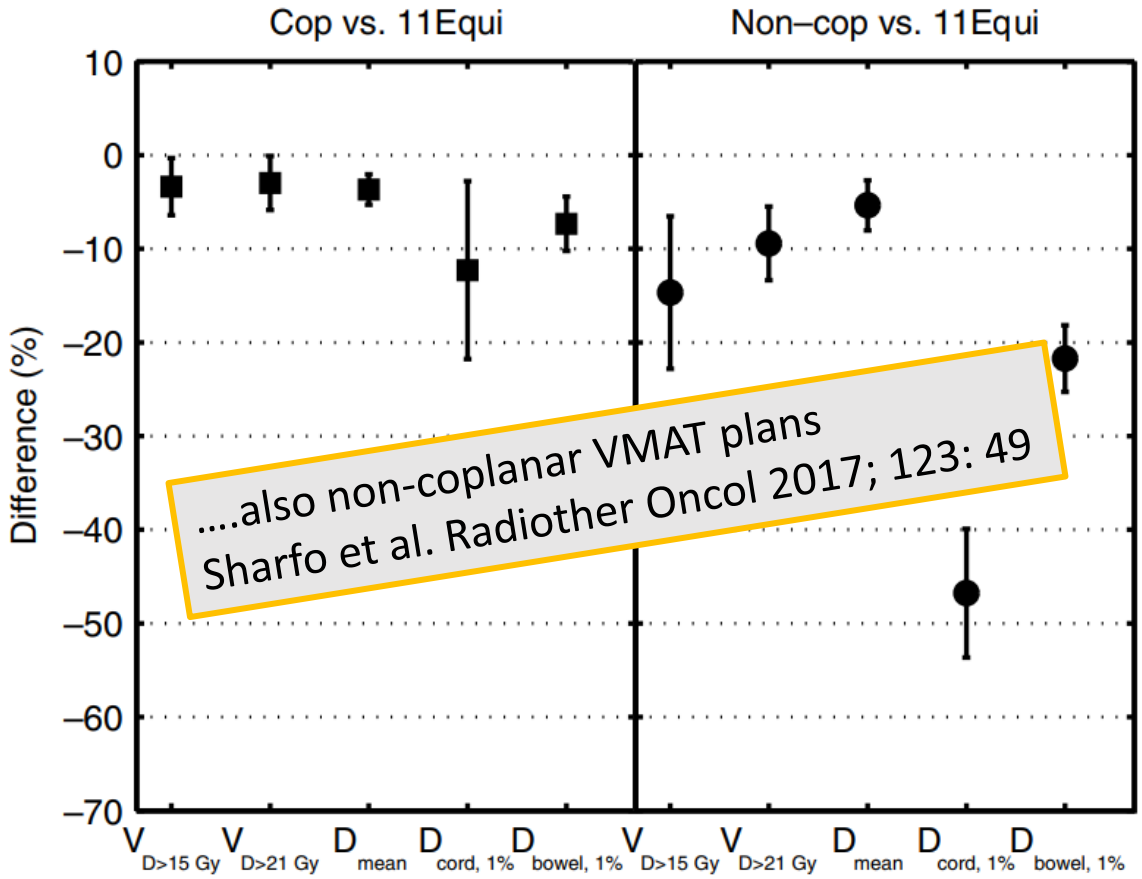



Stomach S95
II
III
IVb
LPV
RTAPV
VIII
I
RHV
RPPV
VII
Adrenal R
LargeBowel
SmallBowel
Pancreas
CA
SV
Pancreas
Spleen
Adrenal_L
Kidney_R
IVC
SpinalCanal
Aorta
Kidney_L

Non-coplanar beam arrangement

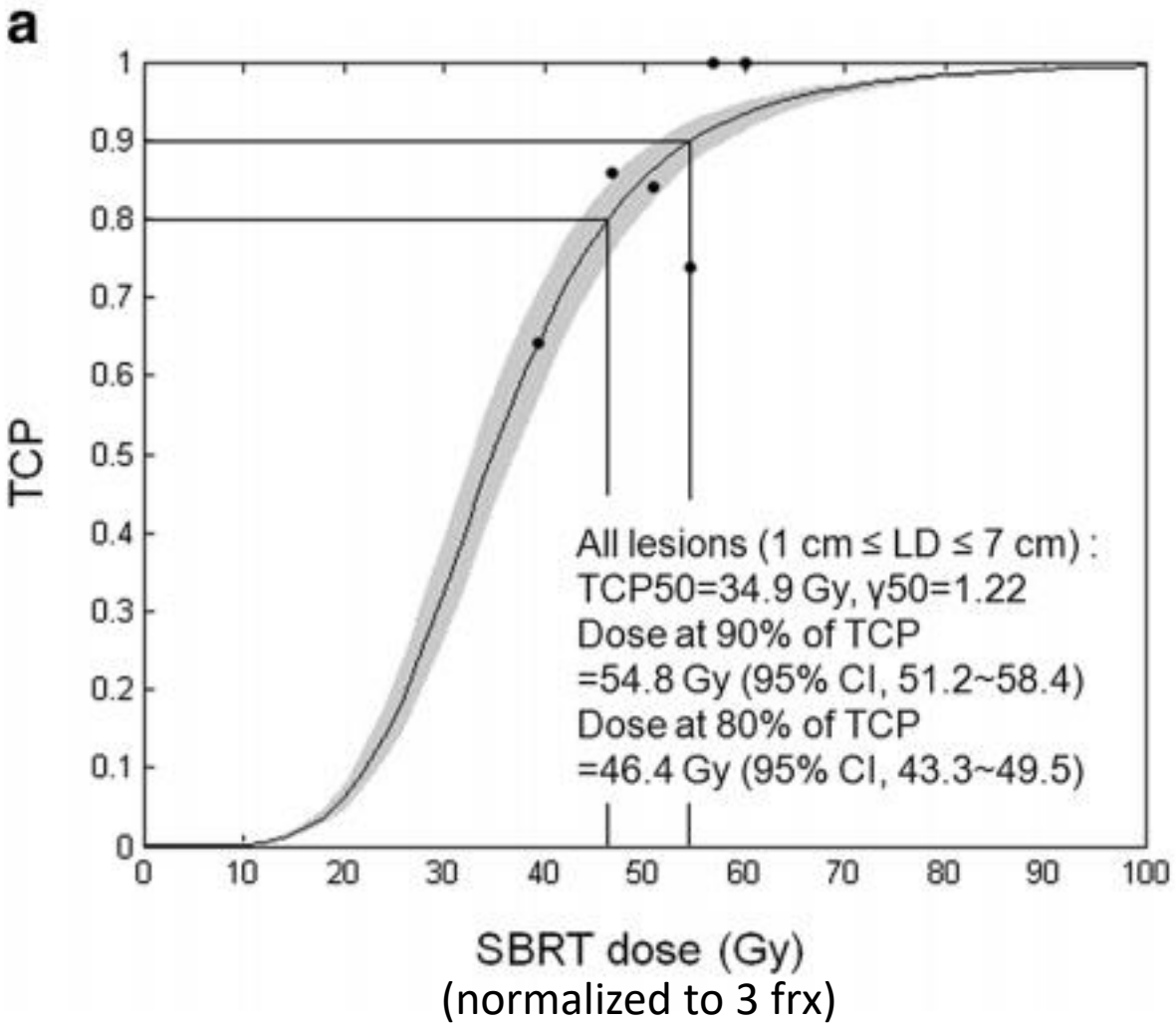


Coplannar or non-coplanar



De Pooter et al Radiother Oncol 2008; 88: 376

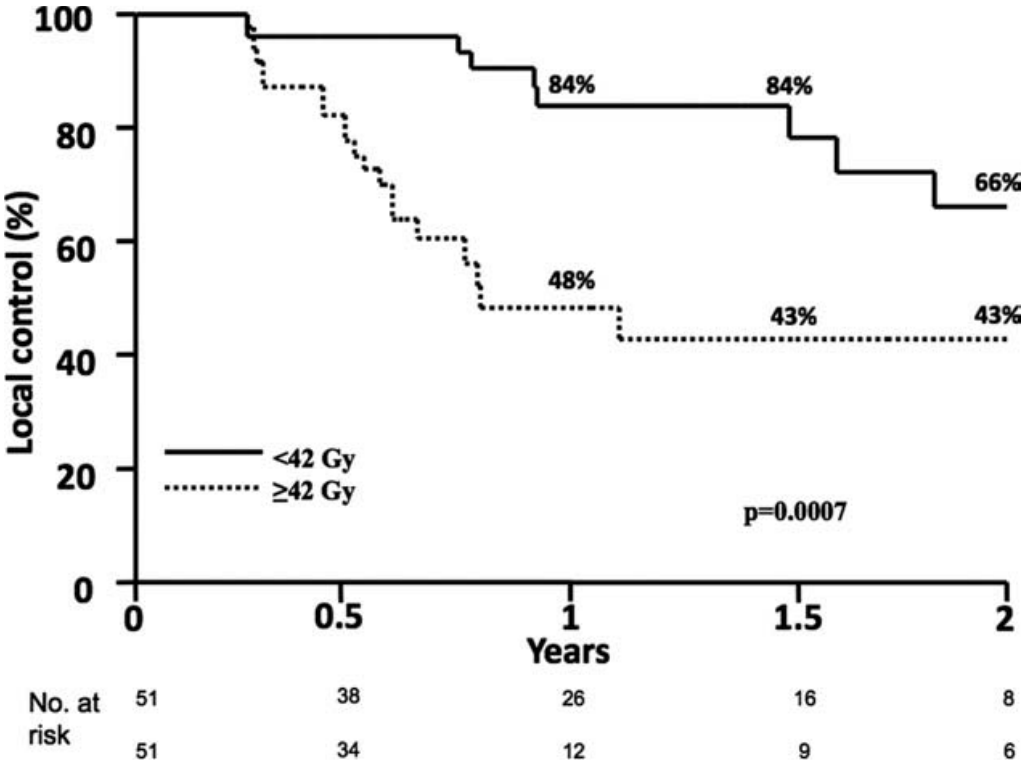
Dose-effect in SBRT for HCC



Jang et al. Radiother Oncol 2013; 8:230

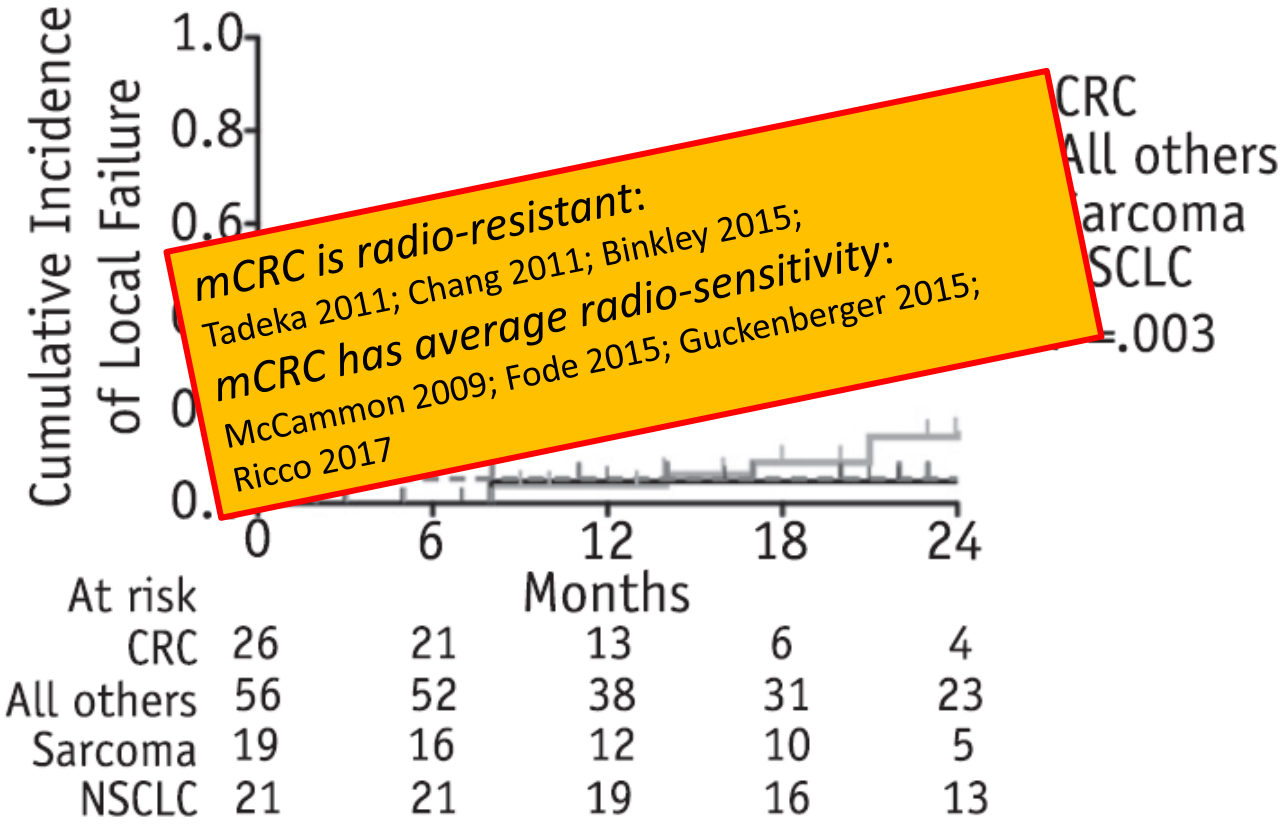
Radiation dose and local control in mCRC

65 mCRC patients



Chang et al. JCO 2011; 117: 4060

Local failure by histology

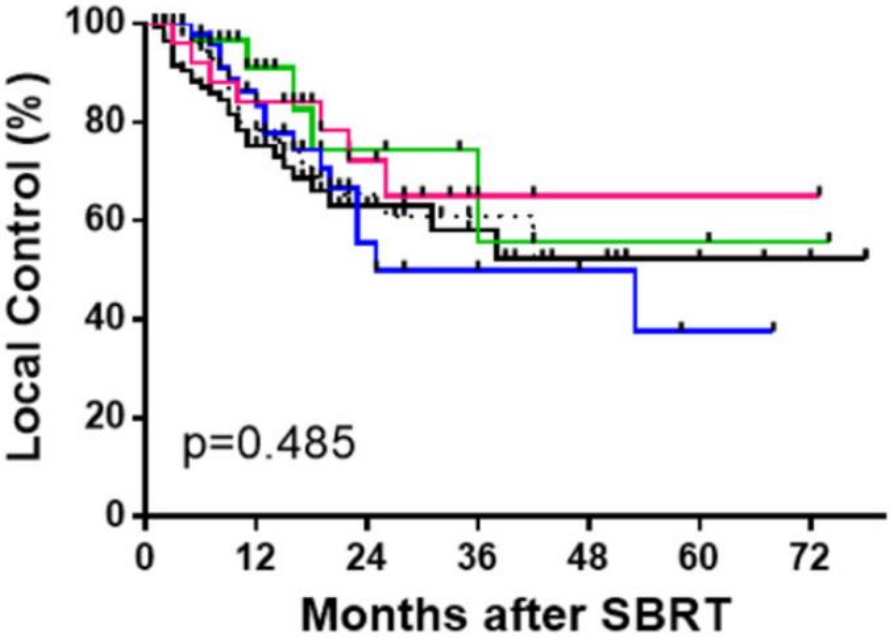


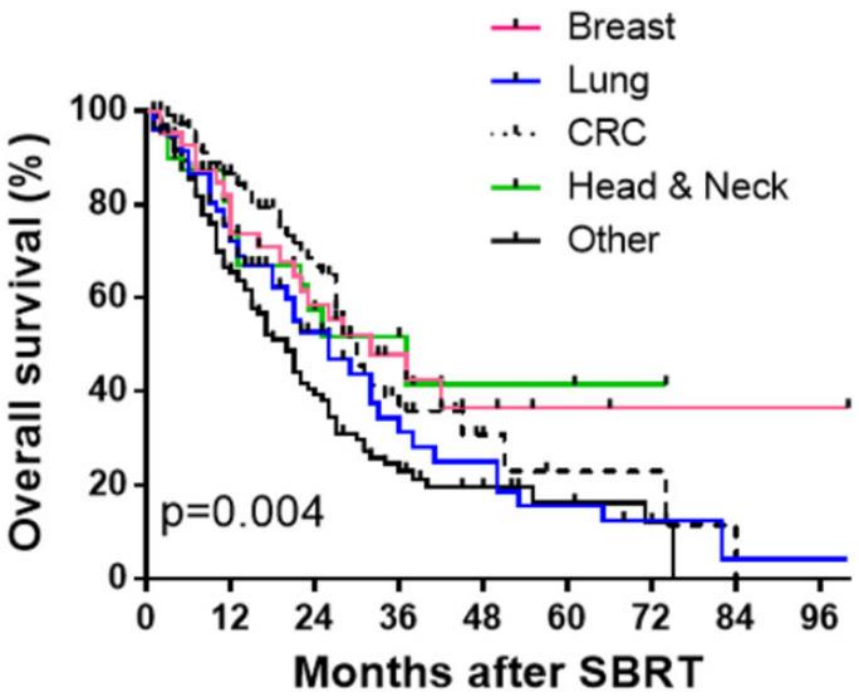
mCRC is radio-resistant:
Tadeka 2011; Chang 2011; Binkley 2015;
mCRC has average radio-sensitivity:
McCammon 2009; Fode 2015; Guckenberger 2015;
Ricco 2017

Competing risk analysis

Binkley et al. IJROBP 2015; 92(5): 1044

Local control and survival by histology





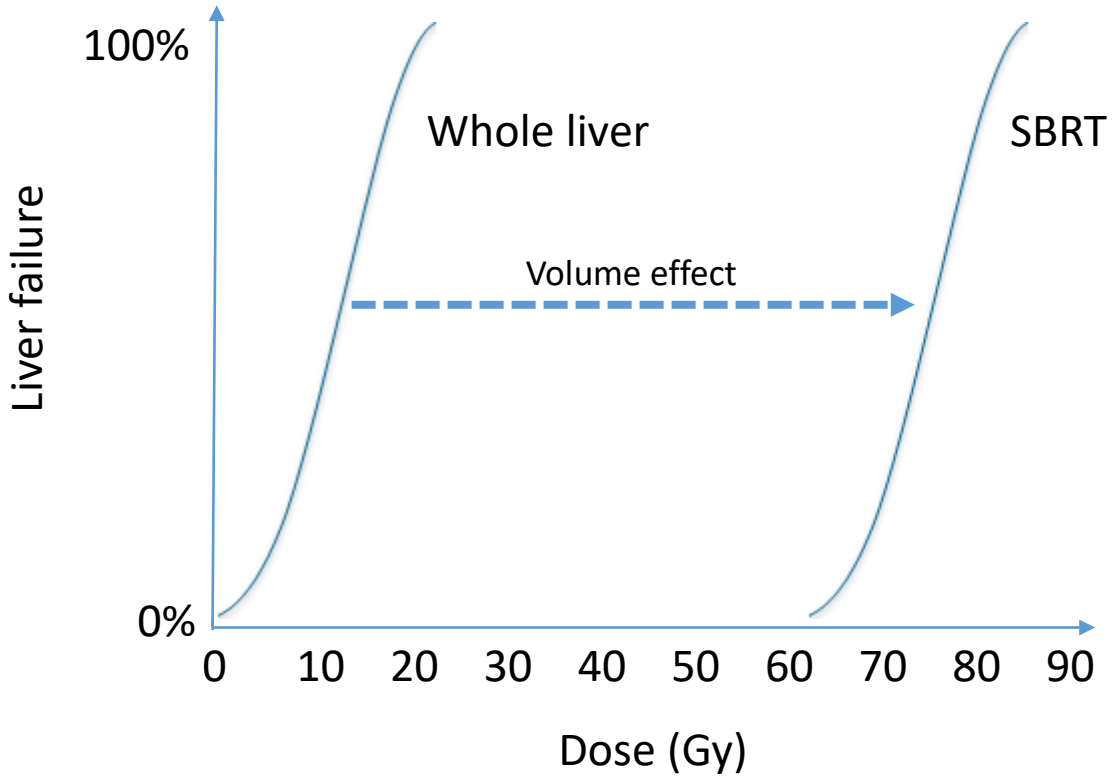
Multi-institutional database; 702 pts.

Ricco et al. Radiat Oncol 2017; 12: 35

OAR: Liver

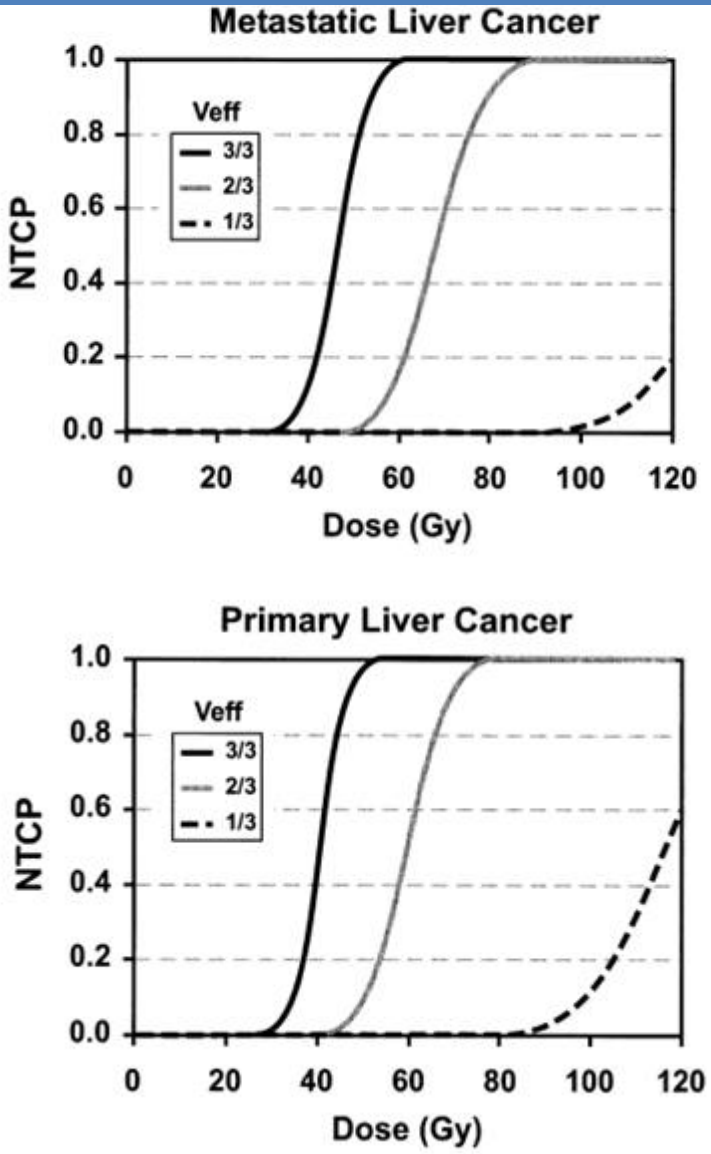
Risk of liver failure

Dose-response of normal liver with radiotherapy given in 3 fractions



Radiation tolerance with 2 Gy fraction radiotherapy of the liver: Dawson et al. **Int J Radiat Oncol Biol Phys 2002;53:810-821**

NTCP based dose prescription
Risk adapted



The risk of RILD calculated using LymanKutcher-Burman (LKB) NTCP model parameters for RILD obtained from patients treated at 1.5 Gy per fraction (n/0.97, m/0.12, TD50 (metastases)/45.8 Gy, TD50 (primary cancer)/39.8 Gy)

Conventional fractionation:

- TD_{50} in metastases patients < 46 Gy
- TD_{50} in primary liver cancer < 40 Gy
  - Dawson et al. IJROBP 53: 810; 2002
- TD_{50} in non-HBV carriers: 50 Gy
- TD_{50} in HBV carriers: 46 Gy
  - Cheng et al. IJROBP 60:1502; 2004

Dawson et al. 2002

Published dose-volume constraints for HCC

Table 1. Published liver dose-constraint recommendations.

Study (year)	Design	Child–Pugh A			Child–Pugh B			Ref.
		Fractionation	*Constraint*	*Dose*	*Fractionation*	*Constraint*	*Dose*	
RTOG 1112	Phase III protocol	5 fx	Mean non-GTV liver	≤13 Gy if D = 50 Gy ≤15 Gy if D = 40–45 Gy ≤15.5 Gy if D = 35 Gy ≤16 Gy if D = 30 Gy ≤17 Gy if D = 27.5 Gy	NA	NA	NA	[38]
			Total liver minus GTV volume	≥700 cc				
			V10 of liver minus GTV	<70%				
Klein *et al.* (2013)	Review	3 fx	Mean non-GTV liver Dose to ≥800 cc of normal liver	≤13 Gy ≤18 Gy	4–6 Gy/fx	Mean non-GTV liver	≤6 Gy	[37]
		5 fx		≤13 Gy if D = 50 Gy ≤15 Gy if D = 40 Gy ≤16 Gy if D = 30 Gy				
Pan *et al.* (2010)	Review	3–5 fx	Dose to ≥700 cc of normal liver	≤15 Gy	4–6 Gy/fx	Mean non-GTV liver	≤6 Gy	[22]
		6 fx	Mean non-GTV liver	≤18 Gy				

D: Dose; fx: Fraction(s); GTV: Gross tumor volume; NA: Not available; RTOG: Radiation Therapy Oncology Group; V10: Volume receiving 10 Gy or more.

Klein et al. Future Oncol 2014; 10(14):2227

NTCP based dose prescription
Risk adapted

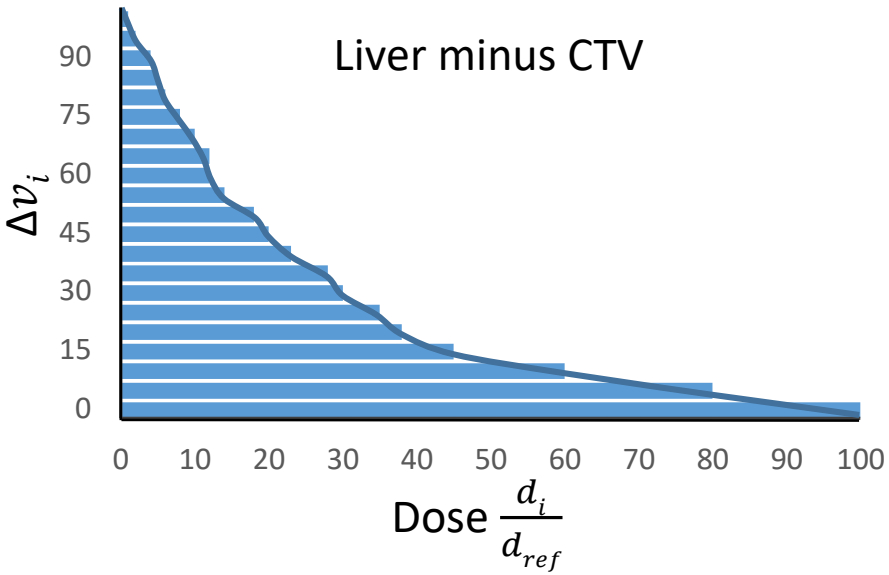
Veff: Effective irradiated liver volume (dose-weighted irradiated volume)

$$V_{eff} = \sum_i \Delta v_i \left(\frac{d_i}{d_{ref}} \right)$$

C-P 6 pts

Veff max 60% (80% in Trial 1)

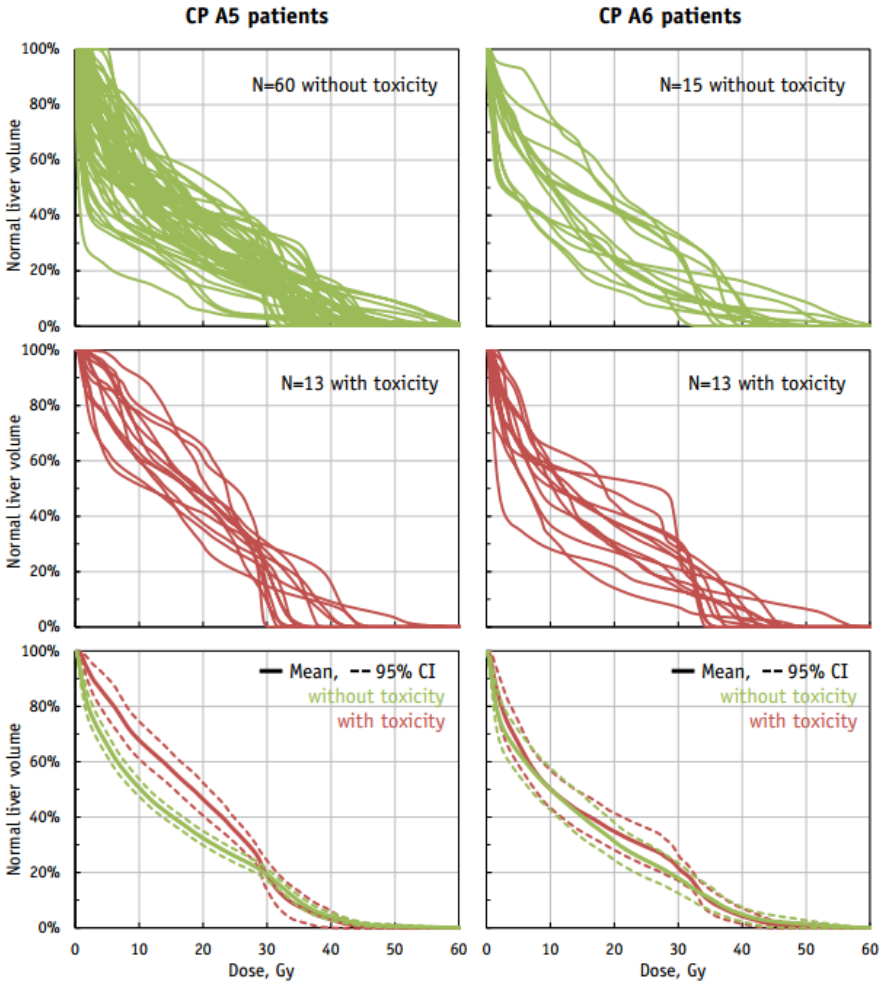
Liver Veff	Prescription dose
<25	6 x 9.0 Gy
25-30	6 x 7.5 Gy
30-40	6 x 6.5 Gy
40-50	6 x 5.5 Gy
50-60	6 x 5.0 Gy
>60	Not suitable

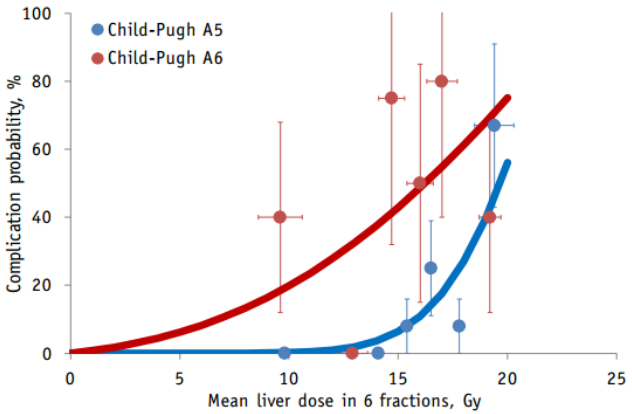


Laura Dawson, PMH Toronto

Prediction of liver toxicity

Increase in C-P score ≥2 at 3 months; 6 fractions



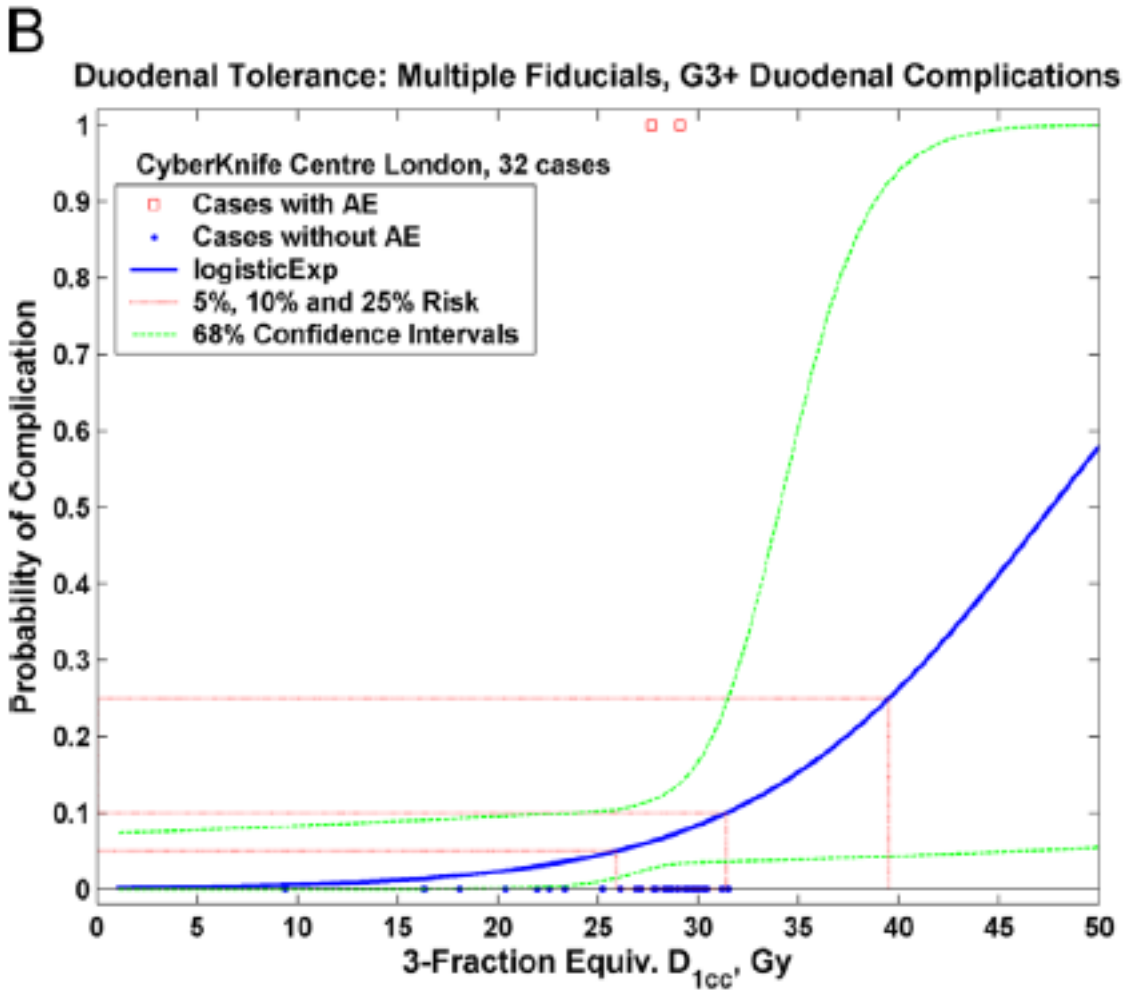


A5		Mean Liver Dose (Gy)						
		≤ 15	≤ 16	≤ 17	≤ 18	≤ 19	≤ 20	≤ 21
D800cc (Gy)	≤ 5	0% (0/17)	0% (0/22)	0% (0/25)	3% (1/29)	6% (2/31)	6% (2/31)	6% (2/32)
	≤ 10	0 % (0/22)	0% (0/30)	0% (0/36)	5% (2/43)	7% (3/45)	7% (3/45)	7% (3/45)
	≤ 15	0% (0/24)	3% (1/34)	2% (1/41)	6% (3/51)	7% (4/56)	7% (4/57)	7% (4/57)
	≤ 20	0% (0/24)	3% (1/35)	5% (2/43)	8% (4/53)	10% (6/60)	11% (7/62)	13% (8/63)
	≤ 25	0% (0/24)	3% (1/35)	7% (3/45)	9% (5/55)	11% (7/63)	12% (8/65)	16% (11/68)
	≤ 30	0% (0/24)	3% (1/35)	7% (3/45)	9% (5/55)	11% (7/64)	13% (9/67)	18% (13/71)

Velec et al. IJOBP 2017; 97(5): 939

OAR: Duodenum

Logistic regression on morbidity data



Goldsmith et al. Semin Radiat Oncol 2016;26:149

Duodenal Doses

- Median time to duodenal toxicity: 6.2 mos
- 6- and 12-mo actuarial rates of toxicity: 11% and 29%

Variable*	Cutoff†	Incidence of Grade 2–4 duodenal toxicity (%)‡	Log-rank *p* value
V5			
	<25 cm^3	28	0.39
	≥25 cm^3	31	
V10			
	<16 cm^3	15	0.015
	≥16 cm^3	46	
V15			
	<9.1 cm^3	11	0.002
	≥9.1 cm^3	52	
V20			
	<3.3 cm^3	11	0.002
	≥3.3 cm^3	52	
V25			
	<0.21 cm^3	12	0.010
	≥0.21 cm^3	45	

* V5 refers to the volume of duodenum receiving 5 Gy.
† Cutoff refers to the median value.
‡ Actuarial incidence at 12 months.

Murphy J, *et al.*, IJROBP, 2012

Selecting patients with liver metastases for SBRT

Selection criteria for liver metastases

RFA

- <30 mm
- Not involving pediculae
- Not adjacent to v. cava
- Not adjacent to gall bladder

SBRT

- No specific restriction on size
- 700 ccm liver <15 Gy
- (Not adjacent to duodenum or stomach)

Conclusions

- Liver SBRT is more complex than lung SBRT
- Low risk of RILD in normal liver
- Moderate to high risk of RILD in cirrhotic liver
- The liver is the most important OAR in patients with cirrhosis
- The duodenum and stomach are the most important OARs in patients treated for livermetastases

- Fractionation and planning procedure for locations like adrenals, **liver**, skeleton etc
- Optimal SBRT fractionation in different organs and dose constraints for OAR
- How to select patients suitable for liver SBRT

Department of Radiation Oncology
Chairman: Prof. Dr. Matthias Guckenberger

SBRT for pancreatic cancer

UniversityHospital Zurich

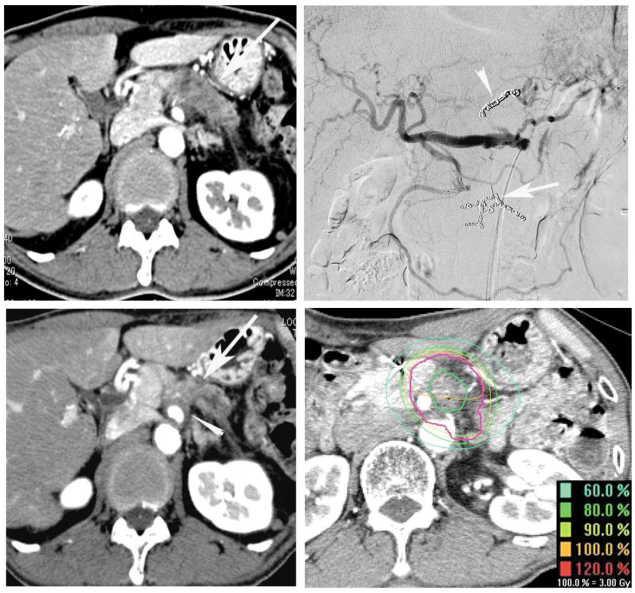
ESTRO

Question 1

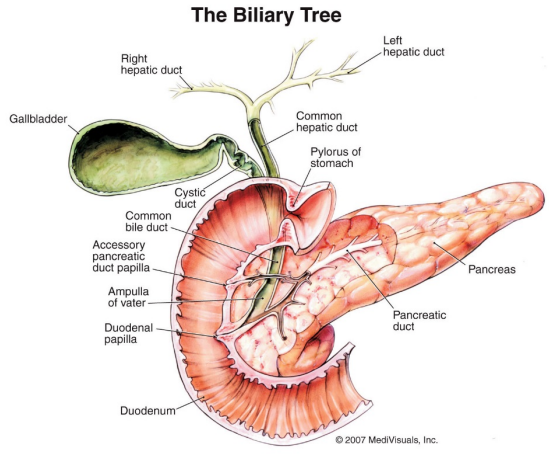
Which answer is correct in pancreatic SBRT?

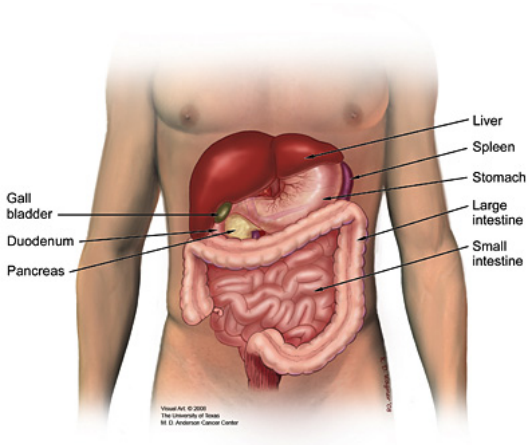
1. SBRT should not be performed outside of clinical trials due to the risk of duodenal toxicity
2. Single fraction SRS is preferred compared to fractionated SBRT.
3. SBRT has replace the need for systemic treatment.

Pancreatic cancer



Pancreatic cancer

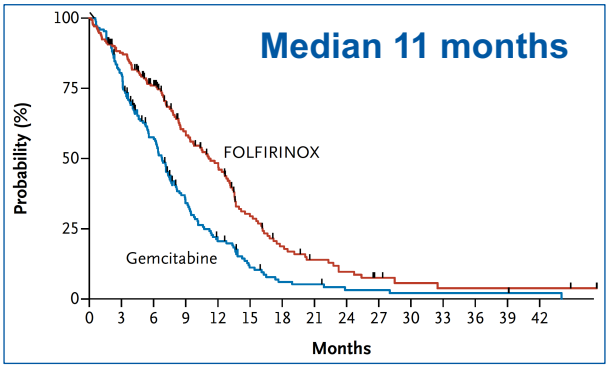




- Location: head 75% tail 25%
- Critical OARs VERY close to target: duodenum, stomach, small bowel

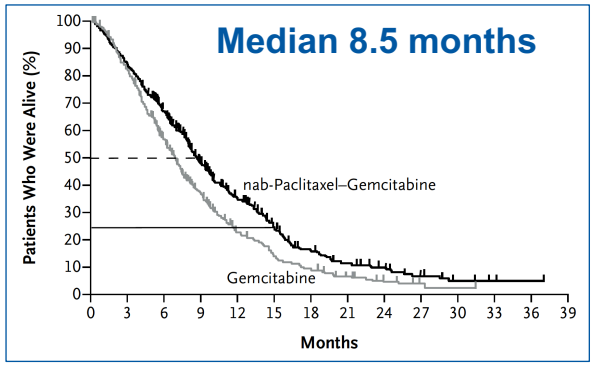
Pancreatic cancer – CT only

FOLFIRINOX



Conroy NEJM 2011

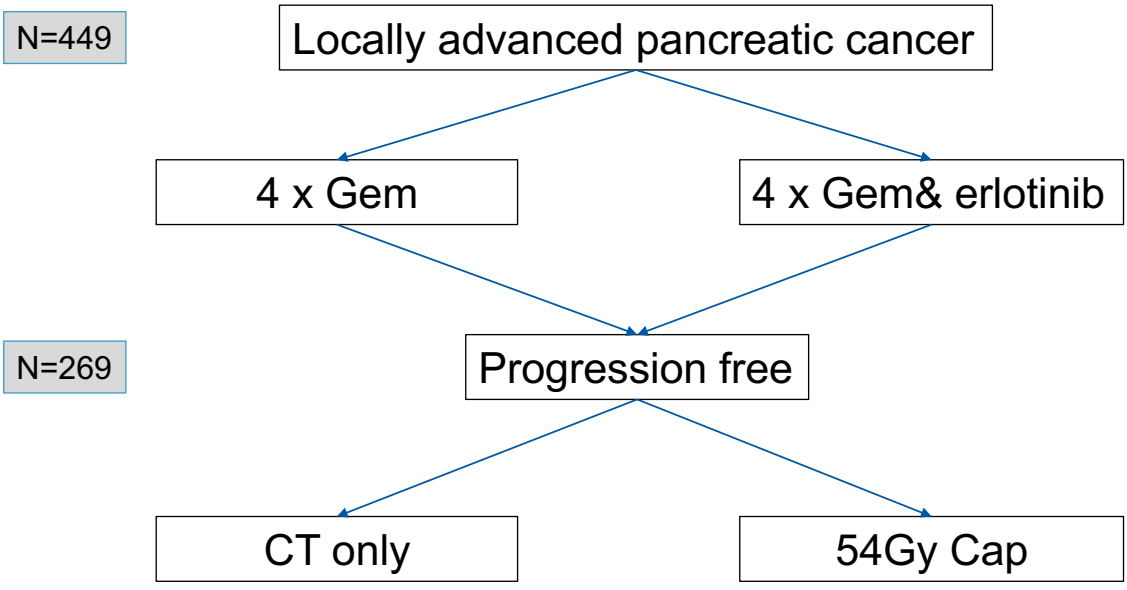
Nab-Paclitaxel



Von Hoff NEJM 2013

- Median OS of 9 – 11 months in metastatic pancreatic cancer with CT alone

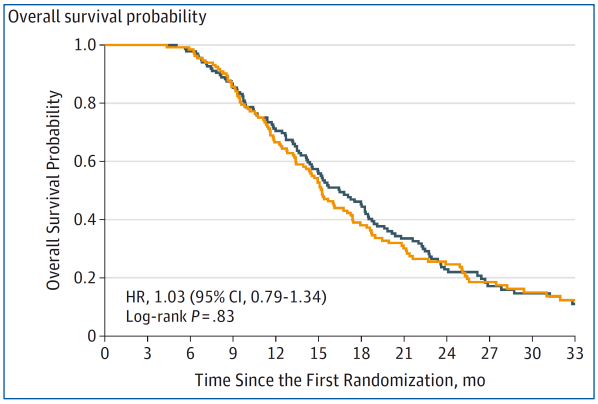
Pancreatic cancer – LAP 007



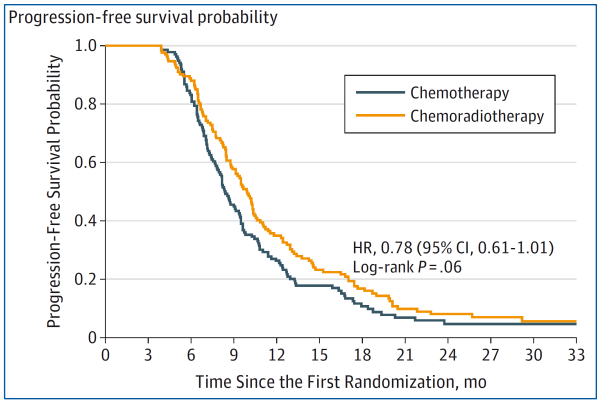
➢ Rapid progression of 1/3 of the patients

Pancreatic cancer – LAP 007

Overall survival



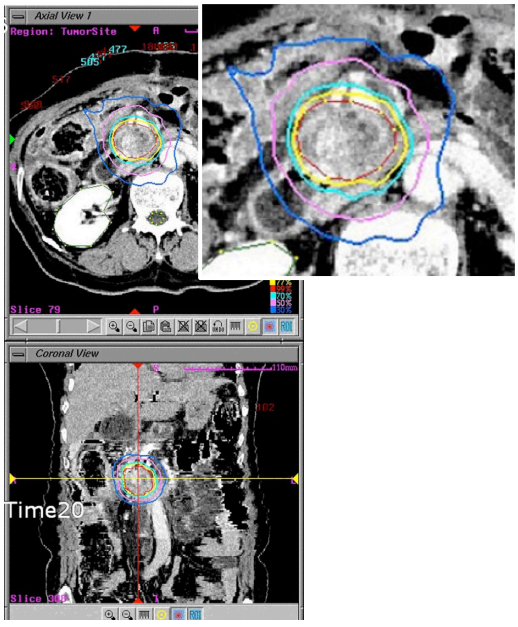
PF survival



Hammel YAMA 2016

- RCHT well tolerated
- No improvement of OS, median 15 – 16.5 mo
- Boarderline improvement of PFS

Pancreatic cancer



Published illustration of pancreatic SBRT:

No (obvious) safety margin:
- Imaging for extension of diease?
- Microscopic disease?
- Residual uncertainties?

Despite small (zero) safety margin:
- Full dose to adjacant duodenal wall
- Relevant doses to intestine

SBRT for locally advanced pancreatic cancer

	Study	Patients	Dose	Chemotherapy
Hoyer 2005	Phase II	22	3 x 15Gy	None
Koong 2005	Phase II	17	45Gy CF 1 x 25Gy Boost	5-FU during CF-RT
Schellenberg 2008	Phase II	16	1 x 25Gy	Between Gem
Schellenberg 2011	Phase II	20	1 x 25Gy	Between Gem

- Very small patient numbers
- How to integrate into systemic treatment ?

SBRT for locally advanced pancreatic cancer

	Study	Patients	Median OS	LC
Hoyer 2005	Phase II	22	5.4 months	57% @ 6m
Koong 2005	Phase II	17	8.3 months	16 / 17
Schellenberg 2008	Phase II	16	11.4 months	81%
Schellenberg 2011	Phase II	20	11.8 months	94% @ 1a

- (Very) short OS – similar to systemic treatment only
- Interpretation of promising LC considering OS ?

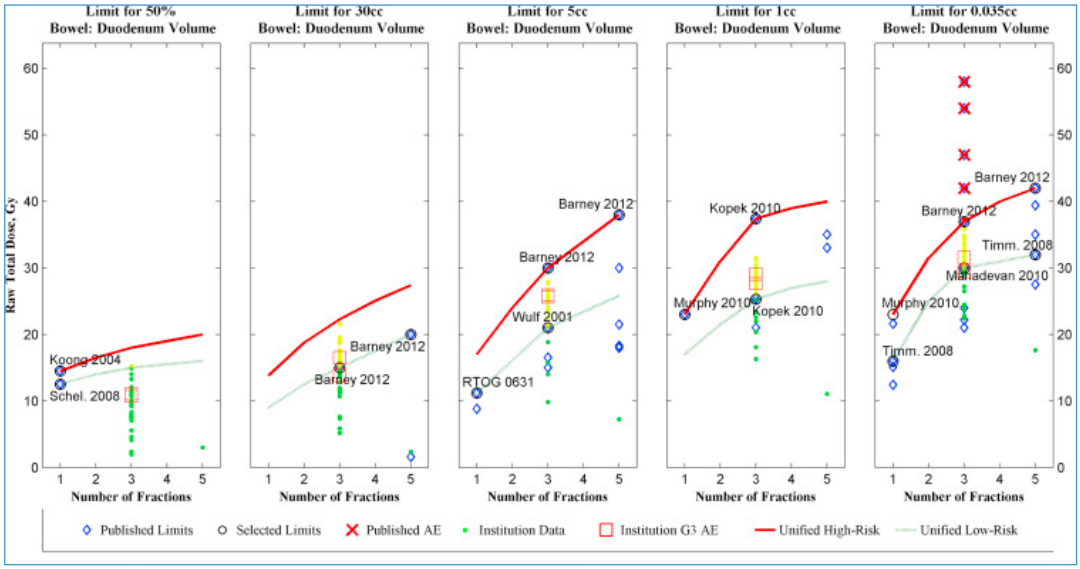
SBRT for locally advanced pancreatic cancer

	Study	Patients	Toxicity
Hoyer 2005	Phase II	22	5 cases with severe GI tox
Koong 2005	Phase II	17	2/17 acute G3 GI
Schellenberg 2008	Phase II	16	Late: 5x G2 ulcers 1x G3 duodenal stenosis 1x G4 duodenal perforation
Schellenberg 2011	Phase II	20	3x G2 ulcers 1x G4 duodenal perforation

- (Very) high rates of GI toxicity DESPITE short FU
- Difficult (impossible) sparing of duodenum

Duodenal toxicity - dose constraints

Goldsmith Sem Radiat Oncol 2016

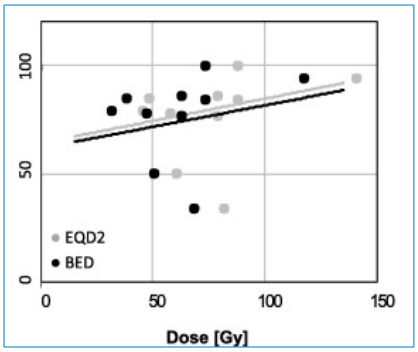


Issues:
- Validation, motion, short FU, chemotherapy, …

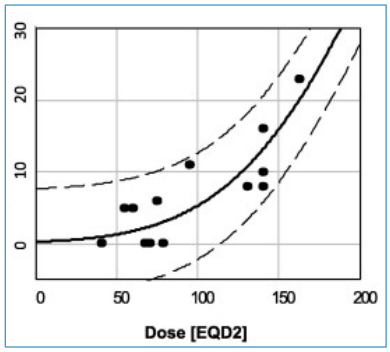
SBRT for locally advanced pancreatic cancer

Systematic literature review: 20 trials / 721 patients

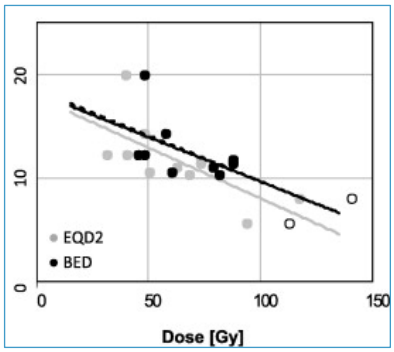
Local control



> G2 toxicity



Overall survival



More SBRT dose results in …

- Slightly better local control
- Substantially incerased toxicity
- Worse overall survival

Brunner Radiother Oncol 2015

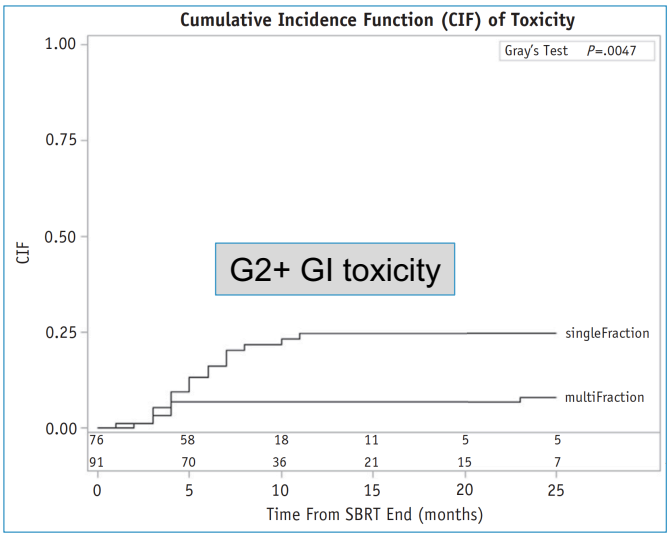
Duodenal toxicity – fractionation

Stanford experience

167 patients

Fractionation	Schema
1 Fx (46%)	1 x 25 Gy
5 Fx (54%)	5 x 6.6 Gy

Pollom IJROBP 2014



- Increased toxicity in SF compared to MF SBRT
- Toxicity risk factor for reduced OS

SBRT to achieve resectability

Borderline resectable
Locally advanced

Gem Cx

- Progression → CX
- No progression → **SBRT**

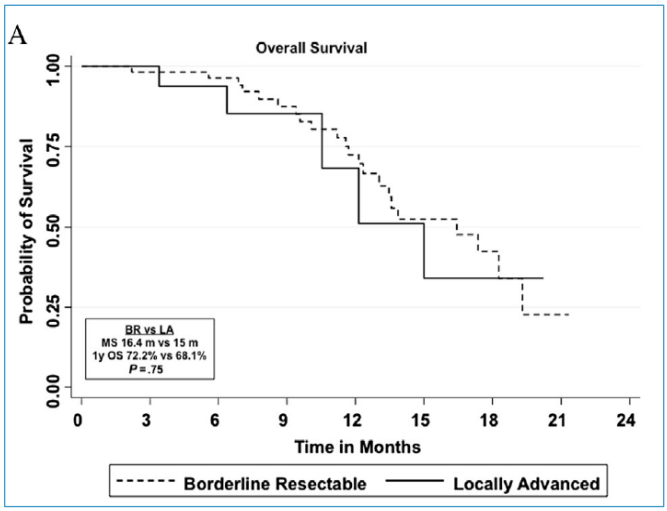
SBRT: 5 x 7Gy to vessle abutting region
5 x 5Gy to remaining tumor

Chuong IJROBP 2013

- N=73 with median FU 10.5 months
- Borderline resectable PC: 31/57 achieved R0 resection
- Locally advanced PC: 0 patient underwent resection
- Late GI grade 3+ toxicity: n=4 (GI bleeding)

SBRT to achieve resectability

Chuong IJROBP 2013



Median OS:

- Borderline resectable PC: 16.4 months
- Locally advanced PC: 15 months

SBRT for locally advanced pancreatic cancer

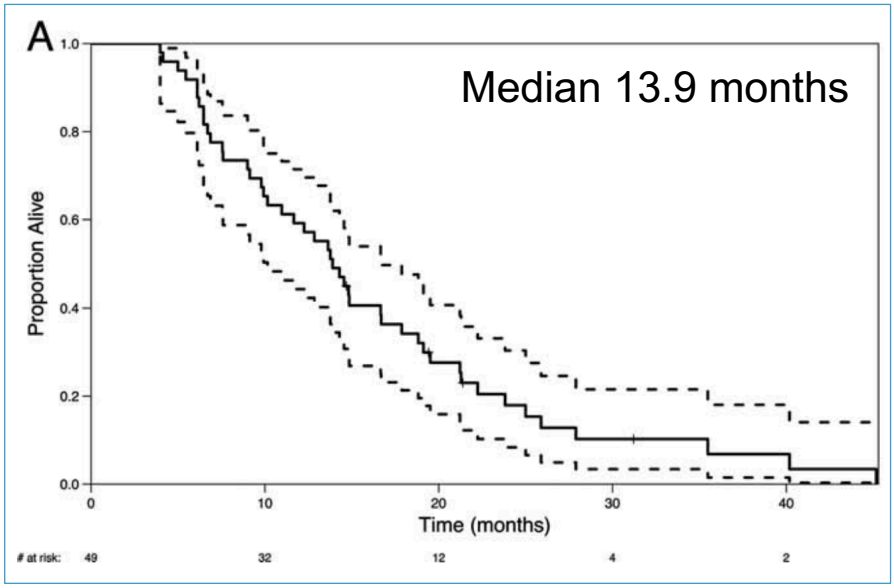
- Phase 2 multi-institutional study
- 49 pat. with locally advanced PC
  - 3 x Gem (1000mg/m2)
  - 1 week break
  - SBRT with 5 x 6.6Gy
- Median FU 14 months

Acute GI Tox G >=2	Late GI Tox G >=2
2%	11%

- Fractionated SBRT with lower SFD well tolerated

SBRT for locally advanced pancreatic cancer

Herman Cancer 2015



- Reasonable OS, despite not being overwhelming
- OS the only relevant endpoint?

SBRT for locally advanced pancreatic cancer

Analysis of National Cancer Data Base 2004 – 2012:

- unresected nonmetastatic pancreatic adenocarcinoma receiving chemotherapy
- CT alone or combined with EBRT, IMRT, SBRT
- Propensity Score matching: age, sex, race, comorbidity, insurance, type of treatment center, tumor location, and clinical stage

	CT	CT & EBRT	CT & IMRT	CT & SBRT
Median OS	10.2 mo	11.6 mo	12.2 mo	13.9 mo

De Geus Cancer 2017

- Addition of SBRT to CT improved OS compared CT alone or CT & EBRT

CONCLUSIONS

- Small patient numbers treated in prospective trials
- Local tumor control appears favourable
- Very limited overall survival, similar to Cx only
- High rates of severe GI toxicity

➢ **SBRT with <u>moderate intensity</u> to <u>complement</u> systemic Tx with <u>effective but well tolerated</u> local Tx**

➢ **Should not be practiced outside of prospective trials**

Department of Radiation Oncology
University Hospital Zurich
Chairman: Prof. Dr. Matthias Guckenberger

SBRT for Prostate Cancer

Matthias Guckenberger

UniversityHospital Zurich

Question

Which answer is <u>correct</u> in prostate SBRT?

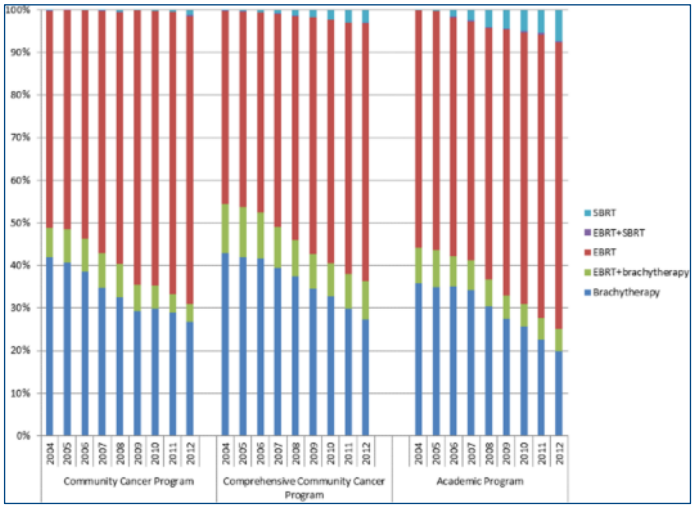
1. SBRT for prostate cancer is especially well evaluated in high-risk disease.
2. Especially GI and not GU toxicity is an issue of concern in SBRT for prostate cancer.
3. SBRT is using most frequently 5 fraction of doses between 35 – 40Gy.

SBRT for prostate cancer

Why SBRT	Why not SBRT
Small well circumscribed target	Risk of extracapsular extension
Low alpha / beta ratio	Really very low
Benefit of dose escalation	Only for bRFS
Technical solutions available	Lack of standardization
Strong competition	Should not be a reason per se

Use of SBRT for prostate cancer

National Cancer Data Base covering 70% of US cancer patients



➢ SBRT for PCa under academic evaluation

Prostate SBRT

1. Dose and fractionation
2. Target volume concept
3. Treatment delivery
4. Outcome

Prostate SBRT

1. Dose and fractionation
2. Target volume concept
3. Treatment delivery
4. Outcome

Experiences from a phase I trial

Phase I dose escalation study

Boike 2011

Fractionation	5 x 9Gy	5 x 9.5Gy	5 x 10Gy
Patients	15	15	15
Median FU	30 mo	18 mo	12 mo
% with G3 Tox	0%	0%	0%

- Endpoint: Freedom from toxicity @ 90 days
- „Dose limiting toxicity not reached“

Experiences from a phase I trial

Predictors of Rectal Tolerance Observed in a Dose-Escalated Phase 1-2 Trial of Stereotactic Body Radiation Therapy for Prostate Cancer

Kim IJROBP 2014

- Median Follow-up: still only 25 months
- 5 x 10Gy arm:
  - 6 / 61 patients with G3+ rectal toxicity
  - 5 / 61 patients required colostomy

- Dose constraints for rectum ?
- „Just too much“ ?

Multi-center analysis: *King et al Radiat Oncol 2013*

1100 patients

8 institutions

All patients enrolled in phase II studies

Risk-group	Follow-up
Low	36 mo
Intermediate	31 mo
High	23 mo

	5-yr bRFS	*p*-Value
Dose 35 Gy	92.5%	*
Dose 36.25 Gy	90.7%	$p = 0.08$
Dose 38–40 G y	95.8%	$p = 0.83$

➢ No difference between 5 x 7Gy to 5 x 8Gy

PSA nadir vs SBRT dose

Sunnybrook experience: 3 prospective trials

- 35 Gy / 5 fractions / 29 days
- 40 Gy / 5 fractions / 29 days
- 40 Gy / 5 fractions / 11 or 29 days

SBRT dose	Median PSA @ 3a	GU toxicity grade 2+
35 Gy	0.64 ng/ml	5%
40 Gy	0.27 ng/ml	48%

Helou Radiother Oncol 2017

➢ Lower PSA nadir worth the increased toxicity?

Dose and fractionation

King 2009

Fractionation	5 x 7.25Gy every day	5 x 7.25Gy every other day
Patients	20	21
EPIC 4-5	38%	0%

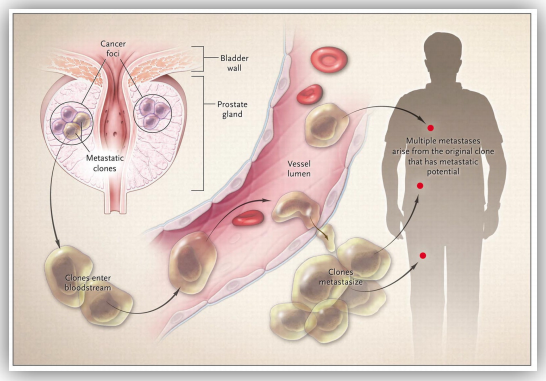
➢ Decreased toxicity with RT every other day

Prostate SBRT

1. Dose and fractionation
2. **Target volume concept**
3. Treatment delivery
4. Outcome

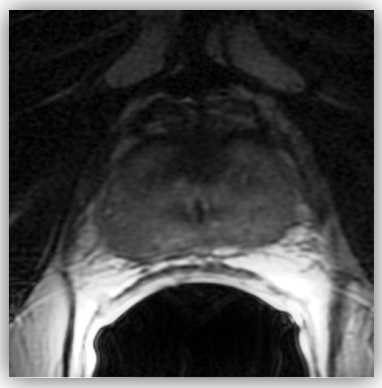
Metastatic spreat of prostate cancer

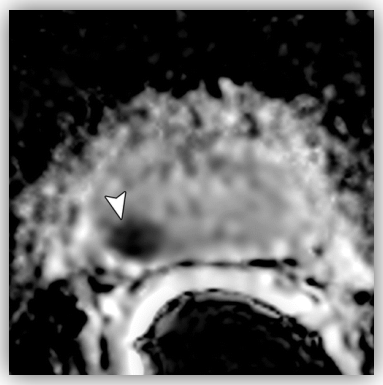
Liu Nat Med 2009
Ahmend NEJM 2009

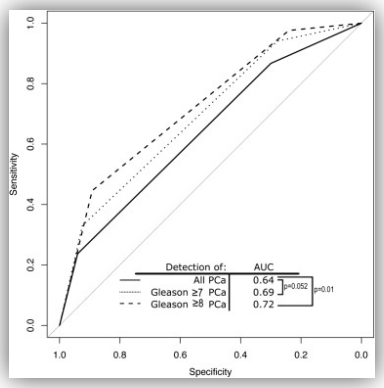


- Prostate Cancer: Multi-focal and poly-clonal disease
- HOWEVER: mono-clonal origin of metastatic spreat
- Clinically significant cancer
  - ➢ GS ≤ 6 w/o G pattern 4 or 5
  - ➢ Organ-confined disease
  - ➢ Tumour volume <0.5 cm^3

Multiparametric MRI for detection of clinically significant cancer





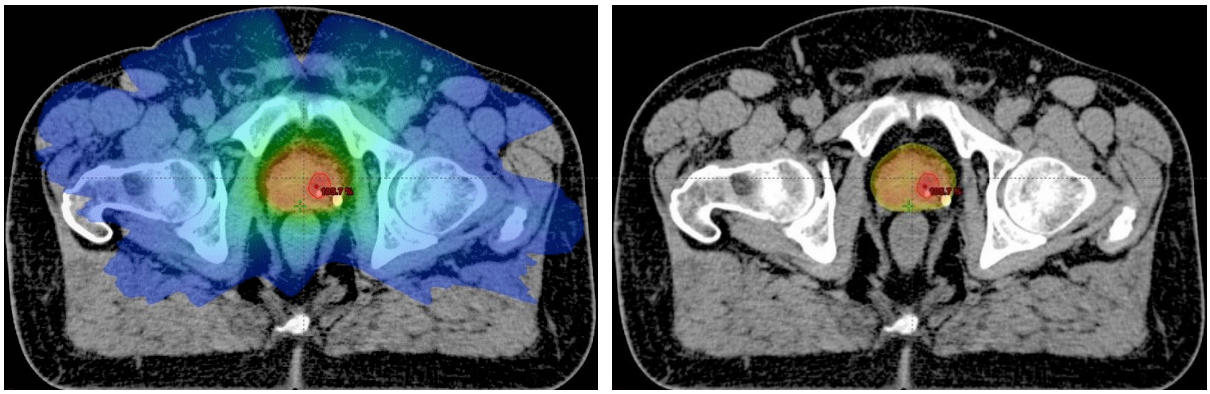


Donati Radiology 2013

Rais-Bahramia Urology 2013

- ➢ MP MRI valuable tool for detection of clinically significant cancer
- ➢ Accuracy insufficient for focal therapy only

Conclusions for SBRT in Zurich



- Integrated Boost concept to take advantage of MP MRI and simultaneously consider its limitations
- Whole gland 5 x 7Gy
- DIL in MP-MRI 5 x 8Gy

Prostate SBRT

1. Dose and fractionation
2. Target volume concept
3. **Treatment delivery**
4. Outcome

Treatment delivery of prostate SBRT

Study	Technology	IGRT	IGRT	Safety margin
McBride 2012	Cyberknife	Implanted markers	Real-time tracking	3 – 5mm
Madsen 2007	Linac	Implanted markers	Daily IGRT	4 – 5mm
Boike 2011	Linac	Implanted markers	Daily IGRT Rectal balloon	3mm
King 2012	Cyberknife	Implanted markers	Real-time tracking	3 – 5mm
Jabbari 2012	Cyberknife	Implanted markers	Real-time tracking	0 – 2mm
Katz 2013	Cyberknife	Implanted markers	Real-time tracking	3 – 5mm

- Daily IGRT using implanted markers
- Intra-fraction motion management strategy

Prostate SBRT

1. Dose and fractionation
2. Target volume concept
3. Treatment delivery
4. **Outcome**

Published data about SBRT for Prostate cancer

Late toxicity

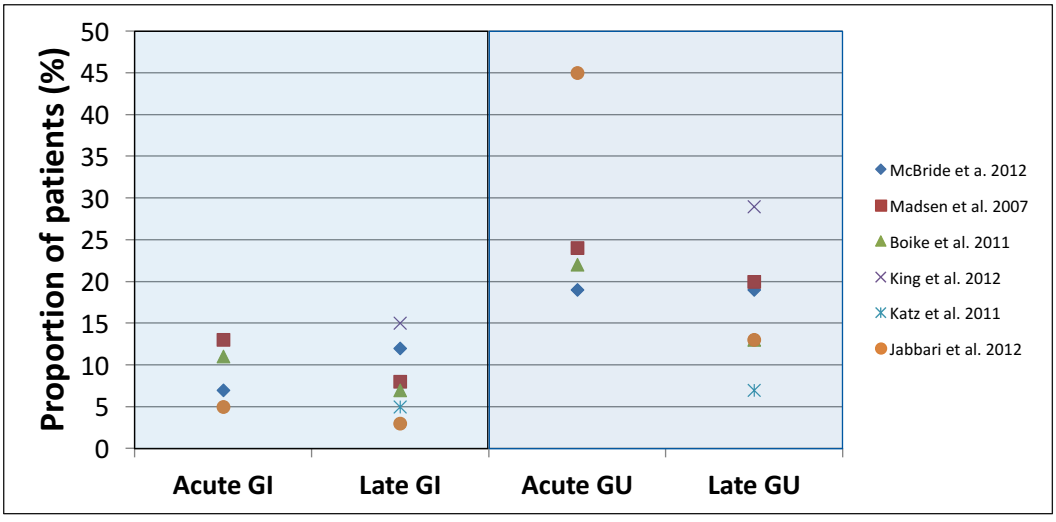
Series	Median Follow-Up
Robotic SABR	
King	2.7 years
Katz	72 months
Chen	28 months
Friedland	24 months
Oliai	Low-dose 27 months High-dose 37 months
Meier	30 months
Gantry-Based SABR	
Kim	24.5 months as per dose group
Menkarios	33 months
Loblaw	55 months
Mantz	Minimum 5 years

Biochemical control

Phase I/II	No .of. Patients	Risk Category	Median Follow Up
King 2013	1100	All risk groups	36 months
Katz 2014	477	Low/Intermediate	72 months
Chen 2013	100	All risk groups	2.3 years
Freidland 2009	112	Low/Intermediate	24 months
Oliai 2012	70	All risk groups	27 months for low dose 37 months for high dose
Meier 2015	309	Low/Intermediate	3 years
Loblaw 2013	84	Low	55 months
Menkarios 2012	80	Low risk	33 months
Mantz 2014	102	Low	Minimum 5 years
Kim 2014	91	Low/Intermediate	42 months

- Few, early studies with small patient numbers and intermediate follow-up

Toxicity



- Late toxicity = preliminary
- Relevant GU toxicity

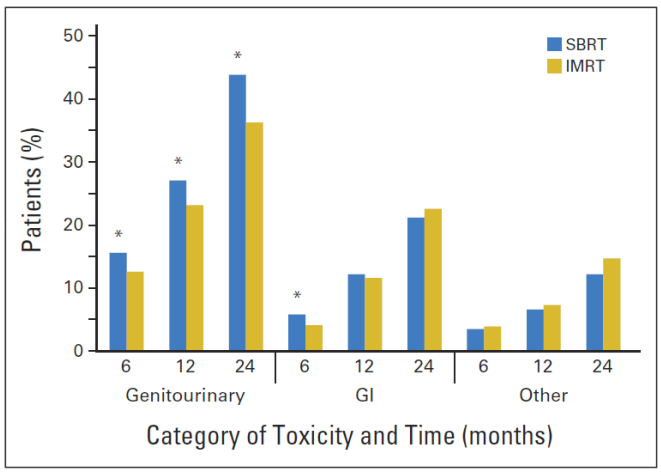
Population based analysis

Stereotactic Body Radiation Therapy Versus Intensity-Modulated Radiation Therapy for Prostate Cancer: Comparison of Toxicity

James B. Yu, Laura D. Cramer, Jeph Herrin, Pamela R. Soulos, Arnold L. Potosky, and Cary P. Gross

JCO 2014

- SEER database analysis
- Treatment 2008 – 2011
- Treatment IMRT versus SBRT
- 2670 versus 1335 patients



Toxicity in perspective

2004 – 2011 SEER analysis:

2a toxicity	SBRT n=176	Brachytherapy n=3885	IMRT n=9148
Gastrointestinal	69 (39.2%)	1493 (38.4%)	3433 (37.5%)
Urinary nonincontinence	26 (14.8%)	1191 (30.7%)	1405 (15.4%)
Urinary incontinence	42 (23.9%)	1501 (38.6%)	1824 (19.9%)
Erectile dysfunction	41 (23.3%)	729 (18.8%)	1129 (12.3%)
Hip fracture	NR	25 (0.6%)	104 (1.1%)
ADT	13 (7.4%)	301 (7.7%)	2701 (29.5%)

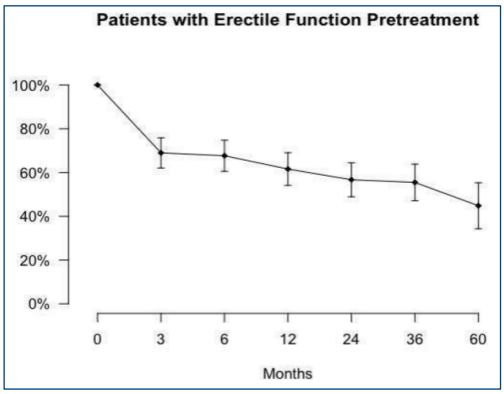
Halpern Cancer 2016

- ➢ Incontinece increased compared to IMRT
- ➢ Highest erectile dysfunction rate

Erectile dysfunction

Single institution experience of n=373

- 35 – 36.25Gy in 5 Fx



Functional erections @ 24mo

SBRT	EBRT	BT
57%	57%	54%

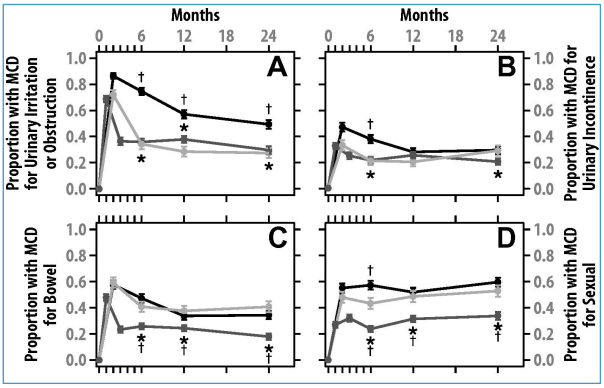
Halpern Cancer 2016

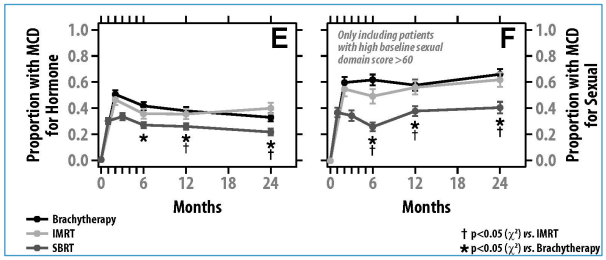
- Sexual function similar to other Tx modalities
- Only penile bulb sparing performed

QoL analysis

Multi-center retrospective analysis

IMRT	SBRT	Brachytherapy
N=160	N=381	N=261
75.6–79.2 Gy	35 – 40Gy in 5Fx	^{125}I or ^{103}Pd

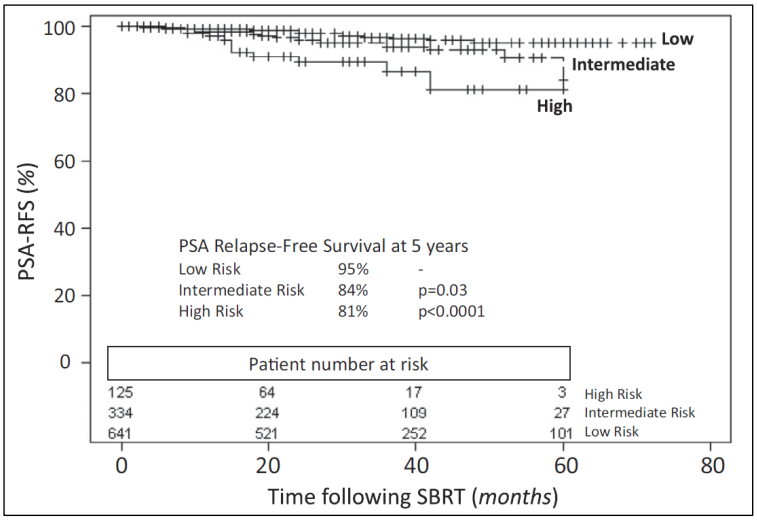




Evans Radiother Oncol 2015
Johnson Radiother Oncol 2016

- „QOL 2-years after brachytherapy, IMRT, or SBRT is very good and largely similar“

Multi-center analysis: *King et al Radiat Oncol 2013*



1100 patients

8 institutions

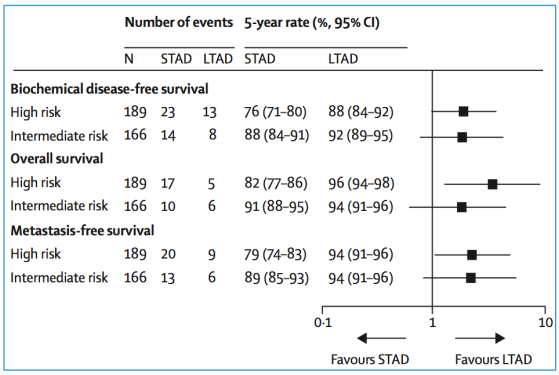
All patients enrolled in phase II studies

Risk-group	Follow-up
Low	36 mo
Intermediate	31 mo
High	23 mo

- Promising results in all risk groups but FU still short
- Very few patients in the high-risk group and no further information about detailed risk

Antihormonal therapy in SBRT

CF-RT with >76Gy



Zapatero Lancet Oncol 2015

MVA in prostate SBRT

	5-yr bRFS	*p*-Value
Low Risk	95.2%	*
Intermediate Risk	84.1%	$p = 0.03$
High Risk	81.2%	$p < 0.0001$
ADT use	92.6%	*
No ADT	91.3%	$p = 0.71$
Dose 35 Gy	92.5%	*
Dose 36.25 Gy	90.7%	$p = 0.08$
Dose 38–40 G y	95.8%	$p = 0.83$

King Radiat Oncol 2015

- No clear recommendation possible
- Most centers practice SBRT for intermediate risk w/o antihormonal therapy

CONCLUSIONS

- Initial results are promising in terms of
  - Biochemical response / control
  - GI Toxicity
- Increased rates of GU toxicity
- Un-answered questions
  - Clinical patient selection factors : P-Vol, IPSS, …
  - OAR tolerance doses
  - Prophylactic / premedication: tamsulosin, steroids …
  - Role in intermediate and high risk patients
  - Toxicity and biochemical control with sufficient FU

➢ Should be practiced within prospective protocols

Oligometastases:

Background and the role of SABR

Professor Suresh Senan
VU University Medical Center
Amsterdam, The Netherlands

Disclosures

- Research support: Varian Medical Systems, ViewRay Inc.
- Advisory Boards: Eli Lilly, AstraZeneca, Merck
- Faculty member, European Society for Medical Oncology

Oligometastases: An overview

- Definitions and biological rationale
- Evidence from clinical trials, meta-analysis, single and multi-institutional data
- Implementation

Oligometastatic paradigm

Patients developing a small number of metastatic lesions might achieve long-term survival if all these lesions are ablated with surgery or stereotactic radiotherapy

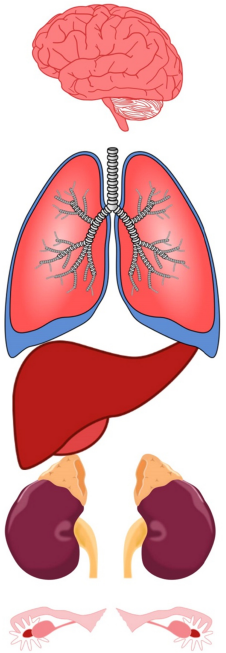
Hellman and Weichselbaum, JCO 1995

Oligometastes – increasing diagnosis

Imaging (PET-CT, brain MRI)

Availability of SABR

Sites of treatable oligometastases



Westover KD, Lung Cancer 2015

Oligometastatic paradigm

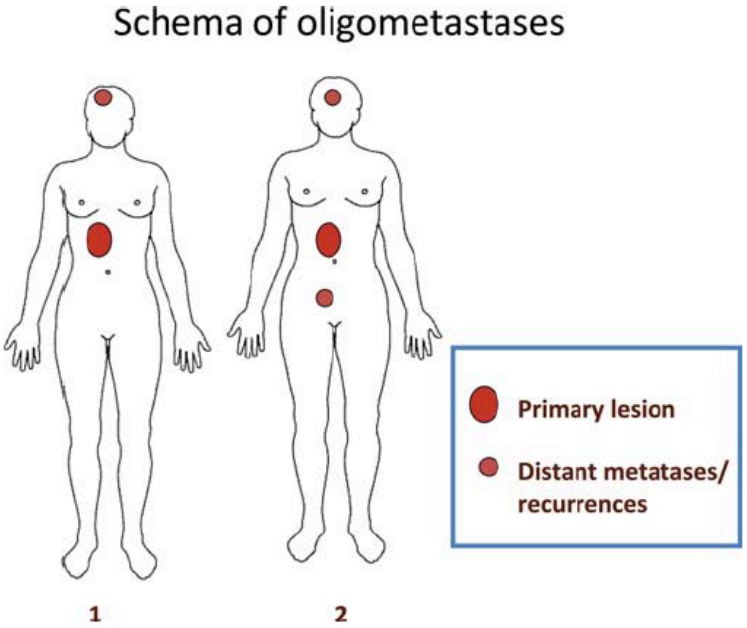


Figure 1. This is a schema of oligometastases. Schema 1 shows one distant metastasis/recurrence with a primary lesion. Schema 2 shows two distant metastases/recurrences with a primary lesion.

Niibe Y, Jap J Clin Oncol 2010

Oligometastatic paradigm

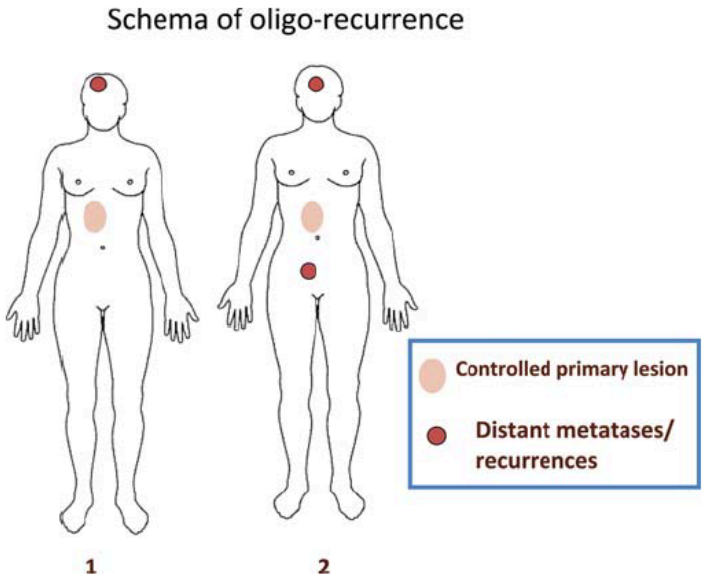


Figure 2. This is a schema of oligo-recurrence. Schema 1 shows one distant metastasis/recurrence with a controlled primary lesion. Schema 2 shows two distant metastases/recurrences with a controlled primary lesion. The biggest difference between oligometastases and oligo-recurrences lies in the uncontrolled or controlled primary lesion. Oligo-recurrence requires a controlled primary lesion.

Niibe Y, Jap J Clin Oncol 2010

Oligometastatic paradigm: Definitions

Oligometastatic
A malignancy that has progressed to a limited number of haematogenous metastases, defined in most studies as 1–3 or 1–5 metastatic lesions.

Synchronous oligometastasis
A clinical scenario in which oligometastatic disease is detected at the time of diagnosis of the primary tumour.[111]

Metachronous oligometastasis
The development of oligometastatic disease after treatment of the primary tumour. The interval for classification of 'metachronous' versus 'synchronous' is not standardized.[111]

Oligorecurrence
Oligometastasis in the setting of a controlled primary tumour.[111]

Oligoprogression
Progression of a limited number of metastatic deposits, while all other metastases are controlled with systemic therapy.

Ablative therapy
A term that includes surgical resection, stereotactic radiotherapy, radiofrequency ablation, although these might differ in efficacy and toxicity profiles.

Palma DA, Nat Rev Clin Oncol 2014

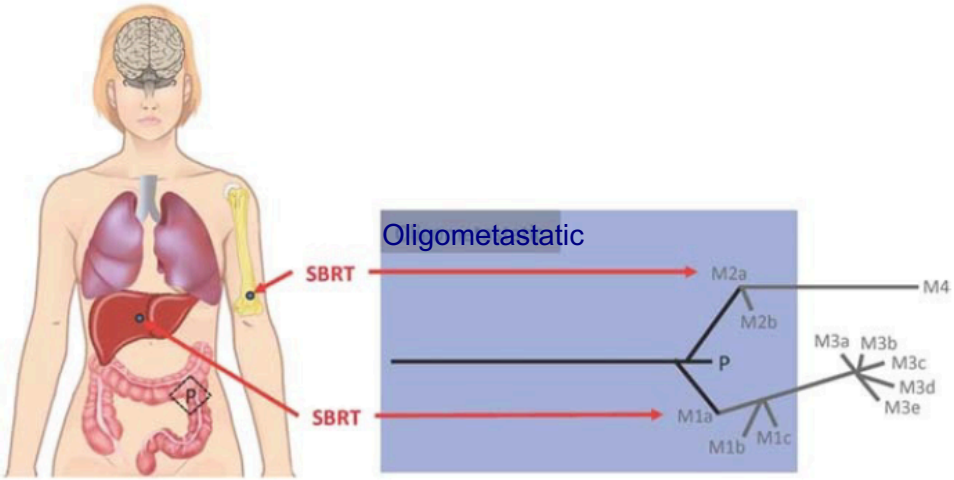
How cancers evolve?

- Cancer cells constantly accrue a variety of genetic alterations
- **Subclones** arising from **founder clones** show heterogeneity in their genetic makeup
- Cancer cells are exposed to a variety of selection pressures induced by decreased blood supply, hypoxia, and treatment-related effects
- Resulting selection and expansion of **subclones** with genetic makeup that is ideal for continued survival

Devarakonda S, Ann Oncol 2017

How metastases evolve

If detected early, ablation of progenitor metastases could pre-empt triggering of metastatic progression



Correa RJ, Cancer J 2016

How metastases evolve

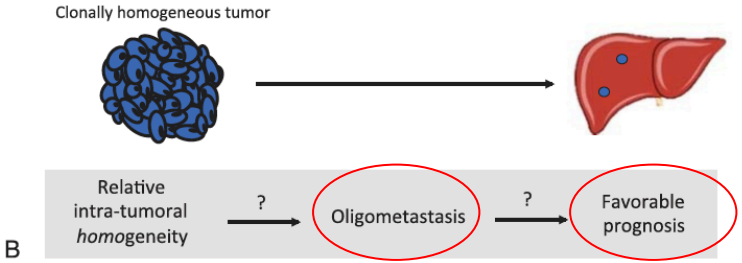
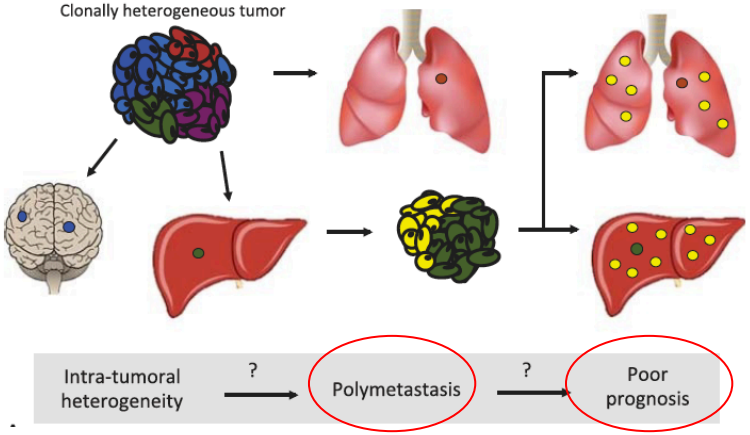
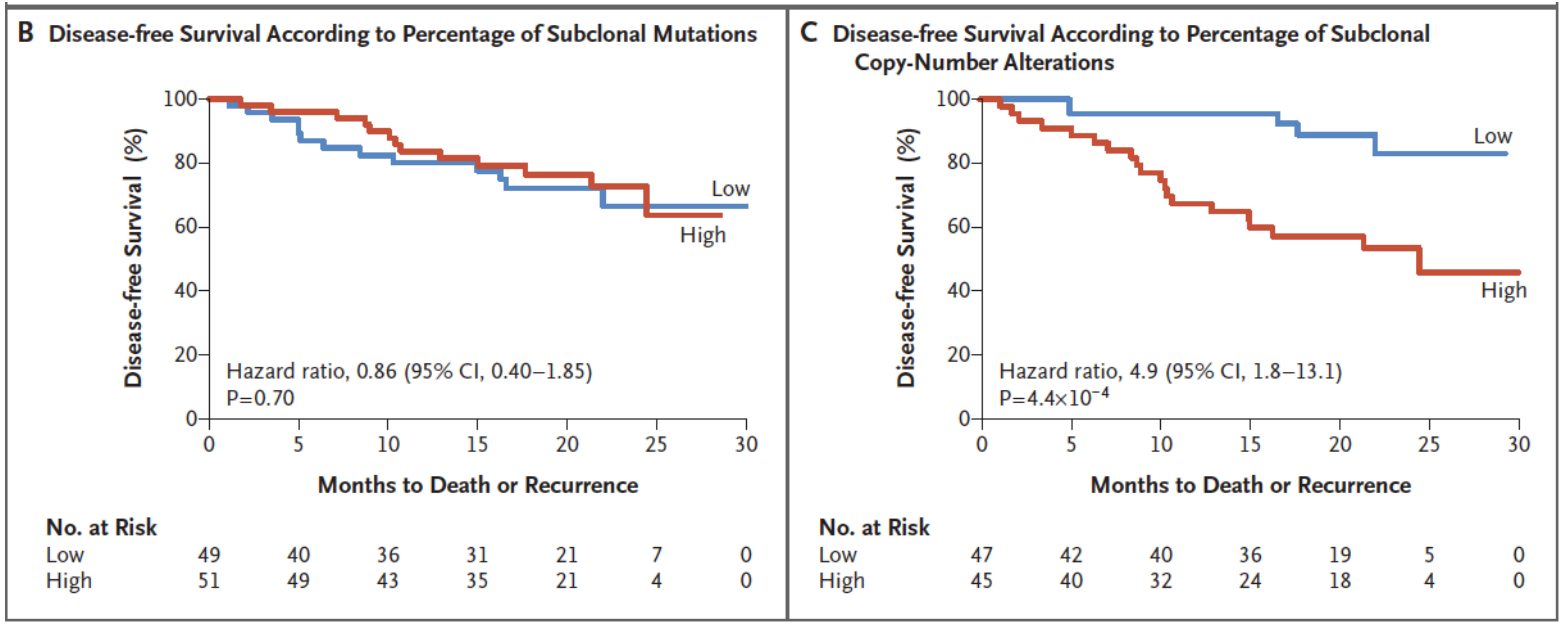


FIGURE 3. Intratumoral heterogeneity and metastasis. A, Greater ITH may supply the clonal diversity needed to mediate the formation of numerous and widespread metastasis, whereas (B) relative genetic homogeneity may extend the latency and limit the extent of metastasis.



Correa RJ, Cancer J 2016

Tracking the evolution of NSCLC (TRACERx)



Jamal-Hanjani M, NEJM 2017

Do we want to treat oligometastases?

Definitive Stereotactic Body Radiotherapy (SBRT) for Extracranial Oligometastases

An International Survey of >1000 Radiation Oncologists

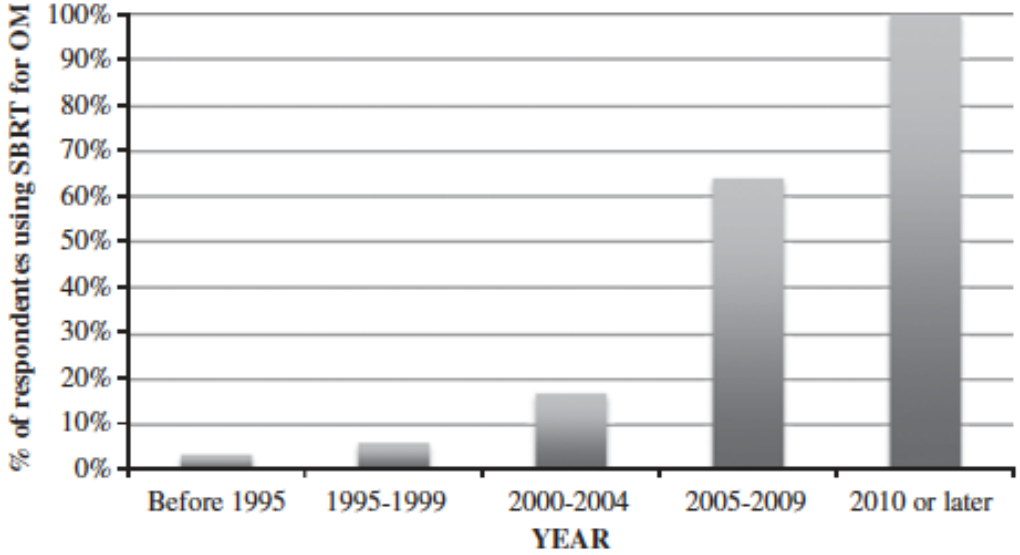


FIGURE 1. Cumulative percentage of respondents using stereotactic body radiotherapy (SBRT) for oligometastases during the defined time intervals.

Lewis SL, AJCO 2015

Definitive Stereotactic Body Radiotherapy (SBRT) for Extracranial Oligometastases

An International Survey of >1000 Radiation Oncologists

Are you treating patients with limited (≦3) metastases with definitive hypofractionated radiotherapy using >4 Gy per fraction?

Lewis SL, AJCO 2015

TABLE 1. Survey Population

Characteristics	Respondents (n [%])	Respondents Using SBRT for OM (%)	Respondents *NOT* Using SBRT for OM (%)
Radiation oncologists	1007 (100)	61.0	39.0
Geographic location			
United States	426 (42)	68.5	31.5
Canada	113 (11)	47.8	52.2
Japan	101 (10)	45.2	54.8
Western Europe	67 (7)	76.1	31.4
Australia/ New Zealand	64 (6)	27.0	73.0
South Korea	26 (3)	78.3	21.3
Miscellaneous			
Practice type			
Academic	421 (42)	66.6	33.4
Private	117 (12)	60.1	39.1
Hospital or stand-alone cancer center	321 (32)	52.8	47.2
Other or unreported	148 (15)	6.8	92.6

OM indicates oligometastases; SBRT, stereotactic body radiotherapy.

Definitive Stereotactic Body Radiotherapy (SBRT) for Extracranial Oligometastases

An International Survey of >1000 Radiation Oncologists

Those using SABR

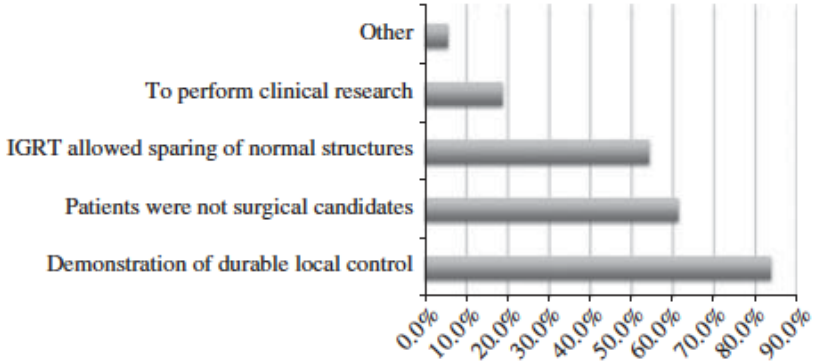


FIGURE 2. Reasons for adopting stereotactic body radiotherapy (SBRT) to treat oligometastases. IGRT indicates image-guided radiation therapy.

Those planning to use SABR

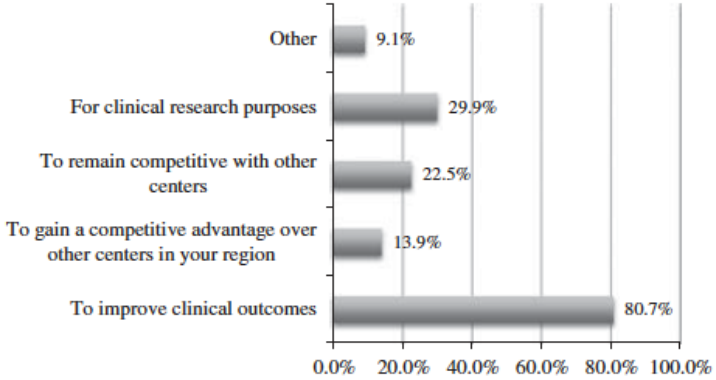


FIGURE 4. Reasons cited by respondents not currently using stereotactic body radiotherapy (SBRT) for oligometastases to start offering this procedure in the near future.

Lewis SL, AJCO 2015

Oligometastatic paradigm

OPINION

The oligometastatic state—separating truth from wishful thinking

David A. Palma, Joseph K. Salama, Simon S. Lo, Suresh Senan, Tom Treasure, Ramaswamy Govindan and Ralph Weichselbaum

Palma DA, Nat Rev Clin Oncol 2014

Oligometastatic paradigm: pitfalls

Immortal time bias

This bias arises when a study includes a span of follow-up time during which an outcome (death) could not occur for patients included in the study.[75,76] Immortal time is also known as a 'death-free interval'.

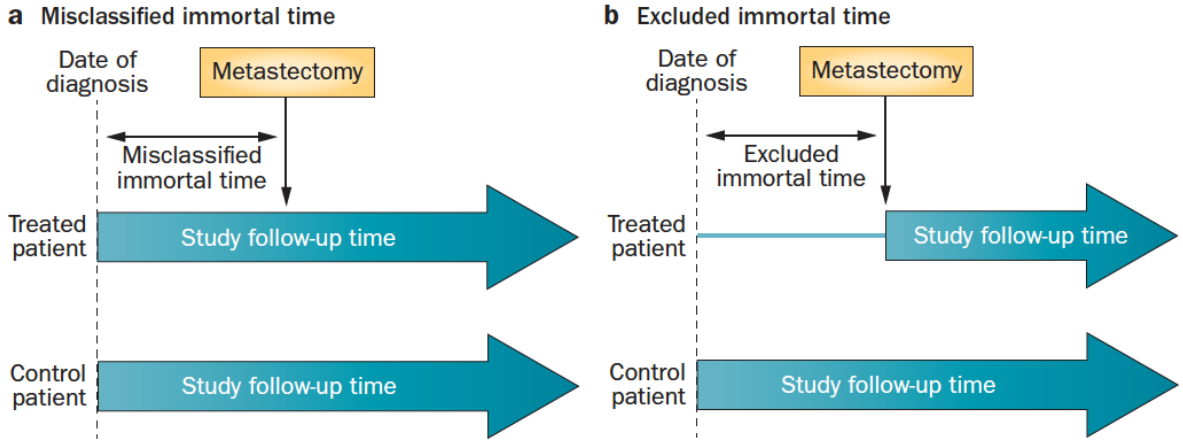


Figure 2 | Types of immortal time bias. Both 'misclassified immortal time' and 'excluded immortal time' lead to a bias in favour of the treated group. Adapted from Levesque *et al*.[75] *BMJ* **340**, b5087 (2010).

Palma DA, Nat Rev Clin Oncol 2014

Oligometastases: An overview

- Definitions and biological rationale
- Evidence from clinical trials, meta-analysis, single and multi-institutional data
- Implementation

Evidence from randomized trials

- Patients with a **single brain metastasis**, the addition of surgical resection to WBRT improved median overall survival from 15 weeks to 40 weeks [Patchell RA, NEJM 1990]

- For patients with **1-3 brain metastases**, radiosurgery in addition to WBRT improved median overall survival from 4.9 months to 6.5 months [Andrews DW, Lancet 2004]

- In non-resectable **colorectal liver metastases**, radiofrequency ablation (RFA) combined with systemic treatment was not superior to systemic treatment alone [Ruers T, Ann Oncol 2012]

Unresectable CRLM Local treatment

CRLM - colorectal liver metastases

OXFORD

JNCI J Natl Cancer Inst (2017) 109(9): djx015

doi: 10.1093/jnci/djx015
First published online March 17, 2017
Article

ARTICLE

Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial

- Phase II study in unresectable colorectal liver–limited metastases
- Randomised to systemic treatment alone (*standard arm*) or systemic treatment plus local treatment by RFA +/- resection (*experimental arm - CMT*)
- Primary end point: 30-month OS rate higher than 38% in CMT arm

- 119 patients were randomized

Ruers T, JNCI 2017

Unresectable CRLM Local treatment

Randomized phase II study

Patient and tumor characteristics	Local plus systemic treatment (n = 60) No. (%)	Systemic treatment (n = 59) No. (%)
Age, y		
Median (range)	64 (31–79)	61 (38–79)
Sex		
Male	37 (61.7)	42 (71.2)
Female	23 (38.3)	17 (28.8)
WHO performance status		
0	47 (78.3)	47 (79.7)
1	13 (21.7)	12 (20.3)
No. of liver metastases		
1	15 (25.0)	7 (11.9)
2	6 (10.0)	4 (6.8)
3	8 (13.3)	7 (11.9)
4	9 (15.0)	8 (13.6)
5	6 (10.0)	10 (16.9)
6	3 (5.0)	9 (15.3)
7	6 (10.0)	8 (13.6)
8	3 (5.0)	2 (3.4)
9	4 (6.7)	4 (6.8)
Median	4.0	5.0
Synchronicity of liver metastases		
Metachronous metastases	37 (61.7)	31 (52.5)
Synchronous metastases*	23 (38.3)	28 (47.5)
Time from surgery for primary cancer to random assignment, d		
Median (range)	290 (28–1802)	308 (30–2754)
Prior chemotherapy for metastatic disease†		
No	51 (85.0)	51 (86.4)
Yes	9 (15.0)	8 (13.6)
Previous liver surgery for CRC metastases		
No	51 (85.0)	49 (83.1)
Yes	9 (15.0)	10 (16.9)
Route of random assignment†		
Before surgery	46 (76.7)	44 (74.6)
During surgery	14 (23.3)	15 (25.4)

*Liver metastases detected within three months after primary cancer diagnosis.
CRC = colorectal cancer; WHO = World Health Organization.
†Stratification factors.

Ruers T, JNCI 2017

Unresectable CRLM Local treatment

Table 2. Local treatment received in the combined treatment arm

Radiofrequency/surgery	Method: RFA only (n = 30) No. (%)	RFA plus resection* (n = 27) No. (%)	Total (n = 57) No. (%)
Means of radiofrequency administration			
At laparotomy	25 (83.3)	26 (96.3)	51 (89.5)
Laparascopically	1 (3.3)	0 (0.0)	1 (1.8)
Percutaneously	4 (13.3)	0 (0.0)	4 (7.0)
No RFA performed	0 (0.0)	1 (3.7)*	1 (1.8)
Worst margin for resected† tumors per patient (n = 27), cm			
≥1	NA	10 (37.0)	–
<1	NA	16 (59.3)	–
Residual tumor	NA	1 (3.7)	–
Worst margin for tumors treated by radiofrequency per patient (n = 56), cm		(n = 26)	(n = 56)
≥1	8 (26.7)	5 (19.2)	13 (23.2)
<1	16 (53.3)	17 (65.4)	33 (58.9)
No margin	4 (13.3)	1 (3.8)	5 (8.9)
Unknown	2 (6.7)	3 (11.5)	5 (8.9)
Treatment of at least one liver metastasis unsuccessful			
No	29 (96.7)	26 (96.3)	55 (96.5)
Yes	1 (3.3)‡	1 (3.7)	2 (3.5)

*One patient was ineligible; all lesions were resected at baseline, no RFA done. RFA = radiofrequency ablation.
†Resection consisted of one segment or wedge resection(s) (n = 16) or resection of two or more liver segments (n = 11).
‡For this patient, one lesion could not be successfully treated by RFA because of its close proximity to the stomach.

Table 3. Site of first progression and main cause of death

Disease and survival status	Local plus systemic treatment (n = 60) No. (%)	Systemic treatment (n = 59) No. (%)
Site(s) of first progression		
Any hepatic progression*	28 (46.7)	46 (78.0)
Site treated by radiofrequency	9 (15.0)	
Extrahepatic only	15 (25.0)	8 (13.6)
Unknown site		2 (3.4)†
Death before first progression	2 (3.3)	1 (1.7)
Survival status		
Lost to follow-up	3 (5.0)	2 (3.4)
Alive at last contact‡	18 (30.0)	4 (6.8)
Dead	39 (65.0)	53 (89.8)
Main cause of death		
Progressive disease	35 (58.3)	49 (83.1)
Cardiovascular disease	1 (1.7)	0 (0.0)
Other	1 (1.7)§	0 (0.0)
Unknown	2 (3.3)	4 (6.8)

*Any hepatic progression with or without extrahepatic disease.
†One patient in the systemic treatment arm died from progressive disease as first event.
‡All patients were followed for a minimum of 7.8 years.
§Sepsis and multiple organ failure (radiofrequency ablation/surgery complication).

Ruers T, JNCI 2017

Unresectable CRLM Local treatment

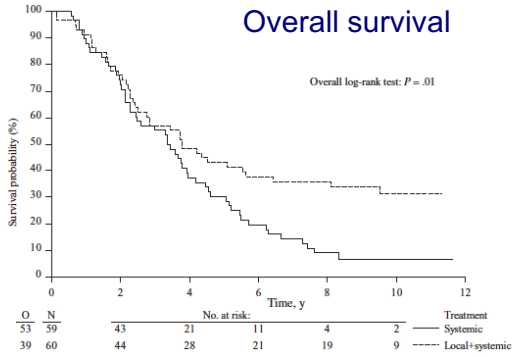


Figure 2. Kaplan-Meier curves for overall survival in patients with unresectable colorectal liver metastases treated by systemic treatment alone or combined modality treatment by systemic treatment plus aggressive local treatment by radiofrequency ablation ± resection (P = .01). P value was calculated using a two-sided log-rank test.

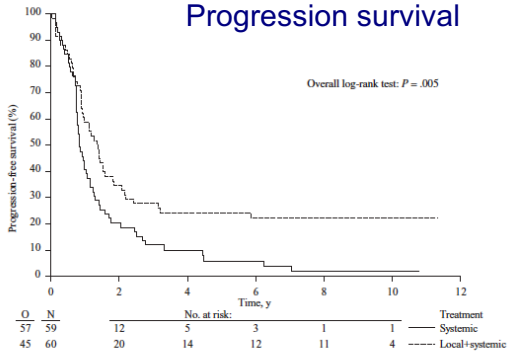


Figure 3. Kaplan-Meier curves for progression-free survival in patients with unresectable colorectal liver metastases treated by systemic treatment alone or combined modality treatment by systemic treatment plus aggressive local treatment by radiofrequency ablation ± resection (P = .005). P value was calculated using a two-sided log-rank test.

Median follow up: 9.7 years. 77% patients had died (65.0% CMT vs 90% systemic treatment arm)

Significant difference in OS for CMT arm (HR 0.58, 95% CI 0.38 to 0.88, P .01)

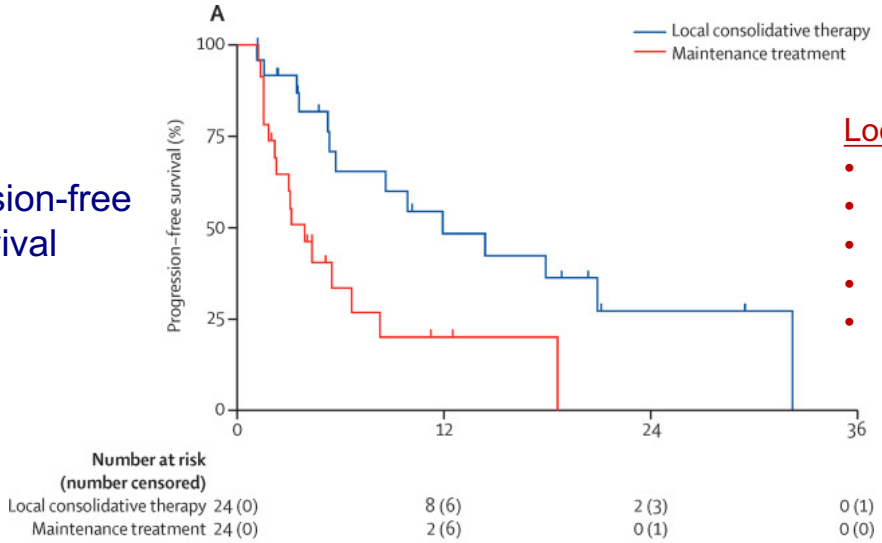
Median OS of 45.6 months in CMT arm versus 40.5 months in standard arm

3-, 5- and 8-year OS were 57%, 43% and 36% in CMT arm versus 55%, 30% and 9% in the systemic treatment arm

Ruers T, JNCI 2917

Oligometastatic NSCLC without progression after first-line systemic therapy: A multicentre, randomised, controlled, phase 2 study

Progression-free survival



Local consolidative therapy regimens used

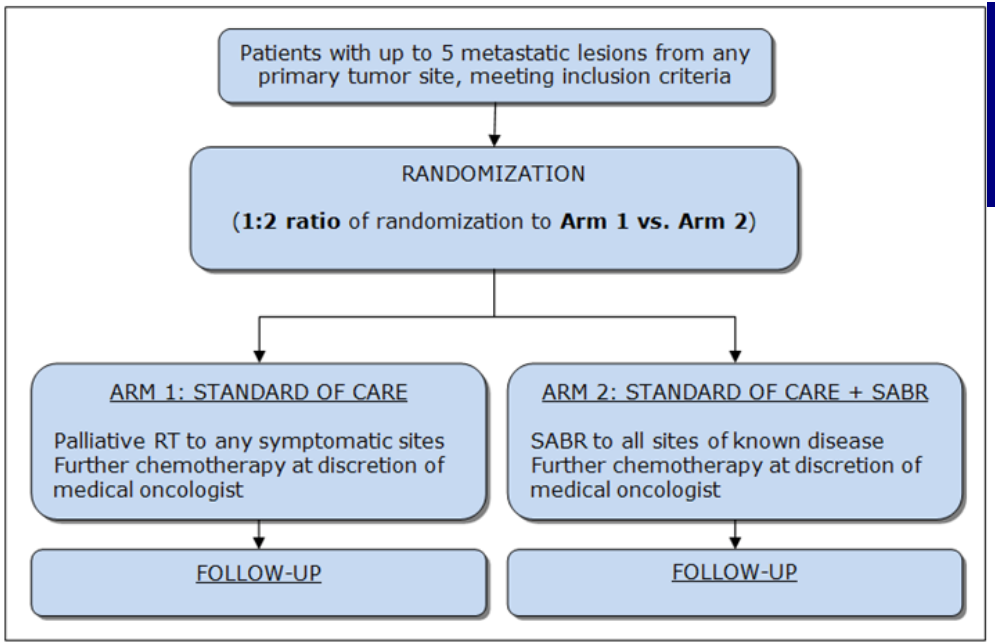
- Hypofractionated RT or SABR in 48% (12 patients)
- Surgery and RT for 24%
- Chemo-RT for 8%
- Hypofractionated RT and CT-RT for 12%
- Surgery only for 4%

11·9 months (90% CI 5·72–20·90) versus **3·9 months** (2·30–6·64) in the maintenance group (HR 0·35 [90% CI 0·18–0·66]; log-rank p=0·0054).

Gomez D, Lancet Oncol 2016

COMET Trial: metachronous oligometastases

STEREOTACTIC ABLATIVE RADIOTHERAPY FOR COMPREHENSIVE TREATMENT OF OLIGOMETASTATIC TUMORS (SABR-COMET): A RANDOMIZED PHASE II TRIAL



http://clinicaltrials.gov/ct2/show/NCT01446744

Primary tumor controlled

Maximum of 3 lesions in any organ

Principal Investigators
D. Palma, S. Senan

Target Sample Size
99

Participants
Canada
Netherlands
Scotland
Australia

Palma D, BMC Cancer 2012

Individual Patient Data Meta-Analysis: NSCLC

757 NSCLC patients with 1-5 synchronous or metachronous mets

Median OS **26 months**, 1-year OS 70.2%, and 5-year **OS 29.4%**

Surgery was the commonest treatment modality for both the primary (n=635, **83.9%**) and for metastases (n=339, **62.3%**)

Recursive Partitioning Analysis for risk groups;

Low-risk: metachronous metastase (5-year OS 48%)

Intermediate risk: synchronous metastases, N0 disease (5-year OS 36%)

High-risk: synchronous metastases, N1/N2 disease (5-year OS 14%)

Ashworth A, Clin Lung Cancer 2014

SABR for pulmonary oligometastases

Systematic review, 29 publications;

Most reports included **3 or fewer synchronous** metastases
Weighted rate of grade ≧3 toxicity: 2.6%

Multiple fraction SABR:

334 patients (564 targets): 2-year weighted local control **78%**

Single fraction SABR:

154 patients (174 targets): 2-year weighted local control **79%**

Siva S, JTO 2010

Modalities for pulmonary oligometastases

- Consecutive patients (2007-2010)
- **Surgery** was preferred, with **SABR** preferred for unfit cases
- 110 patients (surgery, n=68; SABR, n=42)

- Estimated OS rates at 3 and 5 years:
  - 62% and 41% for surgery
  - 60% and 49% for SABR

- 2-year local control: 94% - SABR, 90% - surgery
- Progression-free survival at three years: 17%

Widder J, Radioth Oncol 2013

Pulmonary oligometastases: Surgery or SABR

Updated after minimum follow-up 5.8 years

Table 1. Patient, Tumor, and Pretreatment Characteristics

Characteristic	PME (n = 68)	SABR (n = 42)	All (N = 110)	*p* Value
Male-to-female ratio	37:31	27:15	64:46	0.308
Median age (range), y	61 (18-80)	70 (49-89)	63 (18-89)	**<0.001**
Primary tumor				**<0.001**
Colorectal	39 (57%)	31 (74%)	70 (64%)	
Sarcoma	18 (27%)	1 (2%)	19 (17%)	
NSCLC	0	6 (14%)	6 (5%)	
Renal	5 (7%)	1 (2%)	6 (5%)	
Other	6 (9%)	3 (7%)	9 (8%)	
Median metastasis-free interval (range), mo	18.0 (0-138)	12.7 (0-86)	15.7 (0-138)	**0.045**
No. of lesions				0.821
1	40 (59%)	27 (64%)	67 (61%)	
2	21 (31%)	7 (17%)	28 (26%)	
3	3 (4%)	7 (17%)	10 (9%)	
4	2 (3%)	1 (2%)	3 (3%)	
5	2 (3)	0 (0%)	2 (2%)	
Mean size of largest lesion, cm (95% CI)	2.0 (1.7-2.4)	1.7 (1.4-2)	1.9 (1.7-2.1)	0.162
One or more prior metastasis-directed local therapies	23 (34%)	25 (60%)	48 (44%)	**0.01**
Prior chemotherapy for metastatic disease	8 (12%)	13 (31%)	21 (19%)	**0.013**

Note: Boldface indicates statistical significance.
PME, pulmonary metastasectomy; SABR, stereotactic ablative radiotherapy; CI, confidence interval.

Lodeweges JE, JTO 2017

Pulmonary oligometastases: Surgery or SABR

Minimum follow-up 5.8 years; 5-year OS of 41% for surgery and 45% for SABR

40% of patients free from failure at 5 years, and 20% free from any progression

5-year local control rate was 83% for SABR and 81% for surgery

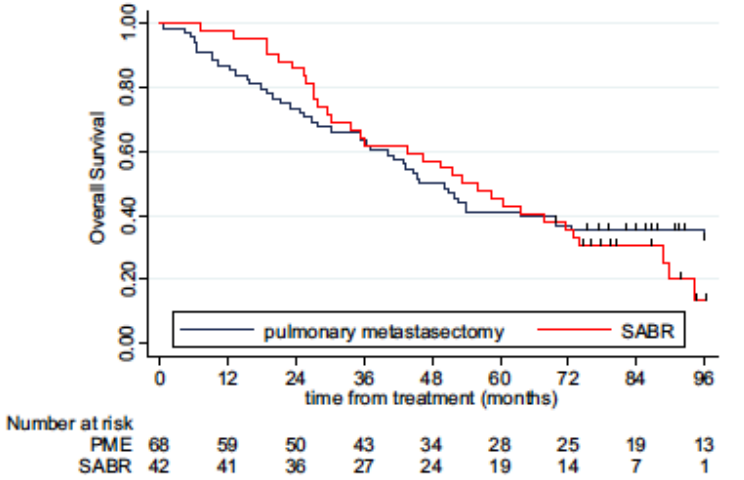
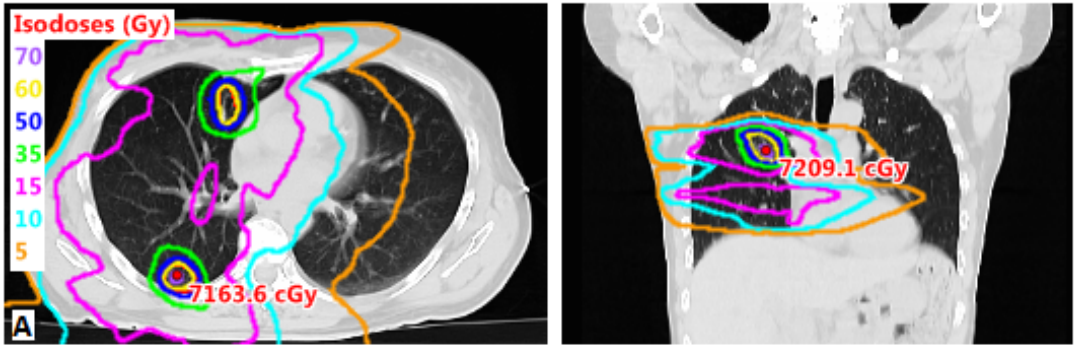


Figure 1. Unadjusted overall survival. PME, pulmonary metastasectomy; SABR, stereotactic ablative radiation.

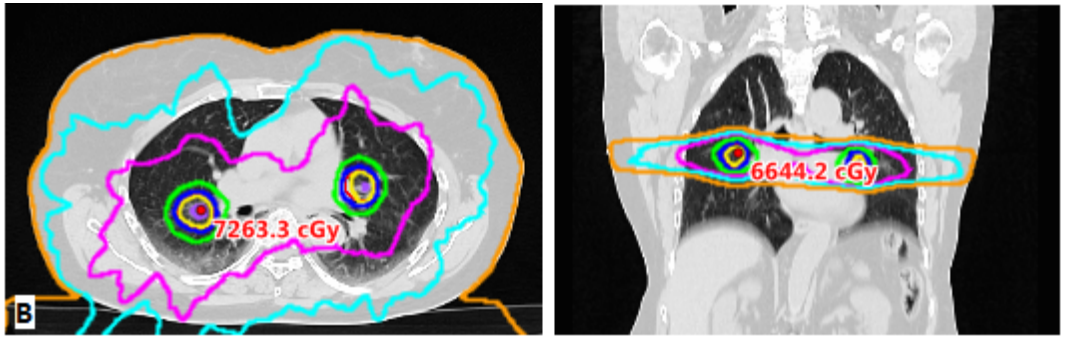
Lodeweges JE, JTO 2017

SABR treatment plans: Low-dose wash

Patient with 3 unilateral metastases

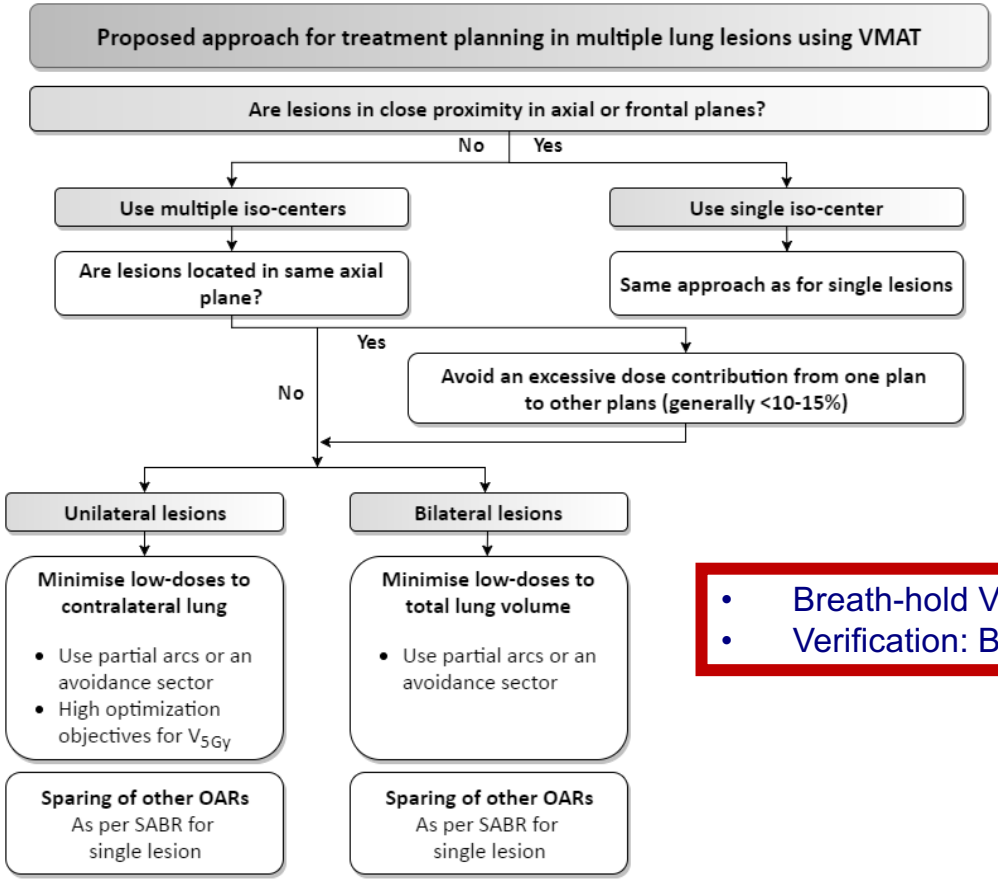


Patient with 2 metastases, bilalateral



Tekatli H, Acta Oncol 2017

SABR multiple lung tumors



- Breath-hold VMAT (selected cases)
- Verification: Breath-hold CBCT

Tekatli H, Acta Oncol 2017

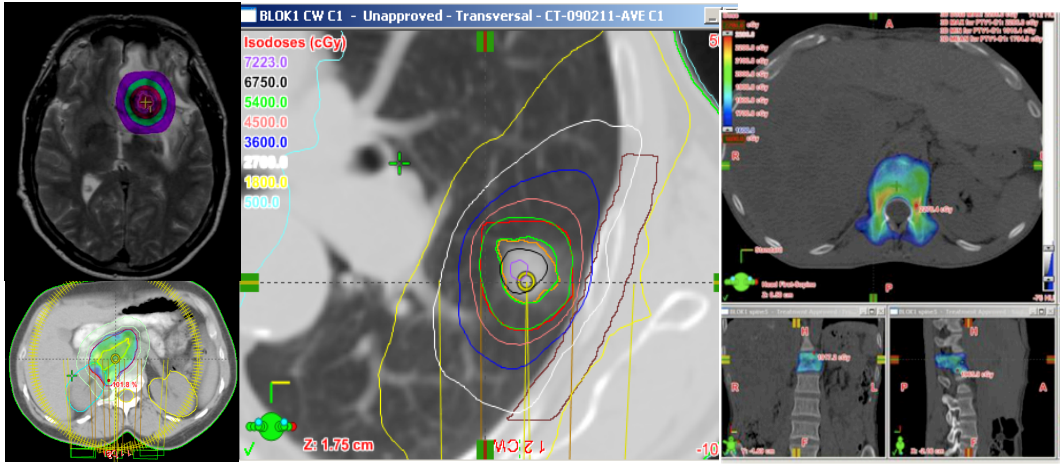
Changing paradigms in metastatic disease

clinical practice guidelines

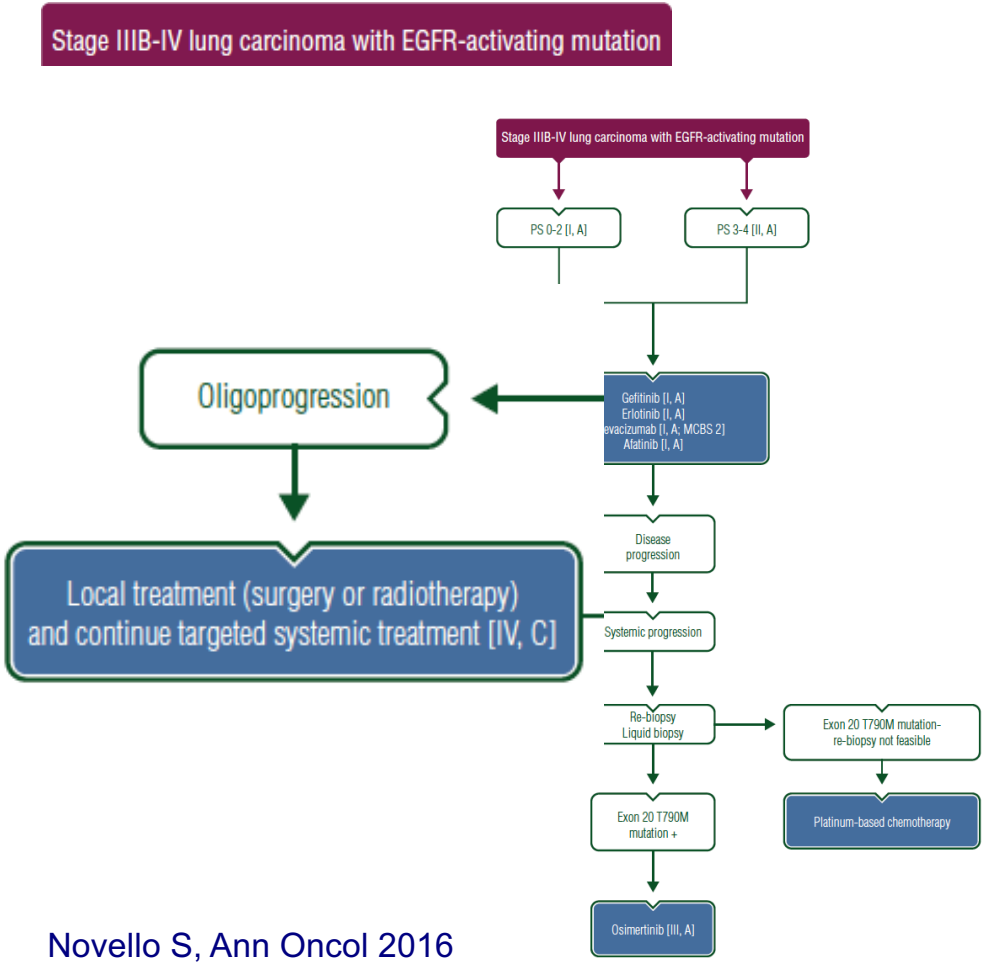
Annals of Oncology 27 (Supplement 5): v1–v27, 2016
doi:10.1093/annonc/mdw326

Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

S. Novello[1], F. Barlesi[2], R. Califano[3,4], T. Cufer[5], S. Ekman[6], M. Giaj Levra[7], K. Kerr[8], S. Popat[9], M. Reck[10], S. Senan[11], G. V. Simo[12], J. Vansteenkiste[13] & S. Peters[14] on behalf of the ESMO Guidelines Committee*



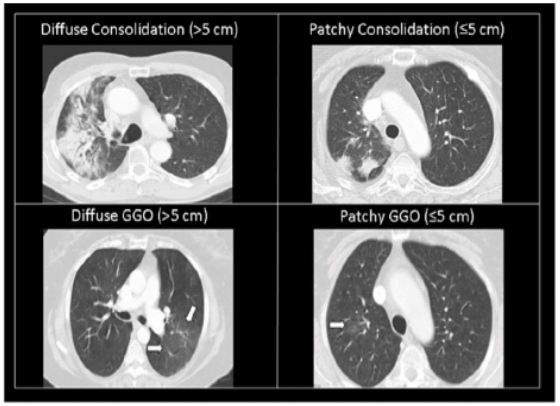
ESMO guidelines 2016



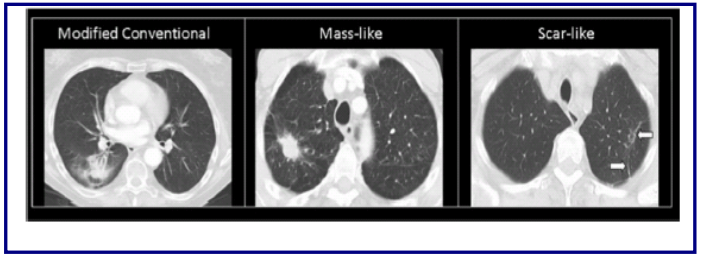
Novello S, Ann Oncol 2016

Educate your MDT on fibrotic changes

Acute toxicity:
Presenting in ≤6 months



Late toxicity:
Presenting >6 months



Dahele M, JTO 2011

Oligometastases: An overview

- Definitions and biological rationale
- Evidence from clinical trials, meta-analysis, single and multi-institutional data
- **Implementation**

Factors influencing choice of ablative modality

Need for tissue (mutations, PDL1 expression, liquid biopsies)

Location (brain, bone/vertebra, liver, liver hilus, central lung)

Size of lesion (>3 cm cutoff)

Previous treatments (high-dose radiation, surgery)

Co-morbidities, patient preferences, institutional experience

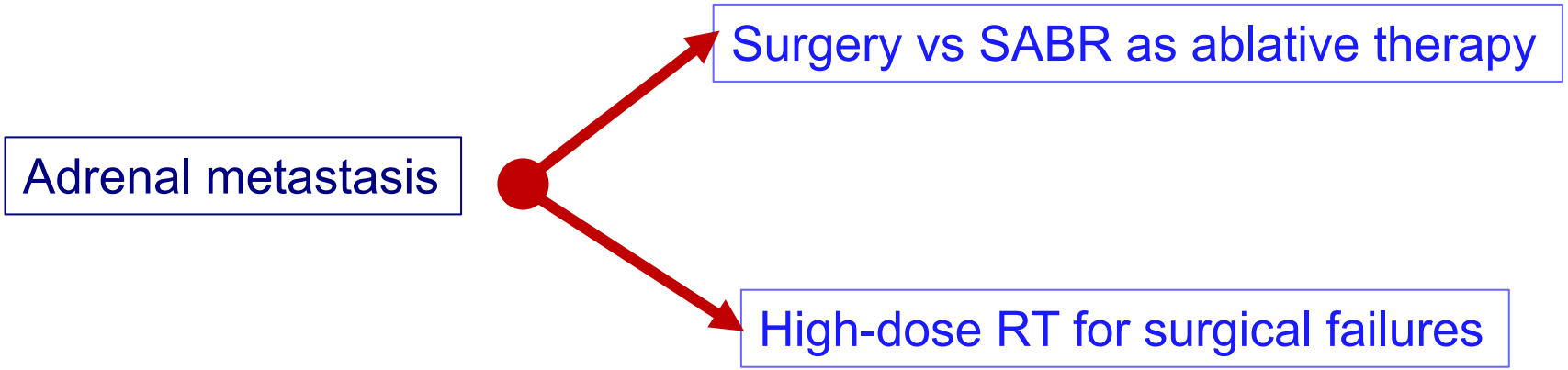
Timing (phased treatments, initial systemic therapy)

Enhancement of immune function (SABR)

Senan S, ESMO 2017

Choose the best modality available at your center
Avoid (or minimize) risk of harm
Optimal planning and image-guidance
Local radiotherapy does not always have to be SABR
Selection panel

Factors influencing choice of ablative modality



Adrenal metastases: surgical data

Systematic review of surgical outcomes

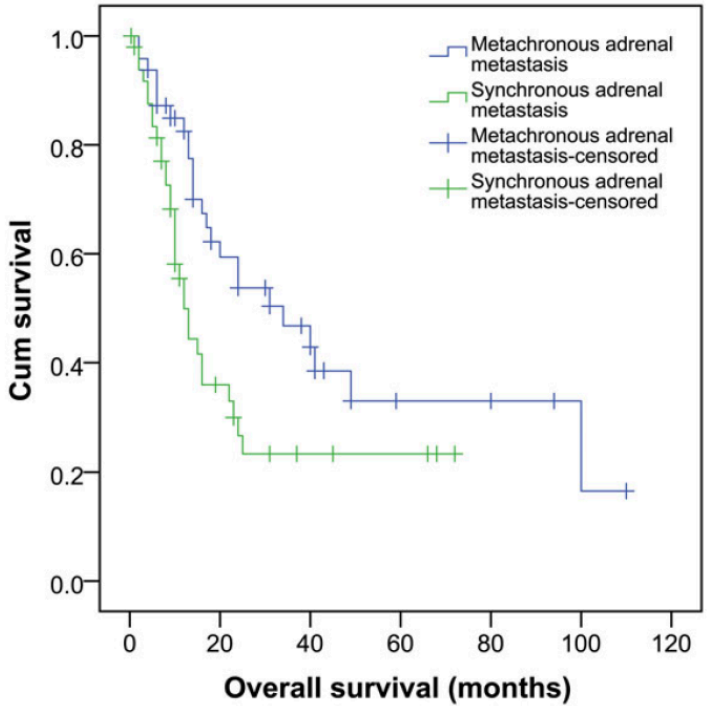


Figure 3: Kaplan–Meier estimates of overall survival: synchronous adrenal metastasis versus metachronous adrenal metastasis.

Gao X-L, ICVTS 2016

13 studies (98 patients)

Median OS of18 months

1-, 2- and 5-year survival rates were 66.5, 40.5 and 28.2%, respectively

Adrenal metastases: a challenge for SABR

Outcomes of SABR versus surgery

- Weighted 2-year local control of **63%** after SABR versus **84%** for adrenalectomy [systematic review, Gunjur A, Ca Treat Rev 2014]
- 1-year freedom from local failure 74% after SABR [Chance WW, PRO 2016]

SABR for adrenal metastases

Single institution, 43 patients, 49 metastases (2009-2015)

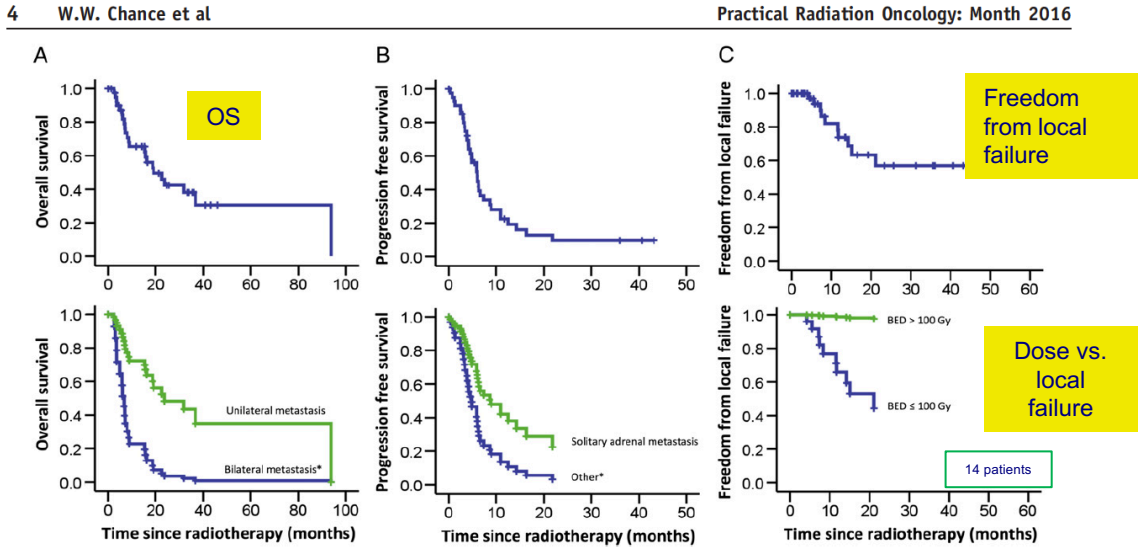


Figure 1 (A) Overall survival (OS) time after stereotactic ablative radiotherapy to adrenal metastases. The median OS time was 19 months; OS after treatment was worse for patients with bilateral adrenal metastases. *P =.01. (B) Progression-free survival (PFS) after stereotactic ablative radiotherapy to adrenal metastases. The median PFS time was 6 months; PFS was better among patients with a solitary adrenal metastasis than among all others. *P = .03. (C) Freedom from local failure after stereotactic ablative radiotherapy to adrenal metastases. The median time to local failure was not reached; no local failures were seen in patients treated with a biologically equivalent dose of >100 Gy (P = .23).

Chance WW, PRO 2016

COMET Trial: Organ at risk constraints

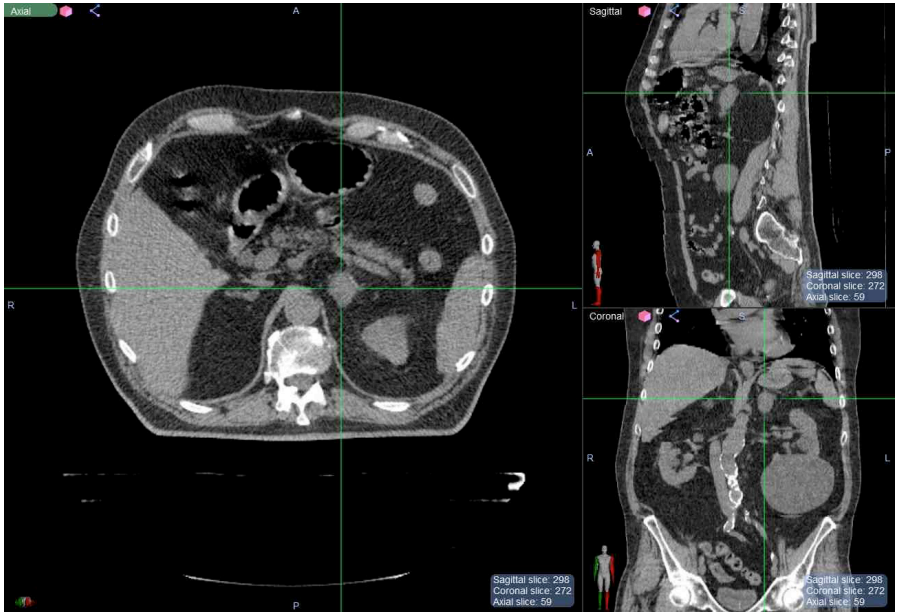
Table 4. Additional normal tissue dose constraints for **EIGHT**-fraction SABR regimens. Dose conformality requirements from Table 5 also apply for lung lesions. Note: for targets overlapping the stomach or esophagus, 12 fractions should be used, with a maximum dose of 48 Gy in 12 fractions for either organ. For any organs not listed, or for OARs for 12 fraction regimens, a biologically effective dose can be calculated using an alpha-beta ratio of 2.

Structure	Maximum Dose
Liver	At least 700 cc below 22 Gy (unless using NTCP calculation method)
Kidney (right and left)	At least 200 cc below 21 Gy
Spinal Cord	32 Gy point dose V(27 Gy) < 0.25 cc V(16 Gy) < 1.25 cc
Stomach	40 Gy point dose V(34 Gy) < 10 cc
Esophagus	40 Gy point dose V(33 Gy) < 5 cc
Great Vessels	65 Gy point dose V(58 Gy) < 10 cc
Trachea and Ipsilateral Mainstem Bronchus	40 Gy point dose V(21.5 Gy) < 4 cc
Ipsilateral Brachial Plexus	39 Gy point dose V(36.5 Gy) < 3 cc
Heart/Pericardium	46 Gy point dose V(39 Gy) < 15 cc
Duodenum	39 Gy point dose V(21.5 Gy) < 5 cc
Jejunum/Ileum	40 Gy point dose V(23 Gy) < 5 cc

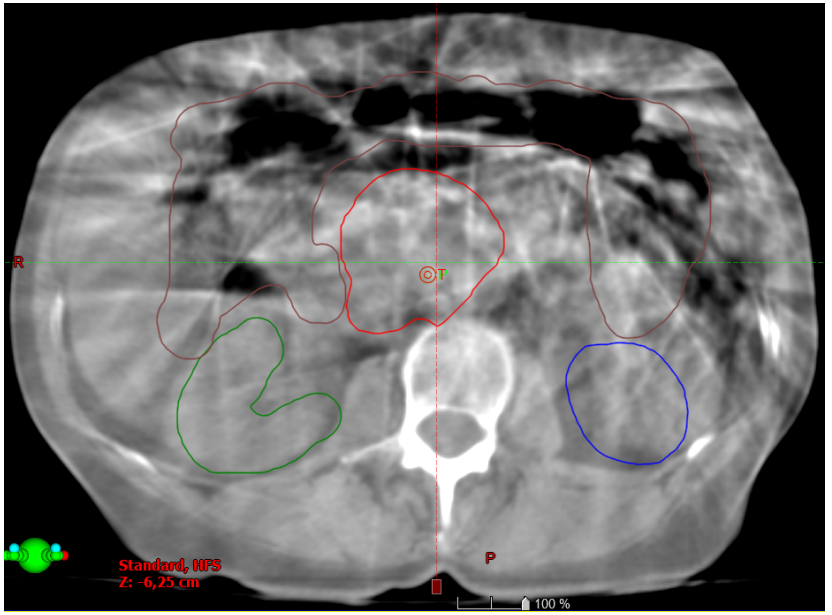
V(X) Gy): volume of structure receiving X Gy or more (i.e. for the stomach, V34 Gy is the volume of stomach receiving 34 Gy or more).

Palma D, BMC Cancer 2012

Upper abdominal imaging in radiotherapy



4-Dimensional CT scan



Cone-beam CT scan

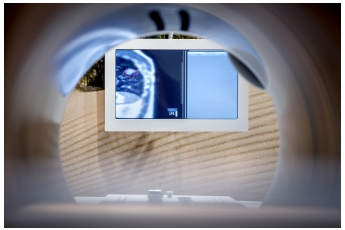
SMART using video-assisted delivery

Stereotactic

MRI-guided

Adaptive

RadioTherapy



MR-guided tumor setup | **Adaptive* planning** | **Online guidance** | **Gated delivery (markerless)**

*Bohoudi O, Radioth Oncol 2017

Advanced Prostate Cancer Consensus (2017)

For discussion, 10 controversial areas related to the management of men with APC that were judged to be most important for discussion were identified:

1. Management of high-risk localised and locally advanced prostate cancer
2. "Oligometastatic" prostate cancer
3. Management of castration-sensitive/naïve prostate cancer (CNCP)
4. Management of castration-resistant prostate cancer (CRPC)
5. Imaging in APC

Gillessen S, Eur Urology 2017

Advanced Prostate Cancer Consensus (2017)

- *No consensus on what constituted oligometastatic prostatic cancer (OPM)*
- *61% voted for a limited bone and/or lymph nodes as a clinically meaningful definition of OPM that influences treatment decisions (local ablative treatment of all lesions ± systemic therapy)*
- *10% voted for an oligometastatic definition including only limited lymph node metastases*
- *13% voted for patients with a limited number of metastases at any location*
- ***10% did not believe that oligometastatic prostate cancer exists** as a clinically meaningful entity*
- *Among the believers, 14% voted for ≤2 metastases, 66% for ≤3 metastases, and 20% ≤5 metastases as a cut-off.*

Gillessen S, Eur Urology 2017

Oligometastases in prostate cancer

Decaestecker *et al. BMC Cancer* 2014, **14**:671
http://www.biomedcentral.com/1471-2407/14/671

BMC Cancer

STUDY PROTOCOL Open Access

Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP): study protocol for a randomized phase II trial

Karel Decaestecker[1], Gert De Meerleer[2], Filip Ameye[3], Valerie Fonteyne[2], Bieke Lambert[4], Steven Joniau[5], Louke Delrue[6], Ignace Billiet[7], Wim Duthoy[8], Sarah Junius[9], Wouter Huysse[6], Nicolaas Lumen[1] and Piet Ost[2*]

Radwan *et al. BMC Cancer* (2017) 17:453
DOI 10.1186/s12885-017-3455-6

BMC Cancer

STUDY PROTOCOL Open Access

CrossMark

A phase II randomized trial of Observation versus stereotactic ablative RadiatIon for OLigometastatic prostate CancEr (ORIOLE)

Noura Radwan[1†], Ryan Phillips[1†], Ashley Ross[2,3], Steven P. Rowe[4], Michael A. Gorin[3], Emmanuel S. Antonarakis[2], Curtiland Deville[1,2], Stephen Greco[1], Samuel Denmeade[2,3], Channing Paller[2], Daniel Y. Song[1,2,3], Maximilian Diehn[5], Hao Wang[2], Michael Carducci[2,3], Kenneth J. Pienta[2,3], Martin G. Pomper[1,2,3,4], Theodore L. DeWeese[1,2,3], Adam Dicker[6], Mario Eisenberger[2,3†] and Phuoc T. Tran[1,2,3*†]

Oligometastases: prostate cancer

Systematic review: SABR in oligorecurrences limited to lymph nodes

- 363 patients, 9 studies; 211 treated with SBRT to 270 lymph nodes
- Mean BED_{3Gy} in fractionated SBRT ranged from 88-216 Gy

- Median follow-up of 19.2 months; local control in 98% of patients.
- Median Pprogression Free Survival (biochemical and/or radiological progression) 22.5 months (range, 11-30)
- Median ADT-free survival was 32.8 months (range, 25-44)
- Acute and/or late grade ≥2 toxicity in 6%; no grade 4 toxicity

CONCLUSIONS:

- SBRT is promising but weak level of evidence based on retrospective studies of single-institution or pooled experiences

Ponti E, Eur Urology Focus 2017

ADT and health-related quality of life

Phase III TOAD trial: Effects of androgen-deprivation therapy on health-related quality of life in asymptomatic patients who have either a rising PSA after curative radiotherapy or prostatectomy but no overt disease, or who have non-curable disease at the outset

- Sexual activity lower in the **immediate therapy group** than in the delayed group at 6 and 12 months, with the differences exceeding the clinically significant threshold of 10 points until beyond 2 years
- **Immediate therapy group** had more hormone-treatment-related symptoms at 6 and 12 months in the immediate group, but differences were below the threshold of clinical significance
- Immediate therapy group had clinically significantly higher incidence of hot flushes over the 5-year period, as were nipple or breast symptoms

Duchesne GM, Lancet Oncol 2017

ADT and cardiac disease

- Prospective cohort study 7637 subjects, nearly 30% exposed to ADT
- **Multivariable analyses:** In men without preexisting CVD, ADT was associated with an increased risk of heart failure **(adjusted HR=1.81**, 95% CI 1.40–2.32**)**
- Only among patients with **preexisting CVD** was elevated risks of **arrhythmia (adjusted HR=1.44**, 95% CI 1.02–2.01), and **conduction disorder (adjusted HR=3.11**, 95% CI 1.22, 7.91) observed

Haque R, BJC 2017

Wait-and-see may be unacceptable

JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

Fear of Cancer Recurrence in an Era of Personalized Medicine

Belinda Thewes, Olga Husson, Hanneke Poort, Jose A.E. Custers, *Radboud University Medical Center, Nijmegen, the Netherlands*
Phyllis N. Butow, *The University of Sydney, Sydney, New South Wales, Australia*
Sue-Anne McLachlan, *St Vincent's Hospital, Melbourne, and The University of Melbourne, Parkville, Victoria, Australia*
Judith B. Prins, *Radboud University Medical Center, Nijmegen, the Netherlands*

Thewes B, JCO 2017

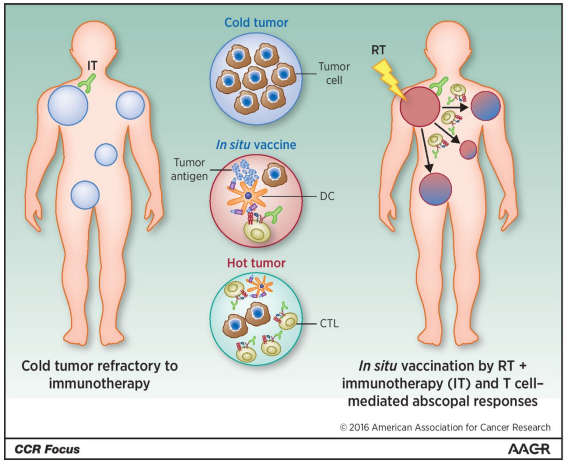
SABR and the immune system

REVIEWS

NATURE REVIEWS | CLINICAL ONCOLOGY

Radiotherapy and immunotherapy: a beneficial liaison?

Ralph R. Weichselbaum[1], Hua Liang[1], Liufu Deng[1] and Yang-Xin Fu[2]



Whiteside TL, Clin Cancer Res 2016

American Journal of Respiratory and Critical Care Medicine/AJRCCM

ATS

STEREOTACTIC ABLATIVE RADIOTHERAPY INDUCES PERIPHERAL T-CELL ACTIVATION IN EARLY STAGE LUNG CANCER PATIENTS

Authors:
Pauline L. de Goeje[1], Egbert F. Smit[2], Cynthia Waasdorp[1*], Merel T.B. Schram[1,3], Margaretha E.H. Kaijen-Lambers[1], Koen Bezemer[1], Mark de Mol[1,3], Koen J. Hartemink[4], Joost J.M.E. Nuyttens[5], Alexander P.W.M. Maat[6], Joost P.J.J. Hegmans[1], Rudi W. Hendriks[1], Suresh Senan[7], Joachim G.J.V. Aerts[1,3]

SCIENTIFIC REPORTS

OPEN

Hypofractionated stereotactic radiation therapy activates the peripheral immune response in operable stage I non-small-cell lung cancer

Received: 17 November 2016
Accepted: 23 May 2017
Published online: 07 July 2017

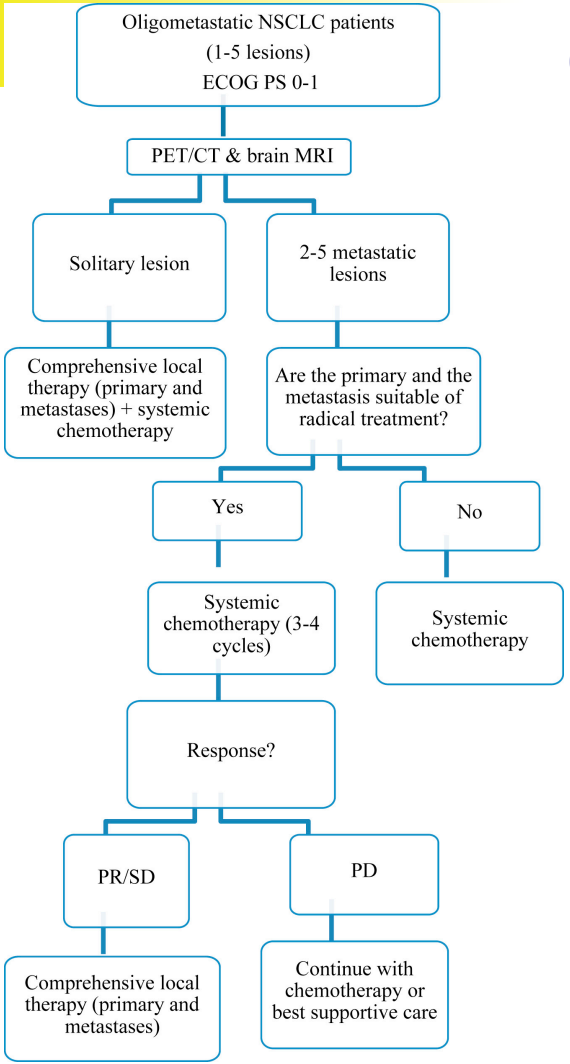
Ting Zhang[1,4], Haifeng Yu[2], Chao Ni[3], Tao Zhang[4], Luying Liu[4], Qinghua Lv[4], Zhigang Zhang[4], Zhen Wang[5], Dang Wu[1,4], Pin Wu[4], Guodi Chen[2], Liancong Wang[3], Qichun Wei[3], Jian Huang[4] & Xiaojian Wang[5]

Oligometastases: An overview

- Definitions and biological rationale
- Evidence from clinical trials, meta-analysis, single and multi-institutional data
- Implementation

Treatment outside studies

Proposed therapeutic Approach for Wild-type NSCLC with oligometastases



Juan O, Clin Lung Ca 2017

Thank you for listening

Department of Radiation Oncology
Chairman: Prof. Dr. Matthias Guckenberger

Stereotactic radiotherapy combined with novel drugs

Matthias Guckenberger

UniversityHospital Zurich

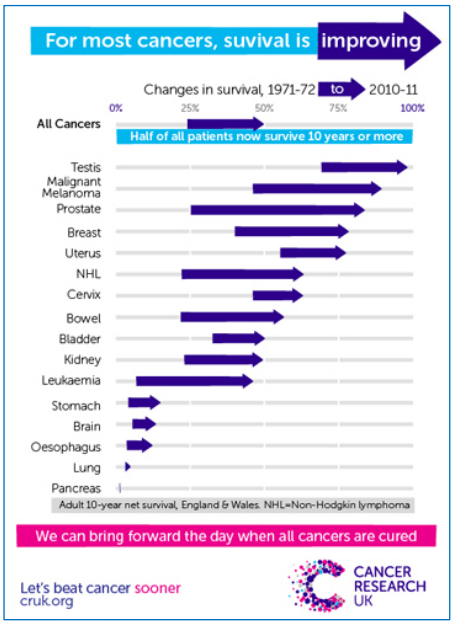
Overview

1. General outline
2. SBRT combined with targeted drugs
3. SBRT combined with immunotherapy
4. Safety of SBRT combined with novel drugs

Overview

1. General outline
2. SBRT combined with targeted drugs
3. SBRT combined with immunotherapy
4. Safety of SBRT combined with novel drugs

Overall survival in cancer patients



- Early detection of cancer
- More effective radical Tx
- More effective systemic Tx

➢Cancer as a chronic disease is coming closer

Approved targeted drugs

Medical Oncology

Cetuximab	Colorectal
Panatimumab	Breast
Bevacizumab	Pancreas
Trastuzumab	NSCLC
Ipilimumab	Glioblastoma
Pembrolizumab	Renal cell cancer
Nivolumab	GIST
Afatinib	Thyroid
Lapatinib	Head & Neck
Axatinib	….
Sorafenib	
Sunitinib	
Pazopanib	
Vandetanib	
….	

Radio-Oncology

Cetuximab	Head & Neck

Unsuccessful

Cetuximab	RCHT Head & Neck
	Rectal cancer
	Esophageal cancer
	NSCLC
Bevacizumab	Glioblastoma

➢ Combining targeted drugs & conventionally fractionated radio(chemo)therapy has been an unsuccessful strategy

Adoption of SBRT in the (oligo)-metastatic situation

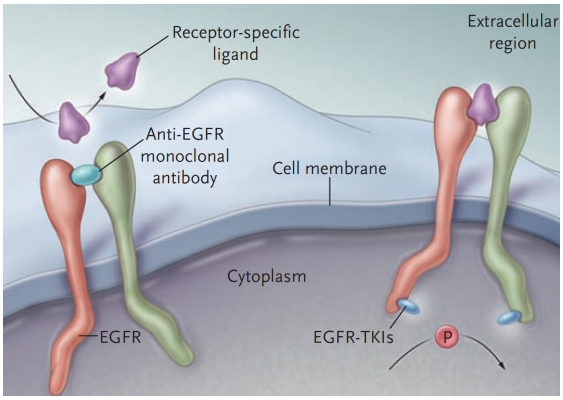
International Survey of 1007 Radiation Oncologists

Adoption of SBRT for oligometastasis	Overall	Western Europe
	61%	76%

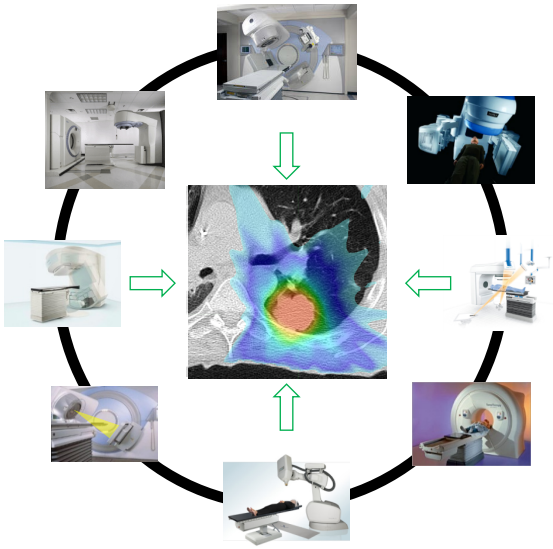
Lewis American Journal of Clinical Oncology 2015

➢ SBRT for oligo-metastasis has become a standard of care

„Targeted“ SYSTEMIC Therapy



„ Targeted“ LOCAL Therapy



Rational for combining SRT and targeted drugs

Locally recurrent disease Re-irradiation	(Oligo)-metastasis (Oligo)-progression	Symtomatic metastases
➢ Radiosensitizer to decrease RT-induced toxicity	➢ Eradication of oligo-resistant clones ➢ Immune modulation	➢ Long term palliation ➢ Symptom prevention

➢Promising field for pre-clinical and clinical research

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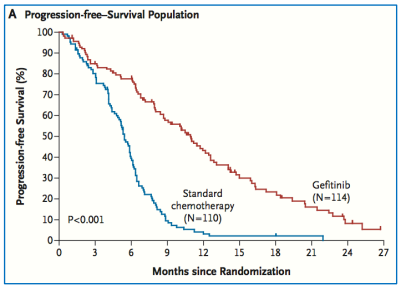
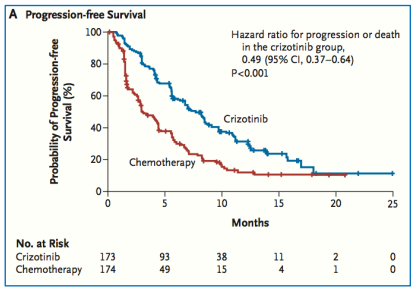
Rational for combining targeted drugs & SRT

Gefitinib
in mutant EGFR



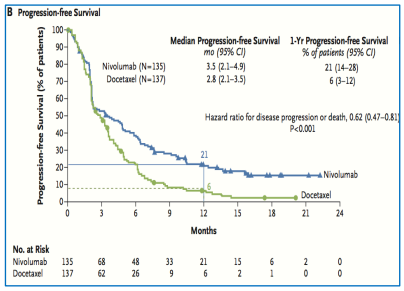
Maemondo NEJM 2010

Crizotinib
in ALK positive



Shaw NEJM 2013

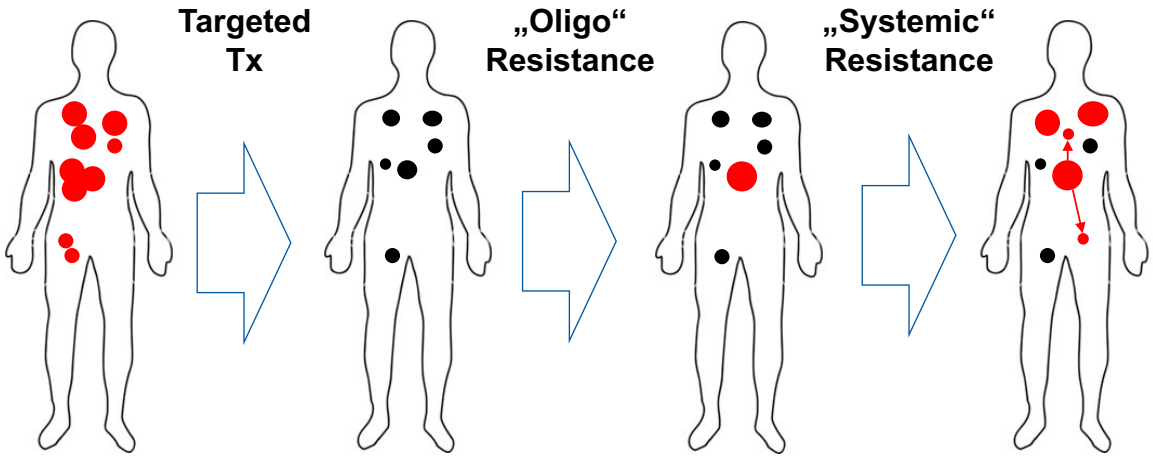
Nivolumab
in unselected patients



Brahmer NEJM 2015

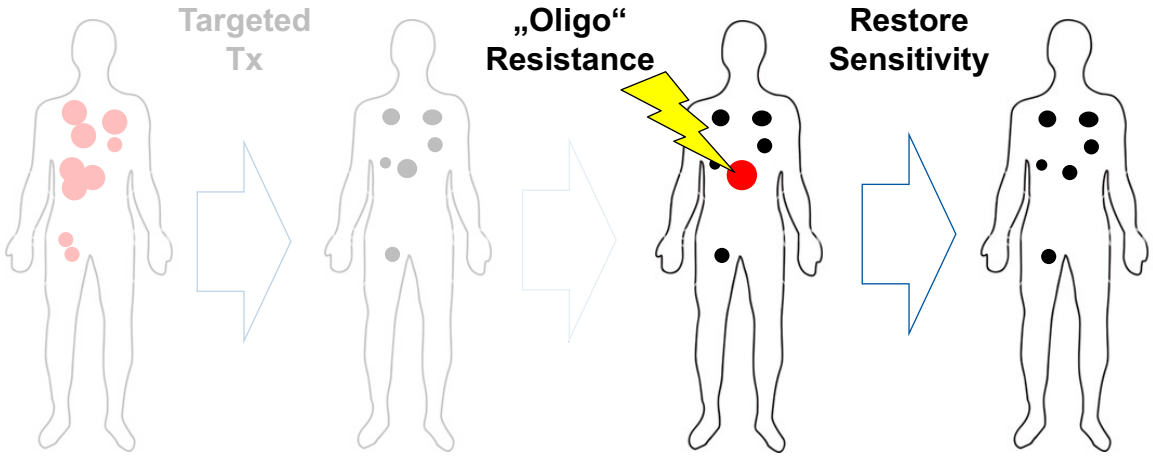
- Substantial and clinically relevant improvement
- Still: 60 – 80% develop PD after 12 months

Acquisition of resistance



- Development of acquired resistance unlikely a systemically parallel process but a cascade of sequential events

Acquisition of resistance:
A potential role for targeted radiotherapy



- Local eradication of the oligo-resistant tumor site(s) to restore a sensitive state and continue the systemic Tx

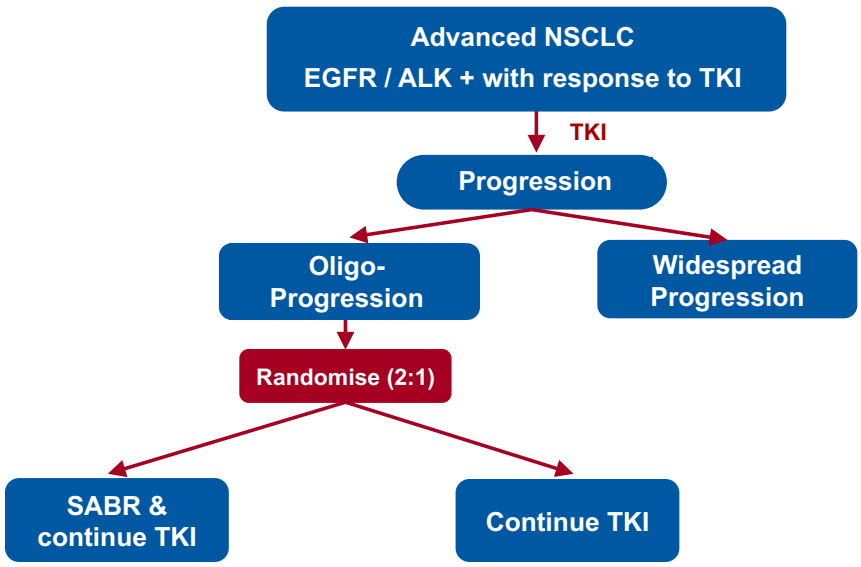
Oligo-progression: SBRT & systemic Tx beyond progression

Retrospective Analysis ***Weickhardt JTO 2012***

- 65 metastatic NSCLC patients
- ALK+ and EGFR-MT treated with Crizotinib and Erlotinib, respectivey

- Oligo-progression in 20 – 50%
- Phase II EORTC HALT study in preparation

HALT study in preparation



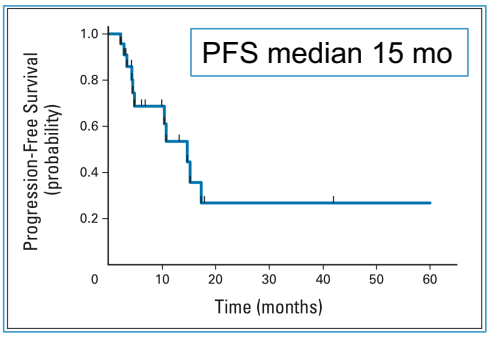
- Oligo defined as max. 3 metastases
- SBRT doses below 100Gy BED

Oligo-progression: SBRT & switch to next line systemic Tx

Prospective Phase II trial: 24 patients with 52 sites

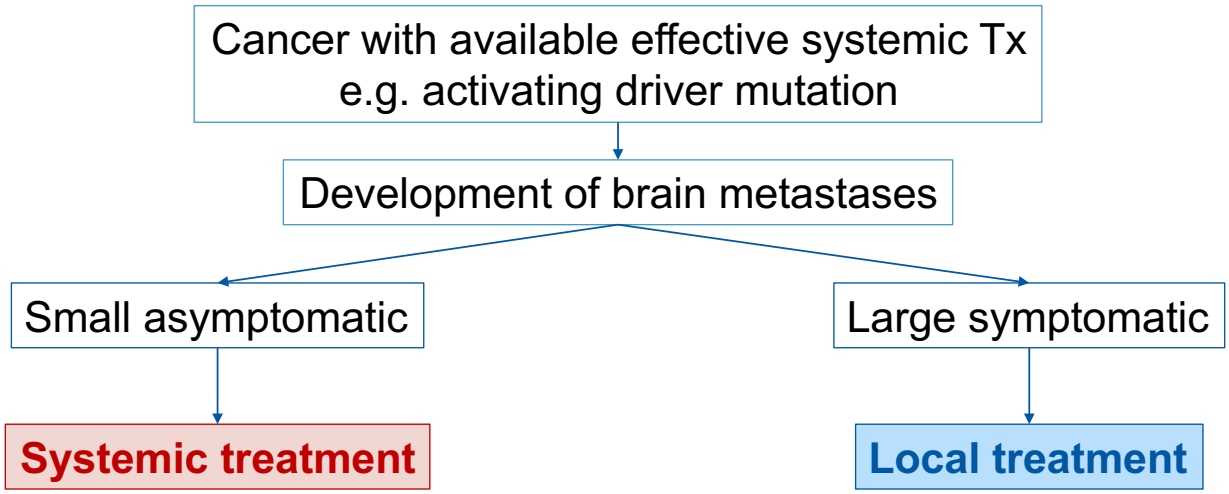
- Maximum 5 Platin-resistant sites based on FDG-PET
- SBRT to all progressive sites,
- Switch to concurrent Erlotinib *Iyenger JCO 2014*

In-field failure	**3 / 21**
Out-field failure	**10 / 21**
No failure	**10 / 21**



- ➢ Highly favorable failure pattern
- ➢ Promising OS (in highly selected patients)

Brain mets in patients with driver mutations



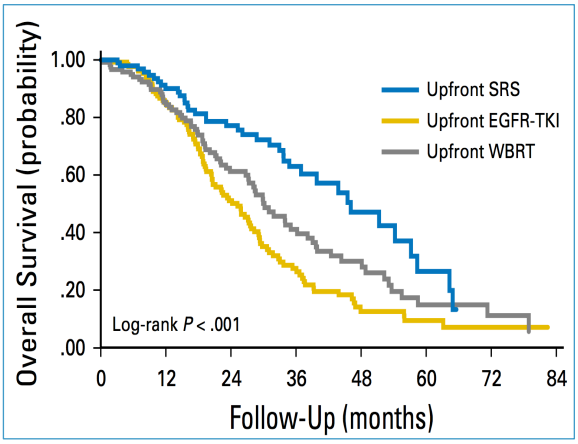
➢ Safe concept to delay local RT / SRS ?

Brain mets in patients with driver mutations

Magnuson JCO 2016

Retrospective multi-institution study: n=351

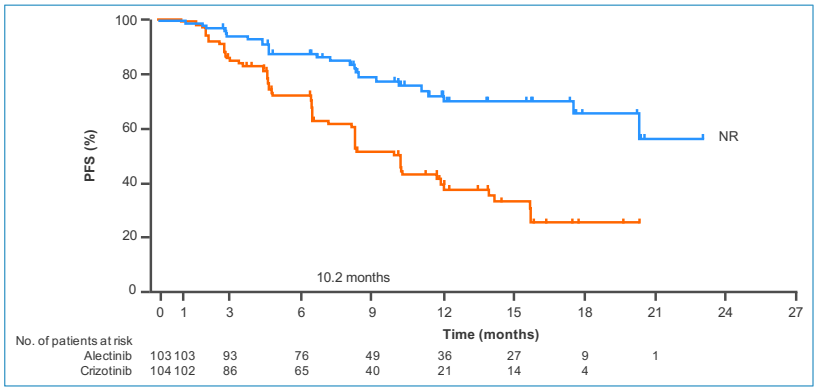
Brain mets	EGFR-TKI N=131	WBI N=120	SRS N=100
n < 5	64%	27%	72%
< 1cm	66%	35%	44%
asymptomatic	88%	49%	51%



➢ Upfront SRS in small & asymptomatic brain mets improves OS

Brain mets in patients with driver mutations

Randomized Japanese study of Crizotibib vs Alectinib in FL
14 – 28% with brain metastases



Primary EP PFS

Overall	With BM
HR 0.24	HR 0.08

Nokihara ASCO 2016

➢ Excellent PFS in patients treated with Alectinib
➢ Role or radiotherapy in drugs with goof BBB penetration?

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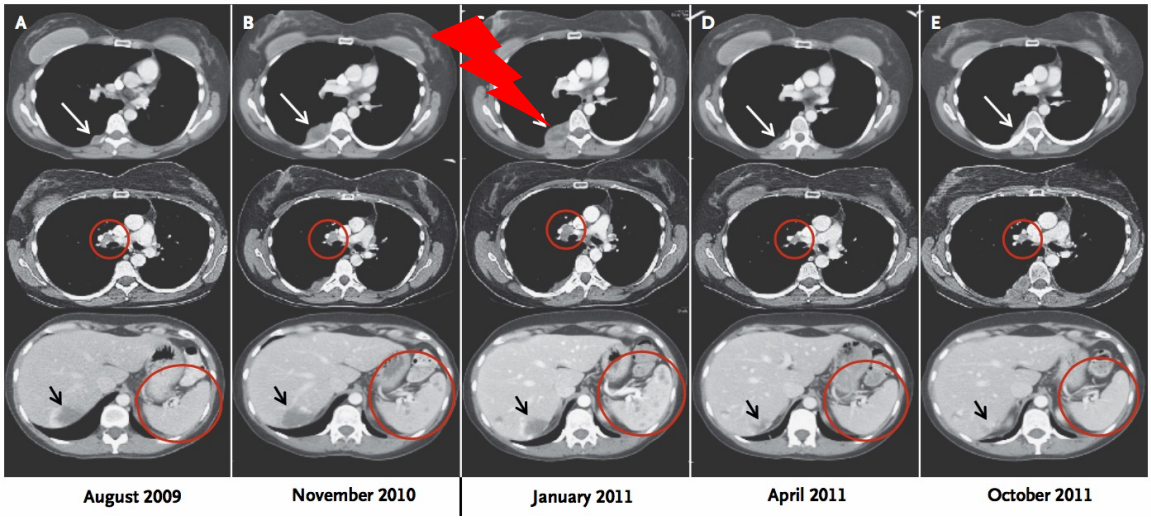
Abscopal effect – a case report



Postow NEJM 2012

Recurrence → Start Ipi → PD → Response → SD

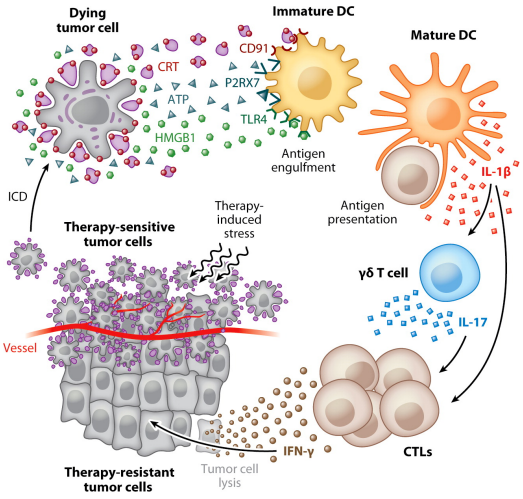
➢ Local RT inducing a systemic immune response

Abscopal effect

„ab-scopus“: away from the target

- ***Systemic*** tumor response induced by ***local*** radiotherapy

Cancer cell: immunogenic cell death



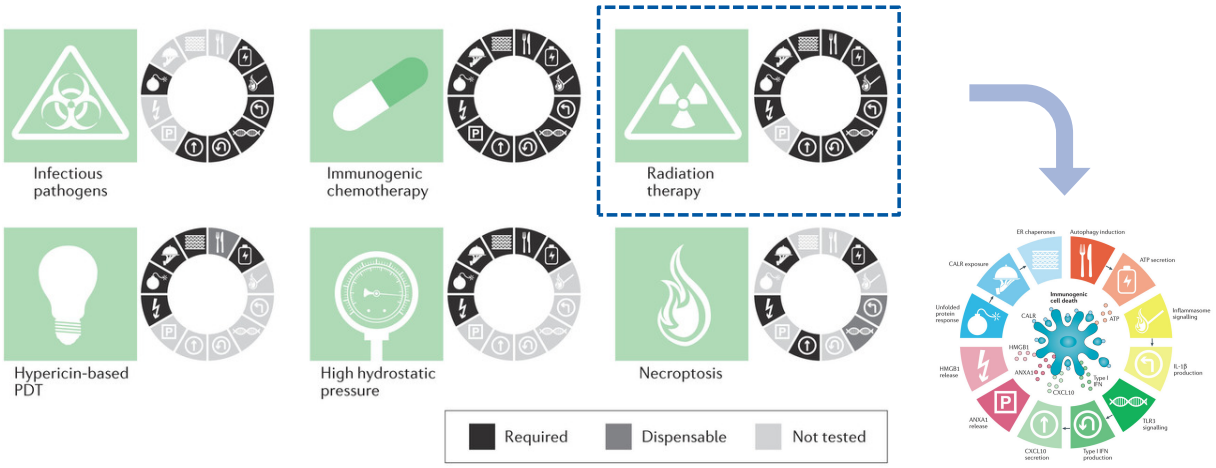
- Changes in the composition of the cell surface
- Release of soluble mediators

➢ Increased presentation of tumor antigens to T-cells via dentitic cells

Kroemer Annual Review of Immunology 2013

➢ „ICD constitutes a prominent pathway for the activation of the immune system against cancer, which in turn determines the long-term success of anticancer therapies“

Triggers of immunogenic cell death

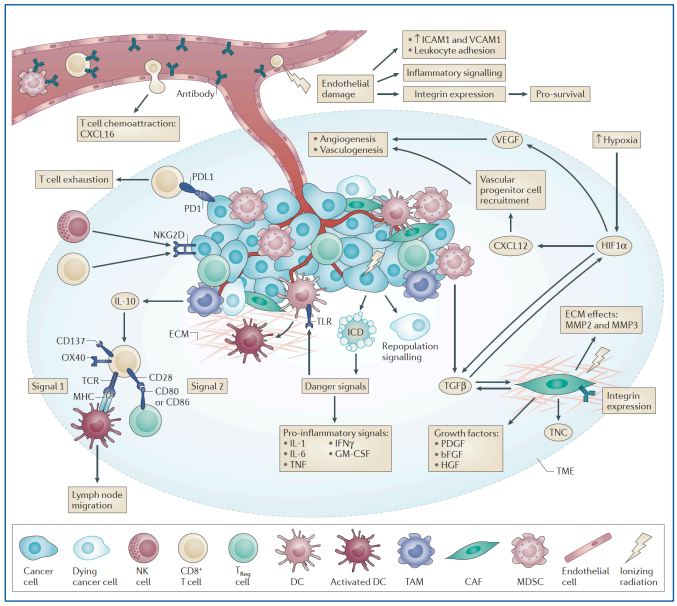


Galluzzi Nature Reviews 2016

- Radiation, photodynamic therapy and high hydrostatic pressure only documented physical triggers of ICD (not freezing or boiling)

Micro-enviroment

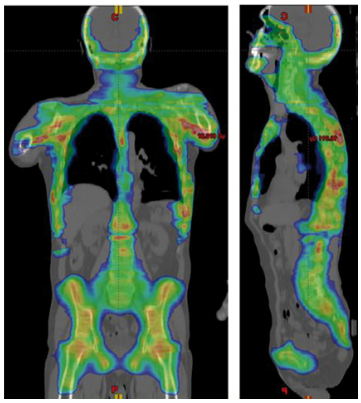
Barker Nature Reviews Cancer 2015



- ➢ Radiation induces vascular, stromal and immunological changes in the tumor microenviroment

Radiotherapy – a double sided sword

Total body / morrow irradiation



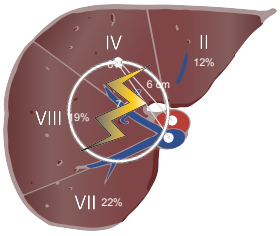
➢ Systemic immunosupression

Painful heel spur irradiation

➢ Local anti-inflammatory

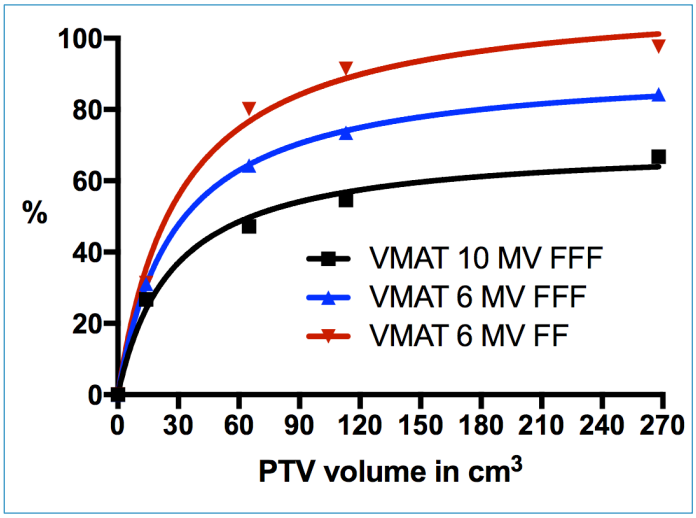
- Radiotherapy established anti-inflammatory and immune-supressive treatment

Immuno-RT – new OARs to consider ?



Proportion of circulating lymphocytes inativated (>0.5%) by liver SBRT

Basler, Tanadini submitted



- Low-dose spread to lymphaytic system (circulating blood, lymph nodes, bone marrow) to be considered

Maximizing immunogenic effect of RT

Abuodeh Curr Probl Cancer 2016:

- **46** reported cases from 1969 to 2014

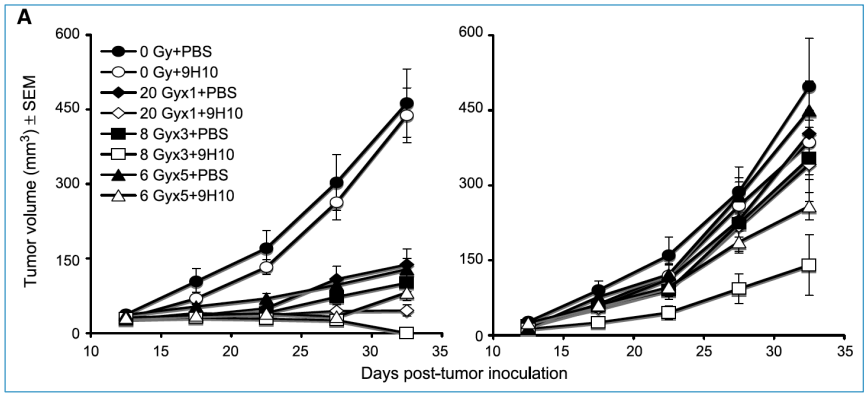
Insufficient

- **How can we influence and maximize the immunogenic effect of radiotherapy?**

Fractionation of RT

0Gy
1 x 20Gy
3 x 8Gy
6 x 6Gy

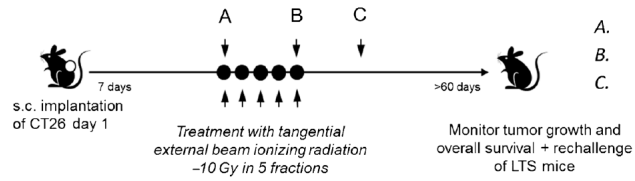
Breast and colon cancer mouse model



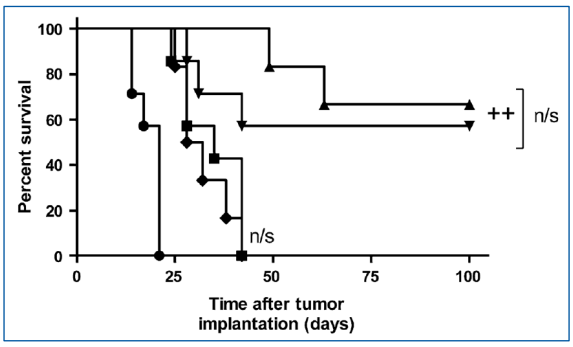
Dewan Clin Cancer Res 2009

- Abscopal effect induced by hypo-fractionated and not single fraction RT combined with anti–CTLA-4

Timing of RT and immunotherapy



A – Start of RT
B – End of RT
C – after RT



concurrent

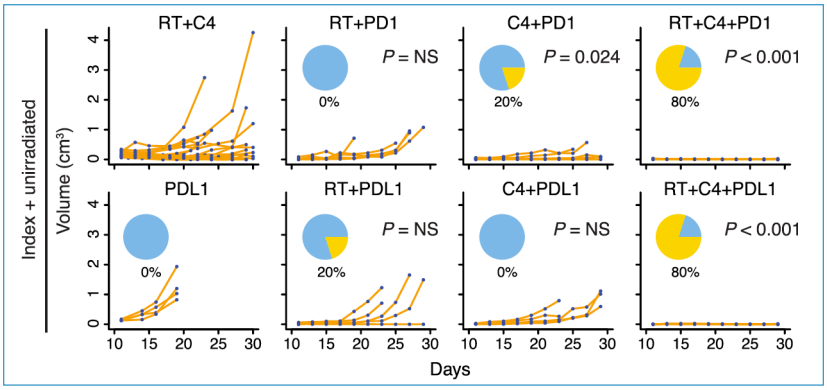
sequential

Dovedi Cancer Res 2014

- Sequencing of RT and immunotherapy relevant
- Concurrent application

Combination of RT with immunotherapy

Melanoma mouse model



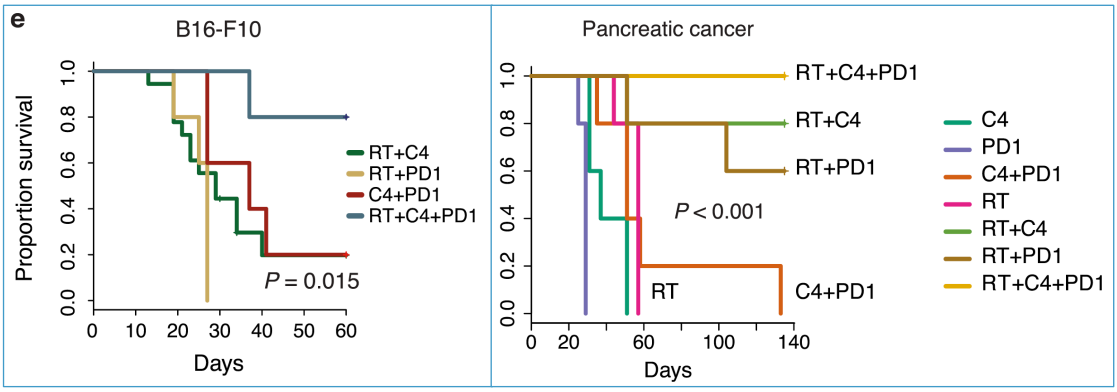
	PDL1	C4 & PDL1	C4 & PD1	RT & C4 & PD1 / PDL1
CR	0%	0%	20%	80%

Twyman-Saint Victor Nature 2015

- Relevant complete response rates only after radiotherapy and double checkpoint inhibition

Combination of RT with immunotherapy

Melanome mouse model **Pancreatic cancer mouse model**



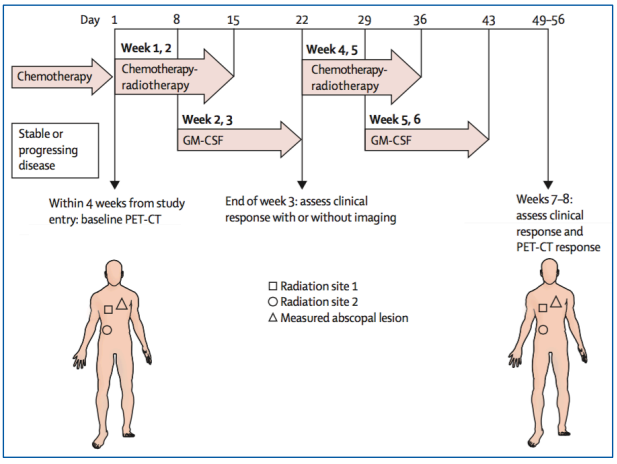
Twyman-Saint Victor Nature 2015

- ➢ High „cure" rates only after RT & double CPI
- ➢ Reproducible in melanoma & pancreatic cancer model

Proof of principle: *Golden Lancet Oncol 2015*

Inclusion criteria:

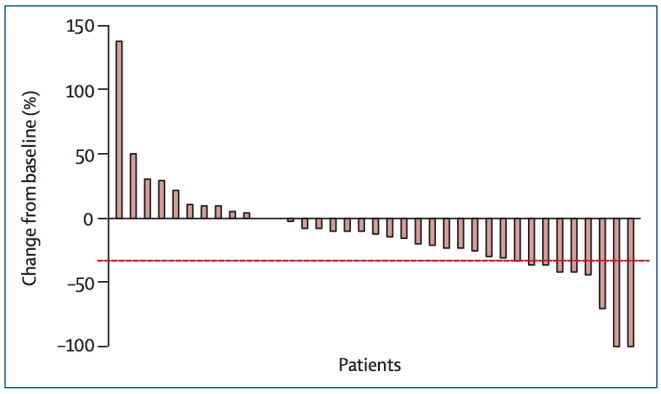
- Stable or progressing metastatic solid tumours
- At least three distinct measurable sites of disease
- On single-agent chemotherapy or hormonal therapy



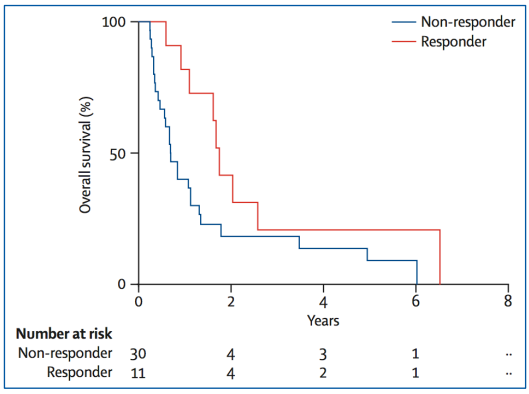
- 80% NSCLC & Breast cancer
- RT 10 x 3,5Gy
- 2 targets irradiated

Proof of principle: *Golden Lancet Oncol 2015*

Response



Survival



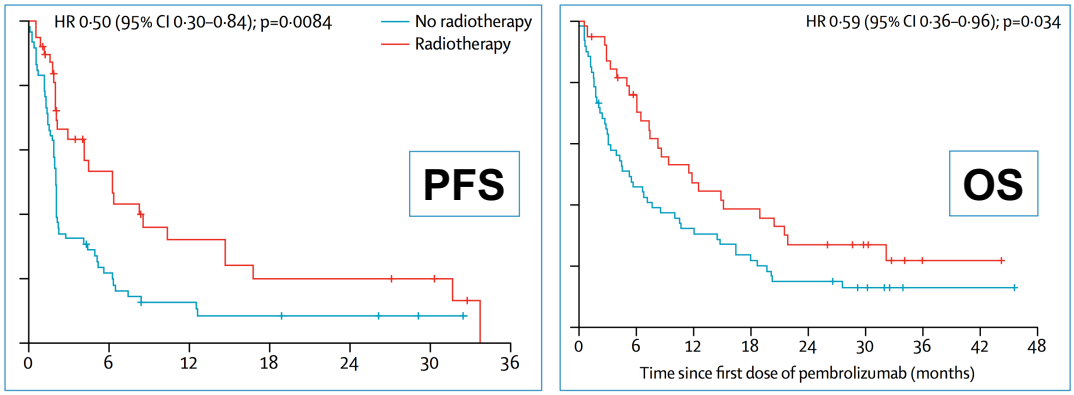
Abscopal response: 11/41 (26.8%) Improved OS in responders

- ¼ of the patients with abscopal effect
- Improved OS in patients with abscopal effect

Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial

Shaverdian Lancet Oncol 2017

Prior RT	42 (43%)



- Palliative RT in 61%; SRT in only 25%
- Tx-related pulmonary toxicity: (n=3) vs (n=1)

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Use of concurrent SRT and novel drugs in the DEGRO society

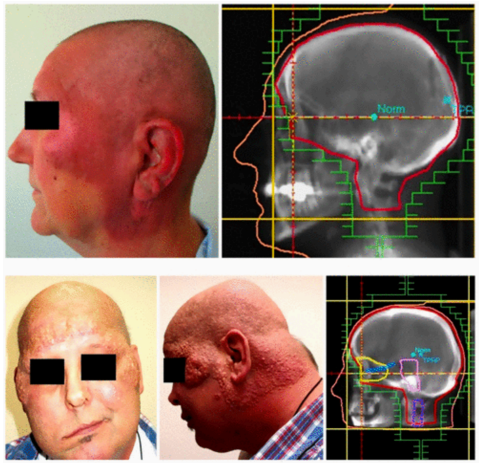
Targeted therapy	Targeted therapy simultan zur SBRT n (%)
Antikörper	
Bevacizumab	0
Ipilimumab	8 (30%)
Cetuximab	7 (26%)
Panitumumab	5 (19%)
Trastuzumab	14 (52%)
Nivolumab	7 (26%)
Pembrolizumab	7 (26%)
Tyrosine Kinase Inhibitoren	
Vemurafenib	2 (7%)
Sorafenib	4 (15%)
Erlotinib	7 (26%)
Lapatinib	6 (22%)
Gefitinib	5 (19%)
Crizotinib	5 (19%)

➢ Concurrent treatment with SRT and targeted drugs performed by many institutions, already

Combination of conventional radiotherapy & targeted drugs

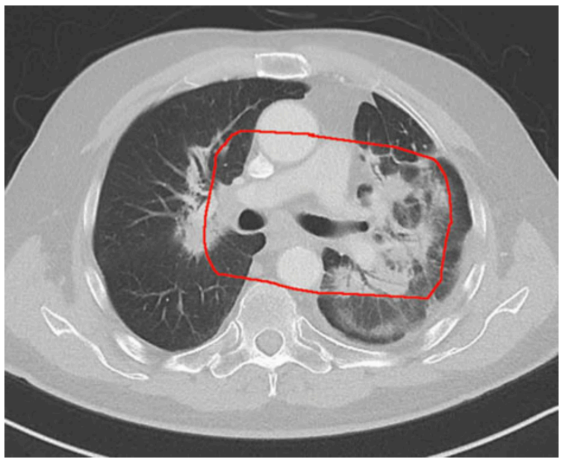
Vemurafenib

Schulz Strahlentherapie Onkologie 2014



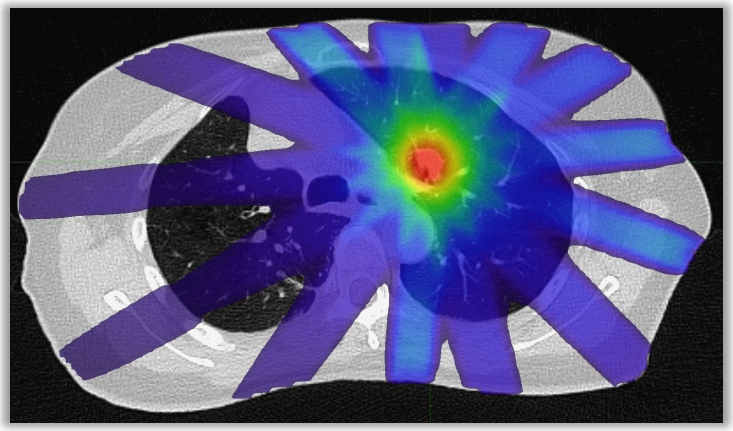
Erlotinib

Award Clinical Oncology 2016



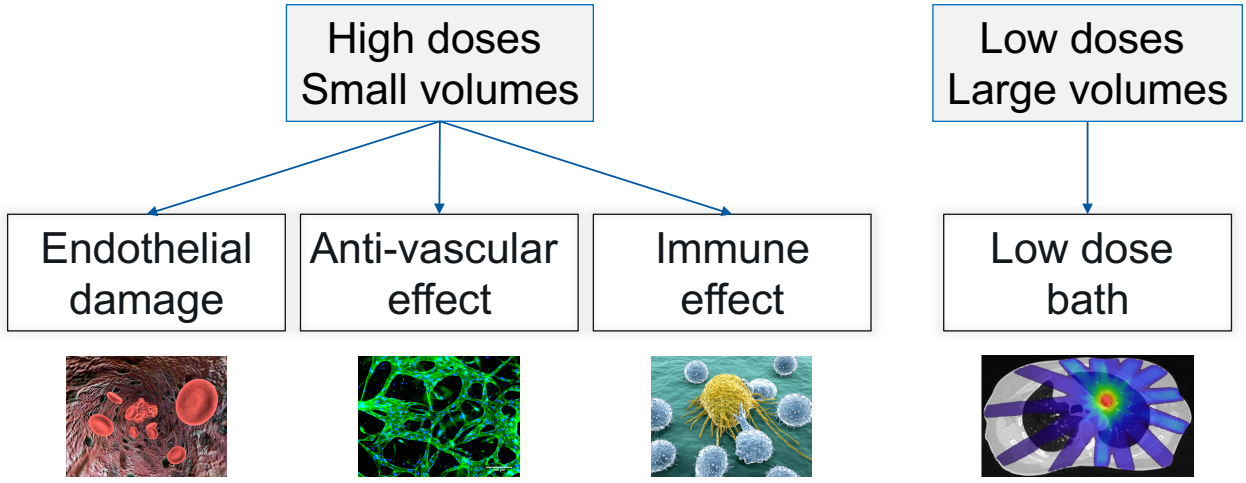
- Relevant and increased risk of severe toxicity

Stereotactic radiotherapy



- Very high doses in gross tumor volume
- Very high doses in small normal tissue volumes
- Intermediate doses in only small normal tissue volumes
- Low doses in large normal tissue volumes

Potential biological consequences of SBRT dose distributions



➢Potential of altered toxicity profile in SRT

Systematic review: SRT & targeted drugs

	Patients	Cranial	Extracranial
Antibodies			
anti-EGFR / VEGF / HER2			
Bevacizumab	215	201	14
Trastuzumab	7	7	0
Cetuximab	244	0	244
anti-CTLA-4			
Ipilimumab	121	119	46
anti-PD-1			
Nivolumab	27	27	0
Small molecules			
EGFRi			
Sorafenib	61	45	61
Sunitinib	76	75	62
Gefitinib/Erlotinib	71	43	48
ALKi			
Crizotinib	39	15	39
BRAFi	129	128	20
MEKi			
Trametinib	4	4	0
Total	**994**	**664**	**534**

- Very little data available considering large number of drugs, cancer types and treatment sites *(Kroeze Cancer Treat Rev. 2017)*

Systematic review: SRT & targeted drugs

	Patients	Cranial	Extracranial
Antibodies			
anti-EGFR / VEGF / HER2			
Bevacizumab	215	201	14
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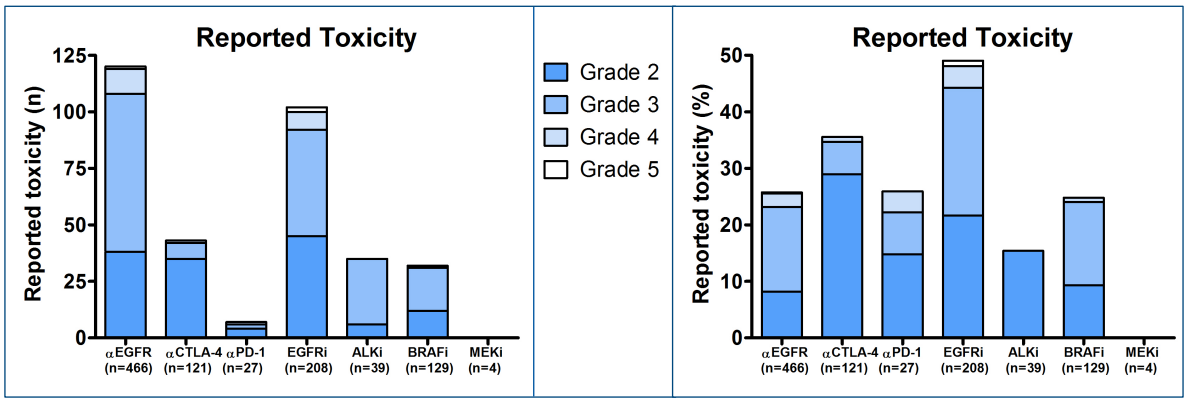
anti-PD-1			
Nivolumab	27	27	0
Small molecules			
EGFRi			
Sorafenib	61	45	61
Sunitinib	76	75	62
Gefitinib/Erlotinib	71	43	48
ALKi			
Crizotinib	39	15	39
BRAFi	129	128	20
MEKi			
Trametinib	4	4	0
Total	**994**	**664**	**534**

Kroeze Cancer Treat Rev. 2017

- **0 - 20** **21 – 100** **>101**

Systematic review: SRT & targeted drugs



Kroeze Cancer Treat Rev. 2017

- Overall, few grade IV and grade V toxicities
- Less toxicity in brain SRS compared to SBRT

Systematic review: SRT & targeted drugs

Concerns of increased toxicity:

Drug	SRT location	Toxicity
Cetuximab	Head and neck	Mucositis, dermatitis, fistula
Sorafenib	Abdomen	Bleeding, bowel obstruction
Gefitinib, Erlotinib	Thoracic	Pneumonitis
Bevacizumab	Abdominal	Ulcer, perforation
BRAF inhibitors	Brain	Hemorrhage

- For many combinations, NO data available

DEGRO AG Stereotaxie Project: TOaSST

Register Study of concomitant use of SRT and targeted drugs

Eligibility criteria:

- Treatment of **any metastatic tumor** with
- **Stereotactic radiotherapy**
- and any **targeted drug** (antibodies, small molecules, immunotherapy)
- within **+ / - 4 weeks** prior and after SBRT

Primary endpoint:

- High grade toxicity > grade II

Secondary endpoints:

- OS, LC, DFS

DEGRO AG Stereotaxie Project: TOaSST

Register Study of concomitant use of SRT and targeted drugs

Study design:

After SRT:
- Patient, tumor, treatment characteristics

3 months:
- Acute toxicity

12 months:
- Late toxicity
- OS, LC, DFS

Discontinuation of TKI

Disease flare: rapid disease progression in patients with TKI resistance after discontinuation of systemic treatment

MSKCC experience on disease flare:

N=61 NSCLC with mEGFR and TKI treatment
Resistance development

⇩

TKI discontinuation

⇩

N=14 (**23%**) Disease flare: hospitalization or death
Median 8 days (3-21)

Chaft Cancer Res 2011

➢ Minimize procedures with risk of discontinuation of systemic Tx

C O N C L U S I O N S

- SBRT in the metastatic situation is growing rapidly
- SBRT is frequently combined with novel drugs
- Lack of efficacy and especially safety data for many drugs and treatment sites

➢ ***Further research needed***

MEDICAL UNIVERSITY OF VIENNA

COMPREHENSIVE CANCER CENTER VIENNA

Universitätsklinik für Strahlentherapie und Strahlenbiologie Wien

The Challenge of Brain Metastases

Karin Dieckmann

Department of Radiotherapy

Medical University of Vienne

Questions

1. OARs tolerance dose for hypofractionated SRS example 30Gy/5#, brainstem? Optic nerves?chiasm?

2. Number of IC mets to be meaningfully
   Number of IC mets to be meaningfully treated with SRS vs. WBRT

3. Are there special concerns with inhomogeneous dosing in brain mets as opposed to for example lung mets?

4. Different fractionation doses/fractionation schedules depending on met size (cut-offs?) and location?

5. Recommandations for patient positioning fixation for SBRT in thorax and CNS

Outline

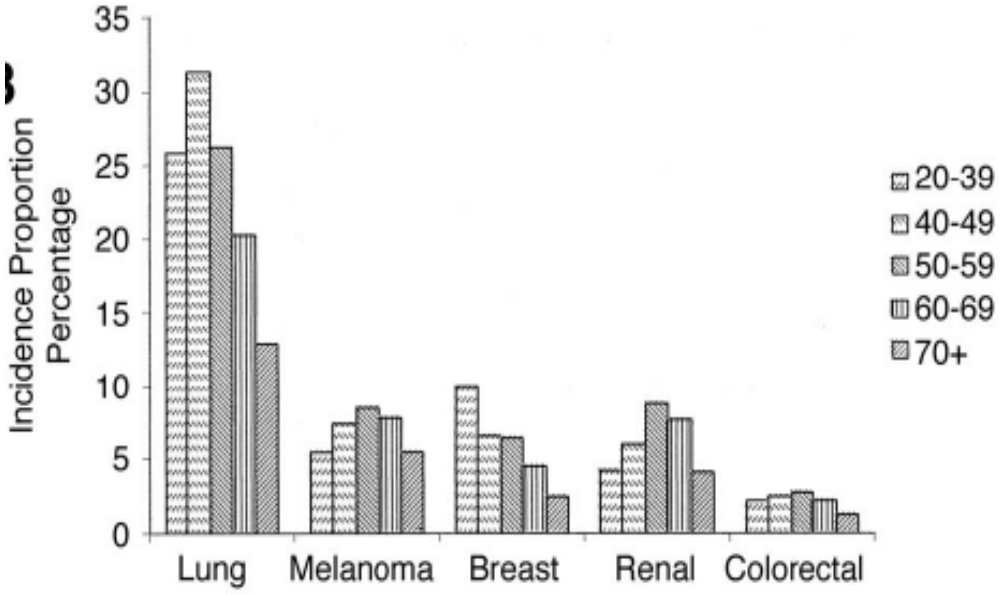
- General aspects
- Treatment options
  - Operation
  - Radiotherapy
    - » Radiotherapy indications
    - » Radiotherapy techniques
  - Chemotherapy
    - » Immunotherapy
    - » Target systemic therapy; tyrosine kinase inhibitors, antibodies

Research Themes over the Decades

Years	Research themes
1970s	Steroids, WBRT
1980s-1990s	Altered fractionation WBRT schemes, surgery for single BM, WBRT and radiosensitizers
1990s-2000s	RS, neurocognition, prognostic scales
2000s and beyond	RS, focal RT techniques, targeted therapies, neurocognition, molecular subtyping for Prognoses and prediction, chemoprevention of brain metastases

Incidence of brain metastases

- Occur in 10-40% of all adult cancers
- Approx. 10 times more frequent than primary brain tumors
- Relative incidence increasing, due to
  - Effective systemic treatments → with longer survival
  - Improved imaging techniques and their increased availability
- Approx. half of all brain mets due to NSCLC, others:
  - Breast cancer
  - Melanoma
  - Unknown primary
  - Renal cell carcinoma

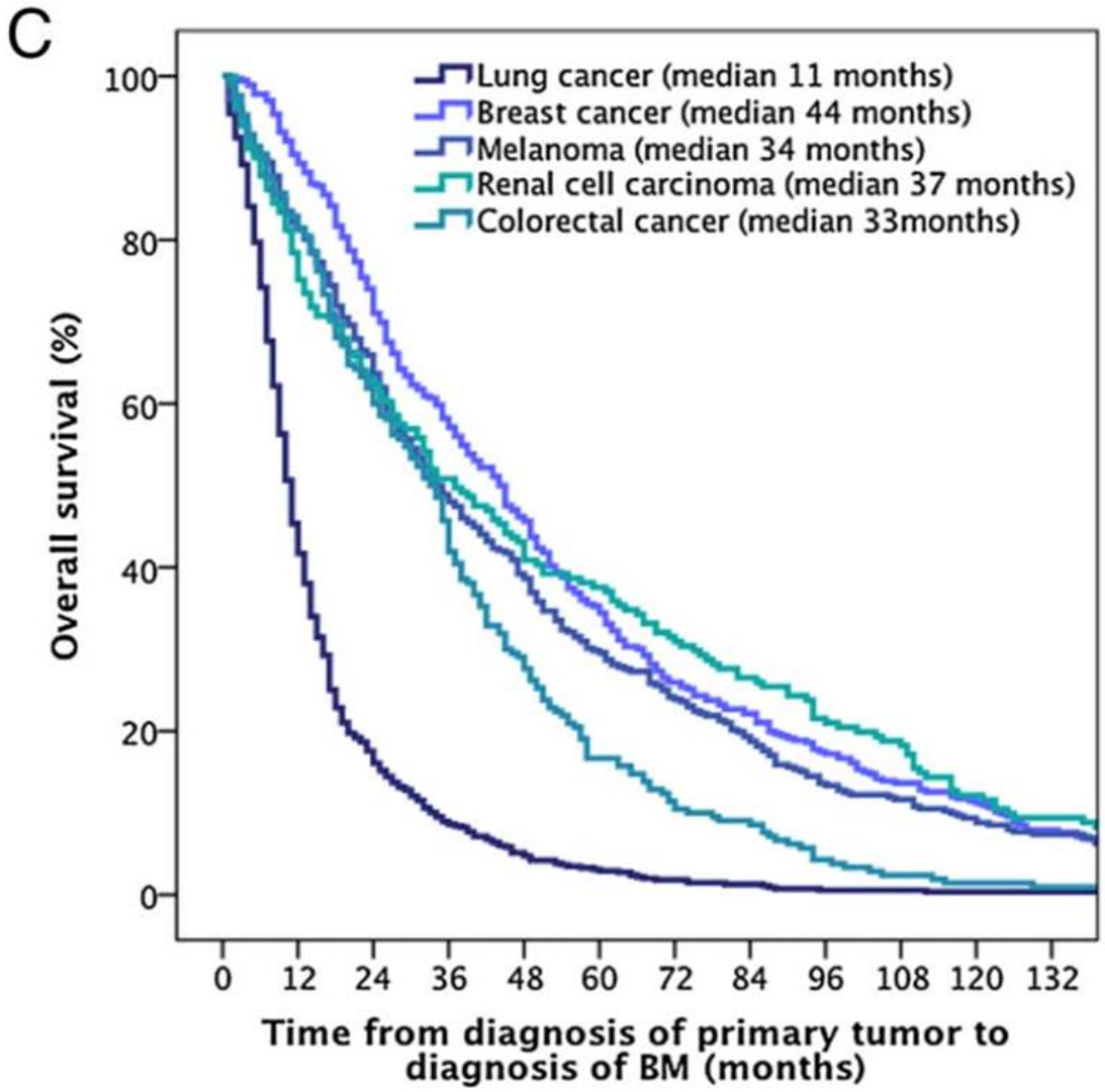


Barnholtz-Sloan… Sawaya RE. J Clin Oncol 22:2865-72, 2004

Descriptive statistical analysis of a real life cohort of 2419 patients with brain metastases of solid cancers

Anna S Berghoff,[1,2] Sophie Schur,[1,2] Lisa M Fü
Karin Dieckmann,[2,4] Georg Widhalm,[2,3] Johann
Christoph C Zielinski,[1,2] Peter Birner,[2,6] Rupert

Time to brain metastases



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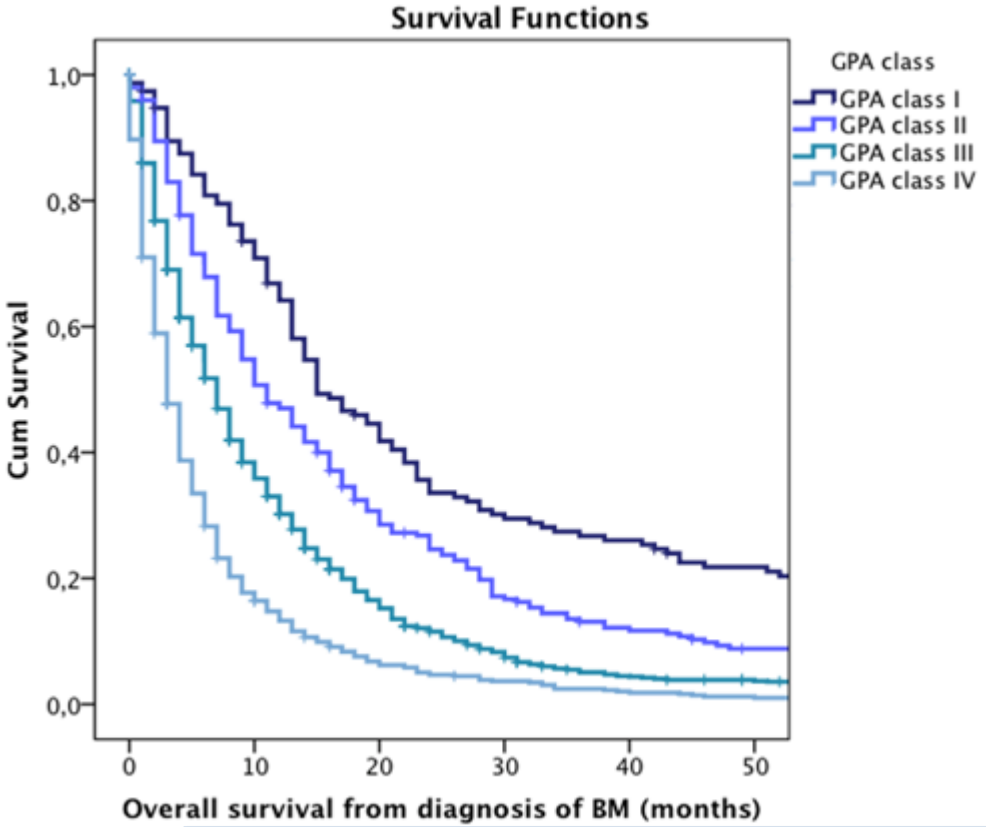
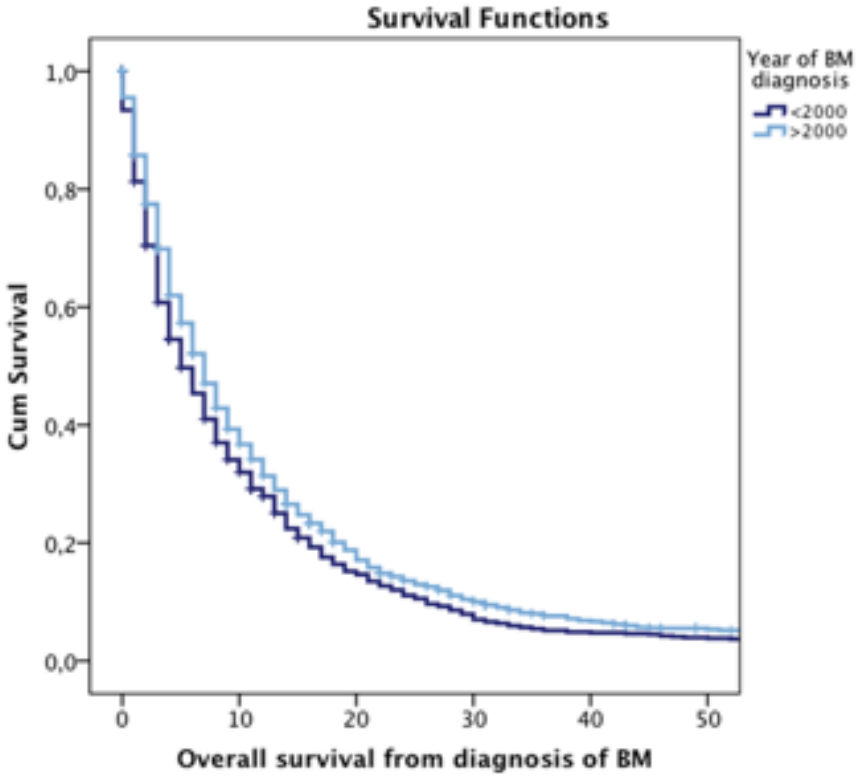
All patients

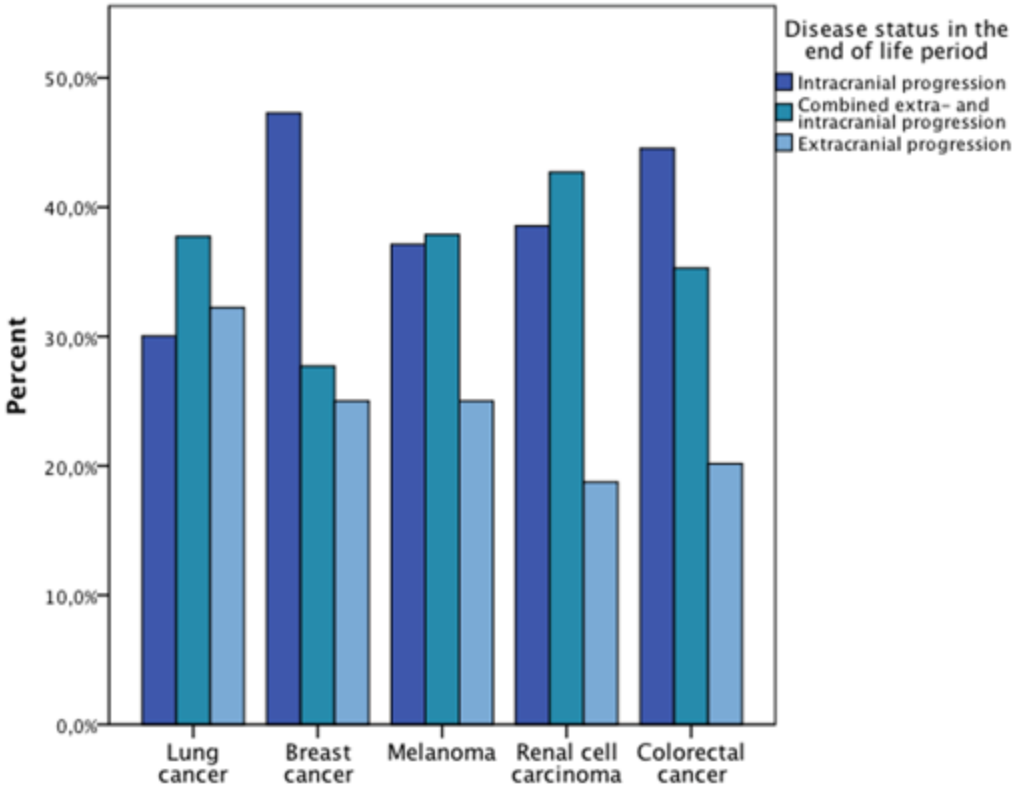




- Survival depends by GPA class

Extra- vs. Intracraniel Disease

- Cause of death in patients with brain metastases
  - 1/3 systemic Progression
  - 1/3 intracranial Progression
  - 1/3 combination
- Differences are depending on histology



Berghoff et al; ESMO Open 2016

Symptoms and clinical presentation

- High variability in clinical presentation of brain metastases

- Symptoms depend on the localization of the cerebral lesions
  - focal neurological deficits
  - aphasia,
  - epileptic seizures
  - signs of increased pressure (headache, nausea)
  - personality changes

- Brain metastases may be asymptomatic over longer periods of time

Treatment approaches

- Neurosurgery
- Radiotherapy
  - Whole brain radiotherapy (WBRT)
  - Stereotactic radiosurgery/radiotherapy (SRS/SRT)
- Systemic therapy
  - Chemotherapy
  - Targeted therapies, e.g. tyrosine kinase inhibitors, antibodies
- Supportive therapy
  - Edema control
  - Anticonvulsants
  - Pain

Neurosurgery

Typical indications:

- Patients with surgically accessible ***single brain metastasis***,
  no or controlled extracranial tumor burden
  and good performance status

- ***Acute decompression*** on patients
  with significant mass effect from one or more brain metastases
  Elimination of the source of perifocal edema

- Patients with an ***unknown primary*** **tumor**
  to *obtain tissue* for histopathological and molecular tumor
  (sub-)typing

Neurosurgery: Open Question after operation

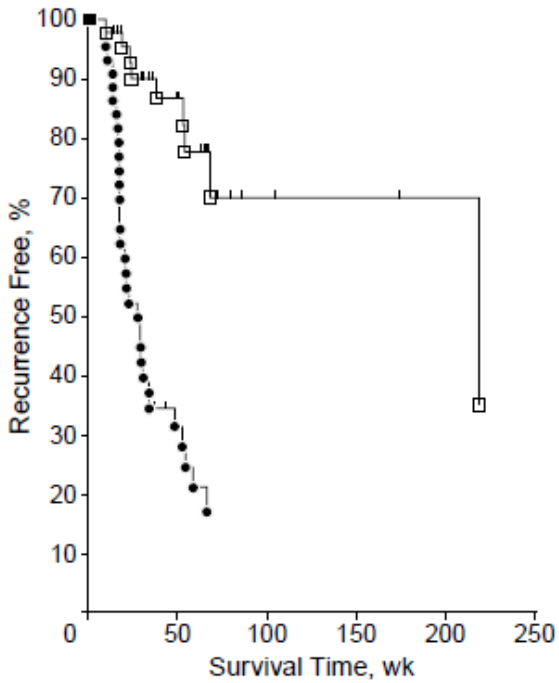
unresolved issue of whether or not perform adjuvant irradiation after neurosurgical resection.

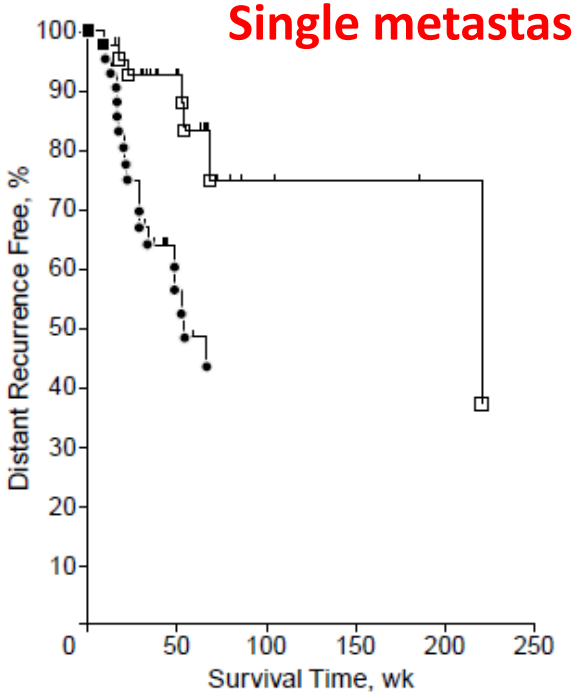
possible strategies:

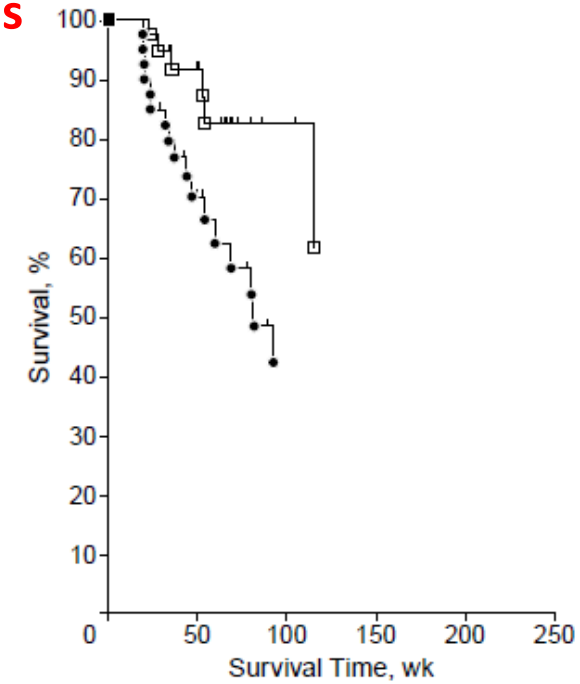
- Wait and see
- WBRT
- SRS/fSRS

Neurosurgery-Results
-Wait and See vs postoperative WBRT - Patchell et al

Single metastasis







WBRT after surgical resection reduces recurrences relapse and neurologic causes of death

- One Year Distant brain failure: 63% to 14% WBRT(P<0.001)
- One Year Local control: 46% to 90% WBRT (P<0.001)

Neurosurgery-Results
-Wait and See vs postoperative WBRT - Patchell et al

One year recurrence rates in different studies
Retrospective Assessment

Source, y	No. of Patients		Patients With Brain Recurrence, %			Median Survival Time, mo		
	Receiving RT	Not Receiving RT	Receiving RT	Not Receiving RT	*P*	Receiving RT	Not Receiving RT	*P*
Dosoretz et al,[4] 1980	12	21	50	52	NS	8	10	NS
Smalley et al,[5] 1987	34	51	21	85	NA	21	12	.02
DeAngelis et al,[6] 1989	79	19	45†	65†	.03‡	21	14	NS
Hagen et al,[7] 1990	12	21	50	52	NS	8	10	NS
Armstrong et al,[8] 1994	32	32	47	38	NS	10	14	NS
Skibber et al,[9] 1996	22	12	32	72	NA§	18	6	.002

- **Local control could be increased between 2 and > 60%**
- **Brain recurrence could not be avoided (between 38 and 85%)**
- **WBRT can increase OS**
- **Post operative WBRT has been the „golden standard“ since the 80ies.**
- **Disadvantage : Neurocognitive decline**

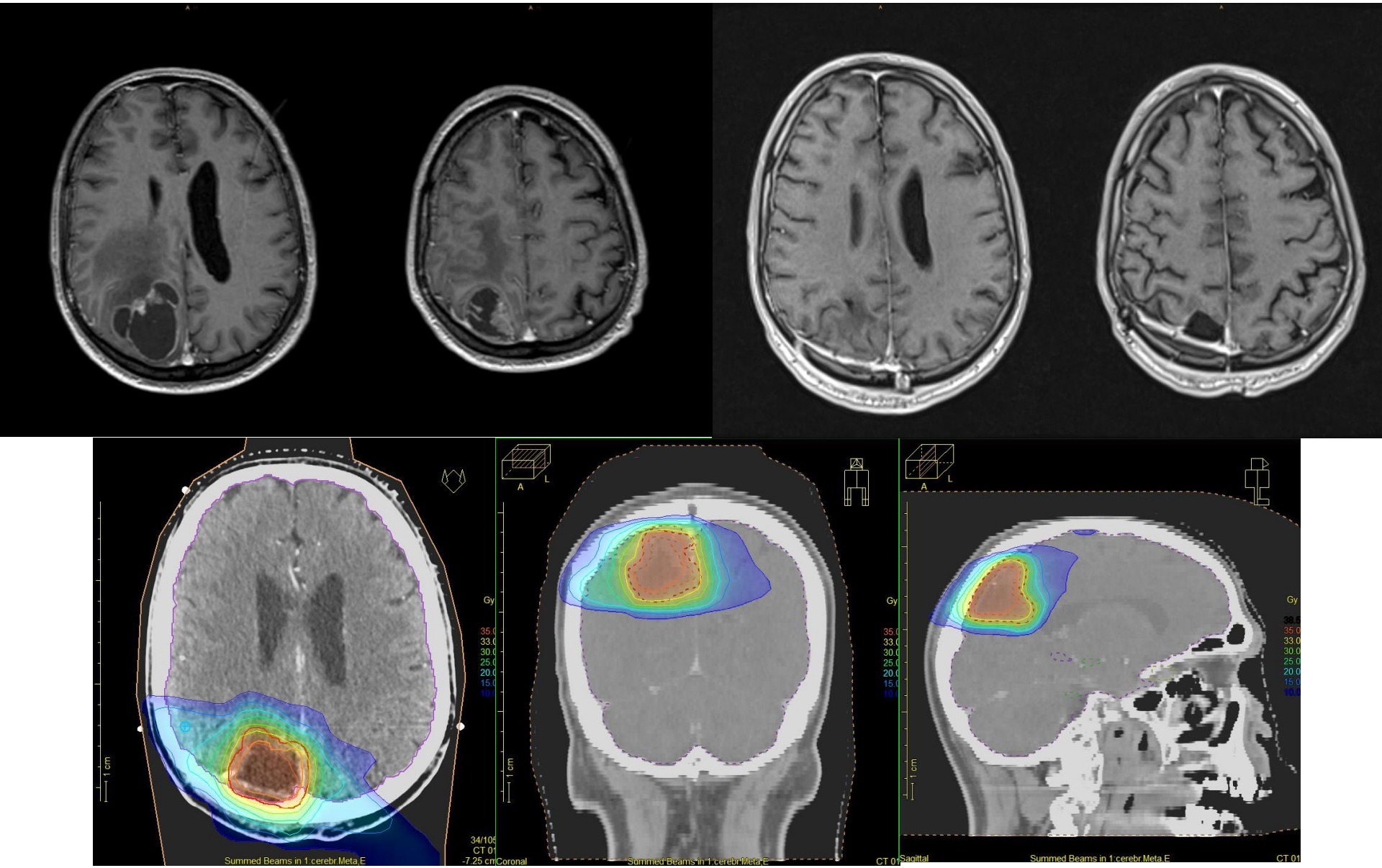
Neurocognitive decline after WBRT

Reference	Patients	Dose PCI	Baseline Abnormalities (free)	Cognitive impairment after a year
Arrigada	294; SCLC	24 Gy	Control: 44% PCI: 50%	Control:36% PCI: 30%
Gregor	314; SCLC	8-36Gy	PASAT	Control: 17% PCI:31%
Wolfson	264; SCLC	25 vs 36Gy		25Gy: 62% 36Gy: 85%
Le Pechoux	720; SCLC	25 vs 36Gy		25Gy :35% 36Gy: 47%
Sun	340; SCLC	30Gy		Control:12% PCI: 41%

- At least one neurocognitve dysfunction could be observed after WBRT
- Grade of impairment depends of the dose

McDuff SGR, *et al. J Neurol Neurosurg Psychiatry* 2013;**84**:1384–1391. doi:10.1136/jnnp-2013-305166

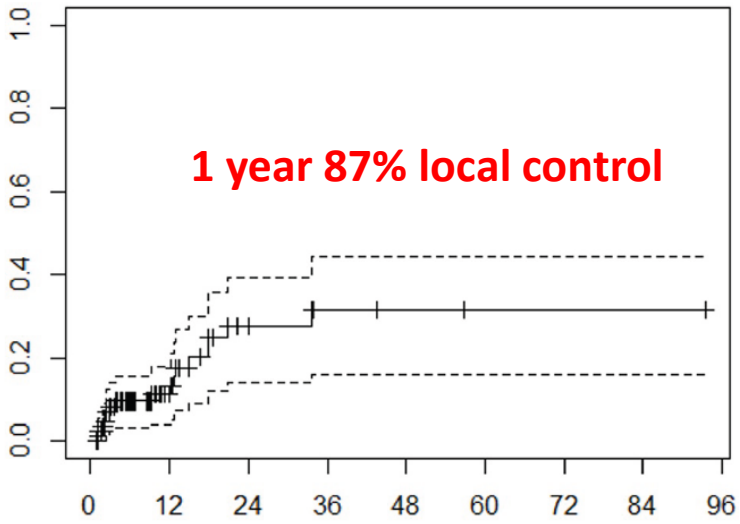
Post operative Radiotherapy of the Tumorbed



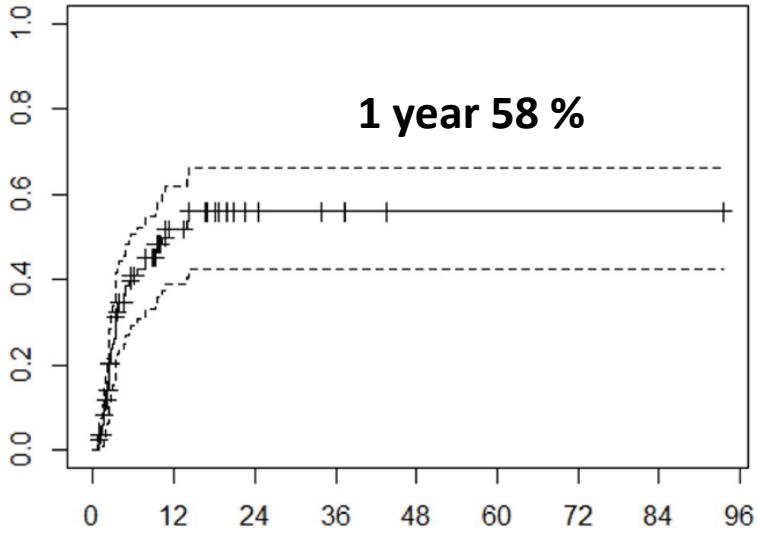
Postoperative Fractionated Stereotactic Radiosurgery
to the Tumor Bed for Surgically Resected Brain Metastases

Ryan K. Cleary

Local recurrence



Distant brain failure



N= 87 pts **(1-3 mets)**

Median target volume 9.8 cm^3

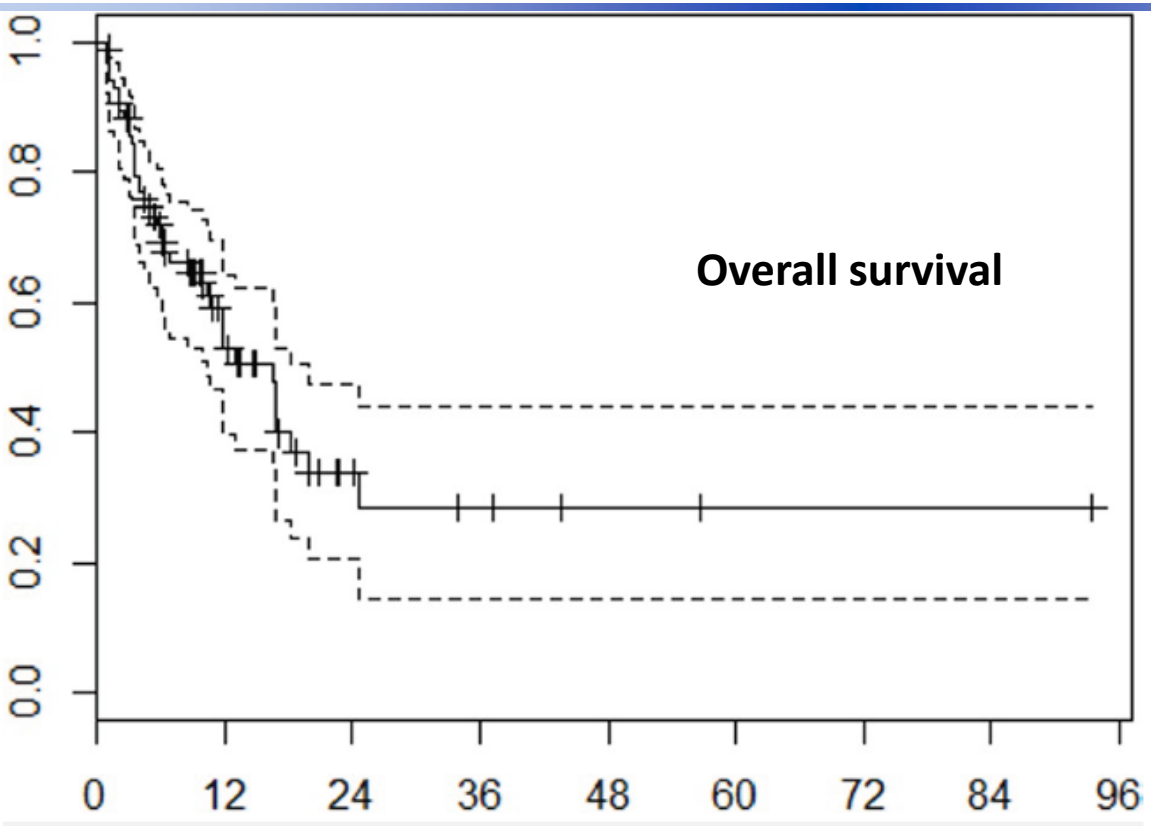
30 Gy / 5 fractions

treated between 2006-2014

- The percentage of distant failure was not significantly higher in Pts with WBRT and in local treatment

Cureus 9(5): e1279. DOI 10.7759/cureus.1279

Postoperative Fractionated Stereotactic Radiosurgery
to the Tumor Bed for Surgically Resected Brain Metastases



Ryan K. Cleary

Median OS 13 months
OS at 6 months 68%
OS at 12 months 52%

- RPA class ($p < .0001$),
- Tumor volume ($p = .0181$), and
- number of fractions ($p = .0181$) were statistically significantly
- associated with OS on multivariable analysis.

2017 Cleary et al. Cureus 9(5): e1279. DOI 10.7759/cureus.1279

Conclusion:
WBRT or Local treatment

- No significant difference in **Local control in** patients who get WBRT or local treatment ~80% within the first year

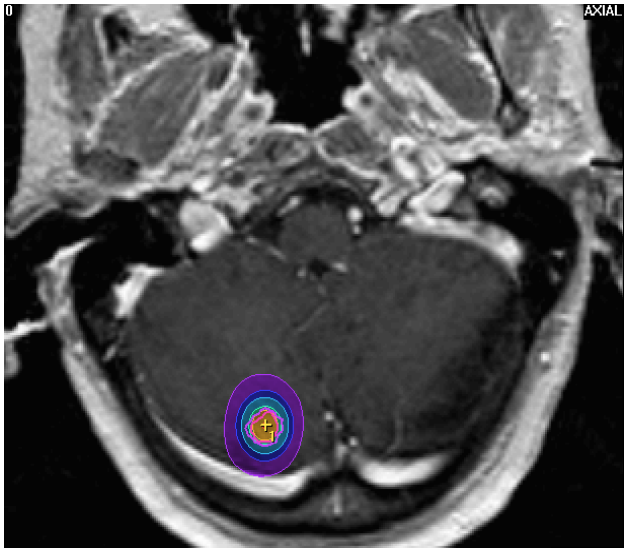
- Increased number of distant failures in Patients without WBRT (statistically not significant)

- Minimal neurotoxicity in patients with local treatment.

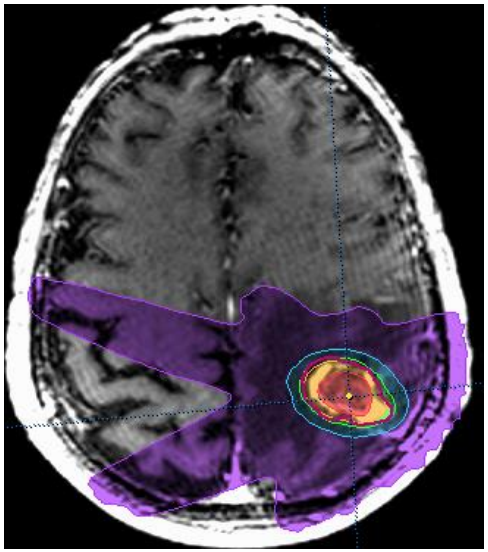
Surgery followed by LBRT for single metastasis is not inferior to WBRT , because survival and necessity of salvage treatment after LBRT were equivalent to those after WBRT

Radiotherapy: SRS

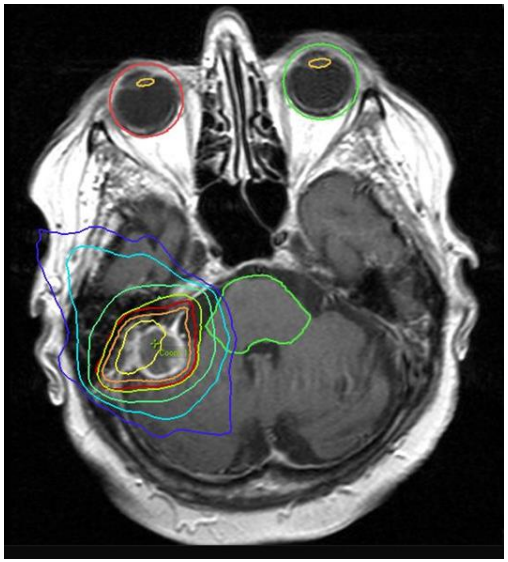
SRS: single-dose high-precision focused radiotherapy, utilizes convergent beams or arcs to irradiate in a single fraction circumscribed lesions with a high dose in the planning target volume (PTV) and a steep dose gradient at the margin.



„Gamma-knife“
„Cyberknife“



Arc technique
LINAC



More field technique
LINAC

- improving local tumor control
- reducing risk of neurocognitive side effects
- faster initiation or less interruption of needed systemic therapies

Dose and fractionations

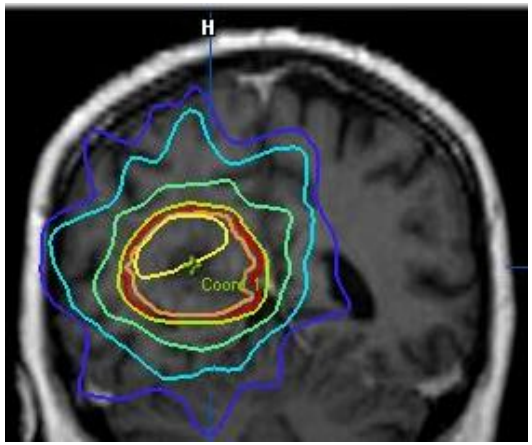
SRS

20-22 Gy volume < 4.3 cm ^{3} ; (~2cm)

18 Gy volume 4.3-14.1 cm ^{3}; (~2,7 cm)

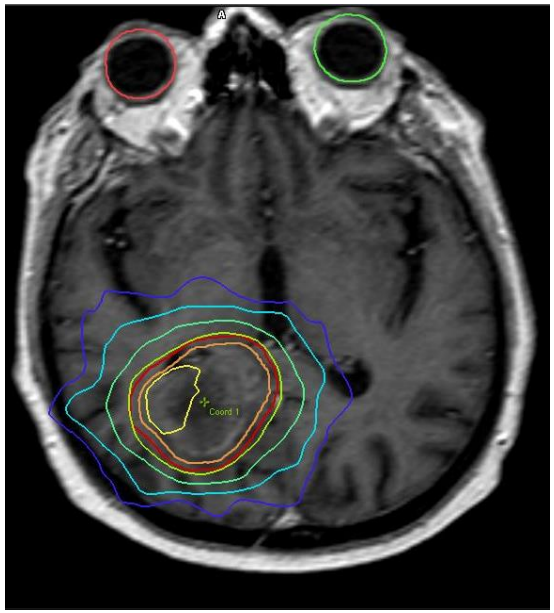
15-16 Gy volume > 14.1 cm ^{3}; (>3cm)

15-16 Gy brainstem



Hypo fSRT

24-27 Gy 3 fractions if V12 >8.5 cm ^{3}



Dose constrains for fractionated RT

OAR	Constraints for adults	
	Primary criteria	Secondary criteria
Optic chiasma	D_{max} < 54 [10,11] D_{max} < 55 [12]	D_{max} < 60 [10]
Cochlea	D_{mean} ⩽ 45 Gy [13,14] D_{mean} < 50 Gy [10]	
Hippocampus	Hippocampus D_{max} ⩽ 6 Gy and $V_{3\ Gy}$ ⩽ 20% Hippocampal avoidance volume D_{max} < 25.2 Gy and $V_{20\ Gy}$ ⩽ 20% [21,22] D_{max} < 12 Gy [23] $V_{7.2\ Gy}$ < 40% [25] D_{mean} < 30 Gy [24]	
Brainstem	D_{max} < 54 Gy [10,29]	D_{max} < 60 Gy [10] $D_{59\ Gy}$ < 10 cc [29]
Pituitary gland	D_{max} < 50 Gy [34] D_{max} < 60 Gy [10]	
Retina	D_{max} < 45 Gy [10, Yamazaki] D_{max} < 50 Gy [Shaffer]	
Lacrimal gland	$V_{30\ Gy}$ < 50% [Sreeraman] D_{max} < 40 Gy [Jeganathan]	
Lens	D_{max} < 6 Gy [Piroth] D_{max} < 10 Gy [10, Yamazaki]	

Silvia Scoccianti
Radiotherapy and Oncology 114 (2015) 230–238

Radiotherapy: SRS/SRT

- Typical indication: small **(maximal diameter of up to 3 cm) and of limited number (less than 3 to 4) of brain metastases (classical)**

- **Advantages**
  - **Better preservation of neurocognitive function** due to sparing of non-affected brain areas
  - SRS is delivered in a single fraction in an outpatient setting and may thus be more convenient for many patients in this palliative disease setting
  - Feasible also in **lesions not amenable to resection** due to sensitive localization in the CNS (e.g. brain stem, eloquent area)
  - Doable in **patients that cannot be operated** on due to co-morbidities

- **Disadvantages**
  - SRS/SRT will not be able to treat microscopic tumor manifestations escaping detection by neuroimaging
  - **No tumor tissue collecti**on

- **Changes**
  - SRS is utilized to treat multiple brain metastases

Stereotactic radiosurgery alone for multiple brain metastases? A review of clinical and technical issues

Oligometastases (1-4)

SRS vs WBRT + SRS	PTs Inclusion criteria	% Single brain mets	Local control	Distant control	OS
Aoyama (n=67) //(N=65)	1-4 met. KPS ≥ 70 Max dia. ≤ 3cm	49% vs 48%	72.5% vs 88.7% @ 1 y (P=.002)	36.3% vs 58.5% @1 y (P=.003)	28.4% vs 38.5% @1 y (P=.42)
Chang (n=30)// (n=28)	1-3 met. KPS ≥ 70 Max dia. ≥ 4cm	60% vs 54%	67% vs 100% @ 1 y (P=.012)	45 vs 73% @ 1 y (P=.02)	63% vs 21% @1y(P=0.003)
Kocher (n=100) // (N=99)	1-3 met.	68% vs 66%	69% vs 81% @ 2 y (P=.04)	52% vs 67% @ 2 y (P=.23)	Median OS: 10.9mo vs 10.7 mo (P=.89)
Brown (n=102)//(n= 111)	1-3 met. Dia. ≤ 3cm	55% vs 56%	72.8% vs 90.1% @ 1 y (P=.003)	69.9% vs 92.3% @1y (P<0.001)	Median OS: 10.7 mo vs 7.5 mo (P=.92)

- Excellent local control with SRS alone **≈ 70%** after one year
- **Improvement** of distant brain control in patients treated with combined WBRT + SRS: 37%–70% (SRS alone) to 59%–92% (WBRT+SRS)
- No significant survival benefit in most of the studies

19, ii2–ii15, 2017 | doi:10.1093/neuonc/nox001

Stereotactic radiosurgery alone for multiple brain metastases? A review of clinical and technical issues

Multi metastases (6-17median ; range 5-35) Arjun Sahgal,

Authors PTS	Range of mets./Total volume/ pts	Inclusion criteria	Median follow up	Local recurrence	DBF/Time to DBF	OS (median)
Yamamoto N=208	5-10 (6) Mean= 3.54 cc	>3 mets Cum.Tu vol ≤ 15cc KPS ≥70% 100% no prior WBRT	12 mo	1 y =6.5% 2 y =9.8%	1 y = 63% 2 y =72% Median 8.04 mo	10.8 mo
Mohammadi N=178	5-20 (6) median 3.2cc	KPS ≥70% (46% no prior WBRT)	6.2 mo	Crude : 3%	Crude 40%/=2.1 mo	6.7 mo
Bhatnagar N=205	4-18 (5) NR=CC	3 brain mets 83% prior or adjuvant brain mets	Mean 8.0 mo	1 y=29%	1 y =43% Median 9 mo	8.0 mo

- Limited data
- In patients up to 10 mets. , the expected distant brain failure rate is not greater than would be expected for patients with limited brain mets.

19, ii2–ii15, 2017 | doi:10.1093/neuonc/nox001

IMRT / VMAT with SIB in Patients with Brain Oligometastases

Author	Endpoint	PTV wb/dose PTV m/dose	Cases (lesions)	Main findings
Bauman 2007	WBRT +SIB (HT) vs WBRT + conventional SRT	30 (60)	14 (1-3)	SIB HT is a feasible alternative for SRT on small volume
Edwards 2010	WBRT + SIB(HT)	30 (40)	11 (1-4)	WBRT + SIB (HT) is feasible without adverse effects
Hsu 2010	WBRT + SIB (VMAT) vs SRT	32.23 (63-70.8)	10 (1-3)	SIB-VMAT plans achieve adequate WBRT coverage with conformal hippocampal avoidance and RS quality dose distributions
Rodrigues 2011	WBRT+ SIB (HT)	30 (35-60)	48 (1-3)	60 Gy in 10 fract. To 1-3 brain metastases synchronously with 30 Gy WBRT
Nichol 2016	WBRT +VRS	20 (47.5 to metastases, 38 to 2 mm PTV)	60 (223)	47.5 Gy in 5 fract.. Volumetric RS was effective for long term control
Ferro 2017	WBRT + SIB (IMRT)	30 (35-50)	30 (1-5)	50 Gy in 10 fract. To 1-5 brain metastases synchron. With 30 Gy WBRT is feasible with IMRT

Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

Masaaki Yamamoto*,

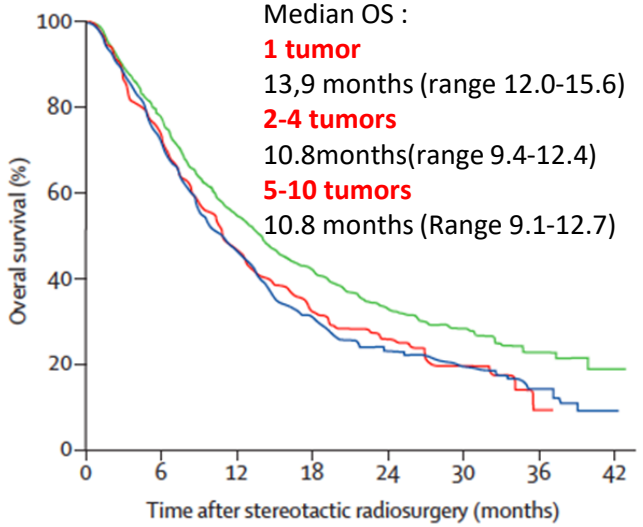
Prospective Study:

- 1194 pts;1-10 brain metastases
  - 455 pts 1 metastasis
  - 531 pts 2-4 metastases
  - 208 pts 5-10 metastases

- Hypothesis :
  - No difference SRS 5-10 metastases to SRS 2-4 metastases

- **Dose:**
  - **22Gy < 4ml**
  - **20 Gy 4-10ml**

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



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

Lancet Oncol 2014; 15: 387–95

Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

Masaaki Yamamoto*,

	Total (n=1194)	1 tumors N=455	2-4 tumors (B) N=531	5-10 tumors (C) N=208	P value B vs C
Died Neurological death	850 (71%) 71(8%)	310 (68%) 32(10%)	392(74%) 25 (6%)	148(71%) 14(9%)	0.46 0.27
Deterioration of neurological function	146 (12%)	56(12%)	62 (12%)	28(13%)	0.53
Local recurrence	138 (13%)	65(16%)	54 (11%)	19(10%)	0.78
New lesions	625 (58%)	199 (48%)	297 (63%)	129 (69%)	0.12

- Treatment with SRS with up to 10 brain metastases is feasible without significant higher number of new brain lesions and local recurrences than in the group of 2-4 metastases.

Yamamoto et al. Lancet 2014

Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

Masaaki Yamamoto*,

	Total (n=1194)	1 tumors N=455	2-4 tumors (B) N=531	5-10 tumors (C) N=208	P value B vs C
Salvage SRS procedures 1 2 ≥3	459 (38%) 256(21%) 113(9%) 90(8%)	148(33%) 79(17%) 45(1%) 27 (6%)	221(42%) 129(24%) 47(9%) 45(8%)	90 (43%) 51 (25%) 21 (10%) 18 (9%)	0.74 0.92
Salvage WBRT	107 (9%)	36(8%)	54(10%)	17 (8%)	0.48
Salvage surgery	23 (2%)	12(3%)	8(2%)	3(1%)	1.00
Systemic anticancer agents Molecular targeted agents	861 (72%) 356 (30%)	308 (68%) 123(27%)	387 (73%) 157 (30%)	166 (70%) 76 (37%)	0.059 0.078

- All local treatment options as Surgery, SRS and WBRT are possible as salvage therapy even after SRS of multiple brain metastases

Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

Masaaki Yamamoto*,

Treatment related adverse events	Total (n=1194)	1 tumors N=455	2-4 tumors (B) N=531	5-10 tumors (C) N=208	P value B vs C
Treatment related advers events					0.891
None	1093 (92%)	422 (93%)	481(91%)	190 (91%)	
Grade 1 and 2	69 (6%)	22(5%)	36(7%)	11(5%)	
Grade 3	20 (2%)	6(1%)	10(2%)	4(2%)	
Grade 4	8 (1%)	3(1%)	3(1%)	2(1%)	
Grade 5	4 (<1%)	2(<1%)	1(<1%)	1(<1%)	
Had MMSE at baseline	1132 (95%)	430 (95%)	504 (95%)	198 (95%)	

- Grade 4 and 5 are very rare (less than 1%) in SRS of brain metastases. They may happen all groups of single-, oligo-, and multi-metastases

Yamamoto et al. Lancet 2014

Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

Masaaki Yamamoto*,

Maintained Neurocognitive function	Total (n=1194)	1 tumors N=455	2-4 tumors (B) N=531	5-10 tumors (C) N=208	P value B vs C
4 months after SRS	623/662 (94%)	243/256 (95%)	263/284 (93%)	117/122 (96%)	0.27
12 months after SRS	333/366 (91)	141/154 (92%)	139/152 (91%)	53/60 (88%)	0.60
24 months after SRS	120/128 (94)	55/60 (92%)	47/48 (98%)	18/20 (90%)	0.20
36 months after SRS	28/30 (93%)	14/15(93%)	10/11 (91%)	4/4 (100%)	1.00

- In long term survivors, decline of Neurocognitive dysfunction is detectable, but not higher than 10% even in the group of multiple brain metastases.

Yamamoto et al. Lancet 2014

Conclusion SRS in multiple brain metastases (up to 10)

1. Not comparable with WBRT
2. Neurocognitive outcome is better
3. RT can be repeated
4. The total tumor volume should be not bigger than 15 cc

Radiotherapy: WBRT
standard of care with the goal of short-term palliation

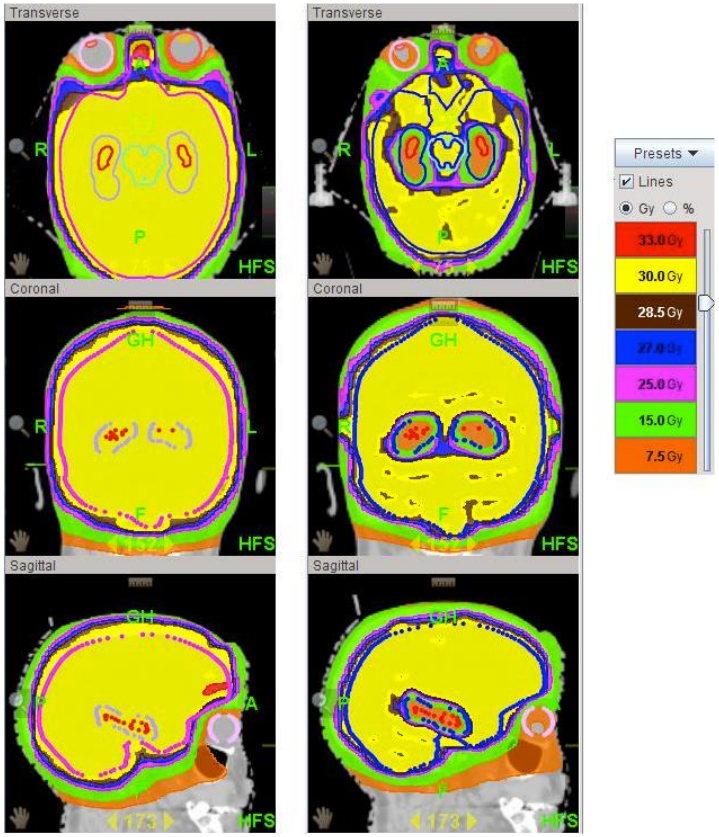
- Typical indication: **multiple brain metastases**

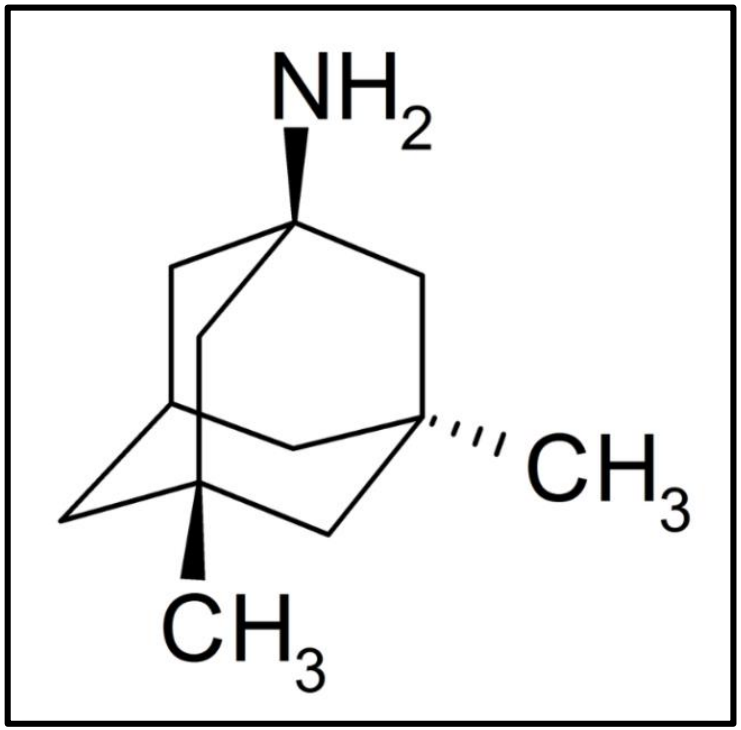
- 30 Gy in 10 fractions or 37.5 Gy in 15 fractions or 20Gy in 5 fractions is considered “standard” dose for WBRT
- Patients with life aspectancy < 3-6 months 20 Gy in 5 fractions
- Leptomeningeal tumor extension
- WBRT regimens demonstrate median survivals 15-18 weeks

Significant risk for **neurocognitive decline** due to damages to the brain parenchyma or induction of intracerebral vascular changes

Radiotherapy: WBRT with hippocampal sparing an alternative to SRS in multiple brain metastases?

- Significant risk for neurocognitive decline due to damages to the brain parenchyma or induction of intracerebral vascular changes
  - Hippocampal-sparing radiotherapy
  - Memantine and other drugs may help to protect neurocognition



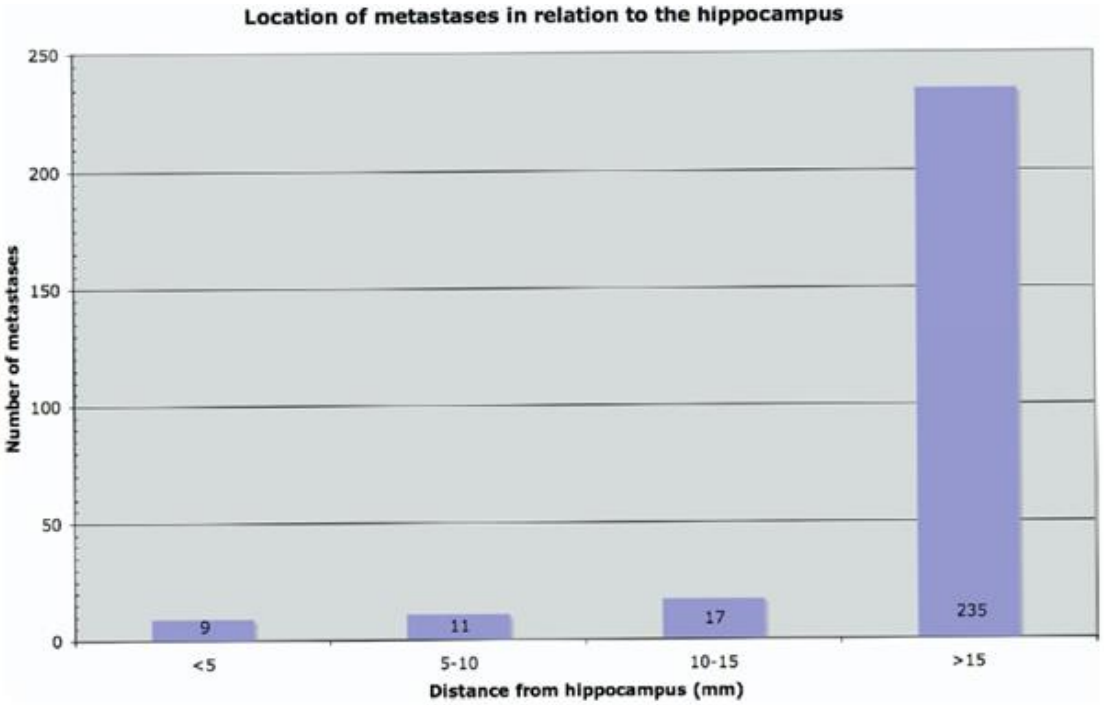


DISTRIBUTION OF BRAIN METASTASES IN RELATION TO THE HIPPOCAMPUS: IMPLICATIONS FOR NEUROCOGNITIVE FUNCTIONAL PRESERVATION

AMOL GHIA, M.D.,* WOLFGANG A. TOMÉ, PH.D.,* SAYANA THOMAS, B.S.,* GEORGE CANNON, M.D.,* DEEPAK KHUNTIA, M.D.,* JOHN S. KUO, M.D., PH.D.,† AND MINESH P. MEHTA, M.D.*

Distribution of brain metastases by location

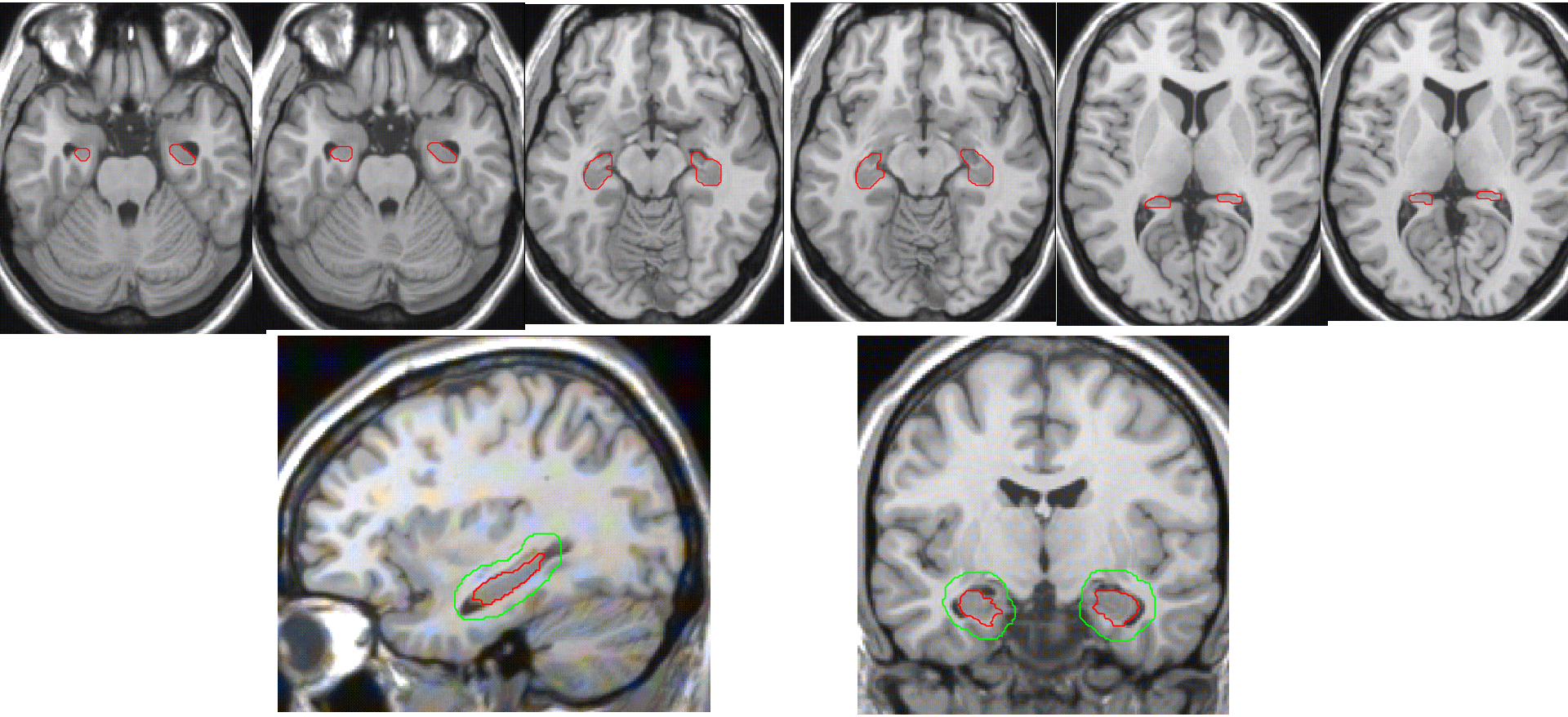
Location	*n*	Percentage
RF	37	13.60
LF	49	18.01
RP	27	9.93
LP	19	6.99
RT	24	8.82
LT	11	4.04
RO	10	3.68
LO	11	4.04
RBG	1	0.37
LBG	10	3.68
RC	33	12.13
LC	30	11.03
CV	3	1.10
BS	7	2.57
Total	272	100.0



Most metastases are located in > 15 mm distance to the hippocampus in the left and right frontal lobe and left/right cerebellum

Int. J. Radiation Oncology Biol. Phys., Vol. 68, No. 4, pp. 971–977, 2007

Hippocampal Contouring: A Contouring Atlas for RTOG 0933



- The ‘‘stem cell niche’’ of the hippocampus has been observed to be exquisitely sensitive to therapeutic doses of cranial radiation
- Neural progenitor cells becoming less proliferative, more apoptotic,

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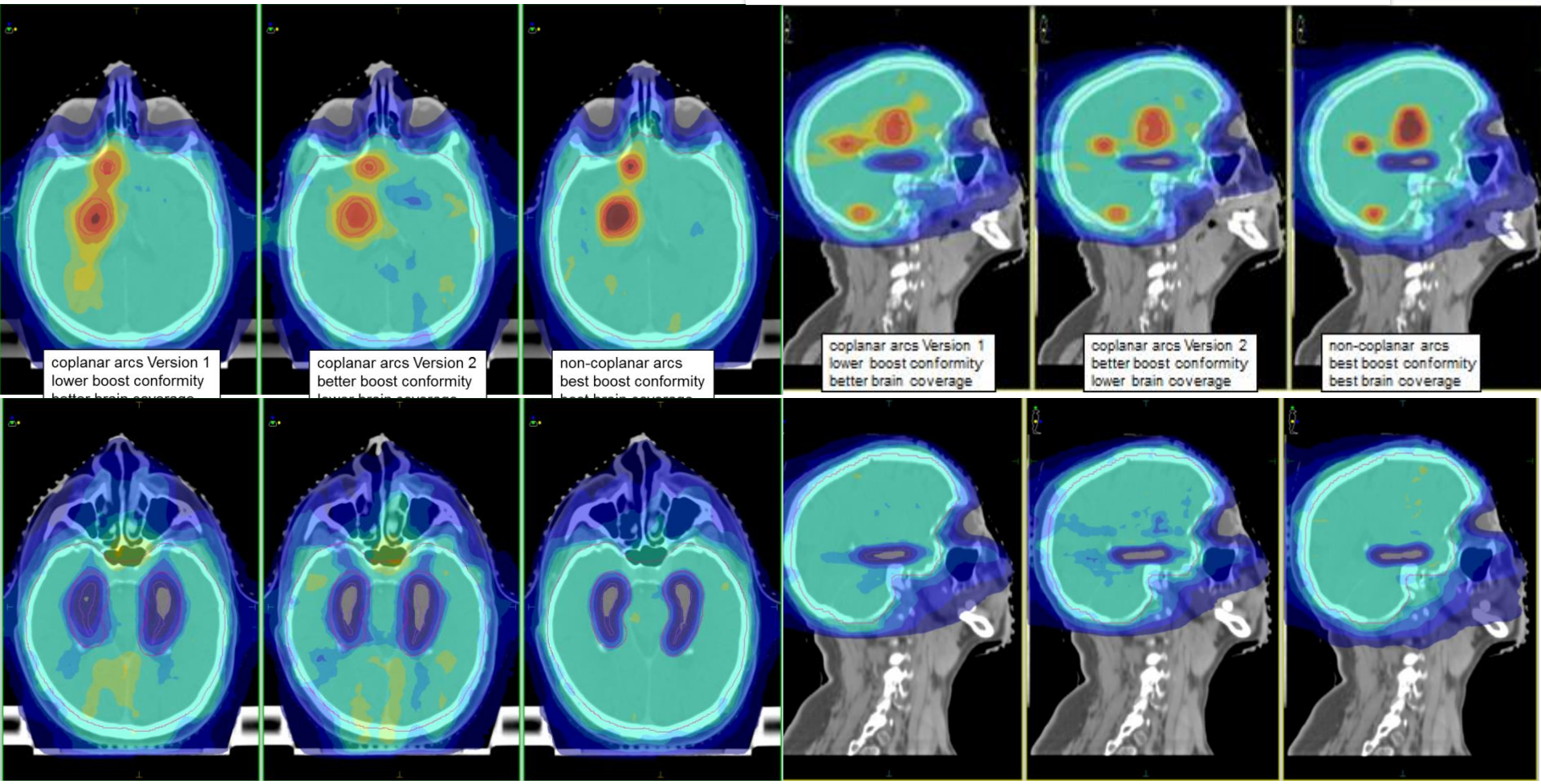
Table 1. Clinical criteria and inverse planning algorithm constraints for helical tomotherapy and LINAC-based IMRT planning

Structure	Helical tomotherapy plan criteria	Penalty	Importance	LINAC-based IMRT plan criteria	Penalty
Whole-brain PTV	Max dose: 30 Gy	100	200	Max dose: 34 Gy	100
	30 Gy to ≥96%			Min dose: 32 Gy	100
Hippocampus	Max dose: 6 Gy	100	500	Max dose: 11 Gy	5
	3 Gy to ≤20%	20		9 Gy to ≤40%	10
Hippocampal avoidance volume	Max dose: 30 Gy	1	5	N/A	N/A
	20 Gy to ≤20%	10			
Eyes*	Max dose: 8 Gy	10	20	Max dose: 7 Gy	5
	5 Gy to ≤20%	10			
Lenses*	Max dose: 3 Gy	20	20	Max dose: 5 Gy	5
	2 Gy to ≤20%	10			



WBRT with SIB (<5-10mets) and hippocampal sparing is depending by the location and size of the metastases

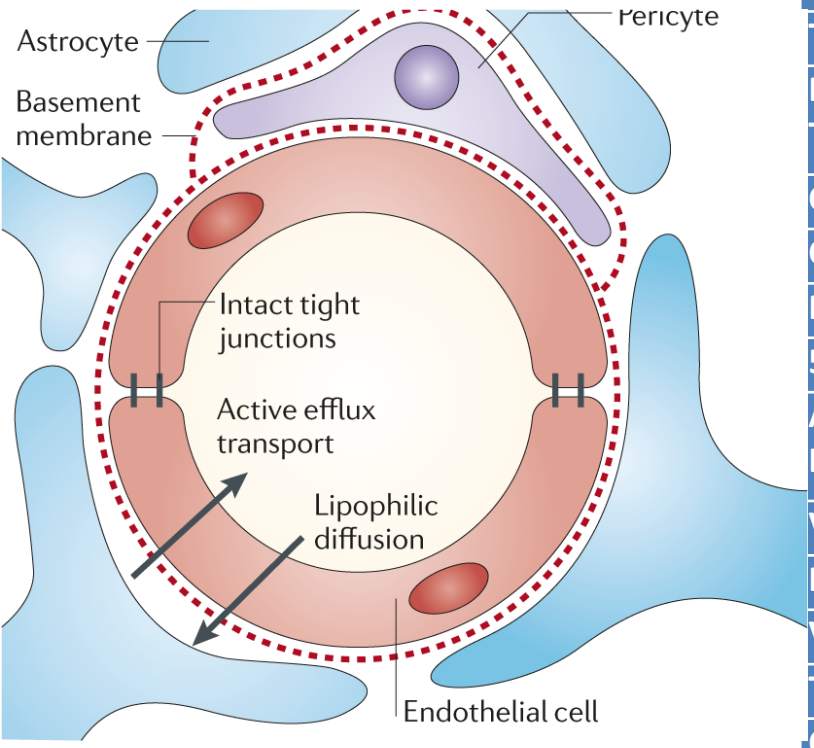
Radiotherapy: WBRT- with integrated boost plus hippocampal-sparing

	Study design	Endpoint Planning comparison	Dose PTV $_{wb}$/dose PTV m(Gy)	Cases (lesions)	Main findings
Hsu 2010	Feasibility	WBRT+SIB(VMAT) vs SRS	32.25 (63-70)	10(1-3)	Adequate WBRT and SRT dose distribution
Rodrigues 2011	Phase 1	WBRT+SIB	30 (35-60)	48(1-3)	60 Gy /10 f. to 1-3 mets synchron.with 30 Gy WBRT feasible
Nichol 2016	Phase 2	WBRT+Volumetric Radiosurgery	20 (47.5)	60 (223)	For non deep BM 47.5 Gy /5f is feasible
Ferro 2017	Phase 1	WBRT+SIB(IMRT)	30 (35-50)	30(1-5)	50 Gy /10f to 1-5 meta feasible

- Treatment planning is possible
- Long term results of neurocognitive decline are not available

Cytotoxic Therapy and WBRT ± SRT

Blood brain barrier



Zytostatikum	Liquorpenetration
Nitrosoureas (ACNU,BCNU; CCNU, Fotemustine)	++
Procarbacin	++
Thiotepa	+
Dacarbacin Temozolomide	(+) ++
Cyclophosphamid, Ifosfamid	+/-
Cytosinarabinosid	++
Methotrexat	-/+
5-Fluorouracil	(++)
Anthracyclins Liposomal doxorubicine	- ++
VM26	-/+
Etoposid	-/+
Vincaalkaloids, Taxanes	-
Topotecan	++
Cisplatin, Carboplatin	-
Cytokines	-

++ : Liquorconzentration 20-30% of the Serumconzentration
+ : Liquorconzentration 10% of the Serumconzentration
– : Liquorconzentration <5% of the Serumconzentration

There is a limited effect of Chemotherapy in brain metastases

B. Müller, M. Bamberg, P. Krauseneck, Maligne Gehirntumoren, 1995

Are there druggable targets brain mets?

EGFR

ALK

ROS1

BRAF V600E

PD1/PD-L1

Angiogenesis

Predictive Biomarker for Targeted Therapy in Brain Metastases

Cancer type	Biomarker	Test method	Discordance rate between primary tumor and brain metastasis	Approved targeted drugs
NSCLC	EGFR mutation	Gene sequencing	0–32 %	Gefitinib, Erolitinib
	ALK rearrangement	FISH	0–12.5 %	Crizotinib
Breast cancer	HER2 amplification	IHC, FISH	0–14 %	Lapatinib, Trastuzumab, Pertuzumab,T-DM1
	ER and PR expression	IHC	30–50 %	Tamoxifen
Melanoma	BRAF mutations	Gene sequencing, IHC, COBAS V600 test	0 %	Vemurafenib, Dabrafenib, Trametinib
Colorectal cancer	RAS mutations	Gene sequencing	Unknown	Cetuximab, Panitumumab
Gastroesophageal cancer	HER2 amlification	IHC, FISH	0 %	Trastuzumab

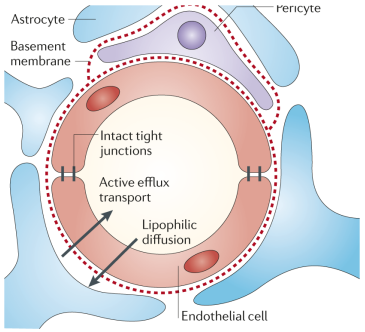
ALK anaplastic lymphoma kinase gene, *BRAF* v-RAF murine sarcoma viral oncogene homolog B1 gene, *EGFR* epidermal growth factor receptor gene, *ER* estrogen receptor, *FISH* fluorescent in situ hybridization, *HER2* human epidermal growth factor receptor 2, *IHC* immunohistochemistry, *NSCLC* non-small-cell lung cancer, *PR* progesterone receptor, *RAS* rat sarcoma gene

- Biomarkers have to be routinely tested for therapy planning in patients with Brain metastases.
- Discordance rate between primary tumor and brain metastases

Berghoff et al, Acta Neuropathol. 2014 Dec;128(6):879-91.

Targeted Therapies

- **Tyrosin** Kinase Inhibitors
  - Small molecules
  - Diffusion passes the intact BBB



- **Monoclonal Antibodies**
  - No diffusion through the intact BBB

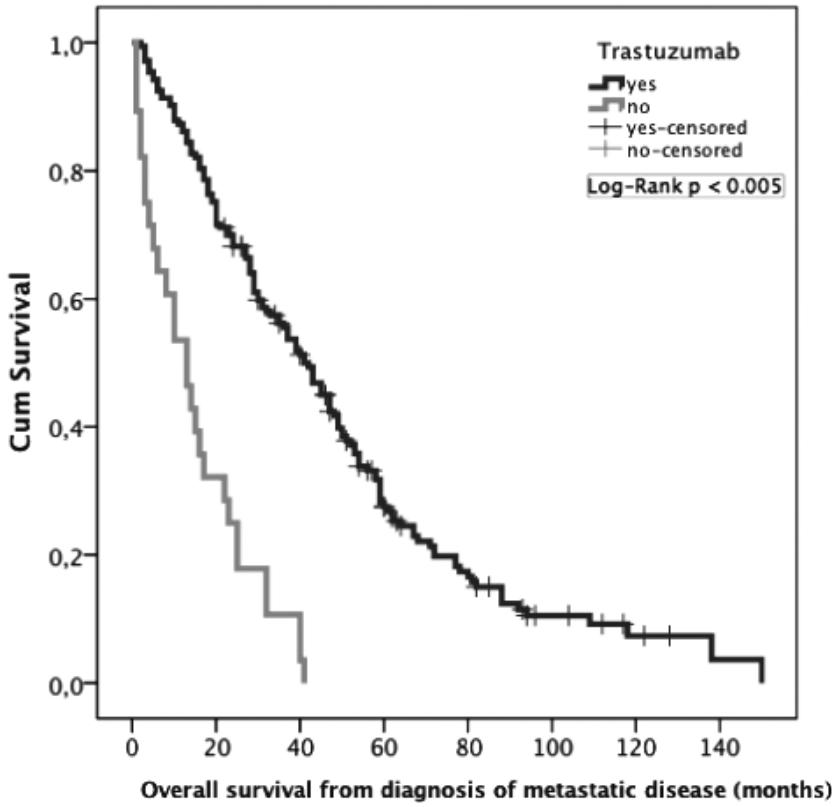
Pre-requisite :

Expression of predictive factors.

Impact of Her-2-Targeted Therapy on Overall Survival in Patients With Her-2 Positive Metastatic Breast Cancer

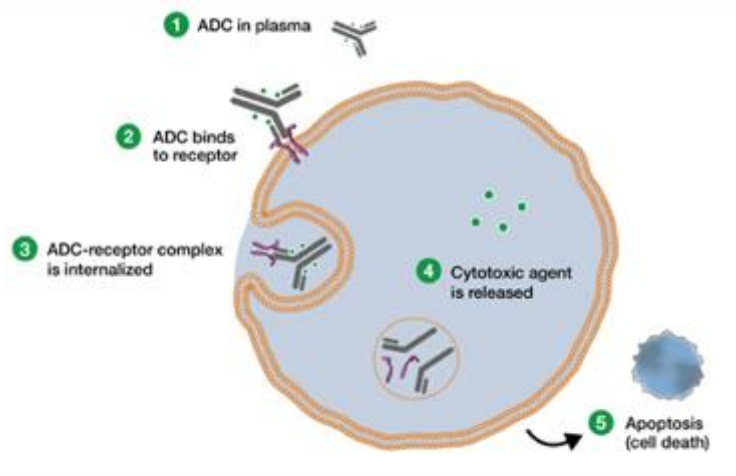
Anna S. Berghoff, MD,[*,†] Zsuzsanna Bago-Horvath, MD,[†,‡] Peter Dubsky, MD,[†,§] Margaretha Rudas, MD,[†,‡] Ursula Pluschnig, MD,[*,†] Christoph Wiltschke, MD,[*,†] Michael Gnant, MD,[†,§] Guenther G. Steger, MD,[*,†] Christoph C. Zielinski, MD,[*,†] and Rupert Bartsch, MD[*,†]

[*]Clinical Division of Oncology, Department of Medicine I, Medical University of Vienna, Vienna, Austria; [†]Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; [‡]Department of Pathology, Medical University of Vienna, Vienna, Austria; [§]Department of Surgery, Medical University of Vienna, Vienna, Austria

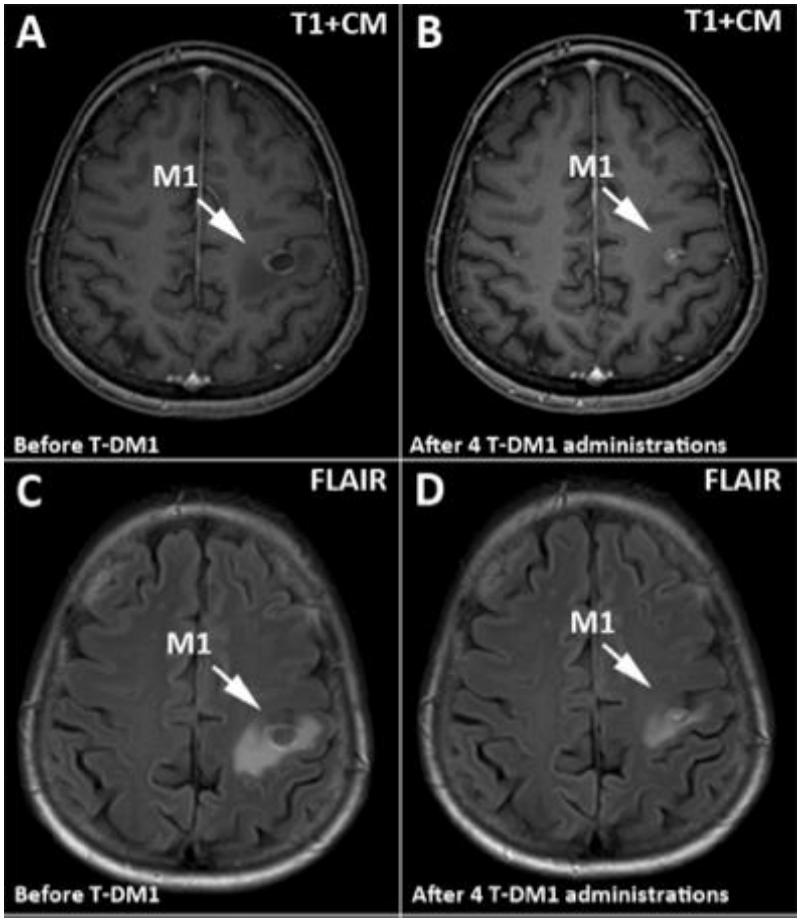


Activity of T-DM1 in Her2-positive breast cancer brain metastases

Rupert Bartsch[1,2] · Anna S. Berghoff[1,2] · Ursula Vogl[3] · Margaretha Rudas[1,4] · Elisabeth Bergen[1,2] · Peter Dubsky[1,5] · Karin Dieckmann[1,6] · Katja Pinker[1,7] · Zsuzsanna Bago-Horvath[1,4] · Arik Galid[8] · Leopold Oehler[3] · Christoph C. Zielinski[1,2] · Michael Gnant[1,5] · Guenther G. Steger[1,2] · Matthias Preusser[1,2]



Best intracranial response		
CR	0	0.0
PR	3	30.0
SD	4	40.0
PD	3	30.0
Cranial Clinical Benefit Rate (CBR)	5	50.0



BRAF inhibitor active in brain metastases of V600E mutant melanoma

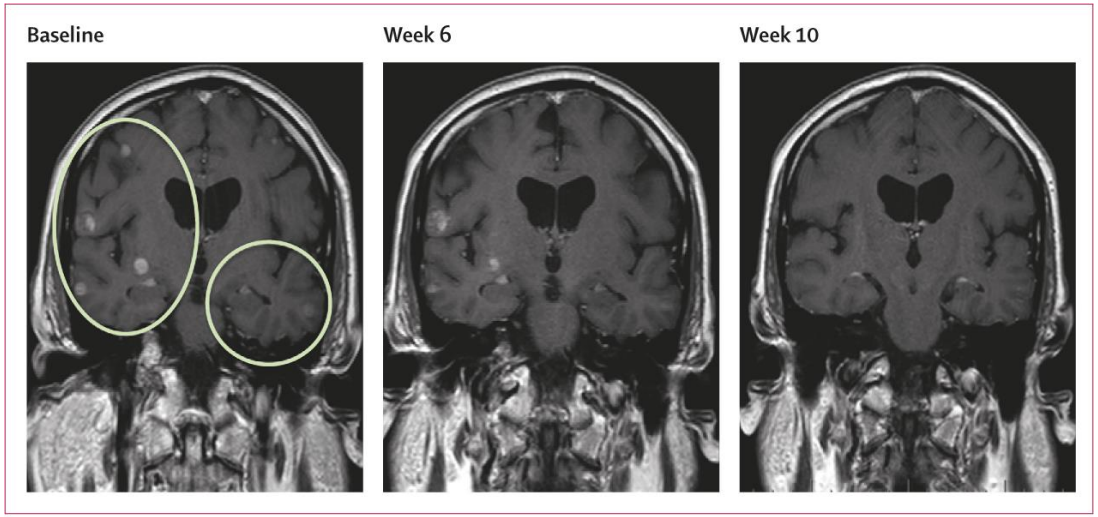


Figure 6: **MRI images from one patient with Val600Glu BRAF-mutant melanoma and untreated brain metastases given the recommended phase 2 dose**
Image from baseline (left), week 6 (middle), and week 10 (right). Circles indicate locations of lesions. Best response was a 71% decrease in tumour size, and the best intracranial decrease was 68%.

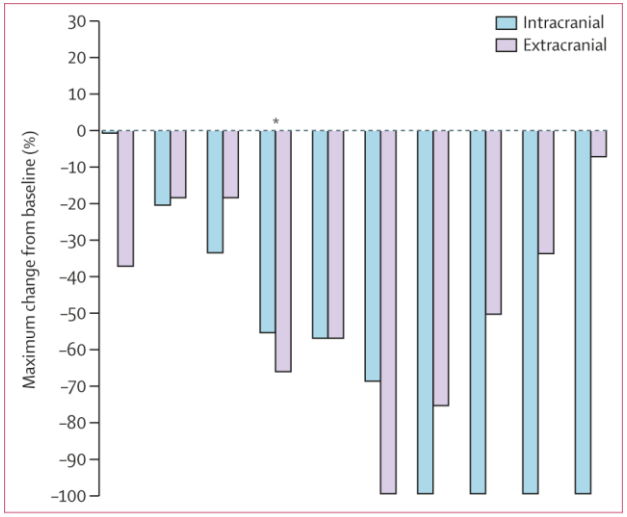
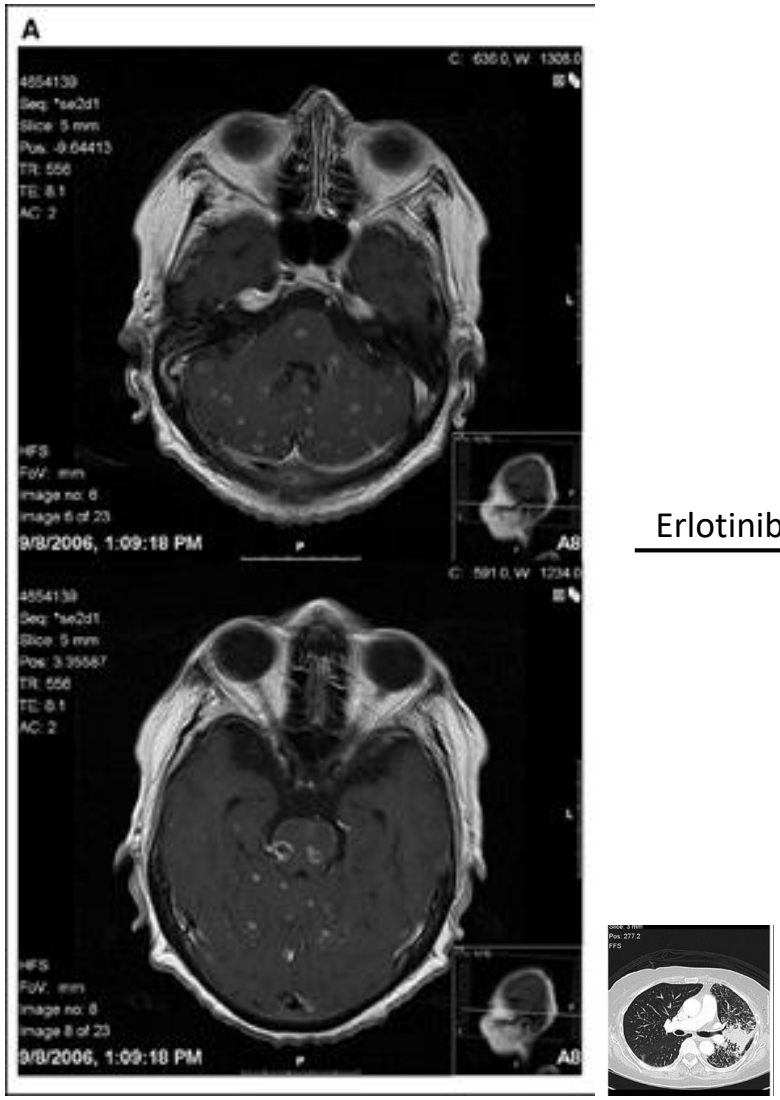


Figure 5: **Change in intracranial and extracranial tumour size in the ten patients with Val600 BRAF-mutant melanoma and untreated brain metastases given the recommended phase 2 dose**
*Patient with Val600Lys mutation.

Falchook et al, Lancet 2012

EGFR inhibitors in NSCLC

3 months after WBRT (30 Gy):



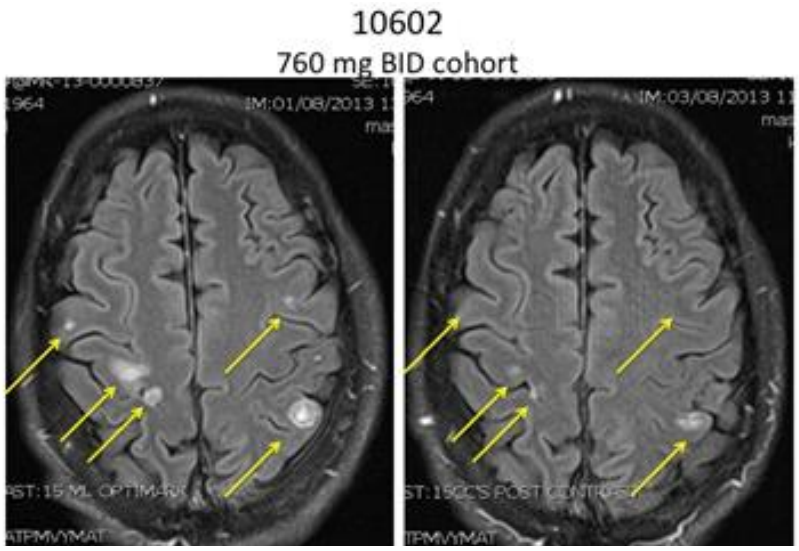
Erlotinib 150 mg →

8 months later

60y, f, NSCLC IV, multiple BM

Fekrazad M H et al. JCO 2007;25:5024-5026

Phase I study of alectinib in crizotinib-resistant ALK-positive NSCLC



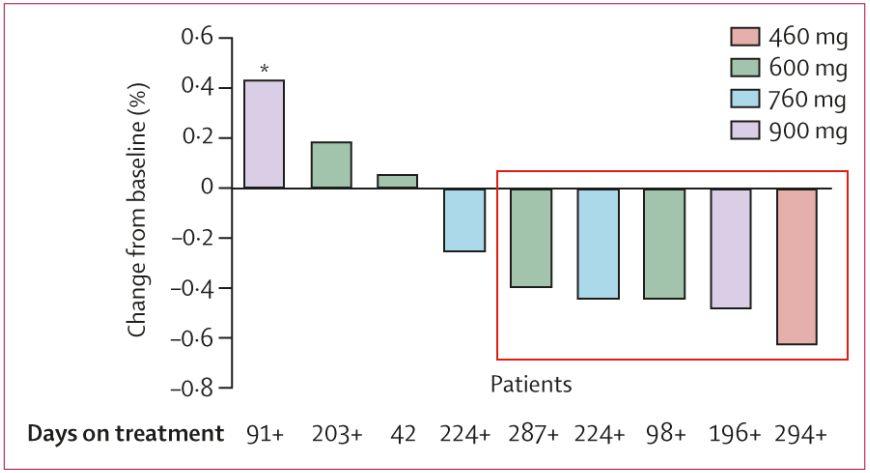


Figure 4: **Waterfall plot of best CNS response**
Bars indicate the change from baseline in the size of CNS tumours, for every assessable patient with measurable CNS lesions at baseline (n=9). Red box indicates patients who had a partial response as their best CNS response. + symbols indicate patients still on treatment. *Radiation necrosis.

„Good response but no cure“
Regular controls are necessary to detect new metastasis

Ou et al, Lancet Oncol 2014

Ongoing trials of targeted therapy in patients with solid tumor brain metastases

Agent	Phase of trial	Target	Patient population	ClinicalTrials.gov identifier
Everolimus+trastuzumab+vinorelbine	II	mTOR	HER2+ breast cancer	NCT01305941
BKM120+trastuzumab	I	PI3K	HER2+ breast cancer	NCT01132664
Lapatinib+WBRT	II	HER2	HER2+ breast cancer	NCT01622868
Neratinib	II	HER2	HER2+ breast cancer	NCT01494662
Afatinib	II	HER2	HER2+ breast cancer	NCT01441596
ARRY-380+trastuzumab	I	HER2	HER2+ breast cancer	NCT01921335
WBRT +/- erlotinib	II	EGFR	NSCLC	NCT01518621
WBRT+bevacizumab	I	VEGF	Solid tumors	NCT01332929
Bevacizumab	II	VEGF	Solid tumors	NCT01898130
Sunitinib+SRS	I	VEGFR	Solid tumors	NCT00981890
Sorafenib+SRS	I	VEGFR	Solid tumors	NCT01276210
Dabrafenib+SRS	II	BRAF	Melanoma	NCT01721603
Vemurafenib	II	BRAF	Melanoma	NCT01781026
Ipilumumab+WBRT or SRS	I	CLTA-4	Melanoma	NCT01703507
Veliparib+WBRT	II	PARP	NSCLC	NCT01657799

- Clinical trials evaluate whether sequencing or combination strategies of novel drugs with radiotherapy are beneficial

Curr Treat Options Neurol (2014) 16:276

Trials on targeted therapies for patients with BM

Entity	n	Targeted Therapies	Intracranial response rate	OS (months)
NSCLC BM; EGFR status unknown	23	Gefitinib or erlotinib	73,9%	18,8
1-3 BSCLC BM; EGFR status unknown	41	Erlotinib plus WBRT and SRS	NA	6.1
NSCLC BM Alk rearrangement	27 5	Crizotinib Crizotinib plus SRT	56,0% 65,0%	13,2 intra-cranial TTP
HER2-positive breast cancer BM	45	Trastuzumab (T-DM1)+chemo plus local therapy	NA	26.8
Oligosymp. Her2-positiv breast BM	45	Laptinib plus capecitabine	66,0%	17
BRAF mutated melanoma BM	74	Dabrafenib	39.2%	8,3
BRAF mutated melanoma BM	24	Vemurafenib	42,0%	5,3

Combined strategies may improve antitumor activity

Future of targeted therapy for BM

Trageted Therapy: Described Side effects

Sperduto PW	Phase III trial (RTOG 0320) WBRT/SRT	Temozolamid Erlotinib	47% grade ¾ Skin reaction including acne Pneumonia Muscle weakness Myocardial ischemia Brain necrosis
Schulze B	Case reports WBRT	BRAF inhibitor Vermurafenib	Skin toxicity
Kies AP	SRS	Ipilimumab	Symptomatic Radionecrosis

- Targeted therapy in combination with RT can increase side effects
- Targeted therapy may have a radiosensitizing effect
- Studies have to be performed evaluating side effects

Questions concerning targeted therapy and SRS/WBRT to be answered into studies

- When is the right time point for RT
  - Sequencing or combination strategies
  - Can SRS or WBRT be omitted or delayed
- Intracranial response, local control rate
- Dose and toxicities; Incidence of serious adverse events.

Conclusions

- Brain metastases are common and a clinical challenge
- Radiotherapy/SRS and surgery are established treatment options
- WBRT is a treatment option in very palliative Patients in in case of salvage therapy
- Brain mets are a promising target for prophylactic and therapeutic intervention based on molecular insights, some mechanisms and drug targets identified and treatments emerging
- Many open questions that require specifically designed trials (e.g. sequencing/combination strategies/ QoL)

Questions

1. OARs tolerance dose for hypofractionated SRS example 30Gy/5#, brainstem? Optic nerves?chiasm?

2. Number of IC mets to be meaningfully
   Number of IC mets to be meaningfully treated with SRS vs. WBRT

3. Are there special concerns with inhomogeneous dosing in brain mets as opposed to for example lung mets?

4. Different fractionation doses/fractionation schedules depending on met size (cut-offs?) and location?

5. Recommandations for patient positioning fixation for SBRT in thorax and CNS

Department of Radiation Oncology
Chairman: Prof. Dr. Matthias Guckenberger

Stereotactic body radiotherapy for vertebral metastases

Matthias Guckenberger

UniversityHospital Zurich

ESTRO

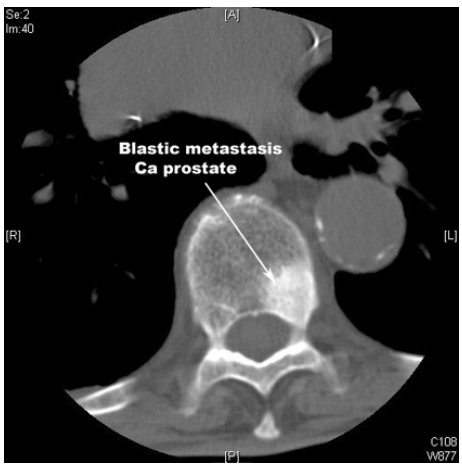
Overview

1. Conventional radiotherapy for painful vertabral metastases
2. Spinal cord tolerance
3. Technique of spinal SBRT
4. Outcome of spinal SBRT

Overview

1. Conventional radiotherapy for painful vertabral metastases
2. Spinal cord tolerance
3. Technique of spinal SBRT
4. Outcome of spinal SBRT

Conventional radiotherapy techniques for treatment of spine metastases



Uncomplicated bone metastases

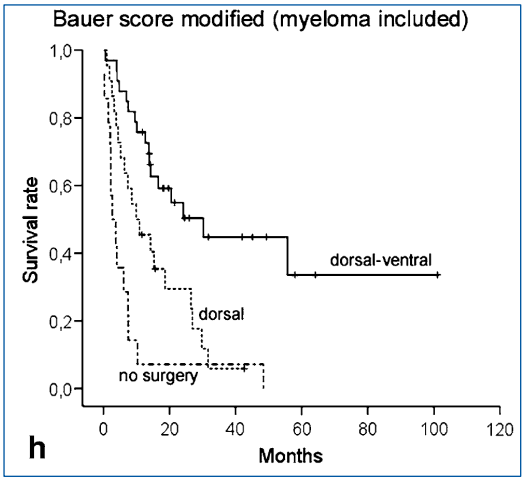
Pain control with conventional radiotherapy for bone metastases

	# patients	Fractionation	Complete or partial pain response
Prince 1986	288	1 x 8Gy 10 x 3Gy	73% 64%
Gaze 1997	280	1 x 10Gy 5 x 4.5Gy	84% 89%
Steenland 1999	1171	1 x 8Gy 6 x 4Gy	72% 69%
Roos 2005	272	1 x 8Gy 5 x 4Gy	61% 53%

- Pain response after conventional RT: ~70%
- Pain control after 3 – 6 months: ~35%

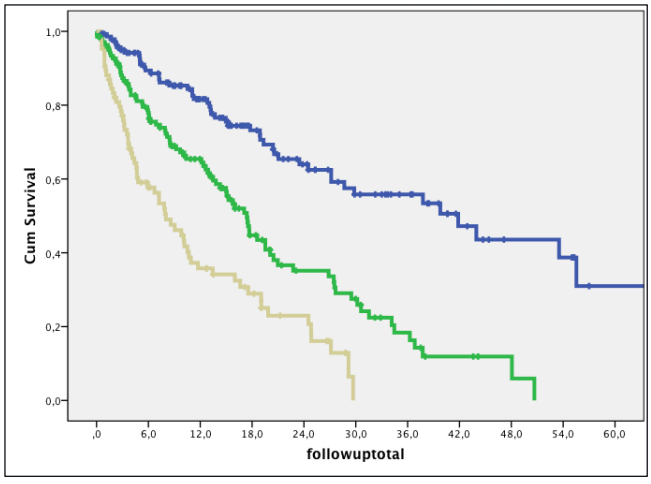
OS in patients with vertebral metastases

Conventional radiotherapy



Leithner Eur Spine J

SBRT



Guckenberger submitted

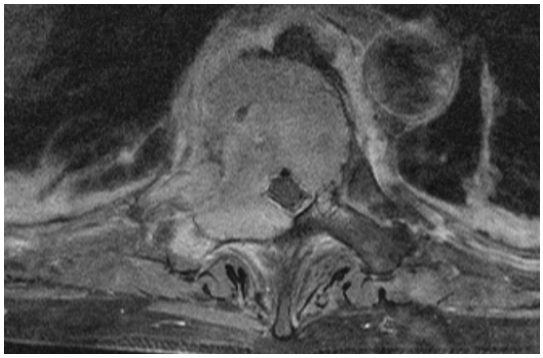
- Favorable OS in selected patients
- Contribution of SBRT?

Complete pain control with conventional radiotherapy for bone metastases

	# patients	Fractionation	Complete pain response
Prince 1986	288	1 x 8Gy 10 x 3Gy	45% 28%
Gaze 1997	280	1 x 10Gy 5 x 4.5Gy	39% 48%
Steenland 1999	1171	1 x 8Gy 6 x 4Gy	37% 33%
Roos 2005	272	1 x 8Gy 5 x 4Gy	26% 27%

- Complete pain response is achieved in 25 – 40% of the patients

Conventional radiotherapy techniques for treatment of spine metastases



Complicated bone metastases

Mass like vertebral metastases

Absence of MSCC

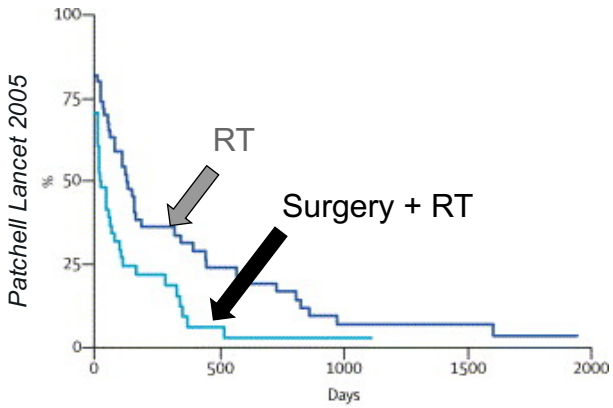
Mizumoto IJROBP 2011

	1 year local control
Non-mass like tumors	86%
Mass like tumors	46%

<u>Very</u> limited overall efficiency of conventional radiotherapy

Mass like vertebral metastases

MSCC



<u>Very</u> limited overall efficiency of conventional radiotherapy

Summary of conventional RT

- Conventional „low-dose“ radiotherapy with 1 x 8Gy is the guideline recommended treatment of choice for painful vertebral metastases
- **Nevertheless:**
  - Lack of any response in 1 / 3 of the patients
  - Incomplete pain reponse in 2 / 3 of the patients
  - Limited palliative effect after 3 – 6 months
  - Limited efficacy in mass-like metastases

Motivation to explore SBRT for vertebral metastases

- Oligo-metastasis
  - Improve OS
- Oligo-progression
  - Delay of systemic treatment
  - Delay change of systemic treatment
- More effective palliation – high-tech palliation
  - Long-term pain control
  - Higher rates of complete pain response
  - Prevention of metastatic spinal cord compression

Overview

1. Conventional radiotherapy for painful vertabral metastases
2. Spinal cord tolerance
3. Technique of spinal SBRT
4. Outcome of spinal SBRT

Safety of spine SBRT: myelopathy

Study	# events	OAR definition	Dose in patients with radiation myelopathy	Conclusion
Ryu 2006	**1 / 177**	SC 6mm CC of TV	9.6Gy to 10%	10% < 10Gy
Gibbs 2009	**6 / 1075**	NS	D_{max} 8.5 – 26.2Gy	1cm^3 < 8Gy
Sahgal 2010	**5 / 24** case control study	Thecal sack	D_{max} median 59Gy ($nBED_{2/2}$)	D_{max} below thresholds using LQ model

- (Very) Few patients developed radiation induced myelopathy
- Dose – response inconclusive
- However: follow-up short in majority of patients

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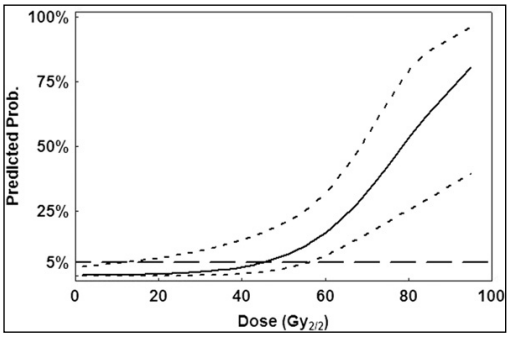
Safety of spine SBRT: myelopathy

Multi-institutional analysis:

- 9 cases with radiation induced myelopathy
- 66 cases w/o radiation induced myelopathy *Sahgal IJROBP 2012*



	1 fraction	3 fractions	5 fractions
1% probability	9.2	14.8	18.2
2% probability	10.7	17.4	21.5
3% probability	11.5	18.8	23.1
4% probability	12	19.6	24.4
5% probability	12.4	20.3	25.3

- Doses converted to 2Gy equivalent dose (EQD2/2)
- Dmax to thecal sack
- LARGE confidence intervals

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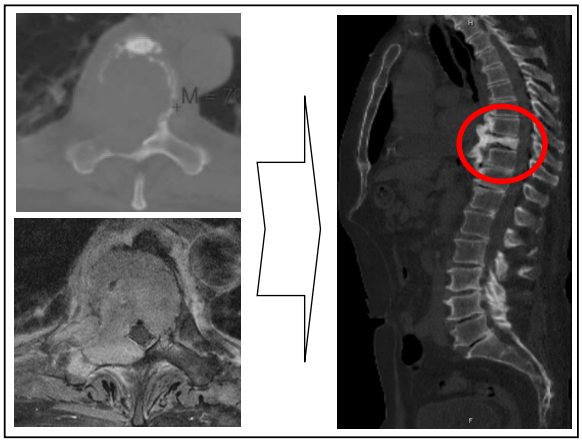
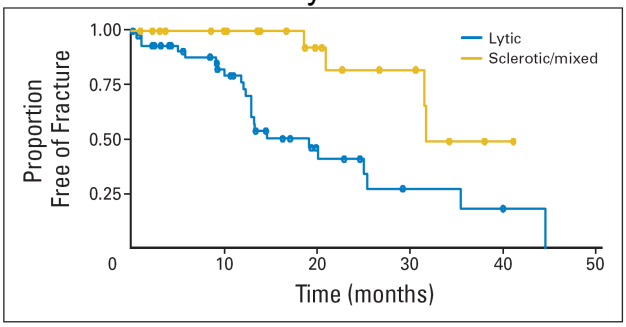
Vertebral compression fractures



Rose JCO 2009
62 patients with 71 target volumes
SF RS with 16 – 24Gy



Predictive factors for compression fractures:

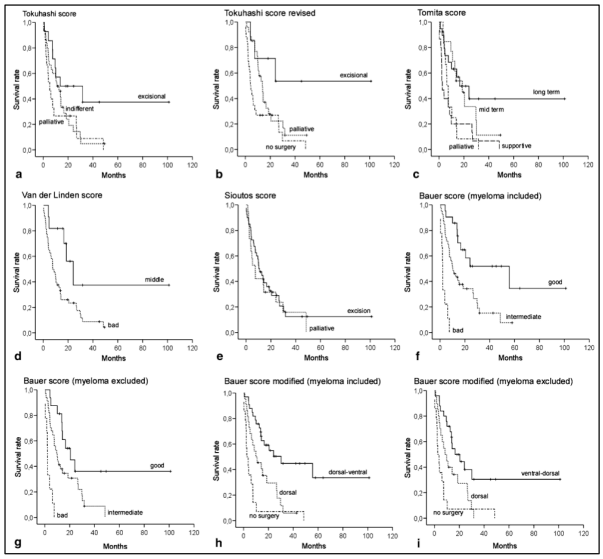
Rose JCP 2009
- Osteolytic metastases
- Size of metastases
- Location below T 10

Cunha IJROBP 2012
- Osteolytic metastases
- Kyphotic/scoliotic deformity

Overview

1. Conventional radiotherapy for painful vertabral metastases
2. Spinal cord tolerance
3. Technique of spinal SBRT
4. Outcome of spinal SBRT

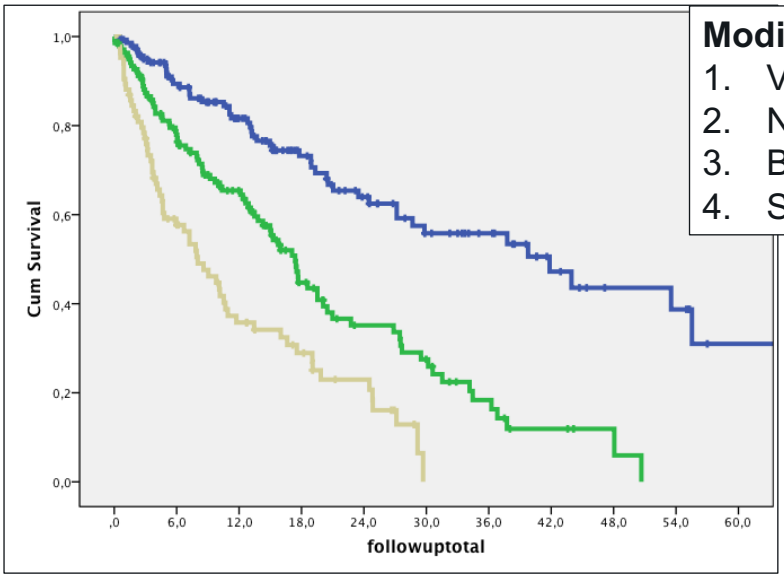
Patient selection: OS expectancy



Leithner Eur Spine J 2008

- Several prognostic scores based on conventionally irradiated patients or patients who received surgery

Patient selection: OS expectancy



Modified Bauer Score:

1. Visceral Mets
2. No lung cancer
3. Breast or prostate or kidney
4. Single bone met

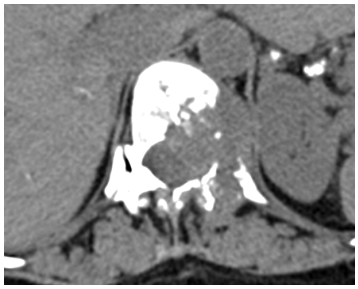
Guckenberger unpublished data

- Simple, clinical factors highly effective in OS prediction
- However, changes due to targeted drugs not considered

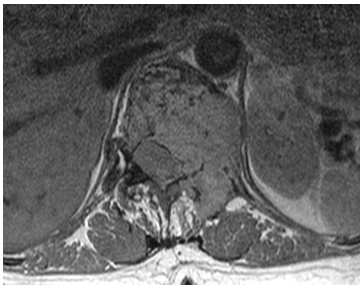
Imaging for target and OAR definition

Dahele IJROBP 2011

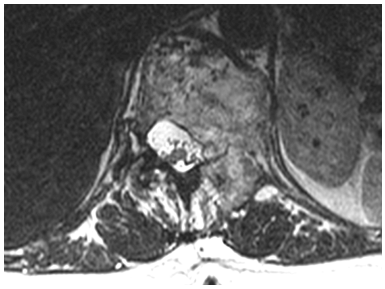
CT



MRI T1



MRI T2



CT imaging:

- Slice thickness 1- 2mm

MRI imaging:

- T1 with and w/o Gadolinium contrast
- T2
- Slice thickness ≤ 3mm or volumetric image acquisition

CT & MRI image registration

Average differences between 5 institutions (mm)			
	X-axis	Y-axis	Z-axis
Average	1.1	0.8	1.3
Range between 5 institutions (mm)			
Average	2.4	1.8	3.0

Toussaint Radiat Oncol 2016

- Rather large inter-observer variability
- ➢ Automatic image registration between CT and MRI images not reliable
- ➢ Manual adjustment / correction of image registration

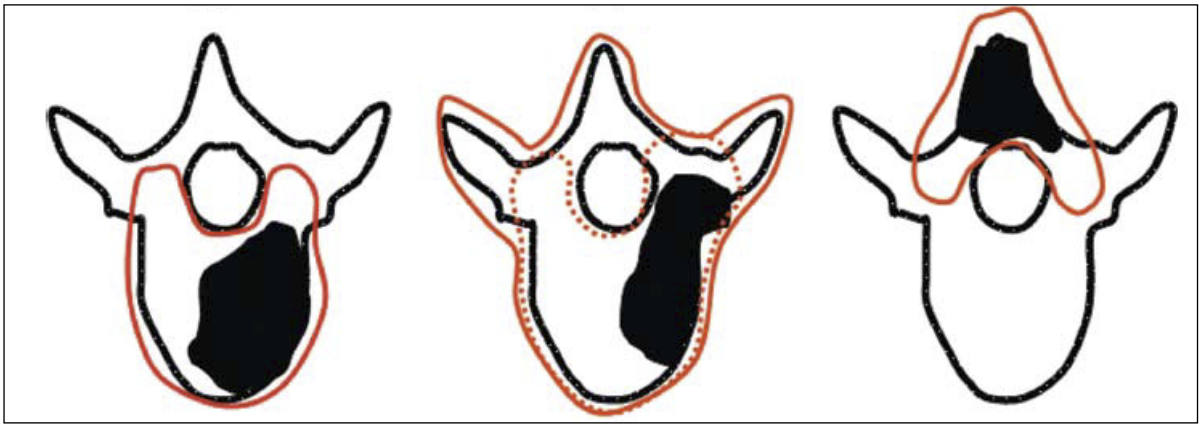
Patterns of failure after spine SBRT

	Total Failures	Adjacant vertebra	Epidural Space	Pedicles / posterior elements
Ryu 2004	9 / 61	33%		
Chang 2007	17 / 74		47%	17%
Gerszten 2007	6 / 51	0%		
Nelson 2008	4 / 33	0%	50%	50%
Nguyen 2010	12 / 55		50%	33%

Conclusions:

- Safety of treating the involved vertebra only
- Areas at risk: epidural space and untreated parts of vertebra

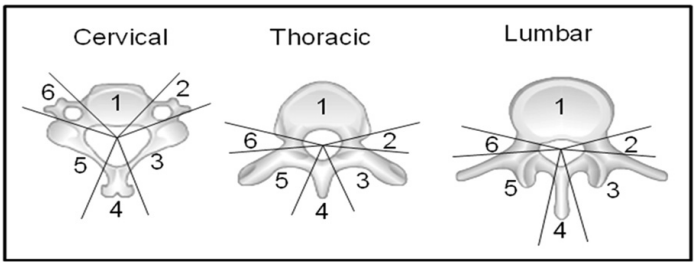
Target volume concept of RTOG 0631



Anatomical target volume concept:

- Inclusion of „volumes-at-risk“ in target volume
- Exclusion of tumors within 3mm distance to spinal cord from practice of single fraction radiosurgery

International Spine Radiosurgery Consortium Consensus Guidelines for Target Volume Definition in Spinal Stereotactic Radiosurgery *Cox IJROBP 2012*



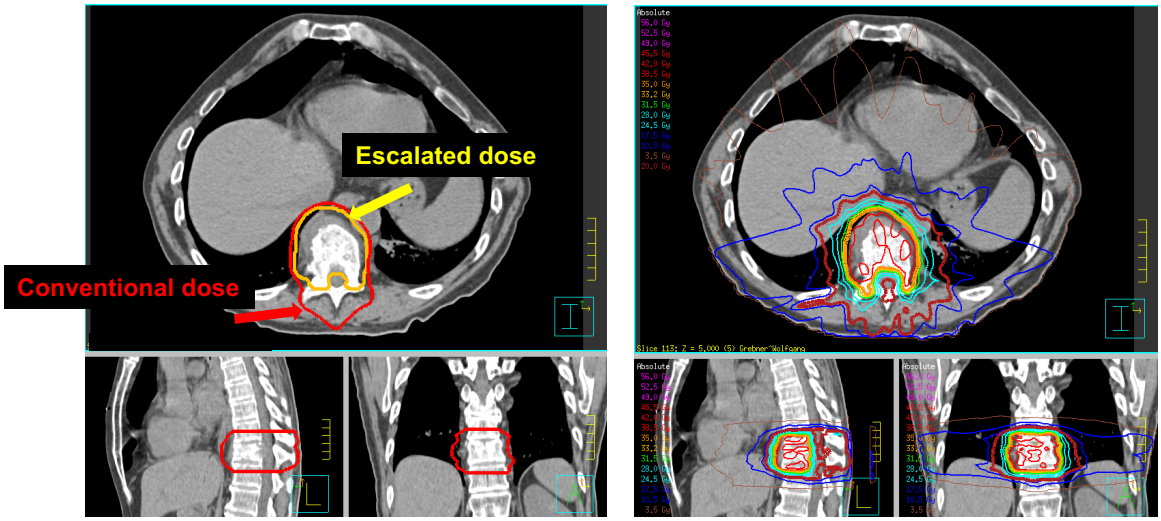
Segmentation of the vertebra

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

CTV definition based on involved segments

➢Not applicable to the re-irradiation situation

Region at risk: untreated parts of the vertebra



➢Simultaneous integrated Boost (SIB) concept to avoid recurrences in untreated parts of the vertebra

Definition of the OAR spinal cord

Conventional CT

T2 weigted MRI

CT Myelography

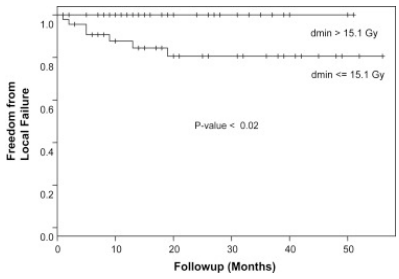
No consensus on planning organ at risk "spinal cord":

- Spinal cord
- Spinal cord + 1-2mm
- Thecal sack (cord + 0.5 – 1.5mm)
- Spinal canal

} **Use a planning OARs with some margin**

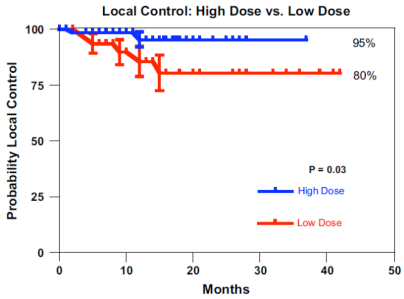
Dose and fractionation

Lovelock IJROBP 2009



1 x 15.1Gy

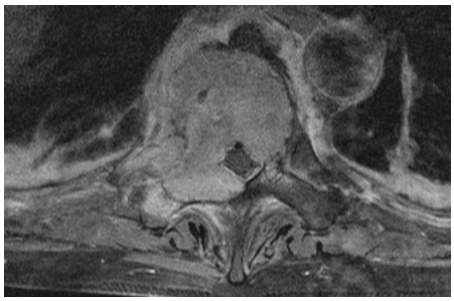
Yamada IJROBP 2008

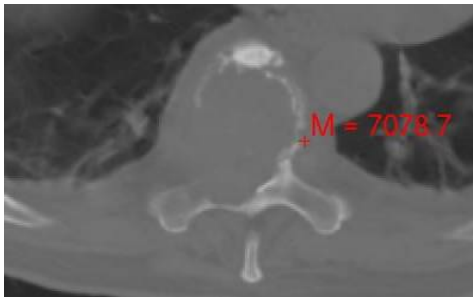


1 x 24Gy

➢Dose effect relationship in single fraction SRS

Region at highest risk: epidural space





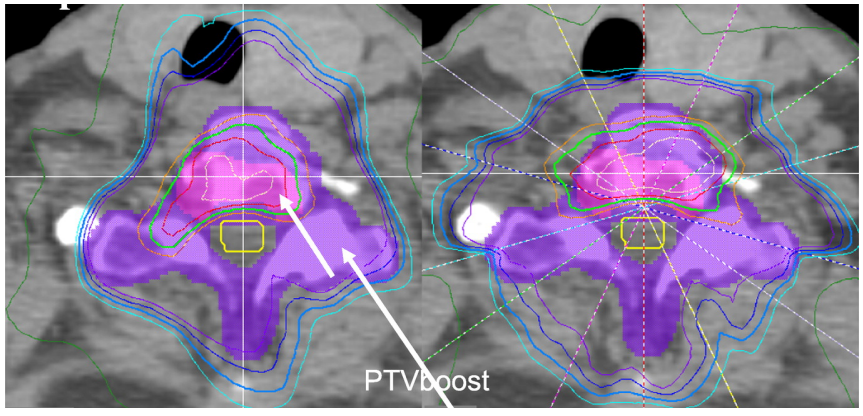
	1 Fx	3 Fx	5 Fx	10 Fx	20 Fx
Spinal cord tolerance	10Gy	18Gy	23Gy	35Gy	45Gy
Epidural tumor [EQD2]	17Gy	24Gy	29Gy	39Gy	46Gy

Implications for target volume definition / fractionation:

➢ More fractionated RT for cases with epidural involvement

IMRT versus VMAT for spine SBRT

VMAT **Step-and-shoot IMRT**



Lee BJR 2013

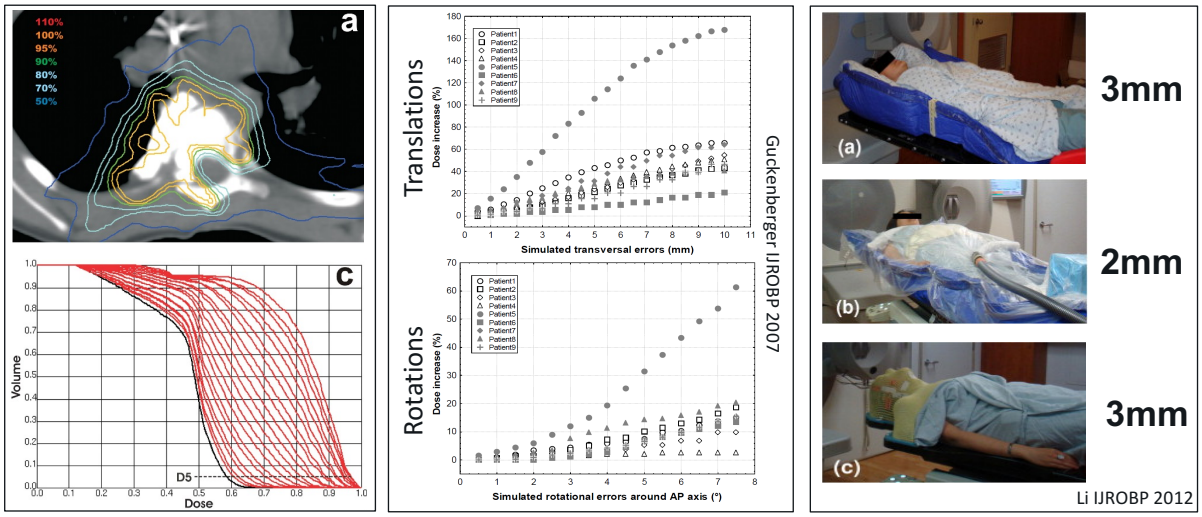
Delivery time:
3.5 min vs 10.5 min

Plan quality:
No difference

- Substantially shorter delivery times
- Comparable dosimetric plan quality

➢ VMAT preferable for patients in pain

Image guided SBRT delivery



- Daily pre-treatment IGRT mandatory
- Dosimetric relevance of rotations << translations
- Intra-fraction management (immobilization +/- active monitoring)

Overview

1. Conventional radiotherapy for painful vertabral metastases
2. Spinal cord tolerance
3. Technique of spinal SBRT
4. Outcome of spinal SBRT

Local tumor control after spine SBRT

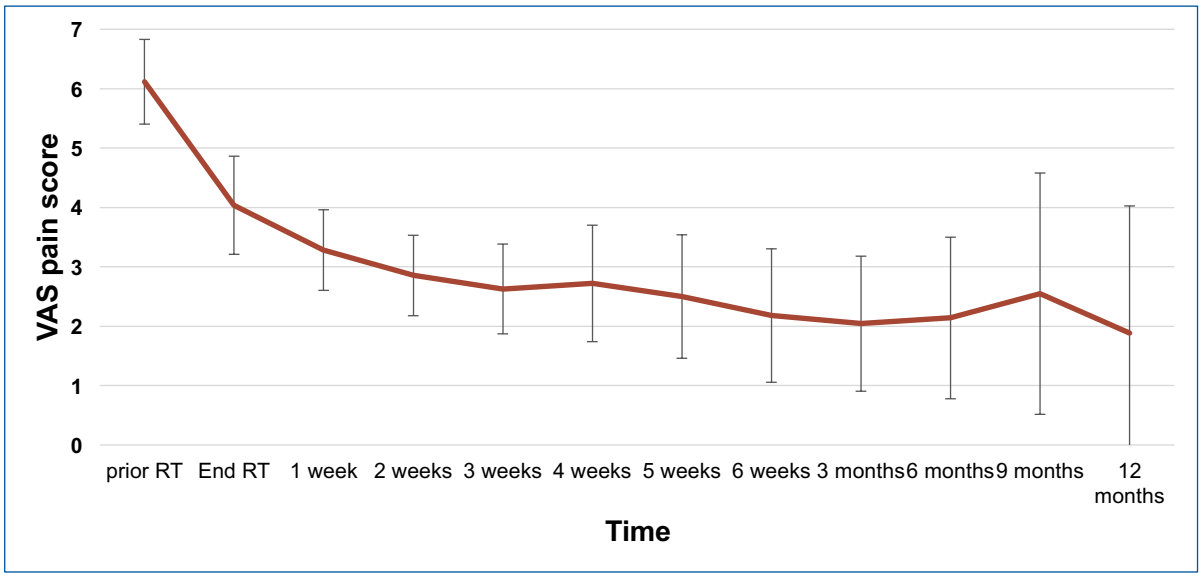
Study	# Pat / Tx	FU (months)	SBRT Dose	Local control
Ryu 2004 Henry Ford Hospital	49 / 61	6 – 24	1 x 10-16Gy	84% @ 1a
Gerszten 2007 Pittsburgh	49 / 65	Median 21	1 x 12.5 - 25Gy	90%
Chang 2007 M. D. Anderson	38 / -	Median 21	6 x 5Gy, 3 x 9Gy	84% @ 1a
Yamada 2008 MSKCC	93 / 103	Median 15	1 x 18 – 24Gy	90% @ 2a
Guckenberger 2009 Würzburg	14 / 16	Median 17	20 x 3Gy	89% @ 2a
Sahgal 2009 PMH / Stanford	14 / 23	Median 9	3 x 8Gy	78%
Balagamwana 2012 Cleveland Clinic	57 / 85	Median 5.4	1 x 15Gy	71% @ 1a
Garg 2012 M. D. Anderson	61 / 63	Median 20	1 x 16-24Gy	88 @ 1.5a
Heron 2012 Pittsburgh and Georgetown	228 / 348	Median 12	1 – 5 Fx	MF: 96% @ 2a SF: 70% @ 2a
Schipani 2012 Henry Ford Hospital	124 / 165	Median 7	1 x 18Gy	

DOSIS: a multi-center phase II trial

Prospective phase II trial

- 54 patients with 60 vertebral metastases
- No exclusion of patients with epidural disease
- Fractionated SBRT
- SBRT using SIB concept:
  - 5 x 4 / 7Gy
  - 10 x 3 / 4.85Gy
- Selection of patients with long OS expectancy

DOSIS: a multi-center phase II trial



- Rapid, deep and durable pain reduction

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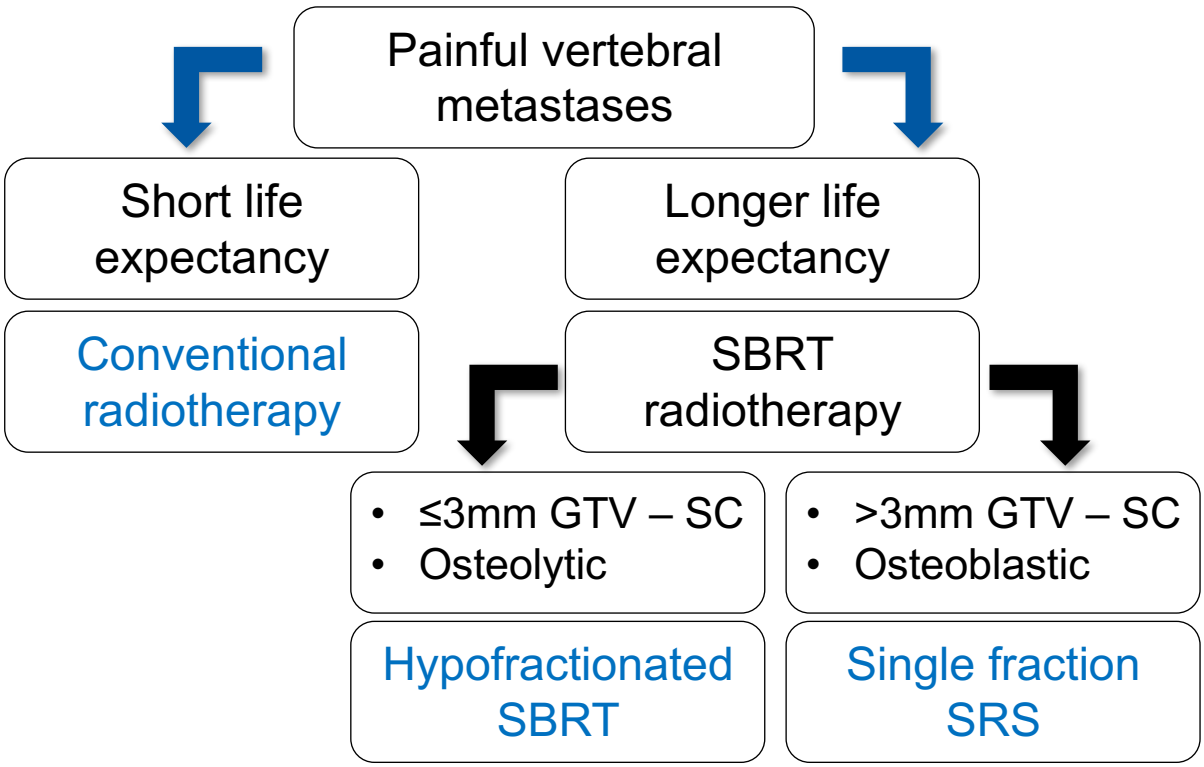

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CONCLUSIONS

INTERDISCIPLINARY

CHALLENGE

UniversityHospital Zurich ESTRO

Department of Radiation Oncology
Chairman: Prof. Dr. Matthias Guckenberger

SBRT for reirradiation

Matthias Guckenberger

UniversityHospital Zurich

ESTRO

Topics

1. Normal tissue tolerance in re-irradiation
2. Re-irradiation of spinal metastases
3. Re-irradiation of NSCLC

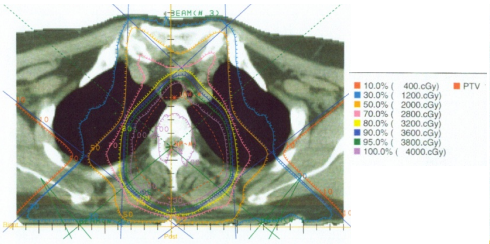
Case example: re-irradiation for verterbral metastasis

- A 50 year old female with a history of papillary thyroid cancer
- In 1979 was treated with Iodine-131
- Followed by external beam radiotherapy consisting of 40Gy Photon radiotherapy and 20Gy Electron radiotherapy
- Details of radiotherapy techniques and doses to organs-at-risk are unknown

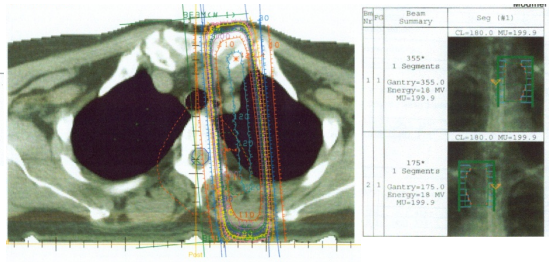
- Developed breast cancer in 2002 and bone metastases in 2007
- In 2008, a palliative radiotherapy of thoracic vertebras 2-4 was performed with a total dose of 40Gy
  - 20 Gy were delivered using posterior wedged fields
  - 20 Gy were delivered using AP/PA fields with sparing of the spinal cord

Case example: re-irradiation for verterbral metastasis

20 Gy wedged fields

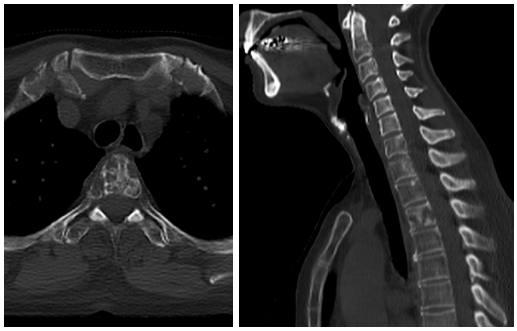


20 Gy AP/PA with SC sparing



- In 2010, the patient suffered from recurrent pain in these vertebras and CT imaging showed progressive osteolytic metastases

➢ Re-irradiation was offered



Question:

What treatment would you offer to the patient ?

1. RT is no option because of spinal cord tolerance is reached
2. Palliative RT with 1 x 8Gy
3. Single fraction radiosurgery
4. Multiple fraction SBRT

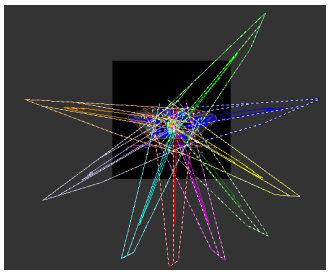
Case example: re-irradiation for verterbral metastasis

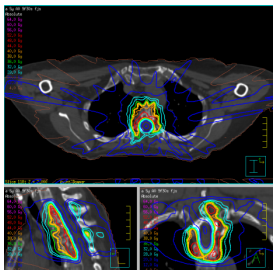
Assumption of spinal cord tolerance:

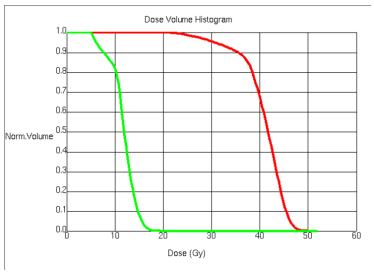
40Gy	-31 years
20 + 2 Gy	-2 years
62Gy	physical dose
30Gy	**residual „damage“**

➢ **Maximum dose of 20Gy in 15 fractions**

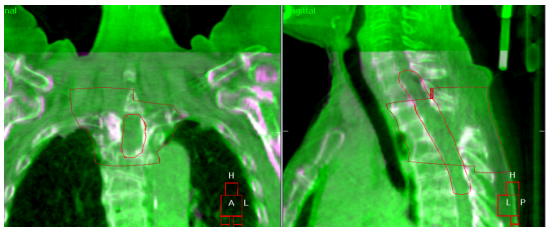
Case example: re-irradiation for verterbral metastasis





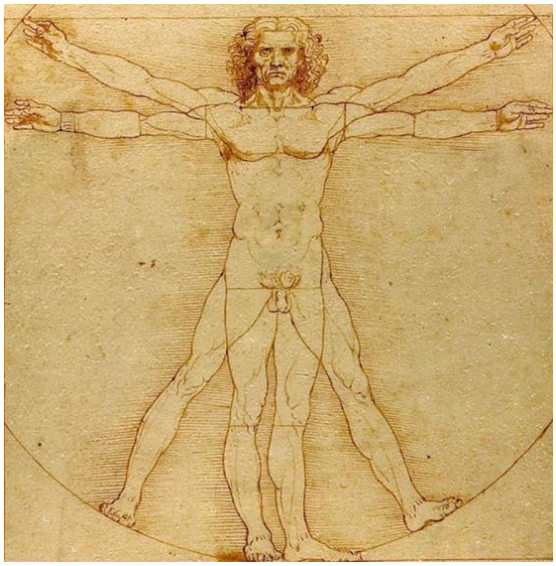


Target definition: only affected parts of the vertebrae included into TV
IMRT planning: 40Gy in 15 Fx with SC_{max} 20Gy



Immobilization: double vacuum BodyFIX
IGRT: daily using CBCT

Loco-regional failure after primary R(CH)T



H&N: 40% *Bourhis Lancet Oncol 2012*

NSCLC: 40% *Auperin JCO 2010*

Esophagus: 40% *Stahl JCO 2009*

Rectum: 6% *Hofheinz Lancet Oncol 2012*

Cercix: 13% *Duenas-Gonzalez JCO 2011*

- Salvage surgery often difficult after radical RT
- Re-irradiation should be a frequent clinical challenge

Frequency of re-RT for NSCLC

Study	NSCLC Patiens treated with EBRT	Patients with Re-irradiation
Green Cancer 1982	774	29 **(3.7%)**
Jackson Med J Aust 1987	270	22 **(8.1%)**
Gressen Am J Clin Oncol 2000	1500	23 **(1.5%)**

- Large variability in the literature
- Re-irradiation for recurrent NSCLC is rarly performed
- Re-irradiation is performed in **highly selected** patients

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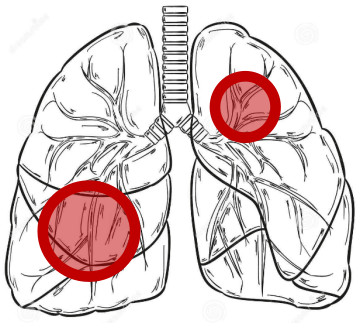
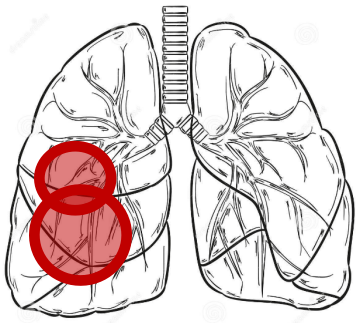
Definition of re-irradiation

Scenario 1



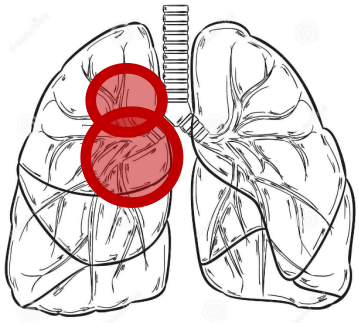
No high-dose overlap

Scenario 2



Overlap in parallel organ

Scenario 3



Overlap in serial organ

- ➢ Cumulative EQD2 doses for interpretation
- ➢ Provided by few studies

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Frequency of re-RT for vertebral metastases

- No data on the overall frequency of re-irradiation in clinical practice
- However, even in a palliative setting of spinal metastases

➢ **Re-irradiation is practiced in only few patients:**

- After multiple fraction RT: 8%
- After Single fraction RT: SF: 20%

Chow JCO 2007

Most likely explanation:
➢ Risk / fear of severe normal tissue complication

Topics

1. Normal tissue tolerance in re-irradiation
2. Re-irradiation of spinal metastases
3. Re-irradiation of NSCLC

QUANTEC Report 2010

- Useful guidelines for normal tissue tolerance in the primary situation
- Very limited information about re-irradadiation situation

Organ-Specific Papers

1. **Brain**
2. **Optic Nerve/Chiasm**
3. **Brain Stem**
4. **Spinal Cord**
5. **Ear**
6. **Parotid**
7. **Larynx/Pharynx**
8. **Lung**
9. **Heart**
10. **Esophagus**
11. **Liver**
12. **Stomach/Small Bowel**
13. **Kidney**
14. **Bladder**
15. **Rectum**
16. **Penile Bulb**

Vision Papers
True Dose
Imaging
Biomarkers
Data Sharing
Lessons of QUANTEC

Each with 10 sections

1. **Clinical Significance**- Describes the clinical situations where the organ is irradiated, and the incidence/significance of organ injury.
2. **Endpoints**- Describes the different endpoints often considered when assessing injury, the impact of endpoint-selection on the reported injury rates, the challenges/utilities of different endpoints, and the time course of organ injury.
3. **Challenges Defining Volumes**- Describes how the organ is typically defined (or segmented) on treatment planning images. Includes a discussion of uncertainties/challenges in organ definition (e.g. changes in organ volume/shape during therapy), and the associated impact on DVH's and dose/volume/outcome analyses.
4. **Review of Dose/Volume Data**- A comprehensive summary of reported 3D dose/volume data for clinically-relevant outcomes.
5. **Factors Affecting Risk**- Other clinical factors affecting the risk of injury are noted (e.g. age, combined modality therapy, dose fractionation).
6. **Mathematical/Biological Models**- Models that have been used to relate 3D dose/volume data to clinical outcomes are summarized, along with associated model parameters, limitations and uncertainties.
7. **Special Situations**- Most of the data discussed relates to conventional fractionation. This section describes situations were the presented data/models may not apply (e.g. hypo-fractionation).
8. **Recommended Dose/Volume Limits**- The available information is condensed into meaningful dose/volume limits, with associated risk rates, to apply clinically.
9. **Future Toxicity Studies**- Describes areas in need of future study.
10. **Toxicity Scoring**- Recommendations on how to score organ injury.

Repair of radiotherapy induced damage

Re-irradiation tolerance and recovery

Full – partial recovery	Partial recovery	No recovery
• Lung pneumonitis • Skin • Mucosa	• Plexus • Spinal cord • Bone • Mesenchymal • Small intestine	• Heart • Lung fibrosis • Heart • Bladder • Kidney

Factors associated with recovery:
- Initial biological dose in relationship to tolerance dose
- Initial volume irradiated
- Time interval between treatment courses

Re-irradiation tolerance and recovery

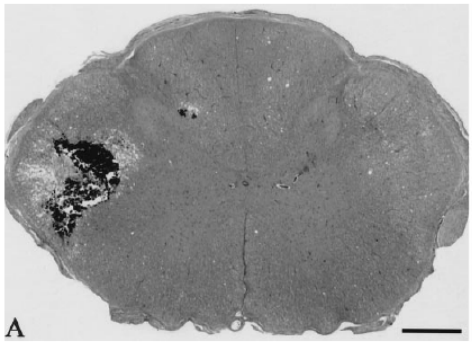
Full – partial recovery	Partial recovery	No recovery
• Lung pneumonitis • Skin • Mucosa	• Plexus • Spinal cord • Bone • Mesenchymal • Small intestine	• Heart • Lung fibrosis • Heart • Bladder • Kidney

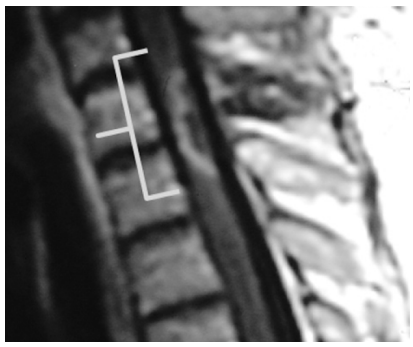
- **Acute toxicity**
- **Relevant for palliative RT**

- **Late toxicity**
- **Relevant for „curative“ RT**

➢ All organs, which are relevant for acute toxicity in the palliative setting, show relevant recovery

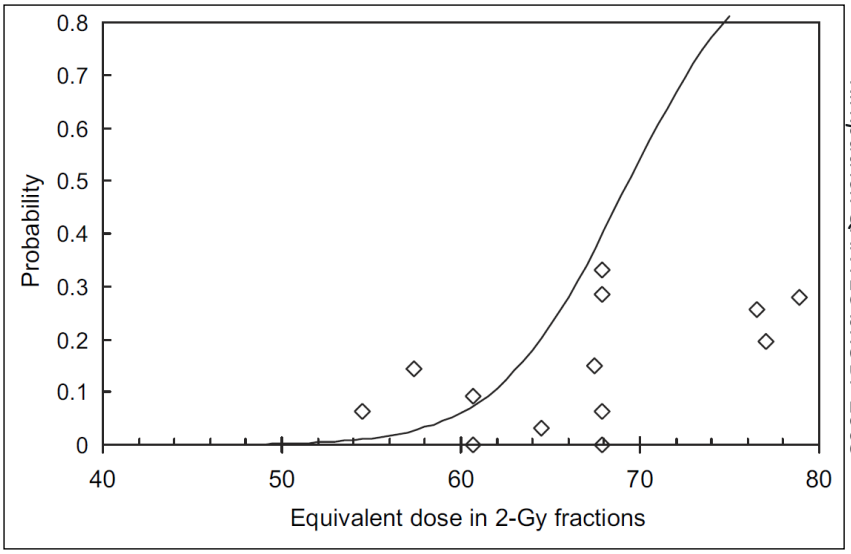
Radiation induced myelopathy





- Appearance of signs/symptoms of sensory or motor deficits, loss of function or pain
- Confirmed by magnetic resonance imaging
- Occurs 6 months to 3 years after RT

Spinal cord tolerance in primary radiotherapy



Risk of myelopathy

50Gy

↓

0.2%

60Gy

↓

6%

Conversion of physical doses into 2Gy equivalent doeses:

➢ LQ model with α/β ~ 2Gy

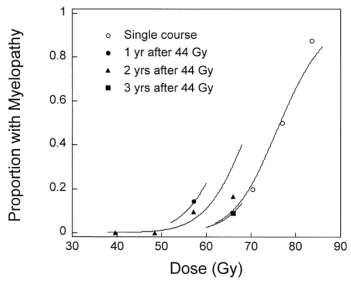
Spinal cord tolerance – reirradiation: Animal studies

56 Rhesus monkeys, SFD 2.2Gy to 44Gy

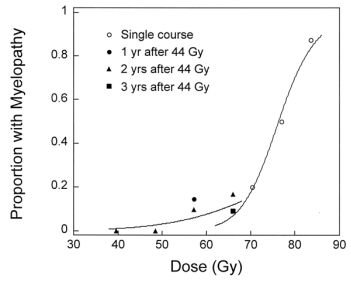
Reirradiation
- 57.2Gy after 1 and 2 years
- 66Gy after 2 and 3 years

➢ **4 / 45 animals developed RMP**

„Optimistic“ model



„Pessimistic“ model



Ang IJROBP 2001

Optimistic model:
➢ Recovery of 76%, 85% and 101% after 1, 2 and 3 years

Conservative model:
➢ Recovery of 61%

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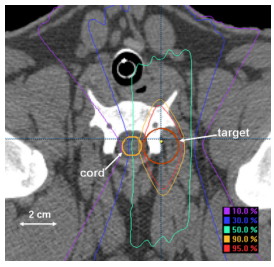
Spinal cord tolerance – reirradiation: Animal studies

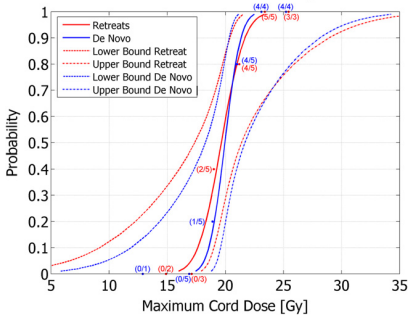
26 minipigs, uniform 30Gy in 10 Fx

Reirradiation after 1 year:
- Inhomogeneous (10-90%) SRS
- 14.9Gy – 25.4Gy

➢ **ED_{50} of 19.7Gy**



De Novo vs Retreated Dose Response



Medin IJROBP 2011

➢ Identical SRS tolerance as in the primary situation

➢ Full recovery of 30Gy in 10 Fx within 1 year

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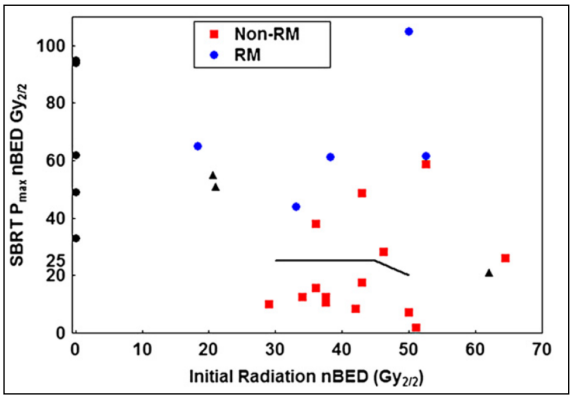
Spinal cord tolerance: re-irradiation with hypofractionation (SBRT)



Sahgal IJROBP 2010:

Case-control study:

- 5 cases of RM after SBRT
- Thecal sack as OAR
- Maximum dose to thecal sack
- 2Gy equivalent with α/β=2Gy

Clinical Practice: **0% risk of myelopathy if**

- Initial course <50Gy (EQD2/2)
- SBRT course <25Gy (EQD2/2)
- Interval >5 months

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Topics

1. Normal tissue tolerance in re-irradiation
2. Re-irradiation of spinal metastases
3. Re-irradiation of NSCLC

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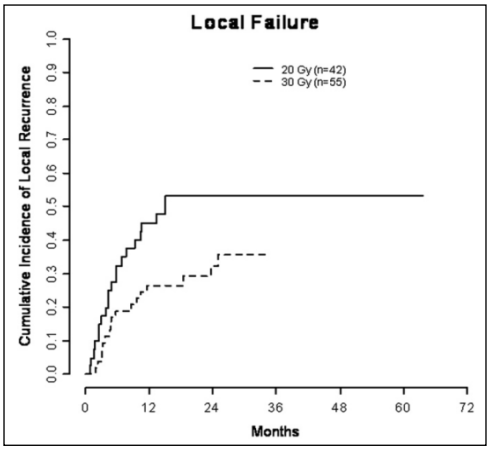
Dose and fractionation

Damast IJROBP 2010



Significantly improved LC after

5 x 6Gy

Compared to

5 x 4Gy

- Use of fractionated protocols
- 30Gy in 5 Fx, but still 25% recurrences within 12 months

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Spine SBRT as re-treatment

Study	# patients / cases	Dose 1st RT course (median)	Interval (median months)	Reirradiation TD / fraction (median)	Accumulated dose (median)
Milker-Zabel 2003	18 / 19	38Gy	18	39.6Gy / 22	NS
Mahan 2005	8 / 8	30Gy	NS	30Gy / 15	48Gy
Sahgal 2009	25 / 37	36Gy	11	24Gy / 3	NS
Choi 2010	42 / 51	40Gy	19	20Gy / 2	76Gy
Sterzing 2010	36 / 36	30Gy	18	30Gy / 10	45Gy
Damast 2010	94 / 97	30Gy	NS	20-30Gy / 5	54.3Gy
Garg 2011	59 / 63	30Gy	NS	27-30Gy / 3-5	NS
Mahadevan 2011	60 / 81	30Gy	20	24-30Gy / 3-5	NS
Chang 2012	49 / 54	39.2Gy	25	27Gy / 3	83.4Gy

Evidence-based clinical practice:

- 1st RT course with ~30Gy and ~12 months interval
- Fractionated re-irradiation:
  - 30Gy in 5 fractions
  - 3 / 5 studies did not assume spinal cord recovery

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Spine SBRT as re-treatment

Study	Planning	Set-up / imaging
Milker-Zabel 2003	ss-IMRT	Stereotactic
Mahan 2005	Tomotherapy	Daily MV-CT
Sahgal 2009	Cyberknife	kV tracking
Choi 2010	Cyberknife	kV tracking
Sterzing 2010	Tomotherapy	Daily MV-CT
Damast 2010	IMRT	Daily portal images or CBCT
Garg 2011	IMRT	Daily CT on rails or CBCT
Mahadevan 2011	Cyberknife	kV tracking
Chang 2012	Cyberknife	kV tracking

Evidence-based clinical practice:

- IMRT treatment planning required (100% agreement)
- Daily IGRT required (100% agreement)

Spine SBRT as re-treatment

Study	# patients / cases	Follow-up (months)	Myelopathy	Lcoal / pain control
Milker-Zabel 2003	18 / 19	12.3	0%	95%
Mahan 2005	8 / 8	15.2	0%	100%
Sahgal 2009	25 / 37	7	0%	70%
Choi 2010	42 / 51	7	n=1 G4	73%
Sterzing 2010	36 / 36	7.5	0%	63%
Damast 2010	94 / 97	12.1	0%	66%
Garg 2011	59 / 63	13	n=2 G3 peripheral nerve injury	76%
Mahadevan 2011	60 / 81	12	n=3 persistent radicular pain n=1 lower-extremity weakness	93%
Chang 2012	49 / 54	17.3	0%	79%

Evidence-based clinical practice:

- Very low incidence of myelopathy
- Nerve damage a more frequent toxicity
- Promising local control 63 – 100%

CONCLUSION

- Despite week level of evidence, there appears to be spinal cord recovery
- Spinal cord recovery reaches **50** – 100%
- Spinal cord recovery is best if
  - RT interval is > 6 months
  - First RT series was below tolerance dose
- SBRT very promising tool in this situation of limited alternatives

Topics

1. Normal tissue tolerance in re-irradiation
2. Re-irradiation of spinal metastases
3. Re-irradiation of NSCLC

Thoracic re-treatment

Histologies
NSCLC
SCLC
Esophageal Ca
Thyroid Ca
Thymus Ca
Lymphomas
Metastasis

Surgery	Chemotherapy	Targeted agents	Radiotherapy

Multidisciplinary challenge !

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„Low-dose“ re-irradiation for palliation

Literature review:

- 379 patients by 13 publications (1982-2014)
- 86% symptomatic @ time of re-RT
- Median re-irradiation dose 36 Gy

Drodge Ann Palliat Med 2014

➢ Few patients !

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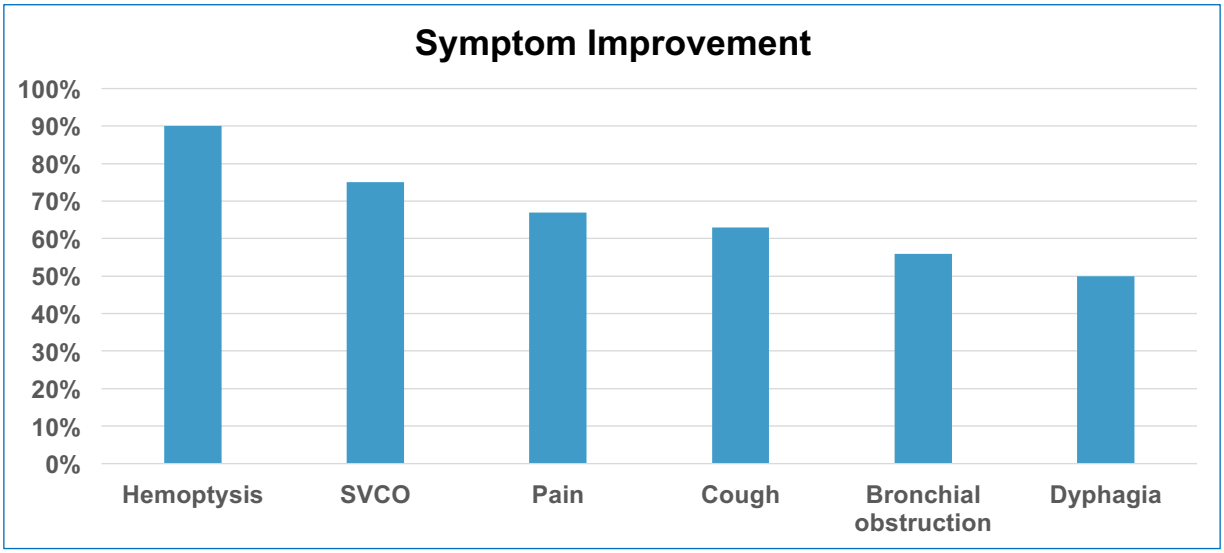
„Low-dose“ re-irradiation for palliation



Drodge Ann Palliat Med 2014

- Excellent palliation, overall 69%

„Low-dose“ re-irradiation for palliation

Toxicity	Rate
Esophagitis	**17%**
Pneumonitis	**12%**
Skin	**4.1**
Myelophathy	**0.5%**
Re-RT related death	**1.6%**

Drodge Ann Palliat Med 2014

- Acceptable toxicity
- However, 1.6% death rate

„High-dose“ re-irradiation

Study	Patients (#)	Interval (months)	Re-irradiation (Gy)	Cumulative (Gy)
Wu 2003	23	13	**51**	NS
Okamoto 2002	34	23	**50**	**110**
Kruser 2013	48	19	**56**	NS
Tada 2005	14	16	**50**	NS
Ebara 2007	44	13	**40**	102
Griffioena 2014	24	51	**60**	**120**

Drodge Ann Palliat Med 2014

- Selected patients: long interval and median target size <100cc in all studies basis for full dose Re-RT

„High-dose“ re-irradiation

Study	Toxicity G V	Median OS
Wu 2003	0	14
Okamoto 2002	0	15
Kruser 2013	0	13
Tada 2005	0	7
Ebara 2007	0	7
Griffioena 2014	N=3	14

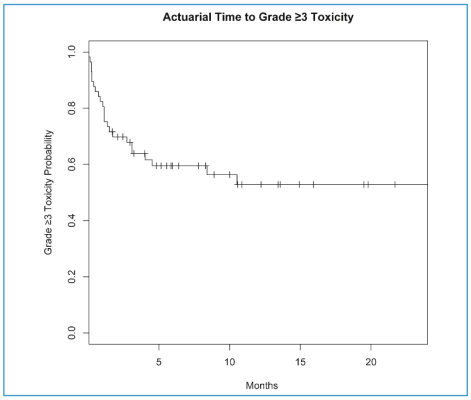
Drodge Ann Palliat Med 2014

- Relevant but manageable toxicity
- Reasonable OS

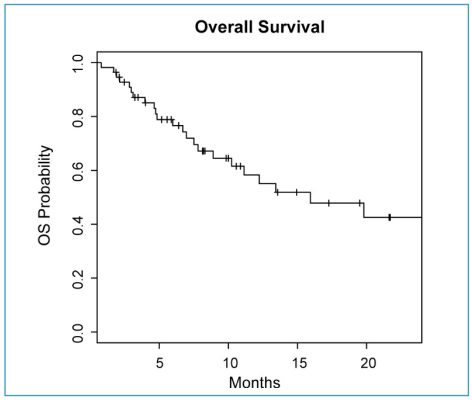
Proton re-irradiation

Multi-Institutional Prospective Study of Reirradiation with Protons:

- Median interval 19 months; median CTV 108cc
- Conventionally fractionated 66Gy, 2/3 concomitant CT



11.5% grade V toxicity



Median OS 15 months

Chao JTO 2017

➢ Overall, results appear similar to Photon re-irradiation

Proton re-irradiation

Factors influencing toxicity

At the initiation of the study, patients were stratified as either low volume (CTV <250 cm3) or high volume (**CTV >250 cm3**).

The high-volume patients in the full thoracic cohort of the proton reirradiation protocol were subsequently **deemed infeasible because of inability to complete the prescribed treatment course owing to toxicity**.

Table 2. Treatment Toxicities and Association with Clinical and Dosimetric Factors

Characteristic	n (%)	*p* Value
Acute grade ≥3 toxicity	22 (39%)	
Treatment factor	Rate of grade ≥3 toxicity	
Central volume overlap		
Low (<41 cm^3)	4 of 28 (14%)	
High (≥41 cm^3)	18 of 28 (64%)	<0.001
Mean heart dose		
Low (<394 cGy)	9 of 34 (26%)	
High (≥394 cGy)	12 of 20 (60%)	0.02
Mean esophagus dose		
Low (<1245 cGy)	7 of 32 (22%)	
High (≥1245 cGy)	14 of 22 (64%)	0.003
Concurrent chemotherapy		
No	3 of 19 (16%)	
Yes	20 of 38 (53%)	0.003

Chao JTO 2017

➢ Limitation of overall volume and central overlap volume

SBRT for re-irradiation

Author publication year [references]	Years of enrollment	Number of patients	Tumor types (no. of patients)	Infield/outfield relapses (no. of patients)	Median target volume (cc, range)	Median RT dose of the primary treatment	Interval between primary and salvage treatment	Salvage SBRT schedule
Coon et al. (2008) [23]	2005–2007	12	Locally recurrent or progressive lung cancer (NA)	NA	14 (3.4–128)	NA	NA	60 Gy/3 fx
Kelly et al. (2010) [24]	2004–2008	36	Primary lung cancer (36)	11/25*	NA	61.5 Gy (range, 30–79)	22 months	50 Gy/4fx 40 Gy/5 fx
Seung et al. (2011) [25]	2009–2010	8	Primary lung cancer (8)	NA	NA	50–68 Gy (1.8–2.5 Gy/fractions)	36 months	40 Gy/5 fx 48 Gy/4fx 50 Gy/5 fx 60 Gy/3 fx
Peulen et al. (2011) [26]	1994–2004	29	Primary (6) and lung metastases (23)	NA	(76, 16–355)	30–45 Gy/2–3 fx 40 Gy/4 fx	14 months	30–45 Gy/2–3fx 40 Gy/5 fx
Trakul et al. (2012) [27]	2004–2010	15	Primary (12) and lung metastases (5)**	17/0**	(31.6, 7.4–119.7)	Not specified	16 months	20 Gy/1fx 40 Gy/5 fx
Liu et al. (2012) [28]	2004–2010	72	Primary (10) and lung metastases (62)	19/53	NA	63 Gy (range, 30–79)	21 months	50 Gy/4fx
Valakh et al. (2013) [29]	2006–2011	9	Primary (8) and lung metastases (1)	3/6	(22.2 +/− 24.5)	60 Gy (range, 30–60) in 3–5 fx	NR	60 Gy (30–60)/3–5 fx
Meijneke et al. (2013) [30]	2005–2012	20	Primary (17) and Lung metastases (3)	0/20	NA	60 Gy/3fx 60–50 Gy/20–25 fx	11 months	60 Gy/5 fx 50 Gy/5 fx
Reyngold et al. (2013) [31]	2004–2011	39	Primary (17) and lung metastases (22)	22/17	(67, 17–473)	61 Gy (range, 30–79)	37 months	48 Gy/4 fx
Trovò et al. (2014) [32]	Not specified	17	Primary lung cancer (17)	17/0	NA	50–60 Gy/20–30 fx	18 months	30 Gy/5–6 fx
Hearn et al. (2014) [33]	2004–2012	10	Primary lung cancer (10)	NA	NA	50 Gy/5 fx 30 or 34 Gy/1 fx	15 months	50 Gy/5 fx 60 Gy/3 fx
Kilburn et al. (2014) [34]	2001–2012	33	Primary (29) and lung metastases (4)***	NA	NA	66 Gy (range, 45–80)	18 months	50 Gy/5 fx 20 Gy/1 fx

De Bari Cancer Treatment Reviews 2015

➢ **Full SBRT dose** given about **1a** after **curative radiotherapy** to mostly **small recurrences**

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SBRT for re-irradiation

Local control @ 1-2 years	Overall survival @ 1-2 years	G3-5 pneumonitis
52% - 92%	59% - 88%	3 – 30%

De Bari Cancer Treatment Reviews 2015

➢Overall effective and well tolerated

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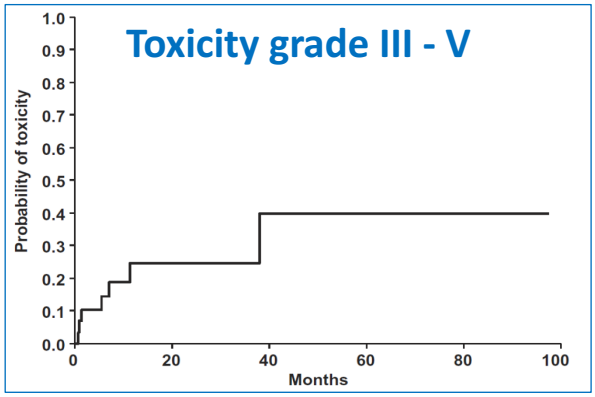
SBRT for re-irradiation after SBRT

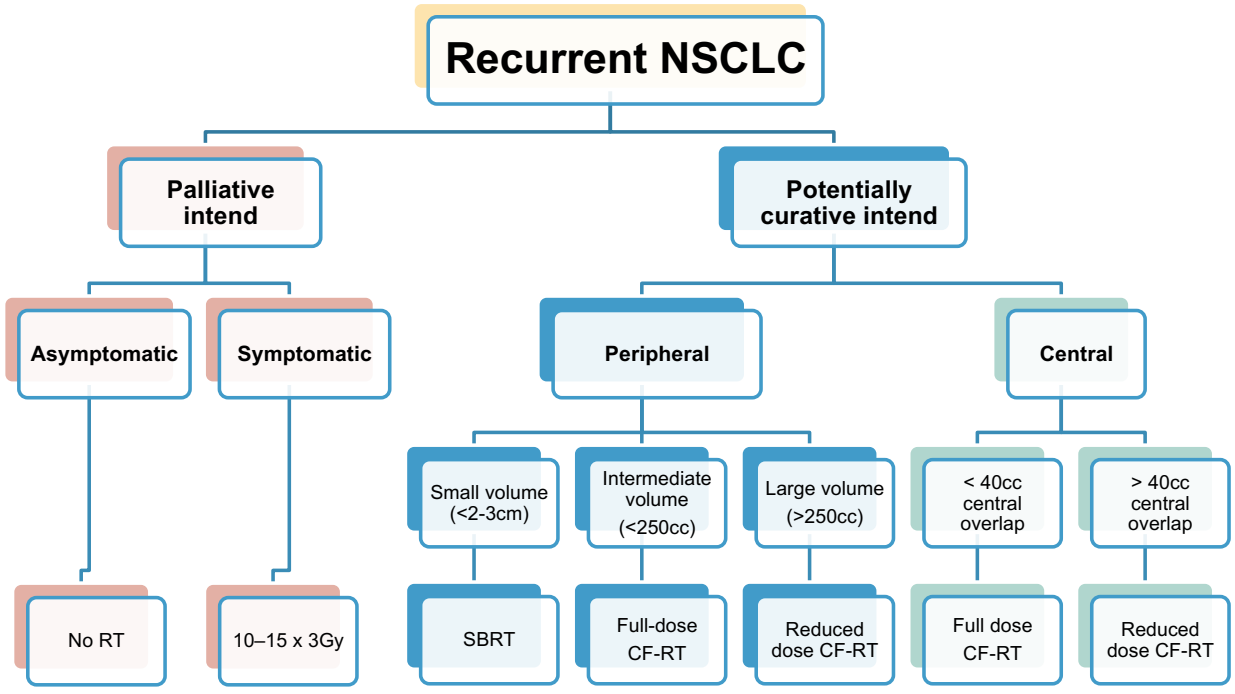
- Retrospective analysis of 32 patients treated with 2 (n=29), 3 (n=2) or 4 (n=1) SBRT courses



Grade V bleeding: n=3
➢ All centrally located

Peulen Radiother Oncol 2011

➢ SBRT reirradiation for central recurrences strongly discouraged!



➢ A proposal for risk-adapted re-irradiation

Starting your SBRT program: RTT perspective

Lineke Berkelaar- van der Weide (MSc)
RTT research
VU University Medical Center
l.vanderweide@vumc.nl

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- **Max Dahele**
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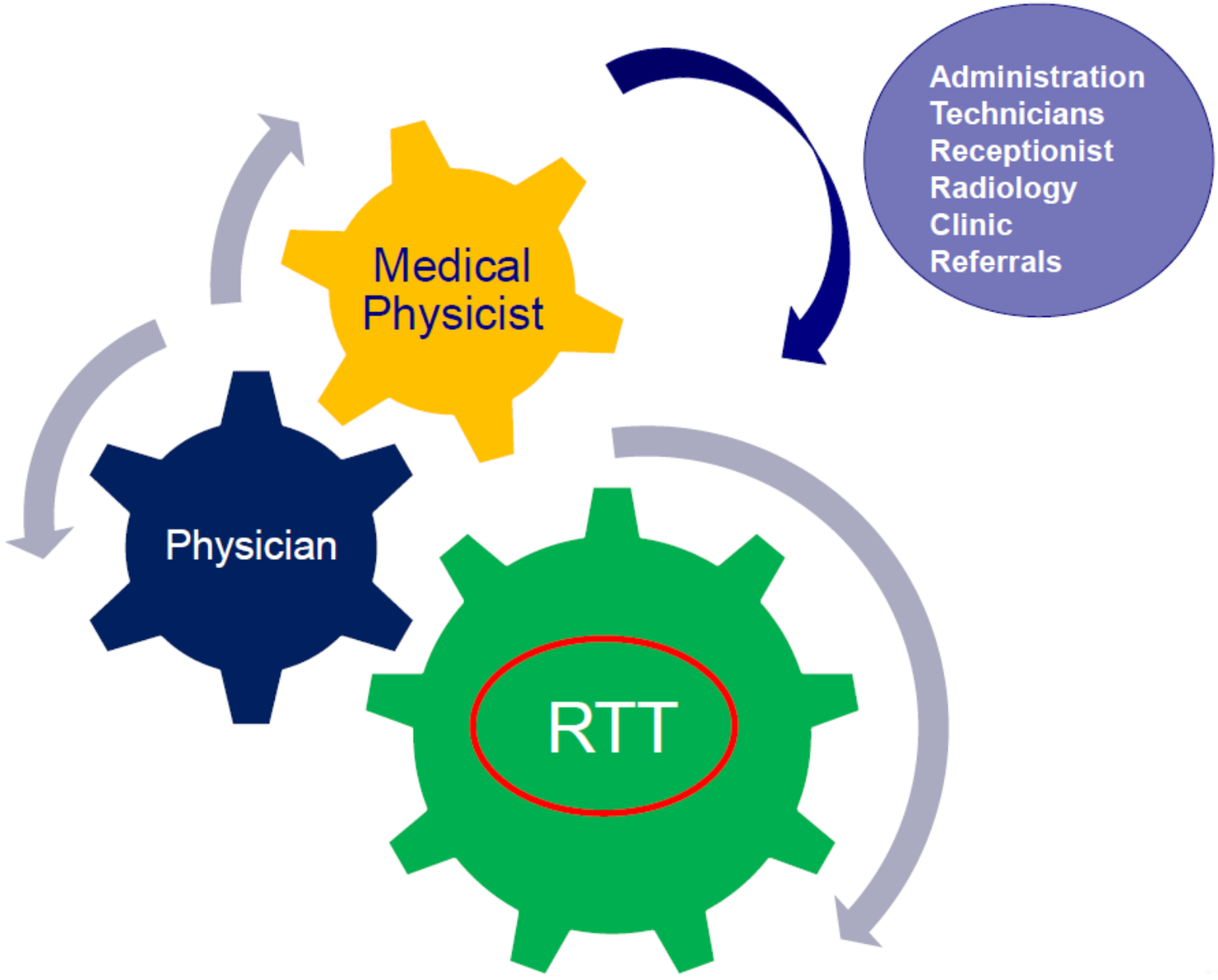
- **Ingrid Kuijper**
- **Colien Hazelaar**
- **Tezontl Rosario**
- **Stereoteam**

Treatment

A clinician in our department said:

Be aware of the responsibility you have as RTT. In surgery, the surgeon plans to treat the patient and is doing it by him/herself, but in radiotherapy the clinician plans to treat a patient, but the RTT is doing the job on the machine.

Interdisciplinary team



Start up a SBRT program

- Part of the implementing team
- Training -> Dedicated team

Training scheme

- Week 1: All theory from a physicists, clinician, planning, IGRT
- Week 2: Match under supervision, different tumorsites and the different protocols
- Week 3 & 4: Match under supervision
- Week 5 - 7: Match independently
- Week 8 & 9: Match independently and to handle with deviations of the target
- Week 10: Evaluation and test

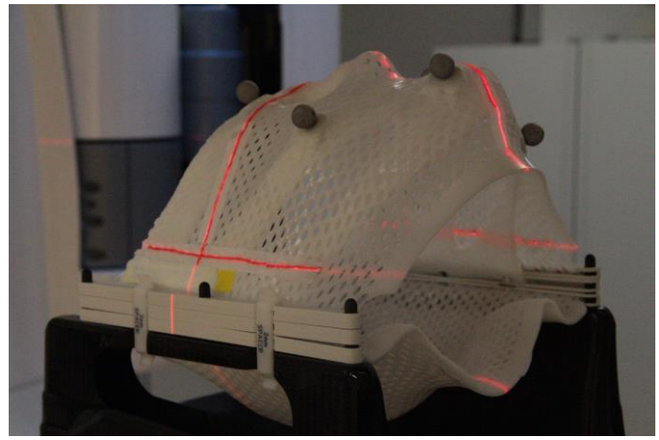
Join the dedicated stereoteam!

RTTs role

- Immobilisation
- (4D)CT
- Planning
- Treatment:
  - Patient positioning
  - IGRT-protocols
  - Motion Management
  - Intrafraction monitoring

RTTs role

- Immobilisation
- (4D)CT
- Planning
- Treatment:
  - Patient positioning
  - IGRT-protocols
  - Delivery
  - Intrafractional movement verification



RTTs role

- Immobilisation
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  - Patient positioning
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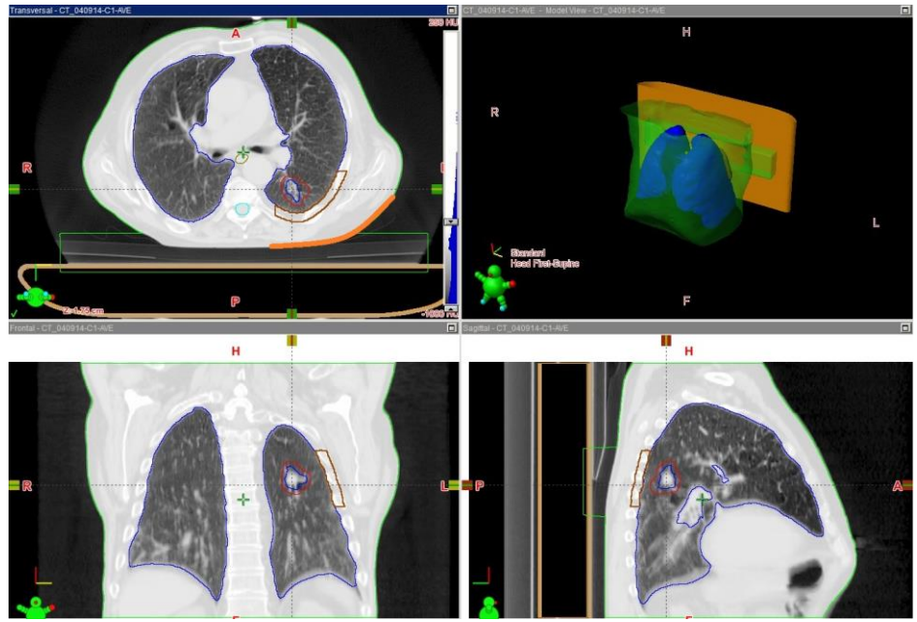


RTTs role

- Immobilisation
- (4D)CT
- Planning
- Treatment:
  - Patient positioning
  - IGRT-protocols
  - Motion management
  - Intrafractional movement verification

Treatment

- Positioning
- IGRT
  - CBCT
  - 6D-couch
  - CBCT halfway treatment
  - CBCT post-treatment

Treatment

- Positioning
- IGRT
  - CBCT
  - 6D-couch
  - CBCT halfway treatment
  - CBCT post-treatment

Motion management

A strategy for motion management is essential in SBRT for anatomical indications effected by breathing motion (e.g. lung, liver, adrenal gland)

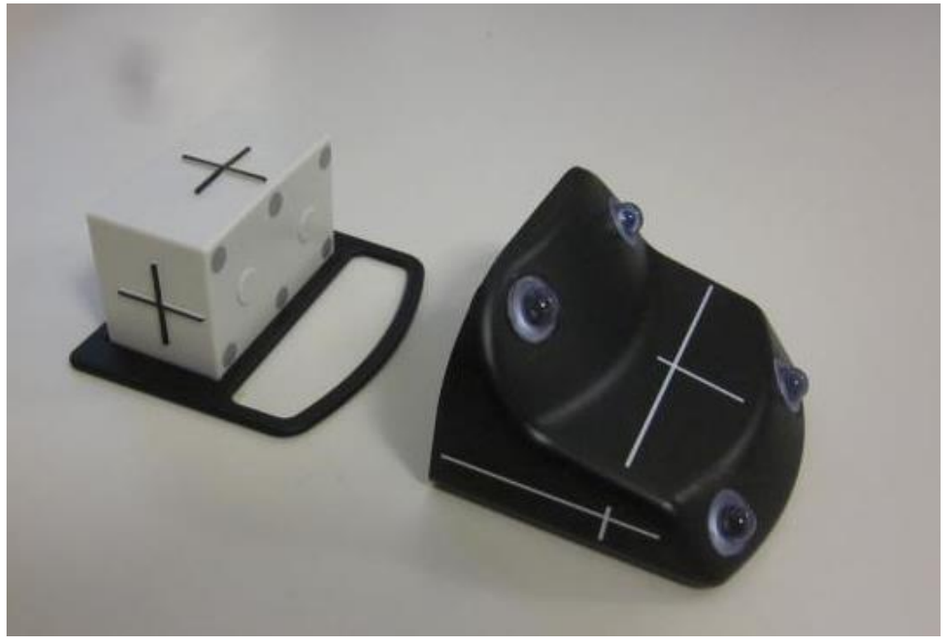
- Role in coaching / training patient
- DIBH/ EBH/ abdominal compression

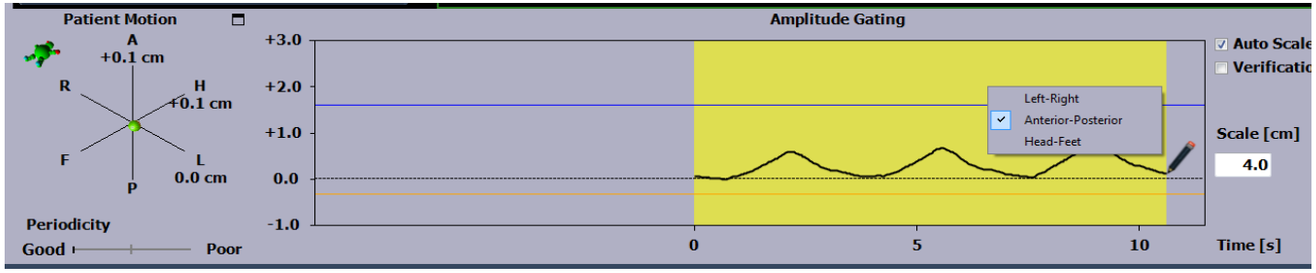
Intrafraction monitoring

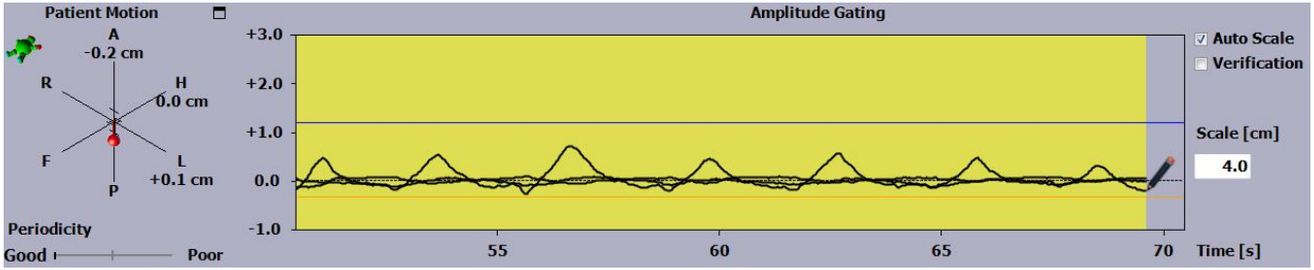
- RPM system
- Exac Trac
- kV images during arc treatment, e.g. triggered images or fluoroscopic images

RPM-system

VARIAN




Patient Motion
A
+0.1 cm
R
H
+0.1 cm
F
L
0.0 cm
P
Periodicity
Good
Poor
Amplitude Gating
+3.0
+2.0
+1.0
0.0
-1.0
0
5
10
Time [s]
Left-Right
Anterior-Posterior
Head-Feet
Auto Scale
Verificatic
Scale [cm]
4.0

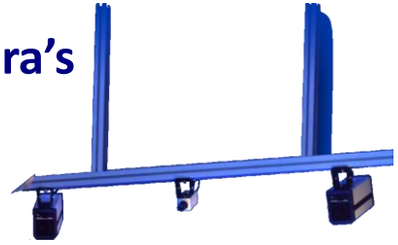

Patient Motion
A
-0.2 cm
R
H
0.0 cm
F
L
+0.1 cm
P
Periodicity
Good
Poor
Amplitude Gating
+3.0
+2.0
+1.0
0.0
-1.0
55
60
65
70
Time [s]
Auto Scale
Verification
Scale [cm]
4.0

ET infrared monitoring

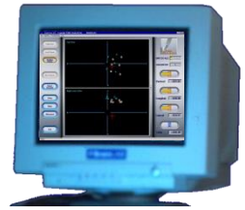
VUmc

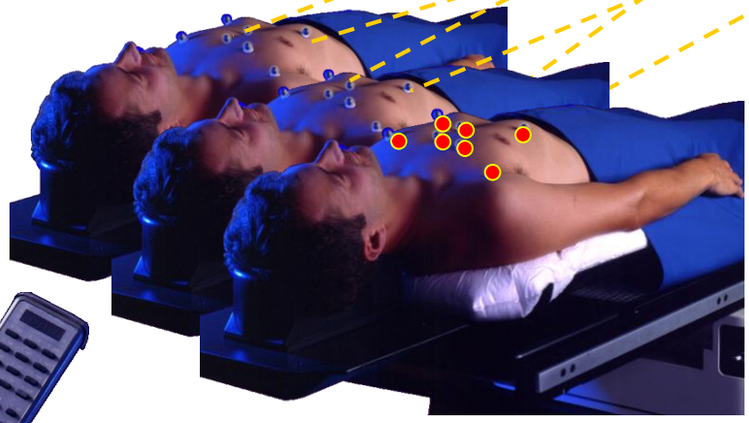
ExacTrac markers

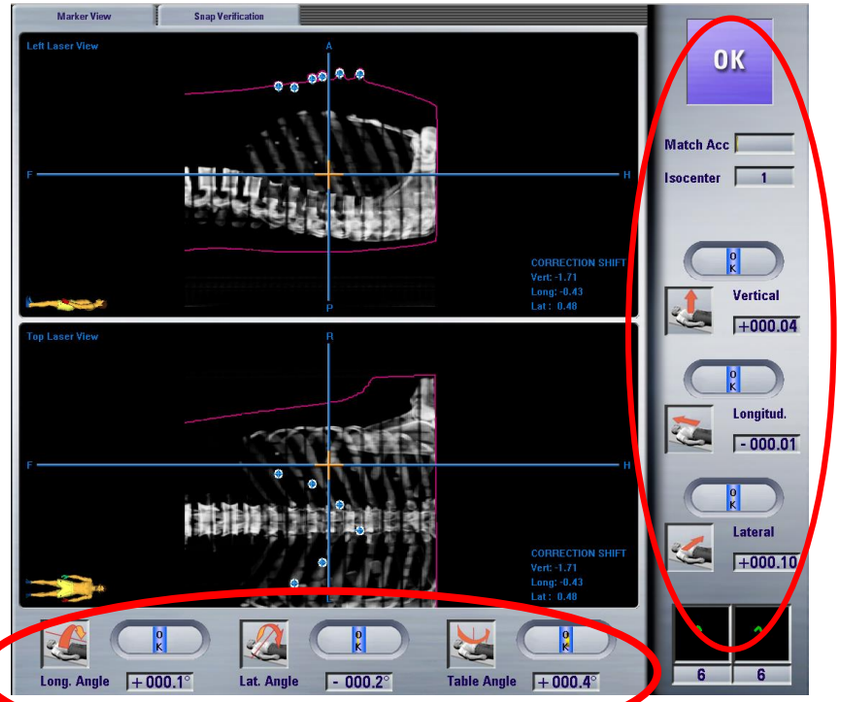
ExacTrac camera's



Procedure







Images during arc

- Triggered images, based on:
  - Respiratory gating, at beam on/off
  - MU
  - Gantry angle (only for RA)
  - Time, minimum interval = 3 sec
  - When fiducials are implanted:
    - Auto-detection
    - Auto Beam Hold
- Fluoroscopic images:
  - Template matching, offline analysis

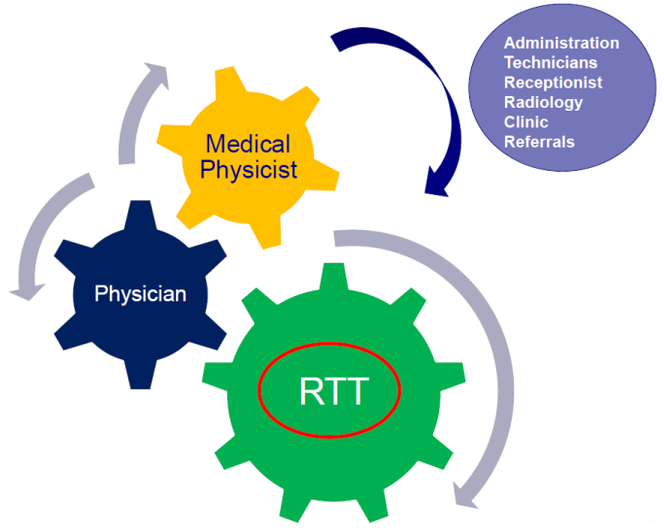
Int J Radiat Oncol Biol Phys. 2016 Apr 1;94(5):1154-62. doi: 10.1016/j.ijrobp.2016.01.006. Epub 2016 Jan 12.

Subsecond and Submillimeter Resolution Positional Verification for Stereotactic Irradiation of Spinal Lesions.

Hazelaar C[1], Dahele M[2], Mostafavi H[3], van der Weide L[2], Slotman BJ[2], Verbakel WF[2].

Some key notes

- RTTs are an important wheel within the whole process
- SBRT uses advanced IGRT techniques which RTTs can perform following appropriate training and competency assessment.
- SBRT offers RTTs the scope for role extension, dedicated team
- Empowering and motivating to be involved in a multi-professional SBRT programme.



Starting a SRT Program for Brain and Body: Clinicians perspective

- Karin Dieckmann

Motivation for SRS / SBRT

- Clinical need to improve outcome
- Research purposes
- Financial purposes
- Differentiation from other RT departments

Outline

- Staff
- QA
- Workflow planning
- Structured follow up

Questions you have to answer when you decide to implement a stereotactic program

- What is the first choice of the SRT

✓ Cranial SRT

✓ Extra-Cranial SBRT

Referral

- Cooperation **partner**
  - Neurologist
  - Oncologist
  - Surgeons
  - Pulmologist
  - …….
- Number of **expected patients**

Low number of patients a day
More than 5-10 patients a day

Based on the Number of expected Patients you have to decide:

One / two patients per day

Much more than one patient per day

Good logistic

- LINAC
- Tomotherapy

Stereotactic Unit

- Dedicated LINAC
- CyberKnife
- GammaKnife

Team building

Team: Build a dedicated team of interested people who will start the program

- Clinician n=3/1 main responsible
- Physicist n=2/1 main responsible
- RTT n=3/1 main responsible

➢ **All three are required and act as a TEAM !**

ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer

Matthias Guckenberger [a,*], Nicolaus Andratschke [a], Karin Dieckmann [b], Mischa S. Hoogeman [c], Morten Hoyer [d], Coen Hurkmans [e], Stephanie Tanadini-Lang [a], Eric Lartigau [f], Alejandra Méndez Romero [c], Suresh Senan [g], Dirk Verellen [h]

Staff teaching training and credentialing

Mandatory (minimum) Requirements	Recommended for best practice
Written departmental protocols	Participation in dedicated SBRT course Participation in Vendor-organized dedicated SBRT training
Multidisciplinary project team for SBRT implementation and application	Hands-on at SBRT-experienced center
Structured follow-up for clinical outcome assessment	Supervision of first SBRT treatments by SBRT-experienced colleague

Radiotherapy and Oncology 124 (2017) 11–17

ESTRO

Do we have to treat every patient in a study ?

- Eligible

- Recommendation based treatment planning and delivery of national Stereotactic working groups. (Guidelines: RTOG, DEGRO,.....)

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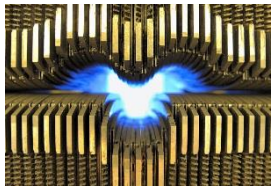
Patient selection

Mandatory (minimum) Requirements	**Recommended for best practice**
Discussion in interdisciplinary tumor board	Biopsy confirmation of malignancy
Minimum ECOG 3	
Minimum life expectancy of a year	

Radiotherapy and Oncology 124 (2017) 11–17

Equipment demands



Linac

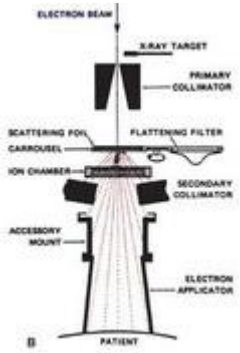
≤ 5 mm leafs/ ≤ 10 mm leafs
circular collimators

Image guidance

3D/ 4D: Cone beam CT
2D: Stereoscopic fluoroscopy

Table

- Brain robotic table if >1 target
- SBRT useful robotic table useful
- table fixation for frame based immobilisation devices *preferable*



FFF

Optional

Equipment demands

- Beam quality
  - MV (3 – 6 MV)
  - kV (80 – 130 kV)
- Beam collimation
  - CBCT
  - FBCT
- Dimensions
  - 2D
  - 3D
  - 4D
- Rail-track-, ceiling/floor-, gantry-mounted systems

Equipment demands

Fixation systems

Masks: Masks plus bite block

Vacuum cushions: for all body sizes

ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer

Matthias Guckenberger [a,*], Nicolaus Andratschke [a], Karin Dieckmann [b], Mischa S. Hoogeman [c], Morten Hoyer [d], Coen Hurkmans [e], Stephanie Tanadini-Lang [a], Eric Lartigau [f], Alejandra Méndez Romero [c], Suresh Senan [g], Dirk Verellen [h]

Equipment

SBRT workflow or equipment	**Mandatory (minimum) Requirements**	**Recommended for best practice**
Equipment	C-arm linear accelerator with volumetric in-room guidance Respiration correlated 4D-CT	Dedicated C-arm stereotactic LINAC (more advanced IGRT, more precise accuracy) High resolution MLC <10mm

Radiotherapy and Oncology 124 (2017) 11–17

ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer

Treatment planning and safty

	Mandatory (minimum) Requirements	Recommend for best practice
Treatment planning	3D conformal treatment planning Type B algorithms Respiration correlated 4D-CT imaging ITV based motion management strategy	Dynamic IMRT planning (VMAT) Use of a fixed dose inhomogeneity in PTV
Dose and fractionation	Risk adapted fractionation schemes for peripheral and central tumors and tumors with broad chest wall contact	
Inter- and intra- fraction image guidance	Daily pre-treatment volumetric image guidance	Daily pre-treatment 4D volumetric image-guidance (in-room 4D-CT, 4D-CBCT

Radiotherapy and Oncology 124 (2017) 11–17

Follow-up

There should be follow-up of all patients treated and maintenance of **appropriate records**
to determine local control, survival and normal tissue injury.

ASTRO REPORT

AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY* AND AMERICAN COLLEGE OF RADIOLOGY PRACTICE GUIDELINE FOR THE PERFORMANCE OF STEREOTACTIC BODY RADIATION THERAPY

Louis Potters, M.D.,* Michael Steinberg, M.D.,† Christopher Rose, M.D.,‡ Robert Timmerman, M.D.,§ Samuel Ryu, M.D.,¶ James M. Hevezi, Ph.D.,‖ James Welsh, M.D.,# Minesh Mehta, M.D.,# David A. Larson, M.D.,** and Nora A. Janjan, M.D.††

Follow-up

Specialized outpatients

Follow up control: SBRT / Brain every 3 months for 2 years
after 2 years every 6 months
after 5 years every year

According to individual follow-up programs of the department.

QA and safety

Coen Hurkmans, Ph.D., clinical physicist

Catharina Hospital, The Netherlands

Content - objectives

- Physics QA procedures
  - Imaging QA
  - Image registration QA
  - Linac QA
  - Patient specific QA
    - Dosimetric QA
    - intra-fraction variation QA

VERY IMPORTANT, BUT NOT IN THIS SESSION!

In this session:

QA: what we can learn from accidents

QA: a team effort

Objectives:

To know what might go wrong – what are the weak links in the chain?

To know how to effectively reduce (potential) errors

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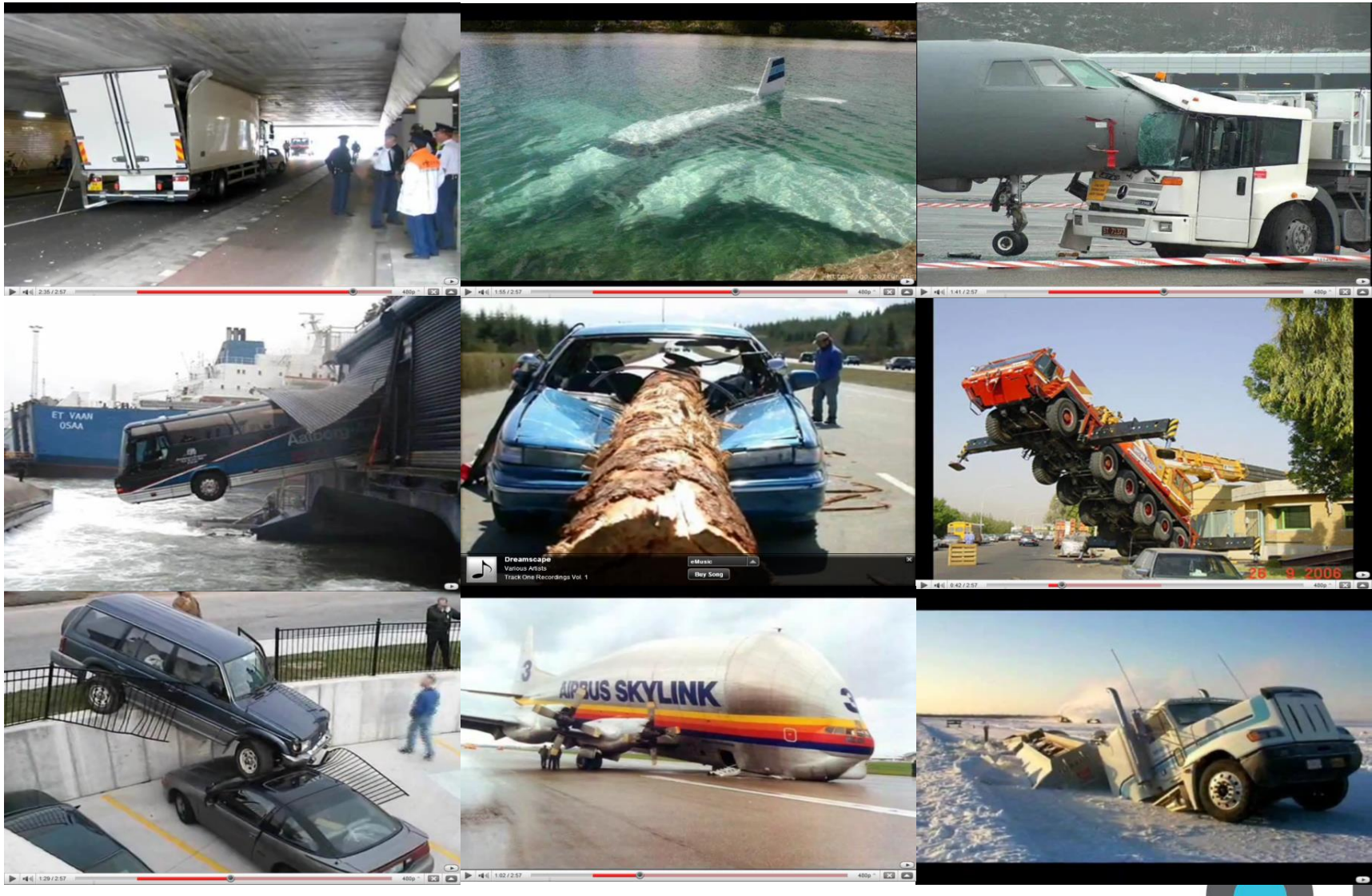
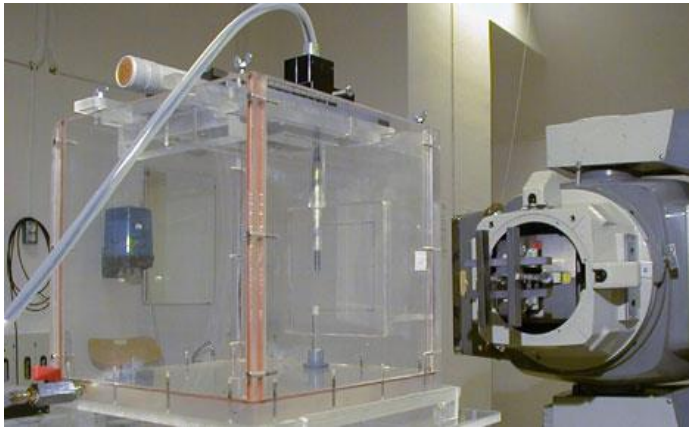
Do Accidents Happen?



Exeter, UK, 1988

- Installation of a new cobalt source
- A physicist calibrated the new source



2/2/88.

O/P calibration of New Source

Scaler Farmer 2570 with probe, in water tank at depth 5.0c

Water tank outside dimensions (perspex) = 32 × 32 × ~21 cm to water surf

T = 293 P = 760·3 . SSD = 800 mm, 100 × 100 mm FIELD

Farmer left on for 45 mins before any measurements

Water tank filled and left to come to room temp overnight

Farmer readings (0·8 mins): ~~90~~ 95, 90·92, 90·90, 90·90, 90·90 → 90.90_5

" " (0·4 mins) 46·47, 46·40, 46·40, 46·42, 46·42 → 46.42_2

Steady state 0·4 min reading 44.48_3

Steady State Dosrate

at 800 mm, 100×100 = 2 × $\frac{293.3}{293}$ × $\frac{760}{760.3}$ × 0·947 × $\frac{100}{79.0}$ × 44·48

(absorbed dose Farmer & limits; 4.00)

= 106·7 cGy/m

1/0.4 = 2.5 not 2 !!!
Should have been 133.4 rtg/min

"Dose effective Time error" = $\frac{90.90_5 - 2 \times 44.48_3}{2 \times 44.48_3}$

= 0·0218 mins

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Outcome

- 205 patients were significantly overdosed (25%) with increased morbidity and possible deaths considered as a consequence.
- The error was not then recognised, possibly because the physicist was working *on his own* and his figures may *not have been checked*.
- The error was detected during a national **external audit**

Lessons:

- **Always independent check of manual input!**
- **External reference audits are crucial**

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North Staffordshire Royal Infirmary, 1982-1991

- Until 1982, the hospital relied on manual calculations for the correct dose to be delivered to the tumour
  - Treatments were generally performed at standard SSD
- A treatment planning system was introduced in 1982
  - Partly because TPS simplified the calculation procedures, the hospital began treating with isocentric techniques more frequently
  - It was assumed that correction factors for non-standard SSD should be applied
- In 1991 a new TPS was installed and a discrepancy was discovered between the new plans and those from the previous system

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North Staffordshire Royal Infirmary, 1982-1991

- The original TPS already contained within it the correction for calculations at non-standard SSD. The INVERSE SQUARE LAW
- During the 9-year period, 6% of patients treated in the department were treated with isocentric technique; for many of these patients it formed only part of their treatment
  - 1045 patients whose calculations were affected by the incorrect procedures, 492 developed local recurrences that could be attributed to the error
- **Under dosage varied between 5 and 35%**

Lesson:

If new software is introduced, DO NOT ASSUME anything!!
Benchmark it against the old system

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Glasgow, Scotland 2005

- Introduced a new and common data base for linacs, TPS and R/V system in 2005.
- Thus all plan data are available among all modules
  - Incl TPS and treatment console at the linacs
- Previously all plans were calculated for 1 Gy as prescribed dose
  - The MUs were scaled to correct dose manually
- Now all plans were made for the correct prescribed dose

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Except for…

- Whole CNS plans still went by the "old system", where TPS calculates MU for 1 Gy with subsequent upscaling for dose per fx
- A "medulla planning form" was used, which is passed to treatment radiographers for final MU calculations
- HOWEVER – "Planner X" let the TPS calculate the MU for the full dose per fx – not for 1 Gy as intended
- Since the dose per fx to the head was 1.67 Gy, the MU's entered in the form were 67% too high for each of the head-fields

Annex 2: A blank copy of the first page of Medulla Planning FM.14.014 as used for Lisa Norris's treatment plan

BEATSON ONCOLOGY CENTRE - QA CONTROLLED DOCUMENT

MEDULLA PLANNING FORM FM.14.014
TWO SPINE FIELDS

Name:	Site:
B.O.C. No:	Unit:
Radiotherapist:	Date:
Physics:	

Setup	Head fields isocentric; asymmetric jaws; customised shielding trays. Physics to move junction after every ..... fractions (see over).			
Site	Head (a)		Upper Spine (b)	Lower Spine (c)
Description	Right Lateral	Left Lateral	Posterior	Post / Sup
Field Size (approx for first ..... fractions				
Jaw Settings	x_1 y_1 x_2 y_2	x_1 y_1 x_2 y_2		
F.S.D.	ISOCENTRIC		100 cm	100 cm
Gantry Angle	90°	270°	0°	.....° (i.e. .....° to sup)
Collimators	.....° (i.e. ....° Sup End Post)	.....° (i.e. .....° Sup End Post)	90°	90°
Floor Rotation	0°	0°	270°	270°
Beam Modifier	Shielding block tray code =	Shielding block tray code =	Wax compensator (a). tray code 17	Wax compensator (b). tray code 17

Beam Weight (%)	100% (a)	100% (a)	100% (b)	100% (c)
Output (MU/100cGy)				
Dose Information	T.A.D. mid brain = 100% Normalisation = ... %		spinal cord: .....% max subcut: .....%	spinal cord: .....% max subcut: .....%

File Name: FM14014	Page Number: 1 of: 1	Date: 11.8.98
Issue Number: 1	Authorised By:	Issued By:

Output (MU/100cGy)

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Lessons

- If something changes somewhere, check how it impacts the following chain of events.
- Always independent check of plan
- Could have been detected by independent (automated) MU check
- Dosimetry check could have detected erroneous dose

Annex 2: A blank copy of the first page of Medulla Planning FM.14.014 as used for Lisa Norris's treatment plan

BEATSON ONCOLOGY CENTRE - QA CONTROLLED DOCUMENT

MEDULLA PLANNING FORM — FM.14.014
TWO SPINE FIELDS

Name:	**Site:**
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Physics:	

Setup	Head fields isocentric; asymmetric jaws; customised shielding trays. Physics to move junction after every ..... fractions (see over).			
Site	**Head (a)**		**Upper Spine (b)**	**Lower Spine (c)**
Description	Right Lateral	Left Lateral	Posterior	Post / Sup
Field Size (approx for first ..... fractions				
Jaw Settings	x_1 y_1 x_2 y_2	x_1 y_1 x_2 y_2		
F.S.D.	ISOCENTRIC		100 cm	100 cm
Gantry Angle	90°	270°	0°	.....° (i.e. .....° to sup)
Collimators	.....° (i.e. ....° Sup End Post)	.....° (i.e. .....° Sup End Post)	90°	90°
Floor Rotation	0°	0°	270°	270°
Beam Modifier	Shielding block tray code =	Shielding block tray code =	Wax compensator (a). tray code 17	Wax compensator (b). tray code 17

Beam Weight (%)	100% (a)	100% (a)	100% (b)	100% (c)
Output (MU/100cGy)				
Dose Information	T.A.D. mid brain = 100% Normalisation = ... %		spinal cord: .....% max subcut: .....%	spinal cord: .....% max subcut: .....%

File Name: FM14014	**Page Number: 1 of: 1**	**Date: 11.8.98**
Issue Number: 1	**Authorised By:**	**Issued By:**

Output (MU/100cGy)

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Jan 2010

The New York Times

- Several articles in NYT early 2010
- Lot's of fuzz in the community
- Hearing in US
- Meetings etc…

THE RADIATION BOOM

Radiation Offers New Cures, and Ways to Do Harm

By WALT BOGDANICH
Published: January 23, 2010

As Scott Jerome-Parks lay dying, he clung to this wish: that his fatal radiation overdose — which left him deaf, struggling to see, unable to swallow, burned, with his teeth falling out, with ulcers in his mouth and throat, nauseated, in severe pain and finally unable to breathe — be studied and talked about publicly so that others might not have to live his nightmare.

SIGN IN TO RECOMMEND
TWITTER
SIGN IN TO E-MAIL
PRINT
REPRINTS
SHARE

GOLDEN GLOBE® WINNER

Enlarge This Image

For his last Christmas, Scott Jerome-Parks rested his feet in buckets of sand his friends had sent from a childhood beach. More Photos »

Sensing death was near, Mr. Jerome-Parks summoned his family for a final Christmas. His friends sent two buckets of sand from the beach where they had played as children so he could touch it, feel it and remember better days.

Mr. Jerome-Parks died several weeks later in 2007. He was 43.

A New York City hospital treating him for tongue cancer had failed to detect a computer error that directed a linear accelerator to blast his brain stem and neck with errant beams of radiation. Not once, but on three consecutive days.

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Energy and Commerce - Subcommittee on Health held a hearing entitled "Medical Radiation: An Overview of the Issues" on Friday, February 26, 2010

Panel I
Mr. James Parks
Dr. Rebecca Smith-Bindman M.D.
Mr. Eric E. Klein Ph.D.
Ms. Cynthia H. McCollough Ph.D.
Ms. Suzanne Lindley

Panel II
Mr. Michael G. Herman Ph.D.
Ms. Sandra Hayden B.S.
Dr. E. Stephan Amis Jr.
Dr. Tim Williams
Mr. David N. Fisher
Mr. Kenneth Mizrach

Chairman Mr Pallone, NJ

Available at:

http://www.youtube.com/watch?v=NcqRgVqeQSg

http://www.youtube.com/watch?v=L_IzTqhghMs

Let's have the story

- Tuesday - March 8, 2005
  - The patient begins an IMRT treatment
  - The plan had passed the QC process
  - The treatment is delivered correctly.
- Friday - March 11, 2005
  - The physician reviews the case after 4 Tx
    - Wants a modified dose distribution (reducing dose to teeth)
- Monday - March 14, 2005
  - Re-planning and re-optimization starts
  - Final calculations are started, where MLC motion control points for IMRT are generated.

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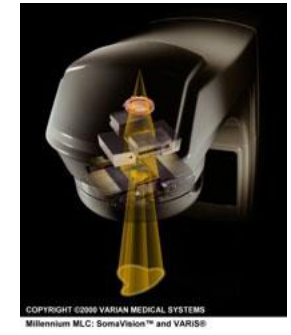
What happened?

- “Save all” is started. All new and modified data should be saved to the DB.
  - In this process, data is sent to a holding area on the server (cache), and not saved permanently until ALL data elements have been received.
- In this case, data to be saved included
  - actual fluence data
  - a DRR
  - the MLC control points



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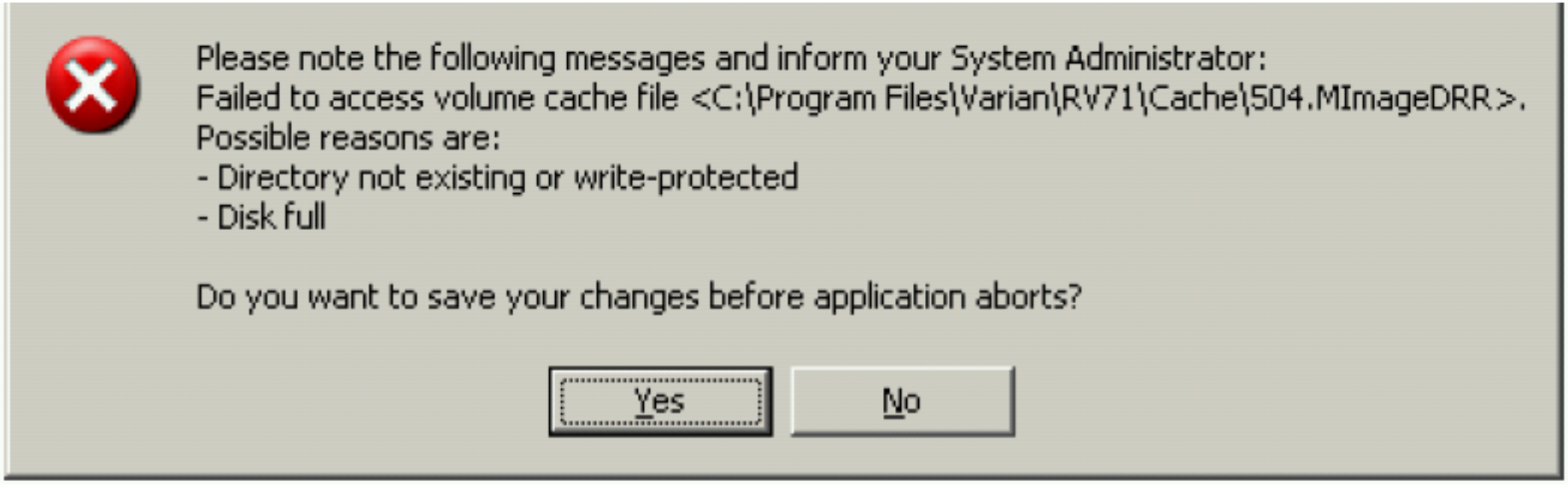
What happened?



The transaction error message displayed

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What happened?

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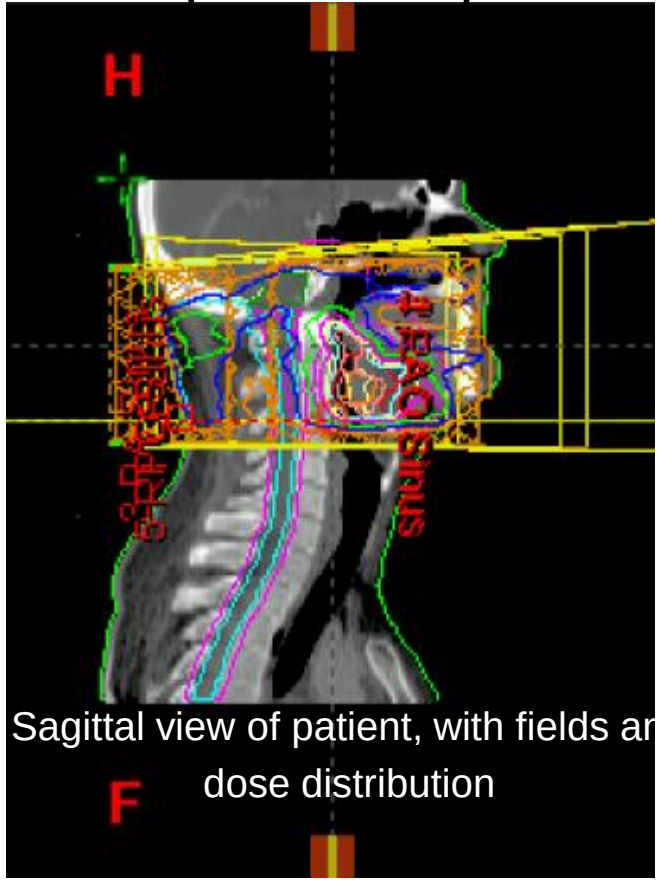
What happened?

Monday - March 14, 2005, 11.a.m.

- Within 12 s, another workstation, WS1, is used to open the patients plan. The planner would have seen this:



Sagittal view of patient, with fields ar
dose distribution

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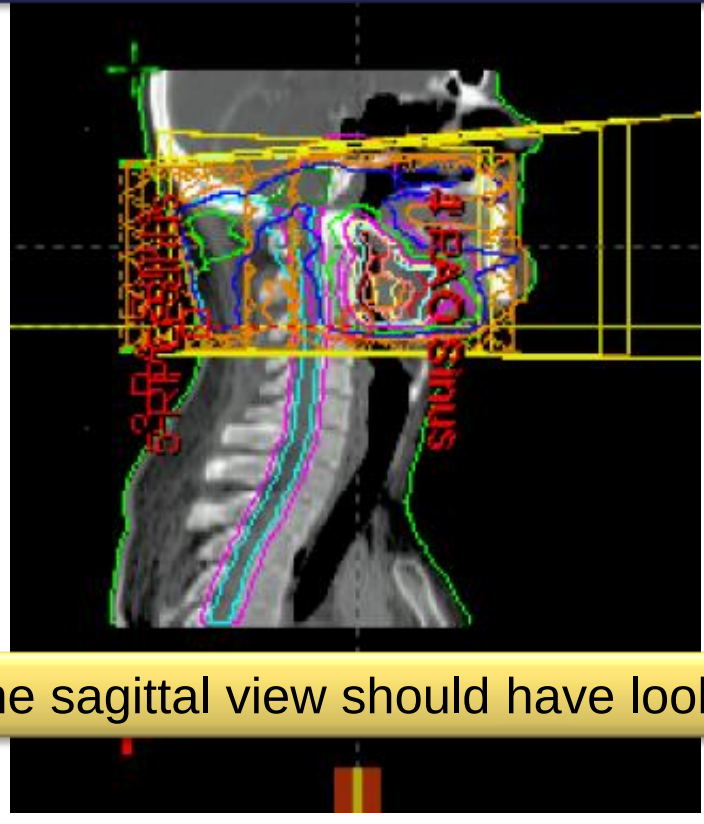
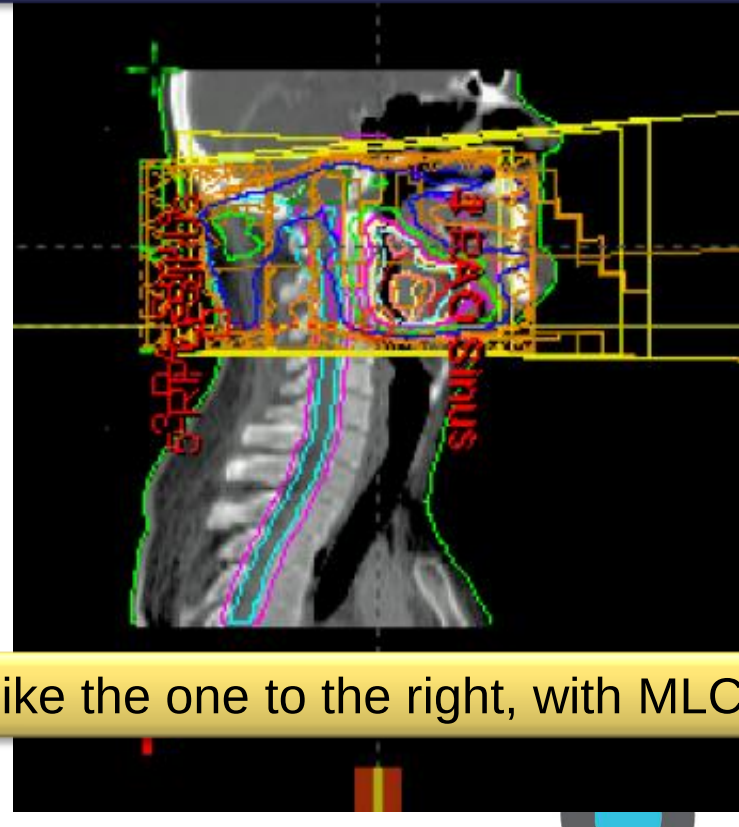
What happened?

Monday - March 14, 2005, 11.a.m.

No MLC control point data is included in the plan, neither required for dose calculation, display and approval !!!

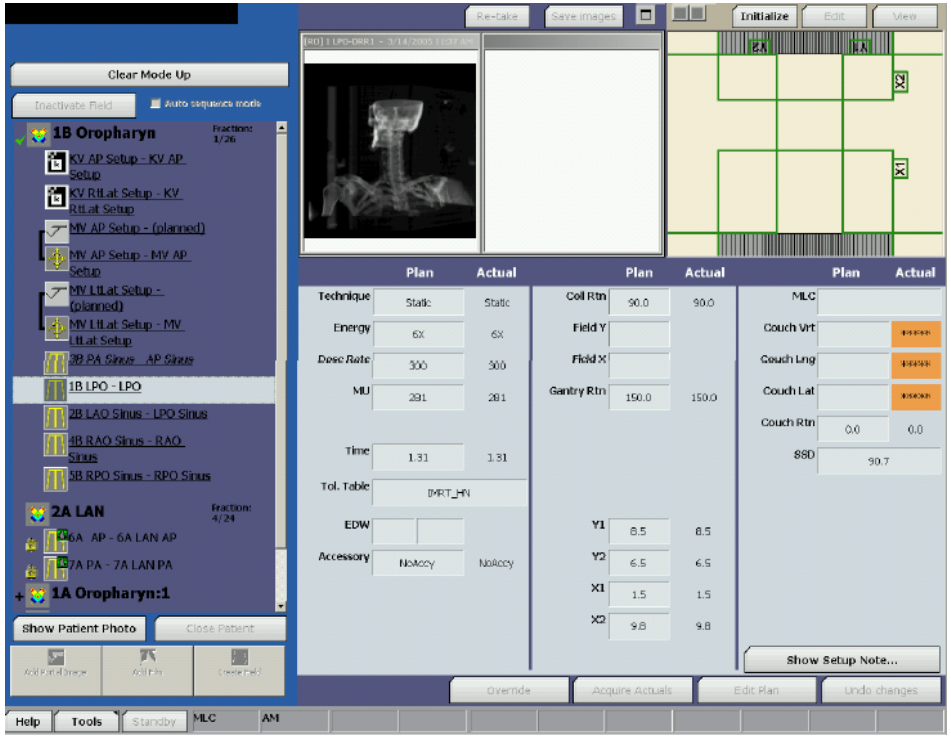


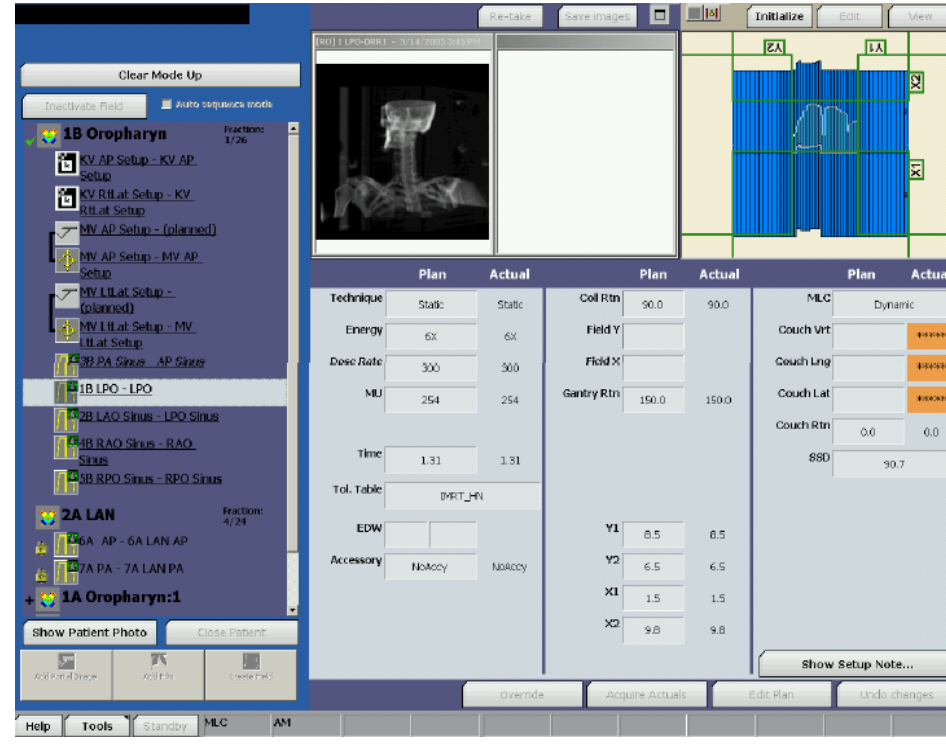


The sagittal view should have looked like the one to the right, with MLCs

What happened?

- Monday - March 14, 2005, 1 p.m.
  - The patient is treated. The console screen would have indicated that MLC is not being used during treatment:





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Discovery of accident

- Monday - March 14, 2005, 11 a.m.
  - No verification plan is generated or used - should be done according to local QA program
  - The plan is subsequently prepared for treatment (treatment scheduling, image scheduling, etc
- It is also approved by a physician
- According to local QA program, a second physicist should then have reviewed the plan
  - including an overview of the irradiated area outline
  - MLC shape
  - Etc

- Tuesday/Wednesday - March 15-16, 2005
  - The patient is treated without MLCs for three fractions
- Wednesday - March 16, a **verification plan** is created and run on the treatment machine. The operator notices the absence of MLCs.
  - A second verification plan is created and run with the same result
- The patient received 13 Gy per fraction for three fractions, i.e. 39 Gy in 3 fractions

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Lessons:

- Do what you should be doing according to your QA program
  - The error could have been found through verification plan (normal QA procedure at the facility) or independent review

- Be alert when computer crashes or freezes, when the data worked on is safety critical

- Work with awareness at treatment unit, and keep an eye out for unexpected behaviour of machine

- The manufacturer should have the default MLC settings on closed!

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Recently… New identical Linac…

- A new Linac is introduced, identical to an existing Linac.
- Linac modelled in TPS for FF beams based on measurement data from existing linac. **However, profiles were from FF beams but pdds from FFF beams! Not clear yet whether due to auto copy mistake (software error) or manual copy mistake**
- After 1 year this error was discovered by scientific research measurements.
- Absolute dose deviations were 3-5%.

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hospital

Recently… New identical Linac…

Why did QART fail?

- Full tests from CT scanning to irradiation of phantoms have been performed. The measurements were performed on the right linac. But the calculations were performed using the existing Linac model in the TPS.
- Routinely EPID patient dosimetry QA is performed at this institution. But this is a relative measurement (scaled to coincide with calculations in normalisation point). Occasionally Matrix-measurements are performed at a linac, e.g., if beams do not fit on the EPID. But on the new linac only small fields were used. (HD 2.5 mm MLC)

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Recently… New identical Linac…

Why did QART fail?

- Also weekly Matrix measurements are performed. But a different algoritm is used for this.
- MU-check accepts 10% deviations. In general, for the existing HD MLC with 2.5 mm leaves the deviations were already a bit bigger than for other linacs with other MLCs.
- The institution started to use another HD MLC model. Looking back at all the data, a systematic deviation could be detected. (this is a strong argument for statistical proces analysis, SPC!)
- An RPC audit had been conducted. But the MU's needed were based on the measurements, not on the TPS calculation. (not mandatory for RPC check-this is now mandatory).

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Recently… New identical Linac…

Lessons:

- Even in an institution with a lot of RTQA incidents can happen.

- It is not sufficient to look at all steps separately, take an integral look at things.

- Very detailed knowledge is required to implement the right RTQA procedures AND people should strictly adhere to it.

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Take home messages

Check!

- Always perform an independent check of manual input
- Always perform an independent check of a treatment plan
- Always perform an independent (automated) MU check

Benchmark!

- Perform external reference dosimetry audits / trial audits based on TPS calculations

When something changes, re-evaluate the whole chain of events

- If new software is introduced, DO NOT ASSUME anything!! Benchmark it against the old system
- If something changes somewhere, check how it impacts the following chain of events.

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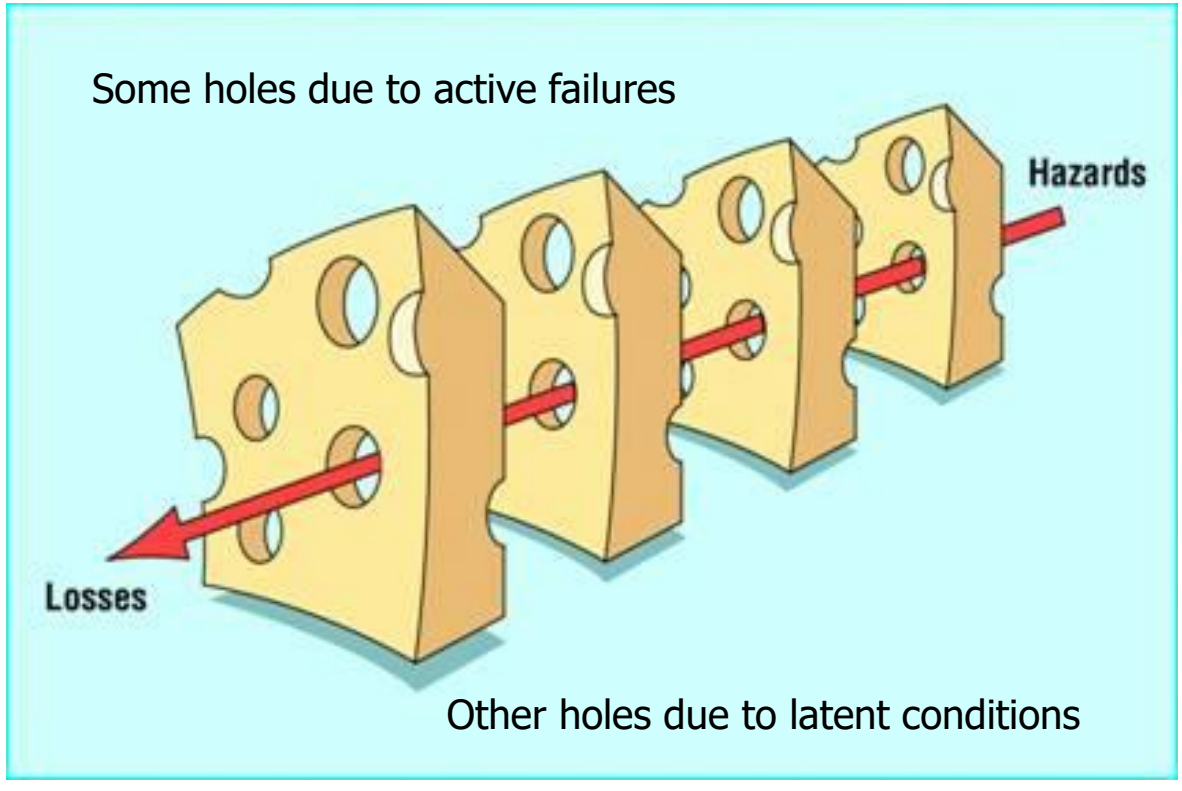
Reason's Swiss Cheese Model of Failure Propagation

Successive layers of defences, barriers, filters and safe guards



When holes line up an error will occur

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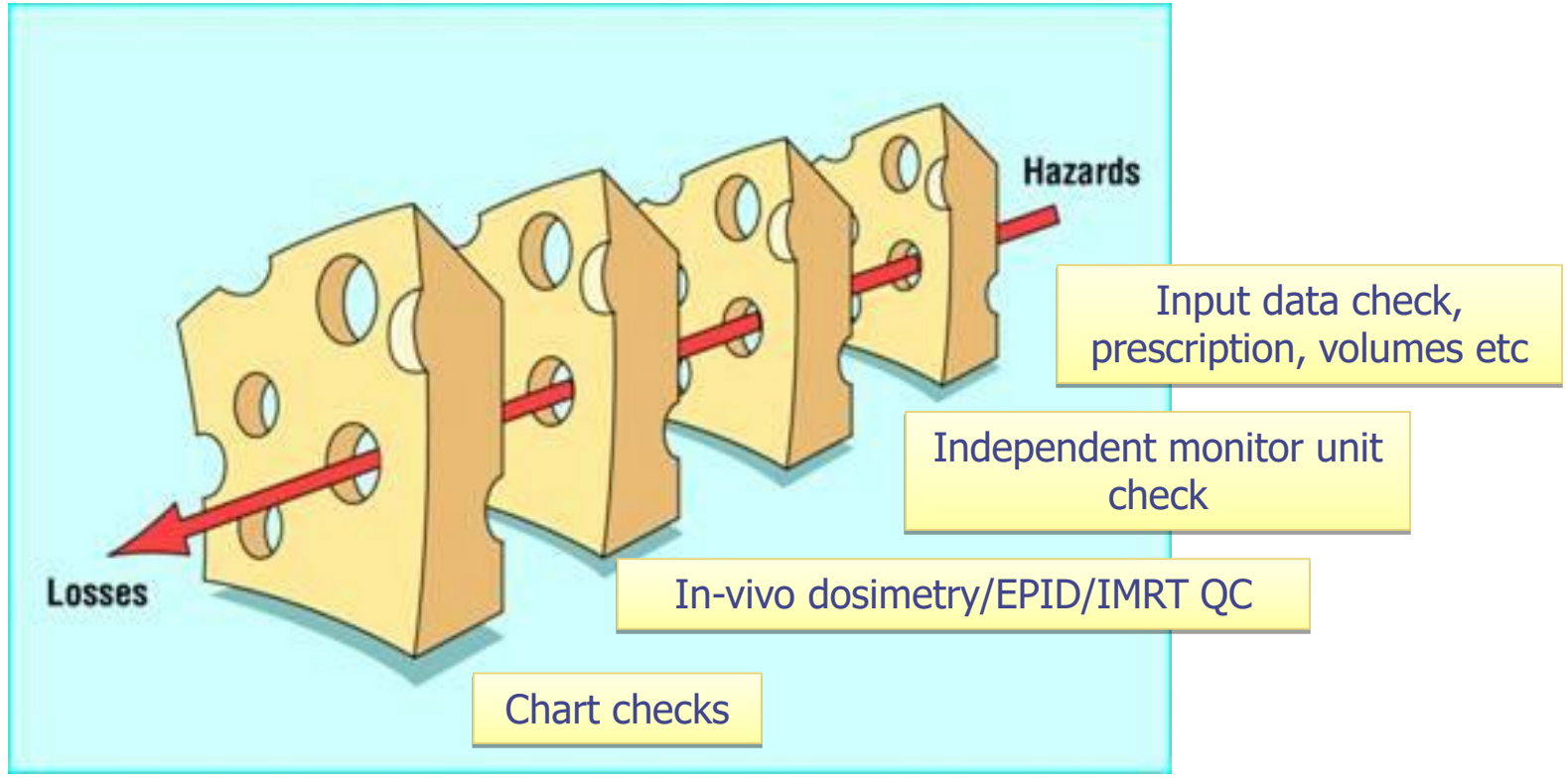
Radiotherapy safety layers

Successive layers of defences, barriers, filters and safe guards



When holes line up an error will occur

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Which QA tools are effective?

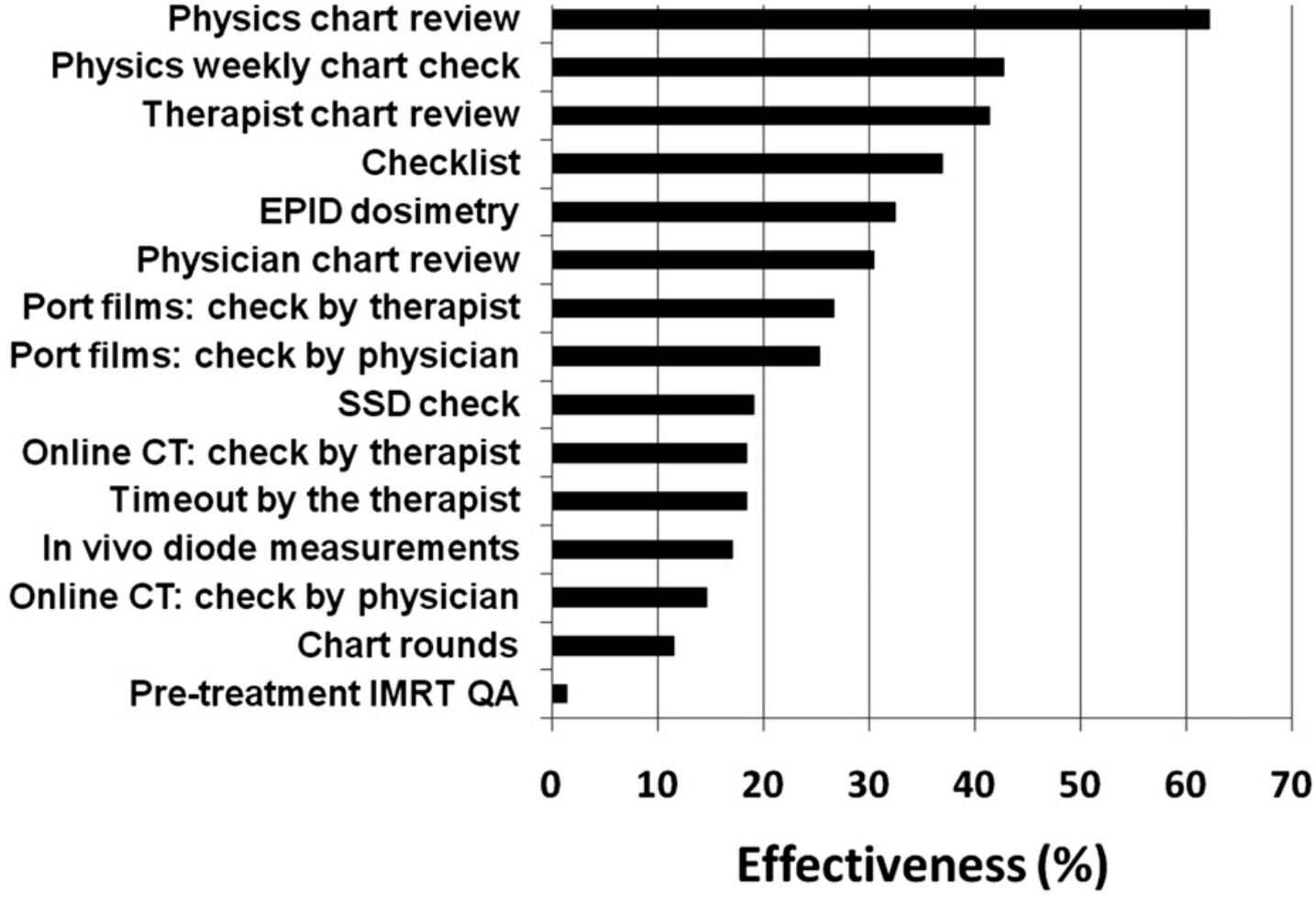

Fig. 2. Effectiveness of each individual quality control (QC) check for detecting the reported high severity incidents.

Ford et al, IJROBP 2012 84(3) e263-269

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Which combination of QA tools are effective?

Table 3 Combinations of QC checks and associated error-detection effectiveness for high severity incidents

	No. of checks in combination							
	1	2	3	4	5	6	7	Common
1. Physician chart review				x	x	x	x	x
2. Physics chart review	x	x	x	x	x	x	x	x
3. Therapist chart review								
4. Pretreatment IMRT QA								x
5. Chart rounds								x
6. Timeout by therapist			x	x	x	x	x	
7. SSD check							o	
8. Port films: check by therapist							o	x
9. Port films: check by physician								x
10. Online CT: check by therapist							o	
11. Online CT: check by physician								
12. *In vivo* diode measurements								
13. Physics weekly chart check					x	x	x	x
14. EPID dosimetry		x	x	x	x	x	x	
15. Checklist						x	x	
Effectiveness (%)	63	80	87	93	95	96	97	97

Abbreviations: CT = computed tomograpy; EPID = electronic portal imaging device; IMRT = intensity modulated radiation therapy; QA = quality assurance; QC = quality control; SSD = source-to-skin distance.
The header row lists the total number of checks in use in a particular combination. The "x" shows which specific checks were in use. The "o" indicates checks for which the effectiveness is the same regardless of which is used in combination. The "Common" column indicates 7 QC checks that are in common use.

Quality Control Quantification

Ford et al, IJROBP 2012 84(3) e263-269

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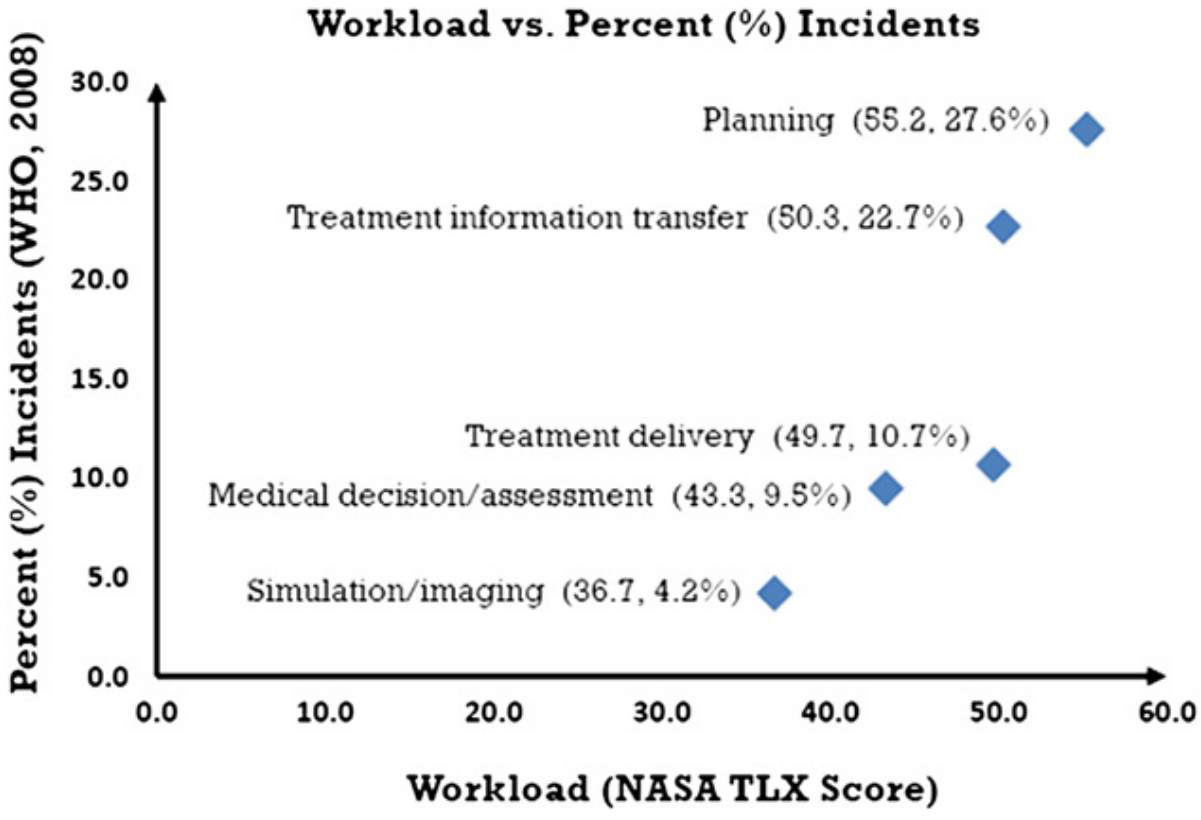
Stress and workload



Quantitative Assessment of Workload and Stressors in Clinical Radiation Oncology

Mazur et al IJROBP 2012 83 (5) e571-576

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Q:What is the main cause of errors?

A) Software bugs
B) Human mistakes
C) Unclear procedures
D) A combination of A, B and C.

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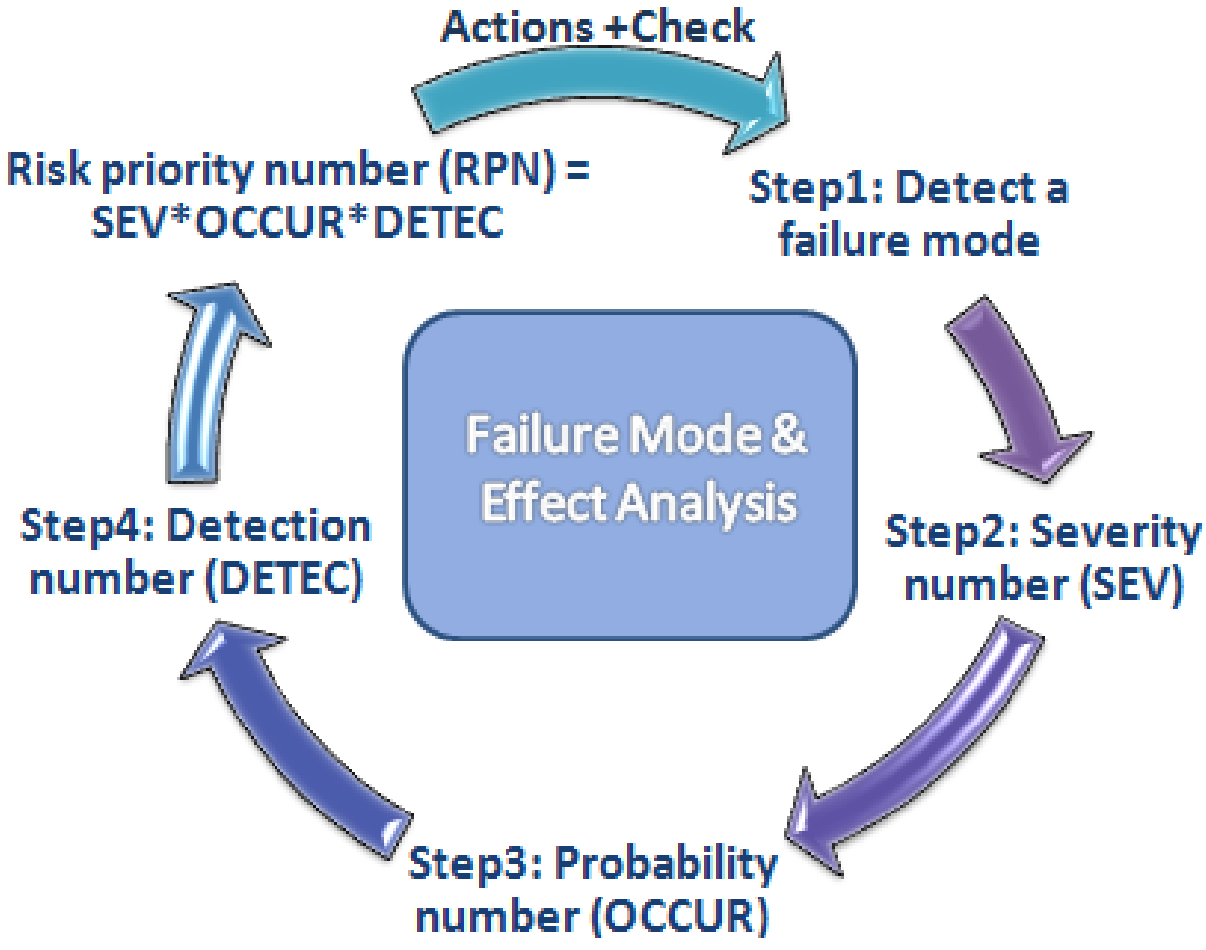
Failure Modes and Effects Analysis



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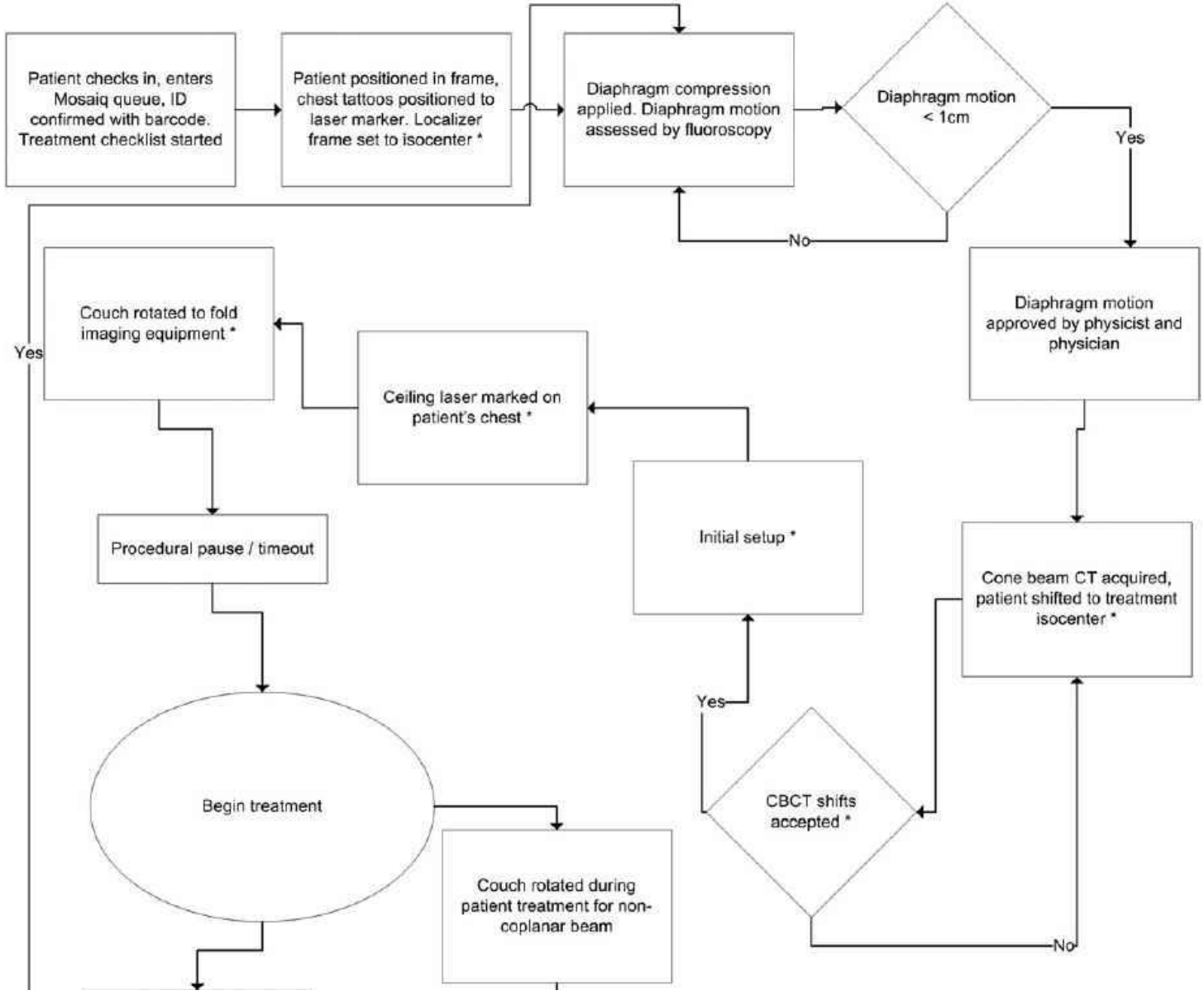
From flow charts



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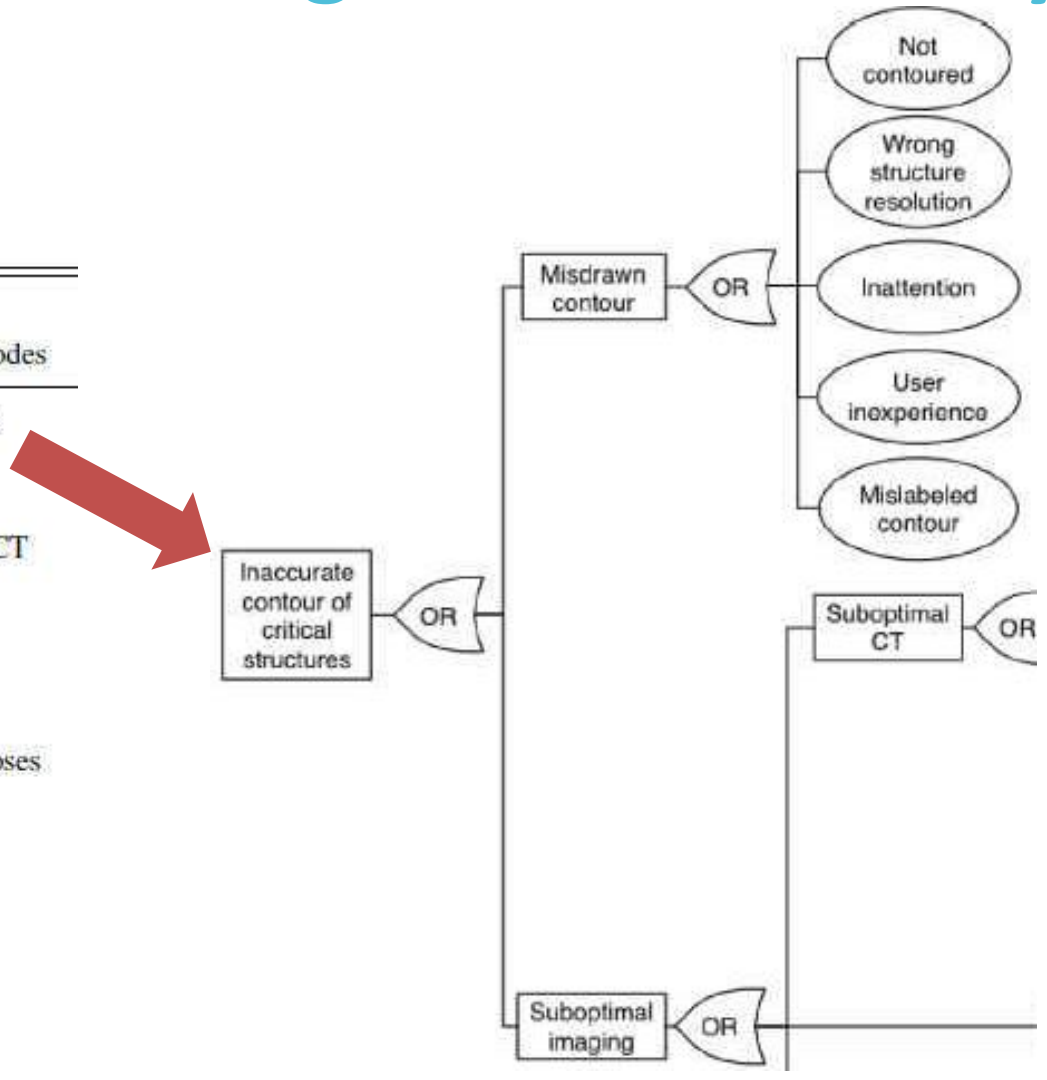
To failure modes using Fault Tree Analysis

TABLE IV. Top ten failure modes ranked by RPN.

Rank	Step	Potential failure modes
1	31. Contour critical structures	Inaccurate contours
1	79. Apply CBCT couch shifts	Inaccurate CBCT–CT registration
3	29. Previous tx CT registered to planning CT	Inaccurate CT–CT registration
4	39. Review OAR statistics	Critical structure doses not checked



Manger et al Med Phys 42 p2449, 2015

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And ranking risks using RPN

Risk probability number (RPN) = O * D * S

	Occurrence	Detectability	Severity
1 – 2	1% of patients	Very easy	No dosimetric effect
3 – 4	5% of patients	Human error	5% dose difference
5	Moderate	Lucky catch	10% dose difference
6 – 8	Once per day	Very difficult	Reportable, 20% difference
9 – 10	Every patient	Almost impossible	Reportable, injury / death

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To reducing risks

- Choose the highest RPN's and change clinical practice
- In the example from UC Davis: Change in practice / planning technique
  - After FMEA we devised a method of planning and rotating the couch to reduce this risk
  - Lower RPN
  - No couch translations after CBCT correction
- Law of diminishing returns

Take home messages

- FMEA can be time consuming and human resource intensive
- Valuable exercise
  - Change in technique
  - Unified protocol
  - Safety conscious
- FMEA process is generic but the results are clinic specific
  - Specific to equipment, procedures, responsibilities etc
- Continuously evolving techniques: keep FMEA process up to date!!

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Acknowledgements

Tommy Knoos, Lund University and Skåne University Hospital, Sweden

Julian Perk, University of California Davis Medical Center, Sacramento, CA, USA

Continued Quality Assurance

… stay alert!

Coen Hurkmans, Ph.D., clinical physicist

Catharina Hospital, The Netherlands

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Content

Examples of tough cases

- Prescription changes
- Unexpected shifts
- Wrong CT for matching with CBCT
- Too low dose due to proximity of OAR
- Too small lesions to detect on CBCT
- Software upgrades
- VMAT Control points
- Beam calibration

Objectives:

- To know what might go wrong once an SBRT program is running– what are the weak links in the chain?
- To know how to keep your SBRT program save

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Example: prescription change

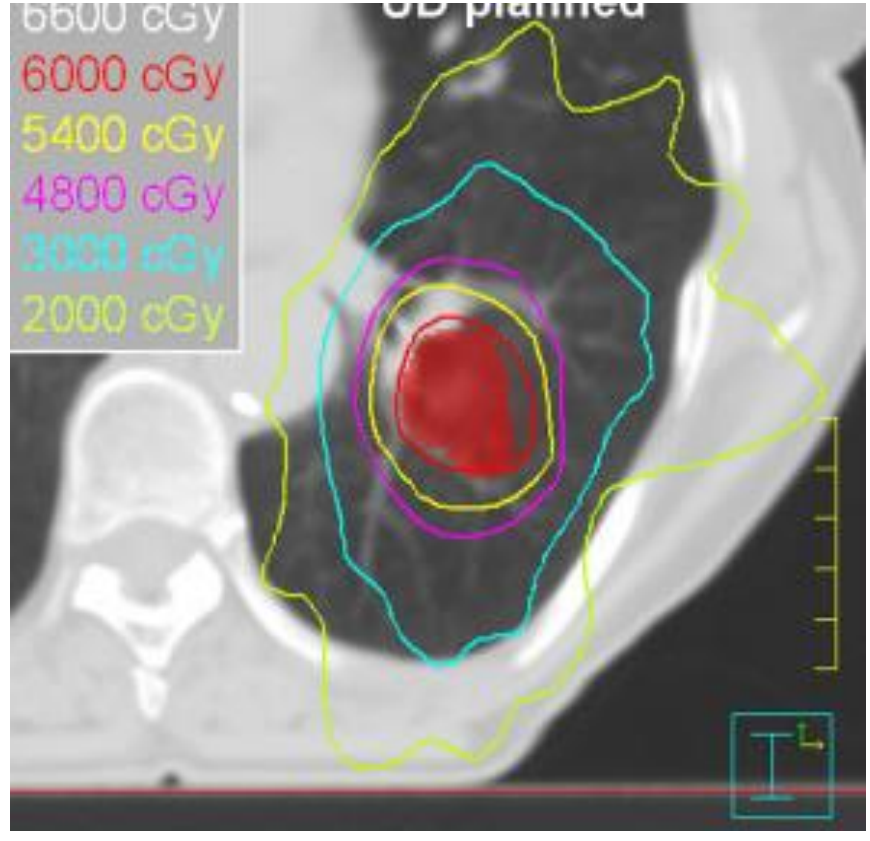
Initial plan and prescription:

Considered as a central lung tumour with probably high dose to vessels:
Save schedule of 8 fractions of 7.5 Gy chosen.

Based on plan with lower dose than anticipated to vessels decision is taken to change prescription to 5 fractions of 12 Gy

Plan recalculated: see changes

Patient already scheduled for 8 fractions…..



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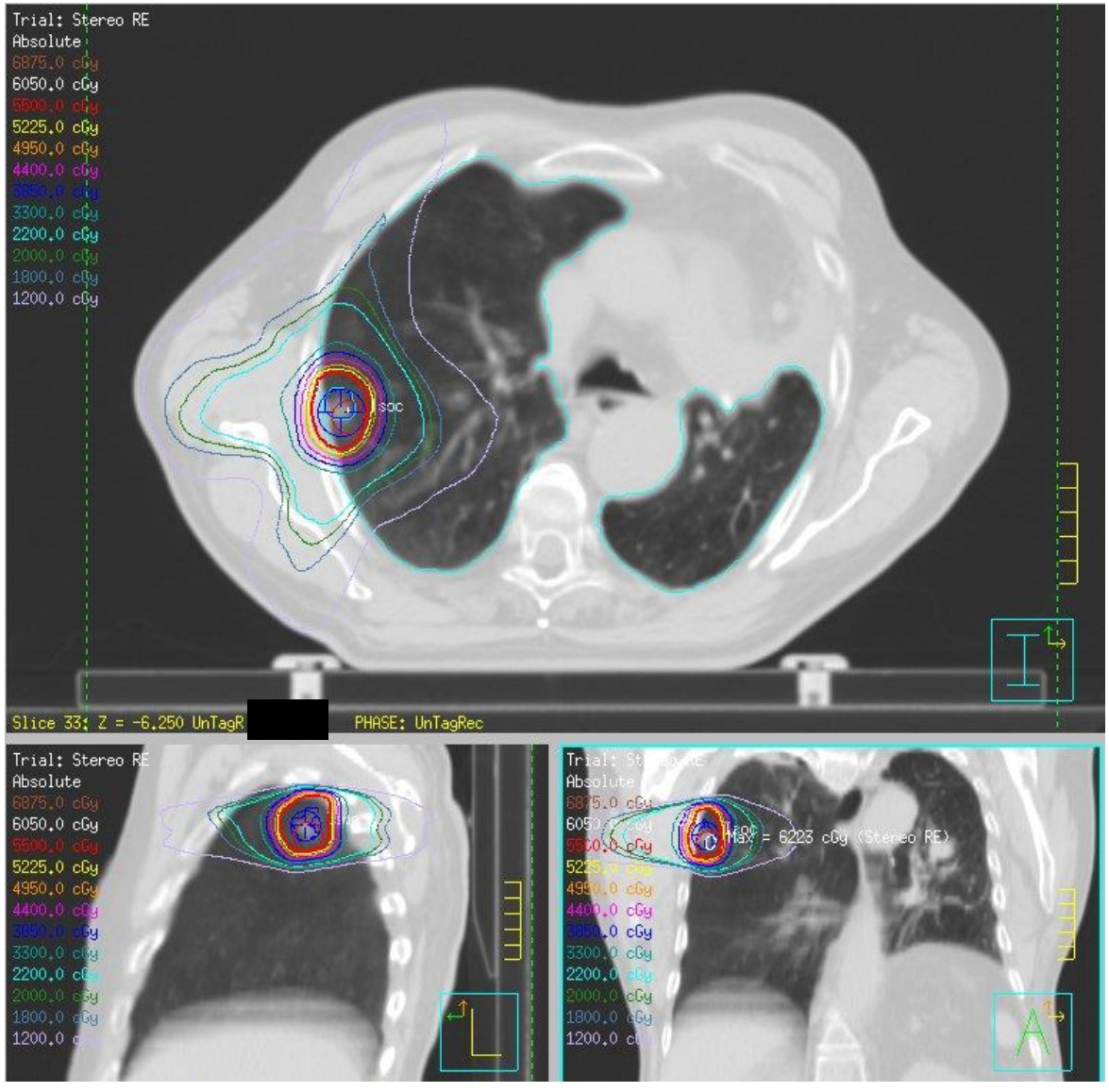
Unexpected shifts



- Patient CBCT after first fraction 8 mm shift
- Suspected to slide down gradually
- Next fractions CBCT after first arc: shift of 3 mm same direction. Corrected
- After second arc: again shift of 3 mm same direction
- Decision to continue this way
- Next fractions shifts ≤ 3 mm.

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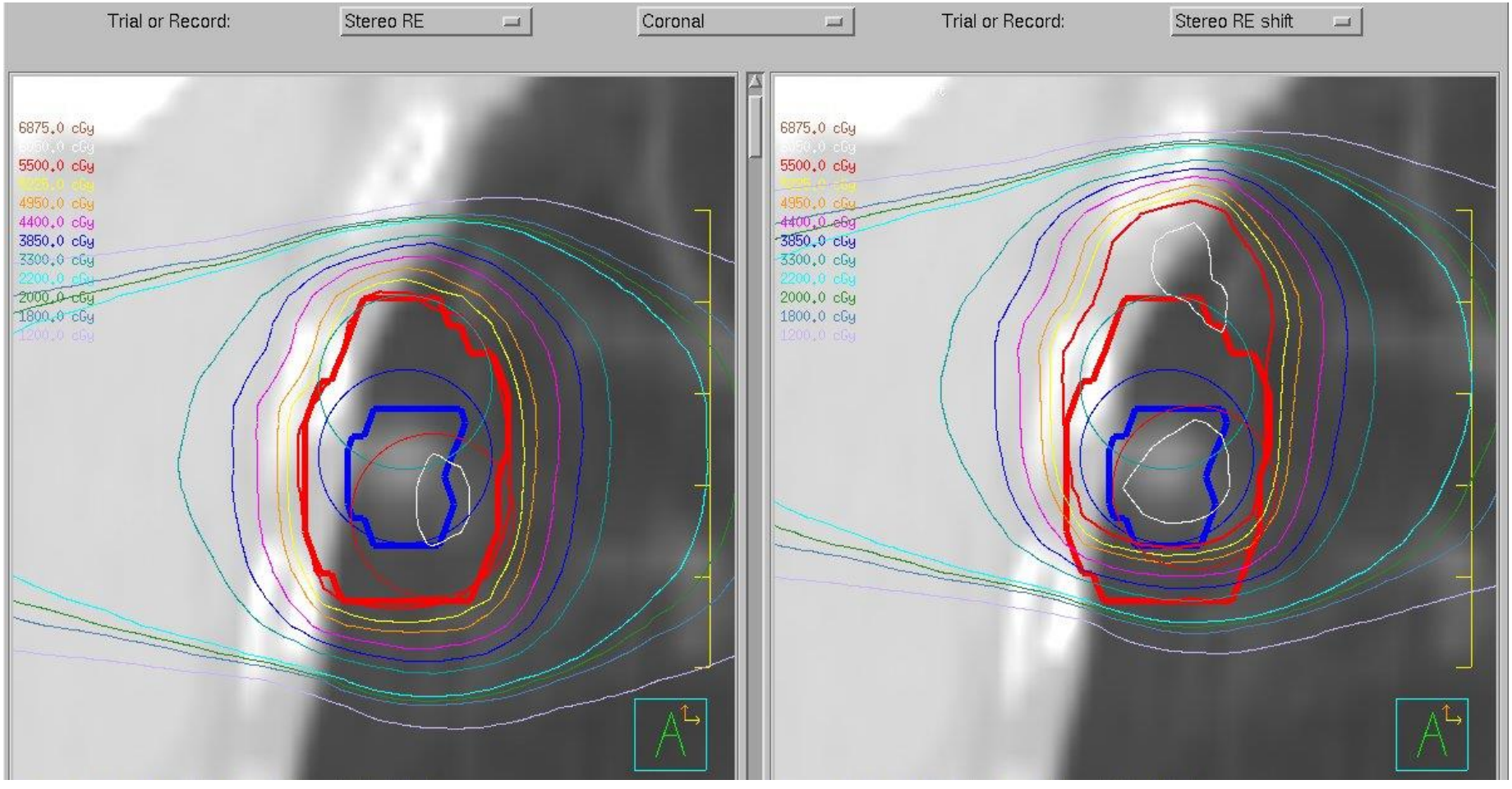
Unexpected shifts: Dose shift



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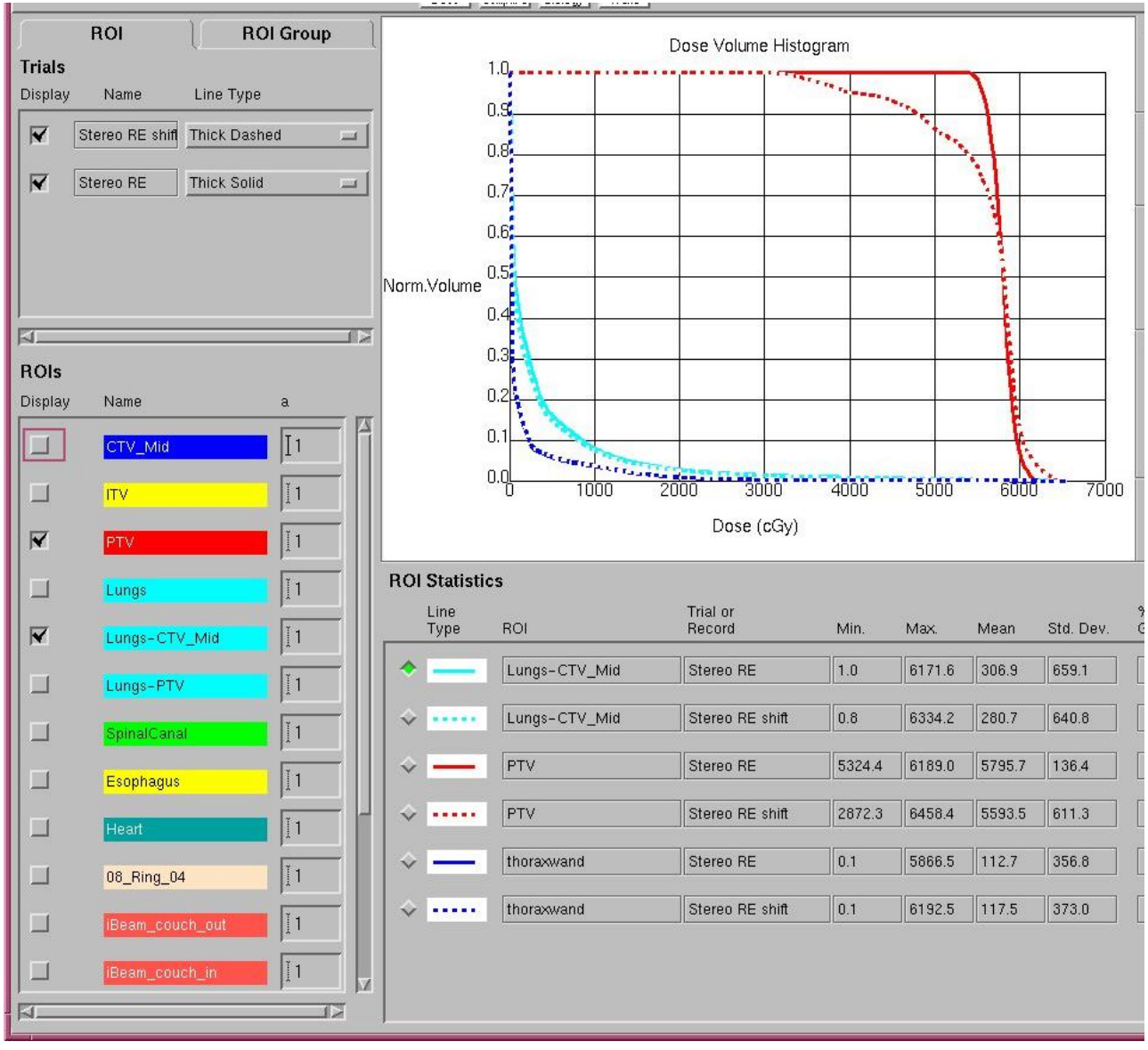
Unexpected shifts: Dose shift



- Thorax dose V37Gy from 14 cc to 18 cc (20 cc allowed)
- V30Gy from 27 cc to 32 cc (if >20 cc, 3*18Gy not allowed

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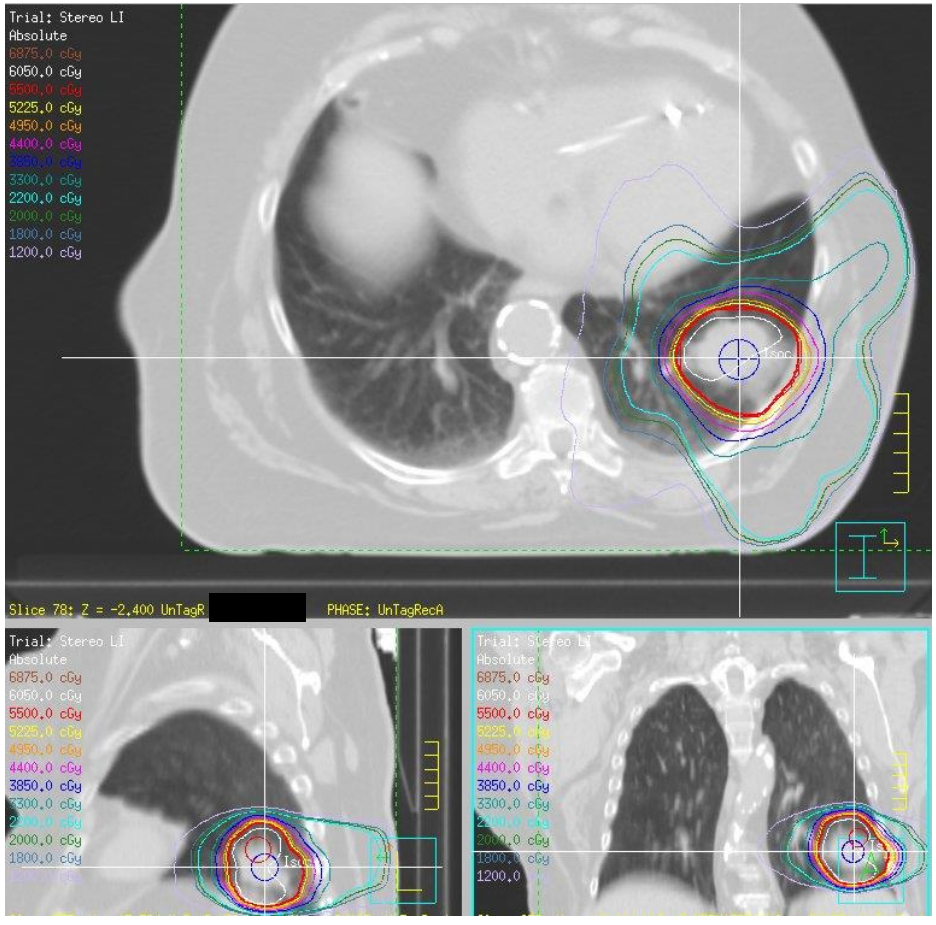
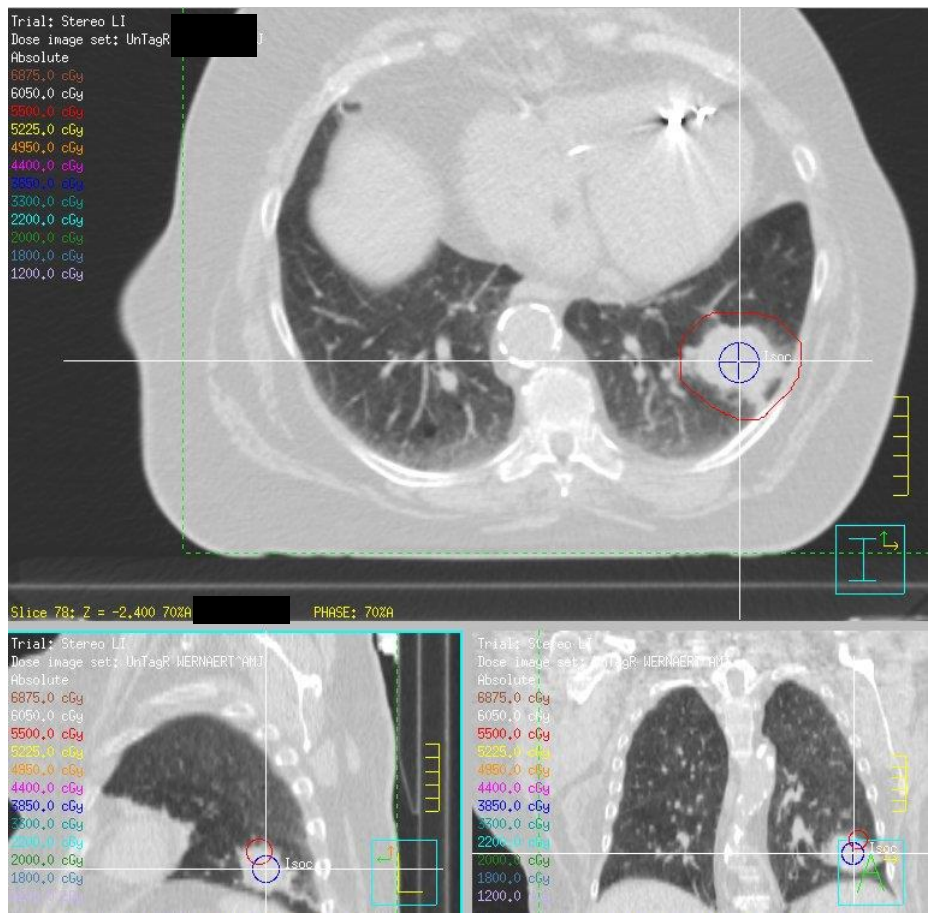
Wrong CT for matching with CBCT

Average CT



Midvent phase



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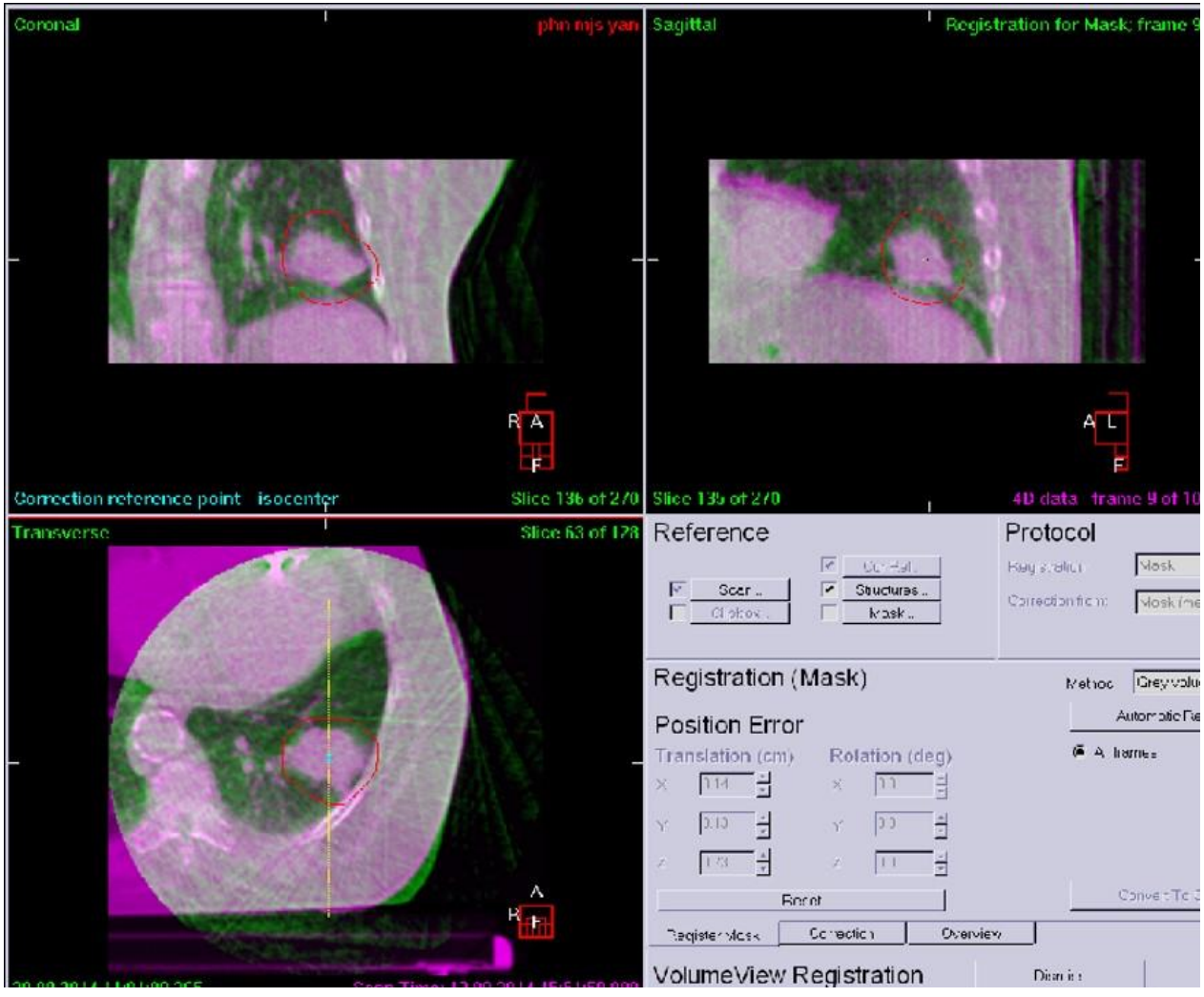
Wrong CT for matching: 4D-CT



- 4D-CT used to generate Midvent plan.
- CTV delineation at Midvent position used to generate PTV and position isocenter
- (Plan calculated on average CT)
- CBCT should be matched on midvent CT
- However, average CT was used, introducing systematic shift! (planned CTV position <> CTV position on reference CT)

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Wrong CT for matching: re-plan

- Big tumour shift detected on CBCT. Risk of too high dose to OAR if shift would be corrected.
- New plan created and send to linacs
- New CT NOT imported
- Next fraction incorrect shift applied.

Or, what has also happened..

- New plan made and send to linacs
- New CT WAS imported, but only in database of one linac (Elekta XVI)
- Patient treated on other, similar linac (Elekta Mosaiq has shared database for linacs)

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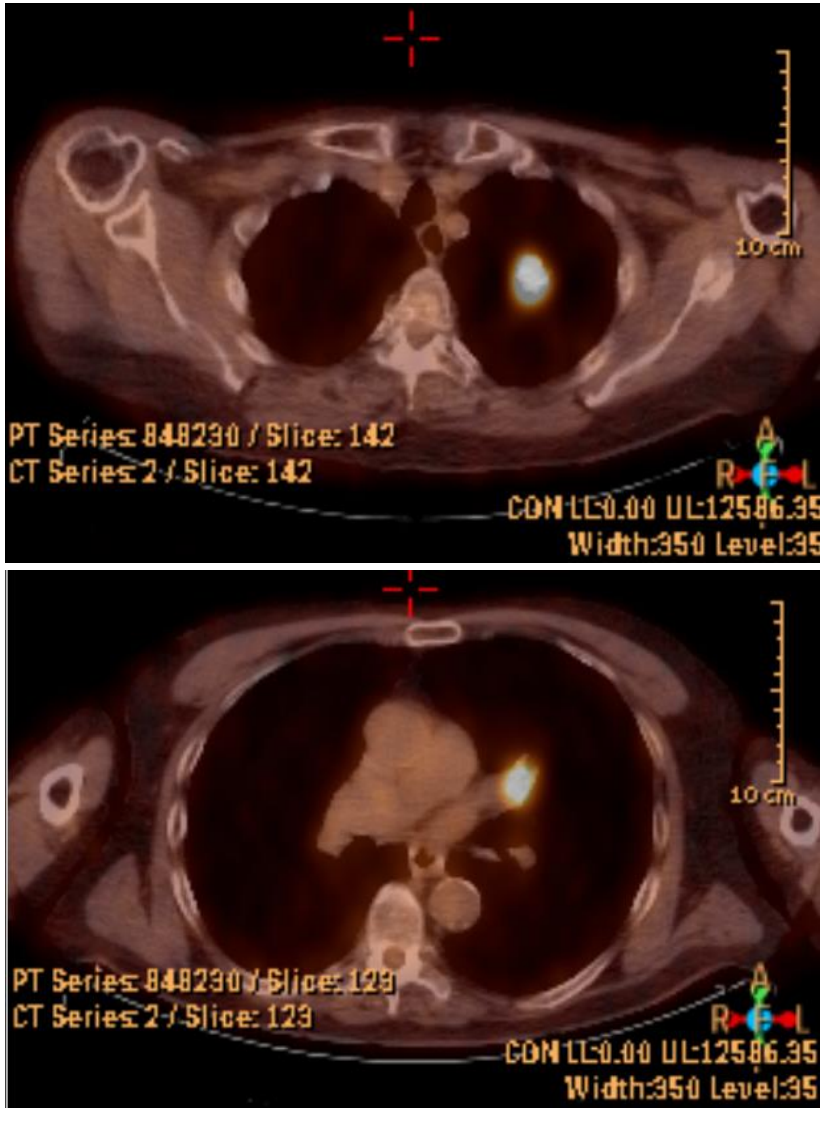
Too low dose due to proximity of OAR



PET-CT diagnosis March 2013

Two lesions

- Upper lesion 3 x 18 Gy
- Central lesions 8 x 7.5 Gy

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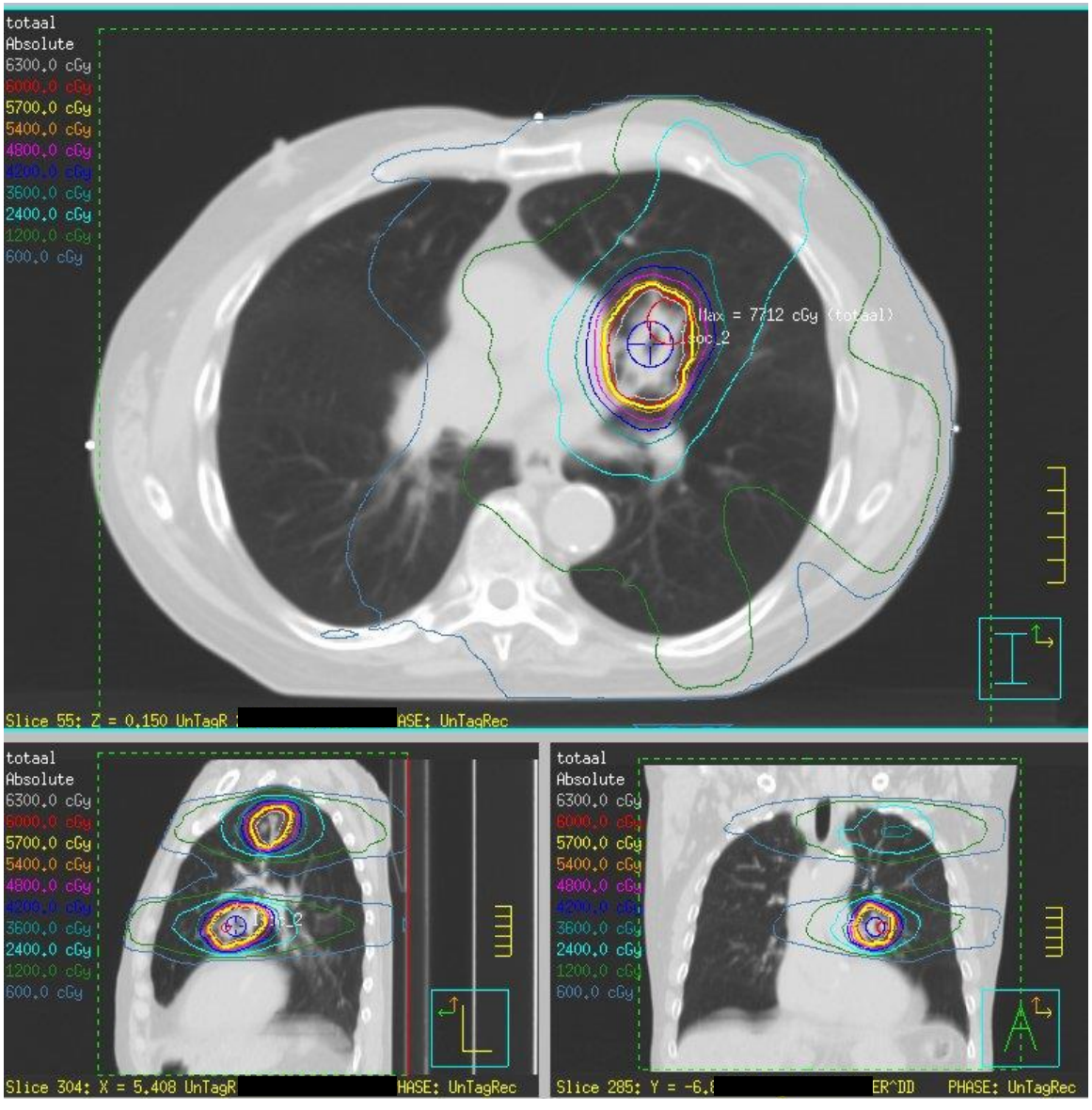
Too low dose due to proximity of OAR



Lungtech guidelines:

-D95% of PTV ≥ 60 Gy (this case: 90%- not ok)

AND

- D99% of PTV ≥ 54 Gy (this case:ok)

Or, in case OAR proximity

- D95% of PTV ≥ 48 Gy (this case:100%)

AND

- D100% of CTV ≥ 60 Gy (this case:ok)

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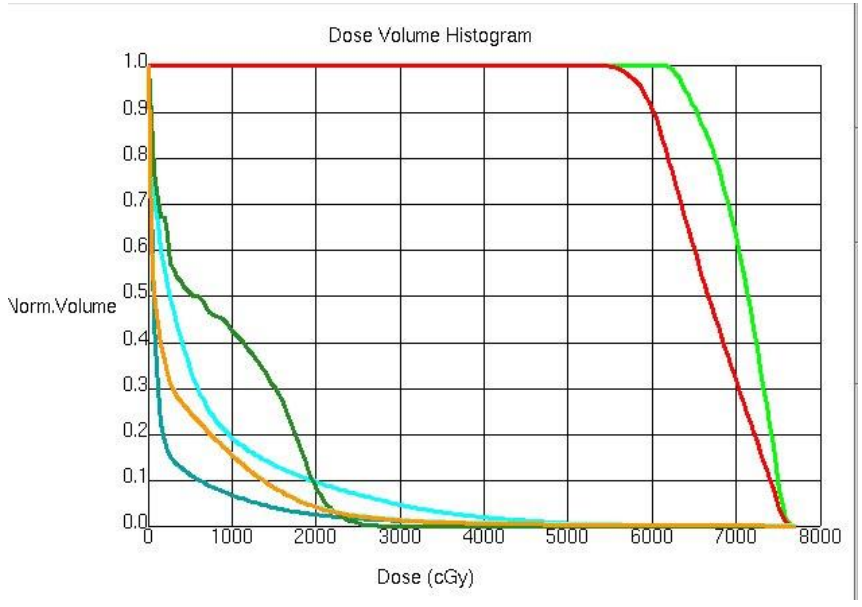
Too low dose due to proximity of OAR



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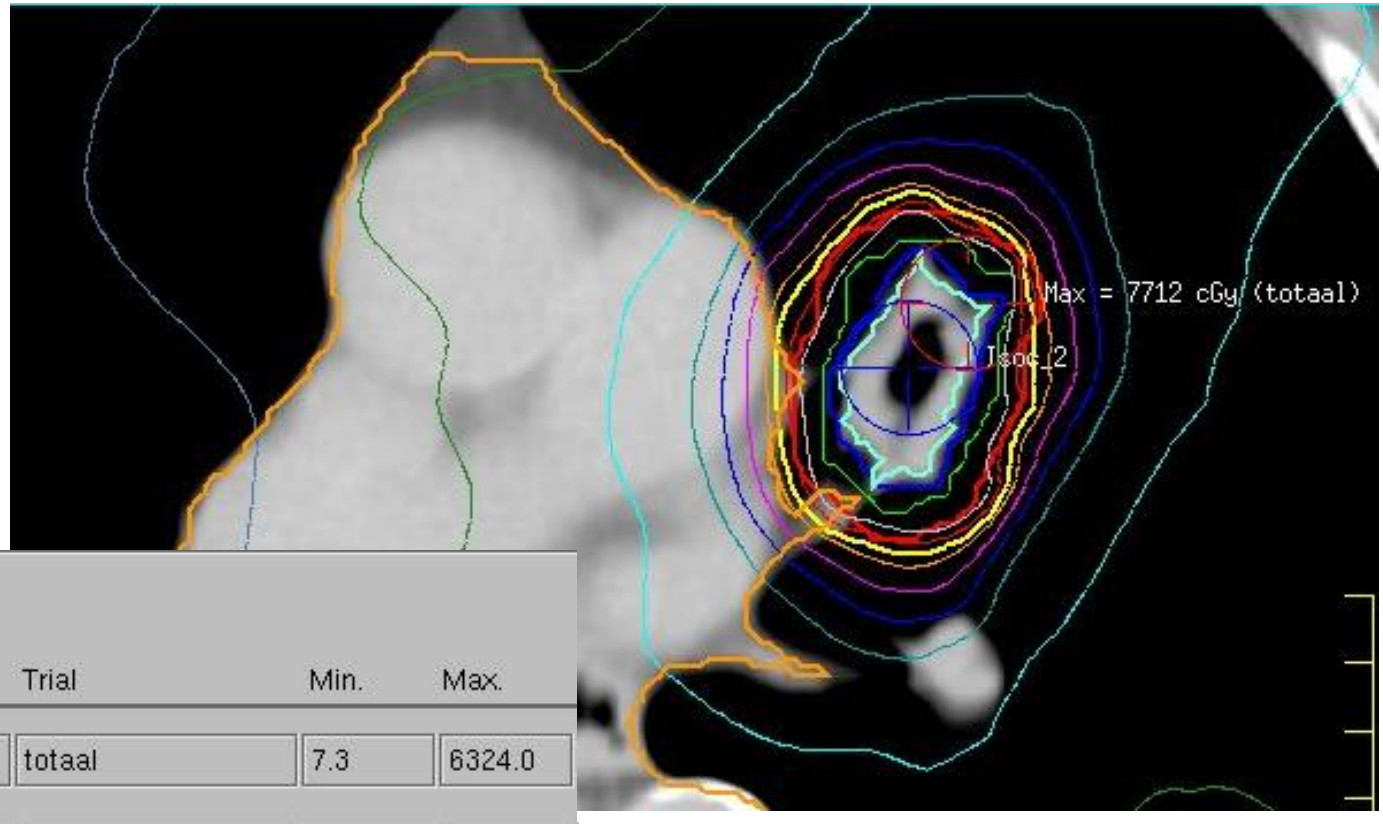
+ Wrong OAR auto-delineation..



ROI Statistics

Line Type	ROI	Trial	Min.	Max.
	Hart	totaal	7.3	6324.0
	mediastinum	totaal	3.4	7683.7
	mediastinum corrected	totaal	3.4	7333.4

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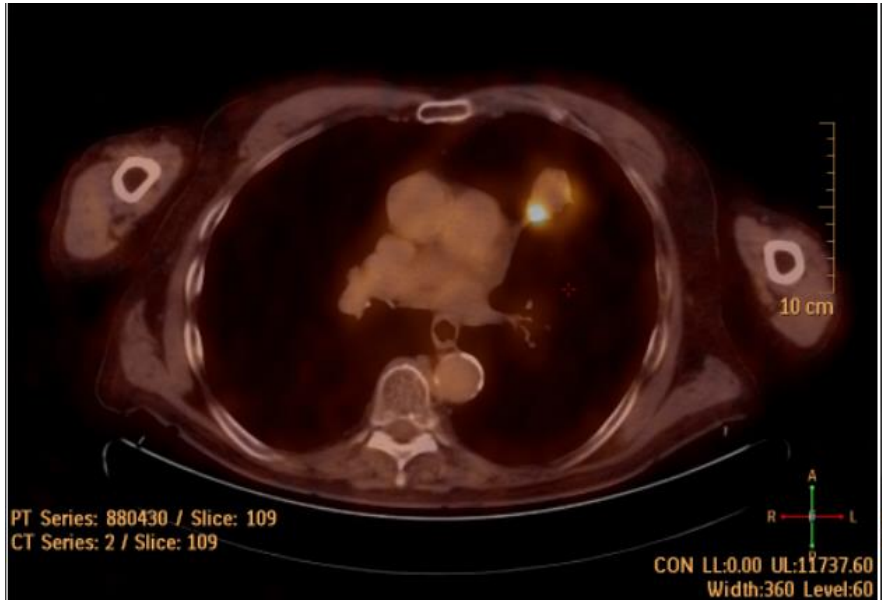
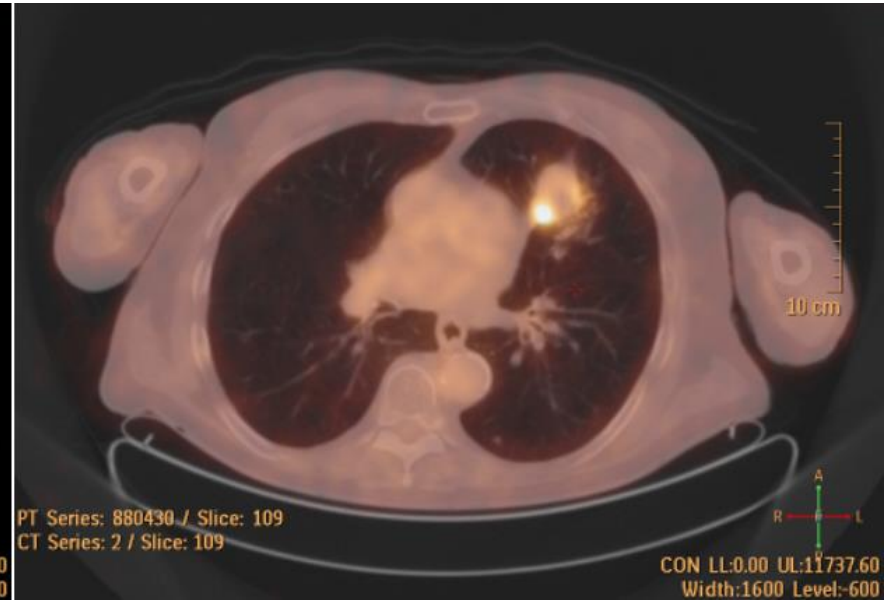
Too low dose due to proximity of OAR?

June 2014 FDG uptake. Recurrence?





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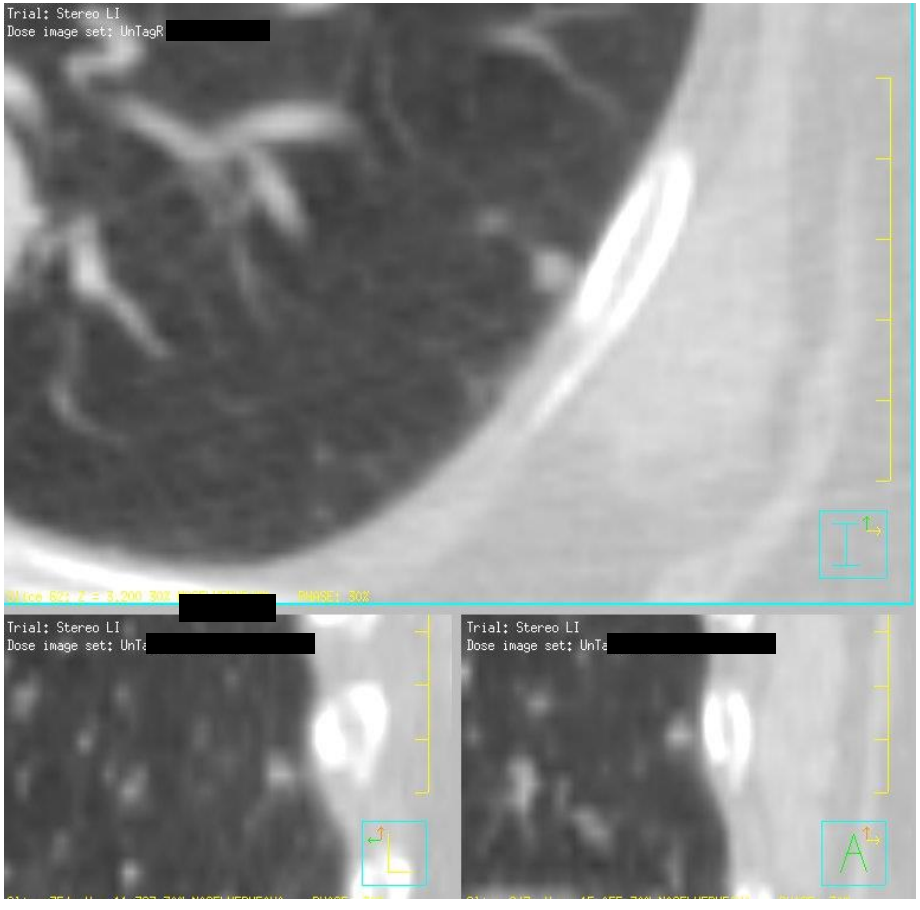
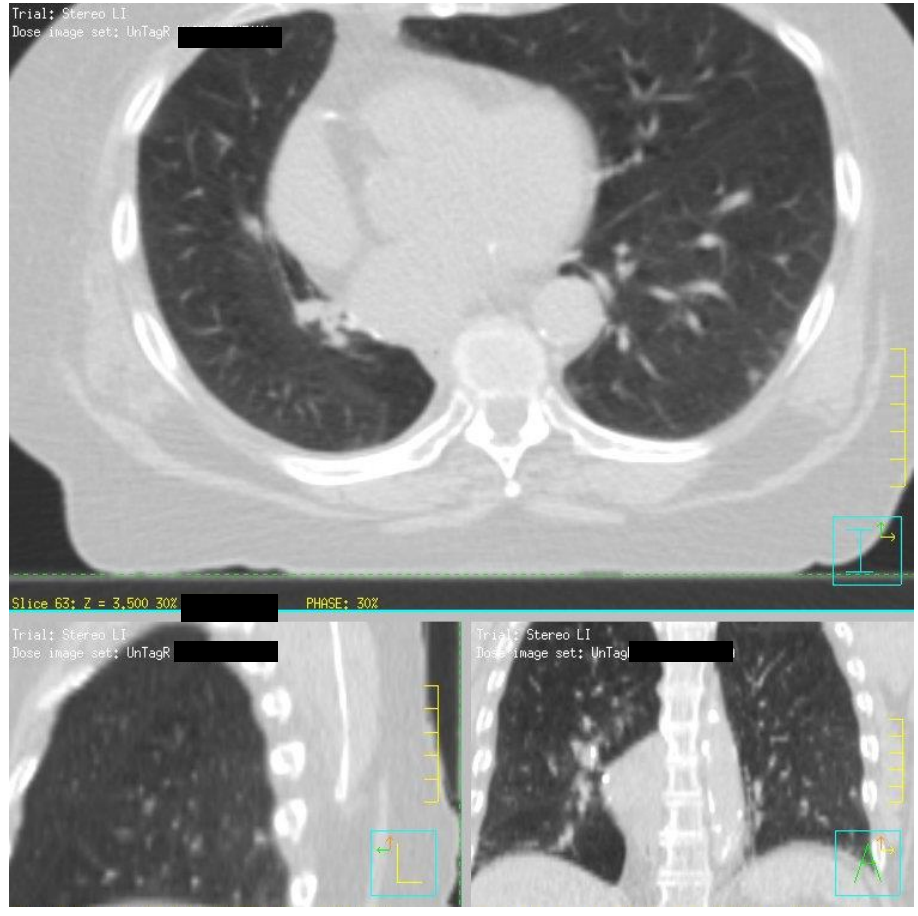
Too small lesions to detect on CBCT





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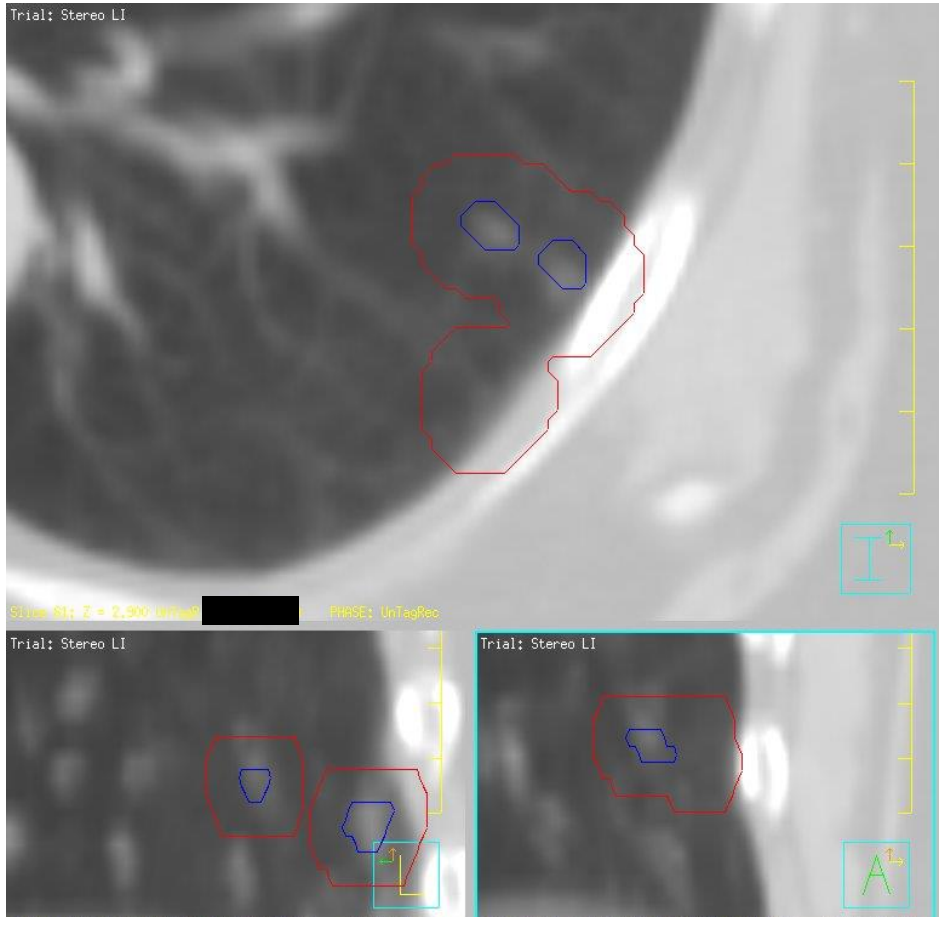
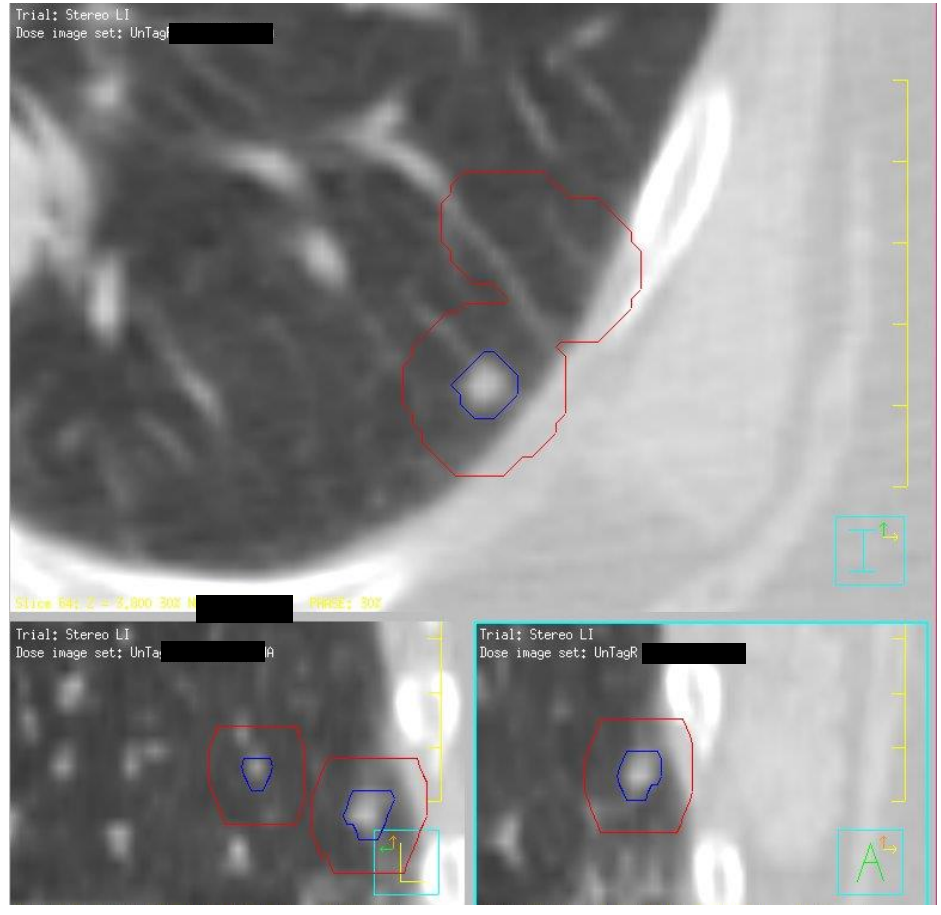
Too small lesions to detect on CBCT

Average



Midvent



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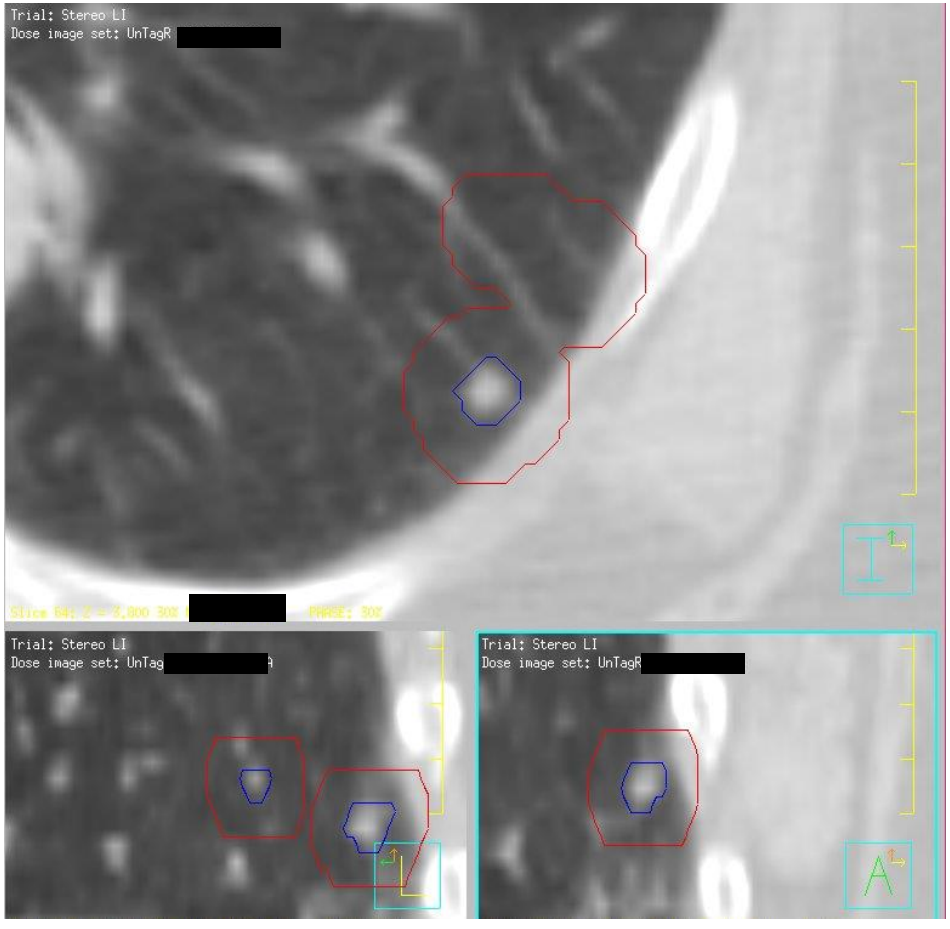
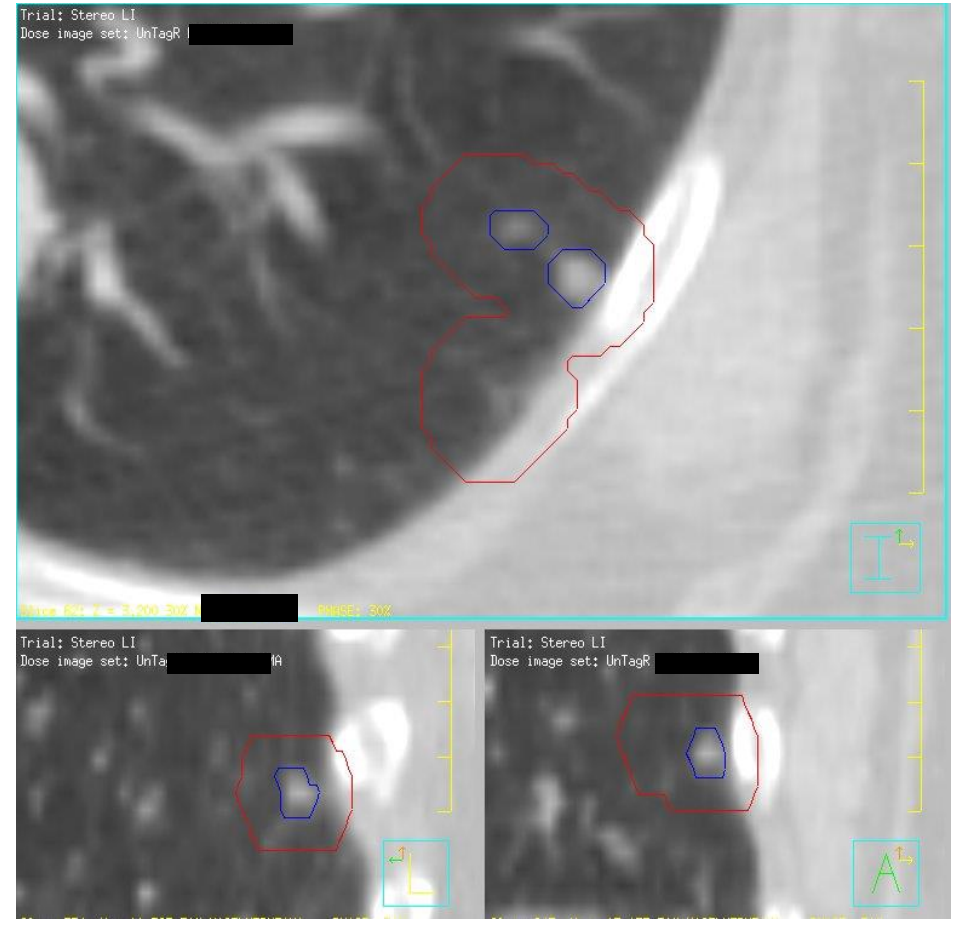
Too small lesions to detect on CBCT

midvent





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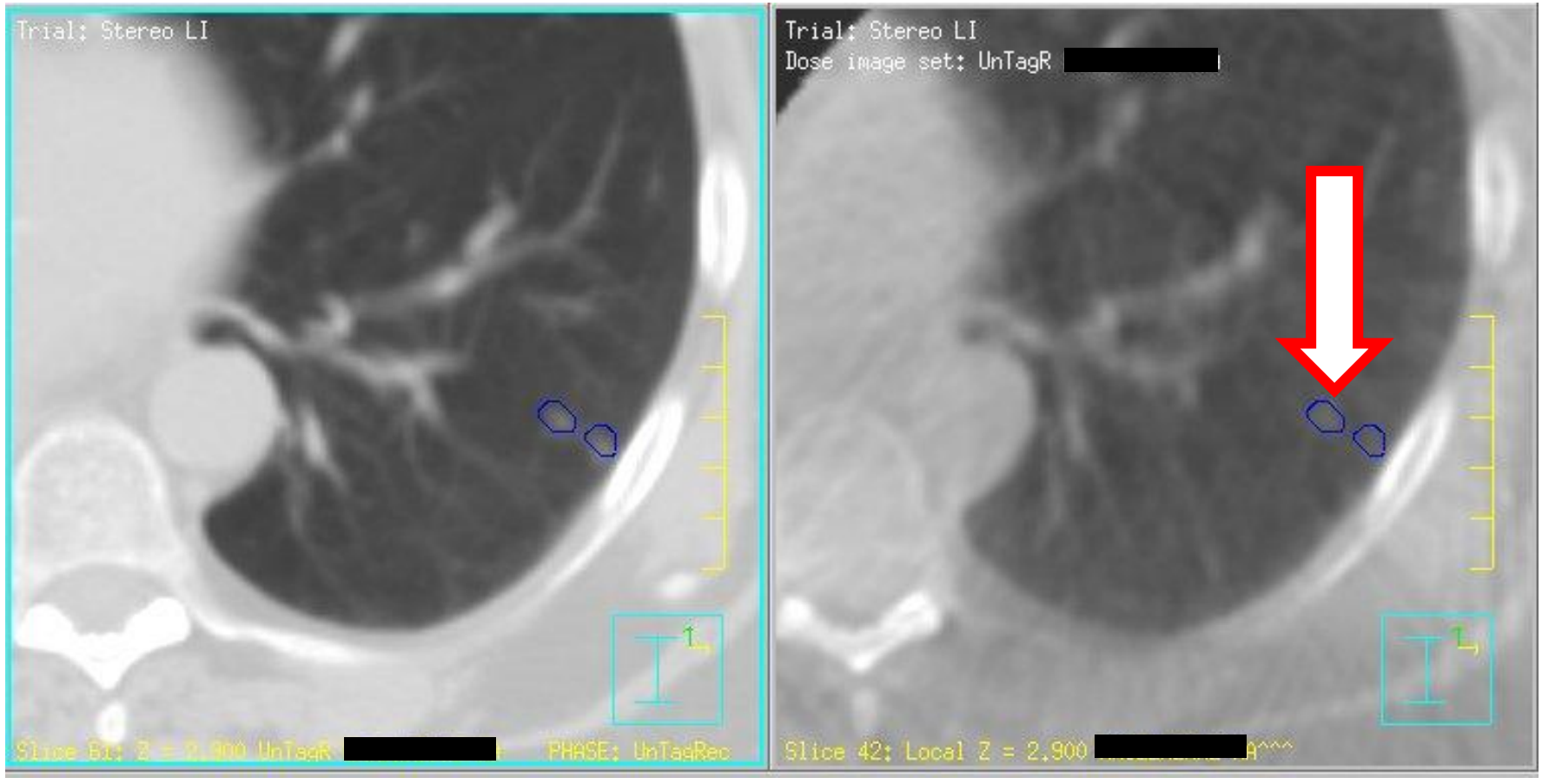
Too small lesions to detect on CBCT

CT

CBCT



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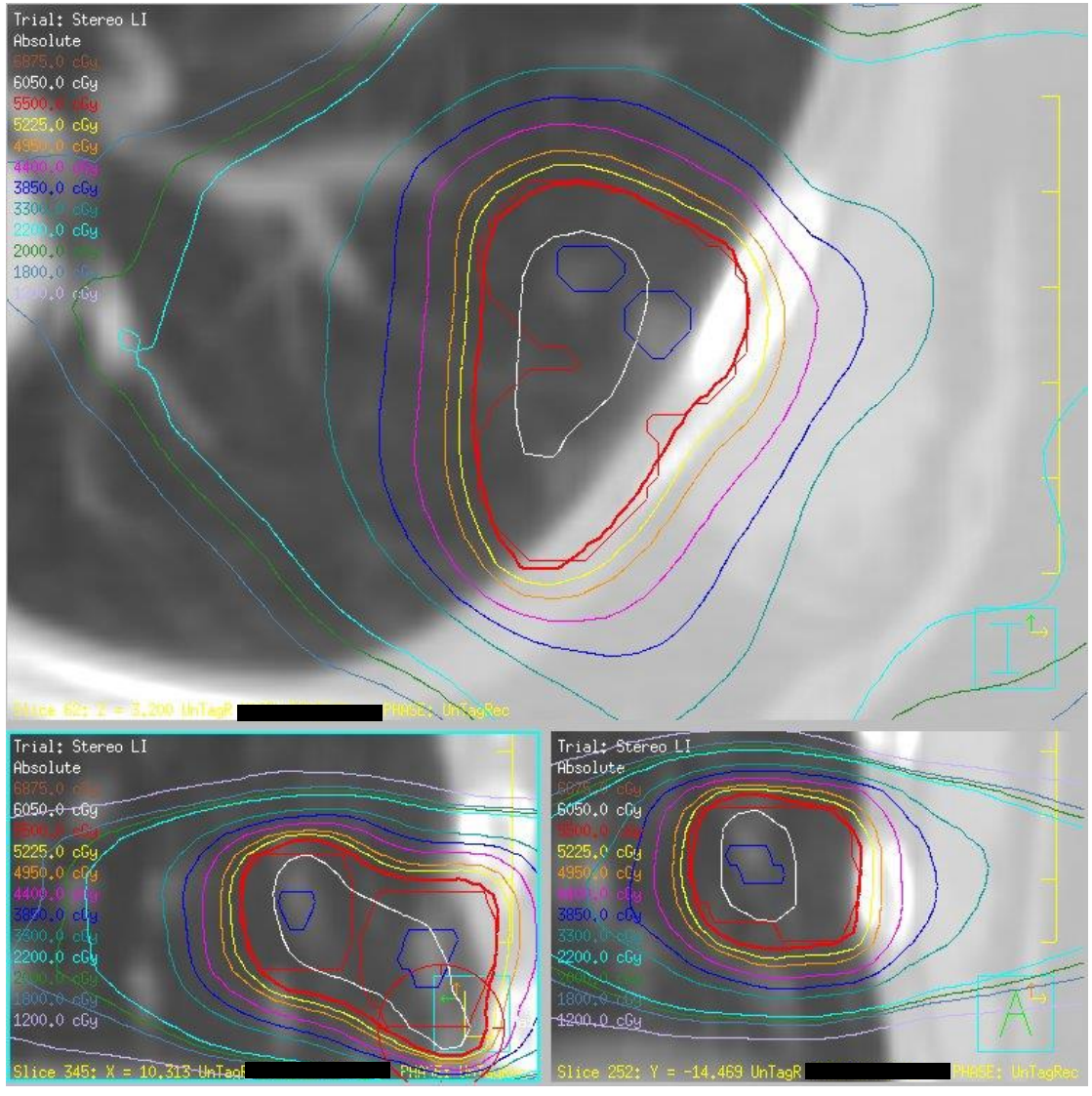
Too small lesions…for dose calculation?



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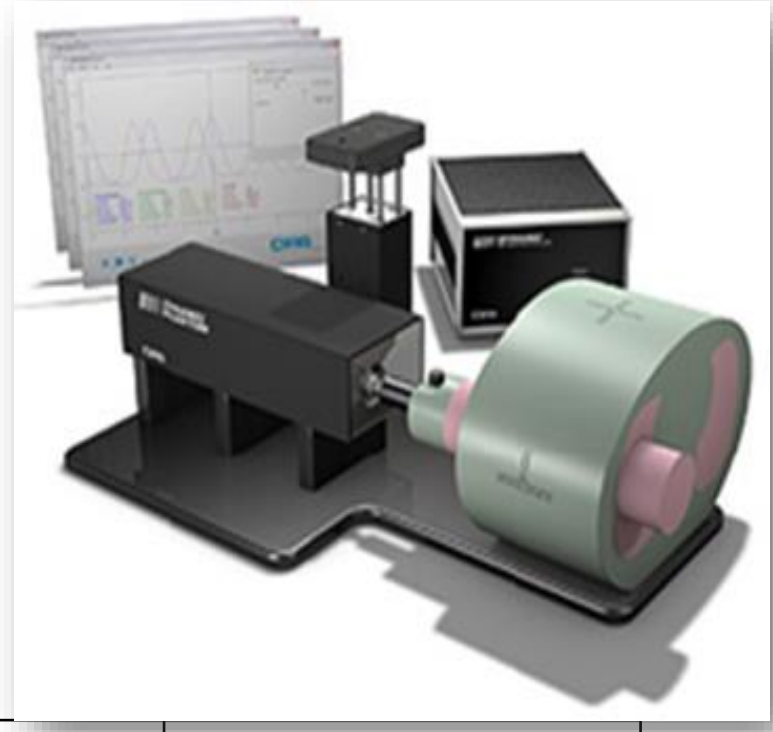
External audit: VMAT control points

- Linac: Elekta synergy
- TPS: Pinnacle
- CIRS phantom with 2 spheres



	1.5cm sphere	2.5cm sphere
Static plan 4° /cp 2° /cp	 **3.8 %** **2.8 %**	 **4.7 %** **0.0 %**
Dynamic plan – 15mm/3s 4° /cp 2° /cp	 **8.6 %** **3.2 %**	

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External Audit: Beam calibration

- Q1= beam quality of the reference Linac
- Q2= beam quality Linac-like condition cyberknife

$$D = M^{*} \times N_{d,w} \times k_{q,q_0}$$

- Approximation of $k_{q,q_0} = 1$ When $k_{q,q_0} =$ **0,996**

(A quantity kQ, the beam quality correction factor, is defined which corrects the absorbed dose-to-water calibration factor ND,w in a reference beam of quality Q0 to that in a user's beam of quality Q1)

Systematic error of 0,4%

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Software upgrades: QA software

- QA phantom (Delta 4) for patient pre-treatment verification
- Software upgrade: No specifics given..
- After upgrade, new calibration method needed
- Ion chamber output modelled differently for small and large fields
- Everything seemed ok, but..
- After some time, doing a statistical process analysis (trend analysis), on average lower pass rates were found.
- Still working on how to handle this issue…

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Take home message / acknowledgements

Everyone at the Catharina Hospital department of Radiation Oncology for

- Knowing what you are doing (get educated!)
- Continue to learn more (stay educated!)
- Knowing the procedures and sticking to it
- Staying alert if things (software) change
- Dealing with challenges and mistakes in an open, non-blaming, culture.

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A multicentre QA study on 4DCT and IMRT/VMAT techniques for lung stereotactic treatments using the 008A CIRS 4D phantom

Marie Lambrecht

PhD Student, Elekta Grant
Catharina hospital,
Eindhoven, The Netherlands

EORTC *The future of cancer therapy*

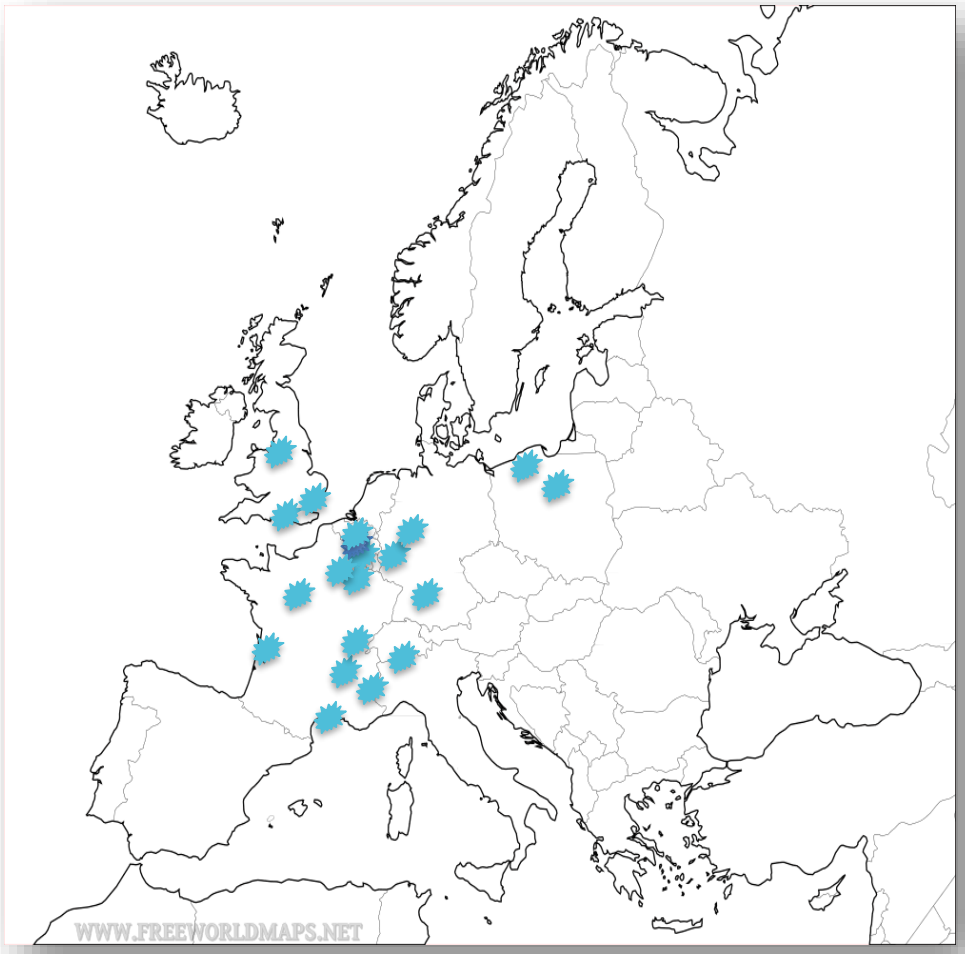
catharina ziekenhuis

Summary

- Context: Lungtech trial
- CT and 4DCT analysis
  - Methodology
  - Preliminary results
- Dosimetric check
  - Methodology
  - Preliminary results

Context: The EORTC Lungtech trial

SBRT for inoperable centrally located NSCLC



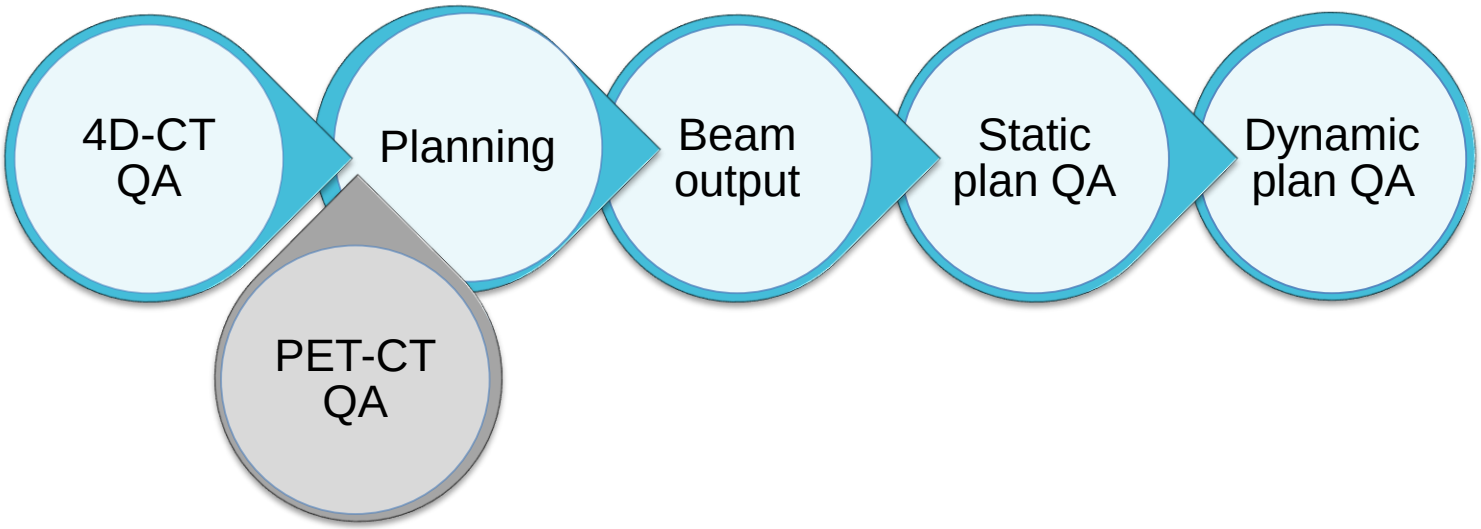
- **Multicentric**
- **International**
- **Challenging tumour location**
  SBRT-high doses per fraction

Timmerman & al 2006
Haasbeek & al 2011

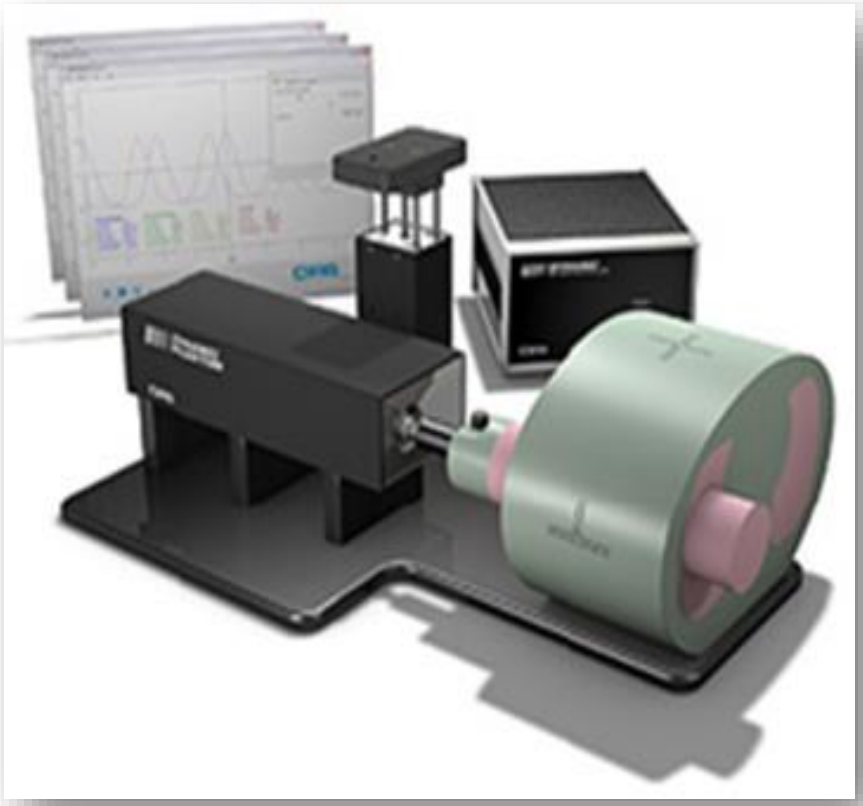
ADVANCED RTQA

Context: The Lungtech trial

EORTC RTQA levels
level 5: Complex dosimetric check

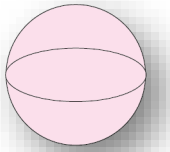


CT and 4DCT Analysis: Methodology

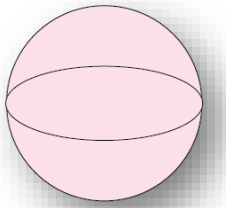


The CIRS 008A phantom with 2 insert sizes is scan 7 times

- **15mm ∅**
  - 1 3D-CT
  - 3 4D-CTs



- **25mm∅**
  - 1 3D-CT
  - 2 4D-CT



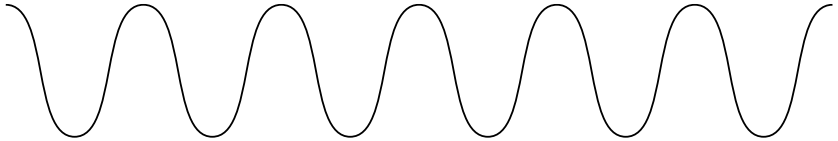
CT and 4DCT Analysis: Methodology

Motion tested

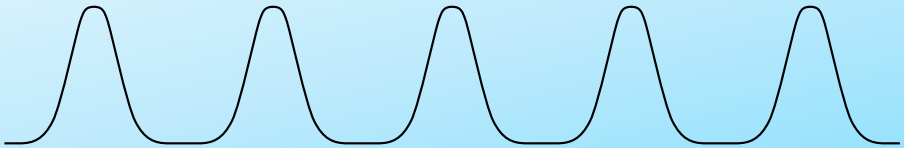
Amplitude (mm)	Period (sec)
15	3
15	6
25	4

Breathing signal

Sinusoidal trace



Lujan breathing patern



Patient respiratory trace

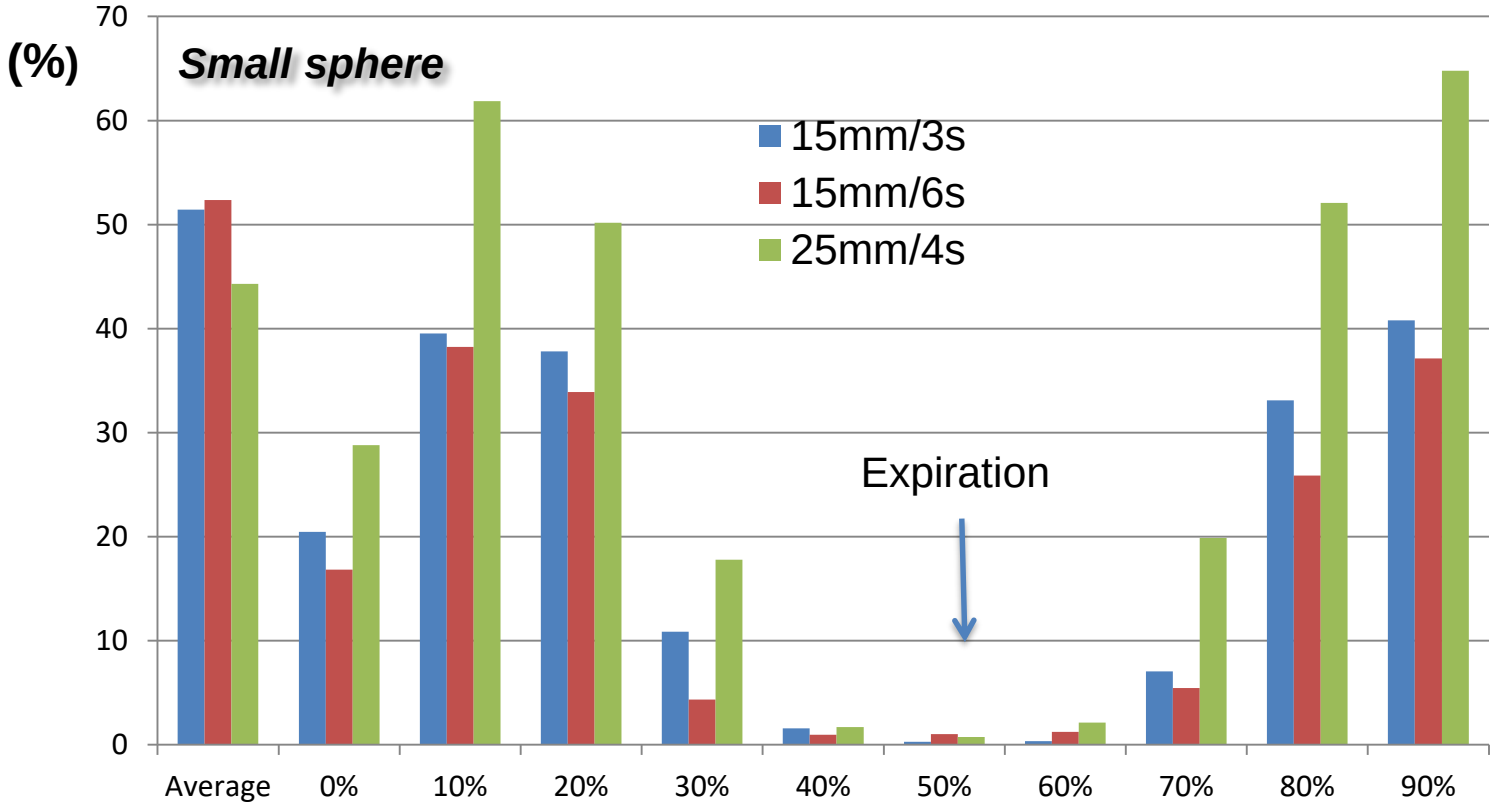
CT and 4DCT Analysis: Methodology

Coronal views (average, phase 10% + all contours)

- Determination of the **HU threshold** on the **static 3D CT** giving the **exact volume of the sphere**
- Threshold based **auto-segmentation** of each phase and the average image
- **Comparison** of the segmented volume to the true volume

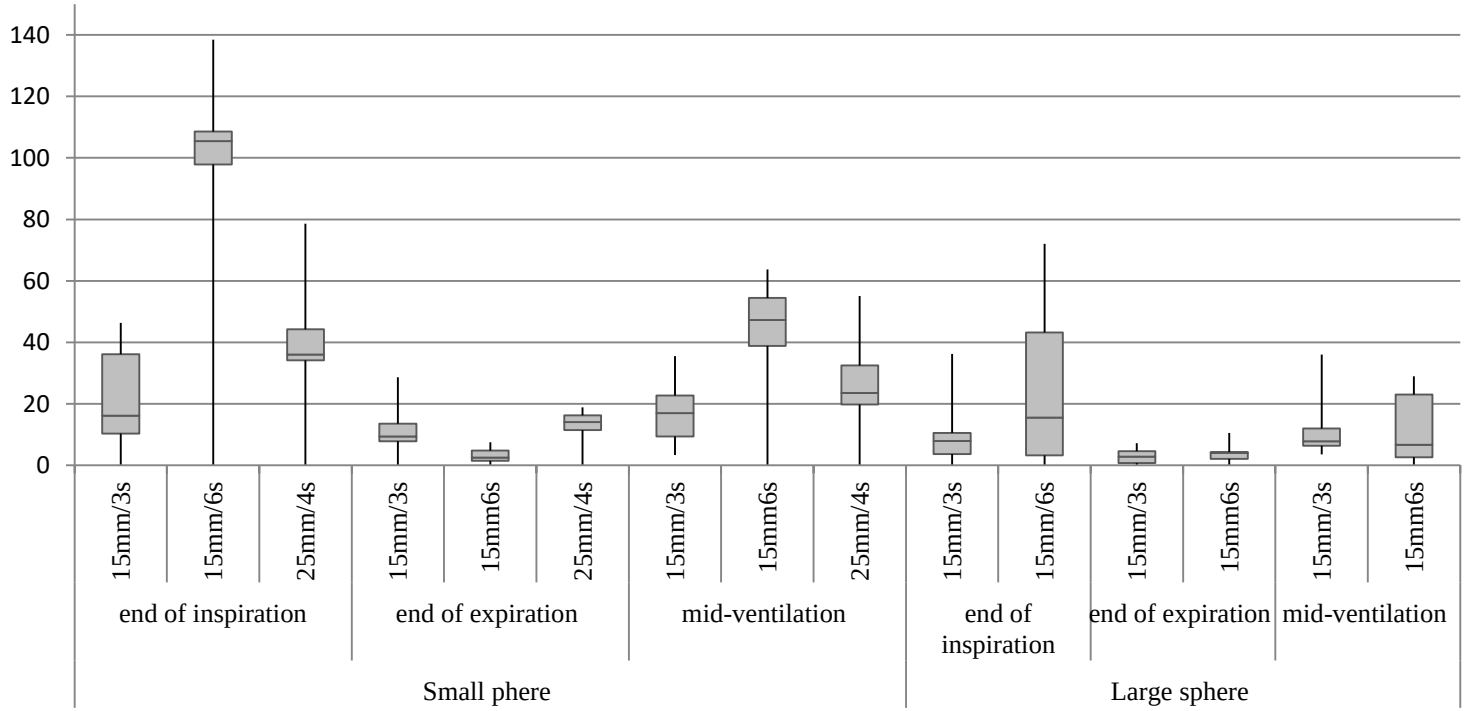
CT and 4DCT Analysis: Volume analysis 1/2:

Volume variations during a breathing cycle expressed in **% of the true volume**

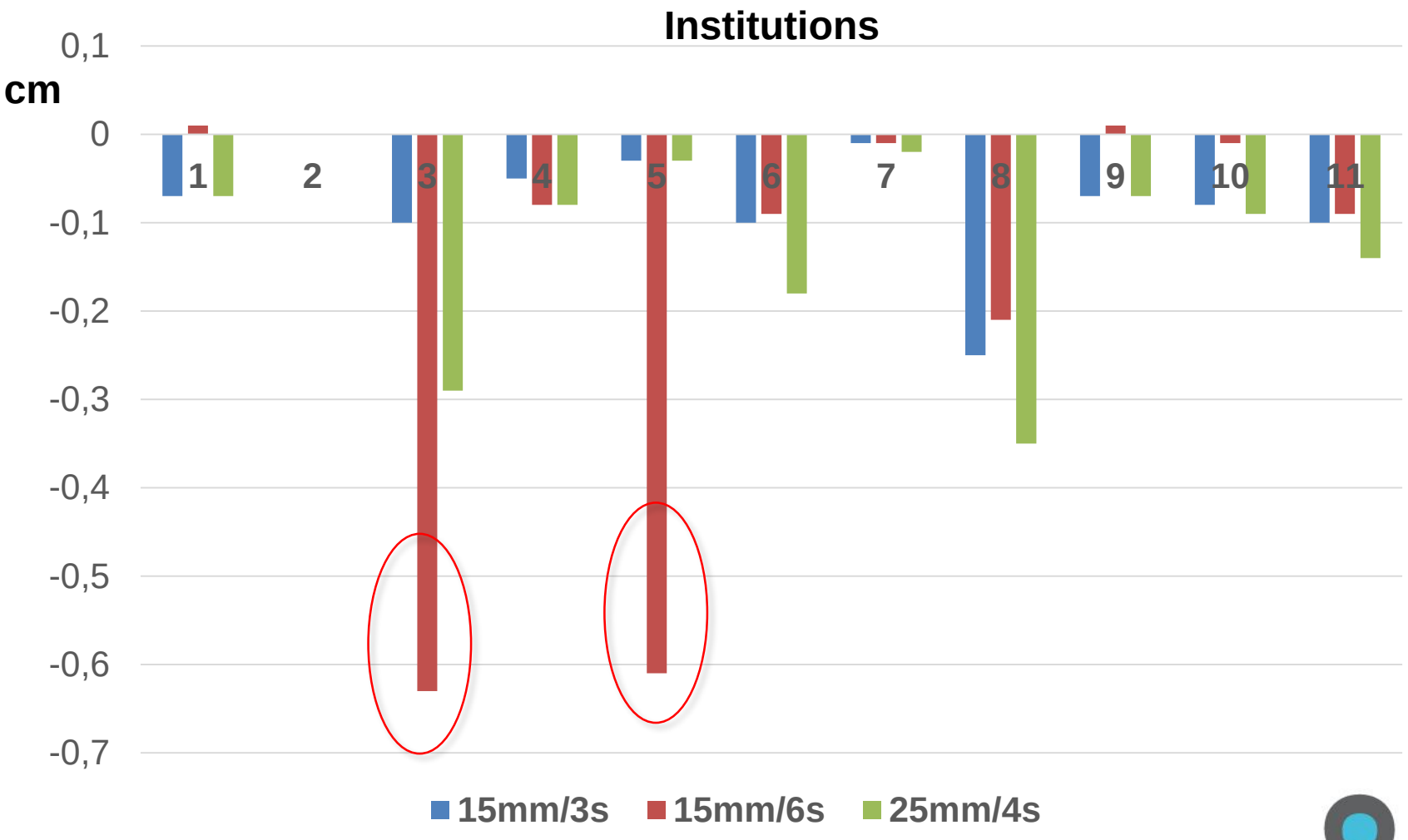


CT and 4DCT Analysis: Volume analysis 2/2:

Volume variations for each selected phase averaged across the institutions visited expressed in **% of the true volume**



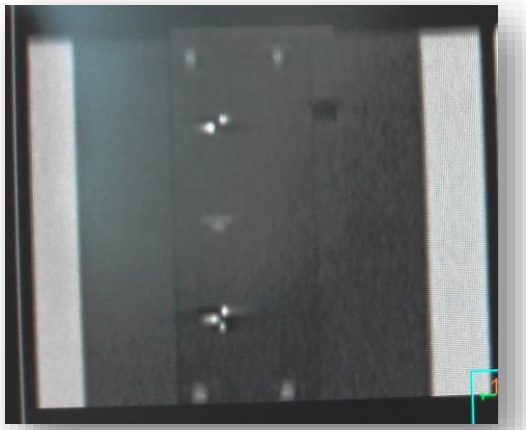
CT and 4DCT Analysis: Amplitude analysis 1/2



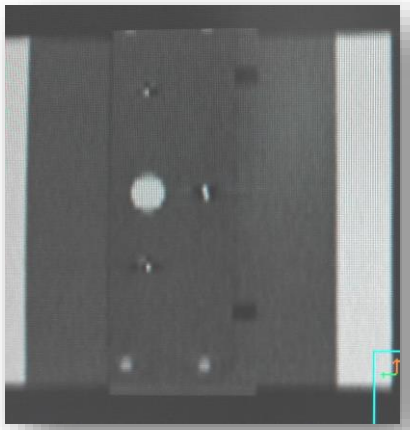
CT and 4DCT Analysis: Amplitude analysis 2/2

1

Inspiration phase

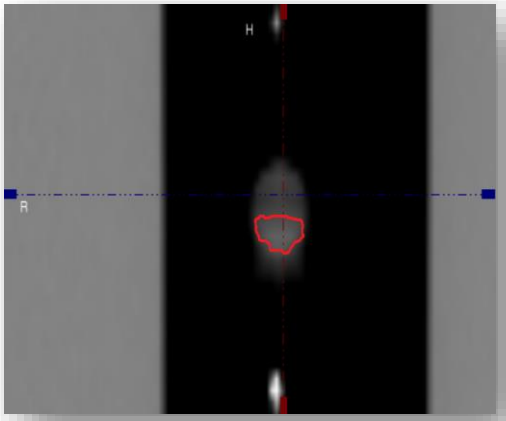


Expiration phase



2

Inspiration phase

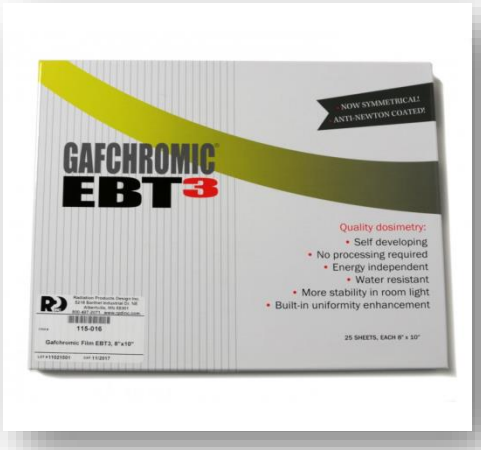


Dosimetric check: Methodology

- CIRS phantom 008A

X 2 15mm and 25mm

- Detectors



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Dosimetric check: Methodology

Beam output results are used for correcting the chamber reading in the phantom measurements

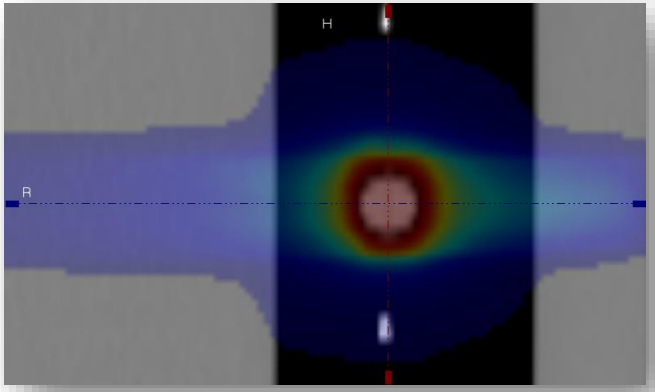
Beam output measurement at the energy used for the trial in the institution reference condition

Across the 13 institutions visited,
The dose mean deviation was **0.57%** (+/- 1.42%)

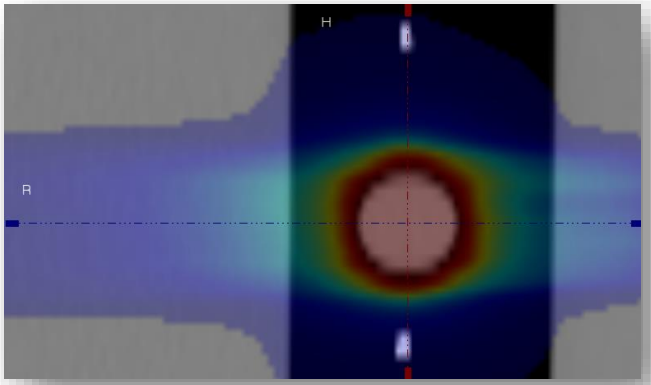
Dosimetric check: Methodology

3 plans are created using the previous scans

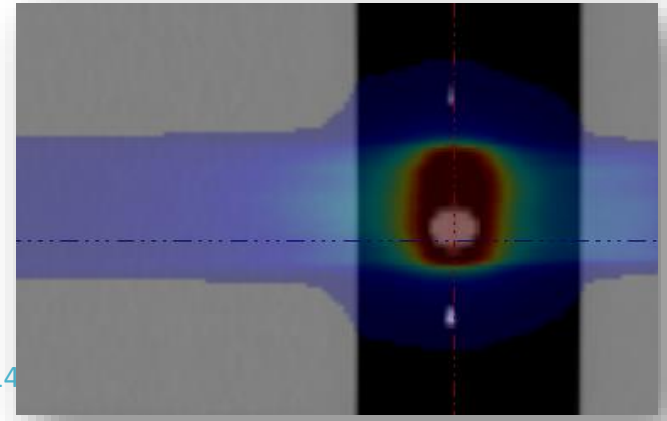
Small sphere static



Large sphere static



Small sphere –dynamic



Dosimetric check : Preliminary results

Results of **point dose agreement** between planned dose and measurements averaged across the institutions visited

	1.5cm sphere	2.5cm sphere
Static plan	**98.9%** *+/- 1.3%*	**99.9%** *+/-2.8%*
Dynamic plan 1.5cm/3s	**98.6%** *+/-0.86%*	

Example 1

Increase the number of control points

Linac: Elekta synergy

TPS: Pinnacle

Technique: VMAT

	1.5cm sphere	2.5cm sphere
Static plan Before correction 4°/cp After correction 2°/cp	 **3.8 %** **2.8 %**	 **4.7 %** **0.0 %**
Dynamic plan Before correction 4°/cp After correction 2°/cp	 **8.6 %** **3.2 %**	

Example 2

Q1= beam quality of the reference Linac

Q2= beam quality Linac-like condition cyberknife

$$D = M^{*} \times N_{d,w} \times k_{q,q_0}$$

Approximation of $k_{q,q_0} = 1$ → When k_{q,q_0} = **0,996**

Systematic error of 0,4%

Dosimetric check

- Film processing

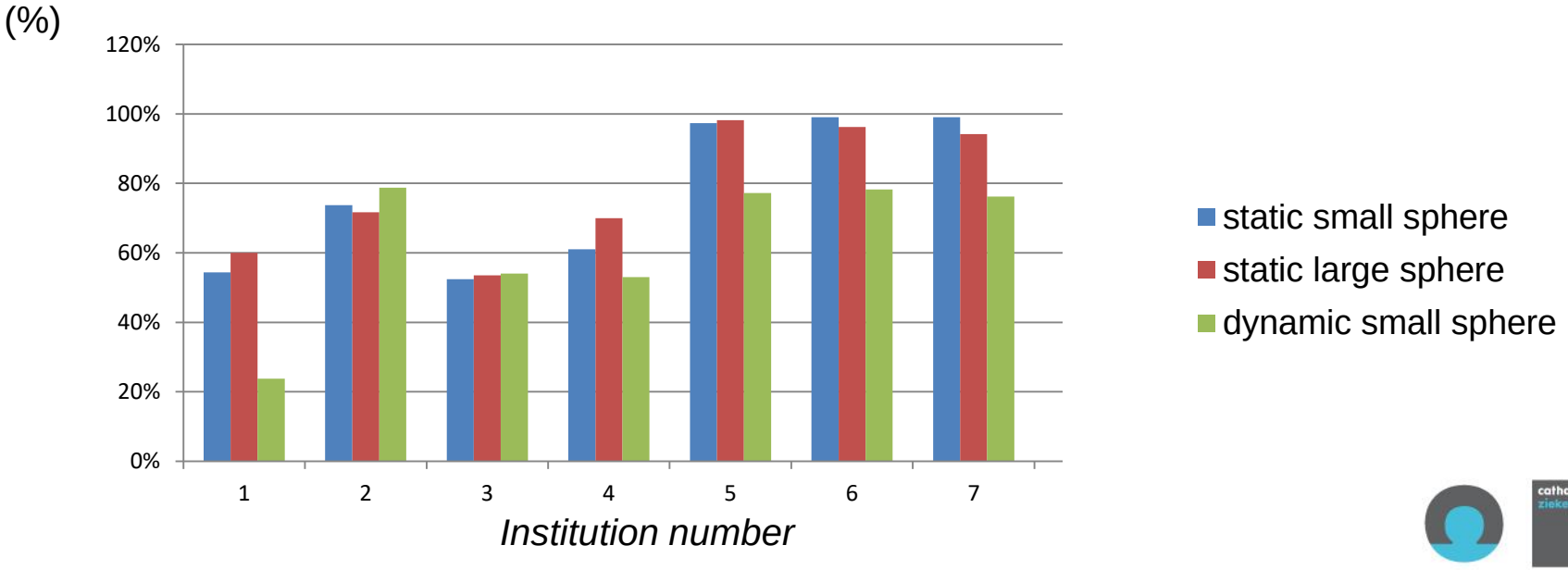
Films are corrected for absolute dose by the result of the chamber

Films are registered to the plan dose thanks to 3 markers

- Film analysis: Gamma index

Gamma criteria: 3%, 3mm

Dose threshold: 20% Dmax measured



Conclusion

- CT and 4DCT
  - Expiration phases are more stable and give a better estimation of the true GTV
  - The average image overestimates the GTV volume around 35%
  - Check the image quality at the end of inspiration
- Dosimetry
  - Good homogeneity in the beam output results
  - Dose comparison at the center of the sphere seems not affected by motion – Nonetheless over the central 2D plan measured by films the dose agreement rate is lower for the dynamic plan
  - Participating in external audits is useful

Overview of treatment techniques and equipment

Institution	# beams/type	MU	TPS	Linac	leave width (mm)
1	1/tomo	13.5 Min.	TOMO	Tomotherapy HD	
2	2/full arcs	1803	ARIA 11.0.47	Varian 2100C/D	
3	14/static	1016	Iplan 4.5.3	Varian Novalis Tx	2.5
4	2/full arcs	1912	ARIA 13.5.37	Varian TrueBeam	2.5
5	3/230 degree arcs	2930	ARIA 13.5.37	Varian 2100C/D	
6	11/static	833	Pinnacle 9.8	Elekta Agility	5
7	1/210 degree arc	1049	Iplan 4.5.4	Varian Truebeam STx Novalis	2.5
8	1/full arc	1160	Hyperion 2.4.4	Elekta, cannot determine model	
9	2/full arcs	2669	ARIA 11.0.42	Varian TrueBeam EDGE	2.5
10	1/full arc	1990	Monaco 5.10.02	Elekta Agility	5
11	1/full arc	2336	Monaco 5.00.04	Elekta Synergy	
12	3/arc	1907	ARIA 11.0.47	Varian Novalis TB	2.5
13	13/static	1155	Iplan 4.5.1	Varian Novalis	2.5
14	2/200 degree arcs	2584	ARIA 11.0.47	Varian, cannot determine the model	
15	2/full arcs	1651	ARIA 10.0.42	Varian 2100C/D	

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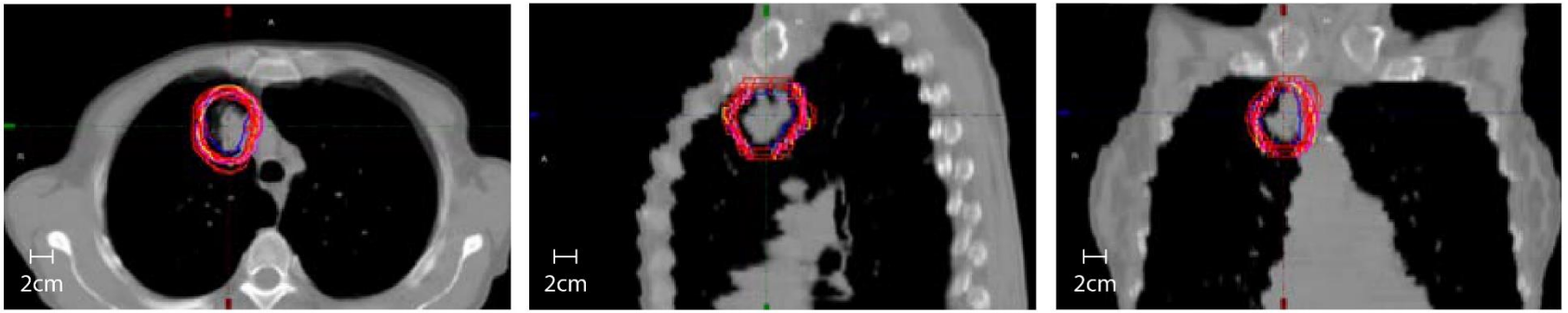
Lungtech delineations

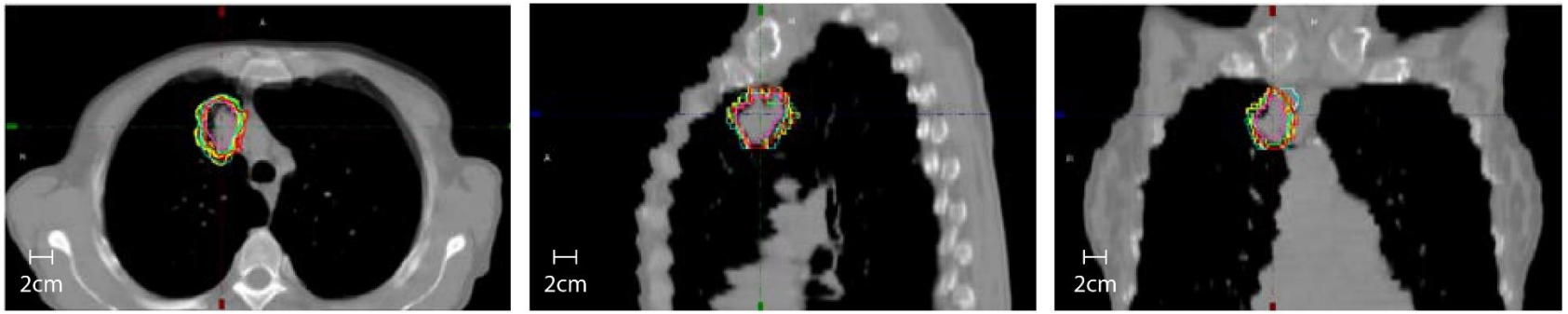
PTV

a)

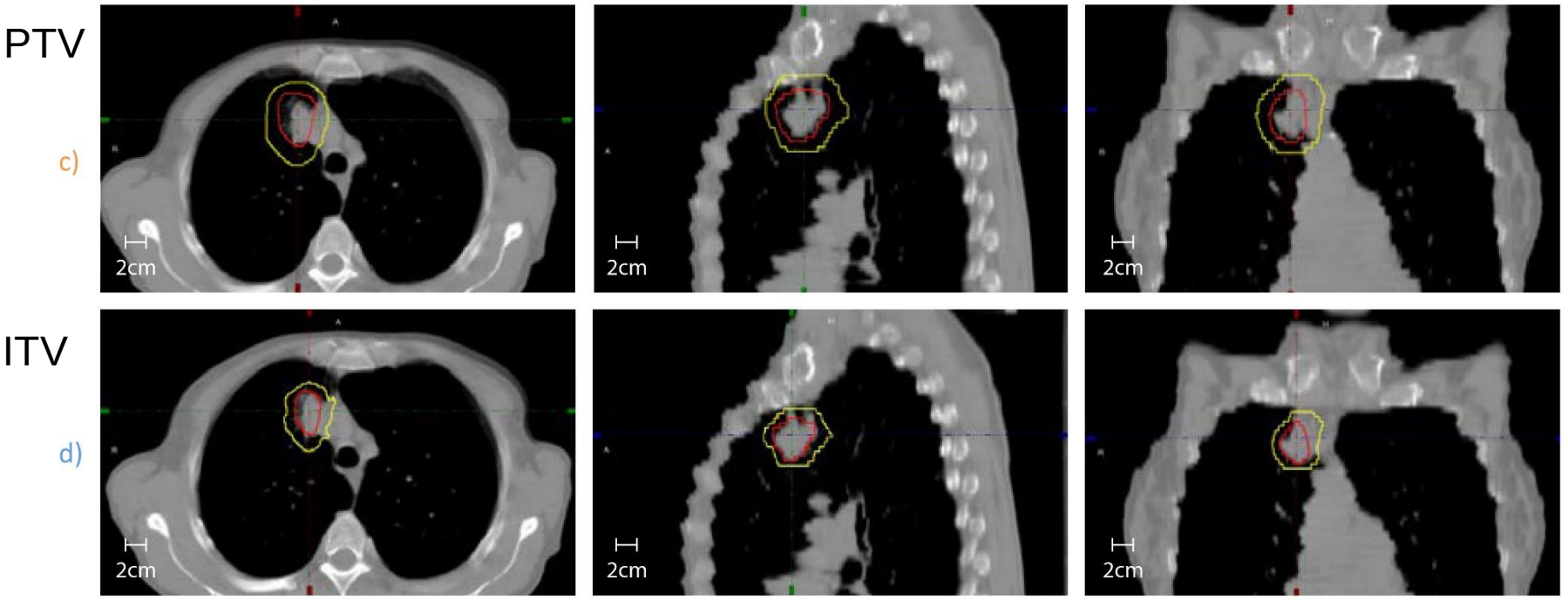


ITV

b)



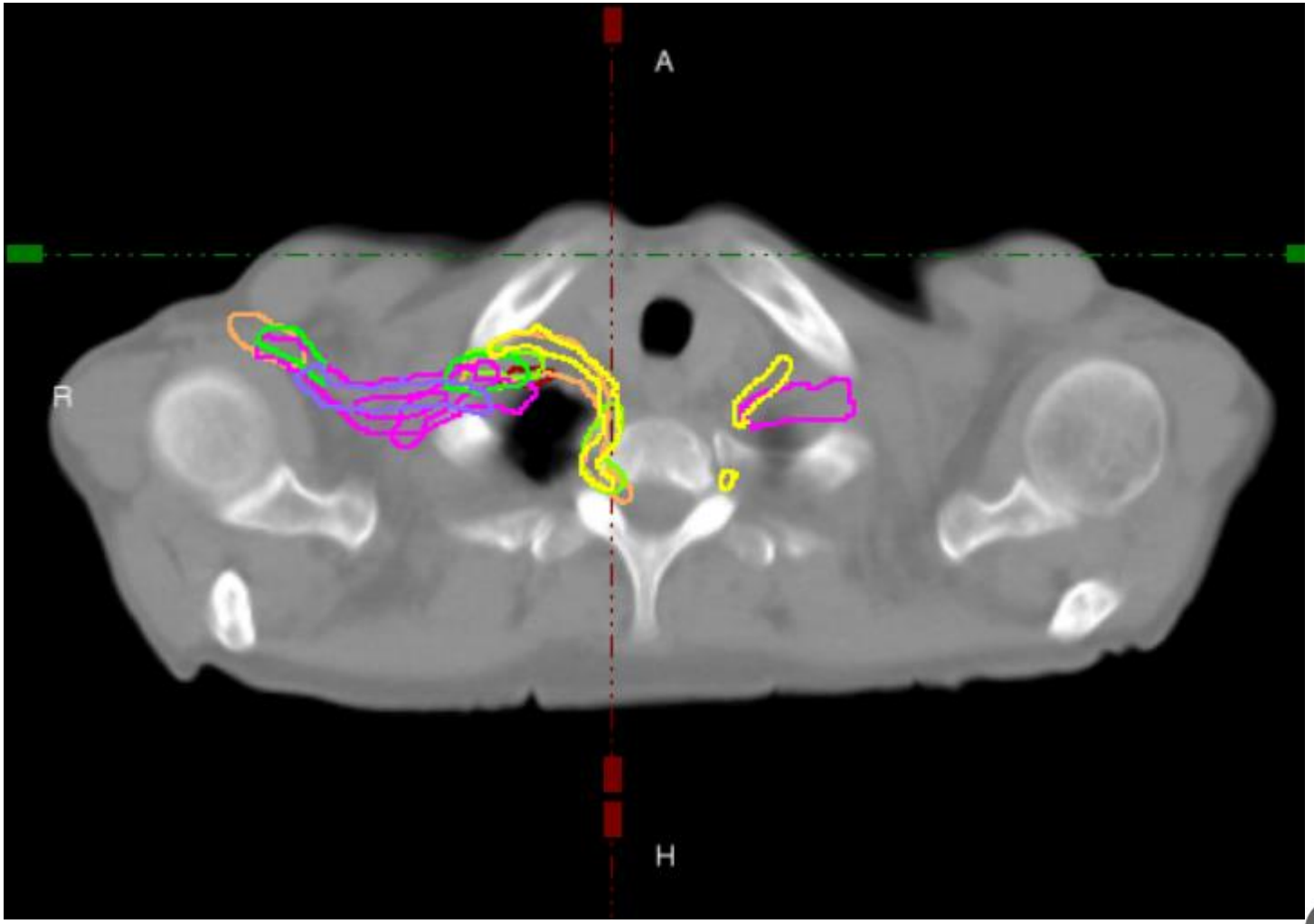
Lungtech delineations



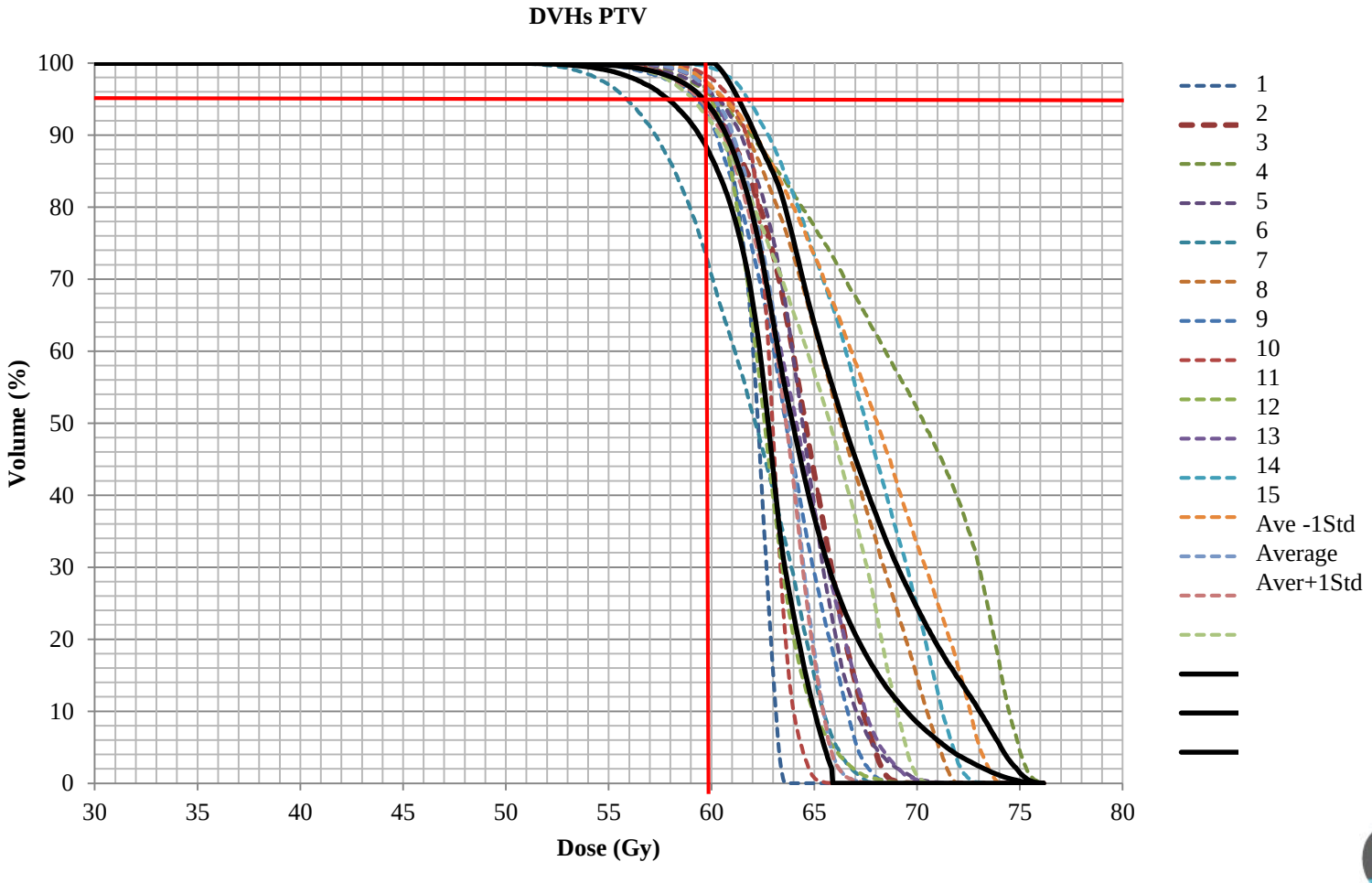
common volume — 13.7 cc c) — 5.7 cc d)

encompassing volume — 52.8 cc c) — 22.5 cc d)

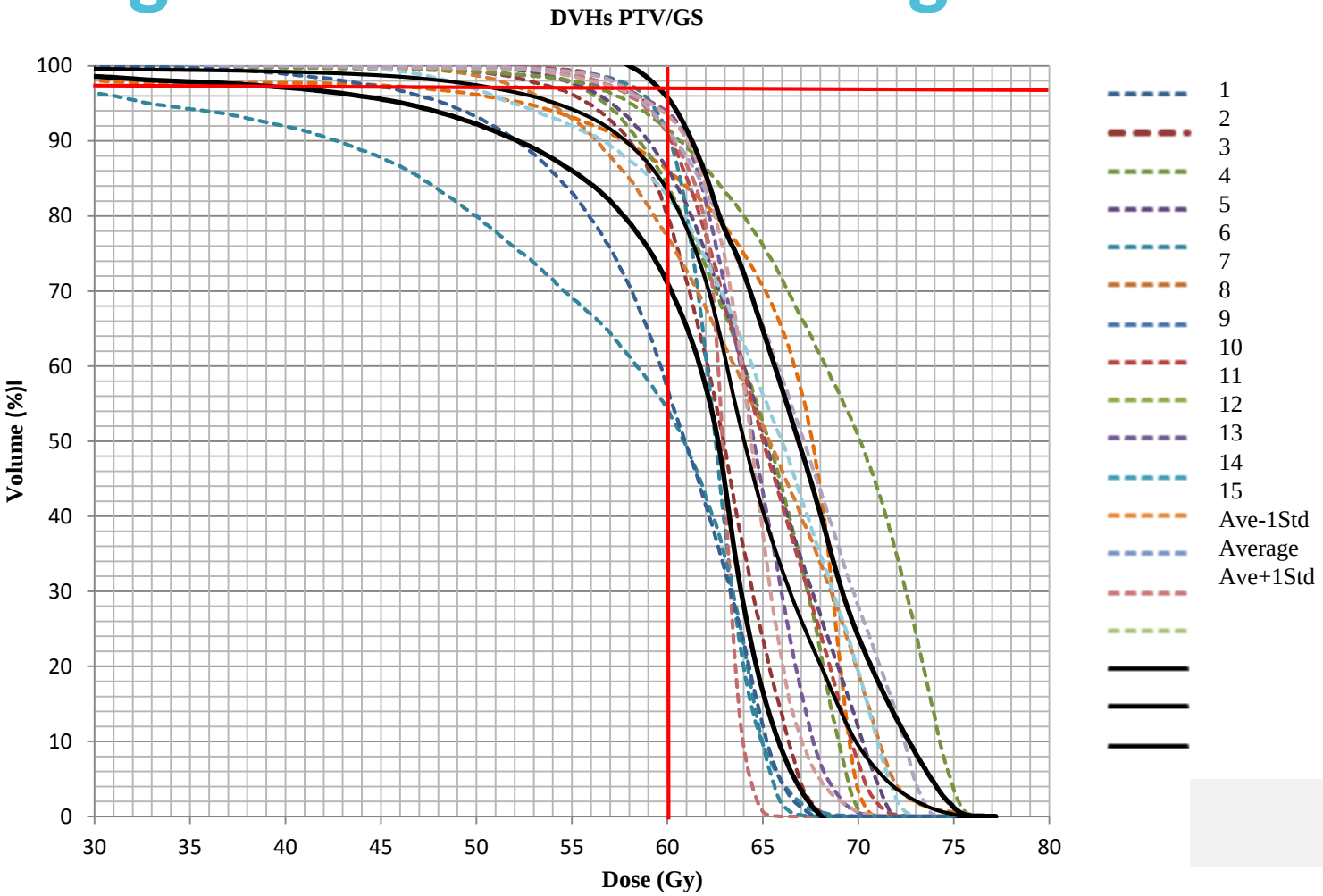
Brachial Plexus

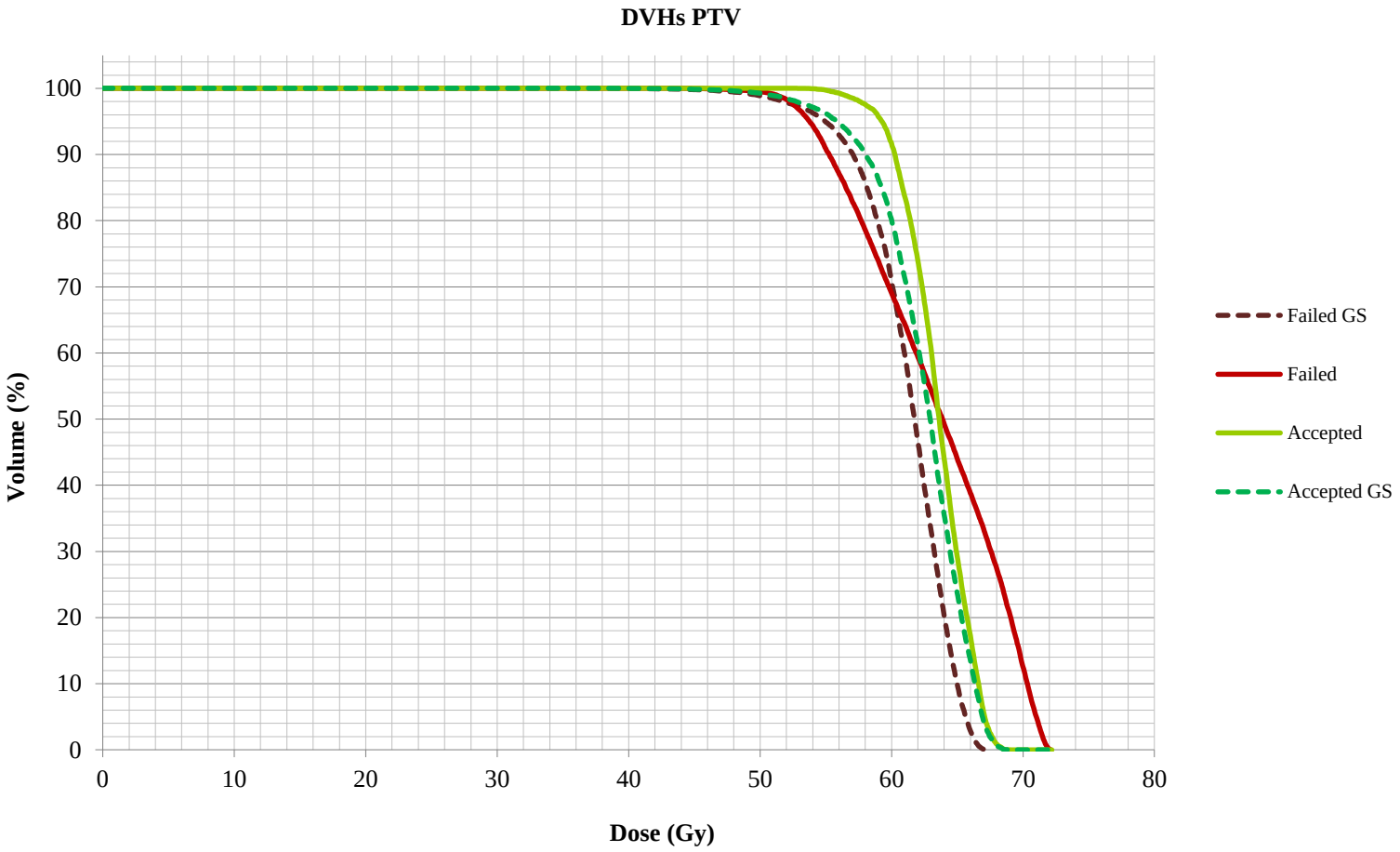


Lungtech approved benchmarks



Lungtech benchmarks on gold standard




DVHs PTV
Volume (%)
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
Dose (Gy)
Failed GS
Failed
Accepted
Accepted GS

Aknowledgement

Catharina hospital

- Coen Hurkmans

The Netherlands Cancer Institute

- Jan-Jacob sonke
- Marcel Verheij

The EORTC

- Coreen Corning
- Enrico Clementel

All the visited centres

Thank you for your attention !

SBRT, CZE experience

Coen Hurkmans, Ph.D., clinical physicist

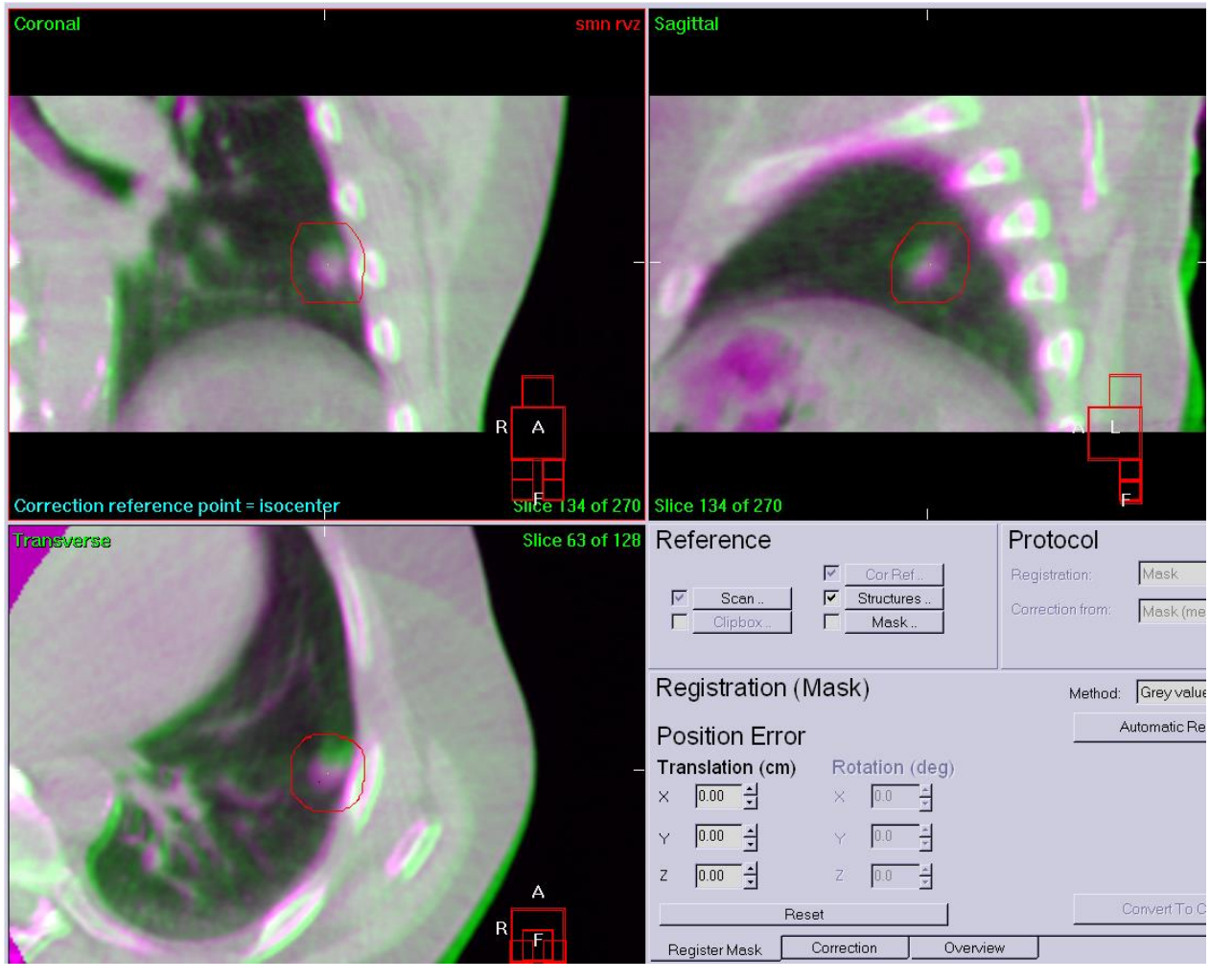
Catharina Hospital, The Netherlands

catharina hospital

Content

- Lung Intrafraction motion
- CVDR
- Online 4D CBCT
- CZE results on set-up and dose verification
- Lungtech trial guidelines
- Brainmets trial guidelines
- Brainmets guidelines

Clinical casus: intra-fraction motion



Fraction 1
unmatched

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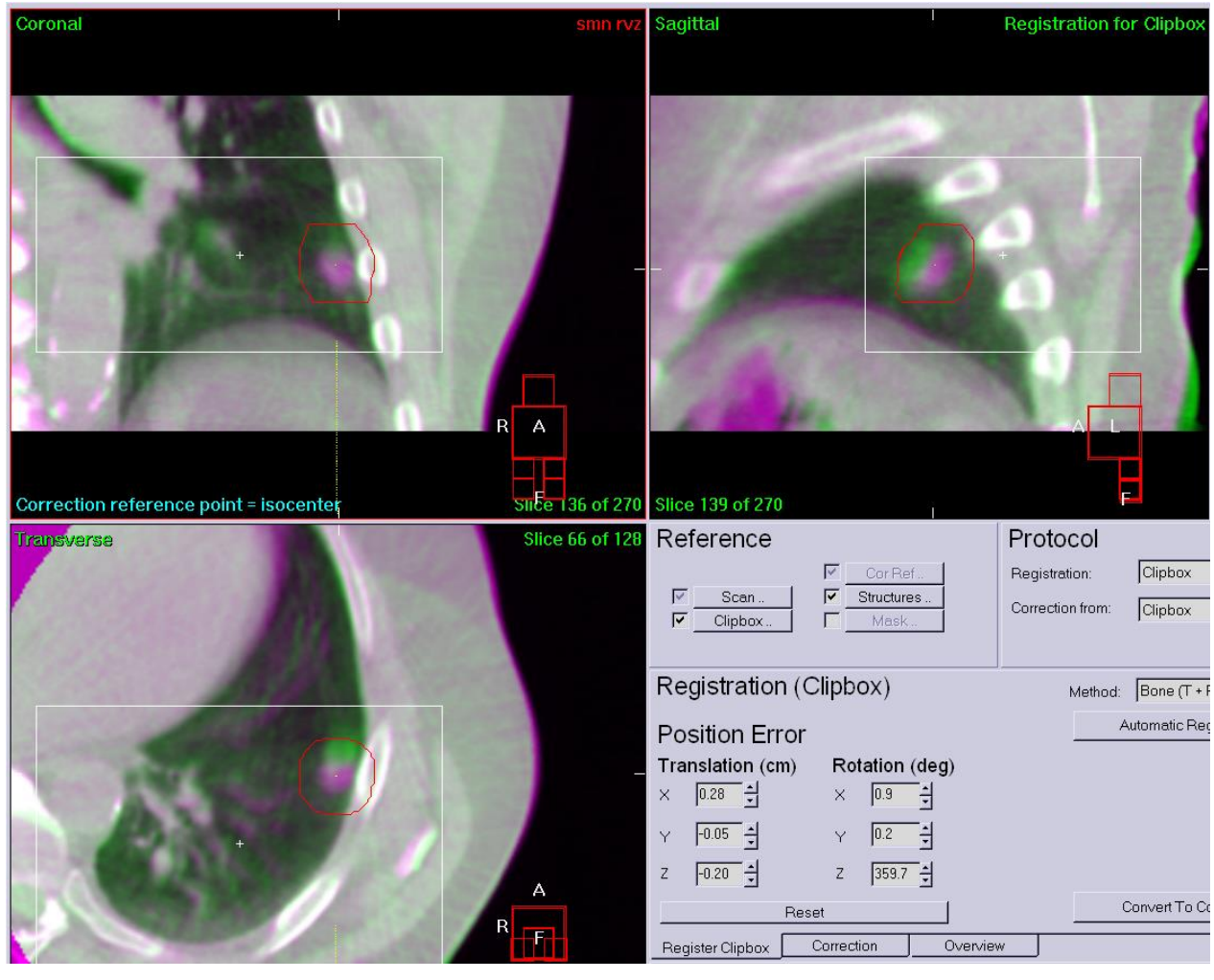

Fraction 1
bone match

X= 0.28

Y=-0.05

Z=-0.20

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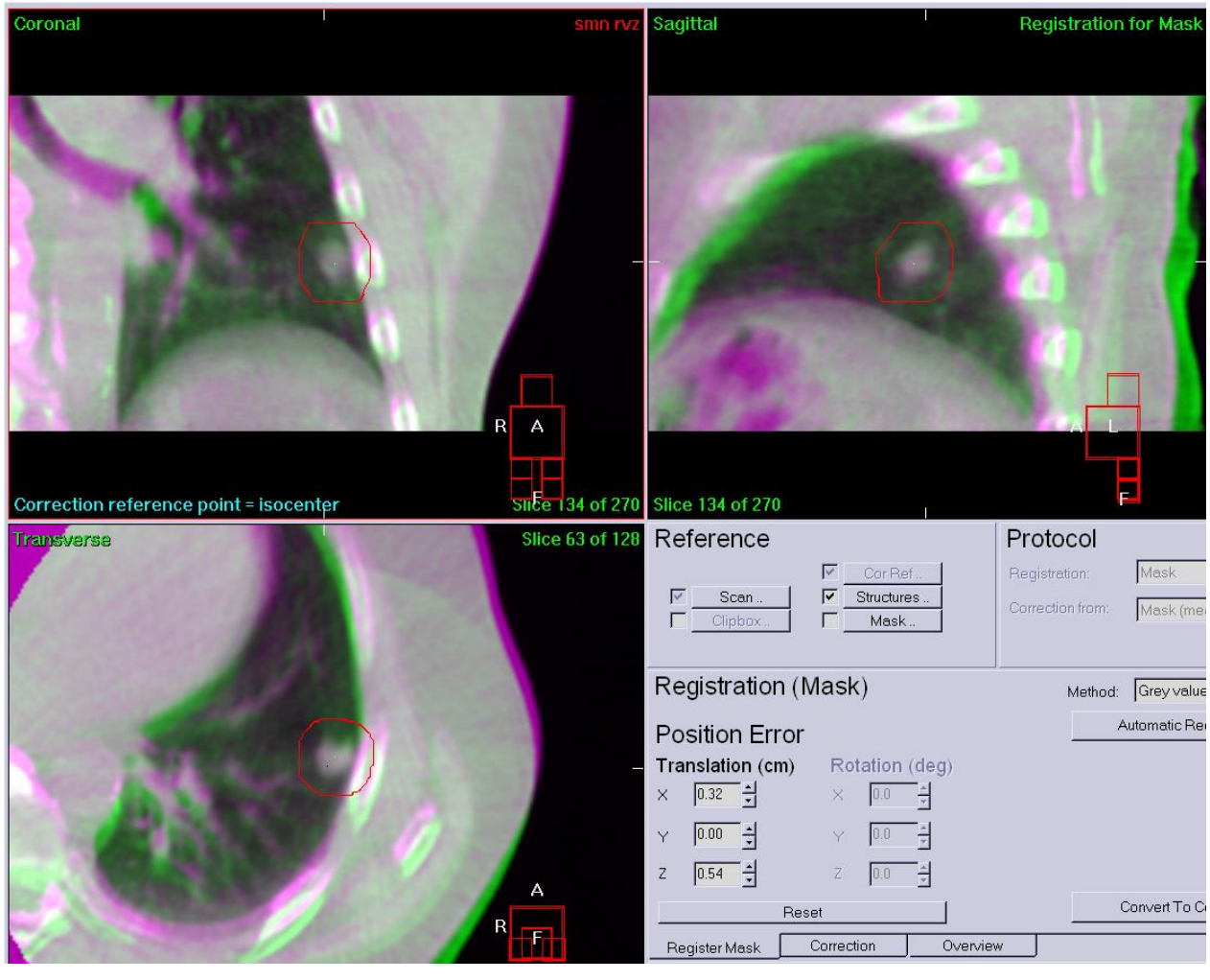
hospital



Fraction 1 tumormatch

X= 0.32 (0.28)

Y=0.00 (-0.05)

Z=0.54 (-0.20)

Tumor shift of >7 mm!

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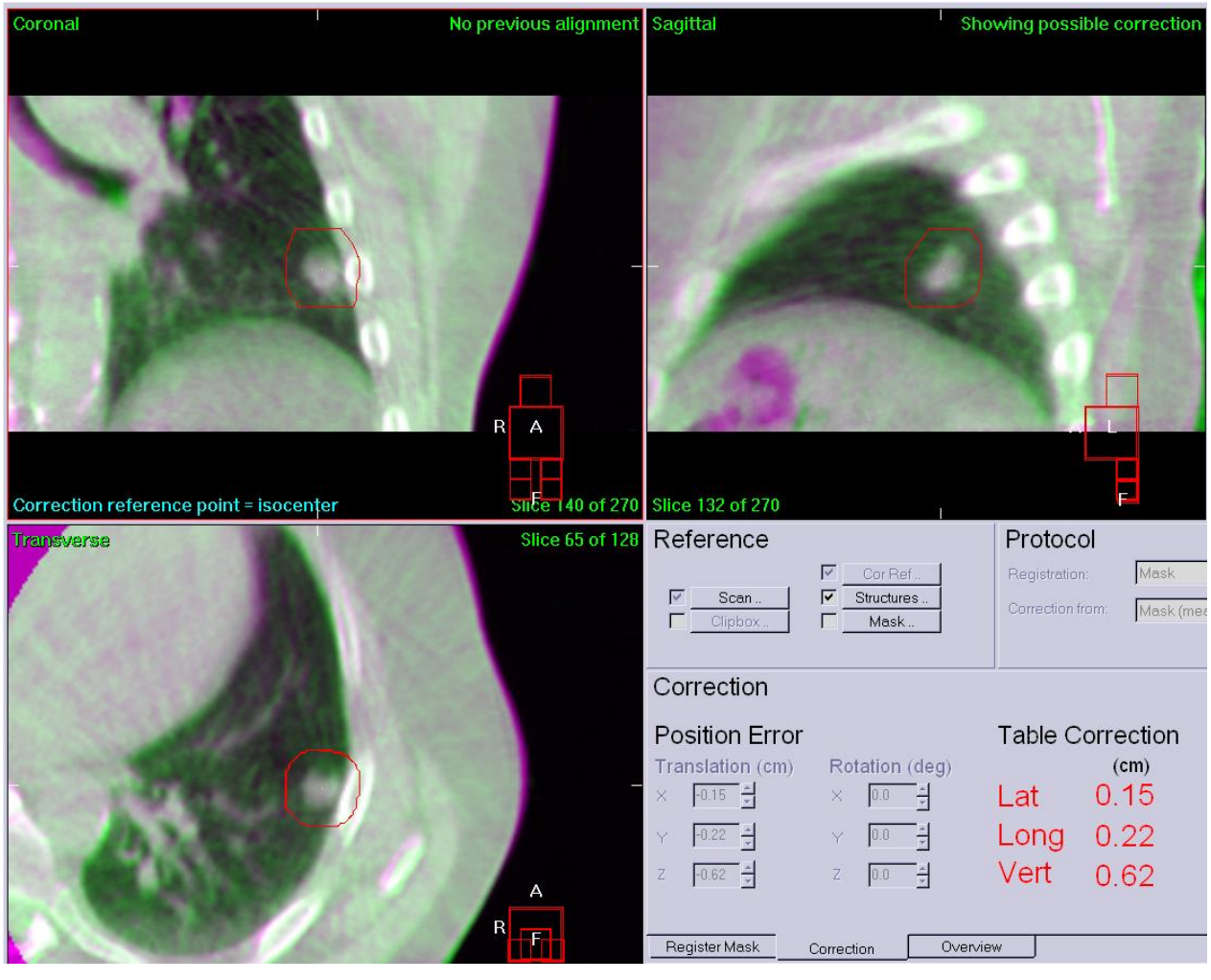

After Fraction 1 tumormatch

X=0.15

Y=0.22

Z=0.62

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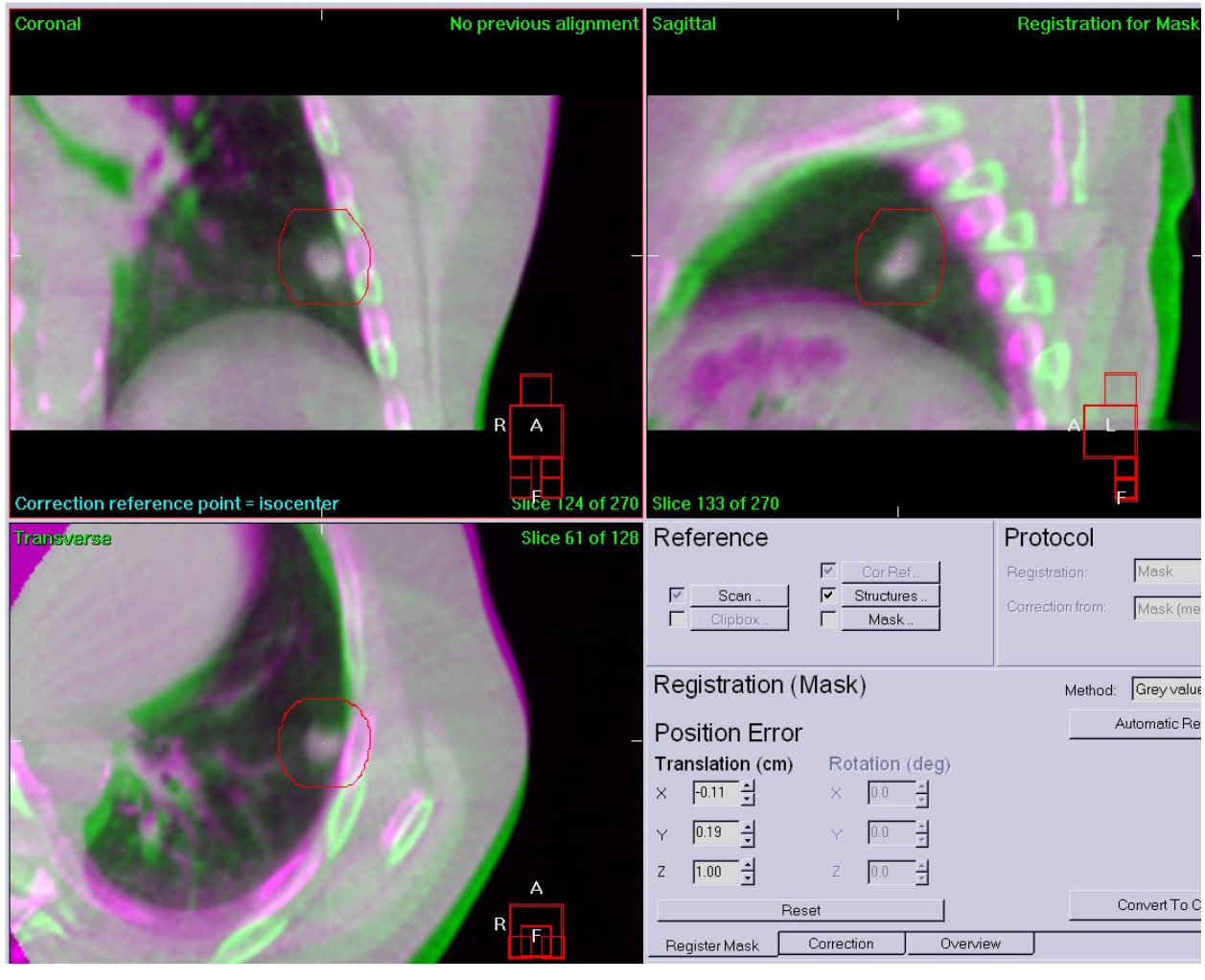

Fraction 3
tumormatch

X=-0.11

Y=0.19

Z=1.00

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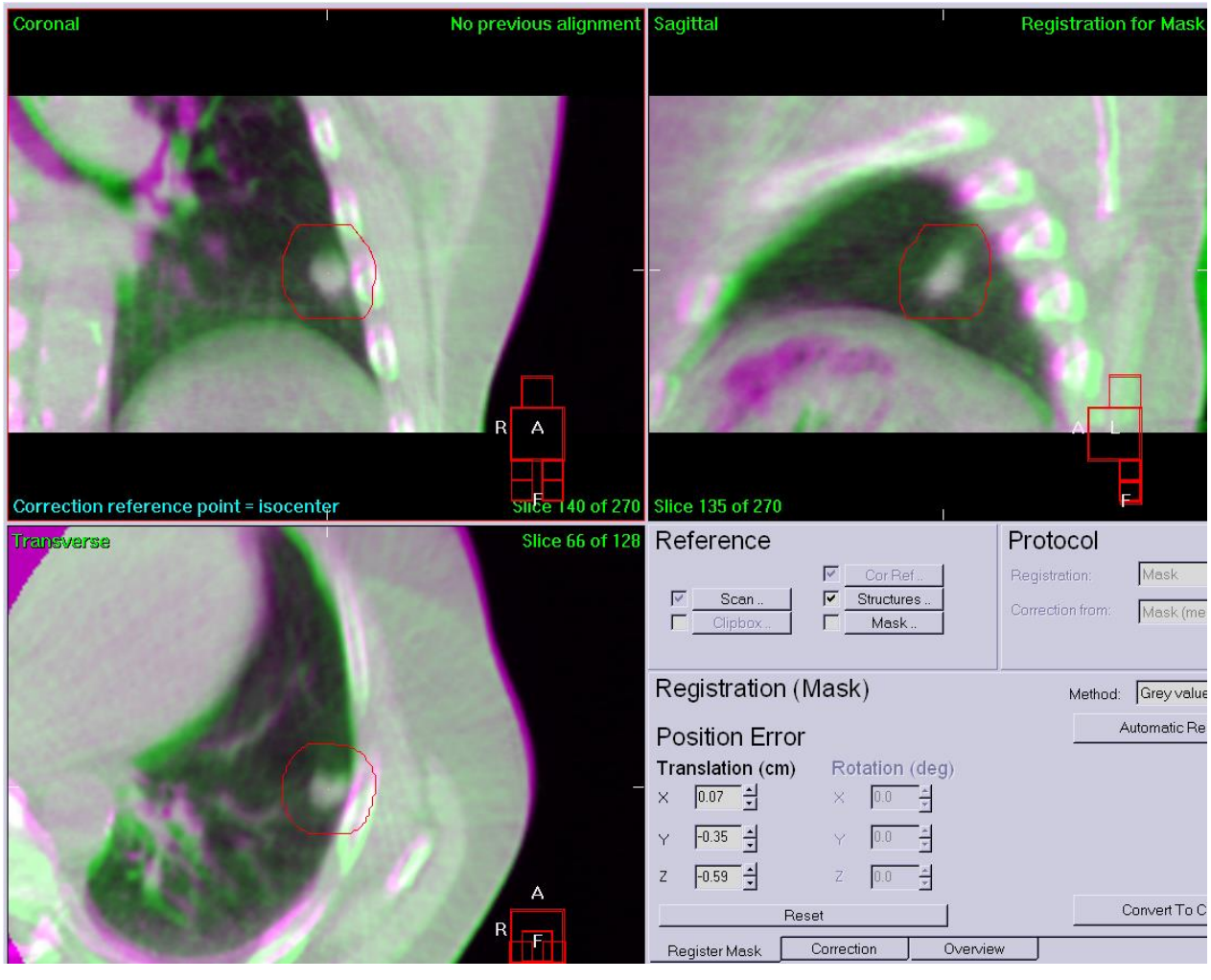
hospital



Fraction 3 after 1 arc tumormatch

X=0.07

Y=-0.35

Z=-0.59

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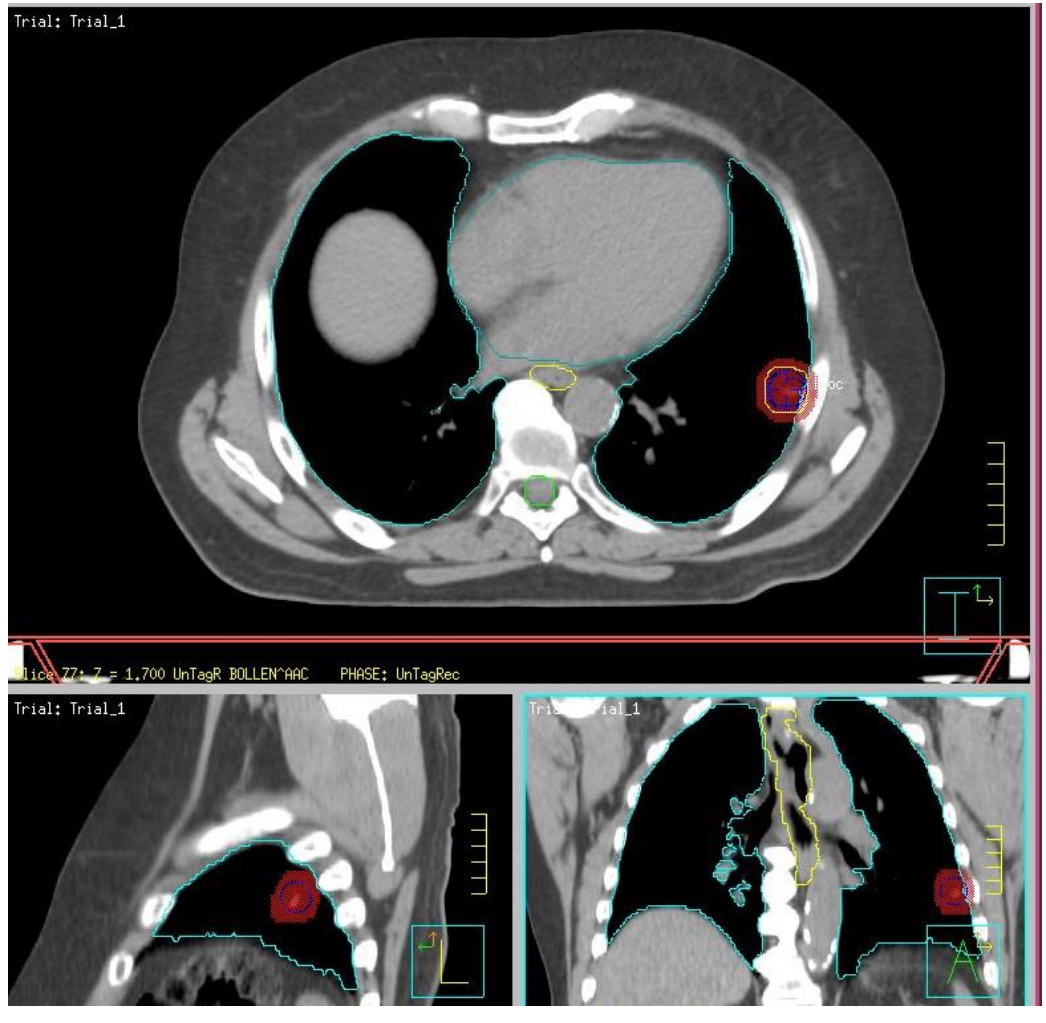

Original plan
5 x 11 Gy

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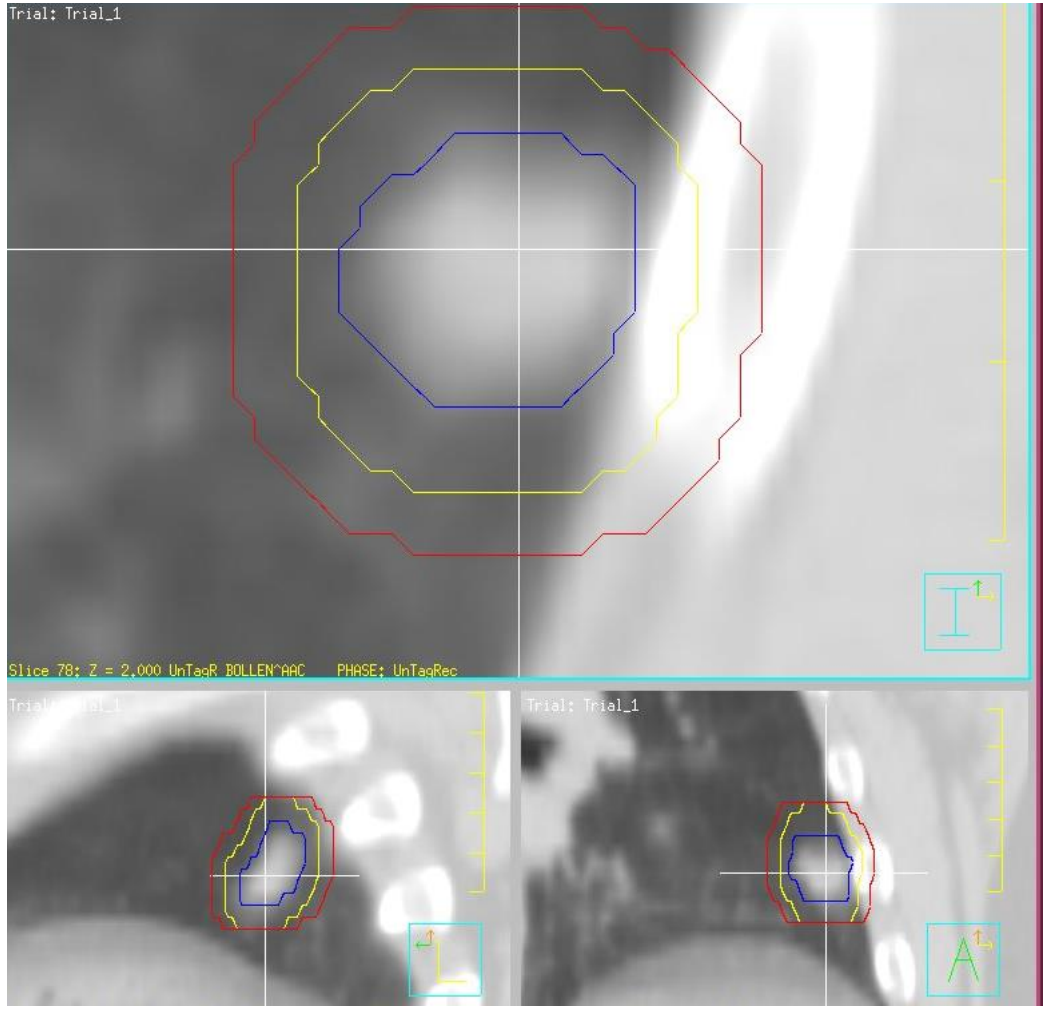
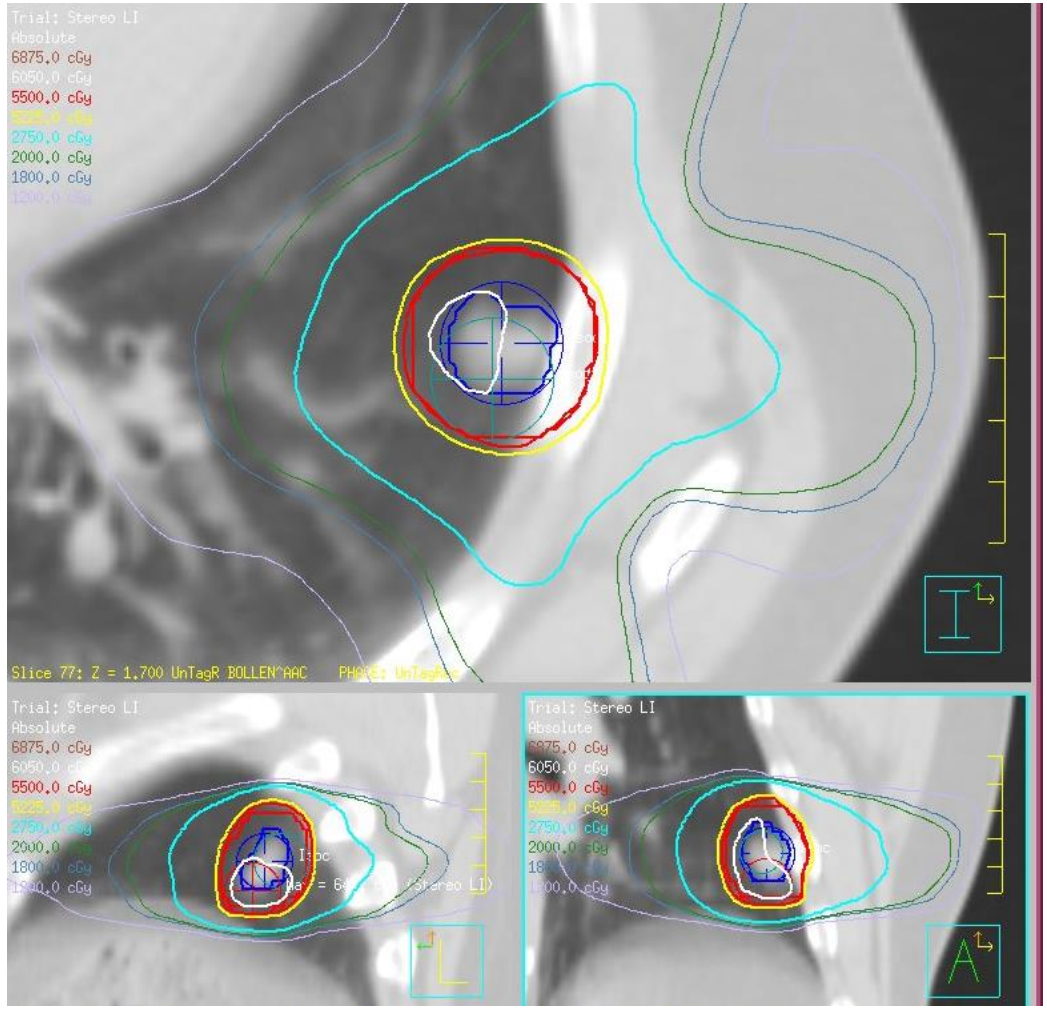


Original plan
5 x 11 Gy

catharina hospital

Original plan



Original plan
5 x 11 Gy

PTV

V100% = 97.8%

Thorax

V37Gy = 16.8cc

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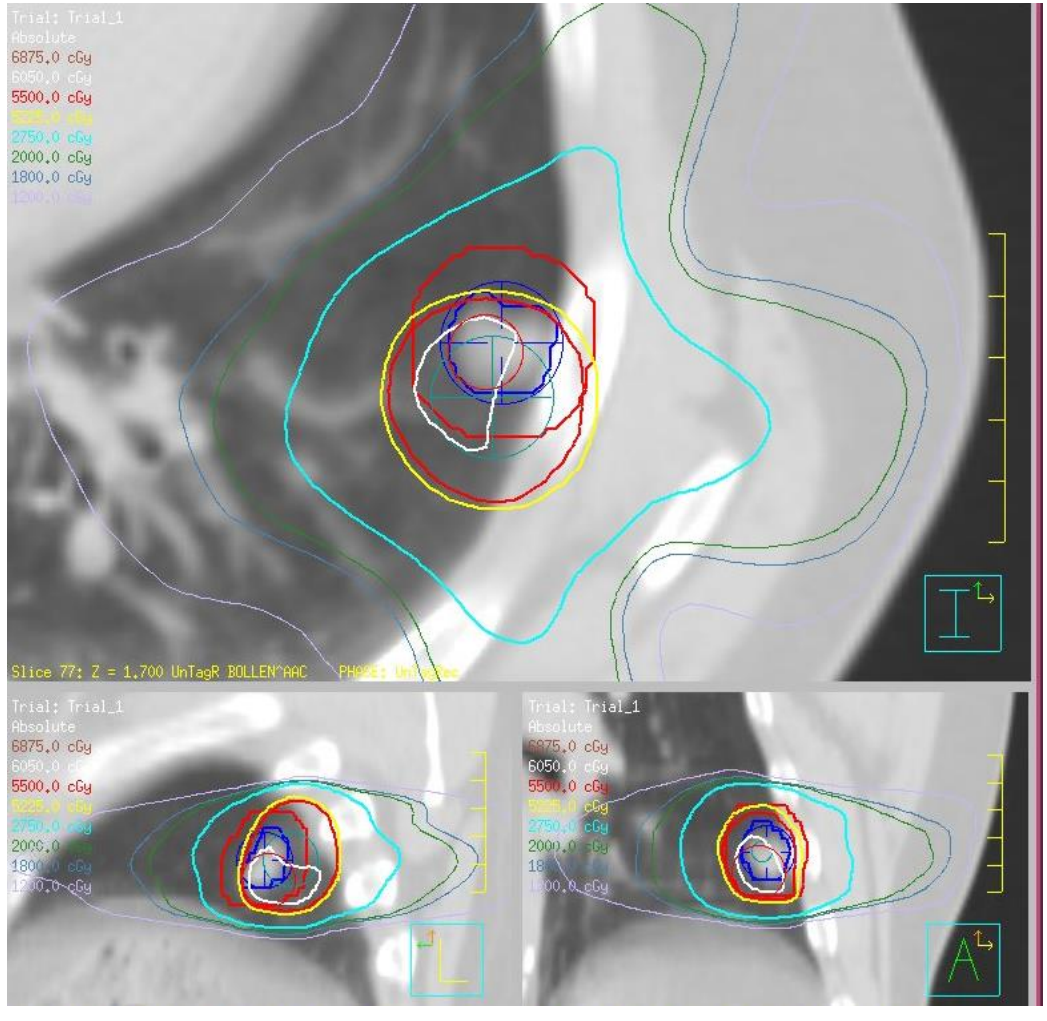
Original plan with shift



isoc shifted by

X= 1.6 mm medial

Y= 8.6 mm posterior

Z= 0.7 mm cranial

PTV

V100% = 64.8%

ITV

V100% = 79.6%

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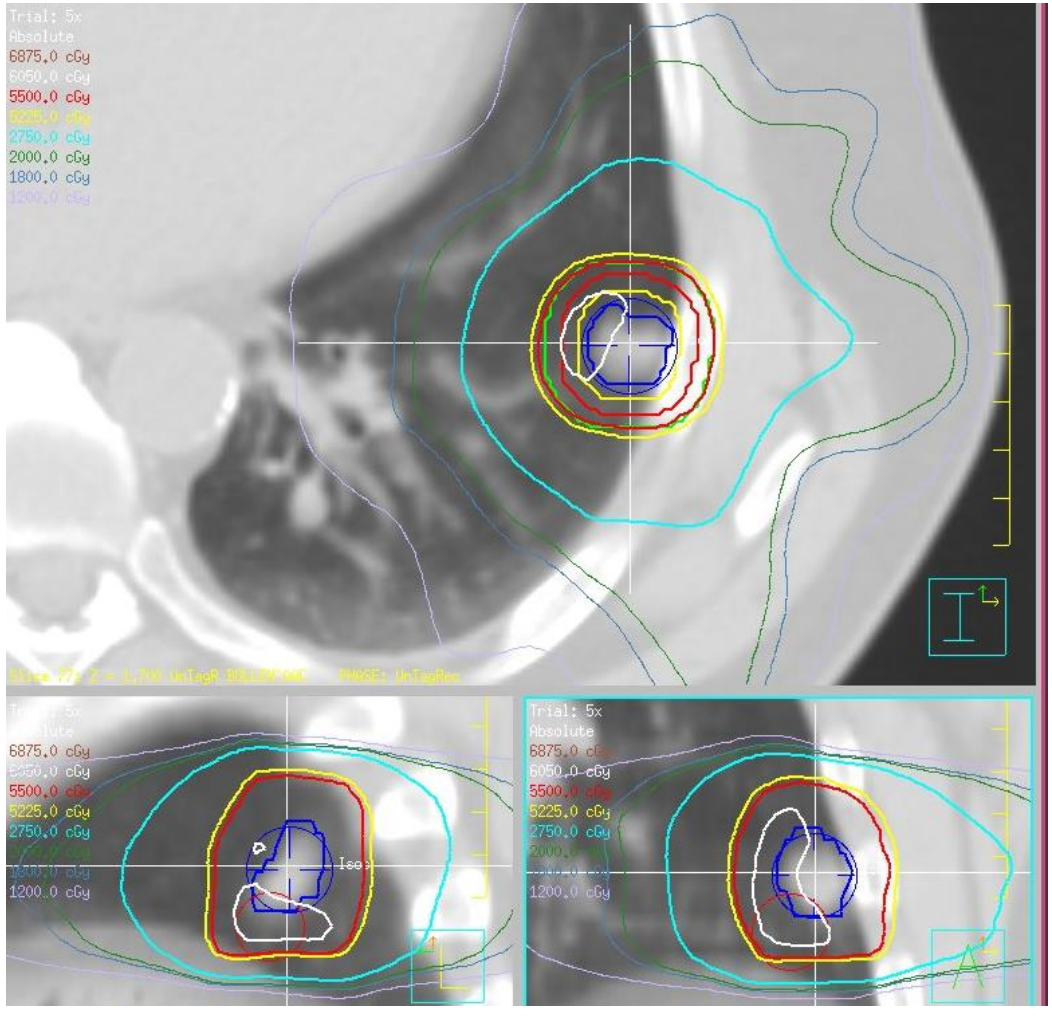
New plan with 3mm extra margin



PTVnew

V100% = 97.2%

PTV

V100% = 100%

Thorax

V37Gy = 26.8cc

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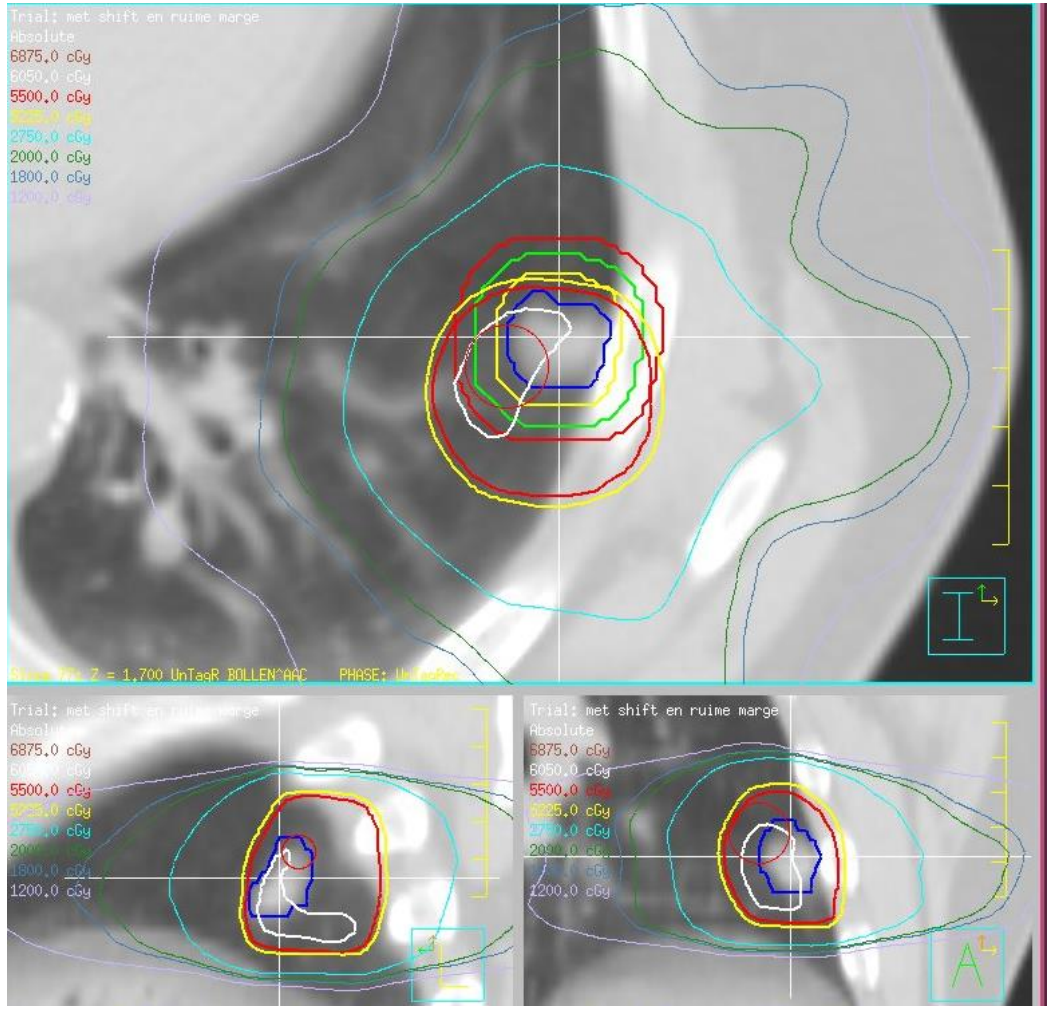
New plan with shift: robust?



Plan with 3 mm extra margin

and shift

PTV

V100% = 79.4%

V95% = 87.3%

ITV

V100% = 93.5%

V95%=98.1%

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Vmat CVDR option

- Improvement of gantry stability
- Possible improvement of dose accuracy
- Possibly less wear of gantry

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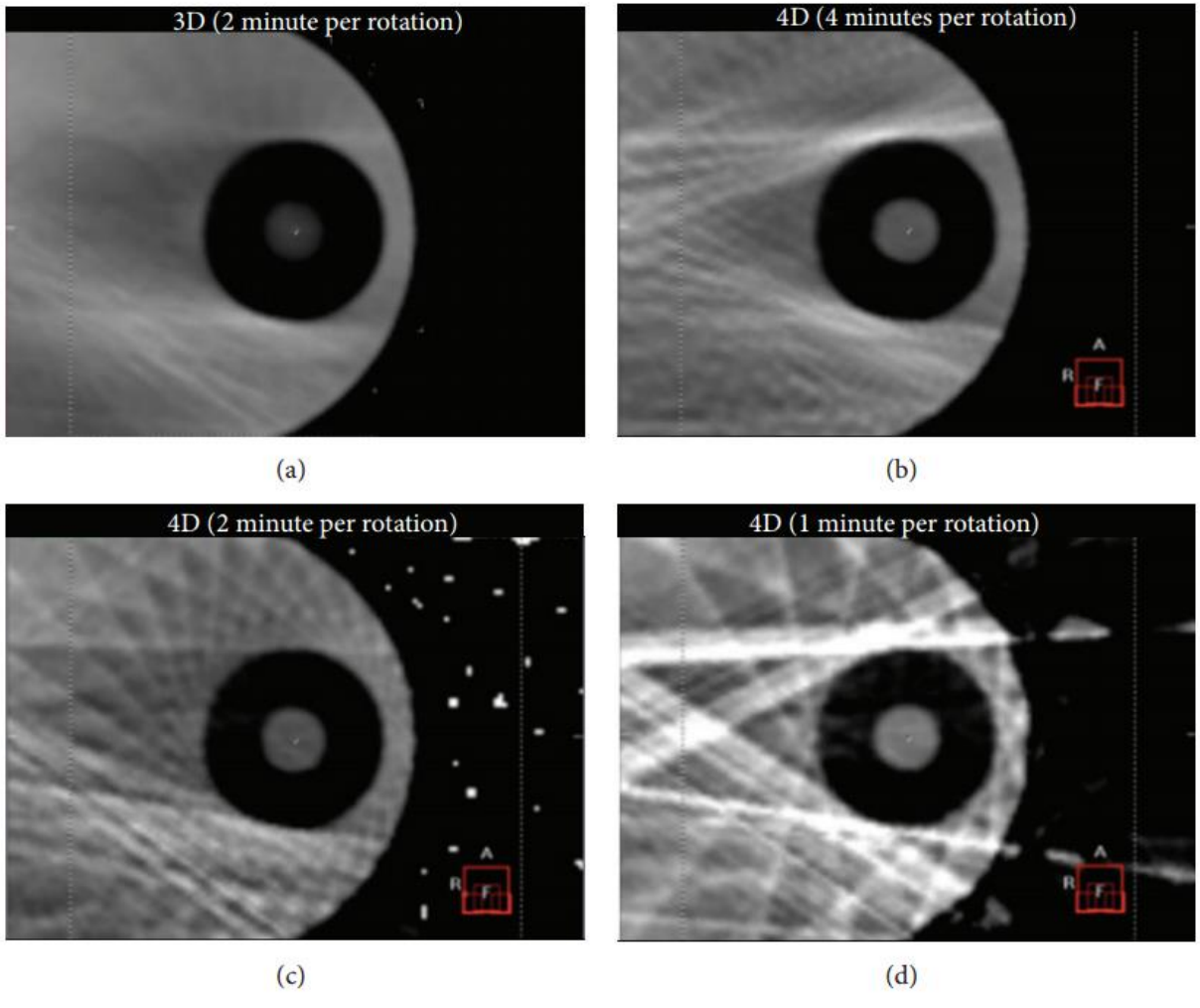
Online 4D CBCT



nages (axial view) for a moving phantom (QUASAR; Modus Medical Devices, Inc.): (a) 3D (2 minute rotation), (c) 4D (2 minutes per rotation), and (d) 4D (1 minute per rotation) images.

Yamashita BioMed Res Int 2014 article ID 136513

20 mA/frame and

40ms/frame

The CT dose index (CTDI) is approximately 12 mGy for 4D

CBCT imaging with 4 minutes per rotation

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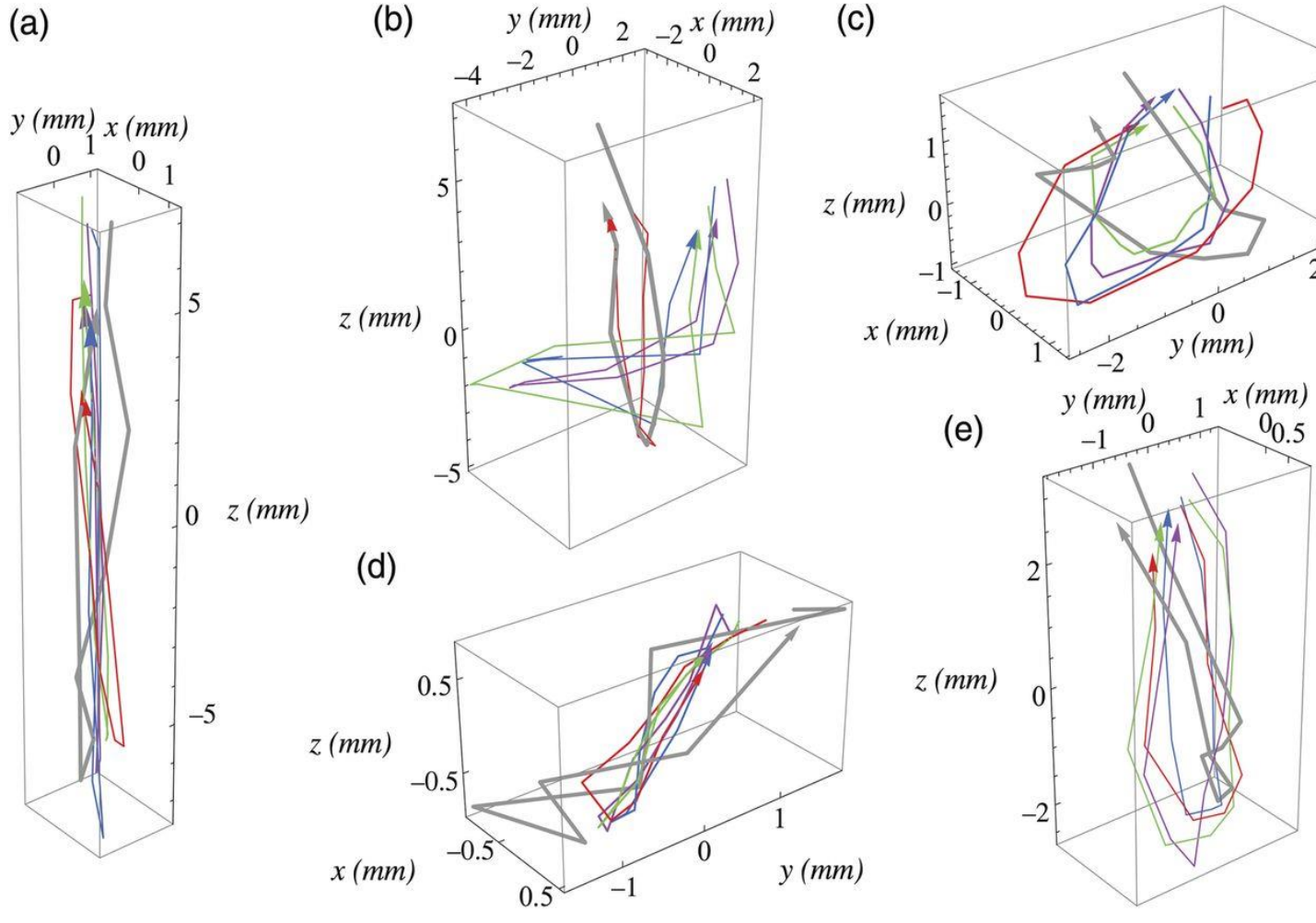
Online 4D CBCT

3D lung tumour trajectories during the planning time (in gray) and pre-treatment times in the four fractions (in red, green, blue and violet) for the five patients.



Nakagawa K et al. J Radiat Res 2014;jrr.rru055

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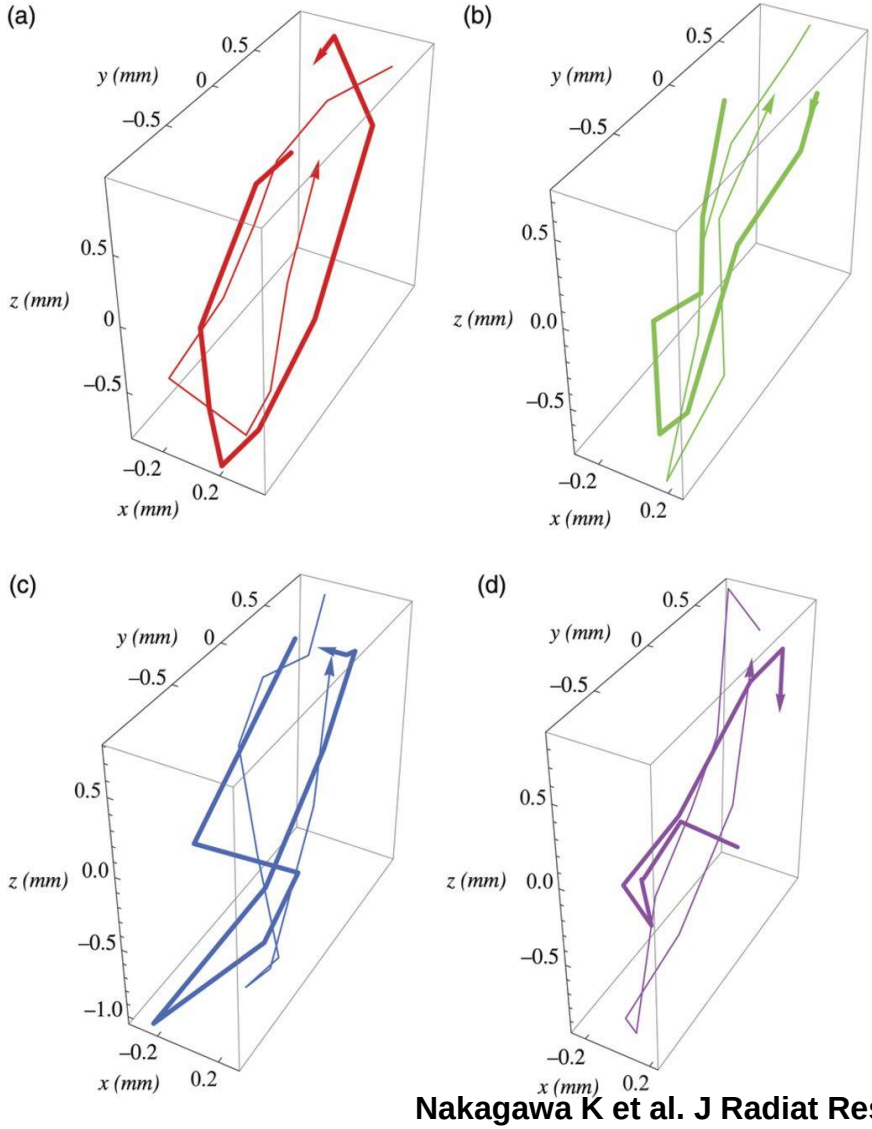
Online 4D CBCT



3D lung tumor trajectories obtained by pre-treatment 4D CBCT (thin line) and those obtained by in-treatment 4D CBCT (thick line), fraction by fraction, for a patient.

Nakagawa K et al. J Radiat Res 2014;jrr.rru055

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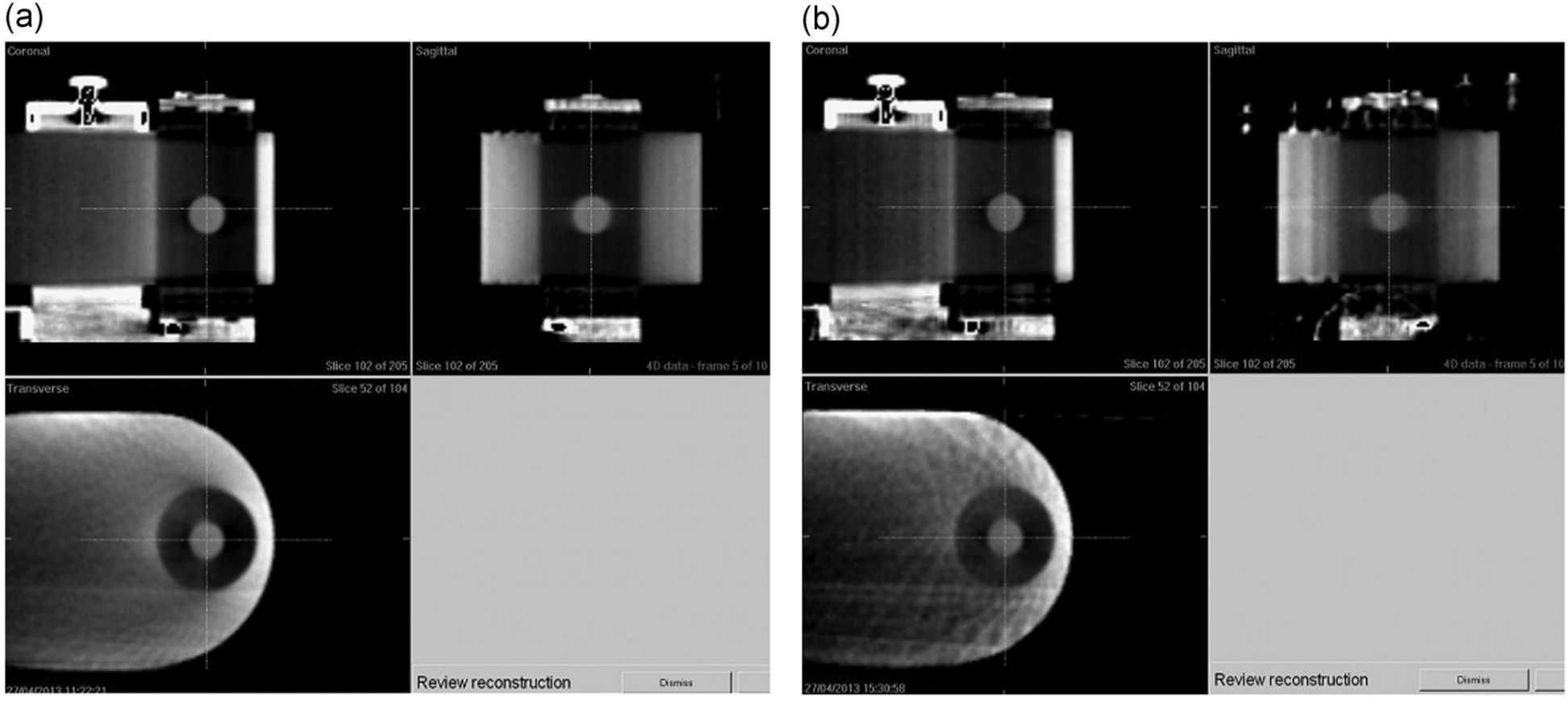
Online 4D CBCT

A comparison of inhalation-phase images of concurrent 4D CBCT during VMAT delivery with (a) FF and (b) FFF.



projection images 1104 (range, 1093–1116) for FF and 490 (range, 481–500) for FFF

12.5 Gy in partial arc, 1 cm amplitude, 3 sec period

12.5 Gy from 200 sec FF to 90 sec FFF with 6 MV Elekta and no concurrent CBCT

Nakagawa K et al. J Radiat Res 2014;55:200-202

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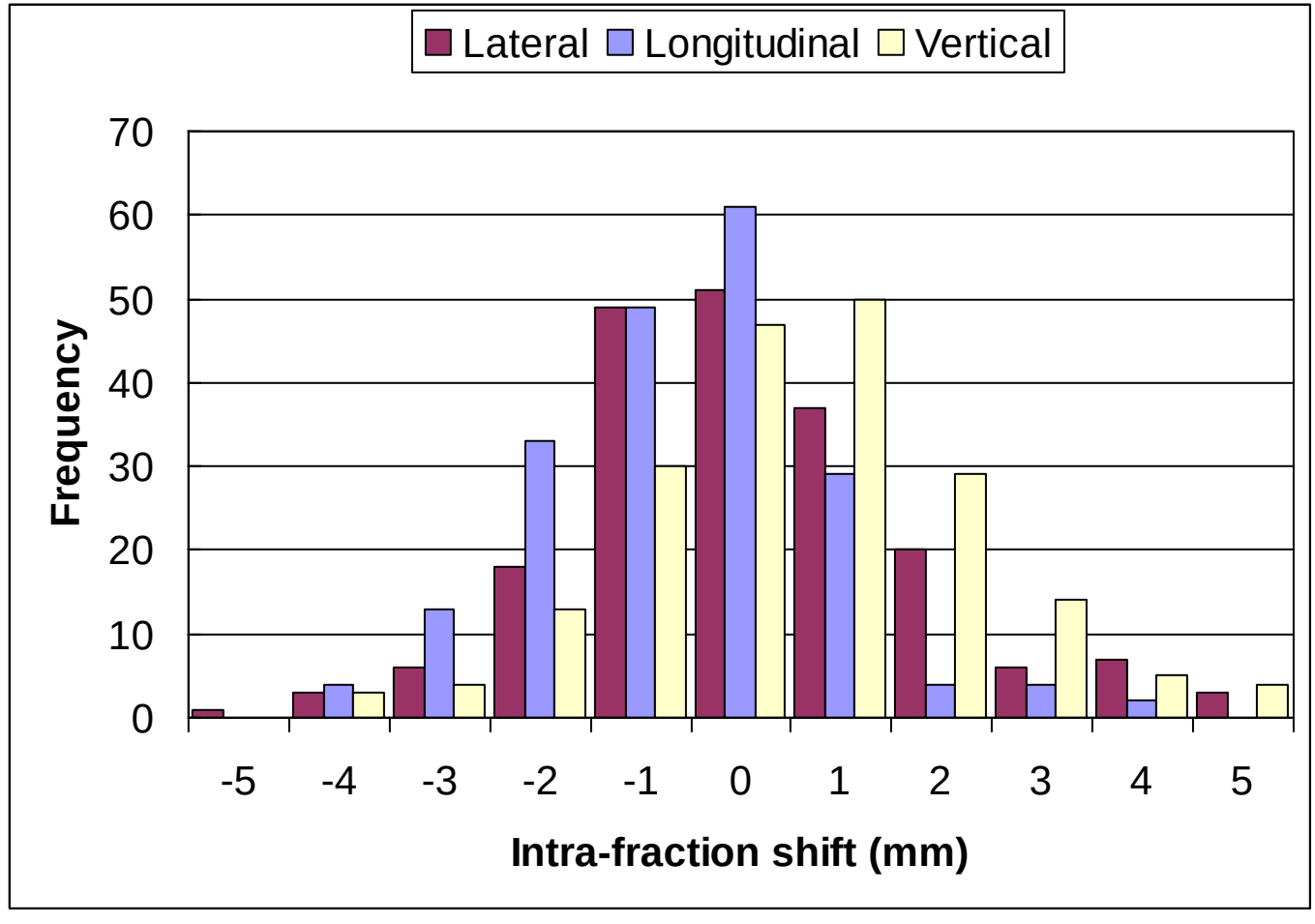
Journal of Radiation Research

Intra fraction stability CZE



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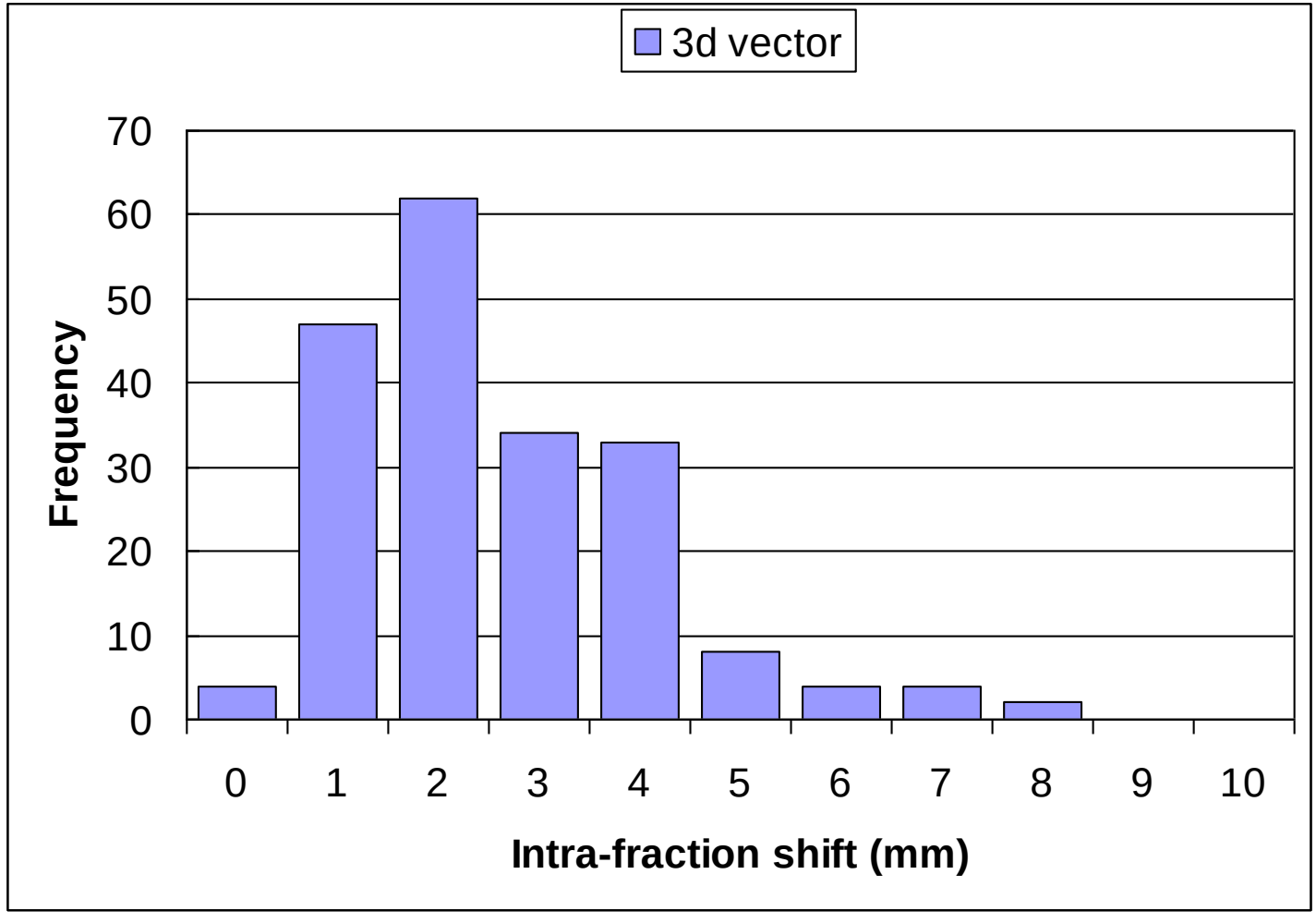
Intra fraction stability CZE



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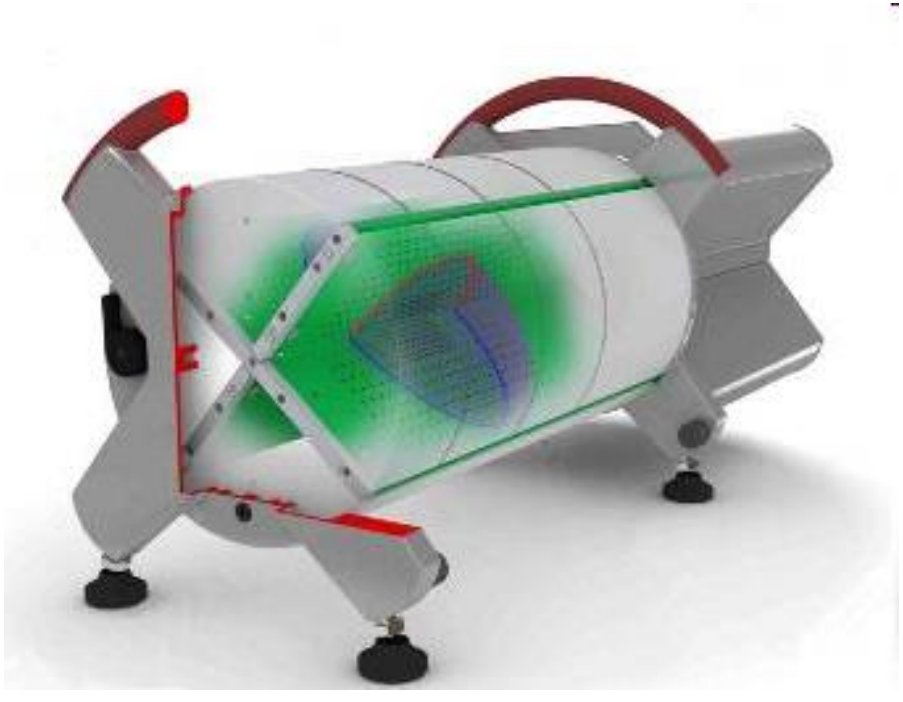
Patient specific dosimetry CZE



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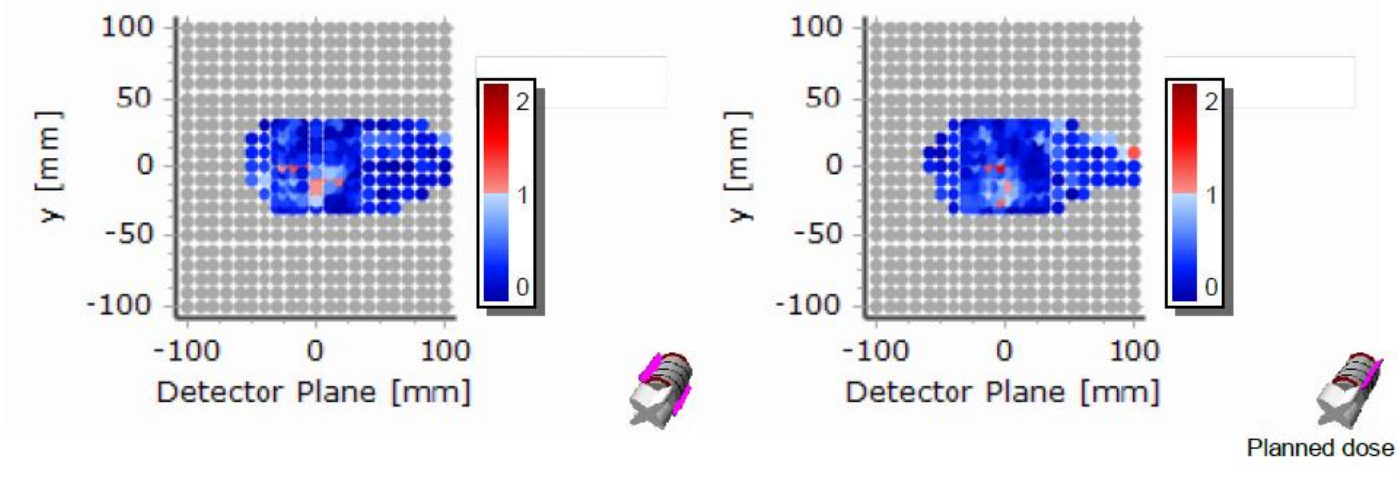
Gamma analysis

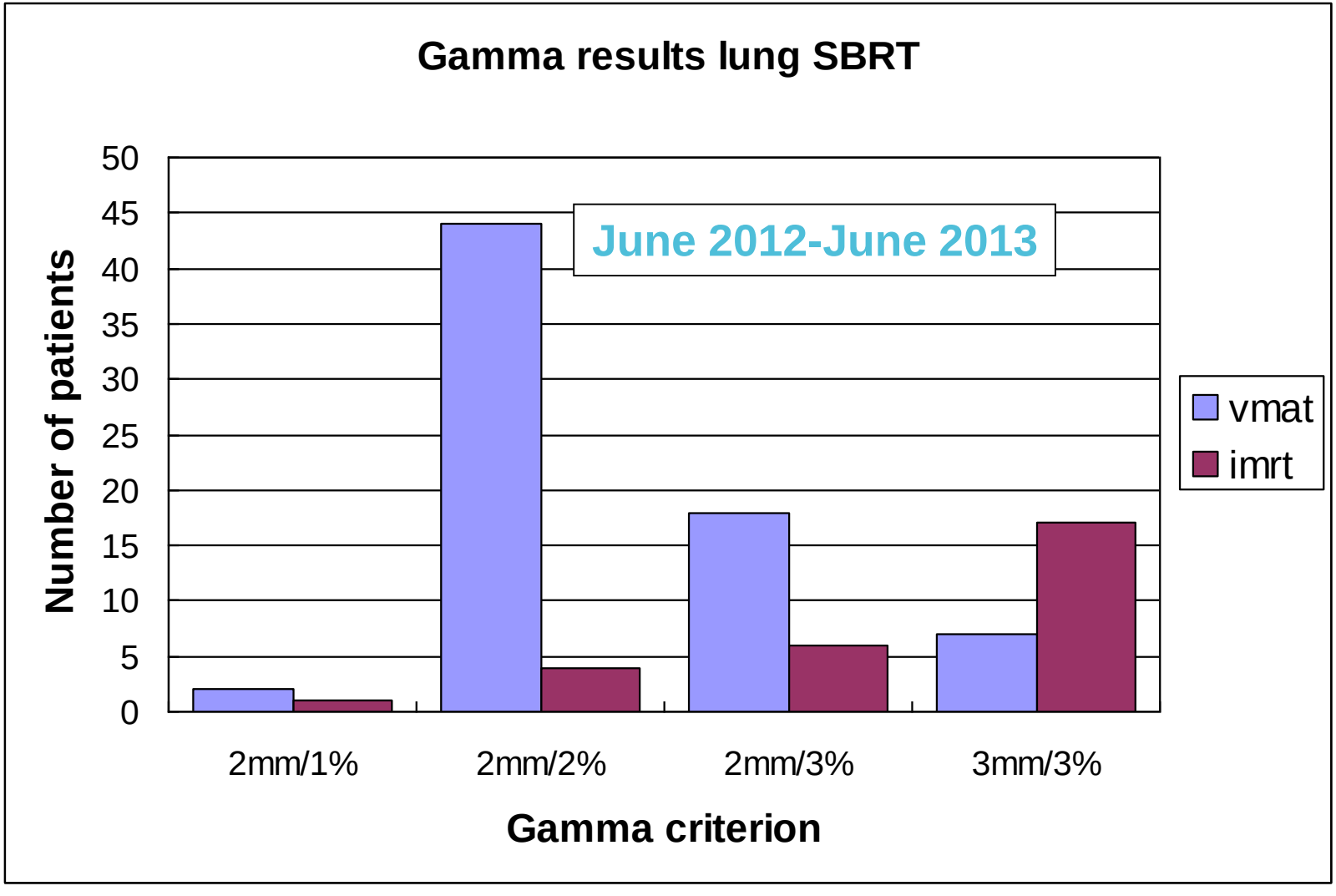
Parameter Definitions & Acceptance Criteria, Detectors

Parameter	Selected Detectors	Δ Dose	Δ Dist	Acceptance Limits
Dose Deviation	Dose from 20% to 500%	n.a.	n.a.	90% within ±3.0%
Dist to Agreement	Gradient >= 1%/mm	n.a.	n.a.	90% with DTA <= 2.0 mm
Gamma Index	Dose from 20% to 500%	±3.0%	2.0 mm	95% with gamma < 1

Gamma index, Fraction



Gamma results



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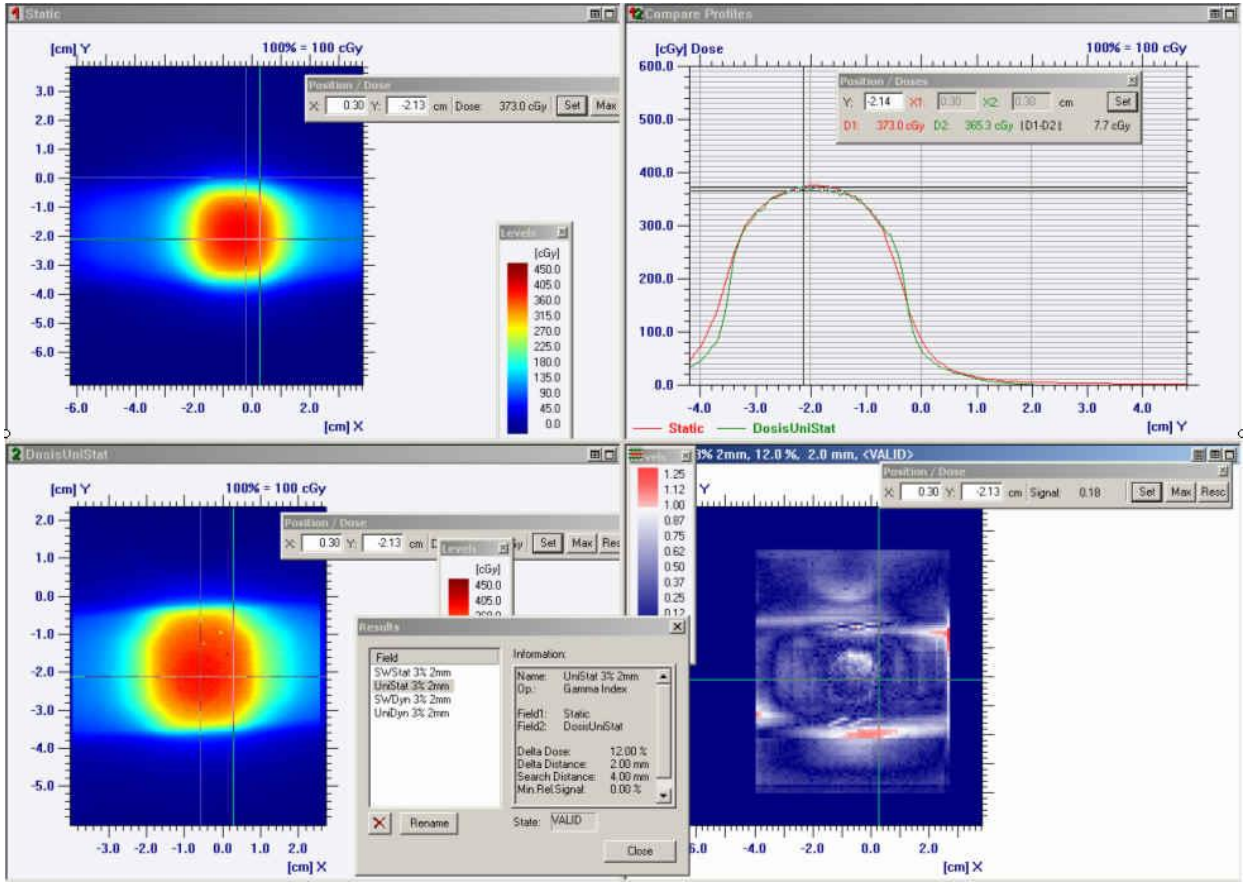
4D Dosimetry QA

Dosimetric audit in a multicentre phase III trial of surgery versus stereotactic radiotherapy (SBRT) for lung cancer.

J.P. Cuijpers, K.H. Spruijt, M.J.T. van Heumen, S. Senan, C.W. Hurkmans.



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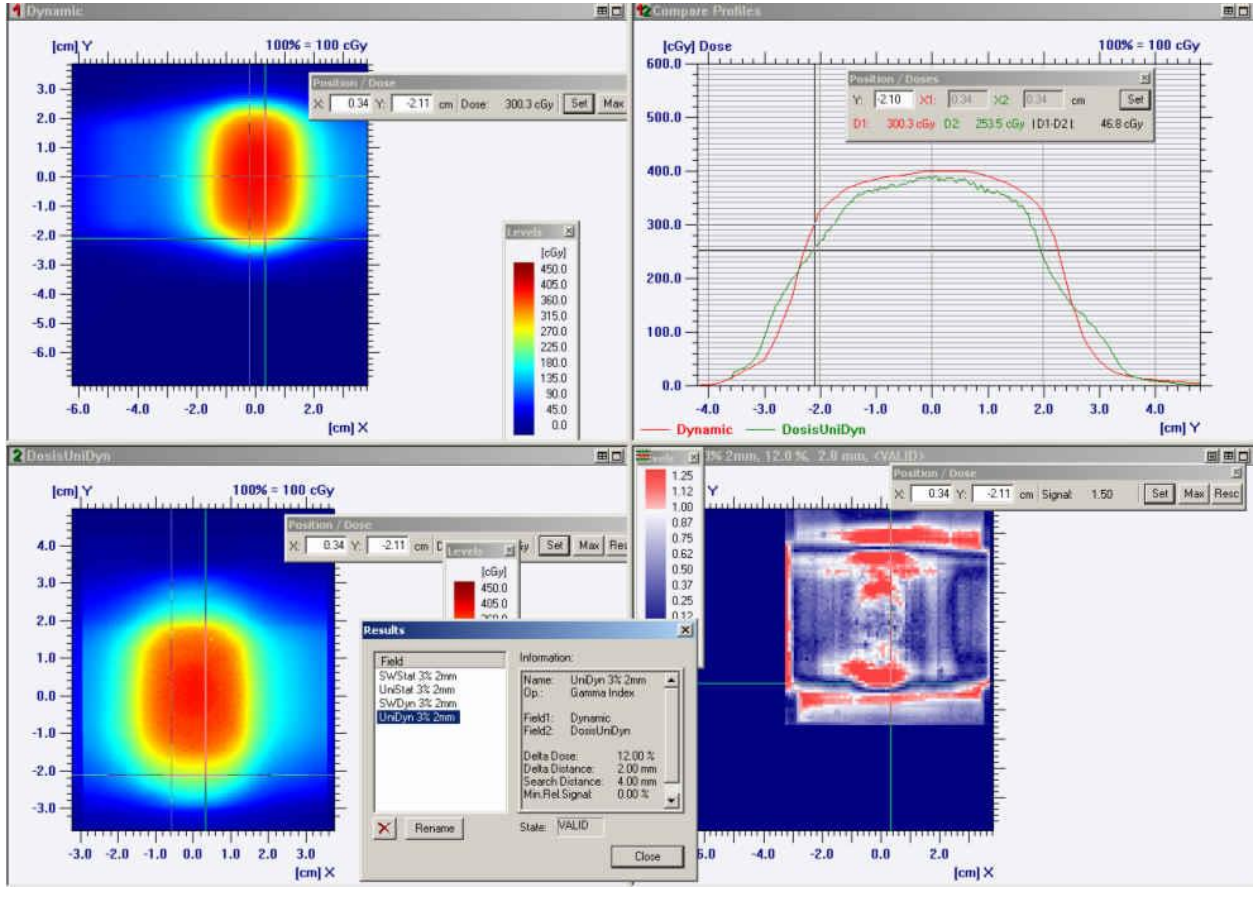
4D Dosimetry QA

In the direction of motion, the width of the 80% isodose was much wider than the calculated width, indicating that a reduction in planned field size should be possible for moving targets, especially when plans are based on the ITV concept.



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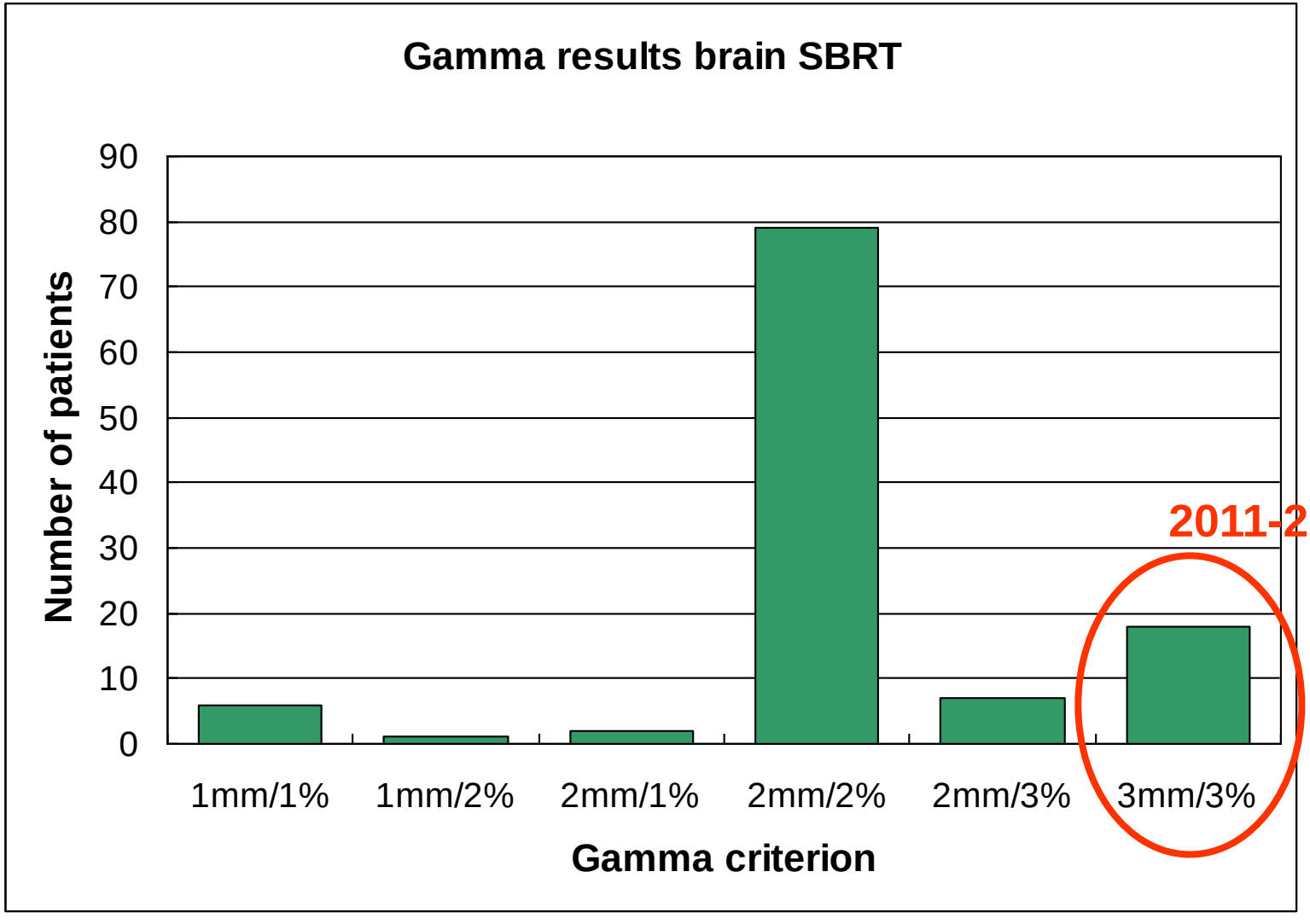
Gamma results brain VMAT



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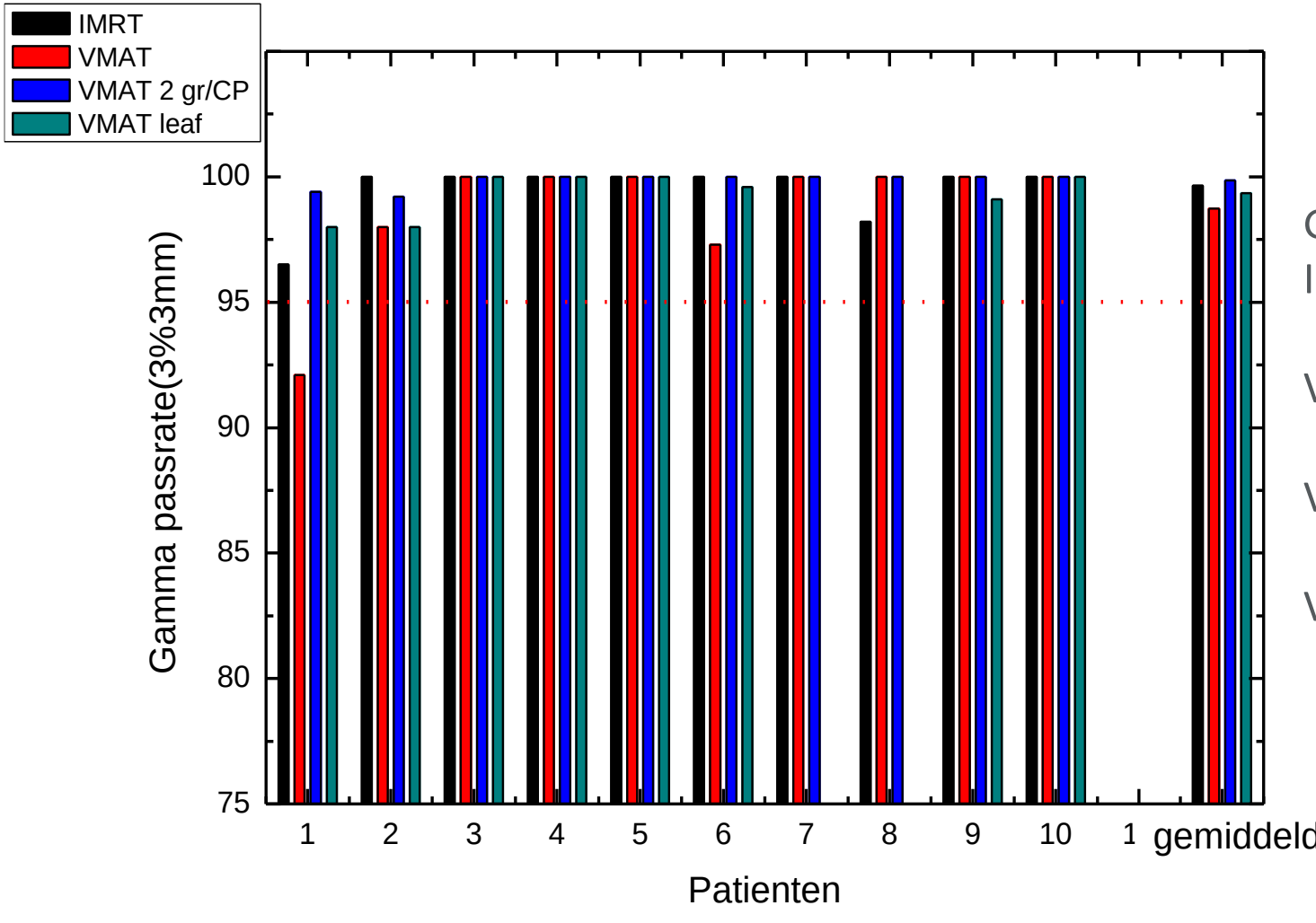
QA VMAT – 3% 3mm



Gemiddeld:

IMRT	99.65%
VMAT	98.74%
VMAT 2°/CP	99.86%
VMAT leaf	99.34%

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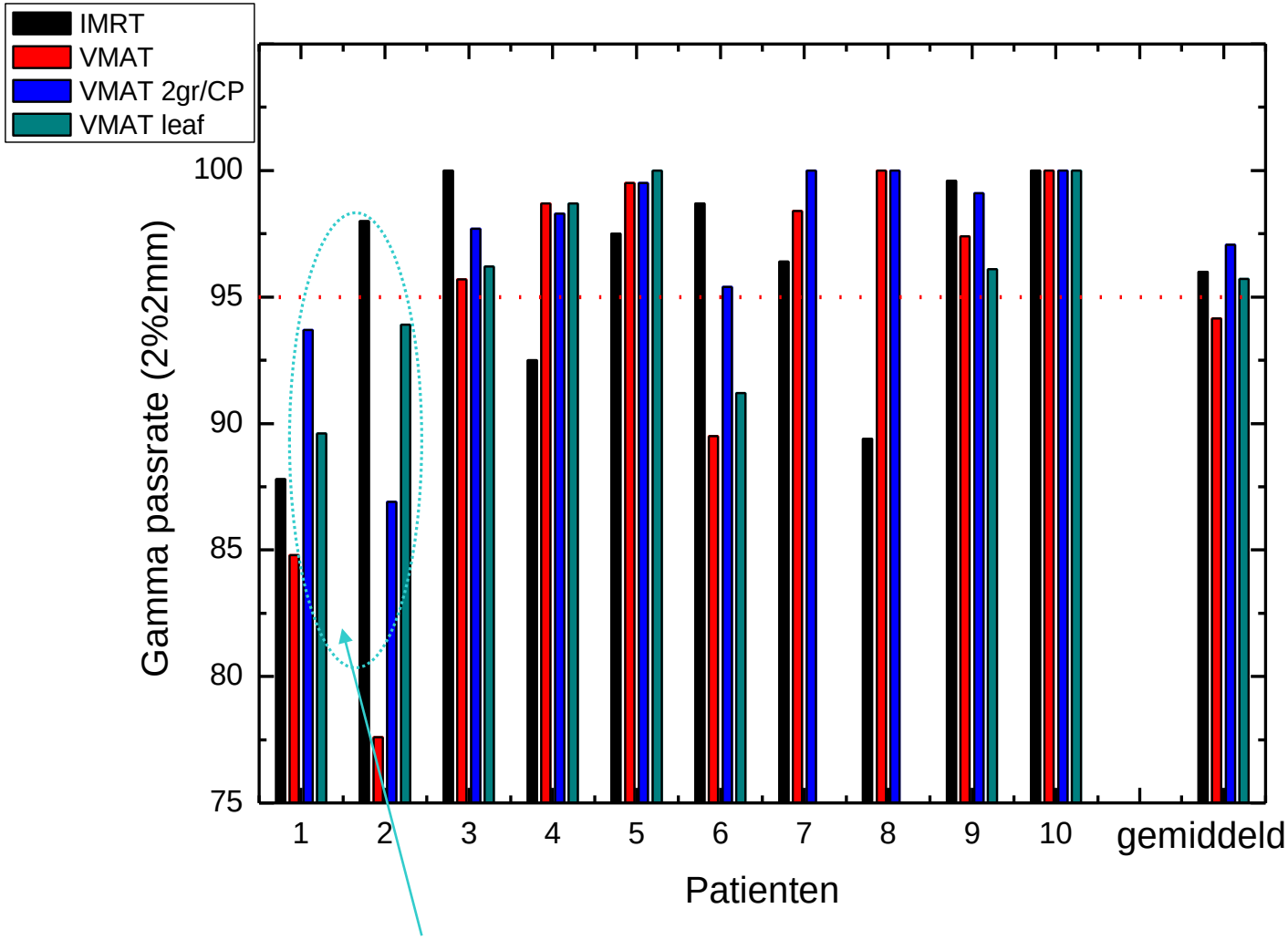
QA VMAT – 2% 2mm



- Gemiddeld:
- IMRT 95.99%
- VMAT 94.16%
- VMAT 2°/CP 97.06%
- VMAT leaf 95.71%

Met combinatie van 2°/CP en beperkte leaf beweging kom je boven 95%

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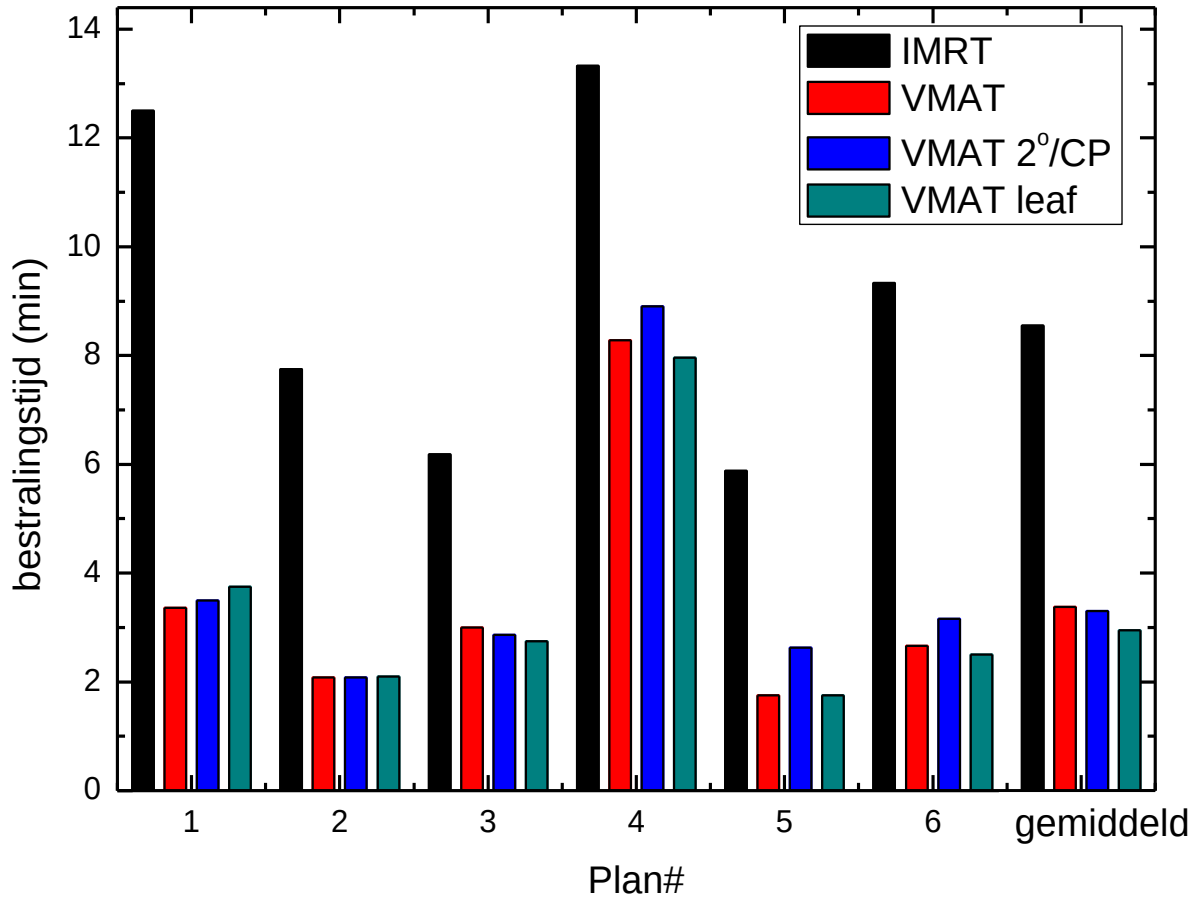
IMRT vs VMAT – irradiation time



- Average treatment time from 8’30” to 3’ (8 Gy/fraction)

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EORTC Lungtech protocol

	α/β	allowed maximum dose (0.5 cc)	EqD2 (Gy)	Volume constraints
Spinal cord	2	8*4 = 32 Gy	48	No constraints specified
Oesophagus	3	8*5 = 40 Gy	64	No constraints specified
Brachial plexus	3	8*4.75 = 38 Gy	58.9	No constraints specified
Proximal trachea	3	8*5.5 = 44 Gy	74.8	No constraints specified
Proximal bronchus tree (ProxBT)	3	8*5.5 = 44 Gy	74.8	No constraints specified
If ProxBT > 44Gy due to tumor location: "Prox BT-Bronch adjacent" and "Bronch adjacent"	3	8*5.5 = 44 Gy and 8*7.5=60 Gy	74.8 126	No constraints specified
Lungs-CTV		no restriction but recording of DVH data for toxicity evaluation		No constraints specified
Chest wall, Vertebral body, Liver, Great Vessels, non-adjacent wall, heart		no restriction but recording of DVH data for toxicity evaluation		No constraints specified

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Lungtech: Dose to bronchial tree

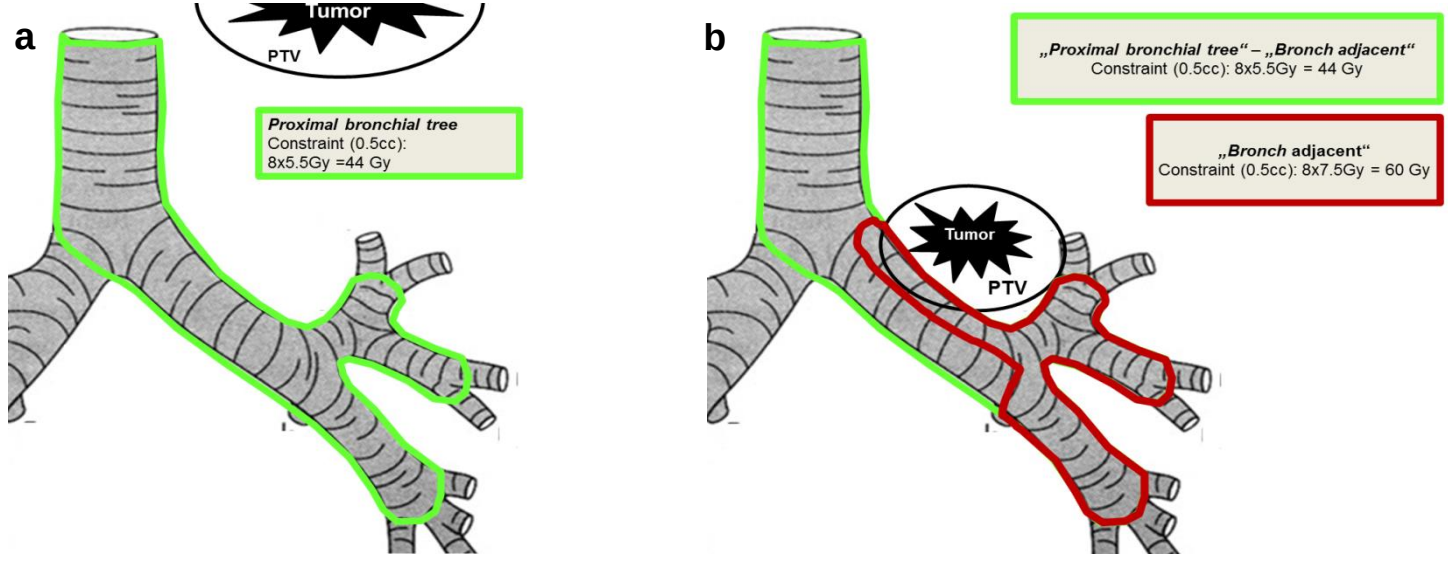

Figure 3: Dose constraints for the proximal bronchial tree
a) The general dose constraint for the whole structure “proxBT” (green) is 44Gy (<0.5cc) in 8 fractions. For PTVs near or abutting the main bronchus (b) a subvolume “Bronch adjacent” has to be generated (red). The dose constraint for this volume (<0.5cc) is 60Gy/8fractions, while the constraint for the rest of the “proxBT” (green) remains 44Gy/8fractions.

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Dutch phase III trial: WBRT vs SBRT 4-10 leasions

Volume	Per protocol D (Gy)	Acceptable variation	Unacceptable variation
PTV (largest leasion)	V100% = 99%	97%<V100%<99%	V100%<97%
PTV (other leasions)	V100% = 99%	97%<V100%<99%	V100%<97%
PTV (all leasions)	Dmax 140%	D2% =140%	D2% > 140%

OAR	D max per protocol (Gy)	Acceptable variation (Gy)	Unacceptable variation (Gy)
Brain stem	16	D 0.1cm3≤16	D 0.1cm3>16
Cochlea	12	D 0.1cm3≤12	D 0.1cm3>12
Chiasm	10	D 0.1cm3≤10	D 0.1cm3>10
Lens_L	5	D 0.1cm3≤10	D 0.1cm3>10
Lens_R	5	D 0.1cm3≤10	D 0.1cm3>10
Optic nerves	10	D 0.1cm3≤10	D 0.1cm3>10
Pituary gland	10	D 0.1cm3≤10	D 0.1cm3>10

0-2 mm CTV-PTV margin, 1-2 mm CT slice thickness

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Dutch consensus guideline 2014 on brain metastases treatment

Volume brainmet PTV	Dose PTV	In brainstem (GTV=PTV)	after WBRT PTV	After SRT PTV
<1 cm3	1 x 24 Gy	1x 18Gy	1x 24Gy	18 Gy
1-10 cm3	1 x 20 Gy	1 x 18Gy	1x 21Gy	18 Gy
10-20 cm3	1 x 18 Gy	1 x 18Gy	1 x 18 Gy	18 Gy
20-65 cm3*	1 x 15 Gy of 3 x 8 Gy	3 x 8 Gy	3 x 8 Gy	3 x 6 Gy

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Dutch consensus guideline 2014: Prescribing

- Dv% (Gy) is the dose in Gray that volume v% should at least get
- Vd% (cc) is the volume in cc that at least gets a dose of d% , where d% is the percentage dose of the prescribed dose.
- GTV en PTV volumes are defined.
- GTV-PTV margins are defined.
- Prescribed dose (Gy) is combined with the v% of the target. e.g. D100% = 20 Gy of D98% = 20 Gy.
- The number of fractions is defined.

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Dutch consensus guideline 2014: Reporting

- Reporting is based on prescribed dose.
- Absorbed dose Dv% (eg D95%), (bv D100%).
- Max dose: D2% or D1mm^3 or both.
- Min dose: D98% or D1mm^3 or both.
- Dmean
- Indices (CI) RTOG: Vprescribed dose/V(PTV)
- Vprescribed dose/V50%
- Heterogeniteit index: D5% /D95%
- Dose to OAR: D1%, D2% and Dmean.

CZE practical case lungstereo

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ziekenhuis

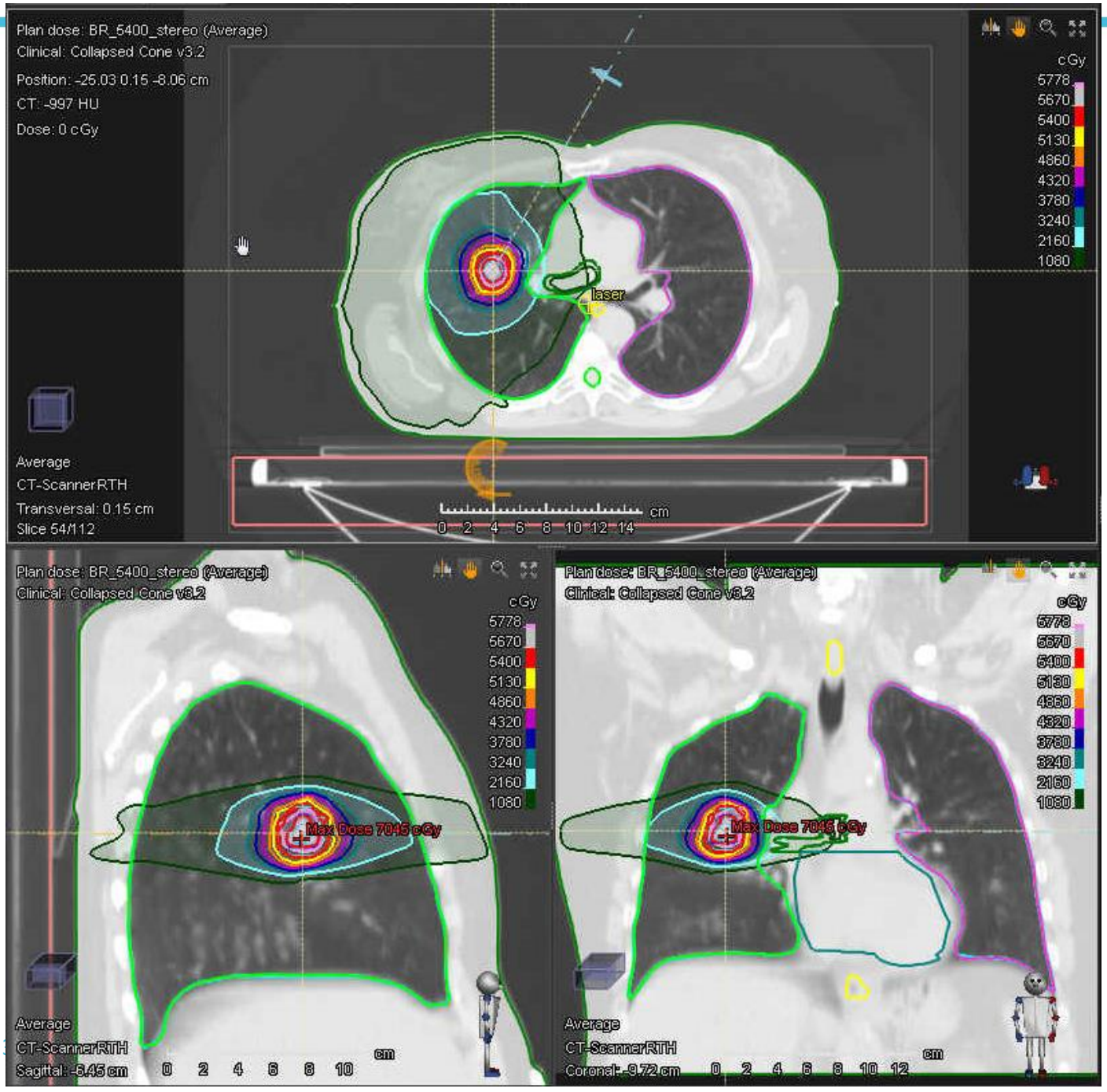
Periferal: 3*18Gy

Dosisvoorschrift (totaal): 5400 cGy

Fracties: 3

16 Criteria	Orgaan	Criterium
1	PTV_tumor	V100% > 95%
2	PTV_tumor	V100% < 97%
3	PTV_tumor	D0.5cc < 130%
4	Lungs-GTV_MID	V20Gy < 15%
5	Lungs-GTV_MID	V5Gy < 26%
6	Lung_L (bij tumor rechts)	V5Gy < 15%
7	Lung_R (bij tumor links)	V5Gy < 15%
8	Esophagus	D0.5cc < 2700 cGy
9	Spinal Canal	Dmax < 1800 cGy
10	Spinal Canal	D0.5cc < 1800 cGy
11	Heart	D0.5cc < 3000 cGy
12	Plexus Brachialis	D0.5cc < 2400 cGy
13	Trachea / Main Bronchi	D0.5cc < 3000 cGy
14	Large Vessels	D0.5cc < 3000 cGy
15	ChestWall	V30Gy < 30 cc
16	ChestWall	V60Gy < 3 cc

catharina ziekenhuis



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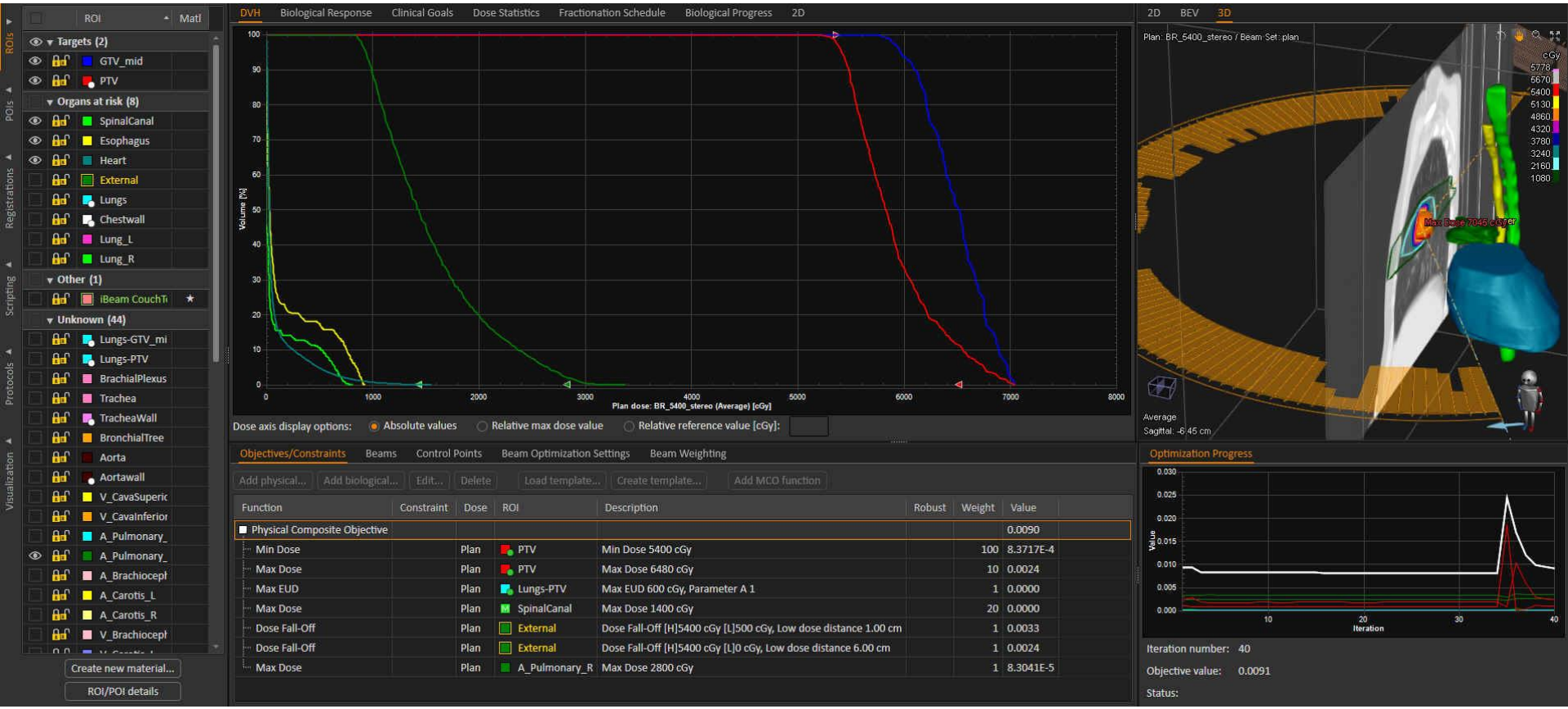
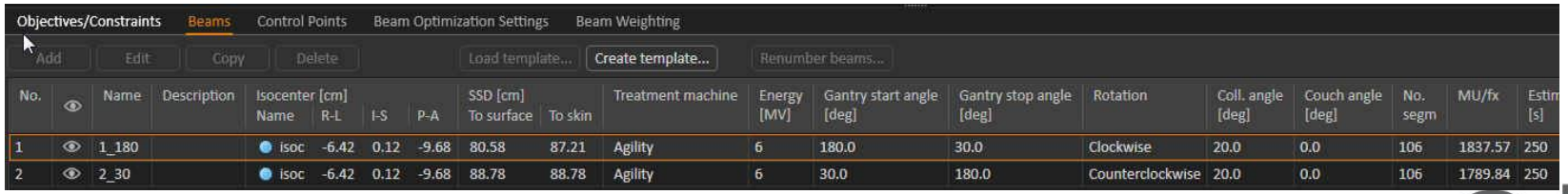
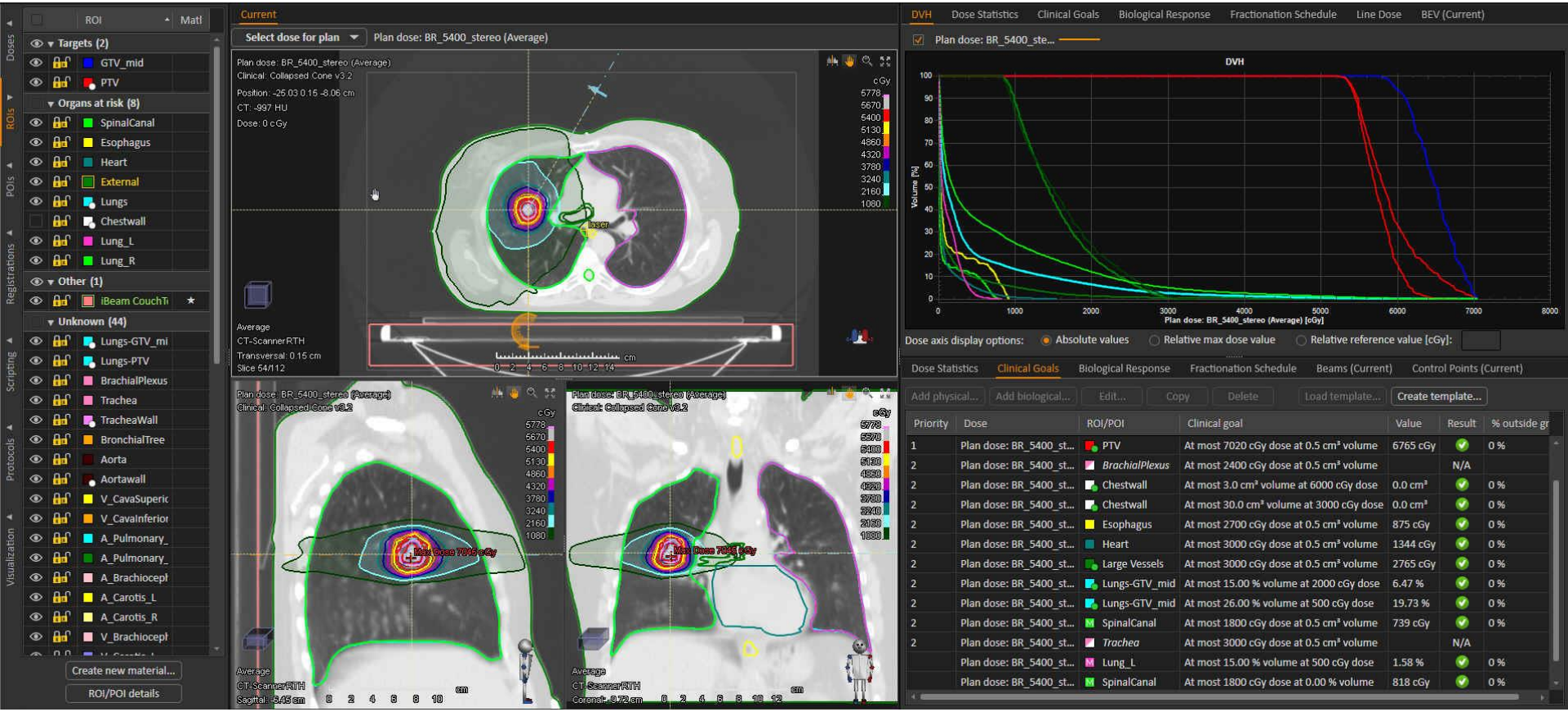
Recording #4.mp4


ROI
Matl
Targets (2)
GTV_mid
PTV
Organs at risk (8)
SpinalCanal
Esophagus
Heart
External
Lungs
Chestwall
Lung_L
Lung_R
Other (1)
iBeam CouchTo
Unknown (44)
Lungs-GTV_mi
Lungs-PTV
BrachialPlexus
Trachea
TracheaWall
BronchialTree
Aorta
Aortawall
V_CavaSuperic
V_CavaInferior
A_Pulmonary_
A_Pulmonary_
A_Brachiocepl
A_Carotis_L
A_Carotis_R
V_Brachiocepl
Create new material...
ROI/POI details
DVH
Biological Response
Clinical Goals
Dose Statistics
Fractionation Schedule
Biological Progress
2D
Volume [%]
Plan dose: BR_5400_stereo (Average) [cGy]
Dose axis display options:
Absolute values
Relative max dose value
Relative reference value [cGy]:
2D
BEV
3D
Plan: BR_5400_stereo / Beam Set: plan
cGy
Average
Sagittal: -6.45 cm
Objectives/Constraints
Beams
Control Points
Beam Optimization Settings
Beam Weighting
Add physical...
Add biological...
Edit...
Delete
Load template...
Create template...
Add MCO function
Function
Constraint
Dose
ROI
Description
Robust
Weight
Value
Physical Composite Objective 0.0090
Min Dose Plan PTV Min Dose 5400 cGy 100 8.3717E-4
Max Dose Plan PTV Max Dose 6480 cGy 10 0.0024
Max EUD Plan Lungs-PTV Max EUD 600 cGy, Parameter A 1 1 0.0000
Max Dose Plan SpinalCanal Max Dose 1400 cGy 20 0.0000
Dose Fall-Off Plan External Dose Fall-Off [H]5400 cGy [L]500 cGy, Low dose distance 1.00 cm 1 0.0033
Dose Fall-Off Plan External Dose Fall-Off [H]5400 cGy [L]0 cGy, Low dose distance 6.00 cm 1 0.0024
Max Dose Plan A_Pulmonary_R Max Dose 2800 cGy 1 8.3041E-5
Optimization Progress
Value
Iteration
Iteration number: 40
Objective value: 0.0091
Status:


Objectives/Constraints
Beams
Control Points
Beam Optimization Settings
Beam Weighting
Add
Edit
Copy
Delete
Load template...
Create template...
Renumber beams...
No.
Name
Description
Isocenter [cm]
Name
R-L
I-S
P-A
SSD [cm]
To surface
To skin
Treatment machine
Energy [MV]
Gantry start angle [deg]
Gantry stop angle [deg]
Rotation
Coll. angle [deg]
Couch angle [deg]
No. segm
MU/fx
Estim [s]
1 1_180 isoc -6.42 0.12 -9.68 80.58 87.21 Agility 6 180.0 30.0 Clockwise 20.0 0.0 106 1837.57 250
2 2_30 isoc -6.42 0.12 -9.68 88.78 88.78 Agility 6 30.0 180.0 Counterclockwise 20.0 0.0 106 1789.84 250


ROI
Matl
Targets (2)
GTV_mid
PTV
Organs at risk (8)
SpinalCanal
Esophagus
Heart
External
Lungs
Chestwall
Lung_L
Lung_R
Other (1)
Unknown (44)
Lungs-GTV_mi
Lungs-PTV
BrachialPlexus
Trachea
TracheaWall
BronchialTree
Aorta
Aortawall
V_CavaSuperic
V_CavaInferior
A_Pulmonary_
A_Pulmonary_
A_Brachiocepl
A_Carotis_L
A_Carotis_R
V_Brachiocepl
Create new material...
ROI/POI details
Current
Select dose for plan
Plan dose: BR_5400_stereo (Average)
Clinical: Collapsed Cone v3.2
Position: -25.03 0.15 -8.06 cm
CT: -997 HU
Dose: 0 cGy
Average
CT-ScannerRTH
Transversal: 0.15 cm
Slice 54/112
Max Dose 7045 cGy
Sagittal: -5.45 cm
Coronal: -9.72 cm
DVH
Dose Statistics
Clinical Goals
Biological Response
Fractionation Schedule
Line Dose
BEV (Current)
Plan dose: BR_5400_ste...
Volume [%]
Plan dose: BR_5400_stereo (Average) [cGy]
Dose axis display options:
Absolute values
Relative max dose value
Relative reference value [cGy]:
Beams (Current)
Control Points (Current)
Add physical...
Add biological...
Edit...
Copy
Delete
Load template...
Create template...
Priority
Dose
ROI/POI
Clinical goal
Value
Result
% outside gr
1 Plan dose: BR_5400_st... PTV At most 7020 cGy dose at 0.5 cm³ volume 6765 cGy 0 %
2 Plan dose: BR_5400_st... BrachialPlexus At most 2400 cGy dose at 0.5 cm³ volume N/A
2 Plan dose: BR_5400_st... Chestwall At most 3.0 cm³ volume at 6000 cGy dose 0.0 cm³ 0 %
2 Plan dose: BR_5400_st... Chestwall At most 30.0 cm³ volume at 3000 cGy dose 0.0 cm³ 0 %
2 Plan dose: BR_5400_st... Esophagus At most 2700 cGy dose at 0.5 cm³ volume 875 cGy 0 %
2 Plan dose: BR_5400_st... Heart At most 3000 cGy dose at 0.5 cm³ volume 1344 cGy 0 %
2 Plan dose: BR_5400_st... Large Vessels At most 3000 cGy dose at 0.5 cm³ volume 2765 cGy 0 %
2 Plan dose: BR_5400_st... Lungs-GTV_mid At most 15.00 % volume at 2000 cGy dose 6.47 % 0 %
2 Plan dose: BR_5400_st... Lungs-GTV_mid At most 26.00 % volume at 500 cGy dose 19.73 % 0 %
2 Plan dose: BR_5400_st... SpinalCanal At most 1800 cGy dose at 0.5 cm³ volume 739 cGy 0 %
2 Plan dose: BR_5400_st... Trachea At most 3000 cGy dose at 0.5 cm³ volume N/A
Plan dose: BR_5400_st... Lung_L At most 15.00 % volume at 500 cGy dose 1.58 % 0 %
Plan dose: BR_5400_st... SpinalCanal At most 1800 cGy dose at 0.00 % volume 818 cGy 0 %

Adjacent to Thoracic wall

Dosisvoorschrift (totaal): 5500 cGy

Fracties: 5

16 Criteria	Orgaan	Criterium
1	PTV_tumor	V100% > 95%
2	PTV_tumor	V100% < 97%
3	PTV_tumor	D0.5cc < 130%
4	Lungs-GTV_MID	V20Gy < 15%
5	Lungs-GTV_MID	V5Gy < 26%
6	Lung_L (bij tumor rechts)	V5Gy < 15%
7	Lung_R (bij tumor links)	V5Gy < 15%
8	Esophagus	D0.5cc < 3250 cGy
9	Spinal Canal	Dmax < 2250 cGy
10	Spinal Canal	D0.5cc < 2250 cGy
11	Heart	D0.5cc < 3750 cGy
12	Plexus Brachialis	D0.5cc < 3000 cGy
13	Trachea / Main Bronchi	D0.5cc < 3750 cGy
14	Large Vessels	D0.5cc < 3750 cGy
15	ChestWall	V30Gy < 30 cc
16	ChestWall	V60Gy < 3 cc

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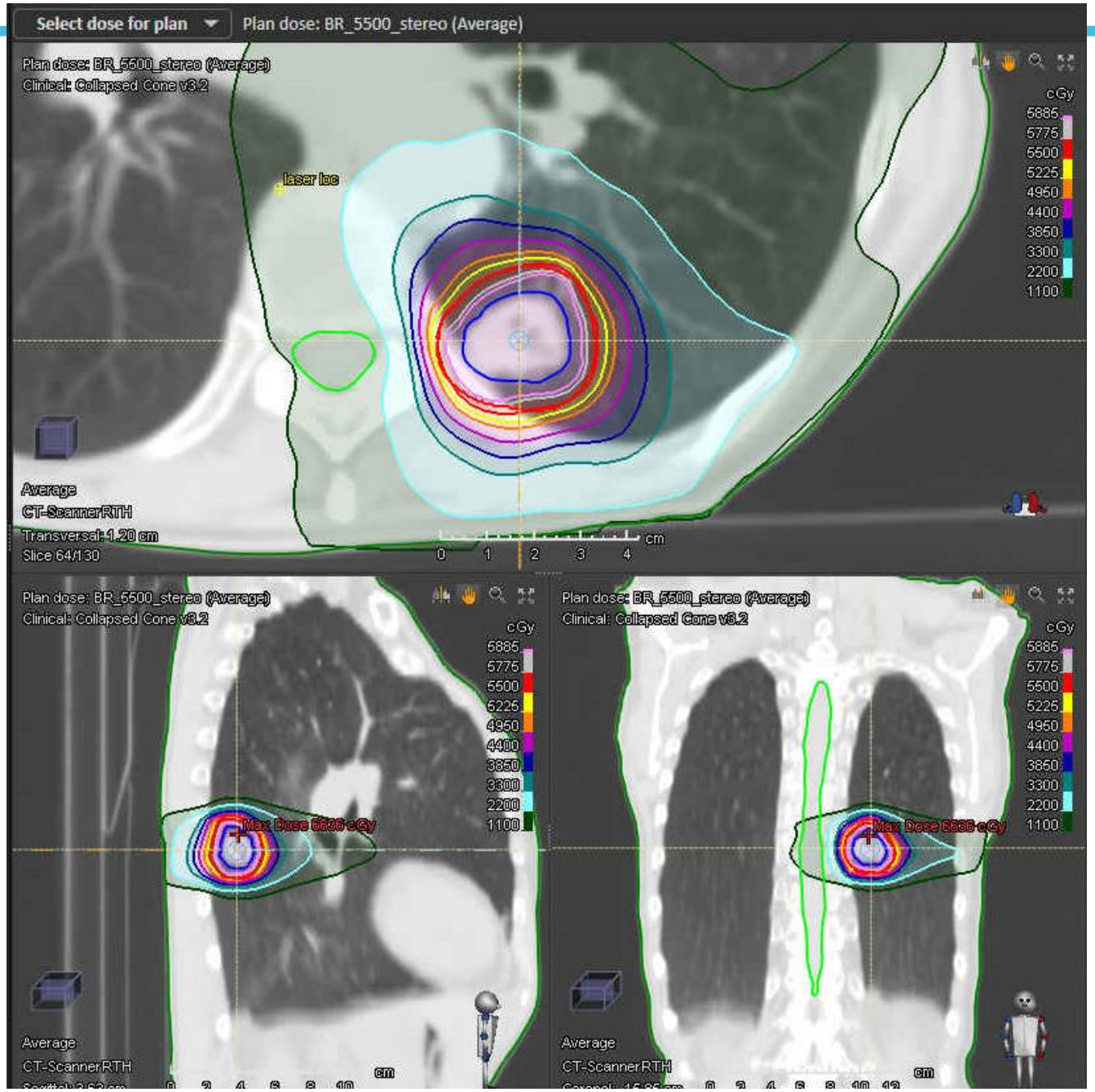
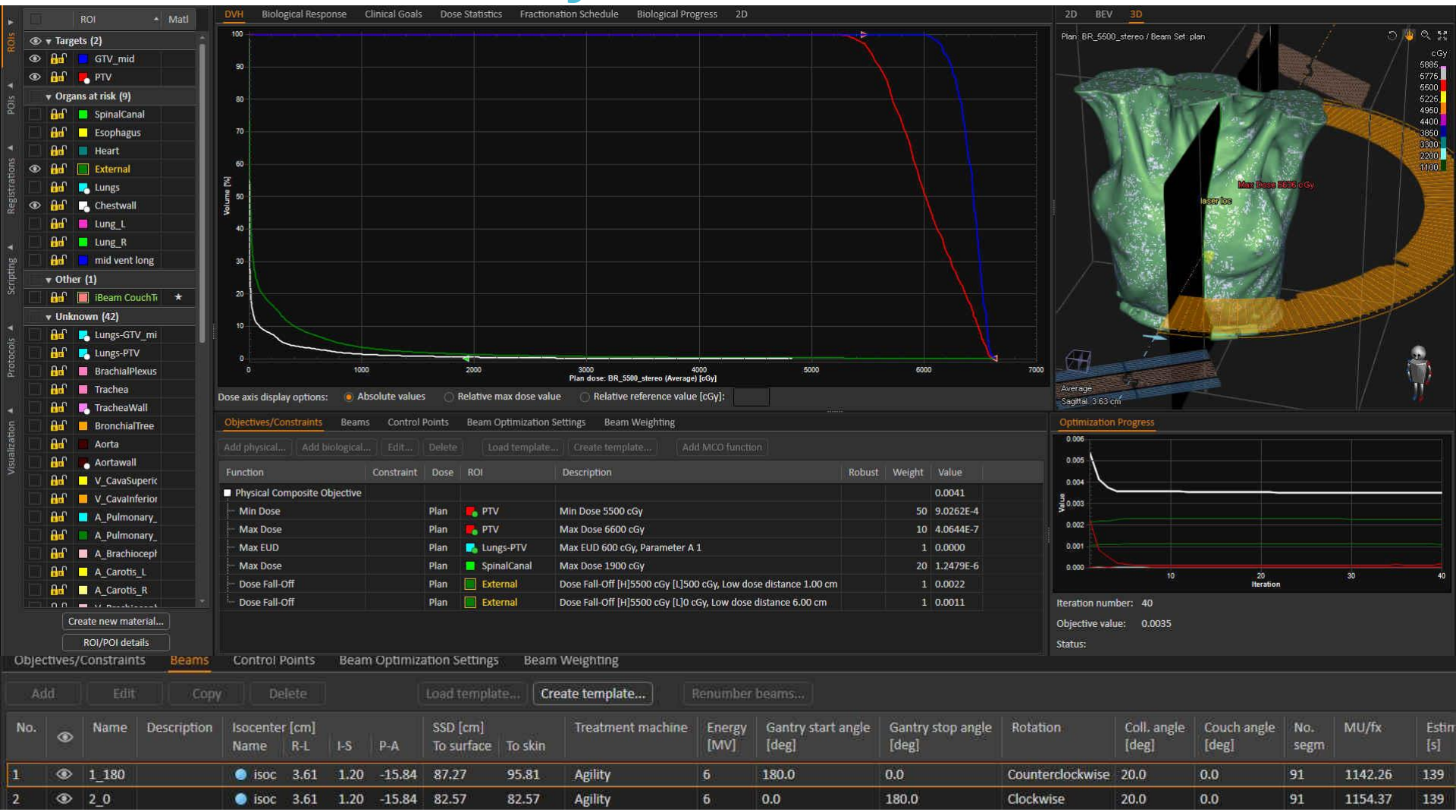
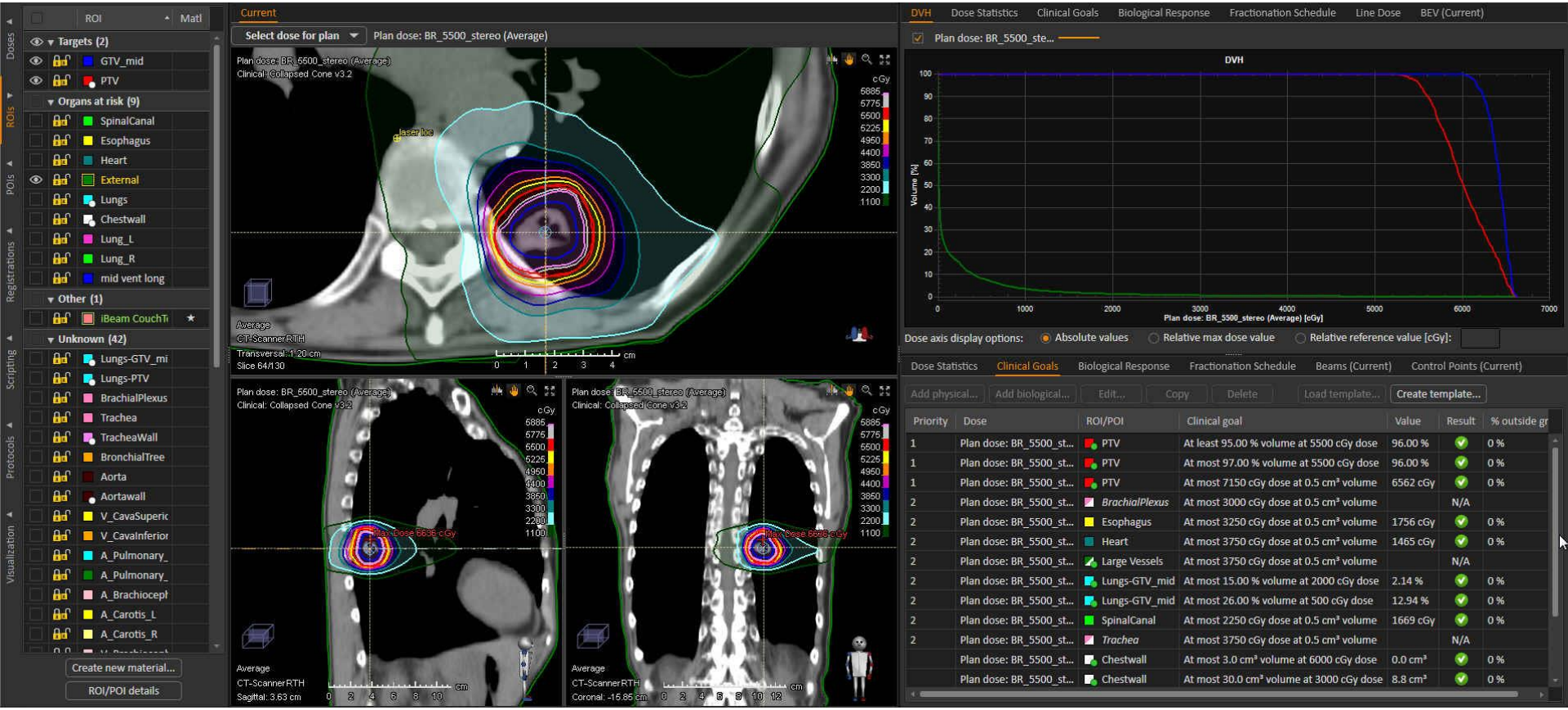

Select dose for plan
Plan dose: BR_5500_stereo (Average)
Plan dose: BR_5500_stereo (Average)
Clinical: Collapsed Cone v3.2
laser loc
cGy
5885
5775
5500
5225
4950
4400
3850
3300
2200
1100
Average
CT-ScannerRTH
Transversal: 1.20 cm
Slice 64/130
0 1 2 3 4 cm
Plan dose: BR_5500_stereo (Average)
Clinical: Collapsed Cone v3.2
Max Dose 5536 cGy
Average
CT-ScannerRTH
cm
Plan dose: BR_5500_stereo (Average)
Clinical: Collapsed Cone v3.2
Max Dose 5536 cGy
Average
CT-ScannerRTH
cm

Periferal: 3*18Gy



Periferal: 3*18Gy



Practice of SBRT:
RTT perspective

Lineke Berkelaar- van der Weide (MSc)
RTT research
VU University Medical Center
l.vanderweide@vumc.nl

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- **Max Dahele**
- **Femke Spoelstra**
- **Ingrid Kuijper**
- **Colien Hazelaar**
- **Tezontl Rosario**
- **Stereoteam**

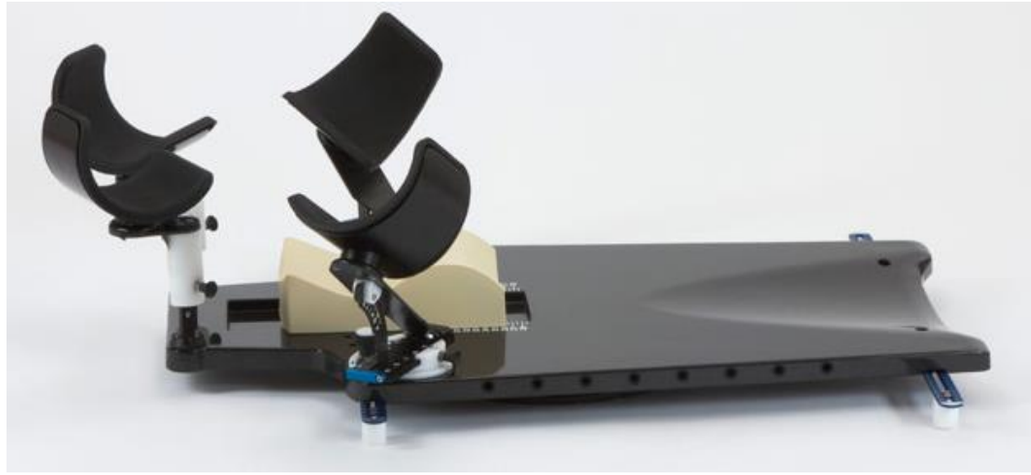
RTTs role in treatment

- Patient positioning
- IGRT-protocols:
  - Orthogonal kV images
  - CBCT (PTV match)
  - ExacTrac (bone match)
- Motion management
- Intrafraction monitoring
  - Real-time Positioning Management (RPM)
  - ExacTrac
  - Fiducial tracking (e.g. Calypso, fluoroscopic images or Auto Beam Hold package)
- ‘Social’ role

Patient positioning (Lung, Spine, Liver)

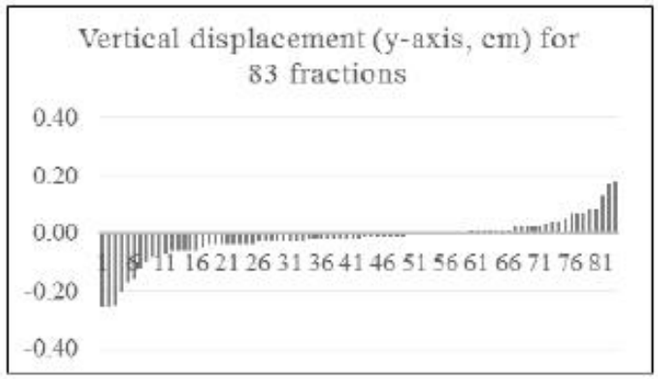
- Thoraxsupport (Macromedics)
- Posirest lung board
- Knee cushion

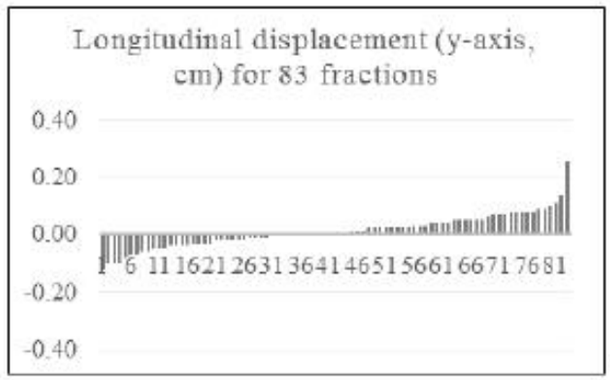
- Vacuum cushion

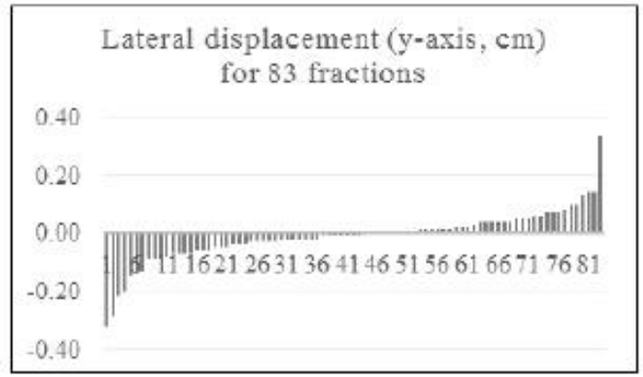


Spine and bony pelvis: 6Dcouch, FFF

patient stability. The mean and SD for vertical, longitudinal and lateral directions were −0.2 (0.7), 0.1 (0.6) and −0.1 (0.9) mm, respectively. The mean (SD) 3D displacement was 1.0 (0.8) mm and 74/83 vectors (89.2%) were ≤2 mm. Maximum







and positioning. Fast treatment delivery, combined with simple positioning techniques and 6D-CBCT registration and couch correction was associated with good translational stability: 90% and 94.4% of displacements were within ±1 and 1.5 mm, respectively. Rotational displacements, which may be especially important for longer target volumes, were small: 97.6% and 98.8% were within ±1 and 1.5°, respectively.

Acta Oncol. 2016 Jun;55(6):795-8. doi: 10.3109/0284186X.2015.1119885. Epub 2016 Mar 30.

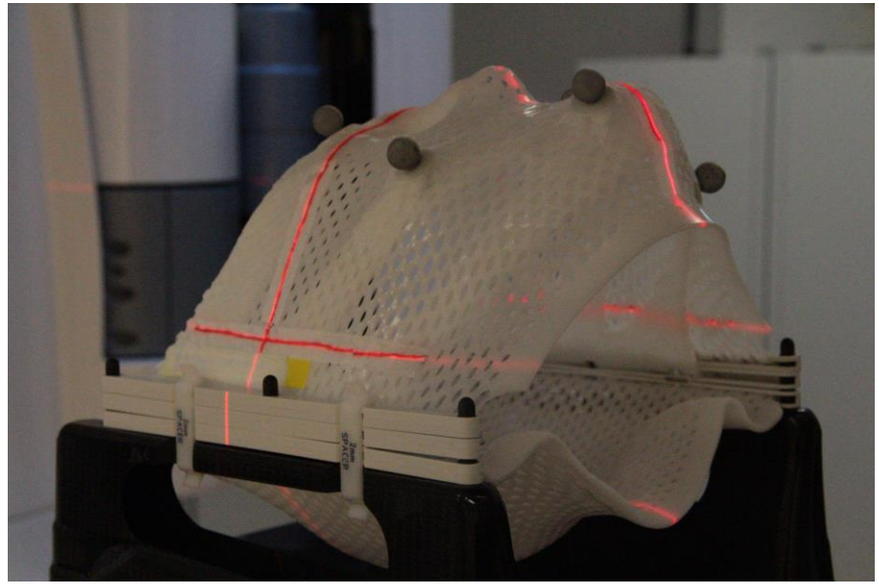
Stereotactic body radiotherapy for spine and bony pelvis using flattening filter free volumetric modulated arc therapy, 6D cone-beam CT and simple positioning techniques: Treatment time and patient stability.

Dahele M[1], Slotman B[1], Verbakel W[1].

Patient positioning

‘

- Mask brain



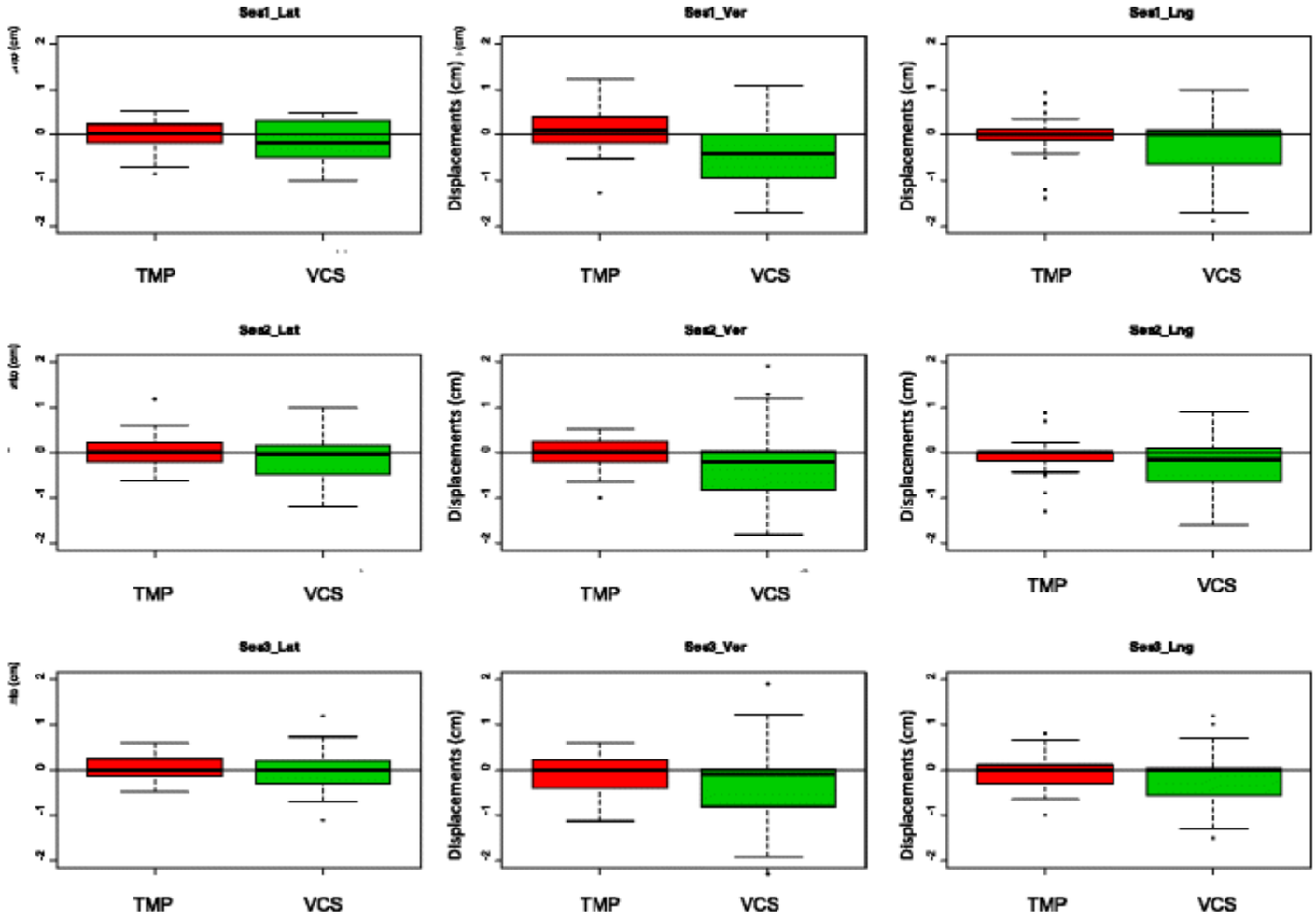
- Mask spine (above T4)
- Cranial lung tumor

Thermoplastic mask vs vacuum cushion

Radiat Oncol. 2015 Aug 20;10:176. doi: 10.1186/s13014-015-0484-7.

Comparative analysis of thermoplastic masks versus vacuum cushions in stereotactic body radiotherapy.

Navarro-Martin A[1], Cacicedo J[2], Leaman O[3], Sancho I[4], García E[5], Navarro V[6], Guedea F[7].



IGRT-options in your department

- MV imaging alone
- MV-CBCT
- (kV-kV and) kV-CBCT/ 4DCBCT
- Exac trac
- Combination of all

IGRT-protocols

Depends on tumorsite

For setup:

- Orthogonal kV-images
- (4D)CBCT:
  - PTV match, when necessary 6D couch
- Exac-Trac (in combination with CBCT)

During treatment:

- CBCT halfway treatment
- CBCT post-treatment

IGRT-protocols

Depends on tumorsite

For setup:

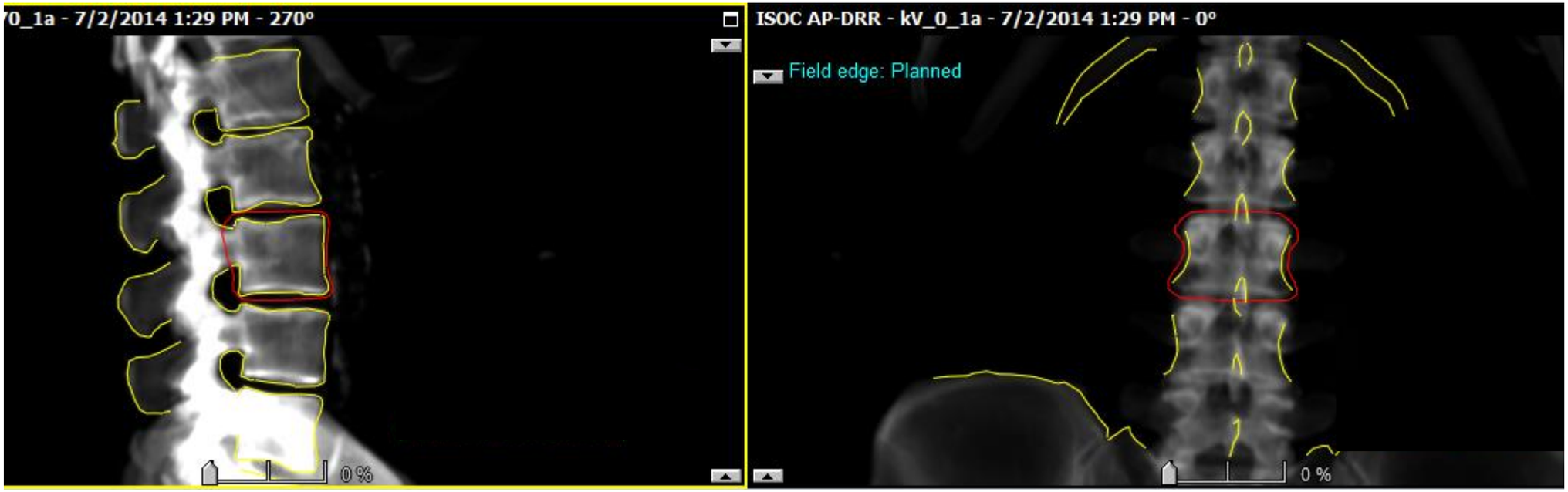
- Orthogonal kV-images
- (4D)CBCT:
  - PTV match, when necessary 6D couch
- Exac-Trac (in combination with CBCT)

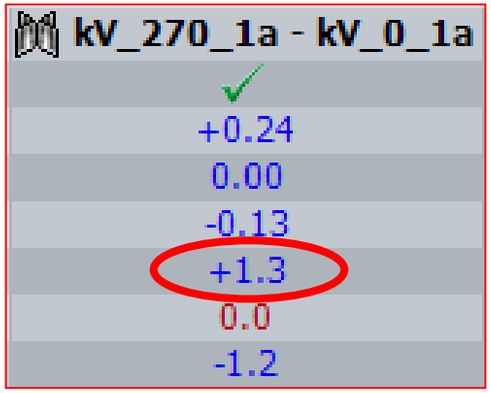
During treatment:

- CBCT halfway treatment
- CBCT post-treatment

Orthogonal kV-images

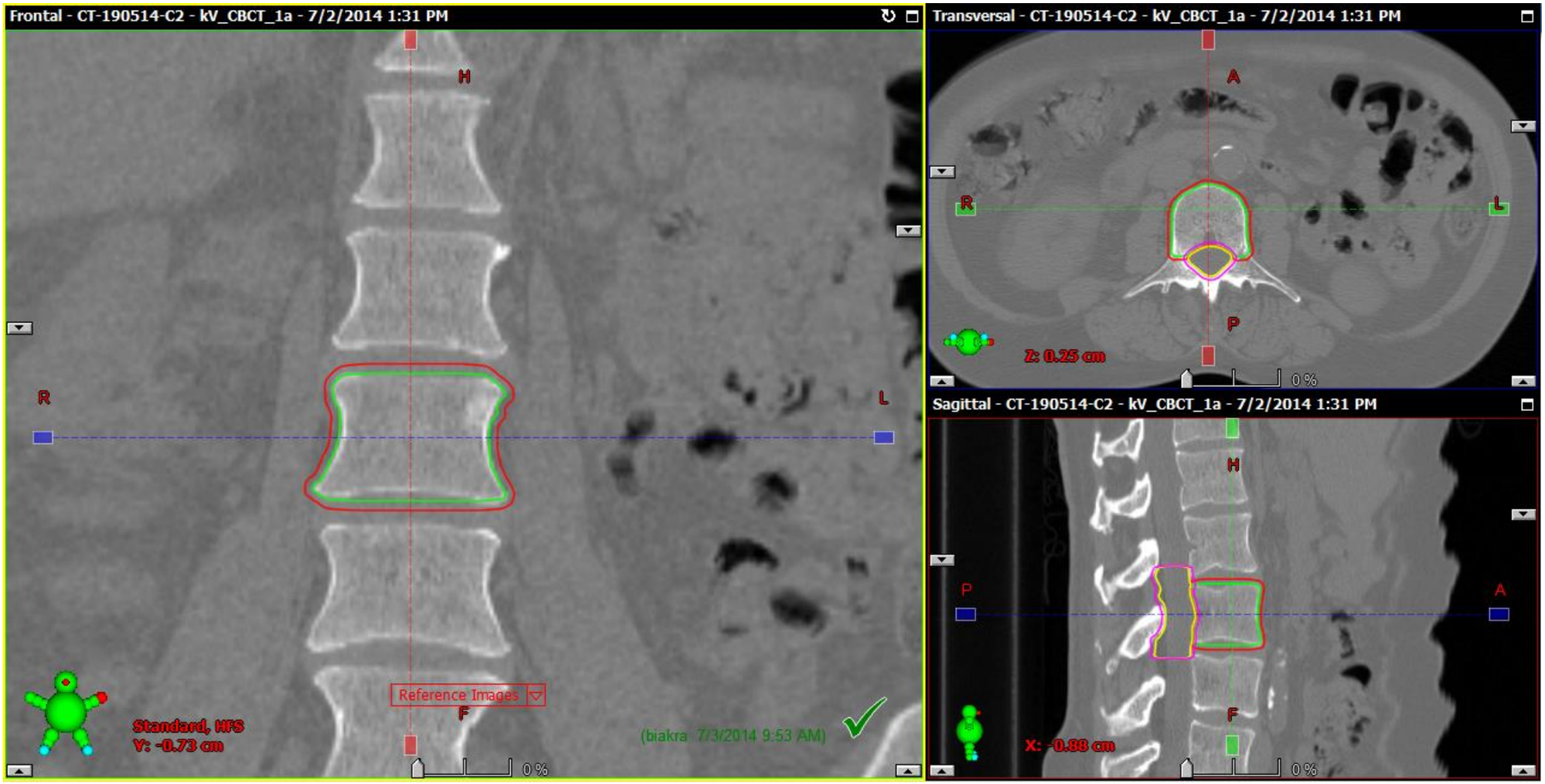
Orthogonal kV-images



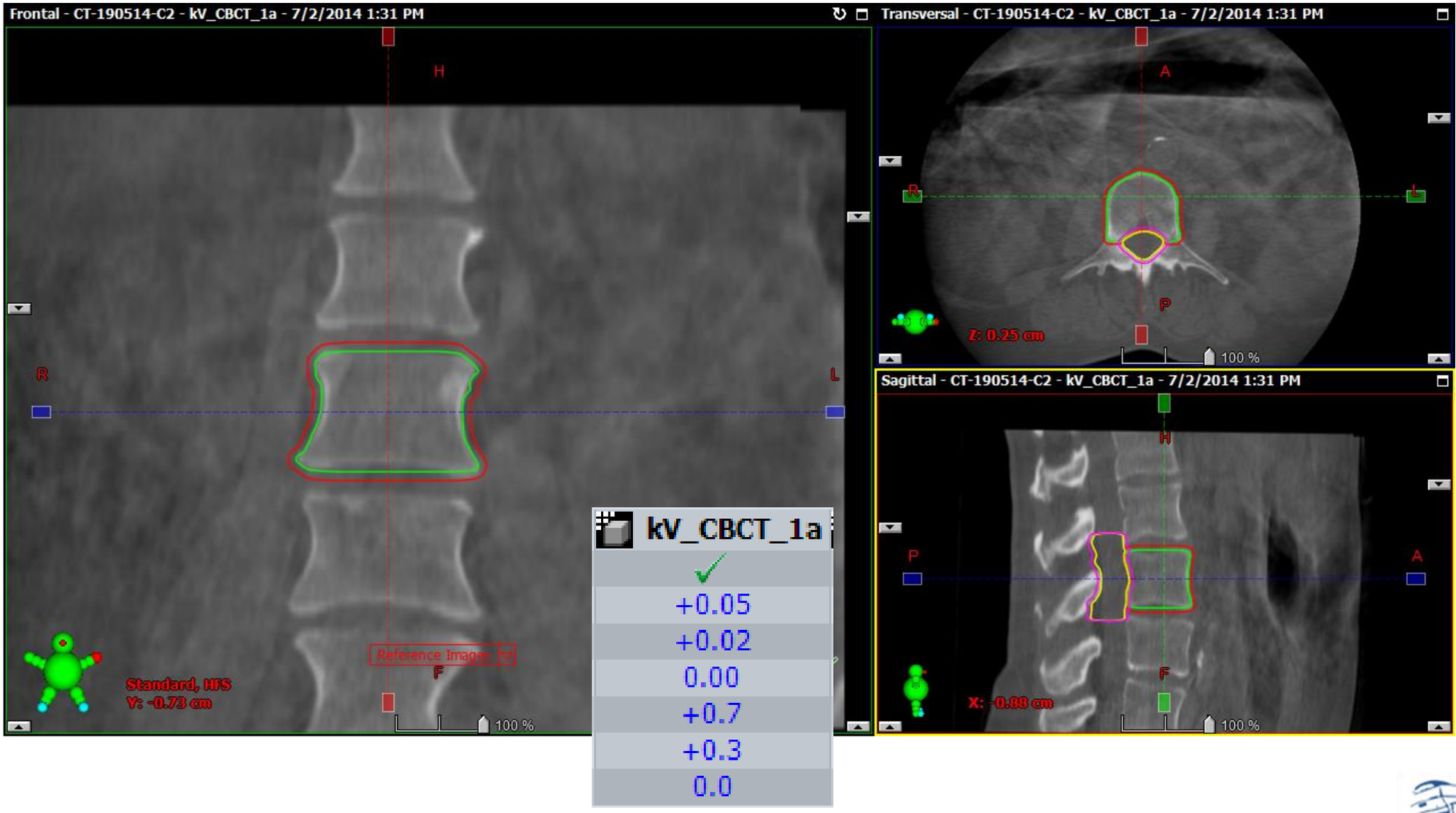


Advantage of use kV-kV first:
- Pitch and roll > 1.0˚ extra CBCT to ensure if patients are not counteracting

CT, normal spine case



CBCT, normal spine case



4D CBCT

- Why 4D CBCT?
  - To better track volume/location changes of moving tumors
  - To verify tumor motion

Varian:

- Because not online available, only on individual basis:
  - Artifacts in 4DCT
  - Different breathing pattern> suspected drift
  - Suspected tumor volume change

IGRT-protocols

Depends on tumorsite

For setup:

- Orthogonal kV-images
- CBCT:
  - PTV match, when necessary 6D couch
- Exac-Trac (in combination with CBCT)

During treatment:

- CBCT halfway treatment
- CBCT post-treatment

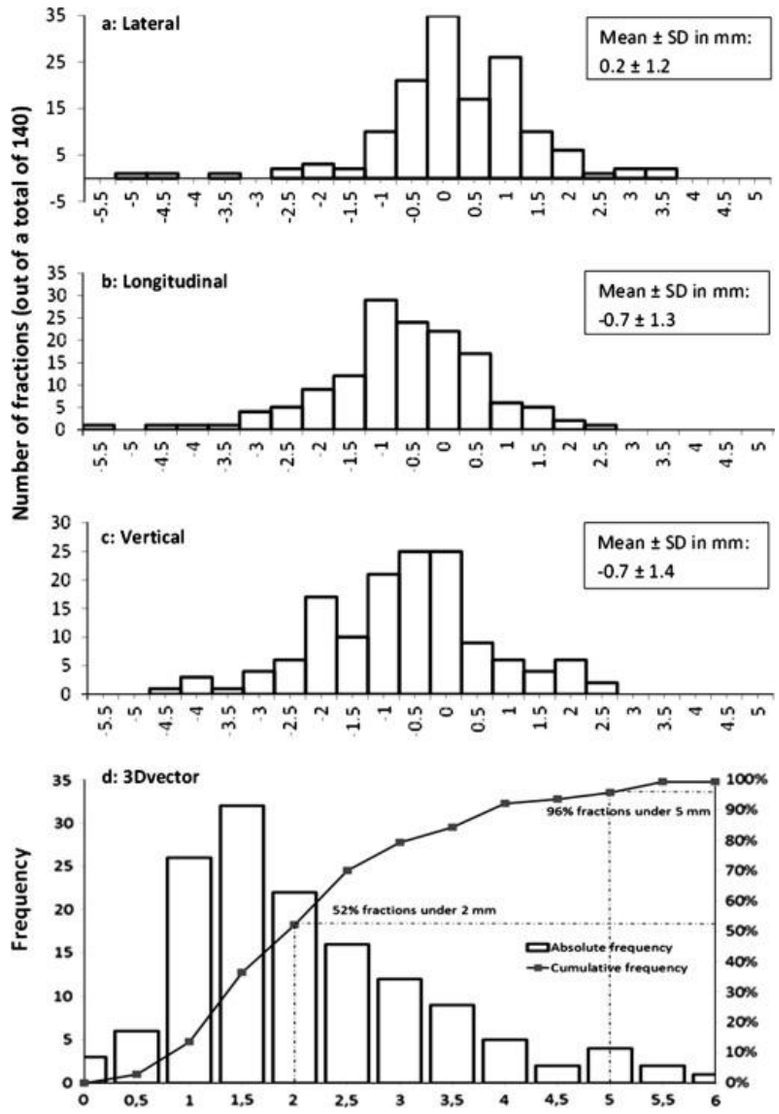
Post-treatment CBCT, SBRT lung

- 140 fractions (32 patients)

Mean translation (±SD):

- −0.7 ± 1.4 mm (vertical),
- −0.7 ± 1.3 mm (longitudinal)
- +0.2 ± 1.2 mm (lateral)
- 3D vector: 2.1 ± 1.2 mm.

- Mean delivery time on TrueBeam with FFF was 4.4 ± 3.4 min (mean beam-on 1.9 ± 0.4 min)



Radiother Oncol. 2013 Jun;107(3):419-22. doi: 10.1016/j.radonc.2013.04.019. Epub 2013 May 23.
Frameless high dose rate stereotactic lung radiotherapy: intrafraction tumor position and delivery time.
Peguret N1, Dahele M,

Motion management

A strategy for motion management is essential in SBRT for anatomical indications effected by breathing motion (e.g. lung, liver, adrenal gland)

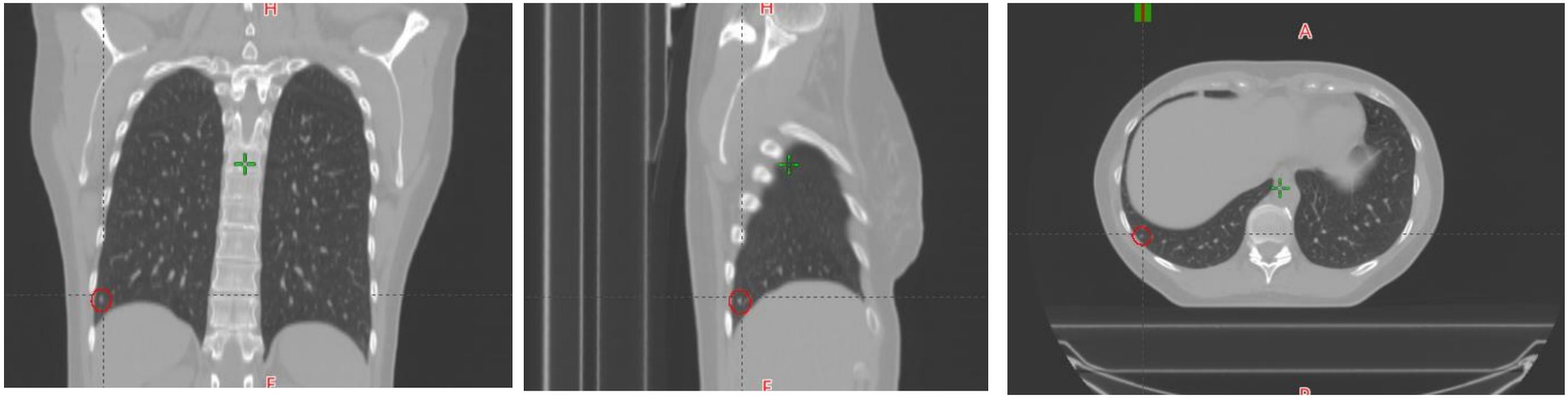
- Depend on departmental availability of kit
- Role in coaching / training patient
- Additional considerations when these techniques are used e.g. longer on treatment couch

Motion management

- Stop / reduce tumor movement
  - Deep Inspiration BreathHold (DIBH)
    - Lung
  - Expiration BreathHold (EBH)
    - Liver, adrenal glands
  - Abdominal compression

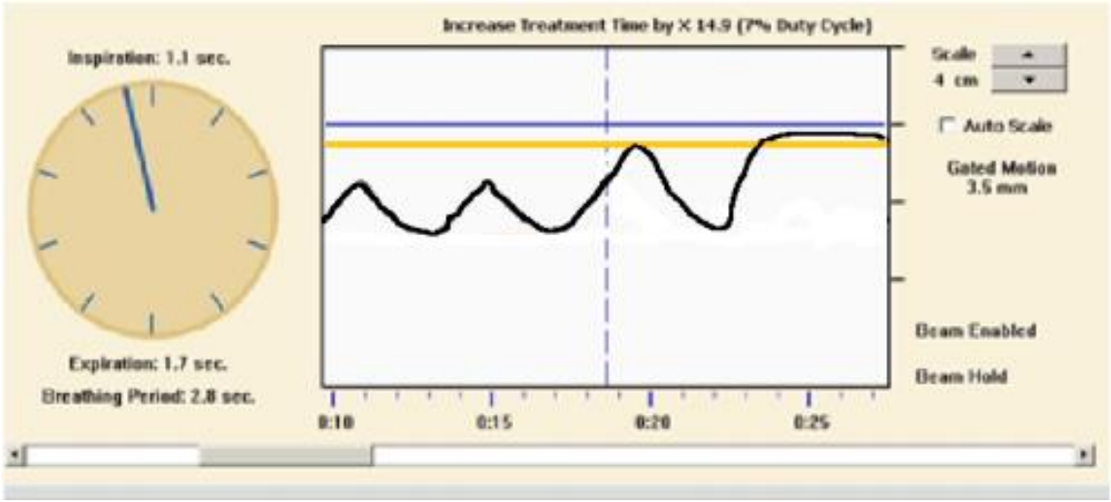
Deep Inspiration Breath Hold (DIBH)

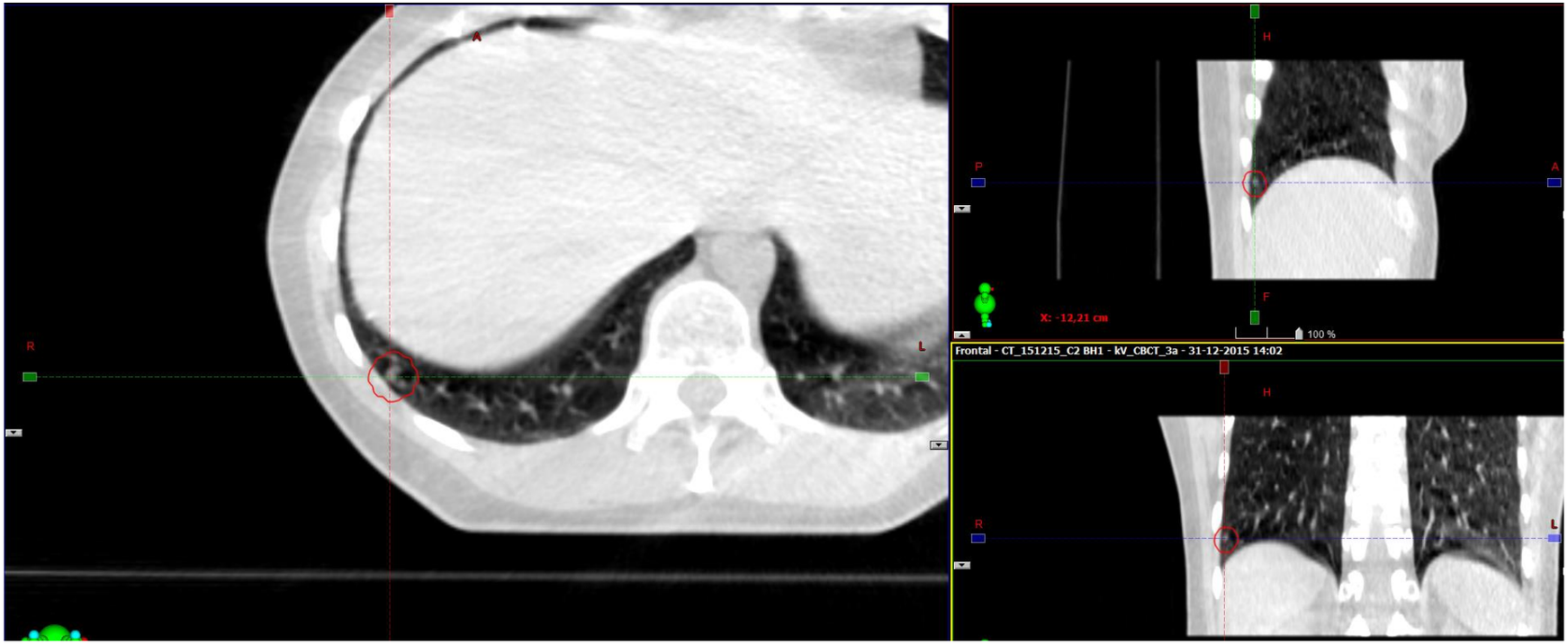
46-yr old patient
4 lesions in lung
1 lesion close to diaphragm



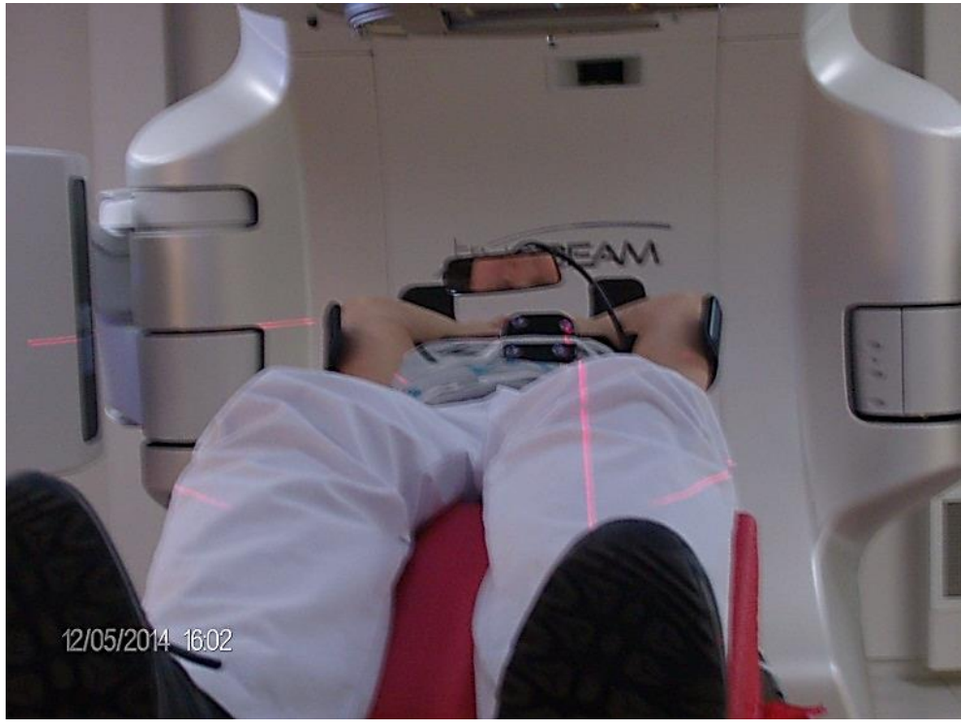
Tumorshift on planning-CT >3cm

Deep Inspiration Breath Hold (DIBH)



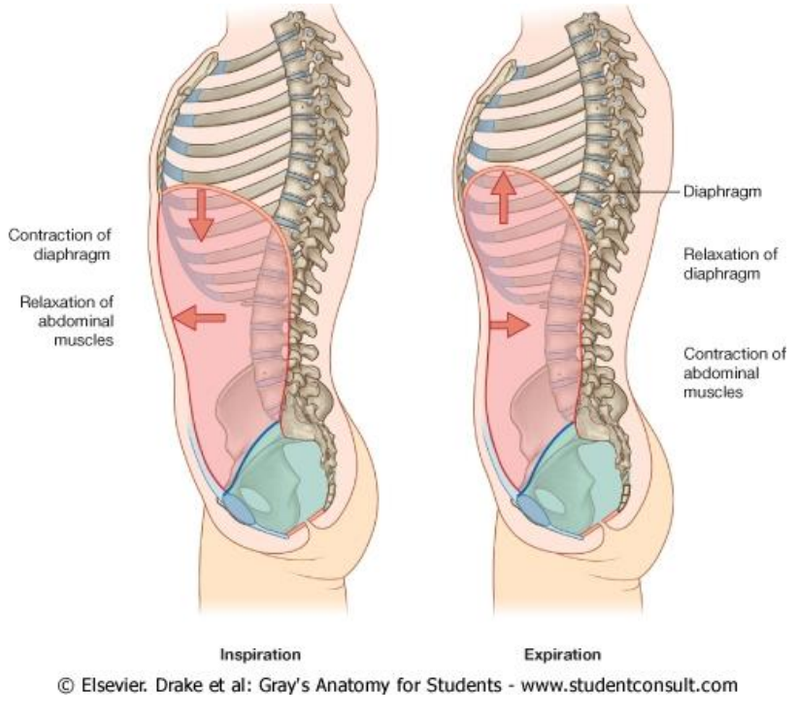


BH and visual feedback

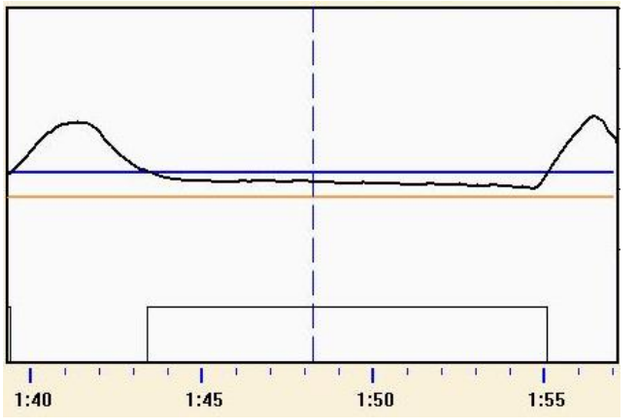


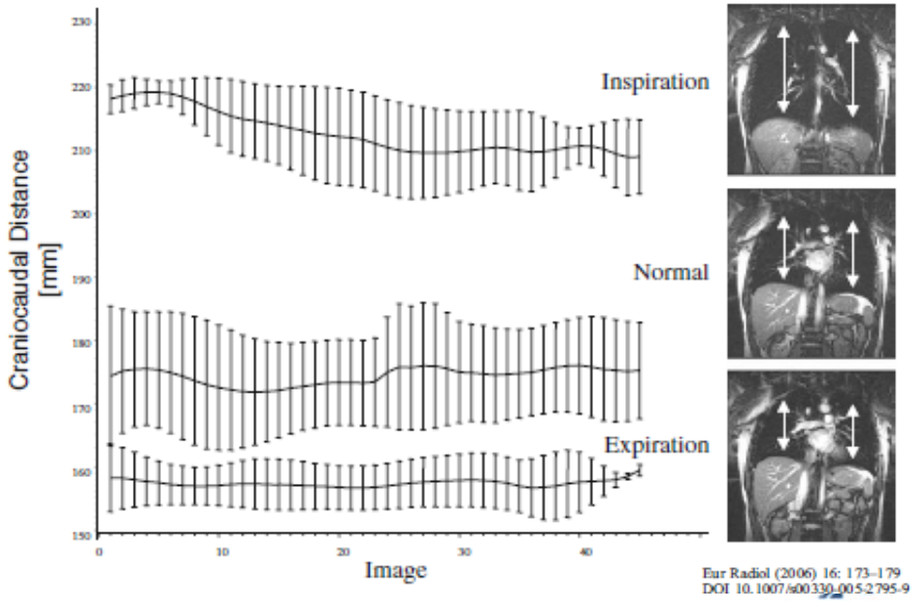
Expiration Breathhold

- Breath-holding in expiration
- Fit patients
- Minimize mobility
- Stability through expiration
- Upper abdomen
- Imaging optimization



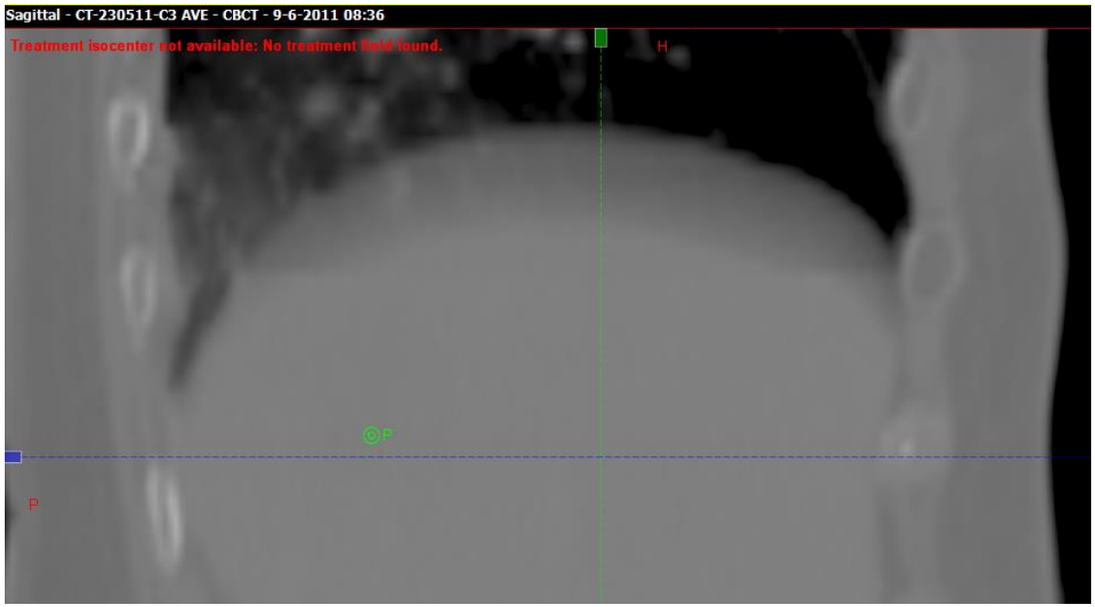
© Elsevier. Drake et al: Gray's Anatomy for Students - www.studentconsult.com

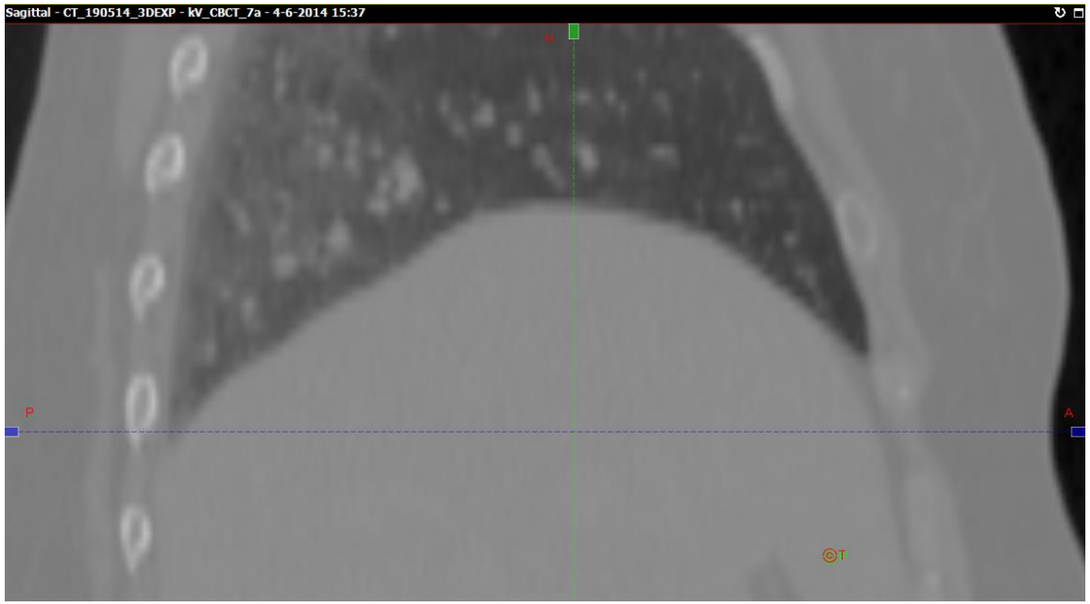




Eur Radiol (2006) 16: 173–179
DOI 10.1007/s00330-005-2795-9

Imaging optimization





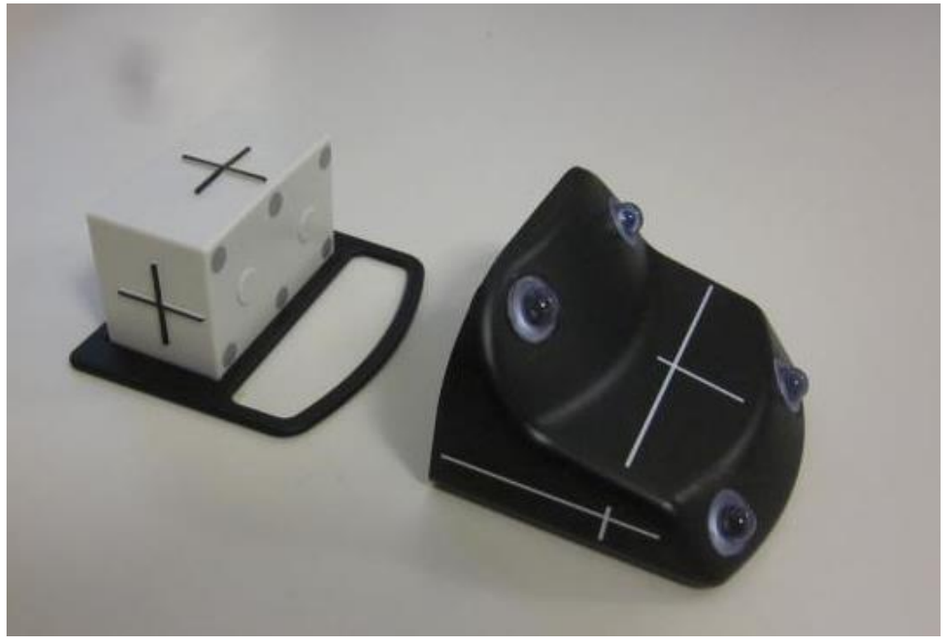
Imaging:
Freebreathing
vs
Expiration
Breathhold

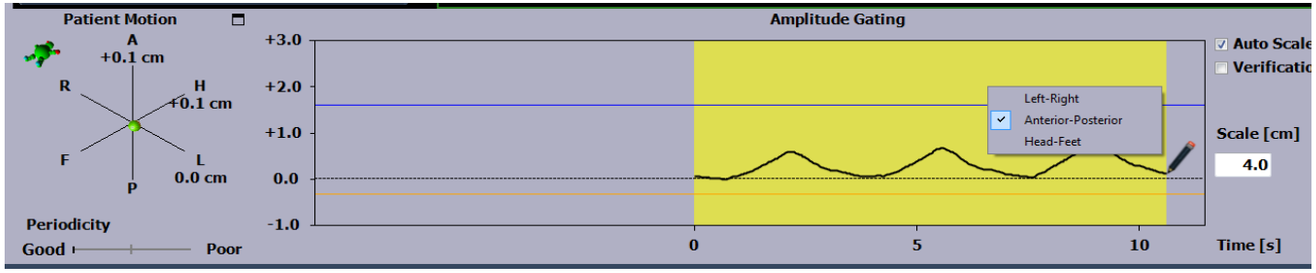
Intrafraction monitoring

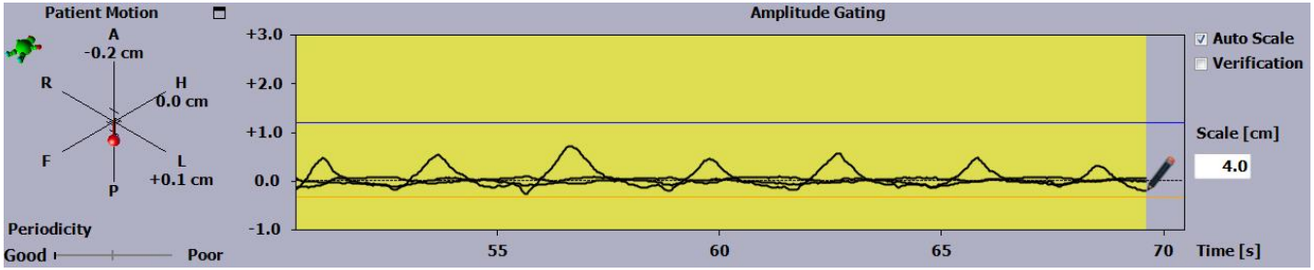
- RPM system
- Exac Trac
- Imaging during arc delivery

RPM-system

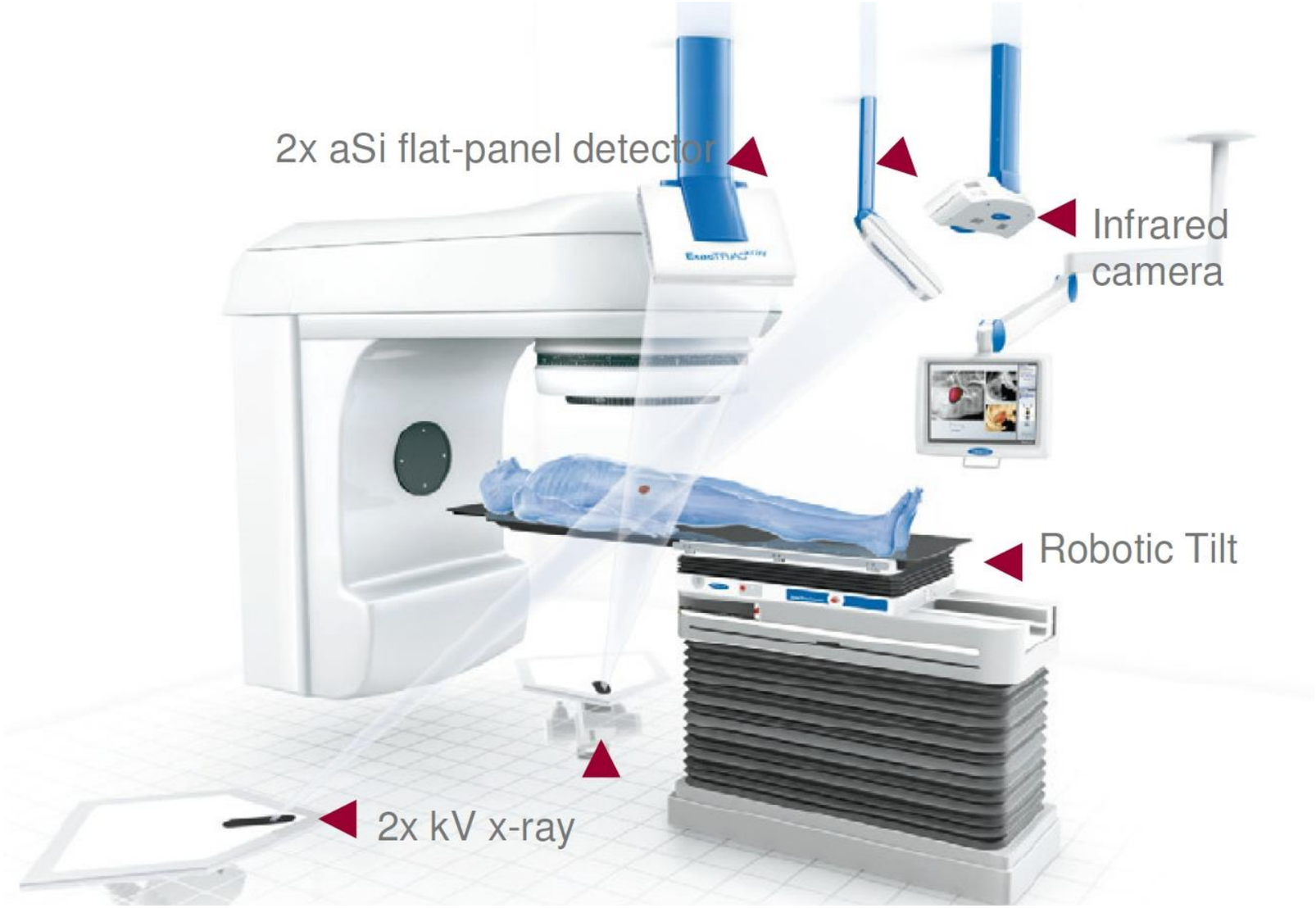
VARIAN



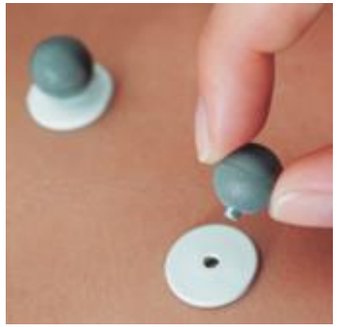

Patient Motion
A
+0.1 cm
R
H
+0.1 cm
F
L
0.0 cm
P
Periodicity
Good
Poor
Amplitude Gating
+3.0
+2.0
+1.0
0.0
-1.0
0
5
10
Time [s]
Left-Right
Anterior-Posterior
Head-Feet
Auto Scale
Verificatic
Scale [cm]
4.0


Patient Motion
A
-0.2 cm
R
H
0.0 cm
F
L
+0.1 cm
P
Periodicity
Good
Poor
Amplitude Gating
+3.0
+2.0
+1.0
0.0
-1.0
55
60
65
70
Time [s]
Auto Scale
Verification
Scale [cm]
4.0

ExacTrac (ET)


2x aSi flat-panel detector
Infrared camera
Robotic Tilt
2x kV x-ray

ET Extra-cranial positioning

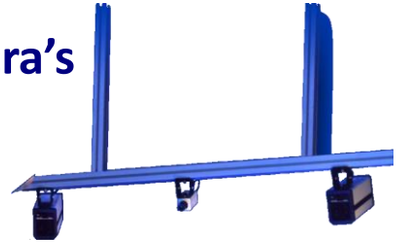


ET infrared positioning

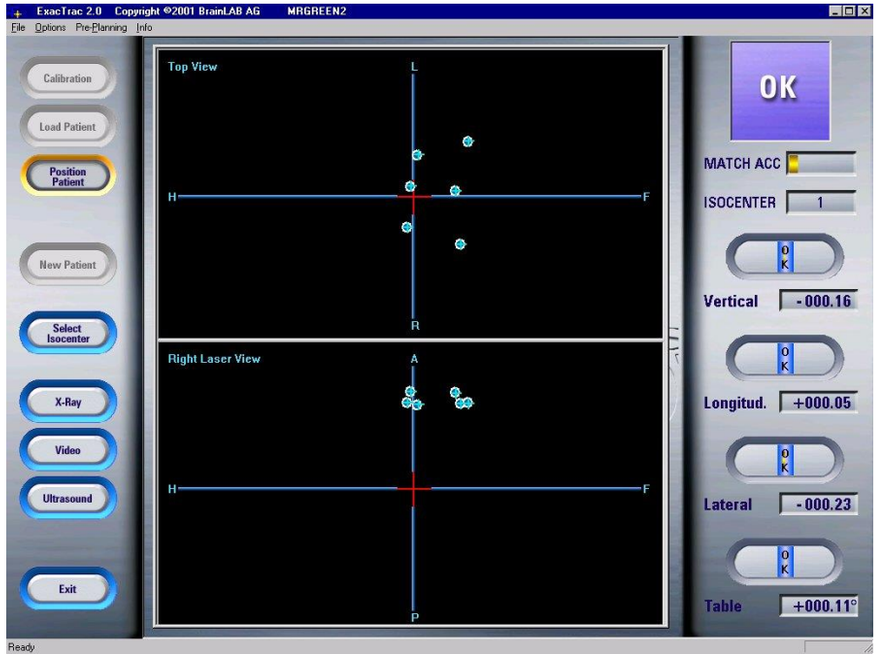
VUmc

ExacTrac markers

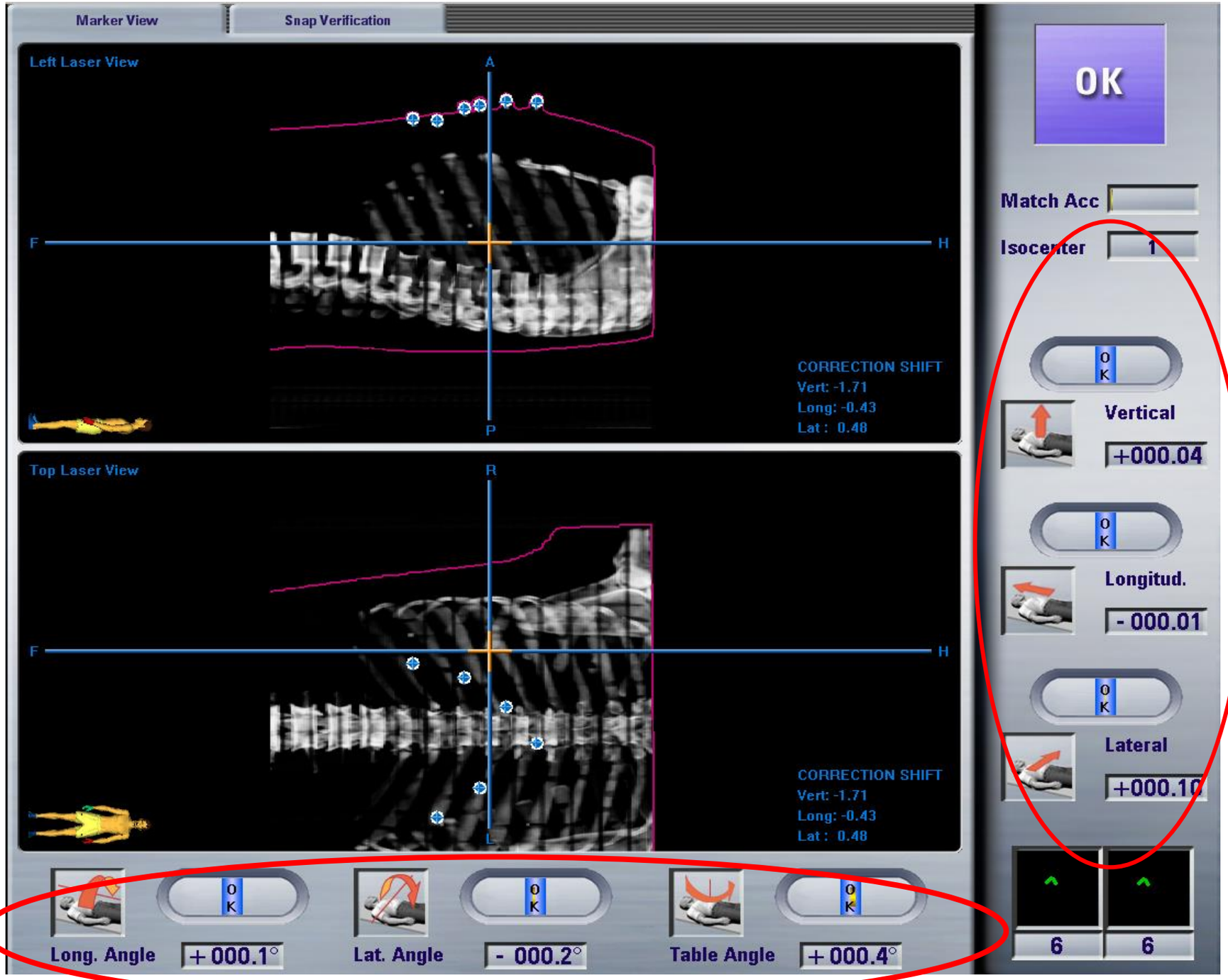
ExacTrac camera's



Procedure



Monitoring ExacTrac markers



Auto Beam Hold package

- Part of TrueBeam ® (TB) 2.0 and onwards

- ABH consists of the following steps:
  1. Triggered Imaging (TI):
     - Respiratory gating, at beam on/off
     - MU
     - Gantry angle (only for RA)
     - Time, minimum interval = 3 sec
  2. Auto detection of fiducially markers on TI (AD)
  3. Beam hold (BH) option to control state of treatme

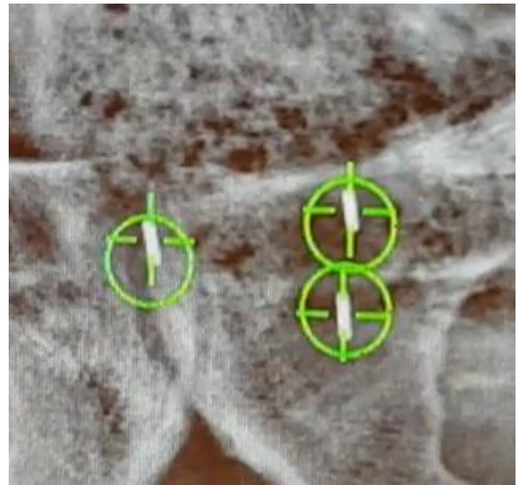
Towards PTV margin reduction for prostate using intrafraction motion correction with online kV imaging and autodetection of implanted gold seeds
T. Rosario, L. van der Weide, M. Admiraal. *Submitted*

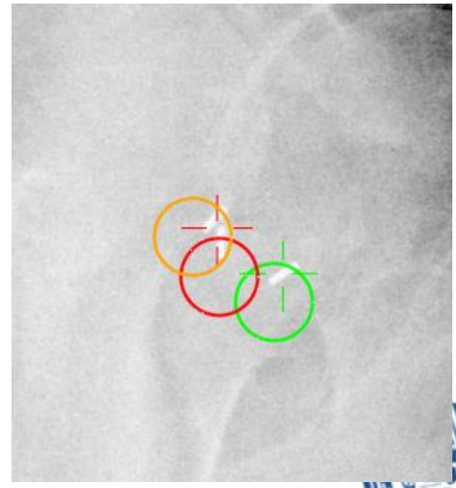
Auto detection and Beam Hold

- **User defines a spherical ROI around these markers : *TI limit***
  - COG marker on TI is marked with a cross
  - If marker on TI is inside TI Limit, circle is projected as green
  - If marker outside TI Limit circle is red
  - and if marker can't be detected, circle is projected as orange

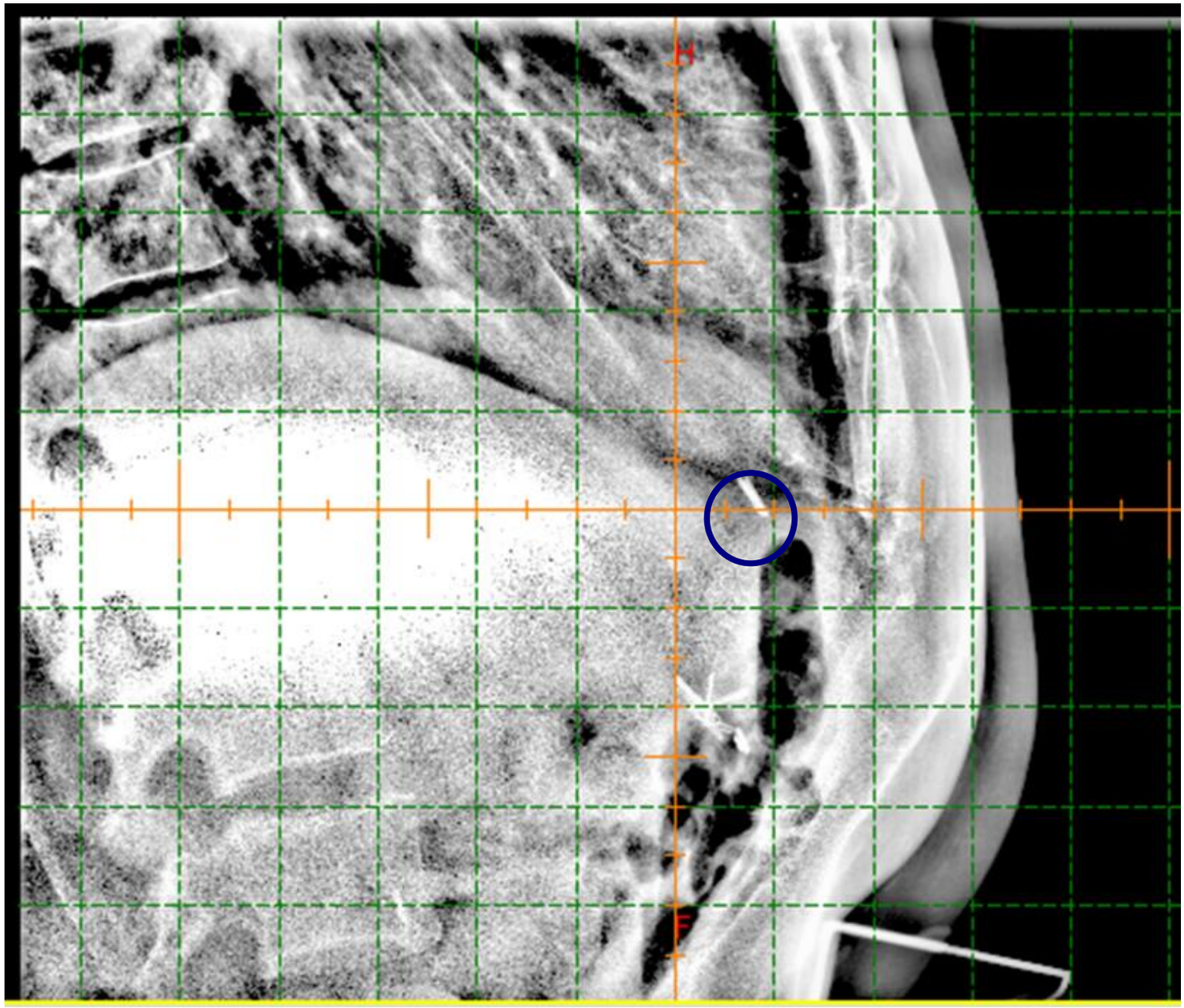
- **If >=1 markers outside TI limit treatment system can *hold (pause)* the treatment beam: beam hold (BH)**
  - If time is chosen as trigger and beam is held the system keeps shooting TI
  - If all markers return within TI limit system continues beam automatically

- **ABH can act in passive or active mode**



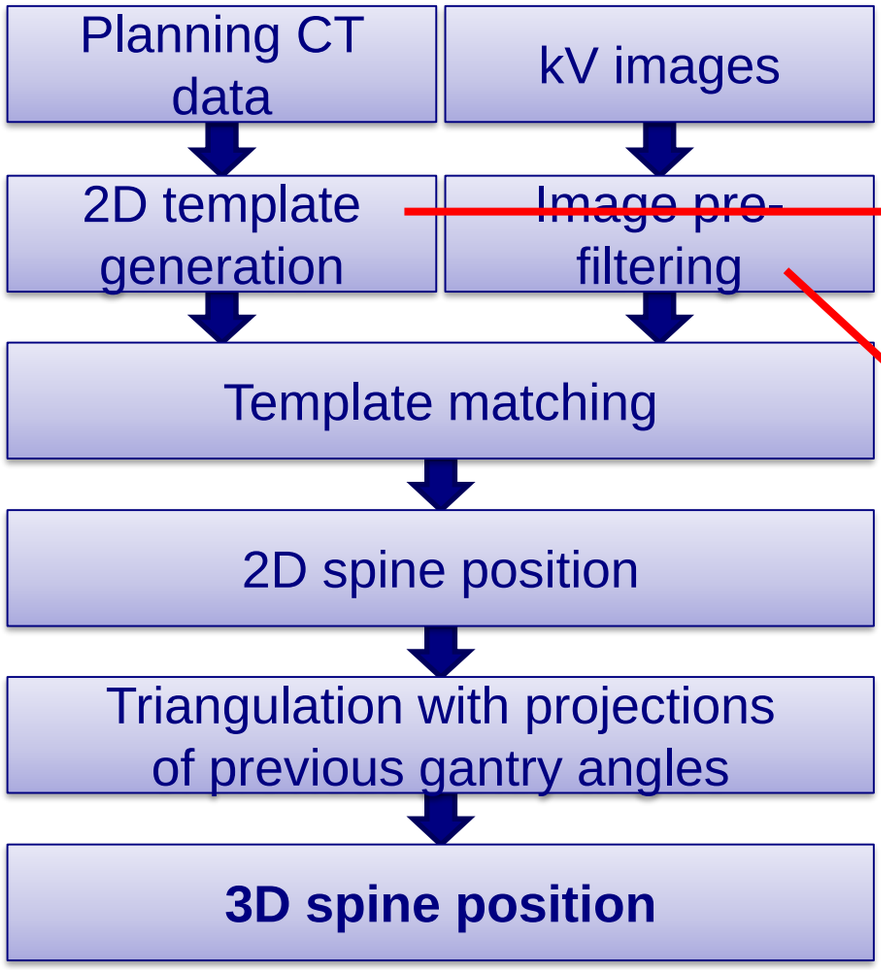


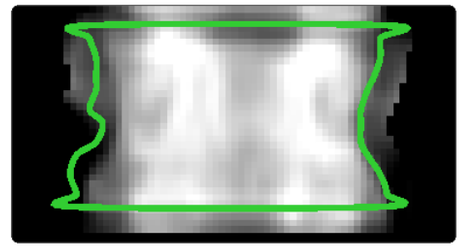
Triggered Imaging

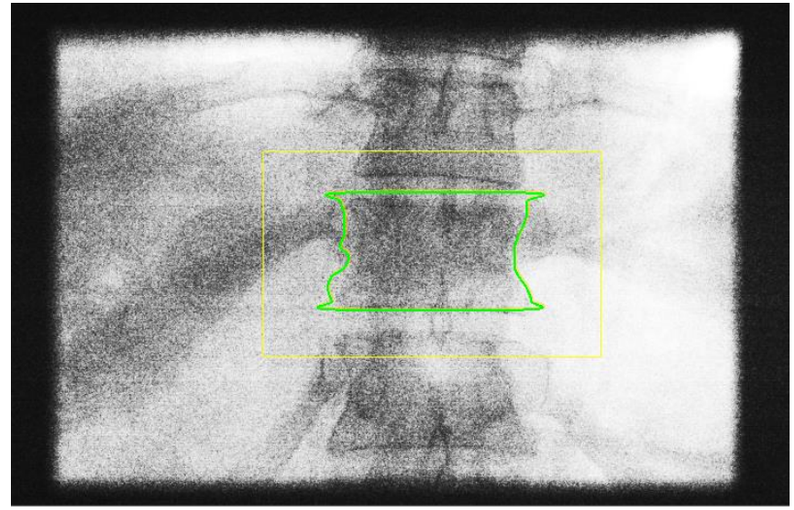


Triggered Imaging

Intrafraction movement monitoring





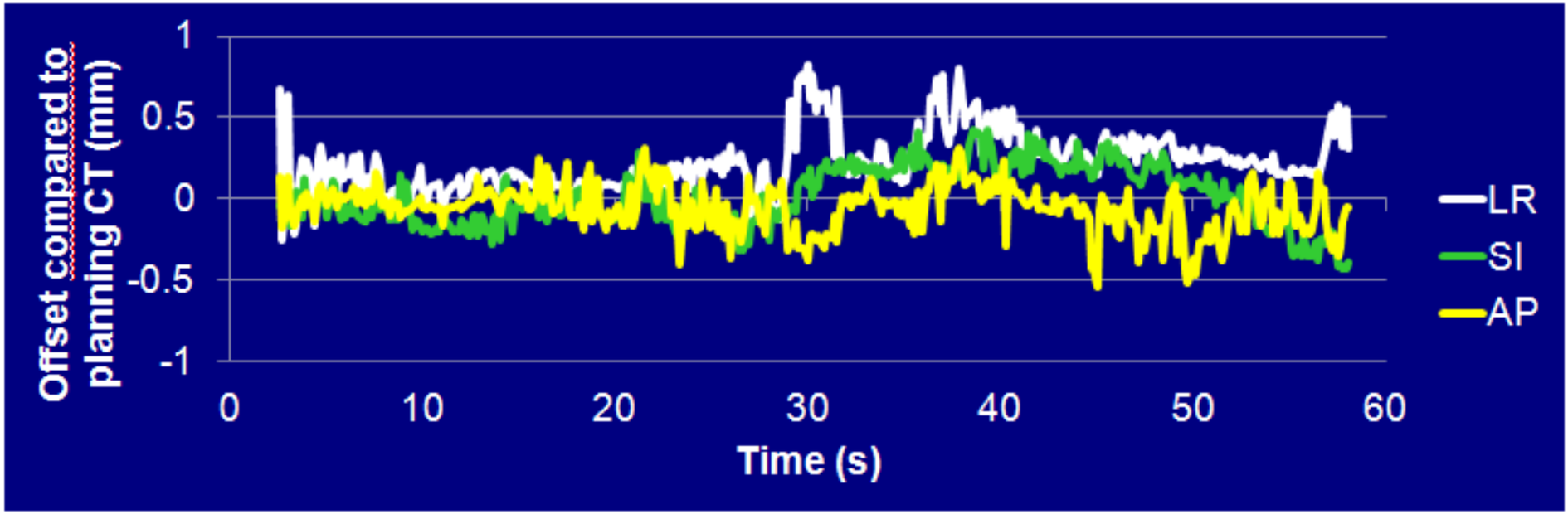


Int J Radiat Oncol Biol Phys. 2016 Apr 1;94(5):1154-62. doi: 10.1016/j.ijrobp.2016.01.006. Epub 2016 Jan 12.

Subsecond and Submillimeter Resolution Positional Verification for Stereotactic Irradiation of Spinal Lesions.

Hazelaar C[1], Dahele M[2], Mostafavi H[3], van der Weide L[2], Slotman BJ[2], Verbakel WF[2].

Results intrafraction monitoring



For all patient data (n=18 patients, 93 datasets):

- Able to determine spine position: 91% of images per dataset
- Mean $SD_{LR,SI,AP}$ < 0.3 mm (range 0.1 – 0.8 mm)
- Average offset ≥ 1 mm: 7 datasets

Patient monitoring

- Before treatment
  - Wellbeing of the patient/ medication
  - Questions?
- During treatment:
  - Intrafraction monitoring

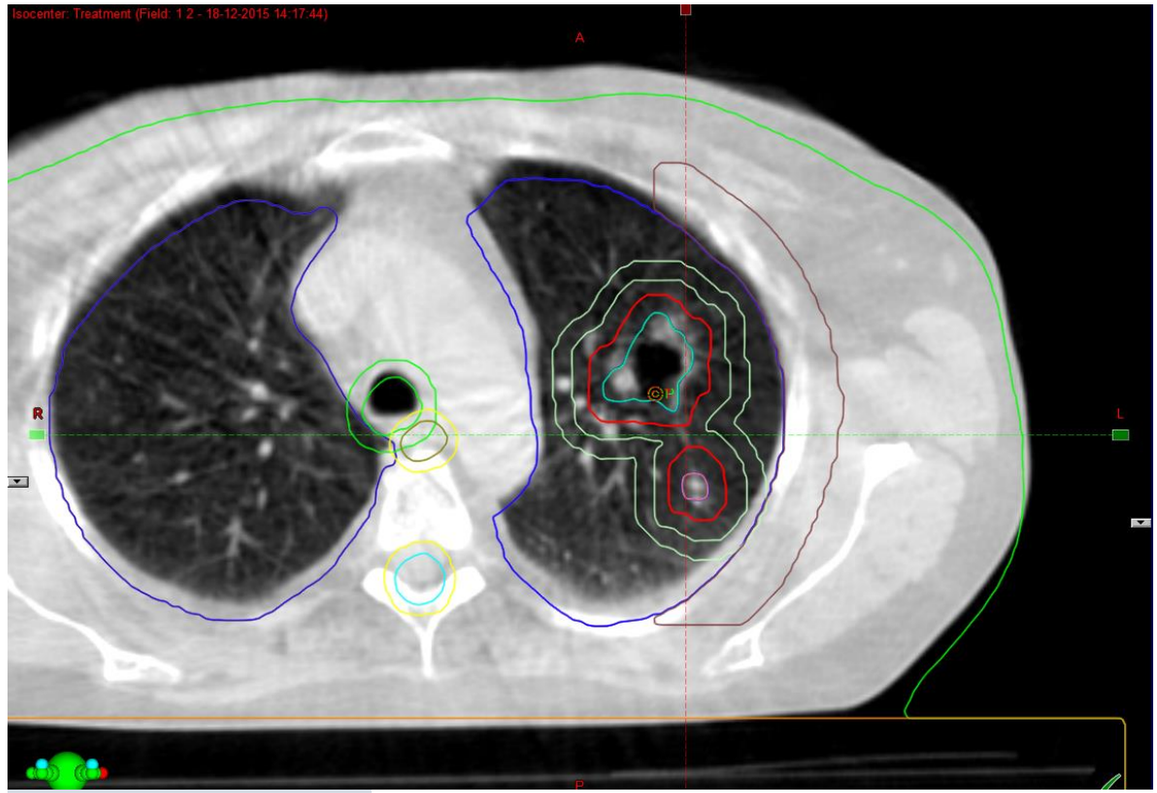
- After treatment:
  - Wellbeing of the patient
  - Questions?

Some cases

- Lung
- Liver
- Kidney
- Lymph node from bladder tumor
- Lymph node from prostate tumor
- Adrenal gland
- Spine

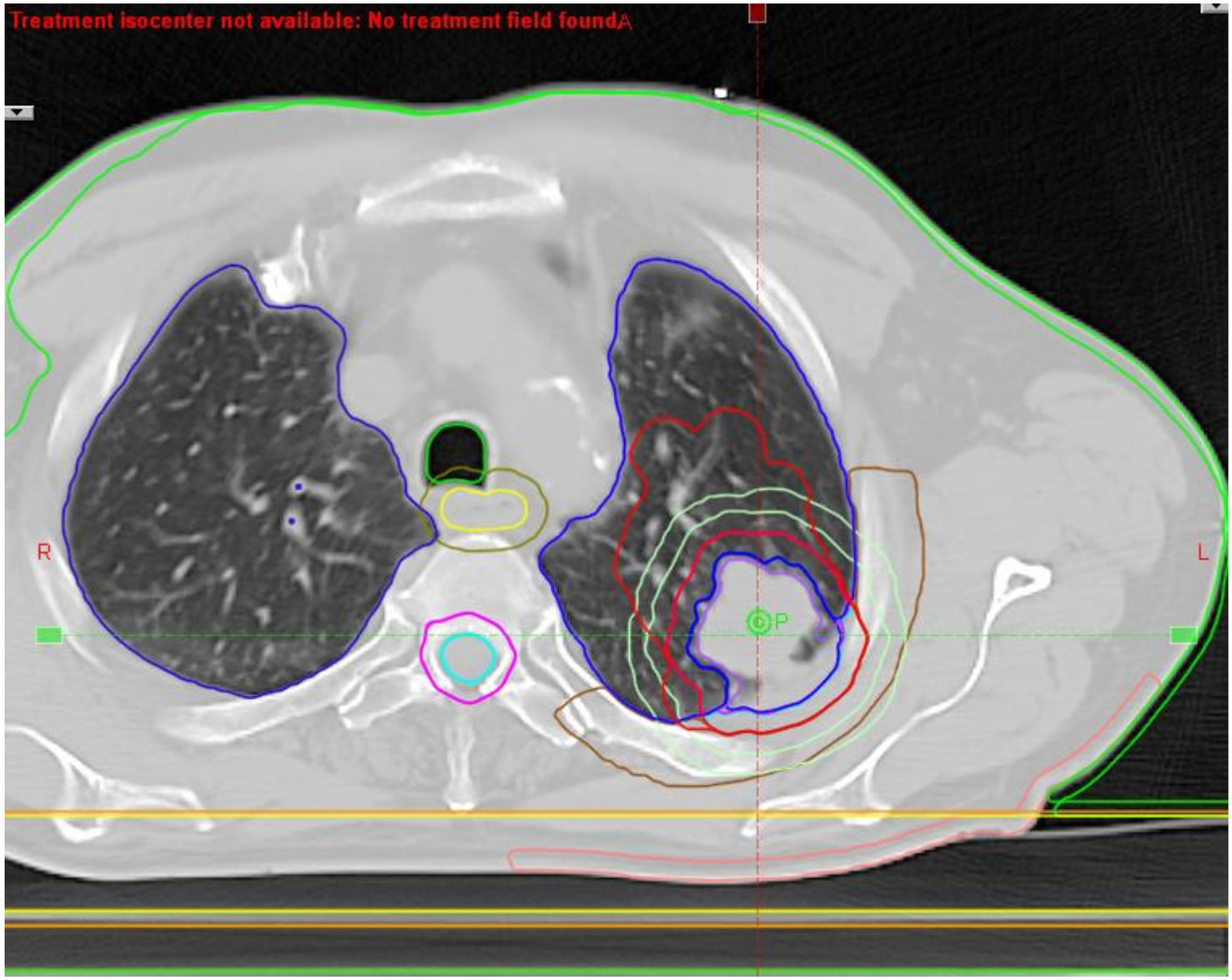
Use of 6D-couch

55-yr old patient
Multiple lesions left lung
2 lesions in 1 PTV
8 x 7,5 Gy

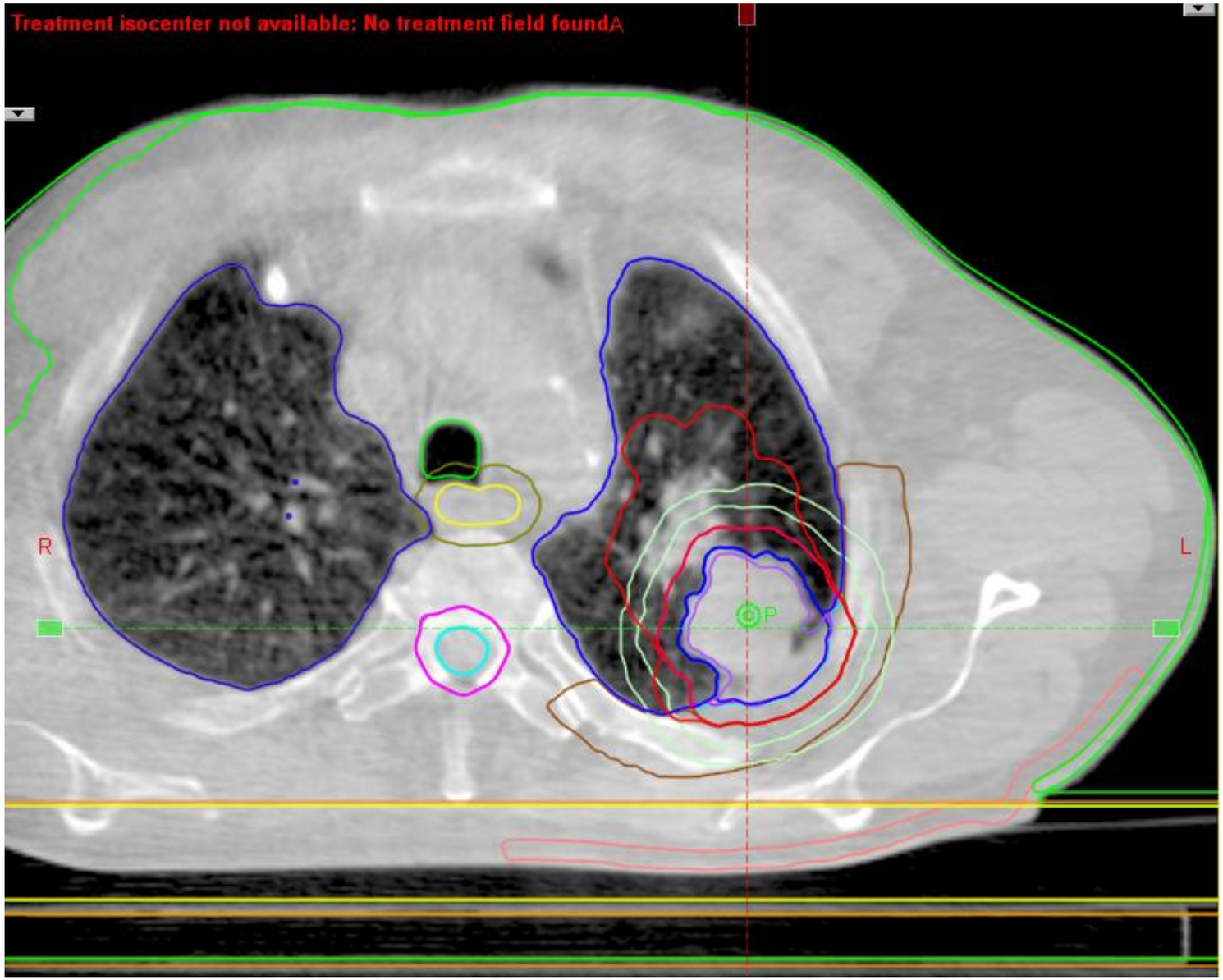


	kV_CBCT_3a
Status	✓
Vrt [cm]	-0,49
Lng [cm]	+0,76
Lat [cm]	+0,53
Pitch [°]	0,0
Roll [°]	-0,8
Rtn [°]	0,0

CT, Lung case

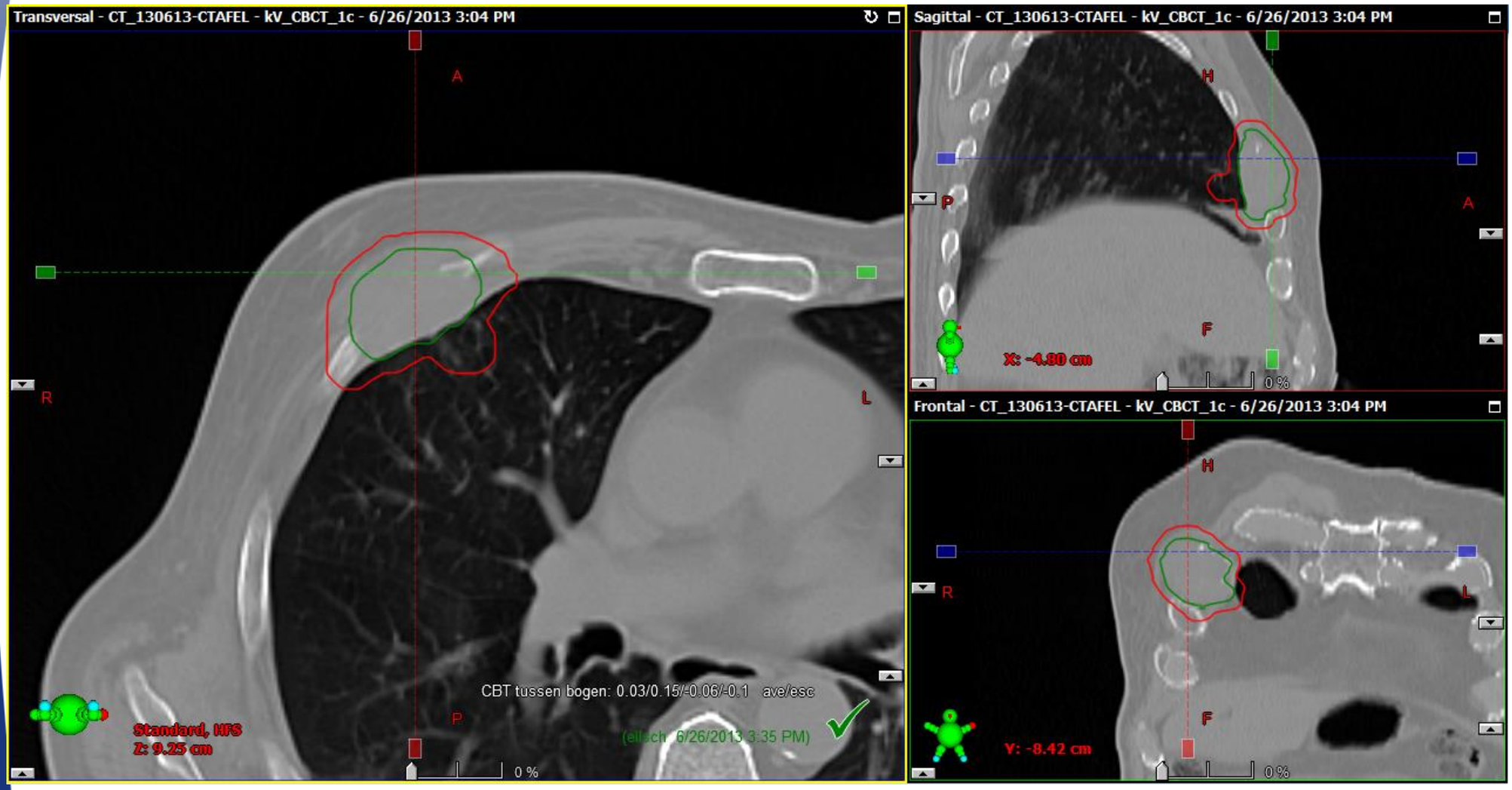

Treatment isocenter not available: No treatment field found
R
L
P

CBCT, Lung case

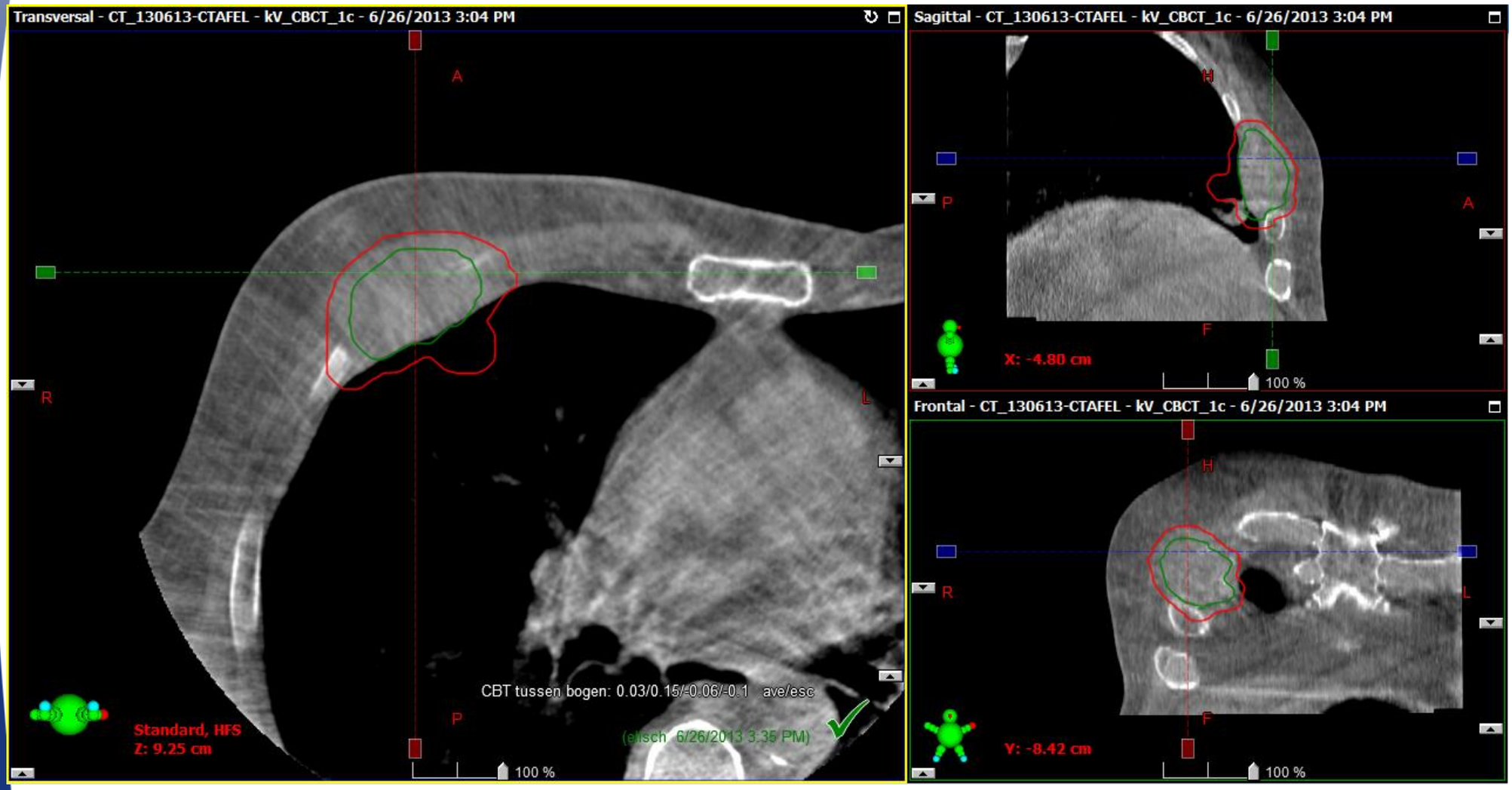


New plan, lung case

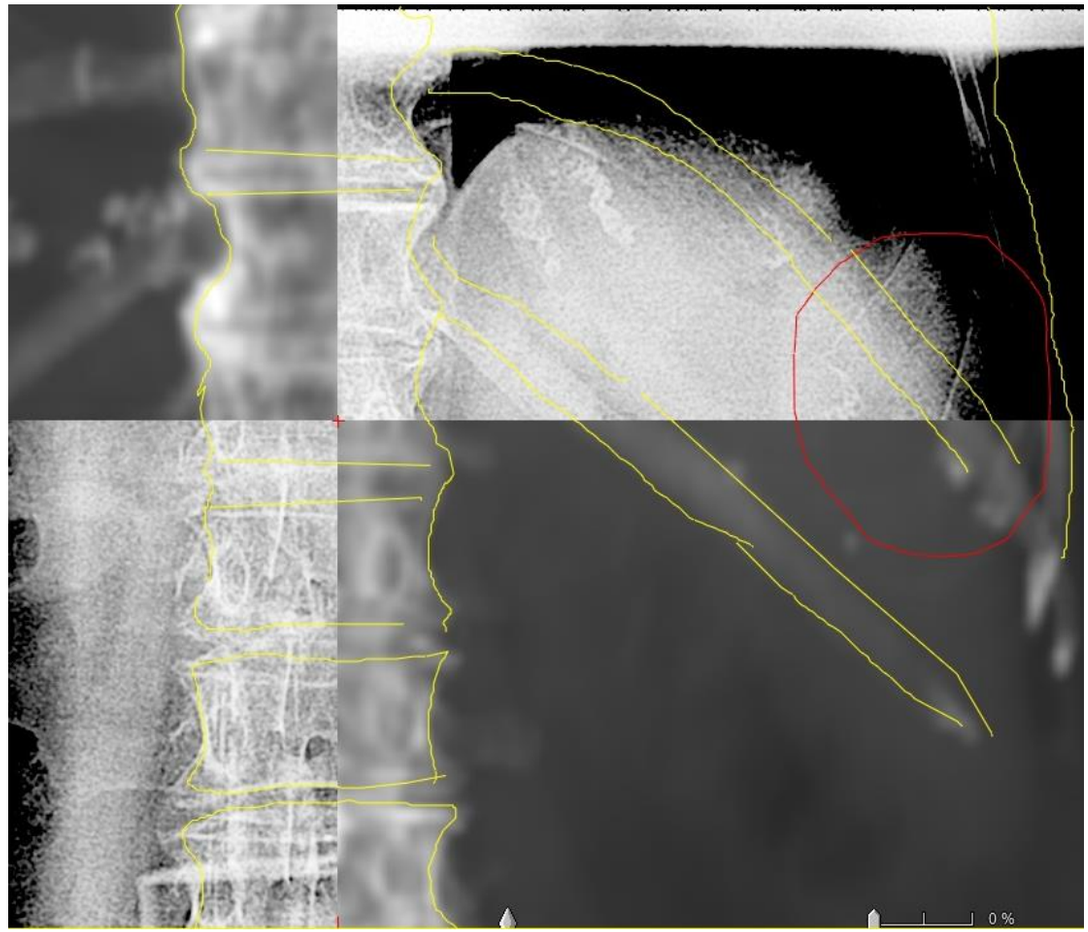
CT, Lung case


Transversal - CT_130613-CTAFEL - kV_CBCT_1c - 6/26/2013 3:04 PM
A
R
L
P
CBT tussen bogen: 0.03/0.15/-0.06/-0.1 ave/esc
(ellisch 6/26/2013 3:35 PM)
Standard, HFS
Z: 9.25 cm
0 %
Sagittal - CT_130613-CTAFEL - kV_CBCT_1c - 6/26/2013 3:04 PM
H
P
A
F
X: -4.80 cm
0 %
Frontal - CT_130613-CTAFEL - kV_CBCT_1c - 6/26/2013 3:04 PM
H
R
L
F
Y: -8.42 cm
0 %

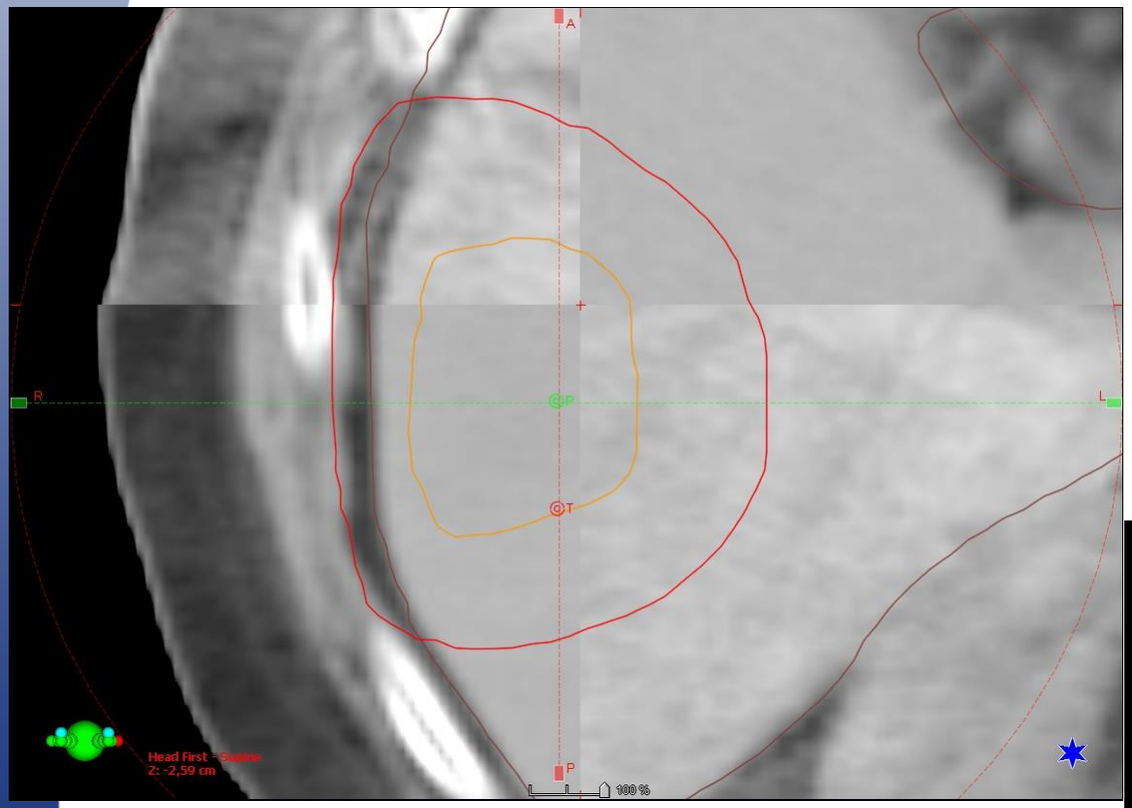
CBCT, lung case

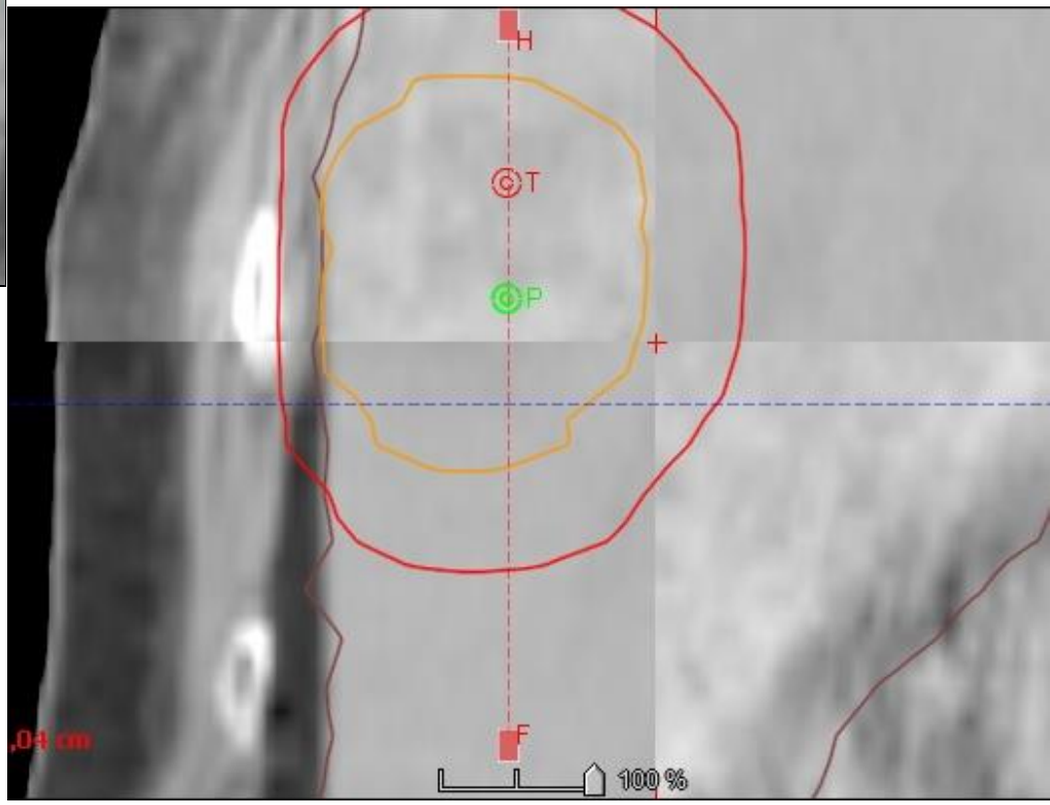


kV-images, liver case



CBCT, liver

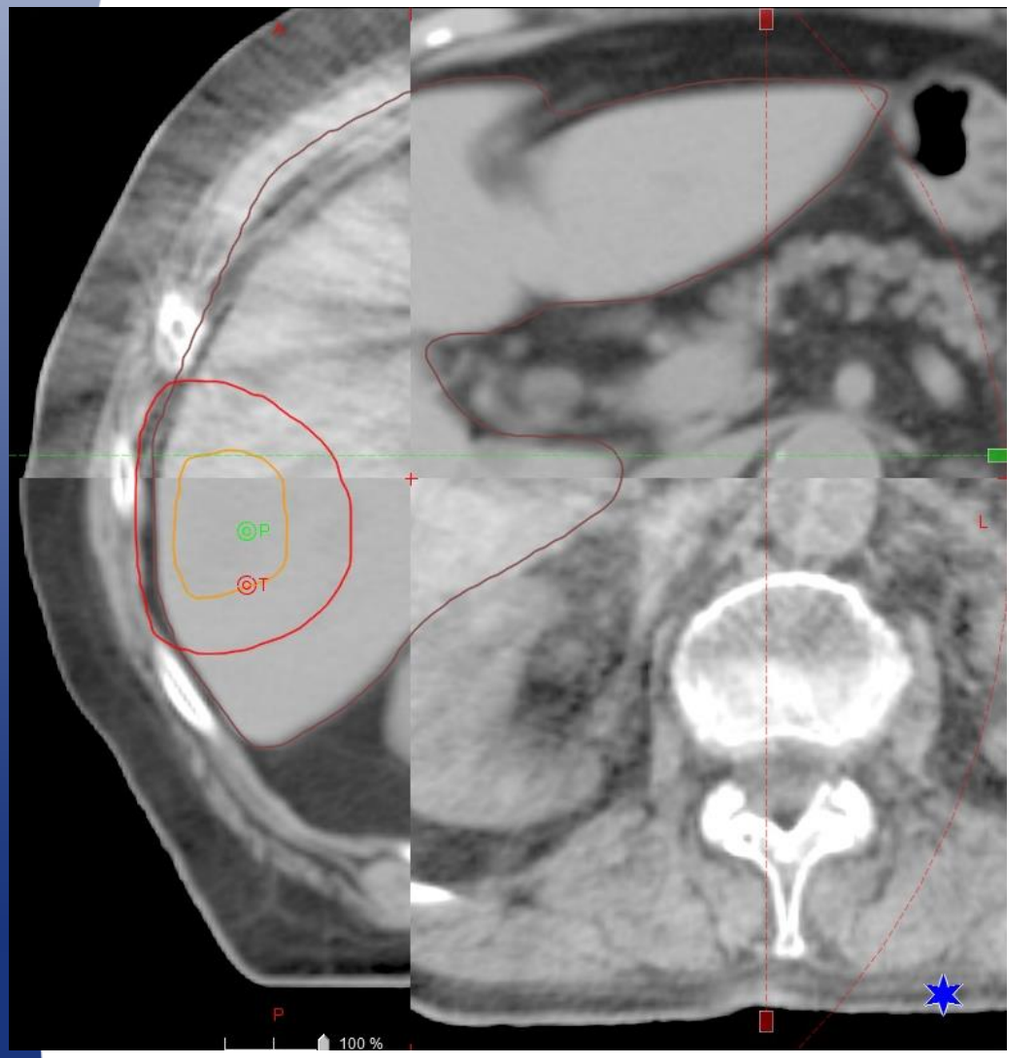


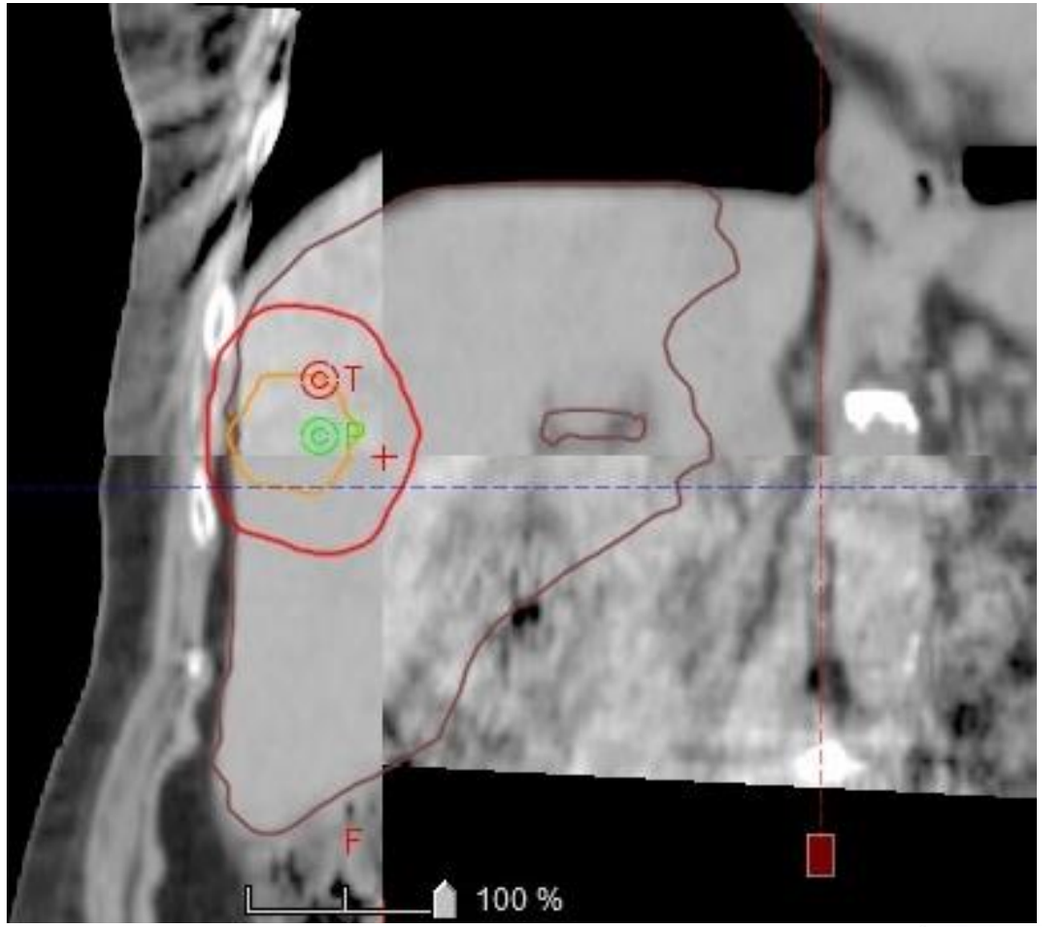


Is the match properly done?

- Yes
- Moreorless
- No

CBCT, liver

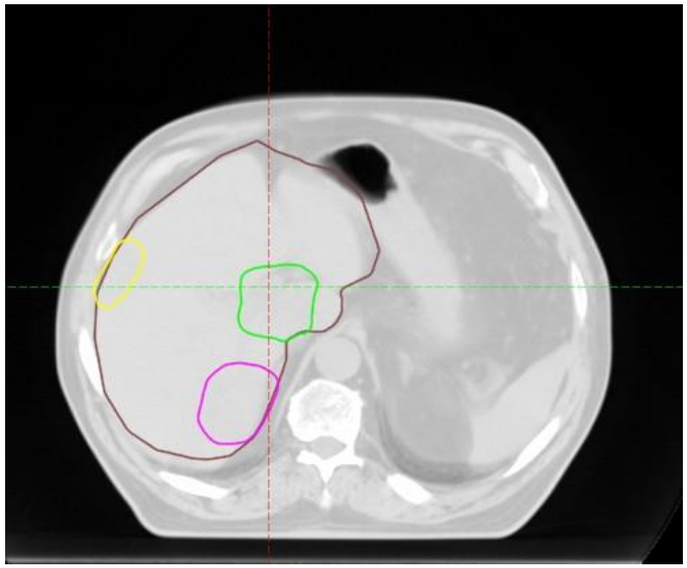
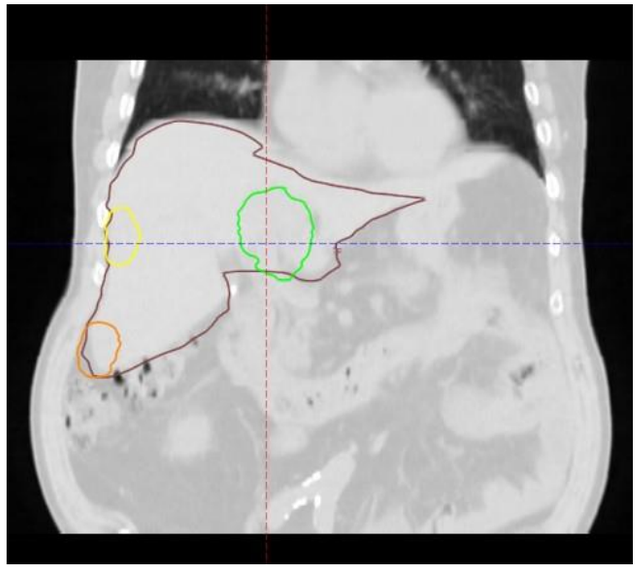
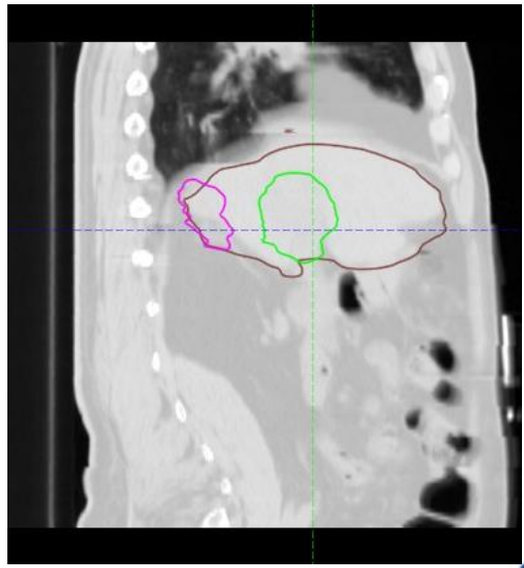




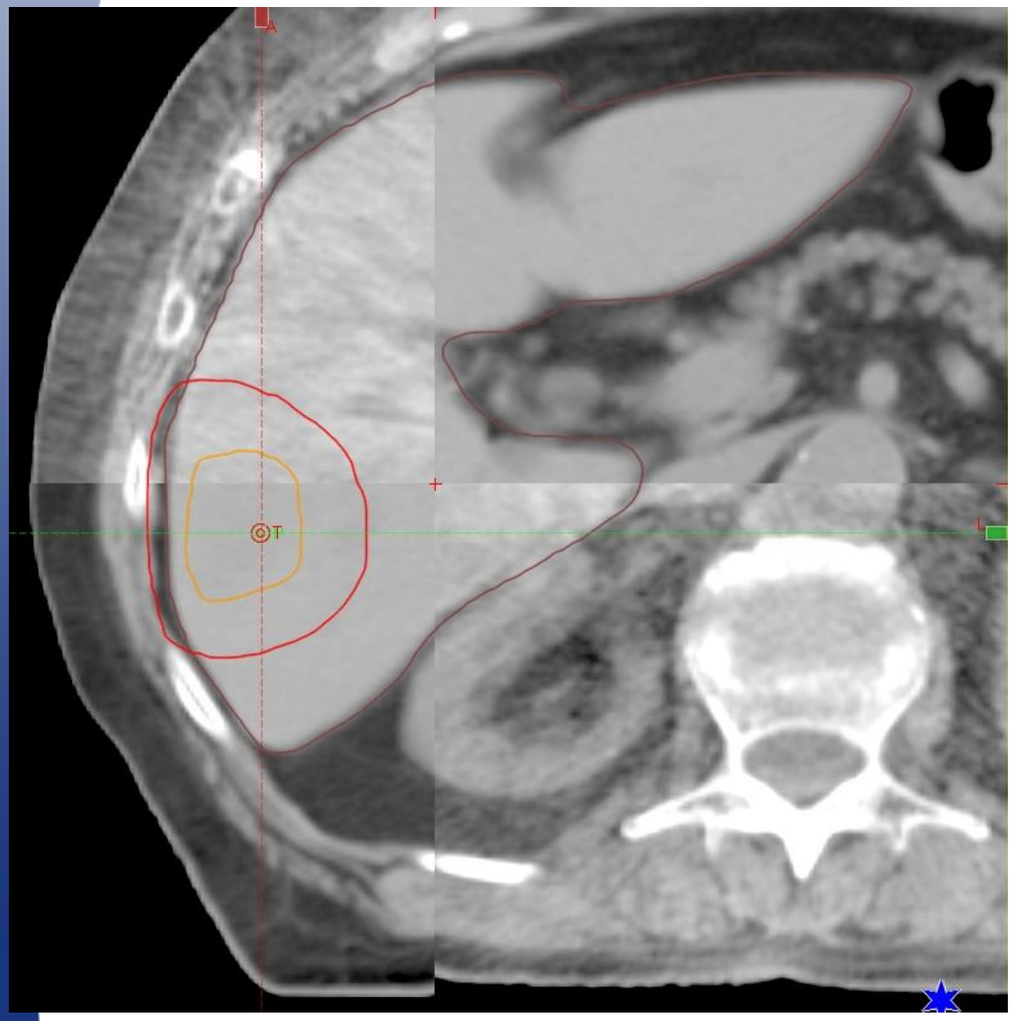
Organs at risk

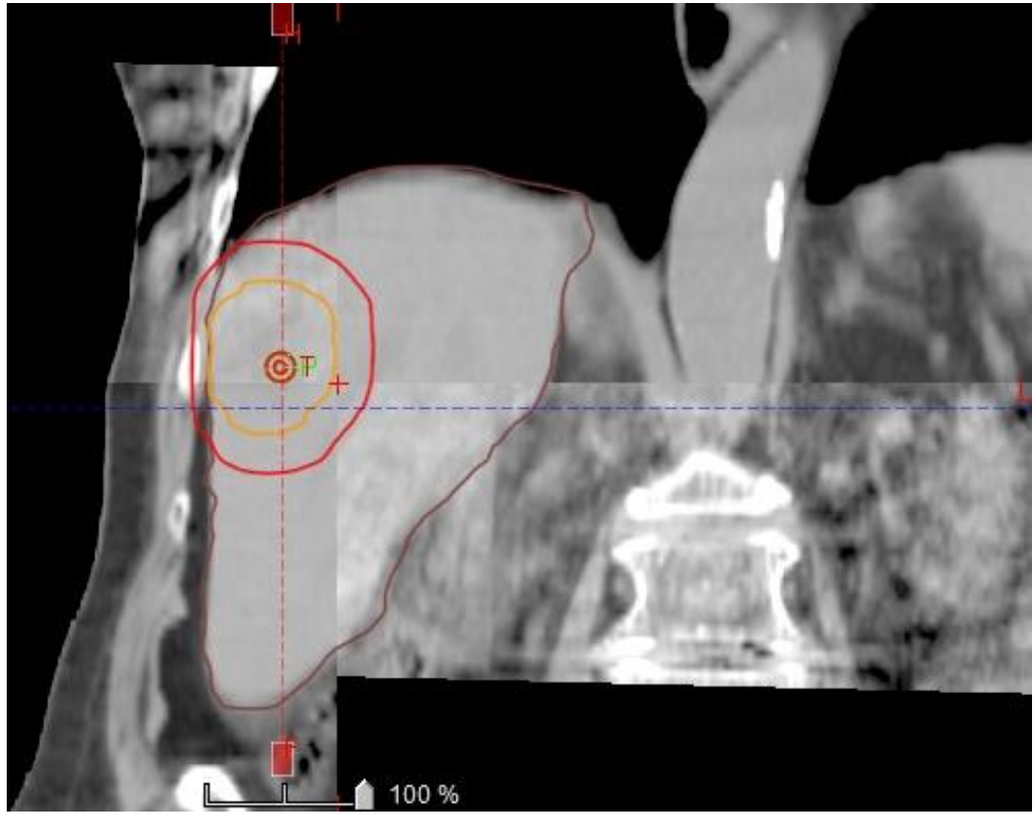
66-yr old patient
4 lesions in liver
1 lesion close to stomach (C1)
1 lesion close to bowel (C4)

Fractionation scheme:
C1-C3: 8*7,5 Gy
C4: 12*5 Gy

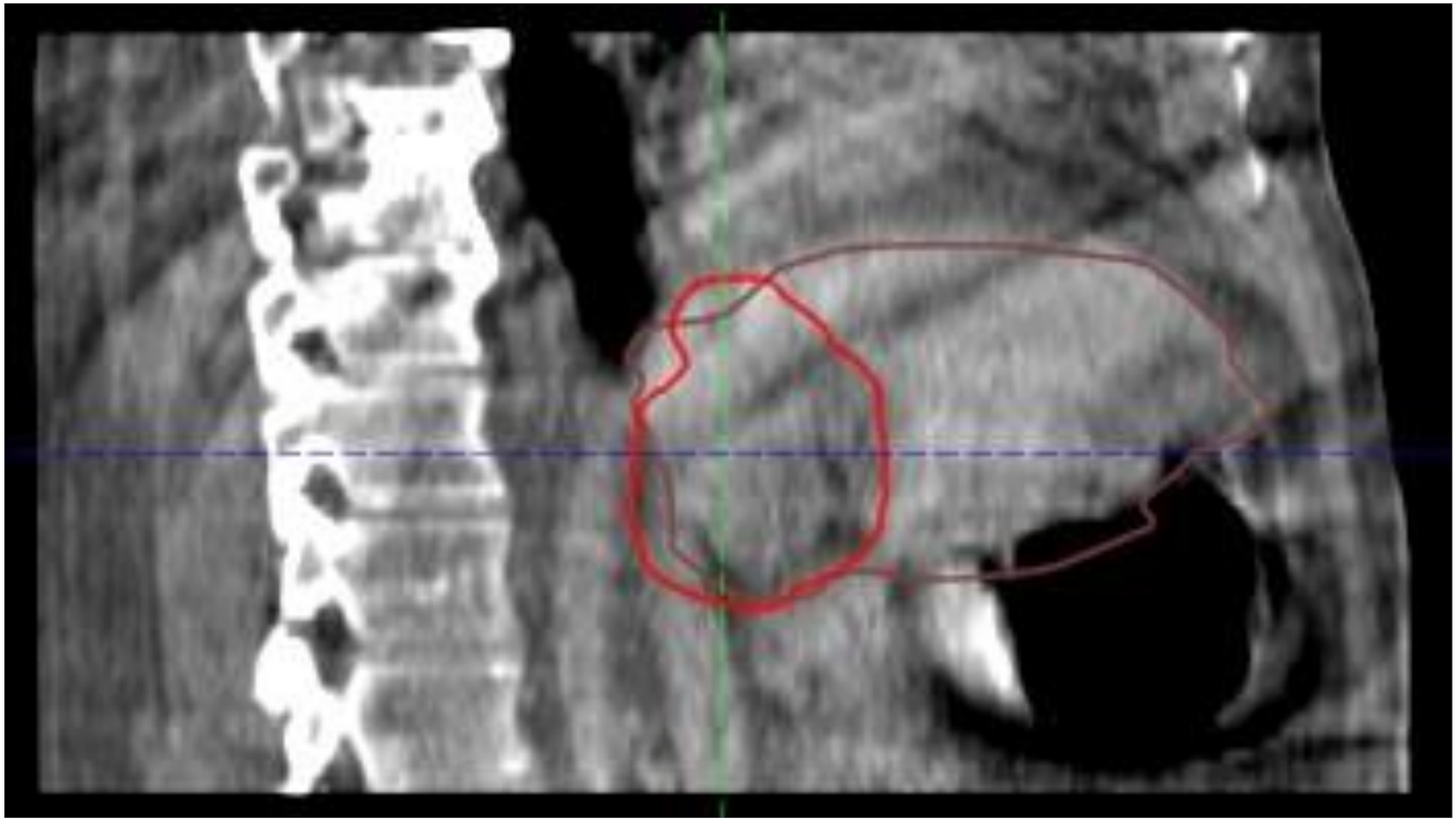
CBCT, liver





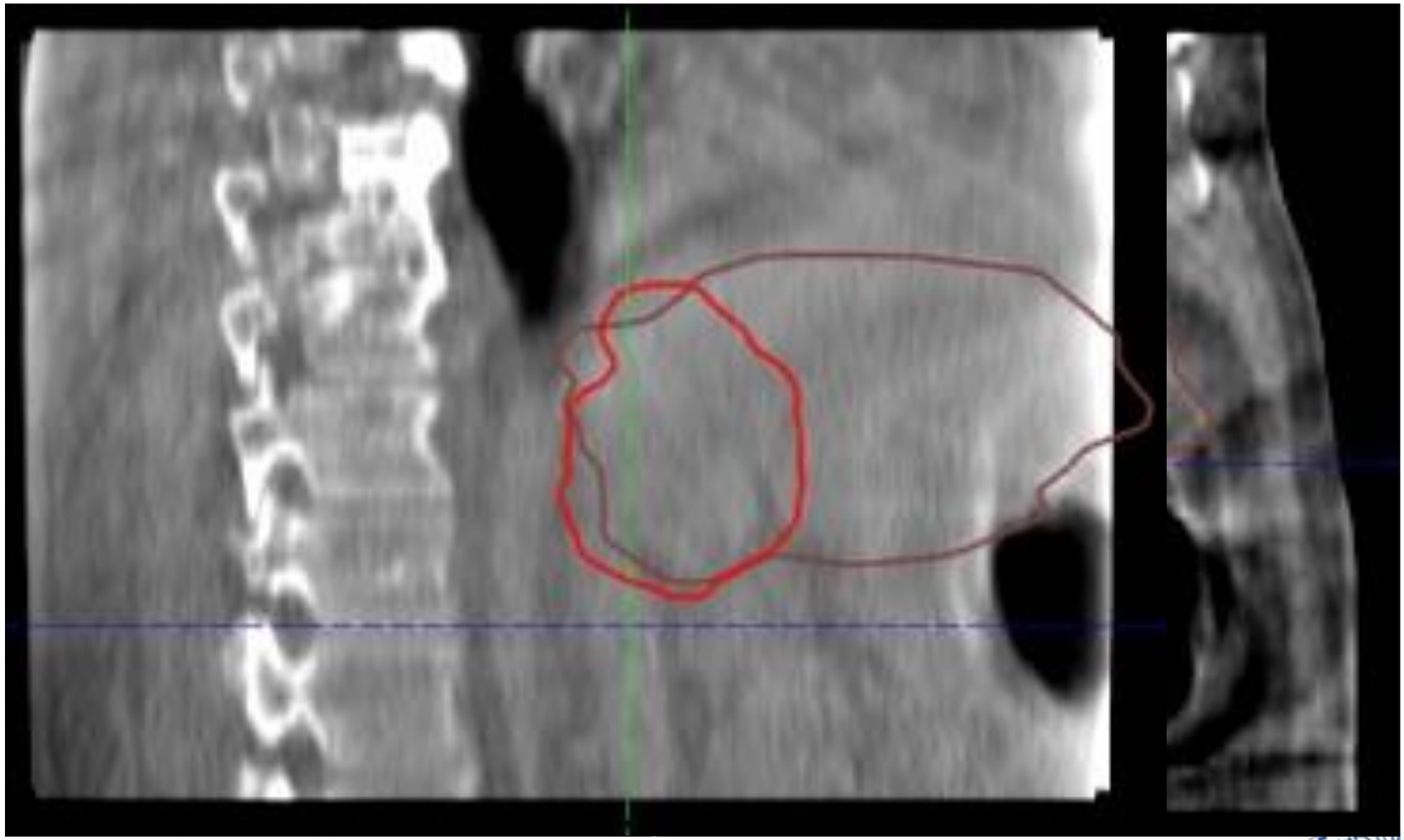
	kV_270_1 - kV_180_1	kV_CBCT_1
Status	*	*
Vrt [cm]		+1,13
Lng [cm]		+1,17
Lat [cm]		-0,08
Pitch [deg]		+0,1
Roll [deg]		-1,9
Rtn [deg]		+1,5

What to do?

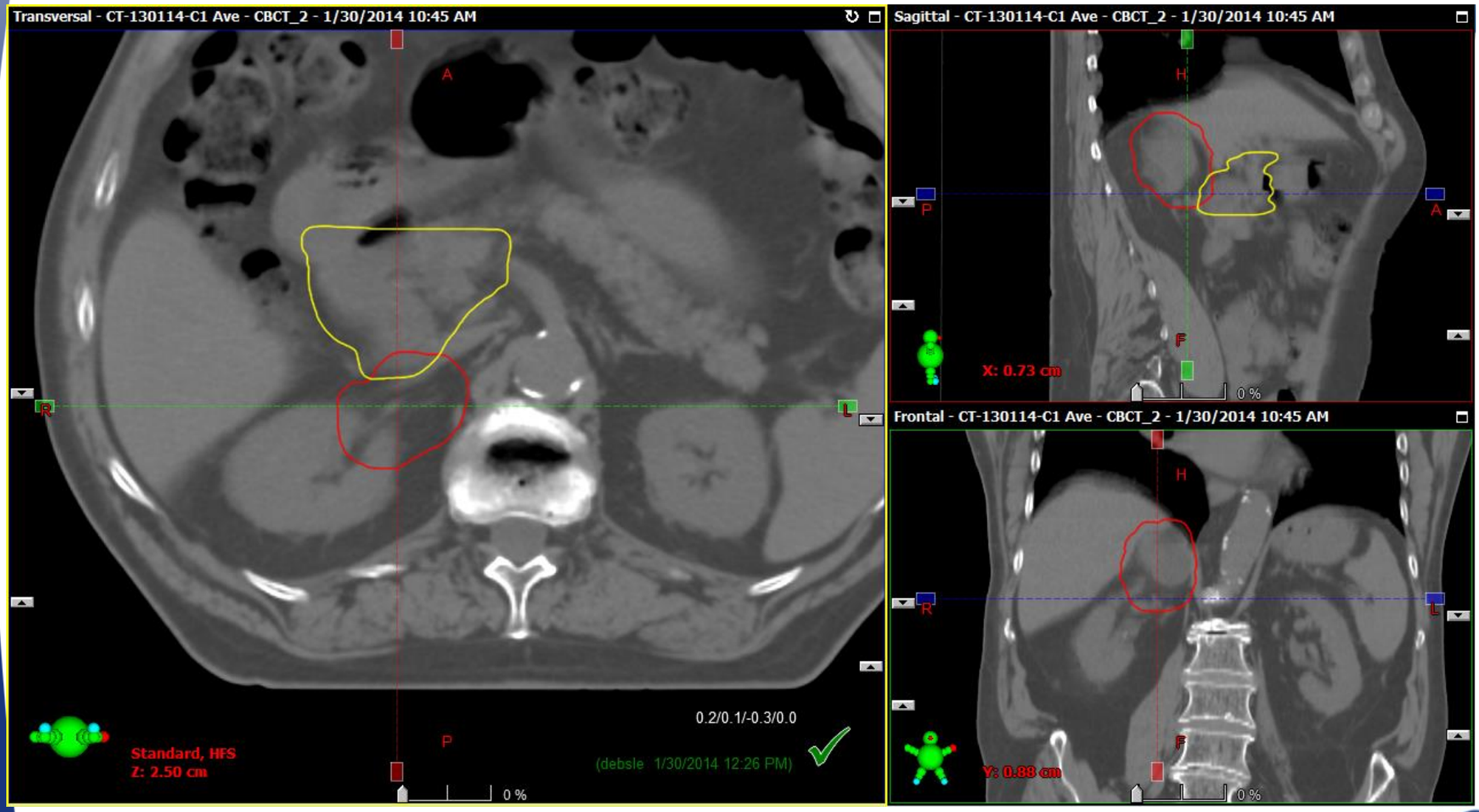


What to do?

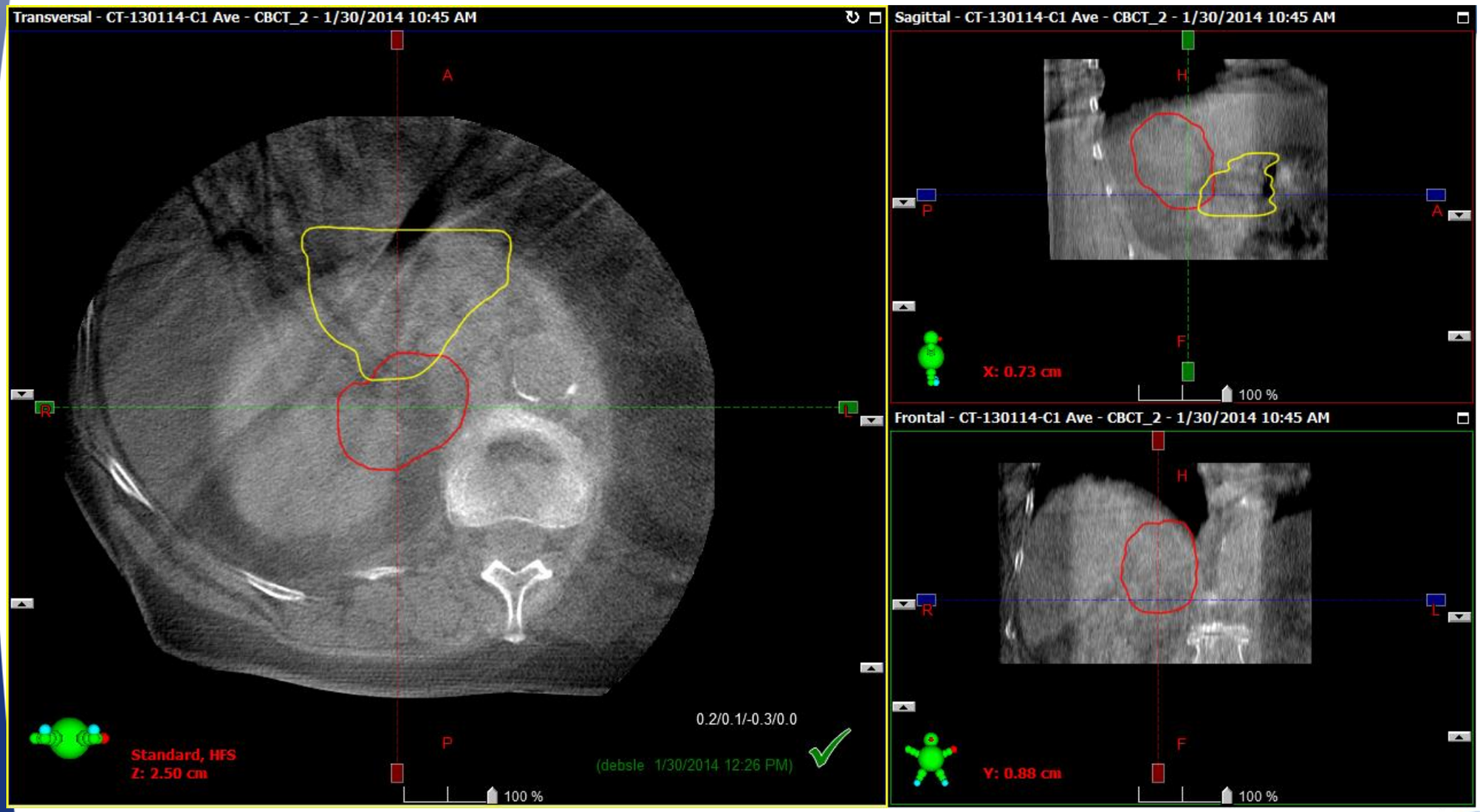
- Ignore the air bubble, match and go on?
- Wait and see what happen?
- Try to let the patiënt belch the air?



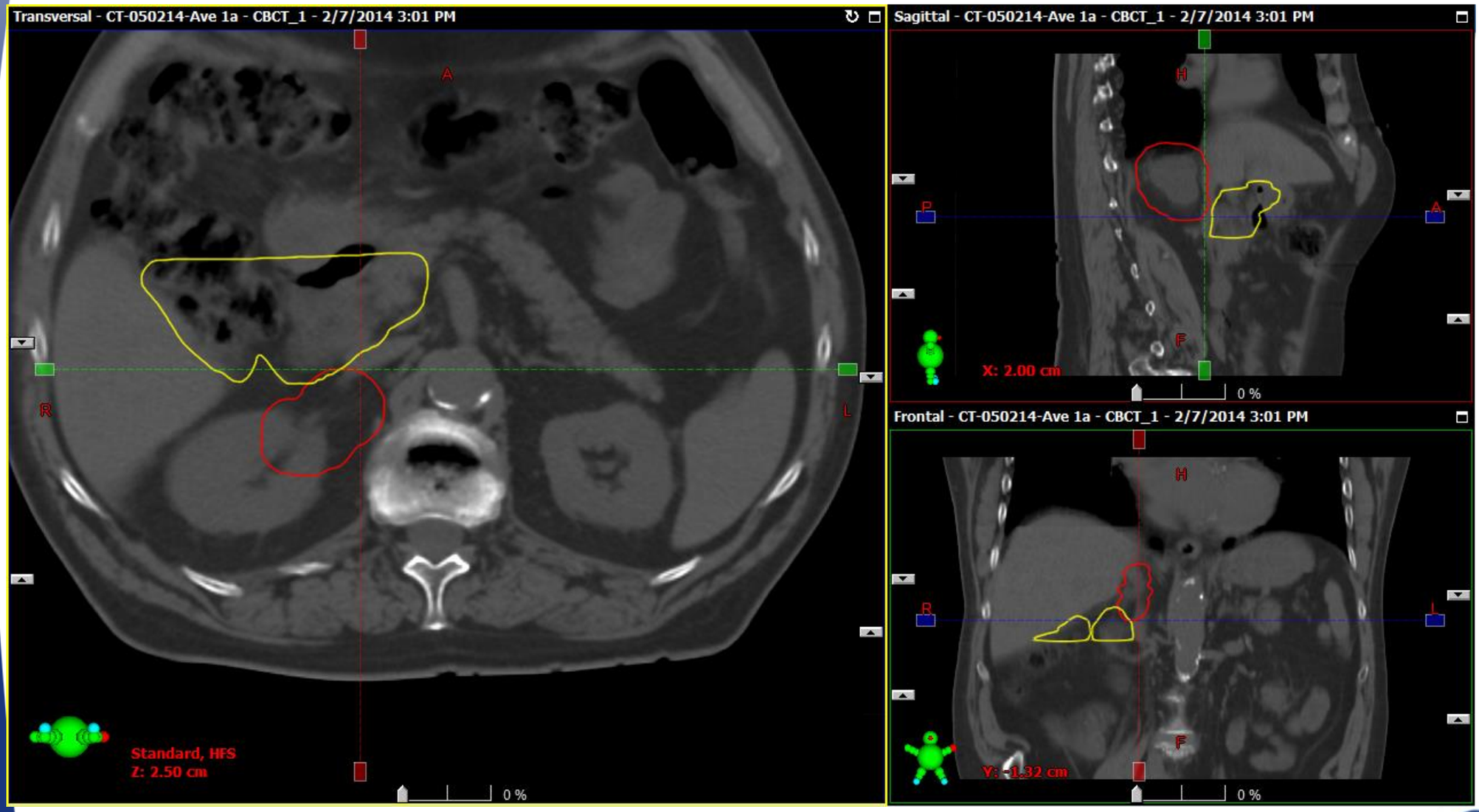
Kidney case


Transversal - CT-130114-C1 Ave - CBCT_2 - 1/30/2014 10:45 AM
A
R
L
P
Standard, HFS
Z: 2.50 cm
0.2/0.1/-0.3/0.0
(debsle 1/30/2014 12:26 PM)
0 %
Sagittal - CT-130114-C1 Ave - CBCT_2 - 1/30/2014 10:45 AM
H
P
A
F
X: 0.73 cm
0 %
Frontal - CT-130114-C1 Ave - CBCT_2 - 1/30/2014 10:45 AM
H
R
L
F
Y: 0.88 cm
0 %

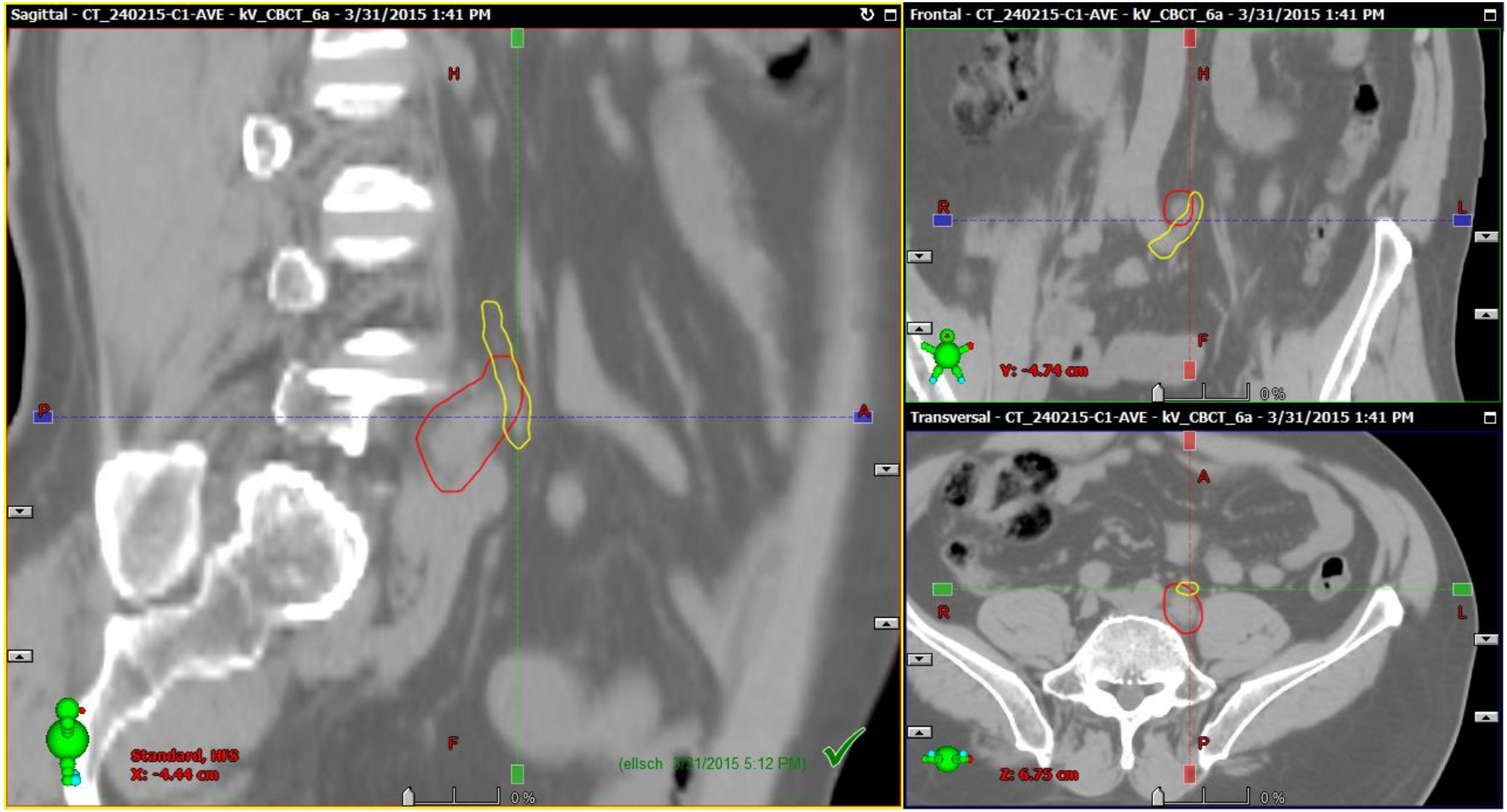
Kidney case


Transversal - CT-130114-C1 Ave - CBCT_2 - 1/30/2014 10:45 AM
A
R
L
P
Standard, HFS
Z: 2.50 cm
0.2/0.1/-0.3/0.0
(debsle 1/30/2014 12:26 PM)
100 %
Sagittal - CT-130114-C1 Ave - CBCT_2 - 1/30/2014 10:45 AM
H
P
A
F
X: 0.73 cm
100 %
Frontal - CT-130114-C1 Ave - CBCT_2 - 1/30/2014 10:45 AM
H
R
L
F
Y: 0.88 cm
100 %

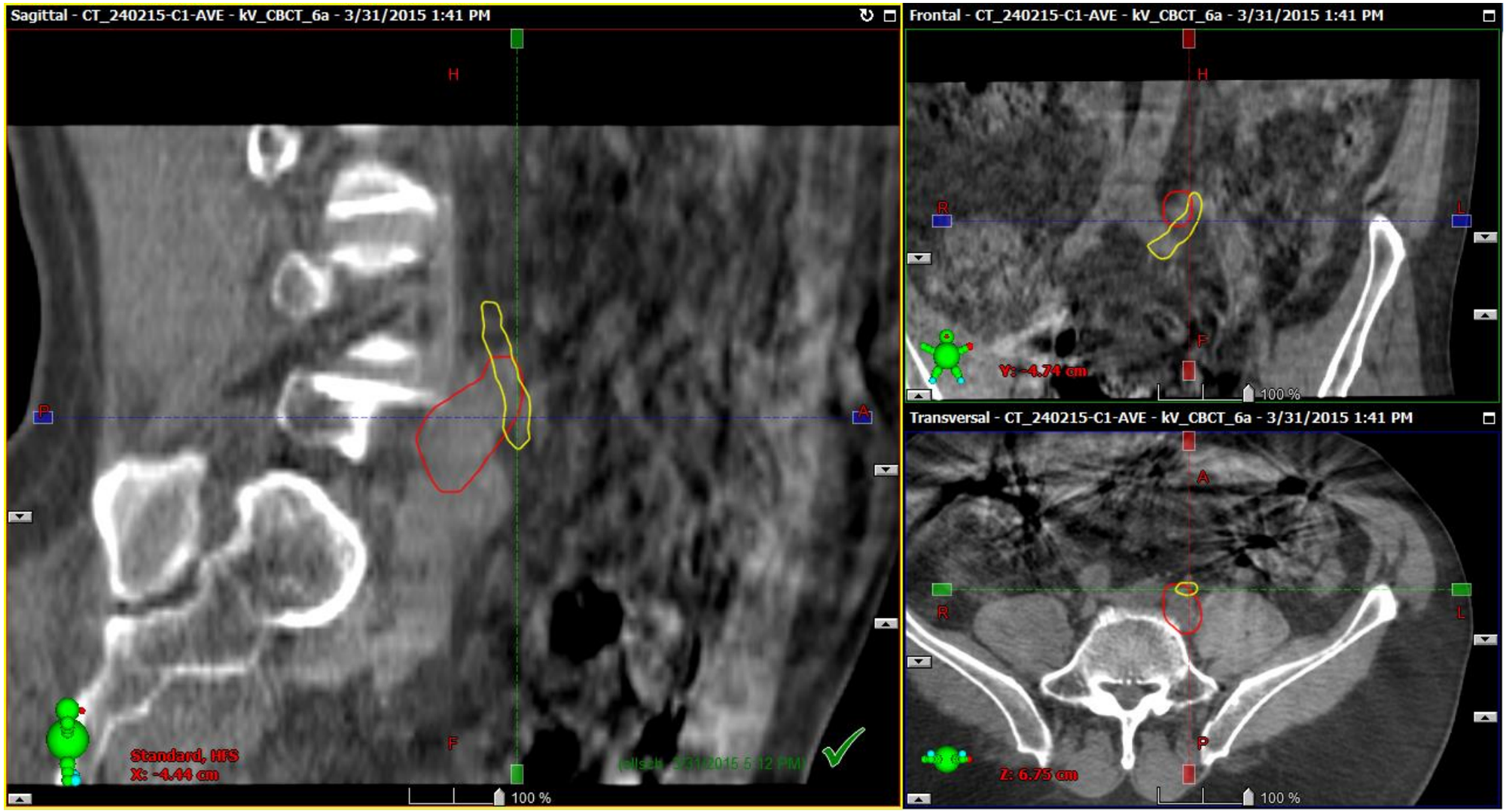
Kidney


Transversal - CT-050214-Ave 1a - CBCT_1 - 2/7/2014 3:01 PM
A
R
L
Standard, HFS
Z: 2.50 cm
0 %
Sagittal - CT-050214-Ave 1a - CBCT_1 - 2/7/2014 3:01 PM
H
P
A
F
X: 2.00 cm
0 %
Frontal - CT-050214-Ave 1a - CBCT_1 - 2/7/2014 3:01 PM
H
R
L
F
Y: -1.32 cm
0 %

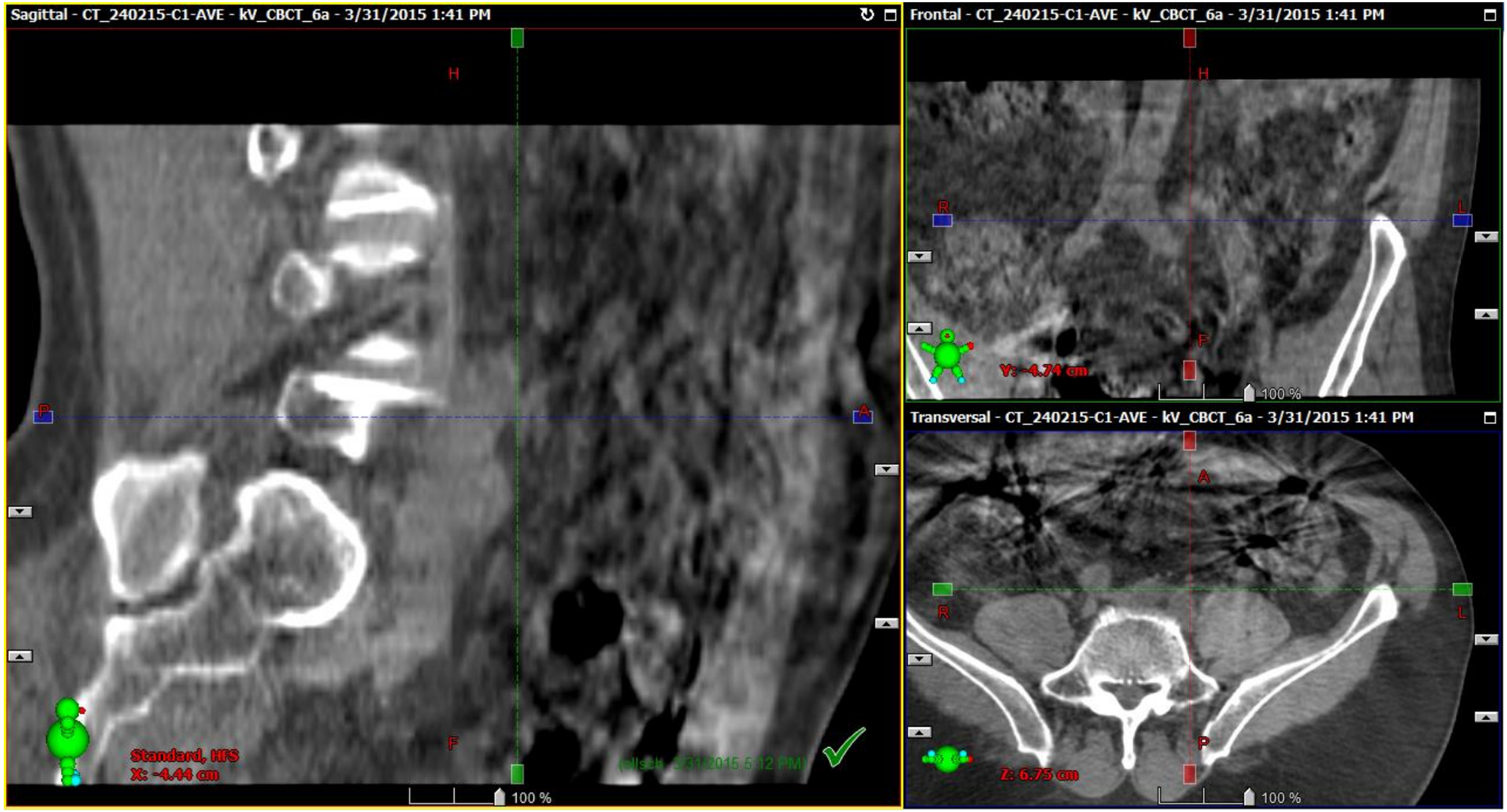
CT, lymph node bladder tumor



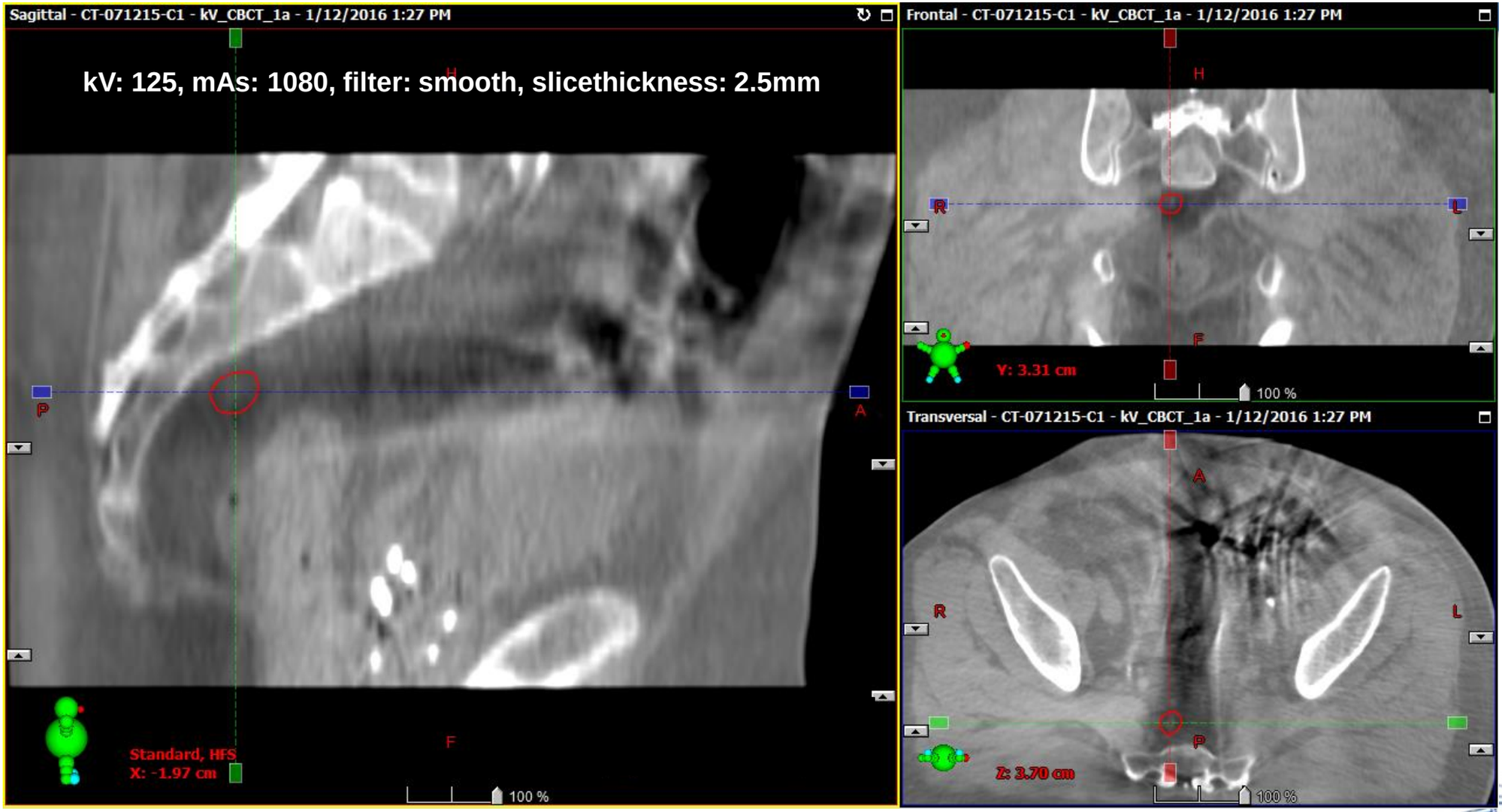
CBCT, lymph node



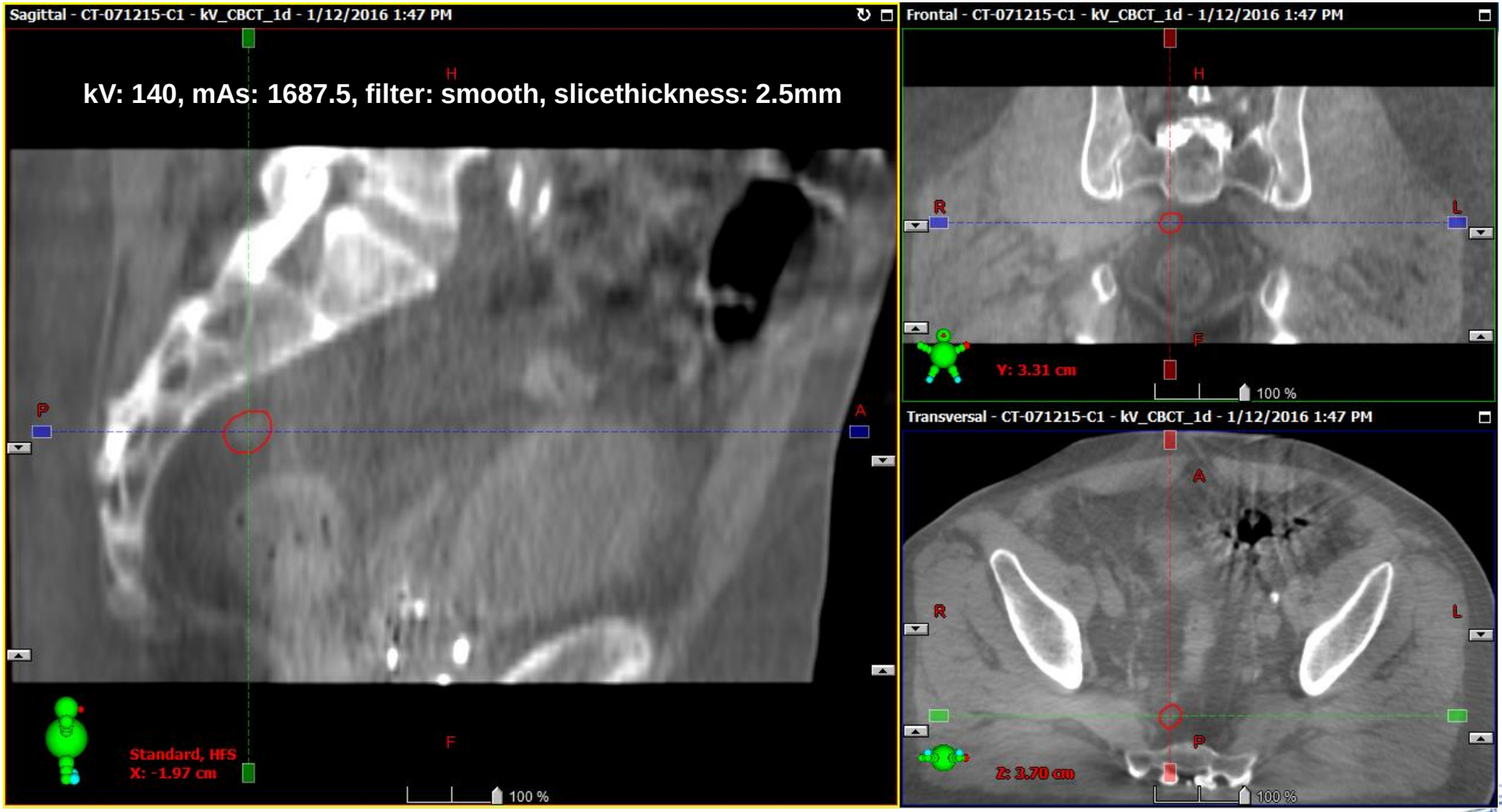
CBCT, lymph node



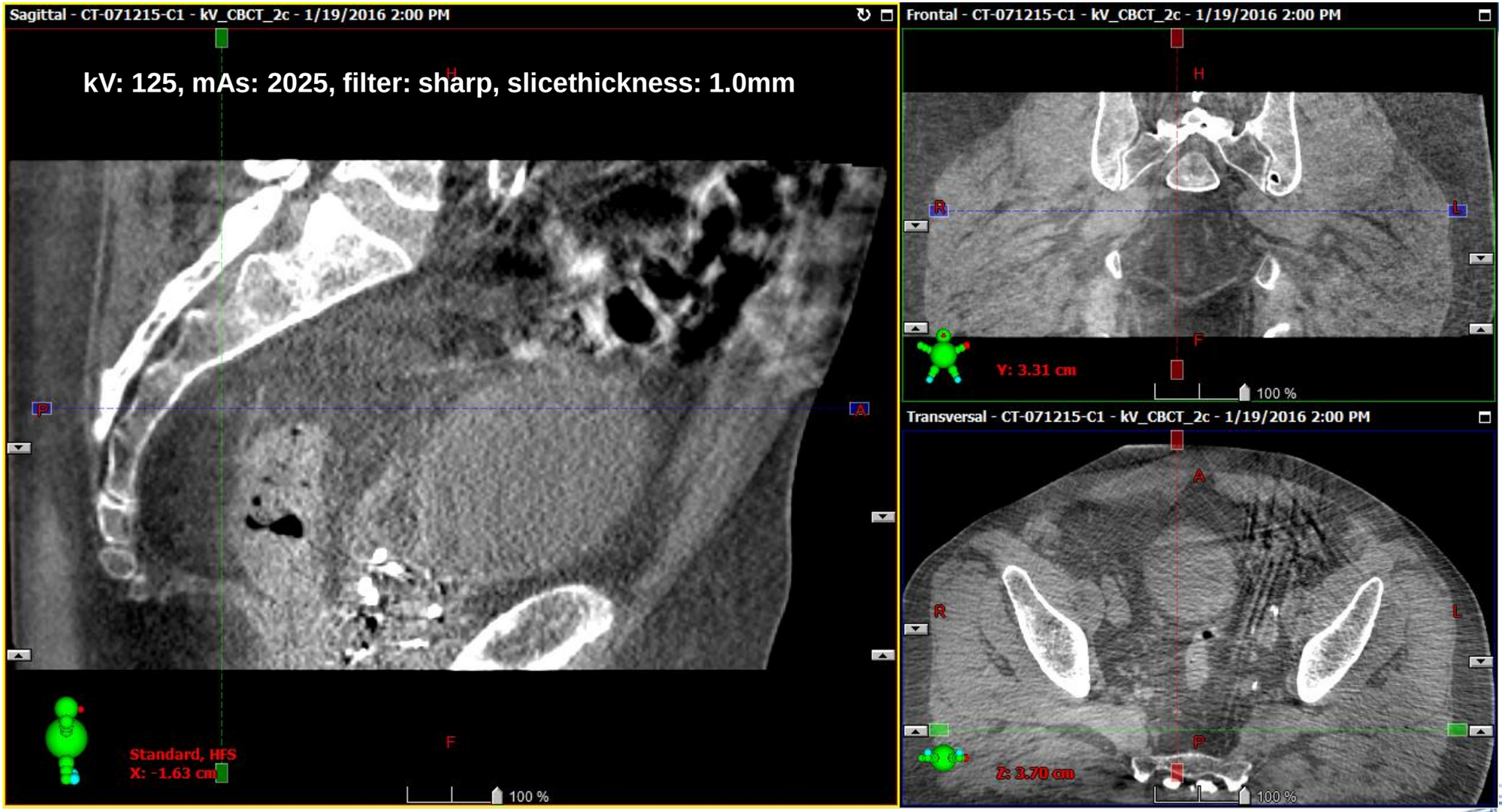
Lymph node from prostate tumor



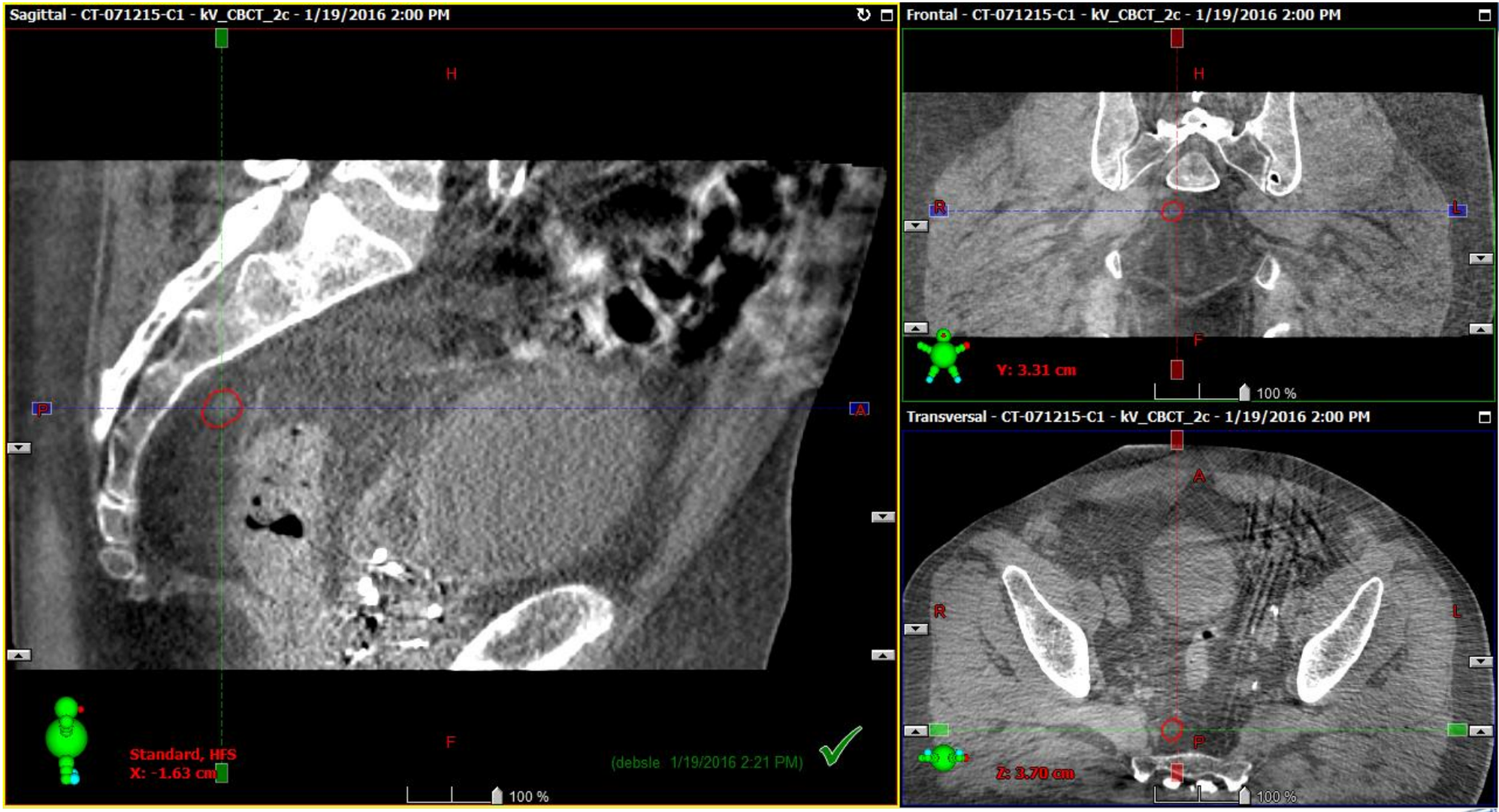
Lymph node from prostate tumor



Lymph node from prostate tumor

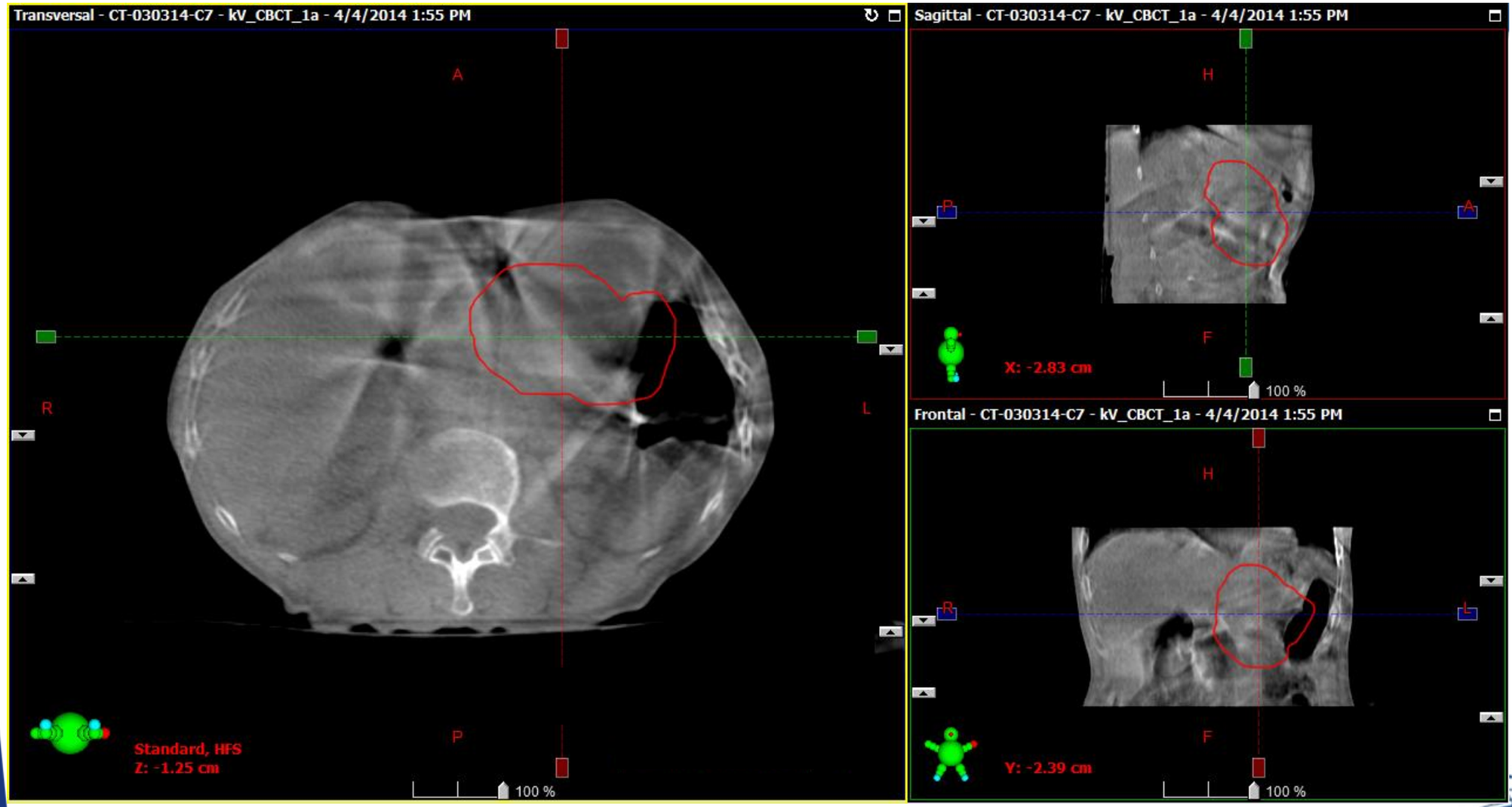


Lymph node from prostate tumor

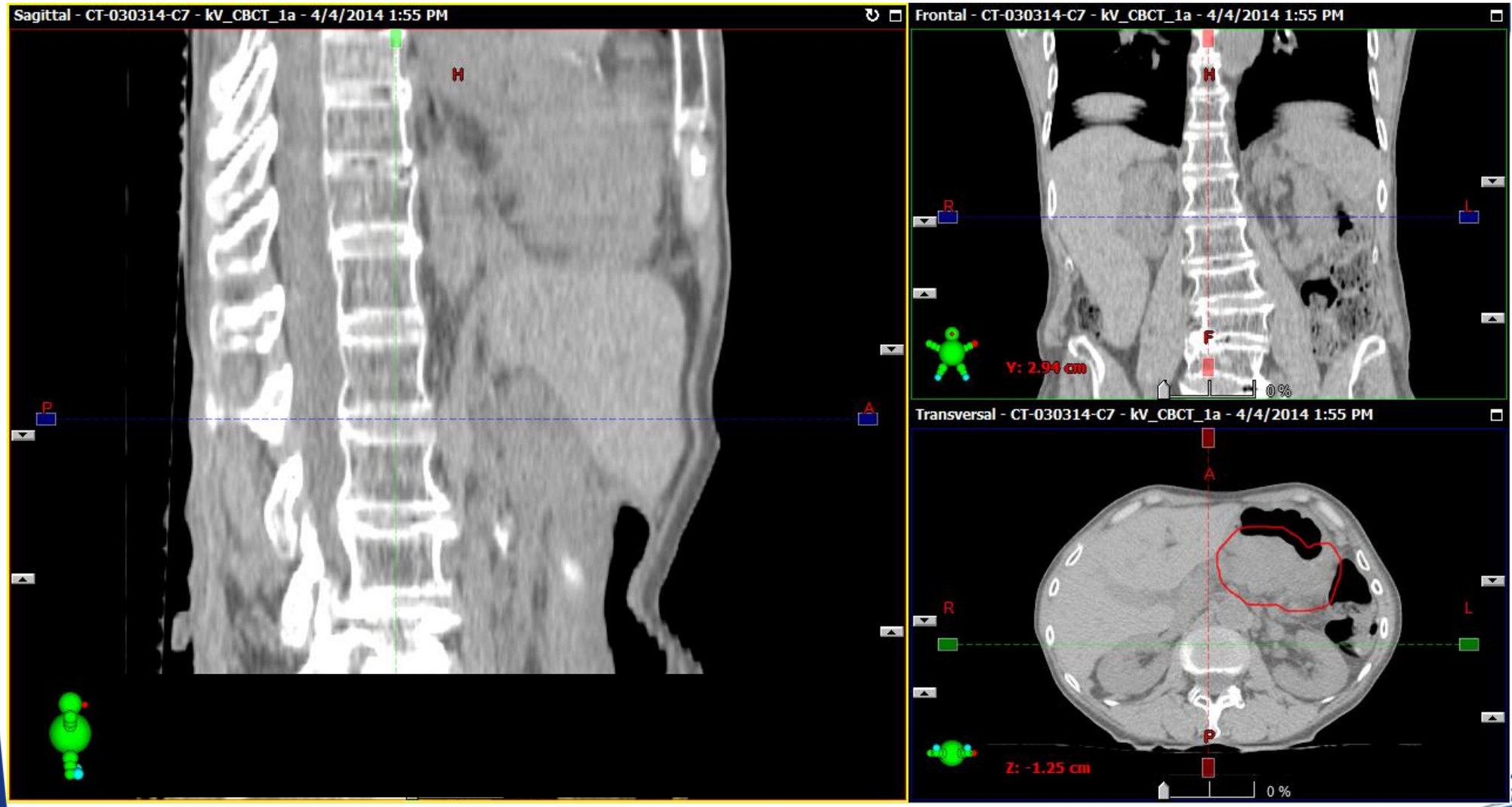


CT, Adrenal gland

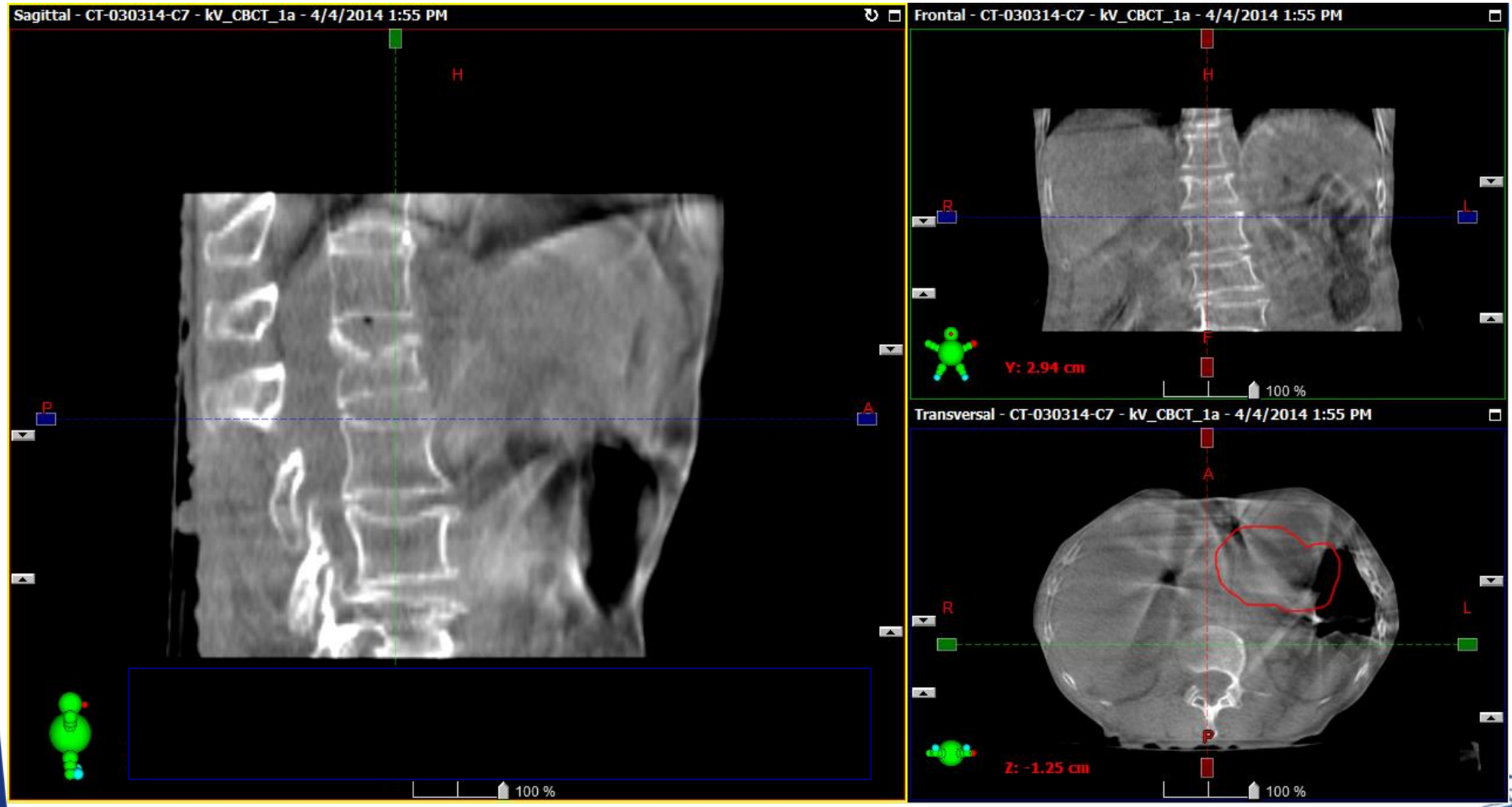
CBCT, Adrenal gland

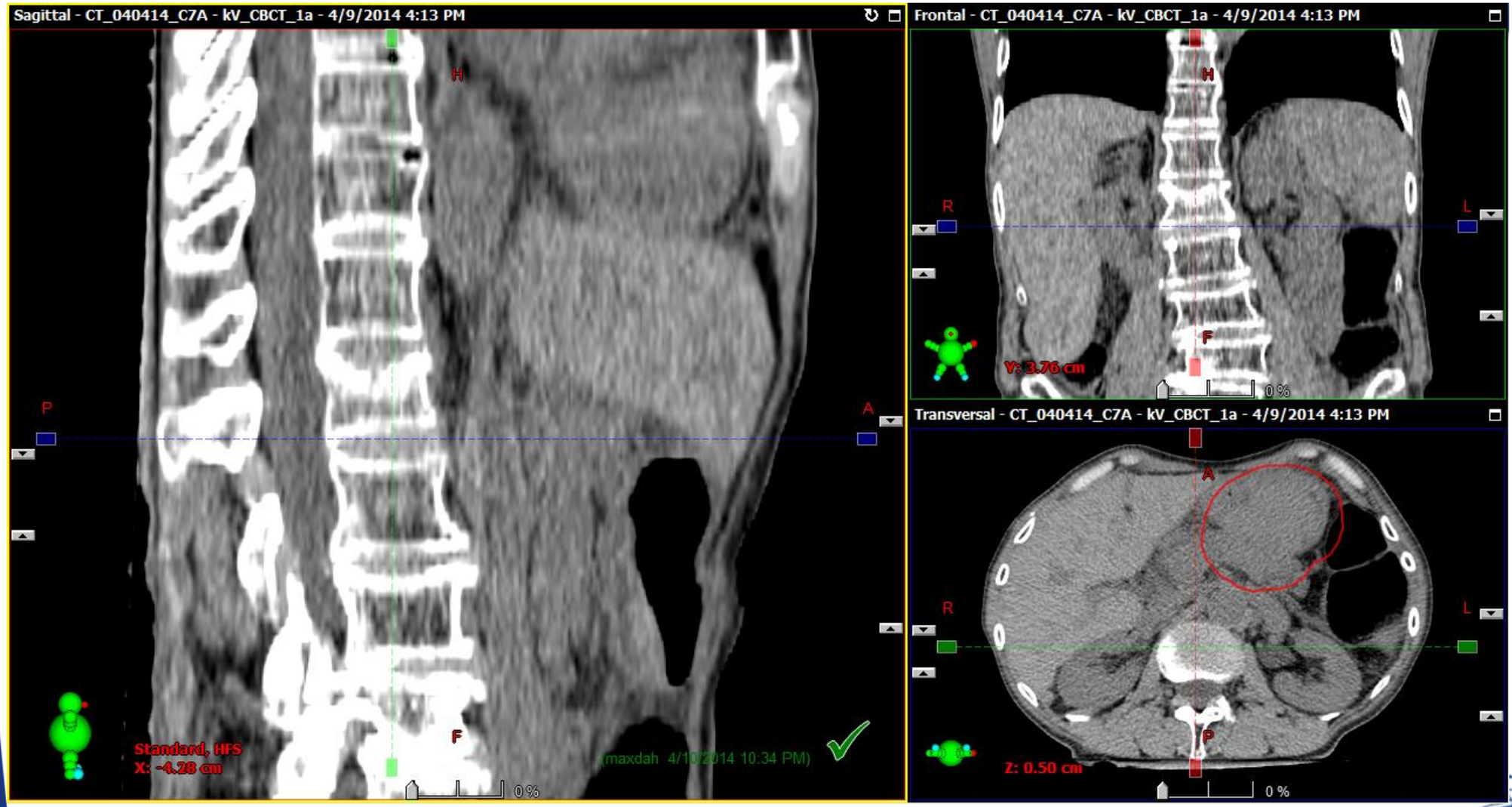


CT, Adrenal gland



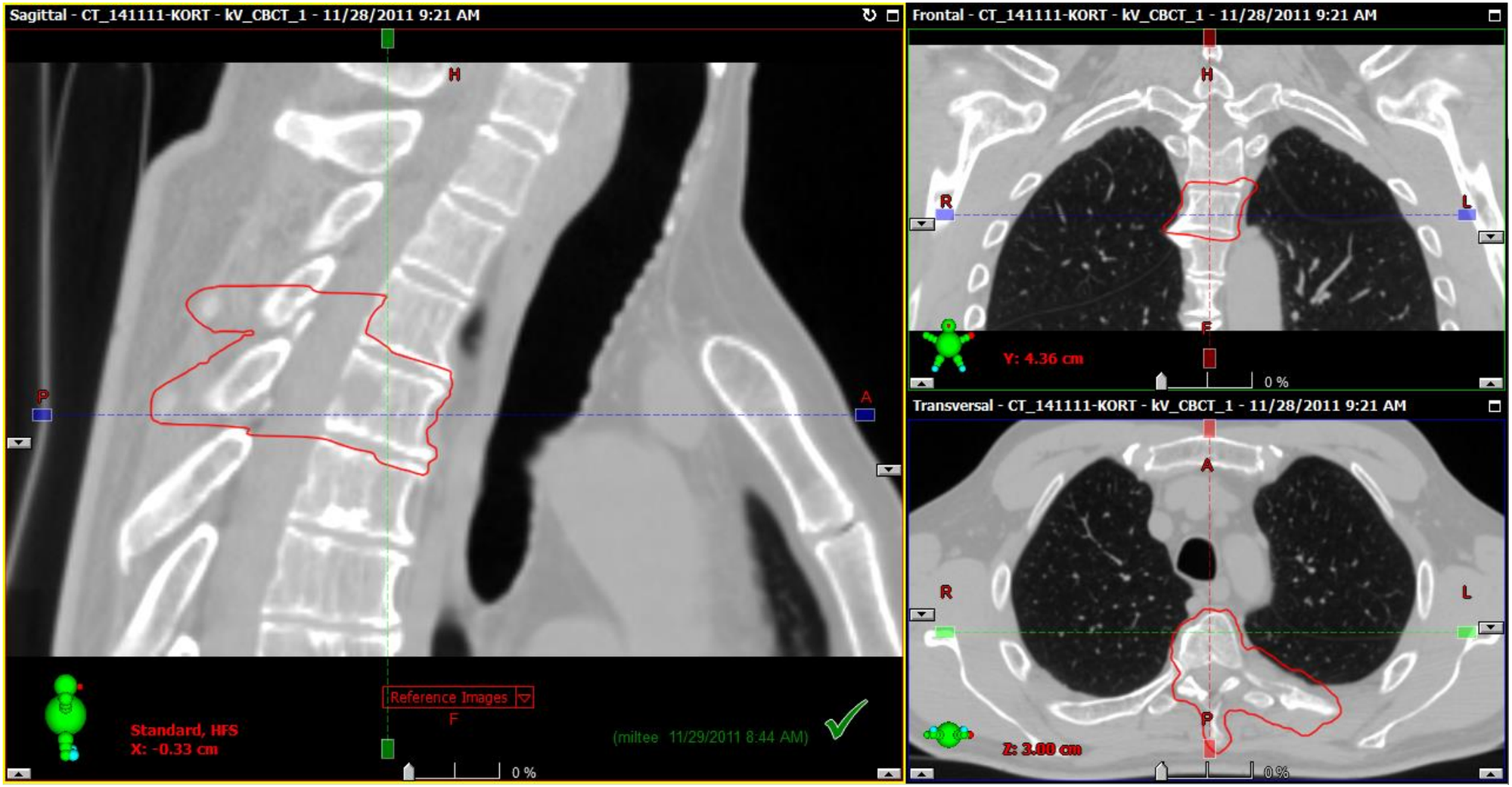
CBCT, Adrenal gland



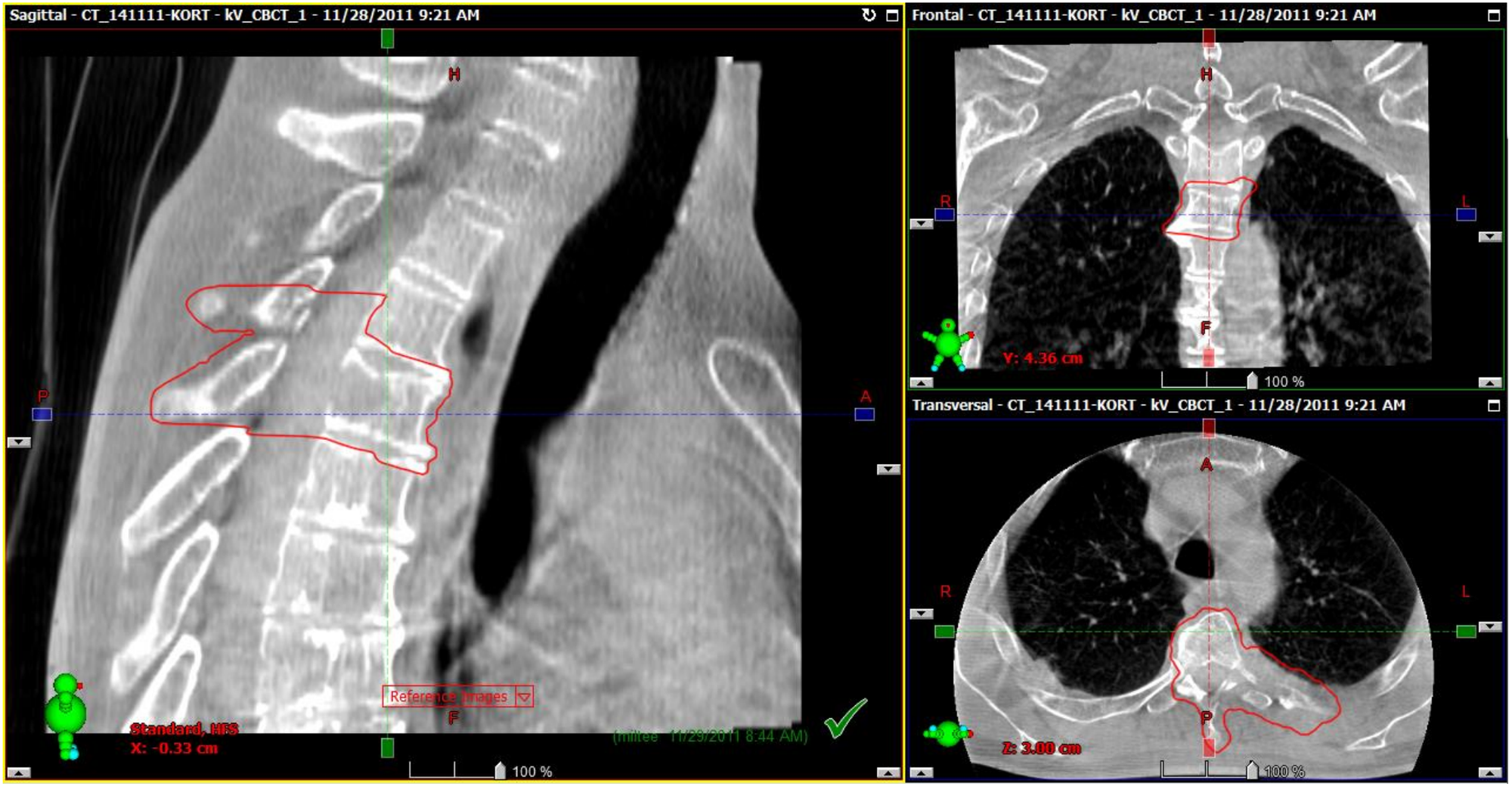

Sagittal - CT_040414_C7A - kV_CBCT_1a - 4/9/2014 4:13 PM
H
P
A
F
Standard, HFS
X: -4.28 cm
(maxdah 4/10/2014 10:34 PM)
0 %
Frontal - CT_040414_C7A - kV_CBCT_1a - 4/9/2014 4:13 PM
H
R
L
F
Y: 3.76 cm
0 %
Transversal - CT_040414_C7A - kV_CBCT_1a - 4/9/2014 4:13 PM
A
R
L
P
Z: 0.50 cm
0 %

Sagittal - CT_040414_C7A - kV_CBCT_1a - 4/9/2014 4:13 PM
H
P
A
F
Standard, HFS
X: -4.28 cm
(maxdah 4/10/2014 10:34 PM)
100 %
Frontal - CT_040414_C7A - kV_CBCT_1a - 4/9/2014 4:13 PM
H
R
L
F
Y: 3.76 cm
100 %
Transversal - CT_040414_C7A - kV_CBCT_1a - 4/9/2014 4:13 PM
A
R
L
P
Z: 0.50 cm
100 %

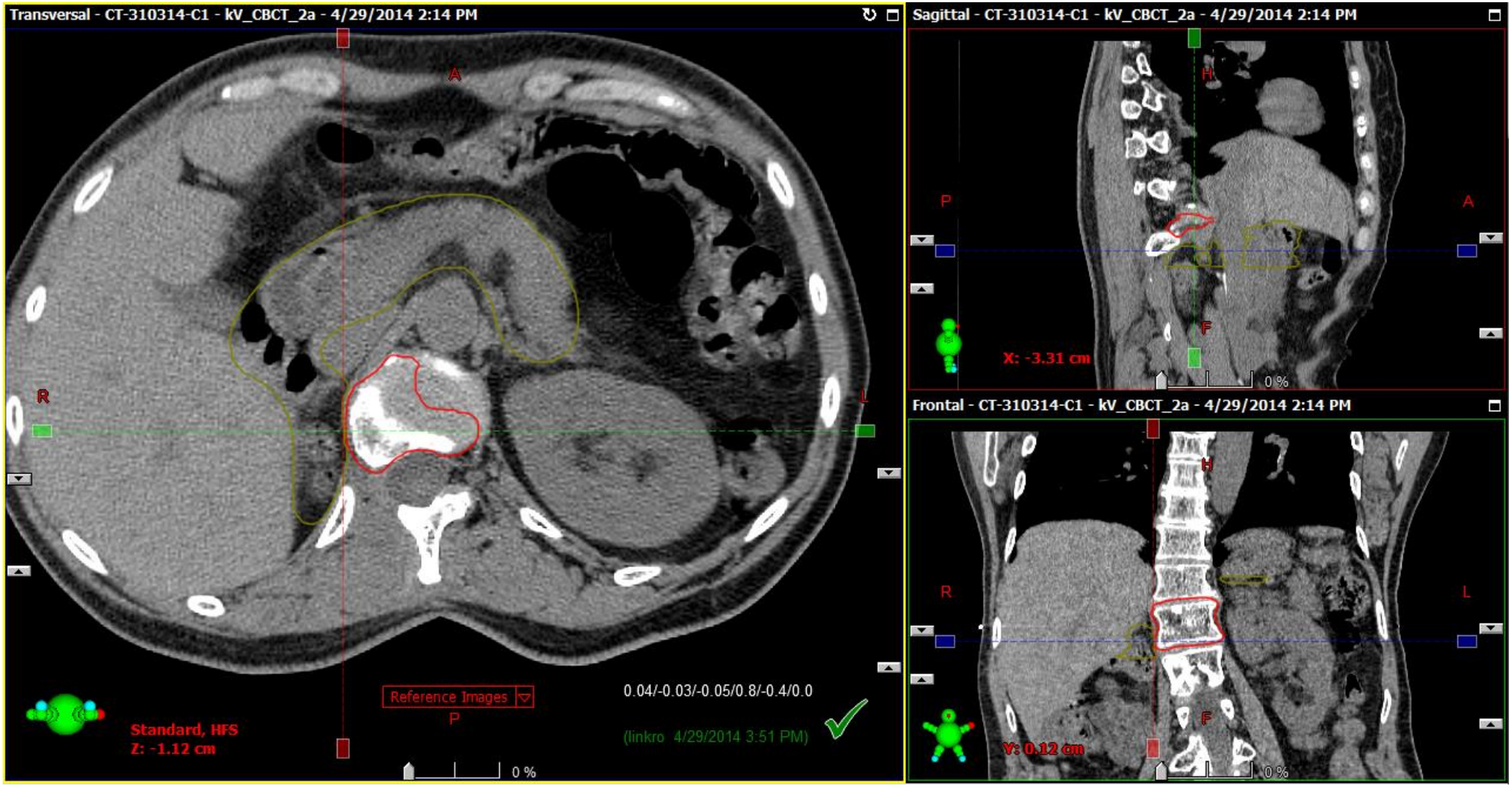
CT, spine case



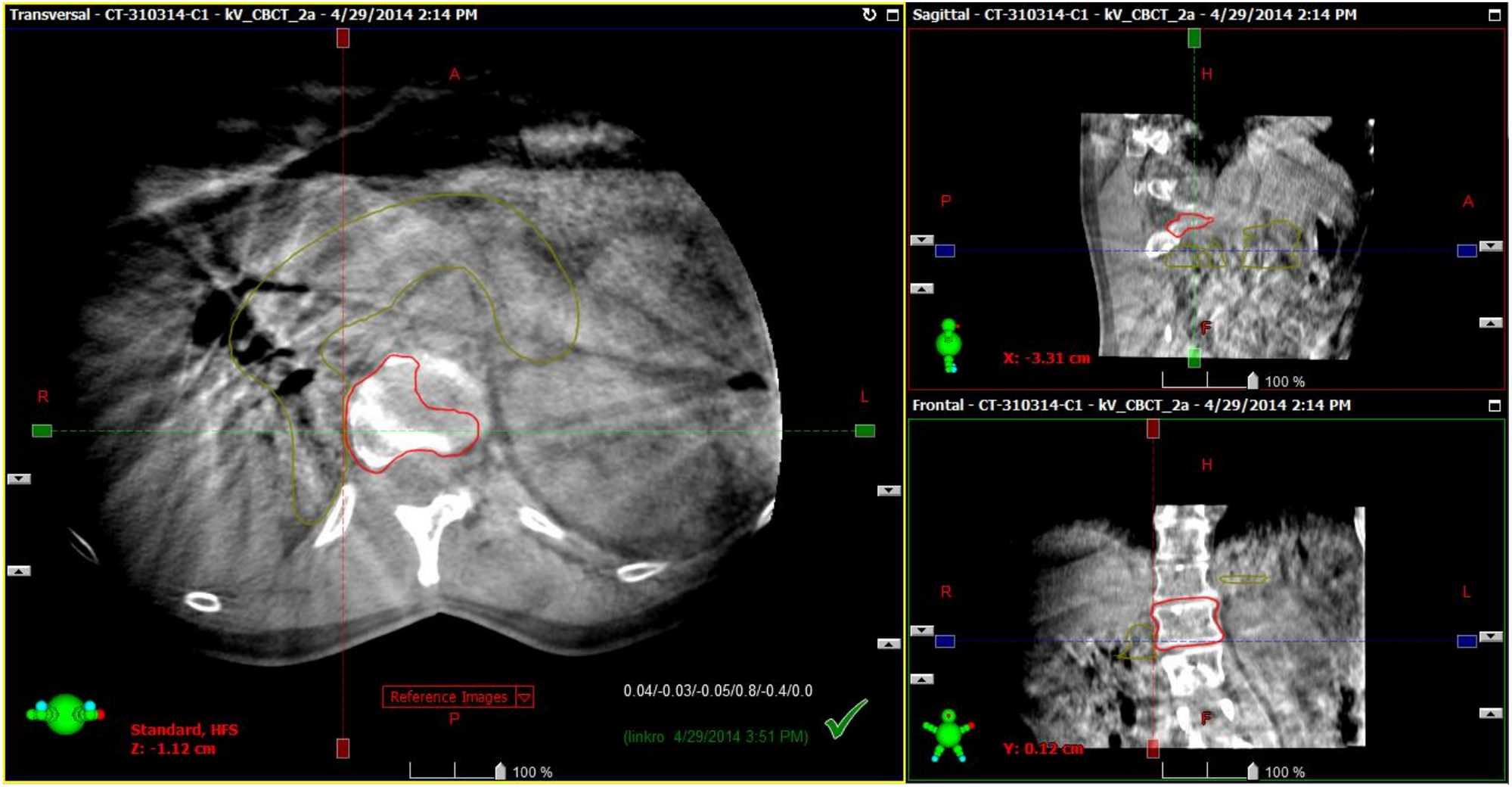
CBCT, spine case



CT, spine case

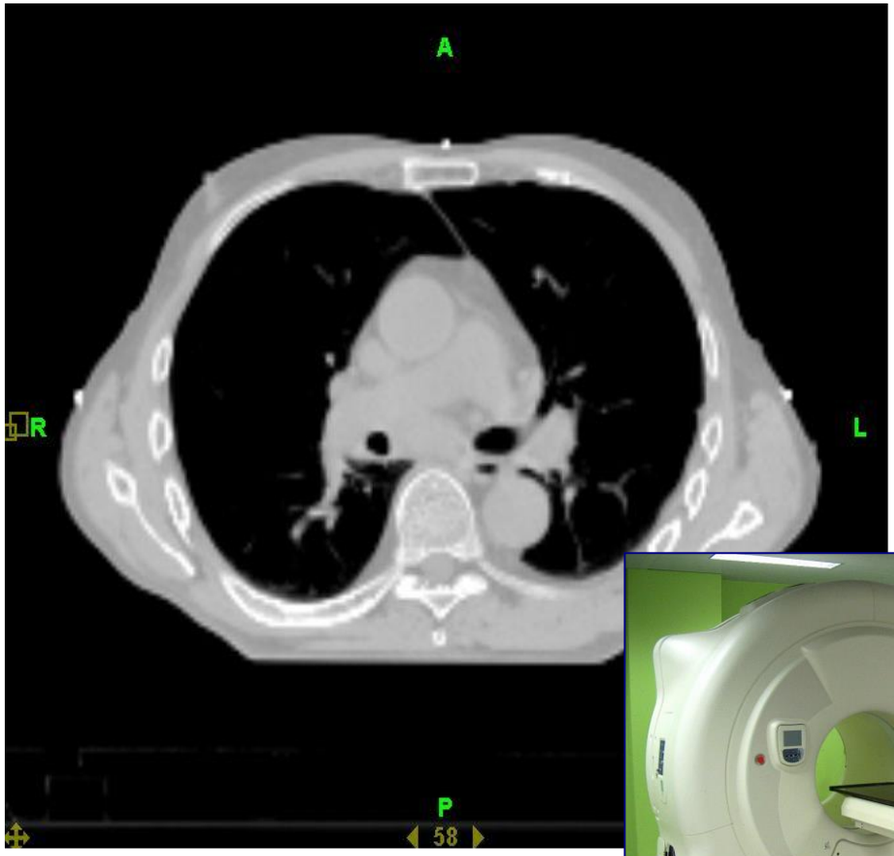


CBCT, spine case

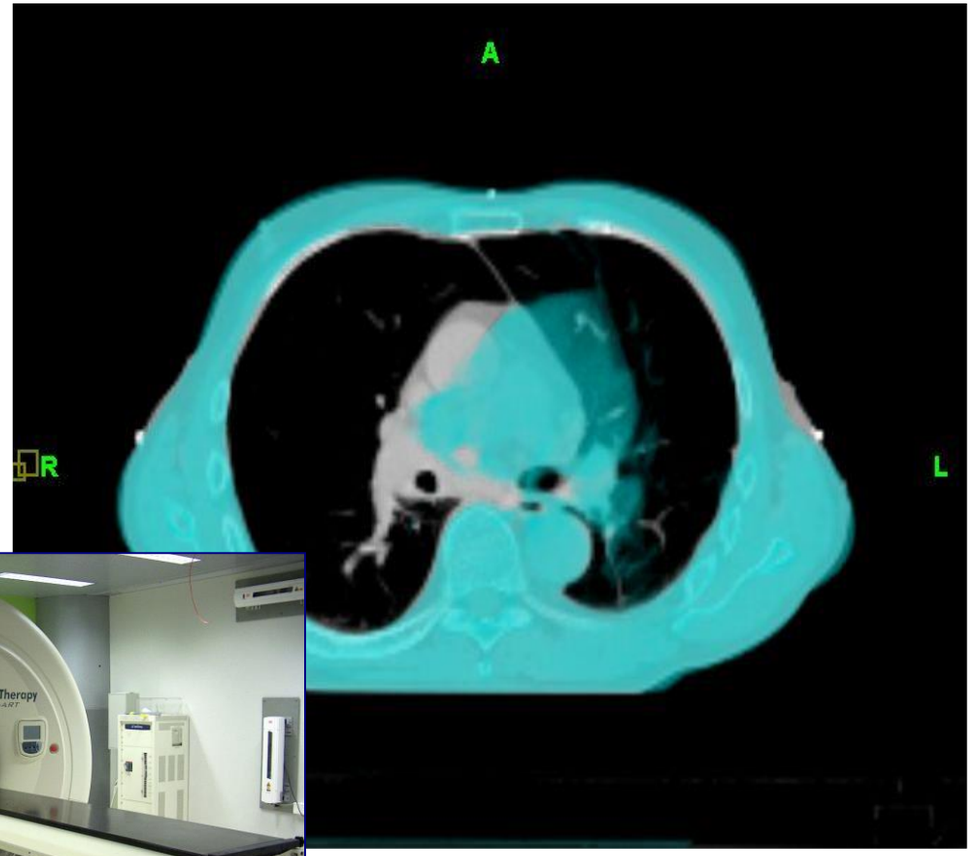


Decision making

Planning CT



Day 2 of treatment

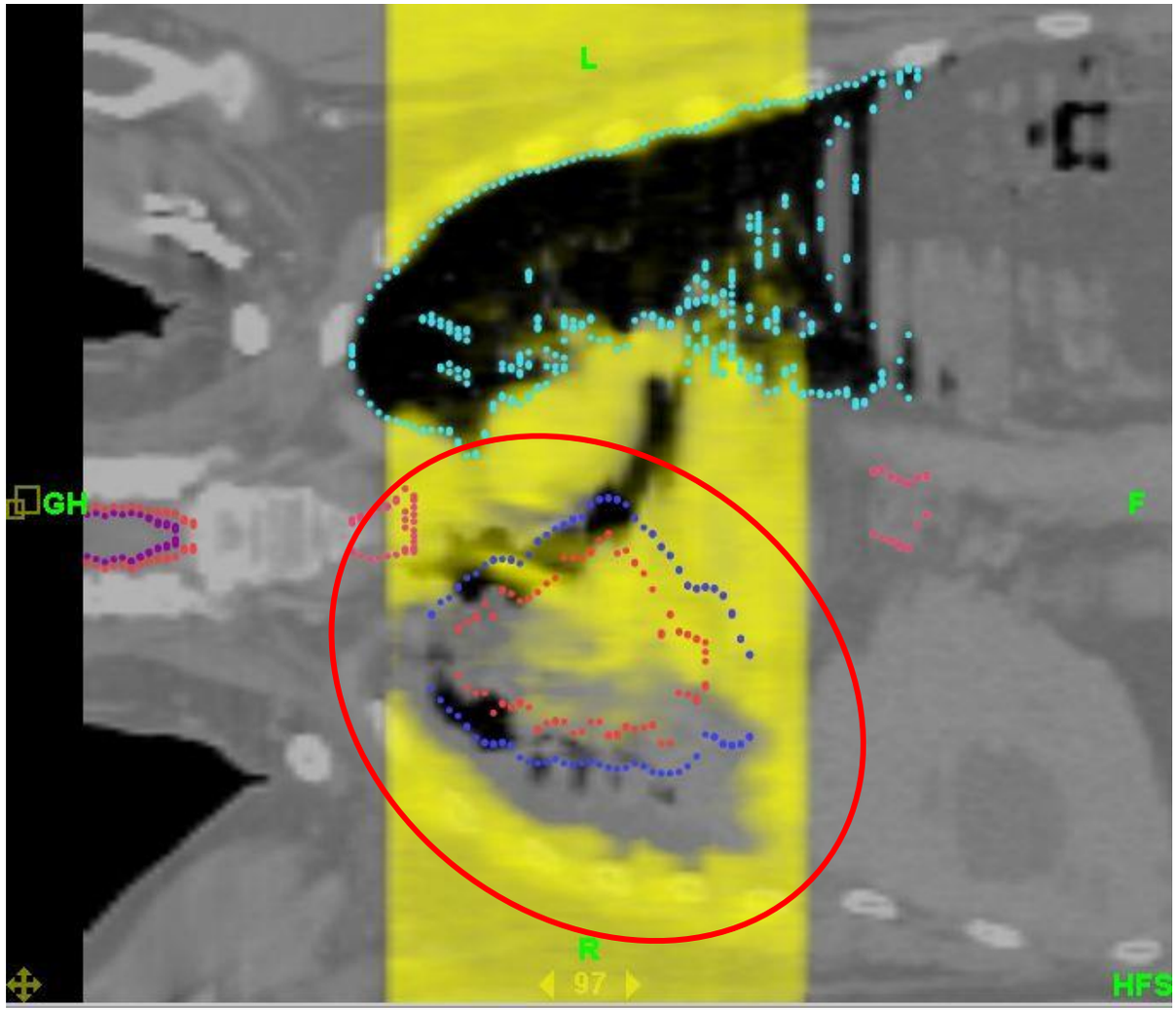


Decision making

- tumor growth

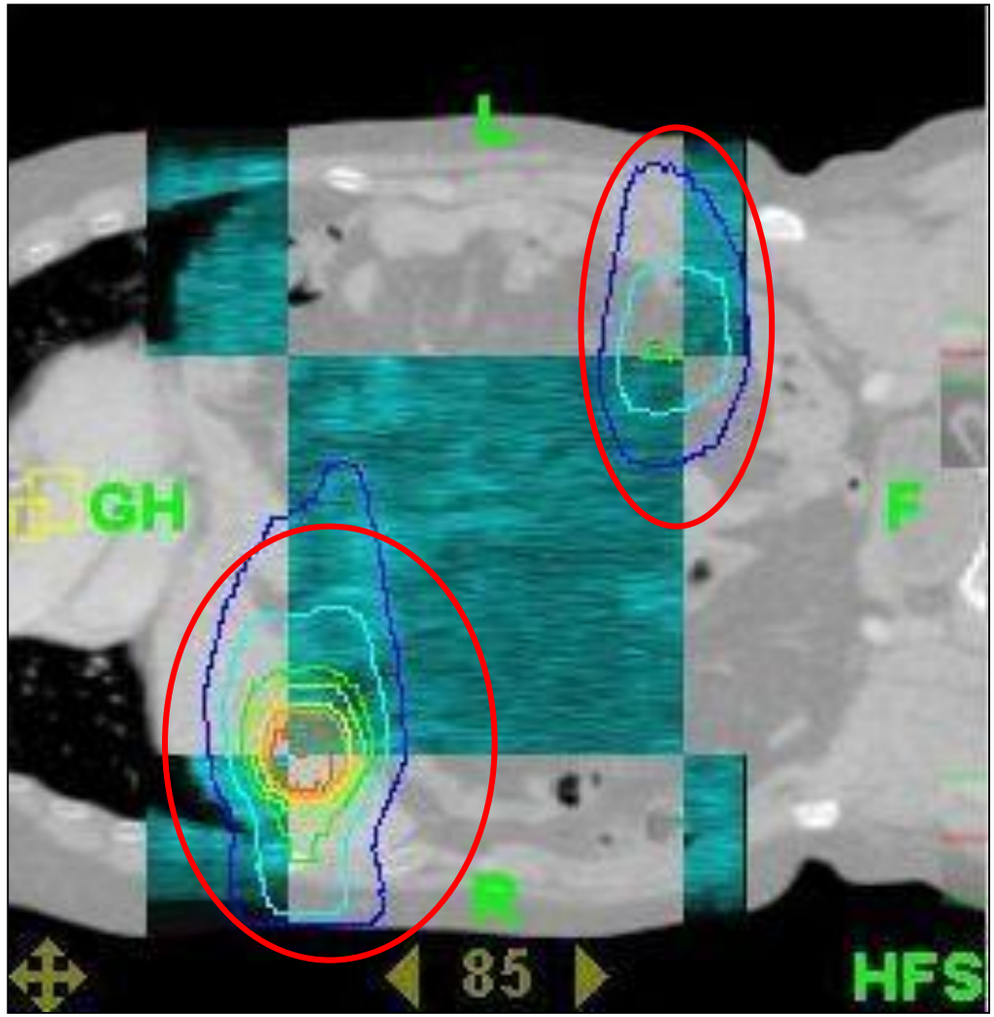
Decision making

- anatomical changes



Decision making

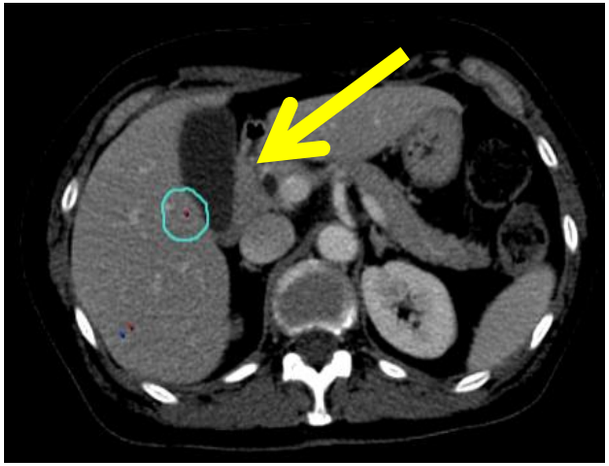
- Multiple PTV's
  - e.g. different metastasis



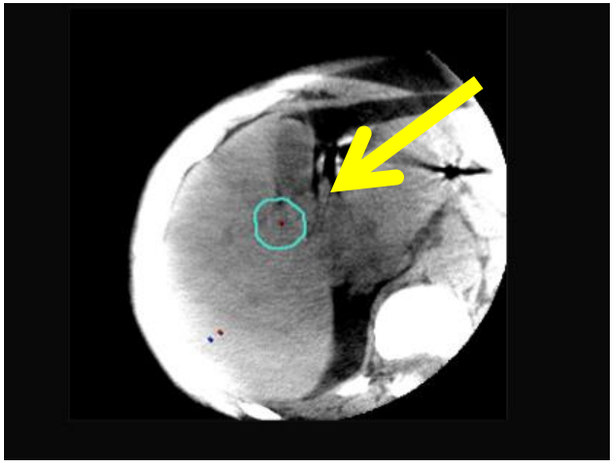
Decision making

- Gating / Real-time tumour tracking
  - Beware of motion of OAR with respect to motion of target

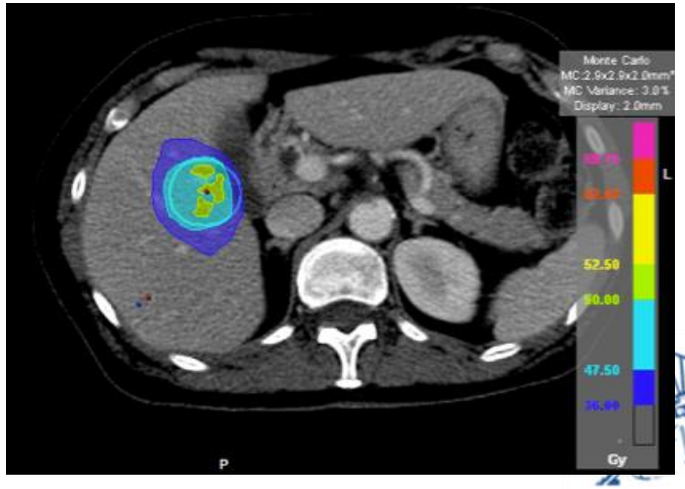
Planning CT: full gall bladder, duodenum @ safe distance



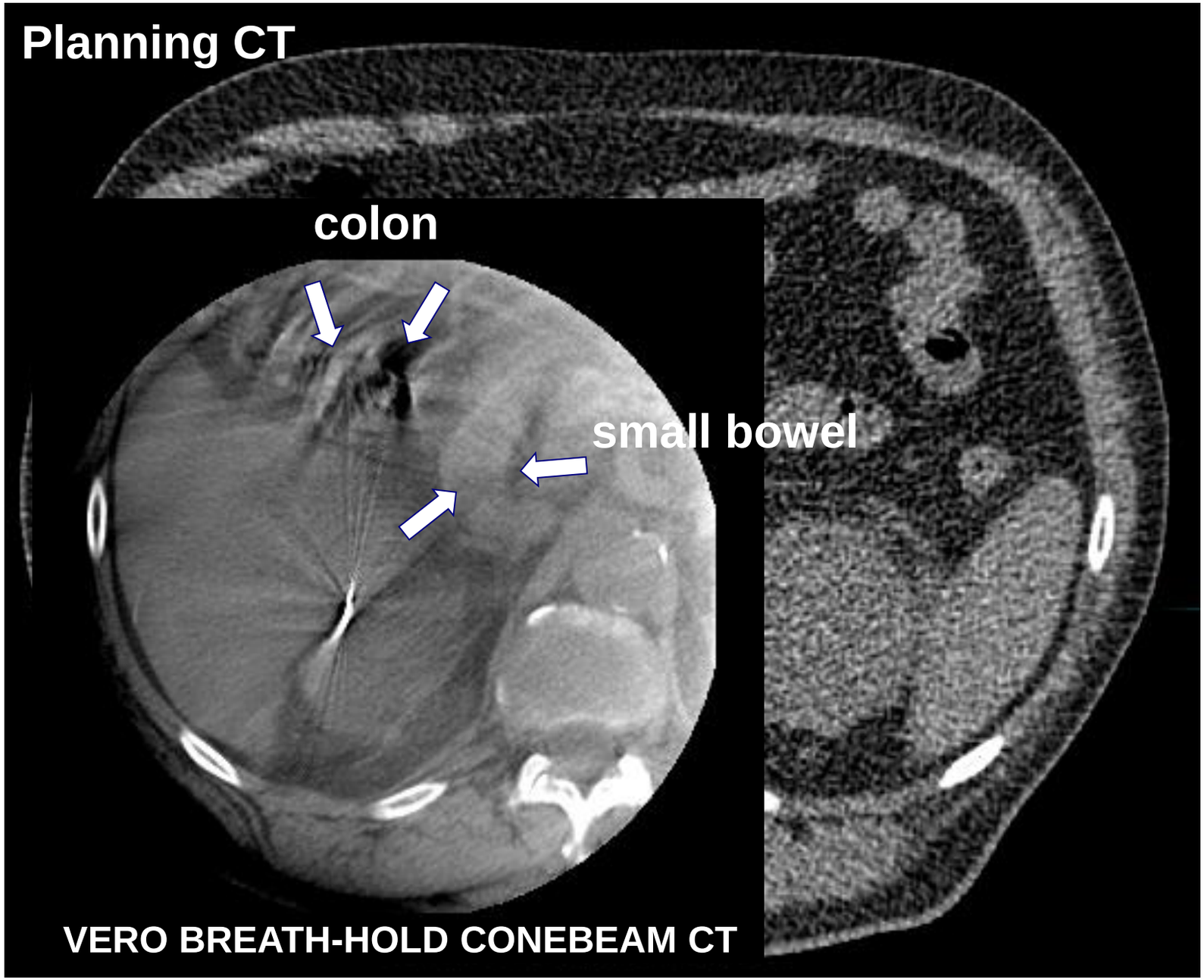
CB-CT: empty gall bladder, duodenum no longer safe



Adapted plan



Decision making

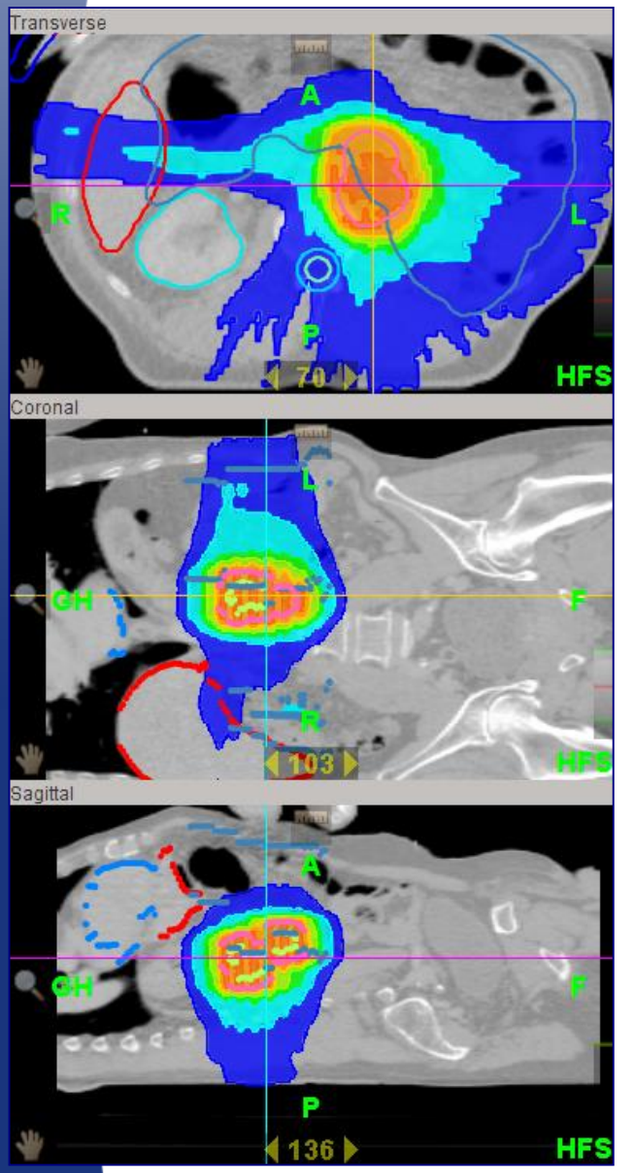


Helical TomoTherapy

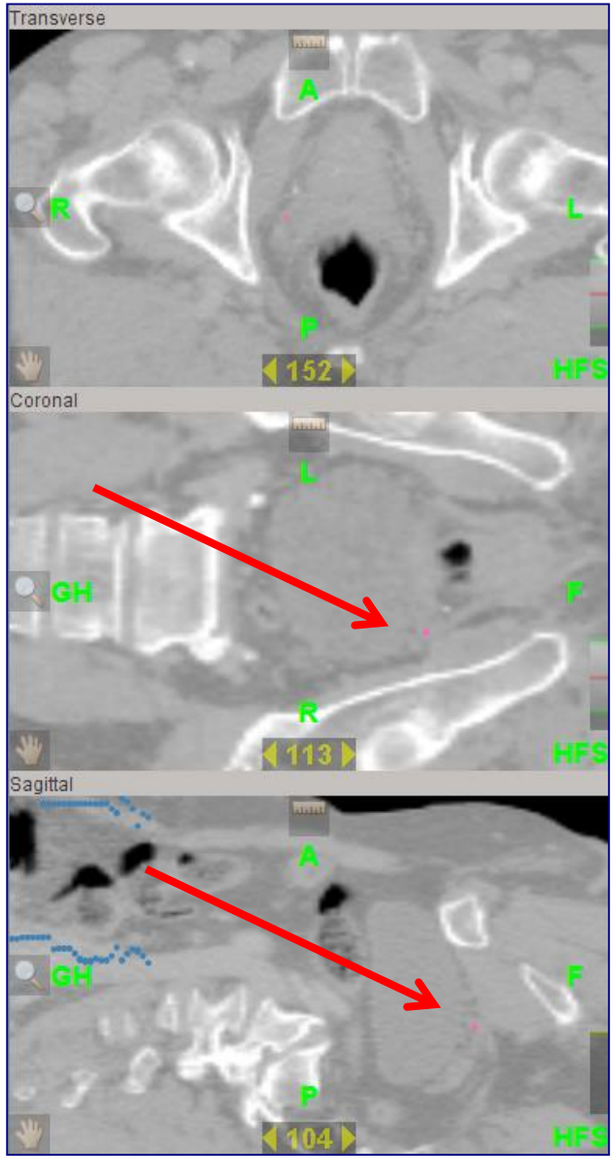
- “Pure” image-guided
  - No visual control of beam alignment
  - Patient slides into the boar for treatment, once properly positioned.
  - TomoTherapy treats all voxels that are designed “target”

Helical TomoTherapy

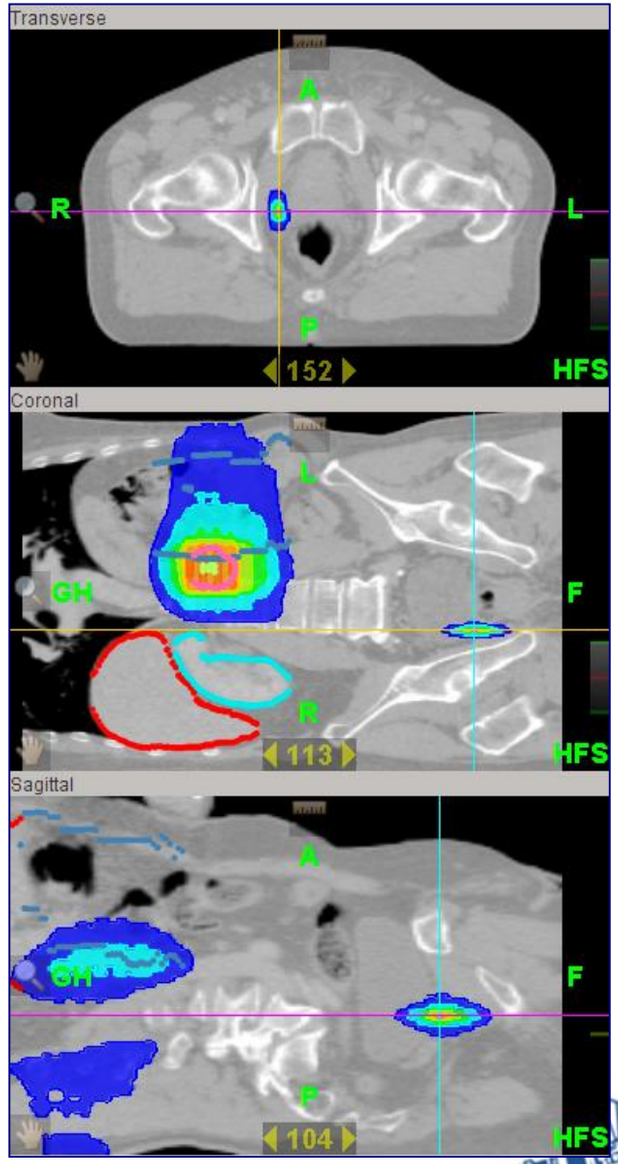
Intended treatment



"Little" delineation problem

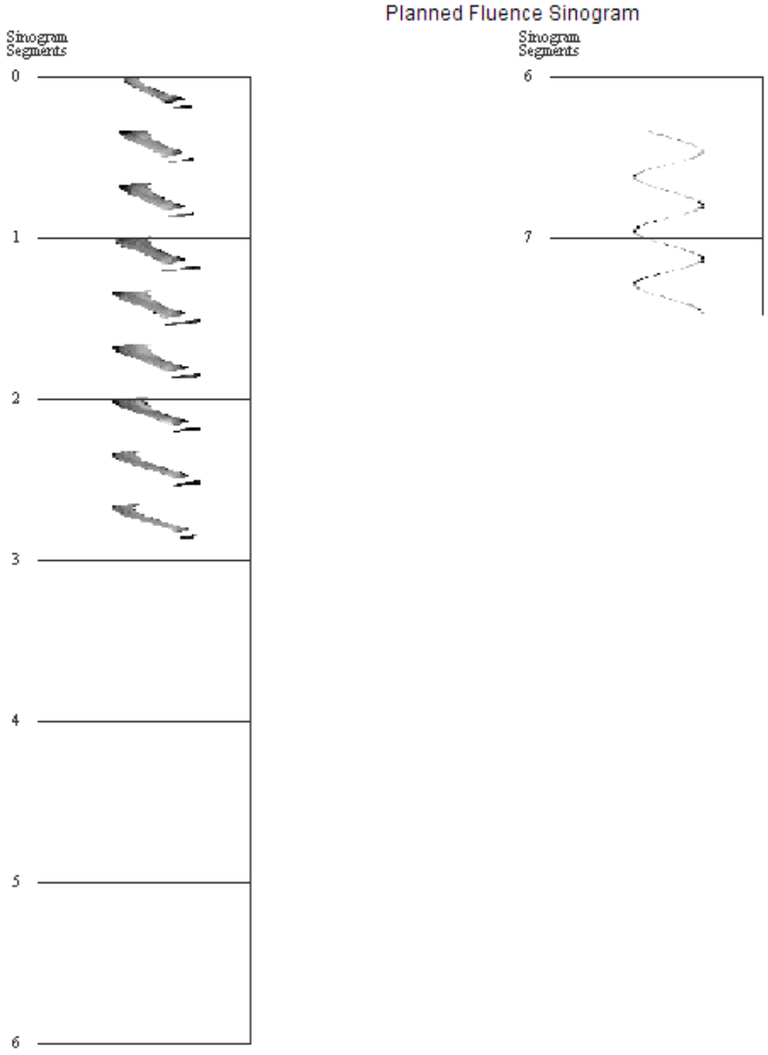


"serious" concequence



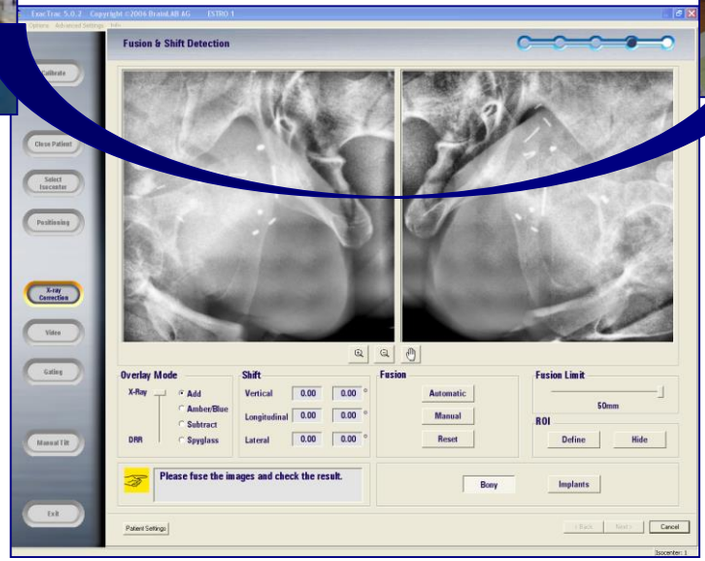
Helical TomoTherapy

- Sinogram, reveals problem



Novalis ExacTrac

- IGRT data base ≠ R&V data base
- Treatment parameters need to be transferred twice



Novalis ExacTrac

- Patient plan was prepared for morning staff
- Treatment parameters transferred to both data bases (Varis and ExacTrac: labeled “ready for approval”) for QA purposes
- CTV was rejected and adjusted at morning staff
- This resulted in a change of isocentre co-ordinates
- Final plan was transferred to Varis R&V (labeled “approved by staff dd/mm/yy) … but not to ExacTrac

- RTT discovered discrepancy in isocentre co-ordinates while dubble checking print out of treatment chart.

Department of Radiation Oncology
Chairman: Prof. Dr. Matthias Guckenberger

SBRT stage I NSCLC

starting an SBRT program

Matthias Guckenberger; Mischa Hoogeman; Lineke van der Weide

UniversityHospital Zurich

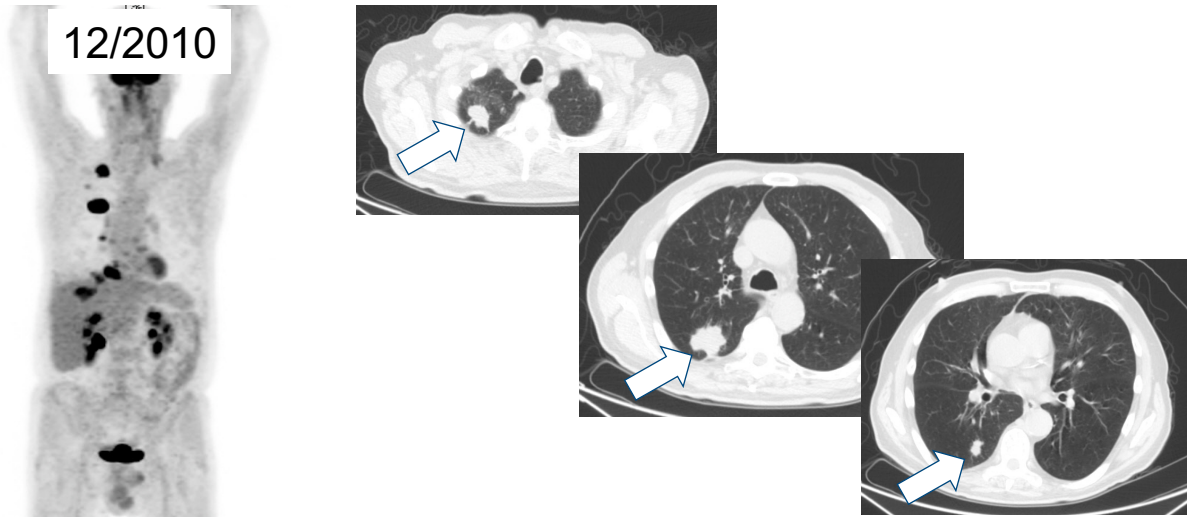
ESTRO

Patient presentation 12/2010

- 70 year old male
- Performance status 90%
- Severe coronary heart disease
- COPD GOLD II
- 60 pack years
- Depressive disorder

- Biopsy upper lesion: SCC
- Multiple simultaneous primaries vs metastases
- Suspicious pleural carcinosis

Initial staging & histopathology



- Biopsy upper lesion: SCC
- Multiple simultaneous primaries vs metastases
- Suspicious pleural carcinosis

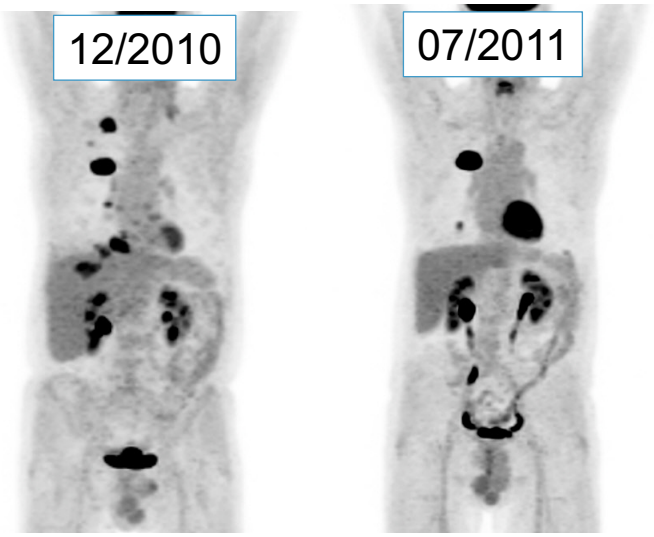
Treatment at PD

Palliative chemotherapy:
- 3 cycles Cisplatin & Taxol

Good PR

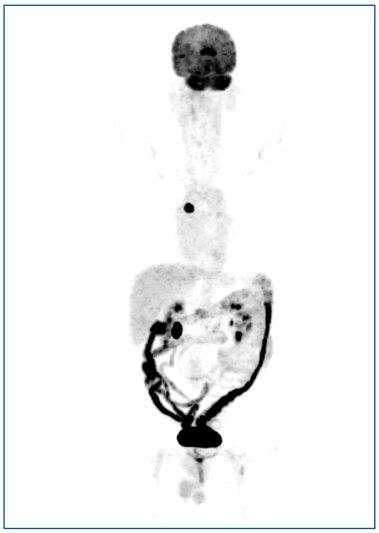
Poorly tolerated:
- EKG changes
- Pleural empyema
- Herpes esophagitis

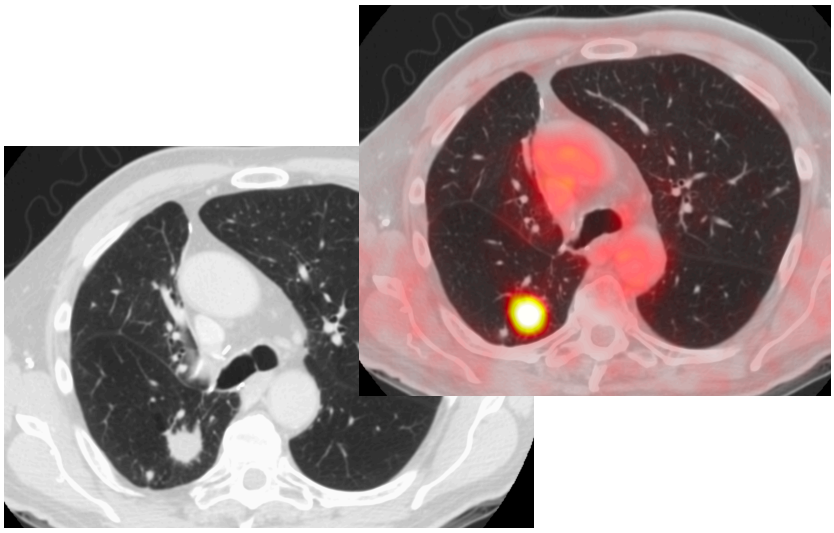
PD at 07/2011



- Re-staging: cT4 (multiple primaries vs metastases) w/o nodal and w/o extra-thoracic disease
- Upper lobectomy and lower lobe wedge resection

Follow-up



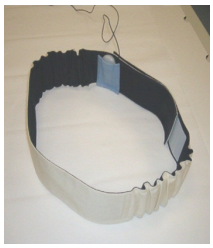


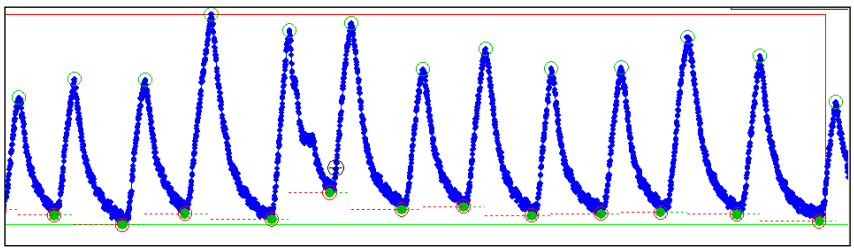
Follow-up 02/2014
- Stage I NSCLC

Treatment planning

Respiration correlated 4D-CT

- Siemens Sensation open 24 slice 4D-CT scanner
- Anzai abdominal pressure belt
  1. Acquisition of a conventional 3D-CT
  2. Acquisition of a respiration correlated 4D-CT
  3. Reconstruction of phases in end-inhalation and end-exhalation





Treatment planning

Respiration correlated 4D-CT

- Siemens Sensation open 24 slice 4D-CT scanner
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  1. Acquisition of a respiration correlated 4D-CT
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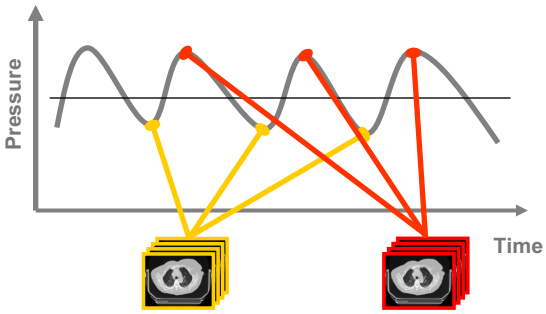
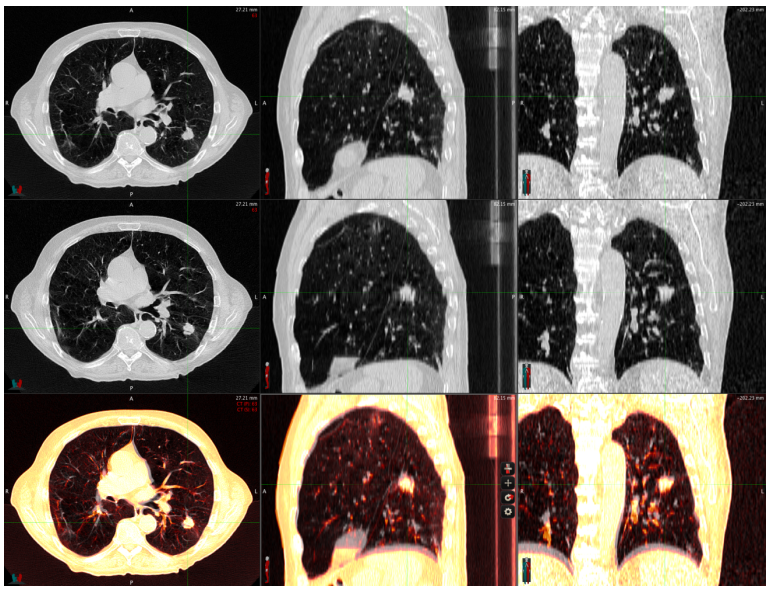


Treatment planning

Target volume definition: respiration correlated 4D-CT

End-exhalation

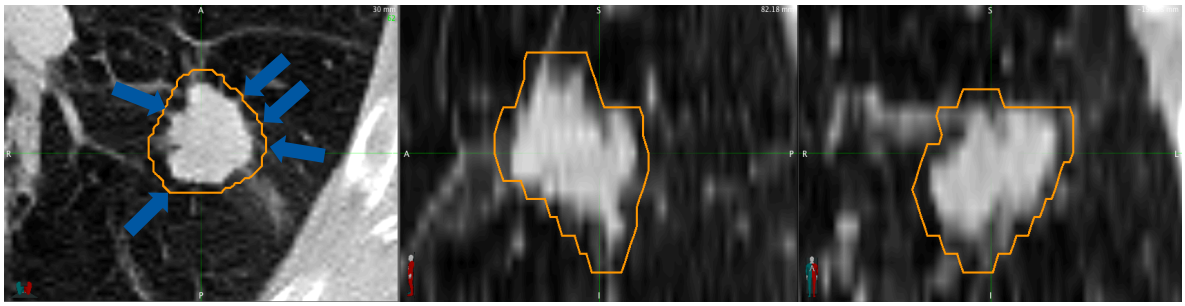
End-inhalation



Treatment planning

Target volume definition:

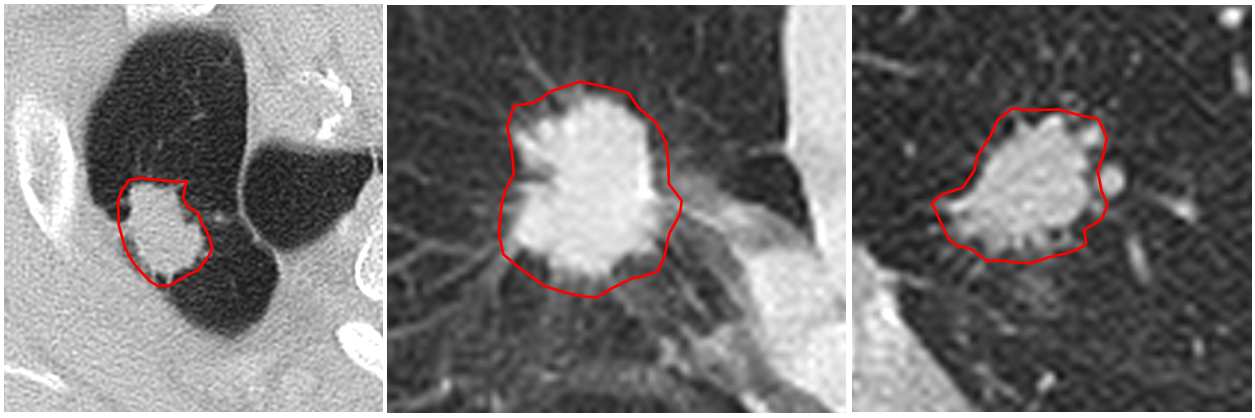
GTV = CTV but spiculae included into GTV



Target volume definition

Target volume definition:

GTV = CTV but spiculae included into GTV



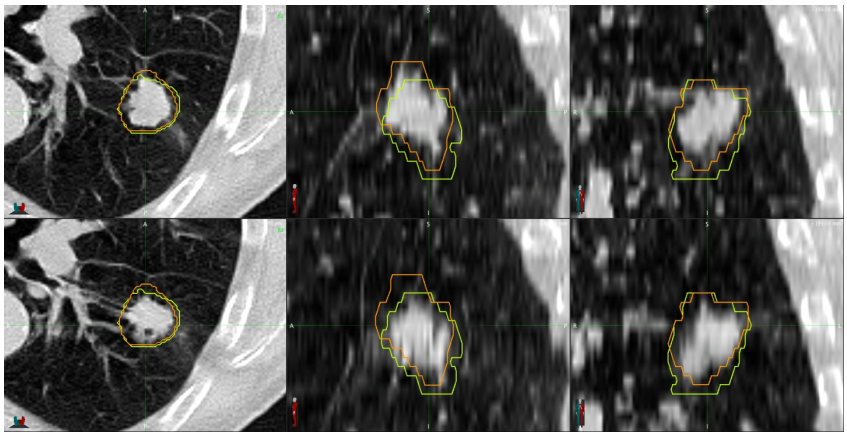
Treatment planning

Target volume definition:

Delineation of the GTV in end-inhalation and end-exhalation CT series

End-exhalation

End-inhalation



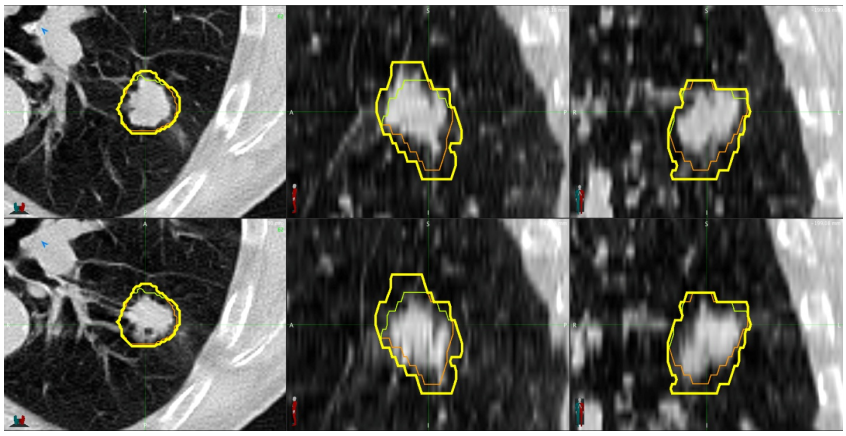
Treatment planning

Target volume definition:

Motion compensation using the internal target volume (ITV) technique

End-exhalation

End-inhalation



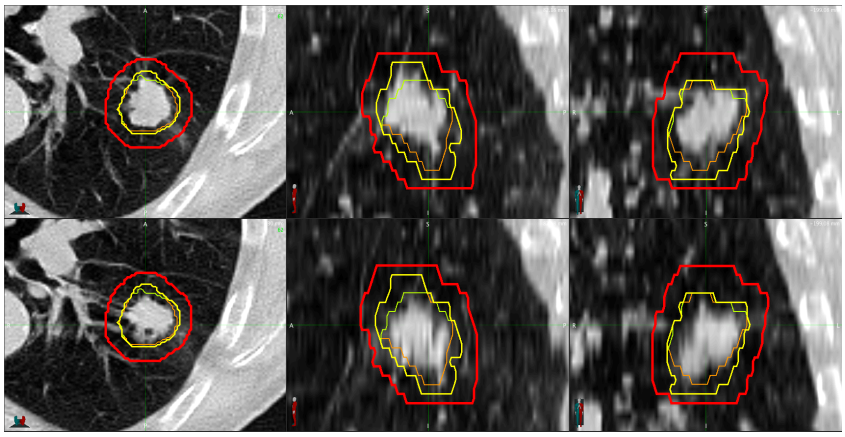
Treatment planning

Target volume definition:

PTV = ITV + 5mm in all directions

End-exhalation

End-inhalation



OAR definition

ELSEVIER

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CLINICAL INVESTIGATION **Normal Tissue**

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

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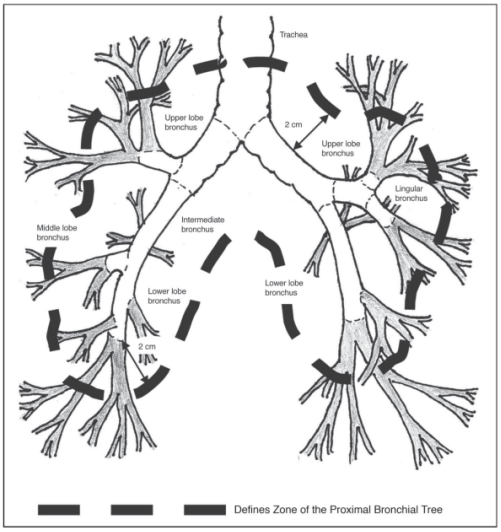
OAR definition

Proximal bronchial tree



OAR definition

Proximal bronchial tree

- Delineated on the mediastinal CT window
- Includes mucosa, submucosa, cartillage rings, and airway channels associated with these structures
- Starts 2 cm above carina and ends at the site of segmental bifurcation of the bronchi

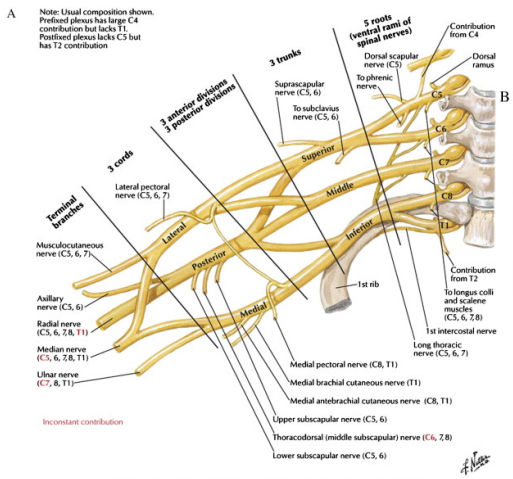
OAR definition

Central tumor location according to RTOG 0813

Tumors that are **immediately adjacent to mediastinal or pericardial pleura (PTV touching the pleura)** also are considered central tumors and are eligible for this protocol.

OAR definition

Brachial plexus



Hall IJROBP 2008, Kong IJROBP 2011

OAR definition

Brachial plexus

1. Identify and contour C5, T1, and T2.
2. Identify and contour the subclavian and axillary neurovascular bundle.
3. Identify and contour anterior and middle scalene muscles from C5 to insertion onto the first rib.
4. To contour the brachial plexus OAR use a 5-mm diameter paint tool.
5. Start at the neural foramina from C5 to T1; this should extend from the lateral aspect of the spinal canal to the small space between the anterior and middle scalene muscles.
6. For CT slices, where no neural foramen is present, contour only the space between the anterior and middle scalene muscles.
7. Continue to contour the space between the anterior and middle scalene muscles; eventually the middle scalene will end in the region of the subclavian neurovascular bundle.
8. Contour the brachial plexus as the posterior aspect of the neurovascular bundle inferiorly and laterally to one to two CT slices below the clavicular head.
9. The first and second ribs serve as the medial limit of the OAR contour.

Hall IJROBP 2008, Kong IJROBP 2011

OAR definition

Chest wall

Different CLINICAL endpoints:

- Rip fracture
- Intercostal neuralgia
- Myositis
- Fibrosis
  - Subcutaneous
- Skin ulceration

OAR definition

Chest wall

Study	CW definition
Dunlap (IJROBP, 2010)	3 cm expansion of ipsilateral lung – [lung, Mediastinum and vertebral body]
Creach (R&O, 2012)	As in Dunlap
Andolino (IJROBP, 2011)	3 cm expansion of ipsilateral lung/liver – [lung/liver, mediastinum and vertebral body] + ribs separately
Bongers (IJROBP 2011)	expansion of the lungs with 2 cm in lateral, posterior, and anterior directions except in the direction of the mediastinum, with inclusion of intercostal muscles but excluding other muscles and skin
Stephans (IJROBP 2012)	arc of all ipsilateral soft tissue outside of lung tissue from the edge of the sternum cir- cumferentially to the edge of the vertebral body including the spinal nerve root exit site

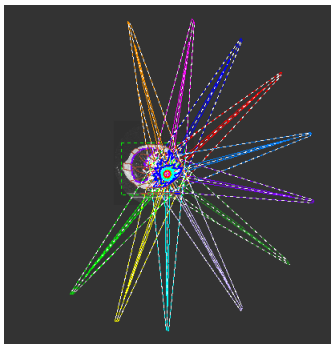
SBRT tolerance doses

Organ at risk	One fraction (RTOG 0915)	Three fractions (RTOG 0618 / 1021)	Four fractions (RTOG 0915)	Five fractions (RTOG 0813)	Eight fractions (Haasbeck et al. 2011)
Trachea and large bronchus	D_{max} 20.2 Gy	D_{max} 30 Gy	D_{max} 34.8 Gy 15.6 Gy <4cc	D_{max} 105% * 18 Gy < 5cc **	D_{max} 44 Gy
Heart	D_{max} 22 Gy 16 Gy < 15cc	D_{max} 30 Gy	D_{max} 34Gy 28 Gy <15cc	D_{max} 105% * 32 Gy < 15cc	---
Esophagus	D_{max} 15.4 Gy 11.9 Gy < 5cc	D_{max} 25.2 Gy 17.7 G< 5cc	D_{max} 30Gy 18.8 Gy<5cc	D_{max} 105% * 27.5 Gy < 5cc **	D_{max} 40 Gy
Brachial plexus	D_{max} 17.5 Gy 14 Gy < 3cc	D_{max} 24 Gy 20.4 Gy < 3cc	D_{max} 27.2 Gy 23.6Gy < 3cc	D_{max} 32 Gy 30 Gy < 3cc	D_{max} 36 Gy
Chest wall	D_{max} 30 Gy 22 Gy < 1cc	30 Gy < 30cc 60 Gy < 3 cc	D_{max} 27.2 Gy 32Gy<1cc	30 Gy < 30cc 60 Gy < 3 cc	---
Spinal cord	D_{max} 14 Gy 10 Gy < 0.35cc	D_{max} 18 Gy (RTOG 0236)	D_{max} 26Gy 20.8Gy < 0.35cc	D_{max} 30 Gy 22.5 Gy <0.25cc	D_{max} 28 Gy

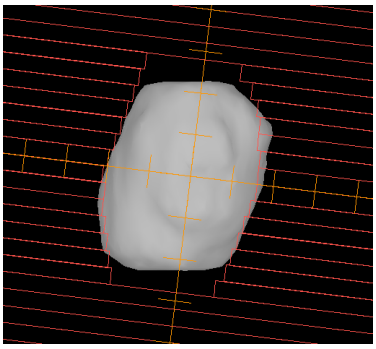
Treatment planning

3D conformal treatment planning:

Inhomogeneous dose distributions by negative “margin” between PTV edge and field size



11 fields
Sparing of contralateral lung

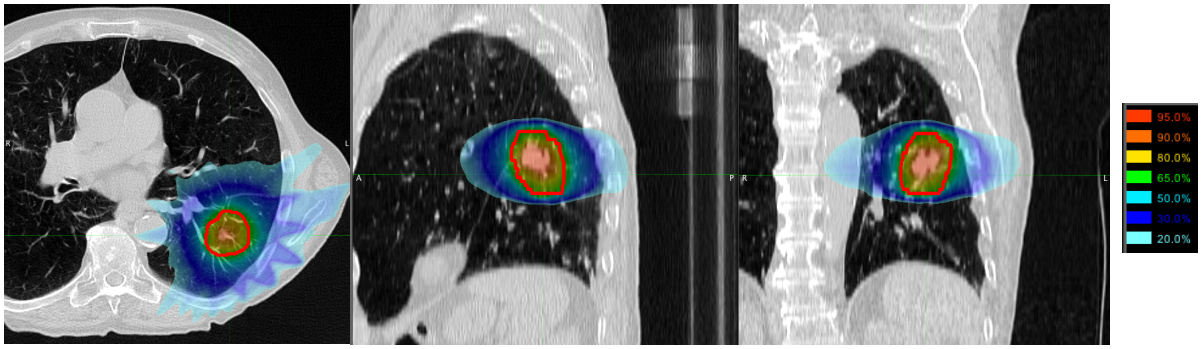


3D conformal beam shaping

Treatment planning

Collapsed cone dose calculation

2mm grid size



Treatment delivery

Immobilization:

- Encourage using immobilization unless rigorous patient monitoring is performed!
- Only 1 – 5 shots and they must do the job

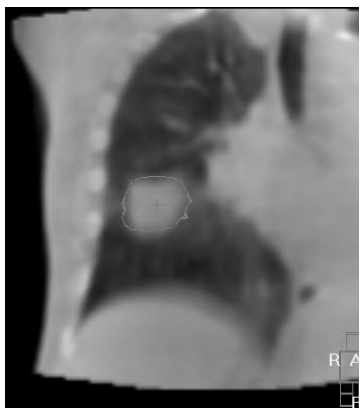
BodyFIX system
with double vacuum

IGRT using 4D CBCT technology

Treatment planning

Treatment delivery

Manual contour registration



Guckenberger Acta Oncol 2006

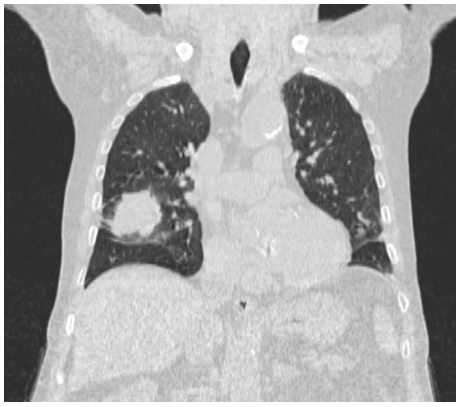
Respiration correlated CT

„Conventional“ slow CBCT

How to incorporate breathing motion into the IGRT work-flow ?

Treatment planning

Treatment delivery

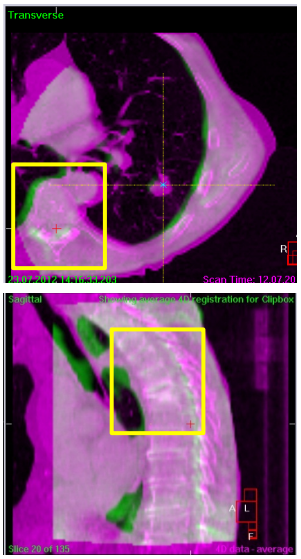


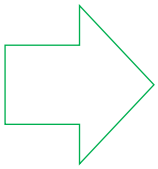
Respiration correlated CT

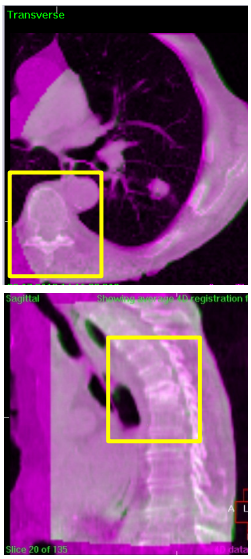
Respiration correlated CBCT

4D IGRT using CBCT technology

- Start with bone registration

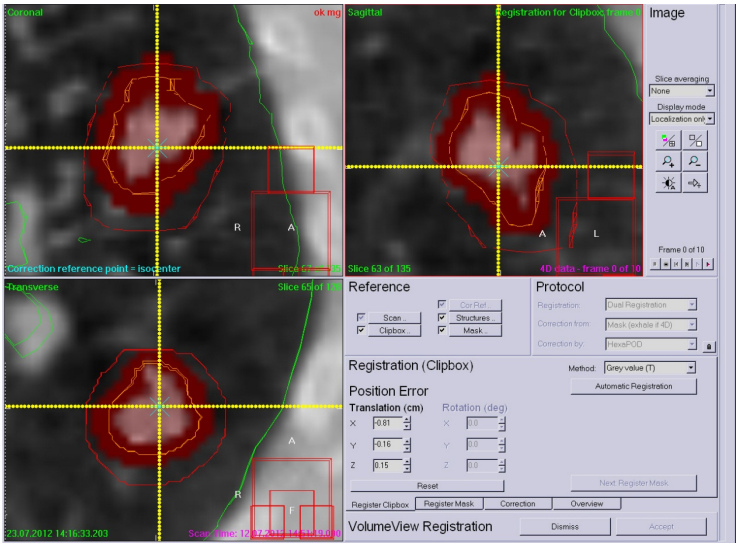






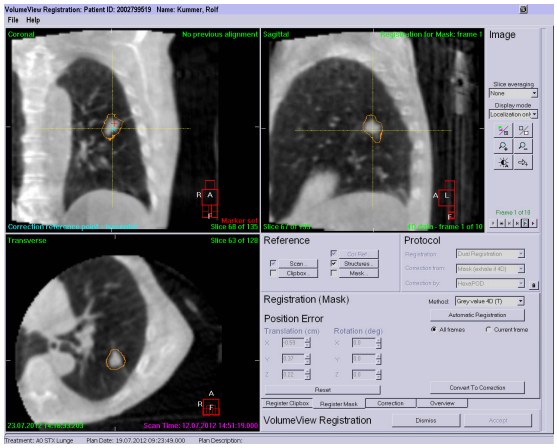
4D IGRT using CBCT technology

- “mask definition”: CTV + 3mm excluding all bony structures



4D IGRT using CBCT technology

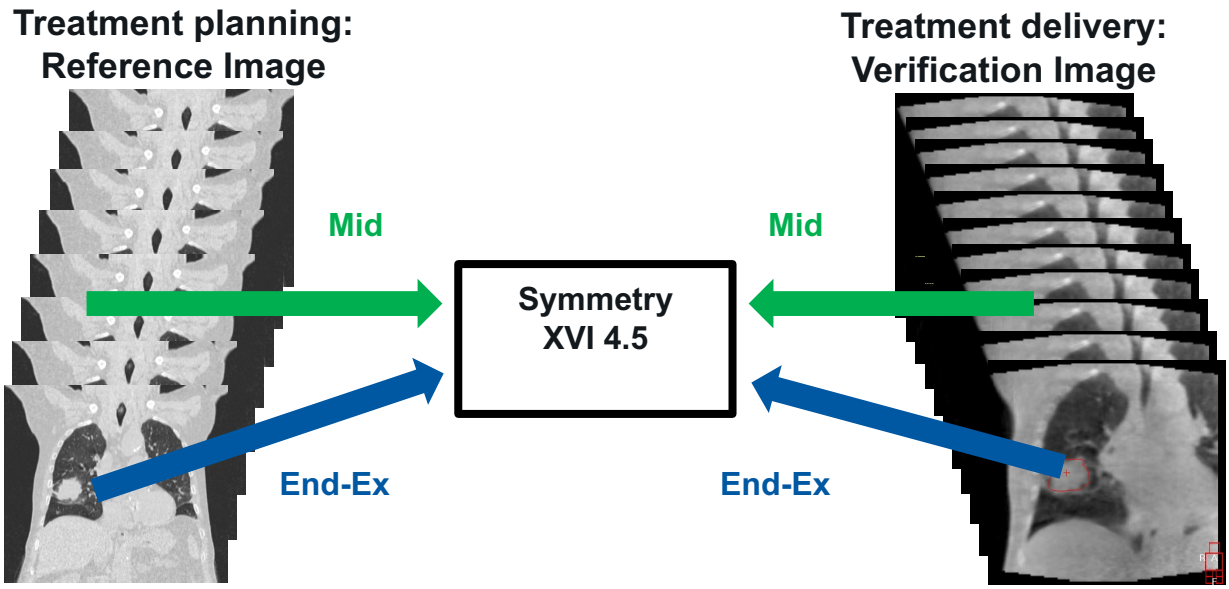
- 4D registration: finding the target in all 4D-CT phases



Target fixed in space

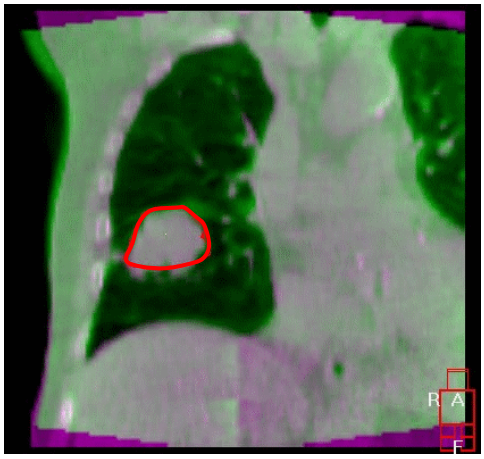
4D IGRT using CBCT technology

4D volumetric image guidance:



4D IGRT using CBCT technology

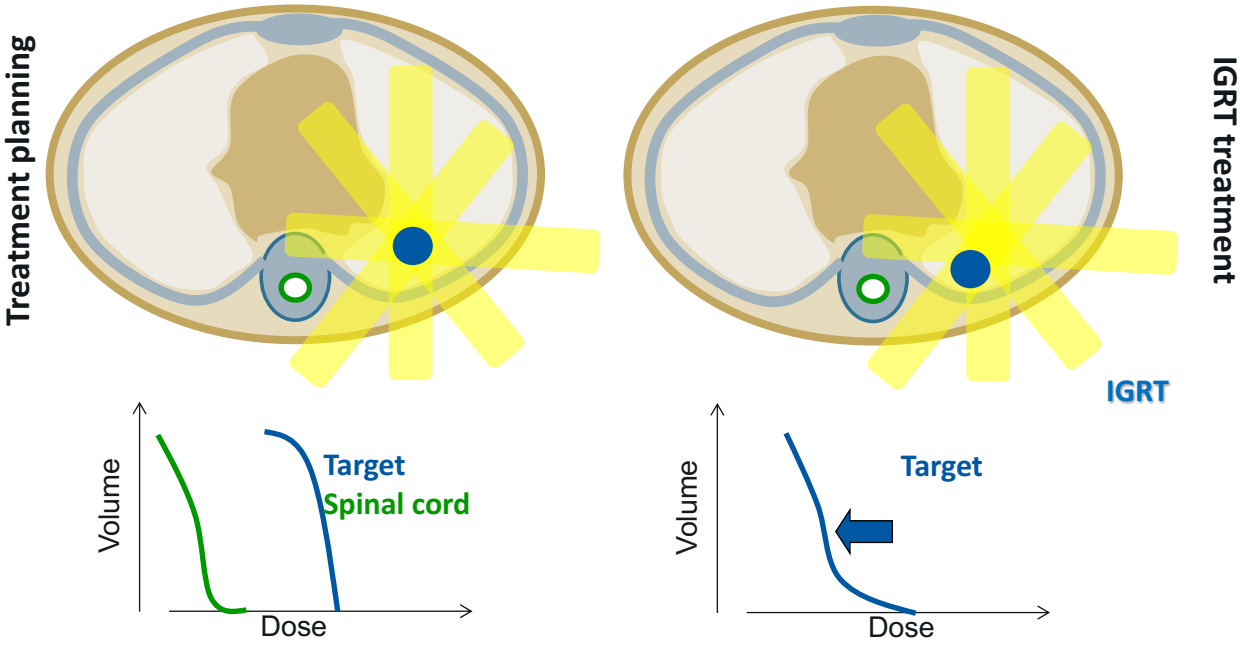
4D volumetric image guidance:



End-exhalation as reference: „tumor moves into the exhalation GTV contour and within the ITV contour“

Pitfalls in IGRT

4D volumetric image guidance:



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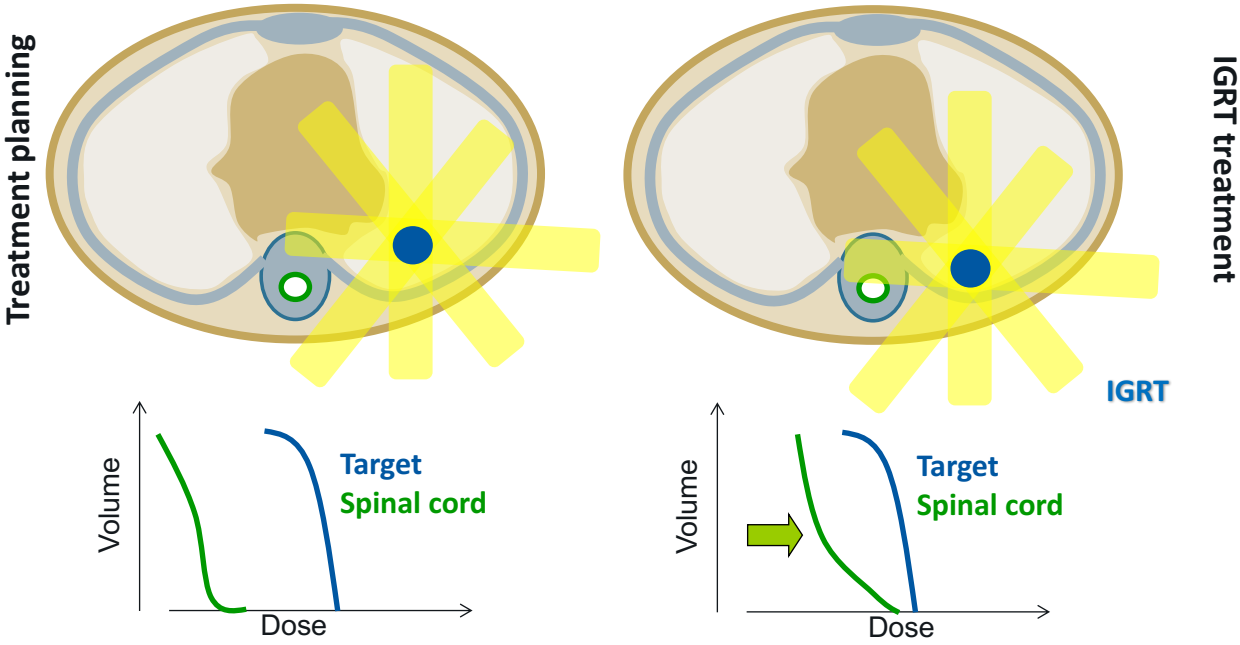
Pitfalls in IGRT

4D volumetric image guidance:



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Radiographic follow-up

Acute changes after SBRT:

- diffuse consolidation
- patchy consolidation
- diffuse ground-glass opacities (GGO)
- patchy GGO
- no change

Late changes after SBRT:

- modified conventional (consolidation, volume loss, and bronchiectasis similar to but less extensive than conventional radiation fibrosis)
- scar-like fibrosis (linear opacity in the region of the original tumor)
- mass-like fibrosis
- no change

Radiographic follow-up

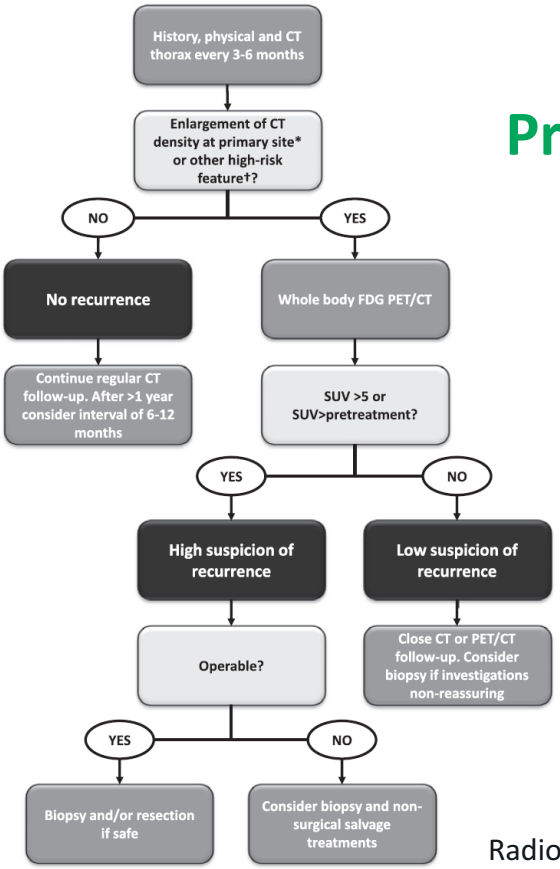
Acute changes

Late changes

Hung Radiother Oncol 2012

Study		Benign acute CT changes (%)					Benign late CT changes (%)				Recurrence features
		Diffuse consolidation	Patchy consolidation	Diffuse GGO	Patchy GGO	No evidence of increasing density	Modified conventional	Scar-like fibrosis	Mass-like fibrosis	No evidence of increasing density	
Dahele et al. [9]	Acute $n = 67$ lesions Late $n = 68$ lesions	16	24	7	6	46	71	11	7	11	Recurrences excluded from study
Kimura et al. [17]	$n = 52$ lesions	38	15	12	2	33	62	22	17	0	Four based on CT enlargement, evolved from scar-like ($n = 2$) and mass-like ($n = 2$) fibrosis
Palma et al. [18]	3DCRT $n = 50$ patients	14	22	4	16	44					Excluded from study
	RA $n = 25$ patients	32	8	4	16	40					
Trovo et al. [19]	6 months $n = 33$ patients 12 months $n = 35$ patients	27	33	12	6	21	46	14	20	20	Three based on CT enlargement and increased SUV, evolved from diffuse GGO ($n = 1$) patchy consolidation and GGO ($n = 2$)
Weighted Averages	Acute $n = 227$ Late $n = 155$	24	21	8	8	38	62	15	14	9	

Proposed FU after SBRT



High-risk features:

- sequential enlargement on repeat CT
- opacity enlargement after 12 months
- bulging margin
- disappearance of air bronchograms
- linear margin disappearance
- ipsilateral pleural effusion or lymph node enlargement.

Hung et al.
Radiother Oncol 2012

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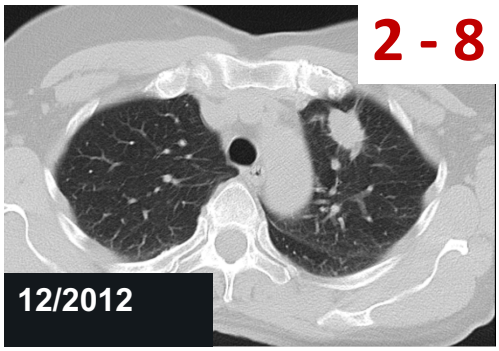
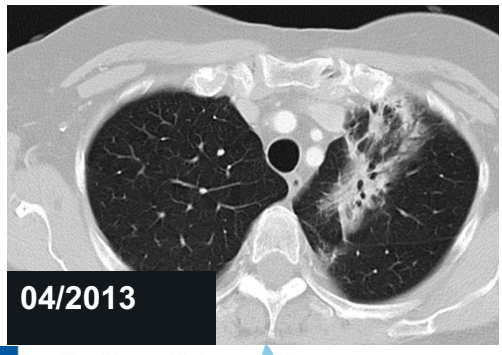
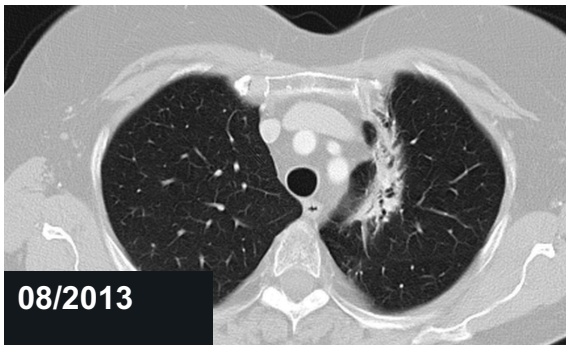
Follow-up: KI

2 - 8 Months







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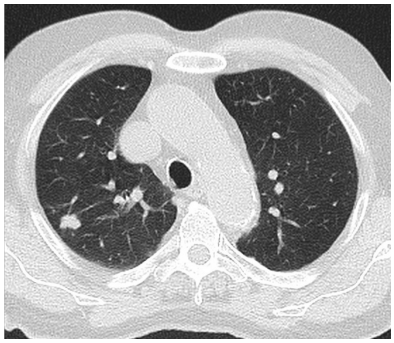
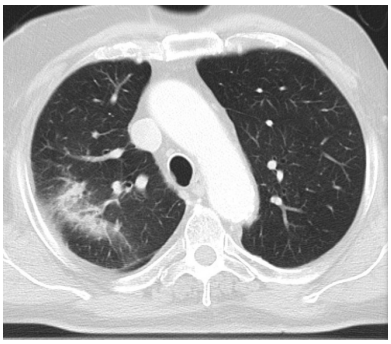
Follow-up: BB

2 - 6 Months

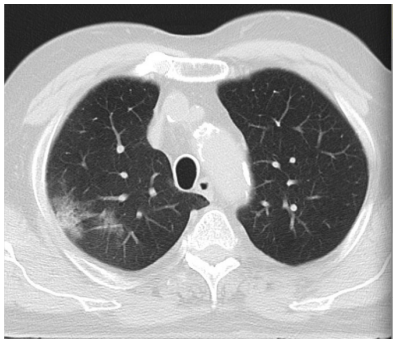
02/2013



05/2013

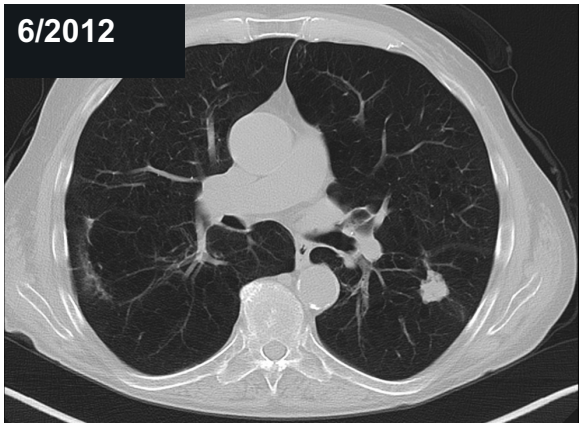


08/2013



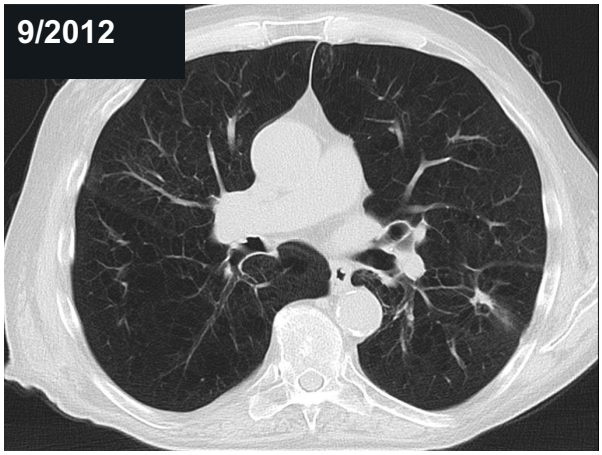
Follow-up: KR

6/2012

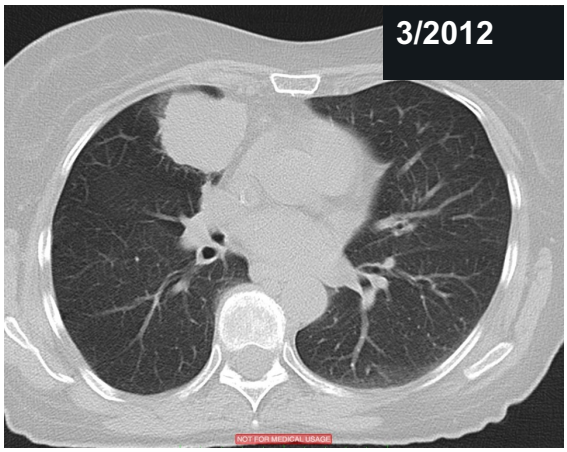


3 Months

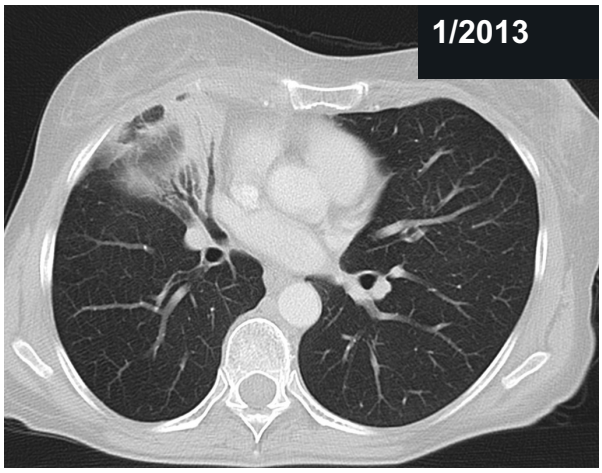
9/2012



Follow-up: SJ



10 Months



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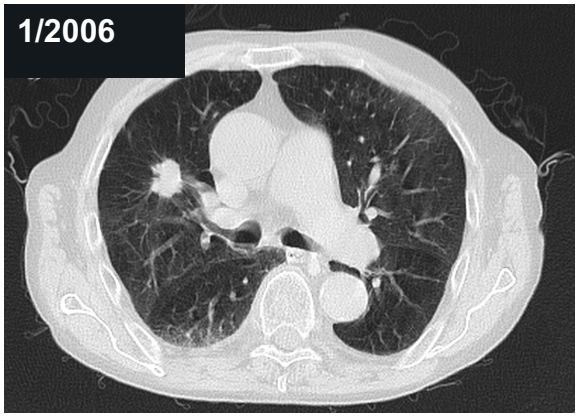
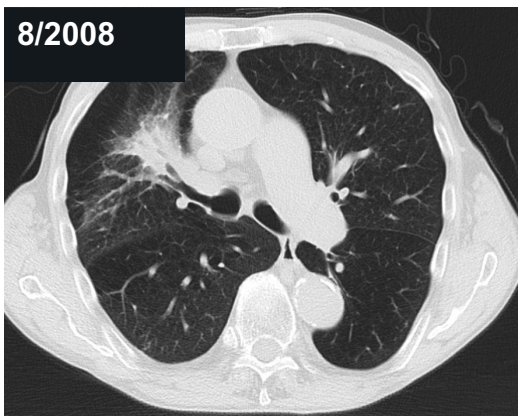
Follow-up: HJ



30 Months



UniversityHospital Zurich ESTRO

Department of Radiation Oncology
Chairman: Prof. Dr. Matthias Guckenberger

Case example Spine SBRT

Matthias Guckenberger

UniversityHospital Zurich

Medical history

55 year old female
Performance status 70%

Diagnosis:
NSCLC Adeno Ca Stage IV
Brain, Bone Lung metastasis
PD 2010

Prior treatments:
Erlotinib
Whole brain irradiation -> local boost

Clinical examination

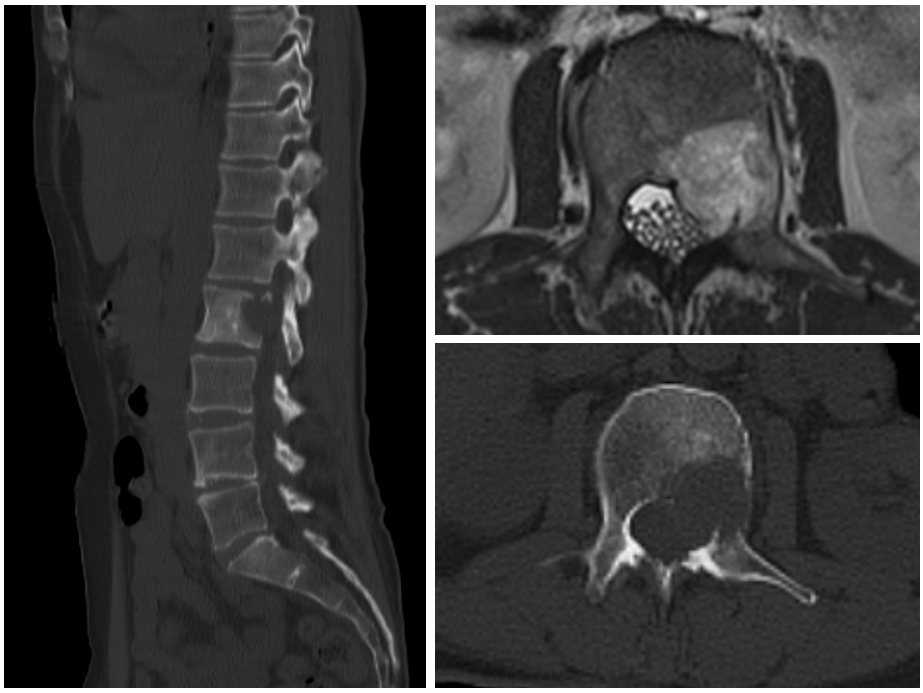
Patient reports pain especially in lower spine
Constant pain of high intensity:

Average VAS	6
Maximum VAS	8

NSAR only with limited pain effect
No opioid medication
No bisphosphonates

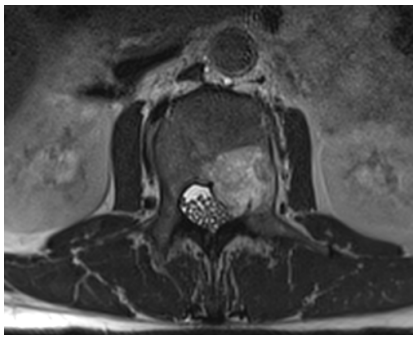
No neurological deficits

Pre-SBRT diagnostic imaging

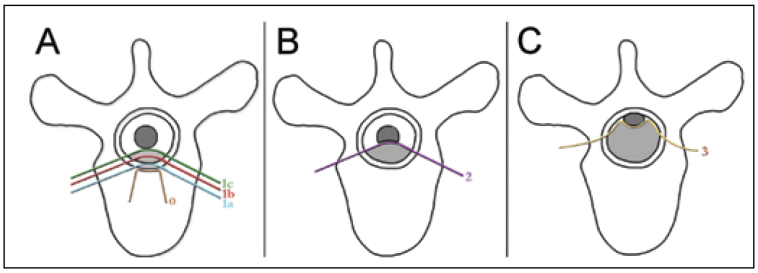


Pre-SBRT risk assessment

Classification of lesion: Epidural involvement



Score 2



Bilsky Score

Bilskey J Neurosurg Spine 2010

Pre-SBRT risk assessment

Classification of lesion: stability

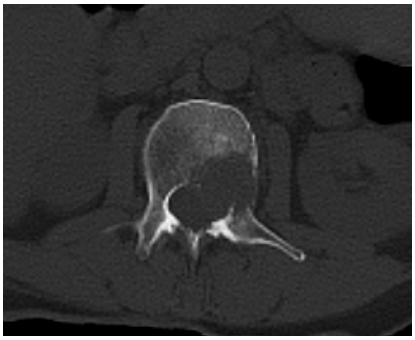
Table 1. SINS

SINS Component	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semirigid (T3-T10)	1
Rigid (S2-S5)	0
Pain*	
Yes	3
Occasional pain but not mechanical	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
> 50% collapse	3
< 50% collapse	2
No collapse with > 50% body involved	1
None of the above	0
Posterolateral involvement of spinal elements†	
Bilateral	3
Unilateral	1
None of the above	0

0 to 6	→ stability
7 to 12	→ indeterminate instability
13 to 18	→ instability

SINS Score

Fourney JCO 2011



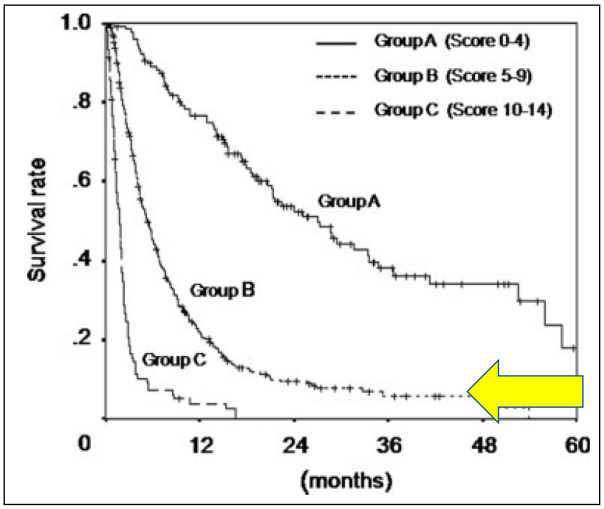
Score 8

Pre-SBRT risk assessment

Significant Prognostic Factors and Score for Each Factor

Prognostic Factor	Score
Type of primary tumor	
Favorable*	0
Unfavorable	3
ECOG PS ≥3	3
Visceral metastases	2
Previous chemotherapy	2
Hypercalcemia	2
Multiple bone metastases	1
Elderly (≥71 y)	1

Type of primary tumor	3
	breast, prostate, thyroid (except anaplastic = 0)
Performance Status <= 70	3
Visceral metastasis	2
Pervious ChT	0
Hypercalcemia	0
Multiple bone metastases	1
Age >= 71 years	0
Mizumoto Score sum	9



Mizumoto Cancer 2008

Dose & fractionation in DOSIS trial

Epidural disease: 10 x 4.85Gy EQD2 60Gy
No epidural disease: 5 x 8Gy EQD2 60Gy

Fractionation Scheme	5x 4 / 8	10x3/ 4.85		5x 4/ 7	10x3/ 4.85
Spinal Cord + 1mm	23.75	35	0.1cm^3	20	30
Cauda Equina	25	37.5	0.1cm^3	20	30
Kidney	-	-		10	12
Bowel	24	37	1cm^3	-	-
Esophagus	30	40	1cm^3	-	-
Liver		-		12.5	17.5

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Universitair Medisch Centrum Rotterdam

Cancer Institute

Physics in Implementing SBRT
QA of Imaging

Mischa Hoogeman

Contents

- **In-room Imaging**
  - Volumetric imaging
  - Planar imaging
- **Imaging for treatment planning**
  - 4D CT scanning
  - MRI
    - 3D geometrical correction
    - Tilted images and treatment planning systems

AAPM tg 179 QA for IGRT with CT

- CT on rails (not further assessed)
- On-board MRI (not further assessed)
- MV cone or fan beam CT (not further assessed)
- kV cone beam CT (Elekta and Varian LINACS)

- kV planar imaging (CyberKnife, Brainlab …)

Quality assurance for image-guided radiation therapy utilizing CT-based technologies: A report of the AAPM TG-179

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Med. Phys. 39 (4), April 2012
http://dx.doi.org/10.1118/1.3690466

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AAPM TG 179: SBRT Requirements

- SBRT is characterized by the accurate delivery of high doses of radiation in five or fewer fractions
  - The relatively high dose per fraction increases the potential for normal tissue damage or serious target underdosing
- The AAPM TG 101 recommends the use of image guidance for all SBRT treatments to eliminate the risk of a geometric miss

- AAPM TG 179: “Perhaps, the most important application of CBCT has been the simplification of hypofractionated, SBRT”

Med. Phys. 37 (8) August 2010
DOI: 10.1118/1.3438081

QA Items

- Patient safety (collision interlock)
- Geometric accuracy
  - Linearity
  - Alignment between imaging system and radiation isocenter
- Image quality
- Spatial resolution

Fortunately, geometric accuracy, localization, and geometric fidelity have been demonstrated, in a number of publications, to be well within 1 mm over extended periods of time[1]

[1]Med. Phys. 39 (4), April 2012

QA Frequency

- SBRT => It may be impossible to correct for radiation delivery errors by modifying subsequent fractions

Because of the critical importance of the imaging system in SBRT patient positioning, ***daily*** *quality assurance checks of geometric accuracy are recommended*[1]

[1]Med. Phys. 39 (4), April 2012

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Summary of QC Tests

TABLE II. Summary of QC tests recommended for CT-based IGRT systems. Tolerances may change according to expectations, experience and performance.

Frequency	Quality metric	Quality check	Tolerance
Daily	Safety	Collision and other interlocks	Functional
		Laser/image/treatment isocentre coincidence OR	±2 mm
		Phantom localization and repositioning with couch shift	±2 mm
		kV/MV/laser alignment	±1 mm
		Couch shifts: accuracy of motions	±1 mm
	Image quality	Scale, distance, and orientation accuracy[a]	Baseline
		Uniformity, noise[a]	Baseline
		High contrast spatial resolution[a]	≤ 2 mm (or ≤ 5 lp/cm)
		Low contrast detectability[a]	Baseline
If used for dose calculation	Image quality	CT number accuracy and stability[a]	Baseline
Annual	Dose	Imaging dose	Baseline
	Imaging system performance	X-ray generator performance (kV systems only): tube potential, mA, ms accuracy, and linearity	Baseline
	Geometric	Anteroposterior, mediolateral, and craniocaudal orientations are maintained (upon upgrade from CT to IGRT system)	Accurate
	System operation	Long and short term planning of resources (disk space, manpower, etc.)	Support clinical use and current imaging policies and procedures

[a]These tests can be performed on a semiannual basis after stability has been demonstrated, 6–12 months after commissioning.

Med. Phys. 39 (4), April 2012

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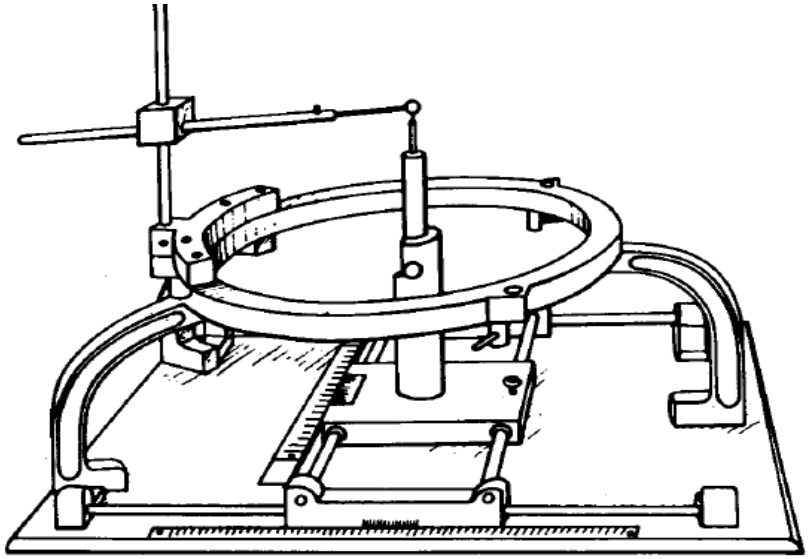
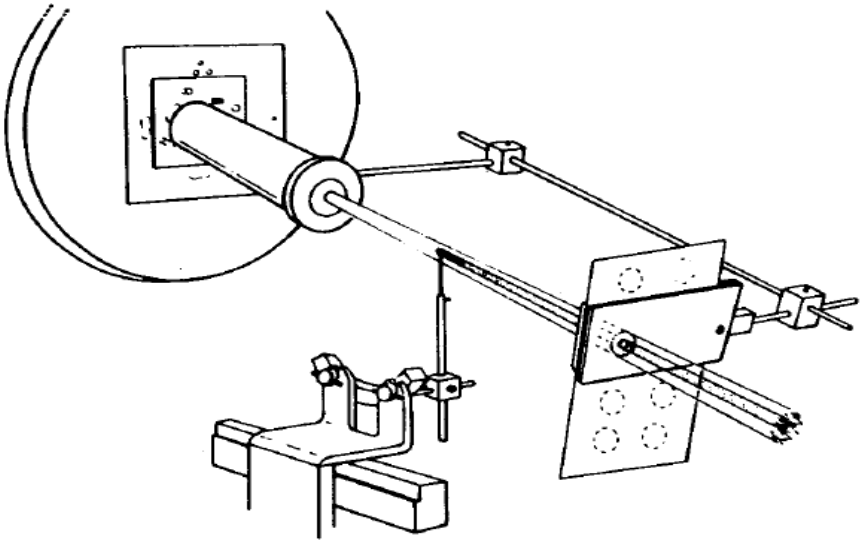
Lutz – Winston Test





W. Lutz, K. R. Winston, and N. Maleki, “A system for stereotactic radiosurgery with a linear accelerator,” Int. J. Radiat. Oncol., Biol., Phys. 14, 373–381 (1988)

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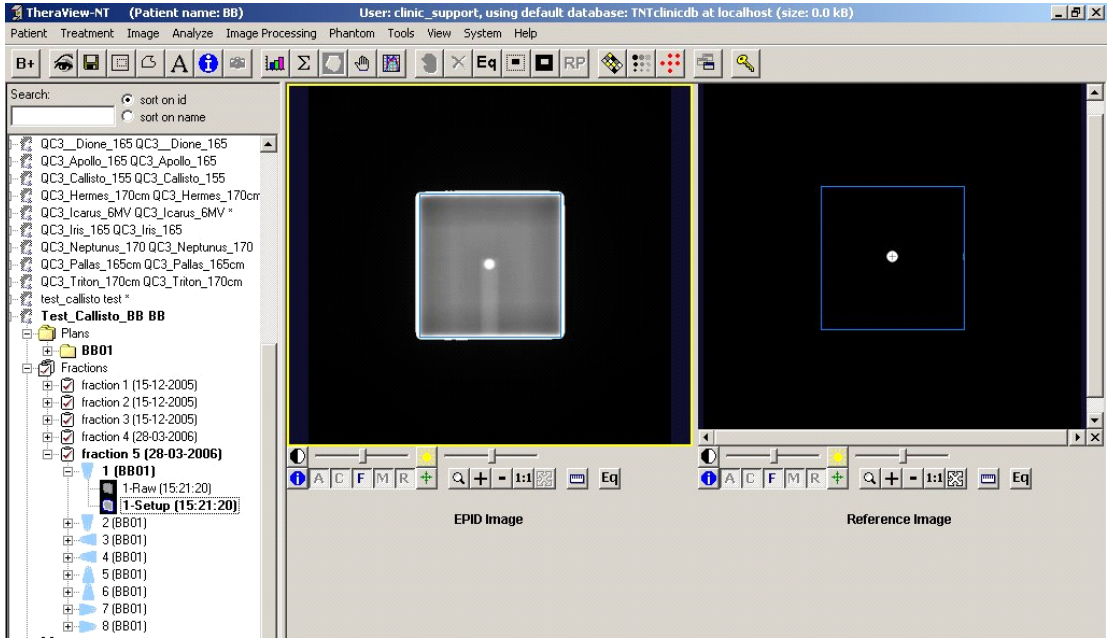
Imaging System and Radiation Isocenter Alignment

- The alignment is done as a function of gantry angle since the components may flex during gantry rotation



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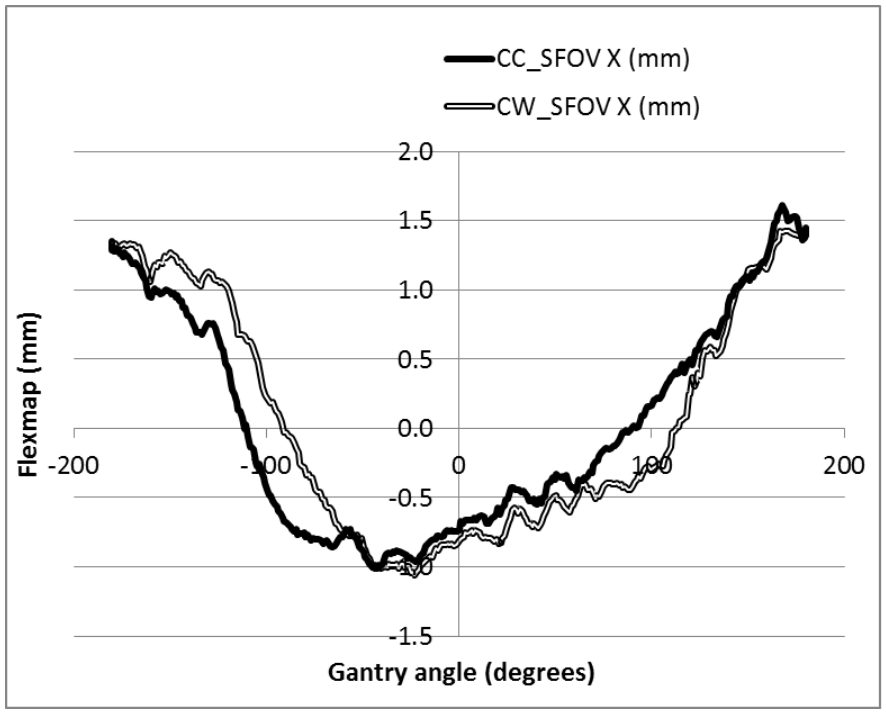
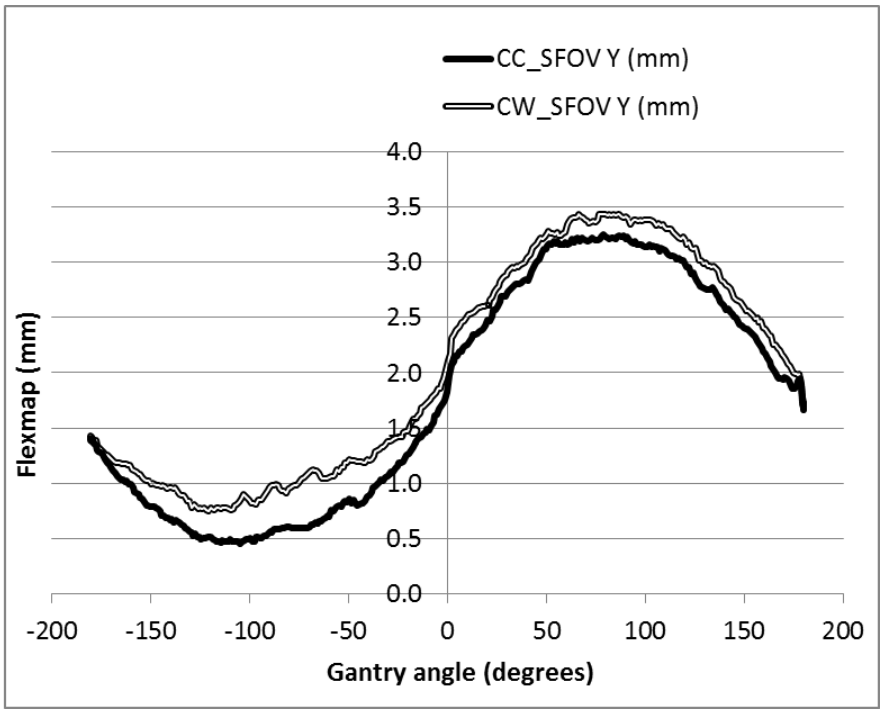
Example Flexmaps





- Varian system compensates flexes by moving the robotic arm

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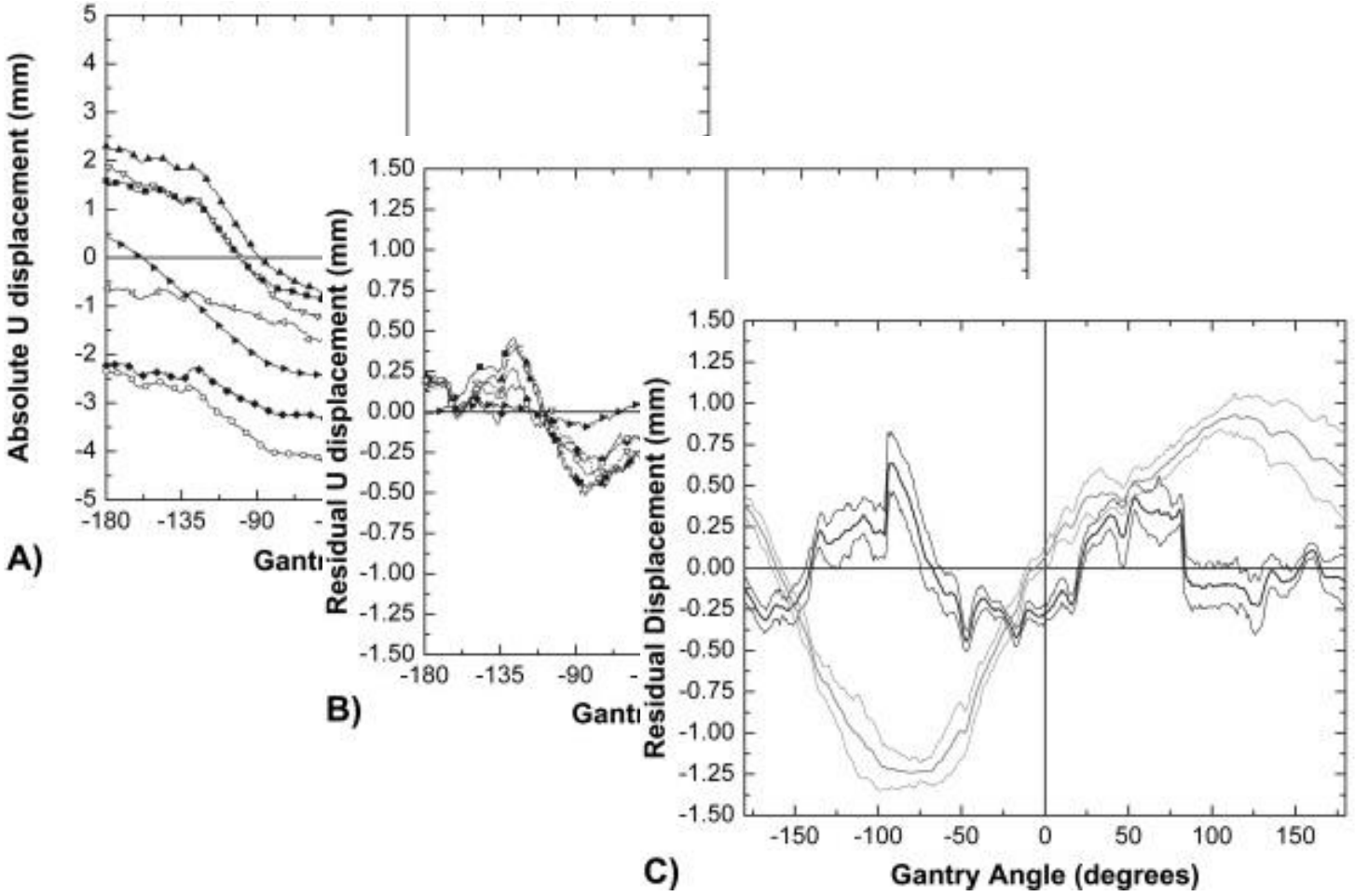
Stability of Flexmaps



[1]J Bissonnette, D Moseley, E White, M Sharpe, T Purdie, D Jaffray, Quality Assurance for the Geometric Accuracy of Cone-Beam CT Guidance in Radiation Therapy. IJROBP, Volume 71, Issue 1, Supplement, 2008, S57–S61

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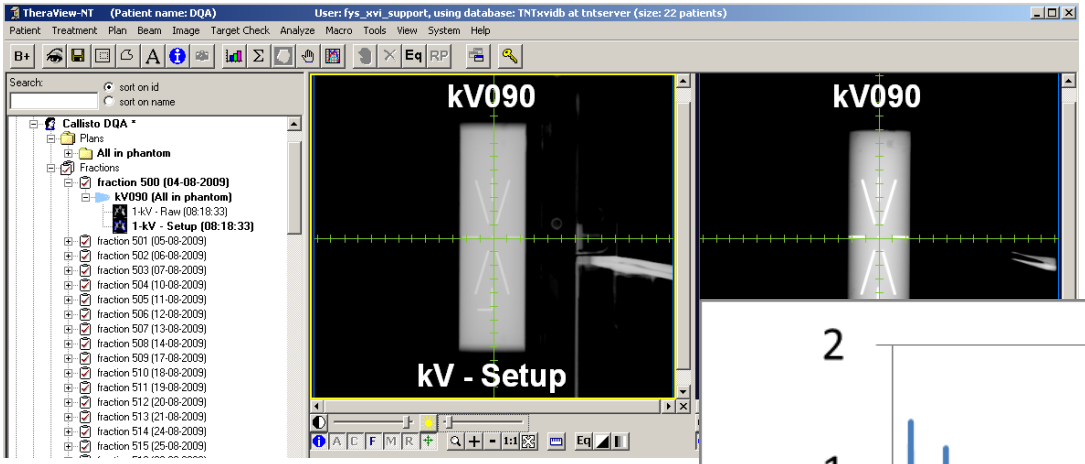
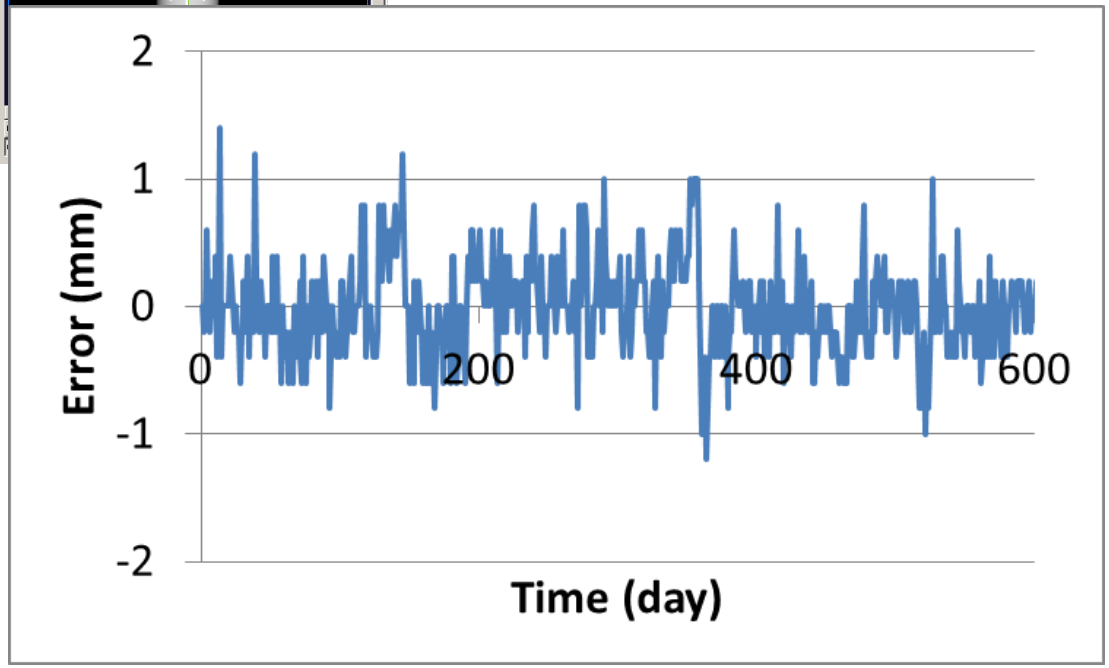
Daily QA Phantom





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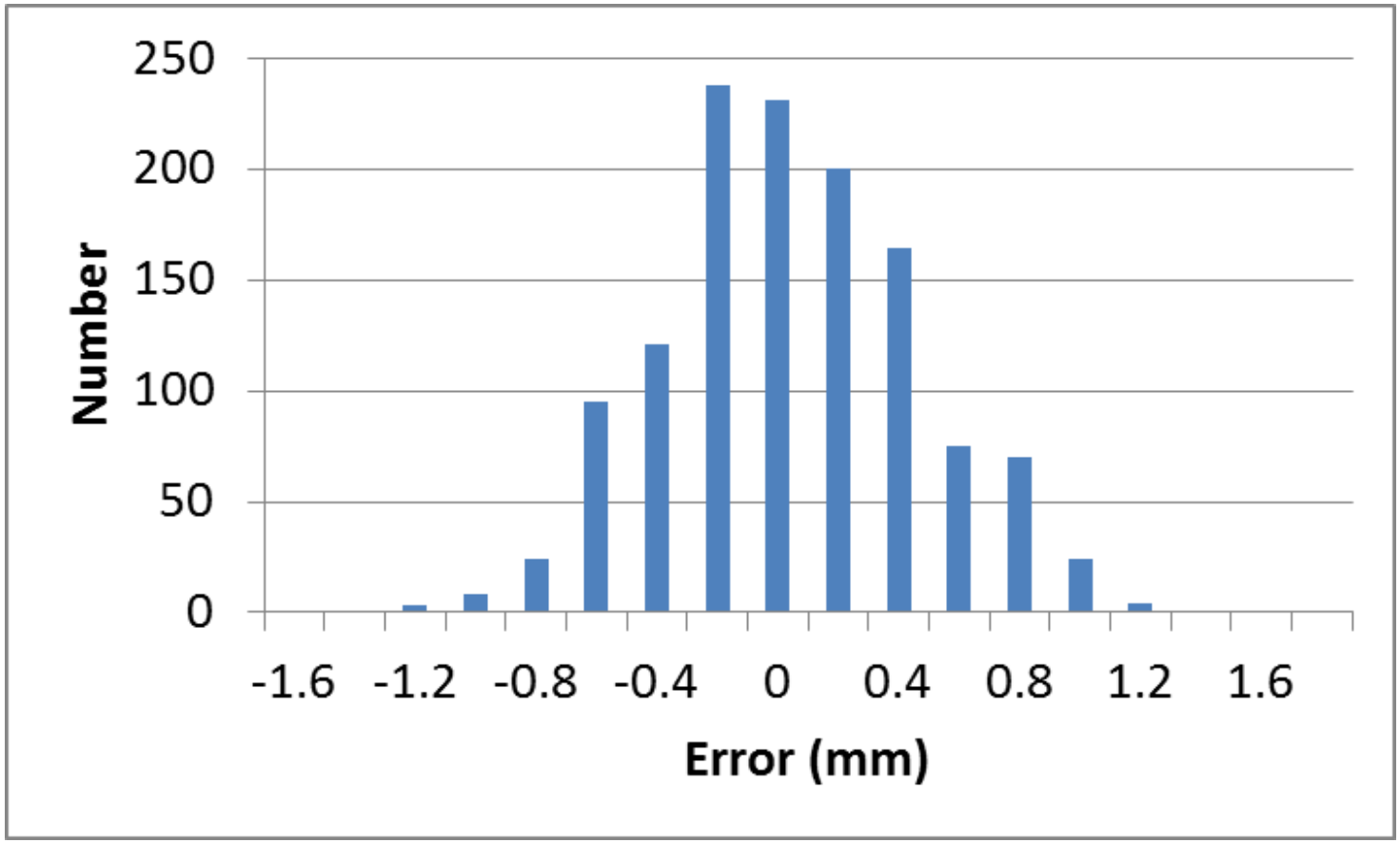
Imaging System - Radiation Isocenter Alignment Error



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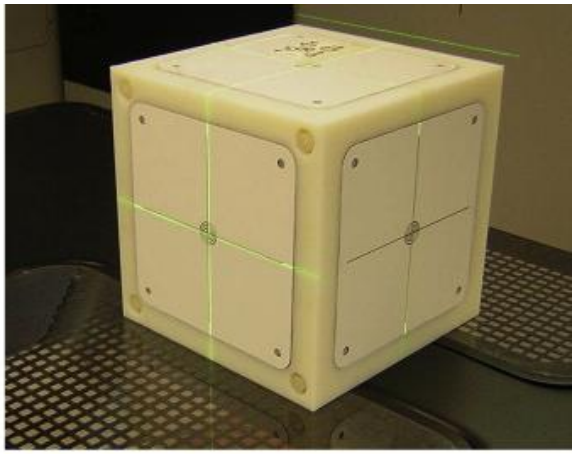
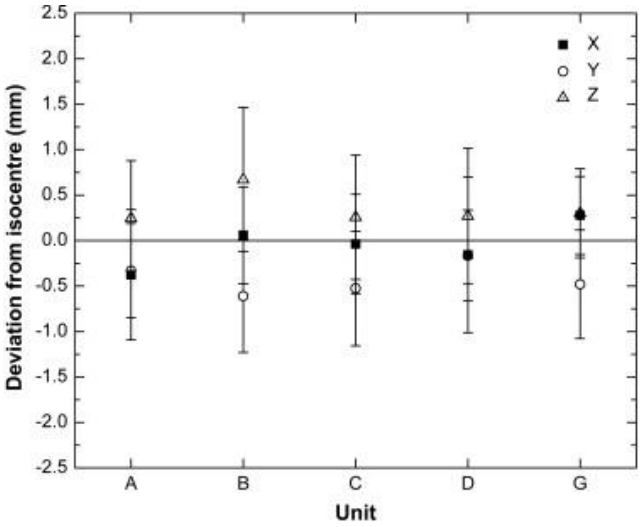
Imaging System and Radiation Isocenter Alignment





- External markers are first aligned with the room lasers before acquisition of orthogonal portal images. The isocenter indicated from these portal images is then compared with that obtained with that obtained with the volumetric imaging system isocenter[1]

1J Bissonnette, D Moseley, E White, M Sharpe, T Purdie, D Jaffray, Quality Assurance for the Geometric Accuracy of Cone-Beam CT Guidance in Radiation Therapy. IJROBP, Volume 71, Issue 1, Supplement, 2008, S57–S61

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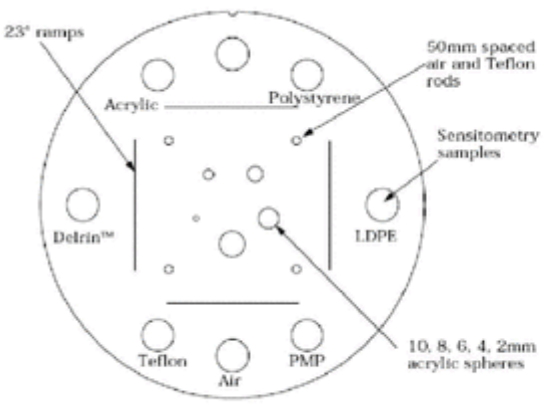
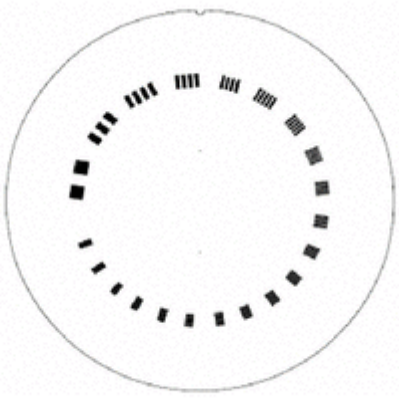
Accuracy of a Remotely Controlled Couch

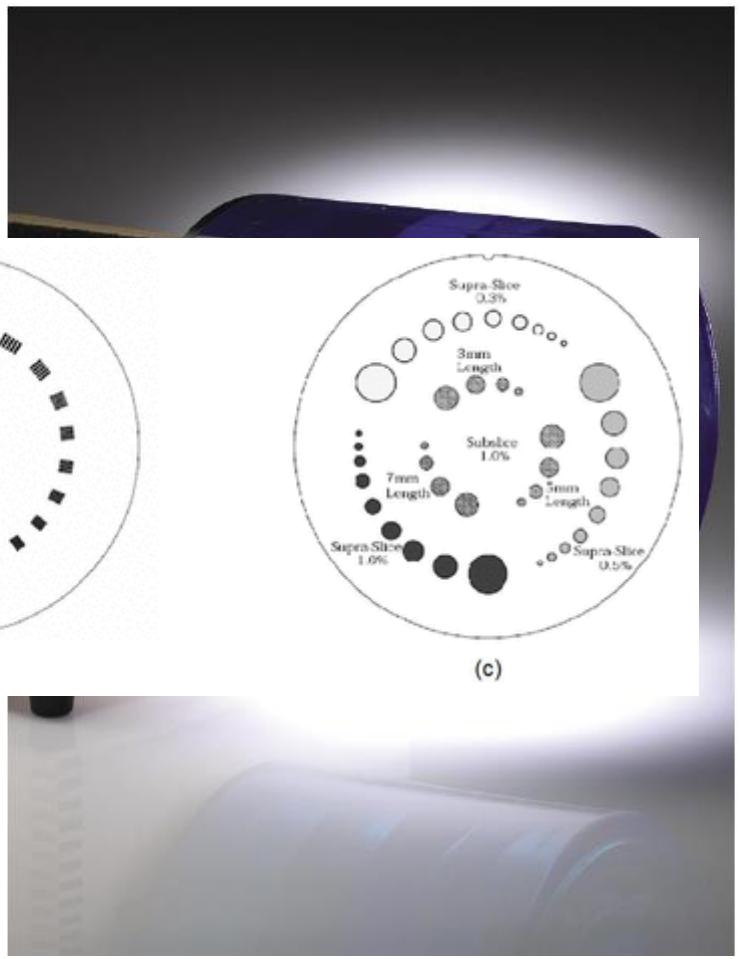
- Remotely controlled couches are available to correct translations or both translations and rotations
- Submillimeter couch position accuracy has been demonstrated (commissioning)
- For daily QA, incorporate couch test in imaging system - radiation isocenter test

Image Quality Assessed with Catphan Phantom

- Scale, distance, and orientation accuracy
- U
- H
  re
- L
- C
  stability







Kamath S, Song W, Chvetsov A, Ozawa S, Lu H, Samant S, Liu C, Li JG, Palta JR. An image quality comparison study between XVI and OBI CBCT systems. J Appl Clin Med Phys. 2011 Feb 4;12(2):3435.

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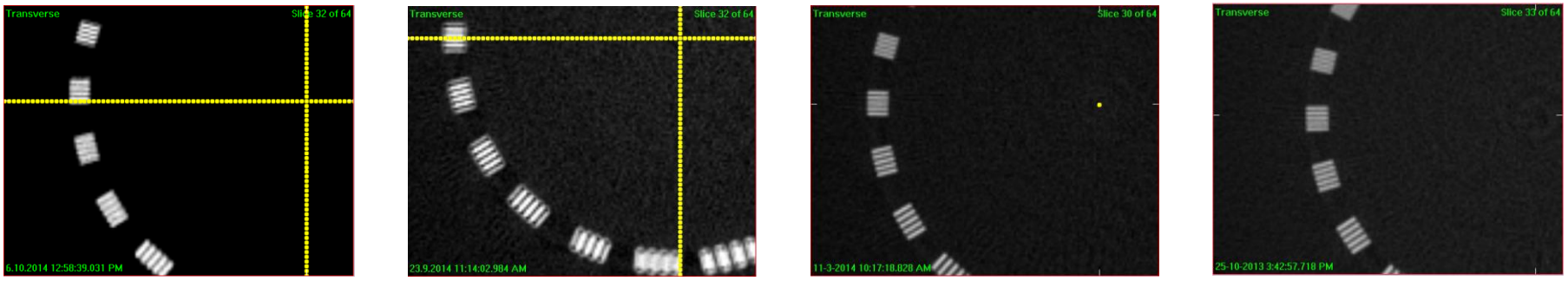
Image Quality Example



time

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Dose

[LarynxS20]
PresetDescription=Larynx S20 volume acquisition
Mode=Clinical
kV=100
NominalmAPerFrame=10
NominalmsPerFrame=10
kVCollimator=S20
kVFilter=F1
StartAngle=-105
StartAcqAngle=-100
StopAcqAngle=100
GantrySpeed=180
Direction=CW
Frames=361

Head and Neck				Dosis [cGy] (10 scans)	Dosis [cGy] (1 scan)
Filters: F0, S20					
Registration: No	Hoofd	A (Plak 4)	Rechter oor	0.6	0.06
Start: 260 deg					
Start: 100 deg		B (Top plak 0)	Bovenkant hoofd	1.5	0.15
Direction: CW					
Energie: 100 kV		C (Plak 4)	Linker oor	2.8	0.28
Frames: 361					
Nominal Scan Dose: 0.9 mGy		D (Plak 2)	In de schedel	1.0	0.10
Total mAs: 36.1 mAs					
		E (Plak 2)	Voorhoofd	1.6	0.16
		F (Plak 9)	Schildklier	1.7	0.17
	Lichaam	G (Plak 17)	Sternum Borstbeen	0.1	0.01
		H (plak 17)	Ribben zijkant borst	0.1	0.01

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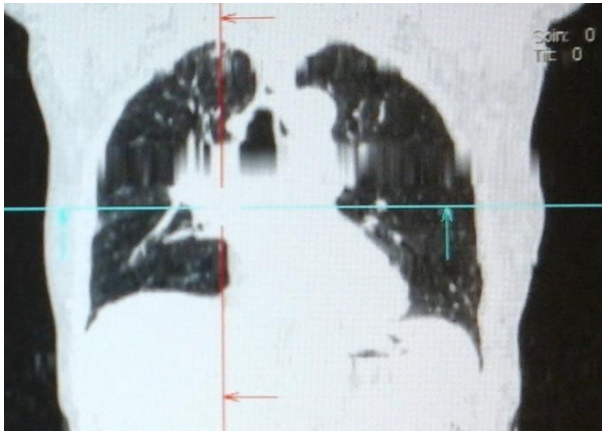
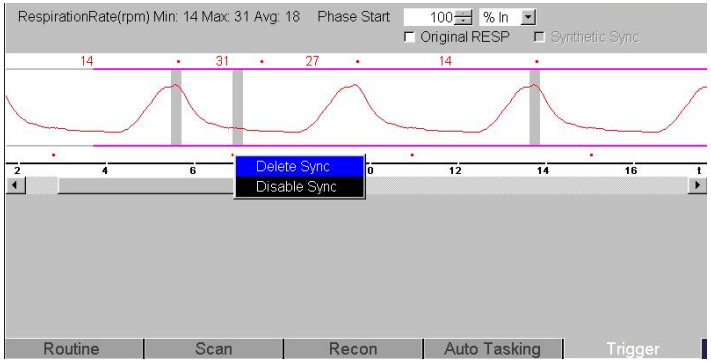
4D CT

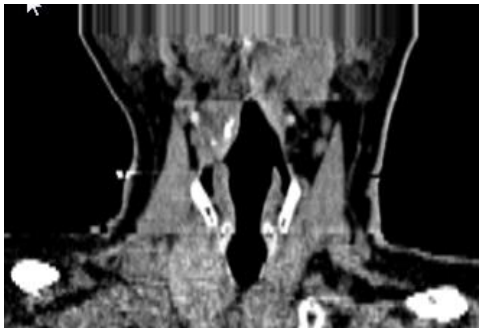
Checklist Reconstruction Improvement

- Correct scan protocol (slow vs. normal breathing protocol)



- Correct placement of synchronization points





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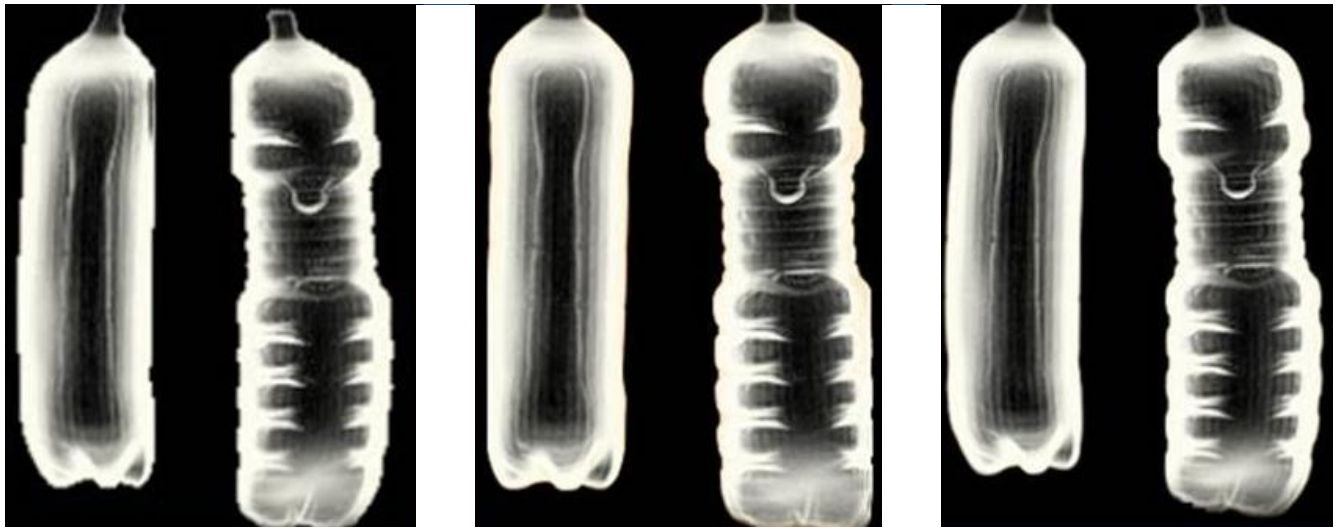
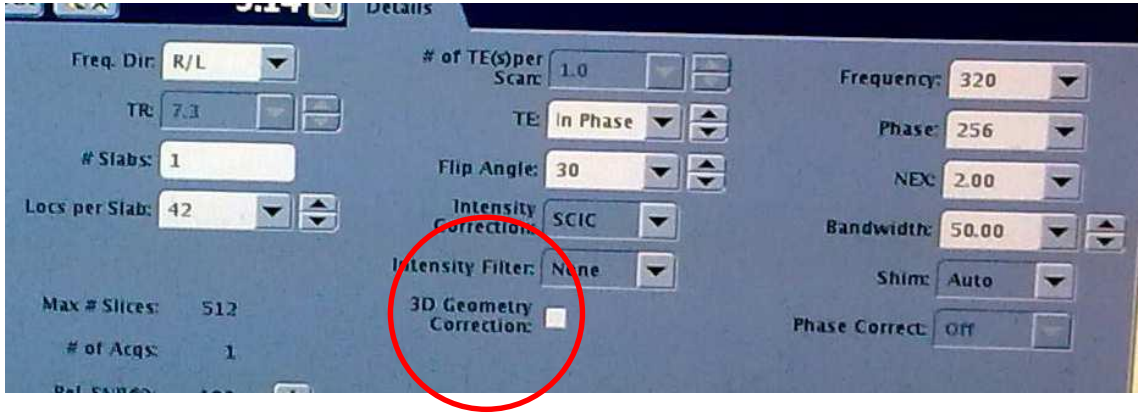
MRI

3D Geometrical Correction





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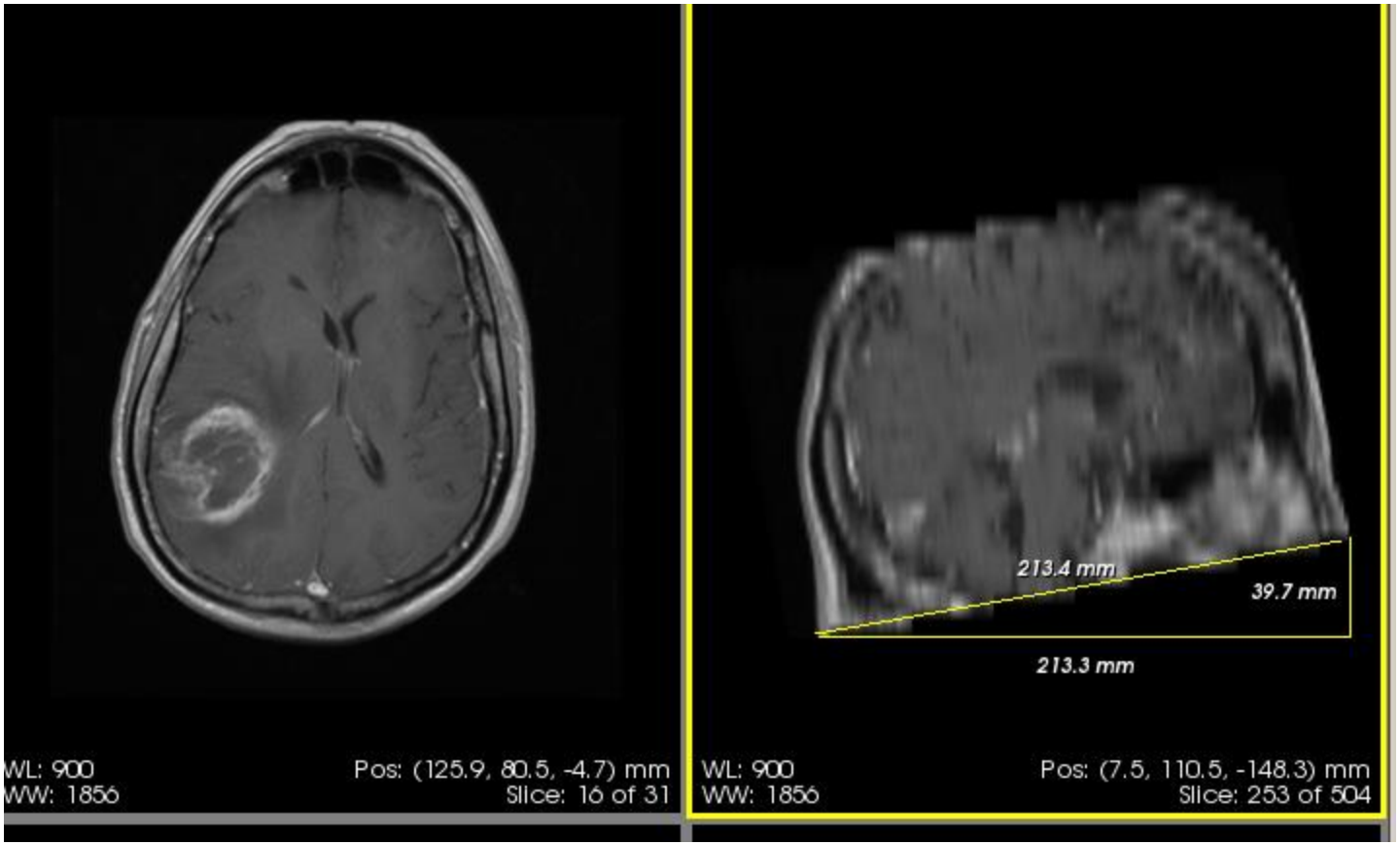
Observations

- The distance to the center of the magnet seems to be an important factor for geometric distortion in the CC direction. It is even more important than whether a T1w or T2w sequence is used
- The 3D geometrical correction seems to only work on the T1w scan. For this sequence the CC-error is reduced to a level below the slice spacing (4 mm)
- For the T2w scan the 3D algorithm does not seem to work: the CC-error can still be as large as 7 mm for points far away from the magnet center

Tilted MRIs



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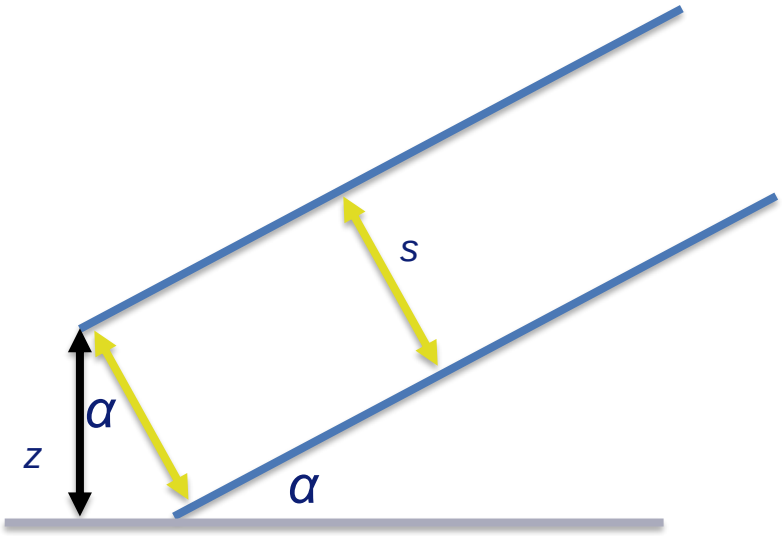
Tilted MRIs

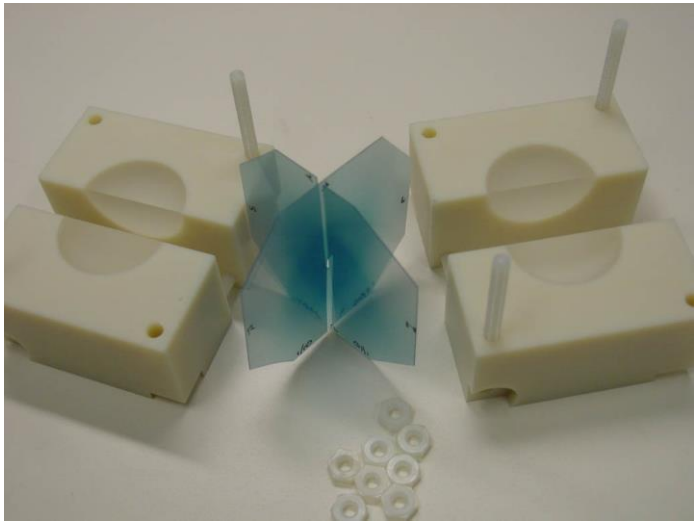


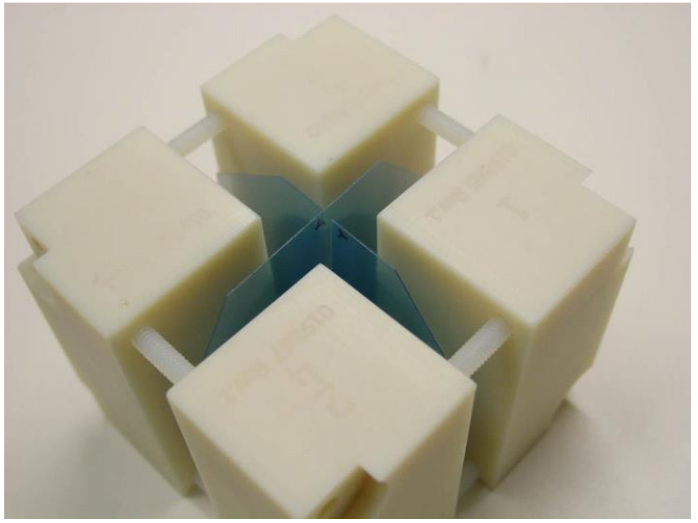
- The slice distance is *s*. Some TPS look up the slice distance by comparing the z-position of adjacent slices. In this case *z*.
- If angle α > 0, *z* is not equal to *s*. E.g. for a tilt of 20^0 the difference is 6%. Pinnacle thus underestimates the length of the scan in the cranial caudal direction.

Q&A

QA OF PLANAR KV SYSTEMS

DeltaMan and End2End testing





- Final alignment of robot coordinate system and image guidance system
- QA tool to check the alignment of both systems

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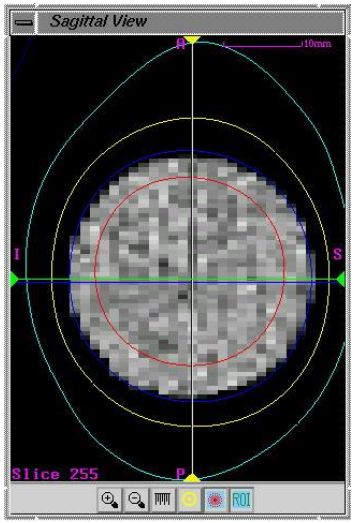
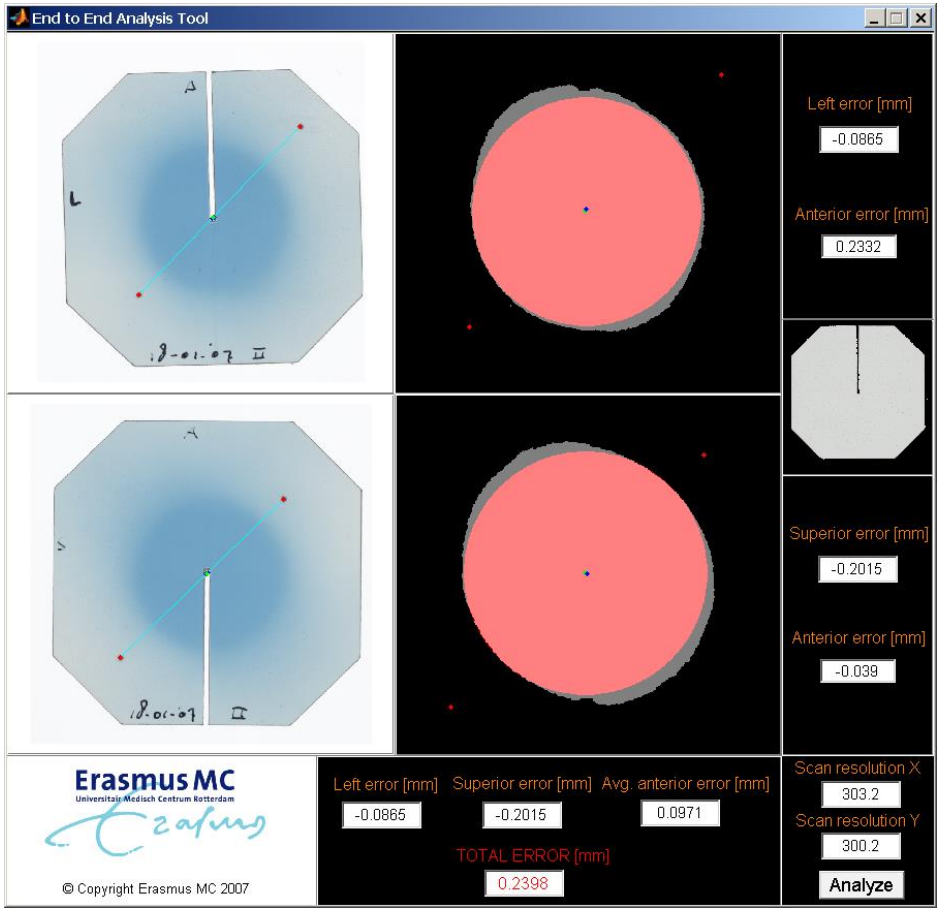
DeltaMan Analysis





Test out of imaging center

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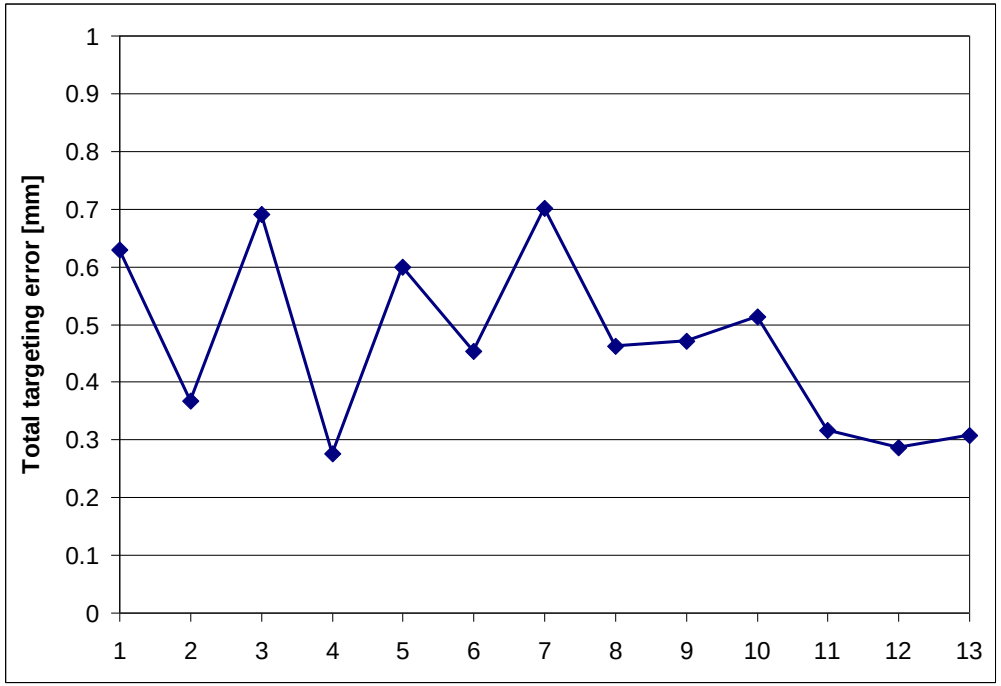
E2E Test Results

- Total 3D targeting error
  - 0.5 ± 0.2 mm



- Accuracy not affected by offsetting phantom
- Accuracy slightly reduced by rotating the phantom

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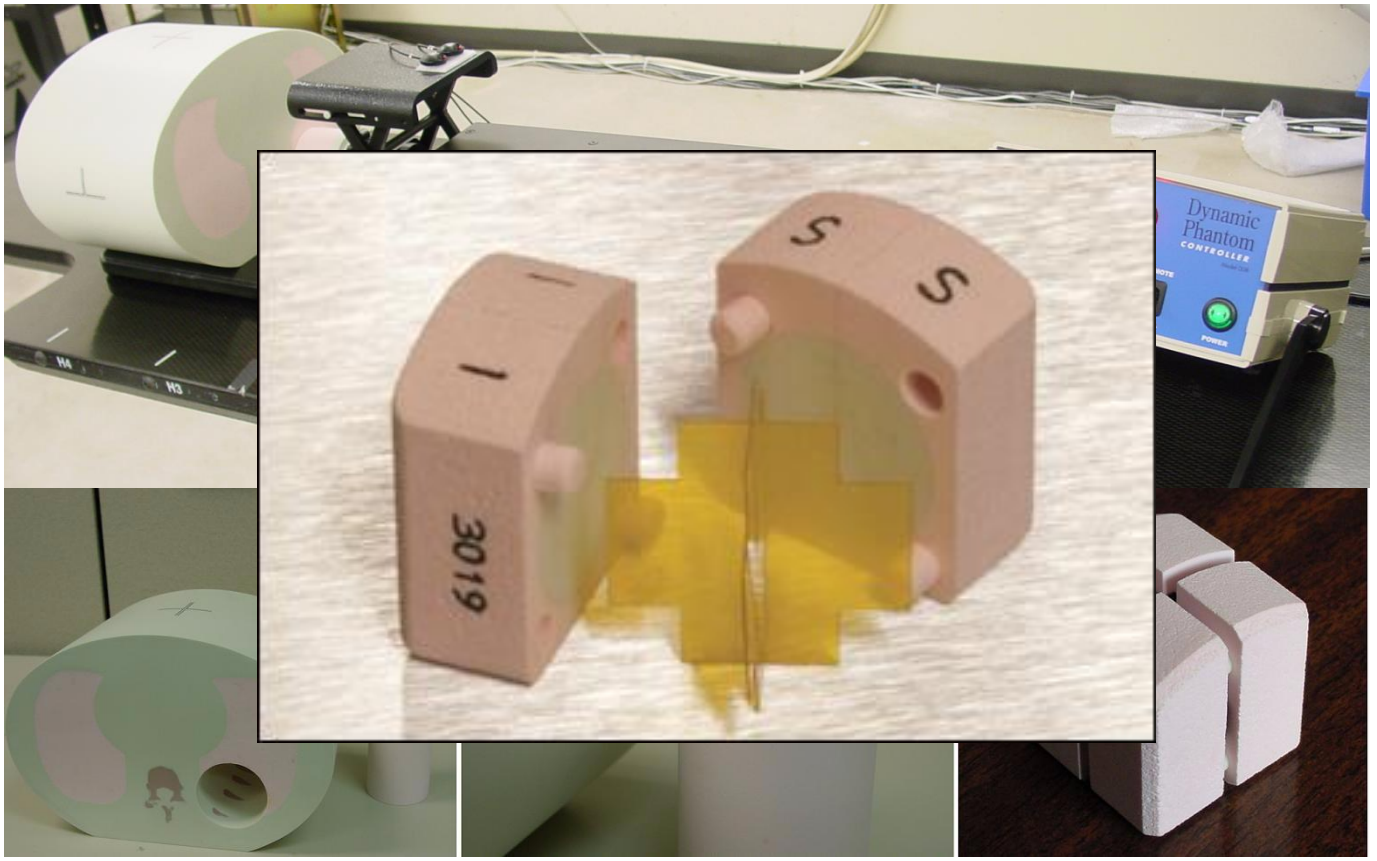
E2E Tests: Direct Target Localization (Xsight Lung Tracking)



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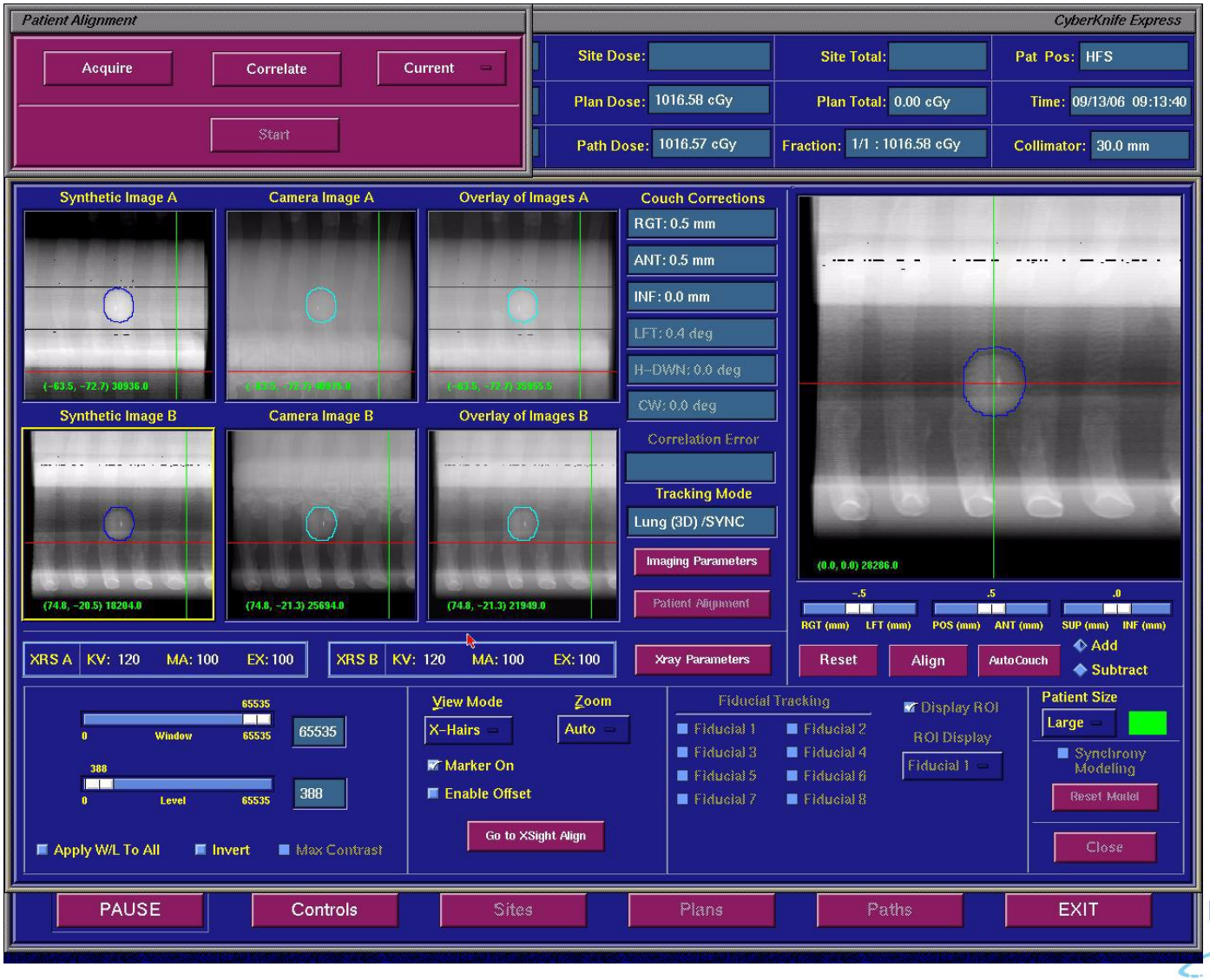
Treatment Delivery



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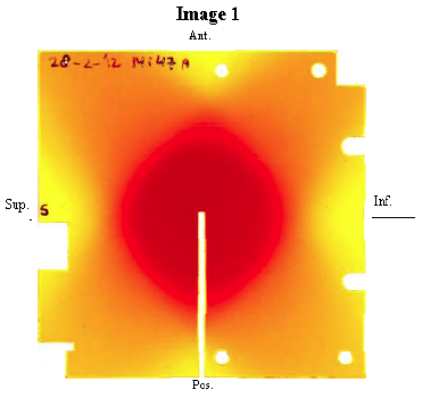
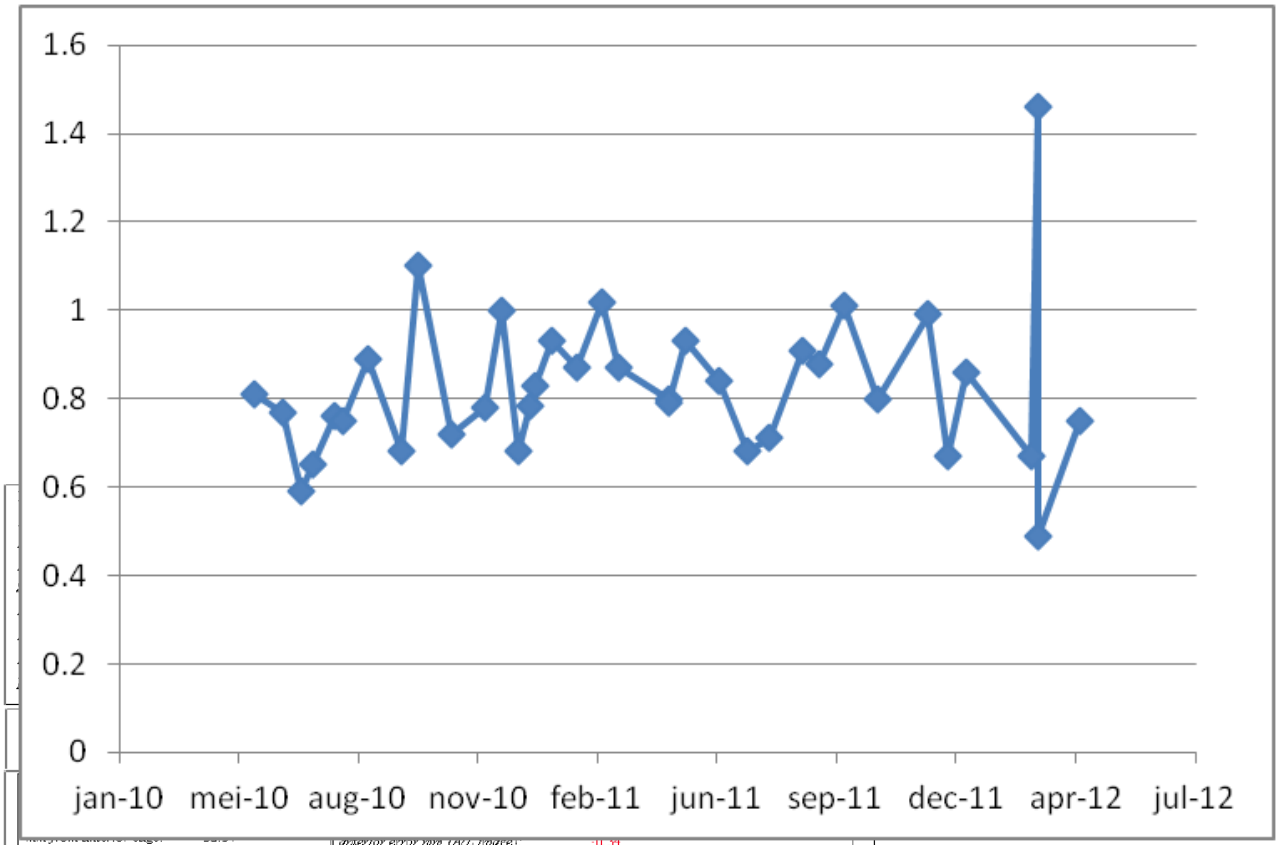
Analysis of Tracking Error





ACCURAY

End-to-End (E2E) Film Analysis

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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